WELCOME
ESTRO Teaching Course

Image-guided radiotherapy & chemotherapy in gynaecological cancer - with a special focus on adaptive brachytherapy

Madrid 2.-6. September 2018

Richard Pötter

Kari Tanderup

ESTRO
European Society for
RADIOTHERAPY
& ONCOLOGY

Image-guided cervix radiotherapy – with a special focus on adaptive brachytherapy In the ESTRO school for 14 years

- 1st edition Vienna 08 2004: 80 participants
- 2nd edition Paris 08 2005: 100 participants
- 3rd edition Vienna 08 2006: 130 participants
- 4th edition Copenhagen 08 2007: 106 participants
- 5th edition London 08 2008: 158 participants
- 6th edition (1st intern.) Manila 01 2009: 160 participants ESTRO-SEAROG
- 7th edition Amsterdam 09 2009: 120 participants
- 8th edition Warsaw 08 2010: 110 participants
- 9th edition Chandigarh (2nd intern.) 03 2011: 102 particip. AROI-ESTRO
- 10th edition Izmir 09 2011: 104 participants
- 11th edition Beijing (3rd intern.) 03 2012: 128 participants ESTRO-CSRO
- 12th edition Budapest 10 2012: 102 participants
- 13th edition Moscow (4th intern.) 06 2013: 180 participants
- 14th edition Barcelona 09 2013: 90 participants
- 15th edition Florence 10 2014: 99 participants
- 16th edition Utrecht 11 2015: 82 participants
- 17th edition Toronto (5th intern.) 04 2016: 110 particip. ESTRO-CARO
- 18th edition Bangalore (6th intern.) : 80 participants AROI-ESTRO
- 19th edition Prague 10 2017: 101 participants
- 20th edition Luchnow (7th intern.) 03 2018: 80 participants AROI-ESTRO
- 21th edition Madrid 09 2018: 83 participants

In total >2300 participants

Discussion of Course Directors

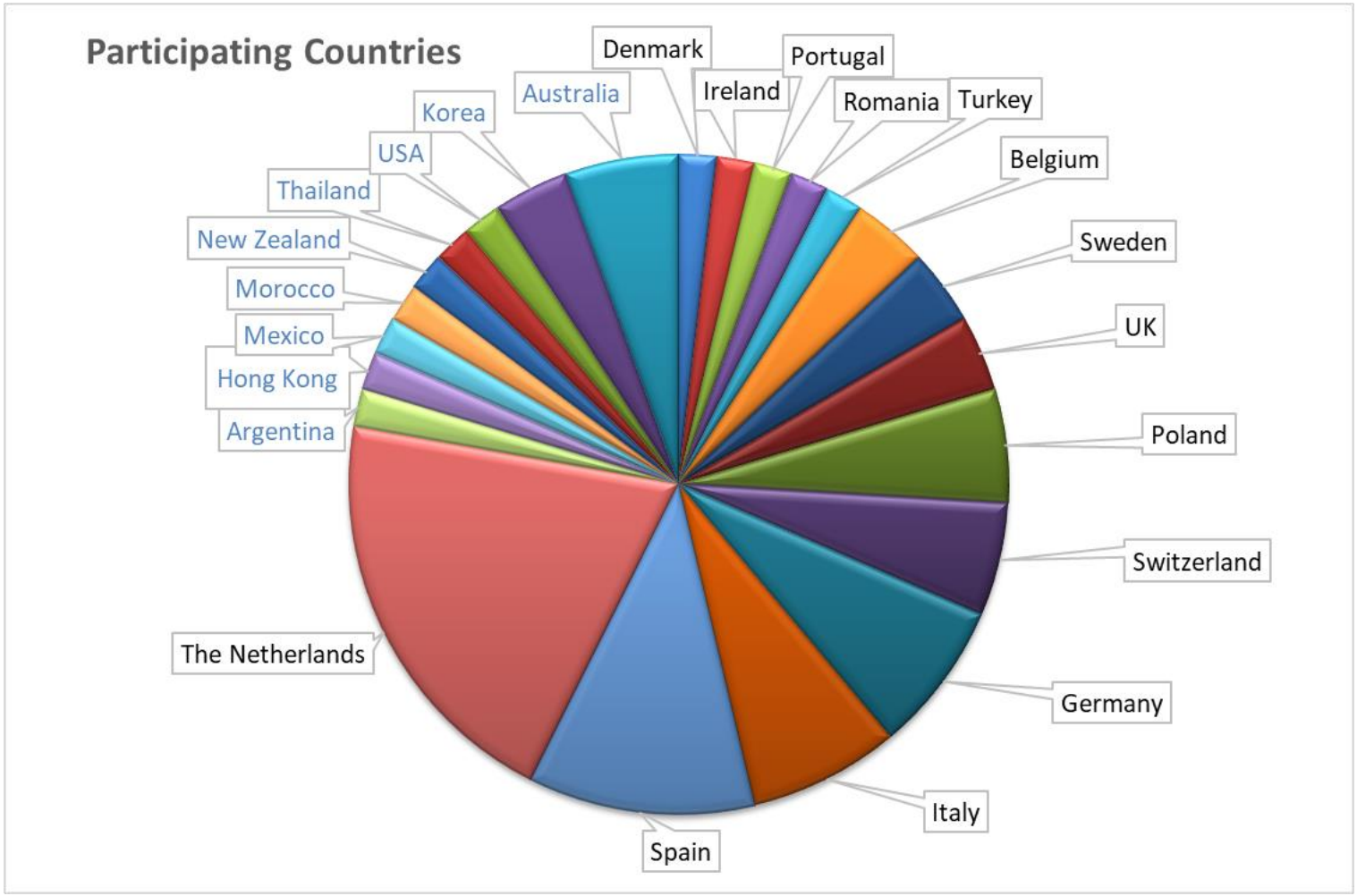
Discussion of Course Directors

Faculty

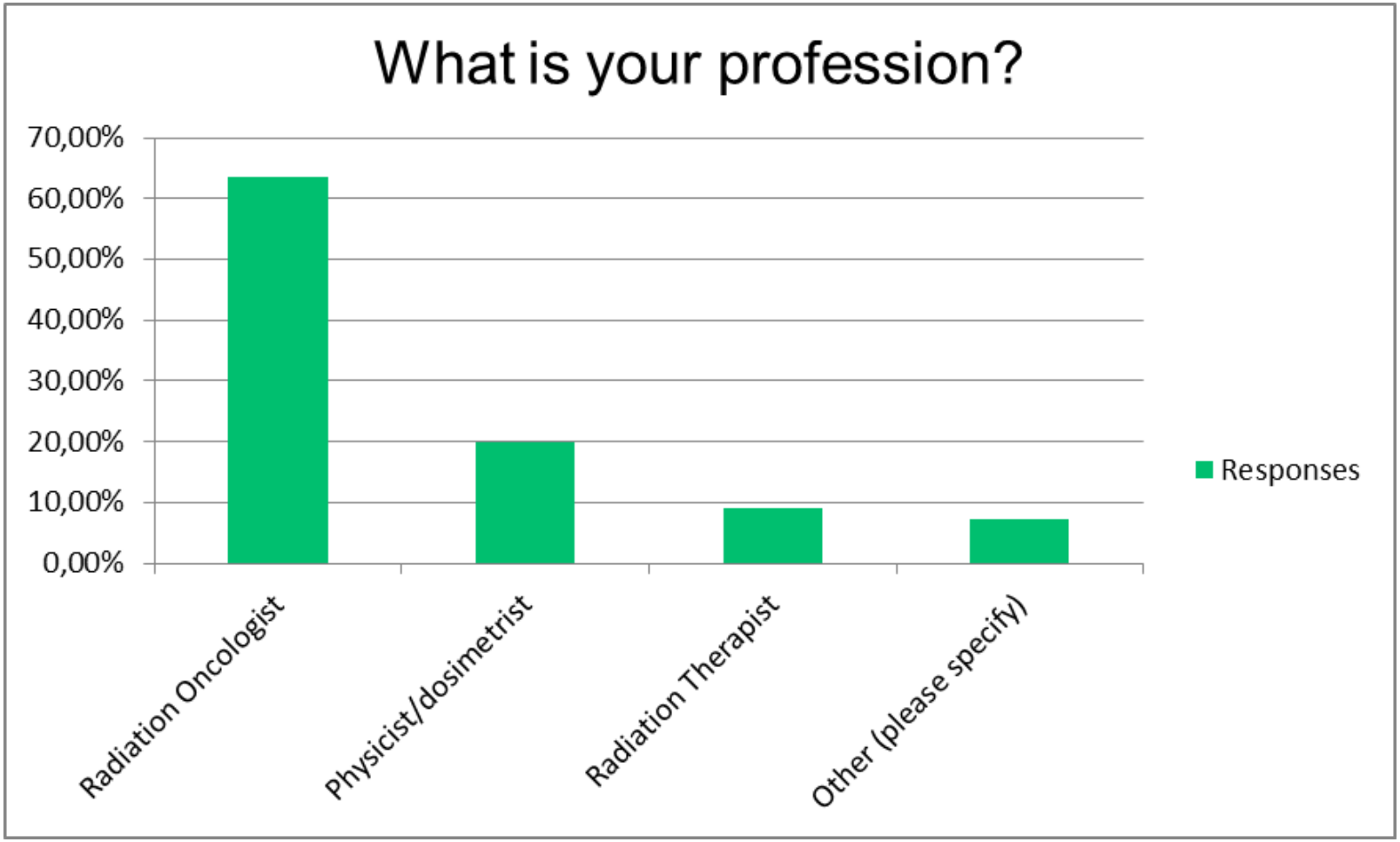
- ***Course directors***
  - Richard Pötter, Rad Onc, Medical University of Vienna (AUT)
  - Kari Tanderup, Physicist, Aarhus University Hospital, Århus (DEN)
- ***Faculty:***
  - Daniel Berger, Medical Physicist, University Hospital, Vienna (AT)
  - Umesh Mahantshetty, Radiation Oncologist, Tata Memorial Hospital, Mumbai (IN)
  - Primoz Petric, Radiation Oncologist, Århus University Hospital, Århus (DK)
  - Remi Nout, Radiation Oncologist, Leiden University Medical Center, Leiden (NL)
  - Jamema Swamidas, Physicist, Tata Memorial Hospital (IN)
  - Li Tee Tan, Radiation Oncologist, Addenbrooke's Hospital, Cambridge (UK)
  - Simon Duke, Clinical Oncologist, Cambridge University Hospitals, Cambridge (UK
- ***Guest Faculty:***
  - Elena Villafranca, Radiation Oncologist, Hospital of Navarra, Pamplona (ES)
- ***ESTRO Faculty „at home":***
  - Ina Jürgenliemk-Schulz, RO, University Medical Center Utrecht (NL)
  - Nicole Nesvacil, Physicist, Medical University of Vienna (AUT)

About you…

- **83 participants from 23 countries**



Multidisciplinary audience

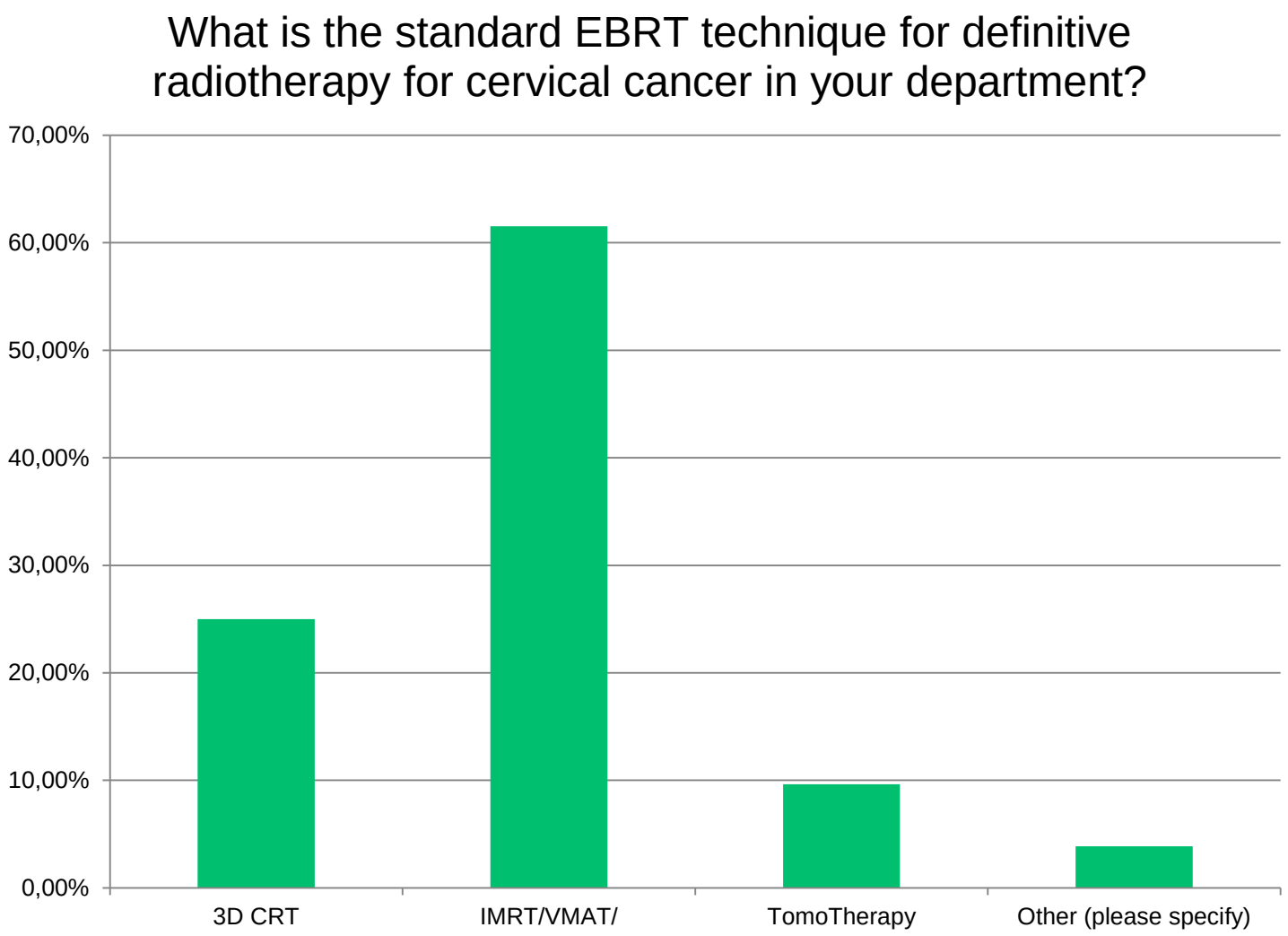


From knowledge to skills and practice…

Your expectations:

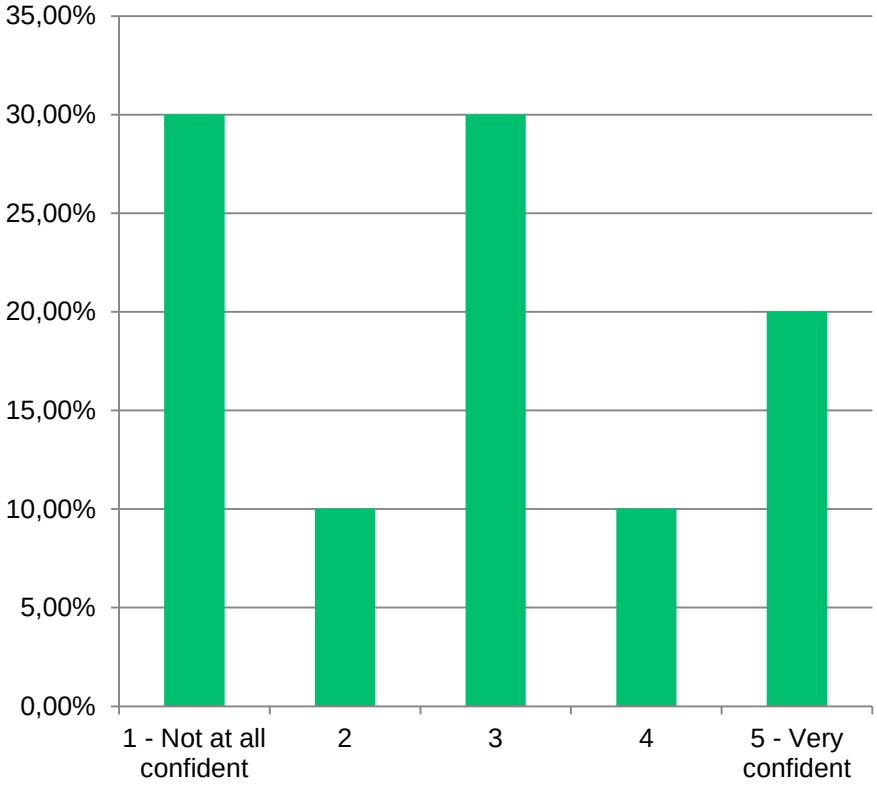
To improve my knowledge and skills in gynae radiotherapy by learning from experts, and will try to implement more up to date practices in my own department.
A good overview of the treatment modalites of gynaecological cancer.
Constraints for OAR for BT especially intestines compromising target doses .CTV PTV margins for definitive RTadjuvant treatment in uterine ca.
Increase my knowledge in treating postoperative Endometrim cancer patients and Primary or postop. Cervix cancer patients.
TO IMPLEMENT MRI IN HDR BRT PLANNING AND IGBT
to get updated guidelines and to know expert european colleagues in the field
We are just about to get an MRI in the department, and we are hoping to get the confidence and Tools to treat all our patients with MRI based BT (instead of CT which is our current practice).
To start to change tecnics
Refresh and know new concepts of EBRT and BT in Gyn Cancer. I had and excelent training in BT during the especiality in Ramon y Cajal Hospital (Madrid) with Alfredo Polo, and in AMC Hospital of A
Voluming guidelines for conformal techniques - in particular ITV expansions to take into account the potential movement of the cervix, parametrium and uterus with variations in bowel and bladder filling
improving imrt applicator in place contouring improve anatomical knowlegdeunderstanding how it's work with needkes and how to settle il in my departementchek my practice
get confident on MRI based planning, Vienna Applicator
learn more about the BT for gynaecological cancer, especially the cervix BT with applicator and interstitial needles and the image guidance used for the EBRT
improvement in coutrouingadaptive EBRT with MRI in cervixbetter understanding of QA
.
I would like to have a overall knowledge of the process. In addition to knowing the aplicator reconstruction techniques and the most suitable IMR adquisition series
I've just started as a new consultant and I want to gain confidence in both EBRT and brachy. I'm also keen to evaluate different protocols to make sure I'm happy with our current approach. It will also h
Identify structures on different type of images. Explore new treatment techniques in treating gynaecological cancer.
Evidence based treatments cervix cancer, endometrial cancer, vaginal cancer. Discus differences in brachytherapy. Image based target defining GTV, HRCTV/LRCTV, PTV.
Learn more about MRI guided RT.
To learn to insert the applicators corectlyWhy I must to use point A if optimization is done in CTV- HR?
- I would like to learn more about interstitial/intracavitary brachytherapy in advanced cervical Cancer- I would like to learn how to plan brachytherapy MRI-based (so far we use only CT-planning in brach
Contouring technique, knowing basic concept about interstitial techniqueHow to due with some of the difficult case , like vaginal relapse after surgery of corpus cancer
I hope this will be an excelent preparation for my training in gynecologic oncology and brachytherapy in particular. I will start treatment of patients with gynecologic oncology in november 2018 as part of
MRI based brachytherapy. Techniques used in different centres.
Hot Topic: Indications neoadjuvant Chemotherapie and indications for Radiochemotherapy After neoadjuvant Chemotherapie+Operation
I would like to get a good overview of the Image Guided Radiotherapy (External+Brachy) and get some experience with These Kind of Treatments in order to slowly bring it into our clinic.

Your practice

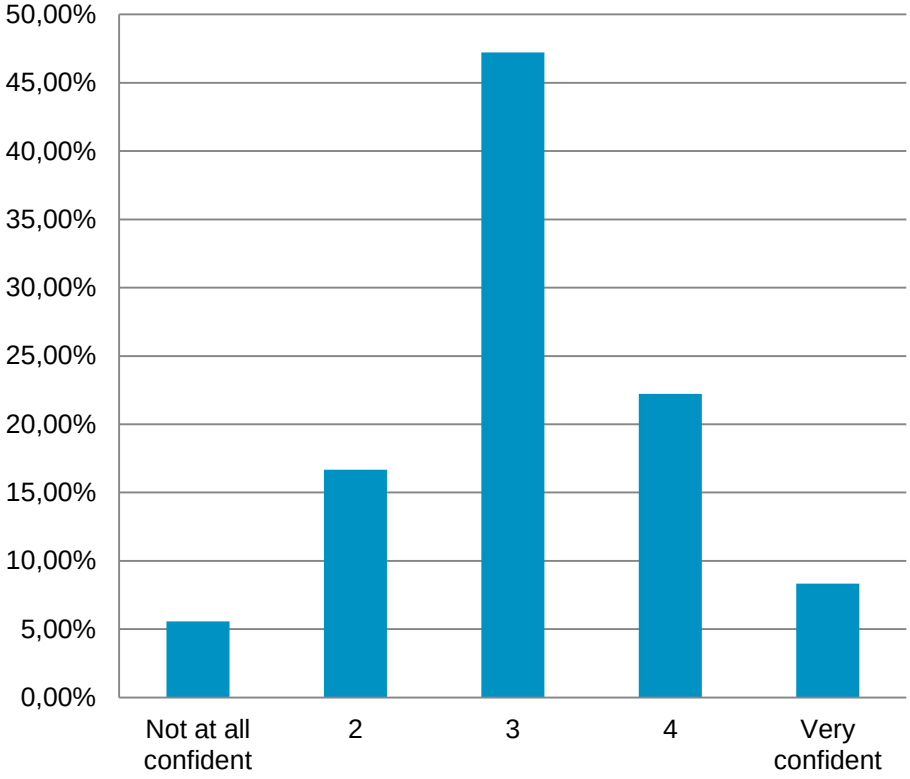


Your confidence

How confident are you at optimising IMRT plans for cervical cancer treatment?

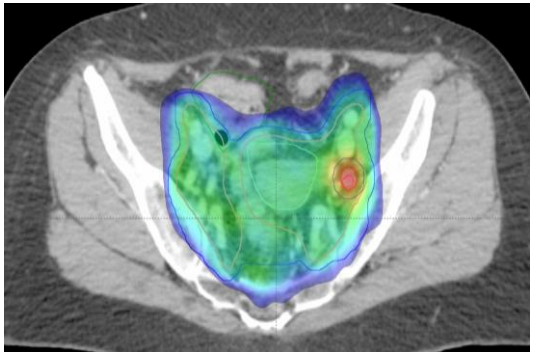


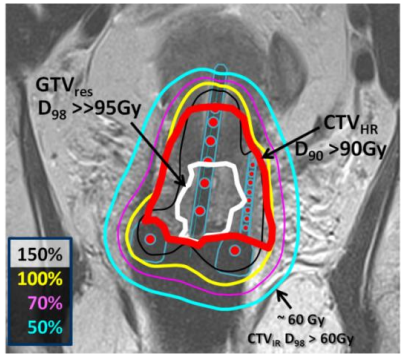
How confident are you at evaluating IMRT plans for cervical cancer?



Our vision…

This course provides understanding of the rationale for advanced image guided external beam and brachytherapy techniques in gynaecological cancer





With this course you will learn tools to update and change clinical practice in your institution

General and experienced tracks

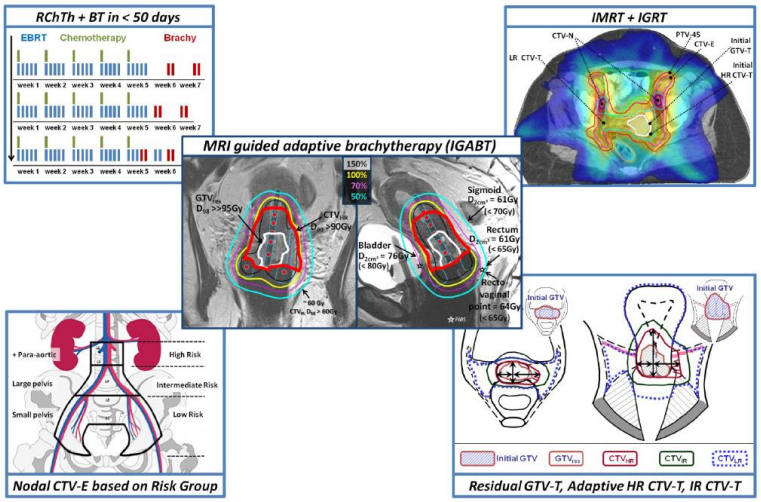
- **General track**
  - **Lectures**
  - **Interactive sessions:**
    - **Contouring**
    - **Quizzes**
    - **Case discussions**
    - **Discussion sessions**
    - **Dose planning**

- **Experienced track**
  - **+ Case presentations and interactive discussions**

EMBRACE { An intErnational study on MRI-guided BRachytherapy in locally Advanced CErvical cancer }

About Embrace | Contacts | Participation | Login

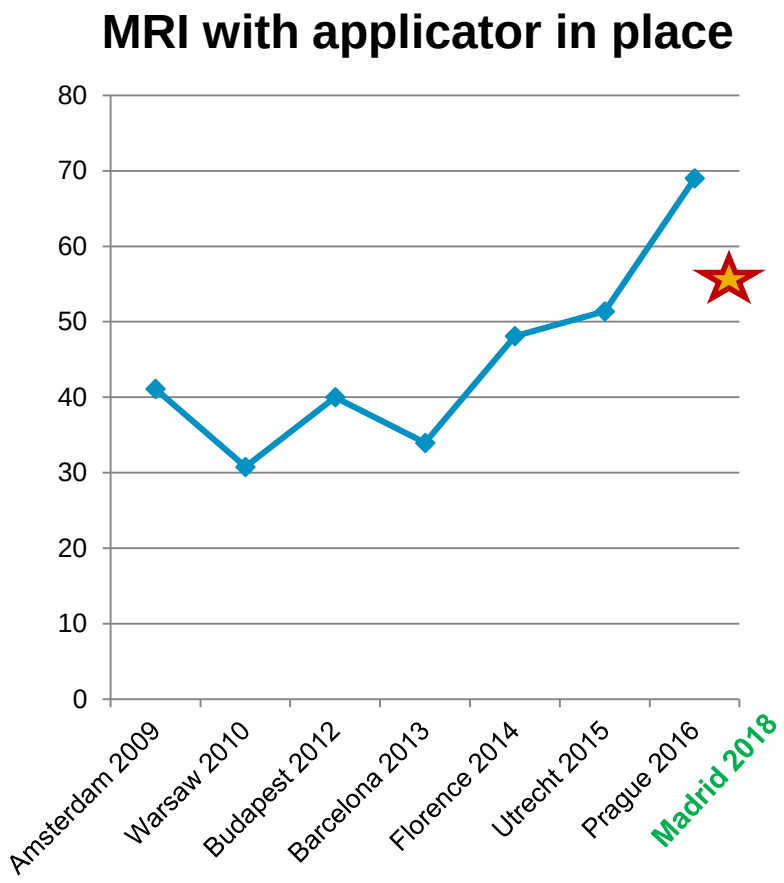
- **Knowledge based on clinical evidence**
- **EMBRACE - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer**
  - **EMBRACE I (2008-2015): 1416 pts accrued**
  - **EMBRACE II (2016-): >200 pts accrued**

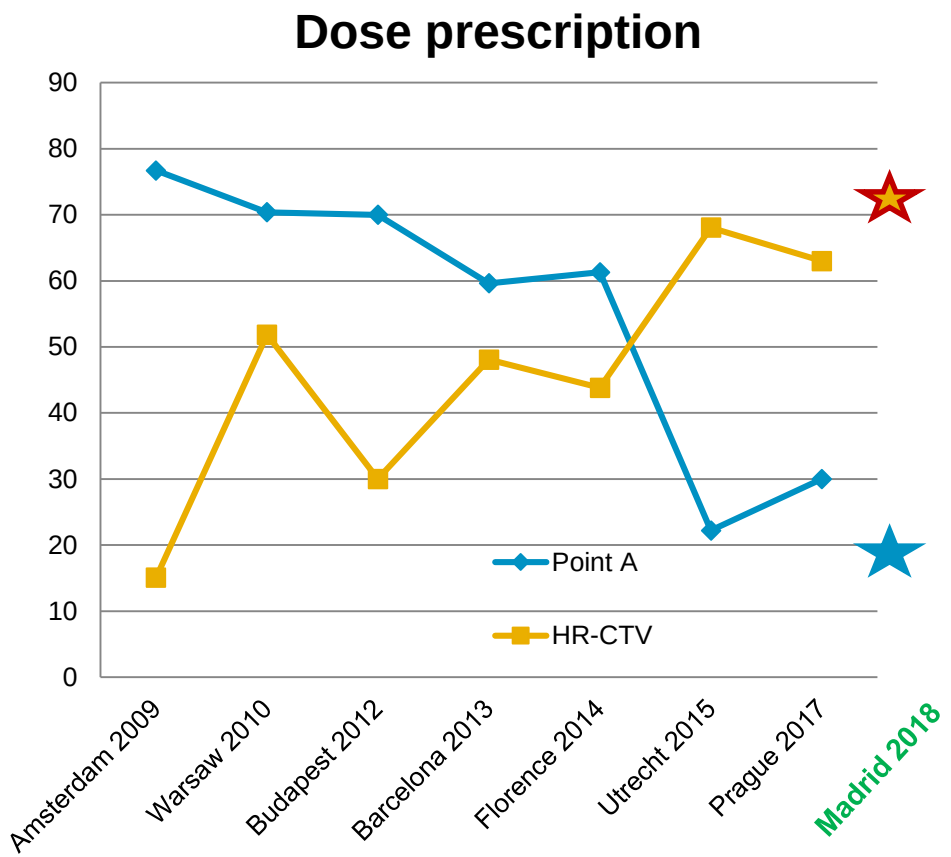


VARIAN medical systems

Elekta

Evolution over time – ESTRO gyn course





Support by industry

Organisation

- ***Local Organisor:***
  - ***Sofia Cordoba Largo, Radiation Oncologist, Hospital Clinico San Carlos, Madrid (ES)***

- ***ESTRO coordinator:***
  - ***Alessandra Nappa, Project Manager, ESTRO, Brussels (BE)***

- ***Above all:***
  - ***The enthusiastic teaching staff***
  - ***The enthusiastic participants***

Anatomical considerations

Role of clinical gynaecological examination

Staging

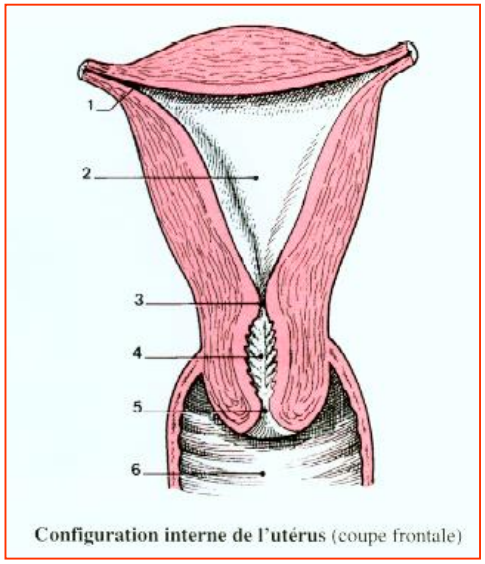
Umesh Mahantshetty,
Professor, Radiation Oncology,
Tata Memorial Hospital, India

C. Haie-Meder ,
Brachytherapy Unit, Gustave Roussy , France

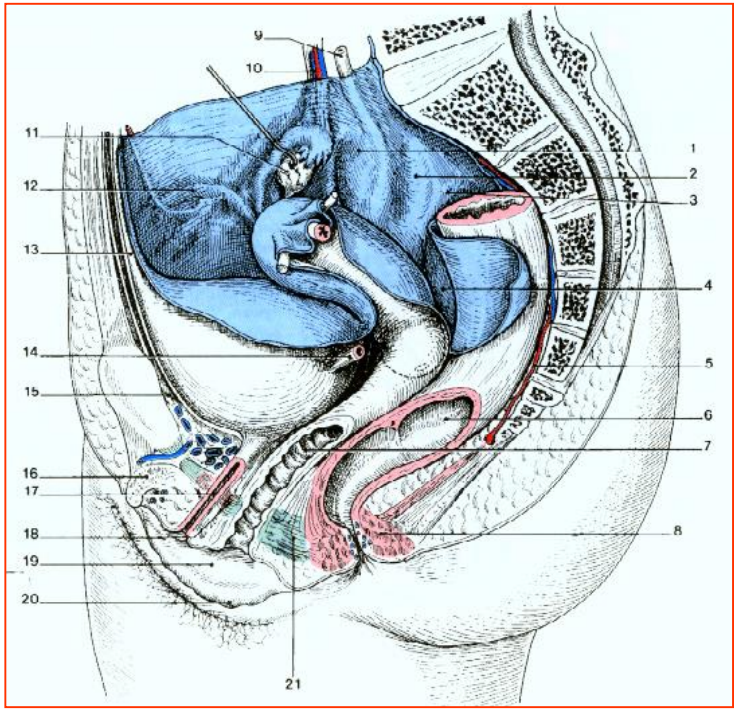
Cervical cancer: General

- 500,000 new cervical cancer cases each year
- 80% of the new cases in developing countries
- 3rd most common cause of female cancer mortality
- 274,000 deaths each year
- Human papillomavirus is responsible for virtually all cases of cervical cancer
- HPV 16 & 18: most prevalent of the Oncogenic types
- Cure Rates high : Depending on the Stage

Anatomical considerations



Configuration interne de l'utérus (coupe frontale)



Cervix

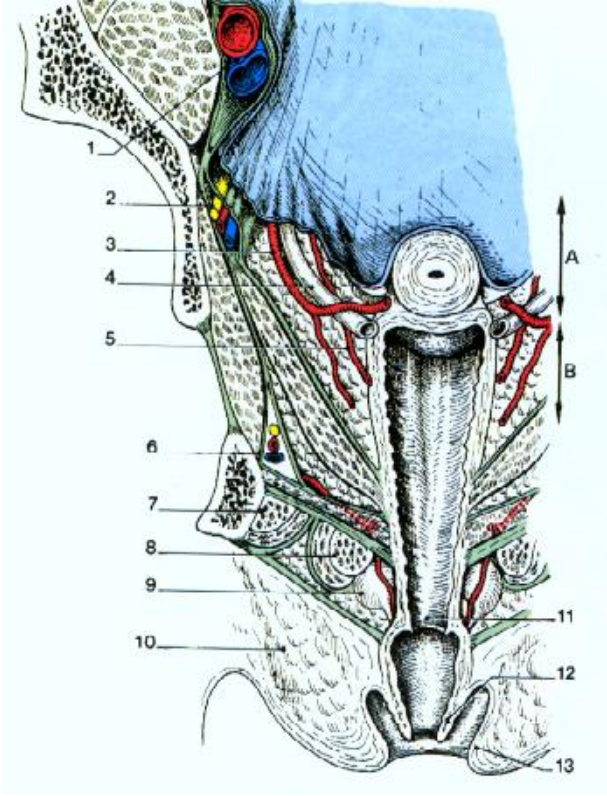
- Approx measures 3x3 cm and is predominantly fibro-muscular organ

- Divided to supra-vaginal and the vaginal portion

- Supra-vaginal part (endo cervix)
  - Bladder and rectum faces covered with peritoneum

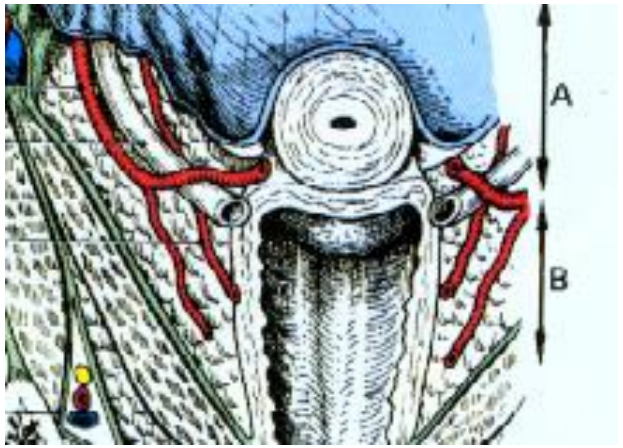
- Vaginal part (ecto cervix)
  - Separated from the vagina by vaginal fornices

Anatomical considerations

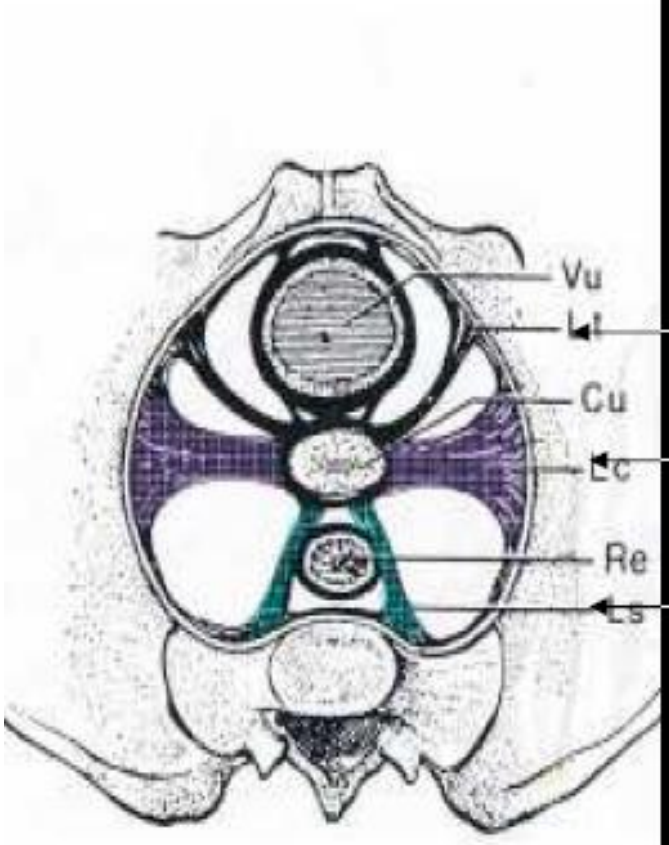


- **Vascularization** : uterine artery arising from internal iliac artery
- **3 segments** : parietal, *parametrial* and mesometrial
- **Parametrial segment** is anteriorly crossed by the **ureter**
- **Located 20 mm** laterally from the isthmus **+/- 15 mm** from the vaginal fornix

Point A



Anatomical considerations



Transverse cervical ligament

Broad ligament

Uterosacral ligament

Anatomical considerations

Parametrial Limits:

Ventral : bladder
Dorsal : perirectal/ mesorectal fascia
Medial : cervical rim/tumor
Lateral : pelvic wall

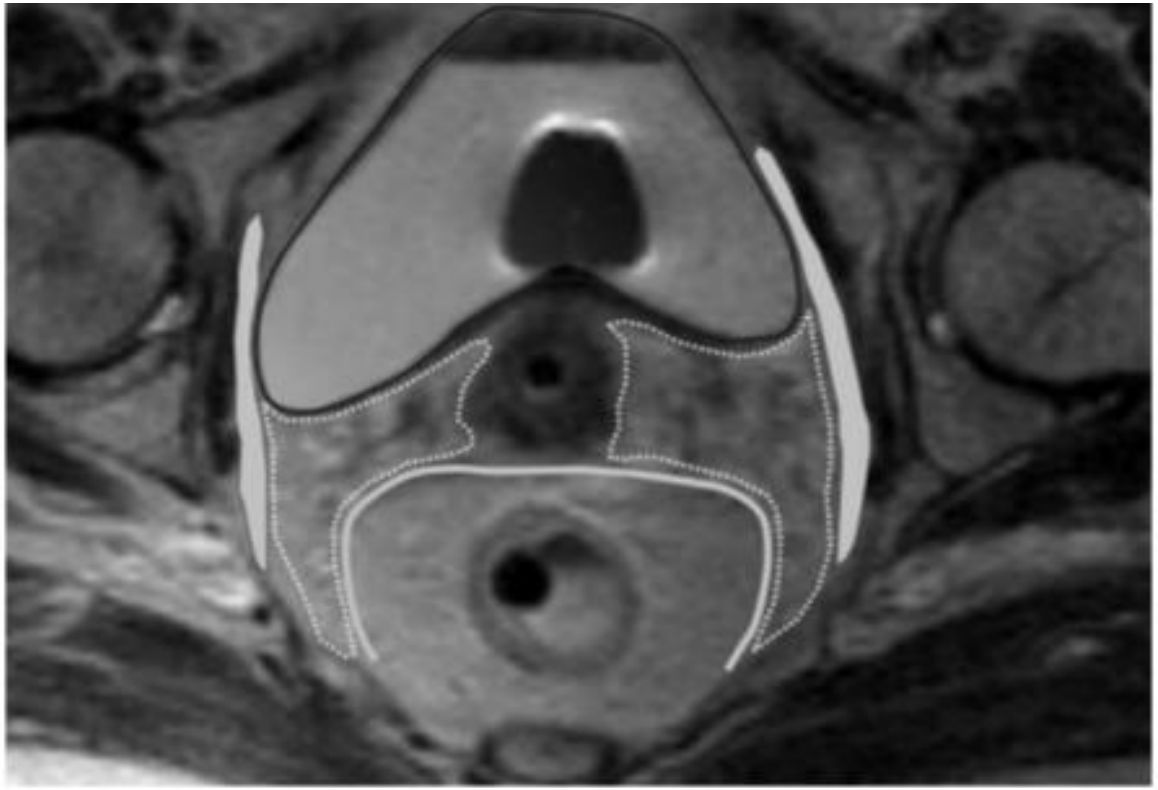


Fig. 2. Definition of parametria according to visible and reproducible radiologic criteria at its borders: ventral = bladder, dorsal = perirectal fascia, medial = tumor/cervical rim, lateral = pelvic wall (PW). At the PW, the space that contains vessels and lymph nodes is particularly indicated. For measurements between tumor and PW, the internal obturator muscle was taken because of its superior visibility.

Anatomical considerations

Classification of radical hysterectomy

Denis Querleu, C Paul Morrow

Lancet Oncol 2008; 9: 297–303

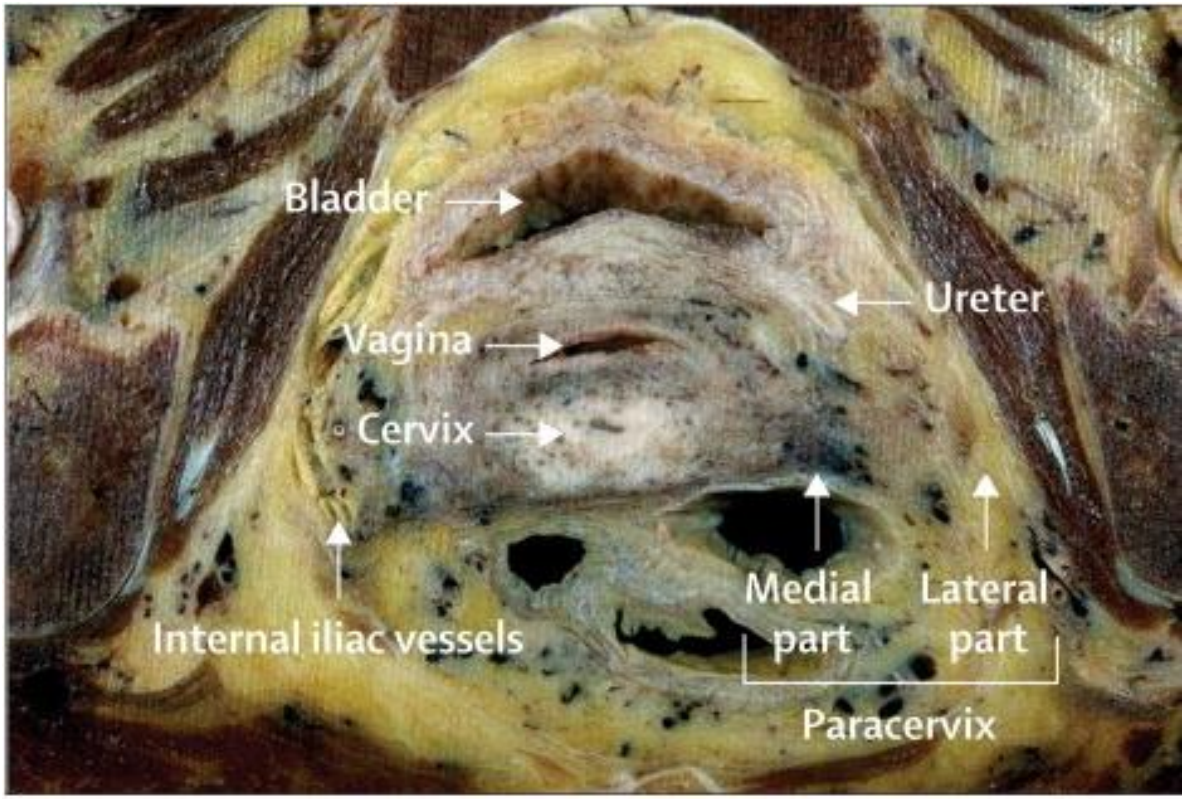


Figure 1

Transverse section of pelvis

Classification of radical hysterectomy

Table 3. Querleu-Morrow classification[5]

Type of radical hysterectomy	Paracervix or lateral parametrium	Ventral parametrium	Dorsal parametrium
Type A	Halfway between the cervix and ureter (medial to the ureter-ureter identified but not mobilized)	Minimal excision	Minimal excision
Type B1	At the ureter (at the level of the ureteral bed–ureter mobilized from the cervix and lateral parametrium)	Partial excision of the vesicouterine ligament	Partial resection of the rectouterine-rectovaginal ligament and uterosacral peritoneal fold
Type B2	Identical to B1 plus paracervical lymphadenectomy without resection of vascular/nerve structures	Partial excision of the vesicouterine ligament	Partial resection of the rectouterine-rectovaginal ligament and uterosacral fold
Type C1	At the iliac vessels transversally, caudal part is preserved	Excision of the vesicouterine ligament (cranial to the ureter) at the bladder. Proximal part of the vesicovaginal ligament (bladder nerves are dissected and spared)	At the rectum (hypogastric nerve is dissected and spared)
Type C2	At the level of the medial aspect of iliac vessels completely (including the caudal part)	At the bladder (bladder nerves are sacrificed)	At the sacrum (hypogastric nerve is sacrificed)
Type D	At the pelvic wall, including resection of the internal iliac vessels and/or components of the pelvic sidewall	At the bladder. Not applicable if part of exenteration	At the sacrum. Not applicable if part of exenteration

Anatomical considerations

Classification of radical hysterectomy

Denis Querleu, C Paul Morrow

Lancet Oncol 2008; 9: 297–303

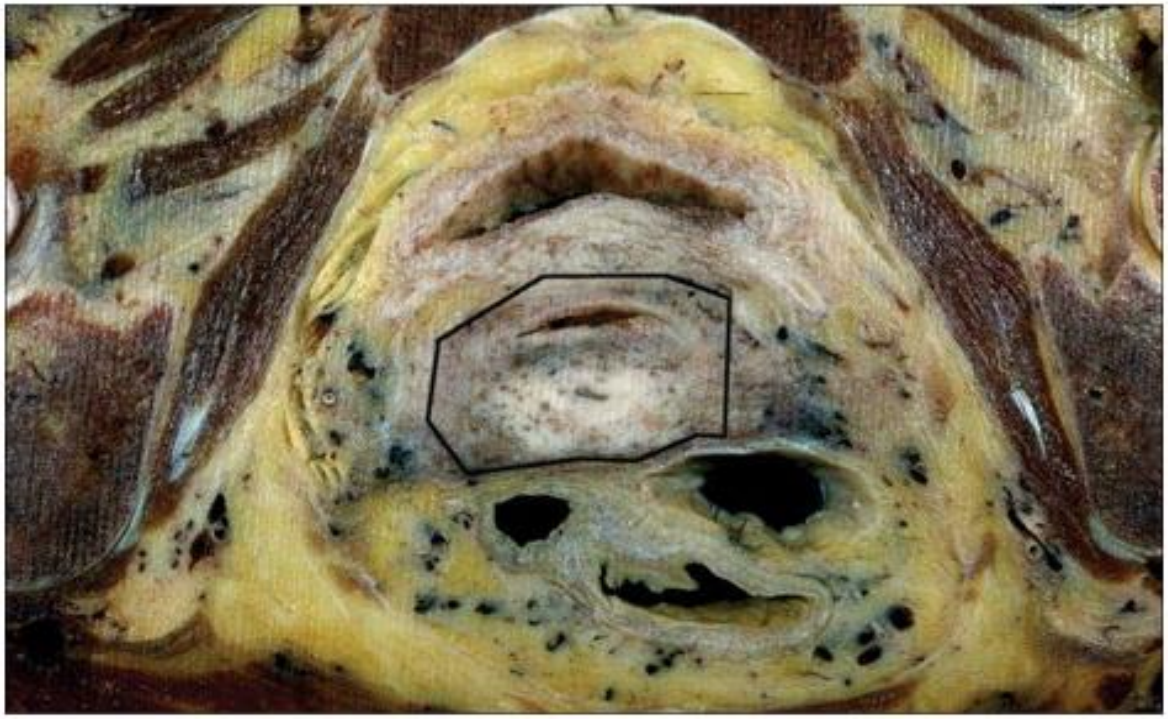


Figure 4

Type A radical hysterectomy

Same anatomical preparation as shown in figure 1 . Border shows area of resection.

Anatomical considerations

Classification of radical hysterectomy

Denis Querleu, C Paul Morrow

Lancet Oncol 2008; 9: 297–303

Figure 5

Type B1 radical hysterectomy

Same anatomical preparation as shown in figure 1 . Border shows area of resection.

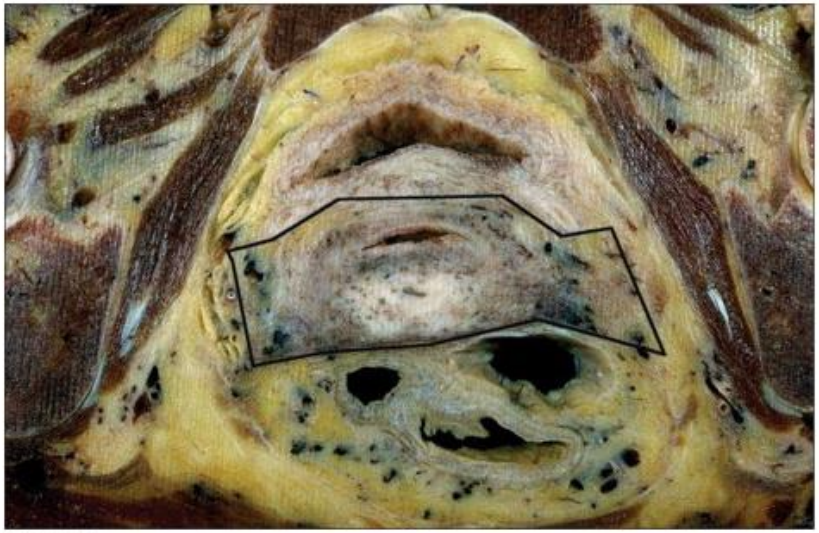


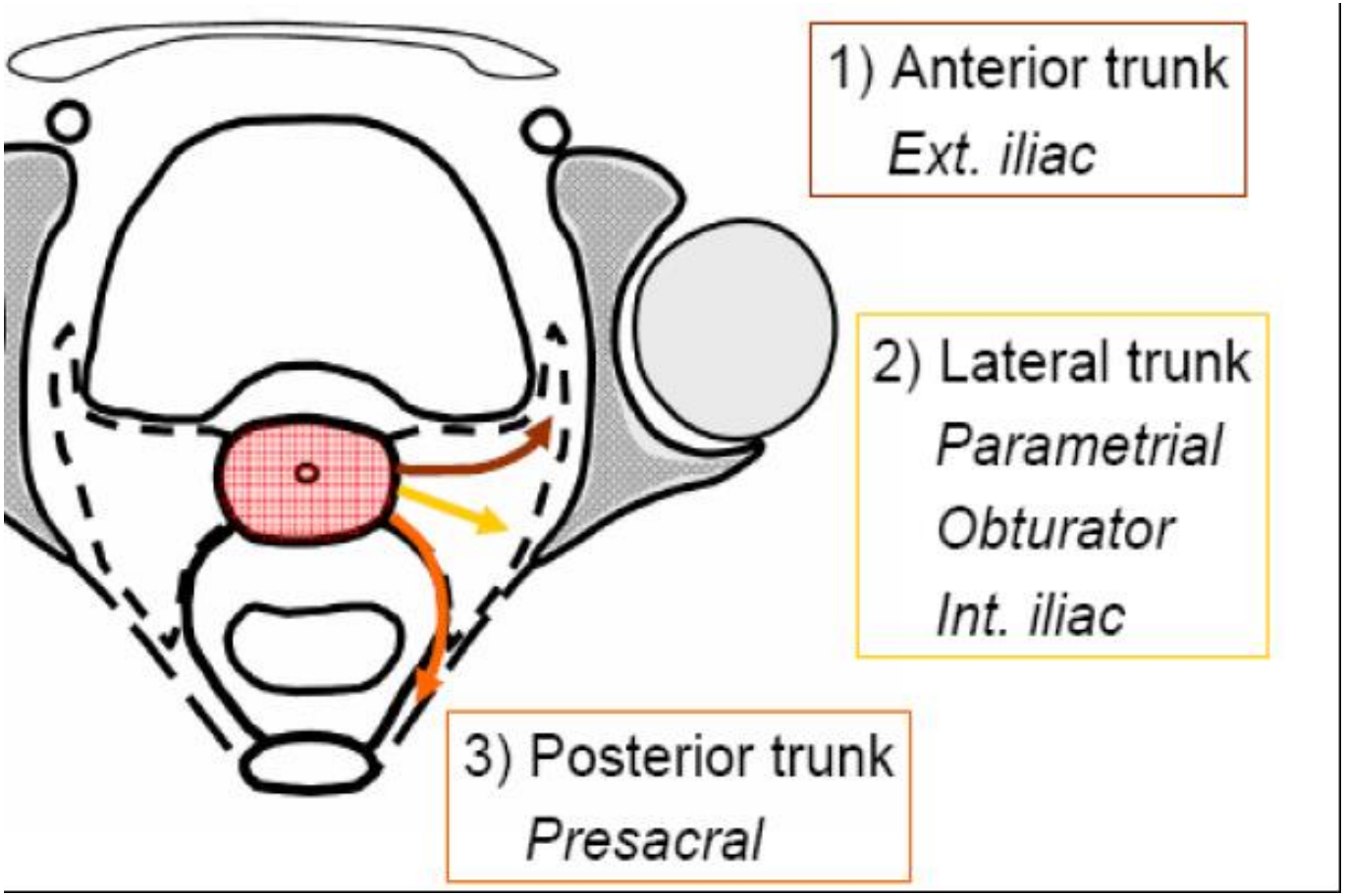
Figure 6

Type C2 radical hysterectomy

Same anatomical preparation as shown in figure 1 . Border shows area of resection.

Anatomical considerations

Lymphatic drainage



Anatomical considerations

Lymphatic drainage

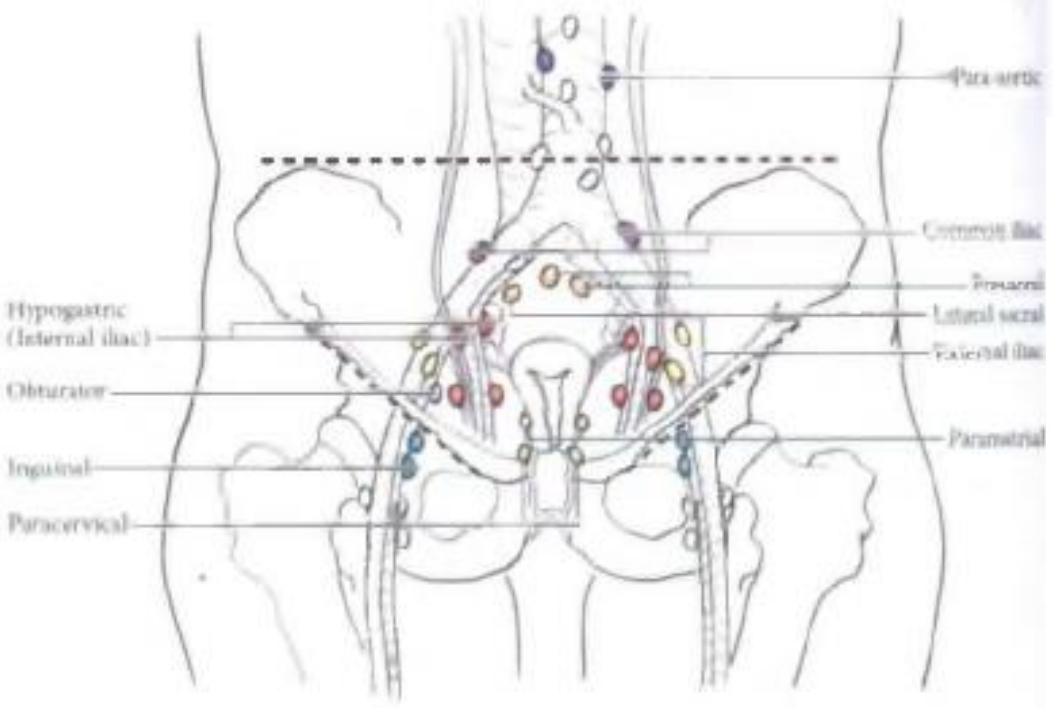


Fig. 52.1 Regional lymph nodes for the cervix uteri

- Parametrial
- Obturator
- Internal iliac (hypogastric)
- External iliac
- Sacral
- Presacral
- Common iliac
- Para-aortic

- **Lower vaginal Involvement: Inguinal Lymph nodes**

- **PA region to mediastinal / Left SC nodes**

Role of clinical examination

- **Accurate tumor characteristics :**
  - type : proliferative / infiltrative / vascular / necrotic ….
- **Staging**
- **General condition and fitness for radical treatment**

Clinical Examination

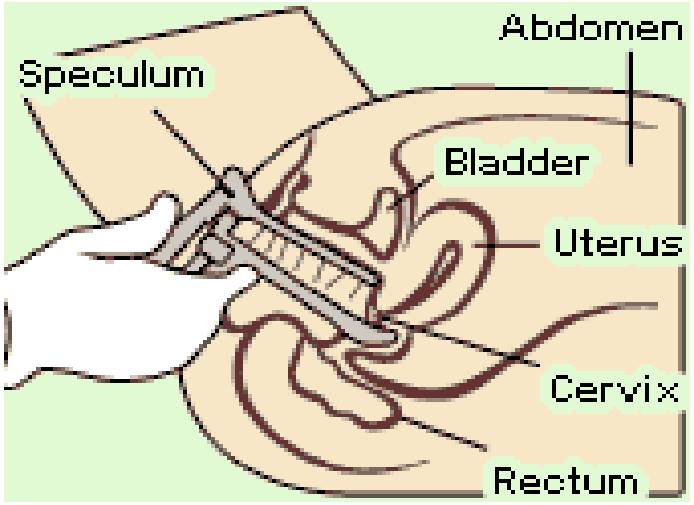
- **Patient Counseling**
- **Parts clean and preferably prepared**
- **General Examination :** Anemia / Lymphadenopathy incl SC nodes
- **Pelvic Examination:**

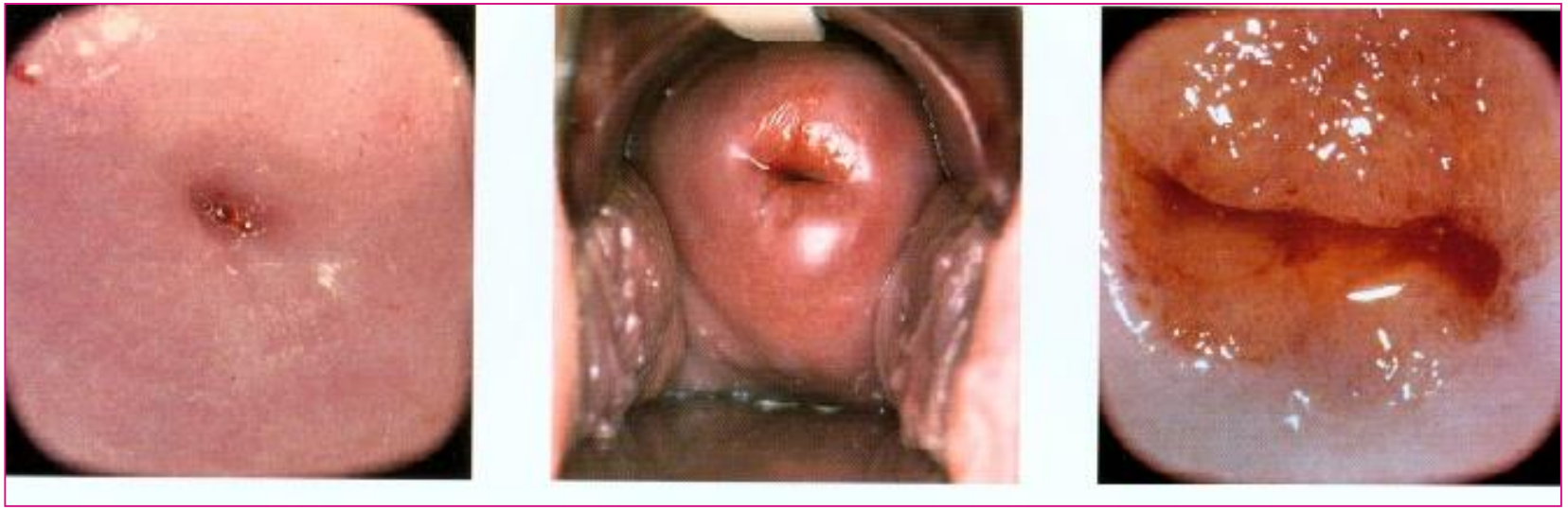
  - Inspection of external genitalia

  - Per Speculum Examination

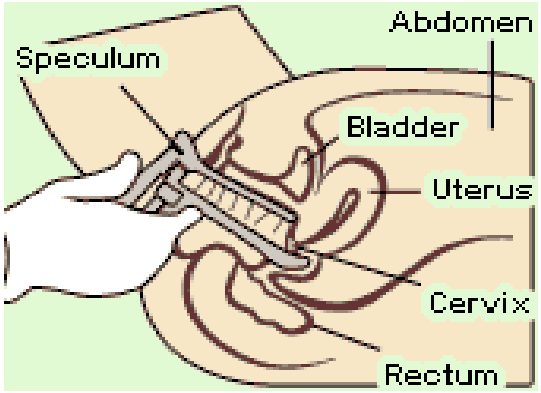
  - Palpation

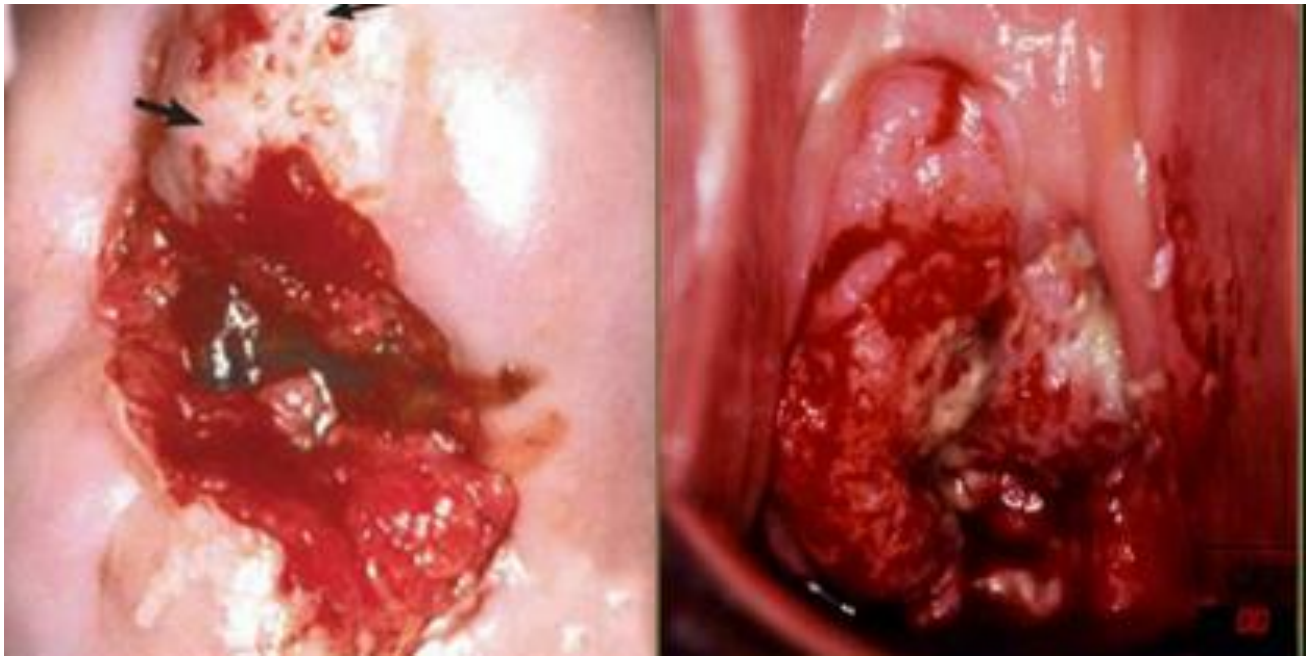
Per Speculum Examination

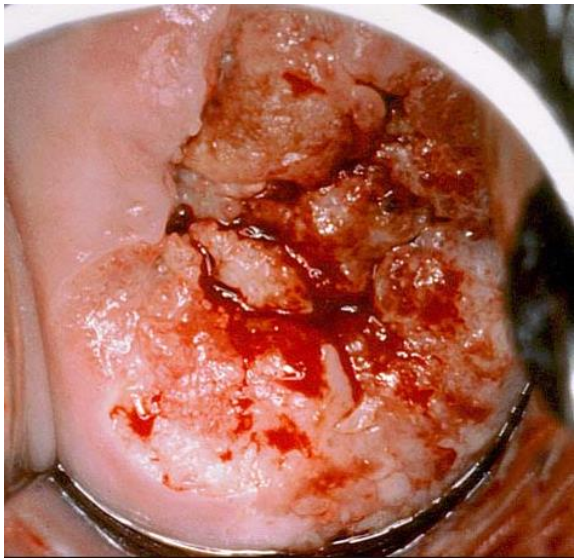


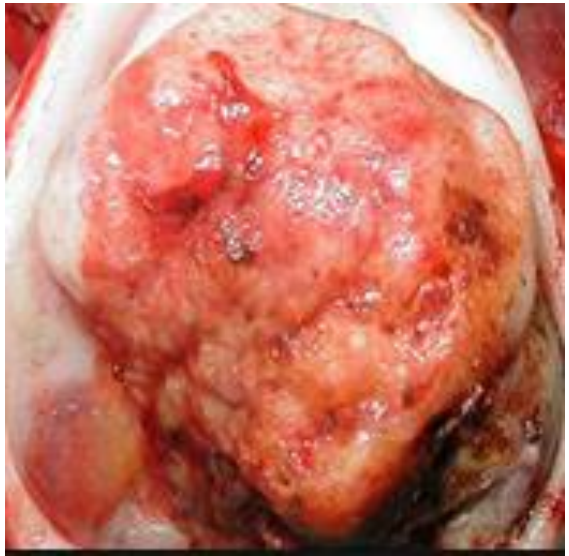


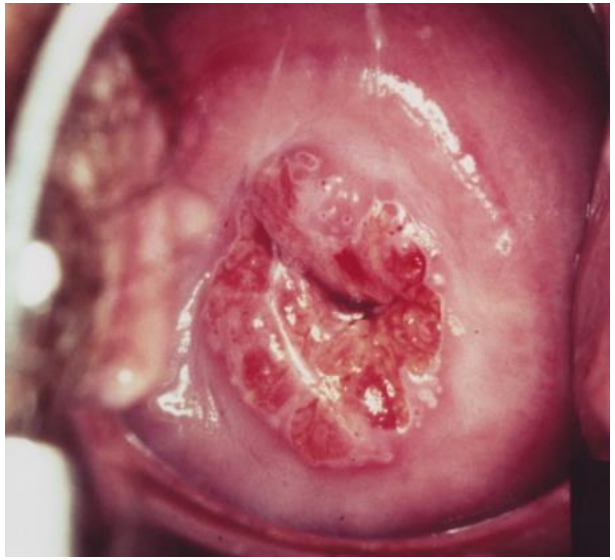
Per Speculum Examination



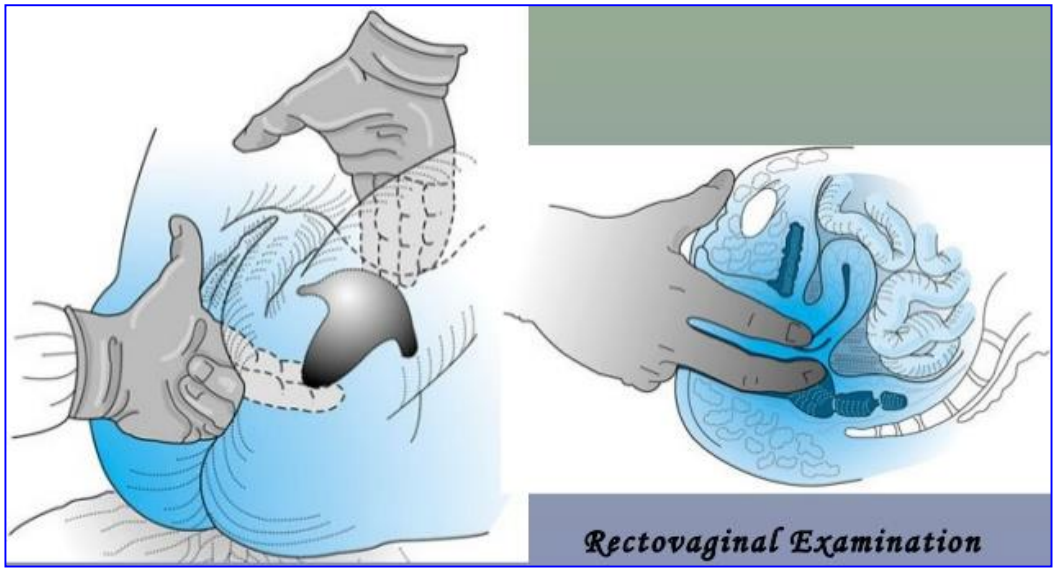








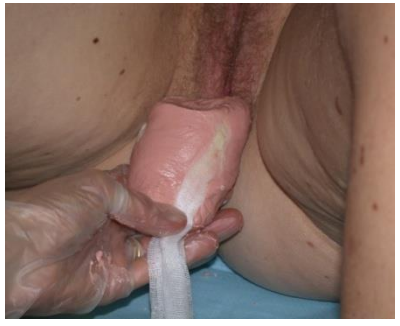
Bimanual Pelvic Examination

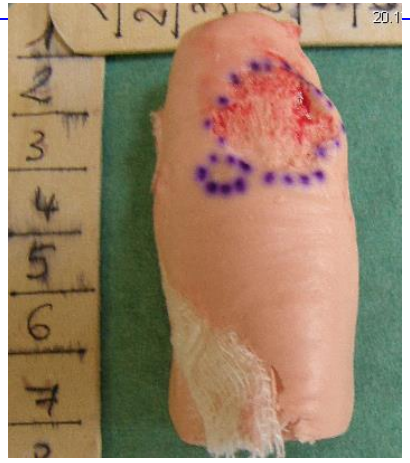


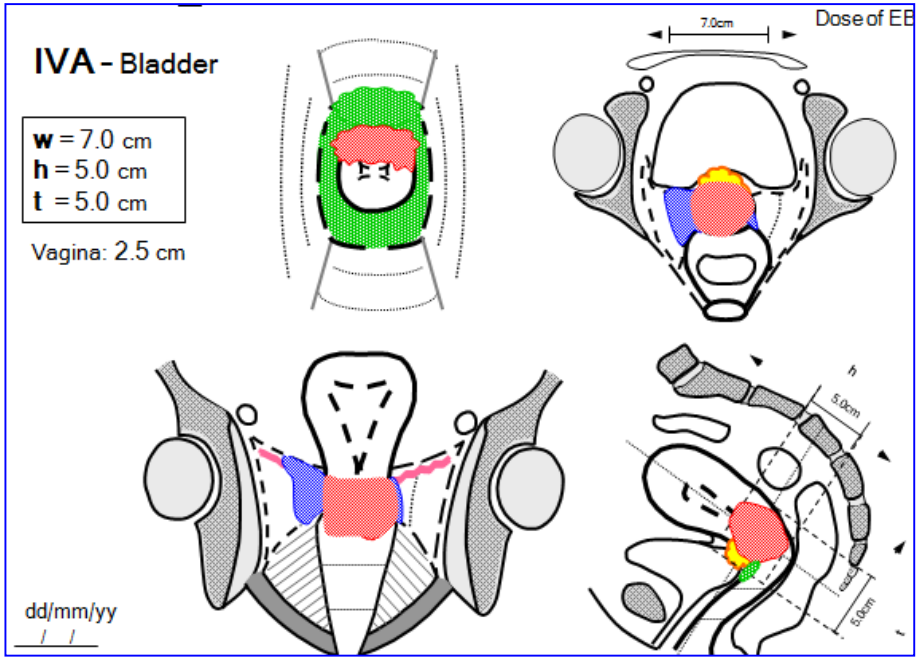
Local Disease Spread

- Cervix
- Vagina
- Parametrium
- Lower uterus

Tumor measurement
Tumor extension:
- **vagina (vaginal impression)**
- parametrium







ESGO ESTRO ESP Guidelines 2017

Local clinical and radiological diagnostic work-up

✓ Pelvic examination and biopsy +/- colposcopy are mandatory components to diagnose cervical cancer.

B Mandatory initial work-up for assessment of pelvic tumour extent and to guide treatment options is pelvic magnetic resonance imaging (MRI).

✓ Endovaginal/transrectal ultrasound is an option if performed by a properly trained sonographer.

✓ Cystoscopy or rectoscopy may be considered to provide a biopsy if suspicious lesions in the urinary bladder or rectum are documented on MRI or ultrasound.

FIGO staging 2008

- **Stage I: confined to cervix**
  - Ia1: minimal microscopic invasion
  - Ia2: invasion ≤ 5mm depth and ≤ 7mm horizontally
  - Ib1: greater than Ia, clinically visible, confined to the cervix, ≤ 4 cm size
  - Ib2: > 4 cm size

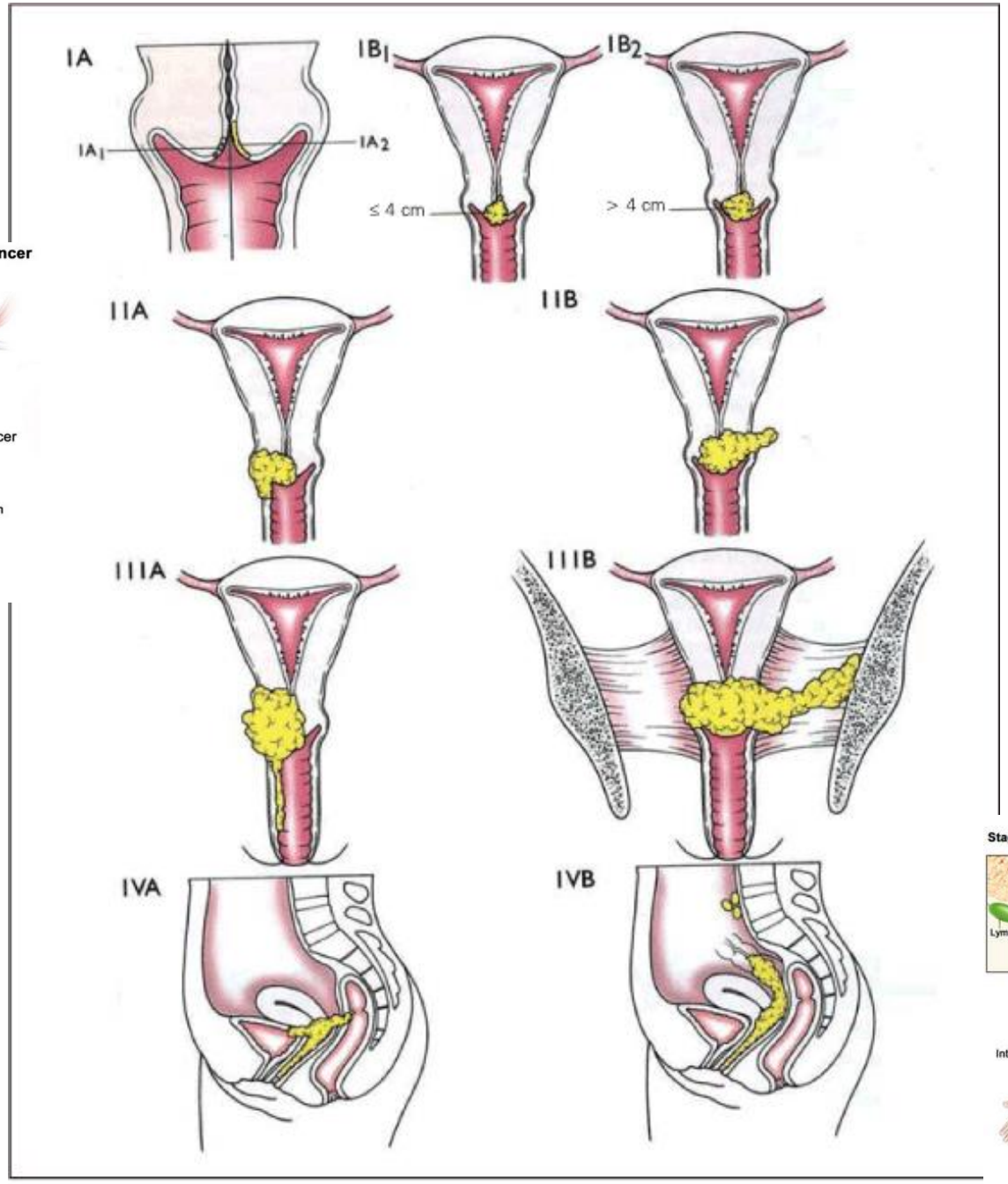
5-year survival: 89.1%

5-year survival : 75.7%

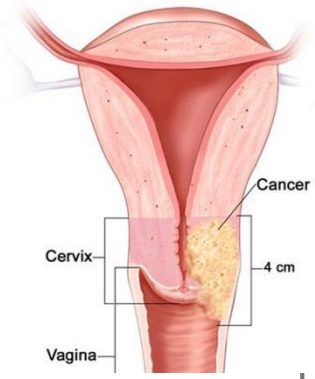
- **Stage II: invades beyond cervix but not to side wall or lower third of vagina**
  - IIa: tumour without parametrial invasion
    - IIa1: ≤ 4 cm size
    - IIa2: > 4 cm size
  - IIb: tumour with parametrial invasion

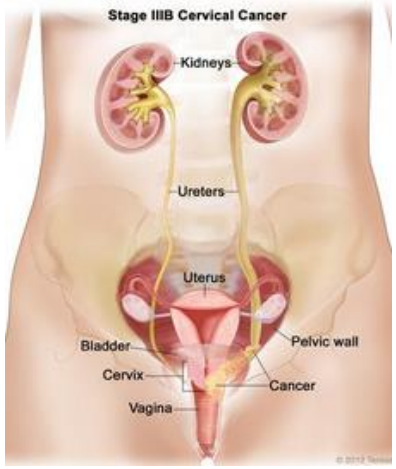
- **Stage III: tumour extends to pelvic sidewall and/or lower third of vagina or causes hydronephrosis or non-functioning kidney**
  - IIIa: lower third of vagina, no pelvic side wall extension
  - IIIb: involving pelvic side wall or causing hydronephrosis

- **Stage IV: tumour invades mucosa of bladder or rectum and/or extends beyond true pelvis**

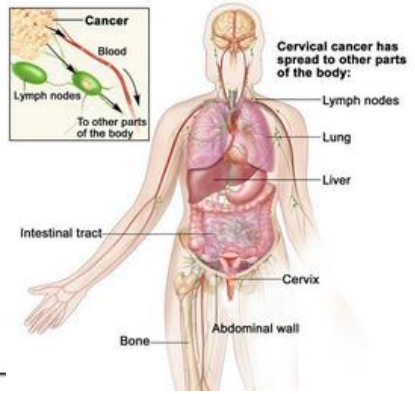


Stages IIA1 and IIA2 Cervical Cancer



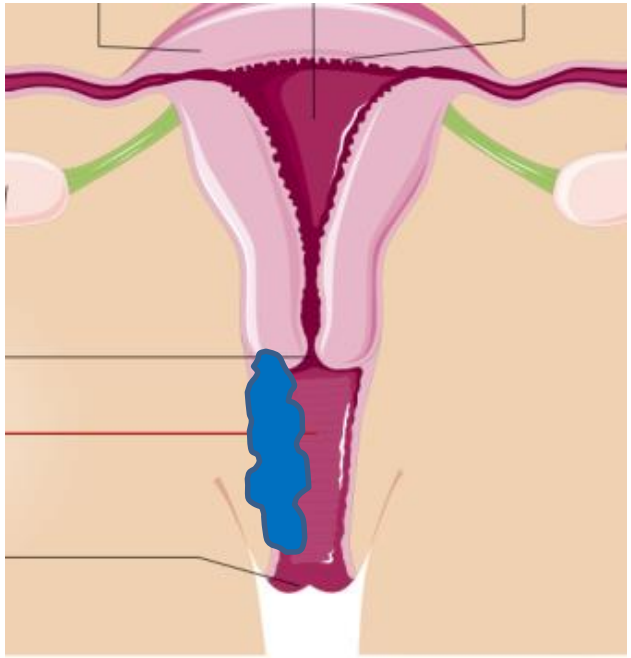


Stage IVB Cervical Cancer

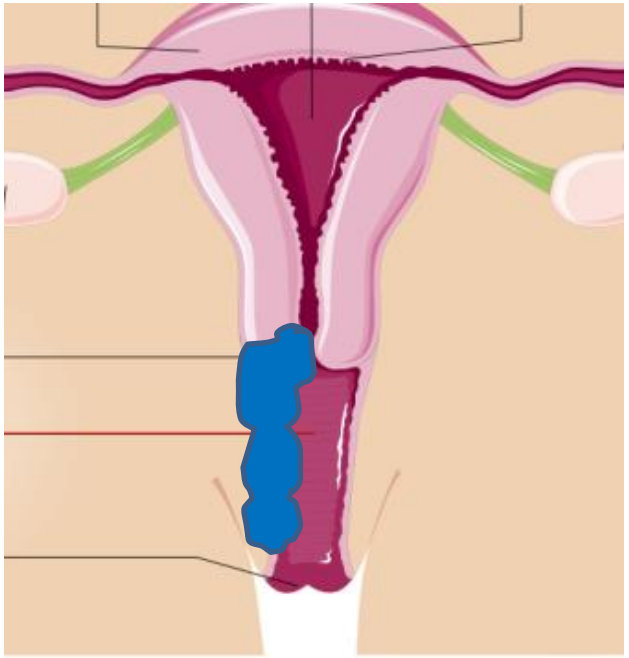


FIGO classification

A



B



According to FIGO staging rules, tumors in the vagina should be classified as :

- **‘cervical’ if the cervical os is involved (even if most of the tumor is in the vagina)**

ESGO ESTRO ESP Guidelines 2017

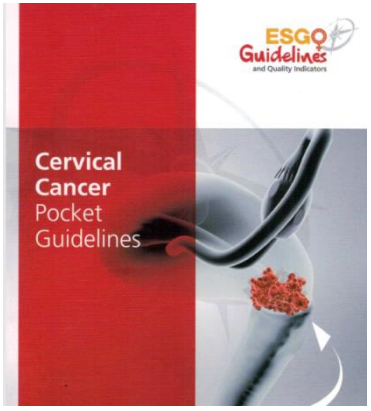
UICC TNM : 8th Edition (2016)

ESGO
European Society of Gynaecological Oncology

POCKET GUIDELINES
CERVICAL CANCER

based on

ESGO-ESTRO-ESP Guidelines for the Management of Patients with Cervical Cancer



STAGING

FIGO staging and TNM classification

✓ Patients with cervical cancer should be staged according to the TNM classification. Clinical staging (FIGO) should also be documented (*Table 1*).

C TNM should be based on a correlation of various modalities (integrating physical examination, imaging and pathology) after discussion in a multidisciplinary forum.

✓ The method used to determine tumour status (T), lymph node status (N) and systemic status (M) i.e. clinical (c), imaging (i) and/or pathological (p) should be recorded.

✓ Lymph node metastases should be classified according to the TNM classification (see Principles of pathological evaluation).

FIGO staging / TNM classification [UICC 8th Ed.(2016)]

Regional Lymph Nodes (N)

TNM CATEGORIES	FIGO STAGES	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIB	Regional lymph node metastasis

Distant Metastasis (M)

TNM CATEGORIES	FIGO STAGES	
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)

ANATOMIC STAGE/PROGNOSTIC GROUPS (FIGO 2008)			
Stage 0*	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIA1	T2a1	N0	M0
Stage IIA2	T2a2	N0	M0
Stage IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	Any N	M0
	T1–3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

AJCC 8TH Edition 2017

T Category	FIGO Stage	T Criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Cervical carcinoma confined to the uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	IA1	Measured stromal invasion of 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm, with a horizontal spread of 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2. Includes all macroscopically visible lesions, even those with superficial invasion.
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to lower third of the vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involving the lower third of the vagina but not extending to the pelvic wall
T3b	IIIB	Tumor extending to the pelvic wall and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)

*The pelvic sidewall is defined as the muscle, fascia, neurovascular structures, and skeletal portions of the bony pelvis. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall.

Definition of Regional Lymph Node (N)

N Category	FIGO Stage	N Criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1		Regional lymph node metastasis

Definition of Distant Metastasis (M)

M Category	FIGO Stage	M Criteria
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread or involvement of the supraclavicular, mediastinal, or distant lymph nodes; lung; liver; or bone)

AJCC 8TH Edition 2017

Para-aortic Lymph nodes : As regional nodes

Para-aortic Lymph nodal Mets : N1

Other sites : M1

Regional Lymph Nodes

The cervix is drained by parametrial, cardinal, and uterosacral ligament routes into the following regional lymph nodes (Fig. 52.1):

- Parametrial
- Obturator
- Internal iliac (hypogastric)
- External iliac
- Sacral
- Presacral
- Common iliac
- Para-aortic

Definition of Regional Lymph Node (N)

N Category	FIGO Stage	N Criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1		Regional lymph node metastasis

Definition of Distant Metastasis (M)

M Category	FIGO Stage	M Criteria
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread or involvement of the supraclavicular, mediastinal, or distant lymph nodes; lung; liver; or bone)

Proposed Revision in FIGO Staging for Cervical Cancer

FIGO Meeting at Dubai - April 2018

Stage I

Stage IA Invasive carcinoma that can be diagnosed only by microscopy with measured deepest invasion <5 mm

Stage IA1 Stromal invasion < 3.0 mm

Stage IA2 Stromal invasion ≥ 3.0 mm < 5.0 mm

Stage IB Invasive carcinoma with measured deepest invasion ≥ 5 mm and size measured by maximum tumor diameter

Stage IB1 Invasive carcinoma ≥ 5.0 mm ≤ 2 cm

Stage IB2 Invasive carcinoma ≥ 2 cm < 4 cm

Stage IB3 Invasive carcinoma ≥ 4 cm

Stage III

Add Stage IIIC to reflect positive lymph node metastasis to pelvic and/or paraaortic lymph nodes, adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate to stage IIIC.

Stage IIIC Pelvic and/or paraaortic lymph node metastasis

Stage IIIC1 Pelvic lymph node metastasis only

Stage IIIC2 Paraaortic lymph node metastasis

Notation of r = imaging and p = pathology, e.g., imaging indicating pelvic lymph node metastasis would be Stage IIIC1r and pelvic lymph node metastasis by pathological findings would be Stage IIIC1p.

Stage IA & B

Stage III to include PA nodal disease

Conclusion

- Natrual histroy of Cervical Cancer
- Knowledge of lymphatic drainage
- Importance of Clinical examination

  - Per speculum & bimanual pelvic examination

- Staging : Clinical + Radiological

  - TNM & FIGO Systems

3D image based pathologic anatomy at time of diagnosis

Radiation Oncologist’s perspective

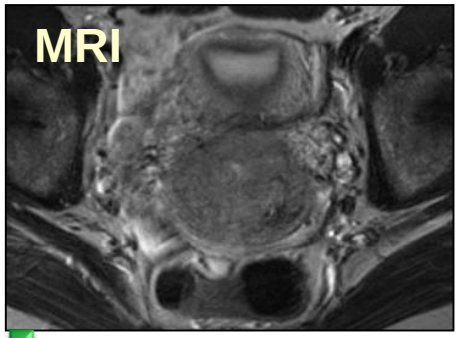
Primoz Petric
Peter Petrow

Overview

- **T:** Primary tumor assessment
  - Modality of choice
  - Normal anatomy of central pelvis
  - Recommendations for MRI
  - Tumor assessment
- **N:** Detection of nodal disease
- **M:** Detection of nodal metastases

Imaging modality of choice for primary tumor assessment in cervix cancer

Choice of imaging modality: primary tumor



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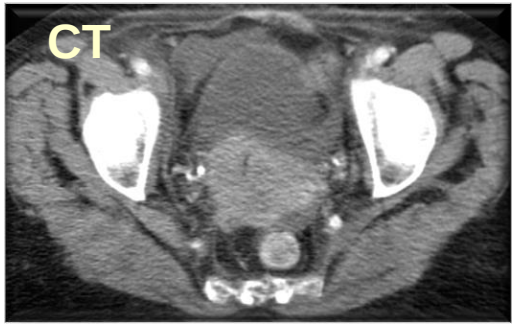
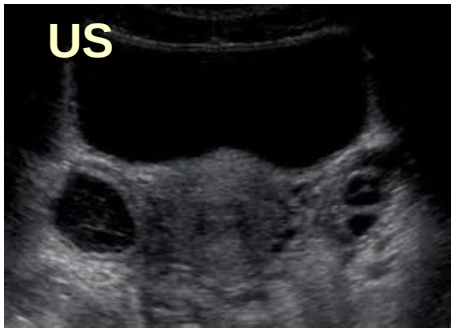




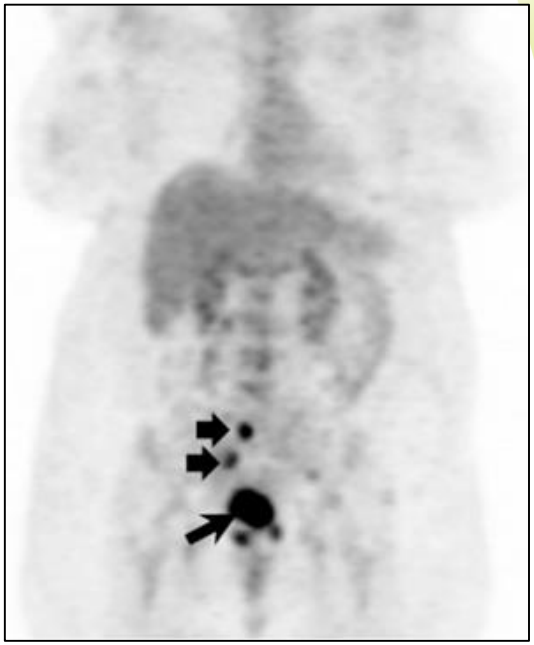
- Superior soft tissue depiction quality
  - normal anatomy
  - tumor
- Major information available from T2w without i.v. contrast
- Multi – planar imaging
- Clinico-pathological studies: ↑ staging accuracy
- No radiation
- Gyn GEC ESTRO Recommendations published
- Functional imaging

Lee SI, et al. JNM 2015;56(3).
Boss EA et al. Obstet Gynecol 1995
Mitchell DG et al. J Clin Oncol 2006
Oszarlak O et al. Radiol 2003
Jung DC et al. Cancer 2008, 44(11): 1524-1528
Hricak H, et al. Radiology 2007;243(1):28-53

Yu KK, et al. Radiology 1997;202(3):697-702
Yu KK, et al. Radiology 1999;213(2):481-488
Sala E, et al. Radiology 2006;238(3):929-937
Dimopoulos J. IJROBP 2006
Dimopouios et al. Radiother Oncol 2011

Role of PET CT

- Detection / Confirmation of primary tumor
- No information on soft tissue details (i.e. PM invasion)
- Important for detection of lymphadenopathy



The choice of primary therapy best achieved when

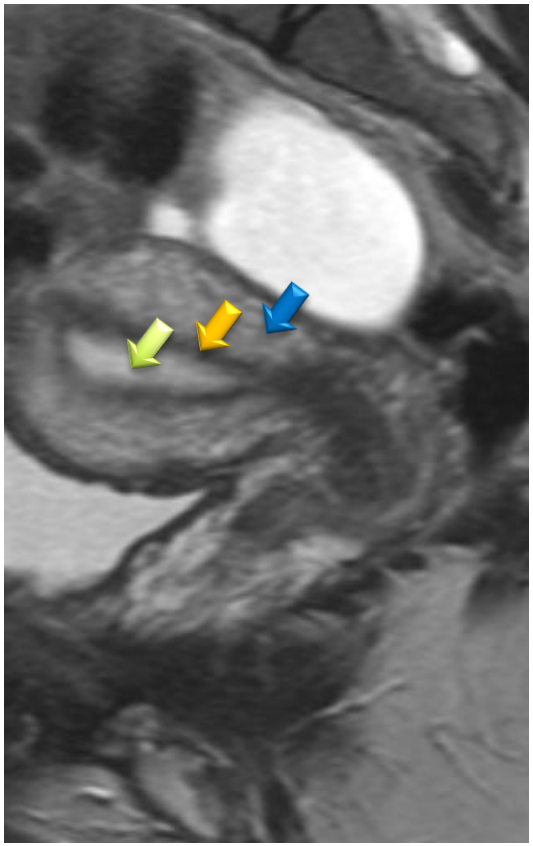
MRI + ^{18}FDG PET/CT are included in workup

Lee SI, et al. JNM 2015;56(3).

MRI normal anatomy
and primary tumor appearance

Unenhanced MRI – Normal anatomy

Uterus



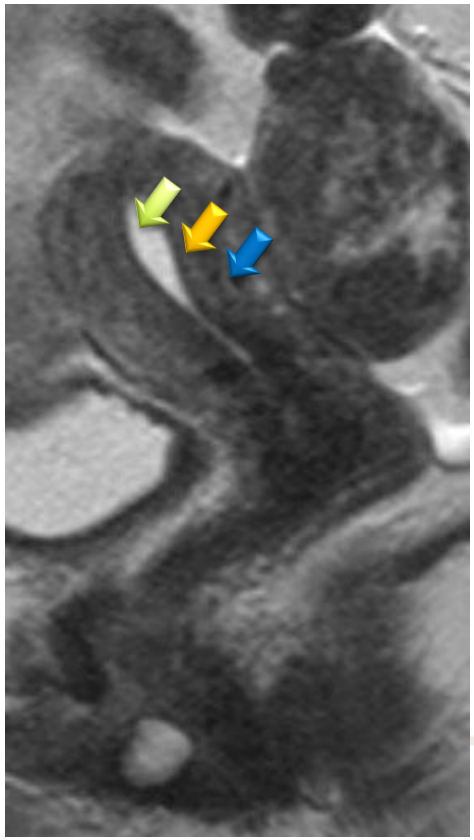
T2 w MRI

Endometrium:
Hyperintense

Inner myometrium=
Junctional zone:
Low signal intensity

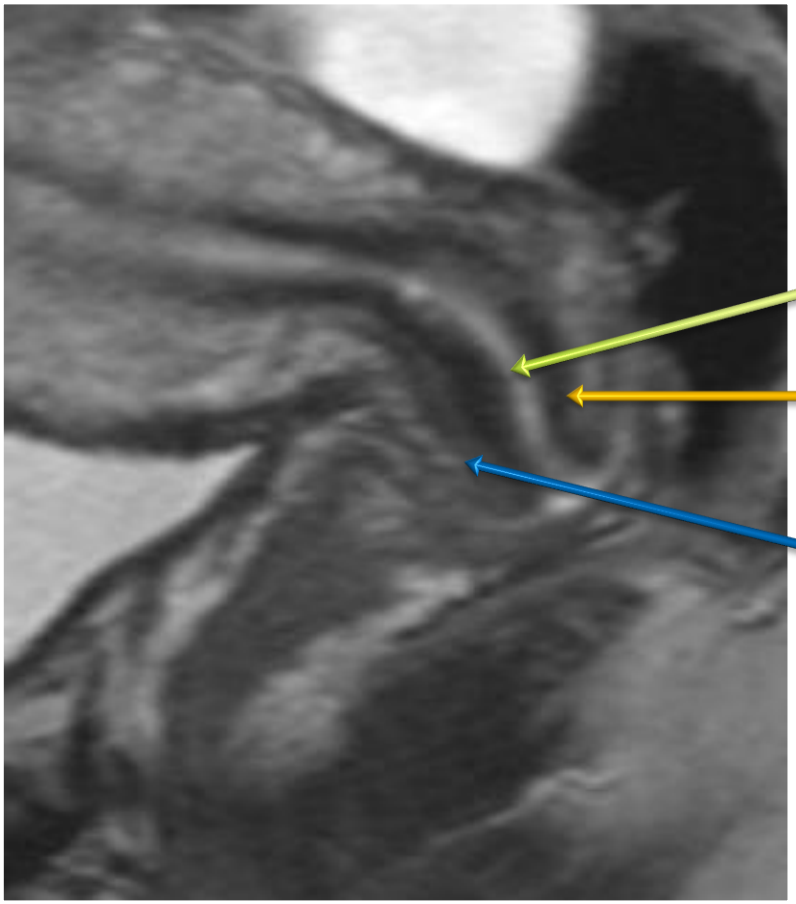
Outer myometrium:
High signal intensity

Signal intensity
decreases with age



Unenhanced MRI – Normal anatomy

Cervix



T2 w MRI

Endocervical mucosal glands:
High signal intensity

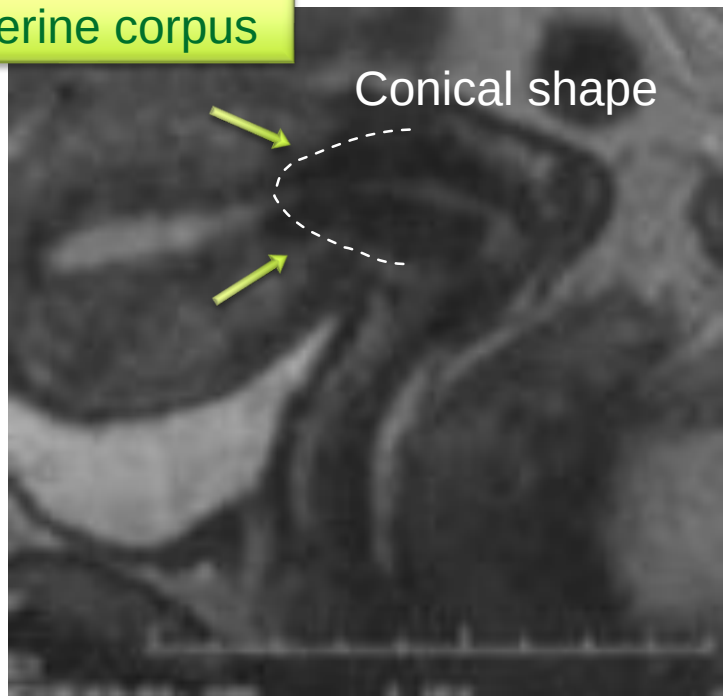
Cervical stroma:
Low signal intensity

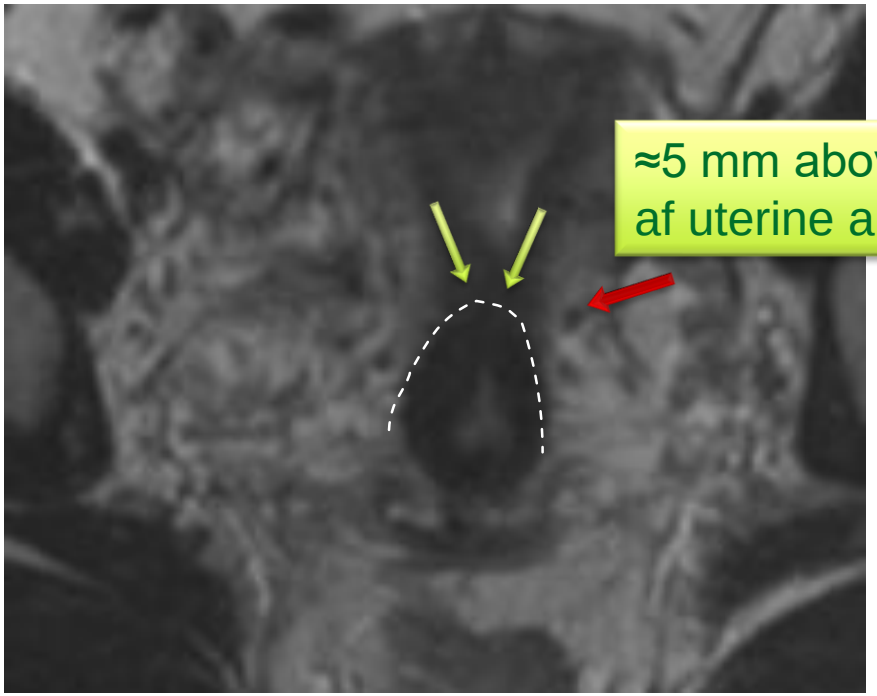
Smooth muscle:
Intermediate signal

Unenhanced MRI – Normal anatomy

Cervix – cranial limit

Uterine corpus



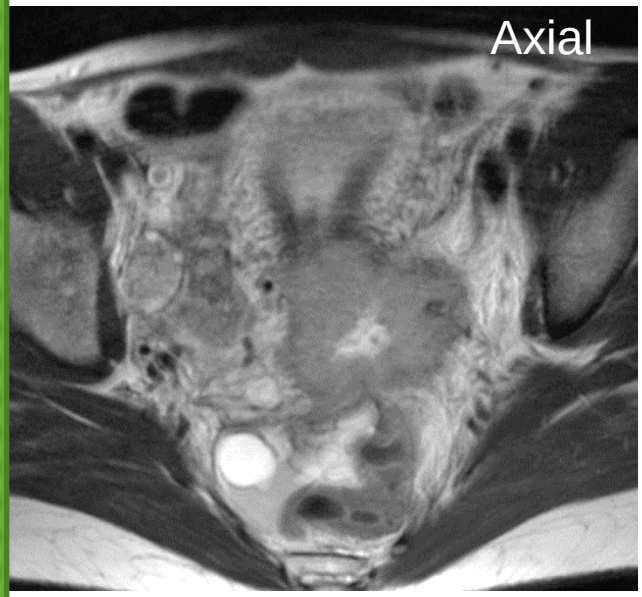


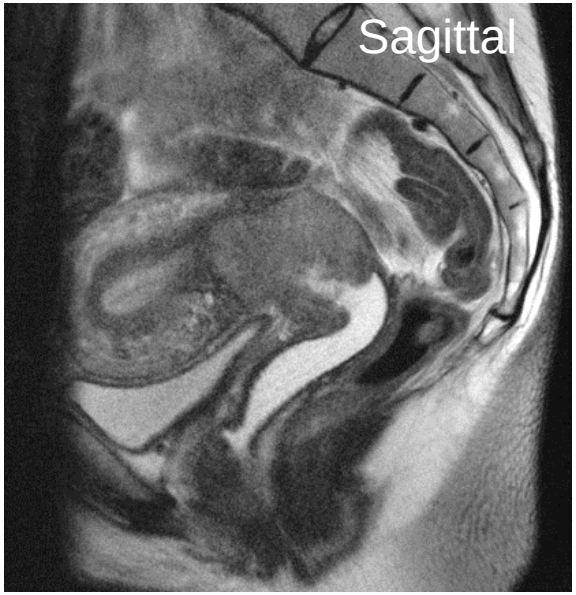
≈5 mm above entry af uterine arteries

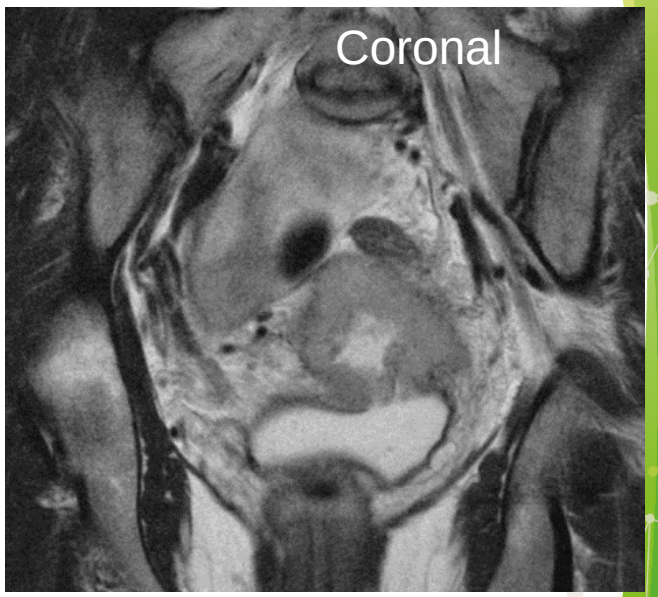
Unenhanced MRI – Pathology

Appearance of tumour tissue

T2w No contrast





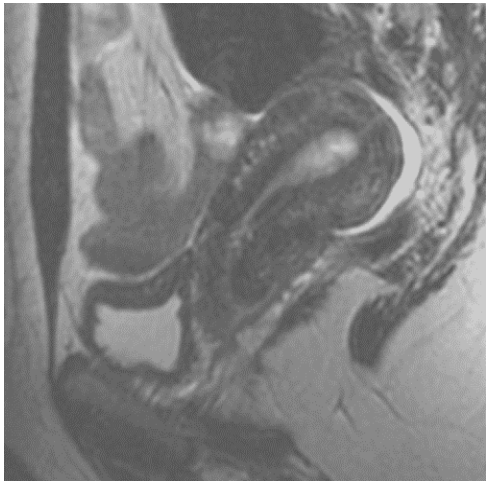


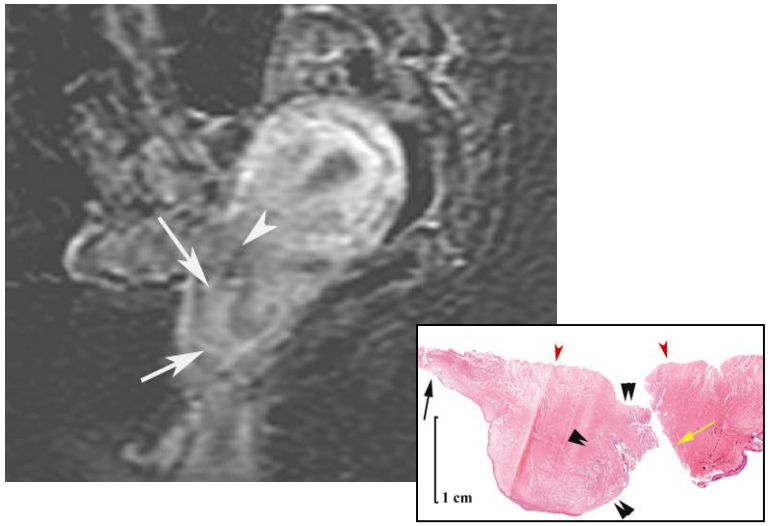
Contrast-enhanced MRI

Indications

Small or non-visible tumor on T2

Example:





33 years old patient

Endocervical Tumor

FIGO IB1

Biopsy: Adenocarcinoma

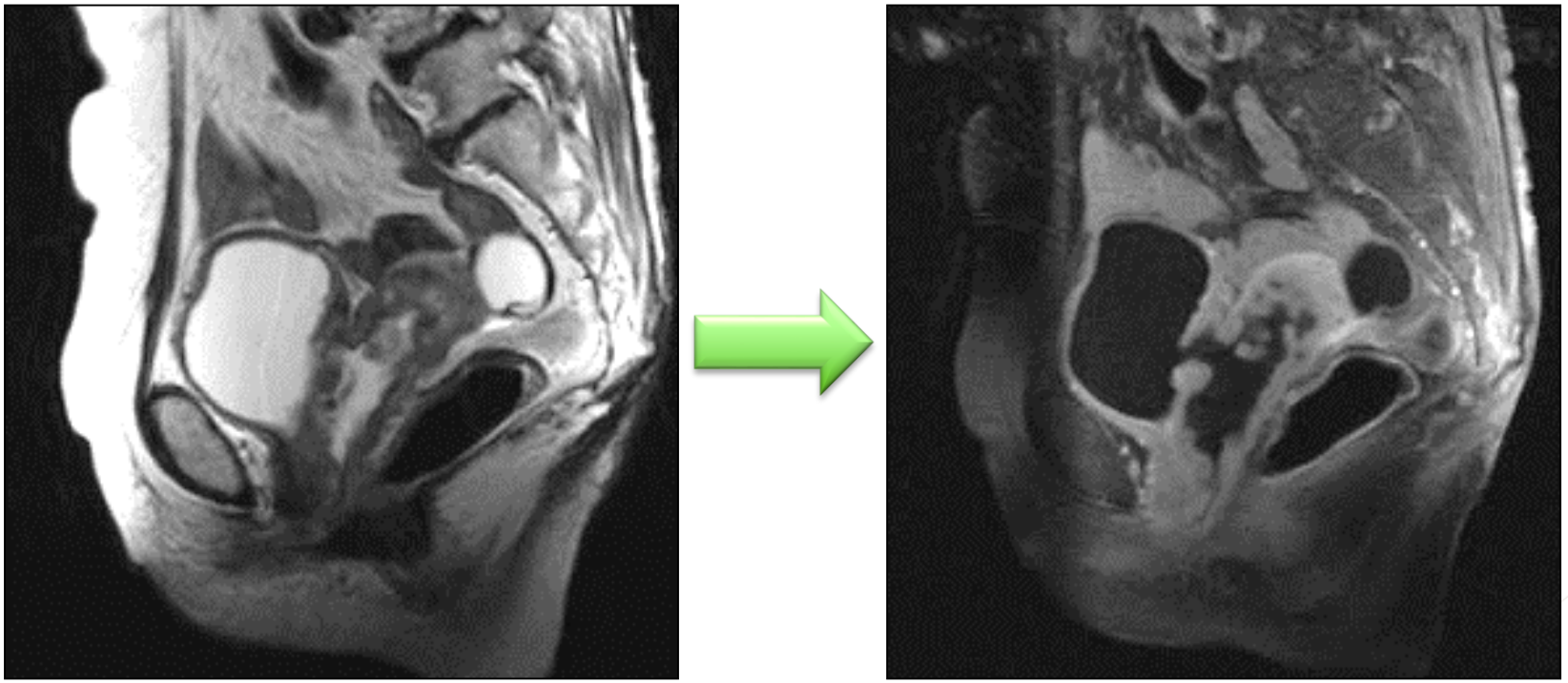
Not visible on T2w

Contrast-enhanced SE T1w

Contrast-enhanced MRI

Indications

Visualization of Vaginal mucosa, Abscess, Fistula



New MRI technologies

- Dynamic Contrast Enhanced (DCE) MRI
- Diffusion-weighted imaging (DWI)

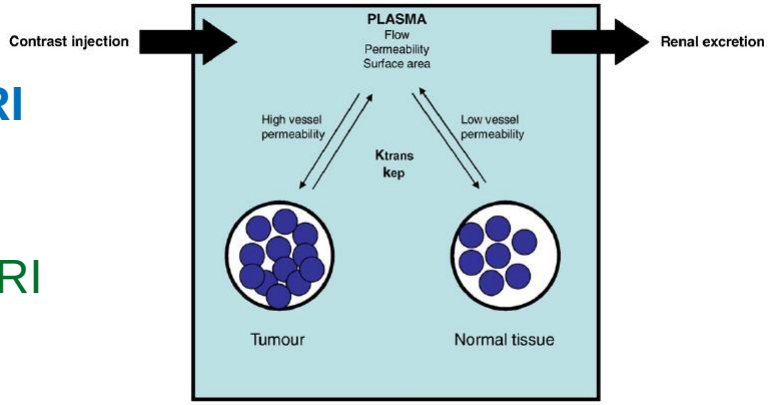
Included in standard protocols

- Blood oxygen level dependent (BOLD) MRI
- Proton spectroscopy

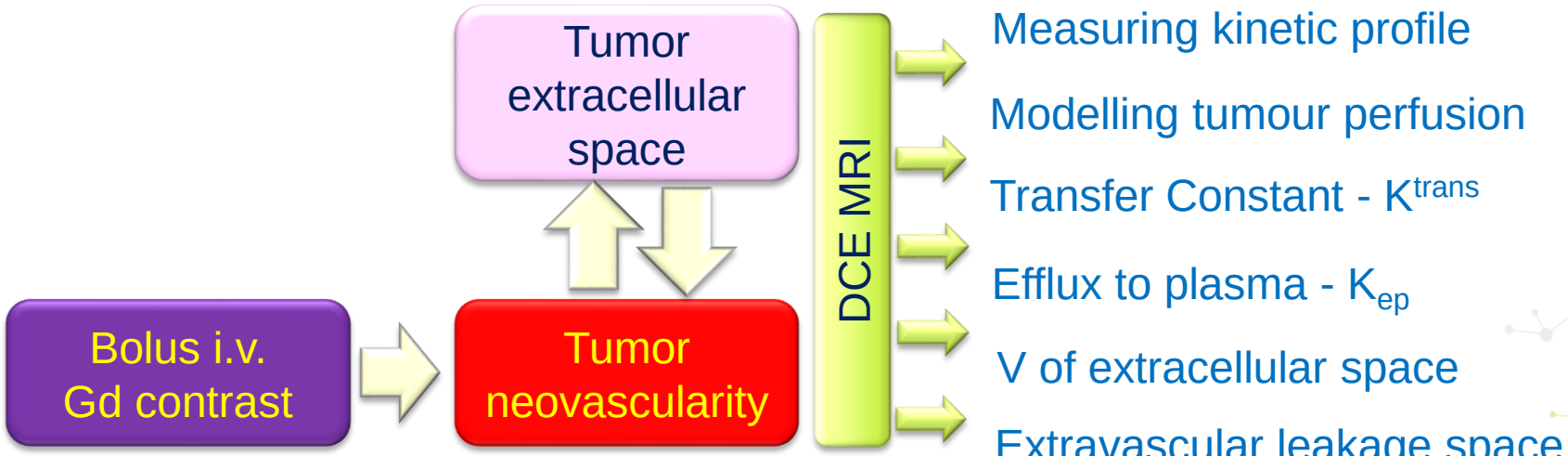
Mainly investigational

New MRI technologies

- **Dynamic Contrast Enhanced (DCE) MRI**
- Diffusion-weighted imaging (DWI)
- Blood oxygen level dependent (BOLD) MRI
- Proton spectroscopy



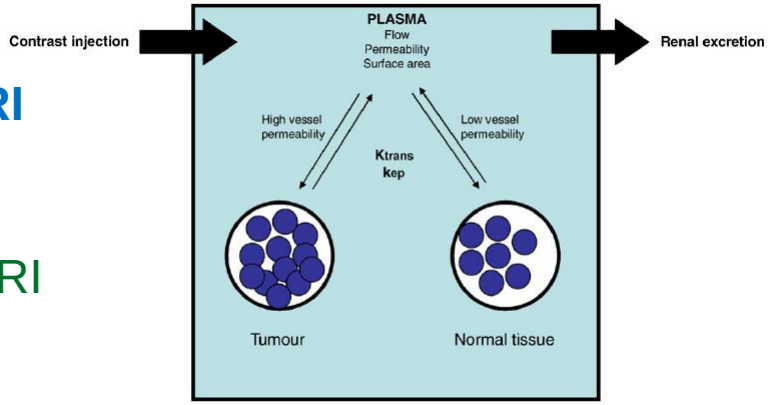
From: Harry VN. Gynecol Oncol 2010



Review:
Lee SI, et al. JNM 2015;56(3).
Harry VN. Gynecol Oncol 2010

New MRI technologies

- **Dynamic Contrast Enhanced (DCE) MRI**
- Diffusion-weighted imaging (DWI)
- Blood oxygen level dependent (BOLD) MRI
- Proton spectroscopy



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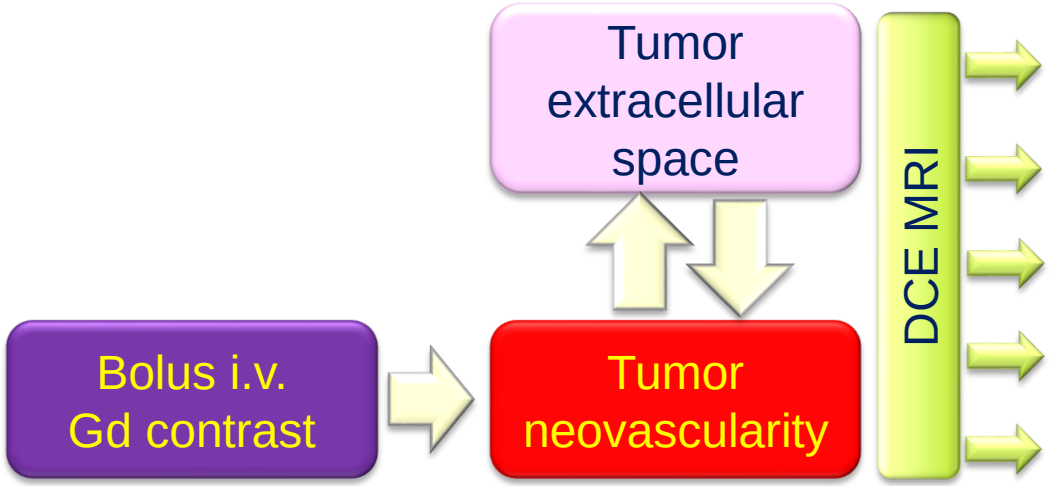
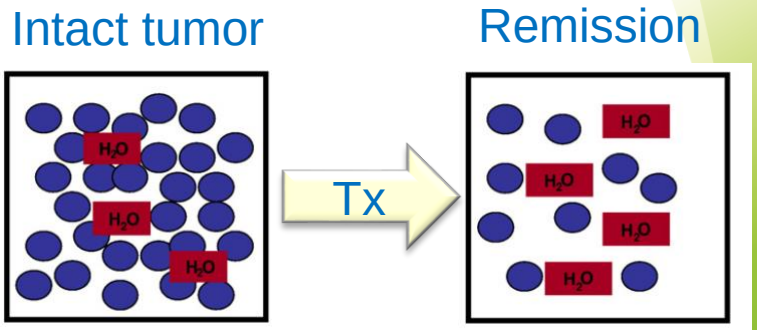


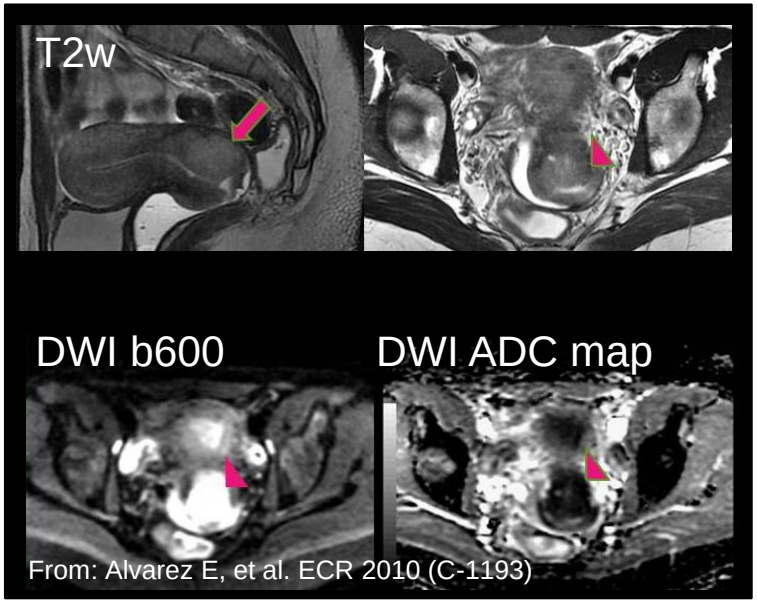
- Lesion Detection
- Benign vs. Malignant
- Outcome prediction

Review:
Lee SI, et al. JNM 2015;56(3).
Harry VN. Gynecol Oncol 2010

New MRI technologies

- Dynamic Contrast Enhanced (DCE) MRI
- **Diffusion-weighted imaging (DWI)**
- Blood oxygen level dependent (BOLD) MRI
- Proton spectroscopy





- Lesion Detection
- Response to treatment
- Predictive biomarker

Review:
Lee SI, et al. JNM 2015;56(3).
Harry VN. Gynecol Oncol 2010

Recommendations for MR imaging in cervix cancer

Gyn GEC ESTRO Recommendations - MRI

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

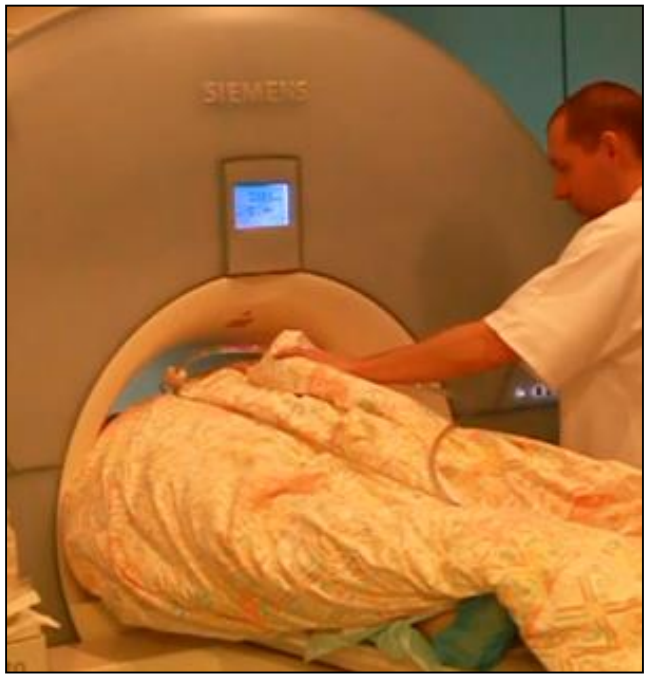
ELSEVIER

GEC-ESTRO Recommendations

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy

Johannes C.A. Dimopoulos[a], Peter Petrow[b], Kari Tanderup[c], Primoz Petric[d], Daniel Berger[e], Christian Kirisits[e], Erik M. Pedersen[c], Erik van Limbergen[f], Christine Haie-Meder[g], Richard Pötter[e,*]

- Field strength
- Magnet configuration
- Coils
- Patient preparation
- Image acquisition
- Sequences & parameters
- Imaging planes
- Equipment compatibility



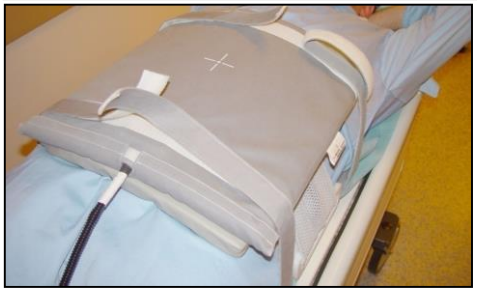
Dimopoulos JCA et al. Radiother Oncol 2012;103:113-22.

Gyn GEC ESTRO Recommendations - MRI

Parameters

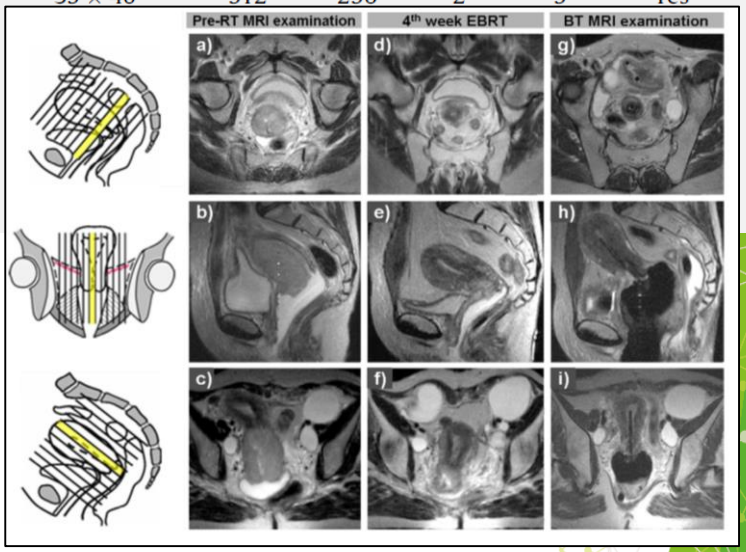
Protocol	Number	Mandatory (M)/ optional (O)	Sequence	Plane orientation	Coverage/borders
Pre-RT MRI scan	1	M	T2 FSE	Para-axial (according to cervix uteri)	Above uterine corpus – inferior border of symphysis pubis/entire vagina if distal vaginal involvement
	2	M	T2 FSE	Sagittal	Pelvic side wall (obturator muscle)
	3	M	T2 FSE	Para-coronal (according to cervix uteri)	Uterine corpus – cervix – vagina – tumour
	4	M	T2 FSE	Axial	Discus L4–L5 – inferior border of symphysis pubis/entire vagina and inguinal regions if distal vaginal involvement
	5	O	T1 FSE or 3D GRE without contrast[a]	Axial	Discus L4–L5 – inferior border of symphysis pubis/entire vagina and inguinal regions if distal vaginal involvement
	6	O	T1 FSE with contrast[a]	Sagittal	Pelvic side wall (obturator muscle)
	7	O	T1 FSE or 3D GRE with contrast[a]	Axial (isotropic 3D GRE)	Uterine corpus – cervix – vagina – tumour

Protocol	Number		Sequence parameters: Fatsat	TR (ms)[a]	TE (ms)[b]	ETL[c]	FOV (cm^2)[d]	M(f)[e]	M(p)[e]	Nex[f]	SW[g]	NPW[h]
Pre-RT MRI scan	1		No	2000–5000	90–120	4–20	35 × 20	512	256	2	3–4	Yes
	2		No	2000–5000	90–120	4–20	35 × 40	512	256	2	5	Yes
	3		No	2000–5000	90–120	4–20						
	4		No	2000–5000	90–120	4–20						
	5	TSE	Optional	500–700	10–20	NA						
		3D GRE[i]	Optional	5–10	2–5	[i]						
	6	TSE	Optional	500–700	10–20	NA						
	7	TSE	Optional	500–700	10–20	NA						
		3D GRE[i]	Optional	5–10	2–5	[i]						



Coils

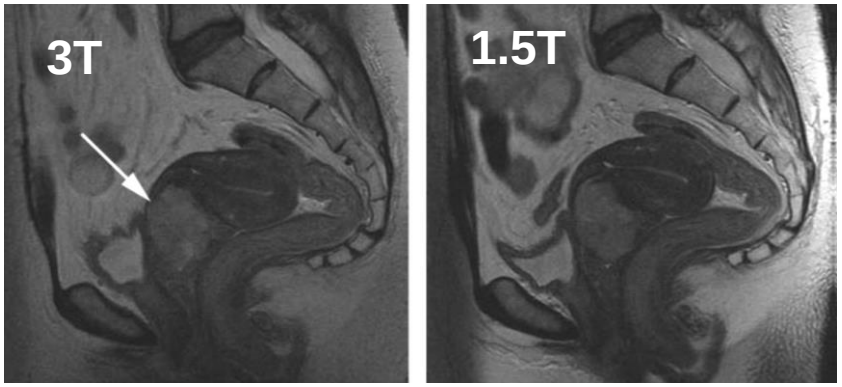
Imaging planes



Dimopoulos JCA et al. Radiother Oncol 2012;103:113-22.

Gyn GEC ESTRO Recommendations - MRI

Magnet field strength

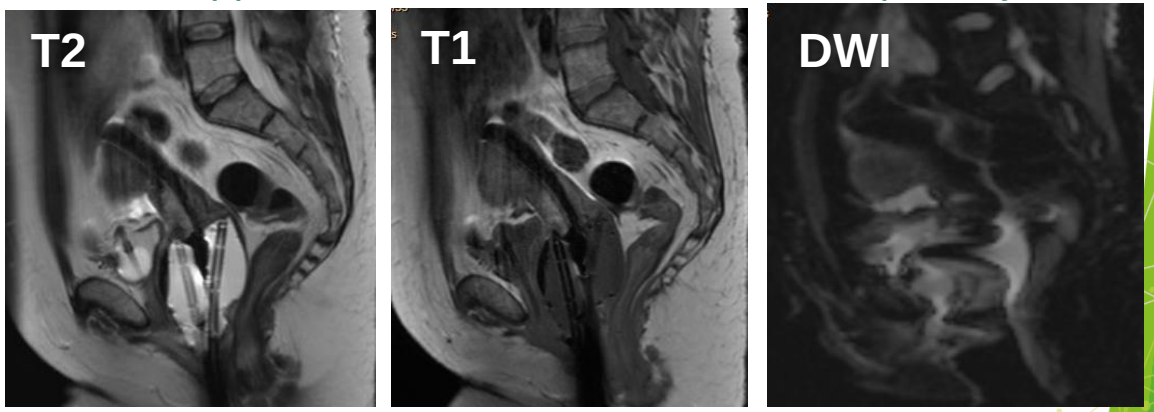


- ↑T - Diagnostic benefits
- Clinical impact in cervix cancer RT?

To avoid differences in contrast and image quality

Recommended to use same imager at Dg and at BT

Titanium applicators: not feasible at >1.5 T, especially DWI

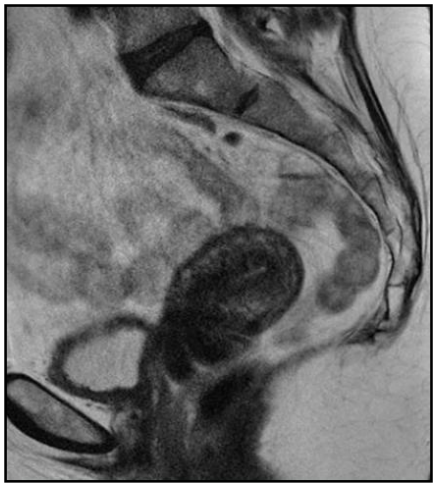


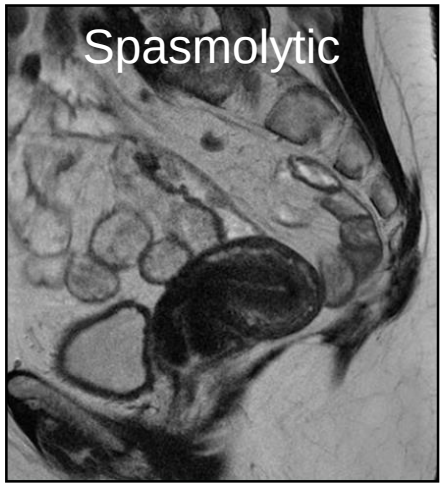
Courtesy: Kari Tanderup, AUH

Dimopoulos JCA et al. Radiother Oncol 2012;103:113-22.

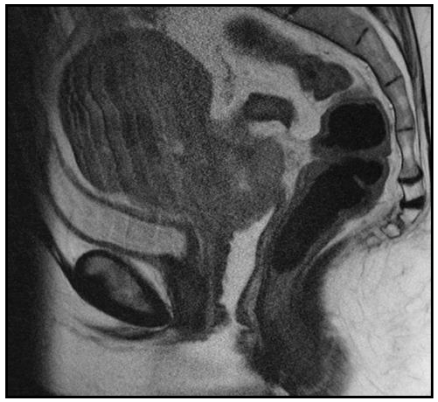
Gyn GEC ESTRO Recommendations - MRI

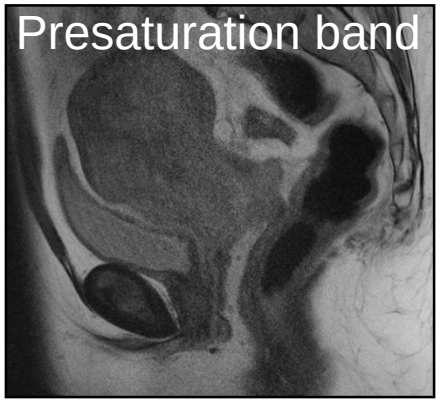
Patient preparation tips





- Reduction of bowel motion
  - Spasmolytic drugs
- Reduction of abdominal wall motion
  - Anterior elastic band
- Reduction of air/fat signal
  - Anterior pre-saturation band

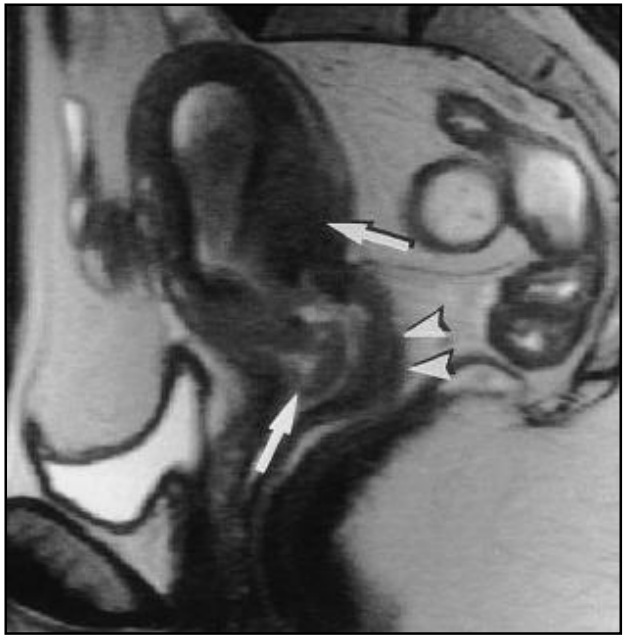


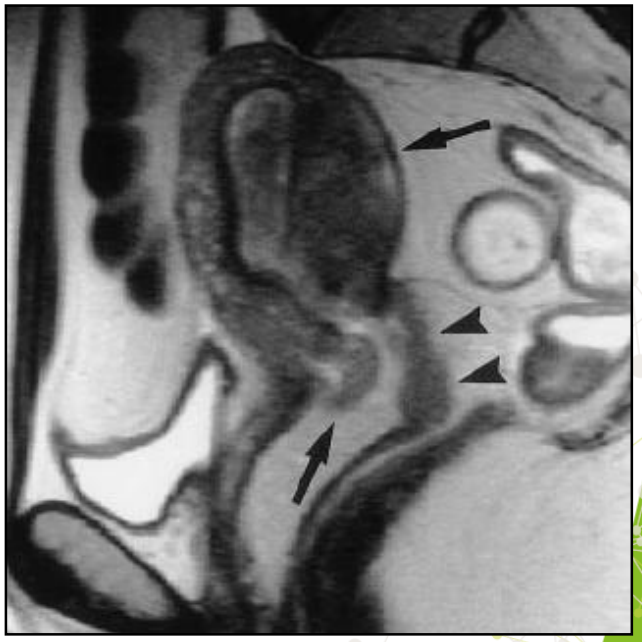


Dimopoulos JCA et al. Radiother Oncol 2012;103:113-22.

Gyn GEC ESTRO Recommendations - MRI

Patient preparation: vaginal filling



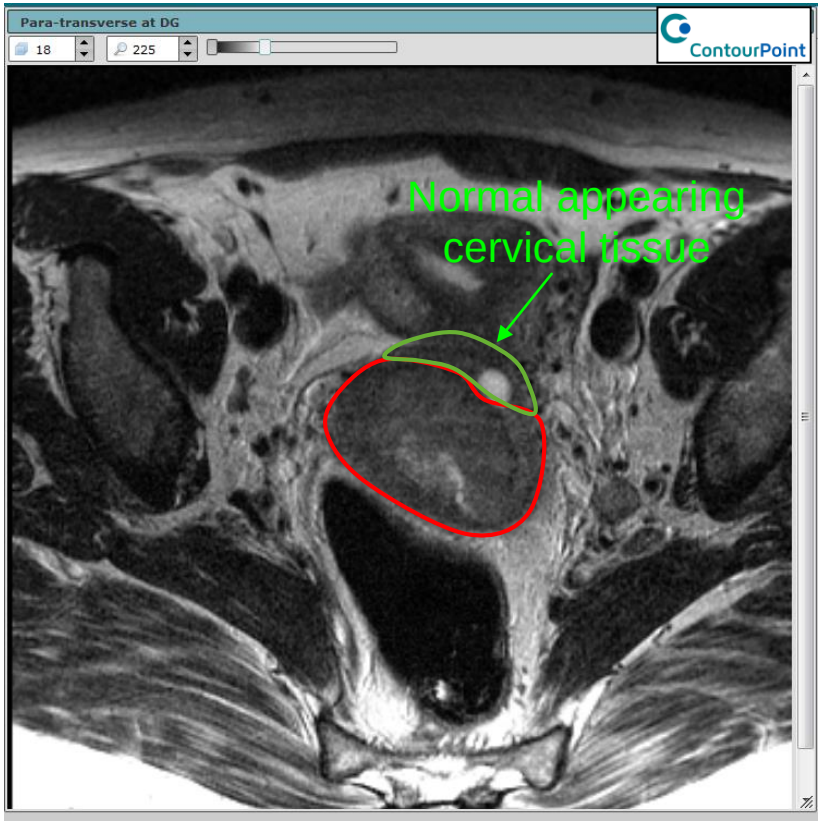


Dimopoulos JCA et al. Radiother Oncol 2012;103:113-22.

Interpretation of Diagnostic MRI by *Radiation Oncologist*

Interpretation of Diagnostic MRI

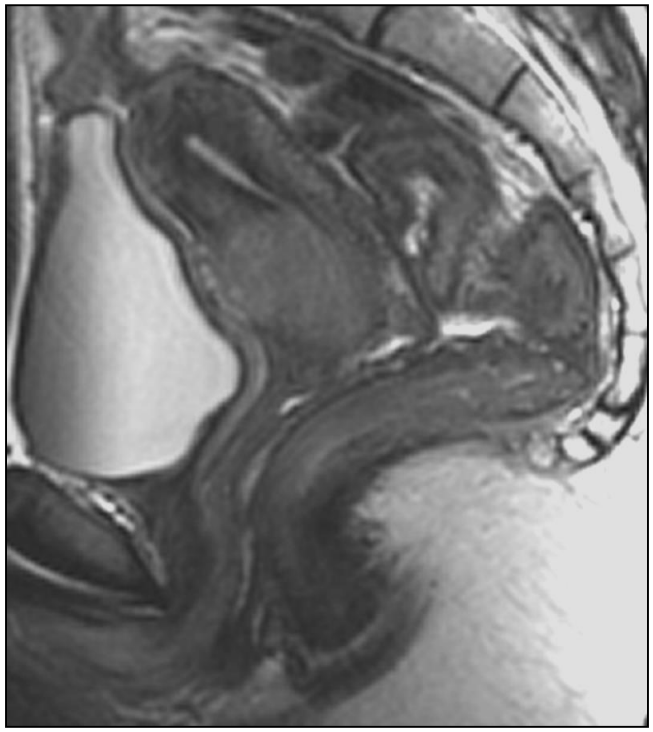
Primary tumor



Interpretation of Diagnostic MRI

Primary tumour- *pattern of growth*

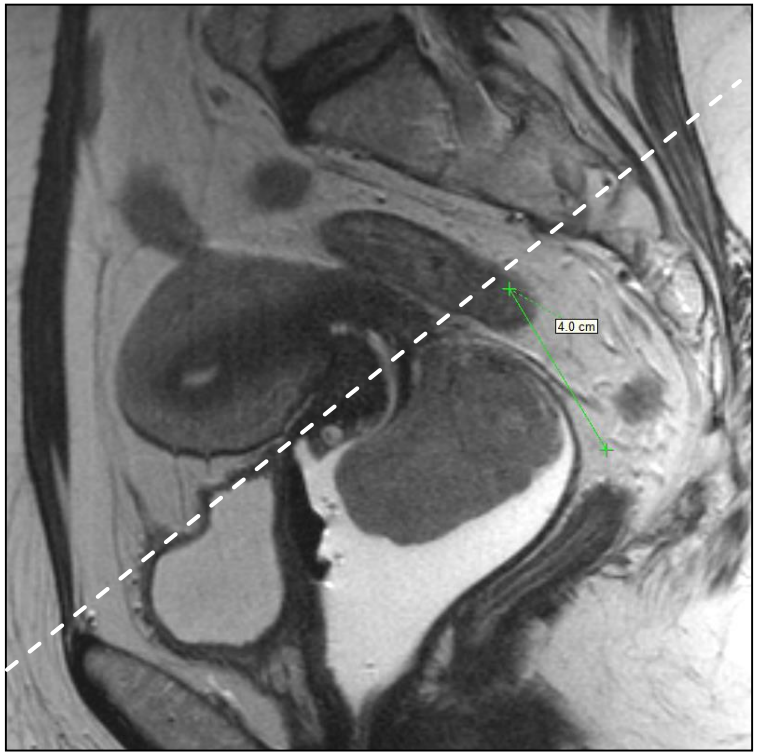
Expansive endocervical



Interpretation of Diagnostic MRI

Primary tumour- *pattern of growth*

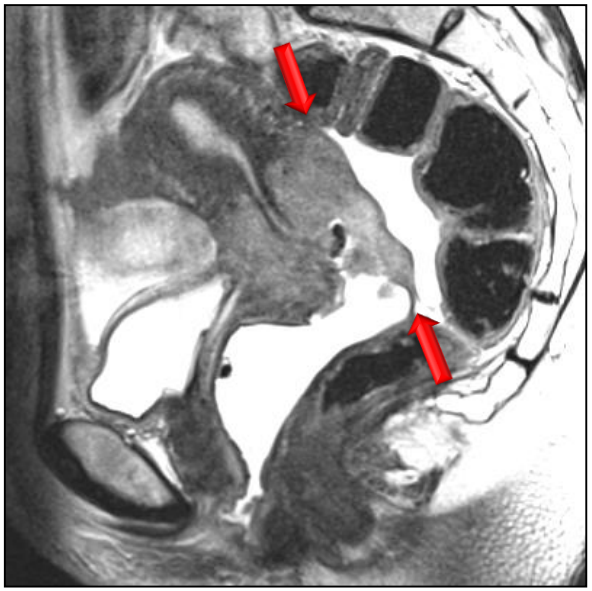
Exophytic

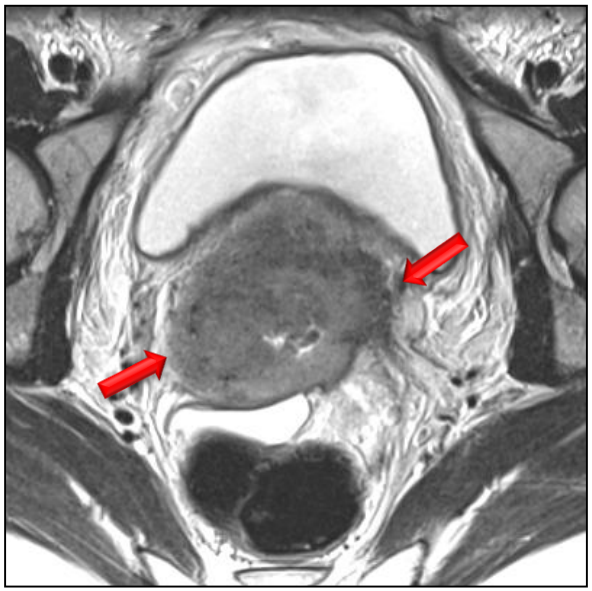


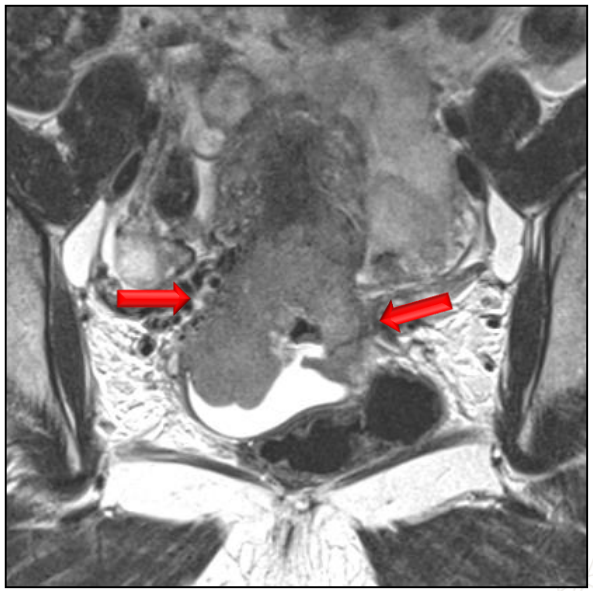
Interpretation of Diagnostic MRI

Primary tumour- *pattern of growth*

Infiltrating

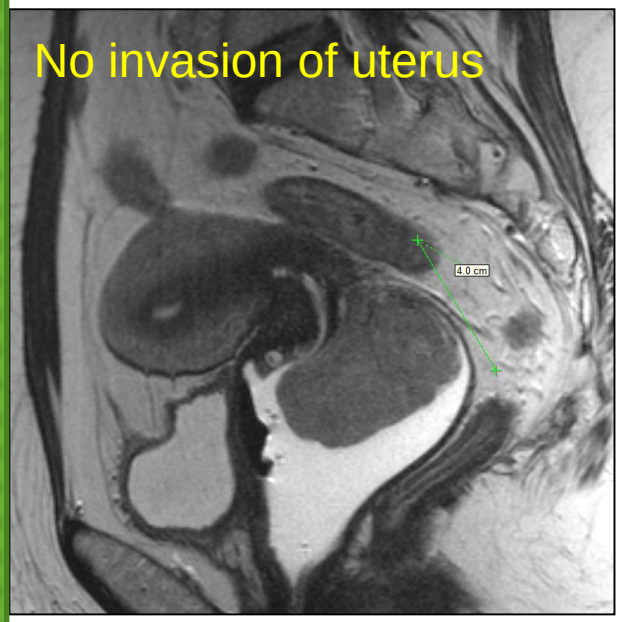


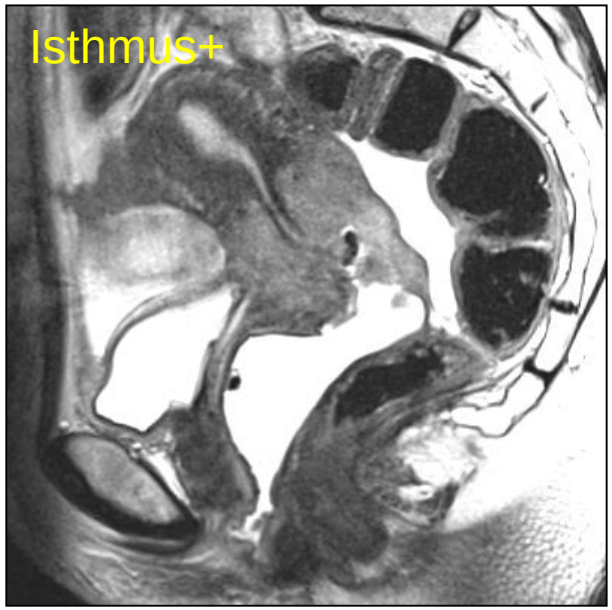


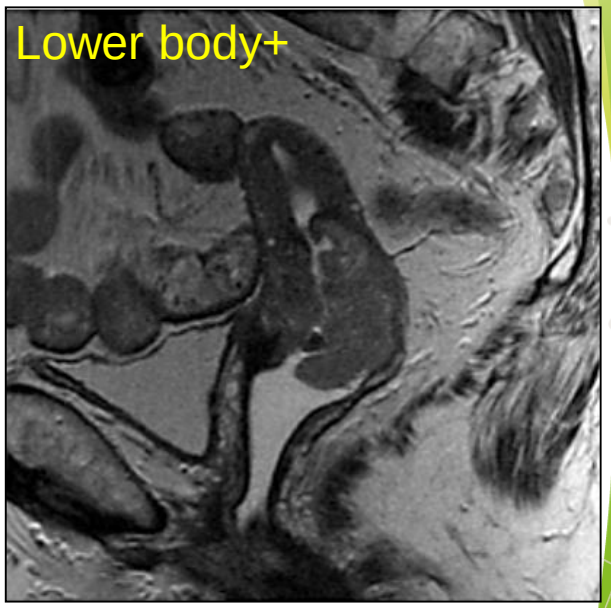


Interpretation of Diagnostic MRI

Assessment of uterus

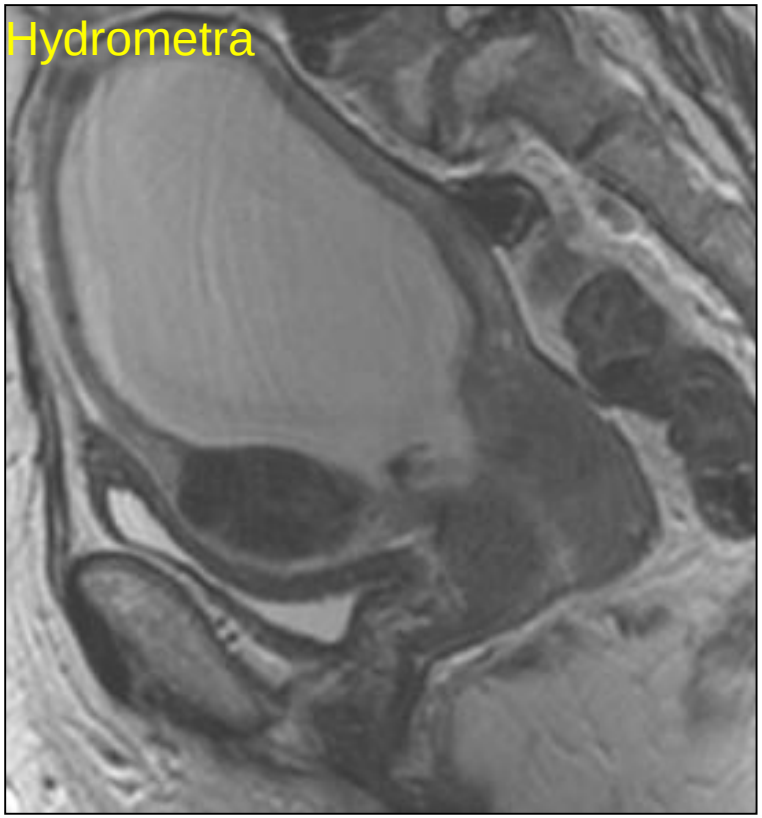


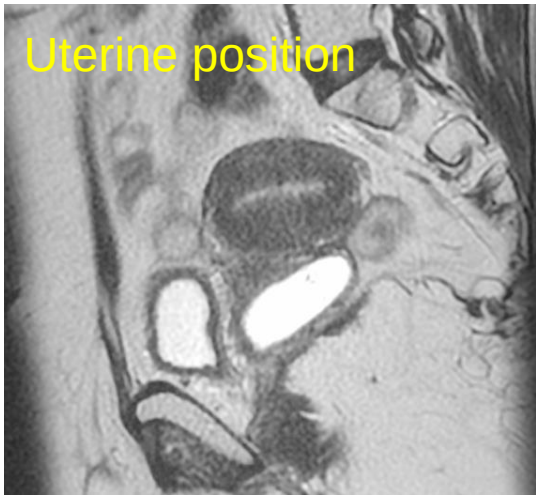


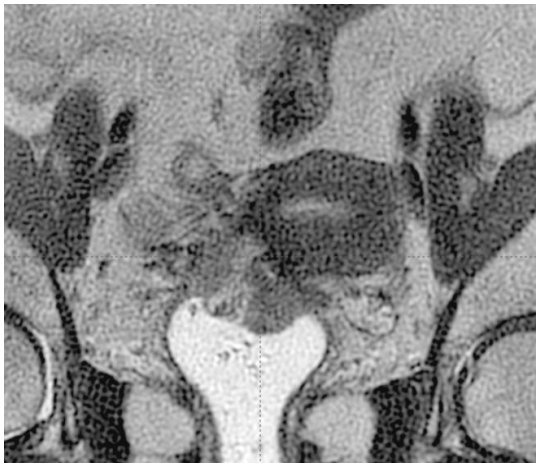


Interpretation of Diagnostic MRI

Assessment of uterus

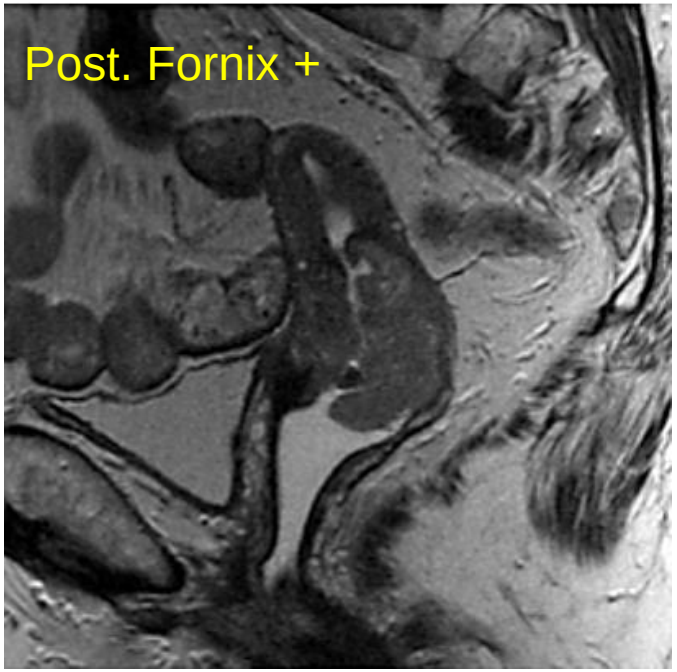


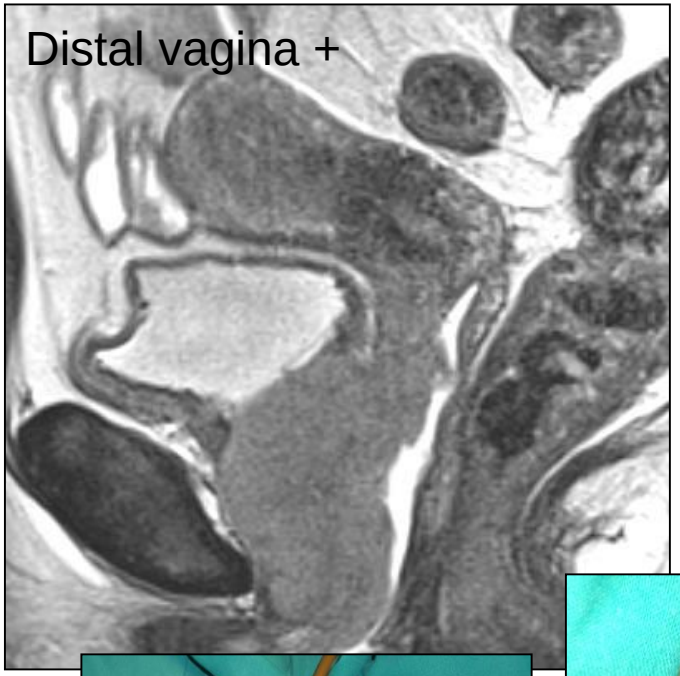




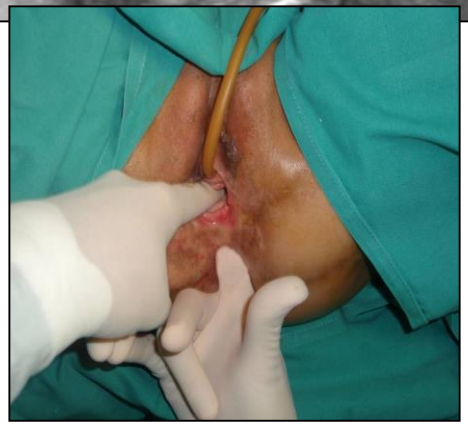
Interpretation of Diagnostic MRI

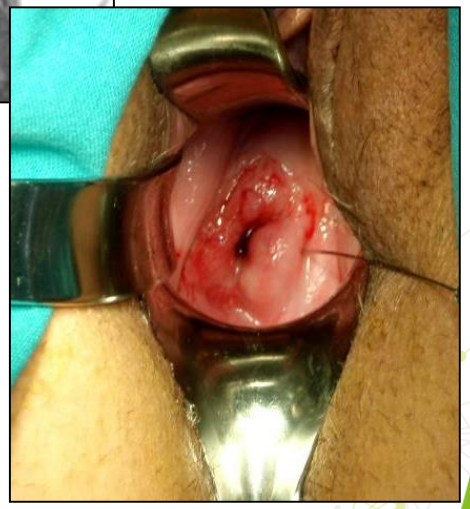
Assessment of vagina





Clinical examination!

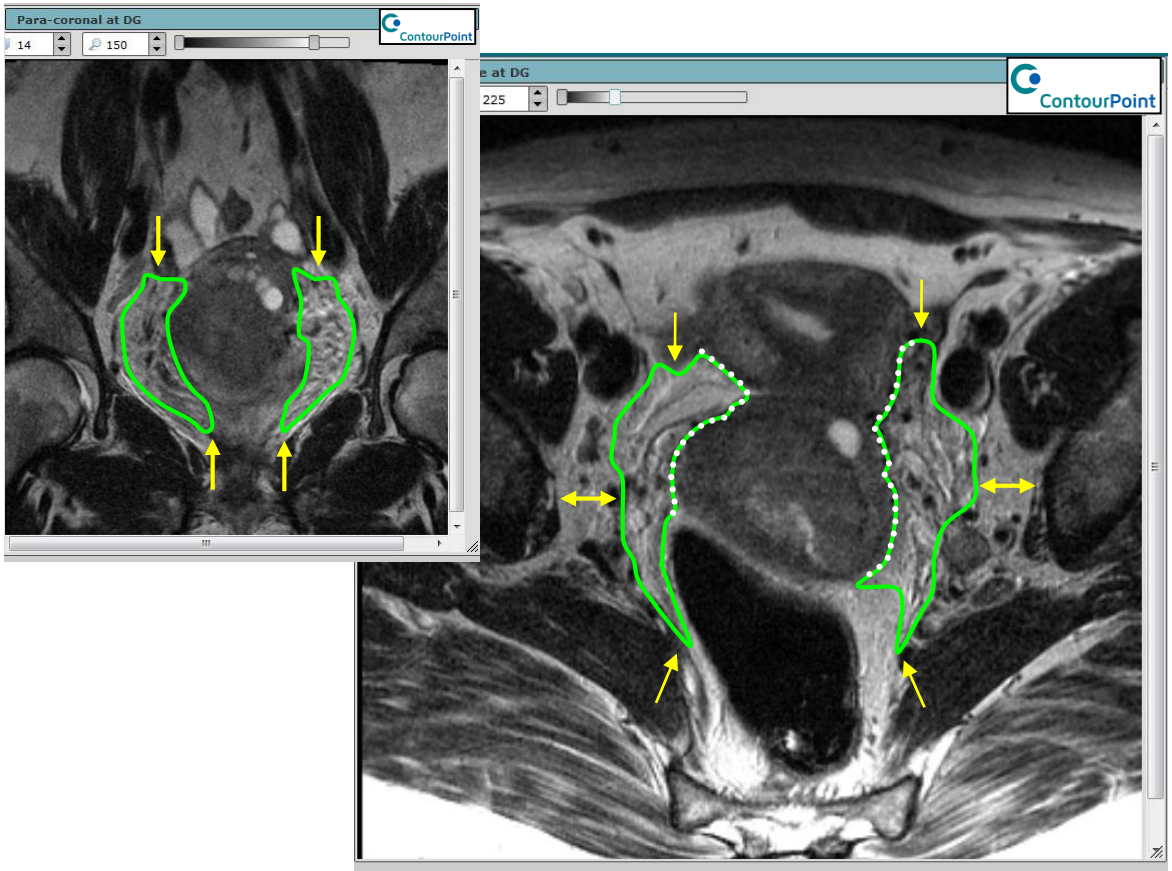




Interpretation of Diagnostic MRI

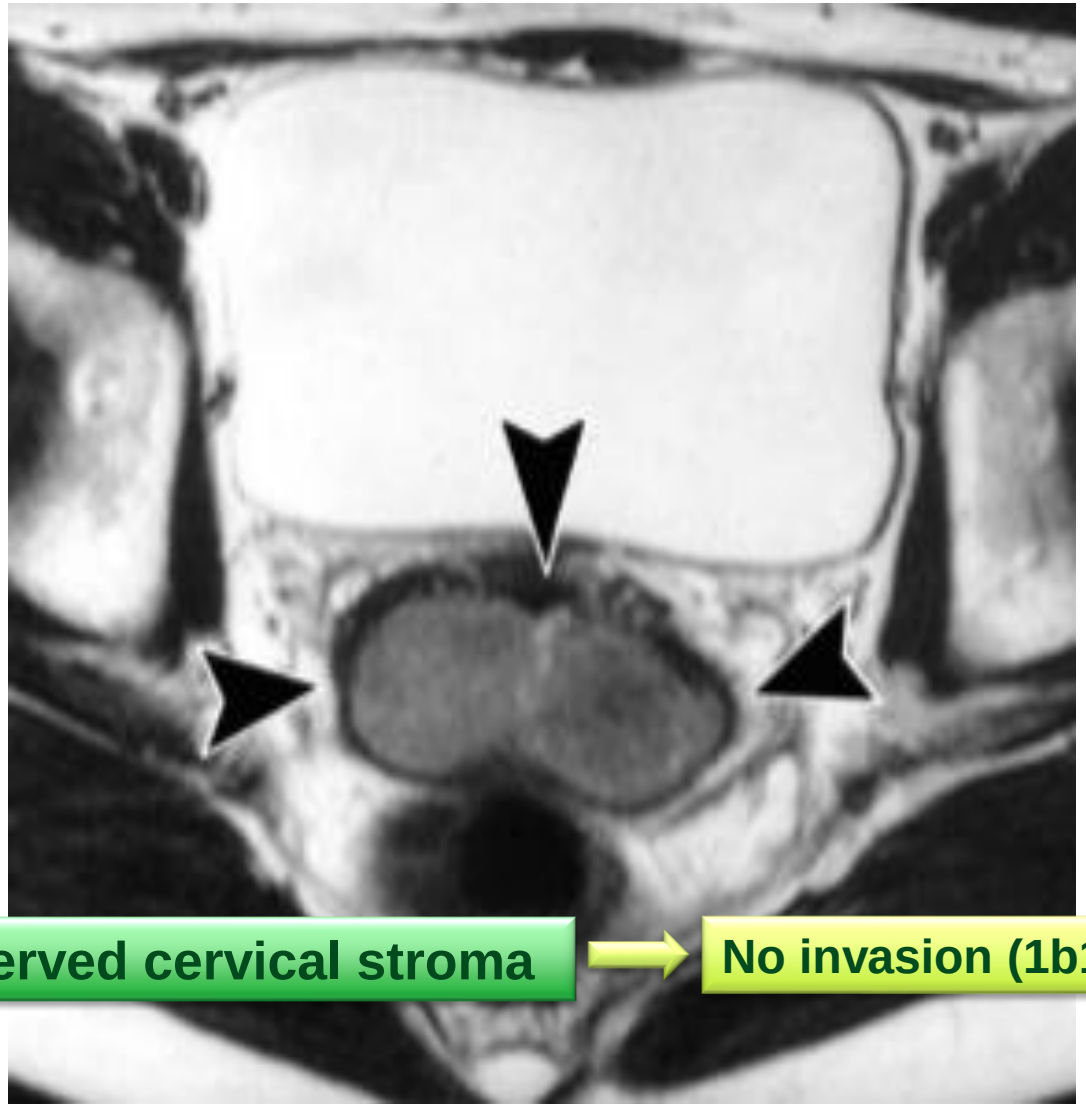
Assessment of parametria

Anatomical borders



Interpretation of Diagnostic MRI

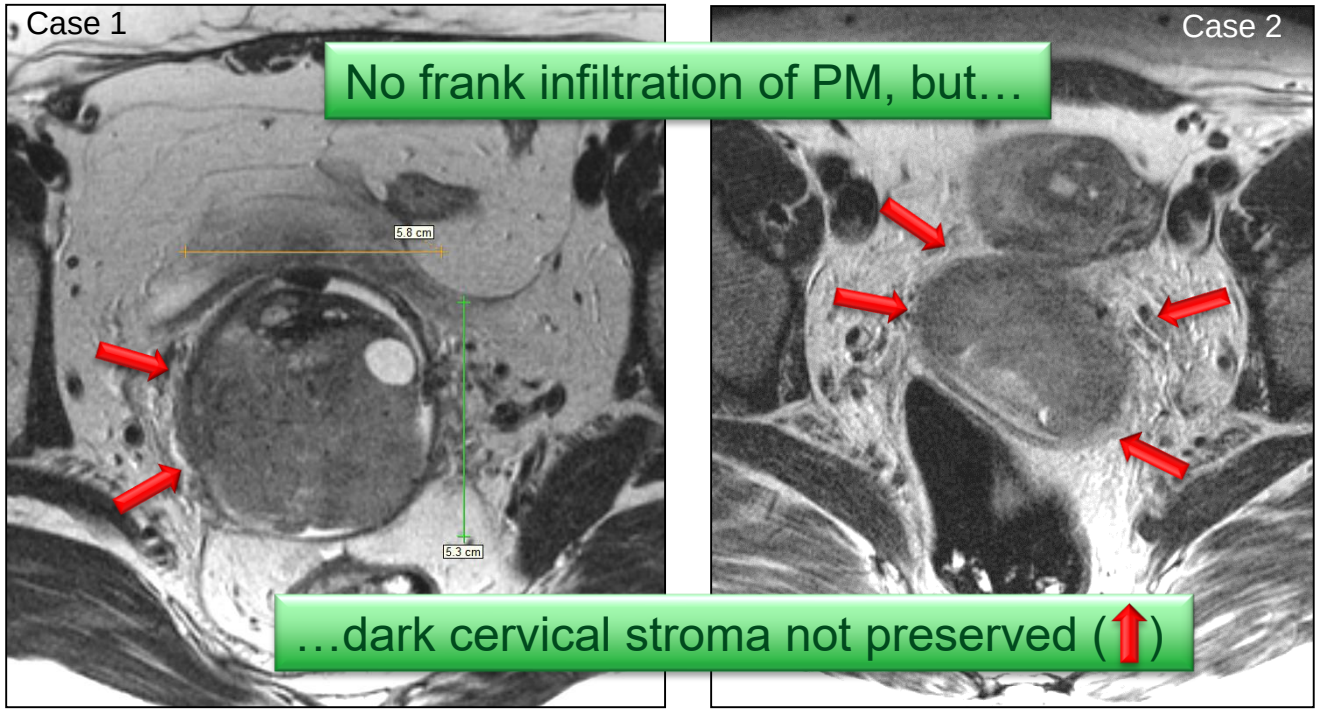
Parametrial invasion



Preserved cervical stroma → **No invasion (1b1)**

Interpretation of Diagnostic MRI

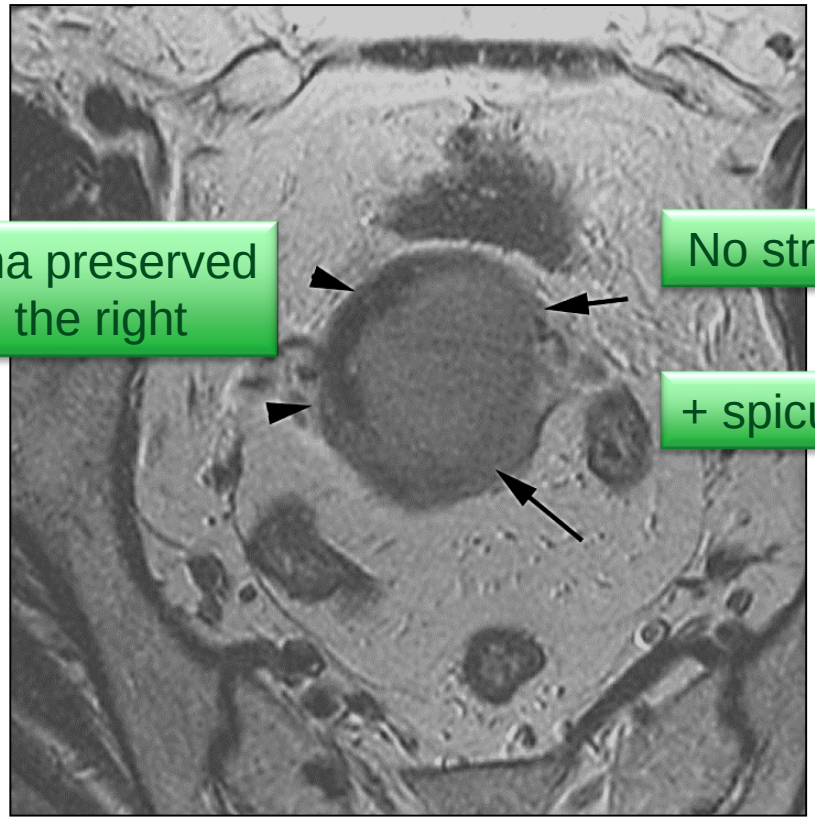
Parametrial invasion



Proximal invasion assumed (2b)

Interpretation of Diagnostic MRI

Parametrial invasion

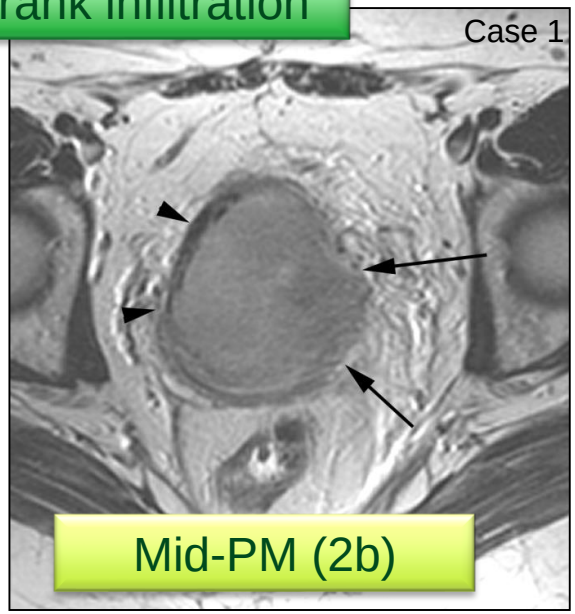


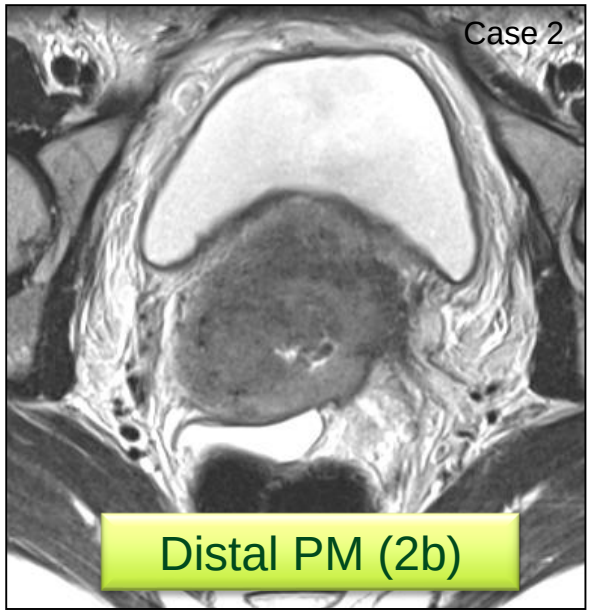
Proximal PM invasion (2b)

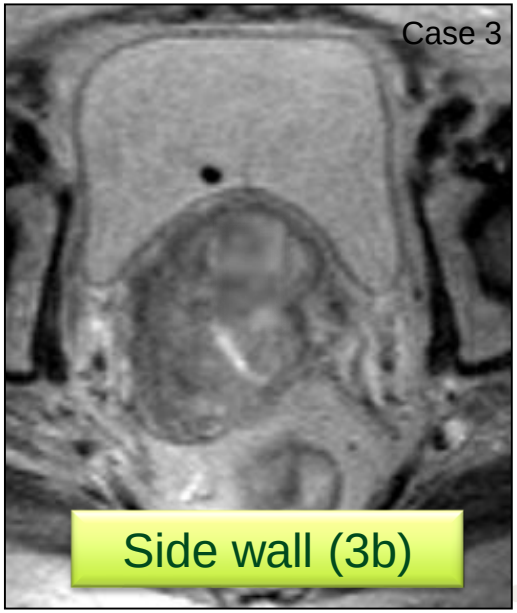
Interpretation of Diagnostic MRI

Parametrial invasion

Frank infiltration

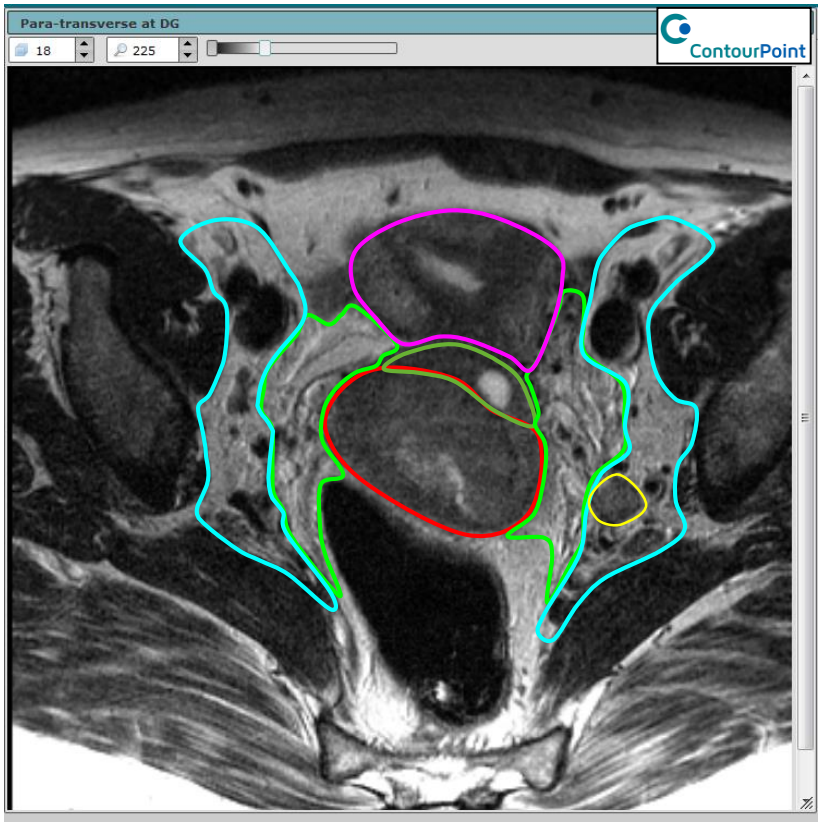






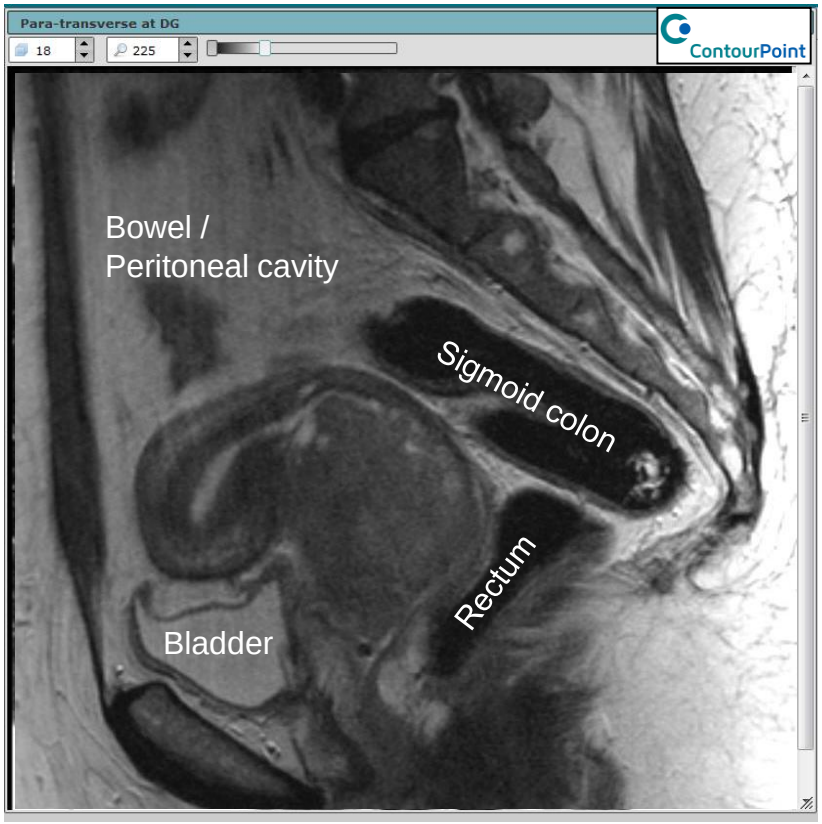
Interpretation of Diagnostic MRI

Vascular compartment



Interpretation of Diagnostic MRI

Relation of primary tumour with surrounding organs

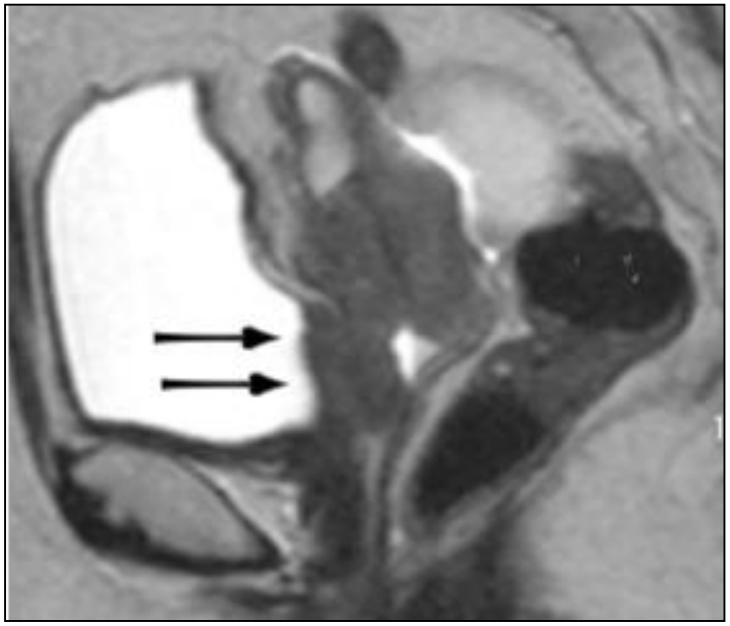


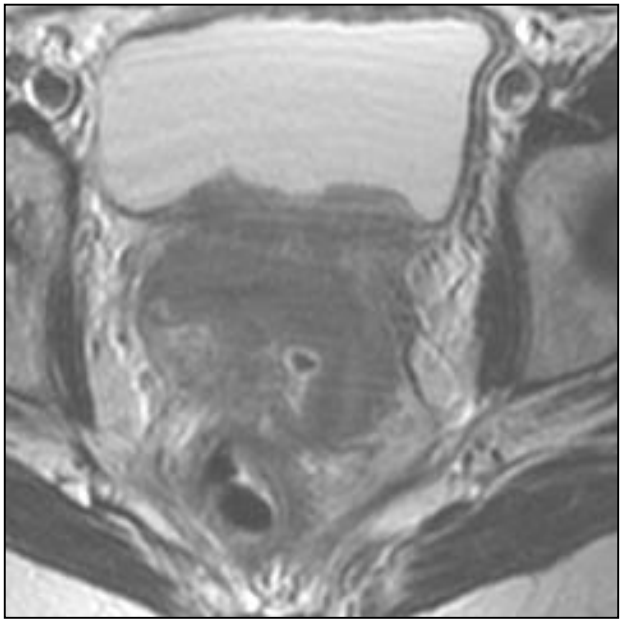
- Integrity of space between tumor and organ wall?
- Organ wall integrity?
- Organ function integrity (hydronephrosis, fistula)?

Interpretation of Diagnostic MRI

Relation of primary tumour with surrounding organs

Bladder invasion

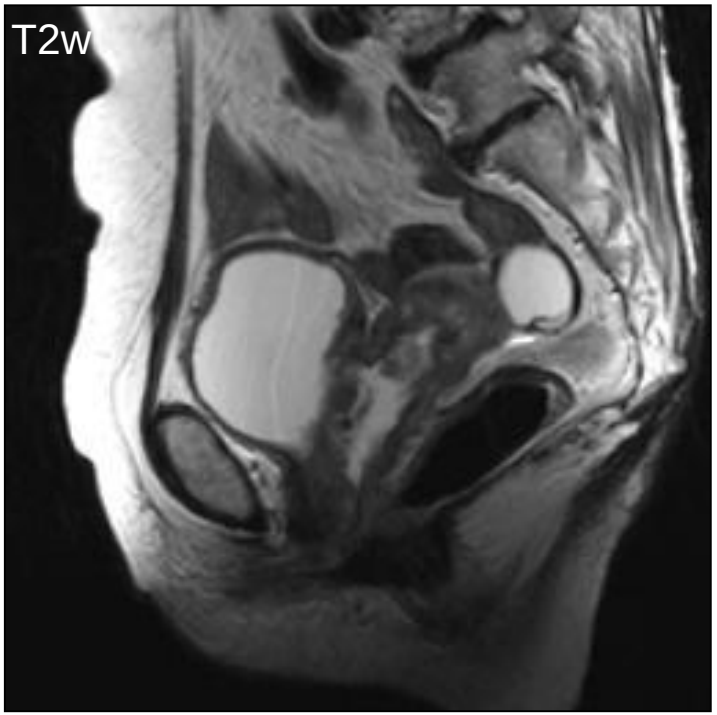


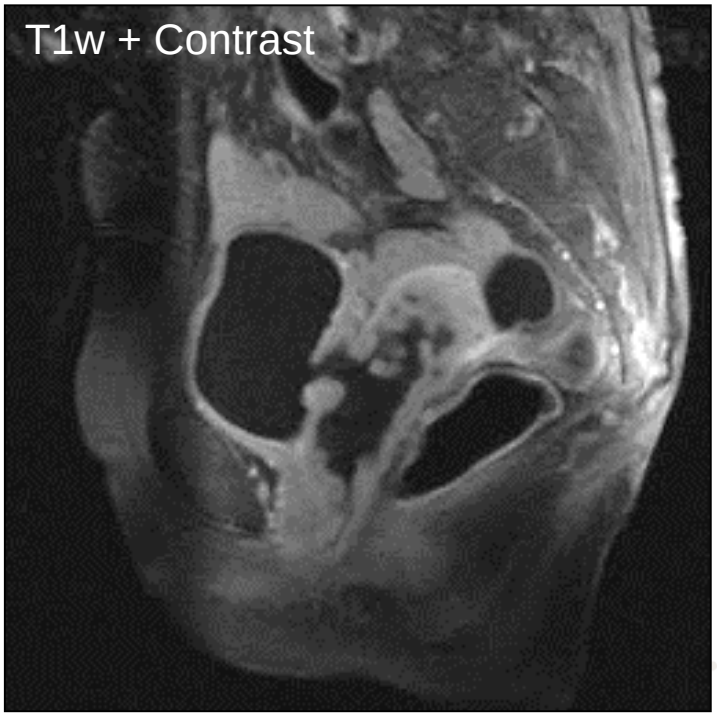


Interpretation of Diagnostic MRI

Relation of primary tumour with surrounding organs

Bladder invasion

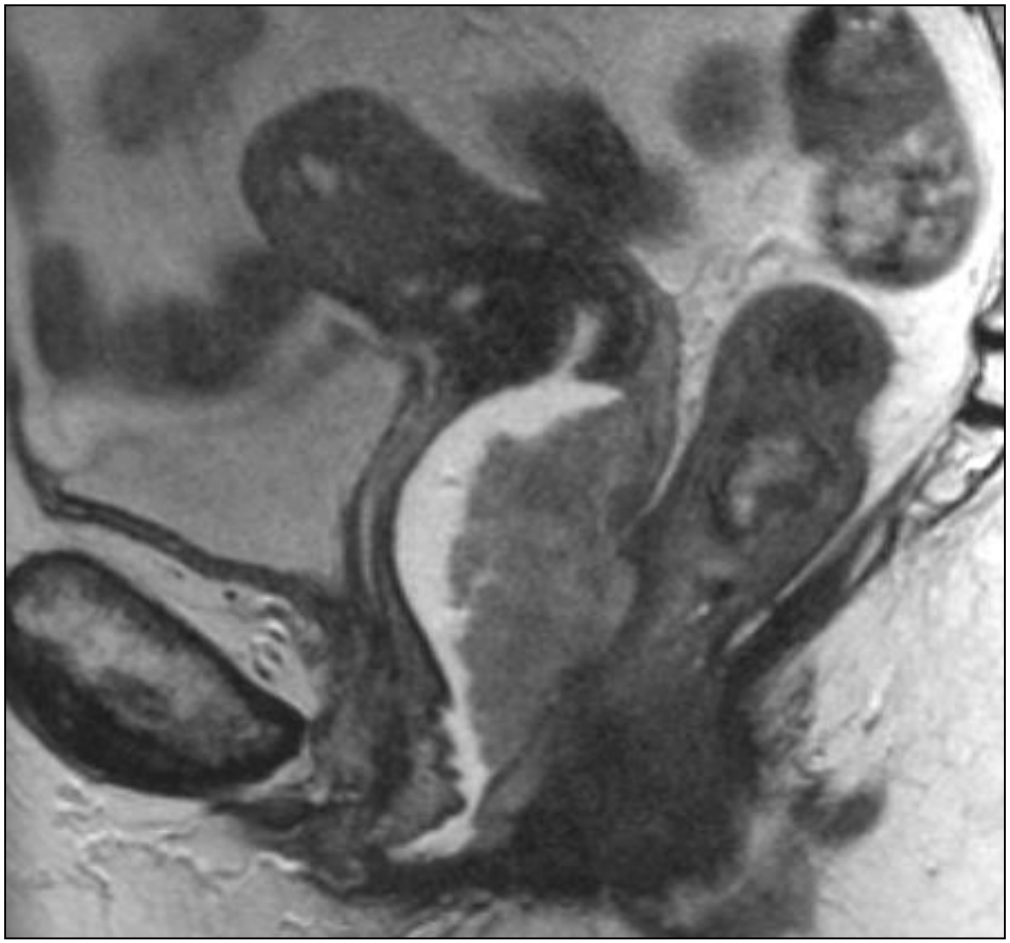




Interpretation of Diagnostic MRI

Relation of primary tumour with surrounding organs

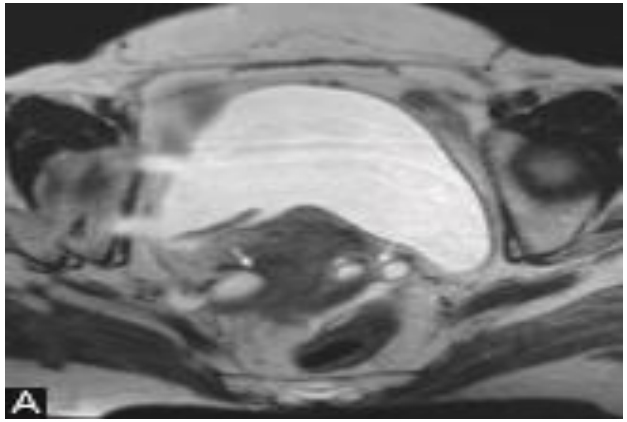
Rectal invasion

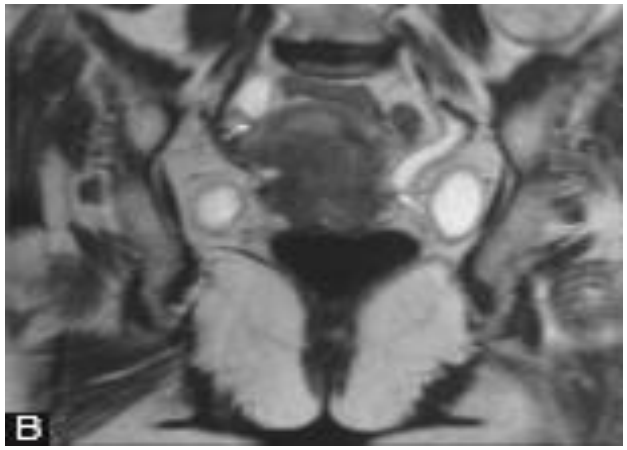


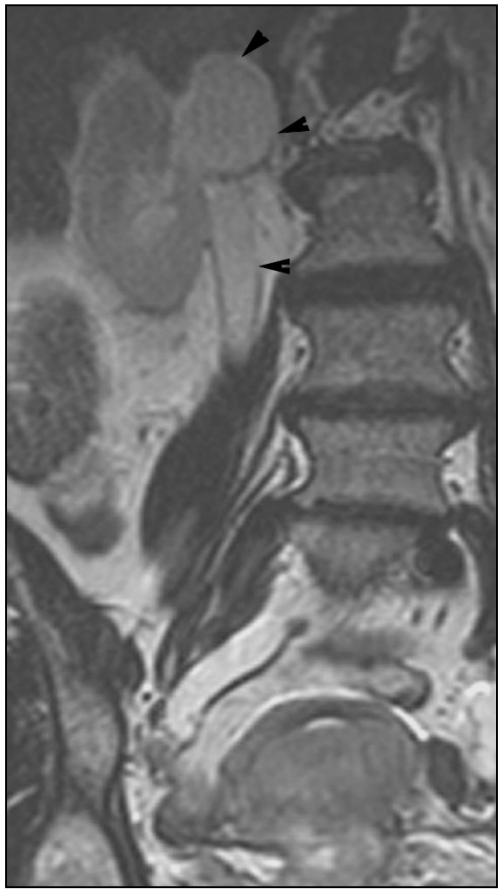
Interpretation of Diagnostic MRI

Relation of primary tumour with surrounding organs

Hydronephrosis



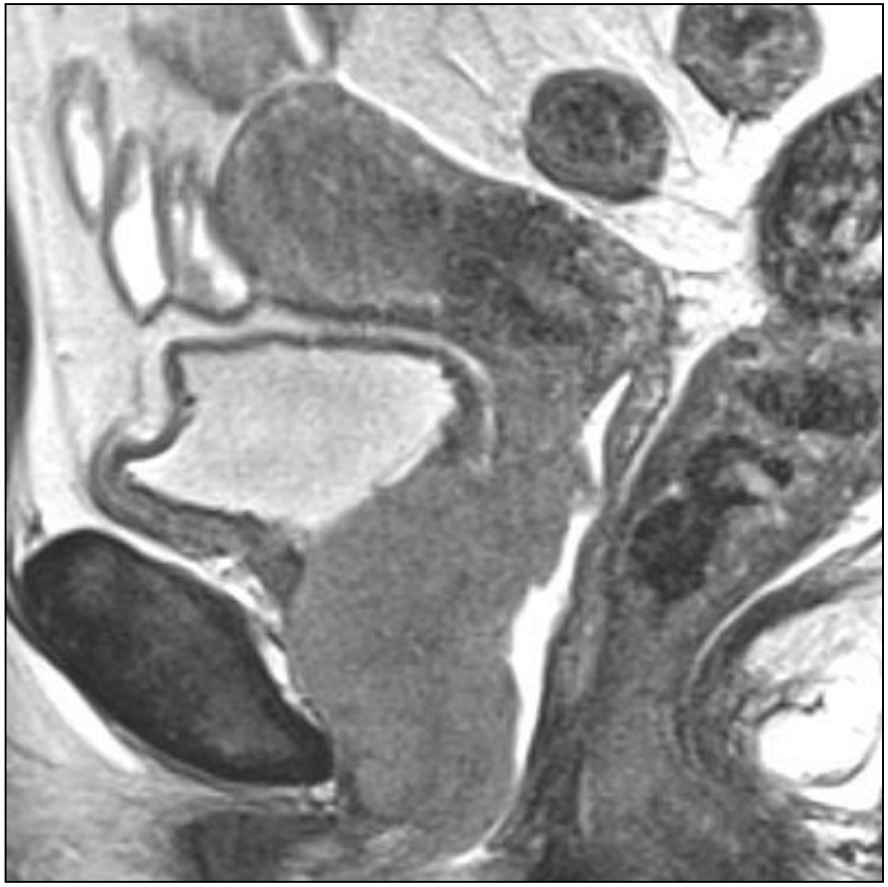




Interpretation of Diagnostic MRI

Relation of primary tumour with surrounding organs

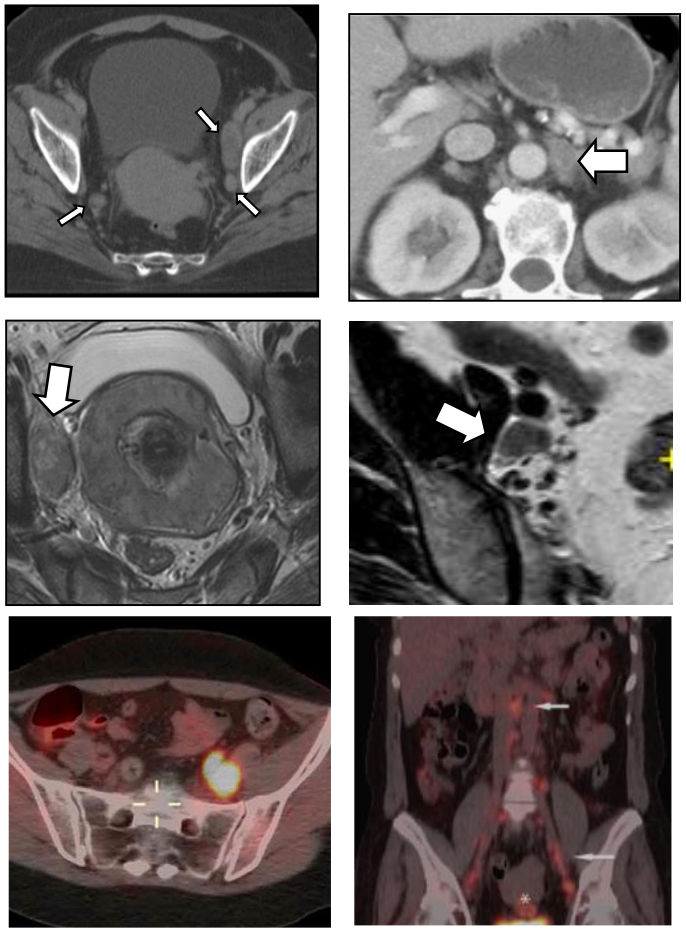
Subvesical – periurethral growth



Interpretation of Nodal Pathology

Detection of Nodal Metastases

Indirect proof, (morphological & functional characteristics)



Diagnostic Performance in Detection of Lymphadenopathy from Uterine Cancer

Modality	Sensitivity	Specificity
CT, cervical (*5,9*)	31%–57%	92%–97%
CT, endometrial (*22*)	28%–64%	78%–94%
MR imaging, cervical (*5,9*)	37%–55%	93%–94%
MR imaging, endometrial (*20,22*)	59%–72%	93%–97%
PET/CT, cervical (*7,8*)	72%–75%	96%–100%
PET/CT, endometrial (*20,21*)	74%–77%	93%–100%

Lee SI, et al. JNM 2015:56(3)

^{18}FDG PET-CT: more sensitive than either CT or MRI in locally advanced tumors

MRI: best to depict GTV-N details

Lee SI, et al. JNM 2015:56(3)
Sironi S, et l. Radiology 2006
Loft A, et al. Gynecol Oncol 2007
Selman TJ, et al. CMAJ 2008
Roh JW, et l. Eur J Cancer 2005

Lin WC, et al. Gynecol Oncol 2003
Hricak H, et al. Am J Roentgenol. 1996
Olpin J, et al. Imaging. In: Gynecol Radiat Therapy...eds. Viswanathan AN, et al.

Are size criteria (short axis <1cm) reliable?

Table 3
Comparision of the diagnostic performance of the size-based criteria and ADC-based criteria.

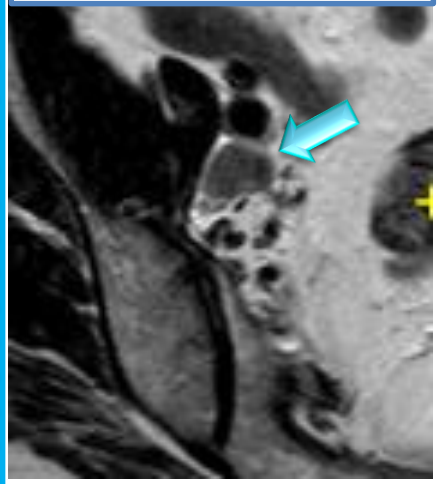
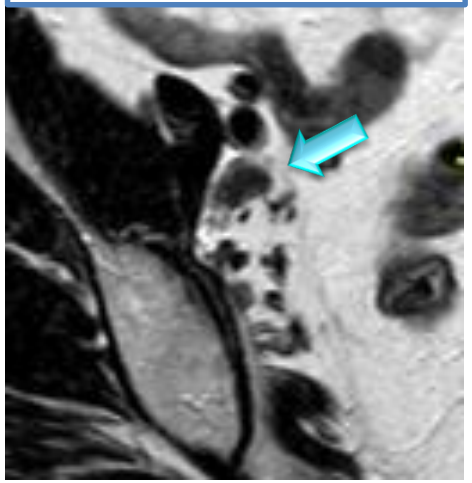
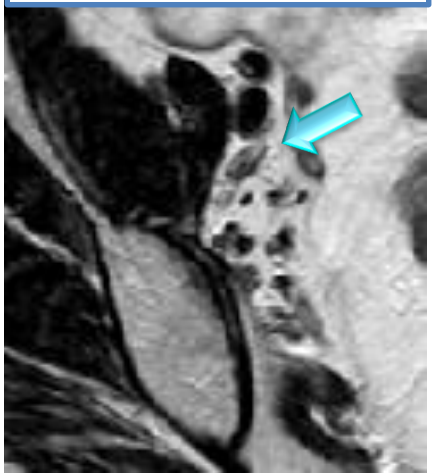
	Short-axis diameter	Long-axis diameter	Mean ADC	Minimum ADC	Mean rADC	Minimum rADC
Sensitivity(%)	76.1	93.5	91.3	95.7	84.8	93.5
Specificity(%)	85.9	66.2	91.5	96.5	91.5	90.8
PPV(%)	62.5	47.3	77.8	89.8	76.5	93.5
NPV(%)	91.0	96.9	97.0	94.9	93.2	97.7
Accuracy(%)	77.7	72.9	91.5	96.3	89.9	91.5

Normalized = relative ADC =rADC = ADC lesion /ADC reference (r gluteus maximus muscle (Liu) ; renal cortex (Park)

Liu Y. et al.,Gynecologic Oncology 122 (2011) 19–24

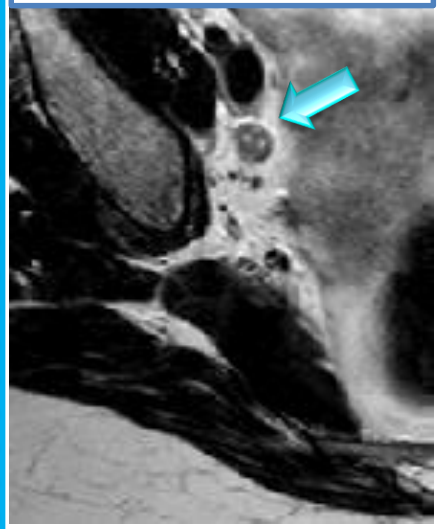
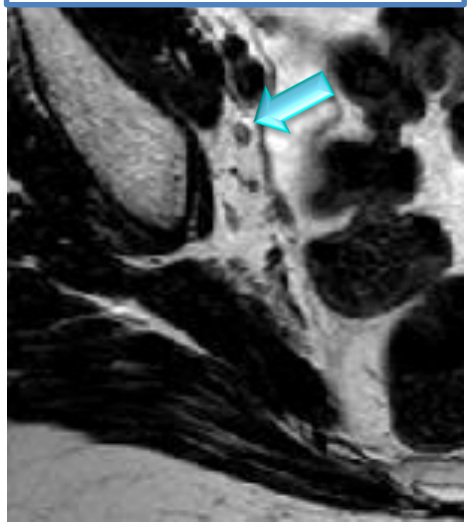
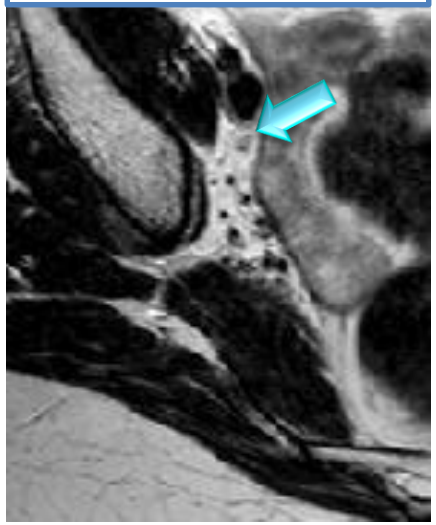
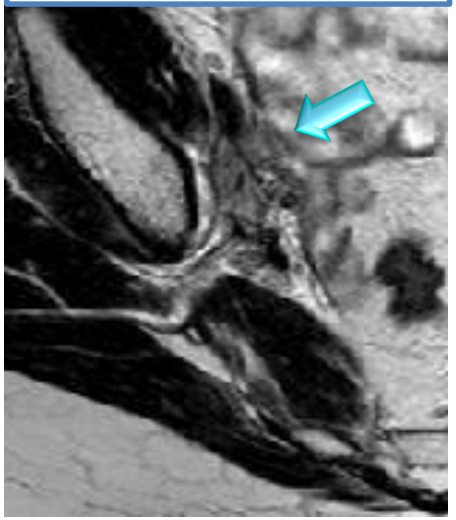
Are size criteria (short axis <1cm) reliable?

Example 1

At Diagnosis	4th Week EBRT	6 Weeks post EBRT	12 Months
			
• Short axis: 15 mm • Irregular shape • High signal (T2) • Inhomogeneous • PET positive	• Boost: 55 Gy in 25 fx • Partial response	• Further response	• No recurrence

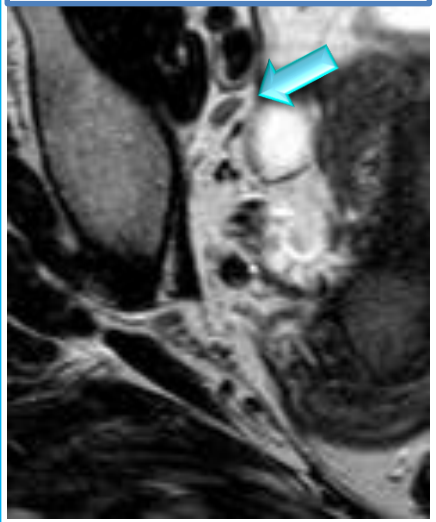
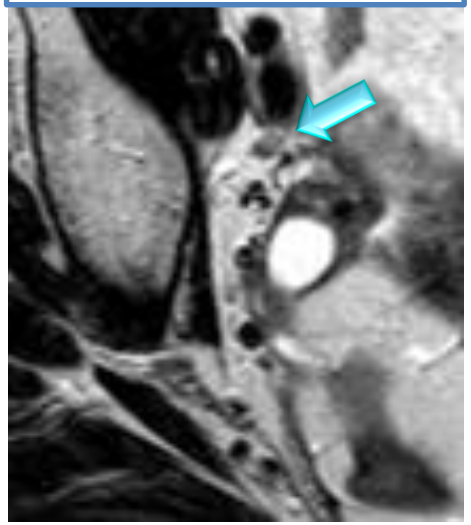
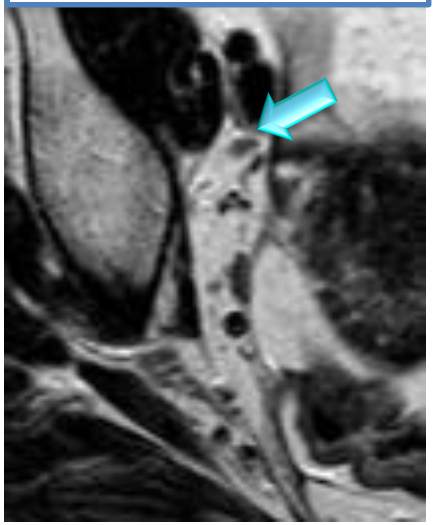
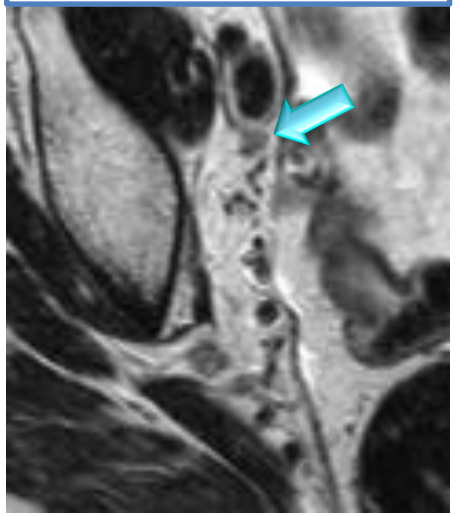
Are size criteria (short axis <1cm) reliable?

Example 2

At Diagnosis	4th Week EBRT	6 Weeks post EBRT	12 Months
			
• Short axis: 8 mm • Irregular border • High signal (T2) • Inhomogeneous • PET negative	• No Boost (45 Gy) • Near compl. resp.	• Minimal residuum	• Nodal failure

Are size criteria (short axis <1cm) reliable?

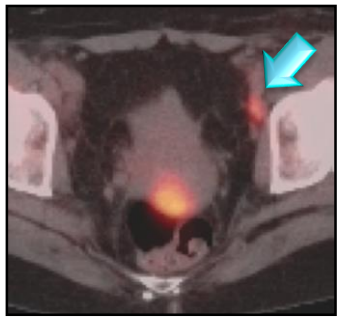
Example 3

At Diagnosis	4th Week EBRT	6 Weeks post EBRT	12 Months
			
• Short axis: 6 mm • Bean shaped • Homogeneous • Sharp border • PET negative	• No Boost (45 Gy) • No change	• No change	• No change

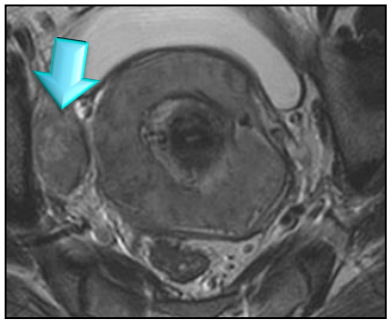
Are size criteria (short axis <1cm) reliable?

Consider N involvement when:

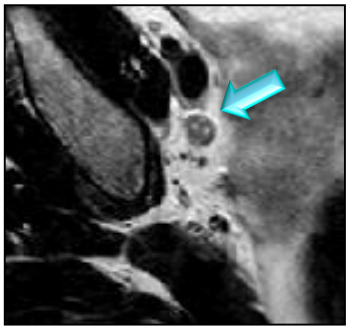
PET positive



Short axis ≥ 10 mm



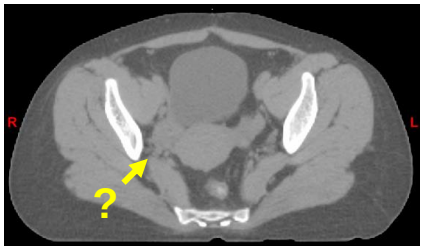
Short axis 5-10 mm And:



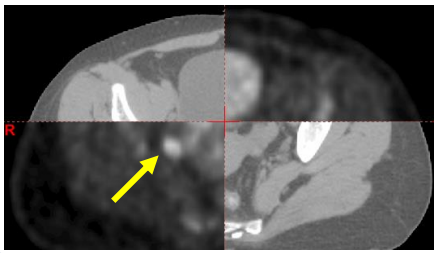
- ↑ Intensity (T2)
- ↓ Diffusion (DWI)
- Irregular border
- Lost architecture
- Round shape
- Inhomogeneous

Co-registration of modalities

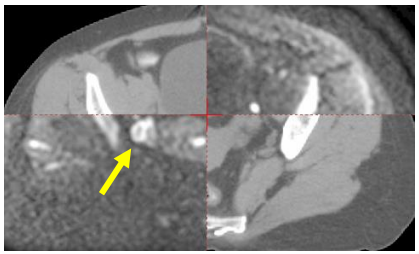
CT



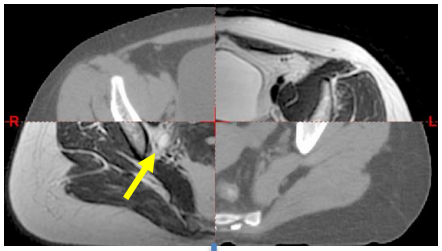
CT + PET



CT + DW MRI



CT + T2w MRI

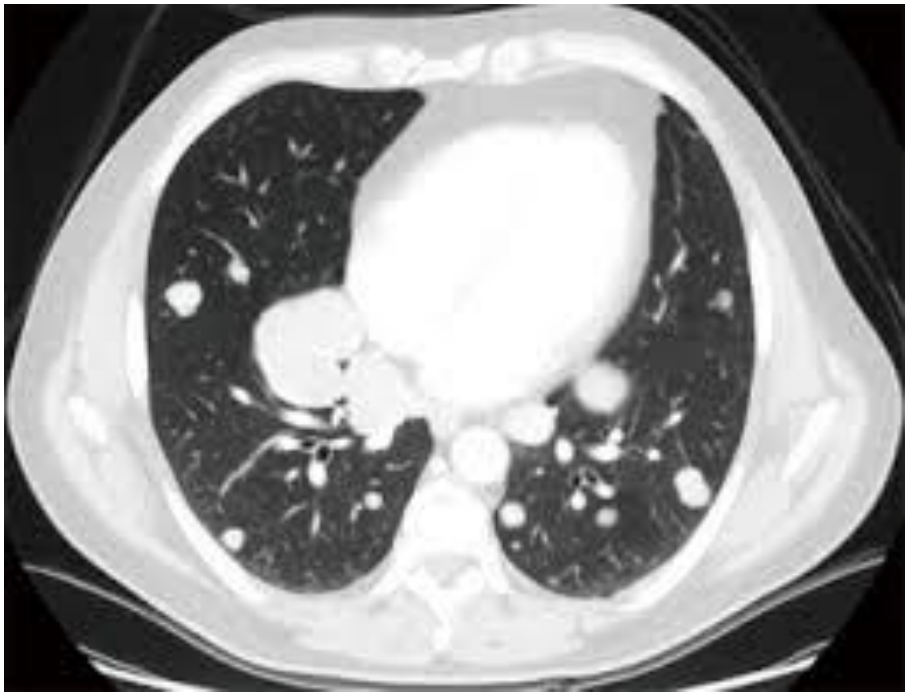


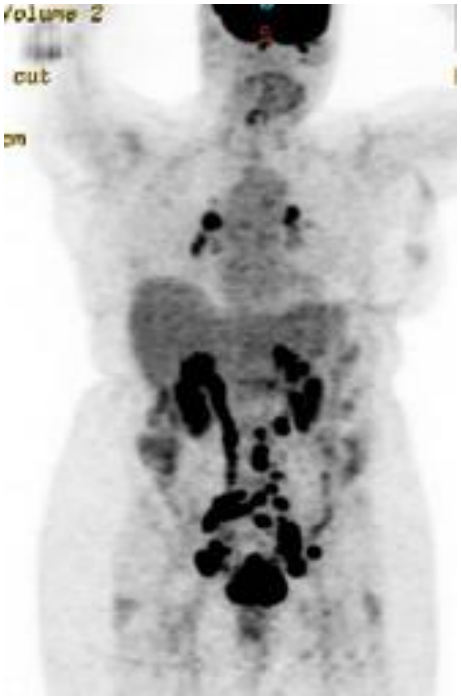
Detection

Delineation

Detection of Distant Spread

pan-CT, PET CT





3D image based pathologic anatomy at time of diagnosis

Radiation Oncologist's perspective

Primoz Petric
Peter Petrow

GTV, CTV and OAR contouring for IMRT

Li Tee Tan

ESTRO GYN teaching course
Madrid 2018

Cambridge University Hospitals NHS
NHS Foundation Trust

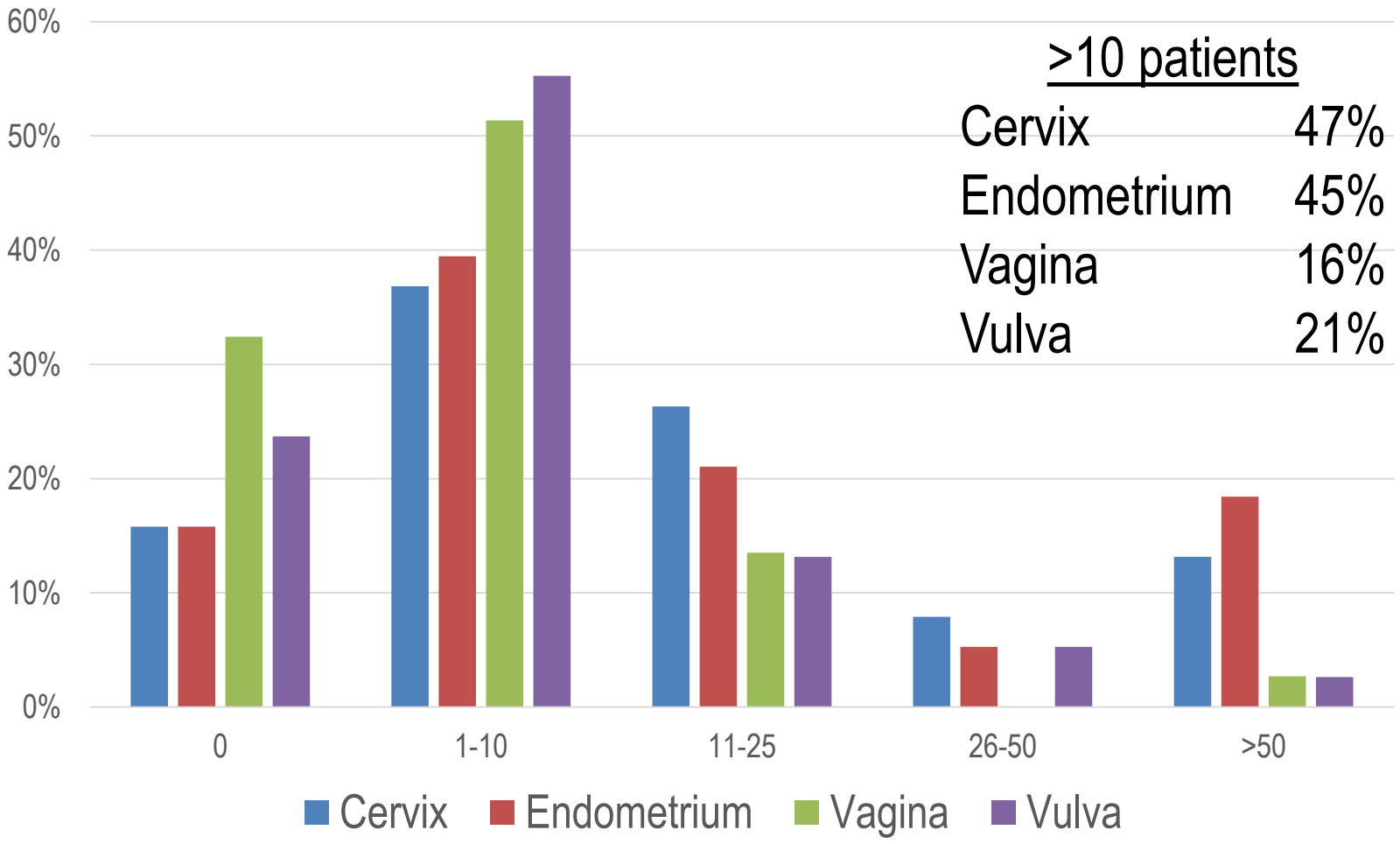
Outline

- Tumour targets
- Nodal targets
- OAR
- ITV

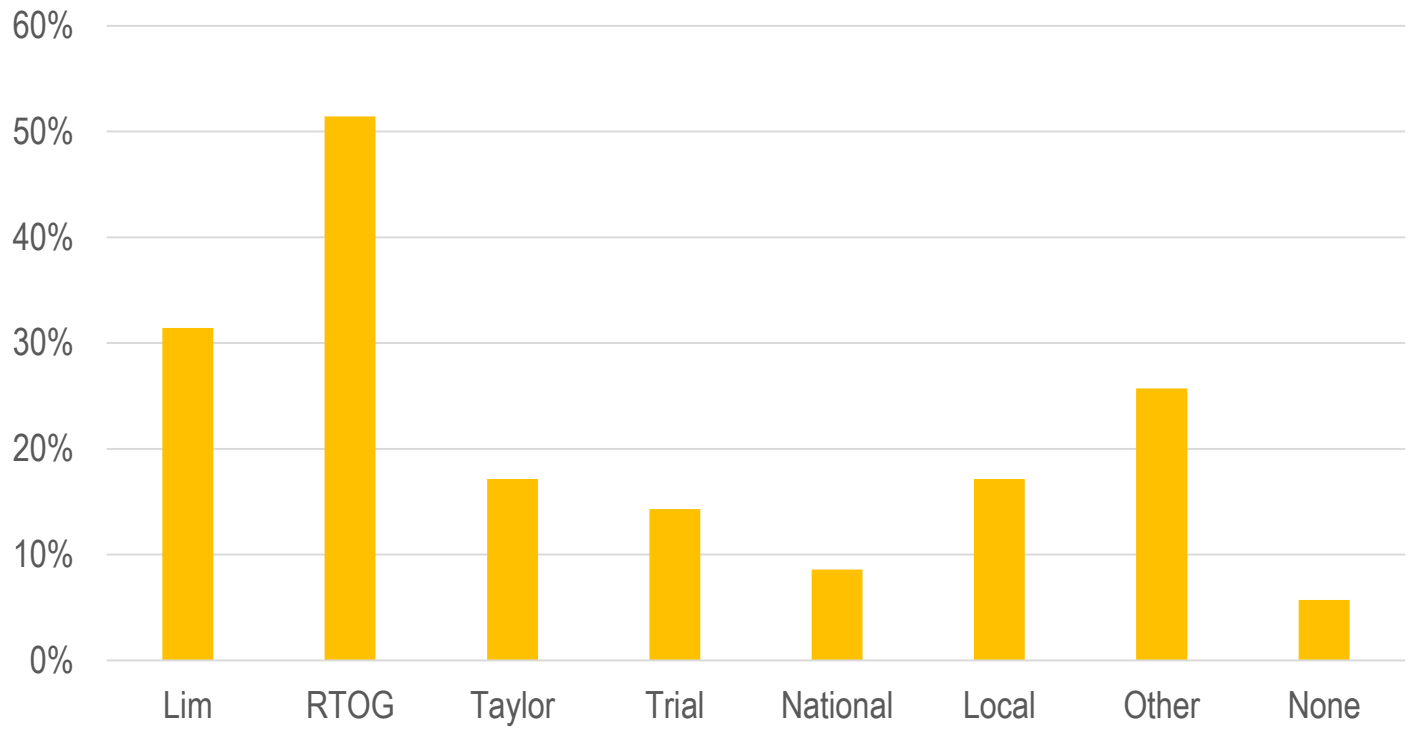
- Results of questionnaire
- Pre-contouring exercise
- Discuss common issues

Tumour targets

Experience of IMRT



Guidelines for contouring IMRT cervix



RTOG GYN = post-op

Taylor = pelvic nodes

Trial	EMBRACE	6
National	Netherlands	1
	Swedish	1
	SEOR	1

Tumour targets

- GTV
- Cervix
- Uterus
- Parametrium
- Vagina
- Margin round involved organ
- Ovaries?

Lim, IJROBP 2011; 79(2)348–355

www.embracestudy.dk

Toita, Jpn J Clin Oncol 2011;41(9)1119–1126

Tumour targets

CTV-T high risk

- GTV
- Cervix
- Uterus
- Parametrium
- Vagina
- Margin round involved organ
- Ovaries?

Lim, IJROBP 2011; 79(2)348–355

www.embracestudy.dk

Toita, Jpn J Clin Oncol 2011;41(9)1119–1126

Tumour targets

- GTV
- Cervix
- Uterus
- Parametrium
- Vagina
- Ovaries?
- Involved organ?

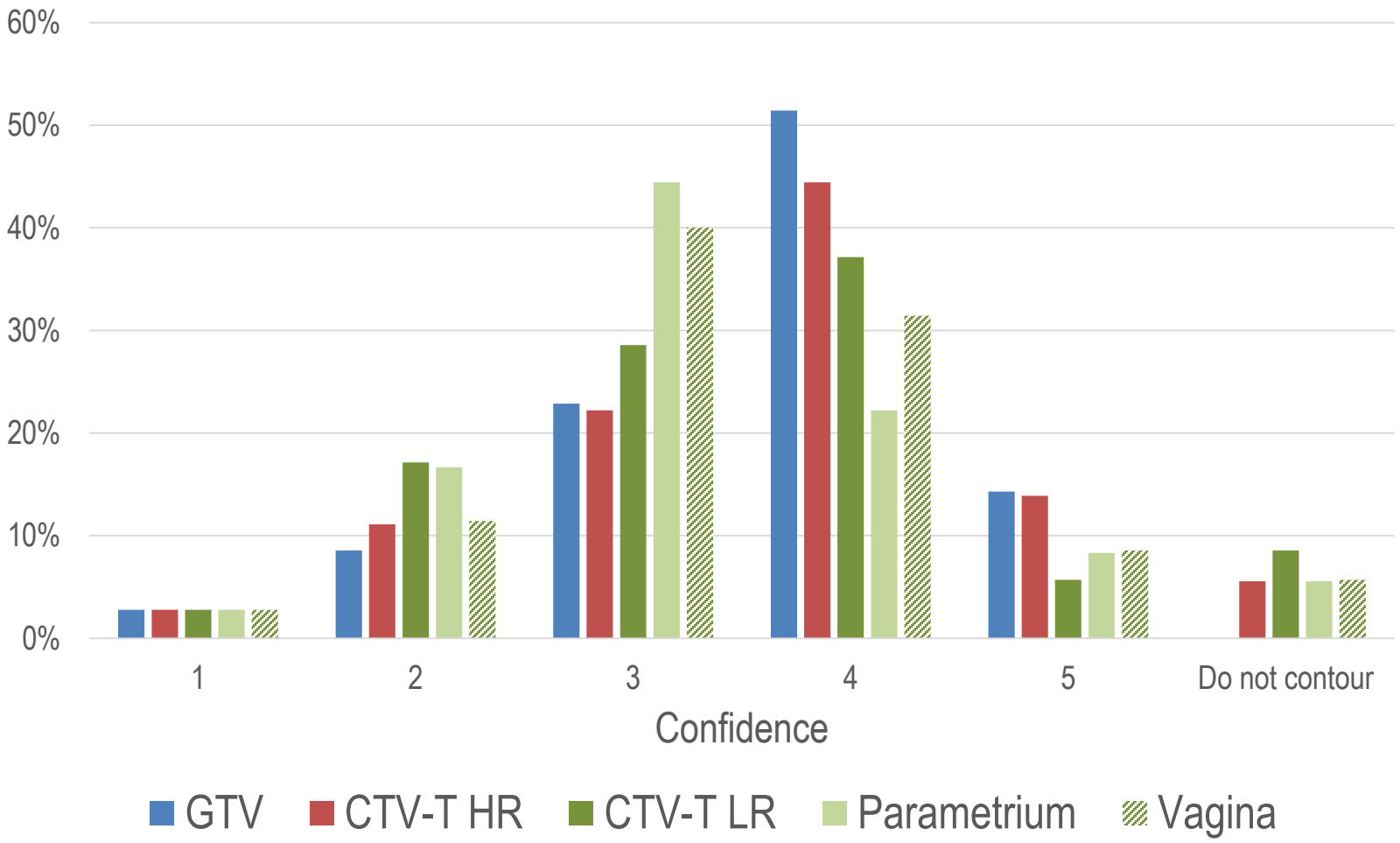
CTV-T low risk

Lim, IJROBP 2011; 79(2)348–355

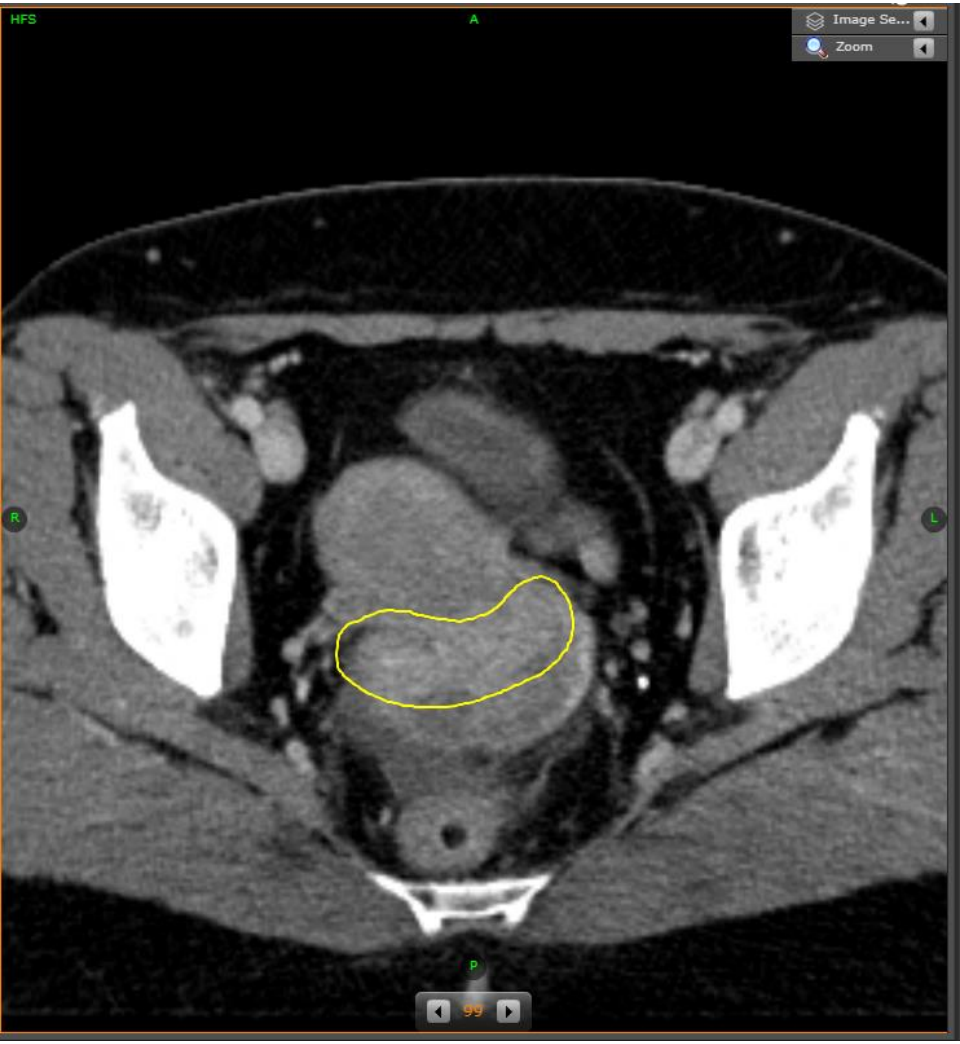
www.embracestudy.dk

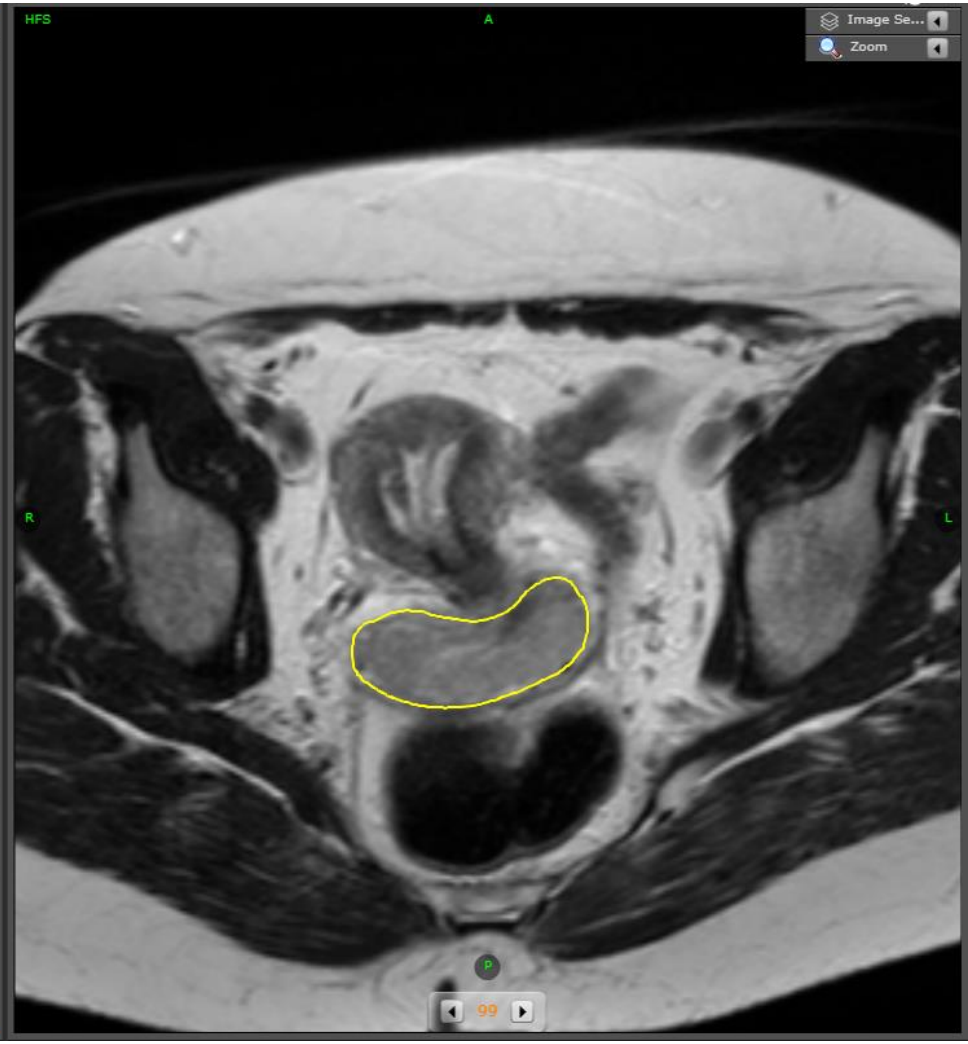
Toita, Jpn J Clin Oncol 2011;41(9)1119–1126

Tumour targets

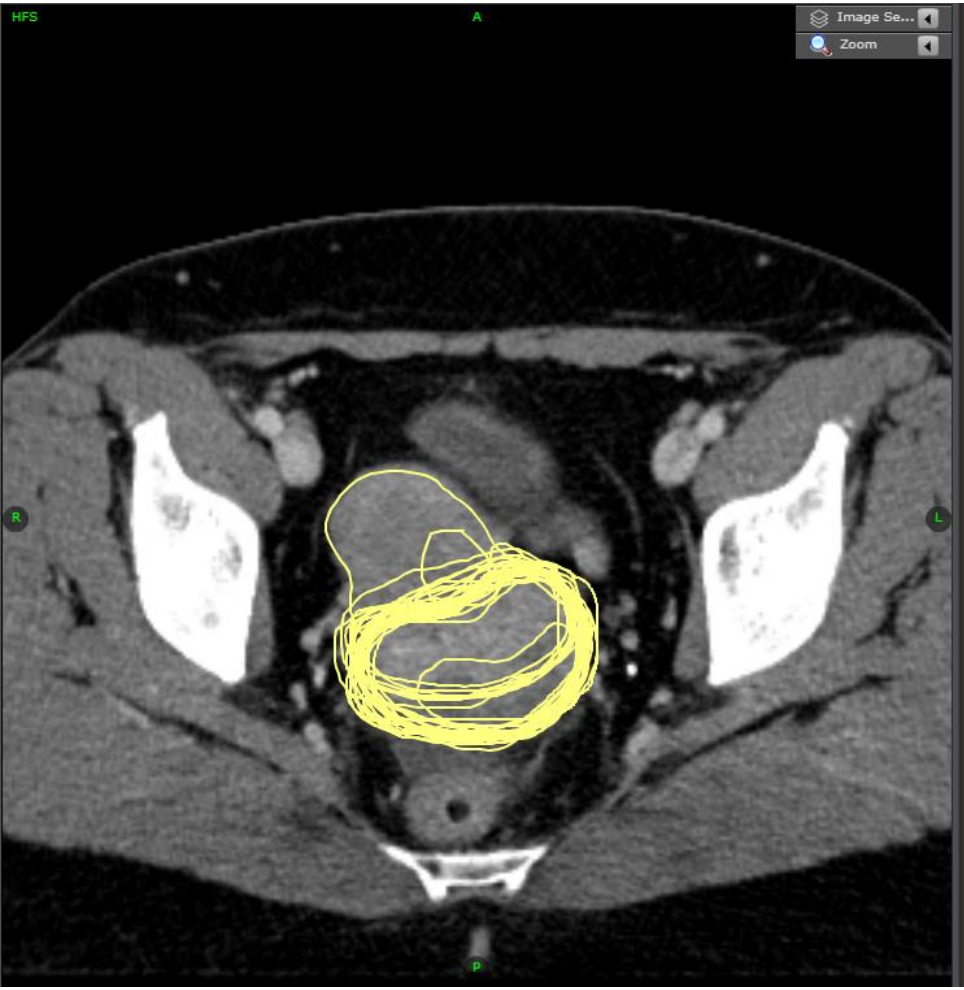


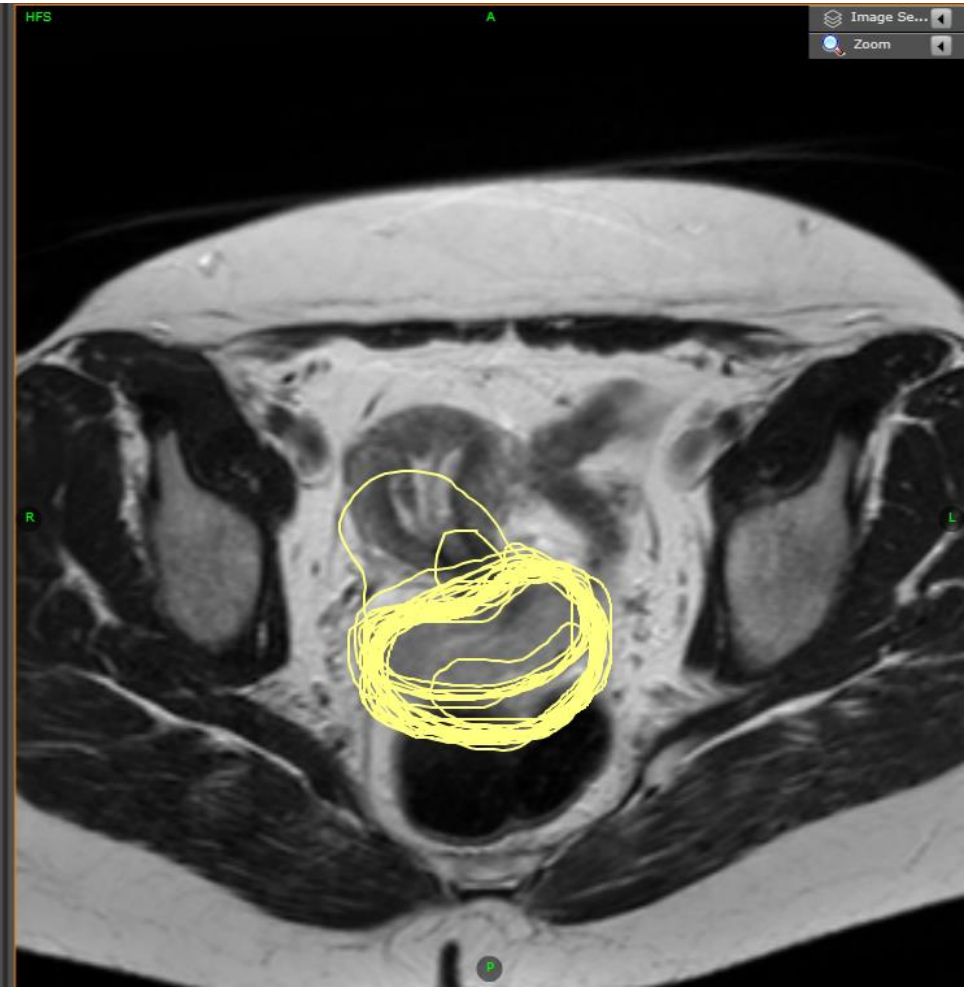
GTV-T reference





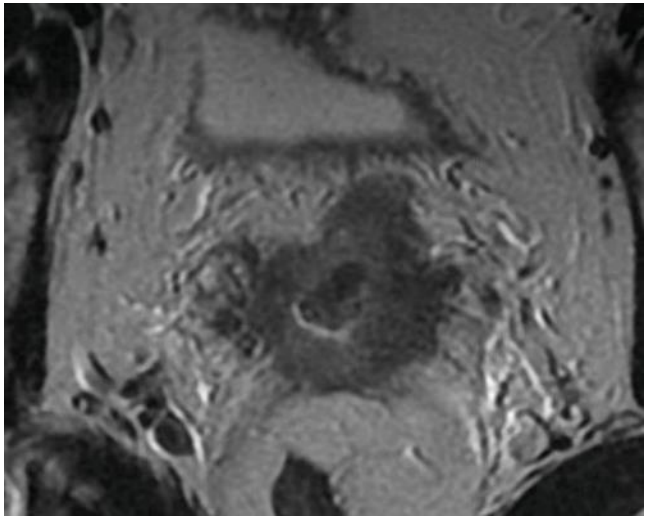
GTV-T participants

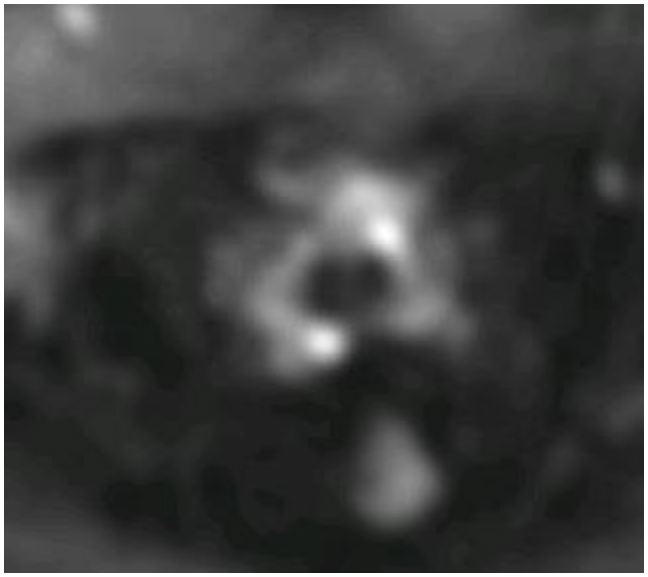


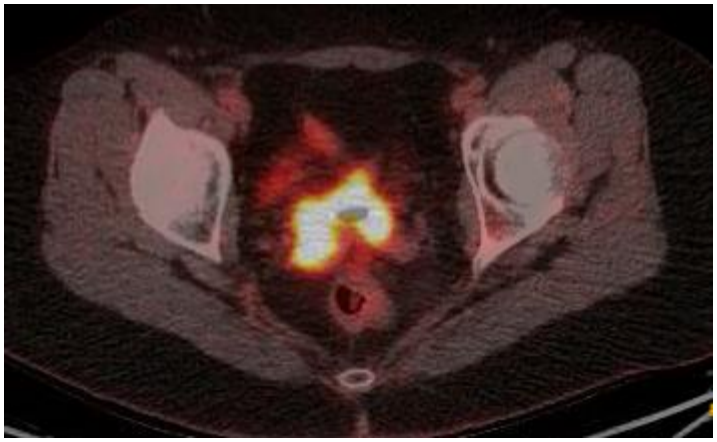


GTV-T

- Imaging
  - MRI
    - High signal on T2WI
    - DWI
    - DCE
  - PET-CT

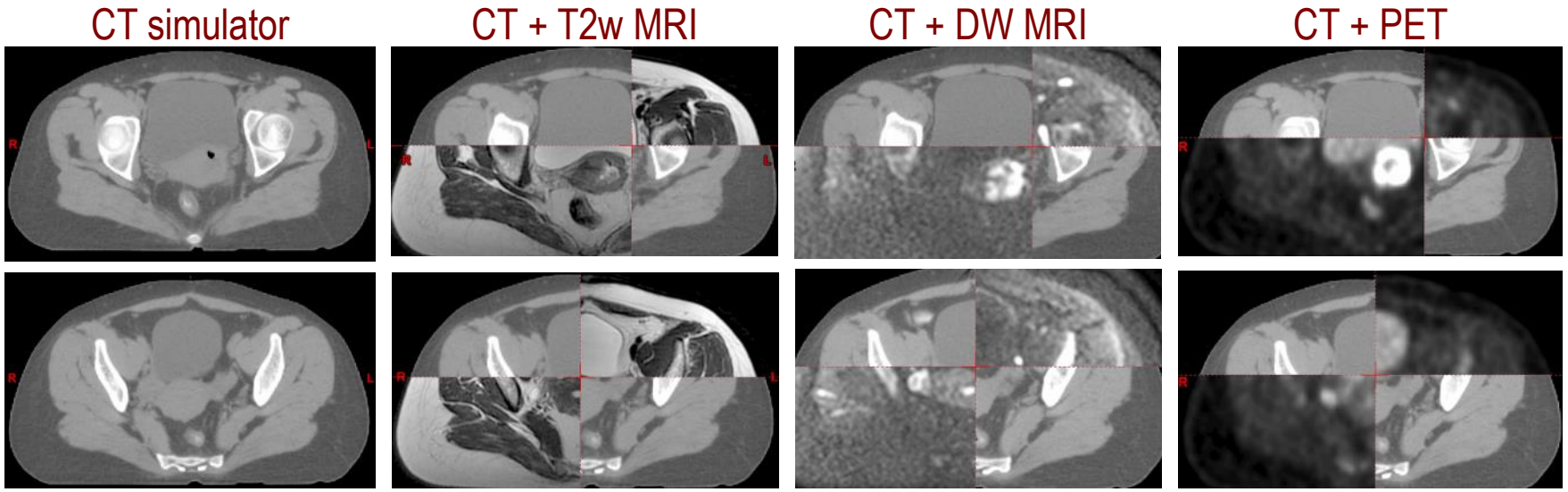






GTV-T

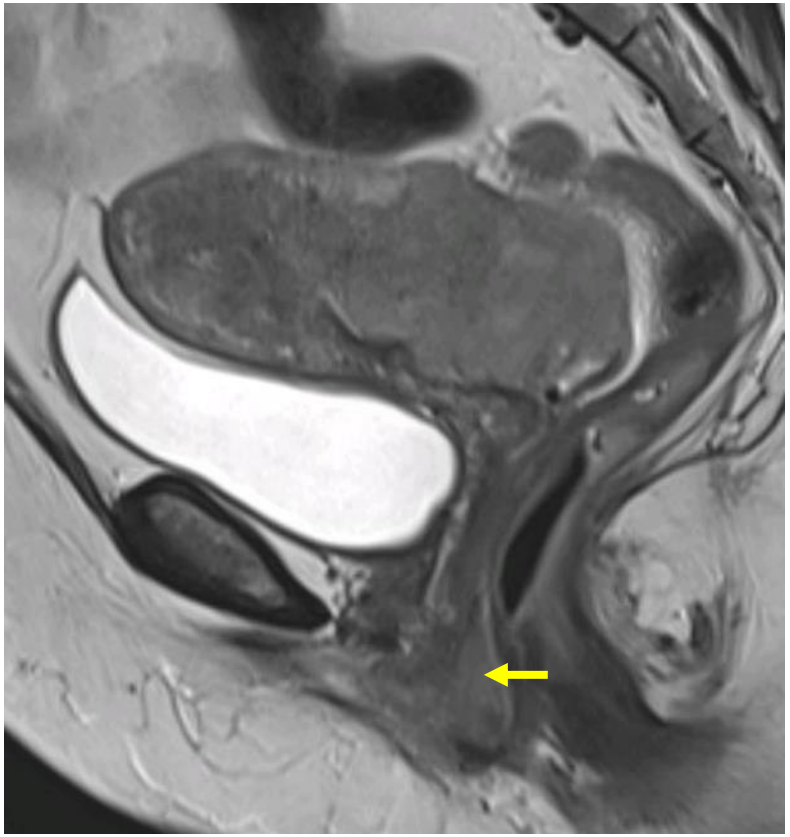
- Co-register to produce composite
  - Imaging in same (treatment) position



- EMBRACE-II – contour on MRI only

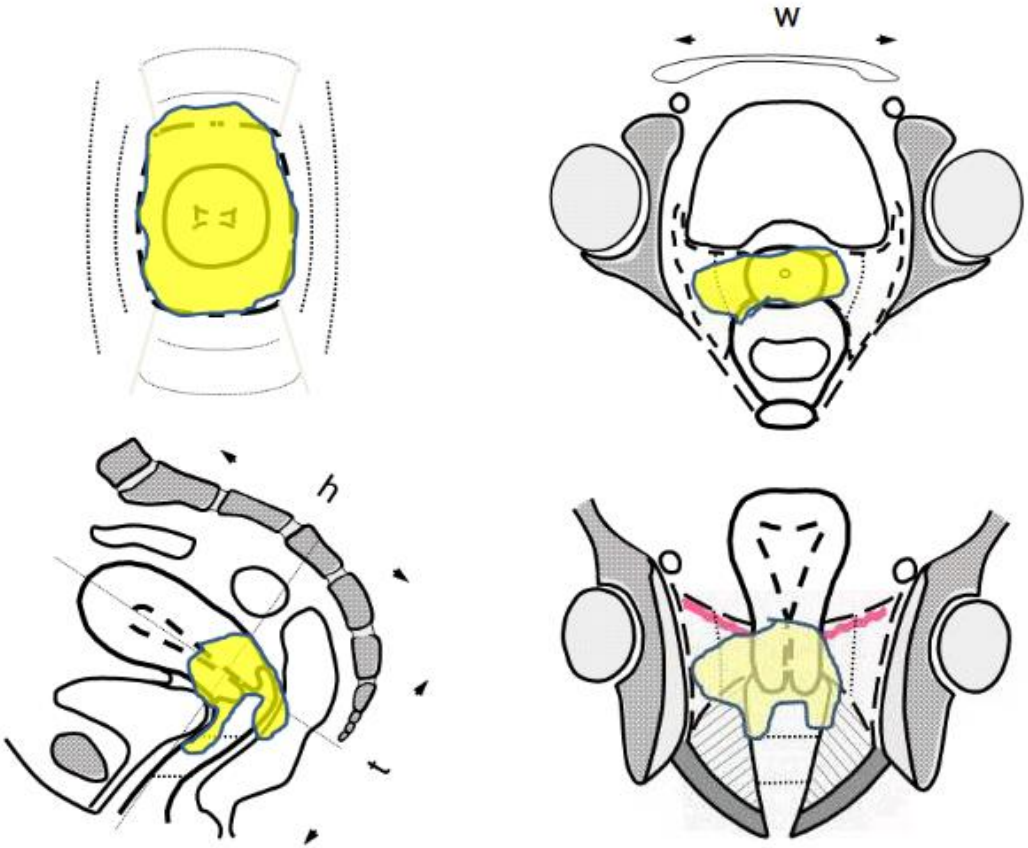
GTV-T

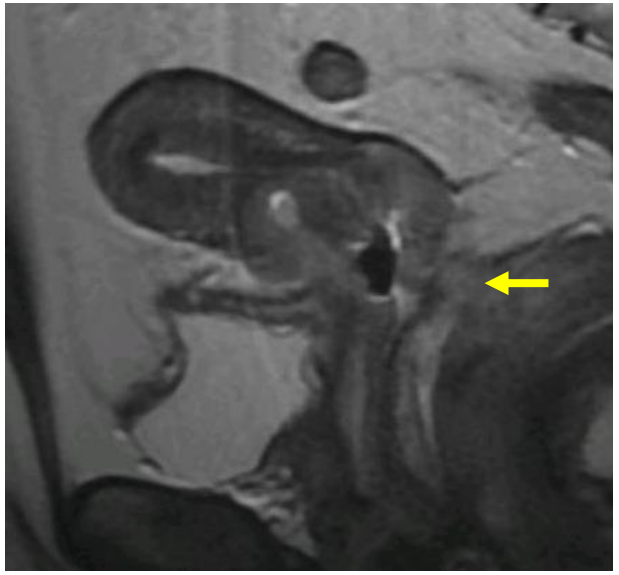
- Clinical examination
  - Vagina

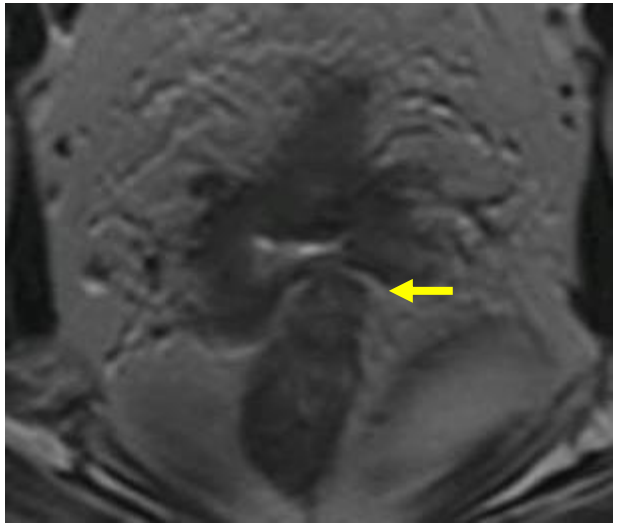


GTV-T

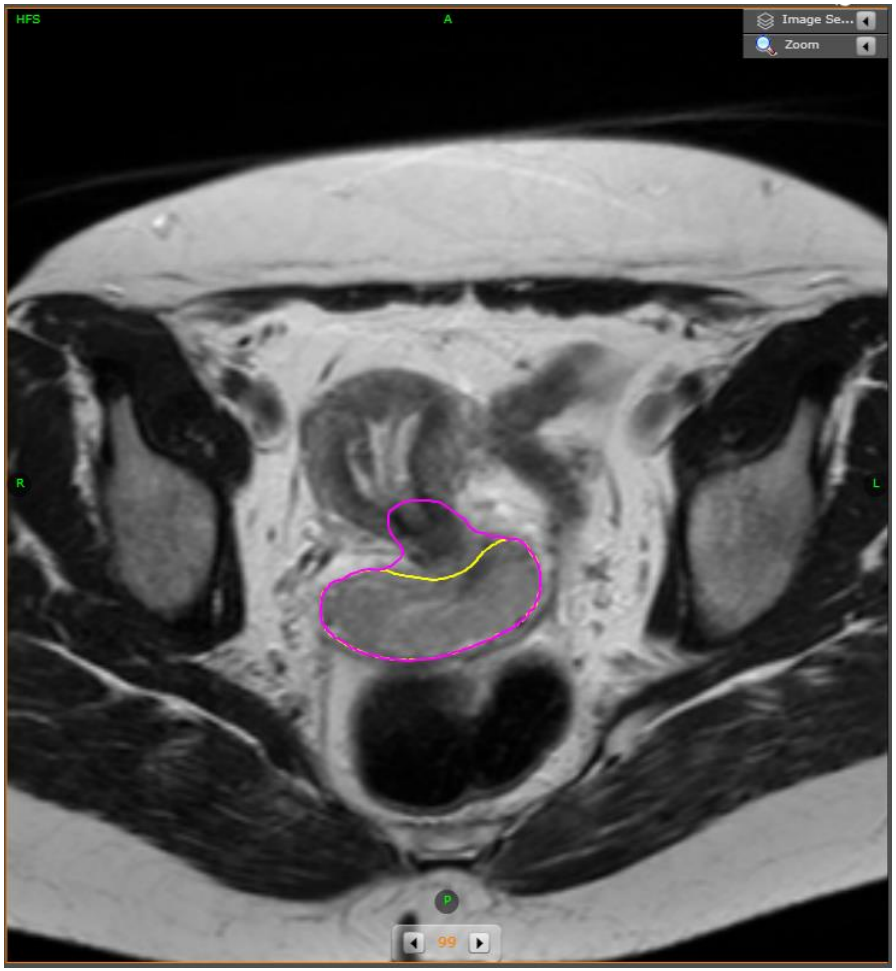
- Clinical examination
  - Parametrium





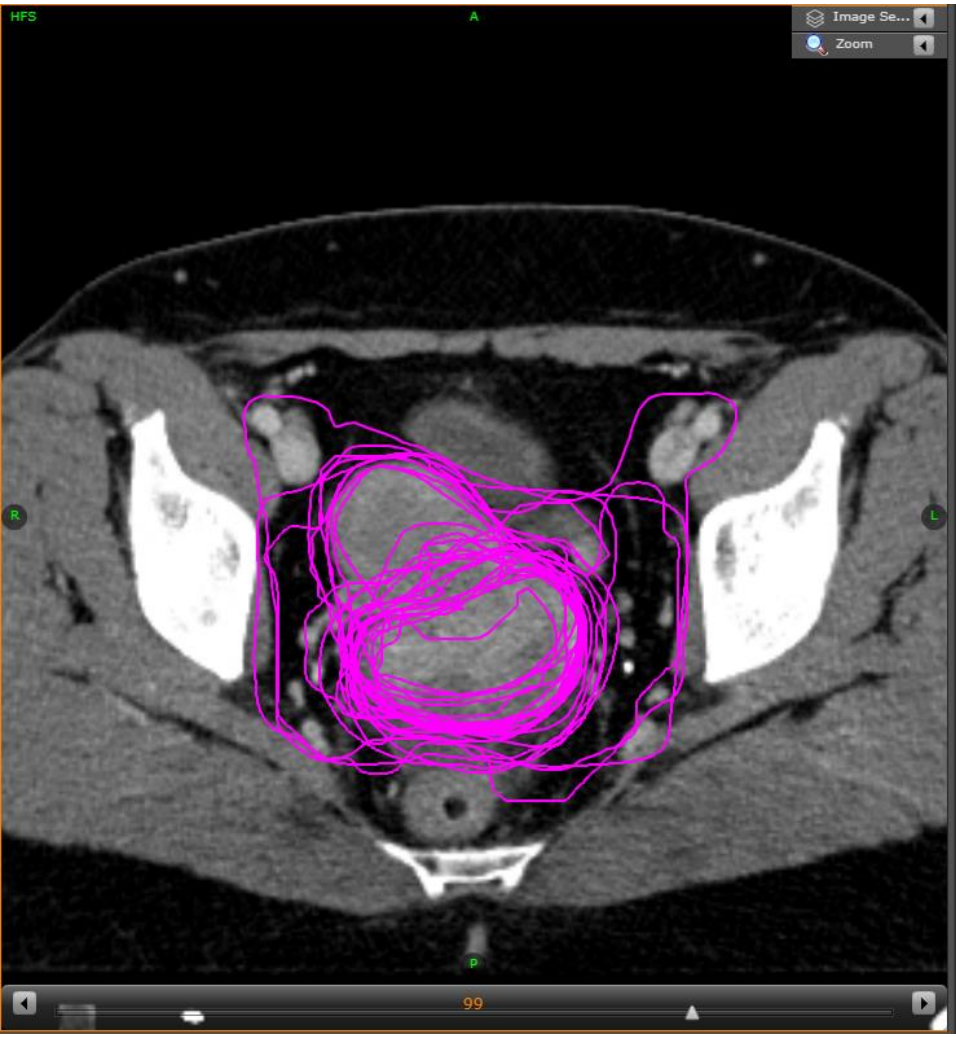


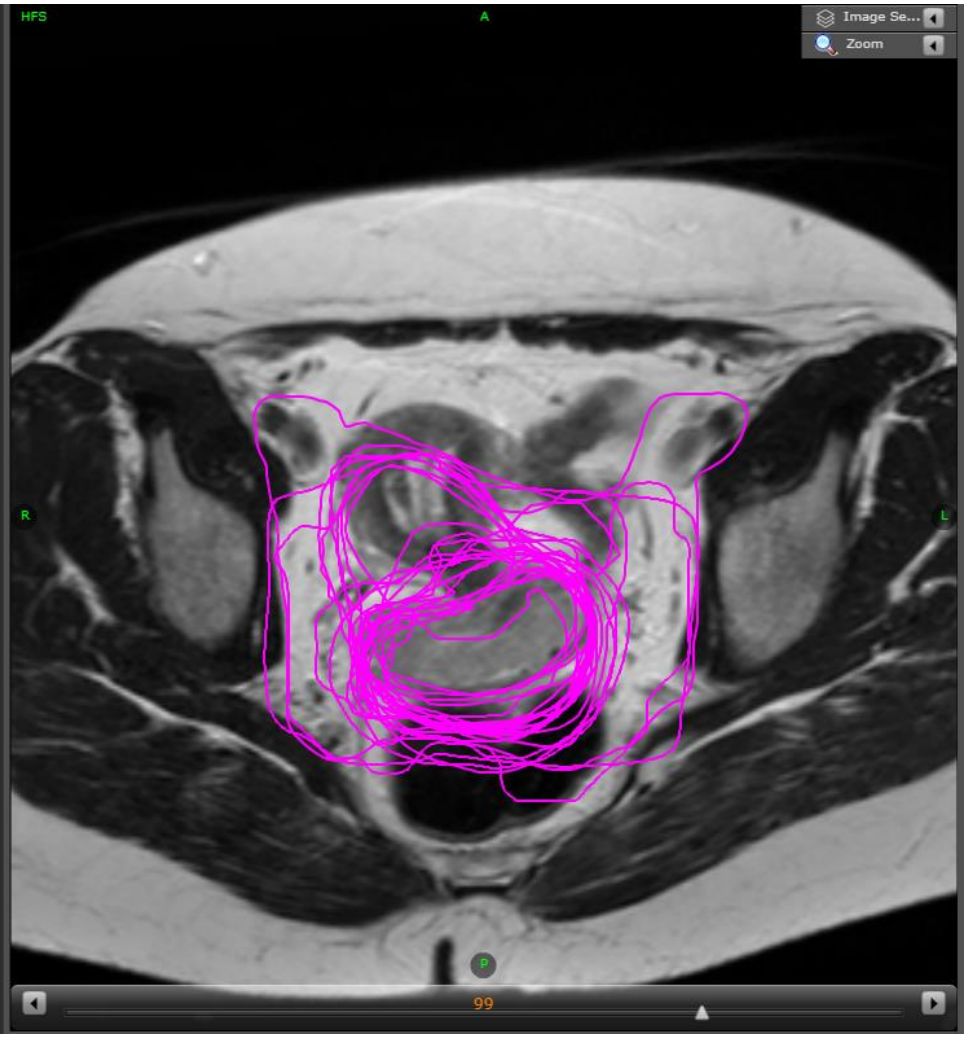
CTV-T HR reference



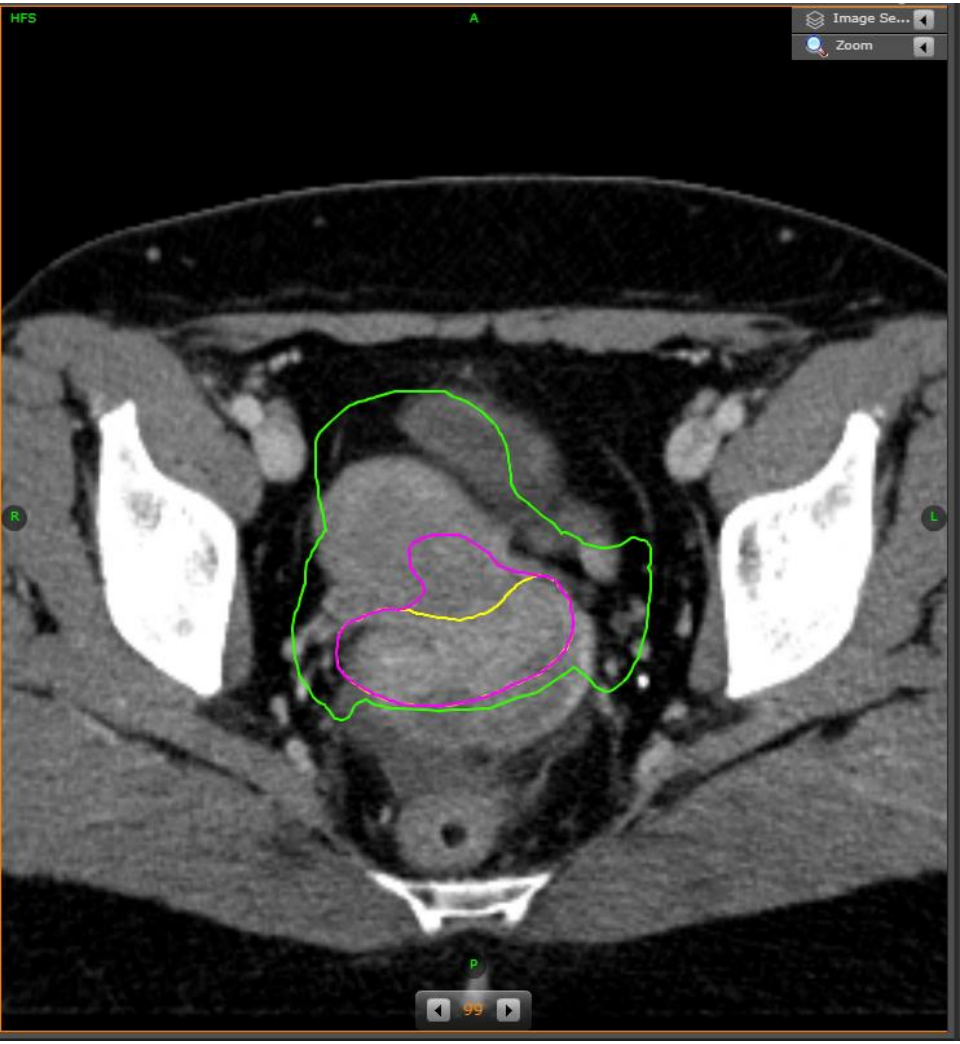
- GTV + uninvolved cervix
- For EBRT, CTV-HR ≈ GTV on MRI

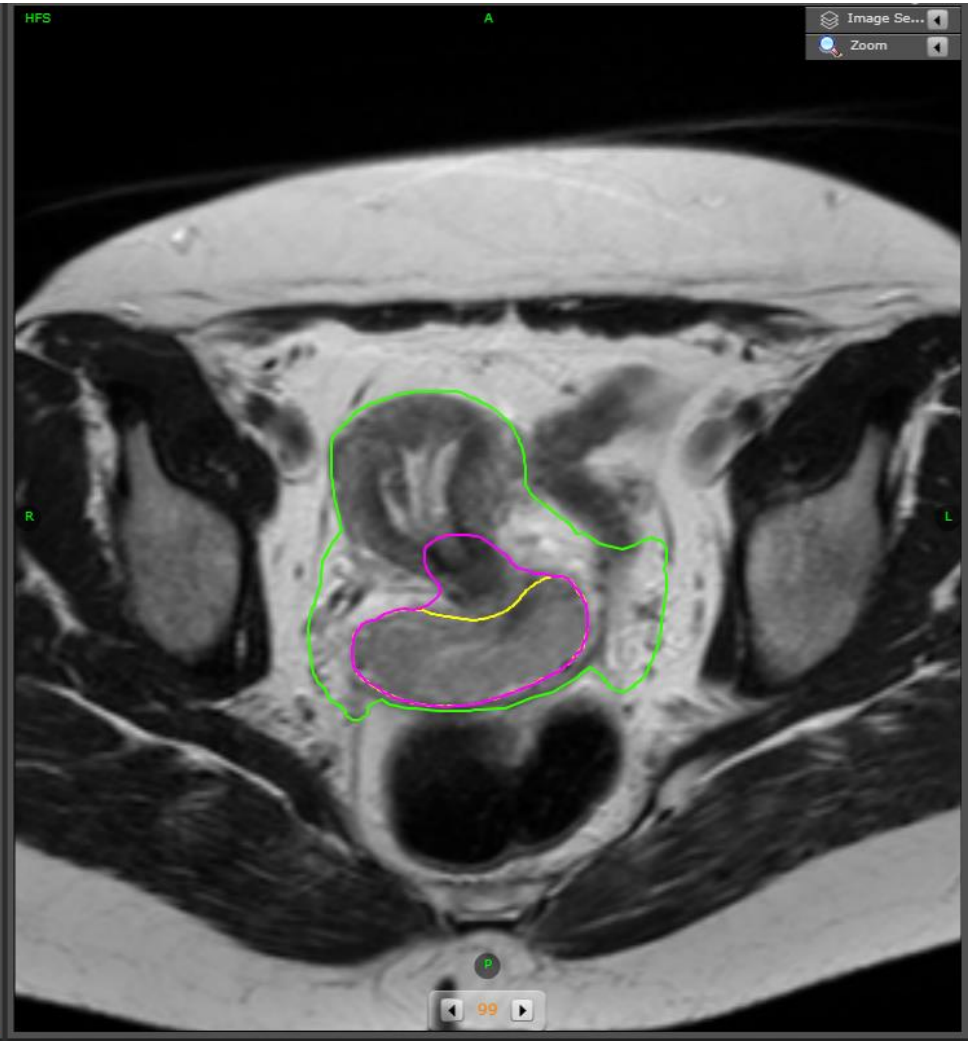
CTV-T HR participants





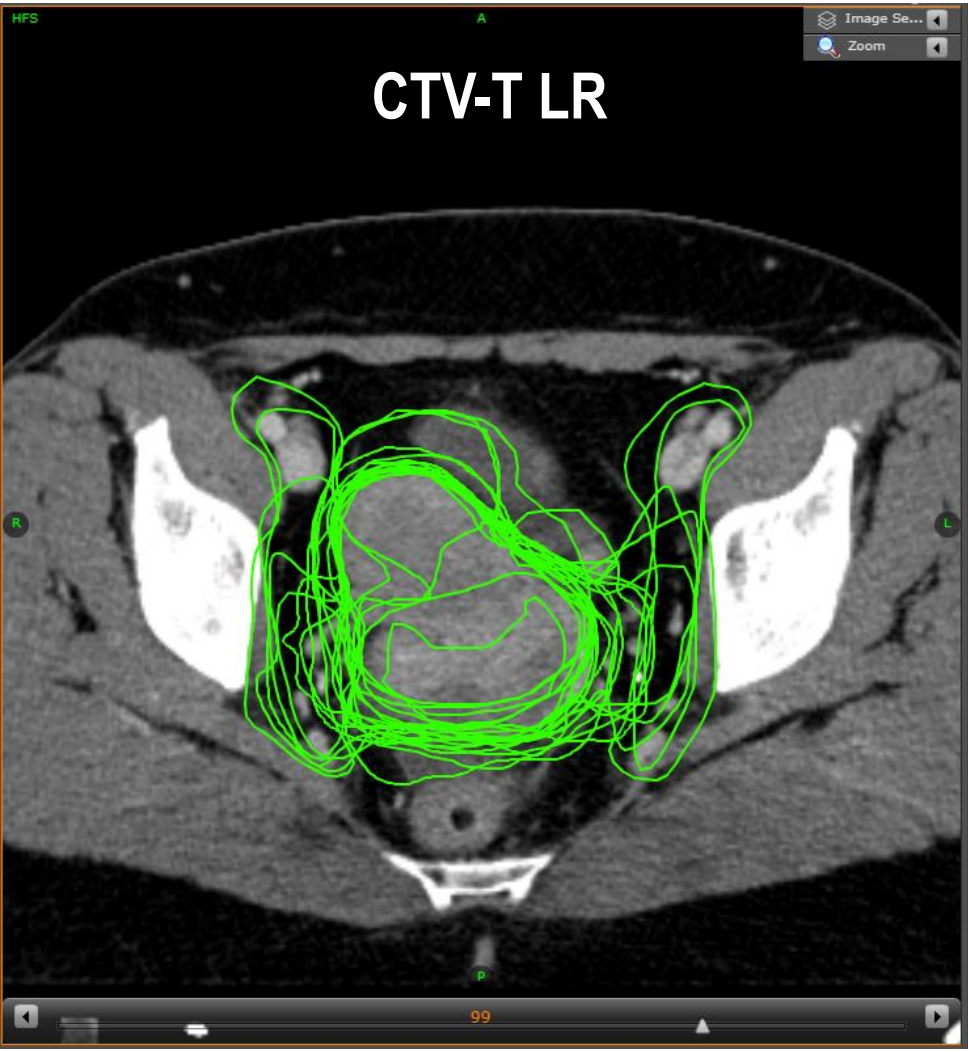
CTV-T LR reference

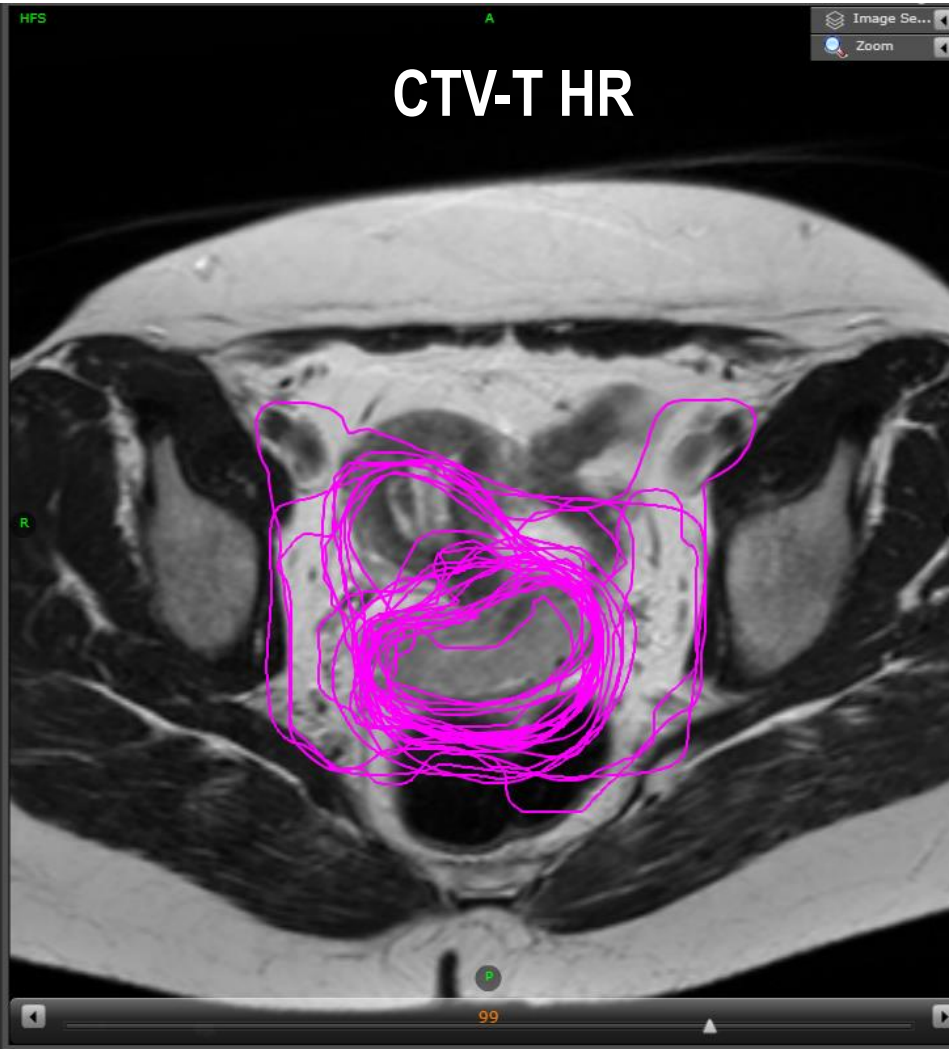




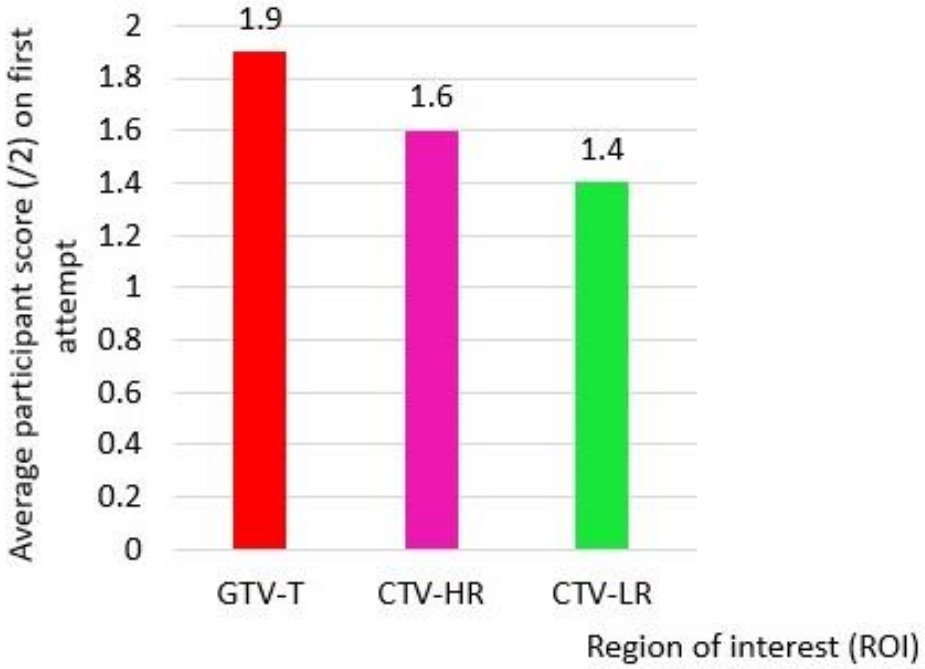
- Contour on MRI or CT

CTV-T LR participants





EMBRACE-II accreditation

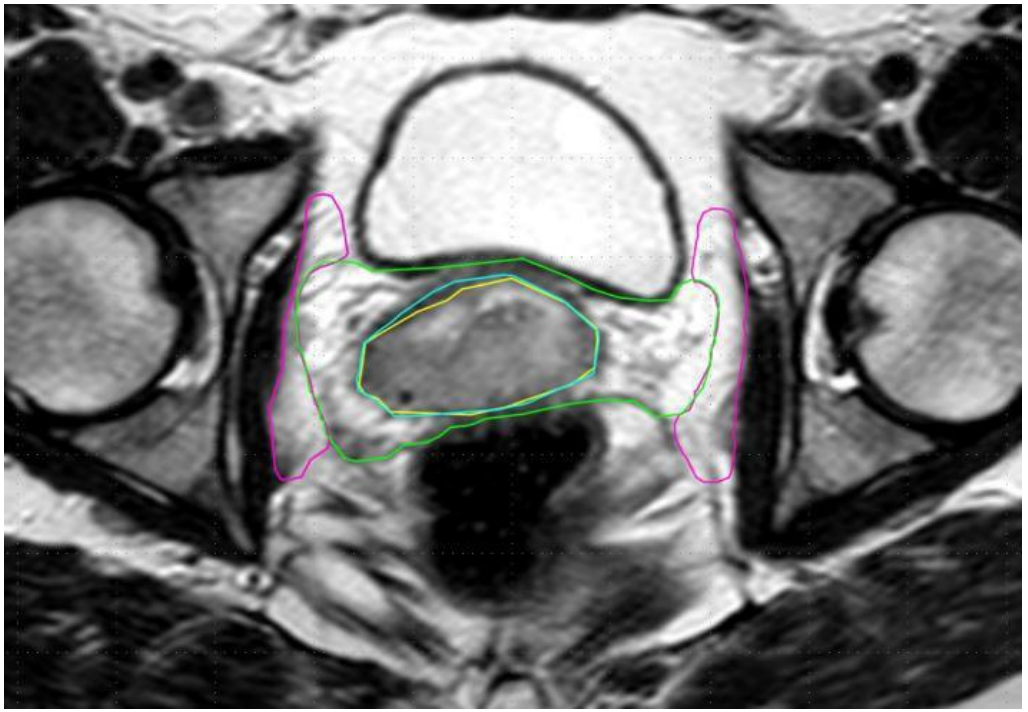


- GTV-T : Gross tumour volume
- CTV-HR : Gross tumour including whole cervix
- CTV-LR : Composed of CTV-HR + parametria, vagina & uterus
- CTV-N : CTV for involved lymph nodes
- CTV-E : Elective lymph node CTV
- ITV45 : CTV-LR + CTV-E + internal margins to compensate for internal motion

Courtesy of Simon Duke

Parametrium - borders

	GYN IMRT consortium	Japanese consortium
Anterior	Posterior wall of bladder or posterior border of external iliac vessel	Posterior boarder of bladder or posterior boarder of external iliac vessels

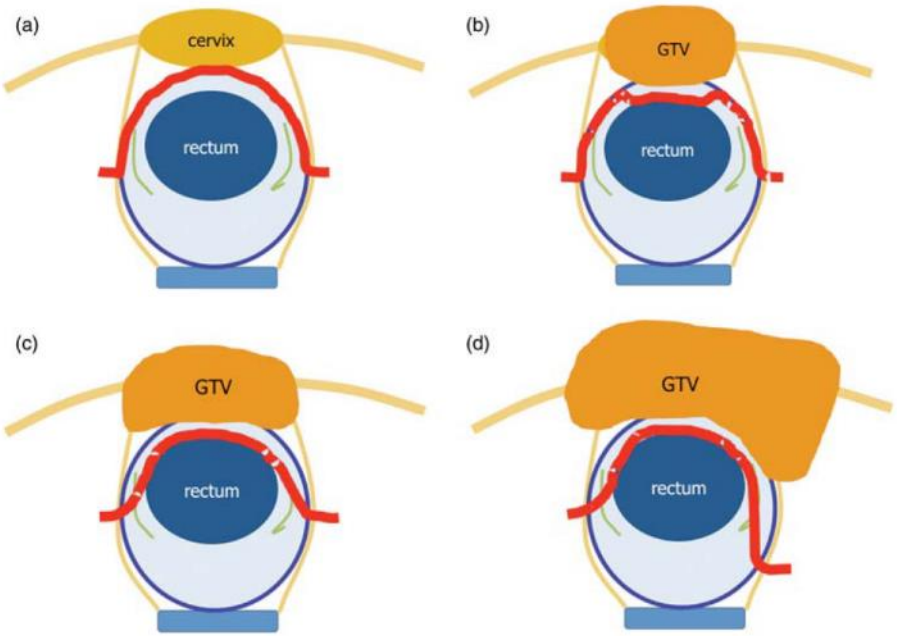


Lim, IJROBP 2011; 79(2)348–355

Toita, Jpn J Clin Oncol 2011;41(9)1119–1126

Parametrium - borders

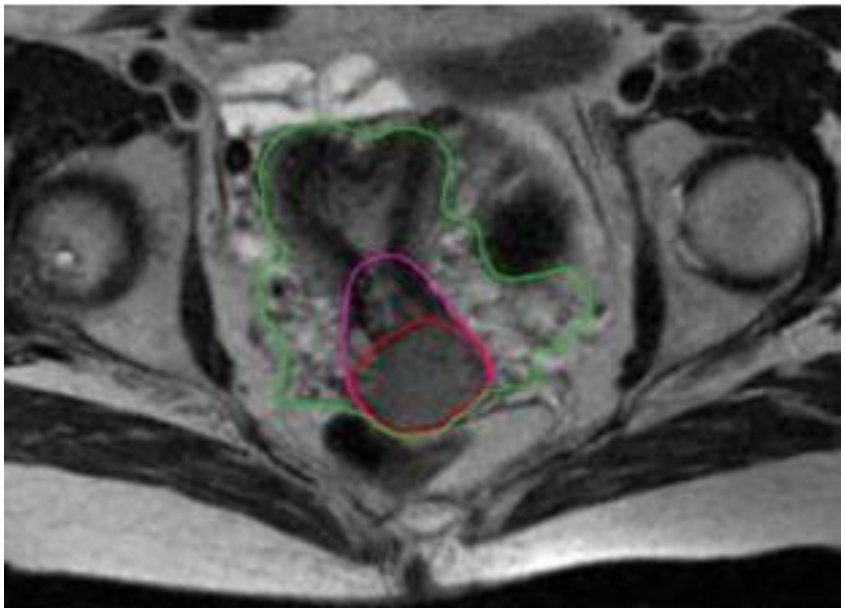
	GYN IMRT consortium	Japanese consortium
Posterior	Uterosacral ligaments and mesorectal fascia	Anterior part (semicircular) of mesorectal fascia *In case with bulky central tumor or significant parametrial invasion, some modification would be considered (Figs 3 and 4)

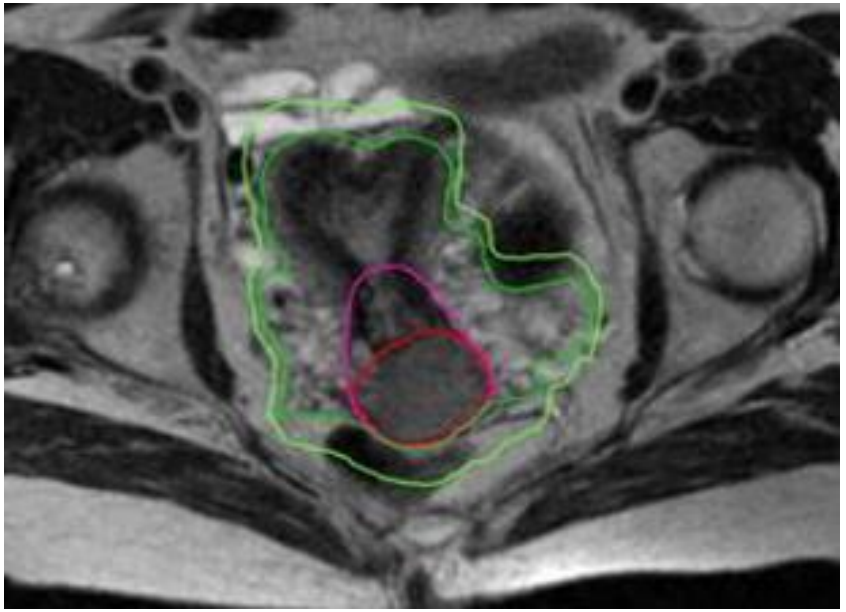


Lim, IJROBP 2011; 79(2)348–355

Toita, Jpn J Clin Oncol 2011;41(9)1119–1126

EMBRACE-II





Parametrium - borders

	GYN IMRT consortium	Japanese consortium
Superior	Top of fallopian tube/ broad ligament. Depending on degree of uterus flexion, this may also form the anterior boundary of parametrial tissue.	Isthmus of uterus (= level where uterine artery drains into) *Contouring would stop at the level where bowel loops are seen

Uterine Cervix

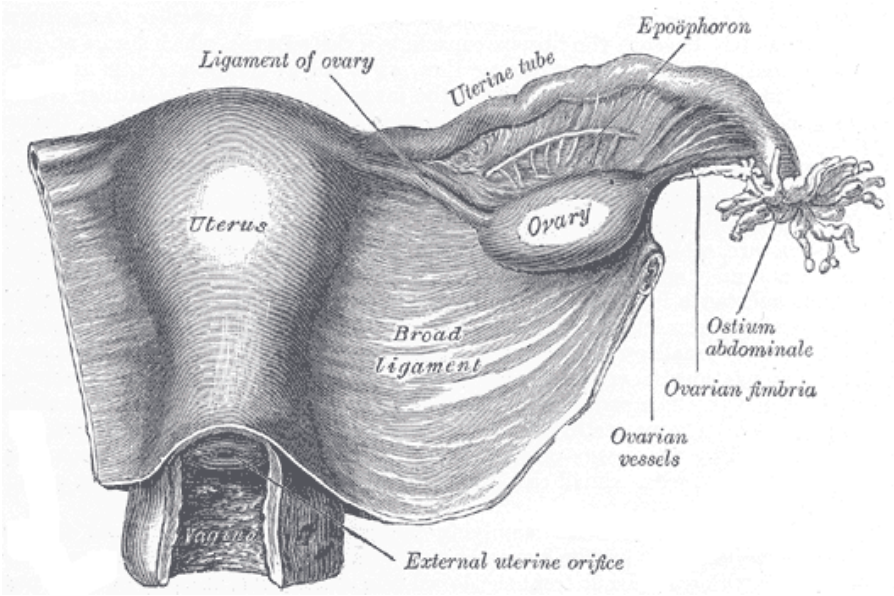
The entire cervix, if not already included within the GTV contour, is to be contoured (13). The cranial margin is defined at the level at which the uterine arteries enter the uterus (same level of the superior border of the parametrium CTV).

The broad ligaments, round ligaments and ovarian ligaments do not need to be included.

Toita, Jpn J Clin Oncol 2011;41(9)1119–1126

Parametrium - definition

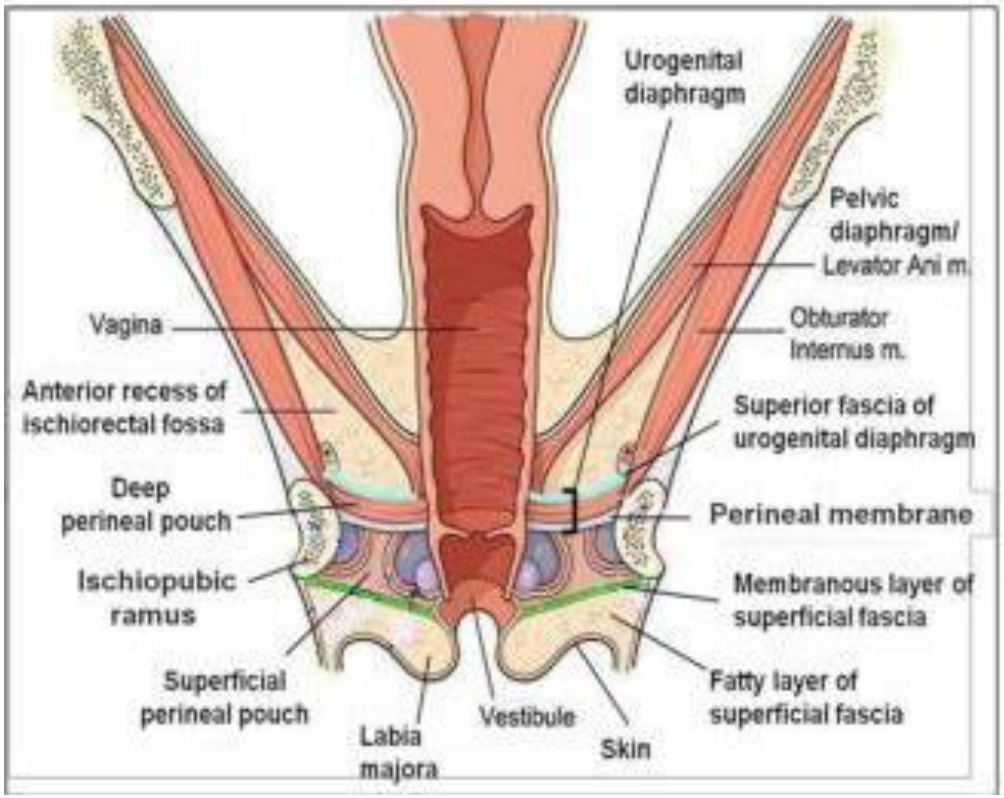
- The parametrium is a band of fibrous tissue that separates the supravaginal portion of the cervix from the bladder. It extends on to its sides and laterally between the layers of the broad ligaments.



https://radiopaedia.org/articles/parametrium

Parametrium - borders

	GYN IMRT consortium	Japanese consortium
Inferior	Urogenital diaphragm	Medial boarder of levator ani

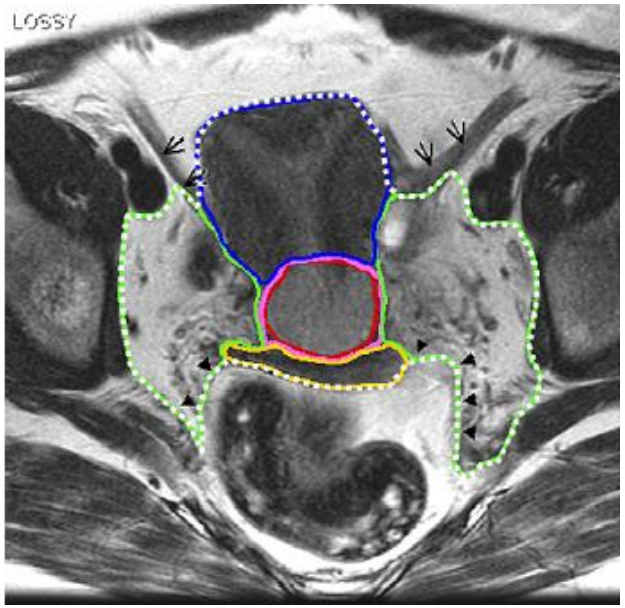


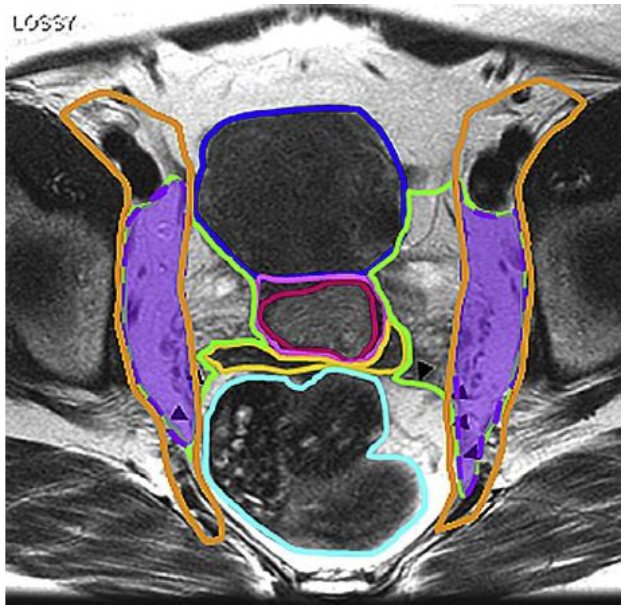
Lim, IJROBP 2011; 79(2)348–355

Toita, Jpn J Clin Oncol 2011;41(9)1119–1126

Parametrium - borders

	GYN IMRT consortium	Japanese consortium
Lateral	Medial edge of internal obturator muscle/ ischial ramus bilaterally	Medial edge of internal obturator muscle, piriformis muscle, coccygeus muscle and ischial ramus





Lim, IJROBP 2011; 79(2)348–355

Toita, Jpn J Clin Oncol 2011;41(9)1119–1126

Parametrium - borders

	GYN IMRT consortium	EMBRACE-II
Anterior	Posterior wall of bladder or posterior border of external iliac vessel	Posterior wall of bladder or posterior border of external iliac vessel
Posterior	Uterosacral ligaments and mesorectal fascia	Uterosacral ligaments and mesorectal fascia
Superior	Top of fallopian tube/ broad ligament. Depending on degree of uterus flexion, this may also form the anterior boundary of parametrial tissue.	Top of fallopian tube/ broad ligament. Depending on degree of uterus flexion, this may also form the anterior boundary of parametrial tissue.
Inferior	Urogenital diaphragm	Urogenital diaphragm
Lateral	Medial edge of internal obturator muscle/ ischial ramus bilaterally	Medial edge of internal iliac and obturator vessels

Lim, IJROBP 2011; 79(2)348–355

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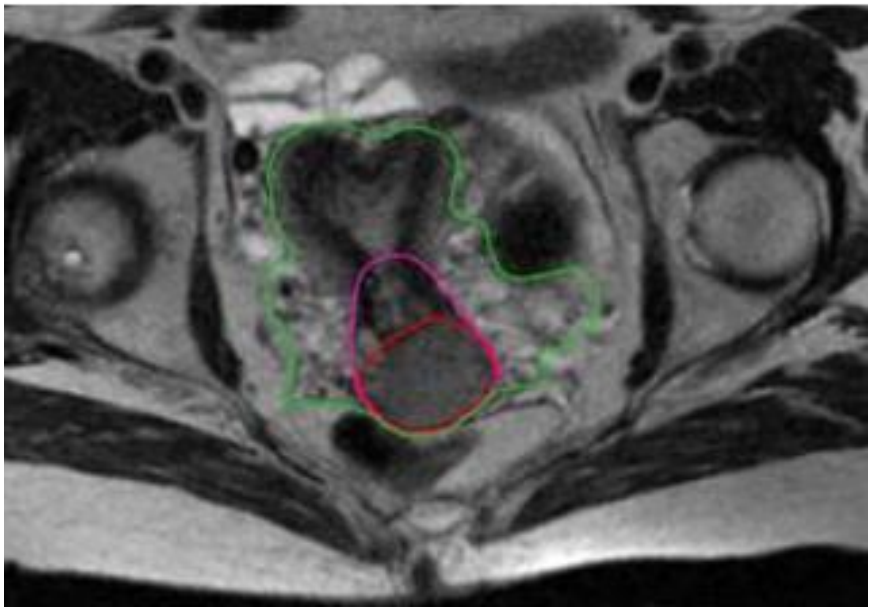
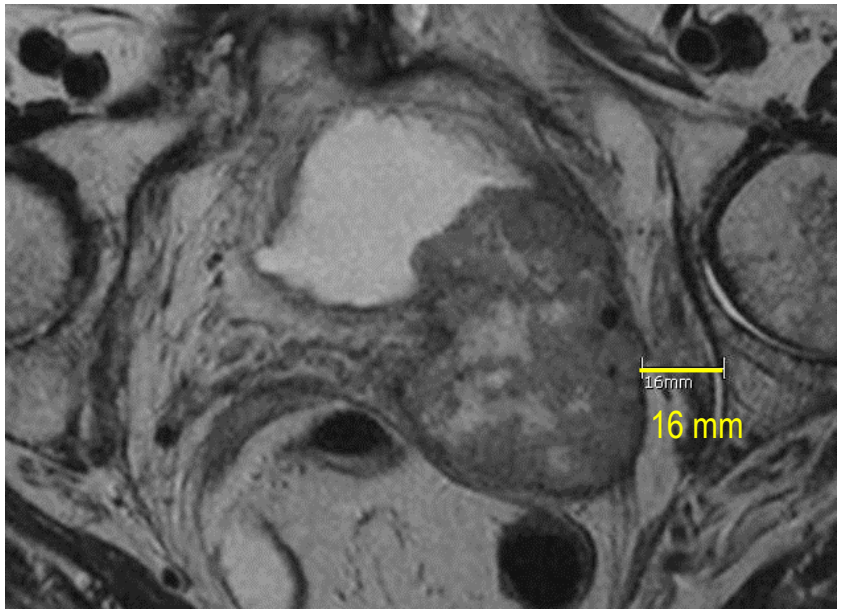
EMBRACE-II

- Lateral border = medial edge of internal iliac and obturator vessels

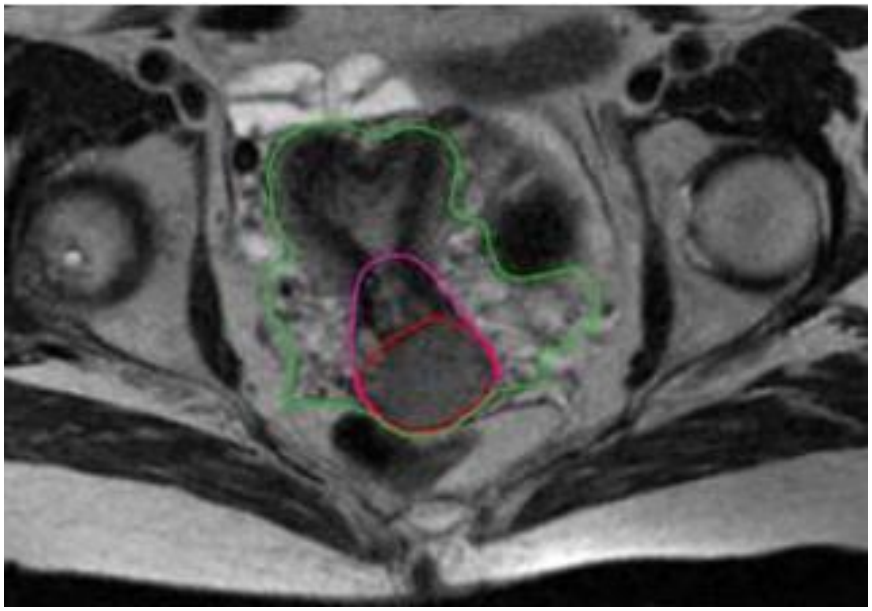


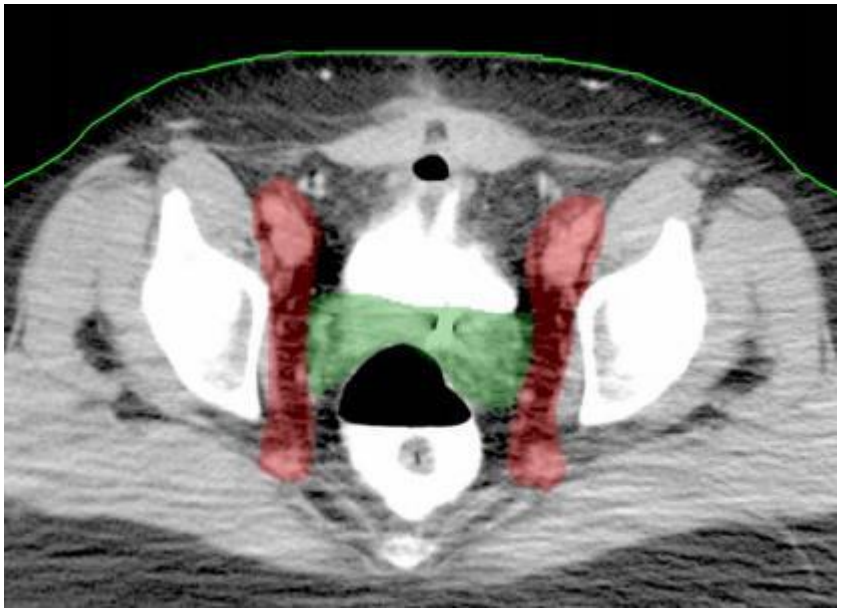


IIIB disease

EMBRACE-II

- Lateral border = medial edge of internal iliac and obturator vessels





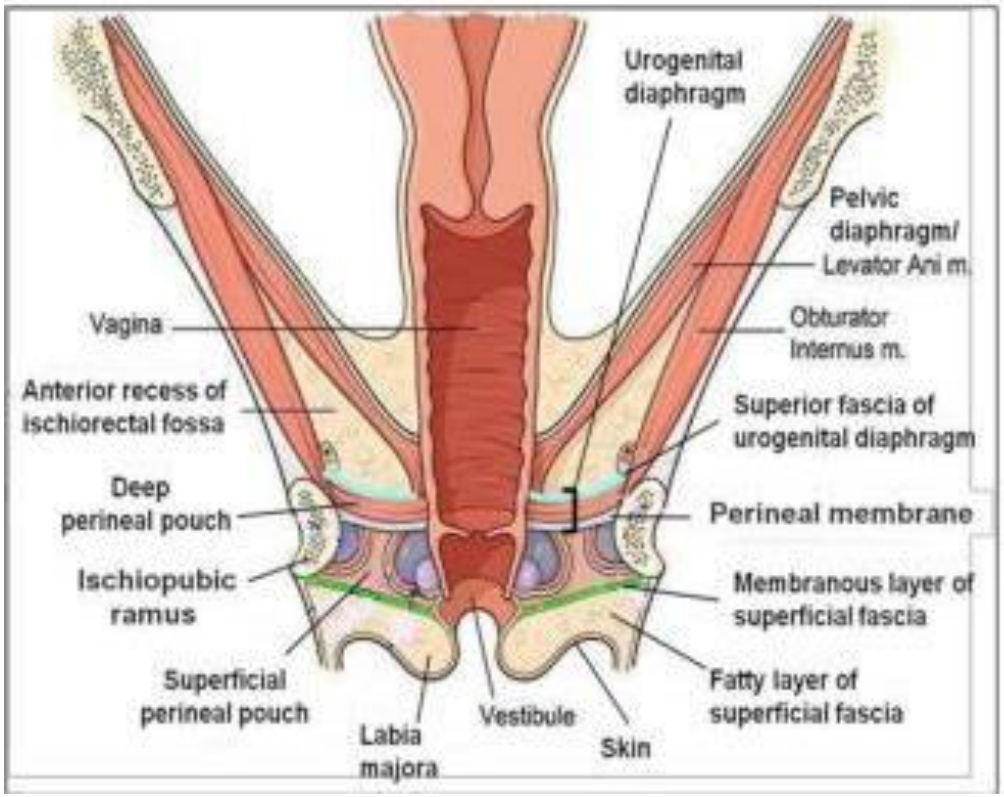
RTOG post-op

Vagina – inferior margin

- GYN IMRT + Japanese consortiums
  - Minimal or no vaginal extension: upper half
  - Upper vaginal involvement: upper two-thirds
  - Extensive vaginal involvement: entire vagina
- EMBRACE-II
  - 20 mm margin of uninvolved vagina measured from the most inferior position of the CTV-T HR

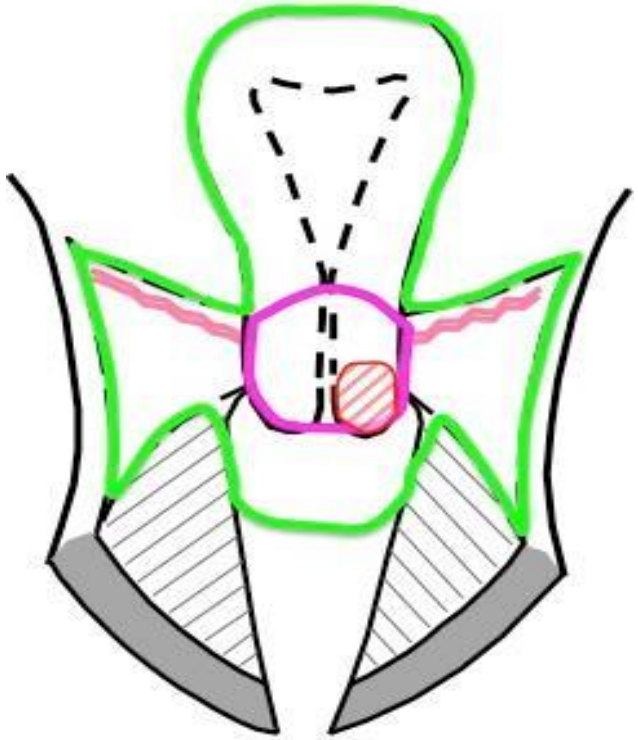
Issue

- Inferior margin of vagina CTV may be superior to urogenital diaphragm/levator ani

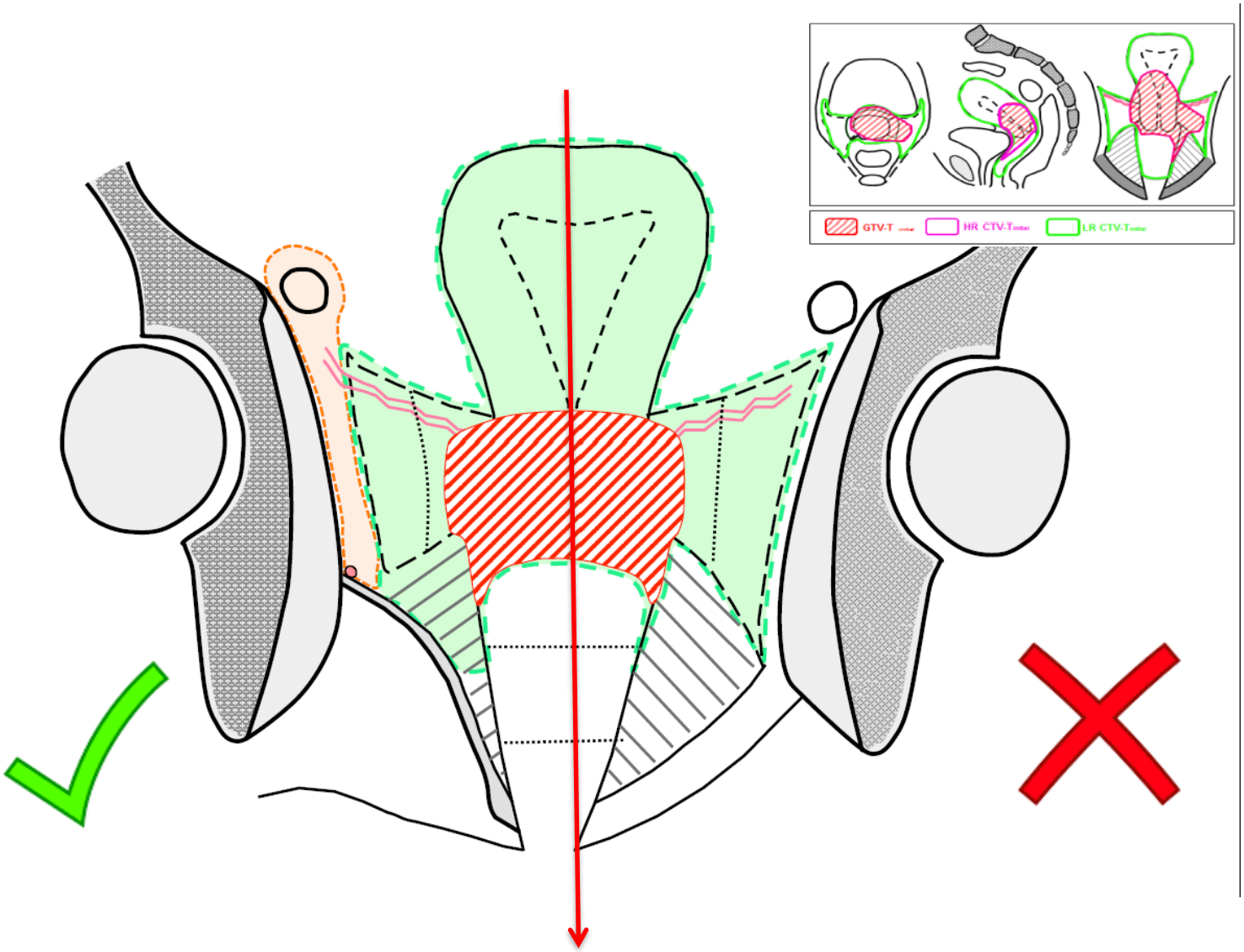


Vagina – lateral margin

- GYN IMRT consortium
  - No mention
- Japanese consortium
  - Paravaginal tissue would be included
- EMBRACE-II
  - No mention

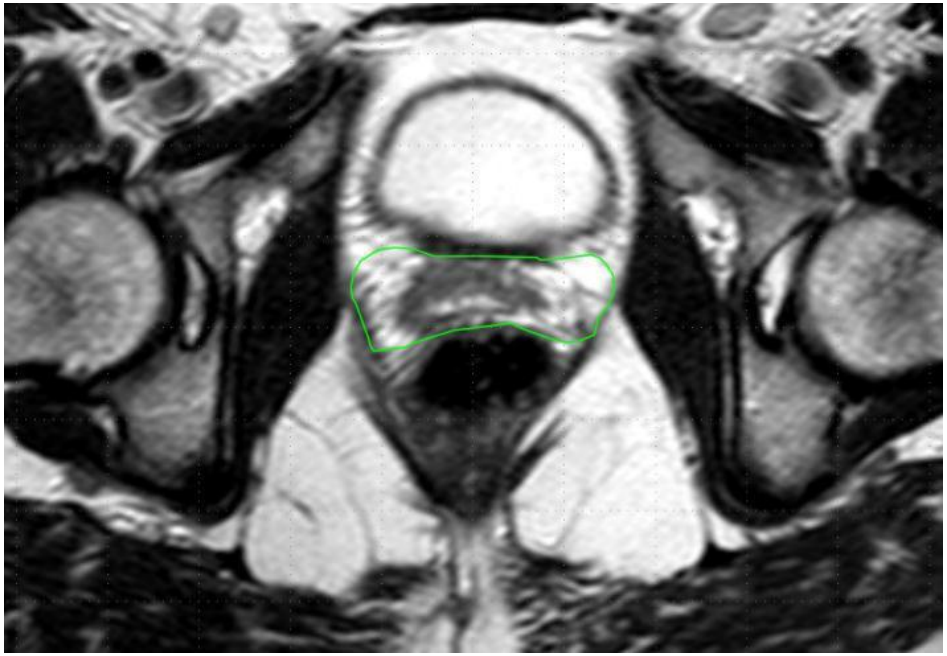


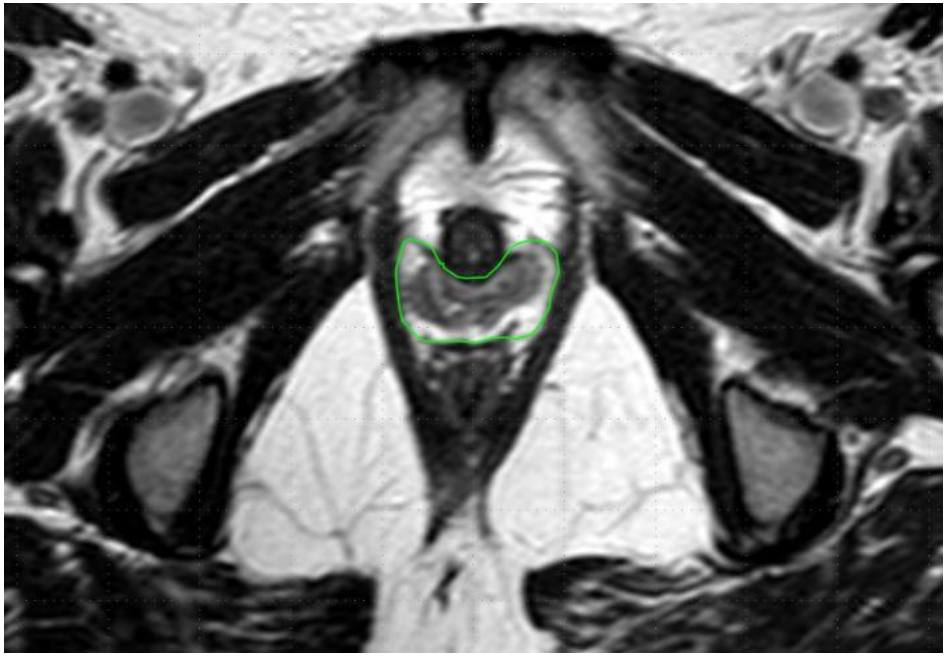
EMBRACE-II



Courtesy of Remi Nout

EMBRACE-II





Margin round involved organ

- GYN IMRT consortium
  - Include entire mesorectum if uterosacral ligament involved
- EMBRACE-II
  - In case of involvement of the pelvic wall, sacro-uterine ligaments, mesorectum or other involved structures a 20 mm margin around the initial HR CTV-T will be extended into these structures

Ovaries

- GYN IMRT consortium

Parametrium	Entire parametrium, including ovaries;

- Japanese consortium

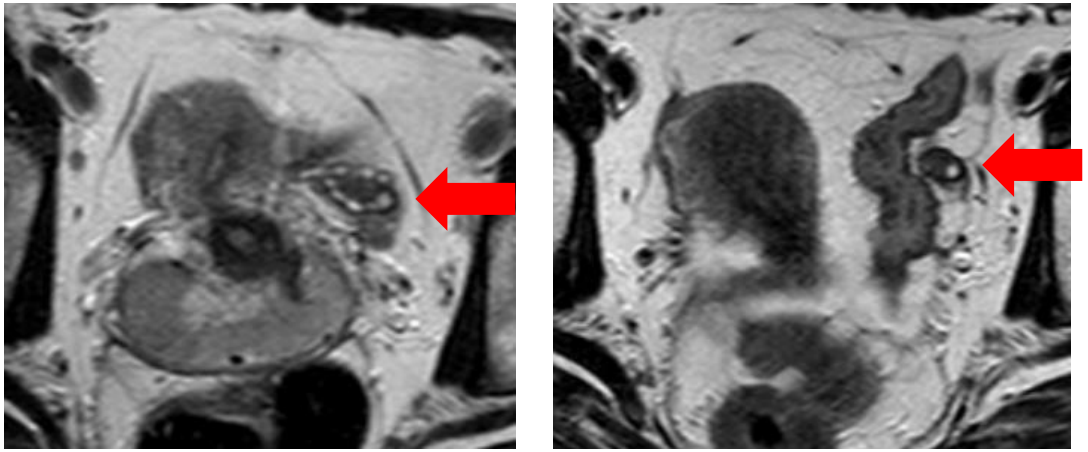
OVARY

Ovaries visible on the CT/MRI would be included.

A consensus was not reached regarding the possibility of excluding the ovaries in selected cases (i.e. non-bulky Stage I or II cases with squamous cell carcinoma).

Ovaries

- Overall risk of ovarian metastases is small. Increased risk reported for
  - Adeno/adenosquamous
  - High grade and LVSI
  - Extension into the uterine corpus
- Ovaries can be highly mobile!



EMBRACE-II

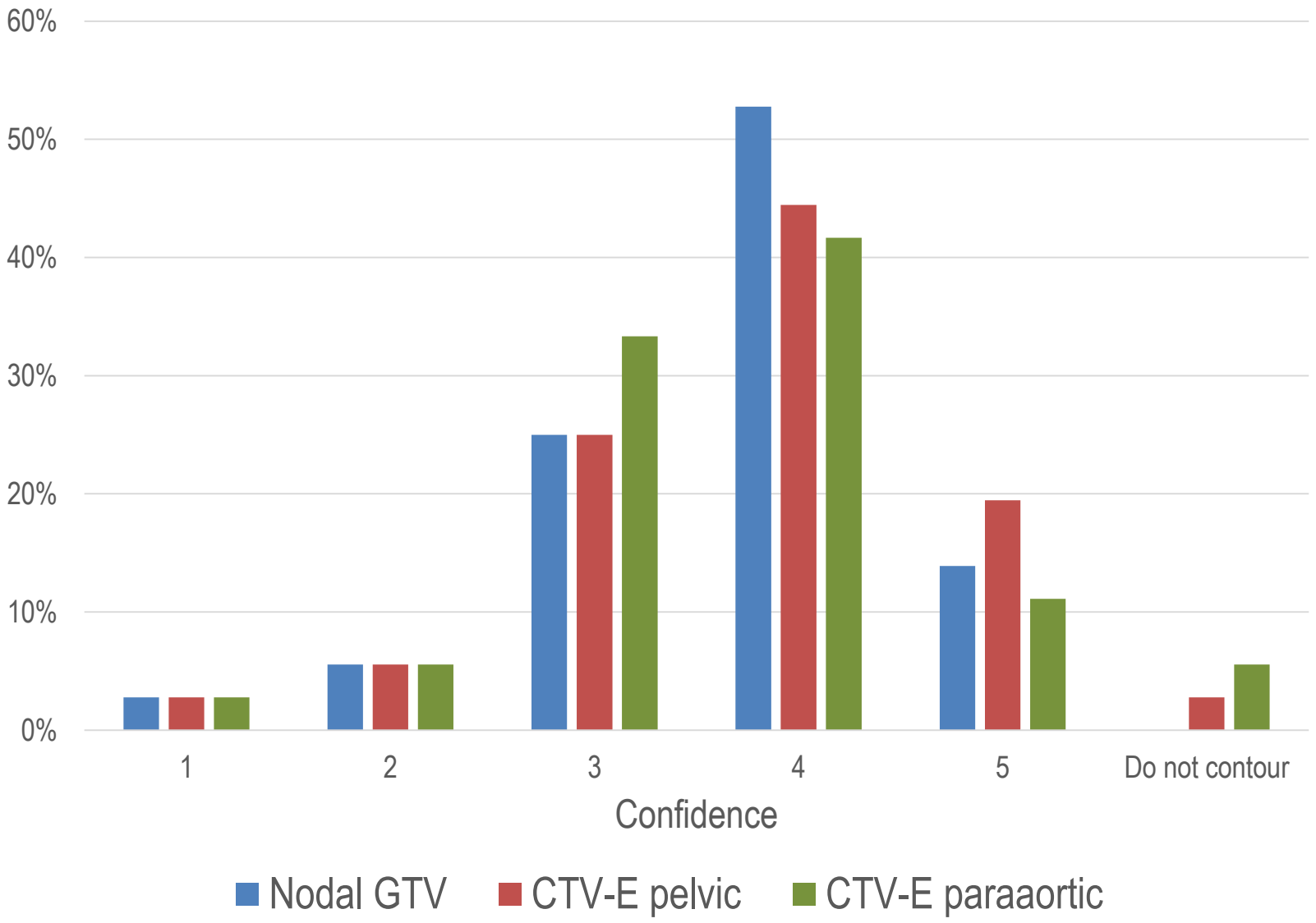
- In case of excessive uterine/ligamentum latum infiltration, consider to include ovaries into CTV-T $LR_{initial}$

Nodal targets

EMBRACE-II

- GTV-N = involved node
- CTV-N
  - Margin round involved node
- CTV-E = uninvolved nodes
  - Pelvic
  - Para-aortic

Nodal targets



CTV margins

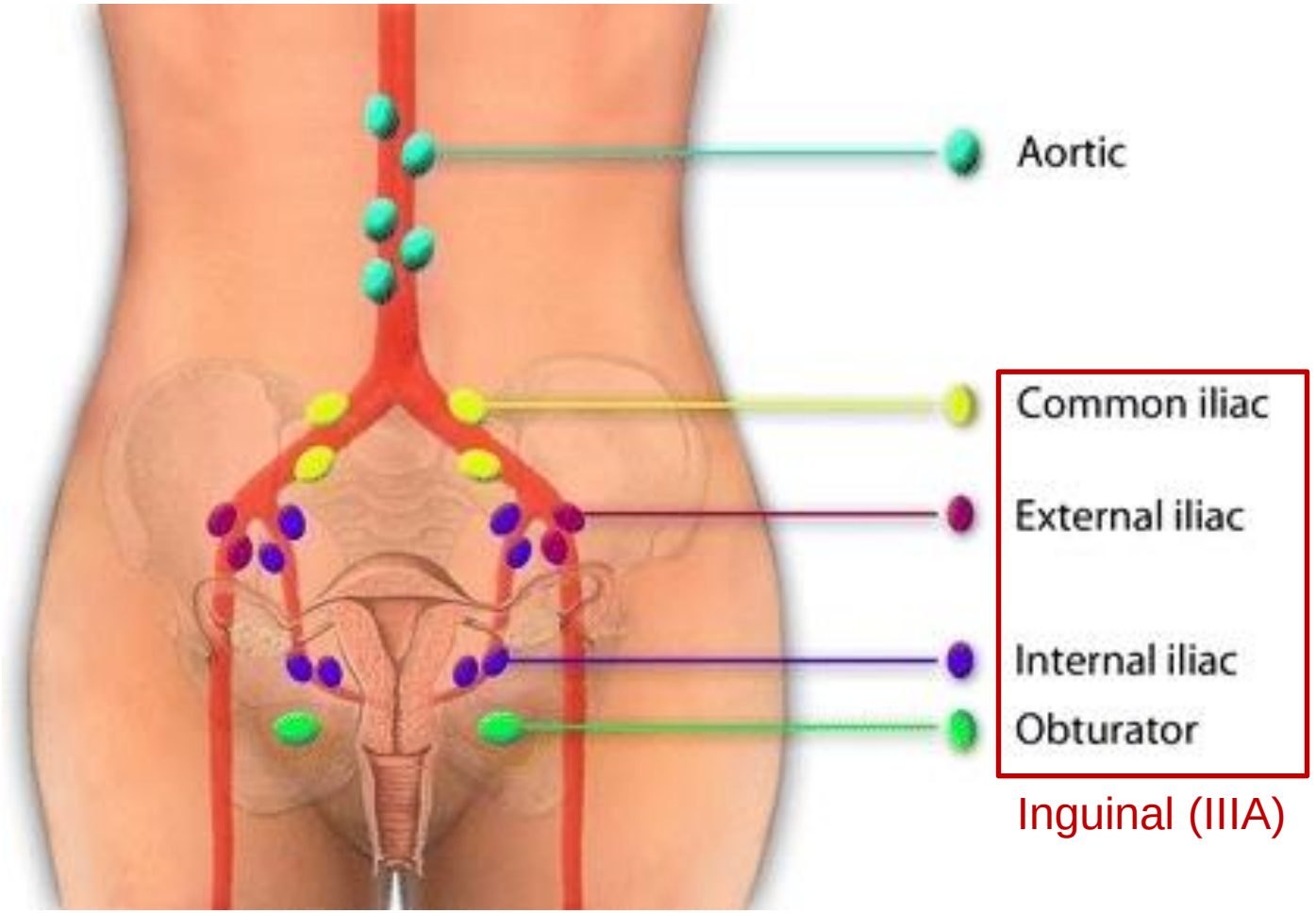
- CTV margin for CTV-N is for extracapsular spread
  - EMBRACE-II recommends 0-3 mm
- CTV margin for CTV-E is for variation in location of nodes

	3D margin around vessels (mm)				
	3	5	7	10	15
Nodal coverage	56 %	76 %	88 %	94 %	99 %

7 mm margin with minor adjustments: 99% coverage of lymph nodes

Taylor A, et al. IJROBP, 2005;63:1604–12

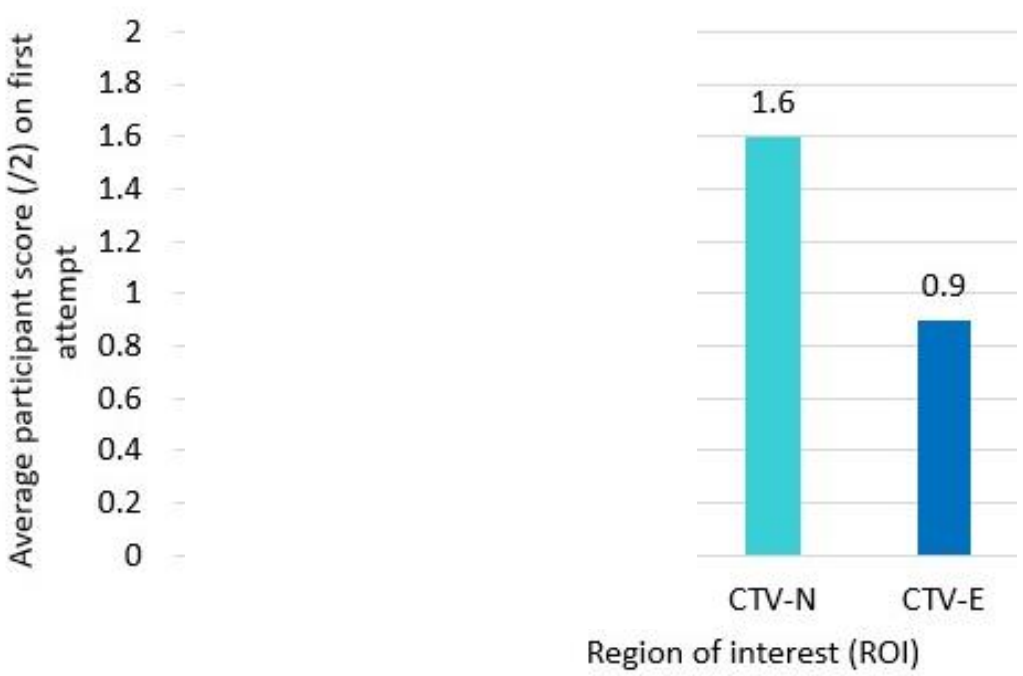
CTV-E



Taylor A, et al. IJROBP, 2005;63:1604–12

Small W, et al. IJROBP 2008;71:428-434 (RTOG)

EMBRACE-II accreditation

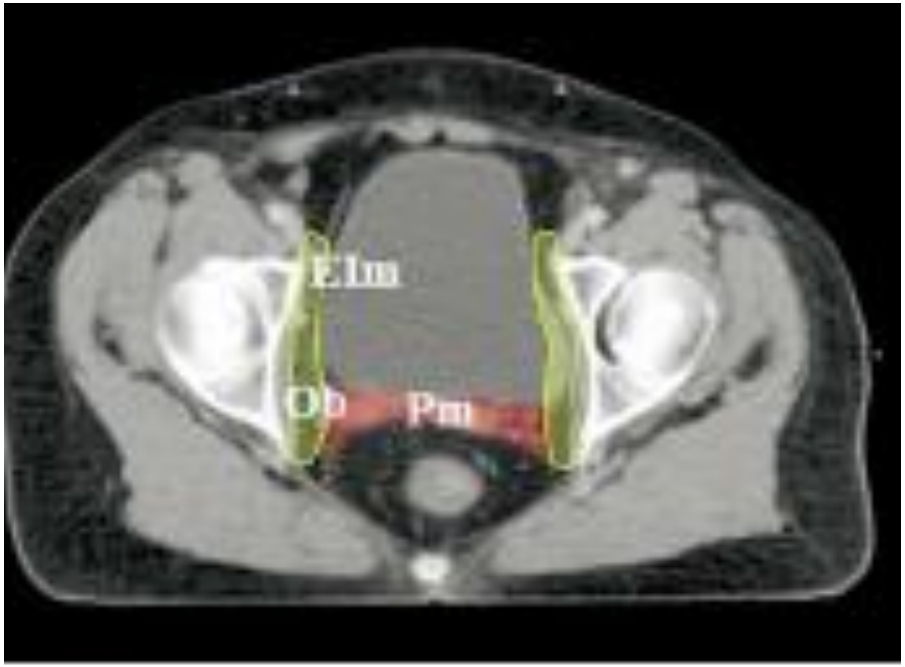


- GTV-T : Gross tumour volume
- CTV-HR : Gross tumour including whole cervix
- CTV-LR : Composed of CTV-HR + parametria, vagina & uterus
- CTV-N : CTV for involved lymph nodes
- CTV-E : Elective lymph node CTV
- ITV45 : CTV-LR + CTV-E + internal margins to compensate for internal motion

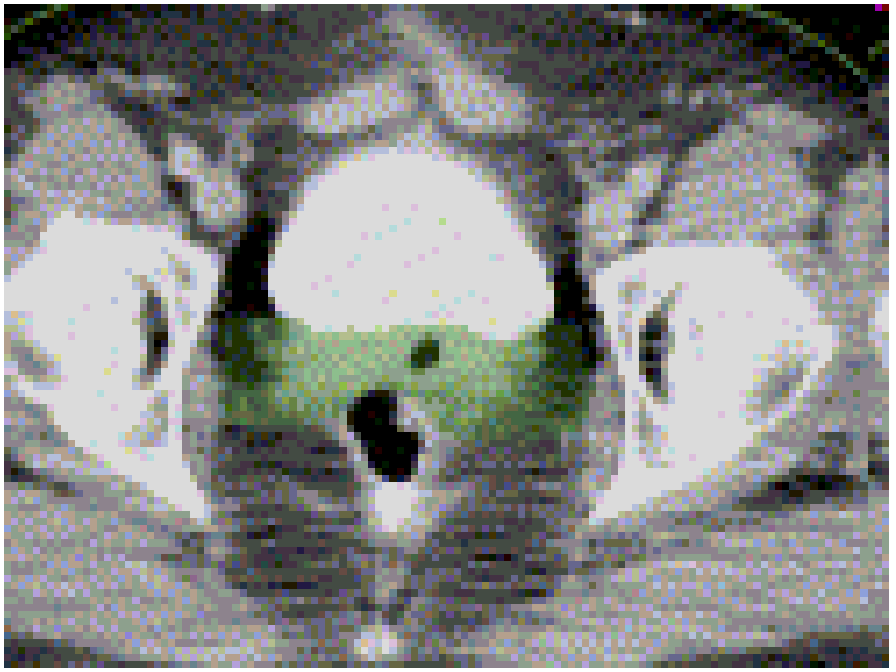
Courtesy of Simon Duke

Obturator – inferior limit

Taylor

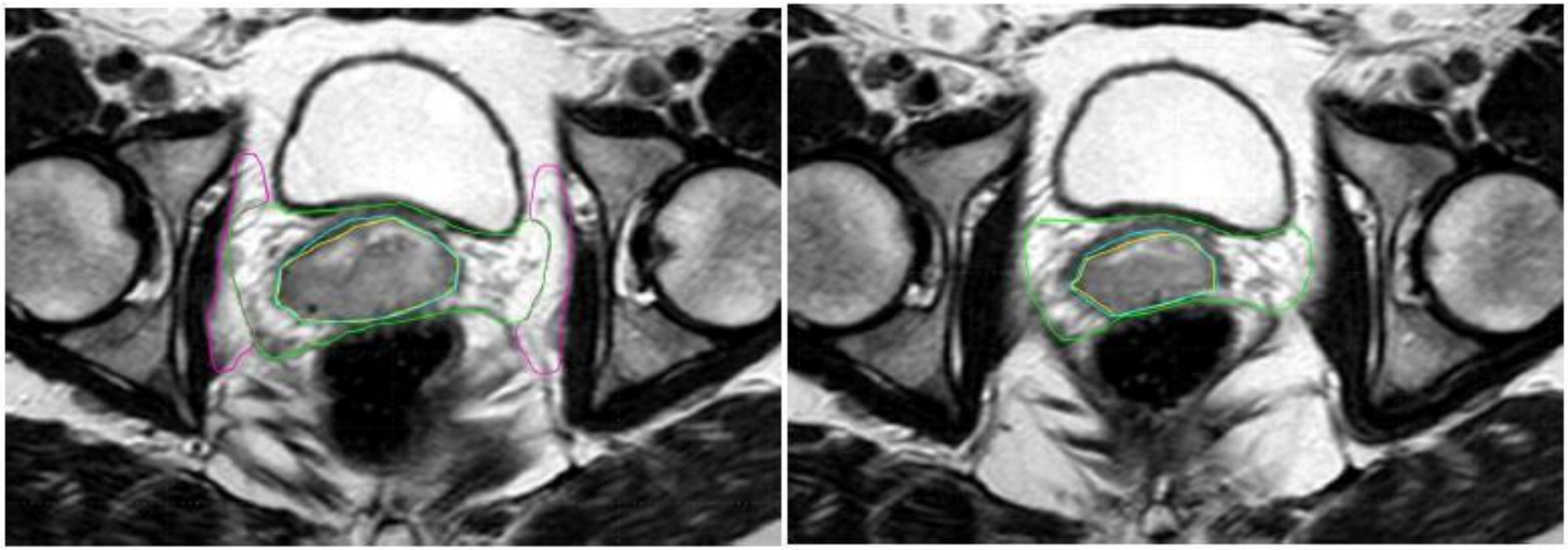


Small

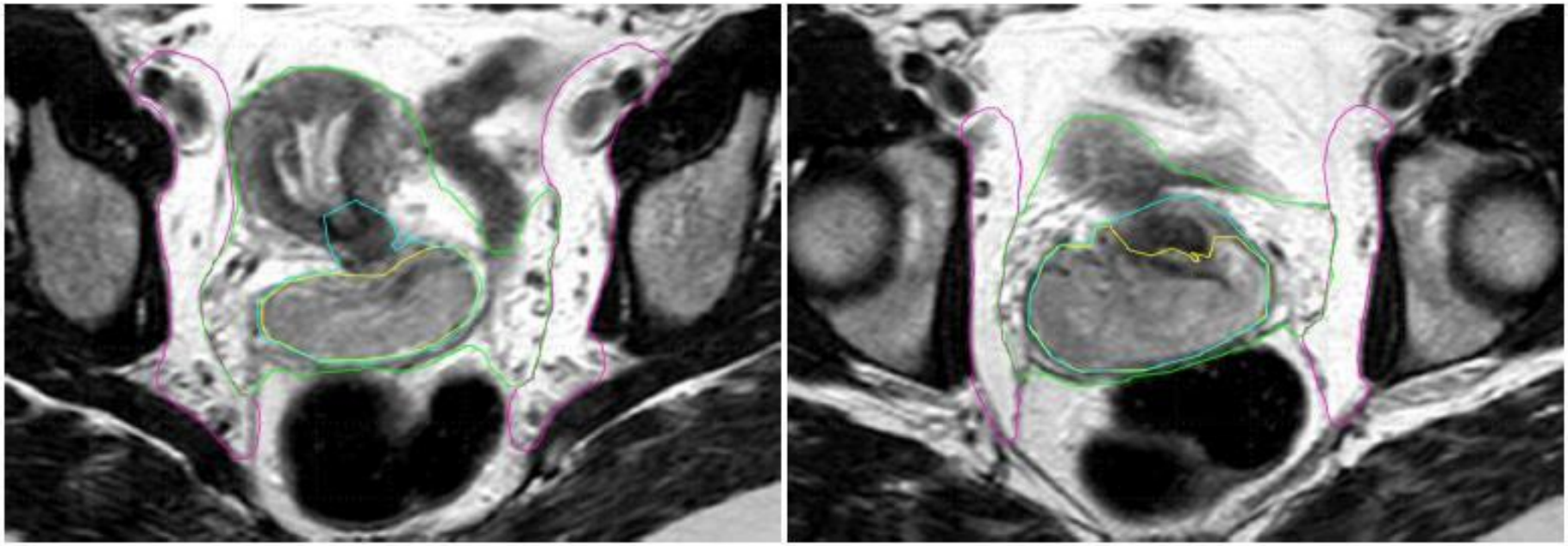


EMBRACE-II

- Where internal iliac vessels enter or leave the true pelvis (usually at the upper part of the obturator foramen, below femoral head)

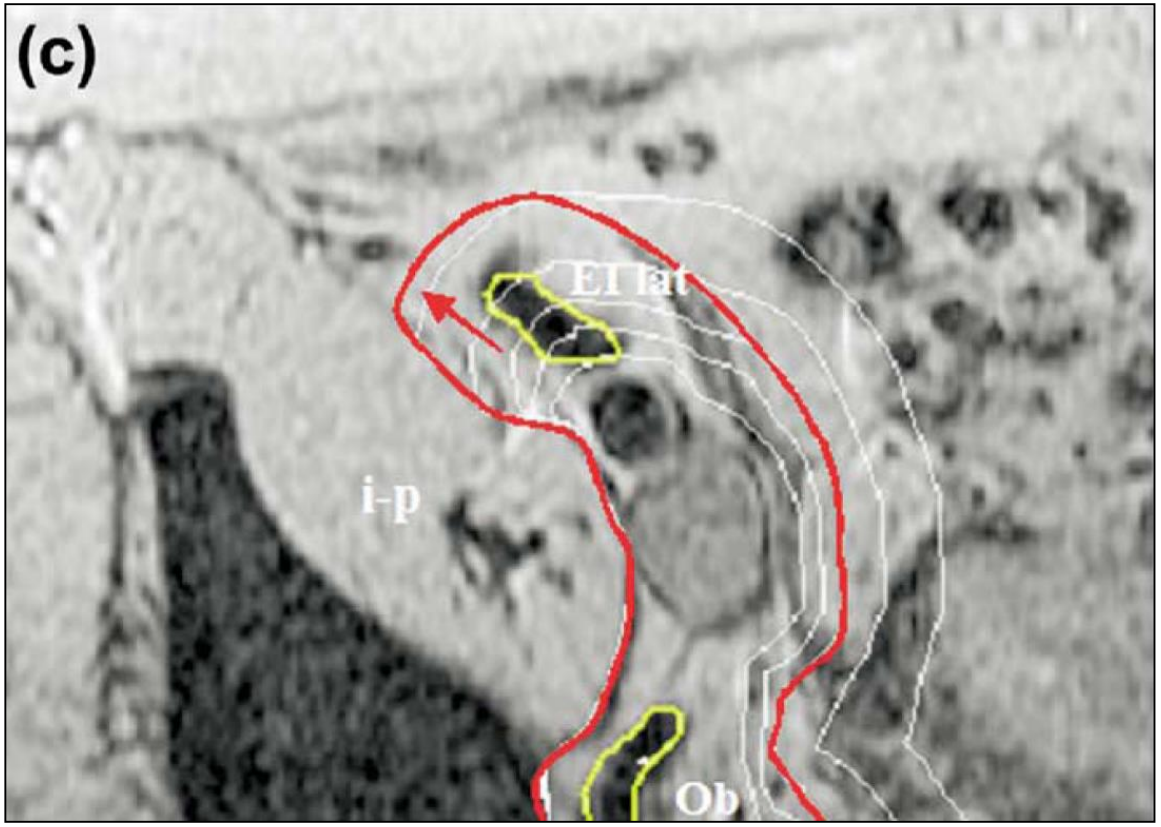


External iliac – anterior limit



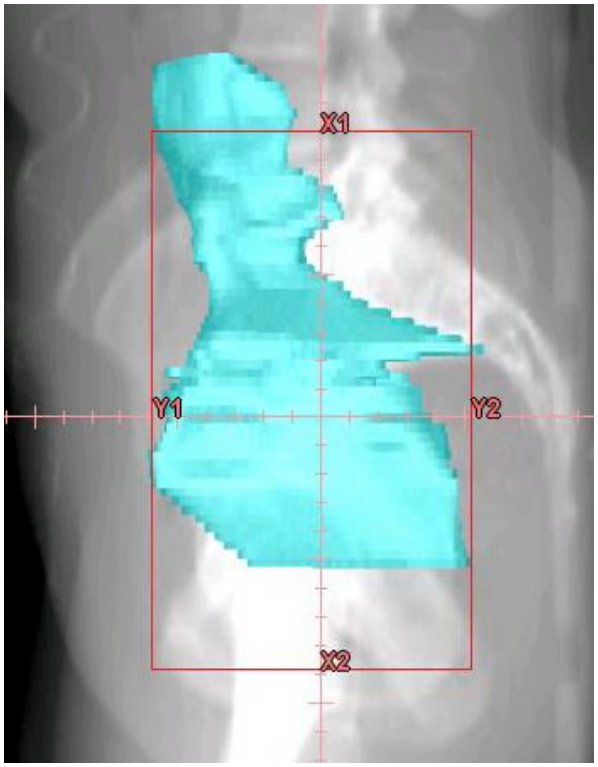
Taylor

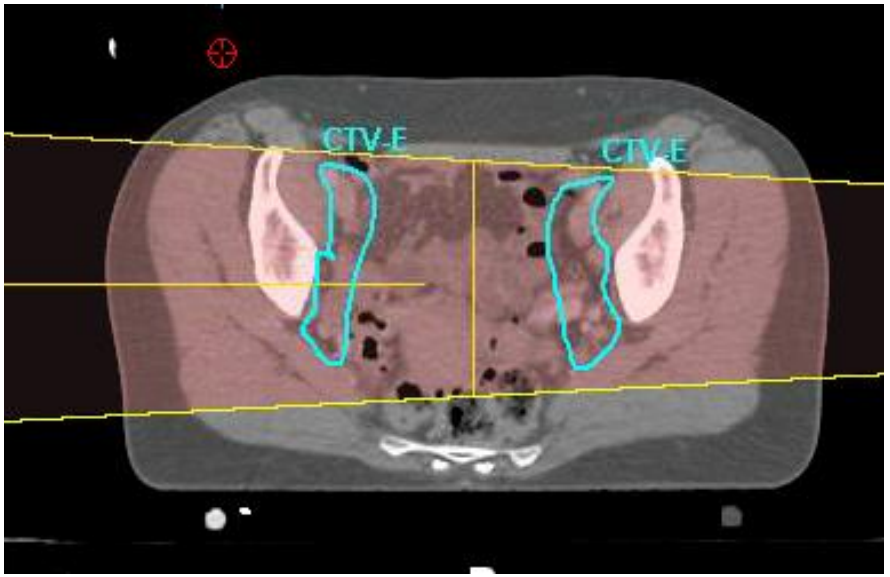
- Extend 10 mm in front of external iliac vessels along iliopsoas muscle



Tip

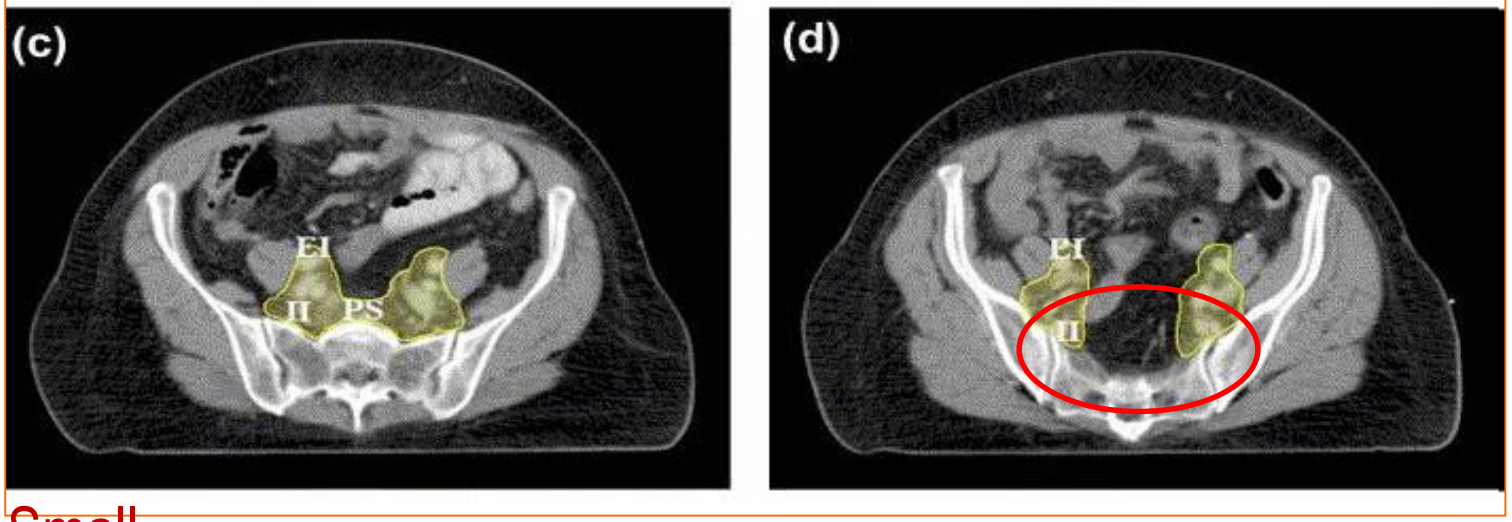
- Use traditional box as guide





Pre-sacral – inferior limit

Taylor



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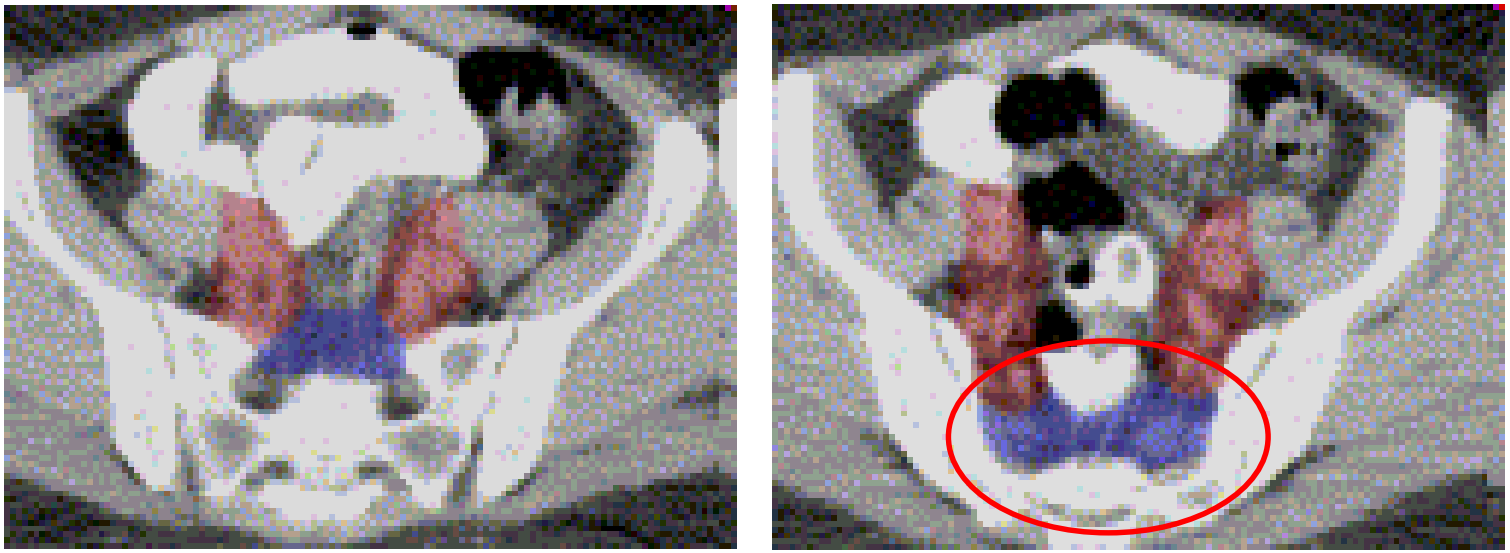
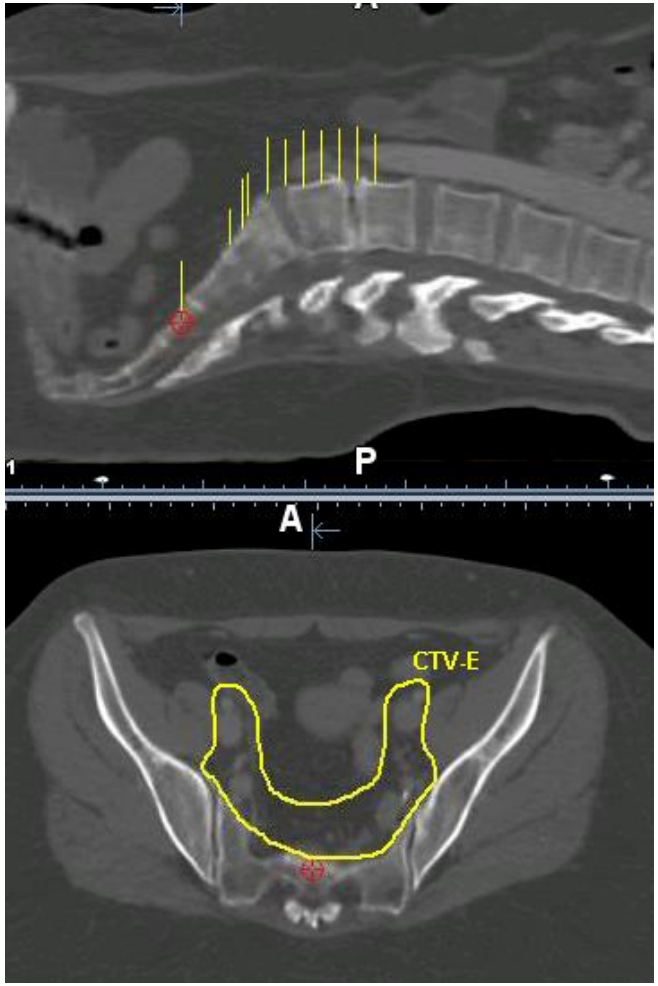
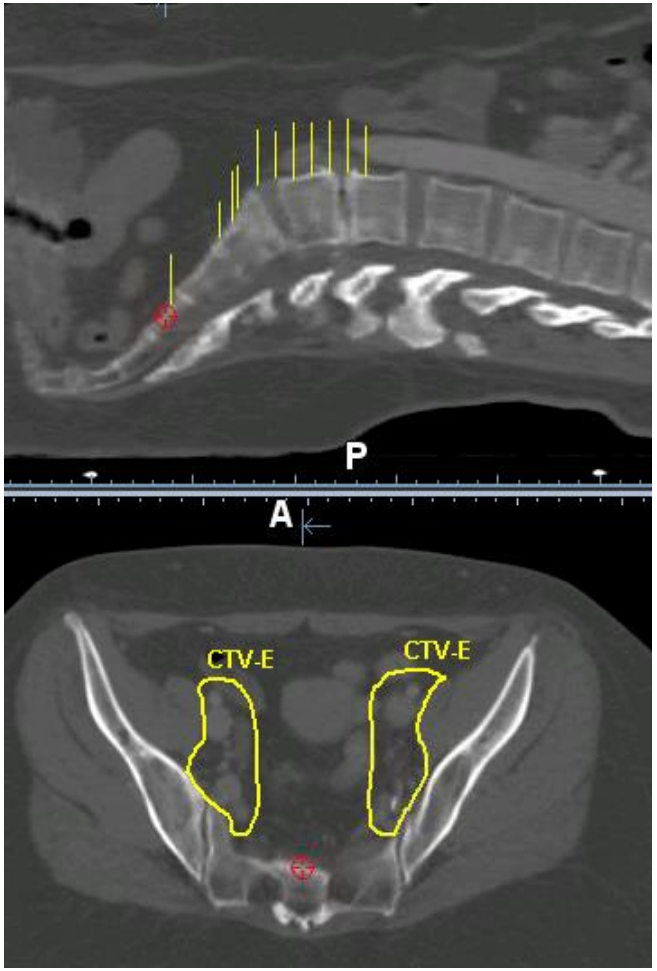


Tip

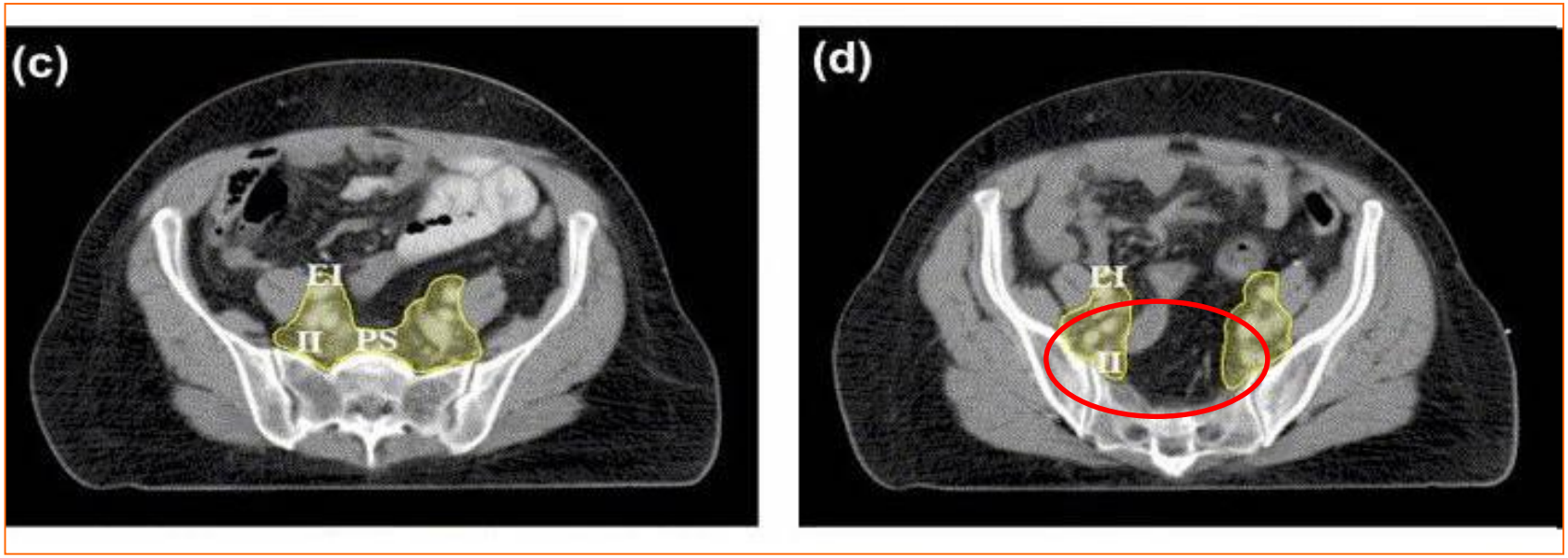
- Do not contour below S2





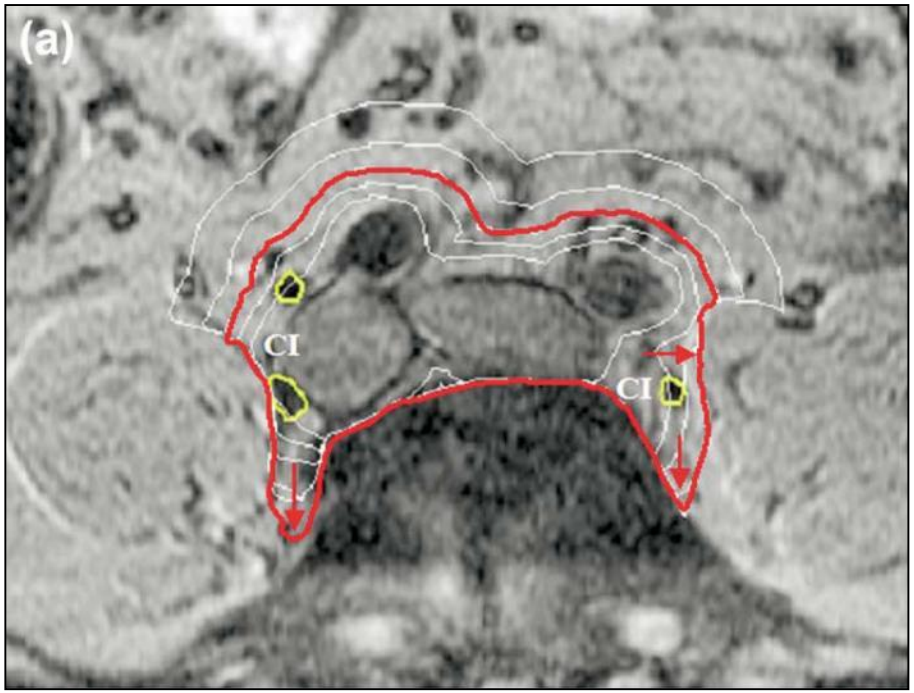
Taylor

- To cover the presacral region, connect the volumes on each side of the pelvis with a 10-mm strip over the anterior sacrum (S1 and S2)



Common iliac – lateral limit

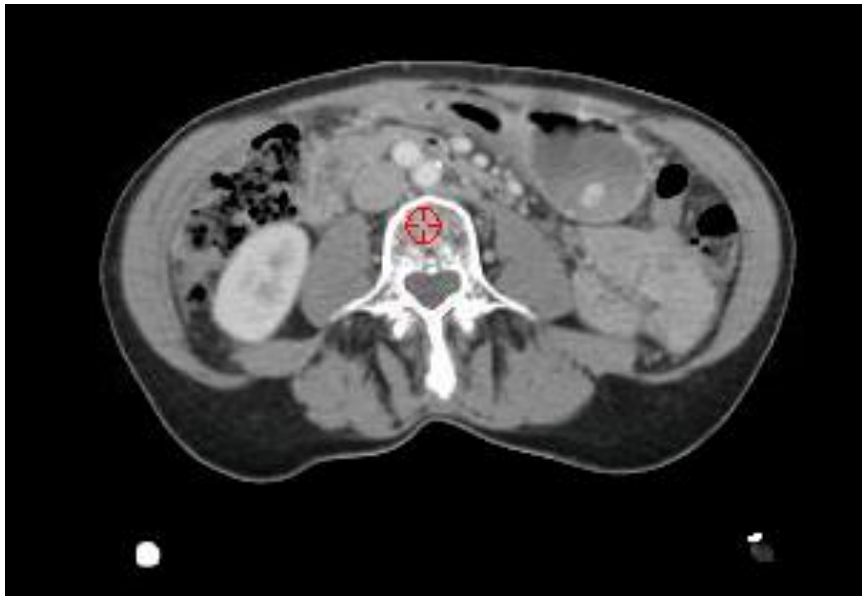
- Taylor
  - Extend posterior and lateral borders to psoas and vertebral body

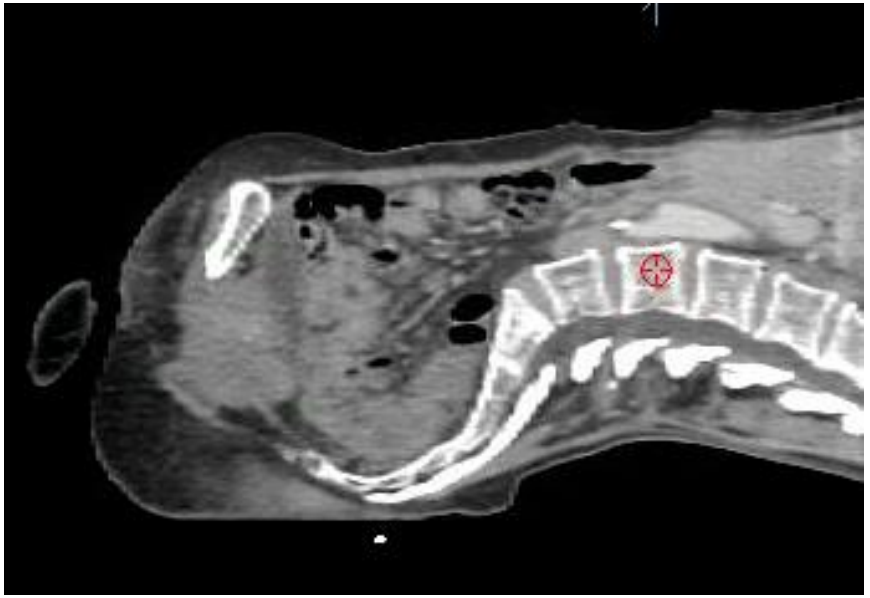


Common iliac – superior limit

- Taylor
  - Bifurcation of aorta
- Small
  - From 7 mm below L4/5 interspace to bifurcation of common iliac arteries

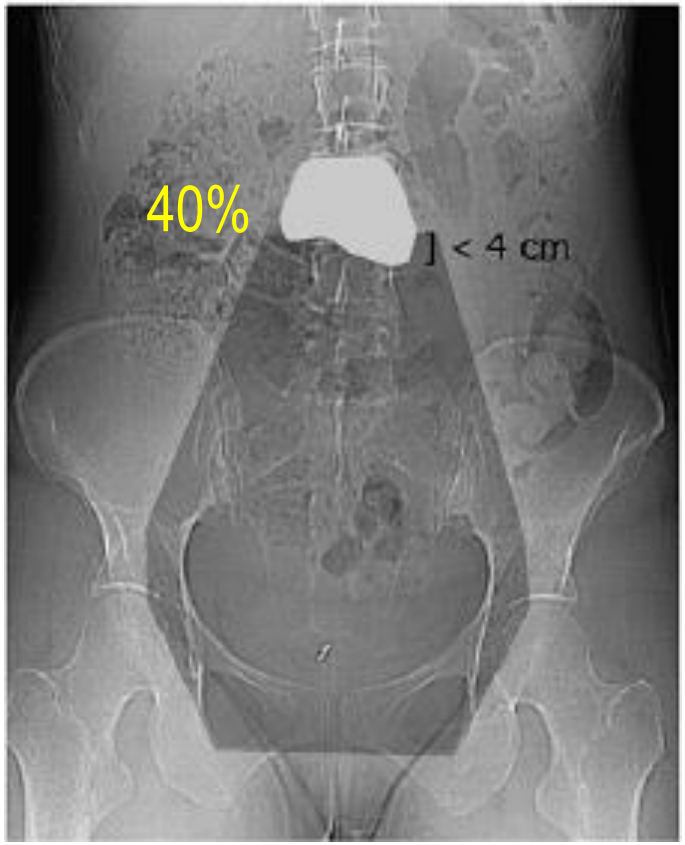
Common iliac – superior limit





Patterns of regional failure

- MD Anderson 1980-2000 (1894 patients)
  - 198 regional (no central) recurrences (33% distant mets)

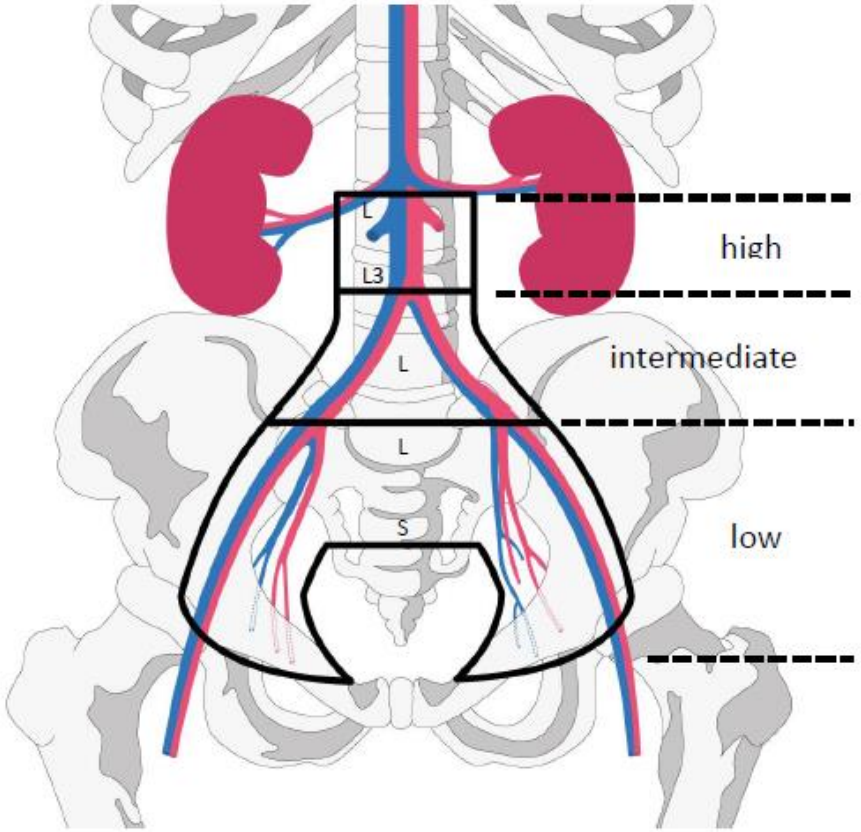


Beadle BM, et al. Int J Radiat Oncol Biol Phys. 2010;76(5):1396-403

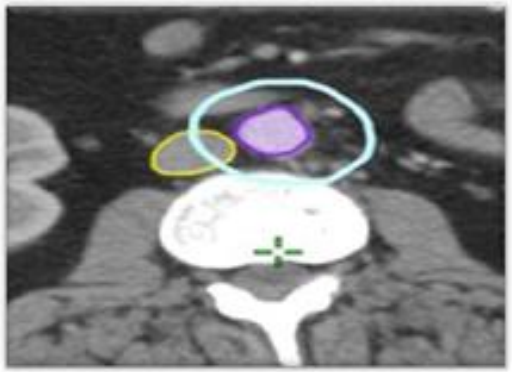
EMBRACE II EBRT CTV

Risk Group LN	Definition
Low Risk (LR LN)	Tumour size ≤4cm AND stage IA/IB1/IIA1 AND N0 AND squamous cell carcinoma AND no uterine invasion
Intermediate Risk (IR LN)	Not low risk No high risk features
High Risk (HR LN)	Based on nodal pathology • ≥ 1 pathologic node at common iliac or above • OR ≥ 3 pathologic nodes

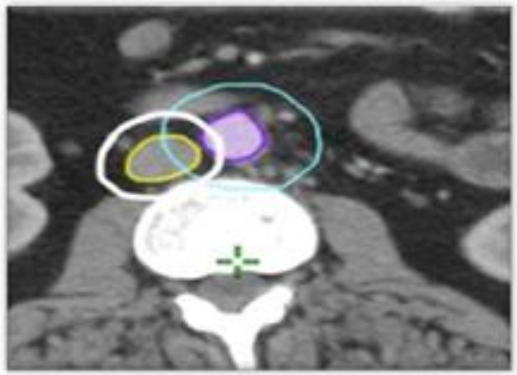
Treat to renal vein (PA nodes above renal vessels incurable)



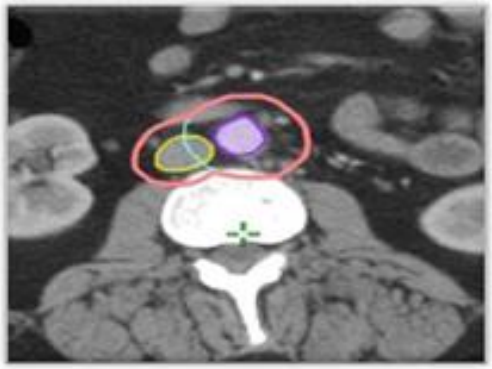
Paraaortic atlas



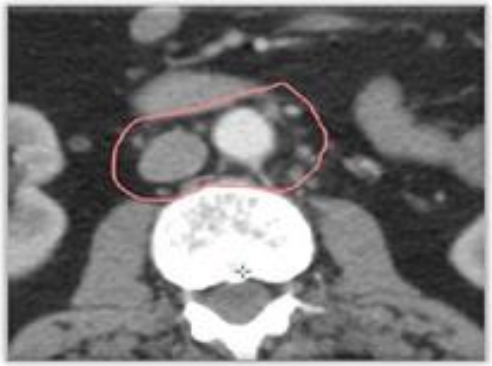
4) Aorta expansion (blue).
1cm aorta circumferentially.
1.5cm laterally.



5) IVC expansion (white).
8mm anteromedially.
6mm posterolaterally.



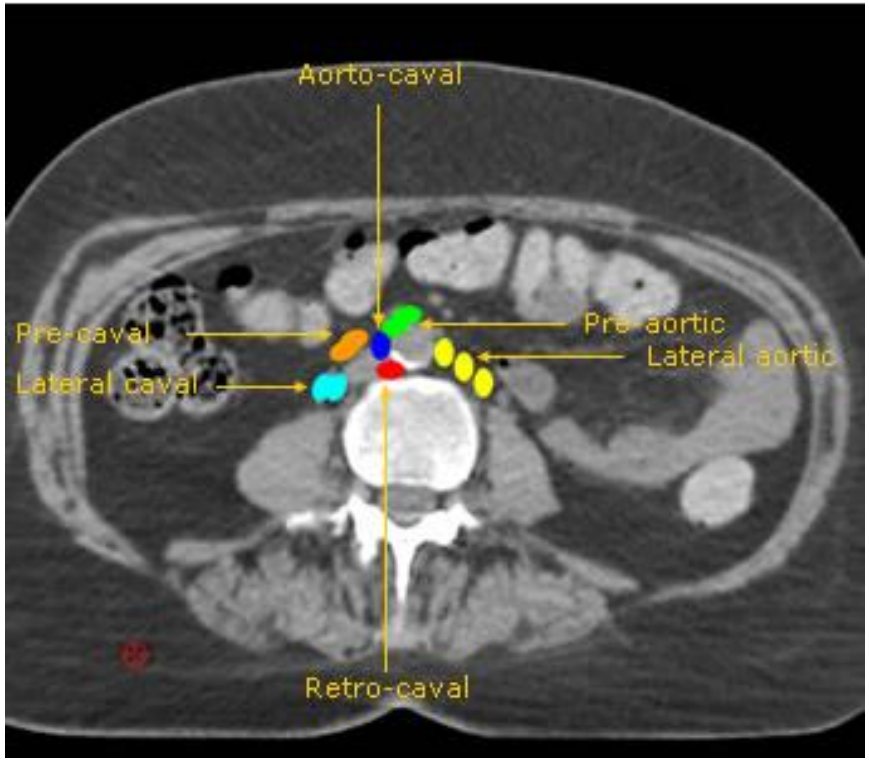
6) Combined expansions (pink).

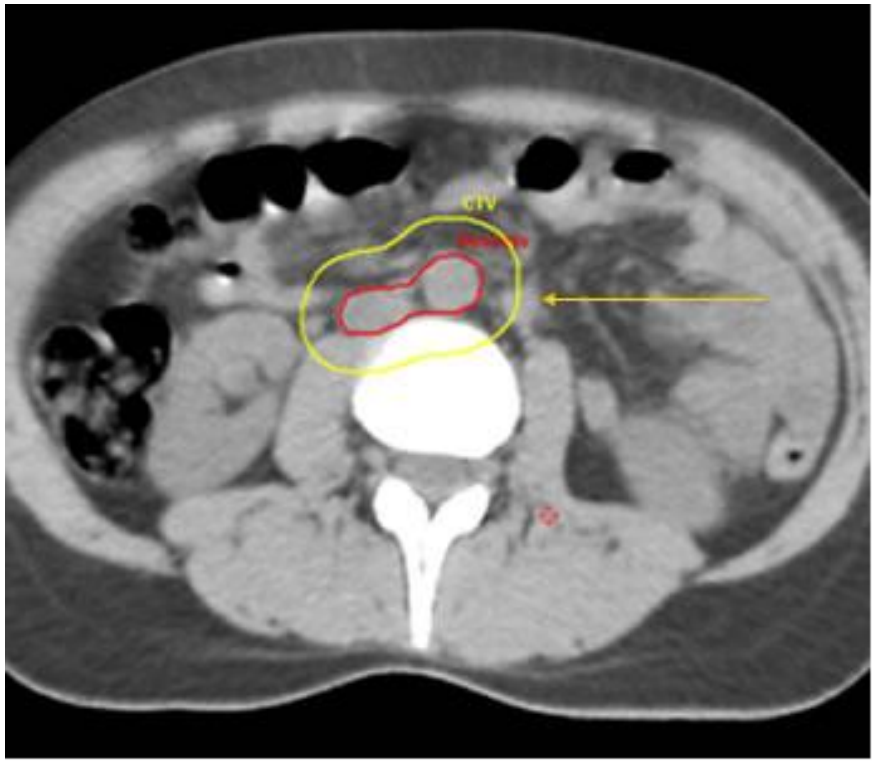


7) Crop from normal boundaries to create final CTV (pink)

Keenan, Lorna G. et al. Radiother Oncol. 2018 Mar 6. [Epub ahead of print]

Paraortic nodes





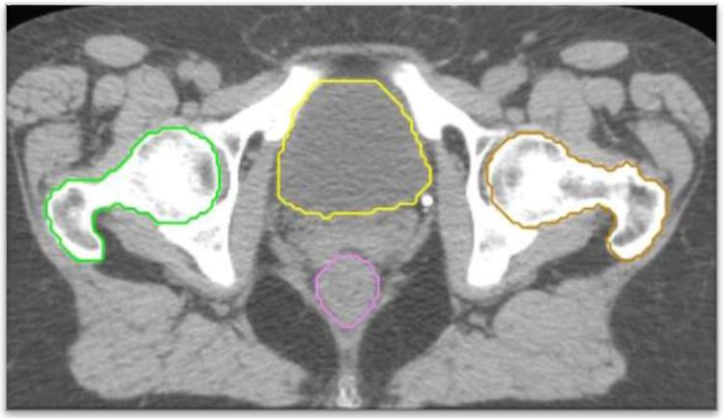
Organs at risk

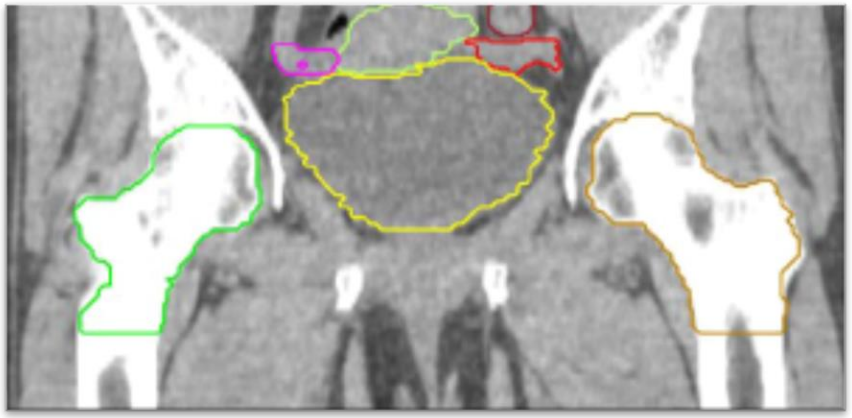
EMBRACE-II

- The **outer contour** of the following organs should be delineated:
  - **Bladder** Whole organ including the bladder neck
  - **Rectum** From the ano-rectal sphincter to the recto-sigmoid junction
  - **Sigmoid** From the recto-sigmoid junction to the left iliac fossa
  - **Bowel** Outer contour of bowel loops including the mesenterium

EMBRACE-II

- **Femoral heads**
  - Both **femoral head and neck** to the level of the trochanter minor



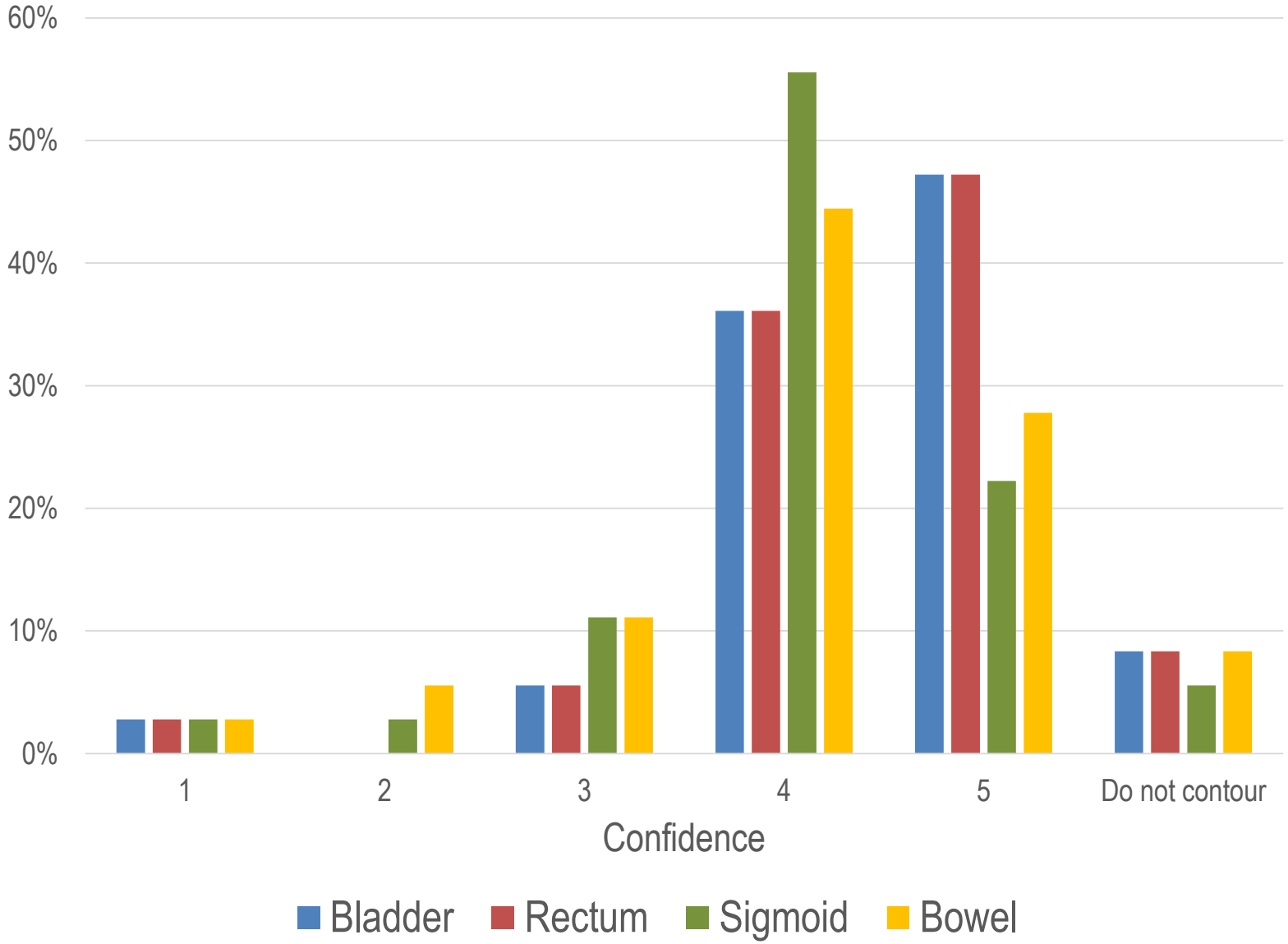


Gay H, et al. Int J Radiat Oncol Biol Phys 2012;83(3):353-362.

EMBRACE-II

- For para-aortic irradiation
  - **Kidneys** Outer contour excluding renal pelvis
  - **Spinal cord** Outer contour
- If para-aortic RT above L1 is applied
  - **Duodenum** Whole organ
- In case of ovarian transposition
  - **Ovary** Outer contour

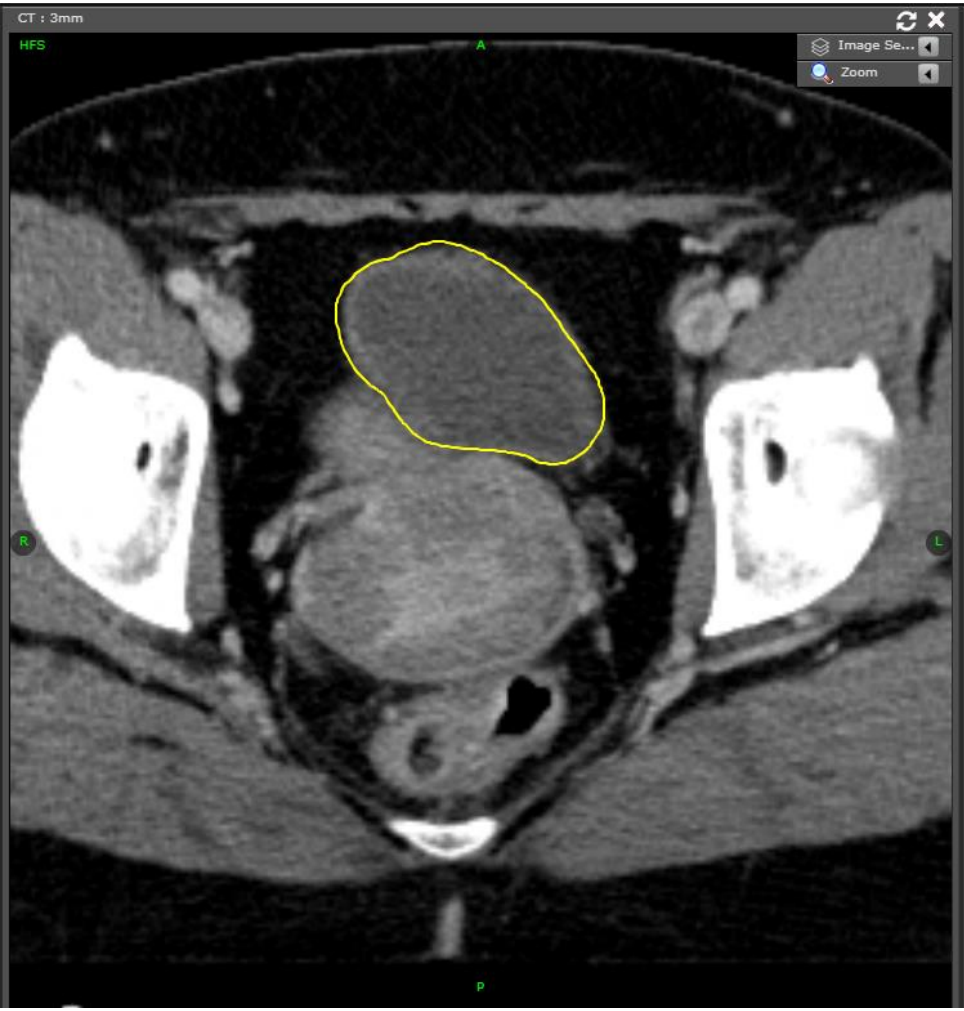
OAR

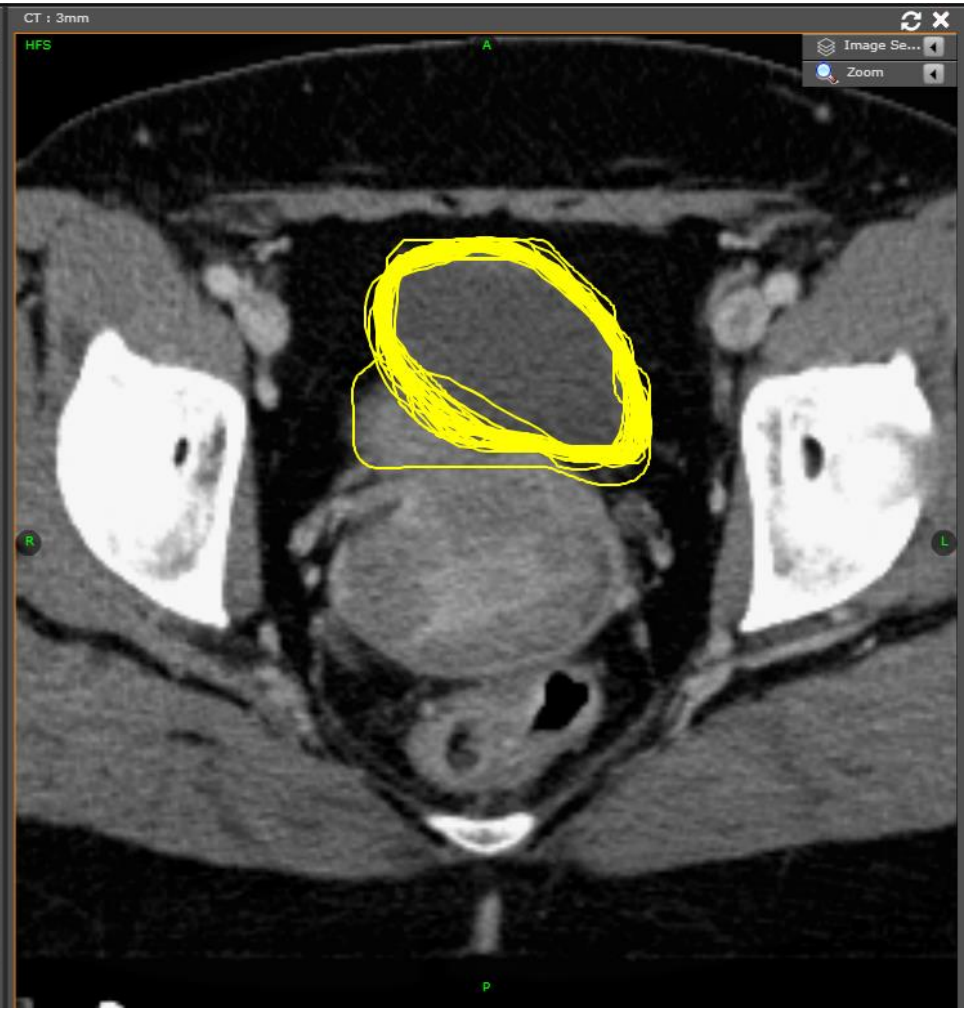

60%
50%
40%
30%
20%
10%
0%
1
2
3
4
5
Do not contour
Confidence
Bladder
Rectum
Sigmoid
Bowel

OAR contouring exercise – bladder

Reference

Participants





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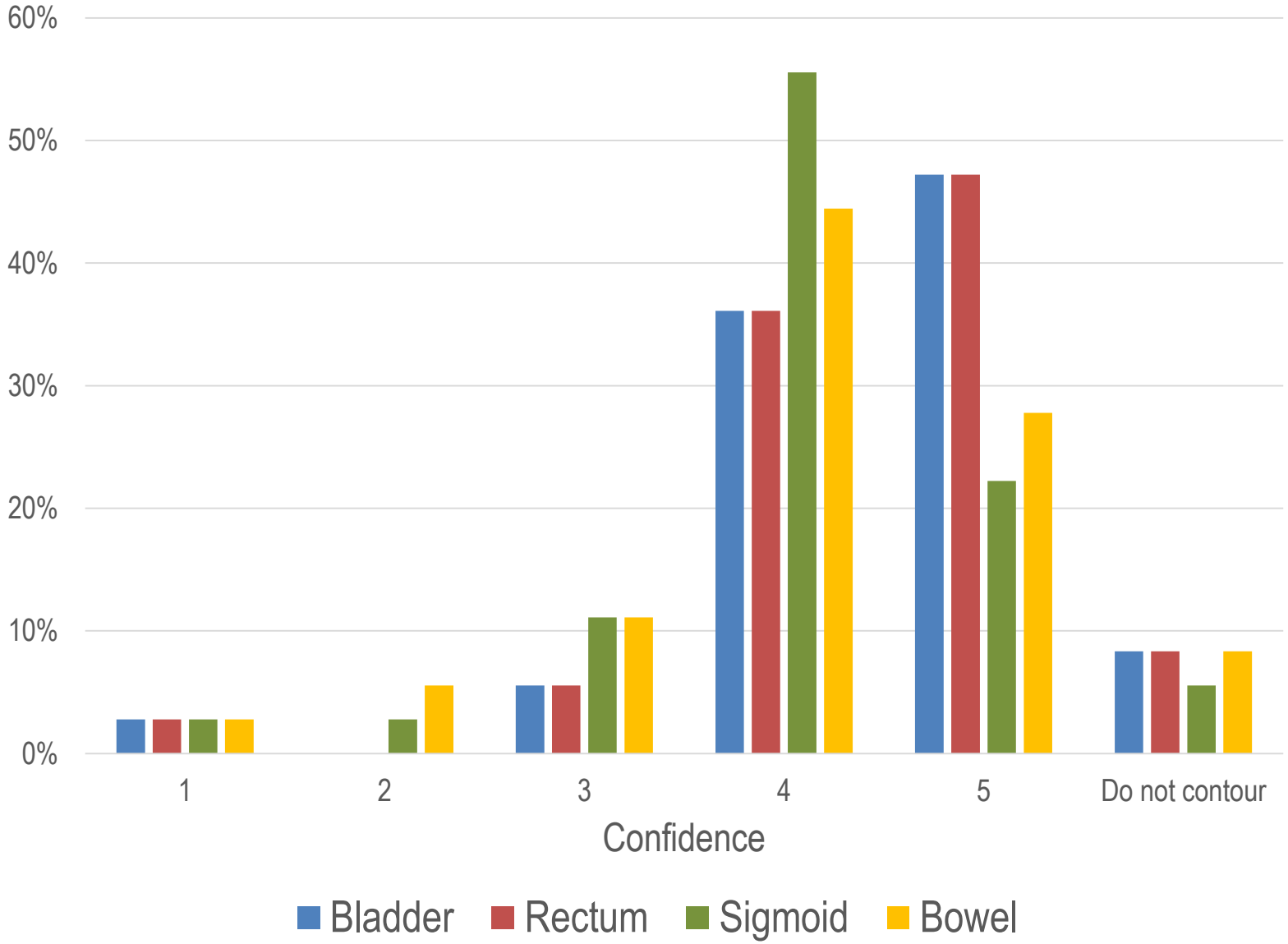

60%
50%
40%
30%
20%
10%
0%
1
2
3
4
5
Do not contour
Confidence
Bladder
Rectum
Sigmoid
Bowel

Varying definitions of rectum in RT studies and practice

- **Superior**
  - Rectosigmoid junction
  - 12 cm from the anus
  - Top of acetabula
  - At the level of ≈ S3
  - Inferior level of sacroiliac joints
  - 1 cm above the PTV
- **Inferior**
  - Anal verge
  - Ano-rectal junction
  - 1 cm below PTV
  - Ischial tuberosities
  - Ischial tuberosities + 2 cm
- **Circumferential**
  - Rectum + contents
  - Rectal wall

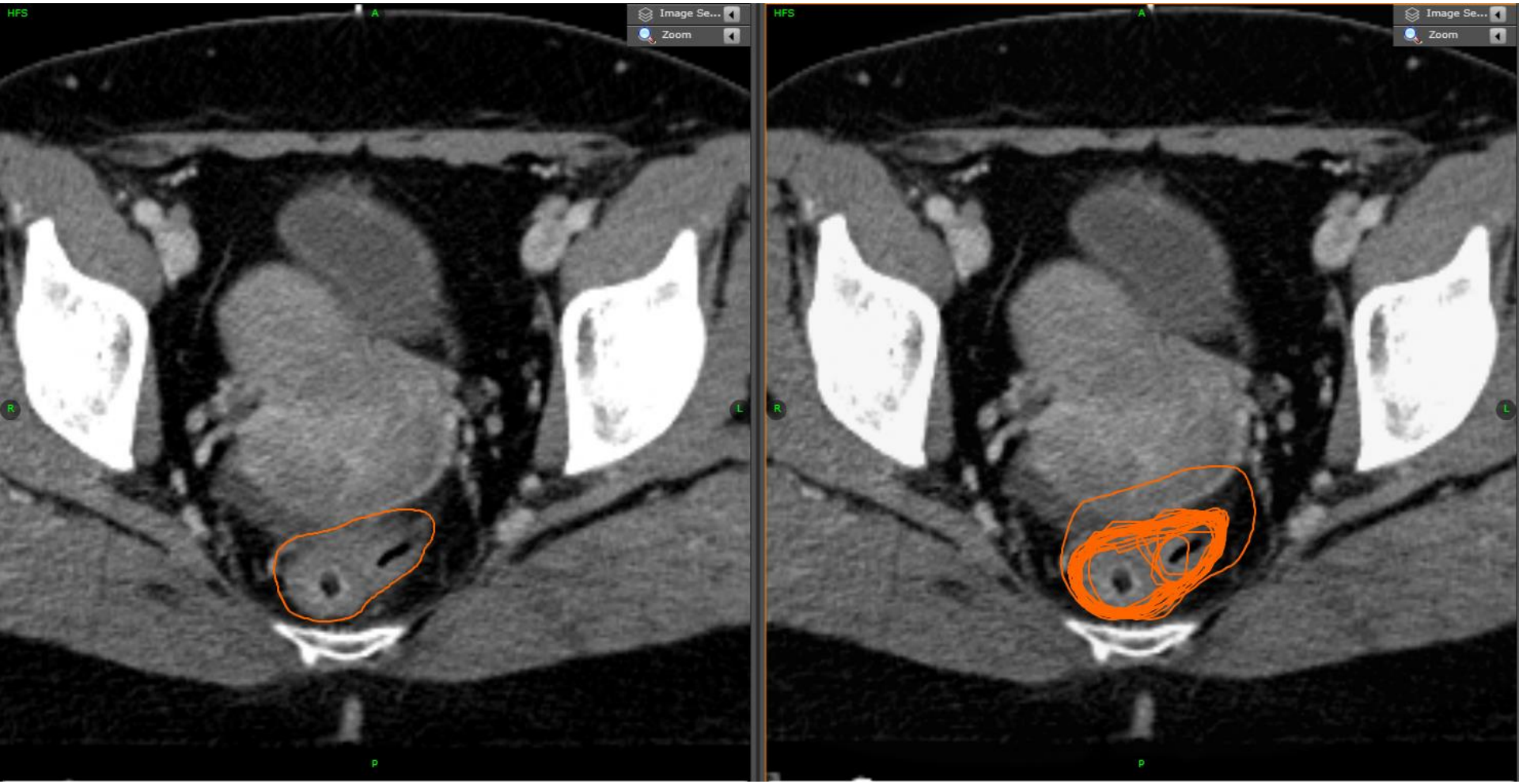
Varying definition of rectosigmoid junction

- Anatomy
  - Cessation of the mesocolon, cessation of the colonic haustra and a blending of the lateral and anti-mesenteric taenia to form a flat anterior muscular band.
- Endoscopy
  - Narrow sharply angulated segment.
- Radiology
  - Anatomists - S3
  - Surgeons - sacral promontory

OAR contouring exercise – rectum

Reference

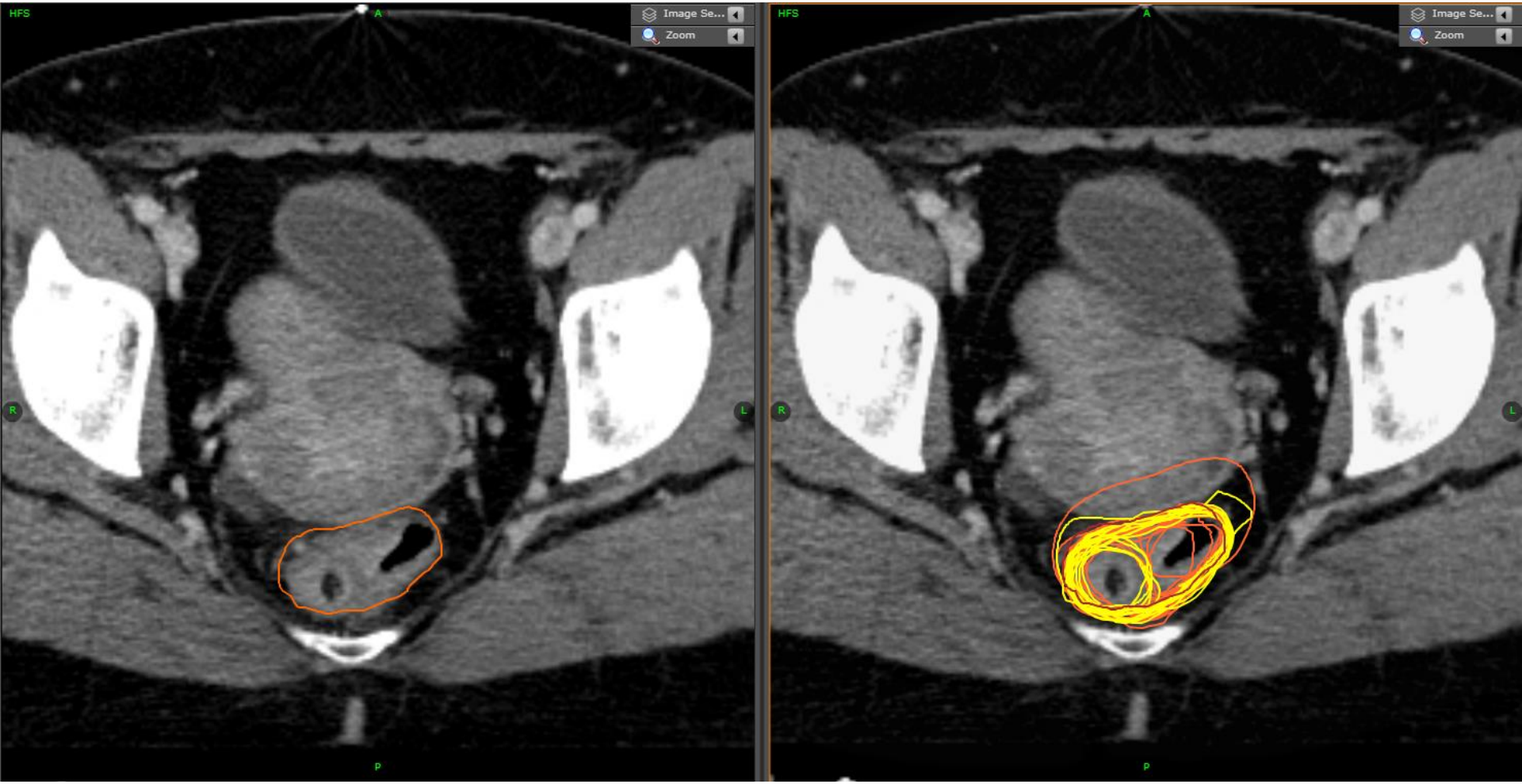
Participants



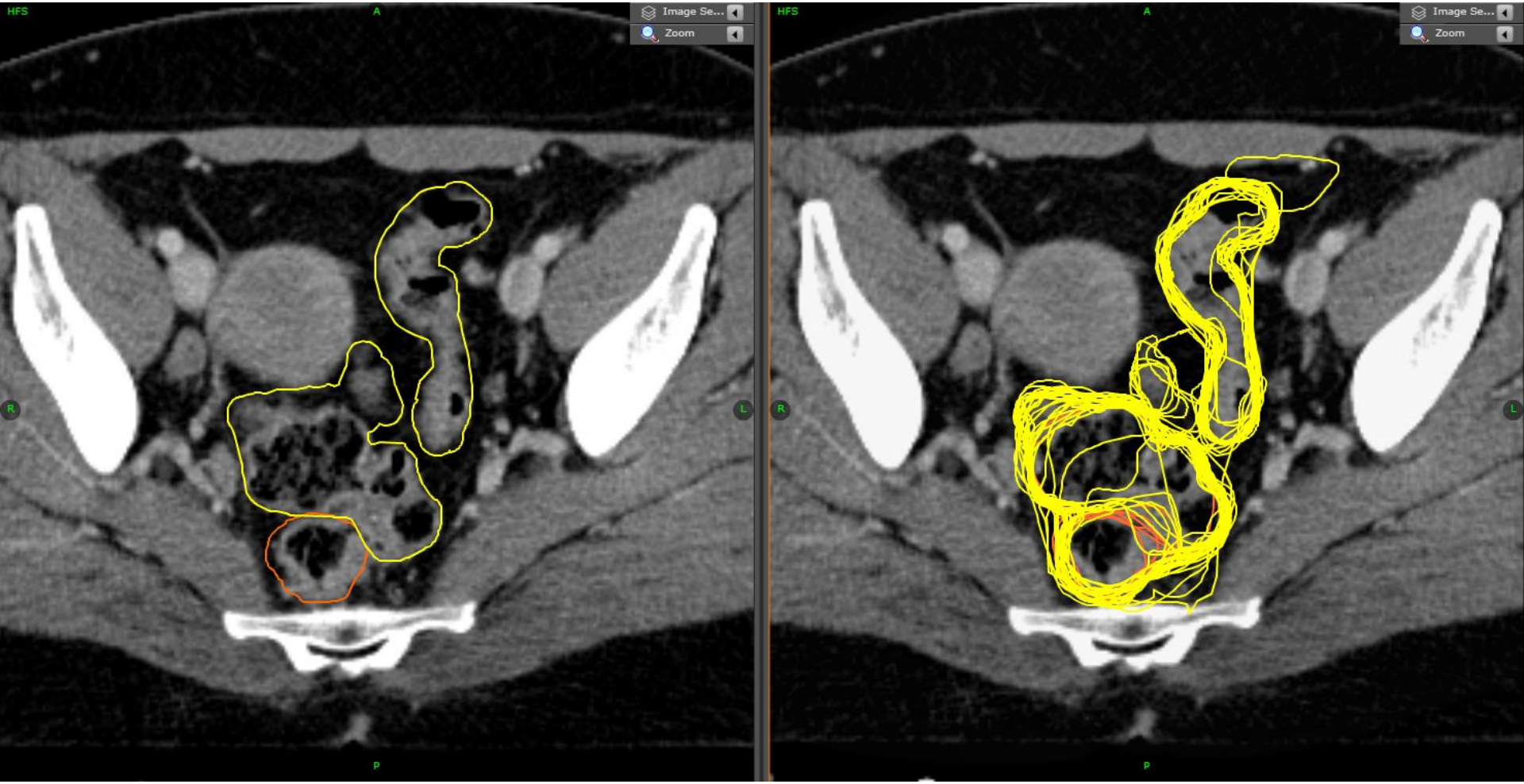
OAR contouring exercise – rectum

Reference

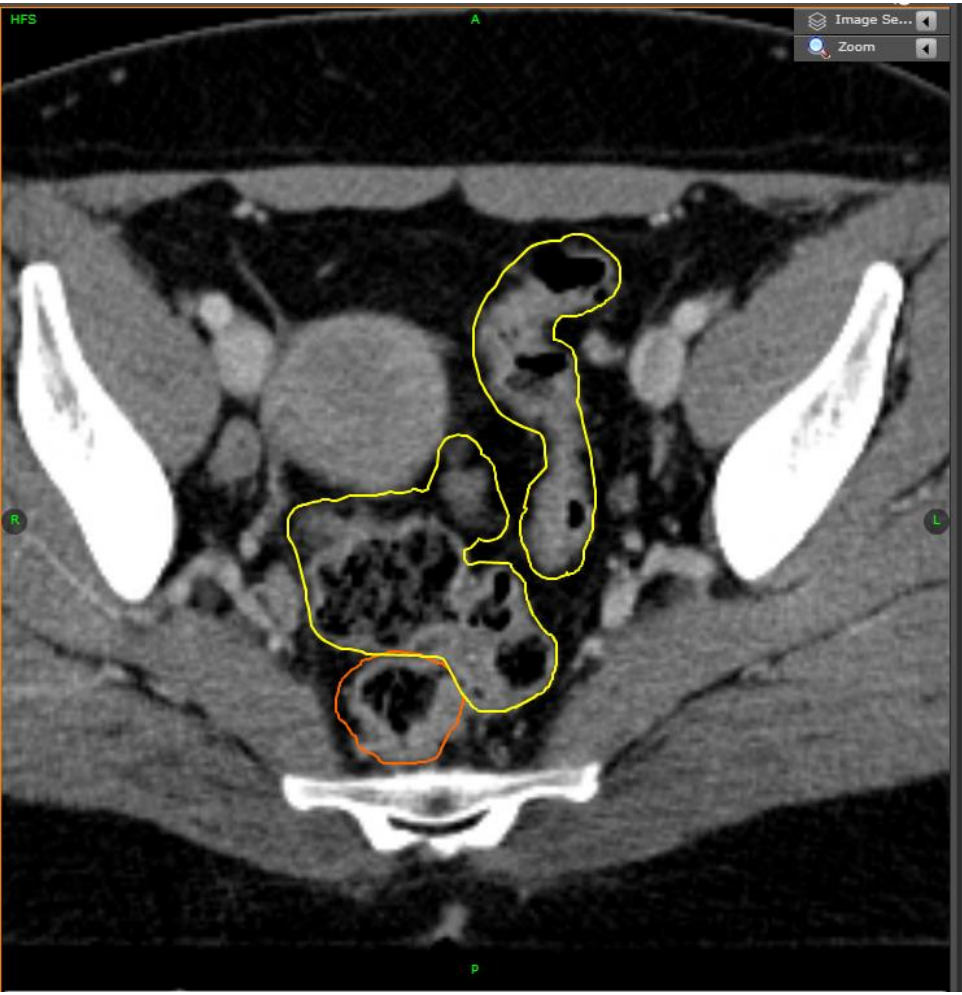
Participants

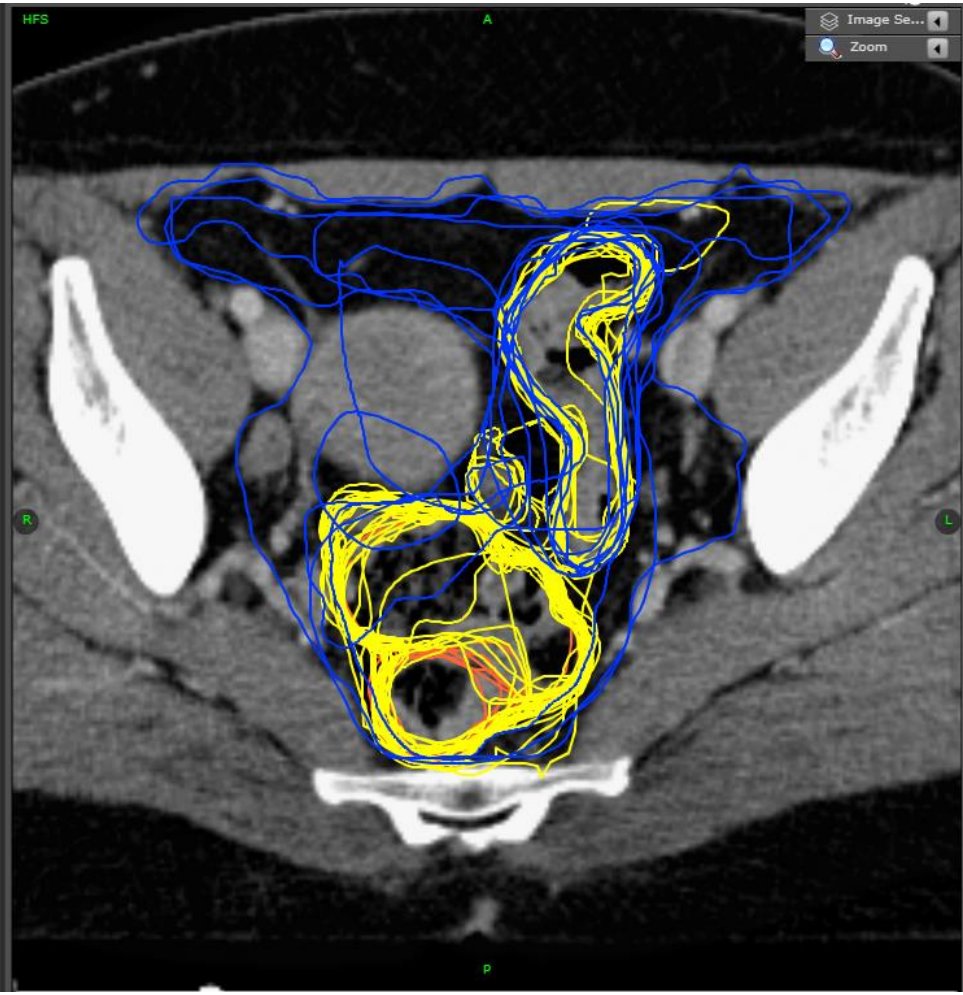


OAR contouring exercise – sigmoid



OAR contouring exercise – sigmoid





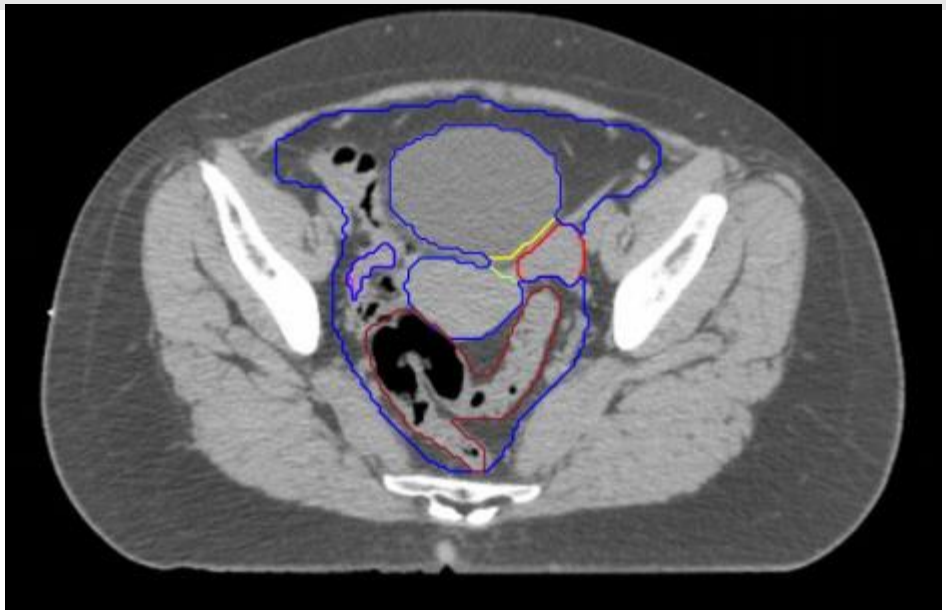
RTOG guidelines

Pelvic Normal Tissue Contouring Guidelines for Radiation Therapy: A Radiation Therapy Oncology Group Consensus Panel Atlas

Received Oct 24, 2011, and in revised form Jan 4, 2012. Accepted for publication Jan 5, 2012

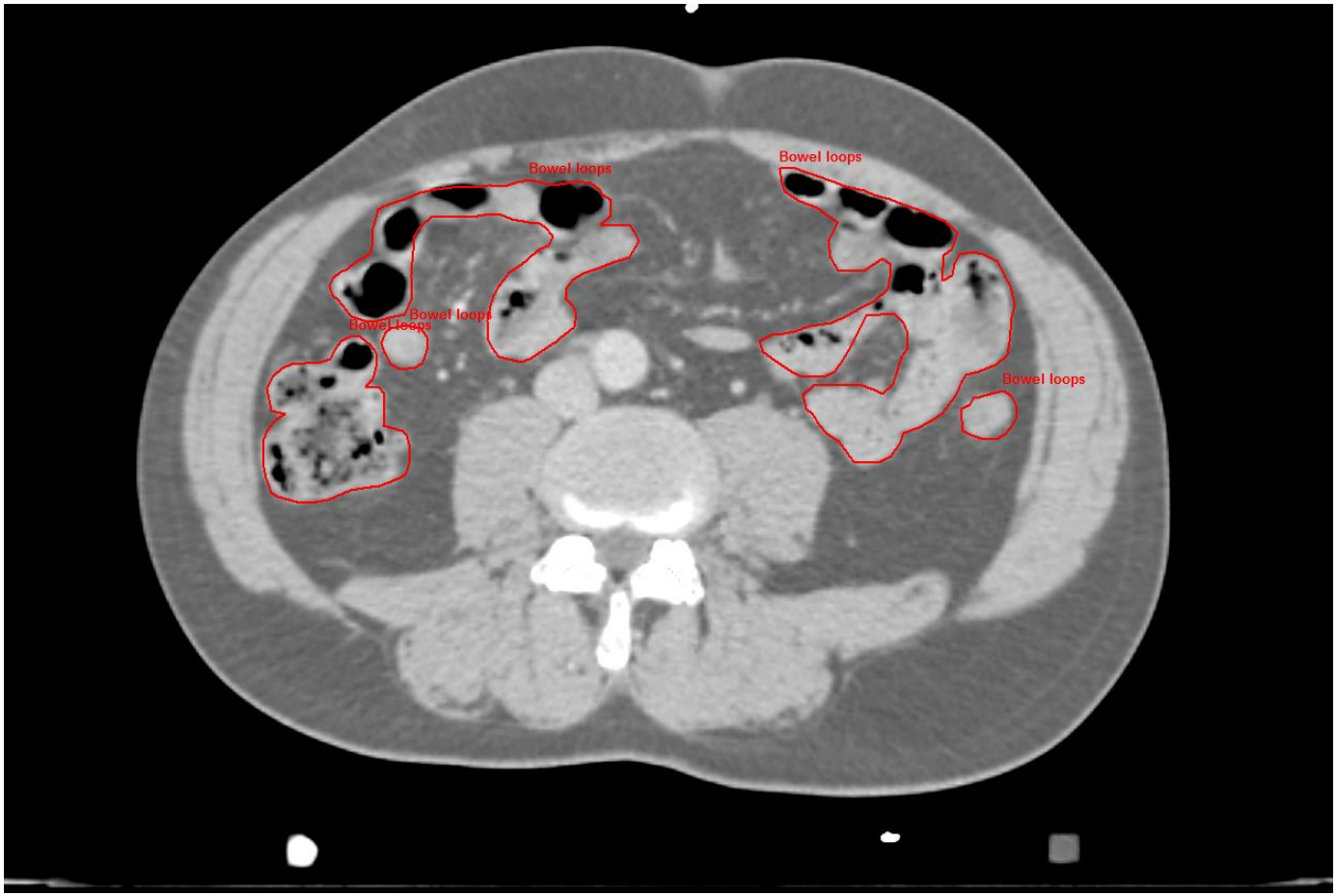
Table RTOG male and female pelvis normal tissue consensus definitions

Organ	Standardized TPS name	Tumor category	Consensus definition
Bowel bag	BowelBag	GU, GYN	Inferiorly from the most inferior small or large bowel loop or above the Rectum (GU) or AnoRectum (GYN), whichever is most inferior.* If, when following the bowel loop rule, the Rectum or AnoRectum is present in that axial slice, it should be included as part of the bag; otherwise, it should be excluded.

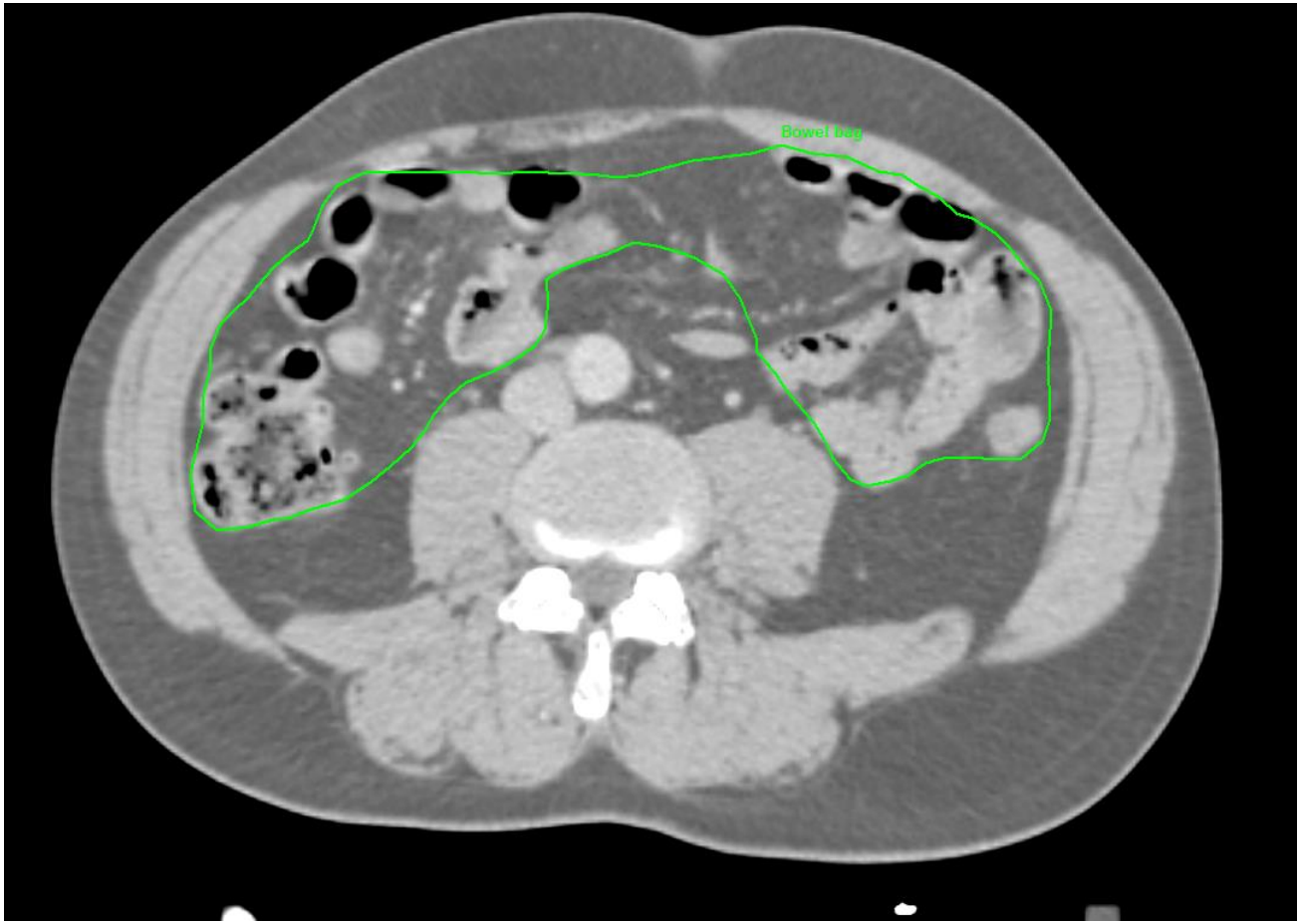


Gay H, et al. Int J Radiat Oncol Biol Phys 2012;83(3):353-362

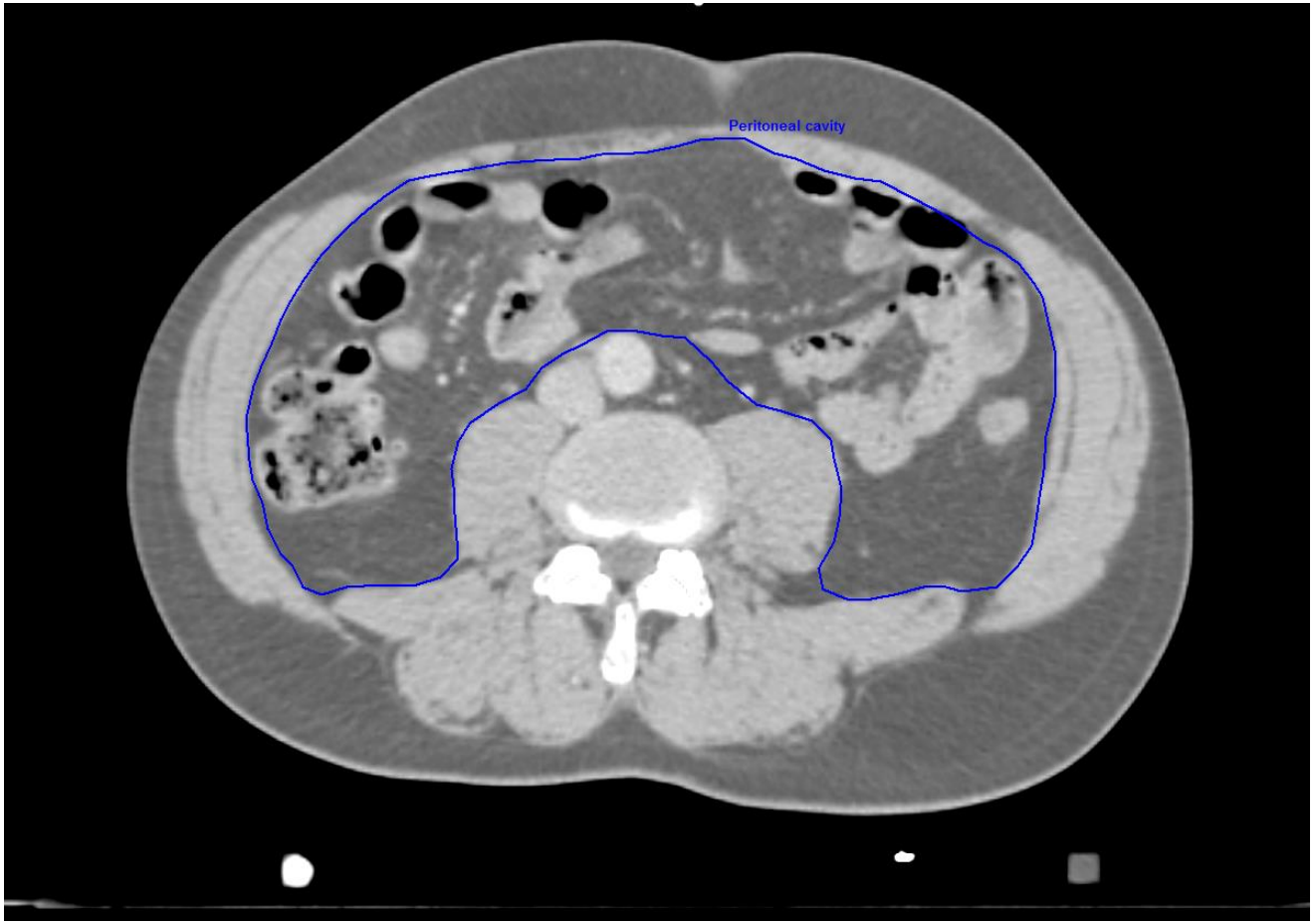
Bowel contouring - bowel loops



Bowel contouring –outermost loops of bowel



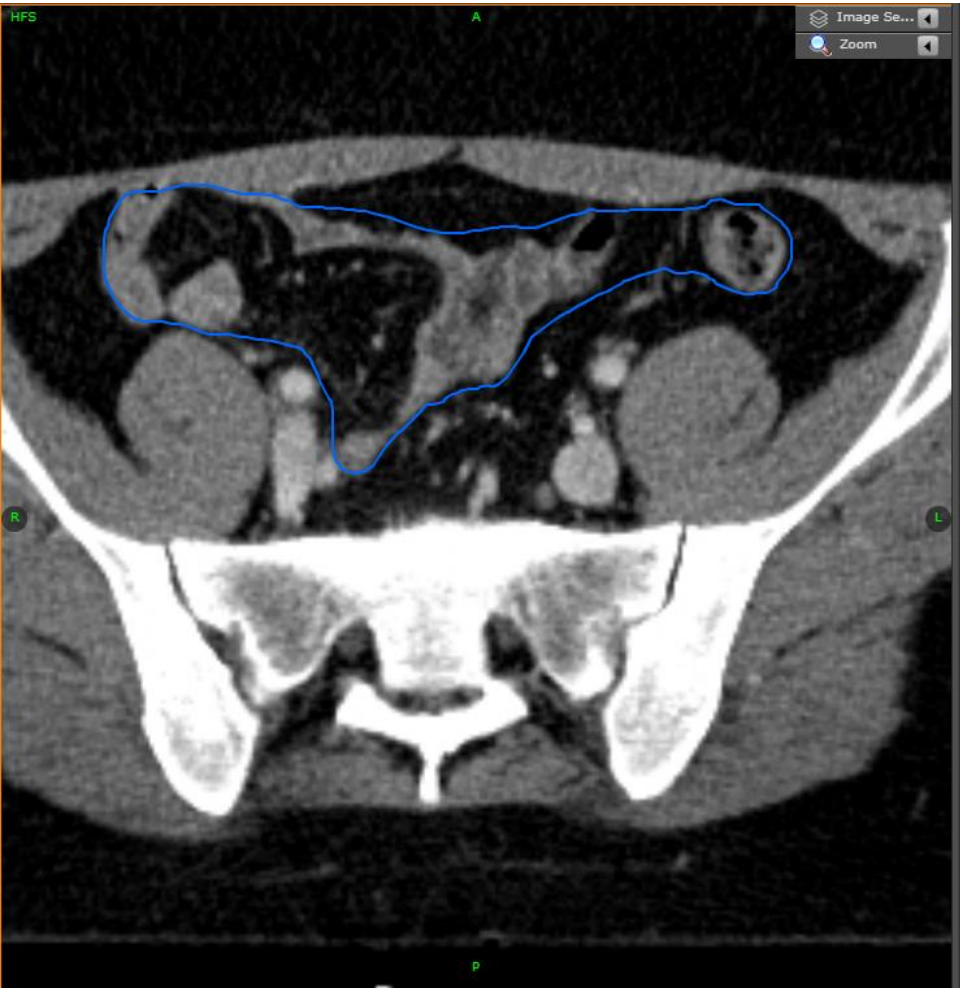
Bowel contouring – peritoneal cavity

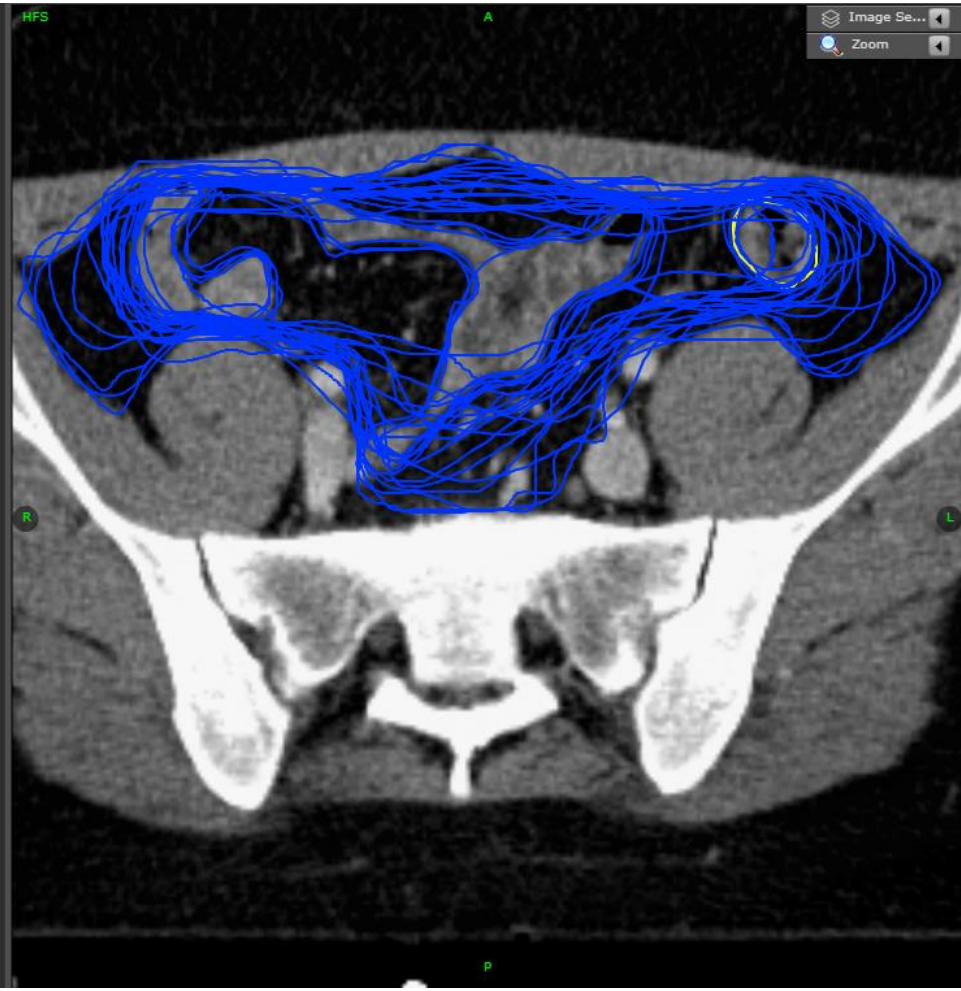


OAR contouring exercise – bowel

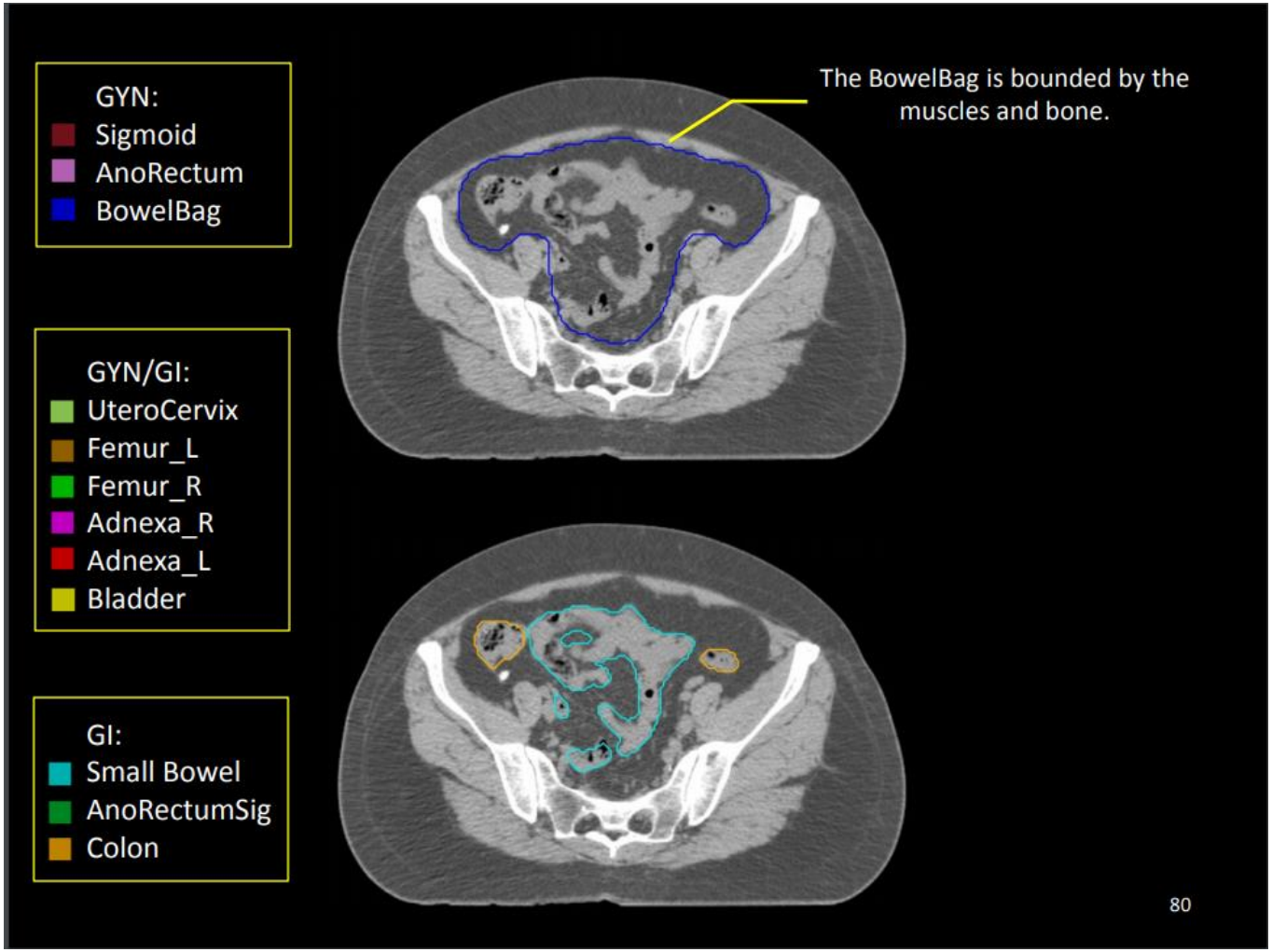
Reference

Participants





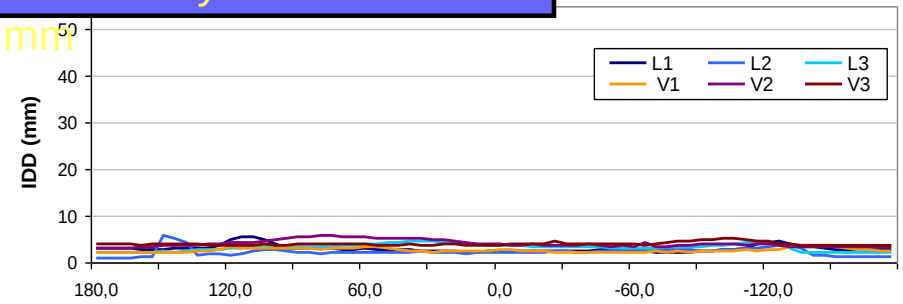
“Bowel bag”

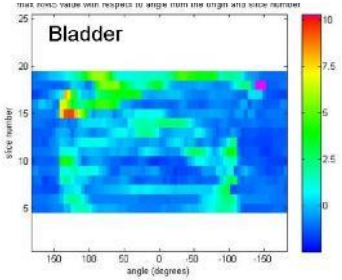


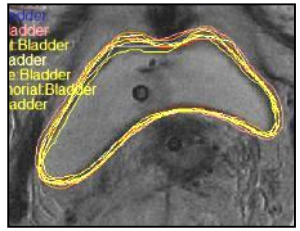
Gay H, et al. Int J Radiat Oncol Biol Phys 2012;83(3):353-362

OAR contouring uncertainty

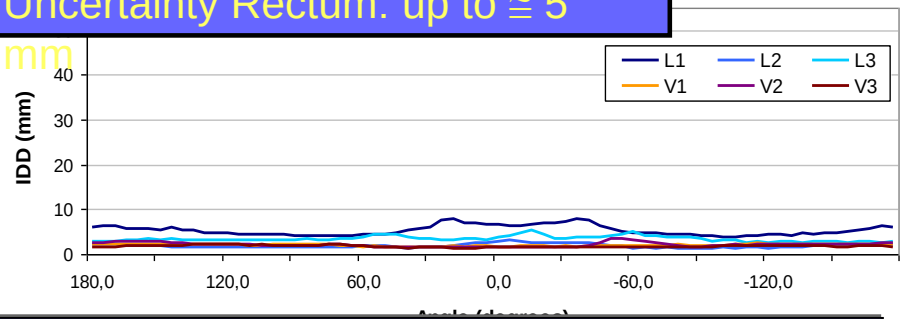
Uncertainty bladder: ≅ 3

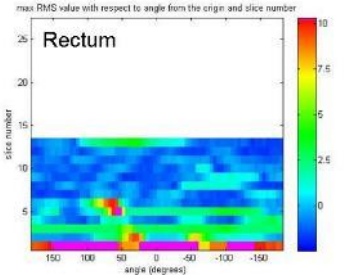


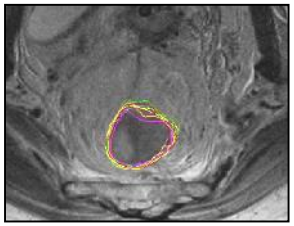




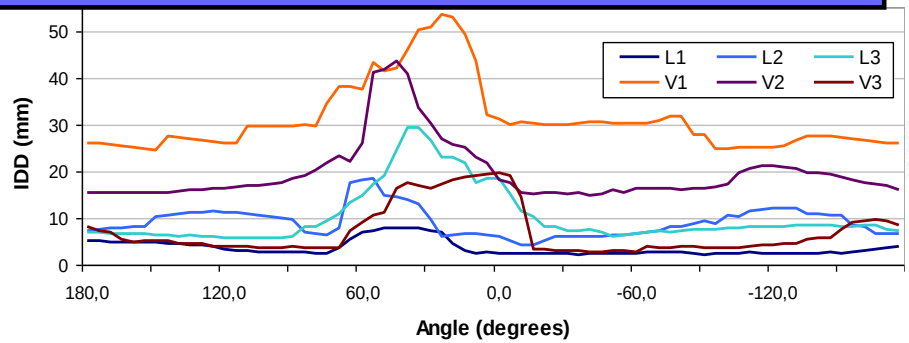
Uncertainty Rectum: up to ≅ 5

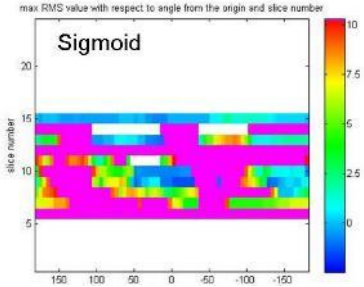


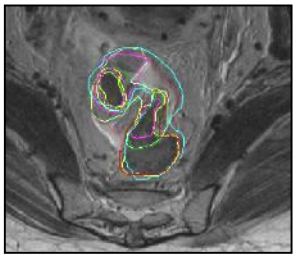




Uncertainty sigmoid colon: up to several cm!



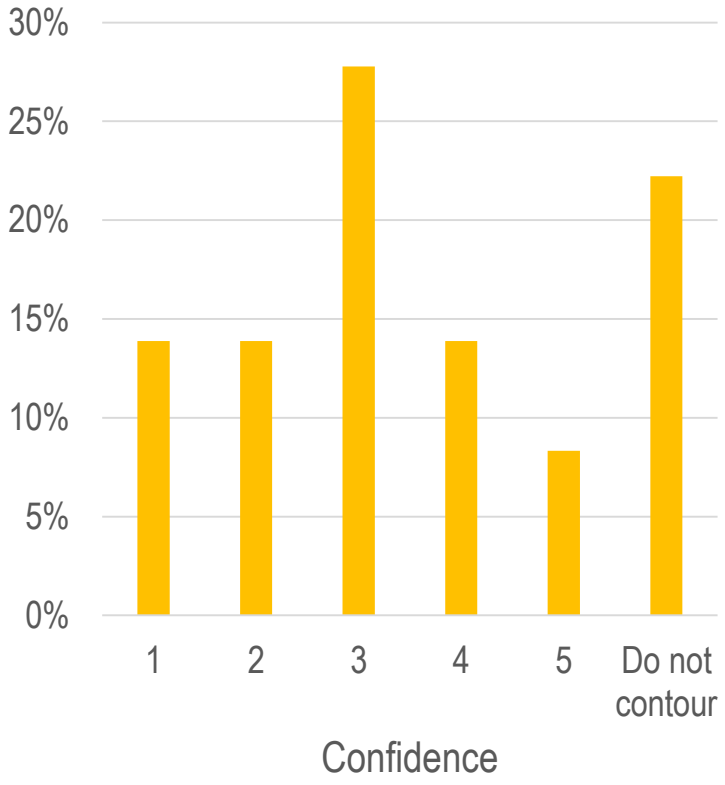


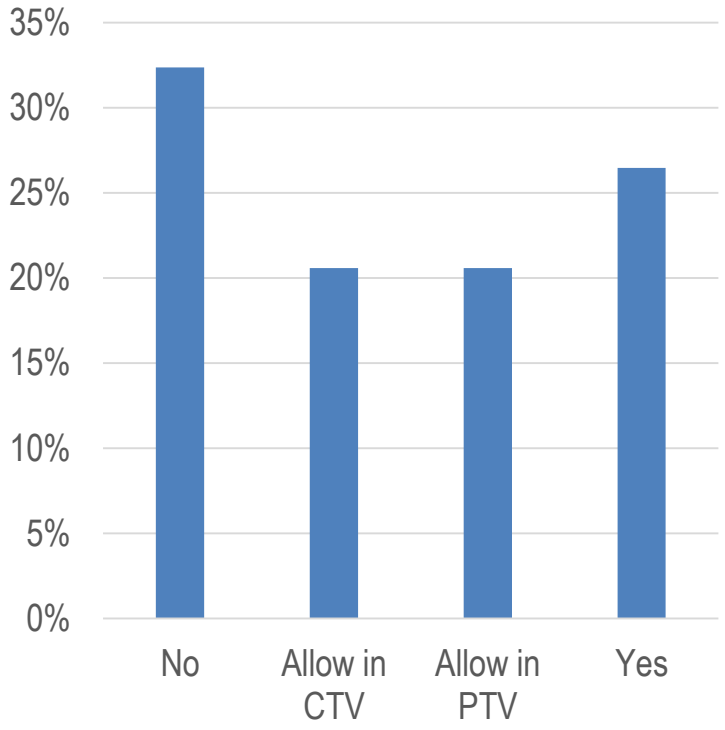


Petric P, et al. Eur J Cancer 2013;49(2):S726

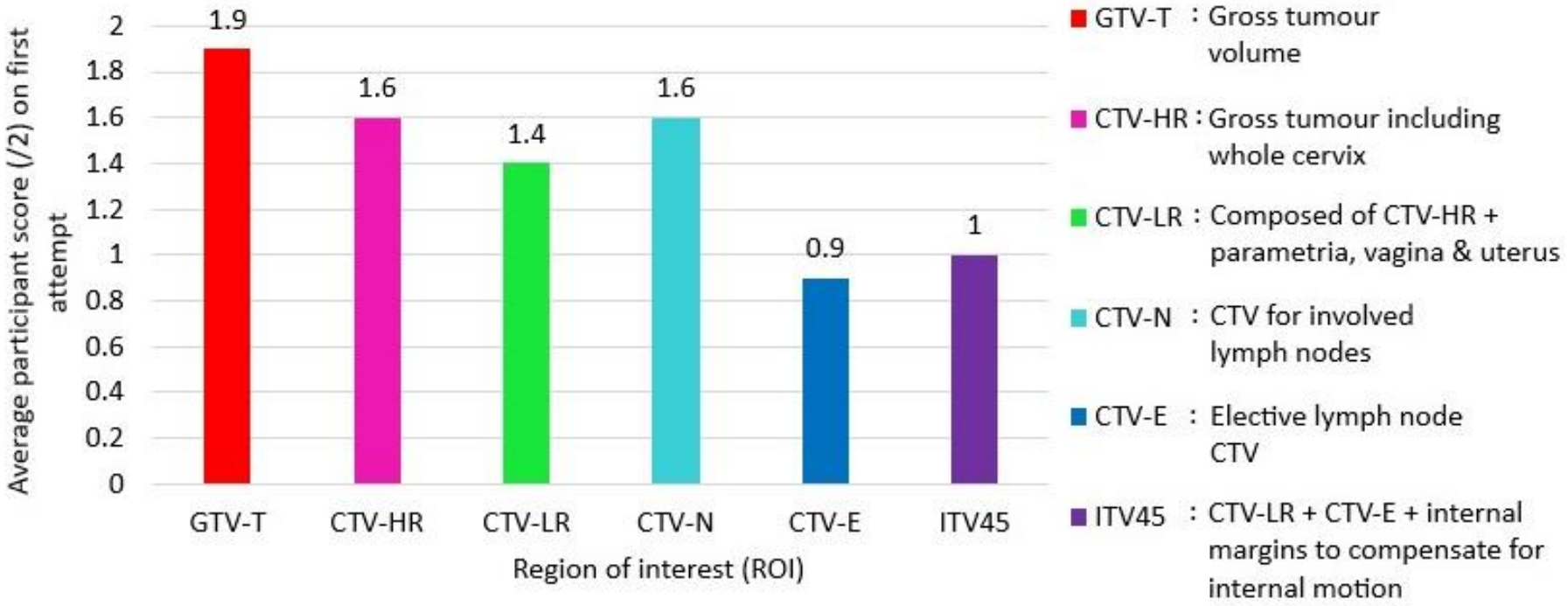
ITV

ITV


30%
25%
20%
15%
10%
5%
0%
1
2
3
4
5
Do not contour
Confidence


35%
30%
25%
20%
15%
10%
5%
0%
No
Allow in CTV
Allow in PTV
Yes

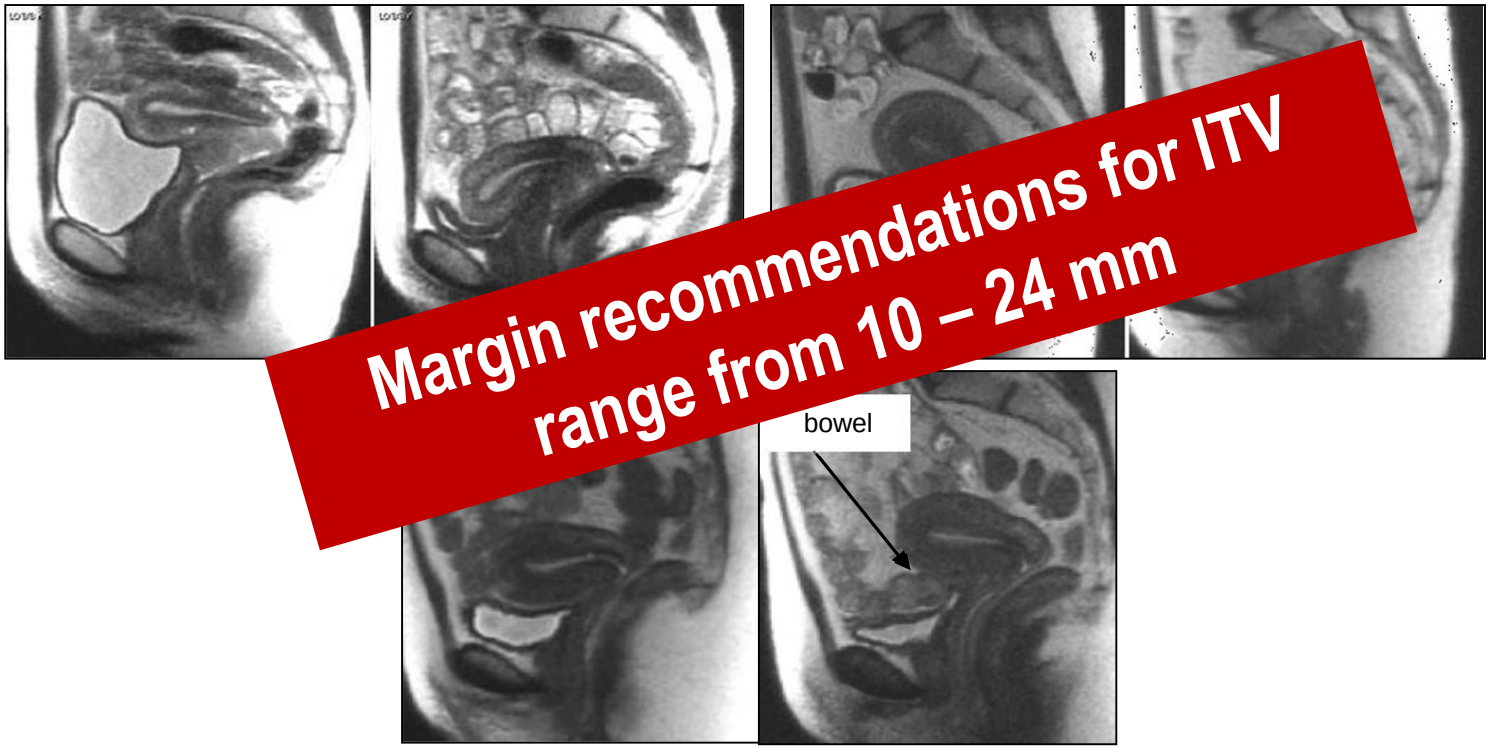
EMBRACE-II accreditation



Courtesy of Simon Duke

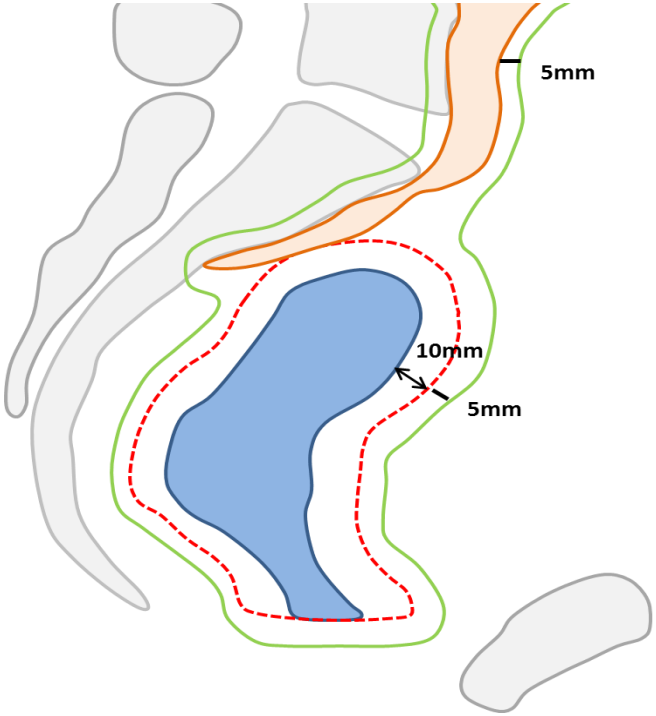
ITV definition

- An internal margin added to the CTV to compensate for internal physiologic movement and variations in size, shape, and position of the CTV.



From: Lim K, et al. Image guidance...In: Viswanathan et al., eds. Gyn Radiat Oncol. Springer 2011 Chan P, et al. IJROBP 2008, Taylor A, et al. Radiother Oncol 2008, Georg D, et al. Strahlenther Onkol 2006, Roeske JC, et al. Radiother Oncol 2003, van de Bunt L, et al. Radiother Oncol 2008, Beadle BM, et al. IJROBP 2009, Dimopoulos J, et al. Strahlenther Onkol 2009.

EMBRACE-II standard margin

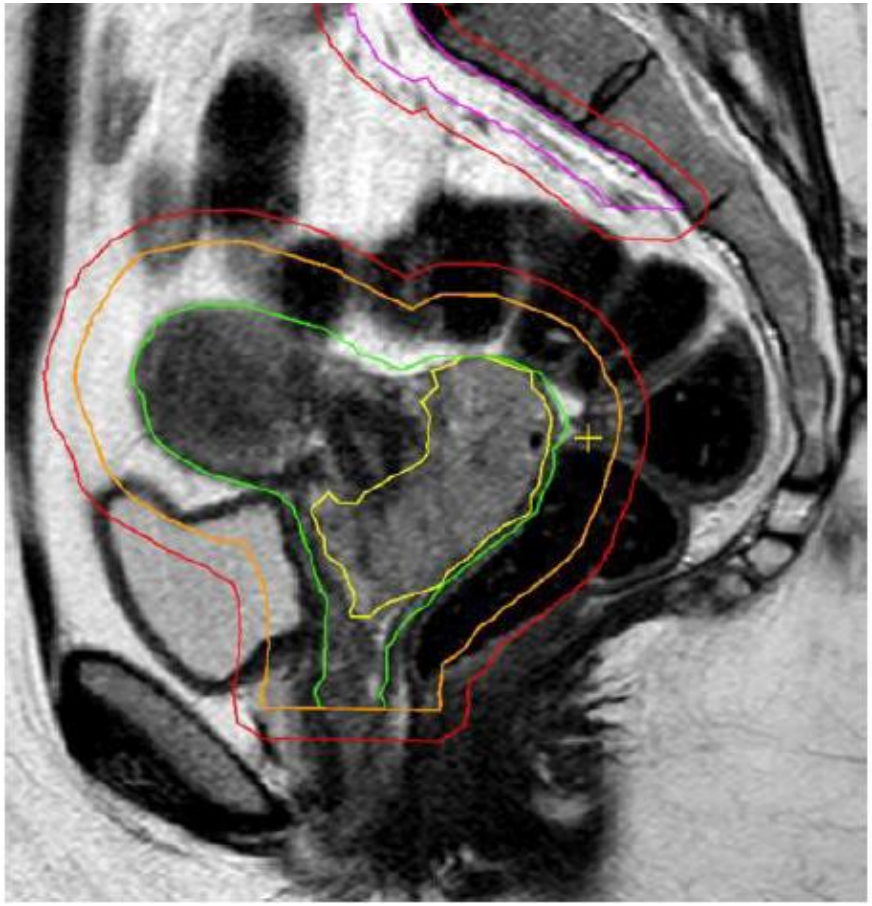


CTV-T LR (CT)

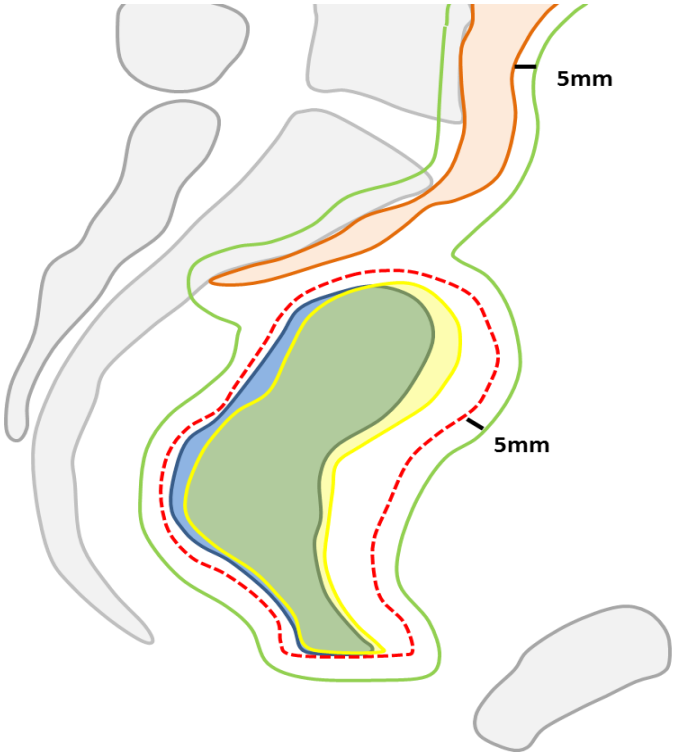
CTV-E

ITV-T LR

PTV-45



EMBRACE-II individualised margin



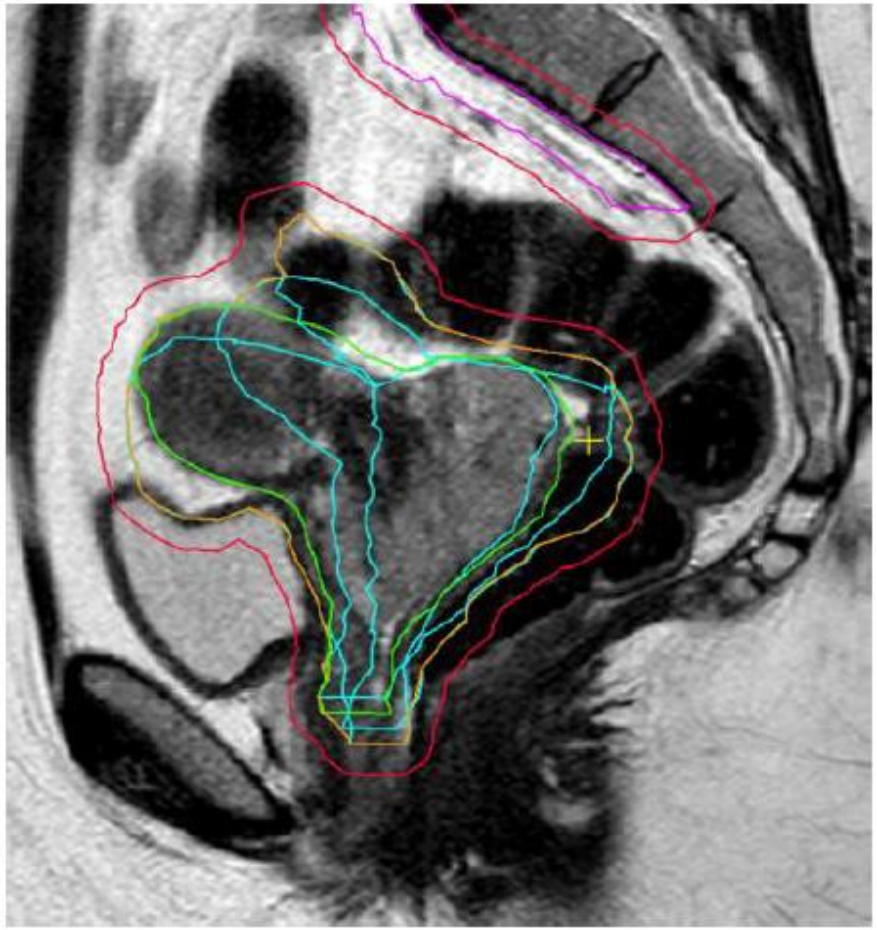
CTV-T LR (CT)

CTV-T LR (MR)

CTV-E

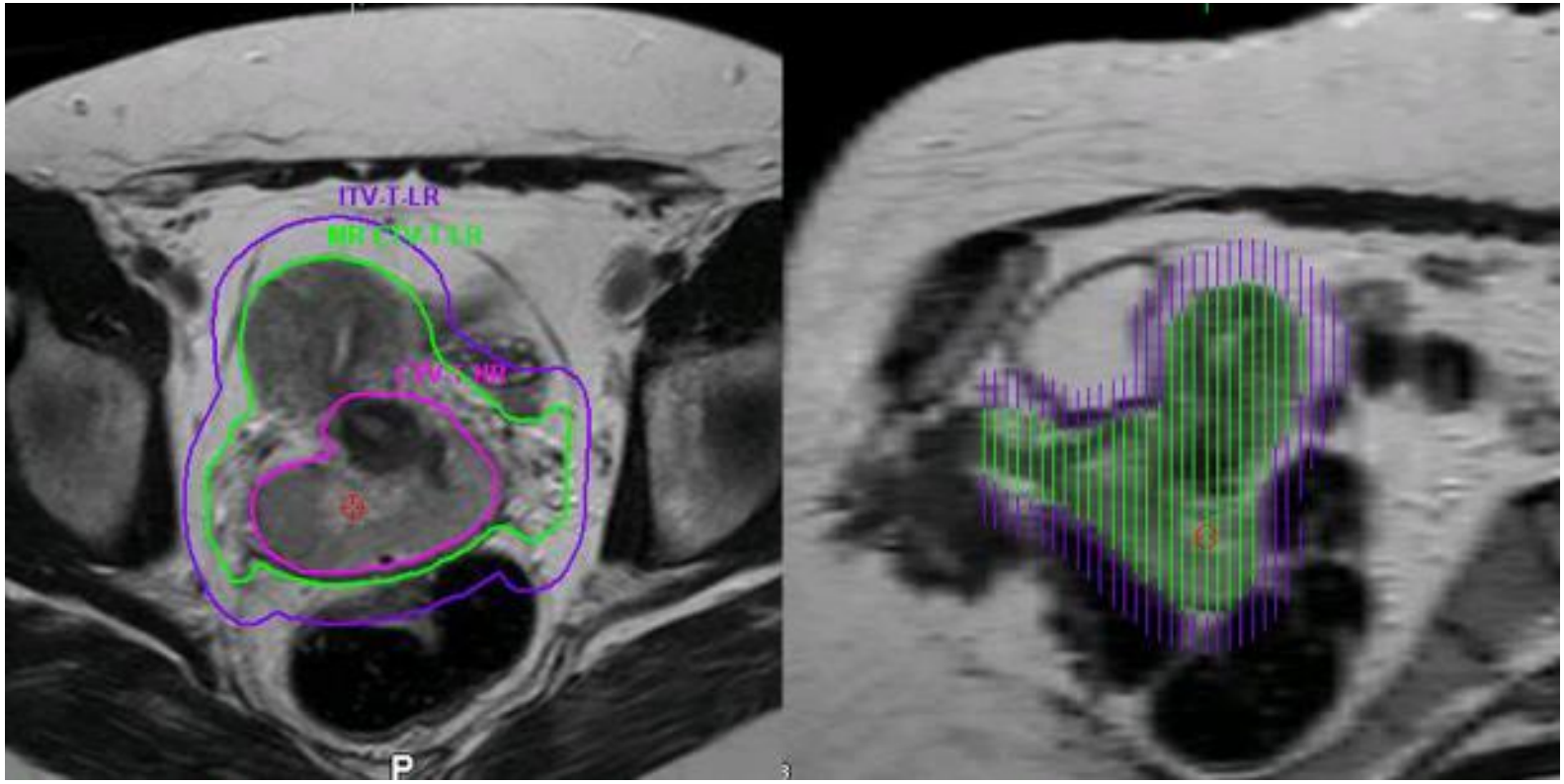
ITV-T LR

PTV-45

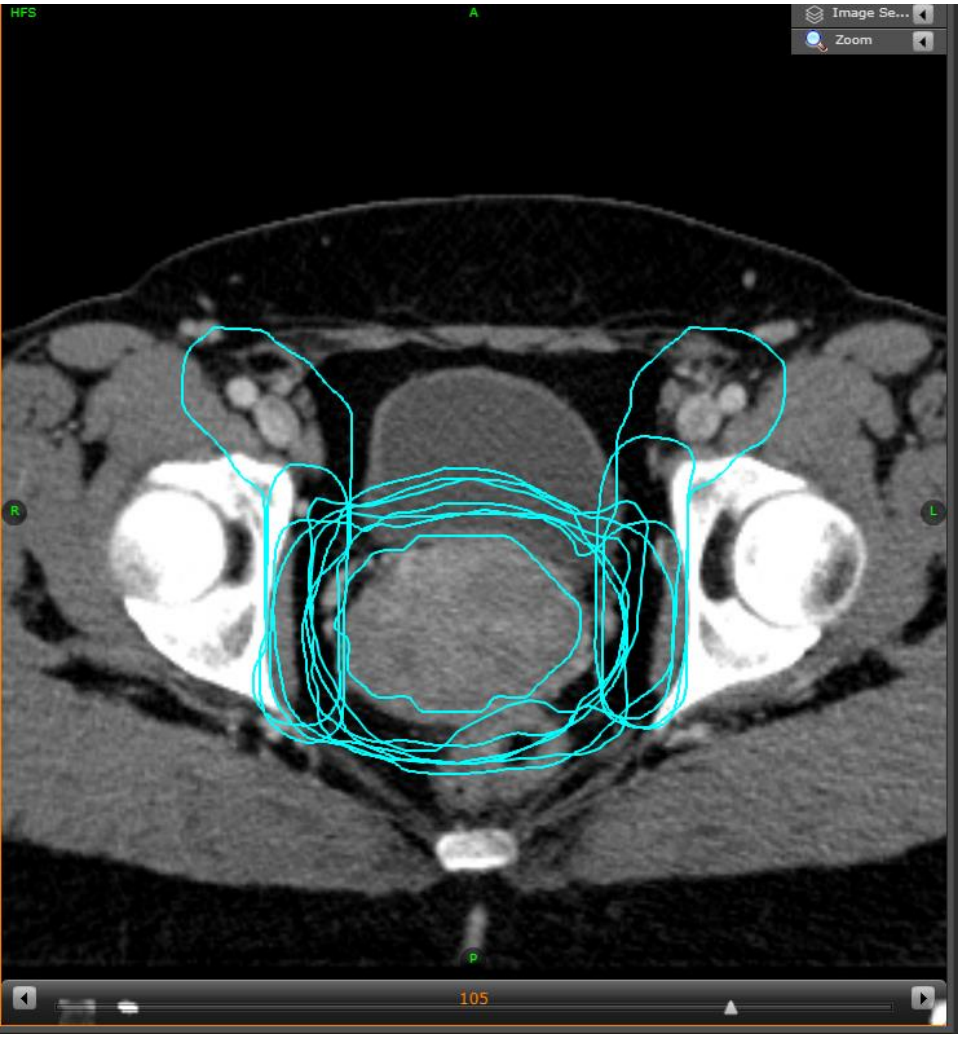


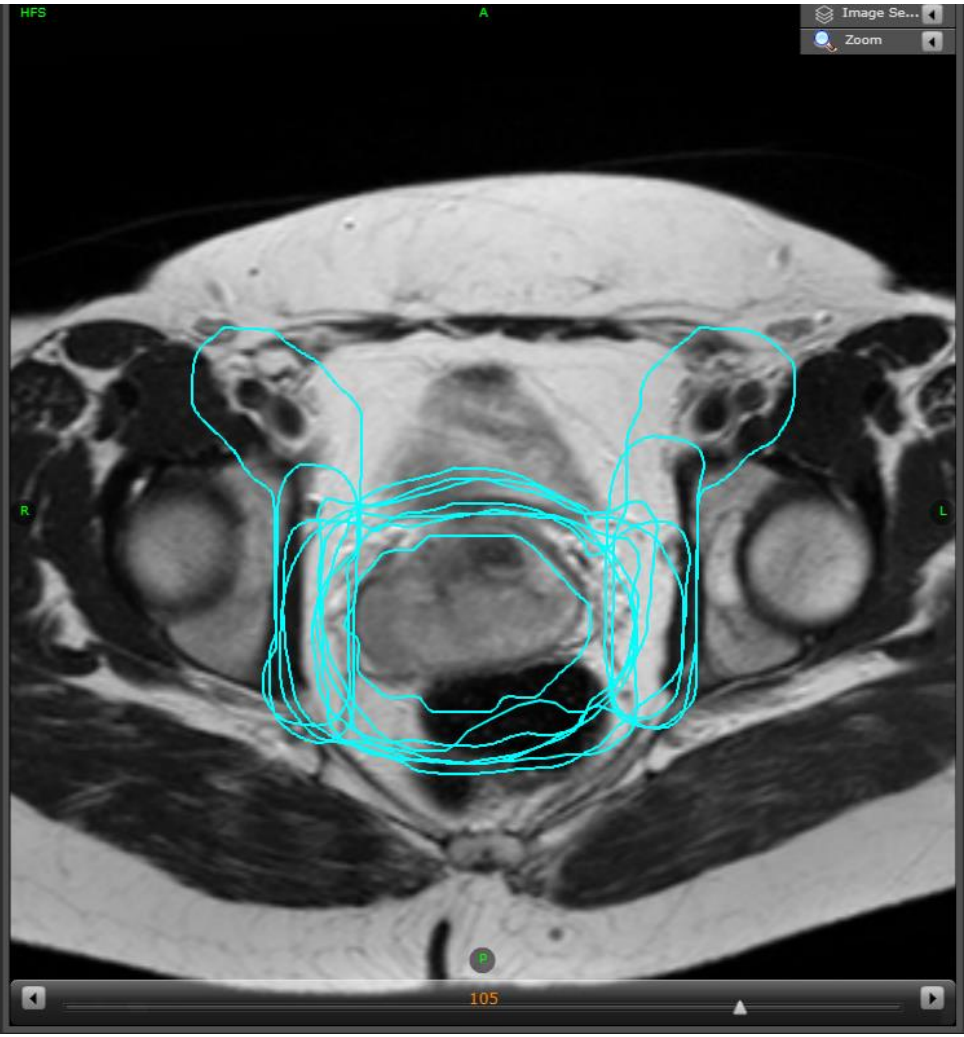
ITV-T

- Most critical area is movement of GTV/CTV-HR.

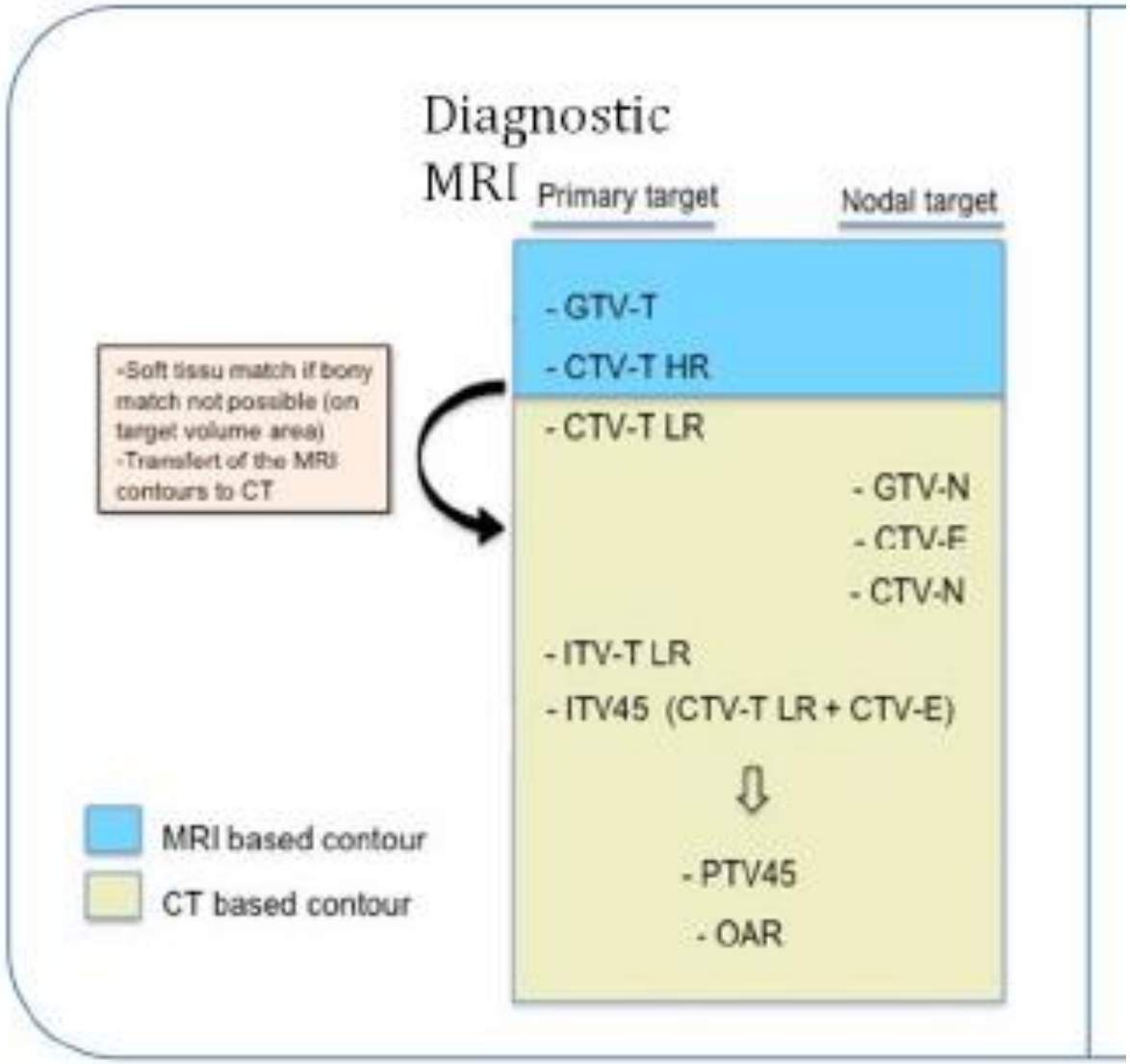


ITV-T LR participants





EMBRACE-II


Diagnostic
MRI
Primary target
Nodal target
- GTV-T
- CTV-T HR
- CTV-T LR
- GTV-N
- CTV-E
- CTV-N
- ITV-T LR
- ITV45 (CTV-T LR + CTV-E)
- PTV45
- OAR
-Soft tissu match if bony match not possible (on target volume area)
-Transfert of the MRI contours to CT
MRI based contour
CT based contour

Tip

- GTV-T MRI
- CTV-T HR MRI
- Cervix CT

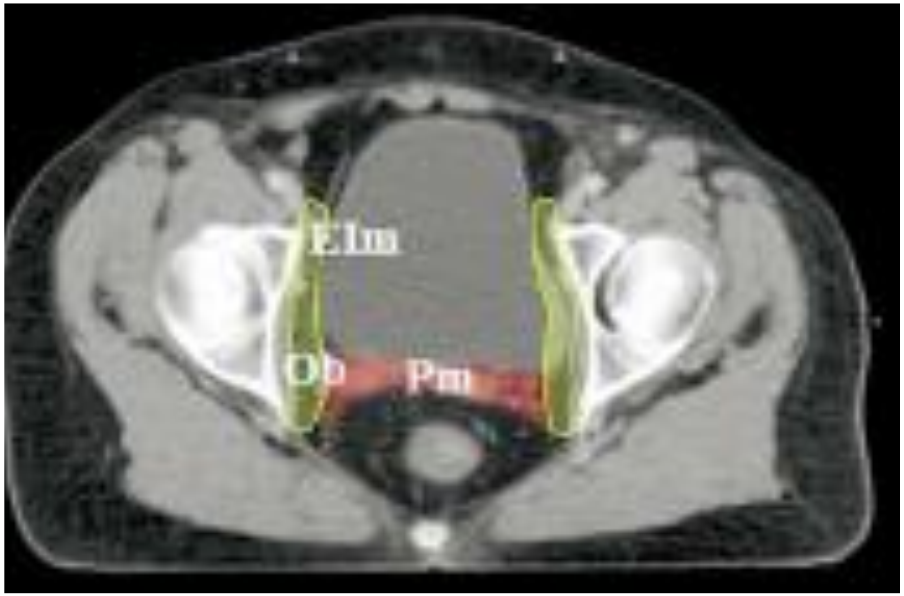
Composite CTV-T HR
+ 5 mm = ITV-T HR

- CTV-T LR CT
- Uterus MRI

ITV-T LR
+ 5=10 mm

ITV for nodes?

- "The CTV is an anatomical-clinical concept"
- Taylor – CTV-E obturator nodes
  - Create a strip medial to the pelvic sidewall that should be at least 18 mm wide.



Conclusion

Summary

- Contouring of targets (tumour + nodal) and OARs for IMRT cervix is complex
- Some inconsistencies in guidelines
- Need to use clinical judgement
  - Understand principles and rationale
- Priority – avoid geographical miss

Image guidance, organ motion and ITV/PTV

ESTRO Teaching Course
Image-guided radiotherapy & chemotherapy in gynaecological cancer - with a special focus on adaptive brachytherapy

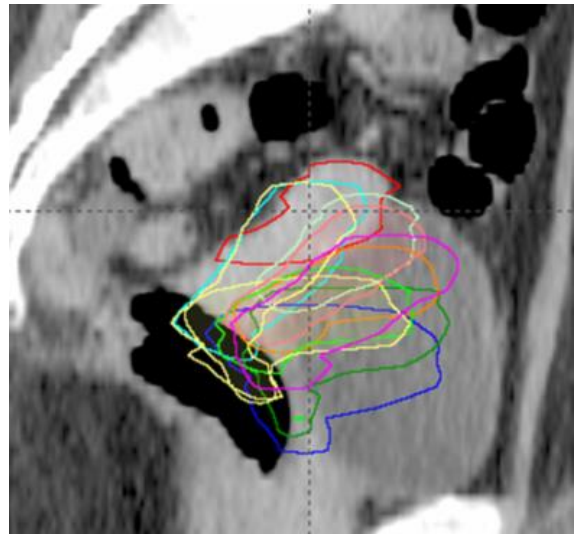
Madrid 2018

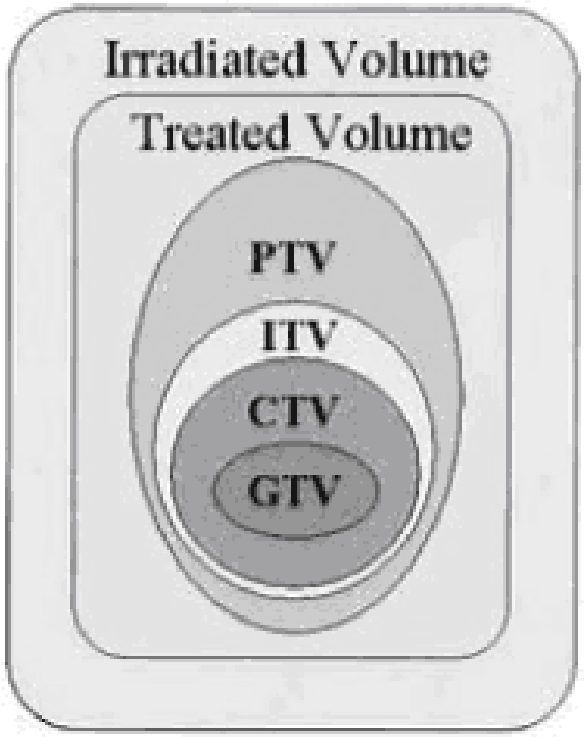
Kari Tanderup

Richard Pötter

ITV and PTV

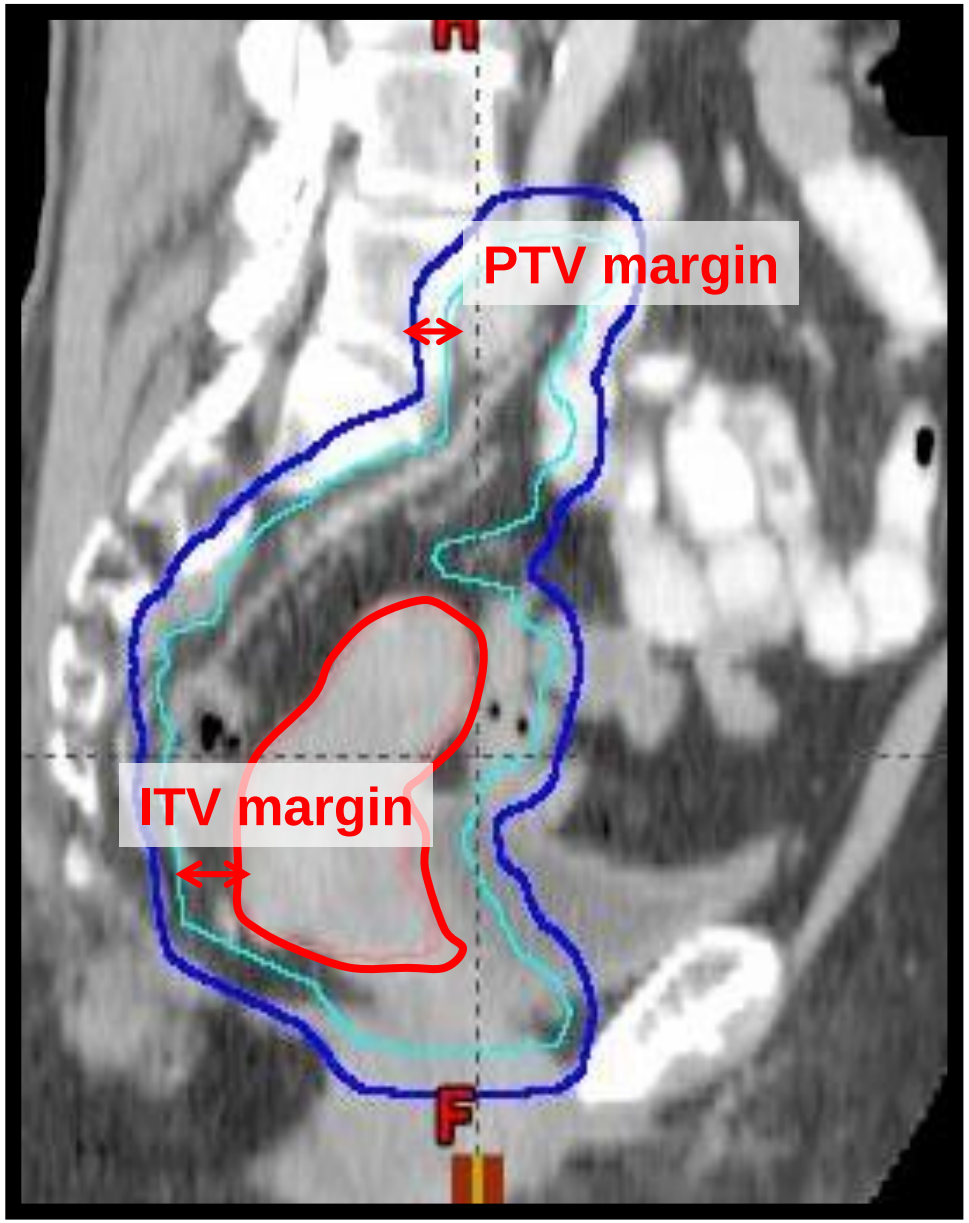
- ITV: Internal variations
  - Position, size and shape of CTV
    - Tumour shrinkage
    - Organ movement
    - Organ deformation
- PTV: External variations
  - Beam positioning
  - Patient set-up (e.g. uncertainties when setting up according to skin marks)





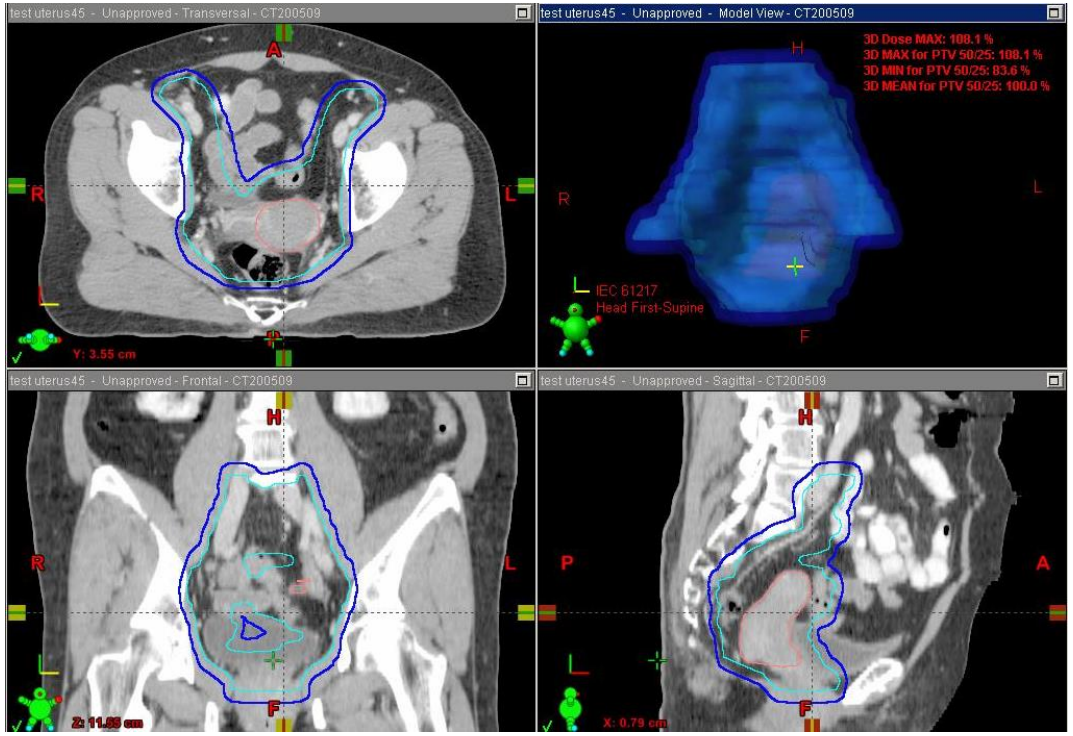
Margins in cervix cancer

- Elective CTV
  - PTV margin
- Pathologic nodes
  - PTV margin
- Primary CTV
  - ITV margin
  - PTV margin



PTV elective lymph node target volume

- Assumption:
  - Lymph nodes are in a fixed relation to bony anatomy
  - Bony registration aligns elective lymph node target
- Image fusion:
  - CBCT/EPID/kV

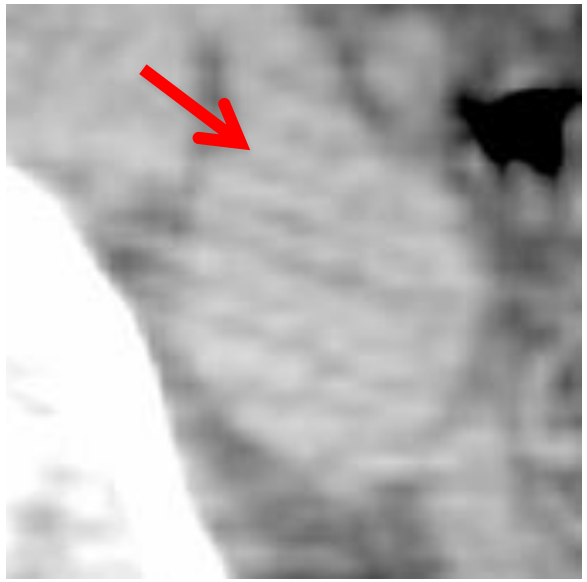


PTV pathological lymph nodes

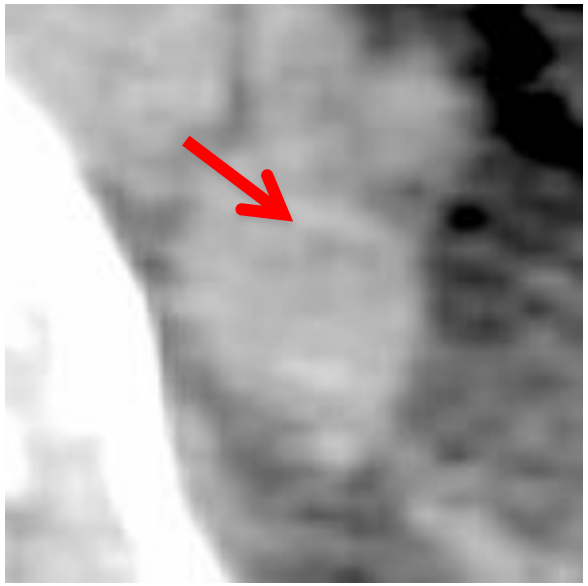
Assumption:

- **Lymph nodes are in a relatively fixed relation to bony anatomy**
- **Bony registration aligns pathological lymph node target**

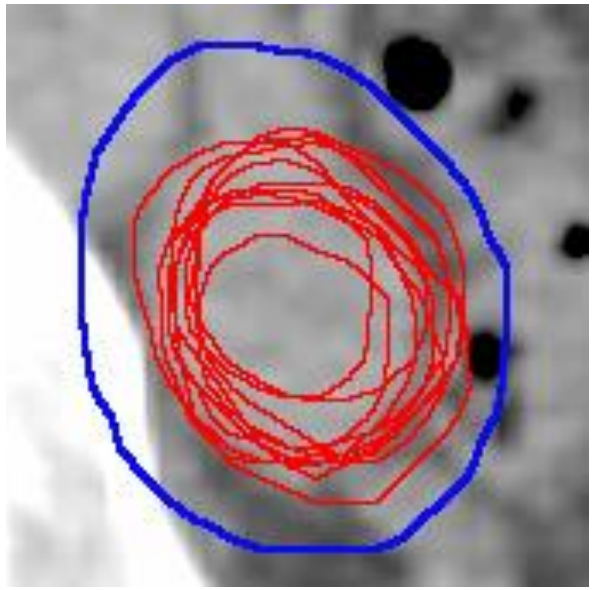
Most often pathological lymph nodes shrink during RT



CBCT 1st treatment



CBCT 24th treatment



PTV (blue)

GTV on 10 CBCT (red)

Anne Ramlov, Radiother Oncol. 2017 Apr;123(1):158-163

Why does the margin matter?

D. Verellen *et al.*, Nature Reviews Cancer 2007

r

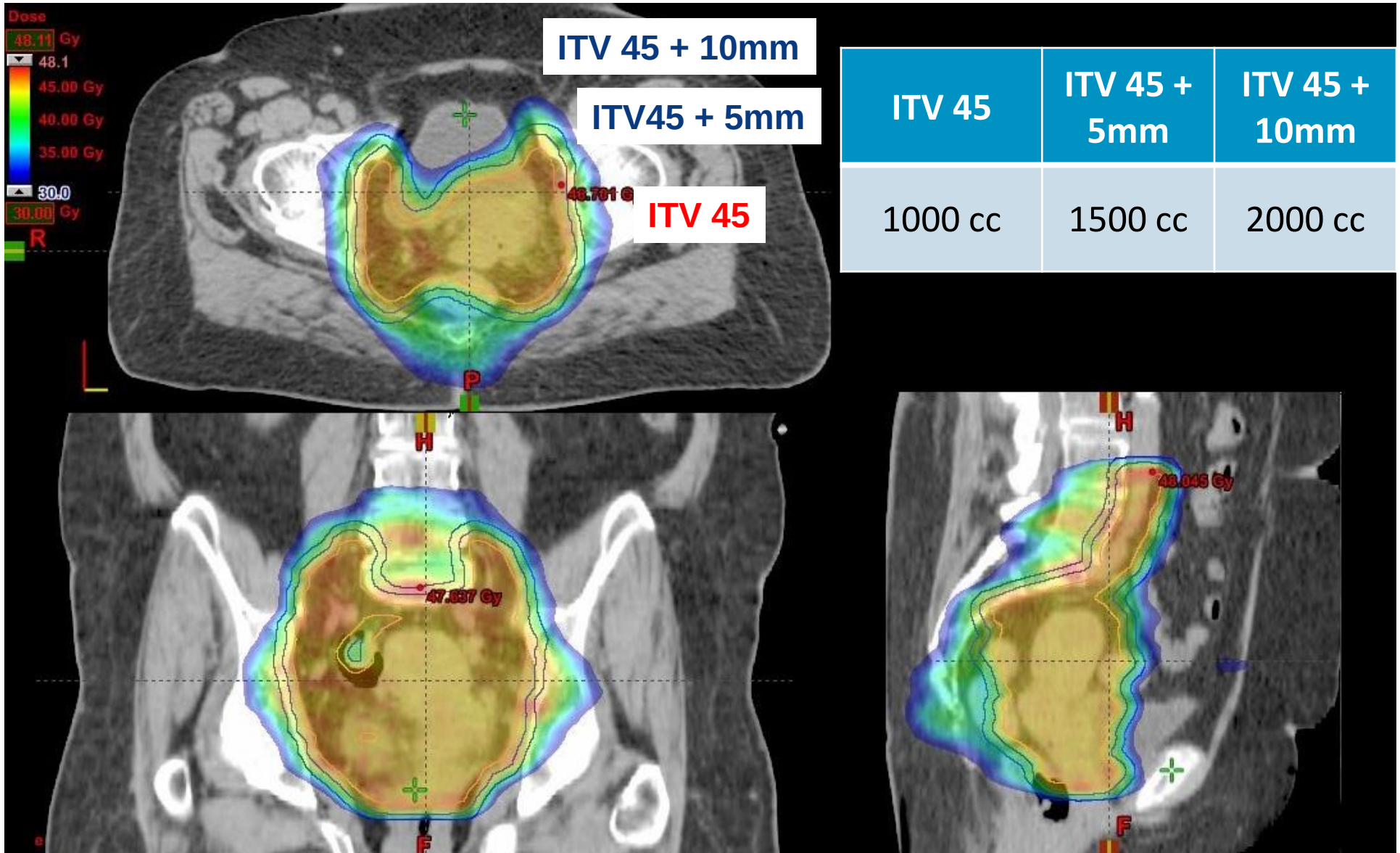
↓

πr^2

↓

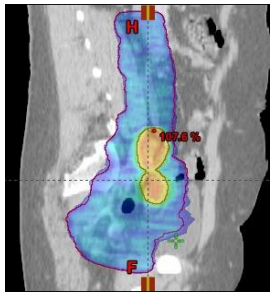
$4/3\pi r^3$

Let’s take a look at the orange and the peel…



ITV 45	ITV 45 + 5mm	ITV 45 + 10mm
1000 cc	1500 cc	2000 cc

EMBRACE I, EMBRACE II: EBRT volume (V43Gy)

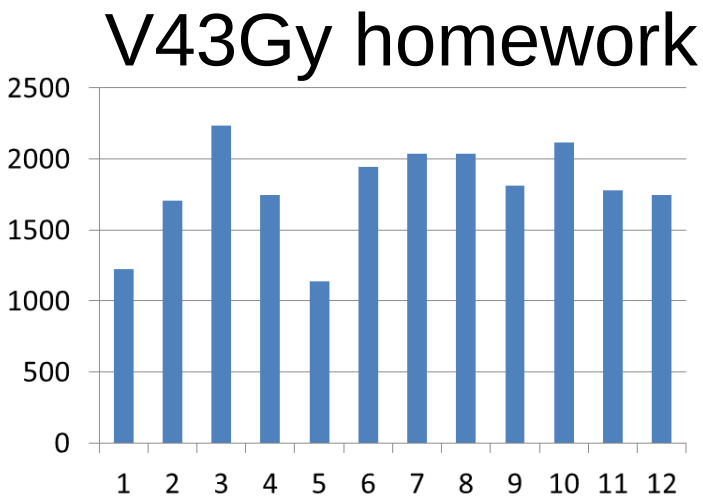


	Pelvic	Para-aortic
CTV vol (cc)	~ 1000 cm^3	~ 1500 cm^3
PTV vol (cc) 5mm margin	~ 1500 cm^3	~ 2000 cm^3
V43Gy (cc) EMBRACE I	~ 2500 cm^3	~ 3000 cm^3
V43Gy (cc) EMBRACE II	~ 1500 cm^3	~ 2000 cm^3

CRT → IMRT : ↘ 500cm^3 (V43)

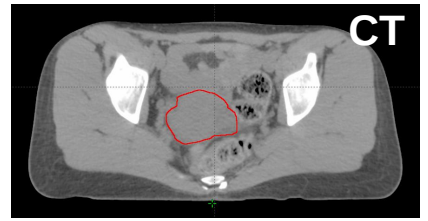
50Gy → 45Gy : ↘ 400cm^3 (V43)

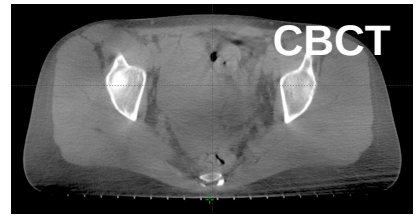
xmm → 5mm : ↘ x cm^3 (V43)



Skin marks versus daily bony registration

- Daily image guidance with bony fusion
  - Initial set-up according to skin marks
  - Image fusion according to bone
  - Verification of fusion
  - Couch correction
  - ***Typically 5mm PTV margin***





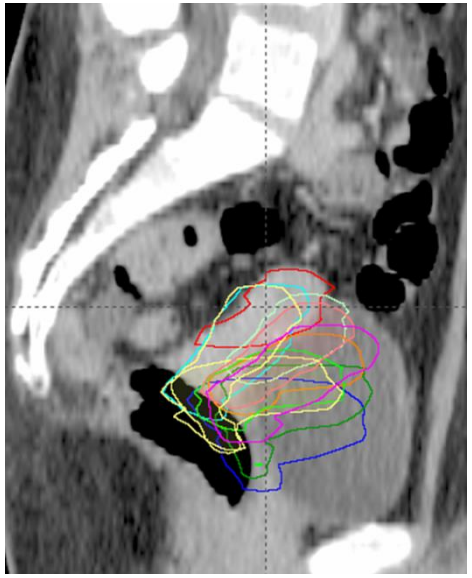
- Set-up on skin marks (no daily image guidance):
  - Imaging at first RT or e.g. weekly
  - ***Typically 7-10mm PTV margin***

L.Laursen, RO 105 (2012) 220–225

Which total dose (EBRT+BT) do you think this patient received to the non-involved uterus?

Patient case:

- 45/25fx EBRT
- 40Gy EQD2 BT
- 1.5cm CTV-PTV margin
- 50% of fractions: uterus outside PTV



EBRT dose: **38Gy**

BT dose: **6Gy**

EBRT+BT dose: **44Gy**

(Normally patients receive >5-10Gy to the uterus from BT)

Sapru et al, Radither Oncol 107 (2013) 93–98

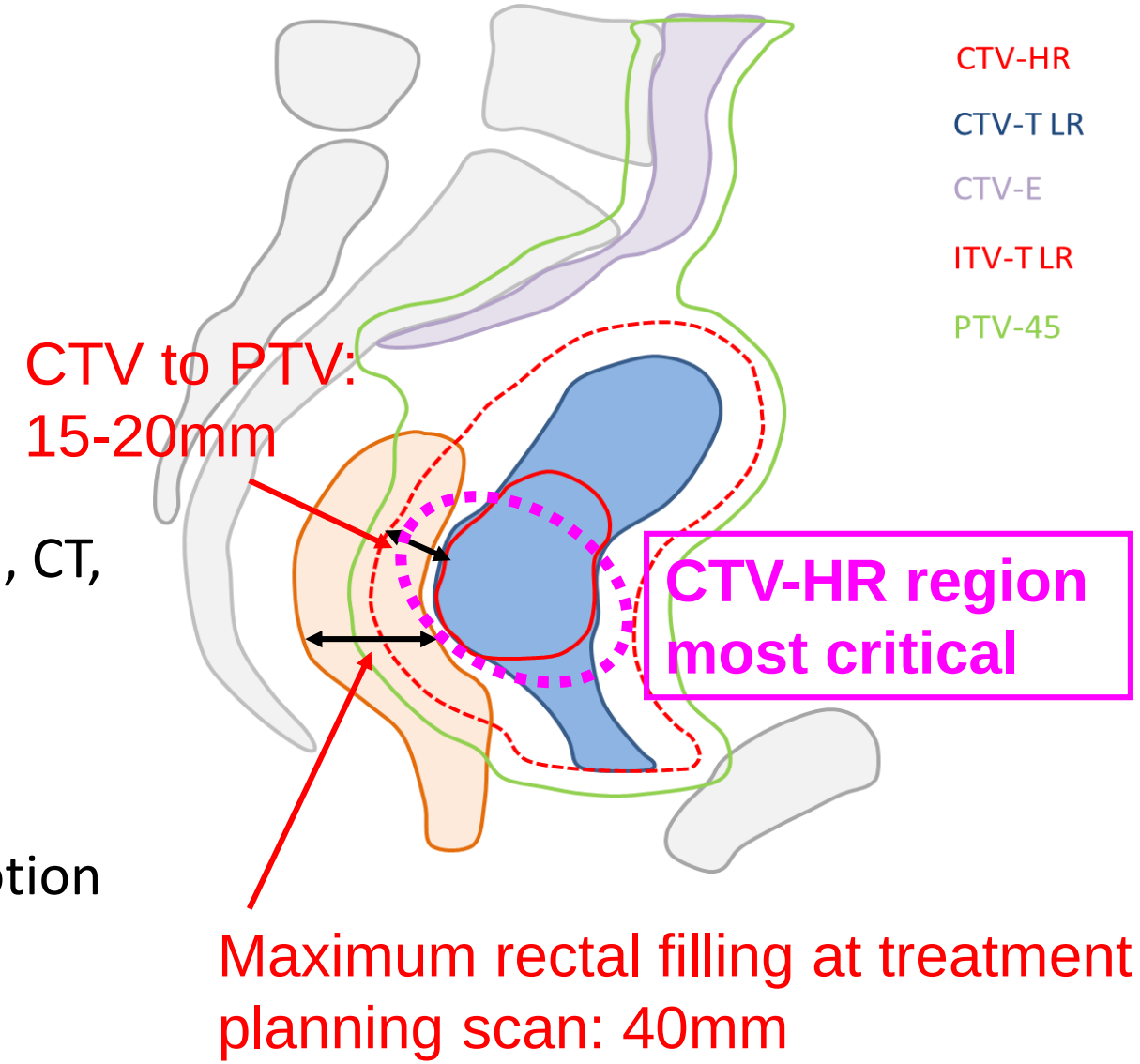
ITV-T LR and PTV-T LR

Standard:

- 10-15mm ITV margin
- 5mm PTV margin
- Total 15-20mm margin

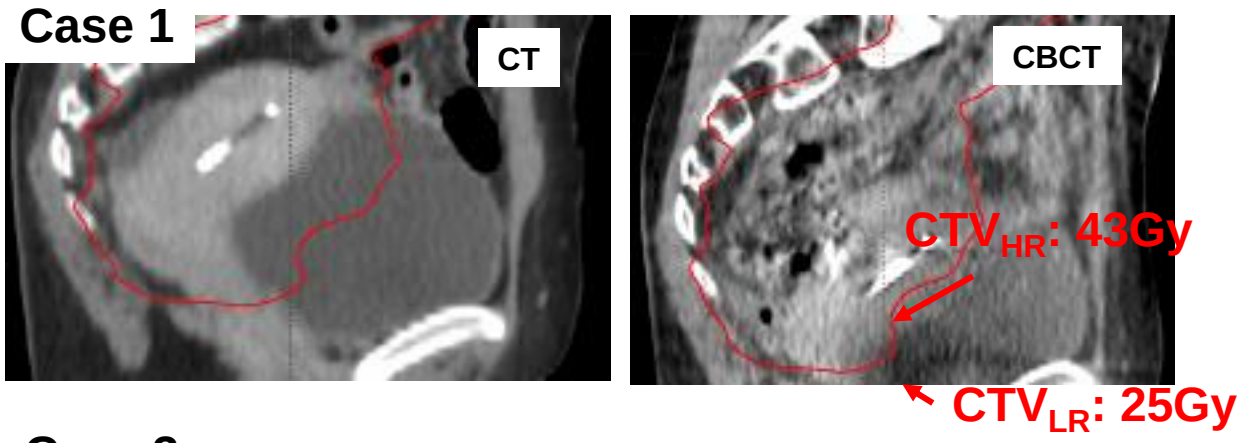
Individualised approach:

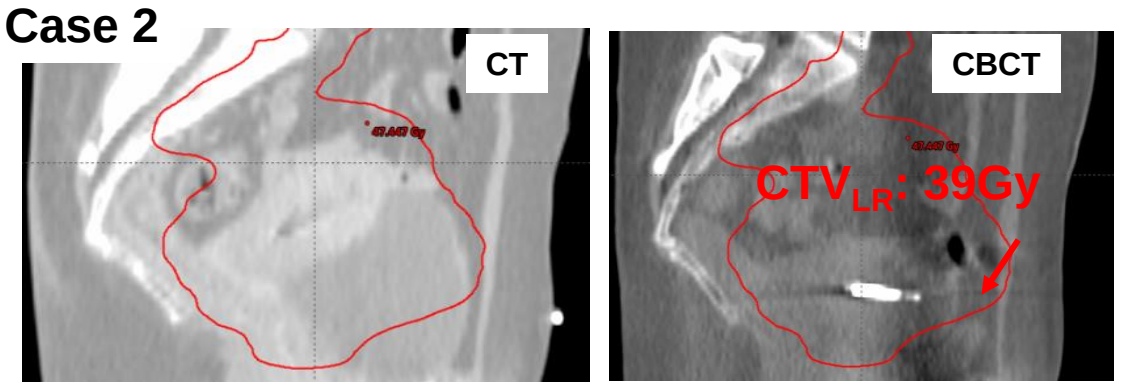
- Several treatment planning images: MRI, CT, full bladder, empty bladder
- Review anatomy on treatment planning images
- Apply margin according to predicted motion
- Monitor on daily CBCT

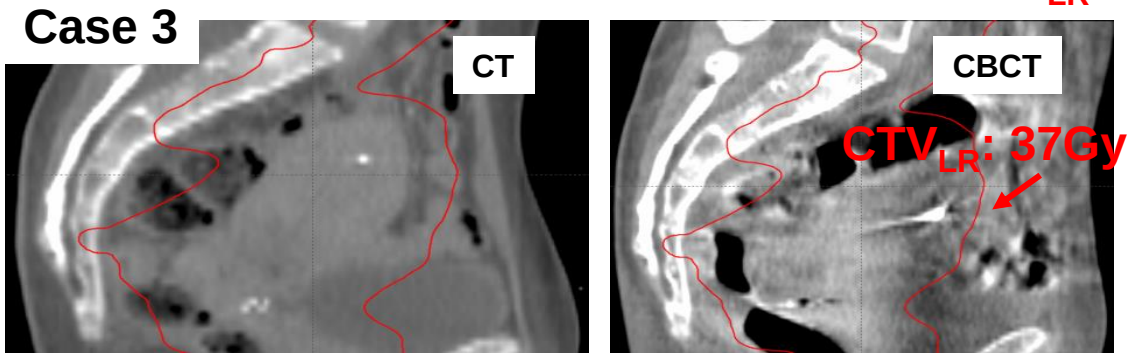


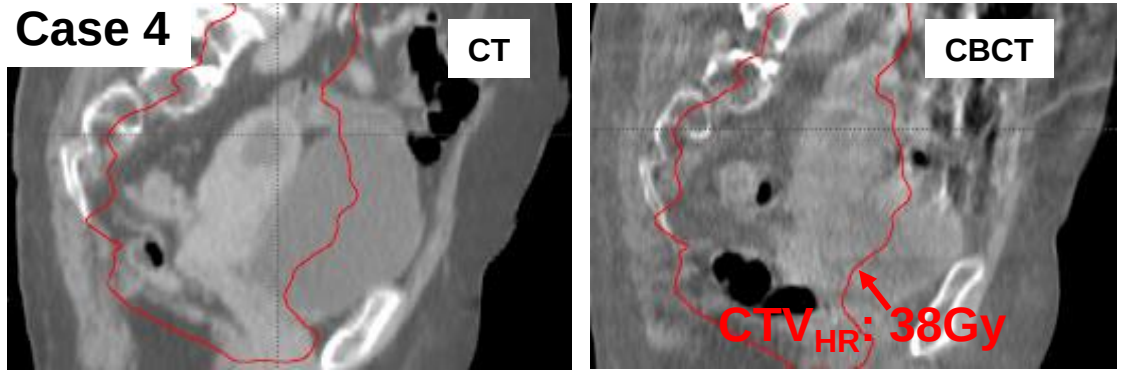
Experience with CBCT monitoring from AUH

- Full and empty bladder planning CT + MRI -> Individualised ITV margin: median 1.2cm, range [1.0-3.5cm]
- Target coverage can be evaluated in 90% of CBCTs
- Prescribed EBRT: 45Gy in 25 fx
- 15% of cases could benefit from re-planning



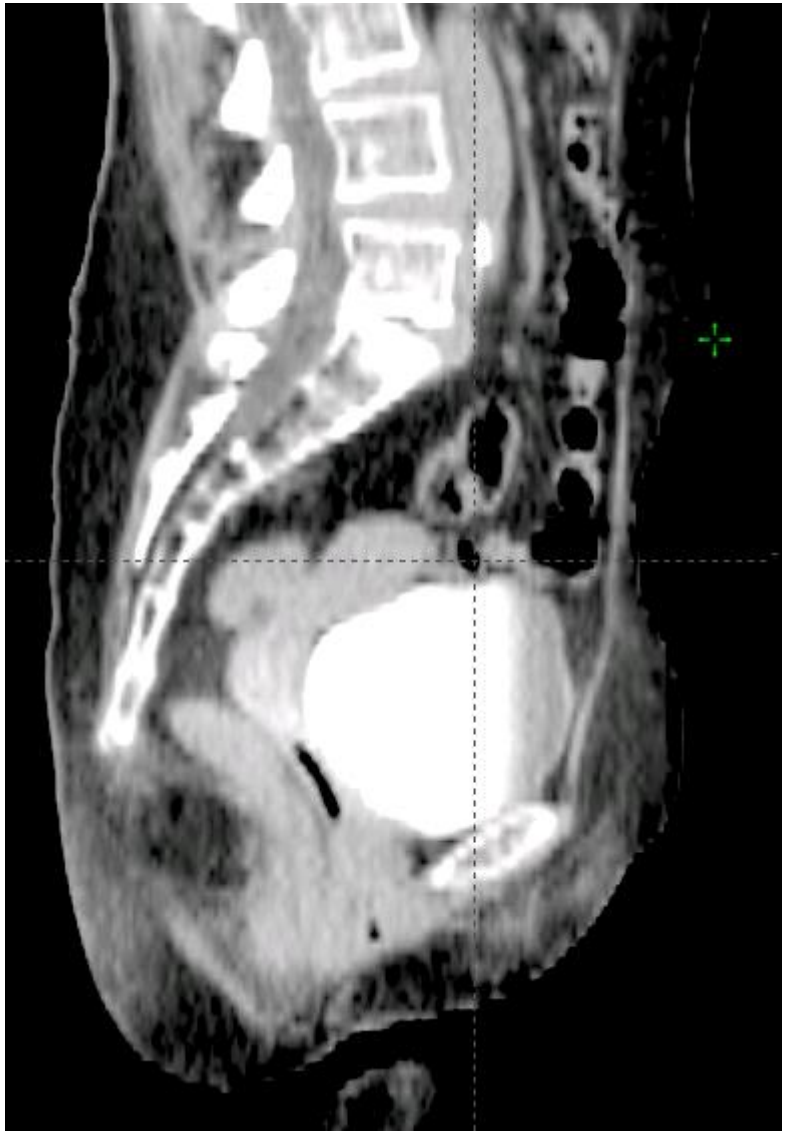






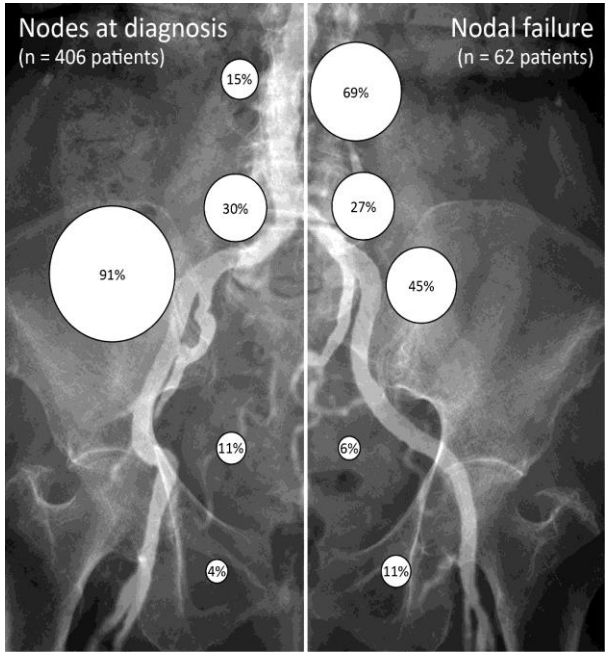
Bladder filling and bowel volume

- **Full bladder versus empty bladder decreases volume of bowel irradiated to a significant dose**
- **Avoid very large filling (>300ml)***
- **Example drinking protocol:**
  - **450-500ml 1 hour prior to planning CT scan and to each treatment**
- **Reproducibility of bladder filling?**
  - **Significant variation**
  - **Main purpose is to push bowel away!**



*Eminowicz et al, Understanding the impact of pelvic organ motion on dose delivered to target volumes during IMRT for cervical cancer. Radiother Oncol 2017;122:116–21

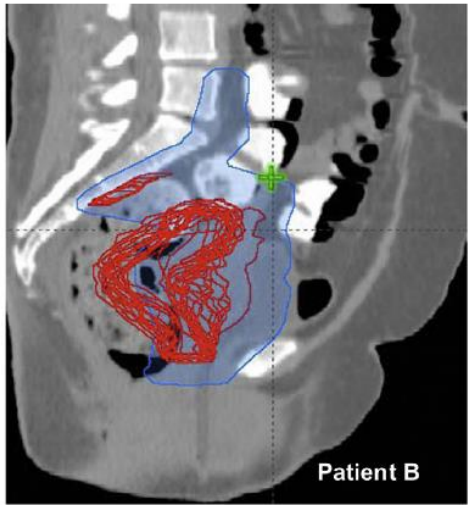
Take home message: nodal CTV

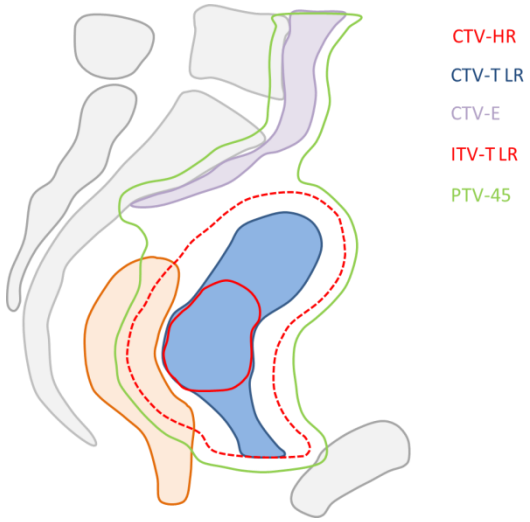


- Margins add to considerable irradiation of normal tissue
- PTV margin for elective target volume:
  - 7-10mm margin without daily image guidance
  - 5mm margin with daily image guidance and bony fusion
- Potential in pelvic elective radiotherapy to reduce irradiated volume by 40% with IMRT and daily IGRT (2500cc → 1500cc)

Take home message: primary CTV

- Secure CTV-HR coverage – macroscopic tumour burden
- Uninvolved uterus is NOT the most critical target – microscopic disease
- Clinical practise:
  - ~15-20mm is common for CTV-T LR to PTV margin
  - Be aware of rectal filling at time of treatment planning! E.g. threshold of 40mm diameter of filling.





Medical aspects of dose constraints including DVH parameters for EBRT planning

ESTRO GYN TEACHING COURSE
Madrid 2018

Ina Jürgenliemk-Schulz
Umesh Mahantshetty
Kari Tanderup
Remi Nout

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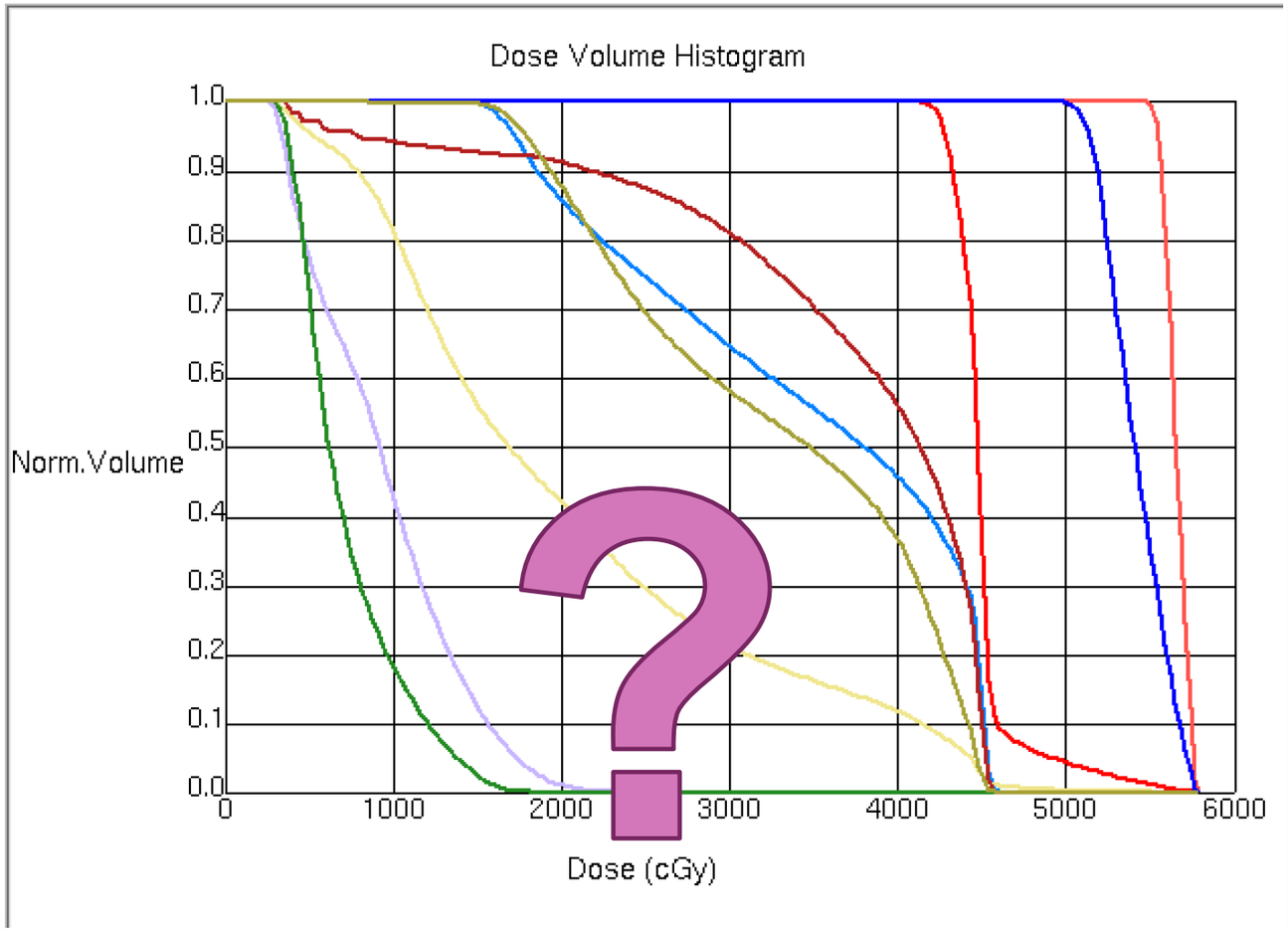
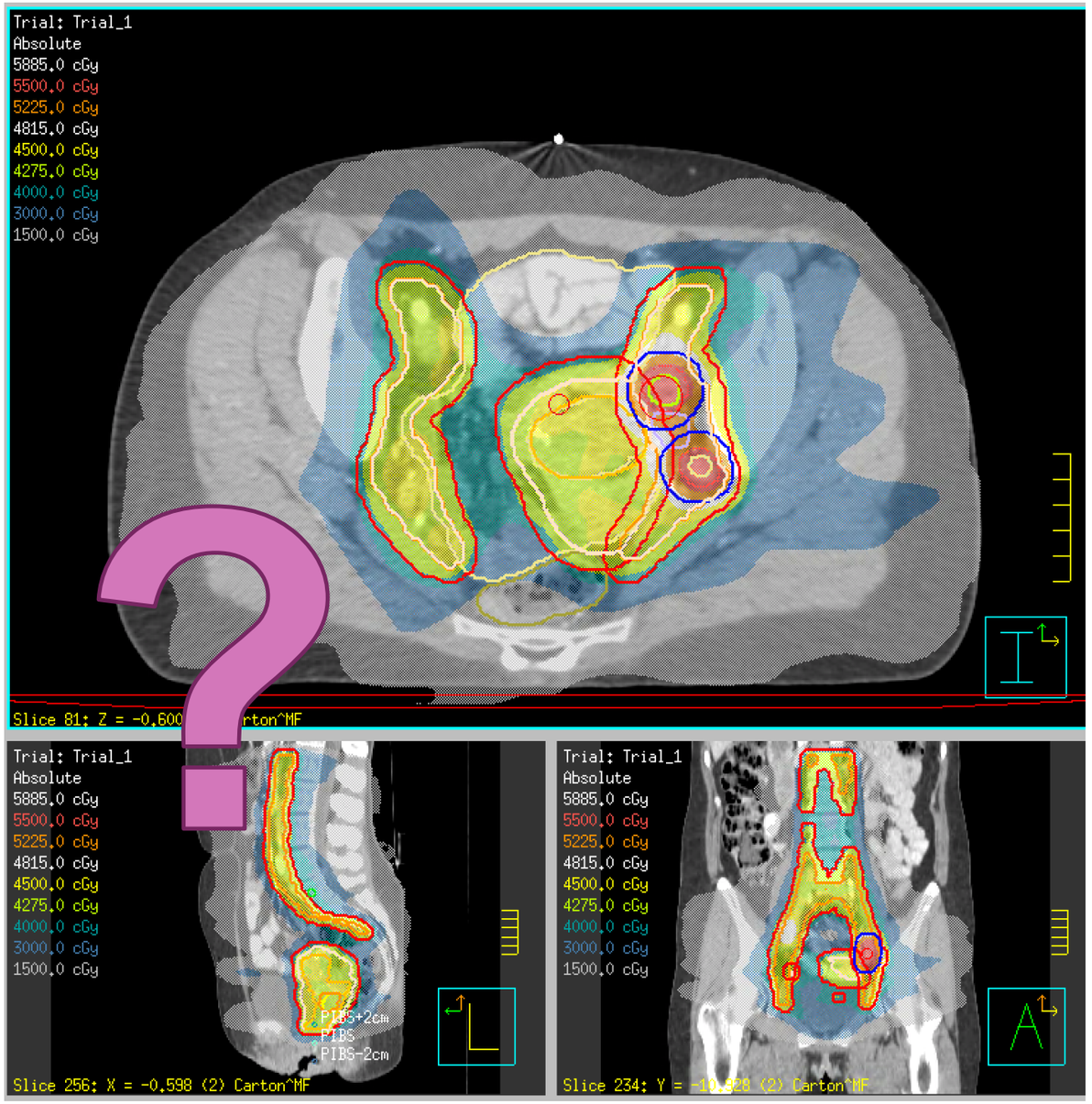
Learning objectives





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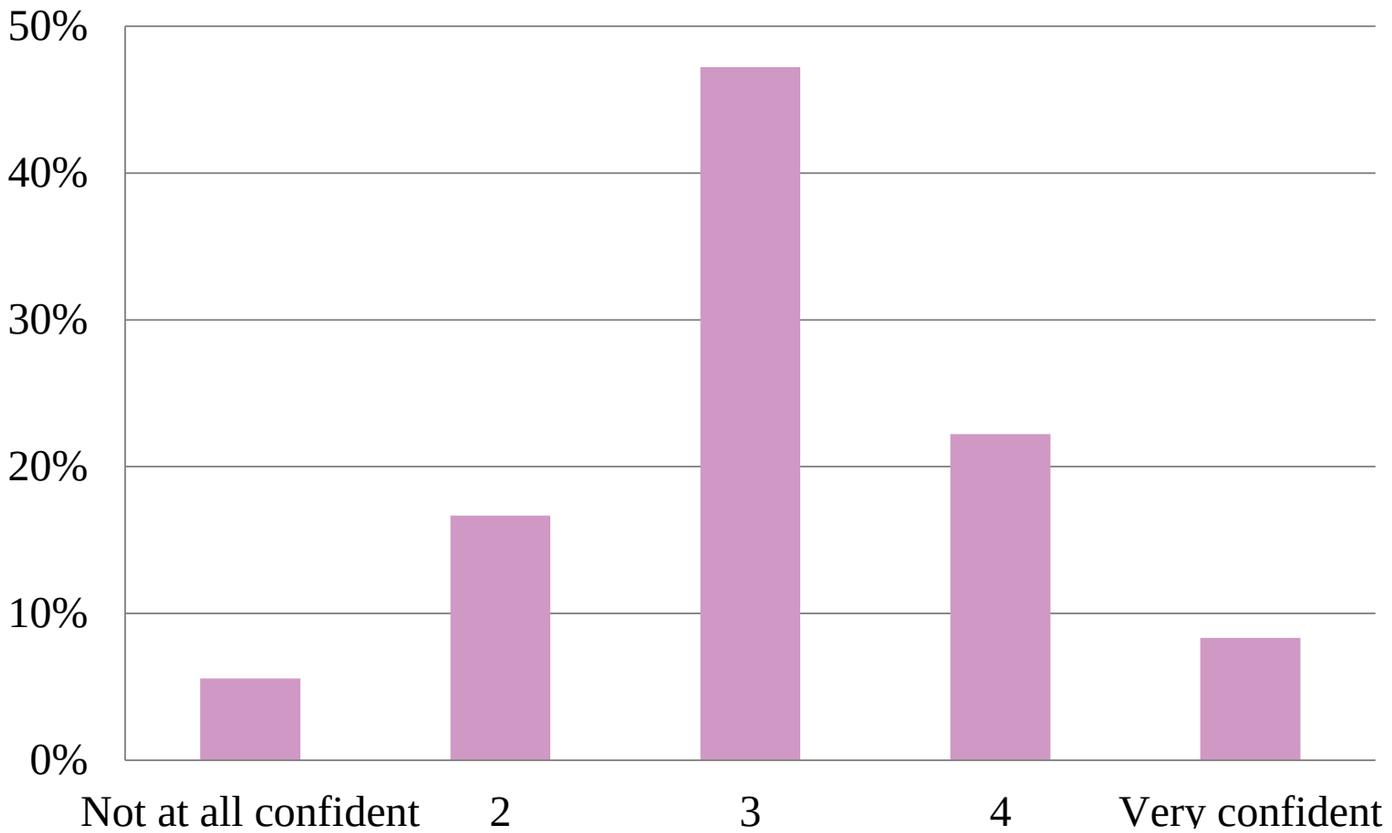
How confident are you at evaluating IMRT plans for cervical cancer?



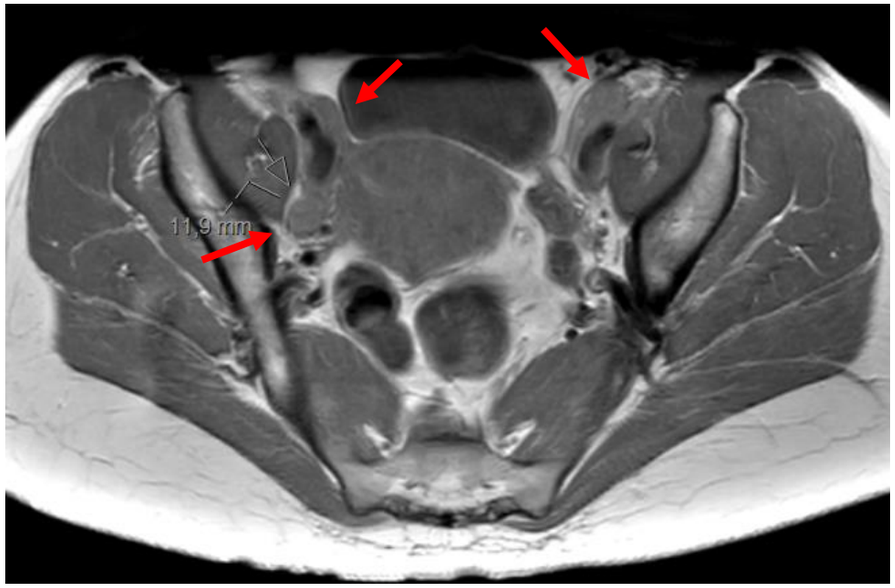
Learning objectives

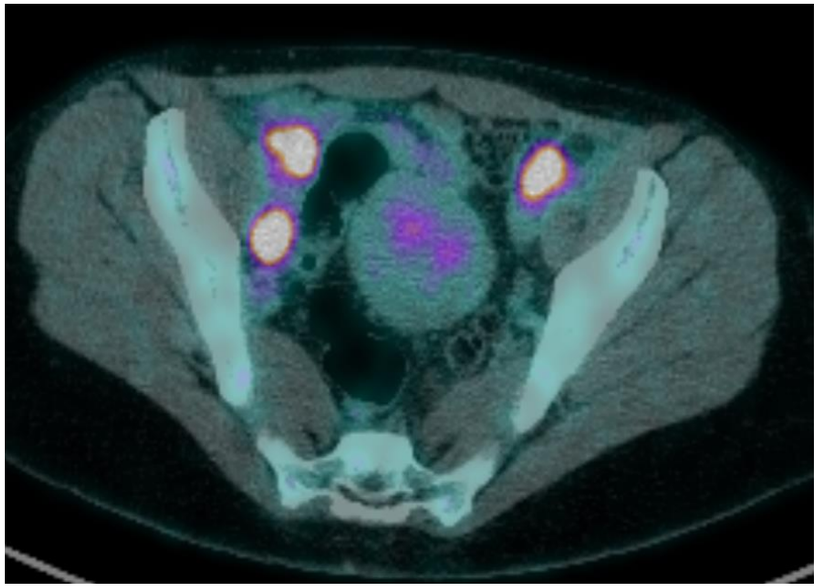
- Evidence for EBRT dose constraints and DVH parameters
- Evidence for dosimetric and clinical gain IMRT
- Importance of DVH parameters for EBRT treatment planning

- Brachy part not included!

EBRT for gynecological cancer treatment

- Elective dose including draining lymphatic system (postoperative EBRT)
- Boost to regional pathologic nodes
- Boost to primary / recurrent tumor if brachytherapy is not feasible





Dose in tumor versus organs at risk

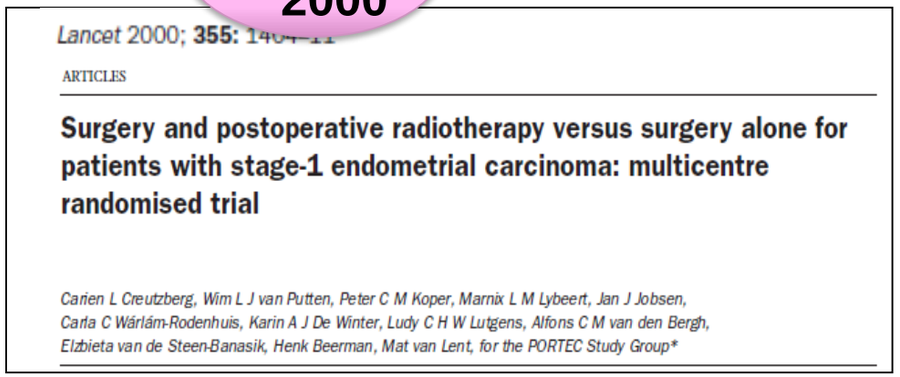
- Which dose is required for tumor control?
  - Microscopic disease
  - Macroscopic tumor
  - Radiosensitizer?
- OAR, which dose is tolerated?
  - Severe morbidity
  - Long term Quality of Life
- Dose constraints and DVH parameters help to balance between tumor dose and OAR dose

Evidence for dose to control elective region

Elective regions need dose

- Effective elective dose in endometrial, vulvar and cervical cancer is 46-50 Gy in 1.8-2.0 Gy per fraction

Creutzberg 2000



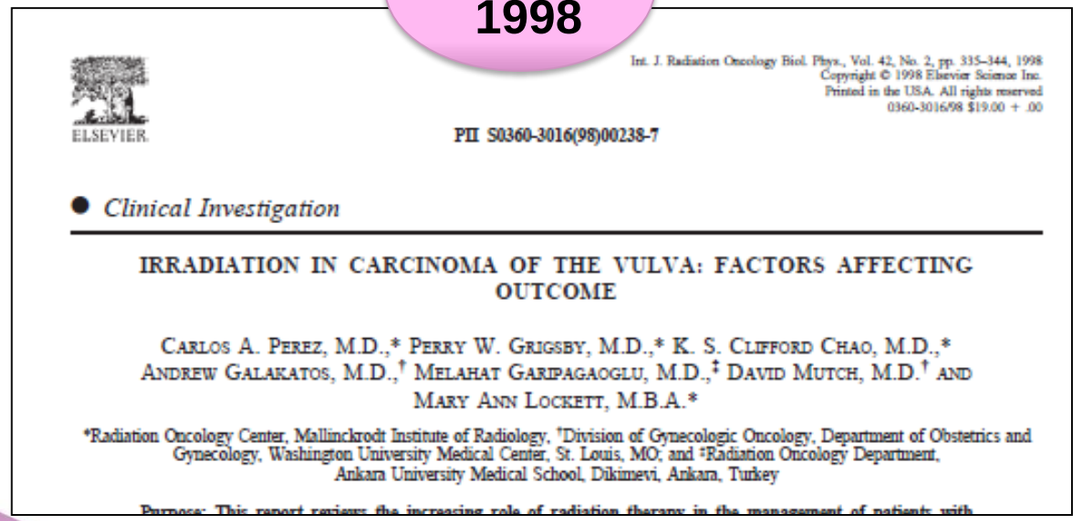
Lancet 2000; **355:** 1404–11

ARTICLES

Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial

*Carien L Creutzberg, Wim L J van Putten, Peter C M Koper, Marnix L M Lybeert, Jan J Jobsen, Carla C Wárlám-Rodenhuis, Karin A J De Winter, Ludy C H W Lutgens, Alfons C M van den Bergh, Elzbieta van de Steen-Banasik, Henk Beerman, Mat van Lent, for the PORTEC Study Group**

Perez 1998



ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 42, No. 2, pp. 335–344, 1998
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PII S0360-3016(98)00238-7

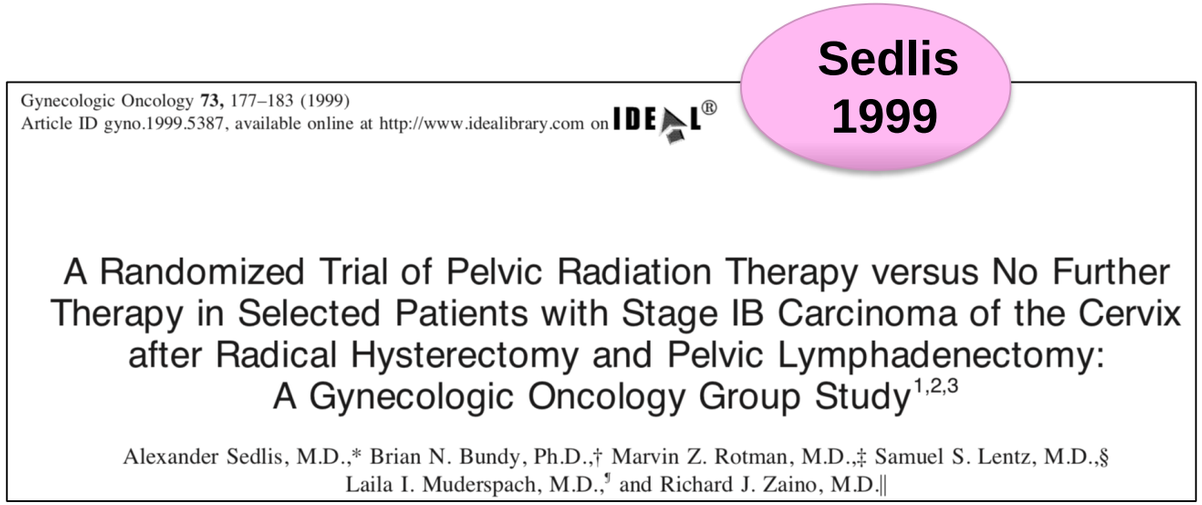
● *Clinical Investigation*

IRRADIATION IN CARCINOMA OF THE VULVA: FACTORS AFFECTING OUTCOME

CARLOS A. PEREZ, M.D.,* PERRY W. GRIGSBY, M.D.,* K. S. CLIFFORD CHAO, M.D.,* ANDREW GALAKATOS, M.D.,† MELAHAT GARIPAGAOGLU, M.D.,‡ DAVID MUTCH, M.D.† AND MARY ANN LOCKETT, M.B.A.*

*Radiation Oncology Center, Mallinckrodt Institute of Radiology, †Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University Medical Center, St. Louis, MO; and ‡Radiation Oncology Department, Ankara University Medical School, Dikimevi, Ankara, Turkey

Sedlis 1999



Gynecologic Oncology **73,** 177–183 (1999)
Article ID gyno.1999.5387, available online at http://www.idealibrary.com on IDEAL®

A Randomized Trial of Pelvic Radiation Therapy versus No Further Therapy in Selected Patients with Stage IB Carcinoma of the Cervix after Radical Hysterectomy and Pelvic Lymphadenectomy: A Gynecologic Oncology Group Study[1,2,3]

Alexander Sedlis, M.D.,* Brian N. Bundy, Ph.D.,† Marvin Z. Rotman, M.D.,‡ Samuel S. Lentz, M.D.,§ Laila I. Muderspach, M.D.,¶ and Richard J. Zaino, M.D.‖

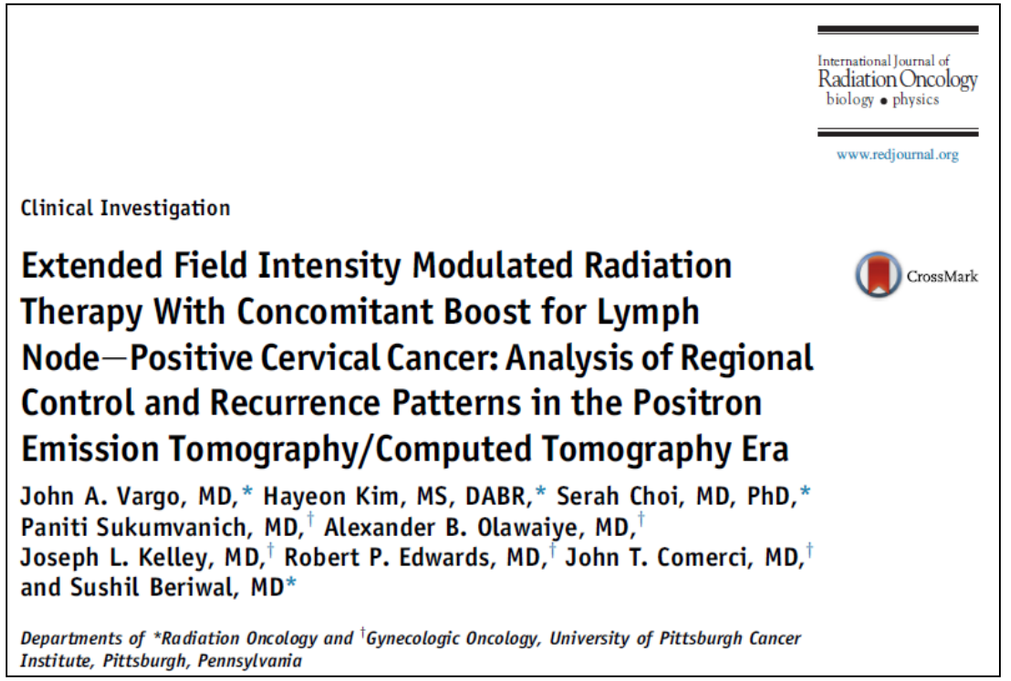
ESTRO School

Evidence for dose to elective region and lymph node metastases

Lymph node metastases need dose

- Elective fields (including PAO) for cervix cancer are controlled with 45 Gy
- Node control is excellent after 55-60 Gy
- More details in next lecture

Vargo 2014



International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Extended Field Intensity Modulated Radiation Therapy With Concomitant Boost for Lymph Node—Positive Cervical Cancer: Analysis of Regional Control and Recurrence Patterns in the Positron Emission Tomography/Computed Tomography Era

John A. Vargo, MD,* Hayeon Kim, MS, DABR,* Serah Choi, MD, PhD,* Paniti Sukumvanich, MD,† Alexander B. Olawaiye, MD,† Joseph L. Kelley, MD,† Robert P. Edwards, MD,† John T. Comerci, MD,† and Sushil Beriwal, MD*

*Departments of *Radiation Oncology and †Gynecologic Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania*

Summary

In the largest series examining extended field intensity modulated radiation therapy for node-positive cervical cancer, we observed a low para-aortic recurrence rate of 2.5% in patients with pelvic-only positive lymph nodes (negative para-aortic lymph nodes by positron emission tomography/computed tomography) without surgical staging, suggesting efficacy of this approach in addressing the 20% to 25% risk of microscopic para-aortic nodal disease. A simultaneous integrated boost of 55 Gy in 25 fractions effectively eradicated disease in involved pelvic and para-aortic lymph nodes, with acceptable risks of late adverse events.

ESTRO School

Evidence for dose needed to control primary tumor

Bigger tumors need more dose

- Local control depends on applied dose in a certain volume

Tanderup 2016

Radiotherapy and Oncology 120 (2016) 441–446

Contents lists available at ScienceDirect

Radiotherapy and Oncology

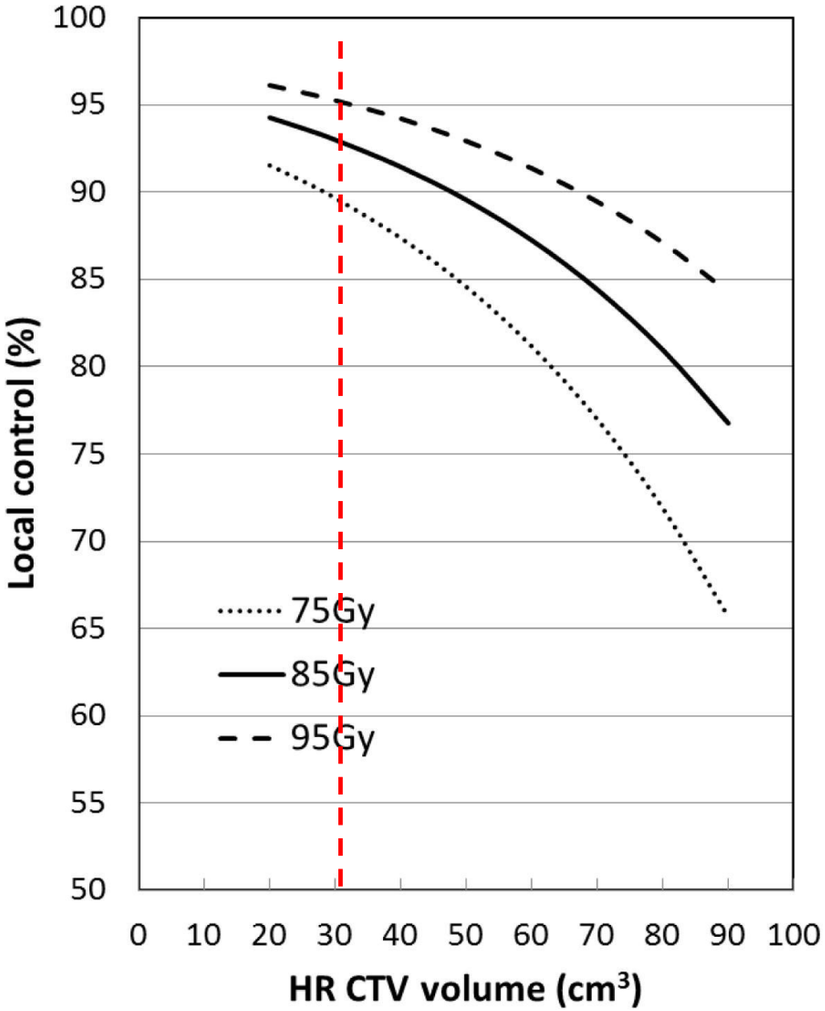
journal homepage: www.thegreenjournal.com

Image guided brachytherapy in cervical cancer

Effect of tumor dose, volume and overall treatment time on local control after radiochemotherapy including MRI guided brachytherapy of locally advanced cervical cancer

Kari Tanderup [a,*], Lars Ulrik Fokdal [a], Alina Sturdza [b], Christine Haie-Meder [c], Renaud Mazeron [c], Erik van Limbergen [d], Ina Jürgenliemk-Schulz [e], Primoz Petric [f,g], Peter Hoskin [h], Wolfgang Dörr [b], Søren M. Bentzen [i], Christian Kirisits [b], Jacob Christian Lindegaard [a], Richard Pötter [b]

[a] Department of Oncology, Aarhus University Hospital, Denmark; [b] Department of Radiation Oncology, Comprehensive Cancer Center, Medical University of Vienna, Austria; [c] Radiation Oncology Department, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France; [d] Department of Radiation-Oncology, University Hospitals of Leuven, Belgium; [e] Department of Radiotherapy, University Medical Center Utrecht, The Netherlands; [f] Department of Radiation Oncology, National Center for Cancer Care and Research, Doha, Qatar; [g] Division of Radiotherapy, National Institute of Oncology, Ljubljana, Slovenia; [h] Mount Vernon Cancer Centre, Northwood, United Kingdom; [i] Greenebaum Cancer Center and Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, USA



ESTRO School

Evidence for dose needed to control primary tumor

Primary gyn tumors need dose (EBRT + BT)

- Local control depends on applied dose
- For cervix brachy contribution essential

Gill 2014

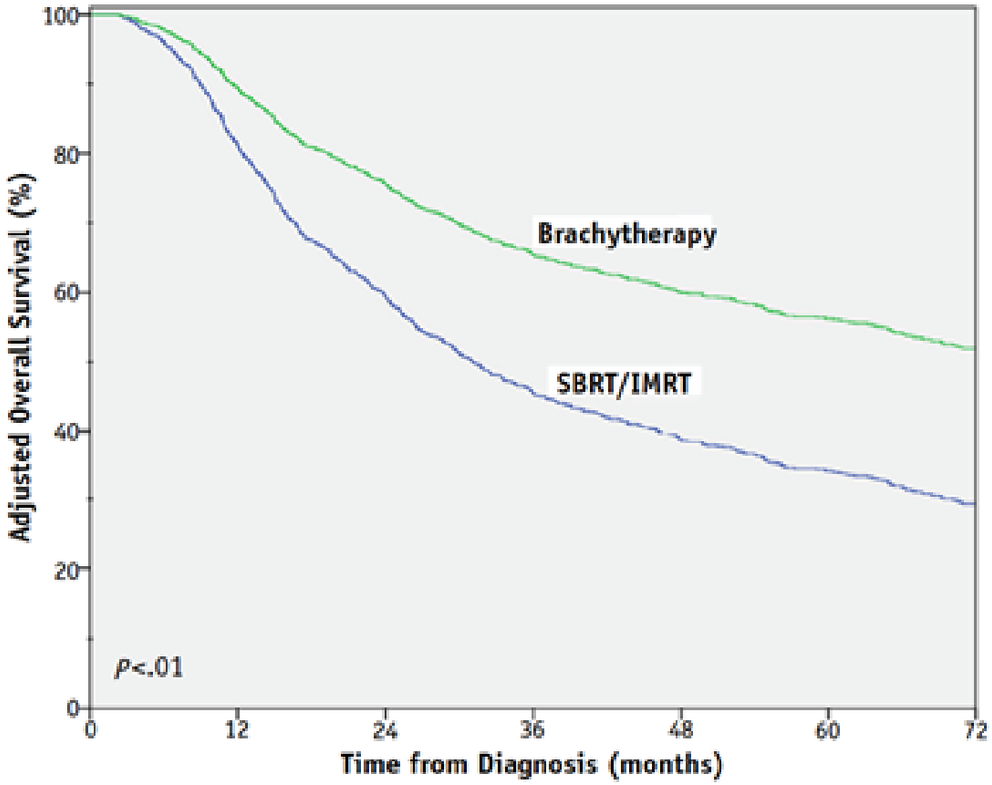
International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

National Cancer Data Base Analysis of Radiation Therapy Consolidation Modality for Cervical Cancer: The Impact of New Technological Advancements

Beant S. Gill, MD,* Jeff F. Lin, MD,† Thomas C. Krivak, MD,‡ Paniti Sukumvanich, MD,† Robin A. Laskey, MD,† Malcolm S. Ross, MD,† Jamie L. Lesnock, MD,† and Sushil Beriwal, MD*

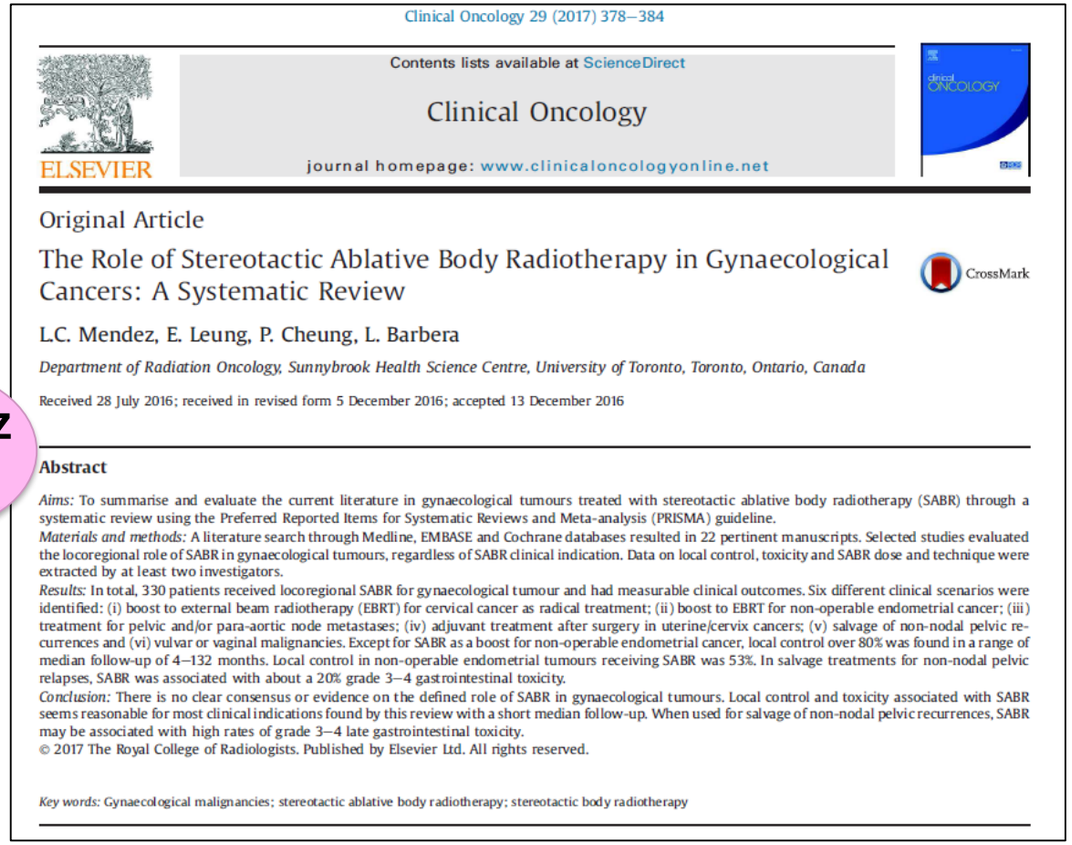


Evidence for dose needed to control primary tumor

Preliminary results with SBRT, no brachy

- Different gyn tumors, primary tumors, recurrences, lymph node metastases

Mendez 2016



Clinical Oncology 29 (2017) 378–384

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

The Role of Stereotactic Ablative Body Radiotherapy in Gynaecological Cancers: A Systematic Review

L.C. Mendez, E. Leung, P. Cheung, L. Barbera

Department of Radiation Oncology, Sunnybrook Health Science Centre, University of Toronto, Toronto, Ontario, Canada

Received 28 July 2016; received in revised form 5 December 2016; accepted 13 December 2016

Abstract

Aims: To summarise and evaluate the current literature in gynaecological tumours treated with stereotactic ablative body radiotherapy (SABR) through a systematic review using the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) guideline.

Materials and methods: A literature search through Medline, EMBASE and Cochrane databases resulted in 22 pertinent manuscripts. Selected studies evaluated the locoregional role of SABR in gynaecological tumours, regardless of SABR clinical indication. Data on local control, toxicity and SABR dose and technique were extracted by at least two investigators.

Results: In total, 330 patients received locoregional SABR for gynaecological tumour and had measurable clinical outcomes. Six different clinical scenarios were identified: (i) boost to external beam radiotherapy (EBRT) for cervical cancer as radical treatment; (ii) boost to EBRT for non-operable endometrial cancer; (iii) treatment for pelvic and/or para-aortic node metastases; (iv) adjuvant treatment after surgery in uterine/cervix cancers; (v) salvage of non-nodal pelvic recurrences and (vi) vulvar or vaginal malignancies. Except for SABR as a boost for non-operable endometrial cancer, local control over 80% was found in a range of median follow-up of 4–132 months. Local control in non-operable endometrial tumours receiving SABR was 53%. In salvage treatments for non-nodal pelvic relapses, SABR was associated with about a 20% grade 3–4 gastrointestinal toxicity.

Conclusion: There is no clear consensus or evidence on the defined role of SABR in gynaecological tumours. Local control and toxicity associated with SABR seems reasonable for most clinical indications found by this review with a short median follow-up. When used for salvage of non-nodal pelvic recurrences, SABR may be associated with high rates of grade 3–4 late gastrointestinal toxicity.

Key words: Gynaecological malignancies; stereotactic ablative body radiotherapy; stereotactic body radiotherapy

- Systematic review
- No consensus yet for dose needed
- Small numbers, different local control rates

Tumors need dose

Microscopic disease: 45-50Gy

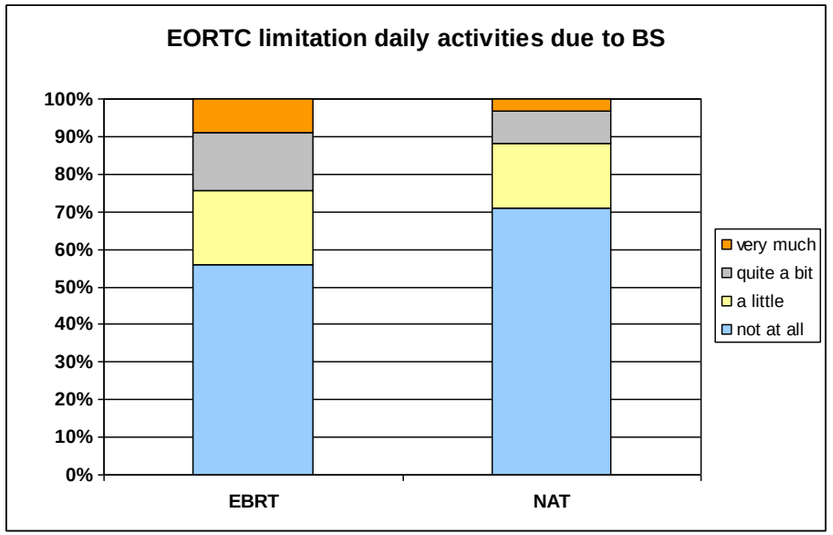
Pathologic lymph nodes: 55-60Gy

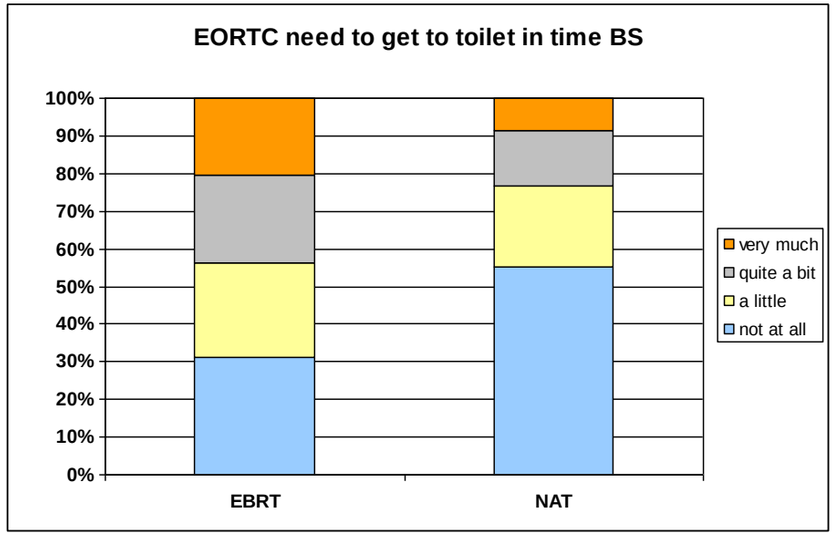
Primary / recurrent tumors: ->Brachytherapy
-If BT not feasible aim 70Gy
-SBRT dose no consensus

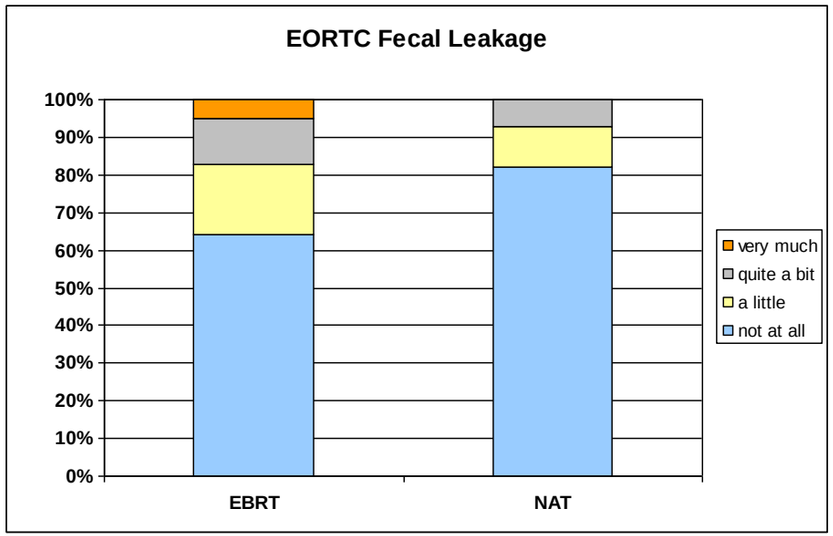
As high as intended and reasonably achievable

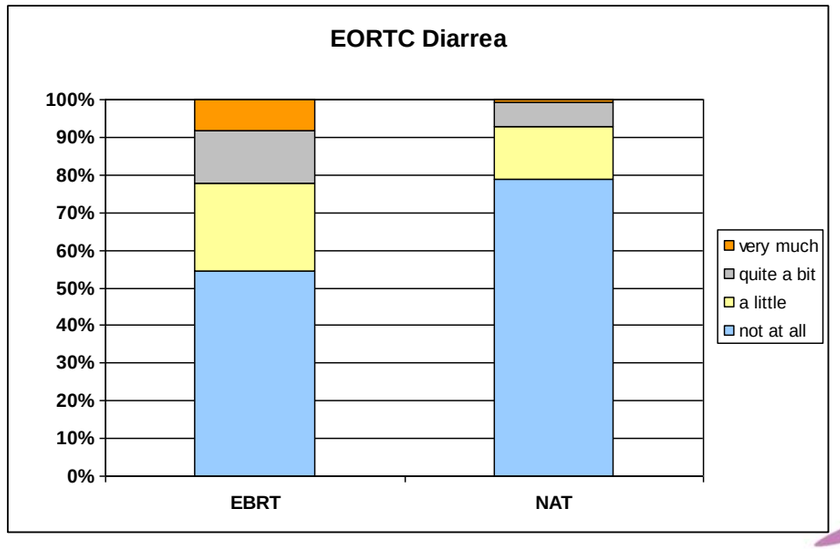
Evidence that OAR do not like dose

PORTEC-1: Patient reported bowel symptoms 15-years after 46Gy









Nout et al, JCO 2011

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Evidence that OAR do not like dose

Surrounding organs do not like dose; example bowel

- 90% of patients develop permanent change in bowel habits after radiotherapy
- 50% report impact on QoL
- 10-20% develop serious complications within 10-20 years after treatment

Andreyev 2007

Clinical Oncology (2007) **19**: 790–799
doi: 10.1016/j.clon.2007.08.011

Overview

Gastrointestinal Problems after Pelvic Radiotherapy: the Past, the Present and the Future

H. J. N. Andreyev

Department of Medicine, Royal Marsden Hospital, Fulham Road, London, UK

ABSTRACT:
Up to 300 000 patients per year undergo pelvic radiotherapy worldwide. Nine out of 10 will develop a permanent change in their bowel habit as a result. Five out of 10 of all patients will say that this change in their bowel habit affects quality of life and two to three out of 10 will say that this effect on quality of life is moderate or severe. Between one in 10 and one in 20 patients will develop very serious complications within the first 10 years after treatment. This number will increase to two out of 10 by 20 years from the end of treatment. Although research carried out into the basic molecular, cytokine and physiological changes underlying radiation-induced bowel symptoms and the optimal treatment that should be provided to symptomatic patients is scant, it does seem probable that a significant proportion of these patients can be cured or improved by specialist gastroenterological intervention. However, most patients never get referred to a specialist gastroenterologist and research into late radiation bowel damage has not been considered a priority. With the advent of more effective cancer therapies leading to greater numbers of affected long-term survivors, much more emphasis is urgently required to provide better information to patients at the start and after treatment, developing techniques that might reduce the frequency of significant bowel toxicity and researching better ways of measuring and treating late-onset side-effects. Andreyev, H. J. N. (2007). *Clinical Oncology* 19, 790–799

Key words: Chronic gastrointestinal toxicity, pelvic radiotherapy, quality of life

The development of bowel toxicity is not entirely dose, volume and fractionation schedule related. It also depends on a complex interaction of physical, patient-related and genetic factors, but these have been poorly characterised

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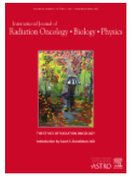
OAR DVH parameters in literature

Emami 1991,2013



Emami et al
Int Journal of Radiation Oncology Biology Physics, 1991

Tolerance of Normal Tissue to Therapeutic Radiation
Dr Emami B
Department of Radiation Oncology, Loyola University Medical Center, Maywood, Illinois, USA
Reports in Radiotherapy and Oncology, 2013

- Evidence for dose volume relations especially for elective dose levels (45 -50 Gy) limited
- But we are learning !
- QUANTEC

Review: Kavanagh DB, IJROBP 2010 (QUANTEC)

Marks: IJROBP 2010 (QUANTEC)

Table 2: Normal Tissue Tolerance for Standard Fractionation

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Brain	Symptomatic necrosis	<3 <5		<60 <65	
Brainstem	Necrosis or cranial neuropathy	<5 <5	D100 <54 Gy D1–10 cc ≤59 Gy	<64 Point	
Spinal cord	Grade ≥2 myelopathy	<1		50	
Optic nerve & chiasm	Optic neuropathy	<3 3–7		<55 55–60	<50
Retina	Blindness	<1		<50	
Cochlea	Hearing loss	<15			≤45
Parotid 1	Grade 4 xerostomia	<20			<20
Parotid 2		<20			<25
Mandible	ORN	<5		<70 Point	
Pharyngeal constrictors	PEG tube dependent Aspiration	<5 <5			<50 <60
Larynx	Grade ≥2 edema	<20	V50 <27%		<44
Brachial plexus	Clinically apparent nerve damage	<5		<60	
Lung	Symptomatic pneumonitis	5 10 20 30 40	V5 <42%, V20 <22% V20 <31% V20 <40%		7 13 20 24 27
Esophagus	Grade ≥2 esophagitis Grade ≥3 esophagitis	<30 ≤10	V35 <50% V50 <40% V70 <20% V60 <30%	<74 Point	 <34
Heart	Pericarditis Long-term cardiac mortality	<15 <1	V30 <46% V25 <10%		<26
Liver	RILD, normal liver RILD, liver disease	<5 <5			≤30 ≤28
Kidney 1	Renal dysfunction	<5	Equivalent of 1 kidney <18 Gy		
Kidney 2	Renal dysfunction	<5			<18
Stomach	Ulceration		D100 <50 Gy		
Small Bowel	Acute grade ≥3 toxicity Late obstruction/perforation	<10 <5	V15 <120 cc V50 <5%		
Rectum	Grade ≥2/≥3 late toxicity Grade ≥2/≥3 late toxicity Grade ≥2/≥3 late toxicity Grade ≥2/≥3 late toxicity Grade ≥2/≥3 late toxicity	<10/<15 <10/<15 <10/<15 <10/<15 <10/<15	V50 <50% V60 <35% V65 <25% V70 <20% V75 <15%		
Bladder	Grade ≥3 late toxicity	<6 ?	D100 <65 Gy V65 ≤50% V70 ≤35% V75 ≤25% V80 ≤15%		
Penile bulb	Severe erectile dysfunction	<35			<50
Femoral head	Necrosis	<5	D100 <52 Gy		

Parotid 1, sparing single parotid gland; Parotid 2, combined parotid glands; Kidney 1, bilateral partial kidney RT; Kidney 2, bilateral whole kidneys; Vx, volume of the organ receiving ≥x Gy; Dx, minimum dose received by x% of the organ; D_{max}, maximum radiation dose; D_{mean}, mean radiation dose.

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Not to forget!

Emami 2013

- Morbidity is not only a matter of dose
- Age, comorbidity, smoking…..
- ’New OARs': duodenum, vagina, bone marrow, etc

Table 1: Variables That Can Impact Normal Tissue Tolerance

I.	Host	Age Comorbid conditions Host response to radiation Smoking KPS	
II	Organ	Pre-radiation organ condition (Poor PFTs; LFTs; COPD) Regional variation of radiosensitivity with the organ Impact of other organs Hierarchal organization of the organ: Serial: dose effect: spinal cord Parallel: volume effect: lung, liver Both: kidney	
III	Natural history of tumor		
IV	Treatment	A—Radiation Dose (max, min, mean) Fractionation (fractional dose): BED Dose rate Overall treatment time Treatment energy Volume (V dose: absolute or relative)	
IV	Treatment	B—Nonradiation Chemotherapy (drug type, dose, schedule) Radiation modifiers (type, dose, schedule) Surgery (interval)	
V	End points ACUTE	Type: Clinical Radiographical: anatomical, functional Biochemical (blood test, functional test) Degree of severity Degree of frequency Impact on quality of life (QOL)	LATE
VI	Issues on reporting of toxicity		

Dose volume effect for acute bowel, impact of V40 and V15

Fiorino
IJROBP, 2009

175 prostate cancer patients
3D CRT or IMRT
12% acute Gr 2-3 bowel toxicity

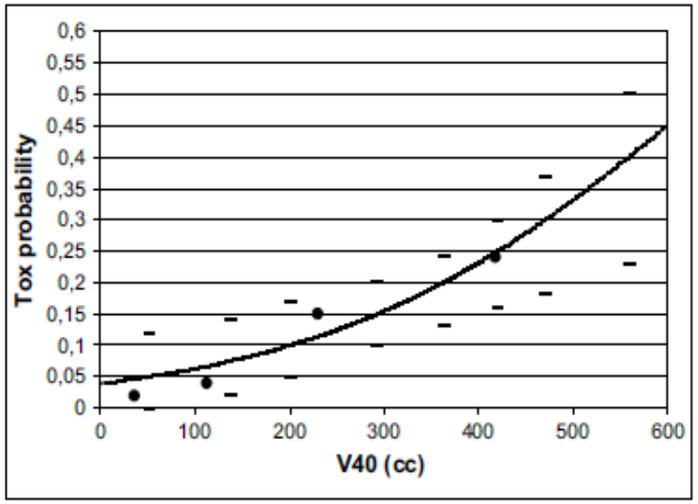


Fig. 1. The relationship between the V40 of the intestinal cavity (outside the planning target volume) and the risk of Grade 2–3 acute bowel toxicity is plotted, together with 95% confidence intervals (lo-

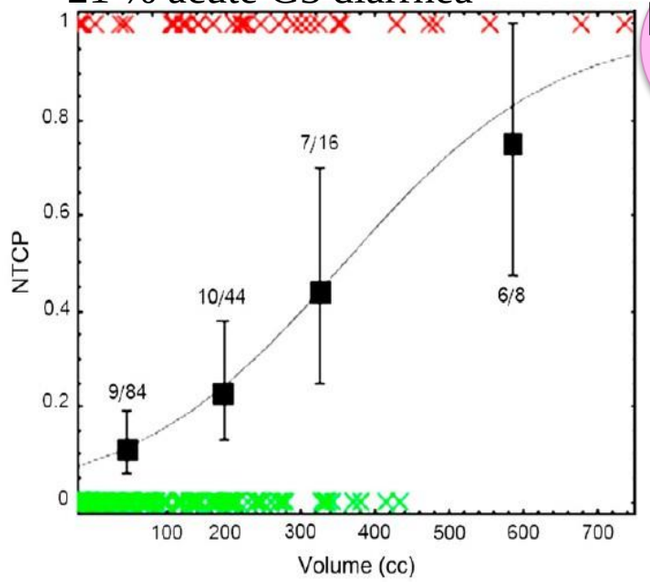
Incidence of toxicity drops from 21% to 3% when:

V40 < 170 cc
V45 < 100 cc
V50 < 33 cc

153 rectal cancer patients
3-field EBRT with concomitant chemotherapy

21 % acute G3 diarrhea

Robertson
IJROBP, 2010



Impact of V15 on diarrhea seemed strongest

V15 should however be seen as a geometrical surrogate for the high dose volumes and not used alone for optimizing IMRT dose distribution

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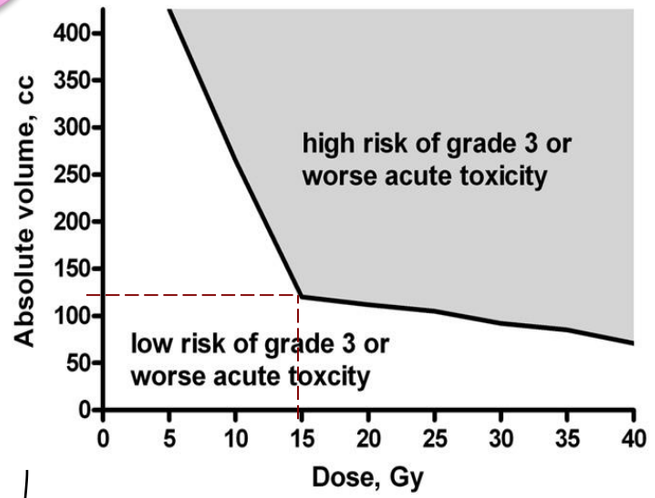
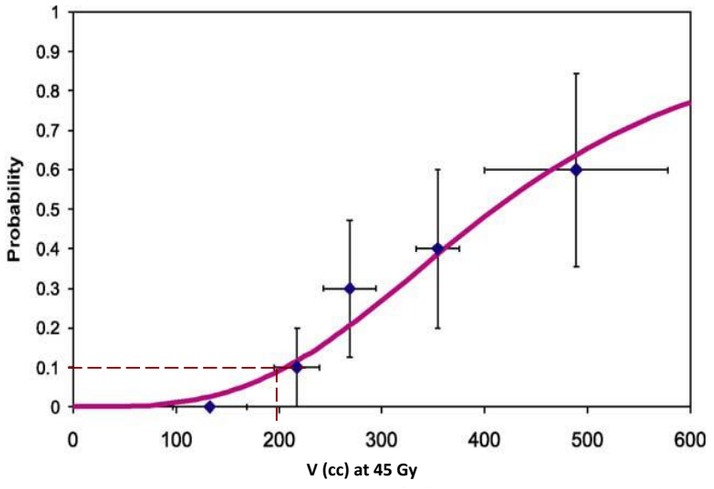
Dose constraints depend on contouring approach

Baglan
IJROBP, 2002

Treshold – based risk models

Roeske
Radiother Oncol 2003





Based on delineation of Bowel LoopS

Based on delineation of Bowel bag

Small bowel	Individual small bowel loops	3D-CRT	Grade ≥ 3 acute toxicity[§]	V15 <120 cc	<10	Volume based on segmentation of the individual loops of bowel, not the entire potential peritoneal space
	Entire potential space within peritoneal cavity	3D-CRT	Grade ≥ 3 acute toxicity[§]	V45 <195 cc	<10	Volume based on the entire potential space within the peritoneal cavity

Review: Kavanagh DB, IJROBP 2010 (QUANTEC)

Marks: IJROBP 2010 (QUANTEC)

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Tumors need dose

As high as intended and reasonably achievable

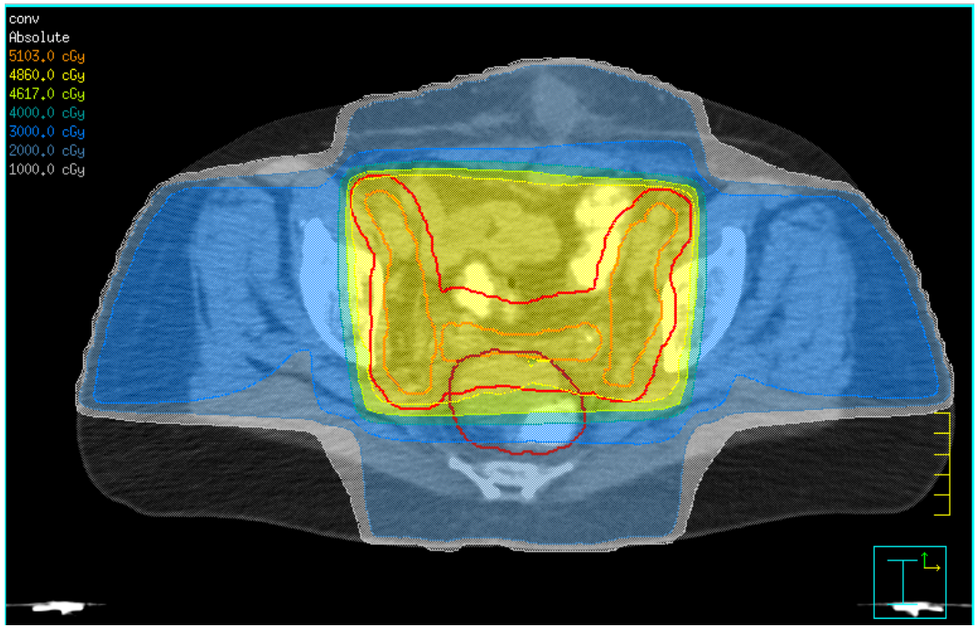
OAR do not like dose

A As
L Low
A As
R Reasonably
A Achievable

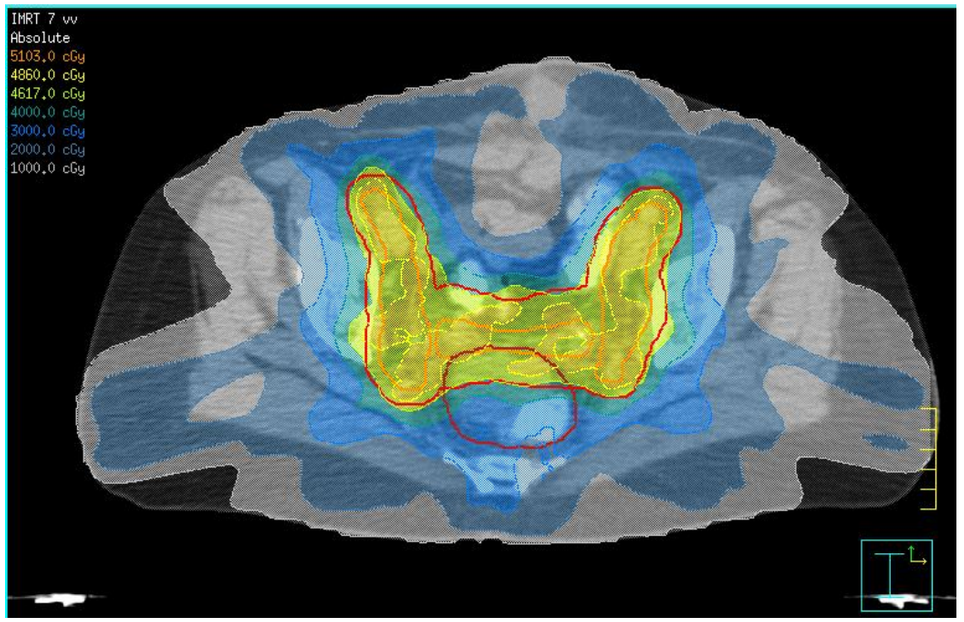
How to achieve the required dose gradients ?

Modern EBRT planning: IMRT - VMAT

3D conformal



7 beam IMRT



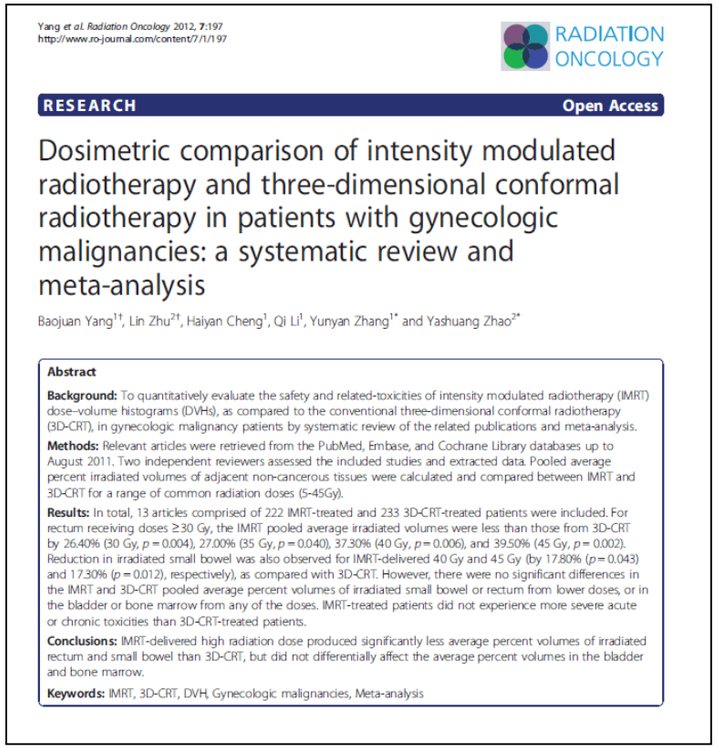
- IMRT treatment planning offers more degrees of freedom
- Predefined dose parameters are essential for clinically acceptable treatment plans

IMRT versus 3D-CRT

Dosimetric comparison: meta-analysis

- 13 papers, 222 IMRT and 233 3D-CRT treated patients
- With IMRT better sparing of high dose volumes of bowel and rectum
- No clear gain for bladder and bone marrow

Yang 2012



Yang et al. Radiation Oncology 2012, 7:197
http://www.ro-journal.com/content/7/1/197

RADIATION ONCOLOGY

RESEARCH Open Access

Dosimetric comparison of intensity modulated radiotherapy and three-dimensional conformal radiotherapy in patients with gynecologic malignancies: a systematic review and meta-analysis

Baojuan Yang[1†], Lin Zhu[2†], Haiyan Cheng[1], Qi Li[1], Yunyan Zhang[1*] and Yashuang Zhao[2*]

Abstract

Background: To quantitatively evaluate the safety and related-toxicities of intensity modulated radiotherapy (IMRT) dose–volume histograms (DVHs), as compared to the conventional three-dimensional conformal radiotherapy (3D-CRT), in gynecologic malignancy patients by systematic review of the related publications and meta-analysis.

Methods: Relevant articles were retrieved from the PubMed, Embase, and Cochrane Library databases up to August 2011. Two independent reviewers assessed the included studies and extracted data. Pooled average percent irradiated volumes of adjacent non-cancerous tissues were calculated and compared between IMRT and 3D-CRT for a range of common radiation doses (5-45Gy).

Results: In total, 13 articles comprised of 222 IMRT-treated and 233 3D-CRT-treated patients were included. For rectum receiving doses ≥30 Gy, the IMRT pooled average irradiated volumes were less than those from 3D-CRT by 26.40% (30 Gy, $p = 0.004$), 27.00% (35 Gy, $p = 0.040$), 37.30% (40 Gy, $p = 0.006$), and 39.50% (45 Gy, $p = 0.002$). Reduction in irradiated small bowel was also observed for IMRT-delivered 40 Gy and 45 Gy (by 17.80% ($p = 0.043$) and 17.30% ($p = 0.012$), respectively), as compared with 3D-CRT. However, there were no significant differences in the IMRT and 3D-CRT pooled average percent volumes of irradiated small bowel or rectum from lower doses, or in the bladder or bone marrow from any of the doses. IMRT-treated patients did not experience more severe acute or chronic toxicities than 3D-CRT-treated patients.

Conclusions: IMRT-delivered high radiation dose produced significantly less average percent volumes of irradiated rectum and small bowel than 3D-CRT, but did not differentially affect the average percent volumes in the bladder and bone marrow.

Keywords: IMRT, 3D-CRT, DVH, Gynecologic malignancies, Meta-analysis

OAR	25 Gy	30 Gy	35 Gy	40 Gy	45 Gy
Rectum	no	- 26.4%	- 27.0%	- 37.3%	-39.5%
Bowel	no	no	no	-17.8%	-17.3%
Bladder	no	no	no	no	no

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Developments in proton therapy for gyn cancers

Proton IMRT versus photon IMRT/VMAT/Tomotherapy

- All dosimetrically adequate for coverage, conformity and homogeneity
- Intensity modulated protons offered best sparing of the bowels and rectum
- IMPT might contribute reduction of acute and late toxicity which should be

Cozzi 2008

Marnitz *et al. Radiation Oncology* (2015) 10:91
DOI 10.1186/s13014-015-0402-z

RADIATION ONCOLOGY

RESEARCH Open Access

Which technique for radiation is most beneficial for patients with locally advanced cervical cancer? Intensity modulated proton therapy versus intensity modulated photon treatment, helical tomotherapy and volumetric arc therapy for primary radiation – an intraindividual comparison

Simone Marnitz[1], Waldemar Wlodarczyk[1], Oliver Neumann[1], Christhardt Koehler[2], Mirko Weihrauch[1], Volker Budach[1] and Luca Cozzi[3*]

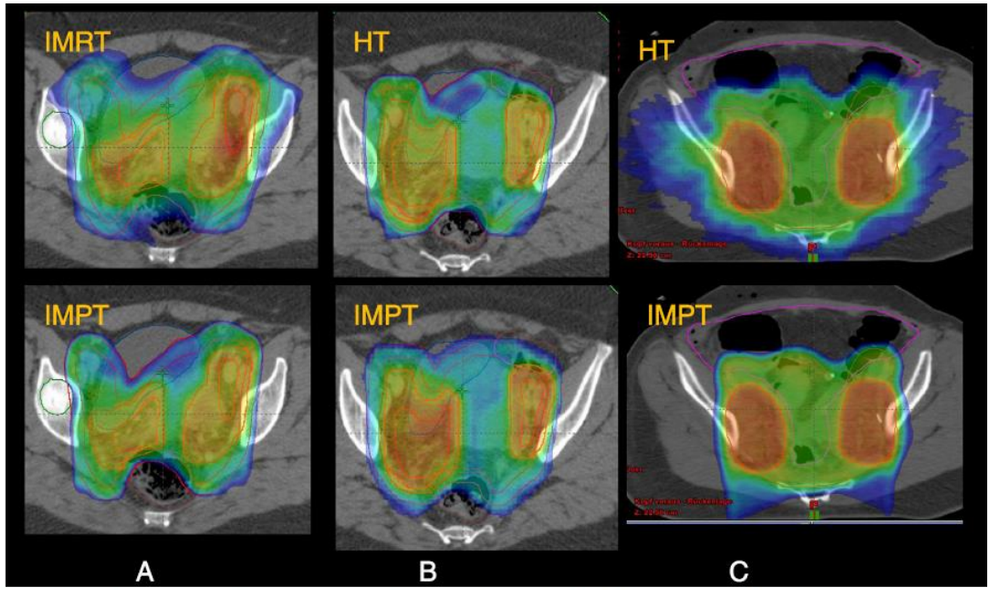

Figure 3 Examples of rectum and bowel sparing potential between techniques. **A** and **B**: rectum, colorwash is at 45 Gy; **B**: SB, colowash is at 30 Gy.

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Clinical outcome including toxicity

Ghandi 2013

IMRT versus conventional pelvic radiotherapy

- 44 patients
- Comparison IMRT, 3D CRT
- DFS comparable

Table 1 Patient characteristics in WP-CRT and WP-IMRT arms

Characteristic	WP-CRT arm	WP-IMRT arm
No. of patients	22	22
Age, median (range) (y)	45 (35-65)	50 (35-65)
FIGO stage, n (%)		
IIB	13 (59)	12 (55)
IIIB	09 (41)	10 (45)
KPS, median (range)	90 (70-90)	90 (70-90)

International Journal of Radiation Oncology biology • physics
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Clinical Investigation: Gynecologic Cancer

Early Clinical Outcomes and Toxicity of Intensity Modulated Versus Conventional Pelvic Radiation Therapy for Locally Advanced Cervix Carcinoma: A Prospective Randomized Study

Ajeet Kumar Gandhi, MD,* Daya Nand Sharma, MD,* Goura Kisor Rath, MD,* Pramod Kumar Julka, MD,* Vellaiyan Subramani, PhD,* Seema Sharma, MSc, DRP,* Durai Manigandan, PhD,* M.A. Laviraj, MSc, DRP,* Sunesh Kumar, MS,† and Sanjay Thulkar, MD‡

*Department of Radiation Oncology, †Department of Obstetrics and Gynecology, and ‡Department of Radiodiagnosis, All India Institute of Medical Sciences, New Delhi, India

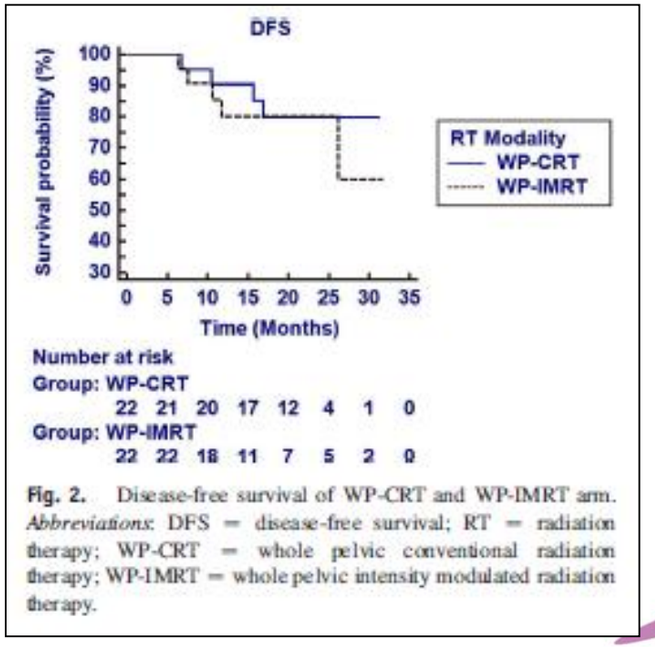

Fig. 2. Disease-free survival of WP-CRT and WP-IMRT arm. *Abbreviations:* DFS = disease-free survival; RT = radiation therapy; WP-CRT = whole pelvic conventional radiation therapy; WP-IMRT = whole pelvic intensity modulated radiation therapy.

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Clinical outcome including toxicity

- Significant reduction in V40 for rectum, bladder and small bowel
- Significant reduction toxicity

Ghandi 2013

Table 2 Dose–volume histogram characteristics for target coverage and OARs

Characteristic	WP-CRT arm	WP-IMRT arm	*P* value
Mean CTV D_{95}, Gy	51.95 ± 0.85	51.26 ± 0 .28	.42
Mean CTV Nodal D_{95}, Gy	52.01 ± 1.1	51.52 ± 0.26	.243
Mean PTV D_{95}, Gy	49.44 ± 4.37	50.68 ± 0.40	.438
Mean rectum V_{40}, % volume	98.37 ± 4.58	42 ± 2.78	.0001
Mean bladder V_{40}, % volume	97.54 ± 3.78	42.44 ± 2.74	.0001
Mean small bowel V_{40}, % volume	61.21 ± 14.63	31.66 ± 3.56	.001
Mean small bowel V_{90}, volume in cm^3	417.54 ± 42.16	199.89 ± 47.08	.005
Mean small bowel V_{100}, volume in cm^3	336.22 ± 37.88	102.47 ± 29.09	.001
Mean bone marrow V_{10} , % volume	99.44 ± 2.85	96.05 ± 3.61	.619
Mean bone marrow V_{20}, % volume	98.95 ± 3.71	87.24 ± 4.70	.618

Table 3 Acute gastrointestinal and genitourinary toxicity in WP-CRT and WP-IMRT arms

Toxicity	WP-CRT arm, n (%)	WP-IMRT arm, n (%)	*P* value	Effect size
Vomiting grade ≥2	8 (36.4)	2 (9.1)	**.034**	**0.273**
Vomiting grade ≥3	1 (4.5)	1 (4.5)	.756	0
GI grade ≥2	14 (63.6)	7 (31.8)	**.034**	**0.318**
GI grade ≥3	6 (27.3)	1 (4.5)	**.047**	**0.228**
GU grade ≥2	7 (31.8)	5 (23.8)	.404	0.08
GU grade ≥ 3	3 (13.6)	0 (0)	.125	0.136

Chronic GI toxicity	CRT	MRT	P value
overall	50 %	13.6 %	**0.011**
G1	27.3 %	9 %	
G2	13.6 %	4.5%	
G3	9.1 %	0%	

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Clinical outcome IMRT versus 3D-CRT for gyn tumors

VOLUME 36 · NUMBER 24 · AUGUST 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

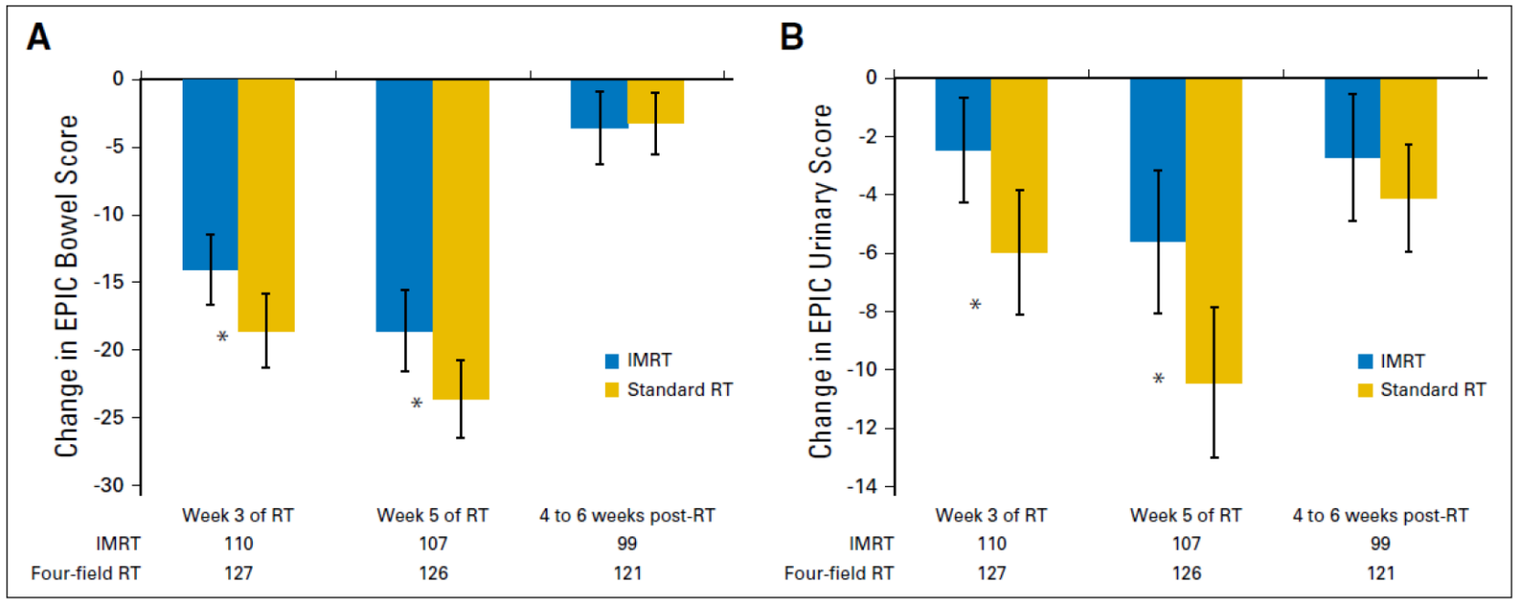
Klopp 2018

Patient-Reported Toxicity During Pelvic Intensity-Modulated Radiation Therapy: NRG Oncology–RTOG 1203

Ann H. Klopp, Anamaria R. Yeung, Snehal Deshmukh, Karen M. Gil, Lari Wenzel, Shannon N. Westin, Kent Gifford, David K. Gaffney, William Small Jr, Spencer Thompson, Desiree E. Doncals, Guilherme H.C. Cantuaria, Brian P. Yaremko, Amy Chang, Vijayananda Kundapur, Dasarahally S. Mohan, Michael L. Haas, Yong Bae Kim, Catherine L. Ferguson, Stephanie L. Pugh, Lisa A. Kachnic, and Deborah W. Bruner

Postoperative cervix and endometrial cancer

- Randomized trial
- 129 patients IMRT, 149 3D CRT
- Reduced GU and GI acute toxicity



Studies on toxicity after IMRT for cervix and endometrial cancer

Gynecol Oncol 130, 2013

	Histology	Postoperative	# patients	Time interval	Acute grade ≥3 toxicity (%)	Chronic grade ≥3 toxicity (%)
Chen MF et al. [25]	cervical	yes	54	3 yr	6	2
Shih et al. [26]	endometrial	yes	46	5 yr	13 (mostly hematologic)	2
Folkert et al.[27]	cervical	yes	34	3 yr	35 (mostly hematologic)	0
Beriwal et al.[30]	endometrial	yes	47	3 yr actuarial	0	2
RTOG 0418 [34,36,37](**abstract**)	both	yes	Cervical - 40 Endometrial - 43	Cervical - 2 yr Endometrial - 3 yr	Cervical - 25 (hematologic)	–
Hasselle et al.[31]	cervical	mixed	111	3 yr	2	7
Kidd et al.[32]	cervical	intact	135 (receiving IMRT)	mean f/u 22 months	–	6
Chen CC et al.[29]	cervical	intact	109	3 yr	27 (mostly hematologic)	11
Beriwal et al.[28]	cervical	intact	36	2 yr actuarial	33 (mostly hematologic)	10

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Ongoing evidence for improving treatment planning

EMBRACE II study protocol v.1.0

Image guided intensity modulated
External beam radiochemotherapy and
MRI based adaptive BRAchytherapy
in locally advanced CErvical cancer

EMBRACE-II

- Initiative EMBRACE study group within GEC-ESTRO
- Start inclusion 2016, 1000 patients intended
- Aims for **EBRT and brachytherapy**
- Exclusive IMRT
- SIB boosting for lymph node metastases
- Extension elective field based on defined risk profile
- ……

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Dose constraint and DVH table for EBRT planning in EMBRACE II

Current version adapted due to growing experience

	No lymph node involvement		Involved lymph nodes	
	Hard dose constraints	Soft dose constraints	Hard dose constraints	Soft dose constraints
PTV45	V42.75Gy > 95% Dmax < 107%	V42.75Gy = 95%	V42.75Gy > 95%	V42.75Gy = 95% Dmax < 107% for helper structure: PTV45 - (PTV-N(#) + 1cm)
ITV45	Dmin > 95%		Dmin > 95%	
CTV-HR + 10mm		Dmax < 103%		Dmax < 103% for helper structure: CTV-HR + 10mm - (PTV-N(#) + 1cm)
PTV-N(#)			D98% > 90% of prescribed LN dose Dmax < 107% of prescribed LN dose	D98% = 90% of prescribed LN dose
CTV-N(#)			D98% > 100% of prescribed LN dose	D50% > 102% of prescribed LN dose
Bowel	Dmax < 105%	V40Gy < 250cm^3* V30Gy < 500cm^3*	Dmax < 105% in regions outside 10-15mm from PTV-N	When no para-aortic irradiation: V40Gy < 250cm^3* V30Gy < 500cm^3* For para-aortic irradiation: V40Gy < 300cm^3* V30Gy < 650cm^3*
Sigmoid	Dmax < 105%		Dmax < 105% in regions outside 10-15mm from PTV-N	
Bladder	Dmax < 105%	V40Gy < 60%* V30Gy < 80%*	Dmax < 105% in regions outside 10-15mm from PTV-N	V40Gy < 60%* V30Gy < 80%*
Rectum	Dmax < 105%	V40Gy < 75%* V30Gy < 95%*	Dmax < 105% in regions outside 10-15mm from PTV-N	V40Gy < 75%* V30Gy < 95%*
Spinal cord	Dmax < 48Gy		Dmax < 48Gy	
Femoral heads	Dmax < 50Gy		Dmax < 50Gy	
Kidney	Dmean < 15Gy	Dmean < 10Gy	Dmean < 15Gy	Dmean < 10Gy
Body	Dmax < 107%		Dmax < 107% in regions outside 10-15mm from PTV-N	
Vagina (if not involved)		$D_{PIBS-2cm}$ < 5Gy		$D_{PIBS-2cm}$ < 5Gy
Conformality		1.10 (V43/Volume of PTV) 1.55 (V36Gy/Volume of PTV)		1.10 (V43Gy/Volume of PTV 1.55 (V36Gy/Volume of PTV)
Transposed ovaries	Dmean < 8 Gy	Dmean < 5 Gy	Dmean < 8 Gy	Dmean < 5 Gy
Duodenum	V55 < 15cm^3		V55 < 15cm^3	

Percentages of 45 Gy unless stated otherwise for nodes
Dmax and Dmin for MC plans based on D99.9% and D0.1%

* Soft constraints which can be used in the treatment plan optimisation. Values are based on the clinical data of EMBRACEII patients entered in the study before June 2017. The constraints are not supposed to be fulfilled by all patients, but rather by ~70-80% of the patients.

Reasonably Achievable…

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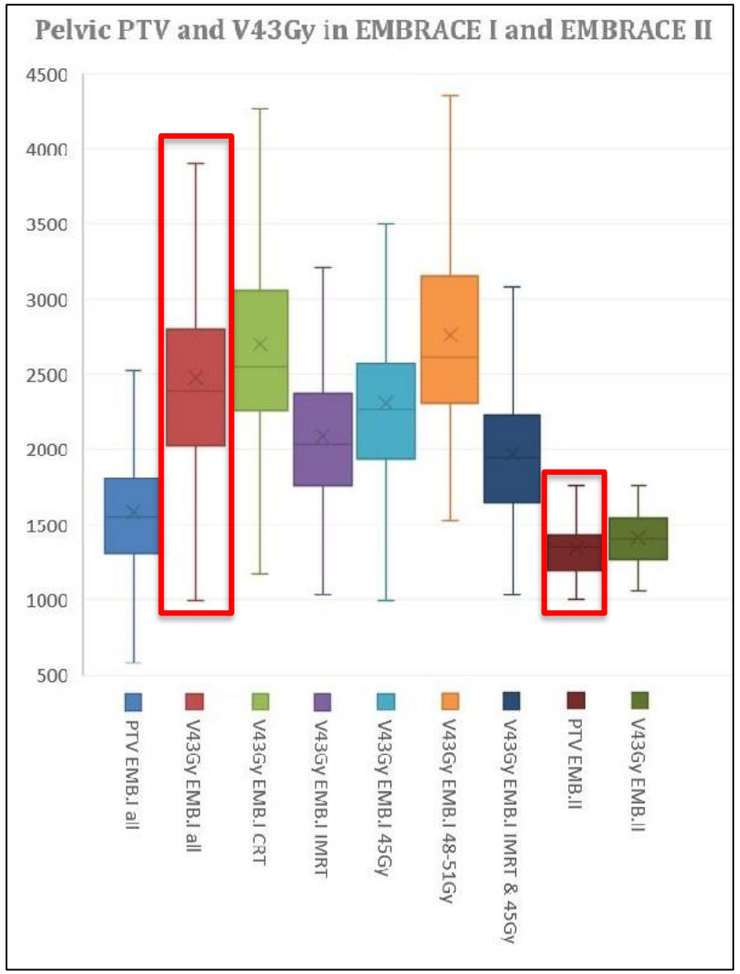
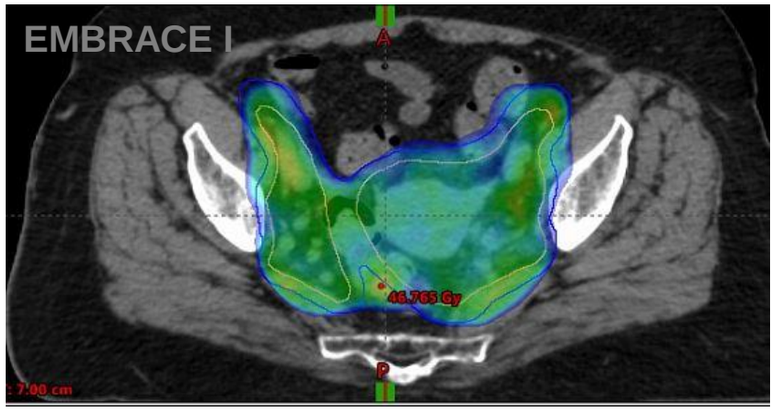
Impact on dose distribution

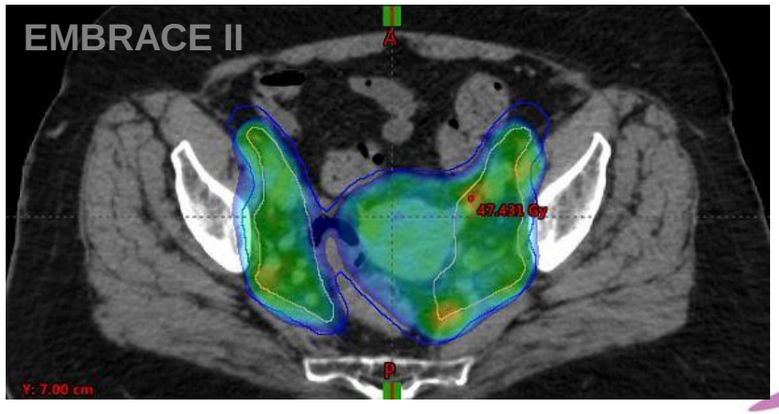
Comparison EBRT volumes treated in EMBRACE I and EMBRACE II

- V 43Gy reduced with about 1000 cc

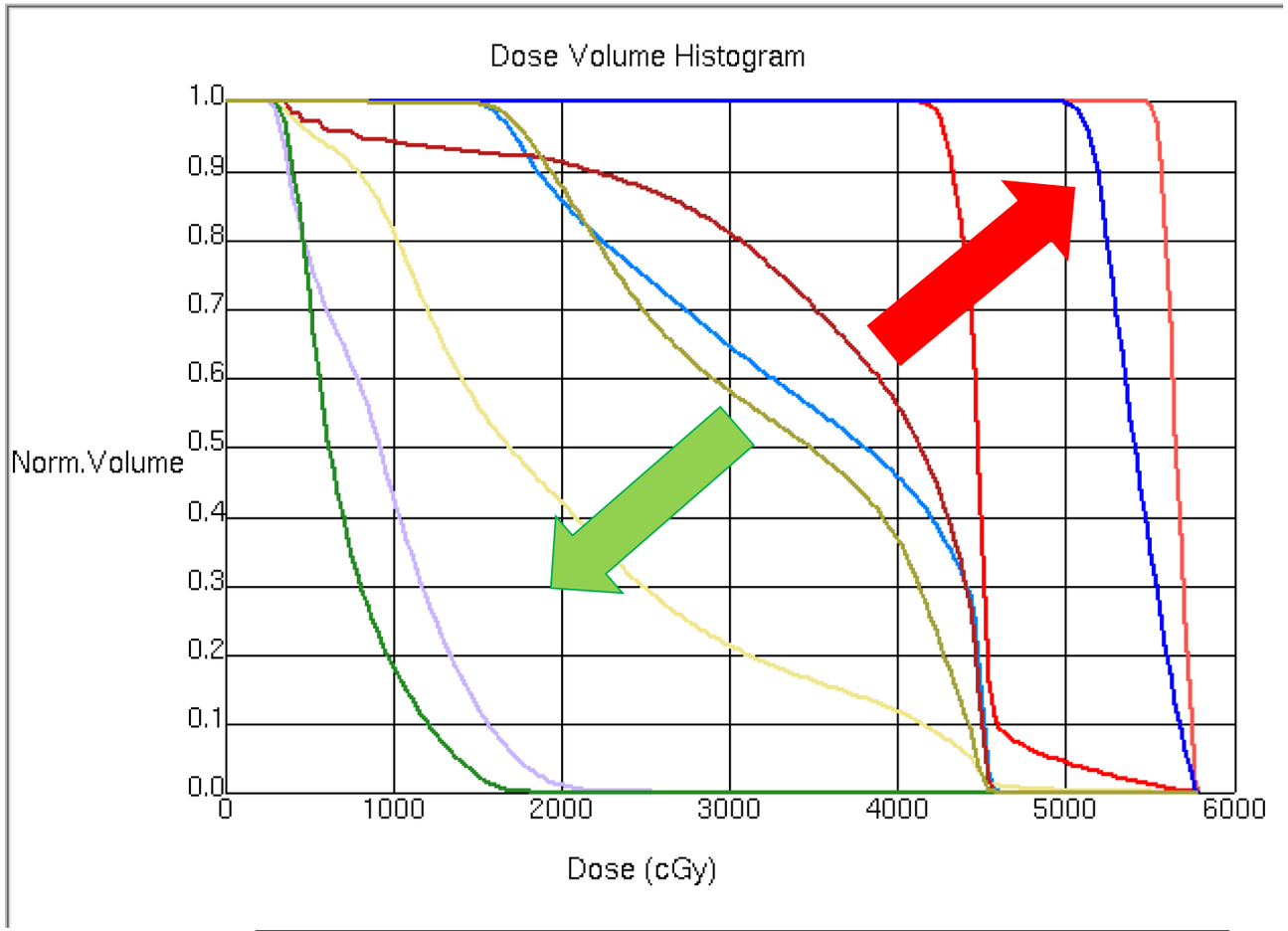


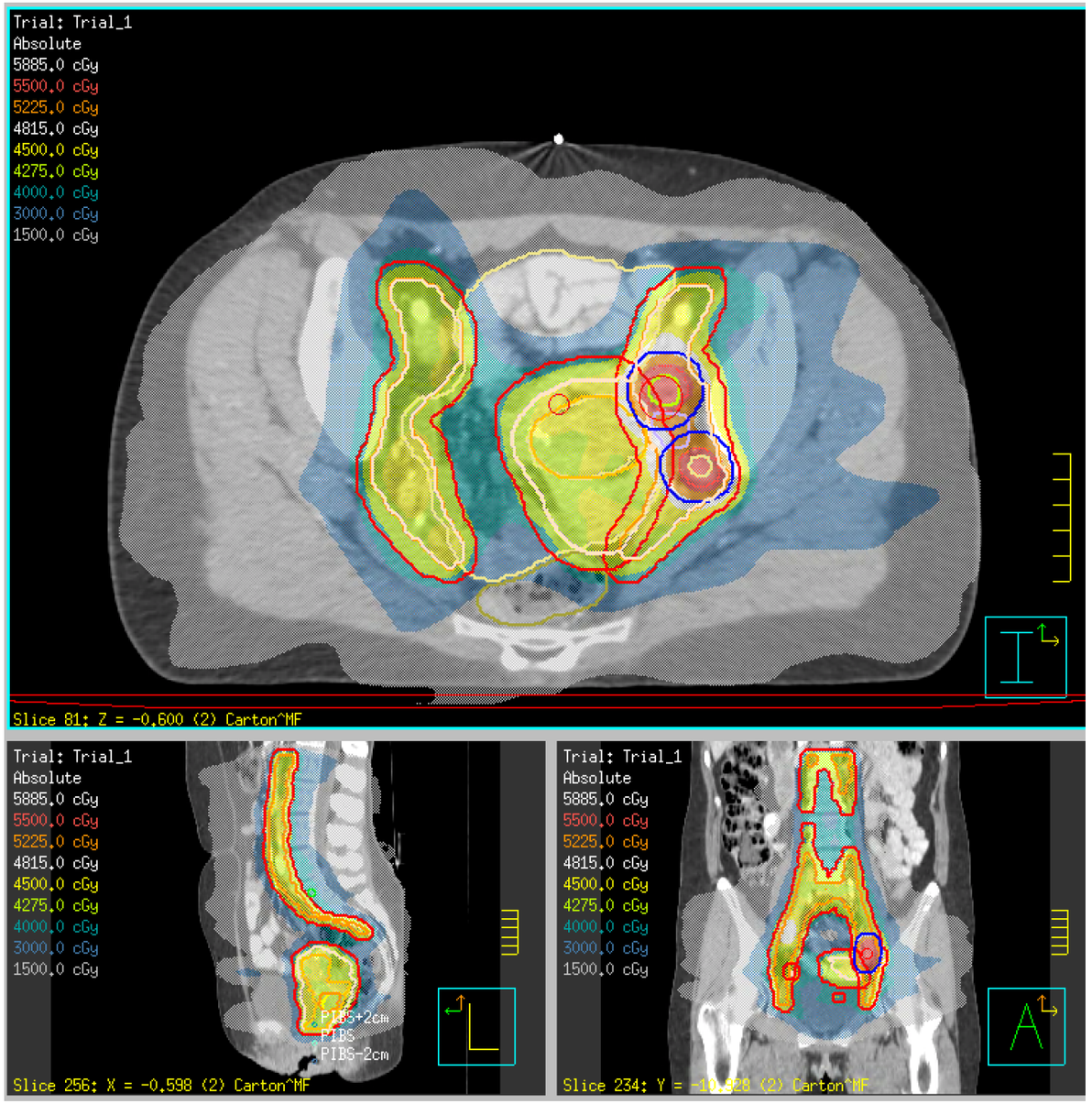
Courtesy Thomas Berger





Practical aspects





Treatment plan evaluation is based on DVH parameters and assessment of spatial dose distribution

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To consider beyond dose constraints and DVH parameters

- Cooperation of radiation oncologist, clinical physicist and RTT essential
- Understand why an individual plan is not further improving
- Important to realize that treatment planning reflects anatomical situation at one moment in time
- Current CTV-ITV-PTV margins take into account anatomical changes of targets but not OAR
- Adaptive IGRT (e.g. library plans) accounts for these changes in a structured way and may further help to improve balance between tumor and OAR dose
- Our knowledge on dose constraints and DVH parameters is constantly improving

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Literature data dose constraints rectum and bladder

Study	Bladder constraints	Rectum constraints	Sigmoid constraints	Femoral heads
Jhingran *et al.*(RTOG 0418)	V45<35%	V45<60%		V30<15%
Gandhi *et al.*(AIIMS)	V40<40% Dmax <50Gy	V40<40% Dmax <50Gy		
Mouttet –Audouard *et al* (Centre Oscar Lambret)	V40<50% V45<20% Dmax<60Gy	V40<50% V45<20% Dmax<60Gy	V40<50% V45<20% Dmax<60Gy	
Mabuchi *et al.*	V50<35%	V50<35%		V30<20%
Summary	**V 40 < 35 – 40%**		**V40 < 40 - 50%**	

Vagina

Also vagina does not like EBRT dose

- Significantly higher chance on G≥2 vaginal stenosis when EBRT dose exceeds 45 Gy

Kirchheiner 2016

Radiotherapy and Oncology 118 (2016) 160–166

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Brachytherapy

Dose–effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study

Kathrin Kirchheiner [a,*], Remi A. Nout [b], Jacob C. Lindegaard [c], Christine Haie-Meder [d], Umesh Mahantshetty [e], Barbara Segedin [f], Ina M. Jürgenliemk-Schulz [g], Peter J. Hoskin [h], Bhavana Rai [i], Wolfgang Dörr [a,j], Christian Kirisits [a], Søren M. Bentzen [k], Richard Pötter [a,j], Kari Tanderup [c], the EMBRACE Collaborative Group [1]

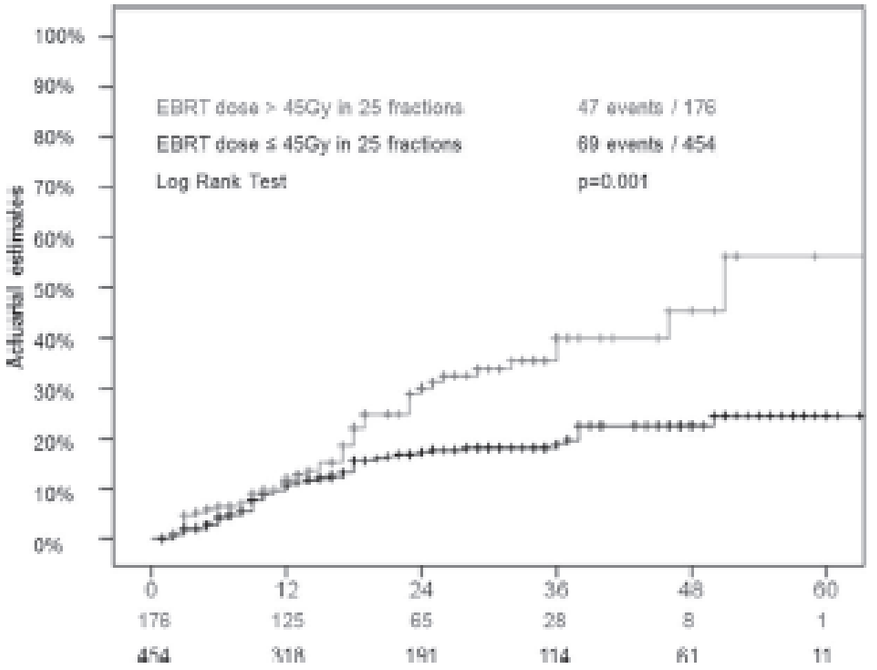
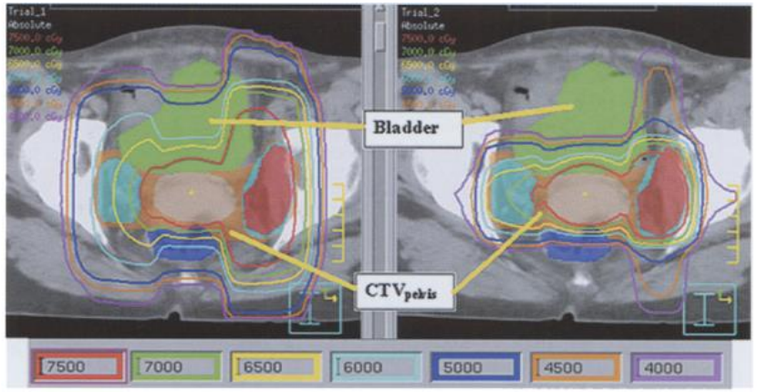
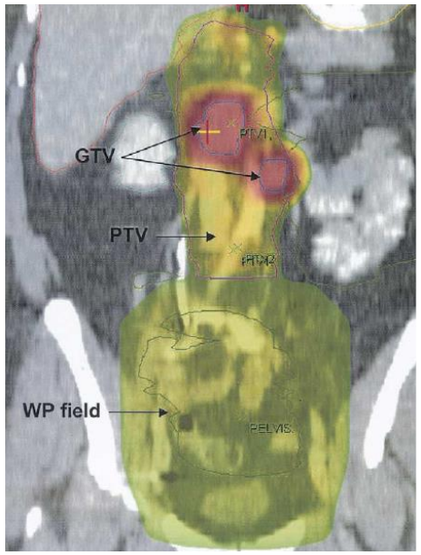


Fig. 3. Actuarial estimates for vaginal stenosis G ⩾ 2 in patients according to the EBRT dose.

Summary IMRT dosimetric gain

- Numerous studies including a meta-analysis
- Dosimetric gain by reducing in high dose volumes for OAR's
- Dosimetric gain by more dose to tumor, simultaneous boosts
- Extended field radiation easier achievable





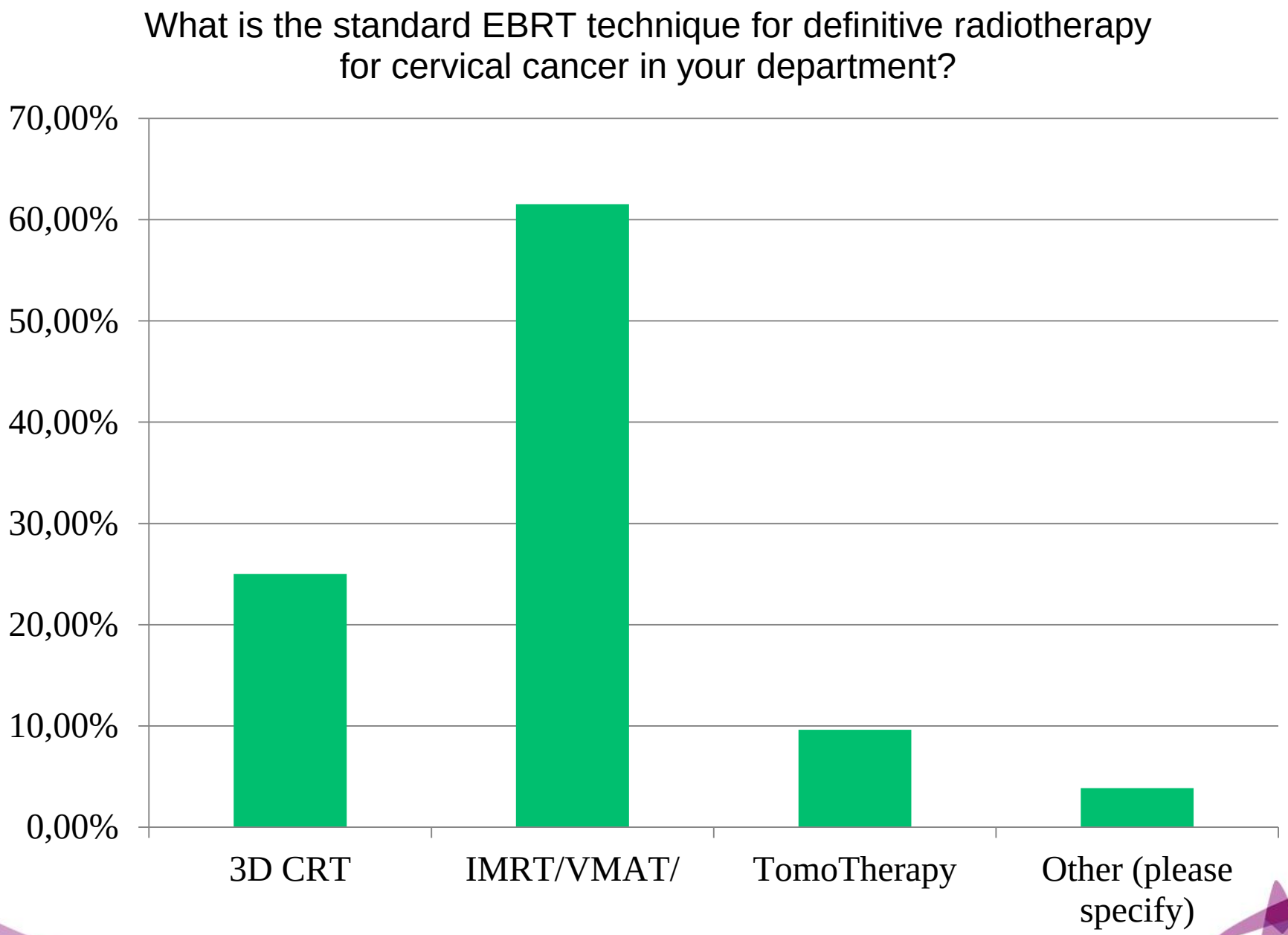
EBRT treatment Techniques

Jamema Swamidas
Kari Tanderup

Learning Objectives

- Review of IMRT/VMAT planning tools for creating optimal plans.
- Familiarization of EMBRACE – II protocol
- Examine the plan quality according to EMBRACE II protocol

Your practice



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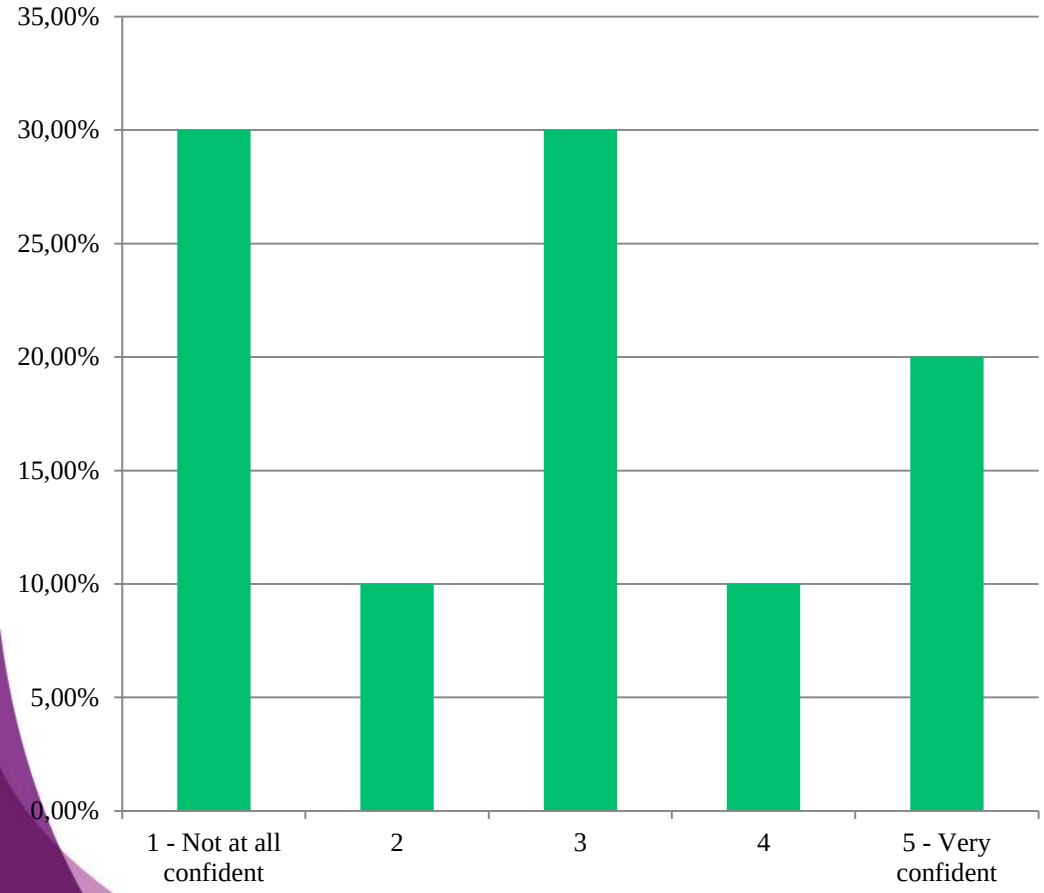
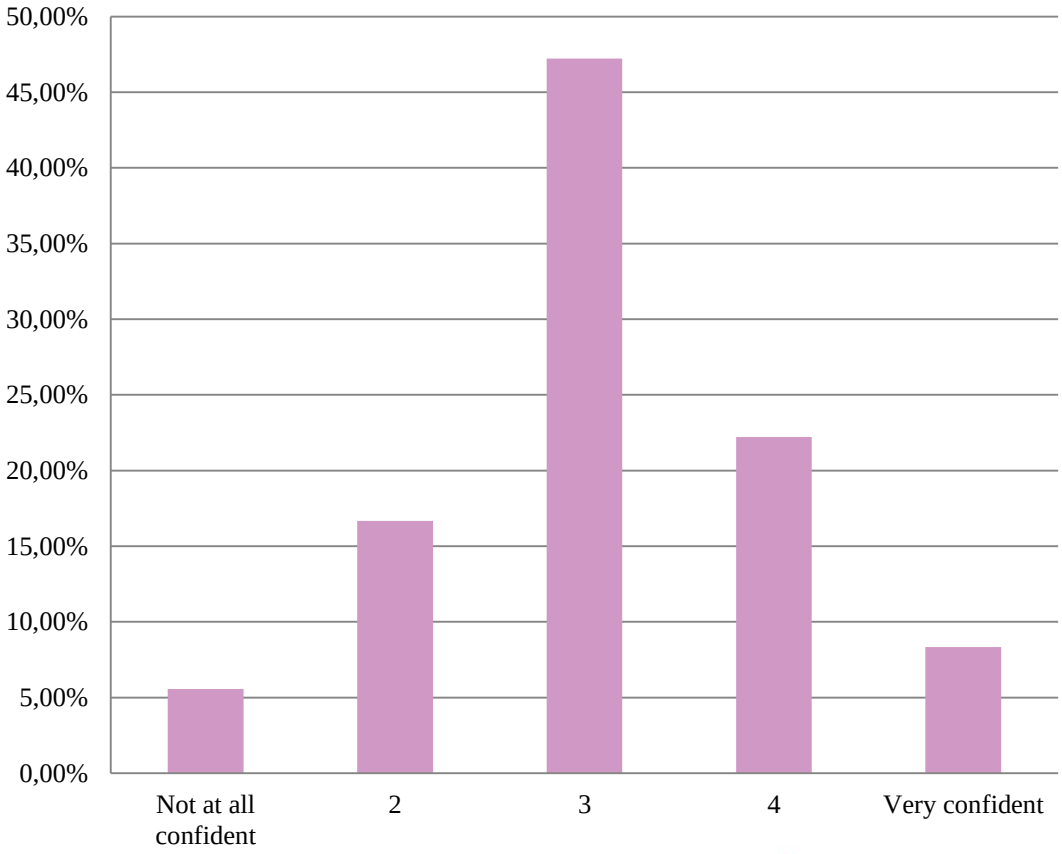
Your confidence

How confident are you at optimising IMRT plans for cervical cancer treatment?



How confident are you at evaluating IMRT plans for cervical cancer?



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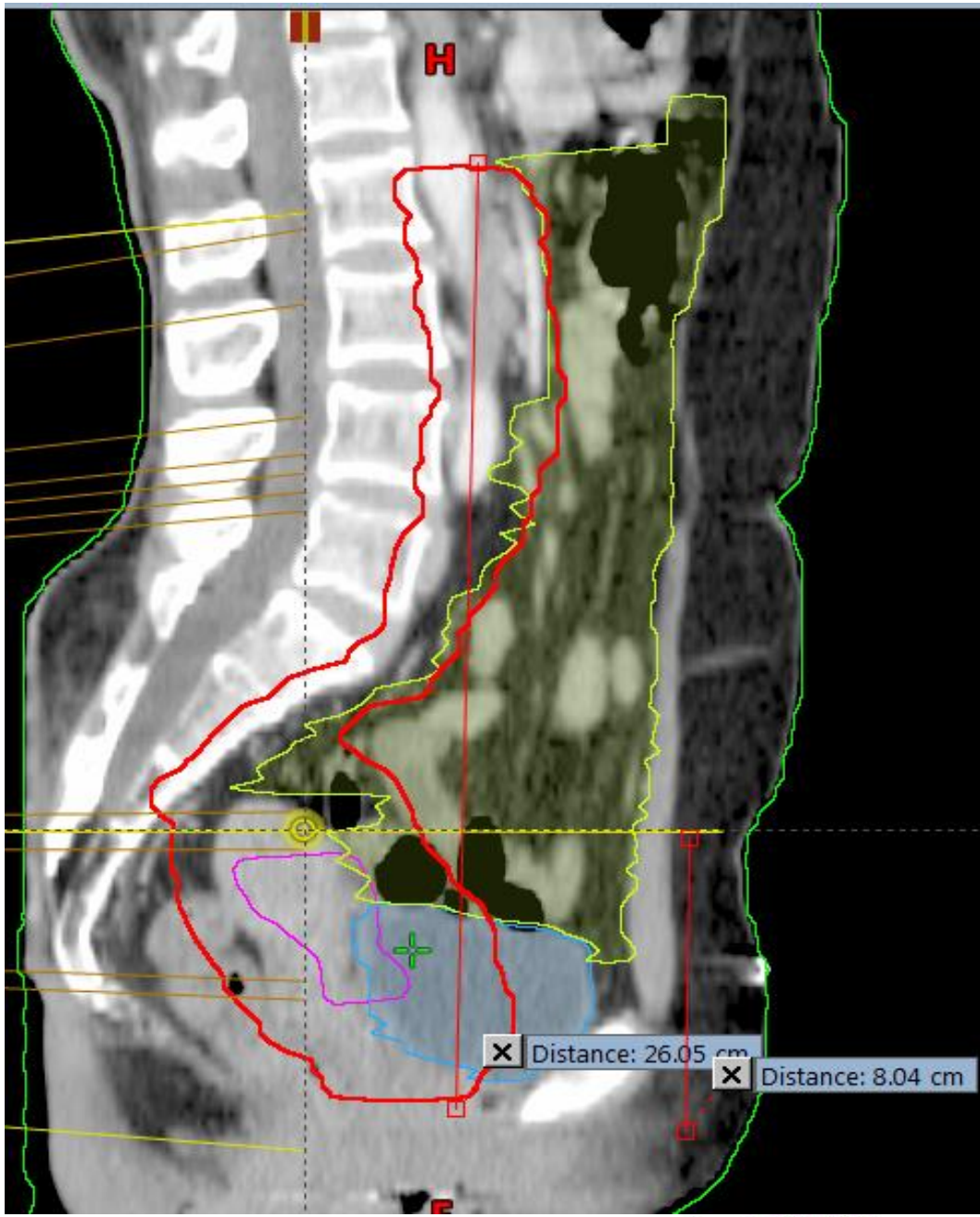
EMBRACE – II Study

- Aim: Optimize EBRT dose to minimize OAR
- Inverse optimization: IMRT / VMAT / HT mandatory
  - Choice of Beam energy: 6/10MV
  - Position of Isocentre
  - Number of arcs: 2-3
  - Dose calculation algorithm
  - Plan Objectives
  - Optimization volumes
  - Plan evaluation

Placement of Isocentre (limited by CBCT FOV)

- Length of PTV > 20cm, Isocentre has to be off-centered
- Limitation of CBCT – 16cm
- To visualize full bladder, and Fundus of the uterus



Planning Objectives for target e.g – EMBRACE II

Primary Target

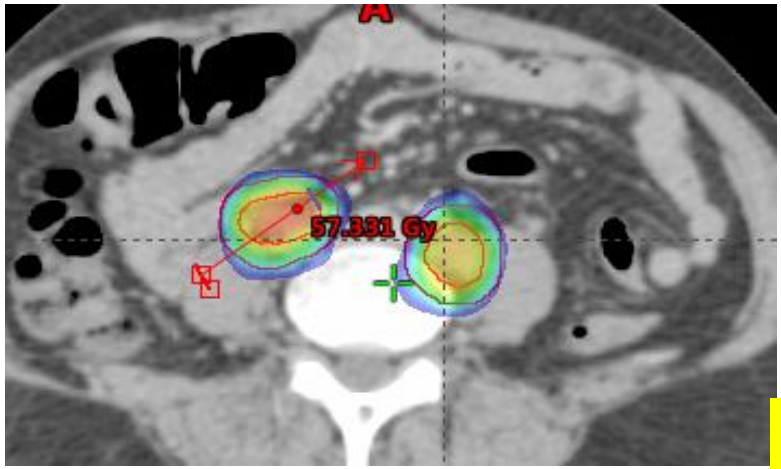
- **PTV 45: V95% > 95% (Hard constraint)**
- **ITV 45 D99.9 > 95% (42.8Gy) (Hard Constraint)**

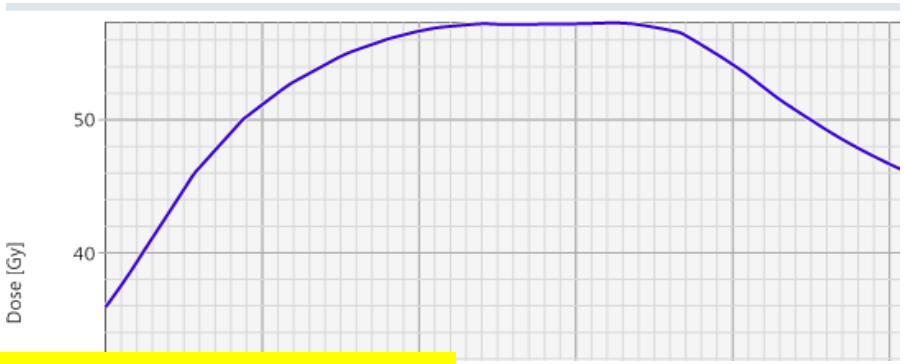
Nodes

- **CTV-(N#) D98 >100% of prescribed dose (Hard constraint)**
- If possible ITV-(N#) D50% > 102% of prescribed dose
- **PTV-(N#) D98 > 90% of prescribed dose (Hard constraint)**

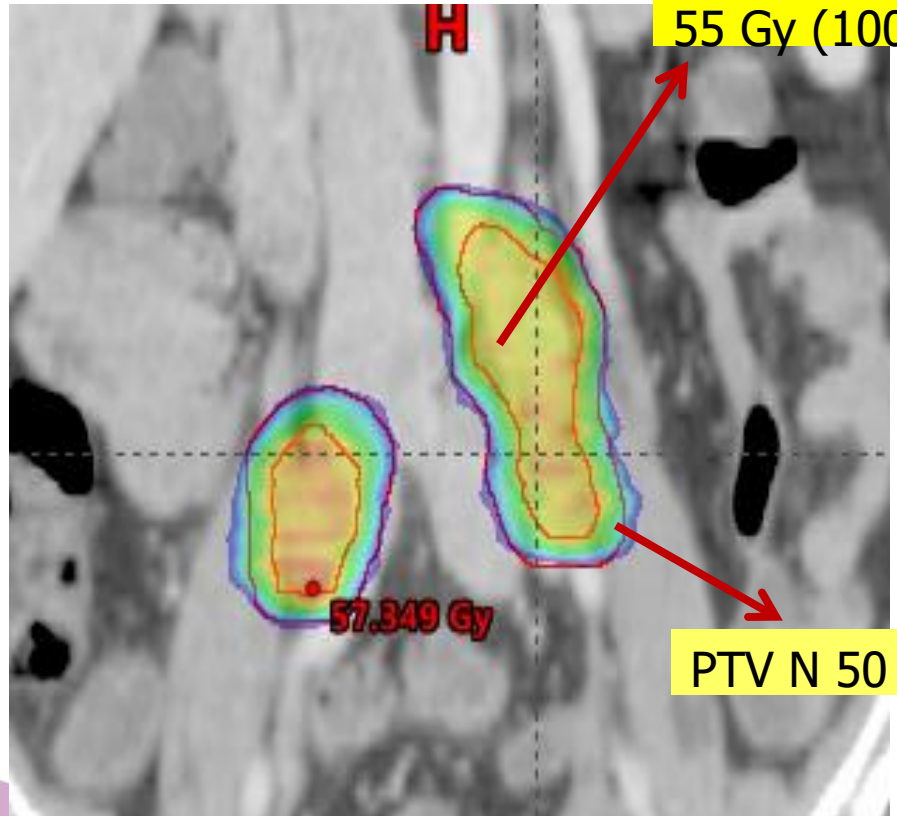
PTV margins: 5mm isotropic for both ITV45 and ITV-(N#)

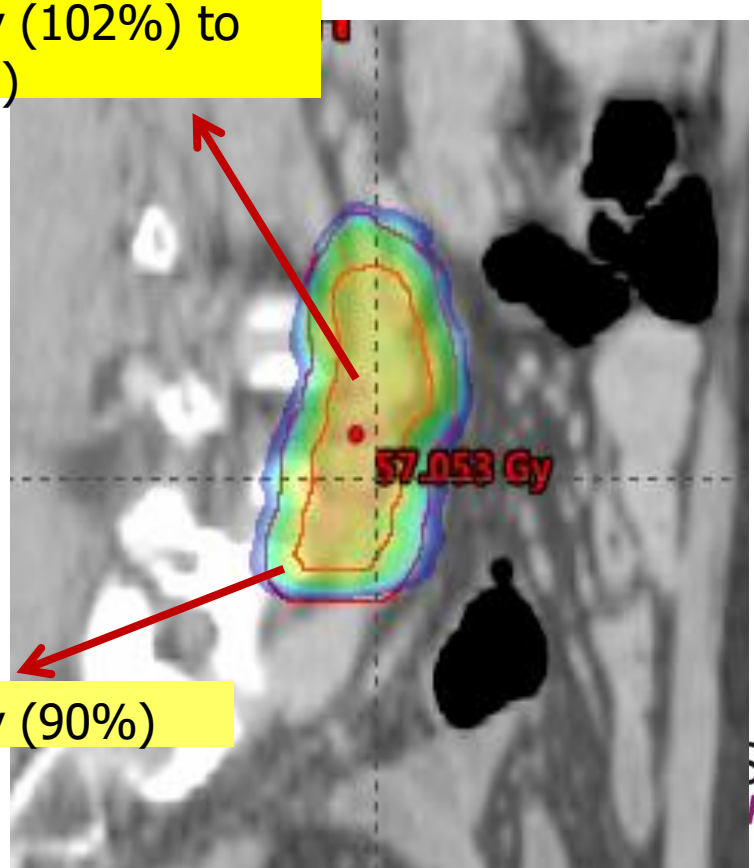
Coverage Probability Principle - Nodal SIB boost





CTV N 56 Gy (102%) to 55 Gy (100%)

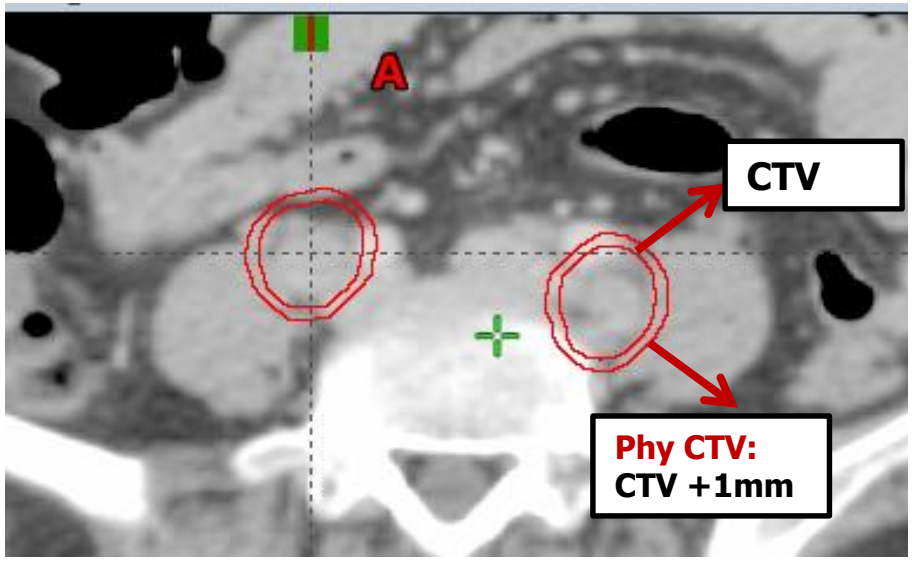




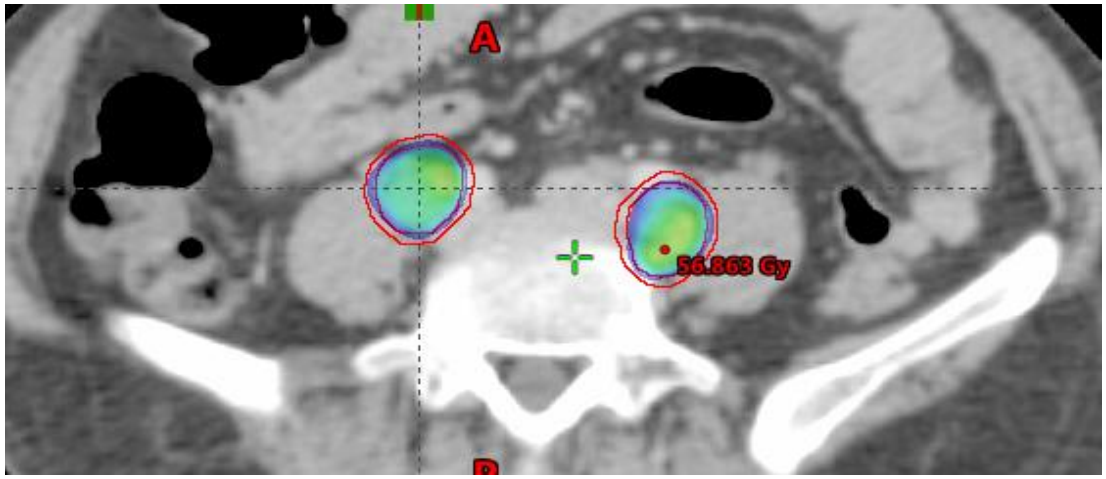
PTV N 50 Gy (90%)

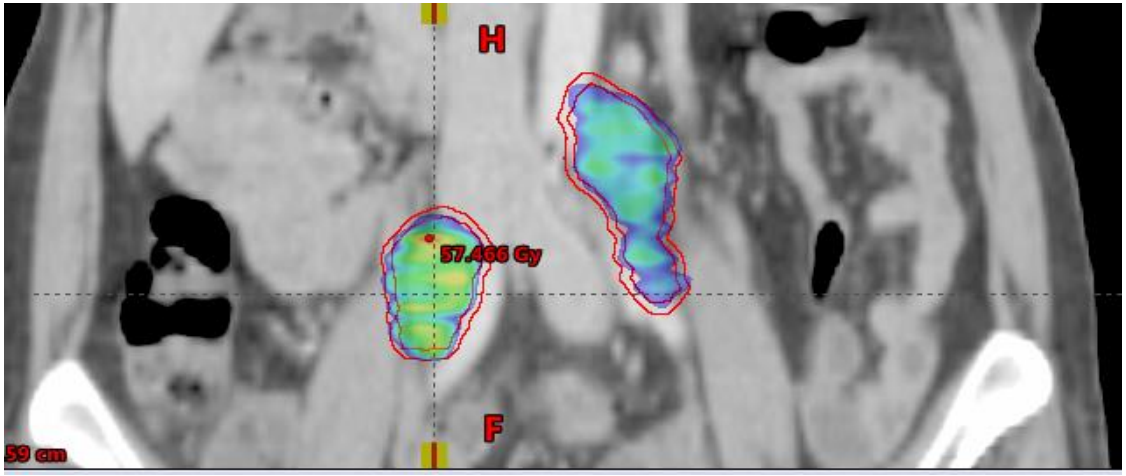
Optimization Volume - CTV Node

- Planning Aim : 55-57.5 Gy /25 fr (SIB)
  - D98% > 100% of LN Dose (Hard constraint)
  - Dmean > 102% of LN dose (Soft constraint)



Phy CTV: CTV + 1 mm





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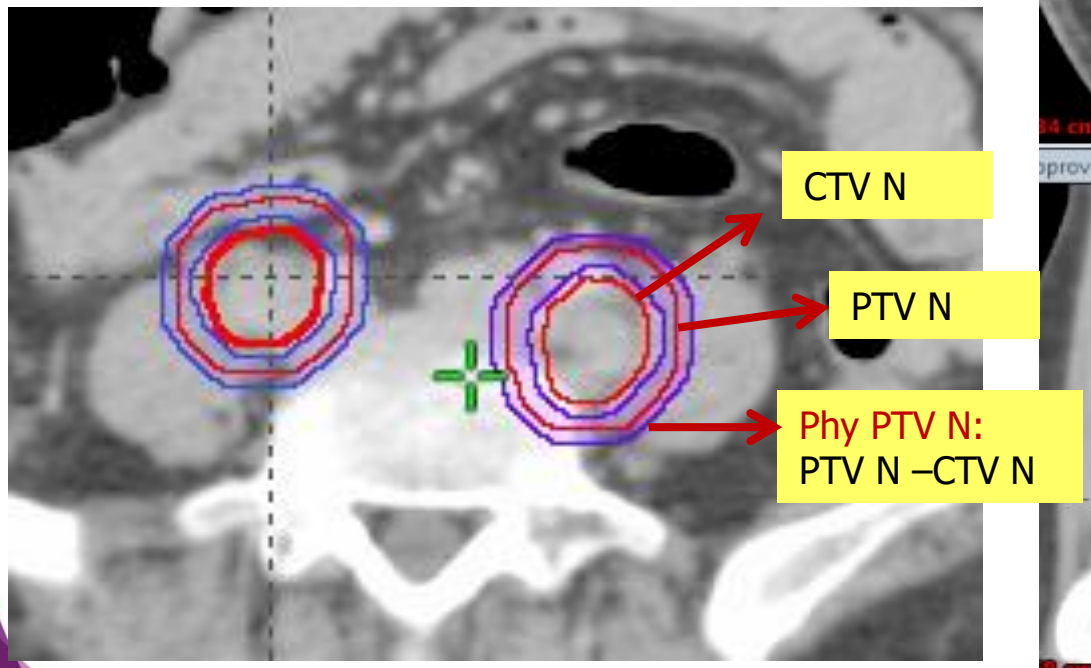
Optimization Volume - PTV node

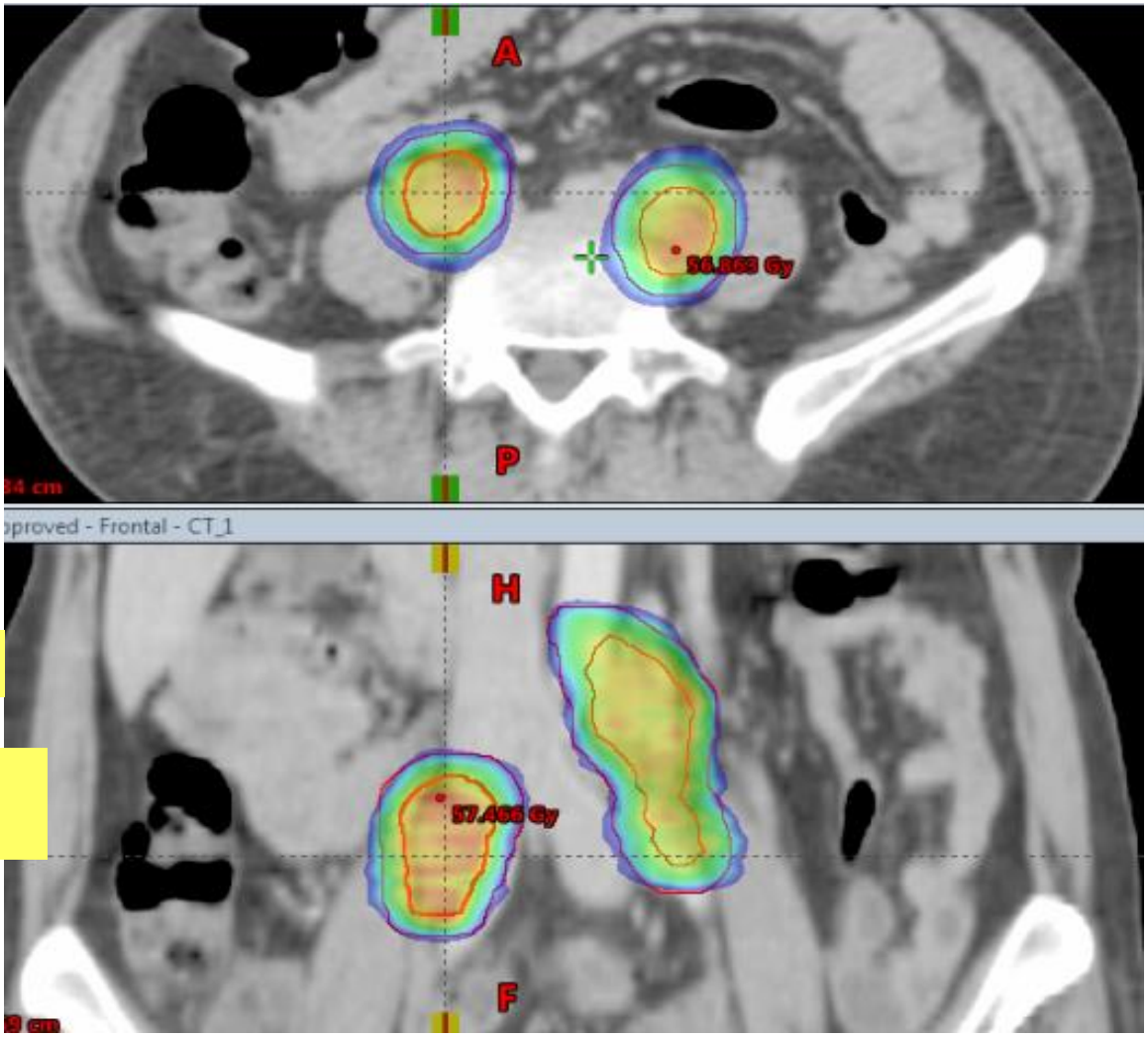
Phy PTV N : PTV N – CTV N

PTV dose constraints

D98% > 90% of LN dose

Dmax < 107% of LN dose





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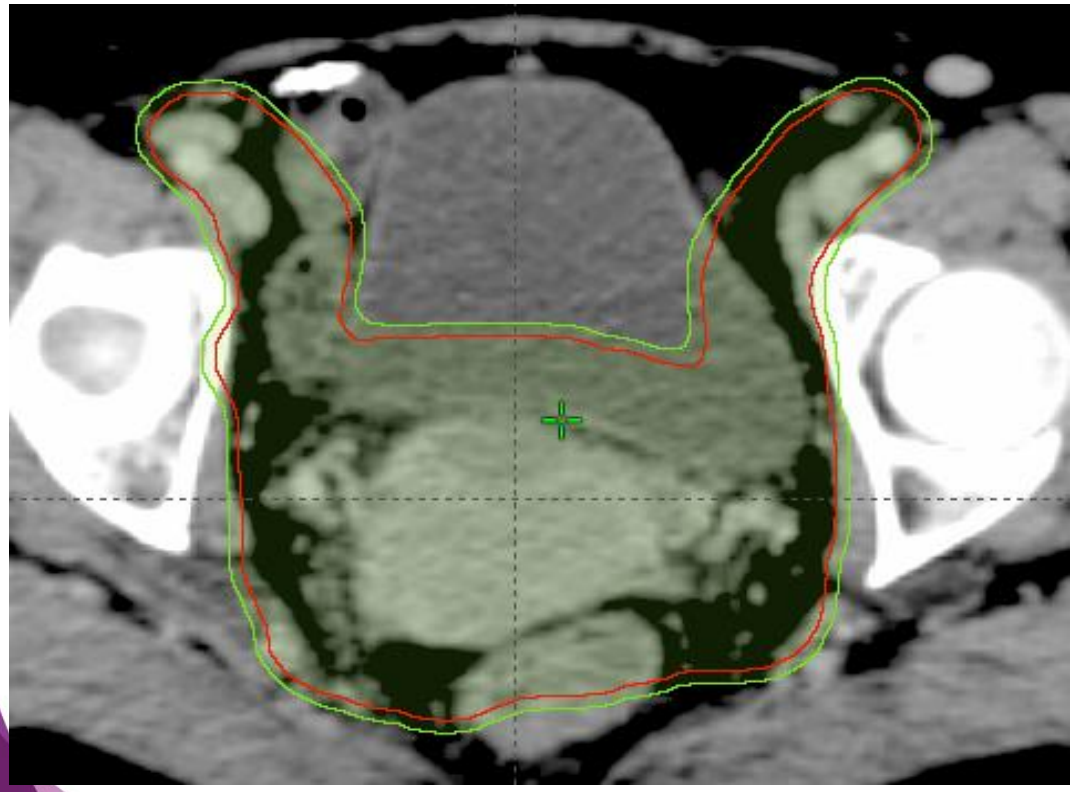
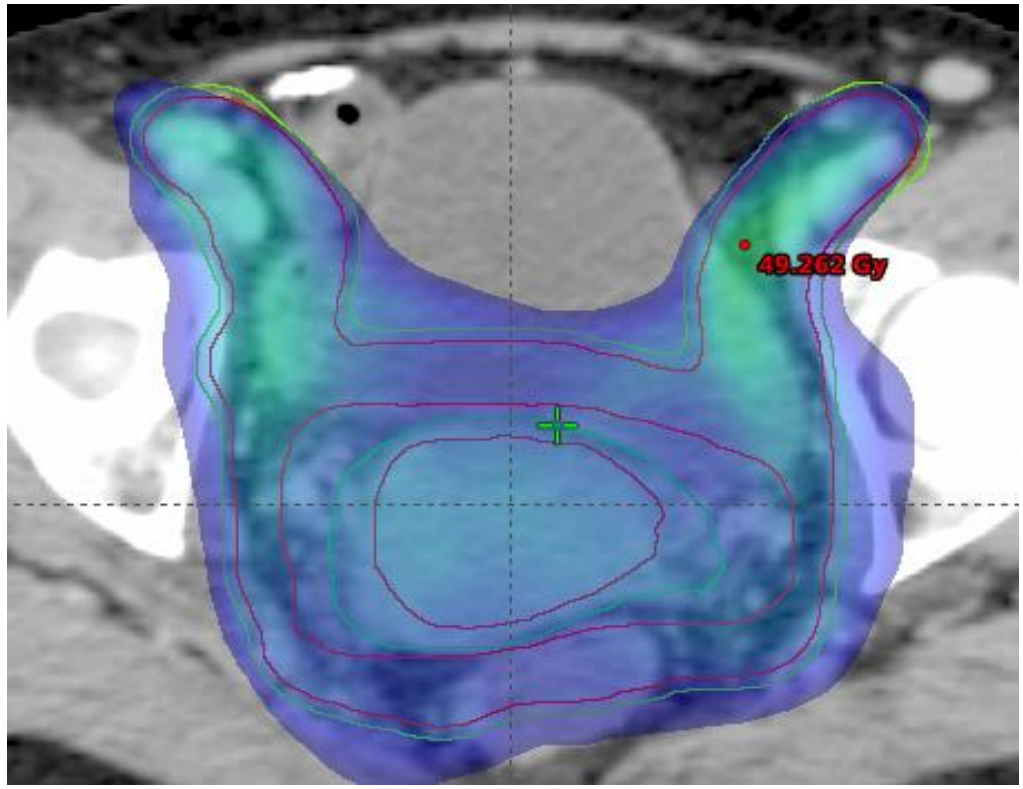
Optimization Volume - ITV 45

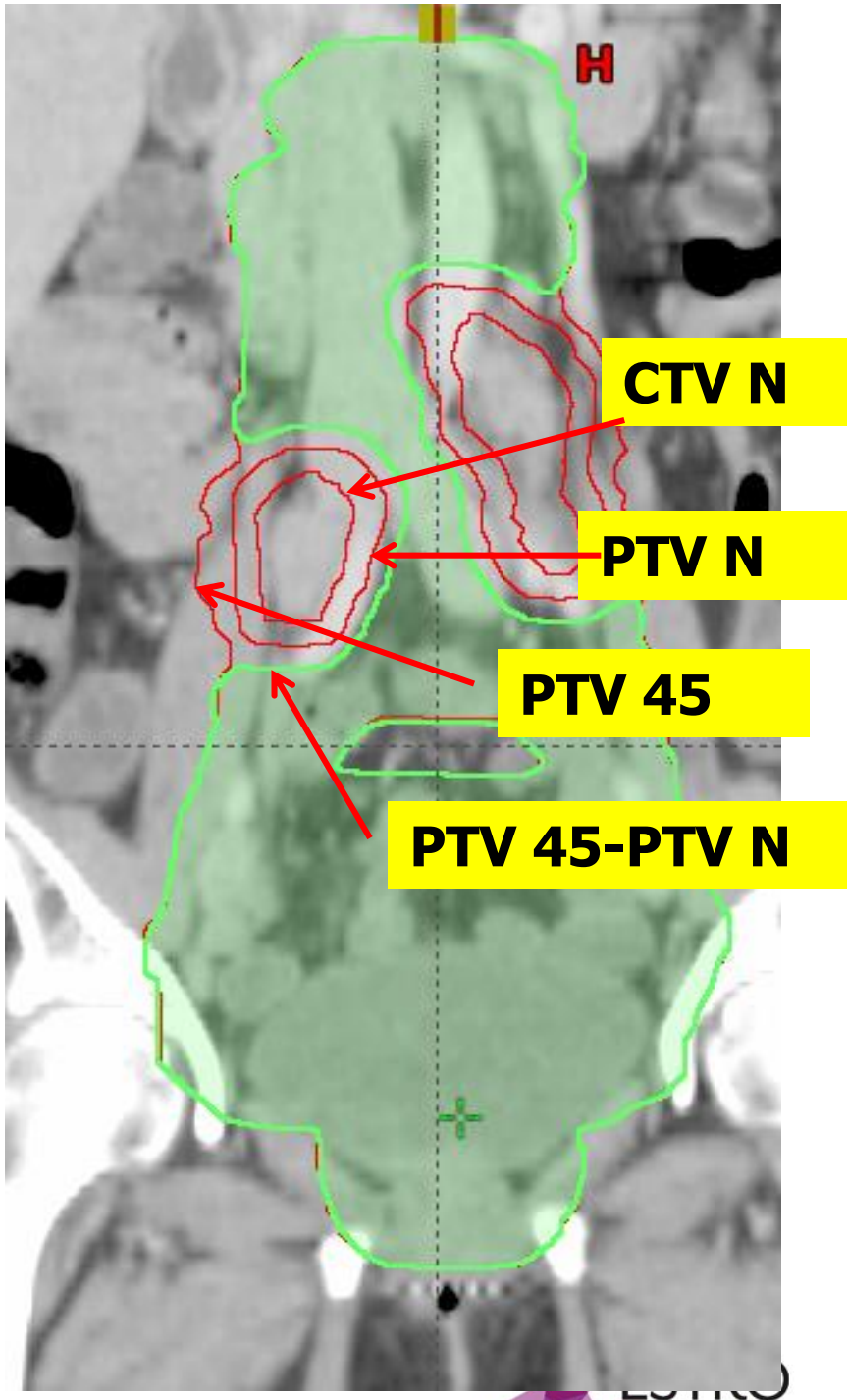
- D99.9 > 95% of prescribed dose , 42.8 Gy (Hard constraint)
- Optimization volume (Phy ITV): ITV 45+1mm



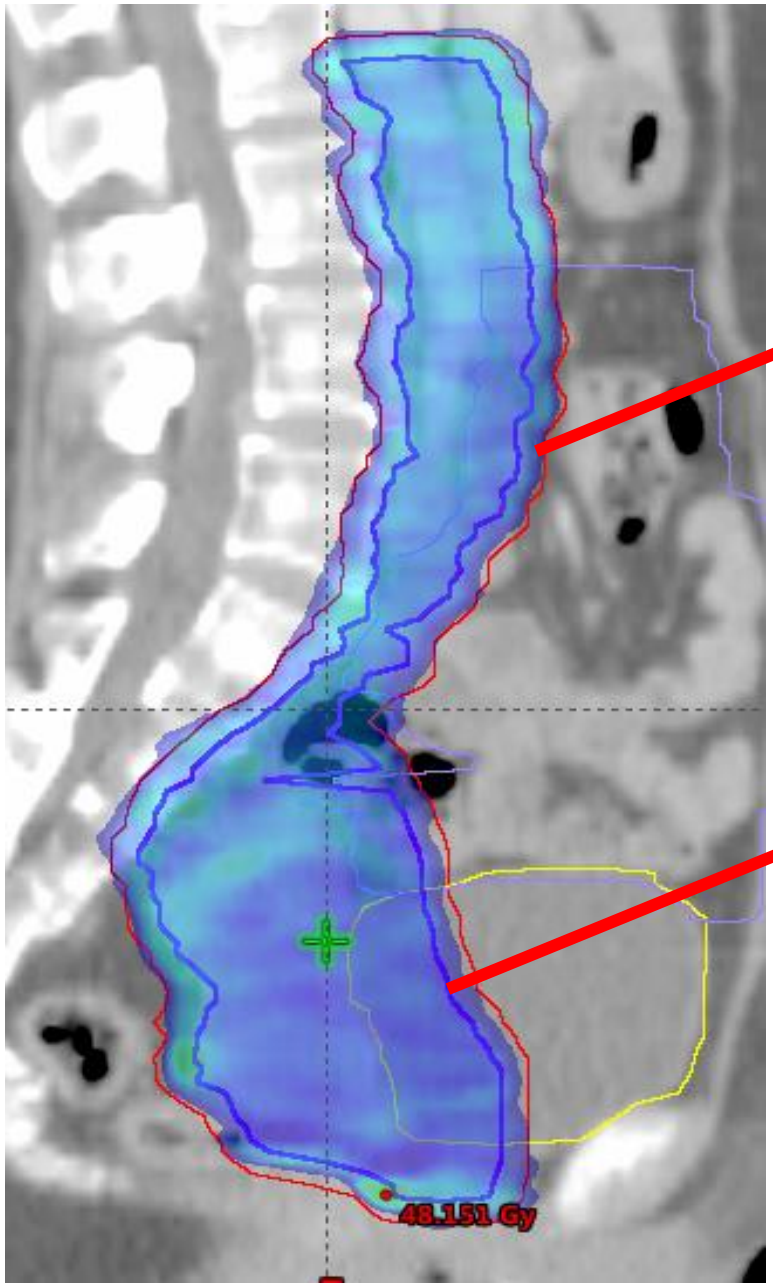


Optimization volume - PTV 45

- V95% > 95%
- Dmax <107% (when Lymph nodes are not boosted)
- Optimization volume (Phy PTV 45:
  - PTV 45-PTV N (crop by 3mm)



PTV 45 - 42.8 Gy Isodose Volume

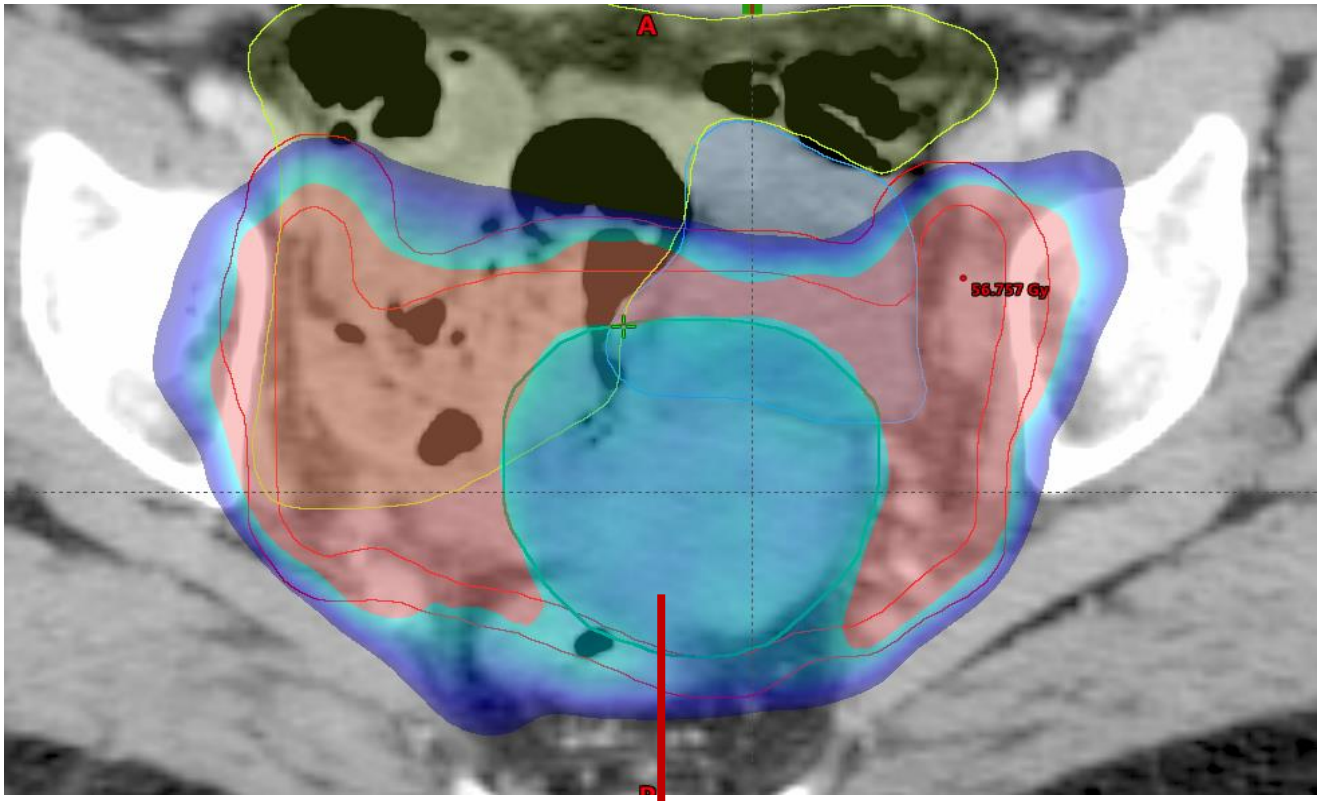


PTV 45

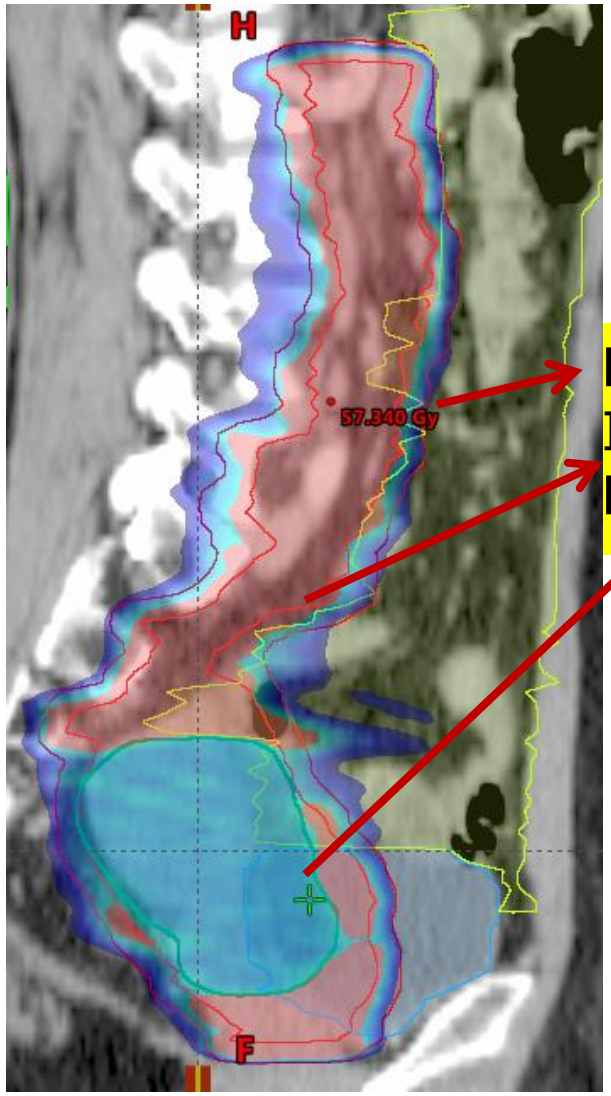
ITV 45

This constraint helps to spare organs better , Eg: Bladder, Bowel

BT region during IMRT - Helper Contour -– Avoid hot spots (D0.1>103% of 45Gy – Soft constraint)



Help contour
Dmax < 103% (46.35 Gy)



PTV45
ITV45
HC

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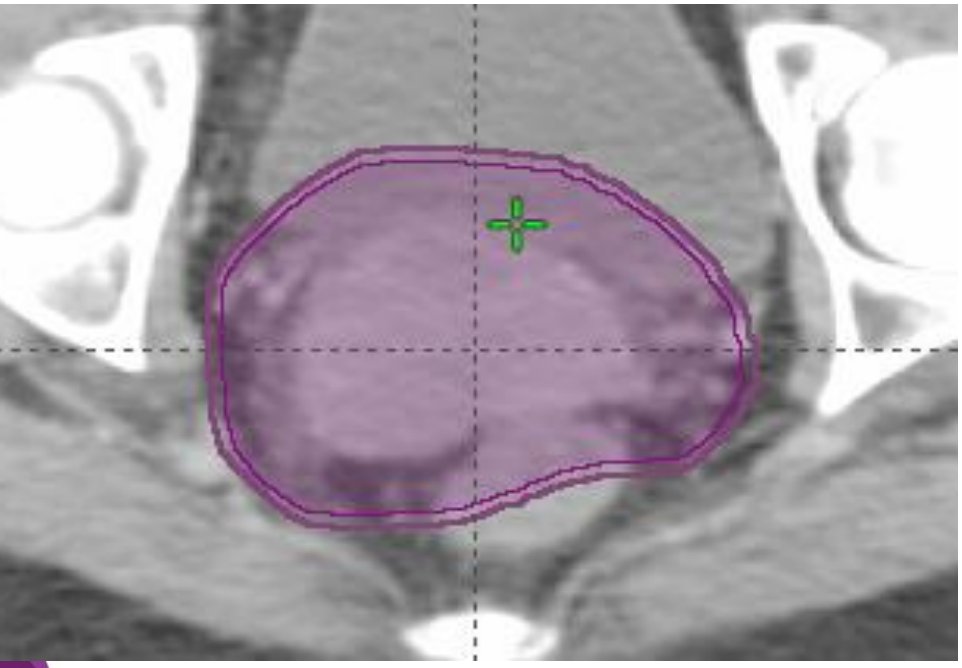
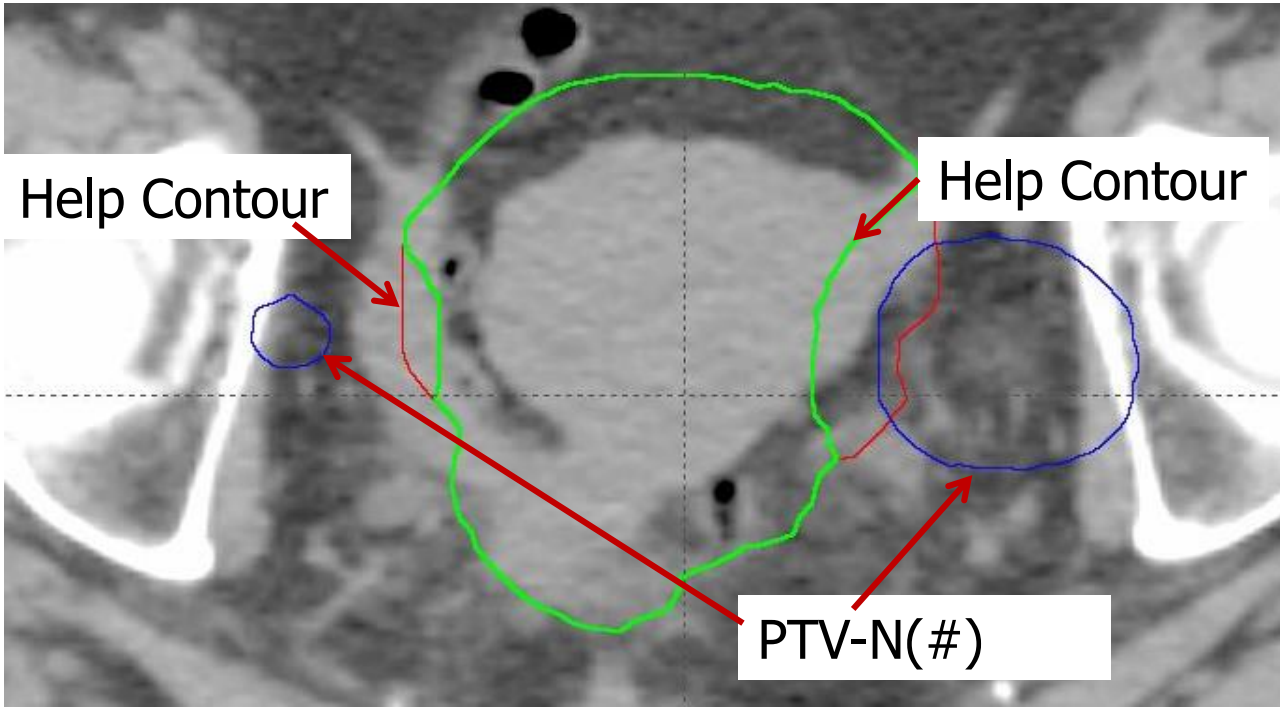
Optimization volume - Help Contour

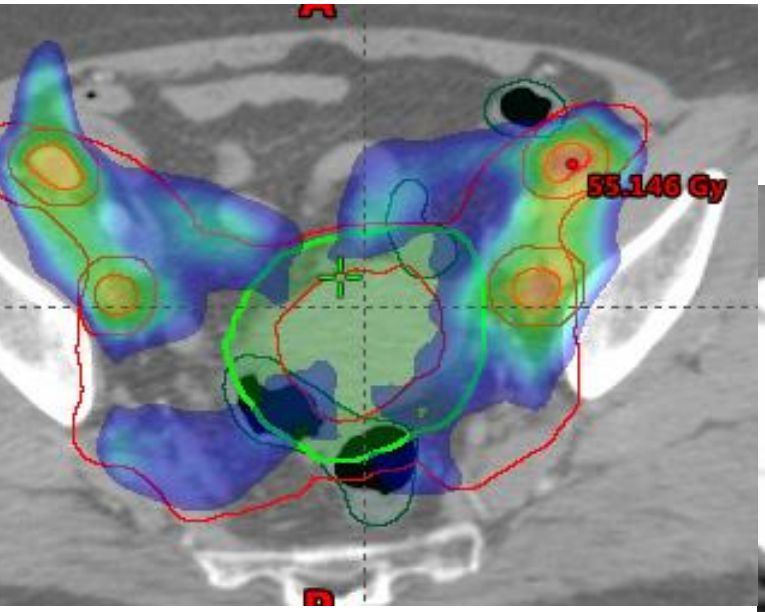
Help contour = HR-CTV plus 1cm (the brachy area)

Help Contour cropped with 1 cm to PTV-N(#).

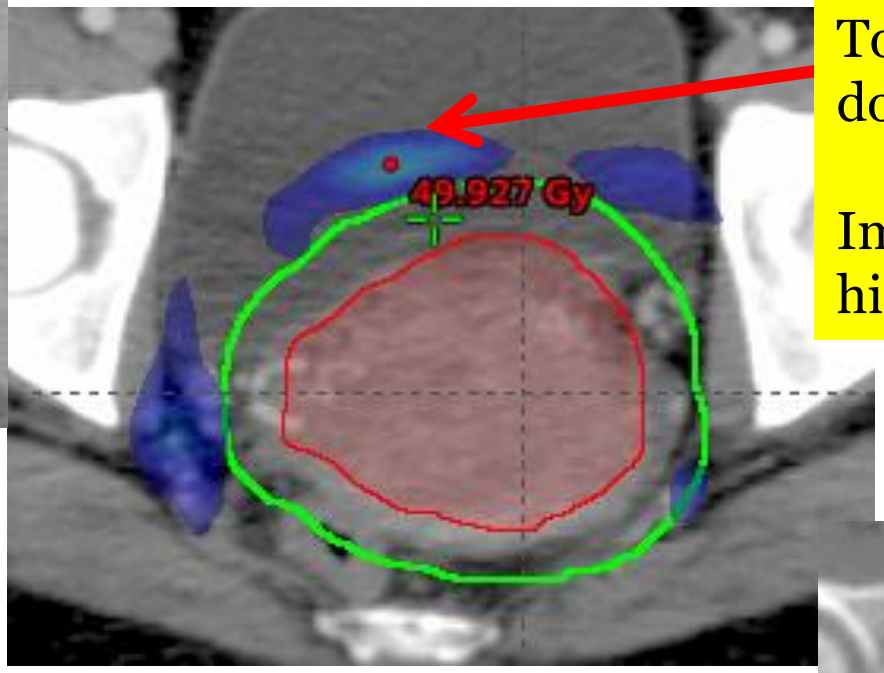




Help contour examples - 46.35Gy Isodose



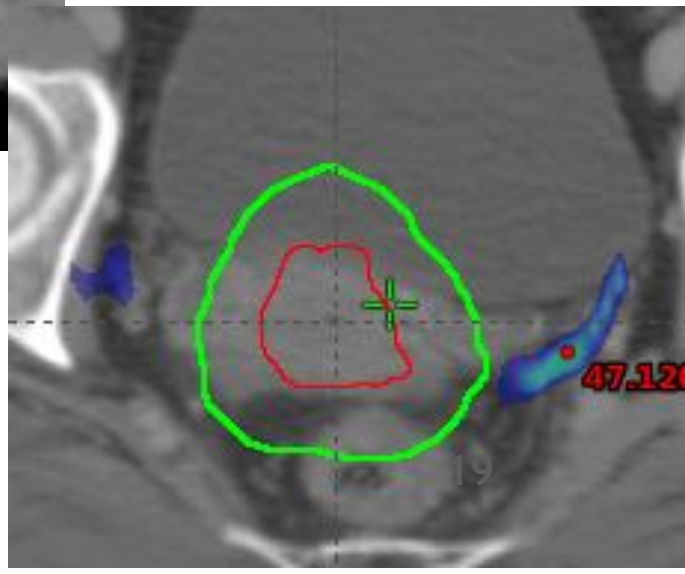
SIB – Multiple nodes



SIB with one node

To avoid: Potential high dose from BT

Imp: Spatial location of high dose in the OAR



Planning Objectives for OAR e.g – EMBRACE II (ALARA)

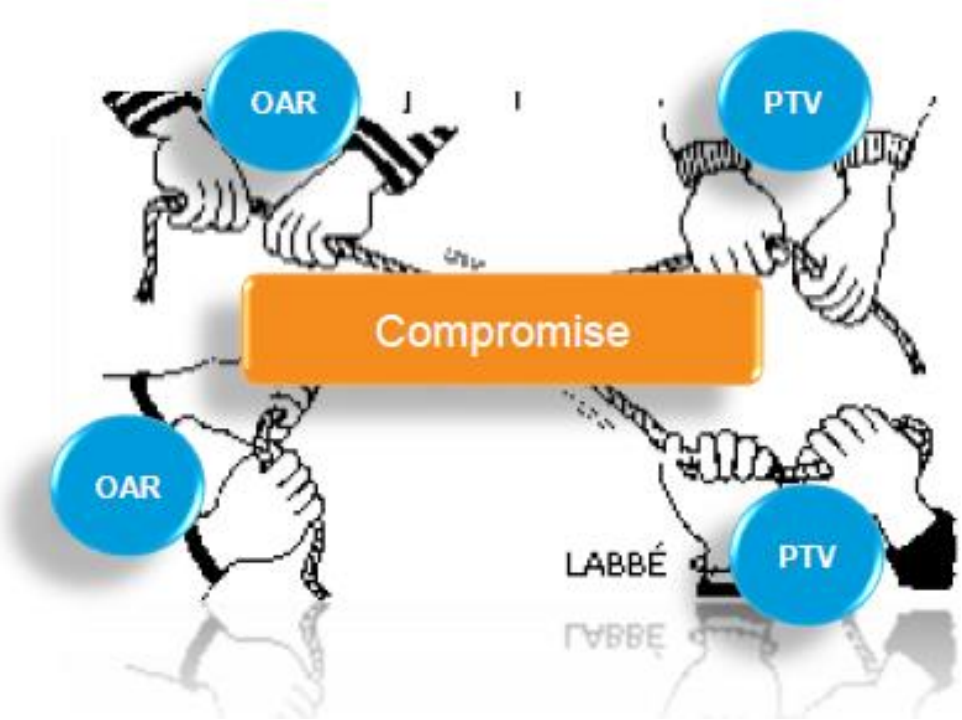
Bowel	Dmax < 105%	V40Gy < 250cm³* V30Gy < 500cm³*	Dmax < 105% in regions outside 10-15mm from PTV-N	When no para-aortic irradiation: V40Gy < 250cm³* V30Gy < 500cm³* For para-aortic irradiation: V40Gy < 300cm³* V30Gy < 650cm³*
Sigmoid	Dmax < 105%		Dmax < 105% in regions outside 10-15mm from PTV-N	
Bladder	Dmax < 105%	V40Gy < 60%* V30Gy < 80%*	Dmax < 105% in regions outside 10-15mm from PTV-N	V40Gy < 60%* V30Gy < 80%*
Rectum	Dmax < 105%	V40Gy < 75%* V30Gy < 95%*	Dmax < 105% in regions outside 10-15mm from PTV-N	V40Gy < 75%* V30Gy < 95%*
Spinal cord	Dmax < 48Gy		Dmax < 48Gy	
Femoral heads	Dmax < 50Gy		Dmax < 50Gy	
Kidney	Dmean < 15Gy	Dmean < 10Gy	Dmean < 15Gy	Dmean < 10Gy
Body	Dmax < 107%		Dmax < 107% in regions outside 10-15mm from PTV-N	
Vagina (if not involved)		$D_{PIBS-2cm}$ < 5Gy		$D_{PIBS-2cm}$ < 5Gy
Conformality		1.10 (V42.75Gy/Volume of PTV) 1.55 (V36Gy/Volume of PTV)		1.10 (V42.75Gy/Volume of PTV 1.55 (V36Gy/Volume of PTV)
Transposed ovaries	Dmean < 8 Gy	Dmean < 5 Gy	Dmean < 8 Gy	Dmean < 5 Gy
Duodenum	V55 < 15cm³		V55 < 15cm³	

Percentages of 45 Gy unless stated otherwise for nodes
Dmax and Dmin for MC plans based on D99.9 and D0.01

* Soft constraints which can be used as optimisation constraints as they are not based on clinical evidence. The constraints are not supposed to be fulfilled by all patients, but rather by ~70-80% of the patients.

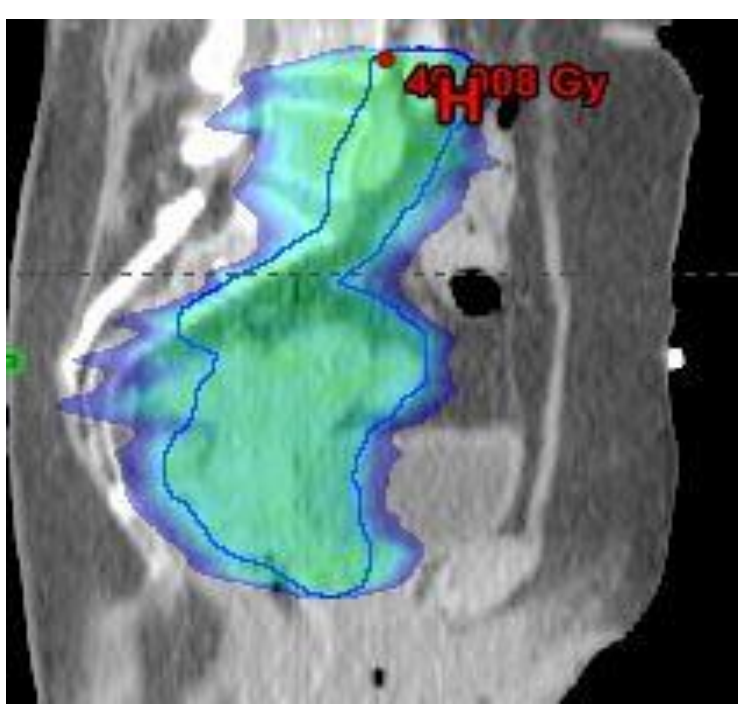
Monaco – Constrained optimization

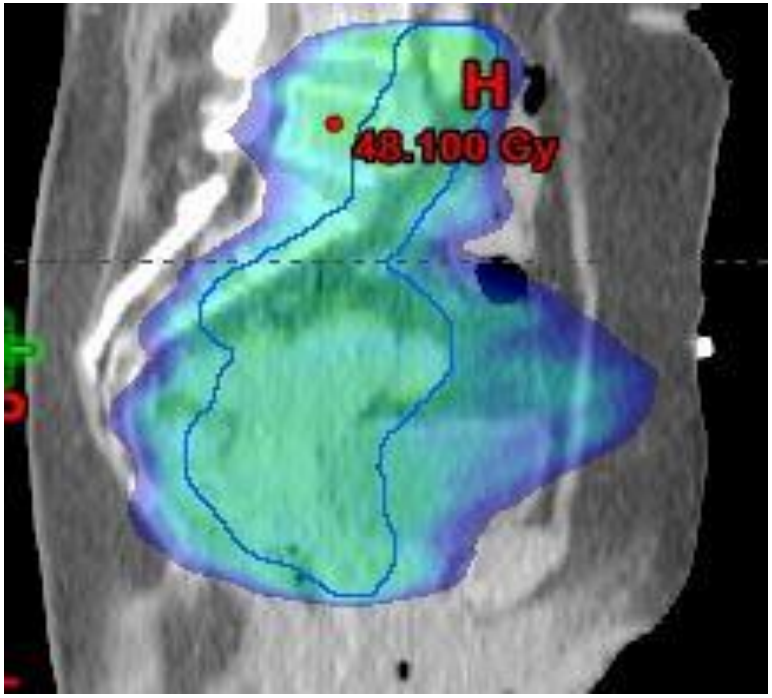
- In traditional systems, we create a plan to achieve target coverage then lower doses to OARs as a secondary process until the target coverage is compromised.
- With Monaco, the OAR doses (dose limiting cost functions) are prioritized and will be achieved before dose to targets (objective functions) are met.
- Only when the OAR doses are achieved will Monaco prioritize target objectives.



Slide Courtesy: Elekta Medical systems

Bowel, Bladder and Sigmoid
36 Gy isodosecurves



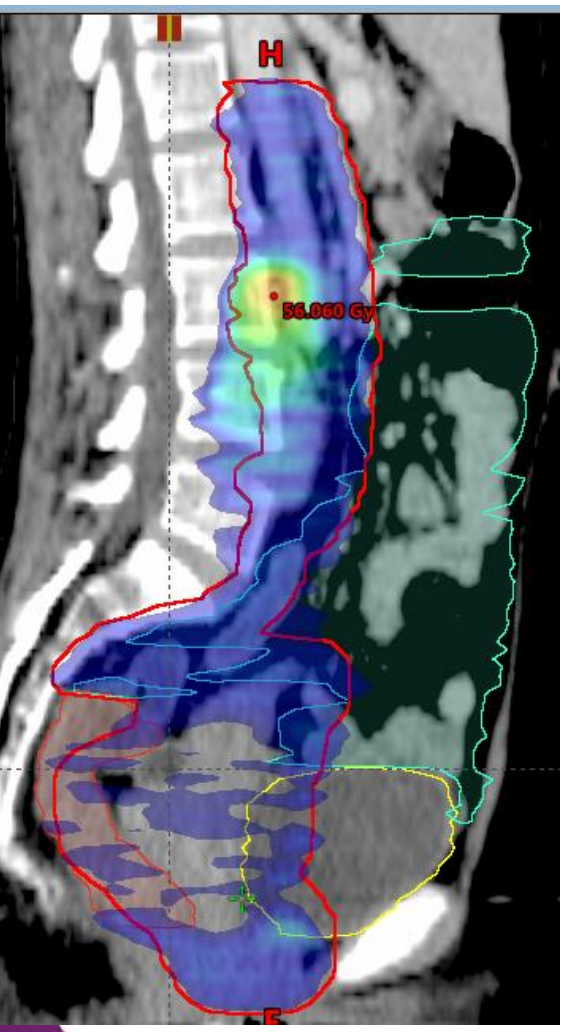


It is important to pay attention to lowdose area.
OAR can be spared from a lot of dose!

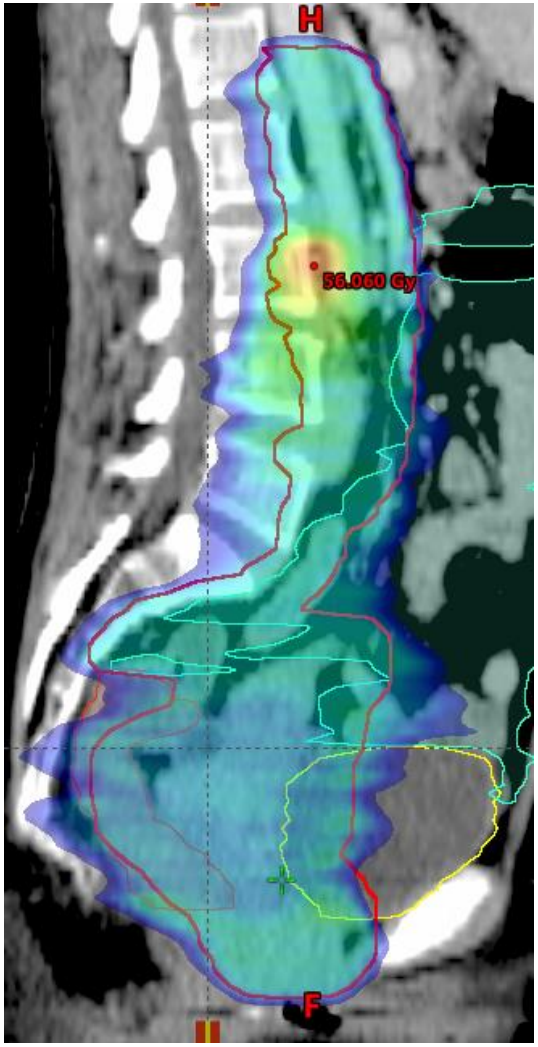
Specially the bowel and the body V43Gy pays for the very good coverage.

Dose fall – off

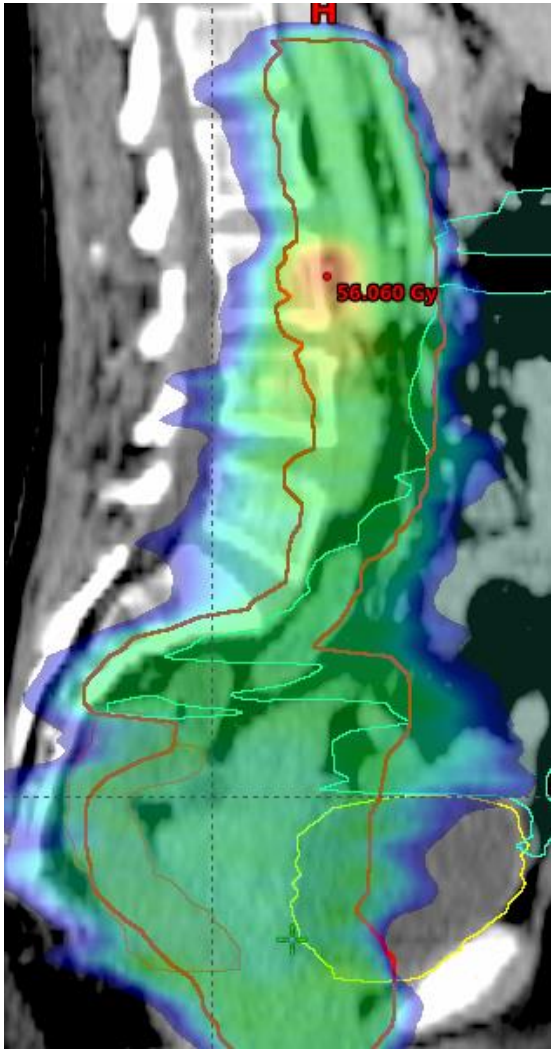
45 Gy



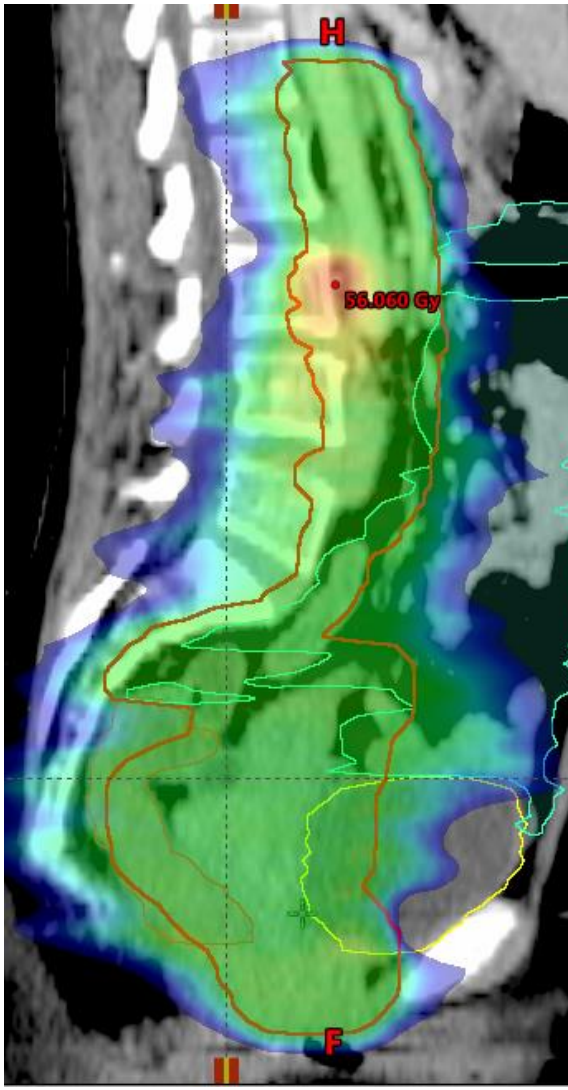
40 Gy



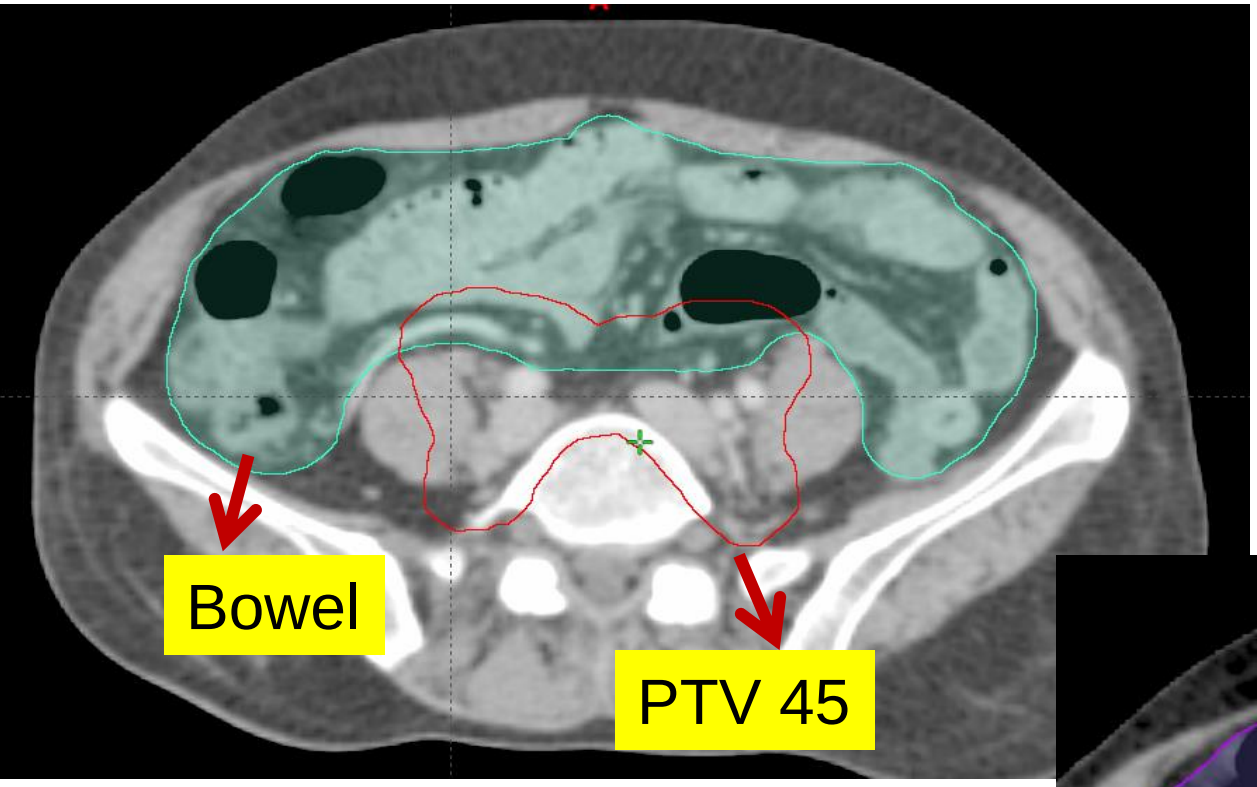
35 Gy



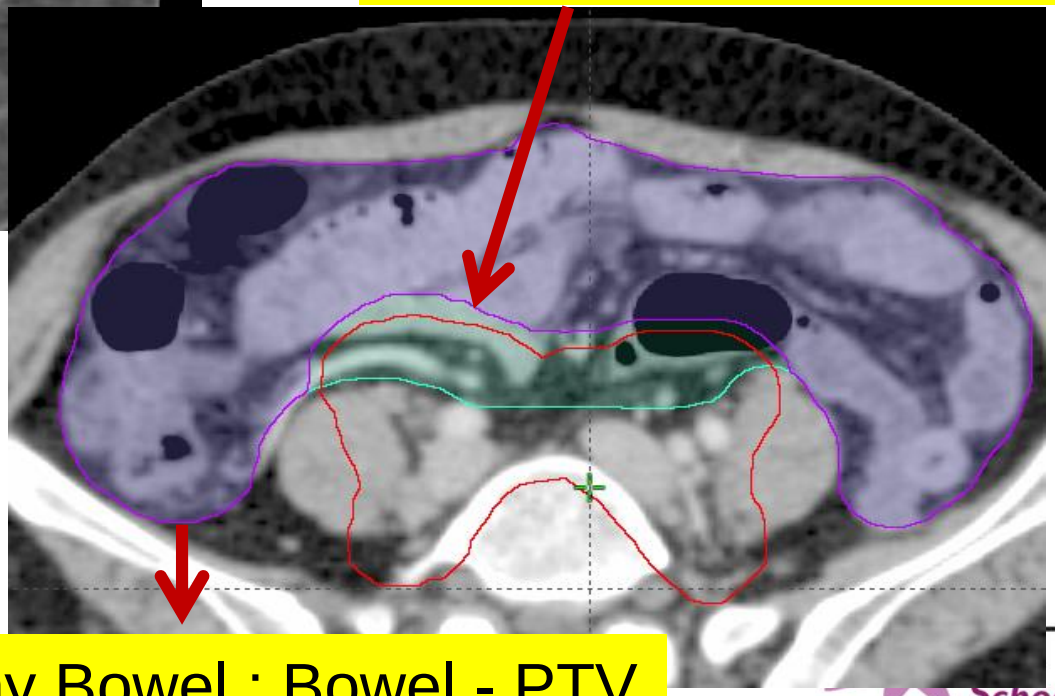
30 Gy



Optimization volumes - Bowel

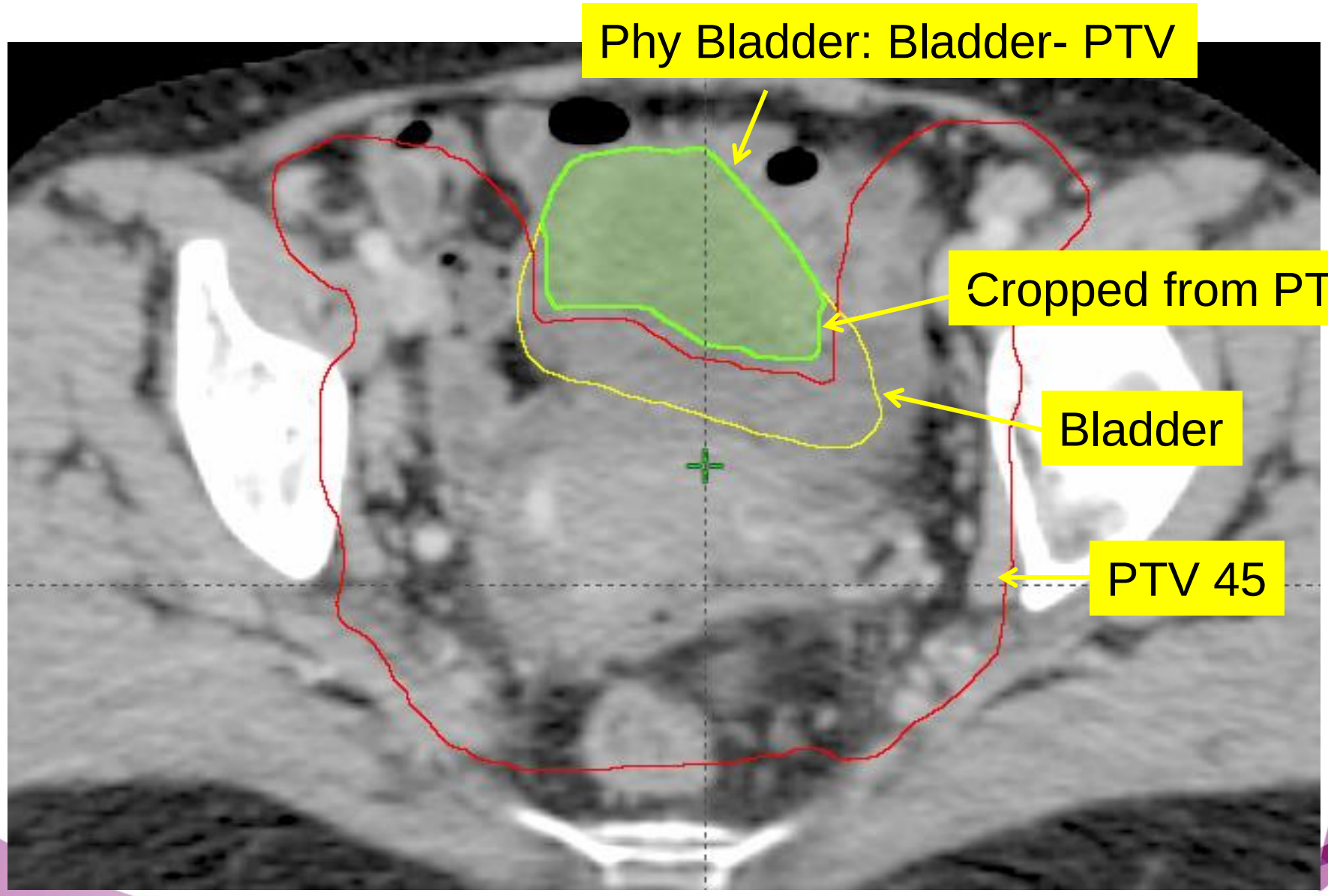


Cropped from PTV by 3 mm



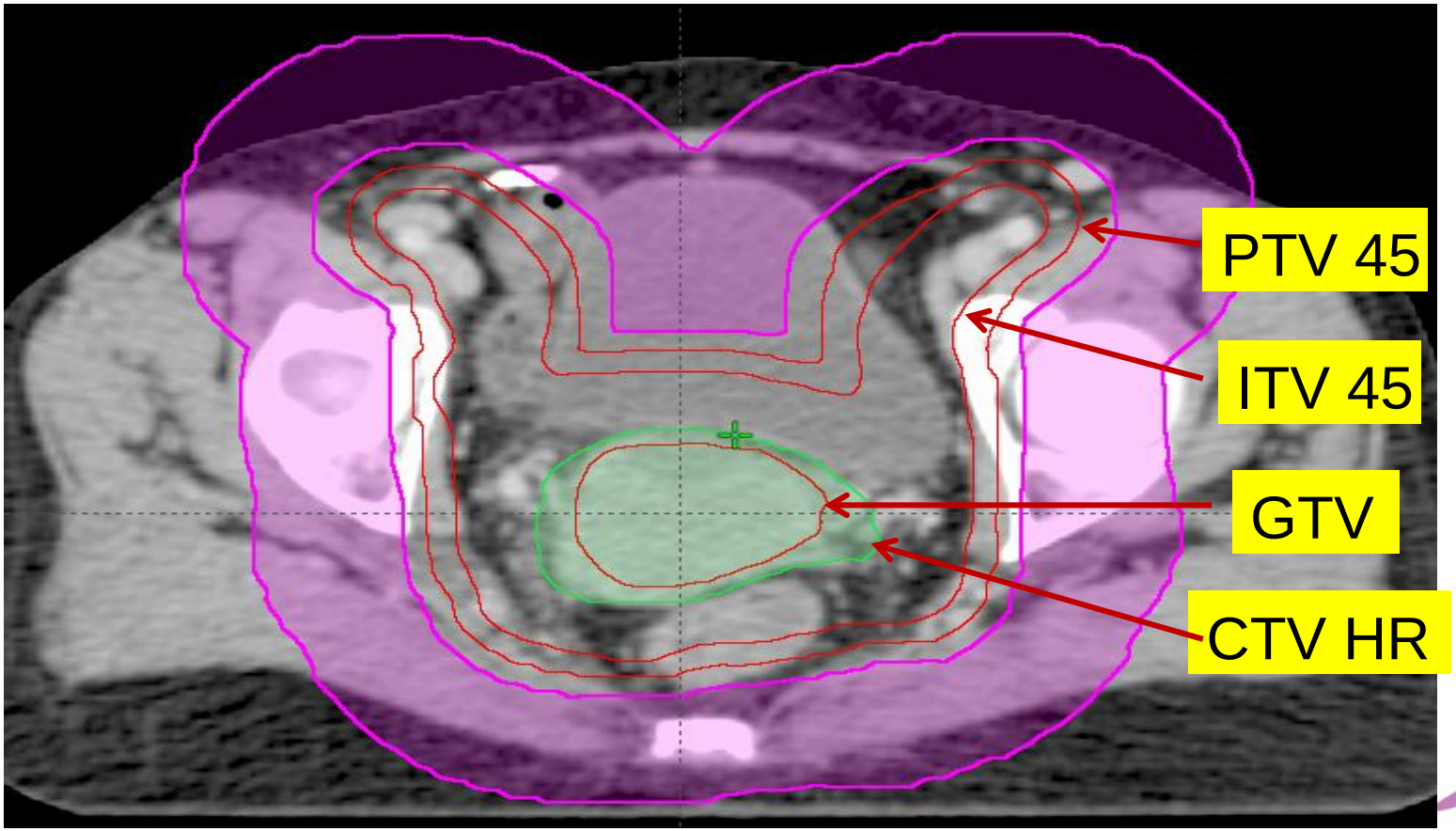
Phy Bowel : Bowel - PTV

Optimization volume - Bladder



Optimization Volume – Shell

- To control the spillage of the high dose
- To control the lower dose, and improve conformity
- V43 Gy / Volume of PTV = 1.1
- V36 Gy / Volume of PTV = 1.55



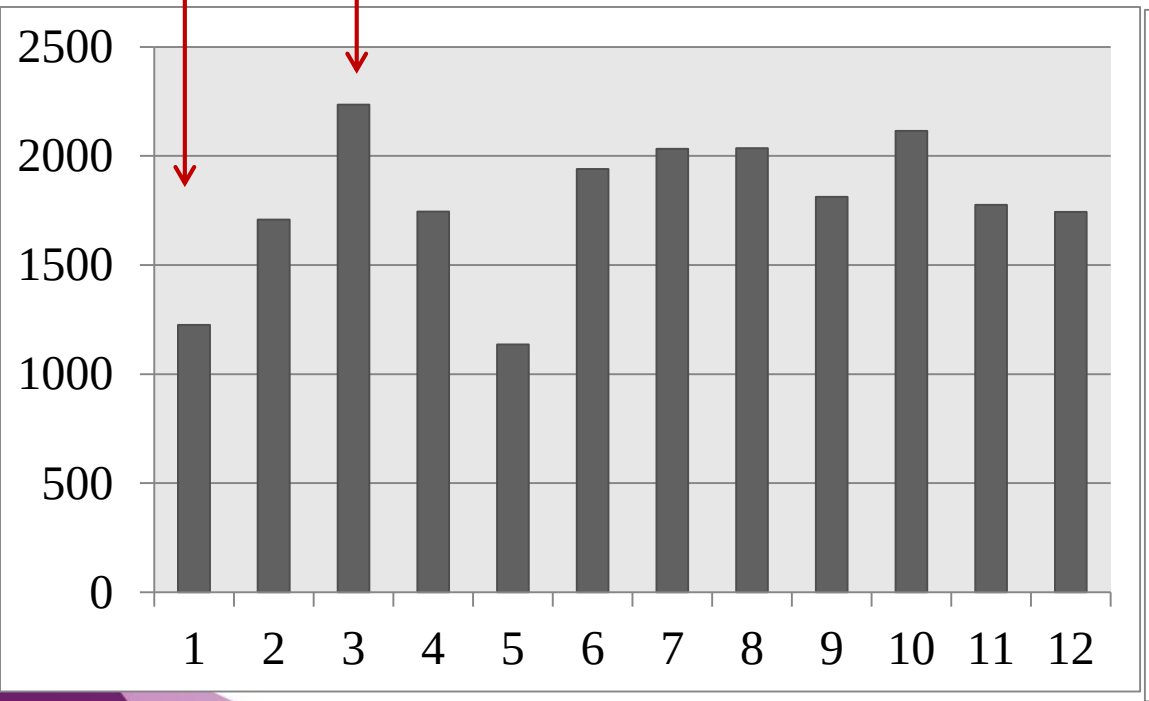
Irradiation of normal tissue – prague Home work

- Difference in irradiated body volume of 1000cm3
- Question of PTV margin
  - 5mm margin expands irradiated volume by 500cm3
  - 10mm margin expands irradiated volume by 1000cm3

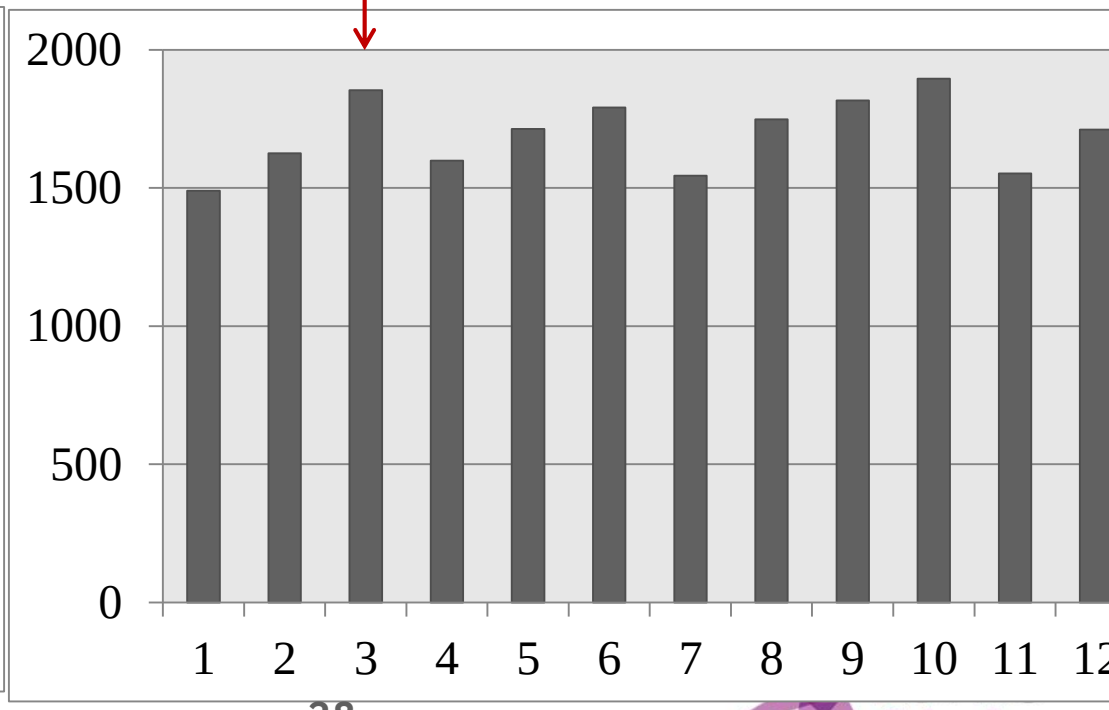
PTV margin 5mm

PTV margin 10mm

Body V43

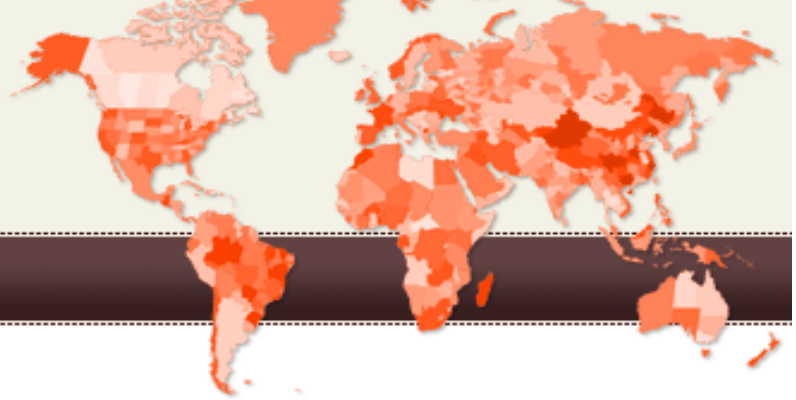


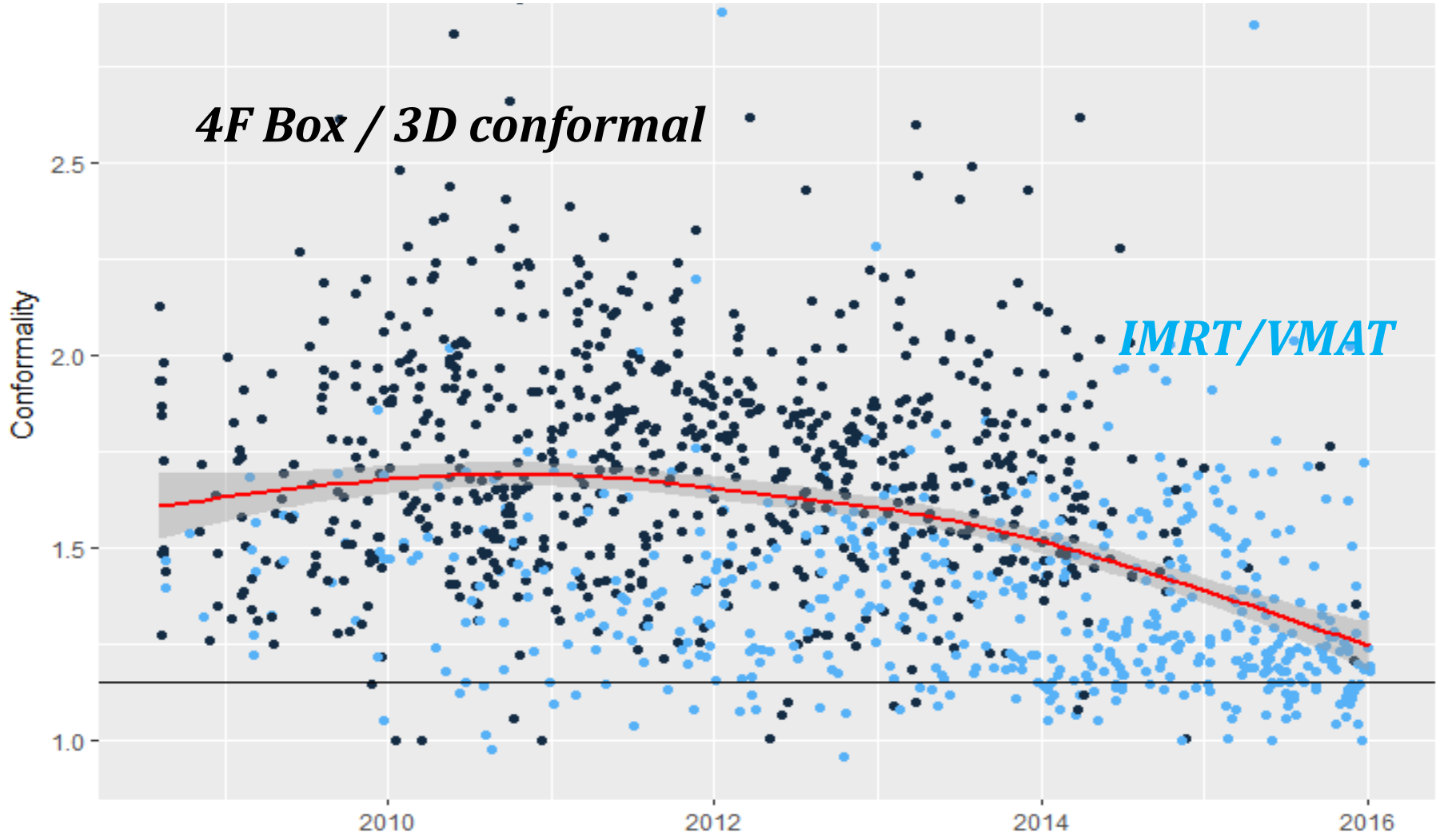
Bowel V15



EMBRACE

An intErnational study
on MRI-guided BRachytherapy
in locally Advanced CErvical cancer





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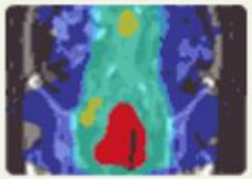
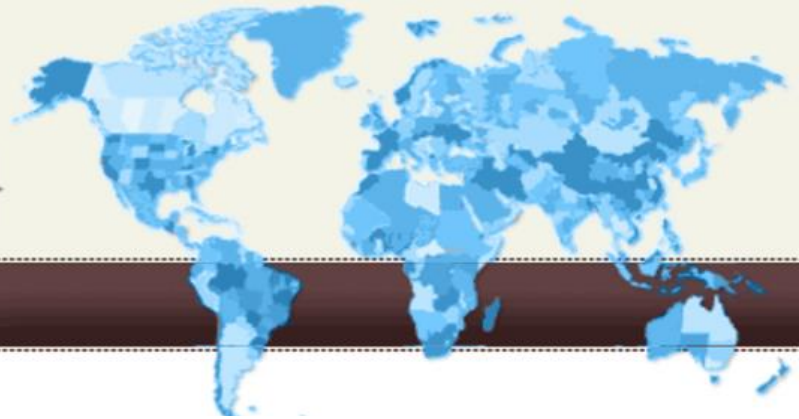
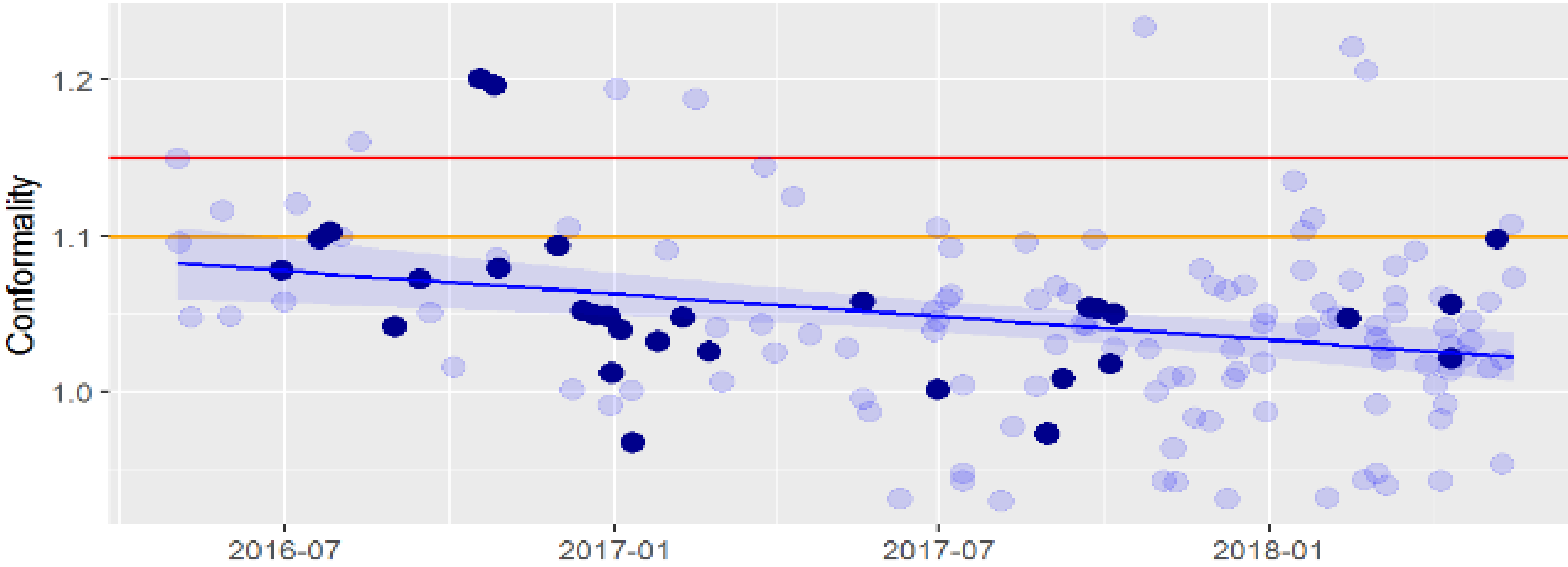


EMBRACE-II

{ Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer }



Development of conformality over time



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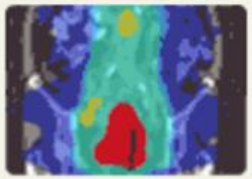
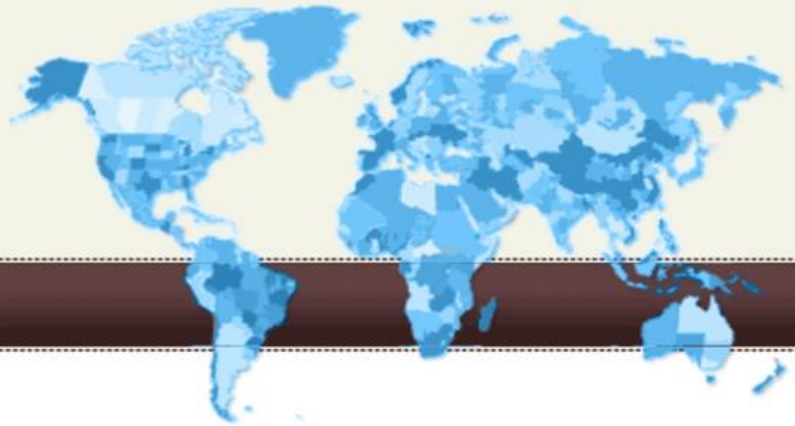
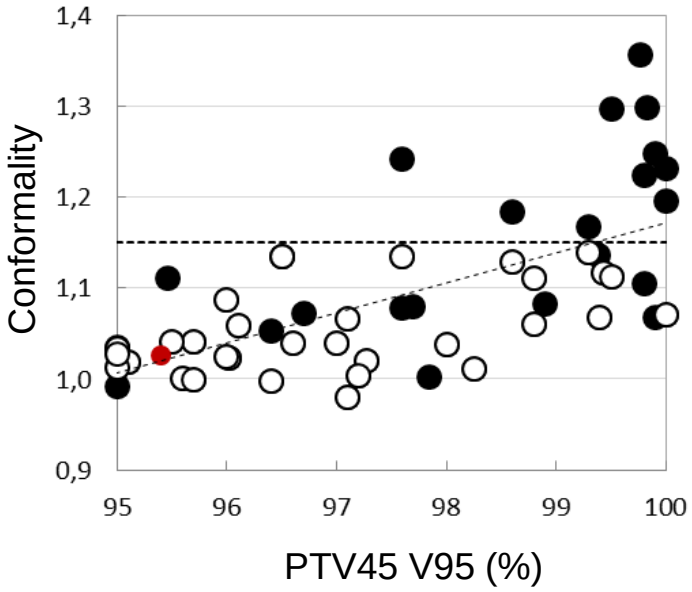
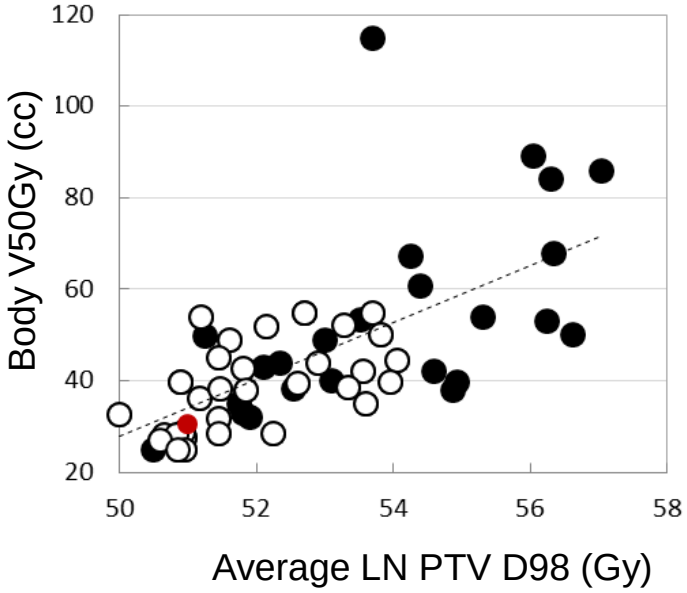
Dummy run EBRT

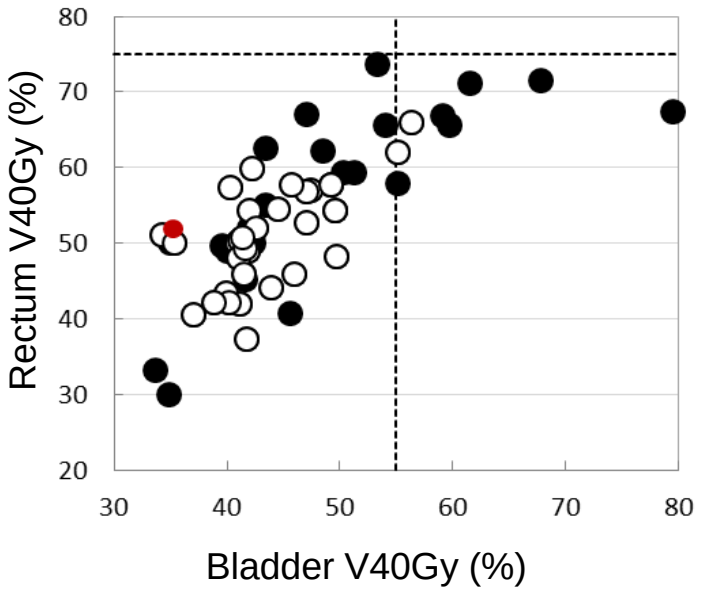


Dummy run EBRT









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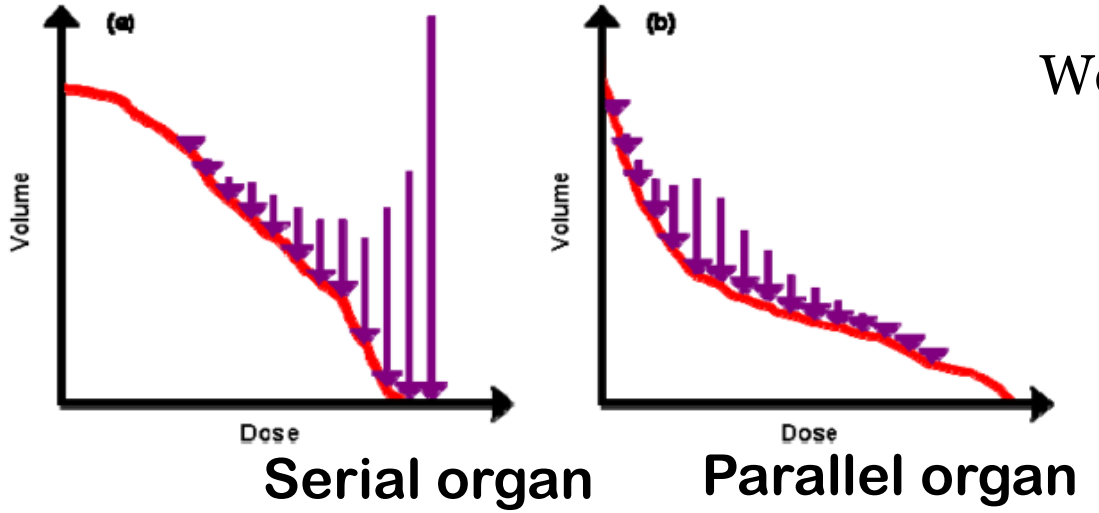
Advances in EBRT treatment planning

- gEUD / Biological Optimization
- Knowledge based plan
- Multi Criteria Optimization
- Plan of the day?
- Online Adaptive
- ML / AI

How a gEUD objective works



Serial organ Parallel organ

Weights of virtual dose-volume objectives

$$gEUD = \left(\sum_i v_i D_i^a \right)^{1/a}$$

- The parameter a is organ specific. It is related to the parameter n, describing the volume effect in the Lyman – Kutcher – Burman NTCP model as n = 1/a.
- a = +∞ (high a values): gEUD tends to the max dose- serial organs
- a = 1 gEUD equals the mean dose - for parallel organs
- a = - ∞ (negative a values): gEUD tends to the min dose- target min dose

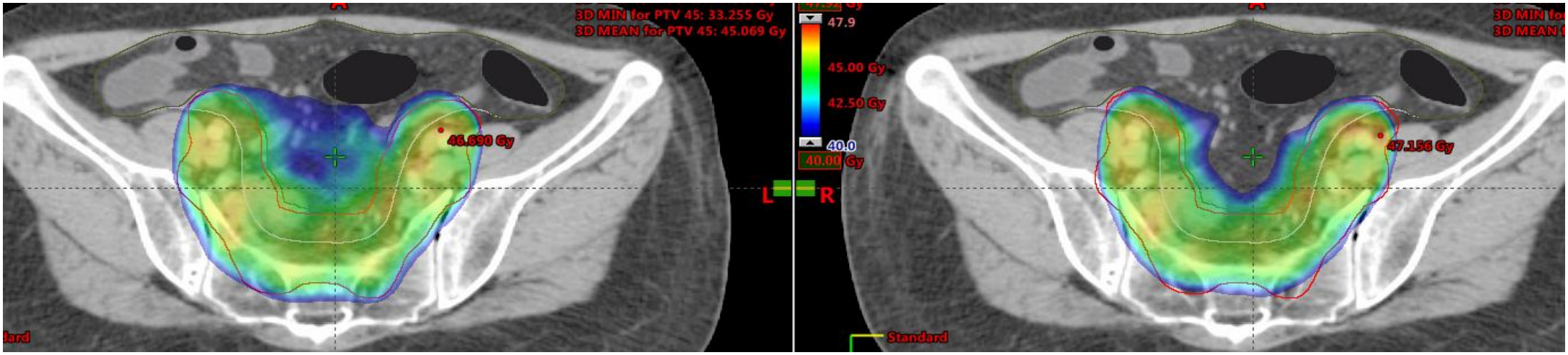
Slide courtesy: Luca Cozzi, Varian Medical Systems

Comparison of DVH parameters Physical objectives vs gEUD plan

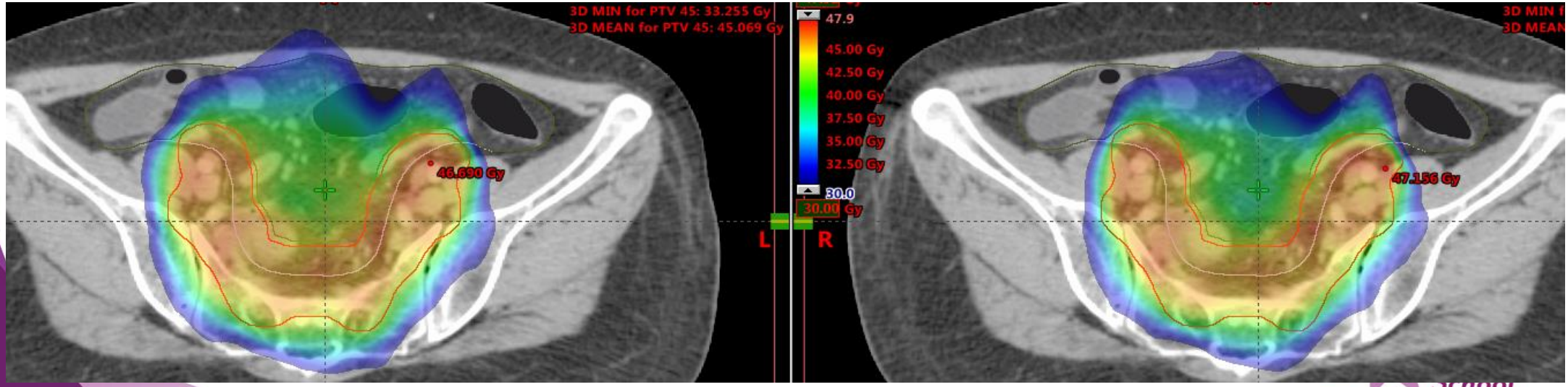
DVH Parameter	DVH Parameter	Physical Objectives plan	gEUD plan	Diff (cc)
Bowel (cm3)	V15Gy	1412	1388	24
Bowel (cm3)	V30Gy	1043	983	60
Bowel (cm3)	V40Gy	598	494	104
Bladder (%)	V30Gy	82	76	6
Bladder (%)	V40Gy	60	51	9
Body (cm3)*	V43Gy	1585	1440	145

Bowel - Physical Objectives Vs gEUD

V40Gy

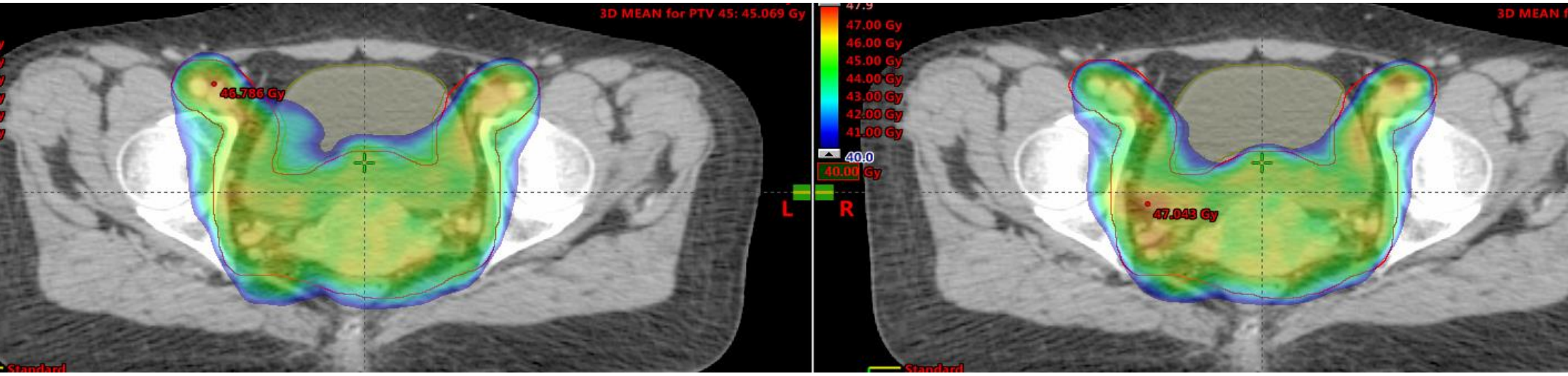


V30Gy

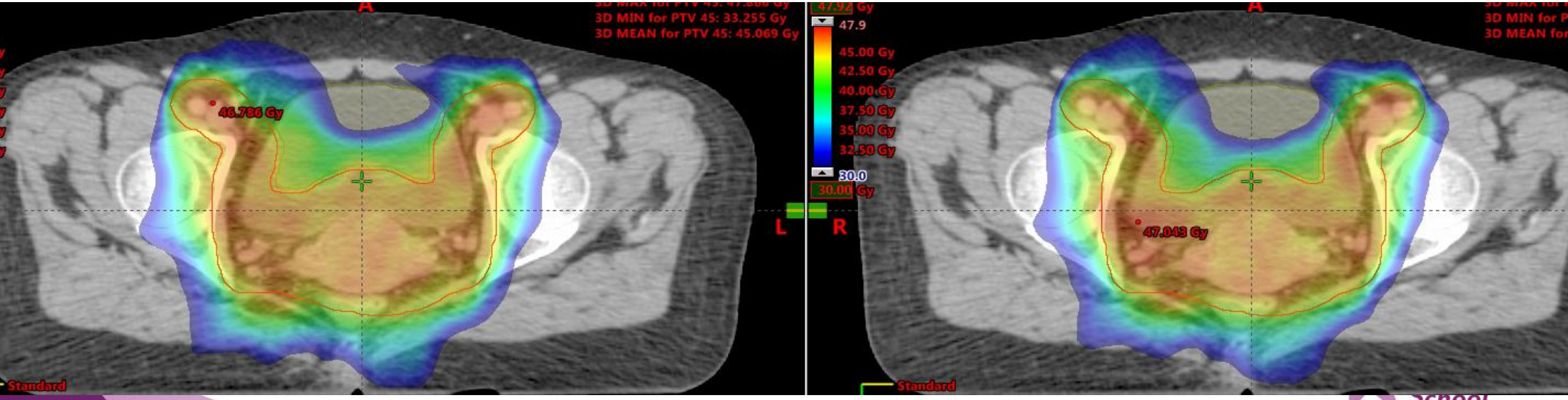


Bladder - Physical Objectives Vs gEUD

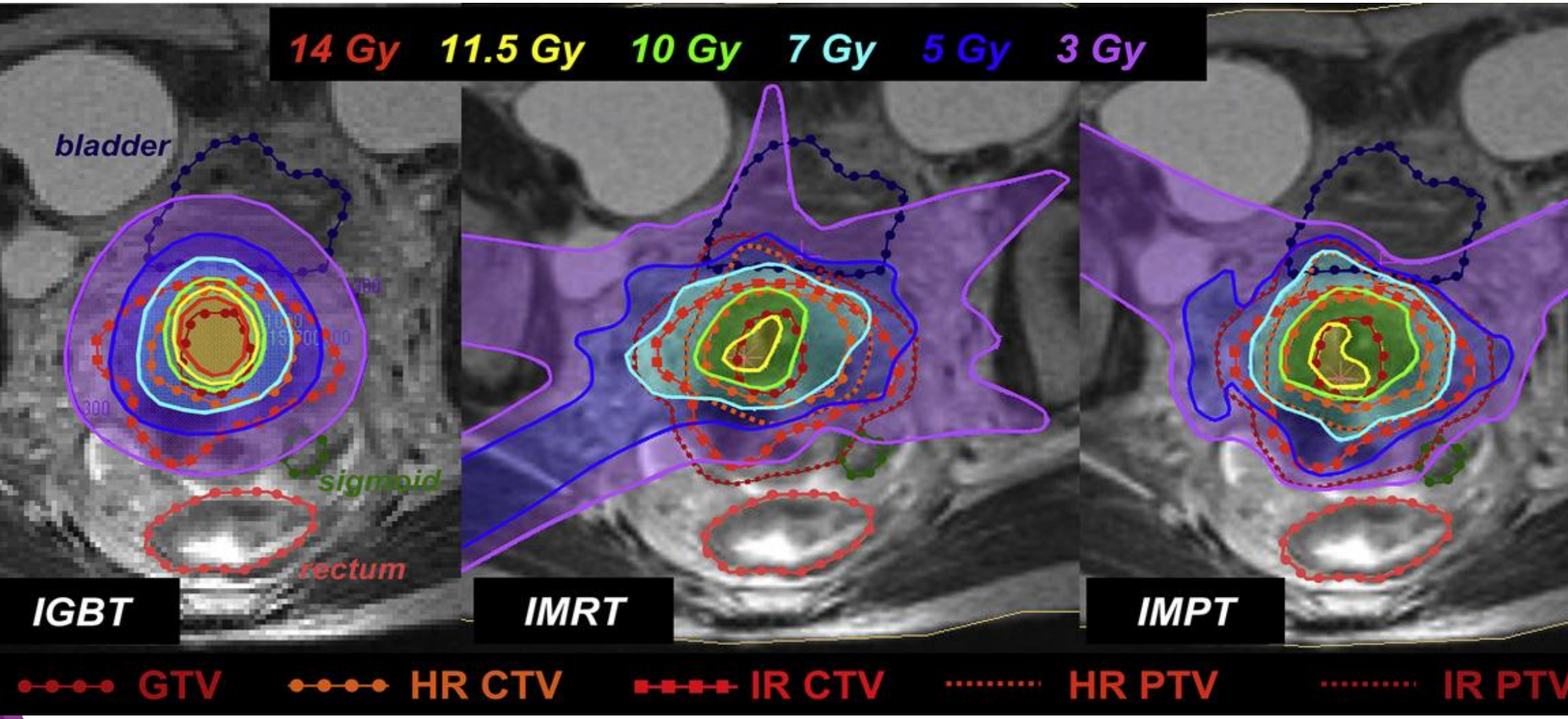
V40Gy



V30Gy



IMRT vs IGBT vs IMPT



George et al, 2008

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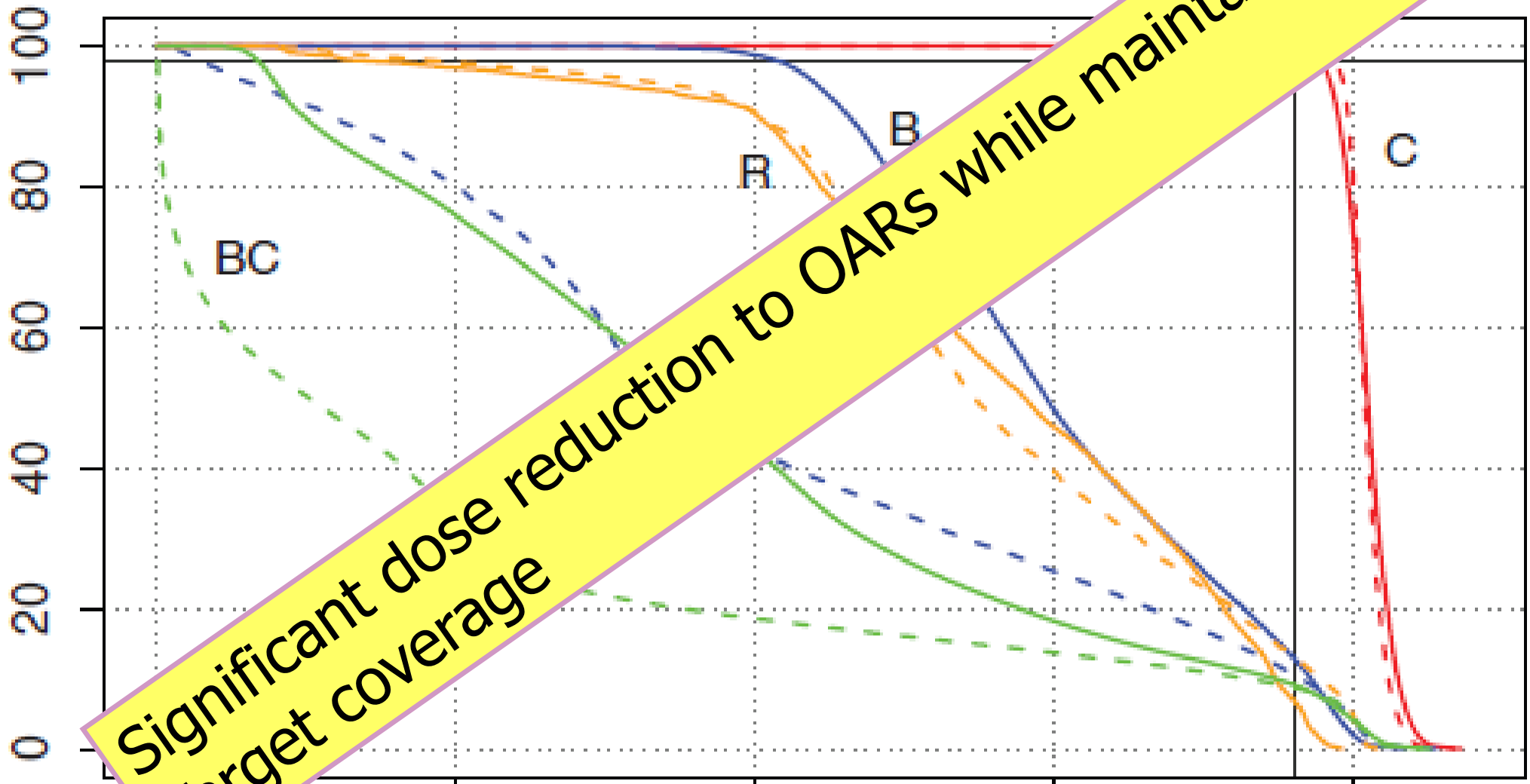
VMAT vs IMPT



Significant dose reduction to OARs while maintaining Target coverage

van de Schoot et al , 2016

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IMRT VS IGBT

- For IMRT CTV-PTV margins is needed, i.e. a larger volume, compared to brachytherapy, has to be treated .
- D90 for IMRT was lower compared to BT for most of the patients.
- The volumes receiving intermediate doses (>60Gy) are much larger for IMRT.
- The importance of very high central doses are most likely of major importance for the excellent local control obtained with brachytherapy

Advanced BT is superior to IMRT

Conclusion

- Tools of how to arrive at an optimal plan in a short time.
- EMBRACE protocol constraints – Achievable for Targets, OAR(some times not achievable especially for bowel).
- IMRT / VMAT produces significant bowel and bladder sparing and hence improved conformity.
- Future tools – Knowledge based planning, MCO!
- Use of gEUD / constraint optimization works well for OARs.
- Advanced IGBT is superior to IMPT

Dose calculation algorithm

AAA (C/S) vs Acuros (MC)

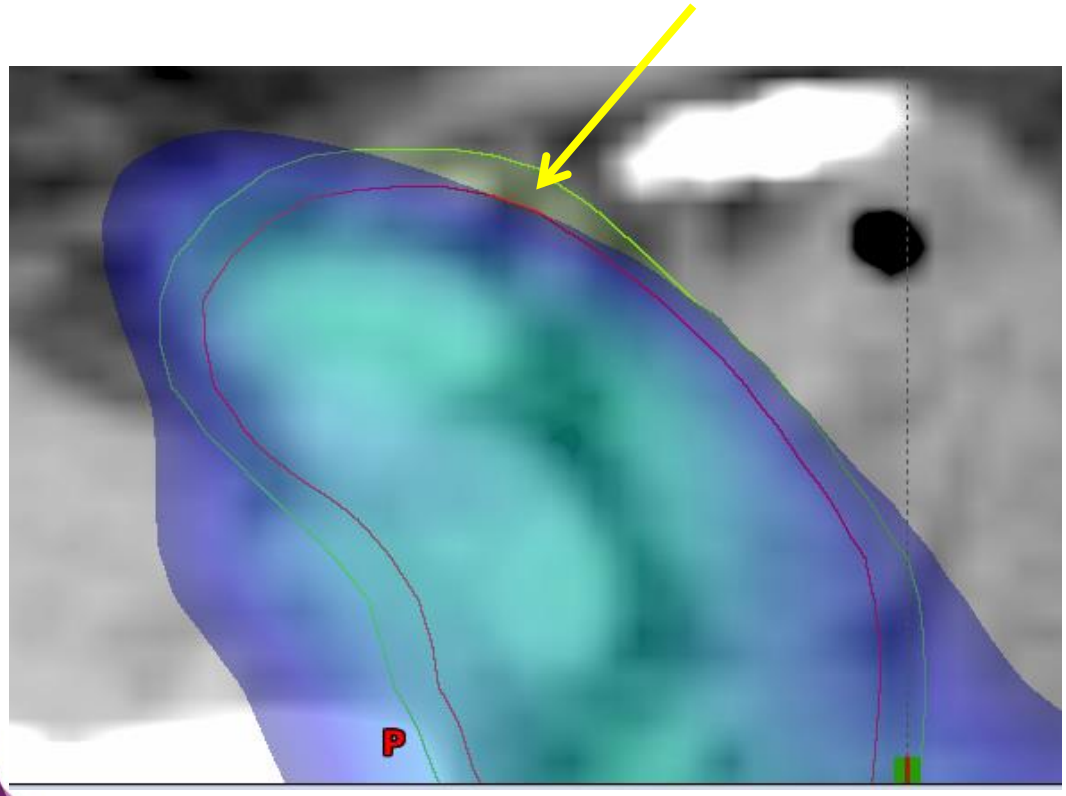
- Dose in the buildup region (Ca Breast)
- Dose in highly in-homogeneous region (Ca Lung)
- Dose in Interface Region(Bone-Tissue, Bone-Lung) Eg: Ca Breast

- In Pelvic IMRT, no marked difference between these two algorithms for dose calculation

ITV Dmin vs ITV D99

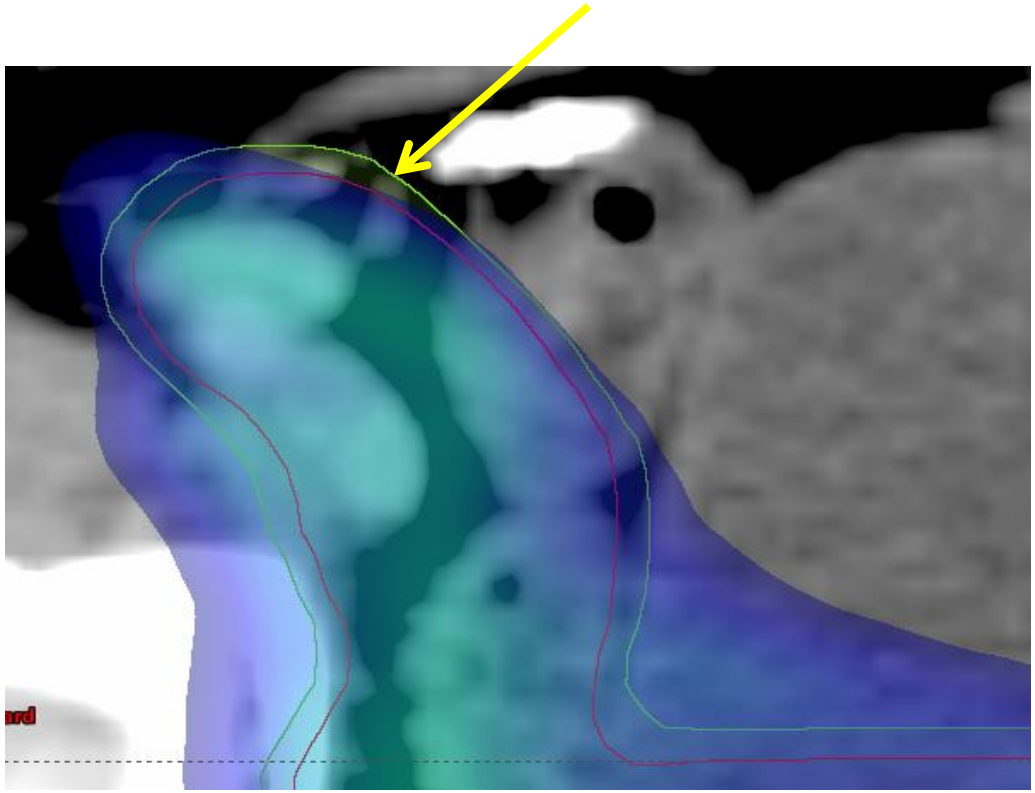
Dose Grid 2.5mm

Dmin 42.1 Gy



Dose Grid 1.0mm

Dmin 42.8 Gy



ESTRO School

- **Varian Eclipse , Siemens Prowess – DAO, Philips Pinnacle (DMPO)**
  - Delivery constraints are included directly into the optimization.
- **Oncentra VMAT developed by Ray Search Laboratories**.

  RaySearch also developed the SA module for Pinnacle (Underlying VMAT planning engine is very similar)
- **Elekta VMAT**
  - Anatomy based Inverse optimization – ERGO ++
  - Monaco (Biology based IMRT Optimization, Sweeping leaf sequencer)

Which of the following statement is **incorrect** regarding dose to OAR in EMBRACE II protocol

1. ALARA principle to be used
2. Bowel constraints : V40 < 250 cc, V 30 < 500 cc
3. Constrained Optimization / gEUD helps in achieving optimal OAR doses
4. None of the above

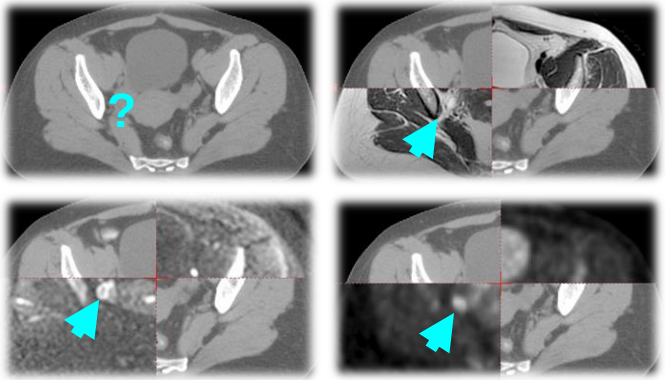
Inverse Planning - Beam Modeling

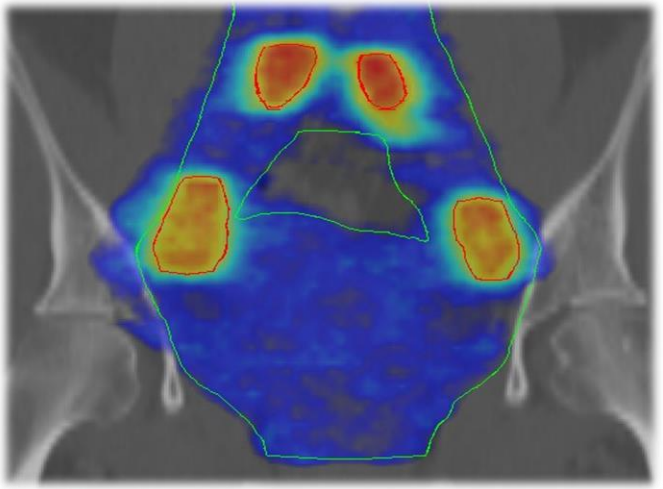
- Dosimetric accuracy of the IMRT plan delivery depends on the accurate representation of

  - ✓ Beam Penumbra – MLC / collimator jaws.
  - ✓ transmission and scattering properties of MLC leaves.
  - ✓ Output factor for small field size.
  - ✓ Accuracy of dose calculation algorithm.
  - ✓ Approximations of leaf sequence generation algorithm.
  - ✓ Leaf positioning accuracy.

Nodal Boost

Volumes, Dose, Techniques





Primoz Petric

Aarhus University Hospital, Denmark

Ina Jürgenliemk-Schulz

University Medical Centre Utrecht, The Netherlands

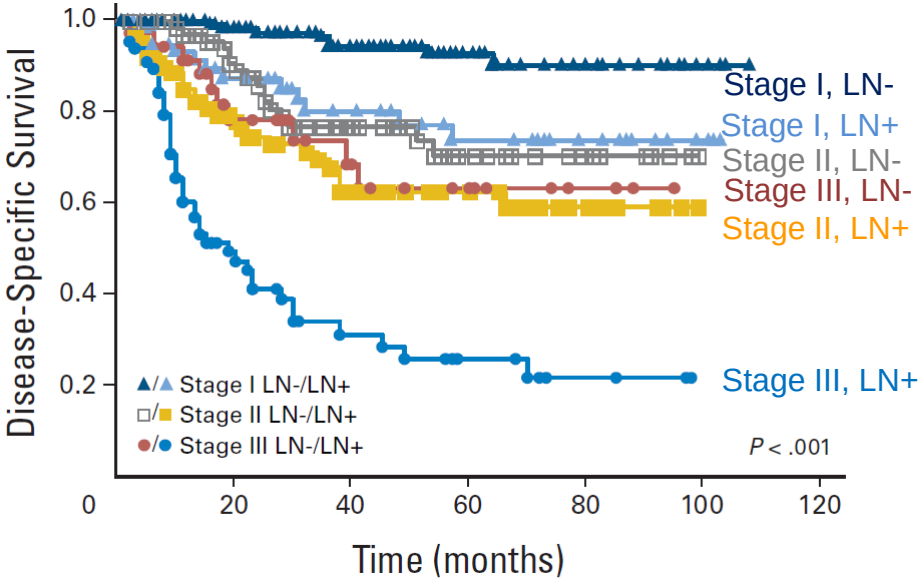
Prognostic Impact of N Status: PET CT era

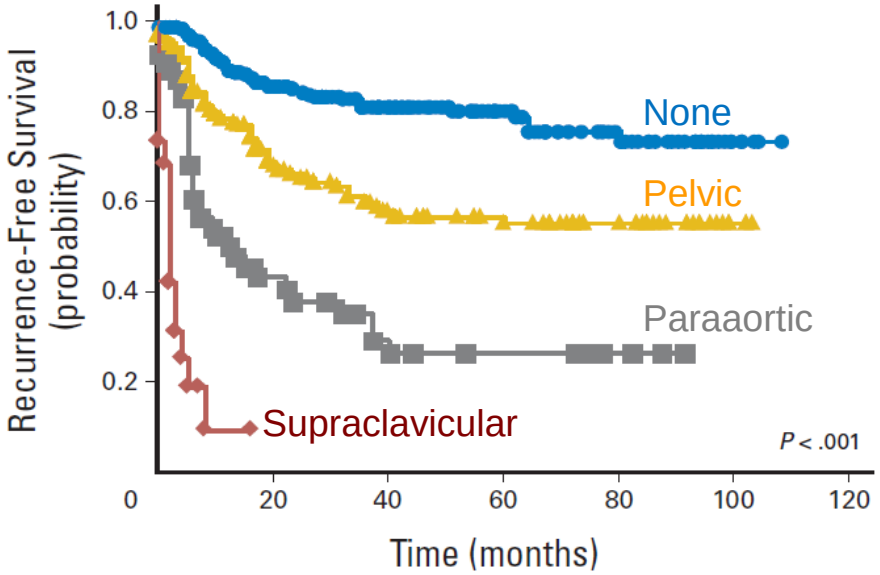
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Lymph Node Staging by Positron Emission Tomography in Cervical Cancer: Relationship to Prognosis

Elizabeth A. Kidd, Barry A. Siegel, Farrokh Dehdashti, Janet S. Rader, David G. Mutch, Matthew A. Powell, and Perry W. Grigsby

560 patients, FDG PET-CT staging





Kidd EA, et al. JCO 2010;28(12):2108-13

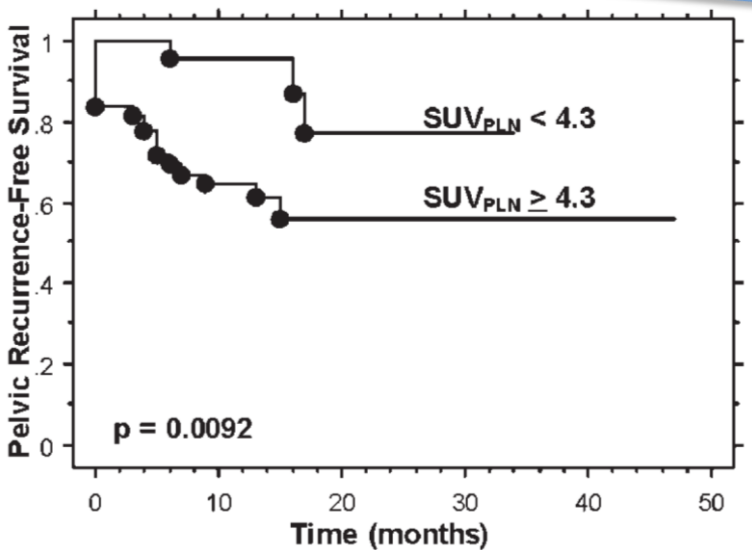
Prognostic Impact of N Status: PET CT era

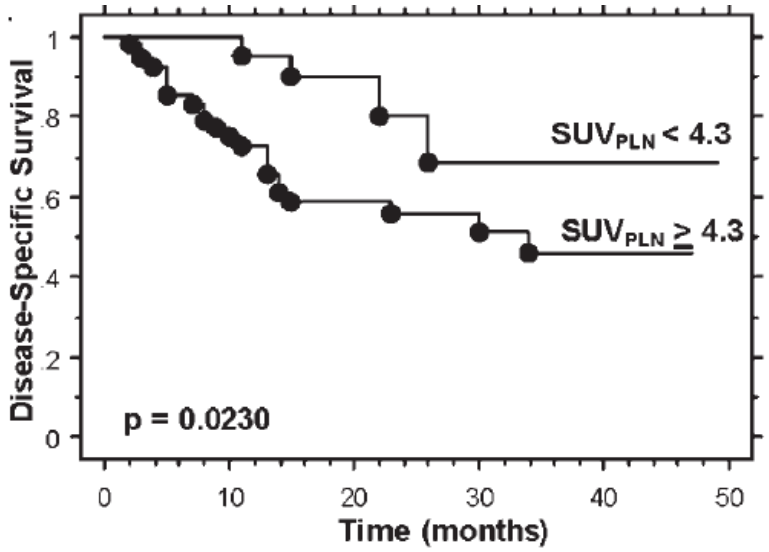
Pelvic Lymph Node F-18 Fluorodeoxyglucose Uptake as a Prognostic Biomarker in Newly Diagnosed Patients With Locally Advanced Cervical Cancer

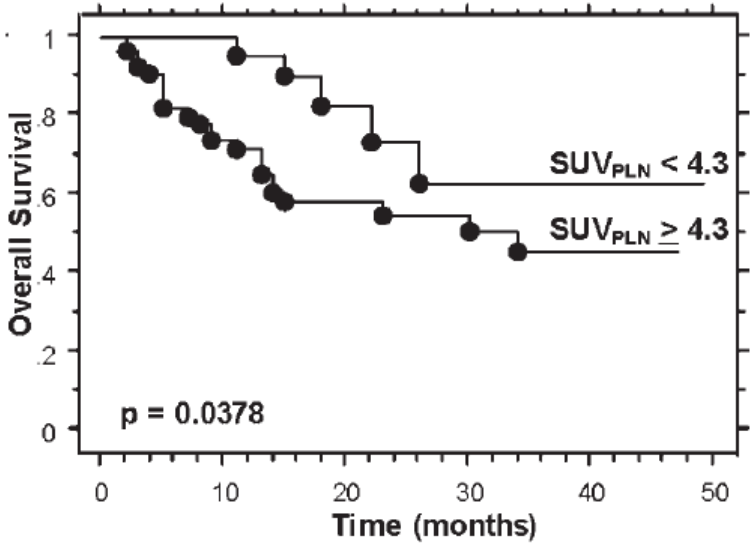
Elizabeth A. Kidd, MD[1]; Barry A. Siegel, MD[2,3]; Farrokh Dehdashti, MD[2,3]; and Perry W. Grigsby, MD[1,2,3,4]

83 patients

FDG PET-CT staging







Standard Uptake Value of PLN is a prognostic biomarker

Kidd EA, et al. JCO 2010;28(12):2108-13

Patterns of Nodal Recurrence

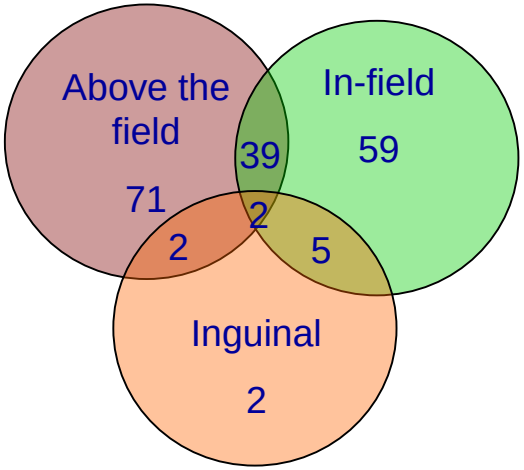
MD Anderson series

Pelvis: 45 Gy in 25 fx

Extended field if ≥ common iliac N+

Dose to positive N: Pelvis ≥ 60 Gy; PAo 45 – 50 Gy

180 patients with recurrence



Geographical miss → Tailor elective target

66%: component of marginal failure

58%: component of in-filed failure

Detection & D - deficiency → Improve detection of N+

Detection & D - deficiency → Apply adequate D to N+

Beadle BM, et al. IJROBP 2010

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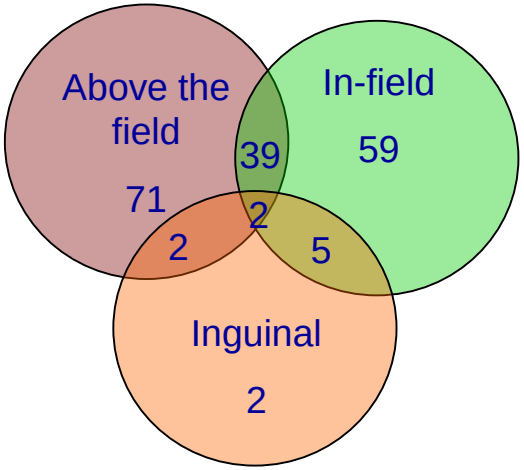

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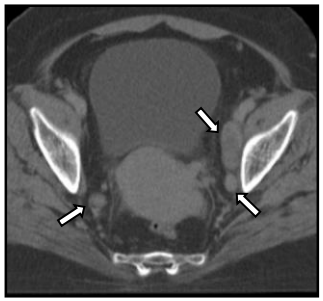
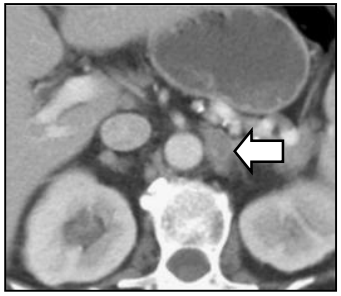
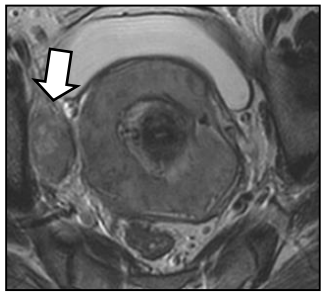
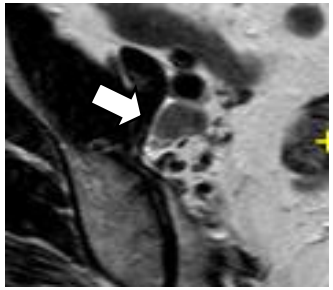
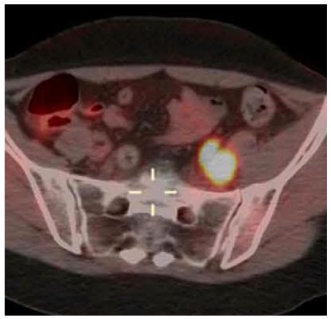
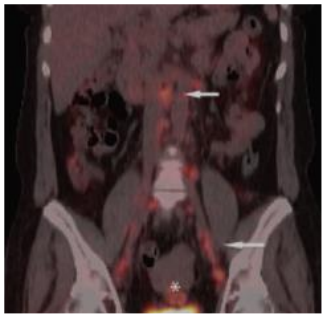
Detection & D - deficiency → **Improve detection of N+**; **Apply adequate D to N+**

Beadle BM, et al. IJROBP 2010

Detection of GTV N

Detection and Delineation of Nodal GTV

Indirect proof, (morphological & functional characteristics)

Lee SI, et al. JNM 2015:56(3)
Sironi S, et l. Radiology 2006
Loft A, et al. Gynecol Oncol 2007
Selman TJ, et al. CMAJ 2008
Roh JW, et l. Eur J Cancer 2005

Diagnostic Performance in Detection of Lymphadenopathy from Uterine Cancer

Modality	Sensitivity	Specificity
CT, cervical (*5,9*)	31%–57%	92%–97%
CT, endometrial (*22*)	28%–64%	78%–94%
MR imaging, cervical (*5,9*)	37%–55%	93%–94%
MR imaging, endometrial (*20,22*)	59%–72%	93%–97%
PET/CT, cervical (*7,8*)	72%–75%	96%–100%
PET/CT, endometrial (*20,21*)	74%–77%	93%–100%

Lee SI, et al. JNM 2015:56(3)

^{18}FDG PET-CT: more sensitive than either CT or MRI in locally advanced tumors

MRI: best to depict GTV-N details

Lin WC, et al. Gynecol Oncol 2003
Hricak H, et al. Am J Roentgenol. 1996
Olpin J, et al. Imaging. In: Gynecol Radiat Therapy...eds. Viswanathan AN, et al.

Are size criteria (short axis <1cm) reliable?

Table 3
Comparision of the diagnostic performance of the size-based criteria and ADC-based criteria.

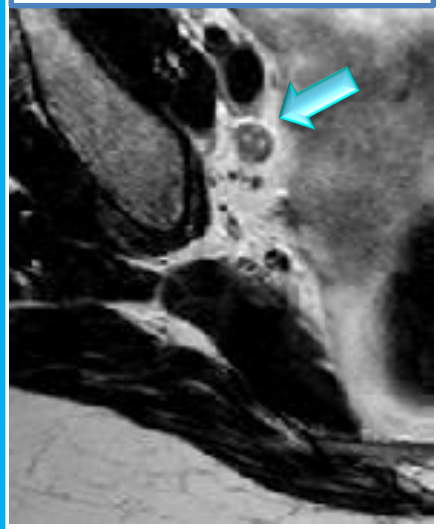
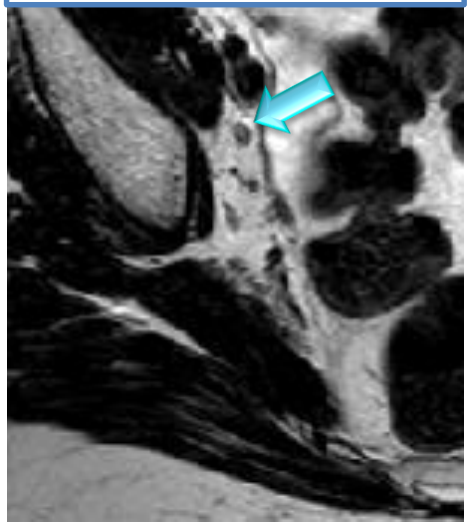
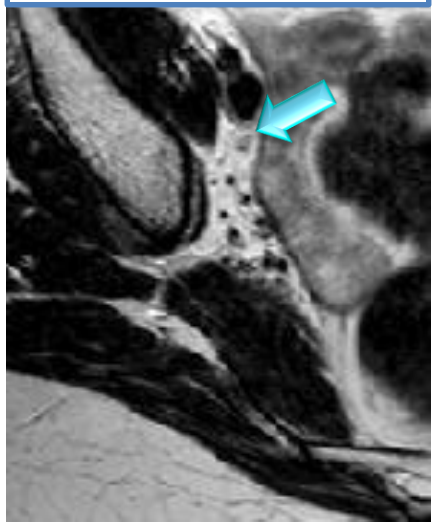
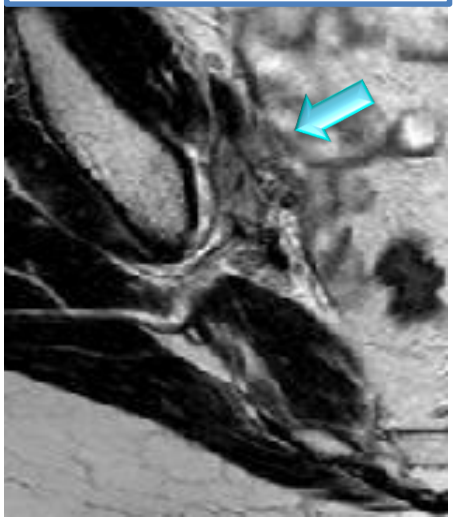
	Short-axis diameter	Long-axis diameter	Mean ADC	Minimum ADC	Mean rADC	Minimum rADC
Sensitivity(%)	76.1	93.5	91.3	95.7	84.8	93.5
Specificity(%)	85.9	66.2	91.5	96.5	91.5	90.8
PPV(%)	62.5	47.3	77.8	89.8	76.5	93.5
NPV(%)	91.0	96.9	97.0	94.9	93.2	97.7
Accuracy(%)	77.7	72.9	91.5	96.3	89.9	91.5

Normalized = relative ADC =rADC = ADC lesion /ADC reference (r gluteus maximus muscle (Liu) ; renal cortex (Park)

Liu Y. et al.,Gynecologic Oncology 122 (2011) 19–24

Are size criteria (short axis <1cm) reliable?

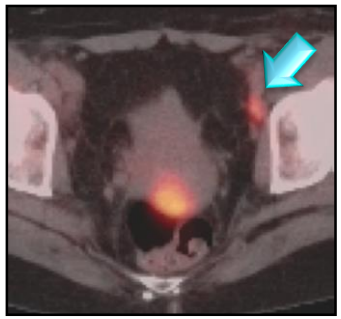
Example 2

At Diagnosis	4th Week EBRT	6 Weeks post EBRT	12 Months
			
• Short axis: 8 mm • Irregular border • High signal (T2) • Inhomogeneous • PET negative	• No Boost (45 Gy) • Near compl. resp.	• Minimal residuum	• Nodal failure

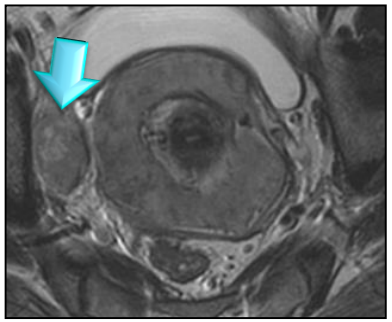
Detection and Delineation of Nodal GTV

Consider N involvement when:

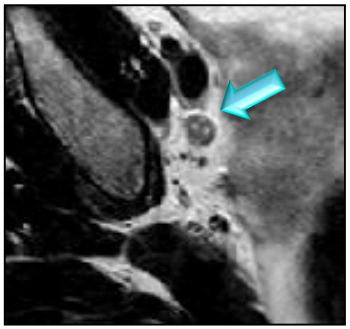
PET positive



Short axis ≥ 10 mm



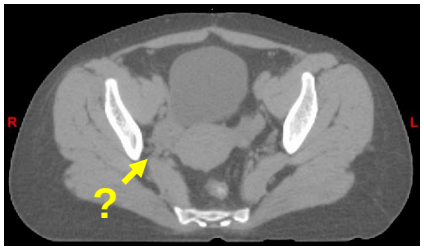
Short axis 5-10 mm And:



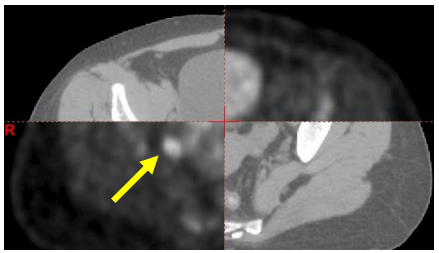
- ↑ Intensity (T2)
- ↓ Diffusion (DWI)
- Irregular border
- Lost architecture
- Round shape
- Inhomogeneous

Co-registration of modalities

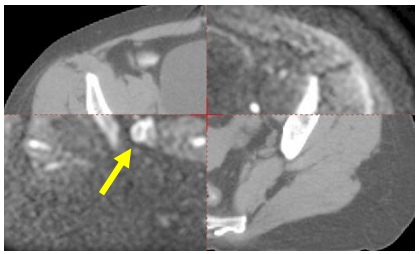
CT



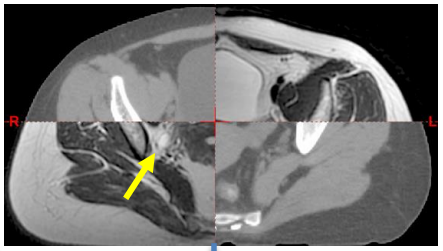
CT + PET



CT + DW MRI

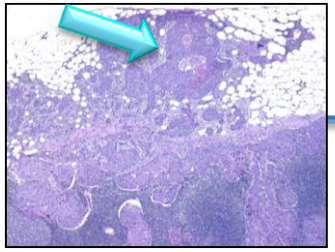


CT + T2w MRI



Detection

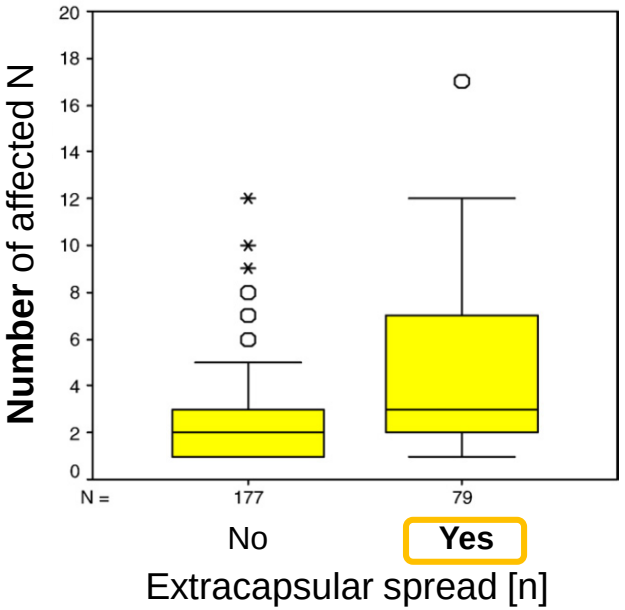
Delineation

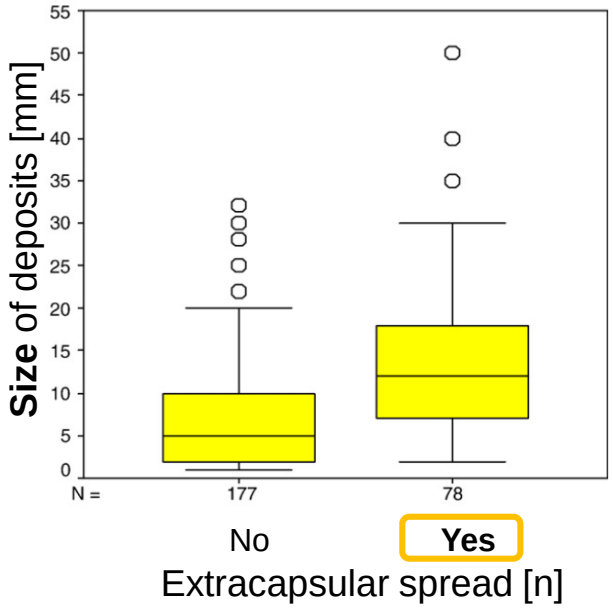


From GTV to CTV

Risk of Extracapsular Extension

H&N Cancer	98 patients	→	**29-48%**
Ghadjar P, et al. IJROBP 2009			
Cervix (Stage I & II)	95 patients	→	**52%**
Metindir J, et al. Eur J Gynecol Oncol 2008			
Cervix (pT1 & pT2)	256 patients	→	**31%**
Horn LC, et al. Gynecol Oncol 2008			





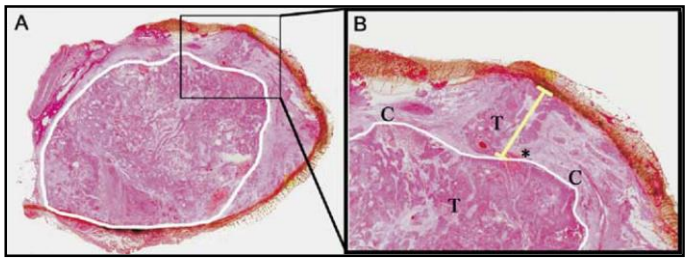
From GTV to CTV

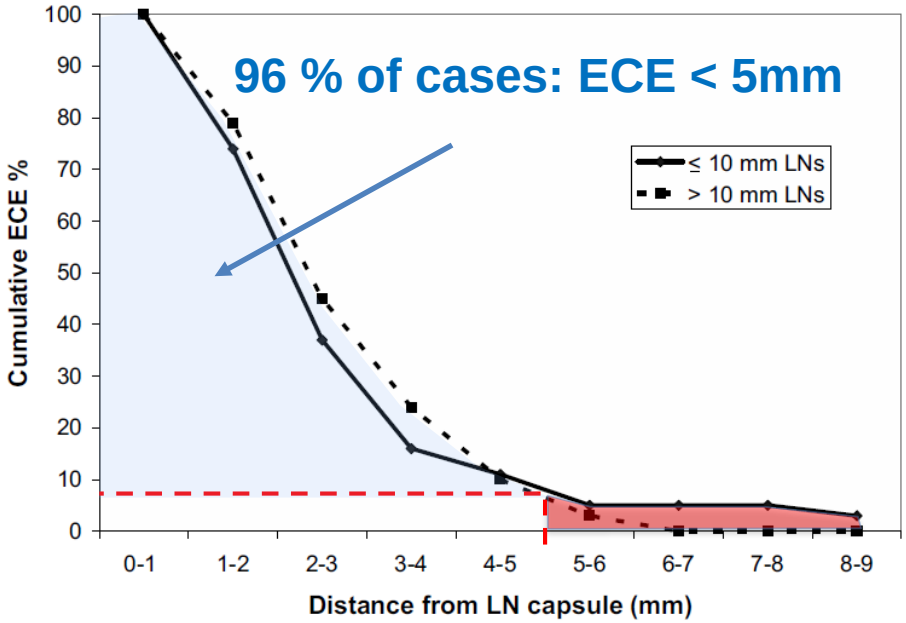
Distance of Extracapsular Extension (ECE)

MDAH

96 nodes with ECE

oropharyngeal cancer

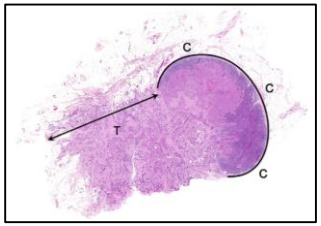




Median ECE: 1.6 mm (0.4 – 9 mm)

Apisarnthanarax S, et al (MDAH). IJROBP 2005

From GTV to CTV +5 mm?



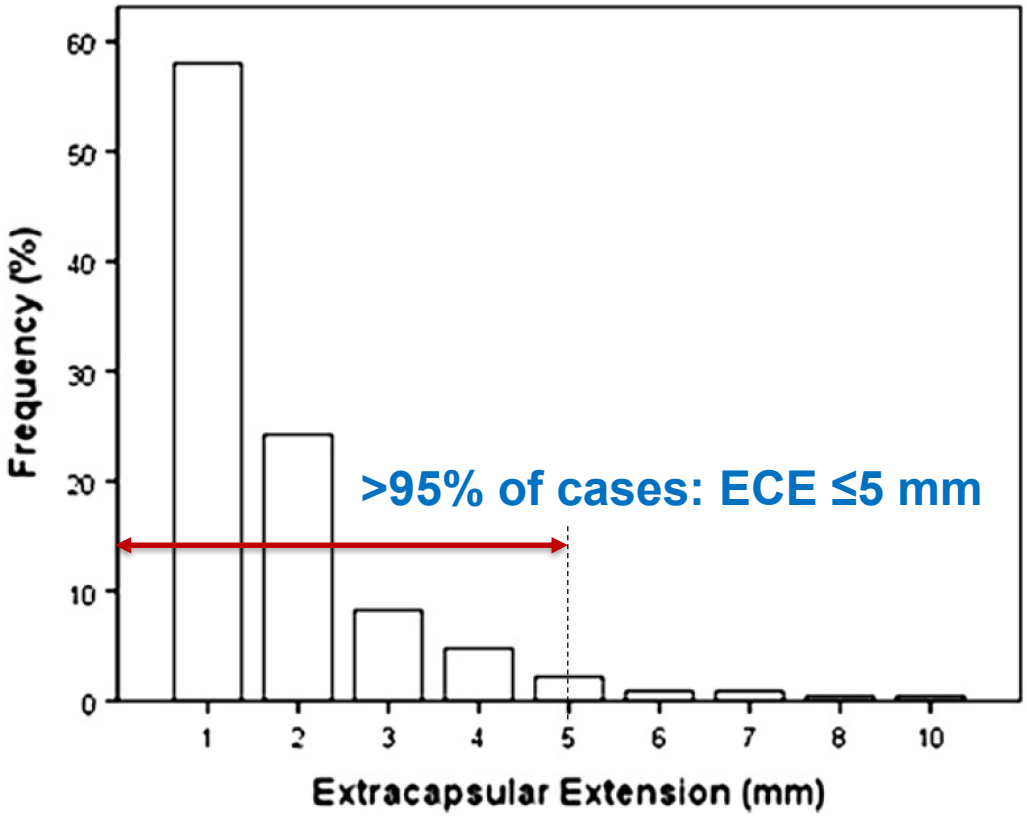
Distance of Extracapsular Extension (ECE)

Bern University Hospital

231 N with ECE

H&N Cancer

- Median ECE: 1 mm (0.4 – 9)
- Larger N – Larger ECE



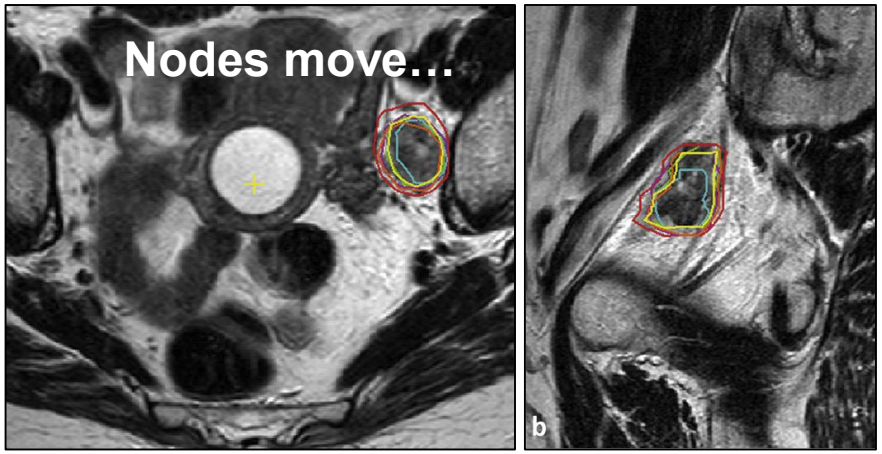
Ghadjar P, et al. IJROBP 2009

From GTV to CTV to ITV +5 mm?

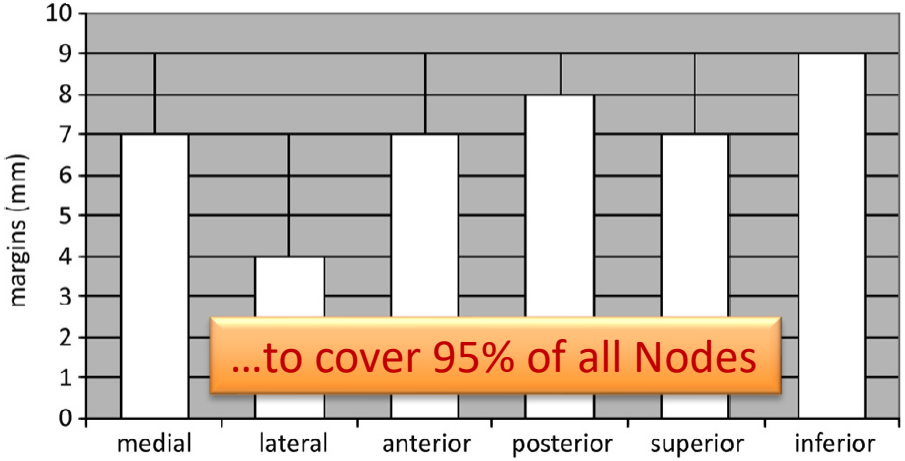
Position shifts and volume changes of pelvic and para-aortic nodes during IMRT for patients with cervical cancer ☆

Maaike G.A. Schippers [a], Gijsbert H. Bol [a], Astrid A.C. de Leeuw [a], Uulke A. van der Heide [a], Bas W. Raaymakers [a], Helena M. Verkooijen [b,c], Ina M. Jürgenliemk-Schulz [a,*]

15 Patients | 48 Nodes | Weekly MRI during RT

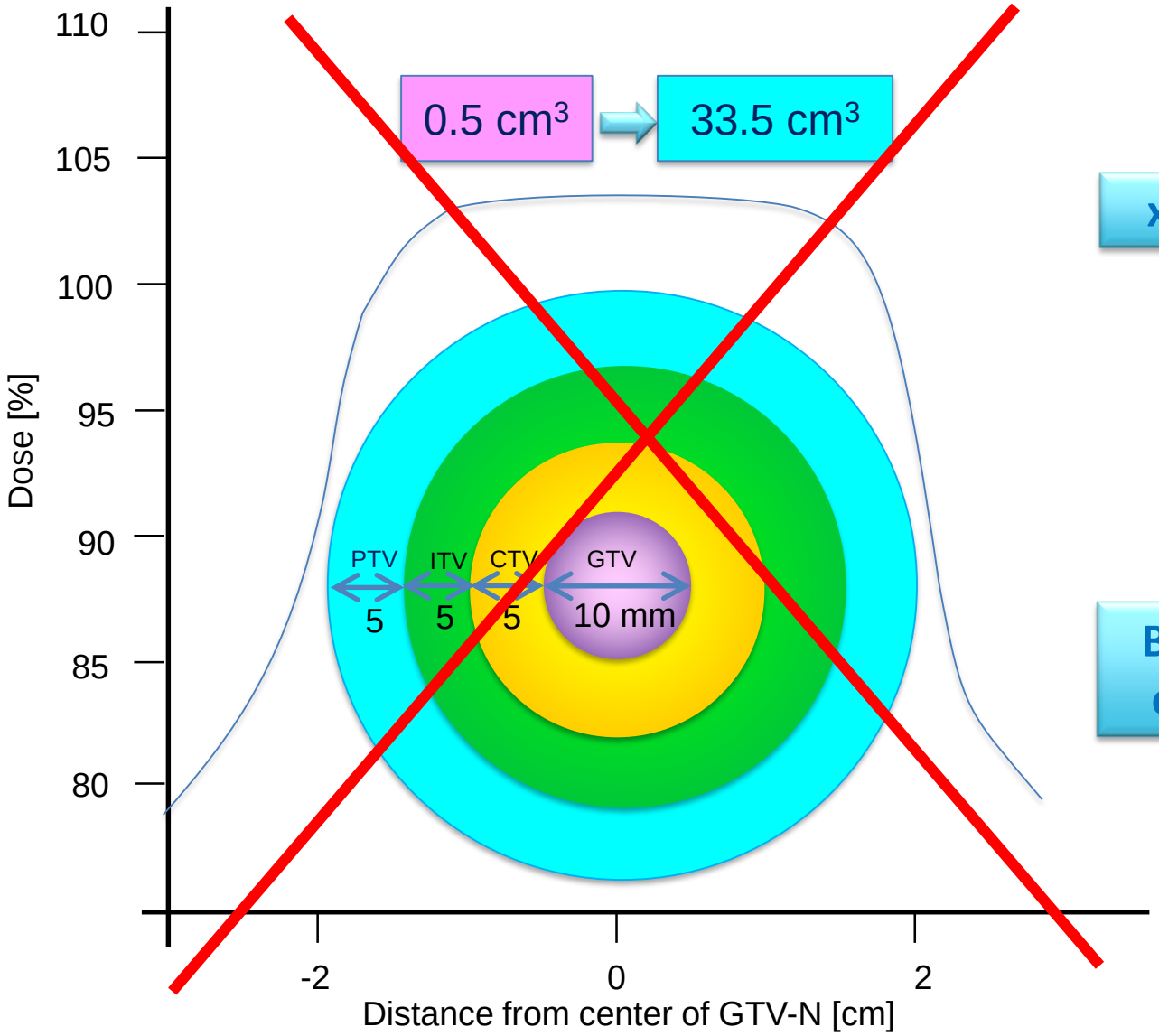


Derived ITV margins: 4-9 mm



Schippers MG, et al. Radiother Oncol 2014;111:442-5

From GTV to CTV to ITV to PTV



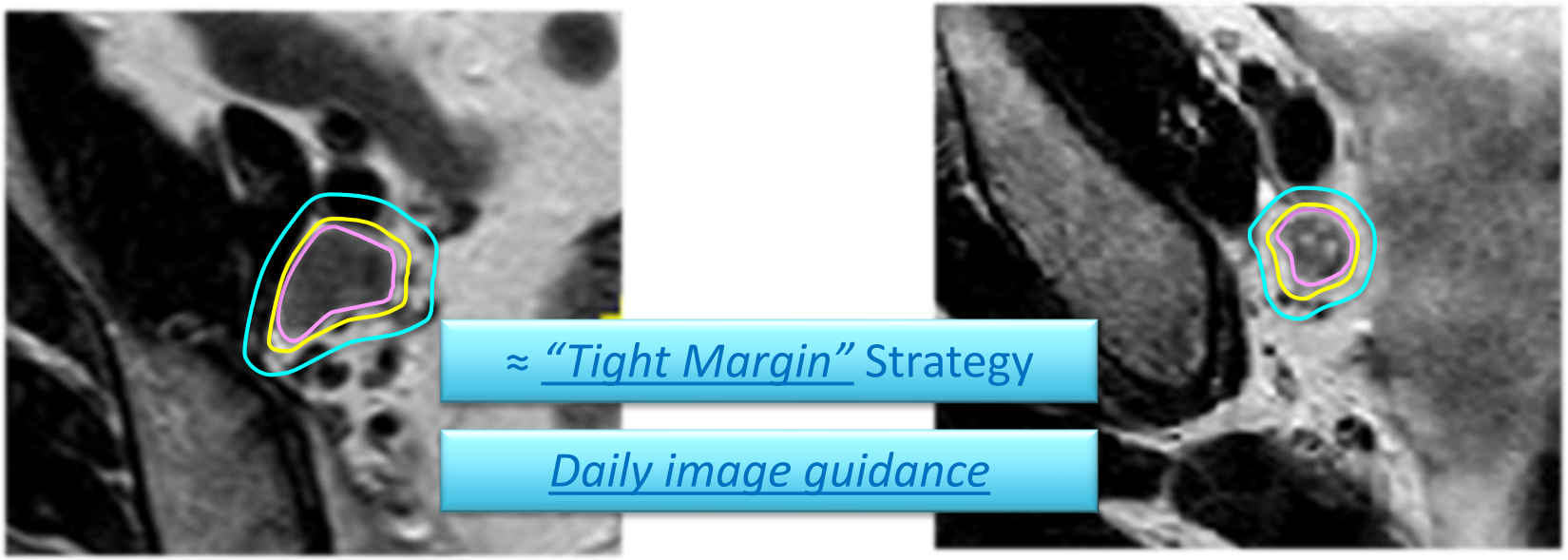
x Multiple Nodes

Boost V would be excessively large

From GTV to CTV to ITV to PTV

GTV-N	CTV-N	PTV-N
Affected node	Individualized margin for microscopic ECE	5 mm Isotropic margin around CTV
Visible ECE	Combine extension from MRI & CT (≈ITV concept)	
	Typically up to 3 mm around GTV	
	Exclude muscle, bone, bowel	

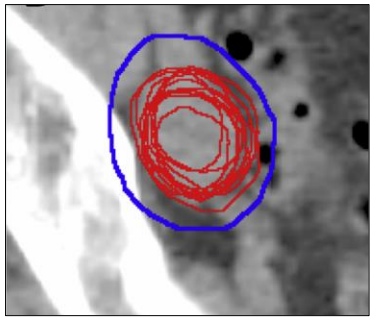
EMBRACE 2 Protocol, Section 9



For a 1 cm node: GTV: 0.5 cm^3 → PTV 2.2 cm^3

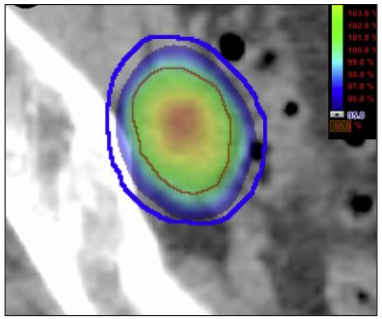
Coverage Probability Planning

Probability of finding CTV at a specific location in the PTV



Tighter Margins

Simultaneous Integrated Boost within PTV

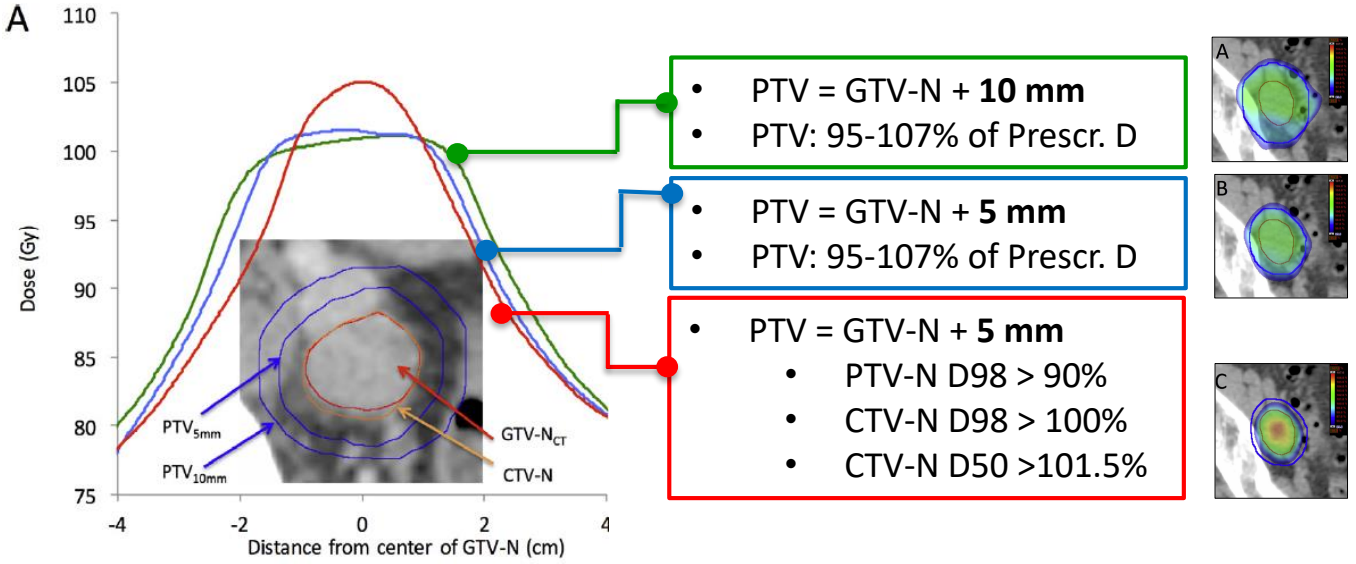


More relaxed D constraints at PTV edge

Ramlov A, et al. Radiother Oncol 2017;123:158-63.

Coverage Probability Planning

3 Simultaneous Integrated Boost Plans (55 – 57.5 Gy in 25 fx):



Plan No.	Plan-1	Plan-2		Plan-3	
Target concept	CT based: GTV-N_{CT}	CT and MR based: CTV-N = GTV-N_{CT} + GTV-N_{MRI}		CT and MR based: CTV-N = GTV-N_{CT} + GTV-N_{MRI}	
PTV margin	10 mm	5 mm		5 mm	
Treatment planning	Full coverage	Full coverage		CovP	
Planning aims	PTV-N D98: 95–107%	PTV-N D98: 95–107%		PTV-N D98 > 90% CTV-N D98 > 100% CTV-N D50 > 101.5%	
PTV volume (cm^3)	19.9 (9.2–8.5)	8.4 (2.9–62.7)		8.4 (2.9–62.7)	
GTV-N_{CT} planned D98 (%)	100.5 (98.4–101.7)	100.5 (99.4–101.5)		100.4 (99.6–102.1)	
GTV-N_{CBCT} D98 (%)	100.4 (98.2–101.8)	100.2 (98.6–101.7)	NS	99.4 (93.1–101.4)	p<0.001
GTV-N_{CT} planned D50 (%)	101.4 (99.6–102.5)	101.5 (100.1–102.4)		102.4 (100.8–103.6)	
GTV-N_{CBCT} D50 (%)	101.3 (100.2–102.5)	101.3 (100.4–103.1)	NS	102.1 (97.8–103.3)	NS
GTV-N_{CT} planned D2 (%)	102.0 (101.0–103.5)	102.5 (100.8–103.3)		103.9 (101.3–105.9)	
GTV-N_{CBCT} D2 (%)	101.8 (100.9–103.5)	102.2 (100.7–103.2)	NS	103.6 (100.8–106.0)	p<0.001
CTV-N planned D98 (%)	100.5 (95.1–101.7)	100.4 (99.3–101.3)		100.0 (99.7–101.2)	
CTV-N planned D50 (%)	100.4 (96.8–102.5)	101.4 (100.5–102.3)		101.9 (100.6–103.0)	
PTV-N planned D98 (%)	97.1 (95.4–99.9)	97.7 (96.3–101.5)		91.8 (90.7–94.8)	
V50 Body (cm^3)	74.6 (32.3–314.9)	48.9 (15.8–209.0)		27.5 (11.6–122.2)	
V50 Pelvic bone (cm^3)	6.9 (0–50.4)	2.2 (0–24.6)		0.9 (0–7.9)	
V50 Bowel (cm^3)	3.5 (0–106.3)	1.9 (0–67.8)		0.7 (0–34.6)	p<0.001

Ramlov A, et al. Radiother Oncol 2017;123:158-63.

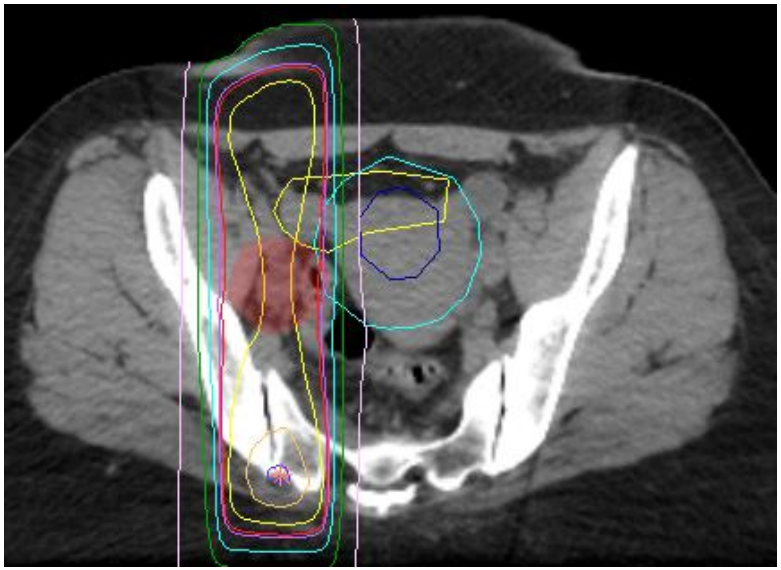
Applying adequate D to N+

Technique

Timing

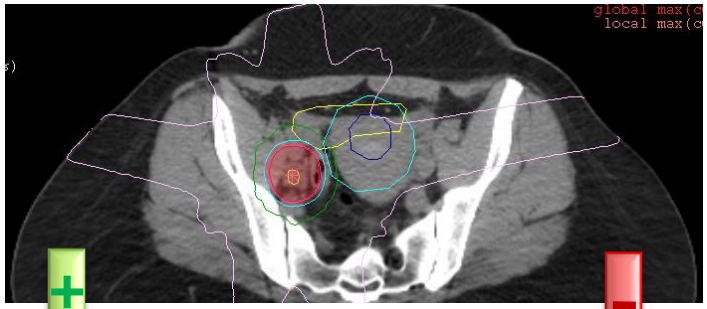
Dose

Technique of Nodal Boost: AP/PA or 3D CRT



- ↓D to central pelvis
- Excessive D along beam entry
  - Large V at high Dose
- Typical timing: Sequential

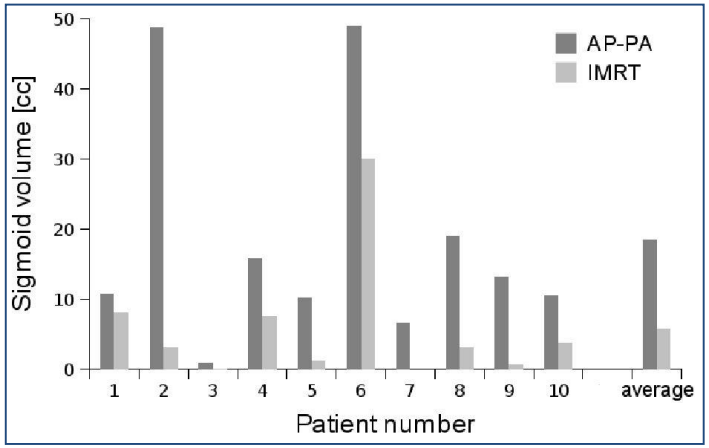
Technique of Nodal Boost: IMRT / VMAT



High D conformity

Smaller V at high D

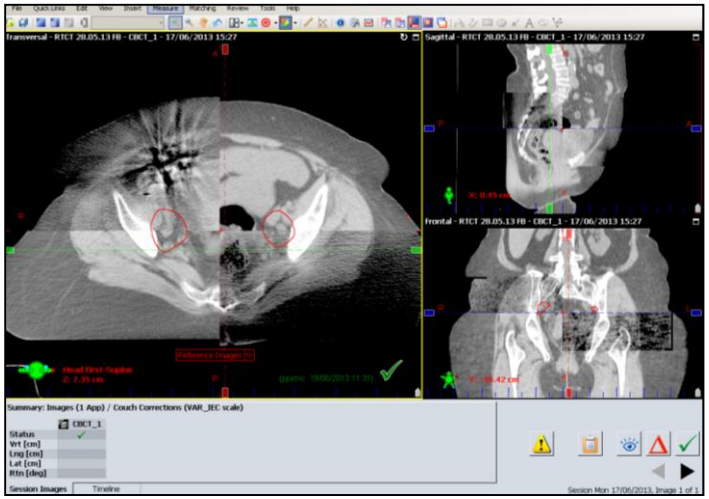
- ↑ D to PTV-N (control)
- ↓ D to OAR (morbidity)



Larger V at ↓ D

- Implications?

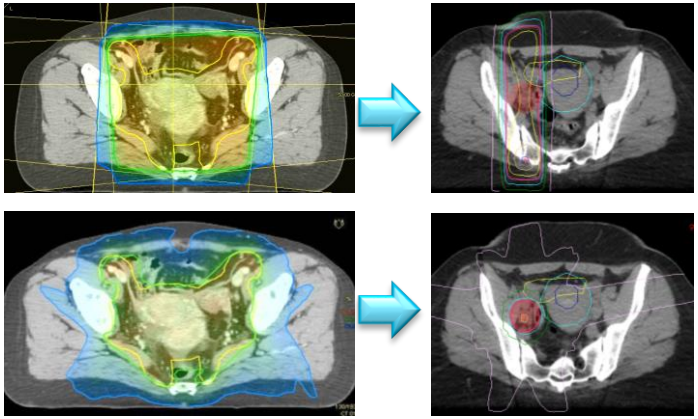
Uncertainties due to movements (need for daily CBCT)



L. Dijkstra, E.Kerkhof

Timing of Nodal Boost

Sequential Boost



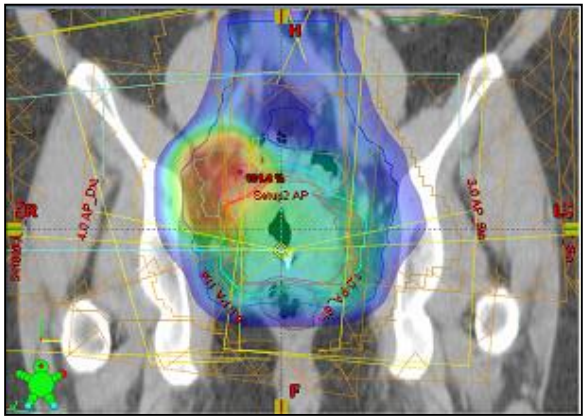
i.e.:

PTV-E:
45 Gy in 25 fx

PTV-N:
16 Gy in 8 fx

- \+ GTV Regression can be considered
- \- ↑ Totally delivered D (“waste D”)

Simultaneous Integrated Boost



i.e.: *(EMBRACE 2 Study protocol)*

PTV-E: 45 Gy in 25 fx
PTV-N: 55 Gy in 25 fx (True pelvis)
57.5 Gy in 25 fx (Outside True p.)

- \+ ↓ Overall Treatment Time
- \+ ↓ Totally administered D
- \- CTV-T & CTV-N move differently
- \- Nodes shrink- Excessive D to OAR?

Nodal Boost **Dose**

Classical radiation dose-control data

Size of Tumor	Control of Tumor Achieved with 6000 rads	Control of Tumor Achieved with Cisplatin and 6000 rads
2 cm	90%	94%
2–4 cm	75%	85%
4–6 cm	65%	80%
6 cm	55%	74%

Kupets R, et al. Gynecol Oncol 2002

Nodal Boost **Dose**

LYMPH NODE CONTROL IN CERVICAL CANCER

PERRY W. GRIGSBY, M.D.,*†§ ANURAG K. SINGH, M.D.,*§ BARRY A. SIEGEL, M.D.,†§ FARROKH DEHDASHTI, M.D.,†§ JANET RADER, M.D.,‡§ AND IMRAN ZOBERI, M.D.*§

*Department of Radiation Oncology and †Division of Nuclear Medicine, Department of Radiology, Mallinckrodt Institute of Radiology; ‡Division of Gynecologic Oncology, Department of Obstetrics and Gynecology; and §Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO

n=208, all stages

N status: CT and PET

	Lymph node status	Patients (no.)	Mean lymph node dose (Gy)	Pelvic lymph node failure
Pelvic Nodes	PET negative	76	66.8	0/76
	PET positive/CT ≤1 cm	89	66.8	3/89
	PET positive/CT >1 cm to ≤2 cm	21	66.9	0/21
	PET positive/CT >2 cm to ≤3 cm	15	69.4	2/15
	PET positive/CT >3 cm to ≤4 cm	5	74.1	0/5
	PET positive/CT >4 cm to ≤5 cm	2	70.1	0/2
	Total	208	67.2	5/208
Paraaortic Nodes	PET negative	175	0	1/175
	PET positive/CT ≤1 cm	24	43.9*	0/24
	PET positive/CT >1 cm to ≤2 cm	5	45*	0/5
	PET positive/CT >2 cm to ≤3 cm	4	33.9	0/4
	Total	208	—	1/208

Even PET⊖ & ≤ 1 cm: 66.8 Gy.

Overall rather high D (67 – 75 Gy)

Excellent N control

Lower D; mean 43, max 59.4 Gy

Excellent N control

Most relapses: Distant

Grigsby PW, et al Int J Radiat Oncol Biol Phys 2004;59(3):706-12.

Nodal Boost **Dose**

EMBRACE

139 patients

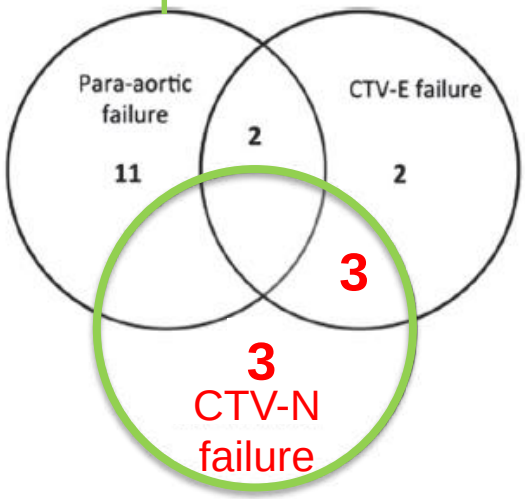
PET CT, MRI

209 N+ in 75 pts.
SUV_{max} = 5 (2-21)

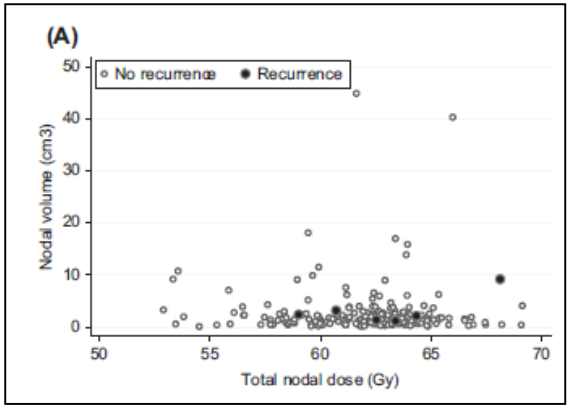
Boost D (EQD2):
D98=62 (53-69) Gy

21 (15 %) pts.:
N relapse

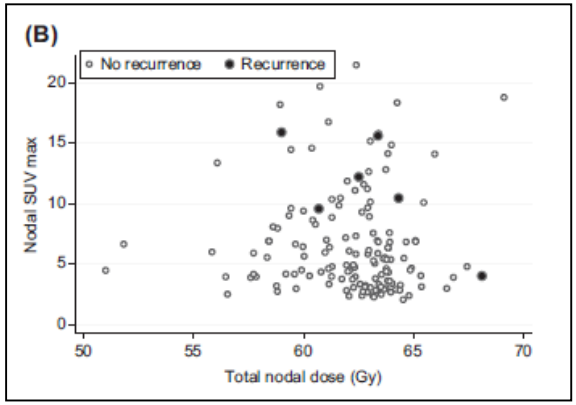
9 isolated PAN recurrences
(1/9: prophylactic PAN RT)



D & V: No significant correlation



Initial SUV_{max} (recurrent N):
11 (4-16); p=0.002



More failures when
< 5 cycles of ChT (p<0.001)

Conclusions:

- Current boost practice: ↑ control of involved N
- ↑ SUV_{max} → negative prognostic factor
- Attention: Chemotherapy & Paraaortic RT

Ramlov A, et al. Acta Oncologica 2015

Nodal Boost **Dose**

245 patients

Initial CT, MRI

78 N1 patients, 129 Nodes → EBRT boost: 55 (43-60) Gy → CT, MRI after 50 Gy

Impact of boost irradiation on pelvic lymph node control in patients with cervical cancer

Masaru WAKATSUKI[1,*], Tatsuya OHNO[2], Shingo KATO[3], Ken ANDO[2], Shin-ei NODA[2], Hiroki KIYOHARA[2], Kei SHIBUYA[2], Kumiko KARASAWA[1], Tadashi KAMADA[1] and Takashi NAKANO

	Long axis after 50 Gy ≥ 10 mm (poor response group)			Long axis after 50 Gy <10 mm (good response group)		
	Rec	Control	Total	Rec	Control	Total
≤58 Gy (EQD2)	9	7	16	1	58	59
>58 Gy (EQD2)	0	21	21	2	31	33
		$P = 0.0003$			$P = 0.604$	
Total	9	28	37	3	89	92
			$P = 0.001$			

Conclusions:

1. Response after RT was more significant predictor for recurrence than initial N size
2. Poor responding nodes require >58 Gy

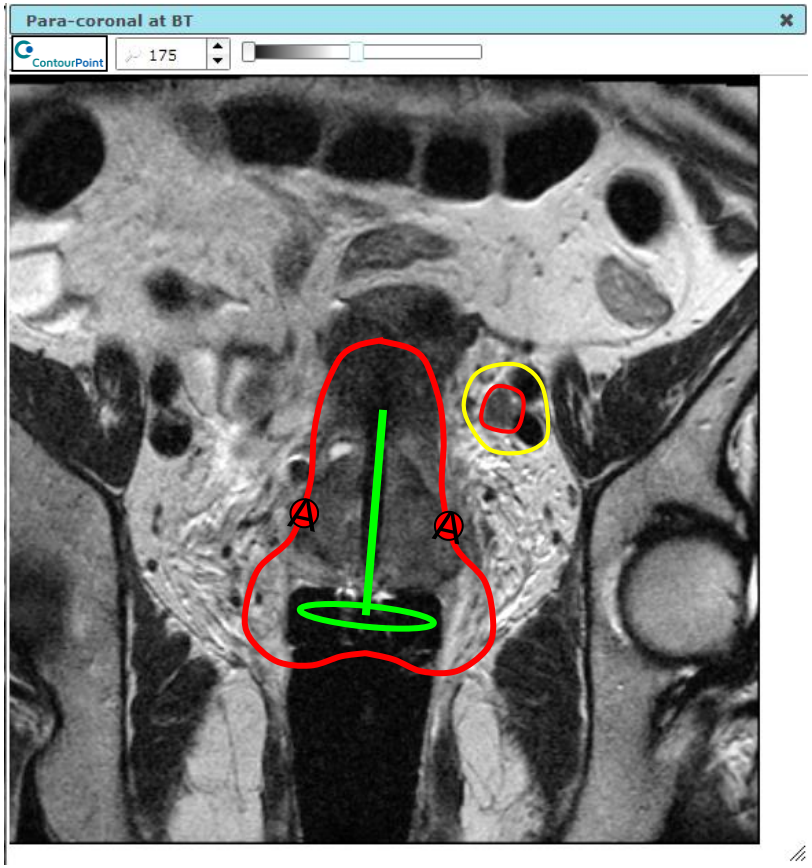
Wakatsuki M, et al. J Radiat Res 2014;55(1):139-45

Nodal Boost **Dose**

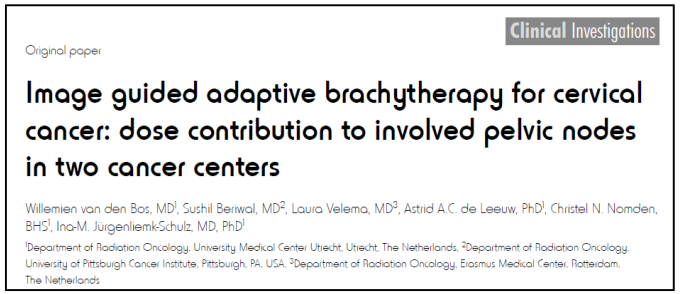
Summary

- Evidence suggests: 55 - 60 Gy
- “Elective” dose: 45 – 50 Gy + boost 10 to 20 Gy
- It’s not only a matter of dose !
  - Initial SUV and SUV regression during EBRT
  - Volume or diameter regression during EBRT
- Don’t forget BT dose contribution

Contribution of Brachytherapy to Nodal Dose



Contribution of Brachytherapy to Nodal Dose



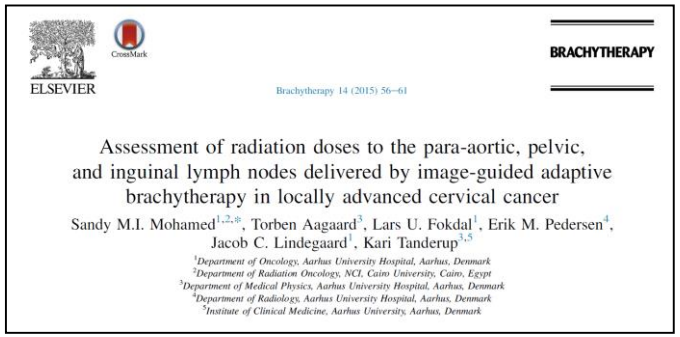
Original paper

Clinical Investigations

Image guided adaptive brachytherapy for cervical cancer: dose contribution to involved pelvic nodes in two cancer centers

Willemien van den Bos, MD[1], Sushil Beriwal, MD[2], Laura Velema, MD[3], Astrid A.C. de Leeuw, PhD[1], Christel N. Nomden, BHS[1], Ina-M. Jürgenliemk-Schulz, MD, PhD[1]

[1]Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands, [2]Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA, [3]Department of Radiation Oncology, Erasmus Medical Center, Rotterdam, The Netherlands



ELSEVIER

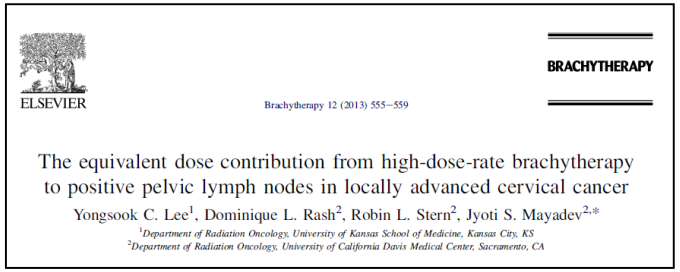
BRACHYTHERAPY

Brachytherapy 14 (2015) 56–61

Assessment of radiation doses to the para-aortic, pelvic, and inguinal lymph nodes delivered by image-guided adaptive brachytherapy in locally advanced cervical cancer

Sandy M.I. Mohamed[1,2,*], Torben Aagaard[3], Lars U. Fokdal[1], Erik M. Pedersen[4], Jacob C. Lindegaard[1], Kari Tanderup[3,5]

[1]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Radiation Oncology, NCI, Cairo University, Cairo, Egypt
[3]Department of Medical Physics, Aarhus University Hospital, Aarhus, Denmark
[4]Department of Radiology, Aarhus University Hospital, Aarhus, Denmark
[5]Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark



ELSEVIER

BRACHYTHERAPY

Brachytherapy 12 (2013) 555–559

The equivalent dose contribution from high-dose-rate brachytherapy to positive pelvic lymph nodes in locally advanced cervical cancer

Yongsook C. Lee[1], Dominique L. Rash[2], Robin L. Stern[2], Jyoti S. Mayadev[2,*]

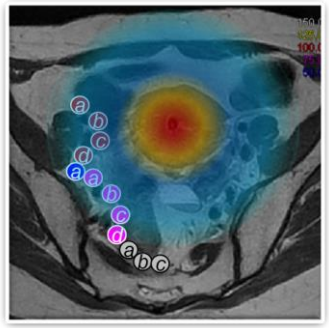
[1]Department of Radiation Oncology, University of Kansas School of Medicine, Kansas City, KS
[2]Department of Radiation Oncology, University of California Davis Medical Center, Sacramento, CA

BT contributes considerable D to pelvic N

Should be considered in evaluation of total D!

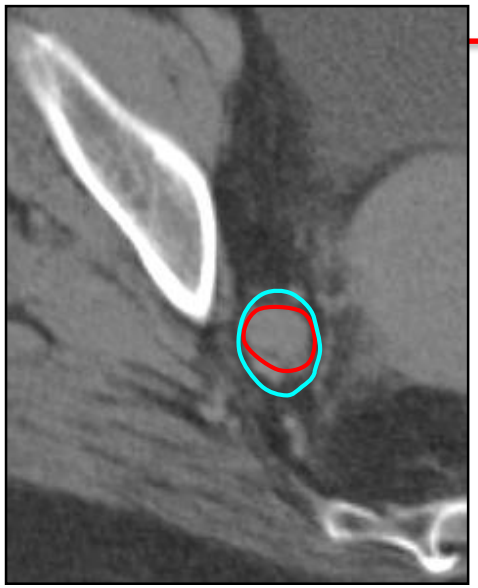
- **External iliac:**
  $D_{98\%} \approx$ 10-25% of p. A Dose*
  *Assumption for intracavitary BT
- **Internal iliac:**
  $D_{98\%} \approx$ 15-30% of p. A Dose*
  *Assumption for intracavitary BT
- **Outside Pelvis:**
  Negligible D

Range for individual Nodes!

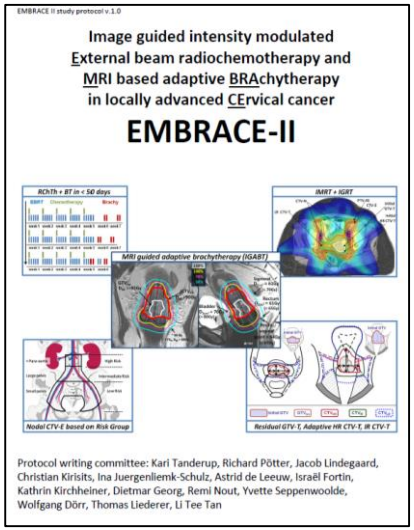


Mohamed SMI, et al. Brachytherapy 2015;14:56-61
Van den Bos W, et al. JCB 2014;6(1):21-7.
Petric P, et al. ASTRO 2014 (Abstract)
Lee YC, et al. Brachytherapy 2013;12:555-9.

Nodal Boost: EMBRACE 2 Protocol Summary



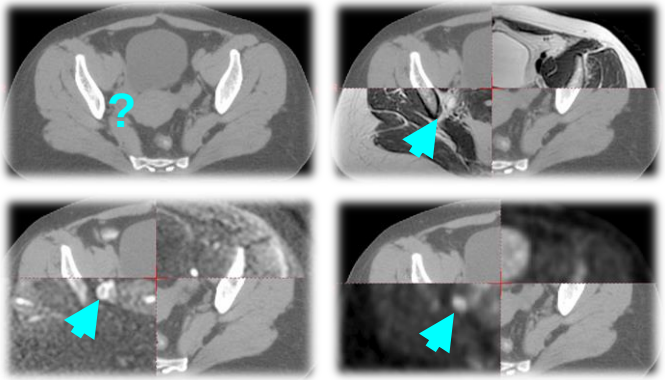
- Number each GTV-N , CTV-N & PTV-N
  - GTV-N to CTV-N: 0 to 3 mm
  - Individualized margins (size, appearance)
  - Respect barriers (muscle, bone,…)
  - CTV-N to PTV-N: 5 mm Isotropic Margin
  - Technique: IMRT/VMAT, (CovP)
  - Timing: SIB
  - D: 55-57.5 Gy in 25 fx
  - Planning aims: D98%, Dmax, D50% (protocol)

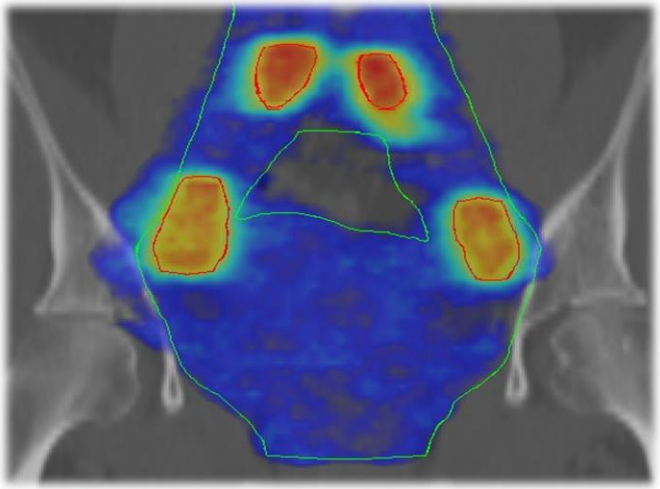


EMBRACE 2 Study Protocol

Nodal Boost

Volumes, Dose, Techniques





Primoz Petric

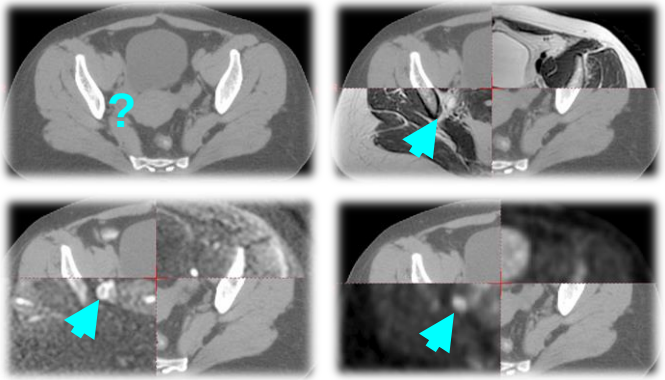
Aarhus University Hospital, Denmark

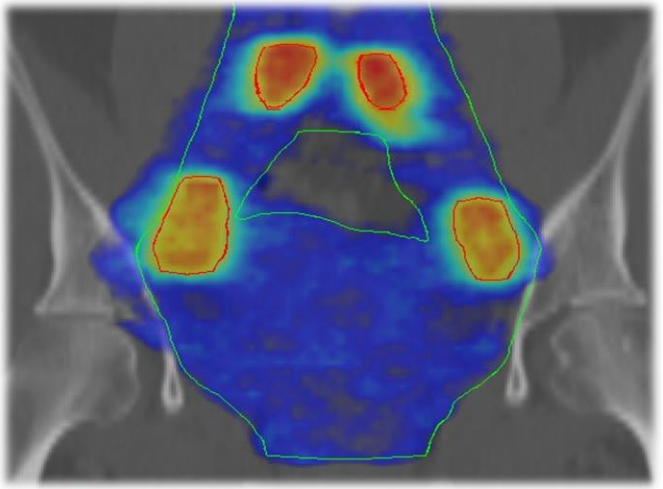
Ina Jürgenliemk-Schulz

University Medical Centre Utrecht, The Netherlands

Nodal Boost

Volumes, Dose, Techniques





Primoz Petric

Aarhus University Hospital, Denmark

Ina Jürgenliemk-Schulz

University Medical Centre Utrecht, The Netherlands

Cervical Cancer
FIGO IIB

PRACTICAL EXAMPLE

AAR 003

Clinical history –status at diagnosis:

Anamnestic information
- o 43 years old
- o No previous history
- o Smoker
- o Moderate bleeding

Clinical examination
- o Performance status = 0
- o Height: 167cm
- o Weight: 99 kg
- o No palpable nodes

Gynaecological examination
- o Dimensions (w*h*t): 35*35*35 mm
- o Left parametrium: Proximal
- o Right parametrium: Not involved
- o Vagina: Not involved
- o Bladder: Not involved
- o Rectum: Not involved

Radiology reports:

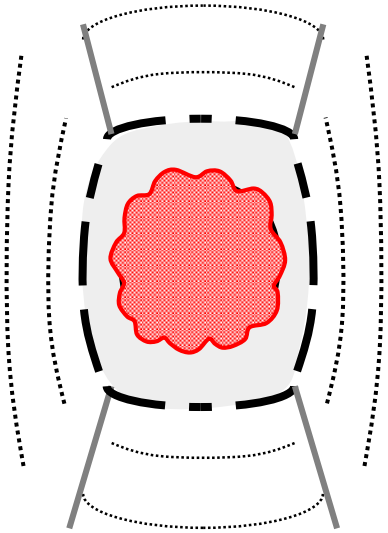
o **PET-CT:** FDG-activity in cervix uteri + FDG-activity in a lymph node laterally to the right common iliac artery + FDG-activity in a lymph node posterior to the right external iliac artery

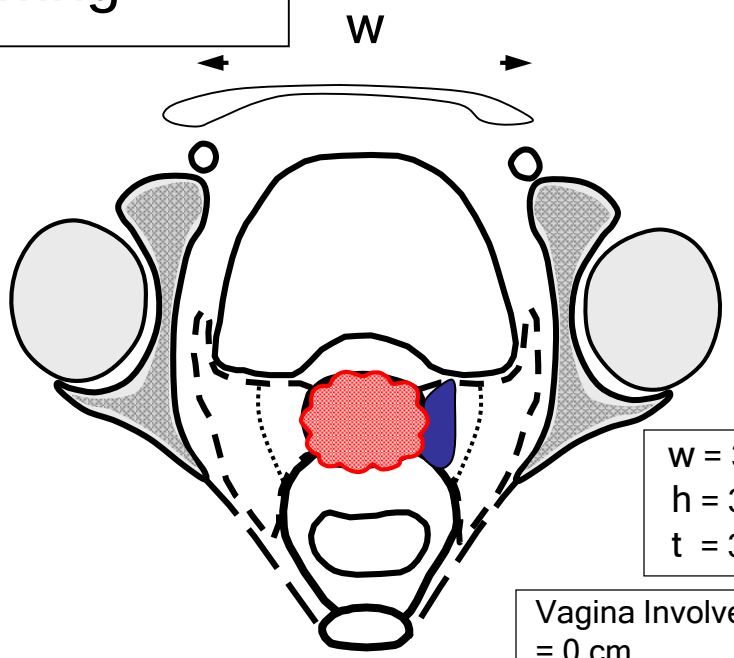
o MRI: Tumour 25 mm with a pathological lymph node in relation to the right common iliac artery and one in relation to the right external iliac artery

Clinical Drawing

At Diagnosis

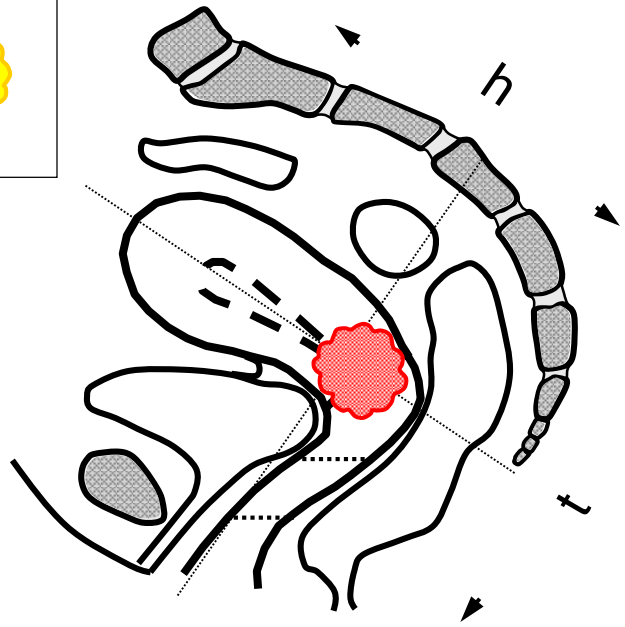
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

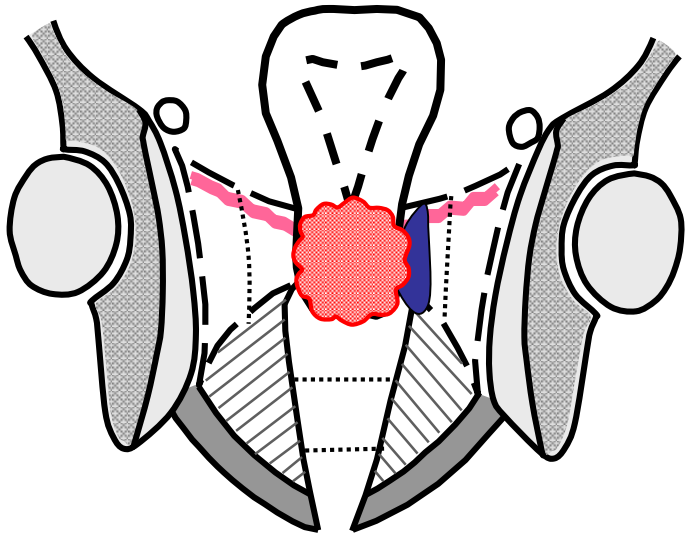




w = 35 mm
h = 35 mm
t = 35 mm

Vagina Involvement
= 0 cm

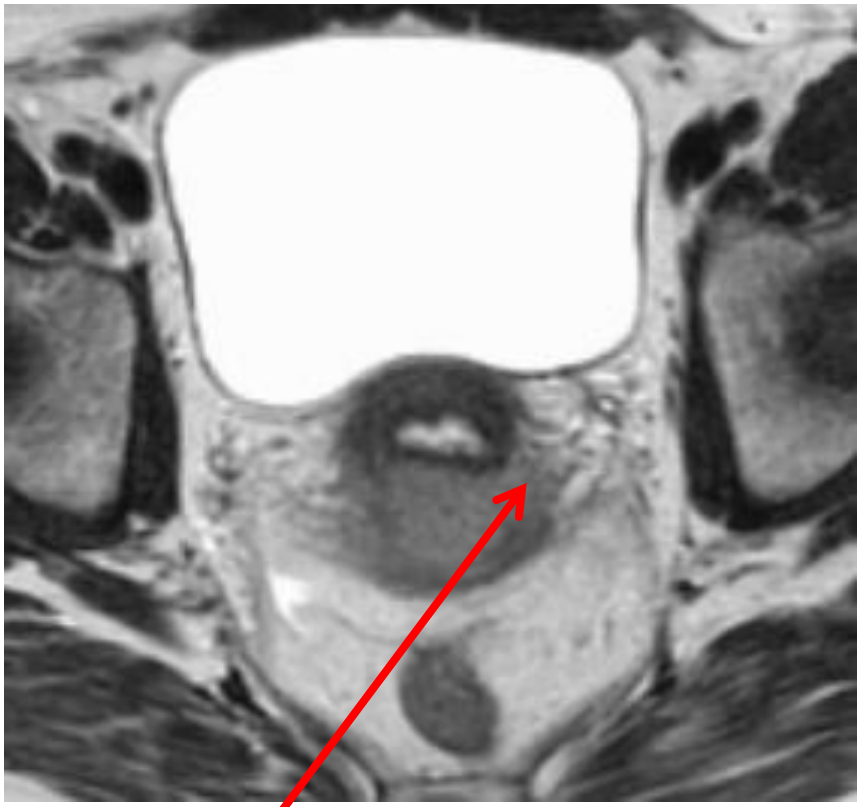




dd/mm/yy

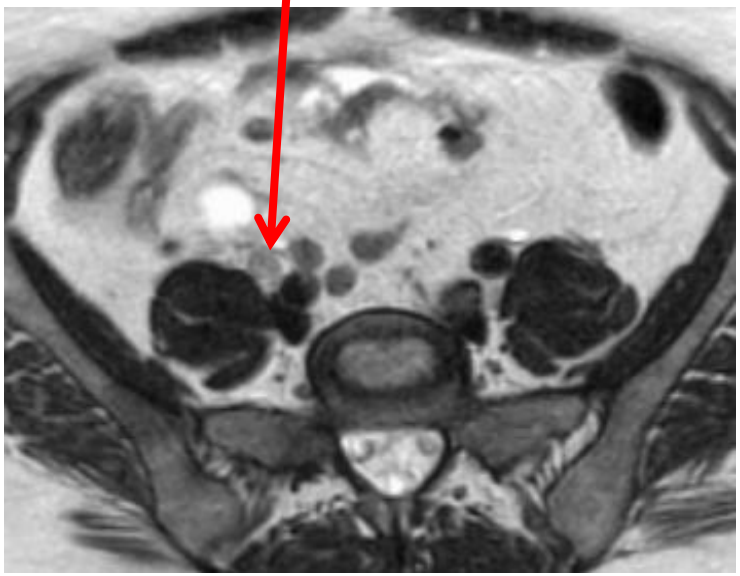
Signature

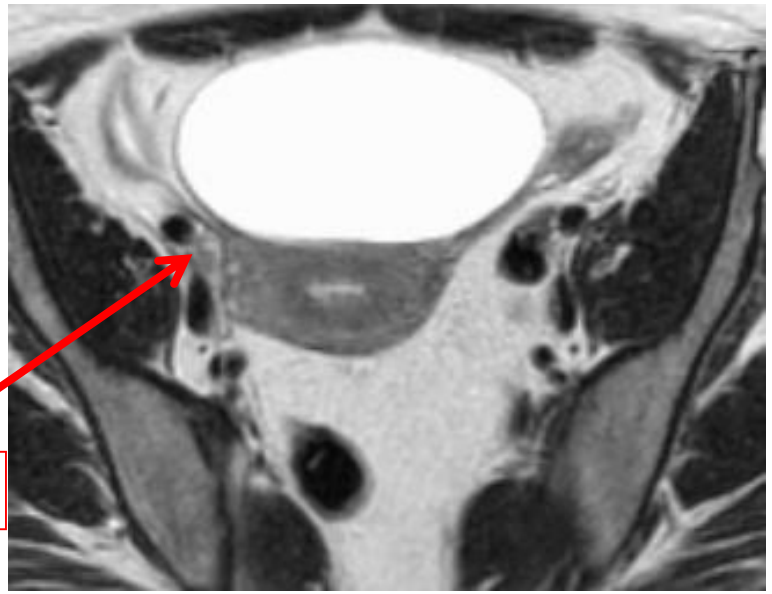
Initial



RT para invasion

RT Common Iliac node





RT Ext Iliac node

Planned for Conformal EBRT, and Chemotherapy

EBRT CONTOURING EXERCISE

EMBRACE II DEFINITIONS

- (MR) GTV-T_init
- (MR) CTV-T HR_init
- (MR) CTV-T LR_init
- (MR) GTV-N1 (ext. iliac)
- (MR) GTV-N2 (common iliac)
- (MR) CTV-E
- CTV-N1 (ext. iliac)
- CVT-N2 (common iliac)

- ITV-T LR_init
- ITV45
- Bladder
- Rectum
- Sigmoid
- Left kidney
- Right kidney
- Spinal cord
- Bowel (outer extension of loops)

Clinical example : cervix cancer

From Gustava Roussy Paris

Christine Haie Meder

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

UNIVERSITÉ PARIS SUD
ÉCOLE DES SCIENCES DU CANCER GUSTAVE ROUSSY

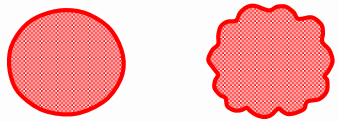
Example : cervix cancer

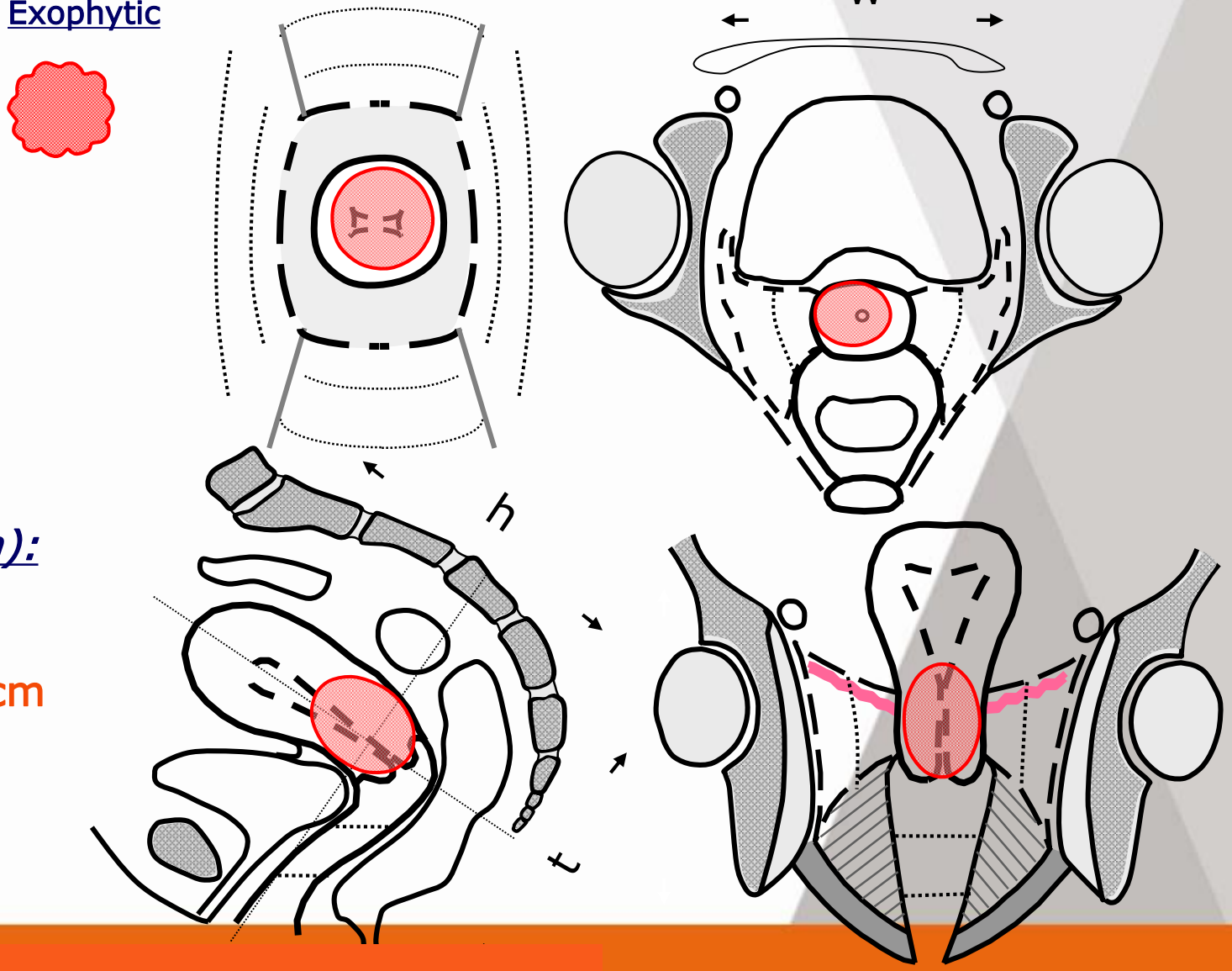
- 57 year-old patient
- WHO = 0
- Vaginal bleeding
- Biopsy: poorly differentiated
  squamous cell carcinoma

Initial clinical drawings

Infiltrative Exophytic

Cervix





Dimensions (cm):

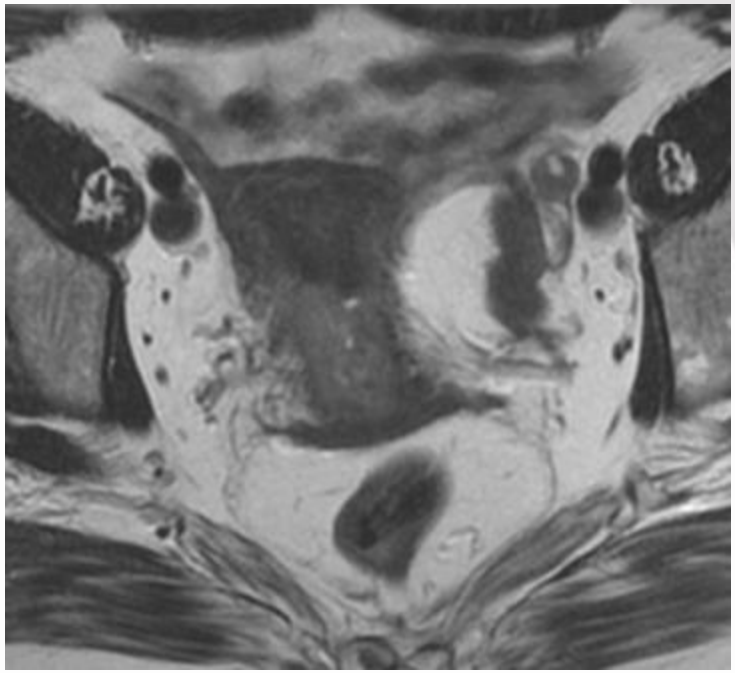
Width: 2.5 cm

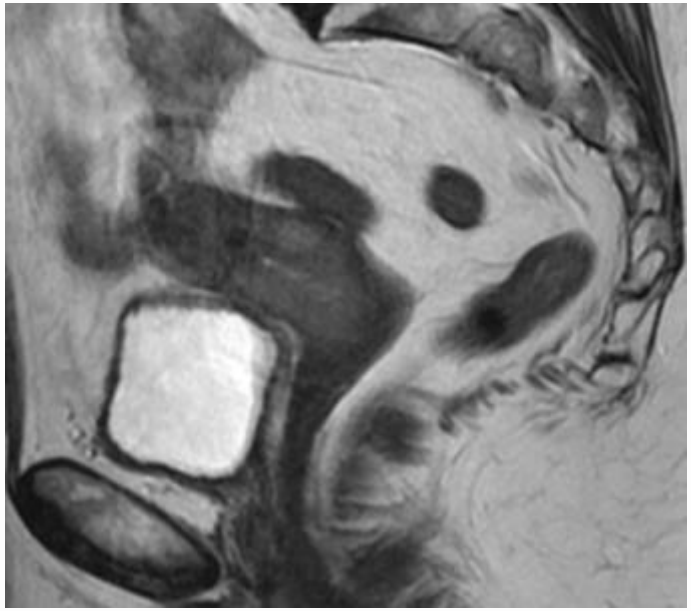
Thickness: 2.5 cm

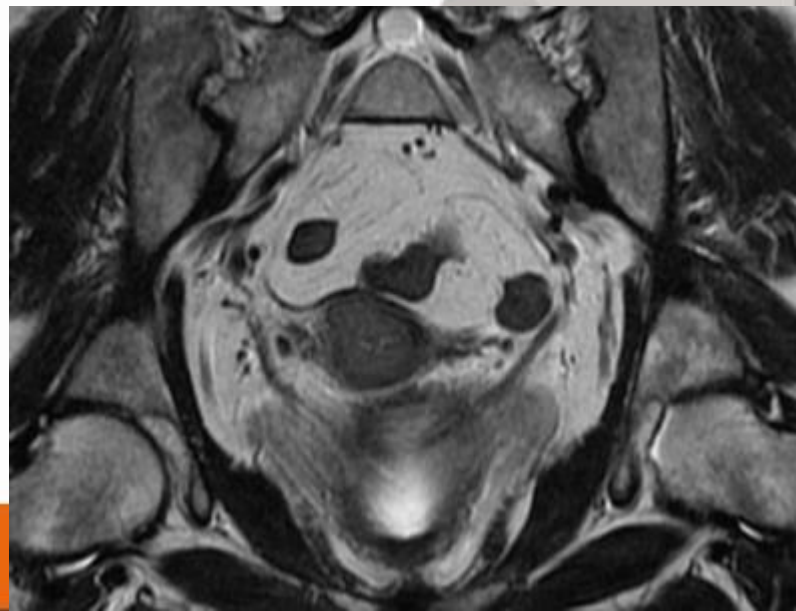
Height: 3 cm

MRI findings at diagnosis

Tumoral assessment

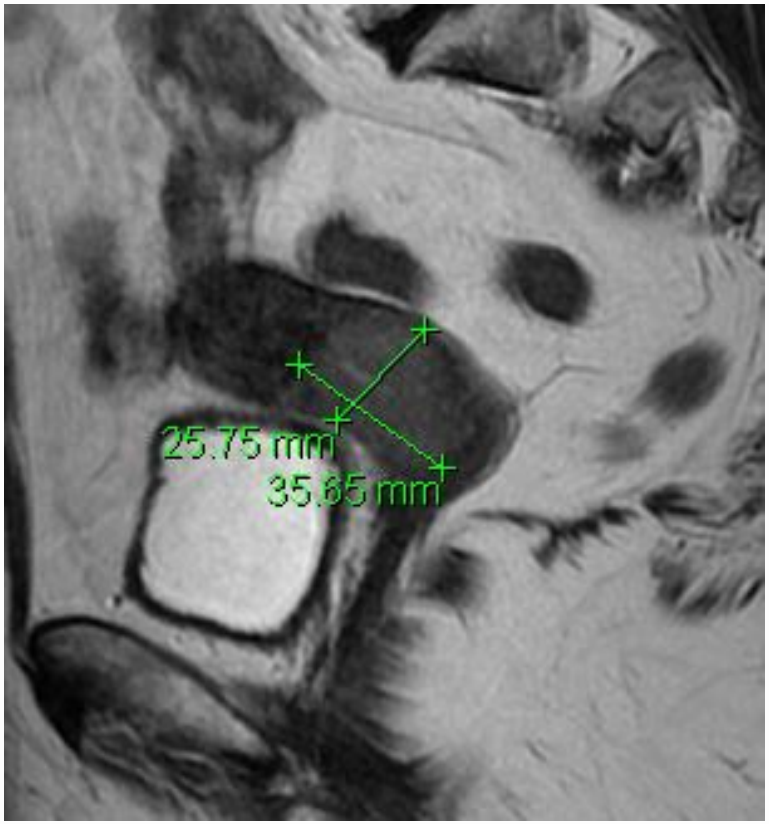


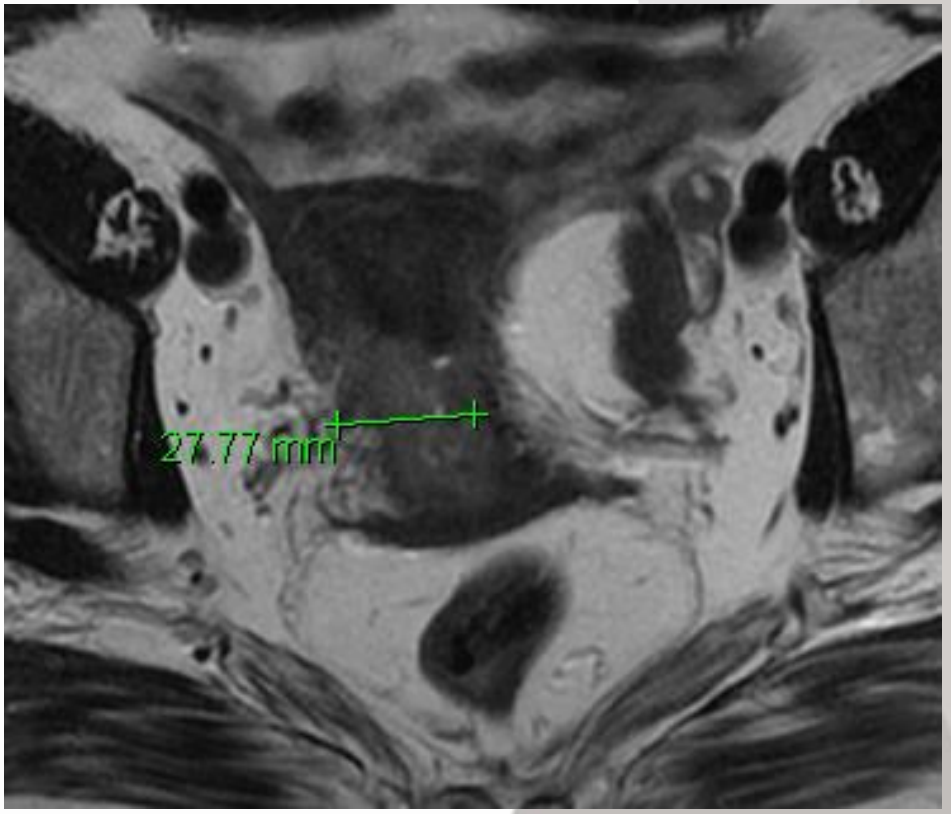




MRI findings at diagnosis

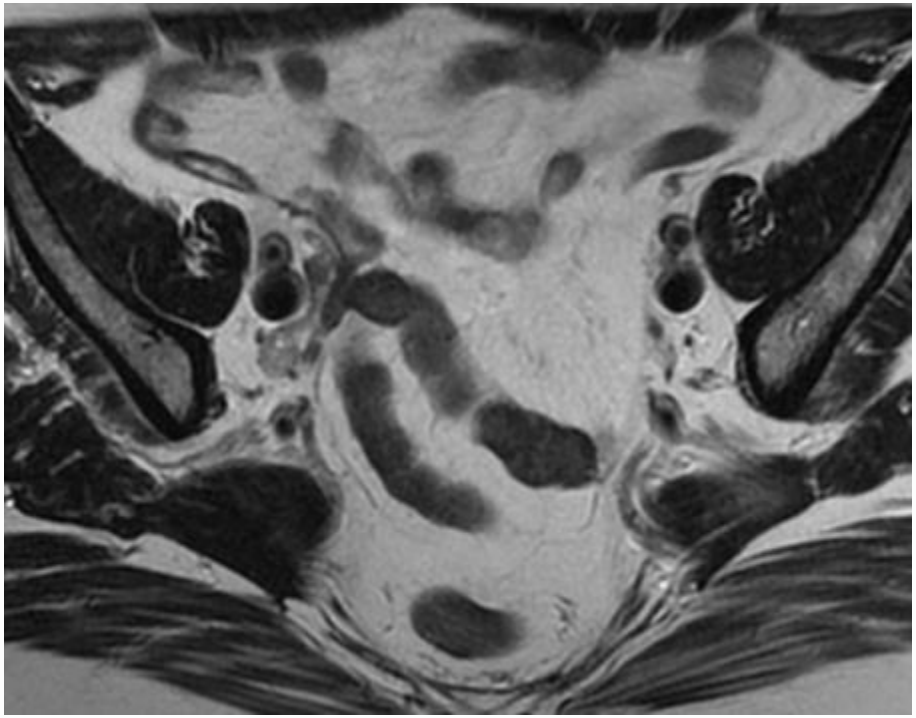
Tumoral assessment

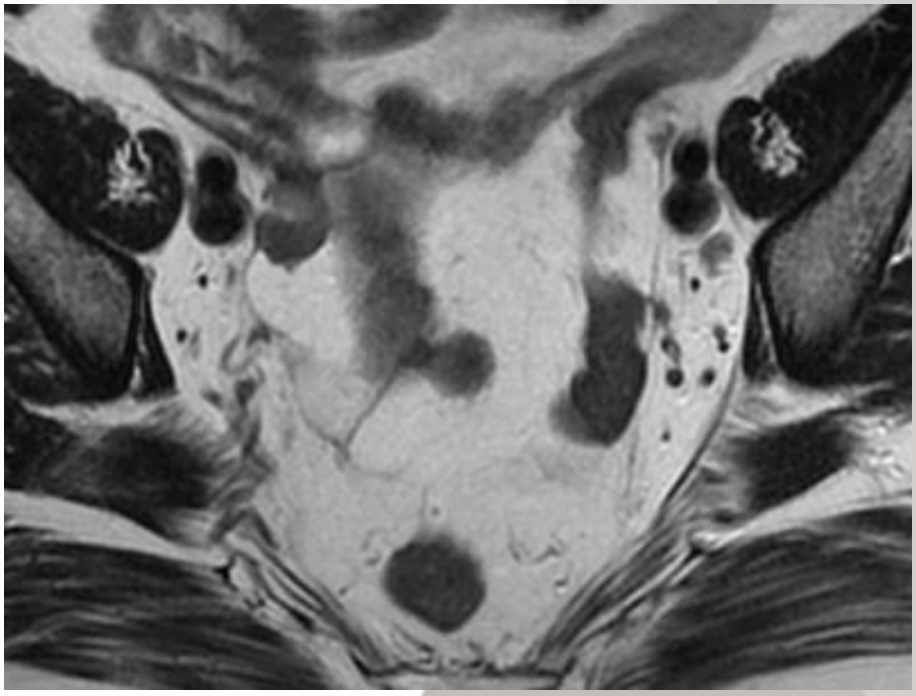




MRI findings at diagnosis

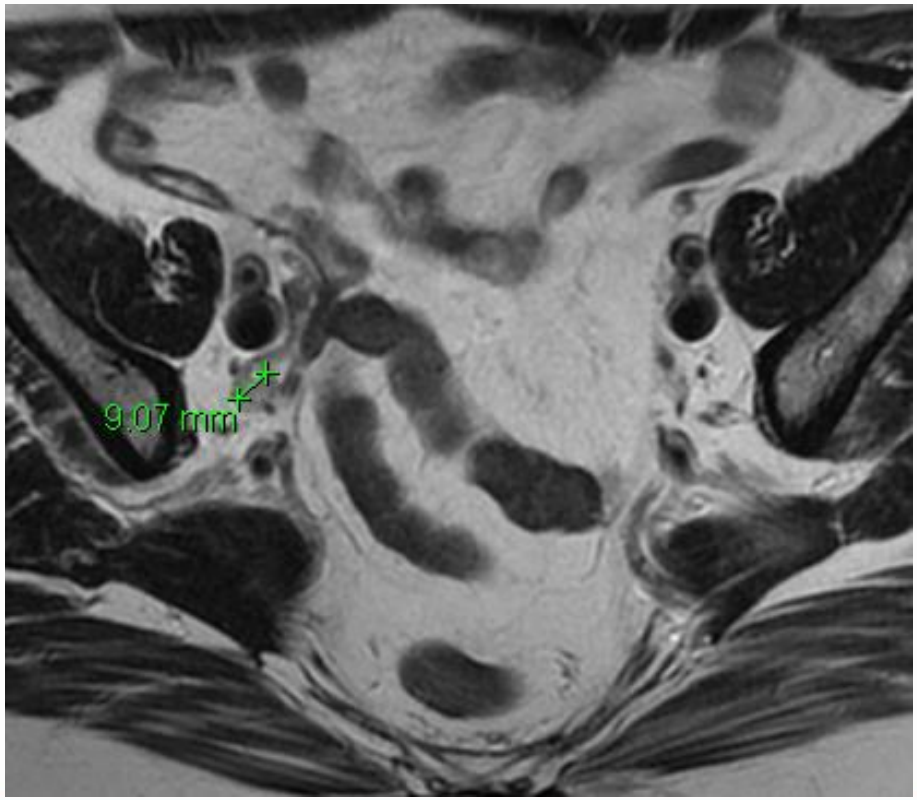
Nodal assessment

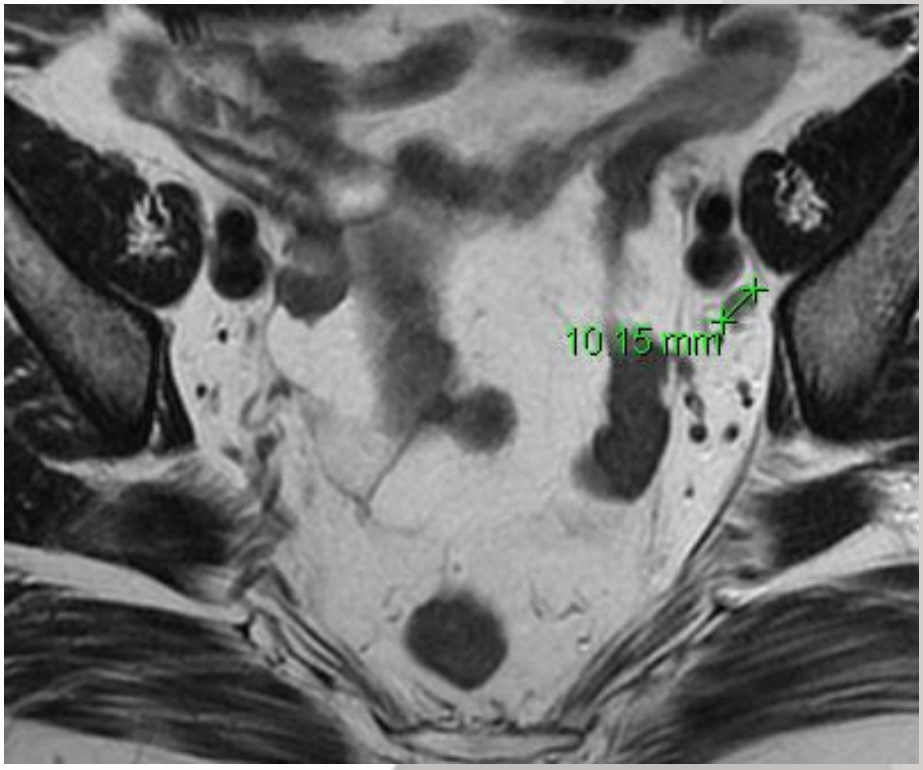




MRI findings at diagnosis

Nodal assessment





FIGO staging?

Complementary exams?

Can nodal status be better assessed?

Treatment?

TASK: EACH GROUP to come up with a consensus in 3-4 SLIDES

Clinical example : endometrial cancer

Case description

65 years old patient

WHO = 0; BMI = 33

Post-menopausal bleeding

Clinical investigation:

No pathological findings

Vaginal ultrasound:

≈50% myometrium invaded no cervical infiltration

Curettage:

G1 **endometrial adenocarcinoma**

no signs of cervical infiltration

Chest x-ray:

No pathological findings

Primary treatment: surgery

- Laparoscopic hysterectomy & bilateral salphingo oophorectomy
- Complete removal, no lymphadenectomy, no suspicious nodes

Histopathological findings:

- G2 endometroid adenocarcinoma (1.8 cm, dorsal wall)
- No lymph vascular space invasion (LVSI)
- Infiltration > ½ myometrium
- No infiltration into cervical stroma, serosa or adnexa

→ **FIGO stage IB grade 2 endometrial cancer**

Postoperative management

1. Lymphadenectomy (complete staging)?
2. Radiotherapy?
    - if yes: EBRT, BT, both?
3. Systemic treatment?
4. What if there was LVSI present?

FIGO IB grade 2 endometrioid

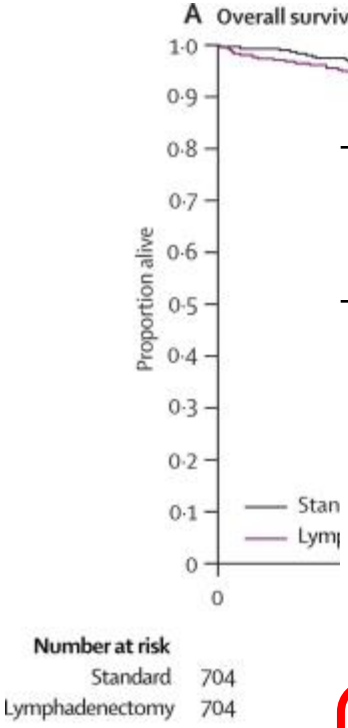
1. Lymphadenectomy (complete staging)?
2. Radiotherapy?
    - if yes: EBRT, BT, both?
3. Systemic treatment?
4. What if there was LVSI present?

Lymph node metastasis (GOG)

Risk of microscopic pelvic metastases for stage 1 without extrauterine disease:

- *low risk (<5%)* — grade 1 <2/3, gr 2-3, no invasion
- *intermediate (5-10%)* — all others
- *high risk (>10%)* — gr 3, >2/3 invasion

Lymphadenectomy trials

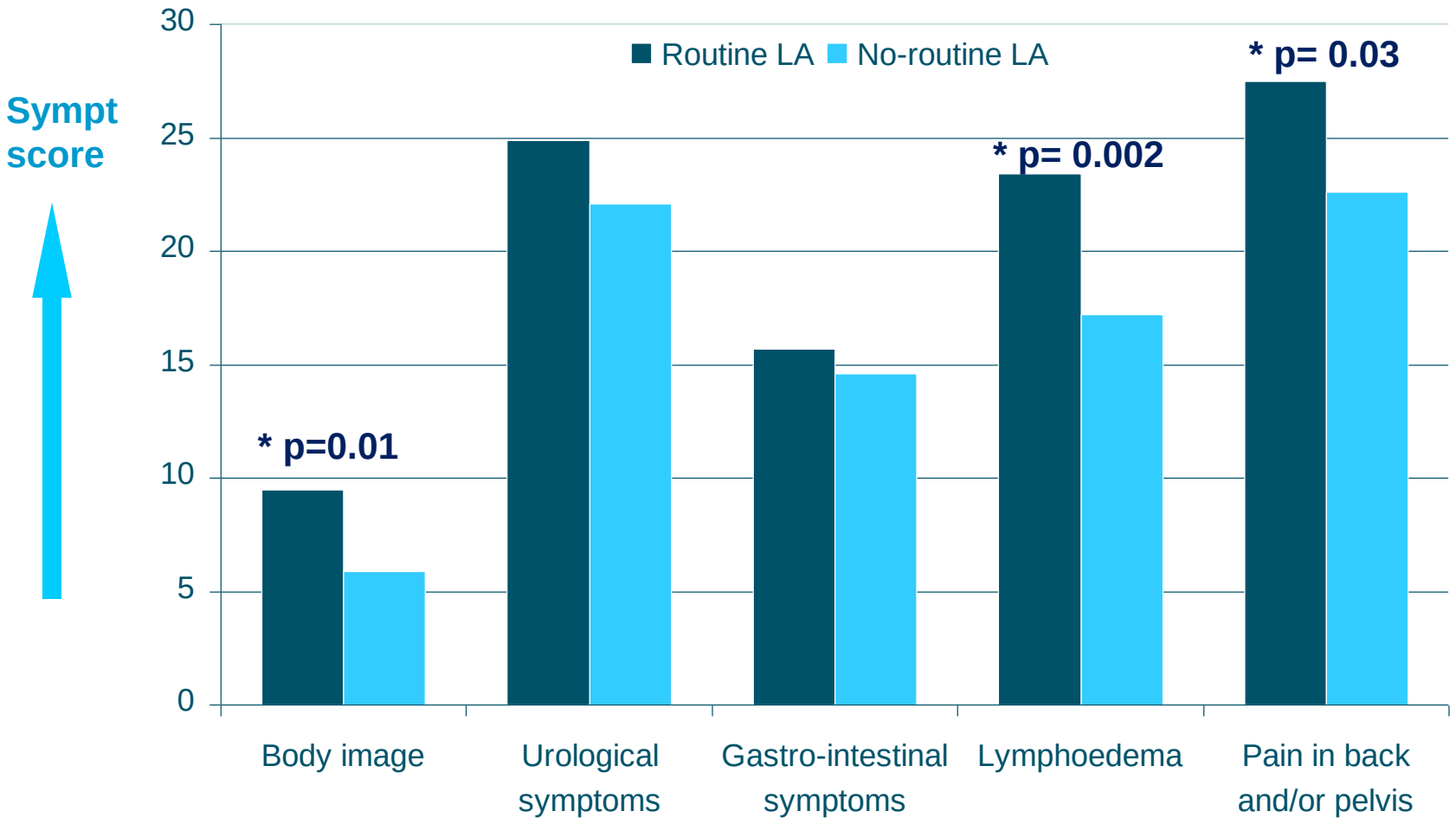


Recurrence site	Lymphadenectomy arm (n = 264)	No-lymphadenectomy arm (n = 250)
No recurrence, No. (%)	231 (87.5)	217 (86.8)
Recurrence, No. (%)	34 (12.9)	33 (13.2)
Lung	8 (3)	8 (3.2)
Intraperitoneum	8 (3)	7 (2.8)
Vagina	7 (2.6)	6 (2.4)
Lymph node	4 (1.5)	4 (1.6)
Bone	4 (1.5)	3 (1.2)
Liver	2 (0.7)	3 (1.2)
Missing data	3 (1.1)	3 (1.2)

no LA
LA

Kitchener et al, Lancet 2009; Benedetti Panici et al, JNCI 2008

Lymphadenectomy Quality of Life



Lymphadenectomy indications ESMO-ESGO-ESTRO

Recommendation 5.5: Patients with low-risk endometrioid carcinoma (grade 1 or 2 and superficial myometrial invasion <50%) have a low risk of lymph node involvement, and two RCTs did not show a survival benefit. Therefore, lymphadenectomy is not recommended for these patients

Level of evidence: II

Strength of recommendation: A

Consensus: 100% yes (37 voters)

Recommendation 5.6: For patients with intermediate risk (deep myometrial invasion >50% or grade 3 superficial myometrial invasion <50%), data have not shown a survival benefit. Lymphadenectomy can be considered for staging purposes in these patients

Level of evidence: II

Strength of recommendation: C

Consensus: 100% yes (37 voters)

Recommendation 5.7: For patients with high risk (grade 3 with deep myometrial invasion >50%), lymphadenectomy should be recommended

Level of evidence: IV

Strength of recommendation: B

C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional

LND to complete staging?

Recommendation 5.8: Lymphadenectomy to complete staging could be considered in previously incompletely operated high-risk patients to tailor adjuvant therapy

Level of evidence: V

Strength of recommendation: C

Consensus: 100% yes (37 voters)

Sentinel Node?

Recommendation 5.3: SLND is still experimental, but large series suggest that it is feasible. SLND increases the detection of lymph nodes with small metastases and isolated tumour cells; however, the importance of these findings is unclear

Level of evidence: IV

Strength of recommendation: D

Consensus: 100% yes (37 voters)

STATEC trial in High Risk EC sub study for sentinel node

Endometrial Cancer Consensus: Adjuvant Treatment

ESMO ESGO ESTRO European Society for RADIOTHERAPY & ONCOLOGY

 Colombo N. et al *Ann of Oncology* 2015

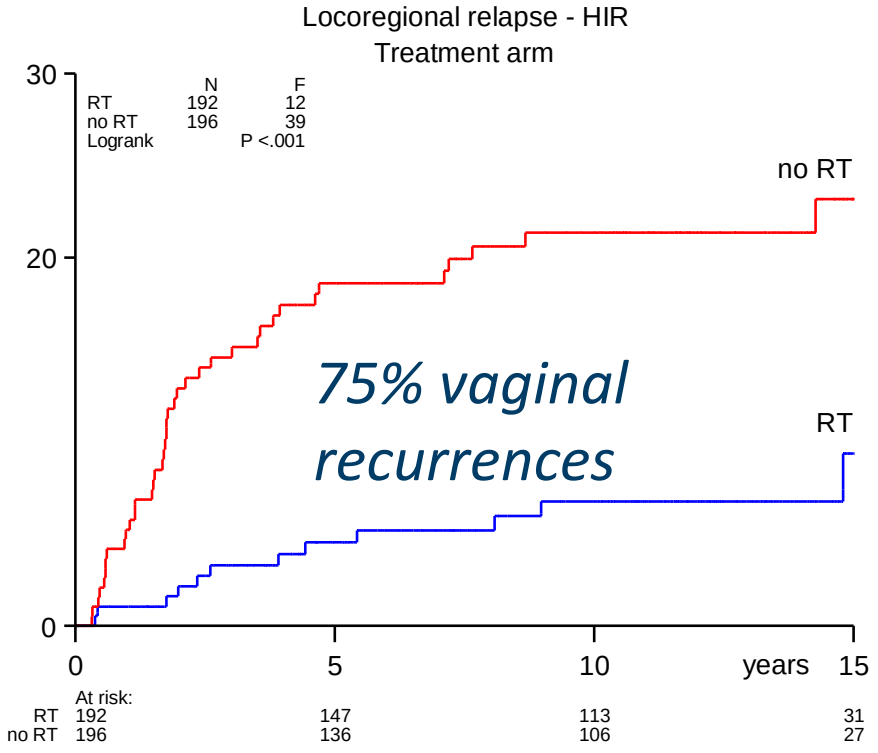
Intermediate Risk – Randomised trials

Trial	No. patients eligibility	Surgery	Randomization	Locoregional recurrence	Survival	Severe complications
Norwegian 1968-1974	540 Stage I	TAH-BSO	Brachytherapy vs. brachy and pelvic RT	7% vs. 2% at 5 years p<0.01	89% vs. 91% at 5 years p=NS	NA
PORTEC 1990-1997	714 IB grade 2-3 IC grade 1-2	TAH-BSO	NAT vs. pelvic RT	14% vs. 4% at 5 years p<0.001	85% vs. 81% at 5 years p=0.31	3% GI at 5 years (actuarial)
GOG-99 1987-1995	392 St IB, IC St II (occult)	TAH-BSO and lymph-adenectomy	NAT vs. pelvic RT	12% vs. 3% at 2 years p<0.01	86% vs.92% at 4 years p=0.56	8% GI at 2 years (crude)
ASTEC/EN5 1996-2005	905 St IAB g3, IC, St II, serous/cc	TAH-BSO +/- lymph-adenectomy	NAT vs. pelvic RT	7% vs. 4% at 5 years p=0.038	84% vs.84% at 5 years p=0.98	3 vs 7% gr 3/4

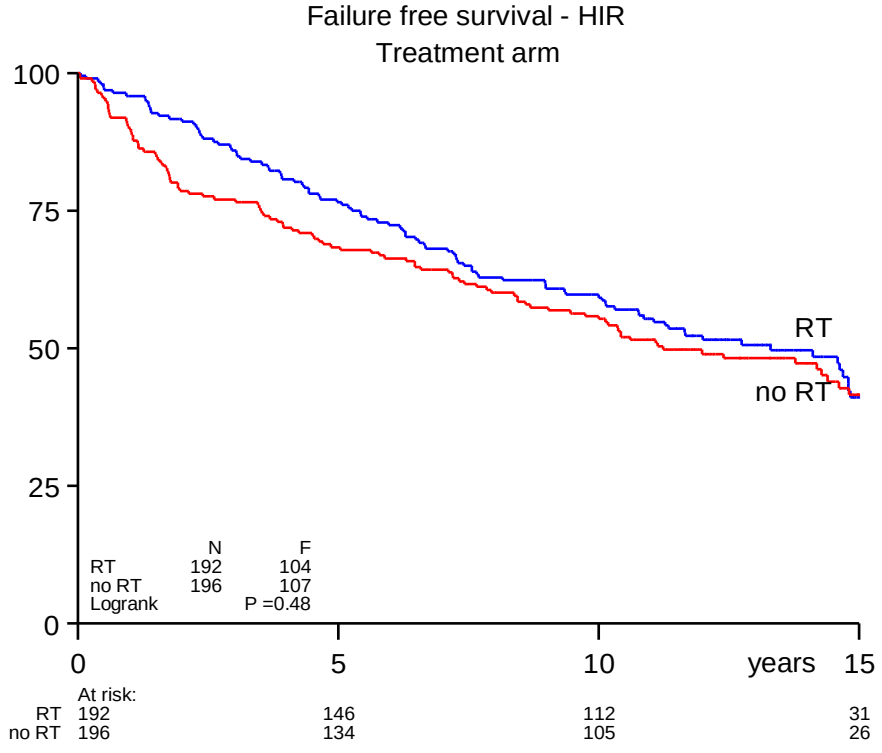
Aalders et al 1980, Creutzberg et al 2000, Keys et al 2004, ASTEC/EN.5 Study Group 2009

PORTEC-1: 15-year outcomes for HIR patients

Locoregional Recurrence



Failure Free Survival



Creutzberg et al, ASTRO 2009, IJROBP 2011

Summary high-intermediate risk

- Brachytherapy effective in preventing vaginal recurrence: 2.9% at 8 years
- More pelvic recurrences after brachytherapy, most with simultaneous distant metastases (isolated pelvic failure 1.5% vs 0.5%)
- No difference in distant metastases and survival
- VBT better QoL/functioning

Lymph vascular space invasion LVSI

- LVSI independent prognostic factor for relapse ($p<0.001$)
- Both in node positive and negative disease
- LVSI positive: 5-fold risk for N+ ($p=0.001$)
- Node negative: LVSI significant prognostic factor for relapse and survival

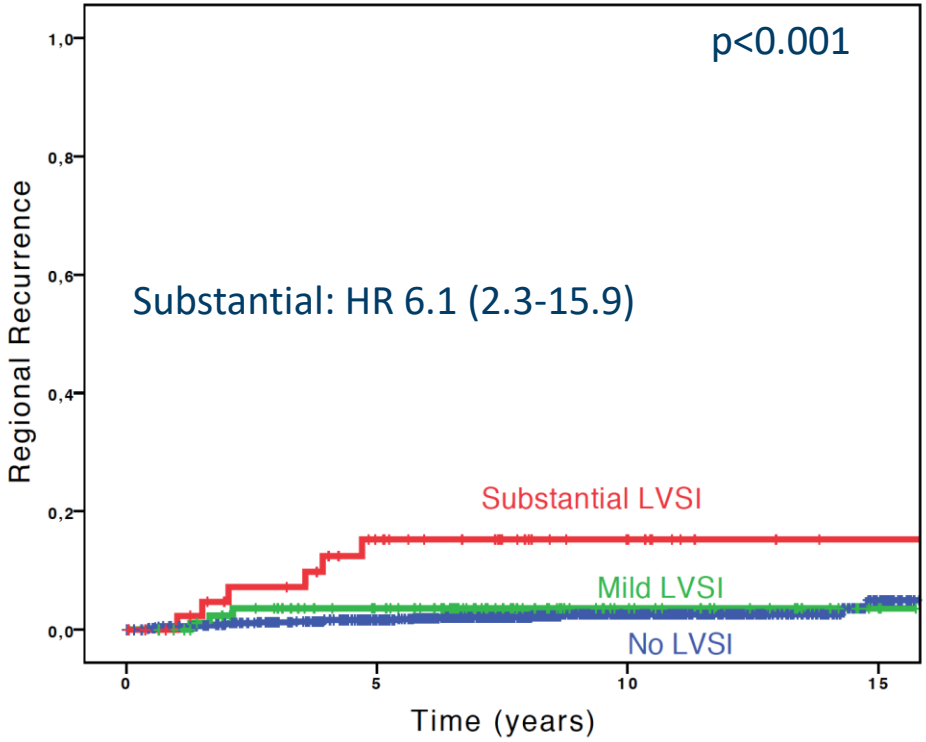
Briet, Gynecol Oncol 2005; Cohn, Gynaecol Oncol 2002; Narayan, Int J Gynecol Cancer 2011

Quatification of LVSI in PORTEC-1 and 2

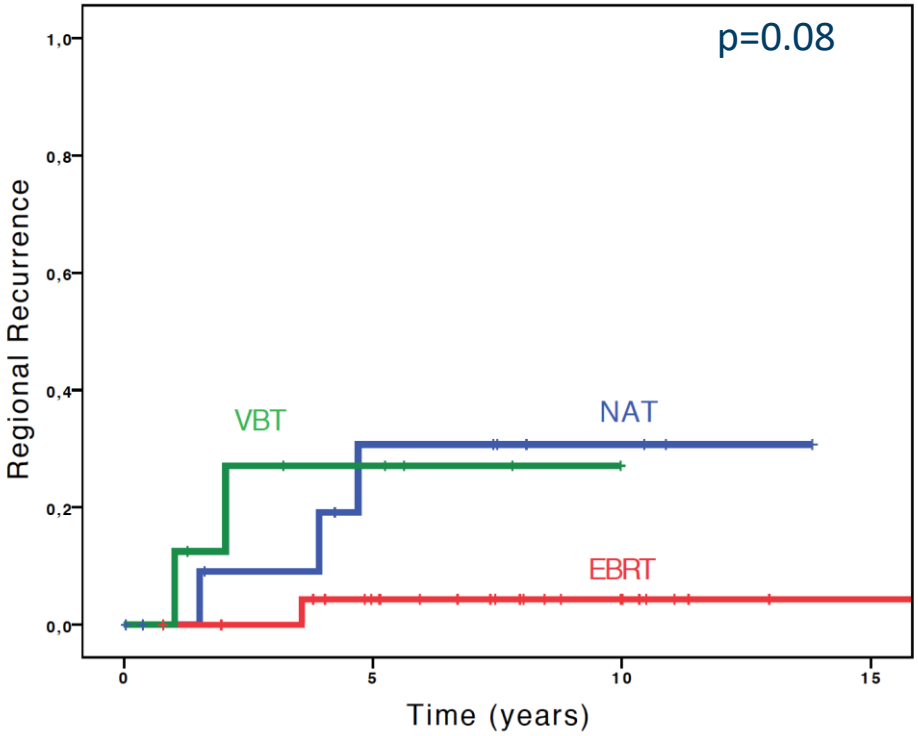
- Pelvic nodal recurrence

5%

All 954 patients



Substantial LVSI: 46 patients



Bosse, T. et al *EJC* 2015, Nout, R. *ASTRO* 2014

Q1: Current best definition of risk groups?

Risk Group	Description (FIGO 2009)	E
Low	• Stage IA Endometrioid + grade 1-2 + LVSI negative	1
Intermediate	• Stage IB Endometrioid + grade 1-2 + LVSI negative	1
High Intermediate	• Stage IA Endometrioid + grade 3, regardless of LVS • Stage I Endometrioid + grade 1-2 + LVSI unequivocally positive regardless of depth of invasion	1 2
High	• Stage IB Endometrioid + grade 3, regardless of LVSI status • Stage II & stage III with no residual disease • Non endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed >10%)	1 1 1
Advanced Metastatic	• Stage III with residual disease & IVA • Stage IVB	1 1

No RT

VBT

Pelvic IMRT

Endometrial Cancer Consensus: Adjuvant Treatment

ESMO ESGO ESTRO European Society for RADIOTHERAPY & ONCOLOGY

Colombo N. et al *Ann of Oncology* 2015

Chemotherapy in the treatment of Cervical Cancers

Umesh Mahantshetty

Professor,

Department of Radiation Oncology

&

GYN Disease Management Group Member

Tata Memorial Hospital, Mumbai, India

Objectives

- To understand the role of chemotherapy in the management of locally advanced cervical cancer

- To learn from the most important clinical series the real benefit of chmeotherapy

Chemotherapy Schemes

- **Neo - adjuvant Chemotherapy:**
  - **NACT followed by RT Vs RT**
  - **NACT followed by Sx Vs RT**
  - **NACT followed by Sx Vs Sx**
  - **NACT followed by Sx Vs Chemo-RT**
- **Concomitant Chemo-radiation (Radiosensitizing CT)**
- **Adjuvant CT / Neo-adjuvant CT followed by CTRT**
- **Palliative Chemotherapy including targetted therapy in recent era**

PERGAMON

European Journal of Cancer 39 (2003) 2470–2486

European Journal of Cancer

www.ejconline.com

Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials

Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration*,1

- Individual patient data from 23 trials
- Two comparisons:
  - *Comparison 1* – NACT followed by RT Vs RT alone
  - *Comparison 2* – NACT followed by Sx Vs RT

Tierney J, et al.

Comparison 1

NACT followed by RT Vs RT

- 18 trials
- N = 2074
- 92% of patients from all eligible trials
- Survival data available from all trials
- Median FU – 5.7 years
- 70% pts had stage II or III disease
- Lymph node status unknown in 60%

Comparison 1

NACT followed by RT Vs RT

Table 3
All endpoints in comparison 1

Endpoint	Number of events/patients	Hazard ratio (95% CI), *P* value	Heterogeneity *P* value
Survival	1084/2074	1.05 (0.94–1.19), 0.393	0.0003
Disease-free survival	938/1724	1.00 (0.88–1.14), 1.000	0.001
Loco-regional disease-free survival	911/1724	1.03 (0.90–1.17), 0.654	0.0002
Metastases-free survival	899/1724	1.00 (0.88–1.14), 1.000	0.002

- Significant heterogeneity among the trials
- It may be inappropriate to combine the trials
- Trials divided in two ways:
  - Cycle interval (> 14 d Vs ≤ 14 d)
  - Cisplatin dose intensity (< 25 Vs ≥ 25 mg/m2/wk)

Overall survival (OS) by frequency of chemotherapy and cisplatin dose intensity in comparison 1 [6]

Variable	Trials	HR (95% CI)	*p* value	Heterogeneity *p* value	5-year OS
Frequency of chemotherapy					
>14 days	11	1.25 (1.07–1.46)	0.005	0.23	↓8%
≤14 days	6	0.76 (0.62–0.92)	0.005	0.19	↑7%
Cisplatin dose intensity					
<25 mg/m^2	7	1.35 (1.11–1.64)	0.002	0.74	↓11%
≥25 mg/m^2	11	0.91 (0.78–1.05)	0.2	0.001	↑3%

- Chemotherapy may select radio-resistant clones due to cross resistance
- Longer cycle duration may lead to accelerated re-growth between cycles
- Dose dense and intensity : better outcome

Comparison 2

NACT followed by Sx Vs RT

- 5 trials
- N = 872
- Planned cycle interval = 10 - 21 days
- Cumulative cisplatin dose = 100 – 300 mg/m2
- RT similar across trials (EBRT 45-60 Gy & ICRT 25-40 Gy)
- One third pts had stage IB & 1/3rd stage II

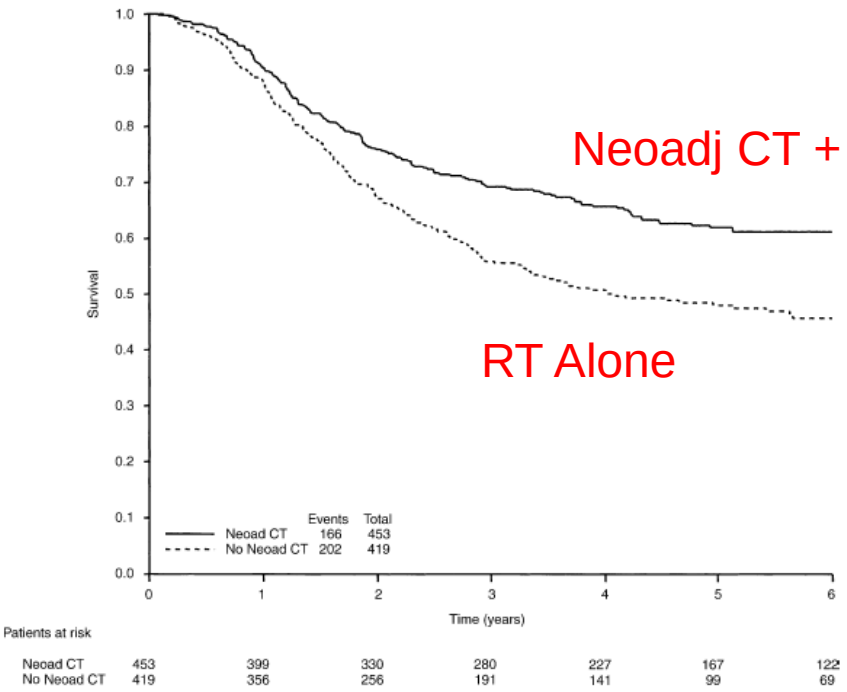


Fig. 5. Kaplan–Meier curves of overall survival in comparison 2. Neoad CT, neoadjuvant chemotherapy.

Neoadj CT + Sx +/ - RT

RT Alone

Caveats

- No of pts/events (872/368):small
- A large fraction of pts in the surgical group received RT
- The RT dose was suboptimal by current standards
- Chemo regimens were not ‘modern’
- There was lack of concurrent chemo in the RT group

NeoAdj CT + Sx Vs Sx alone

[Intervention Review]

Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Larysa Rydzewska[1], Jayne Tierney[1], Claire L Vale[1], Paul R Symonds[2]

[1]Meta-analysis Group, MRC Clinical Trials Unit, London, UK. [2]Department of Oncology, Leicester Royal Infirmary, Leicester, UK

Contact address: Larysa Rydzewska, Meta-analysis Group, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA, UK. lhr@ctu.mrc.ac.uk.

- 6 trials, 1072 pts
- PFS available in all trials (1036)
- OS, resection rates, path response available in 5 trials (909-938 pts)

Cochrane – NACT + Sx Vs Sx

- Use of post-op RT was balanced in the two arms
- 3 trials used high cisplatin dose intensity and 3 used lower intensity
- Chemotherapy drugs
  - Cisplatin
  - Bleomycin
  - Vincristine
  - 5-FU
  - Mitomycin

Cochrane – NACT + Sx Vs Sx

- NACT favorably impacted (or trended in that direction) on many outcome measures like resection rates, pathological characteristics and PFS
- There was a lack of convincing benefit in OS
- Chemotherapy may add benefit to surgery!

Neoadjuvant Chemotherapy + Surgery versus Concurrent Chemoradiation Therapy in Stage IB2 / IIB Squamous Carcinoma of Cervix

Neo-adjuvant Chemotherapy + Surgery

Versus

Concurrent Chemo-radiation (STD)

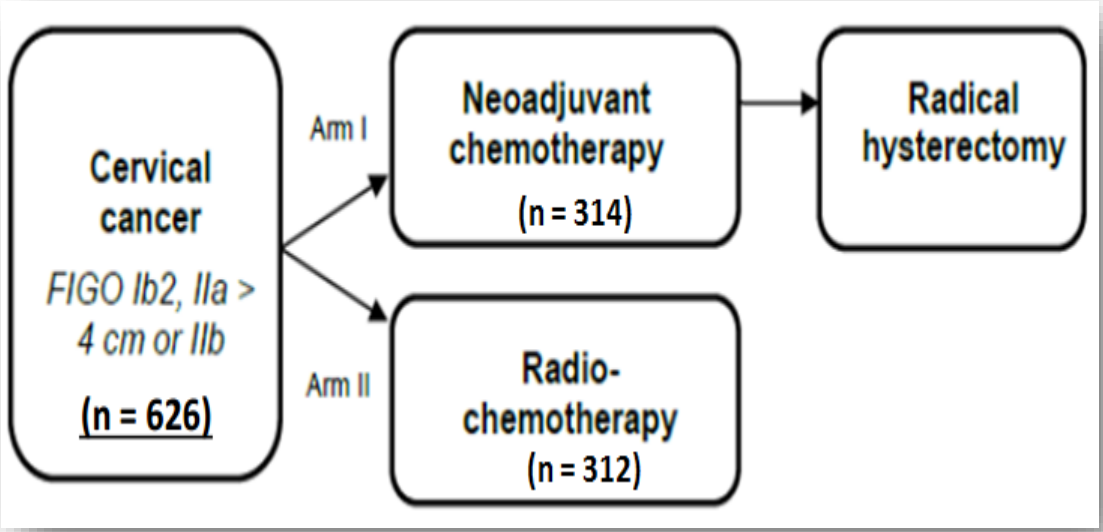
in Stage IB2 / IIB Squamous Carcinoma of Cervix

EORTC – 55994 STUDY

TMH NACT STUDY

EORTC Trial # 55994:
Randomized phase III study of neoadjuvant chemotherapy followed by surgery vs. concomitant radiotherapy and chemotherapy in FIGO Ib2, IIa > 4 cm or IIb cervical cancer.

- Largest multi-centric randomized trial in cervical cancer comparing NACT followed by radical hysterectomy directly with CCRT



Primary endpoint:

- Overall survival at five years

Secondary endpoints:

- Overall survival
- Progression free survival
- Toxicity
- Quality of life

Stratification: Institution; FIGO stage; age (18-50; 51-75); histological subtype (adenomatous vs non-adenomatous)

Completed recruitment in June 2014

Final Analysis: 2019

Short term toxicity & preliminary data on the surgical arm are out.

Results:

- **238 (76%)** patients underwent surgery in NACT arm.
- **54 patients** didn't undergo surgery after NACT due to
  - 23 patients (7.3%)- Treatment-related toxicity
  - 17 patients (5.4%)- Progressive disease
  - 14 patients (4.5%)- insufficient response to chemotherapy
- Pathological examination showed: parametrial invasion in 49 (20.6%), vascular invasion in 57 (23.9%), positive surgical margins in 32 (13.4%), peri-nodal spread in 19 (8.0%), pelvic lymph node metastases in 66 (27.7%), metastatic common iliac lymph nodes in 22 (9.2%) and para-aortic nodes in 7 (2,6%) patients.
- Pathological complete response was found in 53 patients (22.3%).

EORTC GCG 55994

Randomized phase III study of neoadjuvant CT followed by surgery vs. concomitant RTX+CT in FIGO stage Ib2, IIa > 4 cm or IIb cervical cancer.

Conclusions from preliminary data

- This is the largest randomized trial in cervical cancer comparing NACT followed by radical hysterectomy with CCRT
- Short term safety is acceptable, mainly due to CT in both arms
- Discontinuation of protocol is high (**20-30%**)
- Pathological complete/ optimal response in NACT - arm = **37%**
- Complete response based on imaging in arm 2 = **49%**
- Adjuvant therapy in arm 1 for patients who underwent surgery = **27%**
- Survival data will follow **mid 2019**

Abstract No. 3395 / 928O_PR

Neoadjuvant chemotherapy followed by surgery versus concomitant cisplatin and radiation therapy in patients with stage IB2, IIA or IIB squamous carcinoma of cervix: A randomized controlled trial

Sudeep Gupta, M.D., on behalf of

Pallavi Parab, Rajendra Kerkar, Umesh Mahantshetty, Amita Maheshwari, Supriya Sastri, Reena Engineer, Rohini Hawaldar, Jaya Ghosh, Seema Gulia, Swati Godbole, Neha Kumar, Malliga Jeyaraman, Renuka Dalvi, Yogesh Kembhavi, Madhuri Gaikar, Rohit Ranade, Hemant Tongaonkar, Rajendra Badwe and Shyam Shrivastava

Gynecologic Oncology Group, Tata Memorial Centre, Mumbai

MADRID 2017 ESMO congress

Funded by Tata Memorial Centre, Government of India

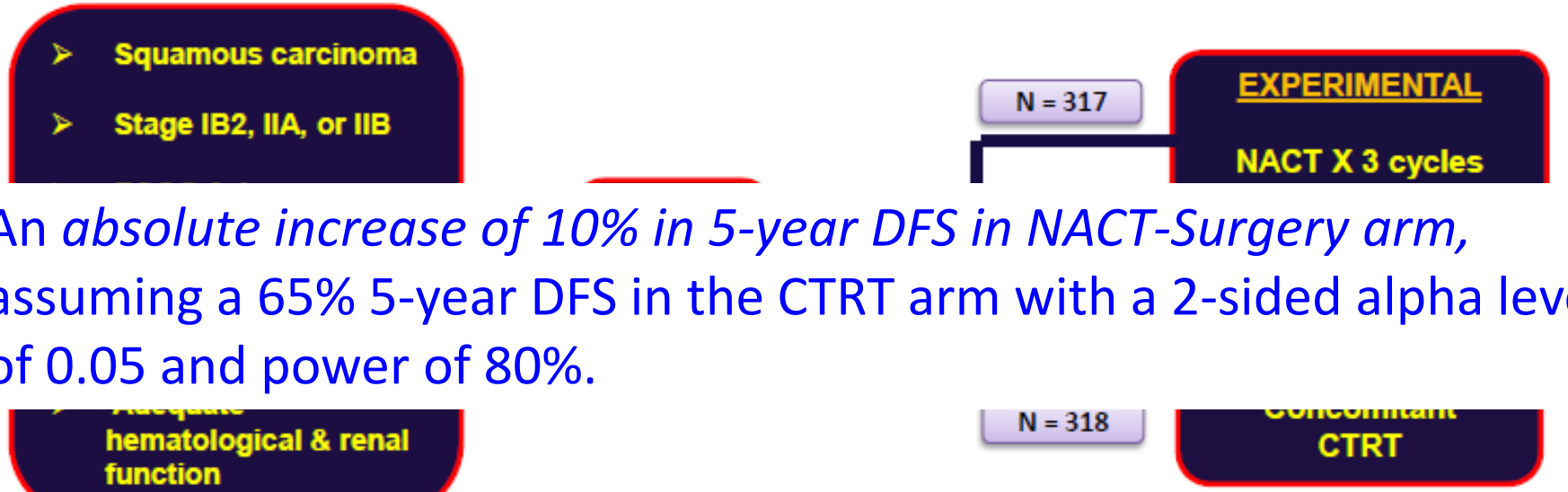
ESMO PLENARY PRESENTATION - 2017

Gupta et al; JCO Feb 2018

ESMO PLENARY PRESENTATION – 2017

TMH NACT STUDY

Study Design



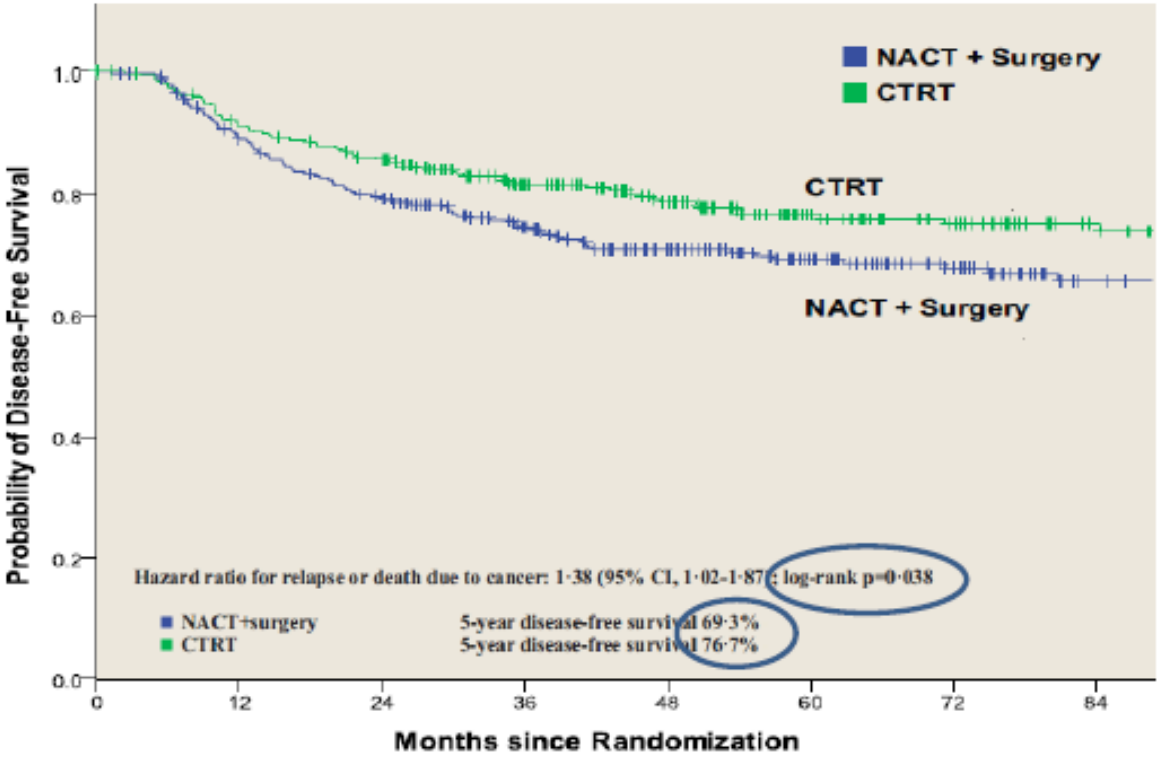
An *absolute increase of 10% in 5-year DFS in NACT-Surgery arm,* assuming a 65% 5-year DFS in the CTRT arm with a 2-sided alpha level of 0.05 and power of 80%.

- **Neoadjuvant chemotherapy**
  Paclitaxel (175 mg/m2) + Carboplatin: (AUC 5-6) every 3 weeks X 3 cycles
- **Concomitant chemotherapy**
  Cisplatin (40/m2/week) X 5 weeks
- **Radiotherapy**
  EBRT: 40 Gy/20 fr/5 weeks + BRT (HDR 7Gy/5 appl or LDR 30 Gy/2 appl)

ESMO PLENARY PRESENTATION – 2017

TMH NACT STUDY

Disease-free survival in intention-to-treat population



No. at Risk								
NACT+Surgery	316	266	233	192	152	114	84	54
CTRT	317	282	261	210	167	116	85	60

Gupta et al; JCO Feb 2018

ESMO PLENARY PRESENTATION – 2017
TMH NACT STUDY

CONCLUSIONS

- Our hypothesis of improved outcomes with NACT-surgery was not proven.
- Concomitant chemoradiation with weekly cisplatin resulted in significantly higher DFS compared with neoadjuvant chemotherapy followed by radical surgery in patients with locally advanced squamous cervical cancer.
  - ✓ The main benefit of CTRT was in stage IIB patients

Gupta et al; JCO Feb 2018

ESMO PLENARY PRESENTATION – 2017
NACT STUDY - TMH

CONCLUSIONS...

- Neoadjuvant chemotherapy and surgery should not be routinely practiced.

- Concomitant chemoradiation should be the standard of care in locally advanced cervical cancer.

Gupta et al; JCO Feb 2018

Rationale for chemo-radiation

1. **Additive effects**

   - Enhanced cell death through cytotoxic DNA cross-links

2. **Synergistic effects**

   - Inhibition of repair of radiation induced damage

   - Promote synchronization of cells into a radiosensitive phase

   - Initiating proliferation in non-proliferating cells

   - Hypoxic cell sensitization and reducing fraction of hypoxic cells

3. **Independent effect**

   - CT may independently increase the rate of death of tumour cells

RATIONALE FOR CONCURRENT CHEMO-RADIATION

- Increased tumor cell kill without delaying the course of RT or protracting the overall treatment time

- Synergistic action with RT
  - potentiates the sub-lethal damage
  - inhibits the DNA damage repair induced by RT

RADIOSENSITIZING CT AGENTS

- HYDROXYUREA
- 5 FLUROURACIL
- CISPLATIN
- CARBOPLATIN
- VINCRISTINE
- ETOPOSIDE
- BLEOMYCIN
- PACLITAXEL
- MITOMYCIN

New Generation CT agents: Gemcitabine, Capecitabine, Targetted therapy etc.

Cisplatin: CT in a dose of 40 - 50 mg/m2 or 50 - 70 mg/m2 three weekly

Phase III trials with concurrent chemo-radiotherapy in stage IB2-IVa CERVICAL CANCER:

Dose of Cisplatin/m2

- **GOG 85** : **Cisplatin 50 mg day 1, 29 + FU infusion**
- **GOG 120** : **Cisplatin 50 mg day 1, 29 + FU infusion +HU**
- **GOG 120** : **Cisplatin 40 mg weekly**
- **GOG 123** : **Cisplatin 40 mg weekly**
- **SWOG8797/GOG 109** : **Cisplatin 70 mg day 1, 22 + FU infusion**
- **RTOG 9001** : **Cisplatin 70 mg day 1, 22 + FU infusion**
- **NCIC** : **Cisplatin 40 mg, weekly**

RCT on Chemoradiation

Study group	No. of Pts	Overall survival (%) CCRT vs control	P-value	Follow-up
GOG 85	388	65 vs 51 (5y)	0.018	104mo
GOG 120	526	66 vs 50 (3y)	0.004	35mo
		67 vs 50 (3y)	0.002	
GOG 123	369	83 vs 74 (3y)	0.008	36mo
SWOG 8797	268	81 vs 71 (4y)	0.007	42mo
RTOG 9001	388	73 vs 52 (5y)	< 0.001	43mo
NCIC	253	62 vs 58 (5y)	0.53	82mo

(Whiteney et al, JCO, 1999. Rose et al, NEJM, 1999. Keys et al, NEJM, 1999. Peters et al, JCO, 2000. Morris et al, NEJM, 1999. Pearcy et al, JCO 2002)

NATIONAL CANCER INSTITUTE
CLINICAL ANNOUNCEMENT

'CONCURRENT CHEMO-RADIATION
FOR
CERVICAL CANCER'

in February 1999

"Five major randomized phase III trials show that platinum based chemo when given concurrently with RT prolongs survival in women with locally advanced cervical cancer stages Ib2 - IVa as well as in women with stage I / IIa found to have metastatic pelvic lymph nodes, positive parametrial disease and positive surgical margins at the time of primary surgery "

NCIC Trial : 6th RCT

Median follow-up: 82 months

Stage IB2 and IIA (5 cm in diameter), IIB, IIIB, IIIA, and IVA (< 5cm if LN + ve)			
Randomization		**CT+RT (CDDP) 127 pts**	**RT alone 126 pts**
OS	**3 yrs**	**69%**	**66%**
	5 yrs	**62%**	**58%**
	HR	**1.13 (95% CI 0.77 to 1.67)**	**P=0.42**

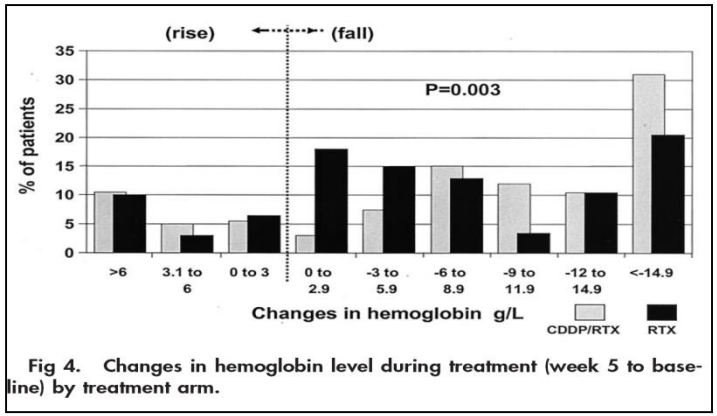


Fig 4. Changes in hemoglobin level during treatment (week 5 to baseline) by treatment arm.

Conclusions:

The best results are certainly achieved by careful attention to RT details, including dose and overall delivery time, the use of ICBT whenever possible, and probably the addition of concurrent CDDP CRT

Approximately 53% of patients on the CRT regimen had decreases in their hemoglobin levels of 9 g/L or more.

Pearcey et al JCO 2002

VOLUME 26 · NUMBER 35 · DECEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration

THE CHEMORADIATION FOR CERVICAL CANCER META-ANALYSIS COLLABORATION- (CCCMAC)

MEDICAL RESEARCH COUNCIL CLINICAL TRIALS UNIT- UK

JCO December 2008

REDUCING UNCERTAINTIES ABOUT THE EFFECTS OF CHEMORADIATION FOR CERVICAL CANCERS: SYSTEMATIC REVIEW AND META-ANALYSIS

OVERALL SURVIVAL AND DISEASE FREE SURVIVAL

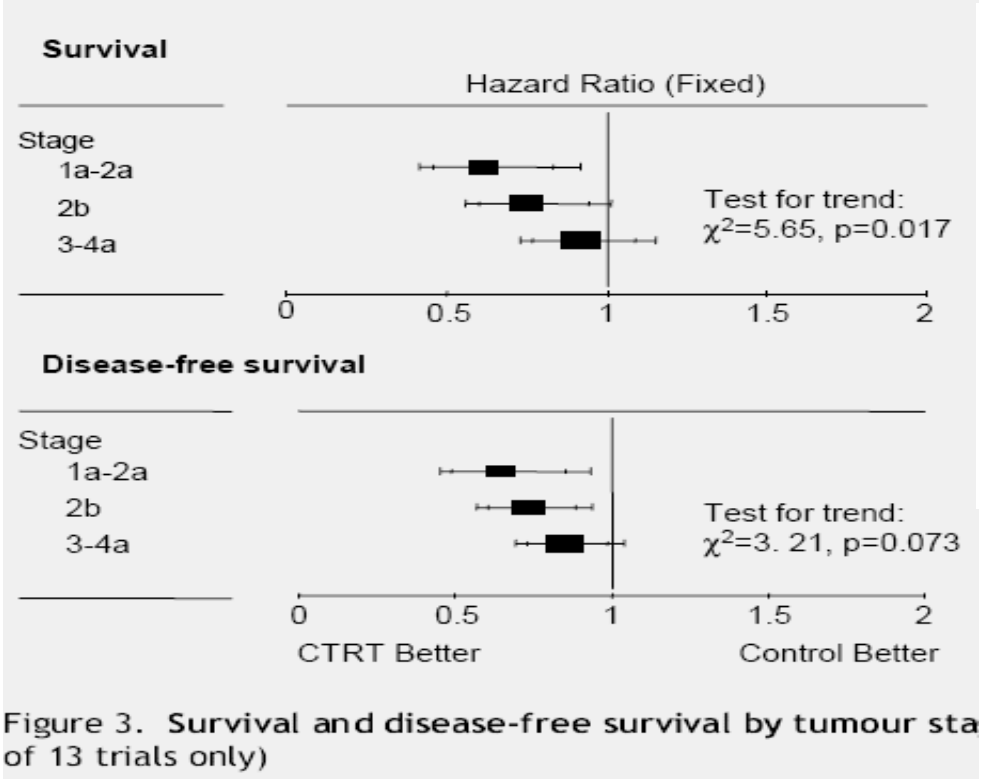
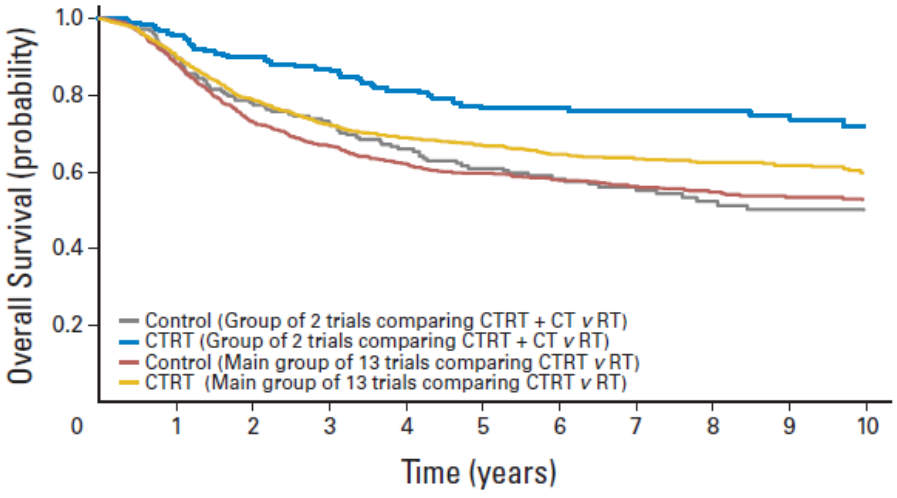


Figure 3. Survival and disease-free survival by tumour sta
of 13 trials only)



Adjuvant CT after CRT needs to be explored further

There was however the suggestion of a decreasing relative effect of chemo-radiation on survival with increasing tumor stage, with estimated absolute survival benefits of 10% (stage1a-2a), 7% (stage 2b) and

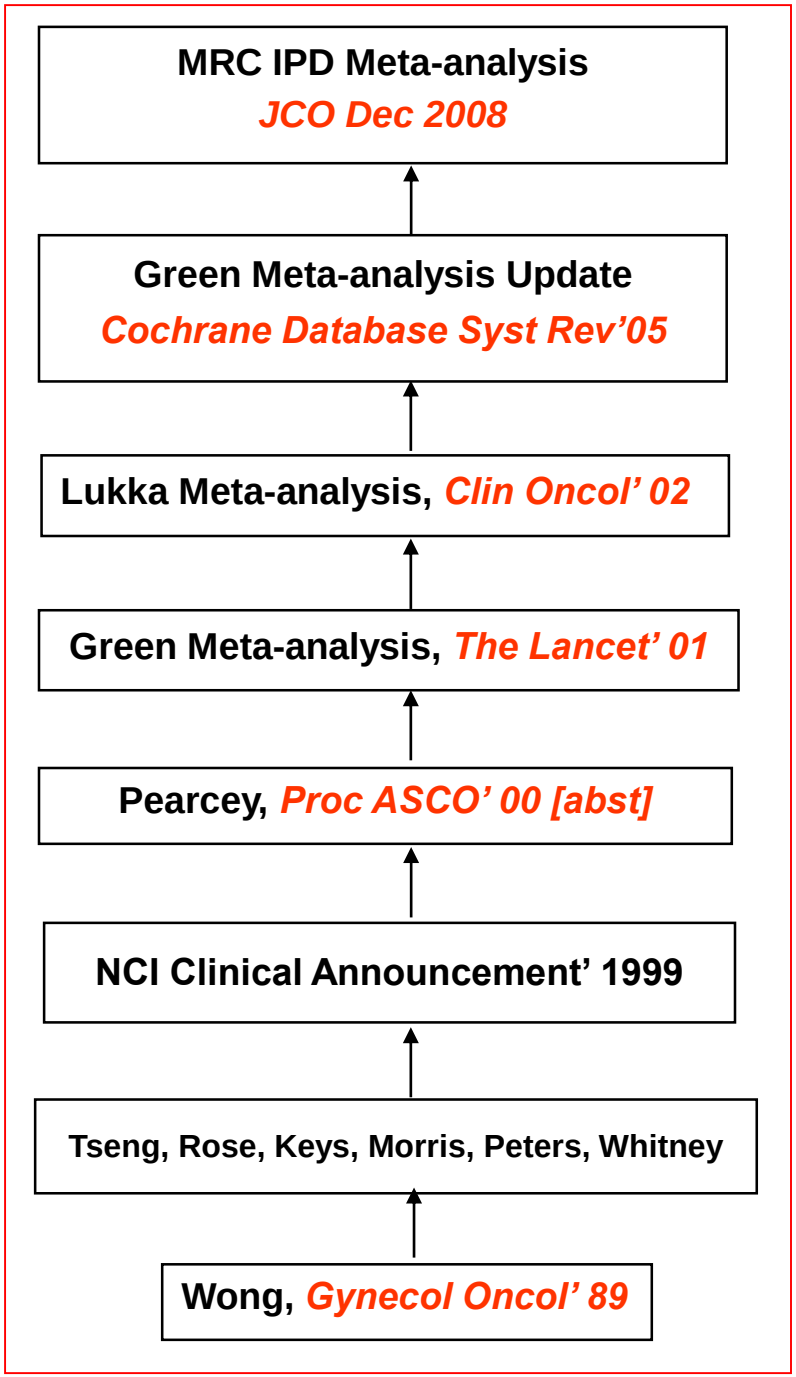
3% (stage 3-4a) at 5-years

JCO Dec '08

A Systematic Review and Meta-analysis
J. A Green - Confessions

- In our review, 68% of patients overall were stage I and II;
- Although an overall reduction in the risk of death with chemo-radiotherapy was shown, ***Gillian Thomas*** advised

"*caution in extrapolation of the results to advanced stages.* Our exploratory analysis *shows less benefit* and *more heterogeneity* in studies with a high proportion of advanced-stage patients than in those with a low proportion of such patients"



CRITICAL REVIEW OF EVIDENCE : IIIB Disease

- Heterogenous patient data
- Suboptimal Radiotherapy Schedules Used
- Non-uniform use of CT drugs and Sequencing
- QOL issues : Unknown
- Cost effectiveness in India including developing countries ? due to
  - Advance Disease at presentation
  - Poor nutritional status (anemia) & low compliance rates
  - inadequate supportive therapy & financial constraints
- Sparse literature from developing countries

*Shrivastava SK et al: JCRT 2013
**Five randomized trial & NCI Alert:1999
** Green JA et al Lancet :2001
** Lukka et al, Clinical Oncology 2002

PLENARY PRESENTATION

Abstract Number: ESGO7-1305

Cisplatin Chemo-radiation Versus Radiation in FIGO Stage IIIB Squamous Cell Carcinoma of the Uterine Cervix - A Phase III Randomized Trial (CRACx Trial: NCT00193791)

U. Mahantshetty, *Professor in Radiation Oncology*

SK Shrivastava, R. Engineer, S. Chopra, R. Havaldar, V. Hande, R. Kerkar, A. Maheshwari, T. Shylasree, J. Ghosh, J. Bajpai, L. Naidu, S. Gulia, S. Gupta

on behalf of

Gynecologic Oncology Disease Management Group, Tata Memorial Centre, India

Funded by Tata Memorial Centre, Government of India

ESGO 20 INTERNATIONAL MEETING OF THE EUROPEAN SOCIETY OF GYNAECOLOGICAL ONCOLOGY (ESGO)
NOVEMBER 04-07, 2017 | VIENNA, AUSTRIA
European Gynaecological Oncology Congress 2017

STUDY DESIGN

Open label phase randomized III Trial

INCLUSION CRITERIA

- ✓ FIGO Stage IIIB
- ✓ SQ CA histology
- ✓ Age > 18 years & < 65 years
- ✓ WHO perf. Status : 0 or 1
- ✓ Hemoglobin ≥ 10 gm %
- ✓ Normal blood counts
- ✓ Normal renal functions

Exclusion Criteria

- ✓ Bilateral HN
- ✓ HIV positive
- ✓ Medical Renal Disease
- ✓ Gross PA nodes on Imaging

1 : 1 randomization

N = 424 → **STUDY ARM**

Concomitant Chemo-radiation
(Cisplatin weekly 40 mg/m2 for 5 cycles atleast)

N = 426 → **STANDARD ARM**

Definitive Radiation

Definitive Radiation:

- **External Beam : 50 Gy / 25 # (MLB at 40 Gy when ever feasible)**
- **Brachytherapy : LDR (25- 30 Gy to point 'A' 1#) or HDR (7 Gy to point 'A' x 3# once weekly)**
- **Total RT (Physical) Doses : 76 Gy – 81 Gy (LDR Equivalent) to Point 'A' ***

* *Orton et al ; Int J Radiat Oncol Biol Phys. 1991*

STUDY END POINTS

- **Primary Endpoint: Disease free Survival (DFS)**

  - *Definition of Event: Cervical cancer recurrence (any) or death whichever was earlier*

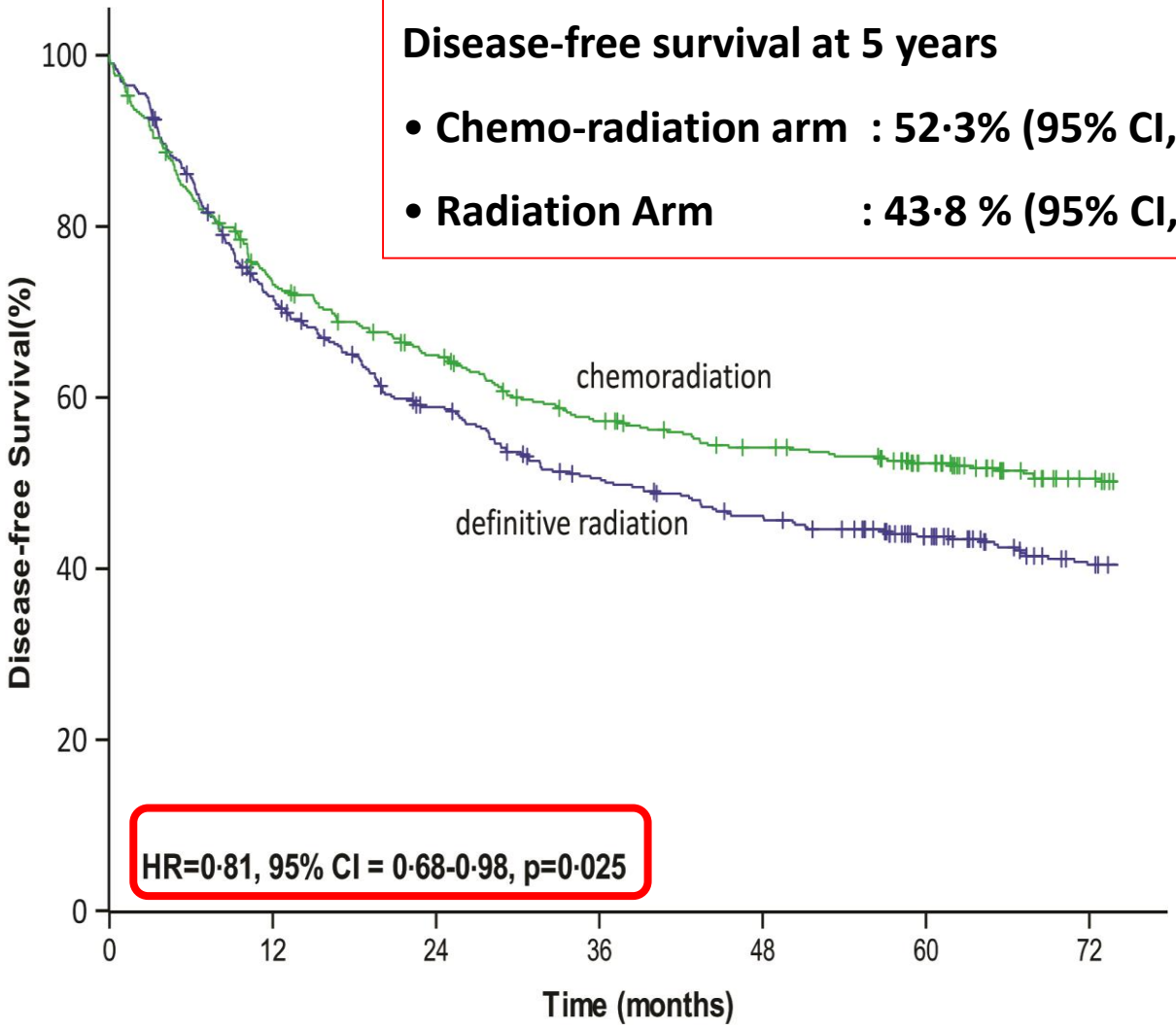
- **Secondary End Points:**

  - *Overall Survival and Toxicities*

Disease free Survival by Arms: ITT Analysis

Disease-free survival at 5 years

- **Chemo-radiation arm : 52·3% (95% CI, 52.25 – 52.35)**
- **Radiation Arm : 43·8 % (95% CI, 43.75 – 43.85)**



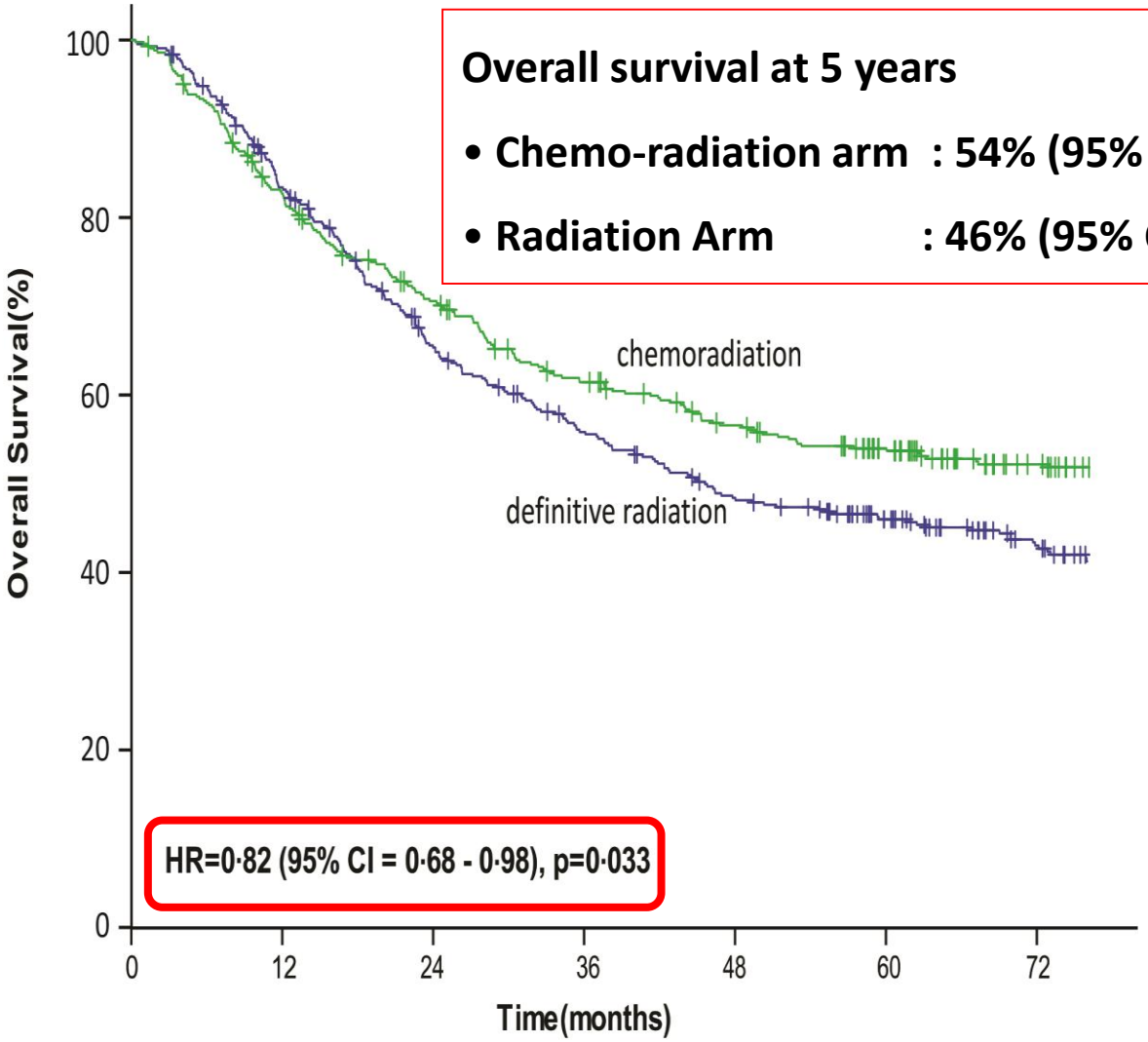
chemoradiation	424	305	265	228	208	188	157
definitive radiation	426	298	236	197	177	147	117

JAMA Oncol. Feb 2018

Overall Survival by Arms: ITT Analysis

Overall survival at 5 years

- **Chemo-radiation arm : 54% (95% CI, 53.95 – 54.05)**
- **Radiation Arm : 46% (95% CI, 45.95 – 46.05)**



chemoradiation	424	345	289	246	219	194	161
definitive radiation	426	347	264	220	187	157	125

JAMA Oncol. Feb 2018

PATTERNS OF FIRST FAILURE BY TWO ARMS

	Chemo-radiation ARM (N = 424)	Radiation Alone ARM (N = 426)
Overall Loco-regional	**90 (21·2%)**	**94 (22·1%)**
Local Only	66	68
Regional Only	16	18
Loco-regional	08	08
Distant only	**58 (13·7%)**	**69 (16·2%)**
Para-aortic	12	13
Lung only	16	18
Liver only	08	08
Bone	06	12
Left Supralavicular node	04	06
Combined /others like brain	12	12
Overall Loco-regional + Distant metastases	**31 (7·3%)**	**43 (10·1%)**
local +distant metastasis	09	14
Regional + distant metastasis	15	20
Loco-regional + distant	07	09
Secondary malignancy	01 (0·2%)	01 (0·2%)

Overall loco-regional and distant metastasis were lower by 5-6% in Chemo-radiation Arm

Acute & Late Toxicities by Arms

	Chemo-radiation ARM (N = 424)		Radiation Alone ARM (N = 426)	
Acute Toxicities	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Gastro-intestinal	-	37(8·7%)	-	24 (5·6%)
Genito-urinary	-	124(29%)	-	119 (27·9%)
Skin	-	141(33·2%)	-	149(35%)
Hematological				
Anemia	351 (82·7%)	24 (5·7%)	341 (80%)	22 (5·5%)
Leucopenia	214 (50·4%)	**19 (4·5%)**	75 (17·6%)	**03 (0·7%)**
Neutropenia	80 (18·8%)	**6 (1·5%)**	23 (5·4%)	**01 (0·2%)**
Thrombocytopenia	108 (25·4%)	04 (0·9%)	46 (10·8%)	02 (0·5%)
Deranged serum creatinine levels	143 (33·7%)	05 (1·2%)	94 (22·1%)	04 (1%)
Late toxicities				
Recto-sigmoid Bleeding proctitis/ Ulceration / Stricture /Fistula	-	**29 (6·8%)** 21 / 05 / 02 / 01	-	**19 (4·4%)** 09 / 07 / 01 / 02
Bladder **T**elangiectasia / Vesico-vaginal fistula	-	**08 (2%)** 08 / 00	-	**12 (2·8%)** 11 / 01 (due to recurrence)

CONCLUSIONS

- **Our hypothesis of benefit of cisplatin based concomitant chemo-radiation in FIGO Stage IIIB is proven**
- **Concomitant cisplatin based chemo-radiation resulted in signficantly improved disease free & overall survivals with an absolute benefit of 8.5 % and 8% respectively in FIGO Stage III B (Squmaous cell carcinoma) Cervical Cancer**

JAMA Oncol. Feb 2018

CONCLUSIONS contd..

- **Our study is the largest trial in a homogenous group of advanced stage (IIIB) cervical cancer to prove the benefit of relatively simple and well tolerated concomitant cisplatin chemotherapy regimen over adequately delivered radiation therapy.**

Our study confirms that concomitant weekly ciplatin based chemo-radiation should be the standard of care in FIGO Stage IIIB Squamous Cell Cervical Cancer

JAMA Oncol. Feb 2018

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 3, pp. 824–829, 2005

0360-3016/05/$–see front matter

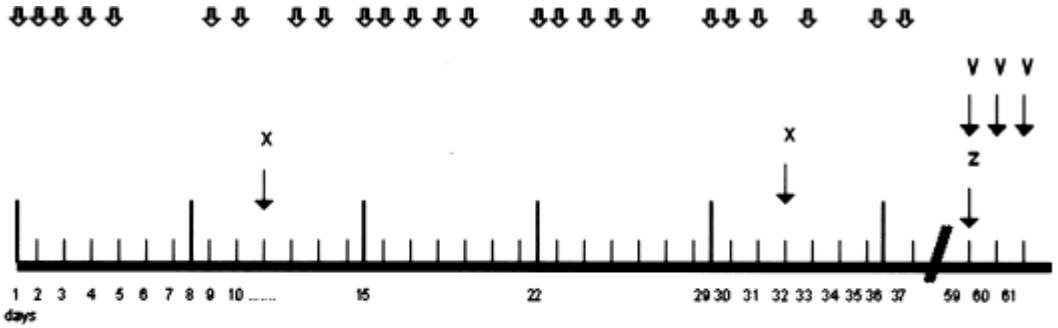
Concomitant Chemobrachytherapy

doi:10.1016/j.ijrobp.2004.06.248

CLINICAL INVESTIGATION **Cervix**

CONCOMITANT CHEMOBRACHYRADIOTHERAPY WITH IFOSFAMIDE AND CISPLATIN FOLLOWED BY CONSOLIDATION CHEMOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX: RESULTS OF A PHASE II STUDY

EDUARD VRDOLJAK, M.D., PH.D.,* TOMISLAV PRSKALO, M.D.,* TOMISLAV OMRČEN, M.D.,* KRISTINA SITUM, M.D.,* TIHANA BORASKA, M.D.,* NIVES FRLETA ILIĆ, M.D.,* STJEPAN JANKOVIĆ, M.D., PH.D.,* AND WOLFGANG HAMM, M.D.†



- external beam radiation 2 Gy
- x intracavitary brachytherapy 30 Gy to point A + Ifosfamide 2000 mg/m² + Cisplatin 75 mg/m²
- y Ifosfamide 2000 mg/m², q21d x 4
- z Cisplatin 75 mg/m², q21d x 4

- **Acute toxicities : High**
- **Grade ¾ Leuckopenia: 35%**
- **No phase III study**

Weekly versus tri-weekly Cisplatin

Randomized Clinical Trial Cisplatin-Based Chemotherapy Concurrent With Radiotherapy in the Treatment of Locally Advanced Cervical Cancer

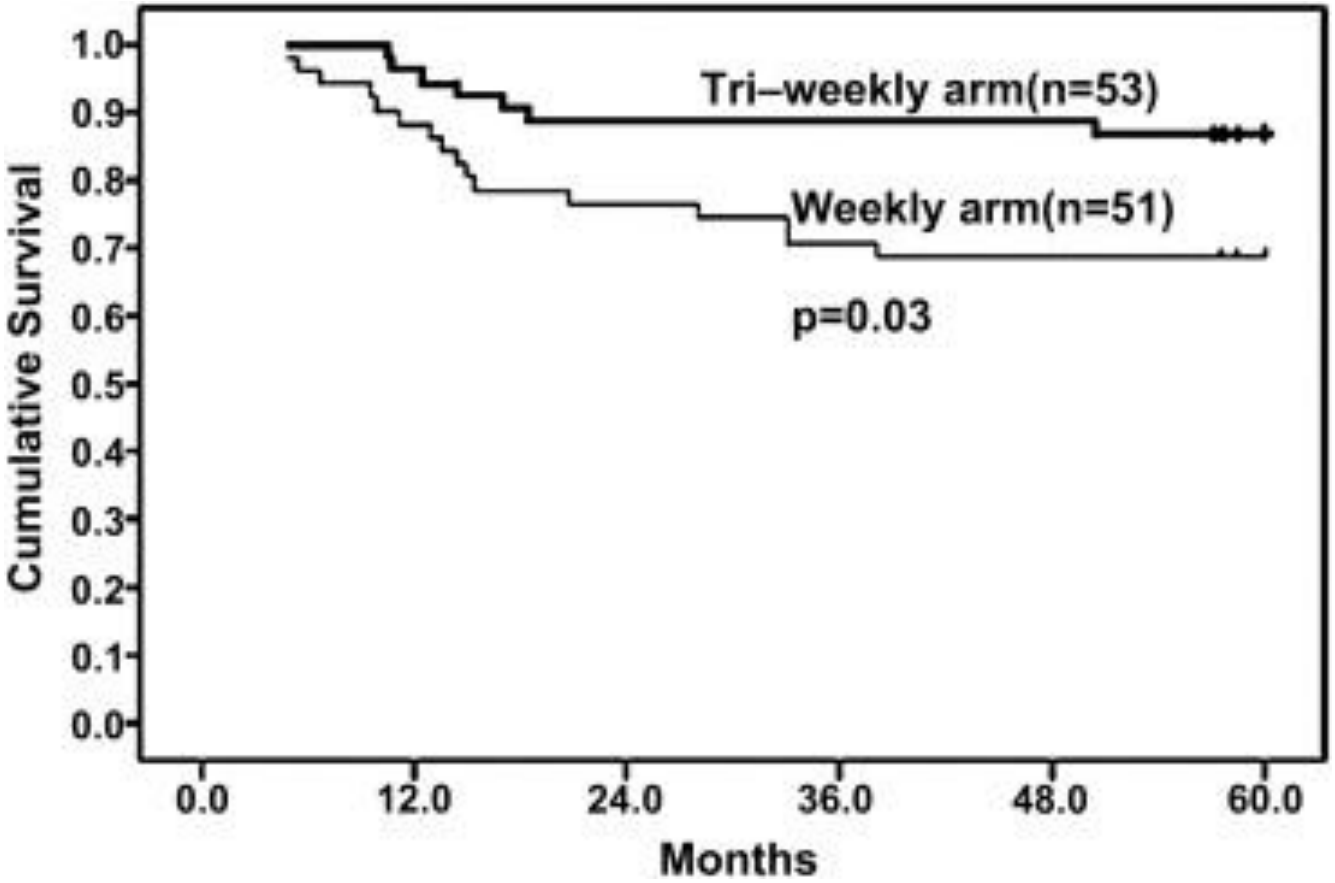


Fig. Kaplan-Meier estimates of survival difference between weekly and triweekly cisplatin-based chemoradiation in patients with locally advanced cervical cancer (taken from original article).

Int J Radiat Oncol Biol Phys 2011;81:e577–e581

Weekly Vs Tri-weekly Cisplatin: Meta-analysis

Concurrent Weekly Cisplatin Versus Triweekly Cisplatin with Radiotherapy in the Treatment of Cervical Cancer: A Meta-analysis Result

Yan Hu, Zhi-Qiang Cai, Xiao-Yan Su*

- Database between 1995 and 2011.
- 7 studies (6 RCT's and 1 retrospective study

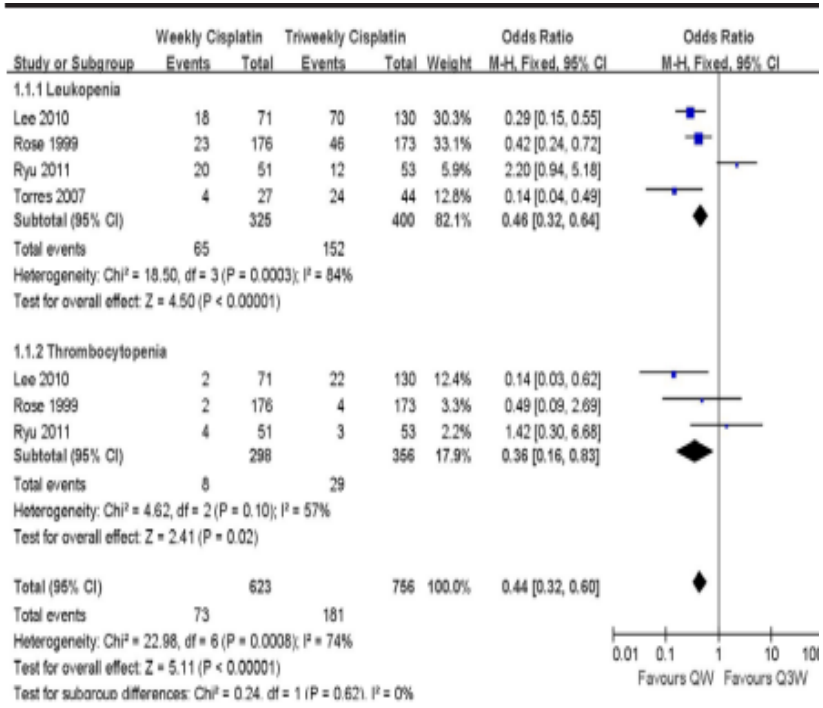
Author Year	Methods	Stage	N(QW/Q3W)	Concurrent Chemotherapy
Ryu 2011	RCT	IIIB-IVa	51/53	QW: Cisplatin 40mg/m^2, 6 cycles; Q3W: Cisplatin 75mg/m^2, 3 cycles
Lee 2010	Retrospective Study	IB-IIB	71/130	QW: Cisplatin 40mg/m^2, 6 cycles; Q3W: Cisplatin 75mg/m^2, 3 cycles Combined FU, Paclitaxel, etc
Kim 2007	RCT	IIB-IVa	77/78	QW: Cisplatin 30mg/m^2,6 cycles; Q3W: Cisplatin 20mg/m^2/d, 5d, 3 cycles combined FU 1gm/m^2/d, 5d
Rose 2007	RCT	IIB-IVa	176/173	QW: Cisplatin 30mg/m^2, 6 cycles; Q3W: Cisplatin 50mg/m^2, 2 cycles combined FU 4gm/m^2/96h, Hydroyurea 2gm/m^2,twice per week
Torres 2007	RCT	I-IV	27/55	QW: Cisplatin 40mg/m^2, 6 cycles; Q3W: Cisplatin 75mg/m^2, 3 cycles combined FU 4gm/m^2/96h
Kim 2005	RCT	IIB-IVa	27/34	QW: Cisplatin 30mg/m^2, 6 cycles; Q4W: Cisplatin 20mg/m^2/d, 5d, 3 cycles combined FU 1gm/m^2/d, 5d, 3 cycles
Rose 1999	RCT	IIB-IVa	176/173	QW: Cisplatin 30mg/m^2, 6 cycles; Q3W: Cisplatin 50mg/m^2, 2 cycles combined FU 4gm/m^2/96h, Hydroyurea 2gm/m^2, twice per week

Asian Pacific Journal of Cancer Prevention, Vol 13, 2012

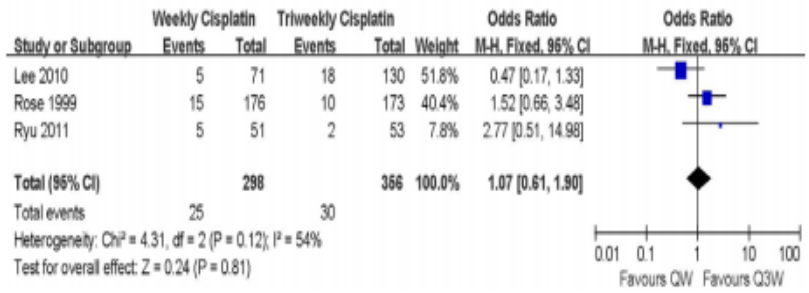
Results

Favorable toxicity

Hematological toxicity

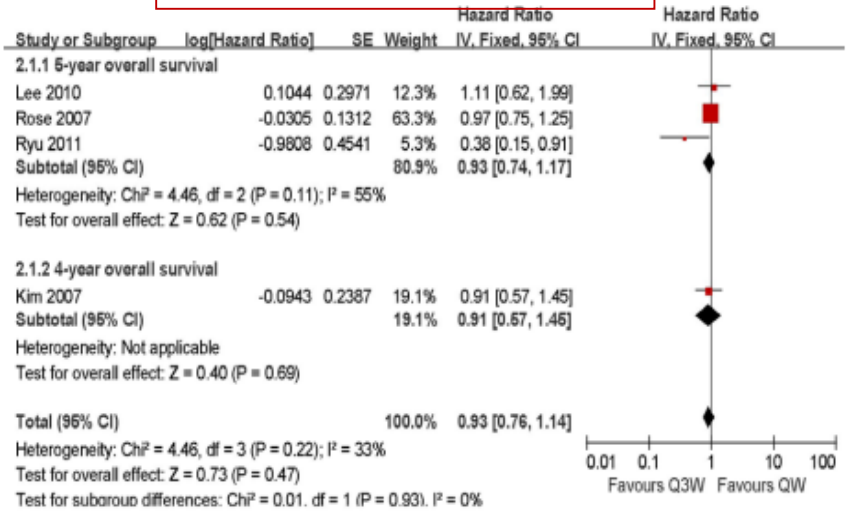


GI toxicity

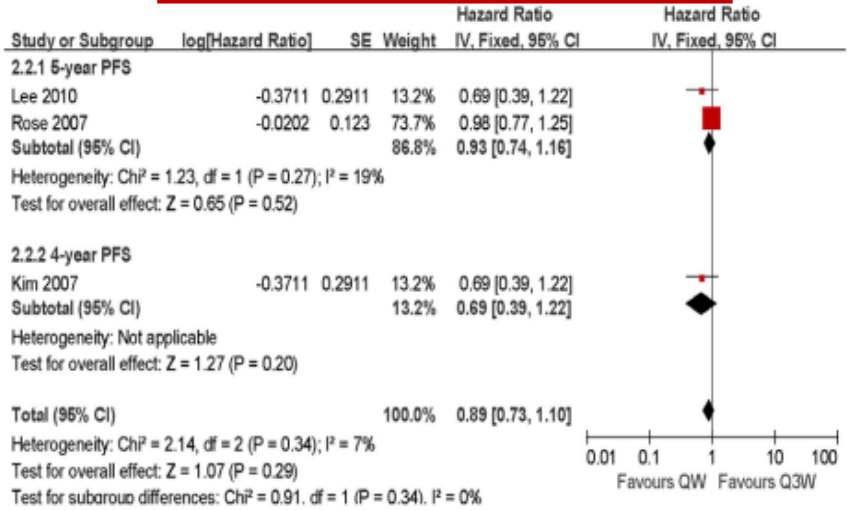


Equal effectiveness

Overall survival



Progression free survival



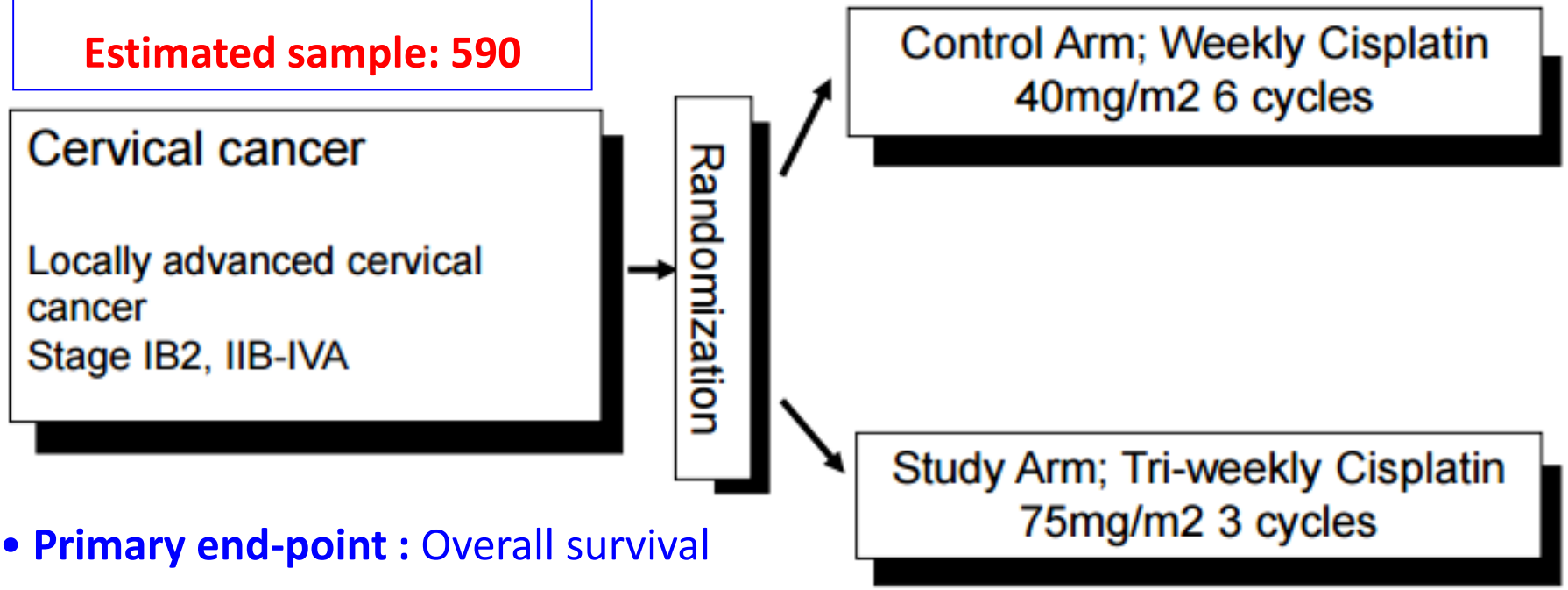
NCT01561586: A Phase III Randomized Trial
Korean GOG study

TACO

(Tri-weekly Administration of Cisplatin in LOcally Advanced Cervical Cancer)

Stage : 1B2 - IVA

Estimated sample: 590



- **Primary end-point :** Overall survival
- **Secondary end-points:** PFS, Toxicity, Compliance to radiation protocol, QOL.

Actual Study Start Date : March 2012
Estimated Primary Completion Date : March 2020
Estimated Study Completion Date : March 2023

OTHER RADIO-SENSITIZERS

- **CARBOPLATIN**

Higgins et al. Gynecol Oncol 2003

  - Fewer GI, renal and neuropathy than Cisplatin
  - Phase I/II studies - different schedules; wkly AUC 2 safe & active
  - Not compared in a phase III study with Cisplatin

- **PACLITAXEL**

Lee et al. Gynecol Oncol 2007

  - Phase II trial of paclitaxel / carbo with concurrent RT - 33 stage IB to IVB patients
  - RT + P (135 mg/m2) + Carboplatin (AUC 4.5) X 2/3 cycles, 4 wkly.

	Stage I-IIA	IIB	III	IV
3 yr DFS	67%	91%	88%	50%
3 yr OS	89%	91%	88%	50%

Concurrent Carboplatin based studies

Study	n	Carboplatin dose-schedule	CR n (%)	Med. FU (M)	DFS n (%)	Hemato. Gr 3–4
Corn, 1999	7	60mg/m2, weekly 3	3 (43)	-	-	-
Duenas-Gonzales, 2003	24	100, 116, 133, 150mg/m2, weekly	18 (75)	8		Leucopenia, Neutropenia
Higgins, 2003	31	60–90mg/m2, weekly	28 (90)	12	23 (74)	<2%
Muderspach, 1997	22	30–50mg/m2, twice a week	19 (86)	15	11 (50)	Aneamia 13.6%, Neutropenia 4.5%
Micheletti, 1997	12	12mg/m2, daily	9 (75)	20	LC-8 (66)	Leucopenia 8.3%
Dubay, 2004	21	300mg/m2, every 3 weeks	-	33	LC-16 (76)	Aneamia 9.5%, Neutropenia 9.5%
Veerasarn, 2007	235	100mg/m2, weekly	170 (72)	11.8	176 (75)	Leucopenia 2%, Neutropenia 2%

No randomized phase III study

OTHER RADIO-SENSITIZERS

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3 yr DFS	**67%**	**91%**	**88%**	**50%**
3 yr OS	**89%**	**91%**	**88%**	**50%**

OTHER RADIO-SENSITIZERS

CAPECITABINE

CAPECITABINE + RT Phase II results

TREATMENT SCHEDULE

- RADIOTHERAPY 45Gy and HDR 25 Gy VBT: 8 weeks
- CAPECITABINE(C) 825mg/m2; Monday-Friday, weeks1-8 + *Adjuvant CT (C) x 6 cycles1000mg/m2 bid D1-14

** In patients achieving response or stable disease after Chemo-radiotherapy*

- **N=60 Patients were treated (Median Follow/up: 18.3 months)**
- **Stage at diagnoses IIB: 58%;IIIA: 2%;IIIB: 40%**
- **Overall Responses Rates: 88.3% (95% CI:77.4-95.2)**
  - Complete Response: 80%
  - Partial Response: 8.3%
- **Percentage of patients without progression was:**
  - 86% (95% CI:77-95) at 12 months
  - 76% (95% CI:65-88) at 23 months

Domingo et al, J Clin Oncol 26, 2008(abst# 5513)

OTHER RADIO-SENSITIZERS

Topotecan

- sabotage repair of sublethal cell injury
- prevent HIF-regulated hypoxic cell survival.

- Dunton and coworkers (2002) maximal tolerance dose (MTD) with RT
  - 1 mg/m^2 daily for 5 days on days 1–5 and 22–26 concomitantly
  - Grade III anemia in one case
  - Grade II leukopenia in two cases
  - Dose limiting toxicity was not reached.
- Bell and associates (2001) Brachy with topiotecan
  - 0.5 mg/m^2.

- Ongoing: Weekly IV Topotecan and Cisplatin With Radiation in Cervical Carcinoma NCT00257816
  - University of california
  - 2004-9

OTHER RADIO-SENSITIZERS

GEMCITABINE

- **Phase I study: 19 patients. MTD not determined.**

Low toxicity profile and highly active (90% CR +PR)

(ASCO 2005, abstr 5142)

- **Randomized phase II: 65 patients stage IIB-IIIB**
  - RT and weekly cisplatin 35 mg/m2 or weekly gemcitabine 150 mg/m2.
  - Similar overall response rate and toxicity
  - Higher CR rate with gemcitabine

(ASCO 2007, abstr 16012)

- ***prompted for further trials especially with concurrent and adjuvant gemcitabine.***

Adjuvant / Neoadjuvnat Chemotherapy after Chemo-radiation

- Disease progression after radical radio-chemotherapy:35%
- Distant relapses are major in locally advanced cervical cancer

after radical Rx

- Adjuvant CT was part of few trials of Chemo-radiation
- No proper large study evaluating Adj. CT

VOLUME 29 · NUMBER 13 · MAY 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III, Open-Label, Randomized Study Comparing Concurrent Gemcitabine Plus Cisplatin and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Patients With Stage IIB to IVA Carcinoma of the Cervix

Alfonso Dueñas-González, Juan J. Zarbá, Firuza Patel, Juan C. Alcedo, Semir Beslija, Luis Casanova,

Women with Ca Cervix IIB – IV A with KPS >70% with no evidence of PA LN

Arm A (n= 259 pts)

CCRT + Brachytherapy + Adj. CT

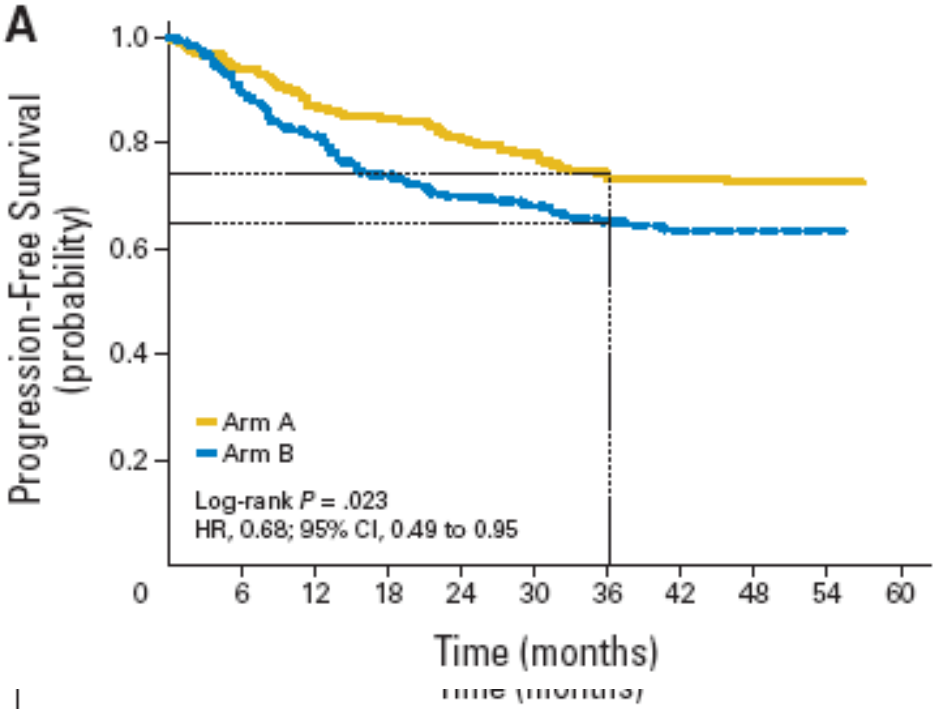
Concurrent Chemo - Weekly Cis 40 mg/m2
+ Gemcitabine 125mg/m2
Adjuvant chemo -2 weeks after brachy
Cisplatin and Gemcitabine 2 cycles

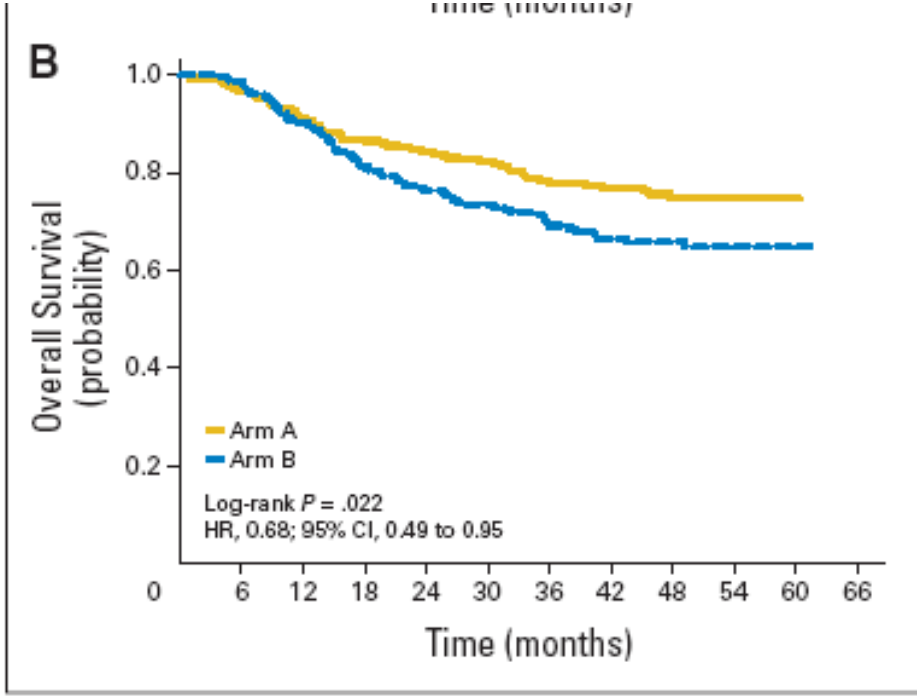
ARM B (n= 256 pts)

CCRT+ BRT
with
Weekly Cis 40mg/m2

Adverse Effects

- Arm A - More Grade 3-4 toxicities (p<0.001)
- Haematologic Toxicity
  - **Grade 3-4 ; 71.9% Vs 23.9 %**
- Non haematologic toxicities
  - Vomiting & diarrhea more in arm A (p=0.002)
- Hospitalization during treatment
  - Arm A -30 pts & Arm B -11 pts (p=0.02)
  - 3 deaths in arm A – 2 due to sepsis and bowel perforation & 1 due to acute encephalopathy
- Late toxicities slightly higher in Arm A
  - Grade 4 GI : 2.3 % Vs 0%





Results

- 3 Y PFS 74.4% Vs 69% (p=0.029)
- Median PFS- HR 0.68
- Statistically significant improvement in median PFS

Conclusion: Gemcitabine + cisplatin CRT followed by Brachy & adjuvant gem/cis CT improved survival outcomes with increased but clinically manageable toxicity compared to standard Rx

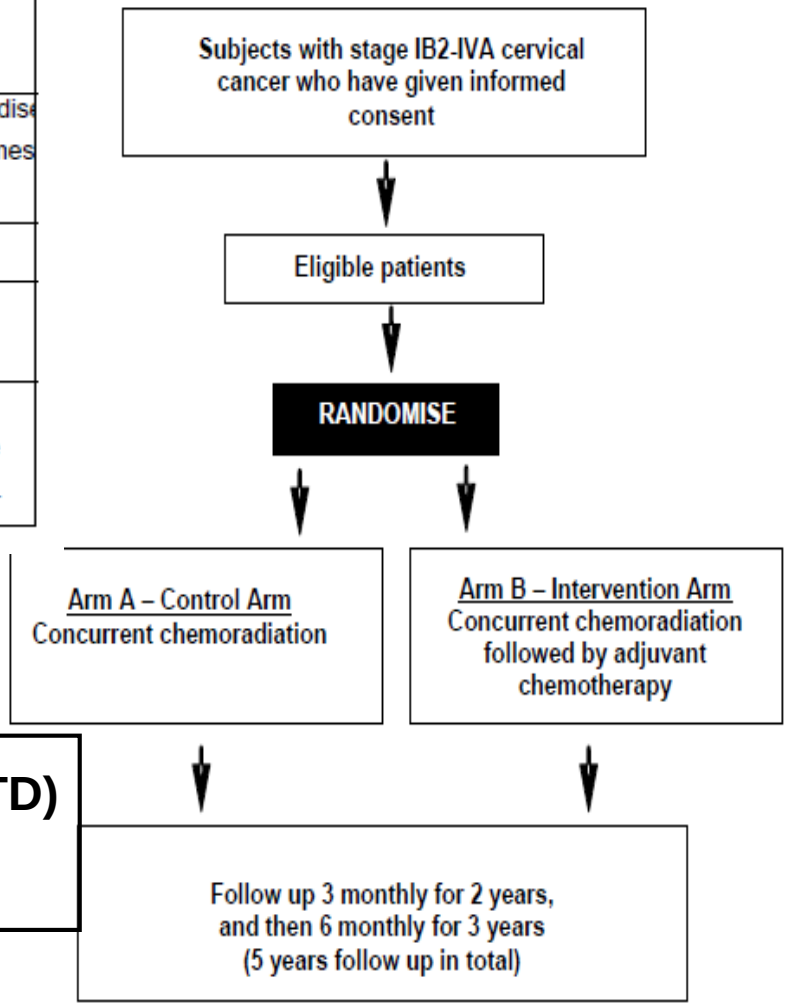
Concurrent CTRT + Adjuvant CT

- Challenges
  - Acute and chronic toxicity
    - Mainly
      - Hematological Toxicity
      - GI toxicity
- Options
  - Non overlapping toxicity drugs
  - Targeted agents
  - Improved radiotherapy techniques to avoid synergistic toxicity

OUTBACK TRIAL

MULTICENTRIC PHASE III STUDY

Primary Objectives:	To determine if the addition of adjuvant chemotherapy to standard cisplatin-based chemo-radiation improves progression-free survival.
Secondary objectives	To determine: overall survival rates, acute and long-term toxicities, patterns of dise recurrence, the association between radiation protocol compliance and outcomes patient quality of life, including psycho-sexual health.
# patients	780
Planned duration	4 years recruitment and a maximum of 5 years follow-up
Statistics	A sample size of 780 provides 80% power to detect an increase in the proportions who are both alive and progression free at 3 years from 55% in the control arm to 65.5% in the experimental arm with a 2-sided type 1 error of 5%.



Cisplatin based concurrent chemo-radiation (STD)

Vs CCRT followed by Pacli + Carbo x 3 cycles

Recruited : 600 pts approx.

Induction Chemotherapy followed by Concomitant Chemo-Radiation in Advanced Stage Carcinoma Cervix: A Phase III Randomized Trial *(INTERLACE Study - NCT01566240)*

Carcinoma Cervix Stage FIGO Ib2-IVA

Based on Phase II Study which evaluated the feasibility of delivering dose dense & dose intense CT (Pacli + Carbo weekly)

385 patients

Concomitant chemo radiotherapy

weekly Cisplatin (40 mg/m2 x 4 - 5 #)

385 patients

Induction chemotherapy with weekly x 6weeks Paclitaxel (80 mg/m2) + Carboplatin (AUC2)

Concomitant chemoradiotherapy

weekly Cisplatin (40 mg/m2 x 4 - 5 #) &

Outcomes:

Primary: Overall Survival

Secondary: Progression free Survival

Acute toxicities

Late Toxicities

Initiated in 2012

Accrual period: 4 years

Completion: 2021

CRT AND BIOLOGIC AGENTS

VEGF IN CERVICAL CANCER

- Intratumoral protein levels of VEGF are increased in patients with cervical cancer when compared to normal cervical tissue (1)
- Increasing intratumoral levels of VEGF correlated with (1):
  - higher stage
  - increased risk of LVI
  - increased risk of lymph nodes metastasis
- Higher VEGF expression was an independent prognostic factor for poor disease-free and overall survival (2)

(1)Cheng et al. Obstet Gynecol 2000;96:721-6

(2)Loncaster et al. Br J Cancer 2000;83(5):620-5

BIOLOGIC AGENTS - BEVACIZUMAB

Phase II study of Bevacizumab in combination with definitive radiotherapy and cisplatin in locally advanced cervical carcinoma (RTOG 0417)

REGISTER

Pelvic RT:

45 Gy given in 25 once-daily fractions (1.8 Gy/fraction) Monday-Friday over 5 weeks

↓

LDR x 2 or HDR x 5

↓

Parametrial boost (if indicated)

Bevacizumab (Avastin®): IV Q2 weeks (Days 1, 15 and 29, total of 3 doses) during chemoradiation, given before cisplatin, on the same day as cisplatin

Cisplatin: Weekly infusion x 6 weeks

- 60 patients from 25 institutions were enrolled between 2006 and 2009
- 49 patients evaluable.
- Median follow-up of 10 months (Mostly IIB 63%, squamous-80%) no treatment-related SAEs.
- There were 15 (31%) protocol specified treatment-related AEs, most common were hematologic (12/15 =80%)

2010 ASCO Annual Meeting : J Clin Oncol 28:15s, 2010 (suppl; abstr 5006)

GOG 240
Schema

Eligibility:

1. Primary stage IVB or Recurrent/persistent carcinoma of the cervix

2. Measureable disease

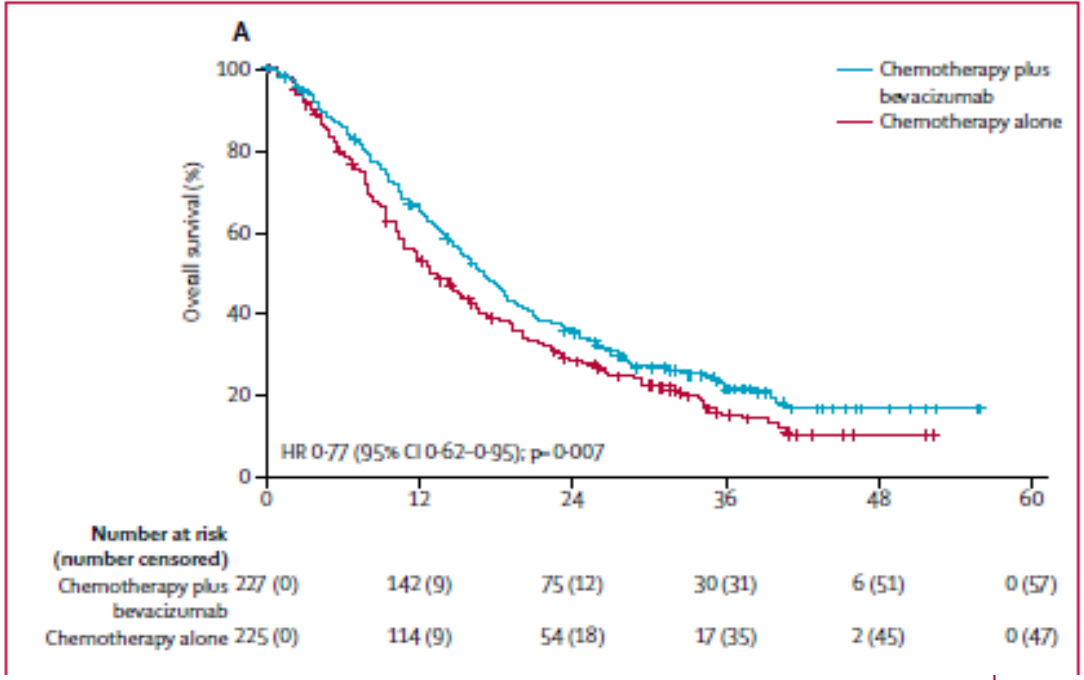
3. GOG PS 0-1

Regimen I
Paclitaxel 135 mg/m^2 IV d1 (24h)
Cisplatin 50 mg/m^2 IV d2
Q21d to progression/toxicity

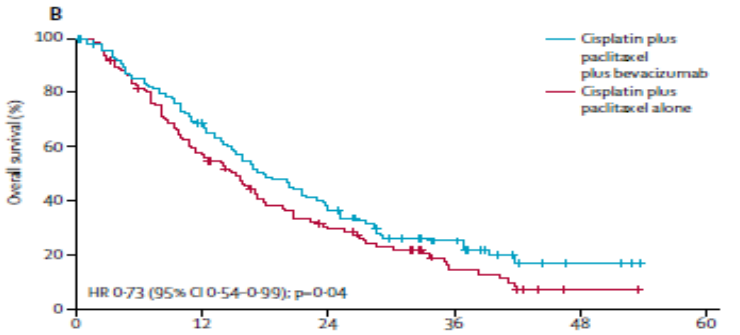
Regimen II
Paclitaxel 135 mg/m^2 IV d1 (24h)
Cisplatin 50 mg/m^2 IV d2
Bevacizumab 15 mg/kg IV d2
Q21d to progression/toxicity

Regimen III
Paclitaxel 175 mg/m^2 IV d1 (3h)
Topotecan 0.75 mg/m^2 d1-3 (30m)
Q21d to progression/toxicity

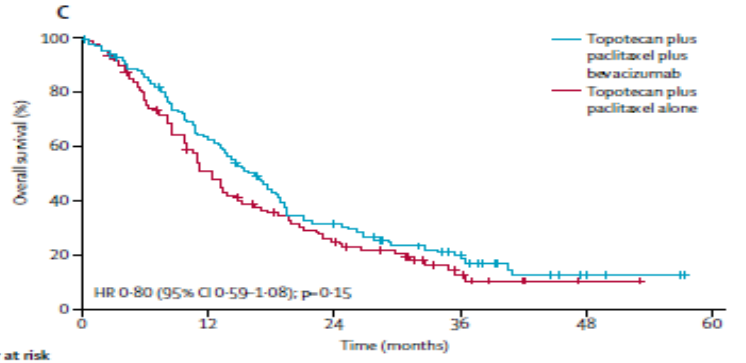
Regimen IV
Paclitaxel 175 mg/m^2 IV d1 (3h)
Topotecan 0.75 mg/m^2 d1-3 (30m)
Bevacizumab 15 mg/kg IV d1
Q21d to progression/toxicity



Number at risk (number censored)						
Chemotherapy plus bevacizumab	227 (0)	142 (9)	75 (12)	30 (31)	6 (51)	0 (57)
Chemotherapy alone	225 (0)	114 (9)	54 (18)	17 (35)	2 (45)	0 (47)



Number at risk (number censored)						
Cisplatin plus paclitaxel plus bevacizumab	115 (0)	73 (6)	41 (6)	16 (18)	3 (29)	0 (32)
Cisplatin plus paclitaxel alone	114 (0)	63 (3)	31 (8)	11 (16)	1 (21)	0 (22)



Number at risk (number censored)						
Topotecan plus paclitaxel plus bevacizumab	112 (0)	69 (3)	34 (6)	14 (13)	3 (22)	0 (25)
Topotecan plus paclitaxel alone	111 (0)	51 (6)	23 (10)	6 (19)	1 (24)	0 (25)

	Cisplatin plus paclitaxel (n=114)	Cisplatin plus paclitaxel plus bevacizumab (n=115)	Topotecan plus paclitaxel (n=111)	Topotecan plus paclitaxel plus bevacizumab (n=112)	Total (n=452)
Complete response	11 (10%)	18 (16%)	6 (5%)	13 (12%)	48 (11%)
Partial response	41 (36%)	40 (35%)	22 (20%)	41 (37%)	144 (32%)
Stable disease	45 (39%)	42 (37%)	54 (49%)	43 (38%)	184 (41%)
Progressive disease	12 (11%)	7 (6%)	21 (19%)	6 (5%)	46 (10%)
Indeterminate	5 (4%)	8 (7%)	8 (7%)	9 (8%)	30 (7%)

Data are n (%).

Table 2: Tumour response

Improvement in response rates (Complete + Partial)

	Chemotherapy alone (n=220)	Chemotherapy plus bevacizumab (n=220)	Risk ratio	p value
Grade 2 genitourinary fistula	1 (<1%)	8 (4%)	8·00 (1·01–63·43)	0·04
Grade 3 genitorurinary fistula	1 (<1%)	6 (3%)	6·00 (0·73–49·43)	0·12
Grade 2 GI fistula	1 (<1%)	11 (5%)	11·00 (1·43–84·48)	0·006
Grade 3 GI fistula	0	7 (3%)	NA	0·02
Grade 2 or higher hypertension	4 (2%)	55 (25%)	13·75 (5·07–37·29)	0·001
Grade 4 or higher neutropenia	58 (26%)	80 (36%)	1·37 (1·04–1·83)	0·03
Grade 3 or higher febrile neutropenia	12 (5%)	12 (5%)	1·00 (0·46–2·18)	1
Grade 3 or higher GI bleeding	1 (<1%)	4 (2%)	4·00 (0·45–35·50)	0·37
Grade 3 or higher proteinuria	0	5 (2%)	NA	0·06
Grade 3 or higher thrombosis or embolism	4 (2%)	18 (8%)	4·50 (1·55–13·08)	0·004
Grade 2 or higher pain	63 (29%)	72 (33%)	1·14 (0·86–1·51)	0·41

Data are n (%) or risk ratio (95% CI). GI=gastrointestinal. NA=not applicable.

Table 3: Adverse events

Increase in AE's

-GU Gr 2-3 fistula

- Hyertension

-- Neutropenia

- Vascular events : Bleed / Thrombosis

GOG 240: Conclusions

- Bevacizumab plus chemotherapy significantly improves OS in stage IVB, recurrent or persistent cervical carcinoma
  - Nearly 4-month improvement in OS is clinically significant
  - Increase in median PFS and ORR are also demonstrated
  - Cisplatin + paclitaxel arm is current standard of care and did not underperform
  - Benefit seen even when recurrent disease is in irradiated pelvis
- Bevacizumab treatment is associated with a higher rate of AEs
  - 3–8% rate of known bevacizumab-related AEs
- The improvement in OS with bevacizumab treatment was not accompanied by a decrease in HRQoL
- First targeted agent to improve OS in a gynecologic cancer

ASCO Plenary Session 2013
Lancet 2017

SUMMARY
Chemotherapy IN Cervical Cancers

- **Neo - adjuvant Chemotherapy:**

  - **NACT followed by RT Vs RT: No Benefit**

  - **NACT followed by Sx Vs RT:** Some Benefit but has major limitations

  - **NACT followed by Sx Vs Sx: CR better but no survival benefit**

  - **NACT followed by Sx Vs Chemo-RT: Chemo-radiation STD of Care**

- **Concomitant Chemotherapy : STD of Care**

- **Concomitant followed Adjuvant CT : Still Investigational**

- **Palliative CT in recent era : Bevacizumab some benefit**

THANK YOU

mahantshettyum@tmc.gov.in

Leiden University
Medical Center

Endometrial Cancer

Techniques and clinical evidence for post-operative radiotherapy, results of clinical trials in intermediate-risk patients

Remi Nout

Dept of Radiation - Oncology

Leiden University Medical Centre, The Netherlands

Learning objectives

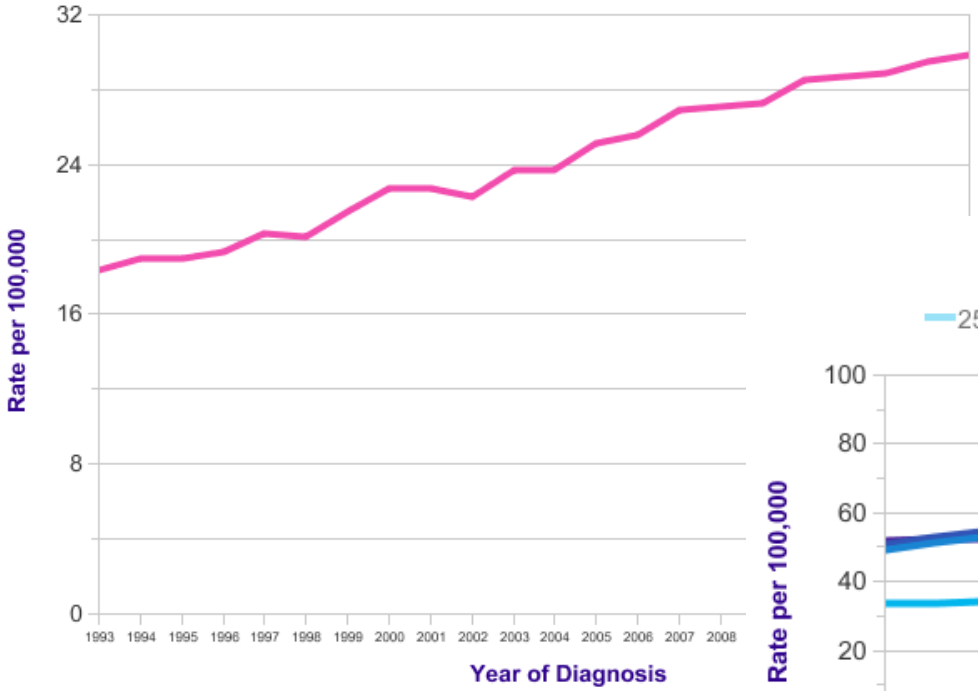
- Prognostic factors & risk stratification for adjuvant treatment
- Clinical trials which form the basis for current treatment
- How different radiotherapy techniques impact on morbidity and quality of life

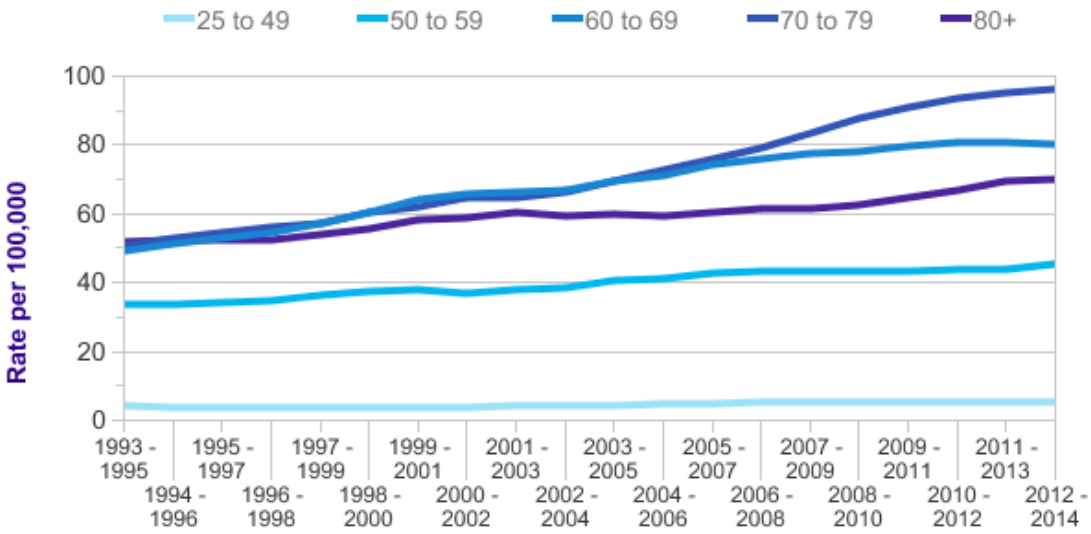
➢ *Upcoming (molecular) prognostic factors and ongoing trials, discussed in next presentation*

Incidence

Uterine Cancer (C54-C55): 1993-2014

European Age-Standardised Incidence Rates per 100,000 Population, Females, UK



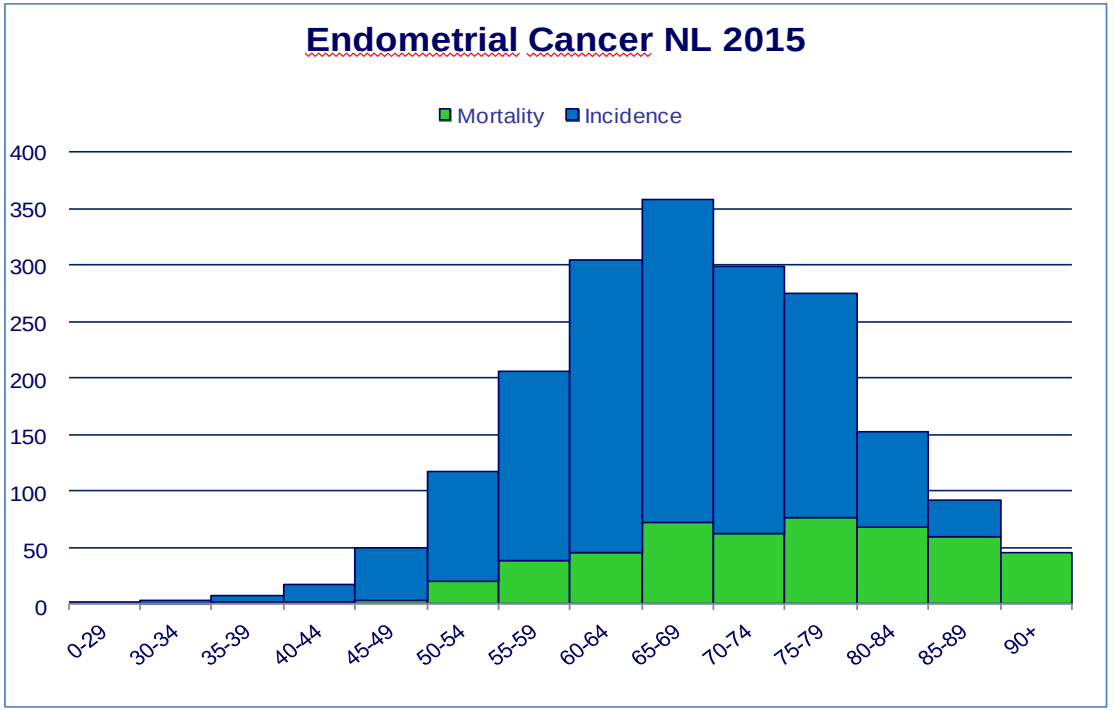


CANCER RESEARCH UK

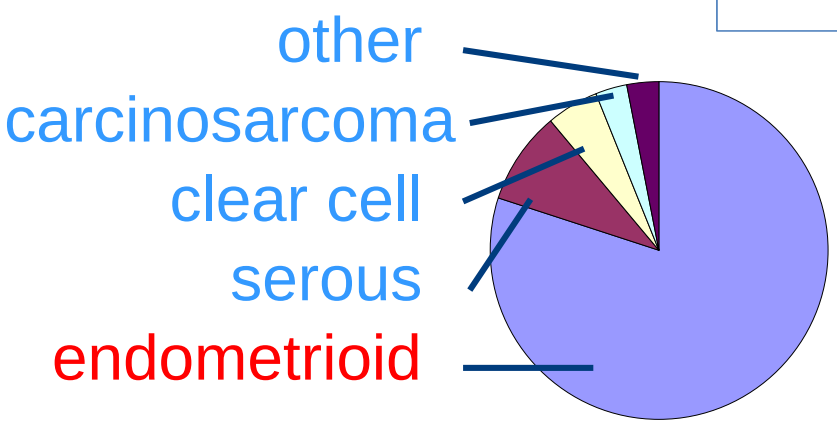
Endometrial Carcinoma

Incidence
22 / 100.000

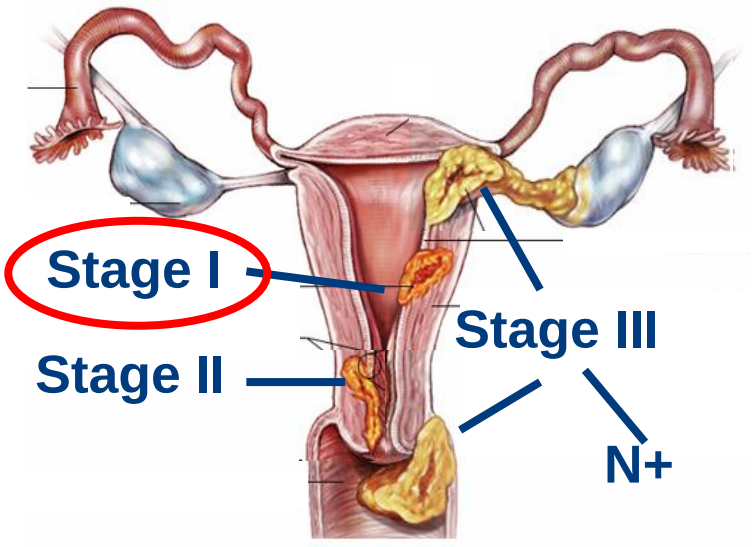
Mortality
5.5 / 100.000

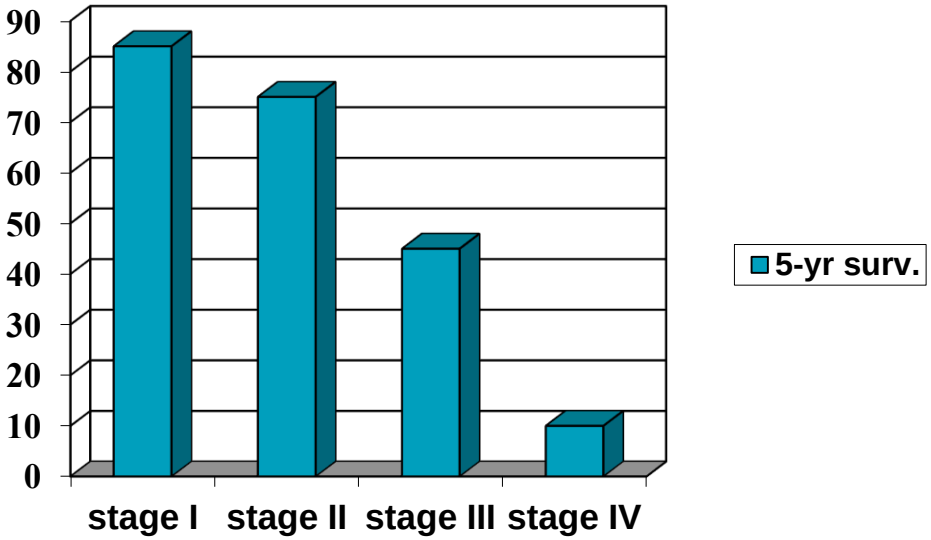


Histology



Stage and histologic subtype





Histological type (5 yr OS)

endometrioid carcinoma: 80-85%

serous carcinoma: 50-55%

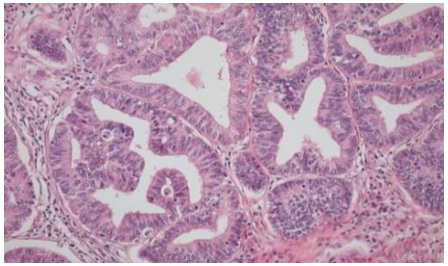
clear cell carcinoma: 60-65%

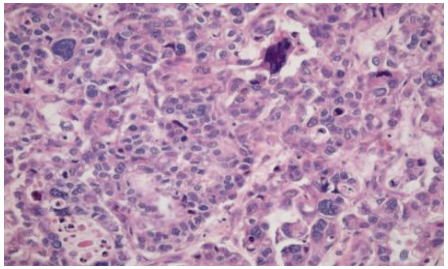
Alektiar, IJROBP, 2002; Scholten, IJROBP, 2002

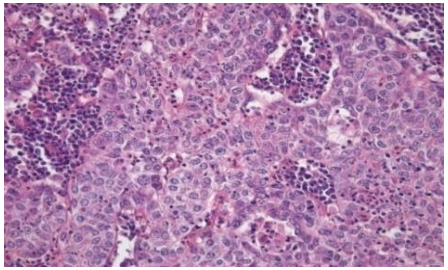
Major prognostic factors

- Age
- Stage
  - Depth of myometrial invasion
- Histology
  - Histological type
  - Grade
  - Lymph-vascular space invasion

- Molecular factors discussed in high risk presentation







Lymph node metastasis (GOG)

Risk of microscopic pelvic metastases for stage 1 without extrauterine disease:

- *low risk (<5%)* — grade 1 <2/3, gr 2-3, no invasion
- *intermediate (5-10%)* — all others
- *high risk (>10%)* — gr 3, >2/3 invasion

Historic Risk Groups

- *Low risk:*
  - stage I grade 1-3 no invasion
  - stage I grade 1 <50% invasion
- *Intermediate risk:*
  - stage I grade 2-3 <50% invasion
  - stage I grade 1-2 ≥50% invasion
- *High risk:*
  - stage I grade 3 ≥50% invasion; stage II / III / IV
  - NEEC: serous, clear-cell carcinoma, carcinosarcoma

Low risk endometrial cancer

Surgery alone

- TLH-BSO
- no lymphadenectomy, no RT
- 95% relapse-free survival

➢ *No vaginal brachytherapy*:

Randomized trial, vaginal recurrence rate:

- Vaginal brachytherapy: 0-2%
- No additional therapy: 2-5%

Poulsen 1996; Mariani 2000 / 2008; Eltabbakh 1997; Webb 2000; Sorbe et al, 2009

Intermediate Risk – Randomised trials

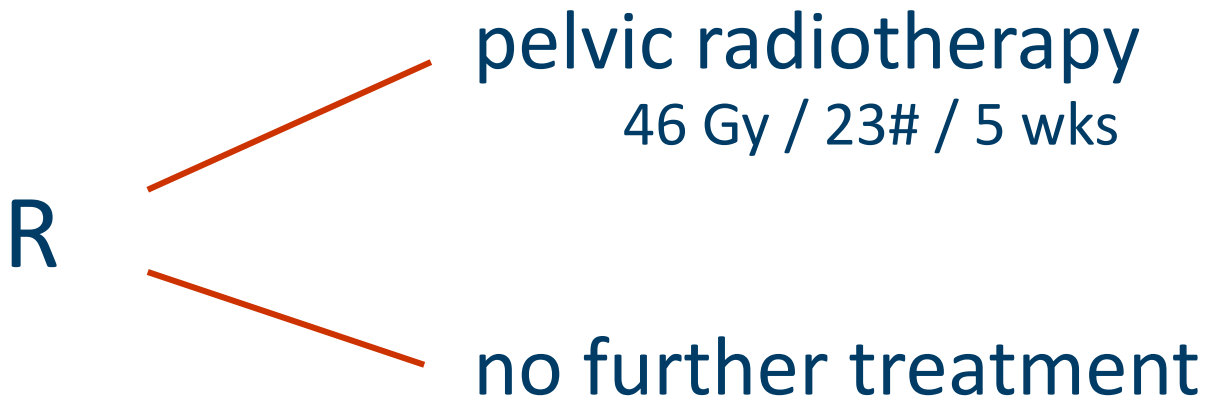
Trial	No. patients eligibility	Surgery	Randomization	Locoregional recurrence	Survival	Severe complications
Norwegian 1968-1974	540 Stage I	TAH-BSO	Brachytherapy vs. brachy and pelvic RT	7% vs. 2% at 5 years p<0.01	89% vs. 91% at 5 years p=NS	NA
PORTEC 1990-1997	714 IB grade 2-3 IC grade 1-2	TAH-BSO	NAT vs. pelvic RT	14% vs. 4% at 5 years p<0.001	85% vs. 81% at 5 years p=0.31	3% GI at 5 years (actuarial)
GOG-99 1987-1995	392 St IB, IC St II (occult)	TAH-BSO and lymph-adenectomy	NAT vs. pelvic RT	12% vs. 3% at 2 years p<0.01	86% vs.92% at 4 years p=0.56	8% GI at 2 years (crude)
ASTEC/EN5 1996-2005	905 St IAB g3, IC, St II, serous/cc	TAH-BSO +/- lymph-adenectomy	NAT vs. pelvic RT	7% vs. 4% at 5 years p=0.038	84% vs.84% at 5 years p=0.98	3 vs 7% gr 3/4

Aalders et al 1980, Creutzberg et al 2000, Keys et al 2004, ASTEC/EN.5 Study Group 2009

PORTEC-1 trial (1990-1997)

Stage I intermediate risk (n=714):

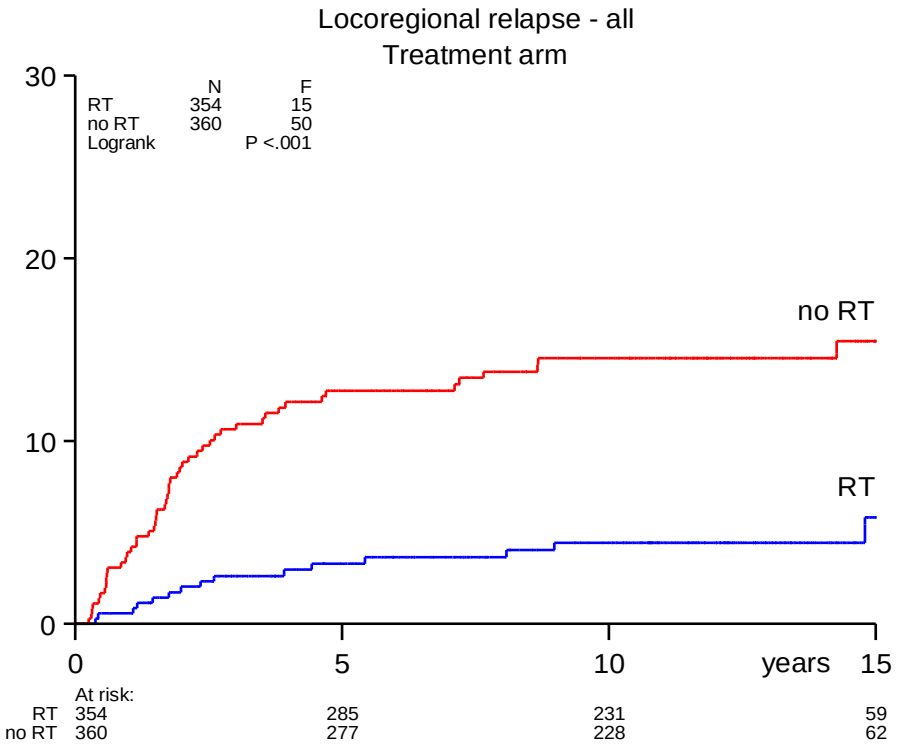
- grade 1 or 2 with ≥50% invasion
- grade 2 or 3 with <50% invasion
- TAH-BSO without lymphadenectomy



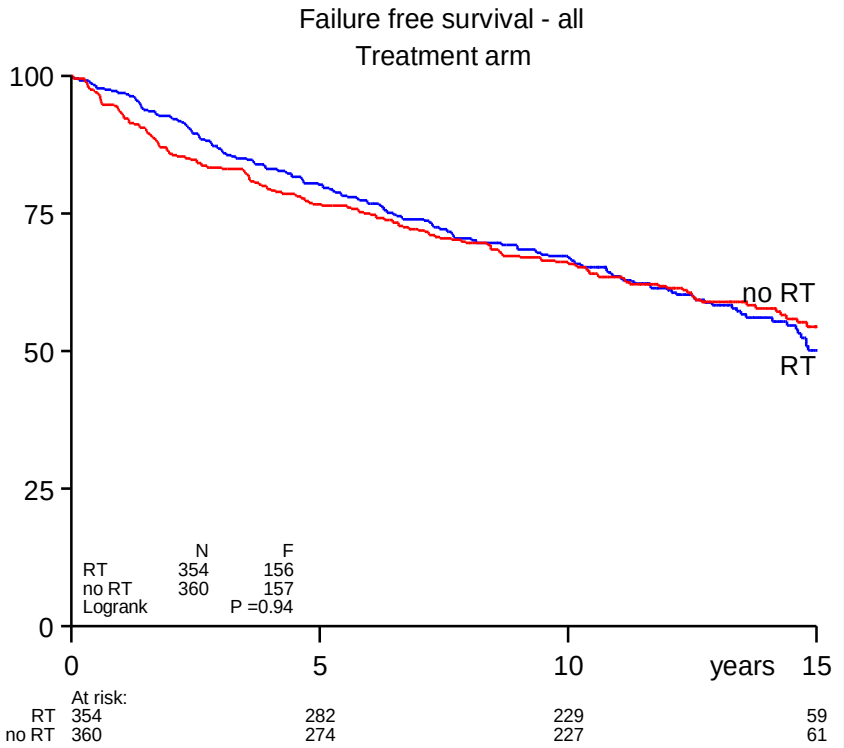
Creutzberg et al, Lancet 2000

15-year outcomes PORTEC-1

Locoregional Recurrence



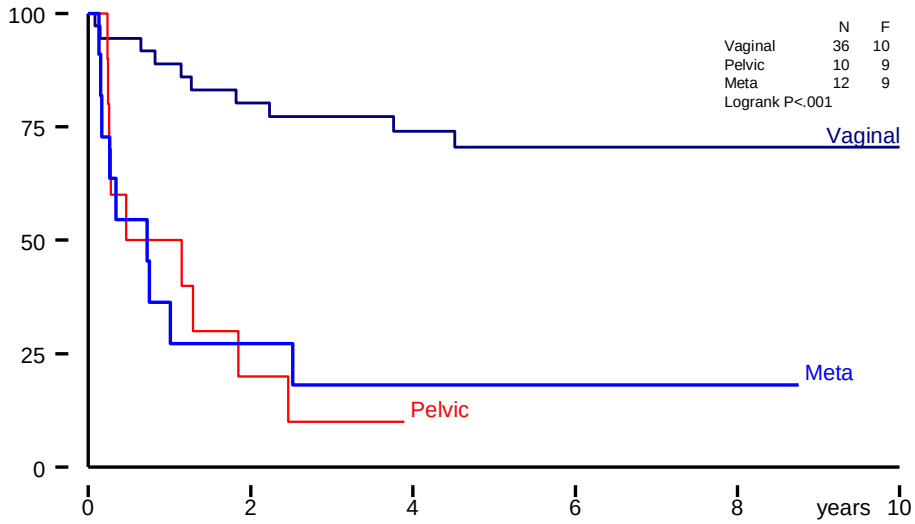
Failure Free Survival



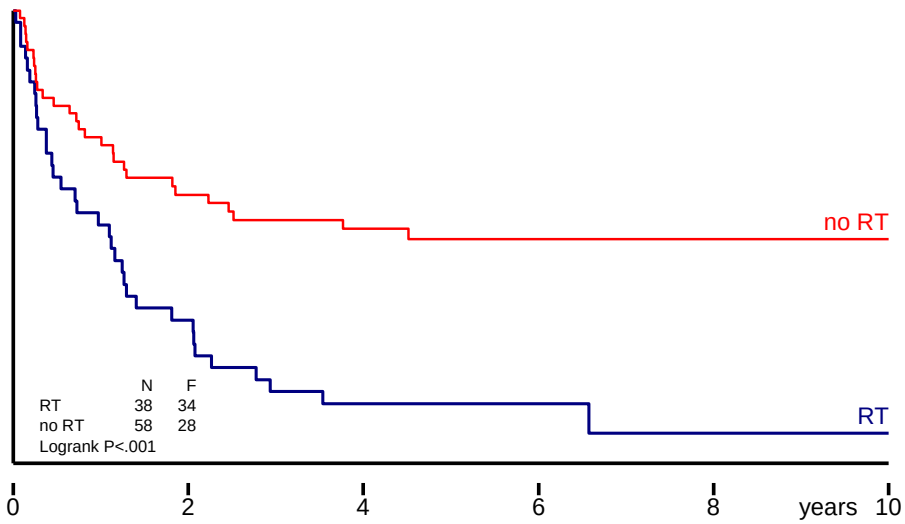
Creutzberg et al, ASTRO 2009, IJROBP 2011

Survival after relapse in PORTEC-1

By site of relapse



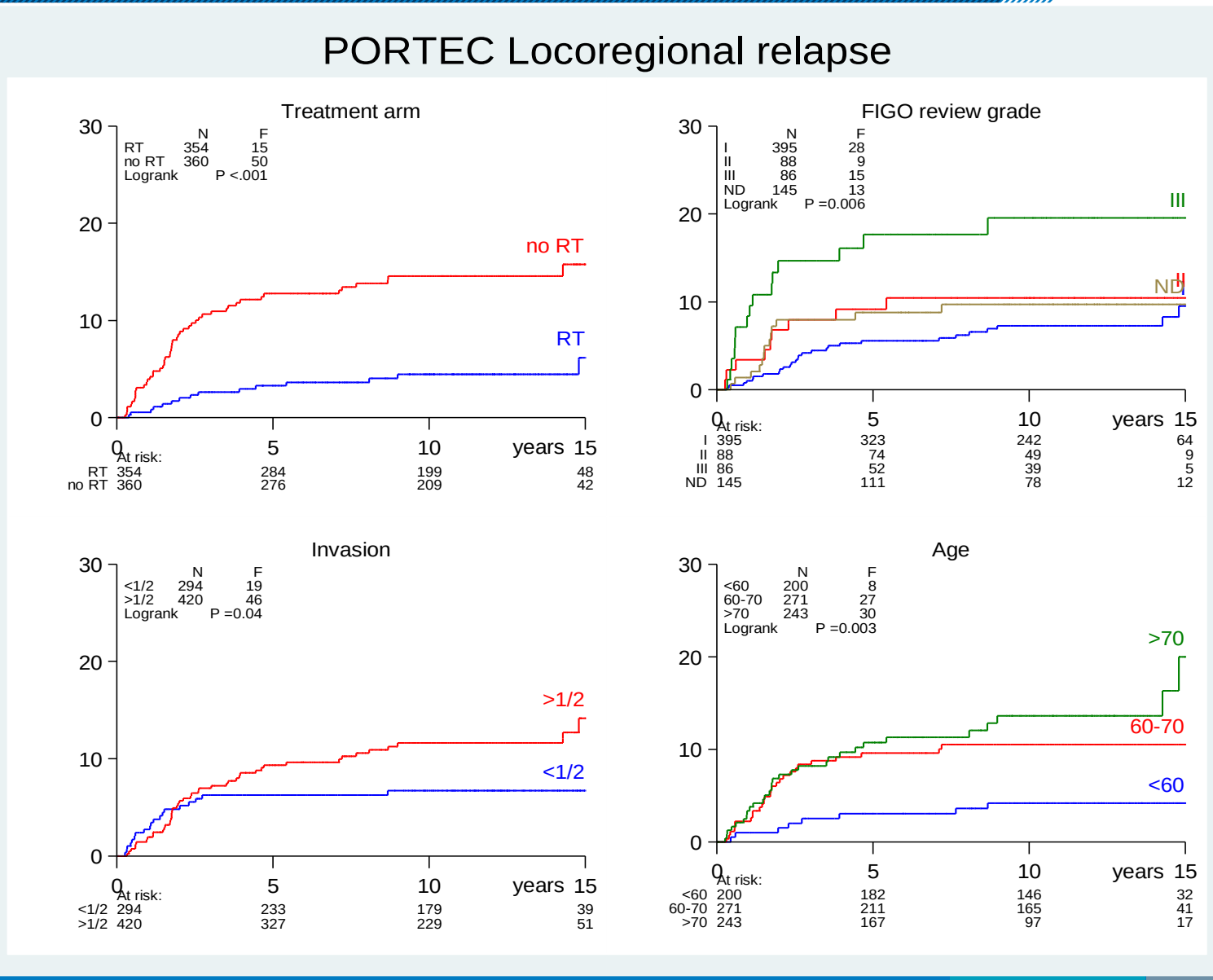
By treatment arm



➢ Vaginal brachytherapy?

Creutzberg et al, Gynecol Oncol 2003

PORTEC-1: risk factors for locoregional relapse



Creutzberg et al, ASTRO 2009, IJROBP 2011

PORTEC-1: high-intermediate risk

3 major risk factors:

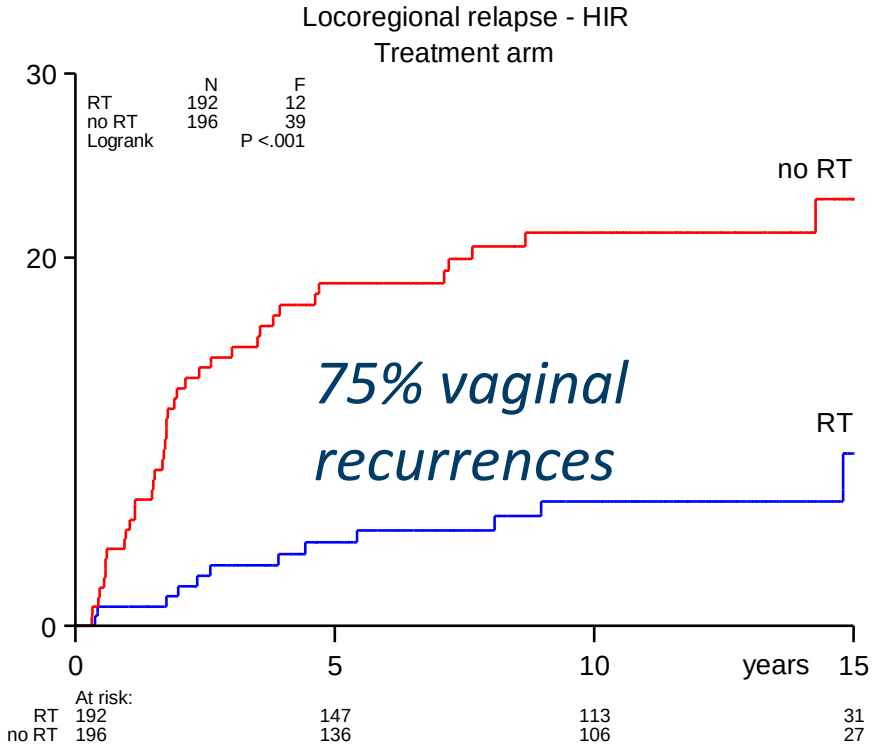
- grade 3
- outer 50% invasion
- age $\geq$ 60 years

RT indication only if 2 or more risk factors

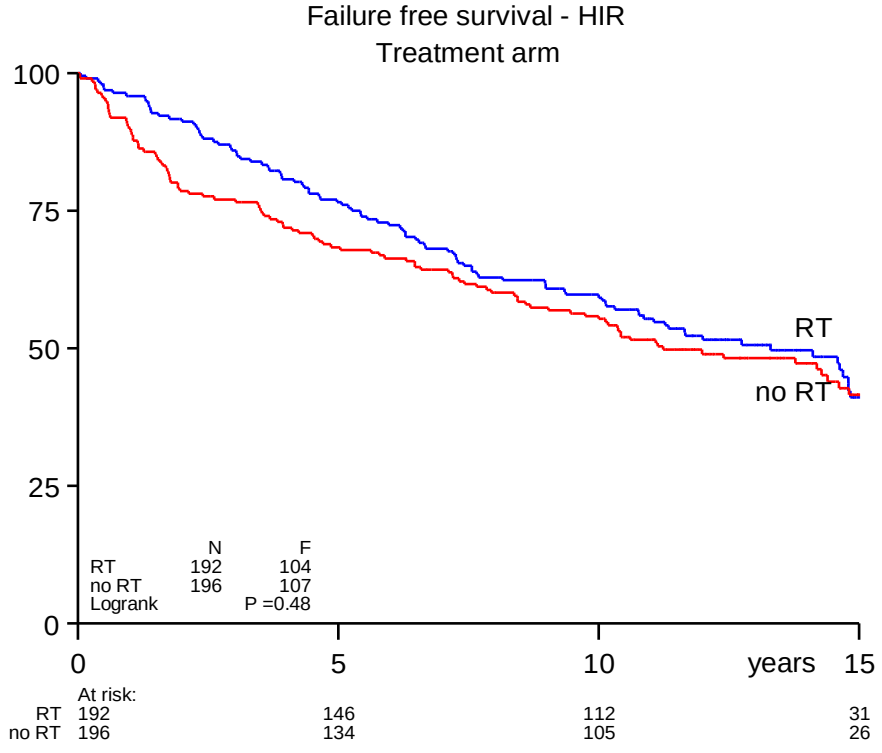
➢ *Reduction of RT-indication by 50%*

PORTEC-1: 15-year outcomes for HIR patients

Locoregional Recurrence



Failure Free Survival



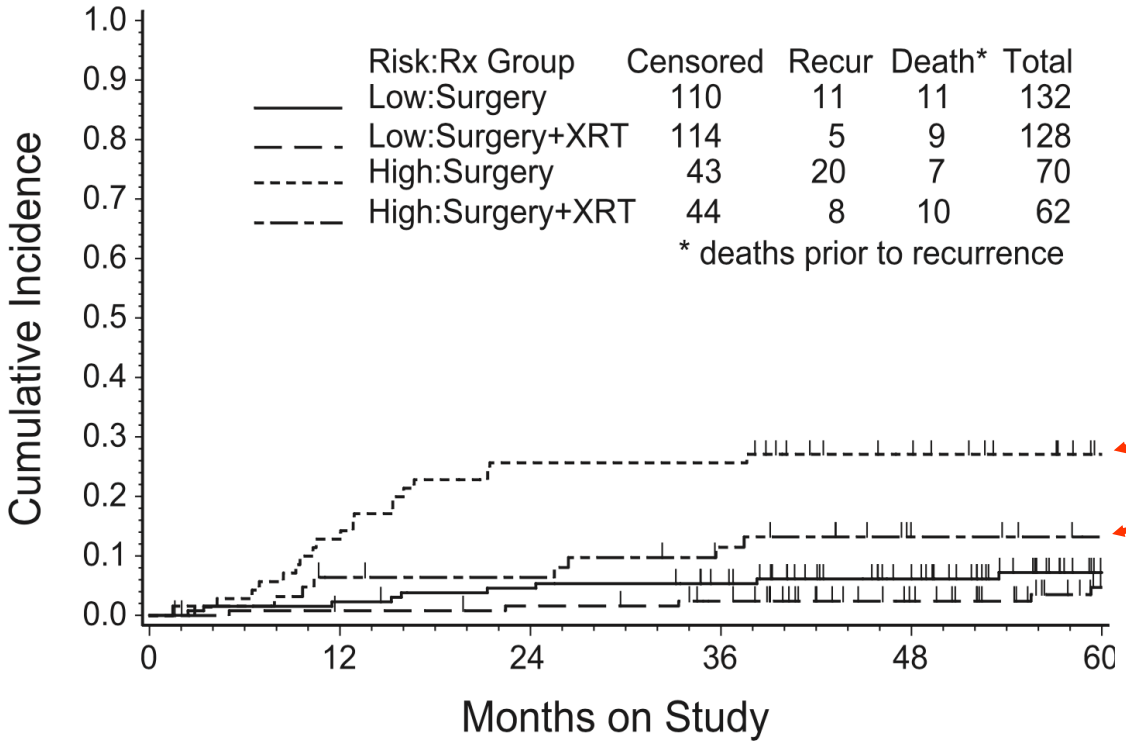
Creutzberg et al, ASTRO 2009, IJROBP 2011

High intermediate risk

	PORTEC-1	GOG #99
Risk factors		
- Age	< 60 vs. > 60	< 50 vs. 50-70 vs. > 70
- Grade	1-2 vs. 3	1 vs 2-3
- Invasion	< 50% vs. > 50%	< 66% vs. > 66%
- LVSI	-	absent vs. present
HIR group	≥ 2 of 3 factors	< 50 ys and 3 factors 50-70 ys and ≥ 2 factors > 70 ys and ≥ 1 factor

Creutzberg et al. 2000; Keys et al 2004

GOG#99 - recurrence



HIR, no RT: 27%

HIR, RT: 13%

RT: 58% hazard reduction; absolute benefit for HIR 14%

- *in patients who had lymphadenectomy and were pN0*

High intermediate risk

	PORTEC-1 NAT vs. RT	GOG #99 NAT vs. RT
PORTEC risk groups		
- 10 yr LR relapse	23% vs. 5% (RR 0.22)	
GOG risk groups		
- 10 yr LR relapse	22% vs. 8% (RR 0.36)	
- 4 yr any relapse		27% vs. 13% (RR 0.48)
- 4 yr local relapse		13% vs. 5% (RR 0.38)

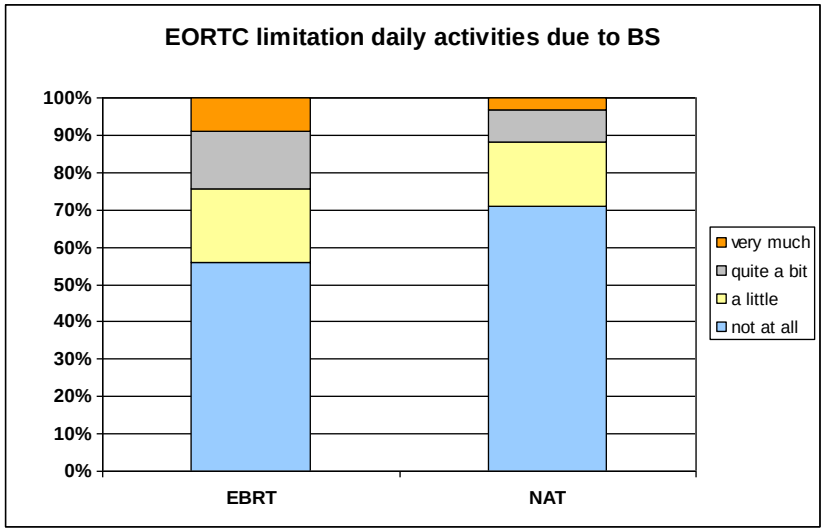
Scholten et al. 2005; Keys et al 2004

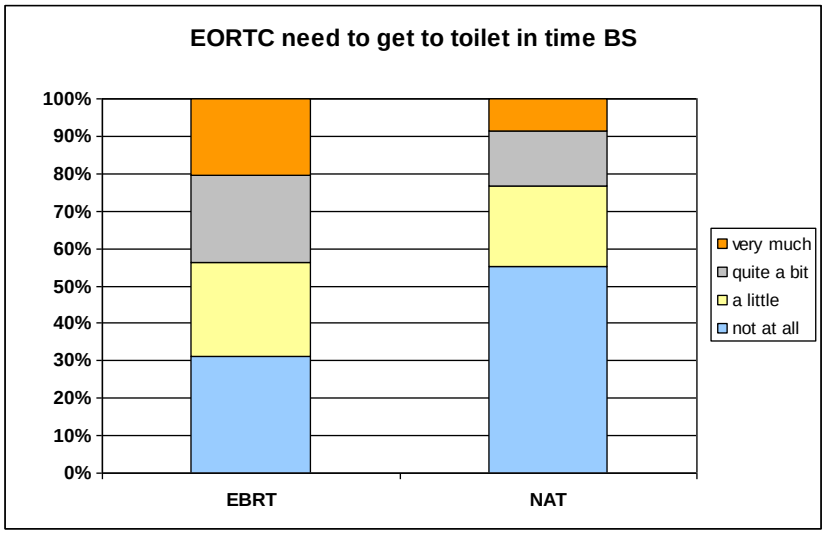
PORTEC-1: morbidity

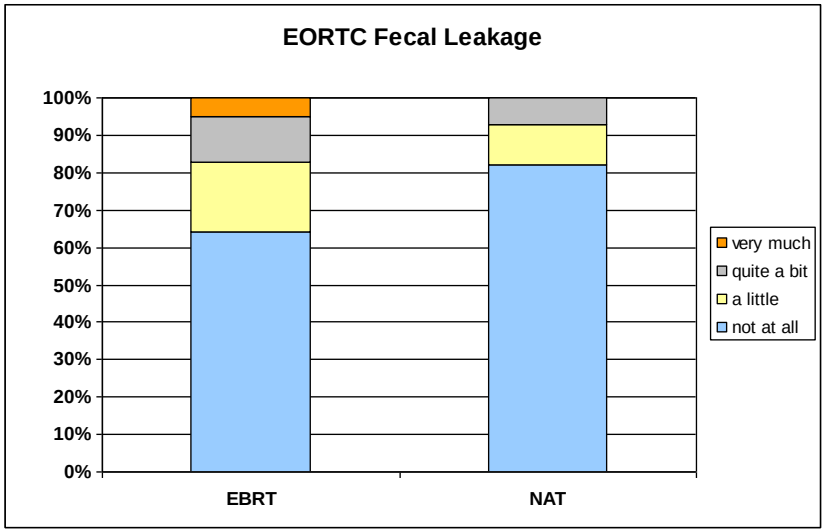
- 5-year actuarial grade 1-4:
  - Overall EBRT 26% versus NAT 4%
  - Grade 1: EBRT 17% versus NAT 4%
  - Majority gastrointestinal tract
- Grade 3-4 after EBRT 3%
- 4-field box technique less late complications
  - 30% treated with parallel opposing fields
- GOG#99 extended surgery + EBRT 13% grade 3-4

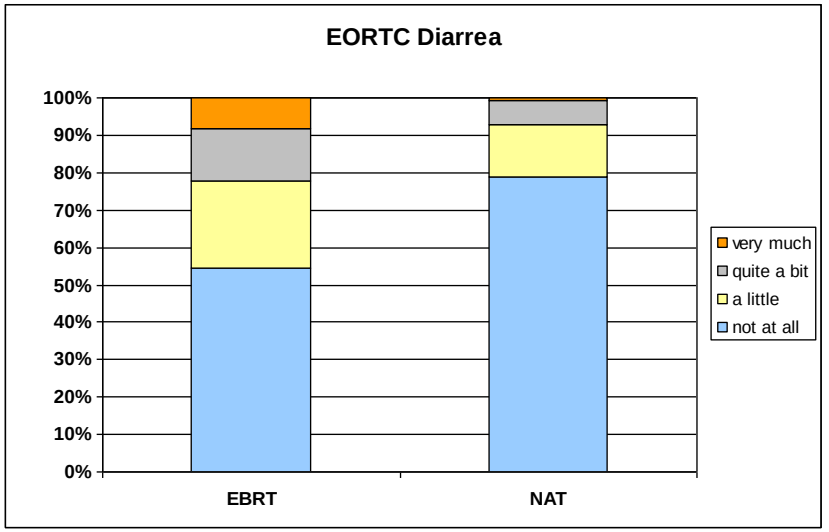
Creutzberg et al, IJROBP2001; Keys et al 2004

Bowel symptoms



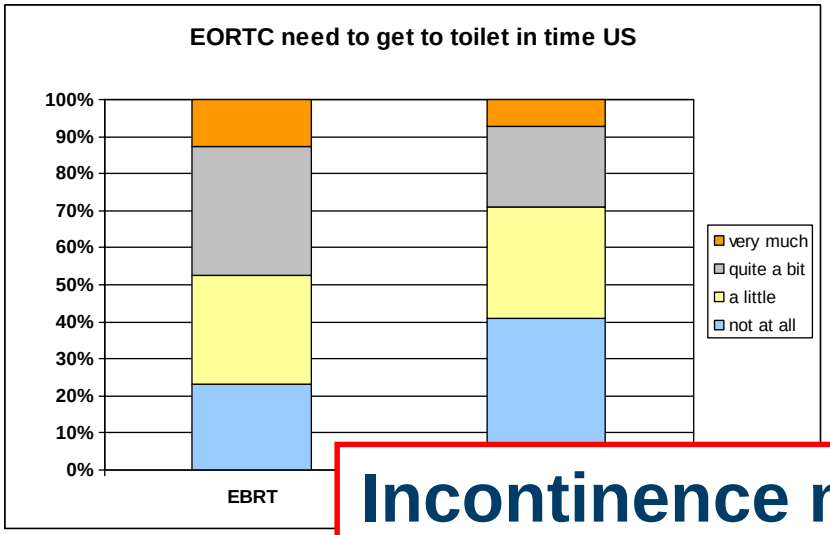


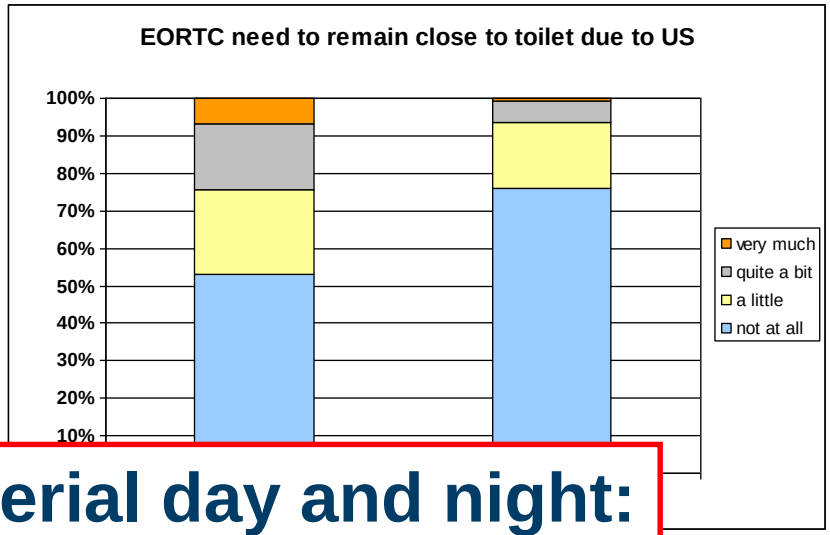




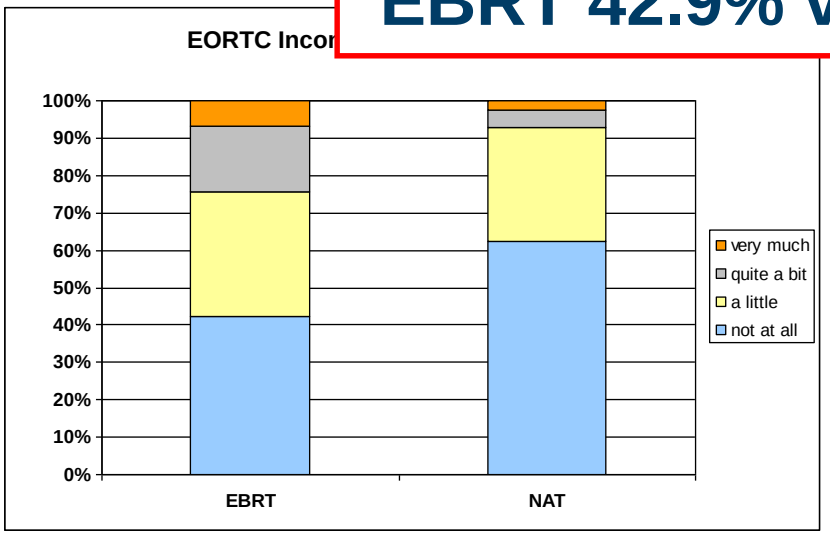
Nout et al, JCO 2011

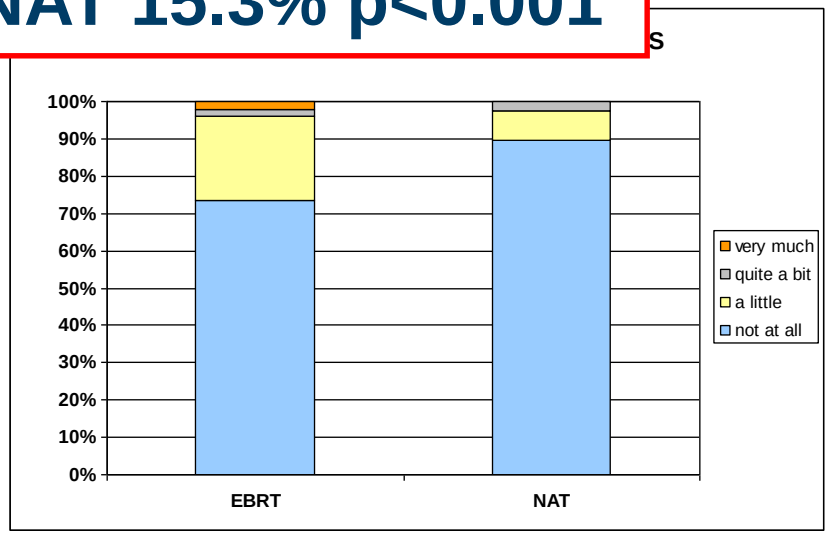
Urinary symptoms





Incontinence material day and night:
EBRT 42.9% vs. NAT 15.3% p<0.001



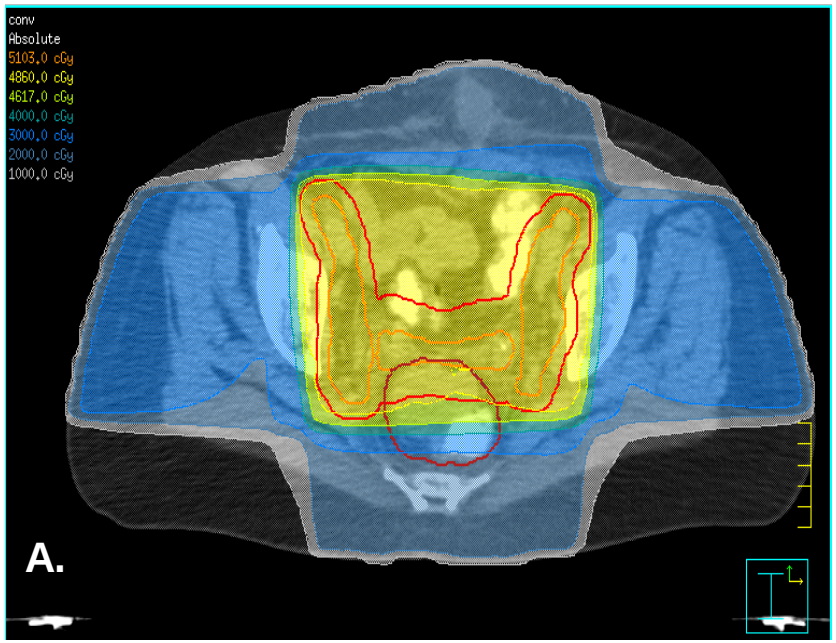


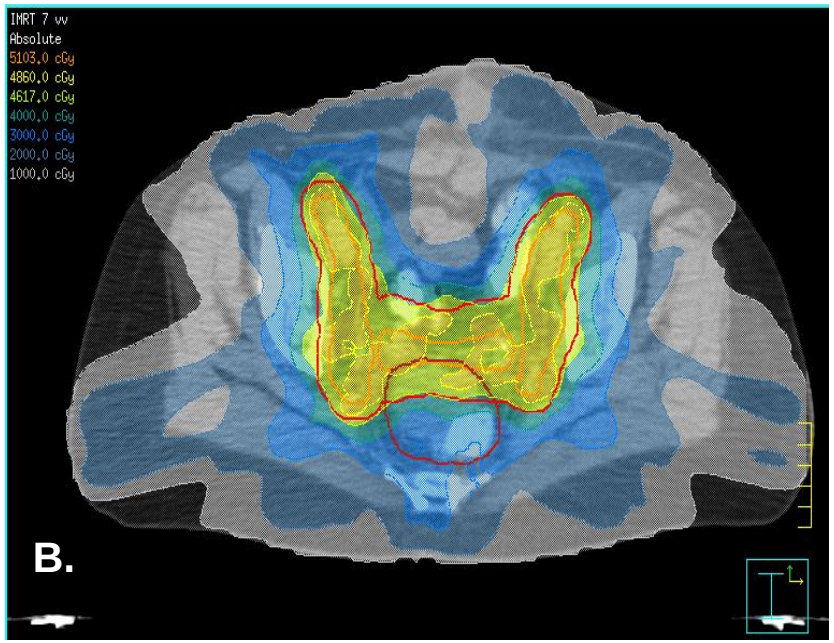
Nout et al, JCO 2011

Improvement of EBRT techniques

PORTEC-1: 30% AP-PA
70% 3-4 fields with shielding

IMRT

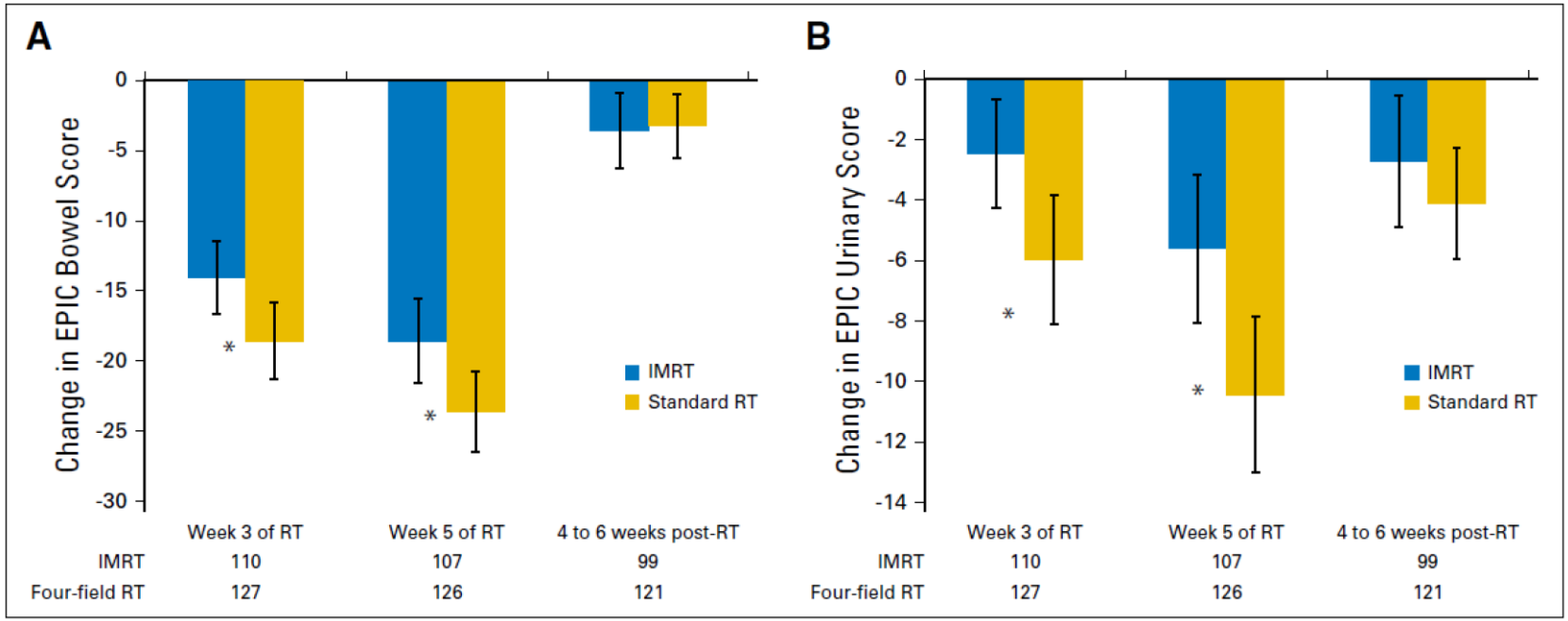




Creutzberg IJROBP 2001; Nout et al, JCO 2011

Pelvic IMRT: reduced toxicity

- NRG – RTOG Time C randomized trial
  - IMRT vs 4-field pelvic radiotherapy
  - Endometrial / Cervix postoperative
- IMRT: less acute GI and GU toxicity at 5 wks
  - Less use of medications during treatment
  - IMRT: better QOL physical functioning



Klopp et al, JCO 2018

Summary – intermediate risk

15 year PORTEC-1 results

- LRR risk reduction with EBRT 67%
- no survival advantage

EBRT has long-term impact on quality of life

- higher levels of bladder & bowel symptoms
- lower physical functioning, more role limitation

EBRT to be avoided in intermediate risk cases

- HIR criteria for treatment selection
- vaginal brachytherapy

Creutzberg et al IJROBP 2011, Nout et al JCO 2011

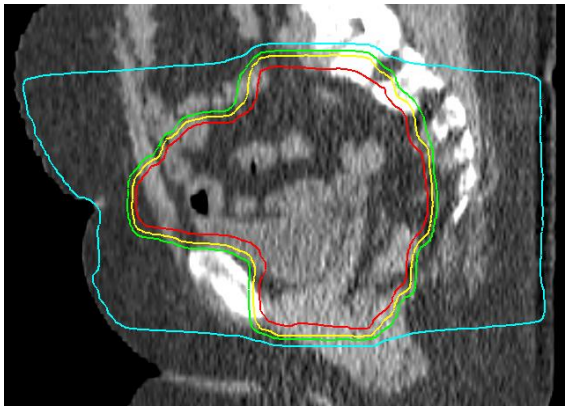
PORTEC-2 trial (2002-2006)

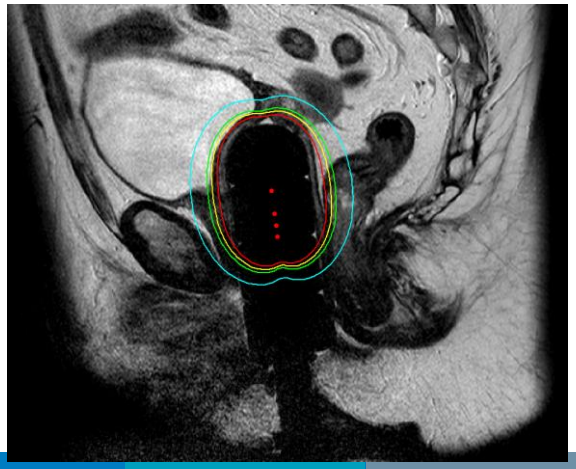
Stage I high-intermediate risk (n = 427)

- *age ≥ 60 and ≥50% invasion grd 1-2 or <50% invasion grd 3*
- *FIGO 1988 stage 2A*
- *TAH-BSO* without lymphadenectomy

R

- pelvic radiotherapy
  46 Gy / 23# / 5 wks
- vaginal brachytherapy
  21 Gy / 3# / 2 wks





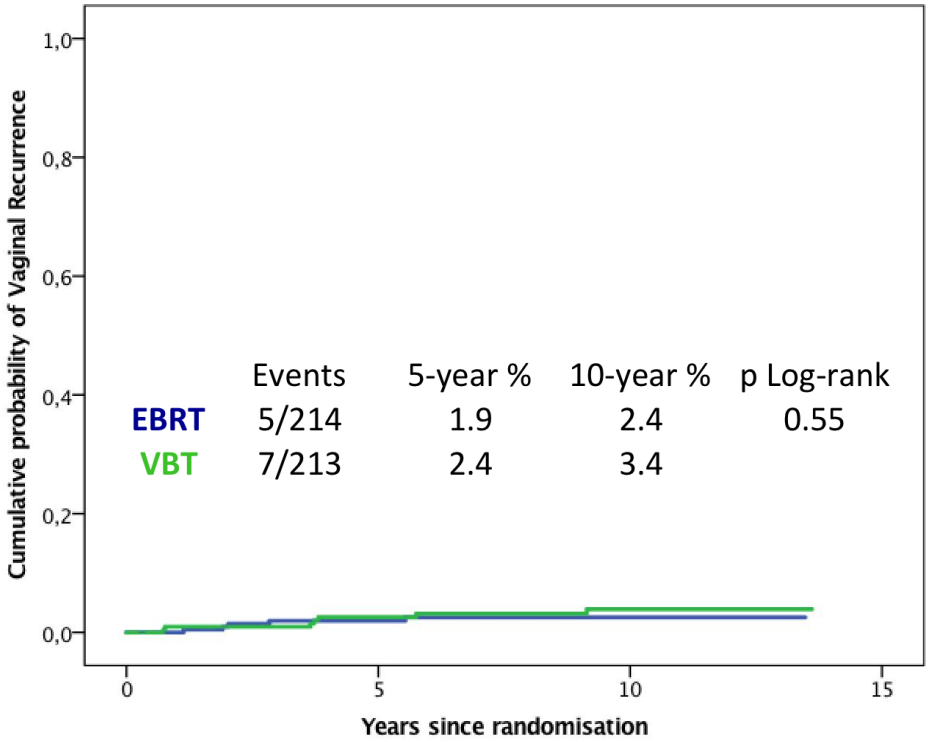
PORTEC 2

Nout et al, Lancet 2010

Vaginal Recurrence & Overall Survival

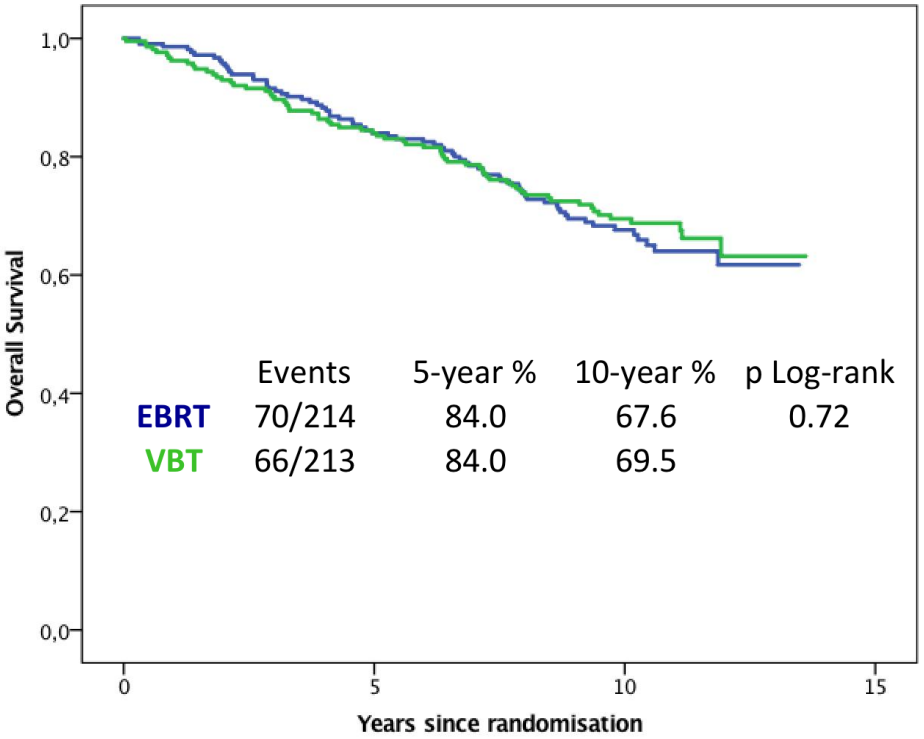
- Median follow-up 10.5 years

Vaginal Recurrence



	Events	5-year %	10-year %	p Log-rank
EBRT	5/214	1.9	2.4	0.55
VBT	7/213	2.4	3.4	

Overall Survival

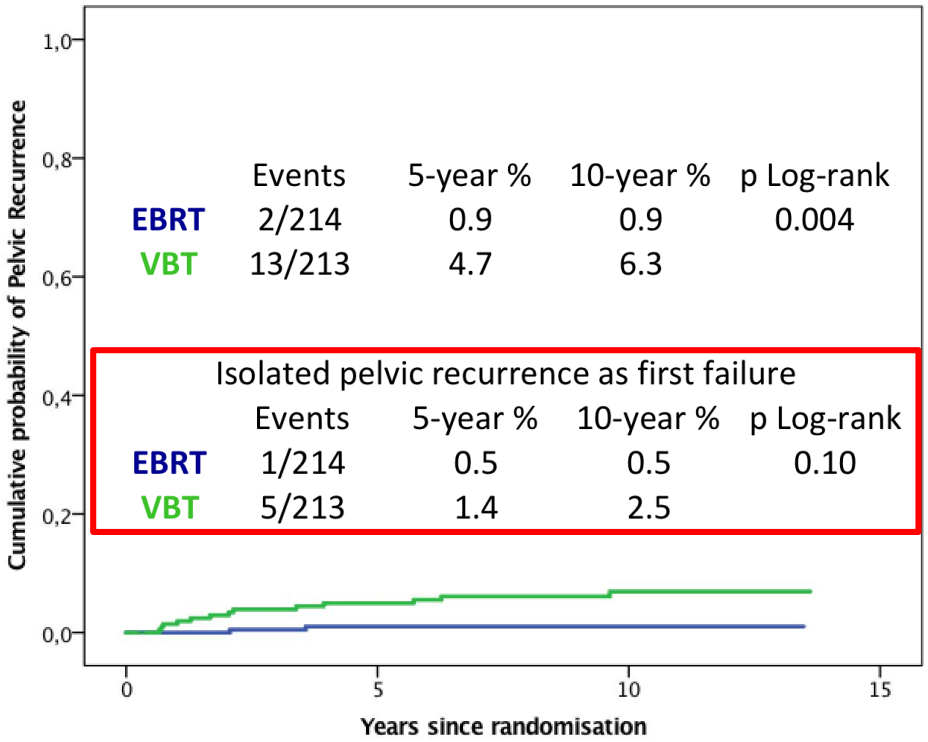


	Events	5-year %	10-year %	p Log-rank
EBRT	70/214	84.0	67.6	0.72
VBT	66/213	84.0	69.5	

Vaginal Recurrence & Overall Survival

- Median follow-up 10.5 years

Pelvic Recurrence

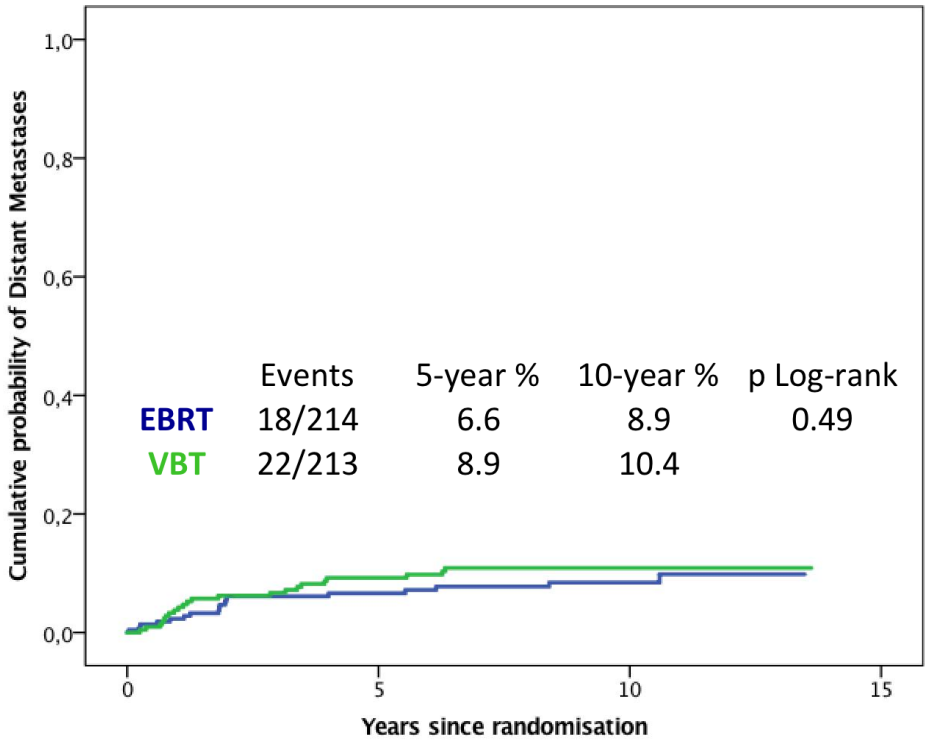


	Events	5-year %	10-year %	p Log-rank
EBRT	2/214	0.9	0.9	0.004
VBT	13/213	4.7	6.3	

Isolated pelvic recurrence as first failure

	Events	5-year %	10-year %	p Log-rank
EBRT	1/214	0.5	0.5	0.10
VBT	5/213	1.4	2.5	

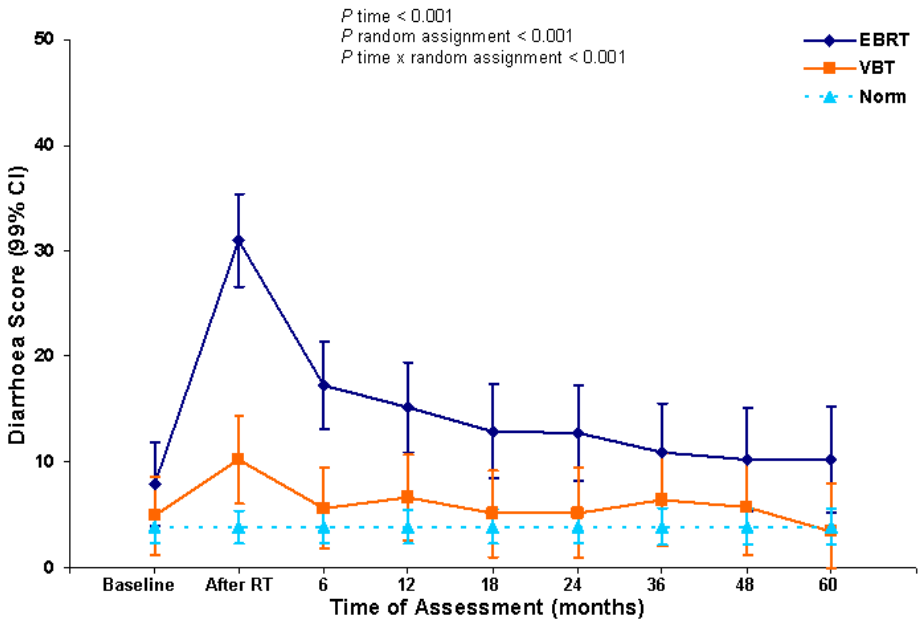
Distant Metastases



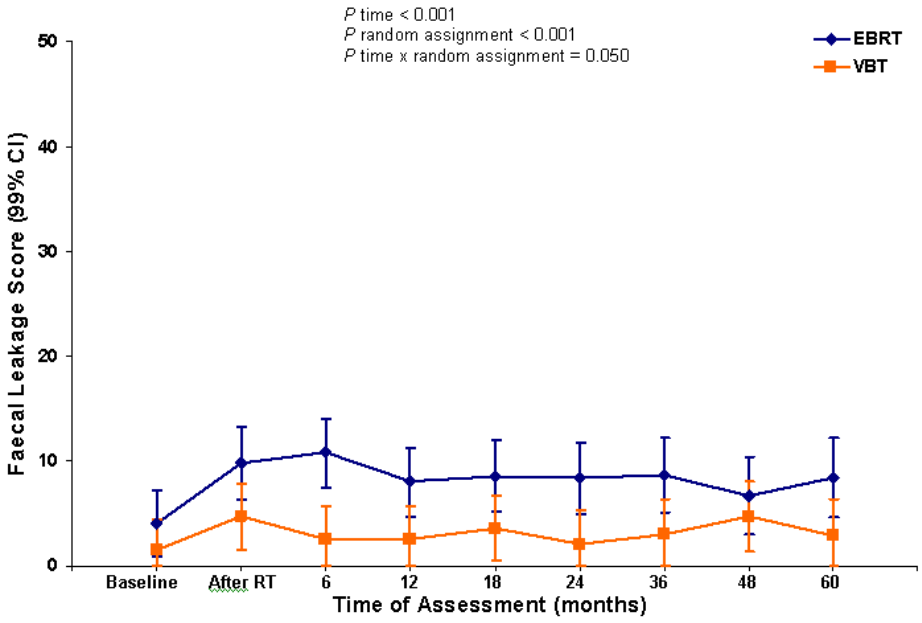
	Events	5-year %	10-year %	p Log-rank
EBRT	18/214	6.6	8.9	0.49
VBT	22/213	8.9	10.4	

Quality of Life – bowel symptoms

Diarrhoea



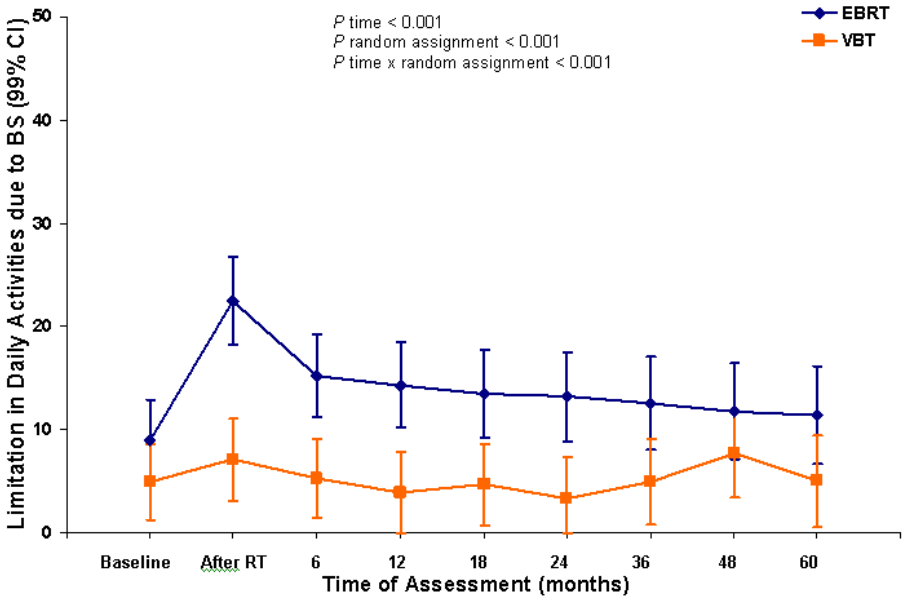
Feacal Leakage



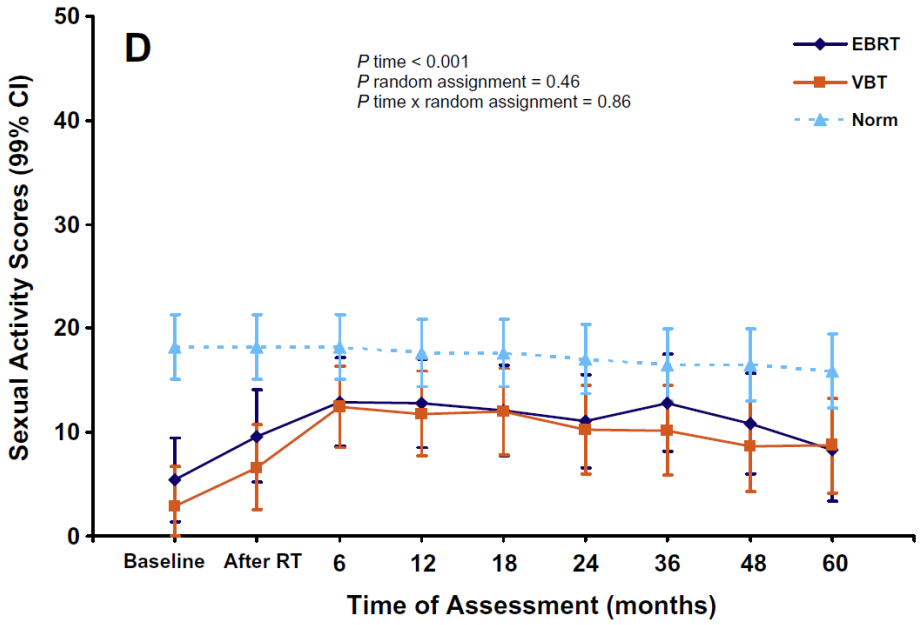
Nout et al, JCO 2009, EJC 2011, de Boer 2014

Quality of Life – bowel symptoms

Daily activities limited by bowel problems?



Sexual activity



Nout et al, JCO 2009, EJC 2011, de Boer 2014

Swedish randomised trial (1997-2008)

Stage I ‘medium risk ‘ (n=527)

		VBT	EBRT+VBT
Vaginal recurrence (crude)		2.7%	1.9%
Locoregional		5.0%	1.5%
Overall Survival		90%	89%
Toxicity Gr 3:	GI	0%	2%
	vagina	0.8%	0%

- Similar QoL results favoring VBT alone

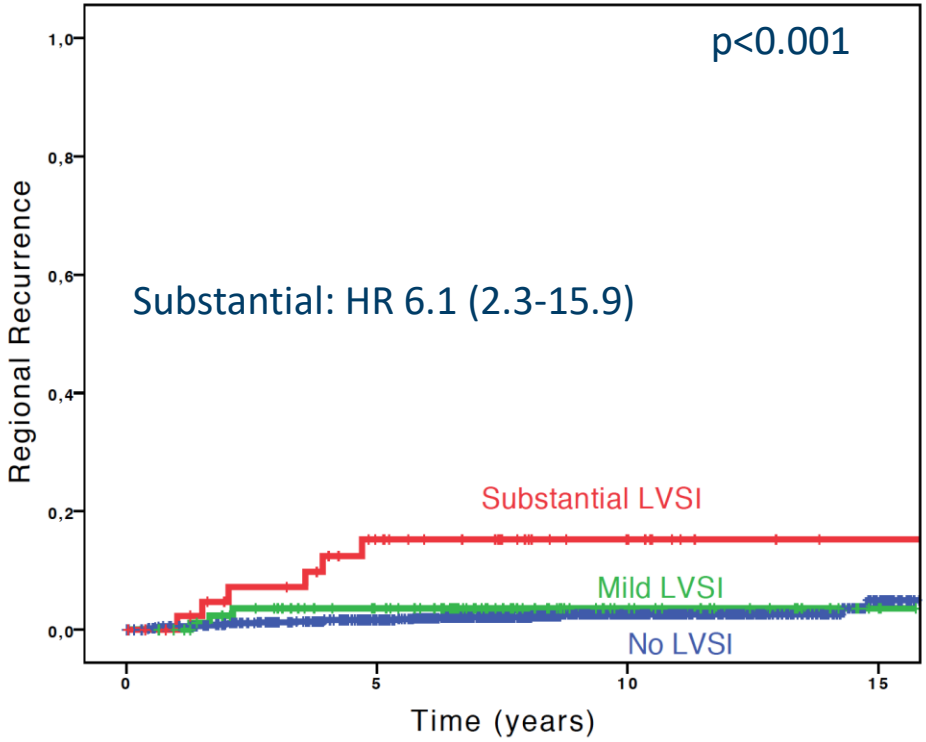
Sorbe et al, IJROBP 2012 + Int J Gynecol Cancer 2012

Quatification of LVSI in PORTEC-1 and 2

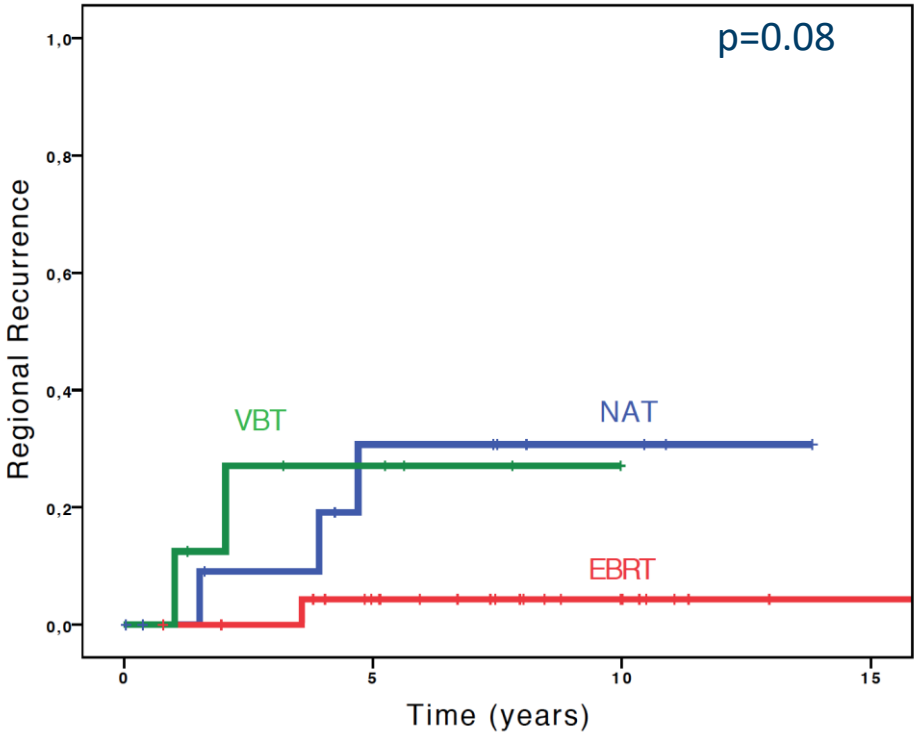
- Pelvic nodal recurrence

5%

All 954 patients

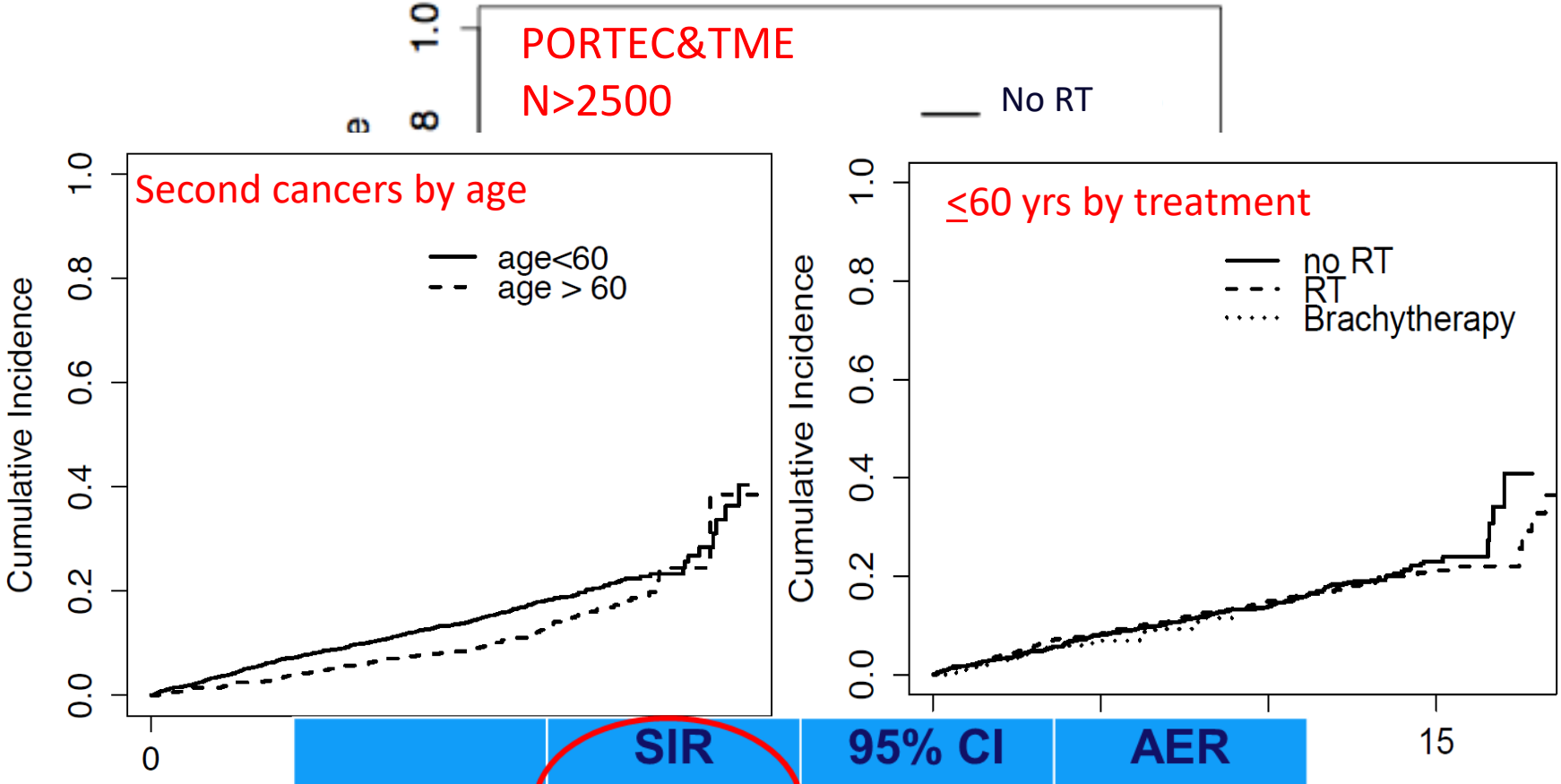


Substantial LVSI: 46 patients



Bosse, T. et al *EJC* 2015, Nout, R. *ASTRO* 2014

Risk of second cancers



	SIR	95% CI	AER
All patients	2.98	2.82-3.14	154
≤60 years	5.47	4.73-6.31	151
>60 years	2.76	2.60-2.93	163

Wiltink et al, J Clin Oncol 2015

Summary high-intermediate risk

- Brachytherapy effective in preventing vaginal recurrence: 2.9% at 8 years
- More pelvic recurrences after brachytherapy, most with simultaneous distant metastases (isolated pelvic failure 1.5% vs 0.5%)
- No difference in distant metastases and survival
- VBT better QoL/functioning
- Substantial LVSI: consider IMRT
- No increased risk of second cancers

Q1: Current best definition of risk groups?

Risk Group	Description (FIGO 2009)	E
Low	• Stage IA Endometrioid + grade 1-2 + LVSI negative	1
Intermediate	• Stage IB Endometrioid + grade 1-2 + LVSI negative	1
High Intermediate	• Stage IA Endometrioid + grade 3, regardless of LVS • Stage I Endometrioid + grade 1-2 + LVSI unequivocally positive regardless of depth of invasion	1 2
High	• Stage IB Endometrioid + grade 3, regardless of LVSI status • Stage II & stage III with no residual disease • Non endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed >10%)	1 1 1
Advanced Metastatic	• Stage III with residual disease & IVA • Stage IVB	1 1

No RT

VBT

Pelvic IMRT

Endometrial Cancer Consensus: Adjuvant Treatment

ESMO ESGO ESTRO European Society for RADIOTHERAPY & ONCOLOGY

Colombo N. et al *Ann of Oncology* 2015

Leiden University Medical Center

Endometrial Cancer

Role of chemo / chemo-radiation in high risk endometrial cancer

Remi Nout
Radiation Oncology, Leiden University Medical Centre, The Netherlands

ESMO-ESGO-ESTRO consensus: risk groups

Risk Group	Description (FIGO 2009)
Low	• Stage IA Endometrioid + grade 1-2 + LVSI negative
Intermediate	• Stage IB Endometrioid + grade 1-2 + LVSI negative
High Intermediate	• Stage IA Endometrioid + grade 3, regardless of LVSI status • Stage I Endometrioid + grade 1-2 + LVSI unequivocally positive, regardless of depth of invasion
High 15%	• Stage IB Endometrioid + grade 3, regardless of LVSI status • Stage II & stage III with no residual disease • Non endometrioid (serous, clear cell, undifferentiated carcin carcinosarcoma, mixed >10%)
Advanced Metastatic	• Stage III with residual disease & IVA • Stage IVB

No RT

VBT

Pelvic IMRT

- Radiotherapy?
- Chemotherapy?
- Both?

ESMO ESGO ESTRO European Society for RADIOTHERAPY & ONCOLOGY

Colombo N. et al *Ann of Oncology* 2015, Nout, R. *ESGO* 2015

GOG-122

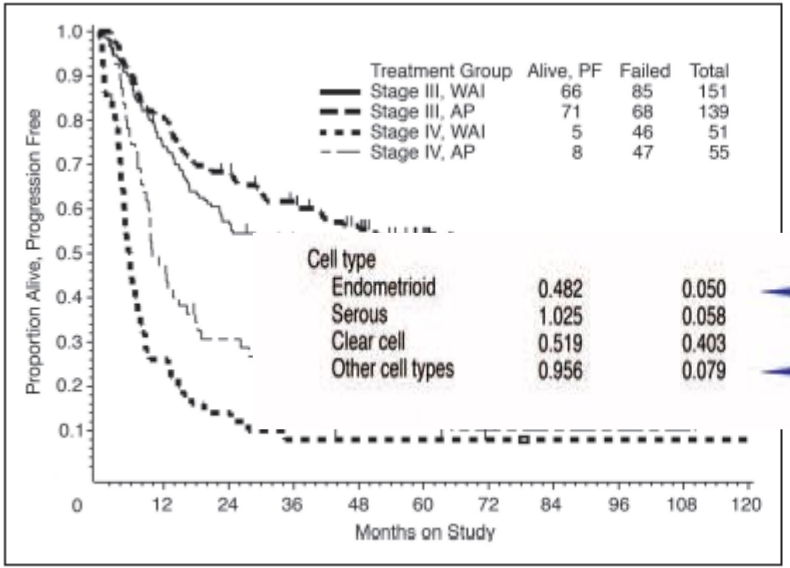


Fig 3. Progression-free survival by treatment and stage. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation; PF, progression free.

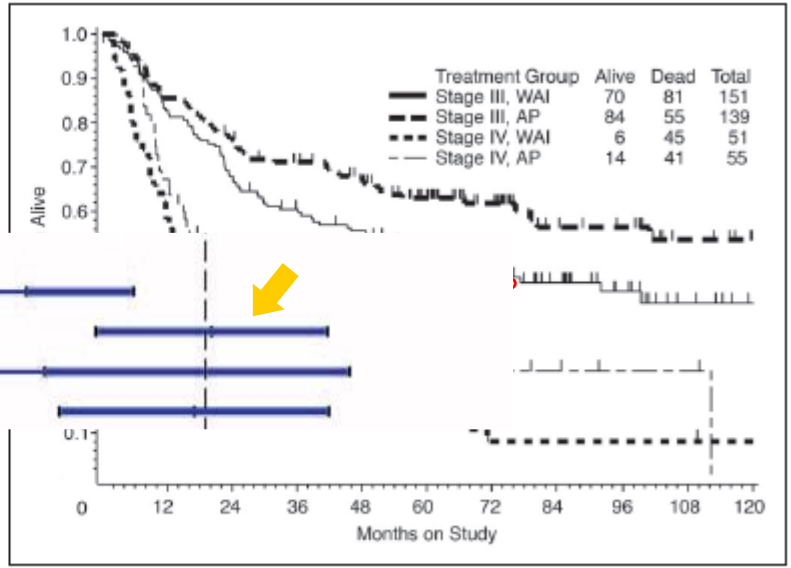


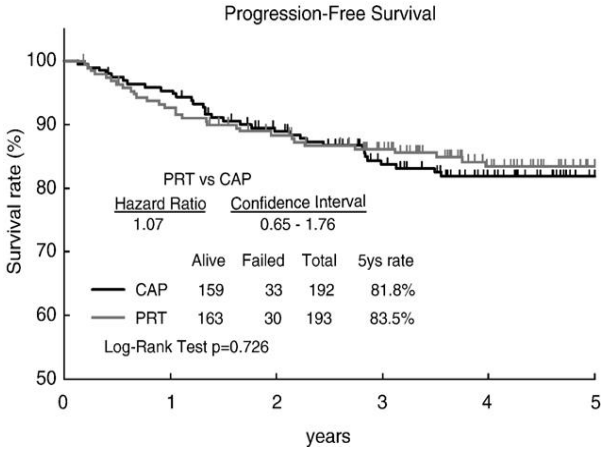
Fig 4. Survival by treatment and stage. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.

Progression-free Survival

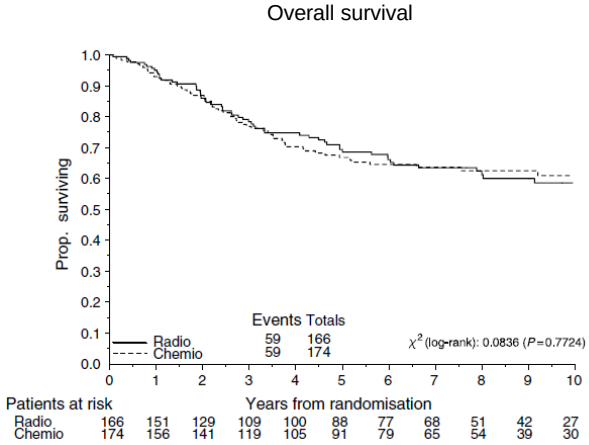
Overall Survival

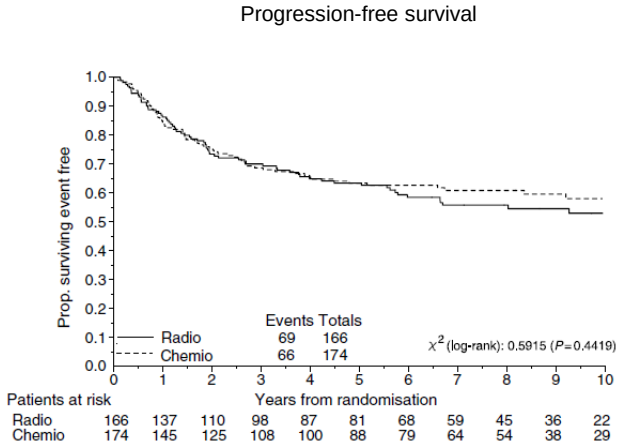
Radiotherapy vs Chemotherapy

JGOG - 385 pts
RT vs chemo* x3



Italian trial - 345 pts
RT vs chemo* x5

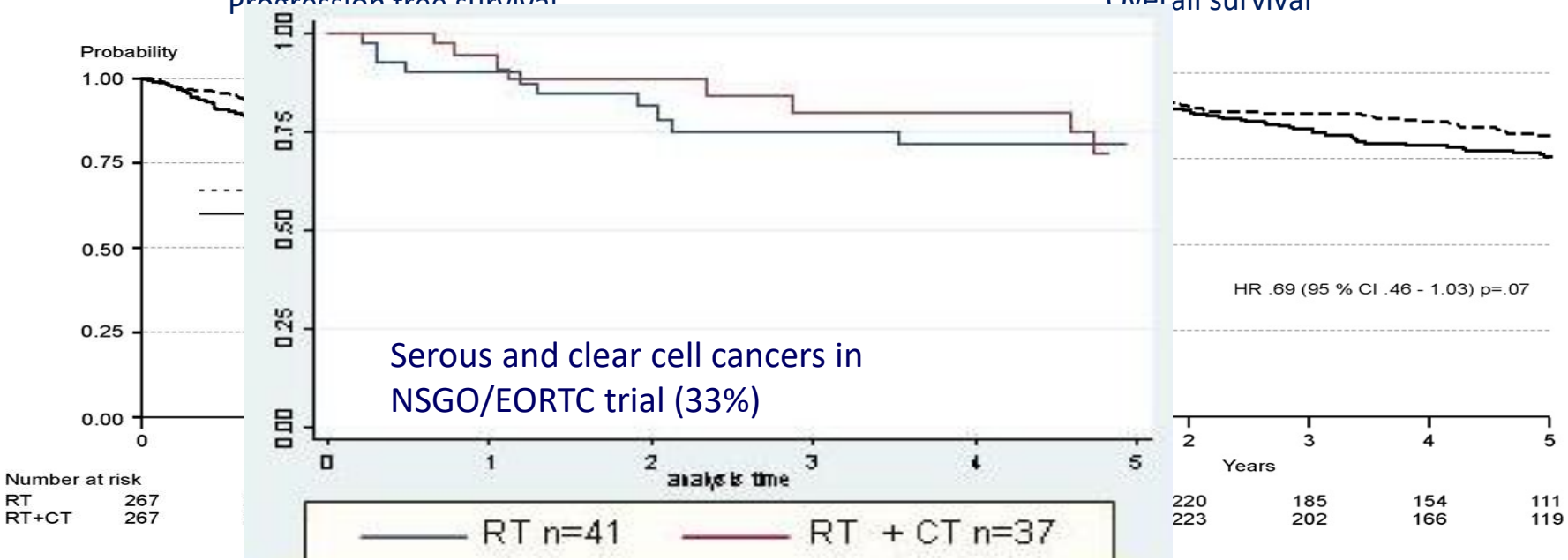




* cyclophosphamide – doxorubicin - cisplatin

- **Radiotherapy delays local recurrence, chemotherapy delays distant metastasis**

Pooled randomised NSGO-EORTC/Iliade trials
Radiotherapy vs RT plus platinum-based chemotherapy x4



PFS 69 vs 78%, p=0.009

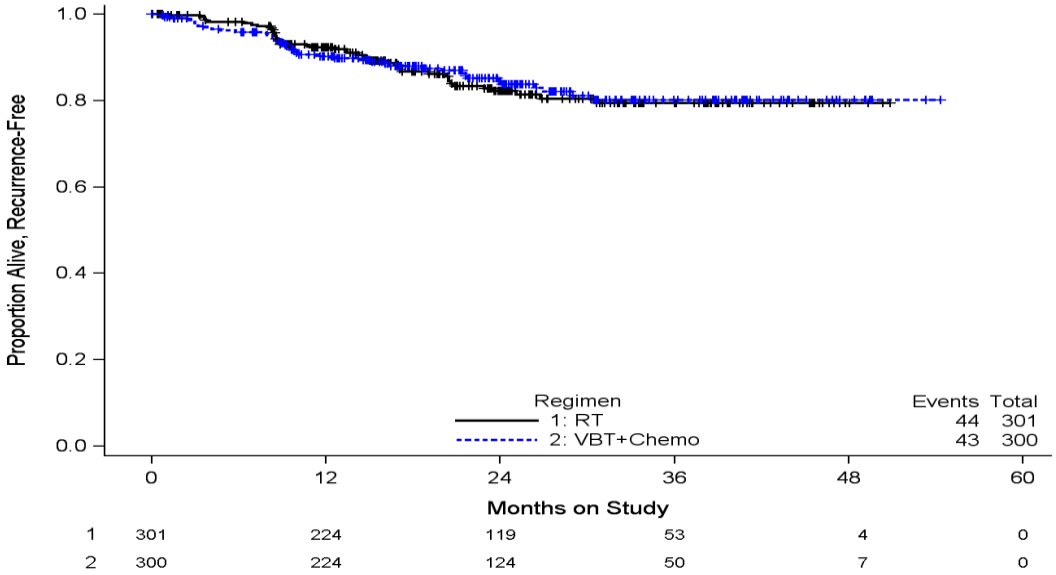
OS 75 vs 82%, p=0.07

First GOG#249 results

- Stage I-II HIR factors
- Stage I-II serous / cc

R → Pelvic RT

R → 3x carboplatin + paclitaxel + VBT



Completed accrual 2012

N=601, primary endpoint PFS

89% underwent lymphadenectomy

15% serous, 5% clear cell, 74% stage I

Update, median FU 53 months

No difference RFS and Overall Survival

First GOG#249 results

Site of Recurrence	Pelvic RT (N=301)	VBT/Chemo (N=300)
Vaginal	5 (1.6%)	3 (1%)
Pelvic	2 (0.6%)	19 (6.3%)
Para-aortic	2 (0.6%)	3 (1%)
Distant	32 (10.6%)	24 (8%)

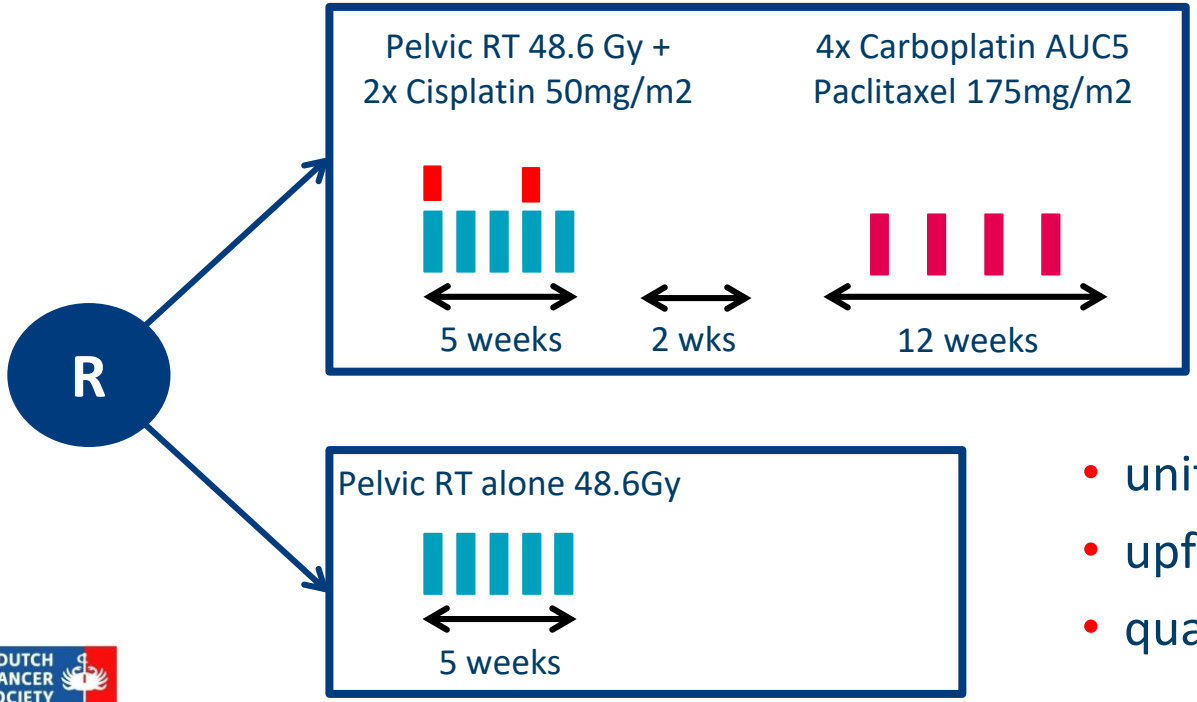
- More acute ≥G3 toxicity with VBT/Chemo N=187 vs 32
- No difference in late ≥G3 toxicity N=37 vs 35

➢ **No superiority of 3 cycles chemo + VBT over EBRT alone**

McMeekin, SGO 2014, Fleming, IGCS 2014; Randall ASTRO 2017

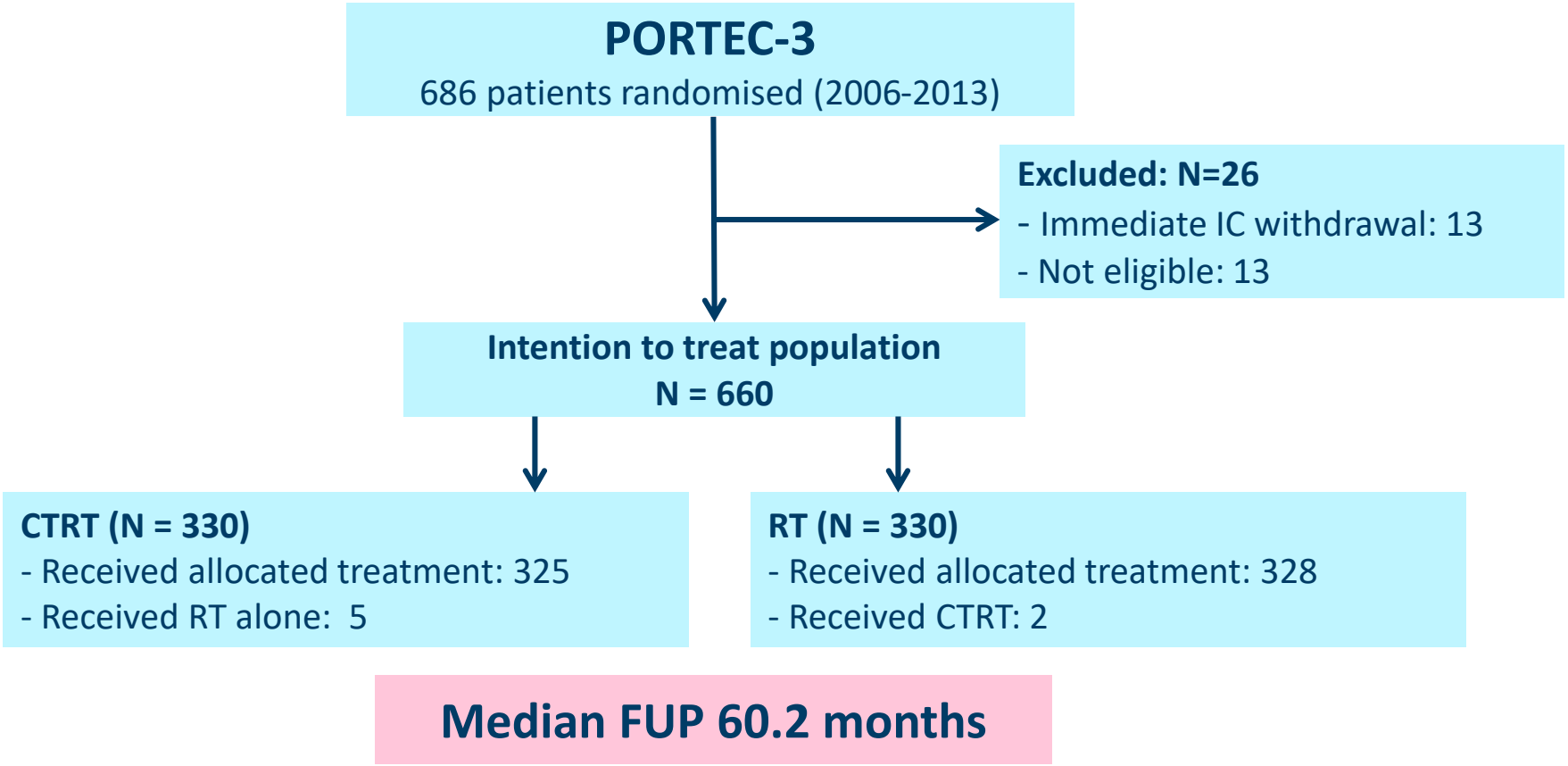
PORTEC-3 trial design

- 686 stage I High risk, stage II/III Endometrial Cancer



- uniform treatment schedule
- upfront pathology review
- quality of life analysis

CONSORT diagram



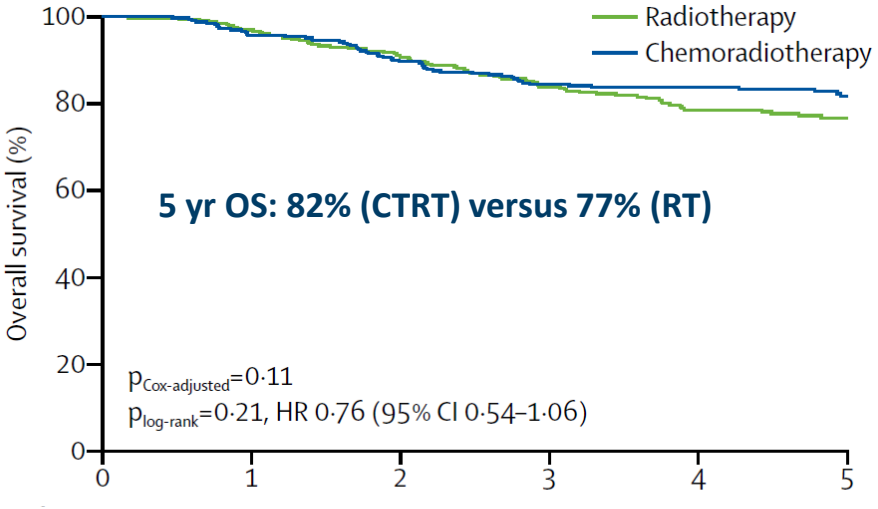
Tumour characteristics

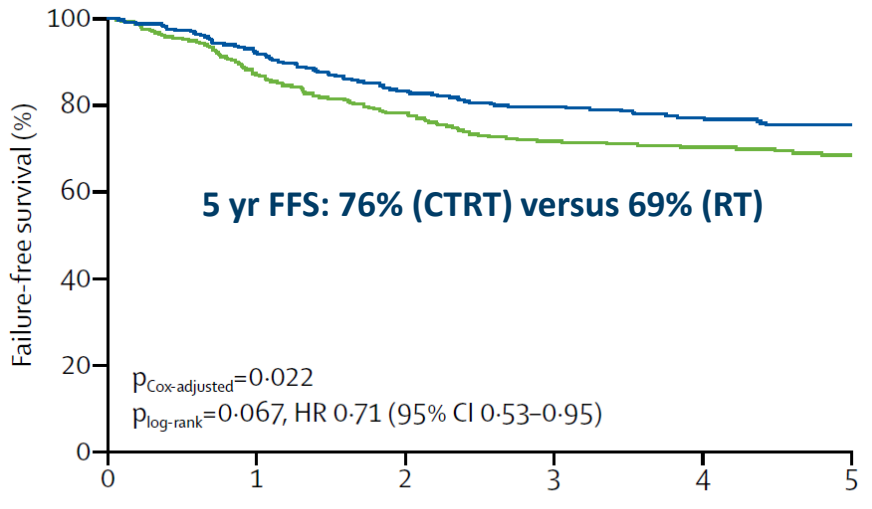
Tumour characteristics	RT alone	CTRT
Histology		
Endometrioid grade 1-2	39.7%	38.5%
Endometrioid grade 3	32.1%	32.4%
Serous/ clear cell/ other	28.2%	29.1%
LVSI		
Yes	58.2%	59.7%
No	41.8%	40.3%
Stage (%)		
I	29.4%	29.7%
II	27.3%	24.2%
III	43.3%	46.1%

Treatment characteristics

Treatment characteristics	RT alone	CTRT
Type of surgery (%)		
TAH or TLH / BSO	41.8%	42.4%
TH/BSO plus LND	58.2%	57.6%
RT completion(%)		
EBRT	98.5%	99.7%
BT boost (cervical invasion)	47.9%	45.8%
CT completion (%)		
2 cisplatin	-	92%
4 carboplatin-paclitaxel	-	79%-71%

Overall & Failure Free Survival





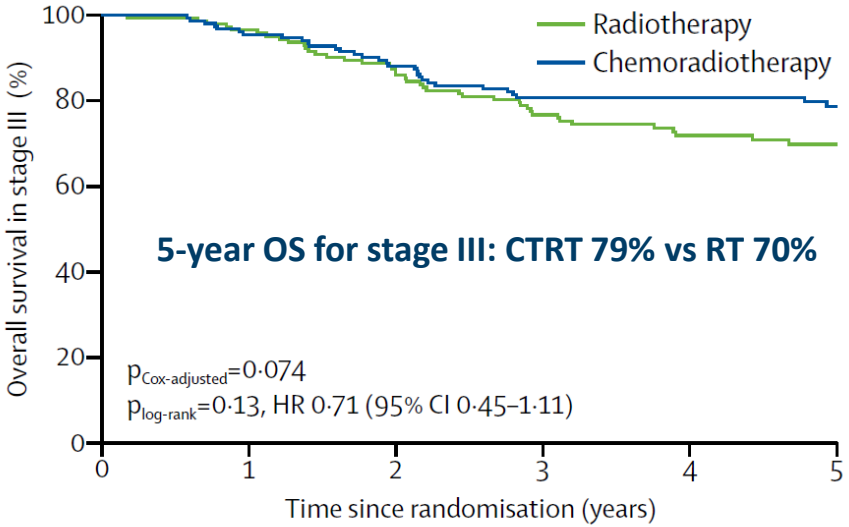
No. at risk (censored)

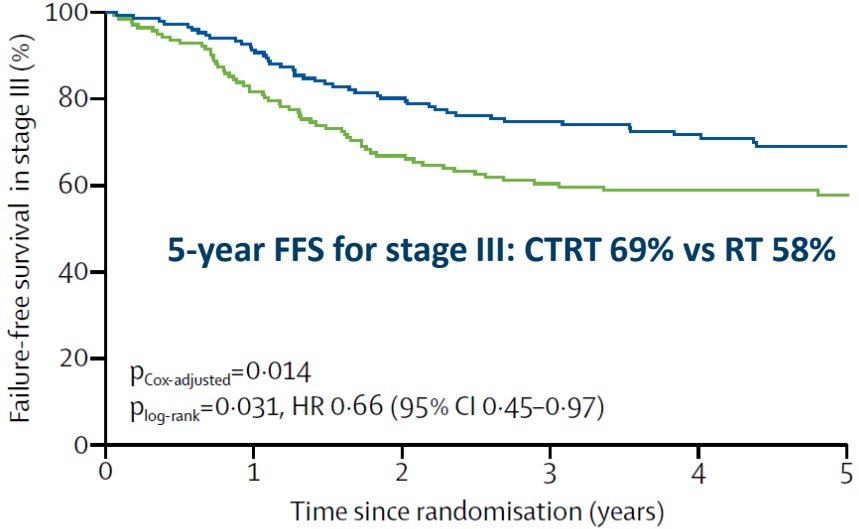
RT	330	319	299	266	202	135	330	286	257	223	178	119
	(0)	(1)	(1)	(11)	(60)	(123)	(0)	(1)	(1)	(10)	(50)	(105)
CTRT	330	316	295	261	208	143	330	304	275	244	192	126
	(0)	(0)	(1)	(18)	(71)	(130)	(0)	(0)	(0)	(16)	(63)	(120)

First sites of recurrence

5 years	CTRT		RT		HR	P-value
	N	%	N	%		
Vaginal recurrence	1	0.30%	1	0.30%	1	1
Pelvic recurrence	3	0.95%	5	1.5%	0.60	0.478
Distant recurrence	76	22.4%	93	28.3%	0.78	0.108
- Distant + vaginal	4	1.2%	4	1.2%	-	-
- Distant + pelvic	11	3.2%	20	6.1%	-	-
- Distant only	61	18.0%	69	21.0%	-	-

Patients with Stage III EC



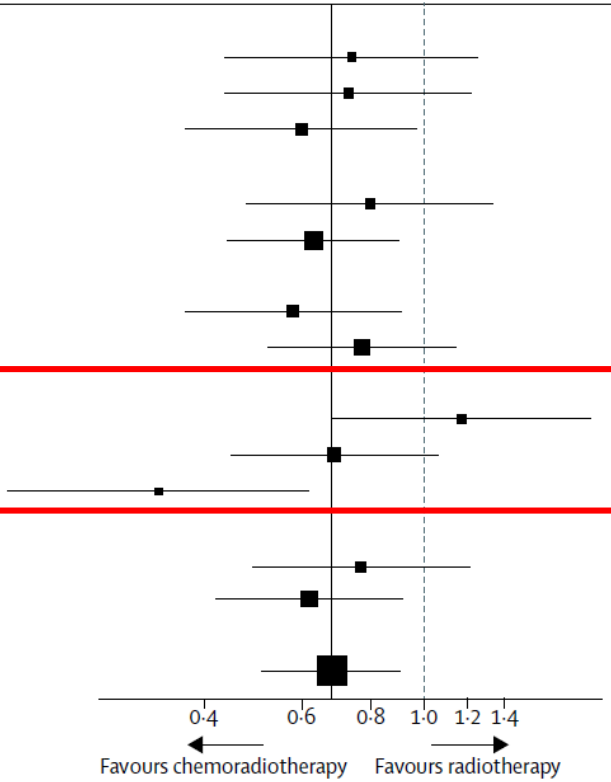


No. at risk (censored)

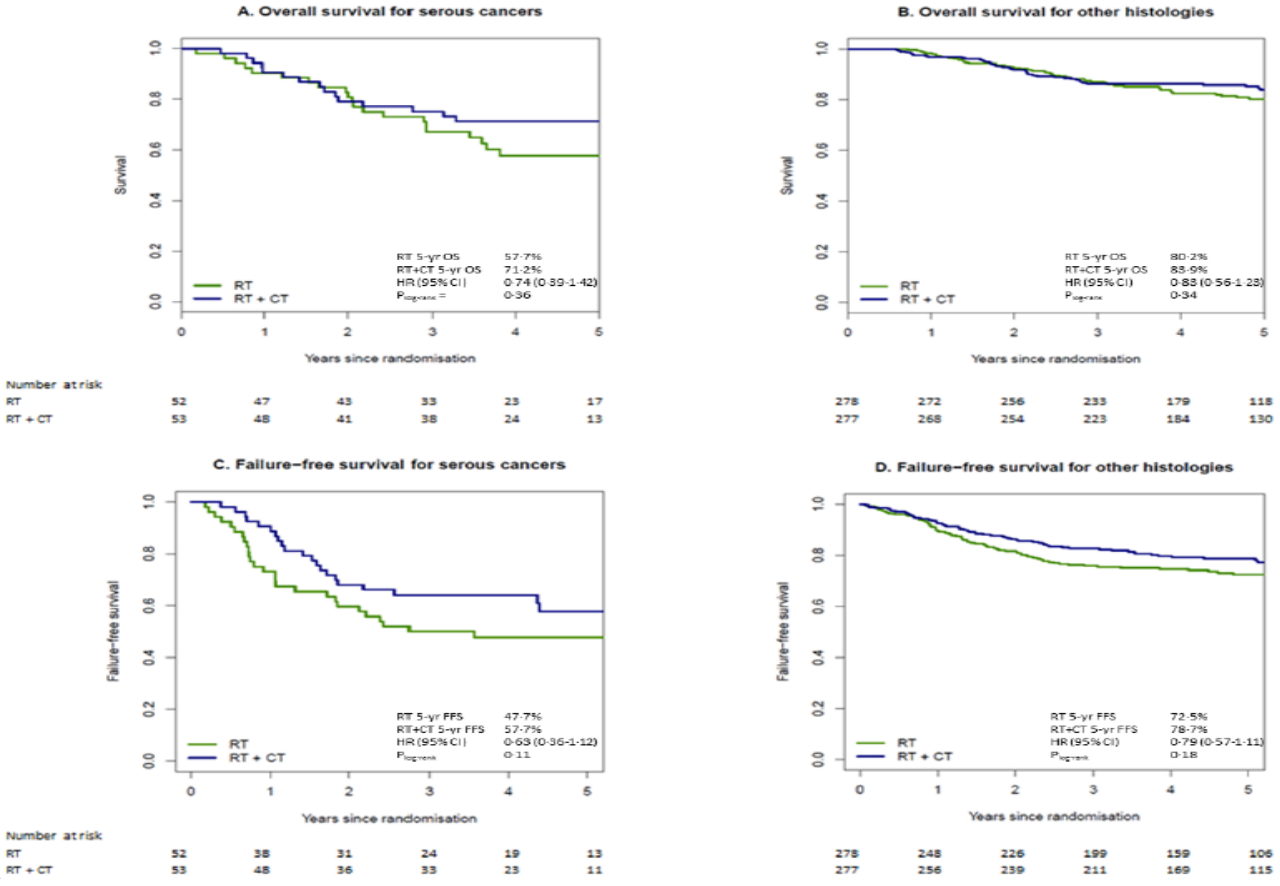
RT	143	137	123	106	81	49	143	116	95	82	67	40
	(0)	(1)	(1)	(4)	(23)	(53)	(0)	(1)	(1)	(5)	(18)	(44)
CTRT	152	145	133	115	98	69	152	139	122	106	88	57
	(0)	(0)	(1)	(8)	(26)	(52)	(0)	(0)	(0)	(8)	(23)	(50)

Forest plot of multivariable analysis (treatment covariate)

	Radiotherapy		Chemoradiotherapy		Chemoradiotherapy vs radiotherapy		
	Events/ patients	5-year failure-free survival (95% CI)	Events/ patients	5-year failure-free survival (95% CI)	HR (95% CI)	p value	$p_{interaction}$
Histology and grade							
Endometrioid grade 1–2	32/131	75% (66–82)	26/127	82% (74–88)	0·74 (0·44–1·26)	0·27	0·79
Endometrioid grade 3	32/106	69% (59–77)	28/106	74% (64–81)	0·73 (0·44–1·22)	0·23	
Serous, clear cell, other	39/93	59% (48–68)	29/93	69% (58–77)	0·60 (0·37–0·97)	0·036	
LVSI							
No	32/138	77% (68–83)	30/133	78% (69–84)	0·80 (0·48–1·33)	0·39	0·45
Yes	71/192	63% (55–69)	53/197	74% (67–80)	0·63 (0·44–0·90)	0·012	
Lymphadenectomy							
No	46/138	67% (58–74)	35/140	76% (68–83)	0·58 (0·37–0·91)	0·016	0·34
Yes	57/192	70% (63–76)	48/190	75% (68–81)	0·77 (0·52–1·14)	0·19	
Age (years)							
<60	26/140	81% (73–87)	28/128	81% (72–87)	1·17 (0·68–2·00)	0·57	0·012
60–69	47/128	62% (53–71)	40/144	71% (62–79)	0·69 (0·45–1·06)	0·094	
≥70	30/62	53% (40–65)	15/58	75% (61–85)	0·33 (0·18–0·63)	<0·001	
FIGO stage							
Stage I and II	43/187	77% (70–82)	35/178	81% (74–86)	0·77 (0·49–1·21)	0·26	0·47
Stage III	60/143	58% (49–66)	48/152	69% (61–76)	0·62 (0·42–0·91)	0·014	
Total	**103/330**	**69% (63–73)**	**83/330**	**76% (70–80)**	**0·68 (0·51–0·91)**	**0·010**	

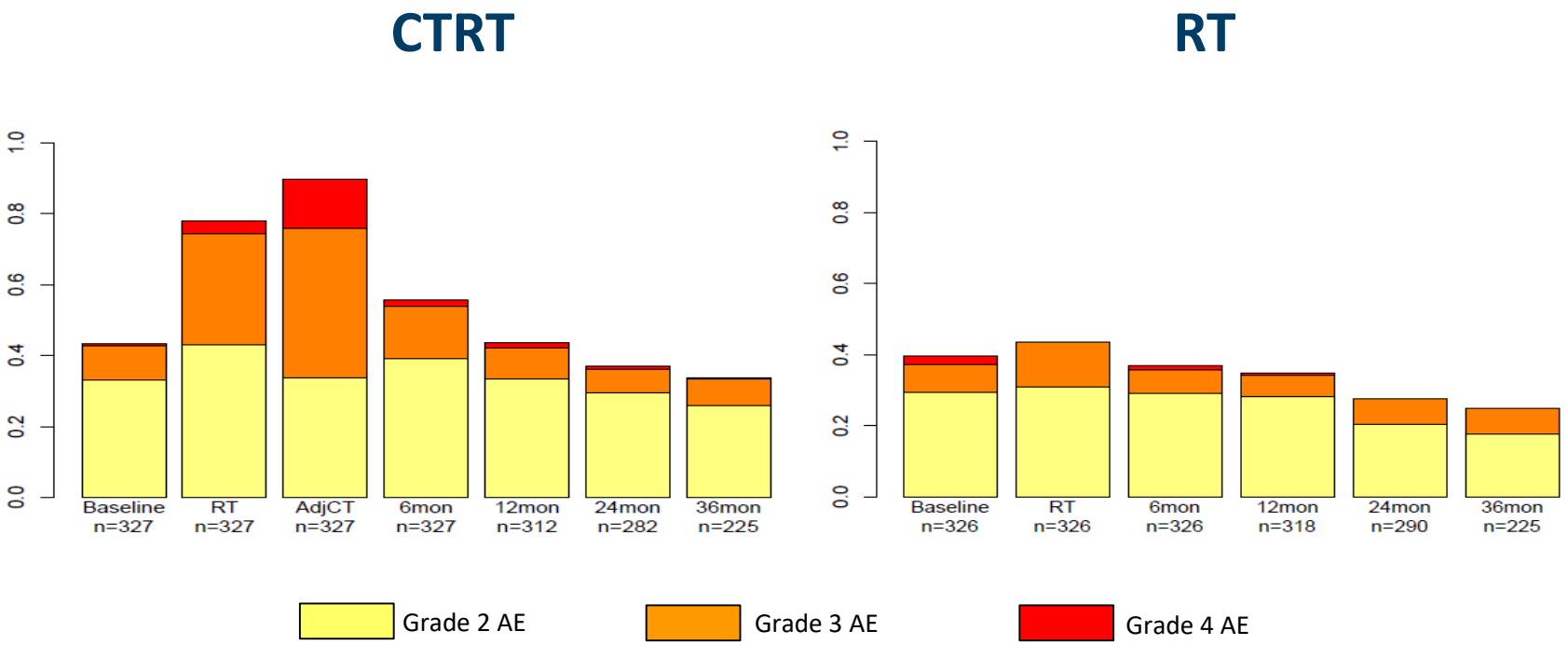


Survival by histology

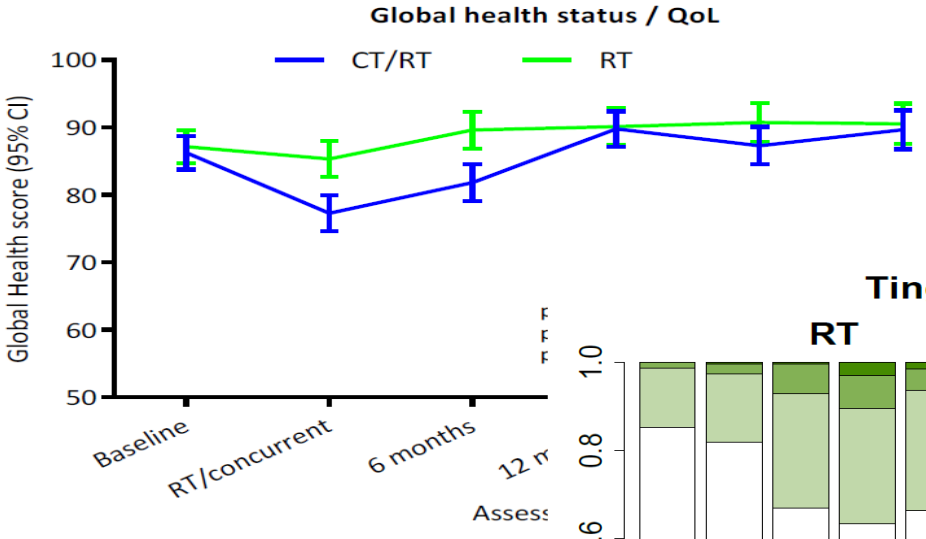


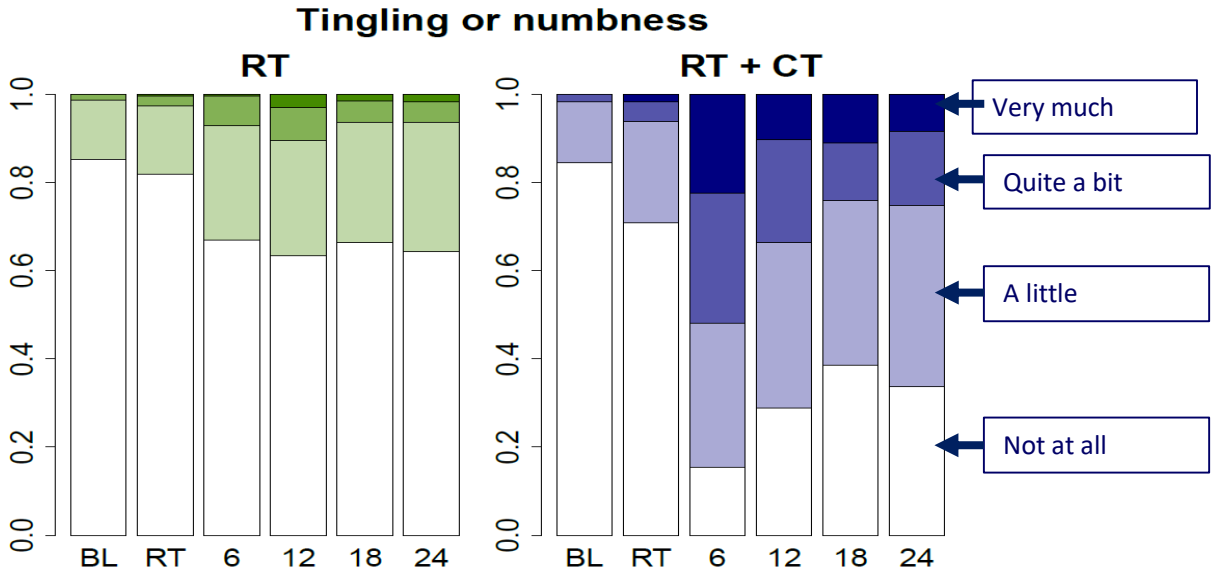
De Boer et al. Lancet Oncology 2018

Adverse events (CTCAE v 3.0)



Quality of life





Conclusions

CTRT vs RT for high-risk endometrial cancer:

- Improved 5-year FFS, no overall survival benefit
  - All patients 7% FFS benefit with CTRT
  - Stage III: 11% FFS benefit with CTRT
- Significantly more toxicity with CTRT in the first 12 months
- OS analysis may need longer follow-up

GOG-258 design

- N= 813 patients
- 18% serous cancer
- Median FUP 47 months

TAH/BSO, Pelvic and para-aortic lymph node sampling optional

Eligibility:
Surgical Stage III or IVA EC (FIGO 2009)
Stage I or II clear cell or serous EC + cytology
GOG Performance Status of 0-2
Adequate organ function

Ineligible Patients
Carcinosarcoma
Recurrent EC
Residual tumor after surgery > 2 cm

Randomization 1:1

Regimen 1: C-RT (n=407)

Cisplatin 50 mg/m² IV Days 1 and 29 plus **Volume-directed radiation therapy (45Gy+/- brachytherapy)**
followed by
Carboplatin AUC 5* plus Paclitaxel 175 mg/m² q 21 days for 4 cycles with G-CSF support

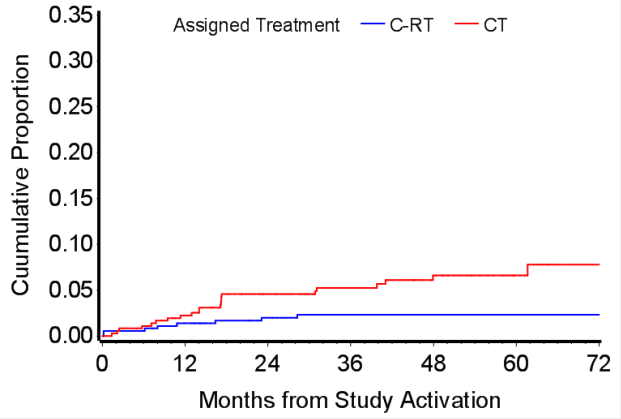
Regimen 2: CT (N=406)

Carboplatin AUC 6 plus Paclitaxel 175 mg/m²
q 21 days for 6 cycles

Stratification:
Age >/< 65
Gross residual disease

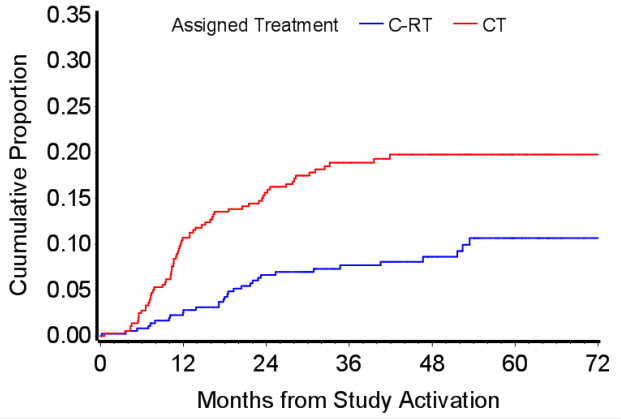
First GOG-258 results

Vaginal Recurrence



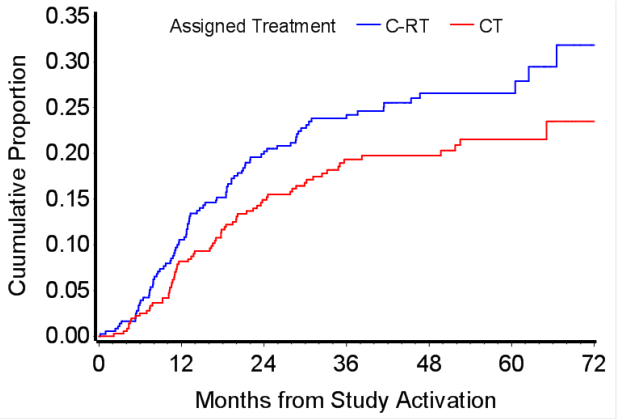
C-RT vs. CT : HR=0.36 (CI: 0.16-0.82)

Pelvic and PA Recurrence



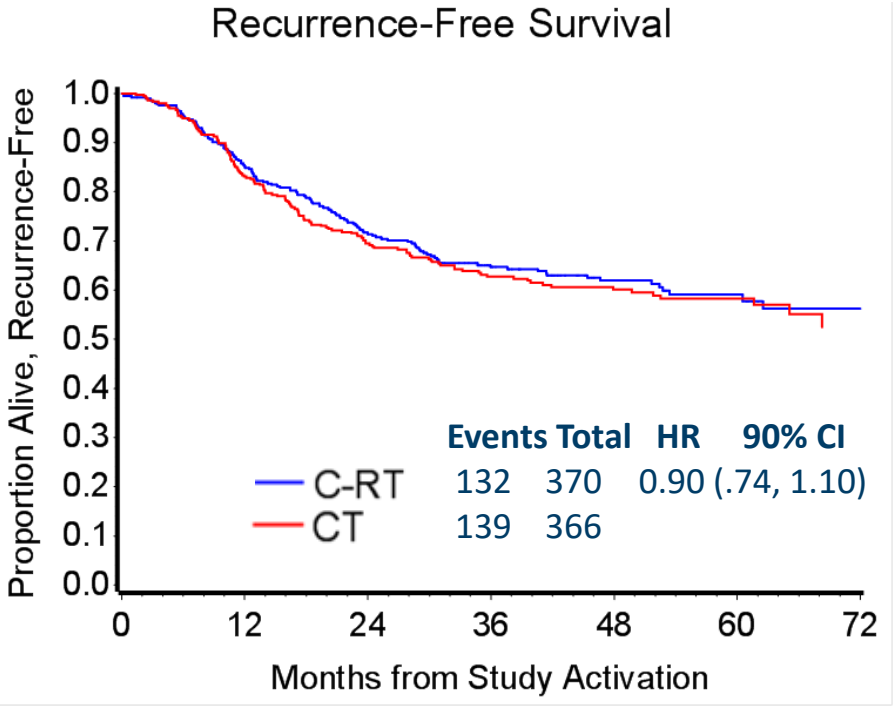
HR=0.43 (CI: 0.28-0.66)

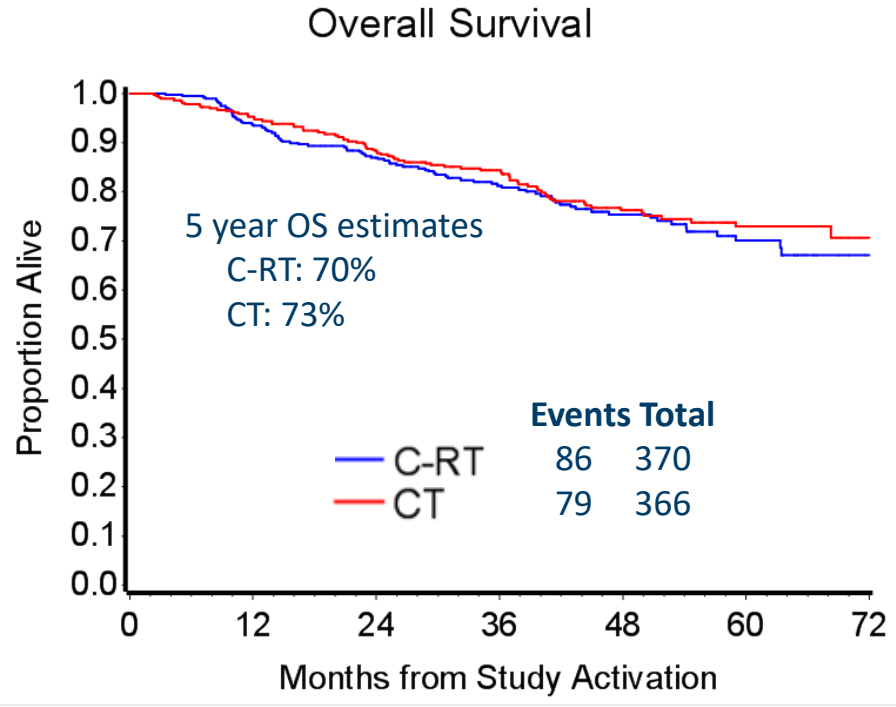
Distant Recurrence



HR=1.36 (CI: 1.00-1.86)

First GOG-258 results





Data cut-off 03/09/2017 Data not mature for final analysis

Conclusion High Risk: CT+RT vs RT

- NSGO-EORTC/Iliade: significant PFS benefit (9%); trend for OS (7%)
- PORTEC-3: trend for improved FFS (7%) with CT+RT
- Does benefit outweigh the added toxicity, without OS benefit?
- Good pelvic control with RT alone (PORTEC-3 and GOG-249)

➢ CT+RT schedule cannot be recommended as standard for stage I-II

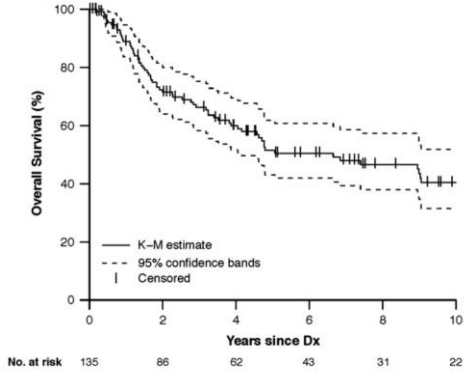
- Translational studies will hopefully identify those who benefit

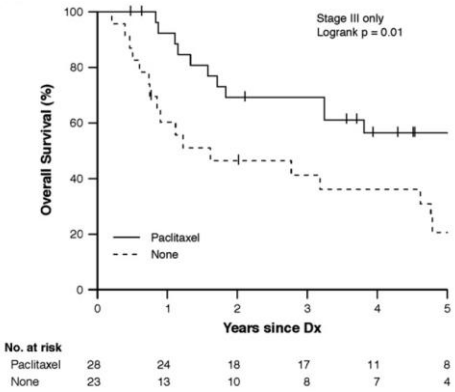
➢ Stage III disease largest FFS improvement with both CT+RT and CT

- PORTEC-3 significant 11% FFS benefit for stage III with CT+RT
- GOG-258 better local control with CT+RT

Serous and clear cell

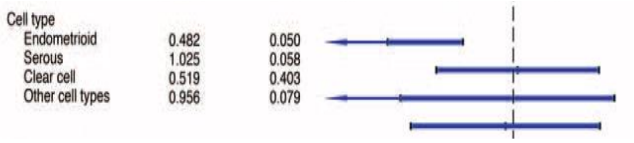
- Largest retrospective analysis suggest benefit of chemotherapy



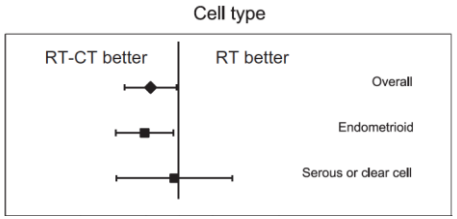


- Subgroups in randomized trials, no clear benefit:

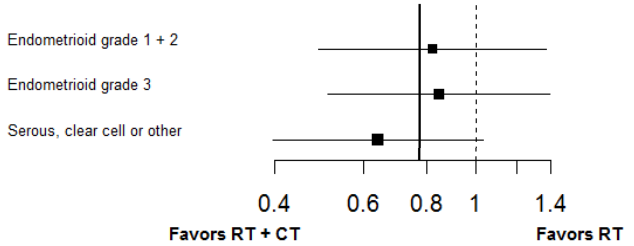
GOG-122



NSGO-EORTC/Iliade



PORTEC-3



Hasegawa K. Int J Gynecol Cancer 2014; Viswanathan Gynecol Onc 2011; Randall JCO 2006; Hogberg EJC 2010; De Boer ASCO 2017

Serous and clear cell

- Stage I serous and clear cell
  - 103 patients: 26% non-invasive; 58% <50% invasion
  - 34% received adjuvant chemotherapy
  - 5-year isolated pelvic recurrence rate 4%, locoregional recurrence 7%
  - 5-year OS 84%

- Vaginal brachytherapy alone sufficient in stage IA

Stage II

Int J Gynecol Cancer 2008, **18,** 1071–1078

Multicenter cohort study on treatment results and risk factors in stage II endometrial carcinoma

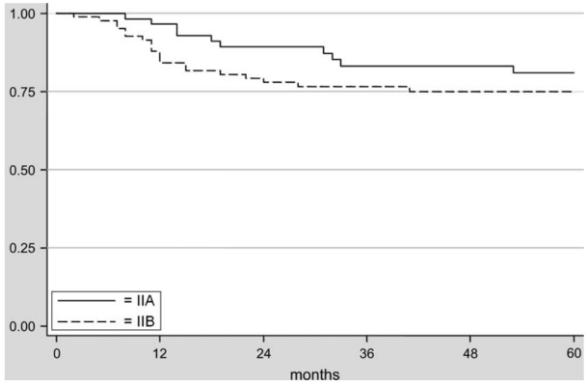
J.J. JOBSEN*, M.L.M. LYBEERT†, E.M. VAN DER STEEN-BANASIK‡, A. SLOT§, J. VAN DER PALEN‖, L.N. TEN CATE¶, A. SCHOLTEN#, V. COEN**, E.M.J. SCHUTTER†† & S. SIESLING‡‡

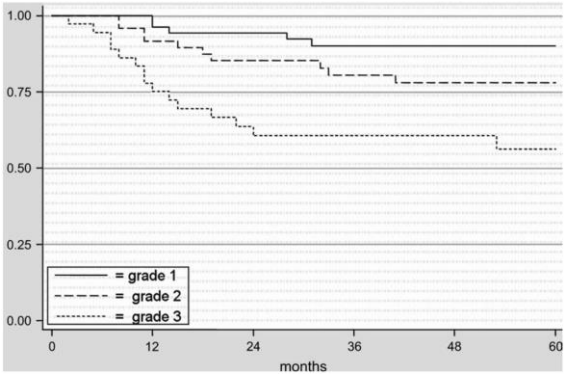
**Department of Radiation Oncology, Medisch Spectrum Twente, Enschede, The Netherlands; †Department of Radiation Oncology, Catharina Hospital, Eindhoven, The Netherlands; ‡Radiotherapeutic Institute Arnhem, Arnhem, The Netherlands; §Radiotherapy Institute Friesland, Leeuwarden, The Netherlands; ‖Department of Epidemiology, Medisch Spectrum Twente, Enschede, The Netherlands; ¶Laboratorium Pathologie Oost Nederland, Enschede, The Netherlands; #Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands; **Zeeuws Radiotherapy Institute, Vlissingen, The Netherlands; ††Departments of Obstetrics and Gynaecology, Medisch Spectrum Twente, Enschede, The Netherlands; ‡‡Comprehensive Cancer Centre Stedendriehoek Twente, Enschede, The Netherlands*

Table 1. Patient and histologic characteristics in 142 patients according to stage

Characteristics	Stage IIA 59 (%)	Stage IIB 83 (%)	*P*
Age (years)			
<60	12 (20.3)	18 (21.7)	NS
≥60	47 (79.7)	65 (78.3)	
Grade			
1	26 (44.1)	28 (33.8)	
2	22 (37.3)	27 (32.5)	NS
3	10 (16.9)	27 (32.5)	
Unknown	1 (1.7)	1 (1.2)	
MI			
>0.5	29 (49.2)	67 (80.7)	<0.001
<0.5	29 (49.2)	16 (19.3)	
Unknown	1 (1.6)	0	
LVSI			
Yes	7 (11.9)	32 (38.6)	<0.001
None	52 (88.1)	51 (61.4)	
Brachytherapy			
Yes	26 (44.1)	47 (56.6)	
None	33 (55.9)	36 (43.4)	NS

		IIA	IIB
vaginal recurrence		5.1% (3/59)	10.8% (9/83)
VBT	yes	1	4
	no	2	5
Grade	1		
	2	3	2
	3		7





Stage II

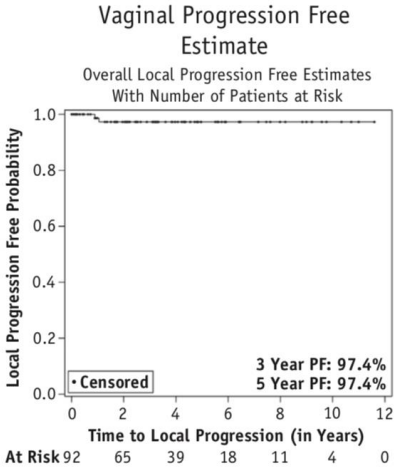
International Journal of Radiation Oncology biology • physics
www.redjournal.org

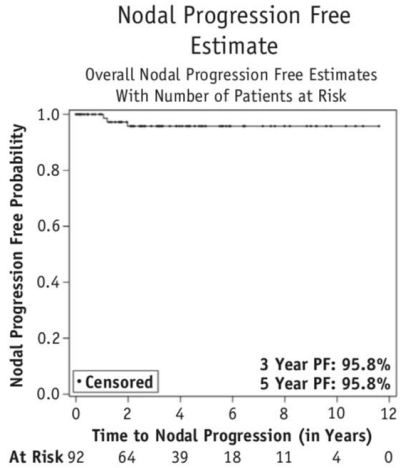
Clinical Investigation

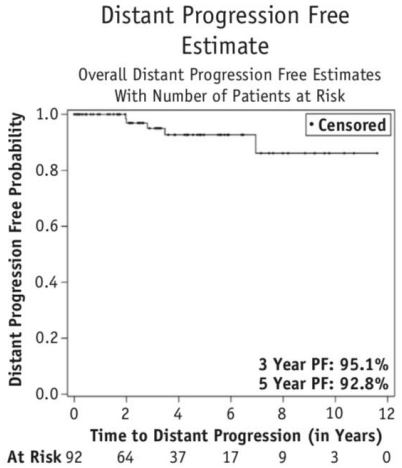
Multi-institutional Analysis of Vaginal Brachytherapy Alone for Women With Stage II Endometrial Carcinoma

Matthew M. Harkenrider, MD,* Brendan Martin, PhD,† Karina Nieto, MD,‡ Christina Small, MPH,* Ibrahim Aref, MD,§ David Bergman, MD,§ Anupama Chundury, MD,‖ Mohamed A. Elshaikh, MD,§ David Gaffney, MD, PhD, FAST Anuja Jhingran, MD,# Larissa Lee, MD,** Ima Paydar, MD, Kisuk Ra, MD,# Julie Schwarz, MD, PhD,‖ Cameron Thorpe, Akila N. Viswanathan, MD, MPH,†† and William Small, Jr, MD, FACRO, FACR, FASTRO*

- Adjuvant VBT alone acceptable in grade 1 or 2 disease and microscopic cervical stromal after pelvic LND.

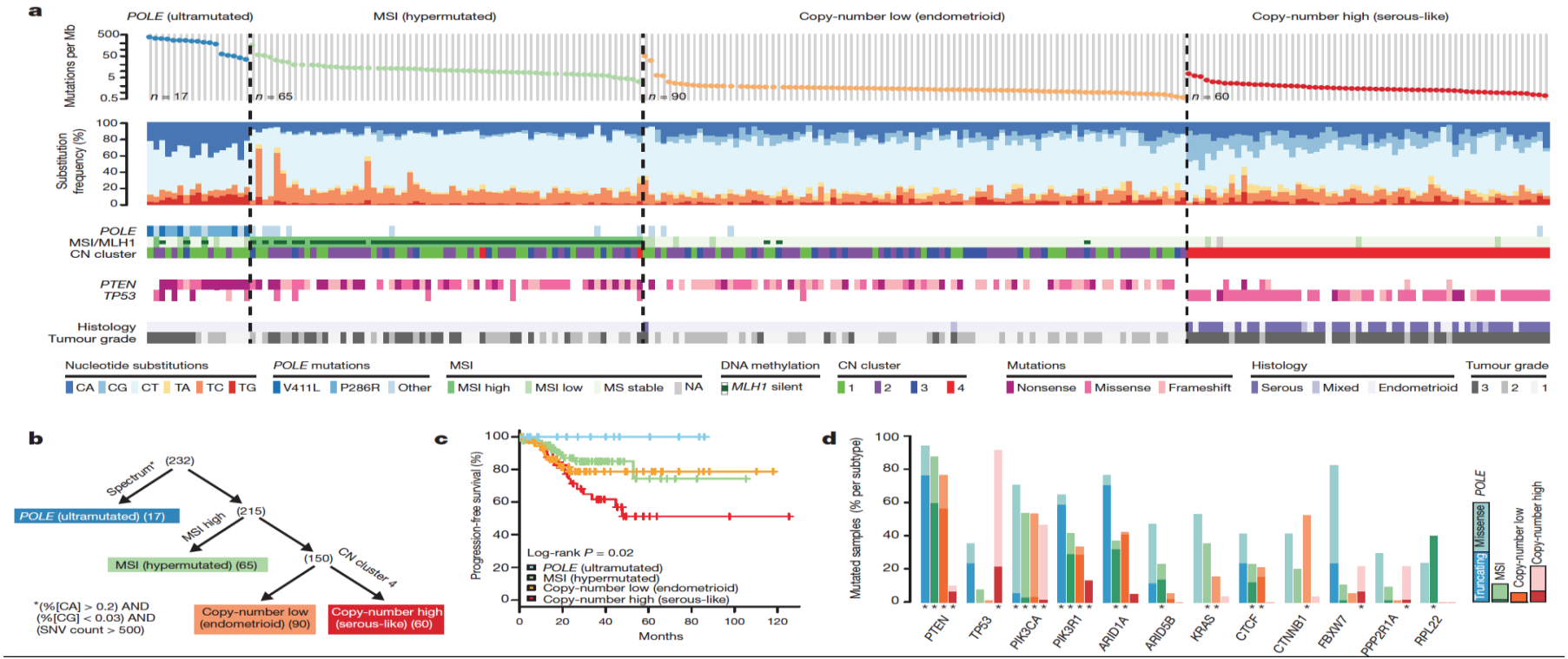






Upcoming molecular prognostic factors and ongoing trials

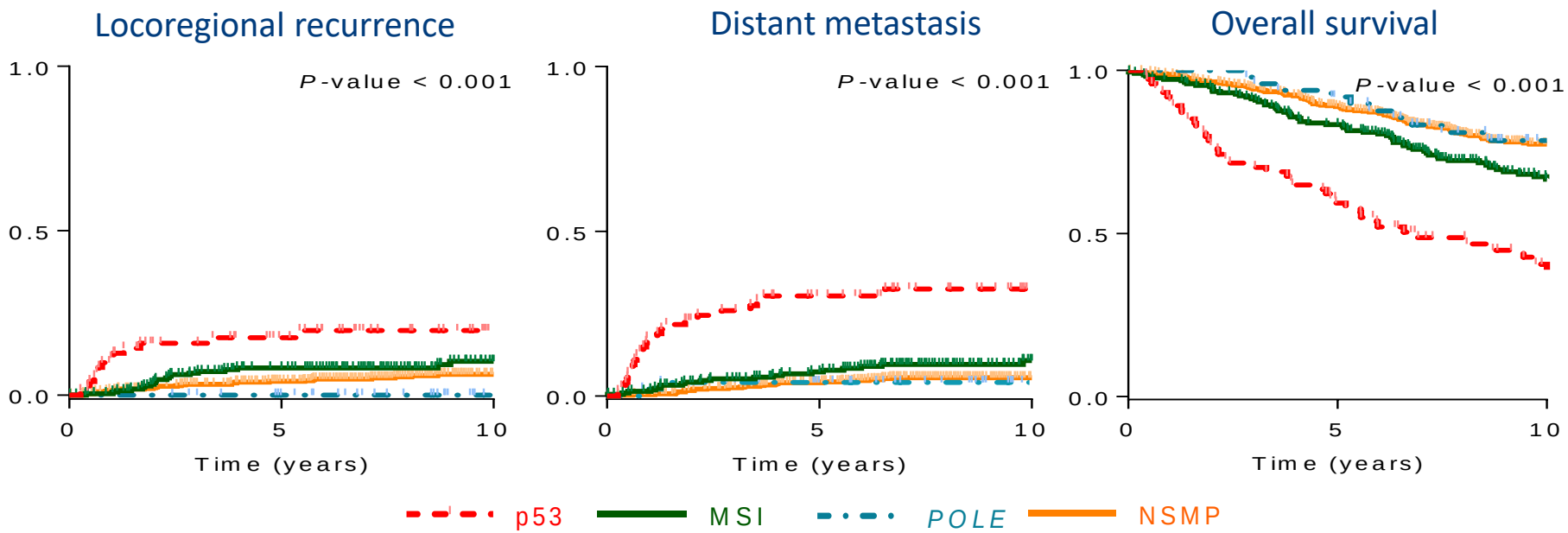
Molecular characteristics of endometrial cancer



TGCA, Kandoth et al, Nature 2013

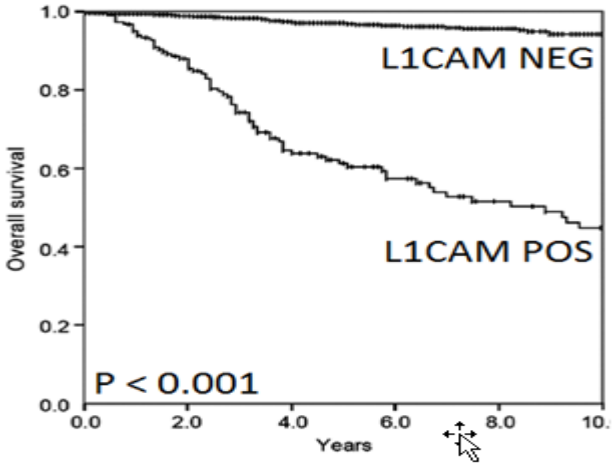
Molecular analysis PORTEC-1 and 2 cohort (N=834)

The 4 TCGA subgroups by surrogate markers

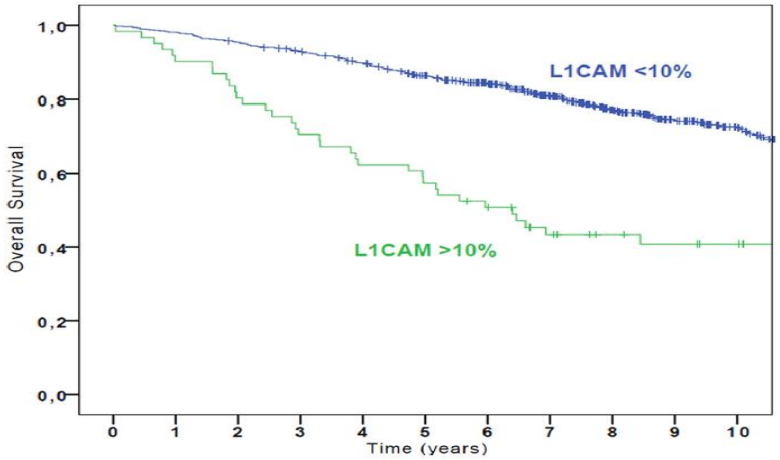


L1-CAM

Zeimet et al 2013



Bosse et al 2014



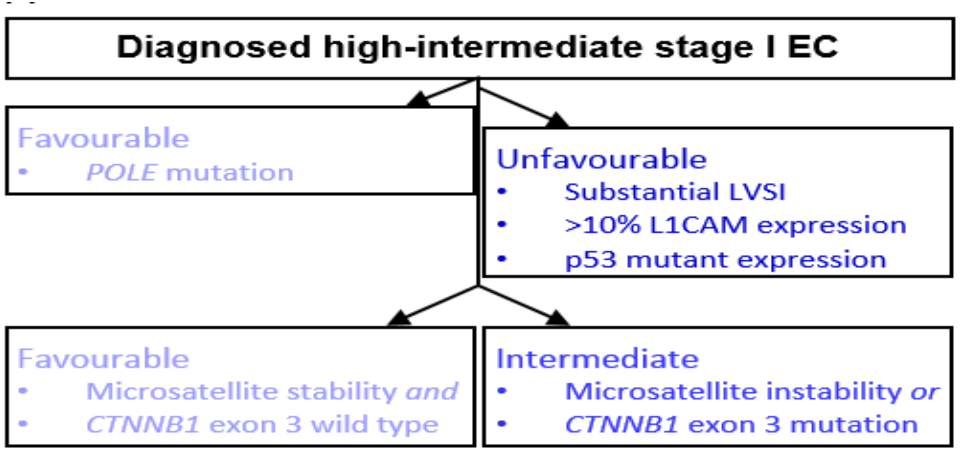
L1-CAM strong negative prognostic factor

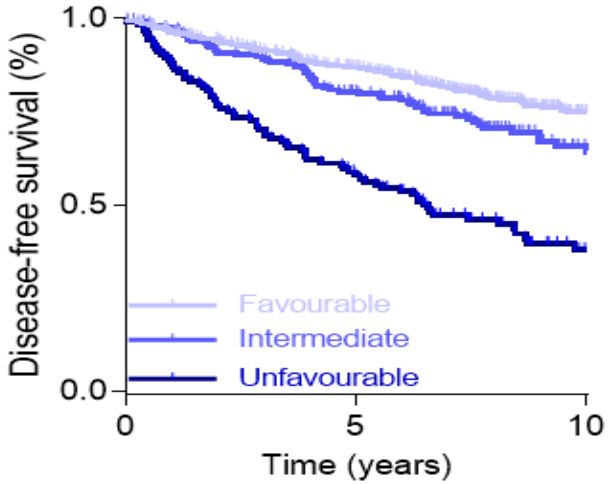
- About 7-10% overall L1CAM+
- More often L1CAM+ in grade 3, p53+, NEEC
- Confirmed in large ENITEC series (n=1200)

ENITEC
ESGO European Network for Individualised Treatment of Endometrial Cancer

Zeimet, JNCI 2013; Bosse, EJC 2014; Van der Putten for ENITEC, Br J Cancer 2016

Molecular integrated risk profile PORTEC-1 and 2 cohort

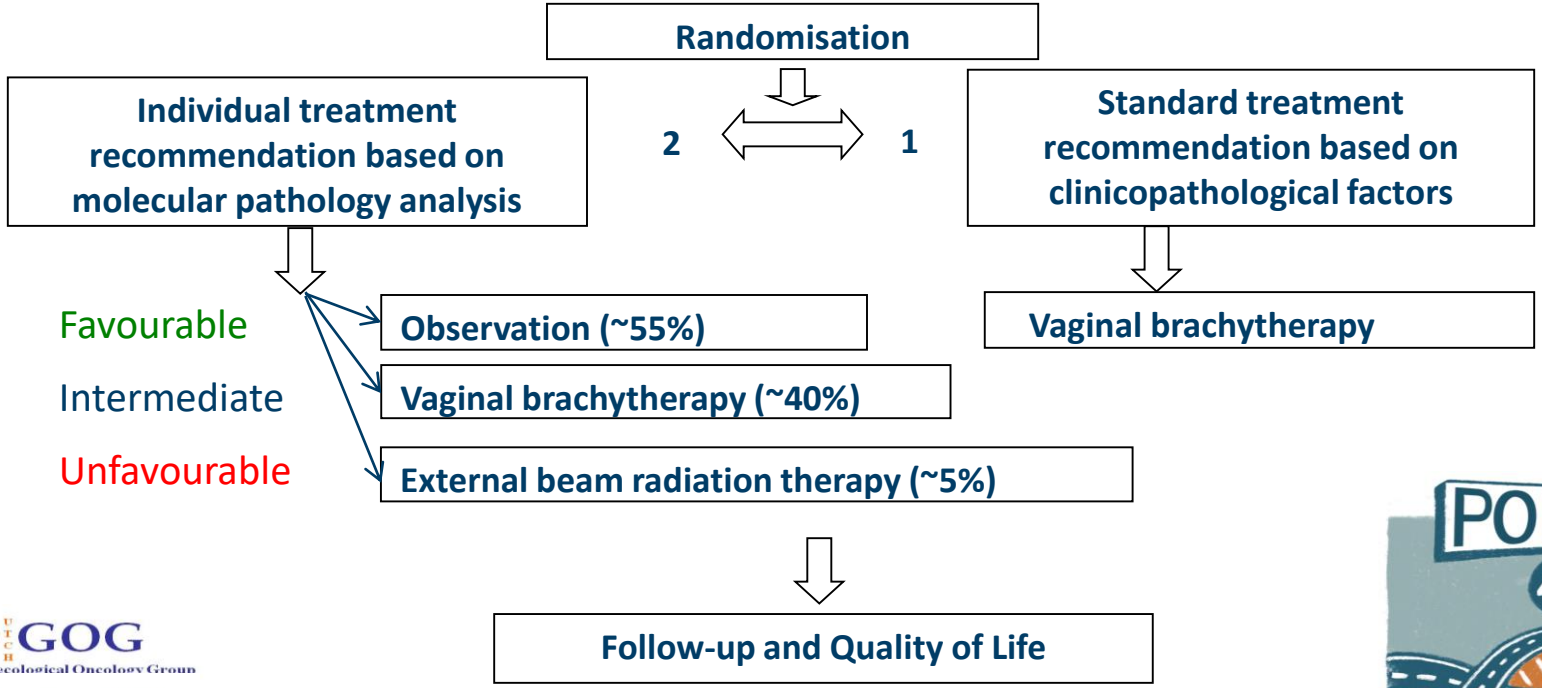




- **55%** of high-intermediate risk patients reclassified to **favourable**
- **15%** of high-intermediate risk patients reclassified to **unfavourable**

PORTEC-4a trial design

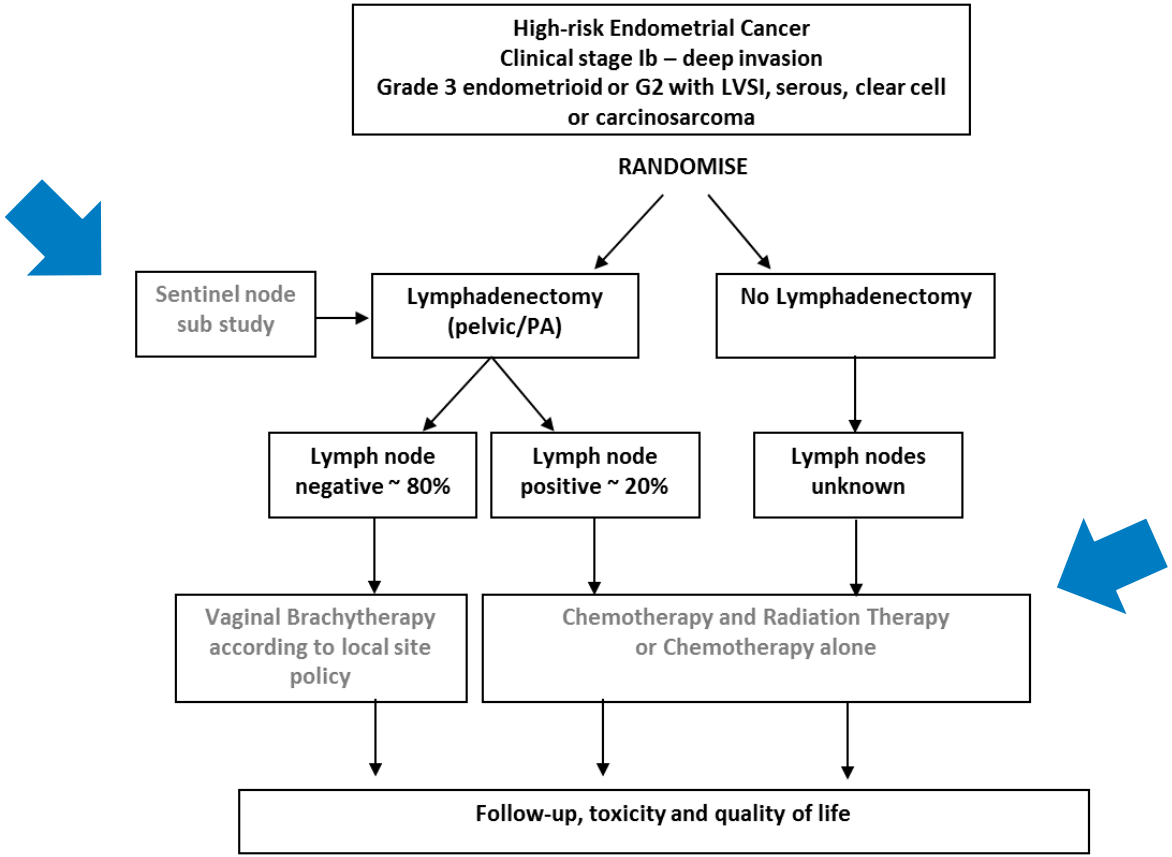
- **Molecular integrated vs standard indications for adjuvant treatment:**



DUTCH GOG
Dutch Gynaecological Oncology Group

DUTCH CANCER SOCIETY

STATEC trial in high risk endometrial cancer



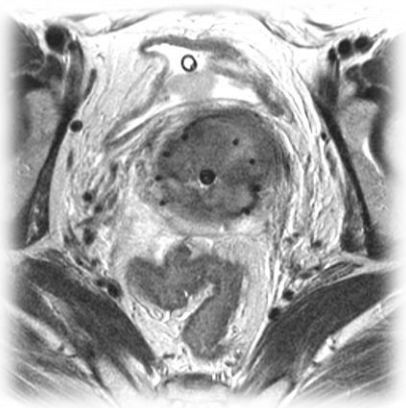
GYNECOLOGIC CANCER INTERGROUP

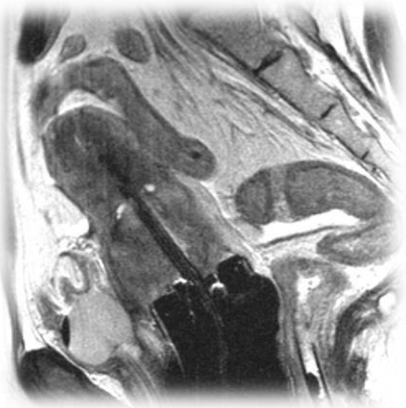
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Thank You!

Interpretation of Imaging at Brachytherapy

Radiation oncologist's perspective





Primoz Petric

Aarhus University Hospital, Denmark

Overview

Presentation:

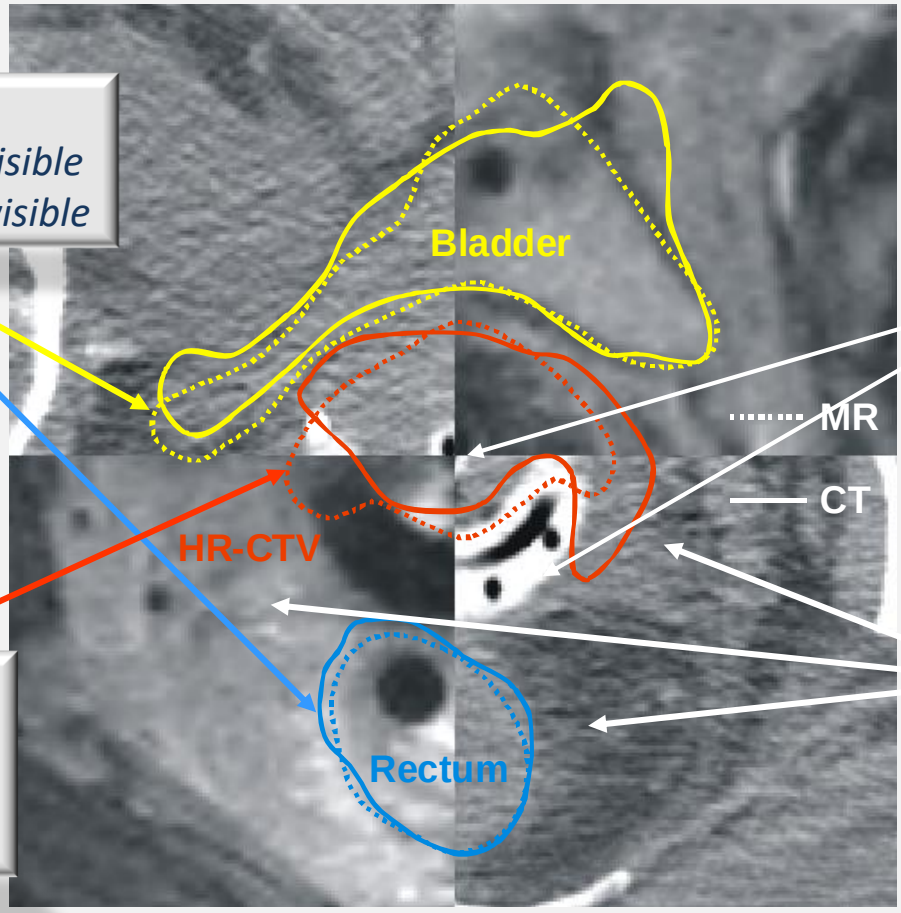
- Choice of imaging modality for IGABT
- MRI protocol
- Interpretation of MRI findings

Slides (if time permits):

- CT protocol for IGABT
- Interpretation of CT findings

Choice of imaging modality for IGABT

Target, Organs, Applicator



OAR
MRI: organ wall is visible
CT: organ border is visible

Applicator
MRI↑
CT↑

Target
MRI: HR-CTV, GTV
CT: +/-HR-CTV
(soft tissue depiction ↓)

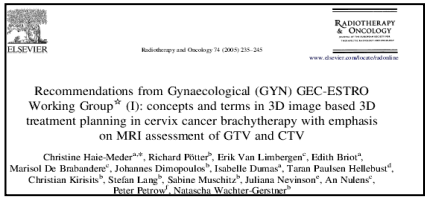
Anatomical Structures
MRI↑
CT ↓

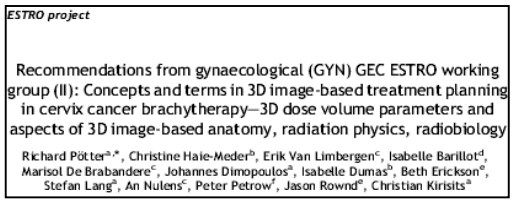
From: Viswanathan et al. IJROBP 2007

Choice of imaging modality for IGABT

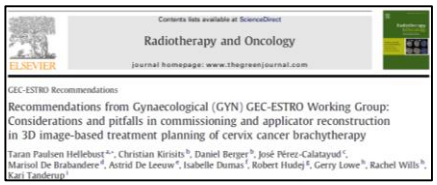
Magnetic Resonance Imaging

- Soft tissue depiction
- Multiplanar imaging
- Published Recommendations
- Clinical Results


Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group* (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV


ESTRO project

Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology


Radiotherapy and Oncology

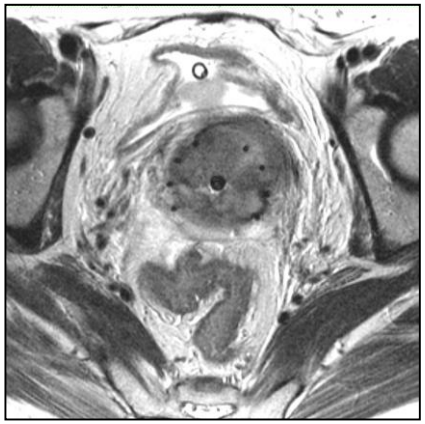
GEC-ESTRO Recommendations

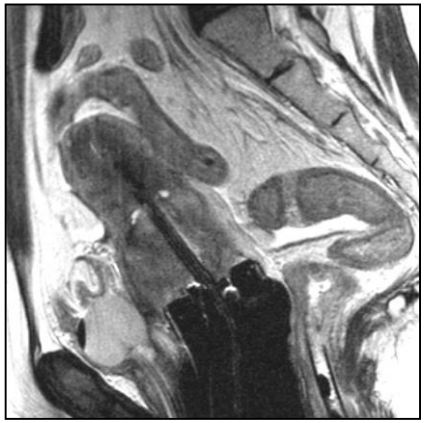
Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group: Considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer brachytherapy

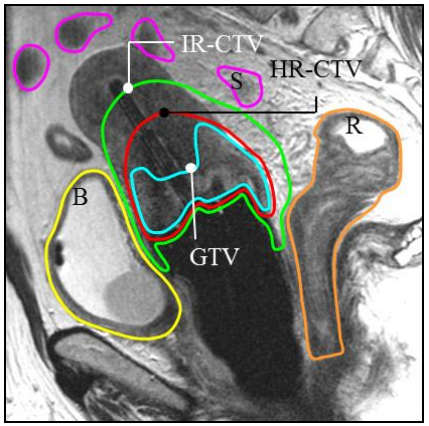

Radiotherapy and Oncology

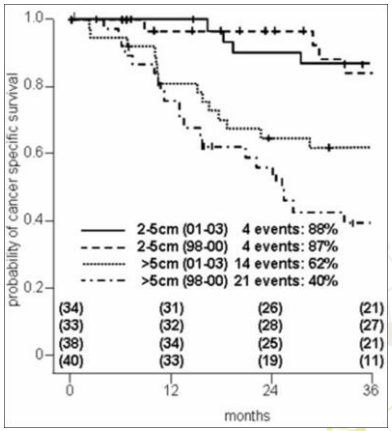
GEC-ESTRO Recommendations

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy









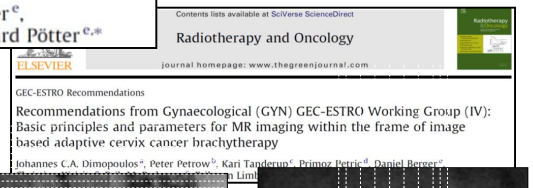
Haie-Meder C et al. Radiother Oncol 2005
Pötter R et al. Radiother Oncol 2006
Hellebust T et al. Radiother Oncol 2010
Dimopoulos JCA et al. Radiother Oncol 2011

Pötter. Radiother Oncol 2011
Pötter. Radiother Oncol 2007
Lindegaard J. Radiother Oncol 2008
De Brabandere M. Radiother Oncol 2008
Jurgenliemk Shulz IM. Radiother Oncol 2009
Cahrgari N. IJROBP 2009

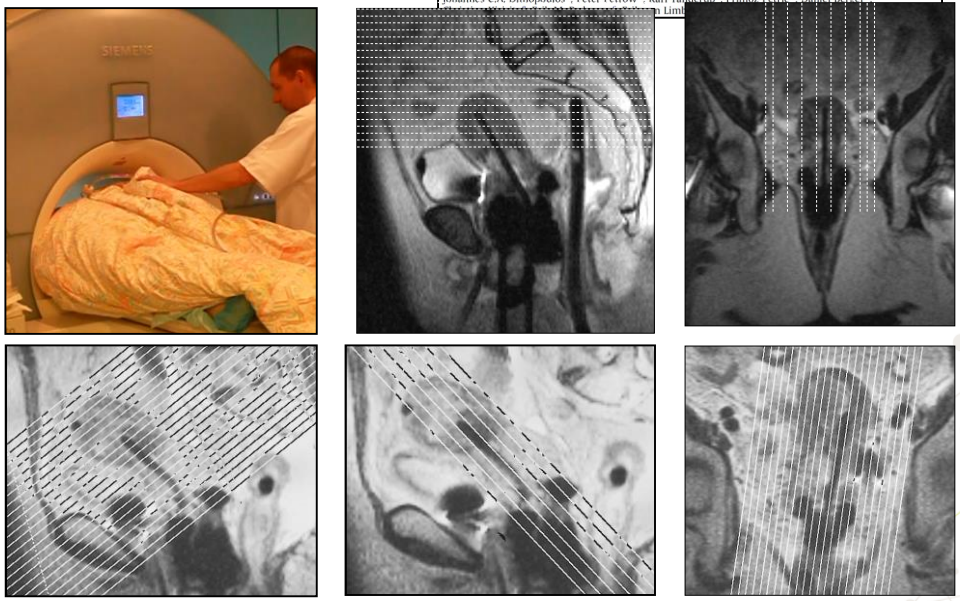
Haie-Meder. Rad. Oncol 2010
Janssen H. Radiother Oncol 2011
Dimopoulos J. Rad Oncol, 2009
Dimopoulos J. IJROBP 2006
Boss EA. Obstet Gyn 1995

Mitchell. J Clin Oncol 2006
Oszarlak O. Radiol 2003
Hricak H. Radiology 2007
Yu KK. Radiology 1997
Sala E. Radiology 2006
Yu KK. Radiology 1999

MRI protocols at Diagnosis & Brachytherapy



- Field strength
- Magnet configuration
- Coils
- Patient preparation
- Image acquisition
- Sequences & parameters
- Imaging planes
- Equipment compatibility

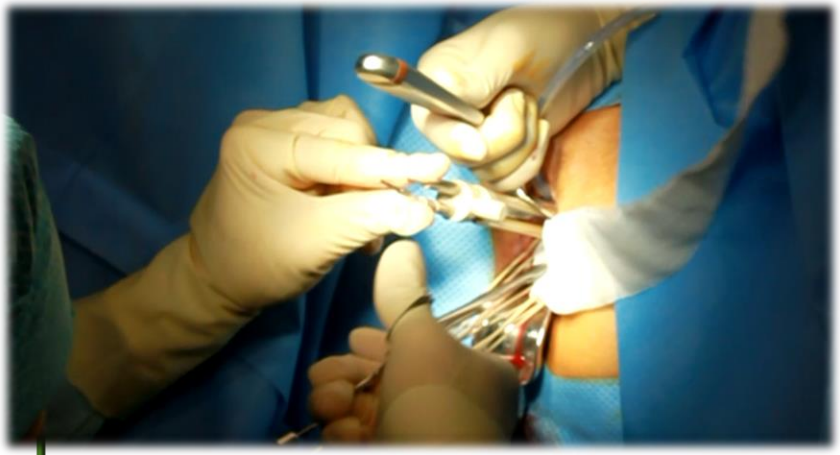


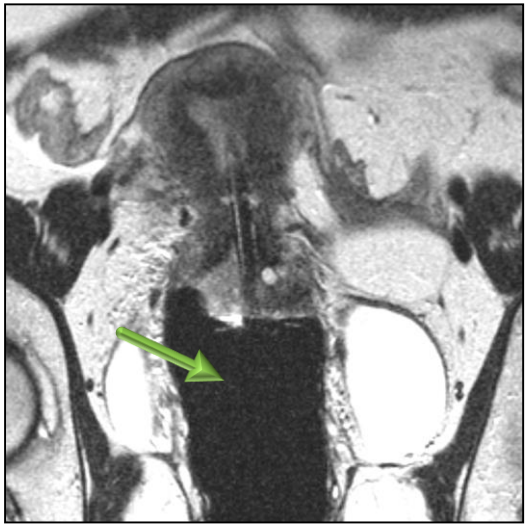
Dimopoulos JCA et al. Radiother Oncol 2012;103:113-22.

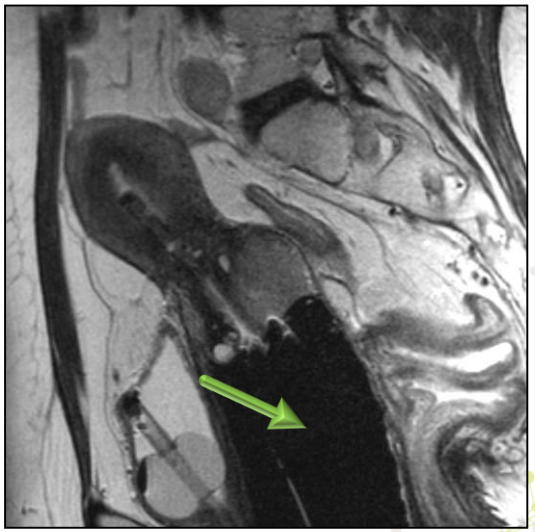
MRI protocol at Brachytherapy

Application protocol

Vaginal packing







- Fixation of applicator
- Displacement of rectum & bladder
- Discrimination: tissues vs. vaginal lumen

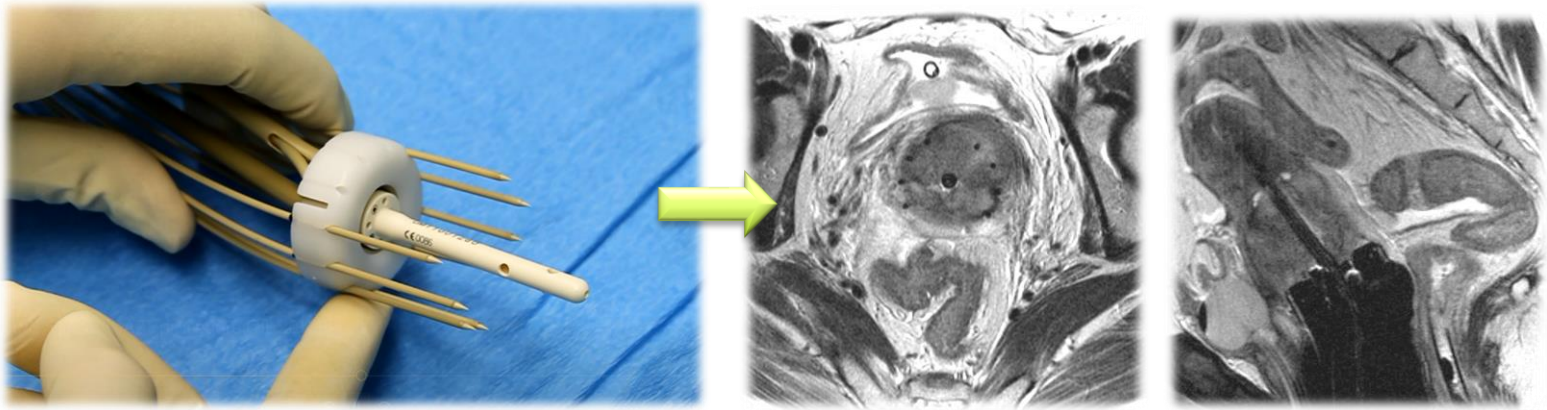
Diluted Gadolinium (1:10 in 0.2 T)	Dry packing (i.e. in 1.5 T)

Dimopoulos JCA et al. Radiother Oncol 2012;103:113-22.

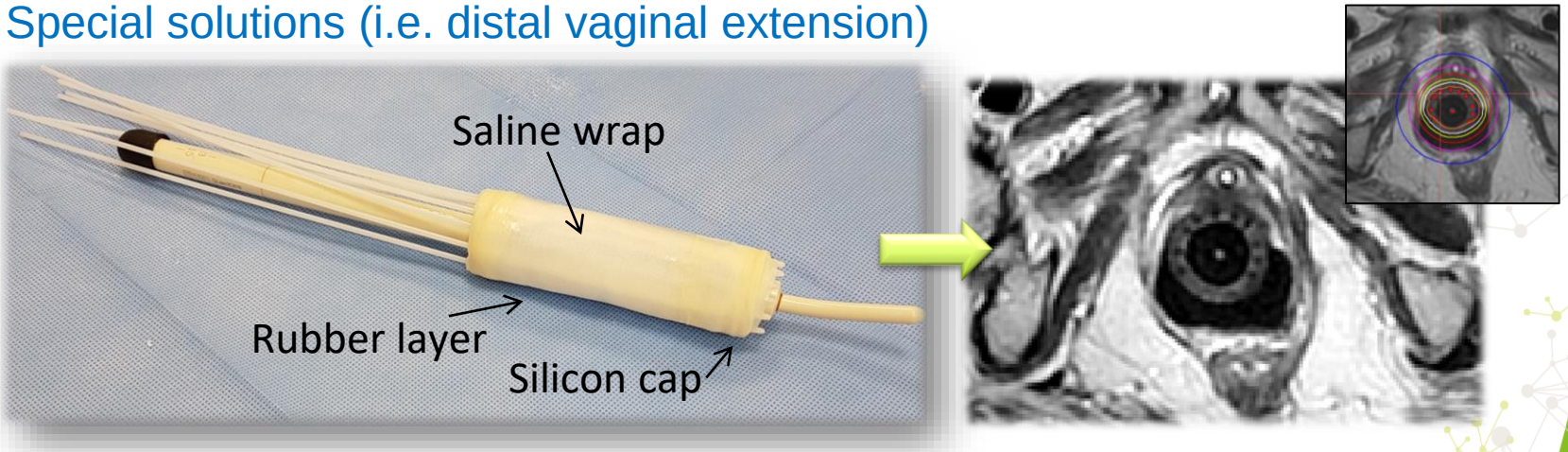
MRI protocol at Brachytherapy

Application protocol

MRI compatibility and Channel visualization



Special solutions (i.e. distal vaginal extension)



Chandramouli S, et al. Doha-Heidelberg Research Conference 2018. Abstract

MRI protocol at Brachytherapy

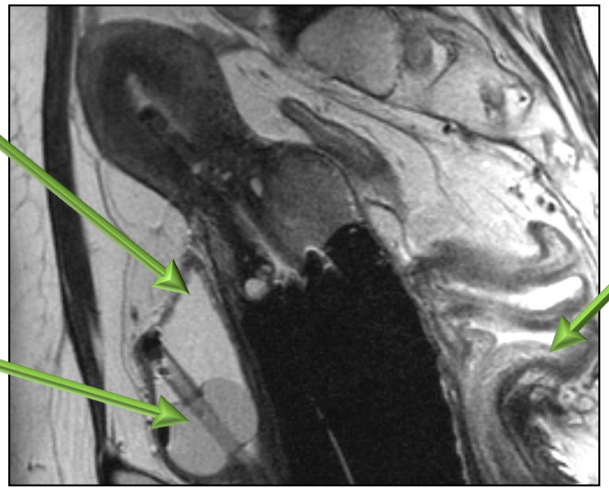
Organ filling

Reproducible bladder filling:

- HDR: 50 ml
- PDR: open catheter

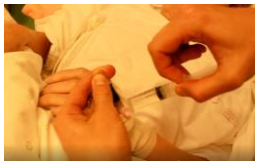
Catheter balloon - 7 ml:

- Gadolinium 1:1 (in 0.2 T)
- Normal saline (high T MRI)

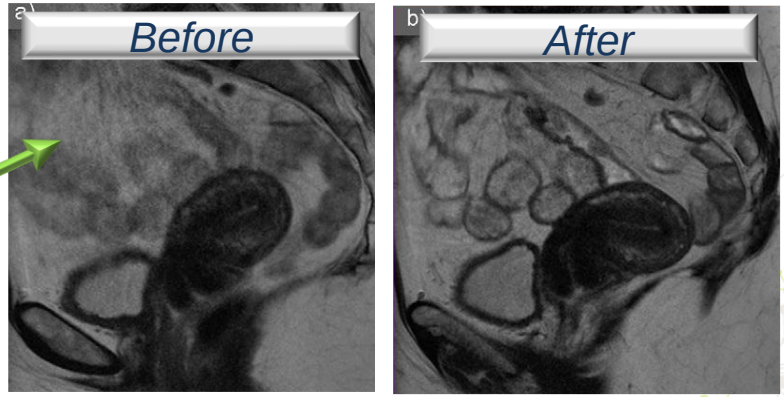


Rectum:

- Empty
- +/- Rectal tube
- +/- Dosimeter

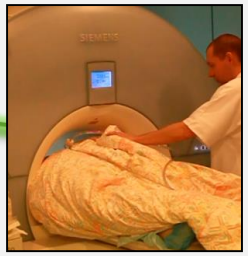


Bowel: antispasmodic drug



Dimopoulos JCA et al. Radiother Oncol 2012;103:113-22.

MRI protocol at Brachytherapy

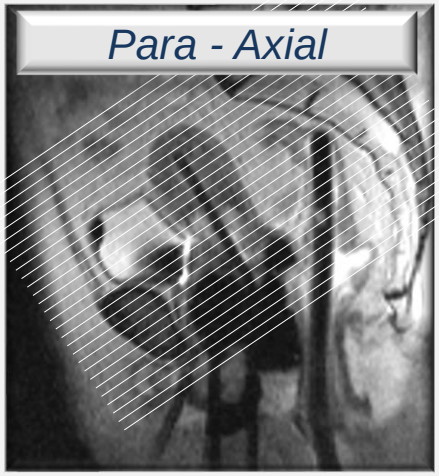


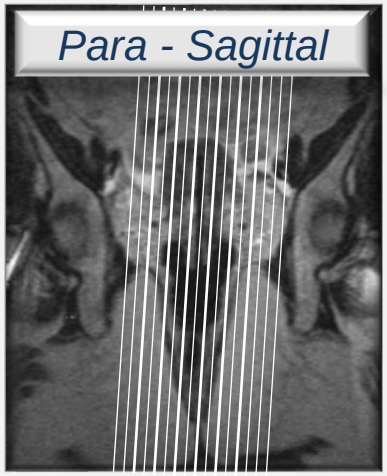
Sequence Parameters

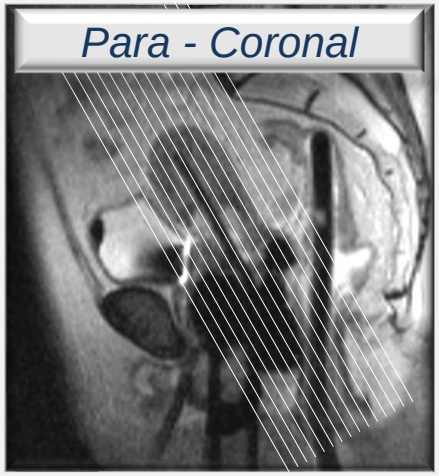
Protocol	Number	Mandatory (M)/ optional (O)	Sequence	Plane orientation	Coverage/borders
BT MRI scan	8	M	T2 FSE	Para-axial (according to cervix uteri)	Above uterine corpus – 3 cm below lower surface of vaginal applicator/ entire vagina if distal vaginal involvement
	9	M	T2 FSE	Para-sagittal (according to cervix uteri)	Pelvic side wall (obturator muscle)
	10	M	T2 FSE	Para-coronal (according to cervix uteri)	Uterine corpus – cervix – vagina – tumour
	11	O	T2 FSE	Axial	Above uterine corpus – 3 cm below lower surface of vaginal applicator/ entire vagina if distal vaginal involvement
	12	O	3D T2 FSE isotropic	Coronal or axial with reconstructions	Large coverage inherent in this sequence
	13	O	T1 FSE, FLASH, T1 GRE 3D	As appropriate	At least entire applicator

3 mm slice thickness improves accuracy

Interslice gap may be omitted (applicator r.)



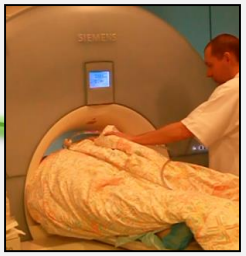




Dimopoulos JCA, et al. MRI Recomm…Radiother Oncol 2012

Petric P, et al. Axial vs. Para-axial…Radiother Oncol 2006

MRI protocol at Brachytherapy



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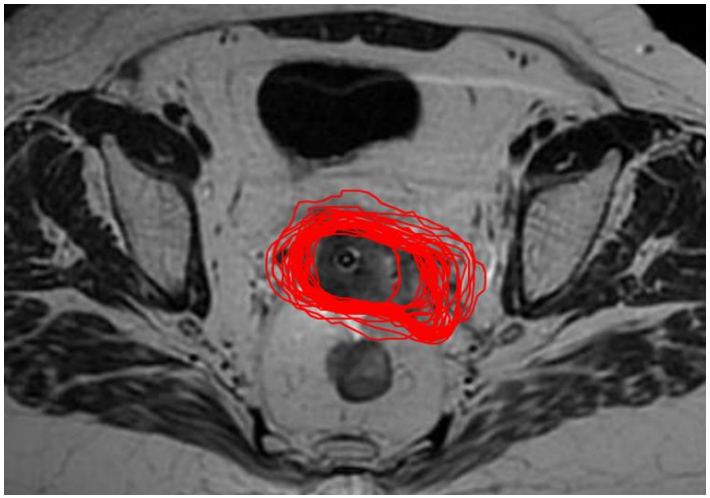
Protocol		Sequence parameters									
	Number	Fatsat	TR (ms)[a]	TE (ms)[b]	ETL[c]	FOV (cm^2)[d]	M(f)[e]	M(p)[e]	Nex[f]	SW[g]	NPW[h]
BT MRI scan	8	No	2000–5000	90–120	4–20	35 × 20	512	256	2	3–5	Yes
	9	No	2000–5000	90–120	4–20	35 × 40	512	256	2	3–5	Yes
	10	No	2000–5000	90–120	4–20	35 × 20	512	256	2	3–5	Yes
	11	No	2000–5000	90–120	4–20	35 × 40	512	256	2	3–5	Yes
	12	No	See Refs. [22,48–56] for sequence parameters								
	13	No									

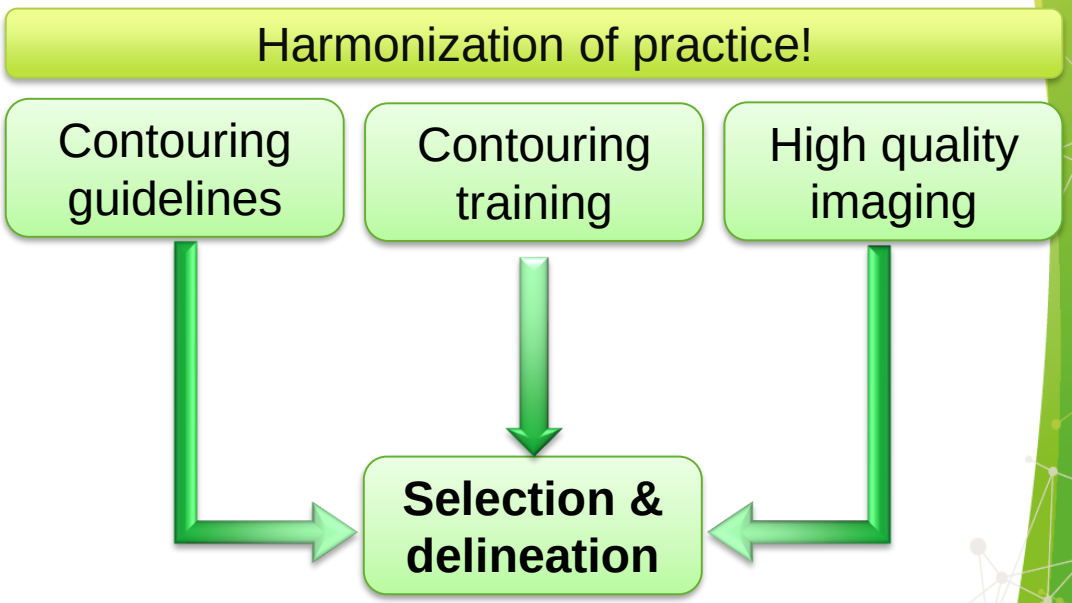
Parameters differ between MRI scanners → Adapt to specific device / institution

Dimopoulos JCA, et al. Radiother Oncol 2012

Interpretation of imaging at BT

Contouring uncertainties: weakest link in Image guided BT?

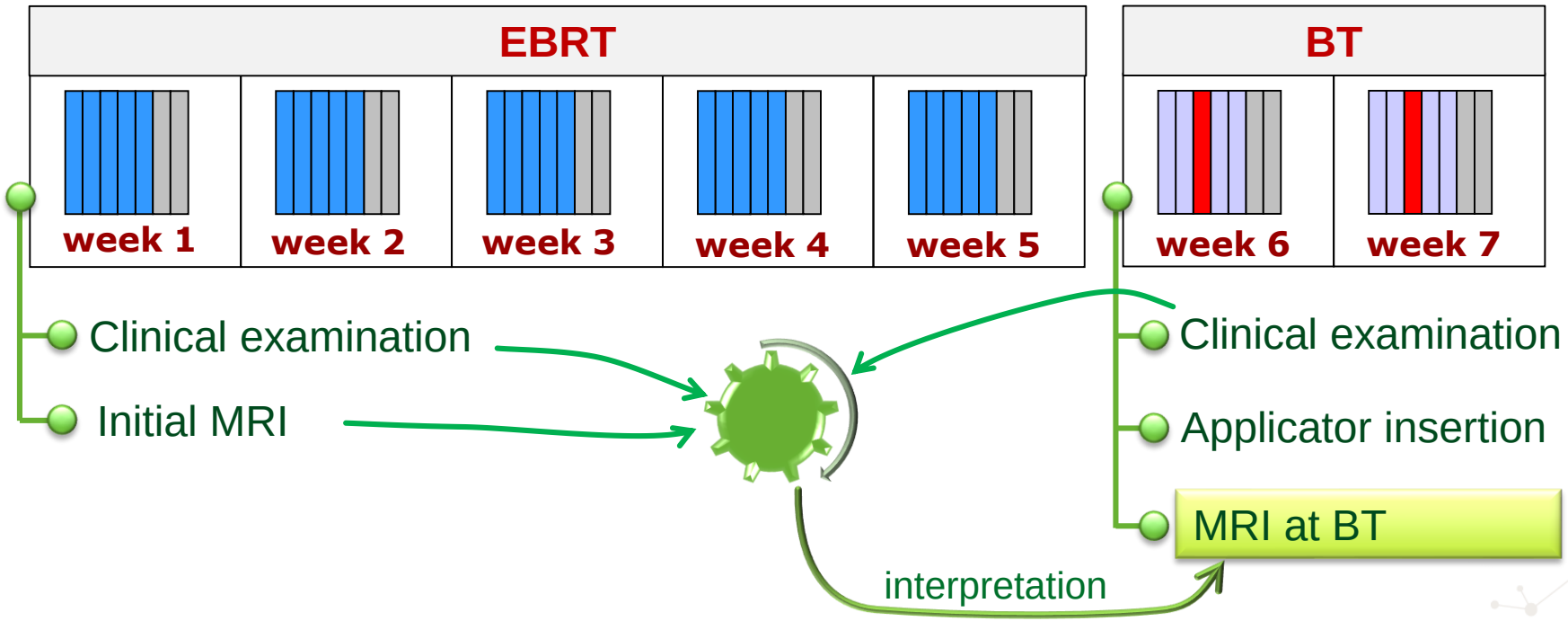




Njeh CF, et al. Med Phys 2008
Hellebust TP, et al. Radiother Oncolo 2013
Petric P, et al. Radiother Oncol 2013

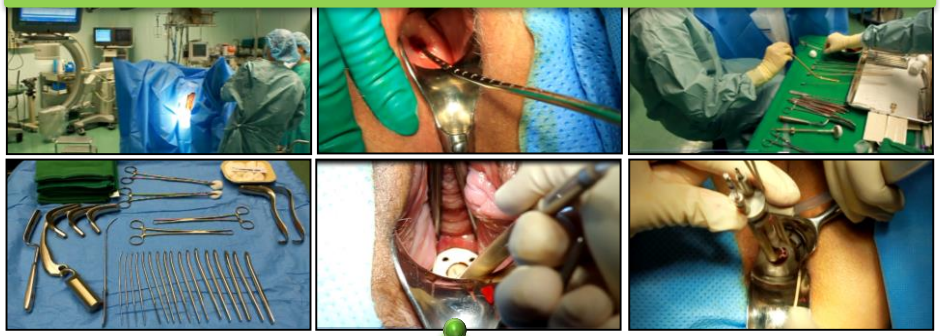
Interpretation of imaging at BT

Take into account all available information



STEPS before contouring

THEATRE



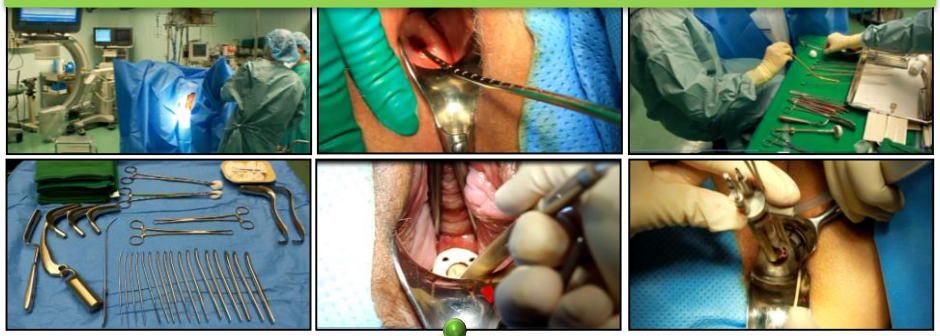
MRI SUITE

1. Rule out ***FLOP***

2. Set the ***STAGE*** for contouring

STEPS before contouring

THEATRE



MRI SUITE

1. Rule out ***FLOP***
2. Set the ***STAGE*** for contouring

1. Rule out **FLOP**

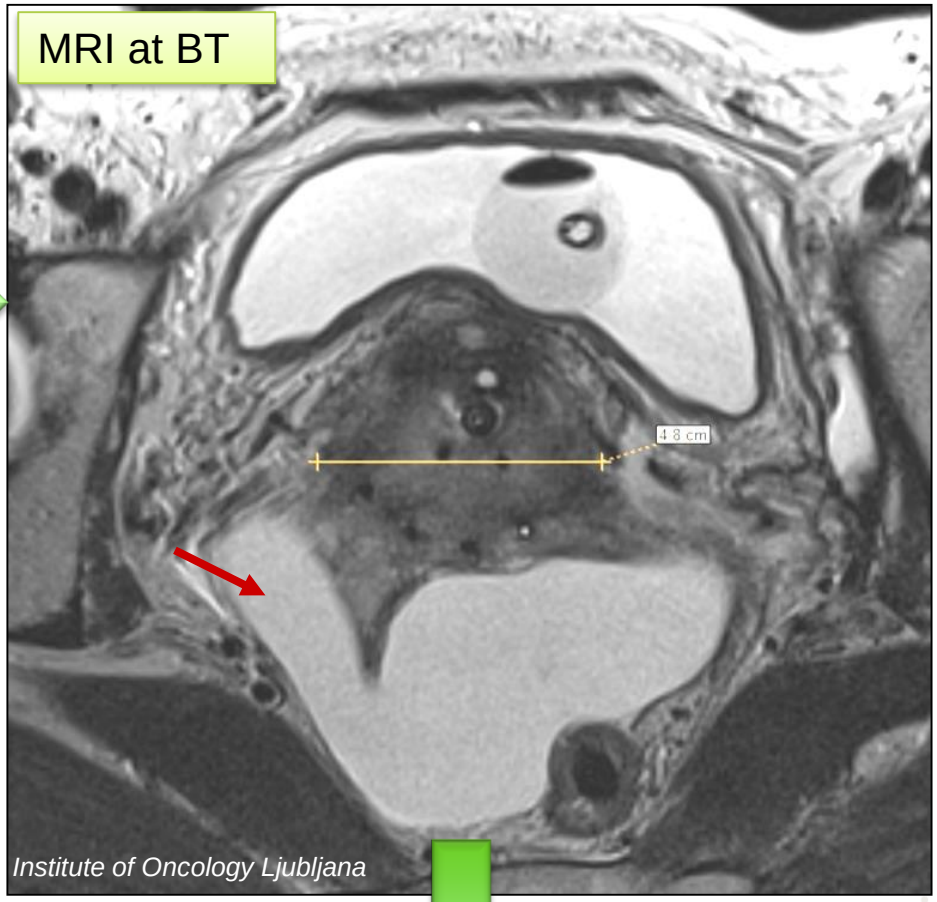
- **FL** **FL**uid in abdomen?
- **OP** **O**rgan **P**erforation?

1. Rule out **FLOP**

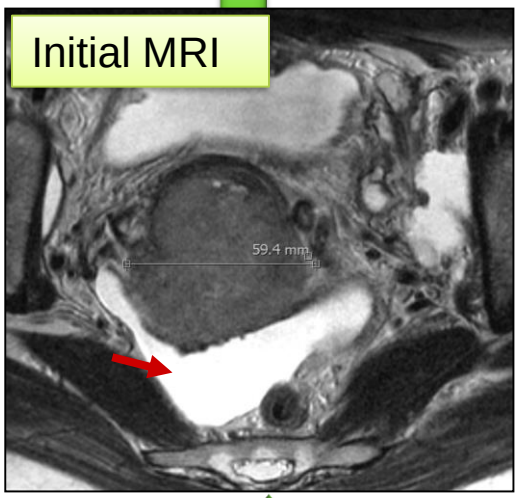
FL **FL**uid in abdomen?

OP **O**rgan **P**erforation?

MRI at BT



Initial MRI

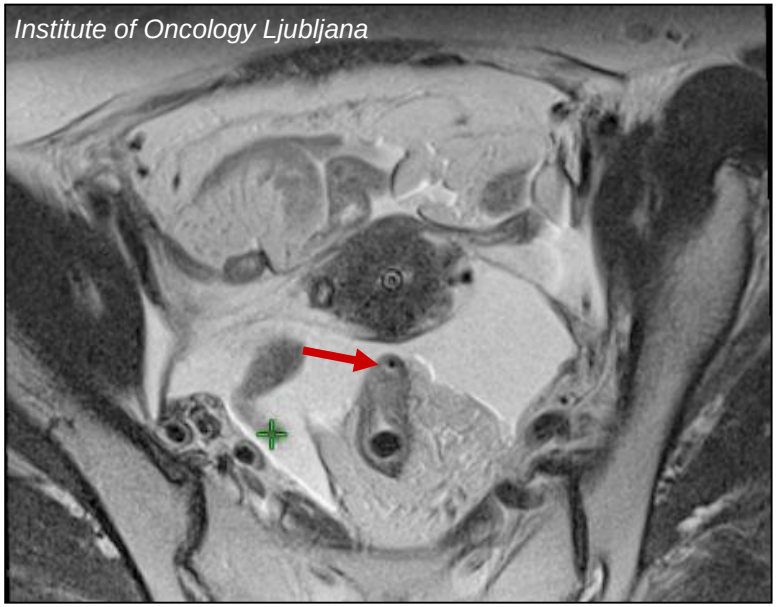


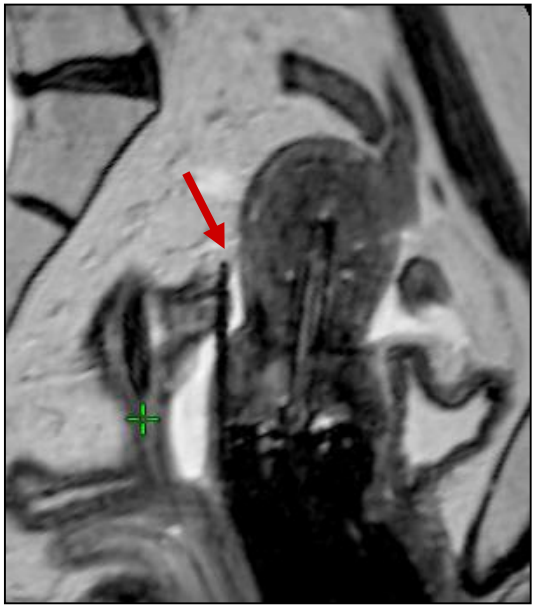
Compare with initial findings!

1. Rule out **FLOP**

FL **FL**uid in abdomen?

OP **O**rgan **P**erforation?





Action? ⇨ Have institutional policies and protocols ready!

1. Rule out **FLOP**

FL **FL**uid in abdomen?

OP **O**rgan **P**erforation?

Irwin W, et al. Gynecol Oncol 2003
Sharma DN, et al. Gynecol Oncol 2010
Davidson MTM, et al. Brachytherapy 2008
MIlman RM, et al. Clin Imaging 1991

Jhingran A, Eifel PJ. IJROBP 2000
Barnes EA, et al. Int J Gynecol Cancer 2007
Lanciano R, et al. IJROBP 1994

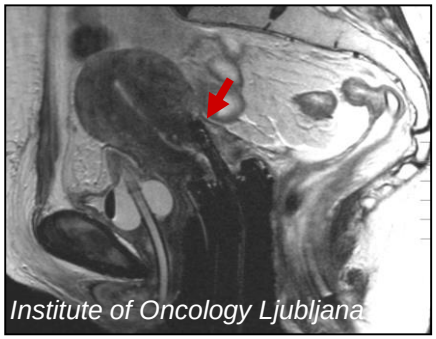
Van Dyk S, et al. IJROBP 2009
Granai CO, et al. Gyn Oncol 1984
Segedin B, et al. Radiol Oncol 2013

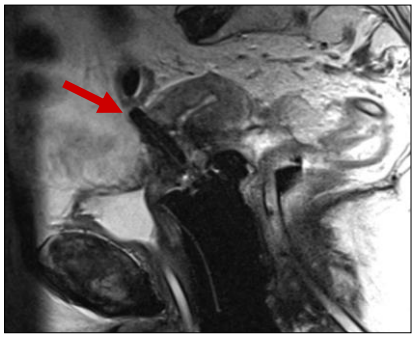
Sahinler I, et al. IJROBP 2004
Irwin W, et al. Gynecol Oncol 2003
MIlman RM, et al. Clin Imaging 1991

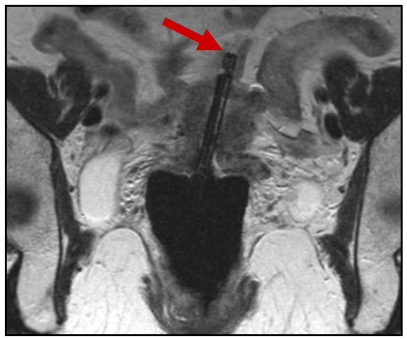
Uterine perforations

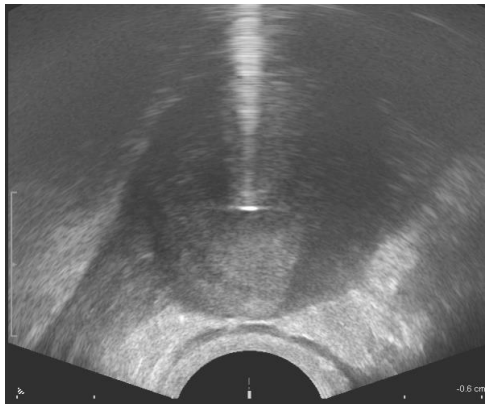
Up to ≈ 14 %

US guidance!



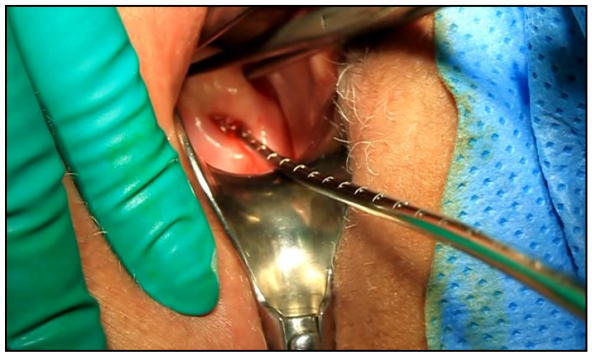






1. Rule out **FLOP**

Risk factors?



Uterine perforation - 5-year experience in 3-D image guided gynaecological brachytherapy at Institute of Oncology Ljubljana

Barbara Segedin[1], Jasenka Gugic[1], Primoz Petric[1,2]

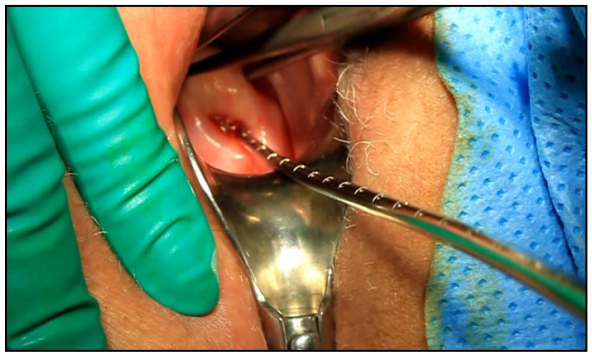
[1] Institute of Oncology Ljubljana, Department of Radiotherapy, Ljubljana, Slovenia
[2] National Center for Cancer care and Research Doha, Qatar

- 219 patients (428 insertions)
- Uterine perforation in 3 % of insertions (4.6 % of pts.)
- Most frequent site: Posterior uterine wall (70 %)
- US guidance at second application: adequate insertion in all cases

Segedin B, et al. Radiol Oncol 2013

1. Rule out **FLOP**

Risk factors?



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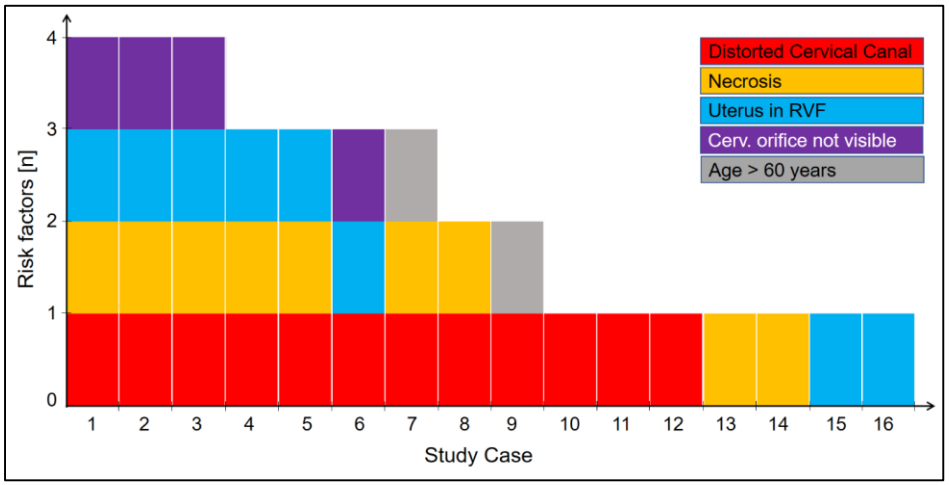
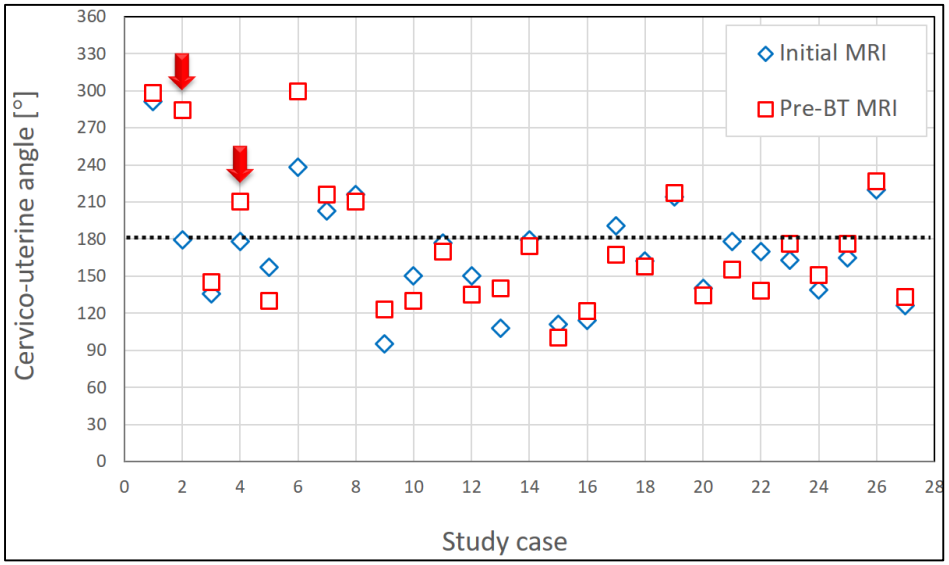
Risk factor	Patient presenting with uterine perforation									
	1	2	3	4	5	6	7	8	9	10
Age > 60 y	•	•	•	•	•		•	•	•	
Necrosis			•			•		•		•
Cervical polyp					•					
Myoma		•							•	
Distorted CC		•	•	•		•		•		
RF uterus				•				•	•	
Conization				•						

Segedin B, et al. Radiol Oncol 2013

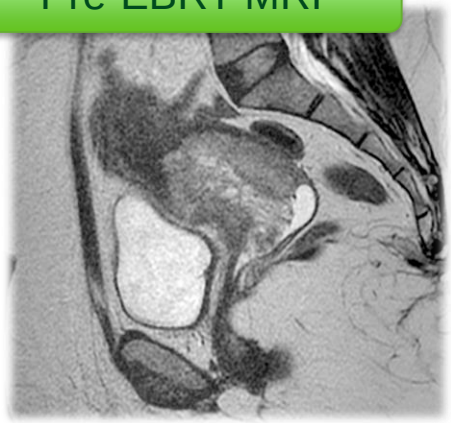
1. Rule out **FLOP**

Risk factors?

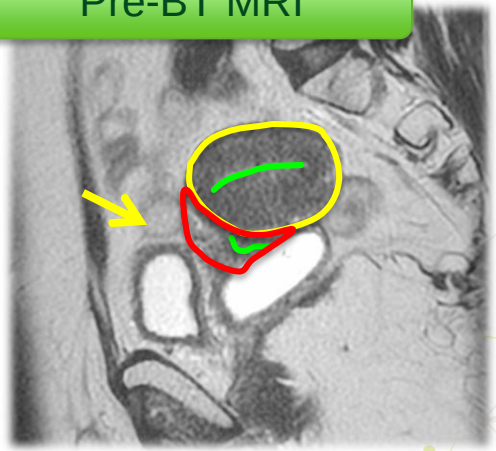




Pre-EBRT MRI



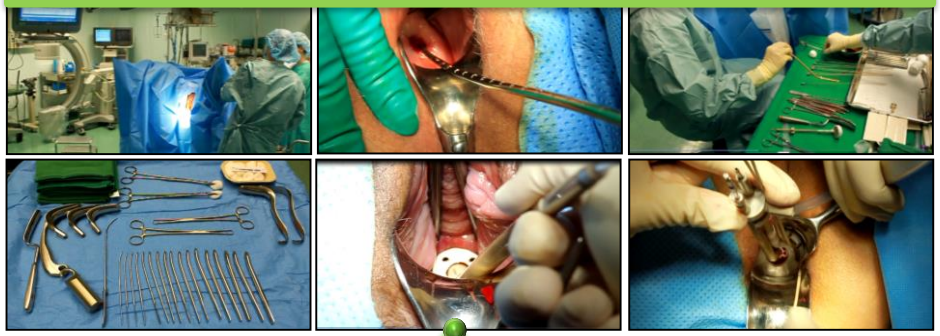
Pre-BT MRI



Al-Hammadi N, et al. J Contemp Brachyther 2017;9(6):519-26.

STEPS before contouring

THEATRE



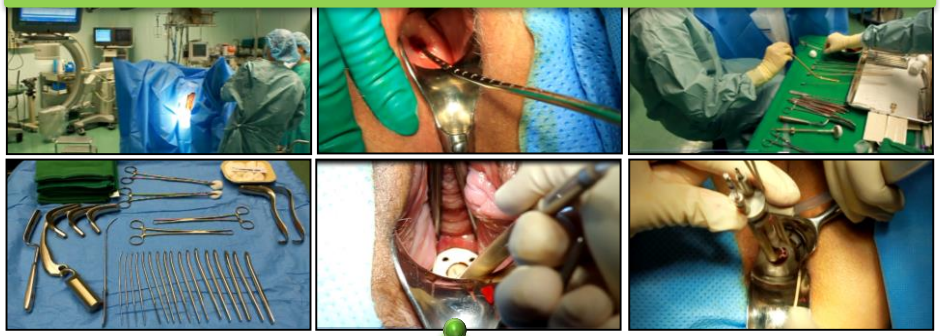
MRI SUITE

1. Rule out ***FLOP***

2. Set the ***STAGE*** for contouring

STEPS before contouring

THEATRE



MRI SUITE

1. Rule out ***FLOP***

2. Set the ***STAGE*** for contouring

Set the **STAGE** for contouring

- **S**ize of the residual tumor?
- **T**opography of the target V?
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

Set the **STAGE** for contouring

- **S**ize of the residual tumor?
- **T**opography of the target V?
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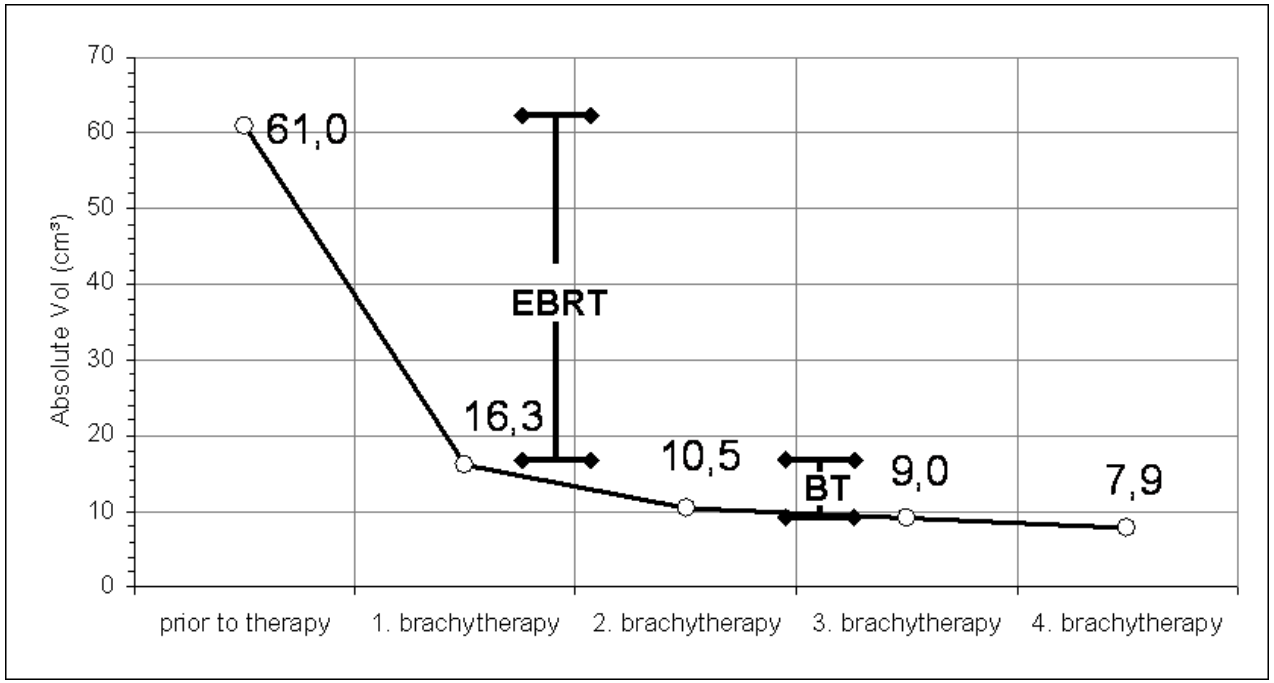
Size of the tumor at Brachytherapy

Volume change during treatment



Dimopoulos J, et al.Strahlenther Onkol 2009

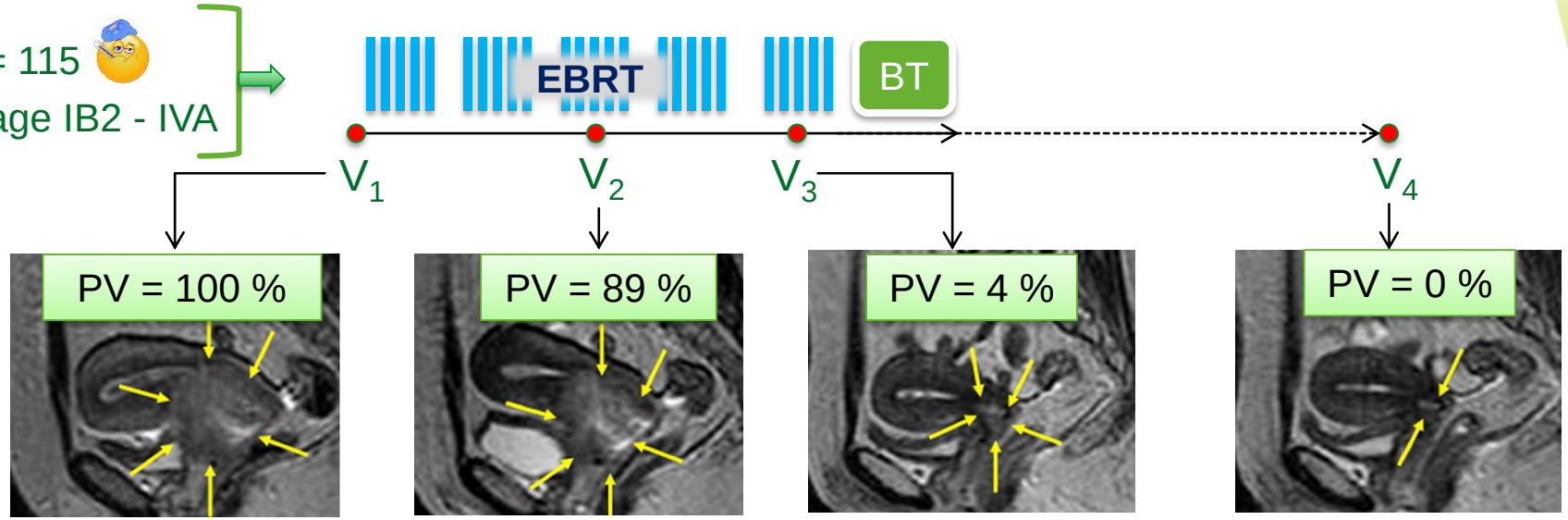
EBRT: tumor regression ≈ 75%
Brachytherapy: tumor regression ≈ 10%

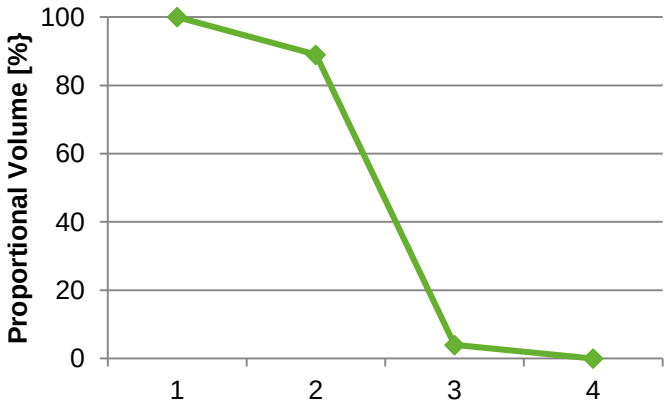
Size of the tumor at Brachytherapy

Volume change during treatment

Regression to **P**roportional **V**olume: **PV = V_x / V_1 [%]**

N= 115
stage IB2 - IVA





- Rapid response: 2.2% / Gy
- Steep slope
- Low AUC (24 %)

→ Alive & well at 7 y

Mayr NA, et al. Int J Radiat Oncol Biol Phys 2010
Wang JZ, et al. Cancer 2010

Size of the tumor at Brachytherapy

Volume change during treatment

Regression to **P**roportional **V**olume: **PV = V_x / V_1 [%]**

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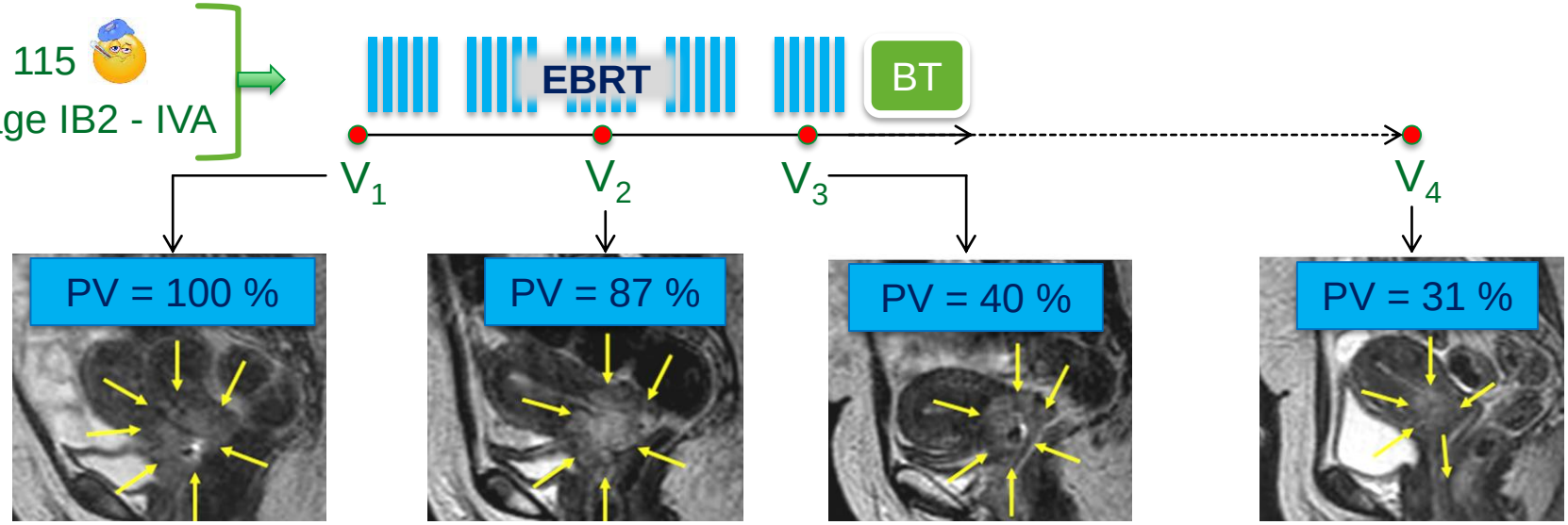

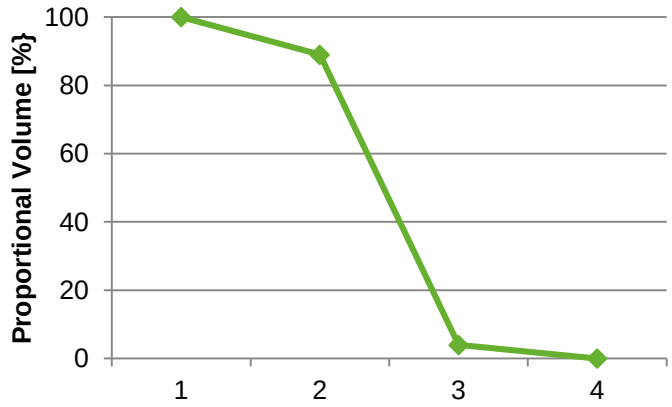

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Volume change during treatment

Regression to **P**roportional **V**olume: **PV = V_x / V_1 [%]**

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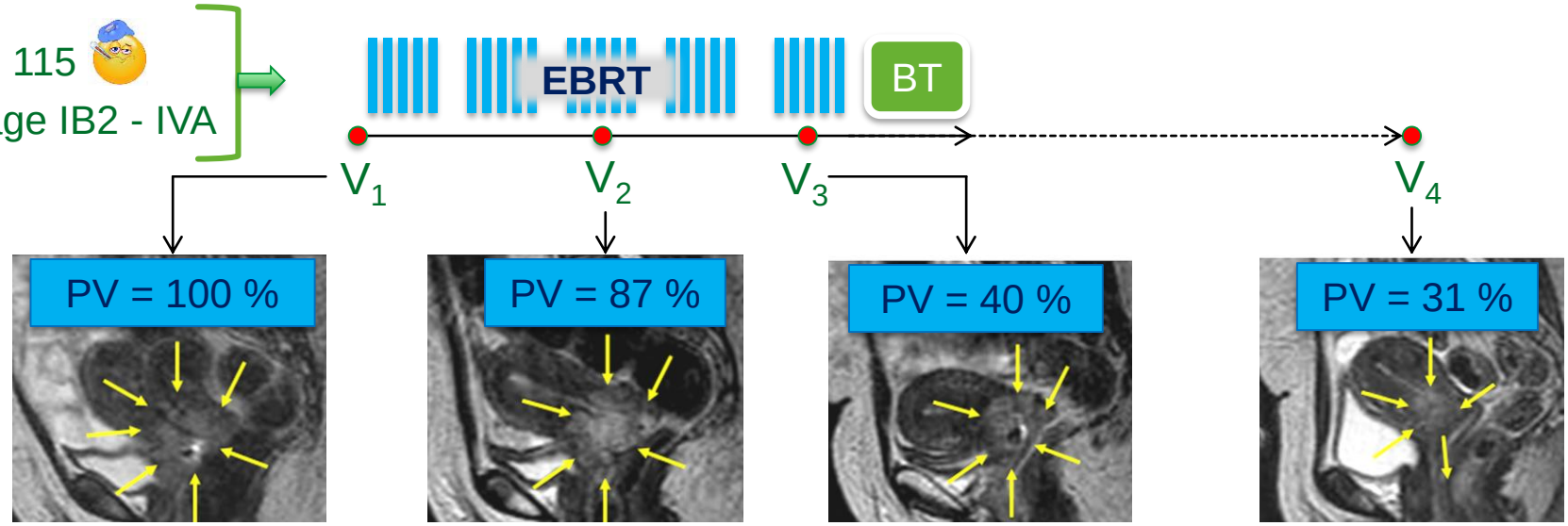
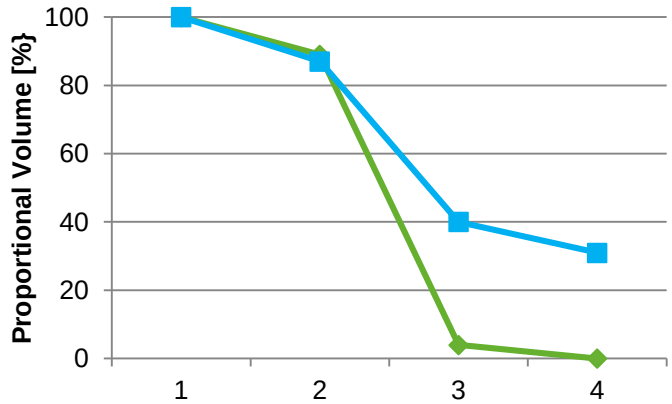




- Rapid response: 2.2% / Gy
- Steep slope
- Low AUC (24 %)

→ Alive & well at 7 y

- Slow response: 0.8% / Gy
- Low slope
- High AUC (50 %)

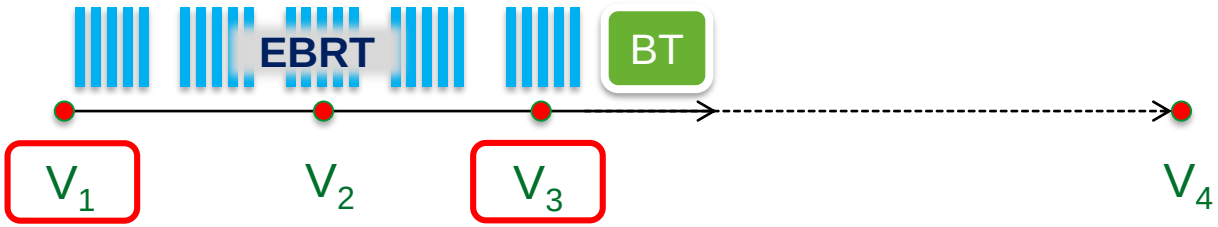
→ LR at 1 y
Death at 2 y

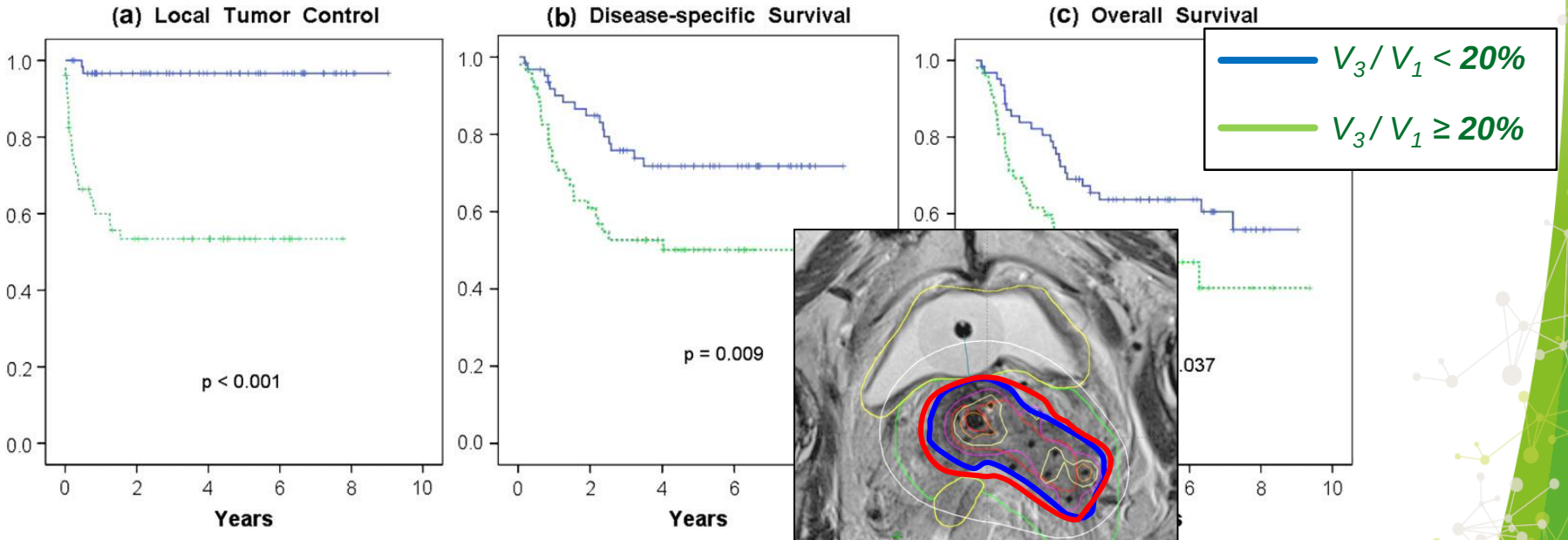
Mayr NA, et al. Int J Radiat Oncol Biol Phys 2010
Wang JZ, et al. Cancer 2010

Size of the tumor at Brachytherapy

Volume change as outcome predictor

N= 115
stage IB2 - IVA



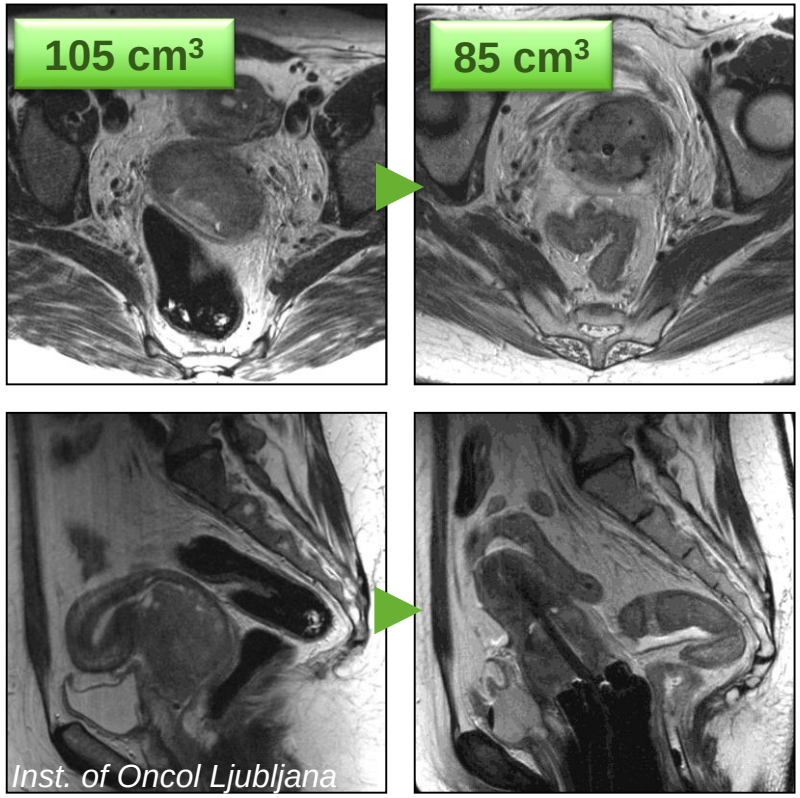
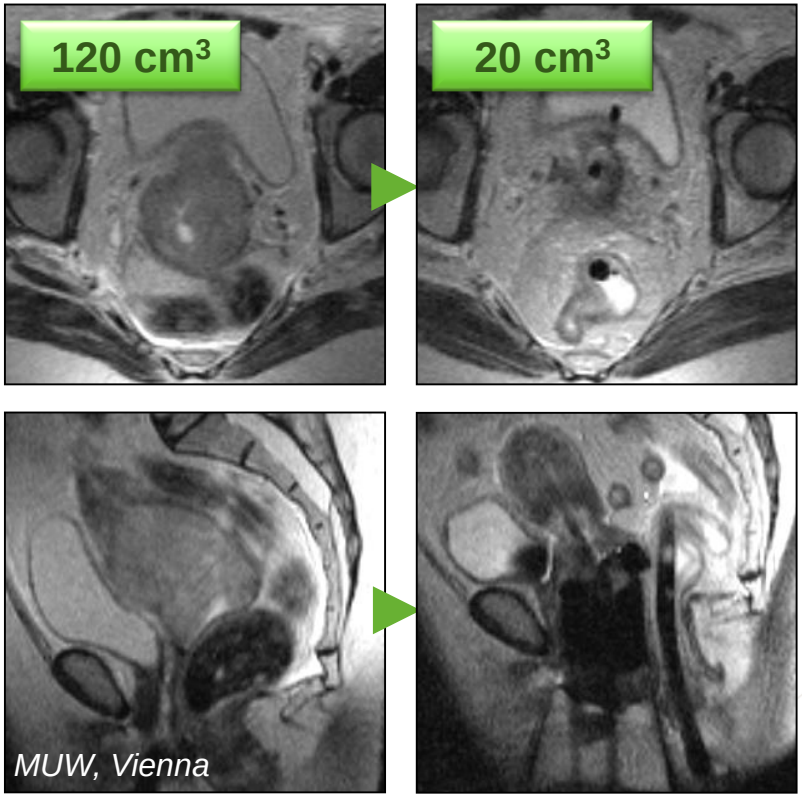


Mayr NA, et al. Int J Radiat Oncol Biol Pl
Wang JZ, et al. Cancer 2010

Rad. Onc. Perspective in context of image guided BT!

Size of the tumor at Brachytherapy

Qualitative vs. quantitative

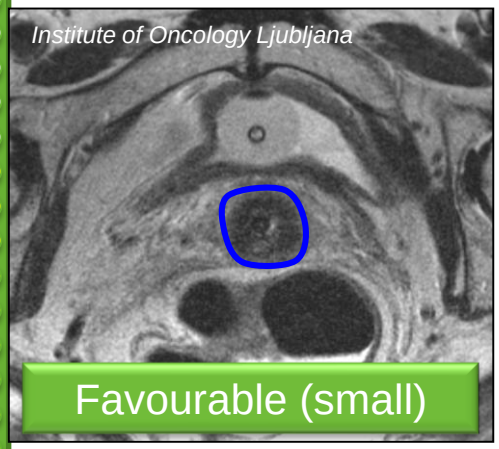
Bad response	Good response
	
81 %	**17 %**

Set the **STAGE** before contouring

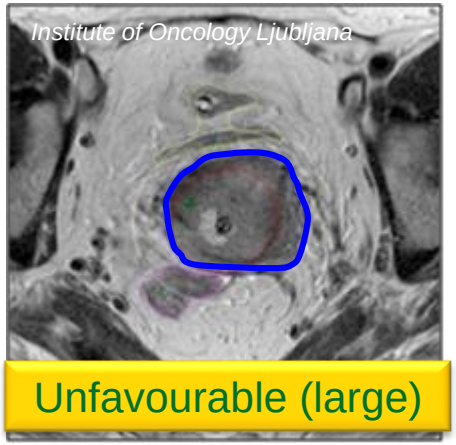
- **S**ize of the residual tumor?
- **T**opography of the target V?
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

Topography of the tumour

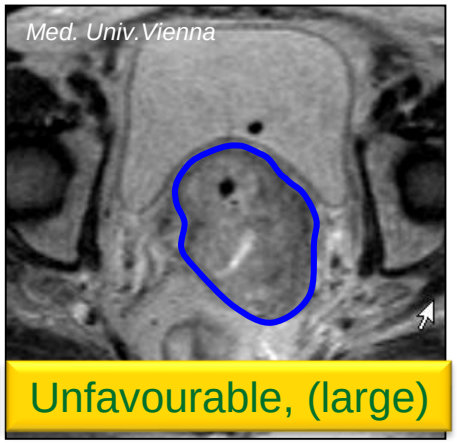
Tumour shape and extent



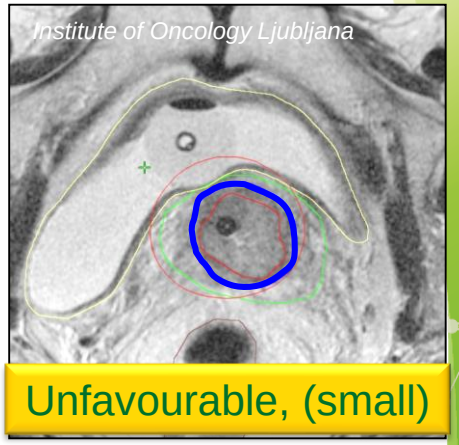
Favourable (small)



Unfavourable (large)



Unfavourable, (large)



Unfavourable, (small)

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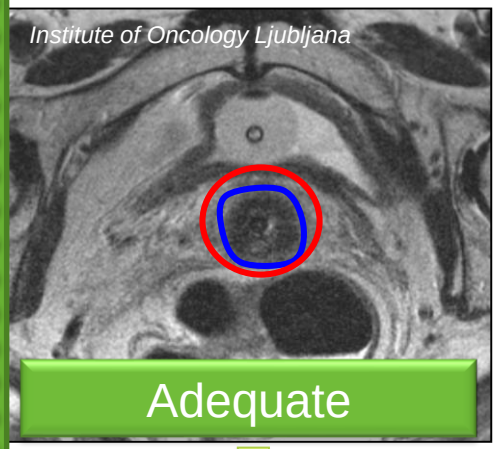
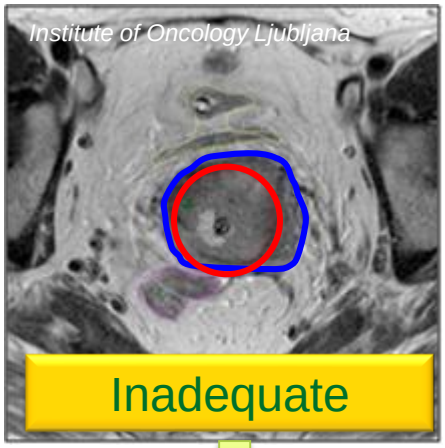
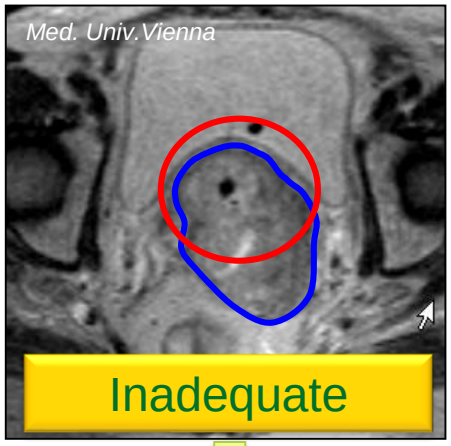
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

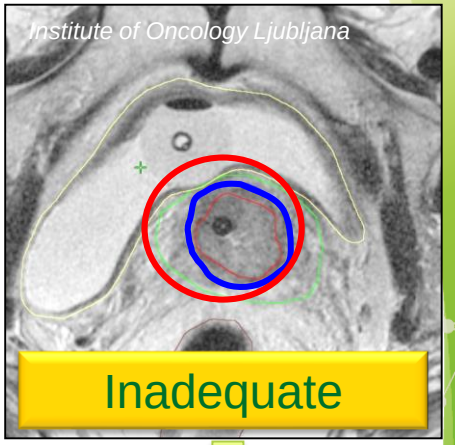
Adequacy of the implant

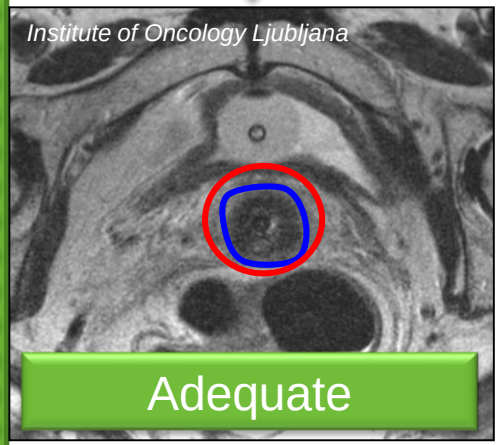
Relation: Applicator(s) - Target V - Organs

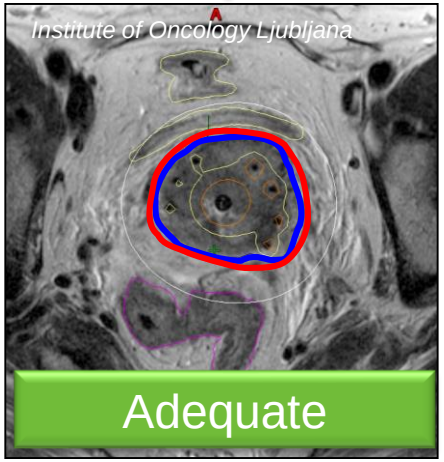


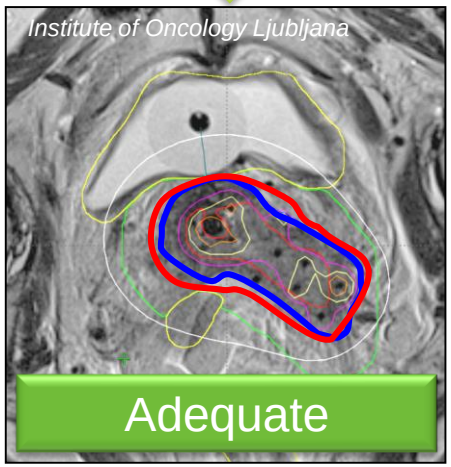


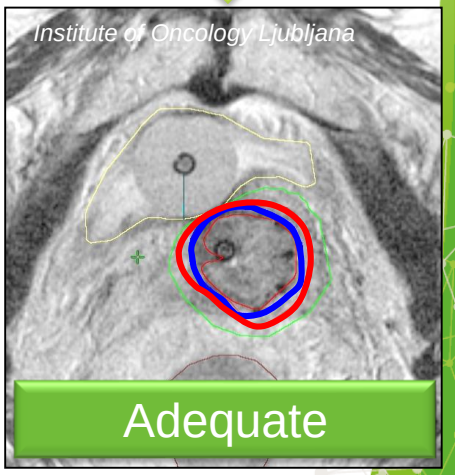












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Magnetic resonance imaging for assessment of parametrial tumour spread and regression patterns in adaptive cervix cancer radiotherapy

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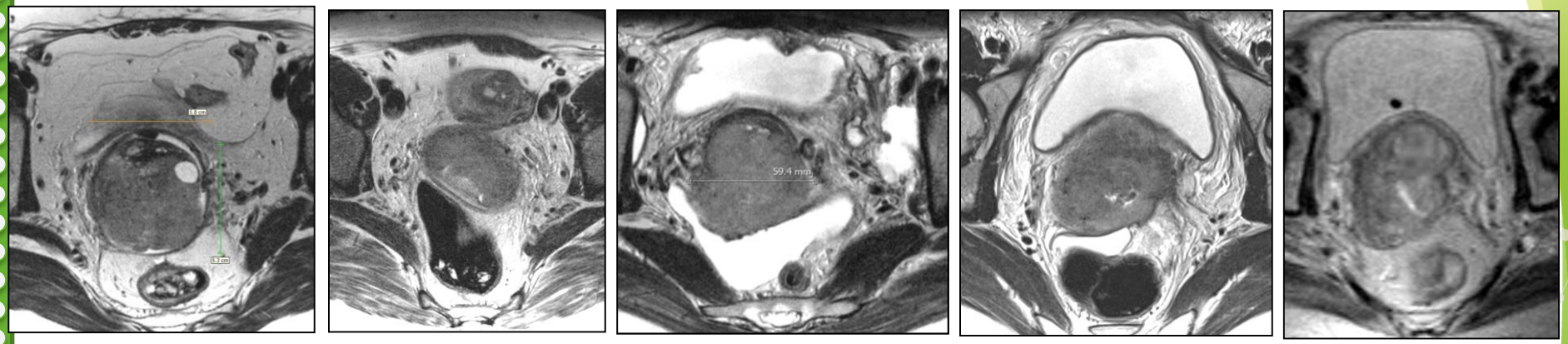

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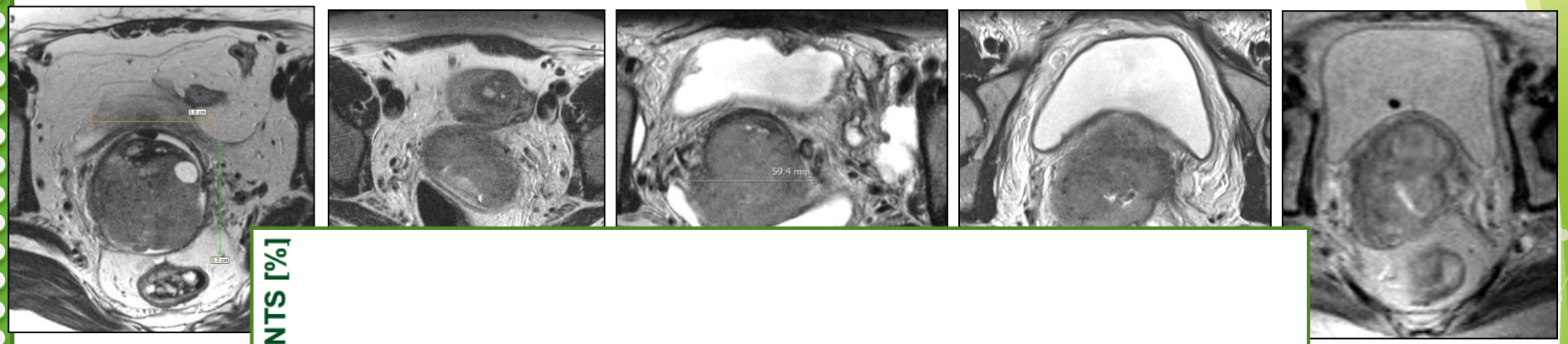

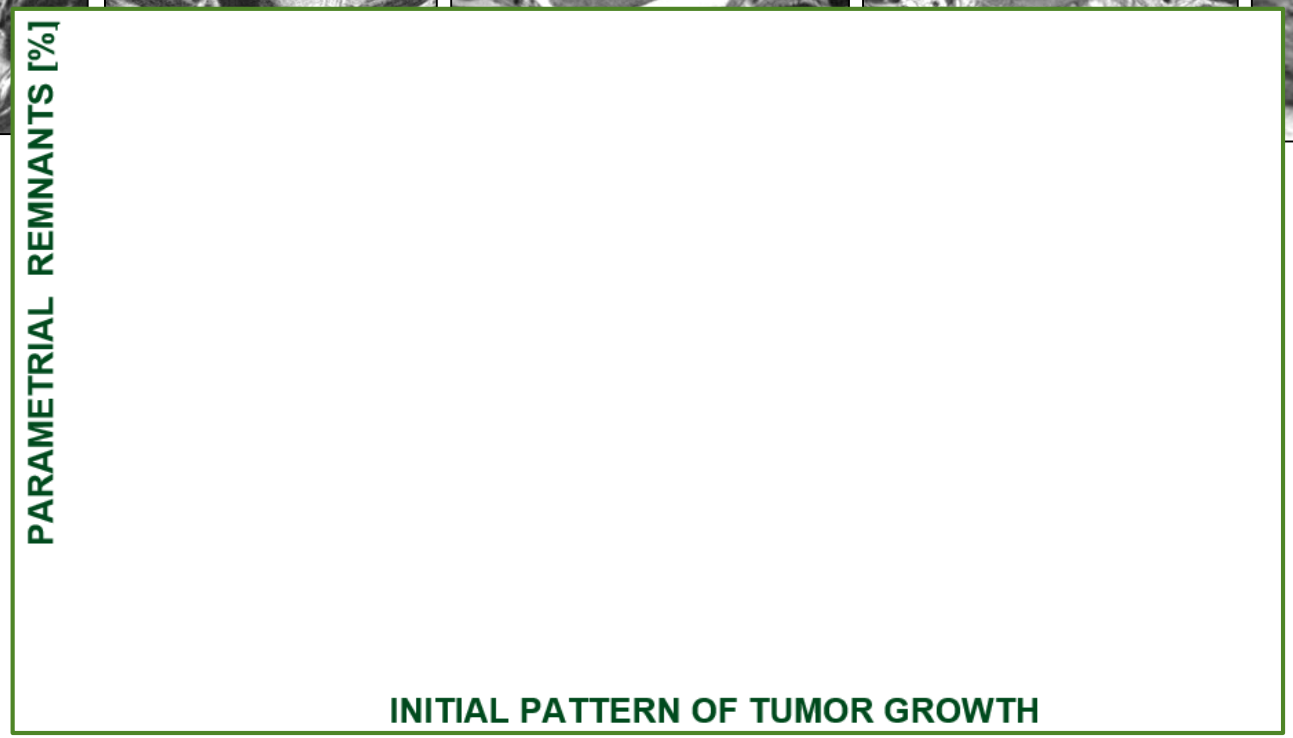

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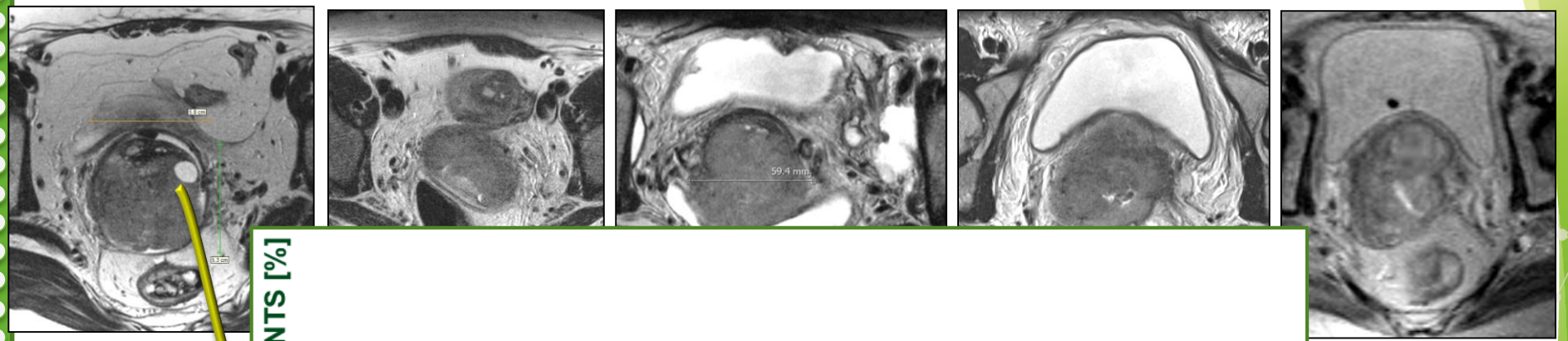

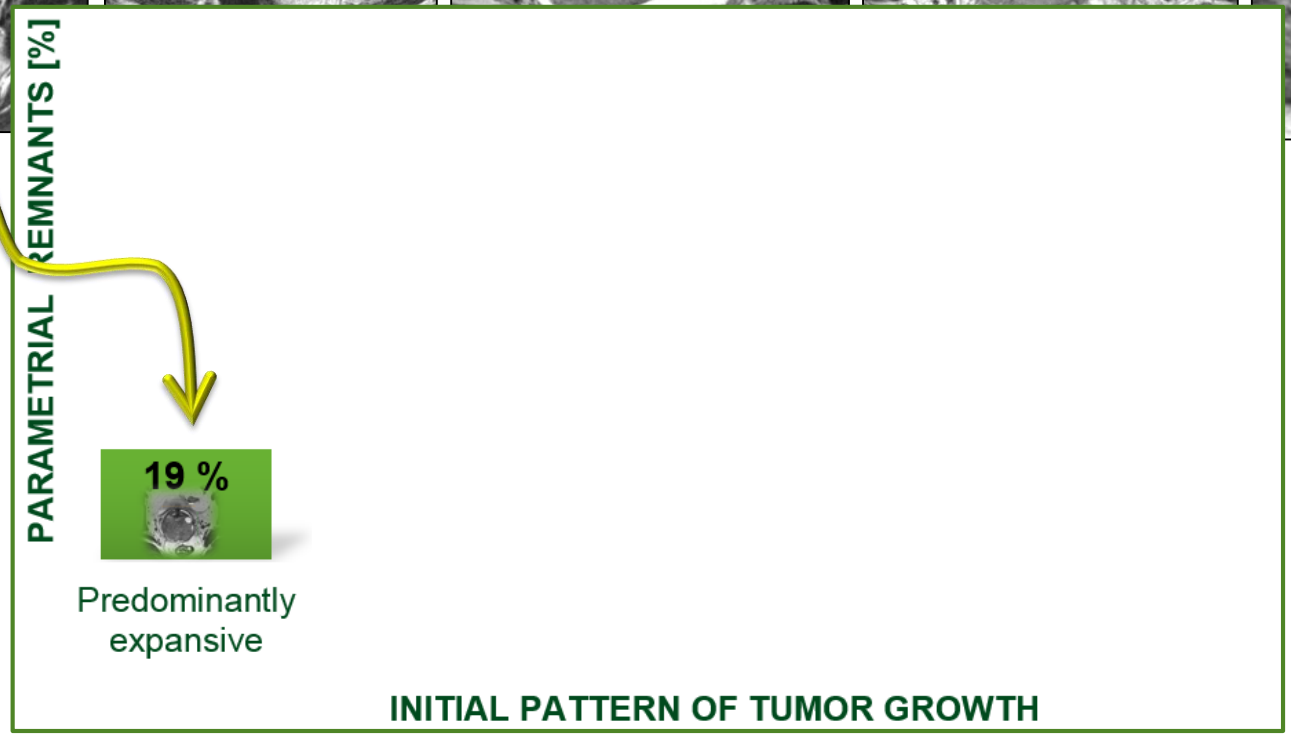

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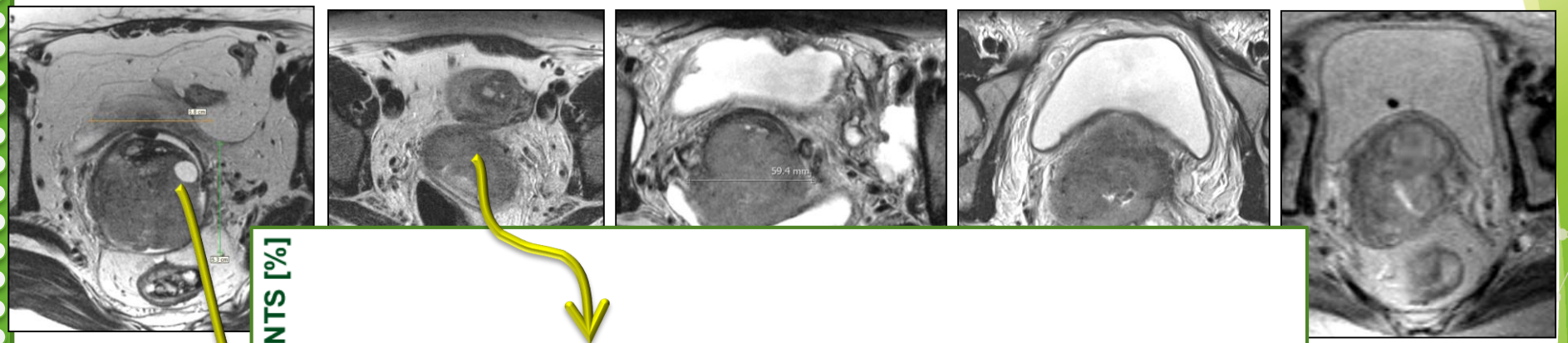

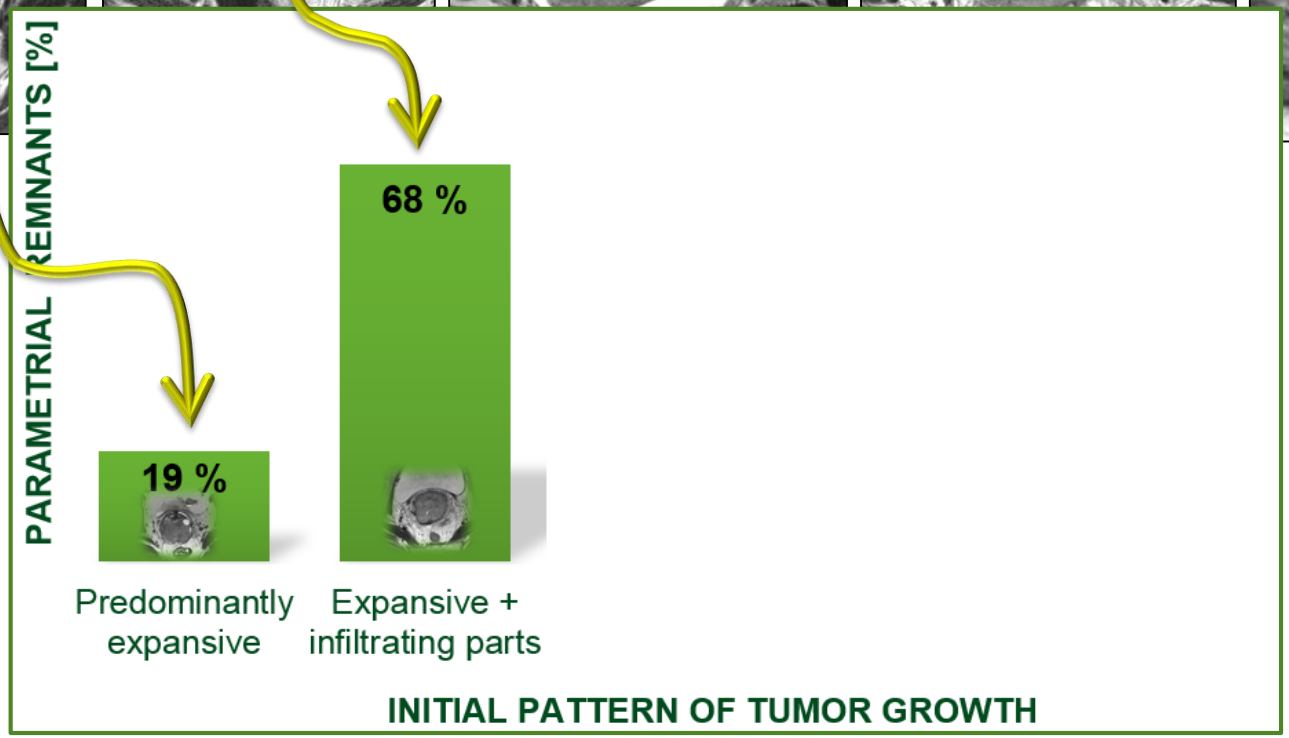

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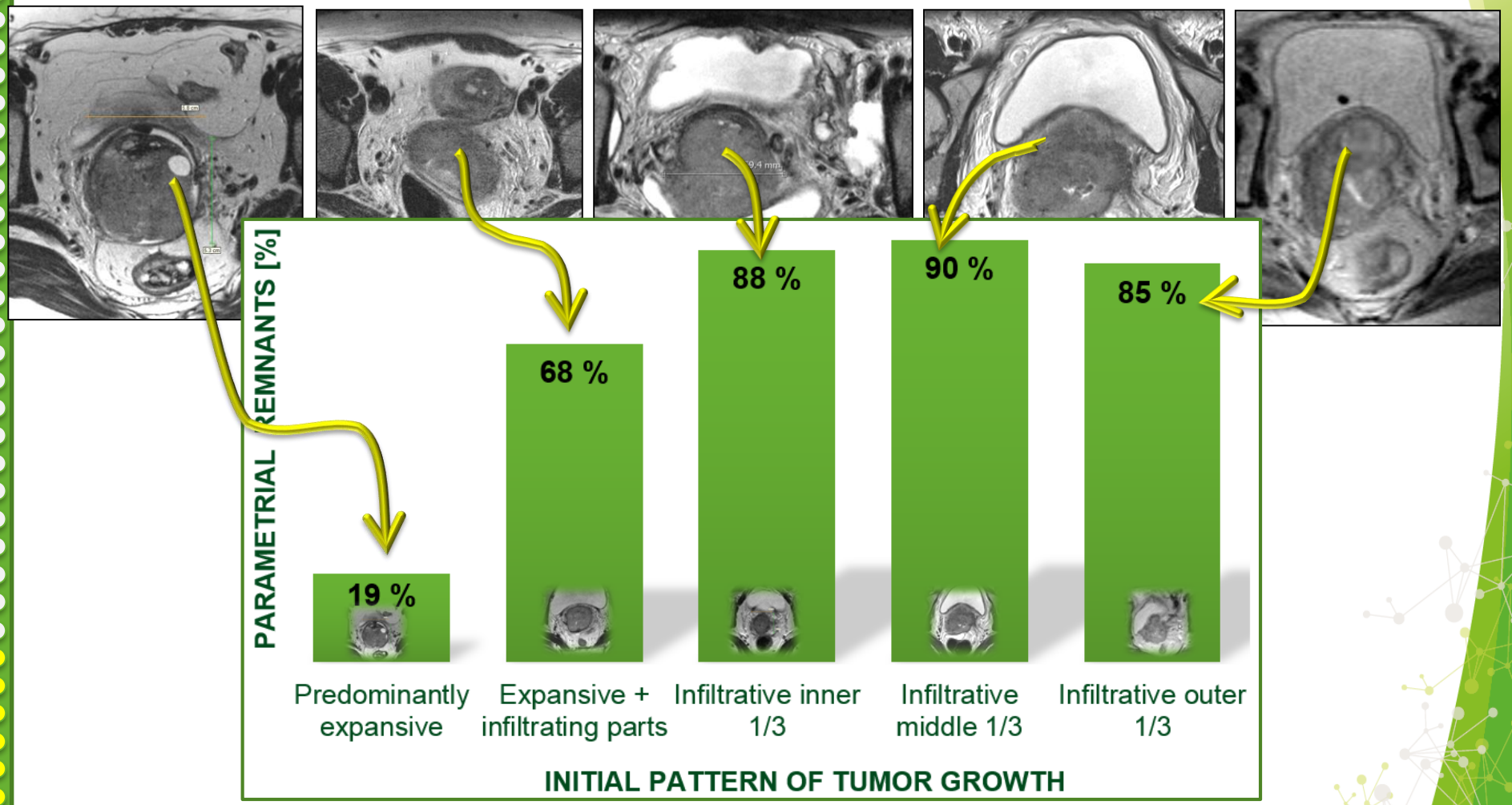

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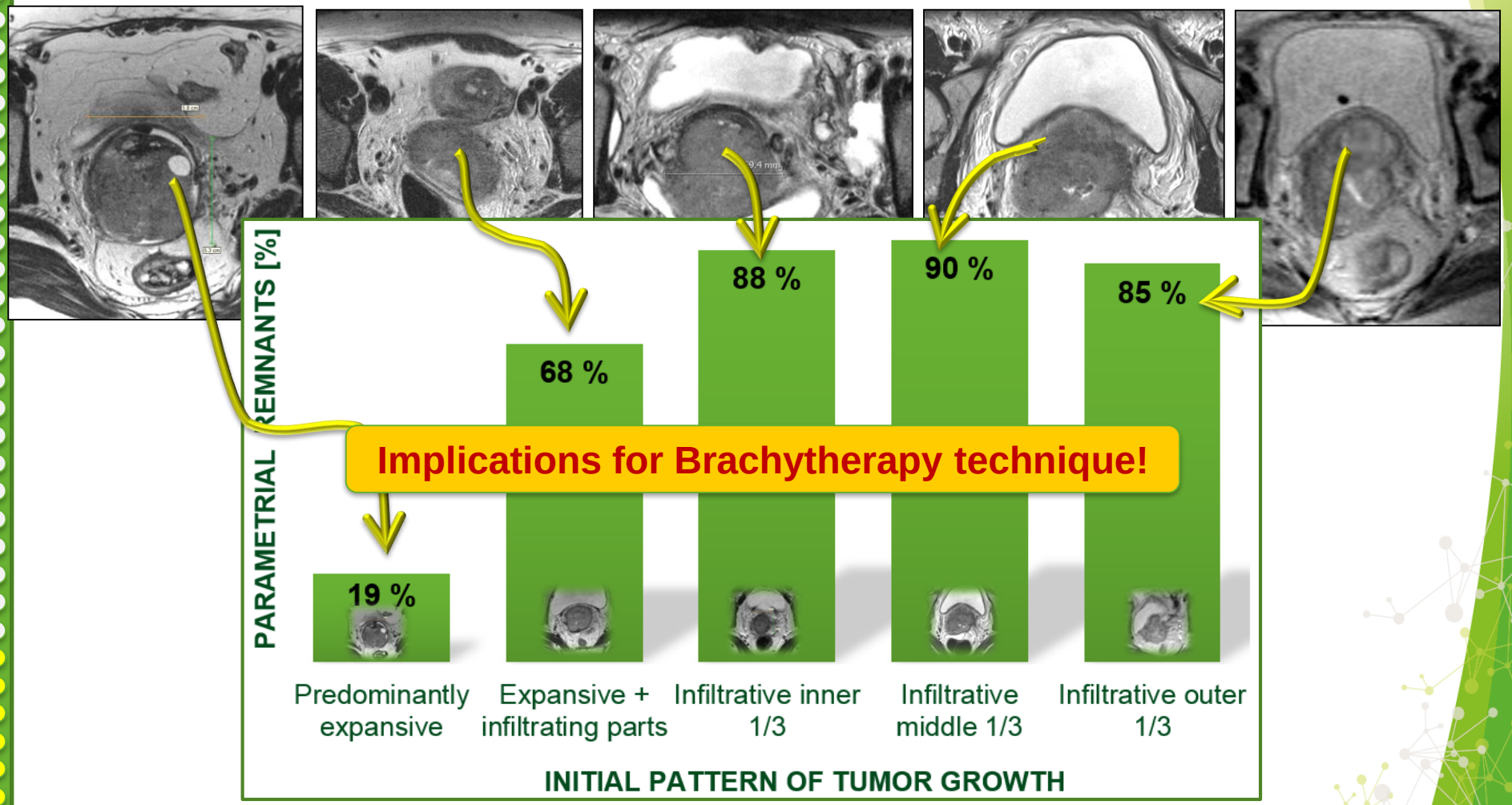

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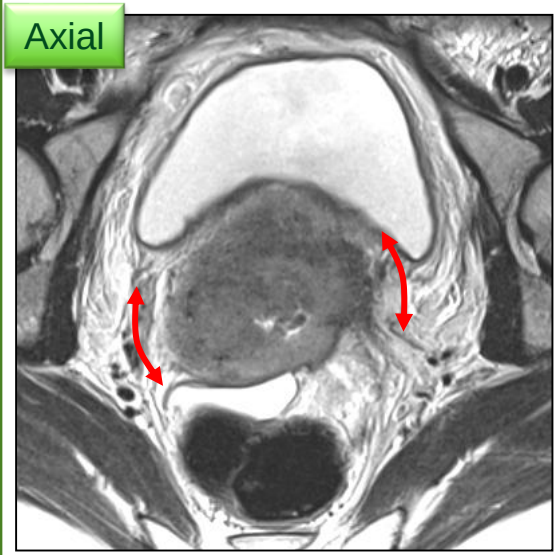
Yoshida K, et al. IJROBP 2016

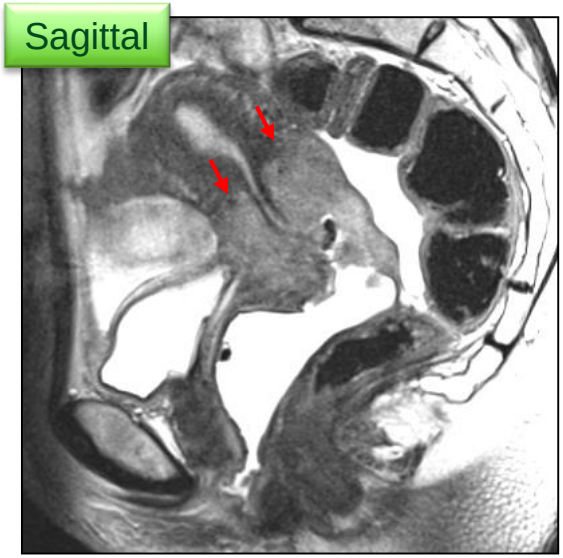
Grey zones

Grey zones at BT correlate with *Initial spread*

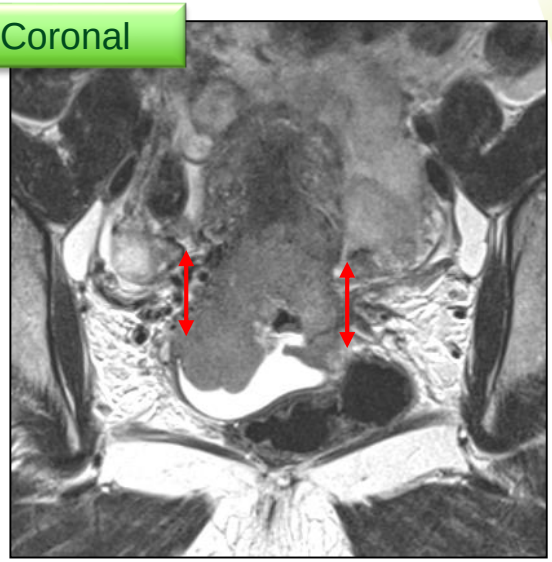
Axial

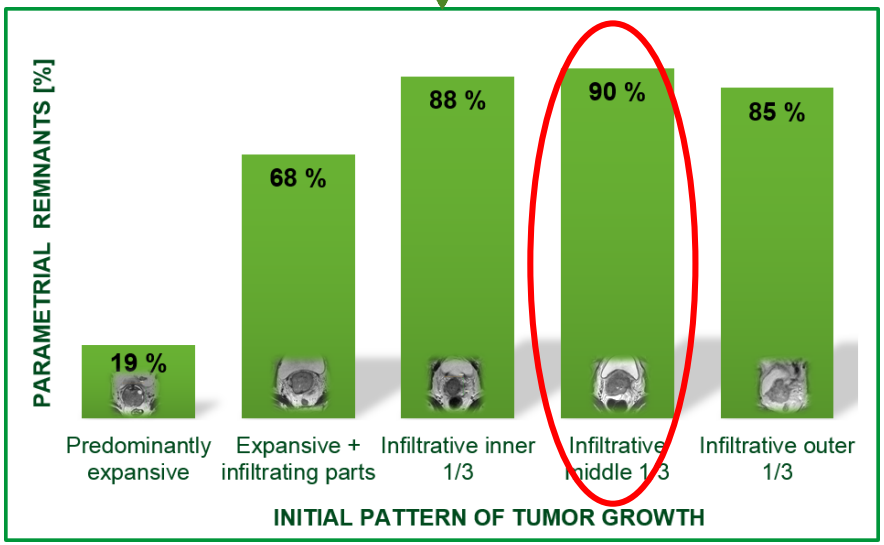


Sagittal



Coronal





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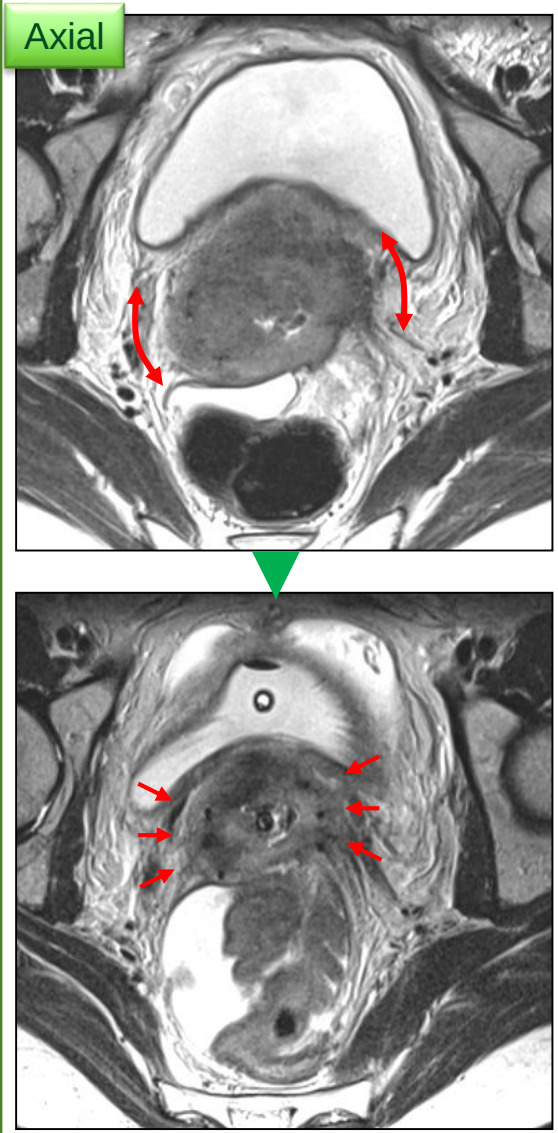

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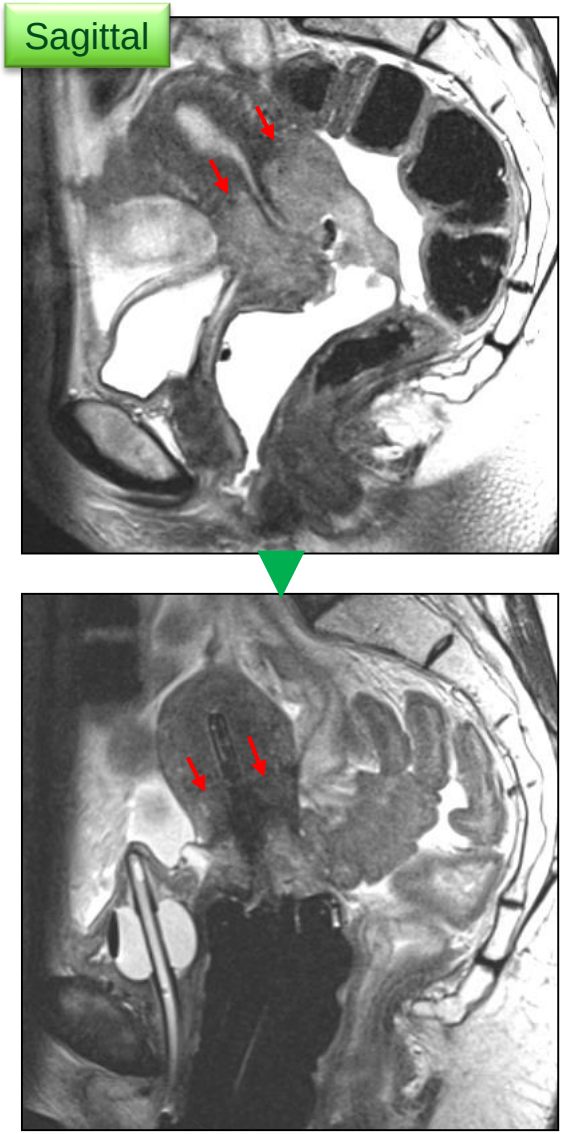

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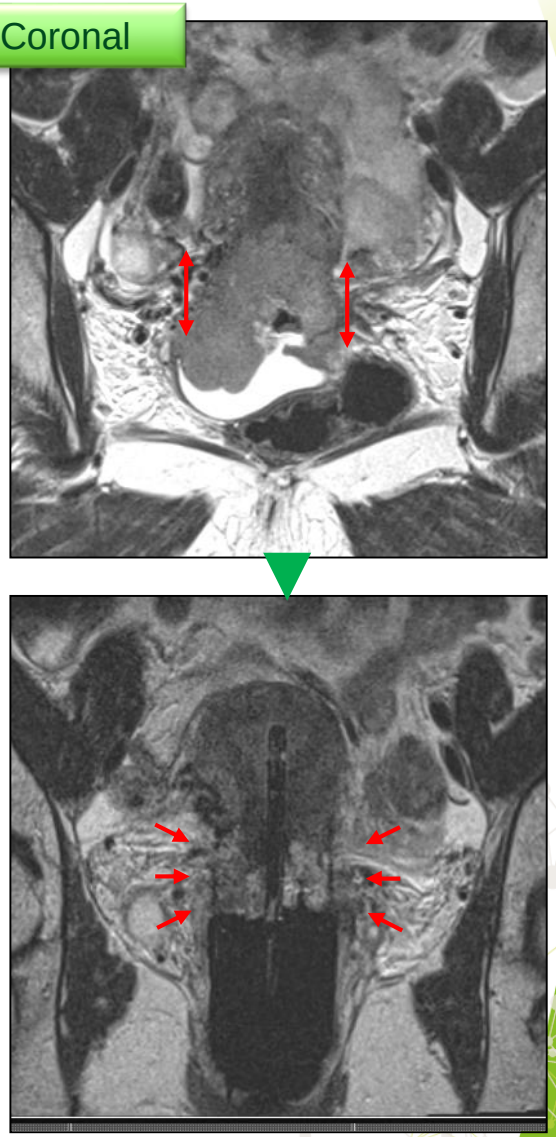

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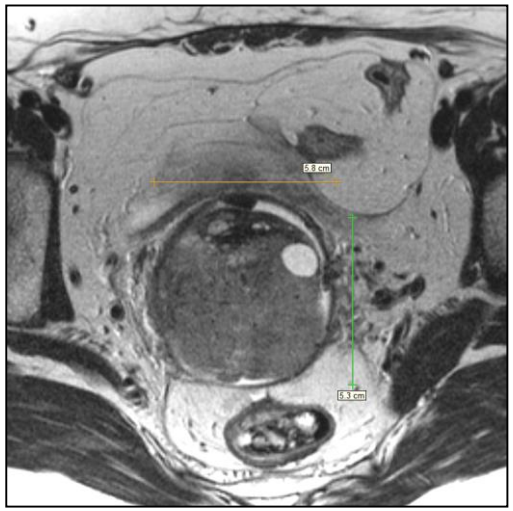

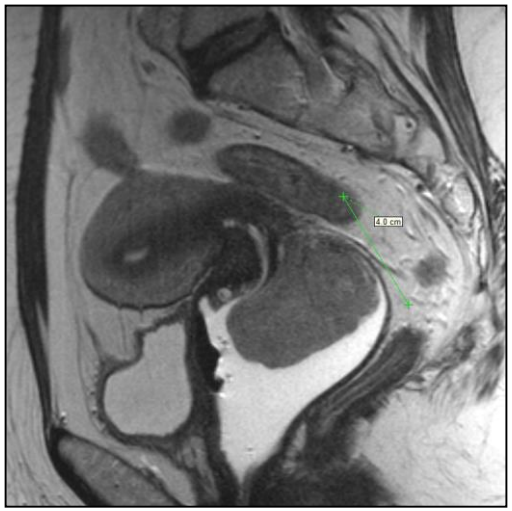

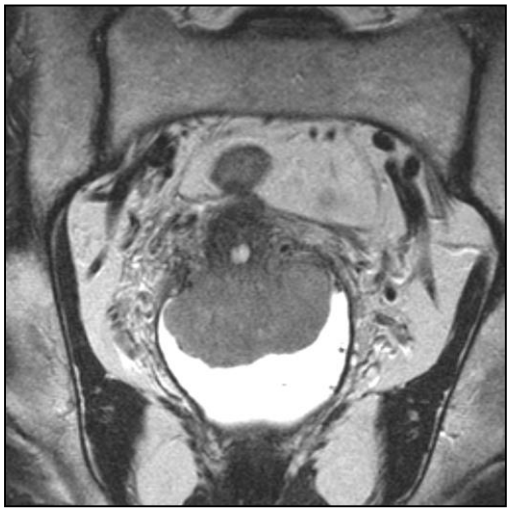

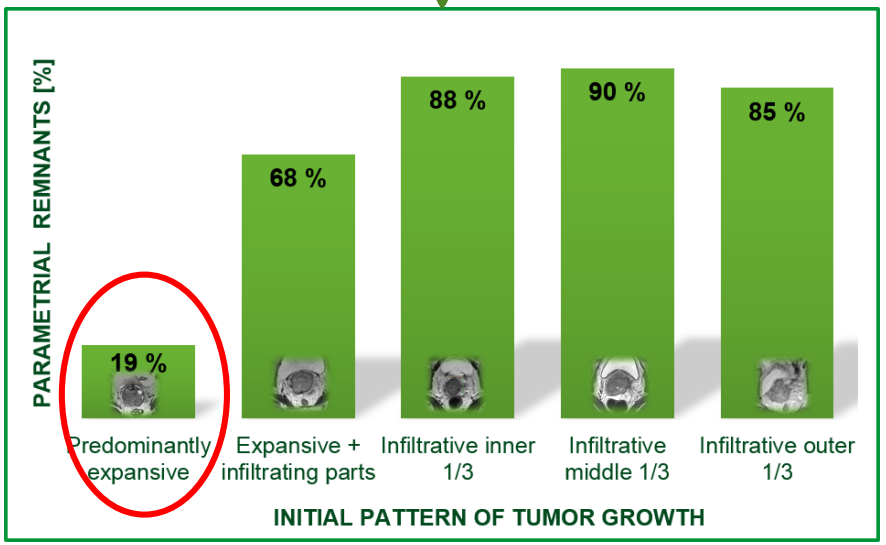

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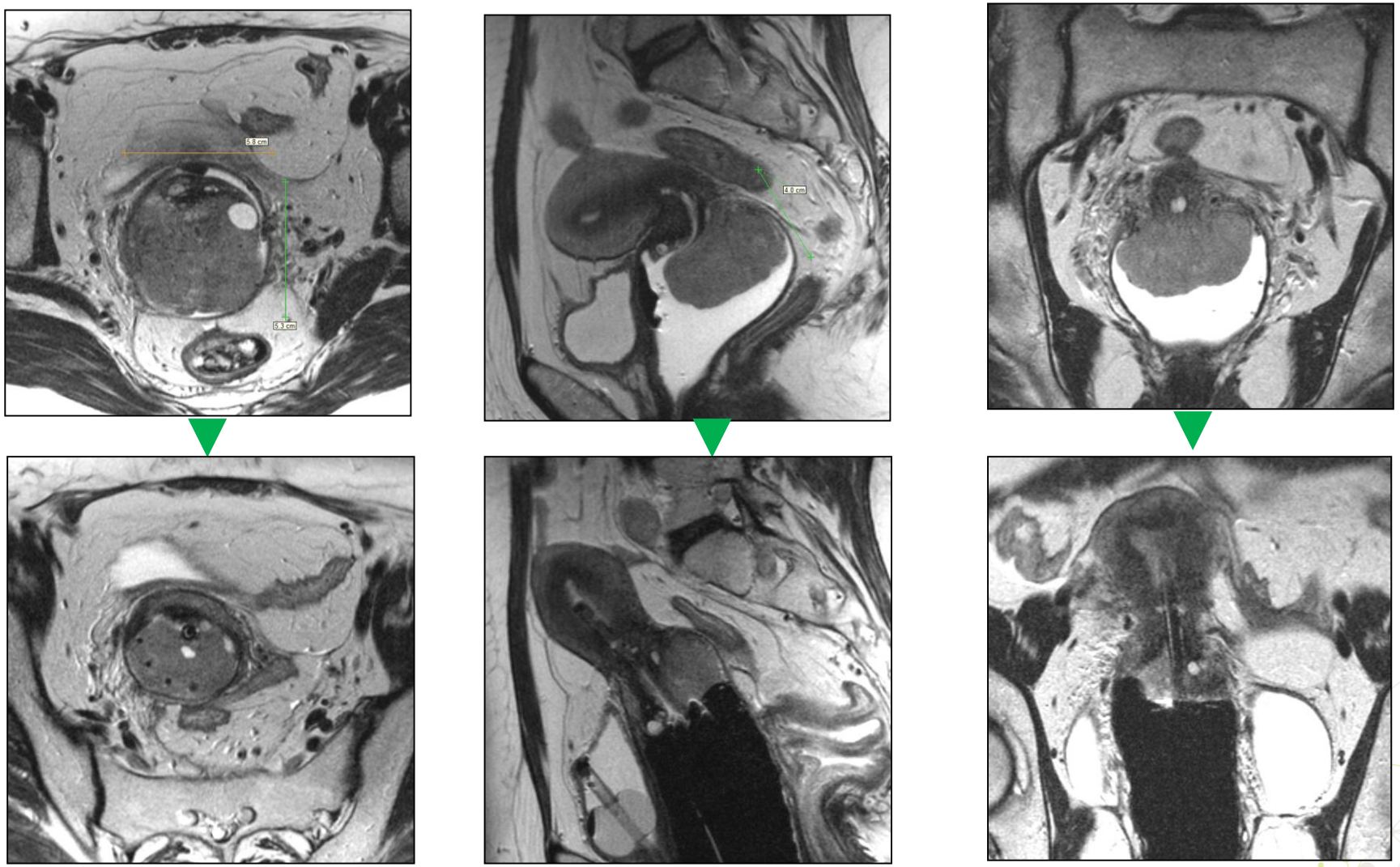

Set the **STAGE** before contouring

- **S**ize of the residual tumor?
- **T**opography of the target V?
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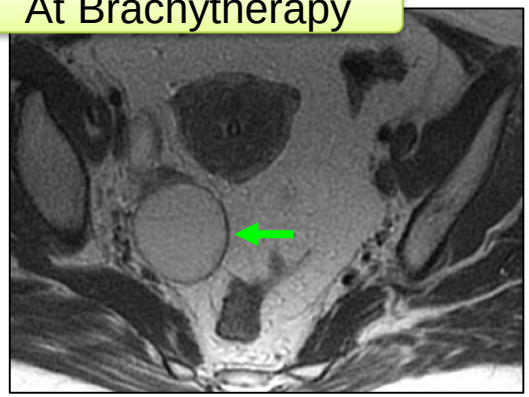
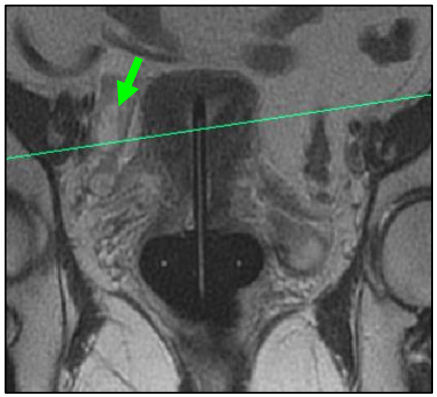
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

“Extra” findings?

Practical Example

At Brachytherapy





- Images were kept in BT dept.
- No radiology report

3 Weeks after BT

- Picture of Pelvic Inflammatory Disease
- Abscess drainage & Antibiotics

2 years follow up

- Alive and well

- There may be other pathology apart from cervix Ca!
- Informed consent before planning MRI...
- Communication & Consultation with Radiologist

Set the **STAGE** for contouring

- **S**ize of the residual tumor?
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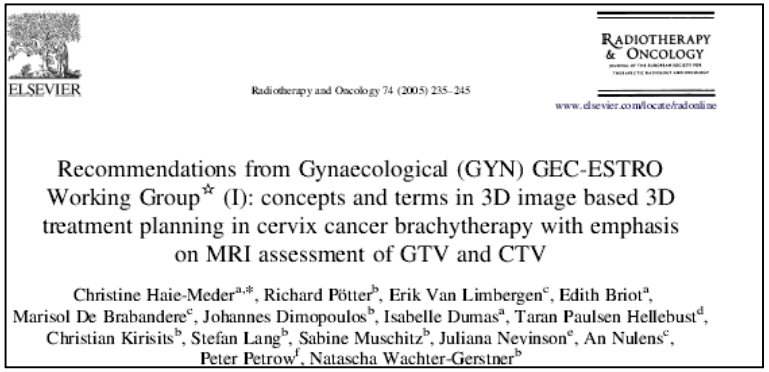
Contouring according to the GEC ESTRO Recommendations


ELSEVIER

Radiotherapy and Oncology 74 (2005) 235–245

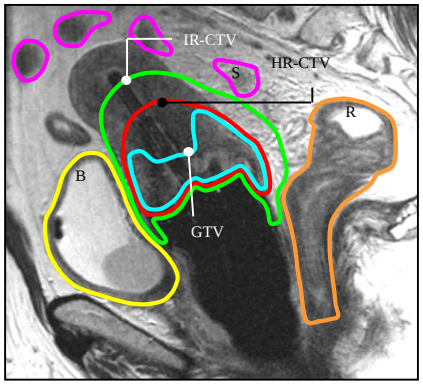
RADIOTHERAPY & ONCOLOGY

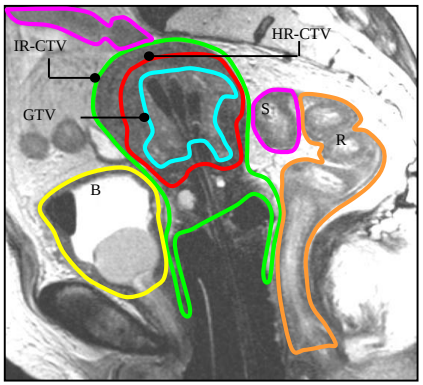
www.elsevier.com/locate/radonline

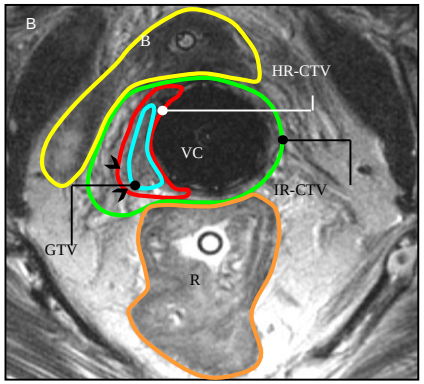
Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group☆ (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV

Christine Haie-Meder[a,*], Richard Pötter[b], Erik Van Limbergen[c], Edith Briot[a], Marisol De Brabandere[c], Johannes Dimopoulos[b], Isabelle Dumas[a], Taran Paulsen Hellebust[d], Christian Kirisits[b], Stefan Lang[b], Sabine Muschitz[b], Juliana Nevinson[e], An Nulens[c], Peter Petrow[f], Natascha Wachter-Gerstner[b]

Haie-Meder C et al. Radiother Oncol 2005







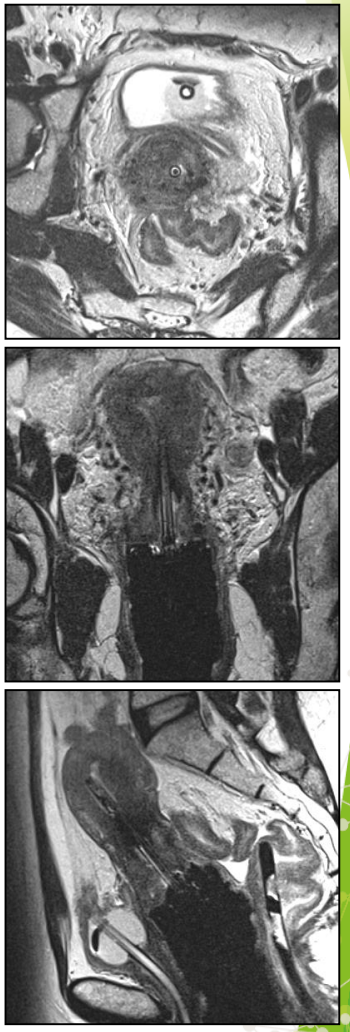
SUMMARY – EXAMPLE T2W MRI at BT from Rad. Onc. Perspective

Rule out **FLOP**

1. No free **FL**uid
2. No **O**rgan **P**erforation (or uterine perforation)

Set the **STAGE** for contourig

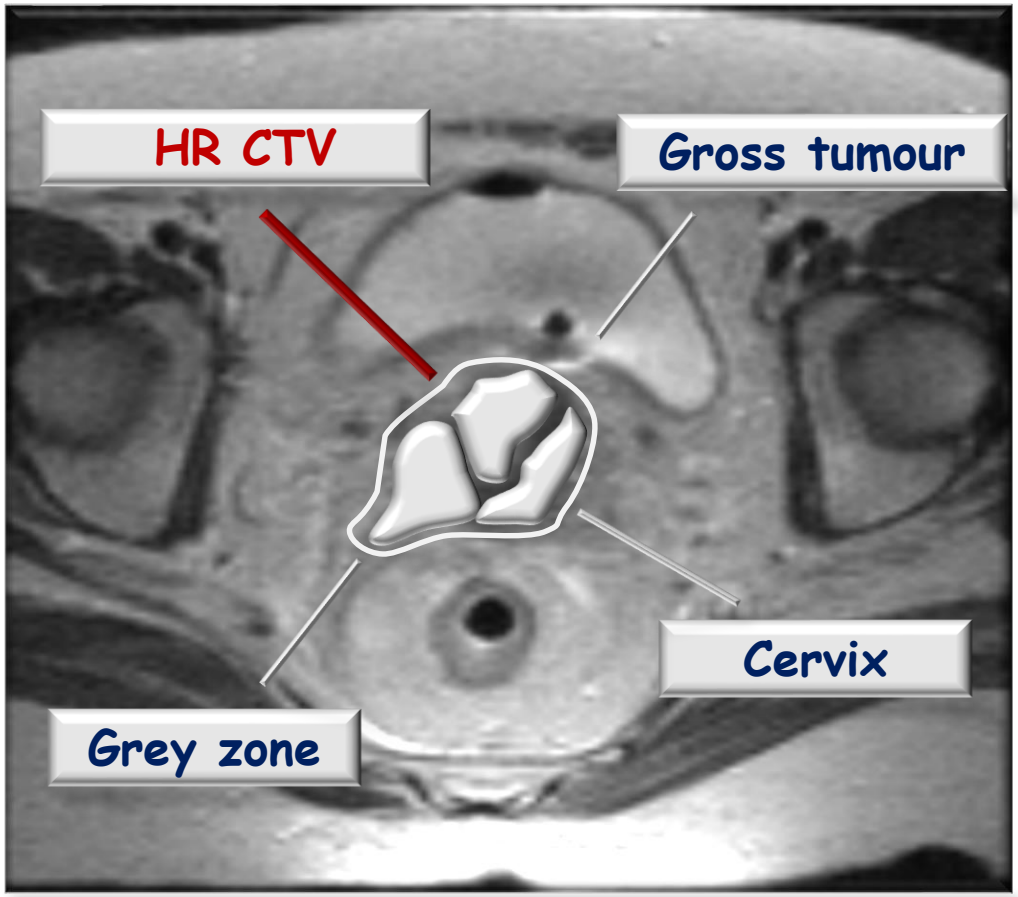
1. **S**ize of the tumor:
   - 8 cm^3 (ellipsoid formula)
   - Regression to Proportional V: PV = 20 % initial V
2. **T**opography: unfavourable due to right parametrial extension.
3. **A**dequate insertion geometry.
4. **G**rey zones correspond to initial infiltrative tumor: proximal third of right parametrium, dorsally.
5. "**E**xtra" findings:
   - Collaboration with radiologist recommended.



CT for IGABT?

Imaging protocols MRI and CT
Key issues when using MRI for IGABT

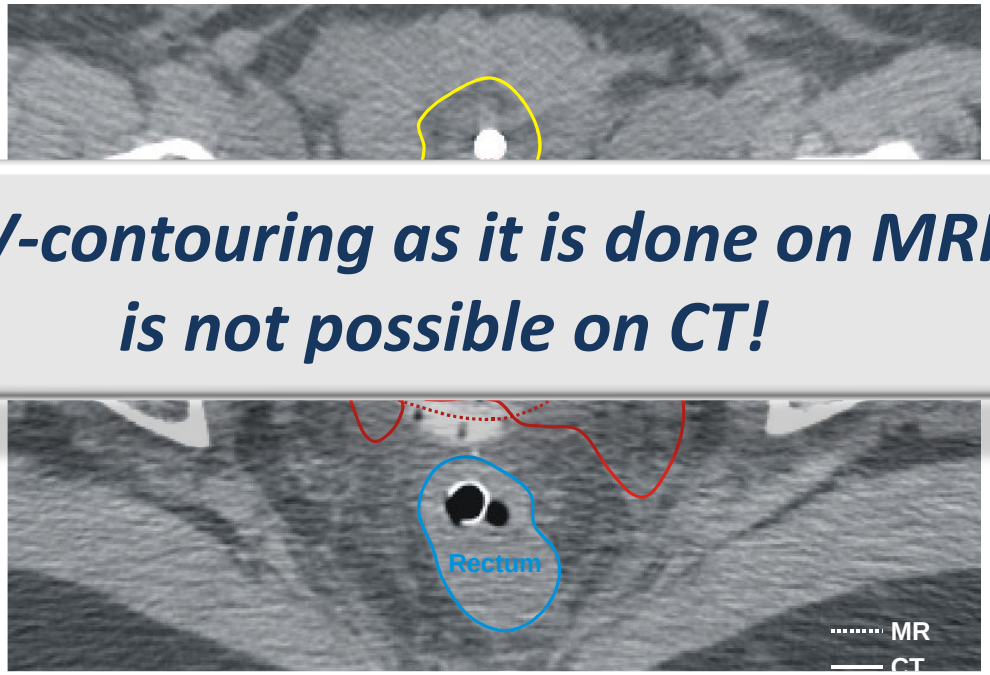
Target / Patho-anatomical structures / GTV, HR-CTV contouring on MRI



ELONGS UNDER
T CONTOURING

Imaging protocols MRI and CT
Key issues when using CT for IGABT

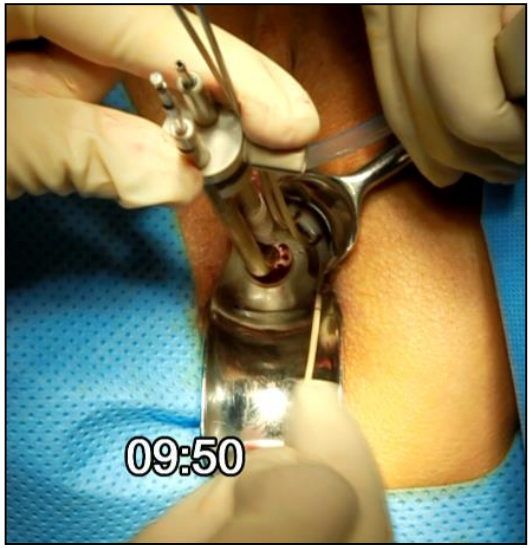
Target / Patho-anatomical structures / GTV, HR-CTV contouring on CT

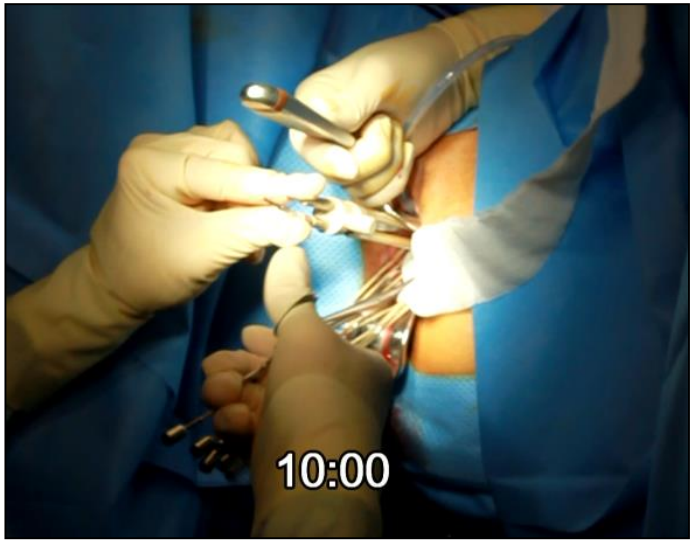


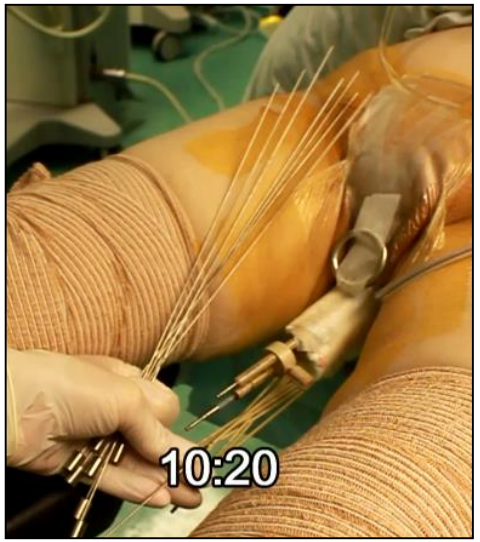
GTV-contouring as it is done on MRI is not possible on CT!

CT for IGABT?

Preparation for contouring starts prior to imaging







Adapt your application technique!

Avoid thick stainless steel applicators / accessories

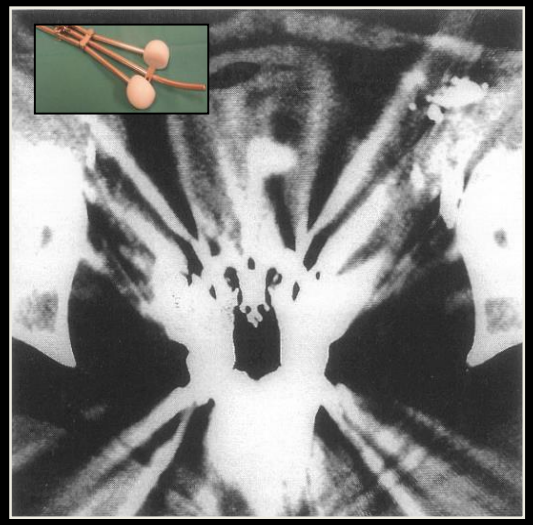
Use CT compatible equipment

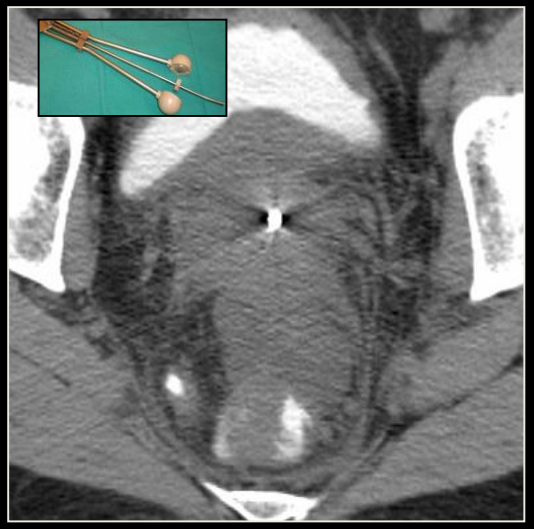
Avoid non-diluted contrast (packing, Foley ballon, bladder...)

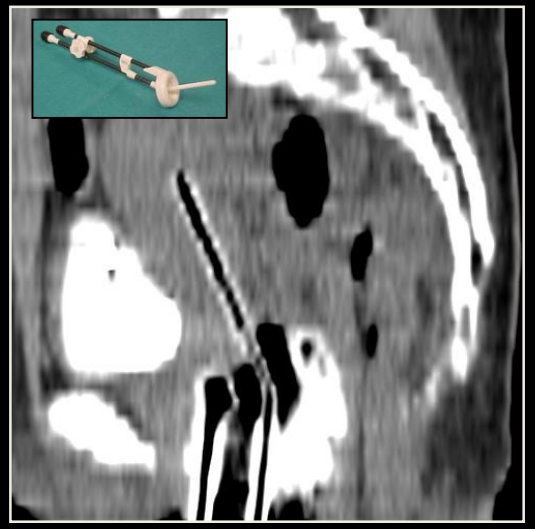
Consider marking vaginal extension (i.e. radio-opaque suture)

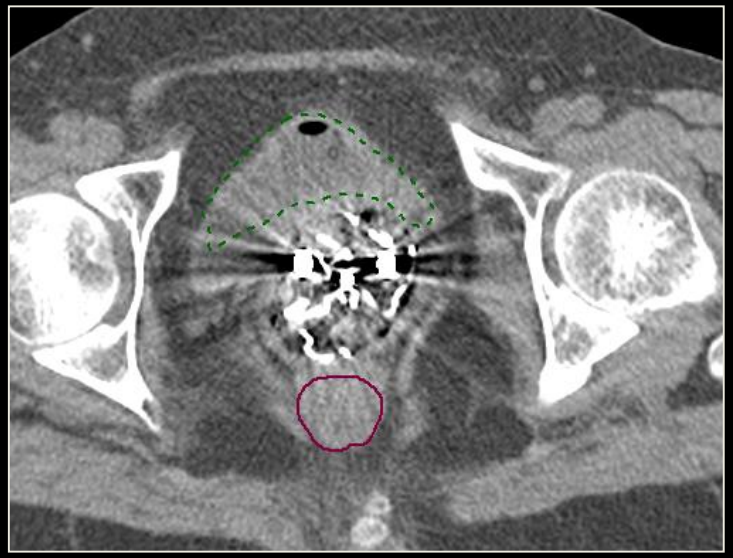
STANDARDIZE YOUR PROTOCOL

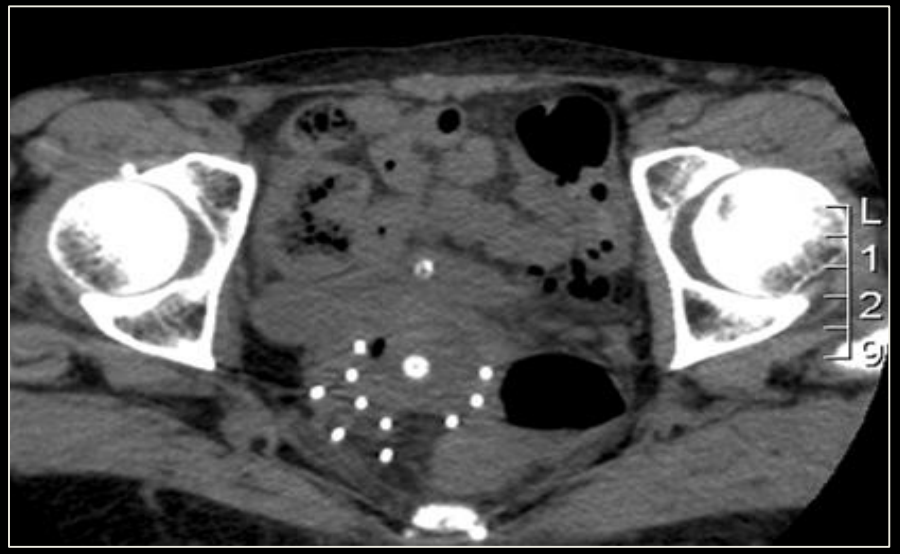
Use CT compatible applicators





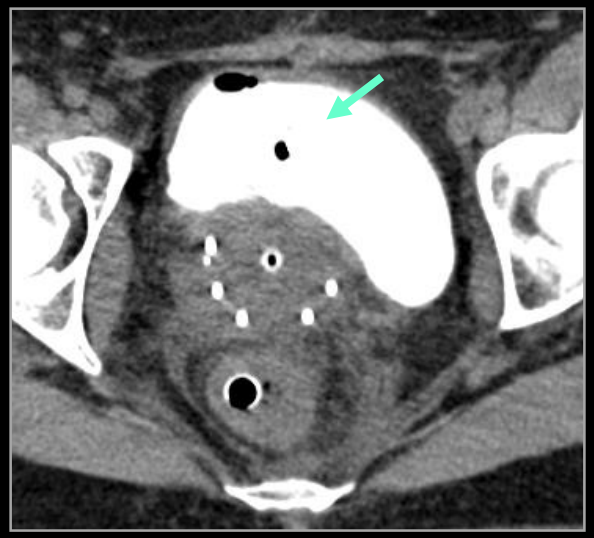


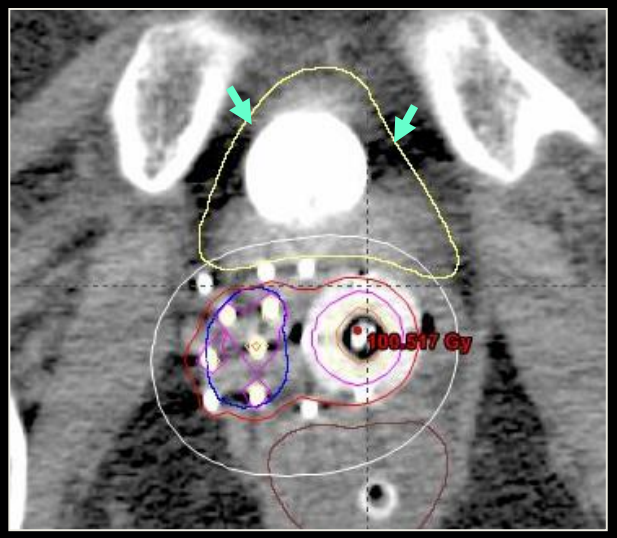


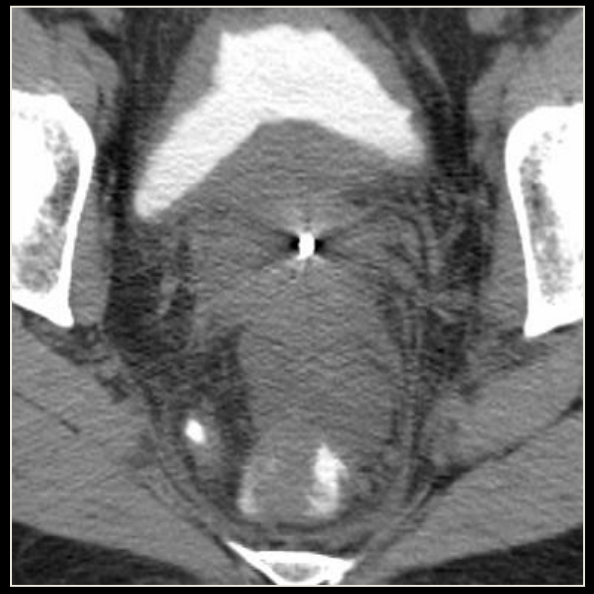


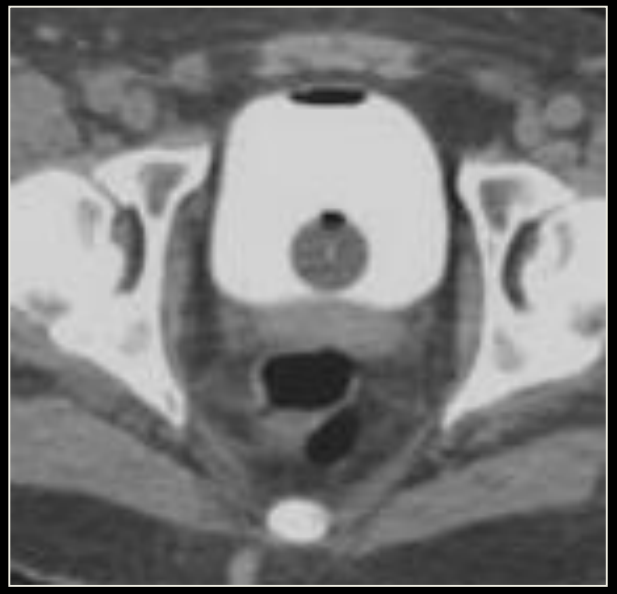
STANDARDIZE YOUR PROTOCOL

Bladder / Foley contrast dilution



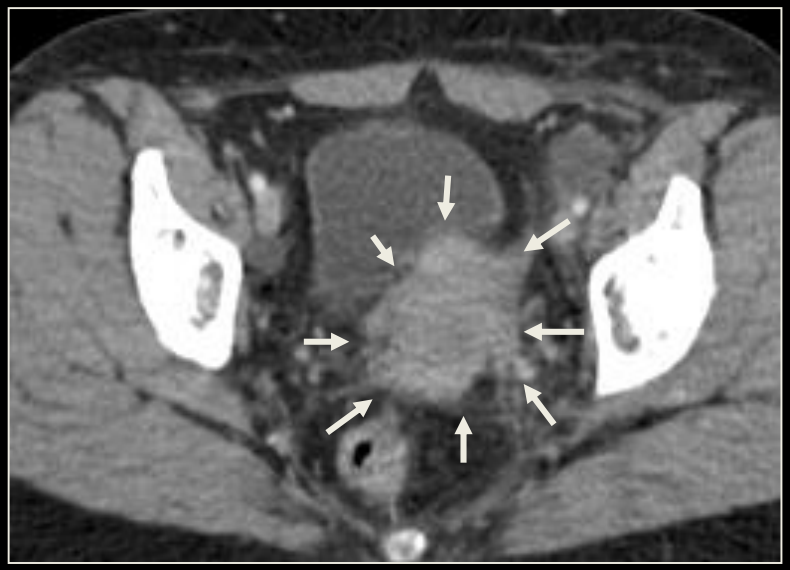


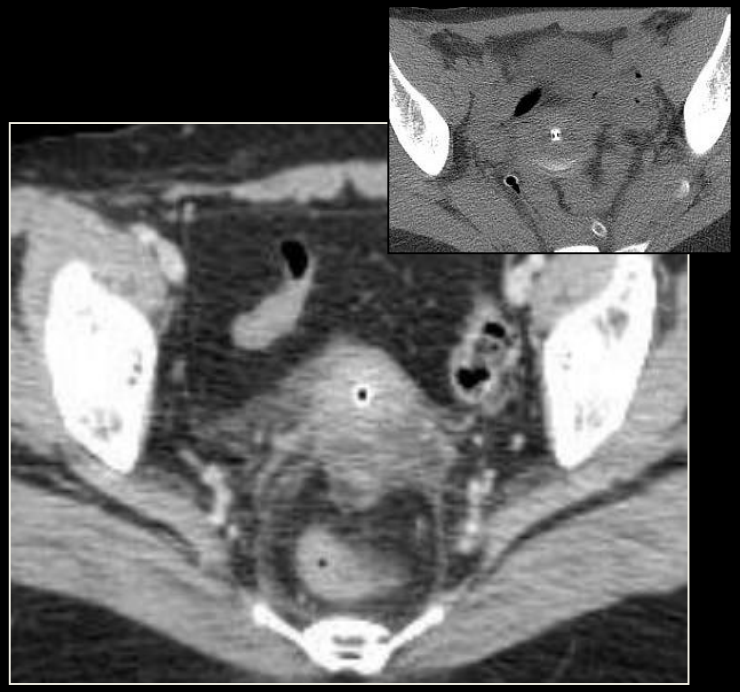




STANDARDIZE YOUR PROTOCOL

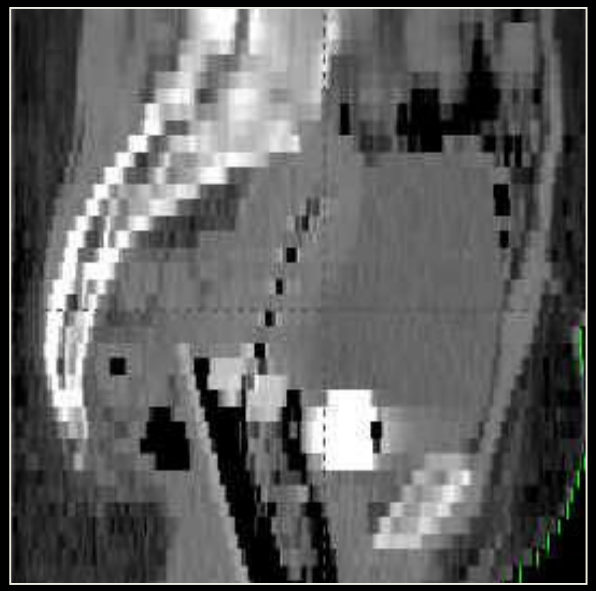
i.v. contrast

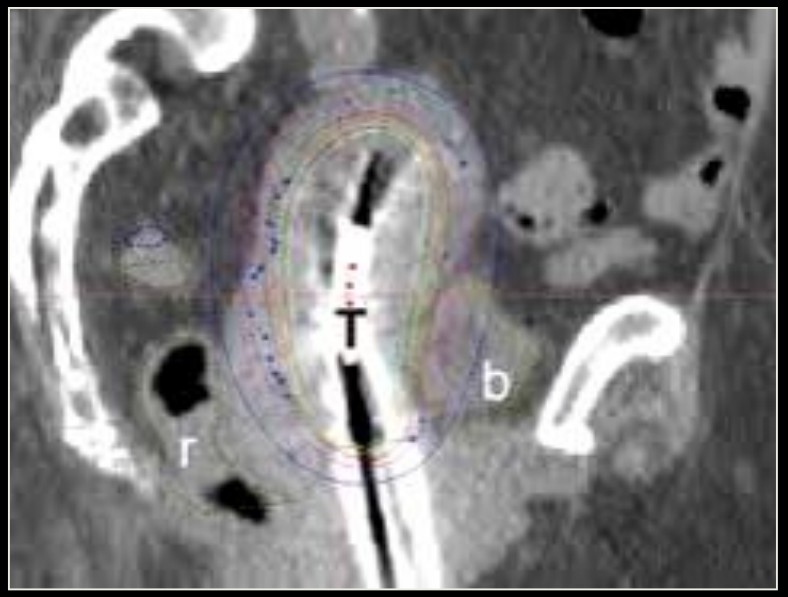




STANDARDIZE YOUR PROTOCOL

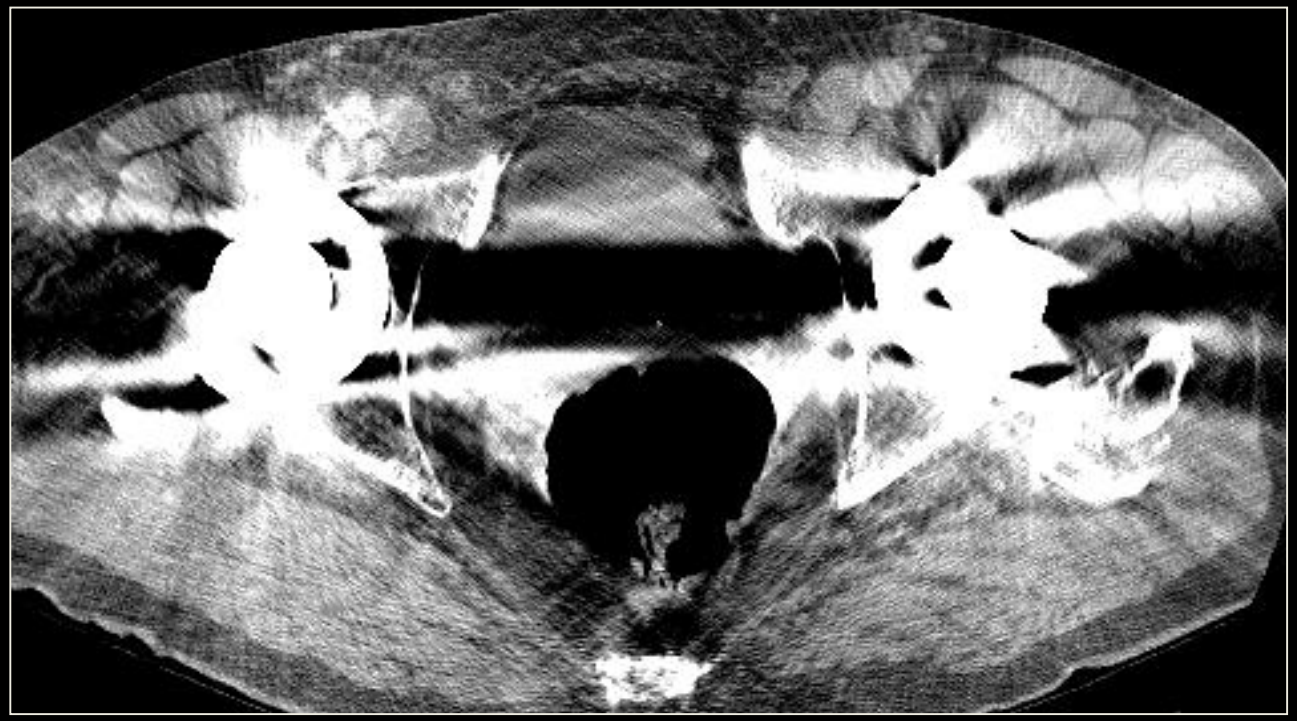
Use thin slices over the areas of interest





STANDARDIZE YOUR PROTOCOL

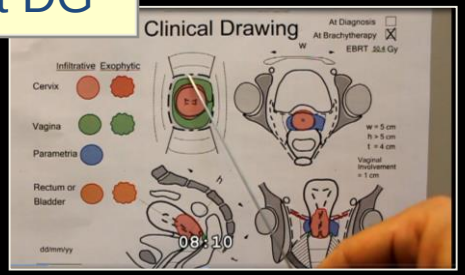
Sometimes there is little we can do...

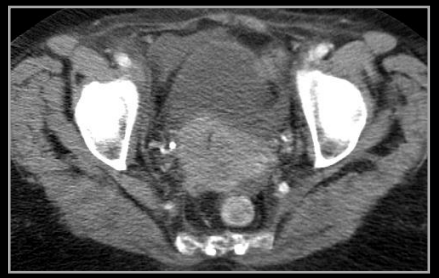


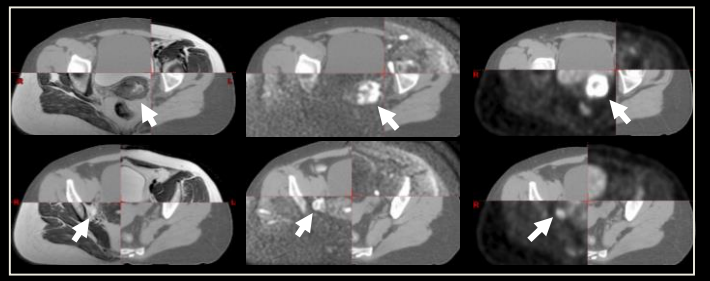
STANDARDIZE YOUR PROTOCOL

Combine all clinical and radiological information

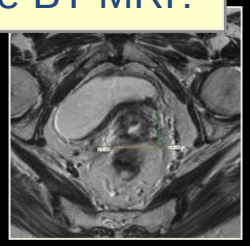
At DG

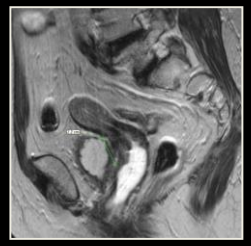


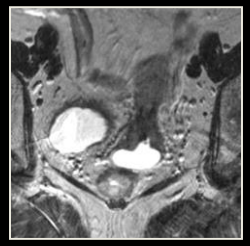




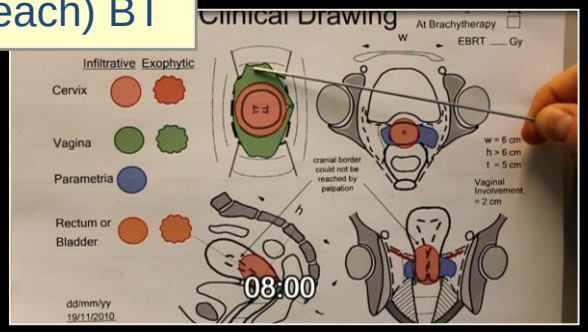
Pre BT MRI?

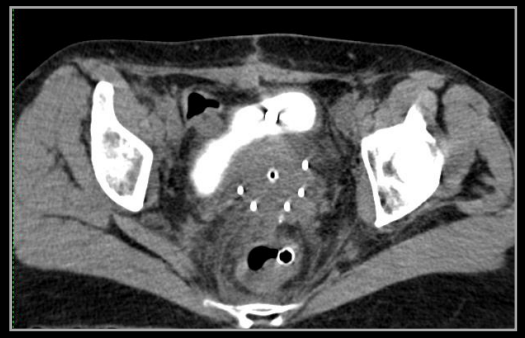






At (each) BT





CT for IGABT?

Understanding MRI concepts: precondition for CT based contouring

ELSEVIER

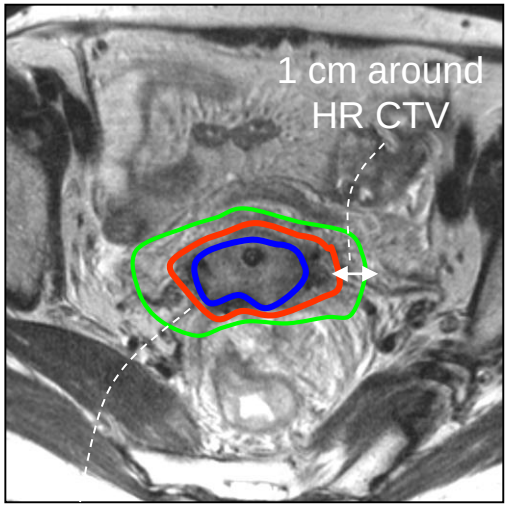
Radiotherapy and Oncology 74 (2005) 235–245

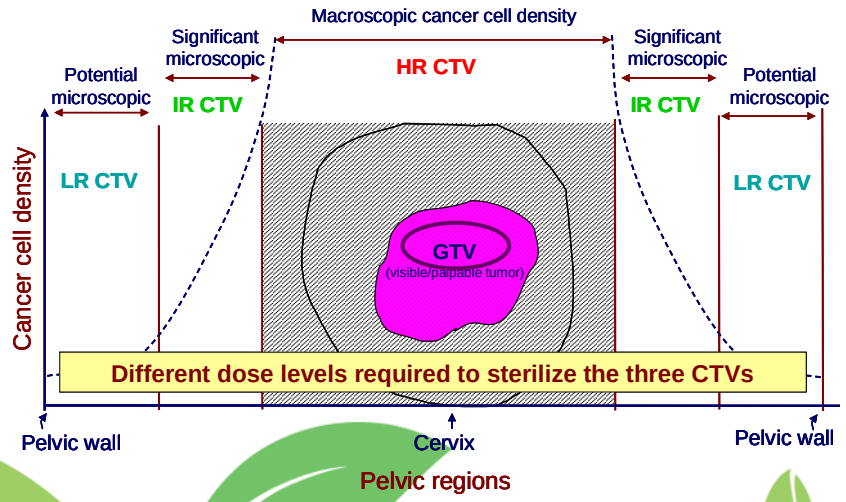
RADIOTHERAPY & ONCOLOGY

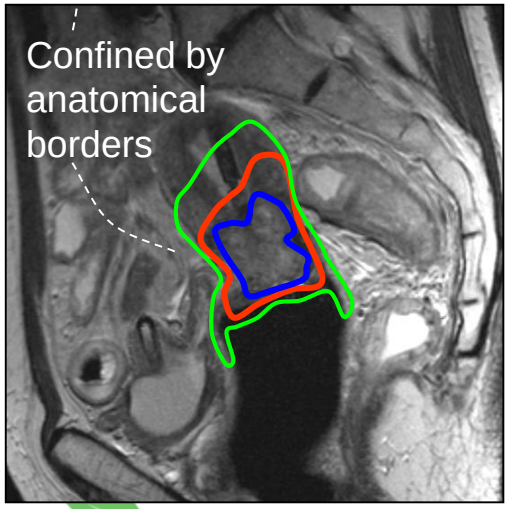
www.elsevier.com/locate/radonline

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group* (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV

Christine Haie-Meder[a,*], Richard Pötter[b], Erik Van Limbergen[c], Edith Briot[a], Marisol De Brabandere[c], Johannes Dimopoulos[b], Isabelle Dumas[a], Taran Paulsen Hellebust[d], Christian Kirisits[b], Stefan Lang[b], Sabine Muschitz[b], Juliana Nevinson[e], An Nulens[c], Peter Petrow[f], Natascha Wachter-Gerstner[b]







CT for IGABT?

	Clinical examination	MR	CT
GTV			
Outline of cervix			
Uterine corpus invasion			
Parametrial ivasion (parametrium paracervix, paracolpium)			
Vaginal invasion			

CT for IGABT?

	Clinical examination	MR	CT
GTV	(good)		
Outline of cervix	(good)		
Uterine corpus invasion	poor		
Parametrial ivasion (parametrium paracervix, paracolpium)	good		
Vaginal invasion	excellent		

CT for IGABT?

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	Clinical examination	MR	CT
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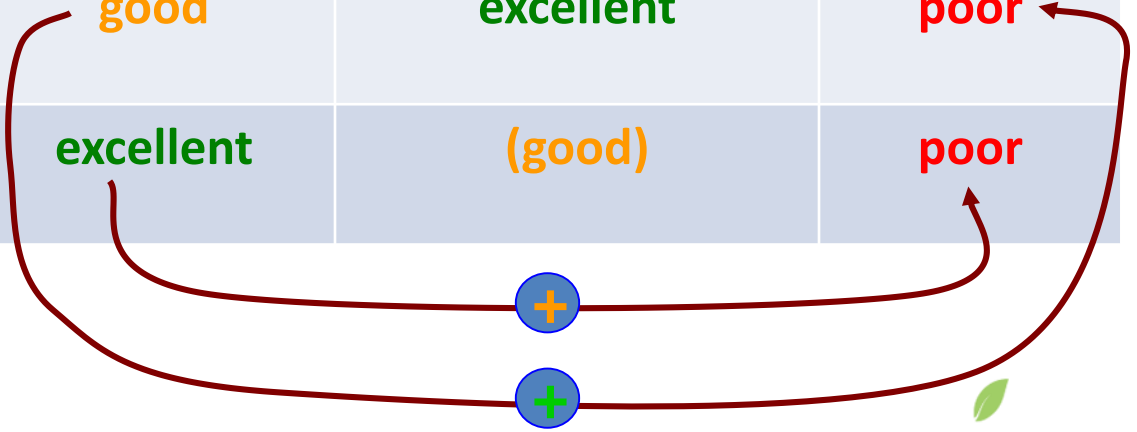

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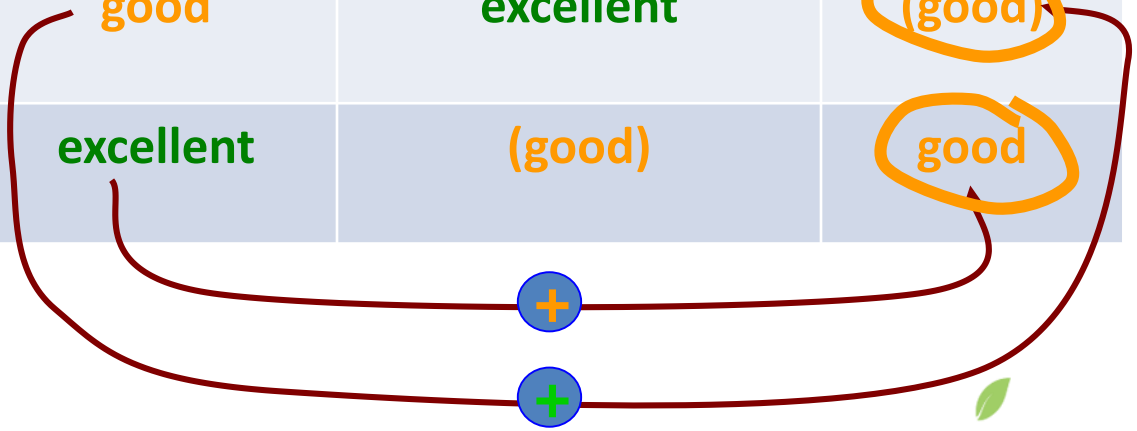

HR CTV
- GTV
- Whole cervix
- Extracervical tumour extension

IR CTV: in principle HR CTV + margins

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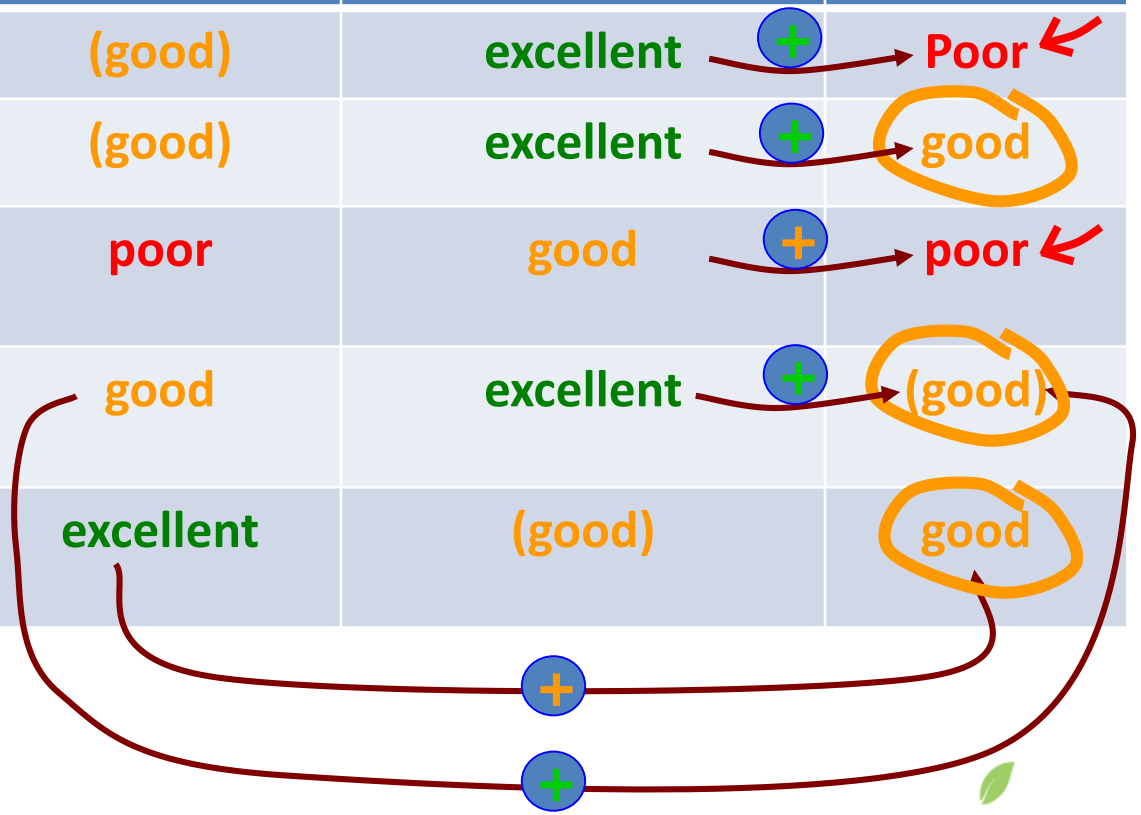

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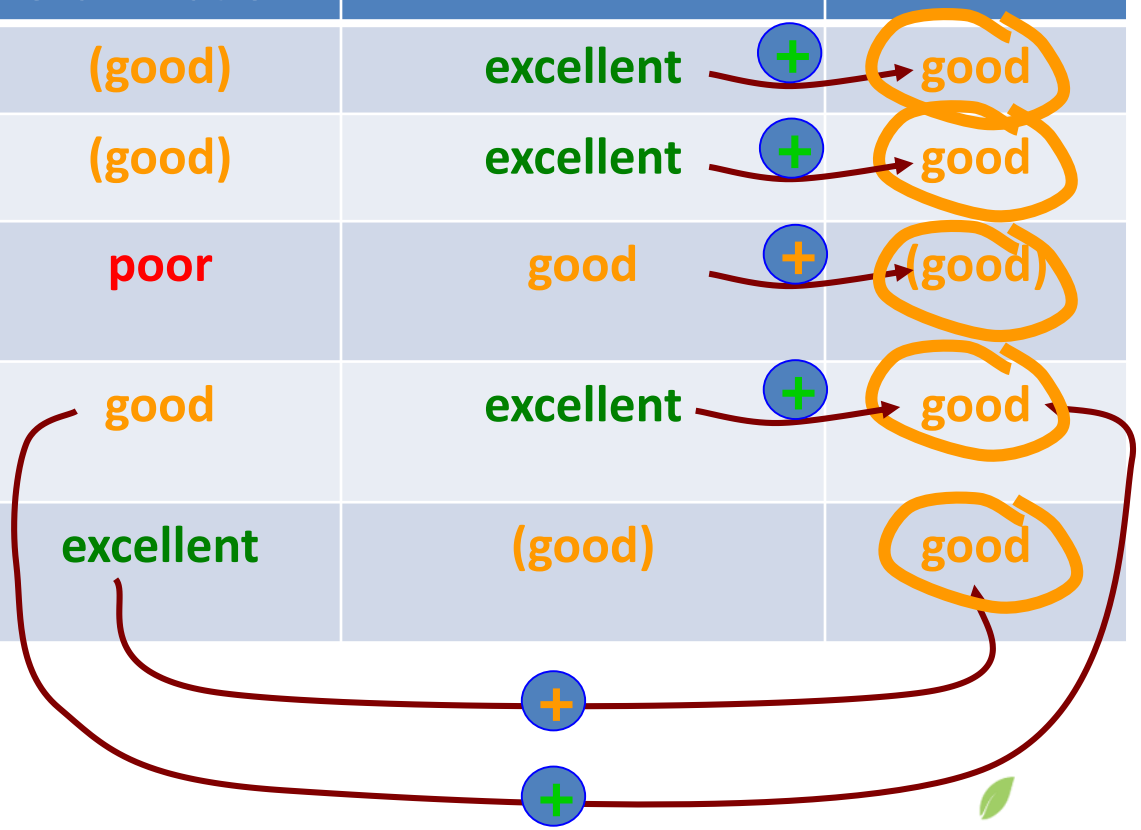

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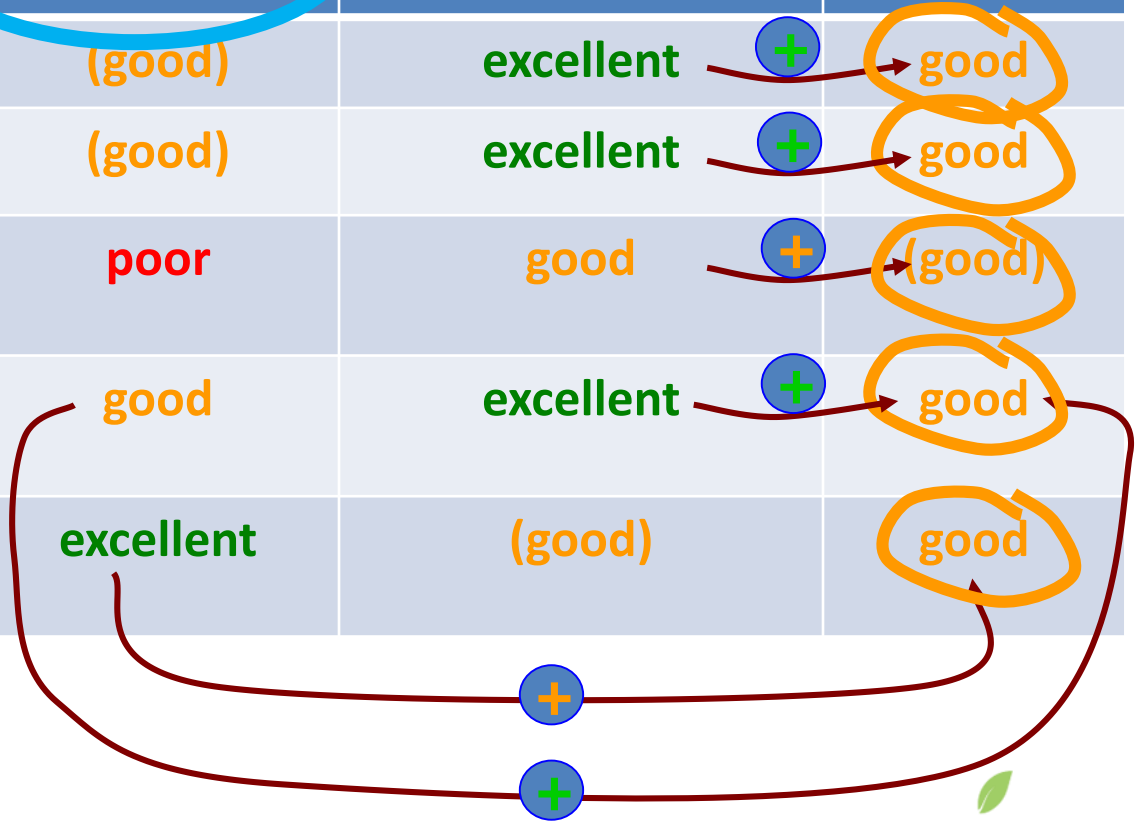

HR CTV
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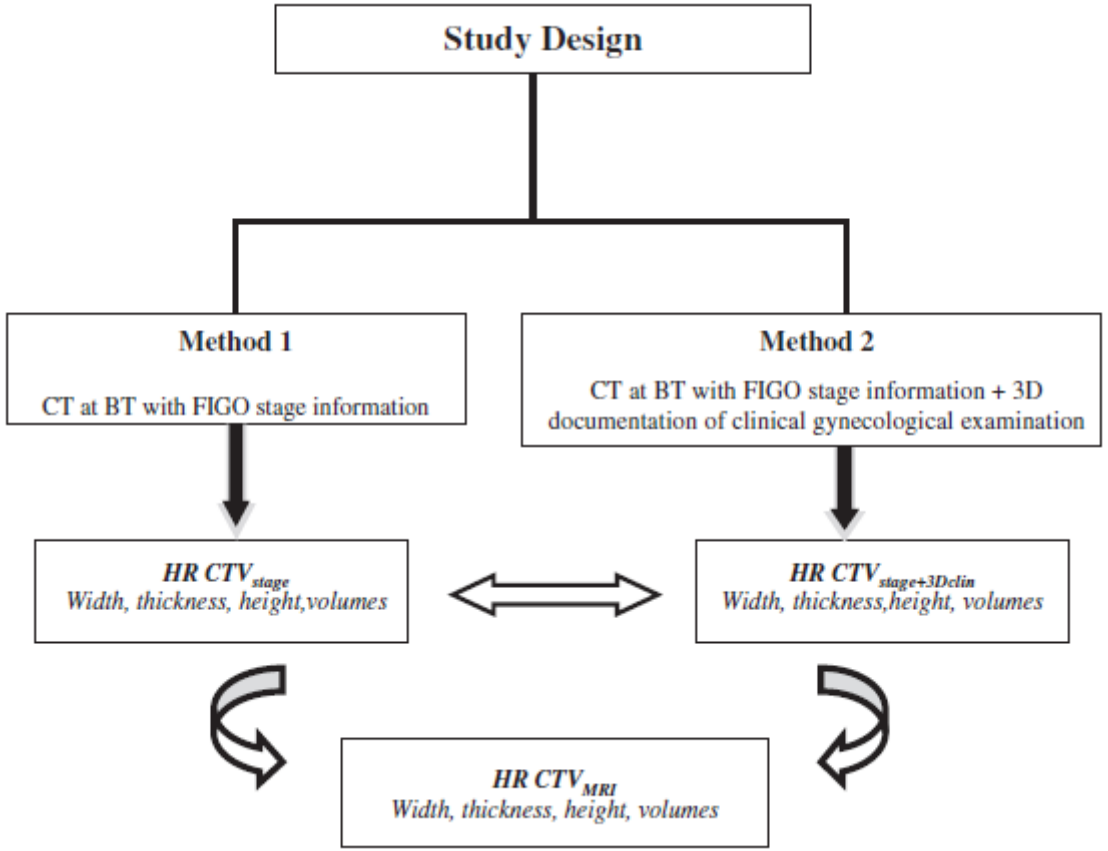
IR CTV: in principle HR CTV + margins

Incorporation of clinical information

High-risk clinical target volume delineation in CT-guided cervical cancer brachytherapy: Impact of information from FIGO stage with or without systematic inclusion of 3D documentation of clinical gynecological examination

NEAMAT HEGAZY[1,2], RICHARD PÖTTER[1,3], CHRISTIAN KIRISITS[1,3], DANIEL BERGER[1], MARIO FEDERICO[1], ALINA STURDZA[1] & NICOLE NESVACIL[1]

[1]*Department of Radiotherapy, Comprehensive Cancer Centre Vienna, Medical University of Vienna, Vienna, Austria,* [2]*Department of Clinical Oncology, Medical University of Alexandria, Egypt and* [3]*Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University Vienna, Austria*

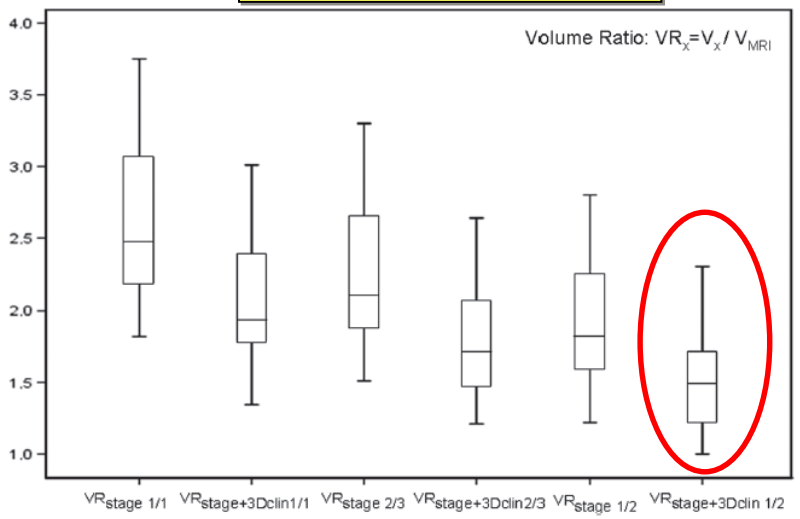


Hegazy N, et al. Acta Oncologica 2013

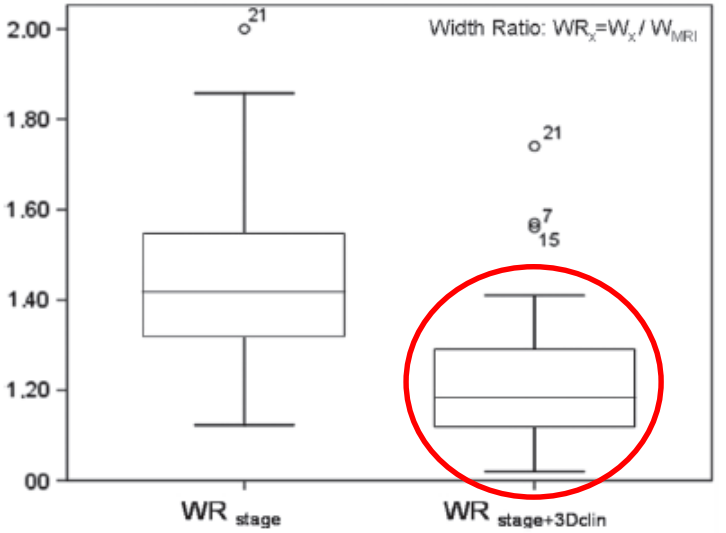
Incorporation of clinical information

High-risk clinical target volume delineation in CT-guided cervical cancer brachytherapy: Impact of information from FIGO stage with or without systematic inclusion of 3D documentation of clinical gynecological examination

CT / MRI V ratio



CT / MRI Width ratio



Conclusion. CT-based HR CTV contouring based on FIGO stage alone leads to large overestimation of width and volume. Target delineation accuracy can systematically improve through incorporation of additional information from comprehensive 3D documentation of repetitive gynecological examination in the contouring protocol, and thus help to improve the accuracy of dose optimization in settings with limited access to imaging facilities at the time of brachytherapy. If CT information is only available, minimum 2/3 of uterine height may be a good surrogate for the height of HR CTV.

Hegazy N, et al. Acta Oncologica 2013

CT for IGABT?

	Clinical examination	PRE-BT MR	CT
GTV	(good)	excellent	good
Outline of cervix	good	excellent	good
Uterine corpus invasion	poor	good	(good)
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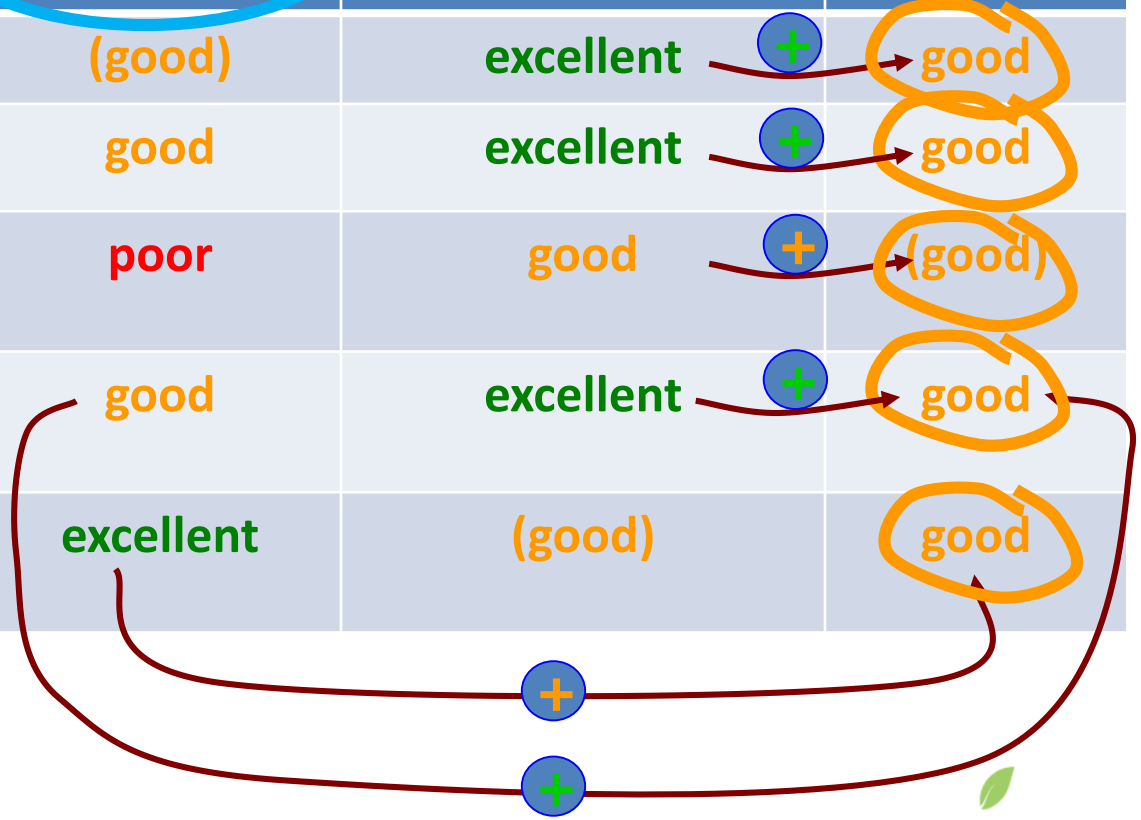


HR CTV
- GTV
- Whole cervix
- Extracervical tumour extension

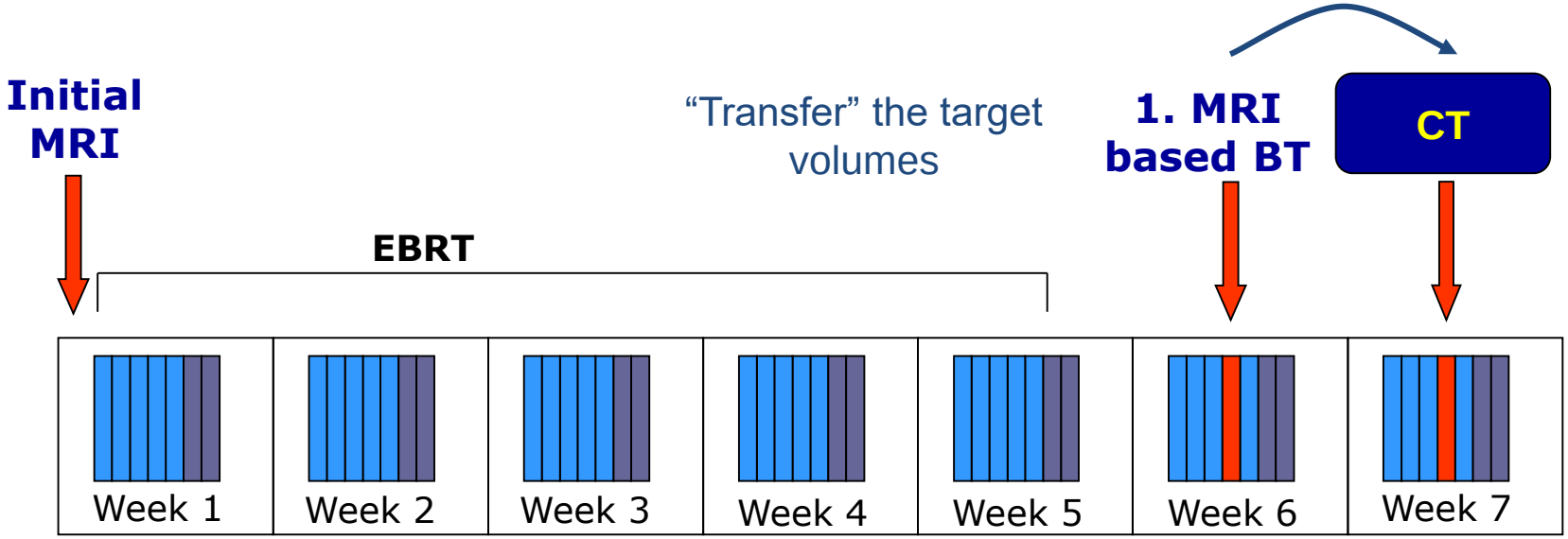
IR CTV: in principle HR CTV + margins

Incorporation of pre-BT MRI information

Adaptive image guided brachytherapy for cervical cancer: A combined MRI-/CT-planning technique with MRI only at first fraction

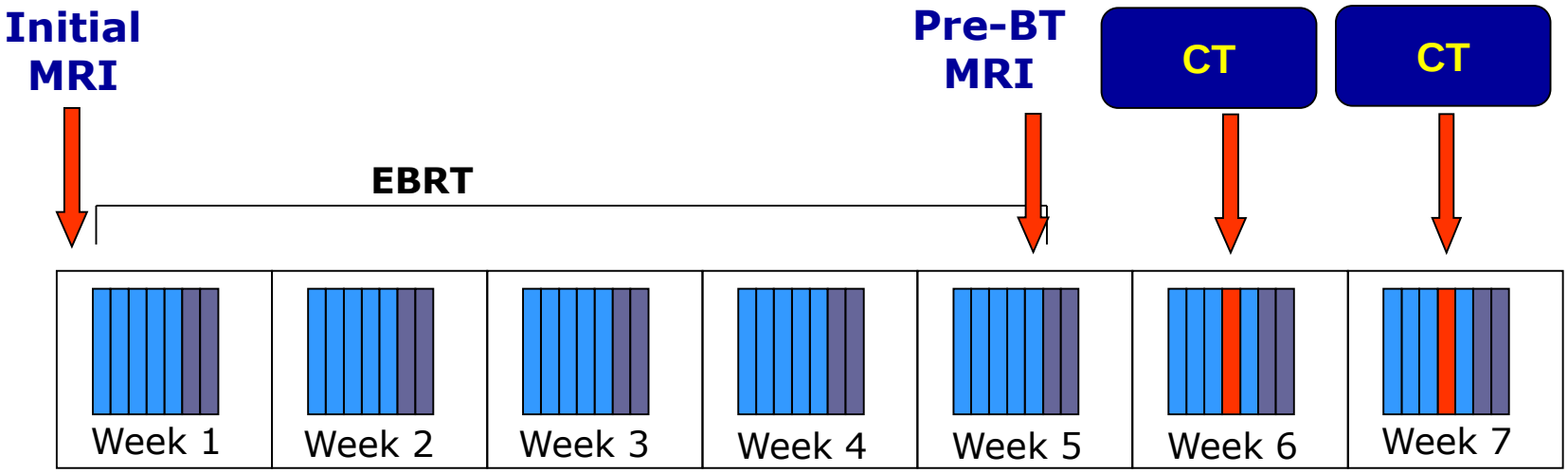
Nicole Nesvacil [a,*], Richard Pötter [b], Alina Sturdza [a], Neamat Hegazy [a], Mario Federico [a], Christian Kirisits [b]

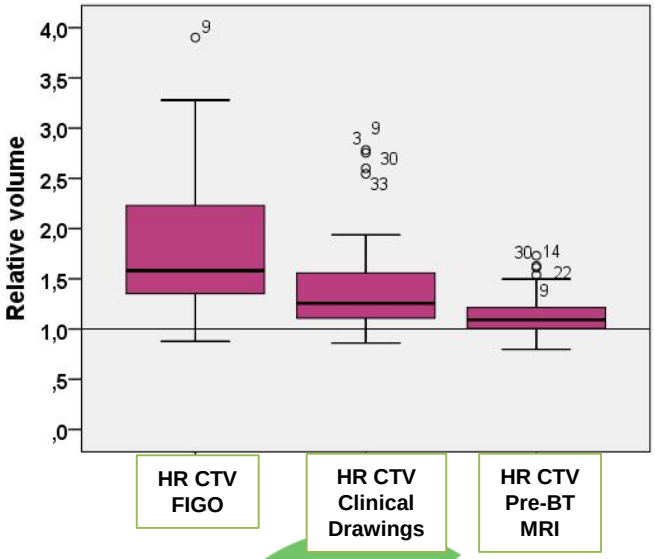
[a] Department of Radiotherapy, Comprehensive Cancer Center, Medical University of Vienna; [b] Department of Radiotherapy, Comprehensive Cancer Center & Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna



Conclusions: A combination of MRI for first fraction and subsequent CT based planning is feasible and easy when automatic applicator-based image registration and target transfer are technically available. The results show striking similarity to fully MRI-based planning in cases of small tumours and intracavitary applications, both in terms of HR CTV coverage and respecting of OAR dose limits. For larger tumours and complex applications, as well as situations with unfavourable OAR topography, especially for the sigmoid, MRI based adaptive BT planning remains the superior method.

Incorporation of pre-BT MRI information





Pre-BT MRI improves the ability to contour on CT!

Federico M, et al. 2012 (published as abstract)

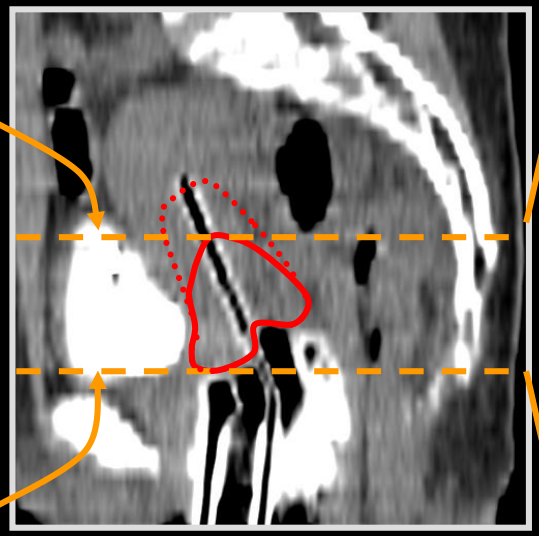
HR CTV contouring on CT: tips

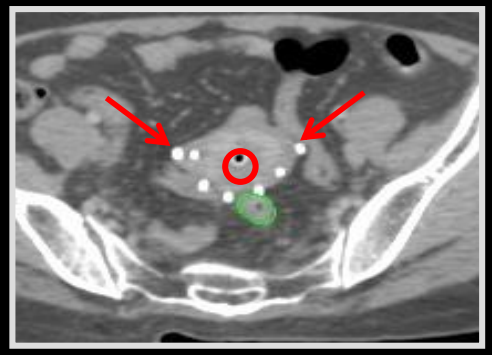
Inferior and superior extent ≅ cervical borders

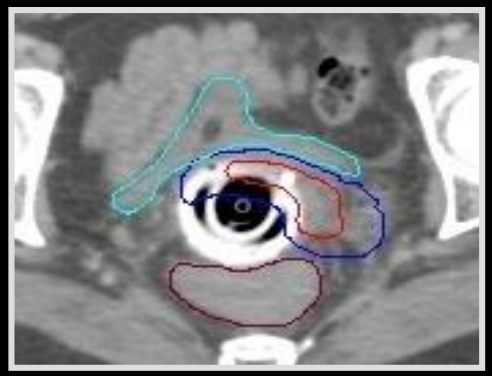
Uppermost contour

Uterine vessels abutting (i. v. contrast)

Superior: Where uterus indents, contour the next 1 cm - pointed shape (cone)







Inferior: ring / ovoids level

Cervical length: 2.5 – 3 cm

Vaginal involvement: add vaginal tissue involved clinically at BT.

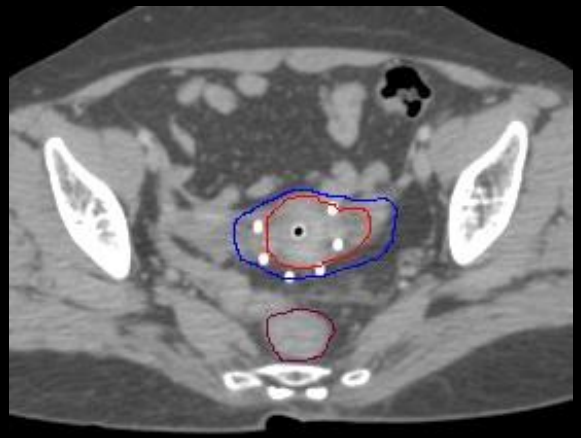
Uterine involvement: more challenging. Clinical / radiological information into account

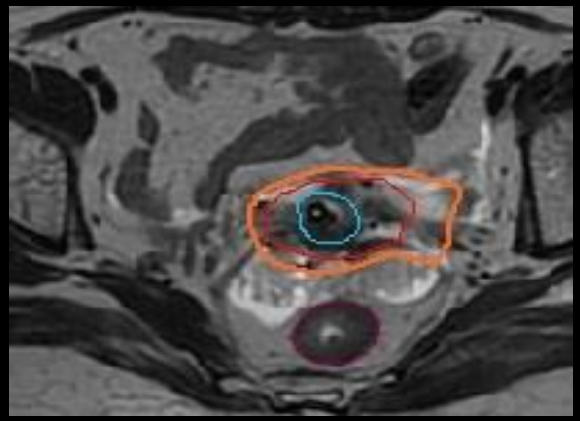
HR CTV contouring on CT: tips

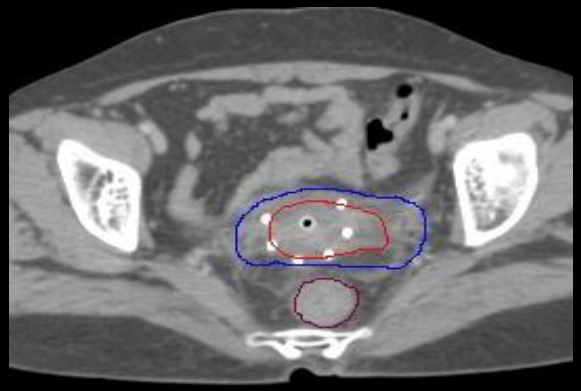
Lateral borders of HR-CTV: Clinical examination & imaging

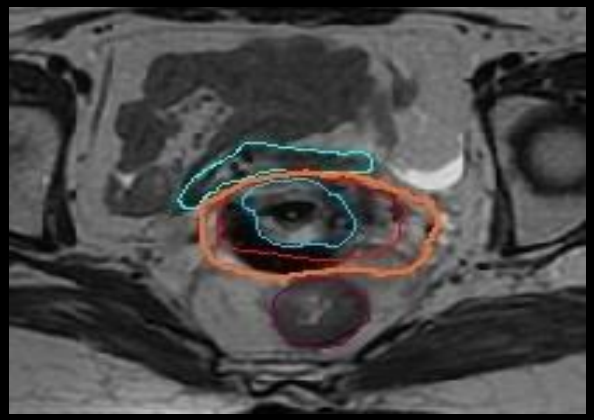
No parametrial invasion: lateral cervical borders

Parametrial invasion: grey structures in parametria (density of cervix)





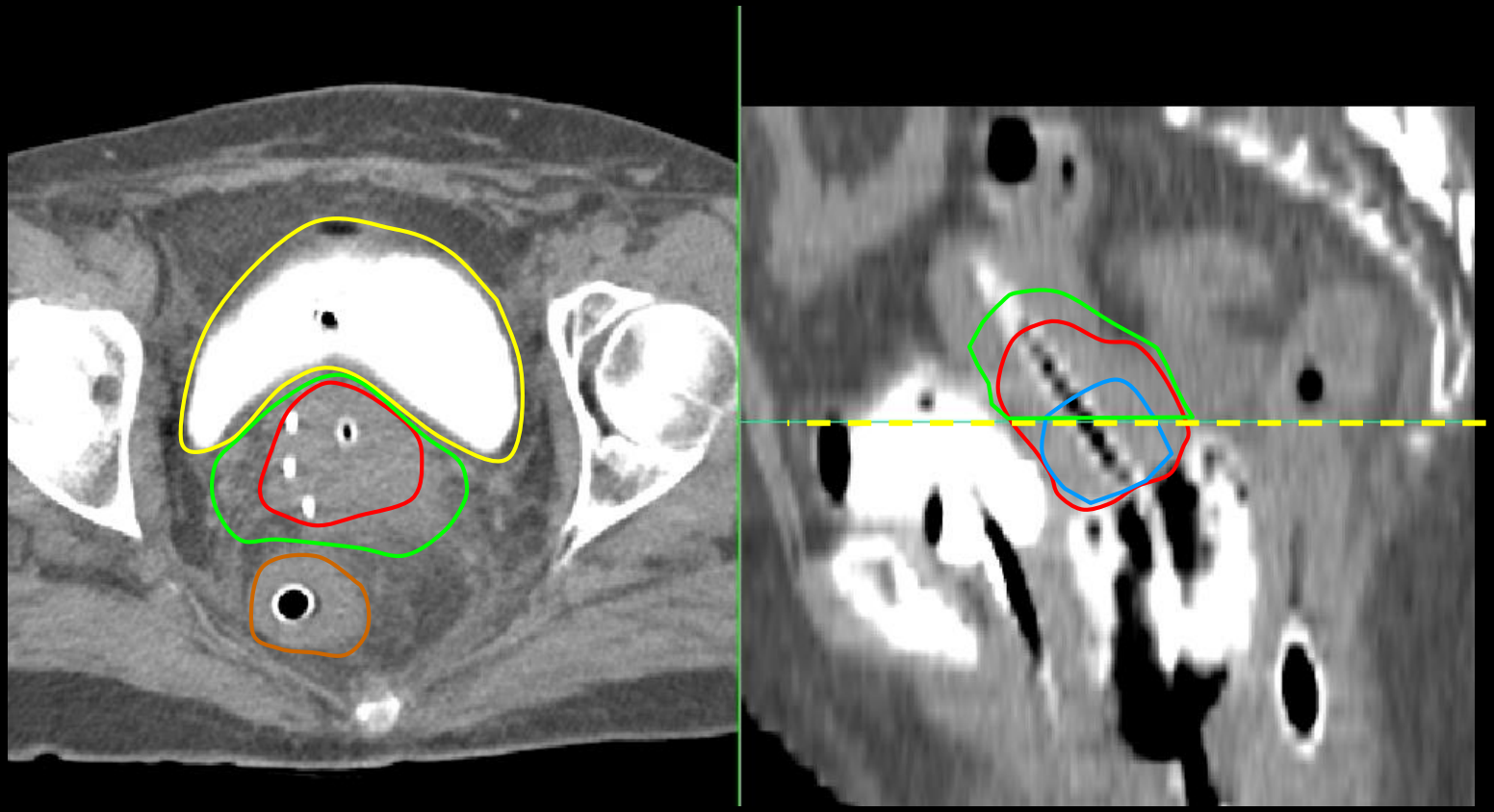




IR CTV contouring on CT: tips

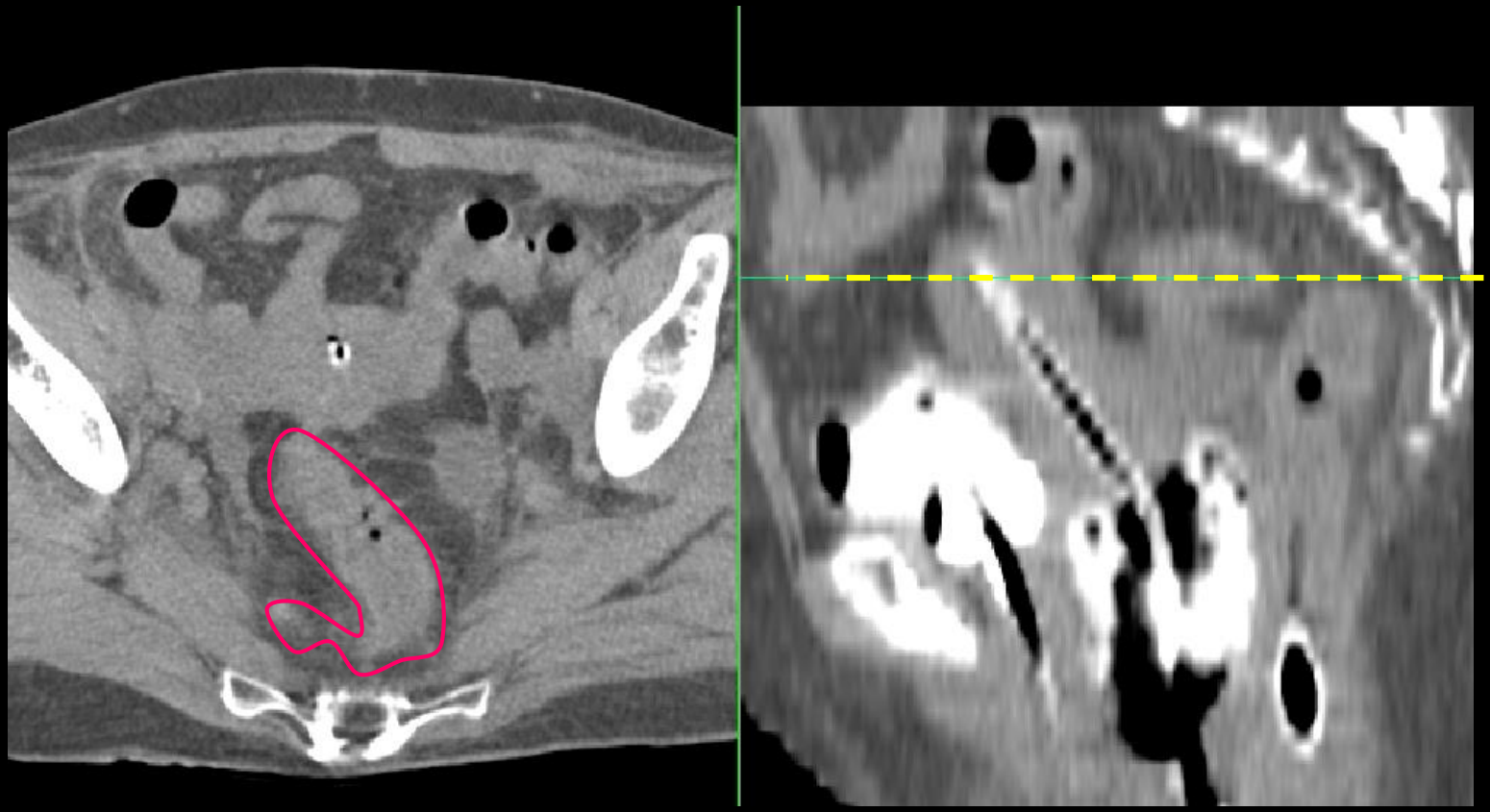
IR CTV ≅ HR CTV with a margin

Respect GEC ESTRO Recommendations for MRI-based contouring



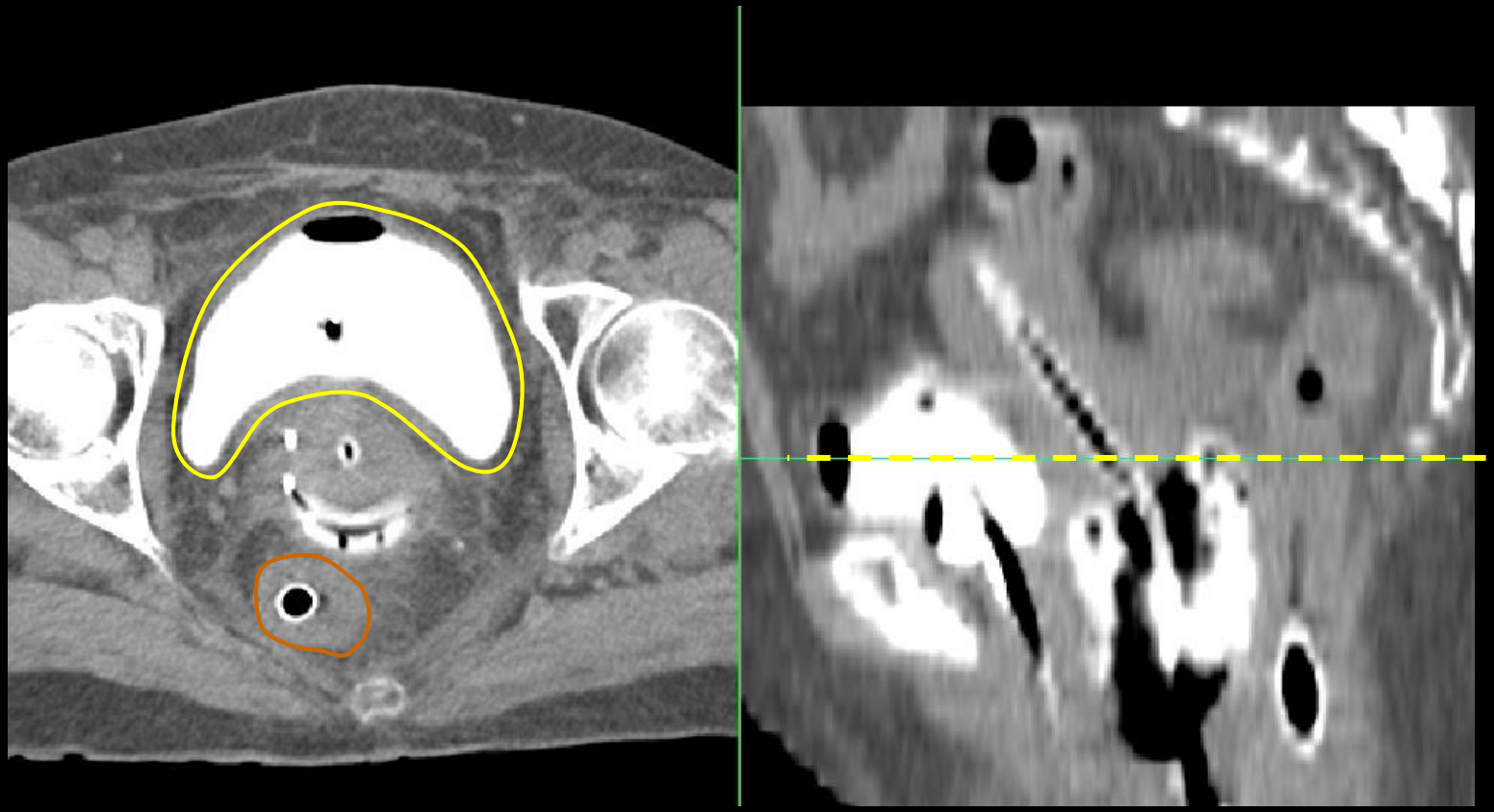
OAR contouring on CT

Sigmoid colon



OAR contouring on CT

Rectum and bladder



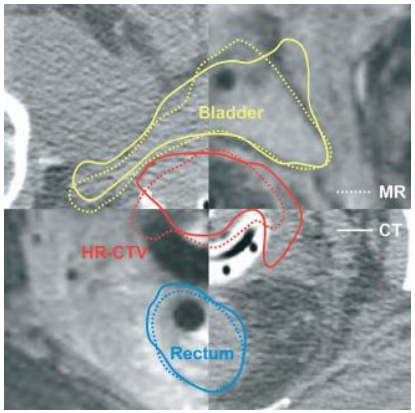
Summary:

CT and MRI *useful* for delineation of outer organ boundaries. However, MRI is superior.

MRI- vs. CT-based contouring: results

COMPUTED TOMOGRAPHY VERSUS MAGNETIC RESONANCE IMAGING-BASED CONTOURING IN CERVICAL CANCER BRACHYTHERAPY: RESULTS OF A PROSPECTIVE TRIAL AND PRELIMINARY GUIDELINES FOR STANDARDIZED CONTOURS

AKILA N. VISWANATHAN, M.D., M.P.H.,* JOHANNES DIMOPOULOS, M.D.,† CHRISTIAN KIRISITS, SC.D.,† DANIEL BERGER, M.SC.,† AND RICHARD PÖTTER, M.D.,†

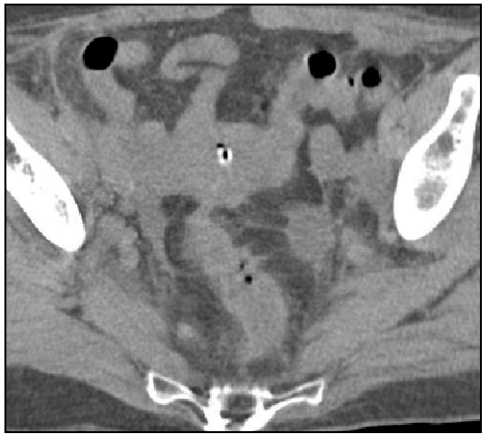


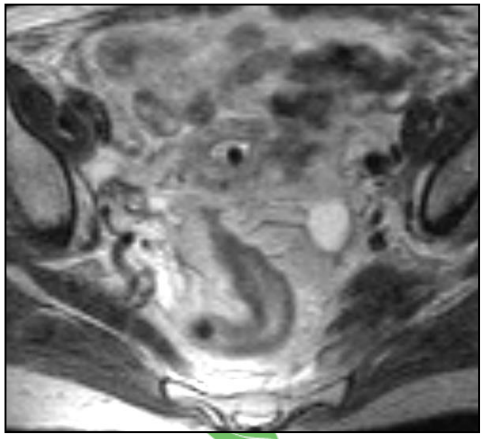
Conclusion: Computed tomography-based or MRI-based scans at brachytherapy are adequate for OAR DVH analysis. However, CT tumor contours can significantly overestimate the tumor width, resulting in significant differences in the D_{90}, D_{100}, and volume treated to the prescription dose or greater for the HR-CTV compared with that using MRI. MRI remains the standard for CTV definition. © 2007 Elsevier Inc.

Common interpretation:

CT is OK for OAR, but suboptimal for HR CTV and IR CTV

...oversimplification for the OAR?





Viswanathan AN, et al. Radiother Oncol 2007

Int J Radiation Oncol Biol Phys, Vol. 90, No. 2, pp. 320–328, 2014

International Journal of Radiation Oncology biology • physics

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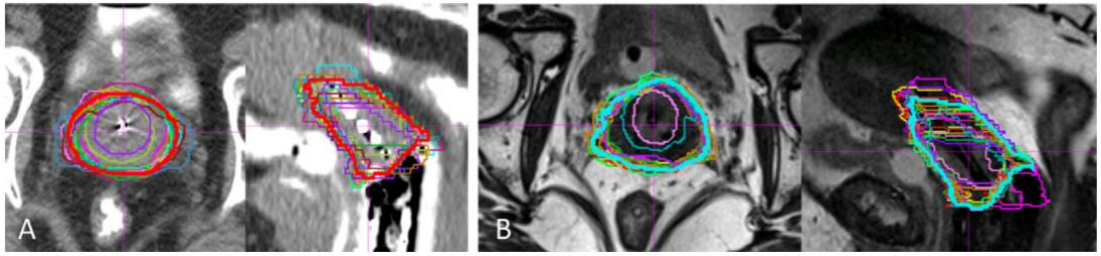

Comparison and Consensus Guidelines for Delineation of Clinical Target Volume for CT- and MR-Based Brachytherapy in Locally Advanced Cervical Cancer

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David K. Gaffney, MD, PhD,‡ Sushil Beriwal, MD,‖
Burnett III, MD,#
D,**
Michael G. Haddock, MD,†† Anuja Jhingran, MD,‡‡
Ellen L. Jones, MD, PhD,§§ Charles A. Kunos, MD, PhD,‖‖
Larissa J. Lee, MD,* Lilie L. Lin, MD,¶¶ Nina A. Mayr, MD, PhD,##
Ivy Petersen, MD,†† Primoz Petric, MD,***,††† Lorraine Portelance, MD,‡‡‡
William Small Jr, MD,§§§ Jonathan B. Strauss, MD,‖‖‖
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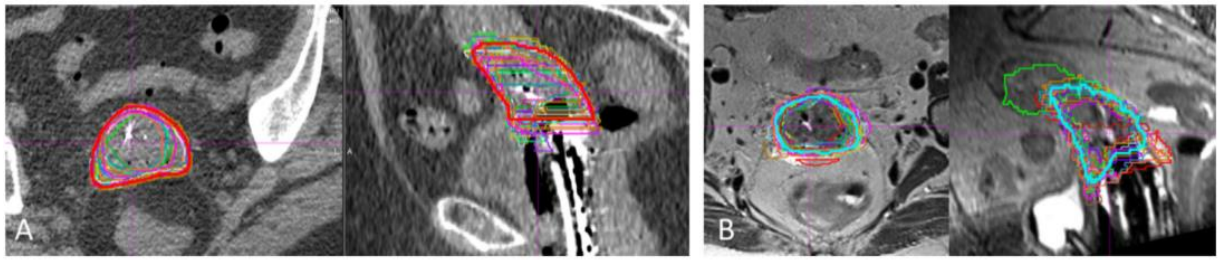
Cancer Care and Research, Doha, Qatar, ‡‡‡University of Miami Miller School of Medicine, Miami,

Caution when interpreting CT results!



MRI should be considered the gold standard for contouring!

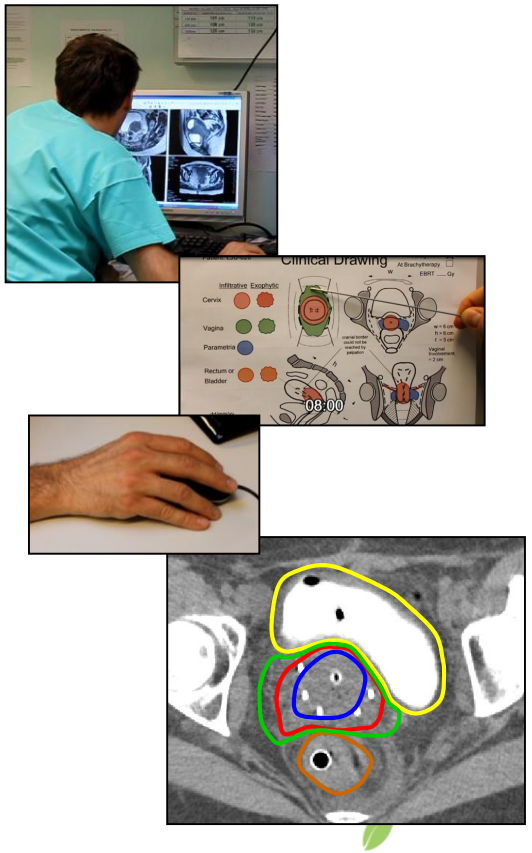
CONCLUSION: In a comparison of MR-contoured with CT-contoured CTV volumes, the higher level of agreement on CT may be due to the more distinct contrast medium visible on the images at the time of brachytherapy. MR at the time of brachytherapy may be of greatest benefit in patients with large tumors with parametrial extension that have a partial or complete response to external beam. On the basis of these results, a 95% consensus volume was generated for CT and for MR. Online contouring atlases are available for instruction at

SUMMARY & CONCLUSIONS

- **MRI-based approach: Gold Standard**

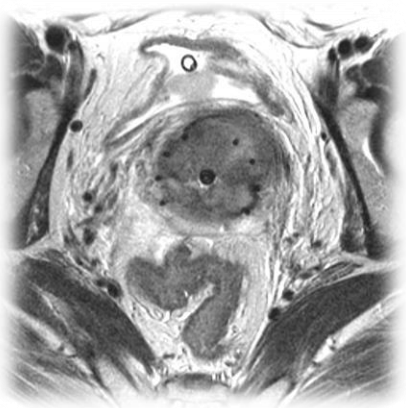
- **CT-based approach: feasible, provided:**

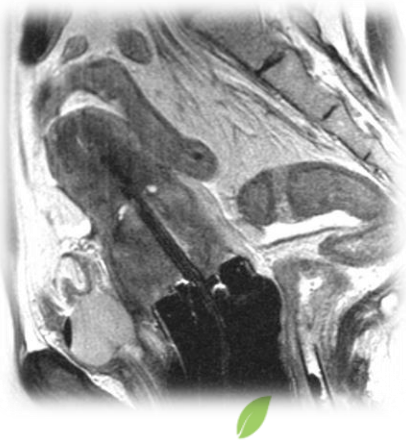
  - **Experience with MRI-Based Approach**
  - **Pre-therapy MRI available**
  - **Standardized CT protocol used**
  - **Clinical findings incorporated**
  - **Pre – BT MRI facilitates CT contouring**



Interpretation of Imaging at Brachytherapy

Radiation oncologist's perspective



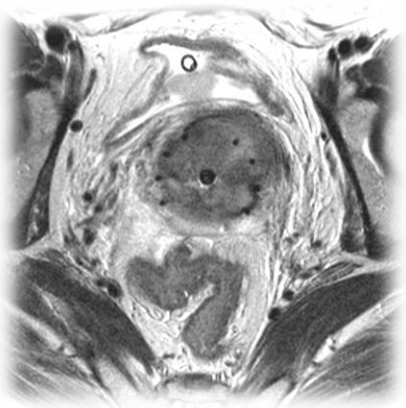


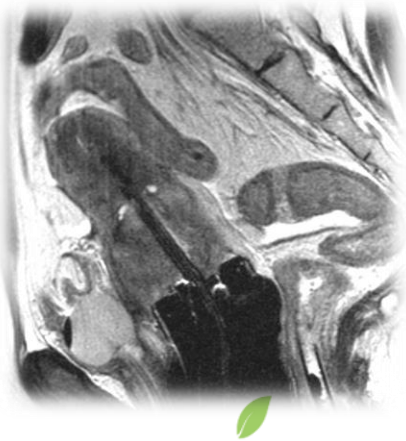
Primoz Petric

Aarhus University Hospital, Denmark

Interpretation of Imaging at Brachytherapy

Radiation oncologist's perspective





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ICRU89-GEC-ESTRO
Recommendations for cervix cancer :

- GTV, CTVs at diagnosis & at time of BT
- OAR delineation

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Journal of the ICRU

ICRU REPORT 89

Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix

OXFORD UNIVERSITY PRESS

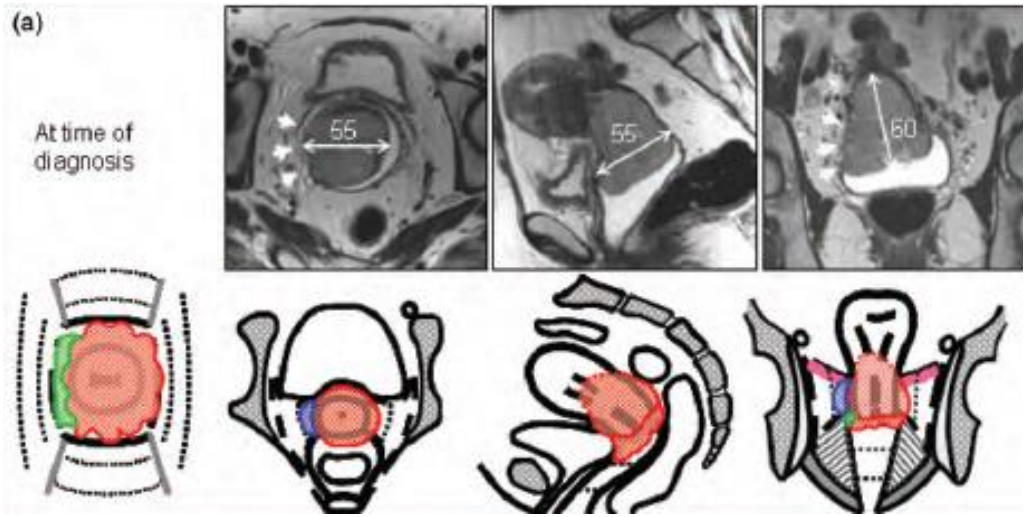
INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS

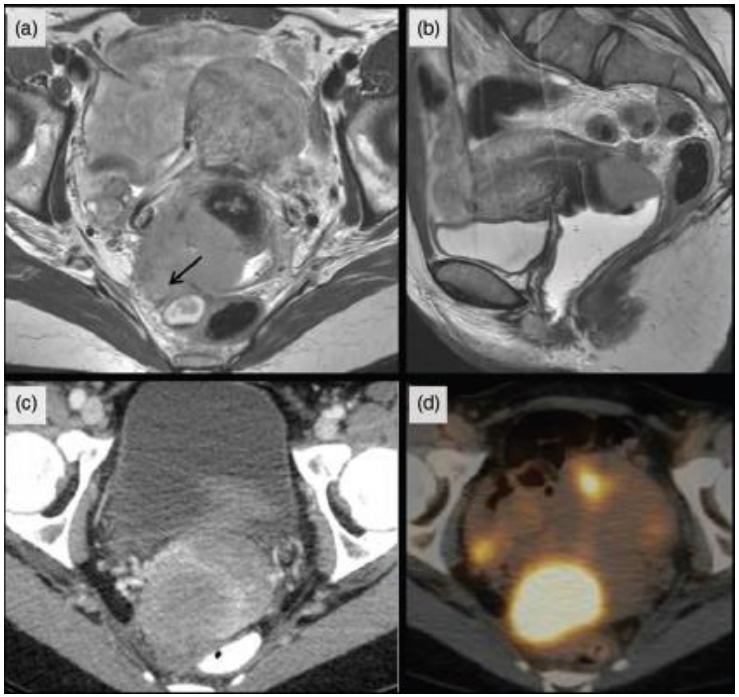
Tumor and target volume definitions for the primary tumor

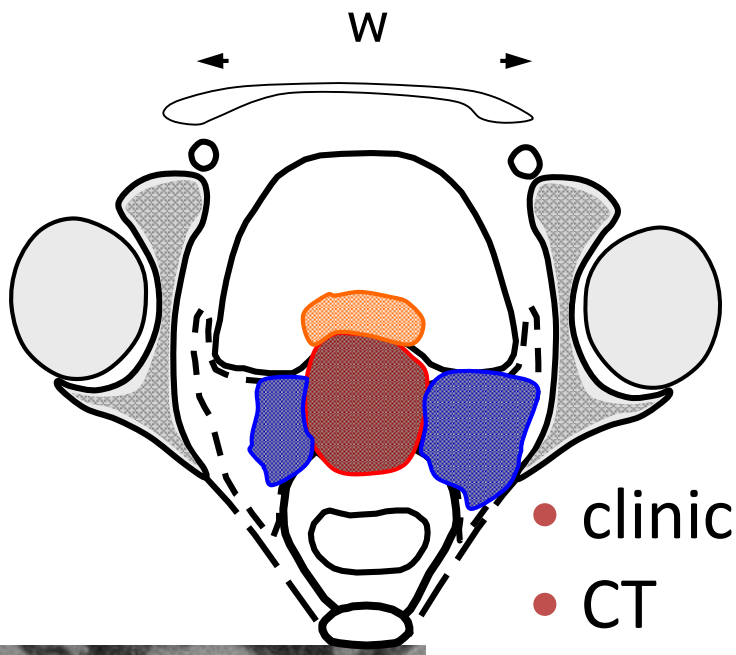
- GTV for the primary tumor (GTV-T)
- CTV for the primary tumor (CTV-T)
- Residual GTV-T ($GTV\text{-}T_{res}$)
- Adaptive CTV-T ($CTV\text{-}T_{adapt}$)
- High-Risk CTV-T ($CTV\text{-}T_{HR}$)
- Intermediate-Risk CTV-T ($CTV\text{-}T_{IR}$)
- Low-Risk CTV-T ($CTV\text{-}T_{LR}$)
- Planning Target Volume (PTV-T)

GTV for the primary tumor (GTV-T)

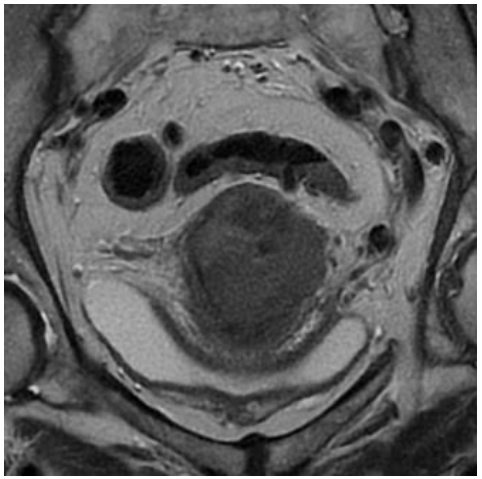
- basis for treatment prescription and planning
- clinical, imaging, and/or pathology investigations assessment
- represents macroscopic demonstrable disease for the primary tumor according to the UICC TNM classification
- composite GTV-T
- context of adaptive radiotherapy : GTV-T_{init} to distinguish this from the GTV-T_{res}



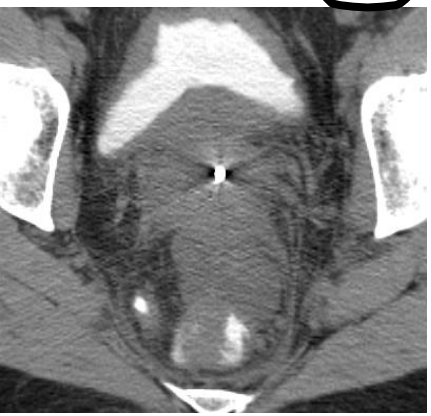


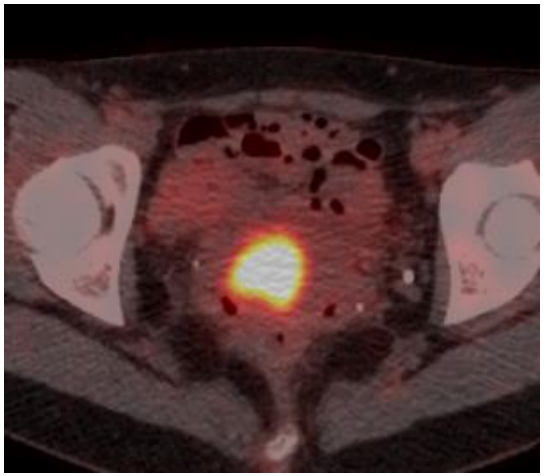


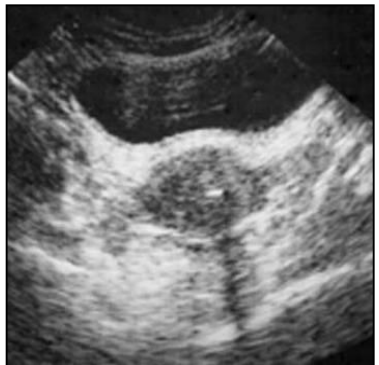
GTV_{init}



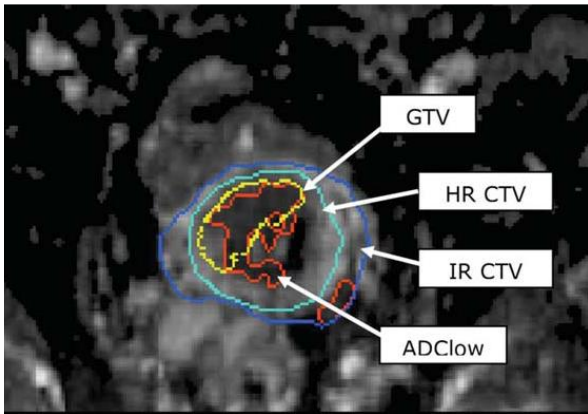
- clinical examination
- CT
- MRI
- PET-CT
- diffusion weighted MRI
- US



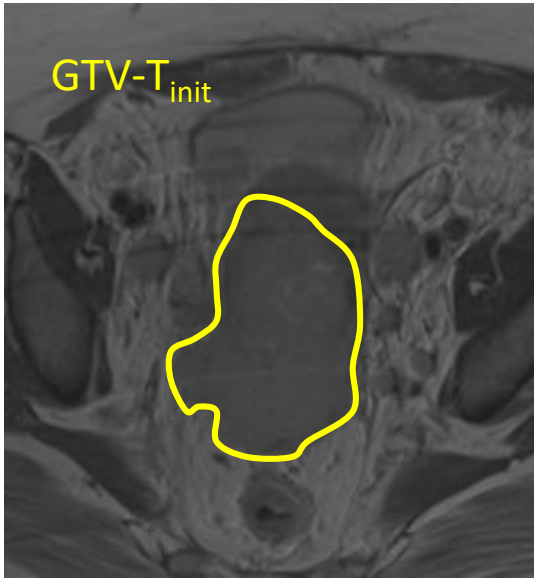


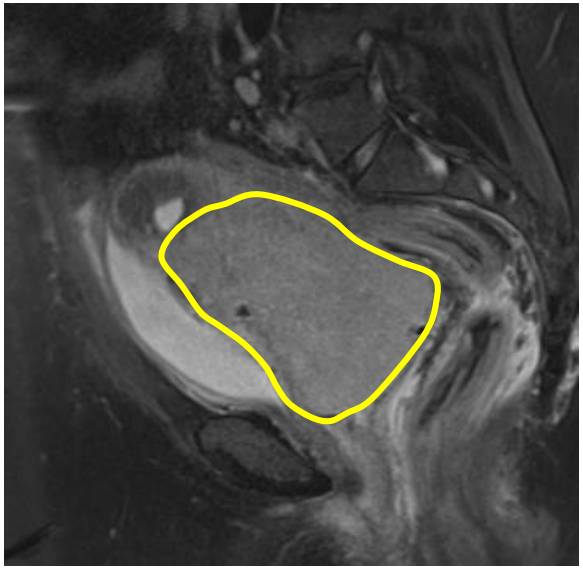


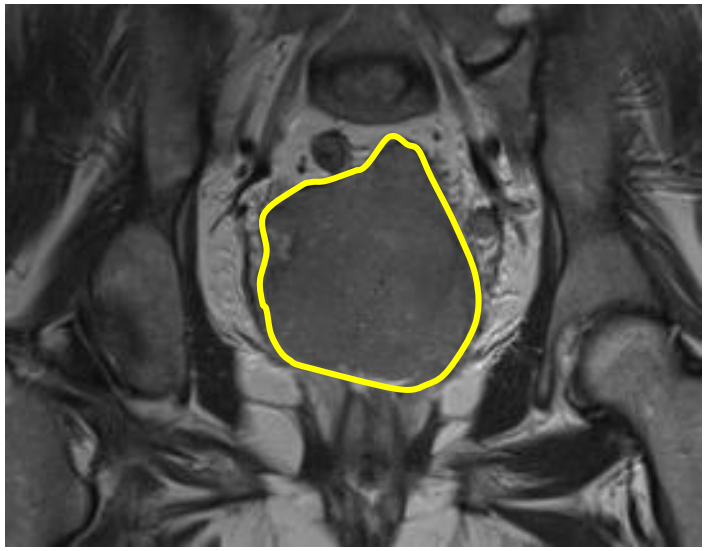
Composite GTV

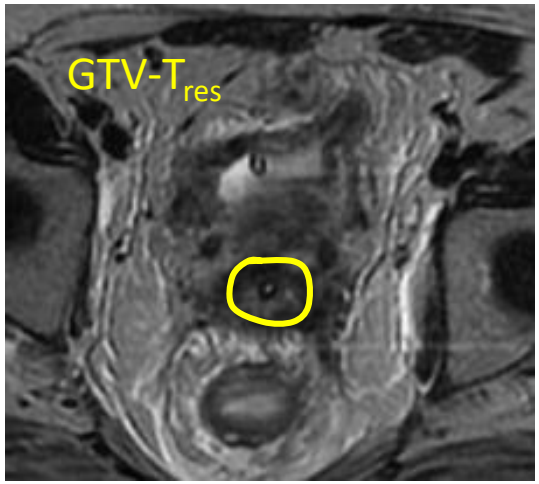


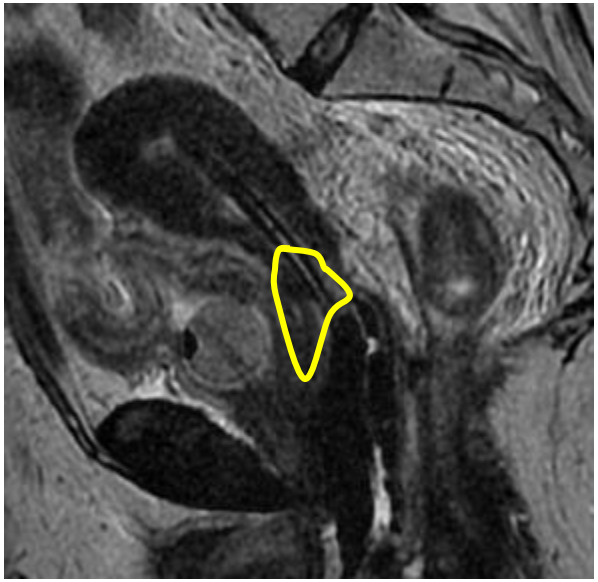
GTV for the primary tumor
Example stage IIIB : GTV-T_{init} / GTV-T_{res}

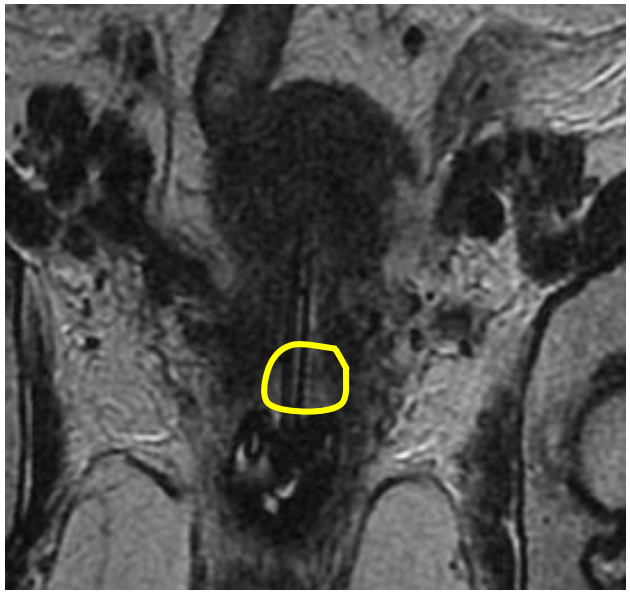












CTV for the primary tumor (CTV-T)

- GTV and assumed sub-clinical malignant disease
- CTV-T encompasses the microscopic tumor spread at the boundary of the primary tumor GTV

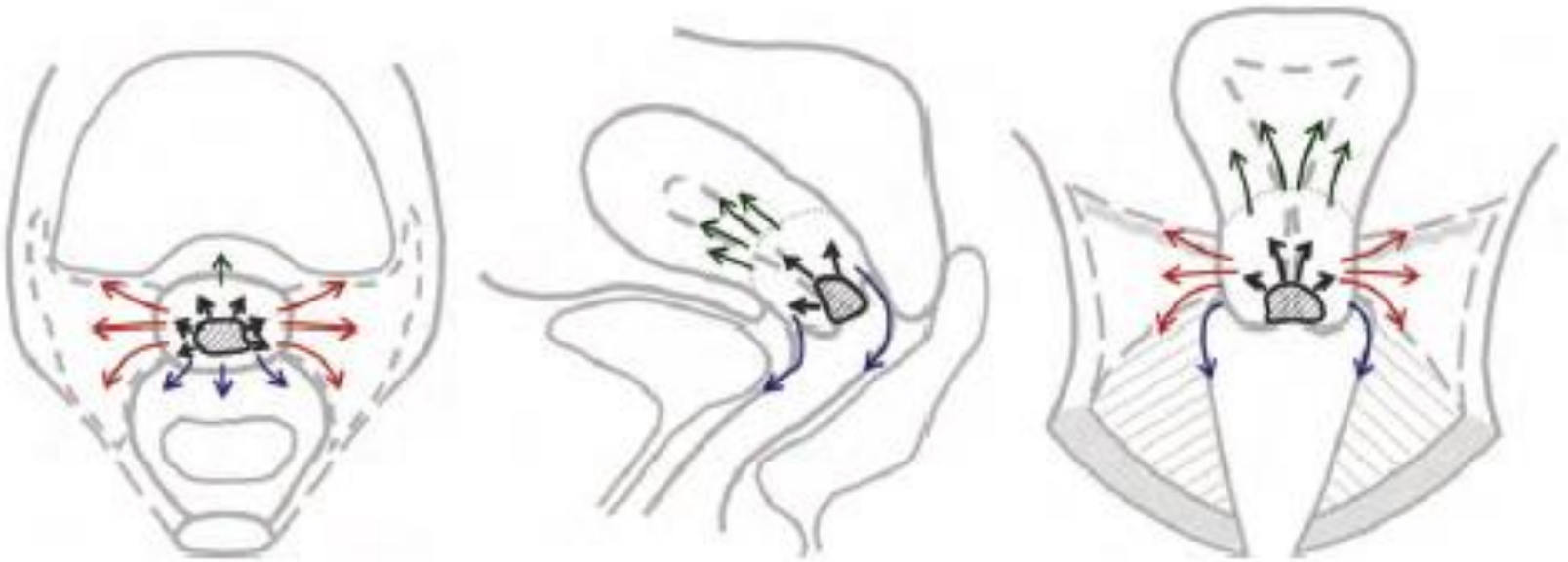


Figure 5.5. Schematic axial (left) mid-sagittal (middle) and mid-coronal (right) views of typical cervix cancer growth in—and outside—the cervix with extra-cervical infiltration into adjacent structures such as parametria, uterine corpus, vagina [see also electronic appendix Gyn GEC ESTRO Rec II (Lim *et al.*, 2011; Pötter *et al.*, 2006)].

CTV for the primary tumor (CTV-T)

Three different CTV-Ts have been defined in the GEC-ESTRO recommendations: “High Risk CTV,” “Intermediate Risk CTV,” and “Low risk CTV”

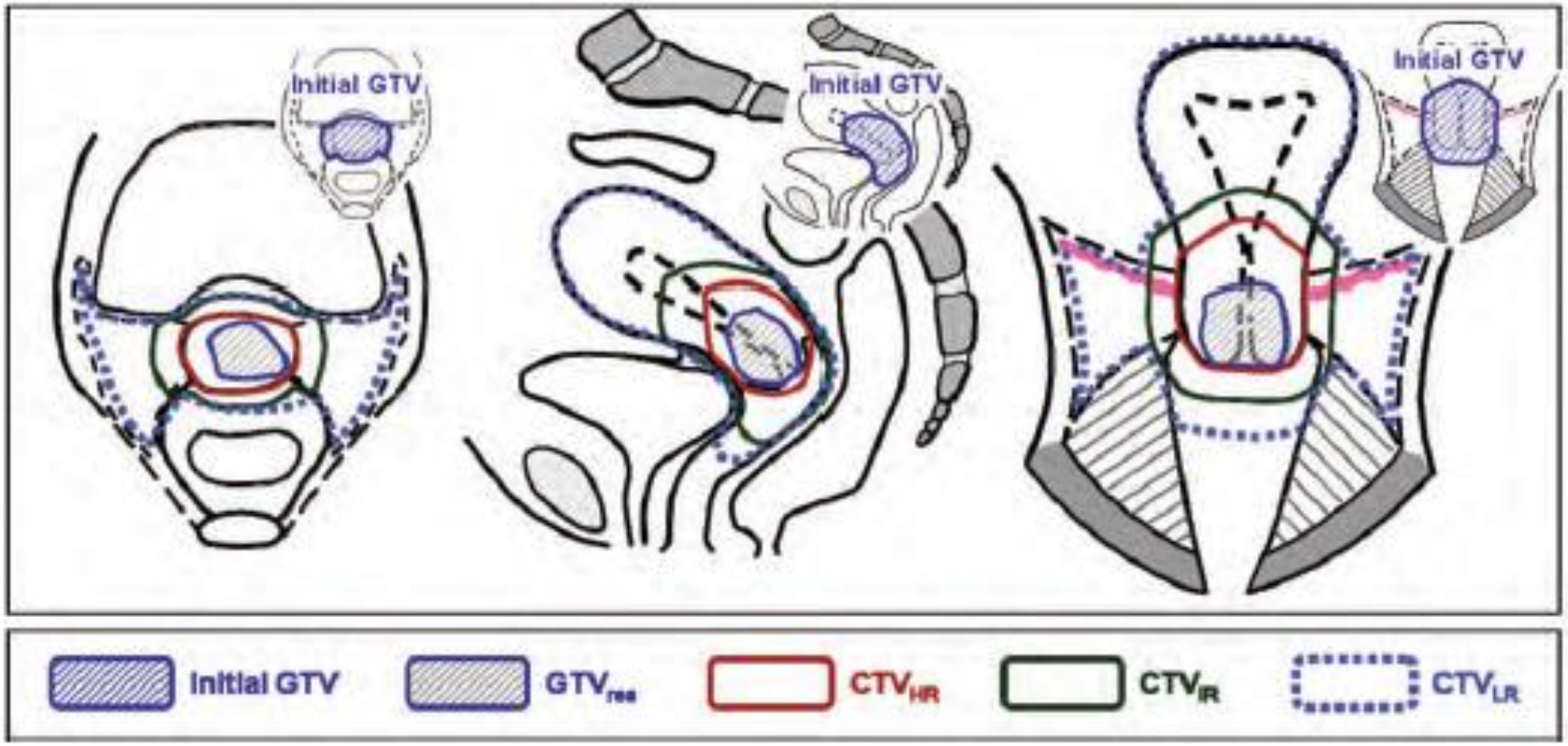
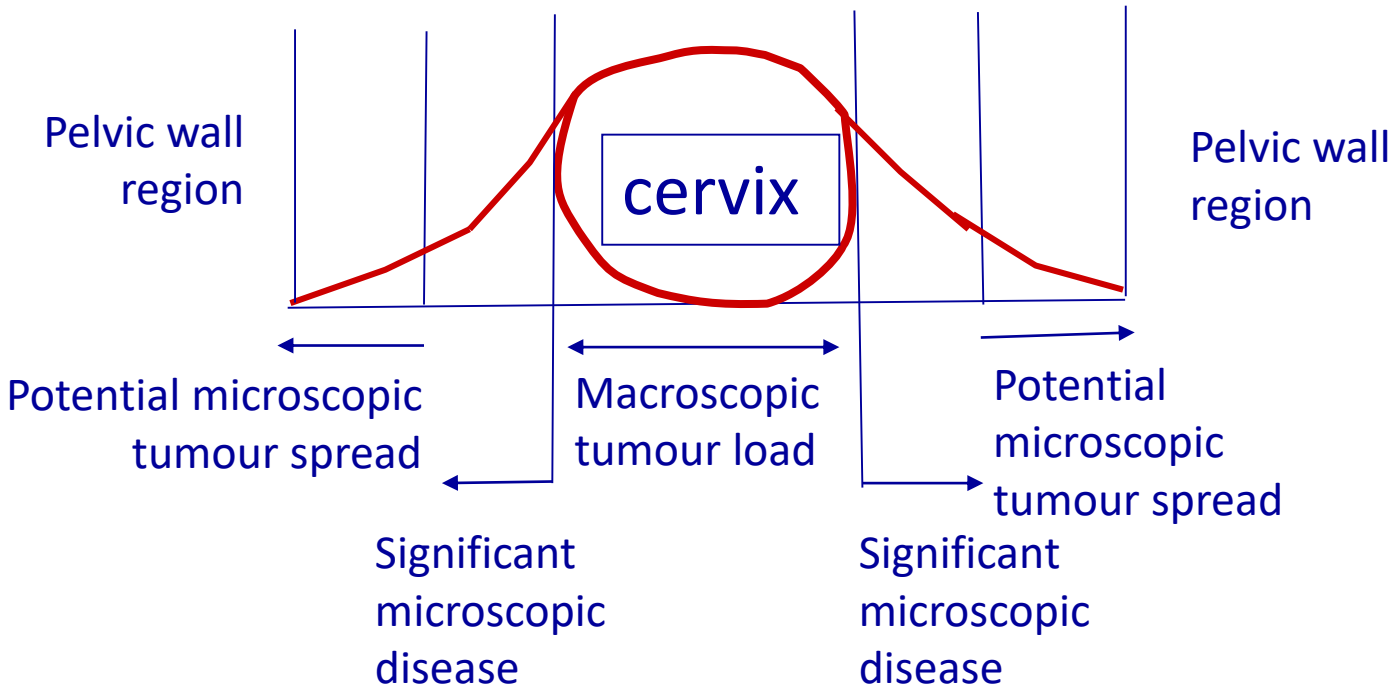


Figure 5.9. Schematic diagram for cervical cancer, Stage IB$_2$ (bulky disease), good response after chemo-radiotherapy: residual GTV-T (GTV-T$_{res}$), adaptive CTV-T (CTV-T$_{HR}$), initial GTV-T (GTV-T$_{init}$), intermediate risk CTV-T (CTV-T$_{IR}$) (GTV-T$_{init}$ plus margins around the CTV-T$_{HR}$), and CTV-T$_{LR}$ for adaptive brachytherapy: coronal, transversal, and sagittal view (see also Appendix Example 2 and 9).

CTVs concepts

Cancer cell density
in 3 different target volumes



CTV for the primary tumor (CTV-T)

CTV-T_{LR} for cervix cancer (for external irradiation) :

- whole uterus
- whole parametria
- upper vaginal third (if the vagina is not involved)

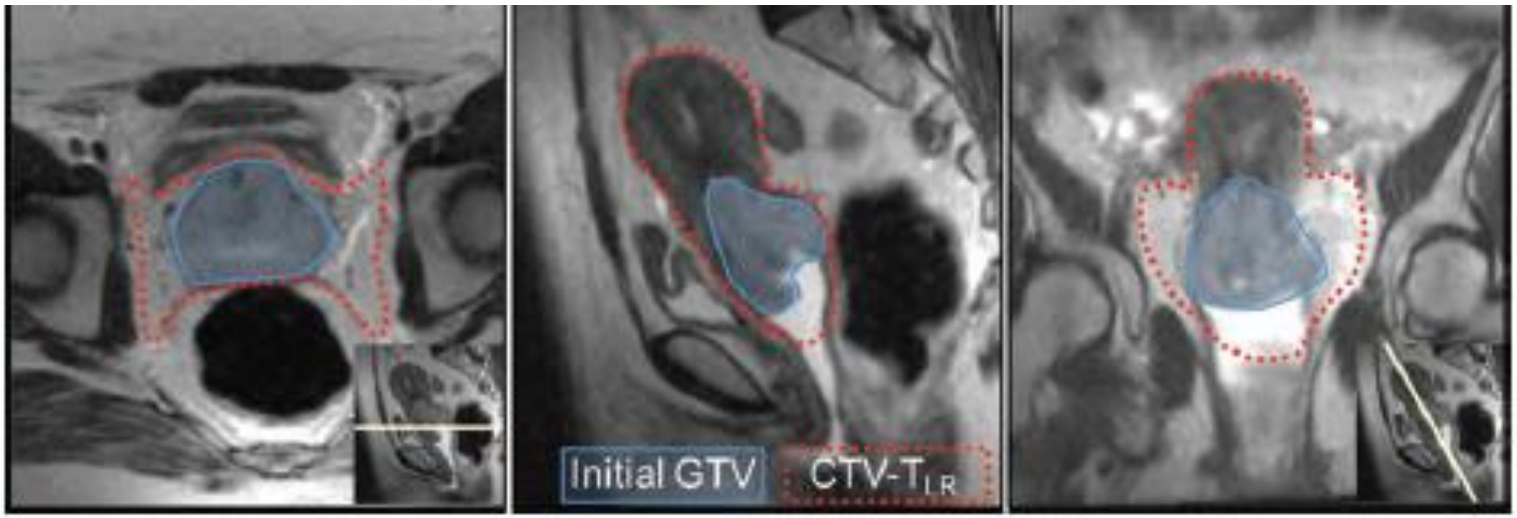
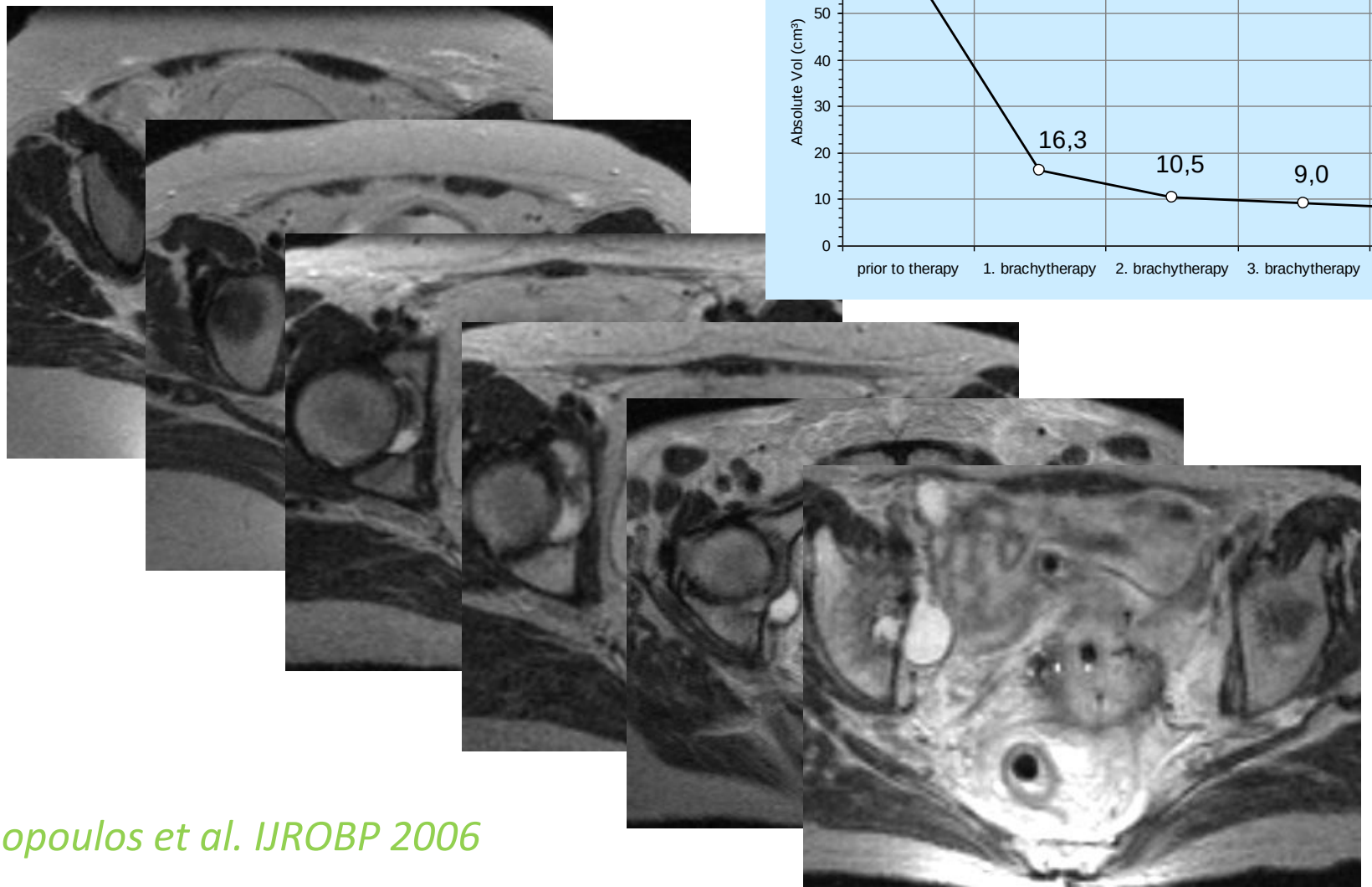
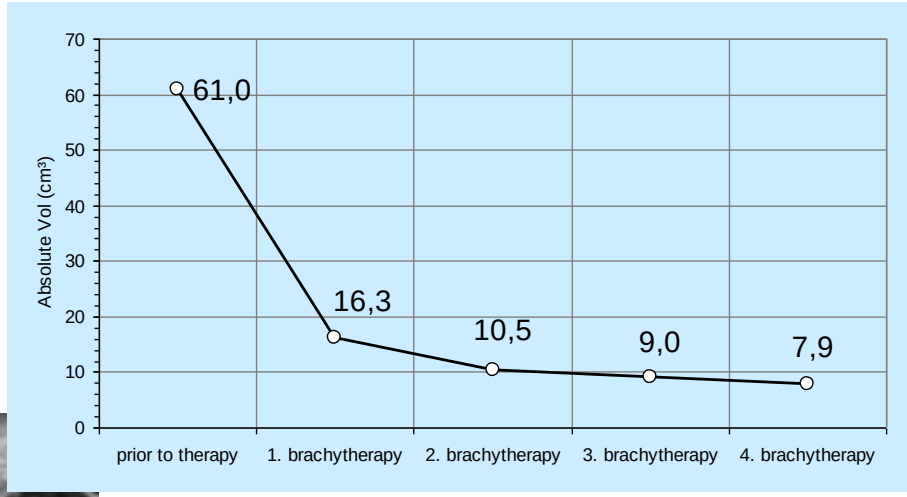


Figure 5.7. Magnetic resonance imaging at diagnosis of Stage IIB cervical cancer infiltrating both parametria with GTV-T_{MR} and CTV-T_{LR}(CTV-T_2) including both parametria, uterine corpus, and upper vagina, contoured for treatment planning of EBRT.

Adaptive MRI based planning concept





Dimopoulos et al. IJROBP 2006

CTV for the primary tumor (CTV-T) : adaptive CTV-T concept

The CTV-T determination for the brachytherapy boost at the end of external therapy takes changes into account by applying the adaptive CTV-T concept with :

- CTV-T_{HR}
- CTV-T_{IR}

CTV for the primary tumor (CTV-T)

HR CTV :

- GTV **at the time of BT**
- CTV if complete response : limited to cervix
- CTV if uncomplete response : cervix plus adjacent structures with presumed residual disease - assessed by both clinical examination and imaging (~30-60 cc) including grey zones
- No safety margins
- Intent : 85 to 90 + Gy total dose to CTV in definitive radiotherapy in advanced disease
- Dose comparable with dose to point A

CTV for the primary tumor (CTV-T)

IR CTV :

- Integrates GTV **at the time of diagnosis**
- Always includes HR-CTV
- In case of major response :
  includes safety margins with regard to initial size GTV
- Intent : 60 + Gy total dose to CTV in definitive radiotherapy in advanced disease
- Dose comparable with dose to the 60Gy isodose (ICRU recommendations)

CTV for the primary tumor (CTV-T)

Intermediate Risk CTV :

GTV at time of diagnosis

In all cases includes:

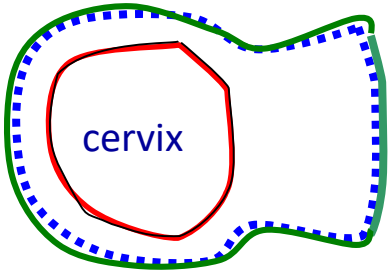
- HR-CTV
- integrates initial CTV

SAFETY MARGINS :
1-1.5 cm cranially
0.5 cm antero-posteriorly
1cm laterally

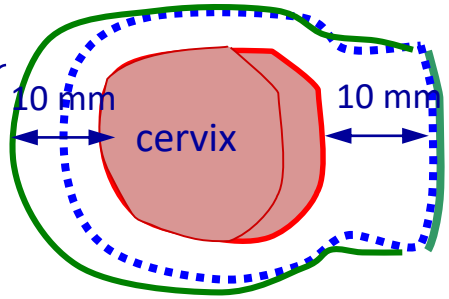
AIM : TO STERILIZE MICROSCOPIC TUMOUR

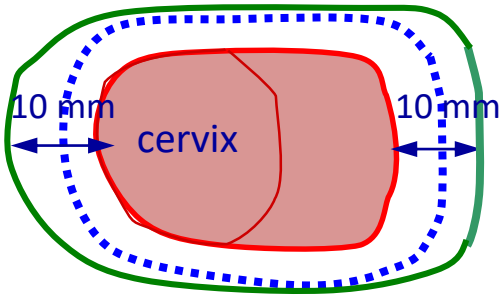
CTV-T

Complete remission

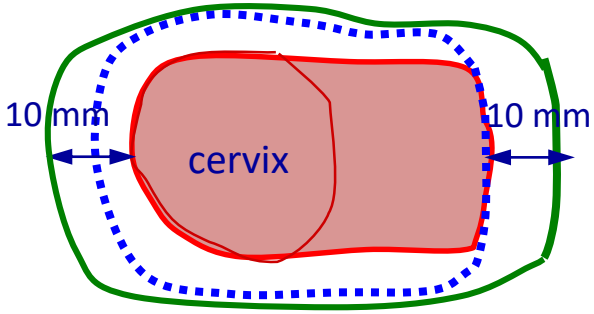


Partial remission





Stable disease



Legend

HR-CTV

IR-CTV

Initial tumour extension (at diagnosis)

Residual disease

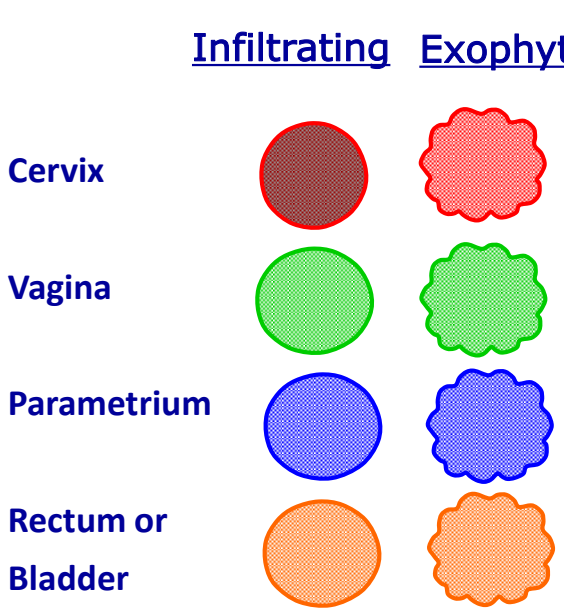
Patient n° 1

Mrs TAM…
56 year-old
WHO=0, 70 kg, 1m69

Vaginal bleeding

Biopsy: moderately differentiated squamous cell carcinoma

Stage IB1 : initial clinical examination



Dimensions (cm):

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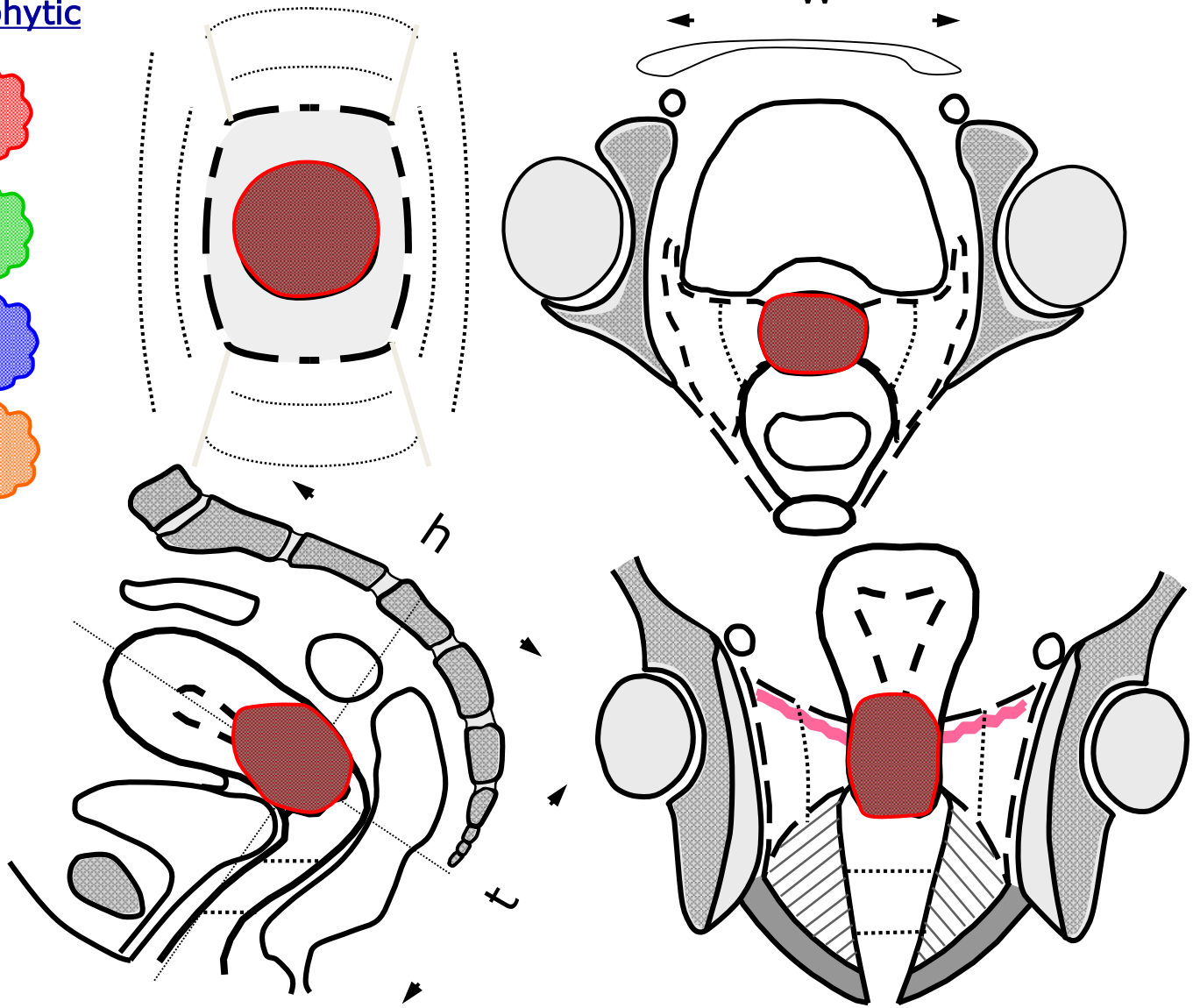
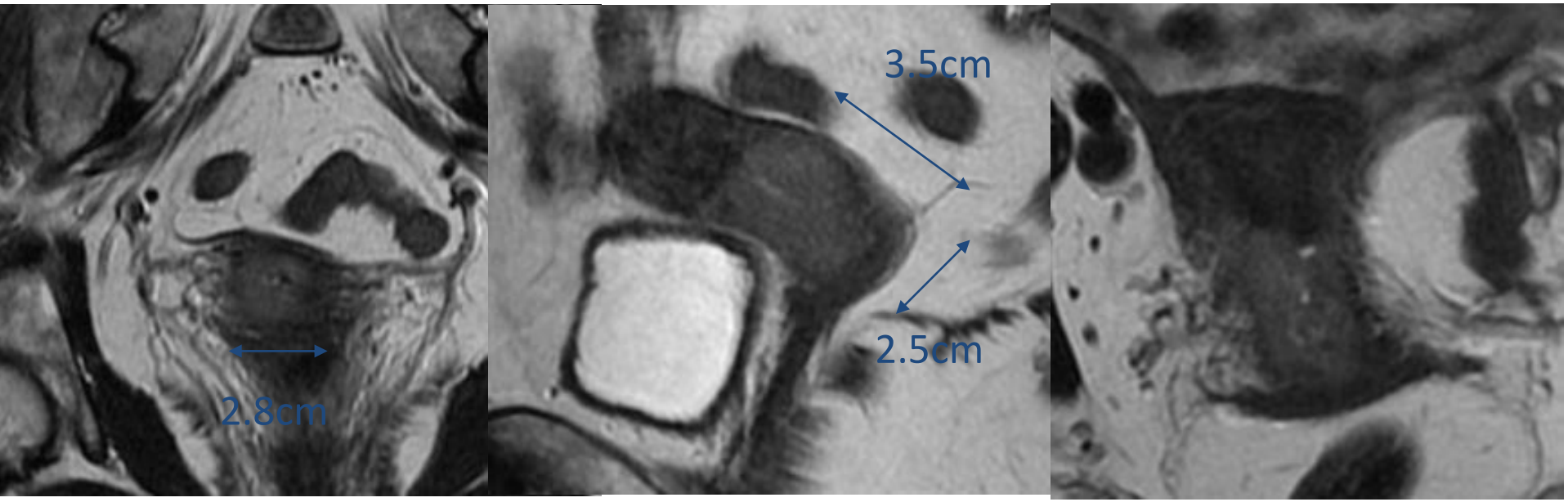
Thickness : 2.5

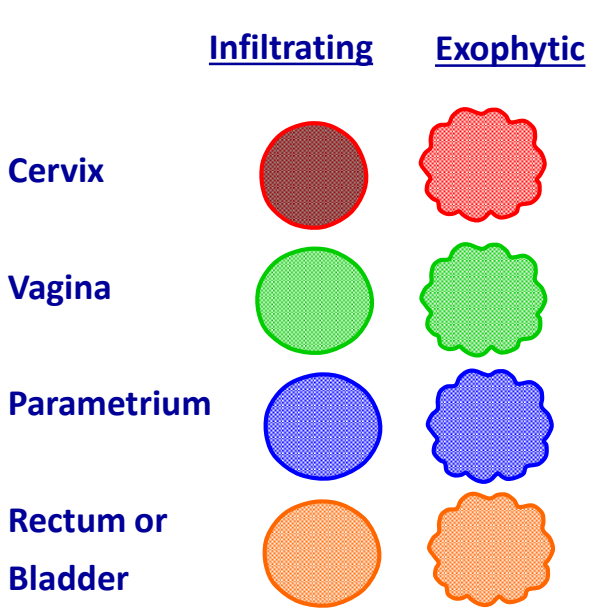
Height : 3



Stage IB1



Stage IB1 : at the time of brachytherapy

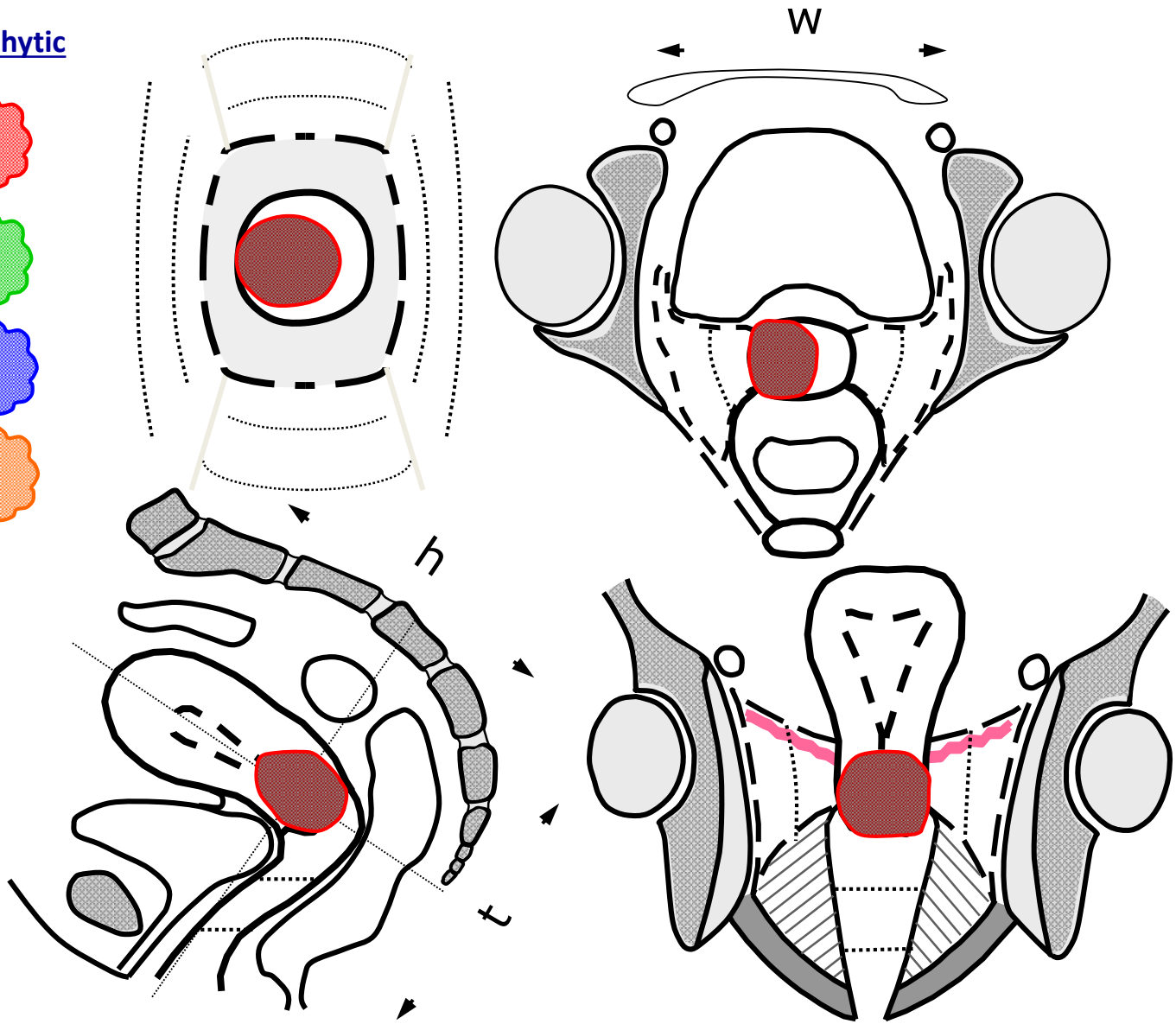


Dimensions (cm):

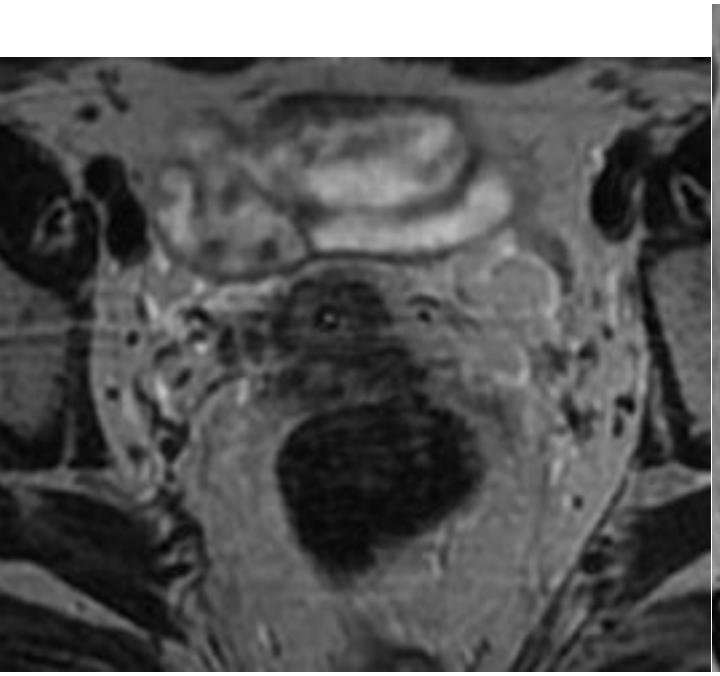
Width : 1.5

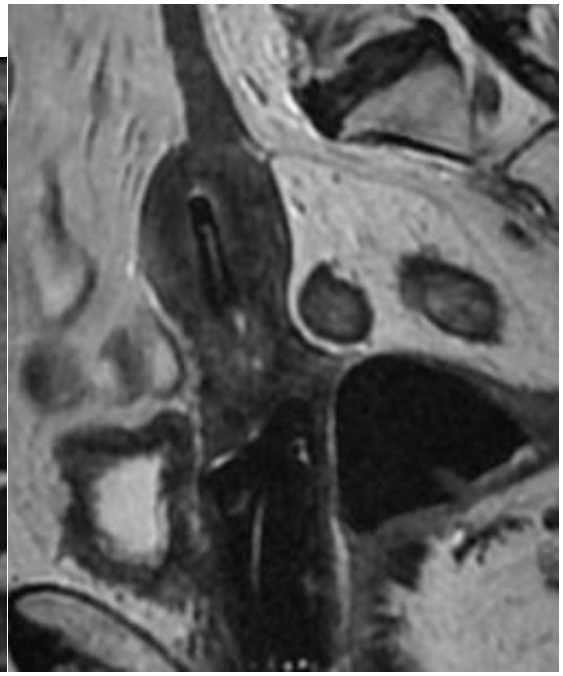
Thickness : 2

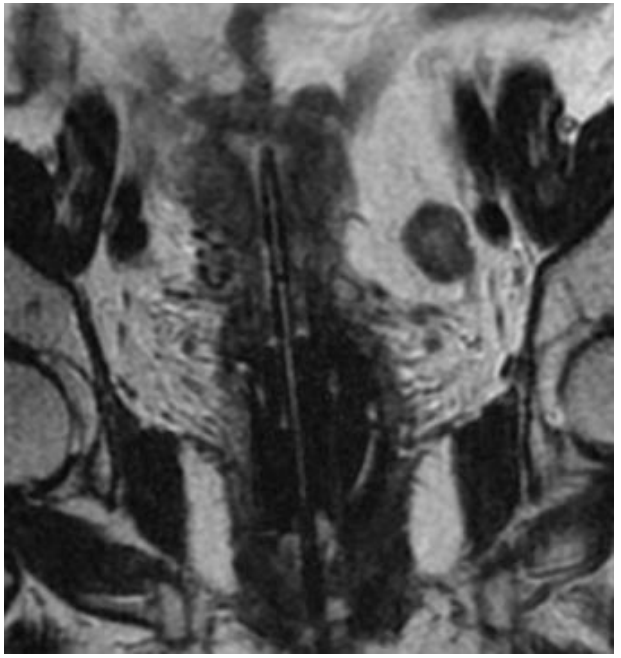
Height : 1.5



Stage IB1







Target volume concepts

High Risk CTV :

GTV at time of brachytherapy
In all cases includes:

- Whole cervix
- [Presumed tumour extension (=0)]
- Clinical assessment
- [Residual grey zones on MRI]

NO SAFETY MARGINS

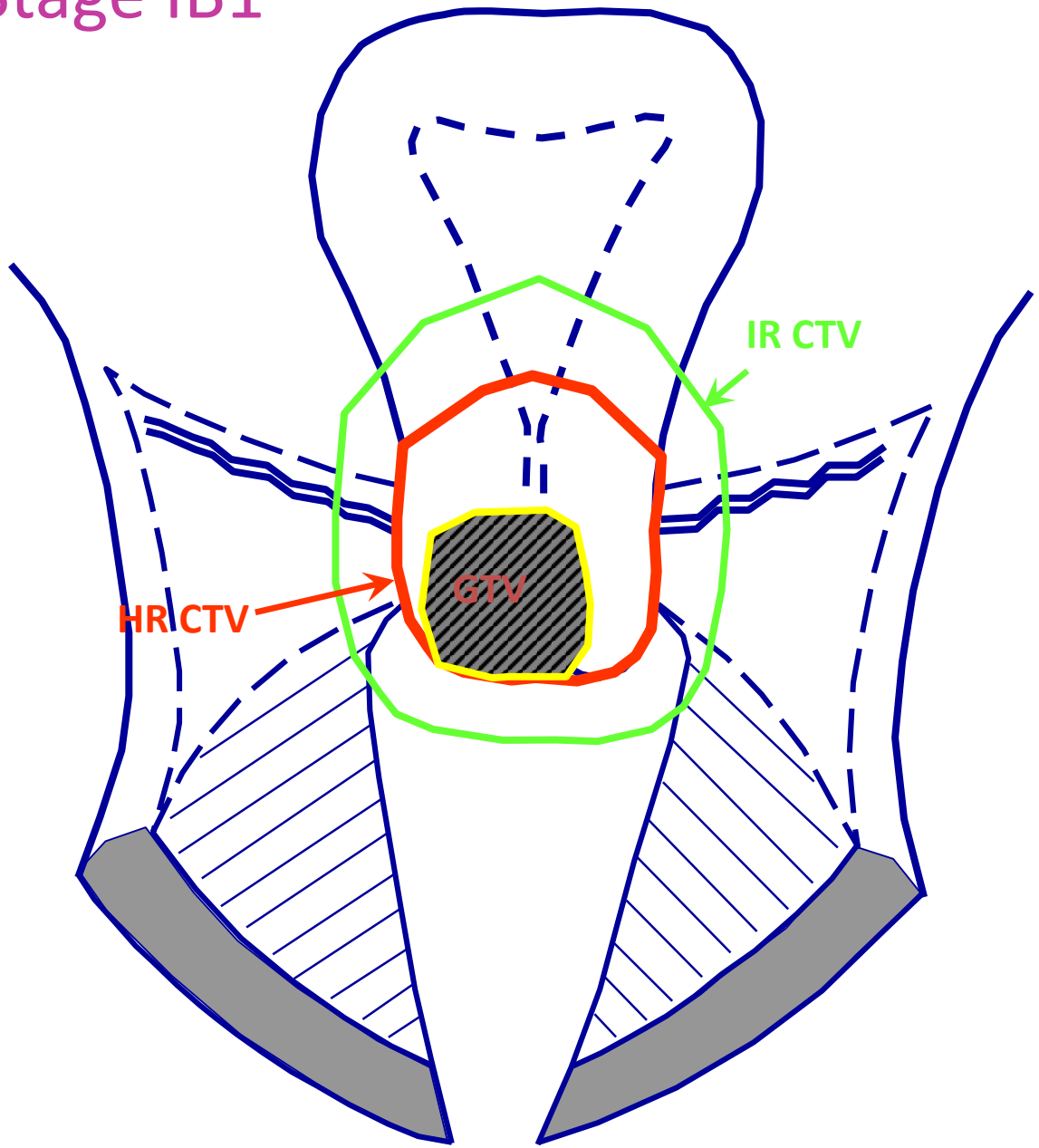
Intermediate Risk CTV :

GTV at time of diagnosis
In all cases includes:

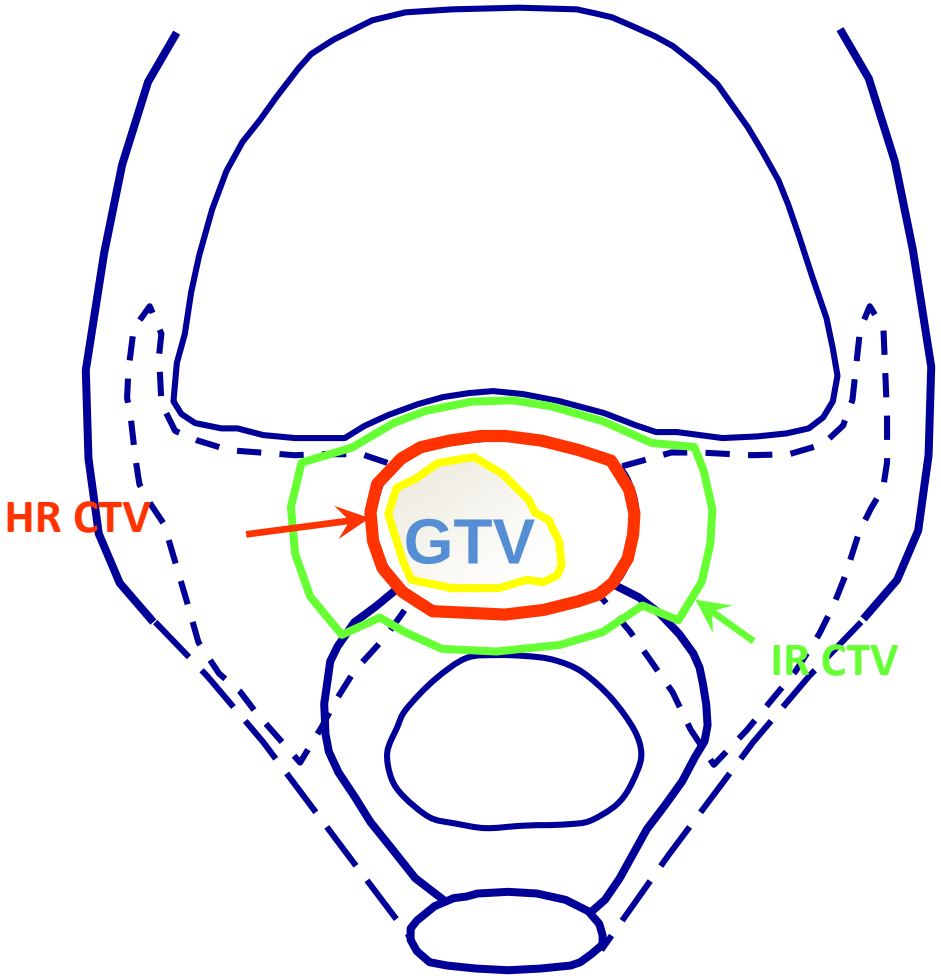
- HR-CTV
- integrates initial CTV

SAFETY MARGINS :
1-1.5 cm cranially
0.5cm antero-posteriorly
1cm laterally

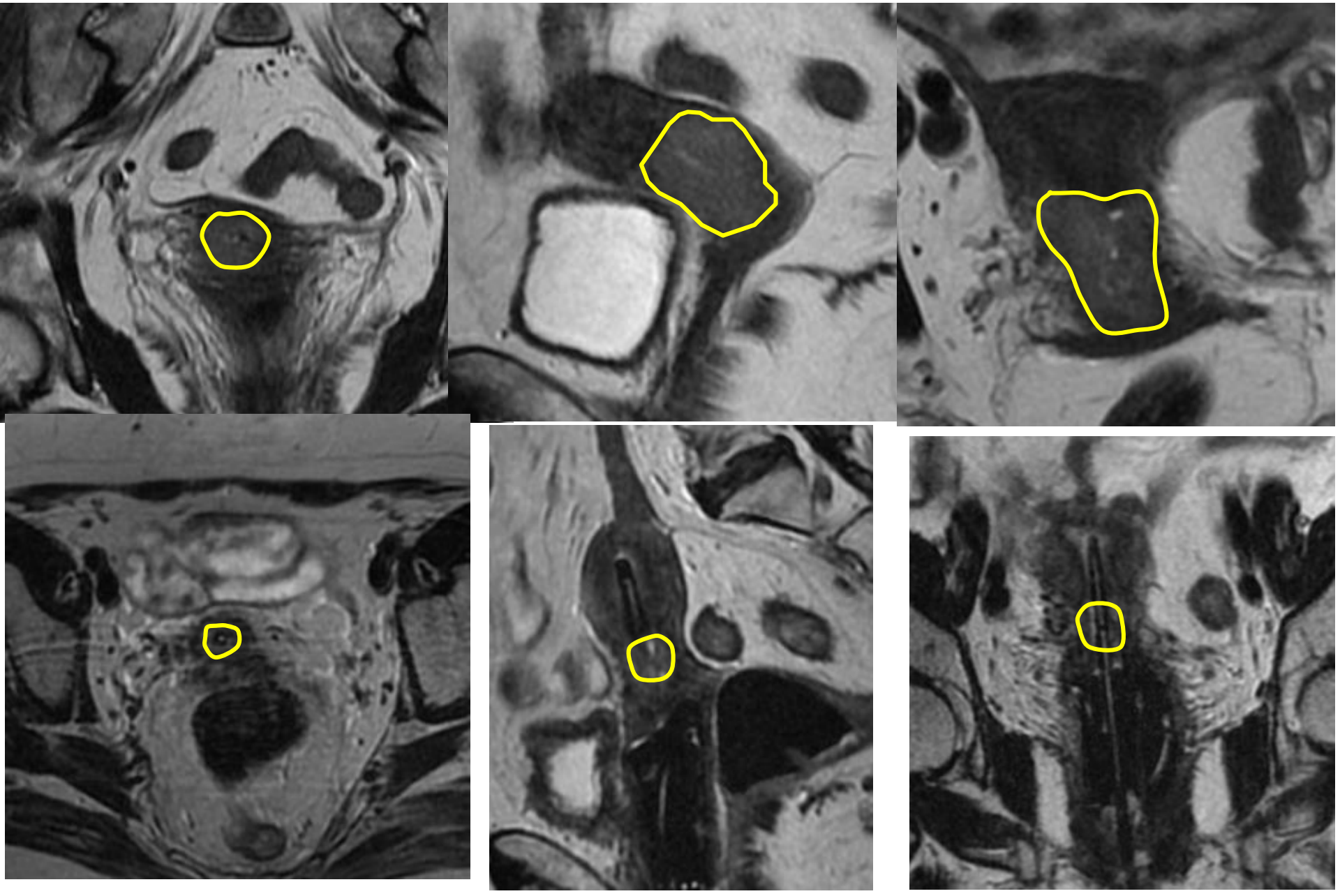
Stage IB1



Stage IB1



Stage IB1



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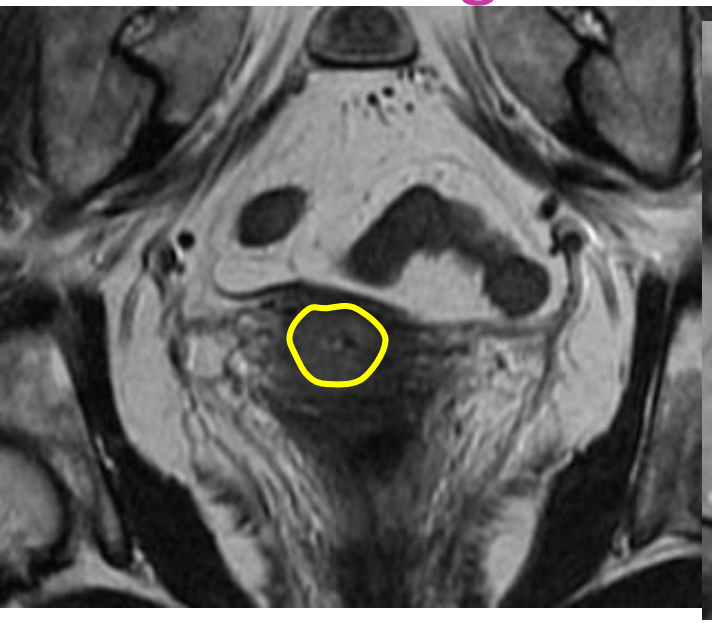
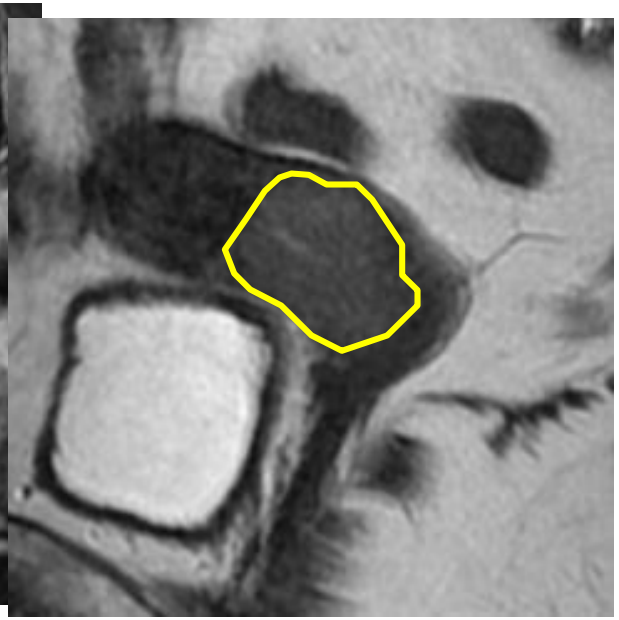
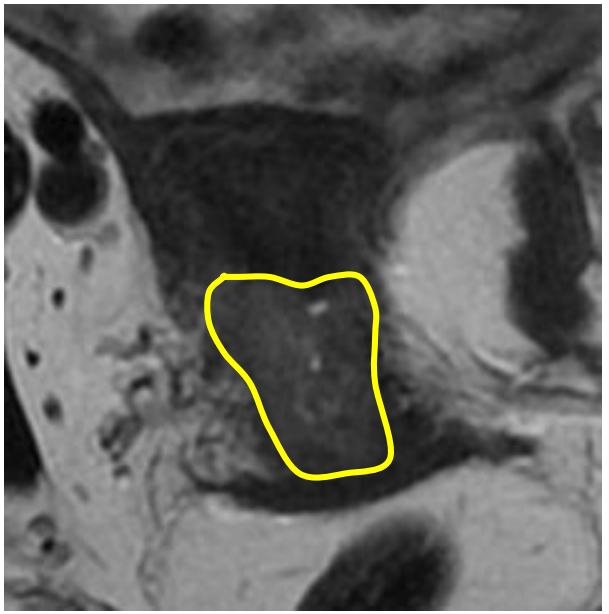
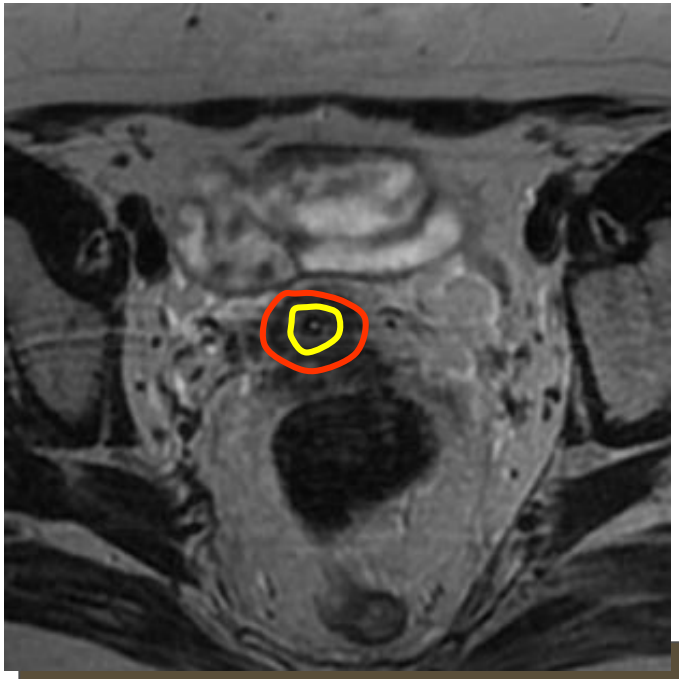
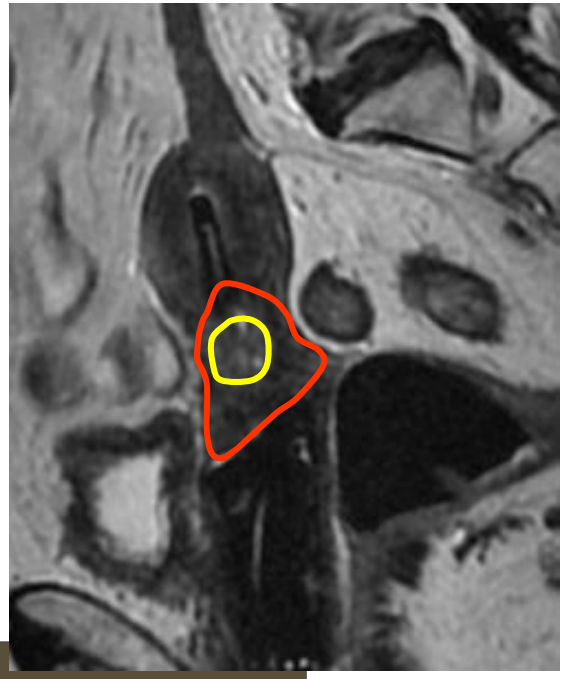
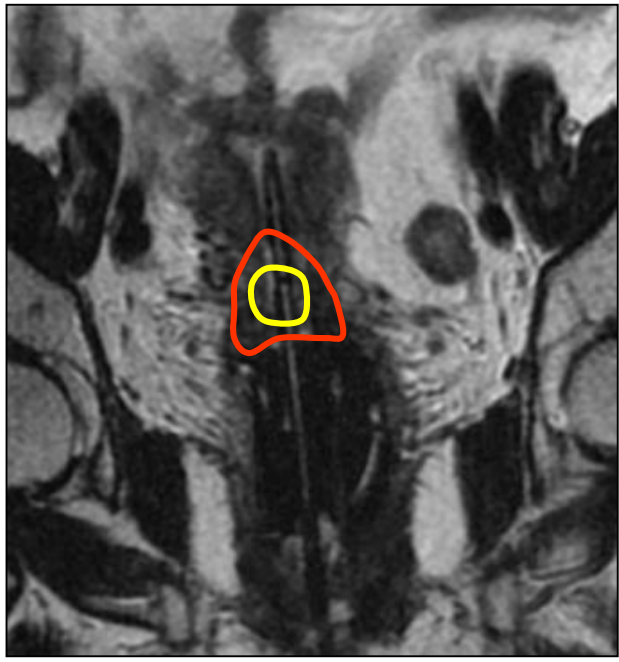




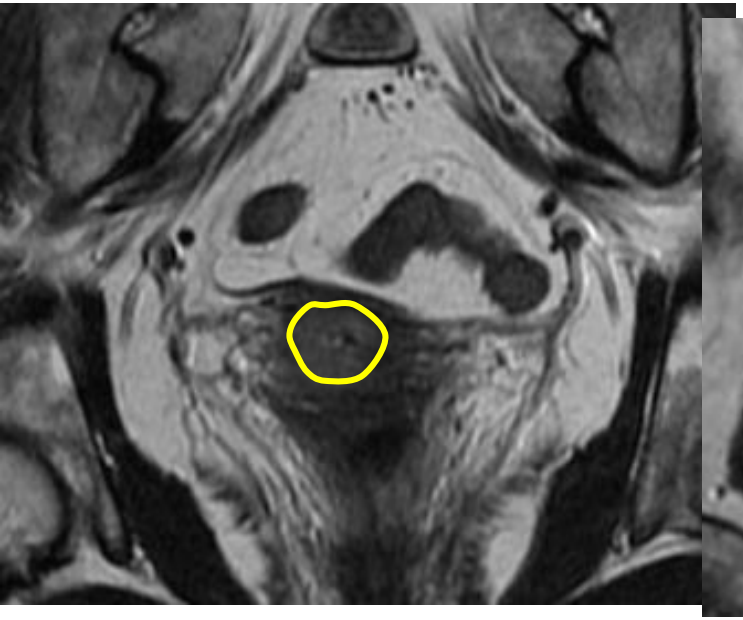


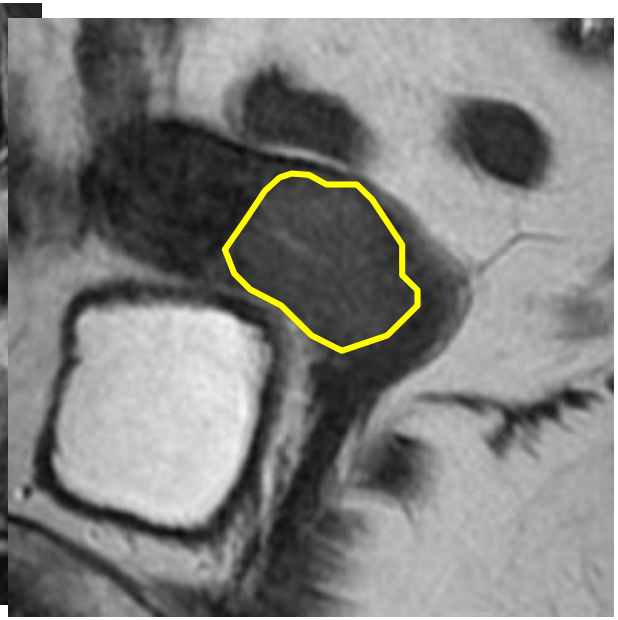


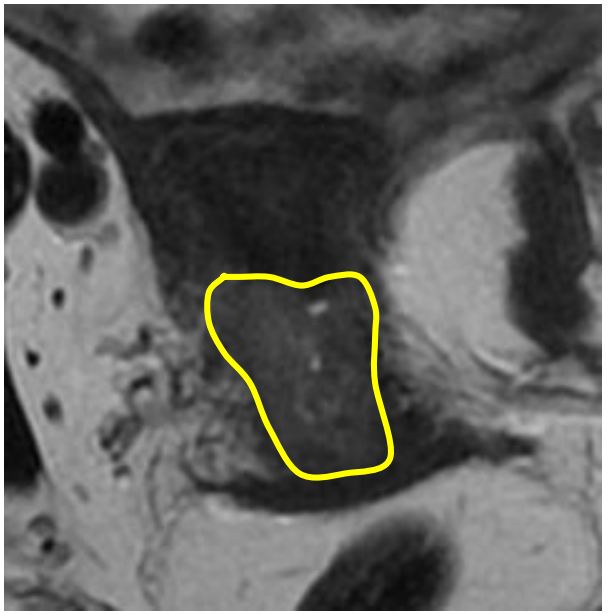


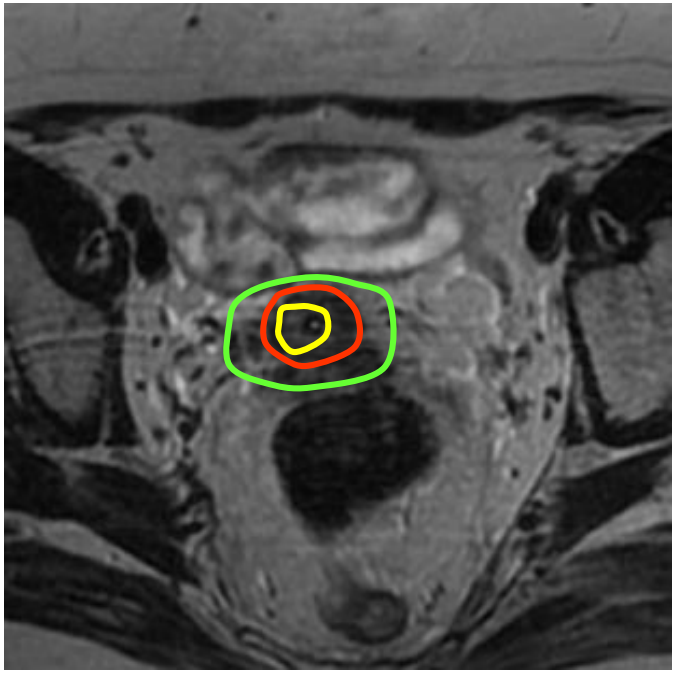


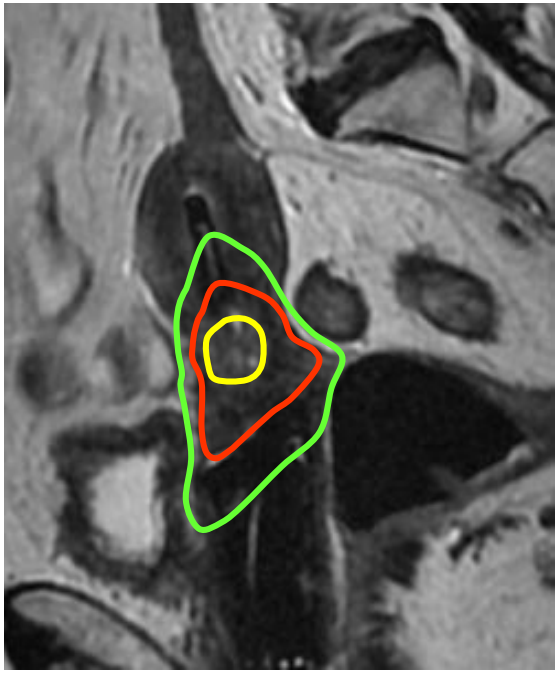
Stage IB1

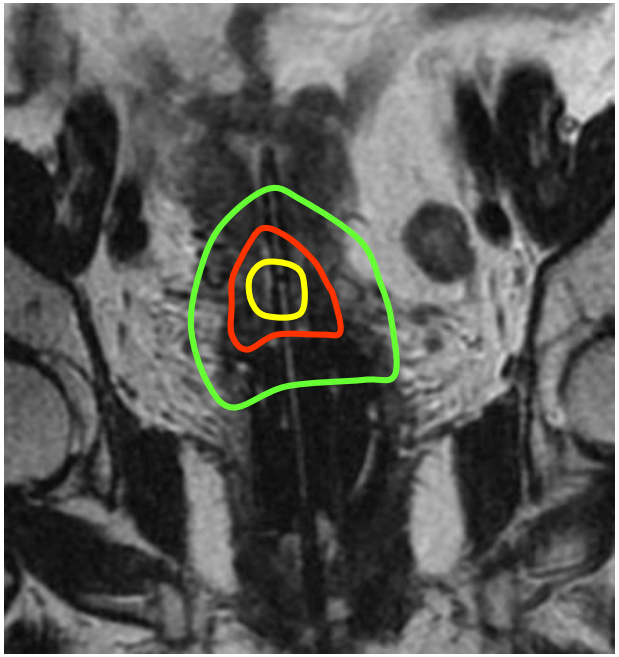












Patient n° 2

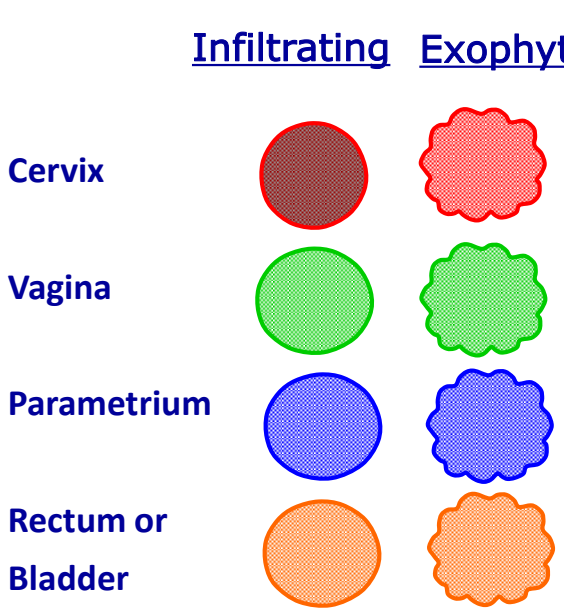
Mrs MAR…
33 year-old
WHO=0, 55 kg, 1m68

Vaginal bleeding

Biopsy: well differentiated squamous cell carcinoma

At clinical examination: large exophytic tumor limited to the cervix

Stage IB2 : initial clinical examination



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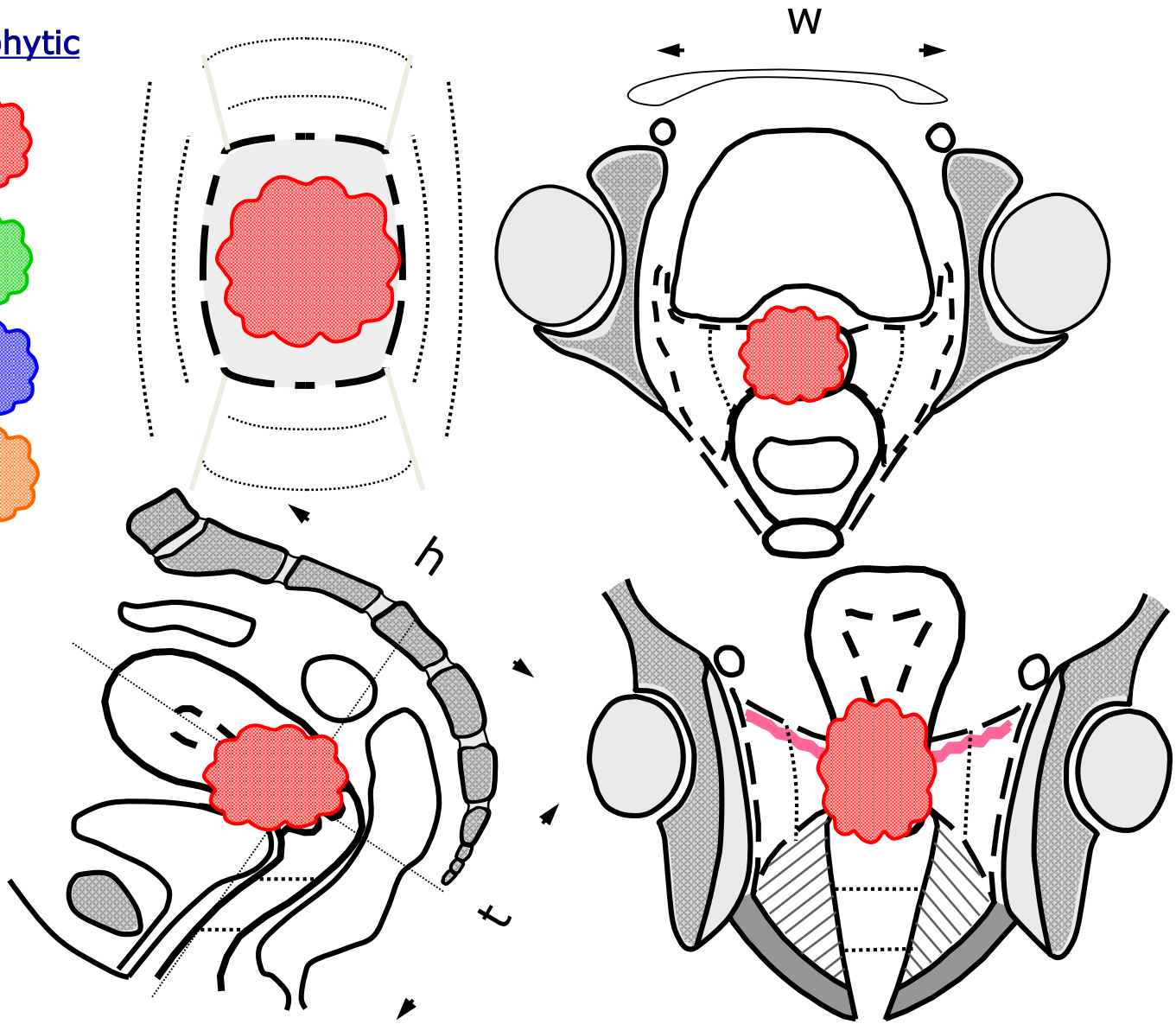
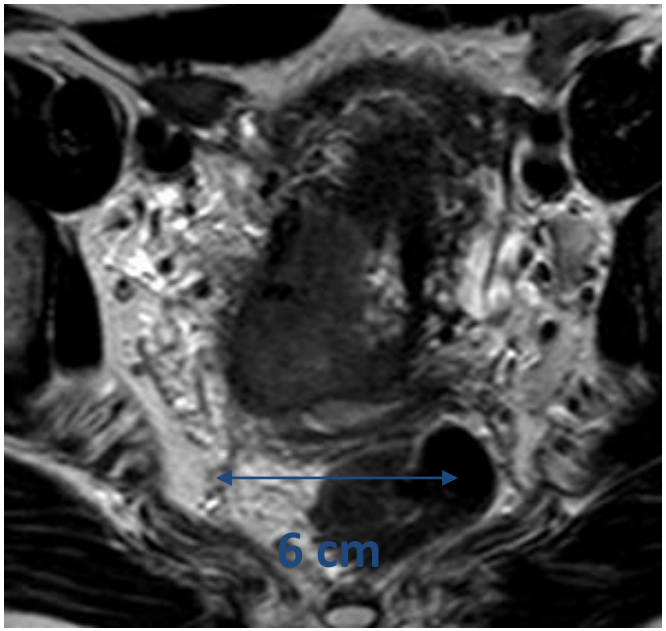
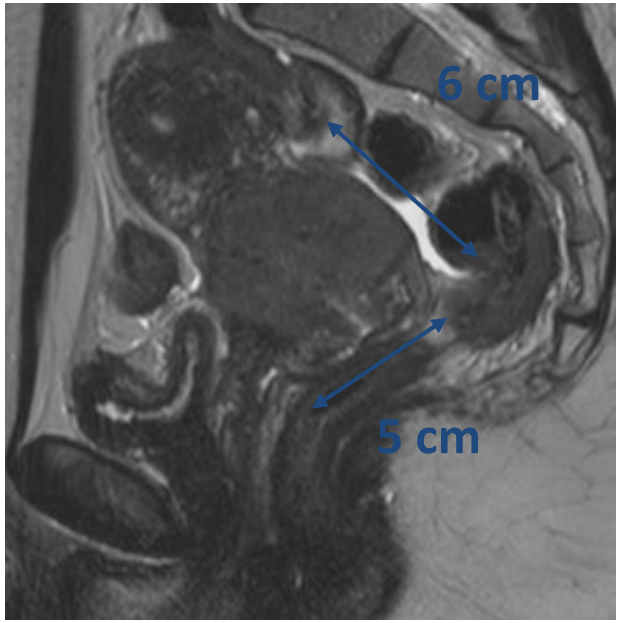
Thickness : 5

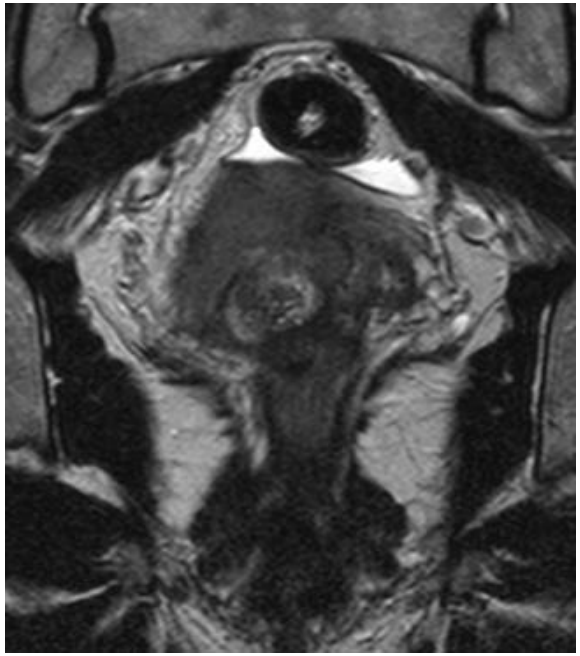
Height : 5



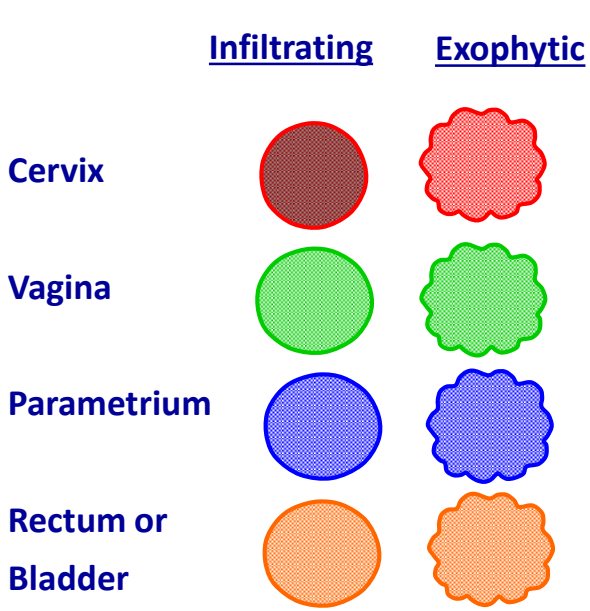
Stage IB2 : initial MRI







Stage IB2 : at the time of brachytherapy



Dimensions (cm):

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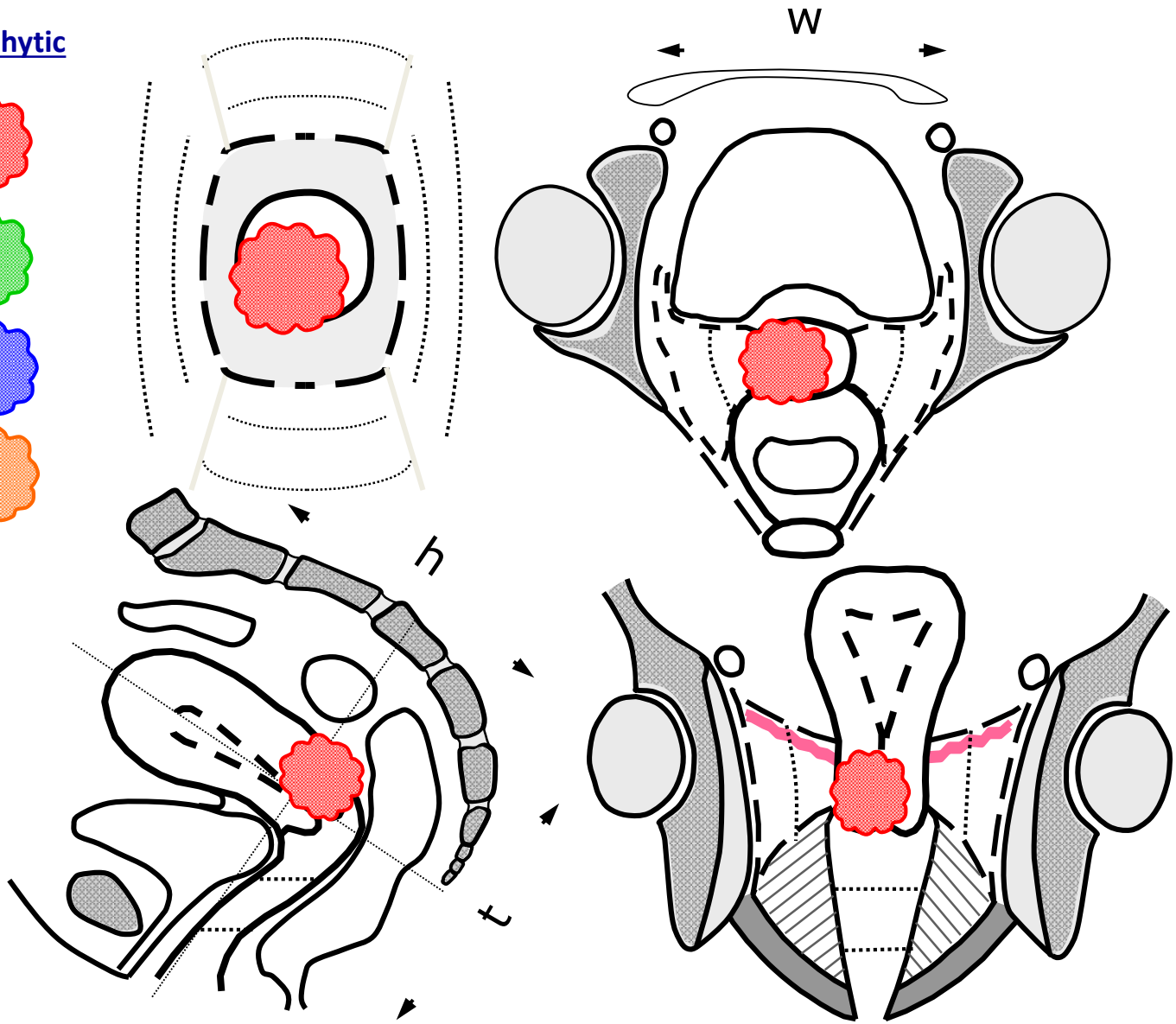
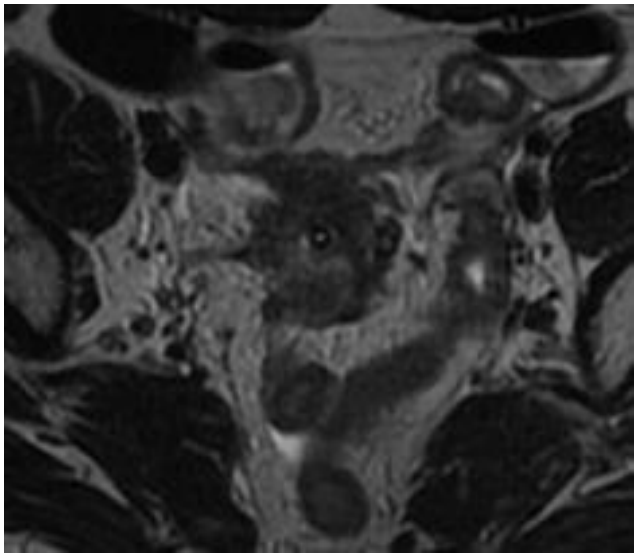
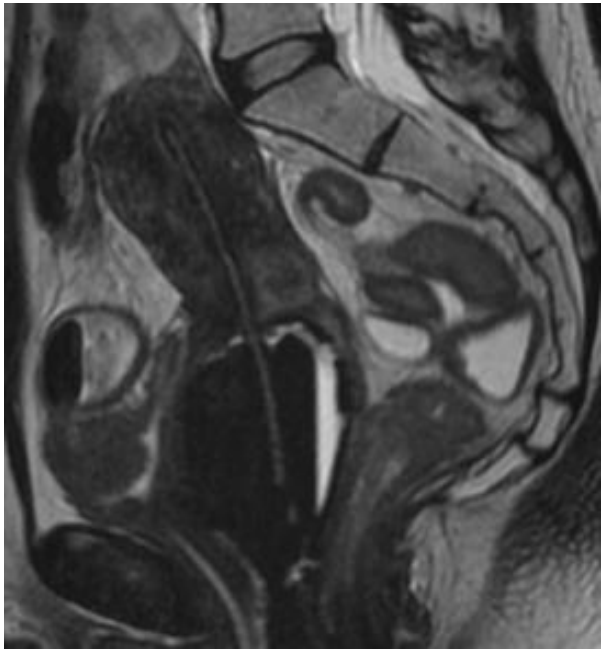
Thickness : 2

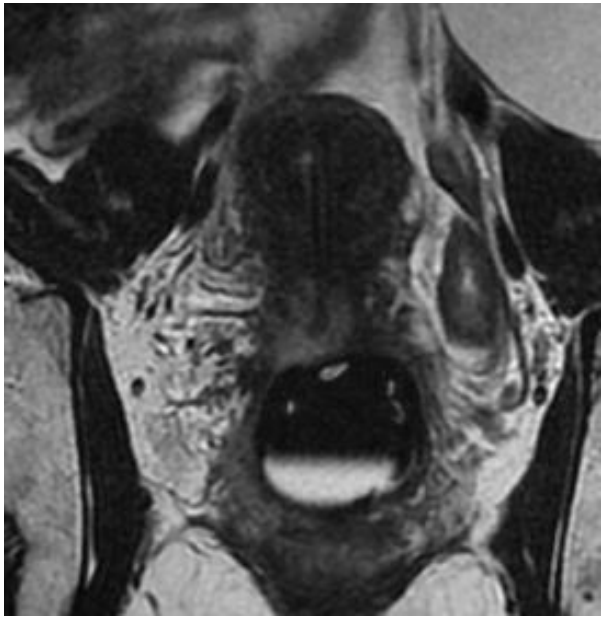
Height : 2.5



Stage IB2 : at the time of brachytherapy







Target volume concepts

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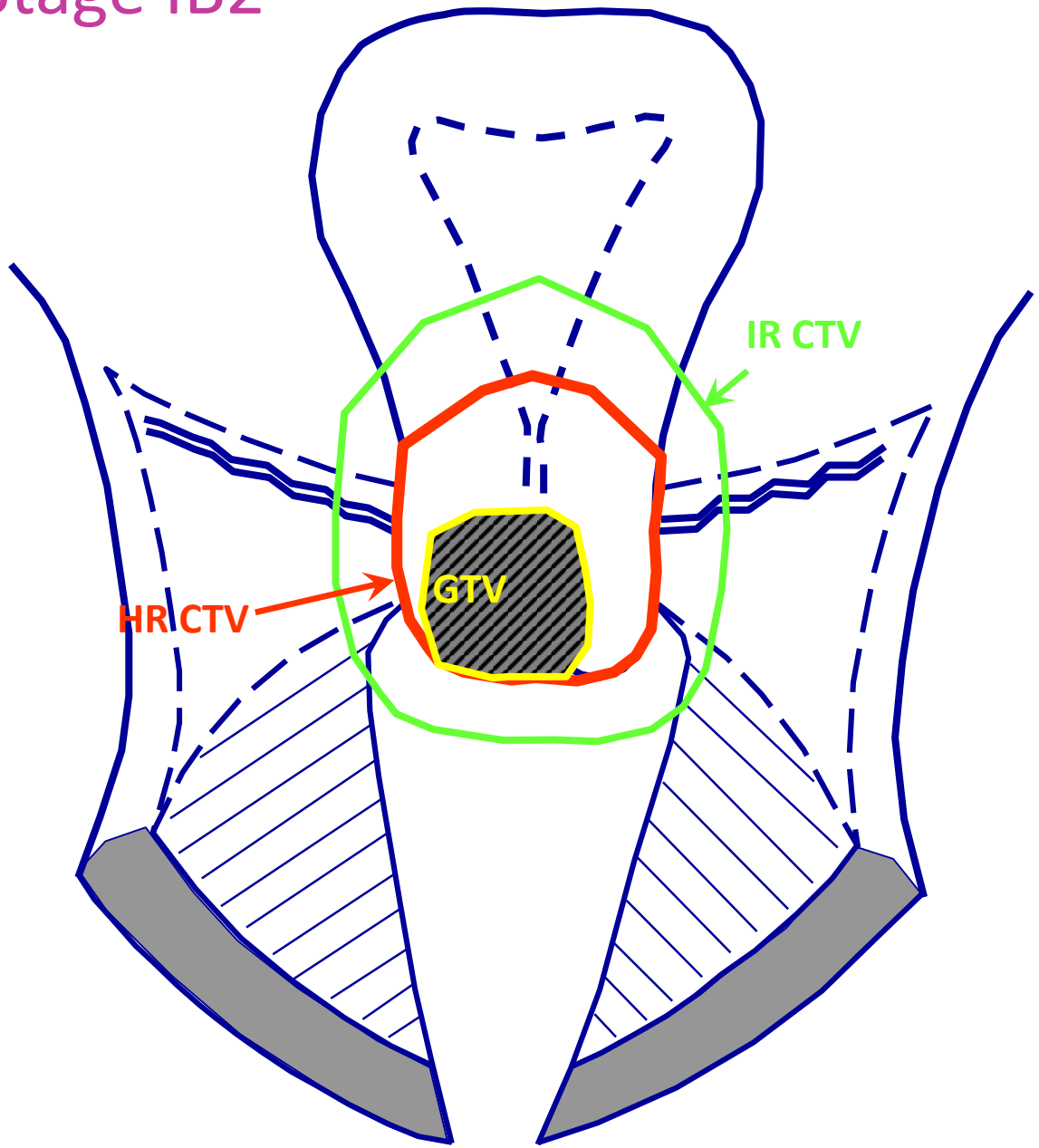
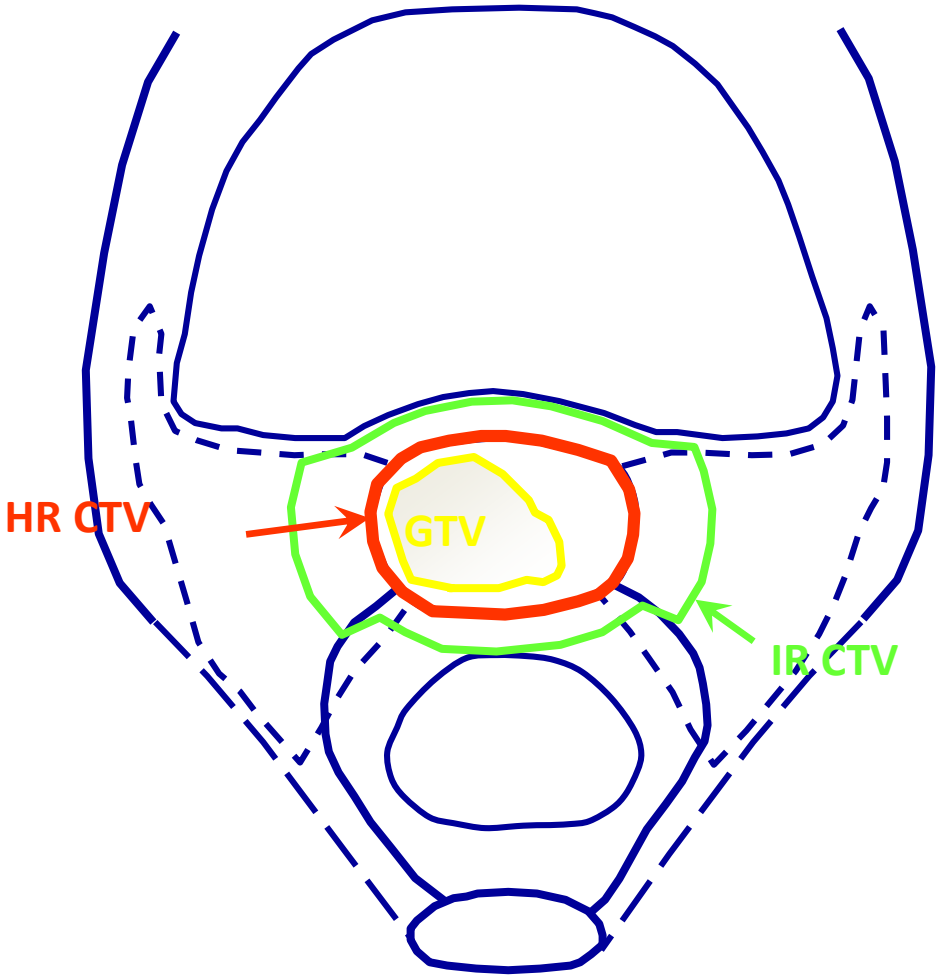
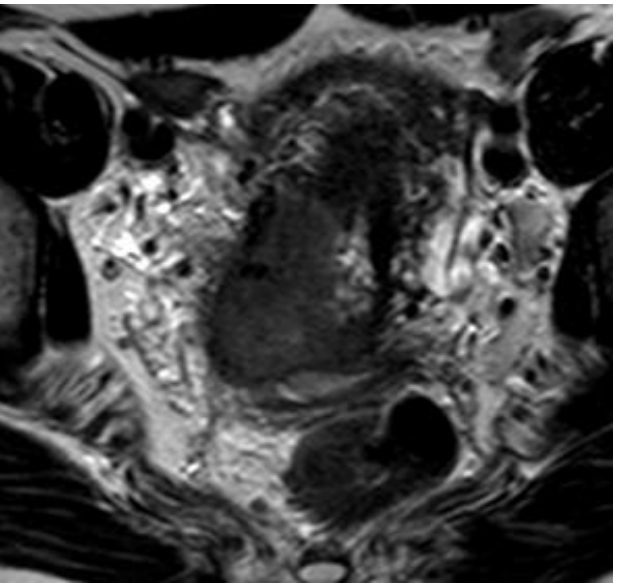
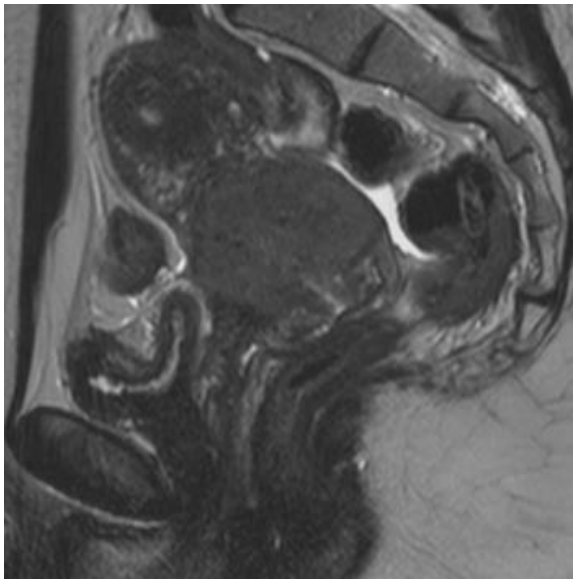
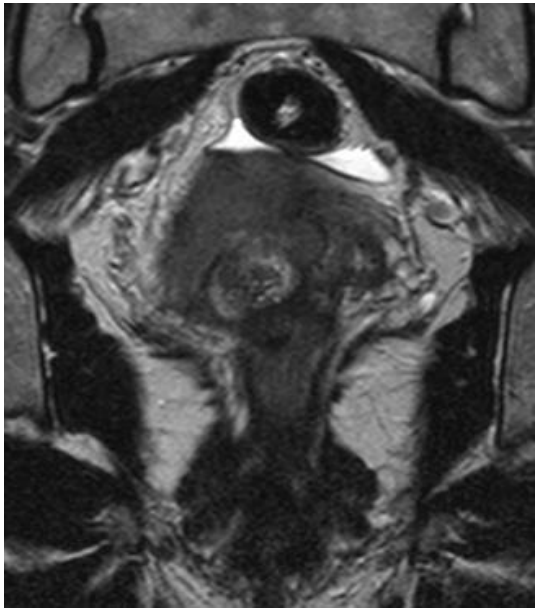
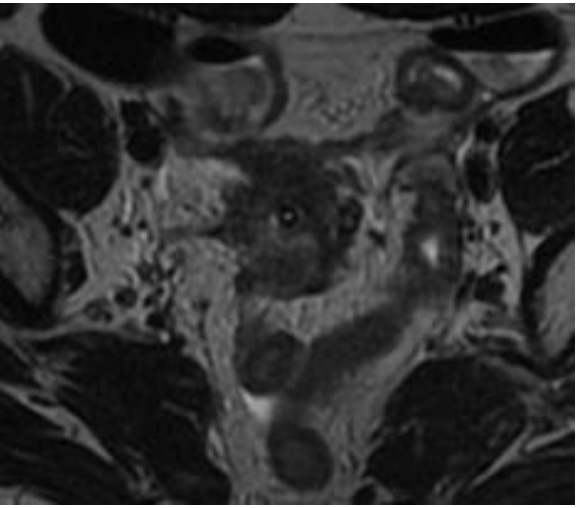
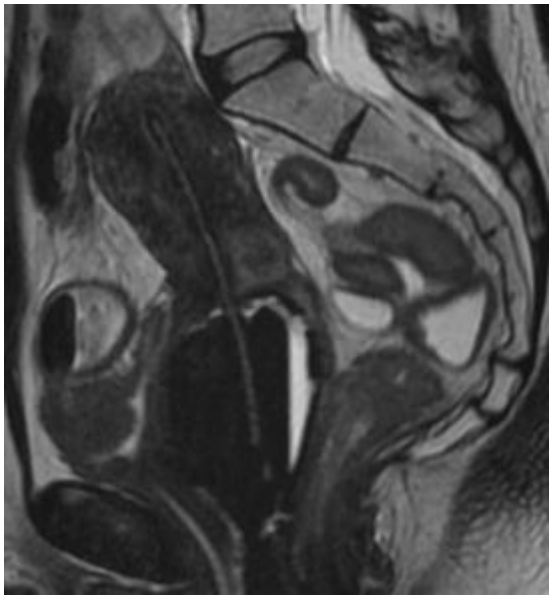
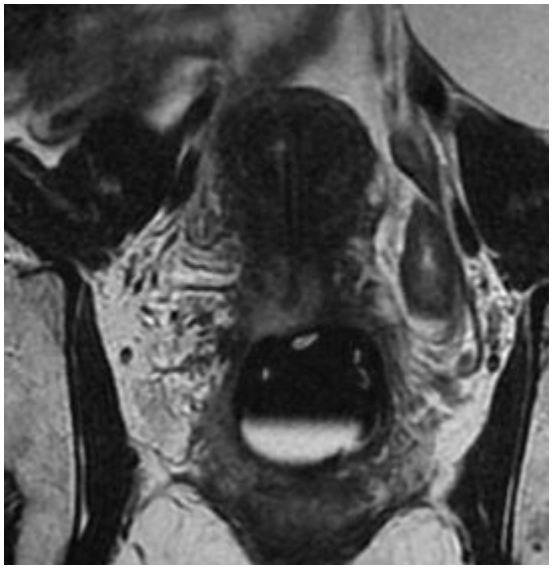
Stage IB2



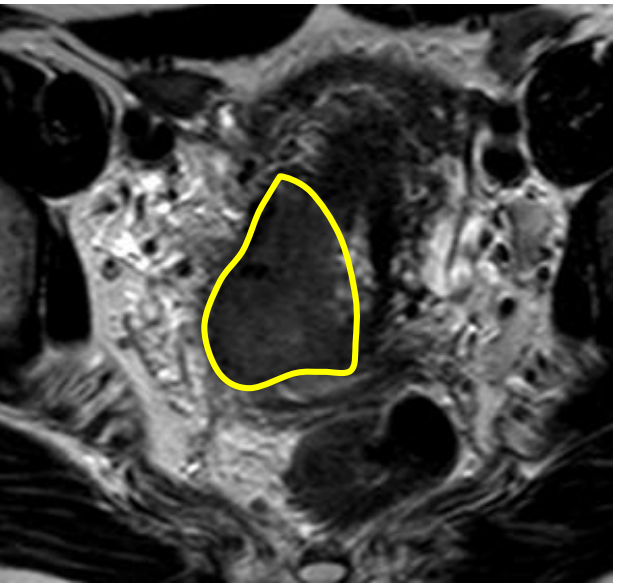
Stage IB2

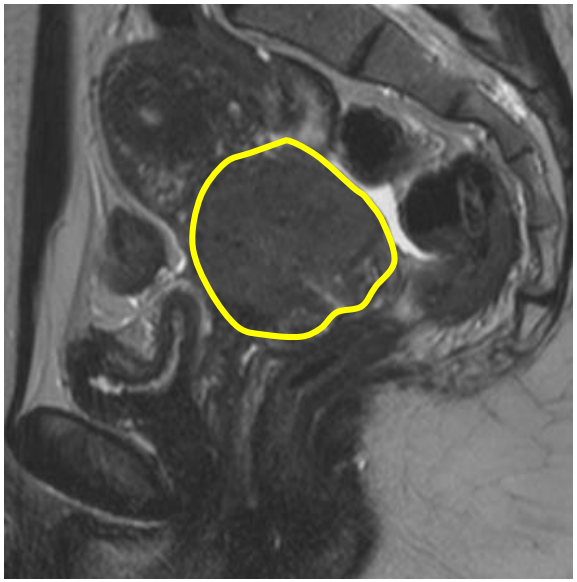


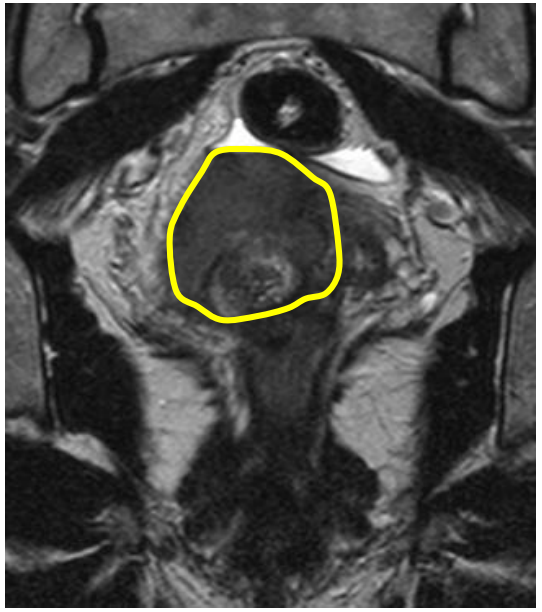
Stage IB2

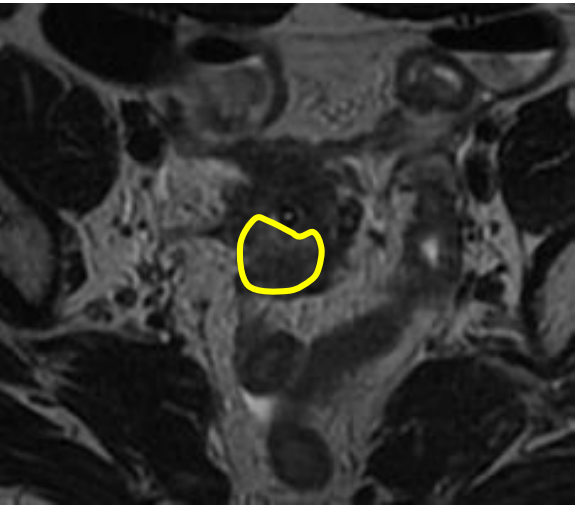







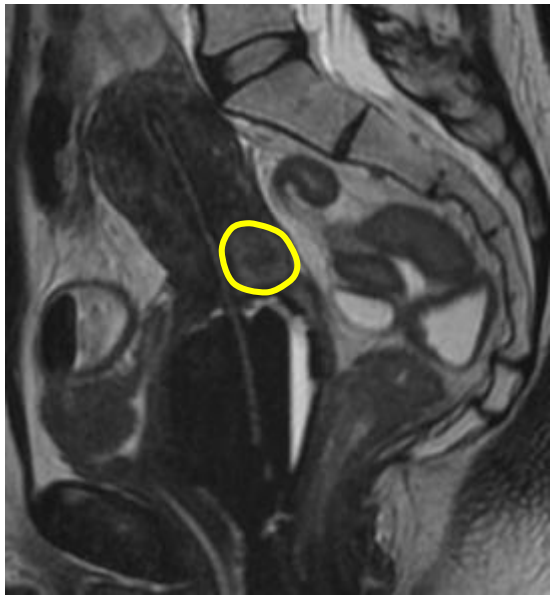
Stage IB2

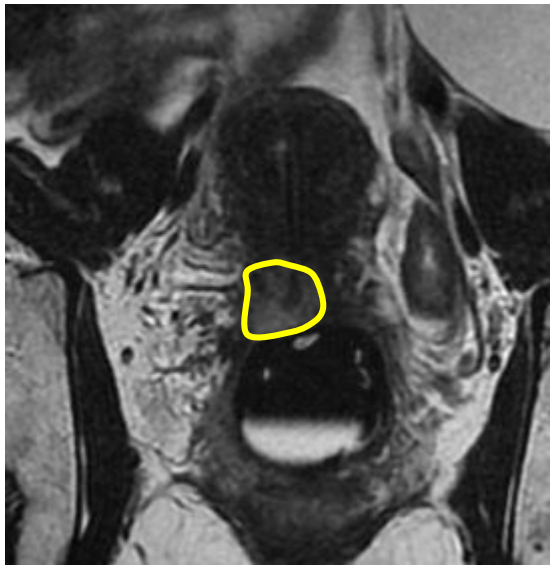




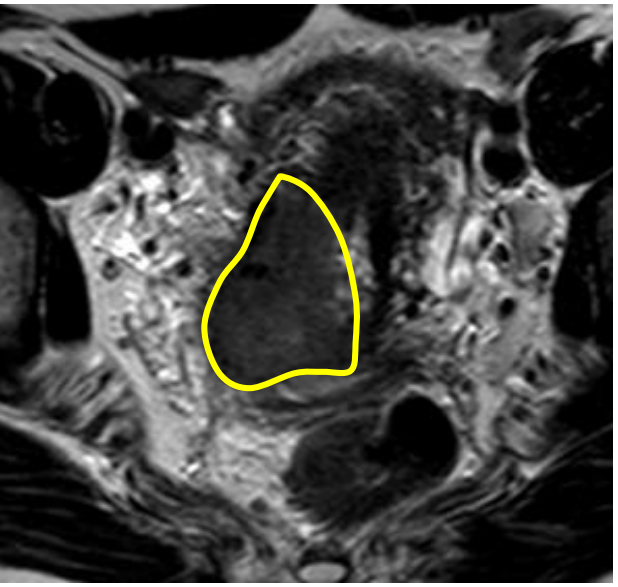
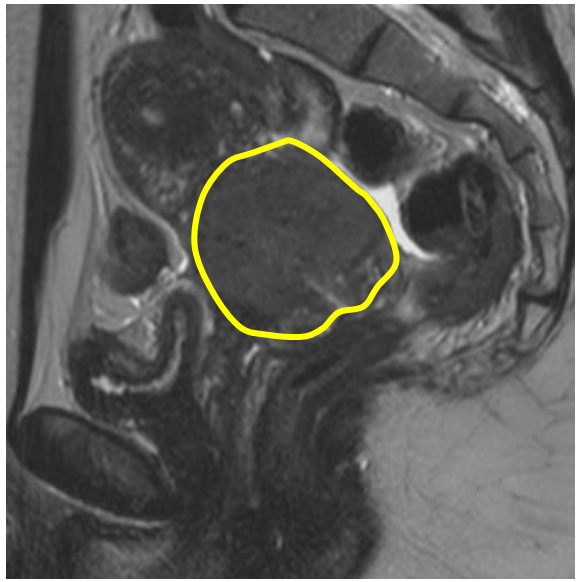
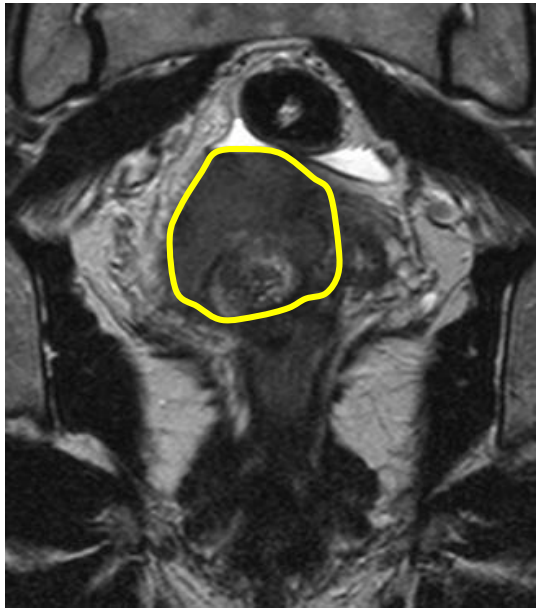
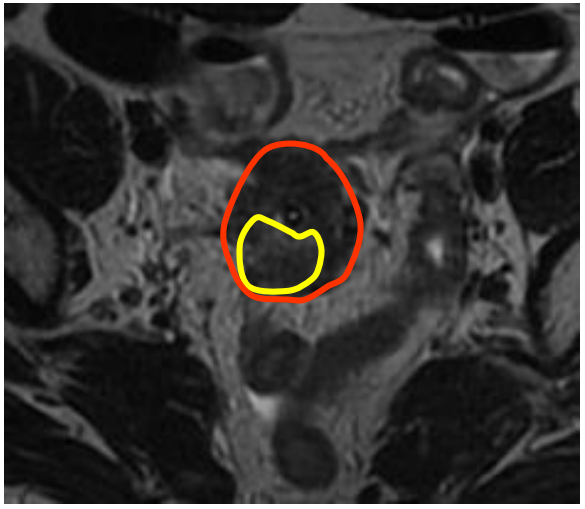
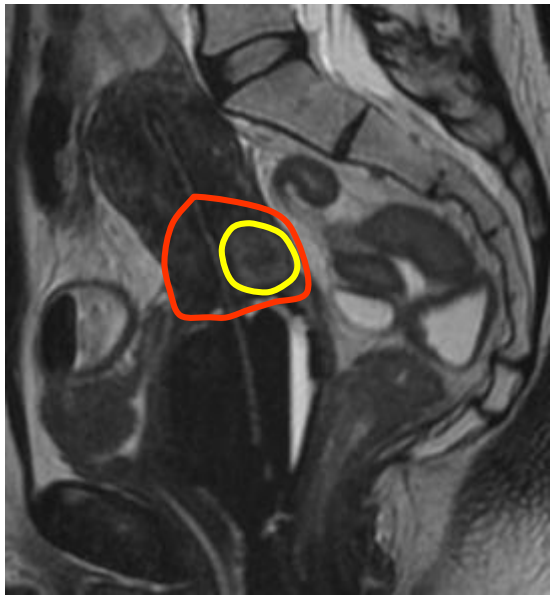
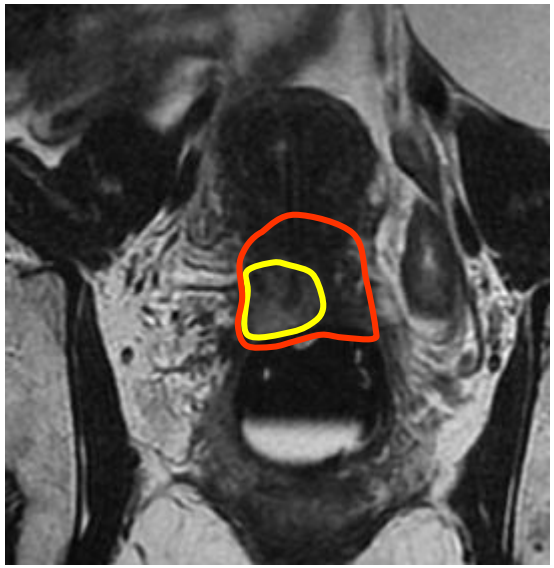




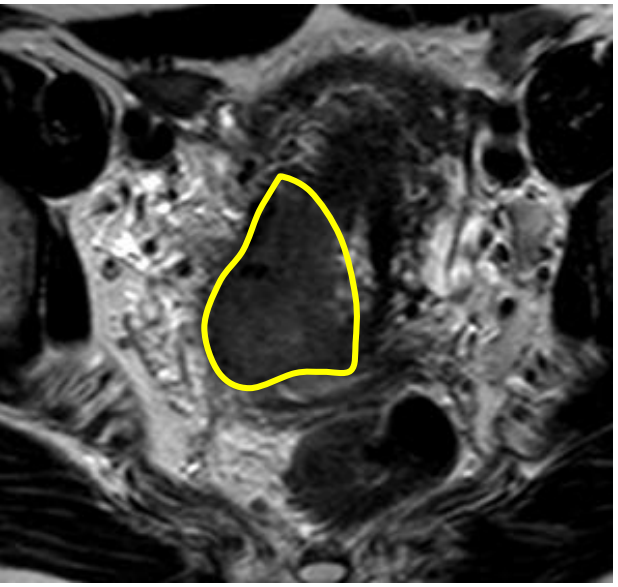


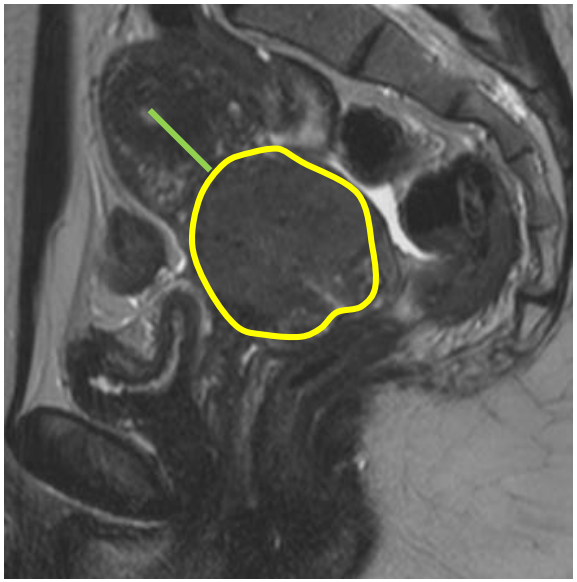


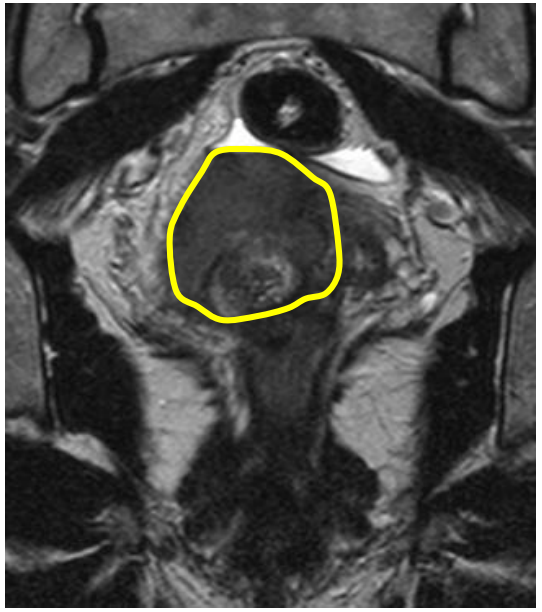
Stage IB2

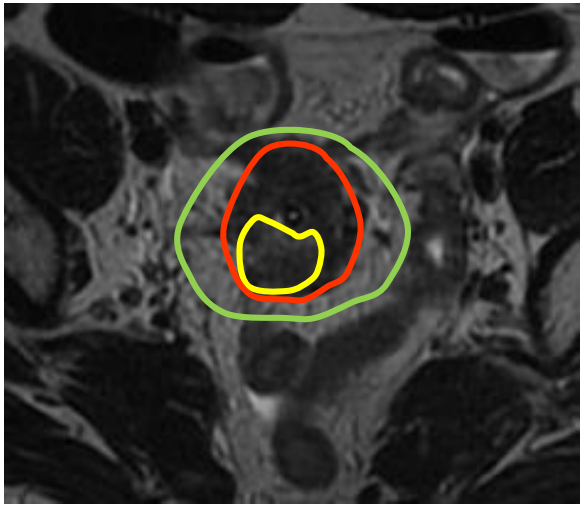







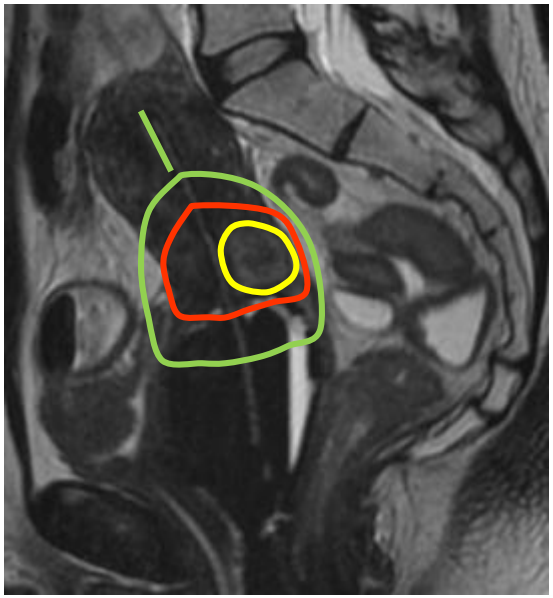
Stage IB2

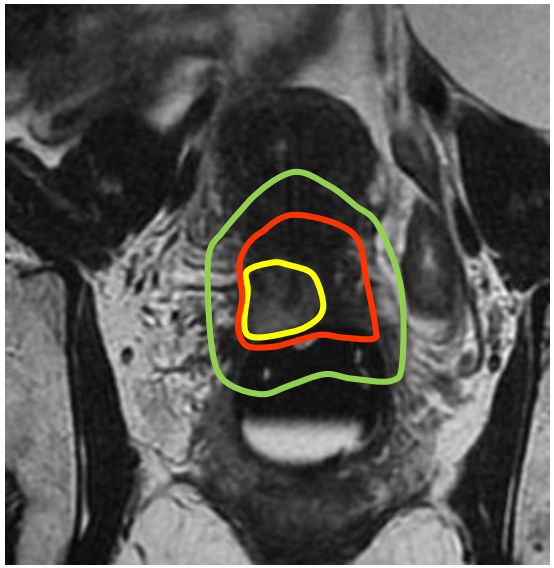












Patient n°4

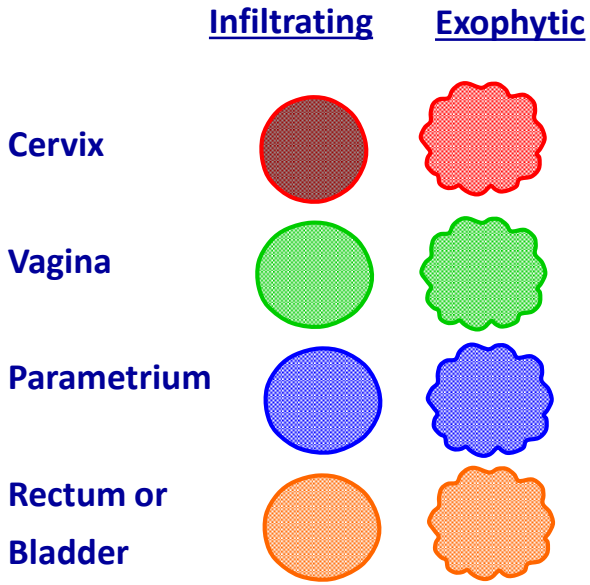
Mrs BOR…
46 year-old
WHO=0, 72 kg, 1m67

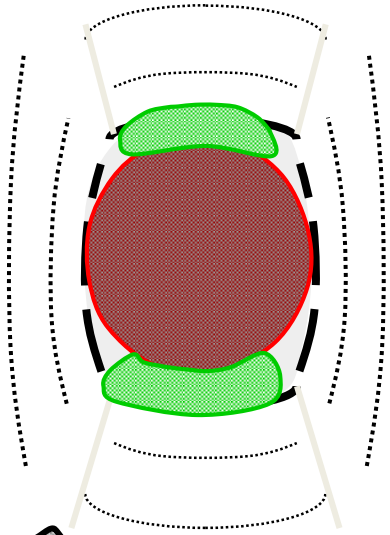
Vaginal bleeding

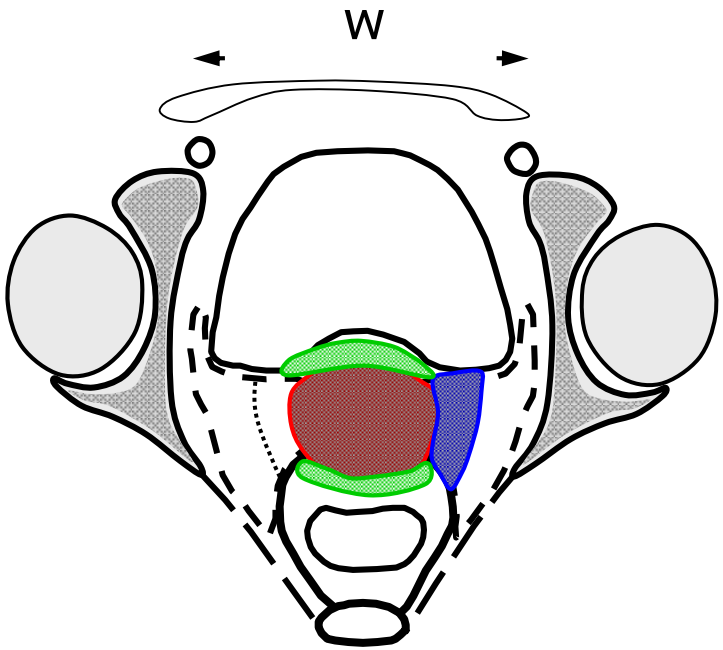
Biopsy: moderately differentiated adenocarcinoma

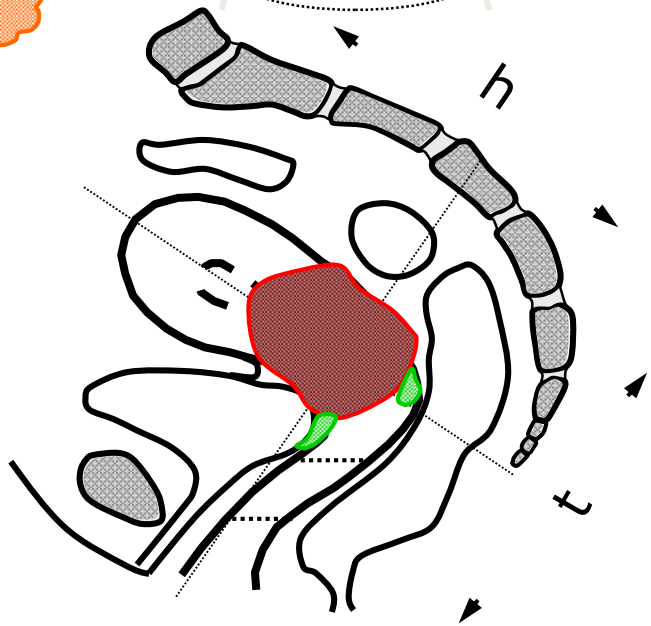
At clinical examination : cervical tumor + infiltration of the anterior and posterior fornices + infiltration of the proximal part of the left parametrium

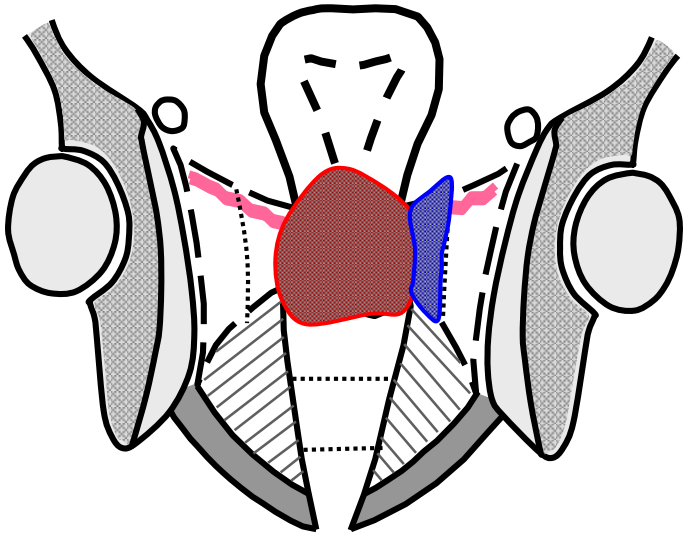
Stage IIB : initial clinical examination











Dimensions (cm):

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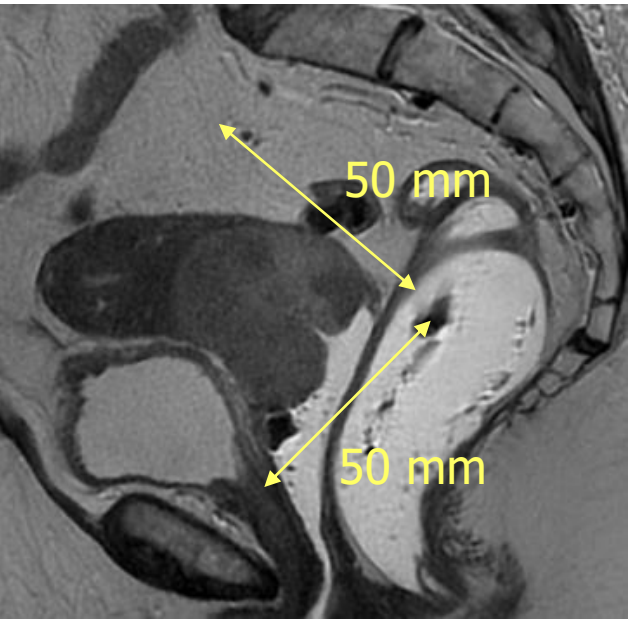
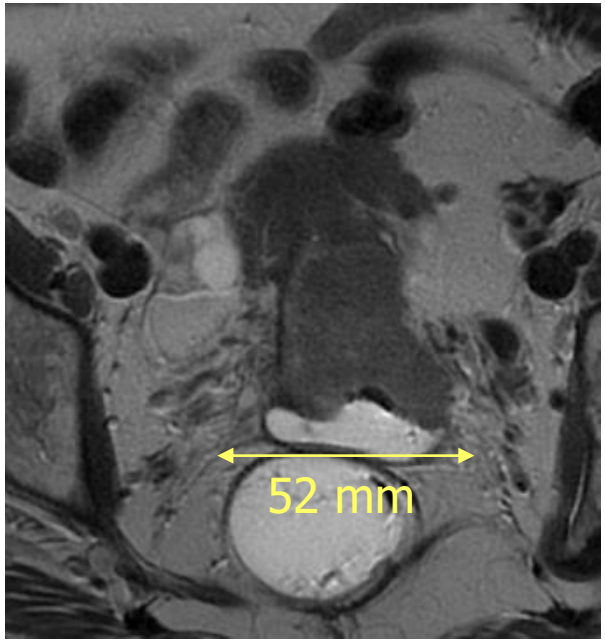
Thickness:5

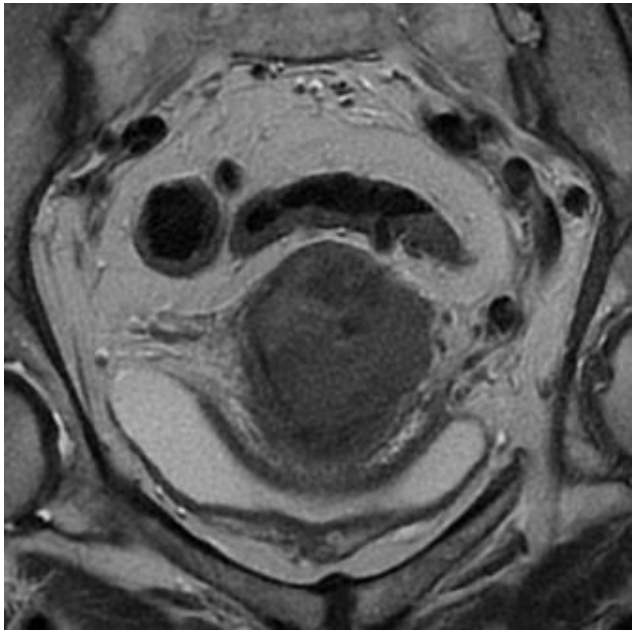
Height : 5

Fornix involv 1

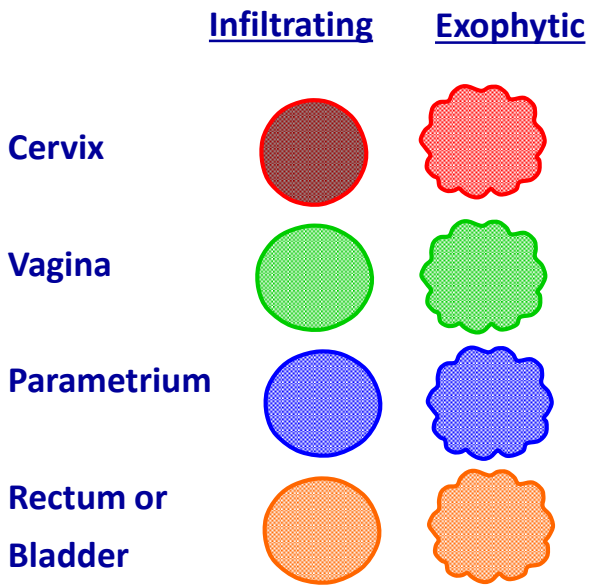
Stage IIB : initial MRI







Stage IIB : at the time of brachytherapy



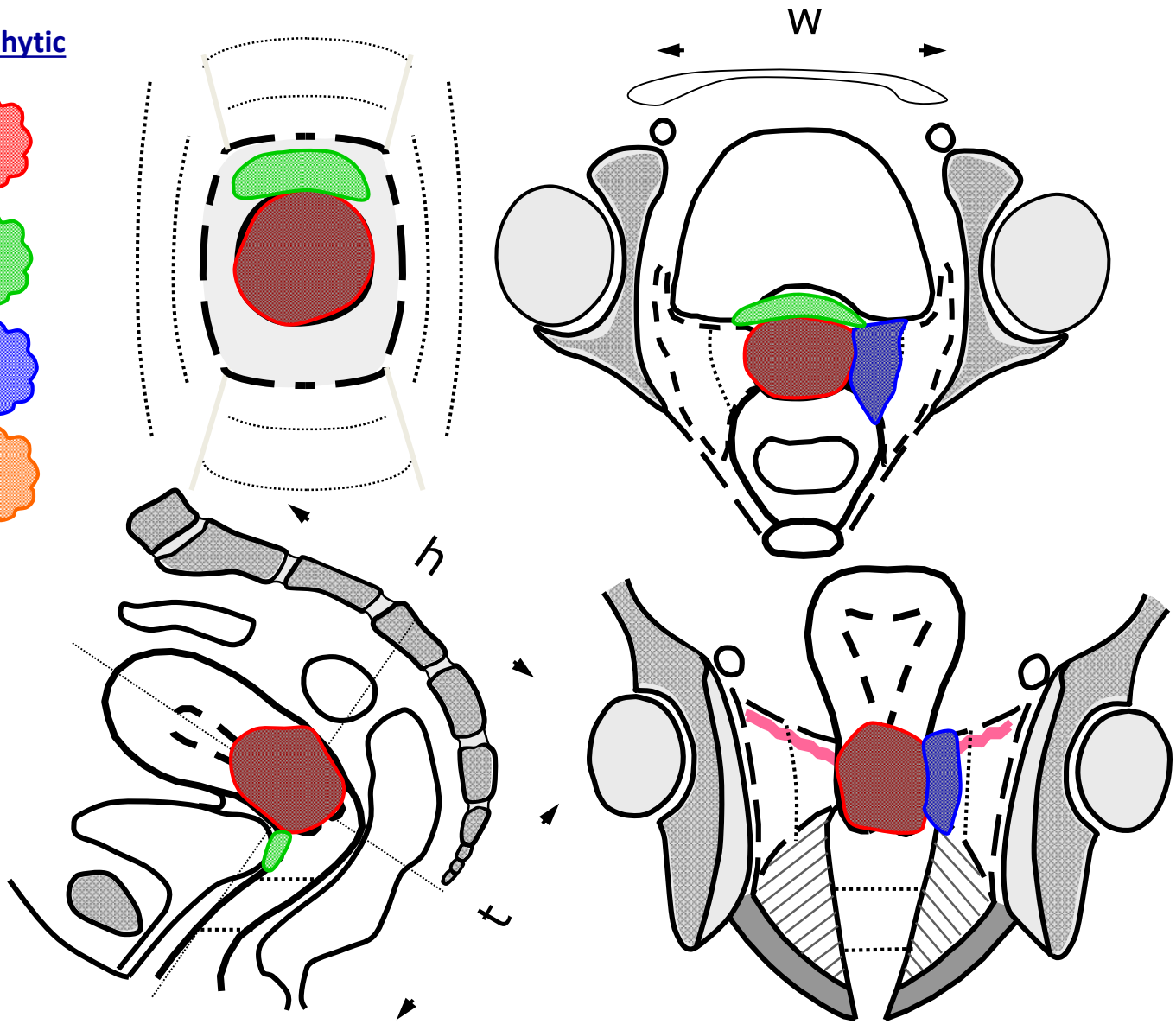
Dimensions (cm):

Largeur : 3

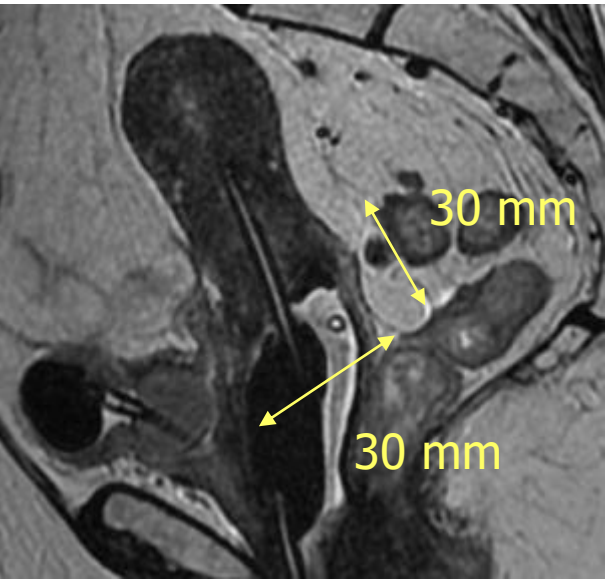
Epaisseur : 3

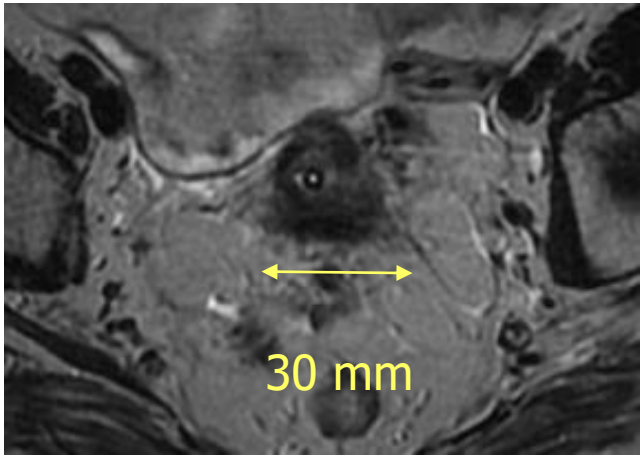
Hauteur : 3

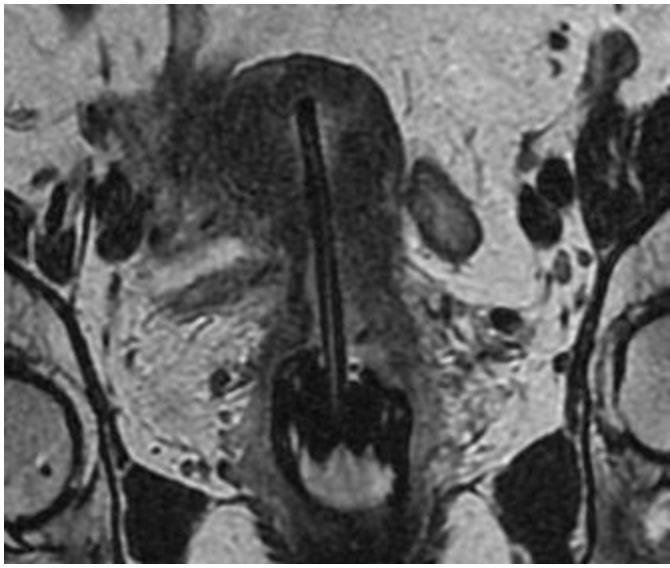
Env. vaginal : 1



Stage IIB : MRI at the time of brachytherapy







Target volume concepts

High Risk CTV :

GTV at time of brachytherapy
In all cases includes:

- GTV + whole cervix
- Presumed tumour extension in adjacent tissues
    - **Clinical assessment**
    - **Residual grey zones on MRI**

NO SAFETY MARGINS

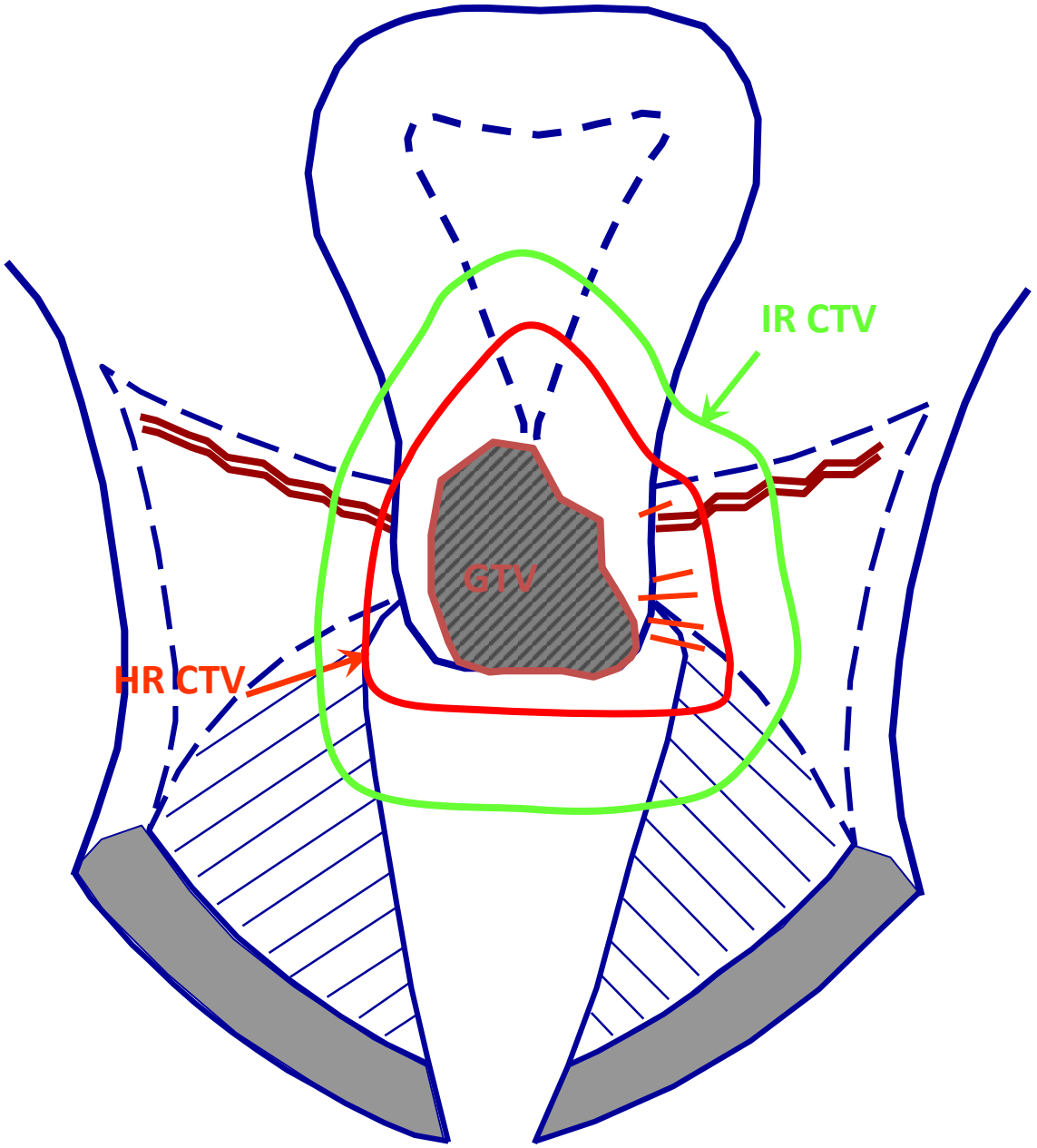
Intermediate Risk CTV :

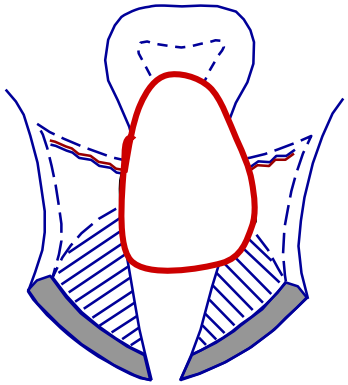
GTV at time of diagnosis
In all cases includes:

- HR-CTV
- integrates initial CTV

SAFETY MARGINS :
1-1.5 cm cranially
0.5cm antero-posteriorly
1cm laterally

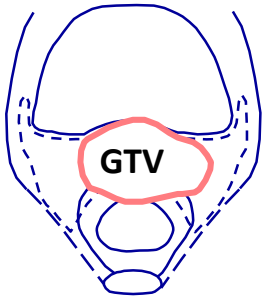
Stage IIB



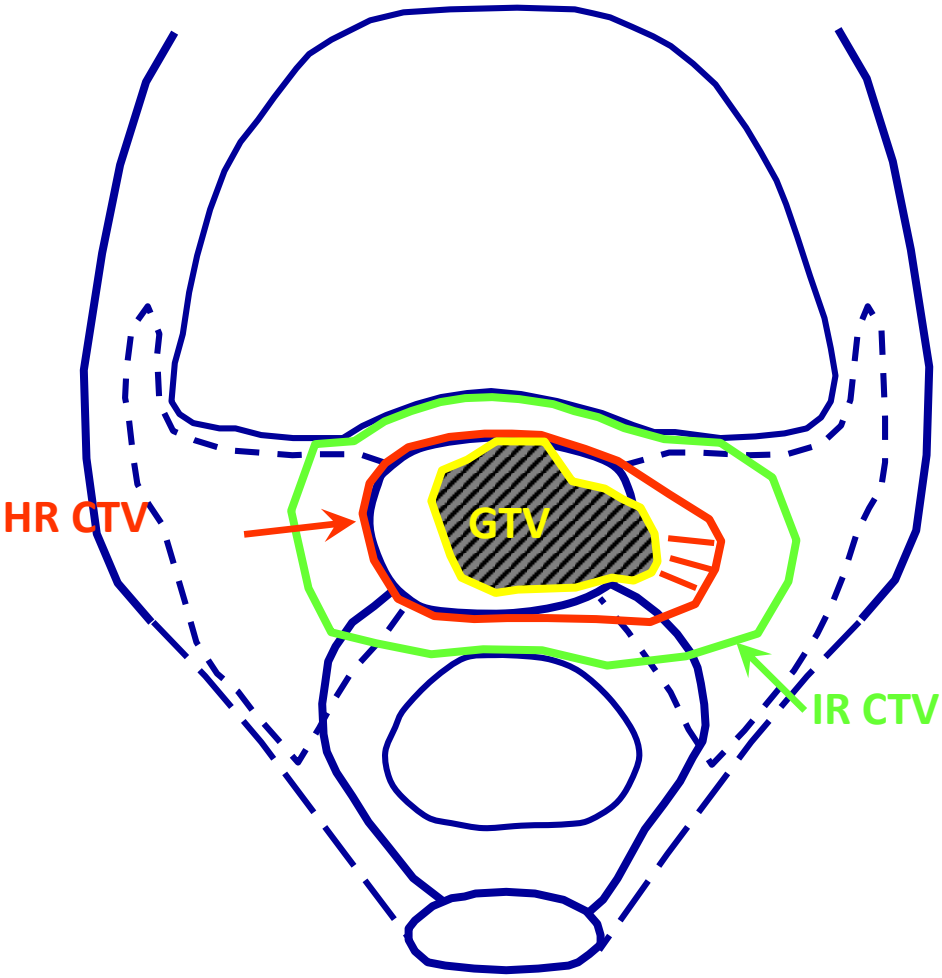


Tumor at time of diagnosis

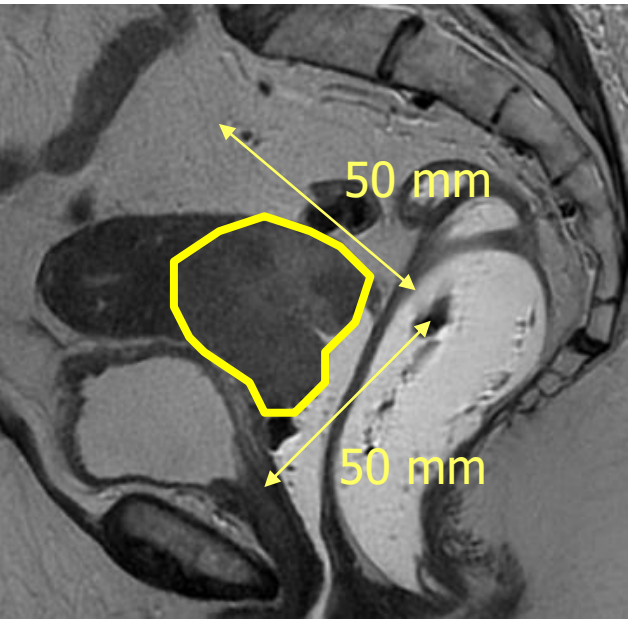
Stage IIB

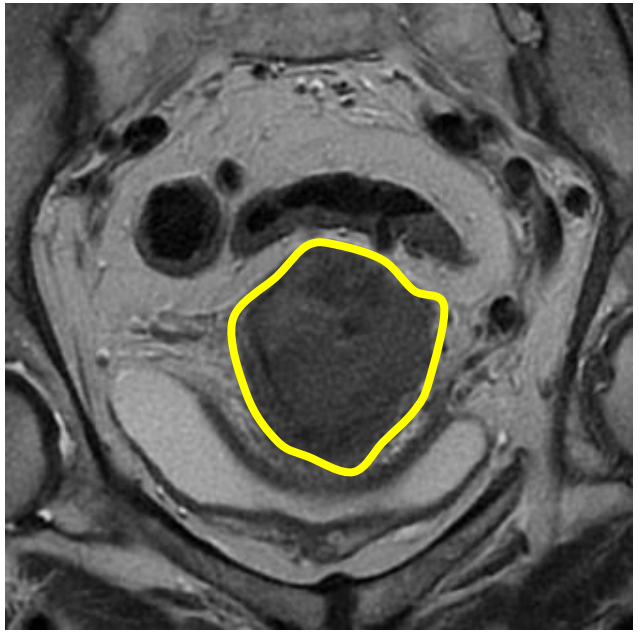


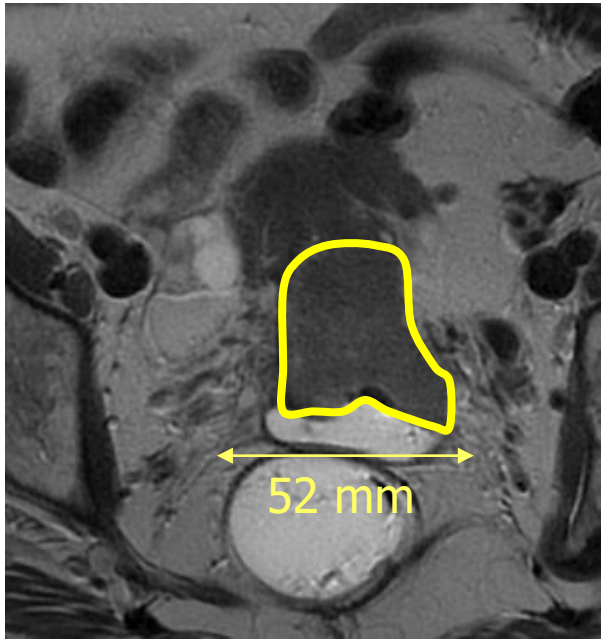
Tumor at time of diagnosis.

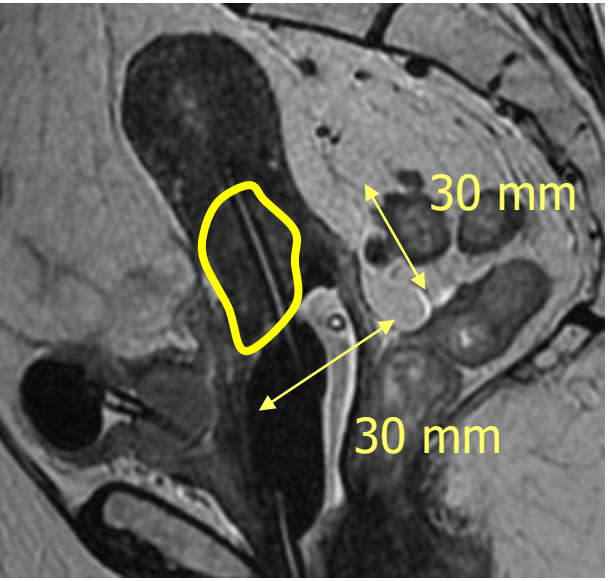


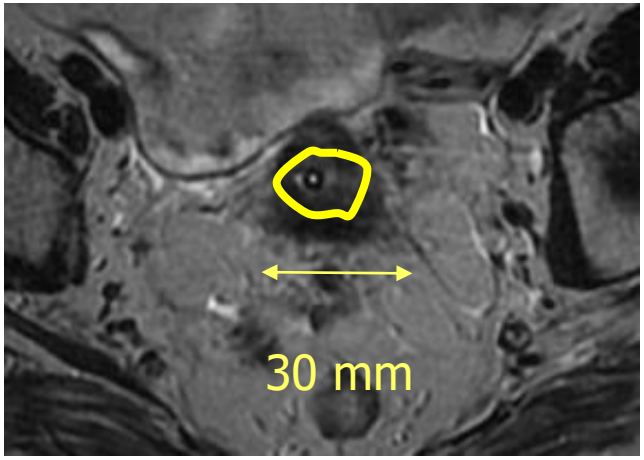
Stage IIB

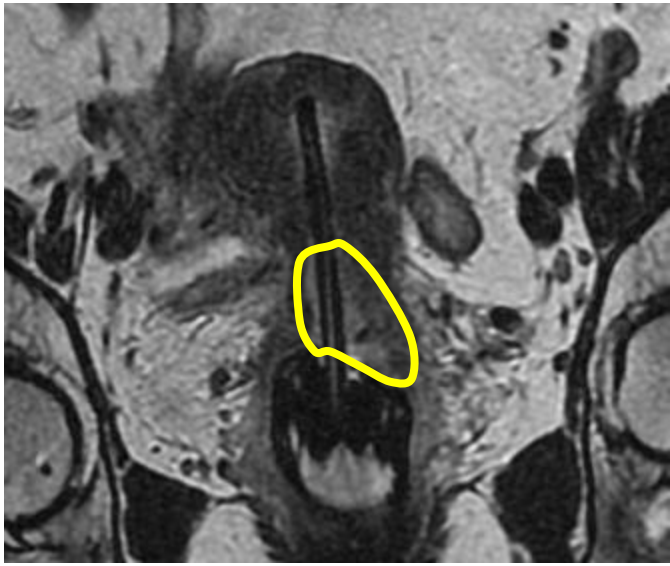




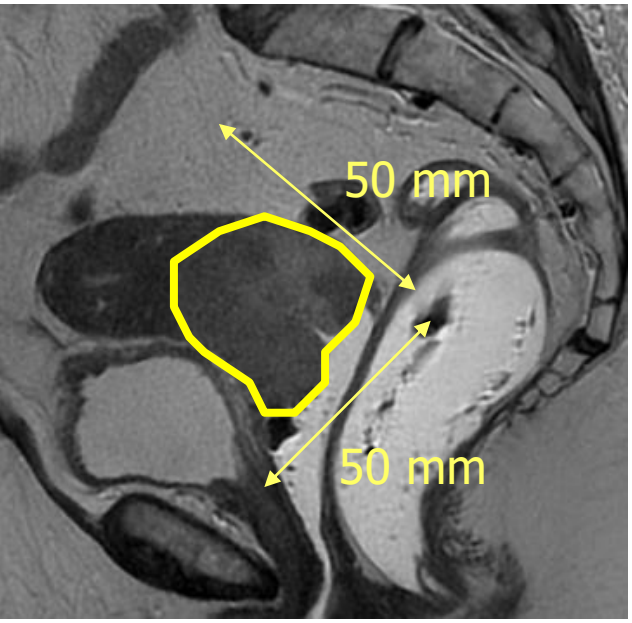


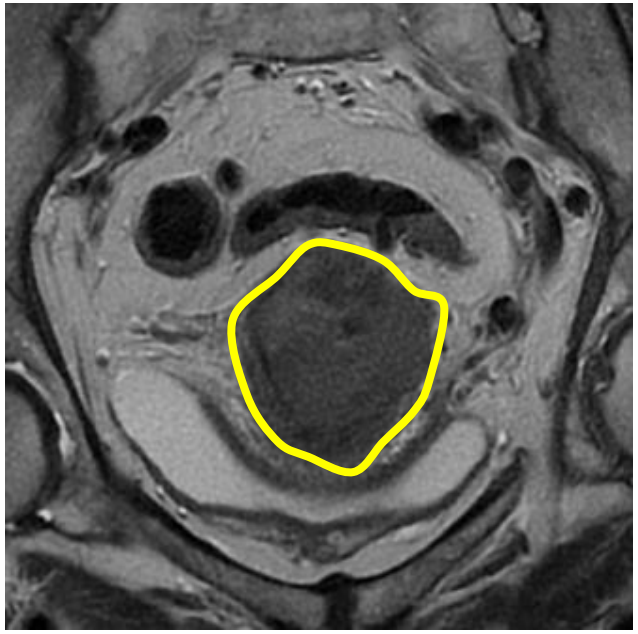


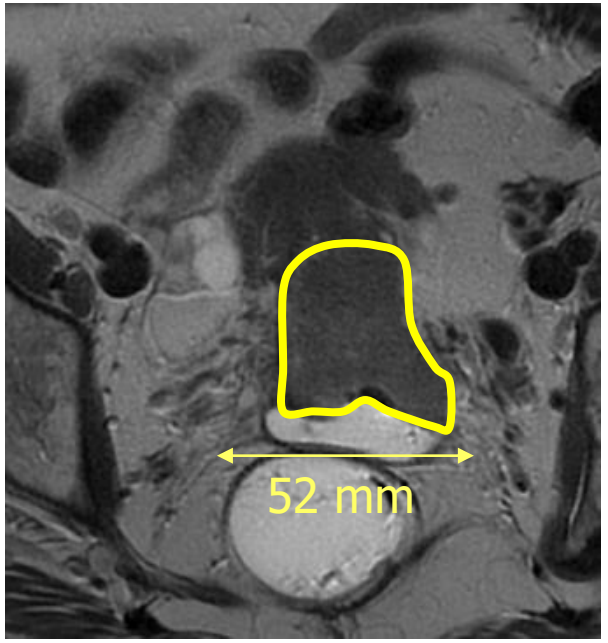


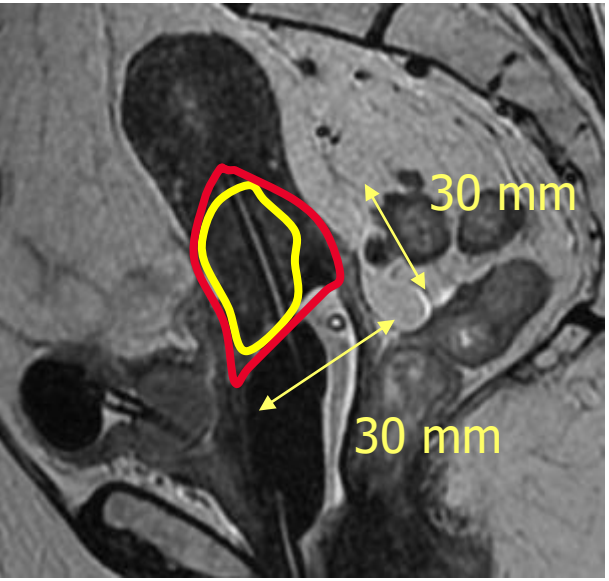


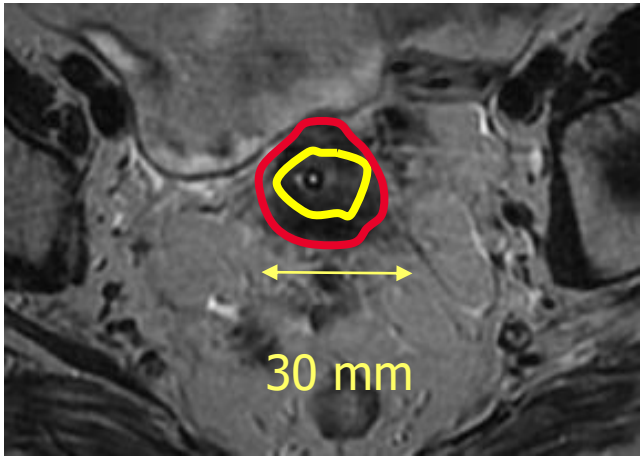
Stage IIB

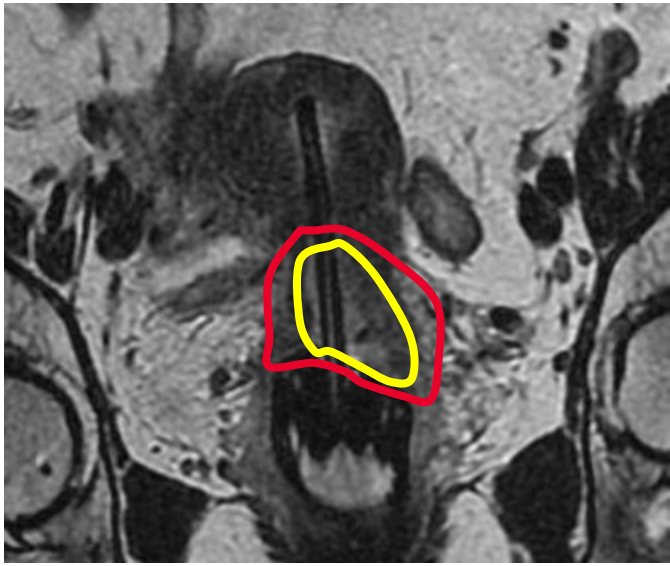




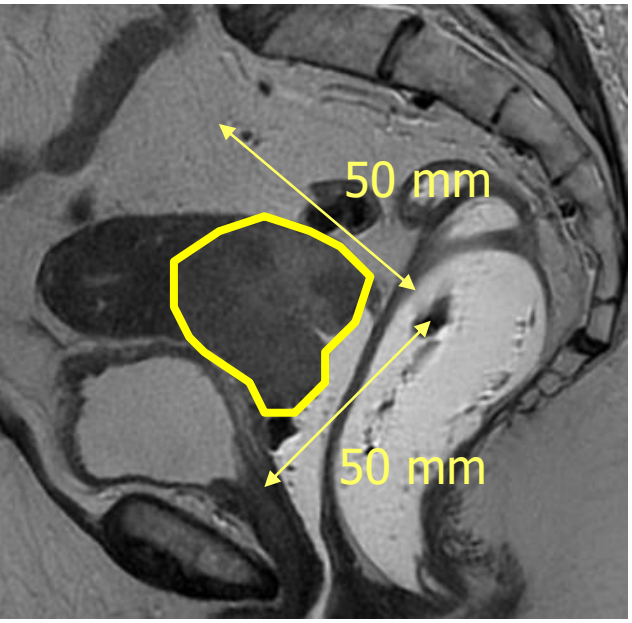


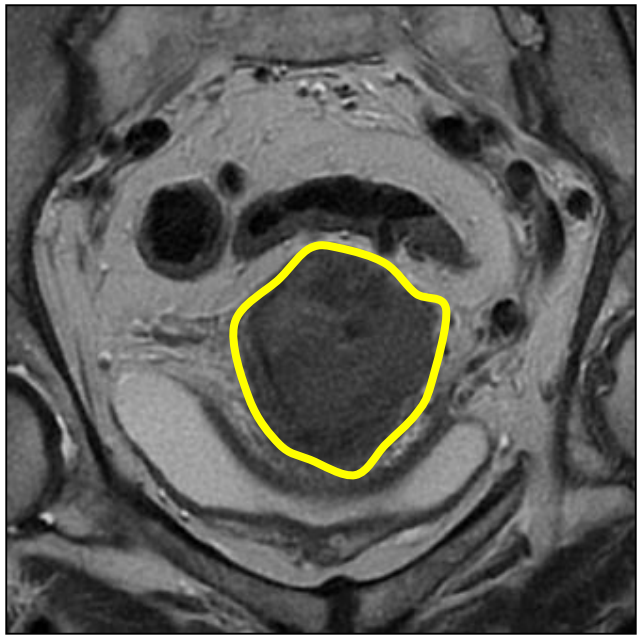


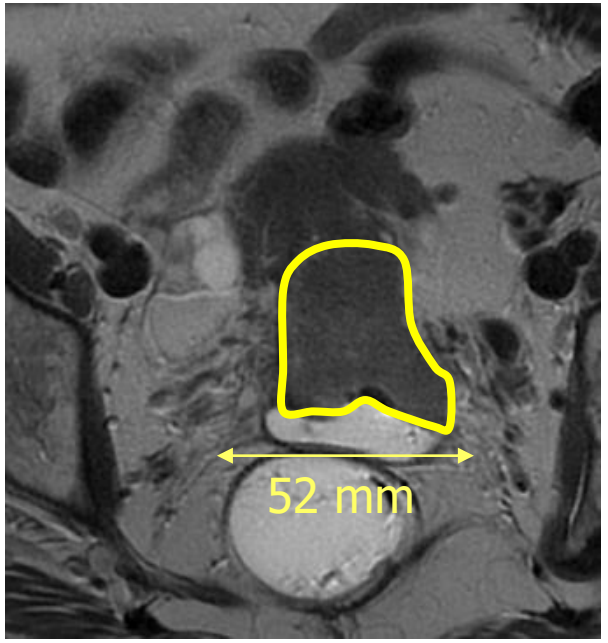


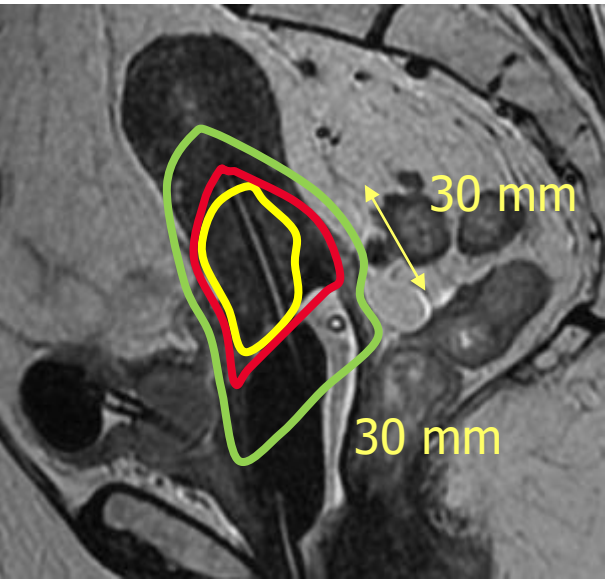


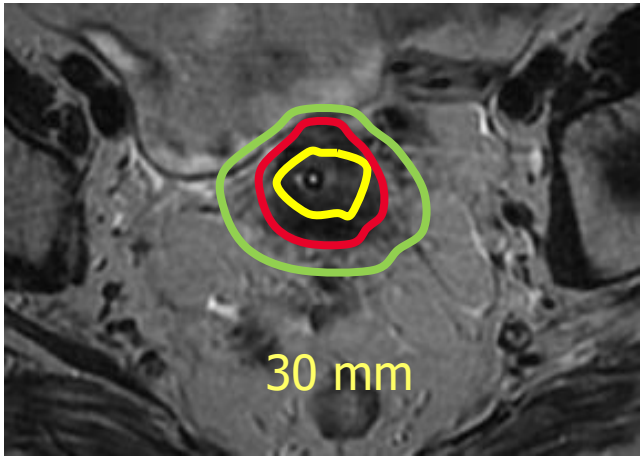
Stage IIB

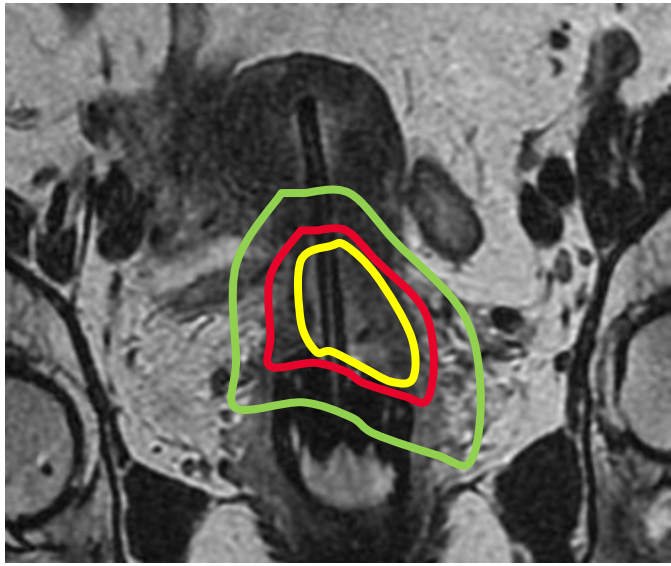












Patient n° 7

Mrs Claudine BAR…
62 year-old

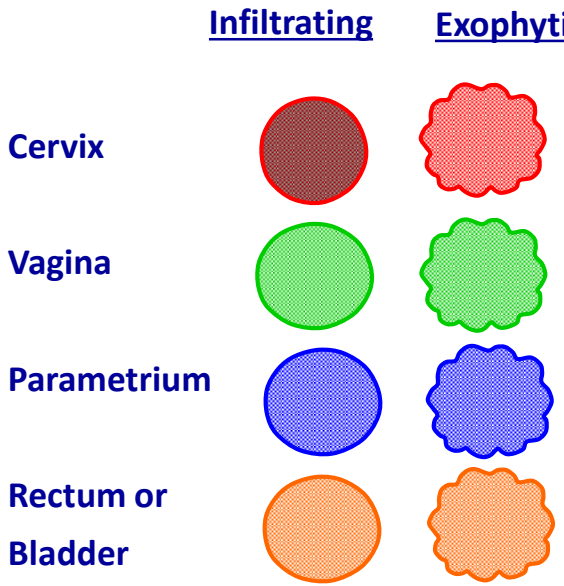
Vaginal bleeding for > 1 year, urinary retention

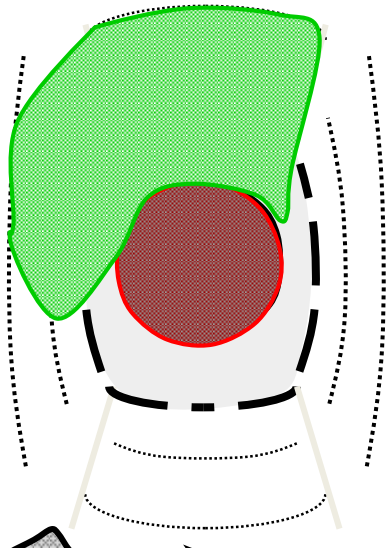
Biopsy: well differentiated squamous cell carcinoma

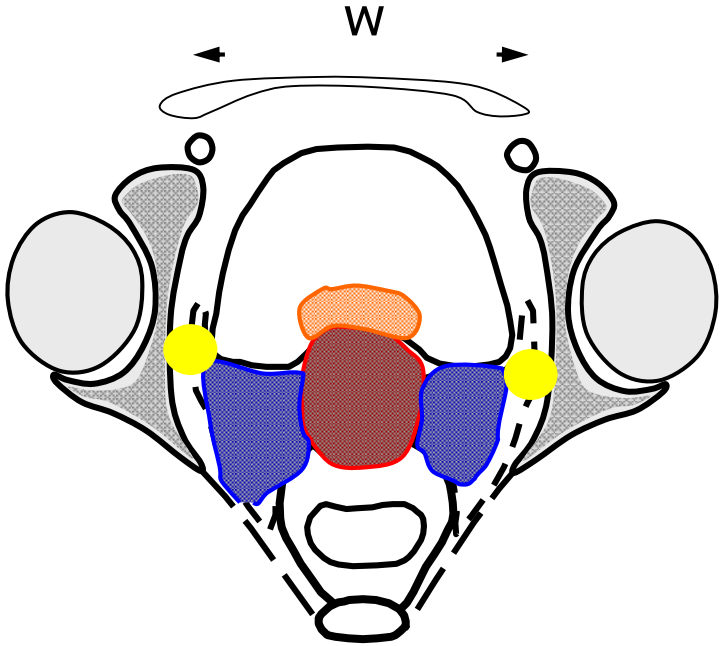
At clinical examination : cervical tumor + infiltration of the whole anterior and right vaginal wall + infiltration of the right parametrium to the pelvic wall + infiltration of the left distal parametrium

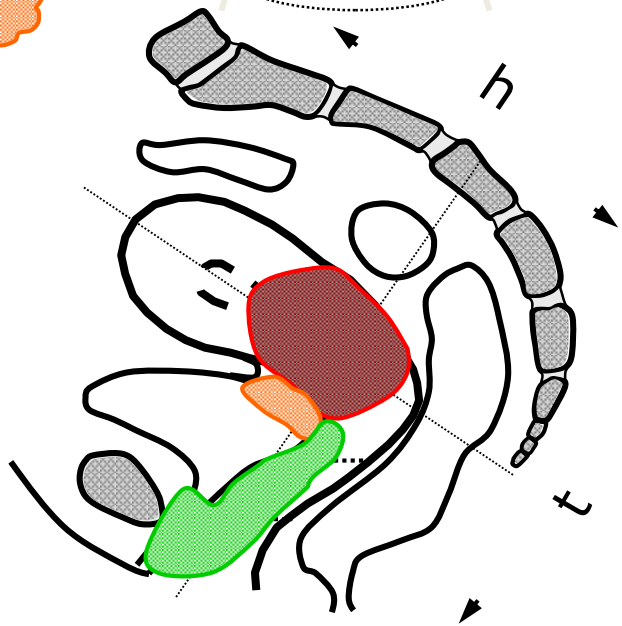
Cystoscopy : involvement of the trigonal area, + biopsy

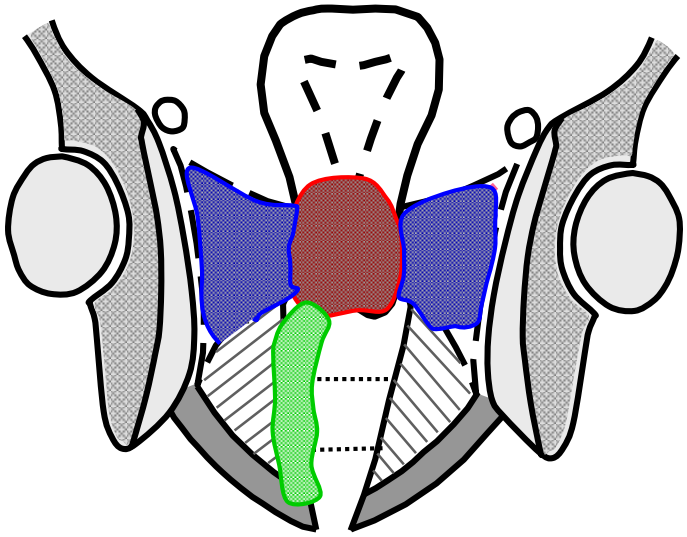
Stage IVA : initial clinical examination











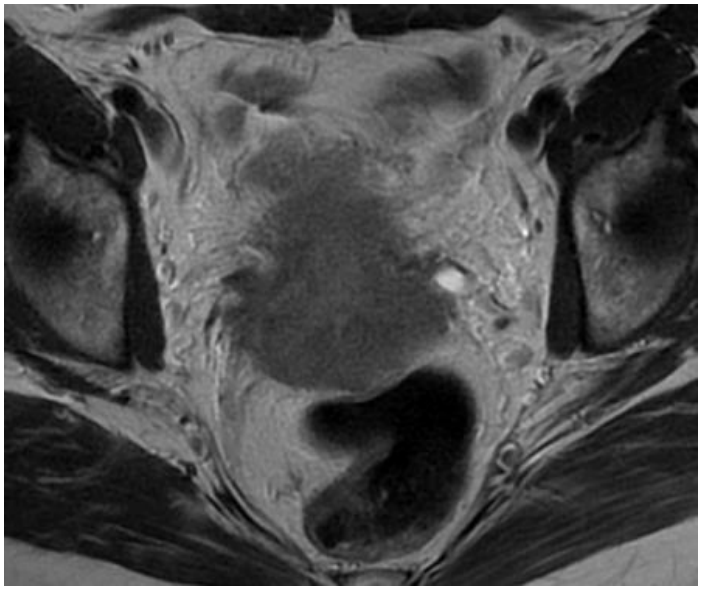
Dimensions (cm):

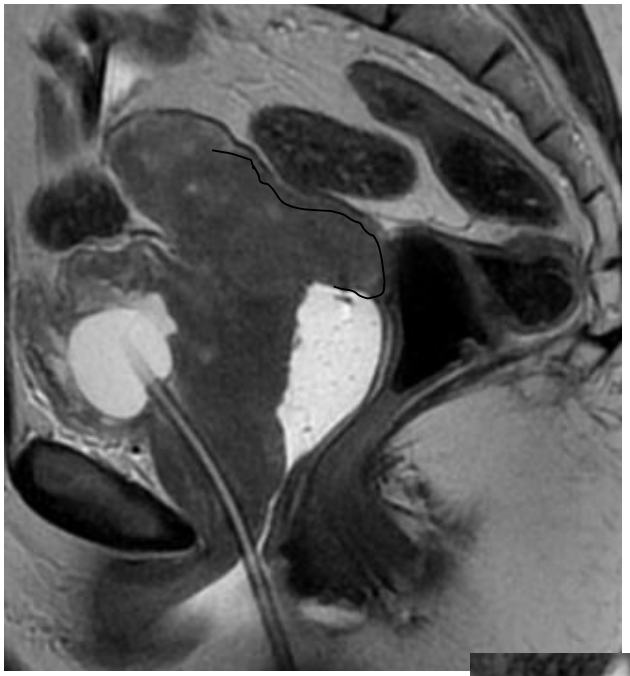
Width : 8

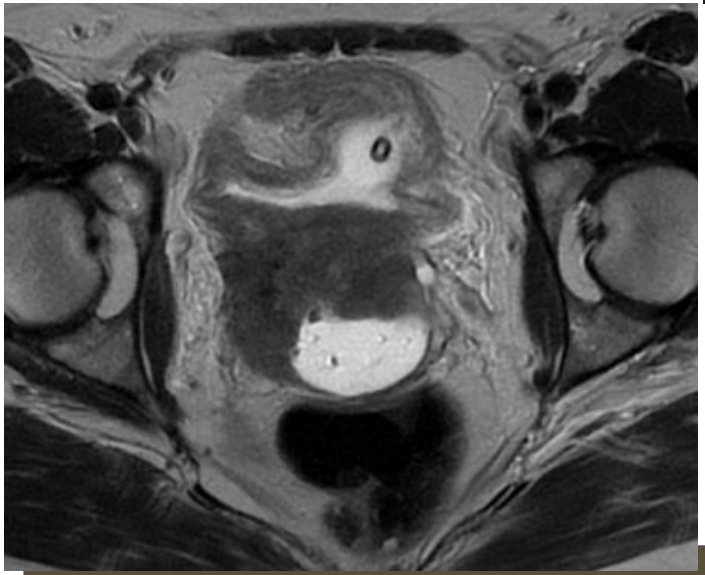
Thickness :6

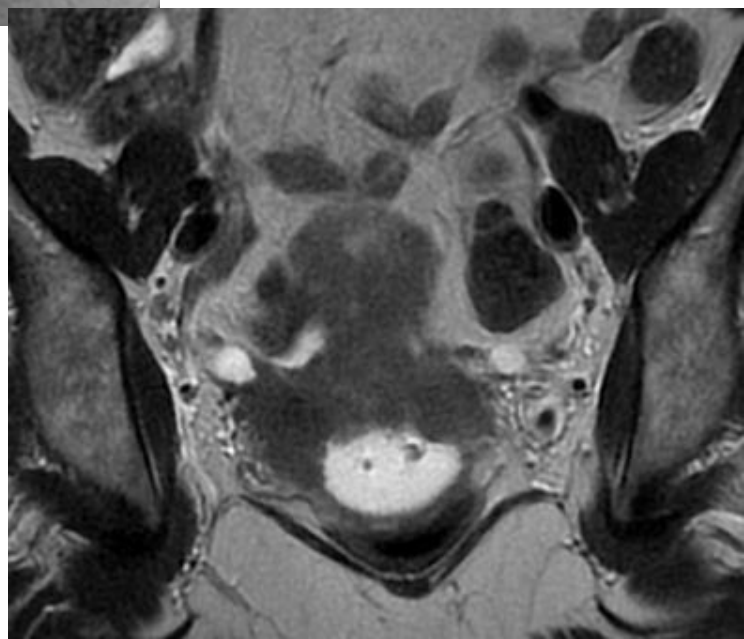
Height : 7

Stage IVA : initial MRI

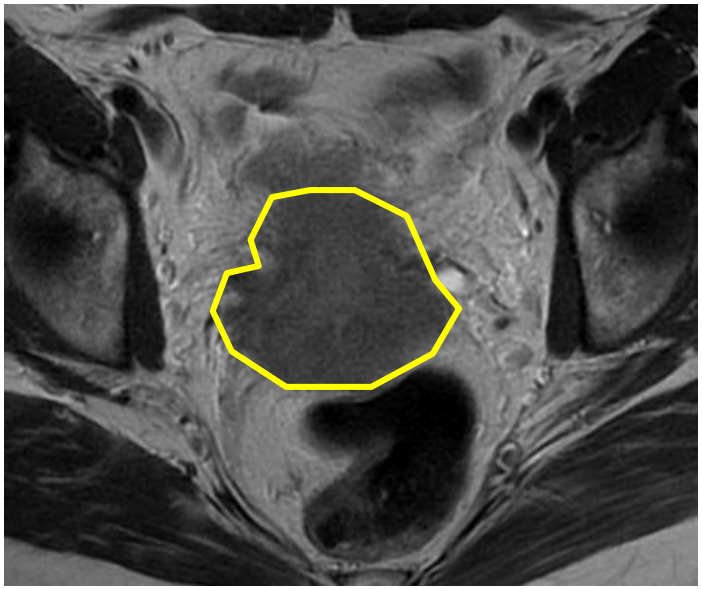


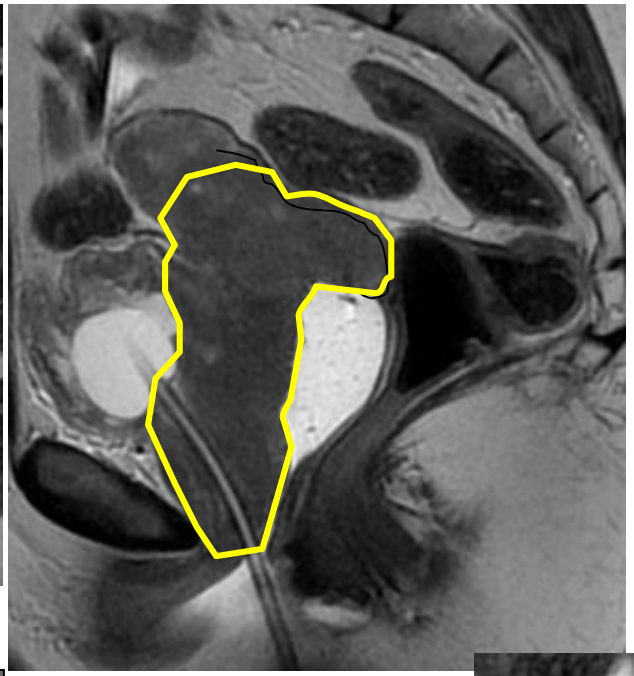


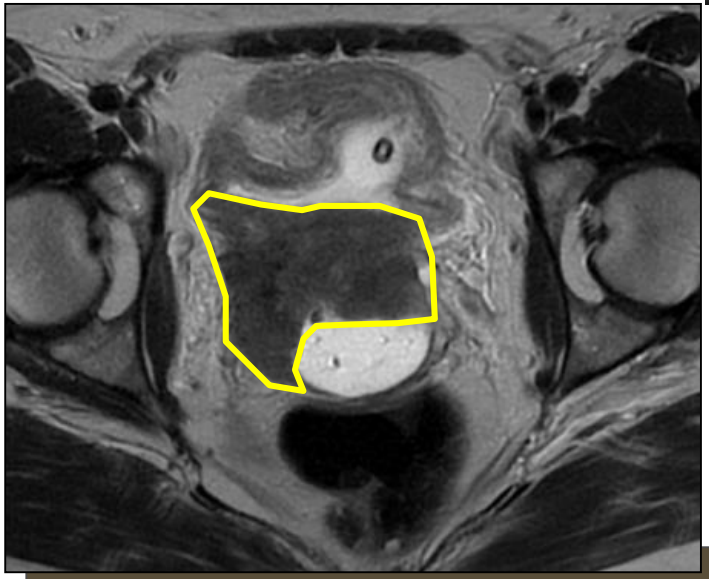


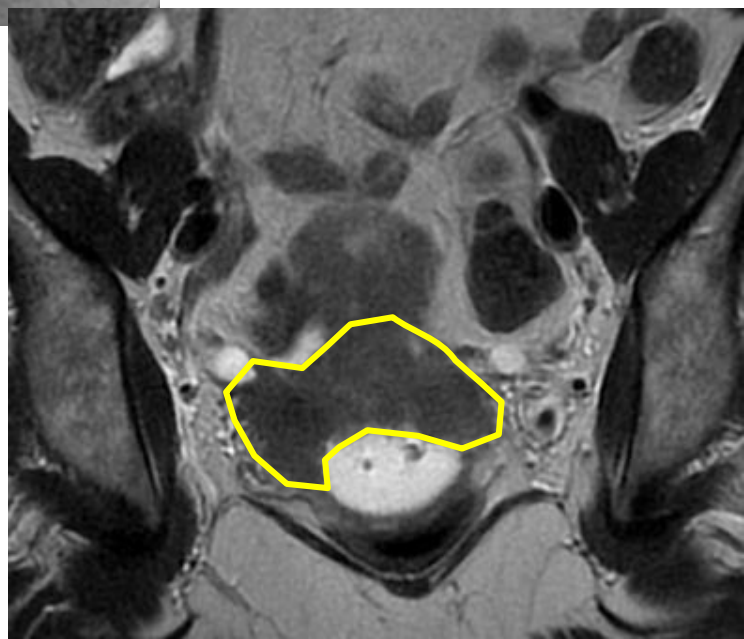


Stage IVA : initial MRI

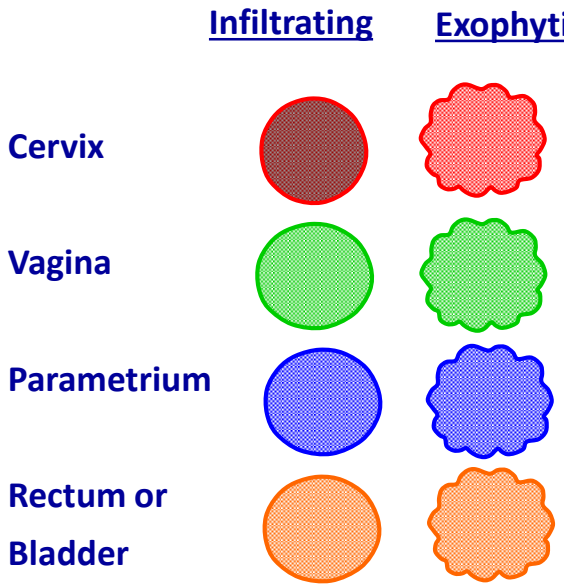


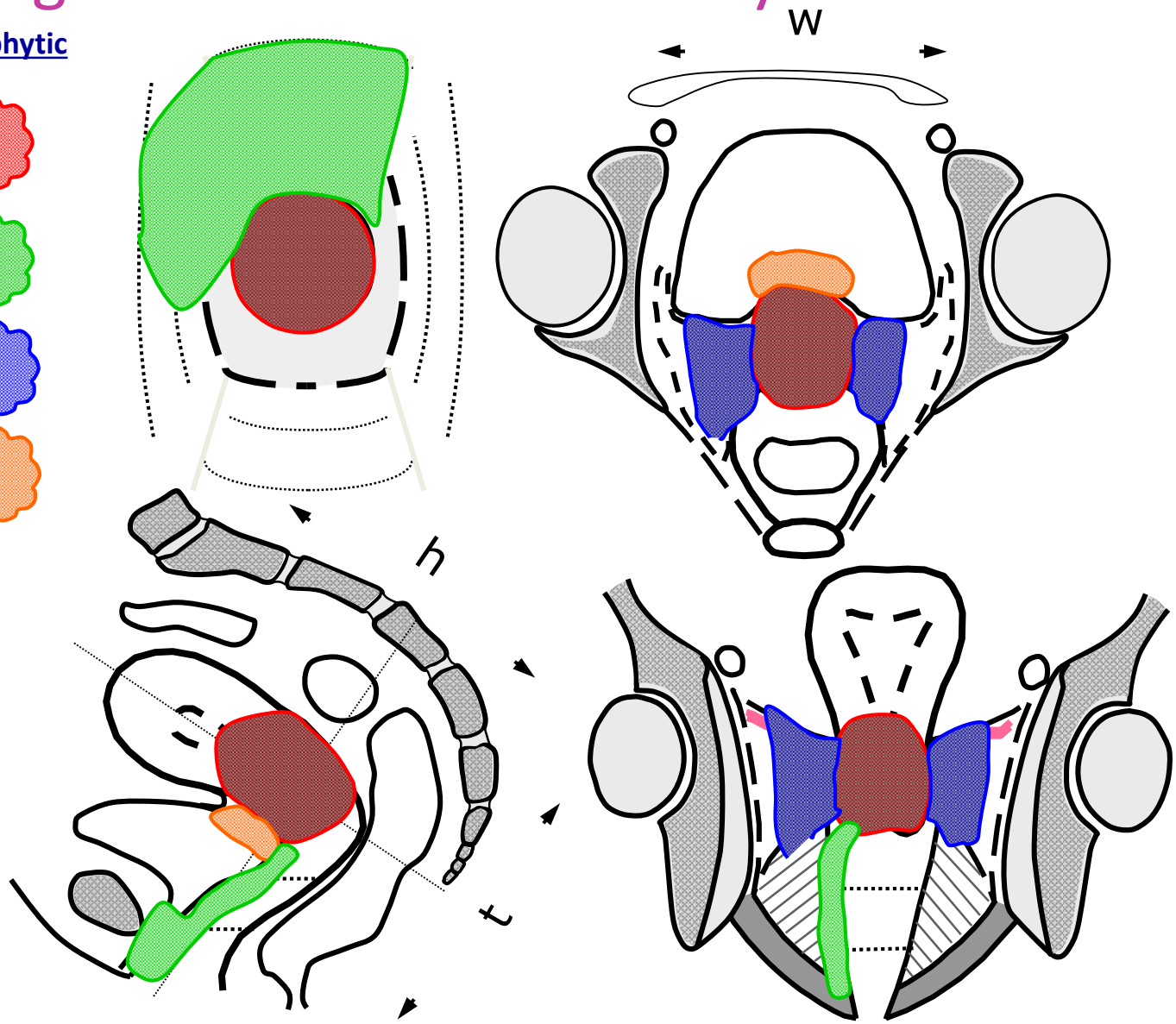






Stage IVA : at time of brachy





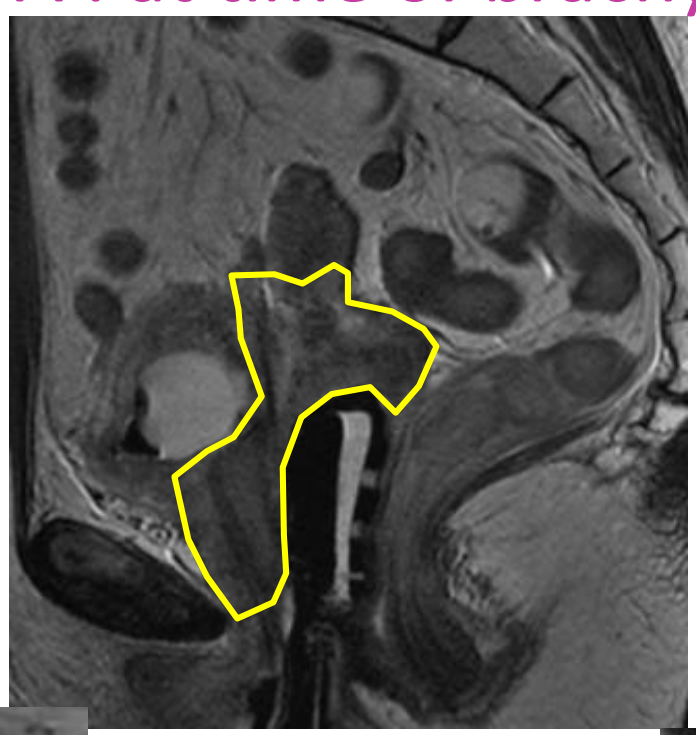
Dimensions (cm):

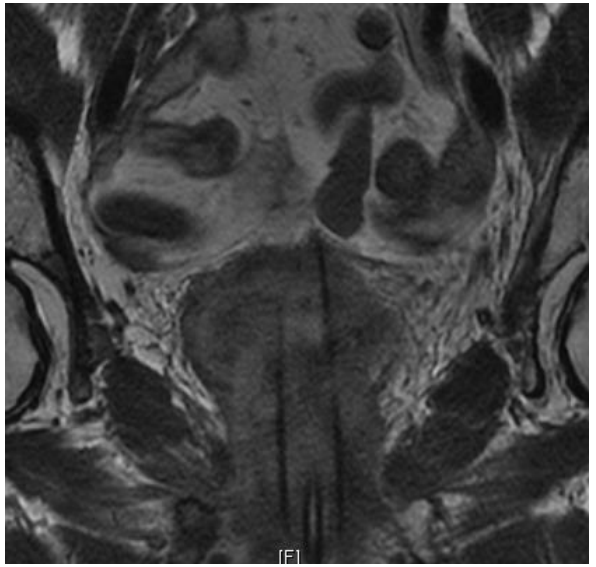
Width : 8

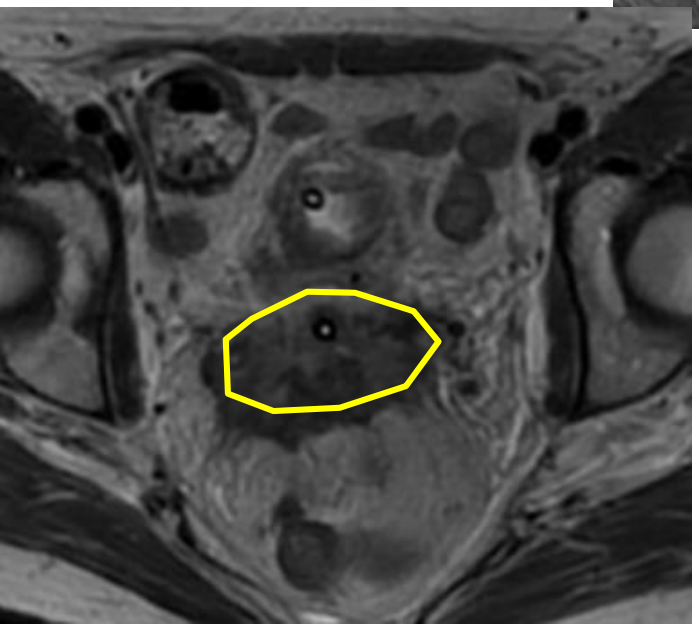
Thickness :6

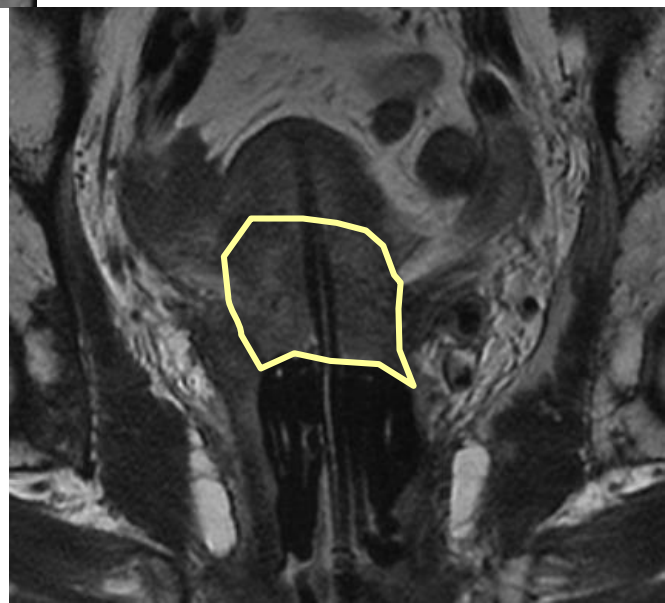
Height : 7

Stage IVA : at time of brachytherapy

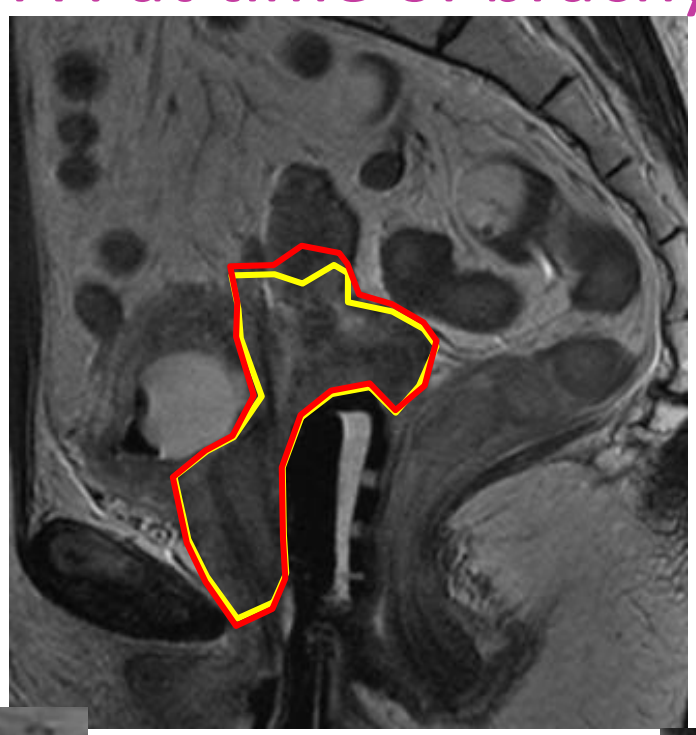


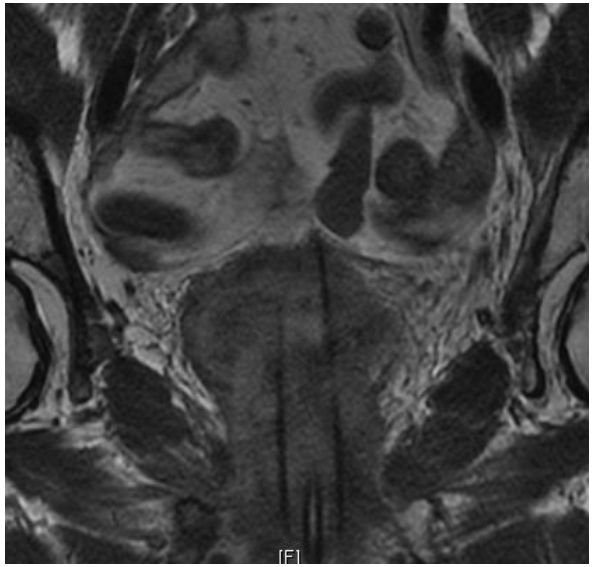


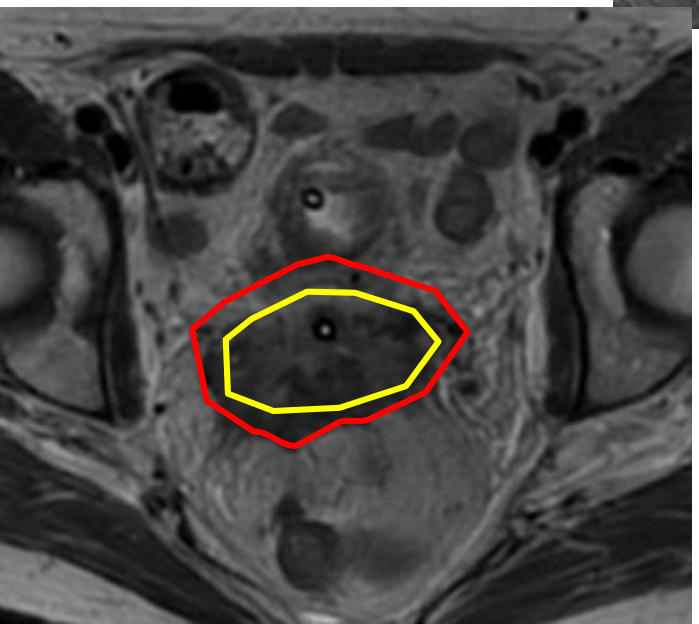


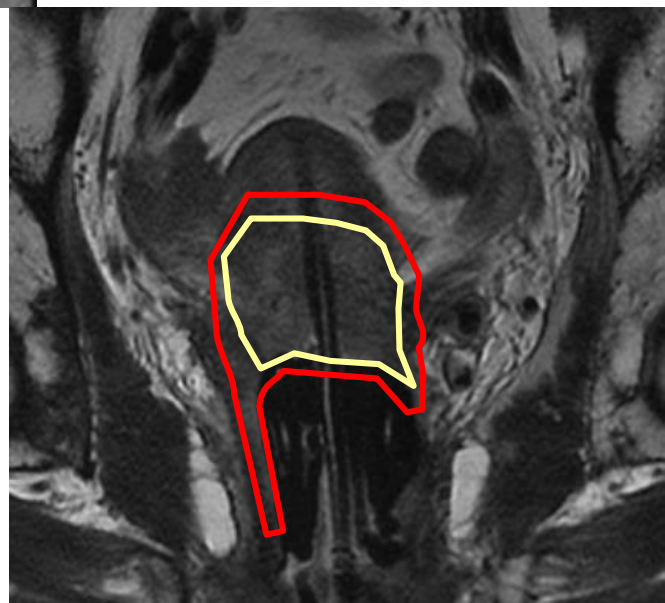


Stage IVA : at time of brachytherapy

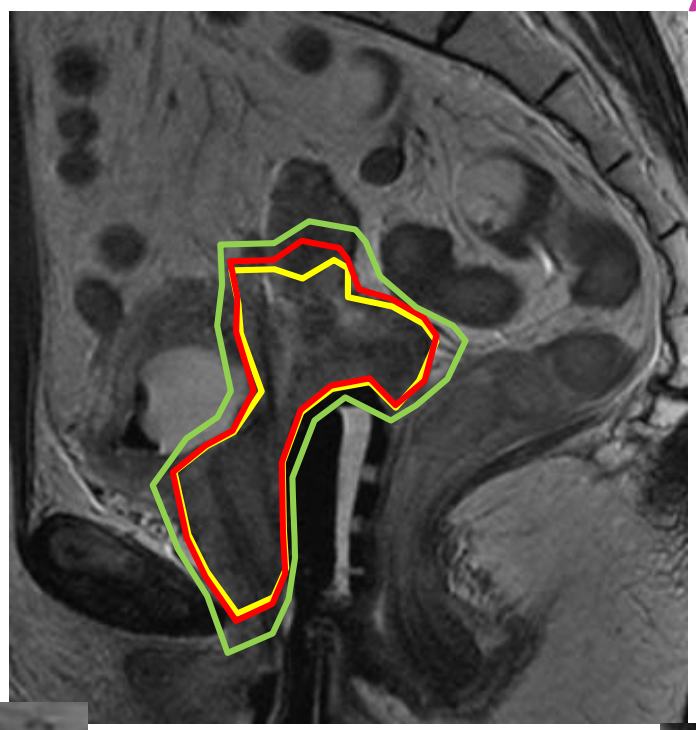


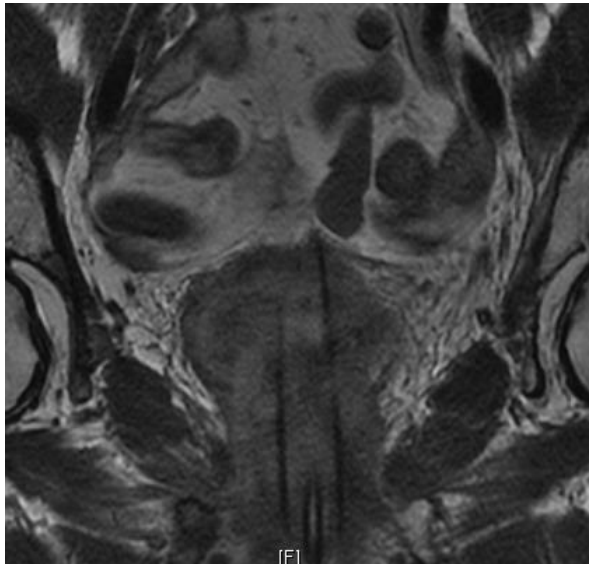


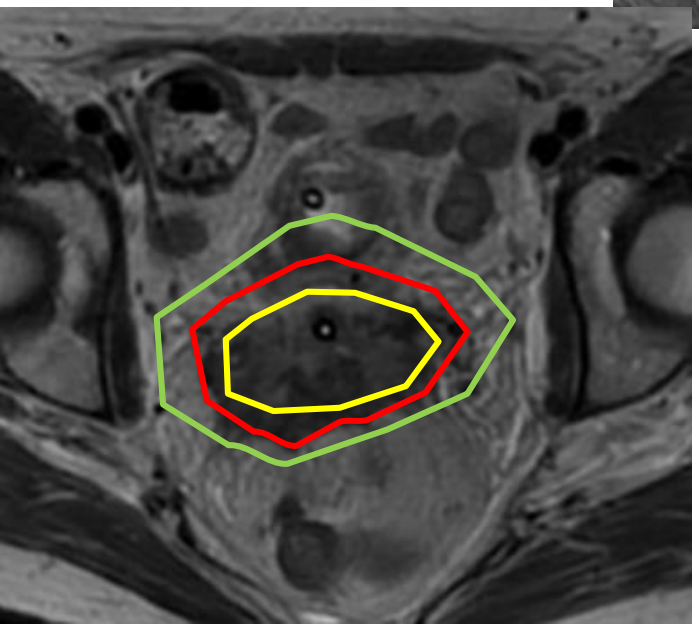


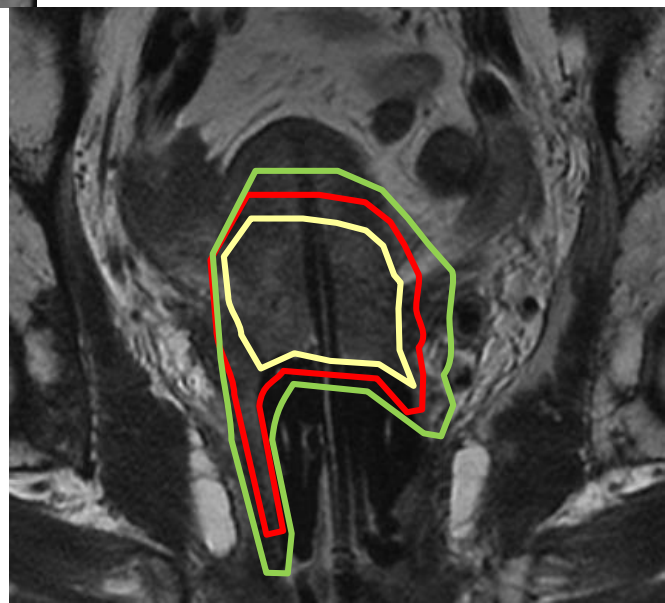


Stage IVA : at time of brachytherapy





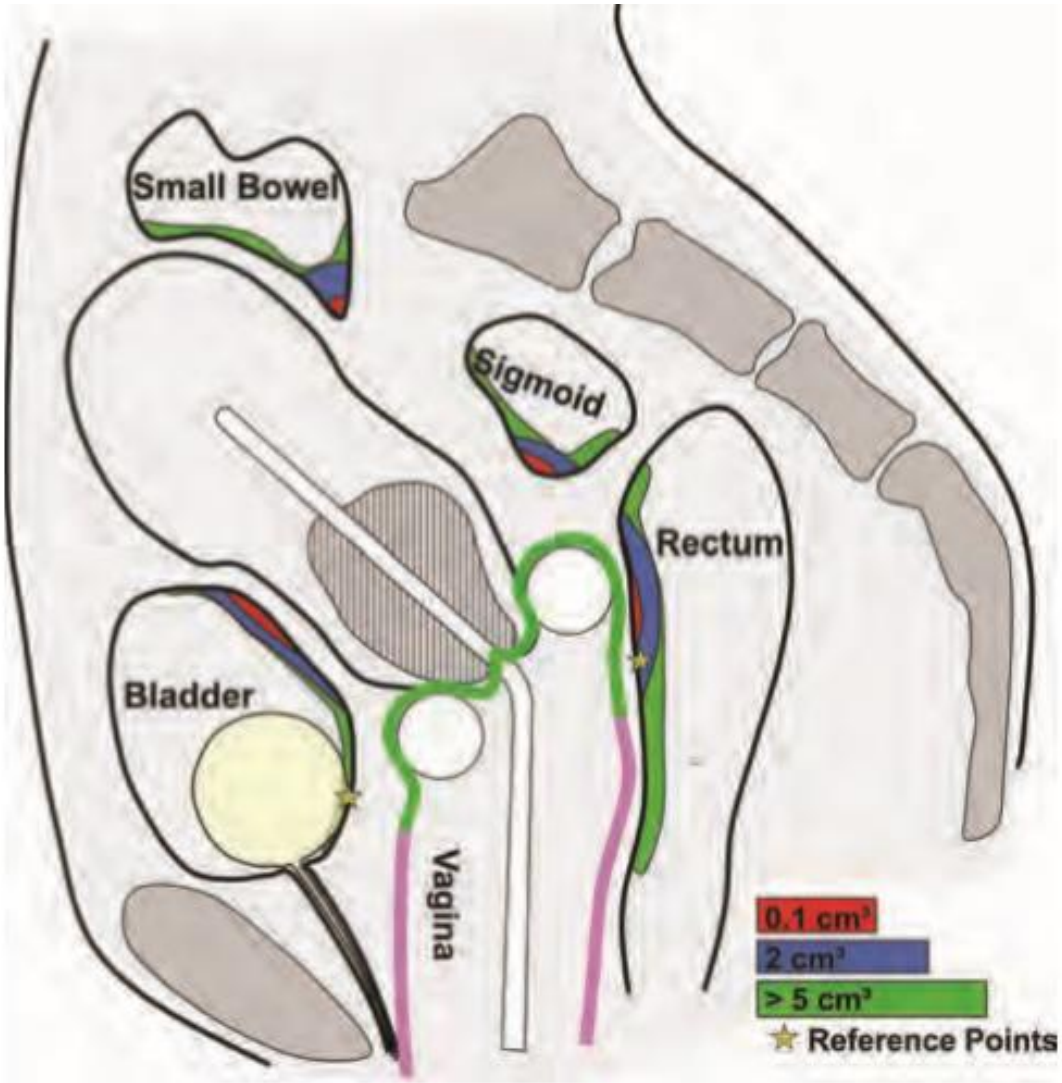




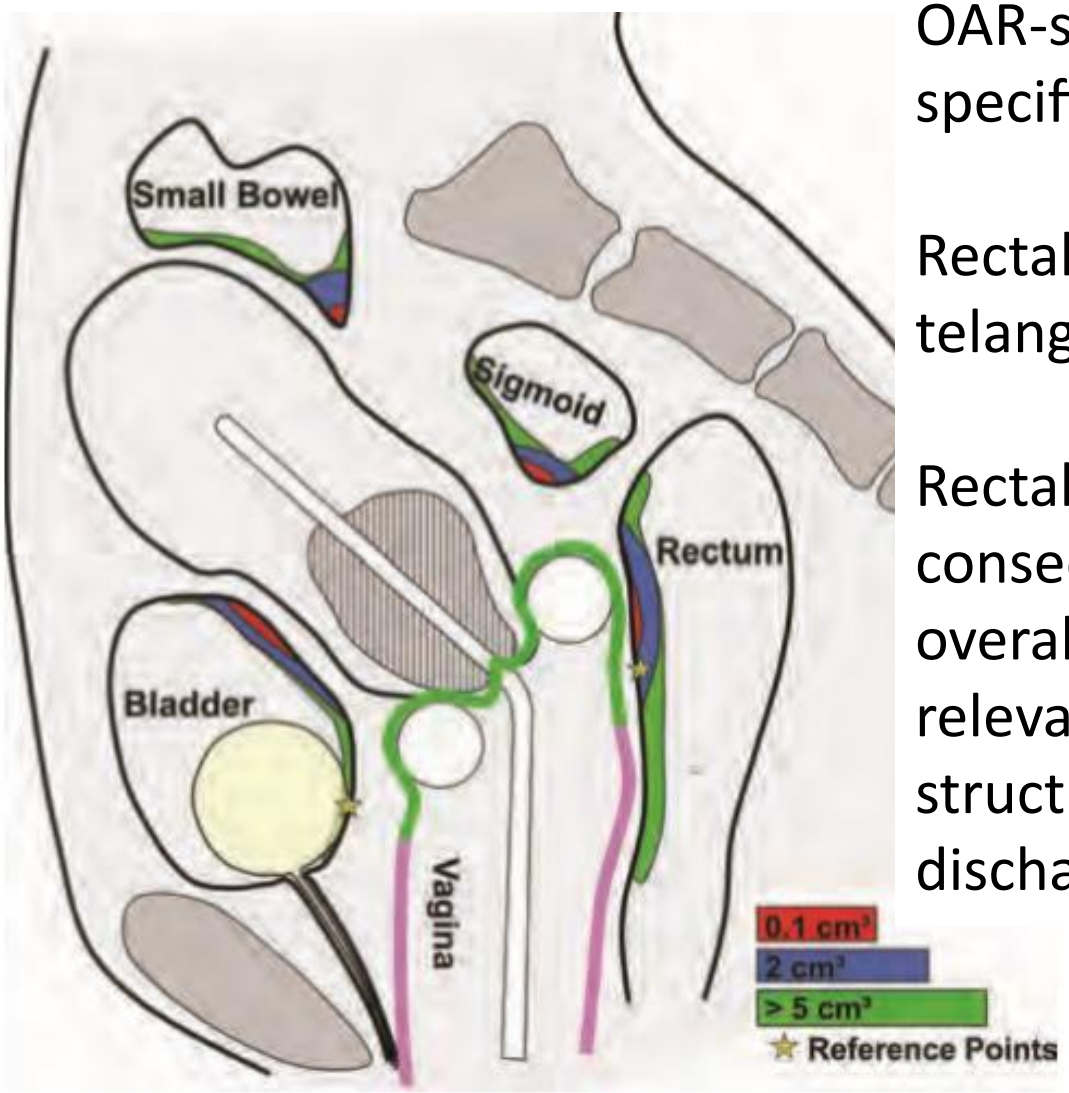
Organs at risk

Organs at risk

Small organ-wall volumes up to 2 cm^3–$3cm^3$
represent typical targets for brachytherapy-related morbidity



Organs at risk



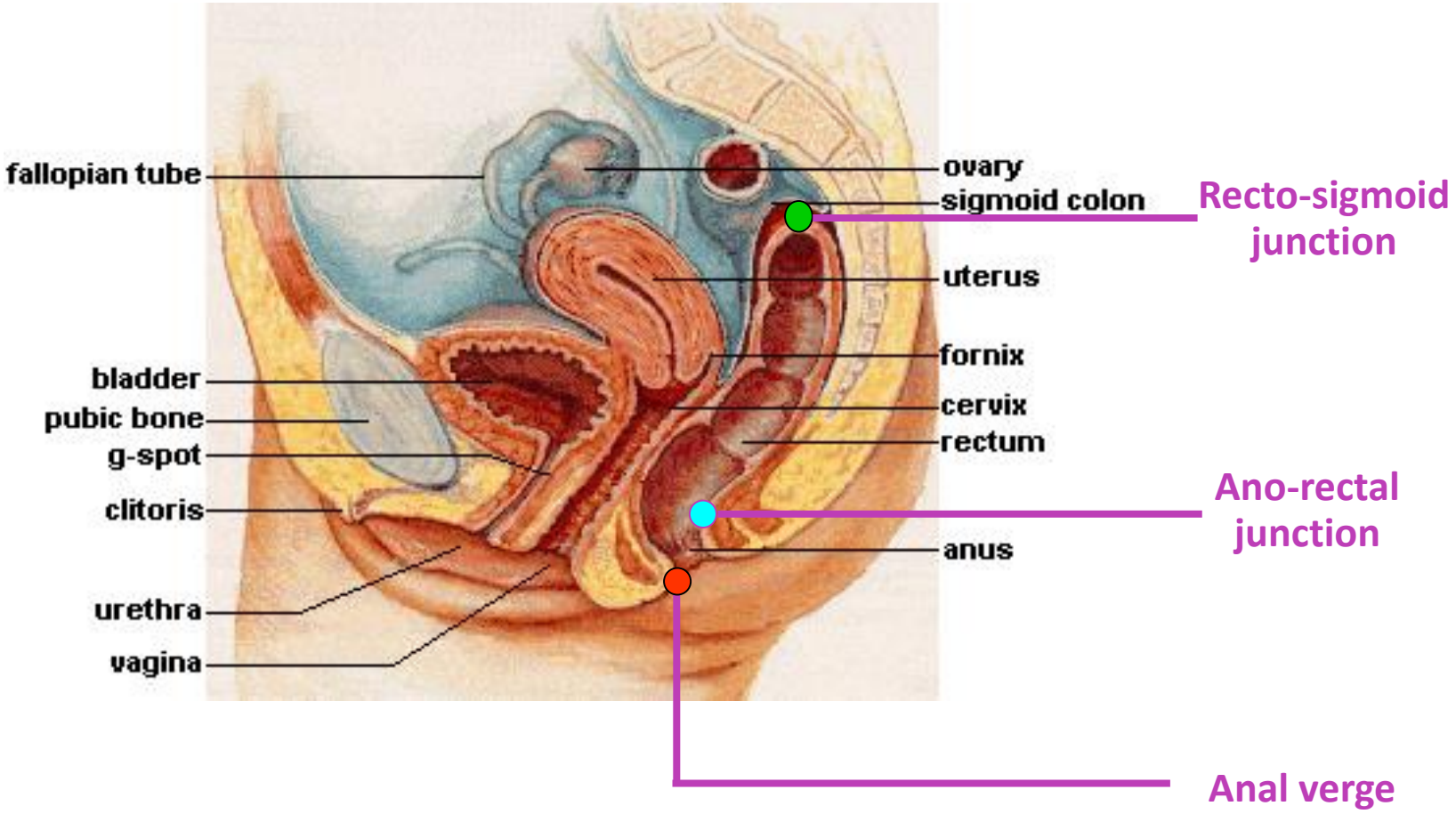
OAR-specific or OAR-sub-volume specific types of morbidity

Rectal and sigmoidal bleeding = telangiectasia even in small volumes

Rectal urgency/ continence = consequence of damage to the overall recto-anal wall, with the relevant muscle and nerve plexus structures regulating the recto-anal discharge

Anorectum

Anatomy



Anorectum

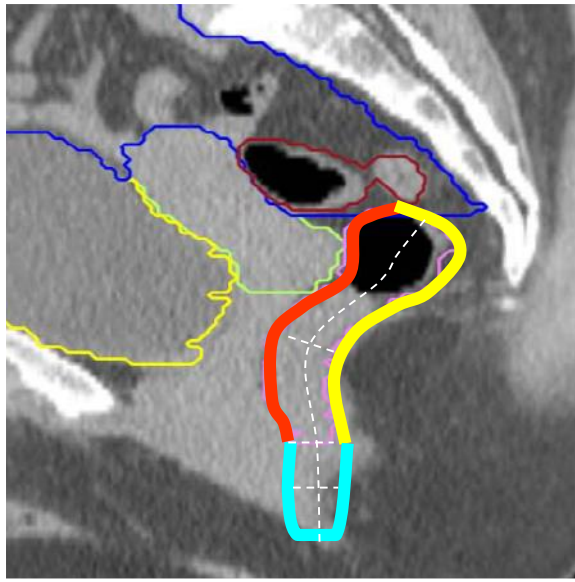
Perspectives

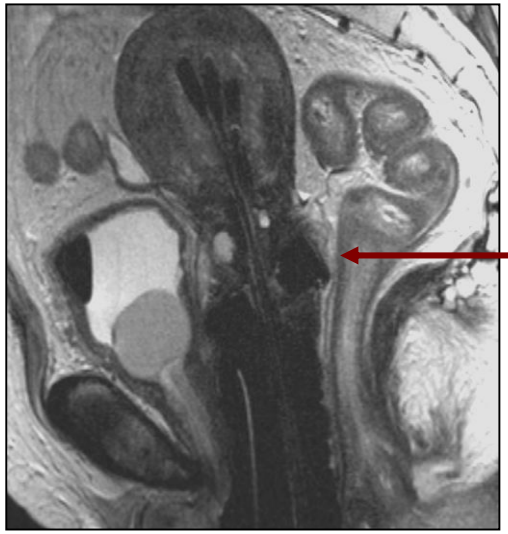
Separate delineation of ano-rectal regions

Separate assessment of DVH to different regions

Separate scoring & modelling of different endpoints

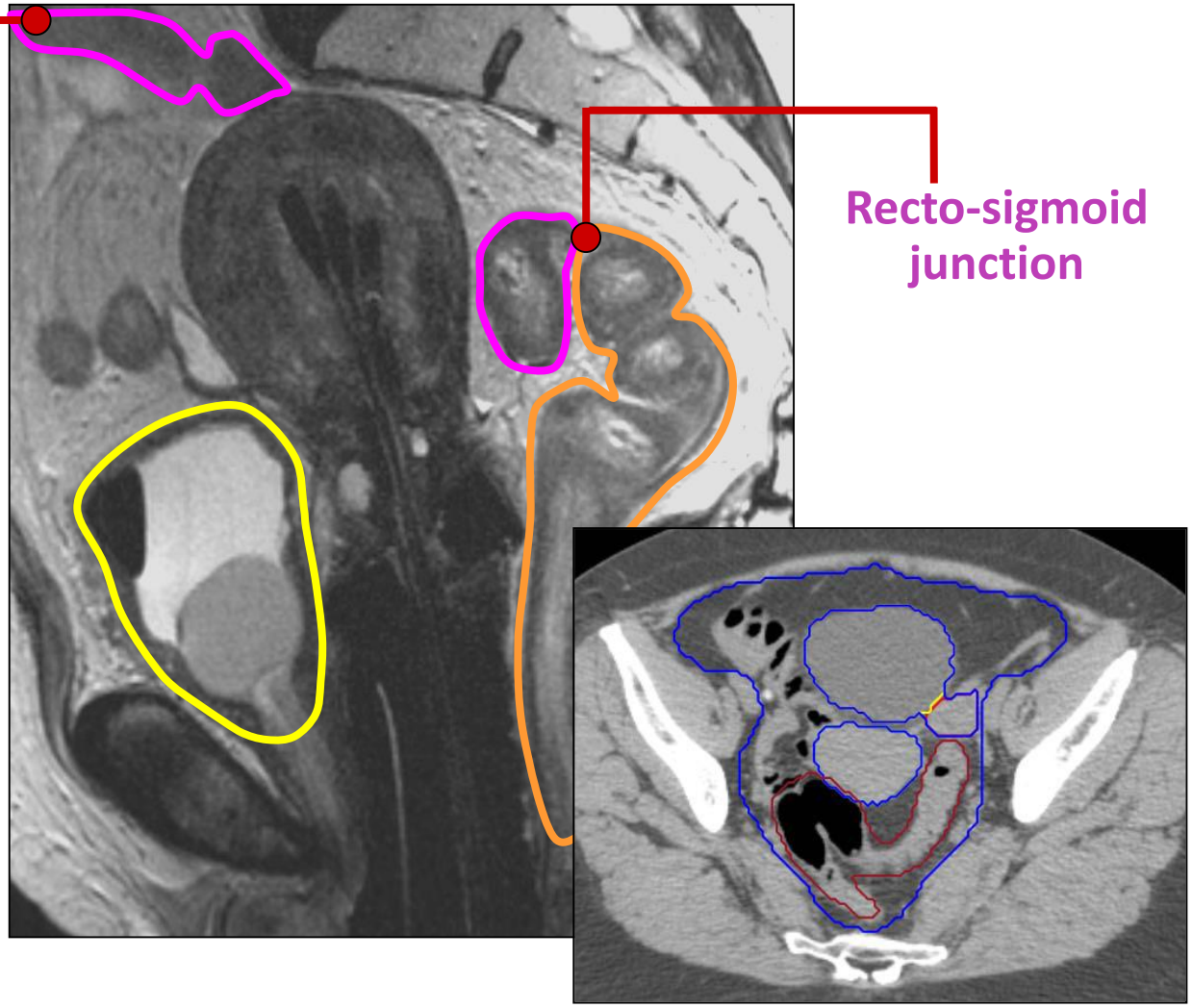
Determination of relevant structures for different endpoints





Sigmoid colon

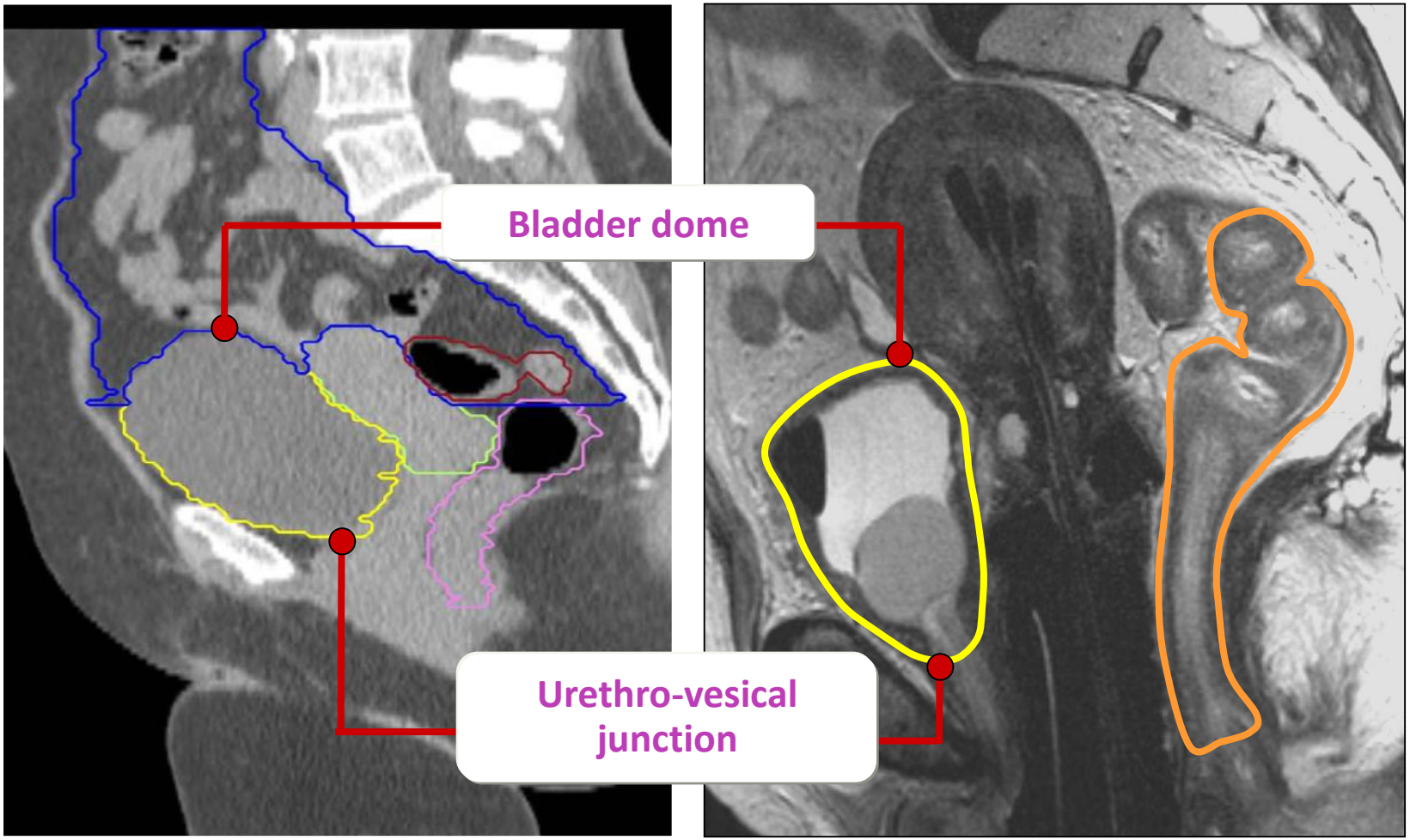
Junction with descending colon (above high dose region)



Recto-sigmoid junction

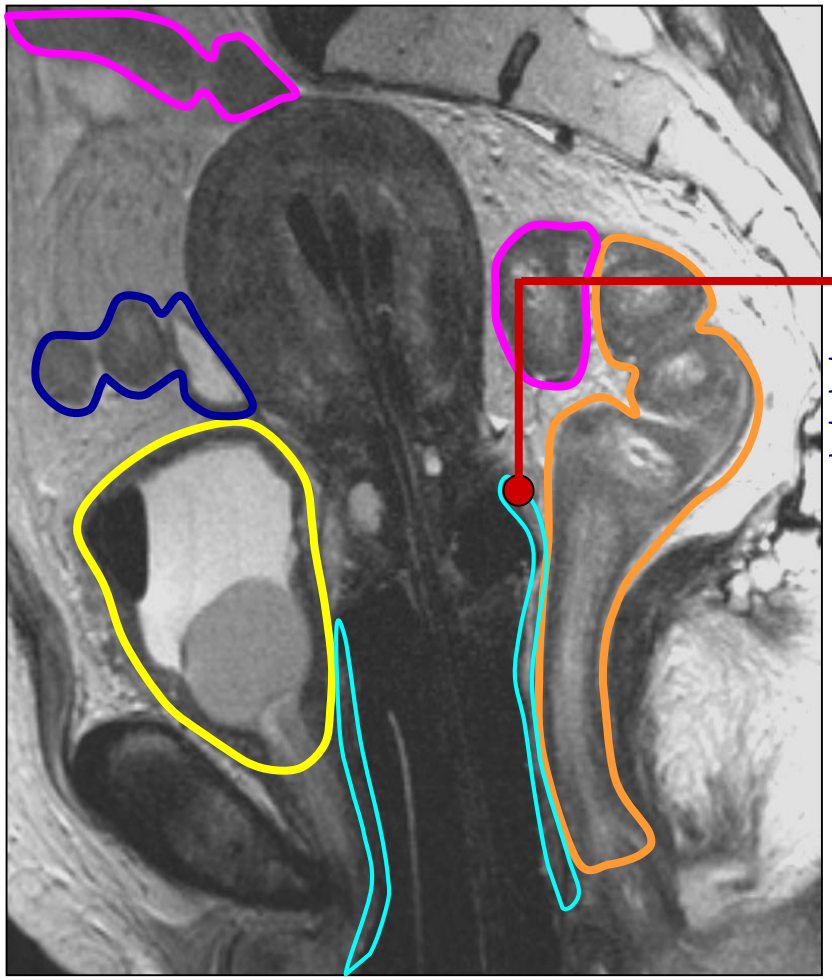
Bladder

What to delineate?



Viswanathan AN, et al. IJROBP 2010

Vagina



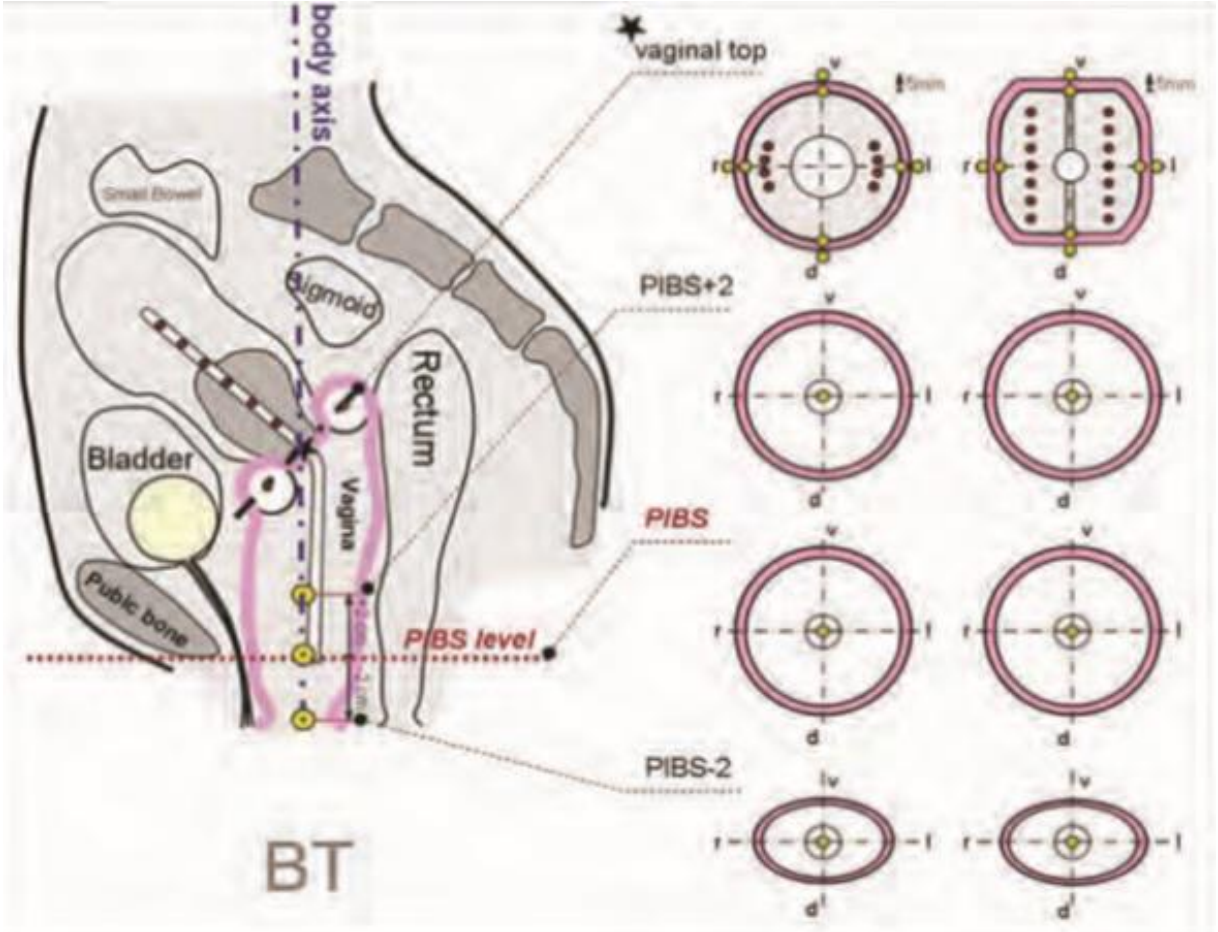
Vaginal wall

Delineation, DVH, Reporting:

- ↑ uncertainties
- ↓ reproducibility

Berger D, et al. IJROBP 2007

Vagina

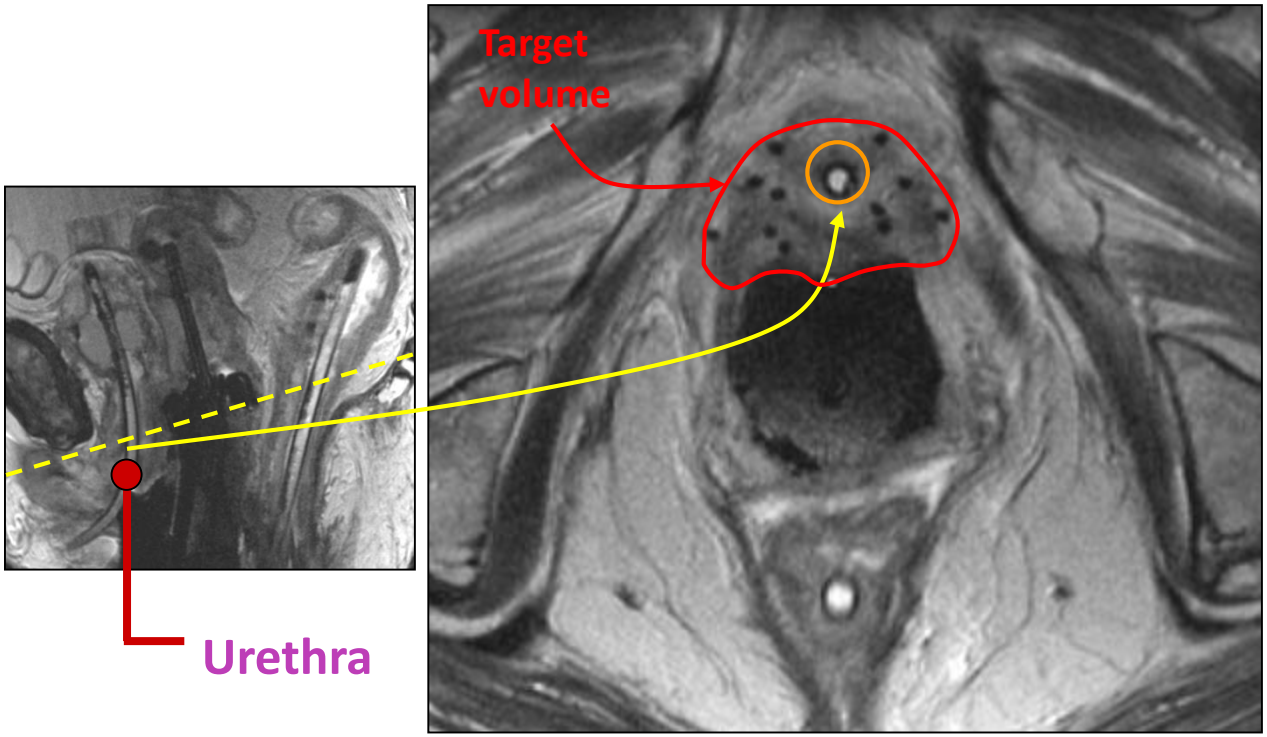


PIBS vaginal-dose point definition : 2 cm posterior from the posterior-inferior border of the pubic symphysis at the point of this line where it crosses the applicator tandem

2 additional points : 2 cm up and down along the vaginal axis PIBS+2 = the mid of the vagina and PIBS-2 = the introitus level

Other organs?

Urethra

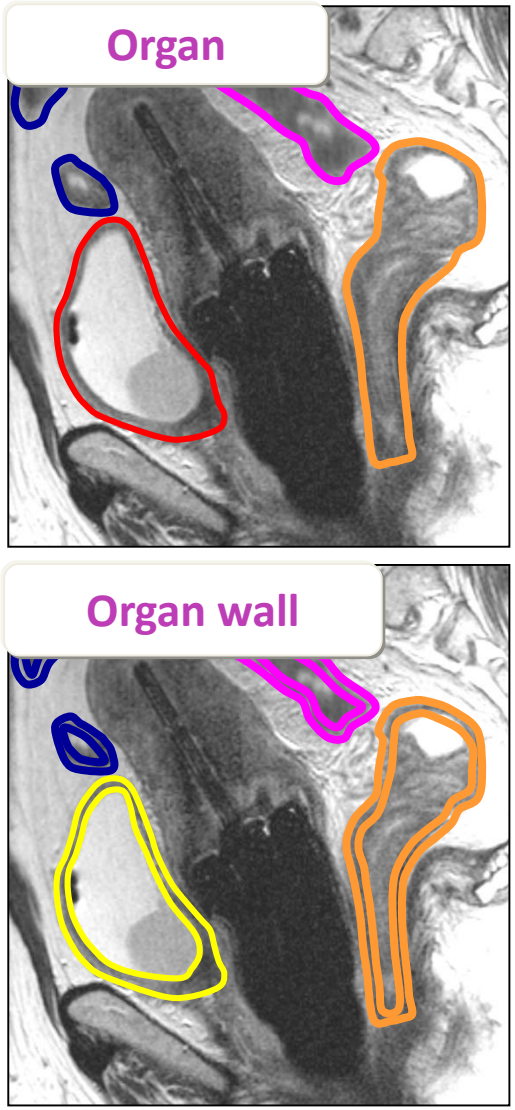


Delineate Organ or Organ wall?

Situation in Brachytherapy

Can we contour organs instead of organ walls?

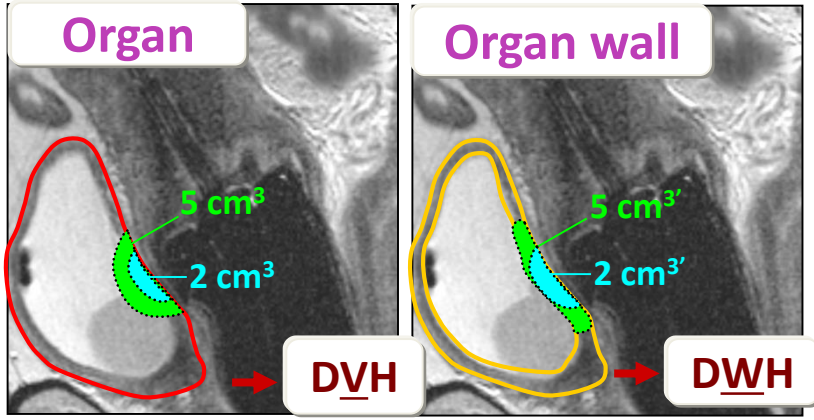
- Wall: More correct
- Demanding & time consuming
- Prone to uncertainties

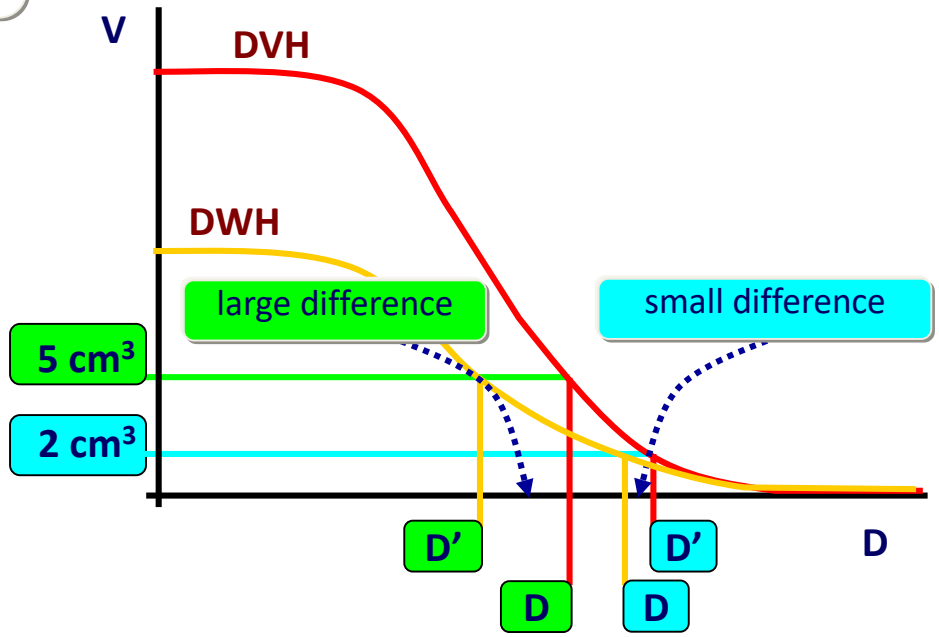


Delineate Organ or Organ wall?

Situation in Brachytherapy

Can we contour organs instead of organ walls?





Yes, if doses up to 2 cm³ are evaluated

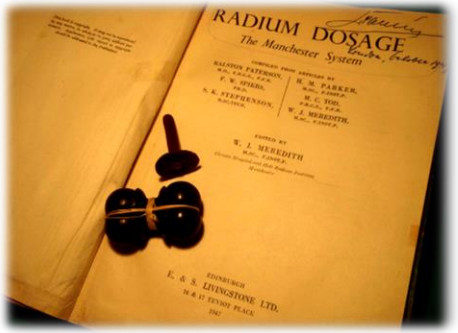
Olszewska AM. Radiother Oncol 2001;61:83-85

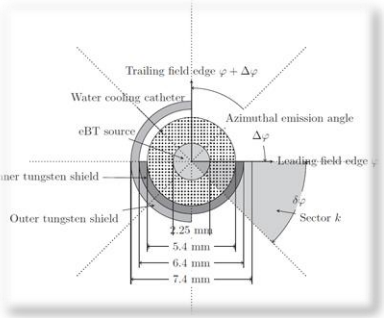
Conclusion

- Importance of GTV and CTV for the primary tumor
- Residual GTV-T (GTV-T_{res})
- Adaptive CTV-T (CTV-T_{adapt})
- High-Risk CTV-T (CTV-THR)
- Intermediate-Risk CTV-T (CTV-TIR)
- OAR delineation

Intracavitary Brachytherapy for Cervical Cancer

Techniques & Limitations



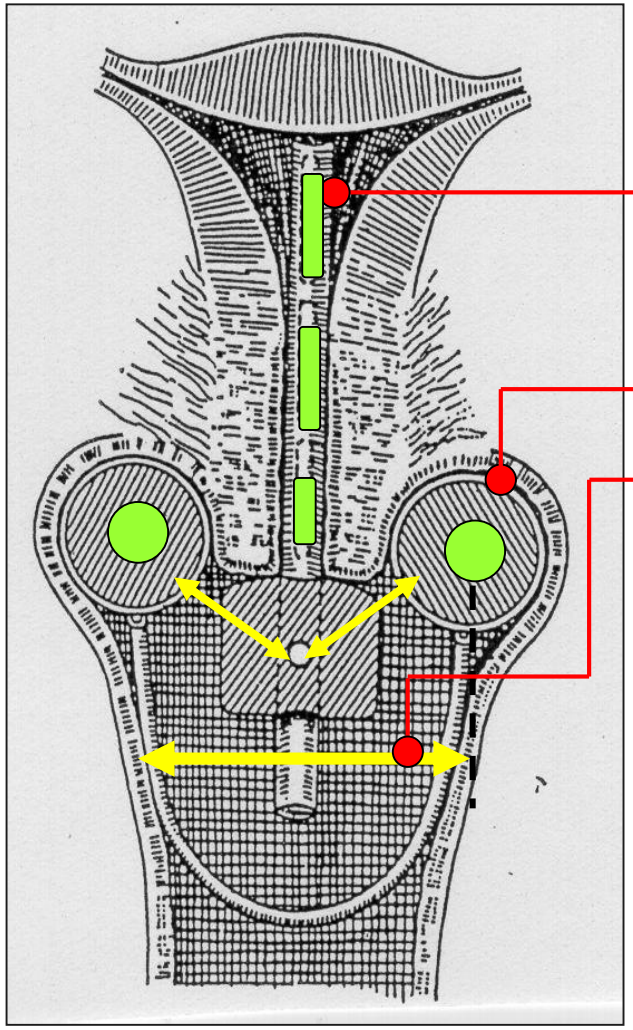


Primoz Petric

Aarhus University Hospital, Denmark

Historical Paris Technique

1910-1920: Curie Institute, Paris, France



GEC ESTRO Handbook of Brachytherapy

Applicator:

- Rubber tandem
- Cork colpostats (paraffin coated)

→ not connected

- Distance – colpostats: not fixed

→ no fixed geometry

^{226}Ra preloading

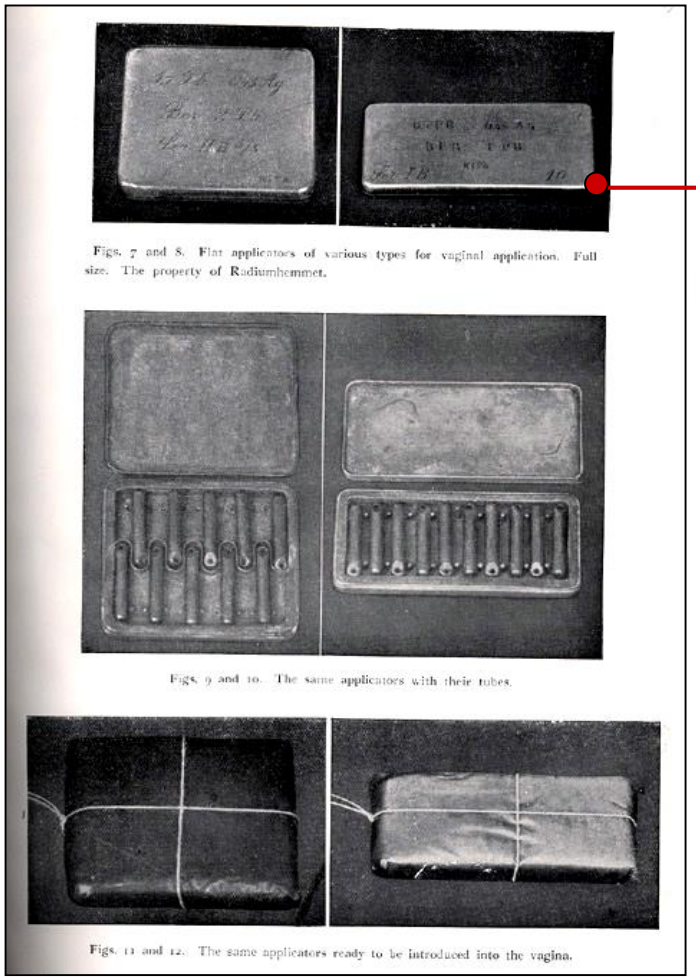
- X mg of ^{226}Ra for Y hours

Typical application

- ≈ 5 days (*120 h*)
- 7000-8000 mgh

Classical Stockholm method

1913-1914: Radiumhemmet, Stockholm, Sweden

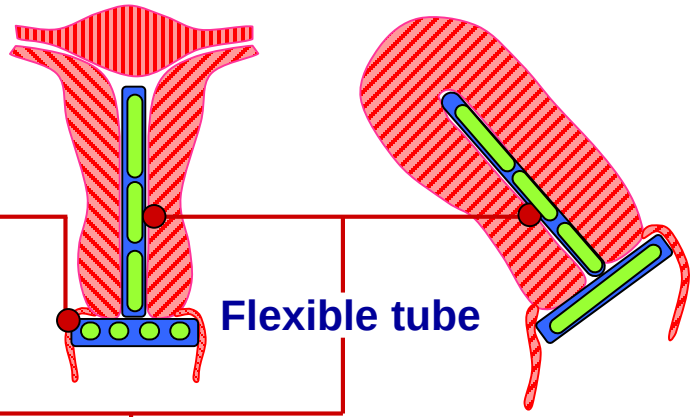


Figs. 7 and 8. Flat applicators of various types for vaginal application. Full size. The property of Radiumhemmet.

Figs. 9 and 10. The same applicators with their tubes.

Figs. 11 and 12. The same applicators ready to be introduced into the vagina.

Applicator:



Flat box (plate) **Flexible tube**

not connected → No fixed geometry

^{226}Ra preloading

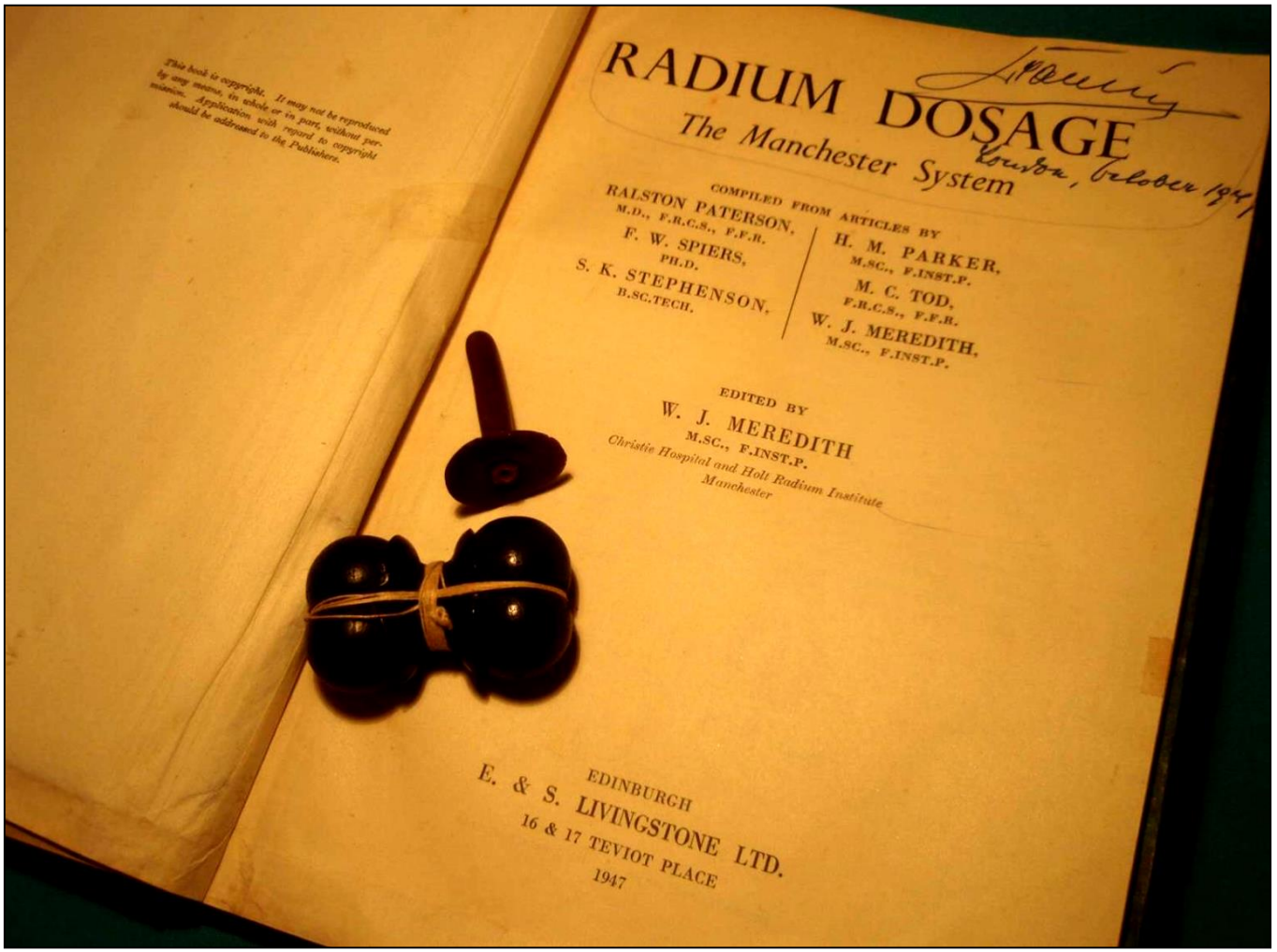
- **X mg of ^{226}Ra for Y hours**

Typical treatment

- **2 – 3 applications (á 20-30 h)**
- **≈ 7000 mgh**

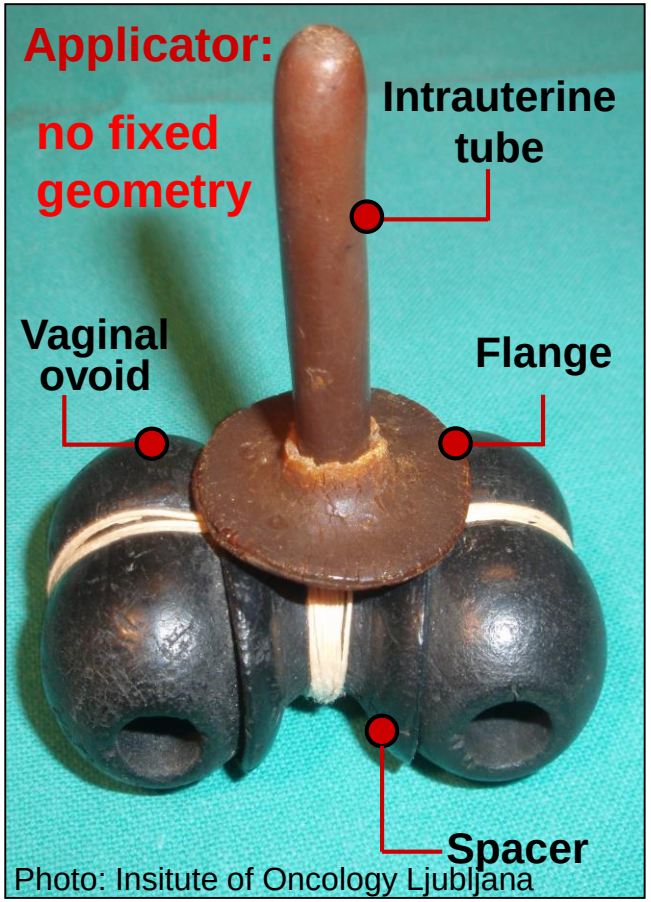
Historical Manchester System

1938: Holt Radium Institute, Manchester, England



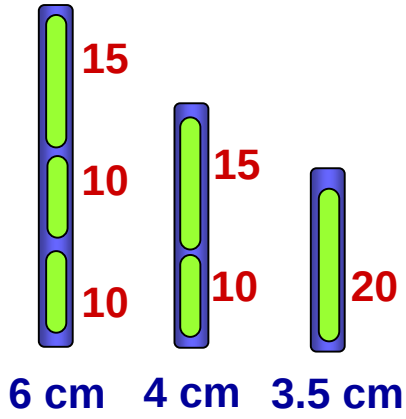
Historical Manchester System

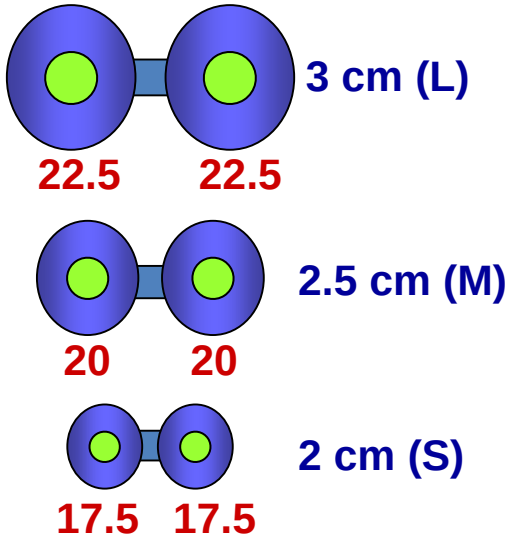
Related to historical Paris technique

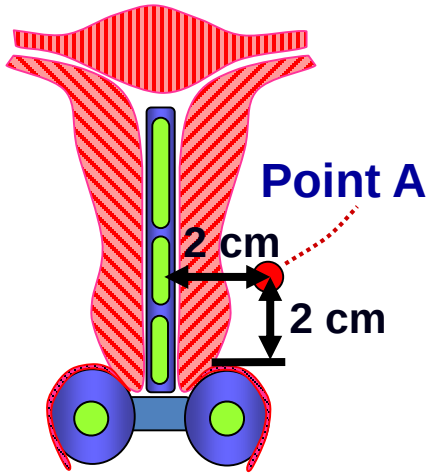


TYPICAL TREATMENT:
140 hours for 7500 R at point A
(dose rate 53 R/h)

^{226}Ra preloading (mg):







Given tumour volume

↓

A set of rules

- **Geometry**
- **mg of ^{226}Ra**
- **Duration**

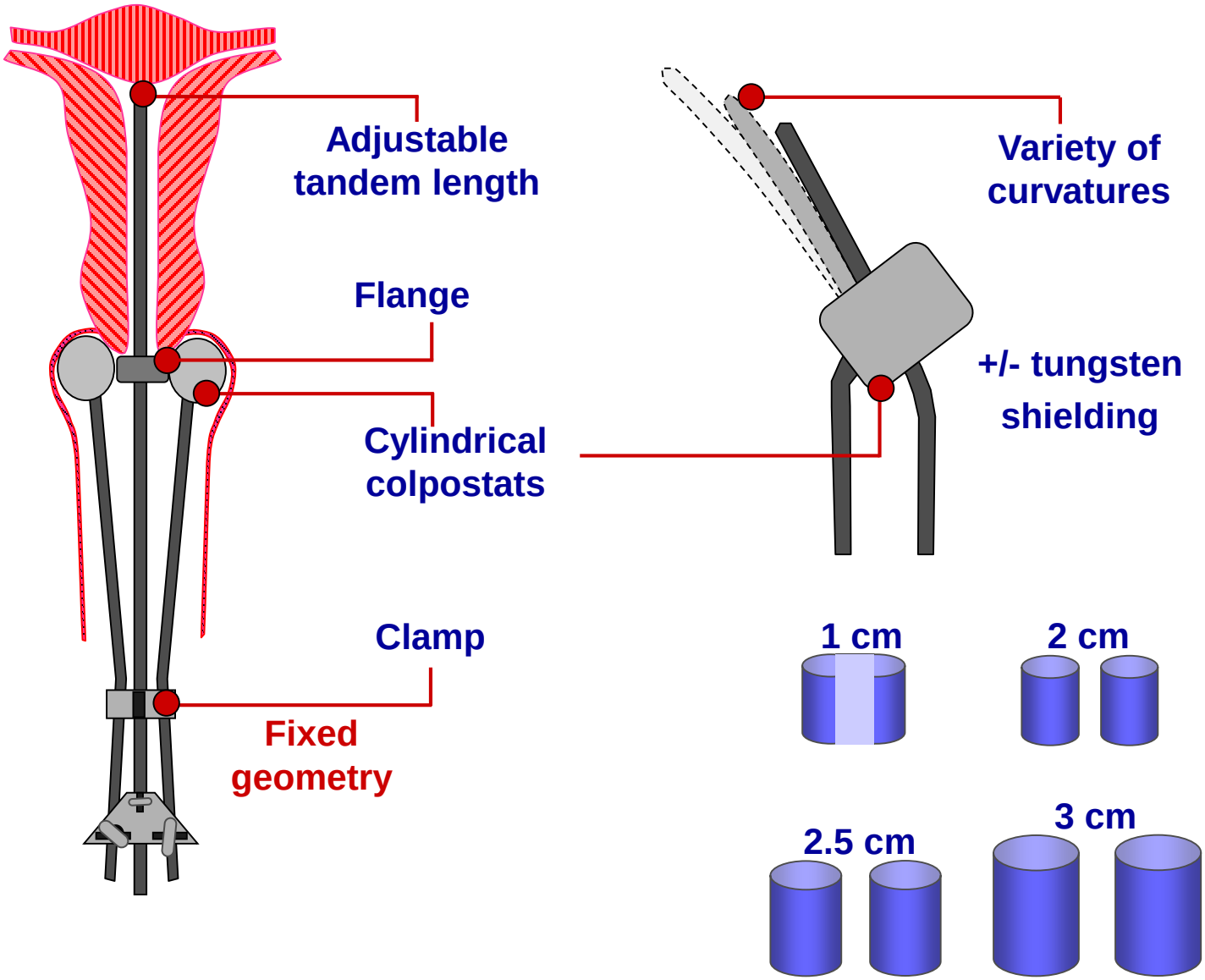
↓

Certain point A dose

Meredith WJ, ed.. Radium dosage. The Manchester system. Edinburgh;1947.

Fletcher–Suit–Delclos–Horiot Technique

1950's: Fletcher

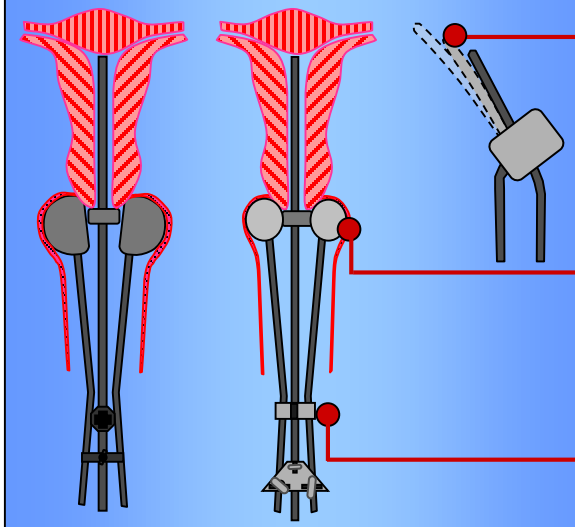


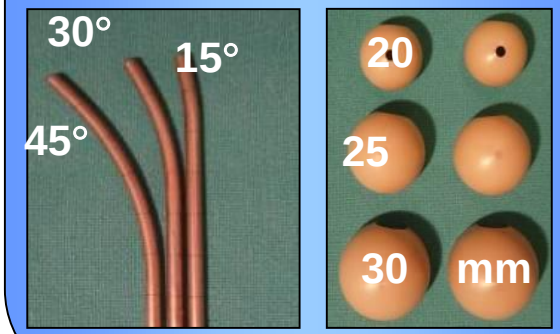
Modern Intracavitary Techniques

Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style

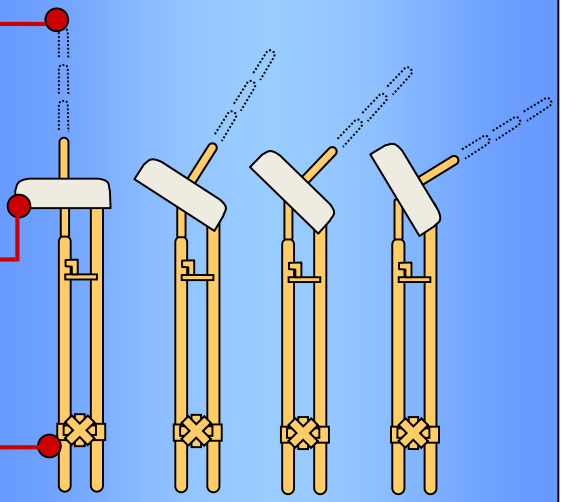


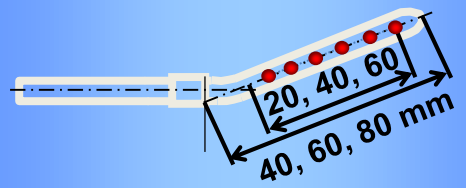


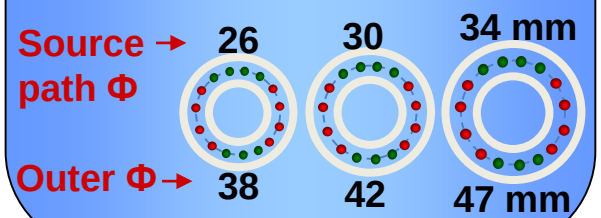
Common features:

- **Uterine Tandem:** various lengths, angles or curvatures
- **Ovoids, cylinders, rings** various outer & source path diameters
- **Clamp**

Stockholm style



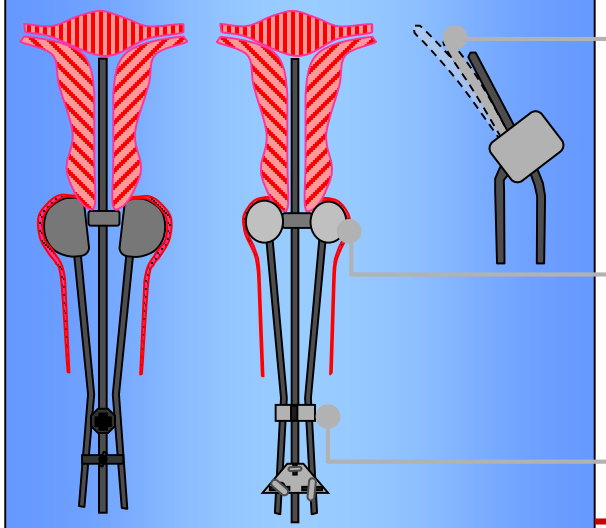




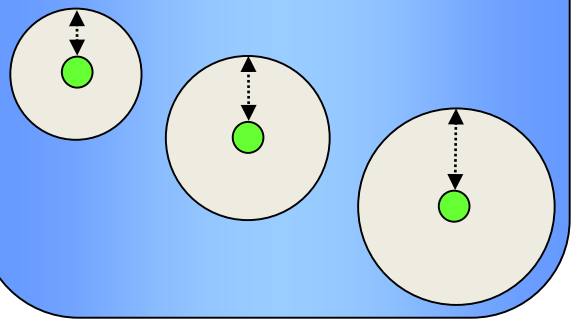
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Varies with diameter



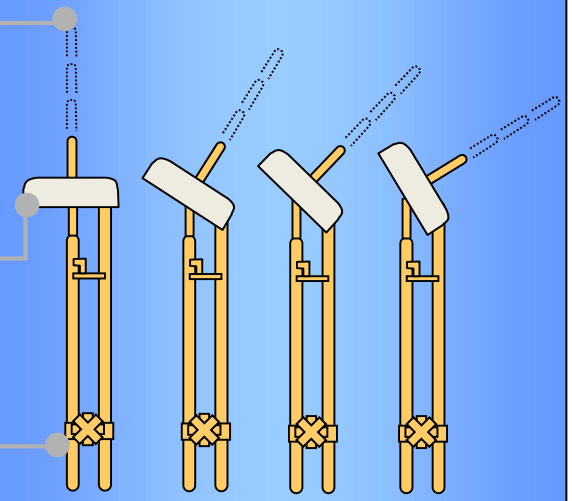
Common features:

- Uterine Tandem: various lengths, angles or curvatures
- Ovoids, cylinders, rings various outer & source path diameters
- Clamp

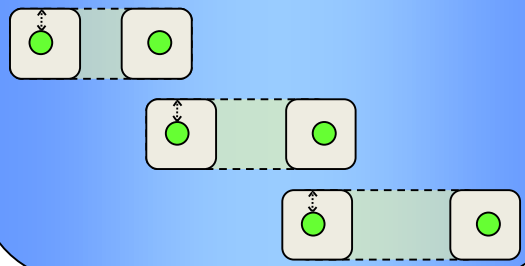
Differences:

Thickness of ovoids and rings

Stockholm style



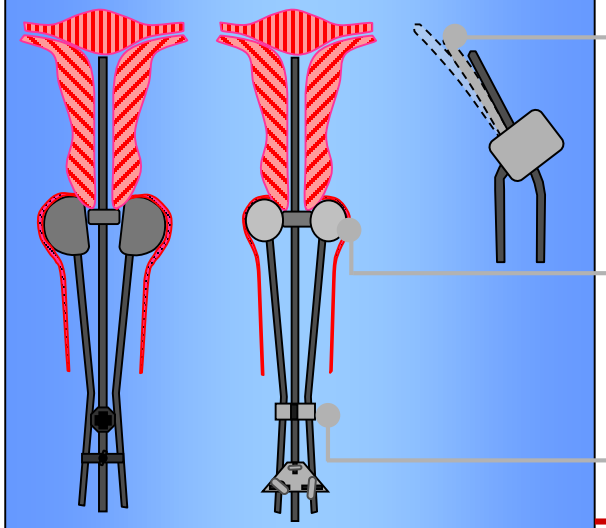
Constant



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



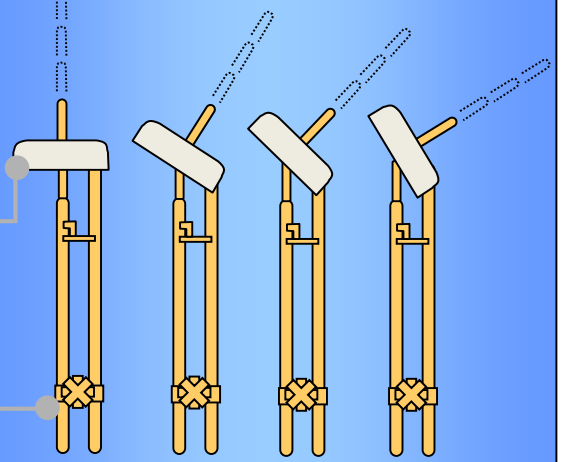
Common features:

Uterine Tandem: various lengths, angles or curvatures

Ovoids, cylinders, rings various outer & source path diameters

Clamp

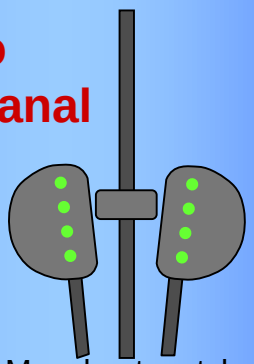
Stockholm style



Differences:

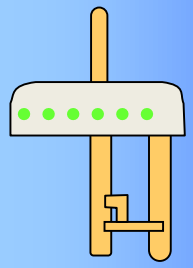
Source path orientation

Parallel to cervical canal



Manchester style

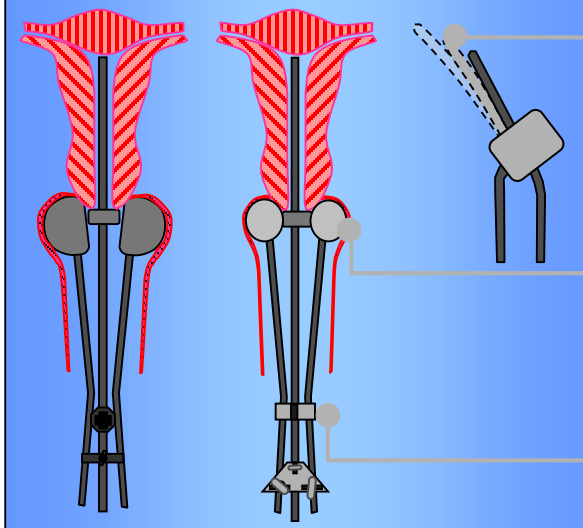
Perpendicular to cervical canal



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Common features:

Uterine Tandem: various lengths, angles or curvatures

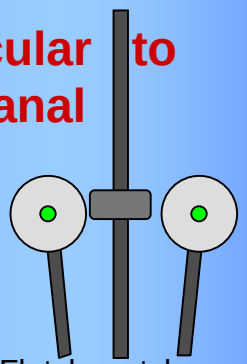
Ovoids, cylinders, rings various outer & source path diameters

Clamp

Differences:

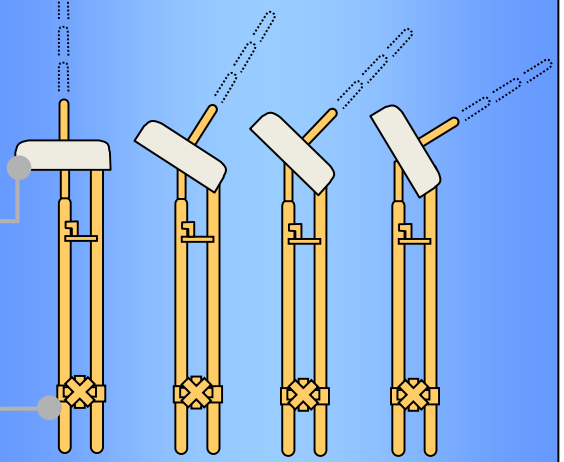
Source path orientation

Perpendicular to cervical canal

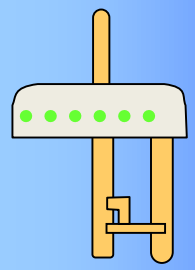


Fletcher style

Stockholm style



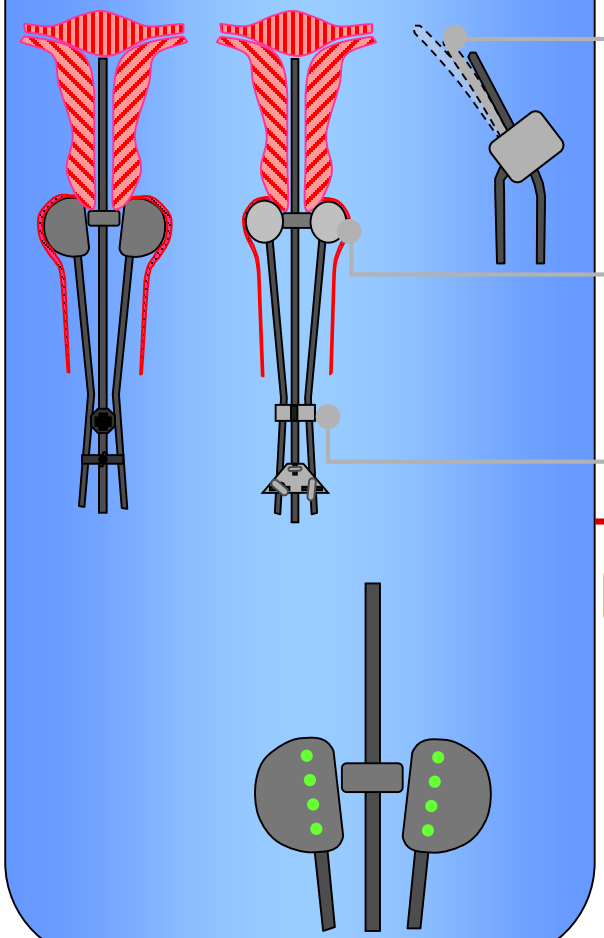
Perpendicular to cervical canal



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



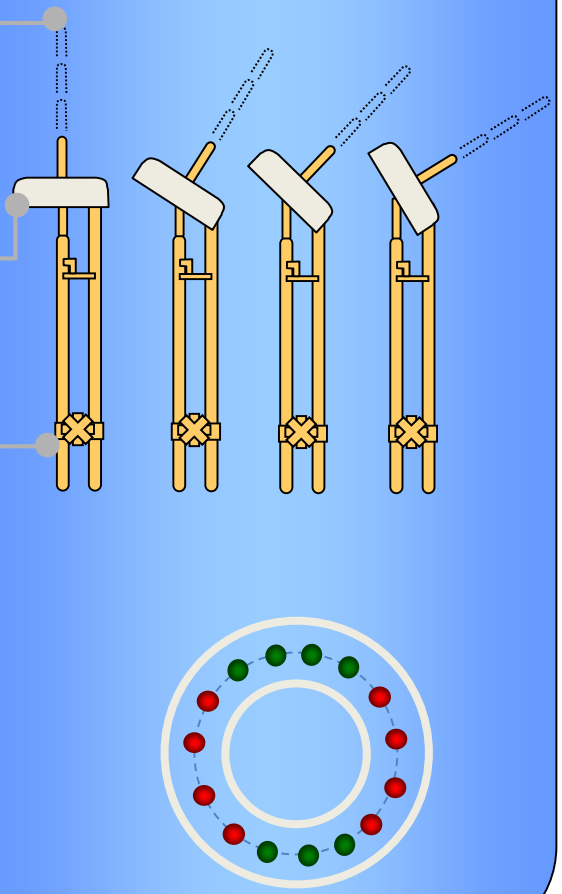
Common features:

- Uterine Tandem: various lengths, angles or curvatures
- Ovoids, cylinders, rings various outer & source path diameters
- Clamp

Differences:

Loading flexibility

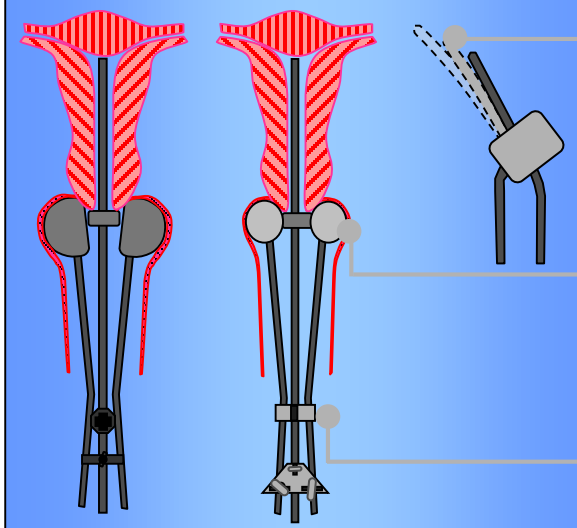
Stockholm style



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



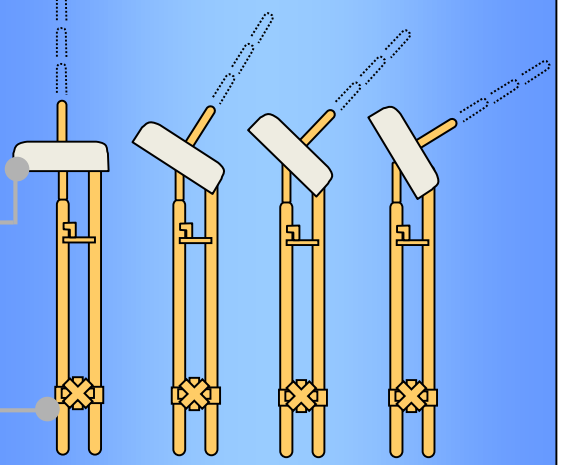
Common features:

Uterine Tandem:
various lengths,
angles or curvatures

Ovoids, cylinders, rings
various outer & source
path diameters

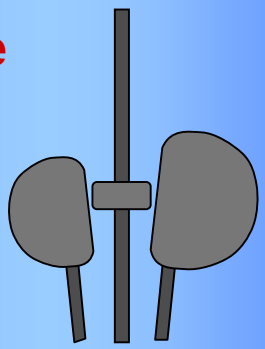
Clamp

Stockholm style



Differences:

Possible



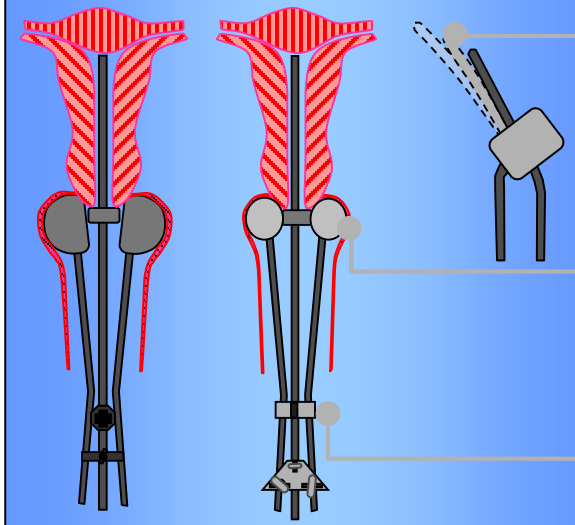
Asymetric insertion

Not applicable

Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



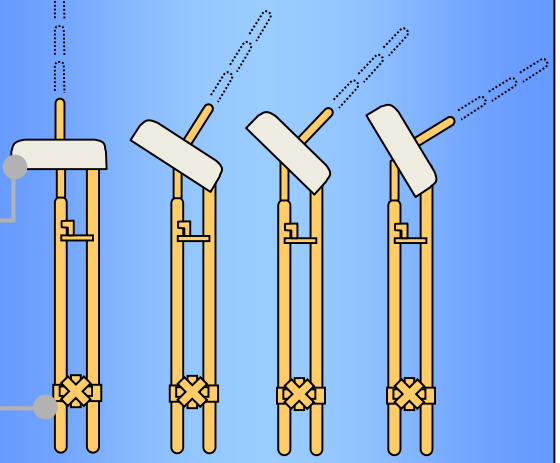
Common features:

Uterine Tandem:
various lengths,
angles or curvatures

Ovoids, cylinders, rings
various outer & source
path diameters

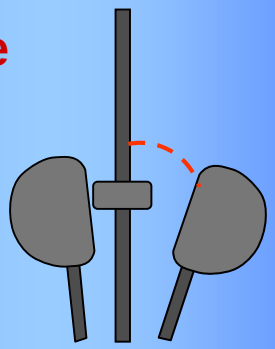
Clamp

Stockholm style



Differences:

Possible



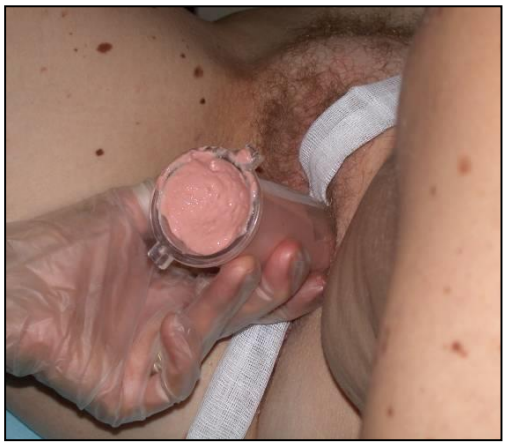
Adjustable spacing

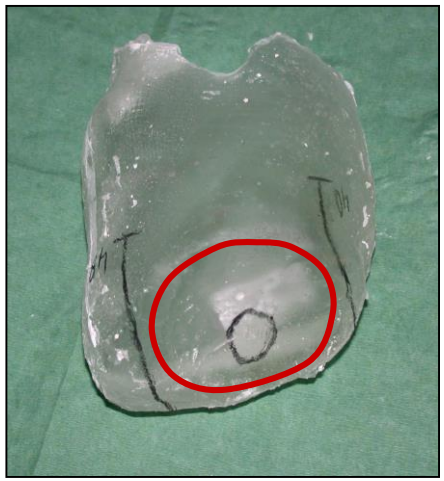
Not applicable

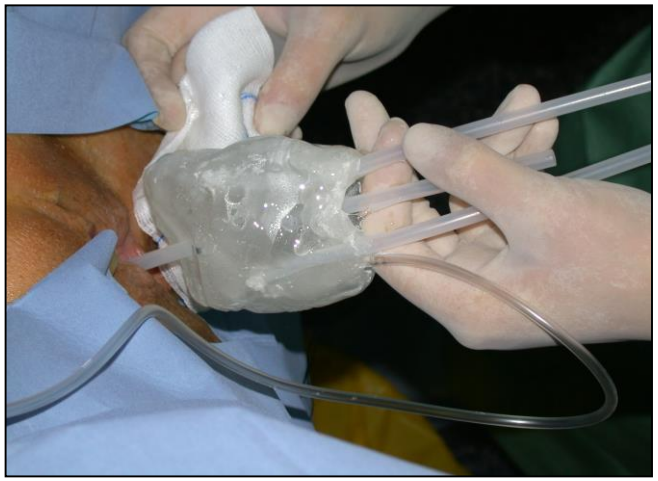
Mould Technique

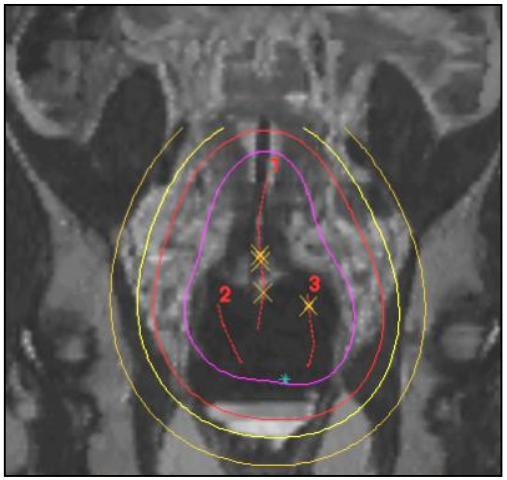
Personalized applicators

- Individually adapted to anatomy, tumour shape and extent
- Personalized intracavitary irradiation
- Good patient tolerance
- No need for vaginal packing
- MRI compatibility
- Prolonged bed rest avoided









Courtesy: C. Haie-Meder, IGR, Paris, France

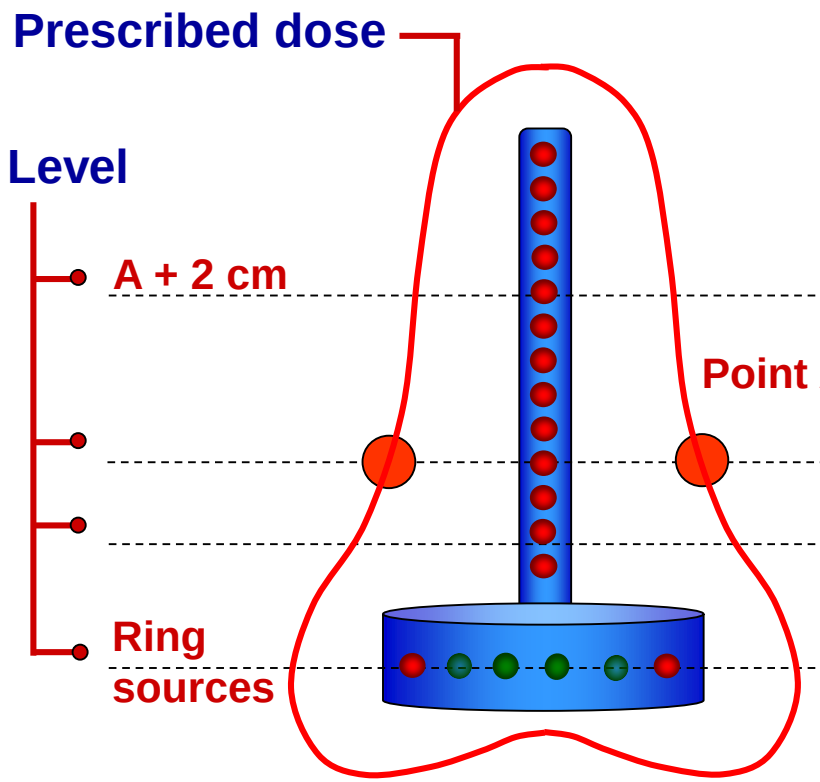
Modern Intracavitary Techniques

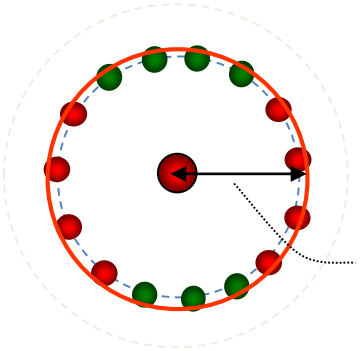
Limitation:

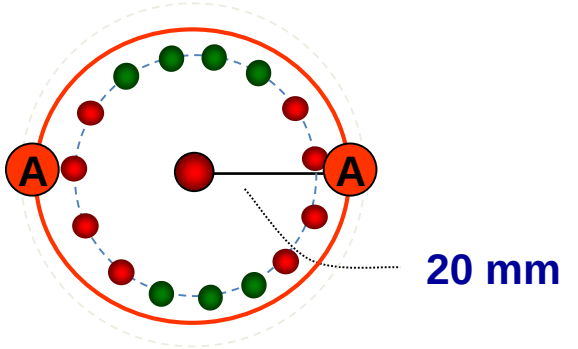
target volume coverage

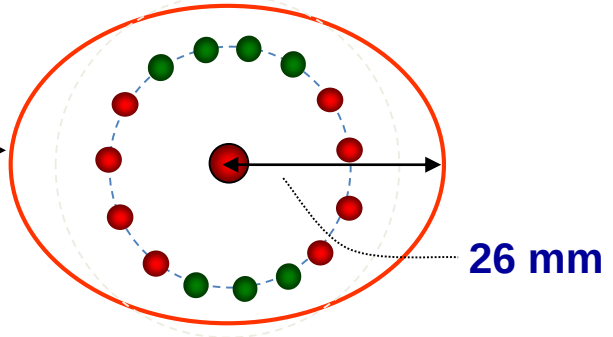
Dimensions of prescribed dose

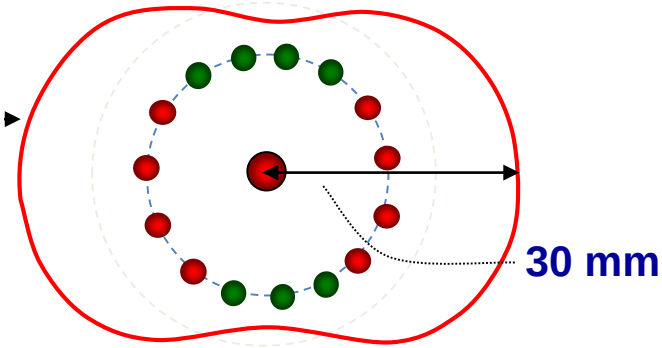
Standard loading









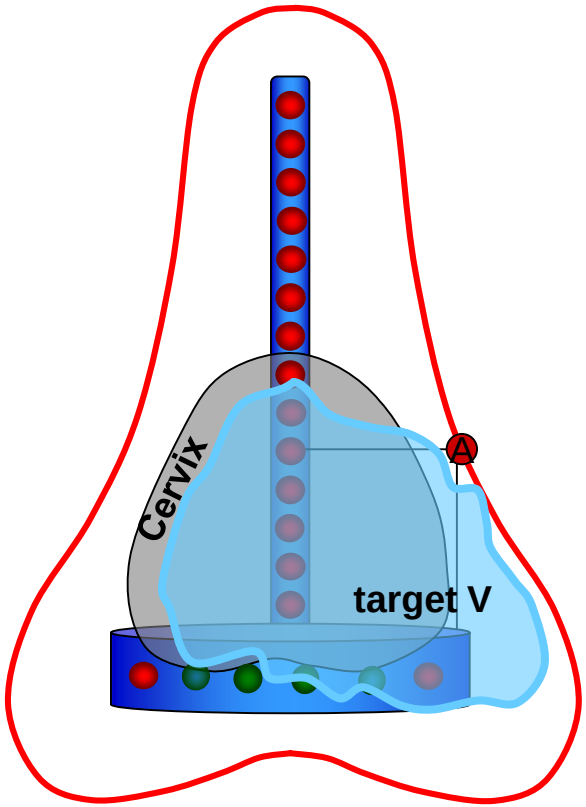


Example:

Tandem & Ring applicator:

30 mm ring & 60 mm tandem

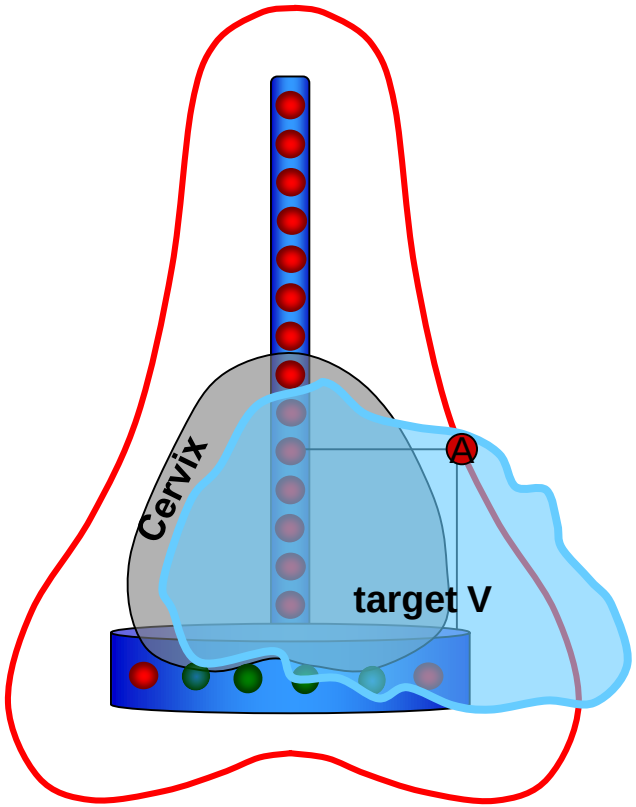
Degrees of freedom for D optimization



Mid-coronal view

Degrees of freedom for D optimization

Dose optimization

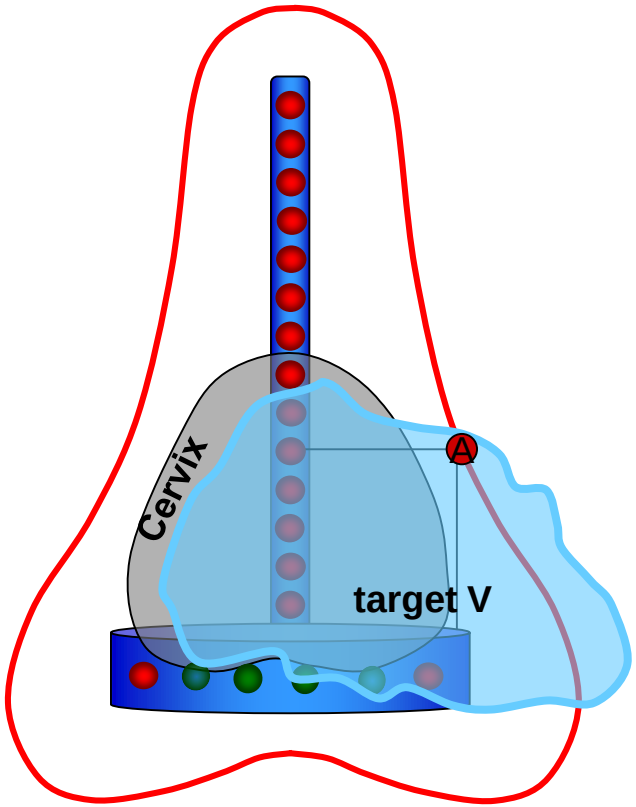


Mid-coronal view

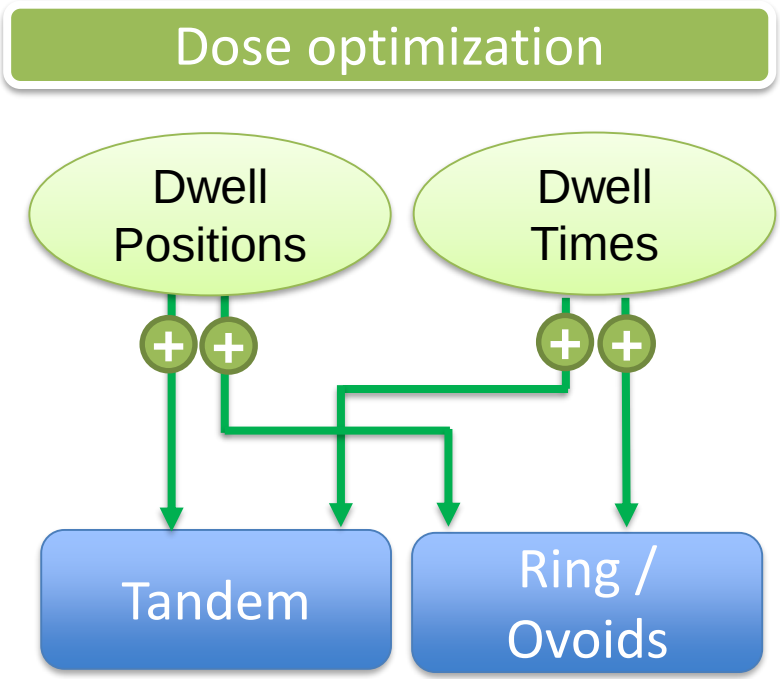
Tandem

Ring / Ovoids

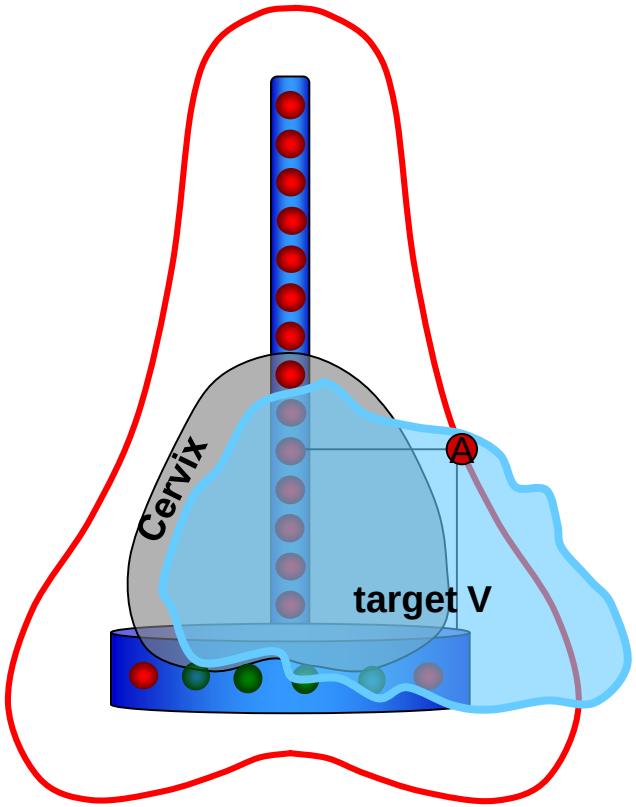
Degrees of freedom for D optimization



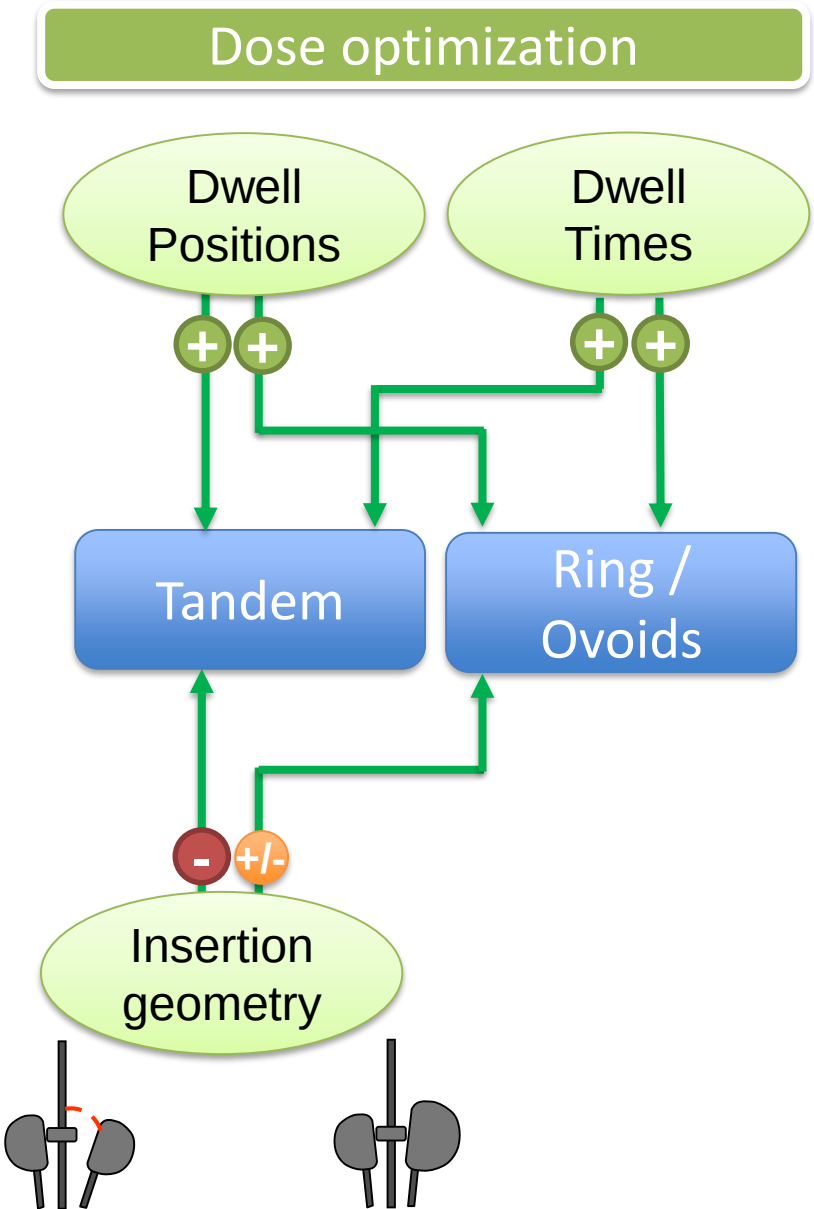
Mid-coronal view



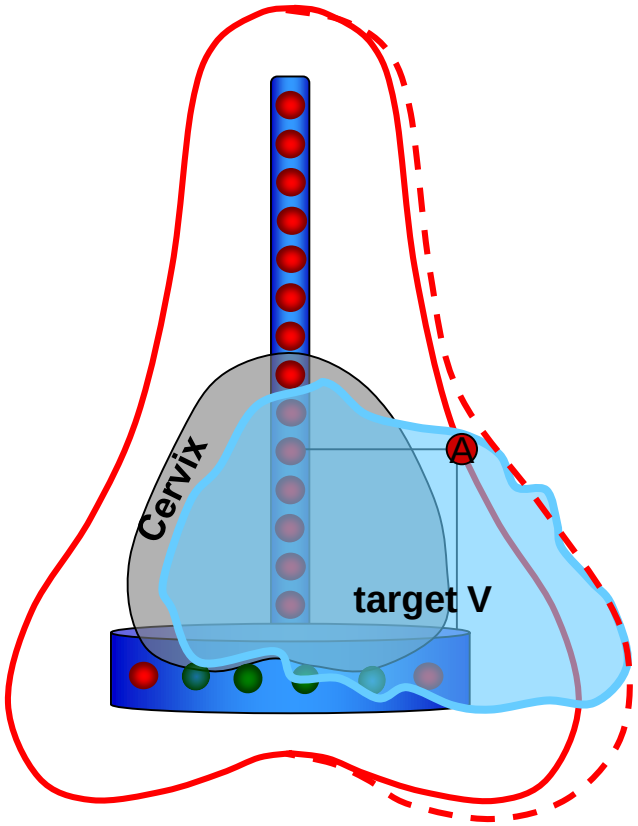
Degrees of freedom for D optimization



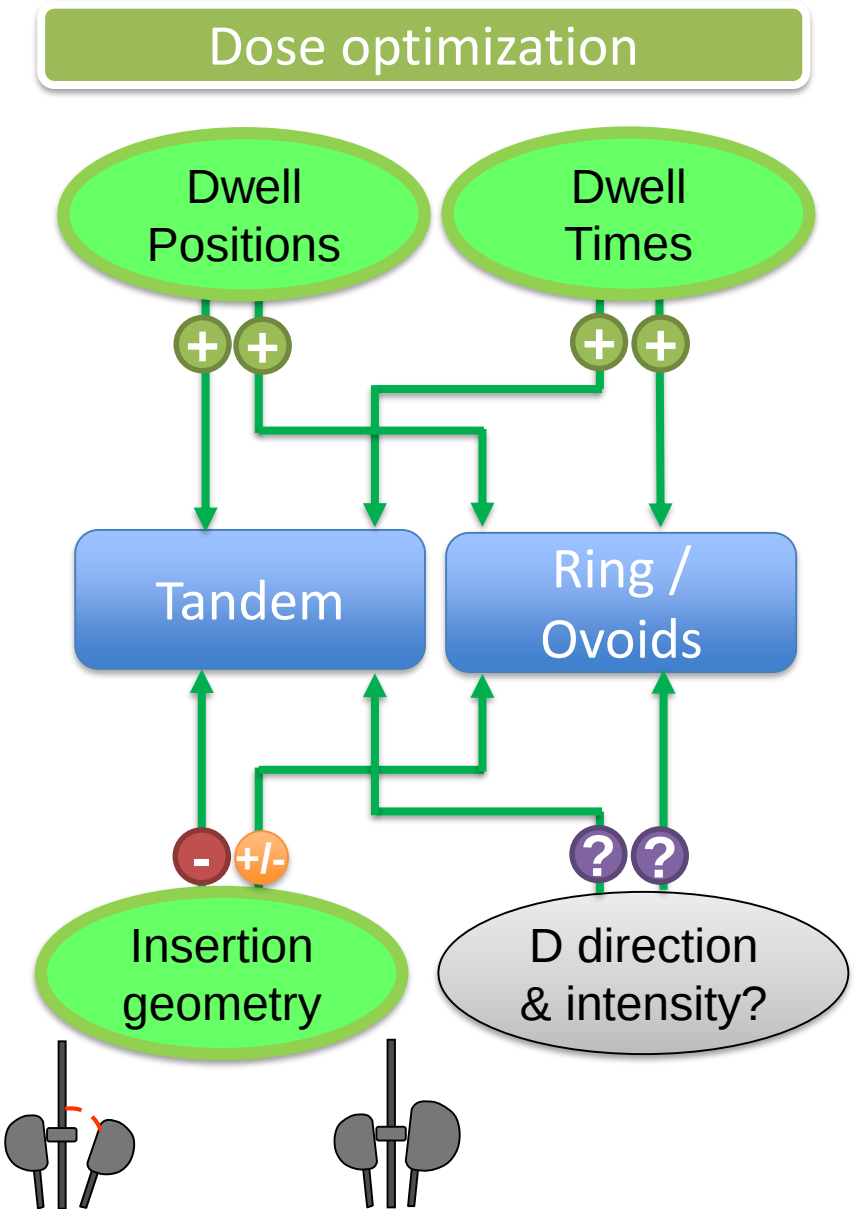
Mid-coronal view



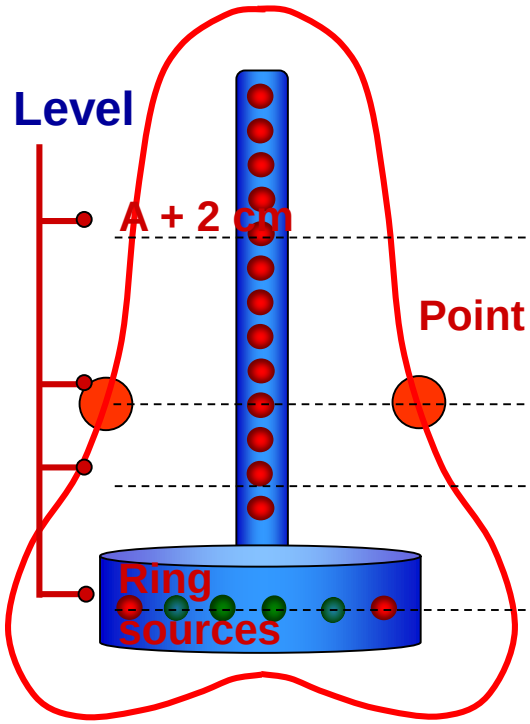
Degrees of freedom for D optimization

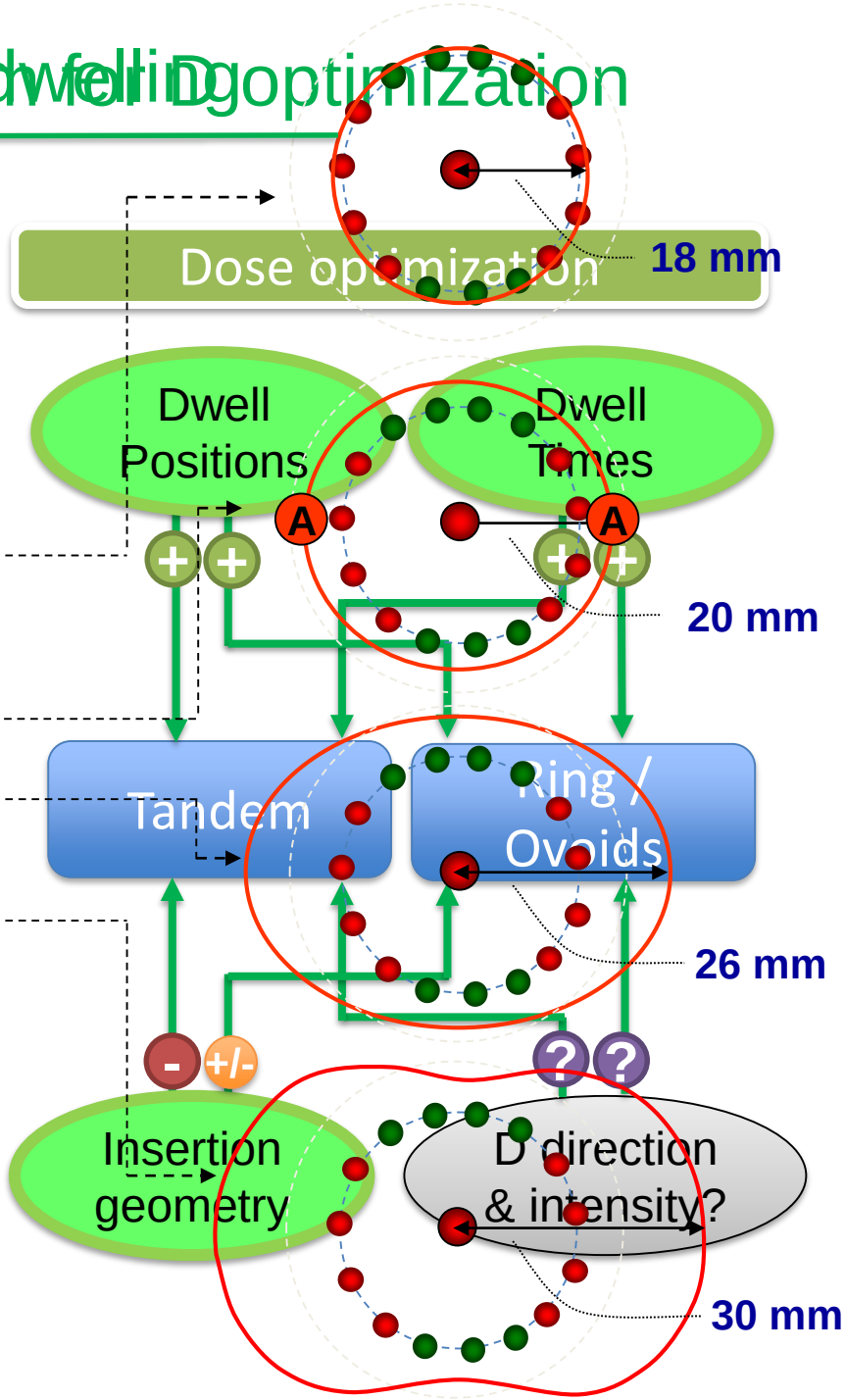


Mid-coronal view

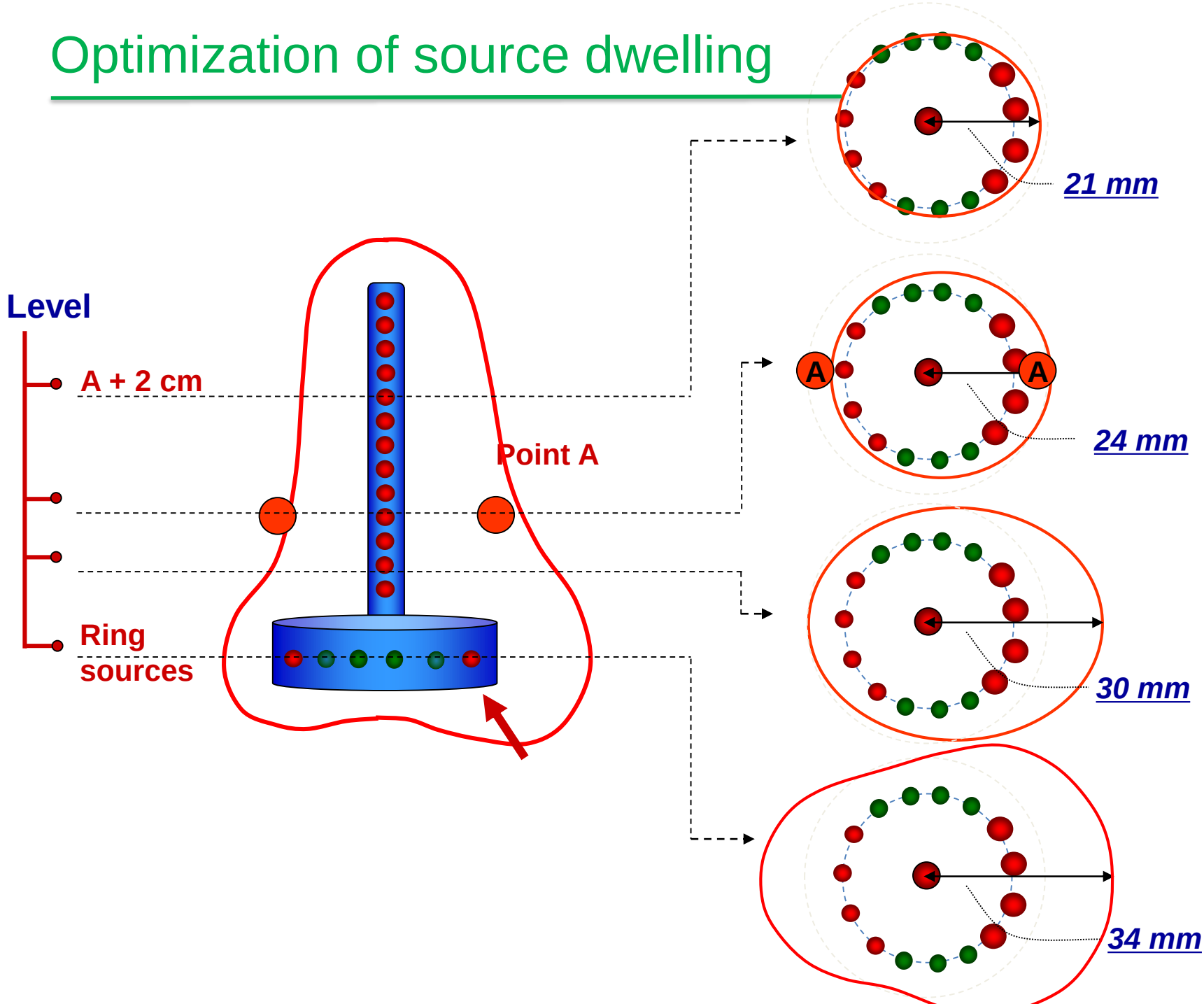


Optimization of source dwell positions and dwell times

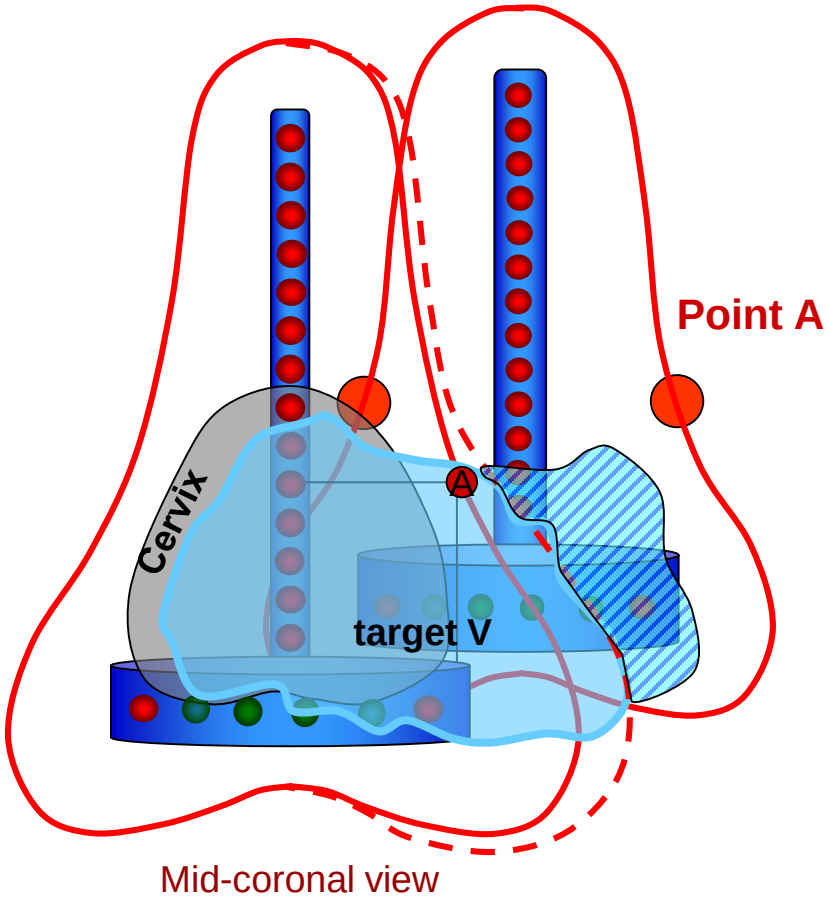


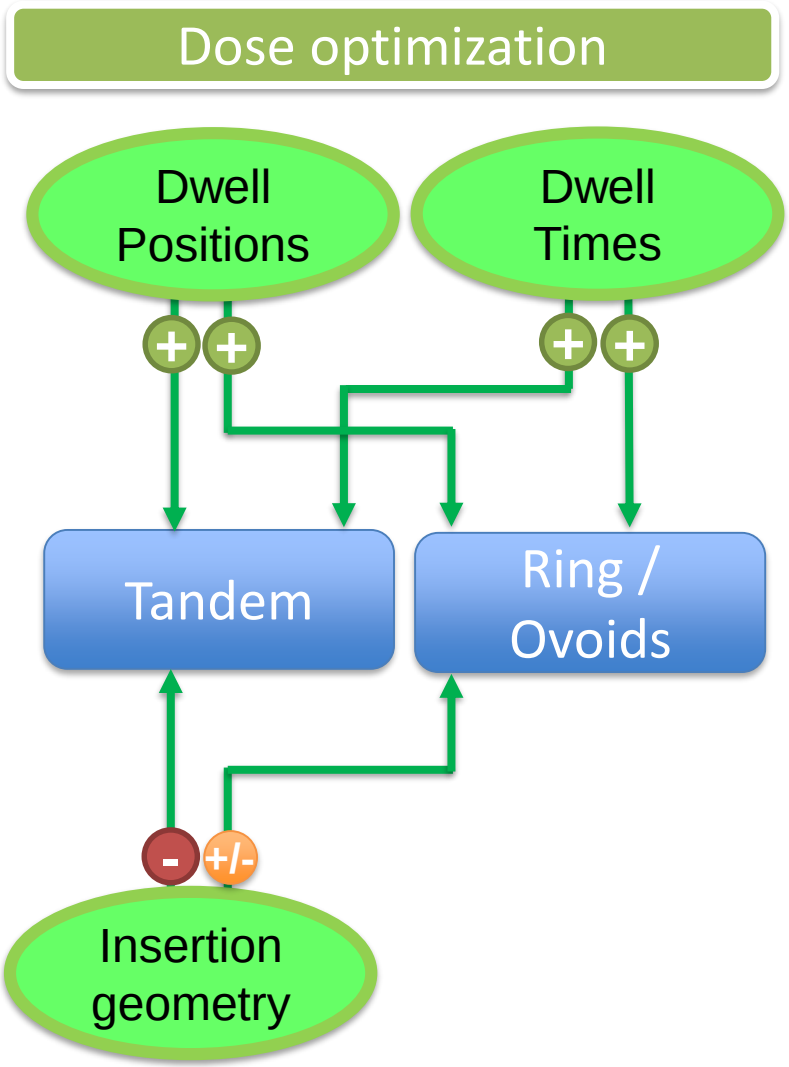


Optimization of source dwelling

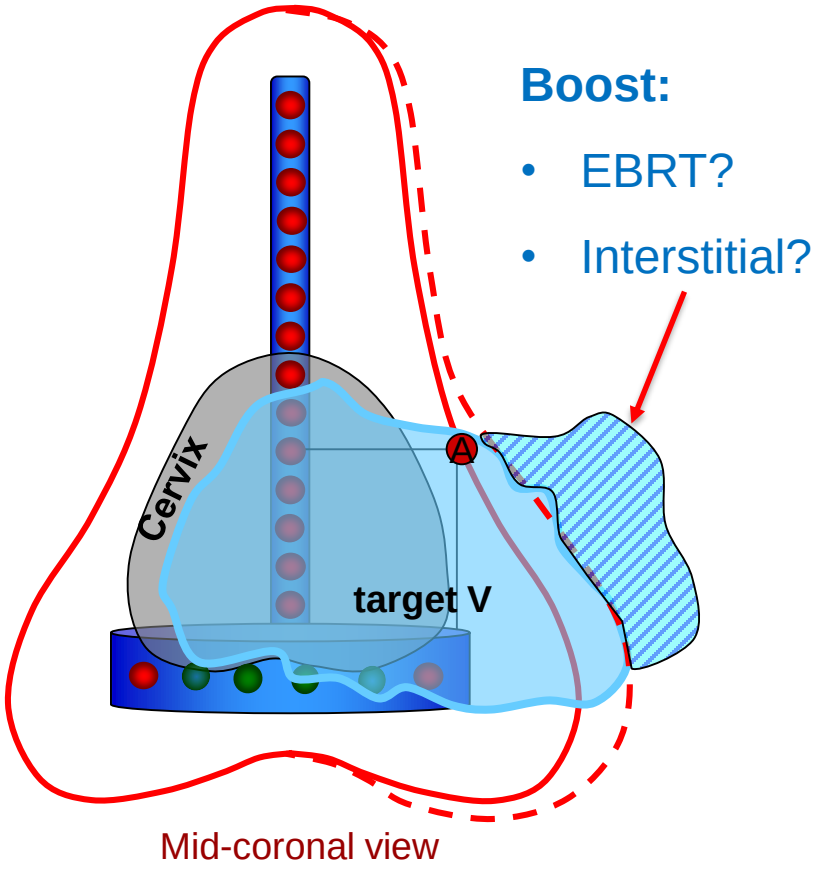


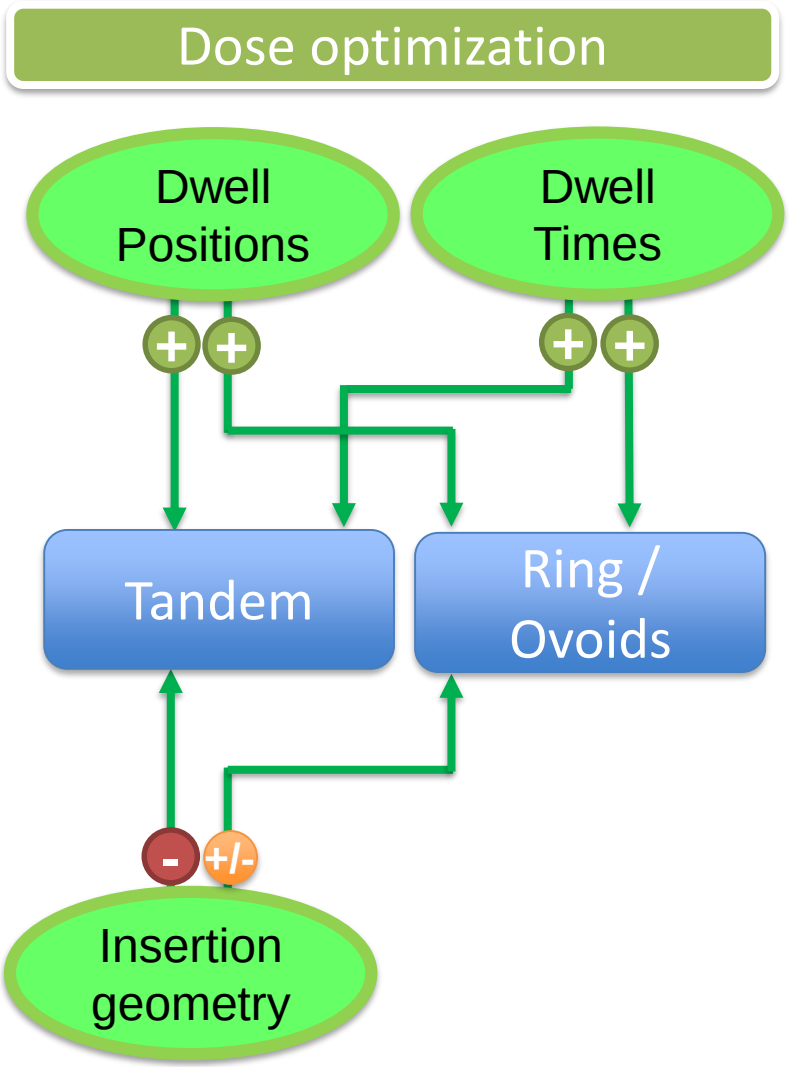
Degrees of freedom for D optimization



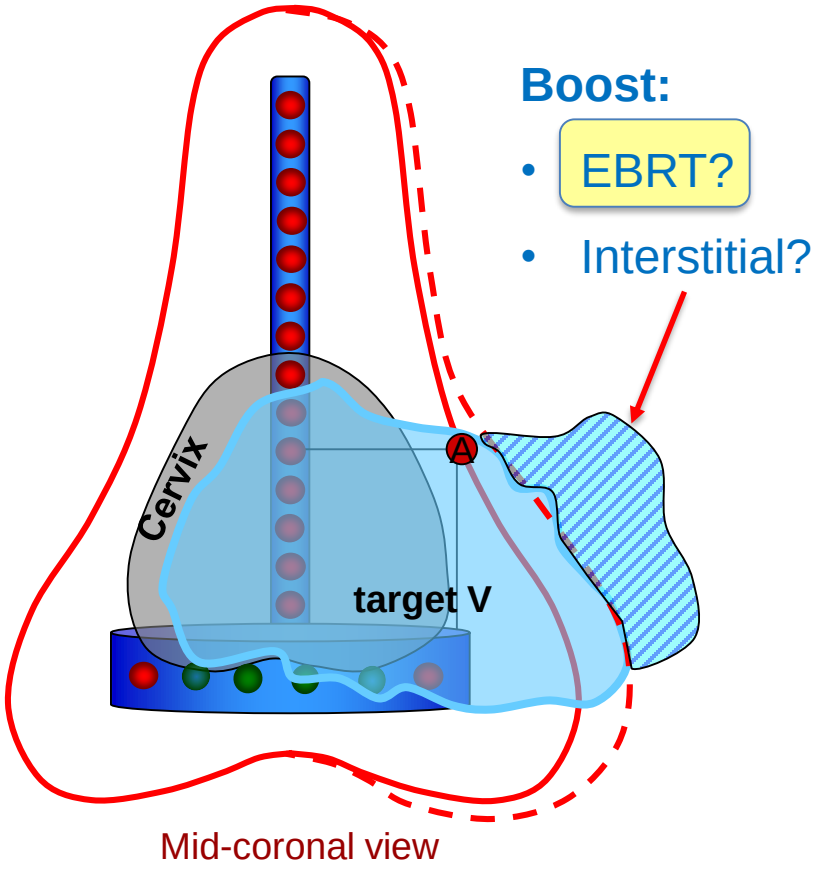


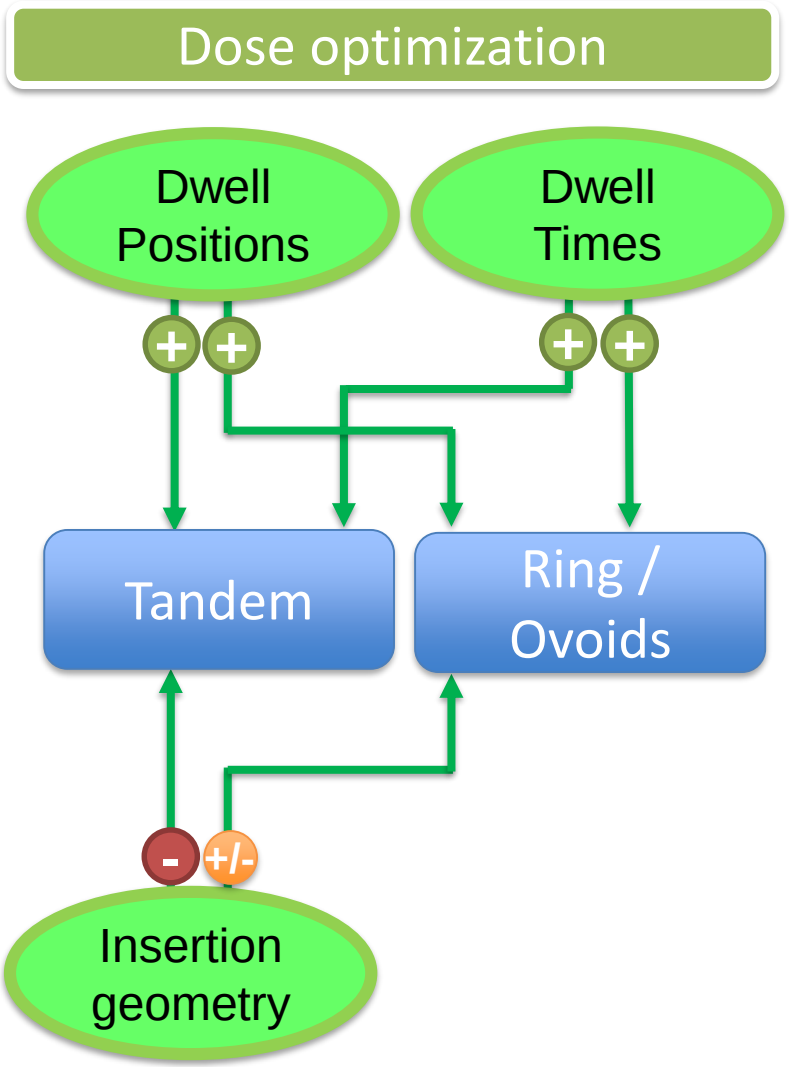
Degrees of freedom for D optimization





Degrees of freedom for D optimization

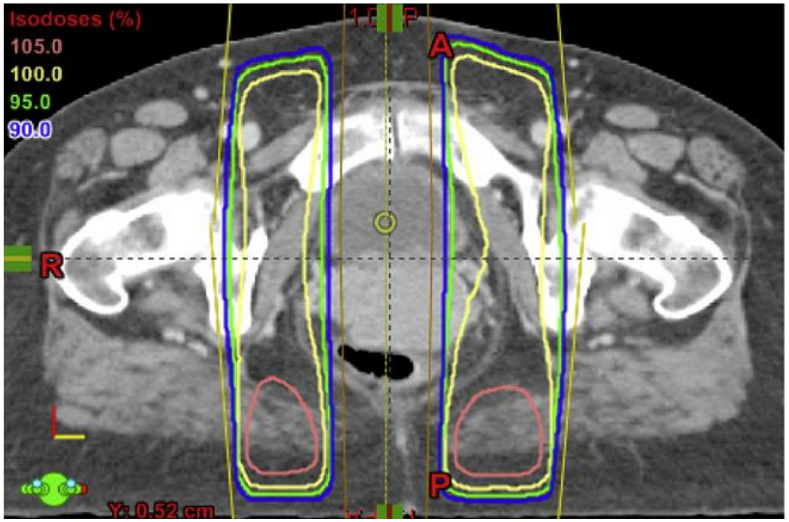


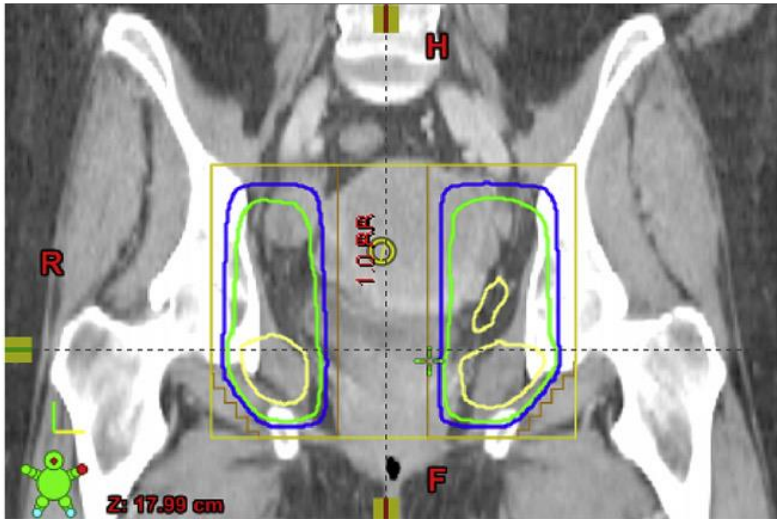


EBRT Boost: *Planning Study I*

6 patients	Box EBRT	MRI guided IC BT	AP-PA Boost
IIB-IVB; 74-376 cm^3	25 x 1.8 Gy	Planning aims…	5 x 1.8 Gy

Central placement of the block (applicator not considered) | 3 cm | 4 cm | 5 cm





EQD2 calculation (LQ model)

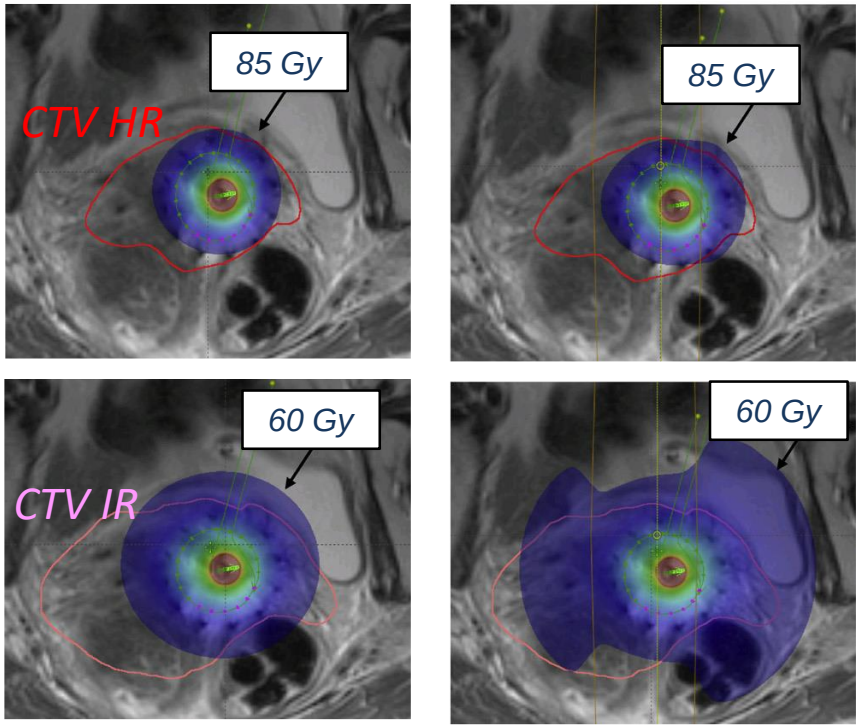
Reporting: CTV HR, CTV IR & OAR

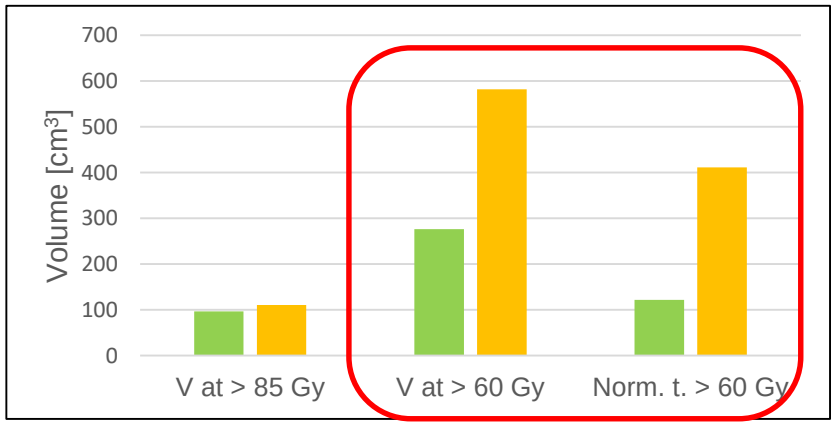
Fenkell et al. IJROBP 2011

EBRT Boost: *Planning Study I*

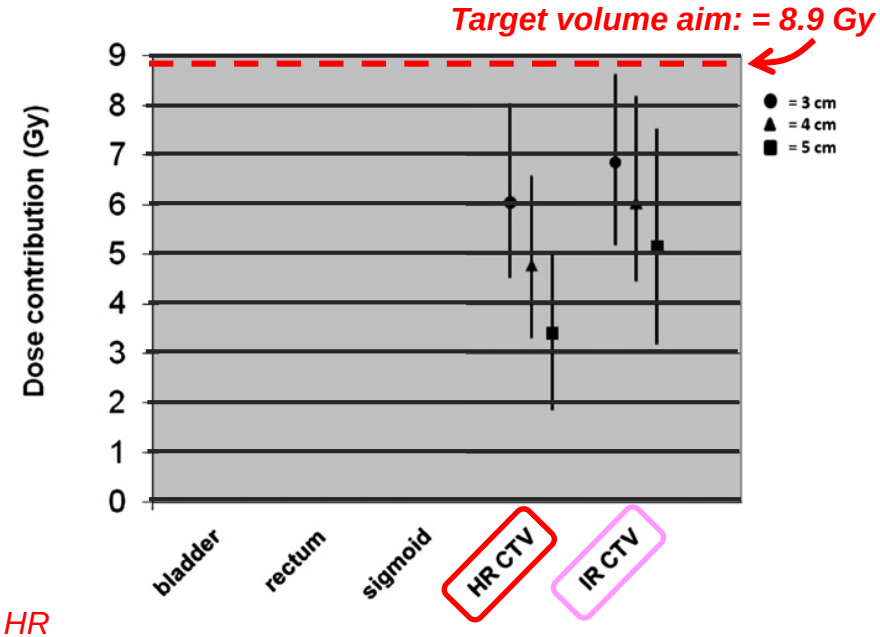
EBRT + BT

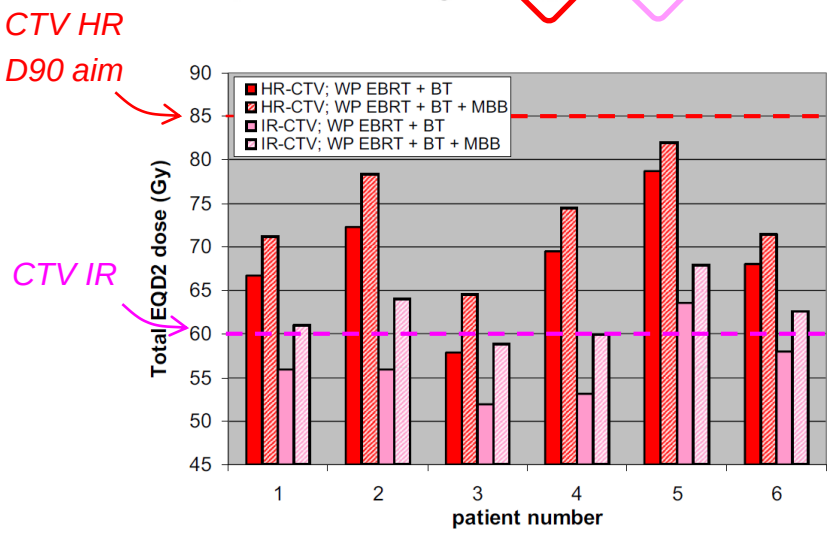
EBRT+BT + PM boost





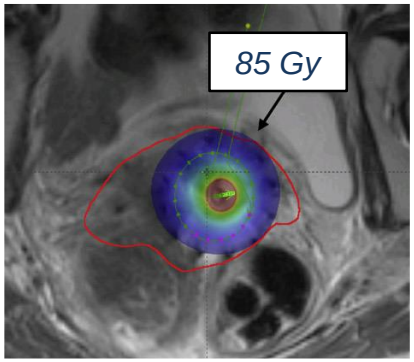
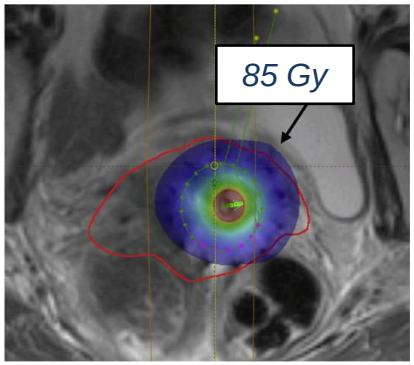
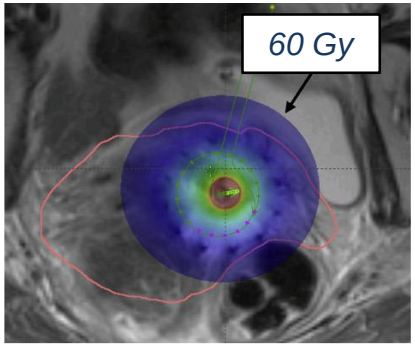
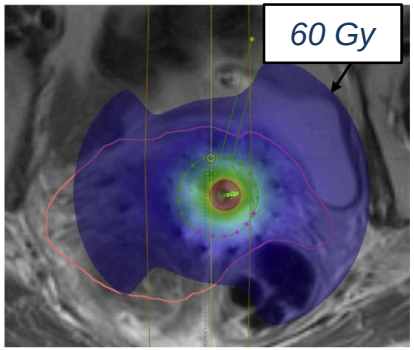
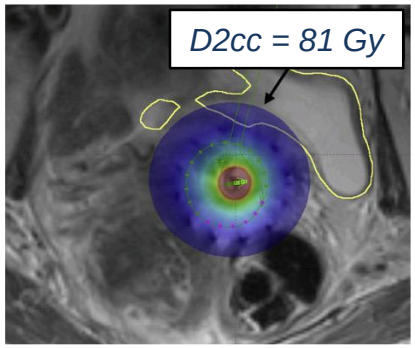
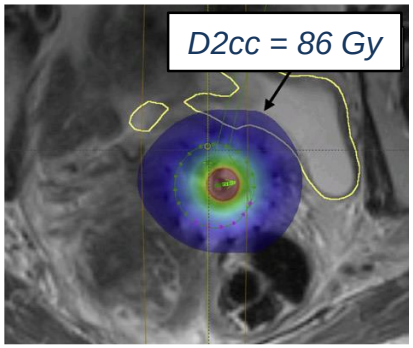
EQD2 Contribution from PM boost



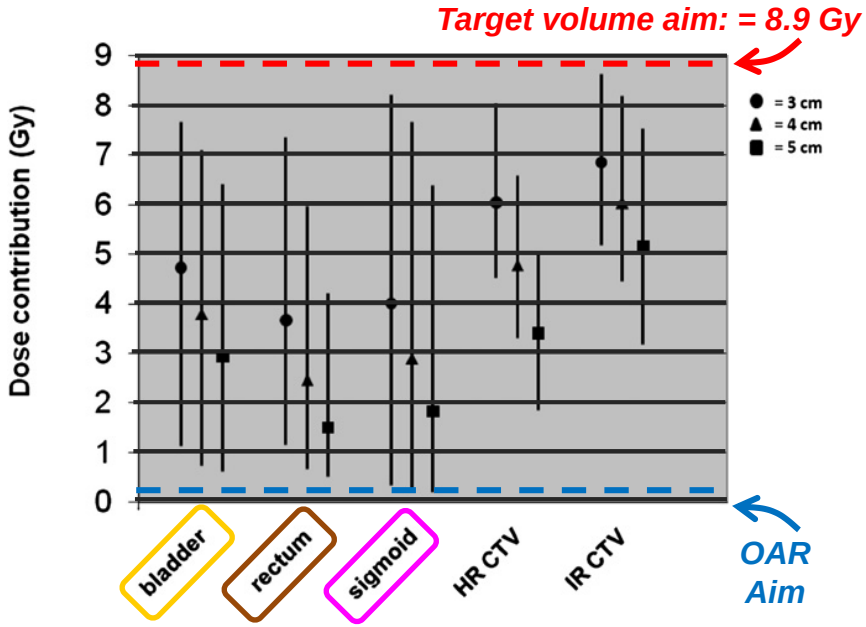


Fenkell et al. IJROBP 2011

EBRT Boost: *Planning Study I*

EBRT + BT	EBRT+BT + PM boost
	
	
	

EQD2 Contribution from PM boost



In 4 out 6 pts:

D2cc to at least one OAR

increased by >50% of PM boost D

Fenkell et al. IJROBP 2011

EBRT Boost: *Planning Study II*

23 patients

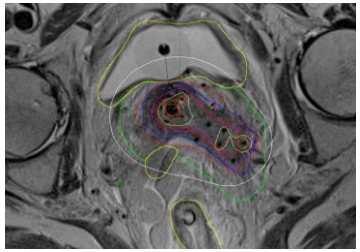
Treatment

Pelvic IMRT

45 - 50 Gy a 1.8 Gy

MRI guided IC+IS BT

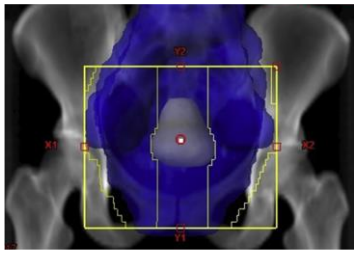
4x7 Gy; pl. aims…



Modelled

Customized Boost

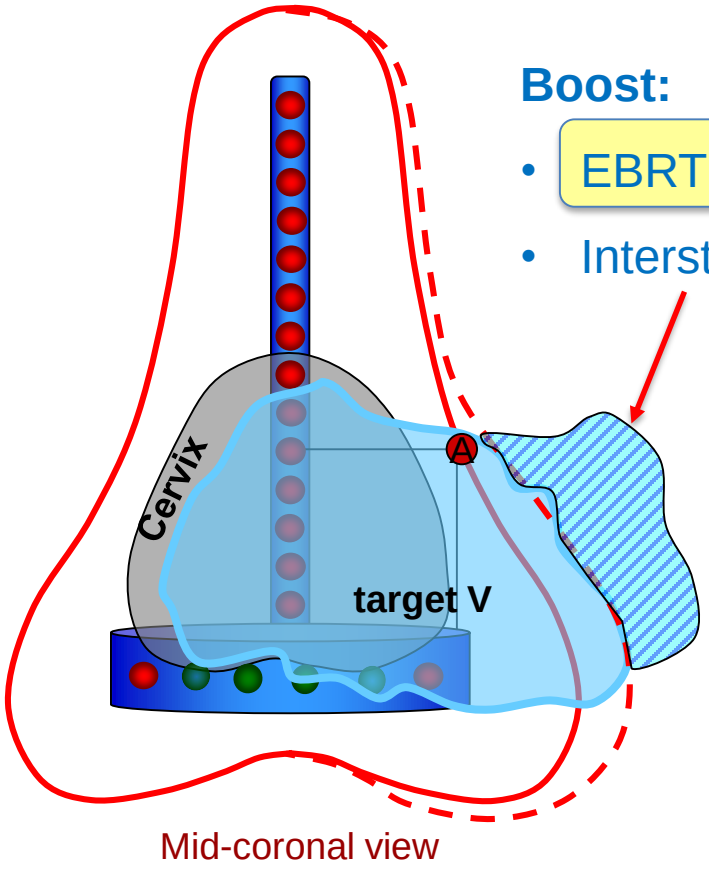
5 x 1.8 Gy



EQD2 (Gy)	Pure IC BT Mean (SD)	IC BT + PB	IC–IS BT	Difference[a] (IC BT + PB) – (IC–IS BT)	Impact of PB	p-Value[a]
GTV D_{90}	109.1 (16.1)	110.5 (15.9)	106.5 (10.5)	4.0 (11.2)		0.10
HR-CTV D_{90}	86.8 (5.8)	88.7 (5.3)	89.0 (3.4)	–0.3 (4.8)	↕	0.79
HR-CTV D_{100}	68.2 (6.4)	71.6 (6.1)	71.7 (4.9)	–0.2 (5.1)	↕	0.88
HR-CTV D_{50}	122.8 (8.8)	124.4 (8.9)	117.6 (7.4)	6.8 (7.4)		<0.001
IR-CTV D_{90}	67.0 (3.5)	71.8 (3.4)	66.5 (2.5)	5.3 (2.2)	↑	<0.001
IR-CTV D_{100}	57.5 (3.8)	59.8 (4.4)	56.7 (3.3)	3.1 (2.9)	↑	<0.001
D_{2cm^3} bladder	75.7 (6.9)	77.2 (5.9)	71.8 (5.0)	5.4 (4.0)		<0.001
D_{2cm^3} rectum	67.4 (6.5)	68.1 (6.3)	64.1 (4.8)	4.4 (2.7)	↑	<0.001
D_{2cm^3} sigmoid	64.8 (7.0)	67.5 (5.5)	62.6 (5.2)	5.0 (2.9)	↑	<0.001
D_{2cm^3} bowel	64.8 (8.8)	68.3 (6.9)	62.1 (6.7)	6.2 (3.5)	↑	<0.001
V60 (cm^3)		*593 (595.6)*	*228.4 (81.5)*		↑	*<0.01*

Mohamed et al. Brachytherapy 2014

Boost options



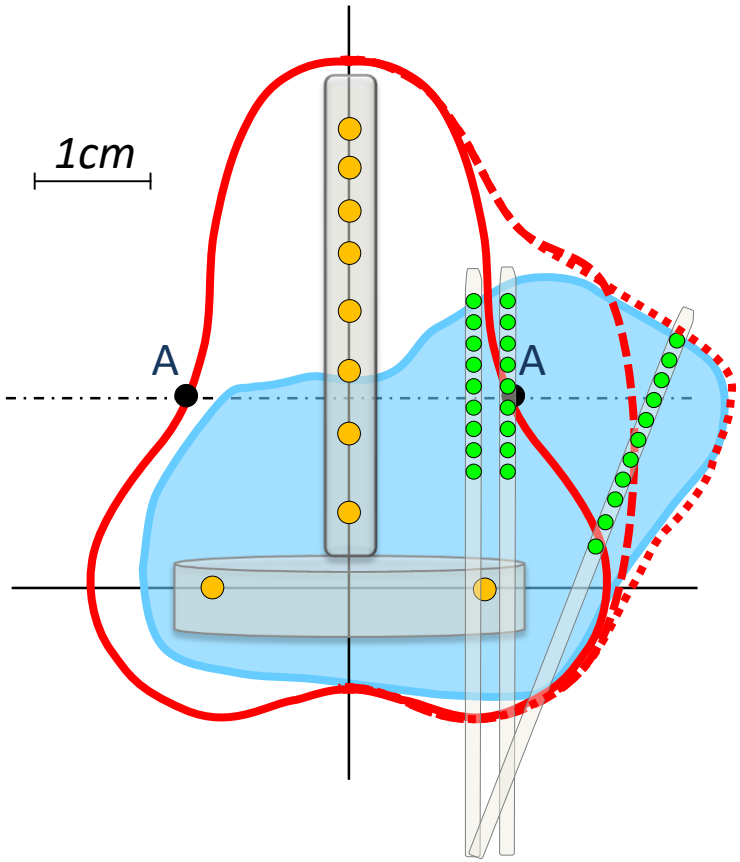
Mid-coronal view

Boost:

- EBRT?
- Interstitial?

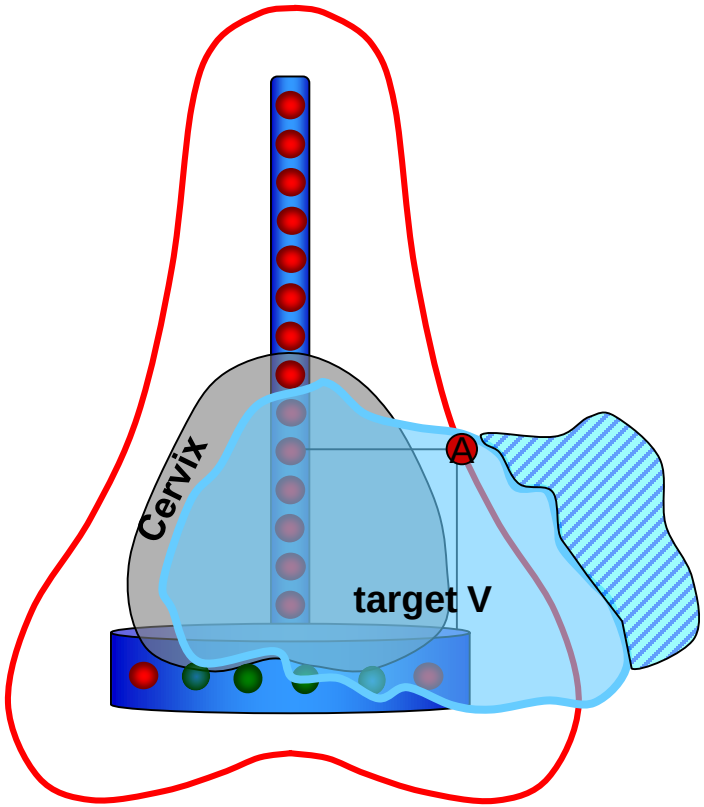
Intracavitary - Interstitial Boost

Parallel & Oblique Needles

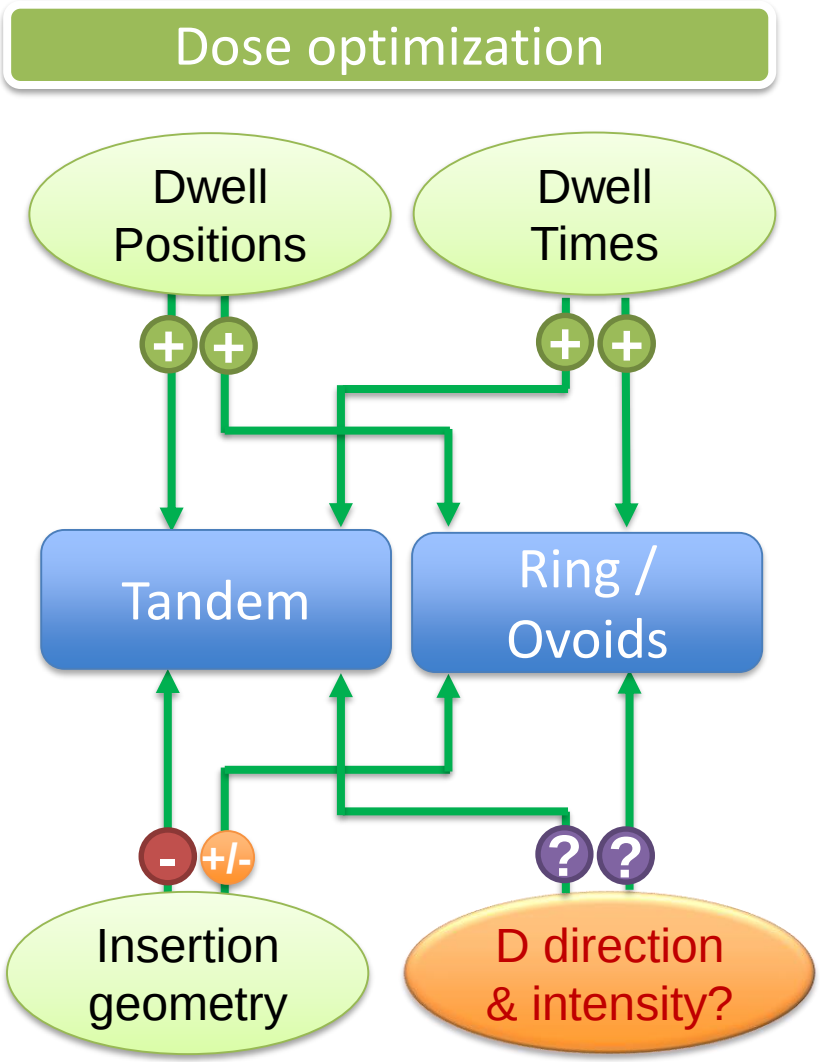


…Topic of next lecture

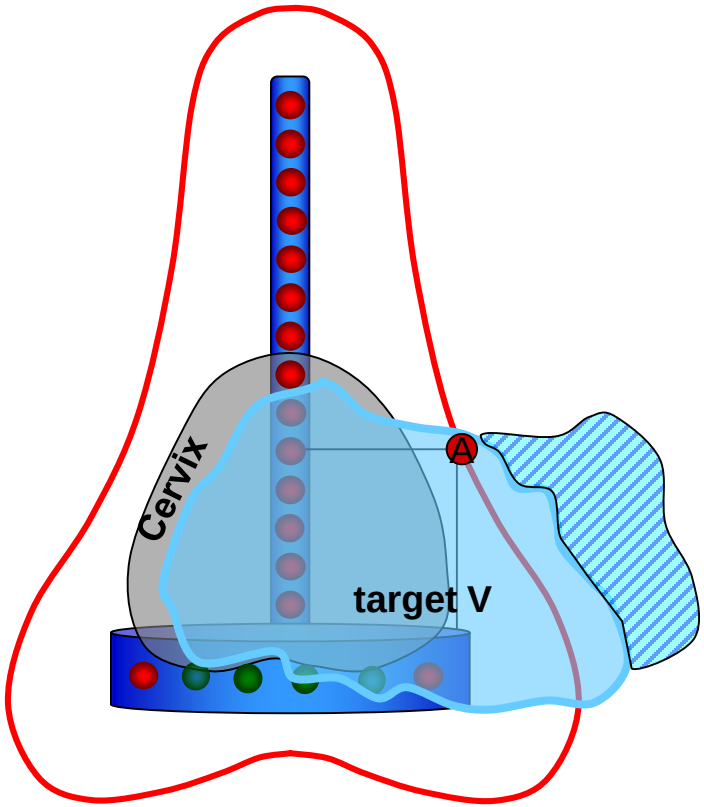
Degrees of freedom for D optimization



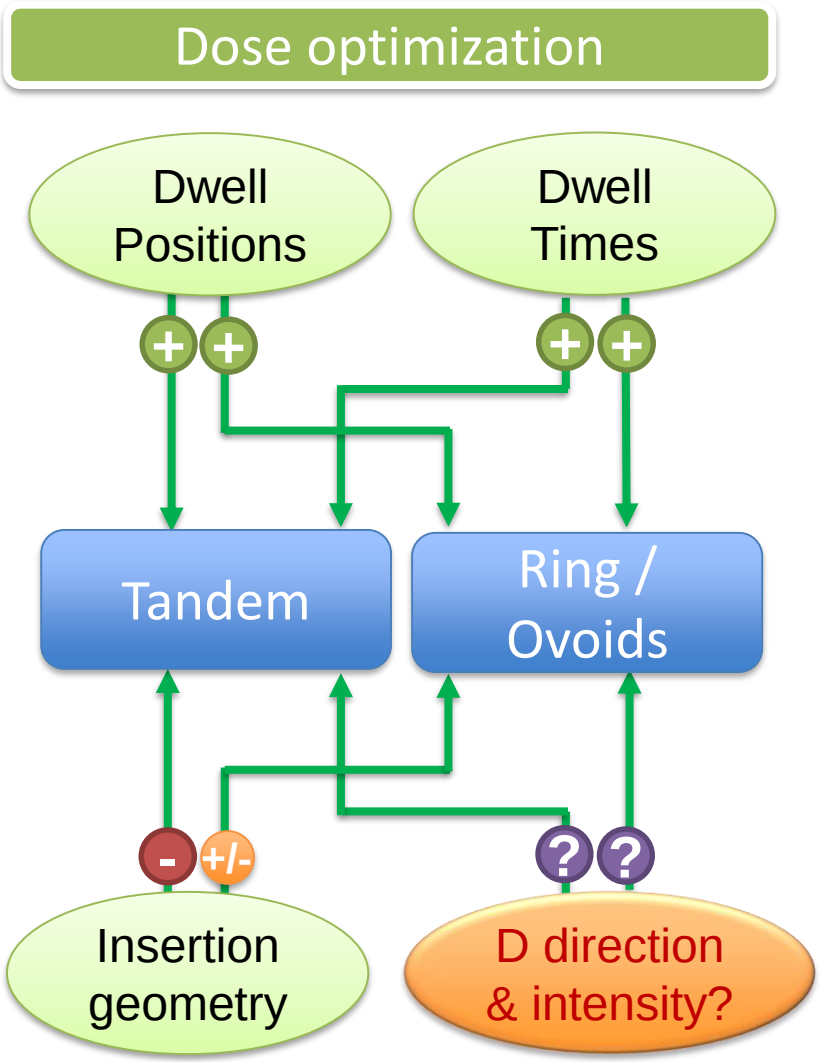
Mid-coronal view



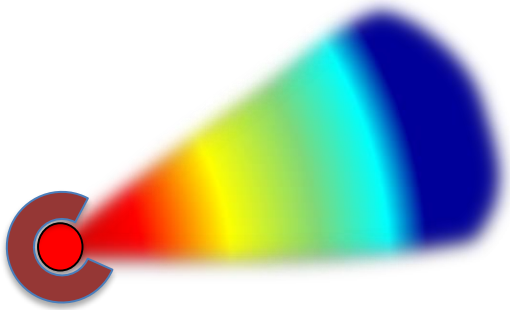
Degrees of freedom for D optimization



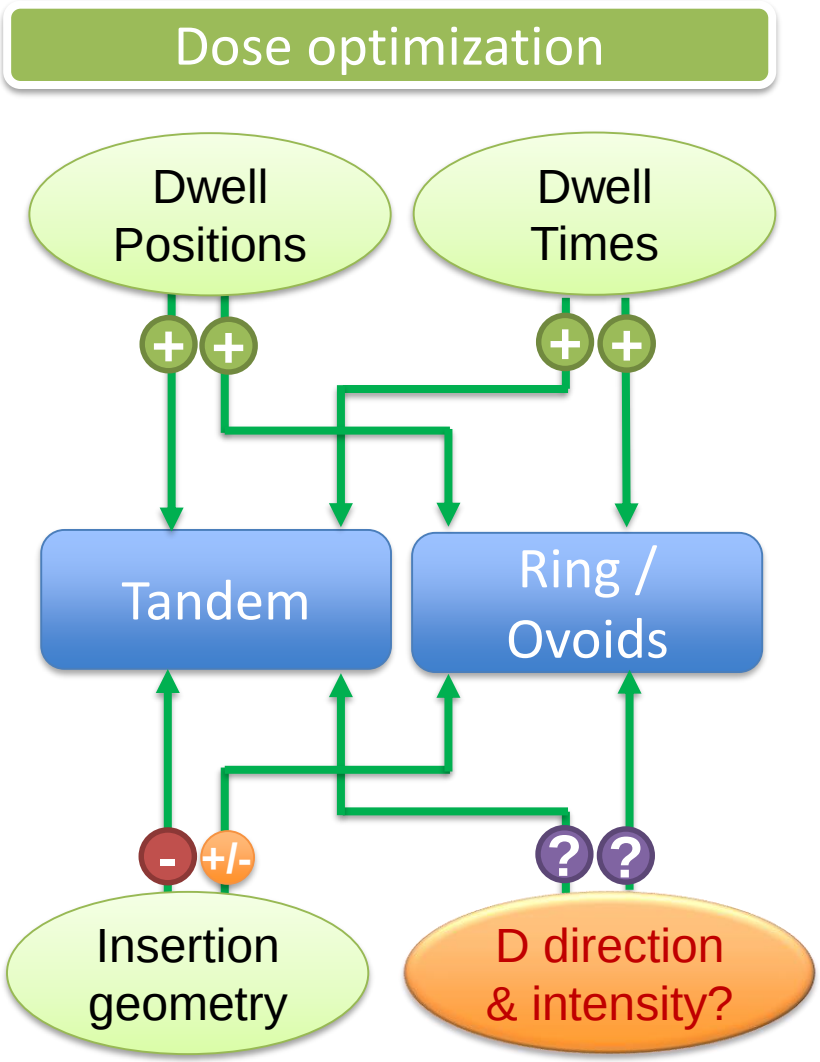
Mid-coronal view



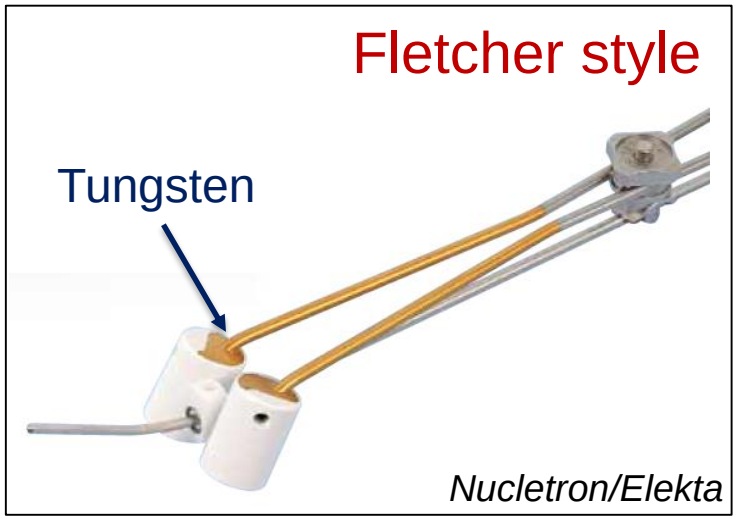
Degrees of freedom for D optimization

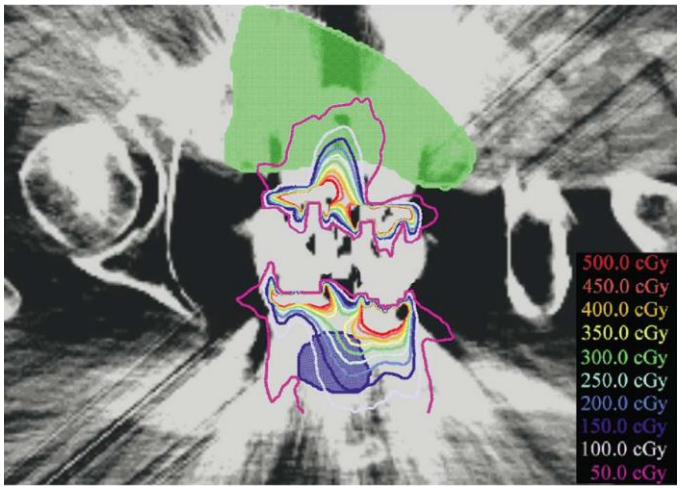


Static / Dynamic Shielding



Static shielding





From: Gifford KA, et al. Int J Radiat Oncol Biol Phys 2005

Reduced bladder & rectal D

Limited imaging possibilities!

- Artifacts on CT
- Lack of MRI compatibility

↓

Uncertainty: target shielding?

Static shielding: CT compatible, MRI conditional

Adjustable shielding

Nucletron/Elekta

Static shielding: Direction-modulated BT (DMBT)

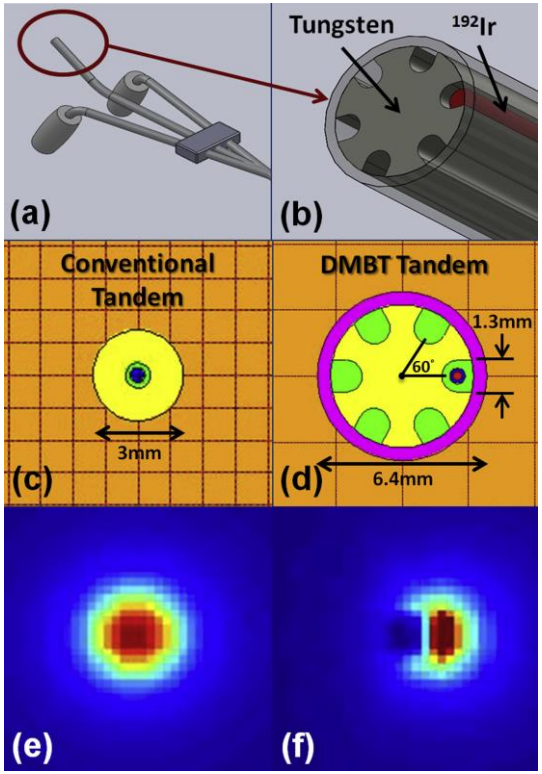
Physics Contribution

International Journal of Radiation Oncology biology • physics

Direction-Modulated Brachytherapy for High-Dose-Rate Treatment of Cervical Cancer. I: Theoretical Design

Dae Yup Han, MSc,*,† Matthew J. Webster, MSc,*,‡ Daniel J. Scanderbeg, PhD,* Catheryn Yashar, MD,* Dongju Choi, PhD,* Bongyong Song, PhD,* Slobodan Devic, PhD,§,‖ Ananth Ravi, PhD,¶ and William Y. Song, PhD*,¶

- MRI compatible tandem design
- 75 plans compared: DMBT vs. standard
- ↓ D2cc for OAR, ≈ D90 for HR CTV



Han DY, et al. Int J Radiat Oncol Biol Phys 2014;89;3:666-73. [UCSF, Quebec, Toronto]

Static shielding: Direction-modulated BT (DMBT)

Special considerations

Low- and High-Dose Volumes, TRAK

Methods:

The clinically relevant parameters (22), such as D0.1 cc and D2cc for OARs, and V100, V150, V200, and D90 for HRCTV, were calculated thereafter.

Results:

2.38 Gy (40.07%), and 1.26 Gy (27.5%), respectively. The total dwell times, normalized to air kerma strength of 40.25 kU (10 Ci) source, increased on average by 27.1% (from 6.3 ± 1.9 to 8.1 ± 2.6 minutes) for the DMBT plans. This

CAUTION

- TRAK increased
- V150, V200 not reported

Han DY, et al. Int J Radiat Oncol Biol Phys 2014;89;3:666-73. [UCSF, Quebec, Toronto]

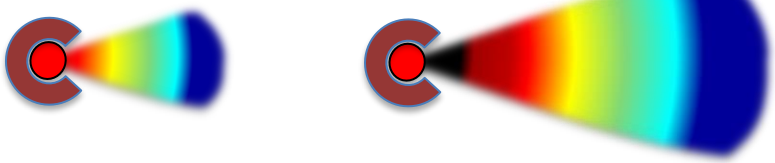
Static shielding: Direction-modulated BT (DMBT)

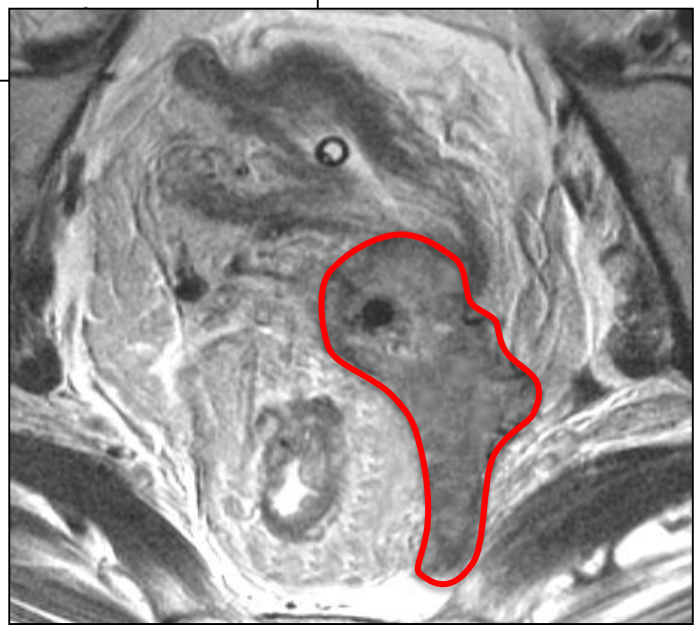
Special considerations

Clinical value / Limitations of DMBT!

Discussion:

out that at least some of the advanced clinical cases in which interstitial needles are necessary (eg, parametrial or utero-sacral extensions) (15) can be replaced with the DMBT applicator. For this study, the selected

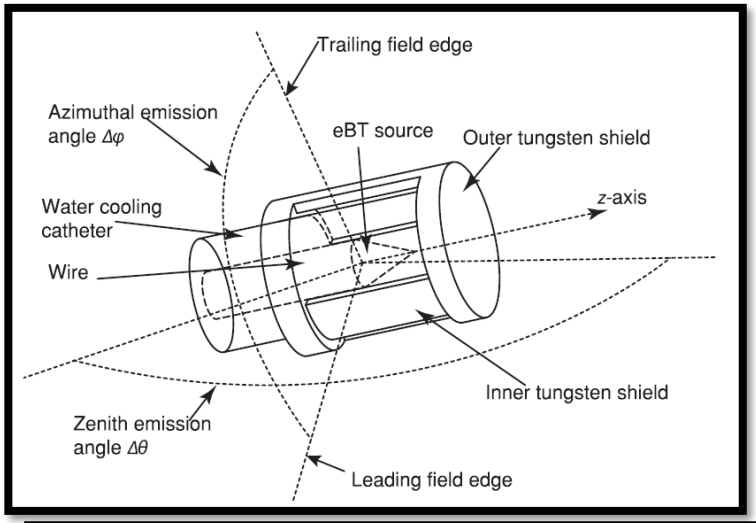


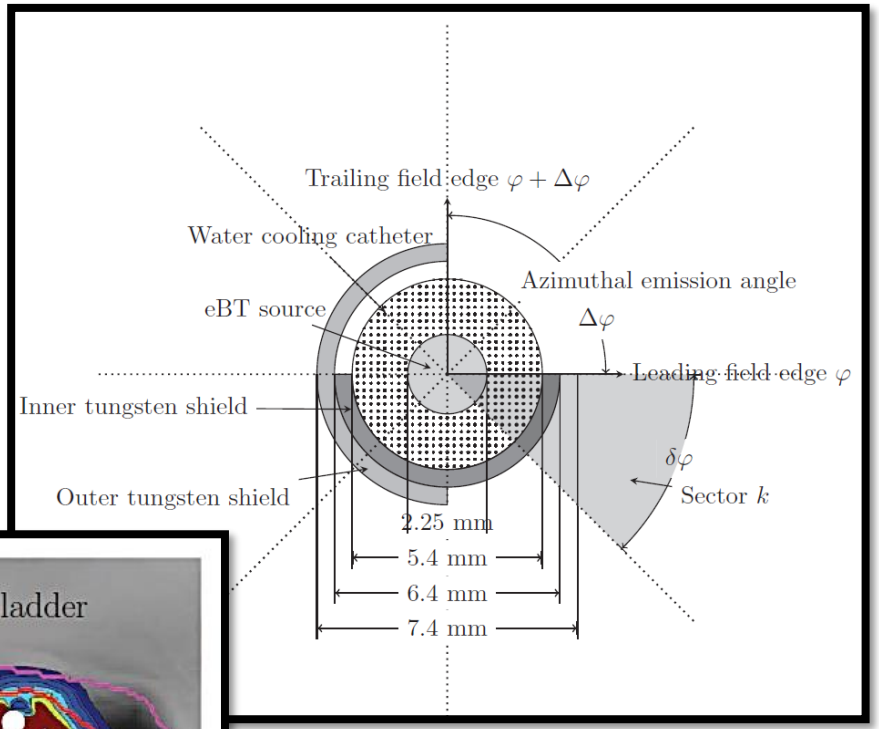


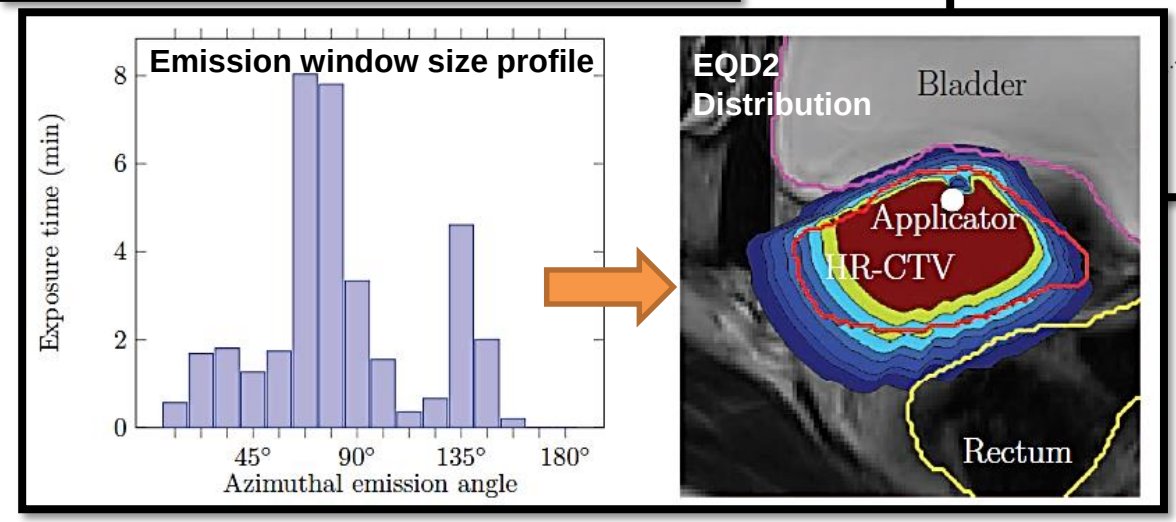
Han DY, et al. Int J Radiat Oncol Biol Phys 2014;89;3:666-73. [UCSF, Quebec, Toronto]

Dynamic Rotating Shield Brachytherapy - D-RSBT

- Electronic brachytherapy source
- Radiation shield capable of changing emission angles



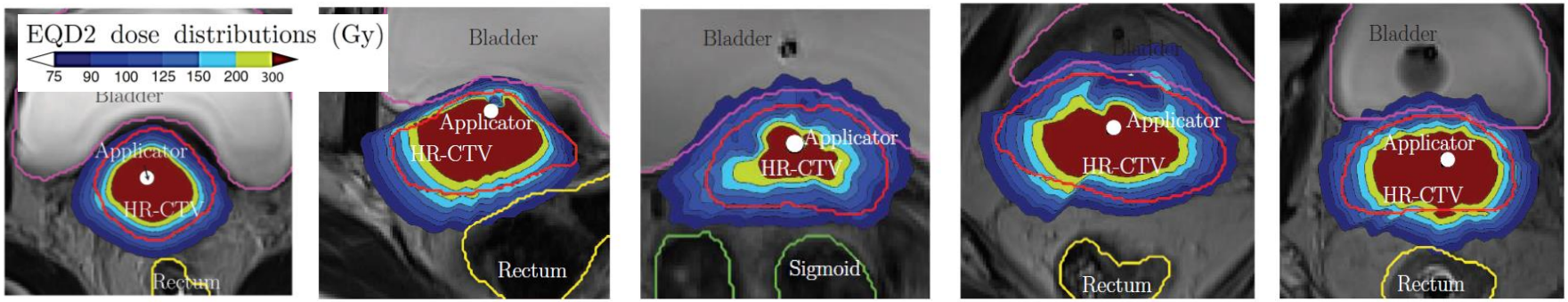




ang W, Kim Y, Wu X, et al.. Phys Med Biol 2013;58(11):3931-41.
u Y, et al.. Med Phys 2013;40(5):051720
•Liu Y, Flynn RT, Kim Y, Yang W, Wu X.. Med Phys 2013;40(12):12703
•Liu Y, Flynn RT, Kim Y, Wu X. Med Phys 2014;41(11):111709
Adams QE, Xu J, Breitbach EK, et al. Med Phys 2014;41(5):051703

Dynamic Rotating Shield Brachytherapy - D-RSBT

HR CTV = 41 cm^3 | HR CTV = 45 cm^3 | HR CTV = 77 cm^3 | HR CTV = 98 cm^3 | HR CTV = 74 cm^3



Plans of 5 cases compared:

- *D-RSBT* vs. *Interstitial + Intracav. BT*
- With 30 additional min. for D-RSBT:
  - D90 improved for 20 Gy (EQD2)
  - OAR doses +/- unchanged

CONCLUSIONS

Patients who need to be treated with HDR-BT may benefit from the D-RSBT technique. Compared to the existing interstitial BT methods such as IS + ICBT, D-RSBT can generate less invasive plans with a better dose distribution at the expense of longer delivery times. D-RSBT is also likely to yield
...e cases where S-RSBT may have difficulty
...e between dose quality and delivery time.

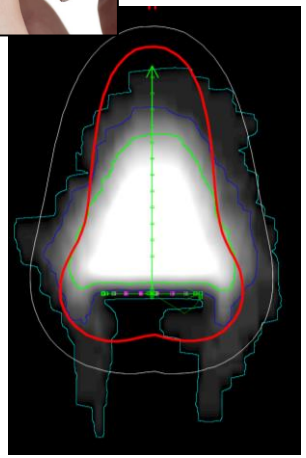
CAUTION…

- IS-IC BT technique not described in this work…
- Extensive Favourable experience with IC-IS BT!
- D-RSBT: Dose emitted from single channel
  - High-D volume increased by 15 - 50 %!
  - D heterogeneity!
  - TRAK?
- Clinical implications?

Liu Y, Flynn RT, Kim Y, Yang W, Wu X.. Med Phys 2013;40(12):12703
Liu Y, Flynn RT, Kim Y, Wu X. Med Phys 2014;41(11):111709
Yang W, Kim Y, Wu X, et al.. Phys Med Biol 2013;58(11):3931-41.
Liu Y, et al.. Med Phys 2013;40(5):051720
Adams QE, Xu J, Breitbach EK, et al. Med Phys 2014;41(5):051703

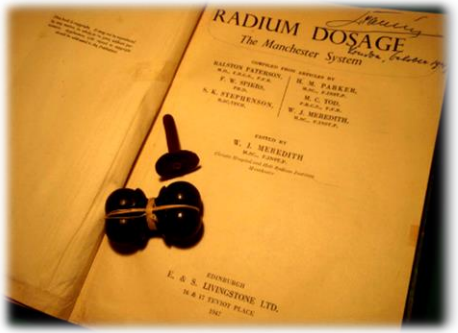
CONCLUSIONS

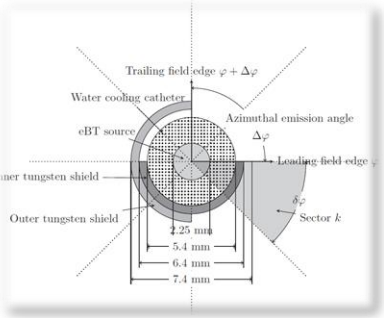
- Modern intracavitary applicators
  - Same concept as historical systems; main differences:
  - CT, MRI compatibility, materials
    - Fixed, adjustable components
    - Smaller channel diameters
- Main types of intracavitary applicators:
  - Tandem & ring (Stockholm style)
  - Tandem & ovoids (Manchester or Fletcher style)
  - Mould technique
- Intracavitary technique alone:
  - limited possibility for D adaptation
- Interstitial boost recommended for unfavourable topography



Intracavitary Brachytherapy for Cervical Cancer

Techniques & Limitations





Primoz Petric

Aarhus University Hospital, Denmark

Combined intracavitary-interstitial technique for cervix cancer

Umesh Mahantshetty, Professor, Radiation Oncology,
Tata Memorial Hospital, Mumbai, India

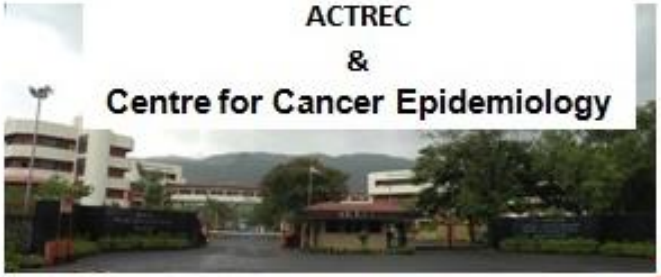
Johannes C. Athanasios Dimopoulos, Head, Radiation Oncology
Metropolitan Hospital, Athens, Greece

Adapted and presented
Richard Pötter, Medical University of Vienna

TATA MEMORIAL CENTRE, MUMBAI, INDIA

TERTIARY CANCER CENTRE EXPERIENCE

ACTREC
&
Centre for Cancer Epidemiology



ADVANCED CENTRE FOR TREATMENT
RESEARCH AND EDUCATION IN CANCER

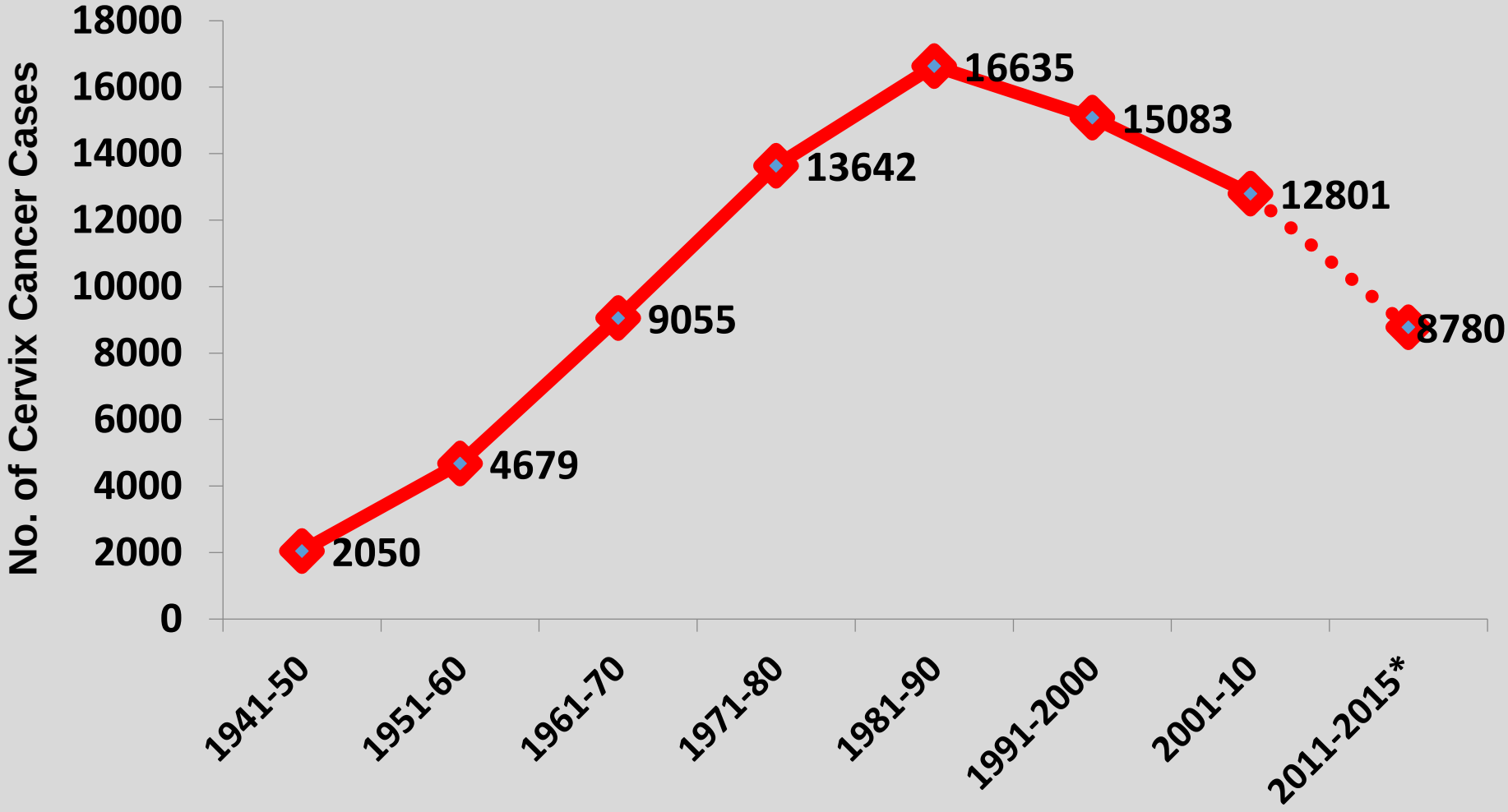
MISSION
Service
Research
Education

New Cases:
42,000 annually

Radiotherapy for
all cancers
5500 annually

TRENDS OF CERVICAL CANCER

TATA MEMORIAL HOSPITAL : 1941-2015*

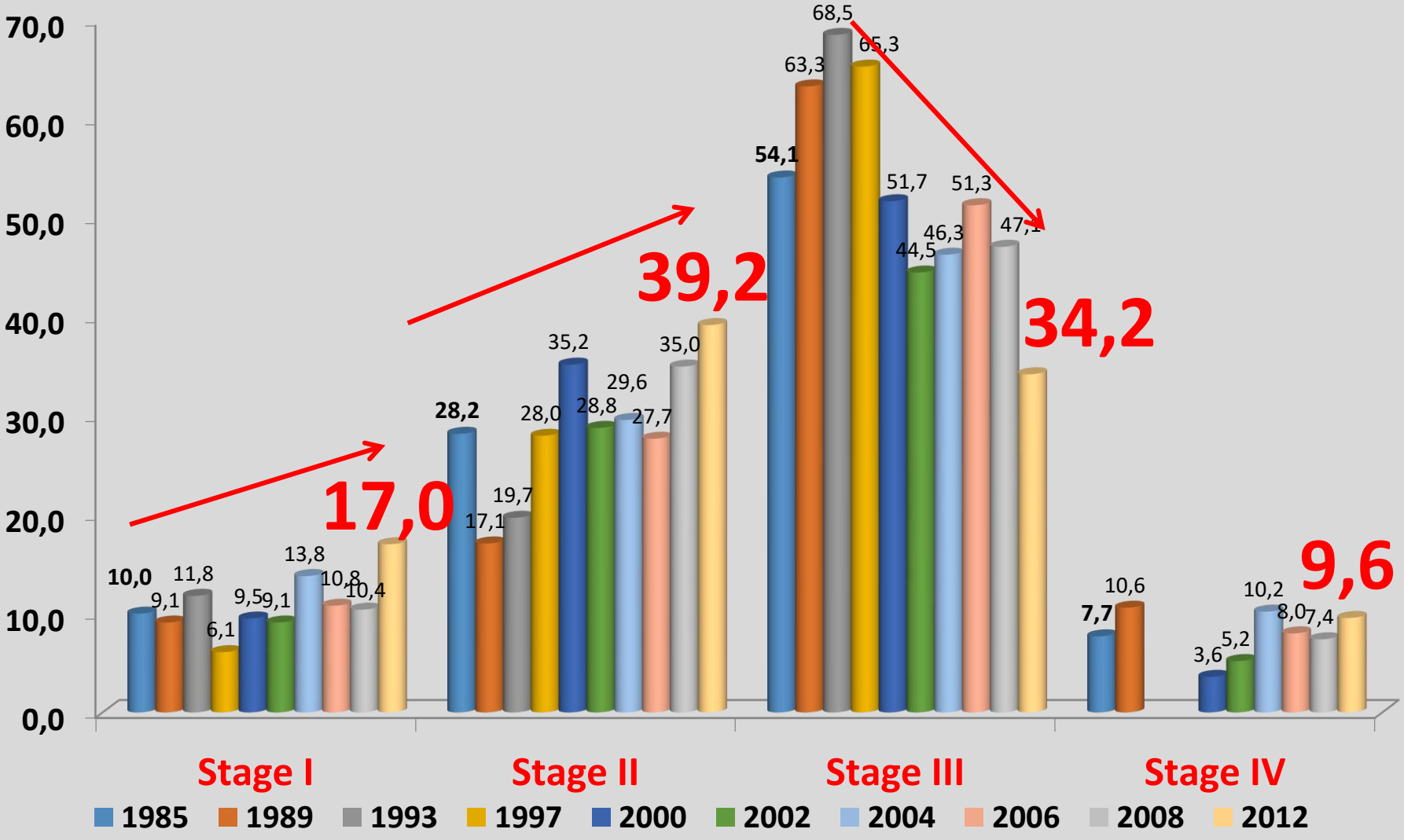


New Cervical Cancer Case every year : 1200 – 1500

Radiation therapy at our Institution : 600-700 pts every year

Tata Memorial Hospital Cancer Registry (1985-2012)

Significant Down Staging!



Tata Memorial Hospital

ROUTINE GYN BRACHYTHERAPY PRACTICE PRINCIPLES

- GYN BT Applications: 4 - 10 (Avg. 6)
- Cervical cancer BT under anesthesia daily: 4-8 (Avg. :6) including IC+ IS
- Vault BT (Endometrium/Cervix post-op): 1 - 2
- Interstitial Templates : 1-2 Interstitial/wk
- Planning Imaging* :

  - 3-4 orthogonal X-ray based

  - 3-4 CT and 1-2 MR Based Planning

** All patient undergo CT based planning mandatory for first #*

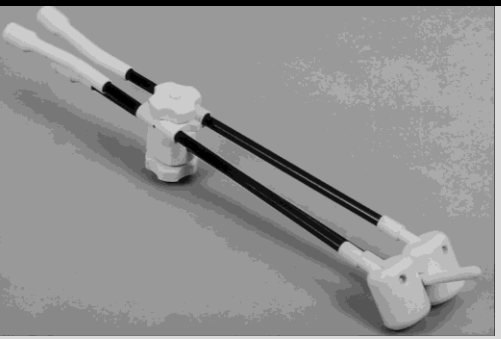
OUTLINE

- *Limitations of STD Intracavitary Applicators*
- *Conventional Interstitial Techniques*
- *Modern Intracavitary + Interstitial Techniques*
- *Optimizing Applicator placement by Image guidance*
- *Principles of Selection of Appropriate Technique*

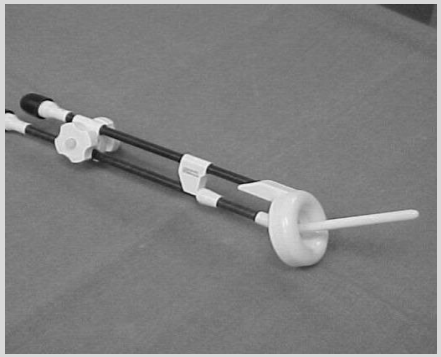
Limitations of pure intracavitary techniques

- *middle/distal parametrial tumor extension*
- *unfavourable topography/unfavourable relation to the applicator (e.g. asymmetrical tumors) (depending on applicator position)*
- *2-3 cm distal intravaginal tumor growth*
- *para-vaginal tumor growth*
- *unfavourable topography of organs at risk (not predictable – correction within the frame of subsequent applications)*

264 patients

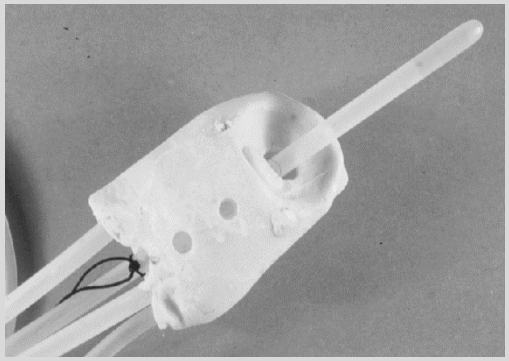


Modern Manchester Applicator

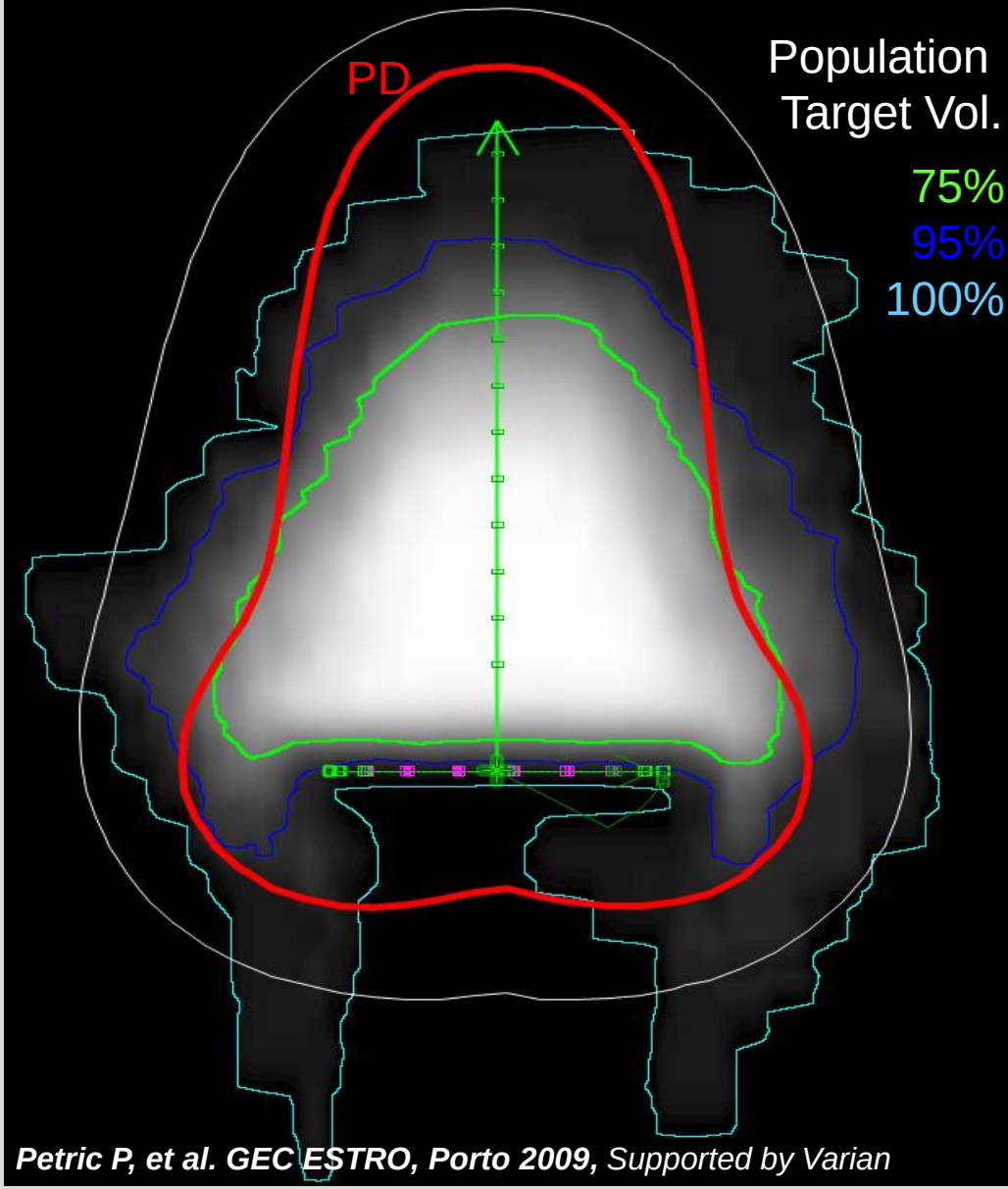


Modern Stockholm Applicator

Ring applicator



Mould Applicator



Petric P, et al. GEC ESTRO, Porto 2009, *Supported by Varian*

Courtesy: P. Petric,D. Berger

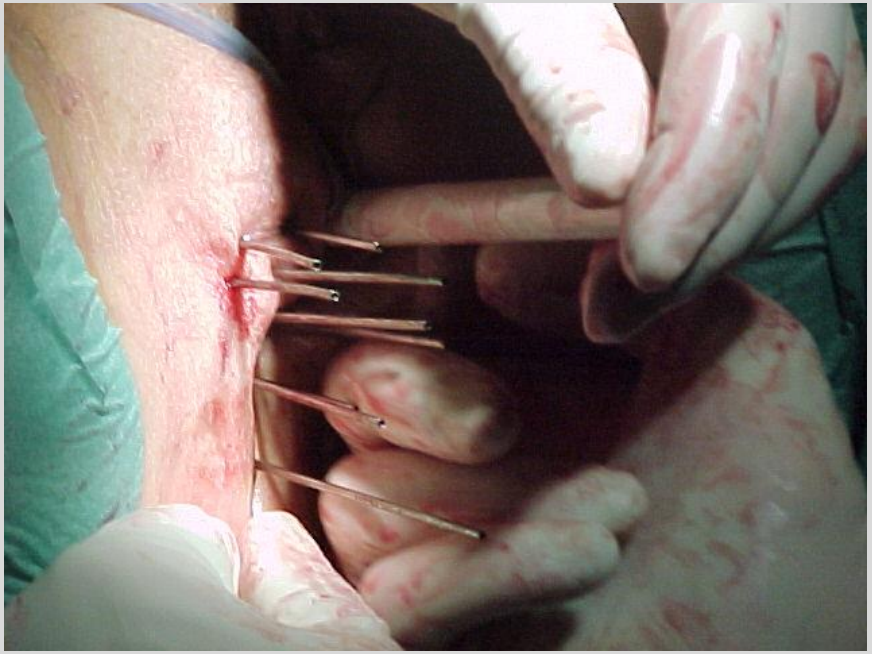
Indications for combined intracavitary/interstitial

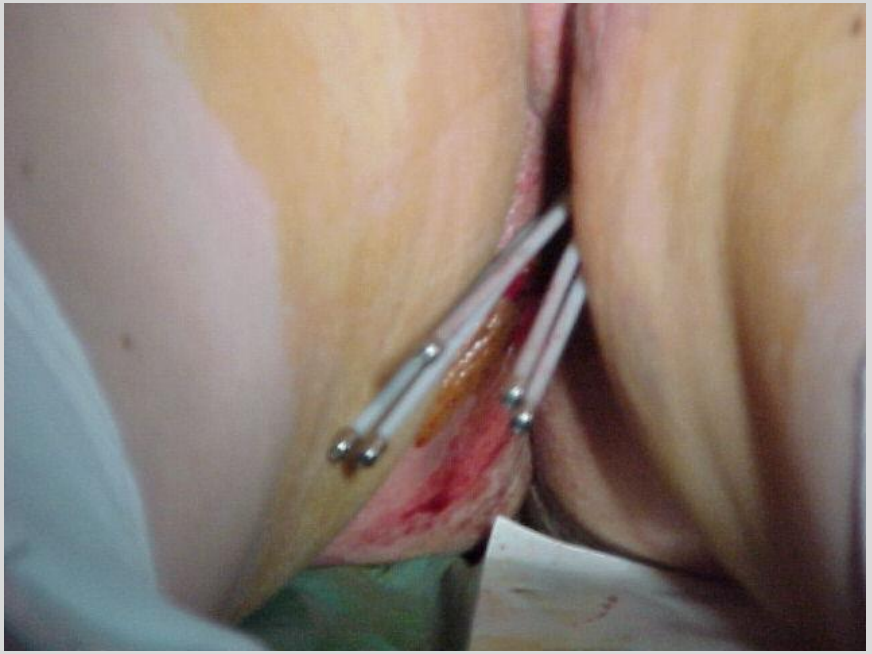
- *middle/distal parametrial tumor extension*
- *unfavourable topography/unfavourable relation to the applicator (e.g. asymmetrical tumors) (depending on applicator position)*
- *distal intravaginal tumor growth*
- *para-vaginal tumor growth*
- *unfavourable topography of organs at risk (not predictable – correction within the frame of subsequent applications)*

INTERSTITIAL TECHNIQUES
AIMS IN LOCALLY ADVANCED DISEASE

- *accurate and reproducible placement of needles*
- *tailor positions of needles to the target*
- *tailor dose distribution to target and OAR*
  - *adequate target coverage*
  - *Optimal sparing of OAR*

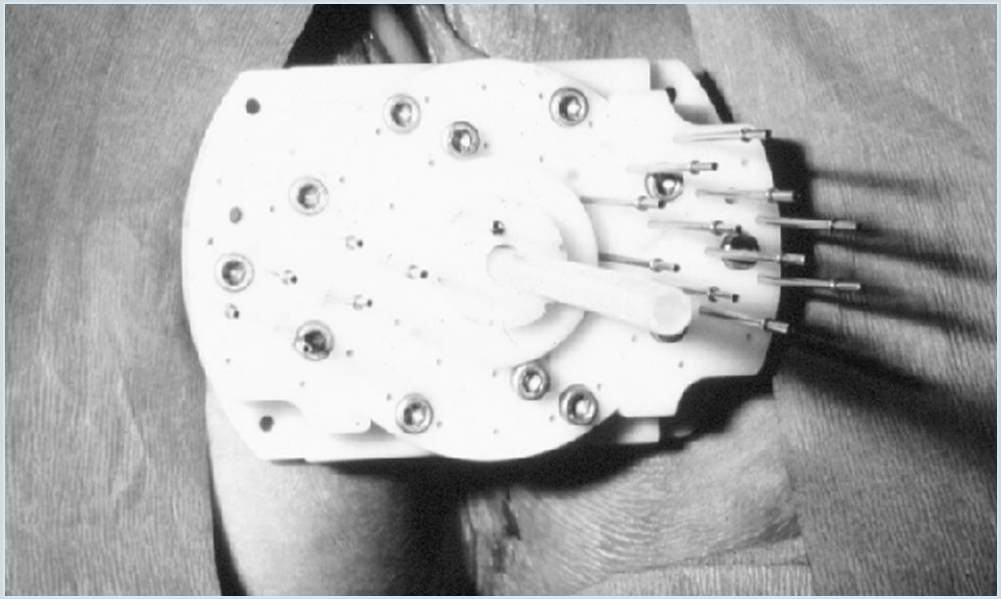
CLASSICAL INTERSTITIAL TECHNIQUES
FREEHAND PLACEMENT



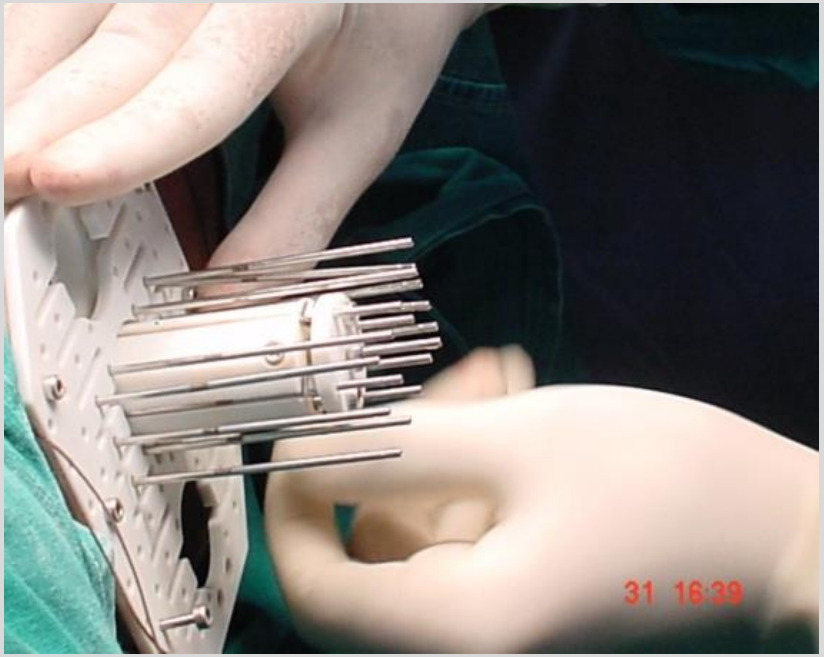


CLASSICAL INTERSTITIAL TECHNIQUES
PERINEAL TEMPLATES

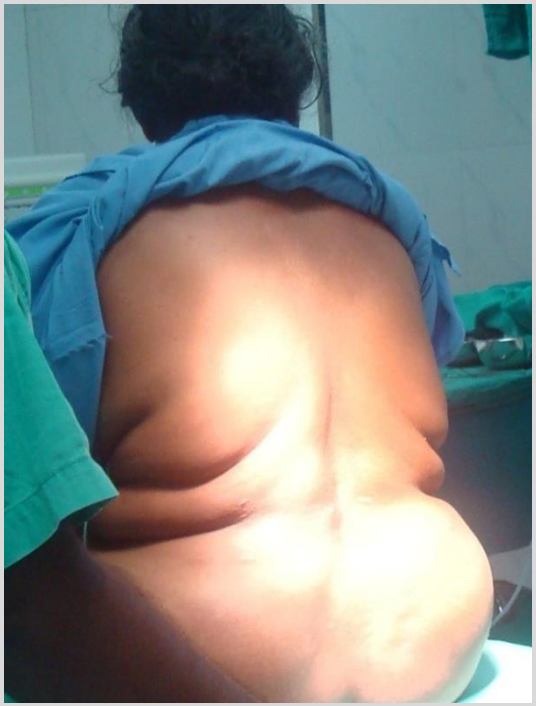
SYED

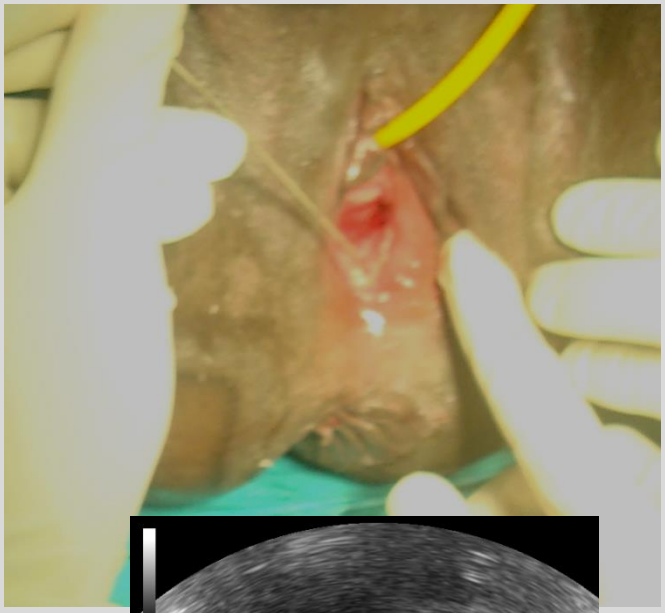


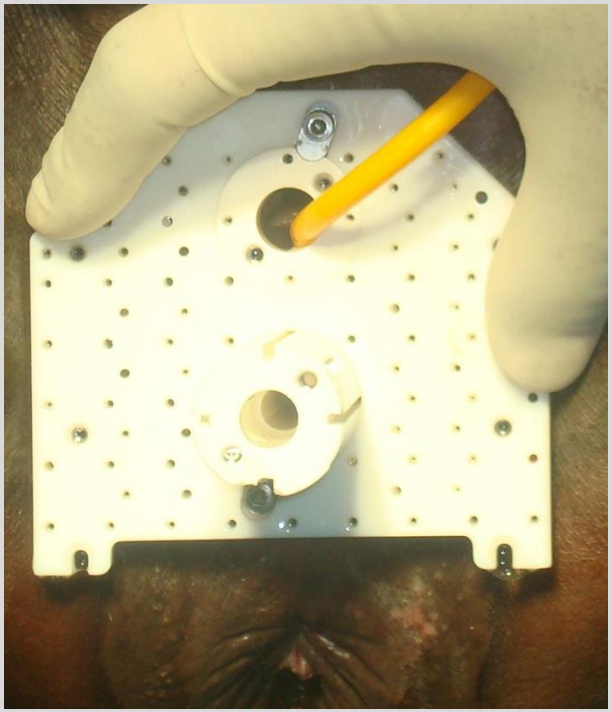
MUPIT

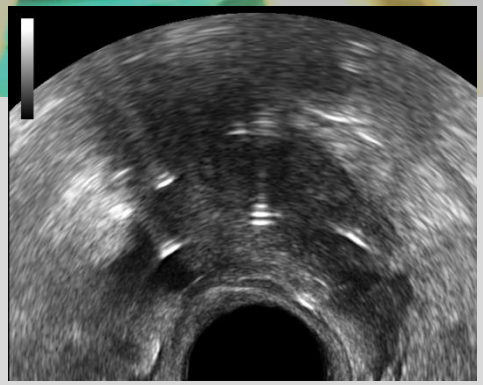


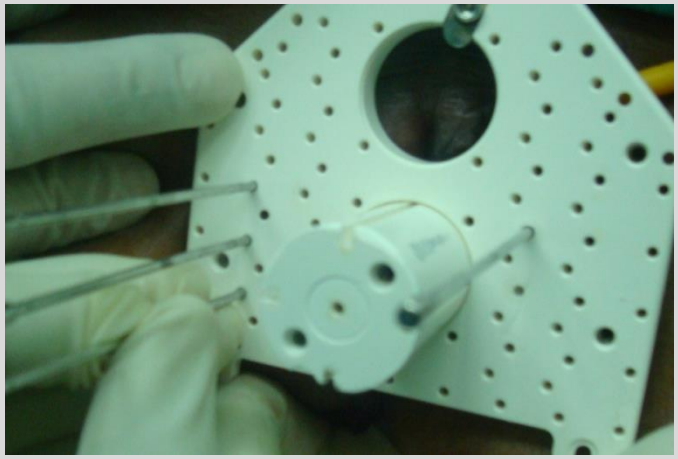
PRINICPLES OF MUPIT PROCEDURE

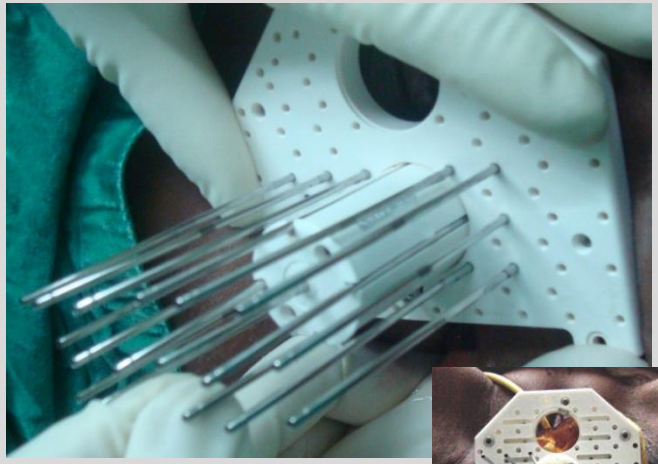


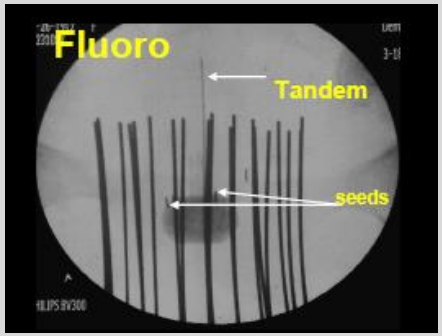


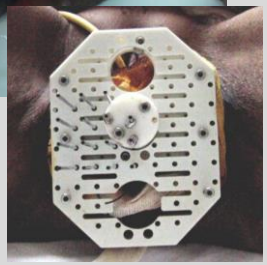






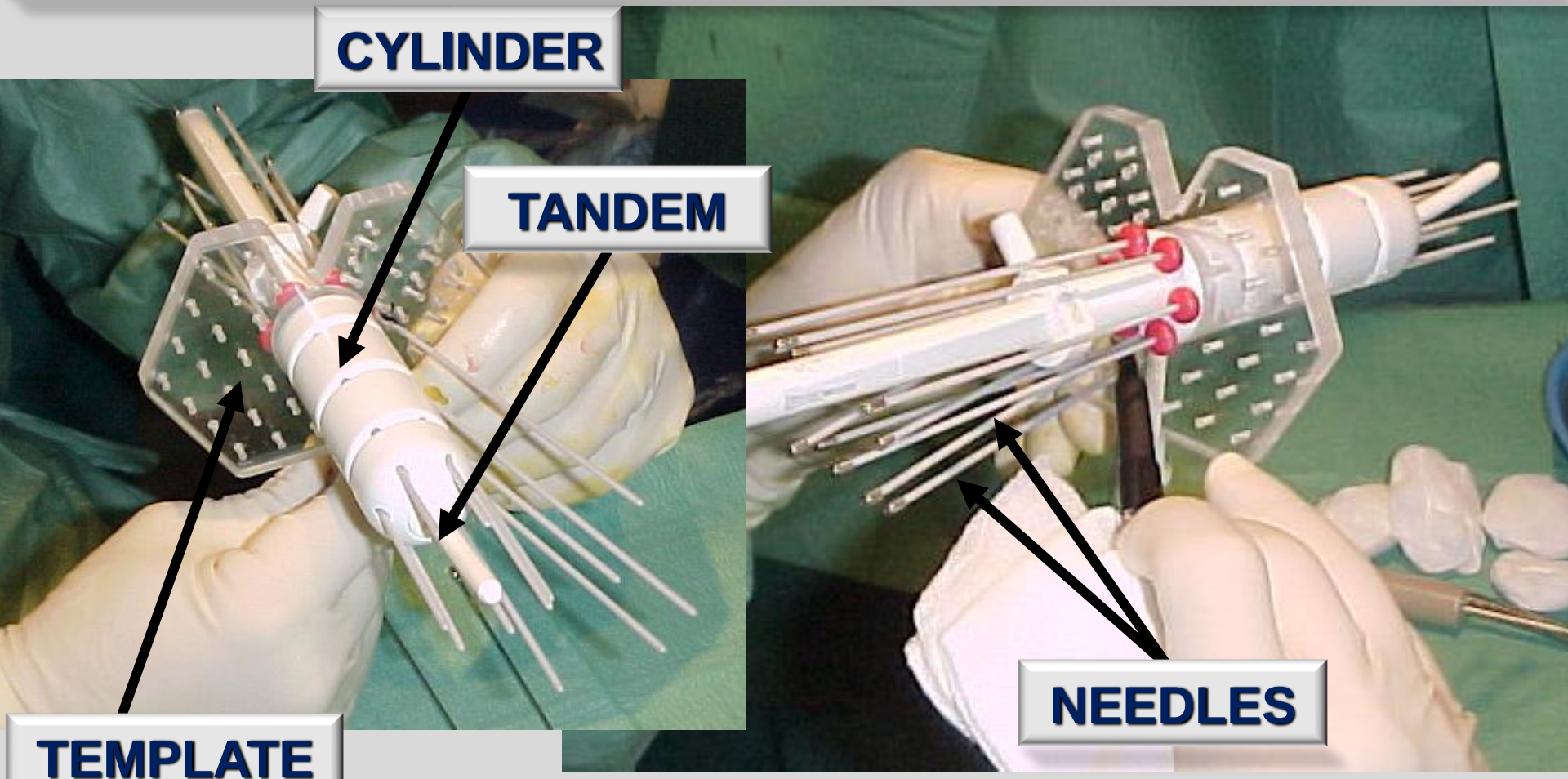






MODIFIED CLASSICAL INTERSTITIAL TECHNIQUES

MRI-compatible cylinder + tandem + template



CLASSICAL & MODIFIED INTERSTITIAL TECHNIQUES

DRAWBACKS

- *Accurate freehand implantation is difficult*
  - *positioning often inaccurate*
  - *loss of parallelism*
  - *not reproducible*

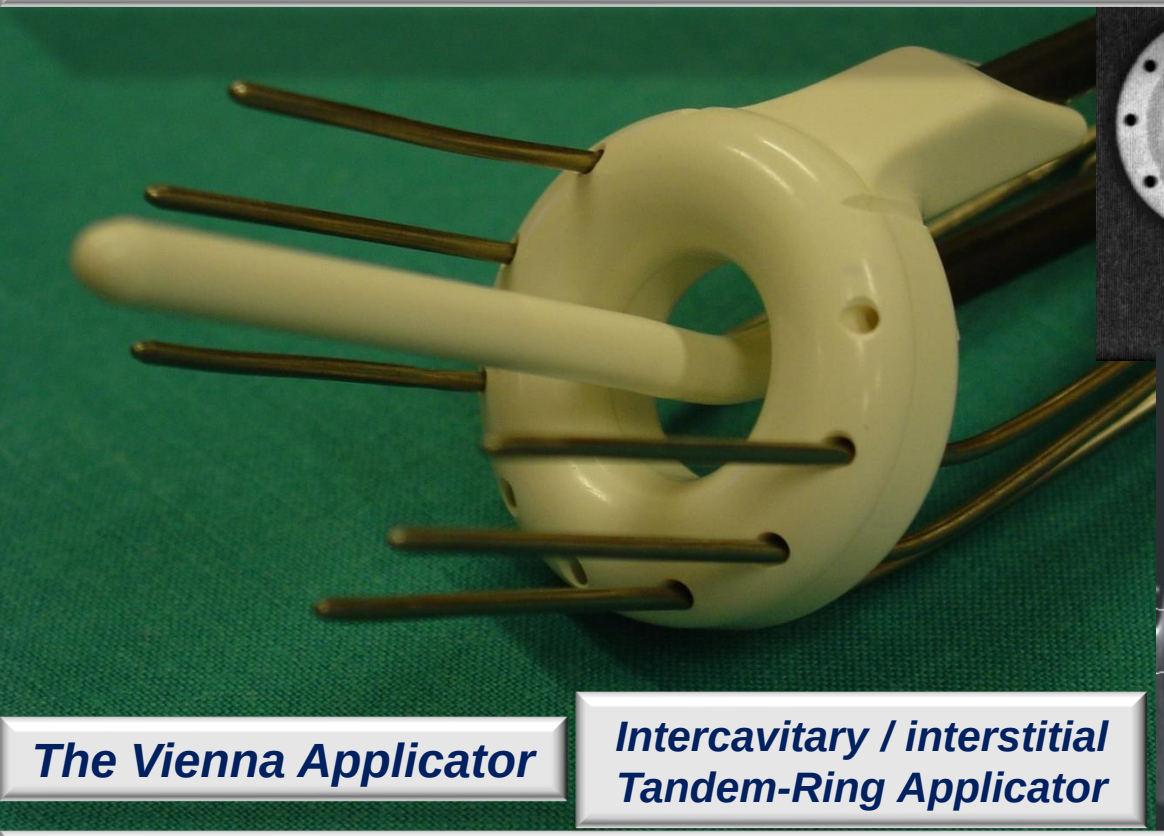
- *Perineal templates (Syed, MUPIT, others)*
  - *high number of needles used*
  - *long distances between template and target (loss of parallelism, inaccurate positioning)*
  - *impediment for general acceptance: considerable risk of serious acute/late complications*

INTRACAVITARY + INTERSTITIAL TECHNIQUES

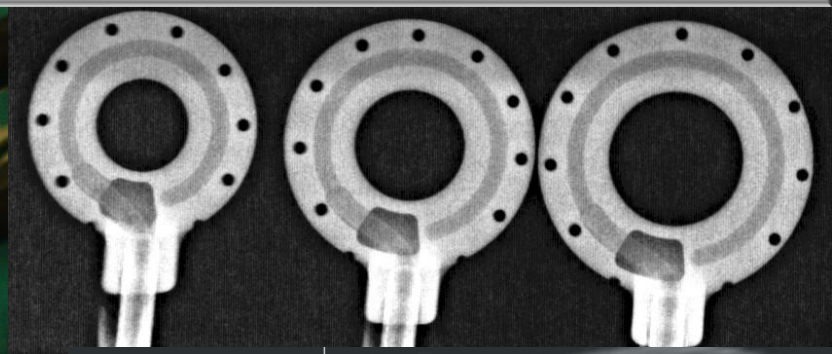
TASKS

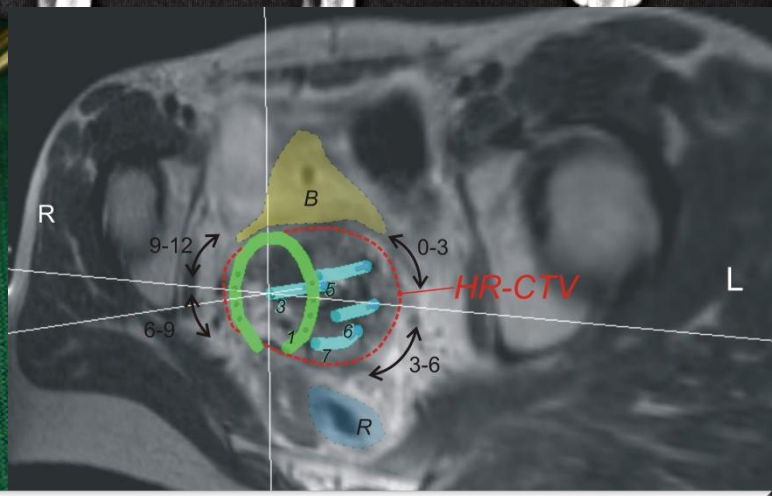
- *improve control over the placement of needles: short distance between template and the target (accurate and reproducible insertion)*
- *lesser number of needles to achieve an adequate target coverage*
- *to be combined with individualised MRI based treatment planning to tailor the dose distribution (improve local control without increasing side effects)*

MODERN INTERSTITIAL TECHNIQUES



The Vienna Applicator





Intercavitary / interstitial Tandem-Ring Applicator

Modified Applicator: drilled holes into ring to insert needles parallel to the Tandem

Kirisits et al. IJROBP 2006 (technical note)
Dimopoulos et al. IJROBP 2006 (clinical results)

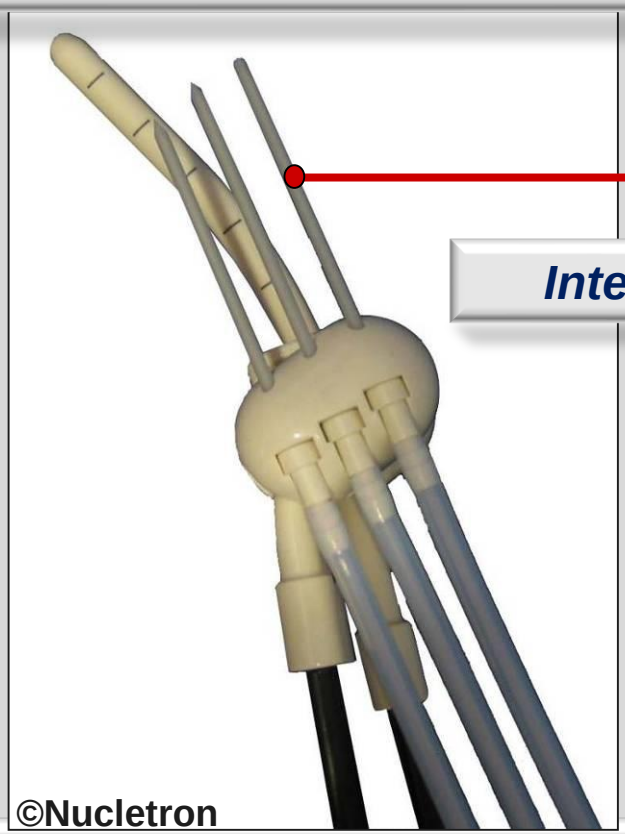
MODERN INTERSTITIAL TECHNIQUES

Applicators – special situations

Cervical cancer with moderate lateral expansion: modified principles of treatment

The Utrecht Applicator

Intracavitary / interstitial Fletcher Applicator



Interstitial tubes/needles

Schulz I, et al. Radiother Oncol., with permission

COMBINED INTRACAVITARY & INTERSTITIAL TECHNIQUES

SELECTION OF APPLICATION TECHNIQUE

Based on clinical examination and sectional imaging:

At the time of diagnosis

- Initial tumor extension

During EBRT

-Quantitative and qualitative tumor regression

At the time of brachytherapy

-Topography of residual tumor in relation to the applicator

Selection of Brachytherapy Technique

In General: depending on residual disease at brachytherapy

- Disease confined to cervix and medial third parametrium and

  favourable topography: IC alone

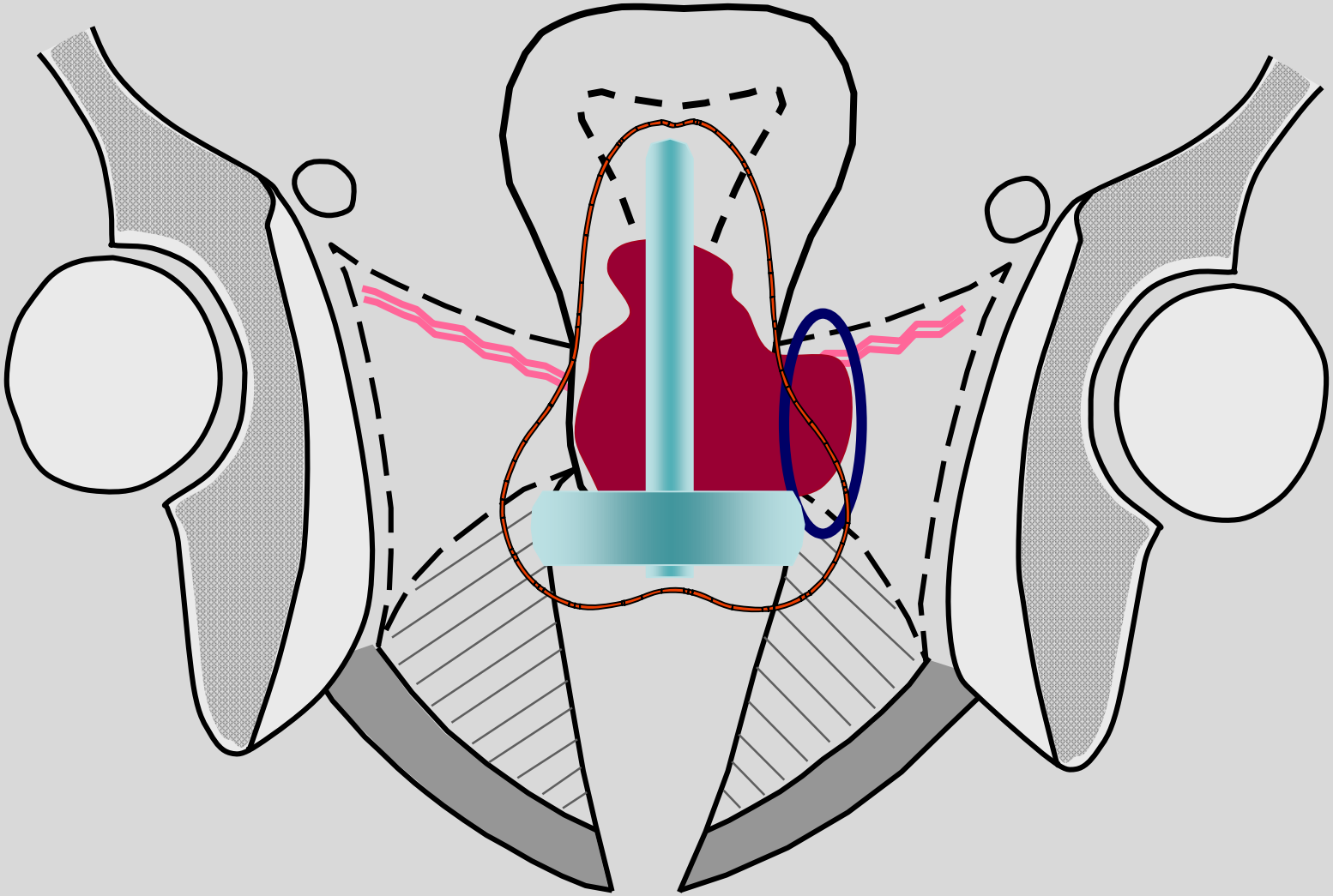
  unfavouable topography: combined IC + IS

- Extensions beyond medial third parametrium: IC + IS combination
- Extensive vaginal disease at BT: vaginal cylinders + IC + IS
- Extensions beyond medial third parametrium: IC + IS combination

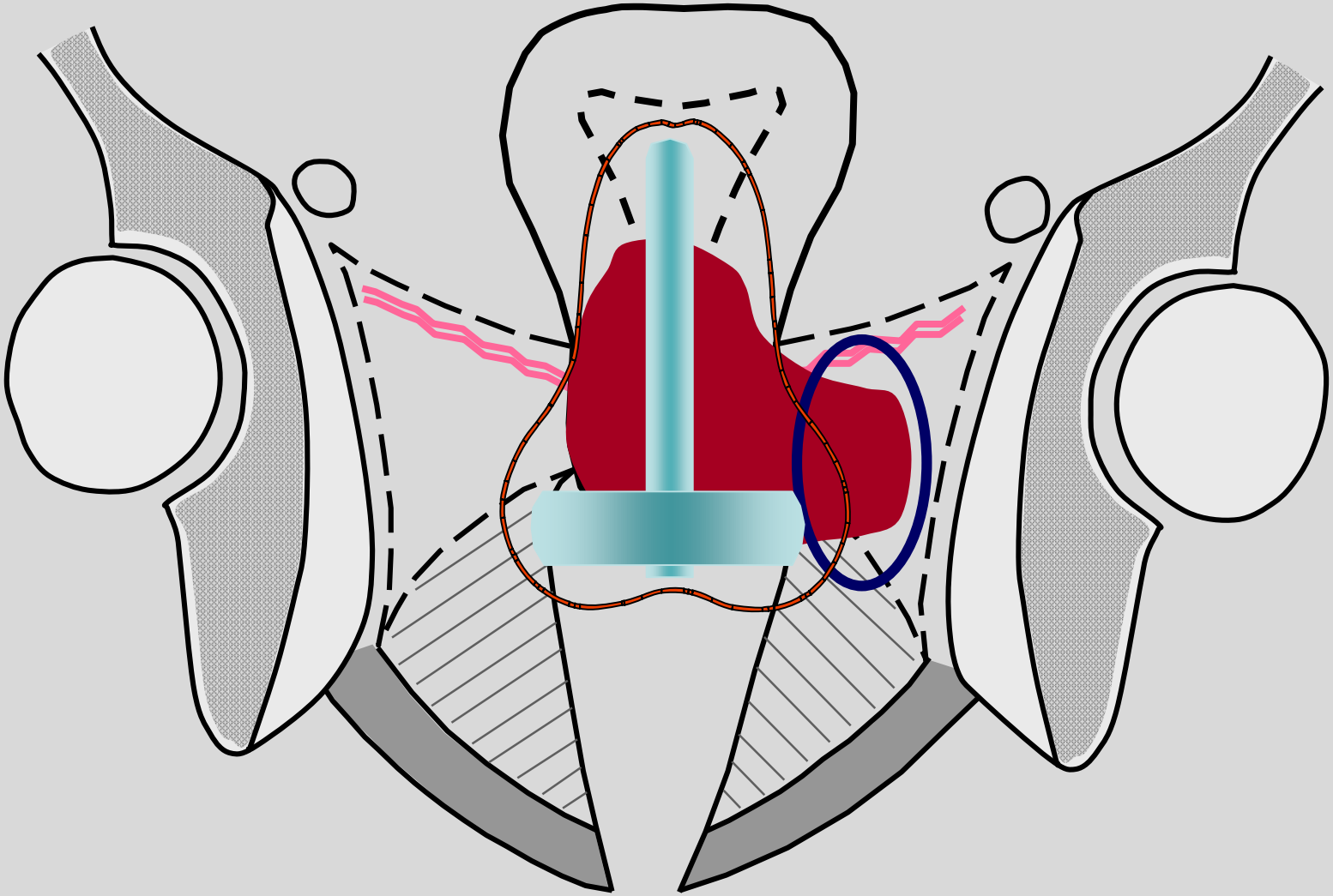
- Extensive disease not amenable to standard situations: IC + IS +…

• Applications my be modified in subsequent fractions (esp. HDR)

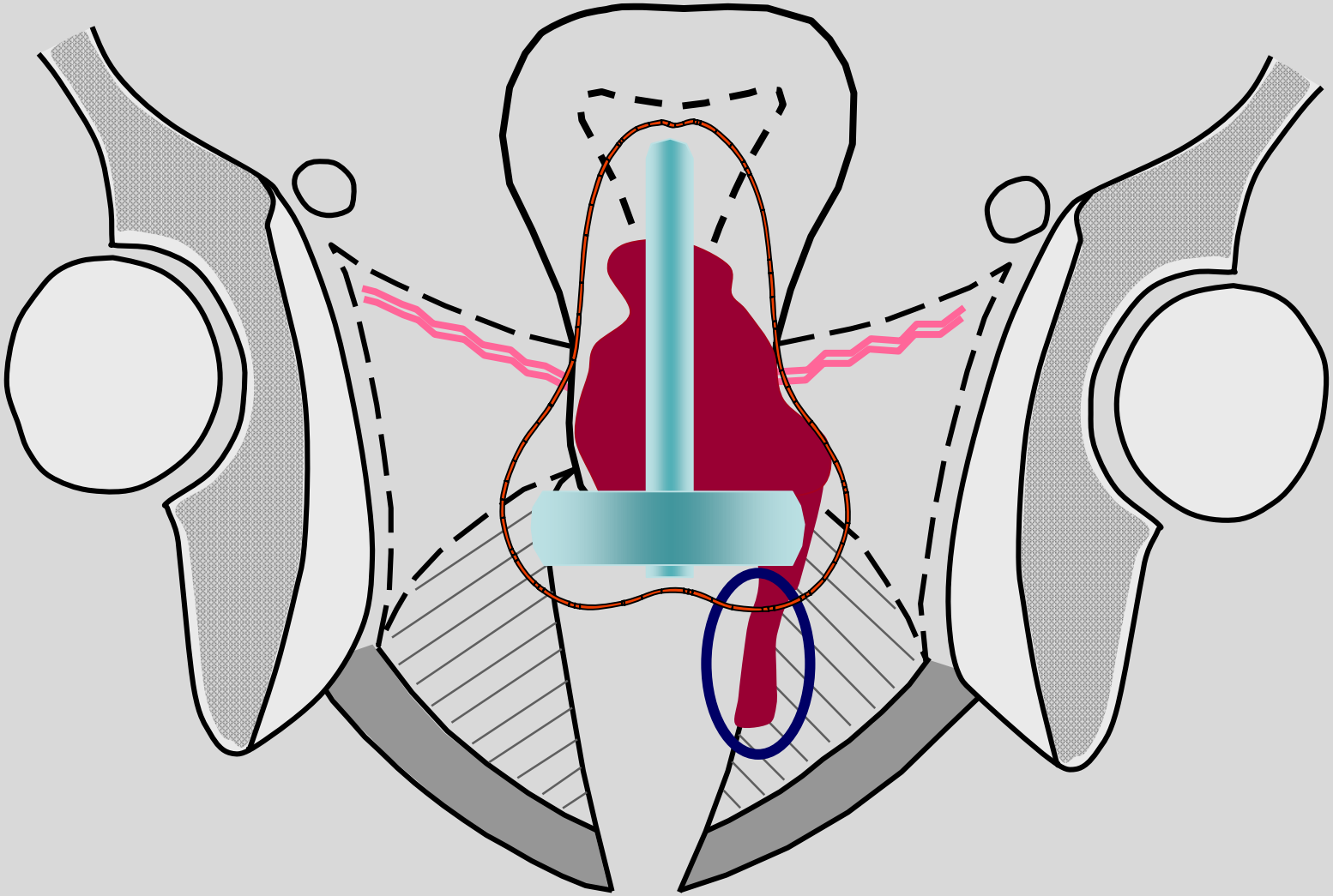
DETECTION OF INAPPROPRIATE COVERAGE: 1



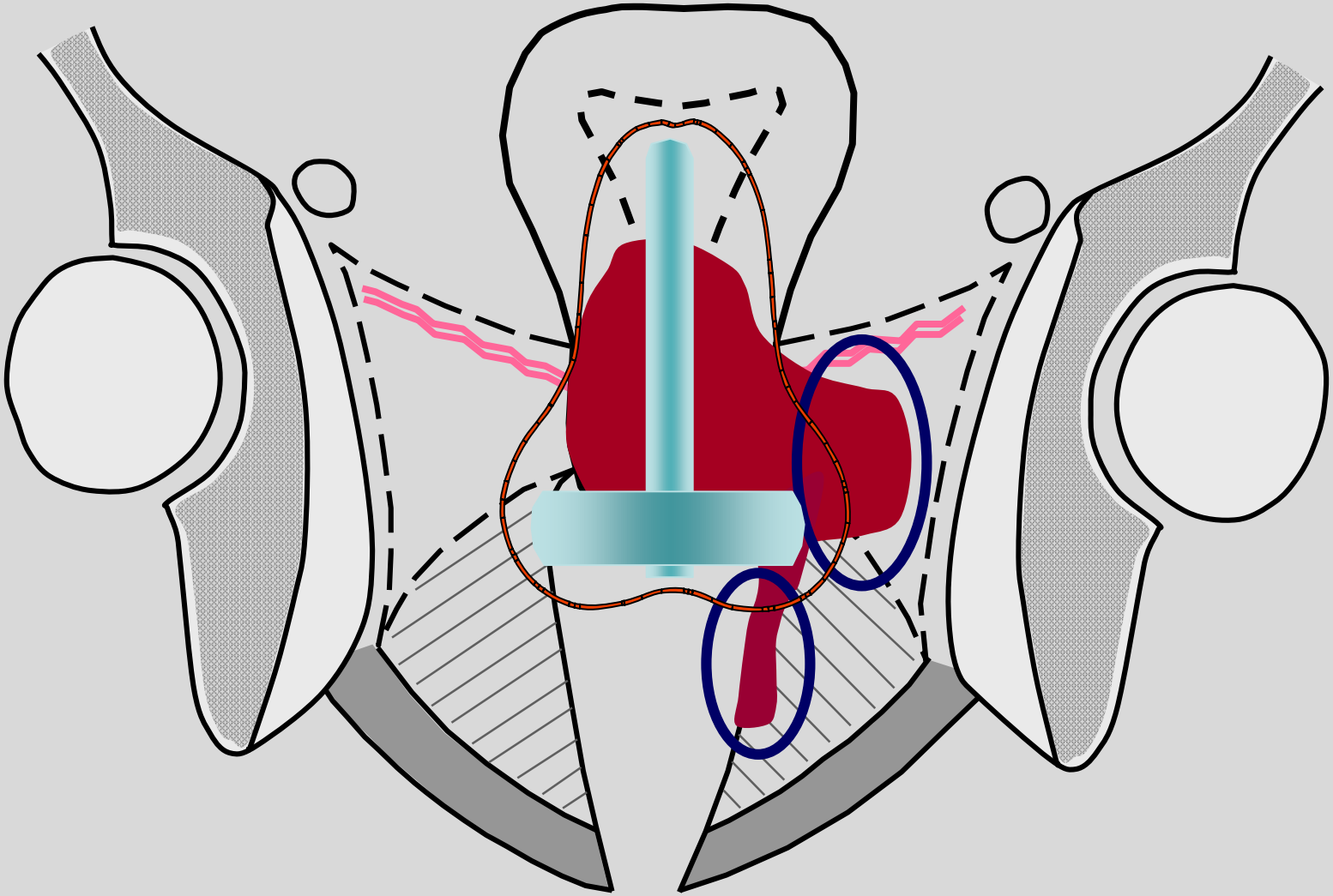
DETECTION OF INAPPROPRIATE COVERAGE: 1A



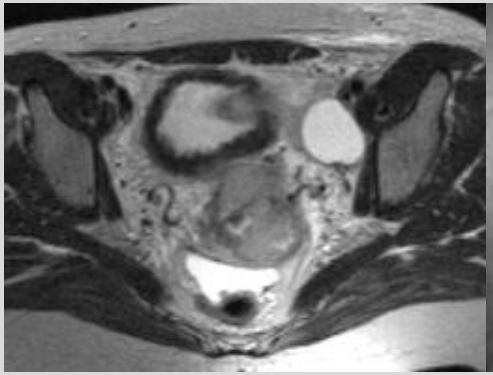
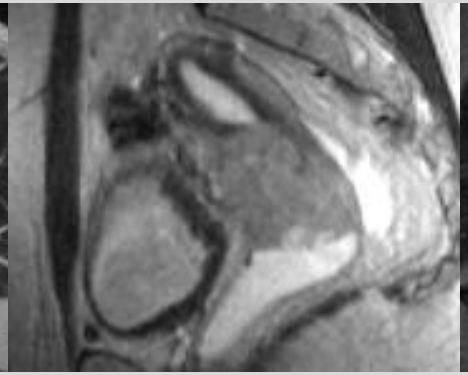
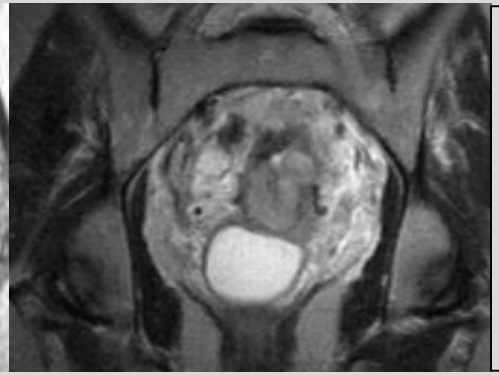
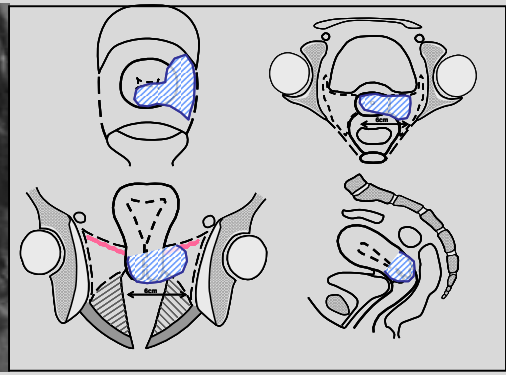
DETECTION OF INAPPROPRIATE COVERAGE: 2

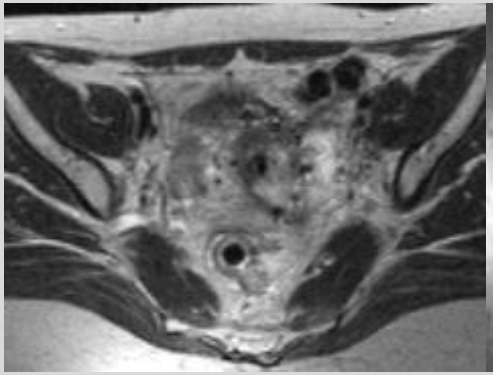
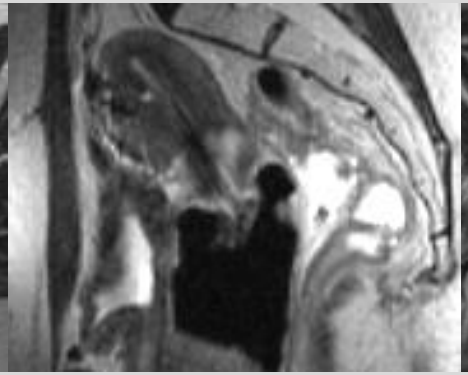
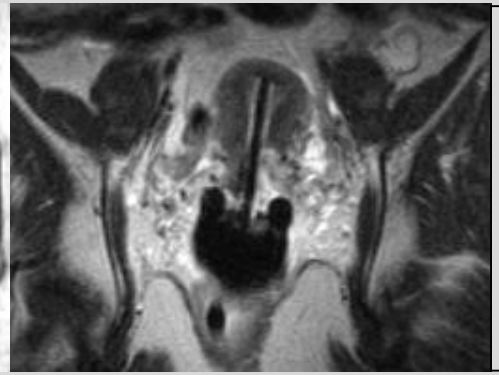
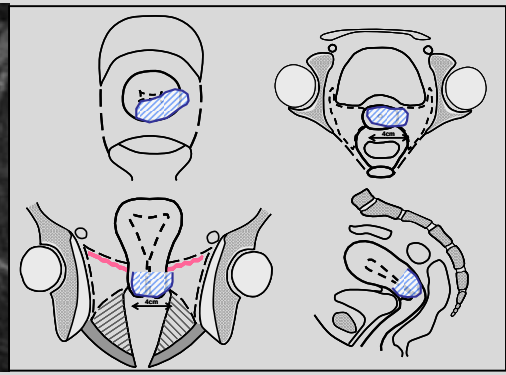


DETECTION OF INAPPROPRIATE COVERAGE: 2A



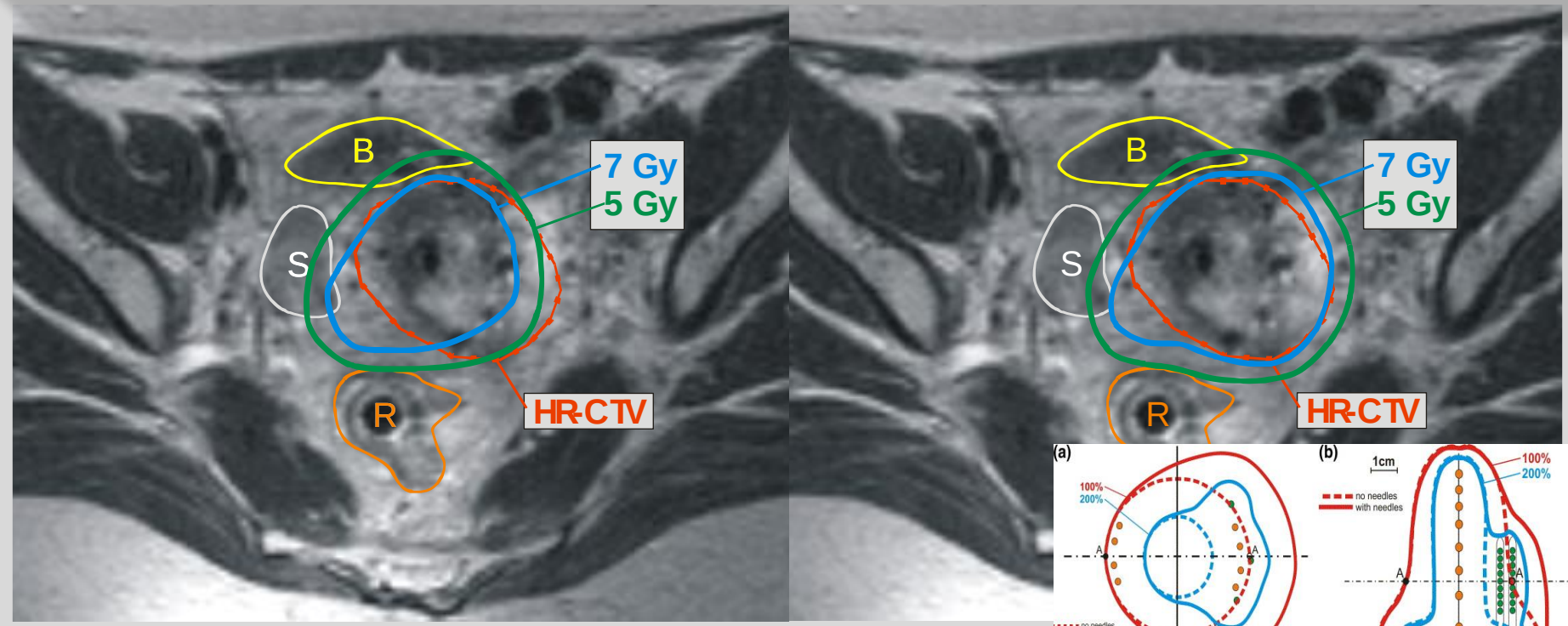
Clinical example
Stage IIB / distal / insufficient response

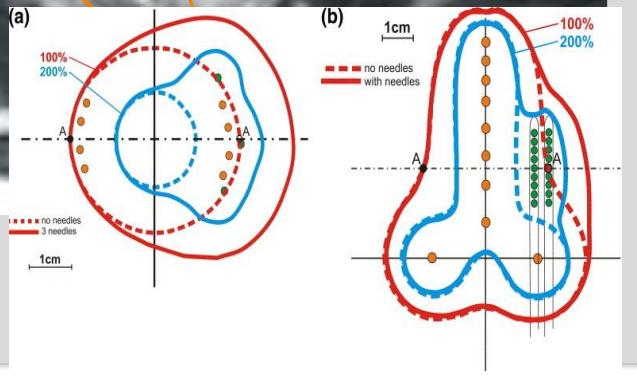





Clinical example - Interstitial Treatment MRI Based Treatment Planning plus Novel Application Technique

standard treatment plan **optimized interstitial**

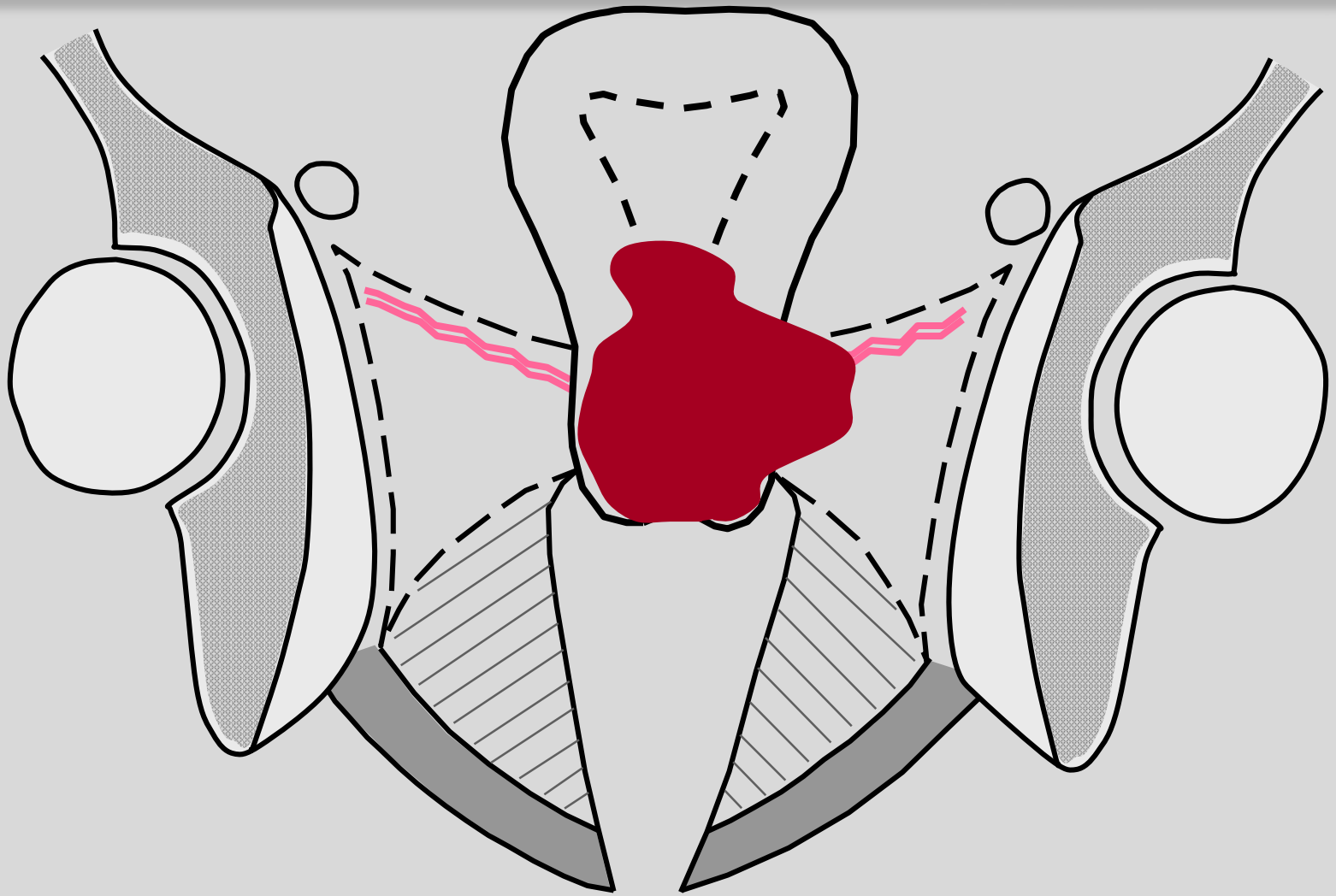




INTRACAVITARY PLUS NEEDLES LEFT PARAMETRIUM

Improved placement control - Low number of needles – Combined with MRI based treatment planning

Pattern of tumor regression: 1



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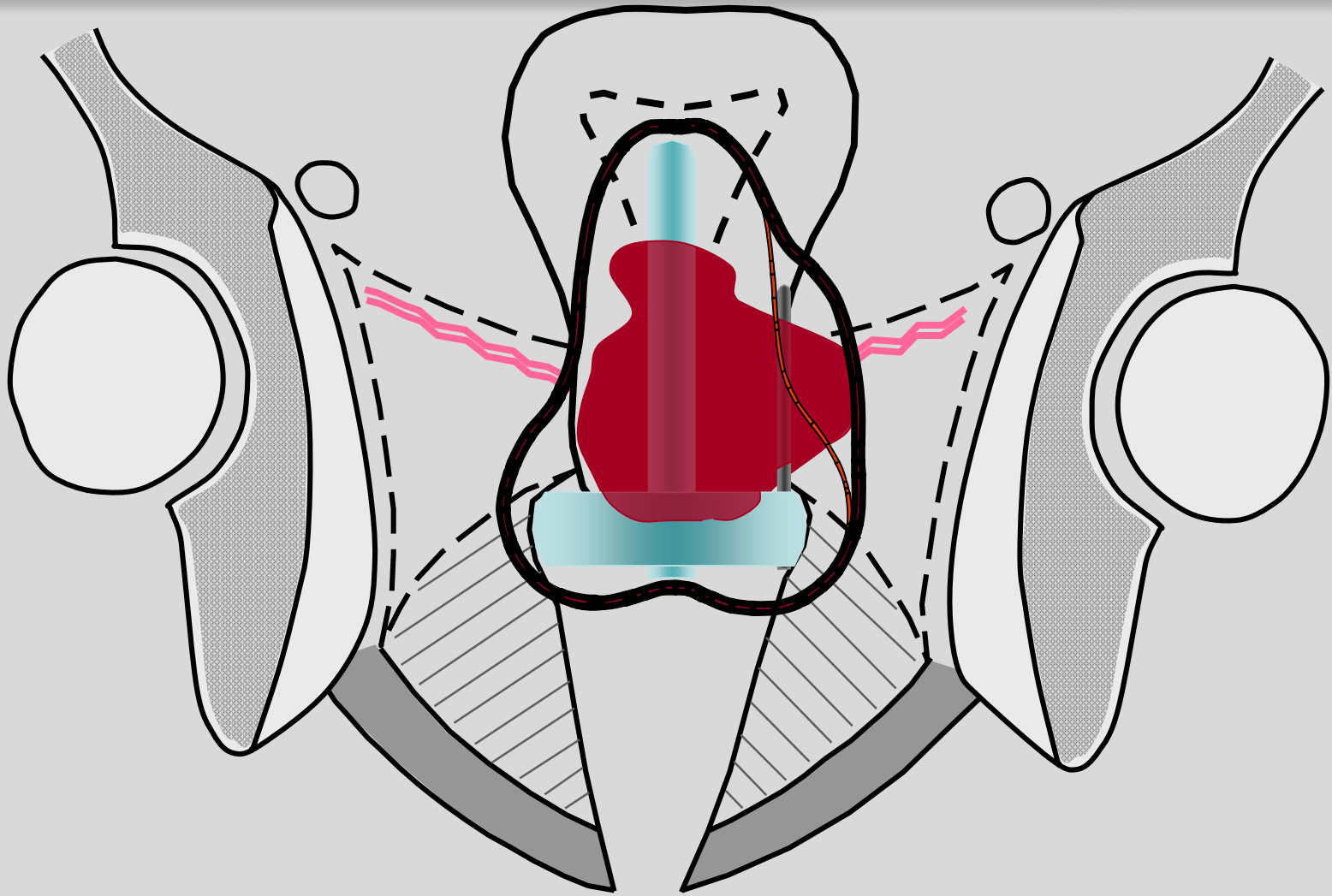
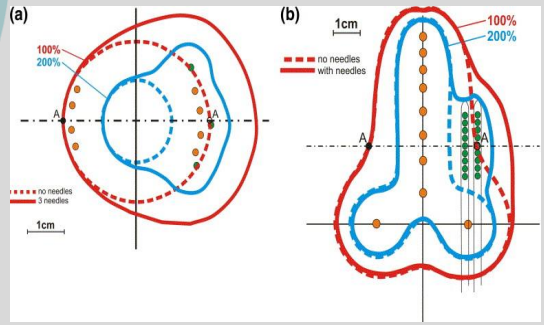


The Vienna Applicator

Intercavitary / interstitial
Tandem-Ring Applicator

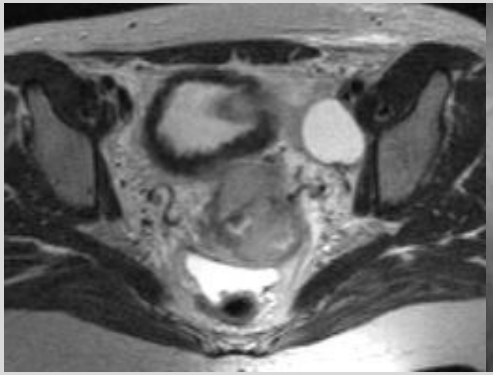
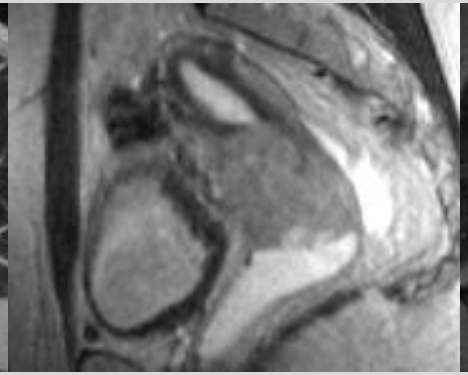
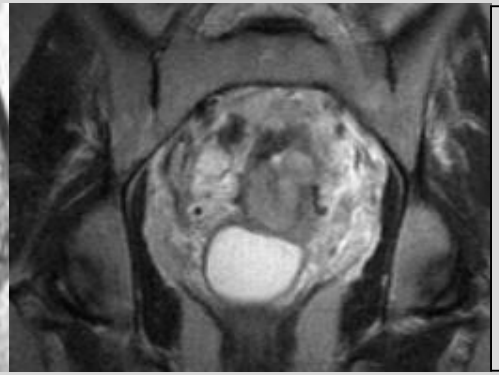
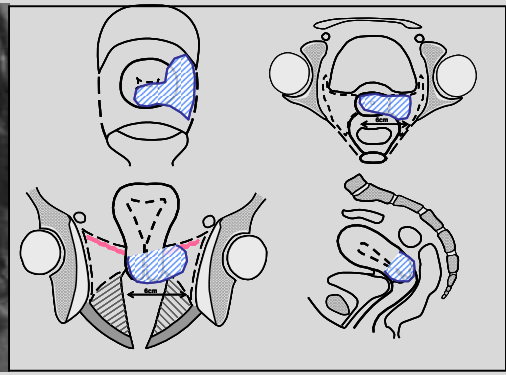


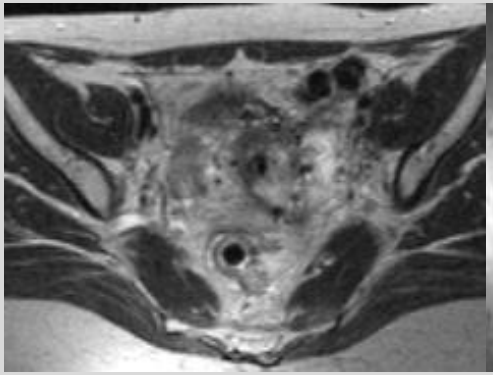
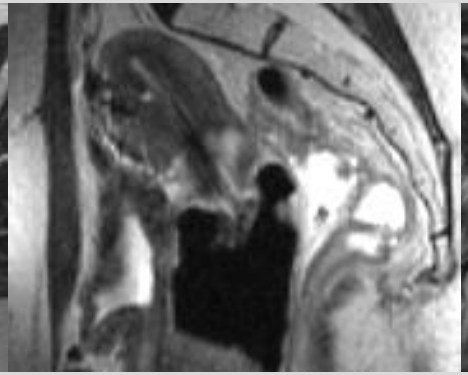
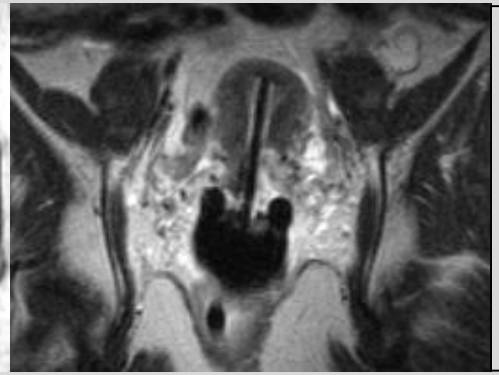
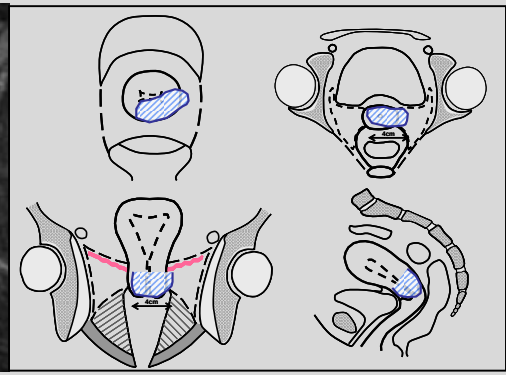
Modified Applicator: drilled holes into ring to insert needles parallel to the Tandem

Kirisits et al. IJROBP 2006 (technical note)

Dimopoulos et al. IJROBP 2006 (clinical results)

Clinical example
Stage IIB / distal / insufficient response

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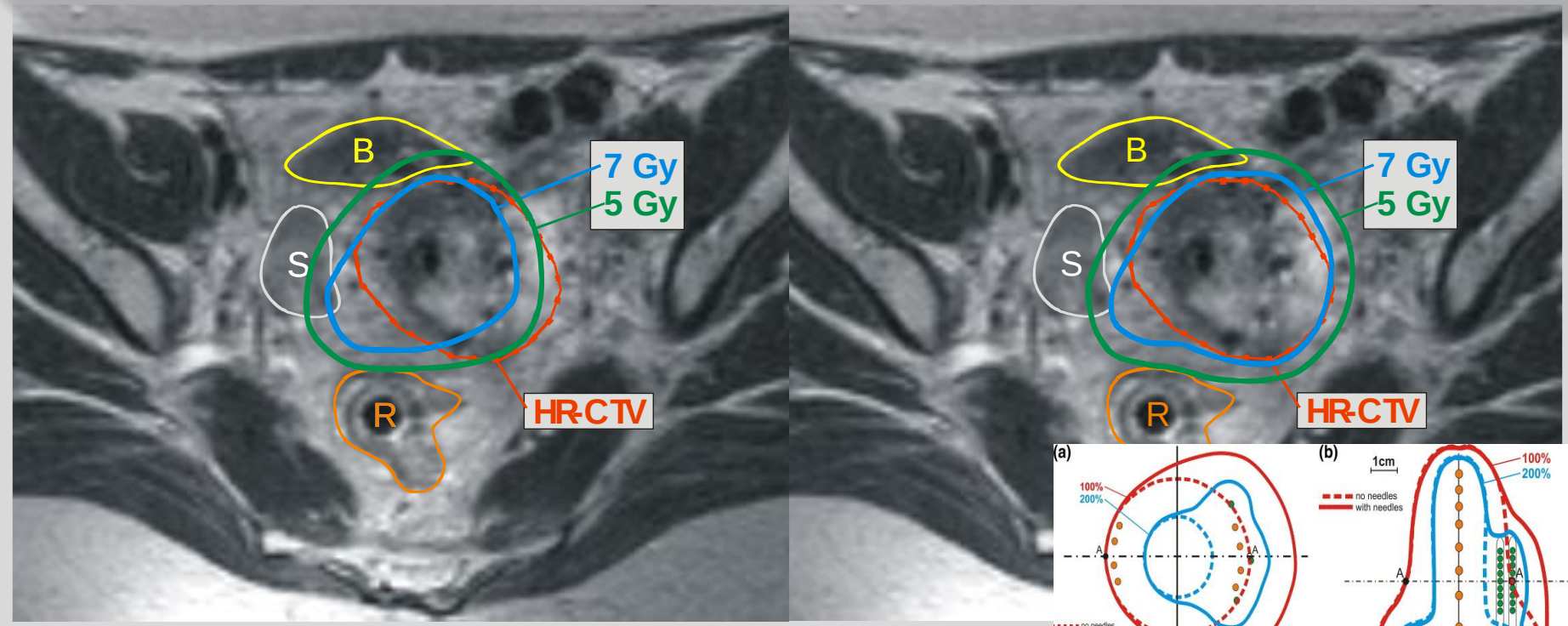
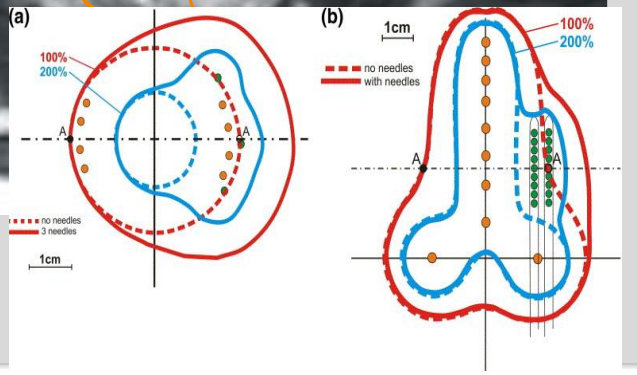




INTRACAVITARY PLUS NEEDLES LEFT PARAMETRIUM

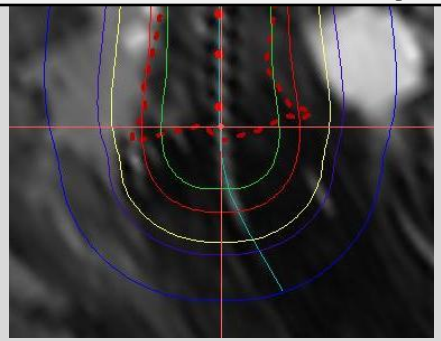
Improved placement control - Low number of needles – Combined with MRI based treatment planning

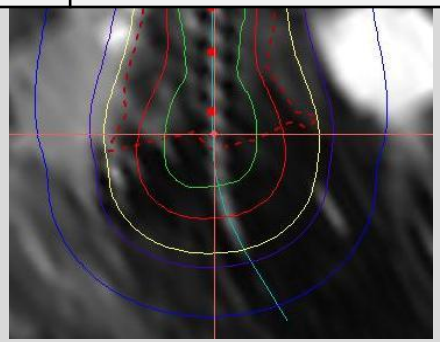
UNFAVORABLE TOPOGRAPHY FOR OAR'S: 1- 2A

STD INTRA-CAVITARY BT

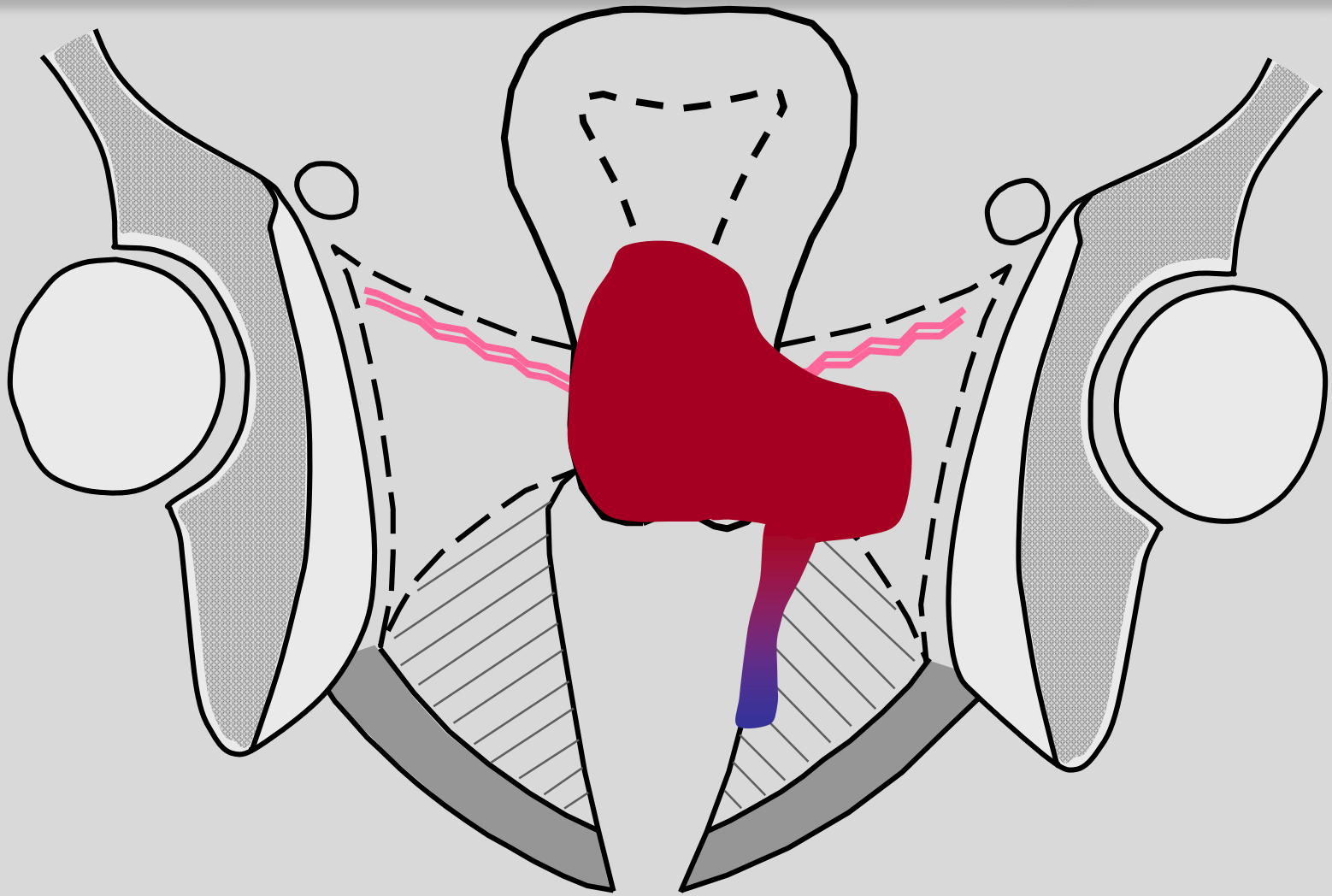
Vienna

Parameters	Ring	Vienna
HRCTV D98 (Gy)	7.6	7.3
HRCTV D90 (Gy)	10.2	8.3
HRCTV V100 (%)	99	99
SIMOID 2CC-Gy	5	4
SIMOID 0.1CC-Gy	7	5.5
BLADDER 2CC-Gy	9	6.3
BLADDER 0.1CC-Gy	11.8	7.8
RECTUM 2CC-Gy	3.9	3.4
RECTUM 0.1 CC-Gy	5.2	4.5

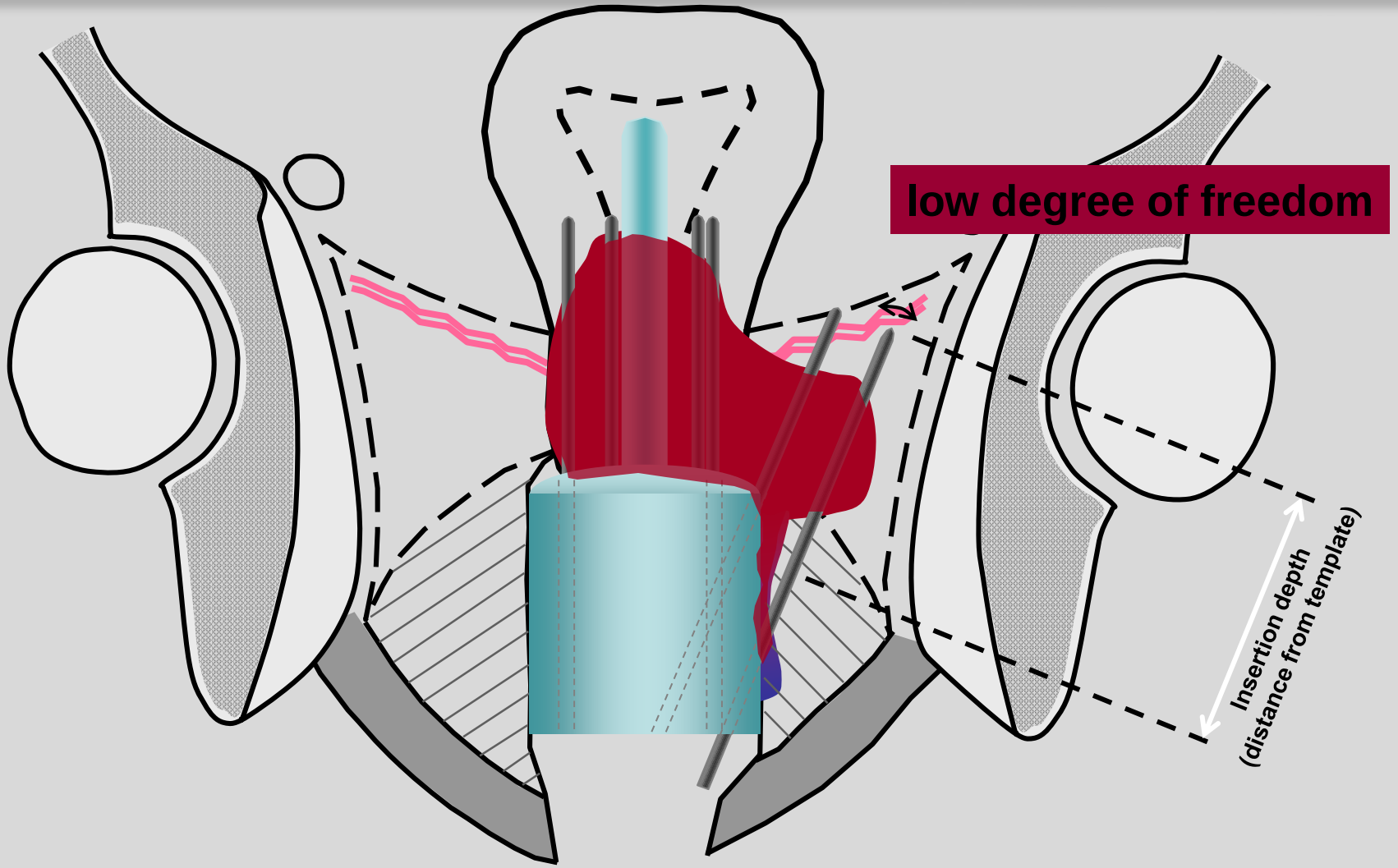




Pattern of tumor regression: 2-2A

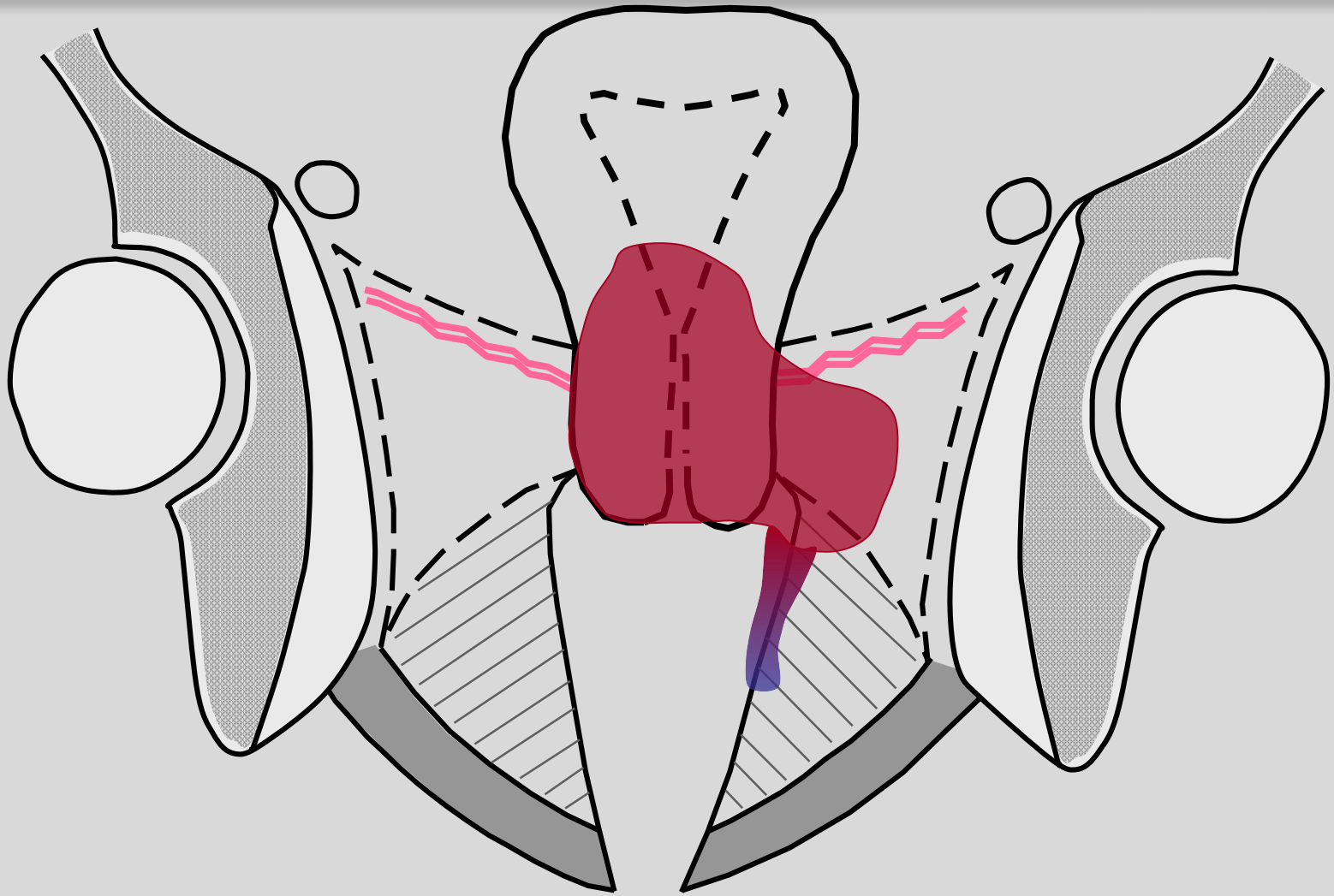


Pattern of tumor regression



Tandem + Cylinder + Needles

Applicator for distal parametrial disease
additional parallel and divergent template guided needles



The Vienna II Applicator

Berger et al. ABS 2010

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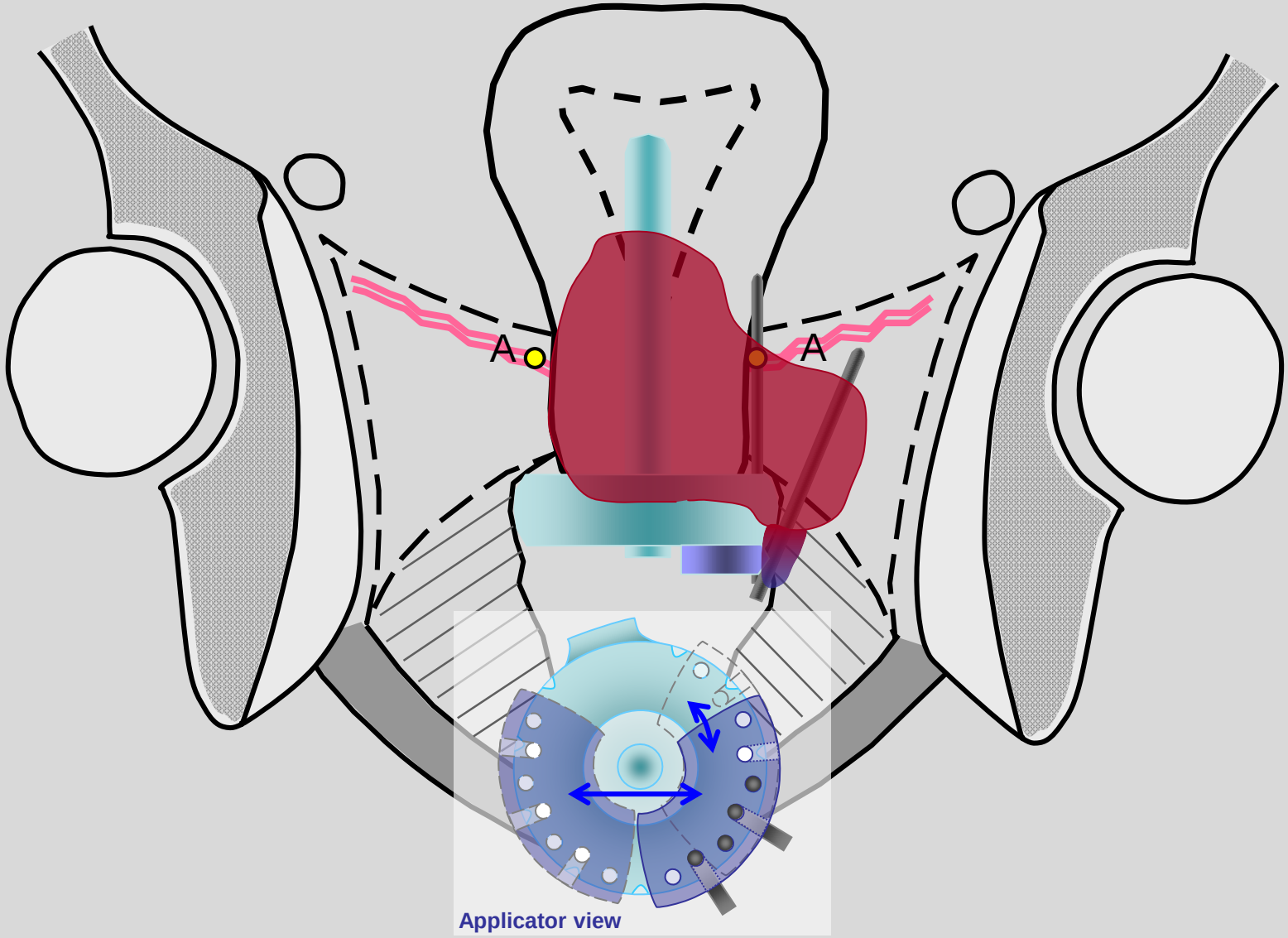


The Vienna II Applicator

Berger et al. ABS 2010

INTRACVITARY +INTERSTITIAL TECHNIQUES

VIDEO PRESENTATIONS

VIENNA I Ring APPLICATION AT AKH VIENNA (Alina)

VIENNA I Ring APPLICATION AT TATA (Umesh)

Intracavitary/interstitial Application at Ljubljana (Primoz)

INTERSTITIAL TECHNIQUES and image guidance
ATTEMPT TO IMPROVE PLACEMENT

NEEDLE PLACEMENT ACCURACY

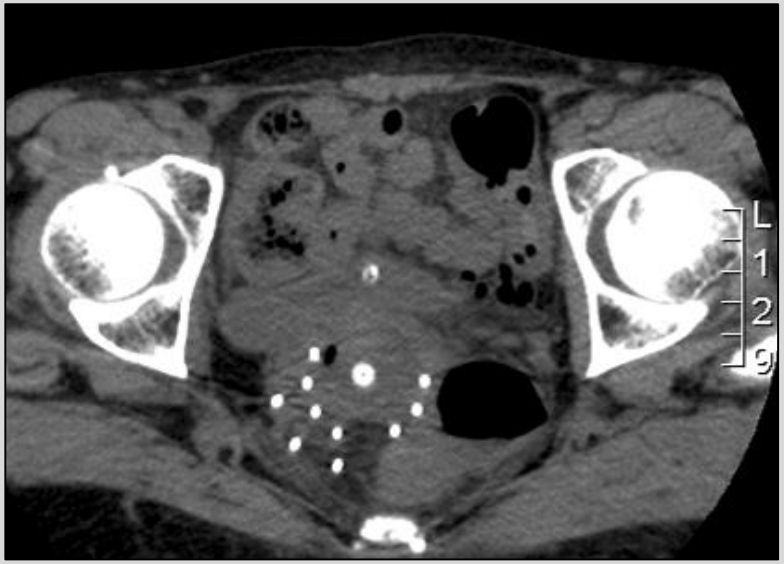
- *(Fluoroscopy)*
- *(Laparotomy guided implants)*
- *Computed tomography*
- *Ultrasound*
- *MRI and open MRI*

Computed Tomography

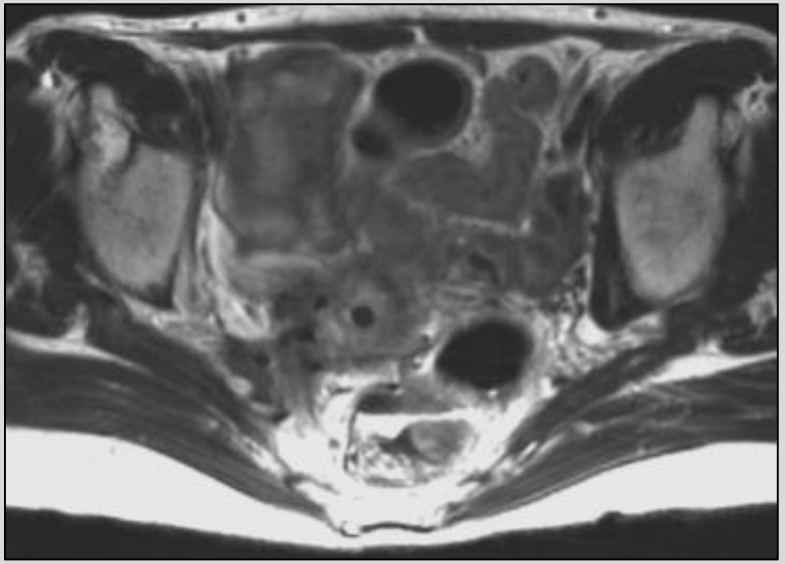
Findings at Brachytherapy

Example: cervix cancer

Assess Tumour size & Topography



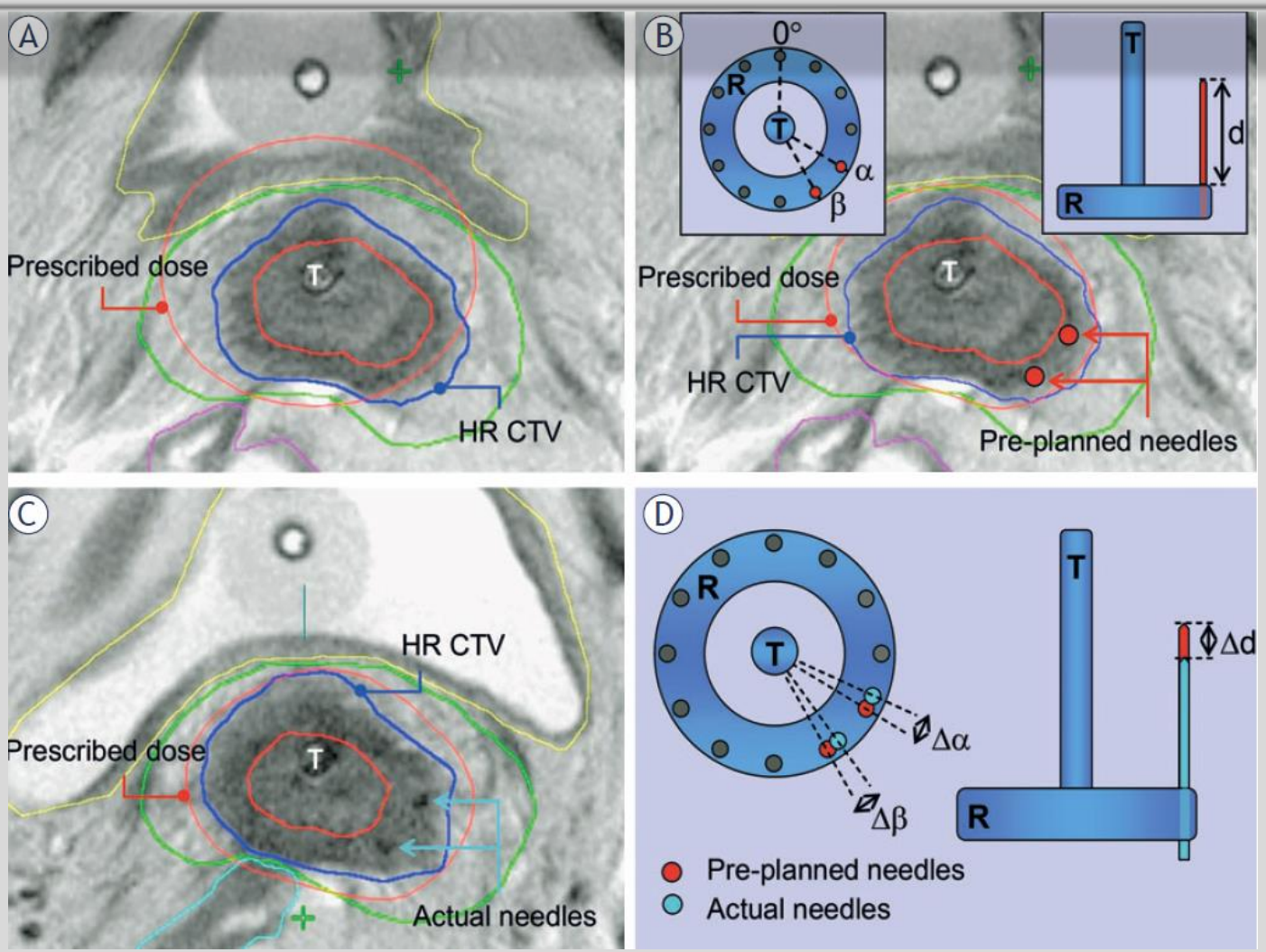
Native CT (no contrast)



T2W FSE MRI (same patient)

Courtesy; Jacob C Lindegaard, Aarhus University Hospital

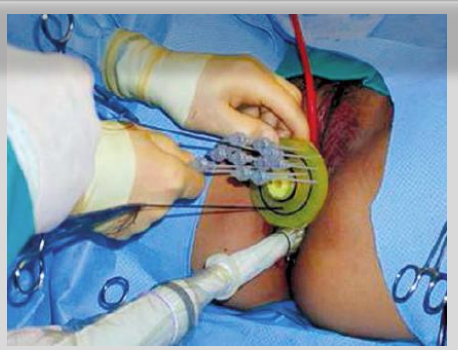
INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

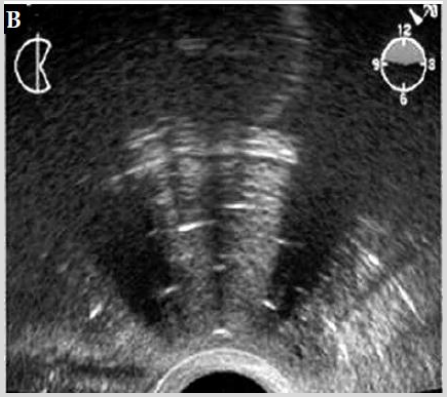


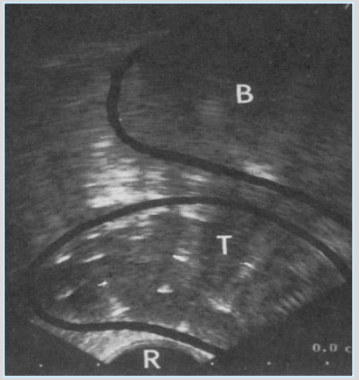
Petric et al. Radiol Oncol 2014; 48(3): 293-300.

INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

	Ultrasound	MRI
Accessibility in the operating room	High	Low
Real-time image guidance	High	Low
Catheter visualization	High	High
Target visualization	High	High
Volume based evaluation	Low	High
Treatment planning	Low	High
Experience with technique	Low	High
Clinical evidence	Low	High

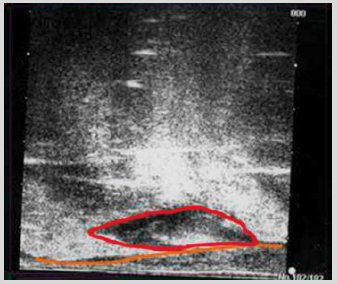


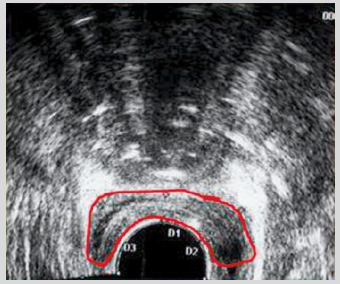




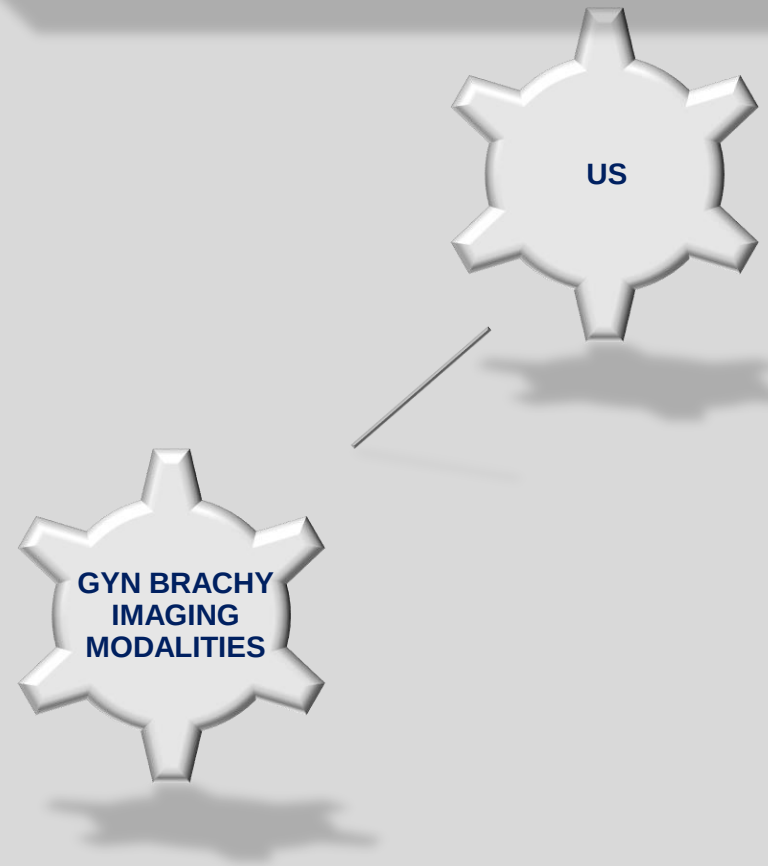
Kamrava M. J Contemp Brachytherapy 2014

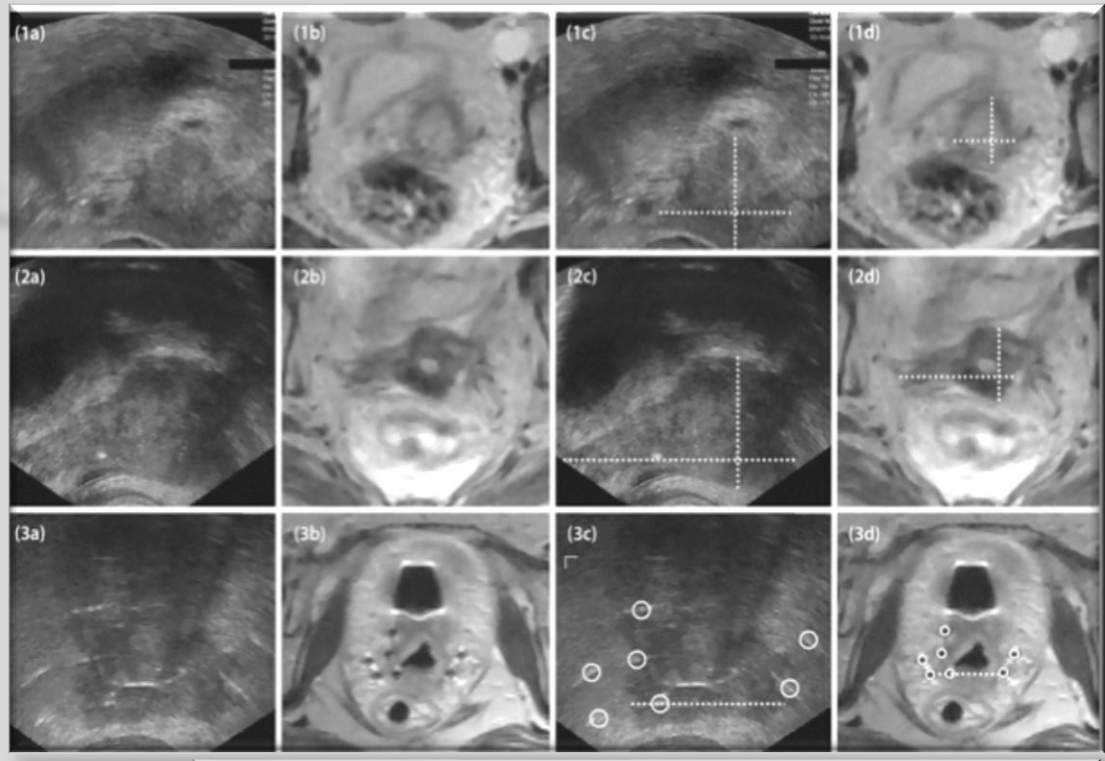
Weitmann HD et al. Strahlenther Onkol 2006; 182: 86-95.
Wenzel W. J Clin Ultrasound 1975; 3: 311-312.
Brascho DJ et al. Radiology 1978; 129: 163-167.
Stock RG et al. IJROBP 1997; 37: 819-825.
Sharma DN et al. J Gynecol Oncol 2010; 21: 12-17.





INTERSTITIAL TECHNIQUES
POTENTIAL OF MODERN US TECHNIQUES





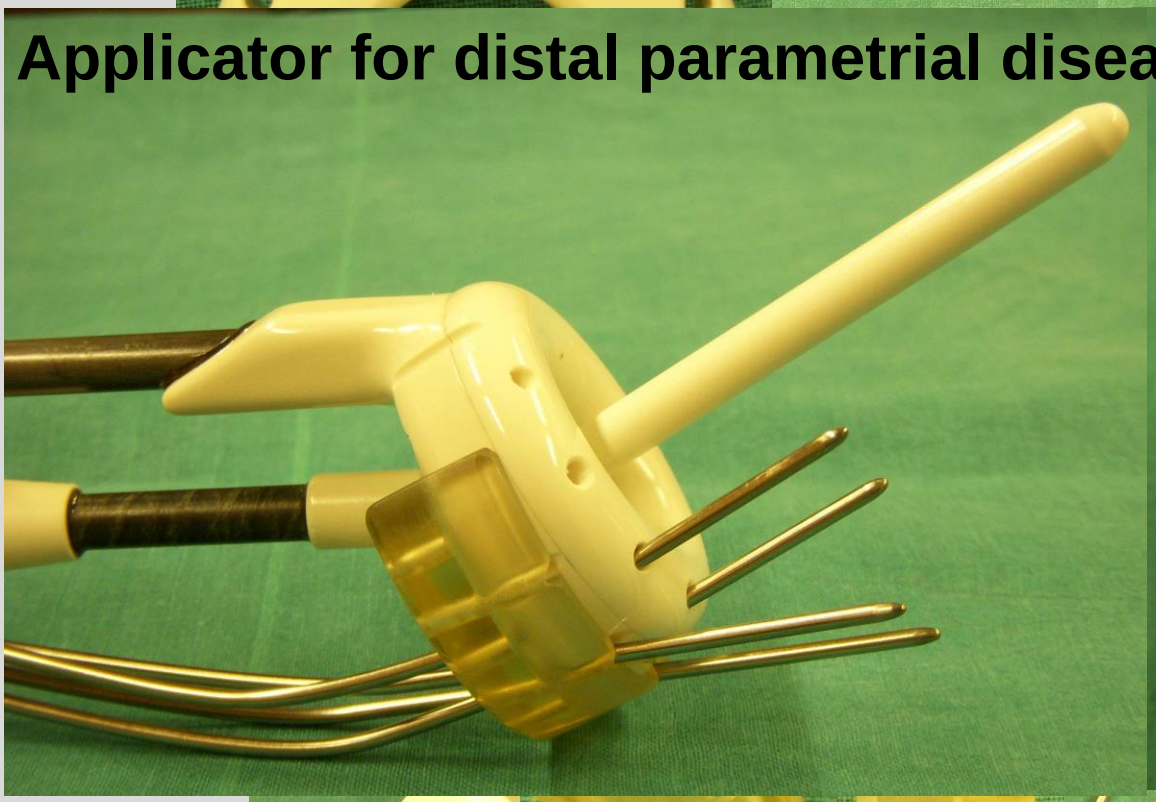
Schmid et al. Strahlenther Onkol 2013

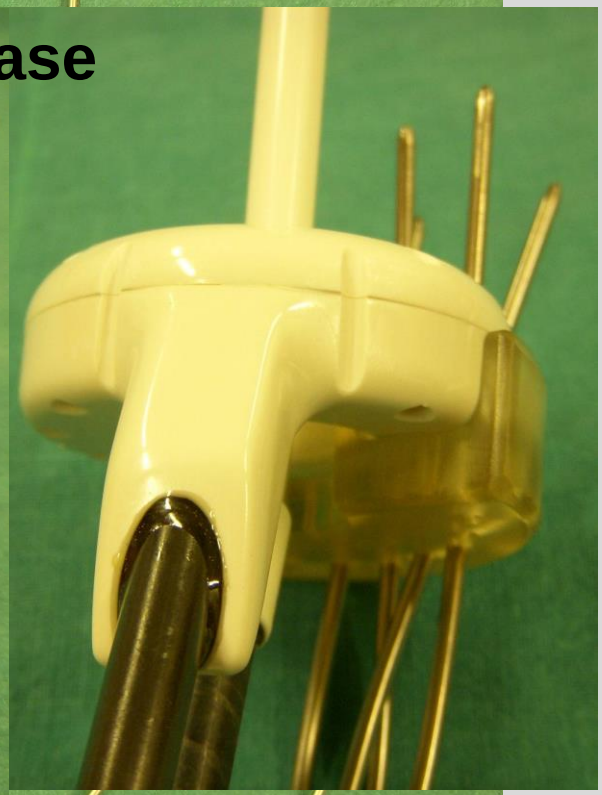
Good correlation between US and MRI

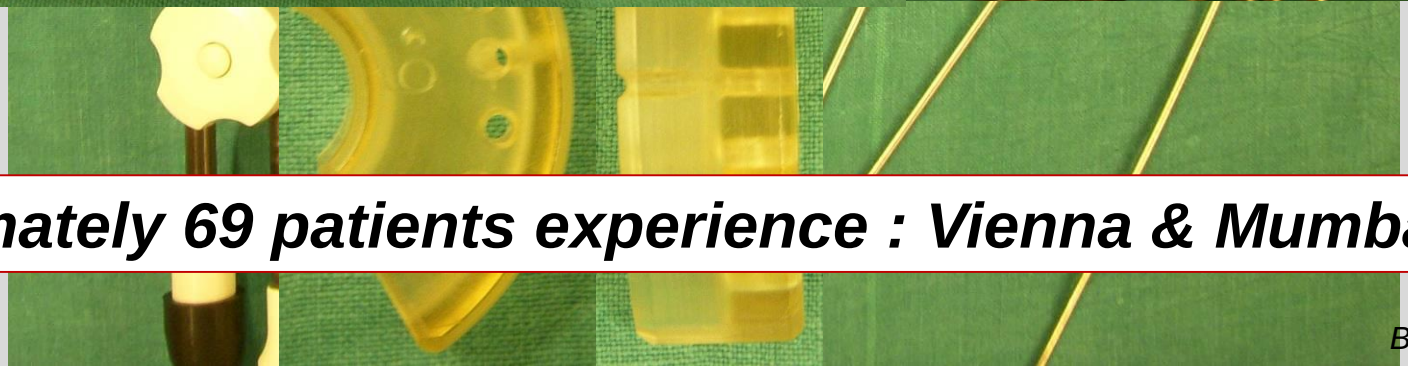
Modified Vienna Ring

Pre-bended needles

Applicator for distal parametrial disease



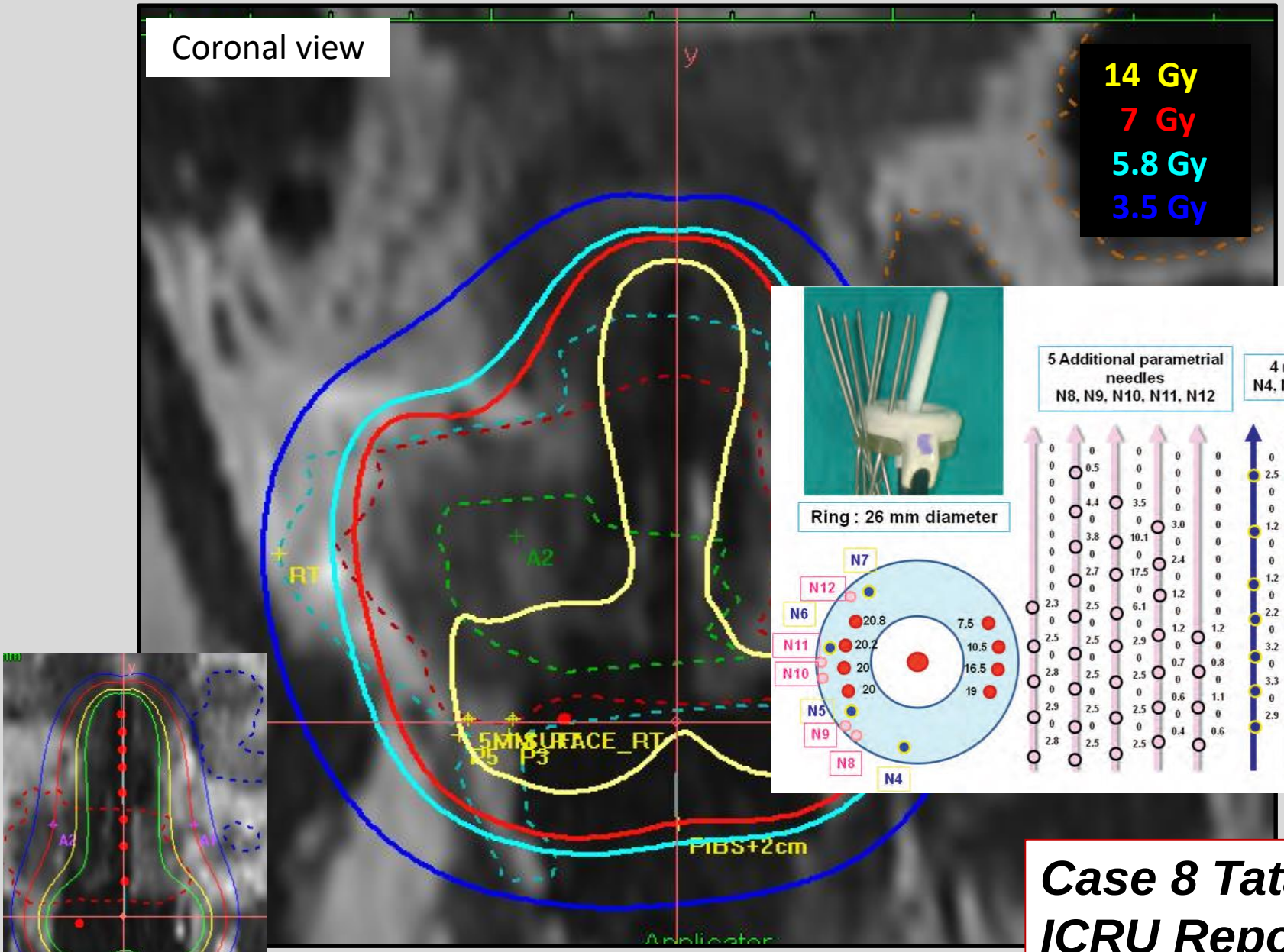


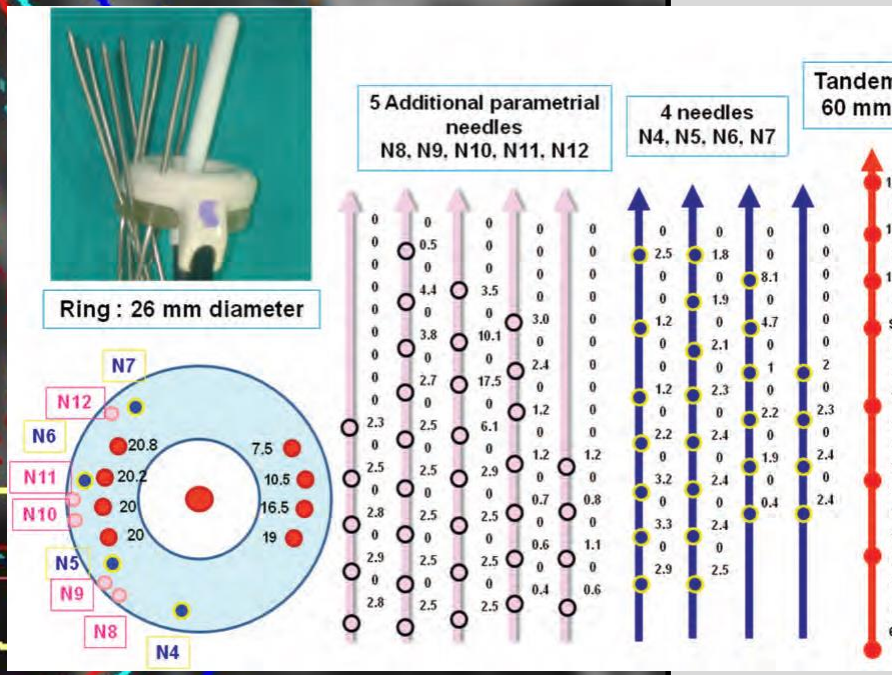


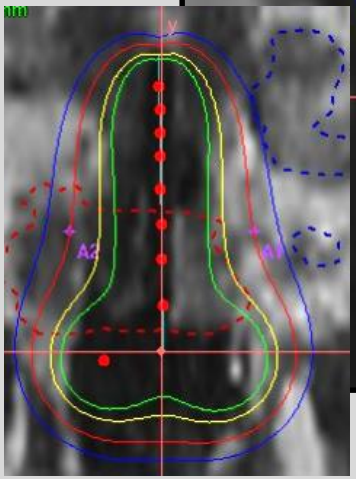
Approximately 69 patients experience : Vienna & Mumbai

Berger et al.

PLAN EVALUATION

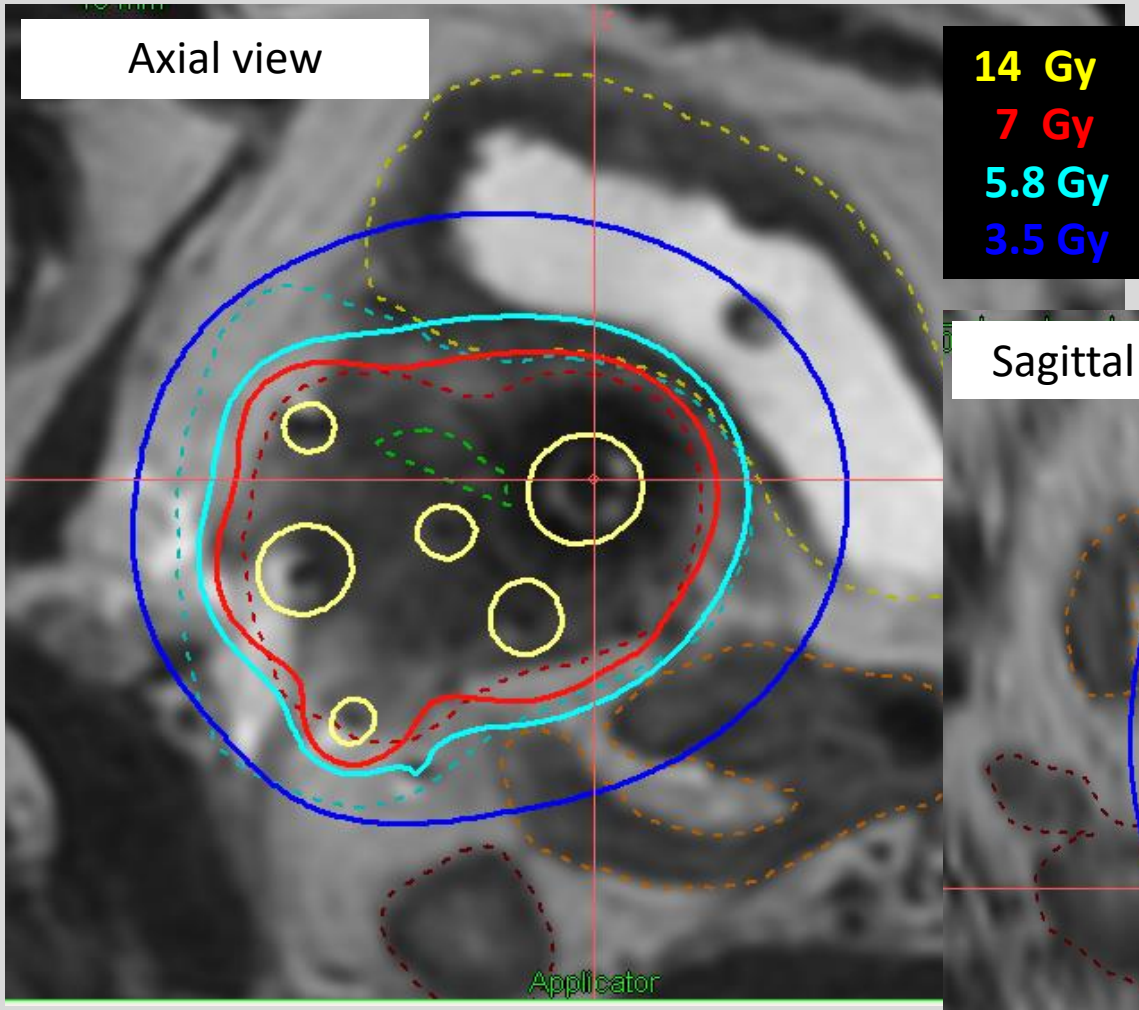






Case 8 Tata
ICRU Report 89
Page 217-224

PLAN EVALUATION



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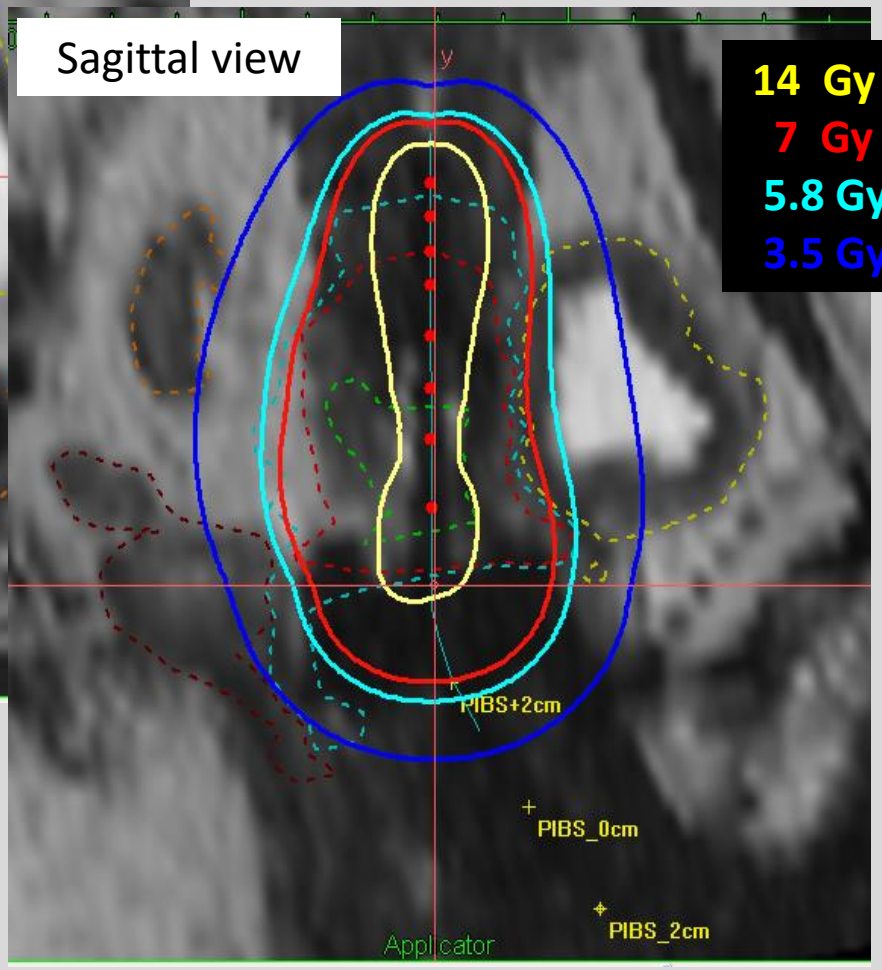


PIBS:Postero-inferior border of pubic symphysis

GEC –ESTRO / ICRU (89)

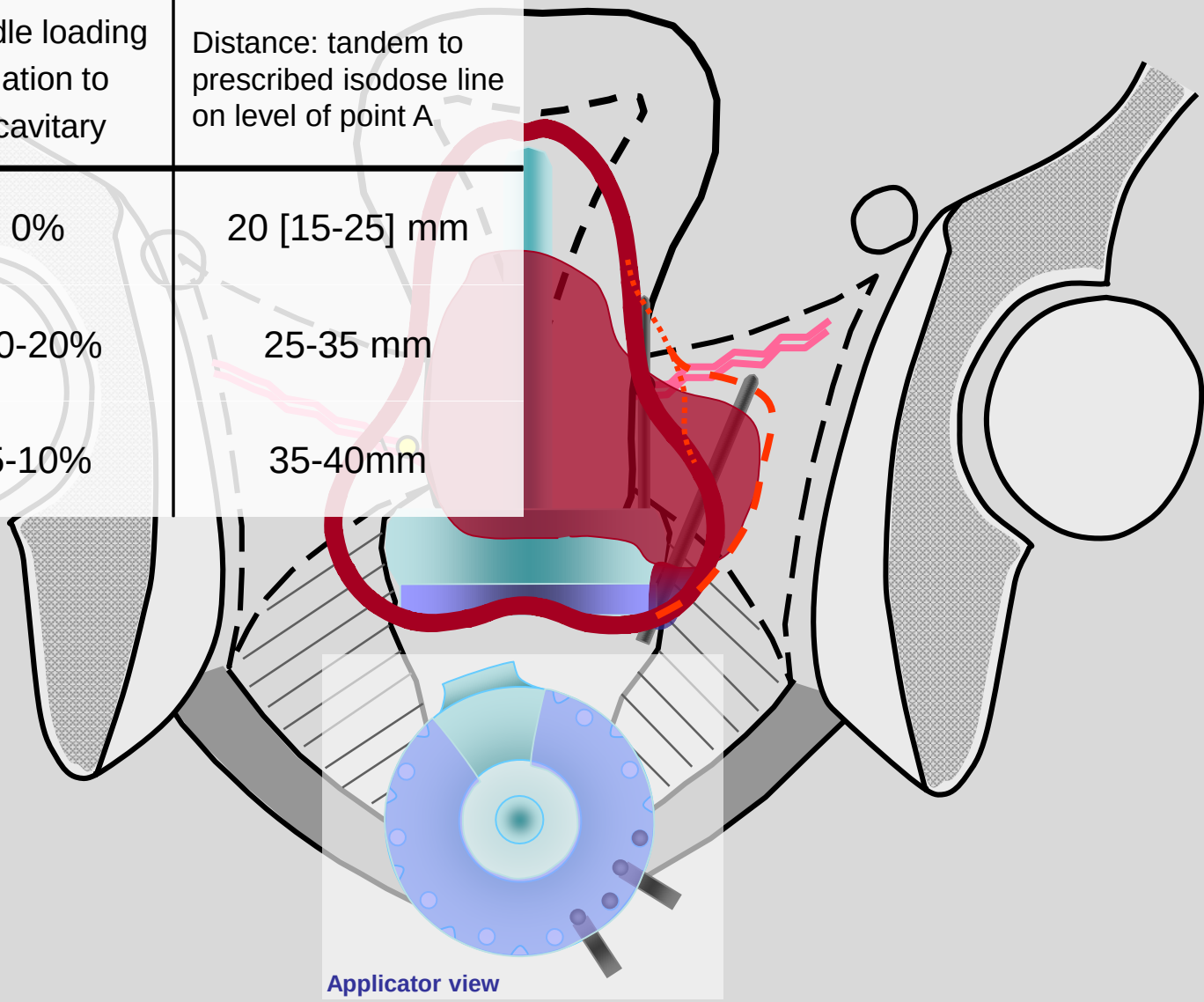
REPORTING OF DOSE VOLUME PARAMETERS

External (45 Gy/ 25#) + HDR-BRT (7 Gy x 4# in 2 Applications)

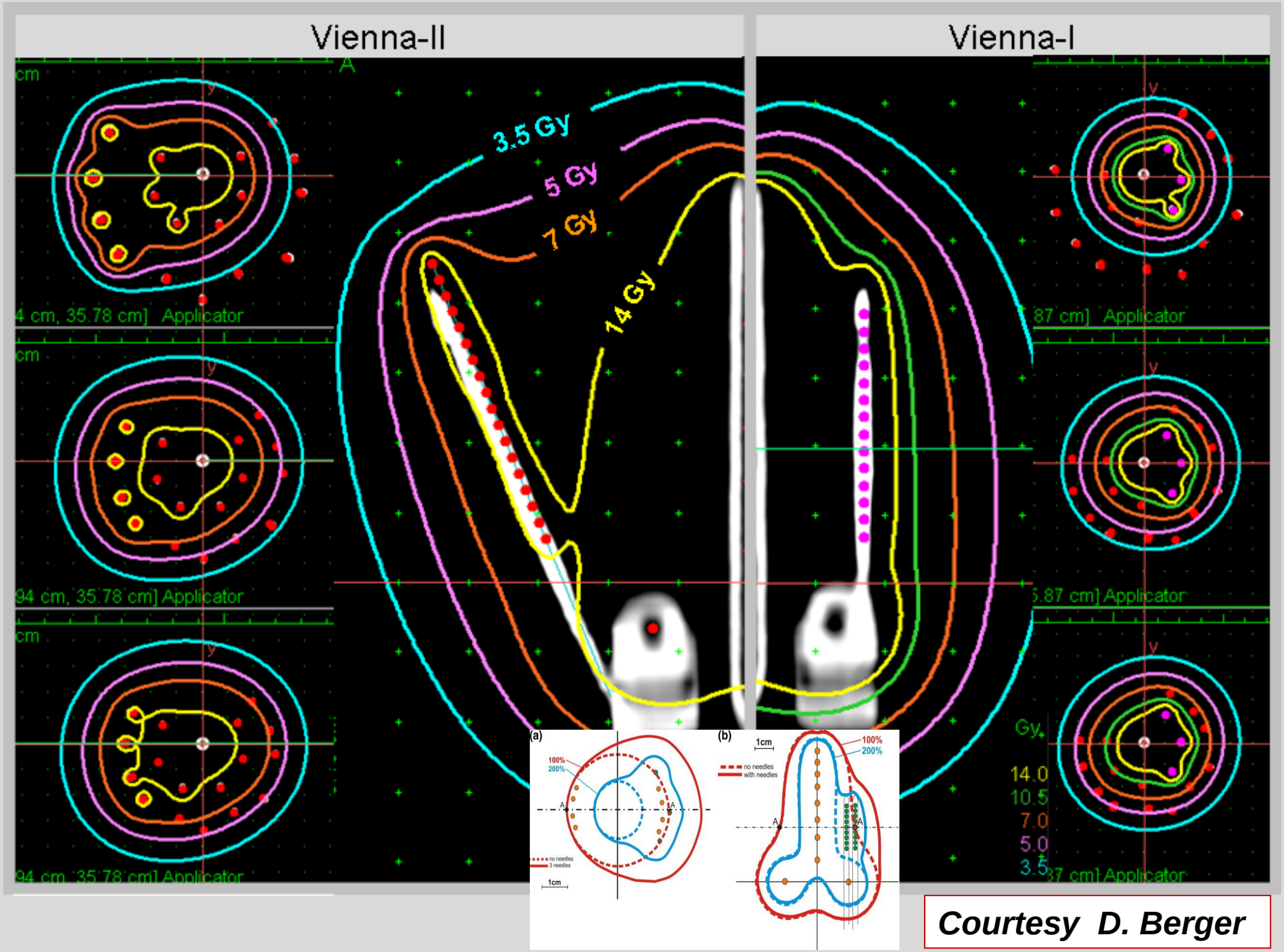
			Planning aim	**Prescribed dose**
CTV_{HR}	**D_{90}**	$EQD2_{10}$	≥ 85 Gy	96.2 Gy
Bladder	**D_{2cm^3}**	$EQD2_3$	≤ 90 Gy	82.9 Gy
Rectum	**D_{2cm^3}**	$EQD2_3$	≤ 70 Gy	68.3 Gy
Sigmoid	**D_{2cm^3}**	$EQD2_3$	≤ 70 Gy	67.4 Gy

Joint Vienna-II project Vienna and Mumbai

Physical distance between tandem and needle	Needle loading In relation to intracavitary	Distance: tandem to prescribed isodose line on level of point A
Intracavitary only No needles	0%	20 [15-25] mm
+ Parallel needles 20mm	10-20%	25-35 mm
+ Oblique needles 20° (23-27mm)	5-10%	35-40mm



D. Berger et al.



Courtesy D. Berger

Mission

264 patients

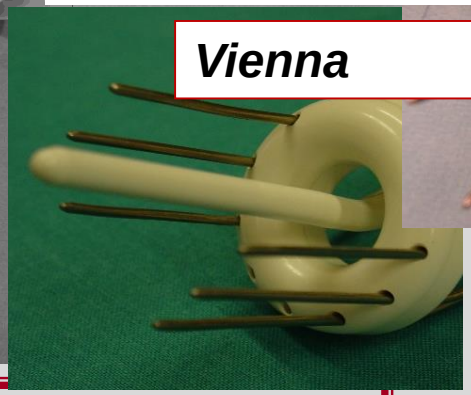
Modern Manchester Applicator

Utrecht

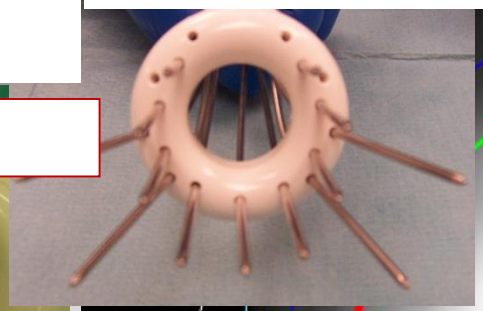
Venezia

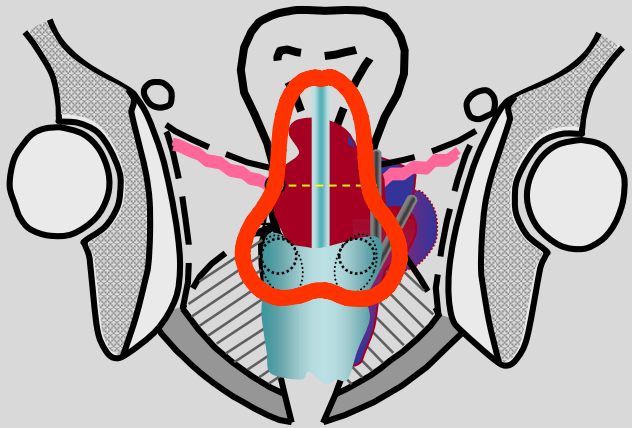
Modern Stockholm Applicator

Ring applicator



Vienna



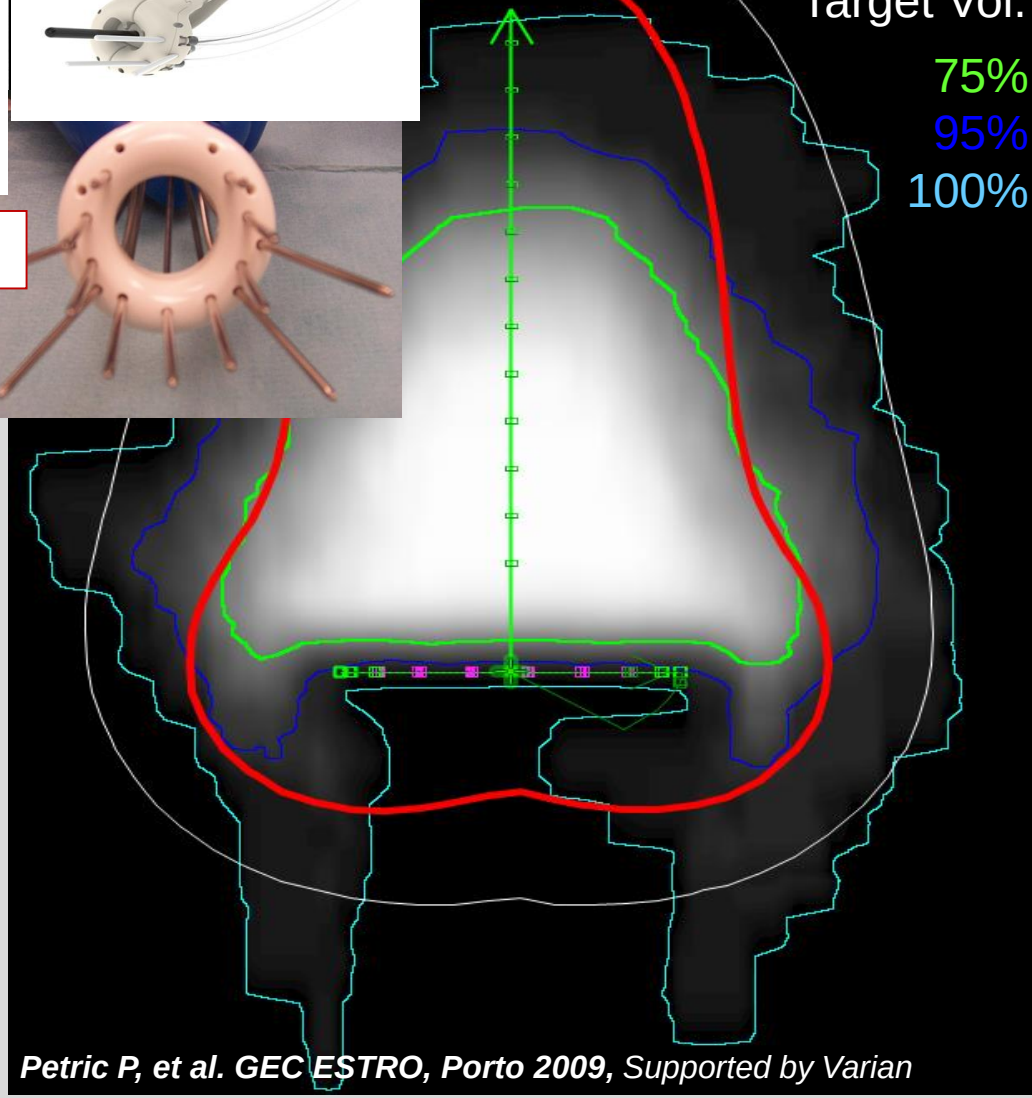


Population Target Vol.

75%

95%

100%



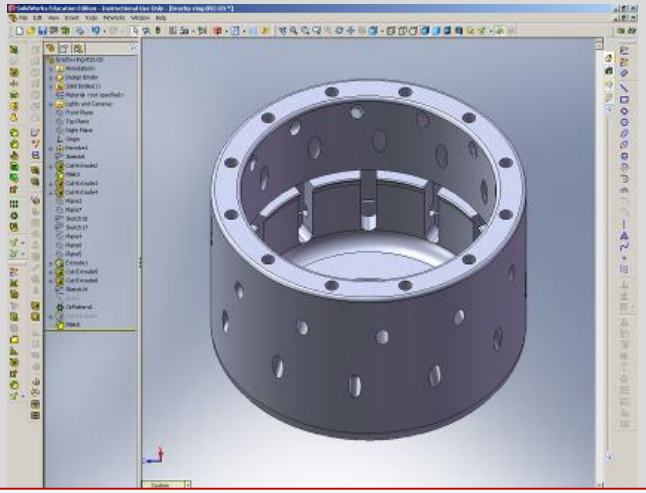
Petric P, et al. GEC ESTRO, Porto 2009, *Supported by Varian*

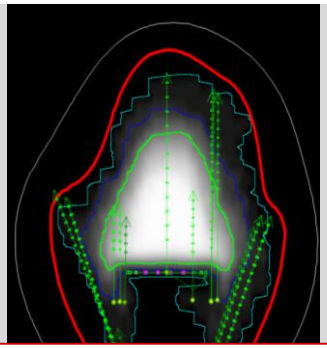
Courtesy: P. Petric,D. Berger

Adaptive BT applicators

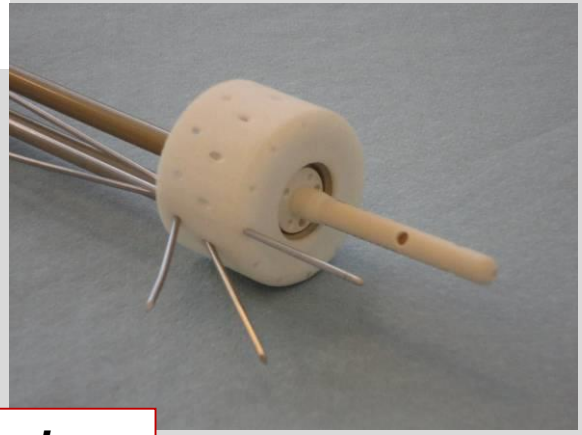
3D Printing

Virtual applicator





New applicator



264 patients with tumour mapping Ljubljana, Vienna, Aarhus

Provided by Primoz Petric and Jacob Lindegaard Ljubljana/Aarhus

SUMMARY & CONCLUSIONS

- *Combined Intracavitary & Interstitial techniques*

  in case of inappropriate coverage (topographic and dosimetric) with pure intracavitary techniques

- *Several approaches (applicators, image guidance) available*
- *Application technique: Various tumor topographies at BT*
- *Straight-forward techniques available*
- *Combined Intracavitary & Interstitial techniques:*

  associated with a learning curve for accurate placement


Uterine Tandem
Additional Needles
Additional Needles
Vaginal Ring / Ovoid

- Please log into Turning Point
- Please log into ESTRO Course Homepage (Moodle) for MiniContour exercises

Clinical diagrams

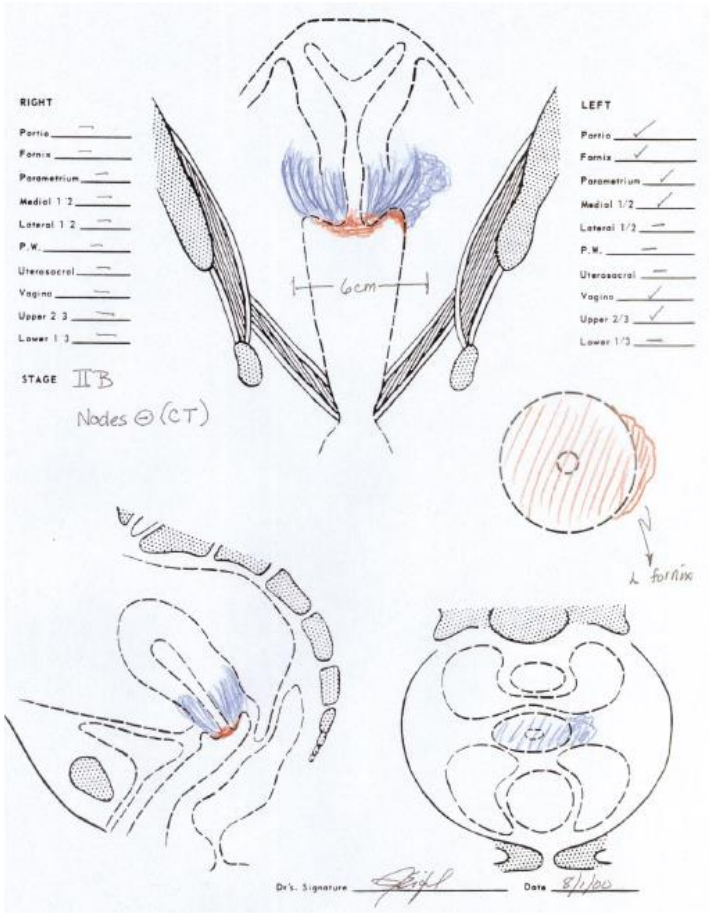
Li Tee Tan

ESTRO GYN teaching course
Madrid 2018

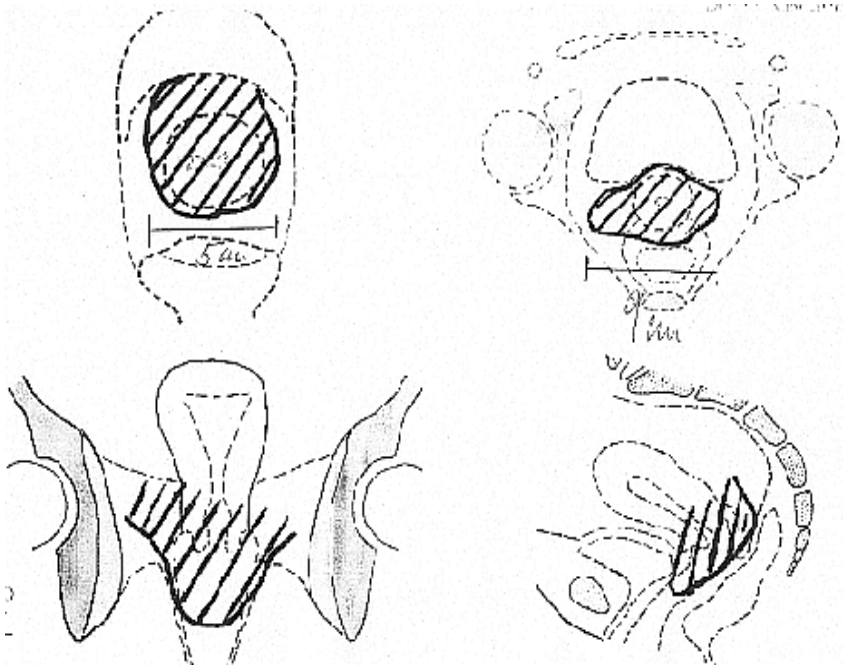
Cambridge University Hospitals NHS
NHS Foundation Trust

Eifel-Levenback (ed)

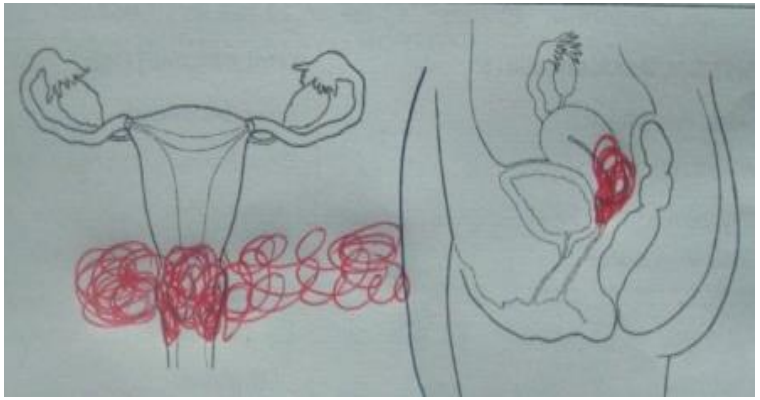
Atlas of clinical oncology 2001



Vienna

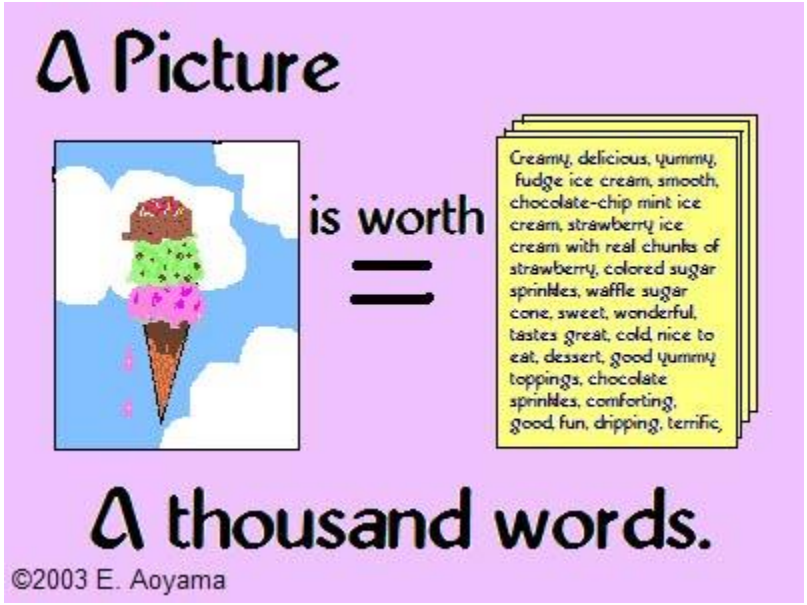


TMH, Mumbai



Advantages

- Improved 3D documentation



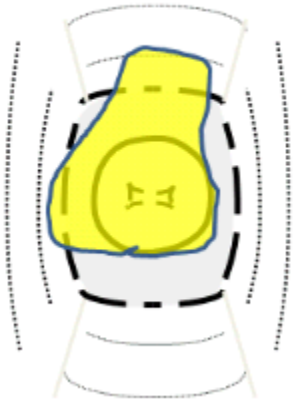
Exercise

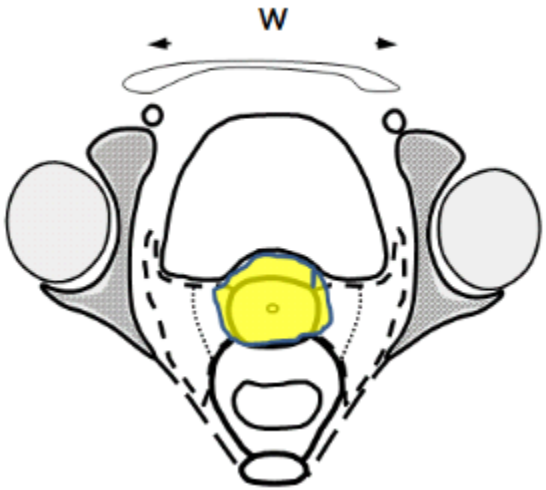
Findings

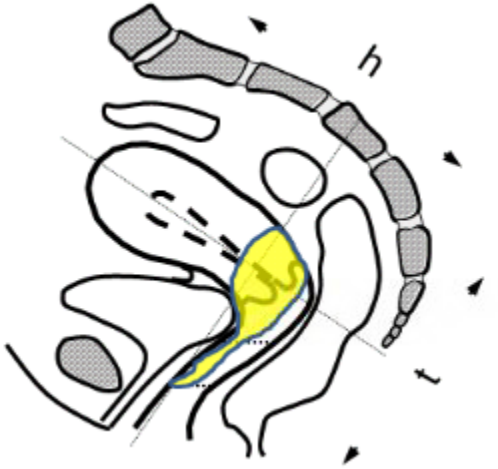
Tumour width (lateral)	40 mm
Tumour thickness (AP)	60 mm (post cervix to lower extent in vagina
Visible cervix	Exo- and endophytic tumour
Necrosis present	yes
Left parametrium	Proximal
Right parametrium	Proximal
Vagina	Lower 1/3
Anterior wall involved	yes
Posterior wall involved	yes
Left lateral wall involved	no
Right lateral wall involved	yes
Max. distal extension from fornix	40 mm
Rectal examination	Palpable impression

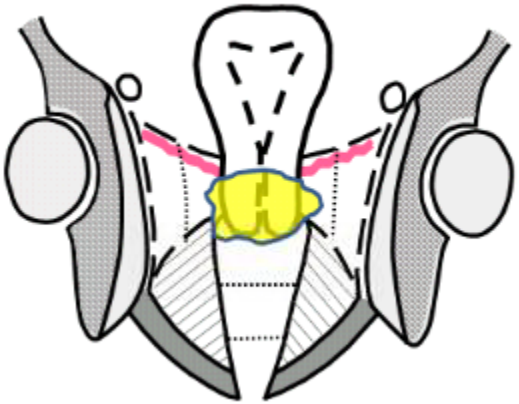
Cystoscopy: Bladder wall distorted by underlying tumour with probably bullous oedema. No tumour.

Exercise



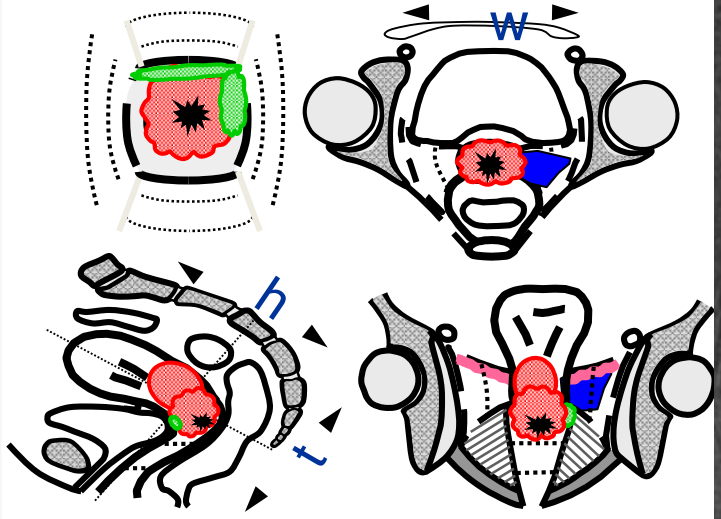


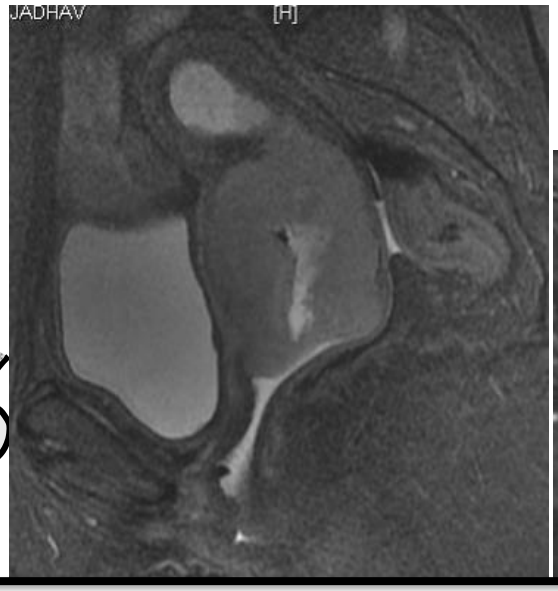




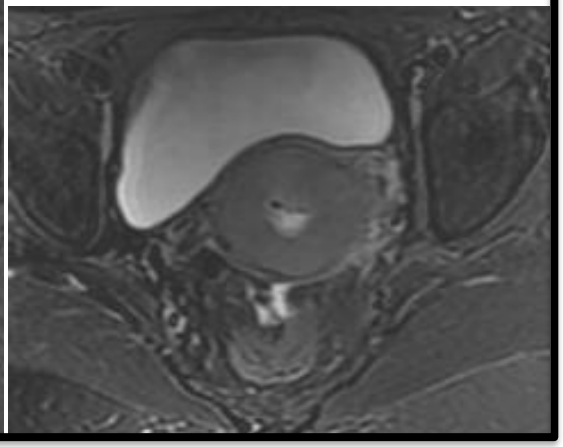
Advantages

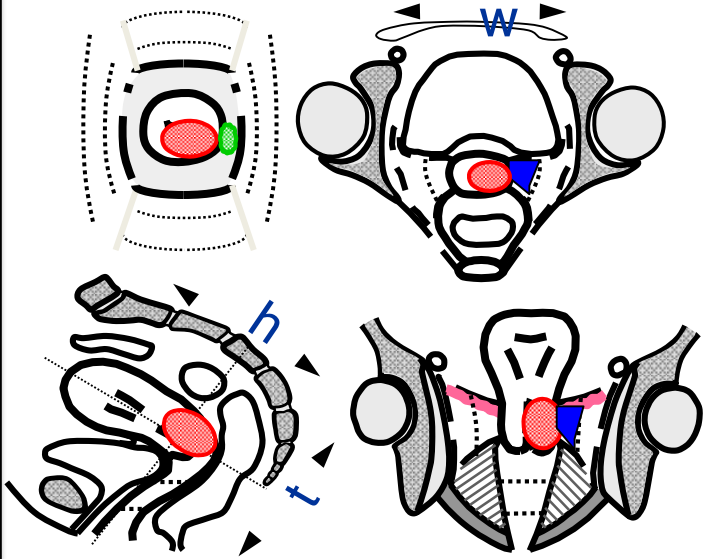
- Improved 3D documentation
- Aid evaluation of response

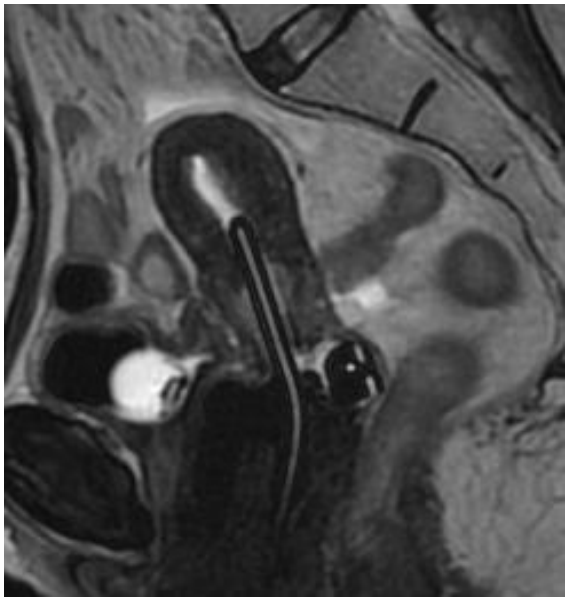




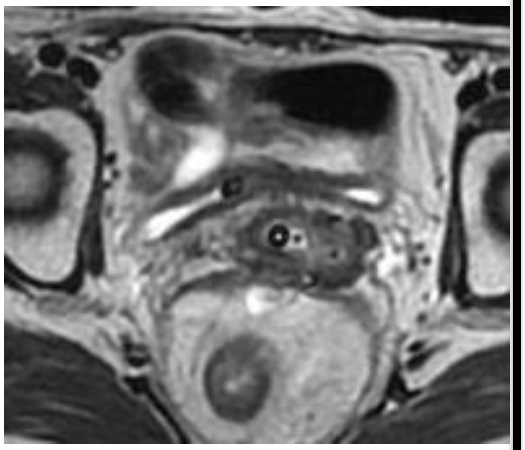
Diagnosis







Brachytherapy



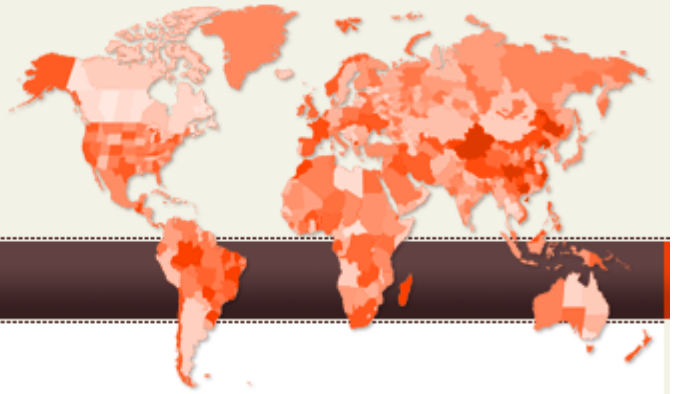
Advantages

- Improved 3D documentation
- Aid evaluation of response
- Selection of BT technique

www.embracestudy.dk/AboutAppendix.aspx

EMBRACE

An intErnational study
on MRI-guided BRachytherapy
in locally Advanced CErvical cancer



About Embrace | Contacts | Participation | Login

Appendix

- Extended CRF 60-120 Month Follow-ups
- Clinical Drawings (PowerPoint)
- Updated CRF July 2013
- CTCAE v3.0(PDF)
- Instructions for dummy-run (PDF)
- GYN GEC-ESTRO Guidelines I (PDF)
- GYN GEC-ESTRO Guidelines II (PDF)
- Applicator reconstruction catalogue (PDF)

ABOUT EMBRACE

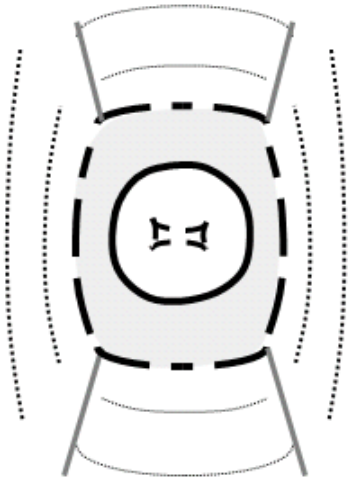
- Synopsis
- Protocol PDF download
- Amendments
- Appendix
- Quality of Life sub-study
- Embrace study commitee
- Participants
- FAQ
- Sponsors

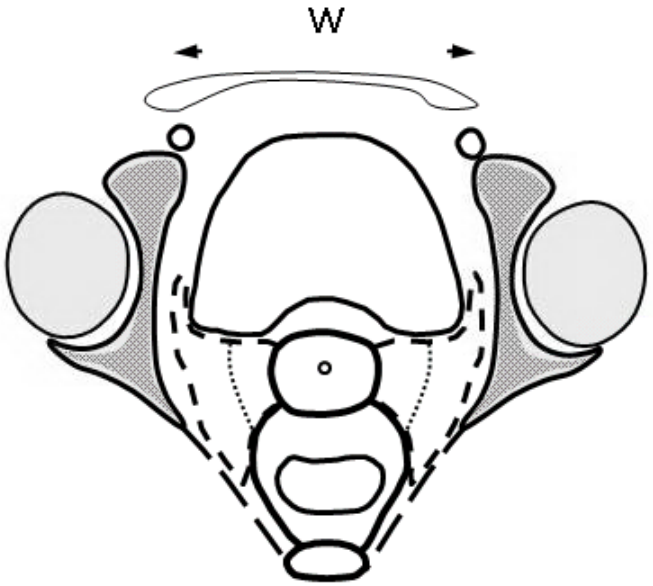
EMBRACE

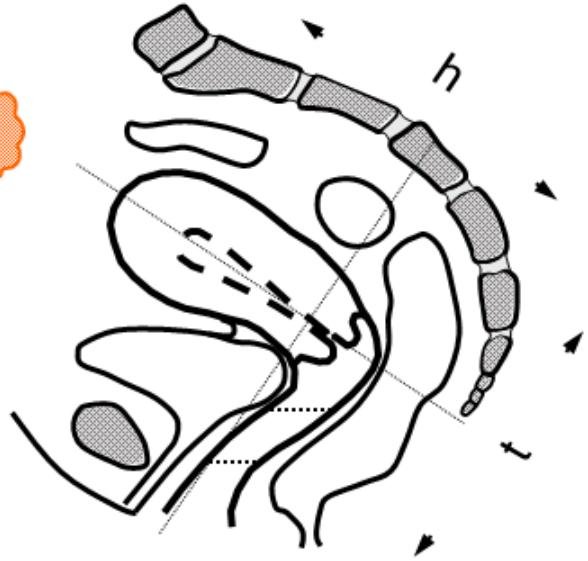
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

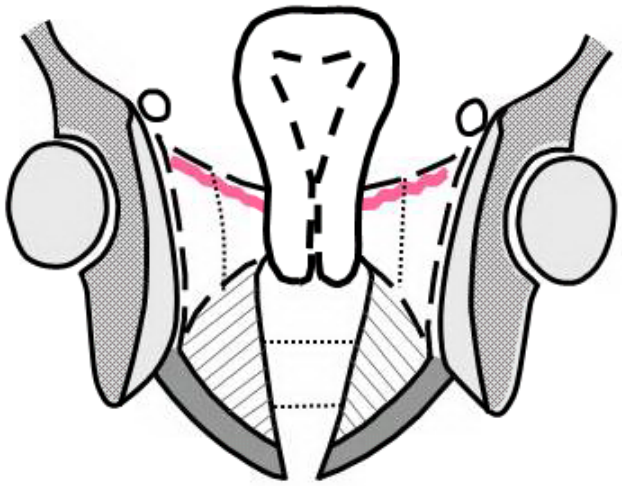
w = ... cm
h = ... cm
t = ... cm

Vagina Involvement = ... cm

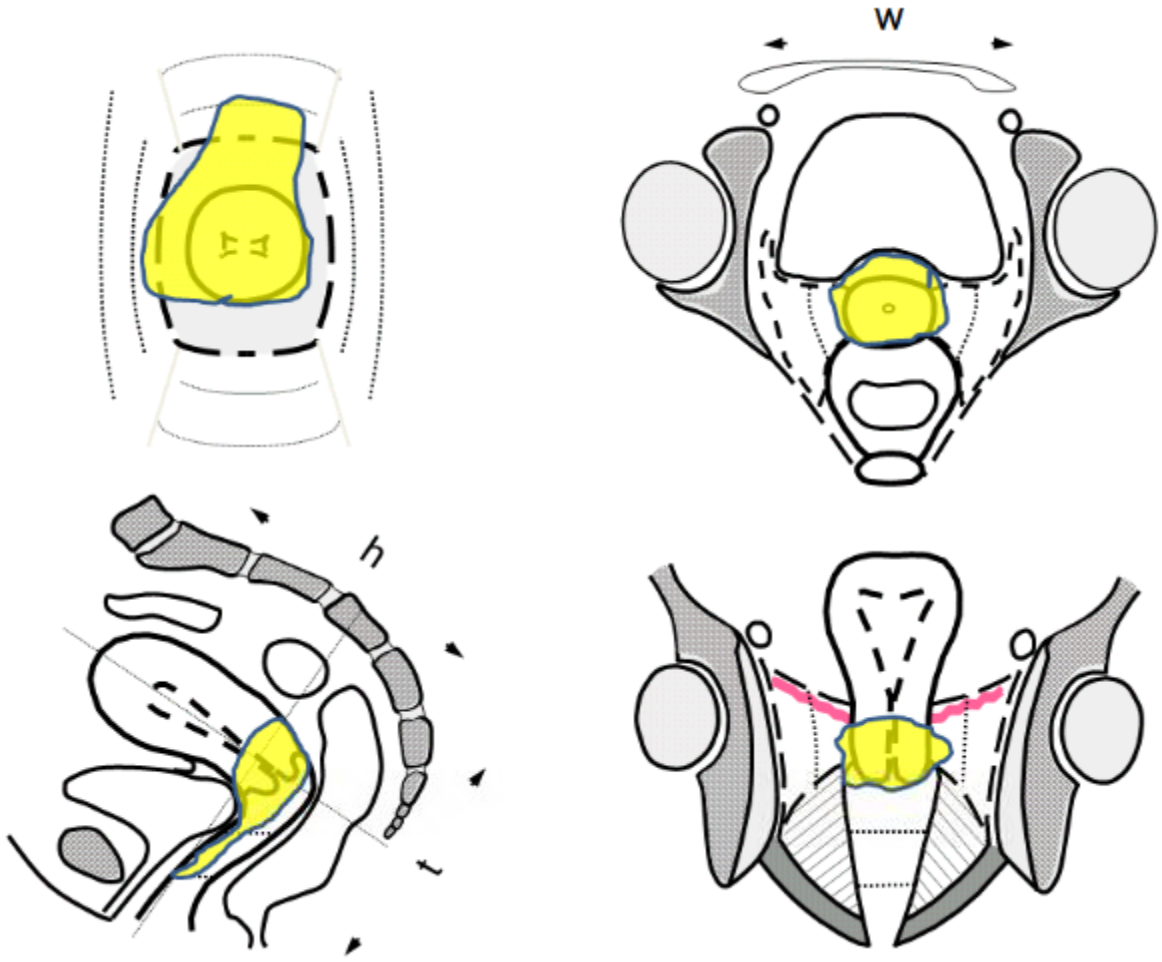




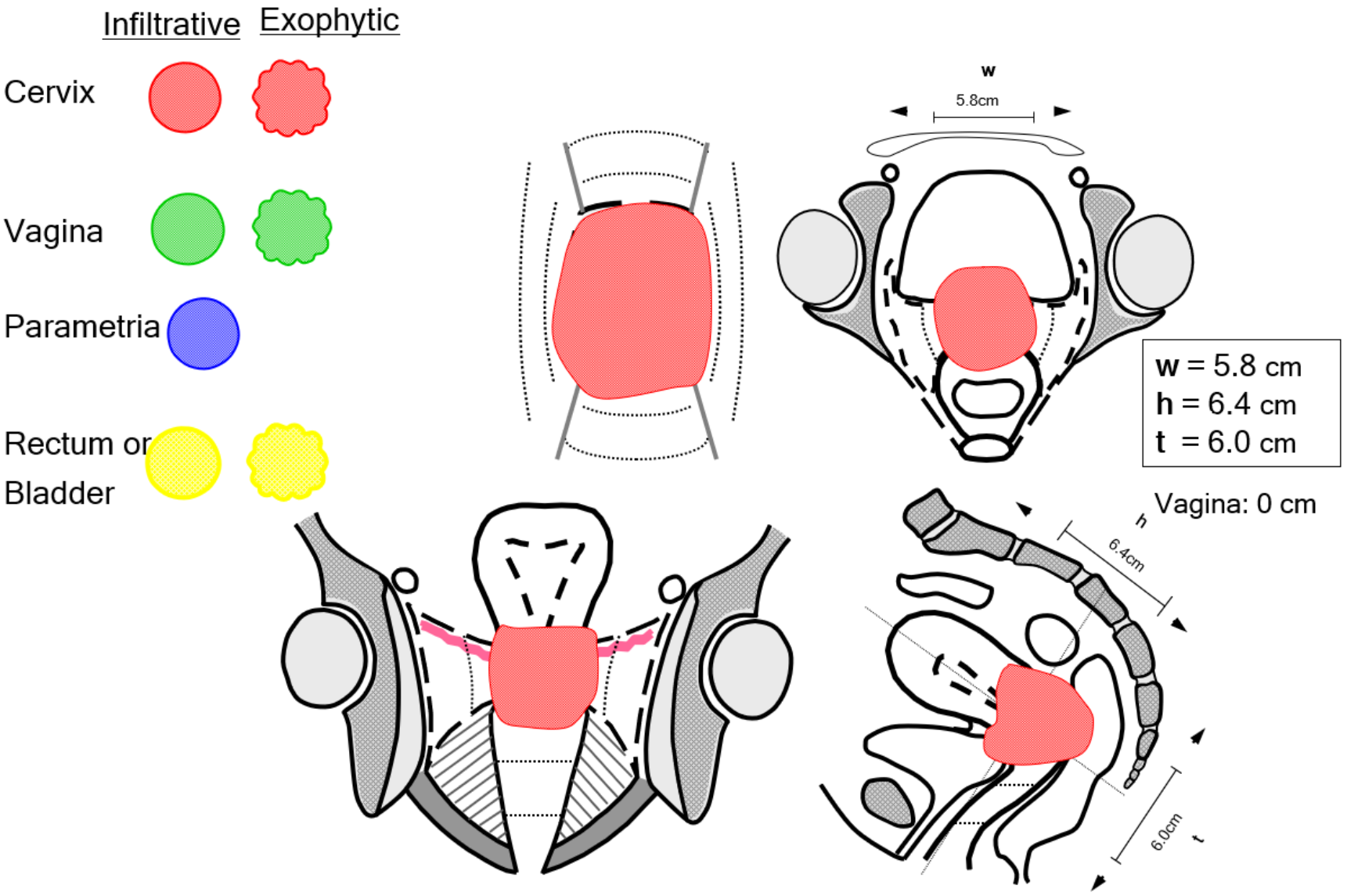




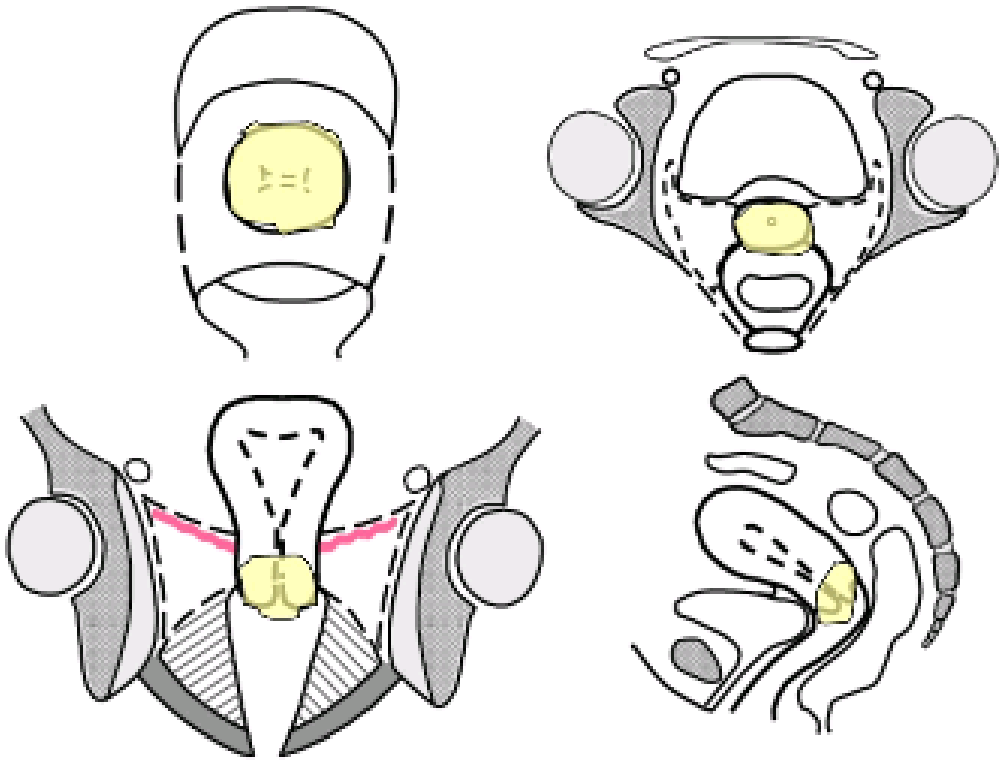
CUH



Ib2 endophytic



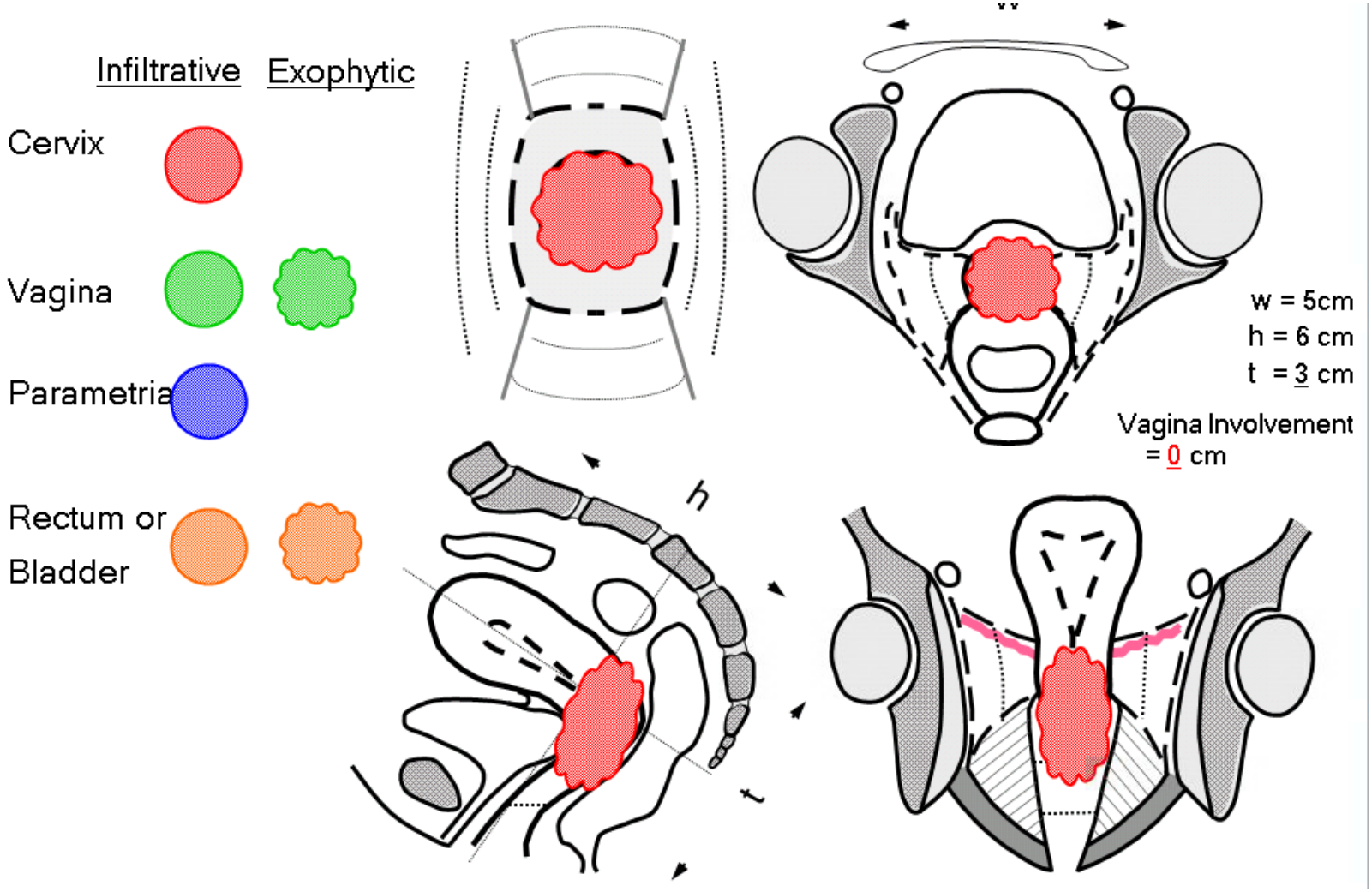
Ib2 endophytic



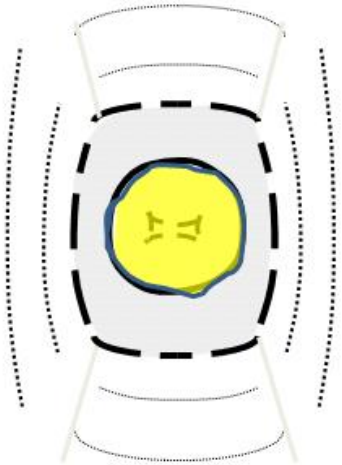
STAGING EUA - FINDINGS

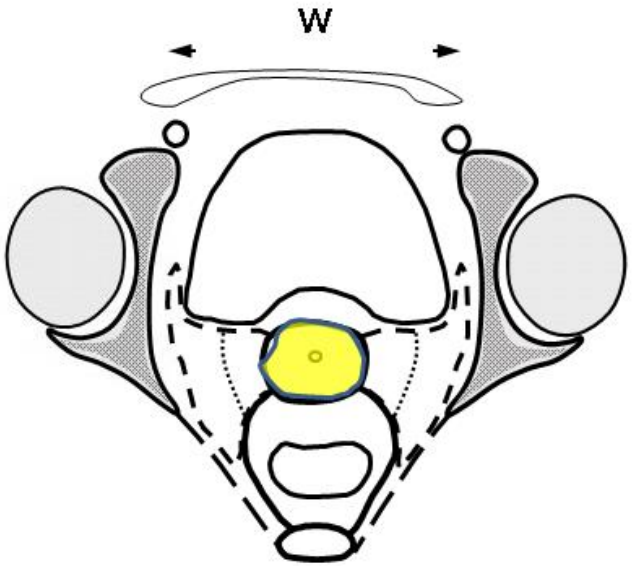
Cervical tumour 4.5 cm in diameter.
No vaginal extension.
No parametrial invasion
Cystoscopy – no evidence of disease.

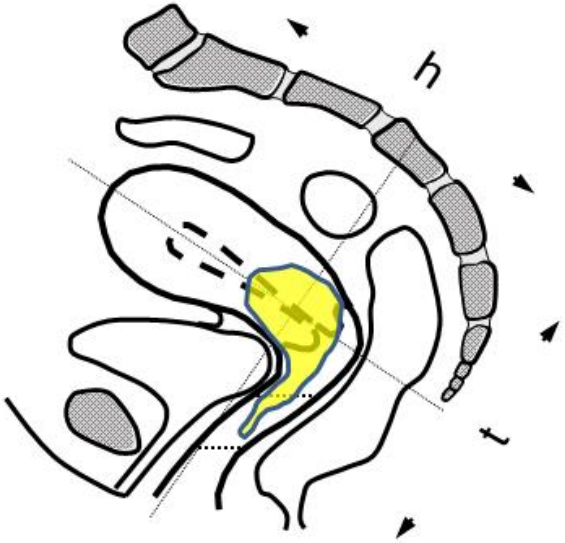
Ib2 exophytic

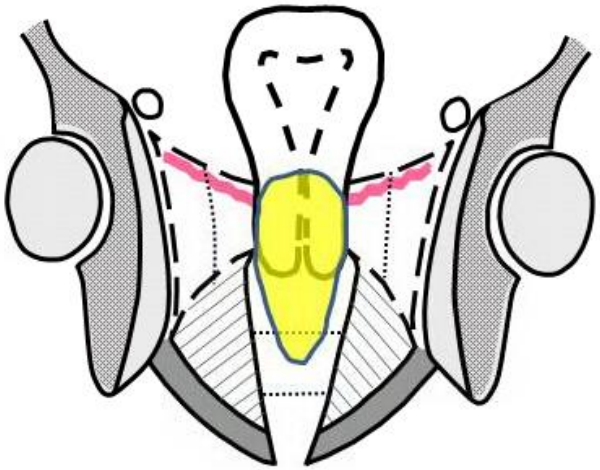


Ib2 exophytic









Exercise

STAGING EUA - FINDINGS

Tumour width (lateral)	50 mm
Tumour thickness (AP)	20 mm
Visible cervix	Exophytic tumour
Necrosis present	yes
Left parametrium	Not involved
Right parametrium	Not involved
Vagina	Lower 1/3
Anterior wall involved	yes
Posterior wall involved	no
Left lateral wall involved	no
Right lateral wall involved	no
Max. distal extension from fornix	60 mm
Rectal examination	Not involved
Bladder, cystoscopy	Not involved

Summary

- Clinical diagrams at diagnosis + brachytherapy invaluable for IGBT cervix
- Associated with small learning curve

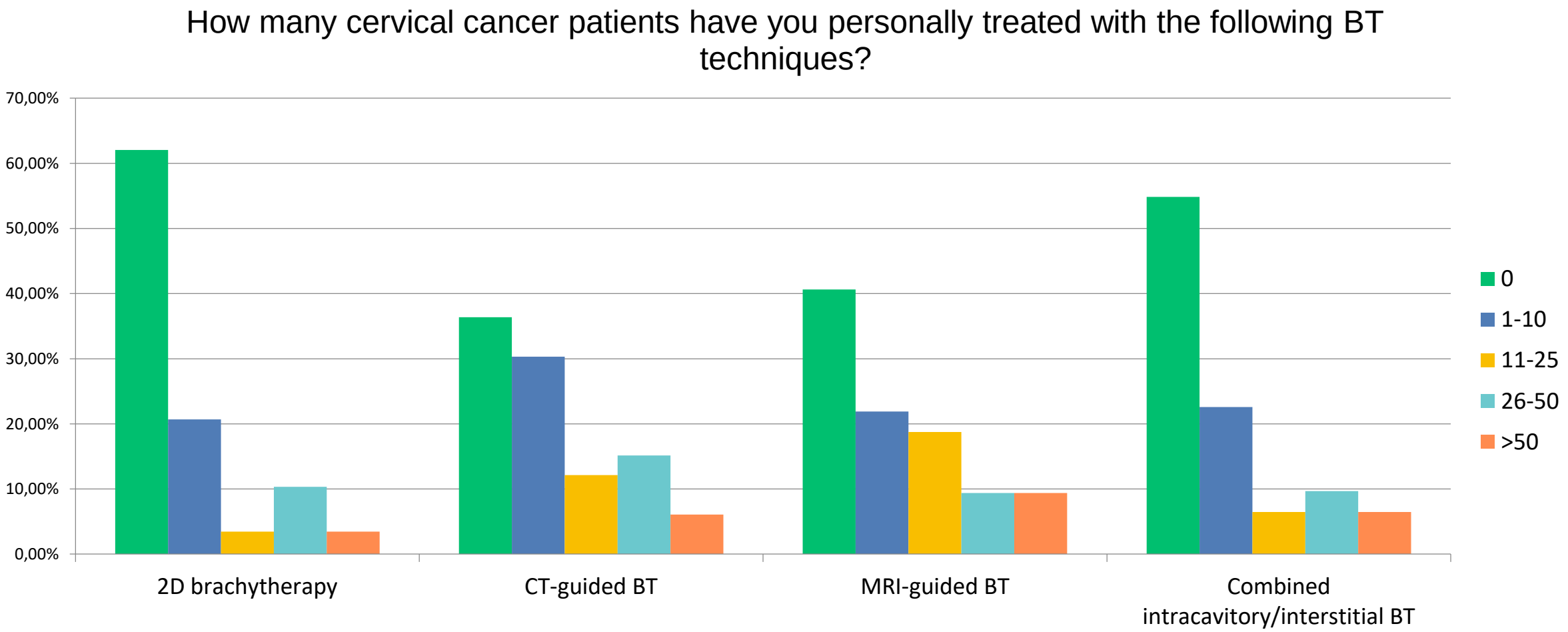
Brachytherapy contouring:

Survey and contouring homework

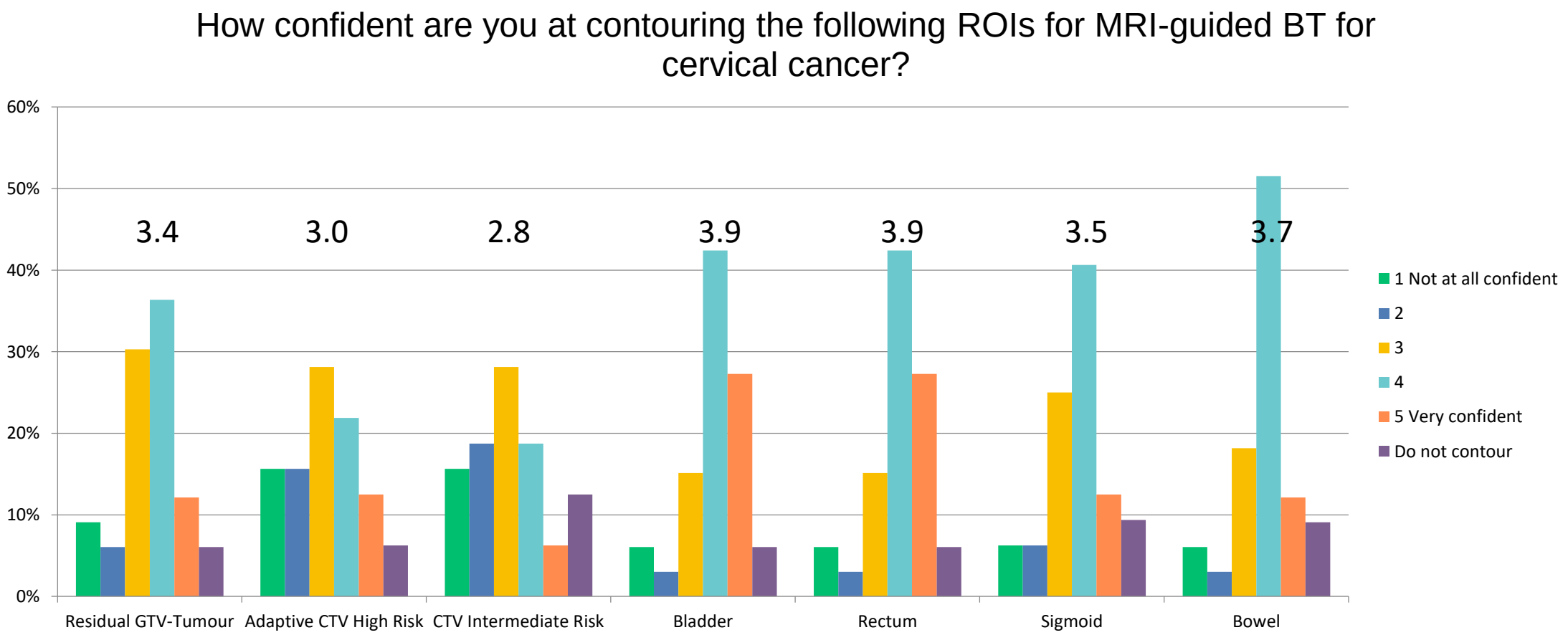
Madrid 2018

Dr Li-Tee Tan, Dr Simon Duke

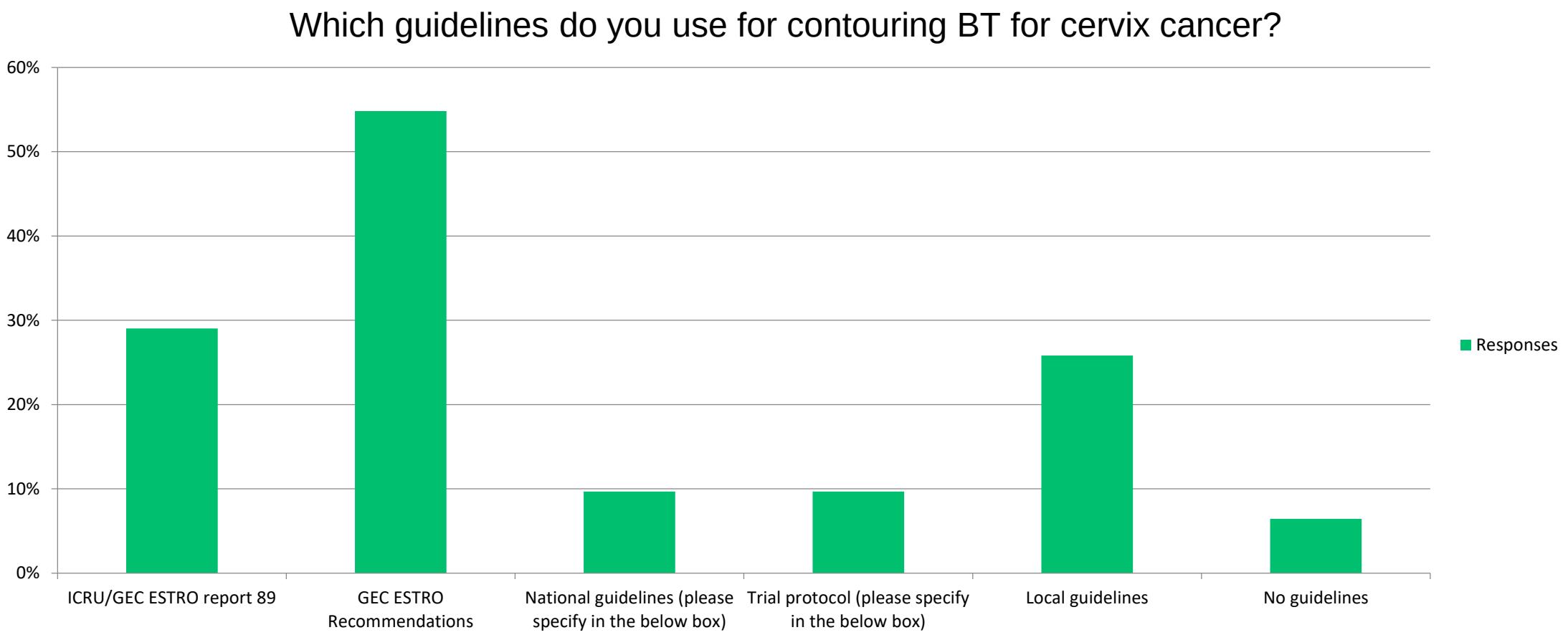
Cervix BT - Previous experience



ROIs for IGABT - confidence

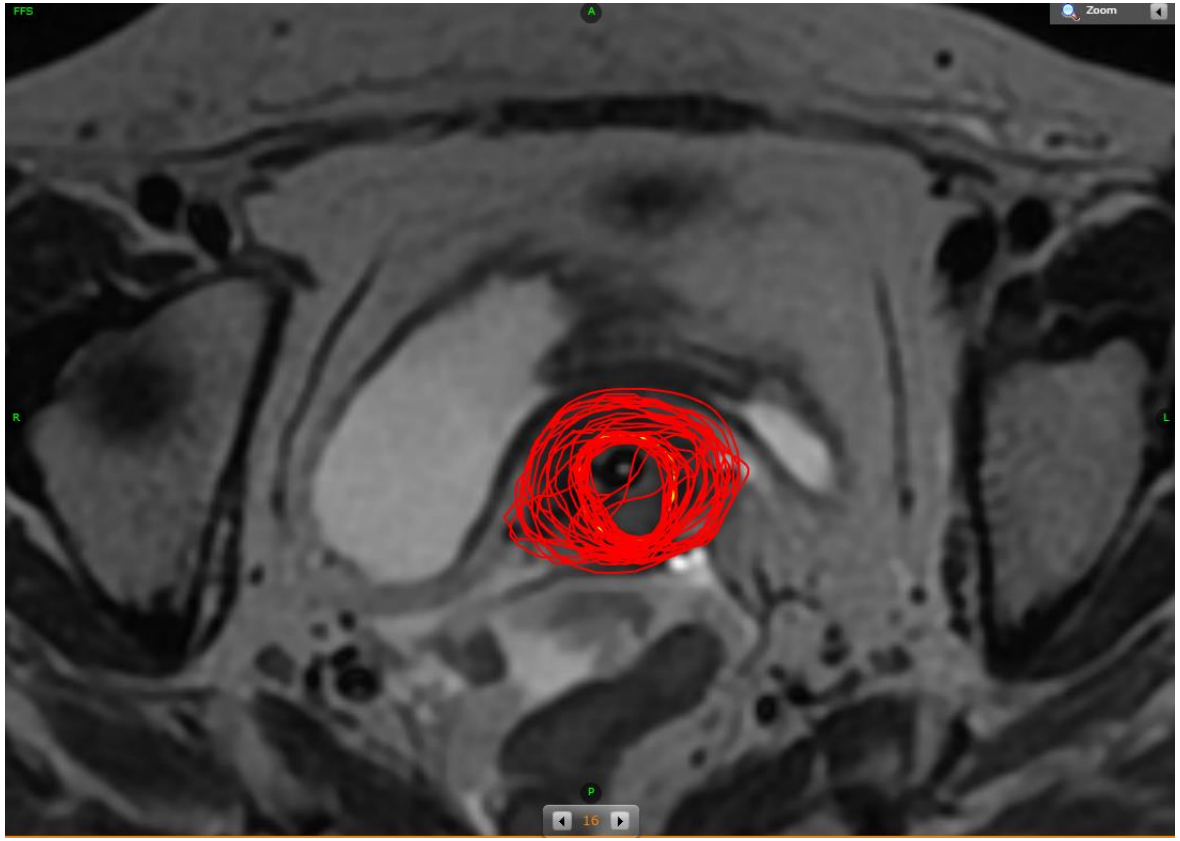


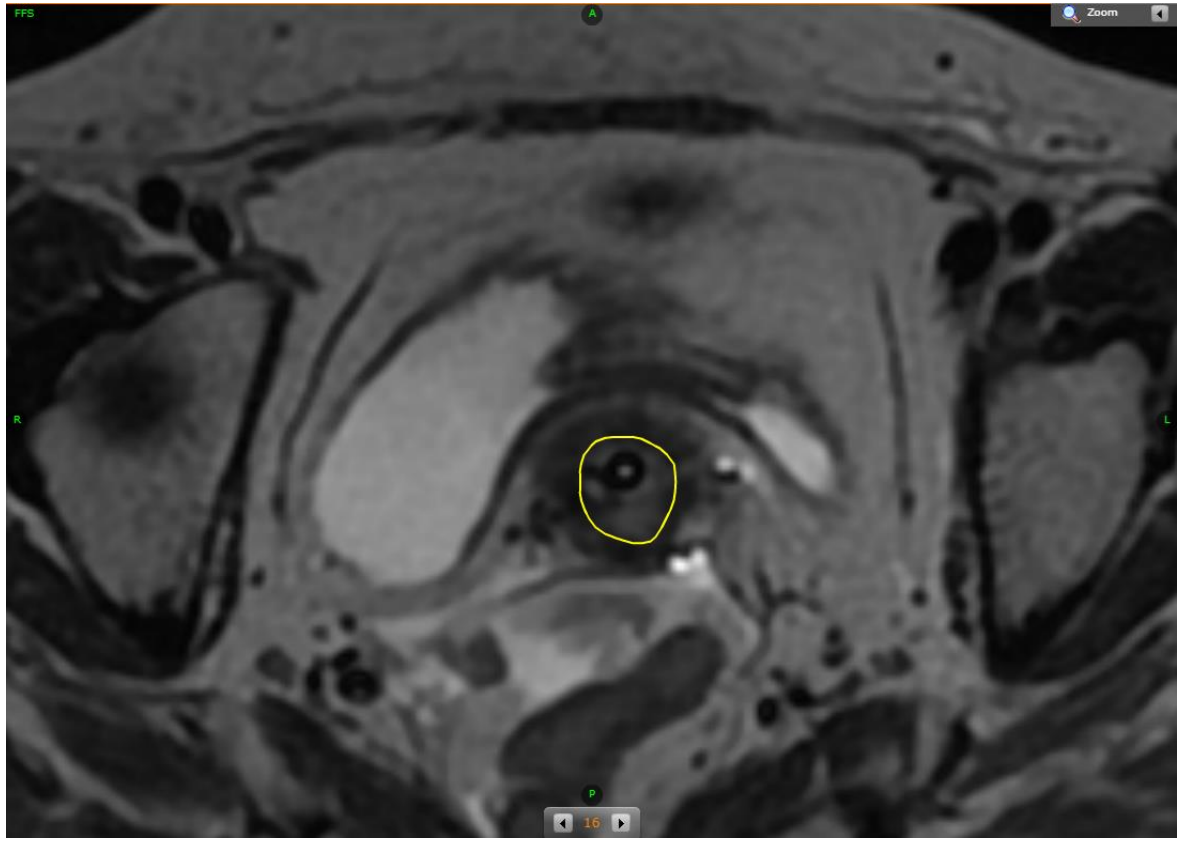
Guidelines


Which guidelines do you use for contouring BT for cervix cancer?
60%
50%
40%
30%
20%
10%
0%
ICRU/GEC ESTRO report 89
GEC ESTRO Recommendations
National guidelines (please specify in the below box)
Trial protocol (please specify in the below box)
Local guidelines
No guidelines
Responses

GTV_{res}

Homework – GTV_{res}





GTV_{res}

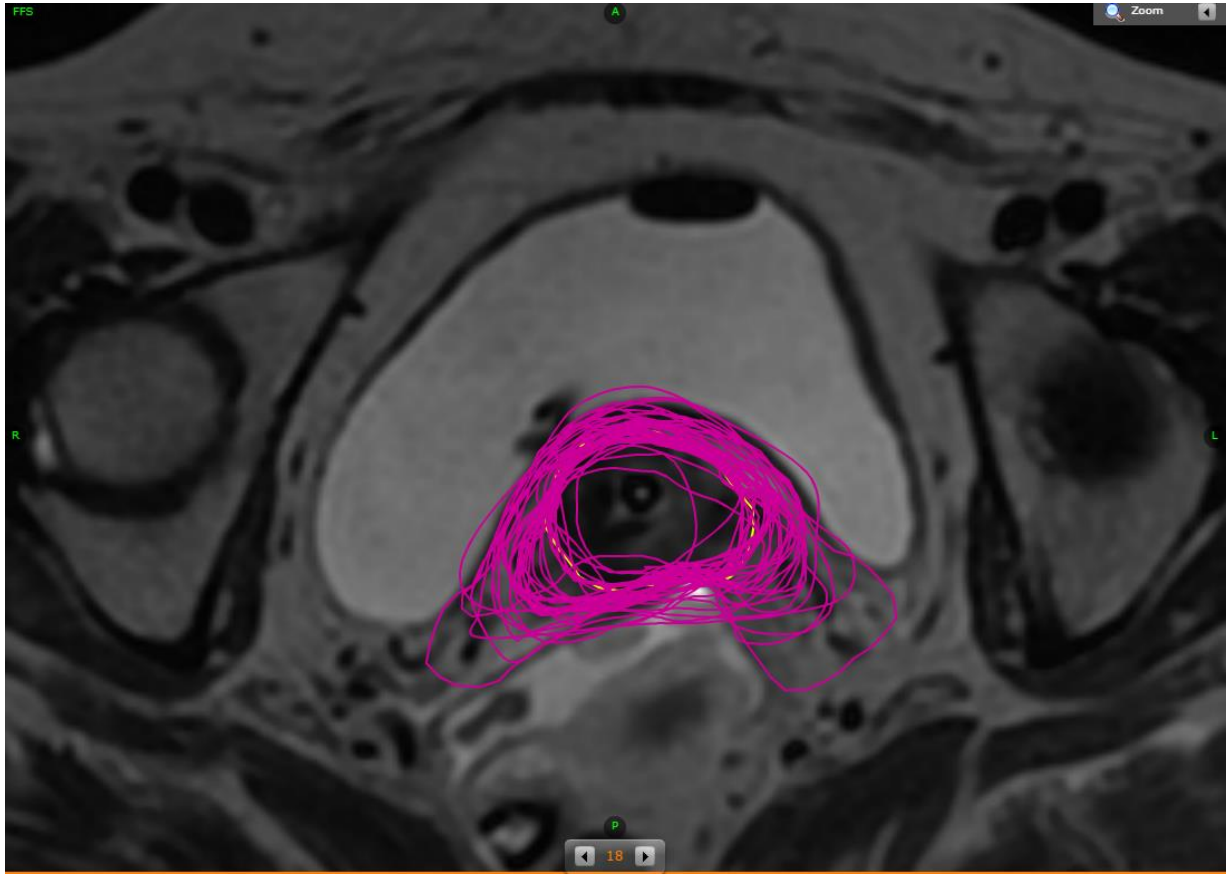
Target	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV_{res} $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy	> 75 Gy	>95 Gy
Limits for Prescribed Dose	> 85 Gy	-	>90 Gy

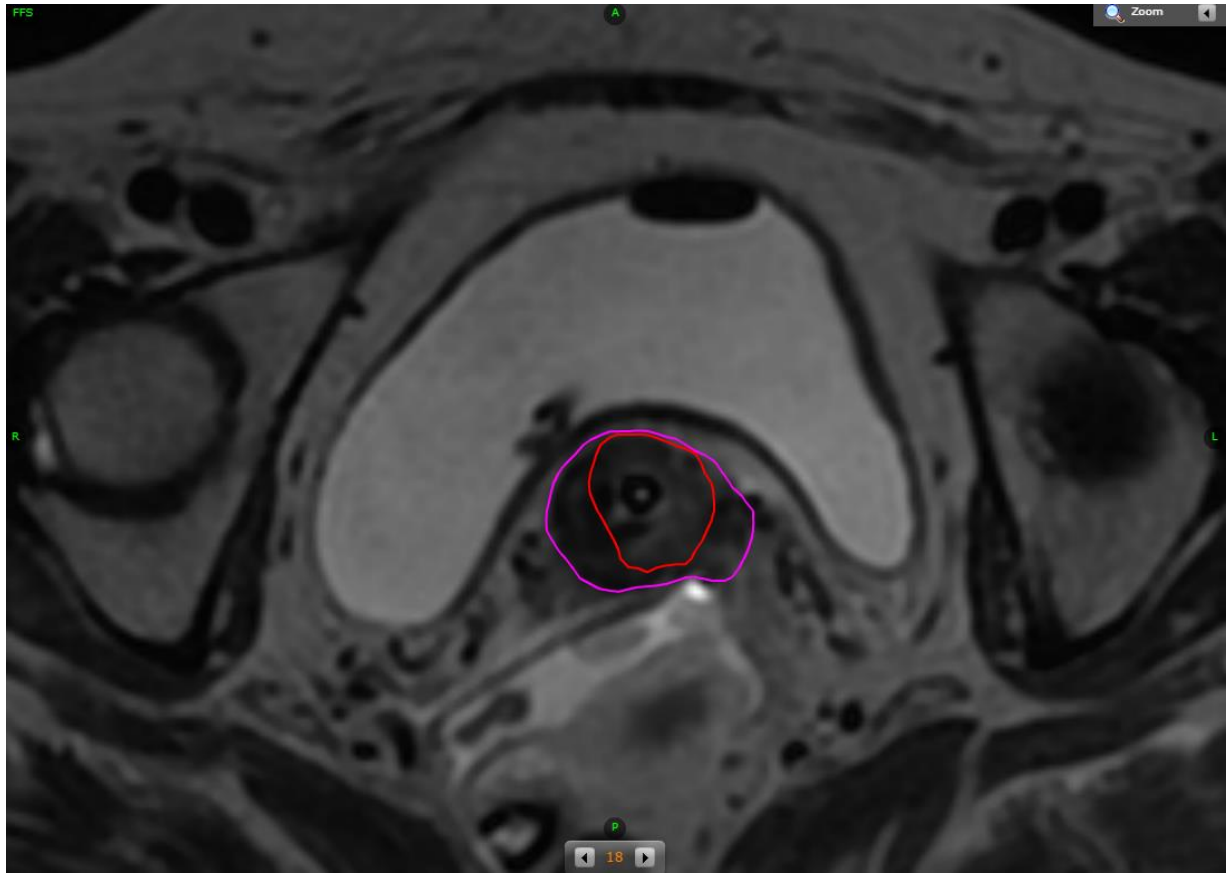
Adaptive CTV-HR

CTV-HR

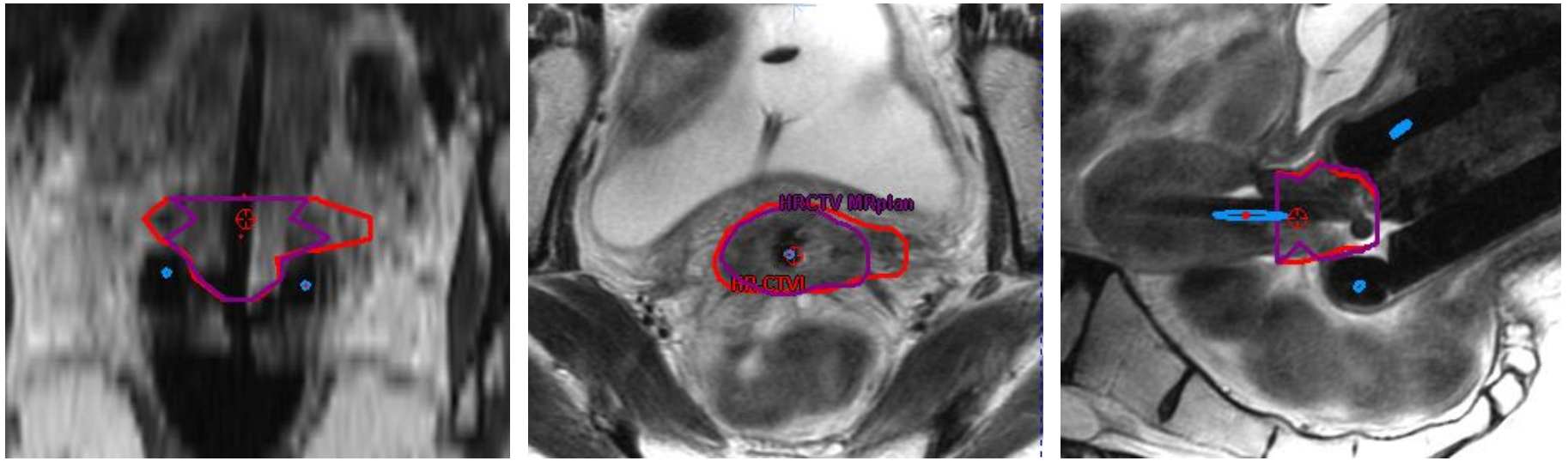
- GTV-T_{res}
- Whole cervix
- Grey zones
- Palpable abnormality in parametrium at EUA

Homework – High Risk CTV





D90 is dependent on contouring

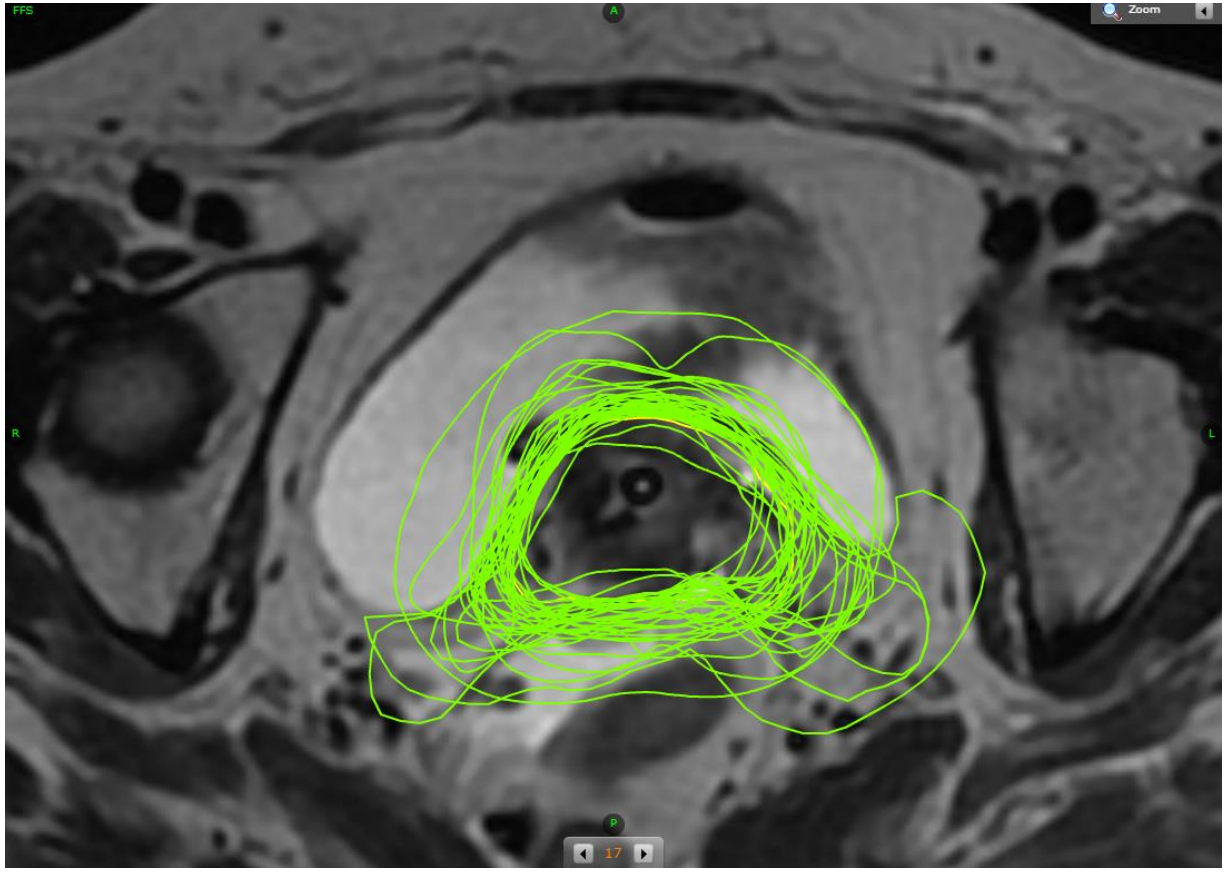


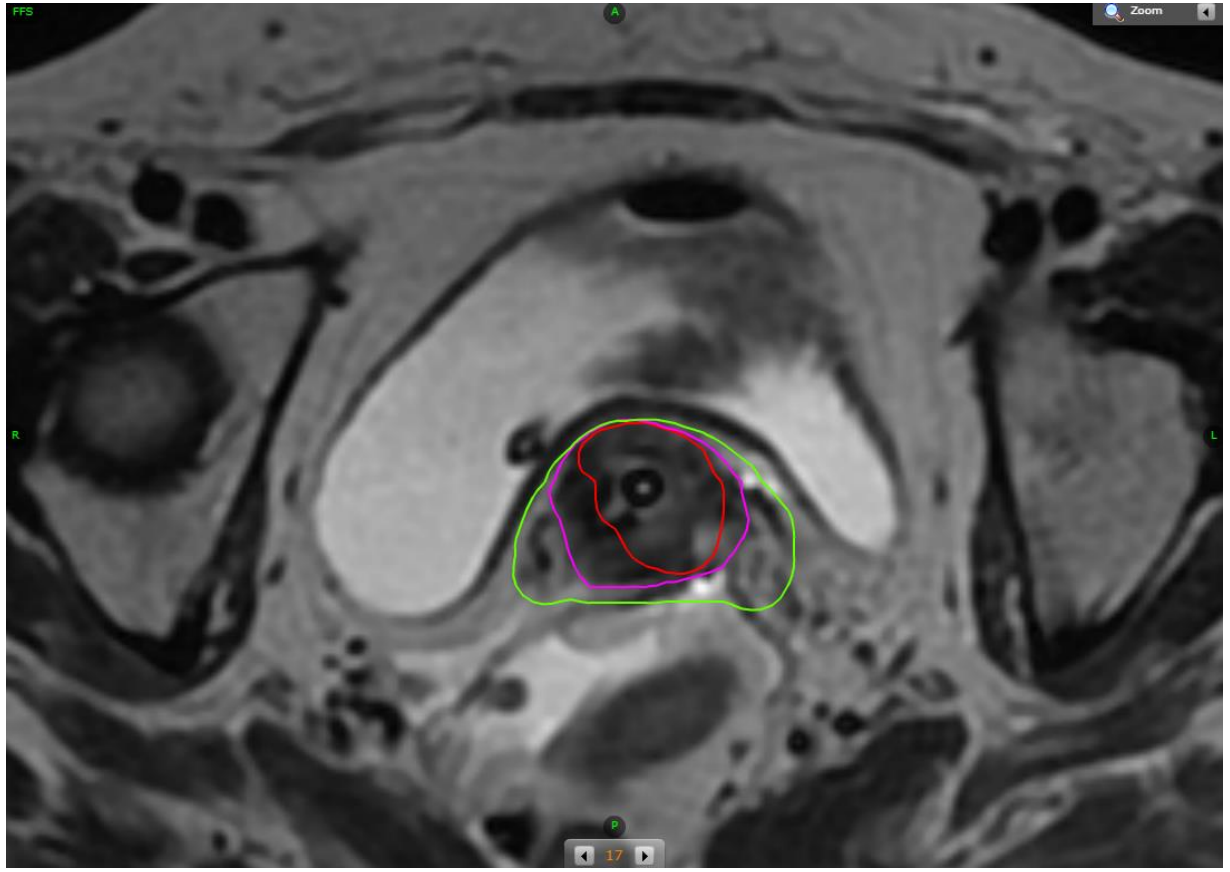
Point A (Gy)	D90 small (Gy)	D90 large (Gy)
7	12.0	9.2

EMBRACE-II Point A EQD2 planning aim: > 65 Gy

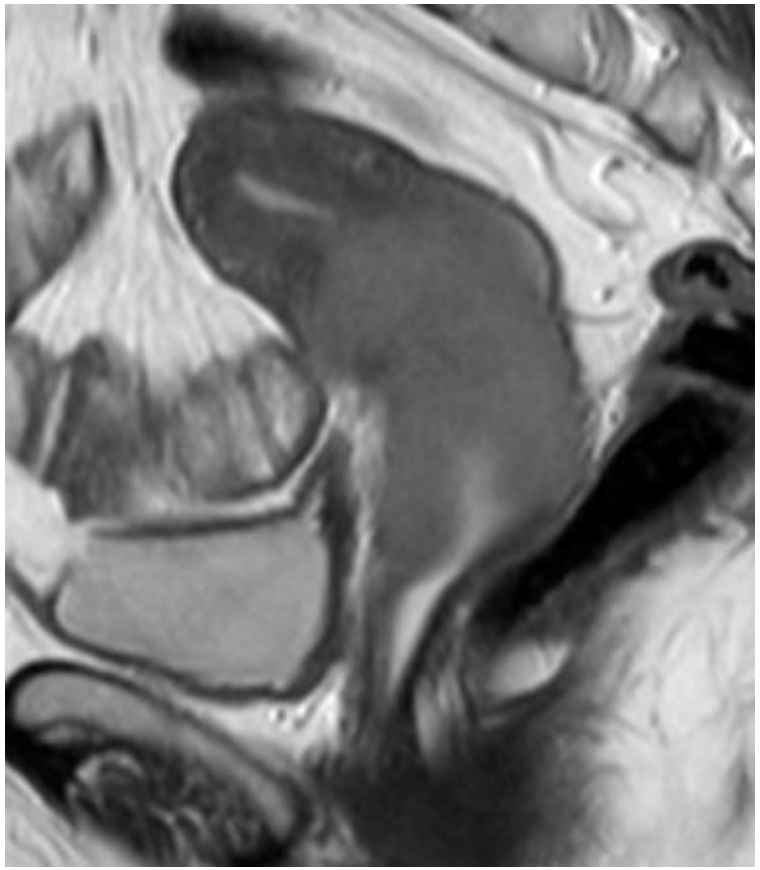
Adaptive CTV-IR

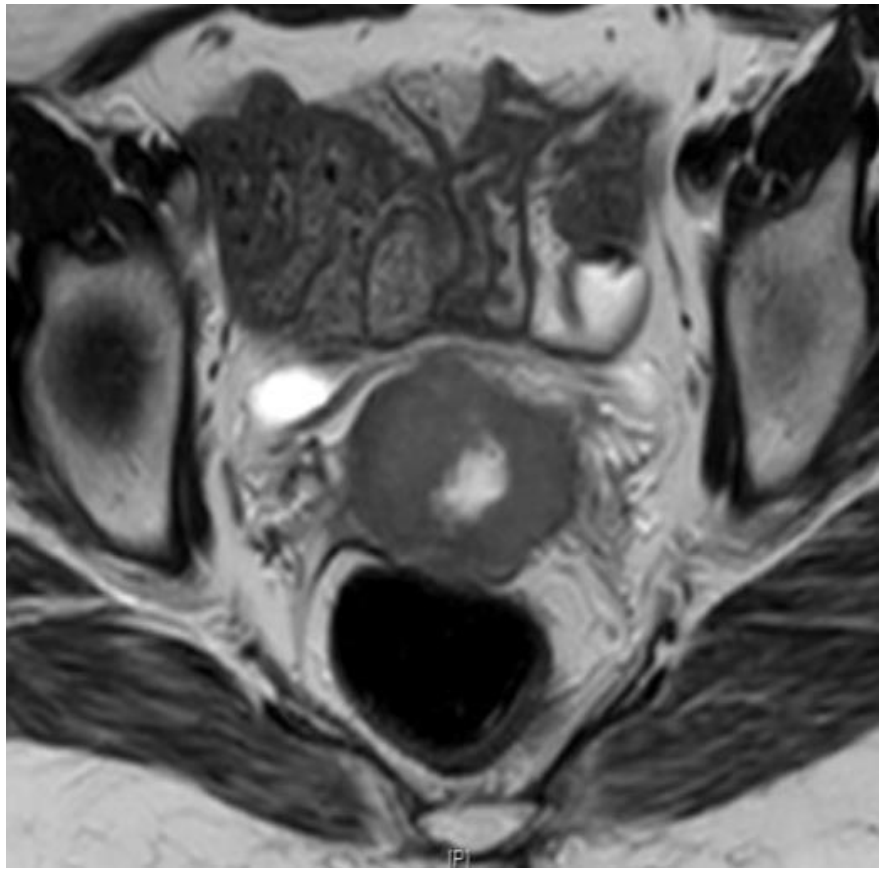
Homework – Intermediate Risk CTV





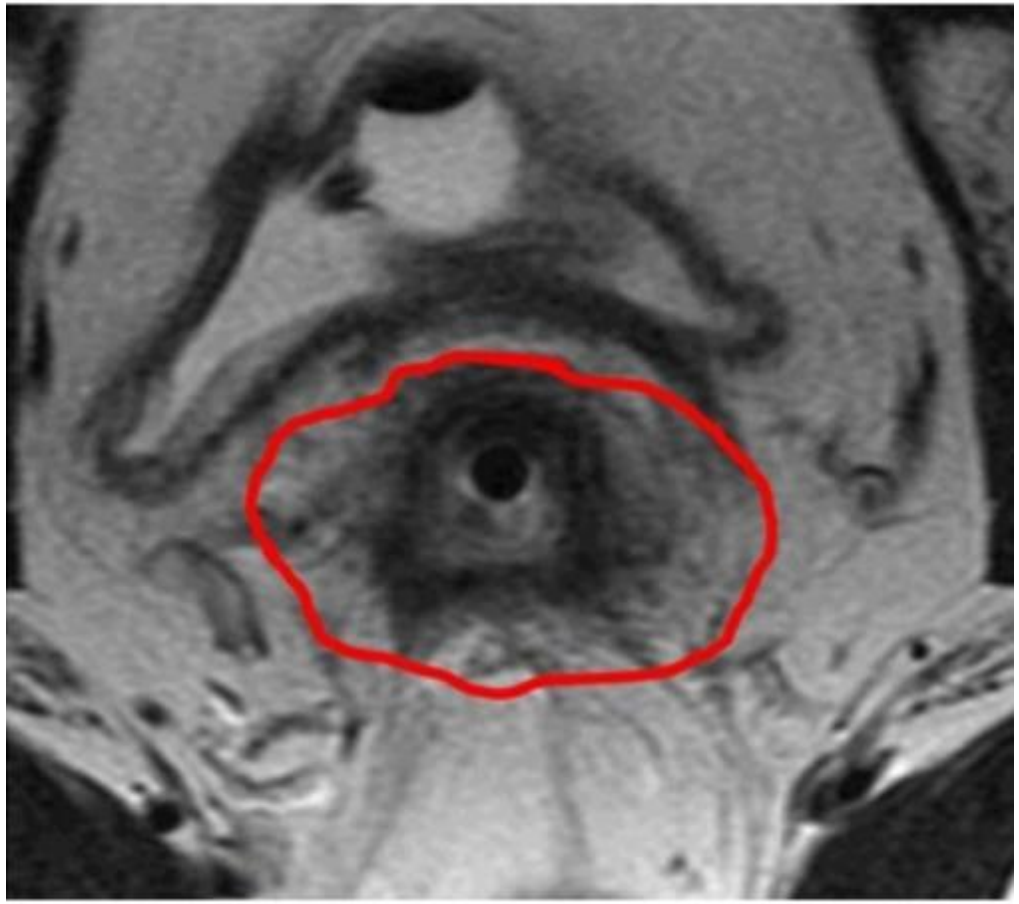
Homework – Intermediate Risk CTV –> initial imaging



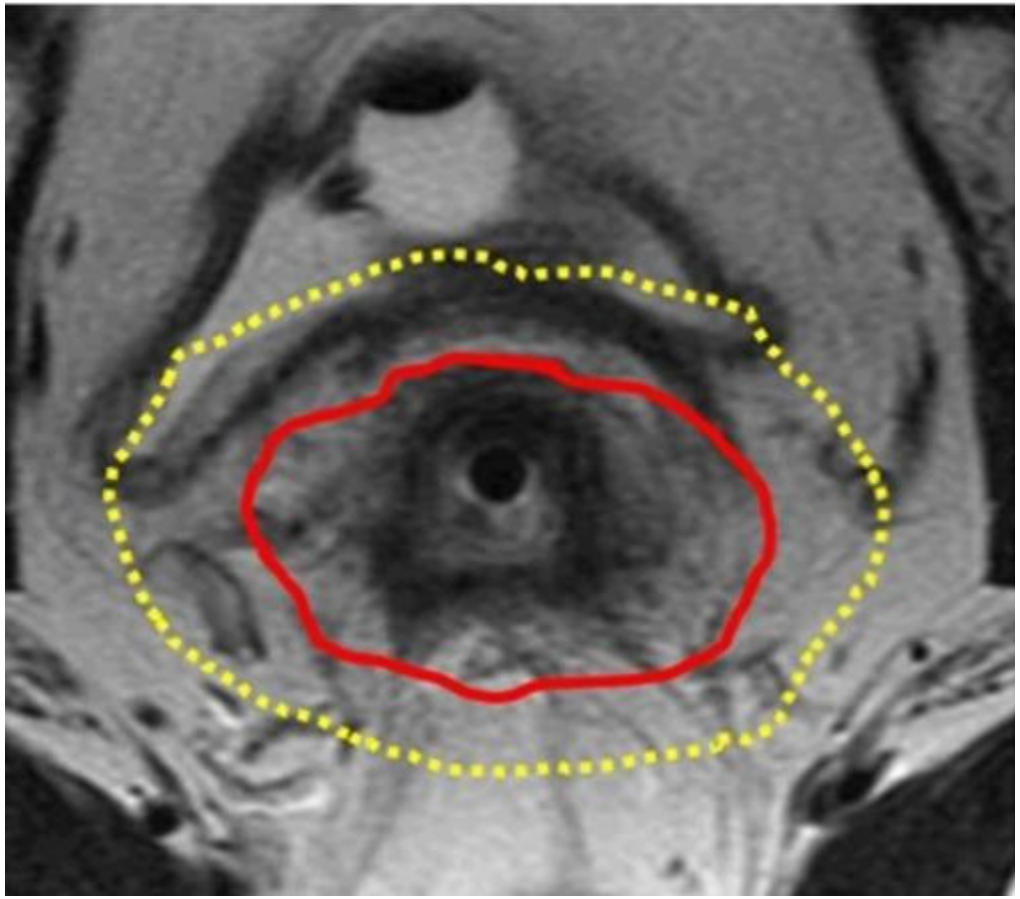


Step-by-step to CTV-IR

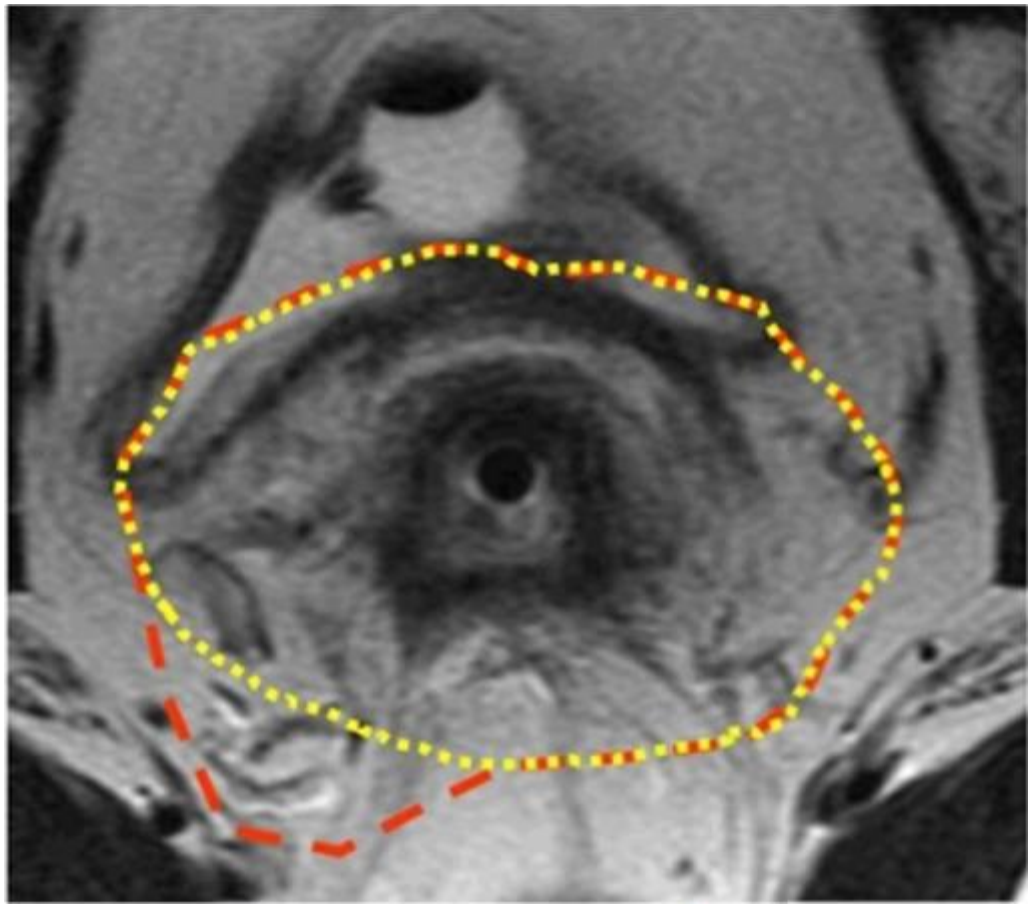
Start with HR-CTV



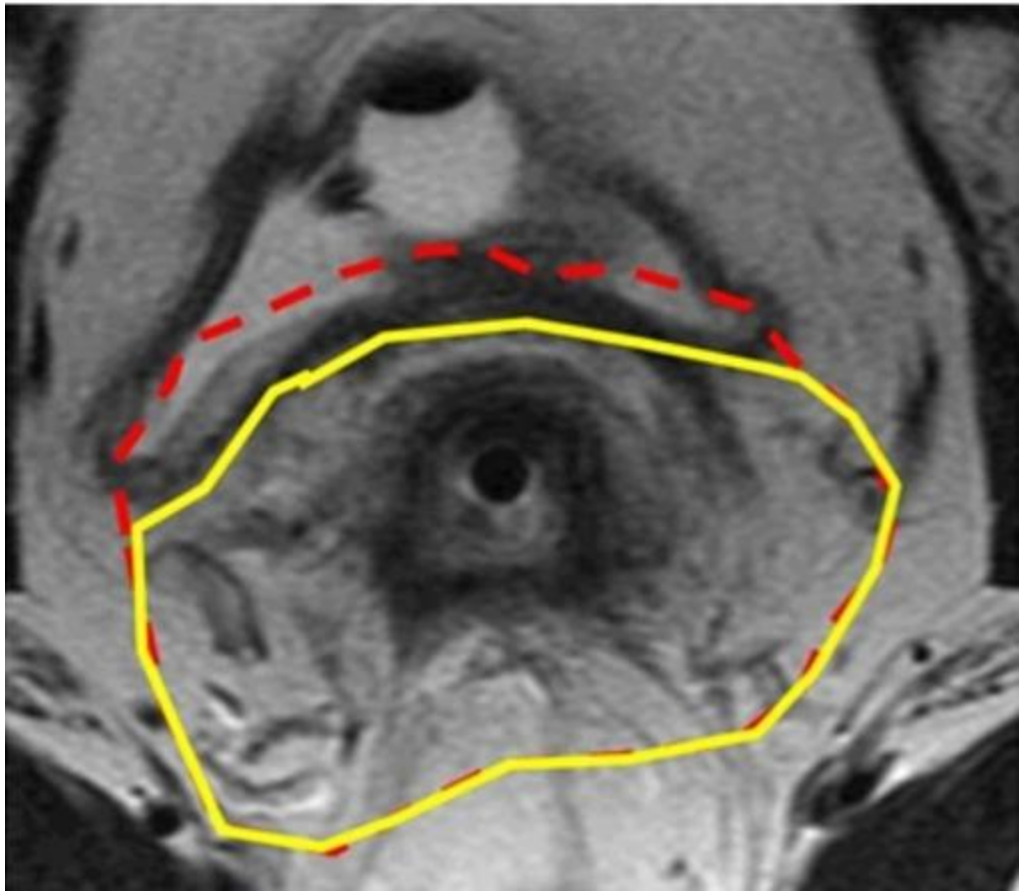
Add 1 cm margin



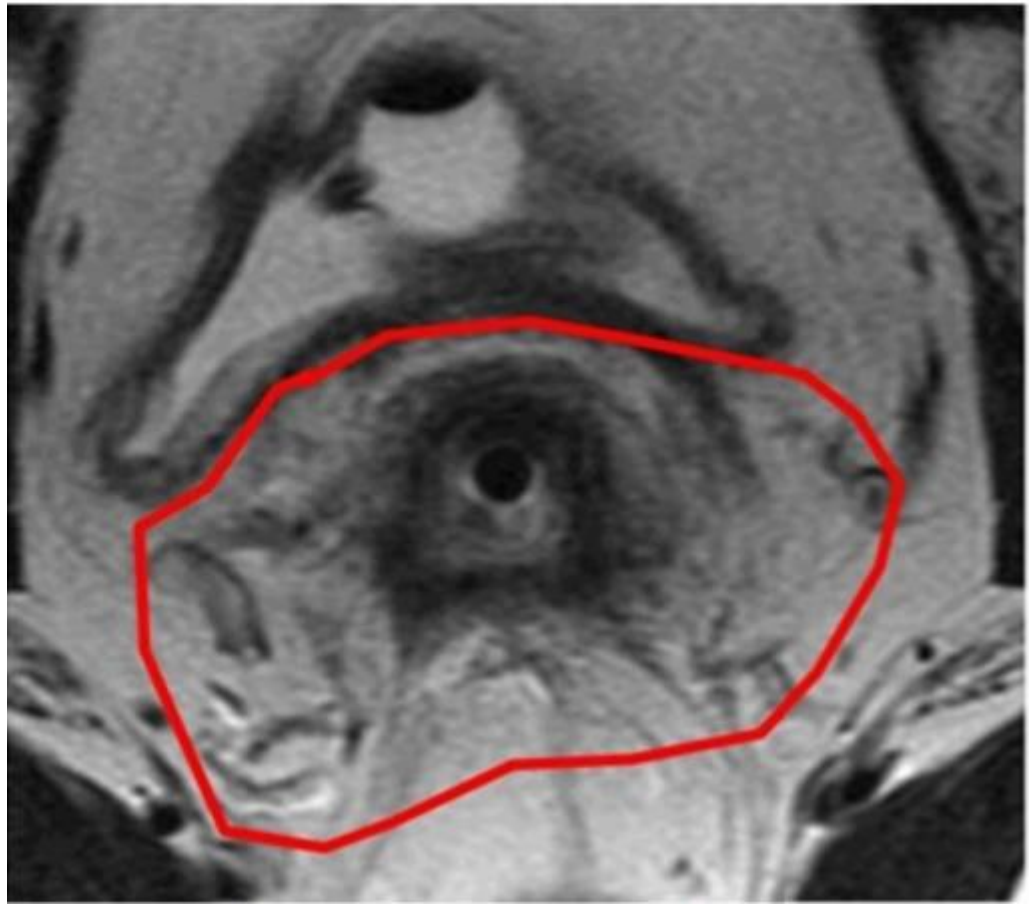
Include GTV at diagnosis



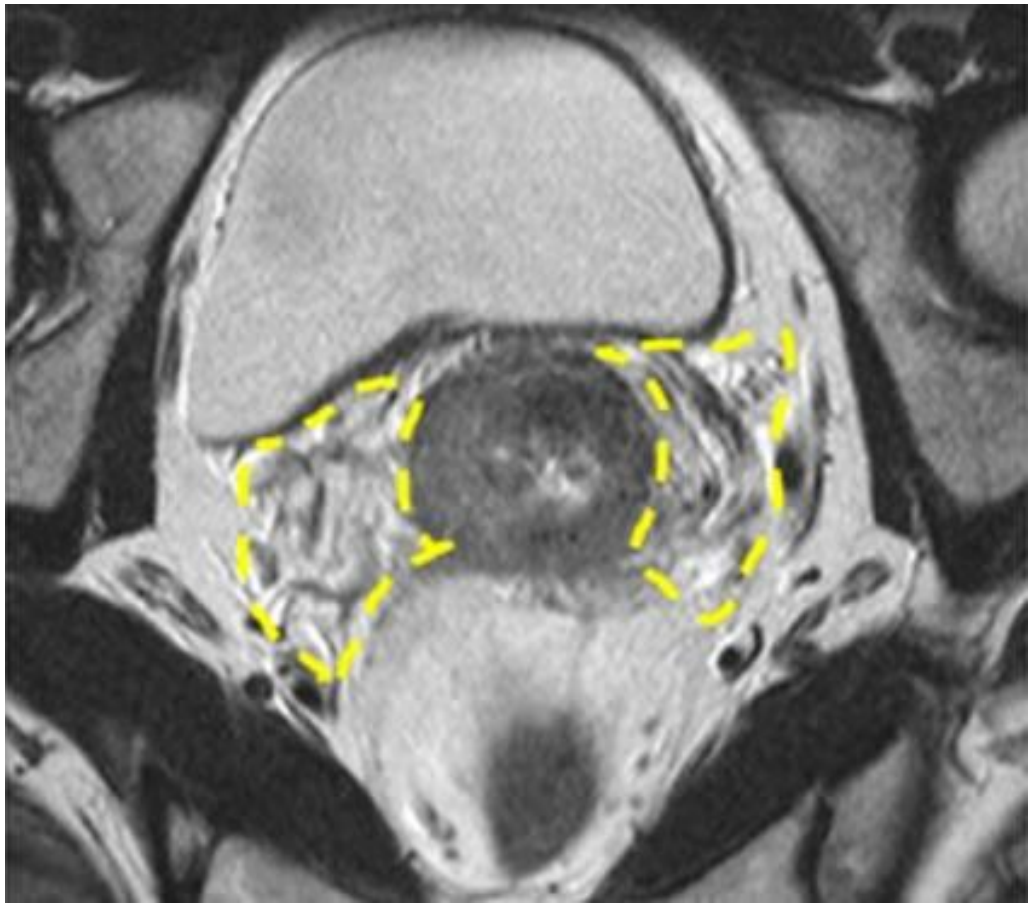
Exclude OAR

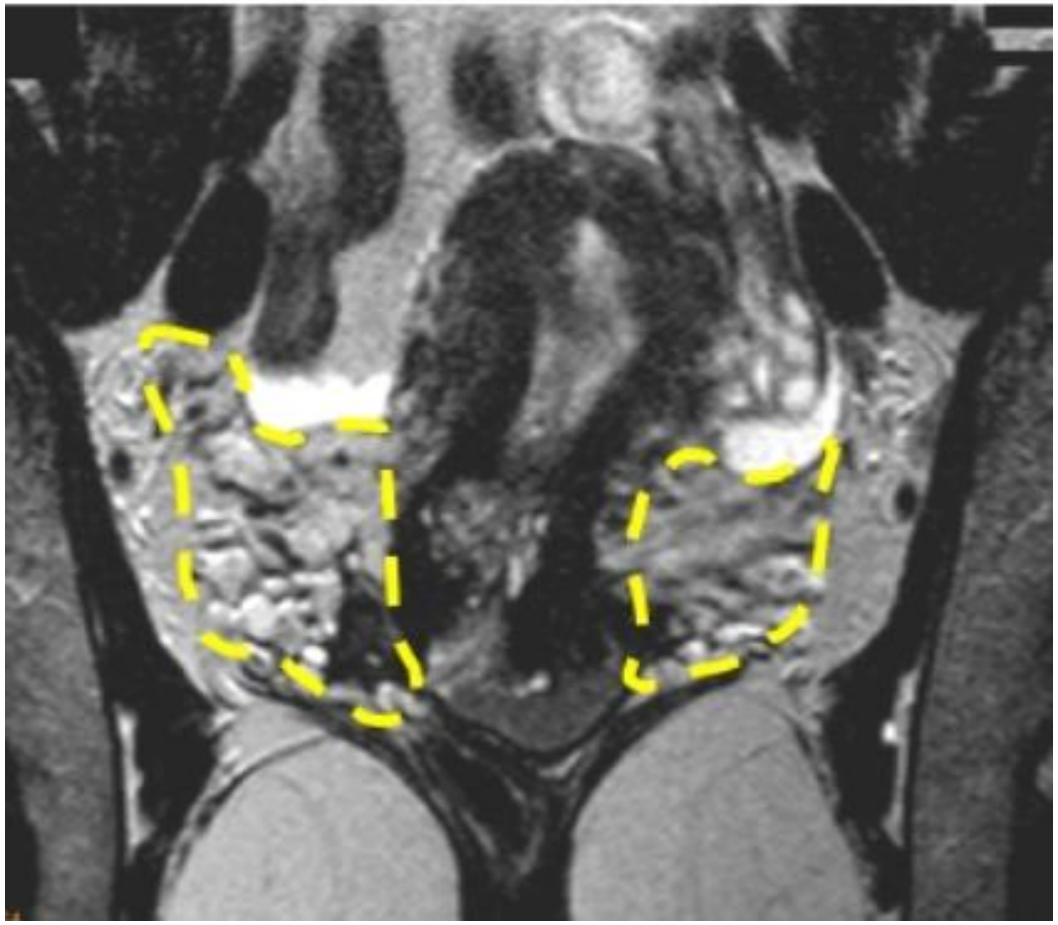


Final IR-CTV



Parametrium borders



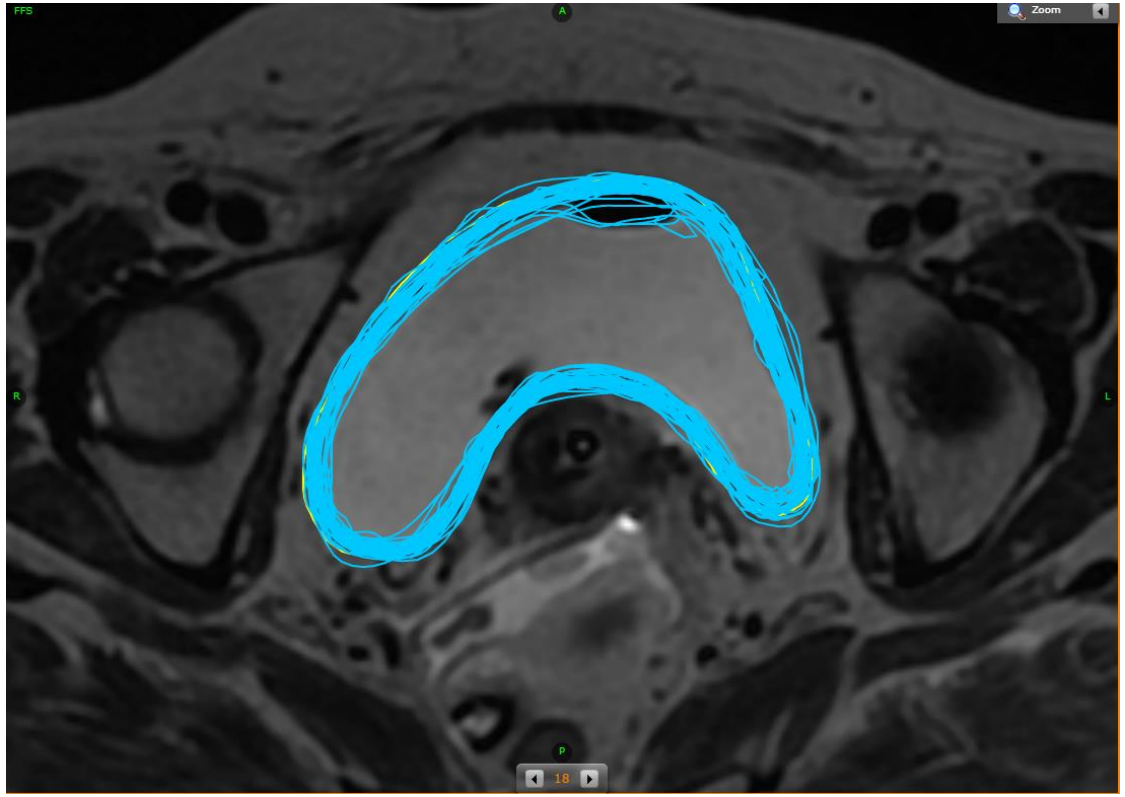


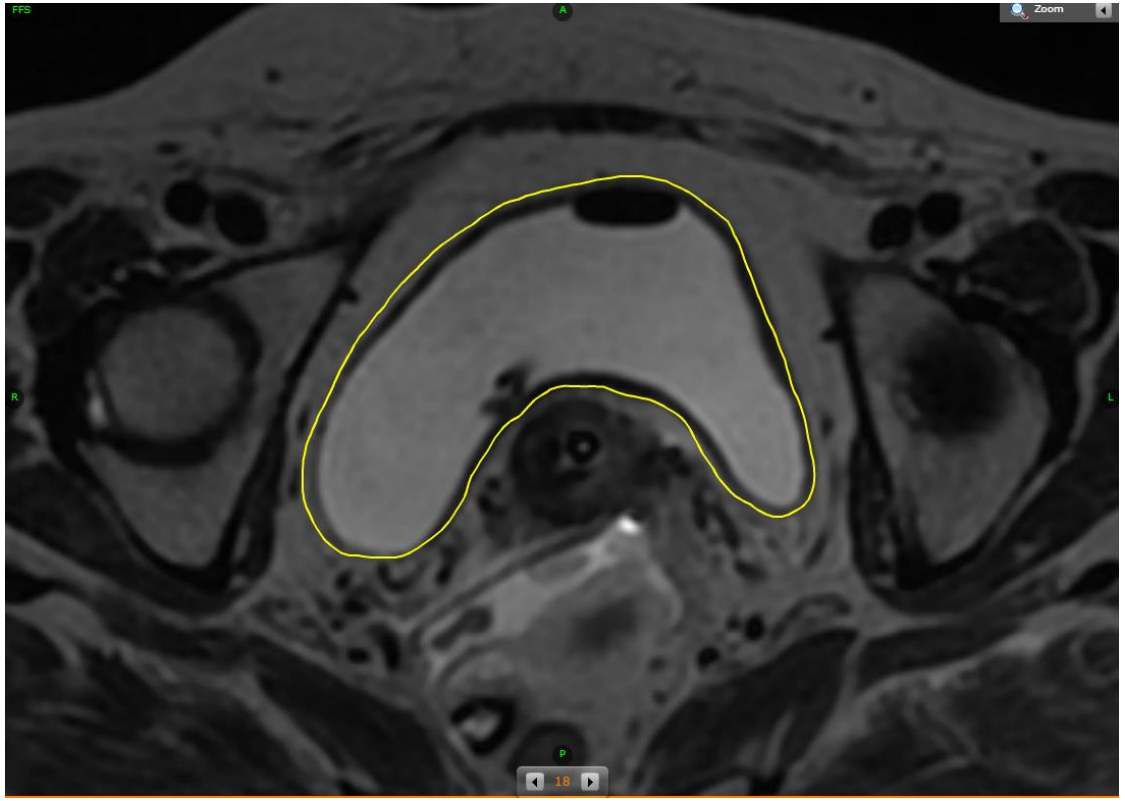
- *Toita, Jpn J Clin Oncol 2011;41(9)1119–1126*

*Contouring would stop at the level where bowel loops are seen

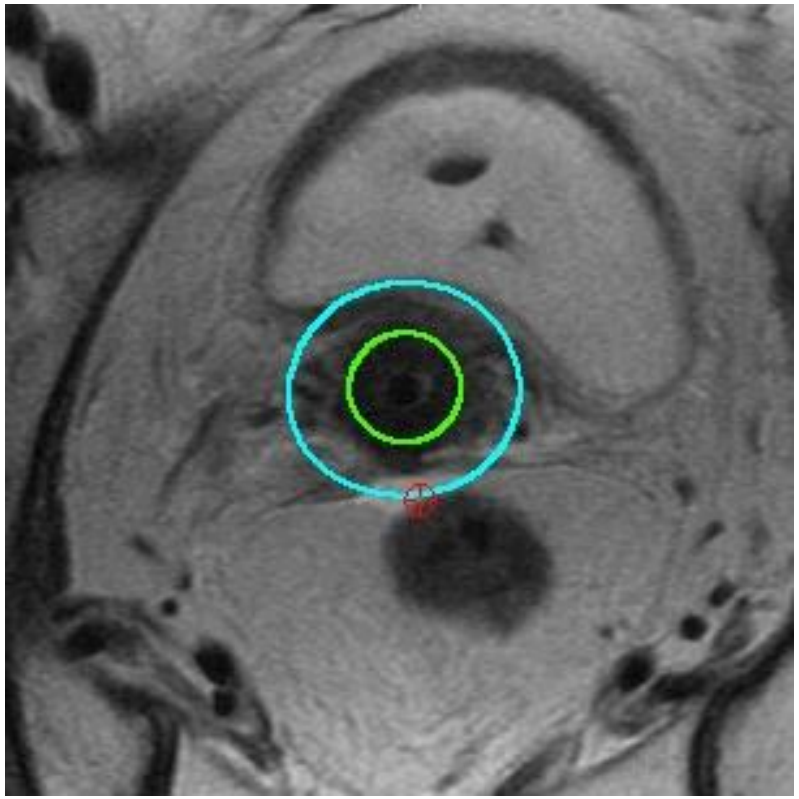
OAR

Homework - Bladder

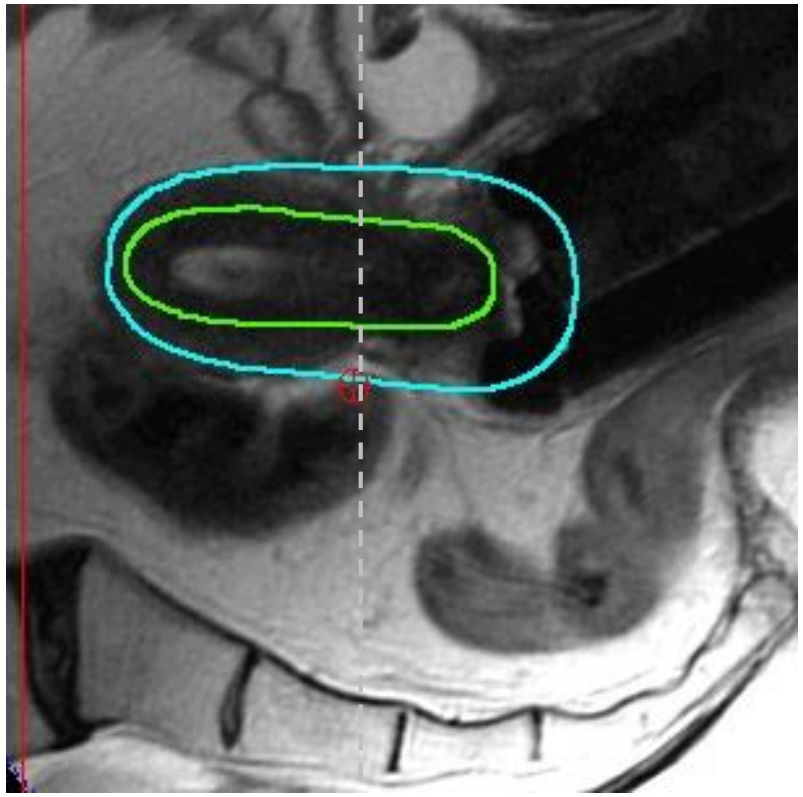




Inter-observer variation OAR contouring

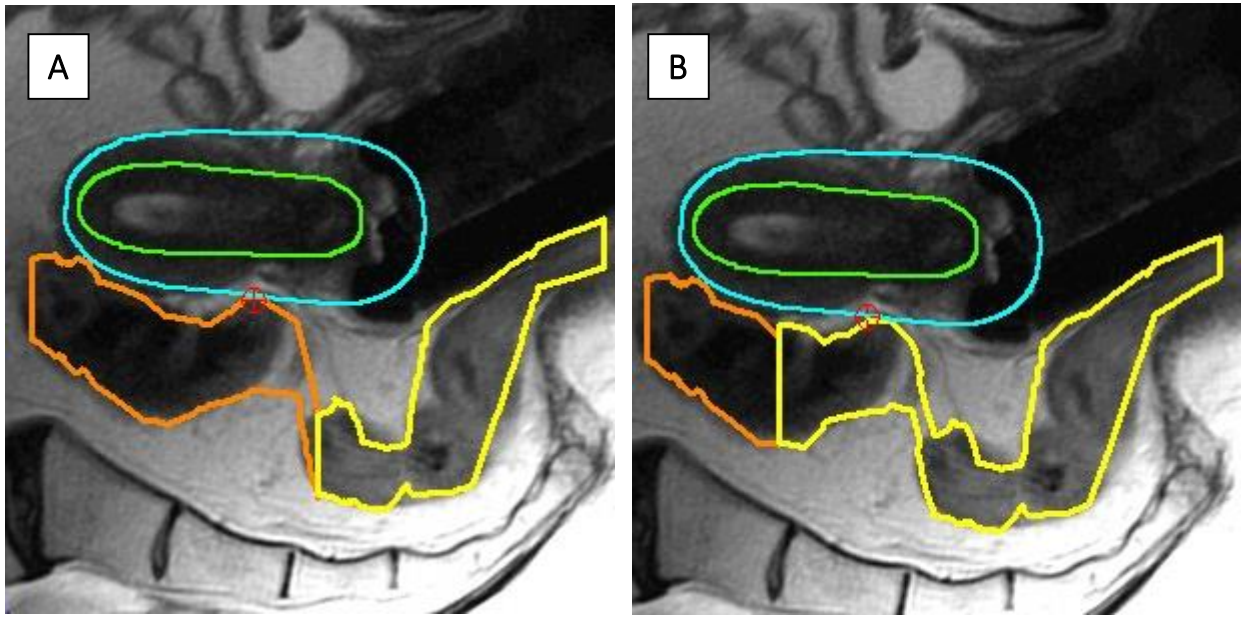


Rectum? (Central)



Sigmoid? (Above S3)

Inter-observer variation

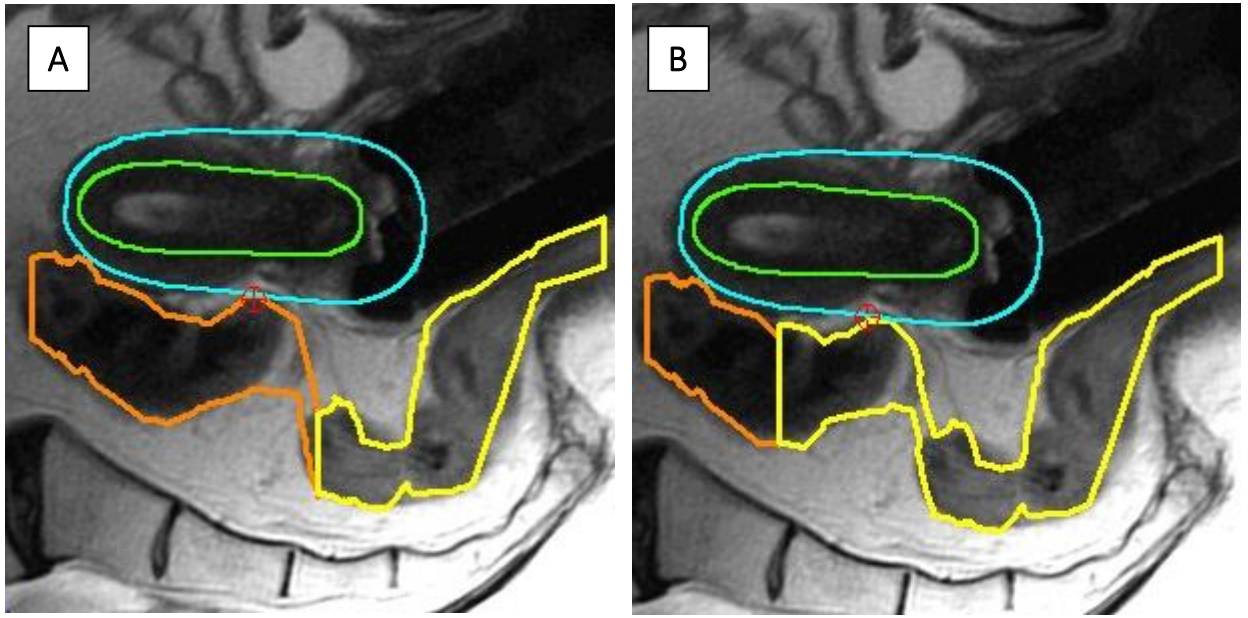


OAR	D2cc sigmoid *(5.0 Gy)*				D2cc rectum *(5.0 Gy)*				EQD2 (45 Gy/25#) *($75\ Gy_3$)*	
	#1	#2	#3	#4	#1	#2	#3	#4	Sigmoid	Rectum
A	5.5	5.5	5.5	5.5	3.5	3.5	3.5	3.5	80.6	61.4
B	4.5	4.5	4.5	4.5	5.5	5.5	5.5	5.5	70.2	80.6

EMBRACE-II planning aims

OAR	Bladder D_{2cm^3} $EQD2_3$	Rectum D_{2cm^3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid D_{2cm^3} $EQD2_3$	Bowel D_{2cm^3} $EQD2_3$
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy*	< 70 Gy*
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*	< 75 Gy*

Interobserver variation



Possible scenarios	D2cc sigmoid *(5.0 Gy)*				D2cc rectum *(5.0 Gy)*				EQD2 (45 Gy/25# *($75\ Gy_3$)*	
	#1	#2	#3	#4	#1	#2	#3	#4	Sigmoid	Rectum
1	5.5	5.5	5.5	4.5	3.5	3.5	3.5	5.5	78	66.2
2	5.5	5.5	4.5	4.5	3.5	3.5	5.5	5.5	75.4	71.0
3	5.5	4.5	4.5	4.5	3.5	5.5	5.5	5.5	72.8	75.8

Mini-Contour exercises

Instructions – “Mini-Contour”

1) Go to estro.org and log in. Click on the moodle button 

2) Go to the course website (where the modules are listed)
   - Scroll to the bottom (section 5) and complete the consent form
   - Click the ‘Mini-Contour’ exercise link
   - If you have technical problems please let us know

3) After completing the exercises, feedback would be very useful – if possible, we would like you to *give **feedback on each hotspot** using the ‘comment’ link*

Thank you very much for your patience and participation!

ARCHIVED

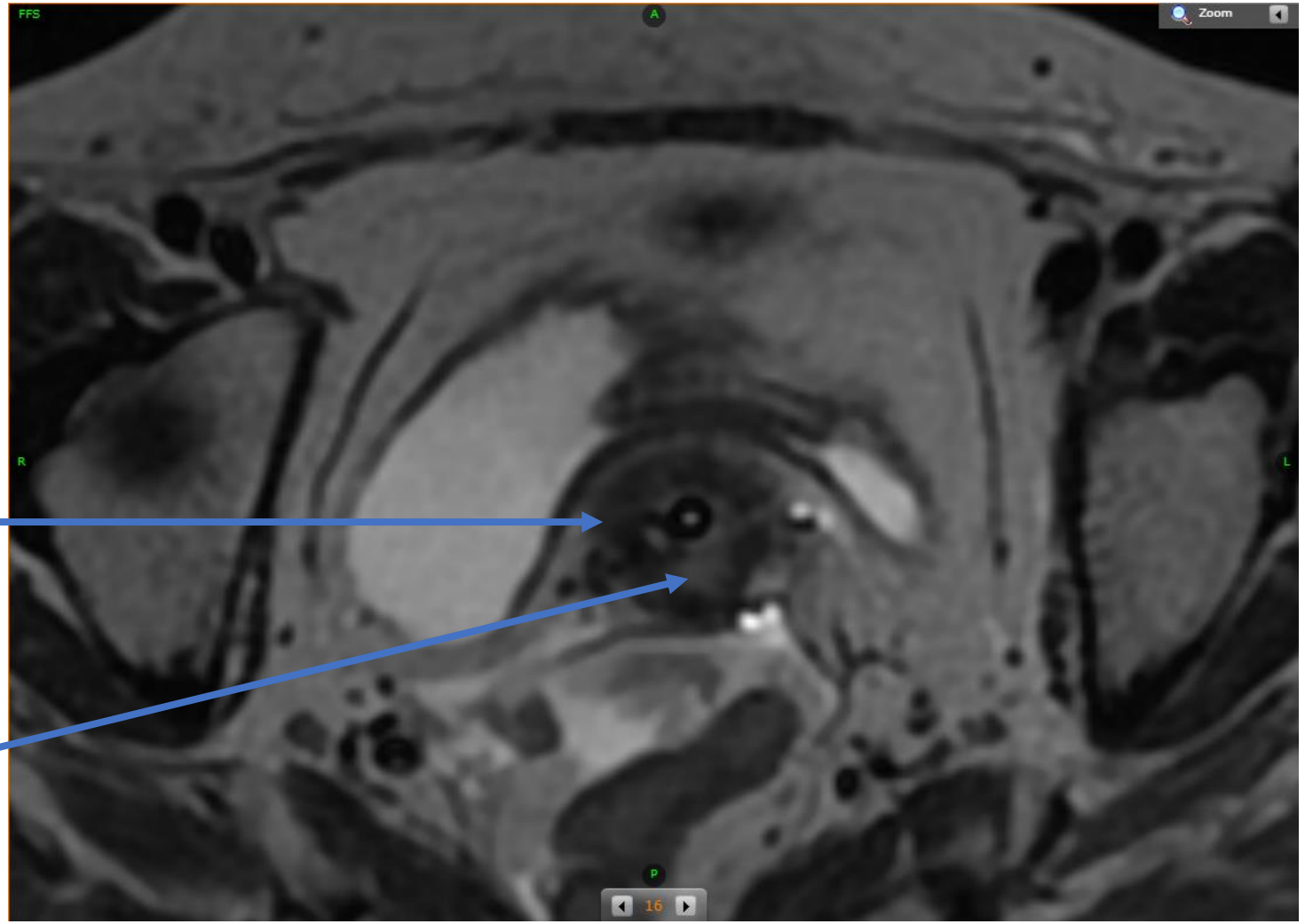
Homework – GTV (2)

Tip:

Identify cervix

Look for outer rim of low signal

Identify where disrupted



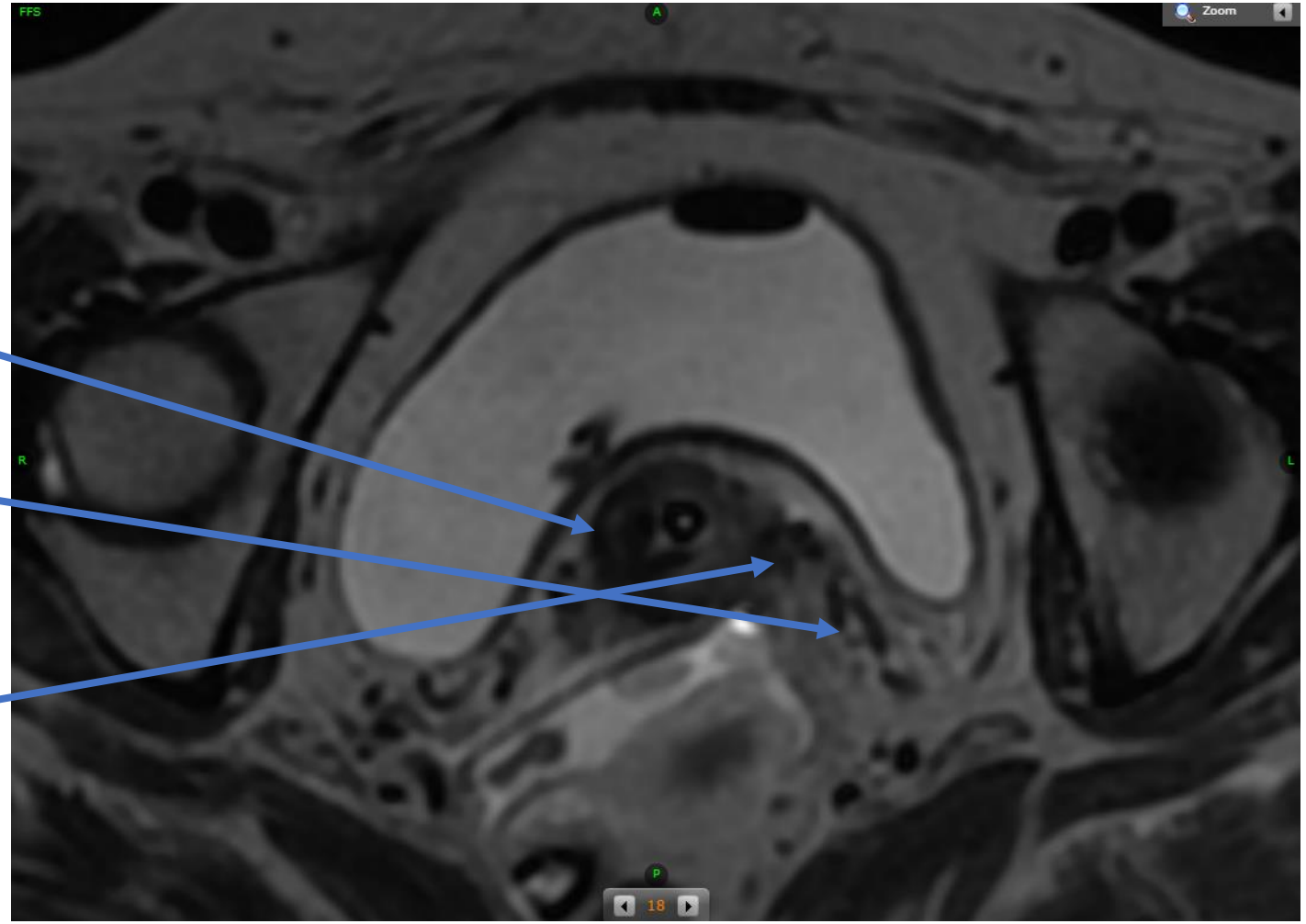
Homework – High Risk CTV

Tip:

Identify dark (low T2) outer rim of cervix

Identify bright (high T2) parametrial fat

Look for intermediate signal zones in between



Homework – Intermediate Risk CTV (2)

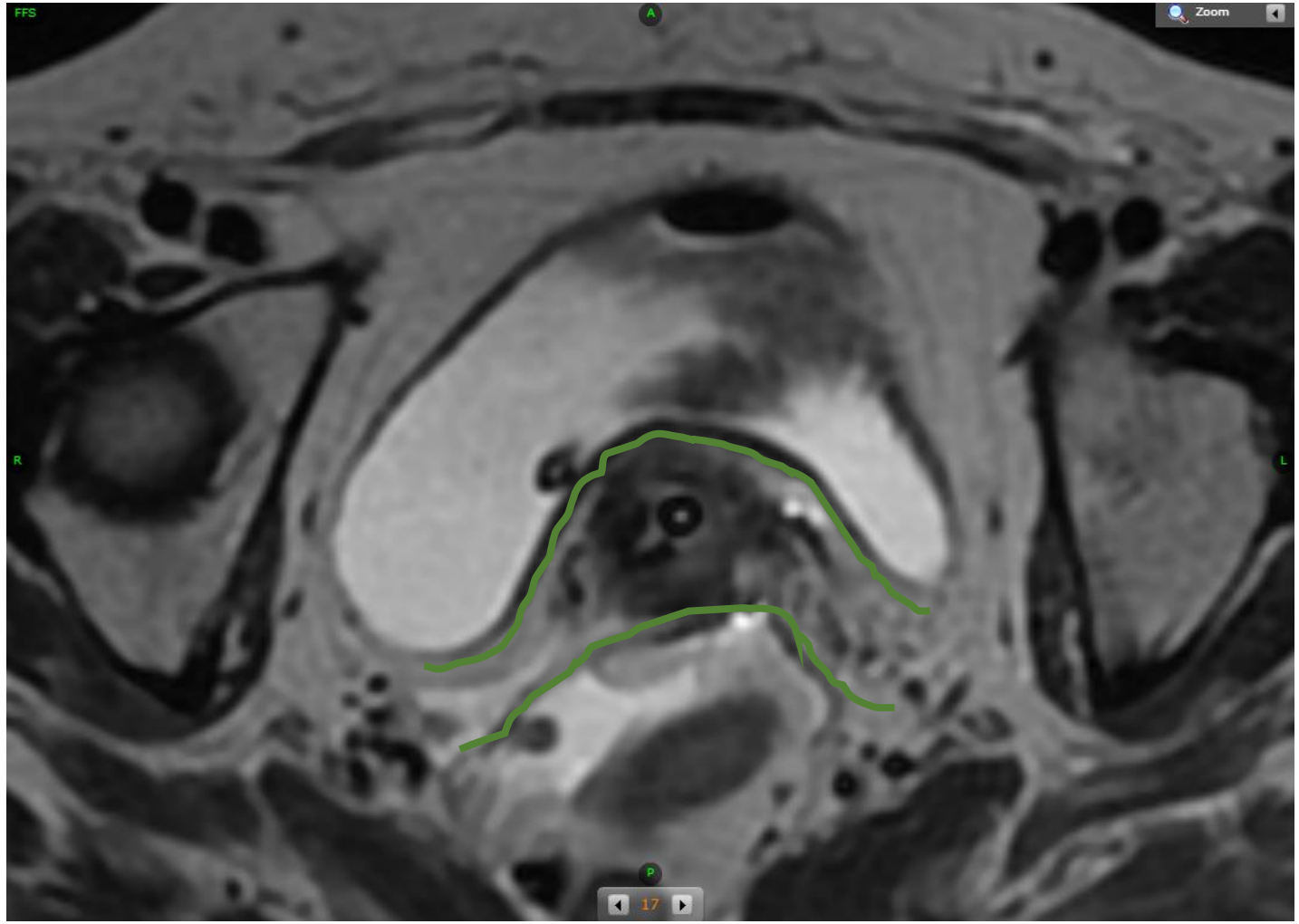
Tips:

1) Outline mesorectum and bladder borders

(if no bladder / mesoretal involvement at diagnosis)

2) Put on expansion from HR-CTV, edited for those lines

3) Decide on extent along parametrial axis based on initial tumour extent



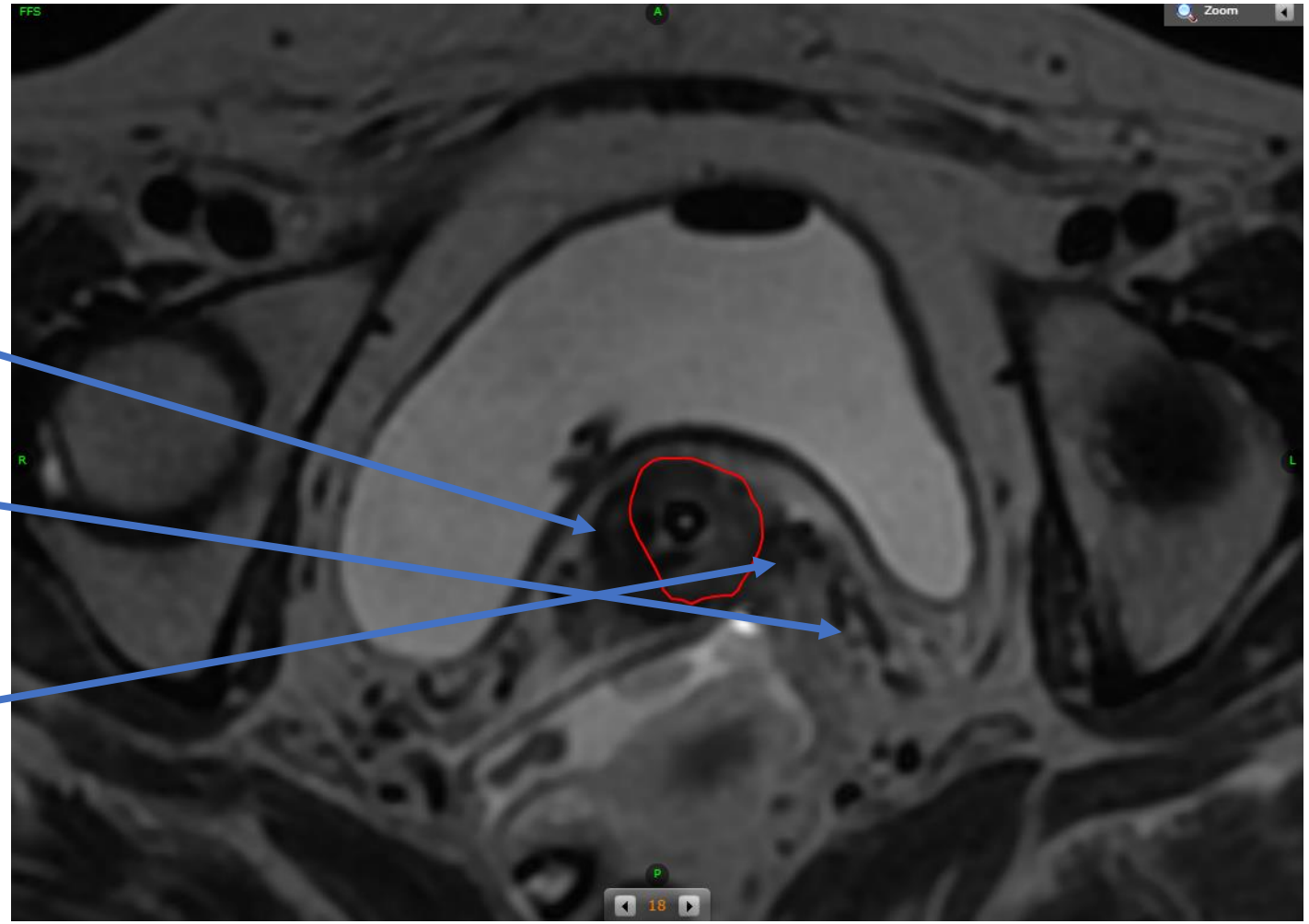
Homework – High Risk CTV (2)

Tip:

Identify dark (low T2) outer rim of cervix

Identify bright (high T2) parametrial fat

Look for intermediate signal zones in between



Basic Physics
and dose planning principles

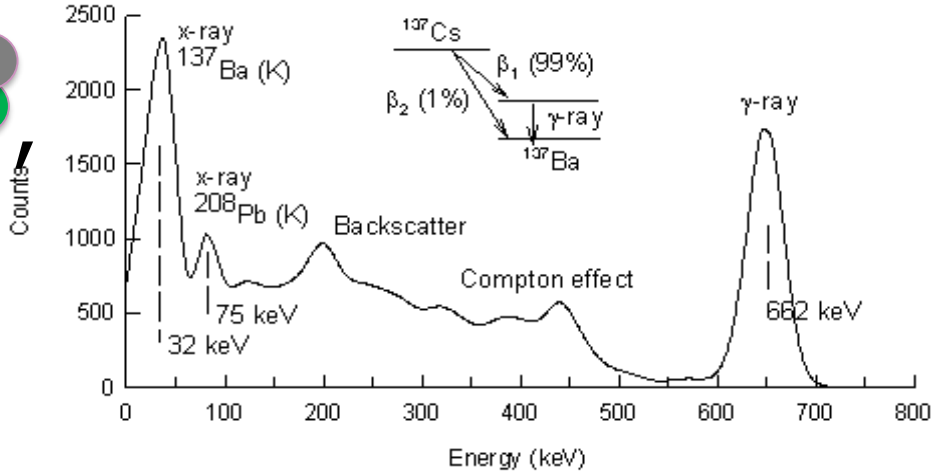
presented by Daniel Berger

General Hospital of Vienna, City of Vienna,
Medical University of Vienna, Department of Radiotherapy

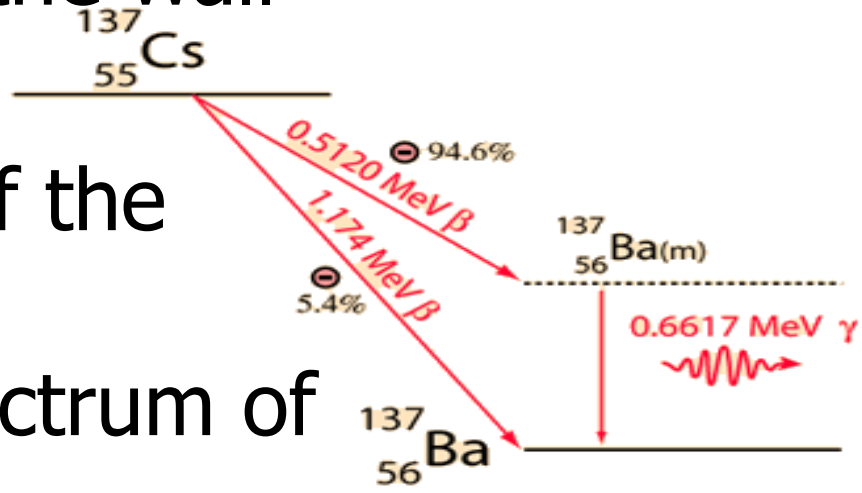
Courtesy Taran Paulsen Hellebust

Spectrum of a Source

- The source can emit alfa-, beta -, and/or gamma ~ radiation



- **Sealed sources**: the alfa- and beta radiation will be absorbed in the wall of the source
- The **type and the energy** of the radiation is **unique for each nuclide** and is called the spectrum of the source

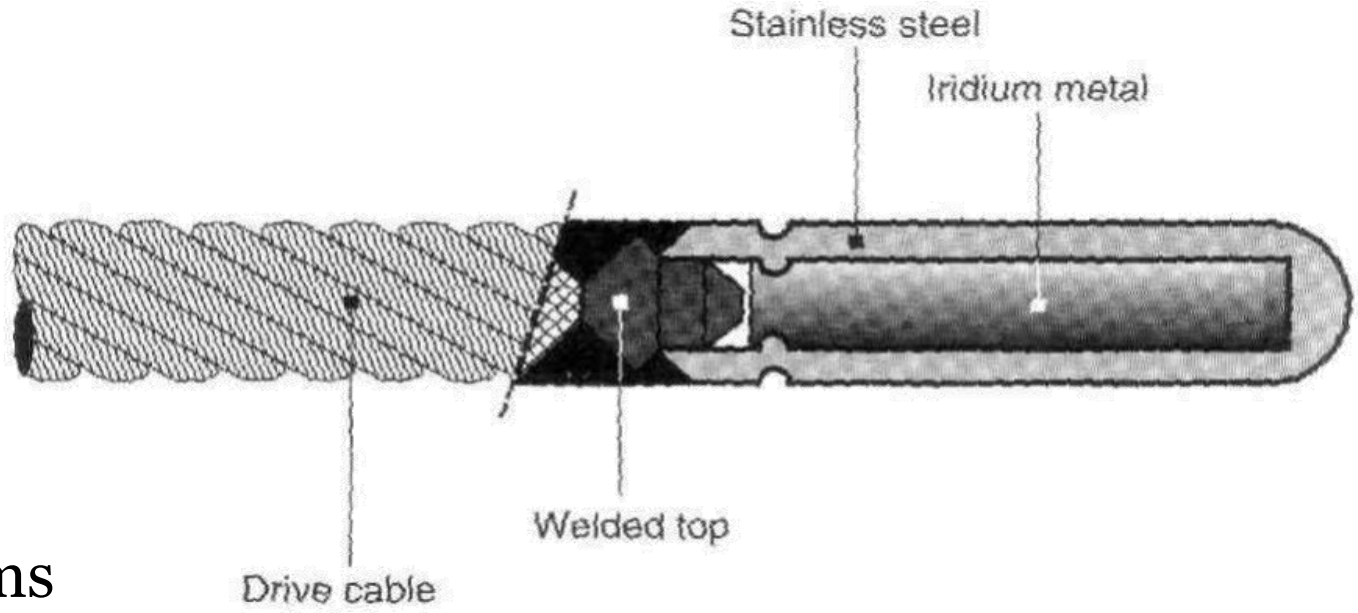


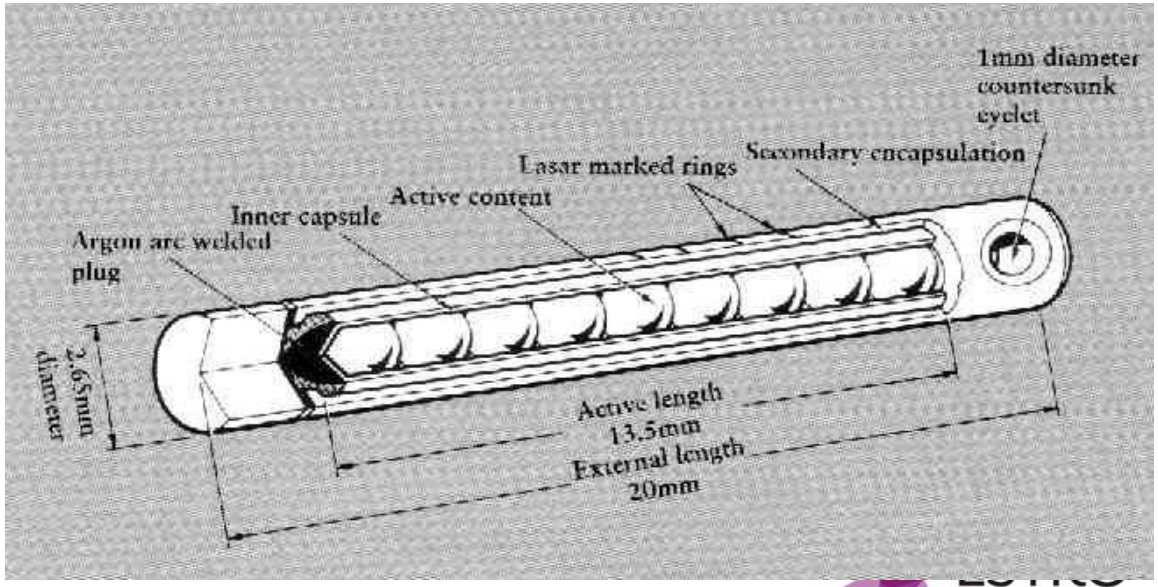
Largely replaced Ra-226 in the mid 1970s.
Caesium-137 is widely used in LDR brachytherpy and is available in several forms needles, tubes, pellets. Formed as one of the more common fission products by the nuclear fission of uranium-235
Availability of sources suitable for remote afterloading devices has declined the use of ^{137}Cs as a LDR BT source.

Sources in GYNaecological BrachyTherapy

Source types

- ***sealed sources***!!
- different physical forms
  - HDR, LDR, PDR
  - tubes, pellets
- small linear sources
- stepping source

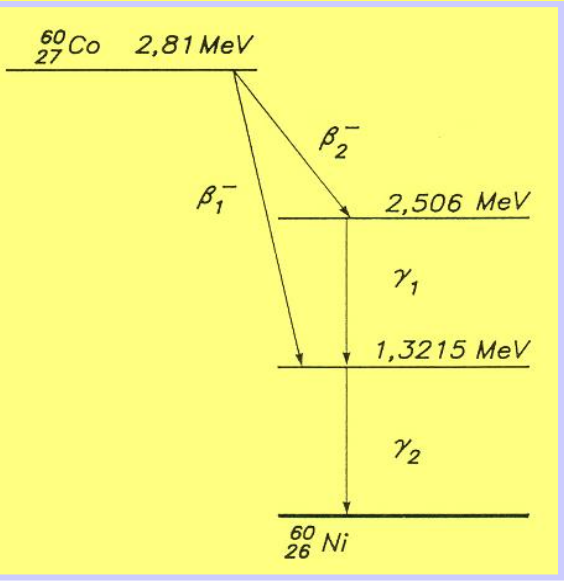


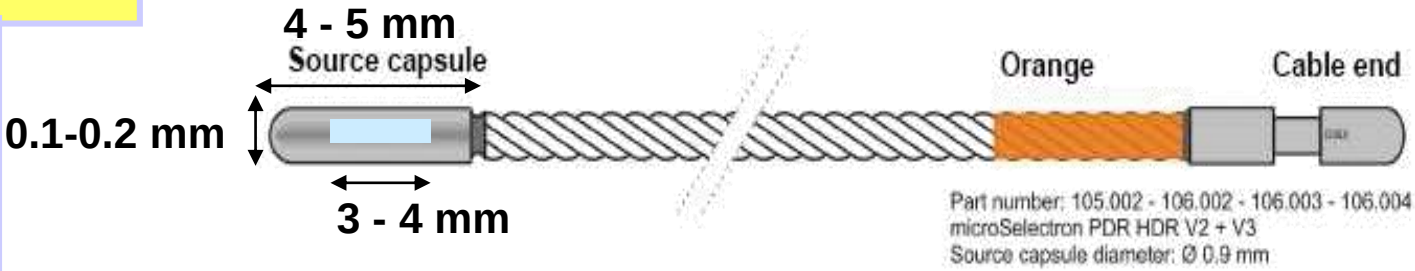


Source Geometry

Co-60 E =1253 keV $T_{1/2}$ = 5.27 a

$$^{60}_{27}Co \rightarrow ^{60}_{28}Ni + ^{0}_{-1}e + \bar{\nu}$$





Ir-192 E = 355 keV $T_{1/2}$ = 73.8 d

$$^{192}_{77}Ir \rightarrow ^{192}_{78}Pt + ^{0}_{-1}e + \gamma + \bar{\nu}$$

Figure 1: Source cable: microSelectron PDR V2 + V3

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Physical properties of some nuclides

Radio Nuclide	Half time $T_{1/2}$	λ (s^{-1})	Average Photon Energy (keV)	Mass for 100 MBq (μg)
^{226}Ra	1600 y	$1.37\ 10^{-11}$	830	45
^{137}Cs	30 y	$7.27\ 10^{-10}$	662	31
^{60}Co	5.26 y	$4.18\ 10^{-9}$	1253	2.4
^{192}Ir	74.2 d	$1.08\ 10^{-7}$	380	0.29
^{125}I	60.2 d	$1.34\ 10^{-7}$	28	0.16
^{103}Pd	17 d	$4.72\ 10^{-7}$	21	0.04

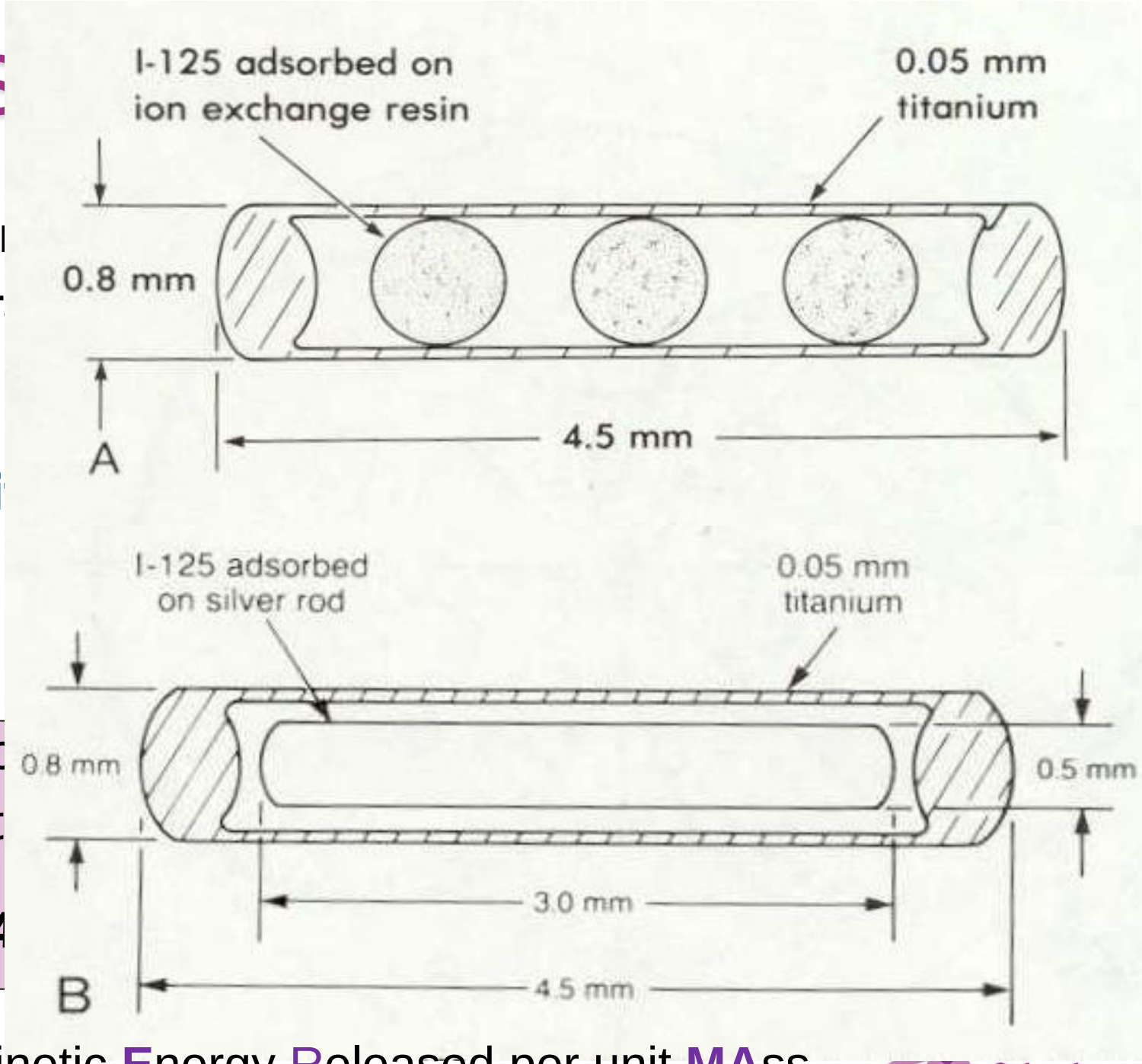
From Baltas et al., The Physics of Modern Brachytherapy 2007
a) NIST Physical reference Data, b) ICRP 21

Source s

Not used anymore

Previously, sou
# of desintegr
- **1 Ci (3.7**
- **in SI-uni**

Now, specification c
deposition, per unit
- ***in air KERMA***



Kinetic **E**nergy R**e**leased per unit **MA**ss

School

Dose calculation accorging to AAPM TG - 43

$$D(r,\Theta) = S_k \cdot \lambda \cdot T \cdot \frac{G(r,\Theta)}{G(r_0,\Theta_0)} \cdot g(r) \cdot F(r,\Theta)$$

S_k … Air kerma strength

λ … Dose rate constant

T … Total time

$\frac{G(r,\Theta)}{G(r_0,\Theta_0)}$ … Geometry factor

g(r) … Radial dose function

F(r,Θ) … Anisotropy function

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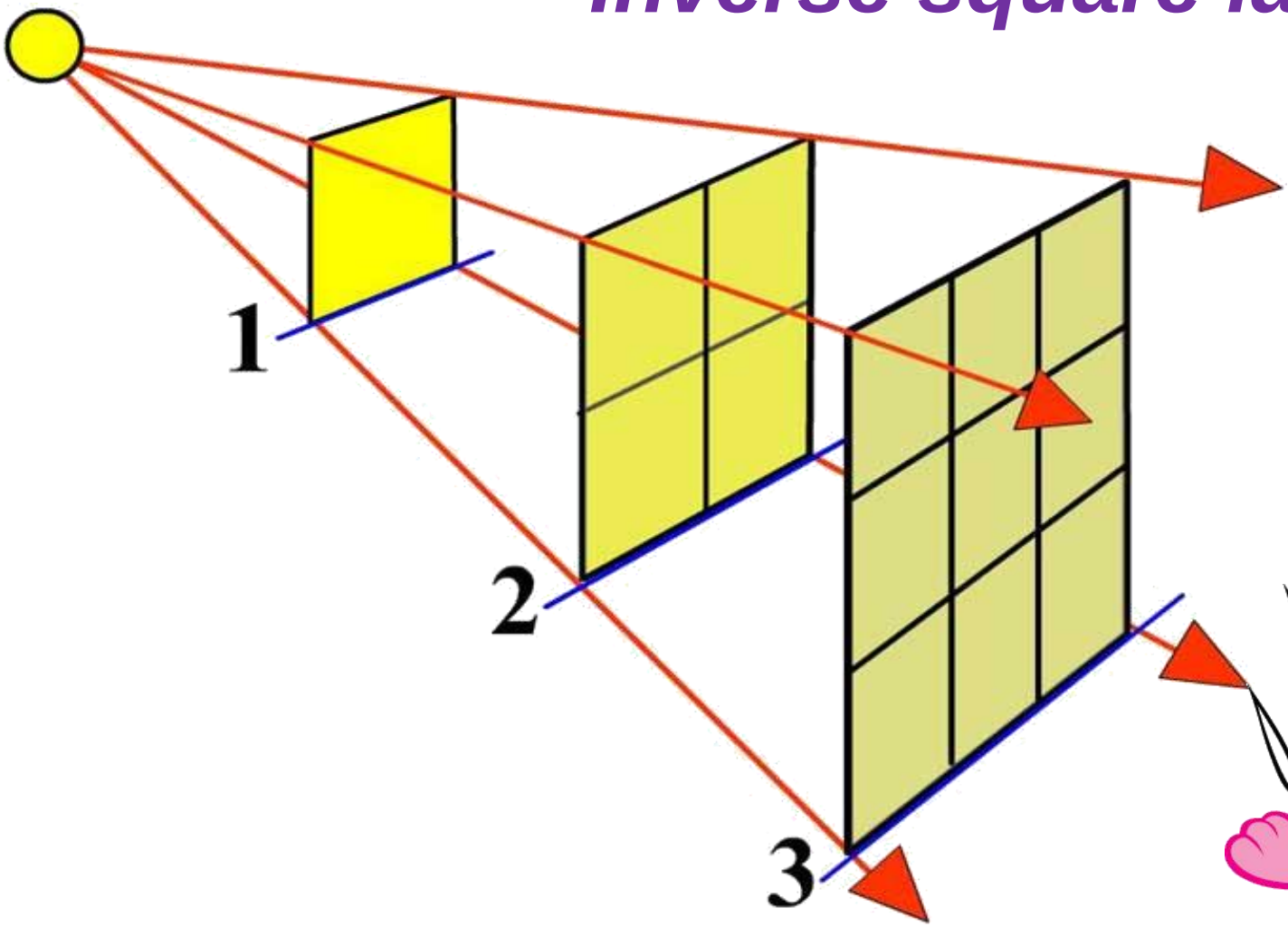
Inverse square law



Dose calculation accorging to AAPM TG - 43

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S_k … Air kerma strength

λ … Dose rate constant

T … Total time

$\frac{G(r,\Theta)}{G(r_0,\Theta_0)}$ … Geometry factor

g(r) … Radial dose function

F(r,Θ) … Anisotropy function

Simple approximation with most varying factors:

$$D \approx T \cdot \frac{1}{r^2}$$

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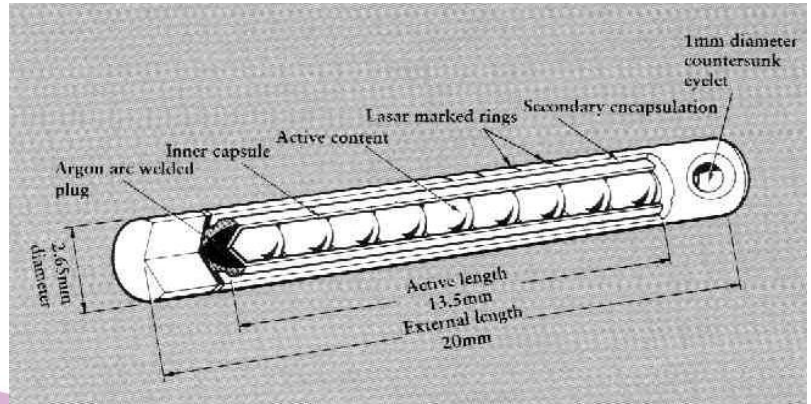
TG43 FORMALISM

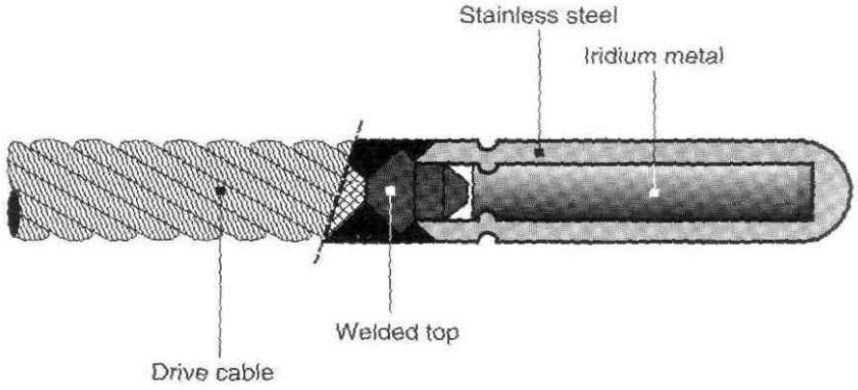
$$D(r,\theta) = S_k \Lambda t \frac{G(r,\theta)}{G(r_0,\theta_0)} g(r) F(r,\theta)$$

*The **Dose Rate Constant, Λ**, has to be given for each source model specifically, in order to include the effects of source geometry, encapsulation, and self-filtration within the source and scattering in water surrounding the source. Its relation with classical formalism is:*

$$\Lambda = \left[\frac{\mu_{en}}{\rho}\right]_{air}^{m} \varphi(r_0) G(r_0,\theta_0)$$

being $\left[\frac{\mu_{en}}{\rho}\right]_{air}^{m}$ *the ratio of average mass attenuation coefficients in m (medium) and air, and φ(r) the function that take into account the attenuation of primary photons and the effect of scattered photons in the medium.*

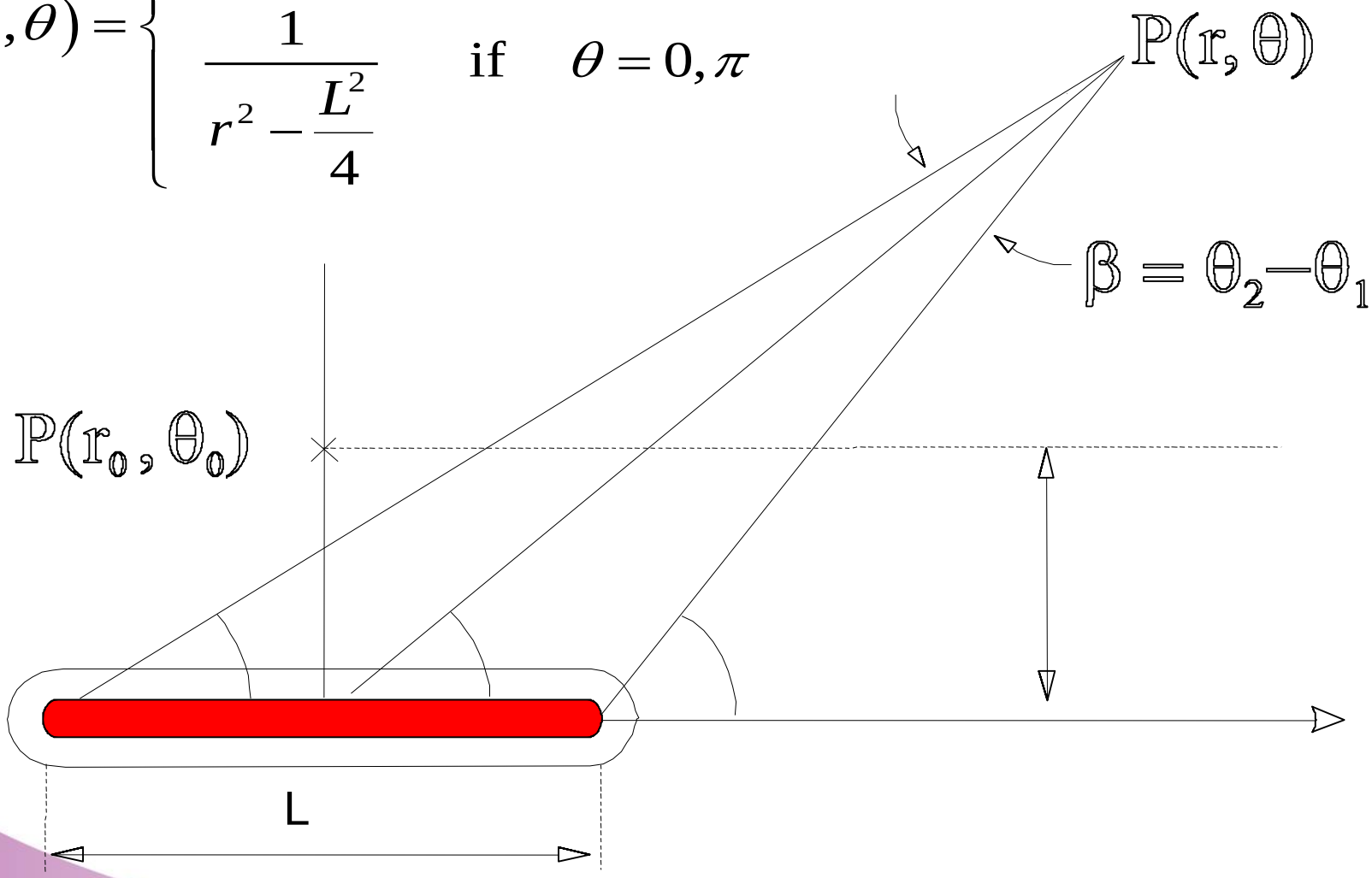




$$D(r,\theta) = S_k \, \Lambda t \frac{G(r,\theta)}{G(r_0,\theta_0)} g(r) F(r,\theta)$$

$$G_L(r,\theta) = \begin{cases} \dfrac{\beta}{L \cdot r \cdot \sin\theta} & \text{if} \quad \theta \neq 0, \pi \\ \dfrac{1}{r^2 - \dfrac{L^2}{4}} & \text{if} \quad \theta = 0, \pi \end{cases}$$

geometry function



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TG43 FORMALISM

$$D(r,\theta) = S_k \, \Lambda \, t \, \frac{G(r,\theta)}{G(r_0,\theta_0)} \, g(r) \, F(r,\theta)$$

*The **Radial Dose Function, g(r)**, describes the dose fall-off along the transverse axis of the source accounting for the effects of absorption and scatter in water. It is defined as:*

$$g(r) = \frac{\dot{D}(r,\theta_0) G(r_0,\theta_0)}{\dot{D}(r_0,\theta_0) G(r,\theta_0)}$$

$$G_L(r,\theta) = \begin{cases} \dfrac{\beta}{L \cdot r \cdot \sin\theta} & \text{if} \quad \theta \neq 0,\pi \\ \dfrac{1}{r^2 - \dfrac{L^2}{4}} & \text{if} \quad \theta = 0,\pi \end{cases}$$

It can also be influenced by filtration of photons by the encapsulation and source materials. Its relation with the classical formalism is the tissue attenuation and scatter function normalized at 1 cm distance:

$$g(r) = \frac{\varphi(r)}{\varphi(r_0)}$$

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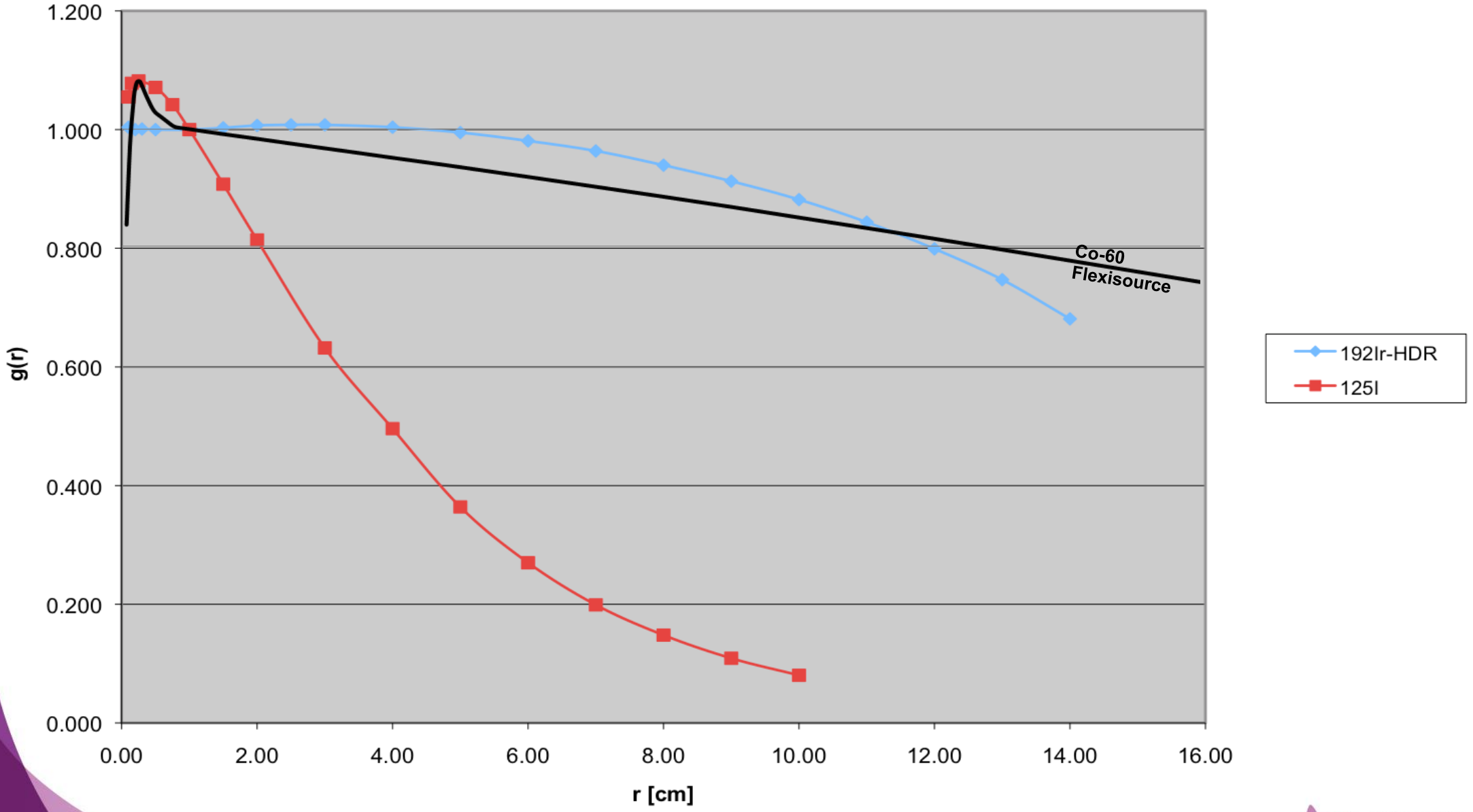
$$D(r,\theta) = S_k \, \Lambda \, t \, \frac{G(r,\theta)}{G(r_0,\theta_0)} \, g(r) \, F(r,\theta)$$

Radial Dose Function



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$$D(r,\theta) = S_k \, \Lambda \, t \, \frac{G(r,\theta)}{G(r_0,\theta_0)} \, g(r) F(r,\theta)$$

TG43 FORMALISM

*The **Anisotropy Function, F(r,θ),** accounts for the anisotropy of dose distribution around the source, including the effects of absorption and scatter in the source construction and water. It gives the angular variation of dose rate around the source at each distance due to self-filtration, oblique filtration of primary photons through the encapsulating material, and scattering of photons in water. It is defined as:*

$$F(r,\theta) = \frac{\dot{D}(r,\theta) G(r,\theta_0)}{\dot{D}(r,\theta_0) G(r,\theta)}$$

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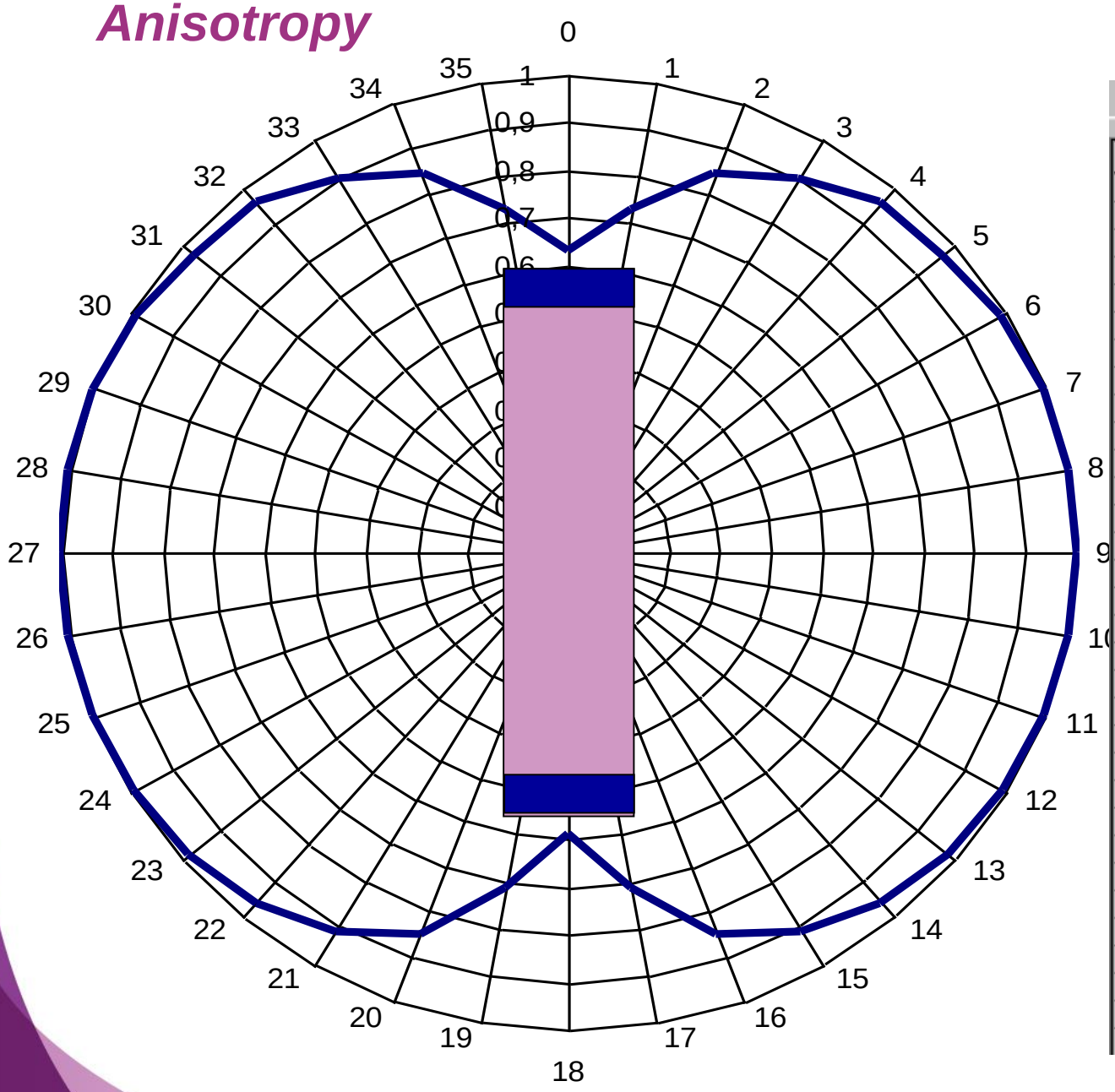
Anisotropy



r(cm)	Radial Dose
0,00	0,8120
0,30	0,9380
0,40	0,9800
0,50	1,0050
1,00	1,0000
1,50	0,9460
2,00	0,8770
2,50	0,7980
3,00	0,7210
3,50	0,6440
4,00	0,5740
4,50	0,5080
5,00	0,4480
5,50	0,3930
6,00	0,3430
6,50	0,2970
7,00	0,2570
8,00	0,2060

Aniso Constant | Aniso Fact

Aniso Constant

0,950

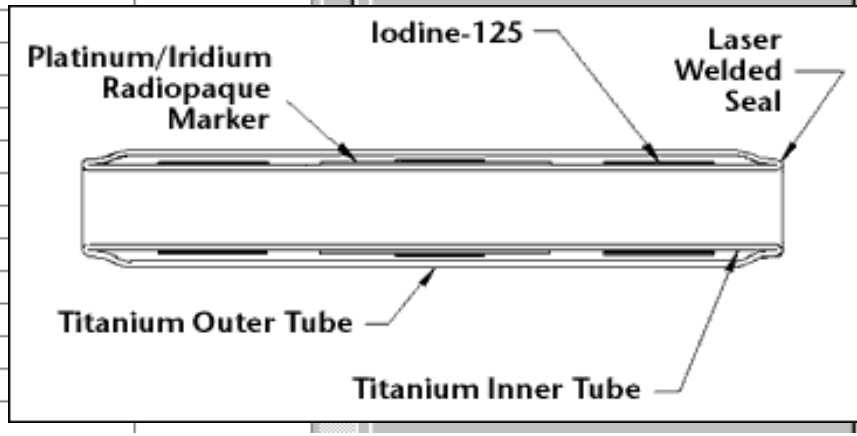
S_k... air - kerma strength

Λ... dose rate constant

$g(r)$... radial dose function

$\bar{\phi}_{an}$... anisotropy constant

$\dot{D}_0$... initial dose rate



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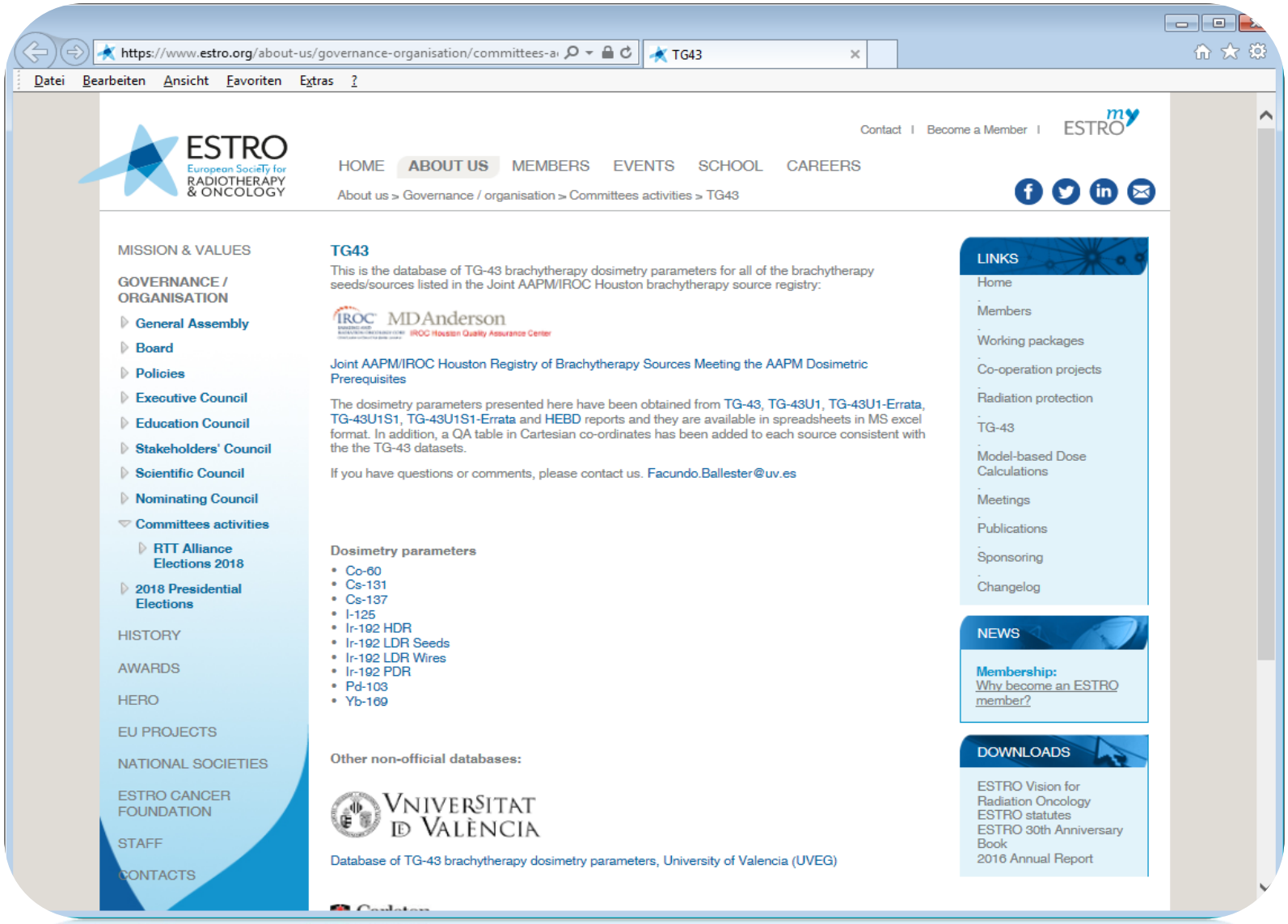
TG43 tables found at



https://www.estro.org/about-us/governance-organisation/committees-activities/tg43

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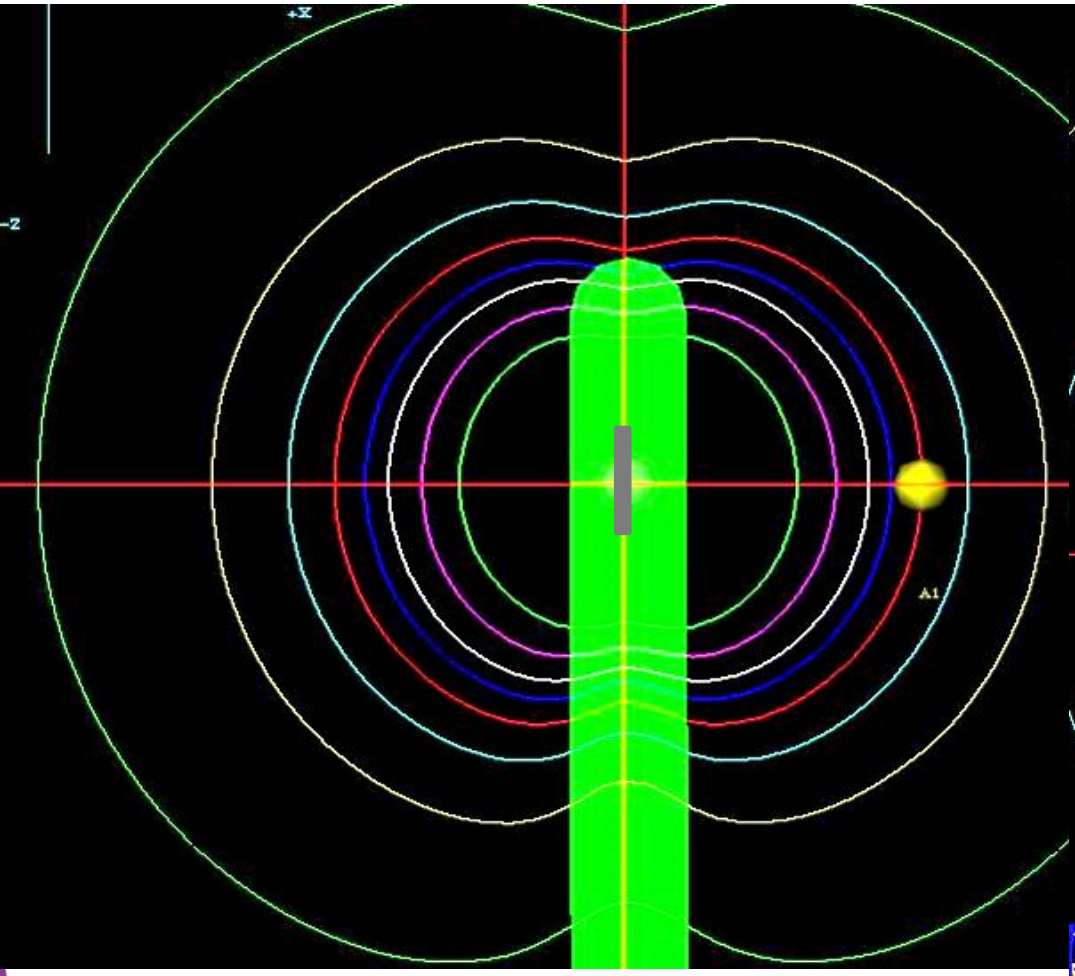
- **TG43 algorithm** is based on water calculation and can be done on CT, MRI and US
- Model based algorithms take tissue into account (based on CT), but has limited impact for GYN-Brachytherapy

MR-based treatment planning will work well for GYN with ^{192}Ir or ^{137}Cs sources, since density correction is not important

Eye Lid	22 ± 37
Gynaecology – Vienna applicator (Polymer)	1 ± 0.2
Gynaecology – Ring applicator (Stainless Steel)	4 ± 0.7

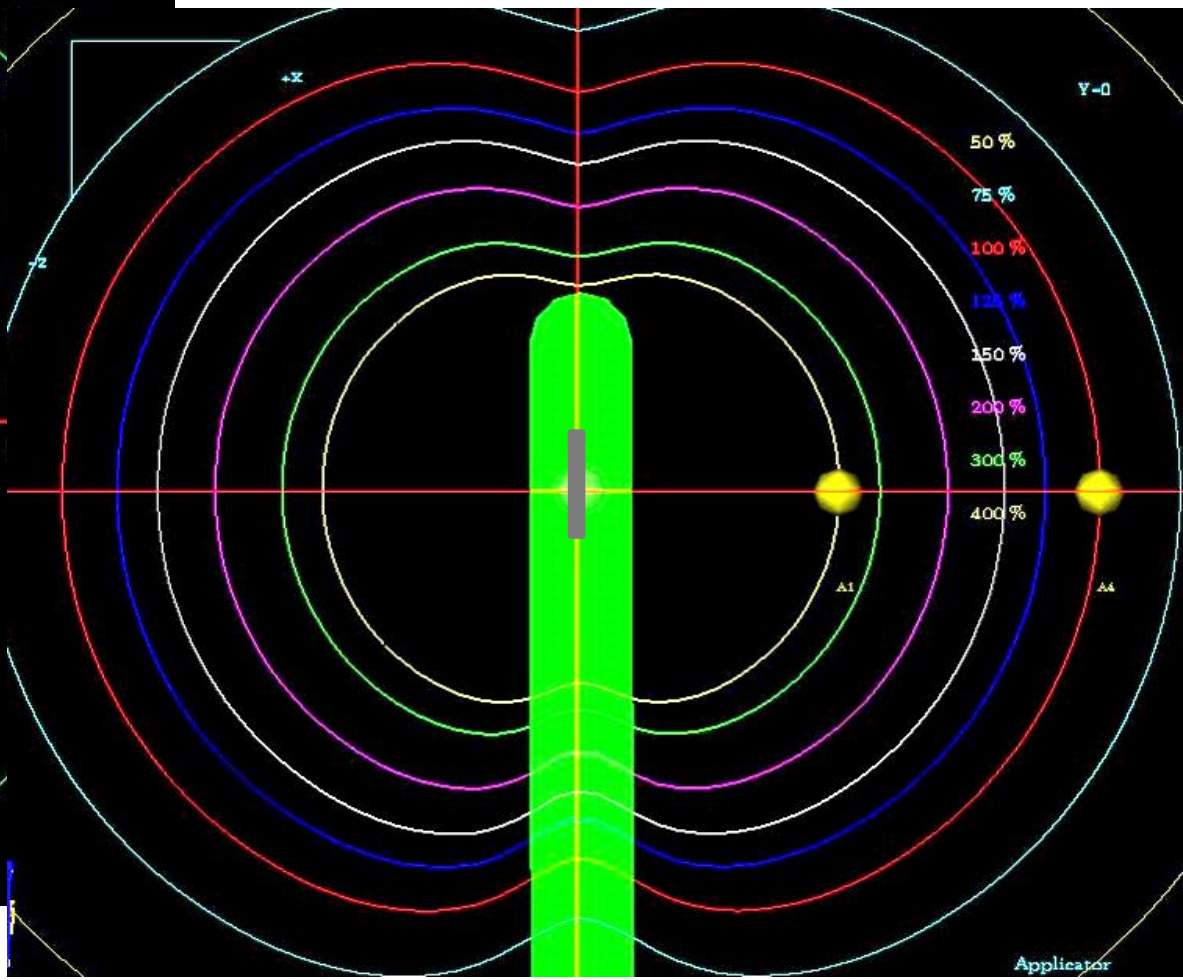
Courtesy Jamema Swamidas

Distribution around one single source



1 Gy at 1 cm distance for a source strength 4.21 cGy/hcm²

15.6 sec



1 Gy at 2 cm distance for a source strength 4.21 cGy/hcm²

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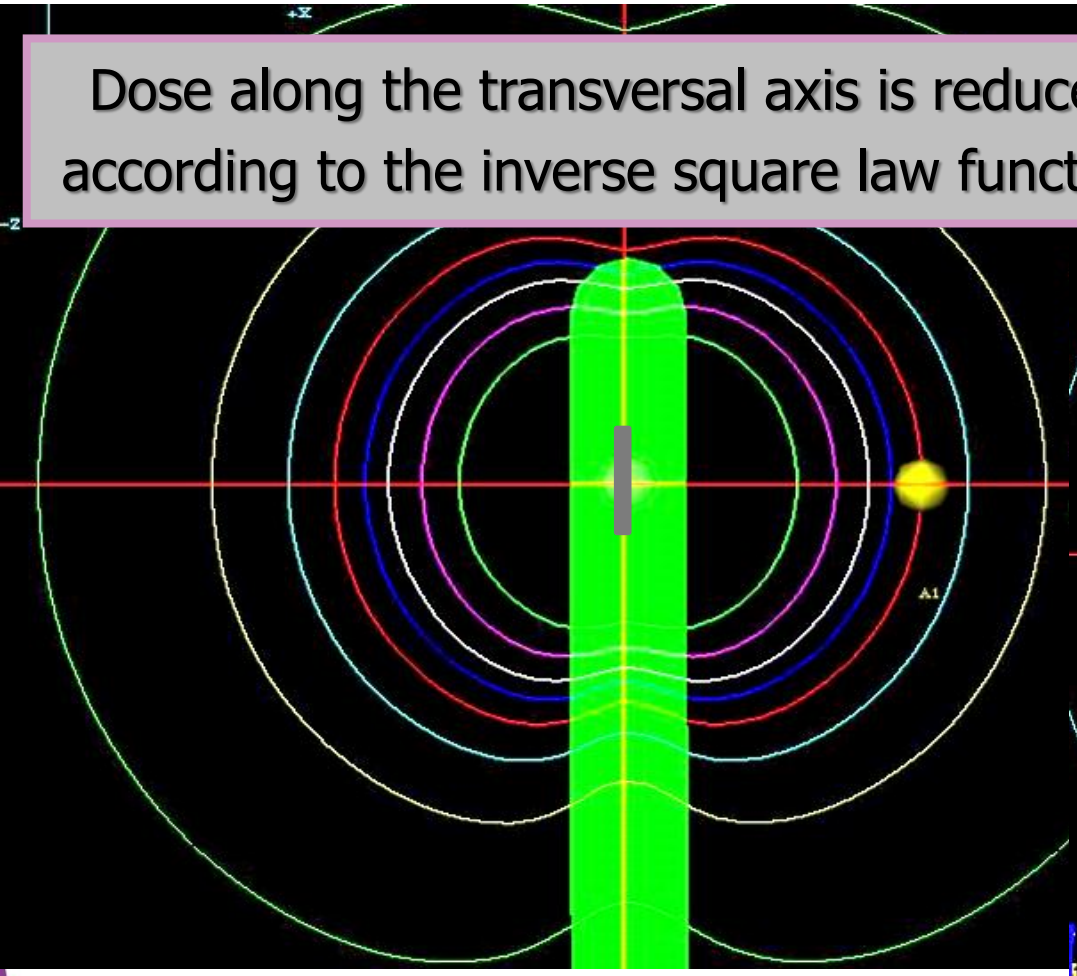
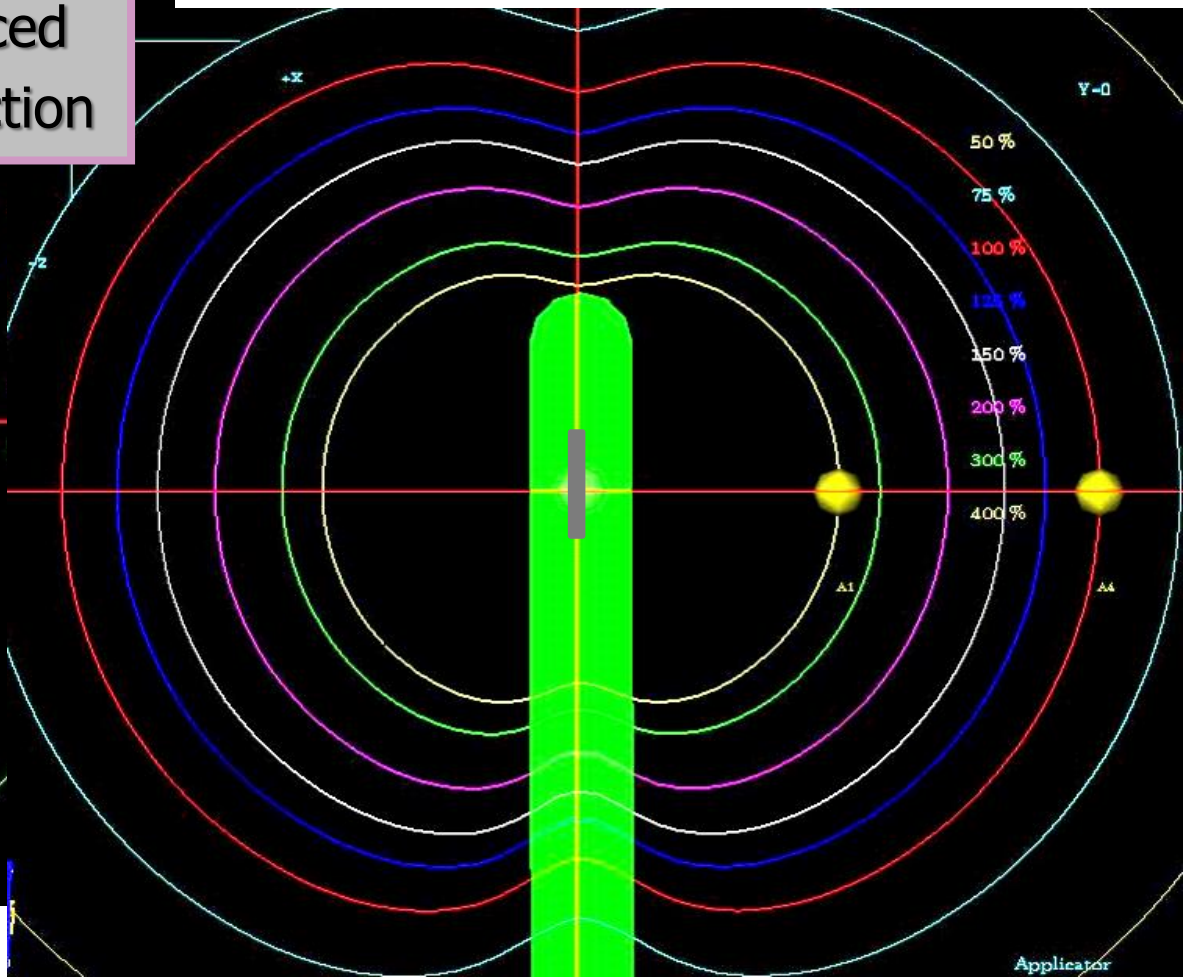
Distribution around one single source

Dose along the transversal axis is reduced according to the inverse square law function



1 Gy at 1 cm distance for a source strength 4.21 cGy/hcm²

15.6 sec



1 Gy at 2 cm distance for a source strength 4.21 cGy/hcm²

62.4 sec

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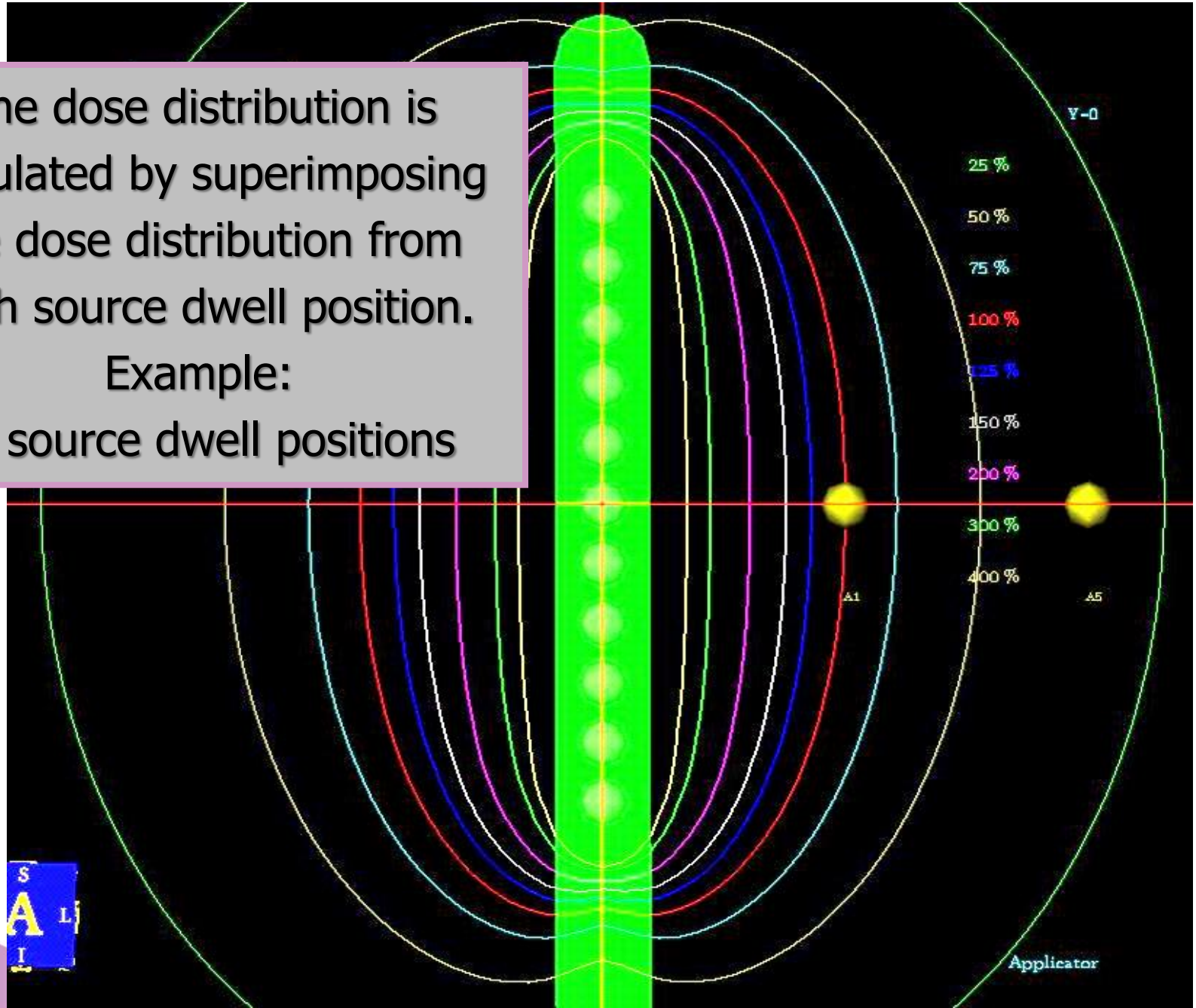
Distribution around a stepping source

The dose distribution is calculated by superimposing the dose distribution from each source dwell position.
Example:
11 source dwell positions



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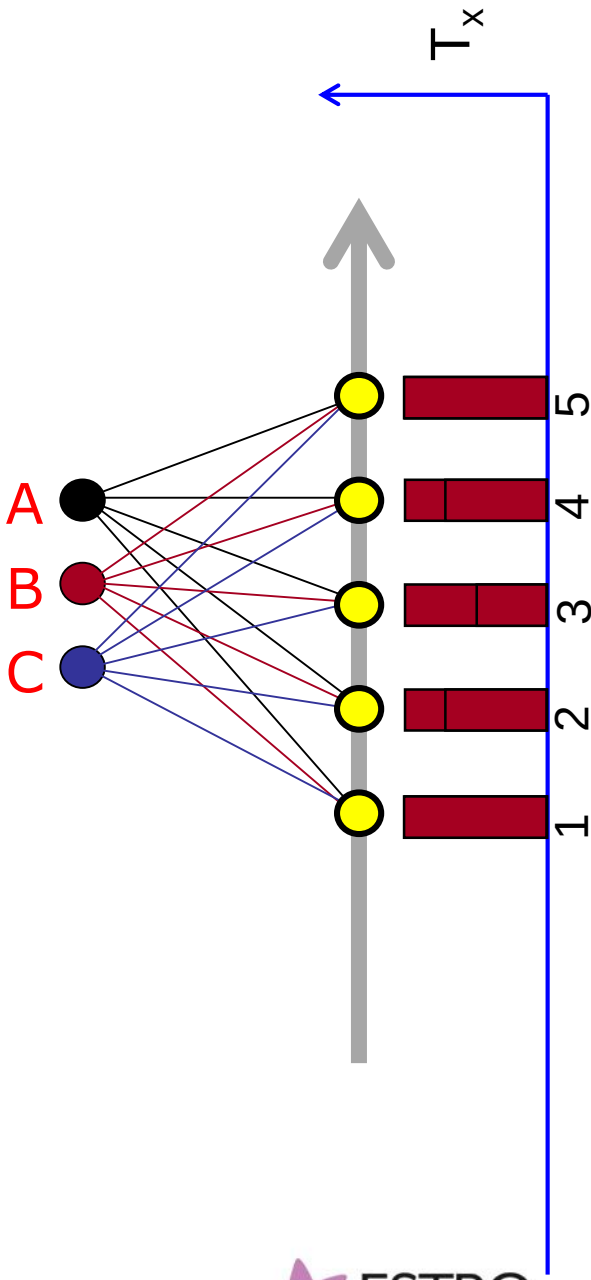
Dose Point Optimization

$$D_A = \left(T_1 \cdot \frac{1}{r_{1A}^2}\right) + \left(T_2 \cdot \frac{1}{r_{2A}^2}\right) + \left(T_3 \frac{1}{r_{3A}^2}\right) + \left(T_4 \cdot \frac{1}{r_{4A}^2}\right) + \left(T_5 \cdot \frac{1}{r_{5A}^2}\right)$$

$$D_B = \left(T_1 \cdot \frac{1}{r_{1B}^2}\right) + \left(T_2 \cdot \frac{1}{r_{2B}^2}\right) + \left(T_3 \frac{1}{r_{3B}^2}\right) + \left(T_4 \cdot \frac{1}{r_{4B}^2}\right) + \left(T_5 \cdot \frac{1}{r_{5B}^2}\right)$$

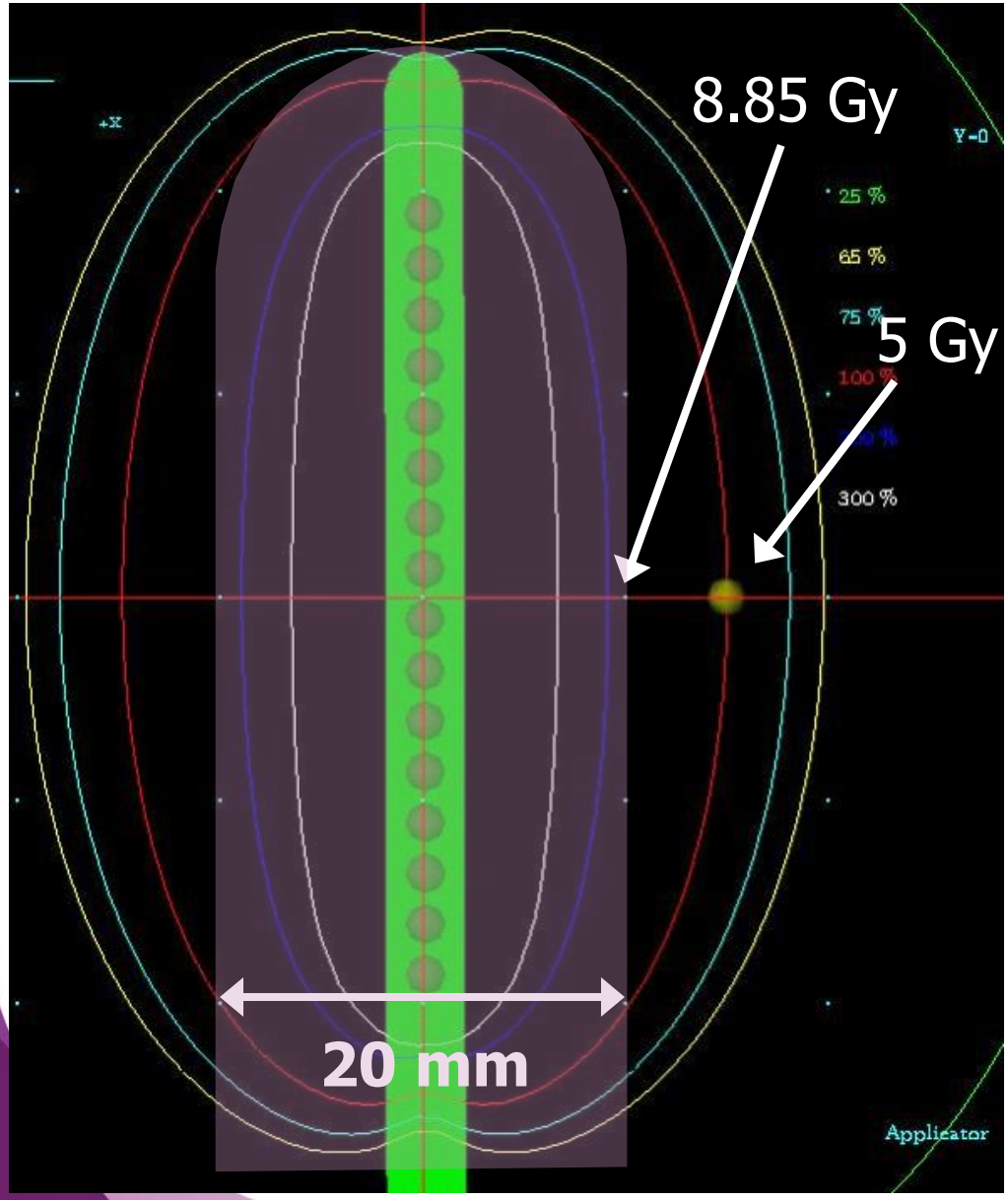
$$D_C = \left(T_1 \cdot \frac{1}{r_{1C}^2}\right) + \left(T_2 \cdot \frac{1}{r_{2C}^2}\right) + \left(T_3 \frac{1}{r_{3C}^2}\right) + \left(T_4 \cdot \frac{1}{r_{4C}^2}\right) + \left(T_5 \cdot \frac{1}{r_{5C}^2}\right)$$

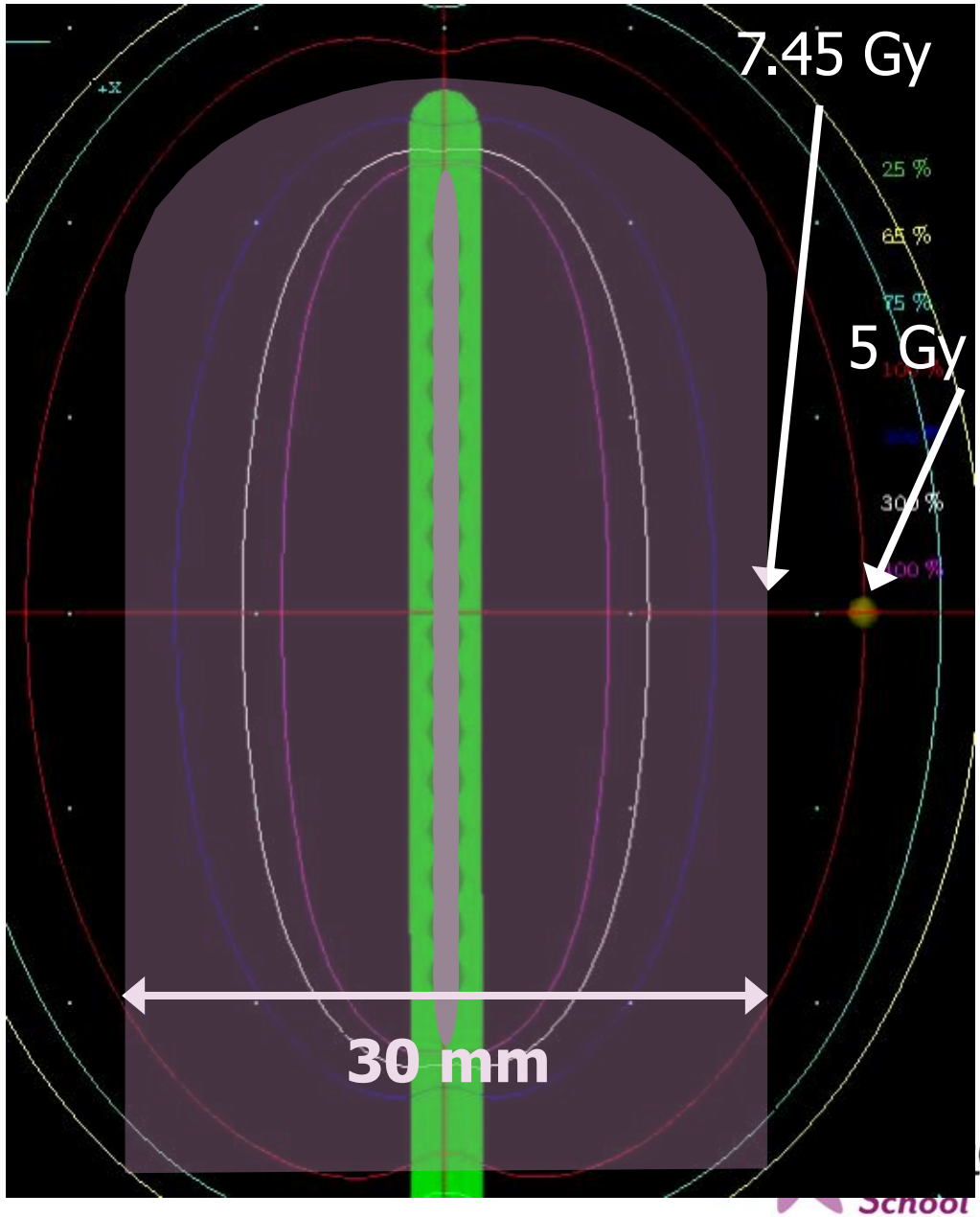


$$D_A = D_B = D_C = 100\%$$

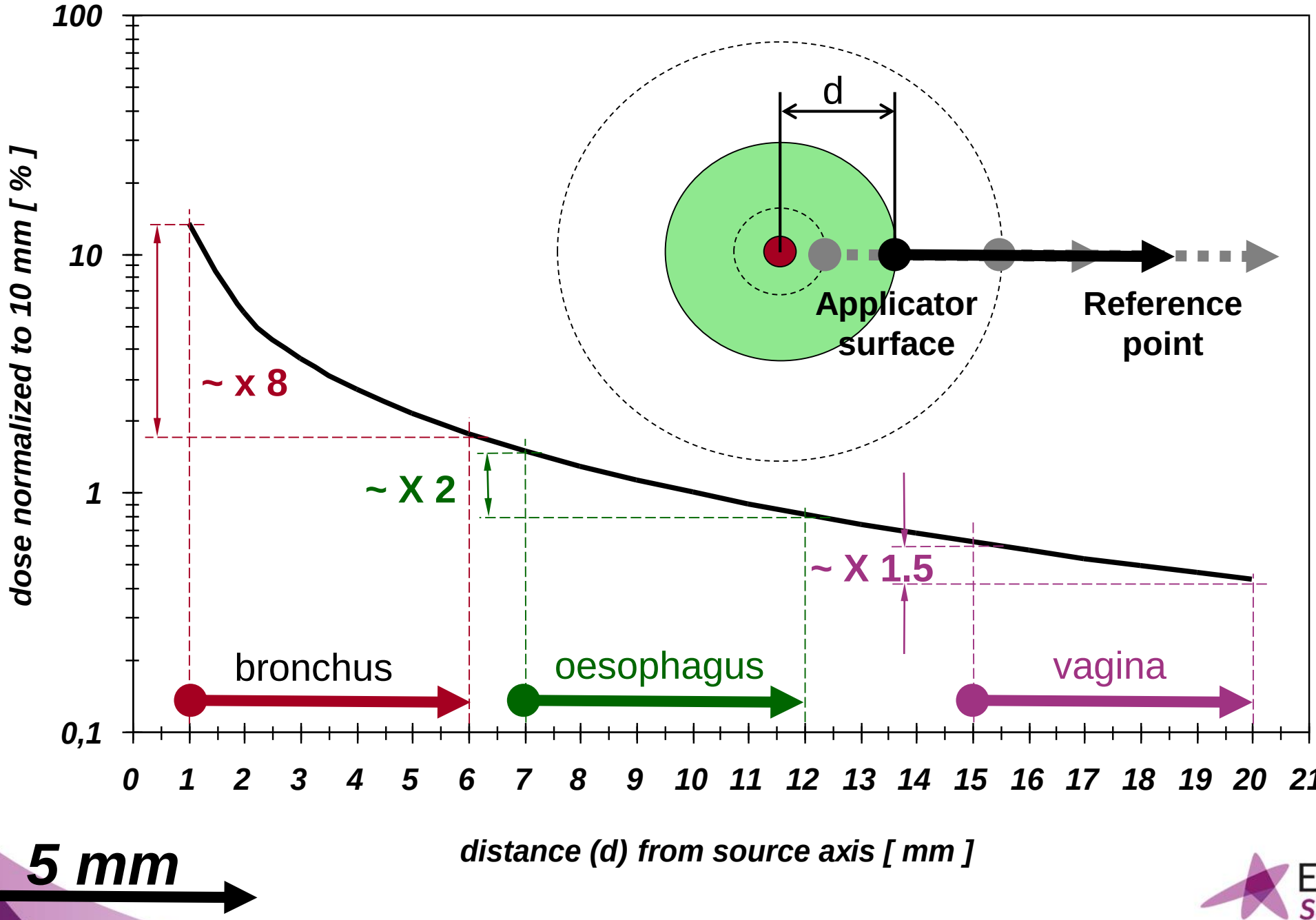
The surface dose is depending on applicator diameter

(Distance from Source !)





Dose on Applicator Surface and at Reference Depth



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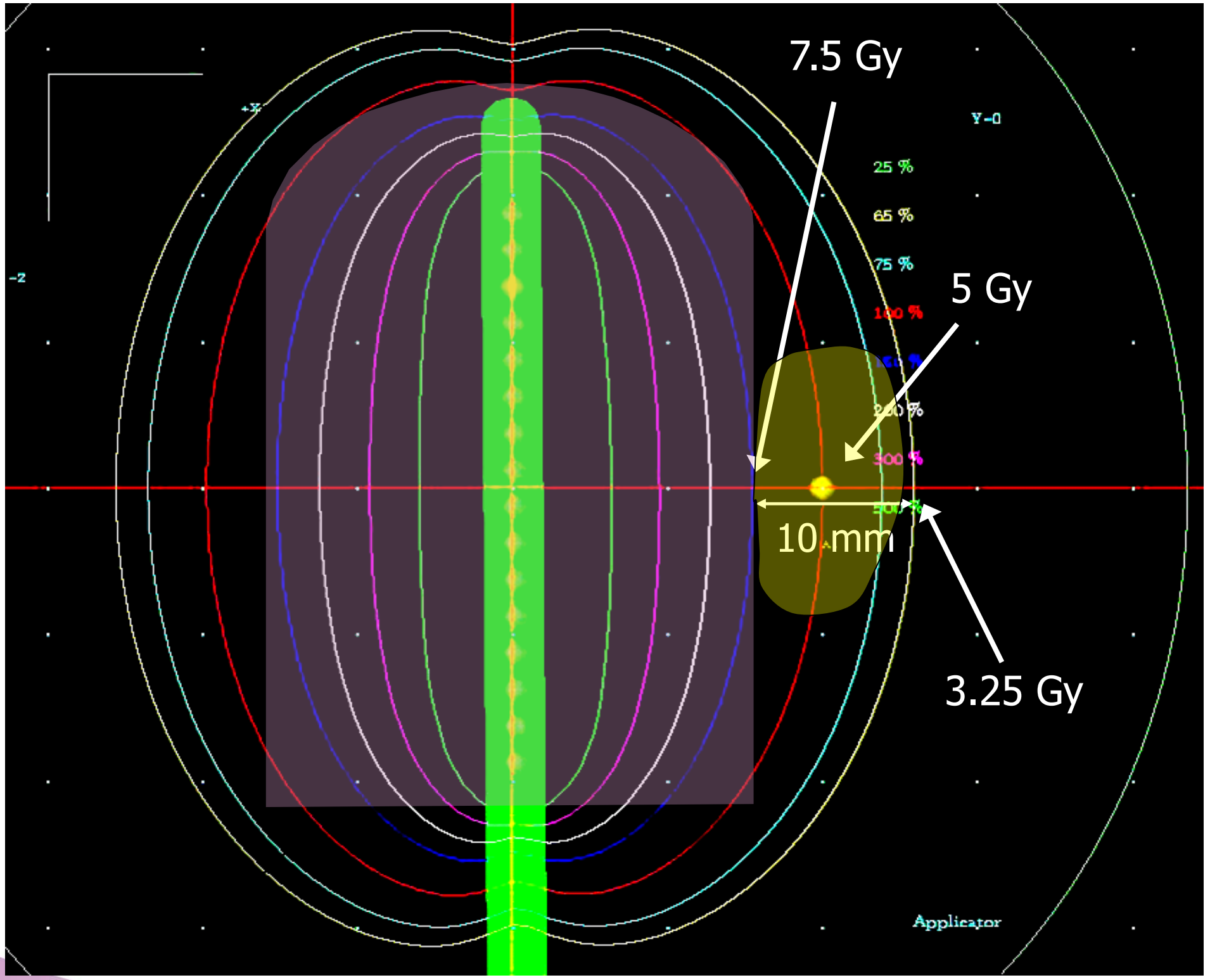
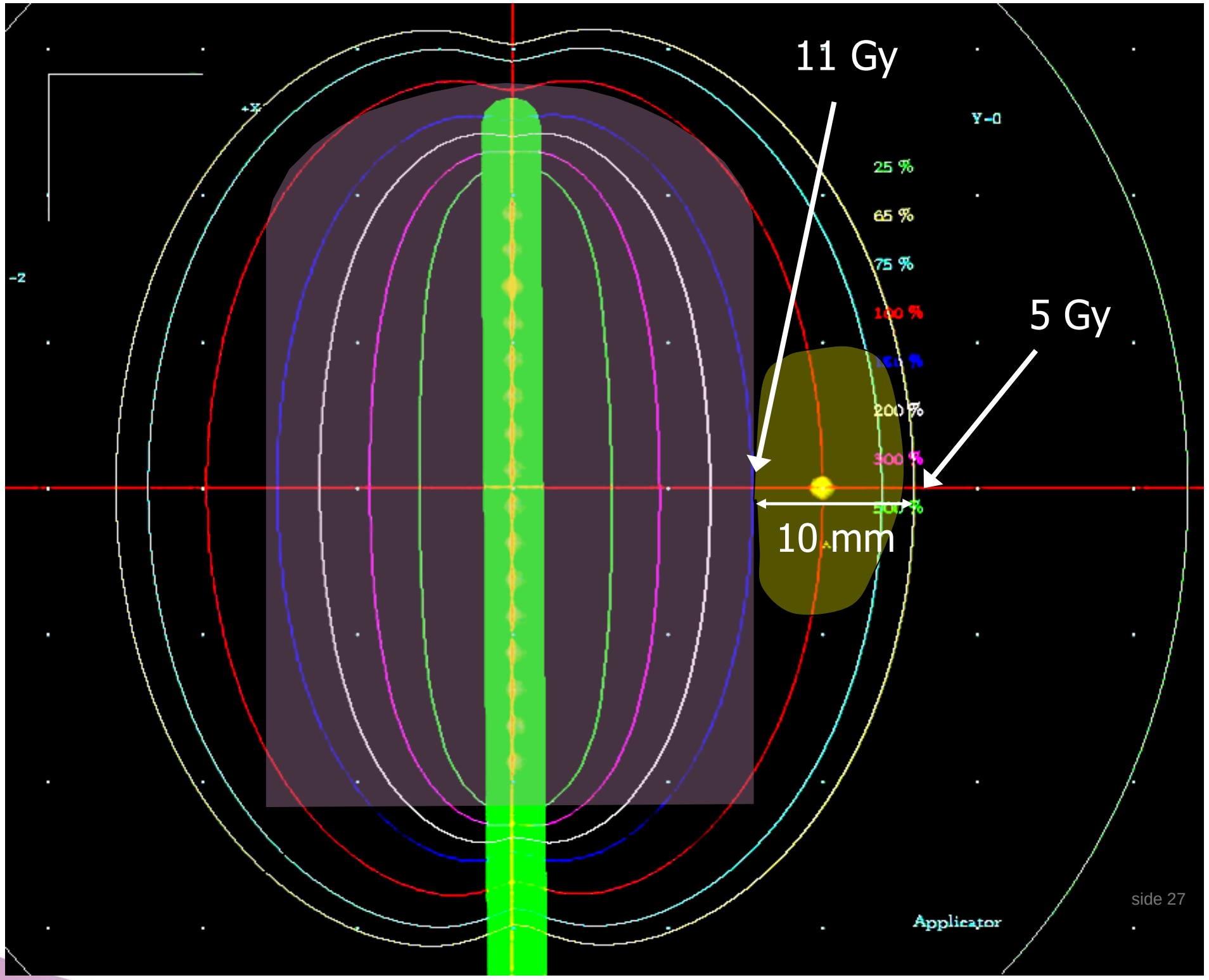
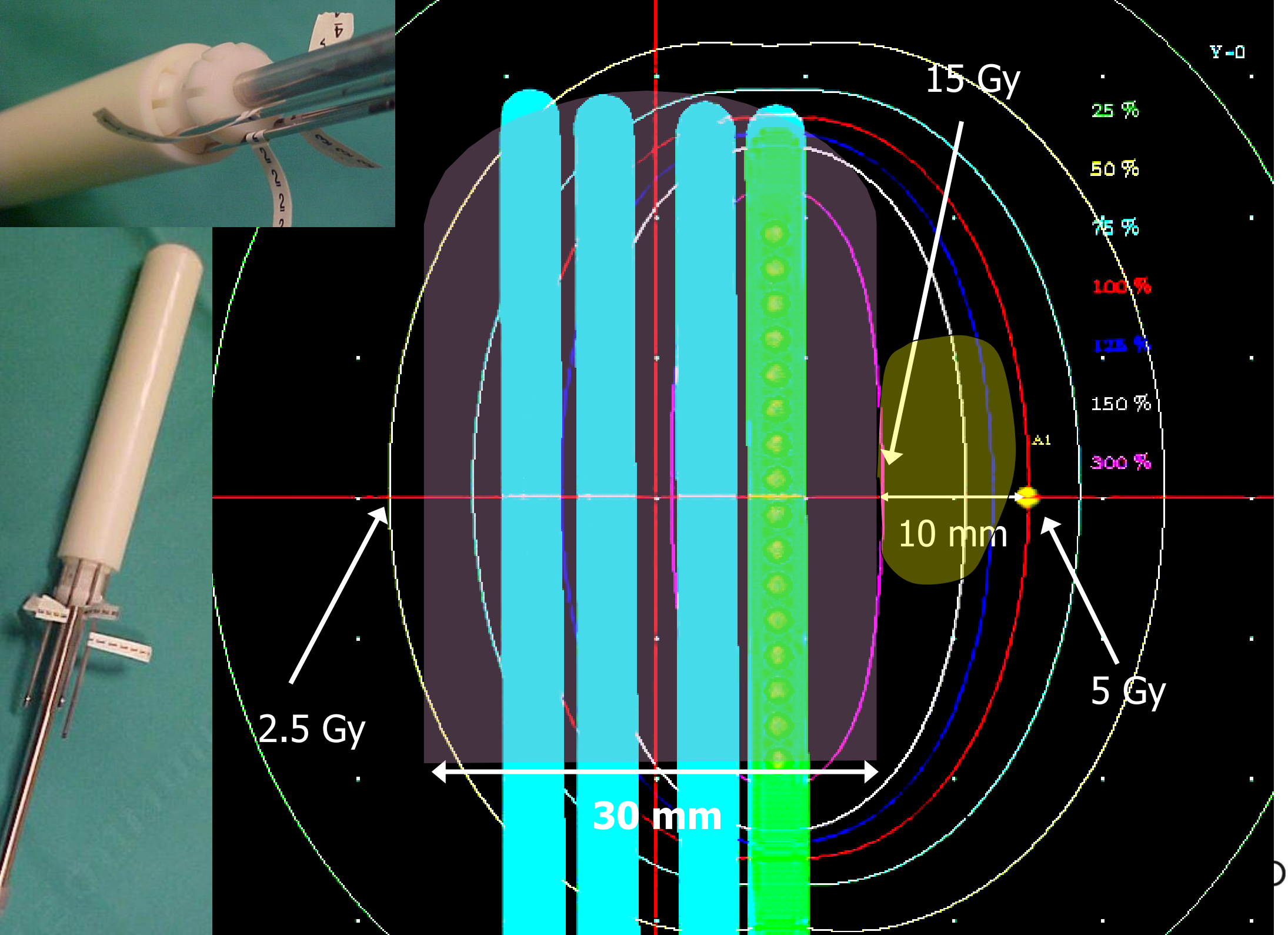

7.5 Gy
5 Gy
10 mm
3.25 Gy
25 %
65 %
75 %
100 %
300 %
Applicator


11 Gy
5 Gy
10 mm
25 %
65 %
75 %
100 %
200 %
300 %
Applicator


15 Gy
10 mm
2.5 Gy
5 Gy
30 mm
25 %
50 %
75 %
100 %
150 %
300 %

Thank You

Merci

Danke

Gracias

شكراً

Department of Radiotherapy
Medical University of Vienna

Applicator commissioning, reconstruction, geometry and fusion

Jamema Swamidas
Taran P Hellebust
Daniel Berger

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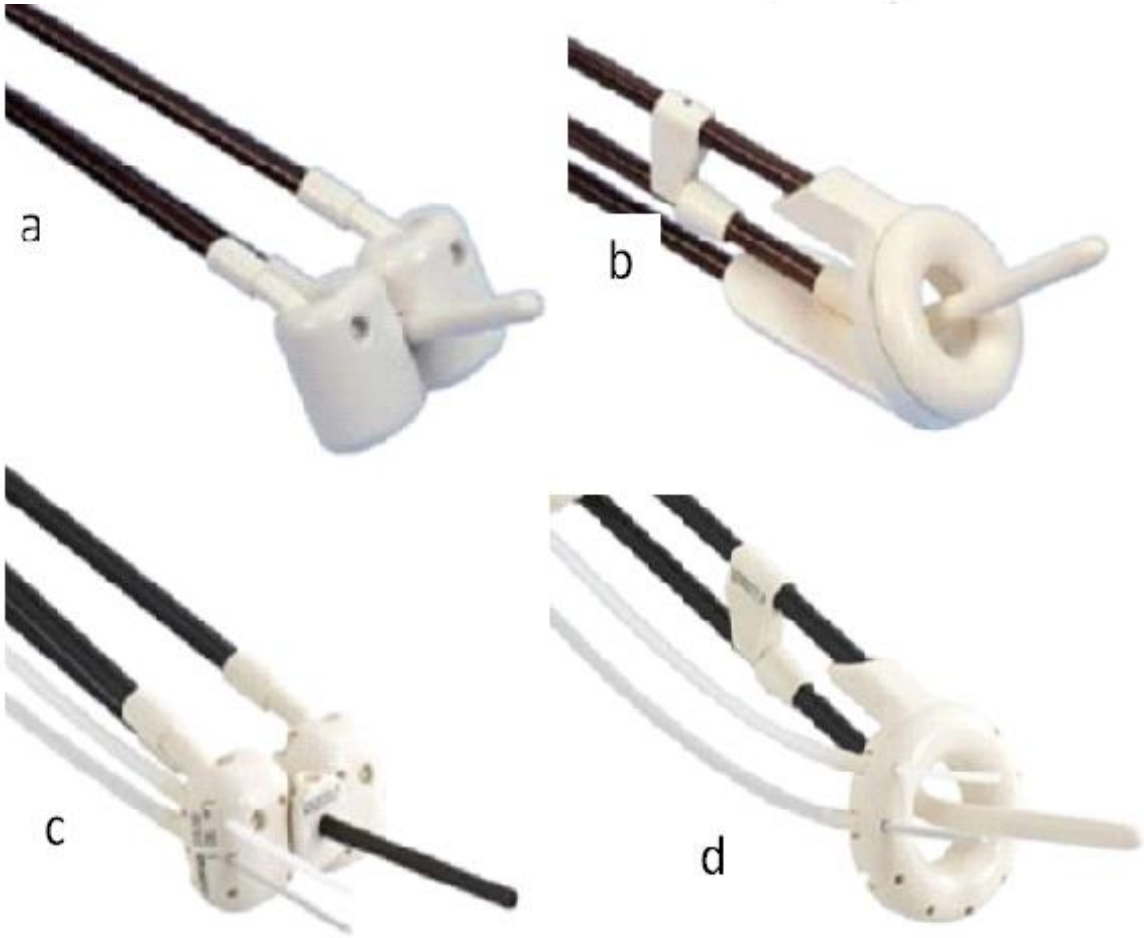
Commissioning



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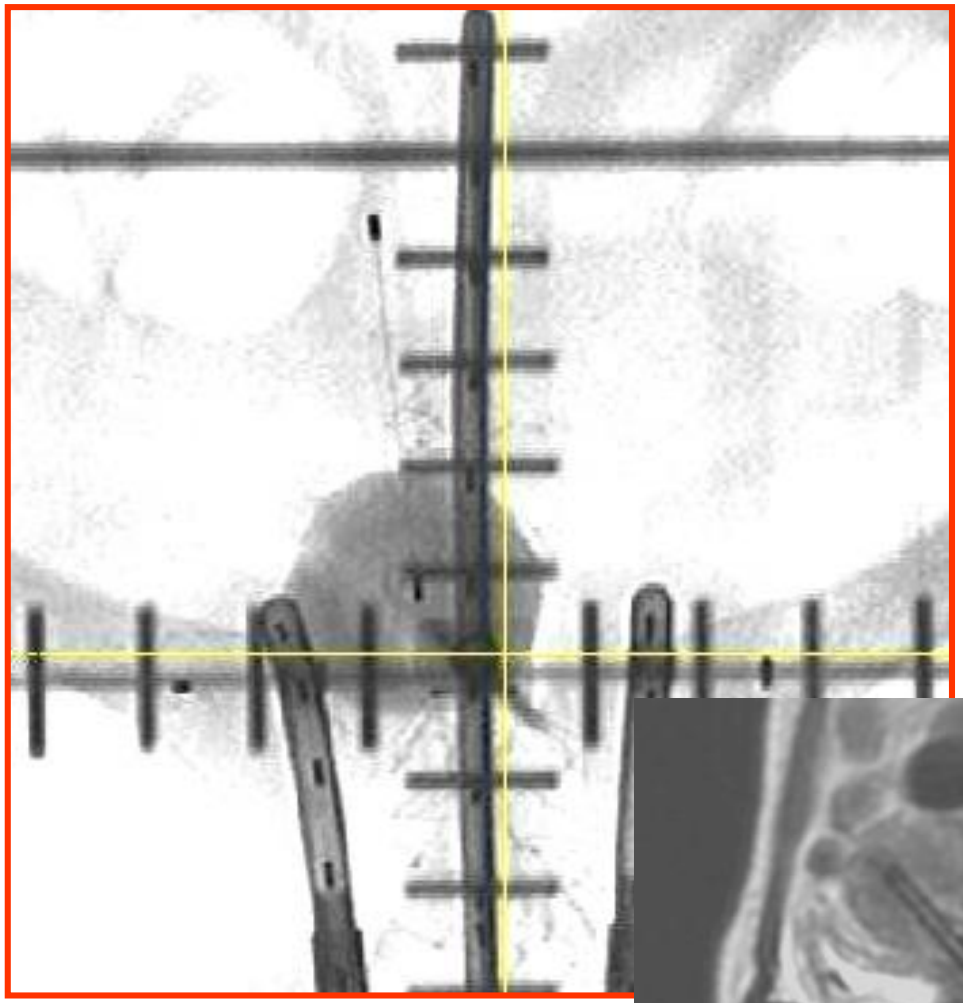
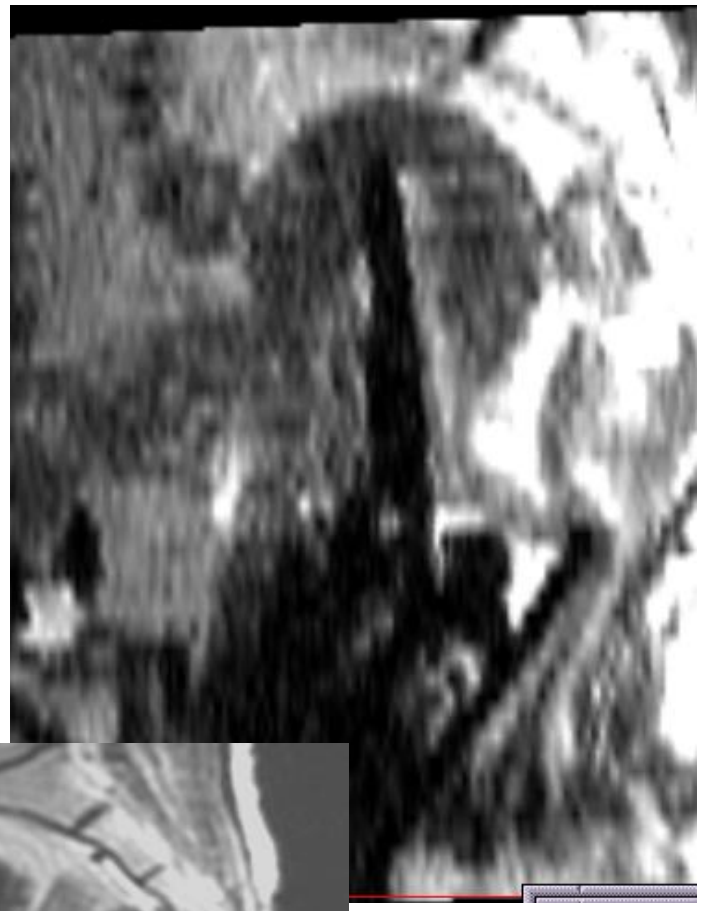
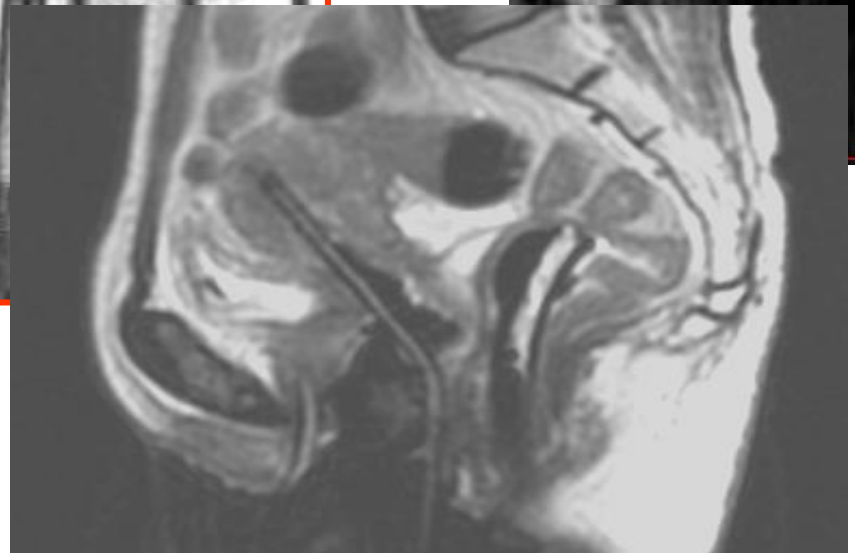
Why so much fuss about Applicator commissioning / reconstruction in 3D BT

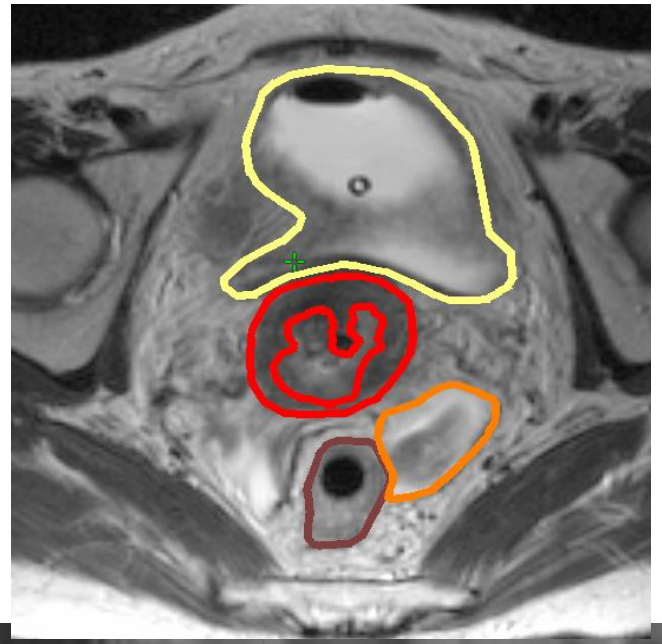


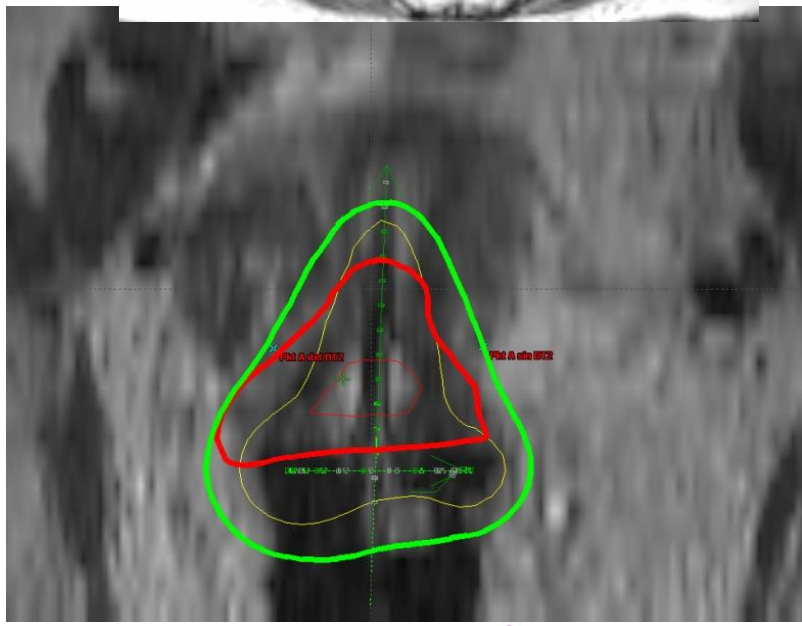




Clinical consequences

- 10 intracavitary cervical cancer patients
- MR scan with ring applicator in situ
- Contouring on transversal T2 images:
  - HR-CTV
  - Bladder
  - Rectum
  - Sigmoid
- Manual 3D dose optimisation
- DVH parameters:
  - D100, D90 for HR-CTV
  - D_{2cc} for bladder, rectum, sigmoid





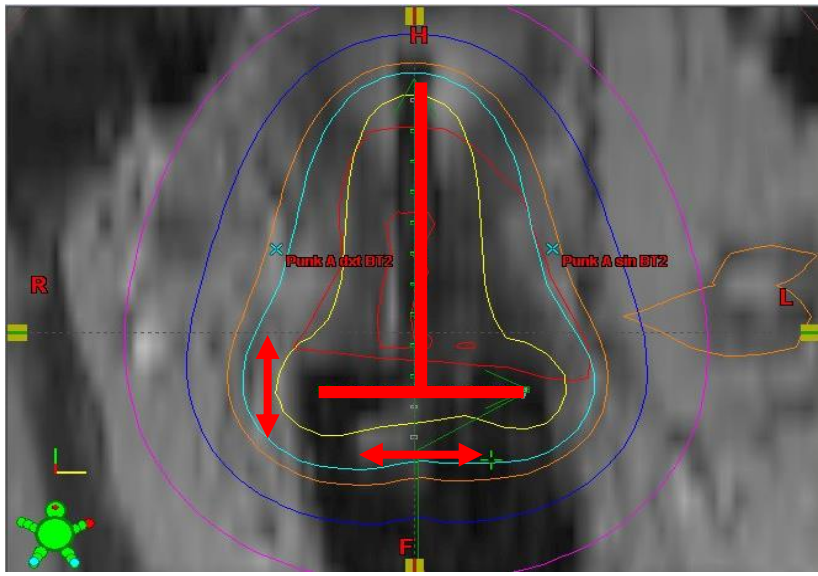
Tanderup et al, R&O 2008

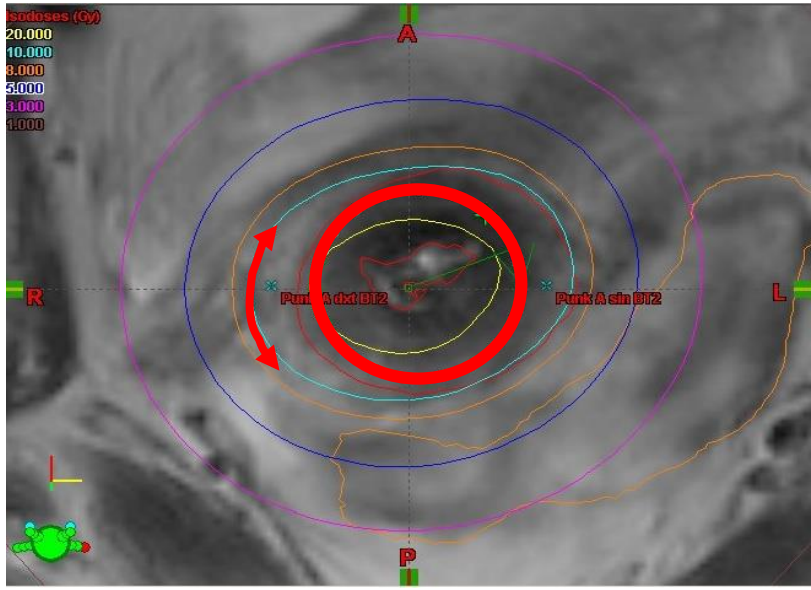
Simulation of un-certainty

- Displacement in directions:
  - Longitudinal (along tandem):
    - ± 3 mm, ± 5 mm
  - Lateral:
    - ± 3 mm
  - Ant-post
    - ± 3 mm

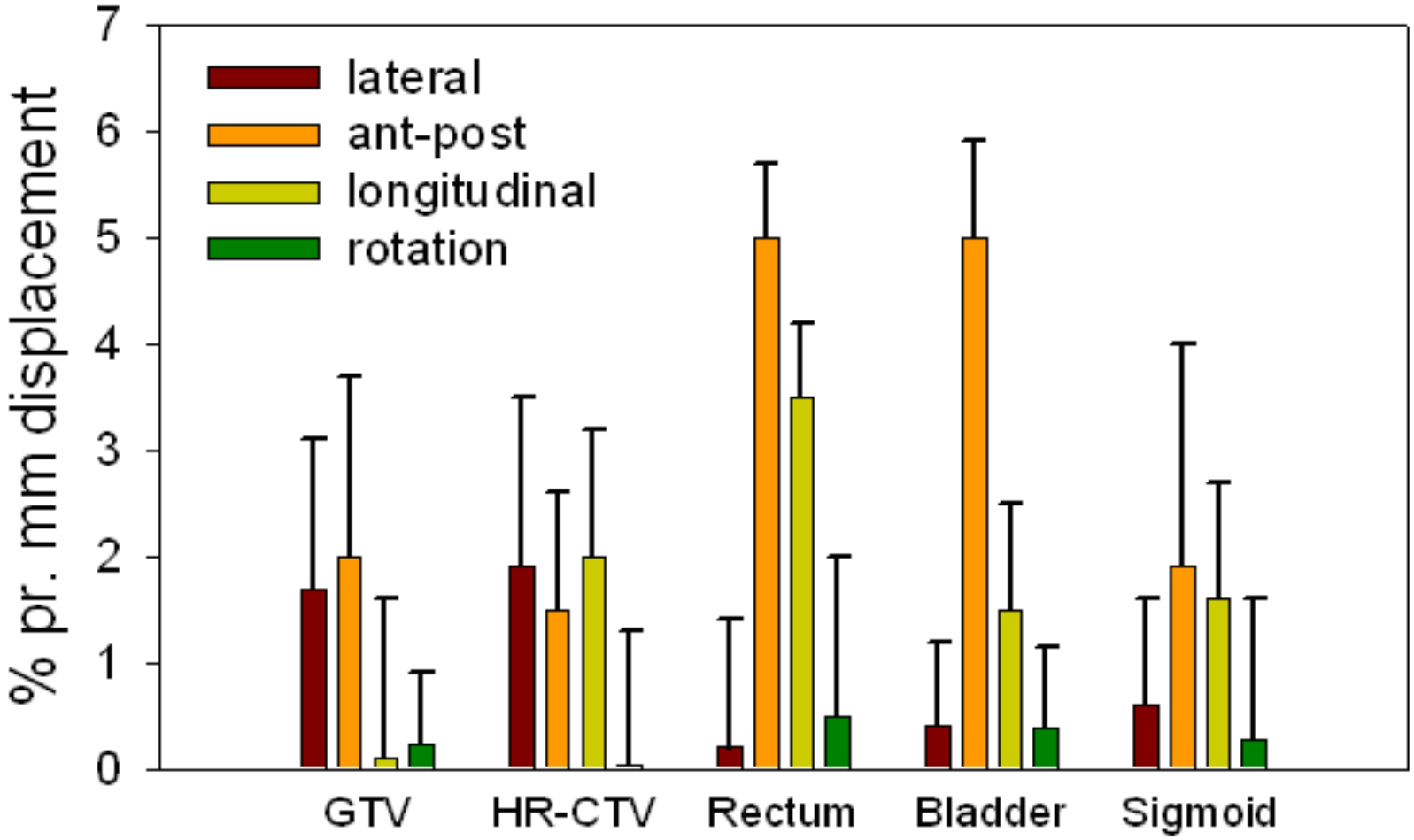
- Rotation of ring:
  - ± 15 dgr (4 mm)

Tanderup et al, R&O 2008





Mean DVH shifts (%) pr mm



Tanderup et al, R&O 2008

Reading material

Contents lists available at ScienceDirect

Radiotherapy and Oncology

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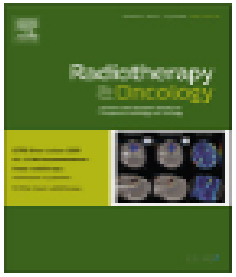

GEC-ESTRO Recommendations

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group: Considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer brachytherapy

Taran Paulsen Hellebust [a,*], Christian Kirisits [b], Daniel Berger [b], José Pérez-Calatayud [c], Marisol De Brabandere [d], Astrid De Leeuw [e], Isabelle Dumas [f], Robert Hudej [g], Gerry Lowe [h], Rachel Wills [h], Kari Tanderup [i]

Radiotherapy and Oncology 96 (2010) 153-160

Inaccuracy in applicator reconstruction can lead to geometrical uncertainties and thus uncertainties in the definition of source positions which influence the accuracy of the delivered dose to both target volumes and organs at risk.

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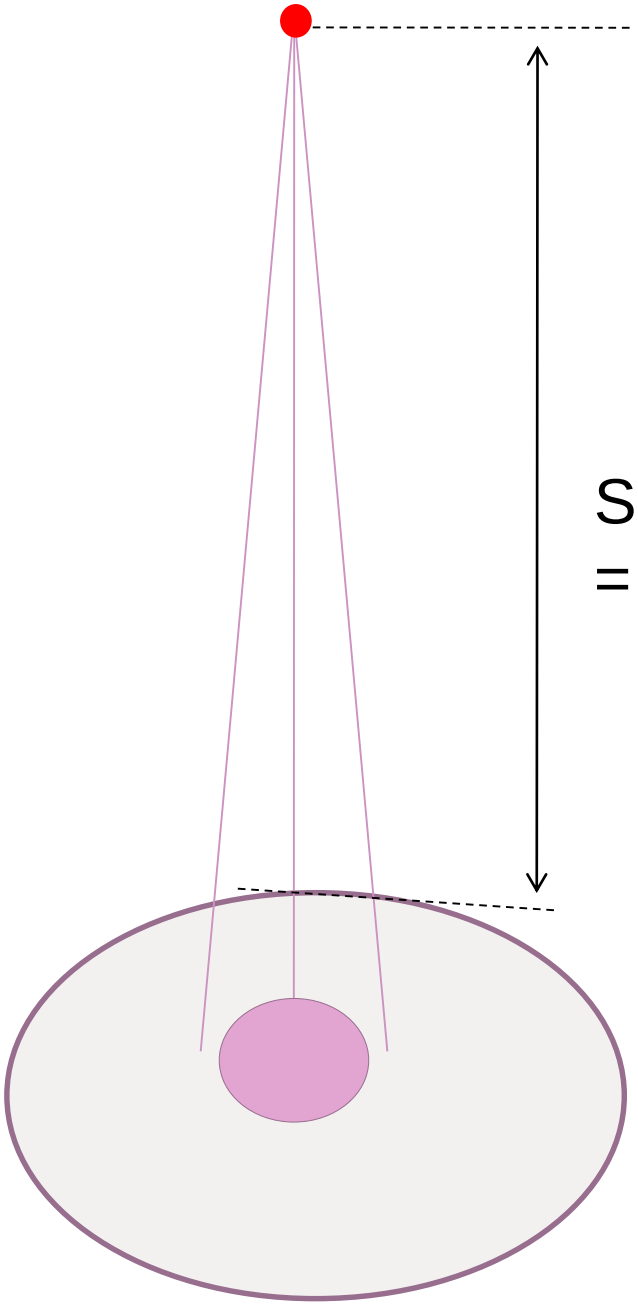
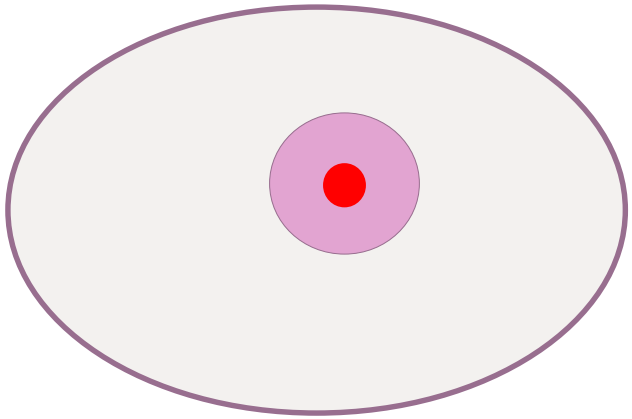
What is Applicator reconstruction in Brachytherapy?



SSD
= 100 cm

External therapy



Brachytherapy

defining a source path inside the applicator

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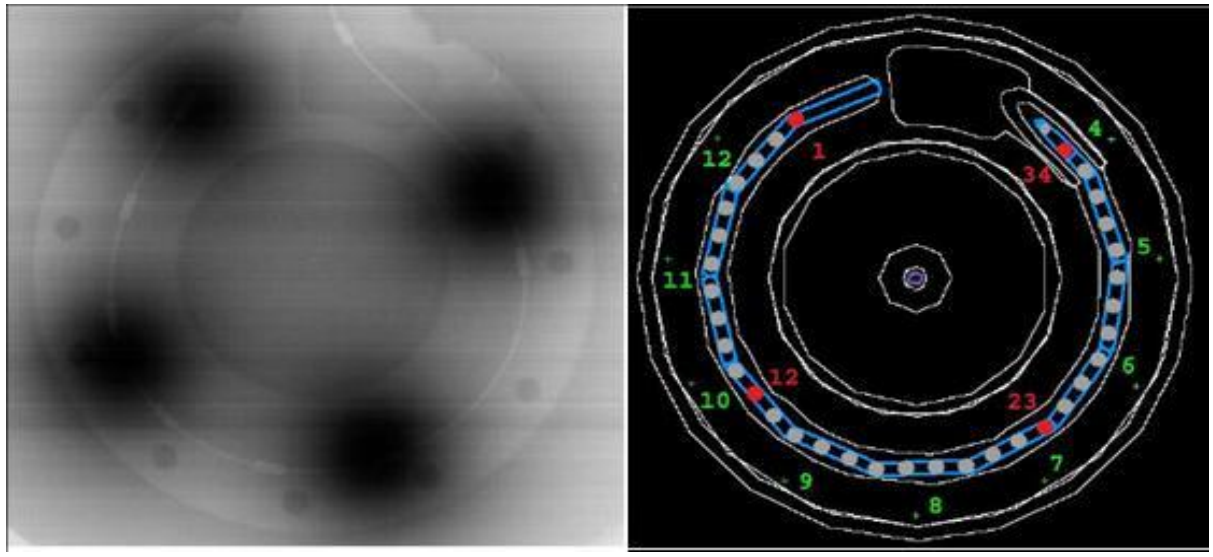
Commissioning of applicator

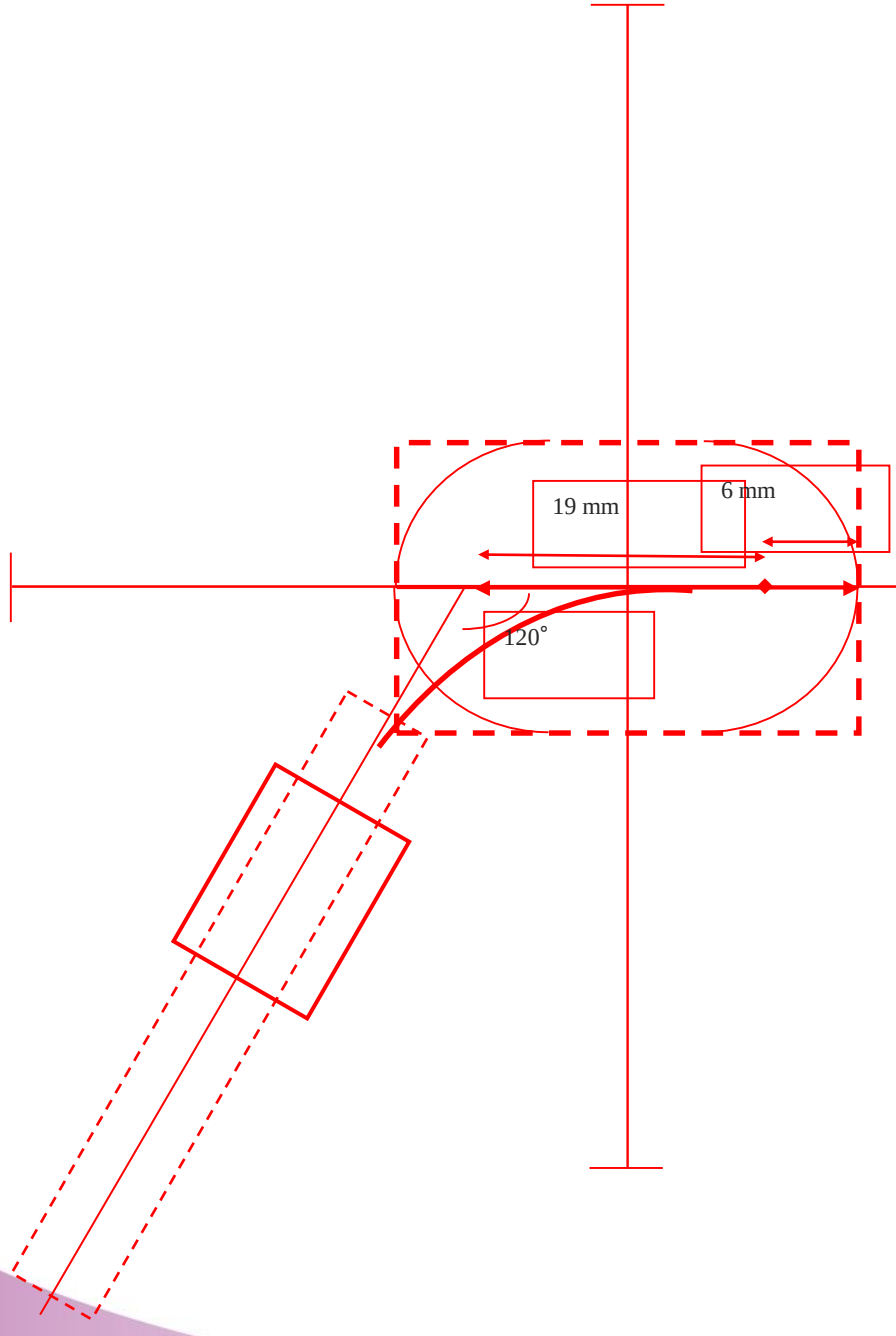


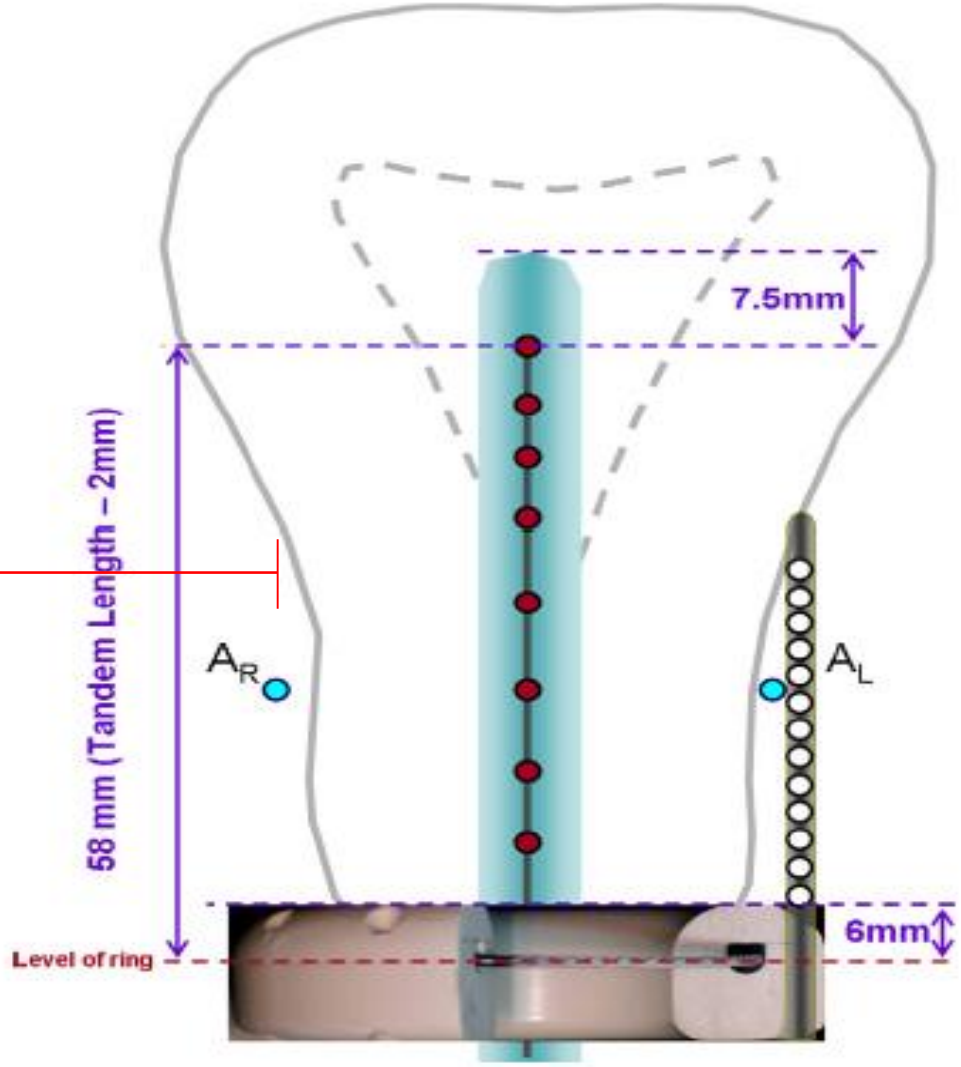
Ack: Hellebust TP

The location of dwell positions is found in relation to one another or in relation to reference points in the applicator,

- e.g., the distance from the tip of the tandem applicator to the first dwell position.

Step 1/5: Understand the geometry





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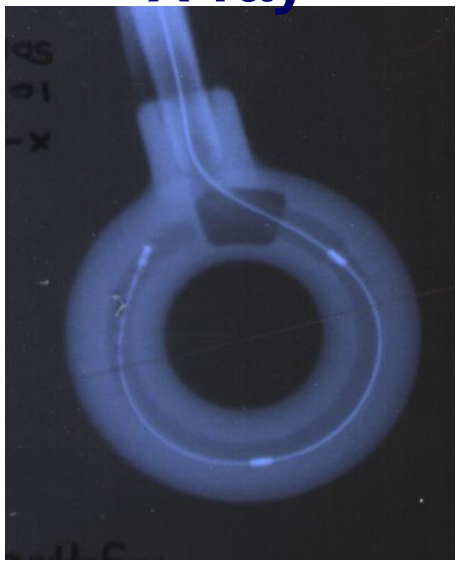
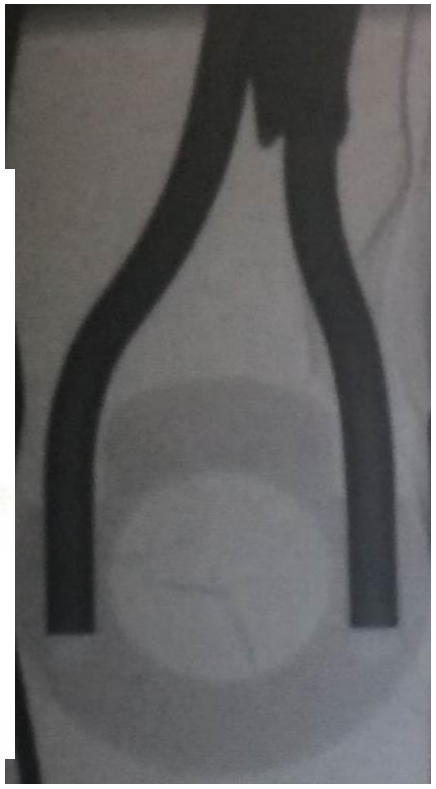
Step 1/5: Understand the geometry

The ring applicator from Bebig vs Elekta

X-ray



X-ray

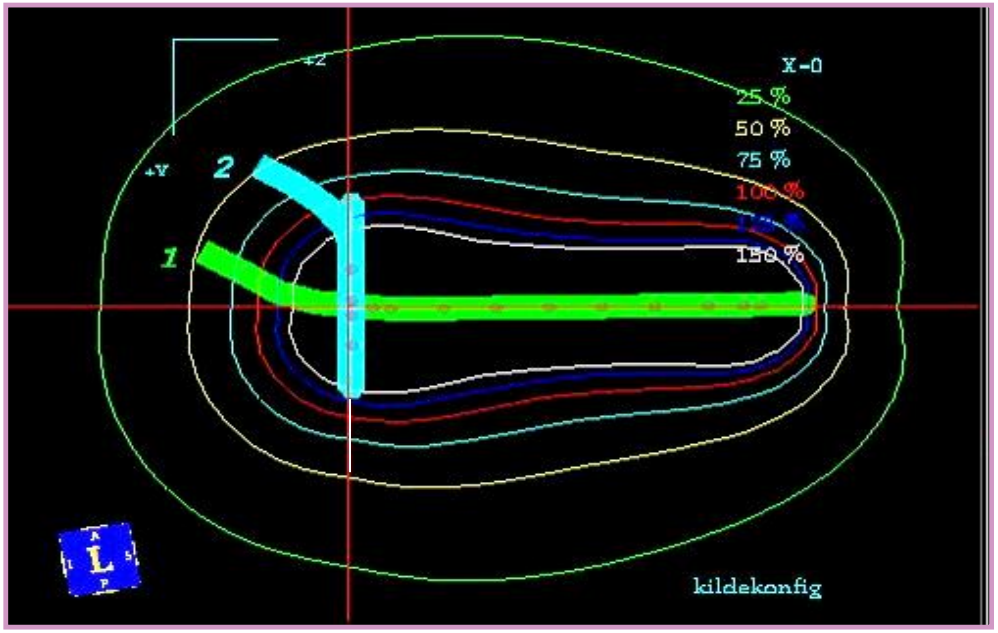


Elekta **Bebig**

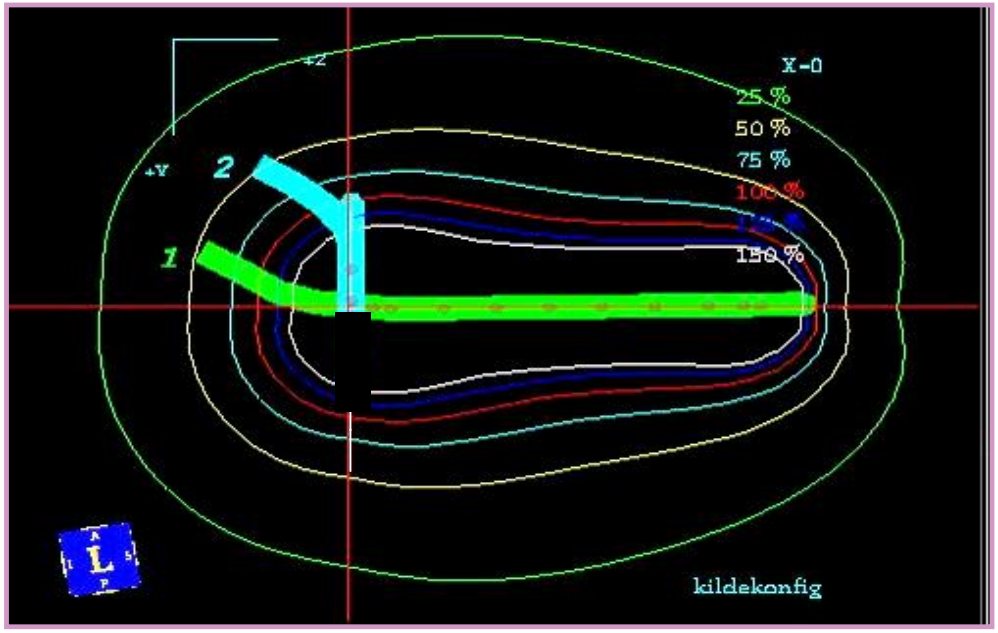
Pictures provided by Hellebust TP, Oslo

The ring applicator from Bebig vs Elekta lateral view on x-ray (only metal part visible)

Elekta



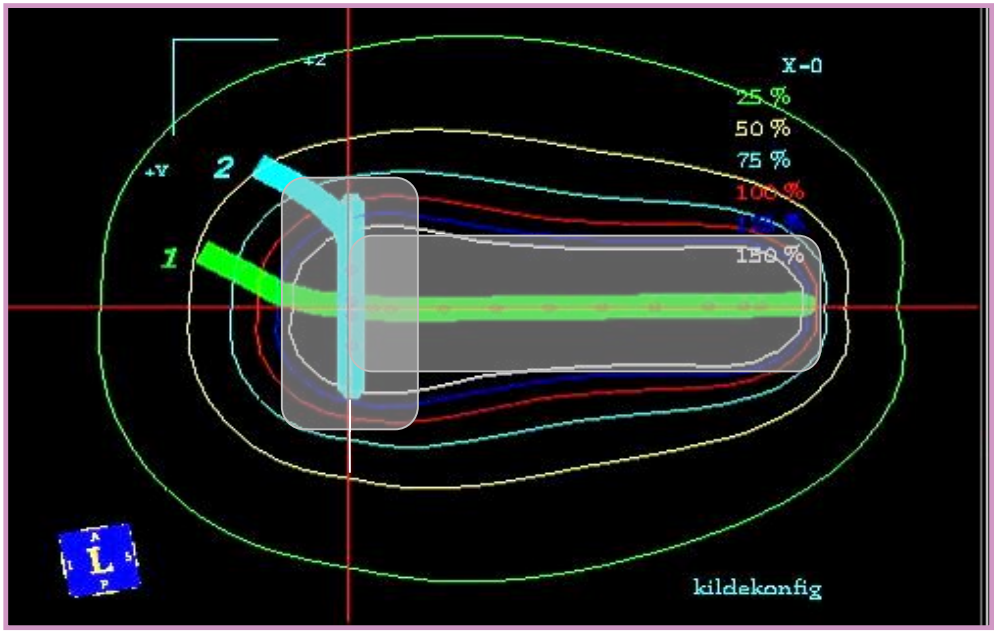
Bebig



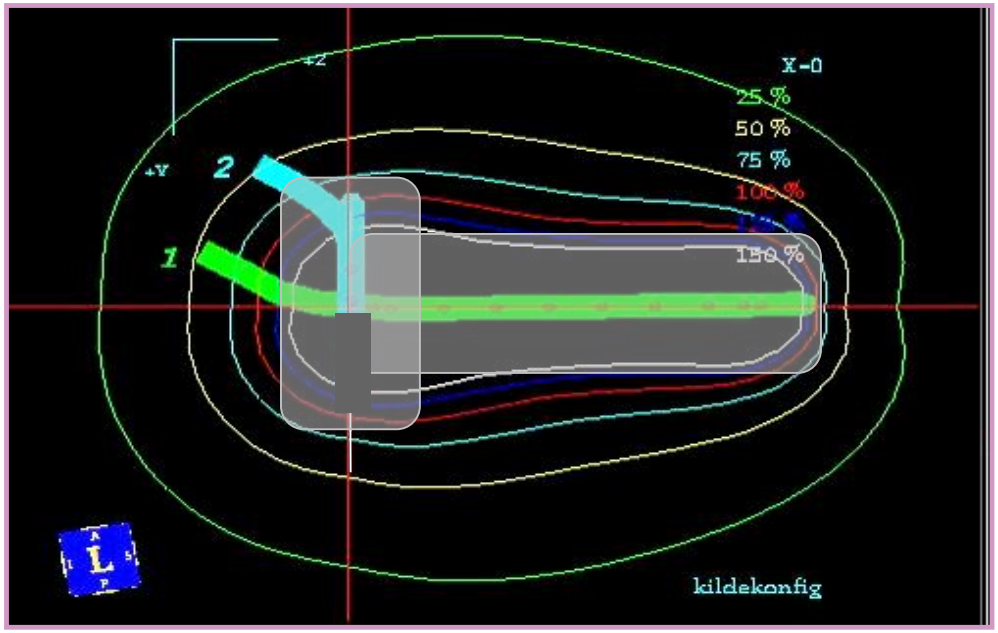
Pictures provided by Hellebust TP, Oslo

The ring applicator from Bebig vs Elekta, lateral view including plastic ring important for localization of ICRU rectum point and vaginal points

Elekta

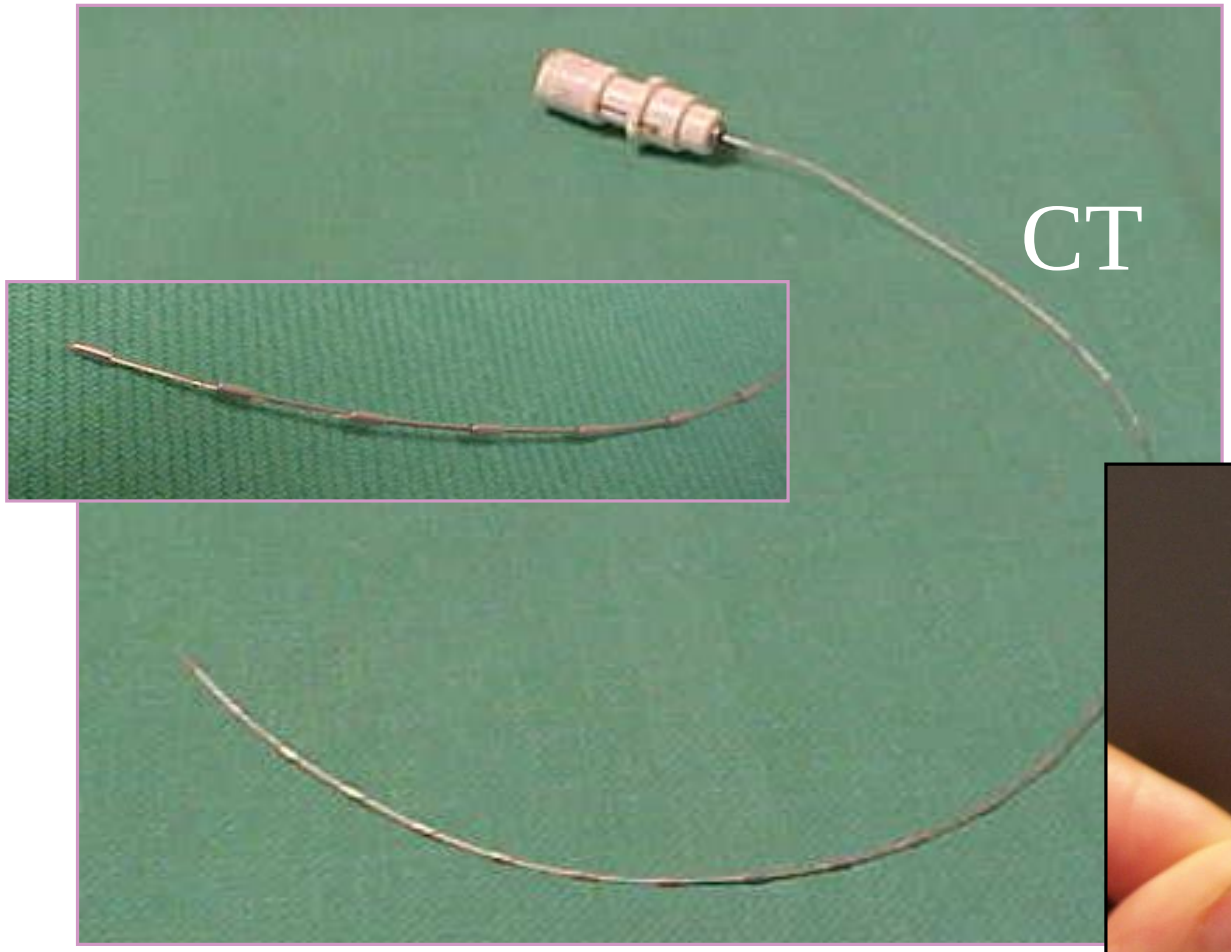


Bebig

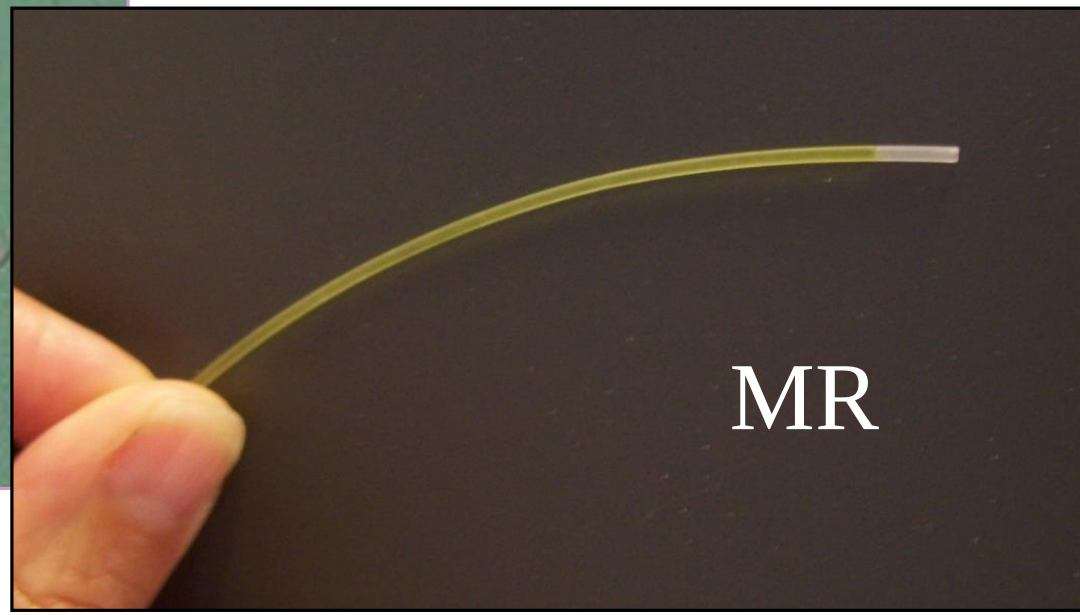


Pictures provided by Hellebust TP, Oslo

Step 2/5: Choose the Markers

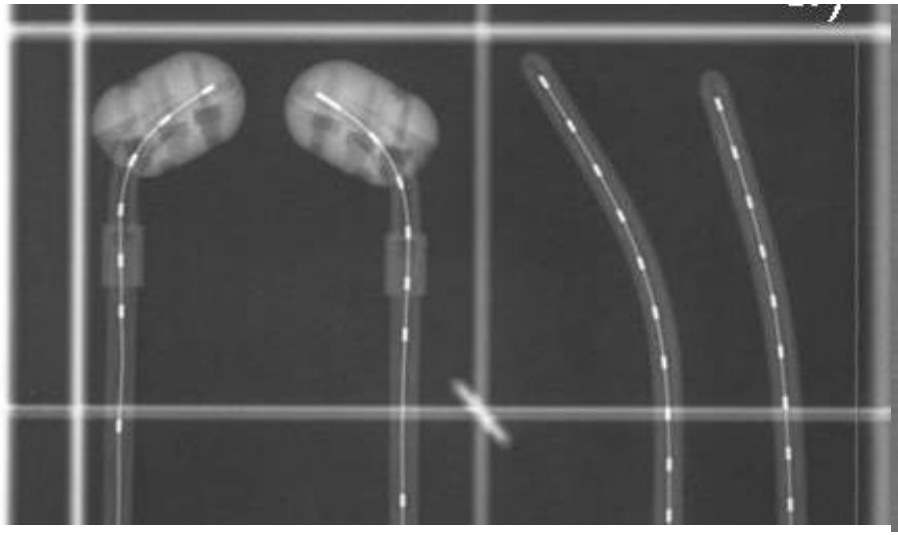


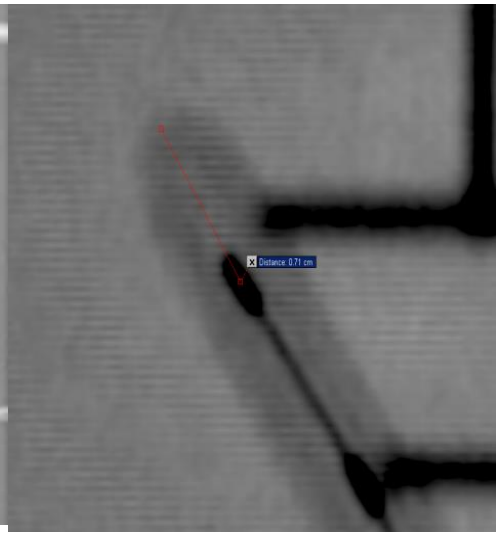
important: Dedicated for each type of applicator, check for locking!!

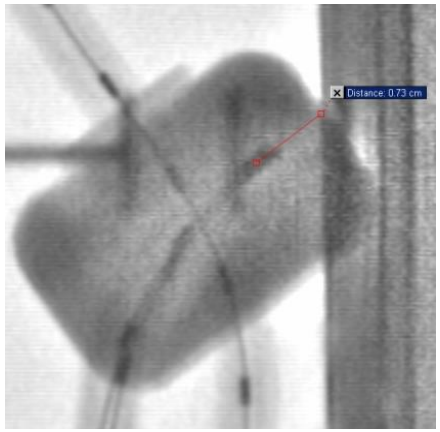


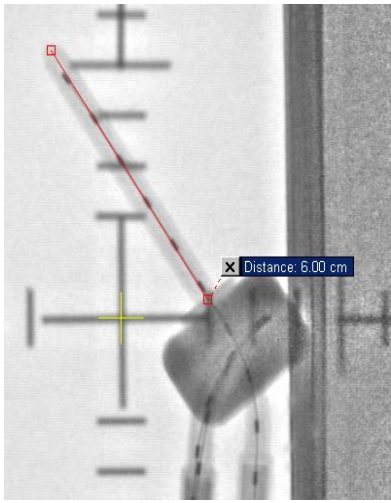
Pictures provided by Hellebust TP, Oslo

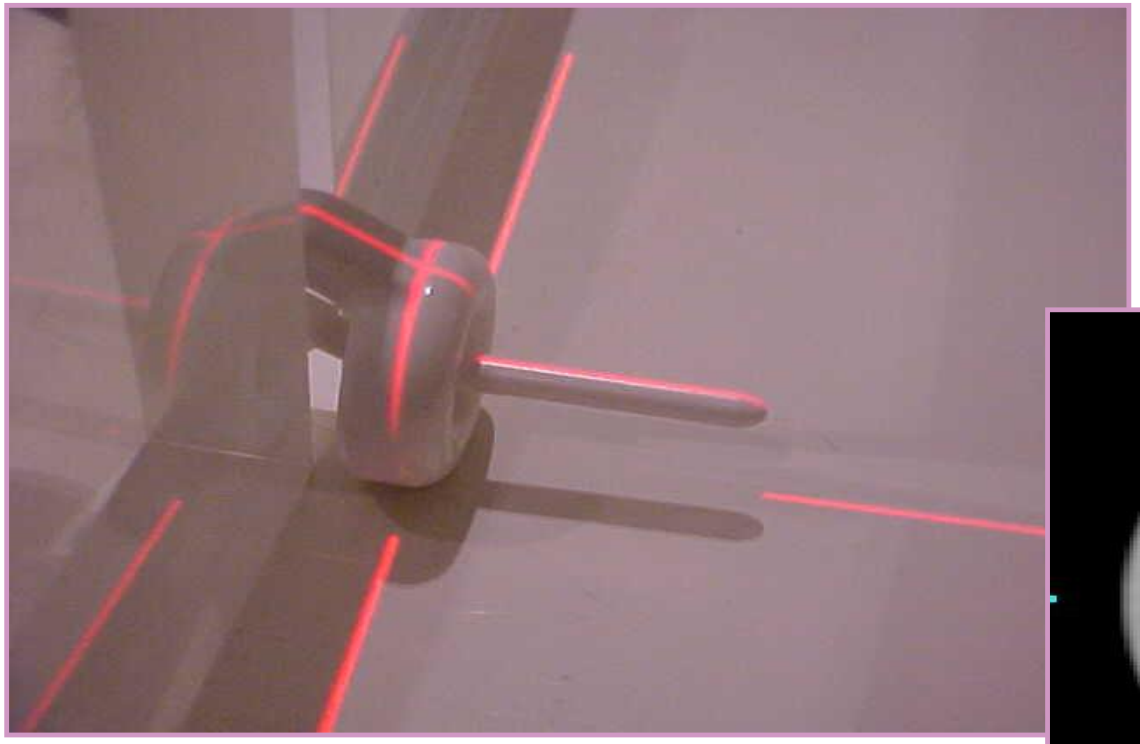
Step 3/5: Radiograph / CT / MR

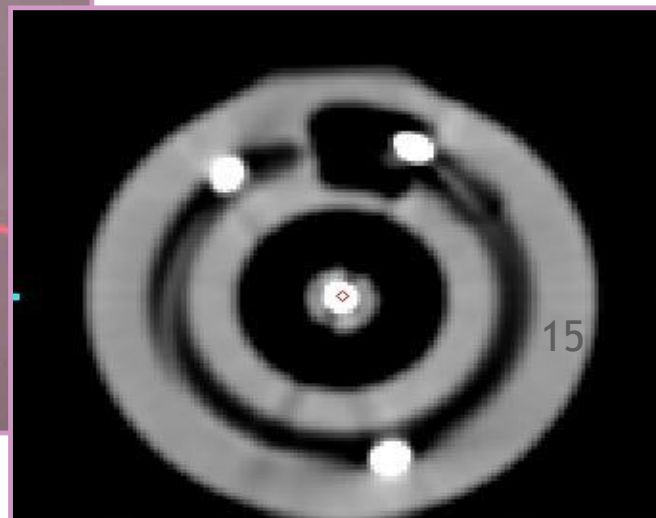






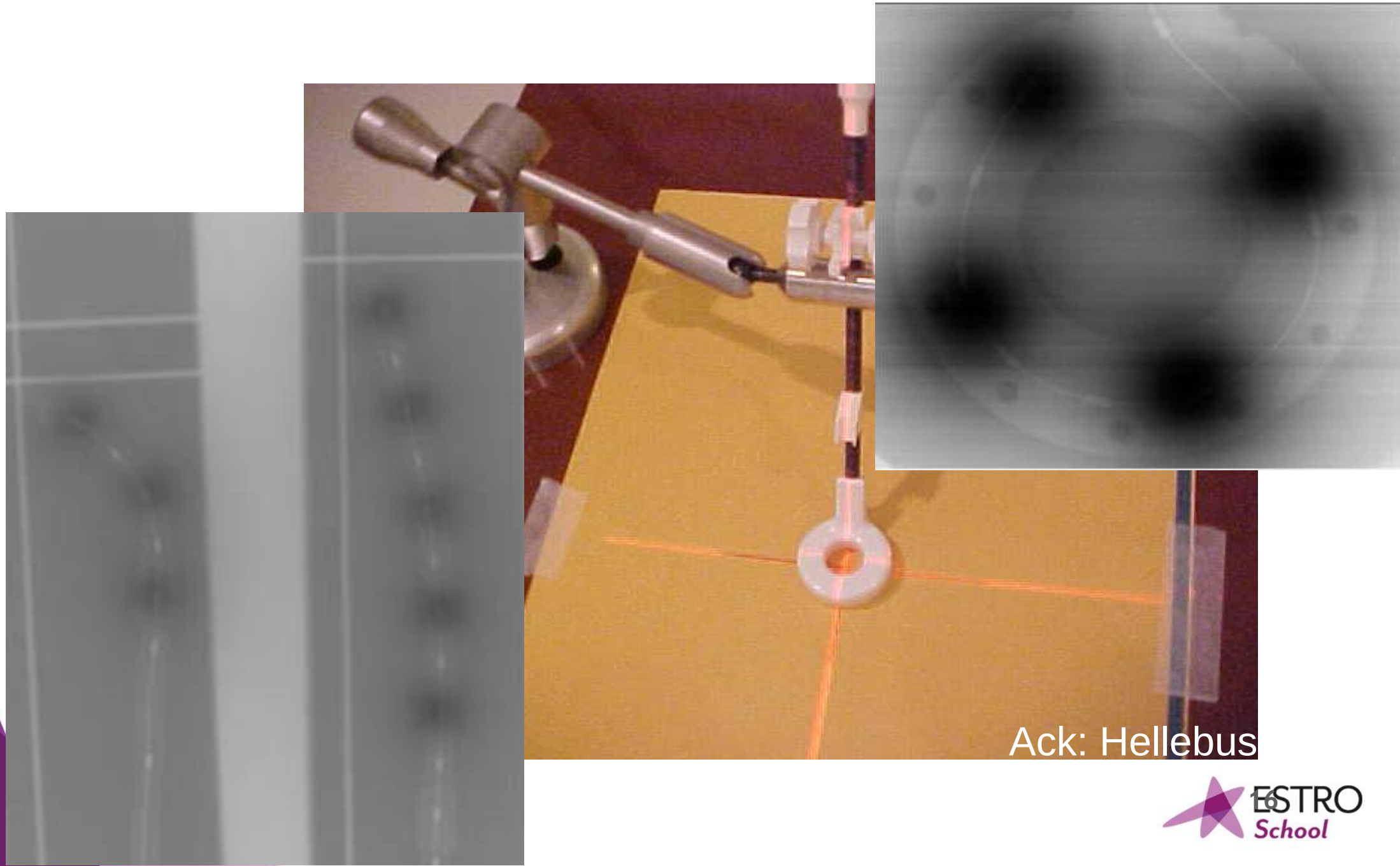






Slide Coutesy: Hellebust TP, Oslo

Step 4 /5 : Auto radiograph

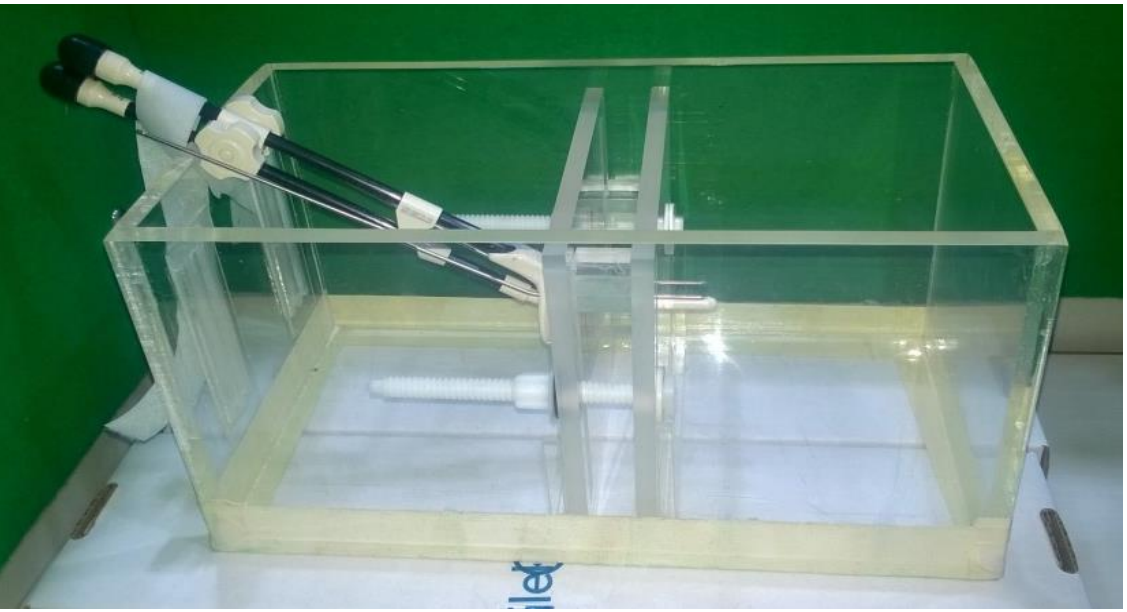


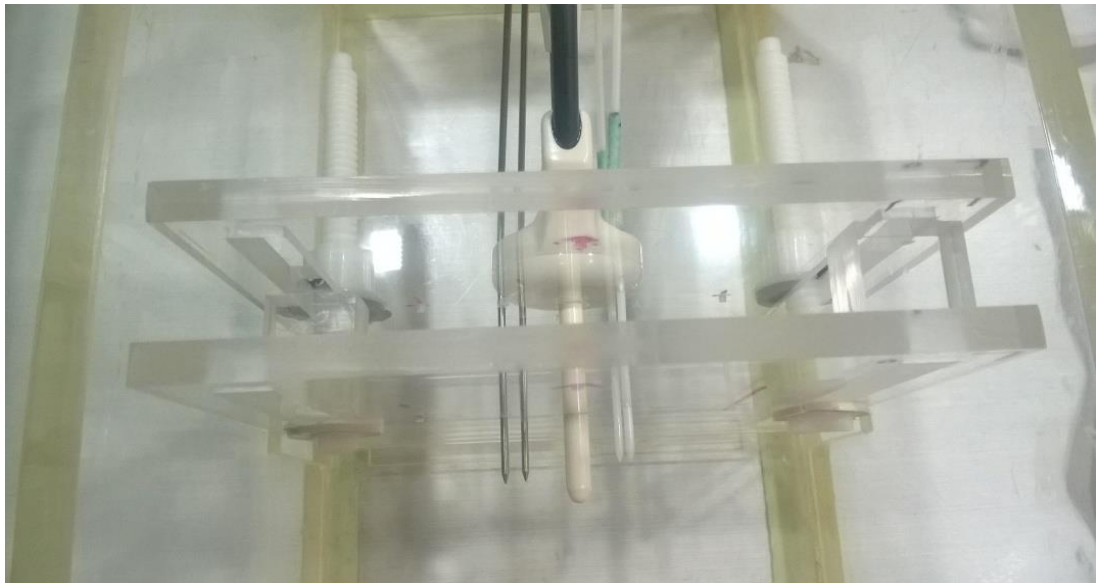
Ack: Hellebus

Step 5/5 : Analysis

- Compare the auto radiograph with the manufacturer specifications
- Image analysis (CT, MRI)

Phantom

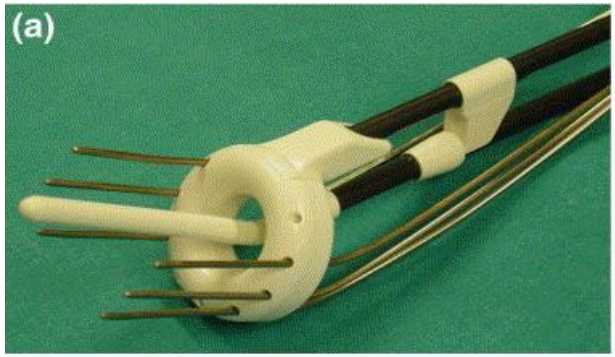


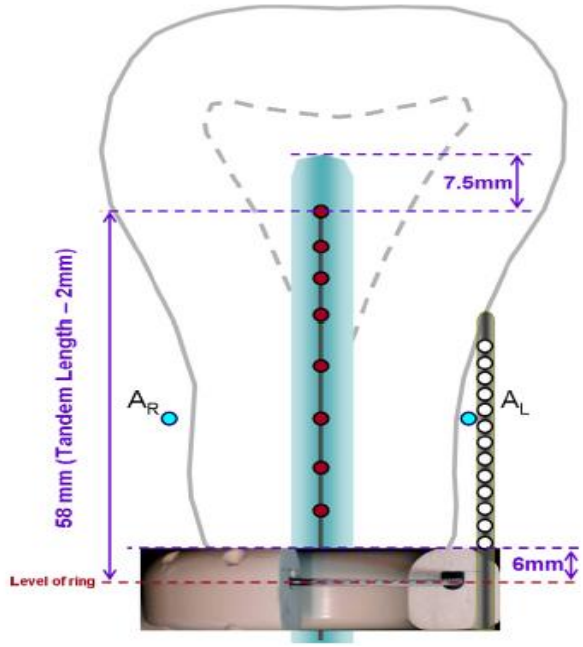


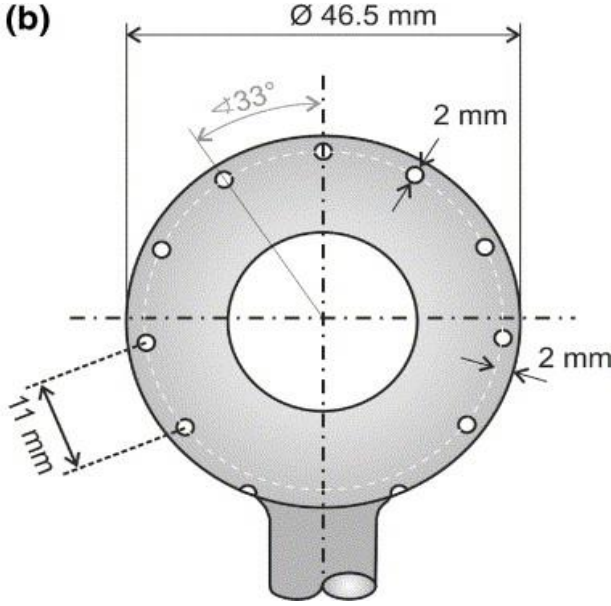
- Should facilitate accurate positioning of the applicator
- External setup markers for proper setup during imaging

Applicator – Elekta -Vienna

- Tandem Length – 60 mm
- Ring Diameter – 26 mm
- Titanium Needles – 2 on left
- Plastic Needles – 2 on right







Photos of a plastic needles cut in two

More plastic in the tip in sharp needles

sharp

round

Pictures provided by Taran Hellebust, Oslo

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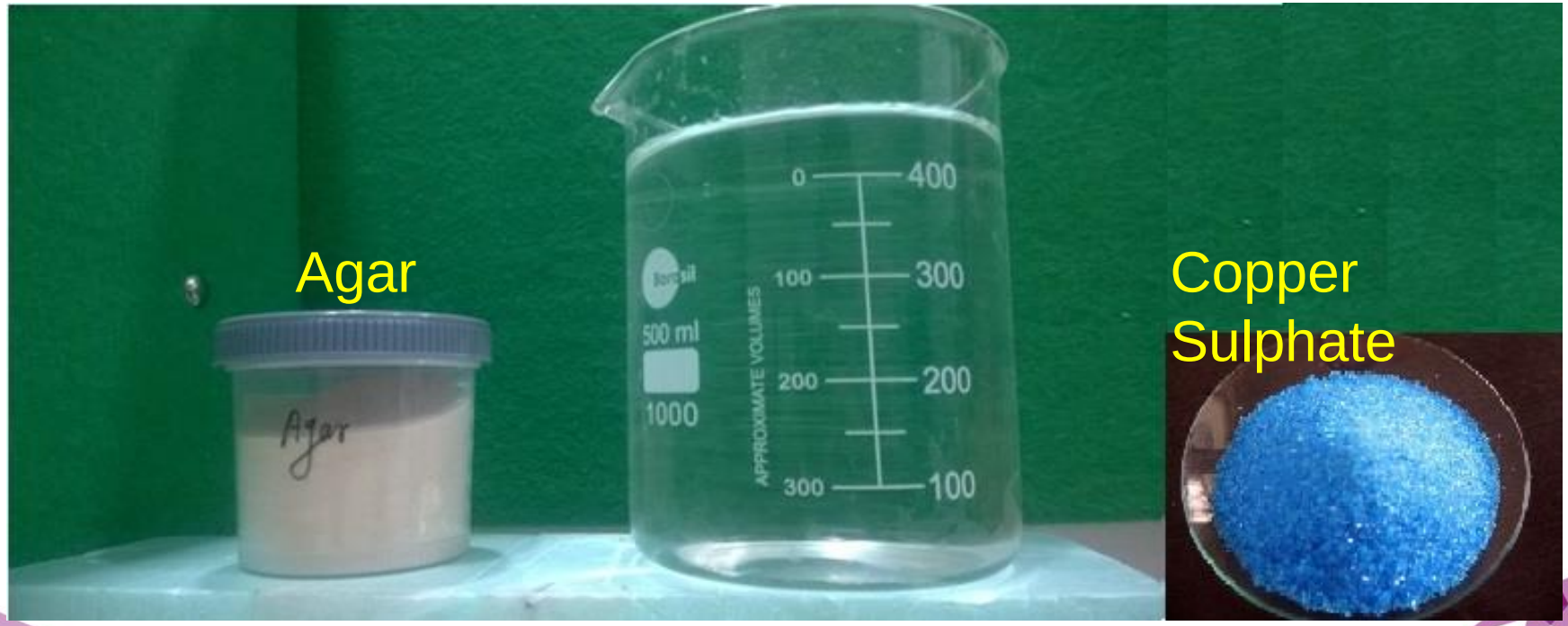
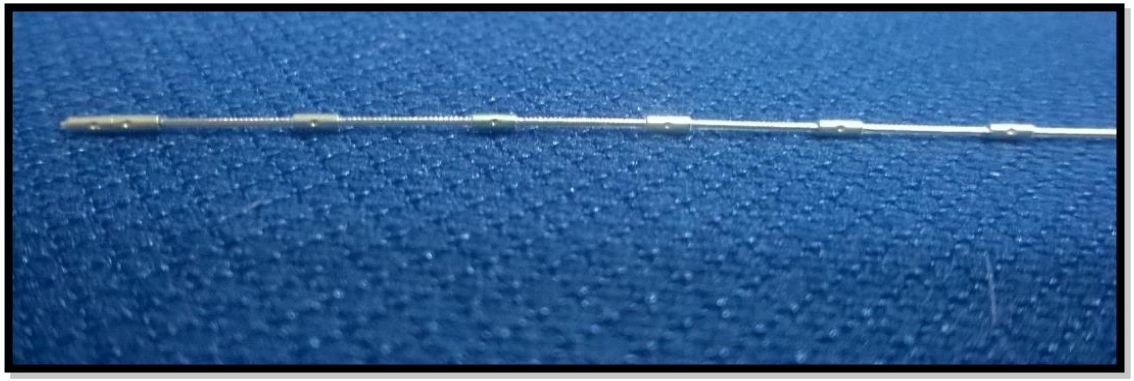
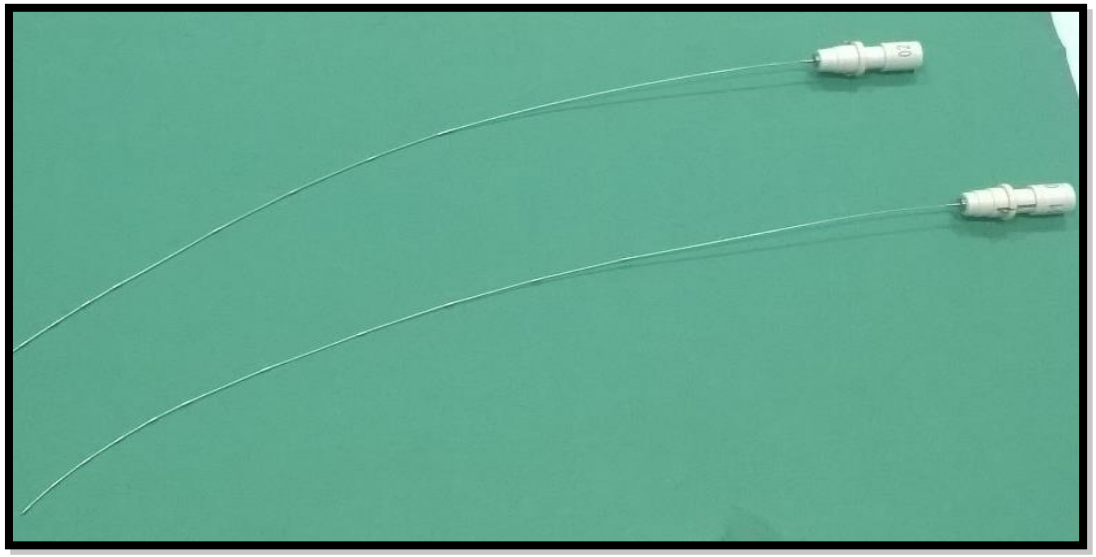
Medium Recipe:

- Preferable if it resembles human tissue imaging qualities.
- Ideal for CT/ MR applicator is Agarose gel (3%) with $CuSO_4$ (1 g/L)

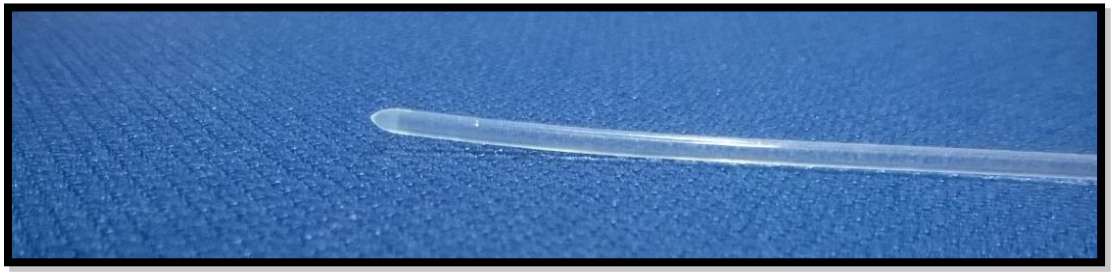


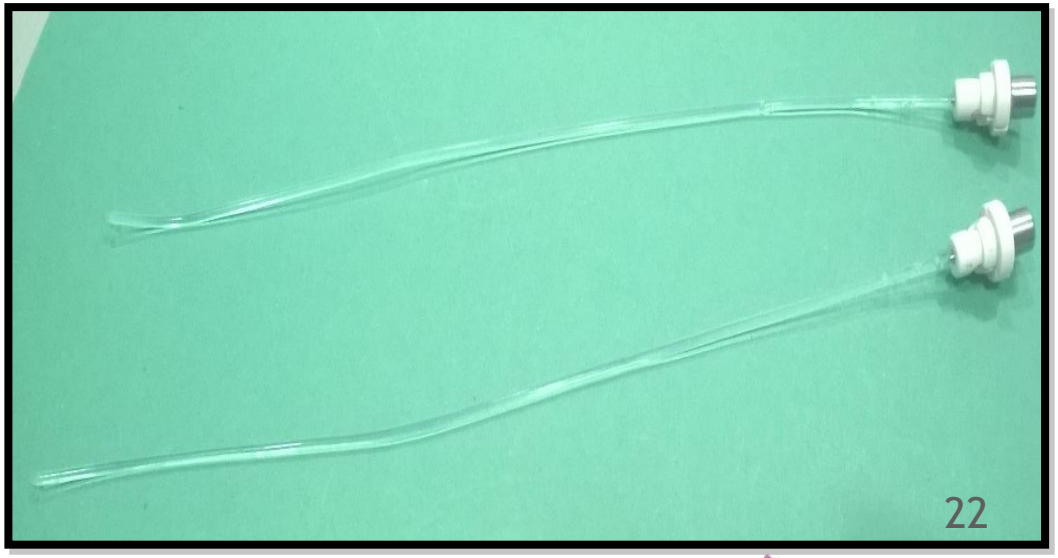




X-ray markers for CT/MR applicator.

DO NOT USE X-RAY MARKER DURING MRI.

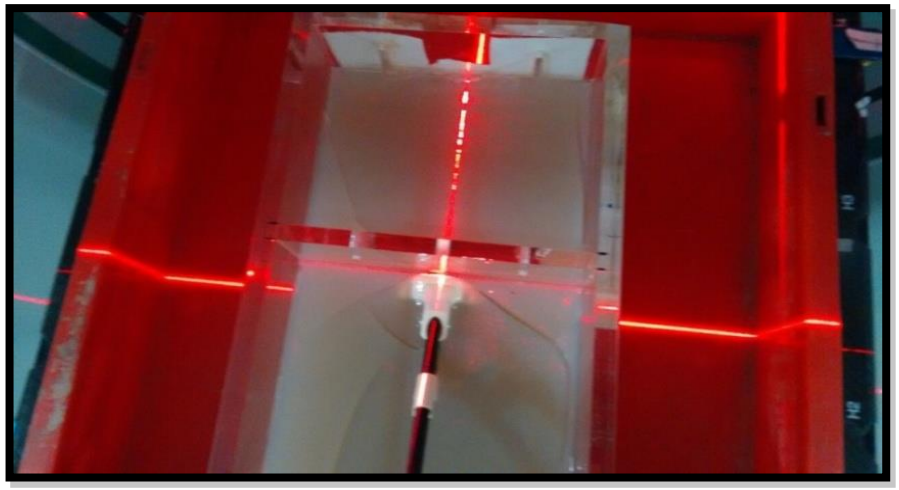




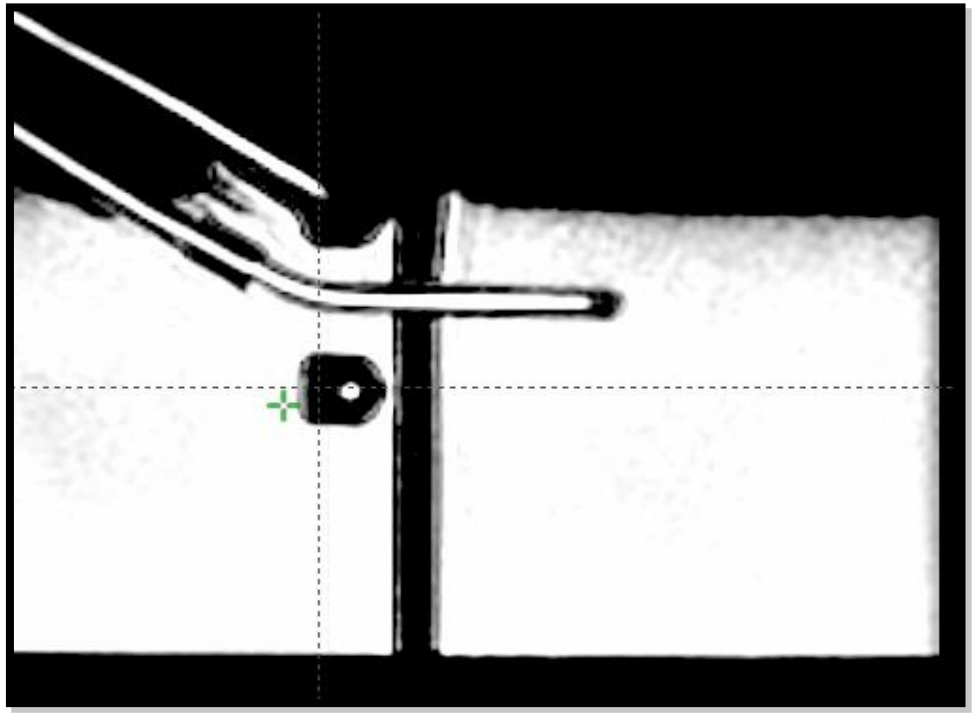
MR markers for CT/MR applicator.
They are filled with water.
$CuSO_4$ can also be used.

Imaging

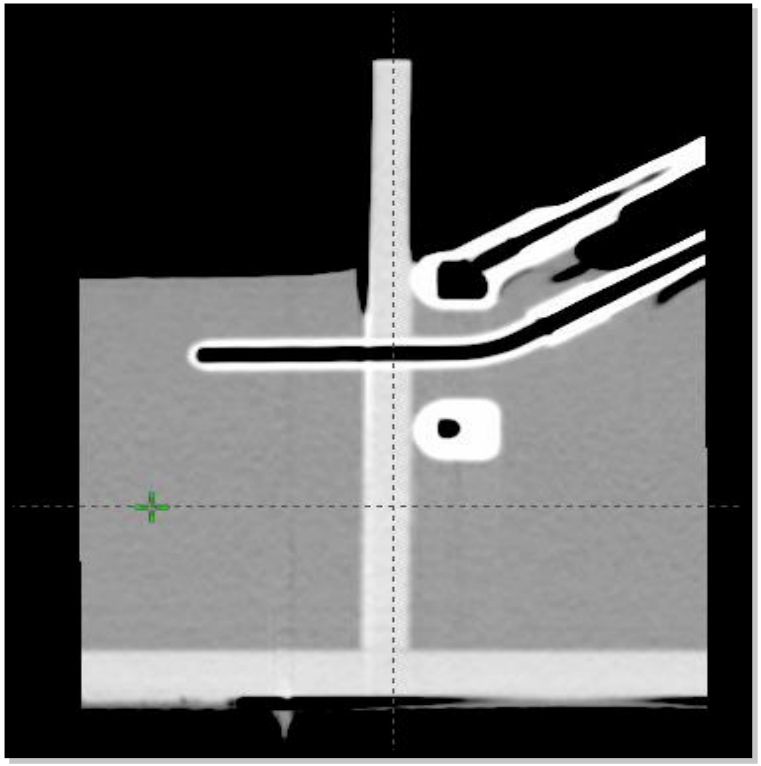
- Setup according to the external markers.
- Align the axis of the applicator along the saggital Laser.
- Imaging Series
  - CT – <1 mm slice thickness
  - MRI – T1, T2 para-axial, para-saggital and para- coronal. 2- 3 mm slice thickness.
  - Zero overlap
  - Other sequences of relevent.

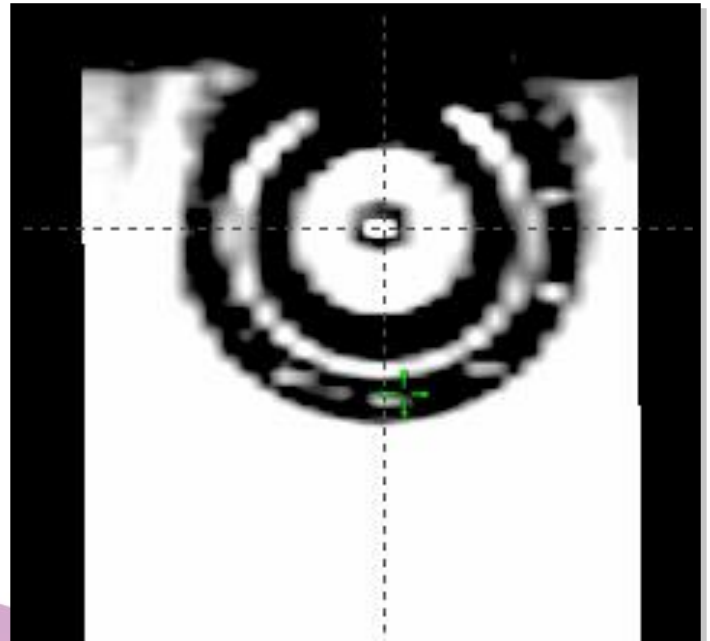


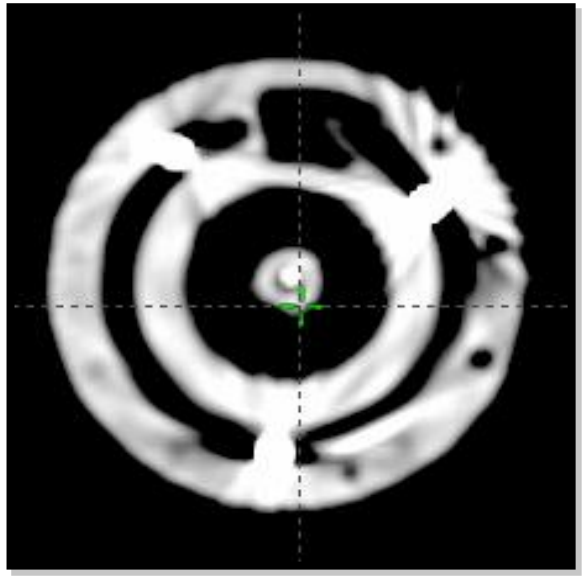
MRI



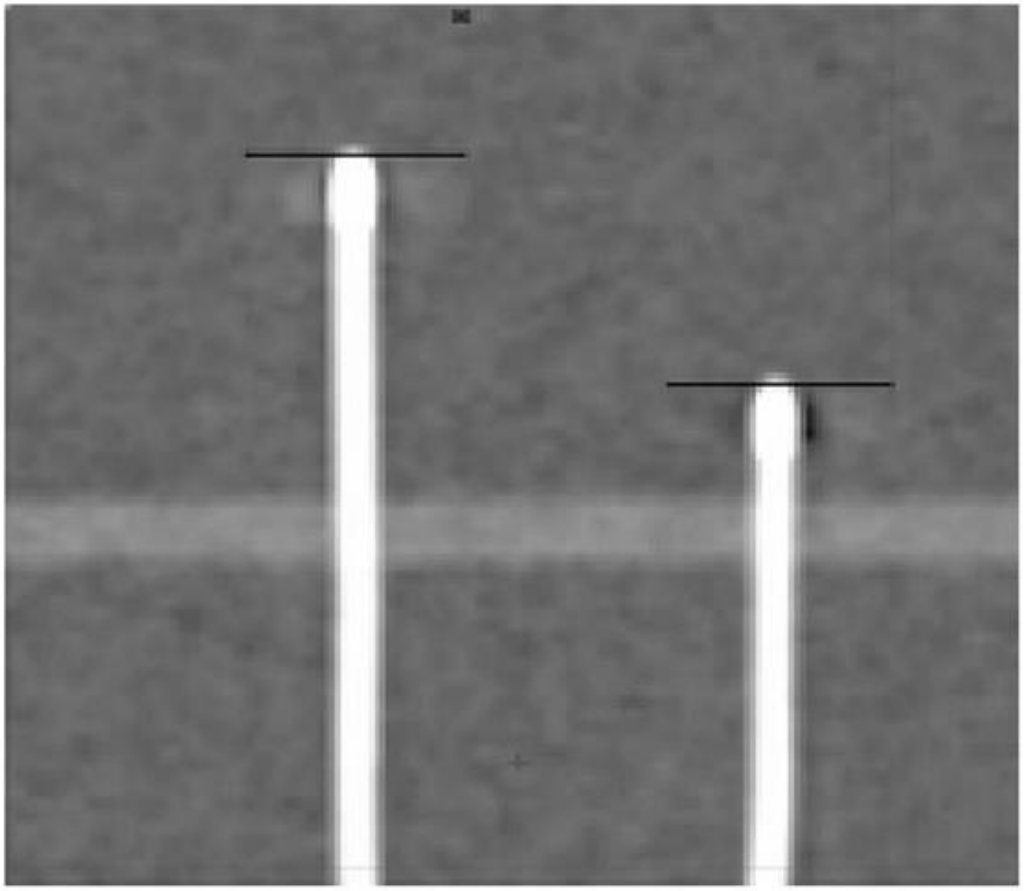
CT



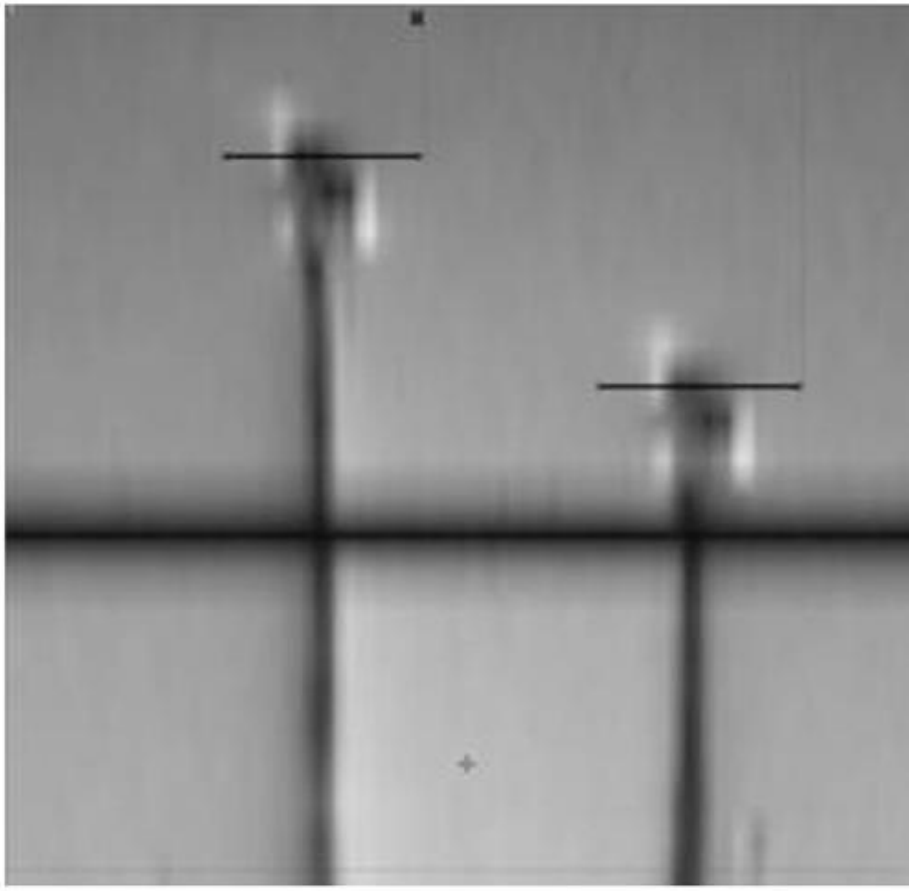




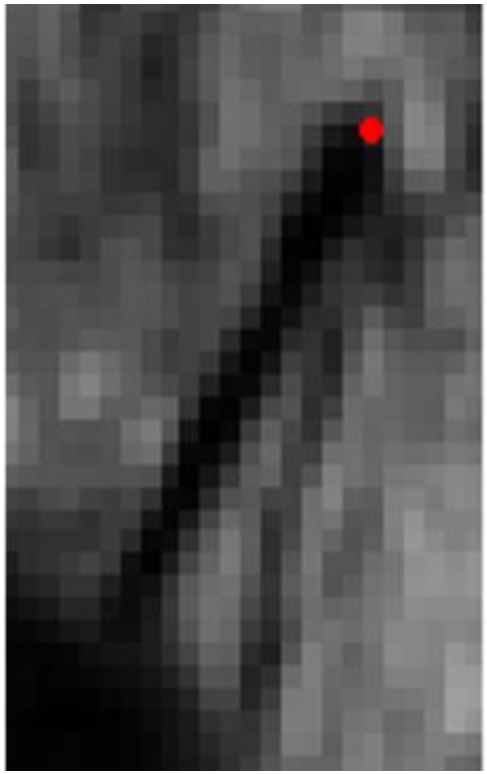
Titanium Needles CT vs MRI



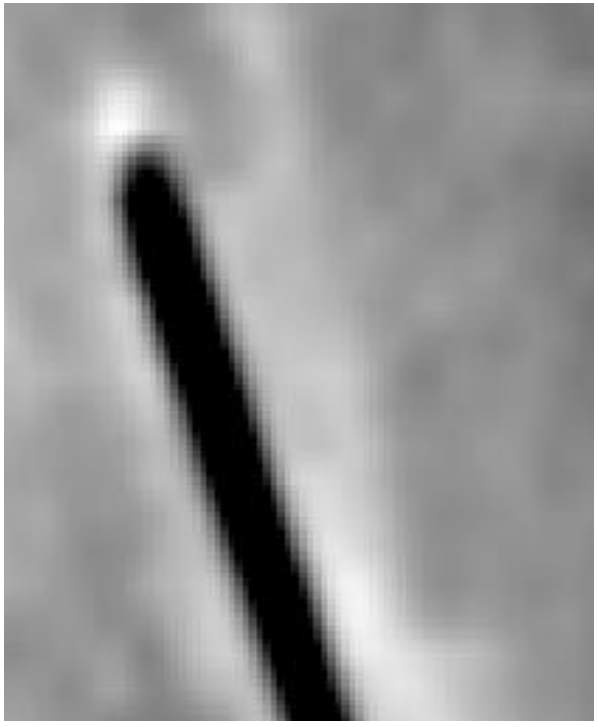
b



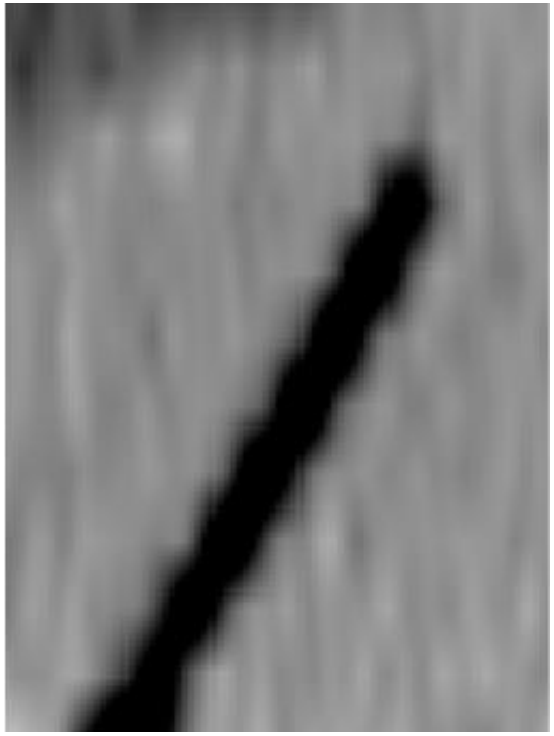
Needle on MR and CT



MRI



CT (1mm slice thickness)



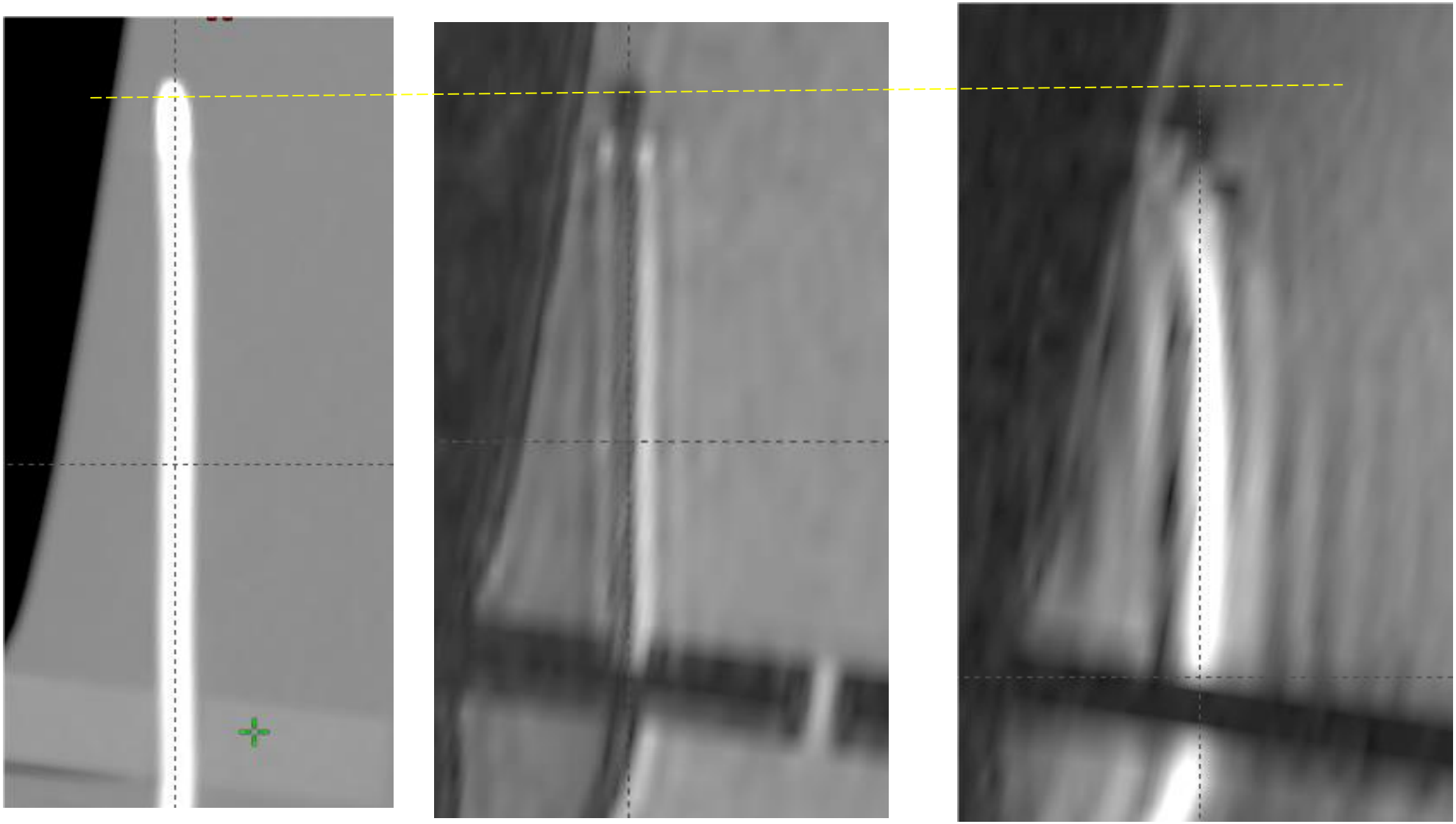
CT (3mm slice thickness)

Pictures provided by Hellebust TP, Oslo

CT

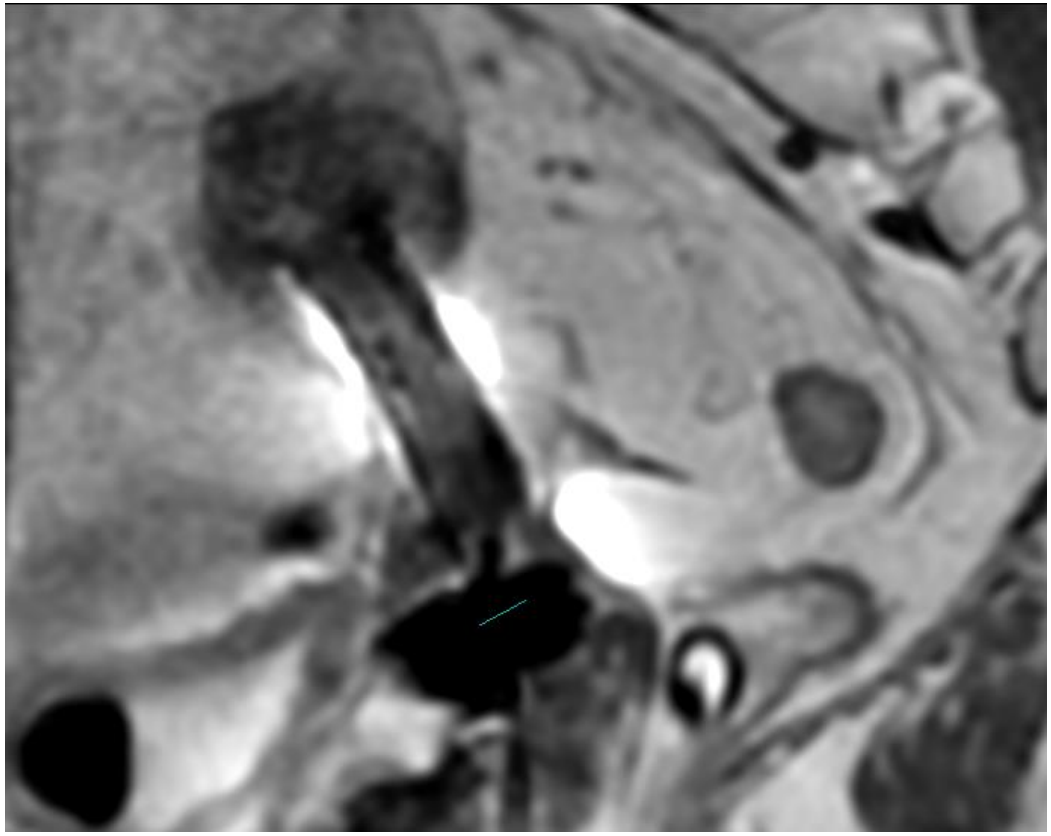
1.5 T

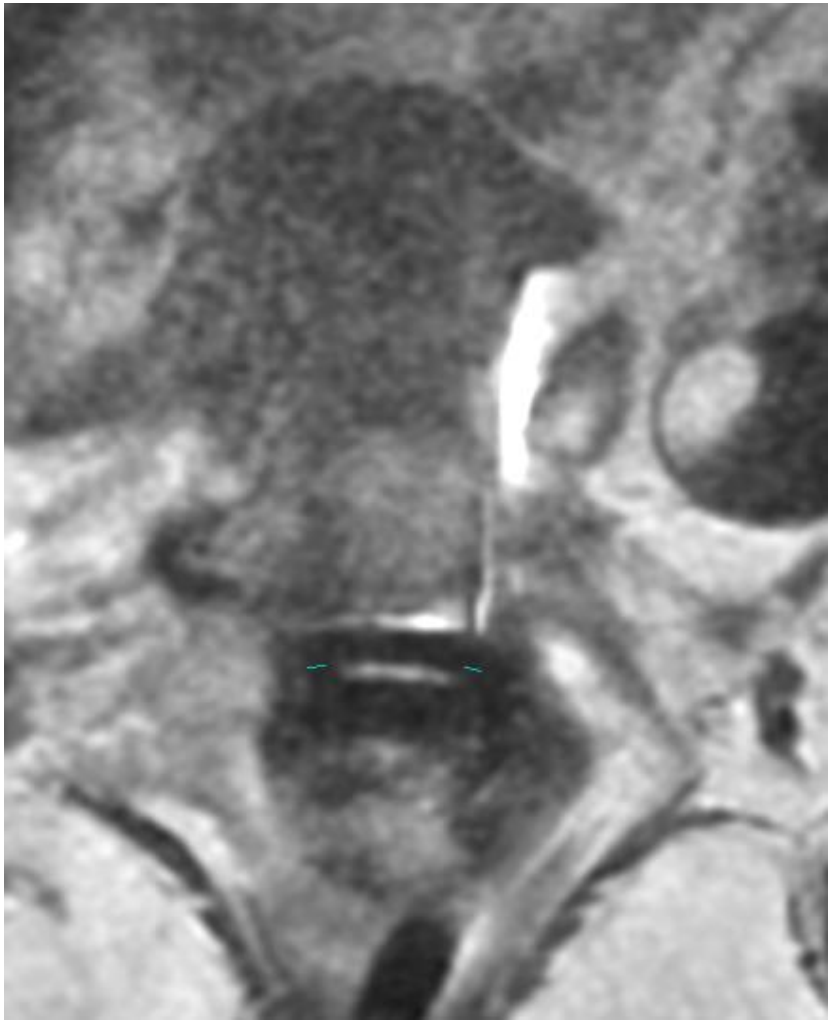
3.0 T



Ti needle

Artefacts of Ti needles in 3T MRI



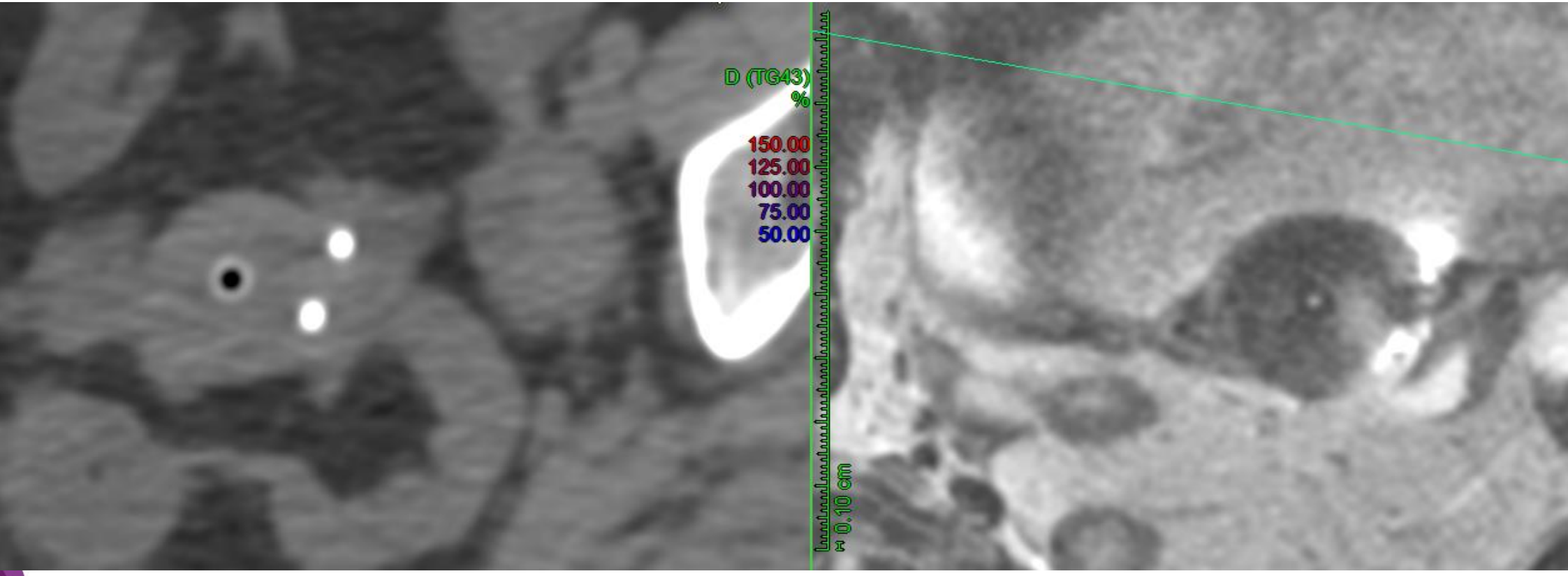


CT

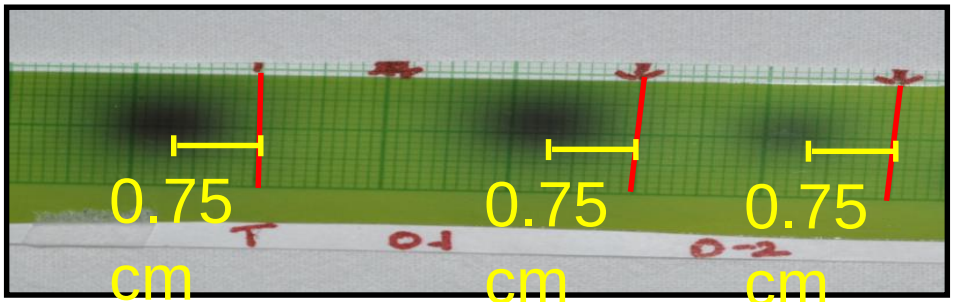
Ti Needles

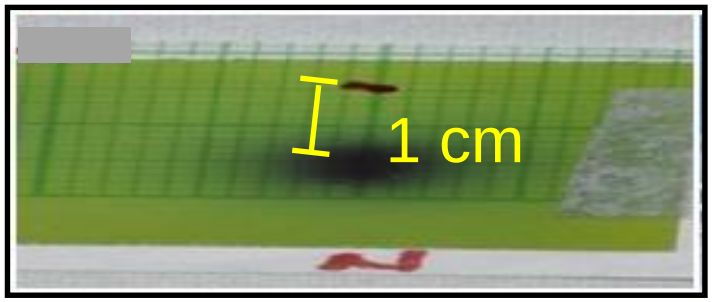
3.0 T MRI

Ti Needles

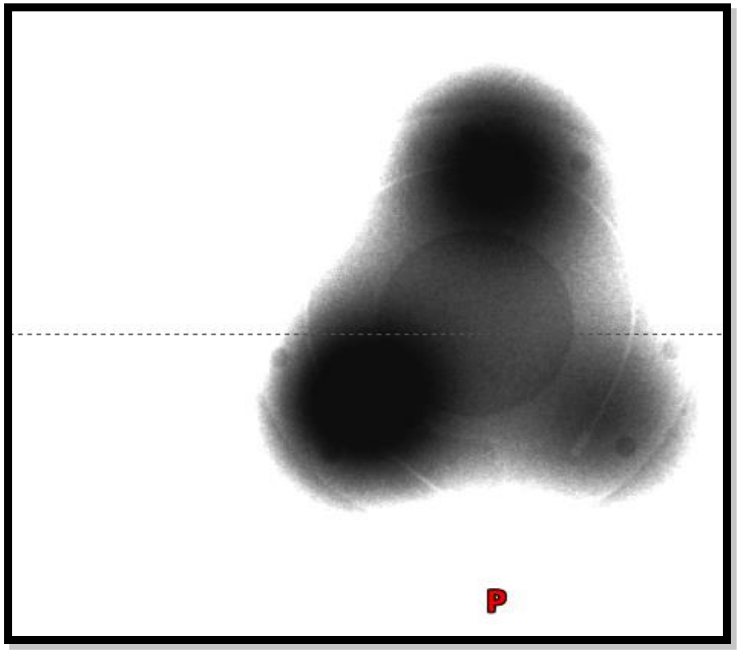


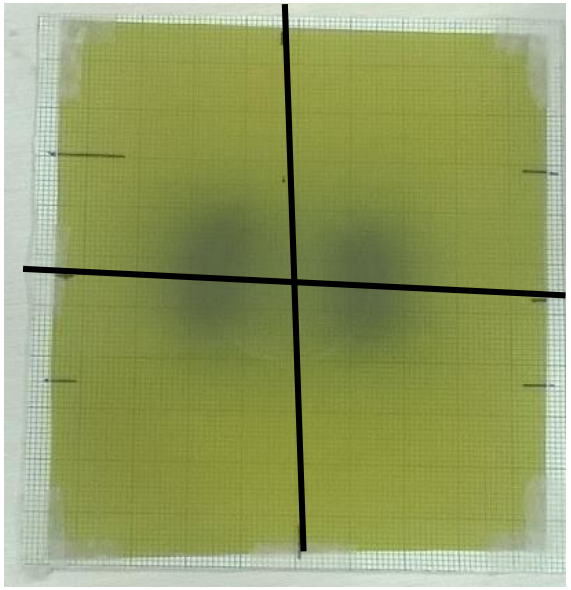
Auto Radiograph



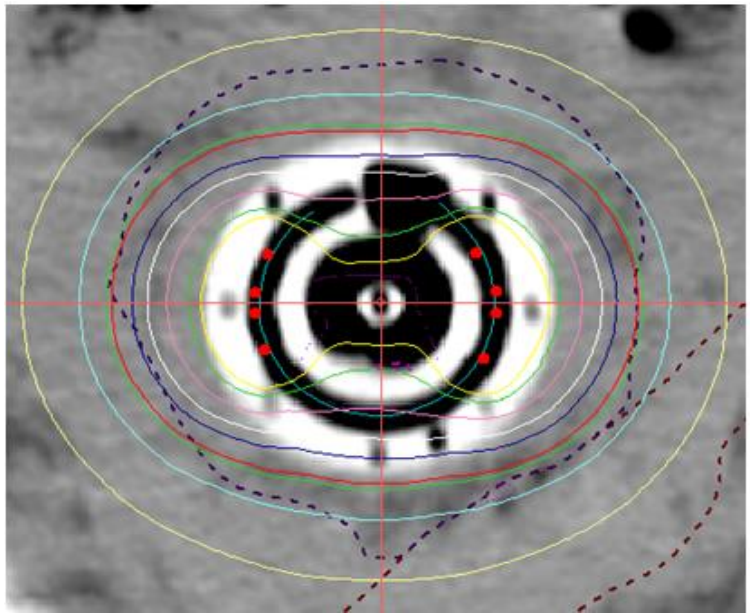


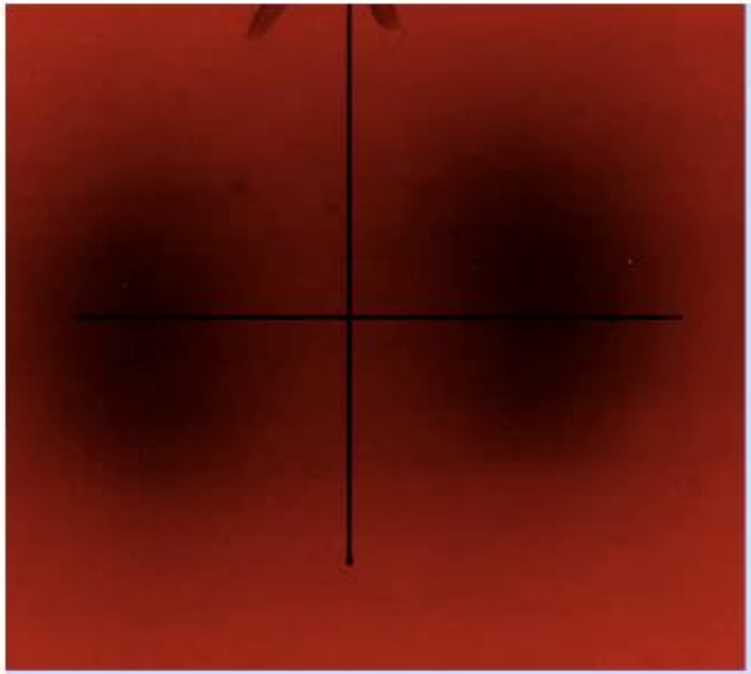
Red line indicates the physical tip

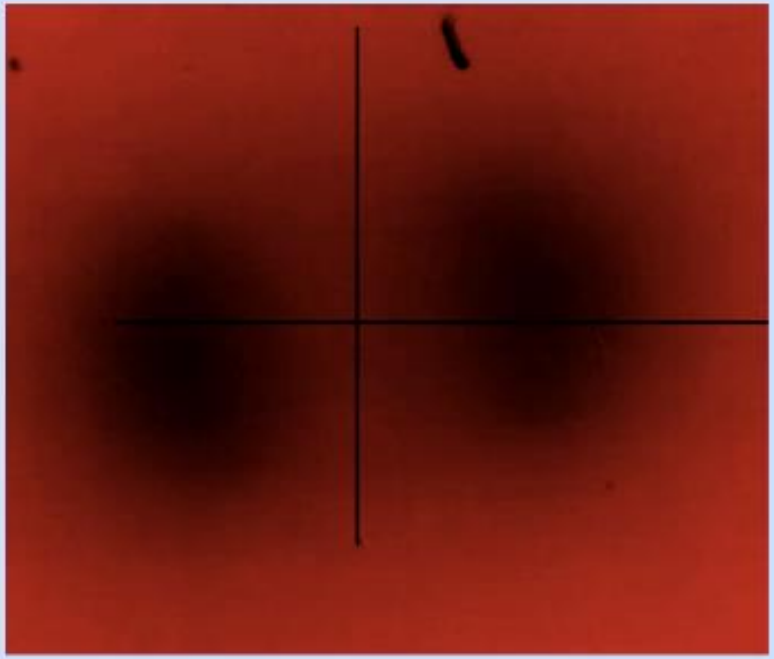




Ring Applicator







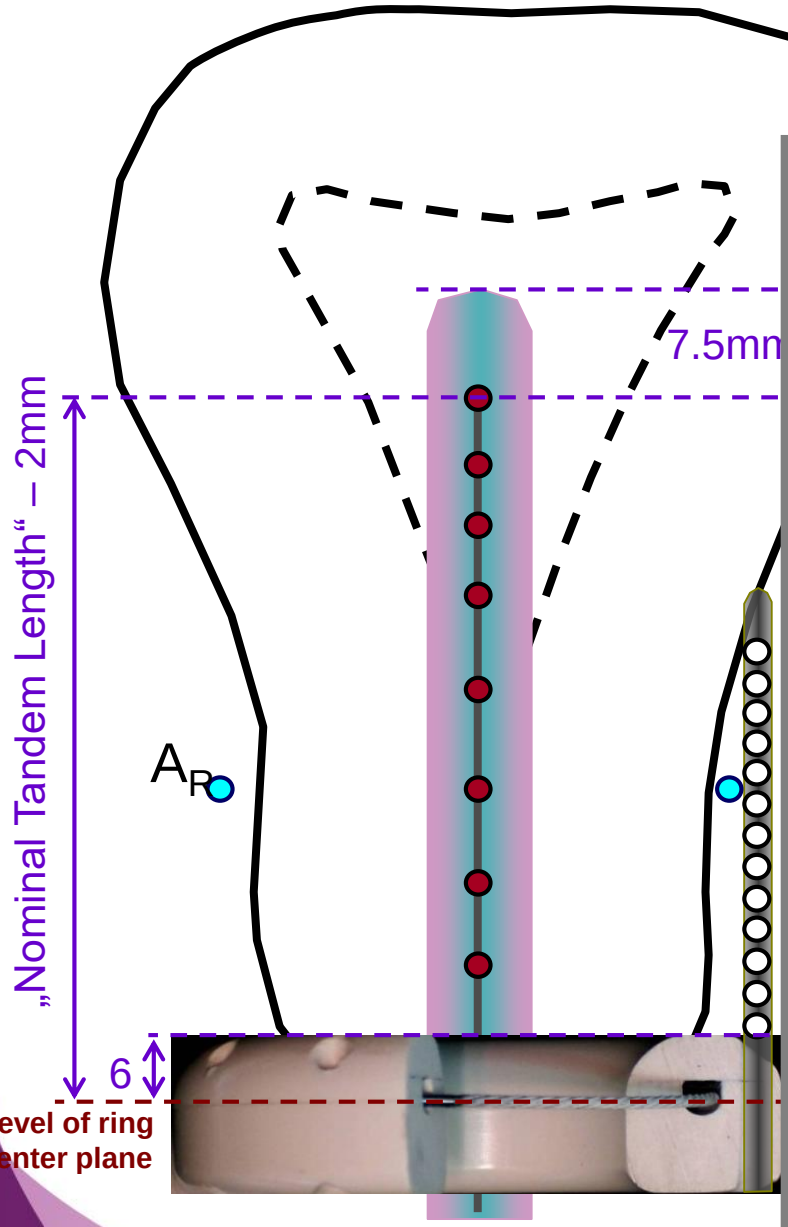
Acceptable

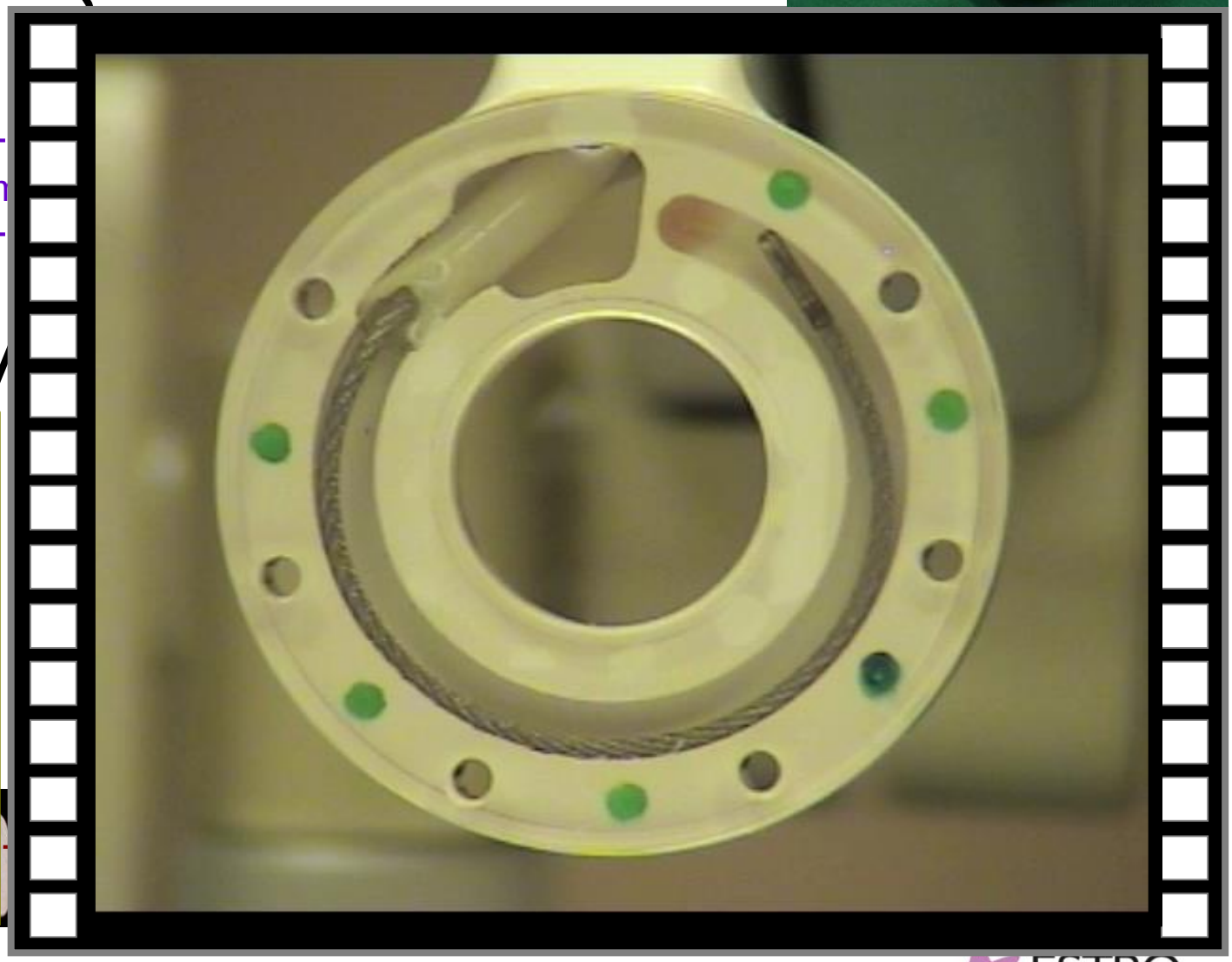
Not Acceptable

Pictures provided by Taran Hellebust, Oslo

Geometry and dimensions of the applicator

Ring Diameter	
nominal	outer
26	38
30	42
34	47





Slide courtesy: Daniel Berger

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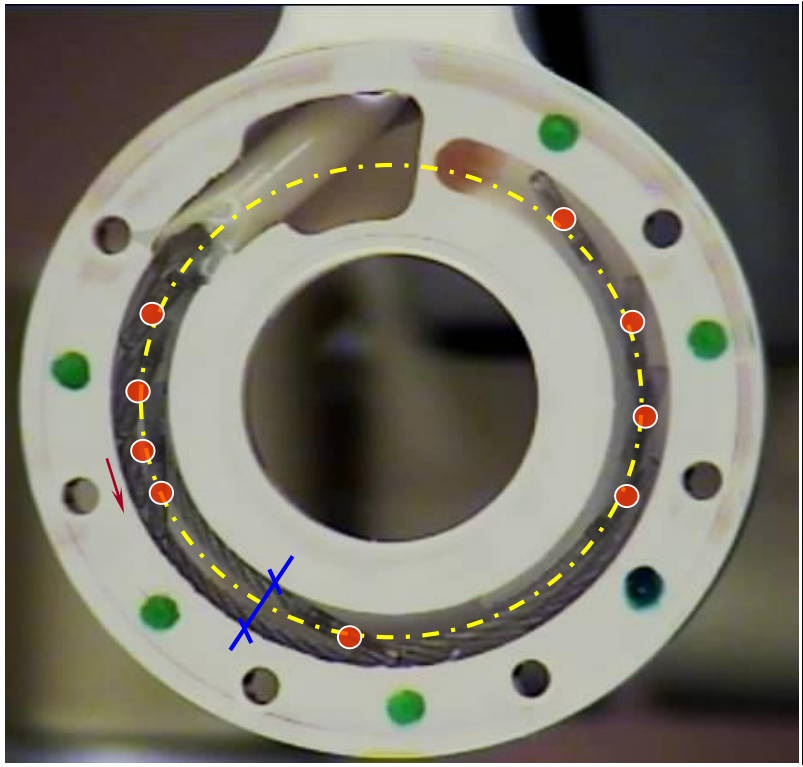
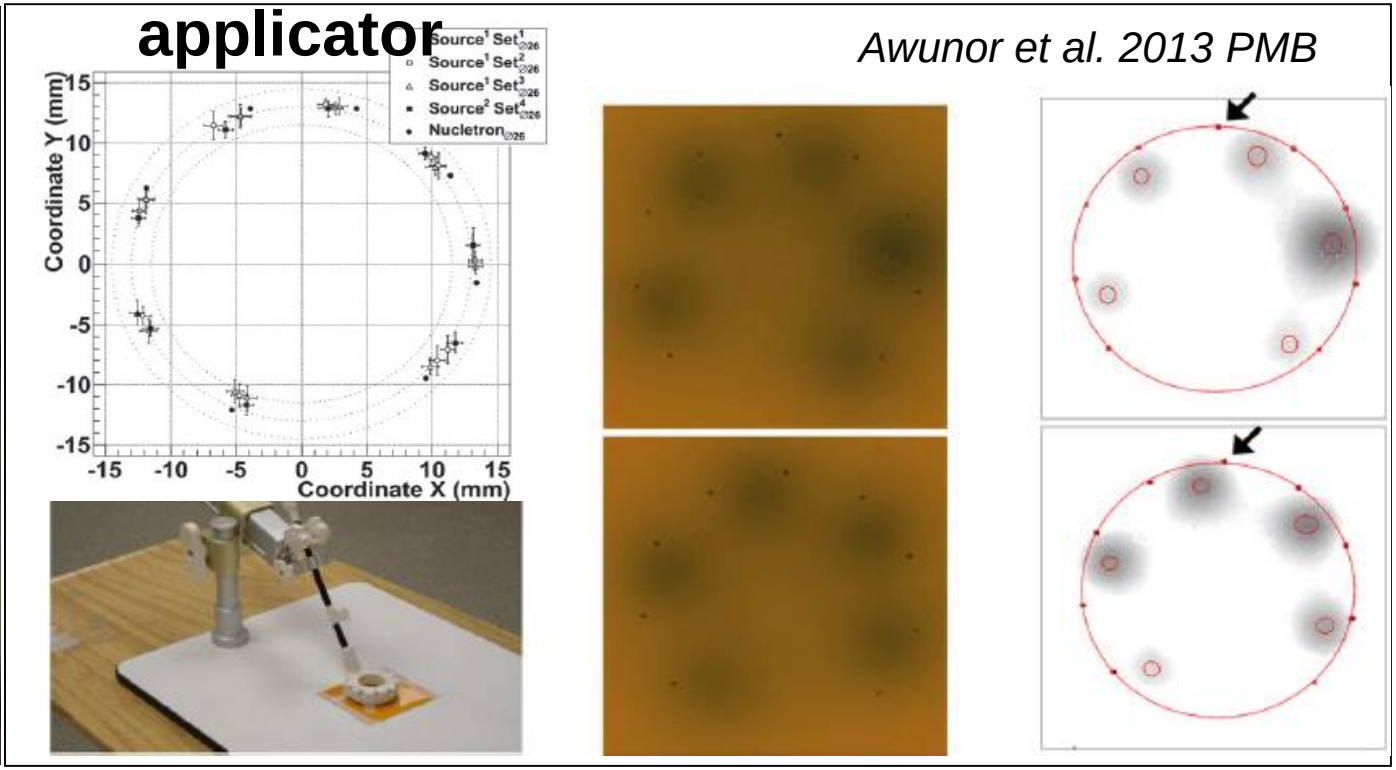
associated uncertainties of 192Ir source dwell positions in ring applicator





The total expanded measurement uncertainty averaged over all dwell positio
observed to be 1.1 ± 0.1mm(Ø26 and Ø30 mm) and 1.0 ± 0.3 mm (Ø34 m

1) Real step-size in ring dwell positions varies depending on the location
2) A dummy wire dose not represent the real source path

Slide courtesy: Daniel Berger

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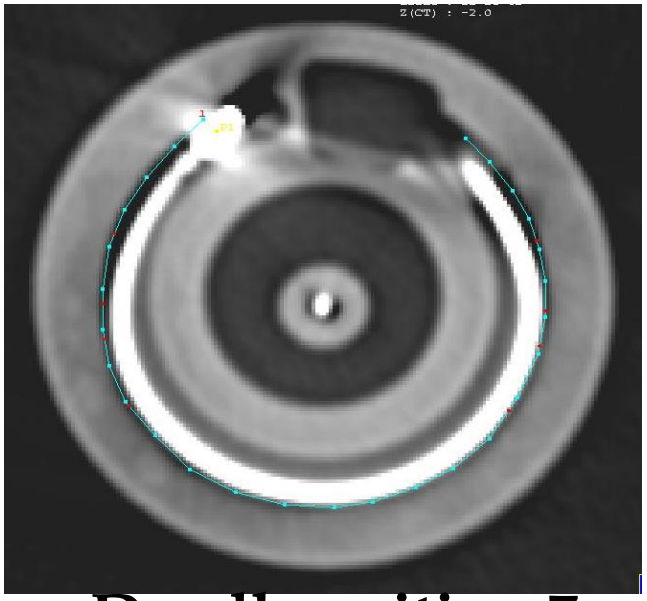
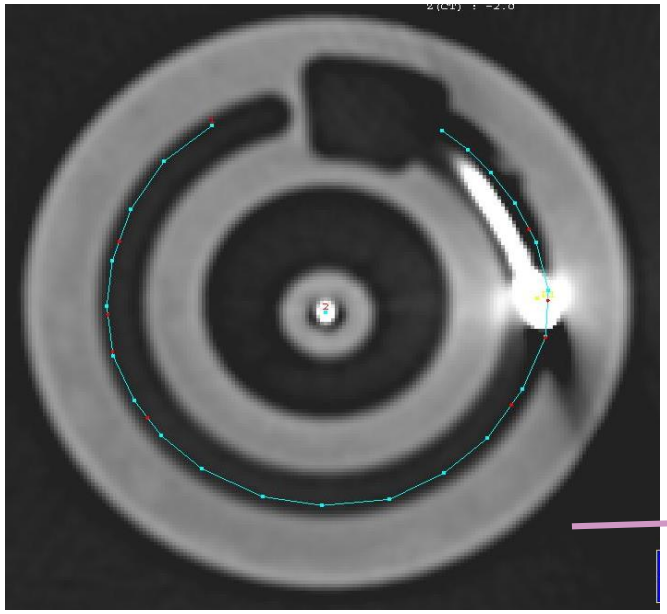
CT images of the ring with the source

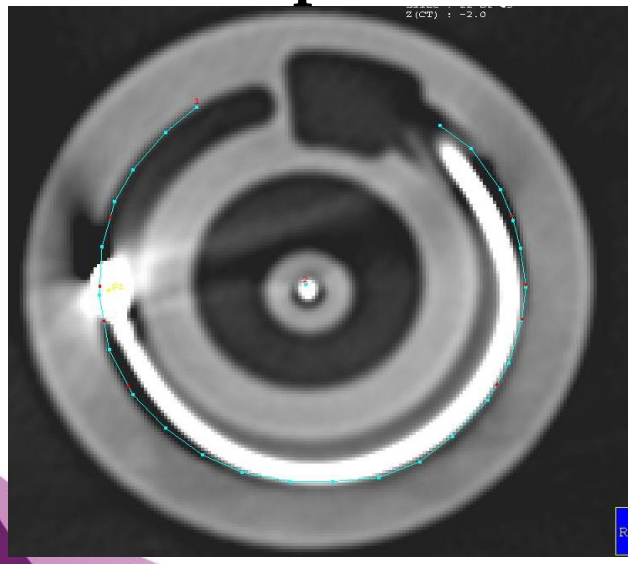
Dwell position 1

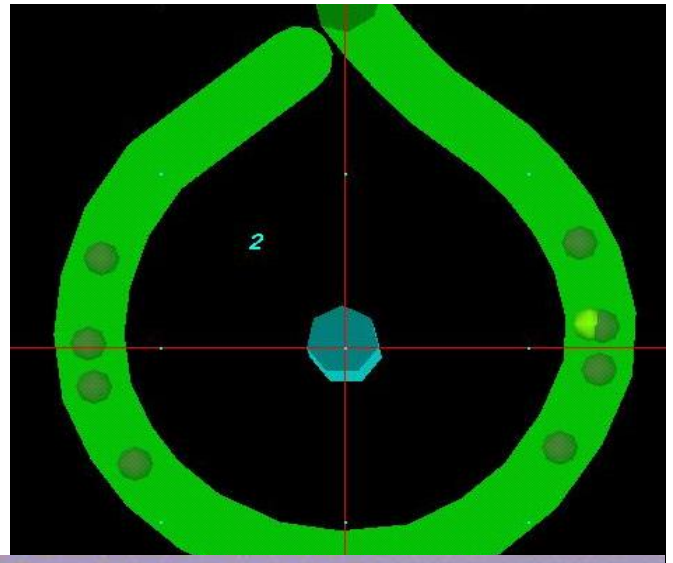


Dwell position 24



Dwell position 7

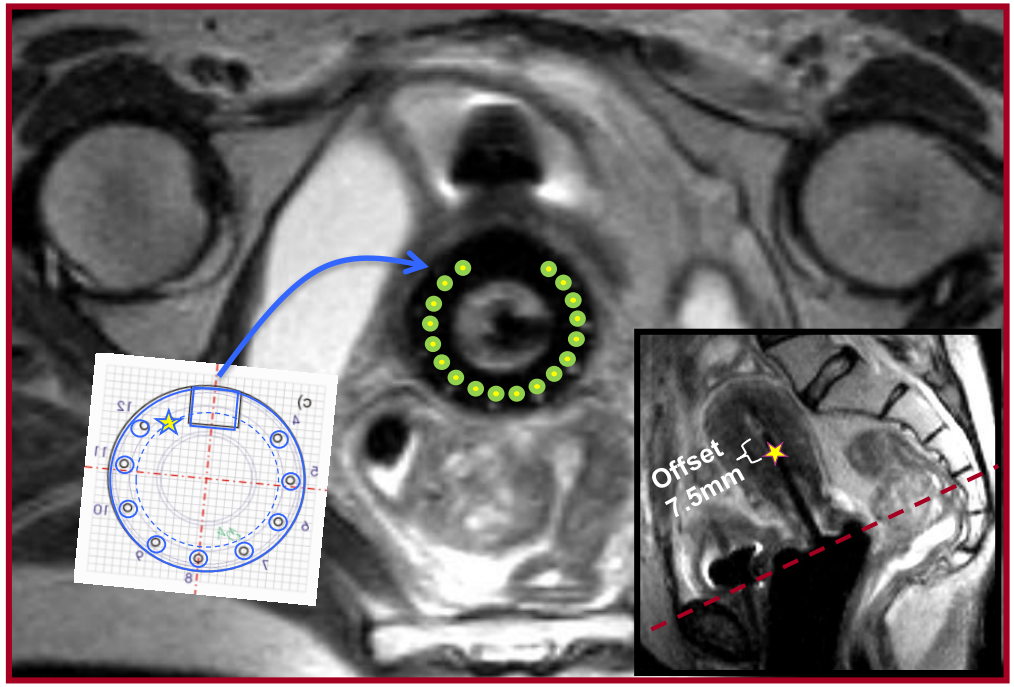


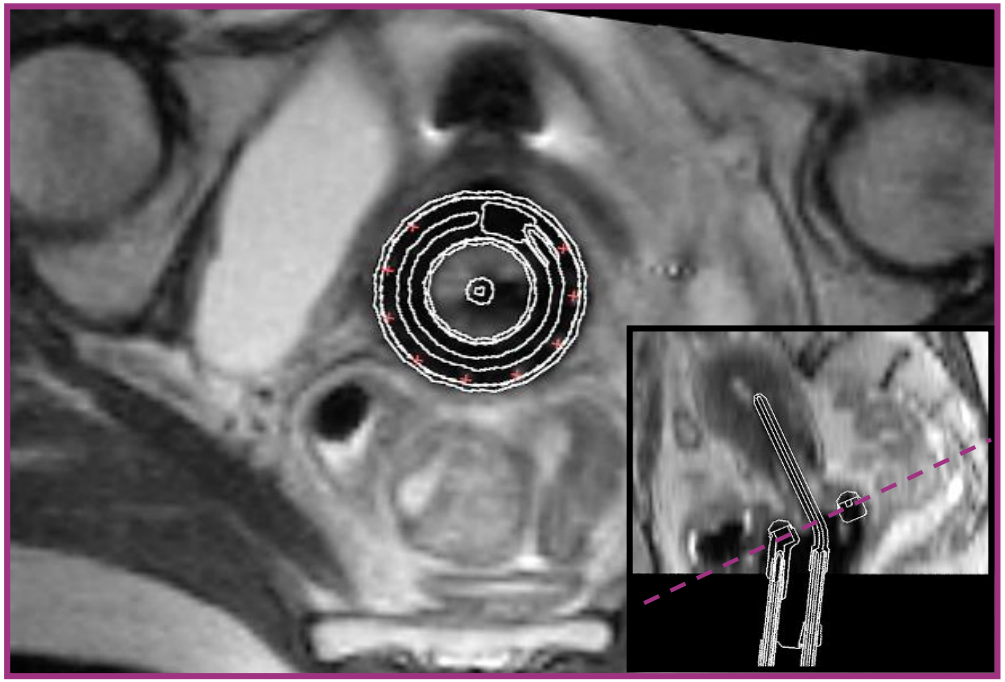


Hellebust et al, PMB 52 (2007)

Applicator reconstruction in 3D

1. manual in-direct source path recon
2. software integrated applicator recon.





5 – 10 min

less than 5 min

If the relation between applicator shape and the source path is defined once,
the reconstruction process can be performed by directly placing the applicator in the MRI dataset.

Slide courtesy: Daniel Berger, MUW

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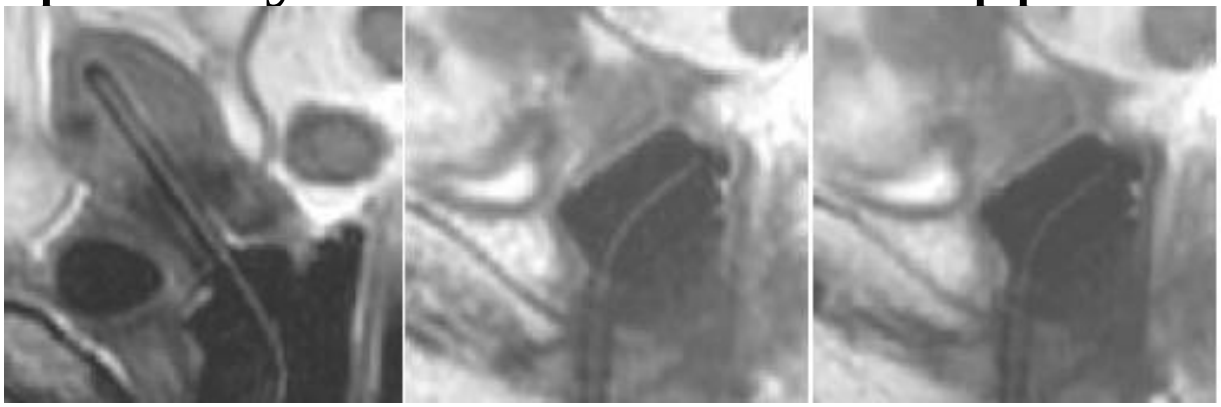
Direct Reconstruction

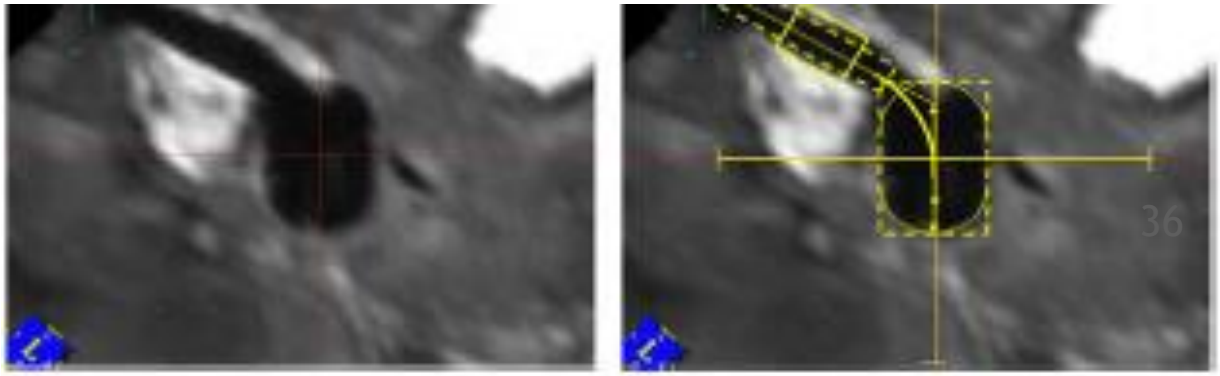
Clear visualization of the source channels in a single plane.

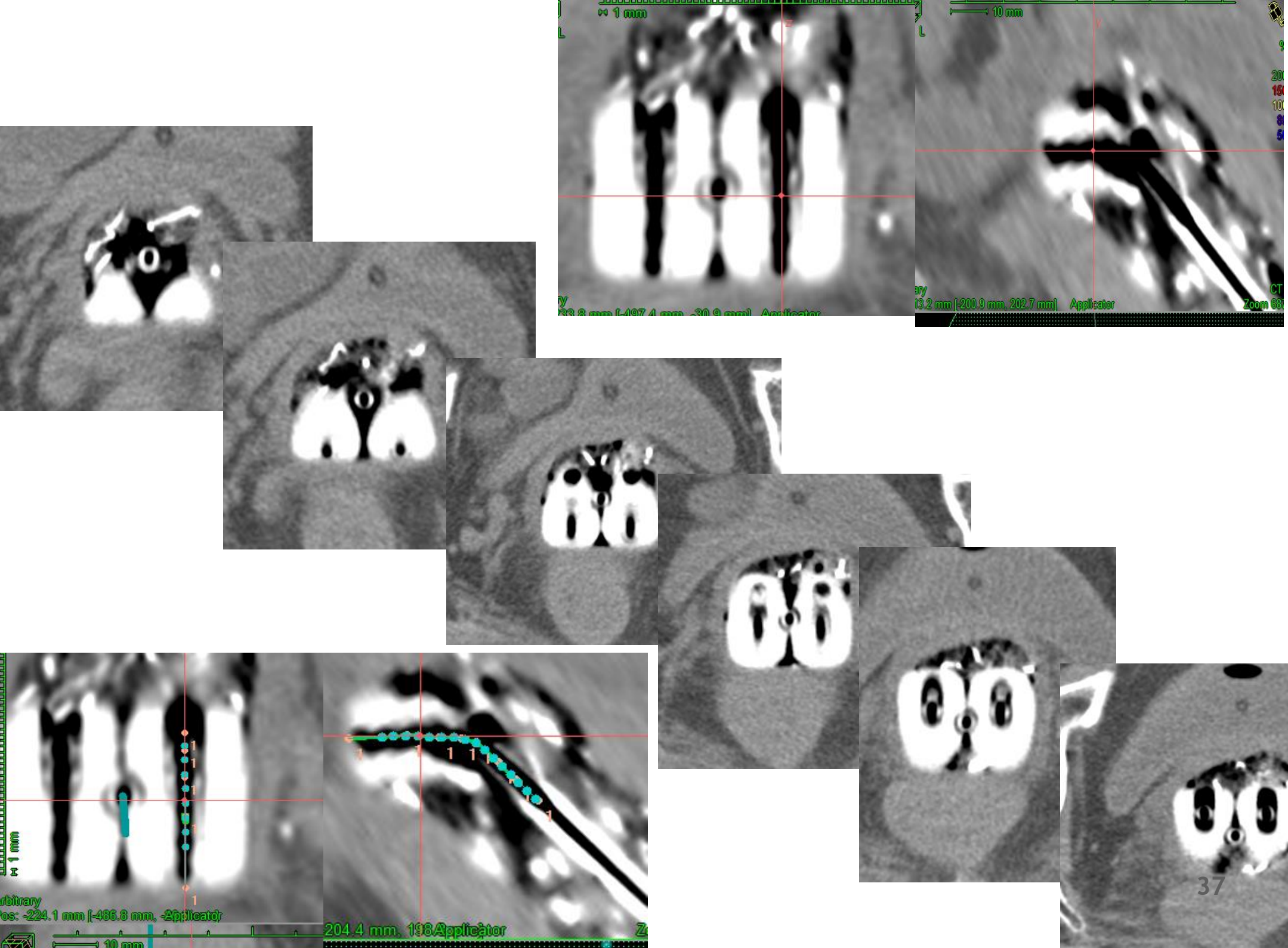
Check the geometry of the applicator verified during commissioning.

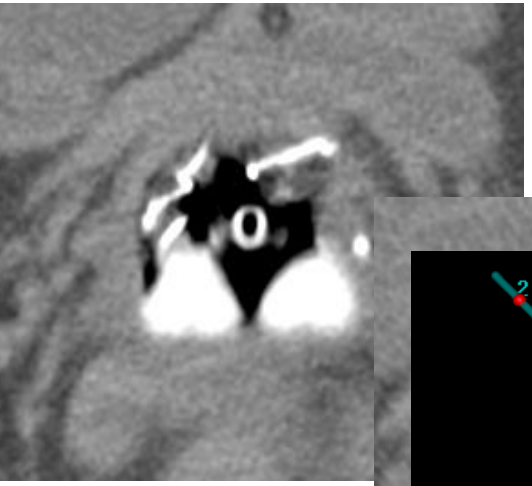
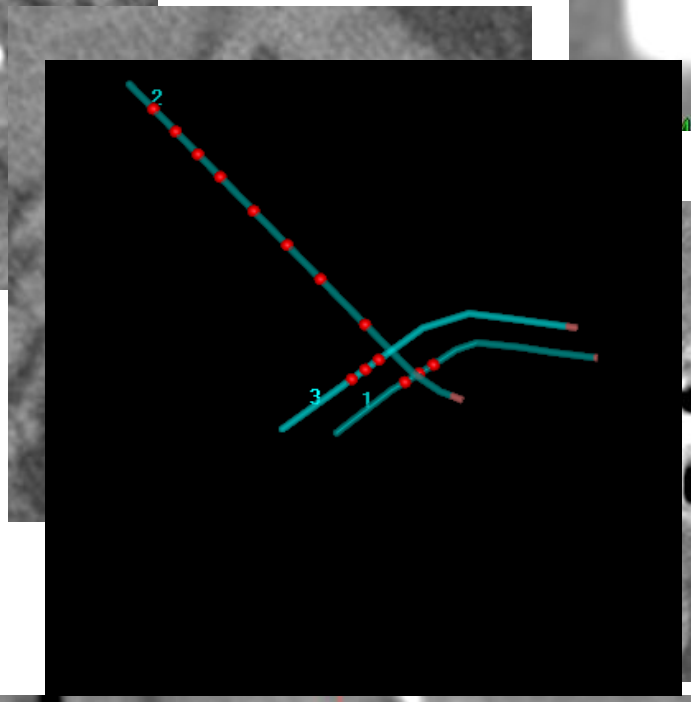
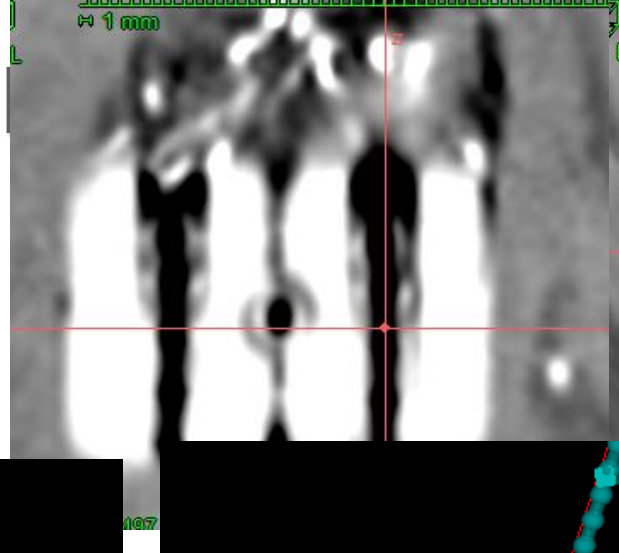
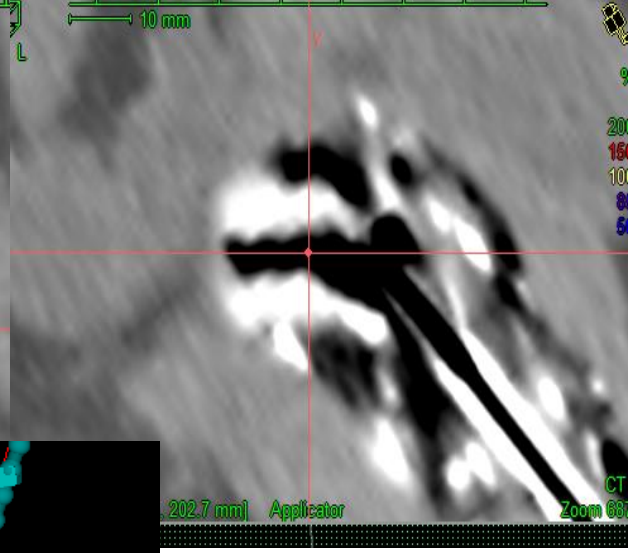
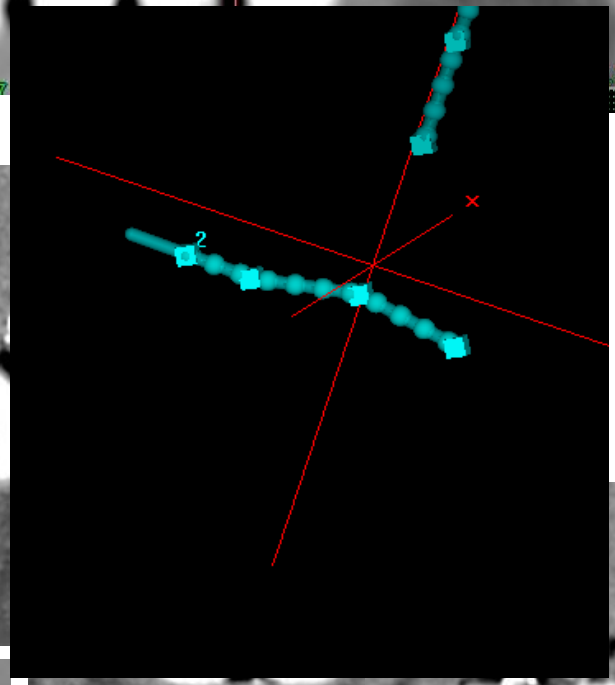
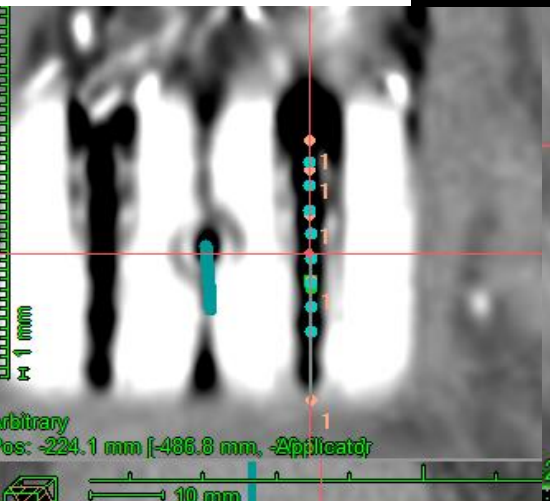
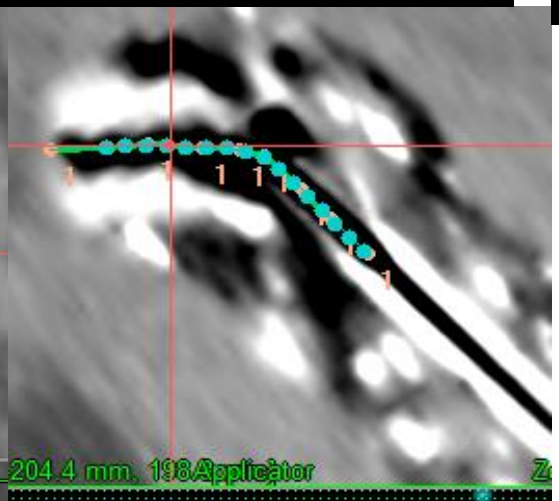
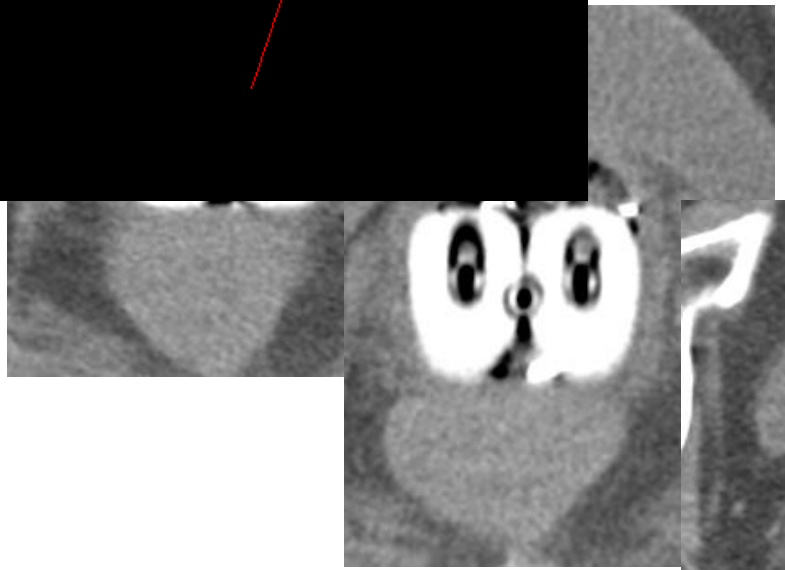
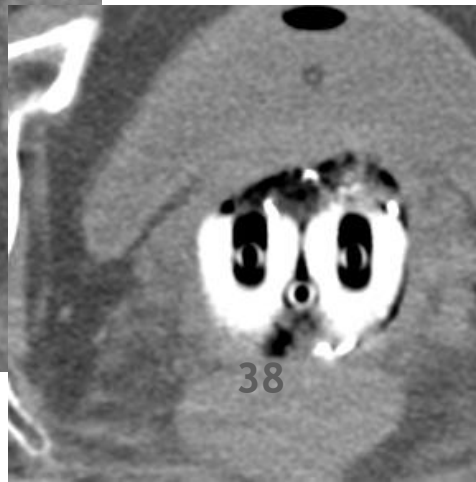
Especially useful for curved applicators (ovoid/ring)



Leeuw et al, RO,2009

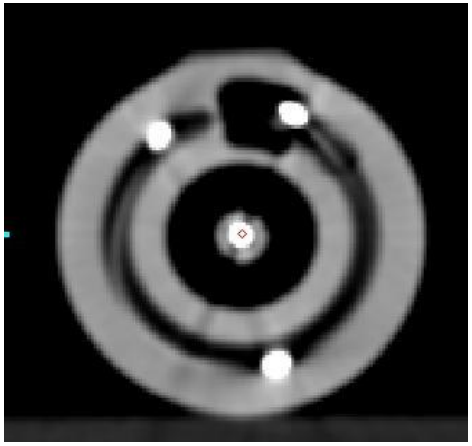


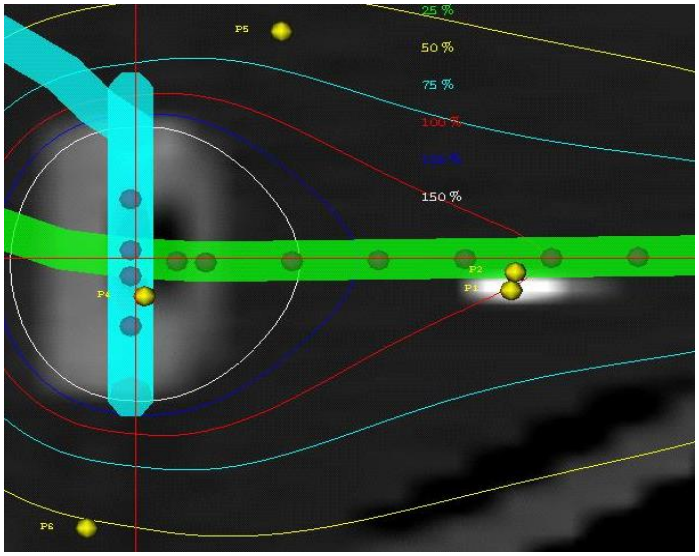

1 mm
10 mm
Applicator
Applicator
204.4 mm. 198 Applicator



2
3
1

1 mm

10 mm
202.7 mm] Applicator

2

1 mm
rbitrary
os: -224.1 mm [-486.8 mm, -Applicator

204.4 mm, 198 Applicator



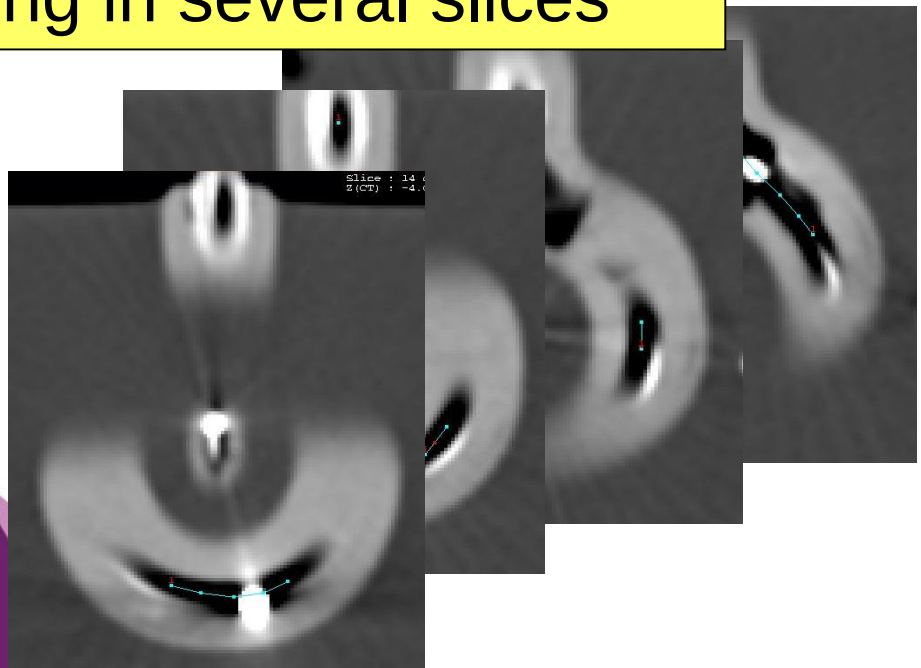
DR - Ring

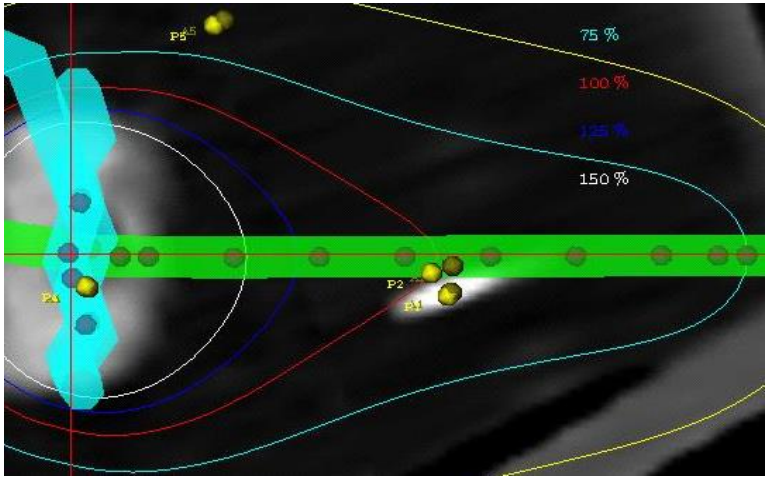
Ring in one slice





Ring in several slices





Ack: Hellebust

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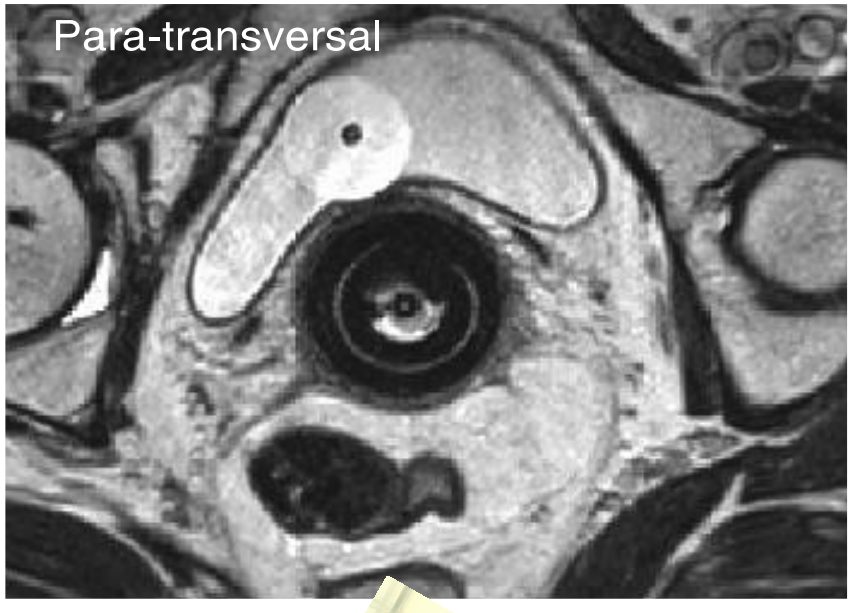
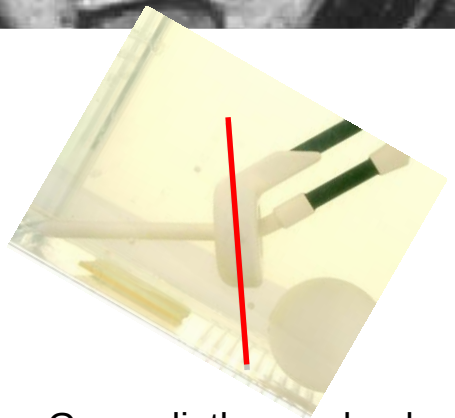
Orientation of the imaging sequence

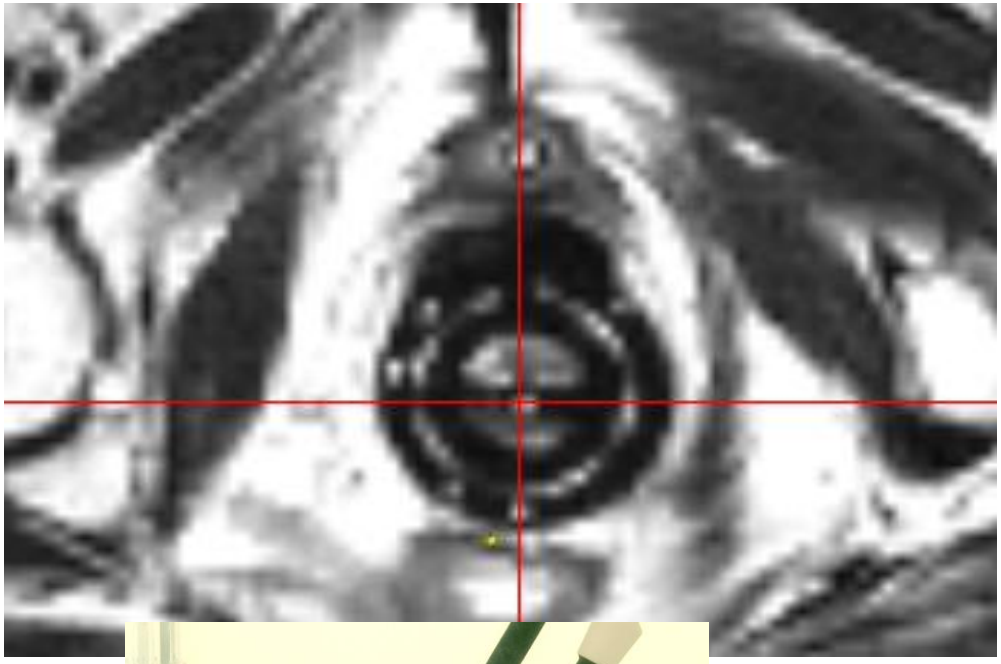
Para transverse

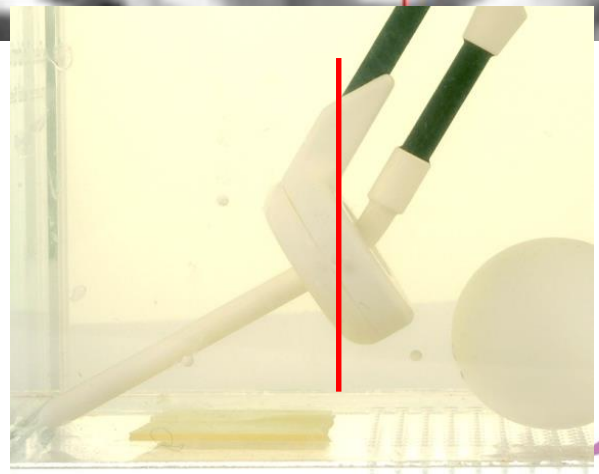




From Gyn radiotherapy book,
Editor: A viswanathan,
Kirisits C, Erickson B, Potter P

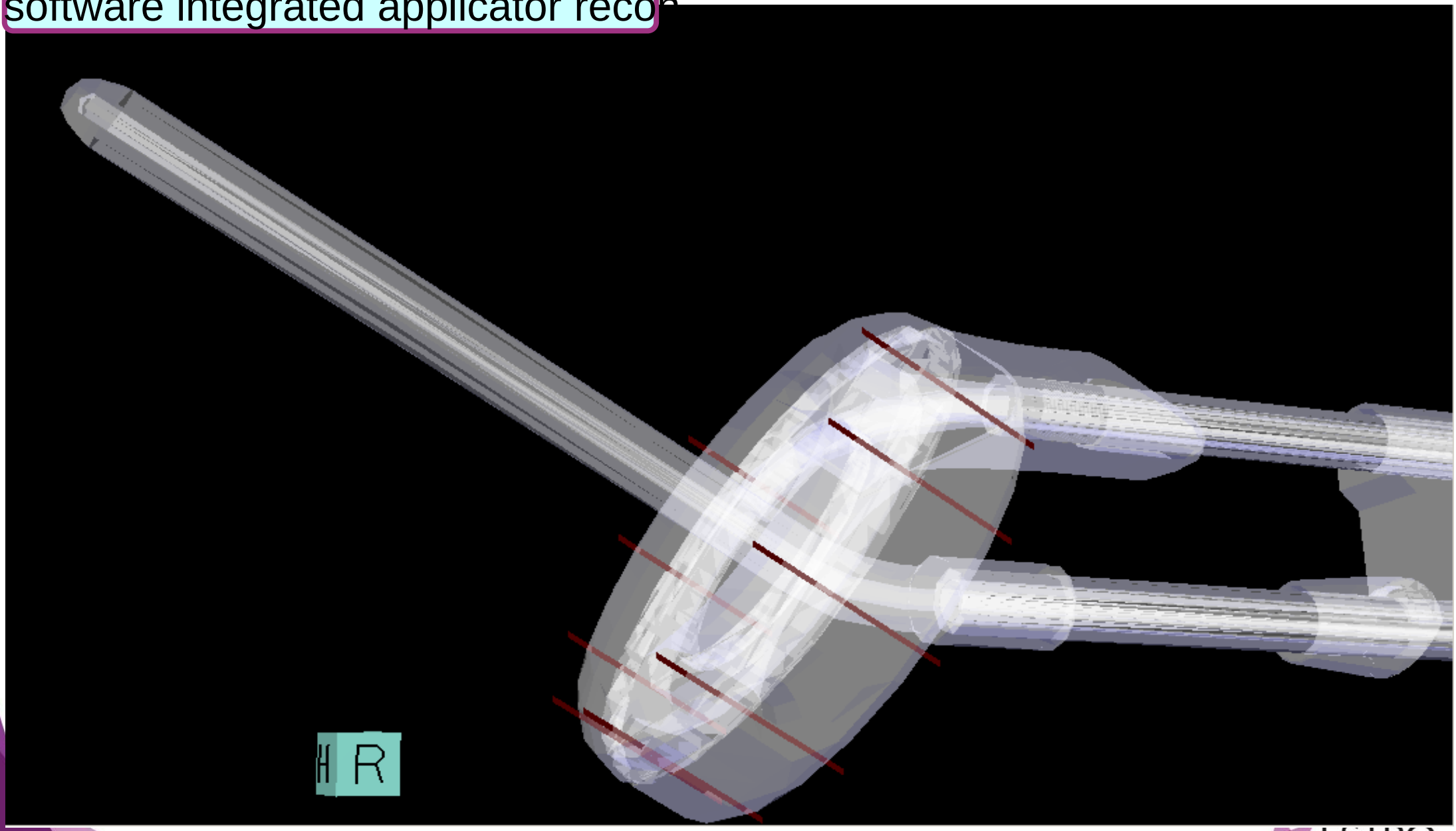
Transverse (MP Reconstructed)





Applicator surface

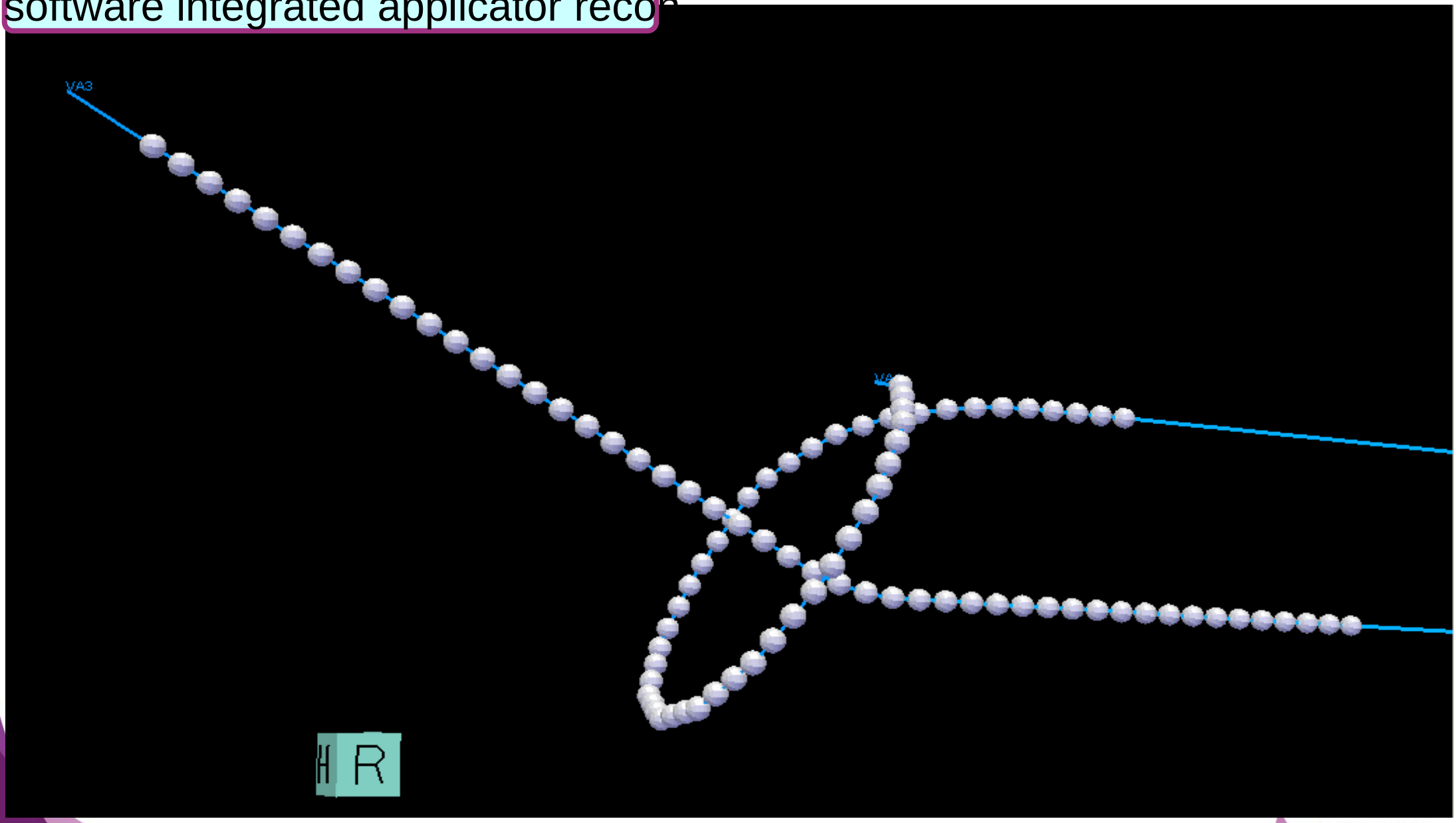
2. software integrated applicator reco



Slide courtesy: Daniel Berger, MUW

Source path

2.software integrated applicator reco



Slide courtesy: Daniel Berger, MUW

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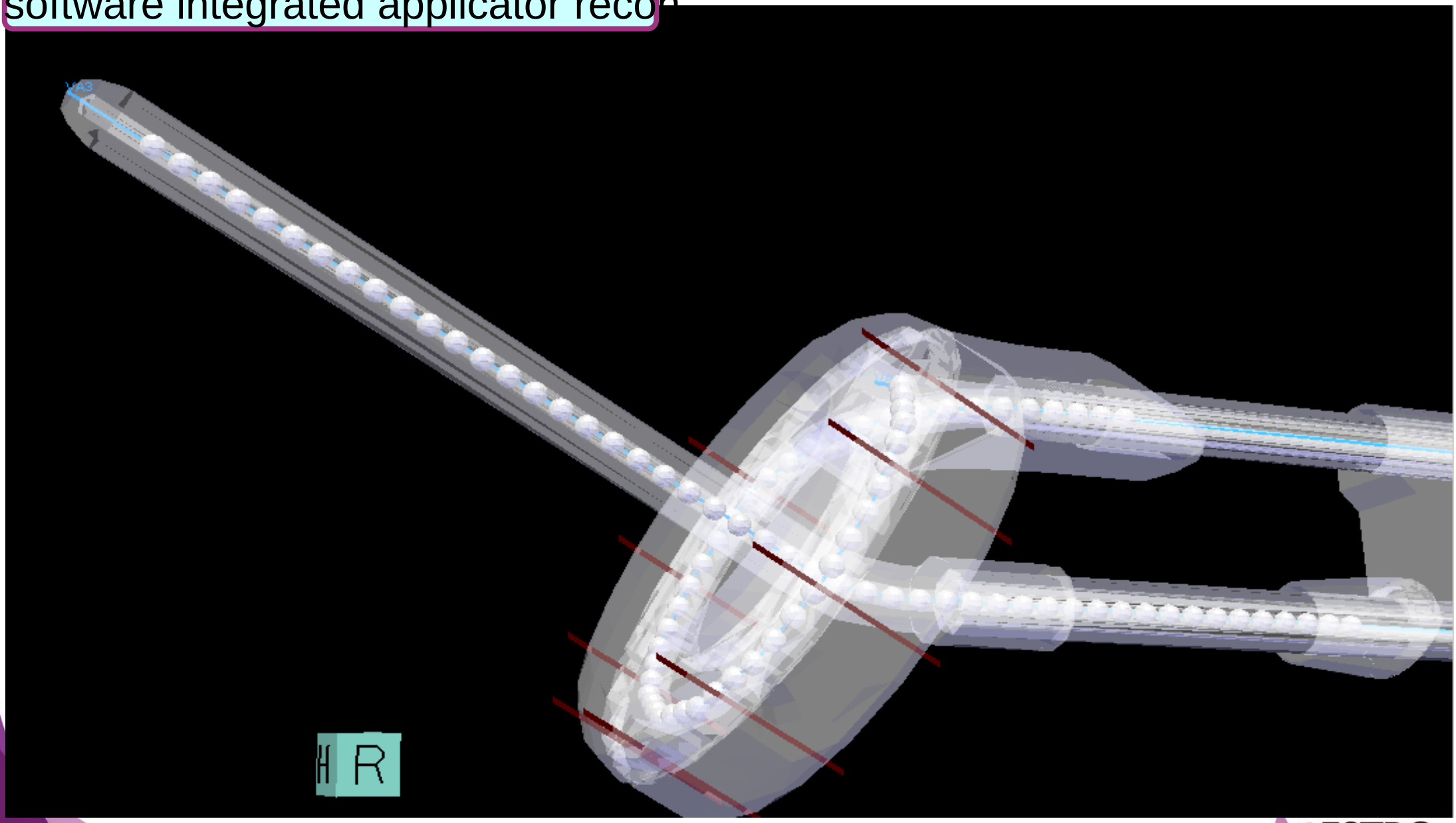
Applicator + Source path

2. software integrated applicator recon



Slide courtesy: Daniel Berger, MUW

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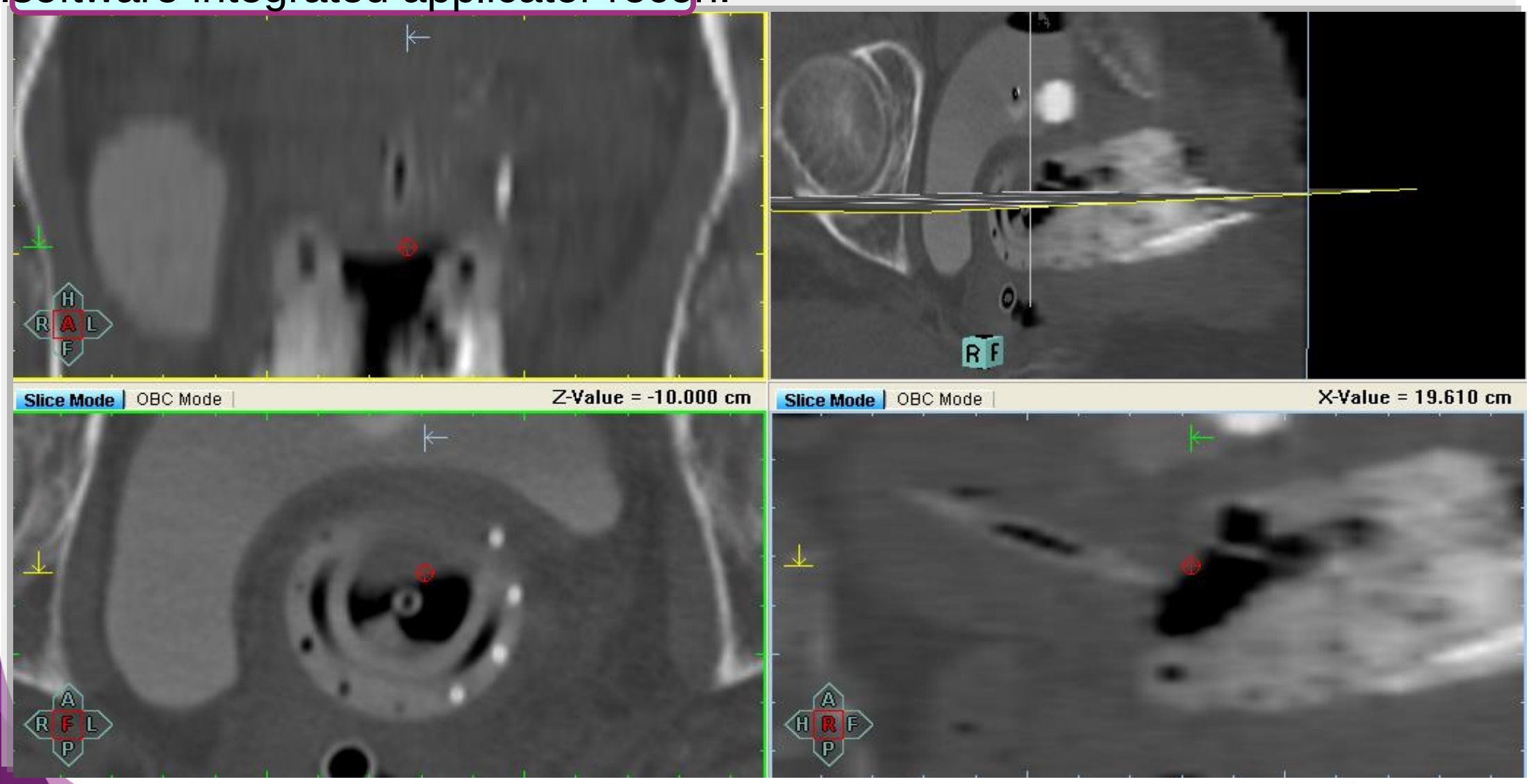
Reconstruction

2. software integrated applicator recon.



Slide courtesy: Daniel Berger, MUW

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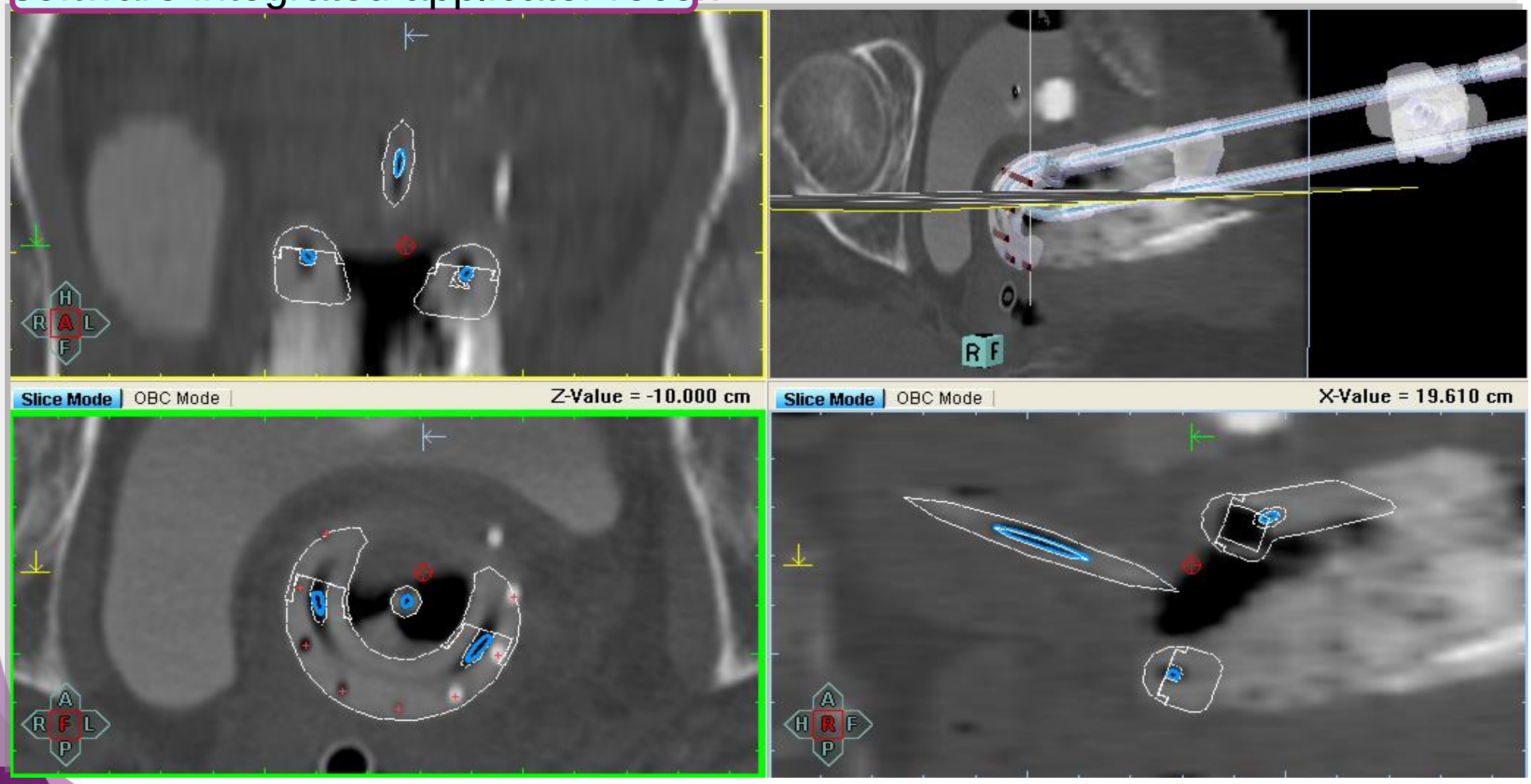
Reconstruction

2. software integrated applicator recon.



Better accuracy less time to reconstruct

Slide courtesy: Daniel Berger, MUW

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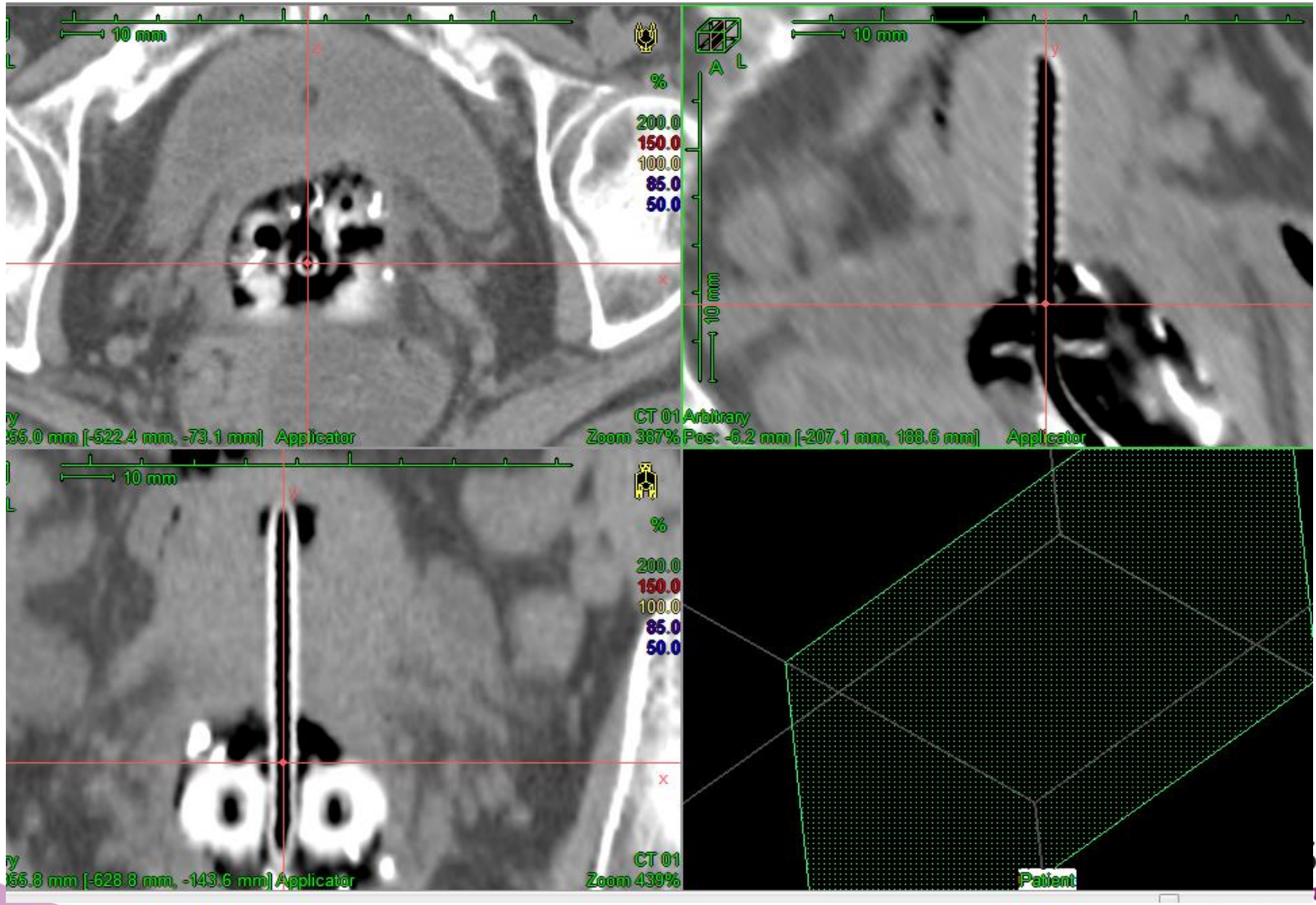
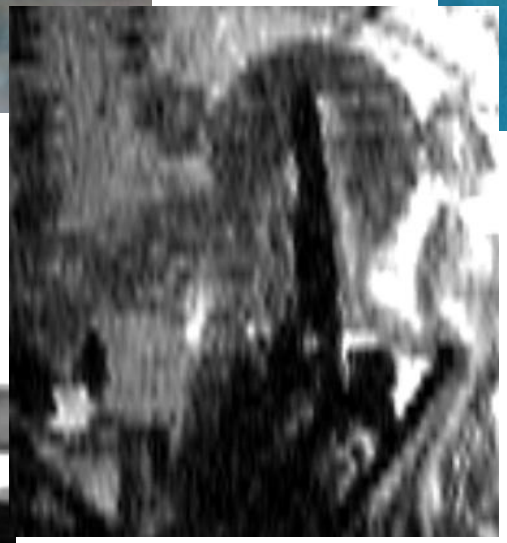
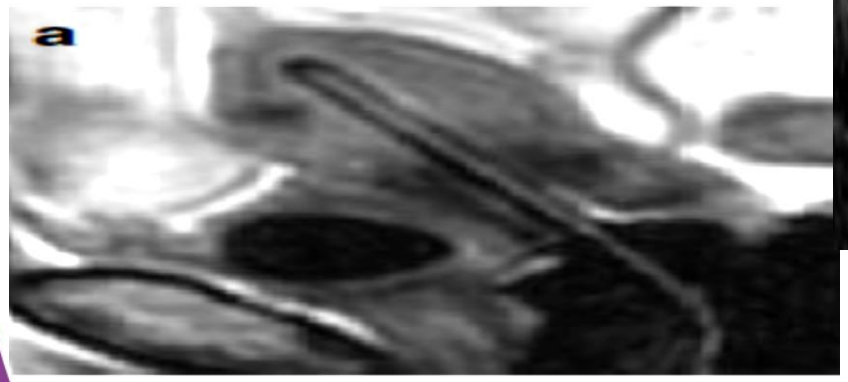
Applicator reconstruction using CT images

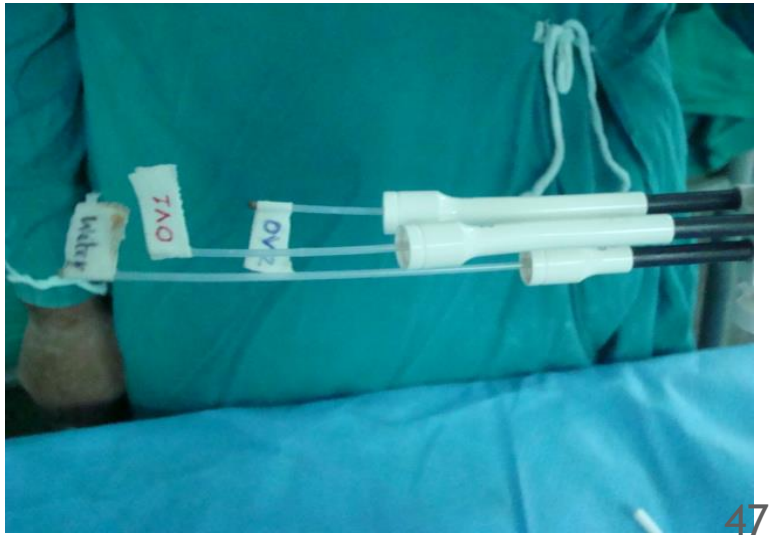


Applicator reconstruction using MR images

Markers: water filled 6F catheters





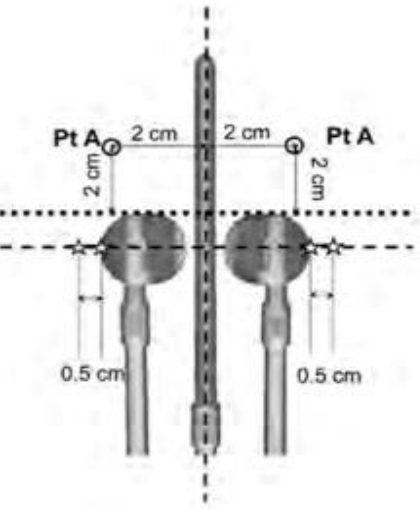


ICRU 89 Reference points

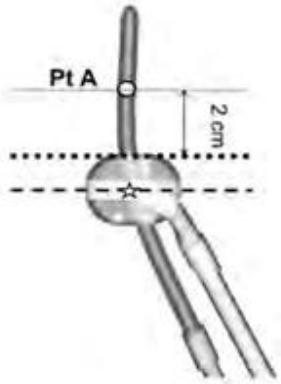
- Point A
- ICRU Bladder
- ICRU Recto Vaginal
- PIBS
- Vaginal points

Point A - Tandem/Ovoid

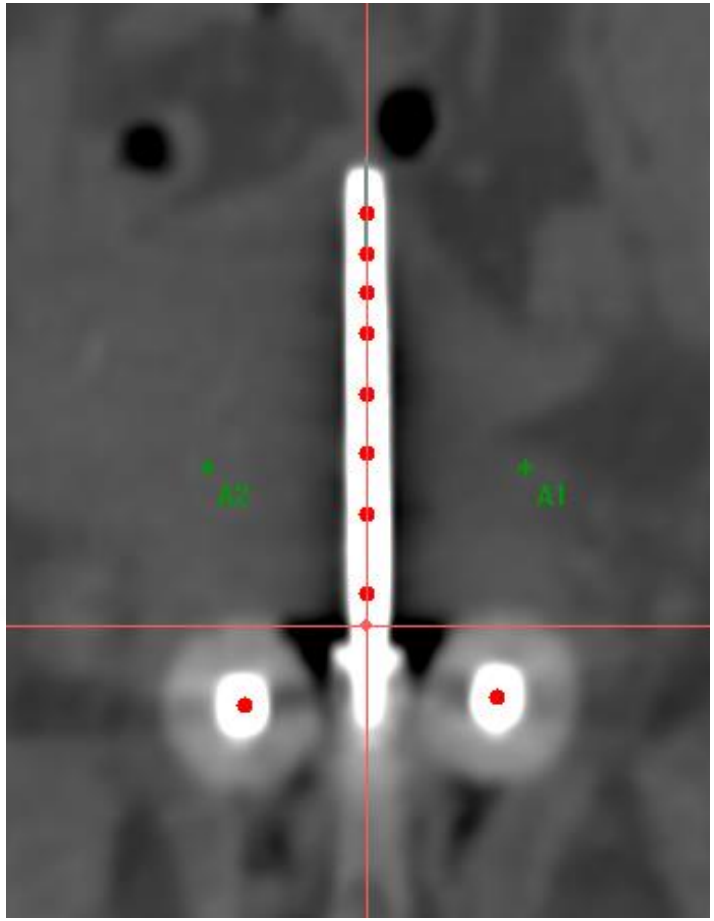
- 2cm lateral to the center of uterine canal and 2 cm above from the mucosa of the lateral fornix

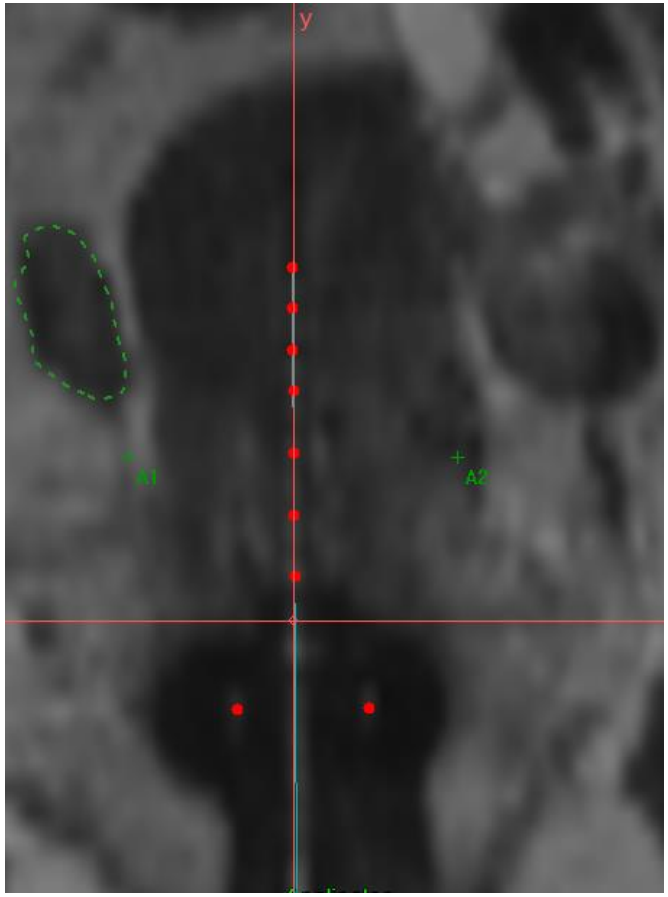


coronal

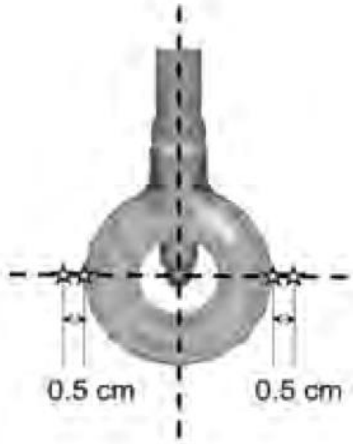


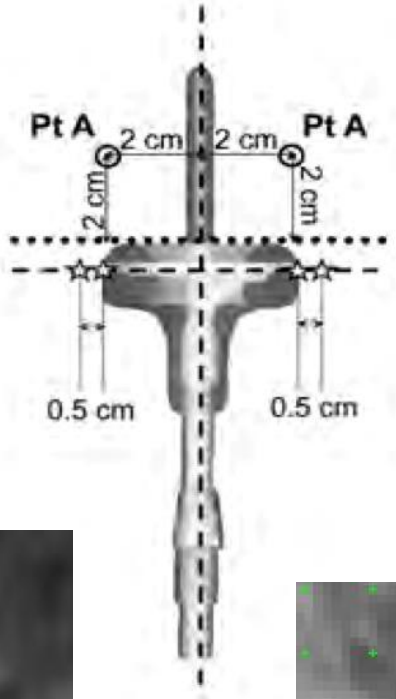
sagittal

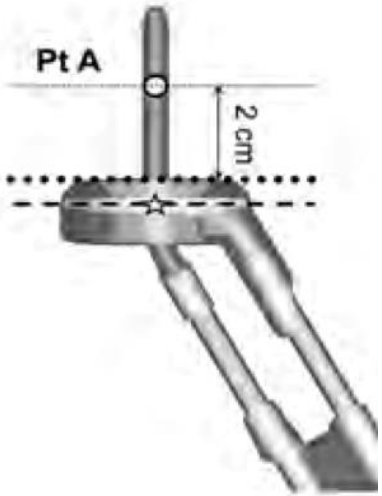


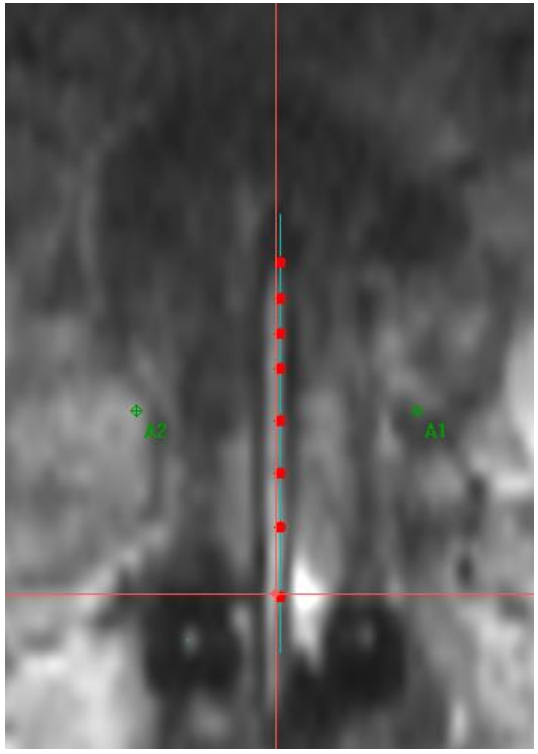


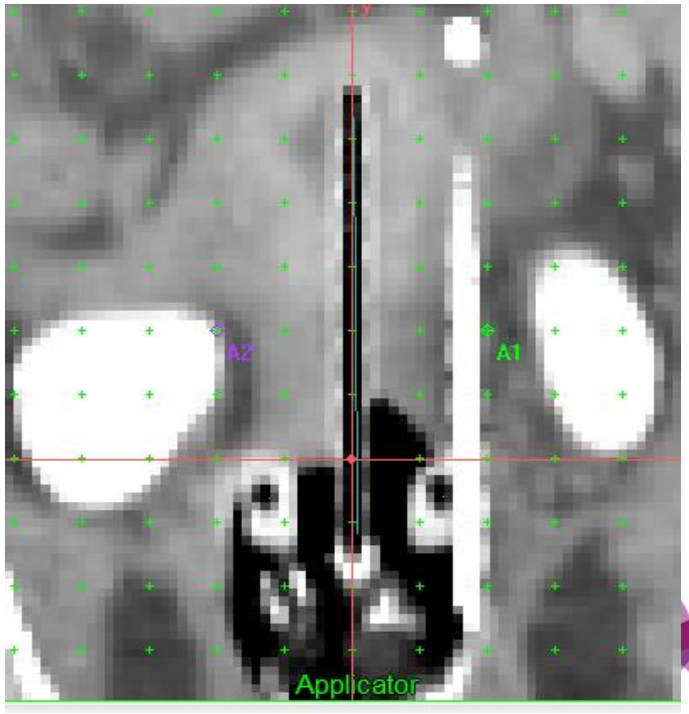
Point A - Tandem/Ring



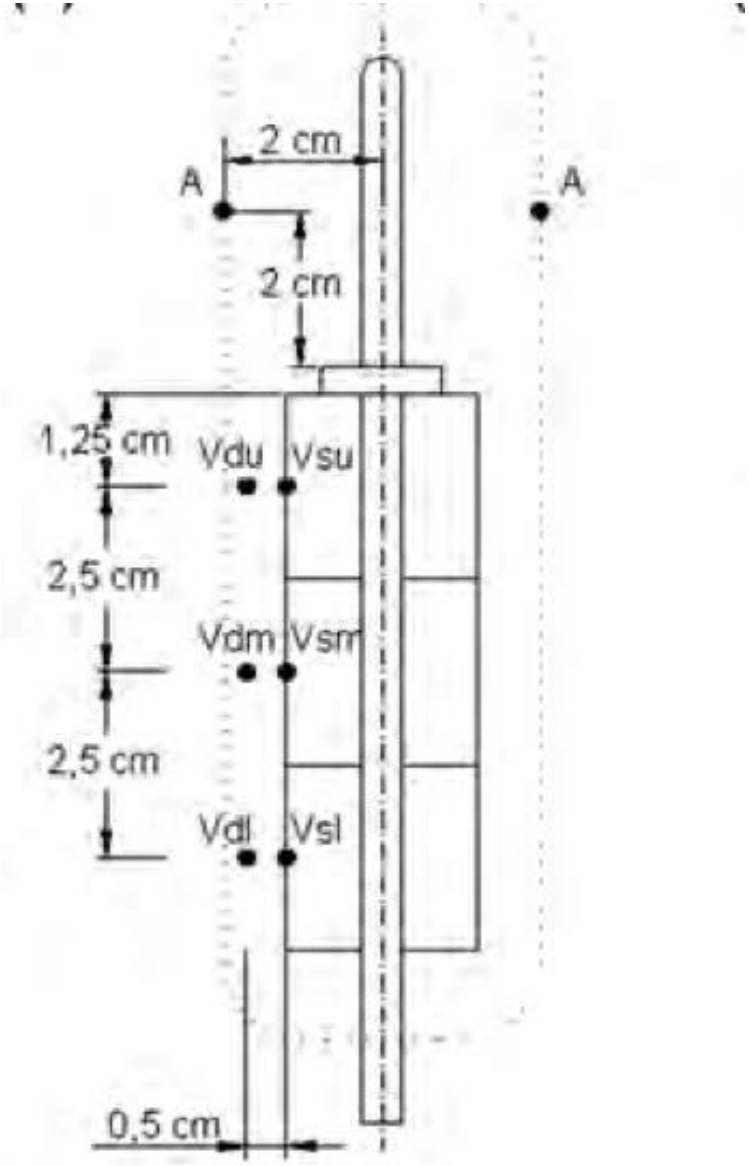


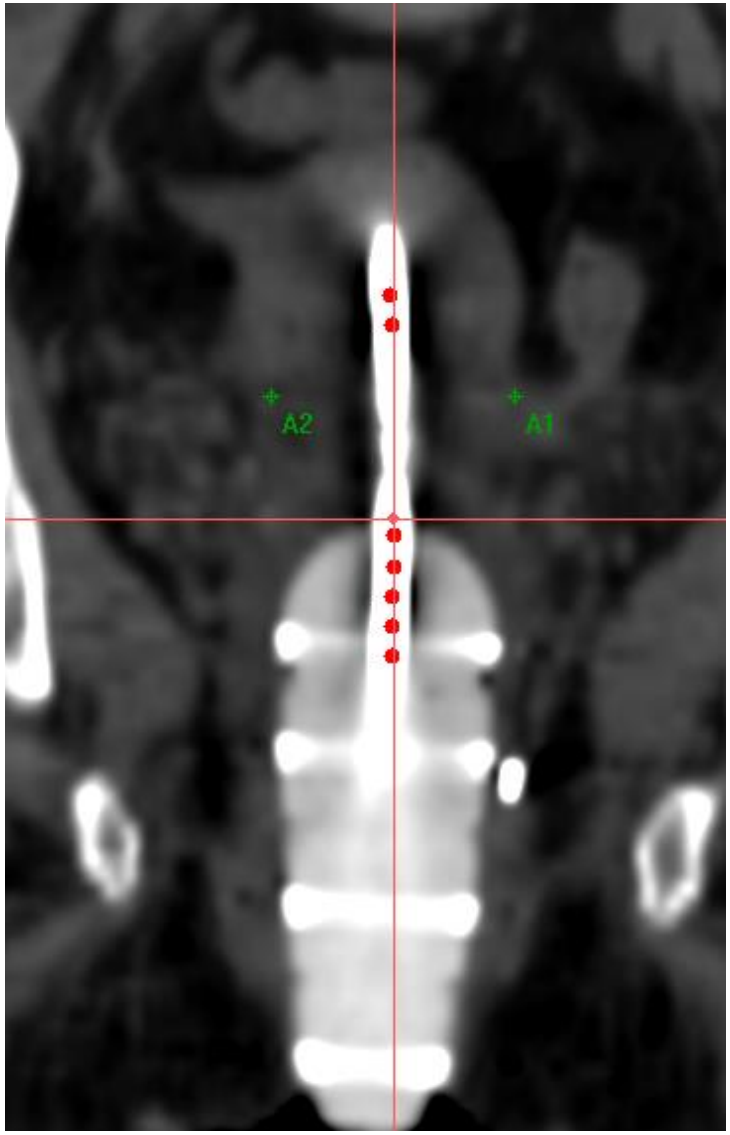




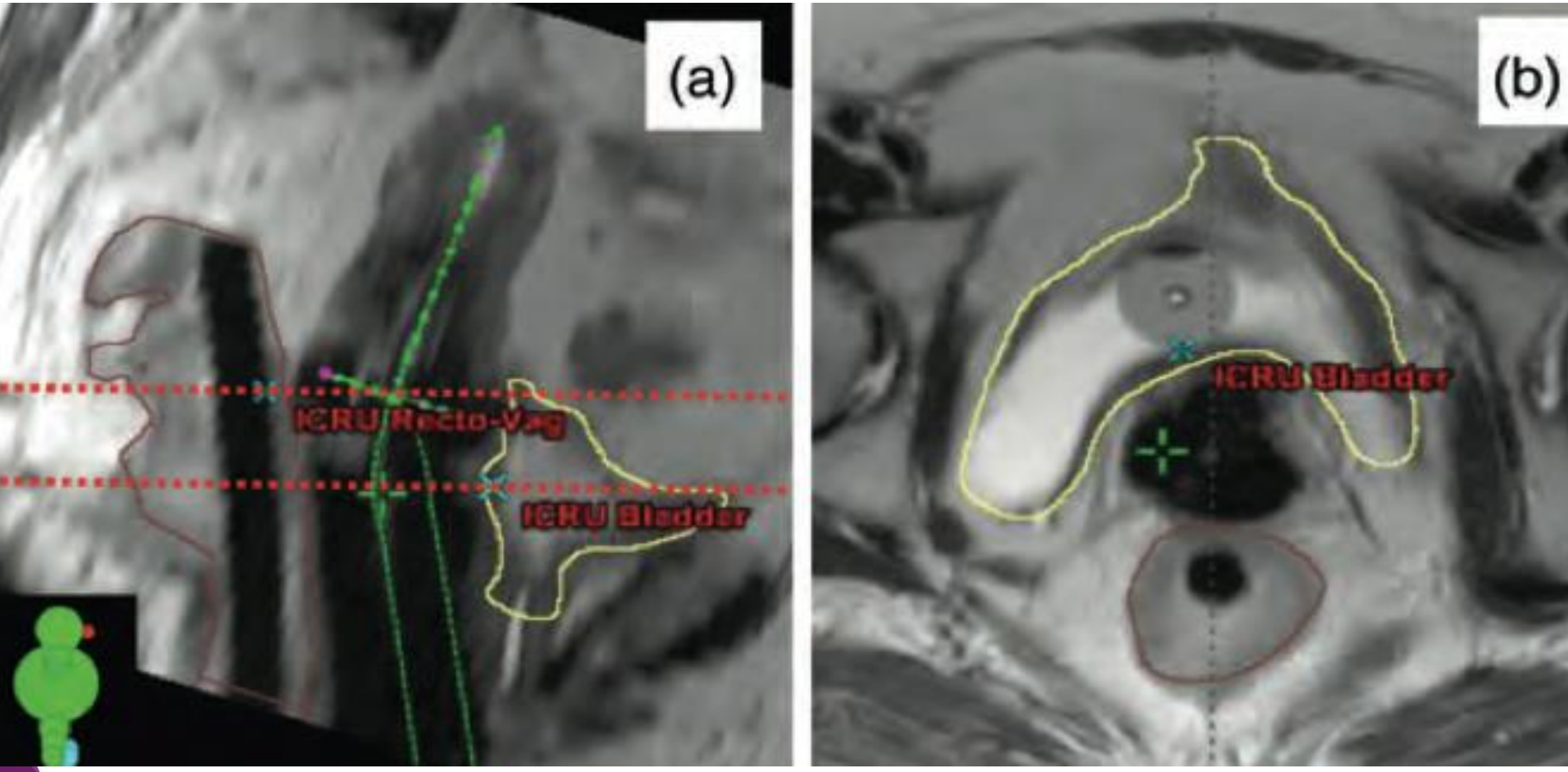


Point A – Vaginal cylinder & tandem



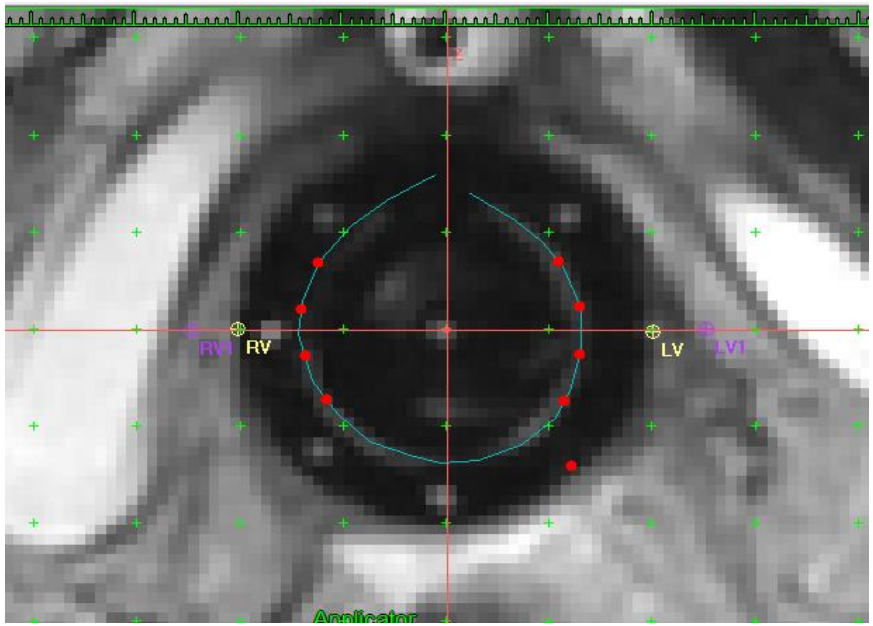


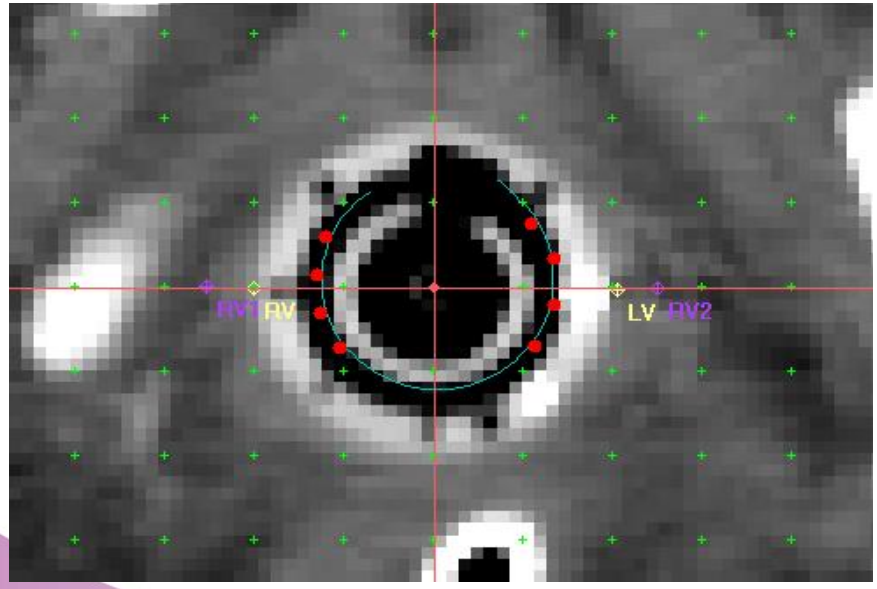
ICRU 89 Bladder and recto vaginal point

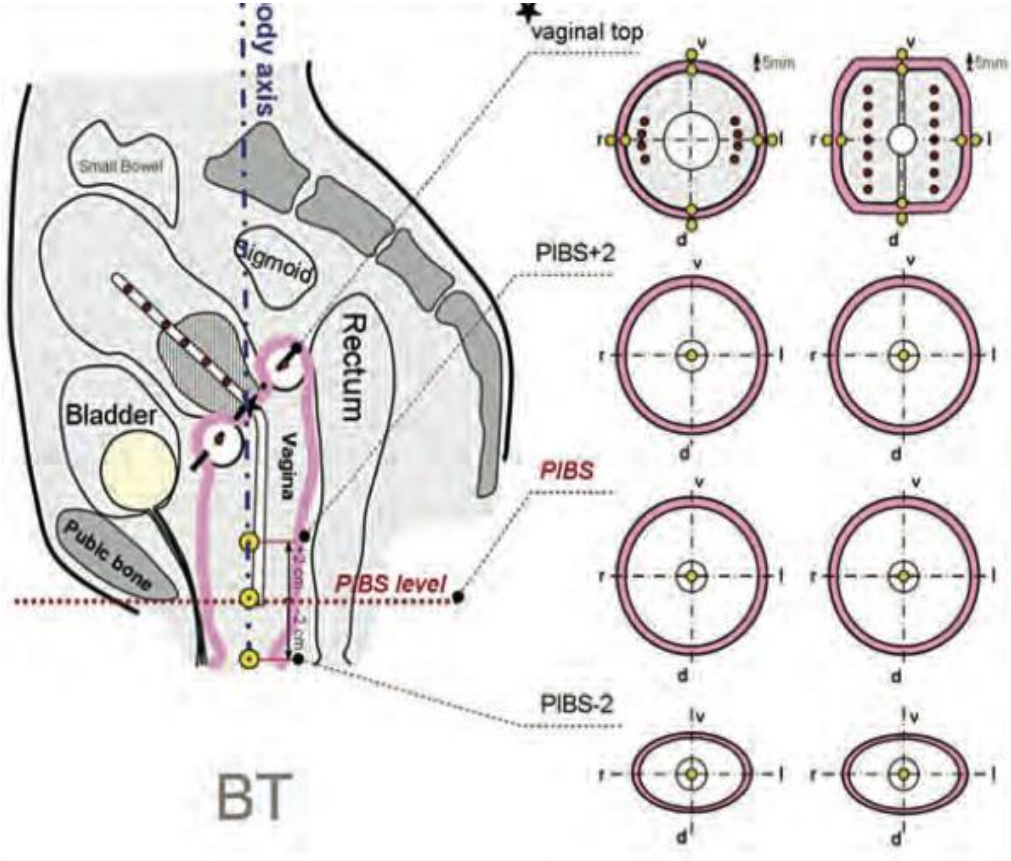


ICRU 89

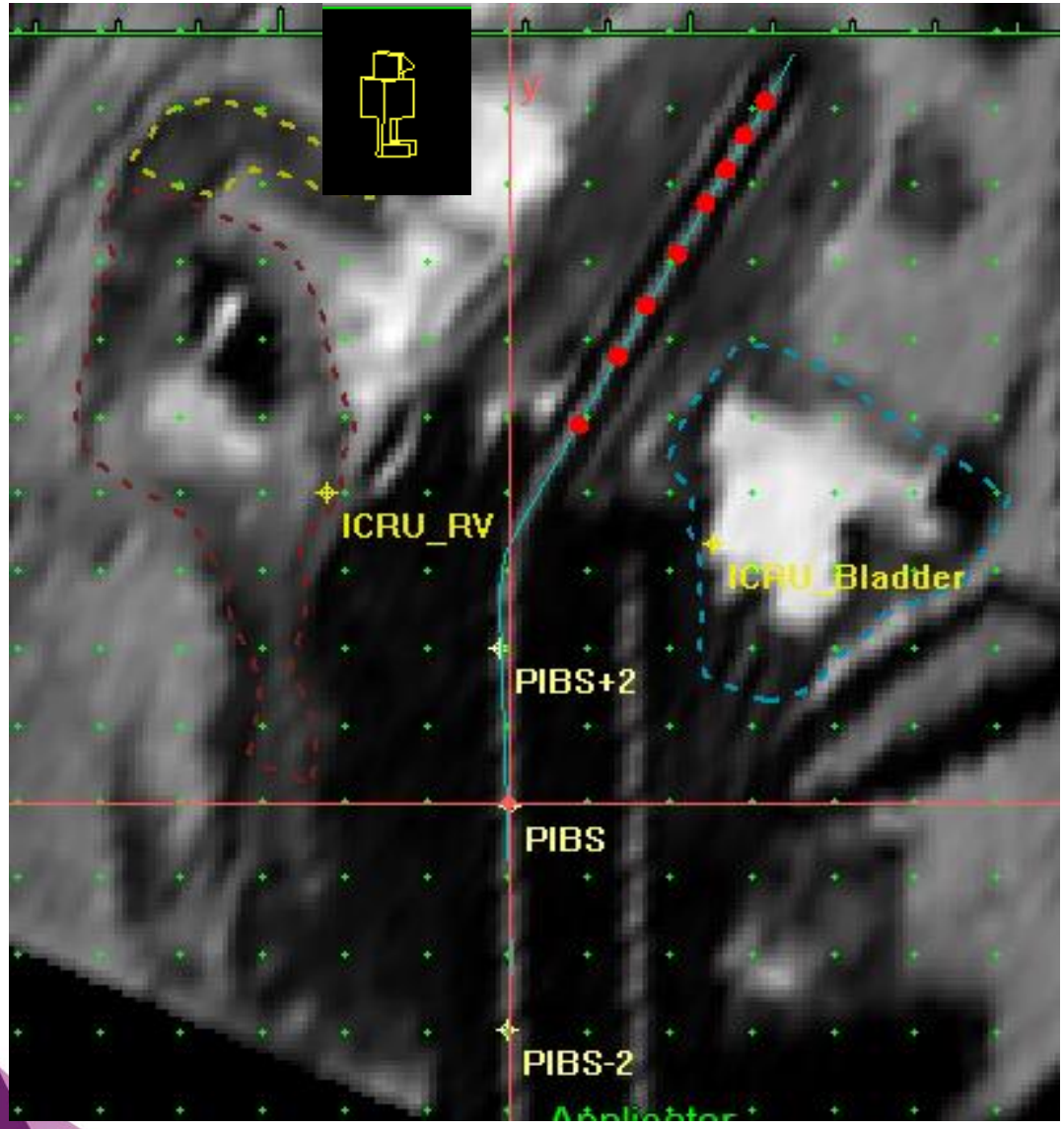
Vaginal points

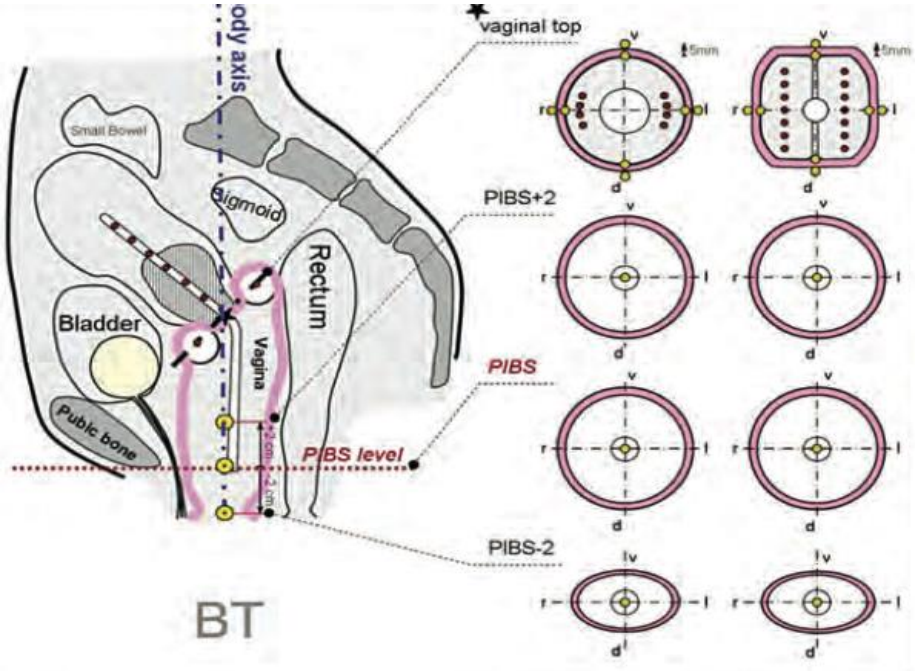


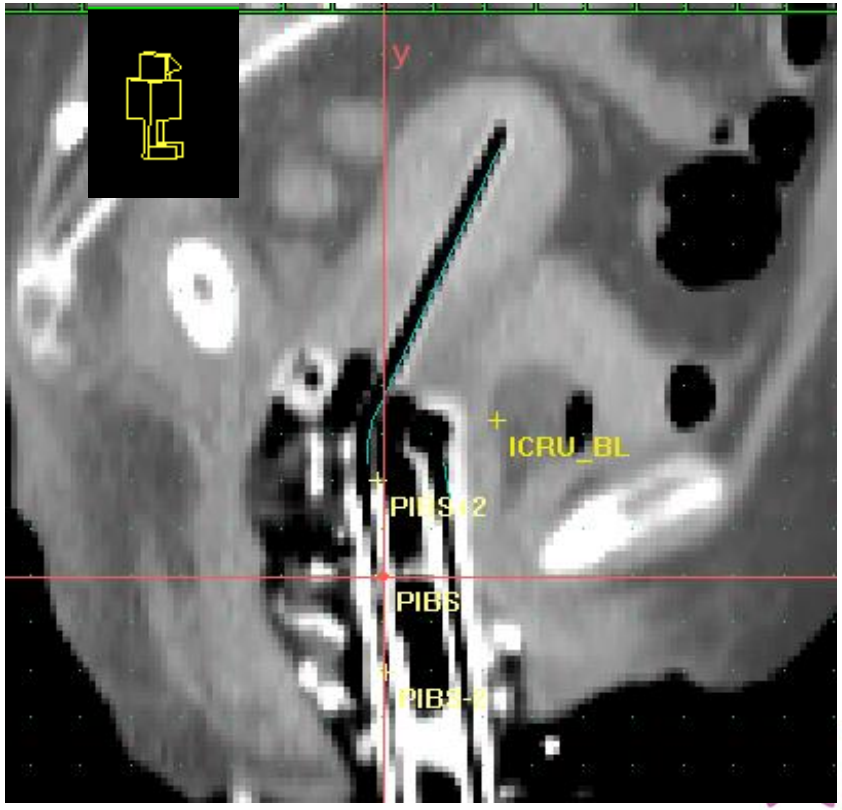




PIBS

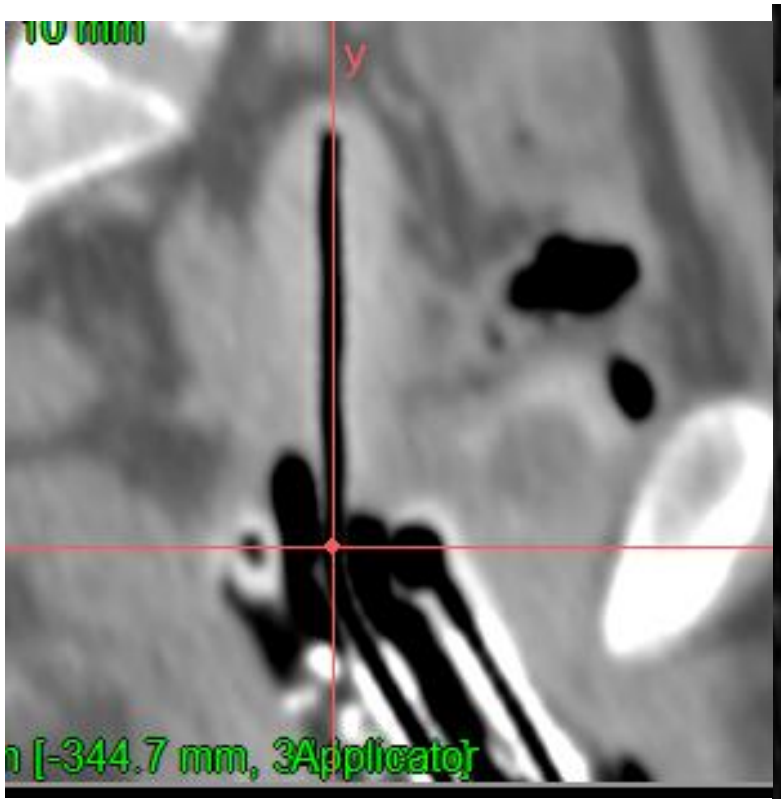

ICRU_RV
ICRU_Bladder
PIBS+2
PIBS
PIBS-2

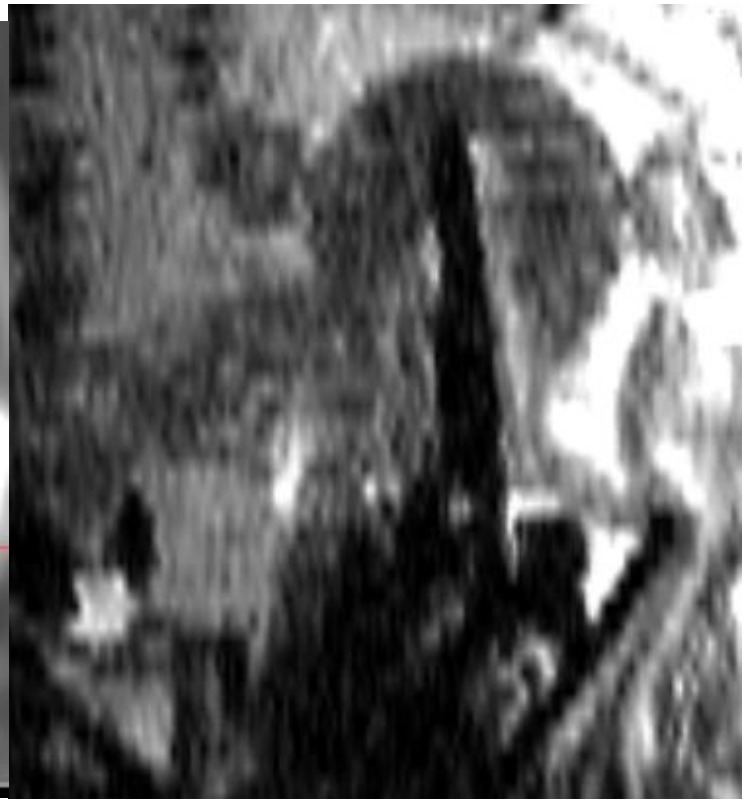

body axis
vaginal top
Small Bowel
Sigmoid
Rectum
Bladder
Vagina
Public bone
PIBS+2
PIBS
PIBS level
PIBS-2
BT

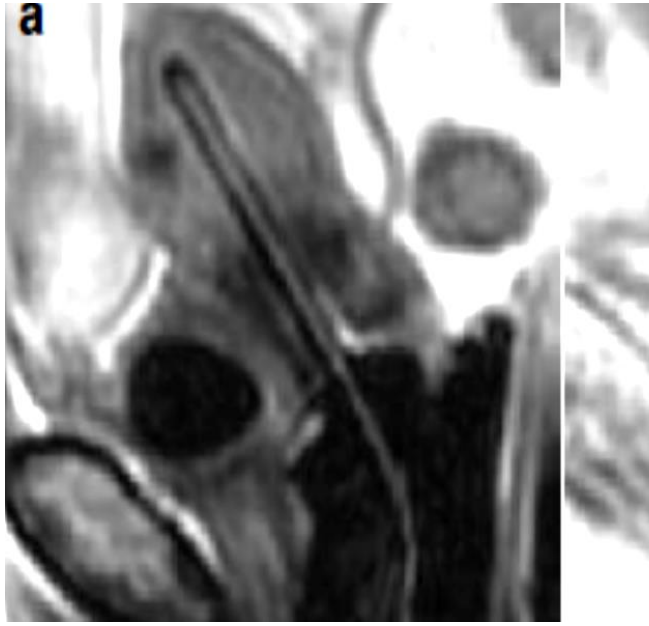

ICRU_BL
PIBS+2
PIBS
PIBS-2

Role of Registration in applicator reconstruction

Role of registration: applicator Reconstruction





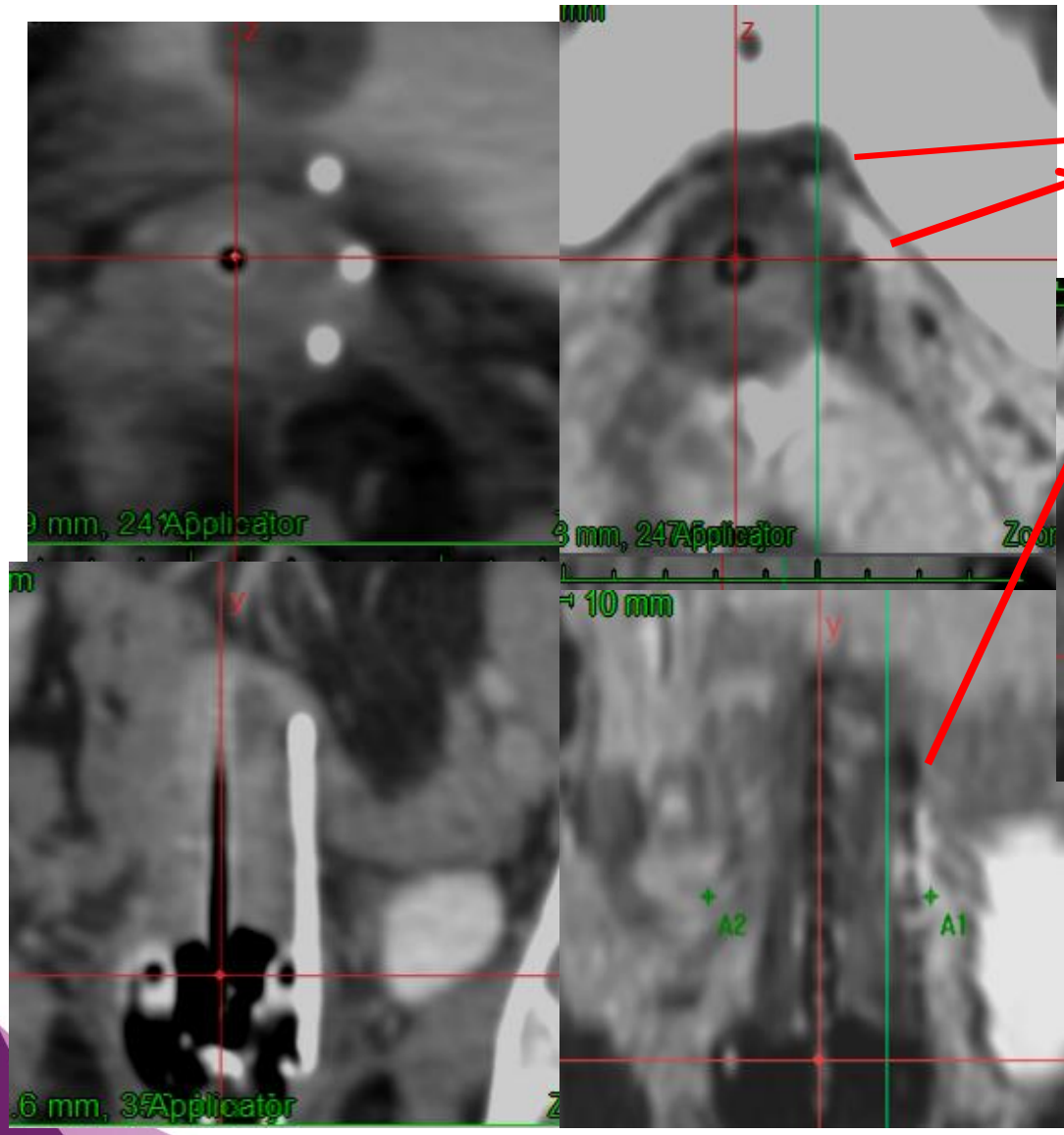


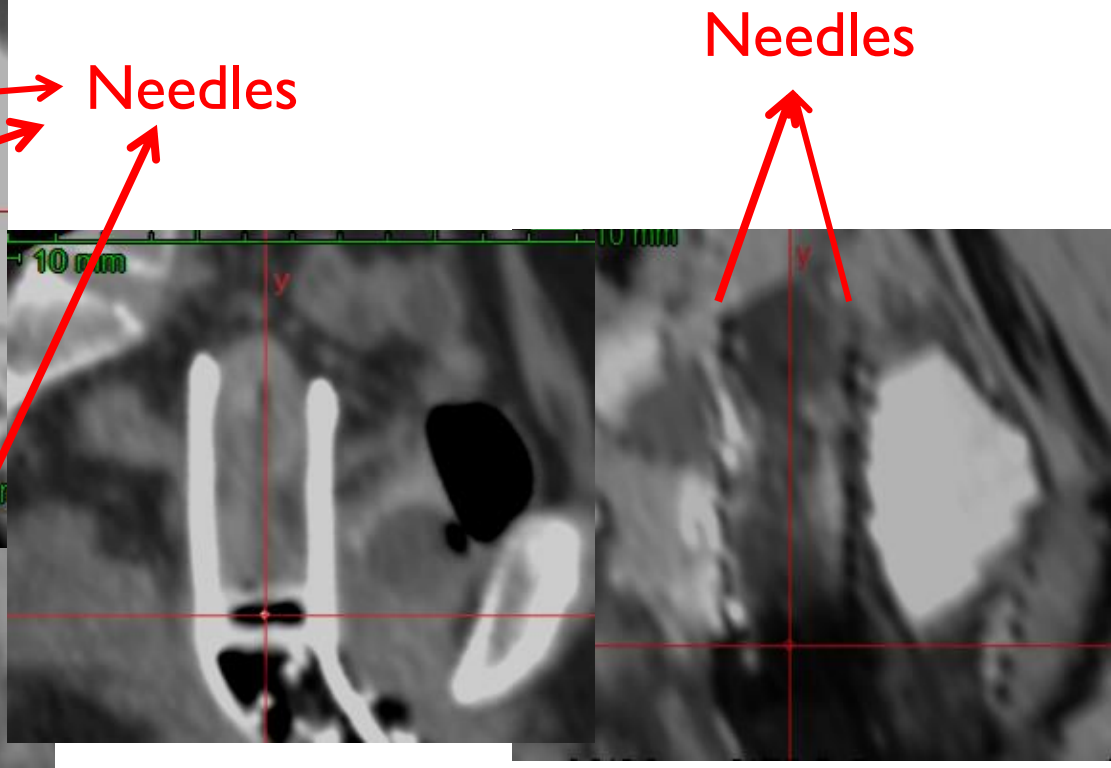
CT – No marker

MR – No marker

MR – Water marker

Needle reconstruction (CT vs MR)

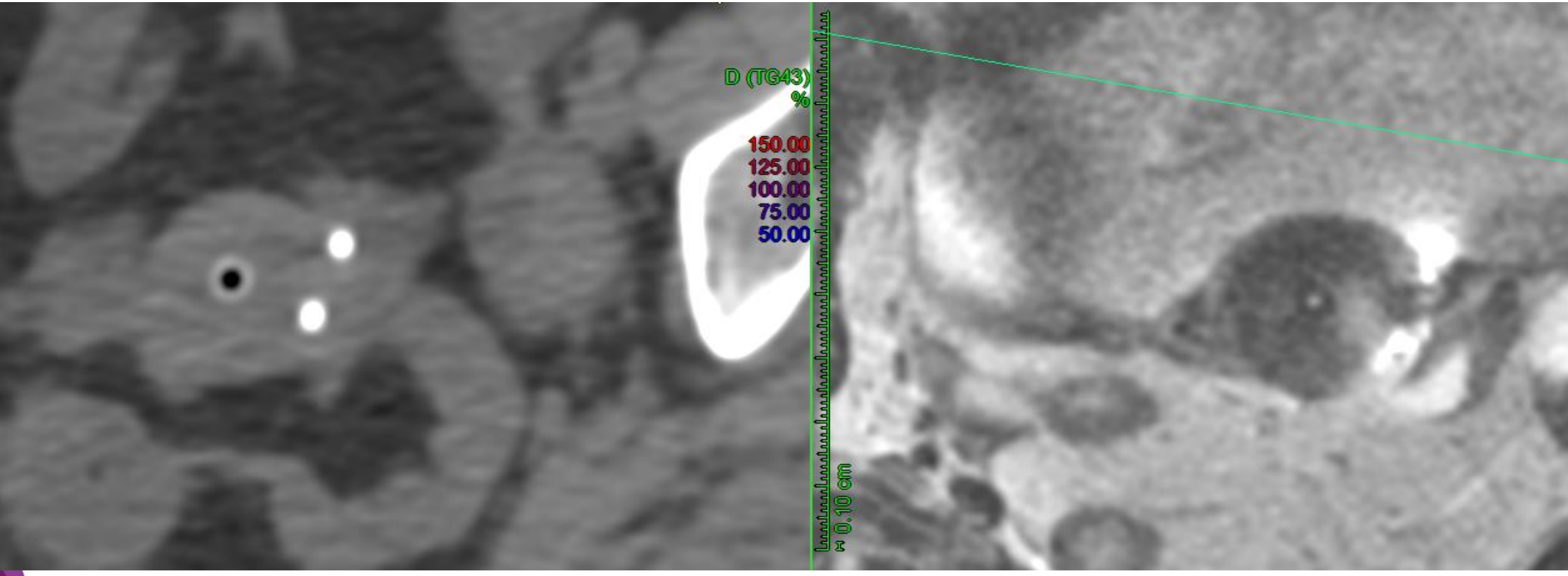




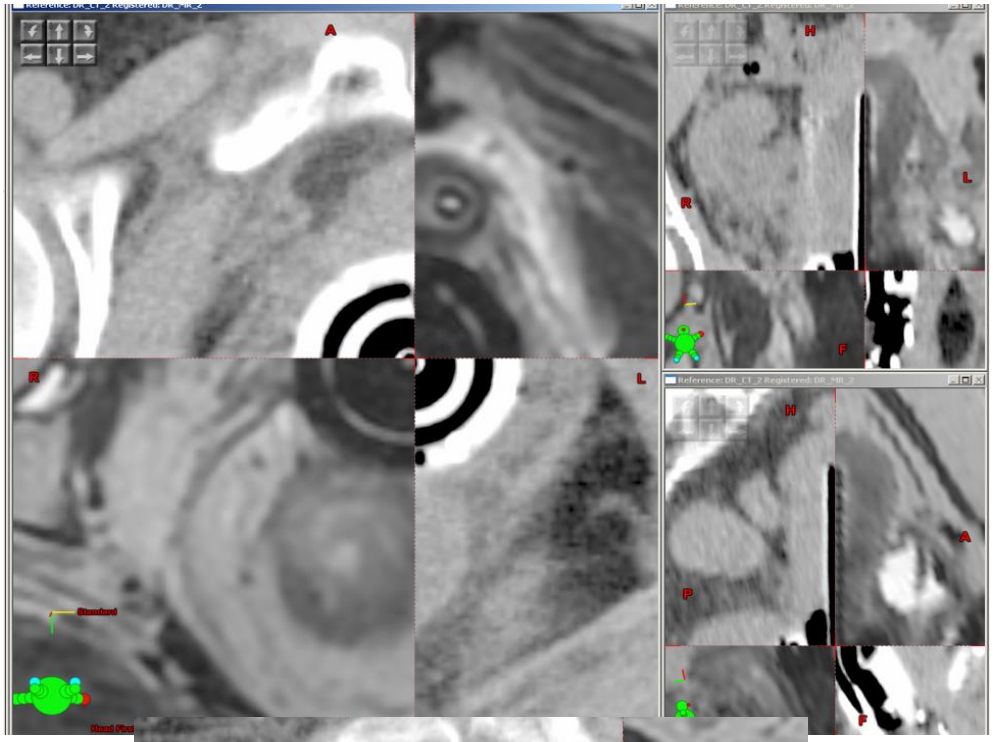
CT
Ti
Needles

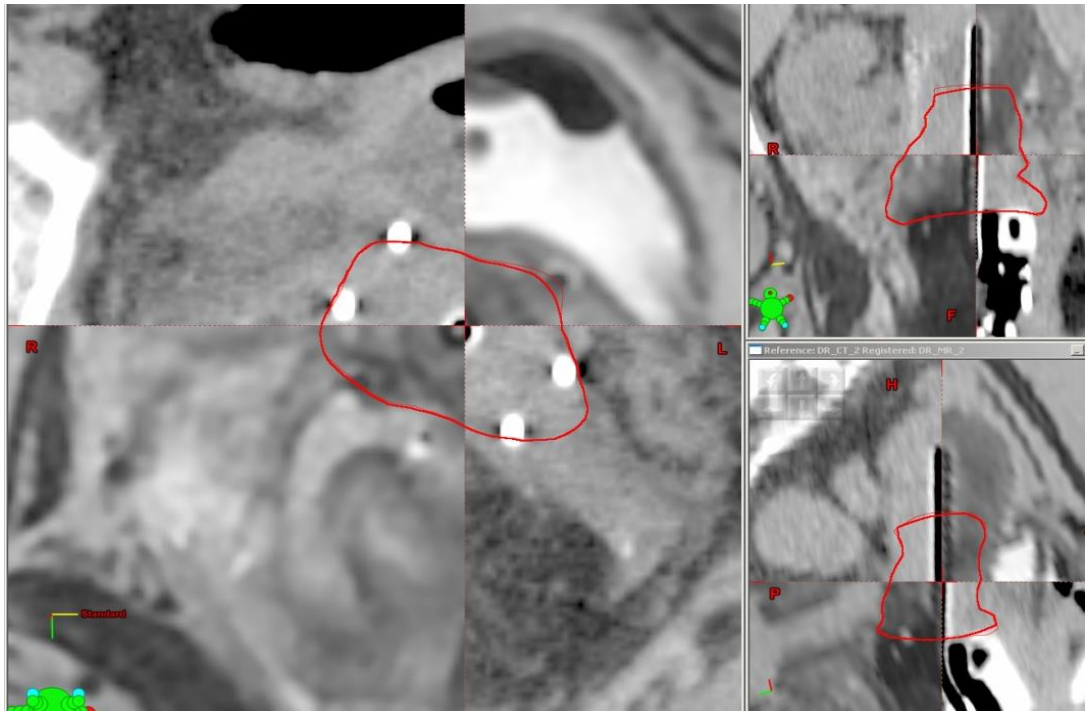
1.5T
Ti
Needles

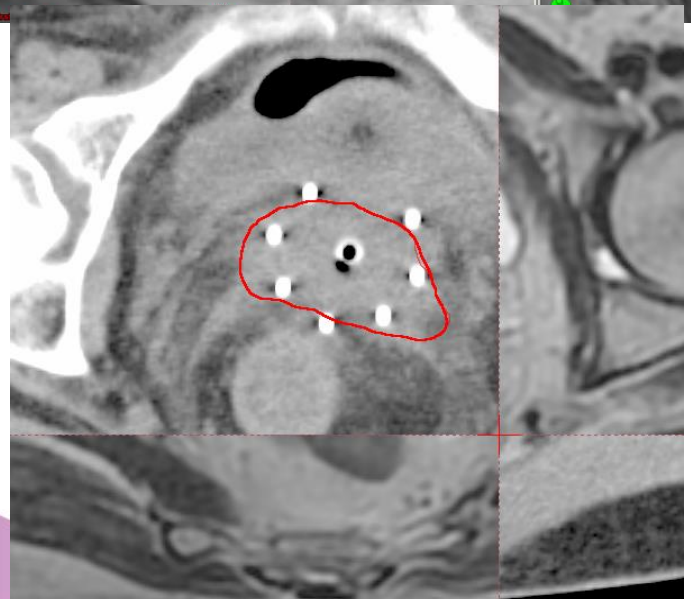
Ti Needle reconstruction (CT vs 3.0 TMR)

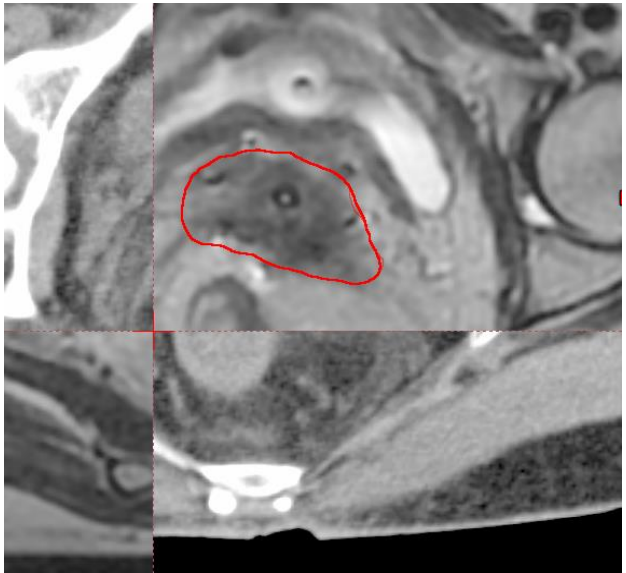


CT vs MR

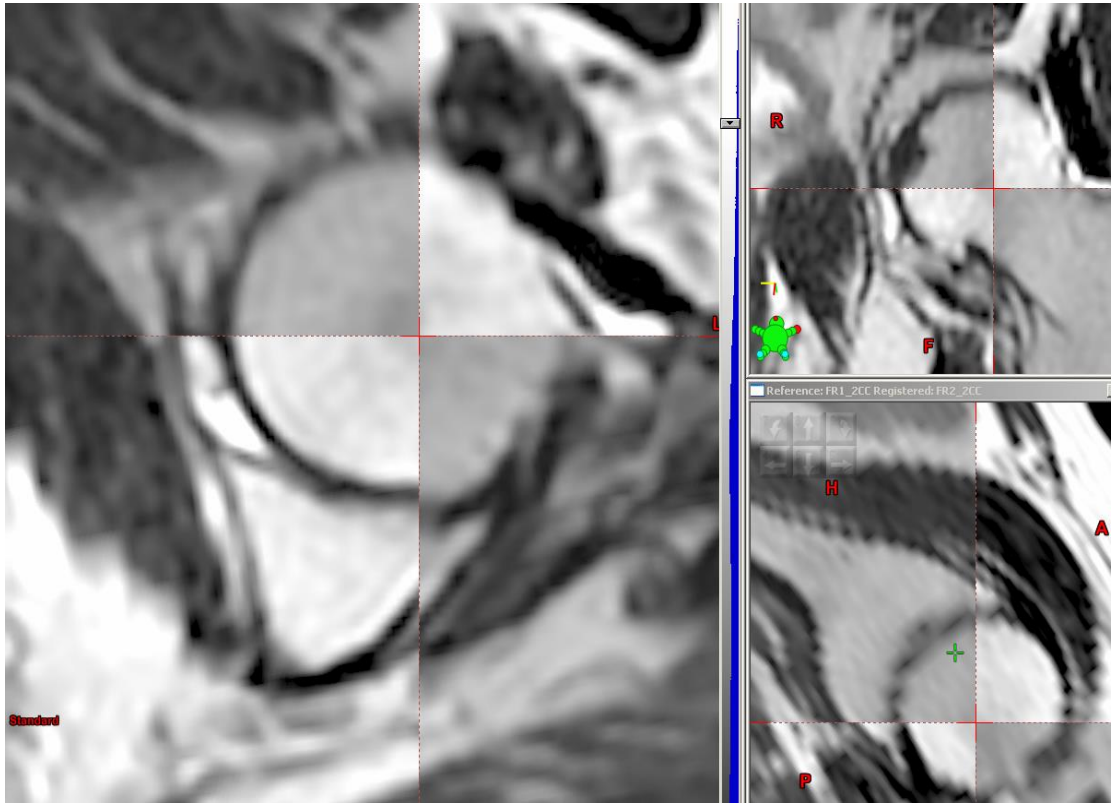




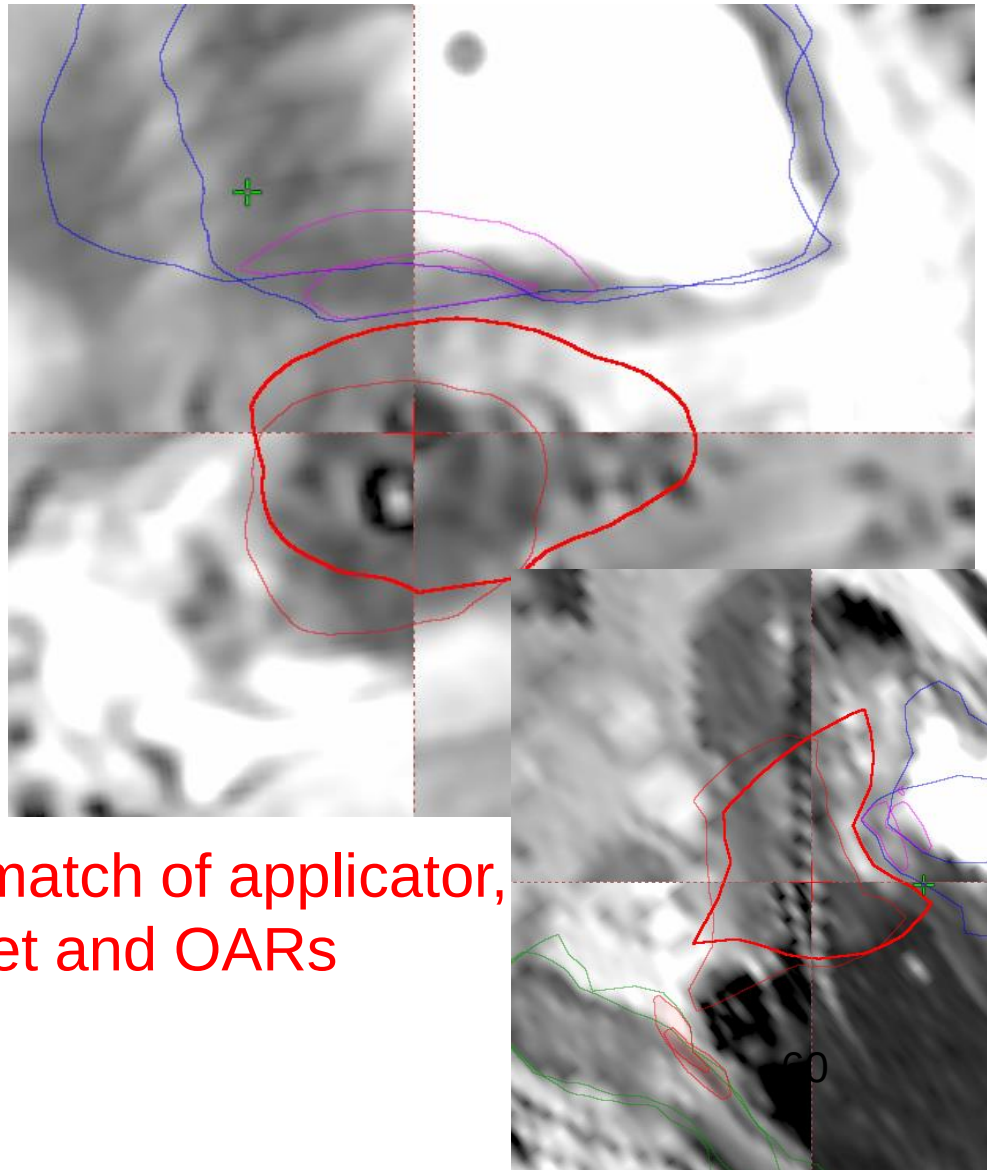




Registration in Brachytherapy – Bone as a reference ? No

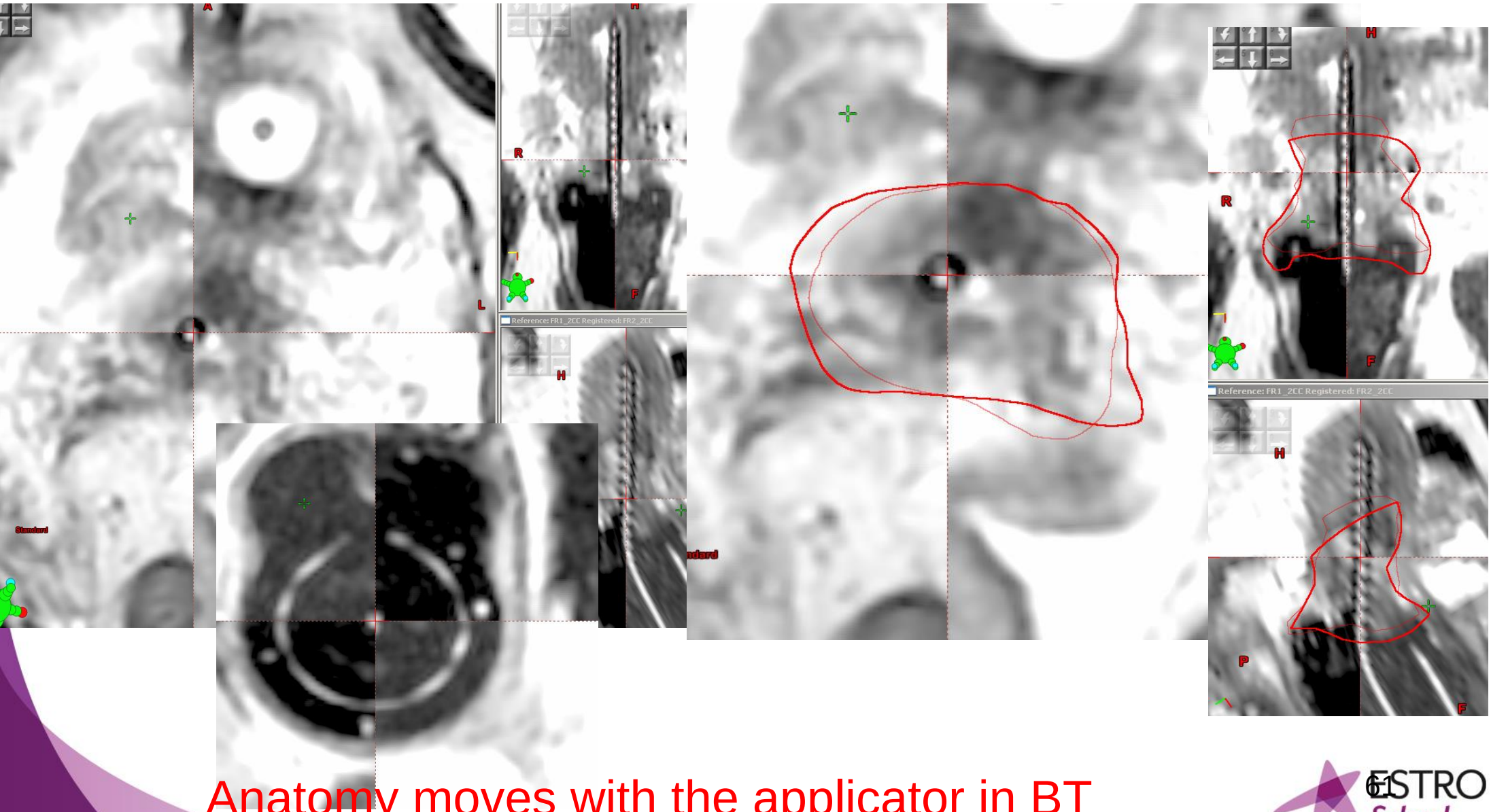


Good matching of bones



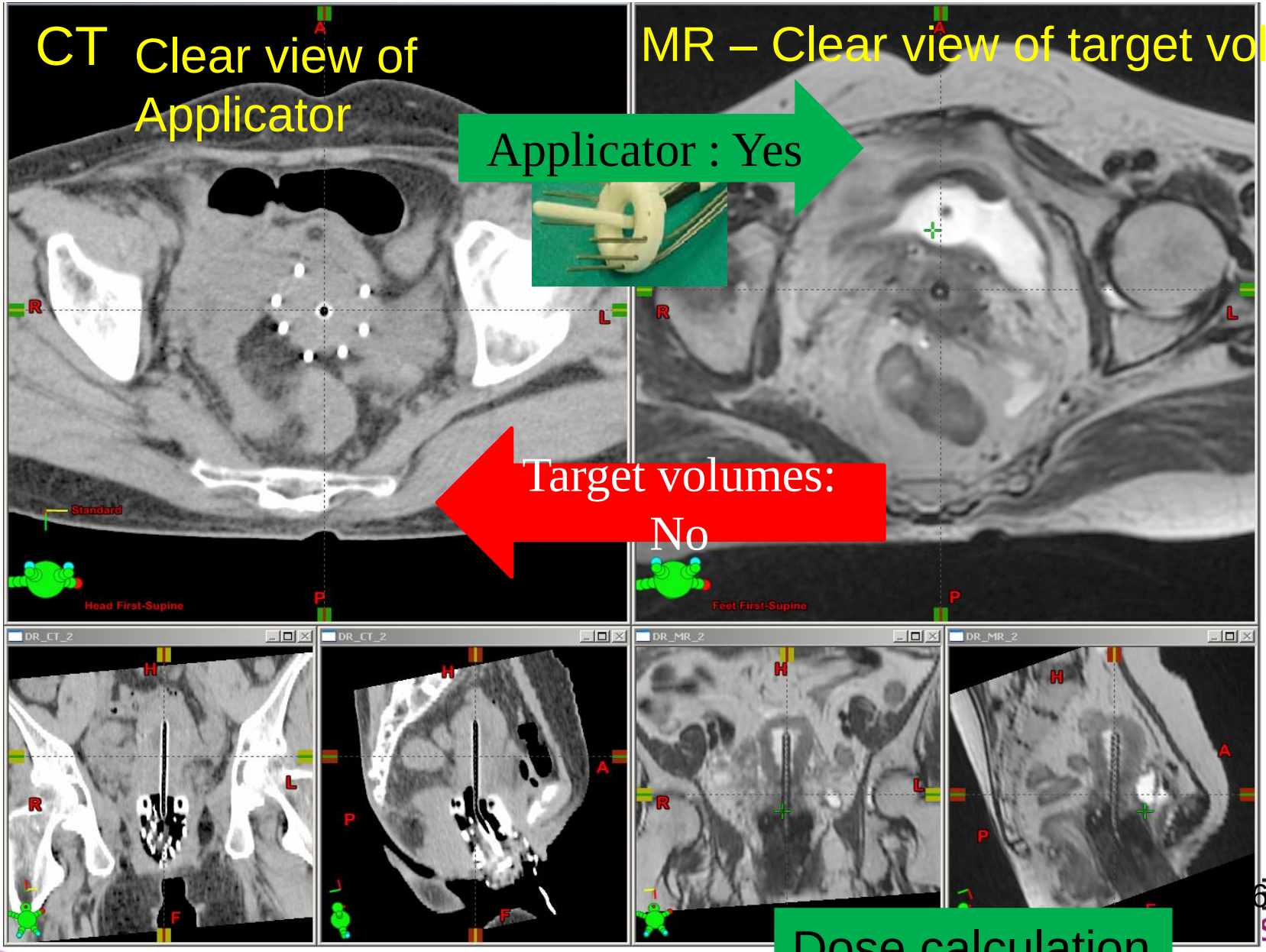
Mismatch of applicator, target and OARs

Registration in Brachytherapy – applicator as a reference? -Yes

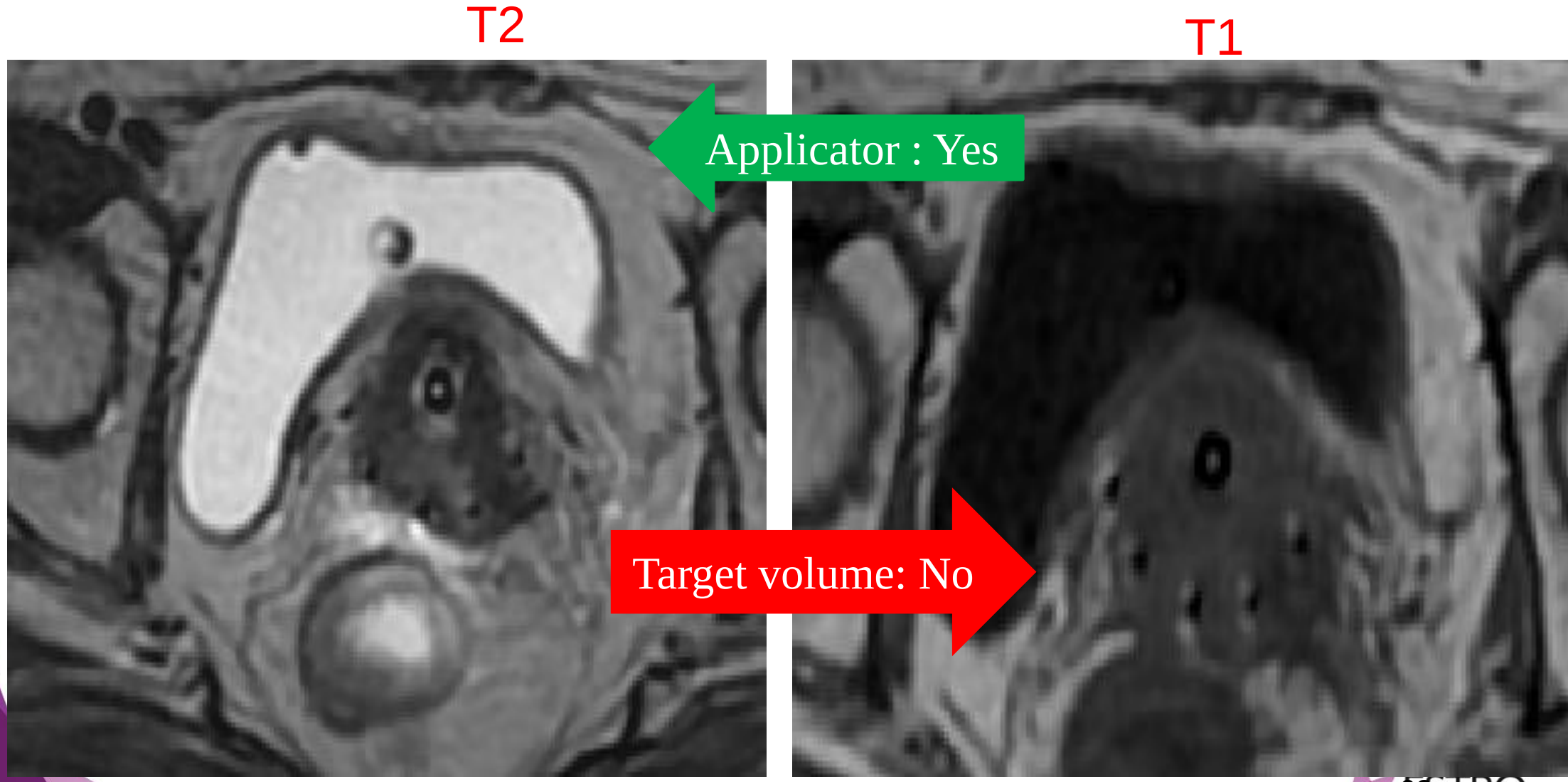


Anatomy moves with the applicator in BT

Registration of CT vs MR – Reconstruction



Registration of T1 vs T2 for Reconstruction

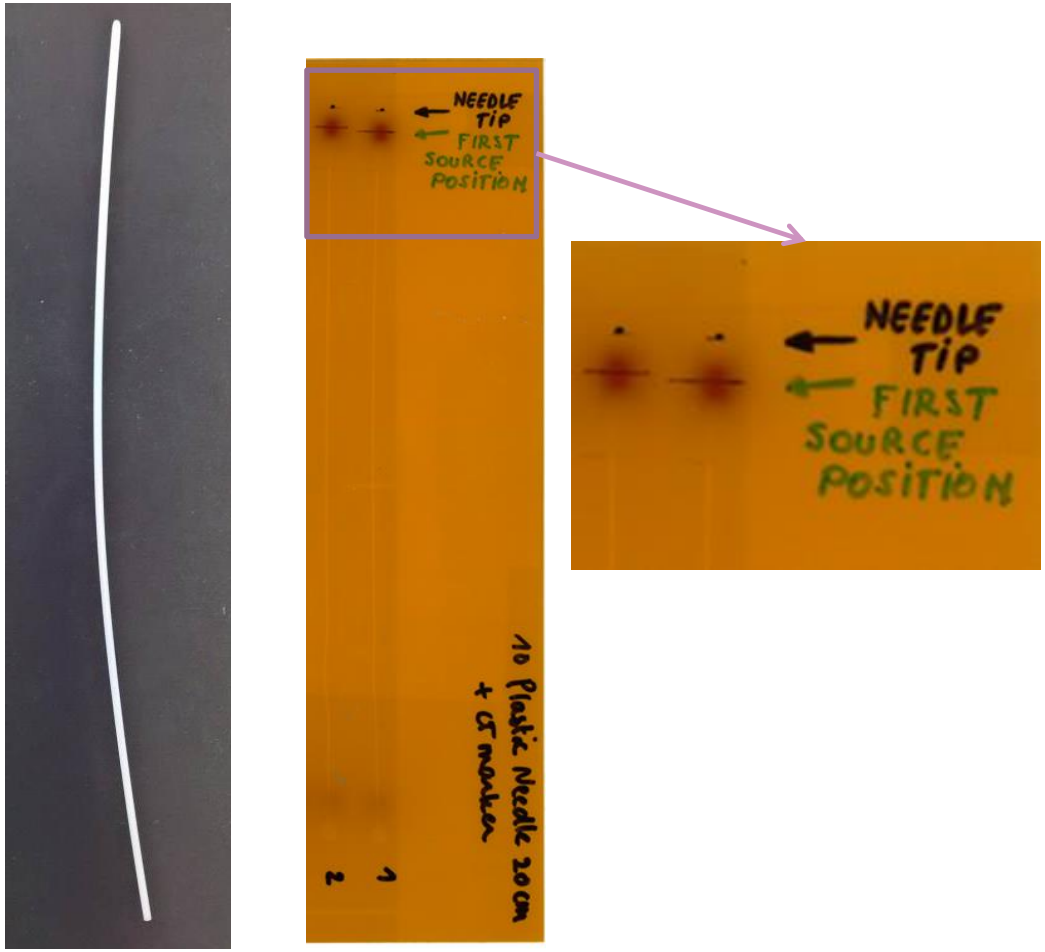


Take home

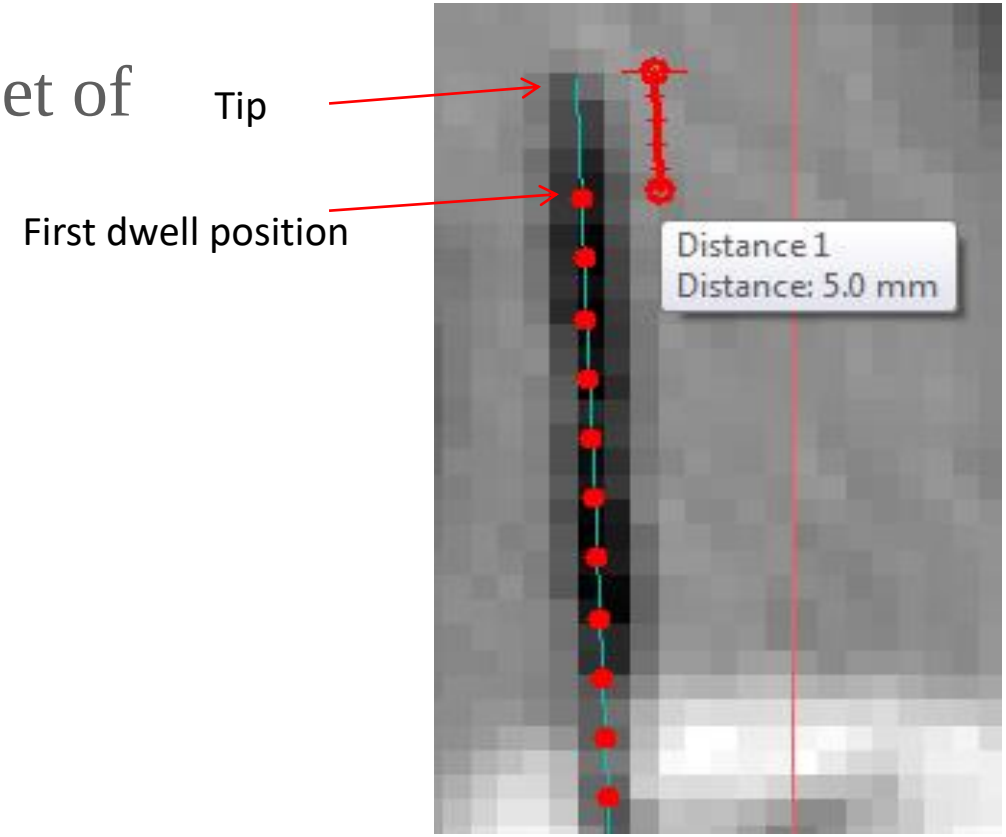
- Applicator commissioning essential especially for MR IGABT
- Commissioning illustrated in simple 5 steps
- Applicator reconstruction
  - Direct reconstruction
  - Library of applicators
- Registration
  - Applicator reconstruction based on bony anatomy and rigid registration

Example from M. de Brabandere

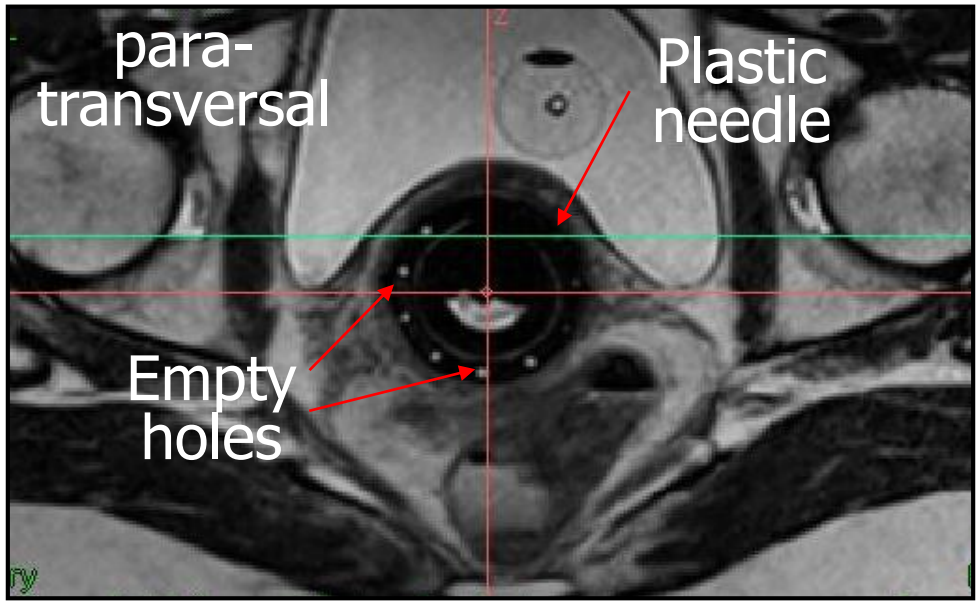
Needle commissioning



Here we have started to digitize the tip of the needle and used a offset of -5mm.

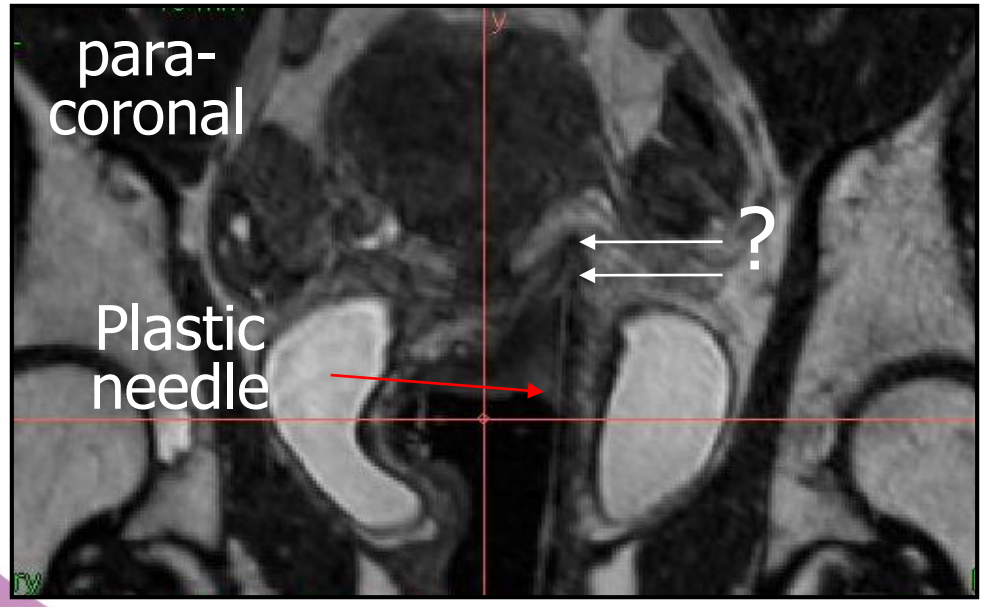


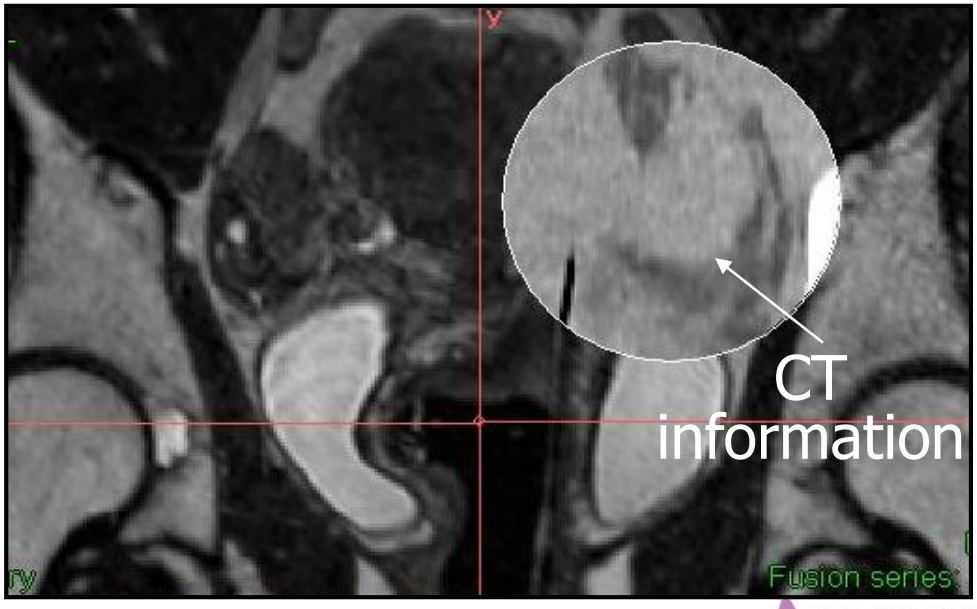
MRI and CT



Landmark image registration:

Two empty holes and the tip of the uterine applicator used as landmarks

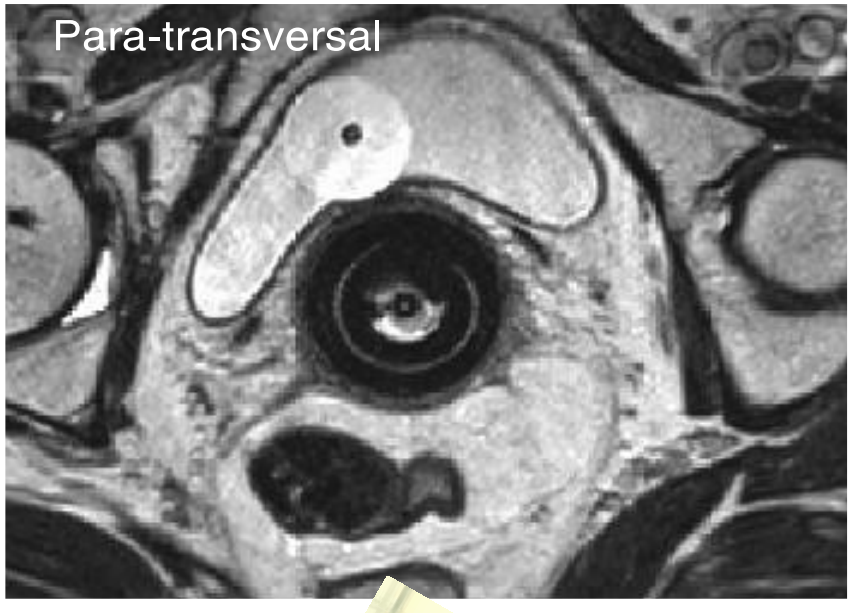


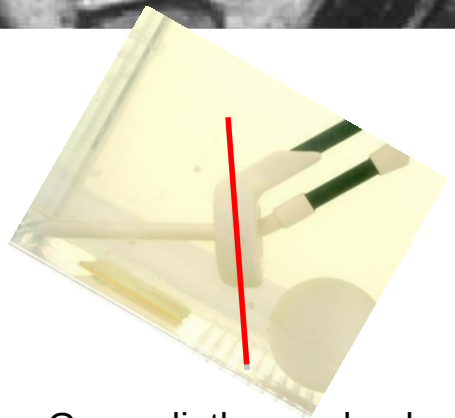


ESTRO School

Orientation of the imaging sequence

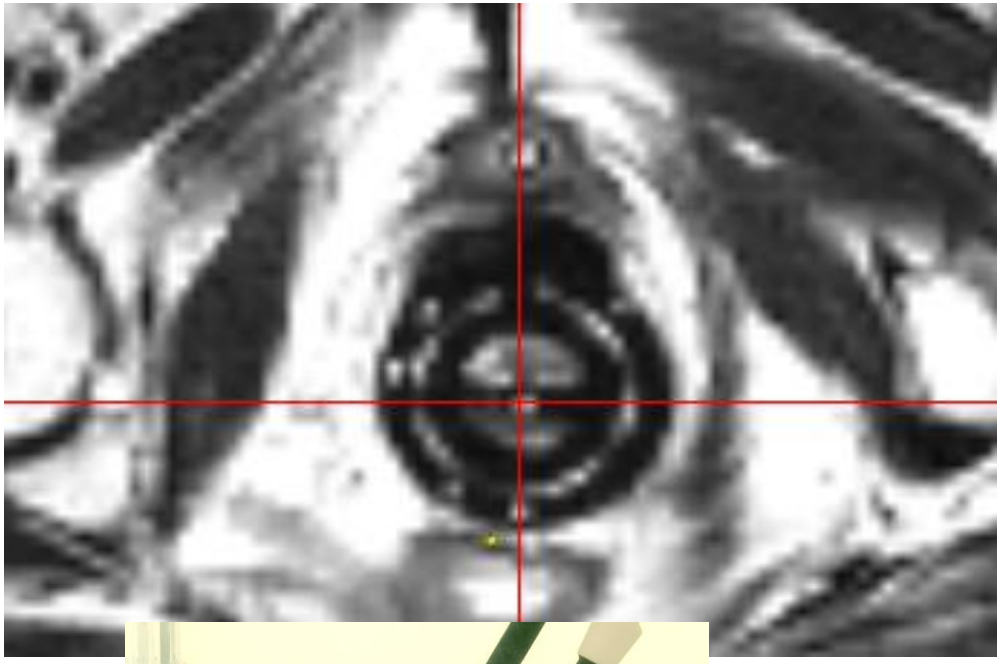
Para transverse

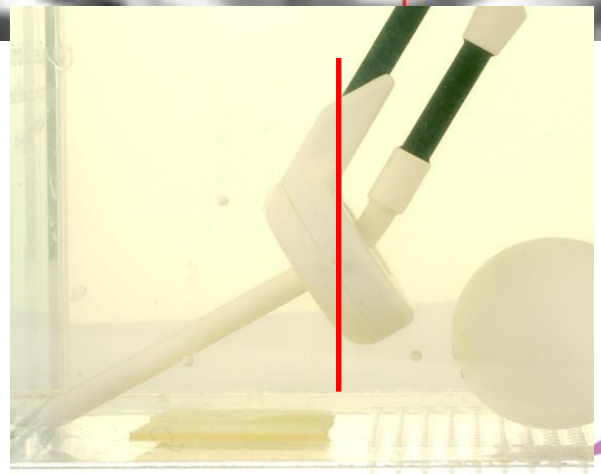




From Gyn radiotherapy book,
Editor: A viswanathan,
Kirisits C, Erickson B, Potter P

Transverse (MP Reconstructed)





Leiden University
Medical Center

Endometrial Cancer

Target volumes and brachytherapy techniques for definitive and post-operative treatment

ESTRO GYN teaching course,

Madrid 2018

Remi Nout

With the help of: Primoz Petric, Ina Jürgenliemk-Schulz, Richard Pötter

Overview

Target concepts & brachytherapy techniques

- Postoperative brachytherapy:
  - Risk stratified approach
- Definitive treatment for intact uterus:
  - Medical inoperable (obesity)

Site of recurrence after surgery

- PORTEC-1: EBRT target volume proximal half of vagina

Outcome	Radiotherapy (n=354)			Control (n=360)		
	Number	5-year %	SE	Number	5-year %	SE
Locoregional relapse	11	4·2	1·3	40	13·7	2·1
Vaginal vault	5	1·6	0·7	19	6·4	1·4
Vagina	2	0·7	0·5	11	3·8	1·2
Pelvic	4	2·0	1·0	10	3·4	1·1

- Approximately 2/3 at vault
- Sub/peri-urethral region ~10%

➢ PORTEC-2: EBRT and VBT target volume proximal half

Creutzberg et al. Lancet 2000; Jereczek-Fossa et al. IJROBP 2000; Nout et al. Lancet 2010

Institutional series >100 patients "radiographic-era"

Author (ref) acrual period	No. patients, eligibili	Treatment	Vaginal recurrence	Locoregiona recurrence	Survival	Severe complications
Institutional series including at least 100 patients						
Sorbe et al.[35] publ 1990	404; Stage I		0,7%	3,0%	92% OS at 5-years	6.9% significant
MacLeod et al.[31] 1985-1993	141; Stage I-IIIA	4 x 8.5 Gy at surface	1,4%	2,0%	91% OS at 5-years	no grade 3/4
Weiss et al.[36] 1987-1993	122; Stage I-II	3 x 7 Gy at surface	1,6%	4,1%	94% NED at 5-years	no grade 3/4
Eltabbakh et al.[2] 1958-1994	332; Stage IA grd 1-2	1 x 30 Gy LDR at surface	0,0%	0,6%	99% DFS at 5-years	2.1% grade 3/4
Petereit et al.[32] 1989-1997	191; Stage IA grd 1-2	2 x 16.2 Gy at surface ovoids	0,0%	0,5%	95% OS at 5-years	0.5% grade 4
Anderson et al.[2(1990-1996	102; Stage I	3 x 5 Gy at 0.5 cm	1,0%	1,9%	84% OS at 5-years	no grade 3/4
Horowitz et al.[29] 1989-1999	164; Stage I-II	3 x 7Gy at 0.5 cm	1,2%	0,6%	87% OS at 5-years	no grade 3/4
Alektiar et al.[25] 1987-2002	382; Stage I-II	3 x 7Gy at 0.5 cm	0,8%	0,0%	93% OS at 5-years	0.5% grd 3/0.3% grd 4
Solhjem et al.[33] 1998-2004	100; Stage I grd 2-3 a IB grd 1-2 if >2cm	3 x 7Gy at 0.5 cm	0,0%	0,0%	98% OS at 3-years	no grade 3/4
Ataham et al.[27] 1994-2005	128; Stage I	5 x 5.5 Gy at 0.5 cm	0,0%	1,6%	96% OS at 5-years	no grade 3/4

- Different: dose/fractionation & prescription
- Different applicators: most cylinder, but also ovoid, ring, mould

Studies comparing different dose levels

Author (ref) acrual period	No. patients, eligibili	Treatment	Vaginal recurrence	Locoregiona recurrence	Survival	Severe complications
Studies with different brachytherapy dose levels						
Kloetzer et al.[30] 1981-1990	108; Stage I-II	4 x 10 Gy at 0.5 cm 4 x 10 Gy at 1 cm 4 x 10 Gy at 1 cm + vag	0,0% 3,1% 0,0%	2,2% 3,1% 0,0%	98% OS at 3-years 97% OS at 3-years 97% OS at 3-years	2.2% / 0.0% grade 3/4 6.2% / 3.1% grade 3/4 6.8% / 12.6% grade 3/4
Osrund et al.[37] 1988-1996	217; Stage I-II	4 x 5.5 Gy at 0.5 cm 4 x 5.5 Gy individualized at 0.3-0.4-0.5 cm	1,0% 2,5%			26% / 8% grade 1/2 17% / 1% grade 1/2 no grade 3/4
Sorbe et al.[34] 1989-2003	290; Stage IA grd 1-2	6 x 2.5 Gy at 0.5 cm vs. 6 x 5.0 Gy at 0.5 cm	0,7%	1,4%	95% OS at 5-years	vaginal shortening 0.3 cm vs. 2.1 cm

- Higher dose + including whole length increased severe morbidity and shortening of the vagina
- Osrund: individualized prescription 0.3 – 0.4 – 0.5 cm less grade 1-2 vaginal morbidity

Randomized trials "radiographic-era"

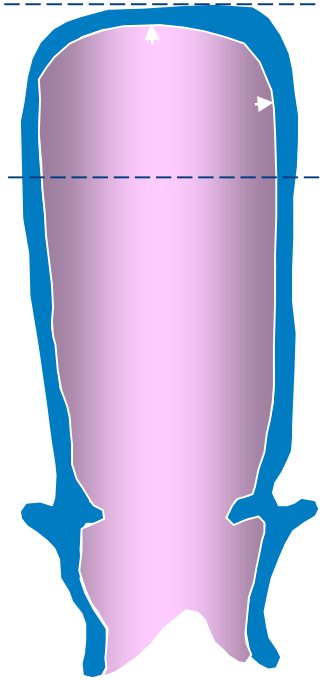
Author (ref) acrual period	No. patients, eligibili	Treatment	Vaginal recurrence	Locoregiona recurrence	Survival	Severe complications
Randomized trial VBT versus NAT in low risk endometrial cancer						
Sorbe et al.[47] 1995-2004	645; Stage 1A grade 1	3 to 6 x 3 to 8 Gy at 0.5 cm vs. NAT	1,2% 3,1%	2,6%	96% OS at 5-years	no grade 3/4
Randomized trials VBT versus EBRT +/- VBT in (high) intermediate risk endometrial cancer						
Norwegian[1] 1968–1974	540; Stage I	1 x 60 Gy LDR at surf		6,9%	91% OS at 5-years	1% grade 4
		vs. EBRT + same VBT		1,9%	89% OS at 5-years	1.1% grade 4/5
PORTEC-2 2002–2006	427, age >60 IA grade	3 x 7Gy at 0.5 cm vs.	1,8%	5,1%	85% OS at 5-years	GI: VBT 0.5% vs 1.9%
	IB grade 1–2 (HIR)	EBRT	1,6%	2,1%	80% OS at 5-years	Vagina: 1.9% vs 0.5%
Swedish[7] 1997-2008	527; Stage I and	6 x 3 Gy at 0.5 cm	2.7%*	5,0%	90% OS at 5-years	grd 3 VBT vs EBRT + VBT
	(grade 3 or deep invasi	3 x 5.9 Gy at 0.5 cm				GI: 0% vs 2%
	or DNA aneuploidy) an	1 x 20 Gy LDR at 0.5 cm				Vagina: 0.8% vs 0%
	nuclear grade 1-2	vs. EBRT + same VBT	1.9%*	1,5%	89% OS at 5-years	

- Different dose/fractionation & prescription
- Treated lengths range proximal 1/3 – 1/2 (3-5cm)
- All seem effective

Summary literature “radiograph-era”

- Approximately 2/3 of recurrences at vault
- Effectiveness of ovoid, ring
- Higher dose and treating more length increases morbidity

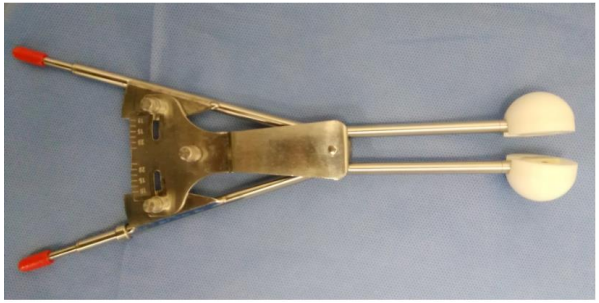
➢ Suggests that proximal 1/3 is long enough (3-4cm)

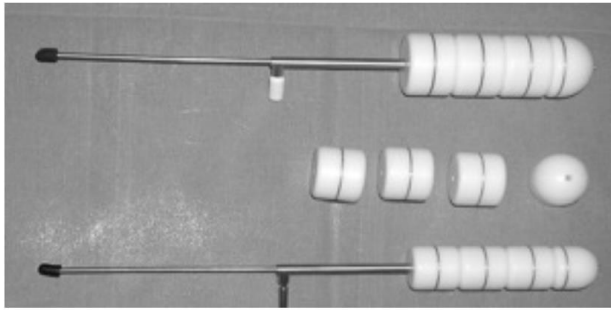


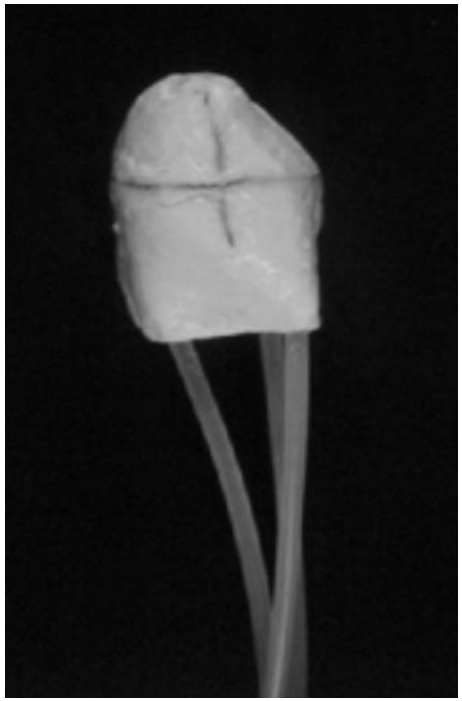
➢ PORTEC-2 & Swedish trial:

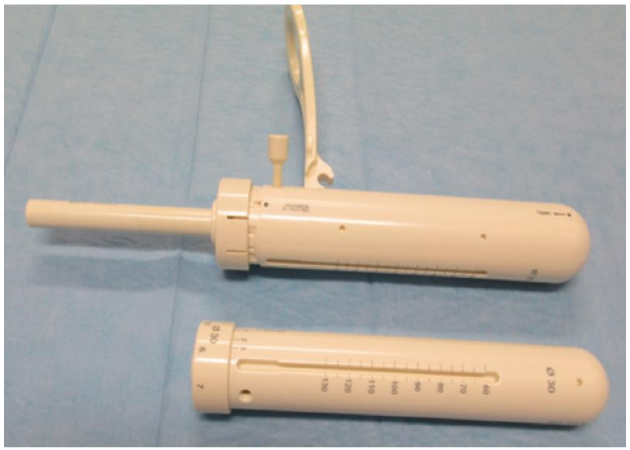
- Vaginal recurrence 2-3%
- Low rates of morbidity

Applicators



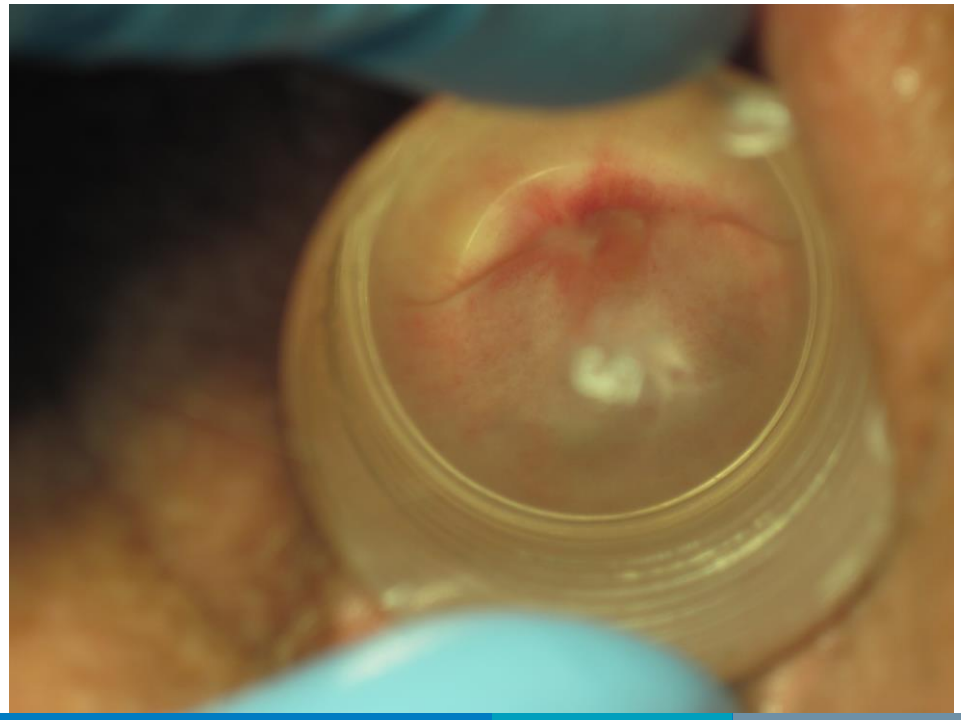






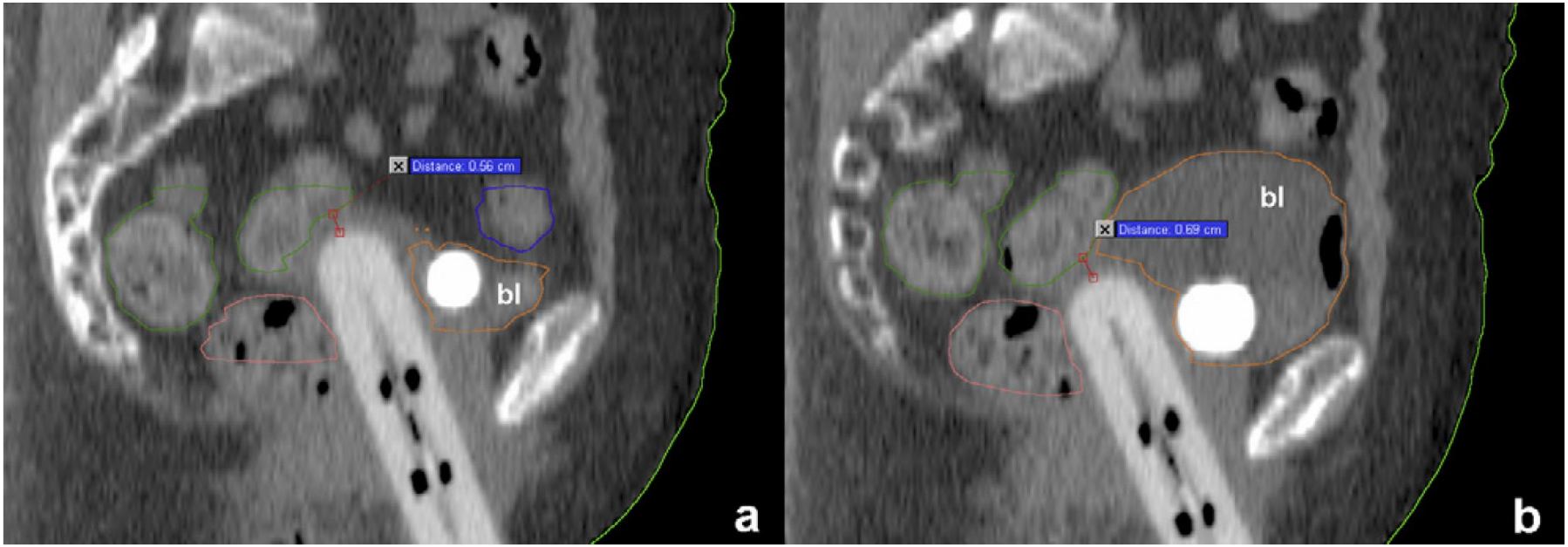
Practical points

- Lubricant
- Pay attention to angle of vagina
- Make sure patient and pelvic floor muscles relax
- Measurement cylinders (plexi-glass) in different diameters
- Scale (cm) on the surface with magnifying effect



CT-based findings

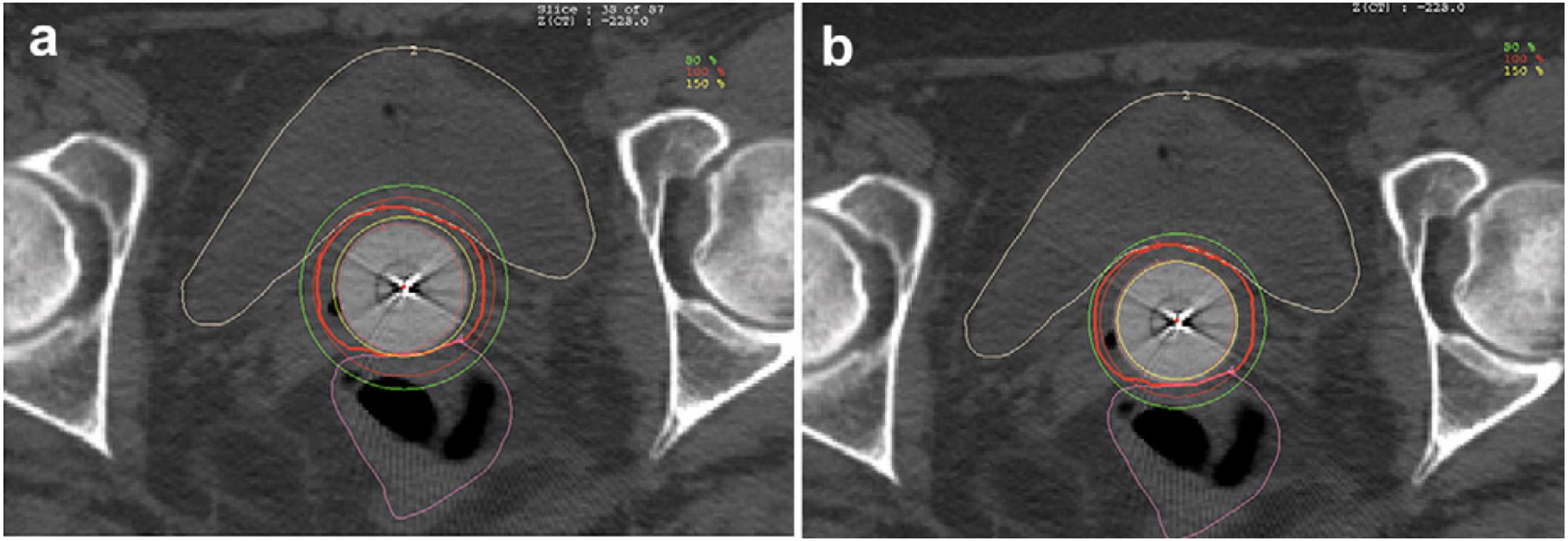
- Only first fraction CT is necessary: small within patient variaton
- Bladder filling: increased dose to bladder, decreased dose to small bowel
- Applictor angle: horizontal reduces bowel dose
- Airpockets: most distal, reduced by repositioning



Hoskin *Br J Rad* 2000; Stewart *IJROBP* 2008; Hung IJROBP 2010; Holloway *IJROBP* 2011

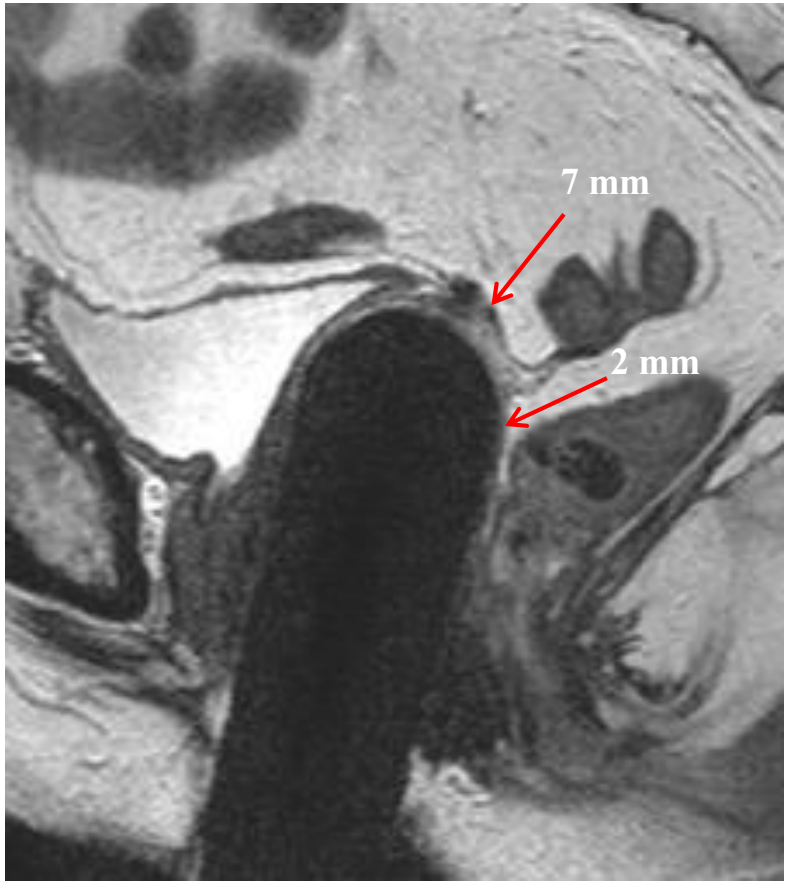
CT: target volume

- CTV (Kim et al.):
- 0.5cm expansion of proximal 2.5cm of cylinder
- Editing to exclude bladder and rectum
- Superiorly edit based on ‘soft tissue seen’



MRI

- Superior soft tissue resolution:
- Visualization of the vaginal wall, thickness
- Surgical scar - ligaments
- Organs at risk

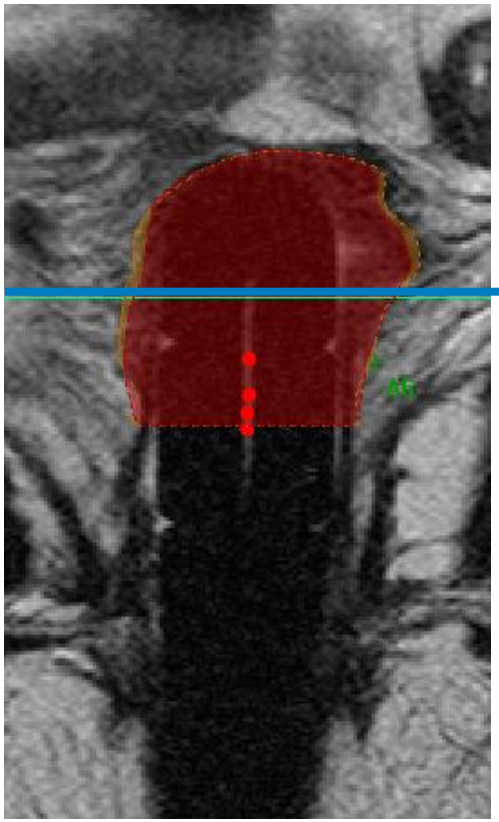


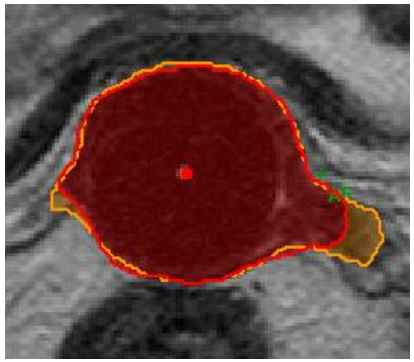
MRI: cylinder

Coronal

Axial

-2 cm





Mean distance to CTV (range)

2.7 mm (2-4 mm)

4.2 mm (1-9 mm)

4.8 mm (2-10 mm)

Maximal 5.2 mm (2-7 mm)

2.0 mm (1-3 mm)

Maximal 9.1 mm (4-20 mm)

MRI: cylinder

- Largest variation cranial and lateral in ‘folds’ and ligament structures

- Pathology study shows that 95% of lymph vessels are located in superficial 3 mm of vaginal tissue.

Consensus for study:

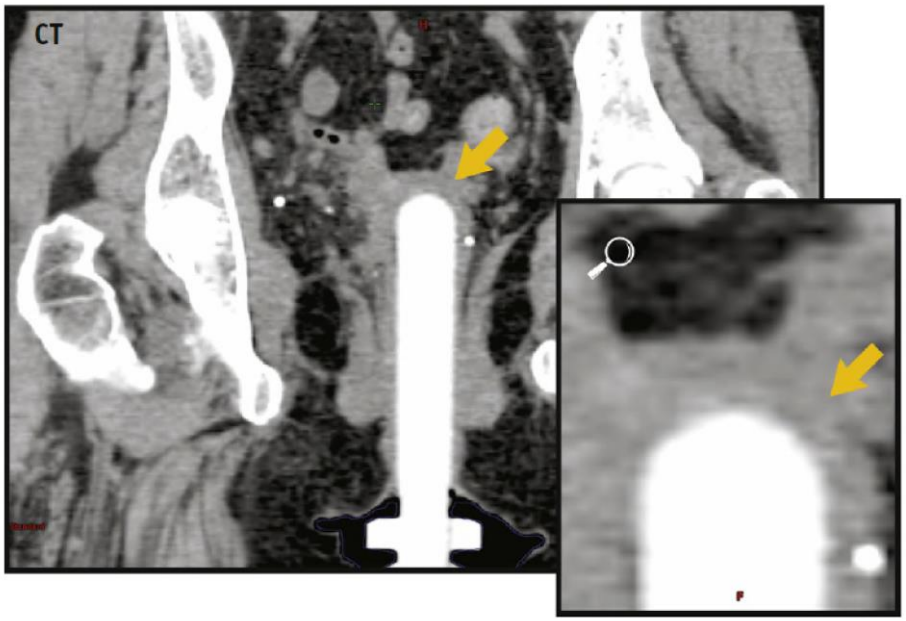
- Cylinder 3 mm ‘ring’ expansion, where necessary further expansion
- Include ‘vaginal folds’ to document dose in folds
- Exclude: ligament structures cranially; air, fluid

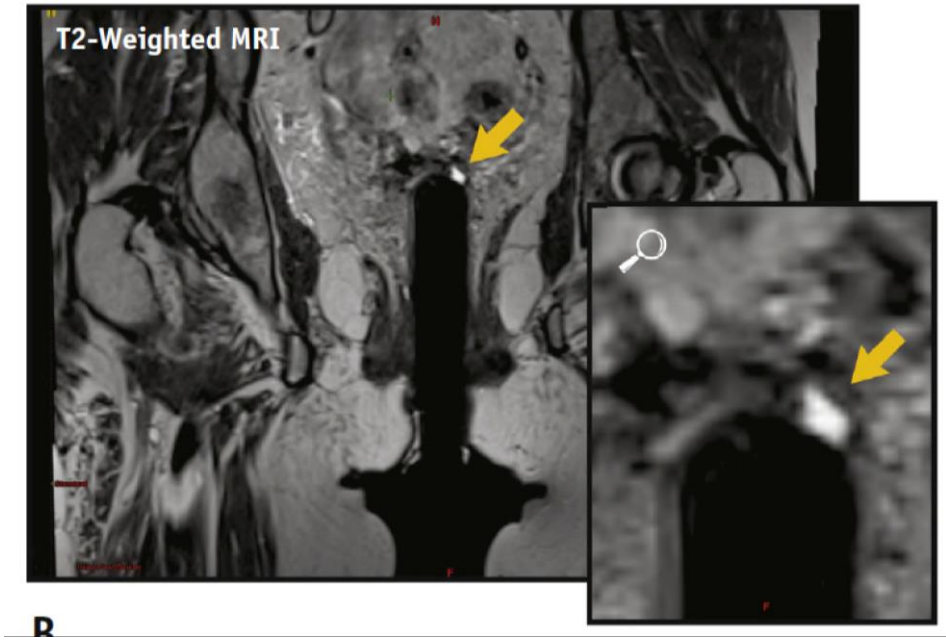
Nout, et al. GEC-*ESTRO* 2011; Choo et al. Brachytherapy 2005

MRI: cylinder

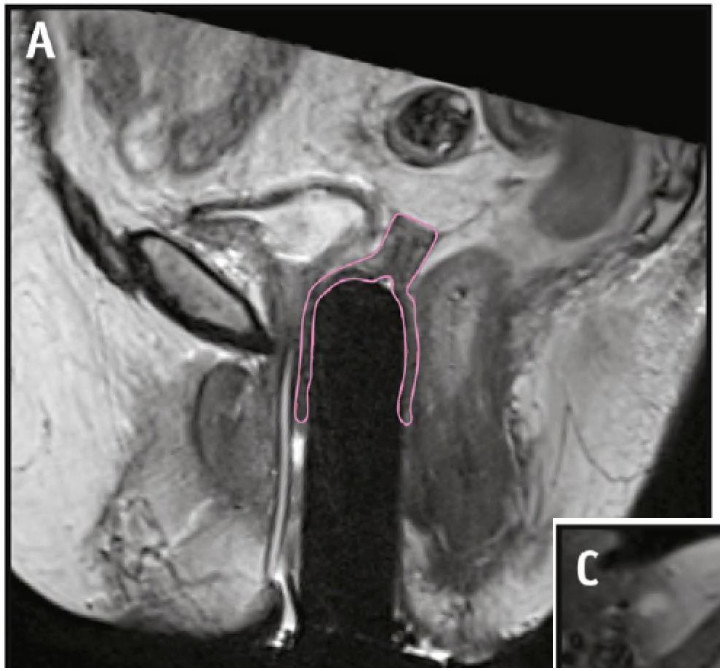
MRI-Based Evaluation of the Vaginal Cuff in Brachytherapy Planning: Are We Missing the Target?

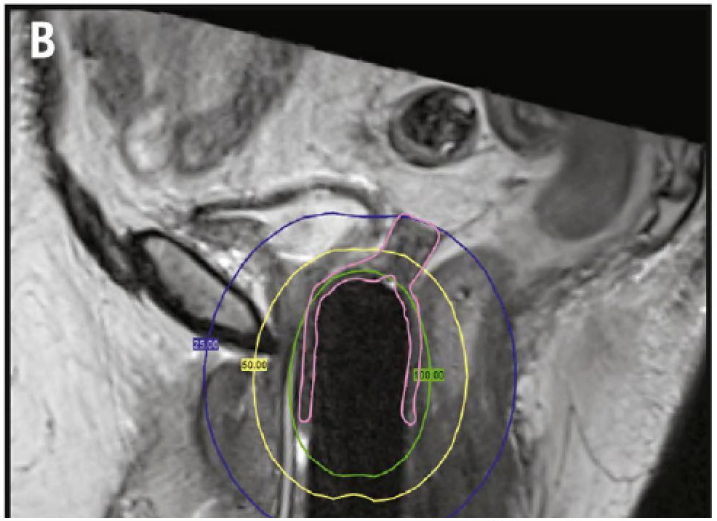
Christina Hunter Chapman, MD,* Joann I. Prisciandaro, PhD,* Katherine E. Maturen, MD,† Yue Cao, PhD,*,†,‡ James M. Balter, PhD,*,‡ Karen McLean, MD, PhD,§ and Shruti Jolly, MD*

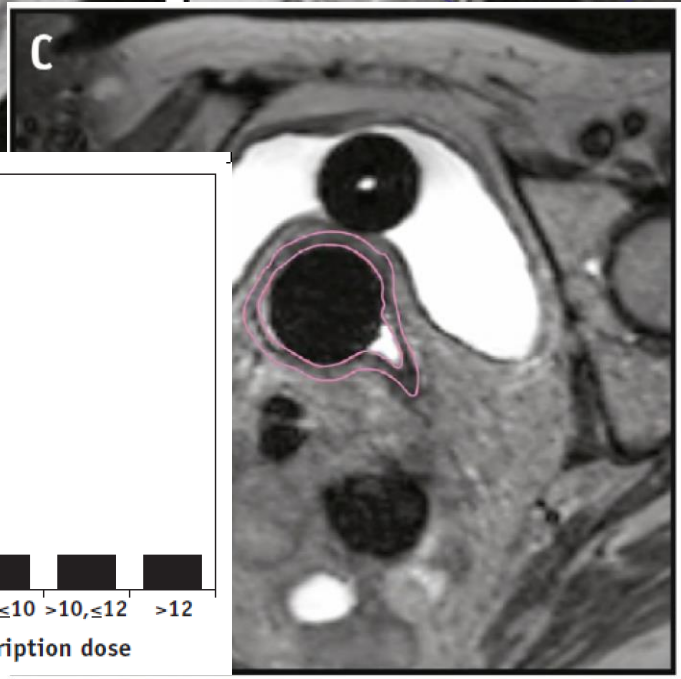


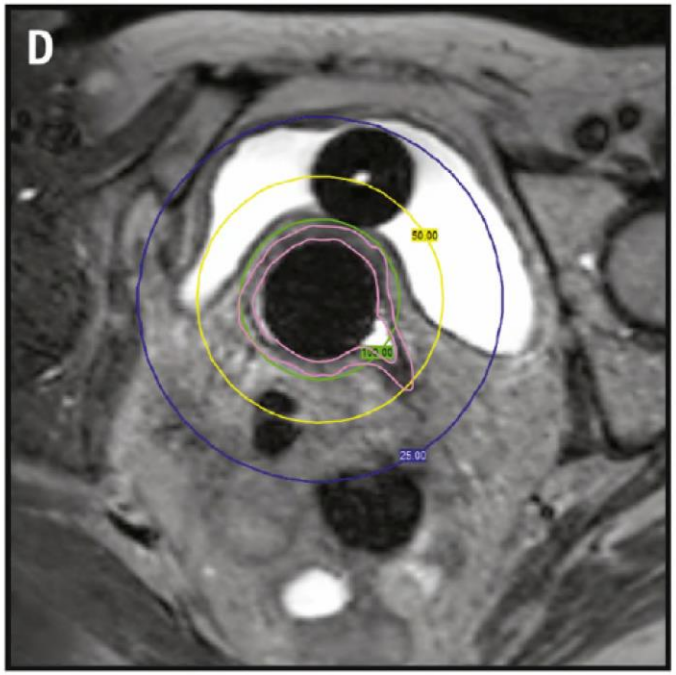


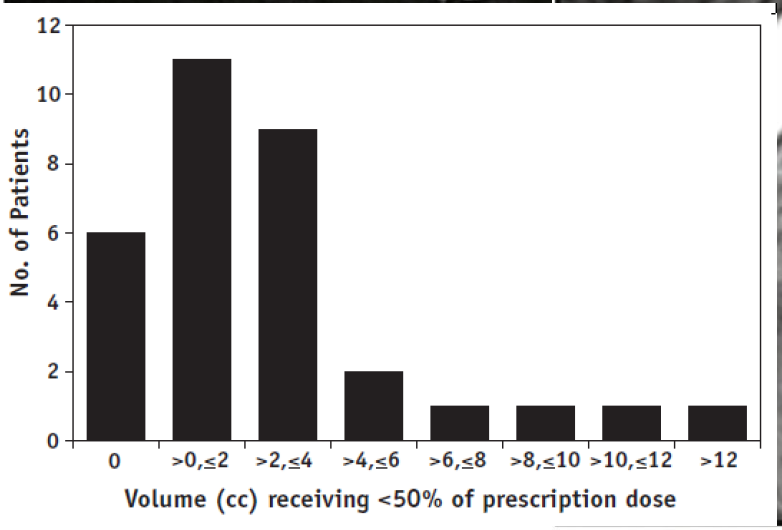
MRI: cylinder











Hunter Chapman et al. *IJROBP* 2015

Summary CT-MRI

- More information on dose to OAR:
- Moderate bladder filling; horizontal angle

- MRI, visualization of vaginal wall:
- 0.3cm thick wall / ring, expand and include folds
- “Dog ears” potential under dosage
- Clinical relevance? (good clinical results)

- Aim: ensure optimal contact between applicator surface and vaginal wall, consider:
- Applicator: size cylinder, ovoid, ring, mould
- Position verification: X-ray, CT (MRI), marker

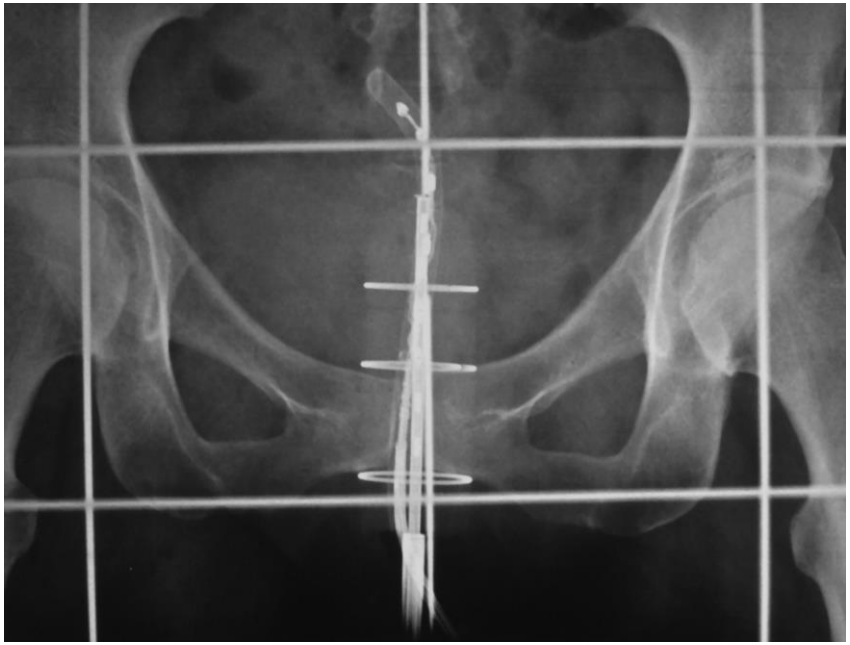
Treatment planning (other presentation)

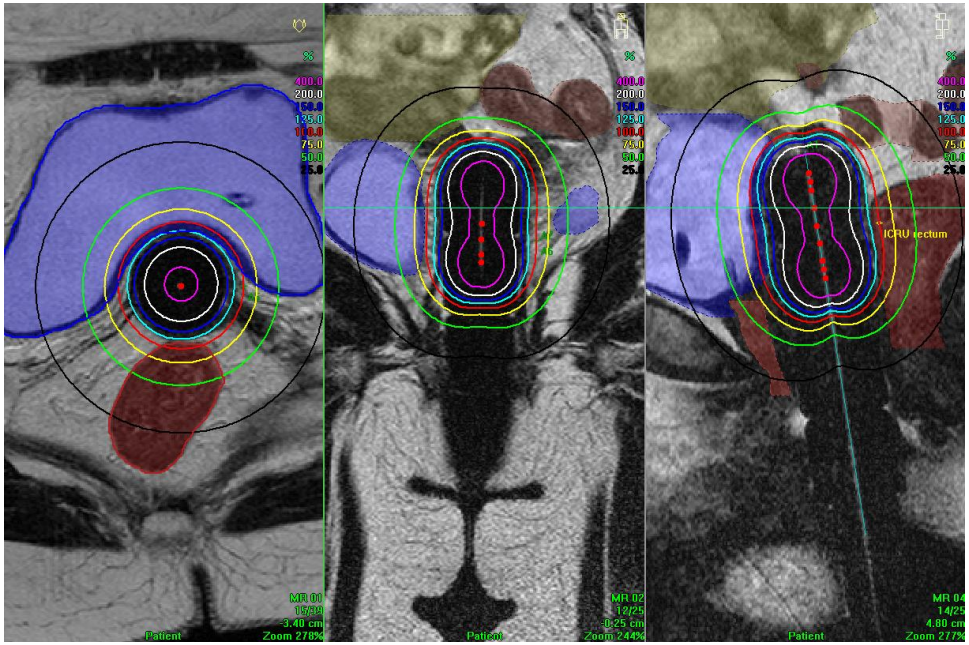
- Traditional standard treatment planning

- Orthogonal radiographs
- based on applicator dimensions, prescription depth and length

- 3D image guided treatment planning

- Based on target volumes and organs at risk

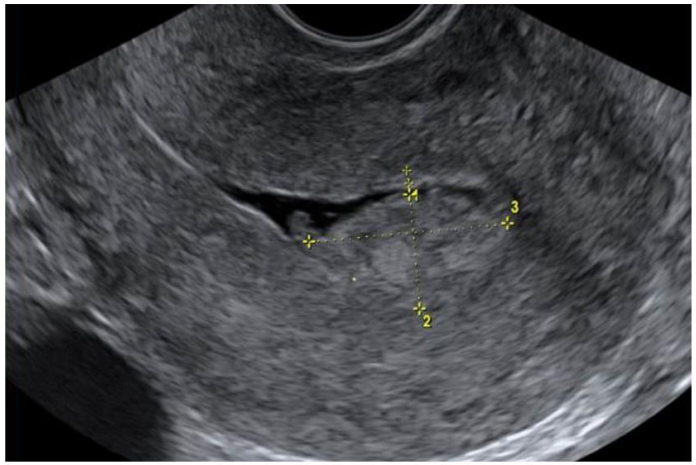




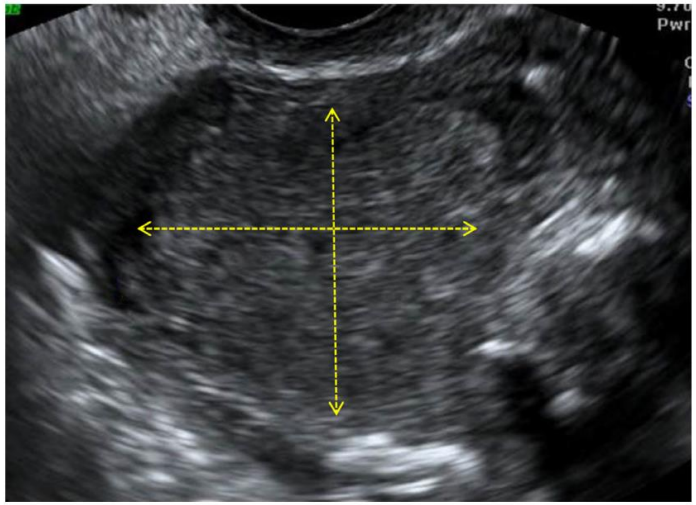
Endometrial cancer: imaging

- Ultrasound

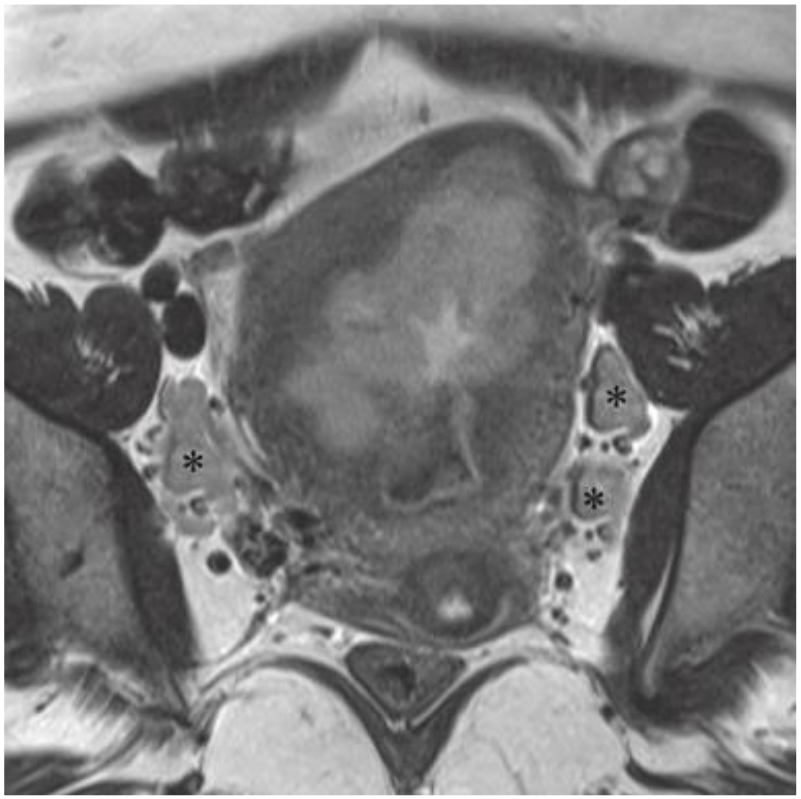
a. Stage IA



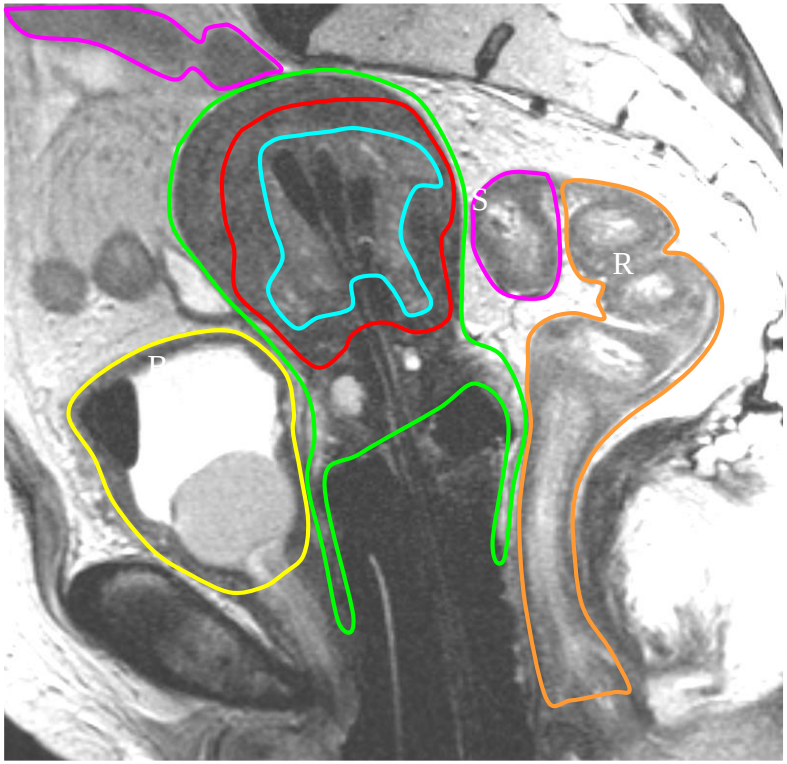
b. Stage IB

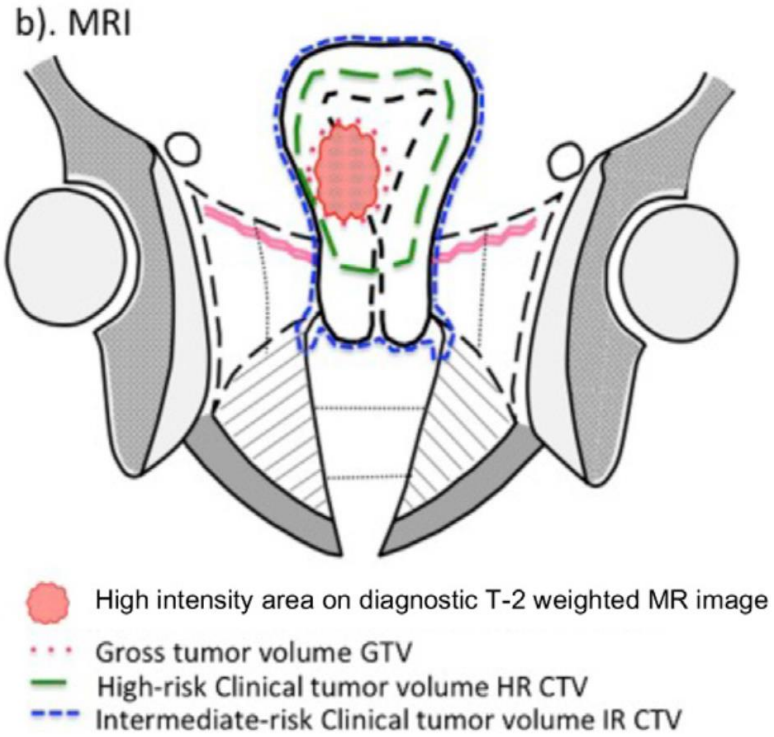


- MRI: gold standard
  - Superior to US/CT
  - Staging accuracy 85-93%



Target concept endometrium

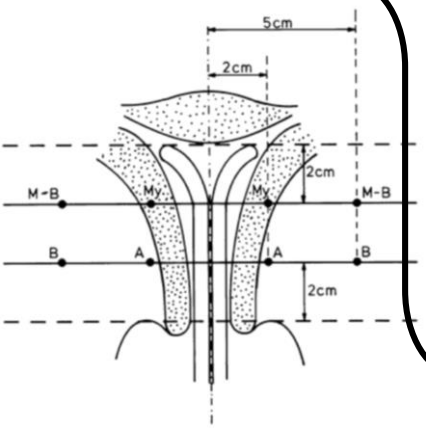




- CTV: whole uterus, cervix and upper 1/3 of vagina
  - Take all information into account (colposcopy, imaging) to delineate GTV
  - Depending of pattern of spread parametrial and paravaginal tissue may be included

Inoperable endometrial cancer: Review

Radiograph-era HDR:
955 patients
Local control
70%-90%



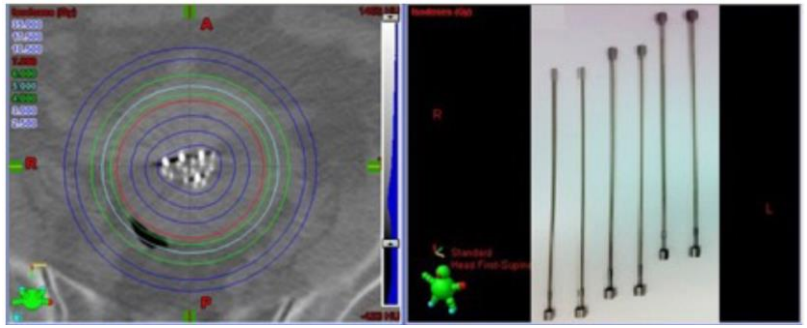
Author	Patient No.	Applicators	Dose prescription	Total dose in EQD2 ($\alpha/\beta = 10$)	Local control rates	Severe late complication rates (Grade 3–4) (%)
2D HDR						
Taghian et al[44]	104	NA	NA	NA	87.6% at 5 years 85.1% at 10 years	17
Rouanet et al[45]	250	NA	NA	NA	75.9% at 5 years	3
Nguyen et al[46]	27	Tandem alone or one tandem and ovoid applicators	HDR alone: 20 Gy/2–3 Fr or EBRT WP 42 Gy + HDR 20 Gy/2–3 Fr	HDR alone: 27.4 Gy, or EBRT + HDR: 69.4 Gy	85.2% at 4 years	11
Knocke et al 1995 and 1997[47,48]	280	One channel intracavitary and intravaginal applicators	4–5 Fr × 8.5 Gy	52.4–65.5 Gy	75.4% at 5 years 70% at 10 years	5.2
Kucera et al[49]	228	One-channel intracavitary and intravaginal applicators	4–5 Fr × 8.5 Gy	52.4–65.5 Gy	76.6% at 5 years 73.9% at 10 years	4.6
Nguyen and Petereit[51]	36	One tandem and ovoid or cylinder applicators	5 Fr × 9 Gy	71.3 Gy	88% at 3 years	21
Fusco et al[50]	41	NA	EBRT WP 45–50 Gy + HDR 2–3 × 6–8 Gy	68.3–86 Gy	NA	10 (GI: Grade 2–3)
Inciura et al[52]	29	Three-channel intrauterine applicators	EBRT WP 16 Gy + HDR 5 Fr × 10 Gy	99.3 Gy	82.8% at 5 years	0 (Grade 1–2: 13.8%)
Ohkubo et al[33]	10	Rotte "Y" applicator	EBRT WP 30–30.6 Gy + HDR 4 Fr × 6 Gy (retrospective dose analysis in 3D)	62 Gy	100% at 5 years	0
3D HDR						
Weitmann et al[32]	13	Norman–Simon applicators with Heyman packing	6 Fr × 7 Gy to CTV (whole uterus, cervix and upper vagina)	59.5 Gy	100% at 4 years	0
Coon et al[34]	18	Rotte "Y" applicators	EBRT WP 45–50 Gy + HDR 5 Fr × 4 Gy, or HDR 5 Fr × 7 Gy b.i.d alone to CTV (whole uterus, cervix and upper vagina)	EBRT + HDR: 69.3–74.6 Gy, HDR only: 49.6 Gy	93.9% at 3 years	0 (13% was reported in 2D cases of this study)

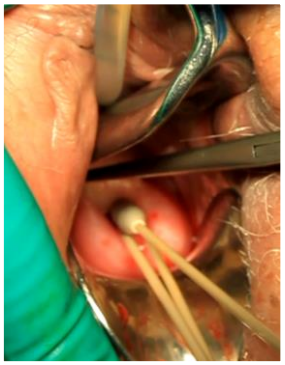
3D-HDR:
31 patients
Local control
90%-100%

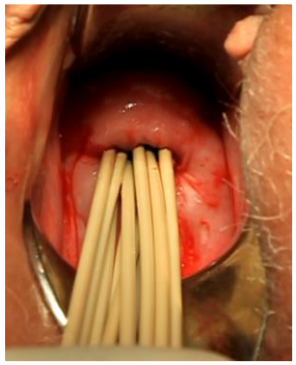
Dankulchai & Hoskin BJR 2014; van der Steen, J Contemp Br 2017

Applicators

Intracavitary techniques





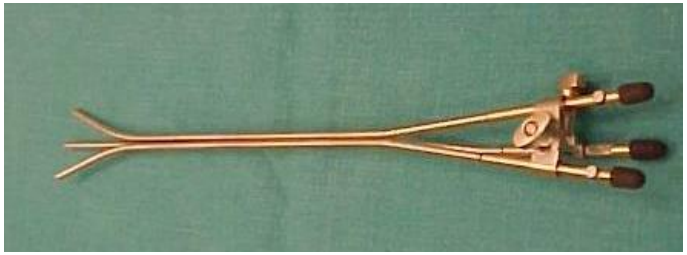


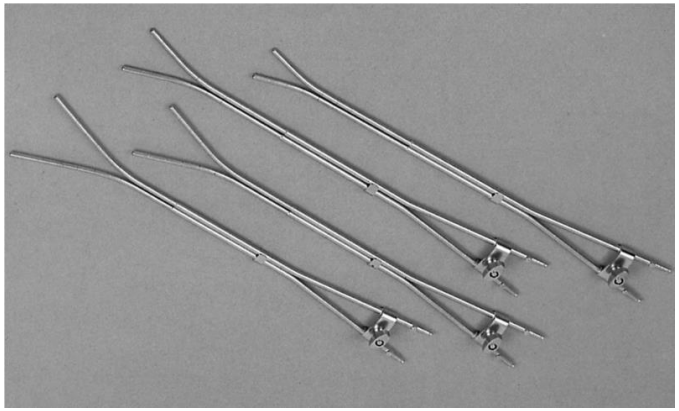
Individualised packing methods:

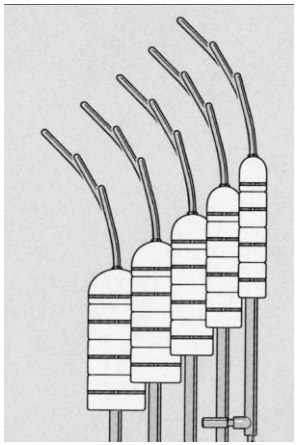
- Modified Heymann Packing
- Umbrella Technique

Standard applicators:

- Two or three channel applicator
- One channel applicator

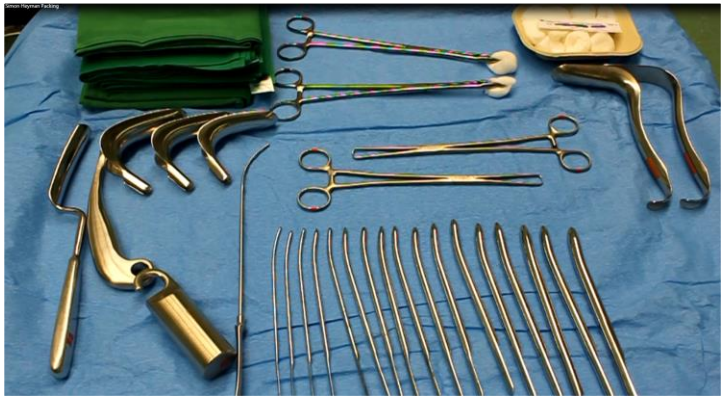


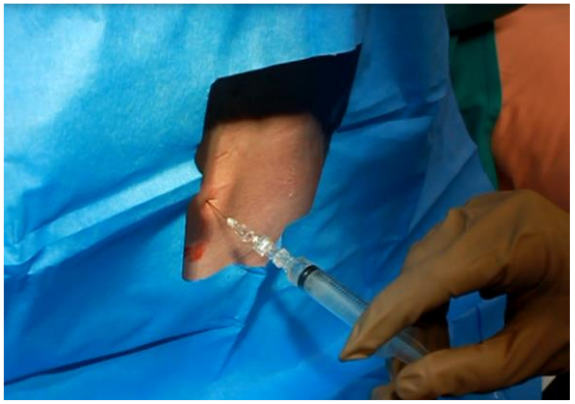


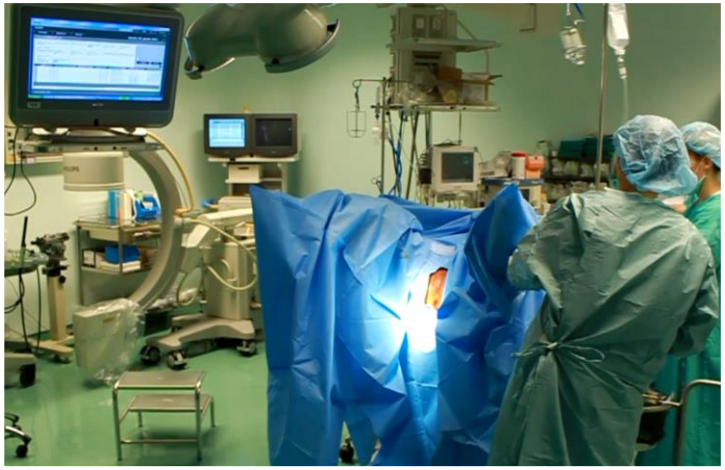


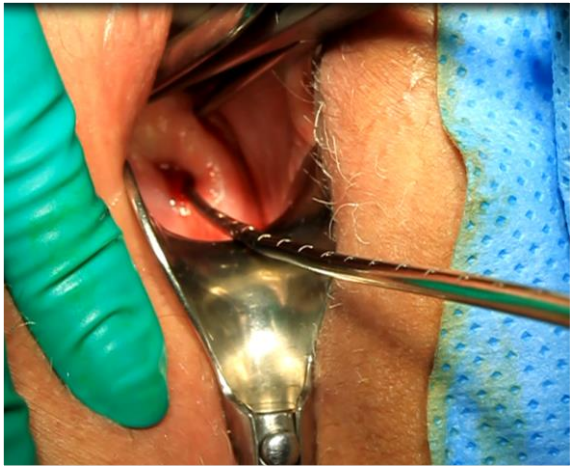
Practical points

- Collaboration anaesthesiologist; consider local anaesthesia
- Co-morbidity & feasibility

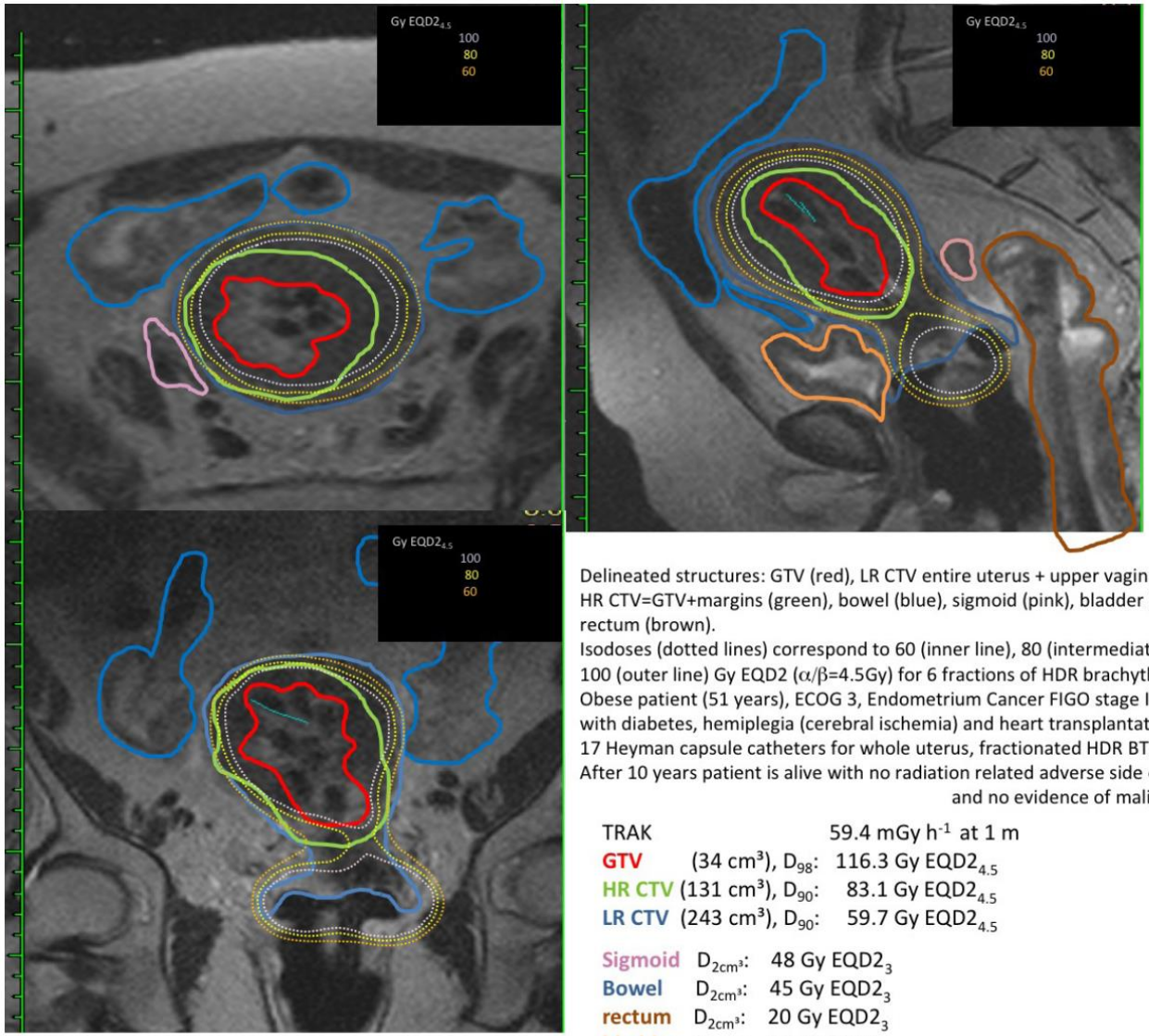








Treatment planning (other presentation)



Delineated structures: GTV (red), LR CTV entire uterus + upper vagina (blue), HR CTV=GTV+margins (green), bowel (blue), sigmoid (pink), bladder (yellow), rectum (brown).
Isodoses (dotted lines) correspond to 60 (inner line), 80 (intermediate line) and 100 (outer line) Gy EQD2 (α/β=4.5Gy) for 6 fractions of HDR brachytherapy alone.
Obese patient (51 years), ECOG 3, Endometrium Cancer FIGO stage II, with diabetes, hemiplegia (cerebral ischemia) and heart transplantation, 17 Heyman capsule catheters for whole uterus, fractionated HDR BT, 2005; After 10 years patient is alive with no radiation related adverse side effects and no evidence of malignant disease..

TRAK 59.4 mGy h^{-1} at 1 m
GTV (34 cm^3), D_{98}: 116.3 Gy $EQD2_{4.5}$
HR CTV (131 cm^3), D_{90}: 83.1 Gy $EQD2_{4.5}$
LR CTV (243 cm^3), D_{90}: 59.7 Gy $EQD2_{4.5}$

Sigmoid D_{2cm^3}: 48 Gy $EQD2_3$
Bowel D_{2cm^3}: 45 Gy $EQD2_3$
rectum D_{2cm^3}: 20 Gy $EQD2_3$
bladder D_{2cm^3}: 53 Gy $EQD2_3$

Vaginal recurrence (other presentation)

Toward four-dimensional image-guided adaptive brachytherapy in locally recurrent endometrial cancer

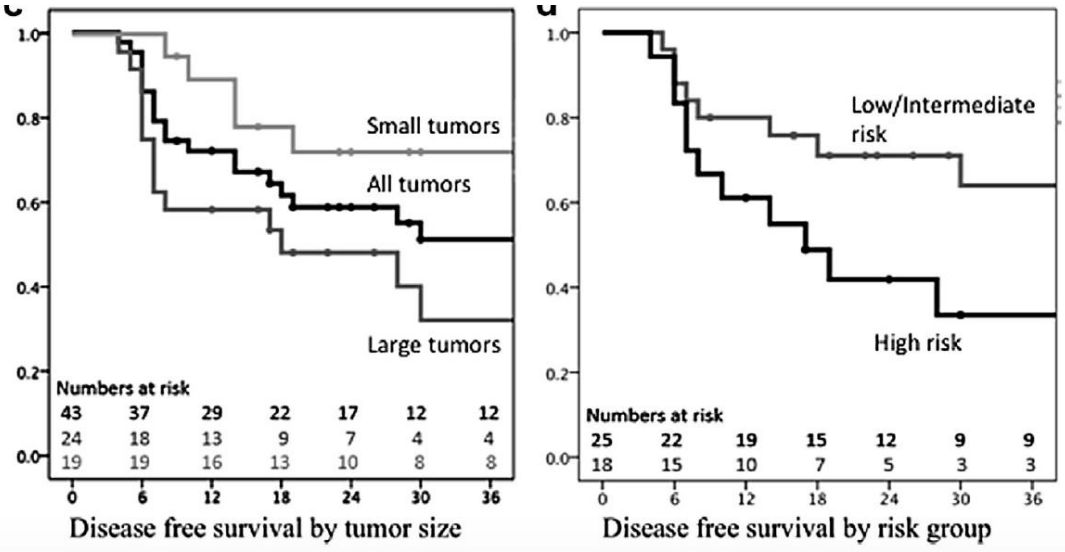
Lars Fokdal[1,*], Gitte Ørtoft[2], Estrid S. Hansen[3], Lisbeth Røhl[4], Erik Morre Pedersen[4], Kari Tanderup[1,5], Jacob Christian Lindegaard[1]

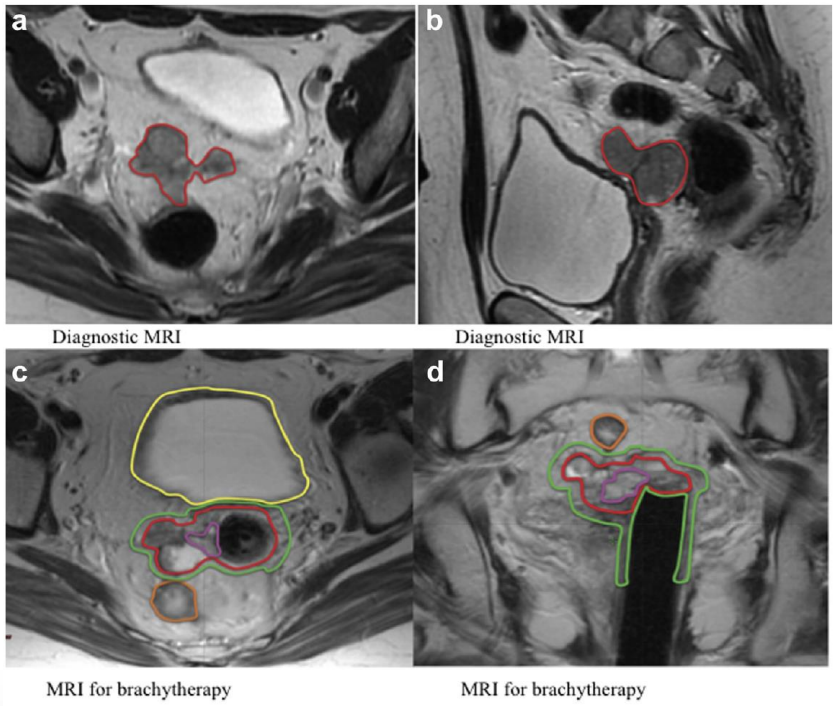
Brachytherapy 2013

Aarhus 2006-2013 N=43; PDR; median follow-up 30 months

24 interstitial – 19 intracavitary

Late grade 3 morbidity 12%





Conclusions

- Postoperative brachytherapy:
- Upper 1/3, ensure optimal contact with applicator
- 3D imaging: position verification
- 3D individualised optimization: for boost or recurrent disease

- Definitive treatment:
- Medical inoperable, rare (obesity)
- MRI gold standard
- Move towards 3D image guided approaches

ICRU-GEC-ESTRO Recommendations

Dose-Volume Reporting

Primoz Petric

Aarhus University Hospital

Richard Pötter

Medical University of Vienna

PRESCRIBING, RECORDING, AND REPORTING BRACHYTHERAPY FOR CANCER OF THE CERVIX (ICRU GEC ESTRO REPORT 88)

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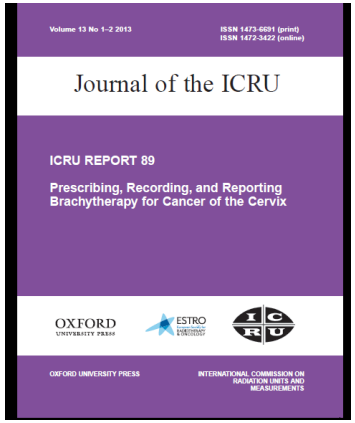
ICRU/GEC ESTRO recommendations for prescribing and reporting brachytherapy for cancer of the cervix



- 1 - INTRODUCTION
- 2 - PREVENTION, DIAGNOSIS, PROGNOSIS, TREATMENT AND OUTCOME
- 3 - BRACHYTHERAPY TECHNIQUES AND SYSTEMS
- 4 - BRACHYTHERAPY IMAGING FOR TREATMENT PLANNING
- 5 - TUMOR AND TARGET VOLUMES AND ADAPTIVE RADIOTHERAPY
- 6 - ORGANS AT RISK-AND-MORBIDITY-RELATED CONCEPTS AND VOLUMES
- 7 - RADIOBIOLOGICAL CONSIDERATIONS
- 8 - DOSE AND VOLUME PARAMETERS FOR PRESCRIBING, RECORDING, AND REPORTING OF BRACHYTHERAPY ALONE AND COMBINED WITH EXTERNAL BEAM RADIOTHERAPY
- 9 - 3D VOLUMETRIC DOSE ASSESSMENT
- 10 - RADIOGRAPHIC DOSE ASSESMENT
- 11 - SOURCES AND DOSE CALCULATION
- 12 - TREATMENT PLANNING
- 13 - SUMMARY OF THE RECOMMENDATIONS
- APPENDIX – EXAMPLES, SPREADSHEETS, DRAWINGS

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Learning Objectives

- Understand the concepts and learn the terms
  of **dose volume and dose point parameters**
  for planning, prescribing, recording and reporting
  the **GTV and the CTV doses** for 3D IGABT;

- Understand the concepts and learn the terms
  of **dose volume and dose point parameters**
  for planning, prescribing, recording and reporting
  the **OAR doses** for 3D IGABT;

- Be able to use brachytherapy related
  dose volume and dose point parameters
  for **planning aims and dose prescription**
  for **GTV, CTV**, and the relevant **OARs** in IGABT.

ICRU 89: Three Levels of Reporting

Level 3

Research oriented :
New concepts; to be established

Level 2

Advanced standard:
↑comprehensive exchange of information

Level 1

Minimum standard:
All centres, for all patients

ICRU/GEC ESTRO Report 89. 2016

ICRU 89: Three Levels of Reporting

Level 1: *Minimum standard for reporting*

Volumetric imaging approximation

- Comprehensive clinical gynecologic examination
- Volumetric imaging (MR, CT, US, PET–CT) at the time of diagnosis and brachytherapy

FIGO/TNM stage

Baseline morbidity and QoL assessment

Schematic 3D documentation on a clinical diagram indicating dimensions (width, thickness, height) and volumes for:

- GTV_{init} (the GTV at diagnosis)
- GTV_{res} (the GTV at brachytherapy)
- CTV_{HR} [the GTV_{res} (if present) plus residua
  (if present) plus whole cervix]
- (CTV_{IR}: area of GTV_{init} and/or CTV_{HR} plus s
  used for prescription)

Dose reporting:

- TRAK
- Point A dose
- Recto-vaginal reference-point dose
- $D_{0.1cm^3}$ and D_{2cm^3} for the bladder and rectun

Dose delivery pattern:

- Absorbed-dose rate/dose per fraction
- Number of fractions
- Time between fractions
- (Pulse number, size, time, if PDR)
- Overall treatment time
- Total EQD2 dose

Source and dose calculation:

- Radionuclide and source model
- Source strength
- Dose-calculation algorithm

Radiographic approximation

- Comprehensive clinical gynecologic examination
- Radiographic imaging (plus additional volumetric 3D imaging if available)

FIGO/TNM stage

Baseline morbidity and QoL assessment

Schematic 3D documentation on a clinical diagram indicating dimensions [width, thickness, (height)] and volumes for:

- GTV_{init} (the GTV at diagnosis)
- GTV_{res} (the GTV at brachytherapy)

Level 2: *Advanced standard for reporting; All from L1 plus:*

Volumetric imaging approximation

3D delineation of volumes (on volumetric images with applicator):

- GTV_{res}
- CTV_{HR}
- (CTV_{IR} if used for prescription)
- With maximum width, height, thickness, and with volume

Dose reporting for defined volumes:

- $D_{98\,\%}$, $D_{90\,\%}$, $D_{50\,\%}$ for the CTV_{HR}
- ($D_{98\,\%}$, $D_{90\,\%}$ for the CTV_{IR} if used for prescription
- $D_{98\,\%}$ for GTV_{res}
- $D_{98\,\%}$ for pathological lymph nodes

Dose reporting OARs:

- Bladder reference point dose
- $D_{0.1cm^3}$, D_{2cm^3} for sigmoid[a]
- D_{2cm^3} bowel
- Intermediate- and low-dose parameters in bladder
  sigmoid, bowel
  (*e.g.*, $V_{15\,Gy}$, $V_{25\,Gy}$, $V_{35\,Gy}$, $V_{45\,Gy}$ or $D_{98\,\%}$, $D_{50\,\%}$, D
- Vaginal point doses at level of sources (lateral at 5
- Lower- and mid-vagina doses (PIBS, PIBS + 2 cm

Radiographic approximation

Topography for volumes (on isodose plan with applicator/on radiographs with applicator)

- GTV_{res}
- CTV_{HR}
- CTV_{IR} (if used for prescription)
- With maximum width, thickness, standard height, and with

Level 3: *Research-oriented reporting; All from L1 & L2 plus:*

Volumetric imaging approximation

Tumor-related volumes:
(1) GTV, CTV_{HR} sub-volumes based on functional imaging (diagnosis, during treatment, and at brachytherapy)
(2) PTV

Isodose surface volumes:
For example

- 85 Gy EQD2 volume
- 60 Gy EQD2 volume

Dose reporting for tumor:

(1) $D_{98\,\%}$ and $D_{90\,\%}$ for the CTV_{IR} even if not used for prescription
(2) $D_{90\,\%}$ for the GTV_{res}
(3) DVH parameters for the PTV
(4) $D_{50\,\%}$ for pathological lymph nodes
(5) DVH parameters for non-involved nodes (ext/int iliac, common iliac)

OAR volumes and points:

(1) Additional bladder and rectum reference points
(2) OAR sub-volumes (*e.g.*, trigonum or bladder neck, sphincter muscles)
(3) Vagina (upper, middle, lower)
(4) Anal canal (sphincter)
(5) Vulva (labia, clitoris)
(6) Other volumes/sub-volumes of interest (*e.g.*, ureter)

Dose–volume reporting for OAR:

(1) Dose–volume and dose–surface histogram parameters for additional OARs and sub-volumes
(2) Vaginal dose profiles, dose–volume, and dose–surface histograms
(3) Length of treated vagina

Radiographic approximation

Isodose surface volumes: For example

- 85 Gy EQD2 volume
- 60 Gy EQD2 volume

OAR volumes, points:

(1) Additional bladder and rectum points
(2) Sigmoid point
(3) Anal-canal point (*e.g.*, low vagina point)
(4) Vulva point (*e.g.*, low vagina point)
(5) Other points of interest

OAR dose reporting:

- Length of treated vagina

Emphasis on
Volumetric imaging approximation

ICRU/GEC ESTRO Report 89. 2016. pp 161-3.

ICRU 89: Three Levels of Reporting

Level 1: *Minimum standard for reporting*

Volumetric imaging approximation

- Comprehensive clinical gynecologic examination
- Volumetric imaging (MR, CT, US, PET–CT) at the time of diagnosis and brachytherapy

FIGO/TNM stage

Baseline morbidity and QoL assessment

Schematic 3D documentation on a clinical diagram indicating dimensions (width, thickness, height) and volumes for:

- GTV_{init} (the GTV at diagnosis)
- GTV_{res} (the GTV at brachytherapy)
- CTV_{HR} [the GTV_{res} (if present) plus residua
(if present) plus whole cervix]
- (CTV_{IR}: area of GTV_{init} and/or CTV_{HR} plus s
used for prescription)

Dose reporting:

- TRAK
- Point A dose
- Recto-vaginal reference-point dose
- $D_{0.1cm^3}$ and D_{2cm^3} for the bladder and rectun

Dose delivery pattern:

- Absorbed-dose rate/dose per fraction
- Number of fractions
- Time between fractions
- (Pulse number, size, time, if PDR)
- Overall treatment time
- Total EQD2 dose

Source and dose calculation:

- Radionuclide and source model
- Source strength
- Dose-calculation algorithm

Radiographic approximation

- Comprehensive clinical gynecologic examination
- Radiographic imaging (plus additional volumetric 3D imaging if available)

FIGO/TNM stage

Baseline morbidity and QoL assessment

Schematic 3D documentation on a clinical diagram indicating dimensions [width, thickness, (height)] and volumes for:

- GTV_{init} (the GTV at diagnosis)
- GTV_{res} (the GTV at brachytherapy)

Level 2: *Advanced standard for reporting; All from L1 plus:*

Volumetric imaging approximation

3D delineation of volumes (on volumetric images with applicator):

- GTV_{res}
- CTV_{HR}
- (CTV_{IR} if used for prescription)
- With maximum width, height, thickness, and with volume

Dose reporting for defined volumes:

- $D_{98\,\%}$, $D_{90\,\%}$, $D_{50\,\%}$ for the CTV_{HR}
- ($D_{98\,\%}$, $D_{90\,\%}$ for the CTV_{IR} if used for prescription
- $D_{98\,\%}$ for GTV_{res}
- $D_{98\,\%}$ for pathological lymph nodes

Dose reporting OARs:

- Bladder reference point dose
- $D_{0.1cm^3}$, D_{2cm^3} for sigmoid[a]
- D_{2cm^3} bowel
- Intermediate- and low-dose parameters in bladde
sigmoid, bowel
(*e.g.*, $V_{15\,Gy}$, $V_{25\,Gy}$, $V_{35\,Gy}$, $V_{45\,Gy}$ or $D_{98\,\%}$, $D_{50\,\%}$, D
- Vaginal point doses at level of sources (lateral at 5
- Lower- and mid-vagina doses (PIBS, PIBS + 2 cm)

Radiographic approximation

Topography for volumes (on isodose plan with applicator/on radiographs with applicator)

- GTV_{res}
- CTV_{HR}
- CTV_{IR} (if used for prescription)
- With maximum width, thickness, standard height, and with

Level 3: *Research-oriented reporting; All from L1 & L2 plus:*

Volumetric imaging approximation

Tumor-related volumes:

(1) GTV, CTV_{HR} sub-volumes based on functional imaging (diagnosis, during treatment, and at brachytherapy)
(2) PTV

Isodose surface volumes:
For example

- 85 Gy EQD2 volume
- 60 Gy EQD2 volume

Dose reporting for tumor:

(1) $D_{98\,\%}$ and $D_{90\,\%}$ for the CTV_{IR} even if not used for prescription
(2) $D_{90\,\%}$ for the GTV_{res}
(3) DVH parameters for the PTV
(4) $D_{50\,\%}$ for pathological lymph nodes
(5) DVH parameters for non-involved nodes (ext/int iliac, common iliac)

OAR volumes and points:

(1) Additional bladder and rectum reference points
(2) OAR sub-volumes (*e.g.*, trigonum or bladder neck, sphincter muscles)
(3) Vagina (upper, middle, lower)
(4) Anal canal (sphincter)
(5) Vulva (labia, clitoris)
(6) Other volumes/sub-volumes of interest (*e.g.*, ureter)

Dose–volume reporting for OAR:

(1) Dose–volume and dose–surface histogram parameters for additional OARs and sub-volumes
(2) Vaginal dose profiles, dose–volume, and dose–surface histograms
(3) Length of treated vagina

Radiographic approximation

Isodose surface volumes: For example

- 85 Gy EQD2 volume
- 60 Gy EQD2 volume

OAR volumes, points:

(1) Additional bladder and rectum points
(2) Sigmoid point
(3) Anal-canal point (*e.g.*, low vagina point)
(4) Vulva point (*e.g.*, low vagina point)
(5) Other points of interest

OAR dose reporting:

- Length of treated vagina

Emphasis on
Volumetric imaging approximation

ICRU/GEC ESTRO Report 89. 2016. pp 161-3.

Reporting Tumor Extent

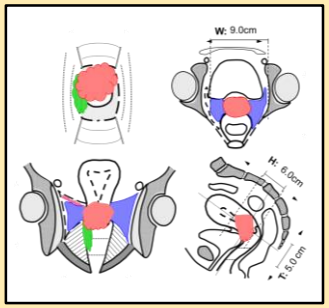
Level 1

At Diagnosis

Dimensions: GTV_{init}

TNM & FIGO stage

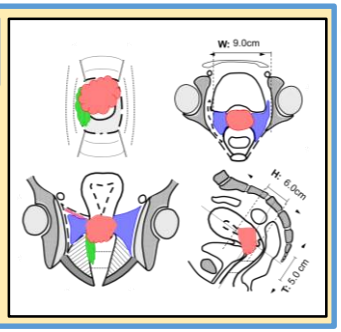
Morbidity & QoL



At Brachytherapy

Dimensions:

- GTV_{res}
- CTV_{HR},
- CTV_{IR}



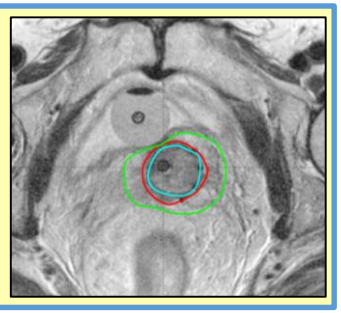
Level 2

Day 2 lecture:
ICRU/GEC ESTRO
Contouring Recommendations

At Brachytherapy

Contouring:

- GTV_{res}
- CTV_{HR},
- CTV_{IR}



Level 3

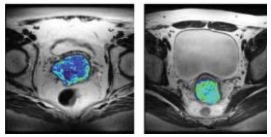
At Diagnosis

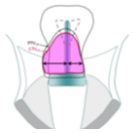
During treatment

At Brachytherapy

Contouring:

- GTV and CTV_{HR} Sub-volumes (functional imaging)
- PTV





ICRU/GEC ESTRO Report 89. 2016

ICRU 89: Three Levels of Reporting

Level 1: *Minimum standard for reporting*

Volumetric imaging approximation

- Comprehensive clinical gynecologic examination
- Volumetric imaging (MR, CT, US, PET–CT) at the time of diagnosis and brachytherapy

FIGO/TNM stage

Baseline morbidity and QoL assessment

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- CTV_{HR} [the GTV_{res} (if present) plus residua
(if present) plus whole cervix]
- (CTV_{IR}: area of GTV_{init} and/or CTV_{HR} plus s
used for prescription)

Dose reporting:

- TRAK
- Point A dose
- Recto-vaginal reference-point dose
- $D_{0.1cm^3}$ and D_{2cm^3} for the bladder and rectun

Dose delivery pattern:

- Absorbed-dose rate/dose per fraction
- Number of fractions
- Time between fractions
- (Pulse number, size, time, if PDR)
- Overall treatment time
- Total EQD2 dose

Source and dose calculation:

- Radionuclide and source model
- Source strength
- Dose-calculation algorithm

Radiographic approximation

- Comprehensive clinical gynecologic examination
- Radiographic imaging (plus additional volumetric 3D imaging if available)

FIGO/TNM stage

Baseline morbidity and QoL assessment

Schematic 3D documentation on a clinical diagram indicating dimensions [width, thickness, (height)] and volumes for:

- GTV_{init} (the GTV at diagnosis)
- GTV_{res} (the GTV at brachytherapy)

Level 2: *Advanced standard for reporting; All from L1 plus:*

Volumetric imaging approximation

3D delineation of volumes (on volumetric images with applicator):

- GTV_{res}
- CTV_{HR}
- (CTV_{IR} if used for prescription)
- With maximum width, height, thickness, and with volume

Dose reporting for defined volumes:

- $D_{98\,\%}$, $D_{90\,\%}$, $D_{50\,\%}$ for the CTV_{HR}
- ($D_{98\,\%}$, $D_{90\,\%}$ for the CTV_{IR} if used for prescription
- $D_{98\,\%}$ for GTV_{res}
- $D_{98\,\%}$ for pathological lymph nodes

Dose reporting OARs:

- Bladder reference point dose
- $D_{0.1cm^3}$, D_{2cm^3} for sigmoid[a]
- D_{2cm^3} bowel
- Intermediate- and low-dose parameters in bladder
sigmoid, bowel
(*e.g.*, $V_{15\,Gy}$, $V_{25\,Gy}$, $V_{35\,Gy}$, $V_{45\,Gy}$ or $D_{98\,\%}$, $D_{50\,\%}$, D
- Vaginal point doses at level of sources (lateral at 5
- Lower- and mid-vagina doses (PIBS, PIBS + 2 cm

Radiographic approximation

Topography for volumes (on isodose plan with applicator/on radiographs with applicator)

- GTV_{res}
- CTV_{HR}
- CTV_{IR} (if used for prescription)
- With maximum width, thickness, standard height, and with

Level 3: *Research-oriented reporting; All from L1 & L2 plus:*

Volumetric imaging approximation

Tumor-related volumes:
(1) GTV, CTV_{HR} sub-volumes based on functional imaging (diagnosis, during treatment, and at brachytherapy)
(2) PTV

Isodose surface volumes:
For example

- 85 Gy EQD2 volume
- 60 Gy EQD2 volume

Dose reporting for tumor:

(1) $D_{98\,\%}$ and $D_{90\,\%}$ for the CTV_{IR} even if not used for prescription
(2) $D_{90\,\%}$ for the GTV_{res}
(3) DVH parameters for the PTV
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(5) DVH parameters for non-involved nodes (ext/int iliac, common iliac)

OAR volumes and points:

(1) Additional bladder and rectum reference points
(2) OAR sub-volumes (*e.g.*, trigonum or bladder neck, sphincter muscles)
(3) Vagina (upper, middle, lower)
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(5) Vulva (labia, clitoris)
(6) Other volumes/sub-volumes of interest (*e.g.*, ureter)

Dose–volume reporting for OAR:
(1) Dose–volume and dose–surface histogram parameters for additional OARs and sub-volumes
(2) Vaginal dose profiles, dose–volume, and dose–surface histograms
(3) Length of treated vagina

Radiographic approximation

Isodose surface volumes: For example

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OAR dose reporting:

- Length of treated vagina

Emphasis on
Volumetric imaging approximation

ICRU/GEC ESTRO Report 89. 2016. pp 161-3.

ICRU 89: Three Levels of Reporting

Level 1: *Minimum standard for reporting*

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- Comprehensive clinical gynecologic examination
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FIGO/TNM stage

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- $D_{0.1cm^3}$ and D_{2cm^3} for the bladder and rectun

Dose delivery pattern:

- Absorbed-dose rate/dose per fraction
- Number of fractions
- Time between fractions
- (Pulse number, size, time, if PDR)
- Overall treatment time
- Total EQD2 dose

Source and dose calculation:

- Radionuclide and source model
- Source strength
- Dose-calculation algorithm

Radiographic approximation

- Comprehensive clinical gynecologic examination
- Radiographic imaging (plus additional volumetric 3D imaging if available)

FIGO/TNM stage

Baseline morbidity and QoL assessment

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- GTV_{init} (the GTV at diagnosis)
- GTV_{res} (the GTV at brachytherapy)

Level 2: *Advanced standard for reporting; All from L1 plus:*

Volumetric imaging approximation

3D delineation of volumes (on volumetric images with applicator):

- GTV_{res}
- CTV_{HR}
- (CTV_{IR} if used for prescription)
- With maximum width, height, thickness, and with volume

Dose reporting for defined volumes:

- $D_{98\,\%}$, $D_{90\,\%}$, $D_{50\,\%}$ for the CTV_{HR}
- ($D_{98\,\%}$, $D_{90\,\%}$ for the CTV_{IR} if used for prescription
- $D_{98\,\%}$ for GTV_{res}
- $D_{98\,\%}$ for pathological lymph nodes

Dose reporting OARs:

- Bladder reference point dose
- $D_{0.1cm^3}$, D_{2cm^3} for sigmoid[a]
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- Intermediate- and low-dose parameters in bladder
sigmoid, bowel
(*e.g.*, $V_{15\,Gy}$, $V_{25\,Gy}$, $V_{35\,Gy}$, $V_{45\,Gy}$ or $D_{98\,\%}$, $D_{50\,\%}$, D
- Vaginal point doses at level of sources (lateral at 5
- Lower- and mid-vagina doses (PIBS, PIBS + 2 cm

Radiographic approximation

Topography for volumes (on isodose plan with applicator/on radiographs with applicator)

- GTV_{res}
- CTV_{HR}
- CTV_{IR} (if used for prescription)
- With maximum width, thickness, standard height, and with

Level 3: *Research-oriented reporting; All from L1 & L2 plus:*

Volumetric imaging approximation

Tumor-related volumes:
(1) GTV, CTV_{HR} sub-volumes based on functional imaging (diagnosis, during treatment, and at brachytherapy)
(2) PTV

Isodose surface volumes:
For example

- 85 Gy EQD2 volume
- 60 Gy EQD2 volume

Dose reporting for tumor:

(1) $D_{98\,\%}$ and $D_{90\,\%}$ for the CTV_{IR} even if not used for prescription
(2) $D_{90\,\%}$ for the GTV_{res}
(3) DVH parameters for the PTV
(4) $D_{50\,\%}$ for pathological lymph nodes
(5) DVH parameters for non-involved nodes (ext/int iliac, common iliac)

OAR volumes and points:

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(1) Dose–volume and dose–surface histogram parameters for additional OARs and sub-volumes
(2) Vaginal dose profiles, dose–volume, and dose–surface histograms
(3) Length of treated vagina

Radiographic approximation

Isodose surface volumes: For example

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OAR volumes, points:

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(5) Other points of interest

OAR dose reporting:

- Length of treated vagina

Emphasis on
Volumetric imaging approximation

ICRU/GEC ESTRO Report 89. 2016. pp 161-3.

Prescribing, Recording & Reporting of D & V

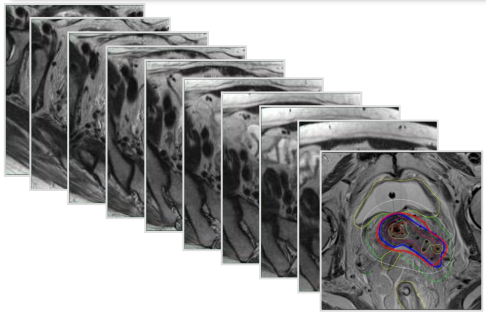
ICRU Report 89. 2016, page 106:

organs are not sufficient.

The overall aim of dose prescription and reporting is to describe the dose distribution related to target volumes and to OARs as completely and precisely as possible. The typical heterogeneity of the brachytherapy absorbed-dose distribution complicates achievement of this goal. In the hypothetical case of a

Reporting treatment: **General Aspects**

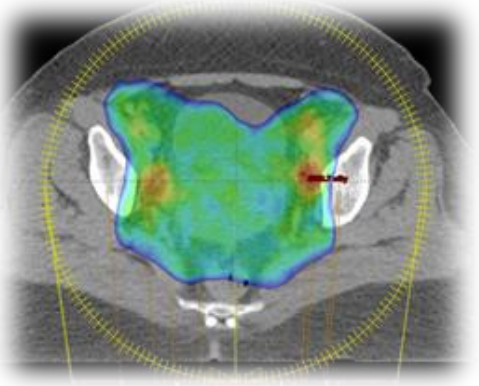
4D BT



Steep dose gradients

Heterogeneous D

4D EBRT



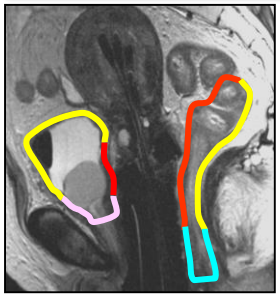
Different time-D patterns

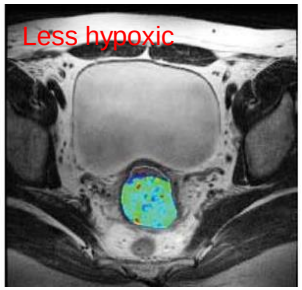
Challenges of D summation

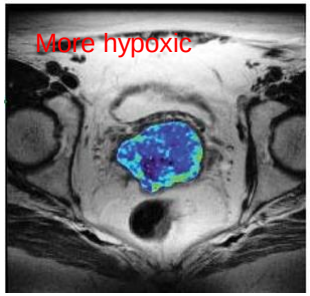
Complex (sub)volumes

Different biological characteristics

Subvolumes of OAR & Target Volumes

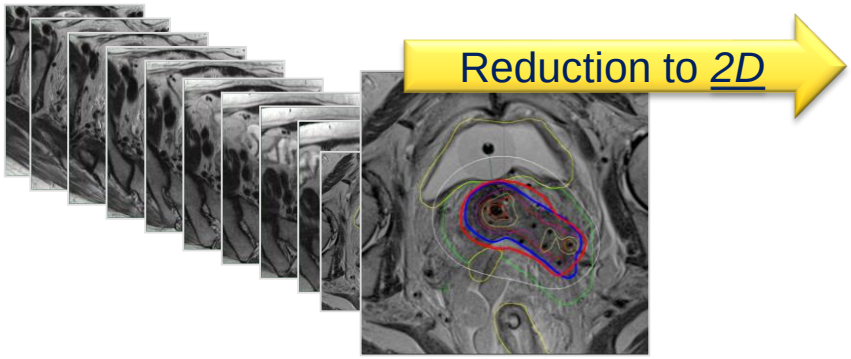


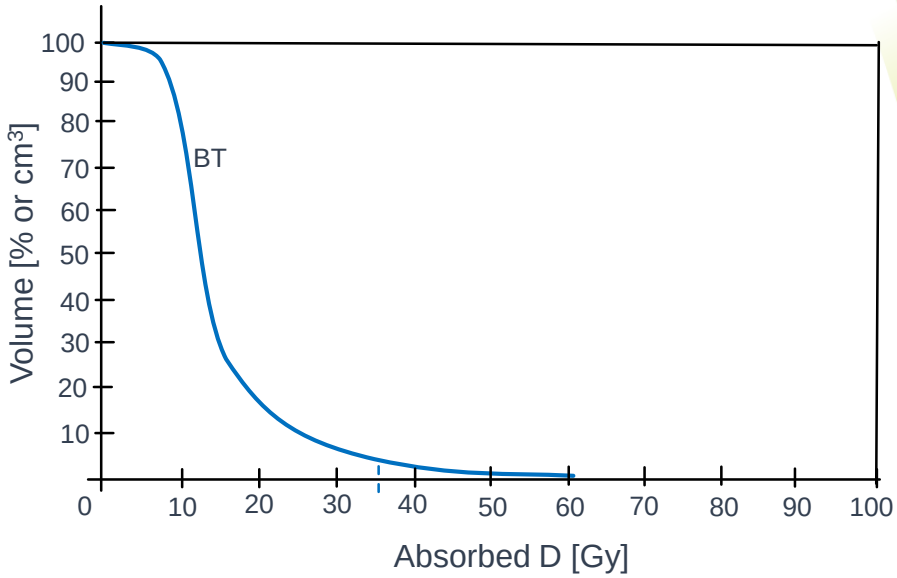




Reporting treatment: **General Aspects**

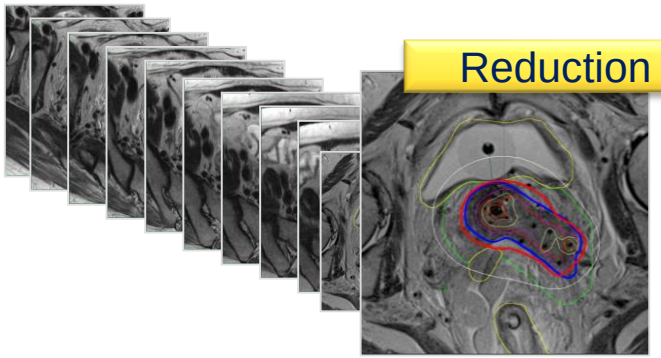
4D BT (V and time)



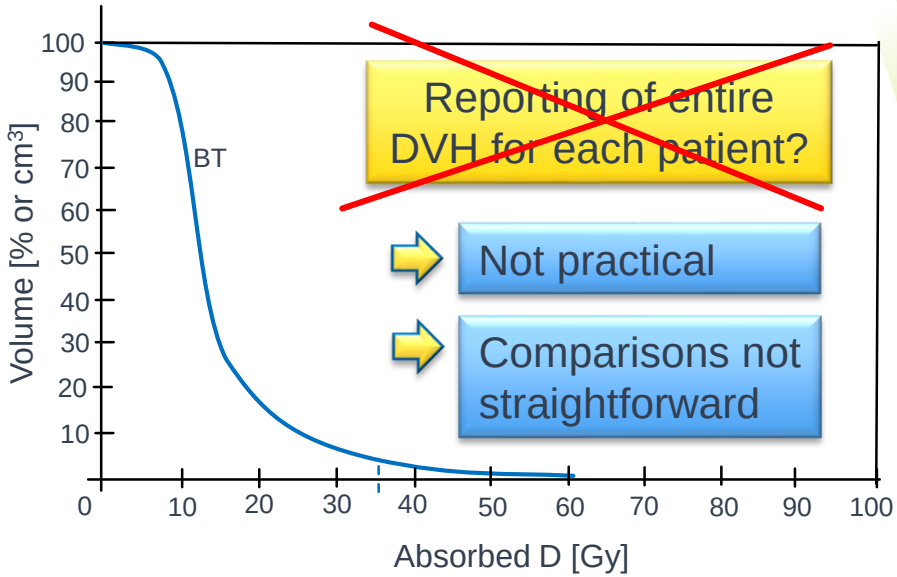


Reporting treatment: **General Aspects**

4D BT (V and time)



Reduction to *2D*



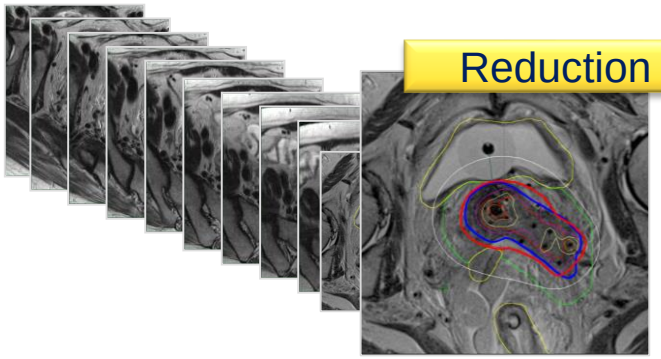
~~Reporting of entire DVH for each patient?~~

Not practical

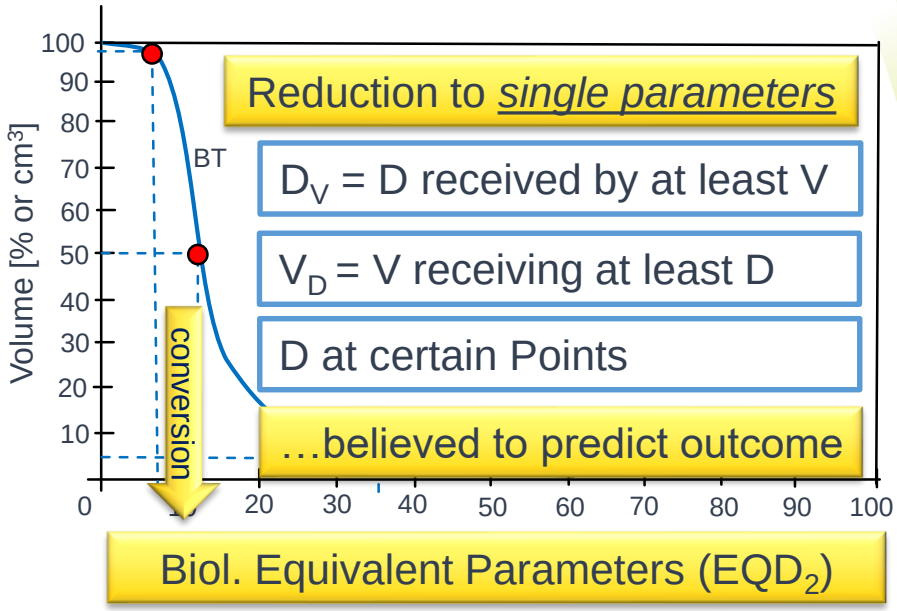
Comparisons not straightforward

Reporting treatment: **General Aspects**

4D BT (V and time)

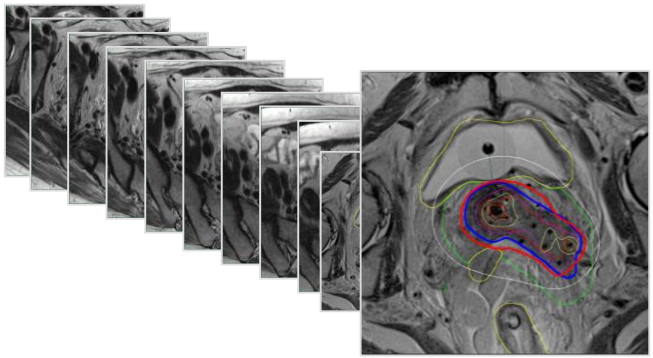


Reduction to *2D*



Reporting treatment: General Aspects

4D BT (V and time)

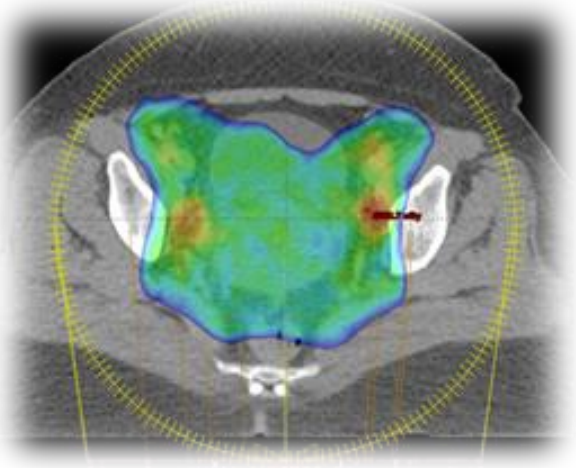


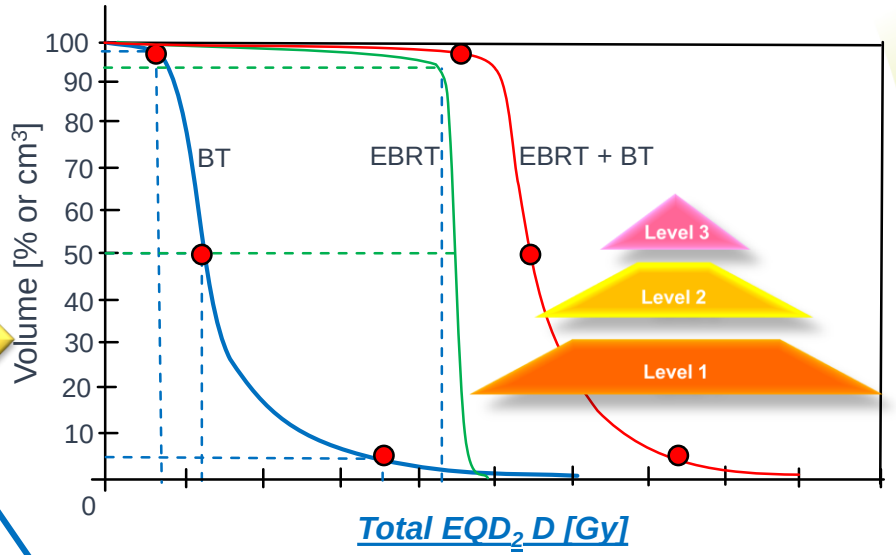
EQD_2

Sum

4D EBRT (V and time)

EQD_2





- BT: Fractional and total EQD2
- EBRT: total EQD2
- EBRT+BT: total EQD2
- *Assumptions: see ICRU 89, chapter 9*
- LQ model
- Limitations…

Wednesday 8:30

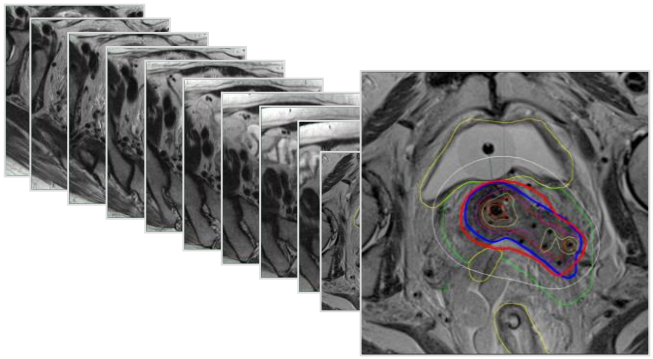
Presentation:

Radiobiological models to combine D from EBRT & BT

Daniel Berger

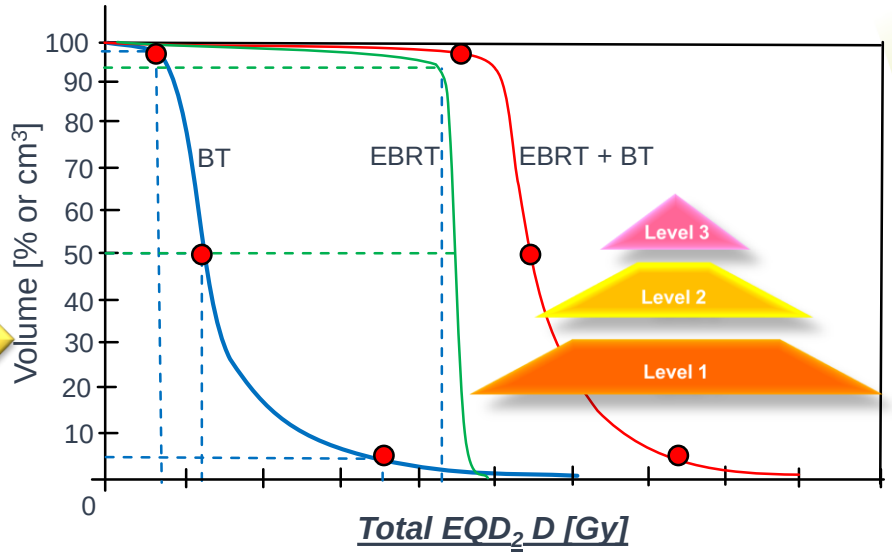
Reporting treatment: General Aspects

4D BT (V and time)

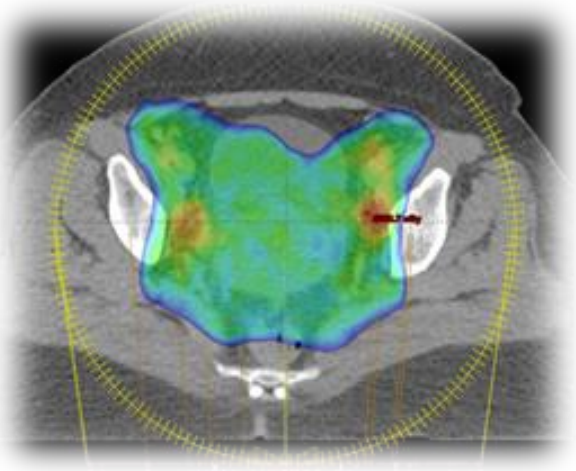


EQD_2

Sum

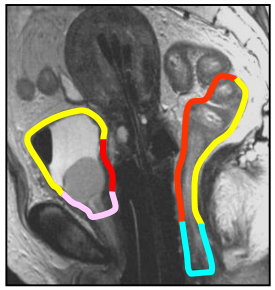


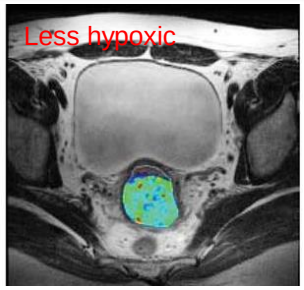
4D EBRT (V and time)

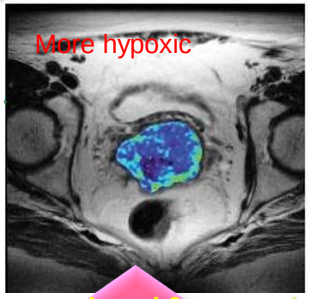


EQD_2

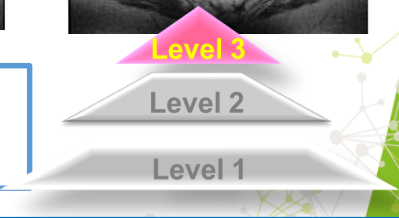
Subvolumes of OAR & Target Volumes







DVH for subvolumes → Link with effects



From treatment planning to dose prescription

From Planning Aim to D Prescription

ICRU 89: process from *planning aim* to *prescription* is defined

Planning Aim

Set of intended D-V parameters

Target

OAR

Treatment planning

Individualized D-V adaptation

Plan review/approval

Achieved D-V parameters

Target

OAR

Prescribed D

Delivered D (?)

Reporting

For a patient cohort:

- Mean / Median
- SD / Range
- Unlikely the same as Planning Aim!

Evidence

ICRU/GEC ESTRO Report 89. 2016

Prescribing, Recording & Reporting of D & V

Q: **Centre X uses *"BT schedule of 4x7 Gy to CTV HR"*.**

What is prescribed dose / fraction to CTV HR in their patients?

A:

A. 10 Gy, according to Linear Quadratic model

B. 7 Gy

C. 28 Gy

D. I can't tell, but all of the above answers are likely wrong. ✓

…the term "4 x 7 schedule" doesn't tell us much…

Planning aims – desired D_V and V_D parameters —i. e.→ D90 > 10 Gy EQD2

⇩

Prescription – achieved D_V and V_D parameters after planning —i. e.→ D90 = 10.4 +/- 0.6 Gy EQD2

⇩

Delivered treatment –D_V and V_D parameters delivered —i. e.→ ???

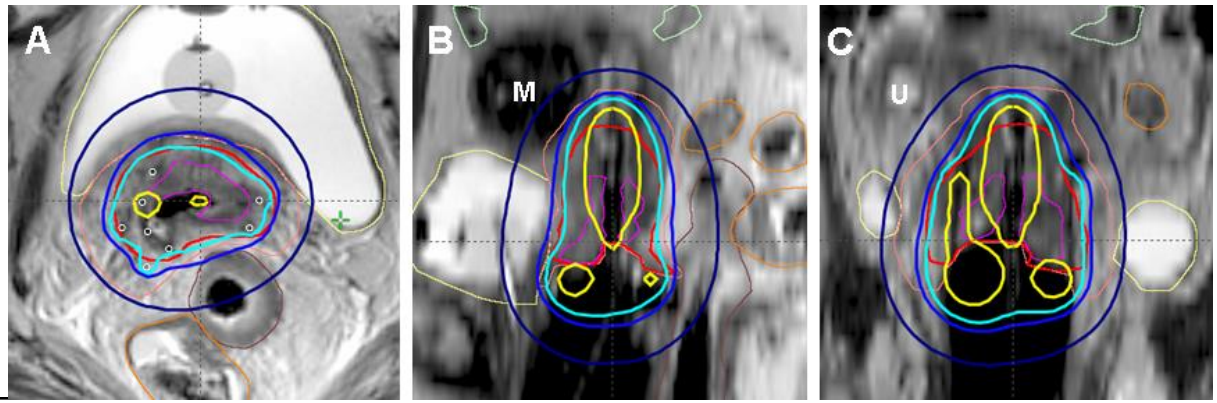
Planning aim and prescription dose

- **Planning aim: what you want to obtain**
- **Prescribed dose: what you decide to treat**

Case 6

Appendix,

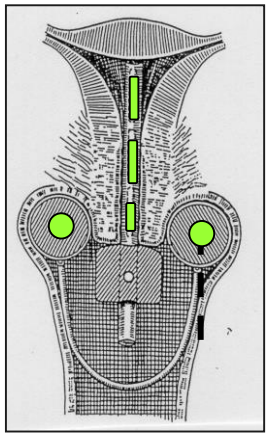
ICRU 89



Structure	Dose-volume parameter	Planning aim, Gy	Prescribed dose Gy
CTV_{HR}	$EQD2_{10}$ D_{90}	≥ 85	88.9
Bladder	$EQD2_3$ D_{2cm^3}	≤ 90	71.1
Rectum	$EQD2_3$ D_{2cm^3}	≤ 70	65.6
Sigmoid	$EQD2_3$ D_{2cm^3}	≤ 70	57.4
Bowel	$EQD2_3$ D_{2cm^3}	≤ 70	53.3

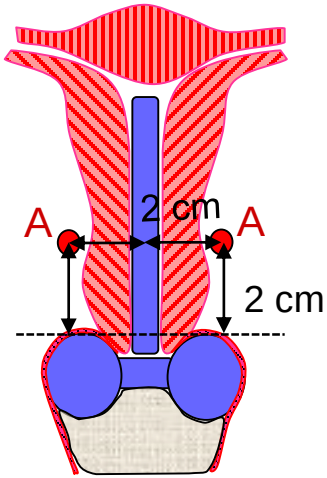
Reporting Parameters for the Target

“Amount” of radiation



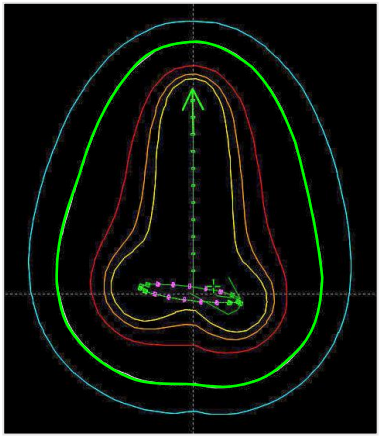
Review: GEC ESTRO Handbook

D to point(s)



Meredith WJ. Radium dosage. The Manchester system.1947.

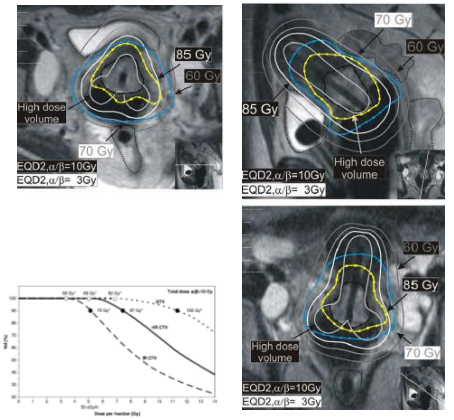
D to isodose surface



ICRU report 38, 1985

ICRU report 89, 2016

D-V parameters



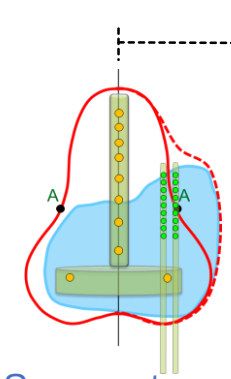
Pötter R, et al. Radiother Oncol 2006

Haie Meder et al. Radiother Oncol 2007

ICRU report 89, 2016

Amount of Radiation

Total Reference Air Kerma (TRAK)



Source strength

KERMA:

Kinetic **E**nergy **R**eleased per unit **MA**ss

At 1 m: *Reference Air Kerma Rate* [Gy/s]

x Dwell Time [s]

Σ All positions

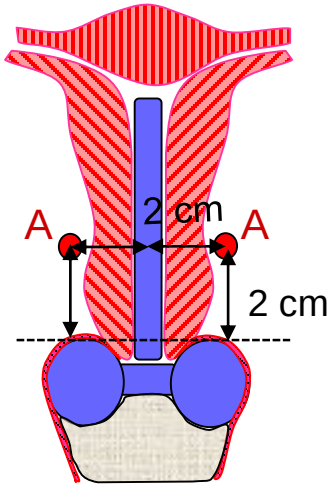
TRAK **[Gy]**

- Corresponds to historical quantity **"mg·h of Radium"**
  - 1mg·h = 7.2 μGy @ 1m
- Physical parameter (not directly associated with effects)
- Extensive experience
- Comparison of treatments
  - within & between institutions

ICRU report 38. 1985

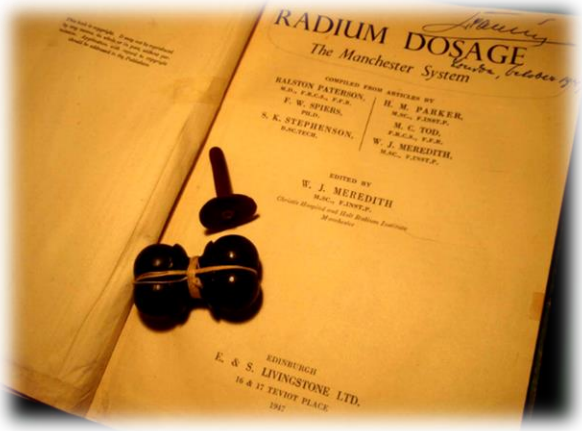
ICRU/GEC ESTRO Report 89. 2016

Point A Dose



- Introduced in the 1930's *(Tod & Meredith)*
- Surrogate for mgh or TRAK (amount of radiation)
- p. A: ≈ Crossing of uterine artery and ureters

Manchester system = set of rules → Given tumour V



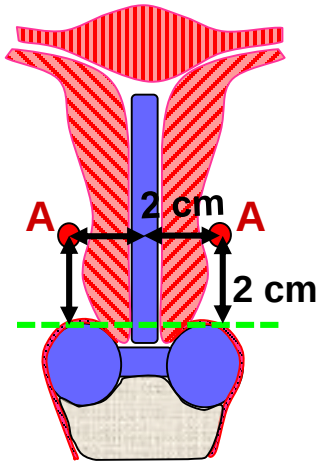
- Given tumour V
- Source Geometry
- mg of ^{226}Ra
- Duration
- Certain p. A Dose

Tod & Meredith, 1938.
Meredith WJ, ed.. Radium dosage. The Manchester system. Edinburgh;1947.

Point A Dose

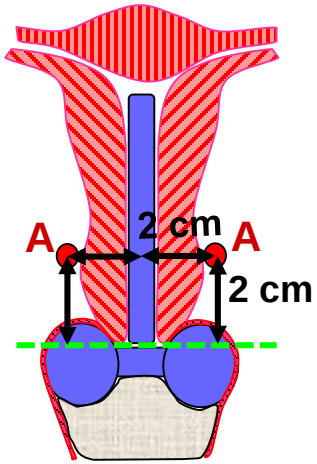
Point A is an applicator point, defined in relation to tandem and colpostats…

Upper surface of ovoids



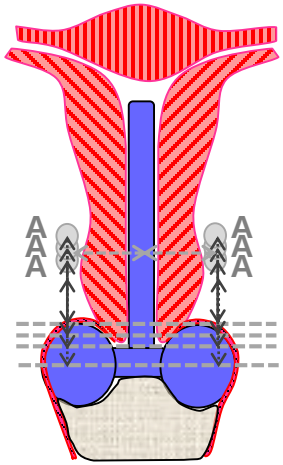
Tod & Meredith, 1938.

Bottom of tandem / Os



Tod & Meredith, 1953.

Various interpretations



Different authors

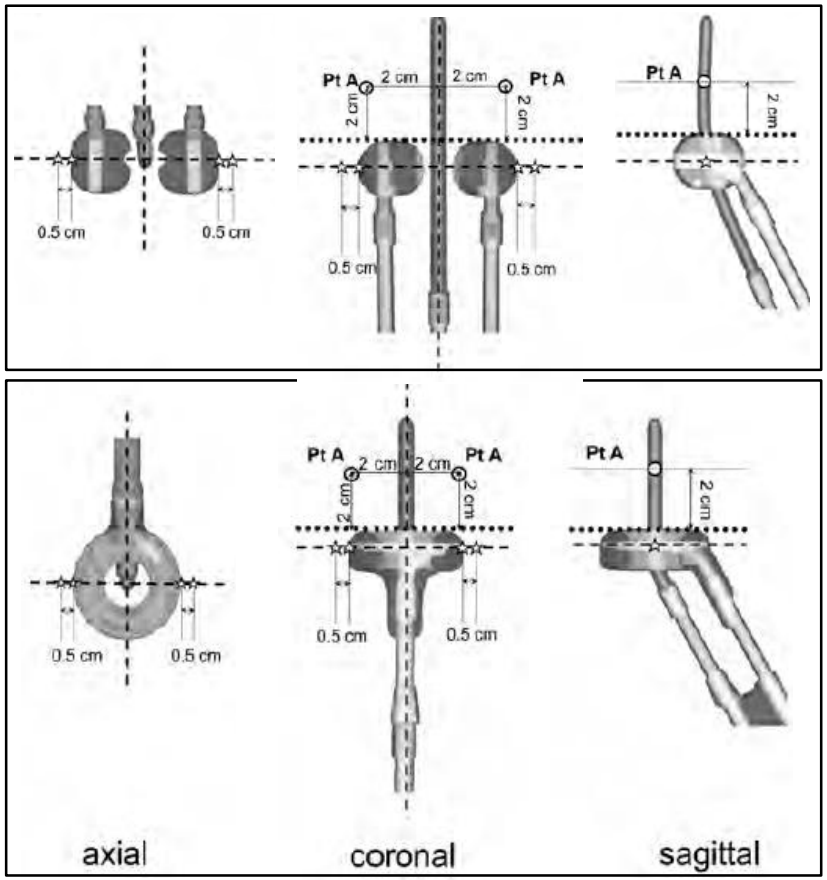
Variation of point A location → Large Variation of reported D

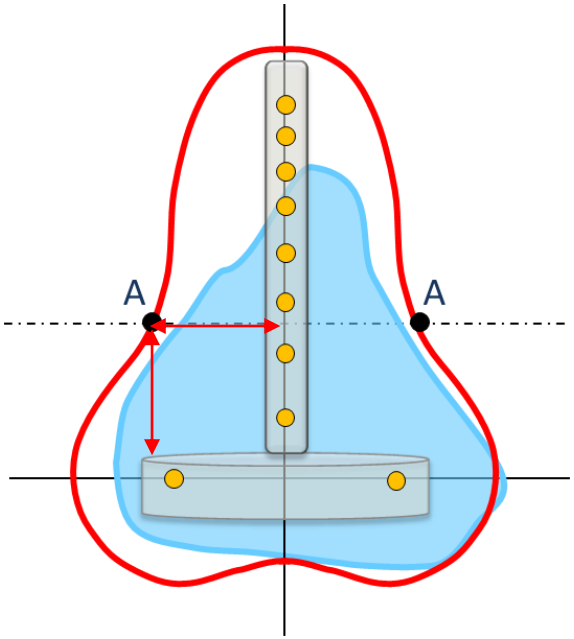
ICRU/GEC ESTRO Report 89. 2016

Point A Dose

ICRU 89 & ABS definition:

- Follows original Manchester definition
- Point A related to the applicator





Provides information on D distribution

only if source-pattern rules are described!

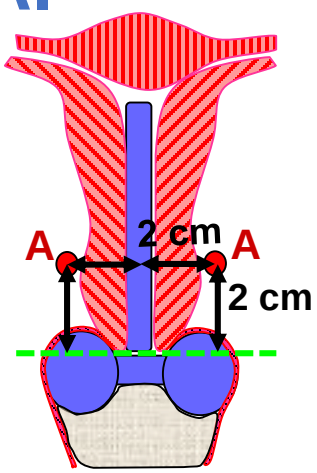
ICRU/GEC ESTRO Report 89. 2016

Viswanathan AN & Thomadsen B. Brachytherapy 2012;11:33-46.

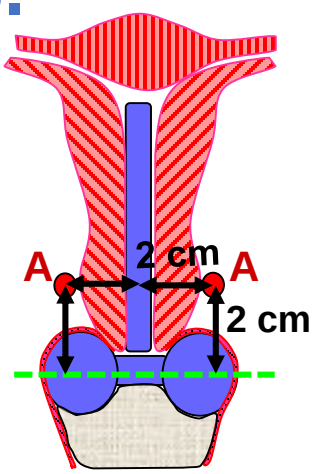
Point A Dose

Q: **How do you define point A at your Institution?**

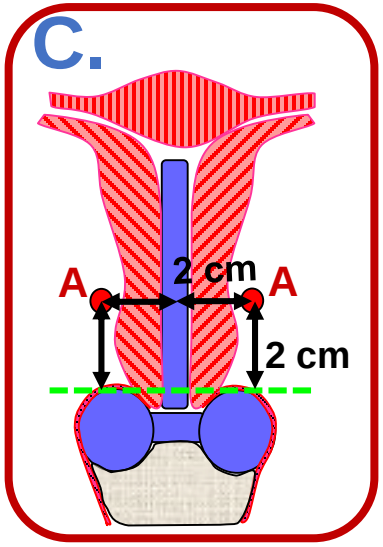
A.



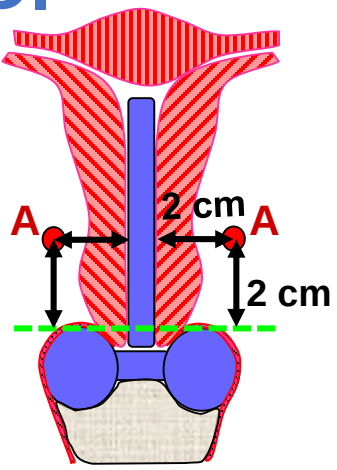
B.



C.



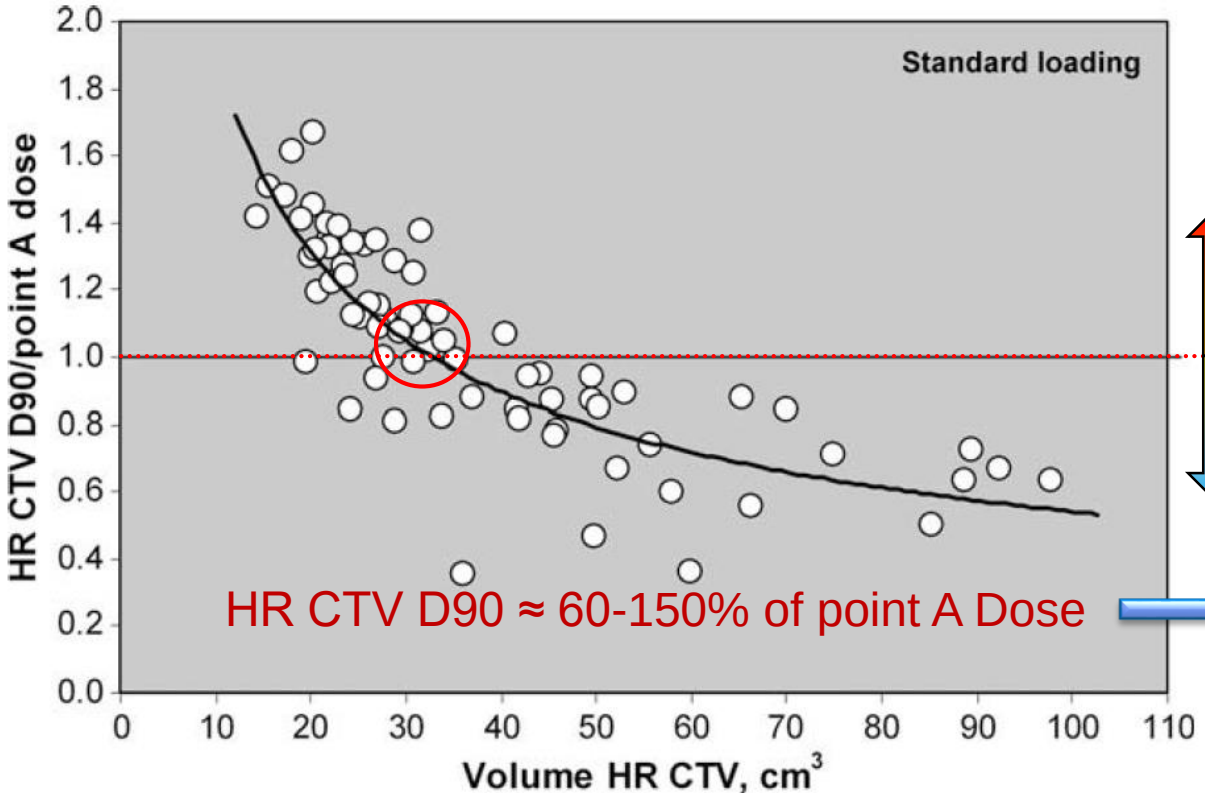
D.



ICRU/GEC ESTRO Report 89. 2016

Point A Dose

Point A Dose in the context of Image Guided Adaptive BT



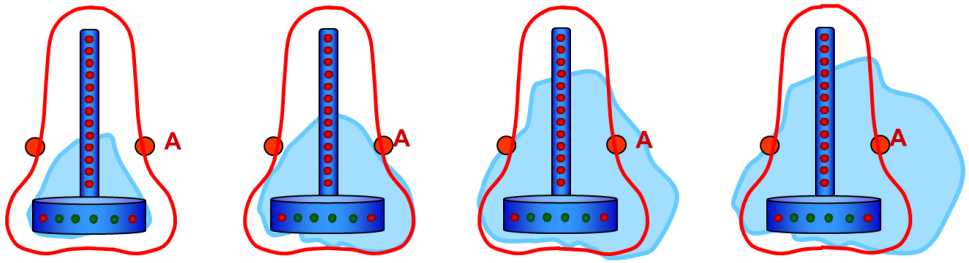
Over-dosing the tumour

+/- Over-dosing the OAR

Under-dosing the tumour

Poor predictor of D90 in individual patients

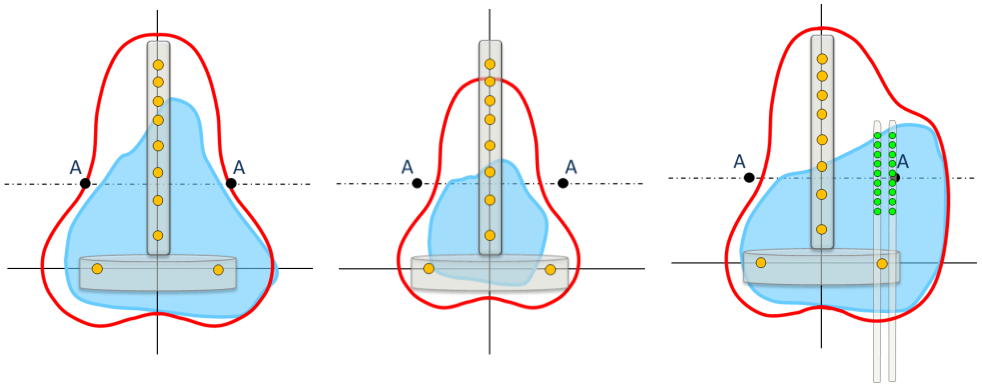
Is it still relevant in IGABT era?



Tanderup K, et al. Radiother Oncol 2010;94:173-80.

Point A Dose

Point A Dose in the context of Image Guided Adaptive BT

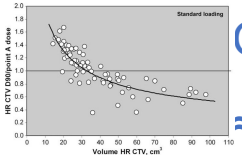


Extensive clinical experience → Link to tradition (“safety” measure)

Independent of contouring

Can be associated with effects

→ Comparison btw. patients & centres with different D schedules / rates



CTV_{HR} D90

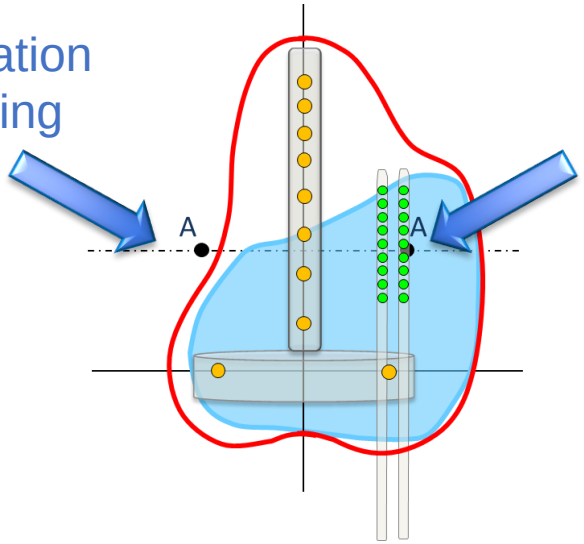
≈ 60–150% of p.A D

→ ≈ Measure for mean D90 of population

Point A Dose

Needles close to point A

Can be used for evaluation during treatment planning

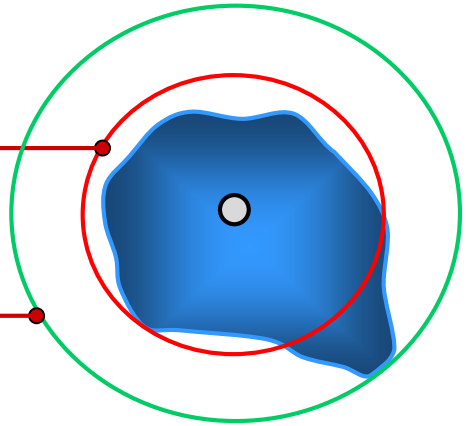


Cannot be used for reporting

Doses to Target Volumes – Primary Tumor

$D_{90\%}$

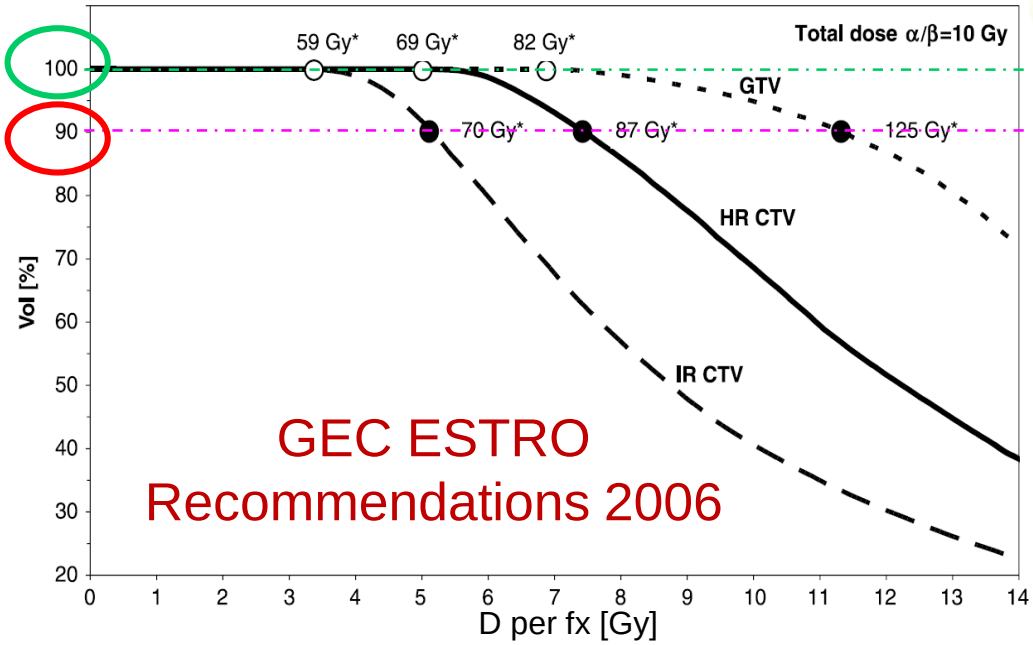
Can be ↑ if 10% receives ↓D



$D_{100\%}$

↑ Sensitive to:

- Contouring uncertainties
- V reconstruction
- D – sampling in the TPS



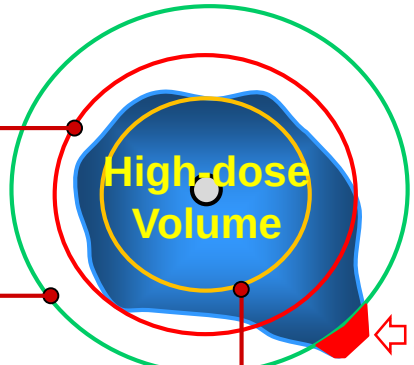
	$D_{100\%}$	$D_{90\%}$
CTV_{HR}	√	√
CTV_{IR}	√	√
GTV_{res}	√	√

Pötter R, et al. Gyn GEC ESTRO Recommendations. Radiother Oncol 2006;78:67-77.

Doses to Target Volumes – Primary Tumor

$D_{90\%}$

Can be ↑ if 10% receives ↓D



⇦2%

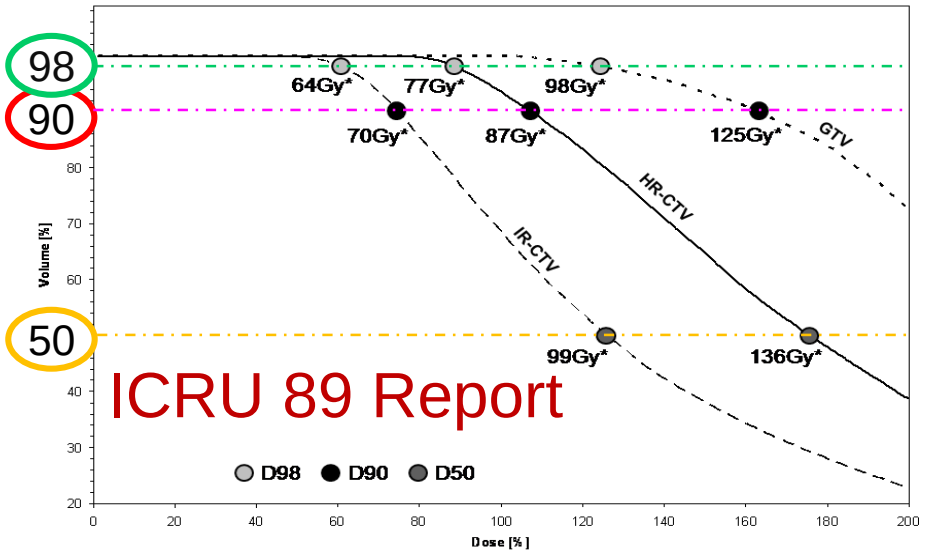
$D_{98\%}$

More robust

Near-minimum D

$D_{50\%}$

Radiobiological uncertainties!



ICRU 89 Report

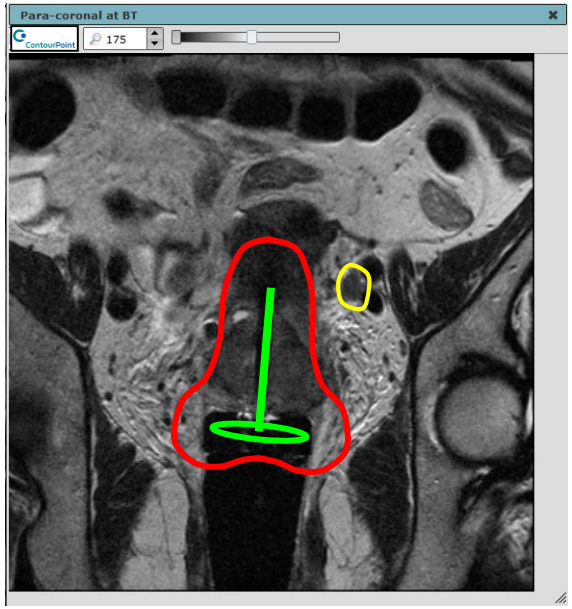
	$D_{98\%}$	$D_{90\%}$	$D_{50\%}$
CTV_{HR}	Level 2	Level 2	Level 2
CTV_{IR}	Level 3*	Level 3*	-
GTV_{res}	Level 2	Level 3	-

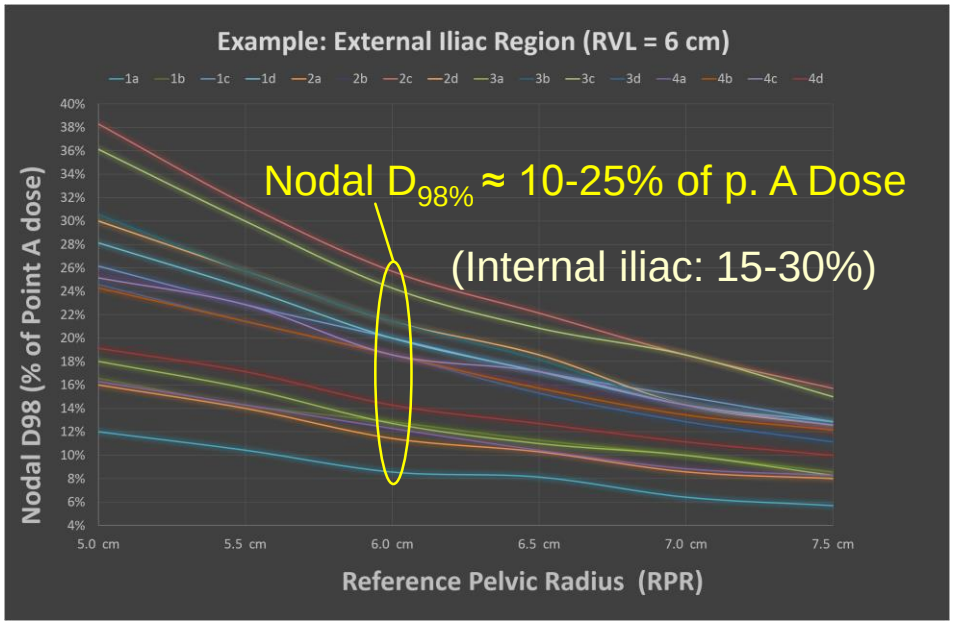
**Level 2 if CTVIR is used for prescription*

DVH for PTV:	Level 3

ICRU/GEC ESTRO Report 89. 2016

Doses to Target Volumes – Involved Nodes





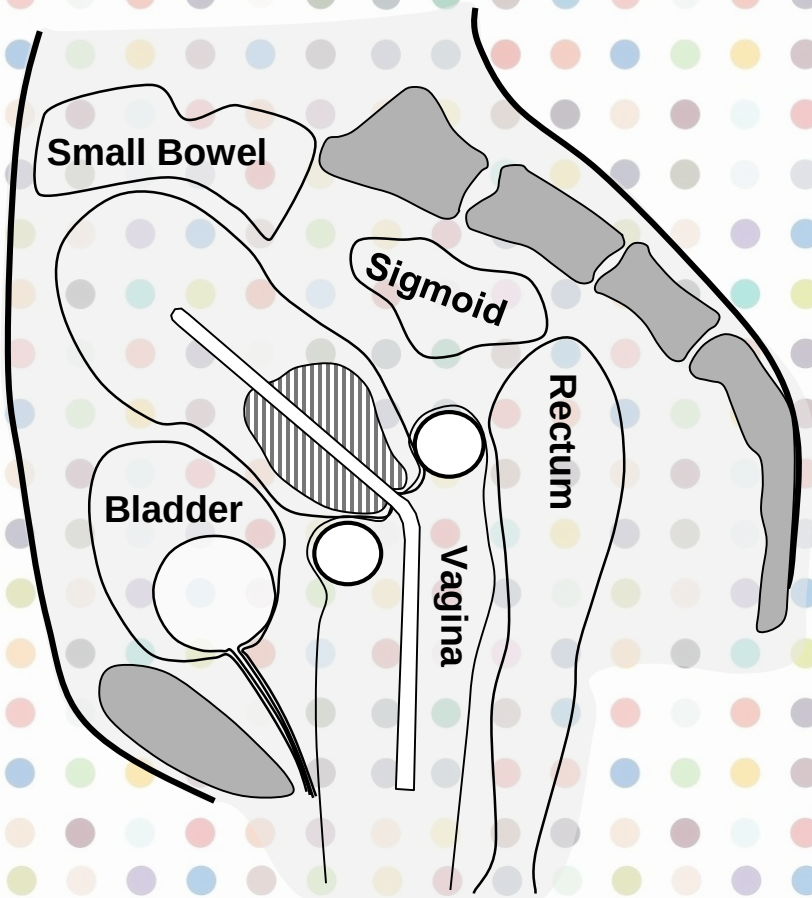
Petric P, et al. ASTRO 2014

	$D_{98\%}$	$D_{90\%}$	$D_{50\%}$
CTV-N	L 2	-	L 3
DVH for uninvolved N			L 3

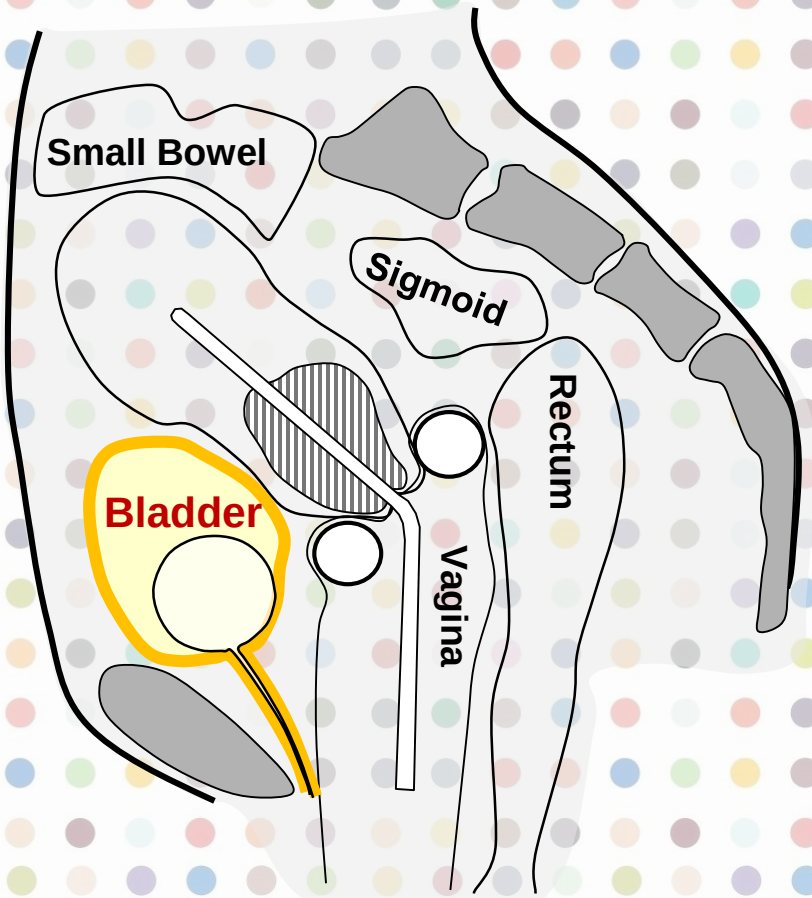
Relevance of these parameters: not validated!

ICRU/GEC ESTRO Report 89. 2016

Organs At Risk: **Doses to Points**

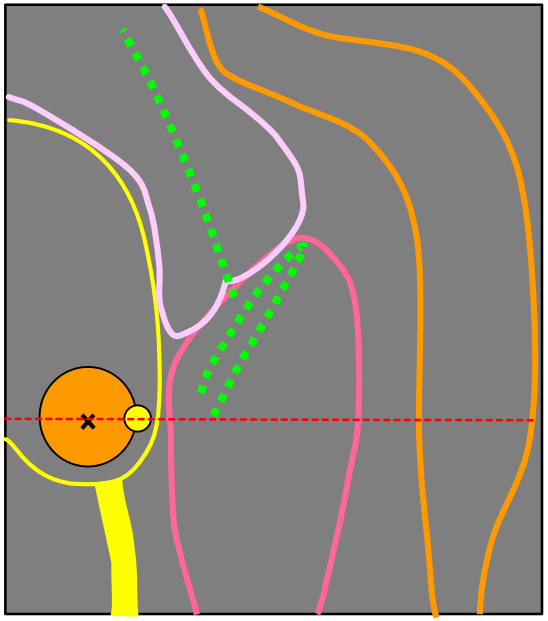


Organs At Risk: **Doses to Points**



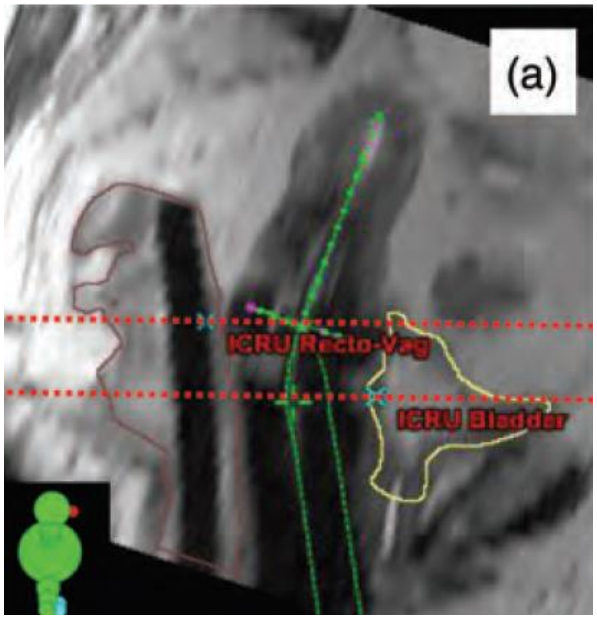
Bladder Reference Point

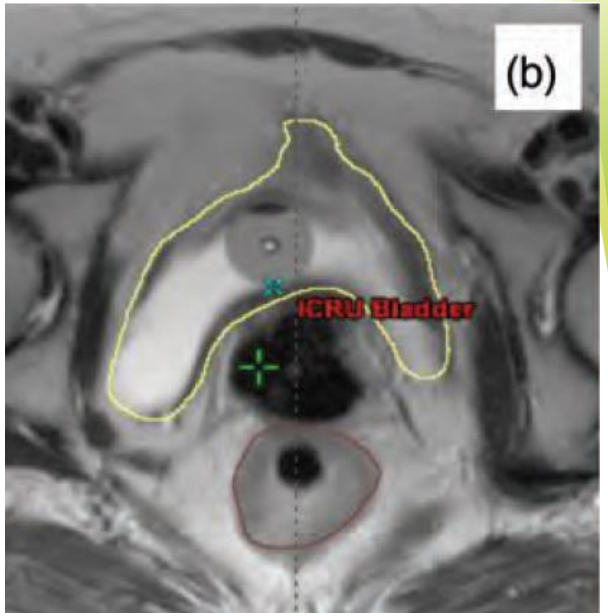
From Radiographs



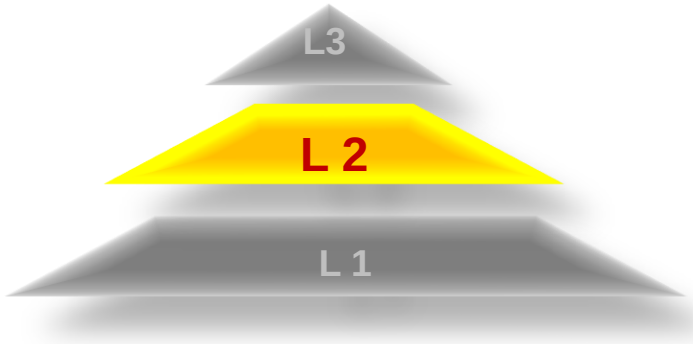
Modified from: ICRU 38; 1985.

From Sectional Images





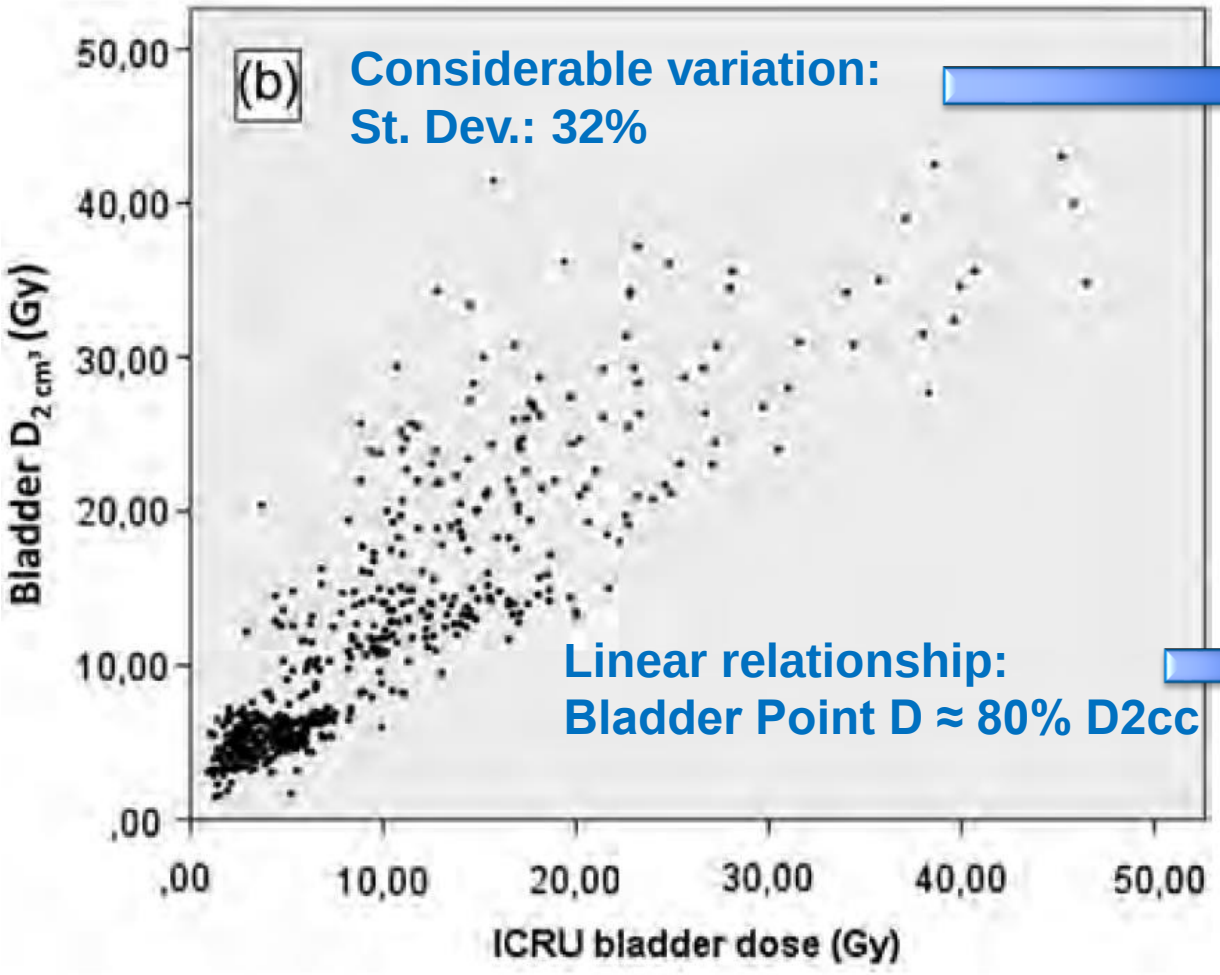
From: ICRU 89; 2016.



- Correlation with D2cc?
- Correlation with morbidity?

Doses to Points: Bladder Reference Point

Correlation with Bladder D2cc



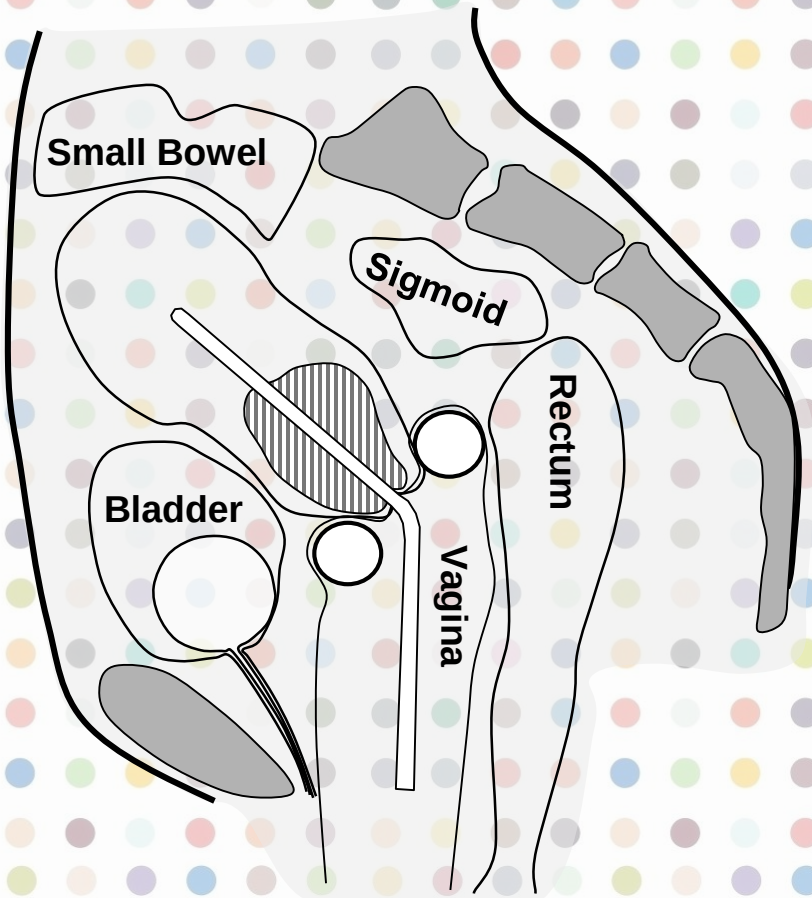
Poor surrogate for D2cc in individual pt.

Can't translate directly into D2cc constraints

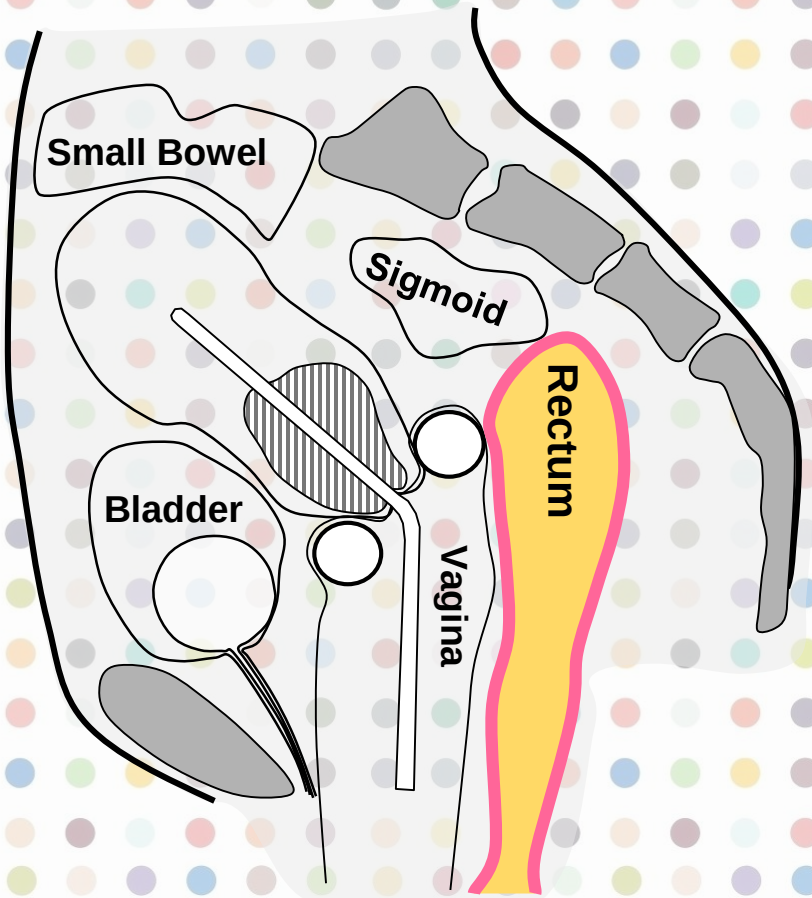
Estimate of average D2cc in population

EMBRACE, 2015; Reproduced from: ICRU 89, 2016.

Organs At Risk: **Doses to Points**

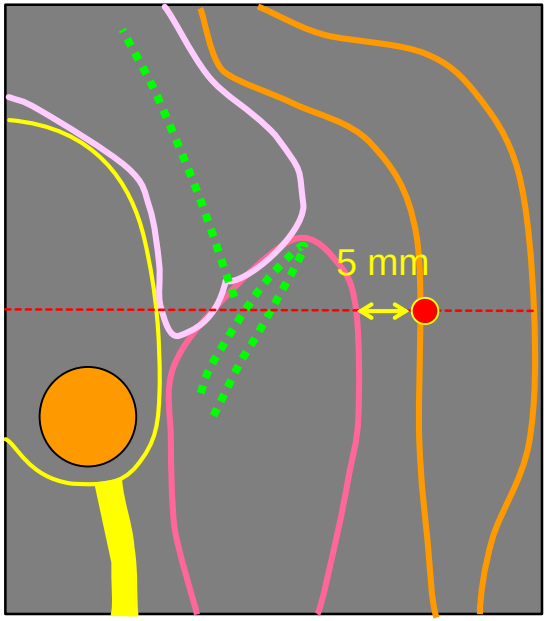


Organs At Risk: **Doses to Points**



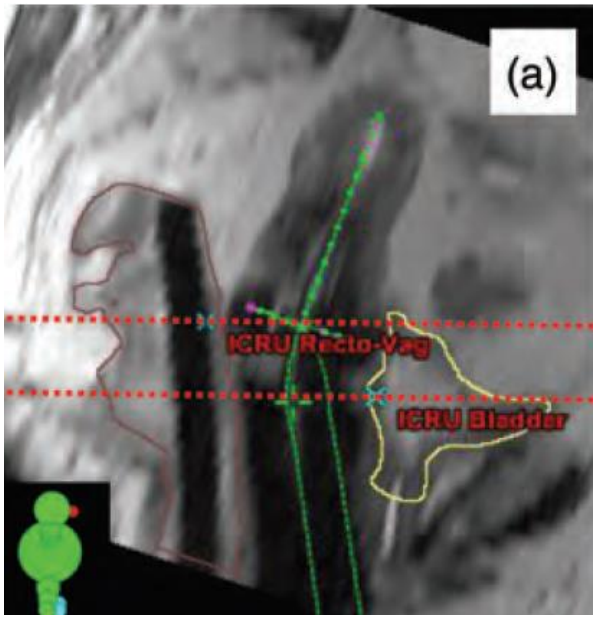
Recto-Vaginal Point

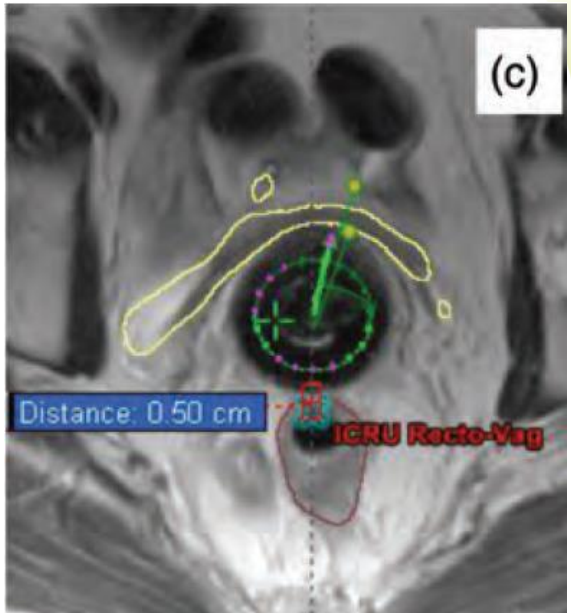
From Radiographs



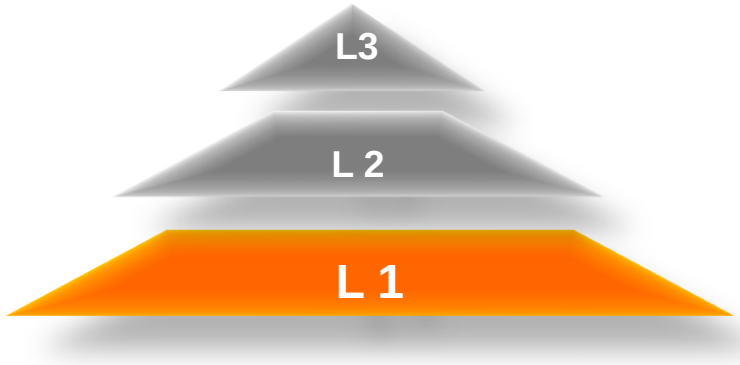
Modified from: ICRU 38; 1985.

From Sectional Images





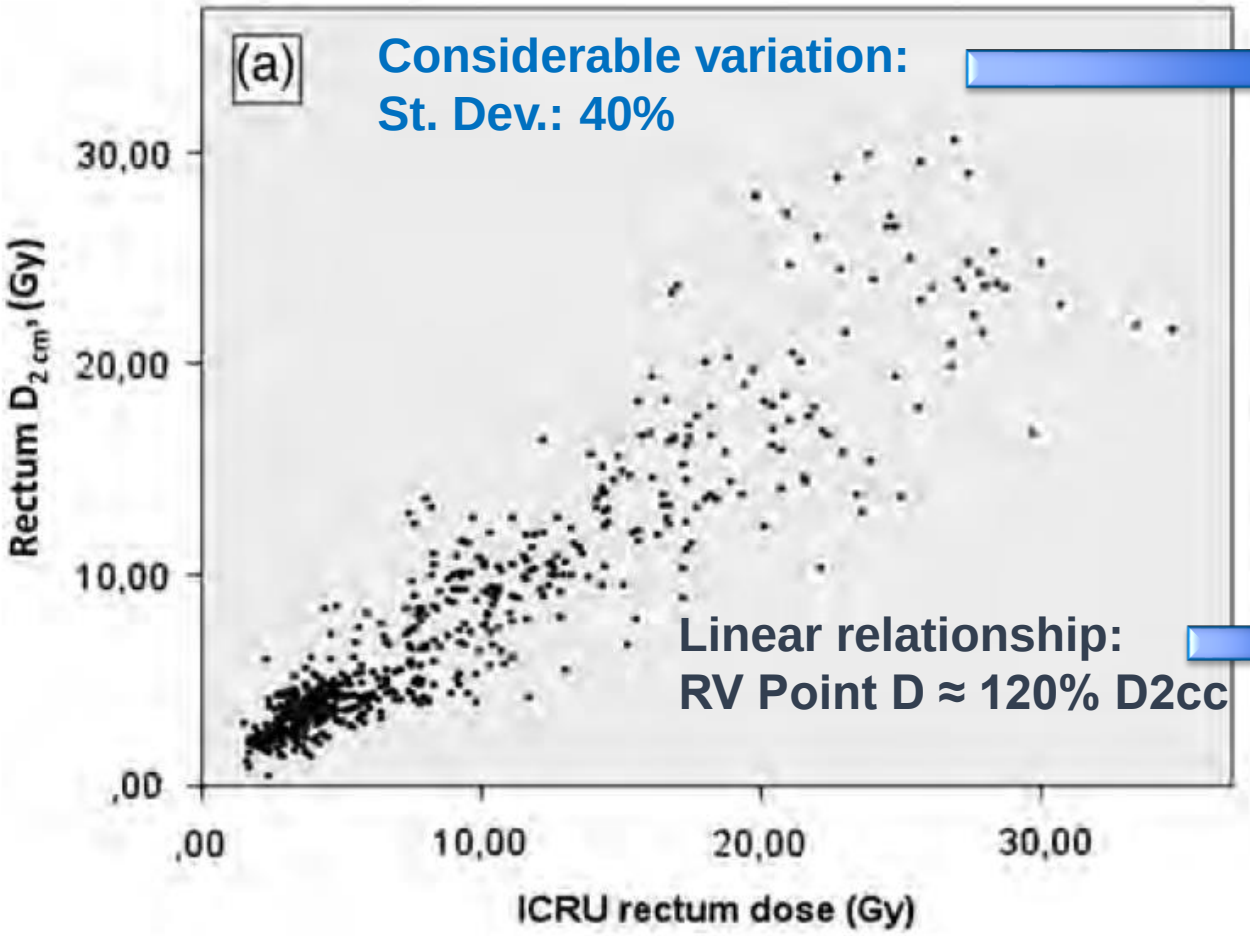
From: ICRU 89; 2016.



- Correlation with D2cc?
- Correlation with morbidity?

Doses to Points: Recto-Vaginal Point

Correlation with Rectal D2cc



Poor surrogate for D2cc in individual pt.

Don't translate directly into D2cc constraints

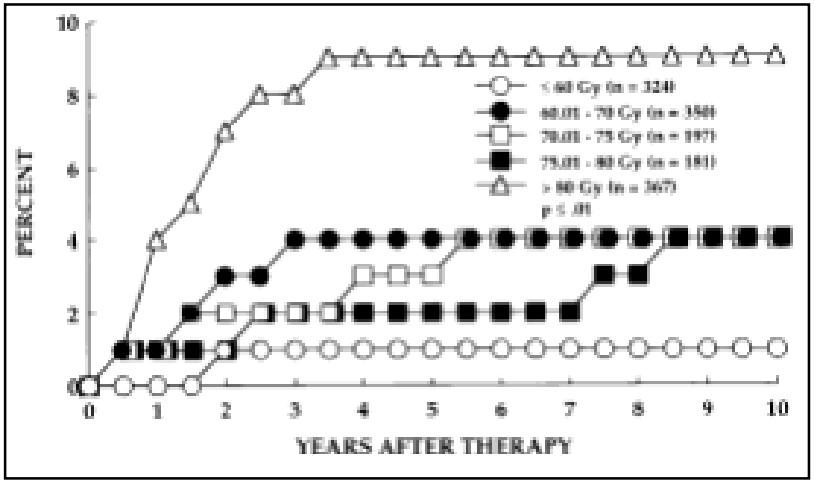
Estimate of average D2cc in population

EMBRACE, 2015; Reproduced from: ICRU 89, 2016.

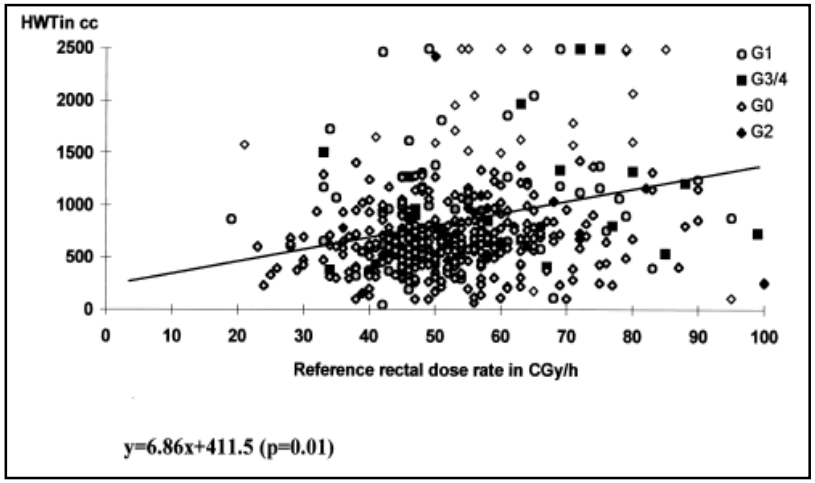
Doses to Points: Recto-Vaginal Point

Correlation with Rectal Morbidity

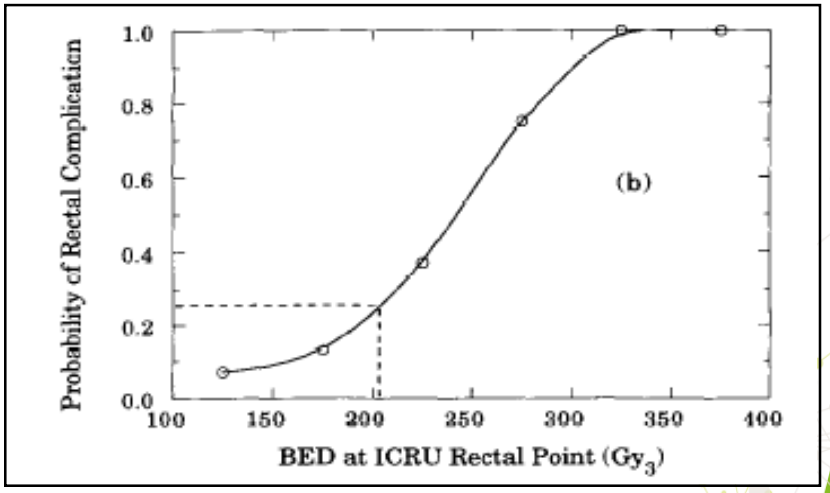
Clinical observations support correlation between rectal complications and ICRU RV point D



Perez CA, et al. IJROBP 1999

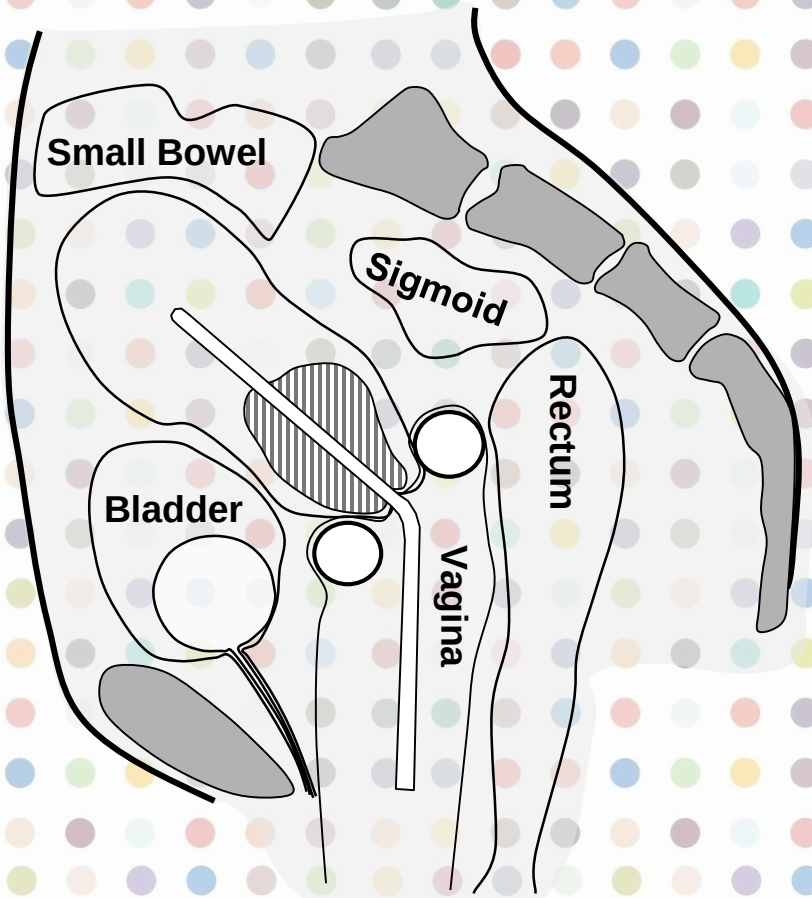


Barillot et al. IJROBP 2000

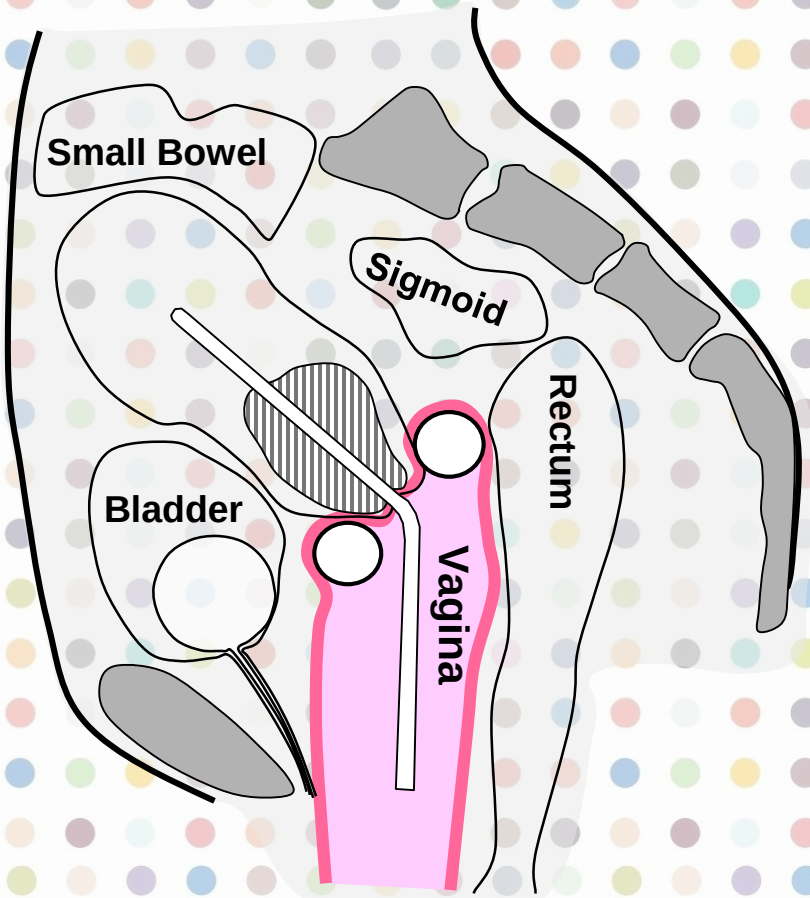


Clark et al., IJROBP 1997

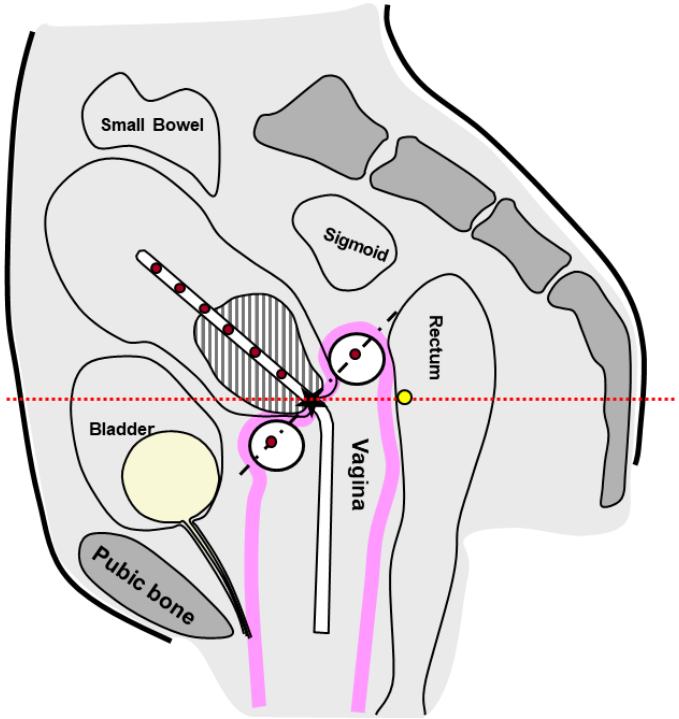
Organs At Risk: **Doses to Points**

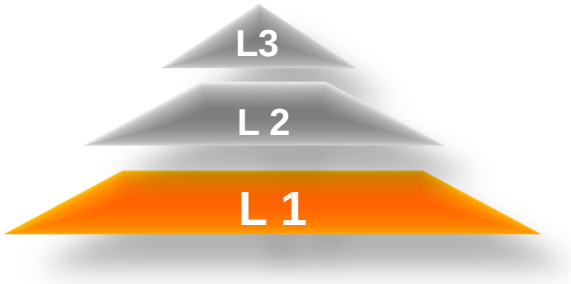


Organs At Risk: **Doses to Points**



Vaginal top: Recto-Vaginal Point





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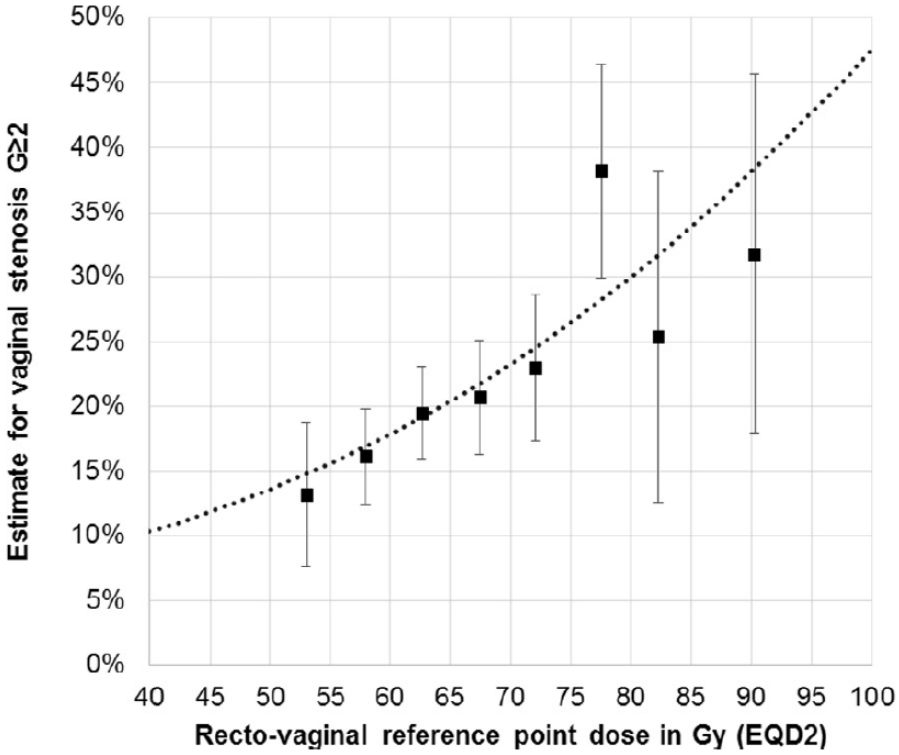
Brachytherapy

Dose–effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study

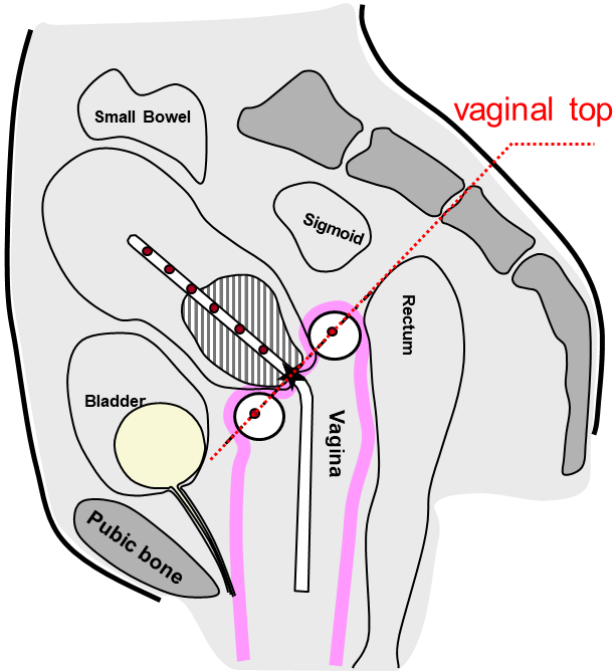
Kathrin Kirchheiner [a,*], Remi A. Nout [b], Jacob C. Lindegaard [c], Christine Haie-Meder [d], Umesh Mahantshetty [e], Barbara Segedin [f], Ina M. Jürgenliemk-Schulz [g], Peter J. Hoskin [h], Bhavana Rai [i], Wolfgang Dörr [a,j], Christian Kirisits [a], Søren M. Bentzen [k], Richard Pötter [a,j], Kari Tanderup [c], the EMBRACE Collaborative Group [1]

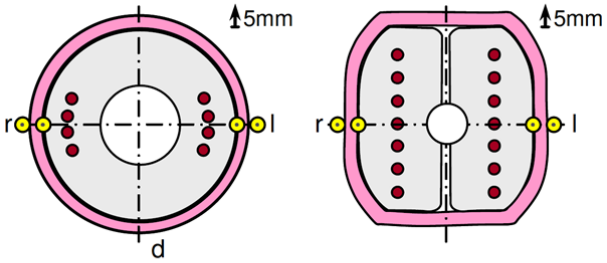


Kirchheiner K, et al. Radiother Oncol 2016;118:160-6.

Vaginal top: Applicator surface & at 5 mm

Traditionally used for vaginal dose reporting / dose constraints





Reference	Vag. Surf. D
Thomadsen 1992	135 - 145%
Nevelsky 2003	130 % - 231%
Noyes 1995	135 - 145 %
Au 2003	175 Gy
Hintz	98 Gy (distal v.)
	140 Gy (upper v.)

Correlation with morbidity not established

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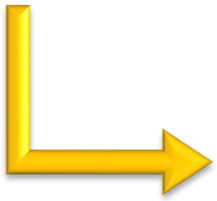
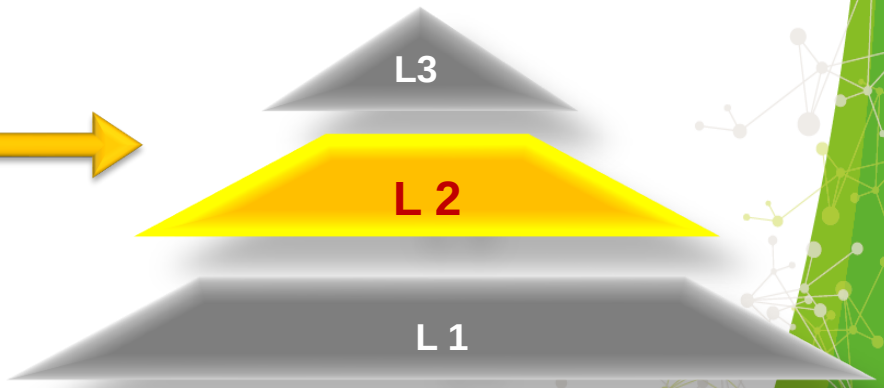
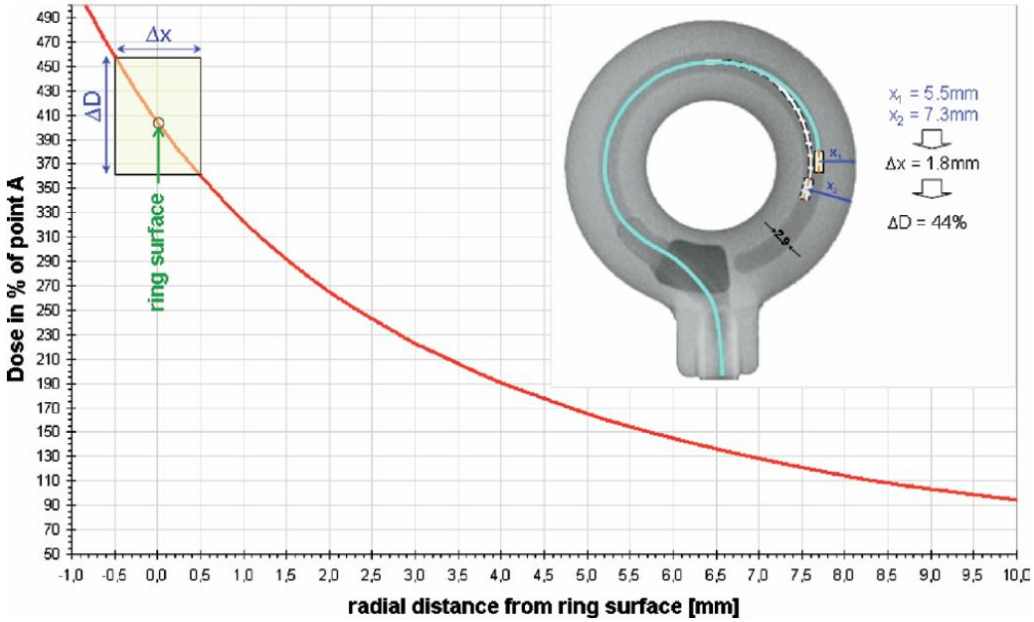




Au SP, Grigsby PW. Radiother Oncol 2003;67(1):77-85
Mai J, et al. Int J Radiat Oncol Biol Phys 2001;51(4):1131-41
Hintz BL, et al. Int J Radiat Oncol Biol Phys 1980;6:711-716
Nevelsky A, et al. Brachytherapy 2003;3(2):101-5
Thomadsen B, et al. Int J Radiat Oncol Biol Phys 1992;24:349-357
Noyes WR, et al. Int J Radiat Oncol Biol Phys.1995;31(1):79-86

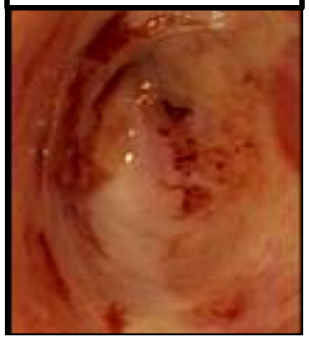
Vaginal top points: Limitations

Sensitive to placement uncertainties

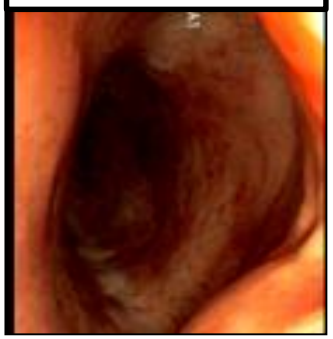


Berger et al, IJROBP 2007

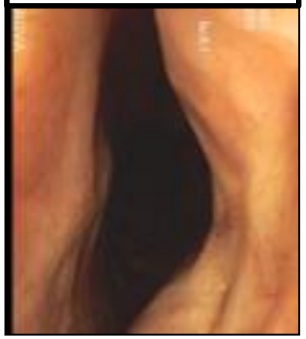
Upper vagina



Mid vagina



Lower vagina



Not representative of D throughout Vagina

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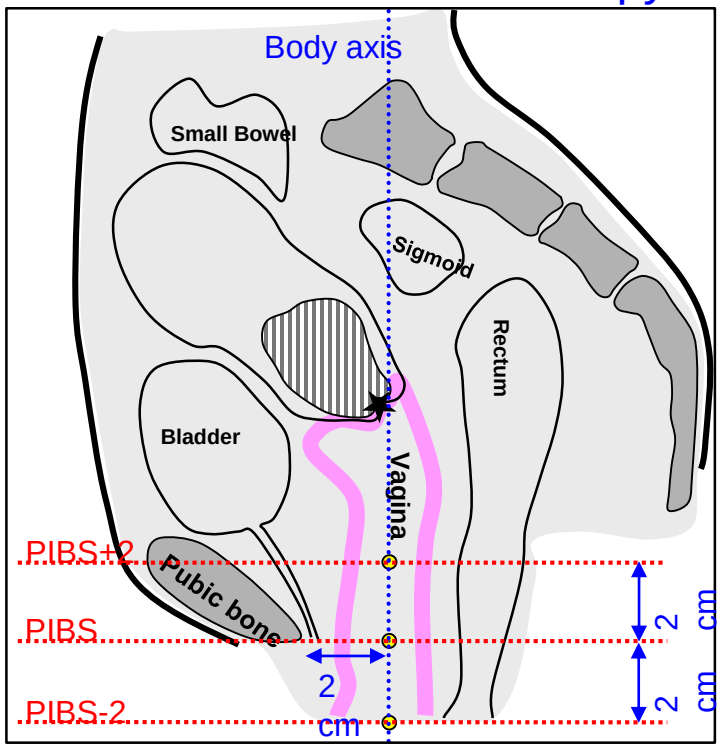
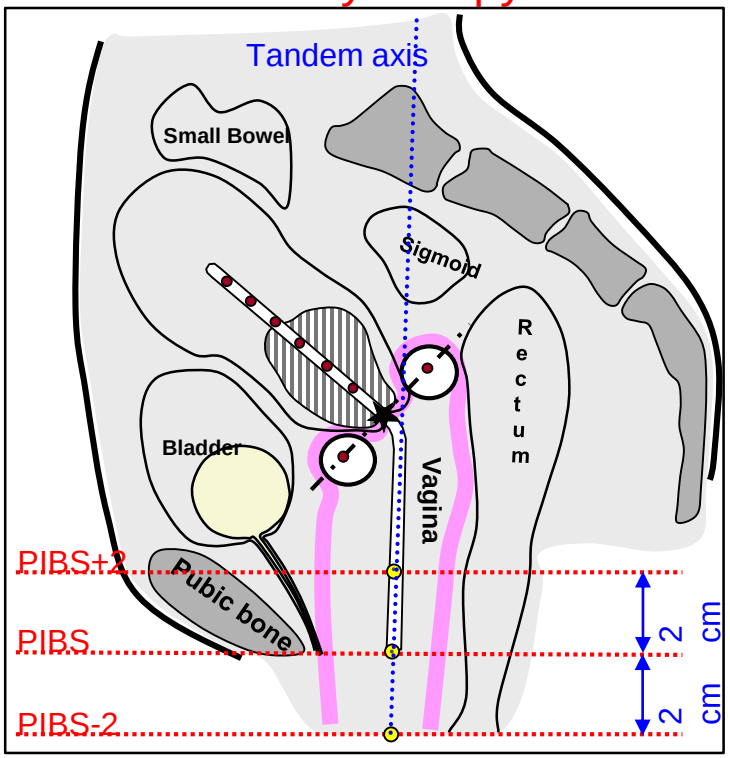
Reference points along vaginal axis: PIBS* points

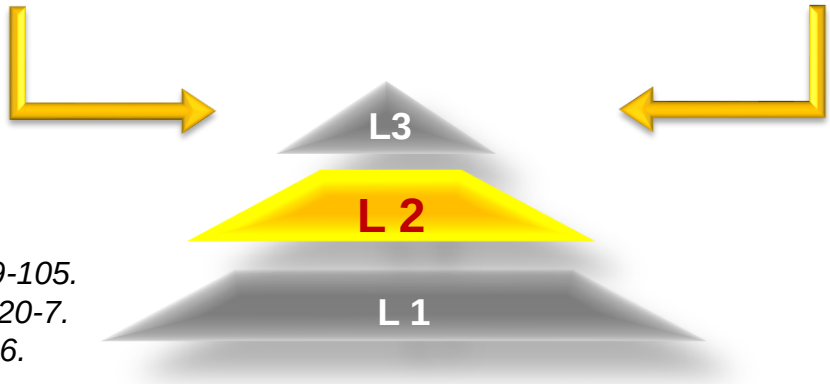
**PIBS = Posterior Inferior Border of Symphisis*

External Beam Radiotherapy



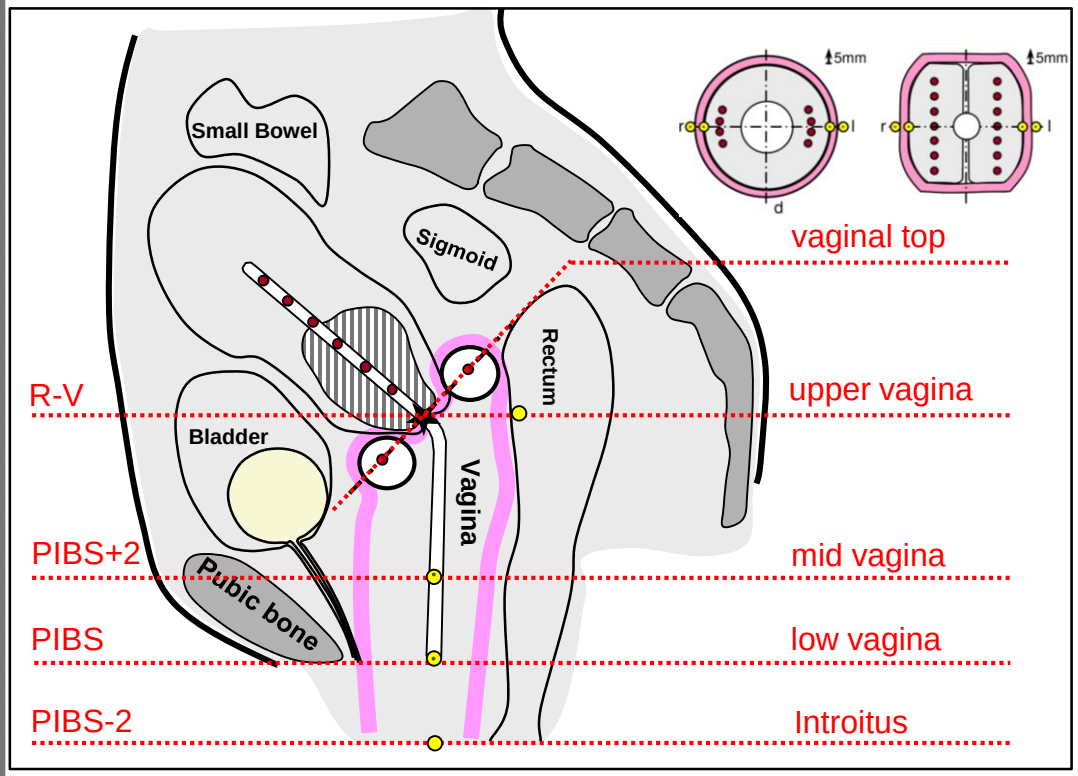
Brachytherapy

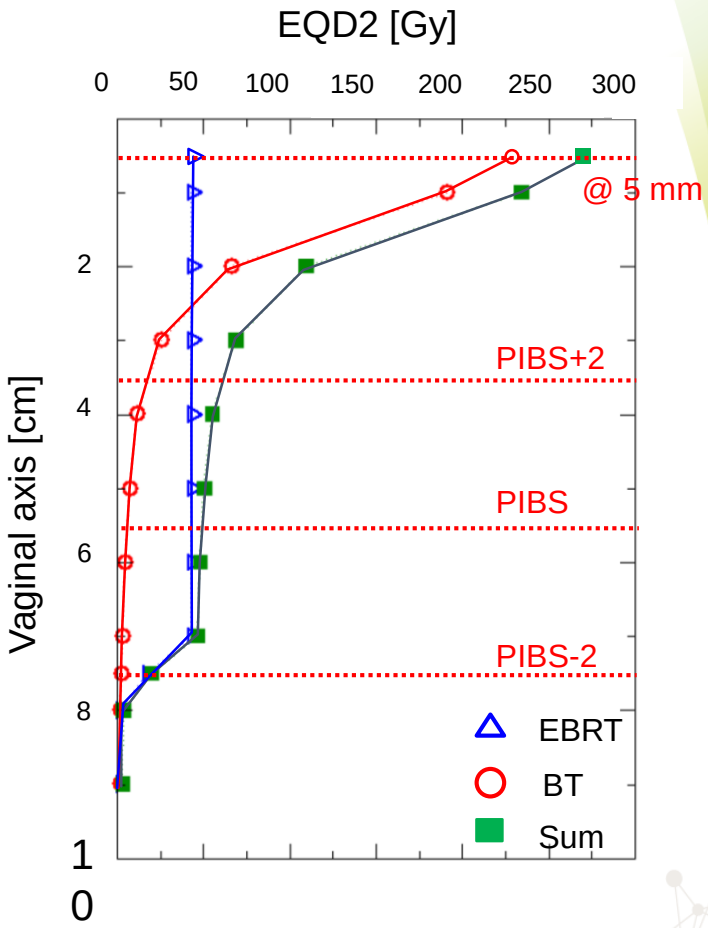




Westerveld et al. R&O 2013;107:99-105.
Westerveld, et al. R&O 2016;120:420-7.
ICRU/GEC ESTRO Report 89, 2016.

Vaginal dose reporting - Summary





	R-V point	@ 5 mm	PIBS points	Other
Reporting Level	L 1	L 2	L 2	L 3

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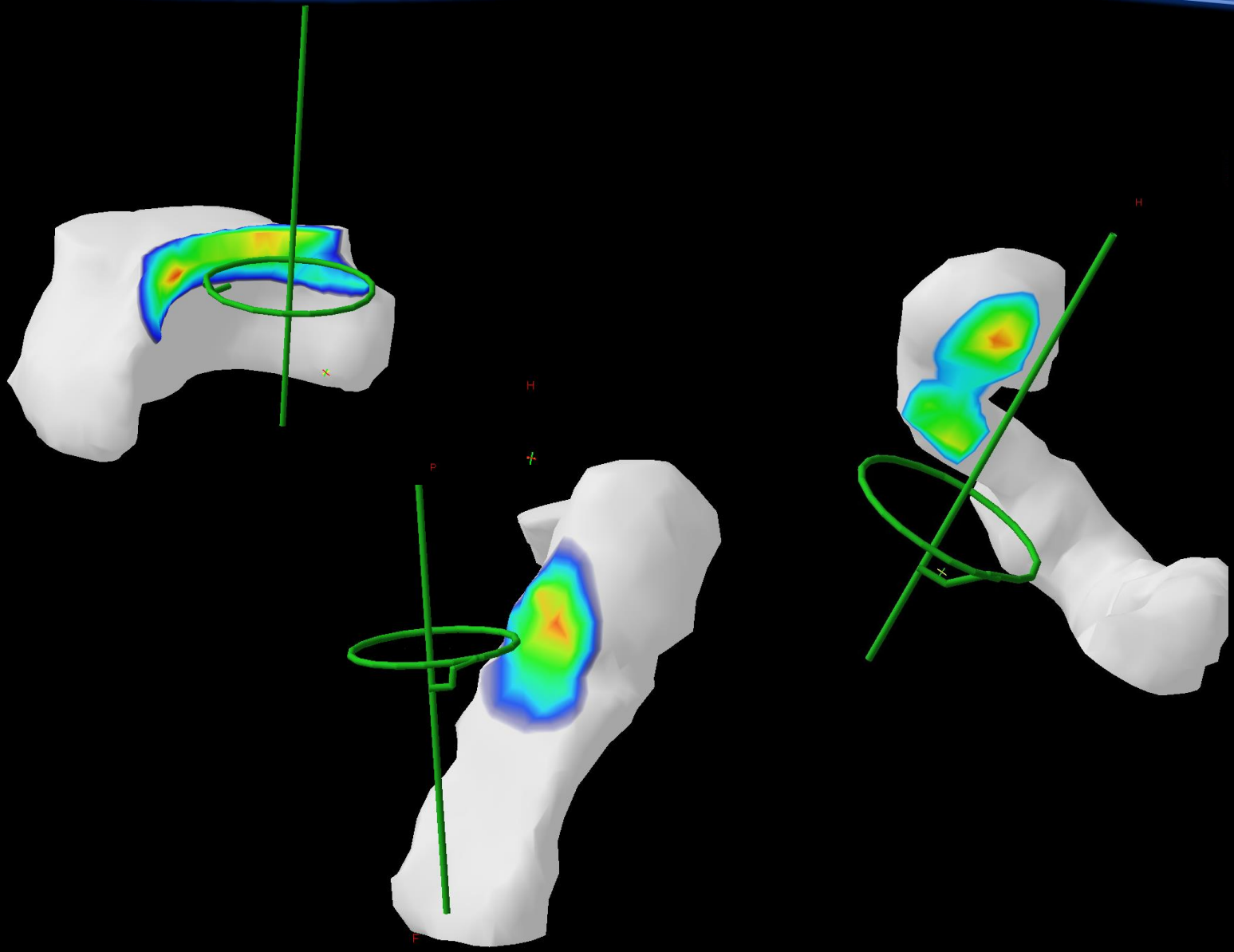
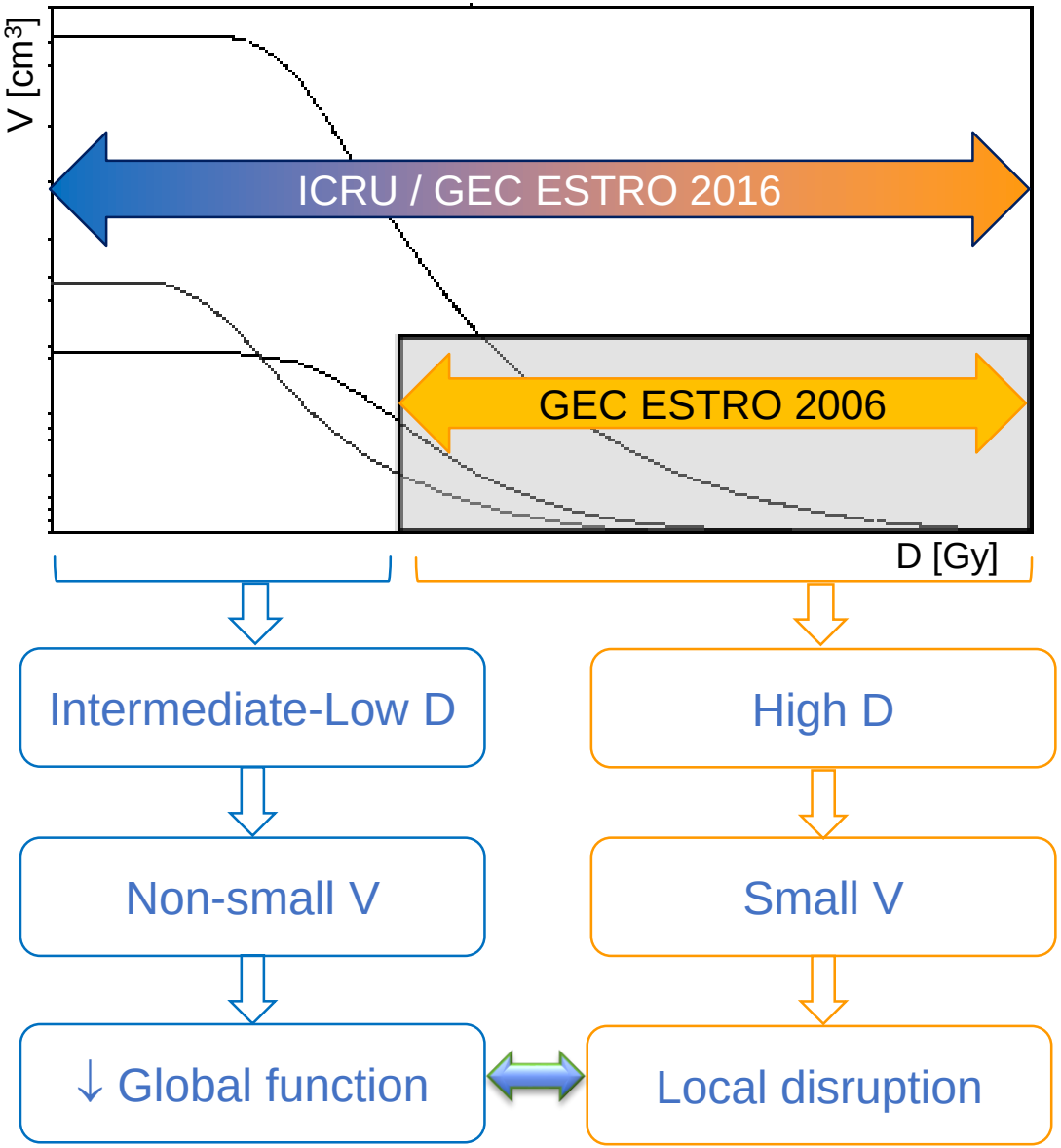
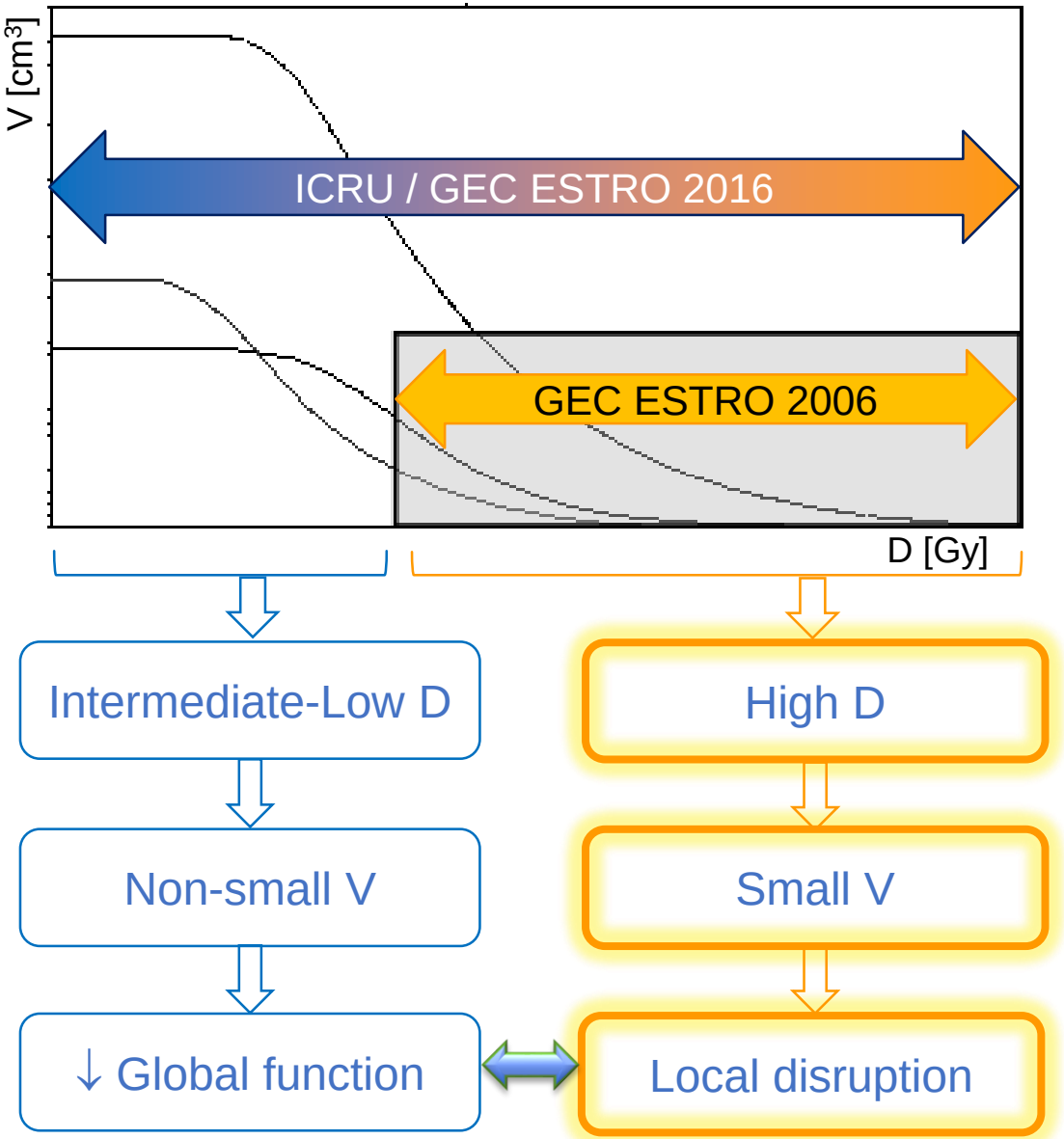
Organs at Risk: Doses to Volumes



Organs at Risk: Doses to Volumes

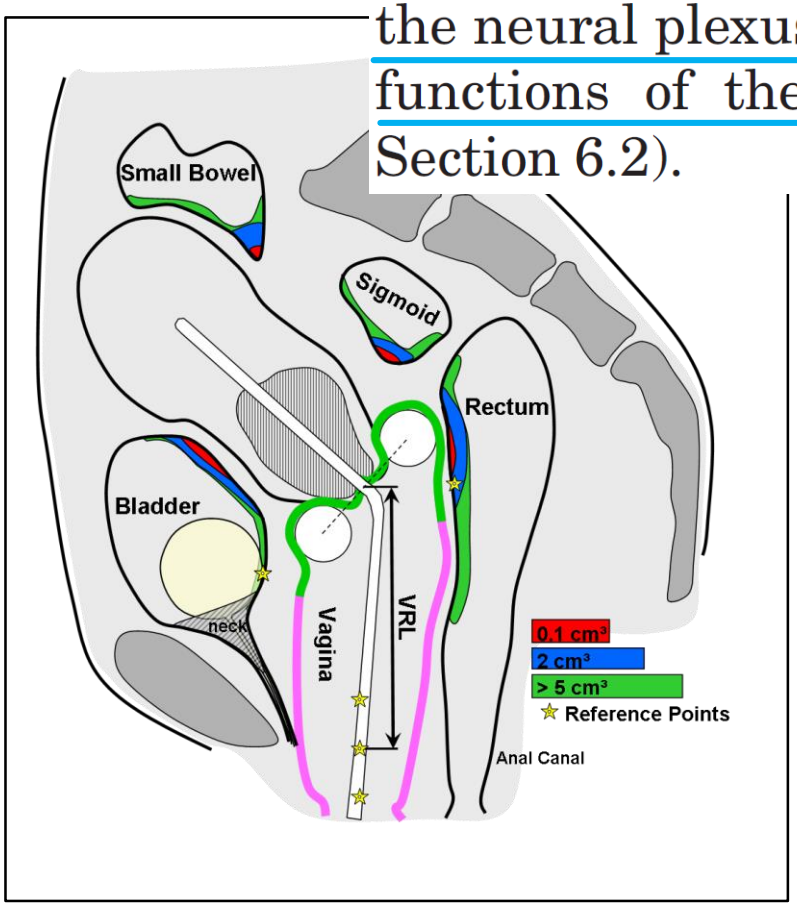


Doses to Organs at Risk



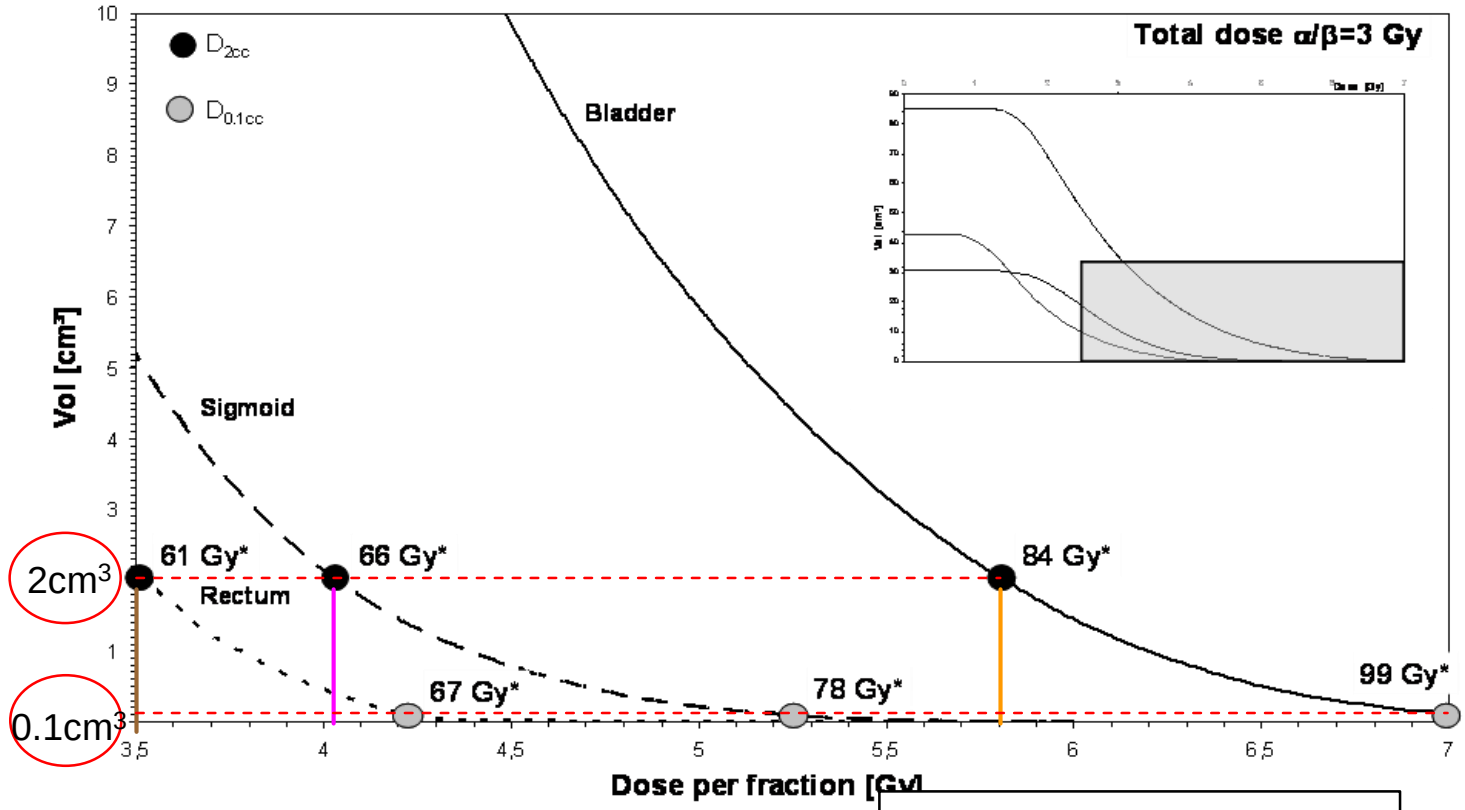
High Doses to Small V

and incontinence. The biological targets are small normal-tissue sub-volumes located mainly in the mucosa and sub-mucosa of the organ walls, and in the neural plexus and muscles that regulate specific functions of the bladder, rectum, and anus (see Section 6.2).

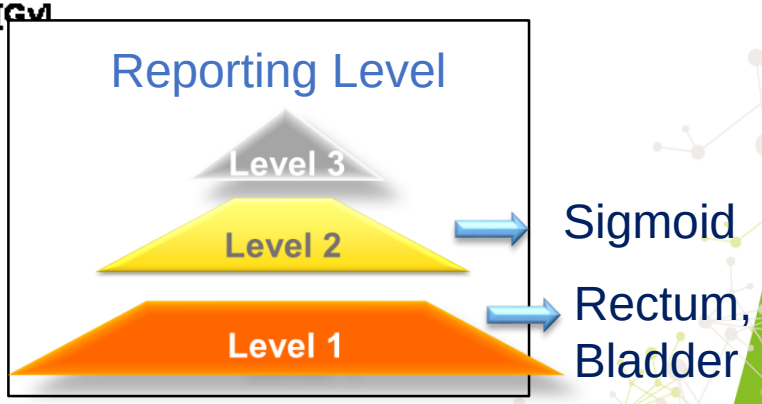


ICRU/GEC ESTRO Report 89. 2016

High Doses to Small V: Bladder, Rectum, Sigmoid Colon, Bowel



+/-Clinical evidence for dose–effects: **Lecture on day 4**

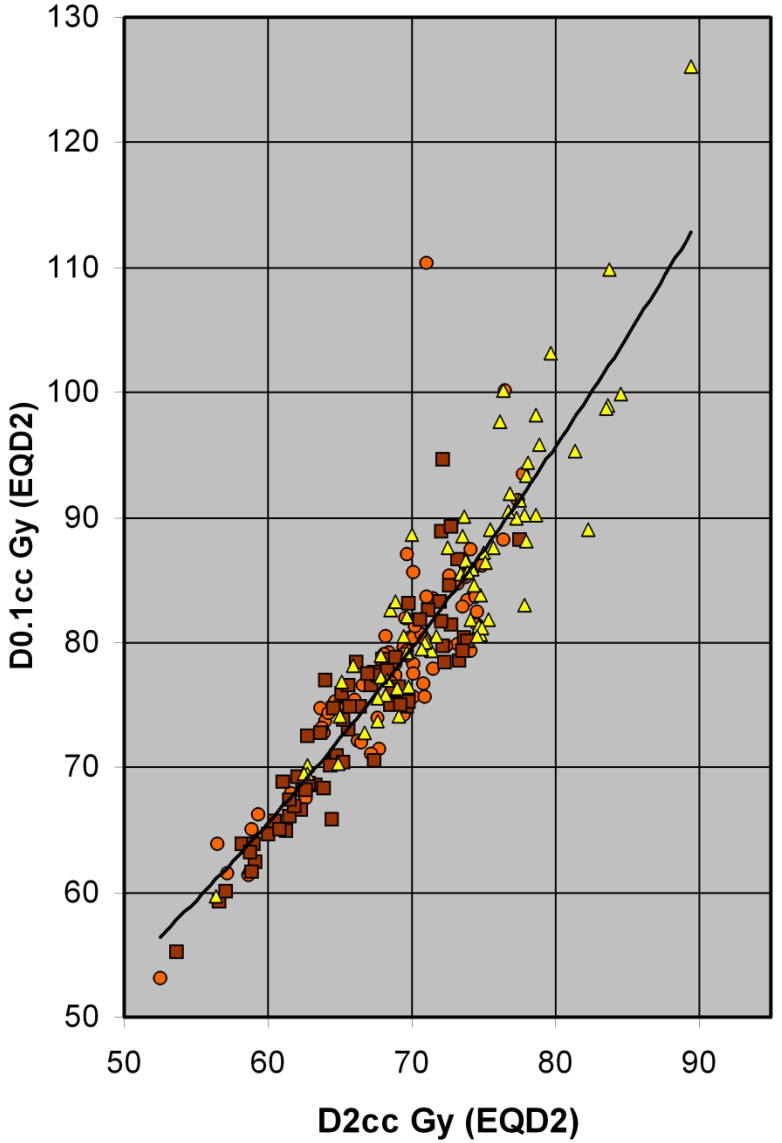


ICRU/GEC ESTRO Report 89. 2016

D2cc and D0.1cc

	D2cc Gy EQD2	D0.1cc Gy EQD2
Bladder	71 ± 7	81 ± 13
Rectum	65 ± 6	72 ± 8
Sigmoid	67 ± 6	74 ± 12

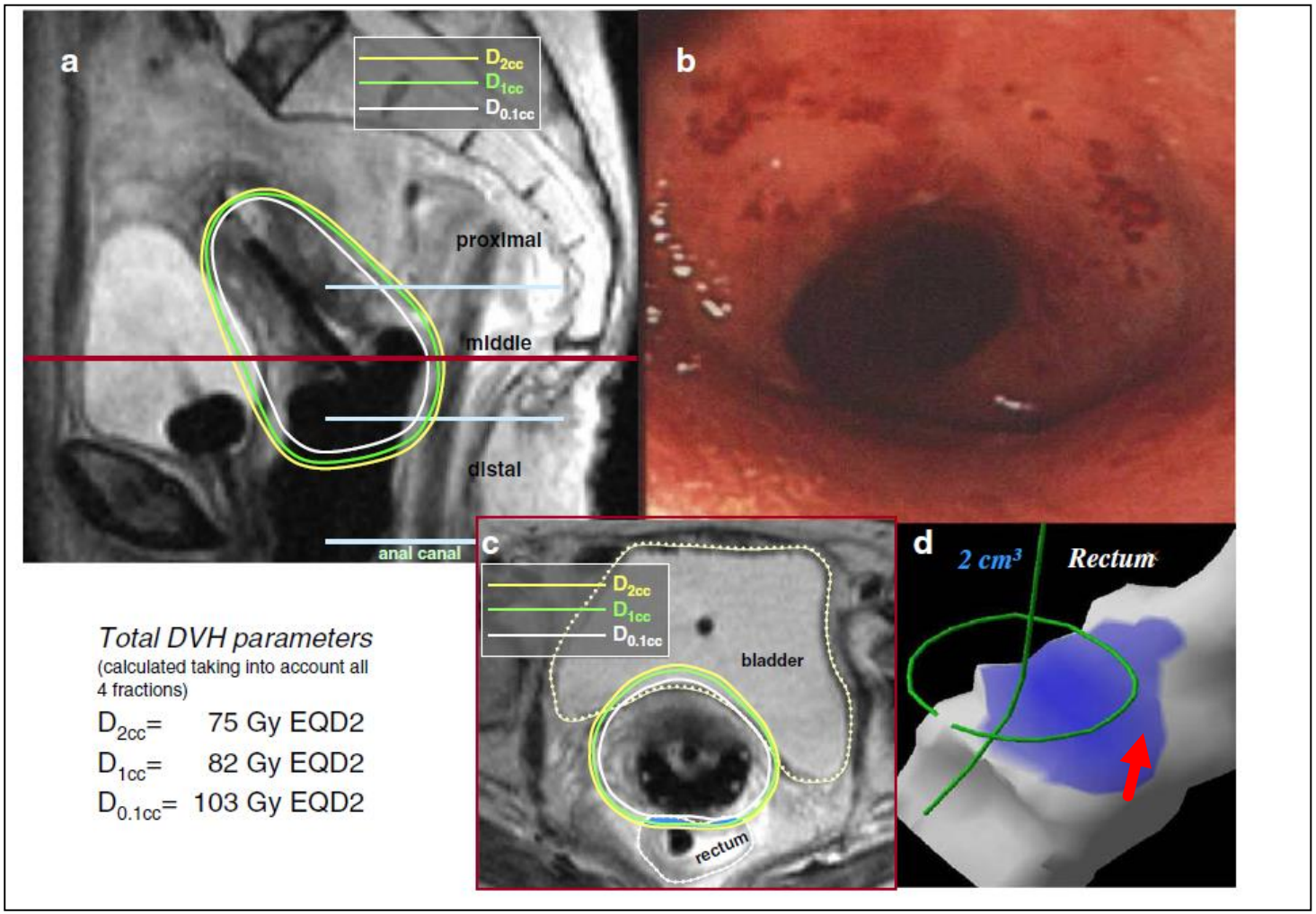
$D_{0.1cc}$ / D_{2cc} : 134% ± 9% (Physical doses)



Aarhus University Hospital: PDR BT

High Doses to Small V

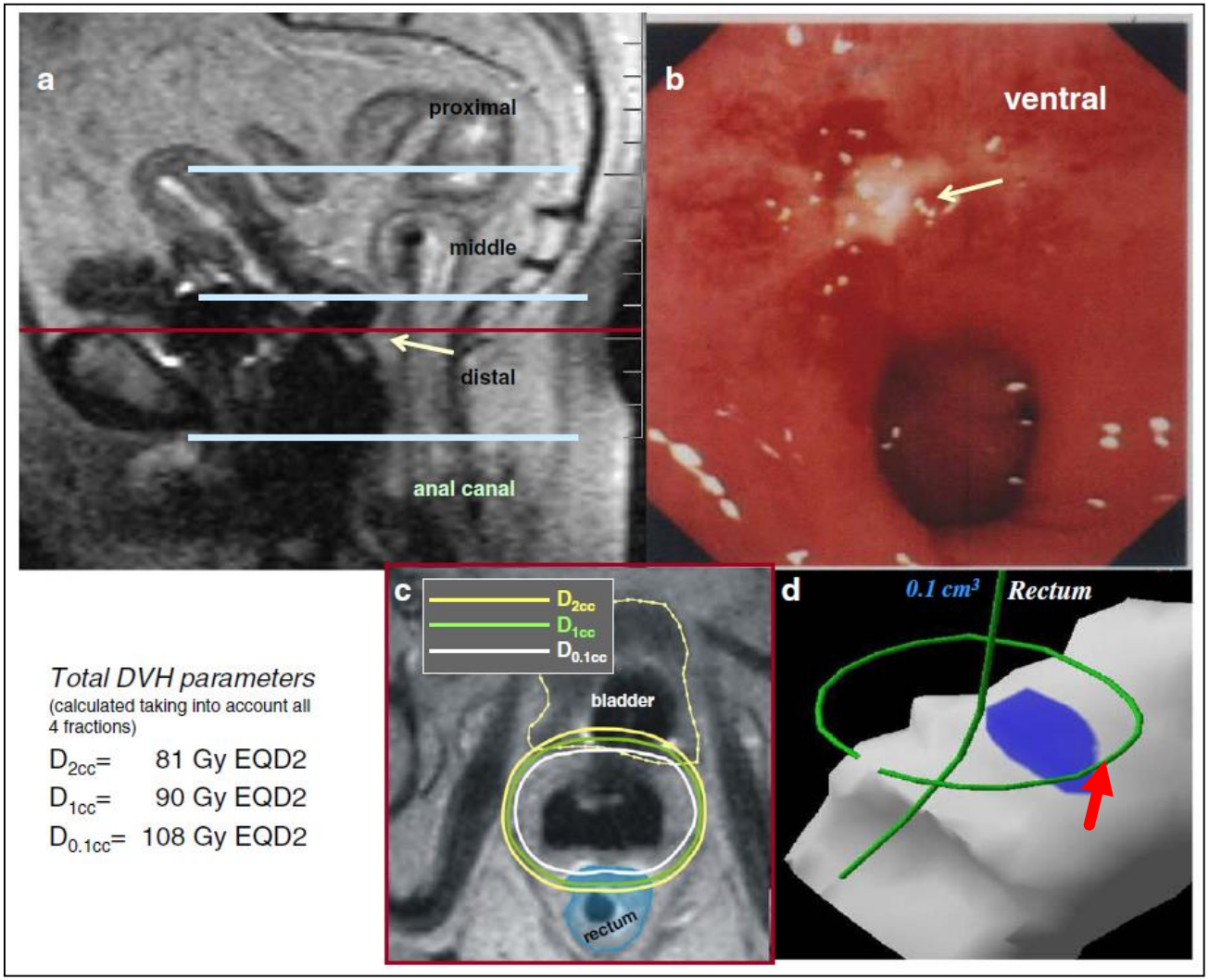
Example: Teleangiectasia / Bleeding



Georg P et al. Radiother and Oncol 2009

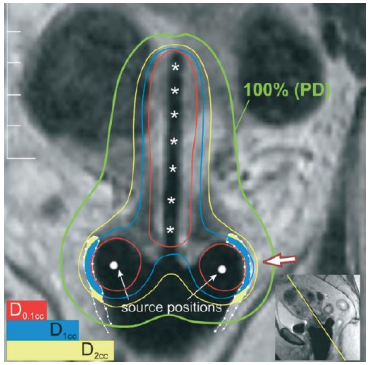
High Doses to Small V

Example: Ulcer / Fistula / Necrosis



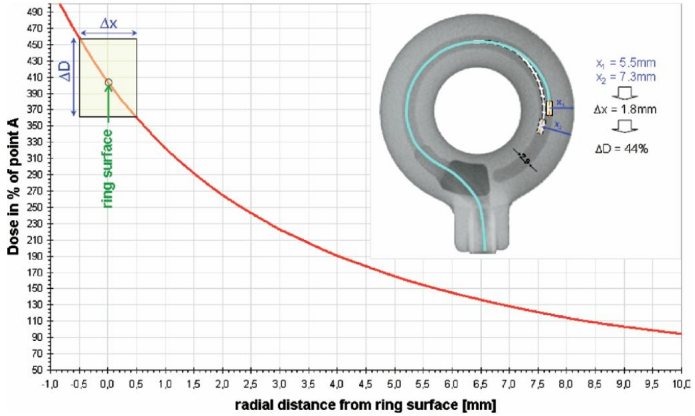
Georg P et al. Radiother and Oncol 2009

High Doses to Small V: Vagina



Contouring of vaginal wall

DVH parameters

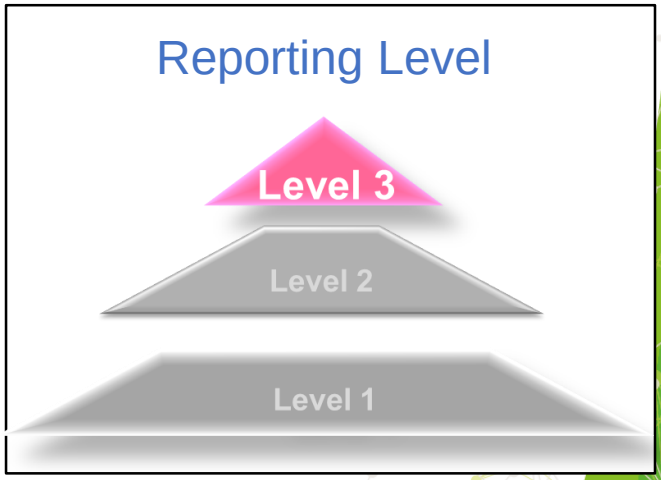


Resolution of imaging

Contouring variation

Applicator reconstruction

DVH parameters have HIGH uncertainty for representative vaginal dose estimation

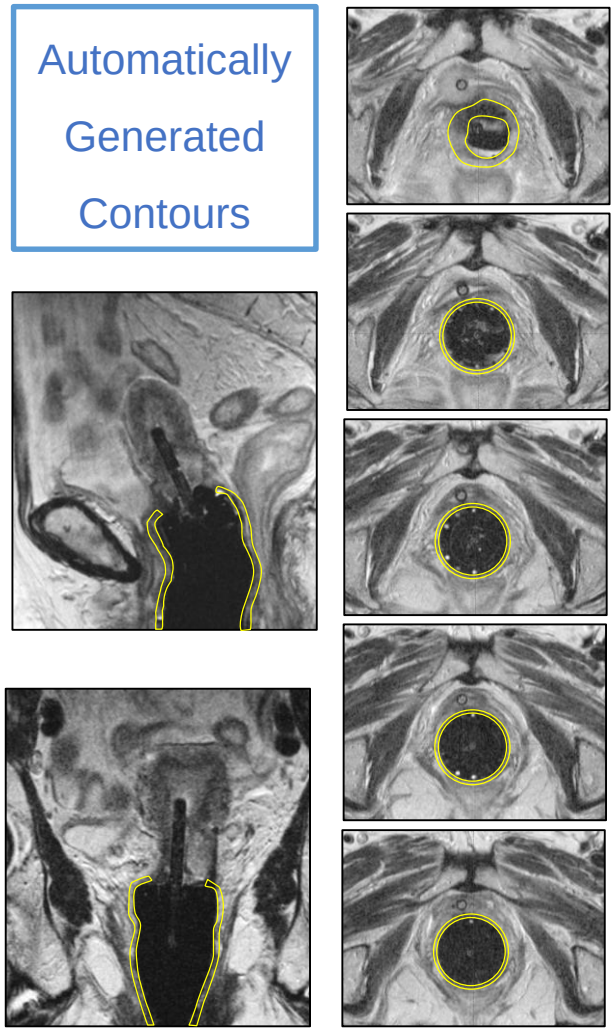


Berger et al, IJROBP 2007

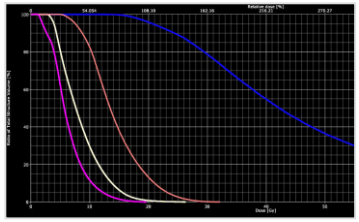
High Doses to Small V: Vagina

Future research

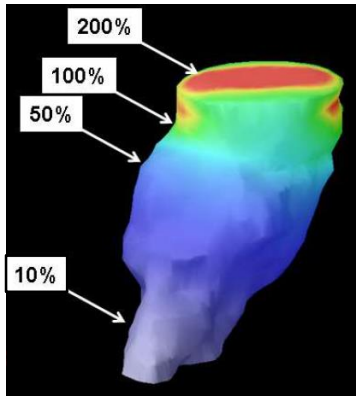
Automatically Generated Contours



DVH



DSH



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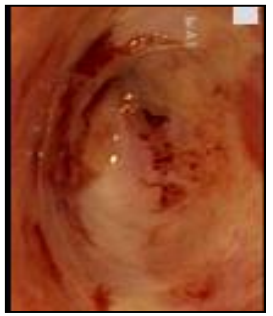
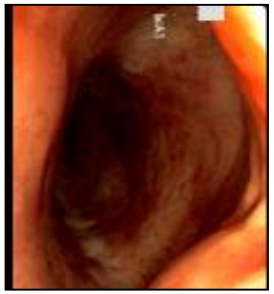
Topography

Morbidity

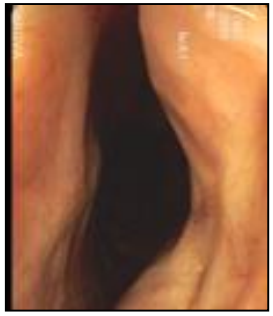
Upper vagina



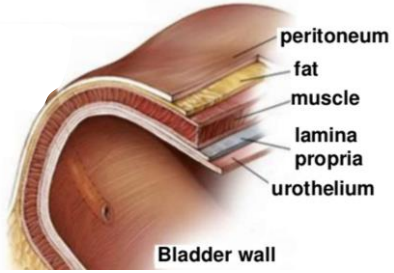
Mid vagina



Lower vagina



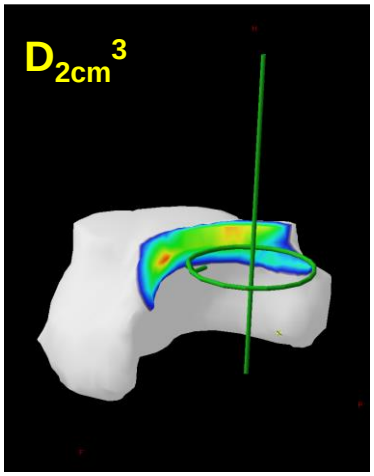
High Doses to Small V: Things to keep in mind

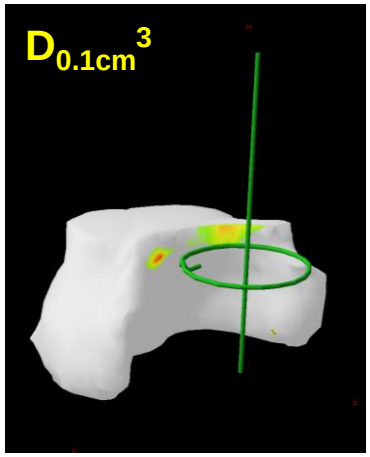


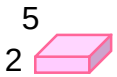
D_{2cm}^{3} and $D_{0.1cm}^{3}$:

Not spherical V

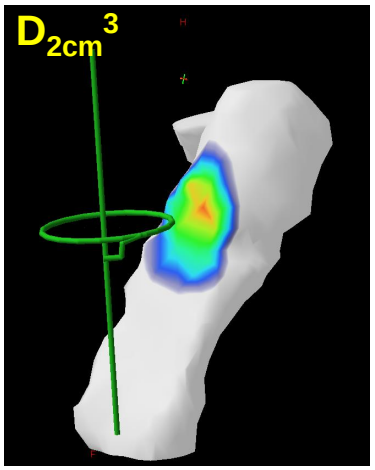
Bladder

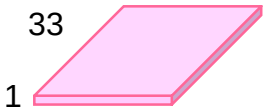


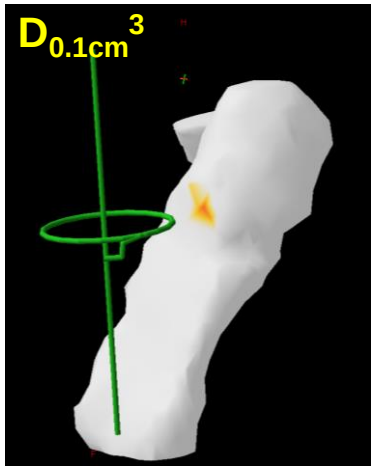


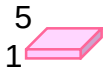


Rectum

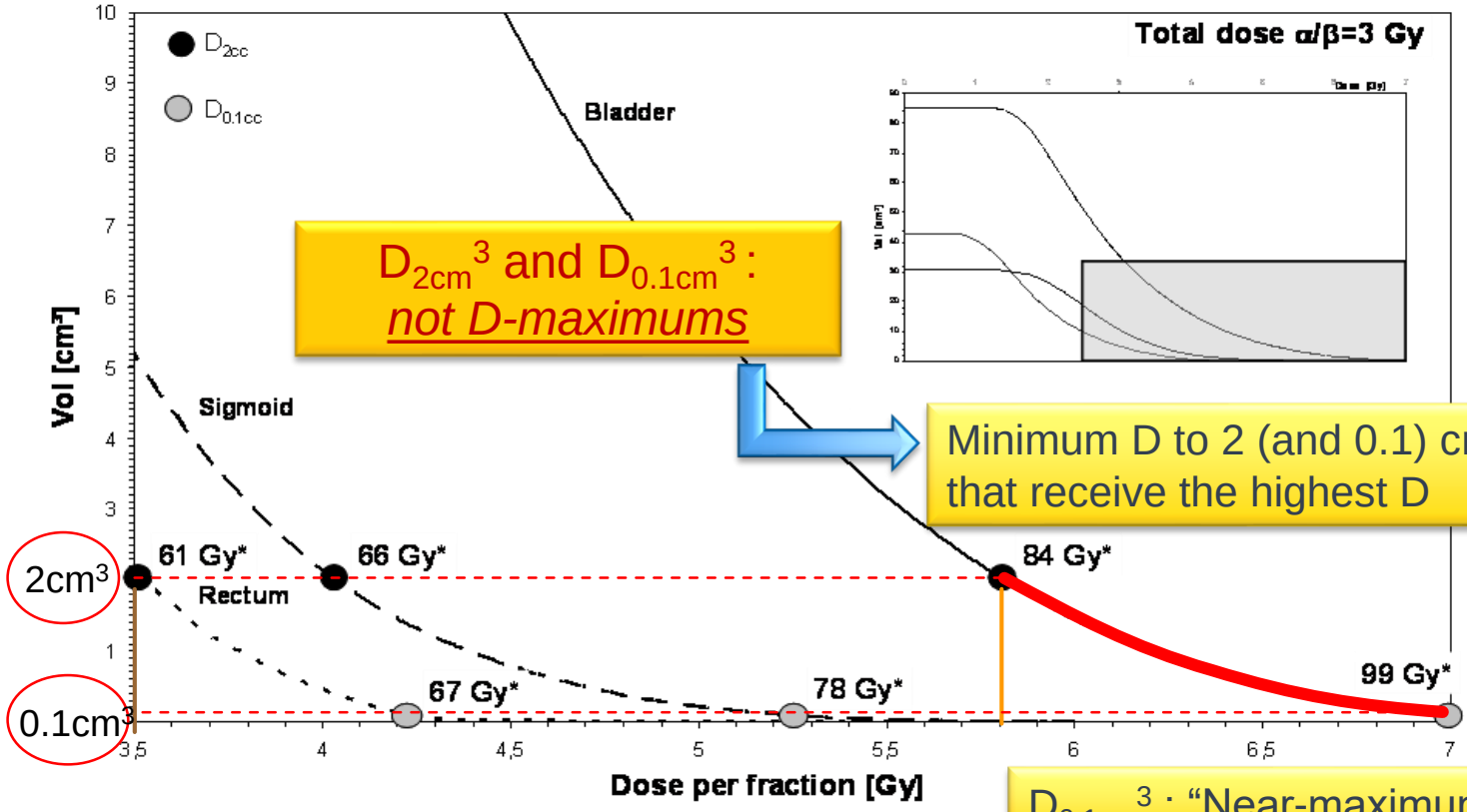








High Doses to Small V: Things to keep in mind



D_{2cm^3} and $D_{0.1cm^3}$: *not D-maximums*

Minimum D to 2 (and 0.1) cm^3 that receive the highest D

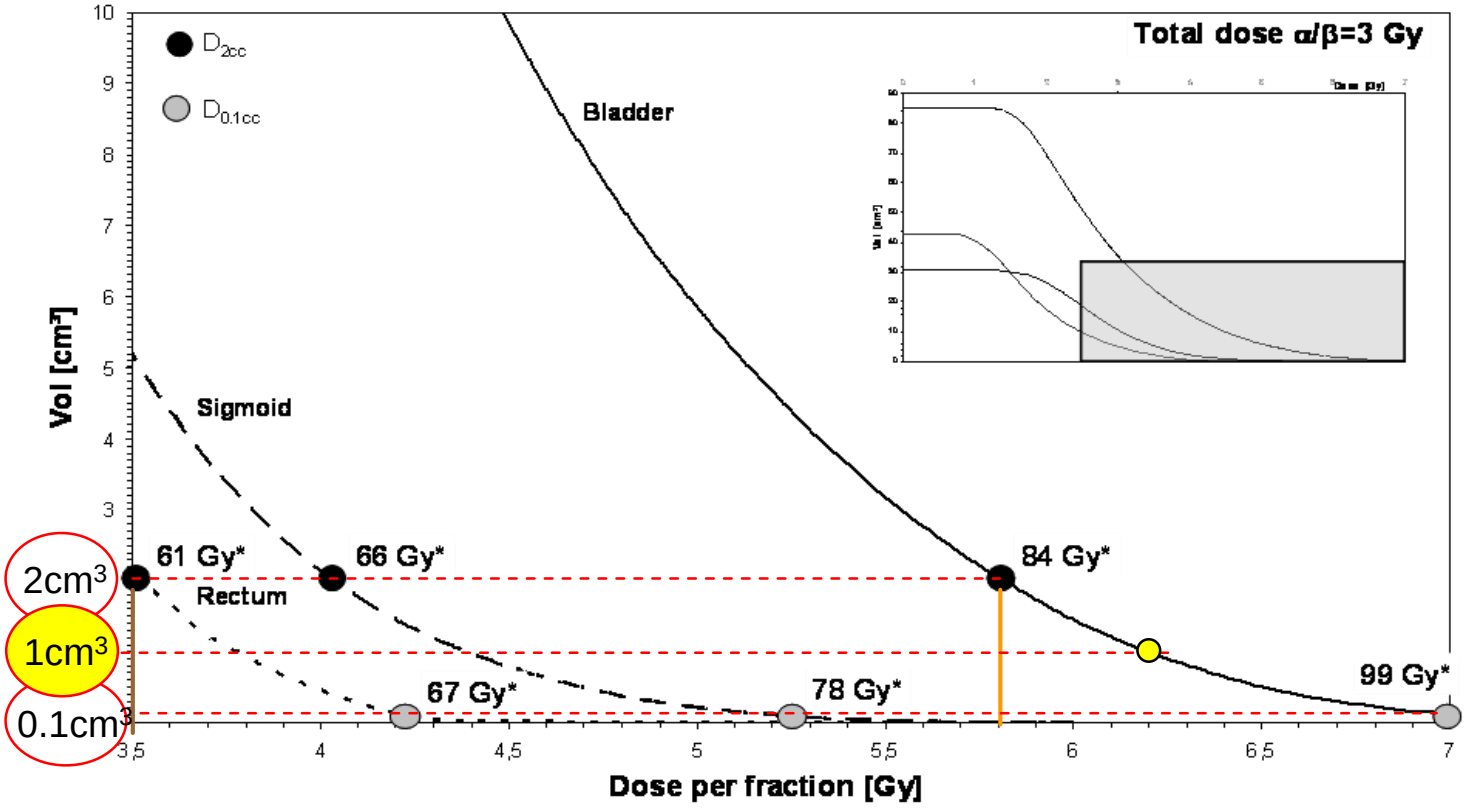
$D_{0.1cm^3}$: "Near-maximum"

TPS uncertainties

Contouring uncertainties

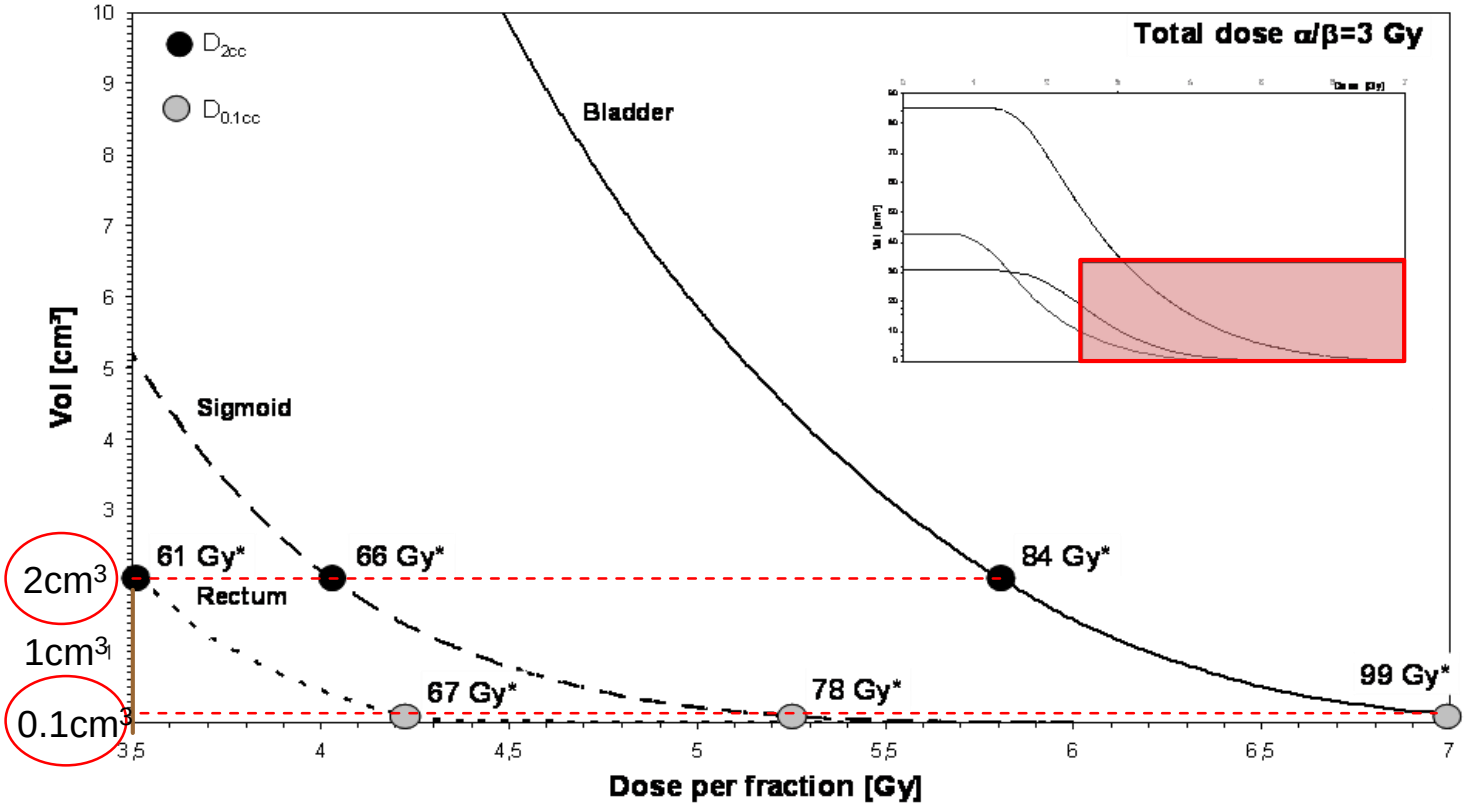
Reporting of max. point-D not recommended

High Doses to Small V: Things to keep in mind



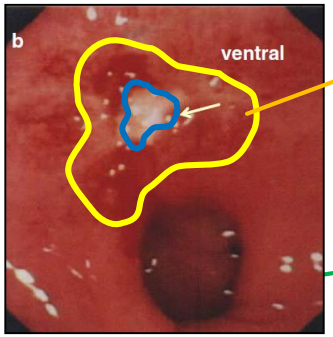
D_{1cm^3}: reporting not recommended (can be interpolated)

High Doses to Small V: Things to keep in mind



Reporting of D_{2cm3} and $D_{0.1cm3}$ describes only the high dose part of the dose distribution

High Doses to Small V: Things to keep in mind

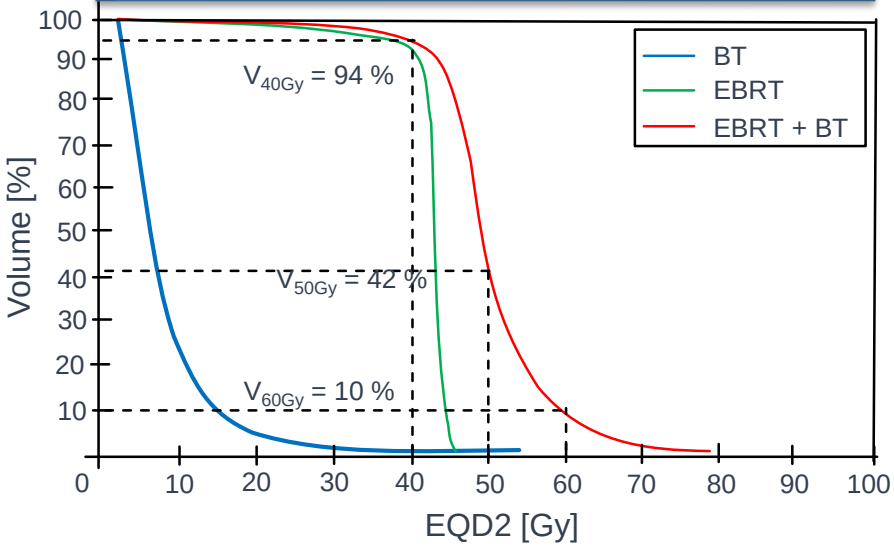


High - D Volumes

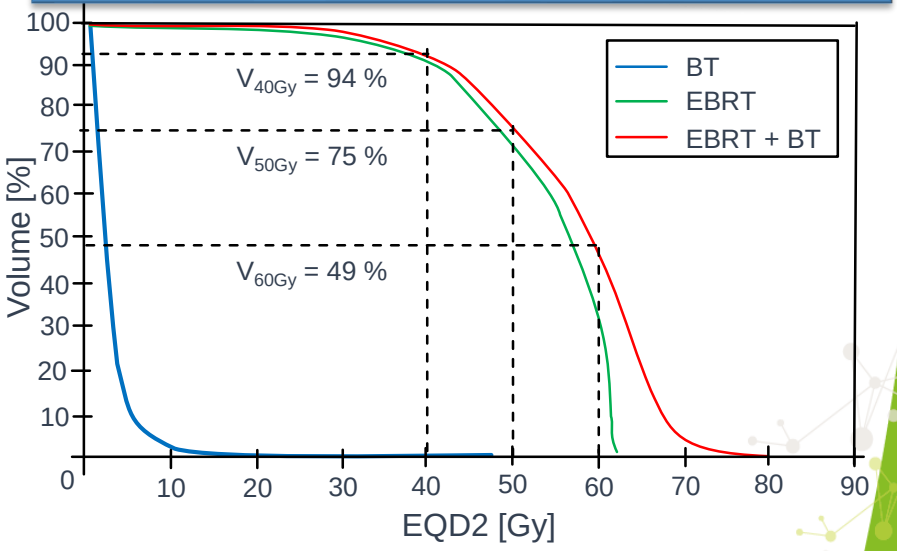
Intermediate- & Low- D Volumes

Clinical effects of D_{2cm3} and $D_{0.1cm3}$

45 Gy EBRT + 4 x BT (EQD2=85 Gy)



45 + 15 Gy EBRT + 2 x BT (EQD2=85 Gy)



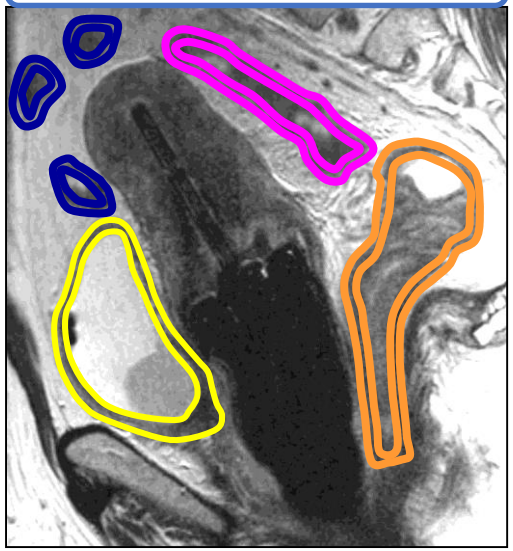
2 Regimens with identical $D2_{cm3}$ → different effects expected due to different EBRT / BT

Example from ICRU 89 Report, p. 113.

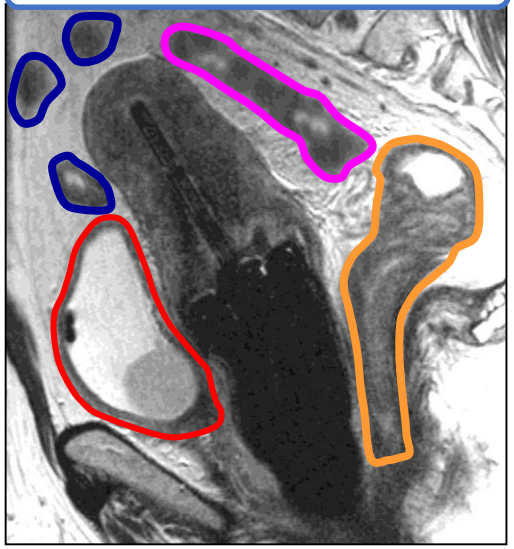
High Doses to Small V: Things to keep in mind

Effects: due to Dose in the *Organ wall*, not Lumen

Organ wall



Organ



More correct, but:

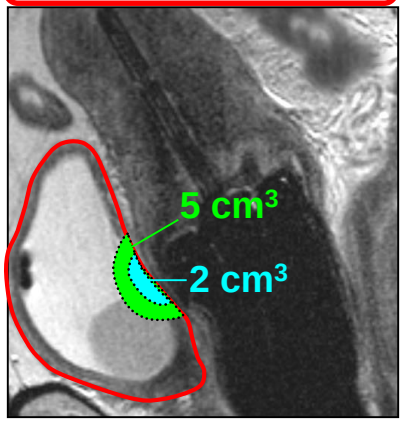
- Time consuming
- Prone to uncertainties

Can we contour organs instead of organ walls?

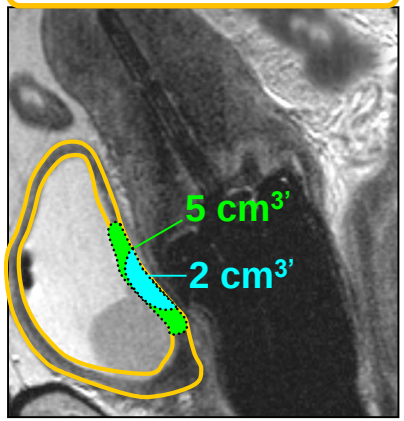
High Doses to Small V: Things to keep in mind

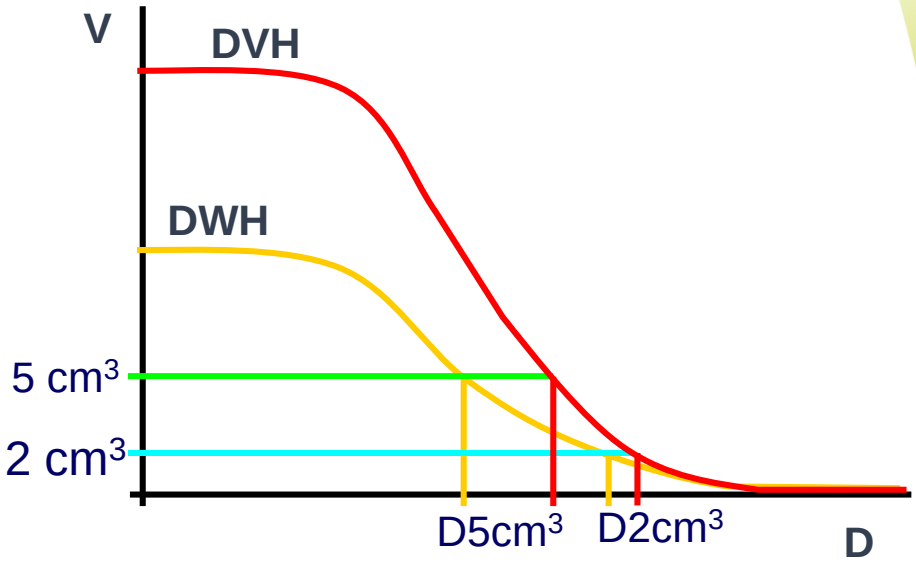
Effects: due to Dose in the *Organ wall*, not Lumen

Organ → **DVH**



Organ wall → **DWH**





$D_{0.1cm^3}$ and D_{2cm^3}: Mainly in the wall → DVH is acceptable

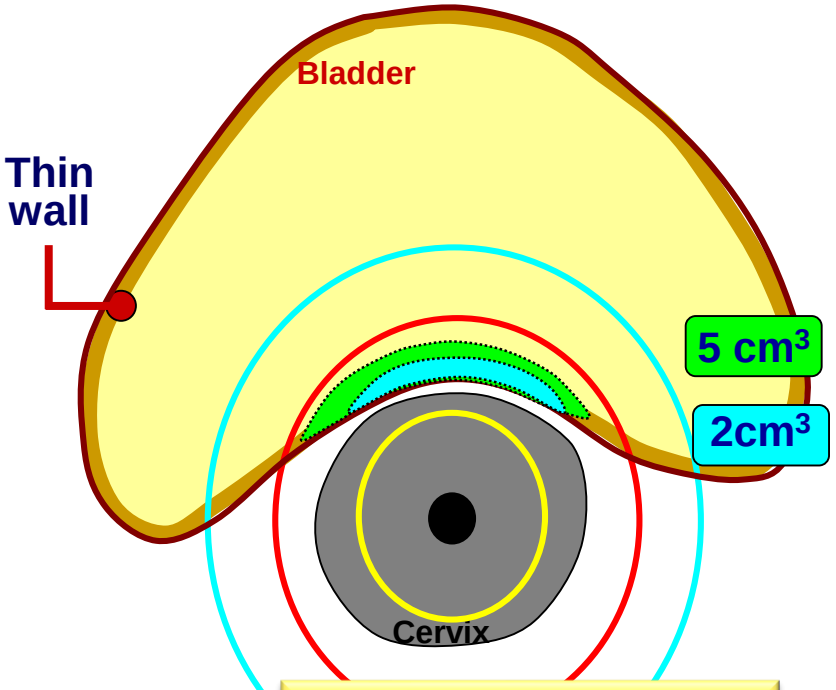
D_{5cm^3} or D to larger V: Mainly in the lumen → DWH is needed

Olszewska AM. Radiother Oncol 2001;61:83-85
Wachter-Gerstner et al. 2003

High Doses to Small V: Things to keep in mind

Effects: due to Dose in the *Organ wall*, not Lumen

Impact of wall thickness



D_{5cm^3} or D to larger V: Mainly in the lumen → DWH is needed

Olszewska AM. Radiother Oncol 2001;61:83-85
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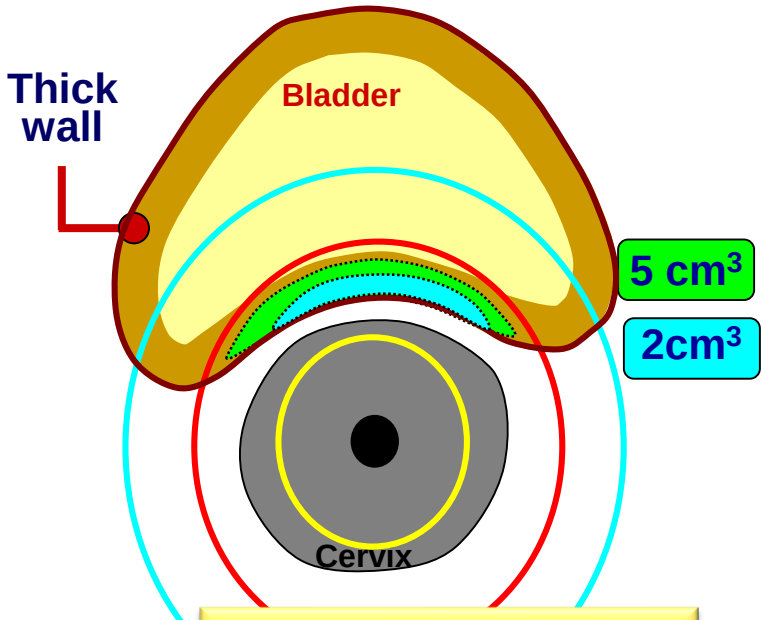
High Doses to Small V: Things to keep in mind

Effects: due to Dose in the *Organ wall*, not Lumen

Impact of wall thickness



$D_{5cm}{}^{3}$ or D to larger V: Mainly in the lumen

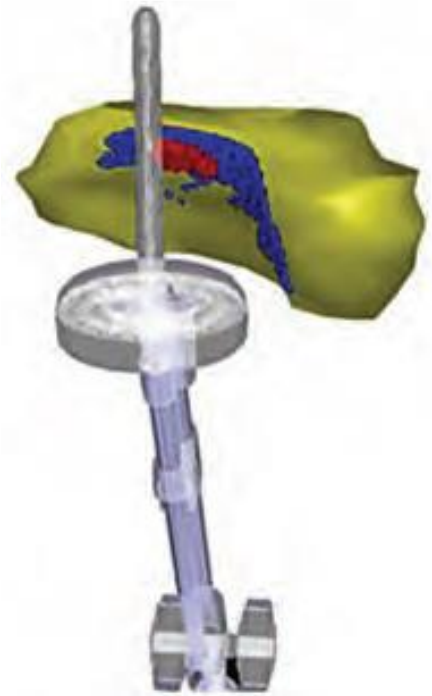
DVH: conditionally acceptable for $D_{5cm}{}^{3}$

Olszewska AM. Radiother Oncol 2001;61:83-85
Wachter-Gerstner et al. 2003

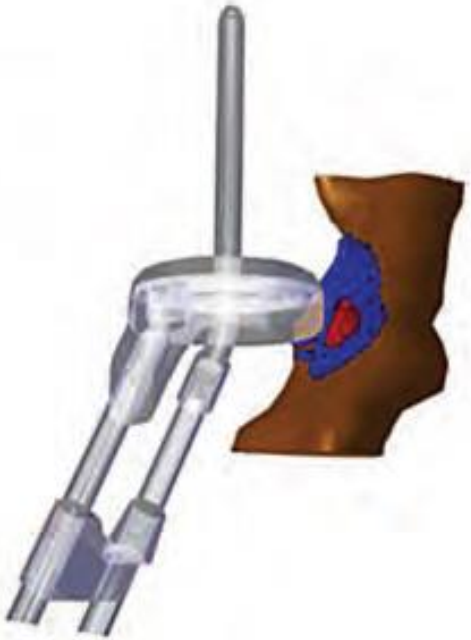
High Doses to Small V: Things to keep in mind

Contiguous vs. Non-contiguous D_{2cm^3}

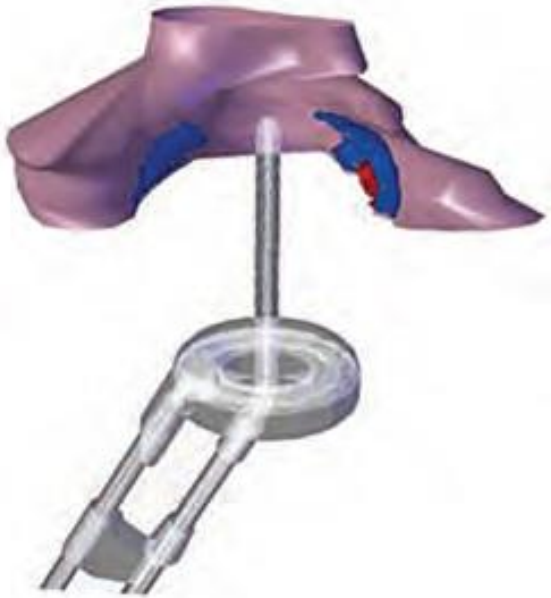
Bladder



Rectum



Sigmoid Colon

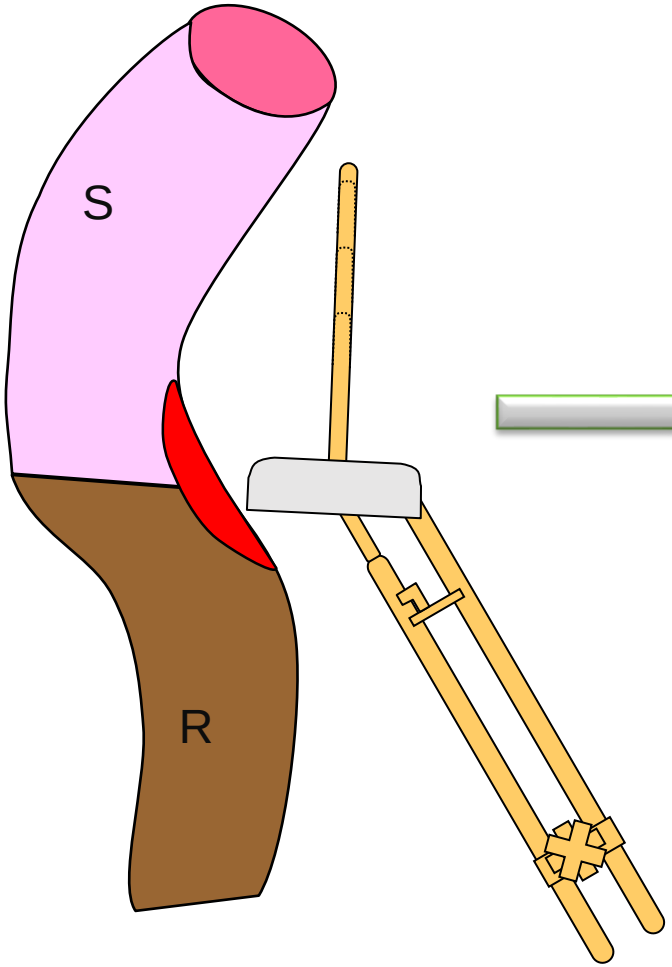


Clinical significance?

Figure from ICRU Report 89. 2016

High Doses to Small V: Things to keep in mind

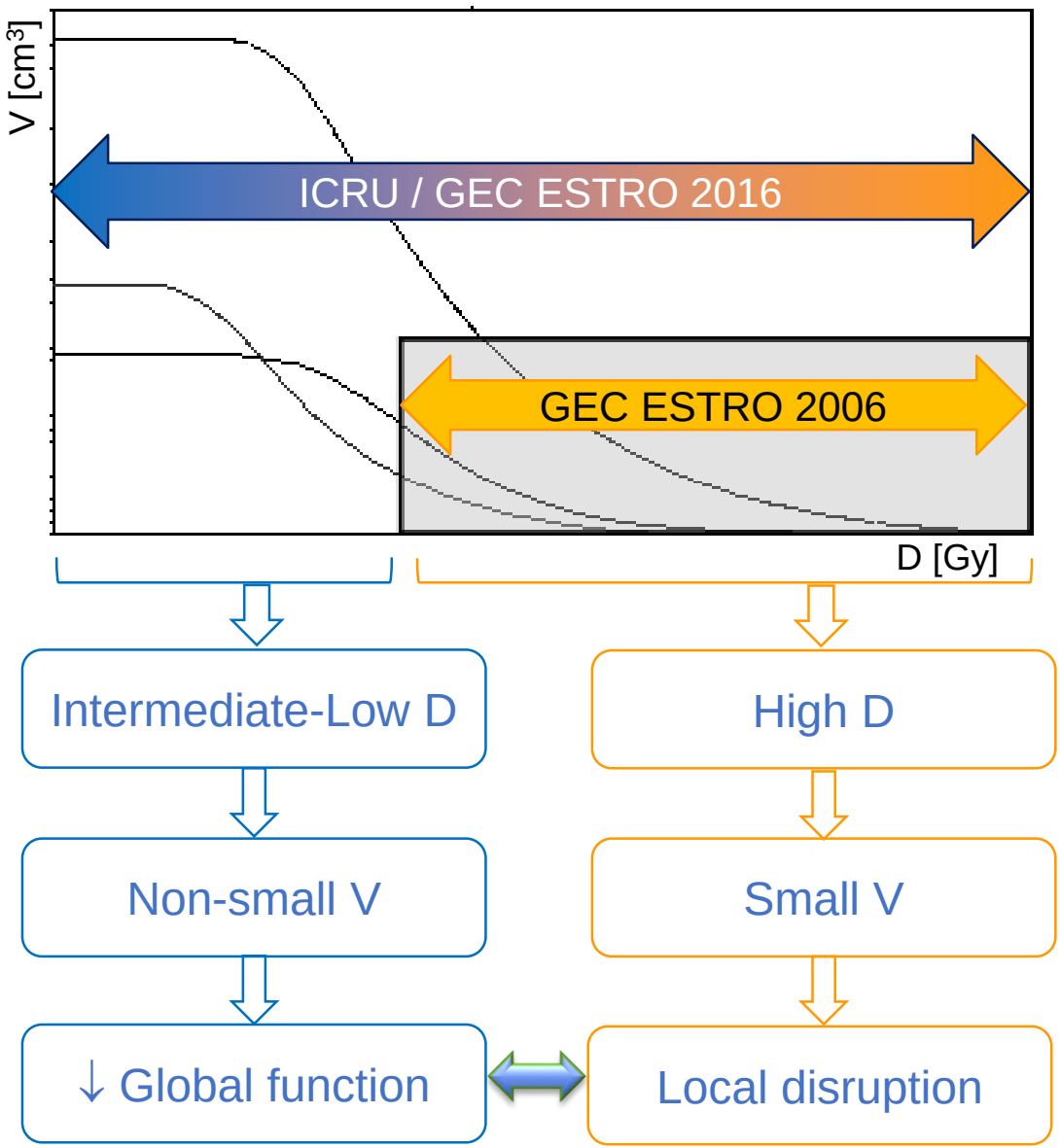
D_{2cm}^{3} at the recto-sigmoid junction



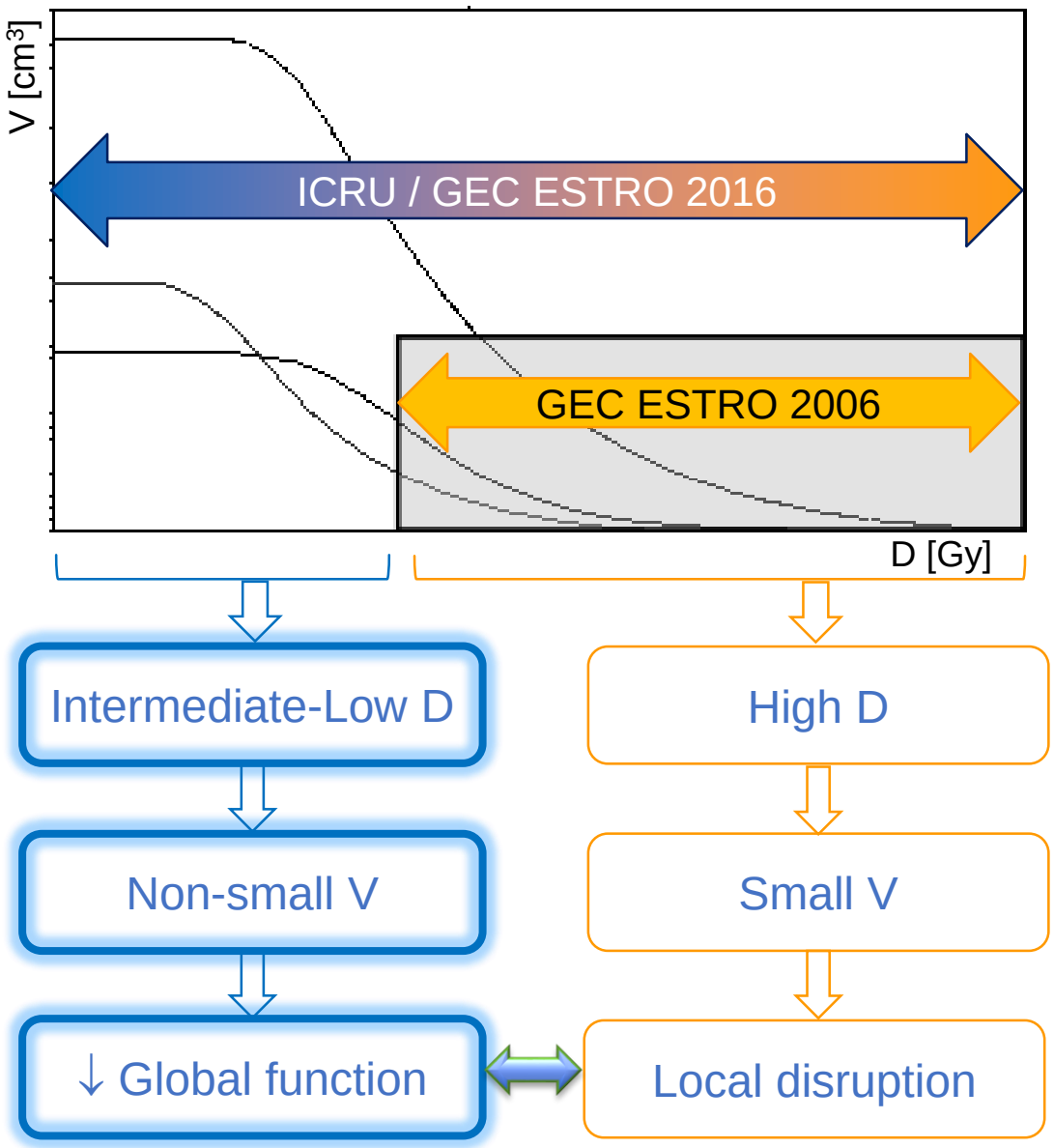
Underestimation of D_{2cm}^{3} when looking at individual organs

Examine isodose distributions anatomically!

Doses to Organs at Risk



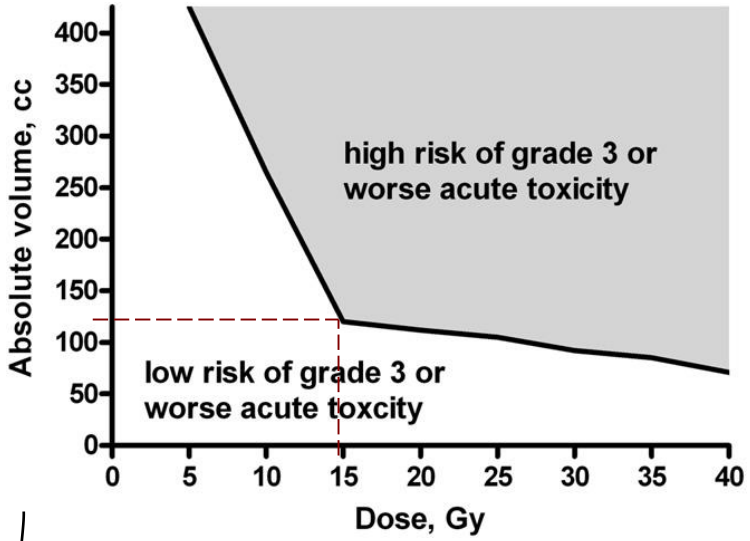
Doses to Organs at Risk



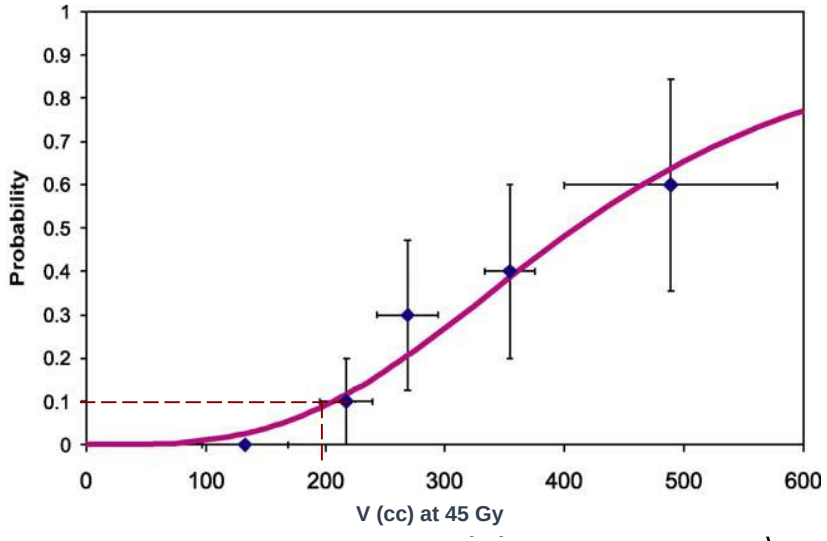
Intermediate & Low Doses to non-Small V of OAR

Treshold – based risk models

Baglan – Robertson, IJROBP 2002



Roeske, Radiother Oncol 2003



Based on delineation of Bowel Loops

Based on delineation of Bowel bag

Small bowel	Individual small bowel loops	3D-CRT	Grade ≥ 3 acute toxicity[§]	V15 <120 cc	<10	Volume based on segmentation of the individual loops of bowel, not the entire potential peritoneal space
	Entire potential space within peritoneal cavity	3D-CRT	Grade ≥ 3 acute toxicity[§]	V45 <195 cc	<10	Volume based on the entire potential space within the peritoneal cavity

Review: Kavanagh DB, IJROBP 2010 (QUANTEC)

Marks, IJROBP 2010 (QUANTEC)

Intermediate & Low Doses to non-Small V of OAR

Marks, IJROBP 2010 (QUANTEC):

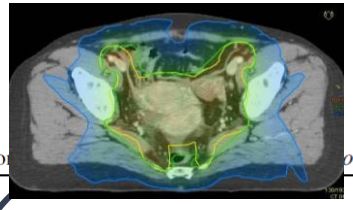
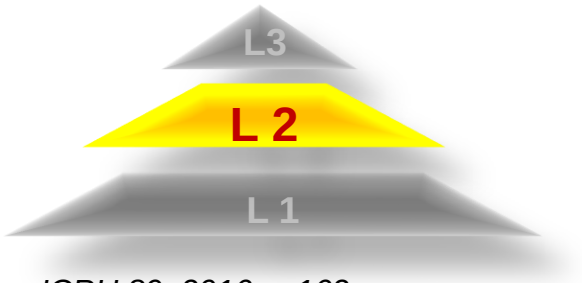


Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractio*ntinued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Rectum	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V50 <50%	<15 <10	experience mainly from prostate cancer
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V60 <35%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V65 <25%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V70 <20%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V75 <15%	<15 <10	
Bladder	Whole organ	3D-CRT	Grade ≥ 3 late RTOG	Dmax <65	<6	Bladder cancer treatment. Variations in bladder size/shape/ location during RT hamper ability to generate accurate data
	Whole organ	3D-CRT	Grade ≥3 late RTOG	V65 ≤50 % V70 ≤35 % V75 ≤25 % V80 ≤15 %		Prostate cancer treatment Based on current RTOG 0415 recommendation

Limited V!

Limited V!



ICRU 89. 2016; p.162

Level 2: *Advanced standard for reporting*
All that is reported in Level 1 plus:

- Intermediate- and low-dose parameters in bladder, rectum, sigmoid, bowel
  (*e.g.*, $V_{15\ Gy}$, $V_{25\ Gy}$, $V_{35\ Gy}$, $V_{45\ Gy}$ or $D_{98\ \%}$, $D_{50\ \%}$, $D_{2\ \%}$)

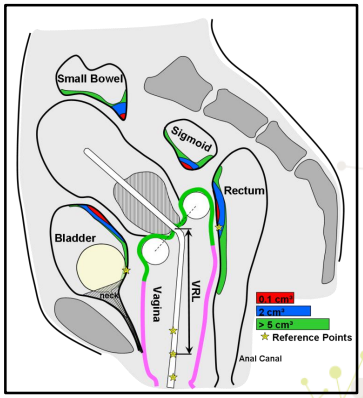
Doses to Volumes - Organs At Risk

Level 3
Level 2
Level 1

Reporting Summary

	High D Parameters		Low-Intermed. Param.	
	$D_{0.1cm^3}$	D_{2cm^3}	$V_{15Gy - 45Gy}$	$D_{2\% - 98\%}$
Bladder	L 1	L 1	L 2	L 2
Rectum	L 1	L 1	L 2	L 2
Sigmoid colon	L 2	L 2	L 2	L 2
Bowel	-	L 2	L 2	L 2

	DVH, DSH, D-profiles
Vagina	L 3
Other OAR	L 3
OAR subvolumes	L 3



ICRU/GEC ESTRO Report 89. 2016

Reporting Dose Delivery Pattern - Level 1

ICRU 89

Minimum standard for reporting

Absorbed dose rate/dose per fraction

Number of fractions

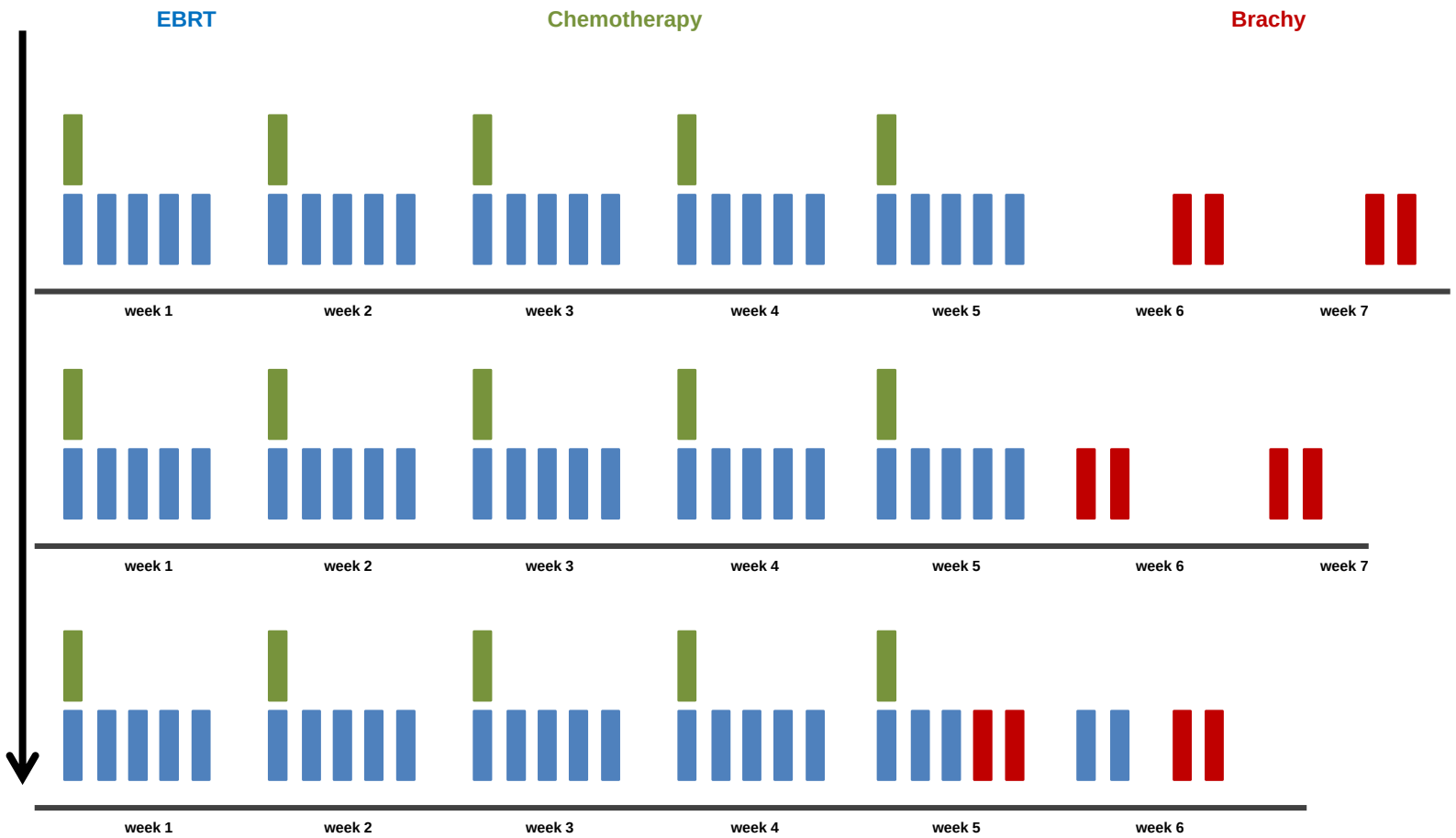
Time between fractions

(Pulse number, size, time, if PDR)

Overall treatment time

Total EQD2

Overall Treatment Time (BT, EBRT, total)



Minimum standard Level 1 reporting

ICRU-GEC-ESTRO Recommendations

Dose-Volume Reporting

Primoz Petric

Aarhus University Hospital

Richard Pötter

Medical University of Vienna

General and image guided adaptive treatment strategies and BT techniques for Vaginal Cancer

Vaginal and Vulvar cancer: frequency

Estimated new cancer cases and deaths, United States, 2008

	Estimated new cases	Estimated deaths
Genital system (female)	**78490**	**28490**
Uterine cervix	11070	3870
Uterine corpus	40100	7470
Ovary	21650	15520
Vulva	**3460**	**870**

Rare gynaecological tumours

Vagina : 1% - 2% female reproductive tract cancers

Vaginal cancer

Primary vaginal cancer :

- **Cervix and the vulva without history of cervix or vulvar cancer within 5 years**
- **80% postmenopausal women**
- **Mean age : 60-65 years**
- **Exception : clear cell adenocarcinoma, young patients (mothers diethylstilbestrol (DES) during their pregnancies)**

Vaginal cancer: natural history and pattern of spread

- 50% of vaginal cancers : upper third of the vagina
even distribution on anterior/posterior/lateral walls

- 40-50% are multifocal

- Lower third of the vagina lymphatics communicate with those of the vulva

- Drainage:
  - either to the pelvic nodes or
  - to the inguino-femoral lymph nodes.

Vaginal cancer: initial work-up

- Clinical examination +++
  - Topography
  - Macroscopic characteristics
  - Drawings +++ / vaginal impression

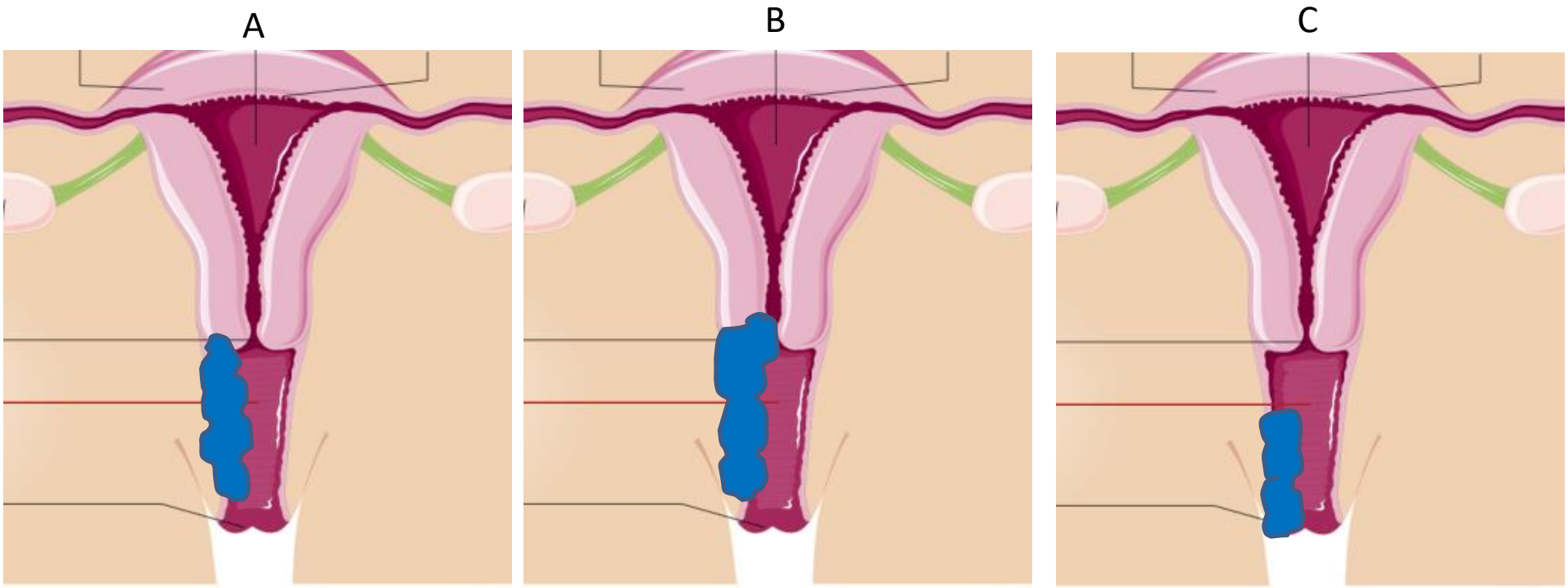
- Transvaginal and/or transrectal sonography :
  - tumour thickness : assists in BT technique

- MRI : tumour dimension, site, extension (bladder, rectum)
  enlarged pelvic and para-aortic nodes

- FDG-PET nodal disease twice as often as CT

- Depending on tumoral extension : anuscopy/rectoscopy / urethrocystoscopy

FIGO classification



According to FIGO staging rules, tumors in the vagina should be classified as :

- **‘cervical’ if the cervical os is involved (even if most of the tumor is in the vagina)**
- **‘vulval’ if any portion of the vulva is involved**

Vaginal cancer : FIGO classification

0	Carcinoma in situ, intraepithelial carcinoma
I	Carcinoma limited to the vaginal wall
II	Paravaginal tissue extension, without reaching pelvic wall
III	Pelvic wall extension
IV	Extension beyond the true pelvis or bladder/rectum mucosa
IVA	Adjacent organs and/or direct extension beyond the true pelvis
IVB	Distant organs spread

Vaginal cancer: treatment

- Rarity of primary carcinoma of the vagina
- No randomized trial to assess :
  - the respective role of surgery and irradiation
  - to explore the value of concomitant chemoradiation
- Role +++ of brachytherapy

Vaginal cancer: treatment of VAIN

- Surgery alone (80%) young patients,
  ovarian function preservation
- Irradiation (5%-10) : exclusive BT
- Chemotherapy (4%-5%)

Results : brachytherapy VAIN

Patients characteristics		n=21
Age at diagnosis	Median (range)	53 (29-78)
Age at brachytherapy	Median (range)	66 (38-80)
History of	Cervical carcinoma	2
	endometrial carcinoma	1
	CIN	20
Multifocal	Yes	2
	No	19
Microinvasive carcinoma	Yes	2
	No	14
	NA	5

Median Follow-up: 79 months

Blanchard, Oncologist 2011;16:182-8

Results: Brachytherapy VAIN

BT characteristics	
Volume 60 Gy isodose (cm^3)	82 (18-121)
Vaginal volume treated	
upper half	14
upper two-third	4
whole vagina	3
ICRU Bladder Dose (Gy)	47 (8-74)
ICRU Rectum Dose (Gy)	69 (32-109)
Application duration (days)	4.5 (3-6)
Intraoperative Lugol staining (%)	18 (82)
Intraoperative fiducial placement (%)	6 (27)

Blanchard, Oncologist 2011;16:182-8

Brachytherapy: outcome

- Follow-up: 79 months
- 1 vulvar relapse (out of field)
- 1 « in field » relapse in a heavily pretreated patient
  - **previous surgery, radiotherapy, chemotherapy and brachytherapy for cervical carcinoma**
  - **unsuccessful interferon and laser therapy for VAIN**
- 19 cured patients

Blanchard, Oncologist 2011;16:182-8

Vaginal cancer: treatment of invasive tumours

- External beam radiotherapy (ERT) and brachytherapy (BT)
- Limited stage I : exclusive BT
- 45 Gy to the pelvis/prophylactic inguinal ERT if lower third tumoral extension
- Concomitant chemoradiation

Vaginal cancer: image-guided adaptive brachytherapy (IGABT)

- No recommendations for CTVs
- CTV_{HR} and CTV_{IR} concepts for cervix
- Transfer and adaptation to vaginal cancer

Target delineation recommendations of the GYN GEC-ESTRO Group for image-guided adaptive brachytherapy in primary vaginal cancer

Vaginal cancer: image-guided adaptive brachytherapy (IGABT)

GTV_{init}: macroscopic tumor at the time of diagnosis

GTV_{res}: macroscopic residual tumor at the time of brachytherapy

Clinical examination: This is the remaining visible and palpable residual macroscopic tumor at gynae examination

Imaging: T2-weighted MRI remaining mass with hyperintense to isointense signal intensity, within the initial tumor extension at diagnosis, *GTV_{init}*

Vaginal cancer: image-guided adaptive brachytherapy (IGABT)

CTV_{HR}: includes the *GTV_{res}* and areas at high risk for significant residual disease

Clinical: *GTV_{res}* and any abnormal thickened or irregular vaginal wall within the initial tumor extension (*GTV_{init}*)

Imaging: includes the *GTV_{res}* and any abnormal thickened or deformed vaginal wall within the initial tumor extension (*GTV_{init}*)

In case of tumors infiltrating the paravaginal or parametrial space at diagnosis, so called „grey zones“are included in the *CTV_{HR}*

Vaginal cancer: image-guided adaptive brachytherapy (IGABT)

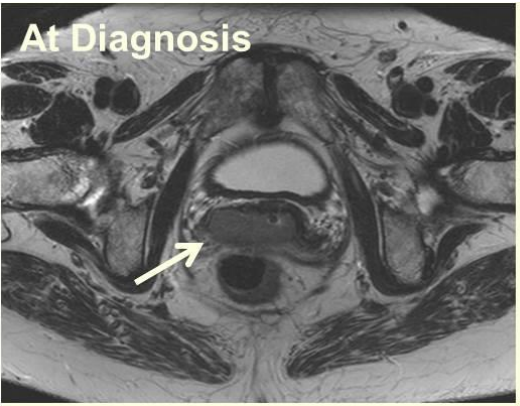
CTV_{IR}: safety margin for presumed adjacent significant microscopic disease

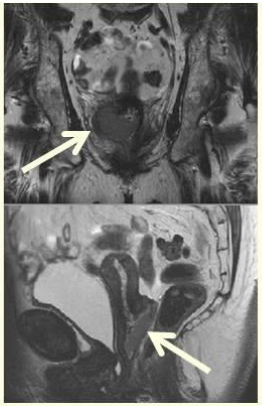
Integrates initial tumor extension at diagnosis (*GTV_{init}*)

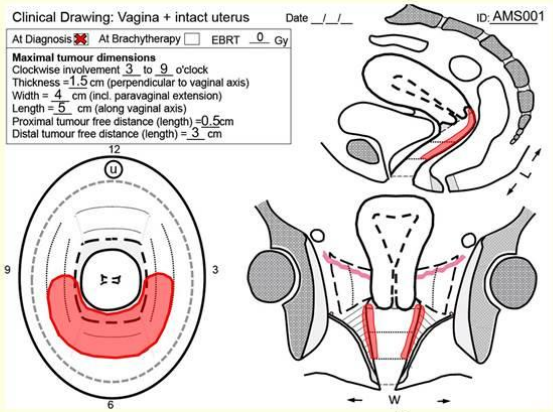
Includes the *CTV_{HR}* plus an isotropic margin of **minimal 5 mm** limited by previously unaffected anatomical borders/compartments: pubic bone, pelvic wall, pelvic floor musculature, bladder, urethra, mesorectal fascia, rectum, anal sphincter

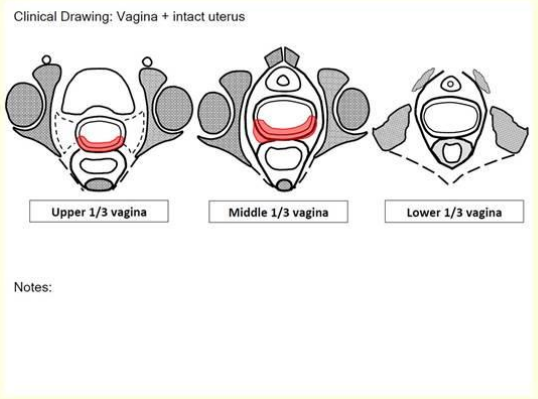
In case of infitration of hollow organs (rectum, urinary bladder) before radiochemotherapy only the organ wall without the lumen should be included

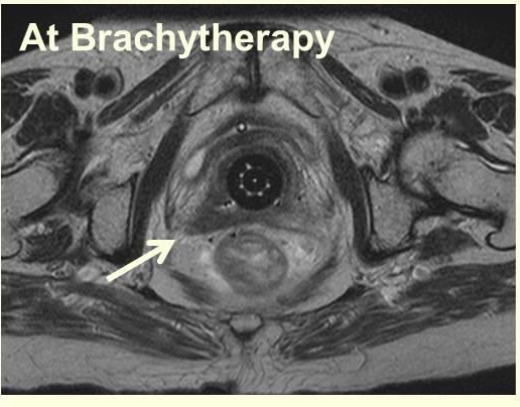
Vaginal cancer: image-guided adaptive brachytherapy (IGABT)

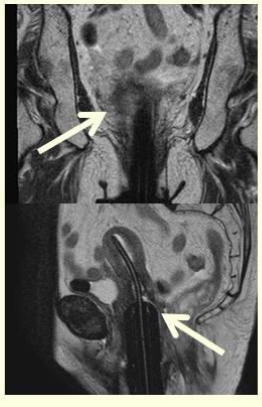


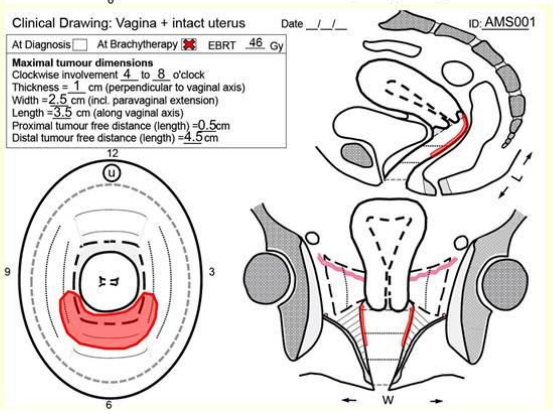


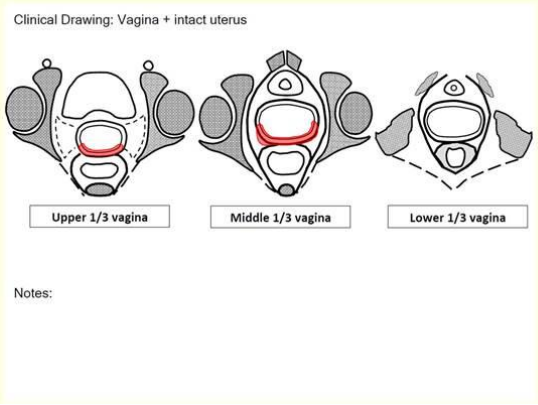




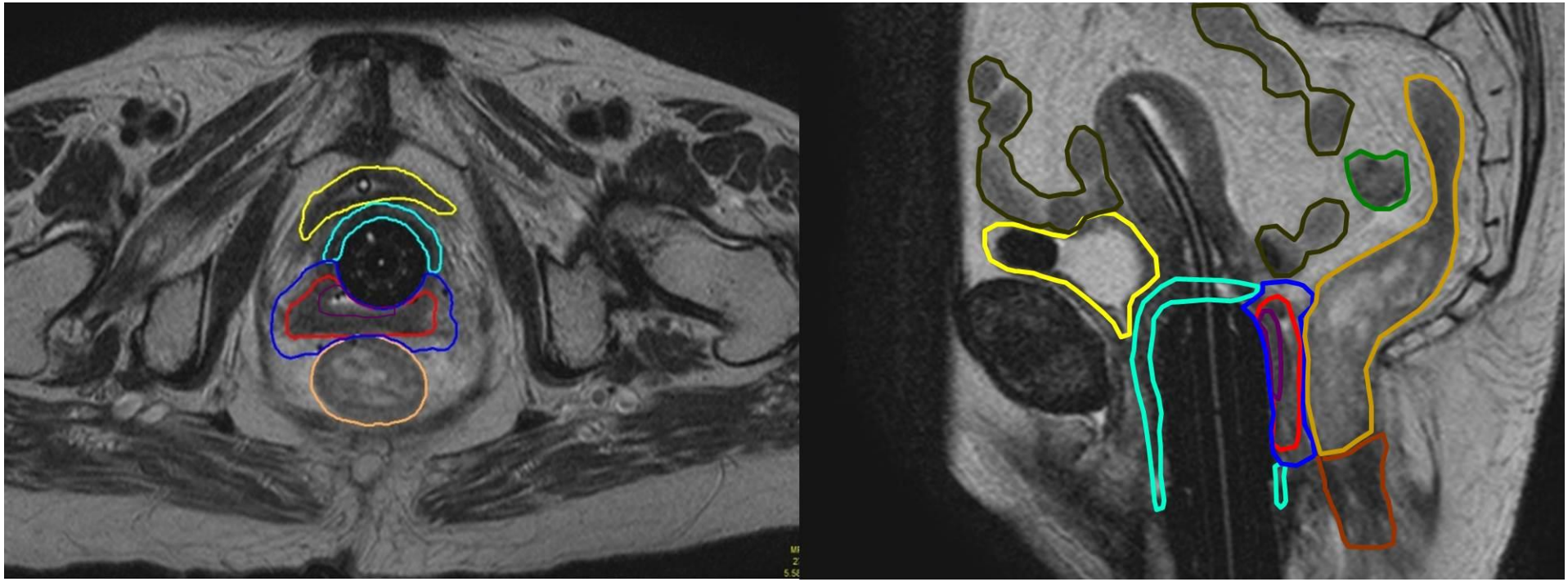








Vaginal cancer: image-guided adaptive brachytherapy (IGABT)



Vaginal cancer: brachytherapy

- Endocavitary
- Interstitial
- Endocavitary and interstitial combination
- Total dose : 80Gy to the GTV

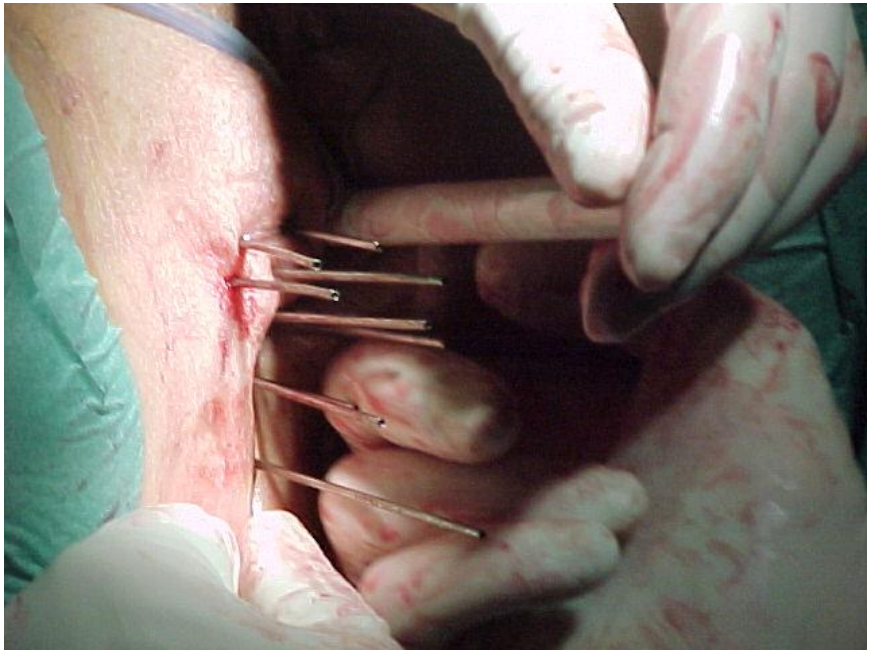
Interstitial Techniques Vagina

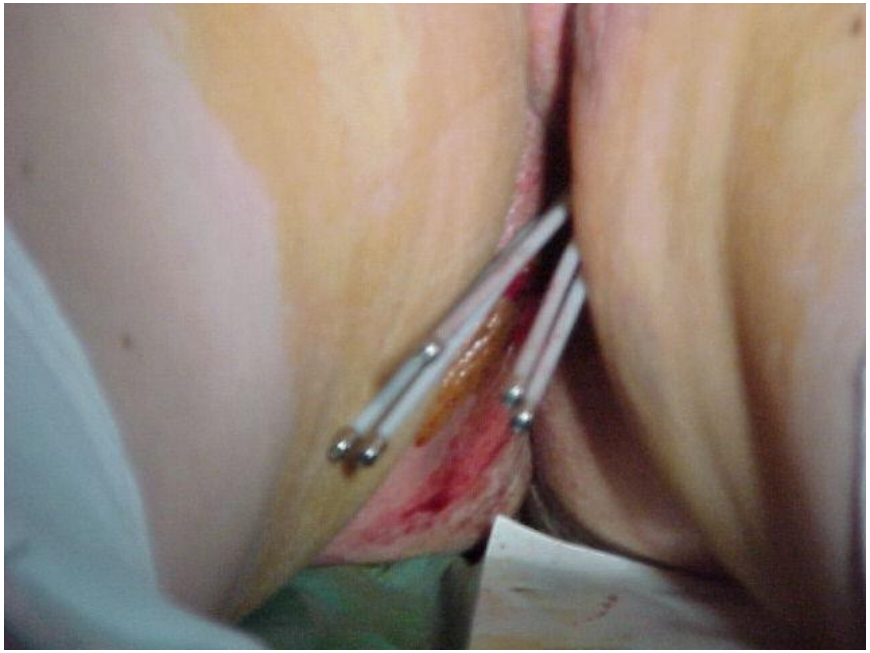
Techniques

- Freehand placement
- Intra-vaginal templates
- Transperineal templates :
  - Syed- Neblett applicator
  - MUPIT…
- (Guide gutter)
- Plastic tube
- Steel – plastic - titanium needles

Interstitial Techniques Vagina

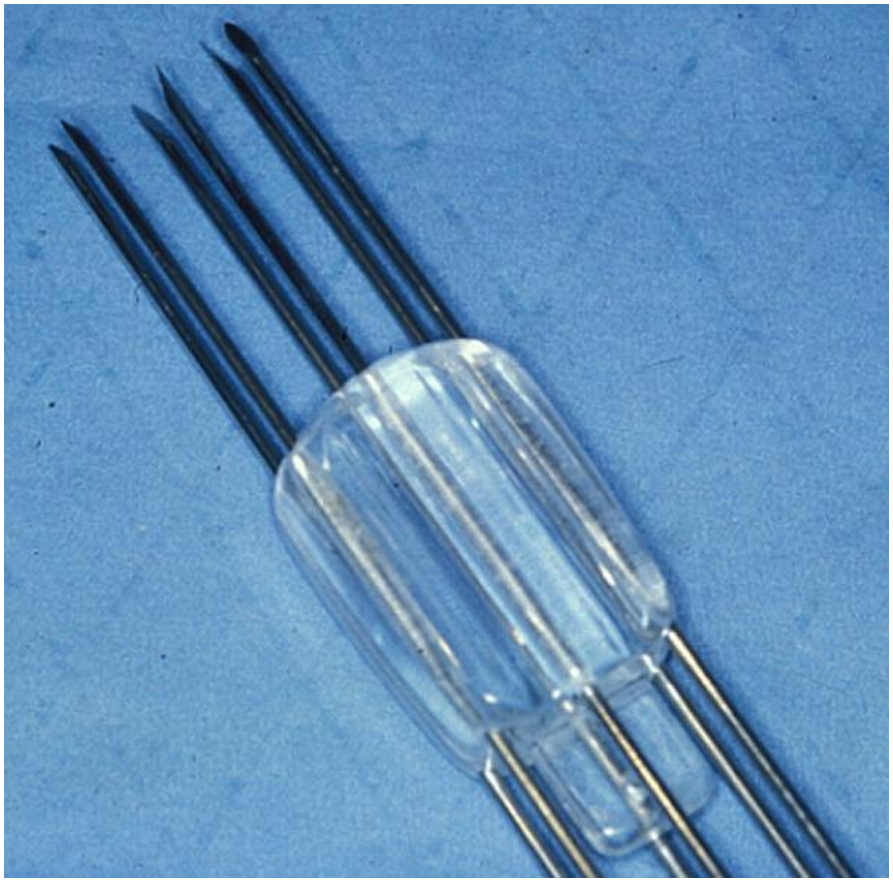
Techniques – Freehand placement





Interstitial Techniques Vagina

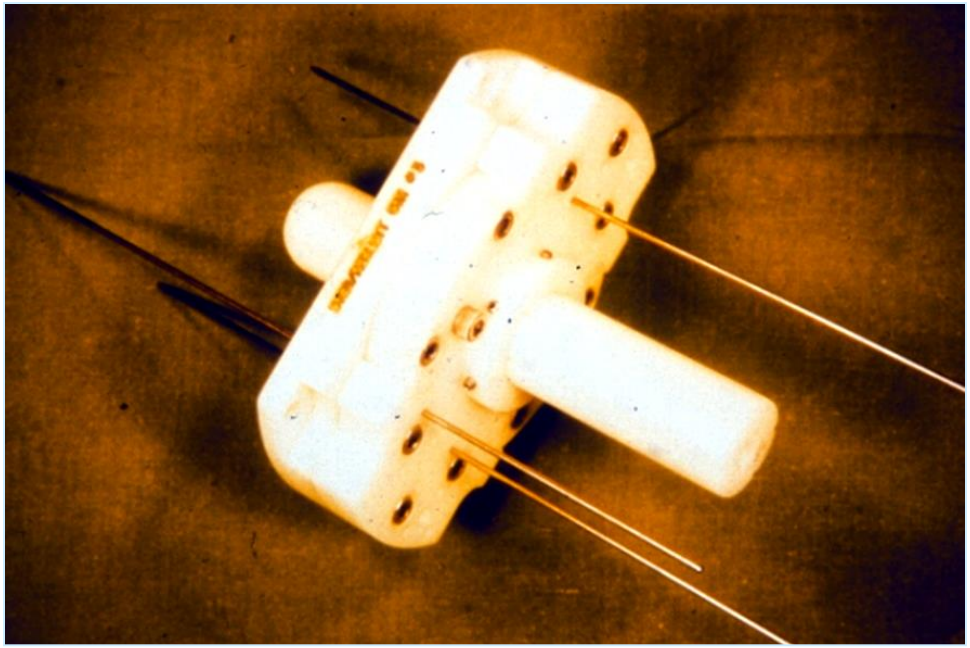
Techniques – Intravaginal template



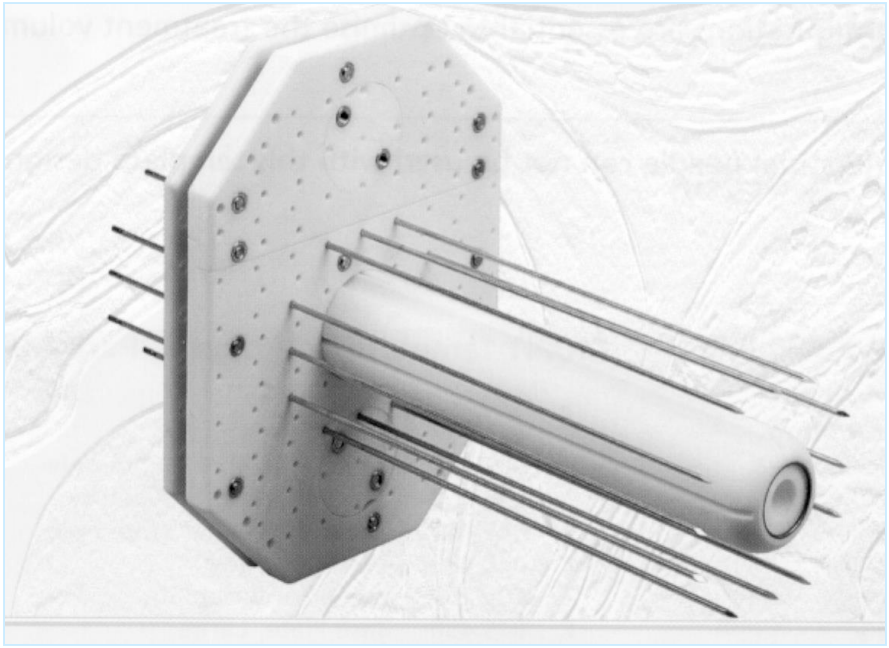
Interstitial Techniques Vagina

Techniques – Perineal templates

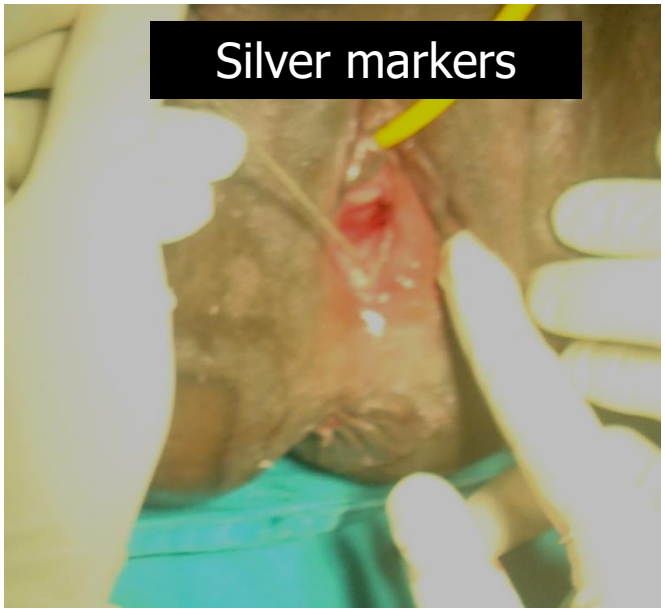
Syed

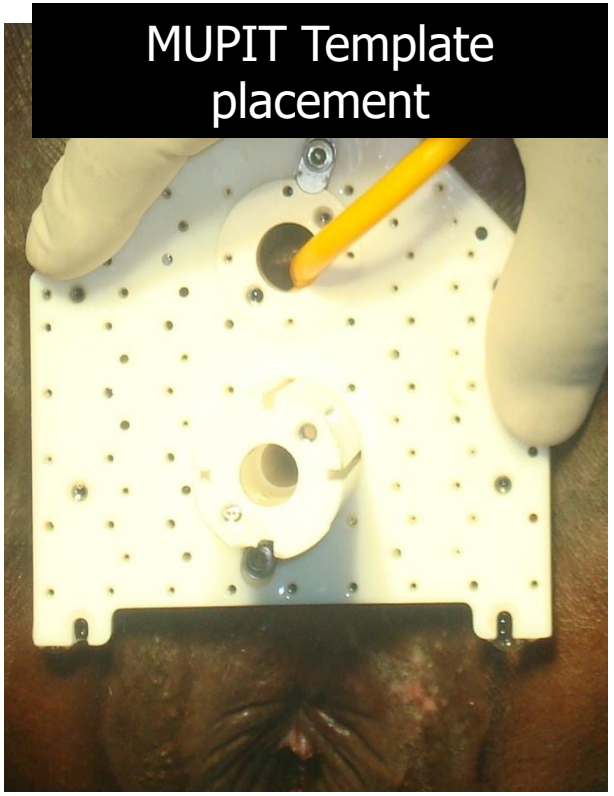


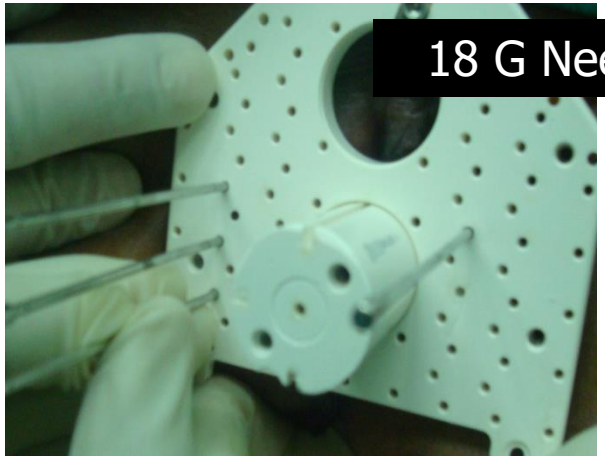
MUPIT

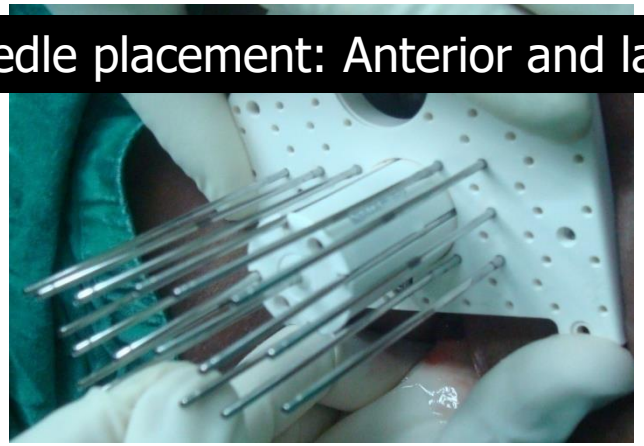


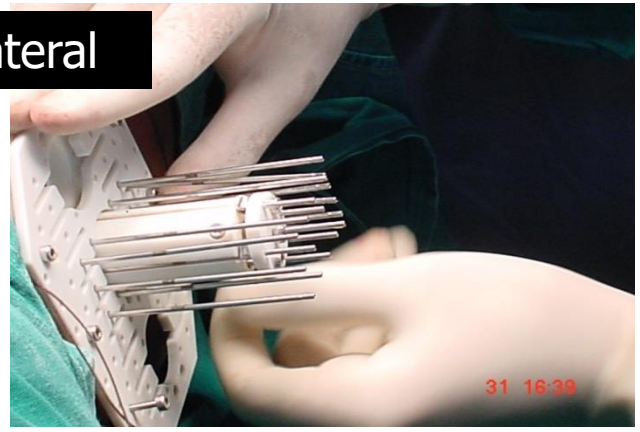
MUPIT Technique









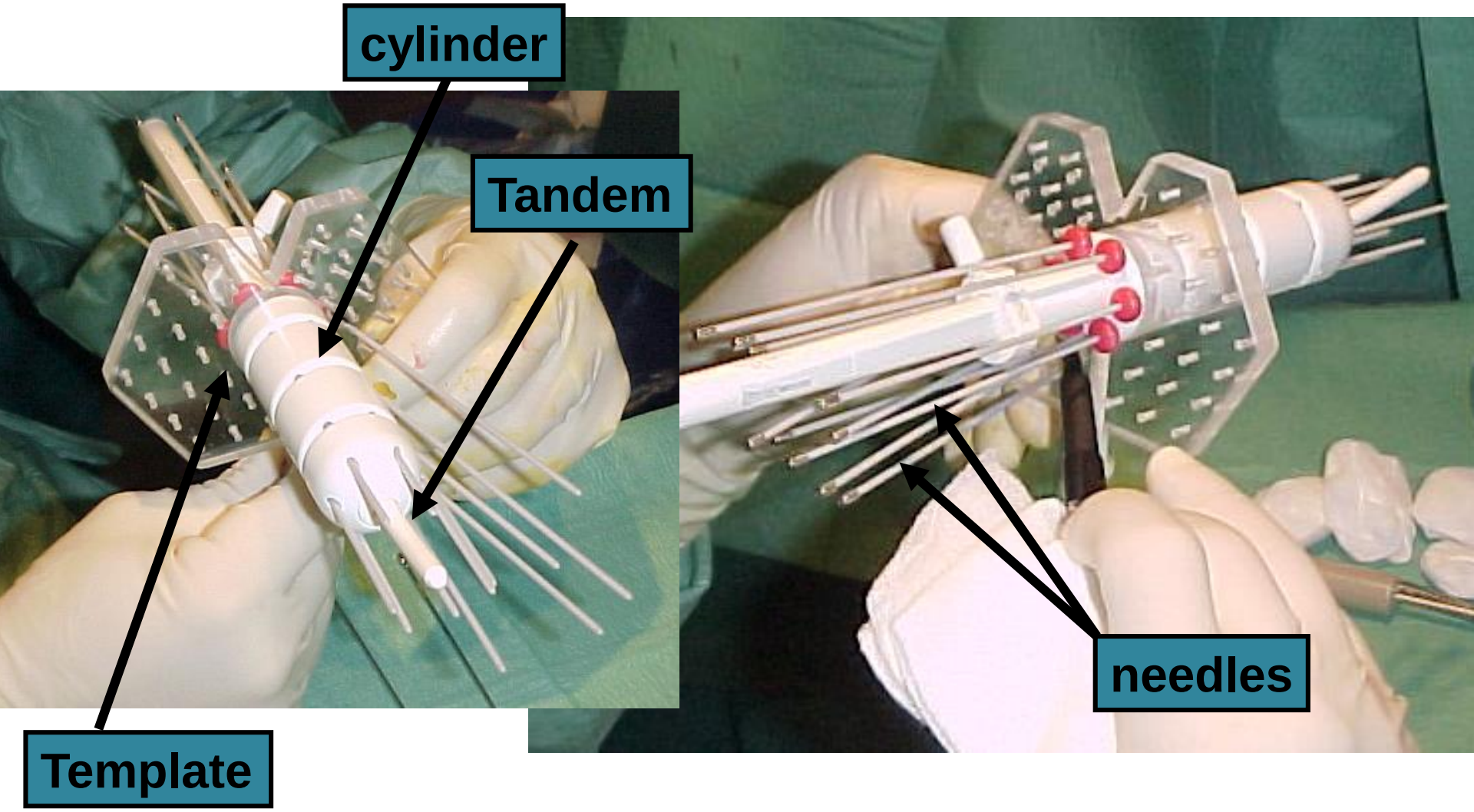


Under digital rectal guidance / Trans-ultrasound Guided

Mahantshetty et al; Brachytherapy 2013

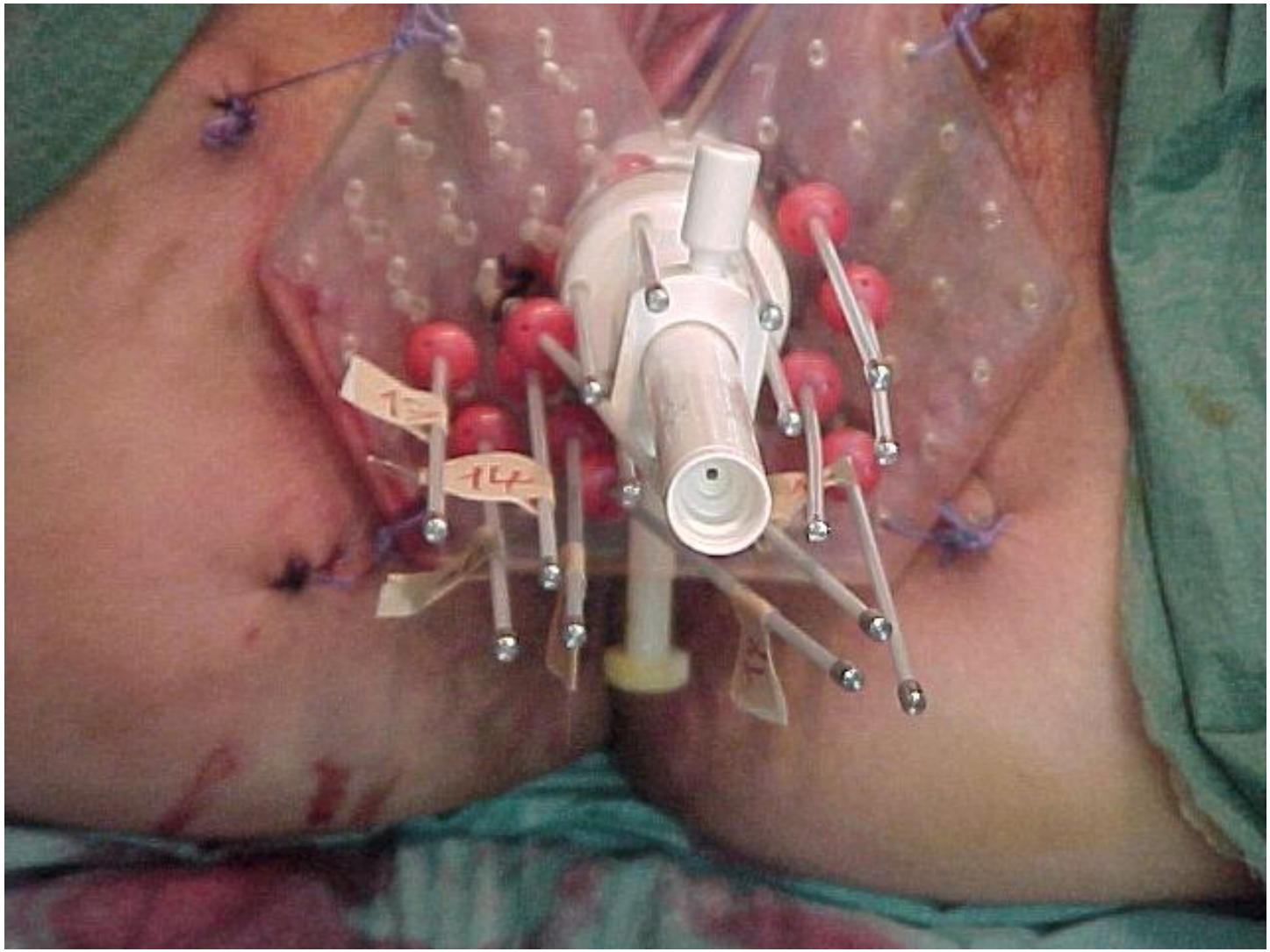
Interstitial Techniques Vagina

Techniques – Perineal templates



Interstitial Techniques Vagina

Techniques – Perineal templates – Completed implant



Interstitial Techniques Vagina

Attempts to improve needle placement

Needle placement accuracy

- Fluoroscopy
- Computed tomography
- MRI : open MRI
- Laparotomy
- Laparoscopy

} guided implants

- Transabdominal ultrasonography
- Transrectal ultrasonography

Published results include studies with diverse GYN tumors

Interstitial Techniques Vagina

Selection of application technique

Based on clinical examination and sectional imaging:

- At the time of diagnosis

  -initial tumor extension

- During EBRT

  -Quantitative and qualitative tumor regression

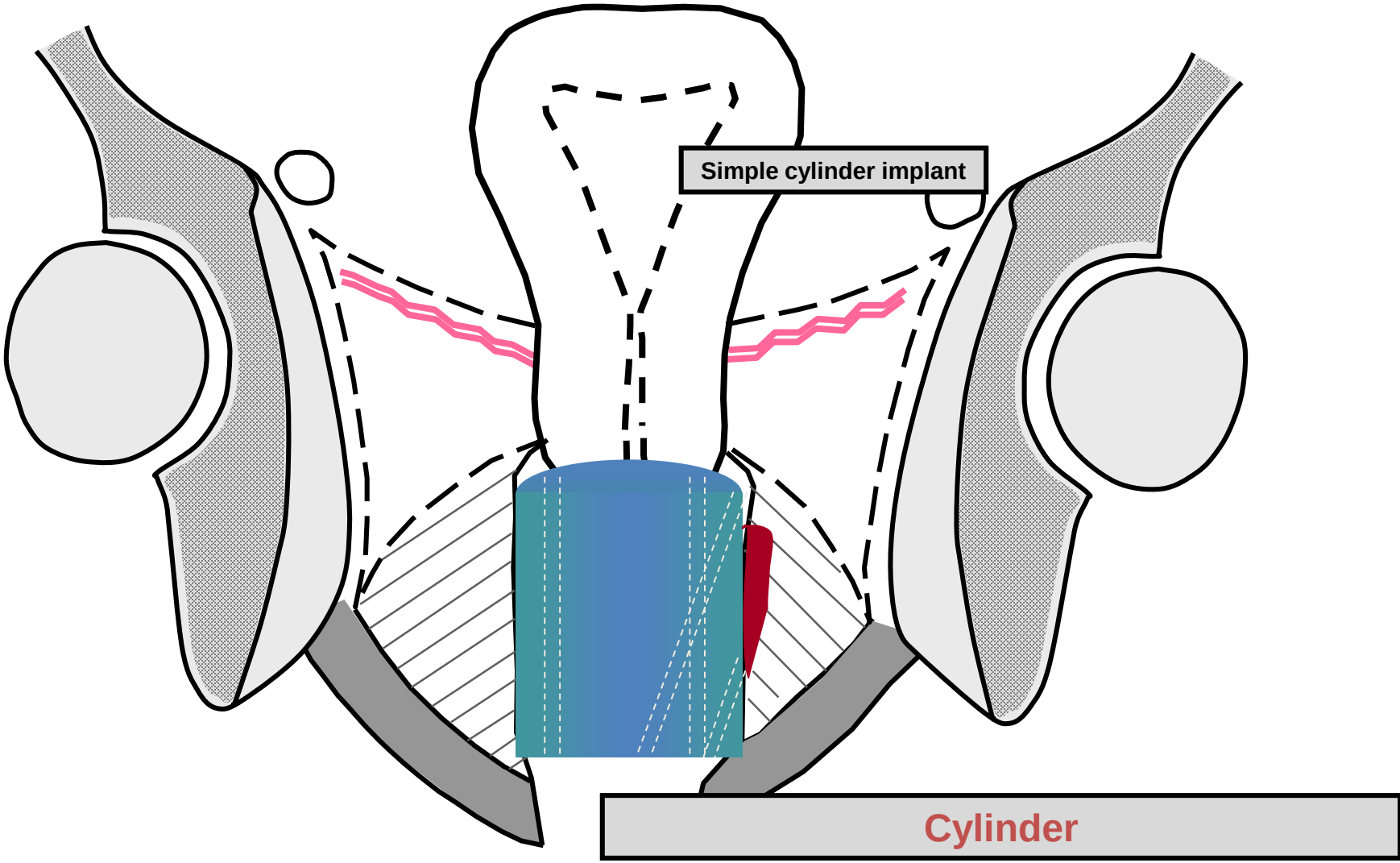
- At the time of brachytherapy

  -Topography of tumor in relation to the applicator

Published results include studies with diverse GYN tumors

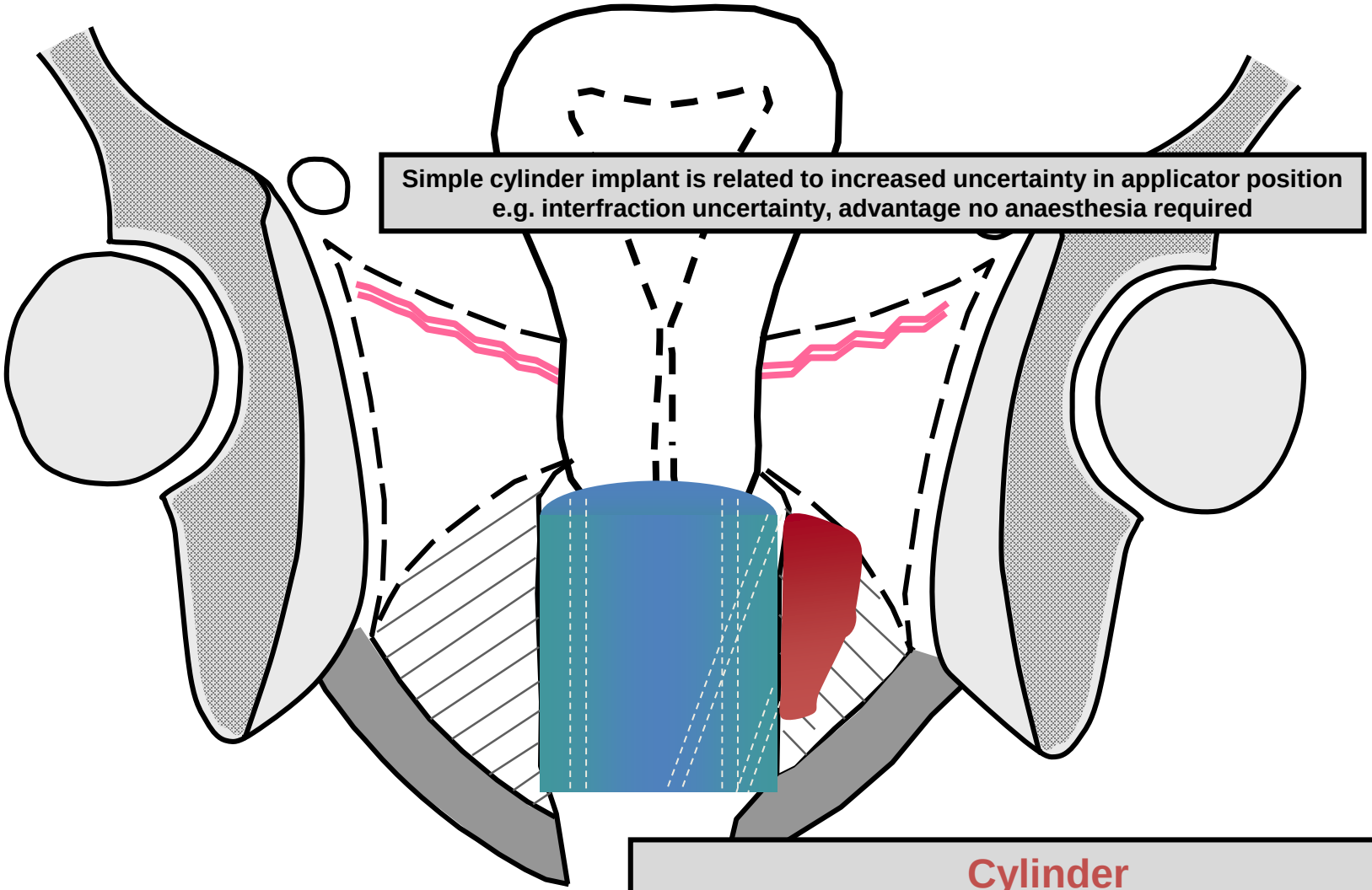
Interstitial Techniques Vagina

Pattern of tumor regression



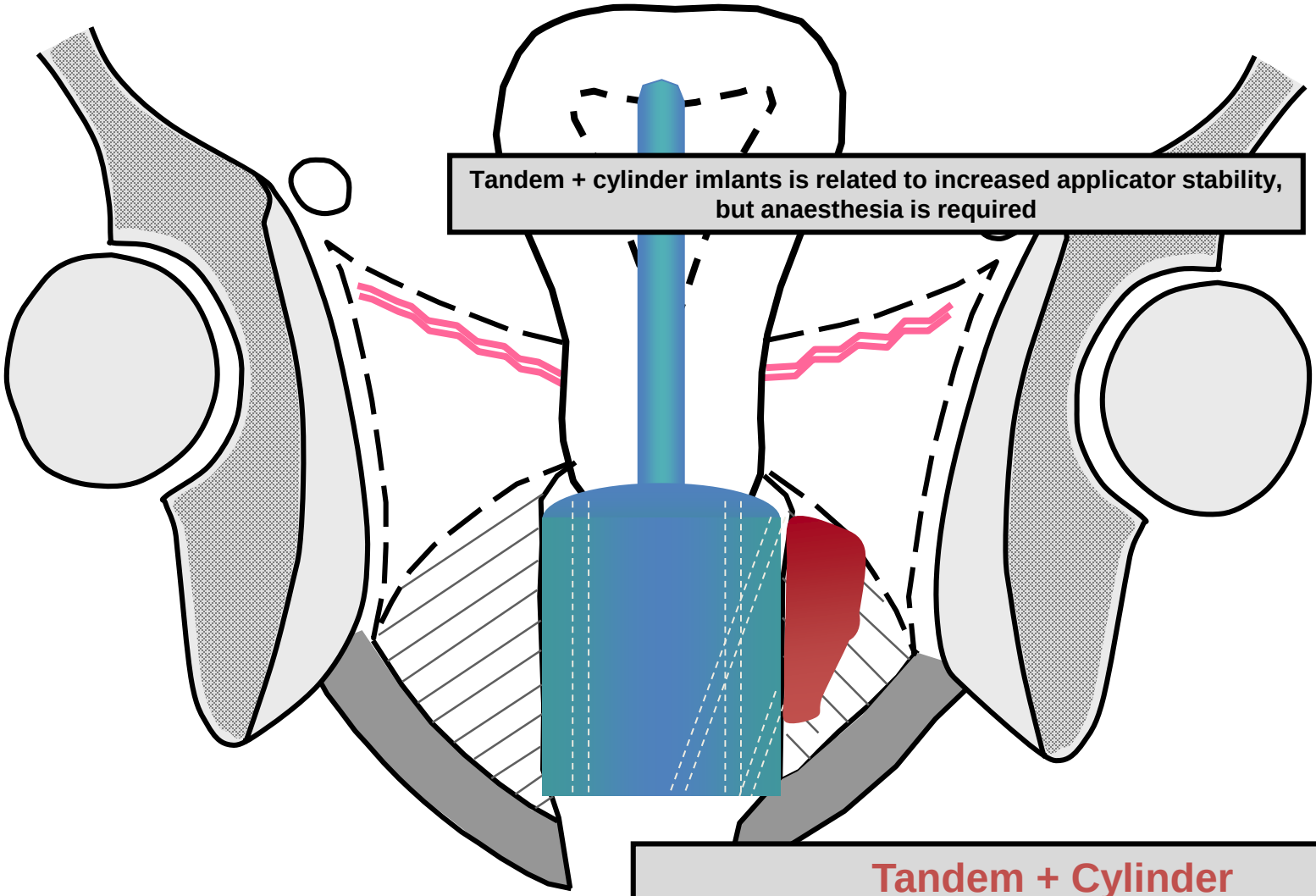
Interstitial Techniques Vagina

Pattern of tumor regression



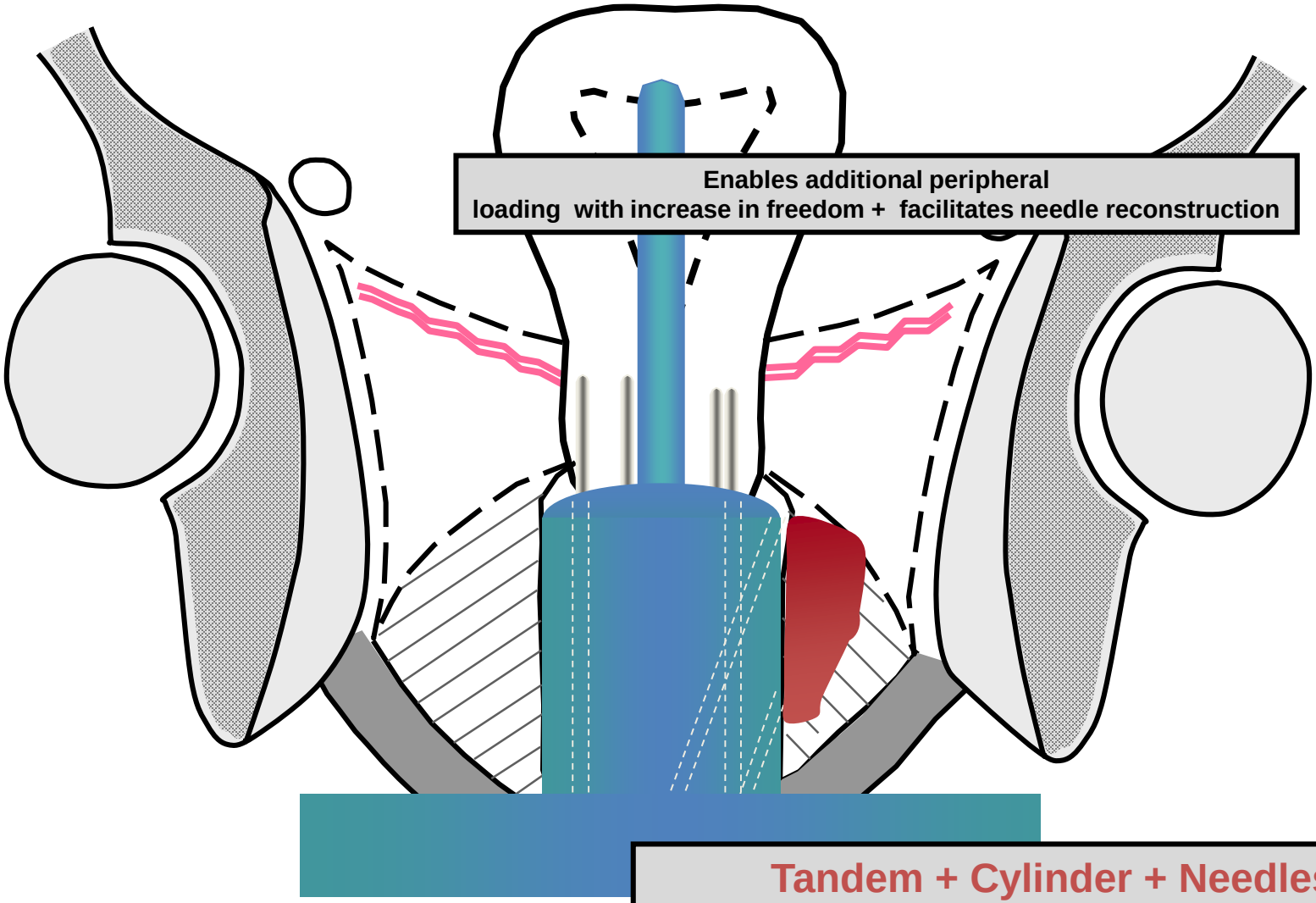
Interstitial Techniques Vagina

Pattern of tumor regression



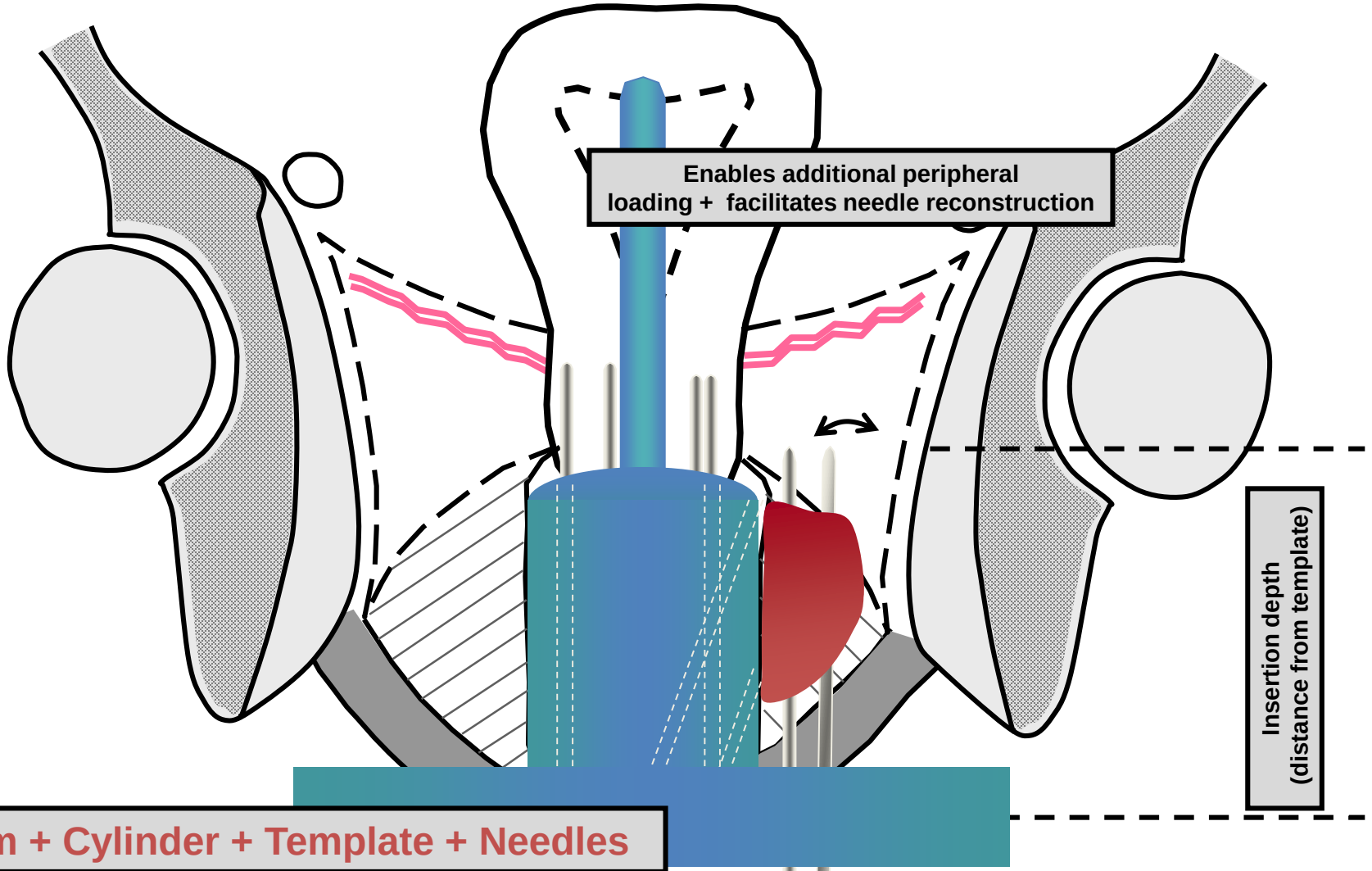
Interstitial Techniques Vagina

Pattern of tumor regression



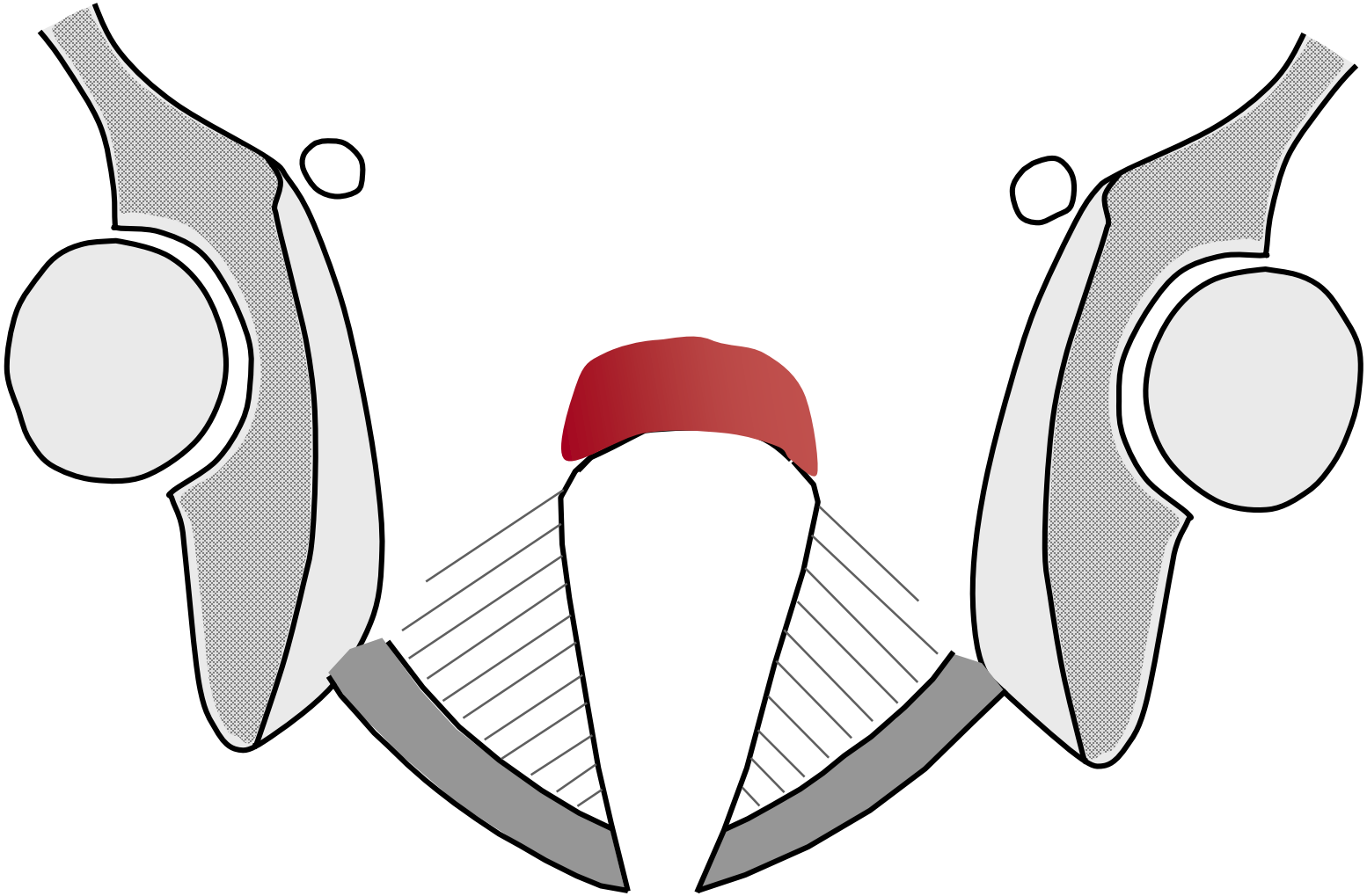
Interstitial Techniques Vagina

Pattern of tumor regression



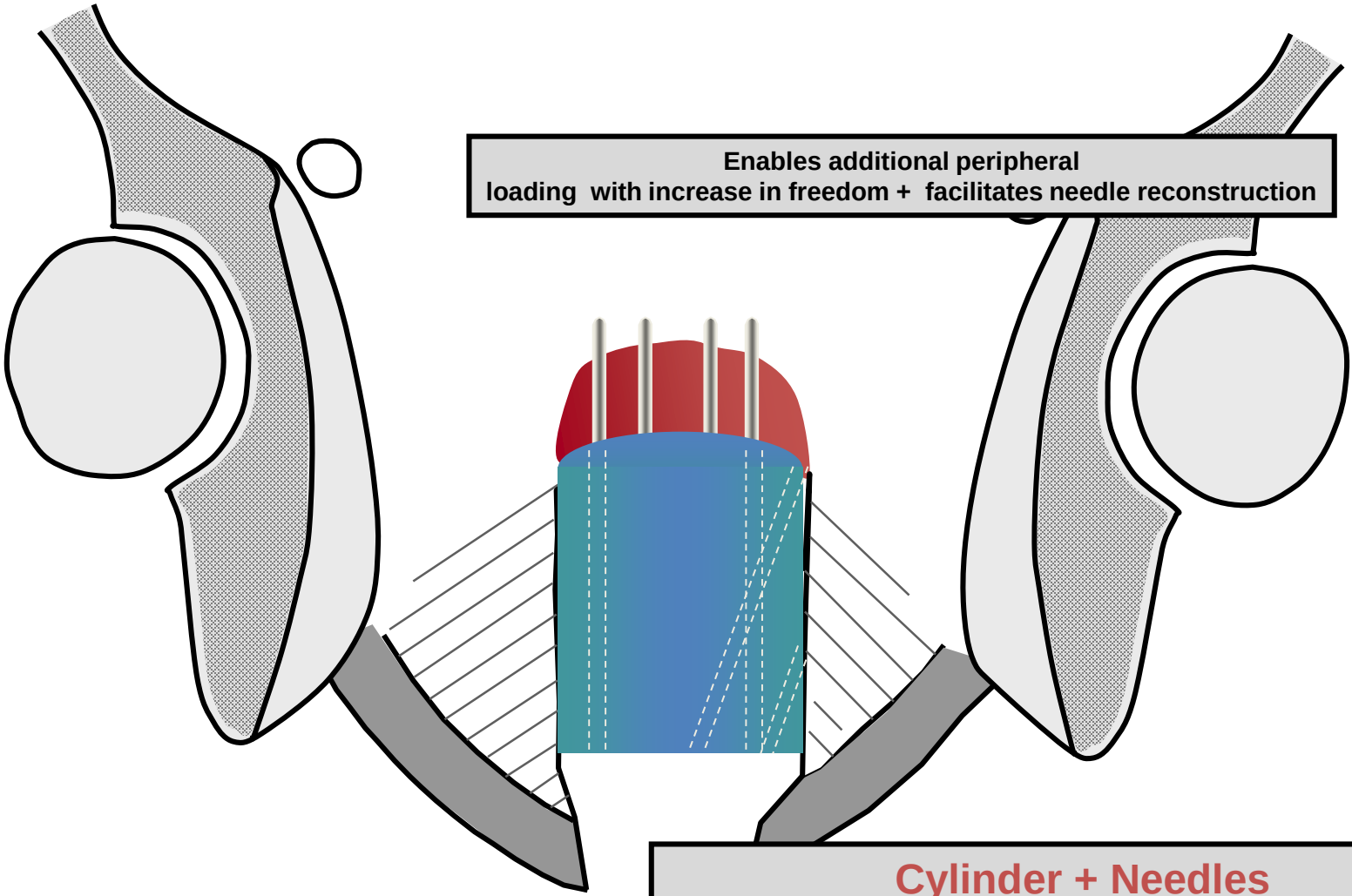
Interstitial Techniques Vagina

Pattern of tumor regression



Interstitial Techniques Vagina

Pattern of tumor regression



Tata Memorial Hospital Experience: 2000 – 2008

MEAN FU 28 Mths, (MEDIAN : 23, RANGE 4 - 99 mths)

	R2 resection CA Cx (N=37)	Vault CA (N=57)	Vaginal CA (N=19)
CONTROLLED	23 (62%)	37 (65%)	13 (68%)
CENTRAL DISEASE	10 (27%)	15 (26%)	3 (16 %)
LOCO-REGIONAL	1 (3 %)	1 (2%)	2 (11 %)
L-R + DISTANT	1 (3%)	2 (3.5 %)	1 (5 %)
DISTANT	2 (5 %)	2 (3.5 %)	0 (0 %)
DFS (months) **MEAN**	57	47	61
MEDIAN	57	49	--
OS (months) **MEAN**	64	54	60
MEDIAN	--	--	--
5 YR DFS	45%	46%	57%
5 YR OS	54%	61%	52%

Mahantshetty et al; Brachytherapy 2013

Mahantshetty U, et al. Brachytherapy 2013

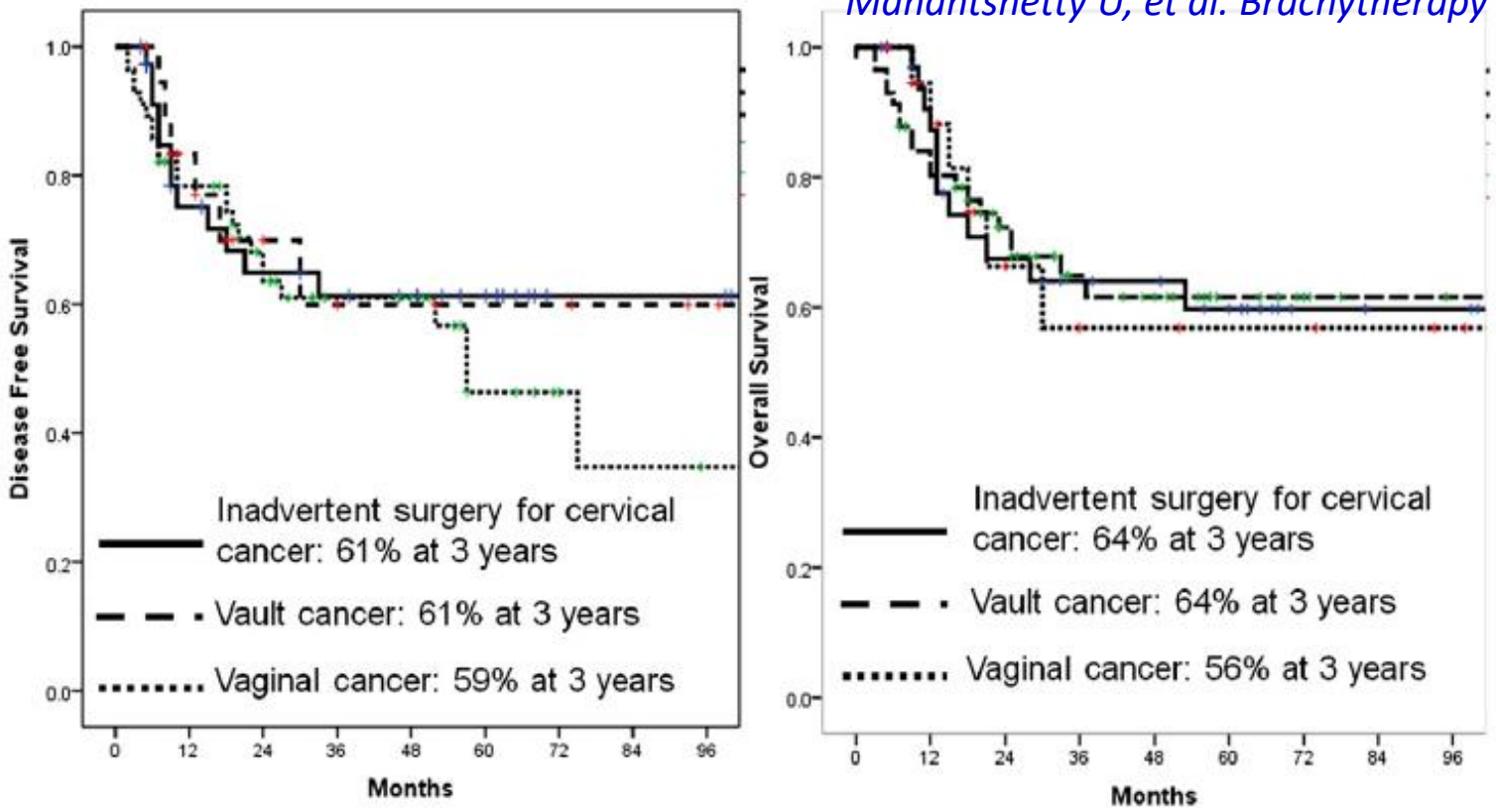


Fig. 2. Kaplan Meier survival curves: disease-free survival and overall survival.

- Late toxicities :

  - Grade III rectal : 10%; grade III bladder: 5%; Small bowel: 6%

CONCLUSIONS: Martinez Universal Perineal Interstitial Template–based high-dose-rate ISBT boost in gynecologic cancer results in a reasonable outcome in terms of survivals with acceptable late toxicities. The use of template-based ISBT is associated with a definite learning curve.

Treatment concept (II)

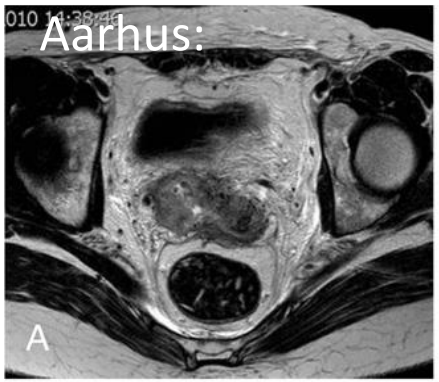
Brachytherapy

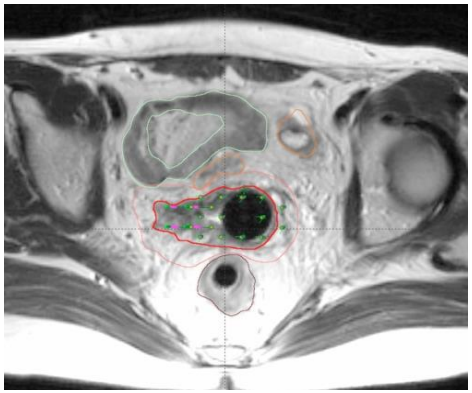
PDR schedule

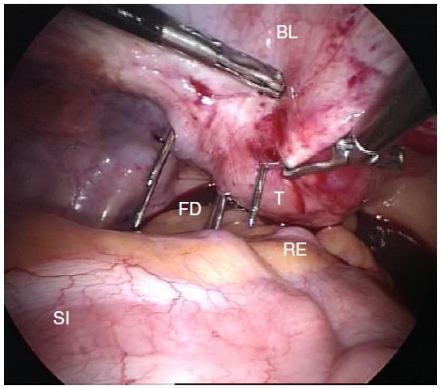
MR image guided treatment planning

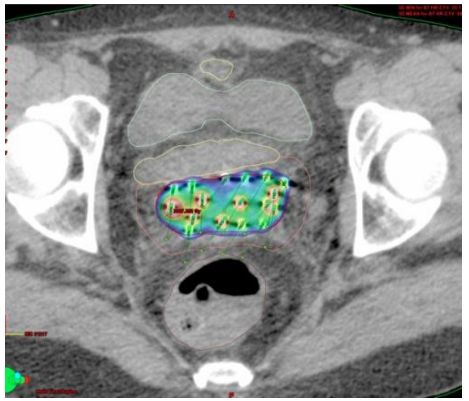
Target concept derived from the GEC-ESTRO Recommendations

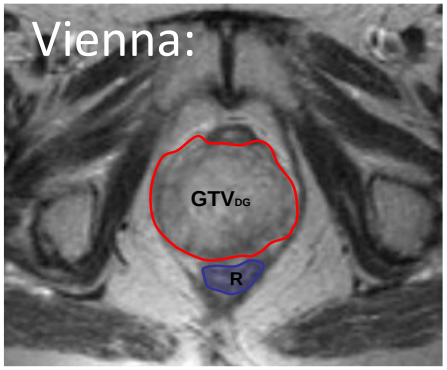
Treatment aim D90 > 80-85Gy for HR CTV

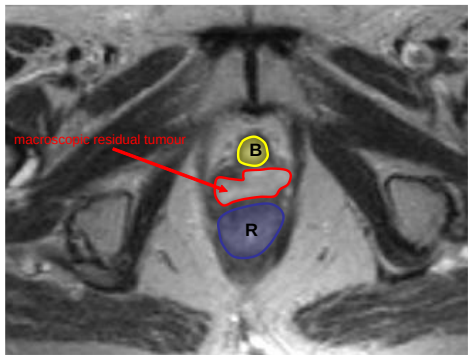


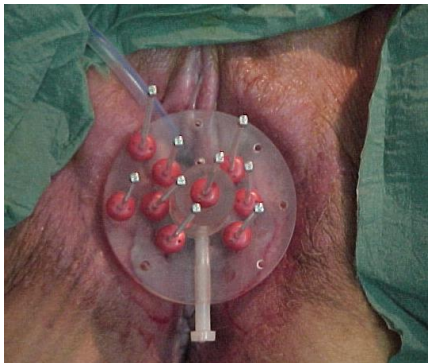


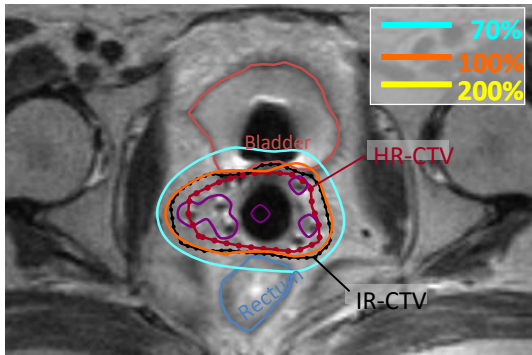












Outcome & DVH parameters

		Aarhus	Vienna
Number of pts.		28	13
Followup (month)		18 (6-61)	43 (19-87)
3 months CR (%)		92	100
	LC (%)	92 (2Y)	92 (3Y)
	OS (%)	74 (2Y)	85 (3Y)
Morbidity G3+ (%)		4	-*
HRCTV	D100 (Gy)	69 (61-80)	71 (55-88)
	D90 (Gy)	82 (77-88)	86 (64-110)
D2cc	Bladder (Gy)	65 (47-81)	80 (55-129)
	Rectum (Gy)	71 (50-77)	70 (46-81)
	Sigmoid (Gy)	52 (44-68)	60 (53-70)

Brachy 2011; IJROBP 2011

Interstitial Techniques Vagina

Conclusions

- Interstitial techniques when inappropriate coverage (topographic and dosimetric) with pure intracavitary techniques
- Several approaches (applicators,guidance) available
- Several pre-conditions for implementation (equipment, experience – specialized centres)
- Adaptation of the application technique to the topography at the time of brachytherapy
- A good portion of cases can be treated with simple techniques
- Tasks: control over placement / few needles / MRI Based Treatment Planning
- Larger clinical data with Image Based Approach: essential

Acknowledgements: Johannes C. Athanasios Dimopoulos

Chrsitine H Meder

Vulval Cancer
General Treatment Strategies
&
Interstitial BT Techniques

Umesh Mahantshetty

Richard Pötter

Christine Haie-Meder

Vulvar cancer

- Post-menopausal women
- Squamous cell carcinoma : 90 - 95%
- Human papilloma virus not reported as often as in cervical cancer
- Lichen sclerosis

Vulvar cancer: natural history and pattern of spread

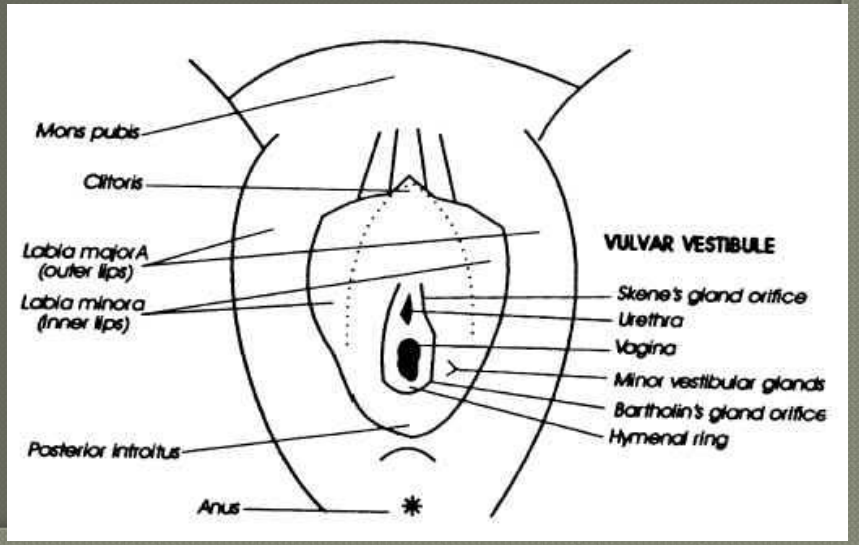
- Diagnosis delay
- Pattern of dissemination : lymphogenic
- Inguino-femoral lymph node metastases
- Lateralized tumours usually drain to the ipsilateral groin
- Median tumours (or less than 1cm of the midline) drain to either groin side
- Clitoris tumours : possible direct drainage to pelvic nodes

Vulvar cancer: natural history and pattern of spread

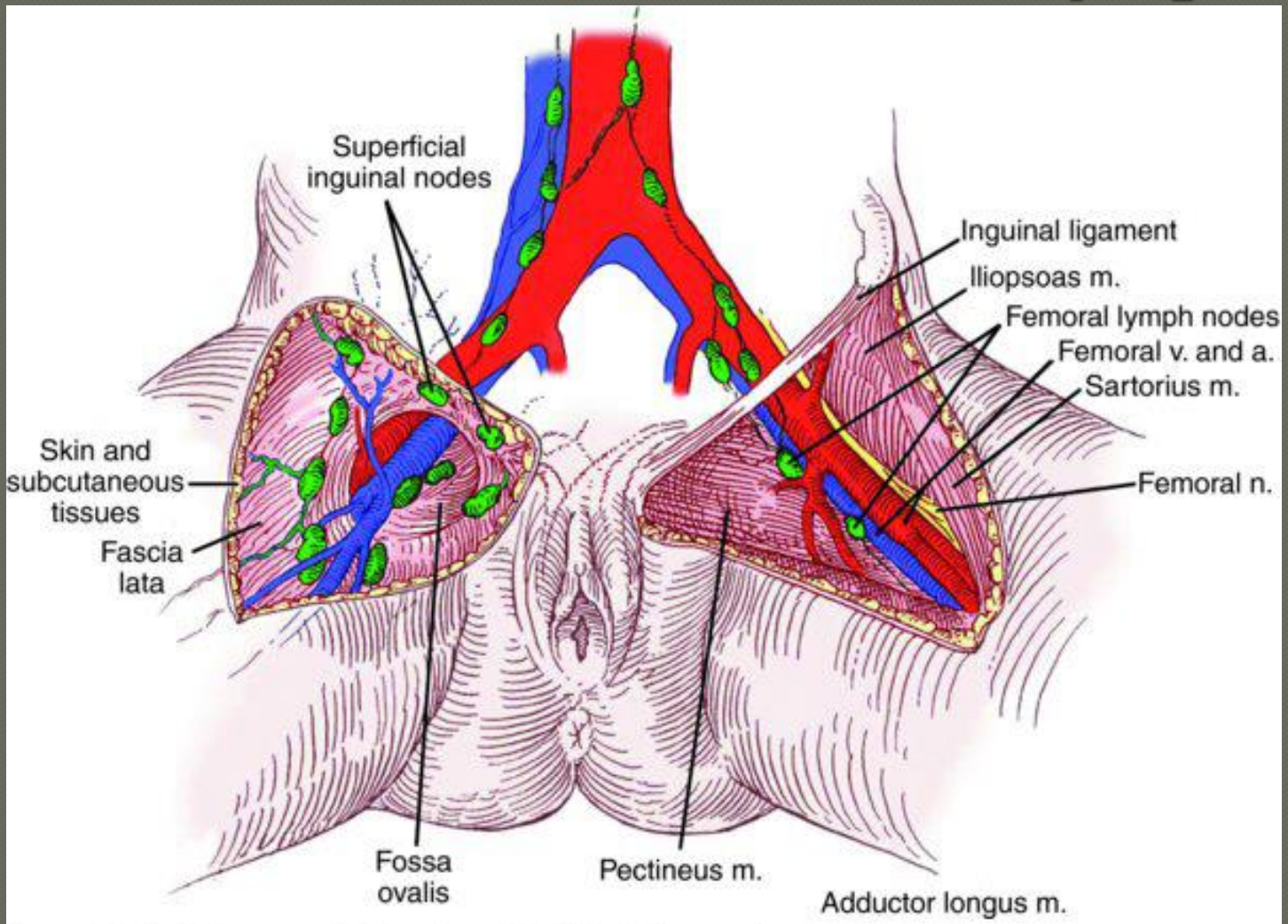
Vulvar cancer: initial work-up

- Vulvar tumours : easily accessible to clinical examination
- Tumour pain ⟶ examination under general anaesthesia
- Potential extension into the vagina
- Urethro-cystoscopy / anuscopy
- Imaging: CT/ MR depending on Stage (essentially for nodes)

Primary tumor mapping



Vulvar cancer: lymph node



Source: DeVita VT, Lawrence TS, Rosenberg SA: *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 9th Edition:* www.lwwoncology.com

Vulvar cancer: FIGO classification 2009

Takes nodal status into account

- **Stage 0** : in situ tumour without nodal metastasis
- **Stage IA** : tumour ⩽ 2cm confined to the vulva or perineum and with stromal invasion ⩽ 1mm, no nodal metastasis
- **Stage IB** : tumour > 2cm or with stromal invasion > 1mm, confined to the vulva or perineum, with negative nodes
- **Stage II** : tumour of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes

Vulvar cancer: FIGO classification 2009

- **Stage III** : tumour of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes

  - **IIIA** : with 1 lymph node metastasis (⩾ 5mm), or 1-2 lymph node metastasis(es) (< 5mm)

  - **IIIB** : with 2 or more lymph node metastases (⩾ 5mm), or 3 or more lymph node metastases (< 5mm)

  - **IIIC** : with positive nodes with extracapsular spread

Vulvar cancer: FIGO classification 2009

- **Stage IV** : tumour invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures
  - **IVA** : tumour invades any of the following :
    - upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or
    - fixed or ulcerated inguino-femoral lymph nodes
  - **IVB** : any distant metastasis including pelvic lymph nodes

Vulvar cancer: treatment modalities

- Standard treatment = surgery
- ERT, BT or chemotherapy :
  - adjuvant treatment options
  - or exclusive treatment options in advanced disease
  - Pre operative radiation in locally advanced tuomrs

Vulvar cancer: surgery
Primary tumor

- Standard surgery used to be :
  - Radical vulvectomy with “en bloc”
    bilateral inguinofemoral and pelvic lymphadenectomy
- Alternative nowadays:
  - wide excision if free microscopic margins of
    at least 8mm and preferably 20mm can be achieved

Nodal treatment

- If inguinofemoral nodes free :
  metastatic pelvic lymph node exceptional
- No pelvic lymphadenectomy in inguinal node negative pts
- Rarity of contralateral inguinofemoral lymph nodes (3%-4%)
  if lateralized tumours : unilateral inguinofemoral lymphadenectomy
- Bilateral inguinofemoral lymphadenectomy standard
  if midline located tumour

Vulvar cancer: surgery

Nodal treatment

- Recent development of sentinel node evaluation
- Mapping has been recently developed
  - isosulfan blue injection
  - combination of either isosulfan blue dye or technetium-99 and lymphoscintigraphy
- Predictive value of 99% out of 12 series collecting 353 pts

Vulvar cancer: irradiation

Indications for Adjuvant therapy for primary tumor

- After wide local excision : positive margins or with margins < 3mm if re-excision is not possible
- Total dose of 45Gy-50Gy in 25-28 fractions to control potential micro-metastases
- EBRT Technique : electrons and photons combination
- Interstitial BT can be combined to external irradiation depending upon tumour location

Vulvar cancer: ERT

Indications for definitive radiation

- Contra-indication to surgery or advanced tumours
- Total dose of 45 Gy to the pelvis ERT
- Interstitial BT total dose of 60 Gy-85 Gy
- Concurrent chemo-radiation (cisplatinum or carboplatinum used alone or in combination with fluorouracil)
  - high response-rate (even in the absence of randomized trials)

Vulvar cancer: ERT

Indications of nodal irradiation

- bilateral inguinal femoral lymph node dissection

or

- external radiation to the groin ?

Stehman et al. Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group study Int J Radiat Oncol Biol Phys 24:389–96;1992

Vulvar cancer: ERT

GOG 88

Vulvar SCC and nonsuspicious (N0-1) inguinal nodes

vulvectomy

groin dissection
If N+ → groin radiation
50Gy, 2Gy fraction
depth of 3 cm below
the anterior skin surface

Stehman et al. Int J Radiat Oncol Biol Phys 24:389–96;1992

Vulvar cancer: ERT

Study closed after interim analysis of 58 patients

Vulvar SCC and nonsuspicious (N0-1) inguinal nodes

vulvectomy

groin dissection
5/25 (20.0%) N+

groin radiation

Relapse :	0/25	5/27 (18.7%)

Stehman et al. Int J Radiat Oncol Biol Phys 24:389–96;1992

Vulvar cancer: ERT

Femoral vessel depth and the implications for groin node radiation

CT of 50 patients with gynaecological cancer

Distance of each femoral vessel beneath the overlying skin surface

Individual femoral vessel depths ranged from 2.0 to 18.5 cm
Mean average depth : 6.1 cm

Koh WJ et al. Int J Radiat Oncol Biol Phys 27:969-74;1993

Vulvar cancer: ERT

Nodal irradiation vs nodal dissection

- Review of 3 series
- No evidence for a better control with external irradiation compared to dissection

van der Velven J. Primary groin irradiation versus primary groin surgery for early vulvar cancer (Cochrane Review). In : The Cochrane library, issue 1. Oxford : Update Sofware (2002)

Vulvar cancer: ERT

Indications of post-operative nodal irradiation

- > 1 involved inguino-femoral lymph node (Stage IIIB)
- Extracapsular extension (Stage IIIC)
- Gross residual nodal disease (Stage IIIC with R + resection)

Vulvar cancer: ERT GOG 37

Pelvic irradiation if involved inguinal nodes ?

Pelvic node dissection

Postoperative radiotherapy
Bilateral pelvic and inguinal irradiation
45-50Gy
Anterior and posterior opposing fields

Homesley HD et al. Obstet Gynecol 68:733-40;1986

Vulvar cancer: ERT

GOG 37

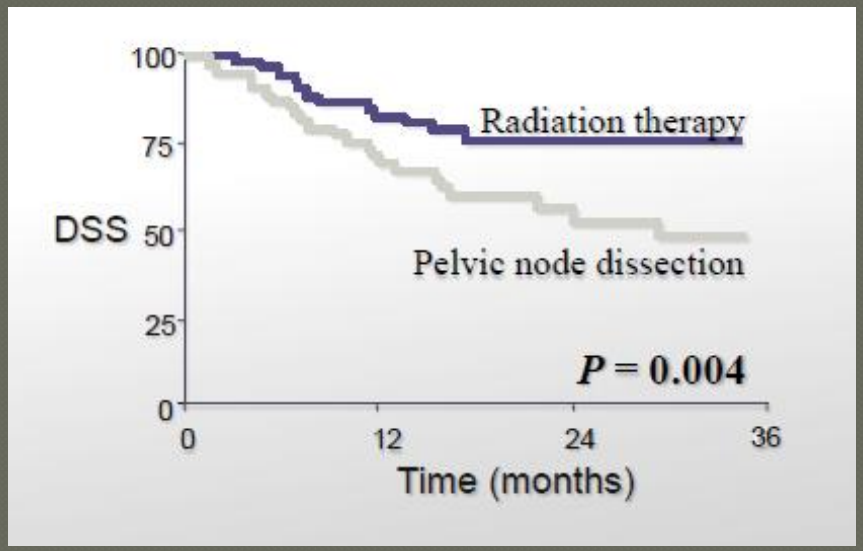
Trial closed after 114 patients interim analysis

Pelvic irradiation if involved inguinal nodes ?

Pelvic node dissection

Postoperative radiotherapy

Relapse :	24%		5%	p=0.02
2-year survival :	54%		68%	p=0.03



Homesley HD et al. Obstet Gynecol 68:733-40;1986

A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study.

Moore, et al Gyn Onc 2012

- T3 or T4 vulvar lesions
- Treatment:
  - Radiation – 1.8 Gy x 32 fx = 57.6 Gy
  - Weekly cisplatin – 40 mg/m2
  - 4-6 wks. later – biopsy or surgical resection
- Results:
  - 58 evaluable patients
  - 37 (63.8%) clinical CR
  - 29 (50%) pathological CR

Treatment results of vulvar cancer

- 5-year survival - pelvic control rates:
  - stage I : 90% - 97%
  - stage II : 70% - 86%
  - stage III : 40% - 65%
  - stage IV : 10% - 27%
- 50% of the failures are local recurrences
- Groin recurrences : 6%-30% of recurrences occur sooner than local relapses

Prognostic factors of vulvar cancer

- **Prognostic factors for local recurrence :**

  - Positive or close margins

  - Presence of capillary space involvement

  - Large invasion depth and large primary size

- **Main prognostic factor for survival :**

  - Inguinofemoral lymph node status

Principles of Brachytherapy for Vulval cancers

- Objective evaluation and Mapping of Disease at Diagnosis and Brachytherapy

- **Natural tumor spread and appropriate techniques**

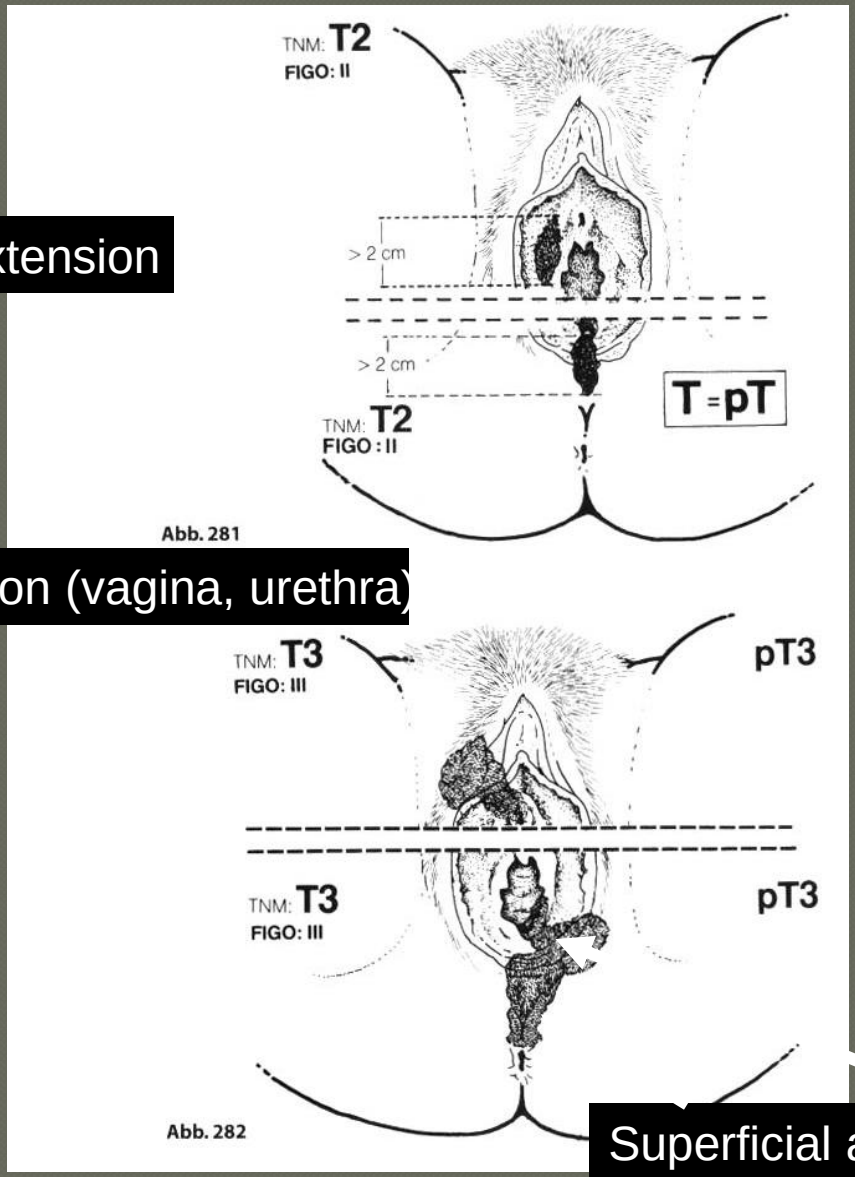
- Adopt some Image Based Brachy principles in terms of Imaging, Dose painting, DVH parameters…….

- **Clinical Outcome : Local Control rates and Toxicities**

Natural History and Tumour spread

superficial tumour extension

deep tumour extension (vagina, urethra)



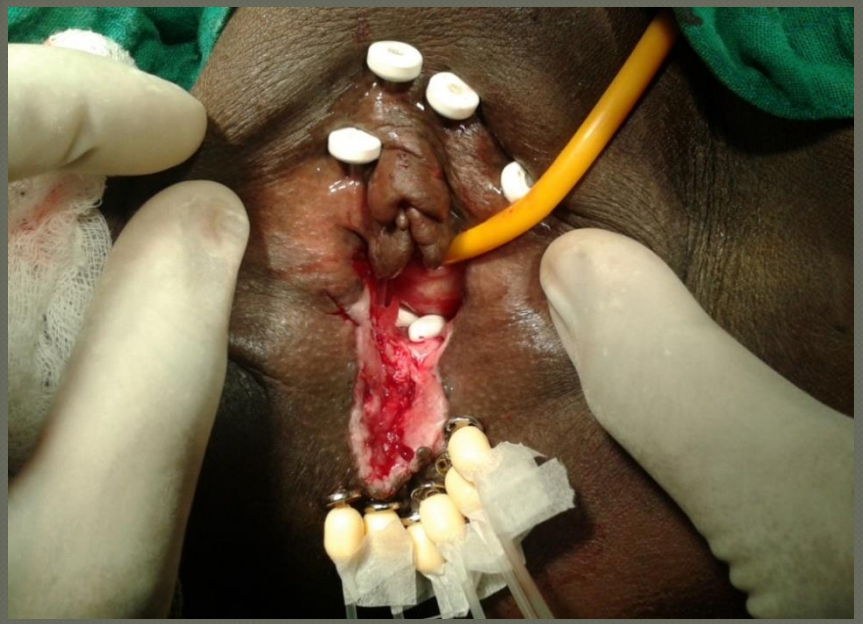
Superficial and deep tumour extension

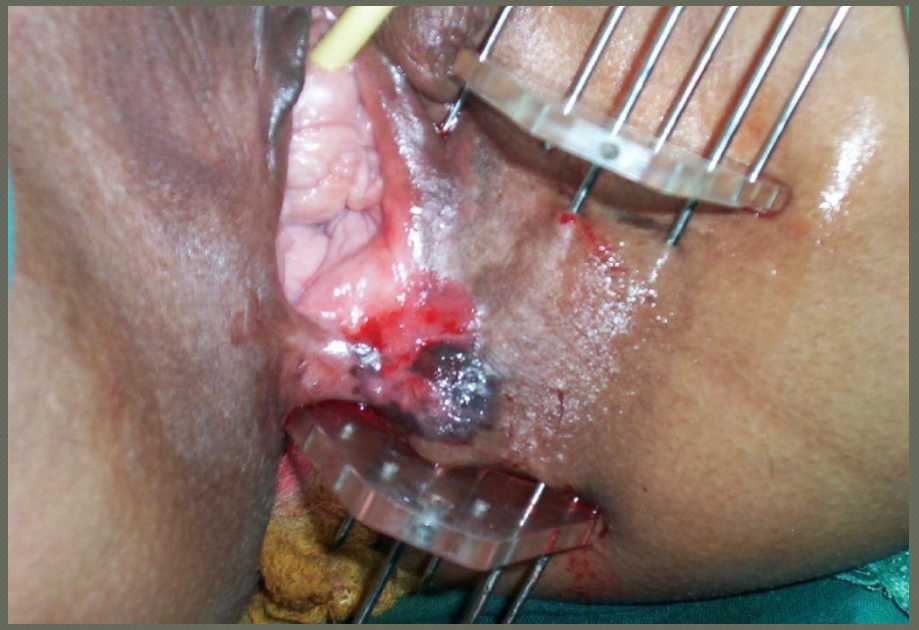
UICC TNM-Atlas

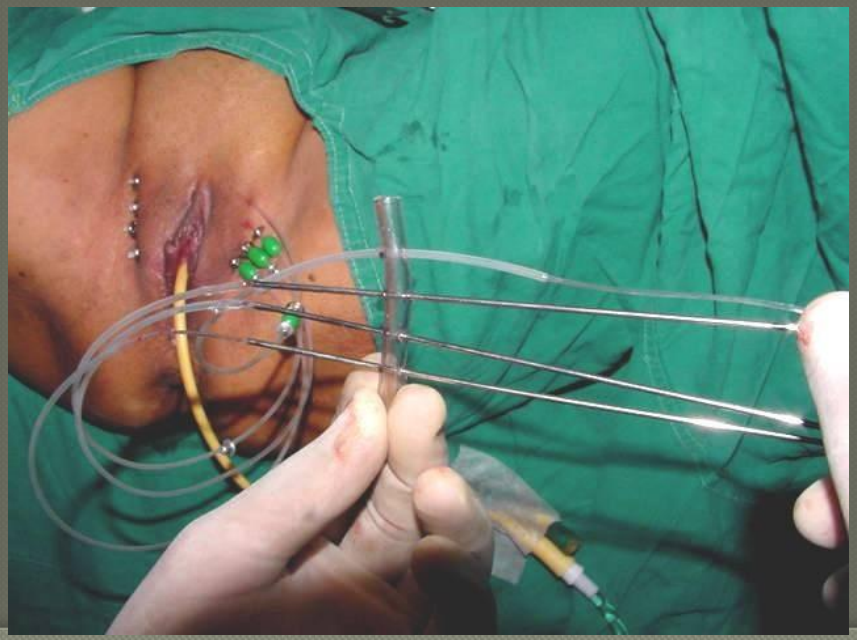
Tumour spread and techniques

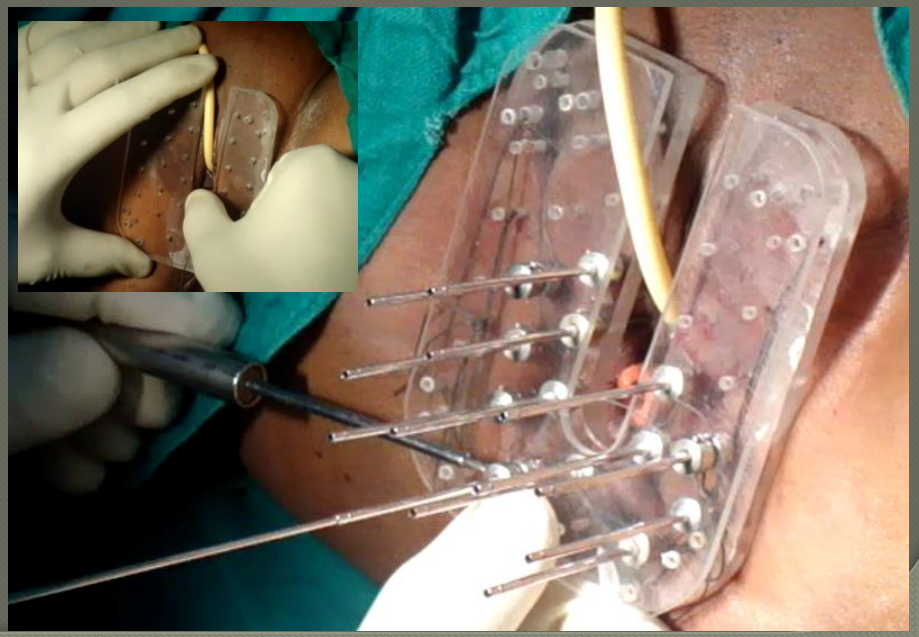
superficial tumour extension	⟷	plastic tube technique plastic tube+needle
deep tumour extension (vagina, urethra, paraurethral, paravaginal)	⟷	cylinder + template guided needle technique
Extensive superficial and deep tumour extension	⟷	Complex combined technique

Brachytherapy and Vulval Cancers: Techniques



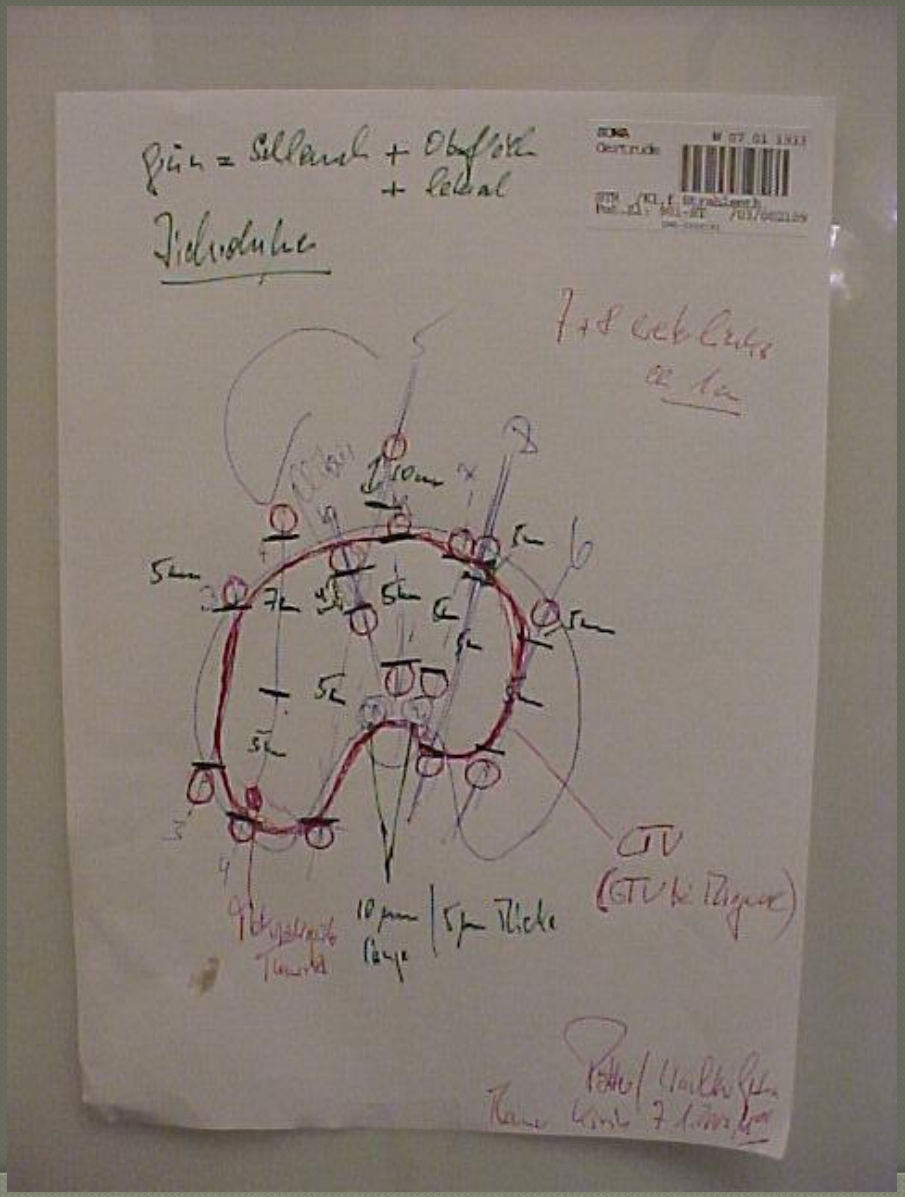




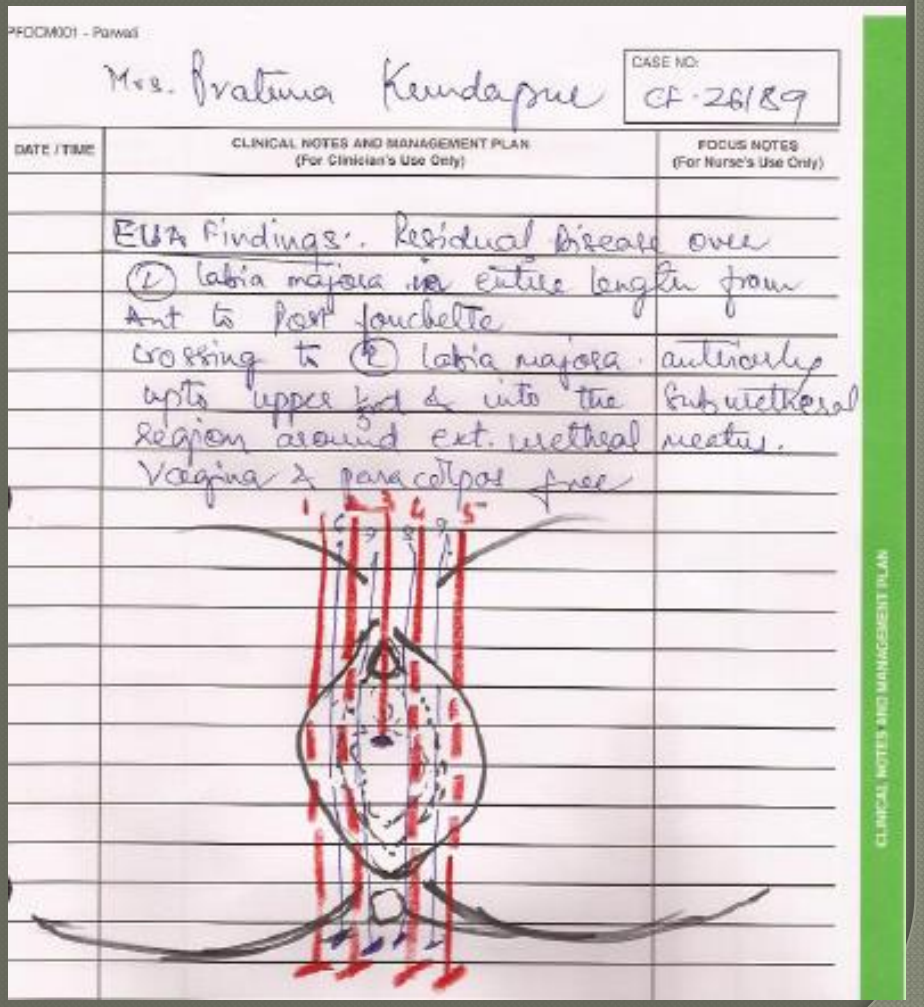


Drawing of target and needle placement

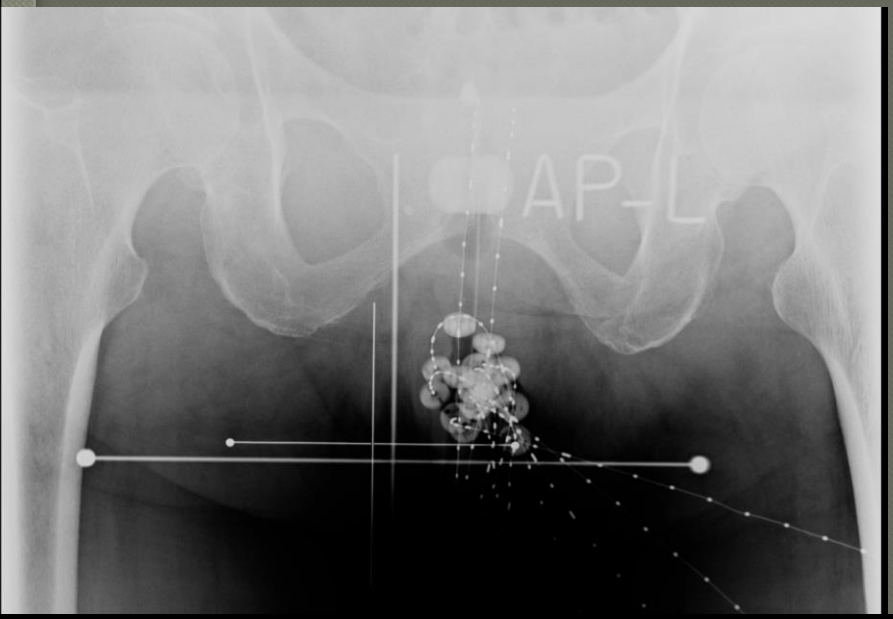
VIENNA

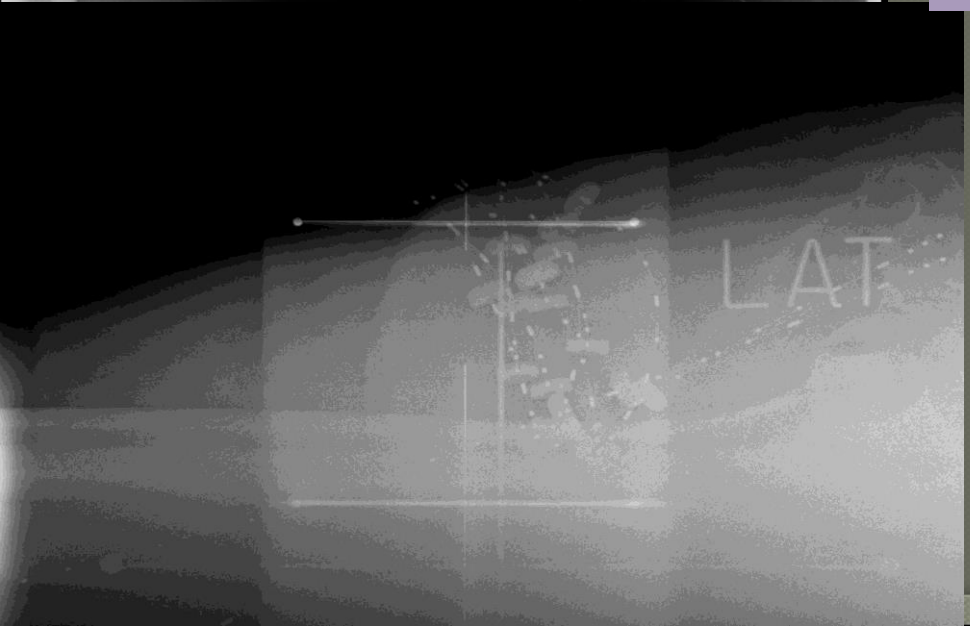


TATA MEMORIAL HOSPITAL, MUMBAI

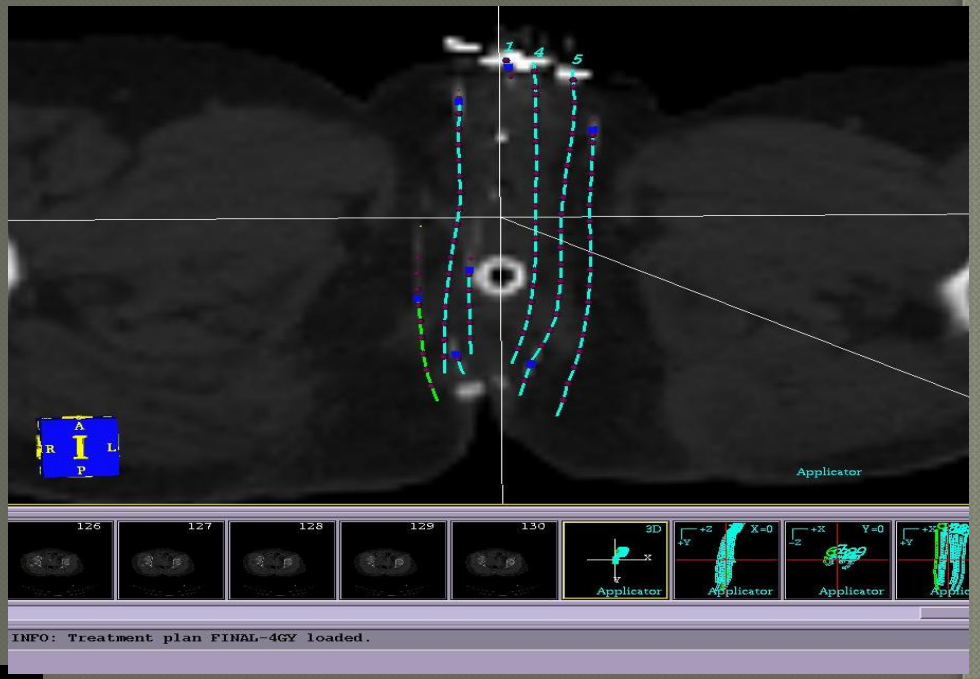


Orthogonal radiographs with dummy sources





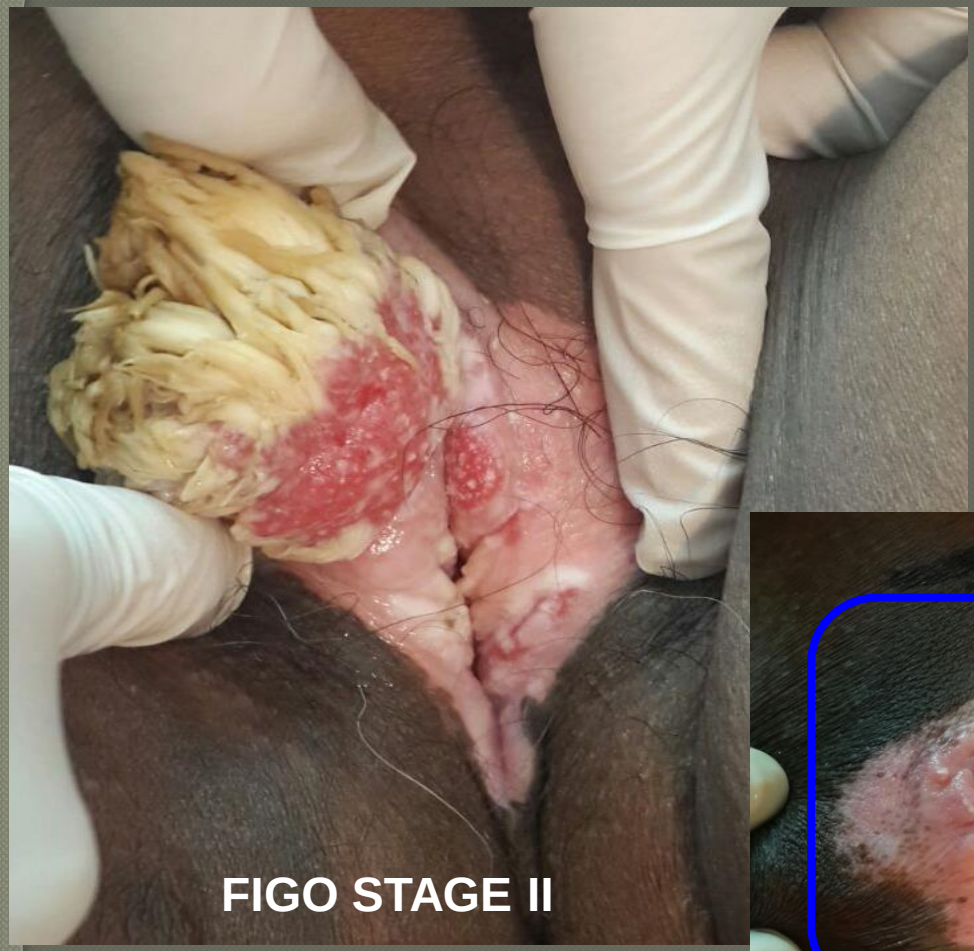
CT Based Planning



Tumour spread and techniques

superficial tumour extension ⟷ plastic tube technique
plastic tube+needle

AT DIAGNOSIS

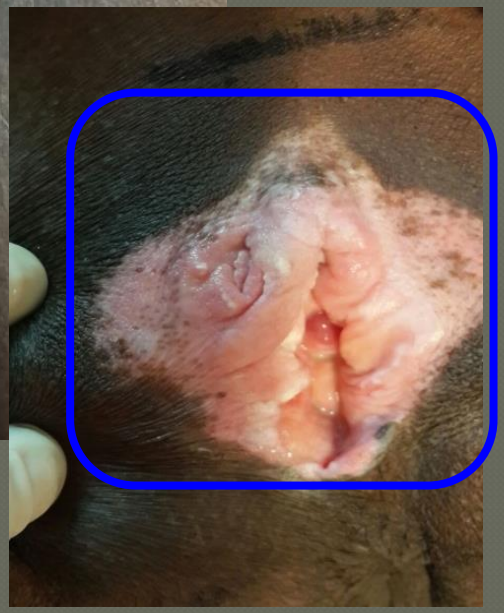


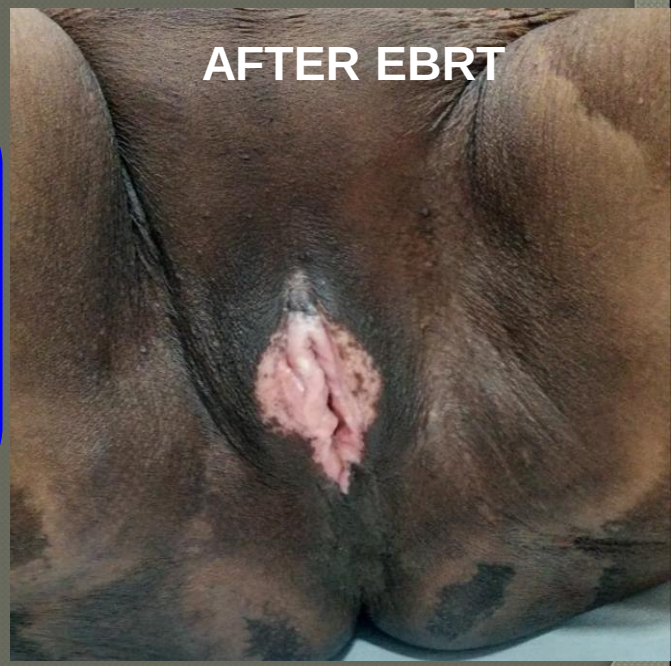
- Biopsy: WD SQ CA
- MRI (21/5/15 – done outside) :

  3.5 X 3 cm exophytic growth in vulva.

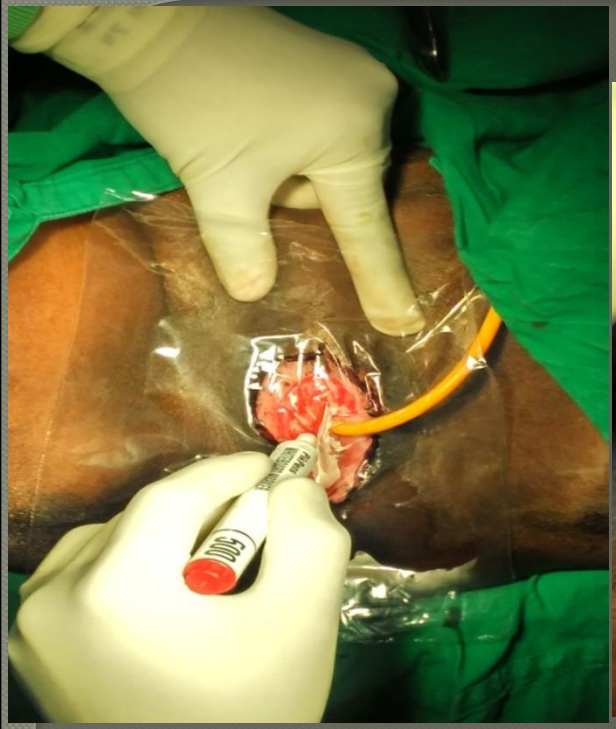
  Uterus and B/L adnexa normal.

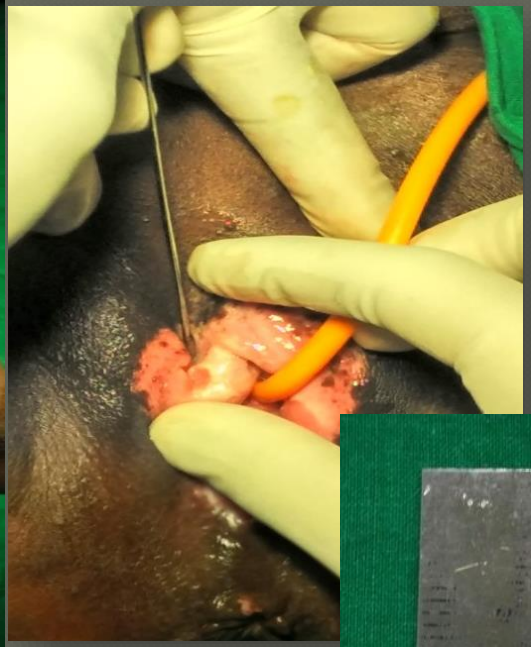
  No lymphadenopathy.
- EBRT + CT : 50 Gy / 25#
- Post EBRT response:

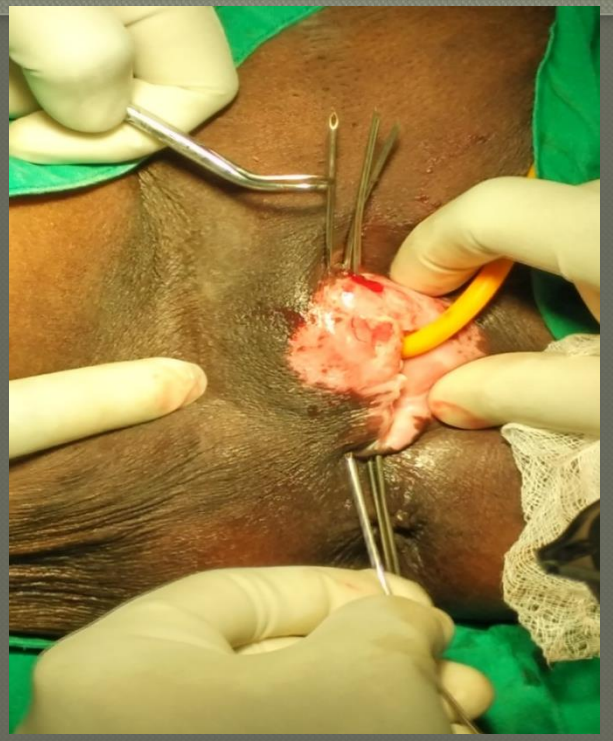


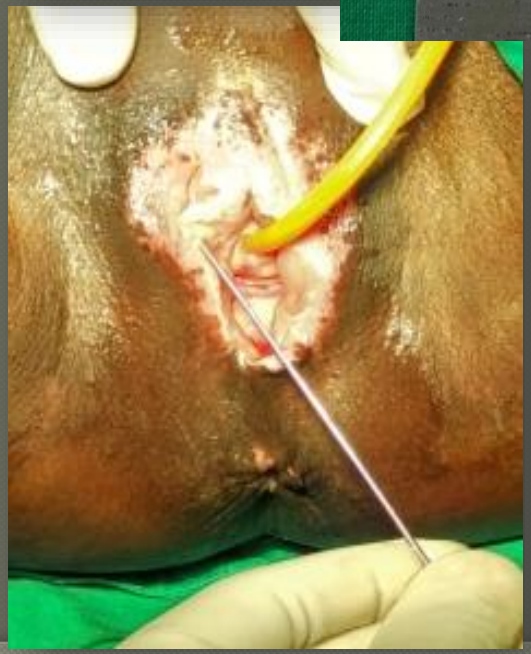


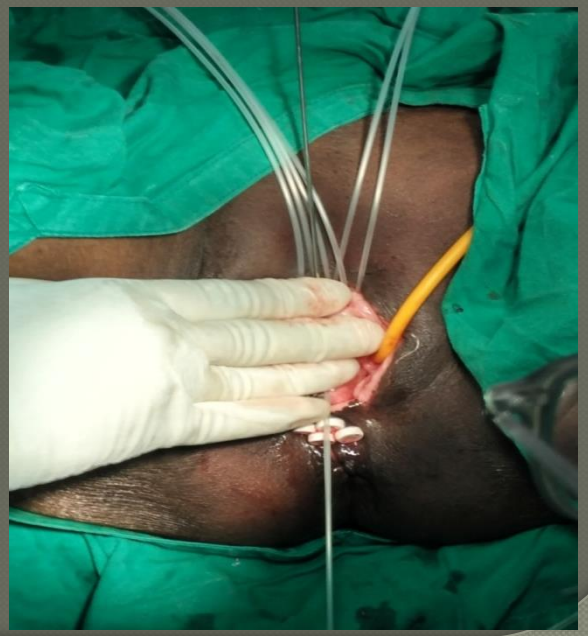
AT BRACHYTHERAPY

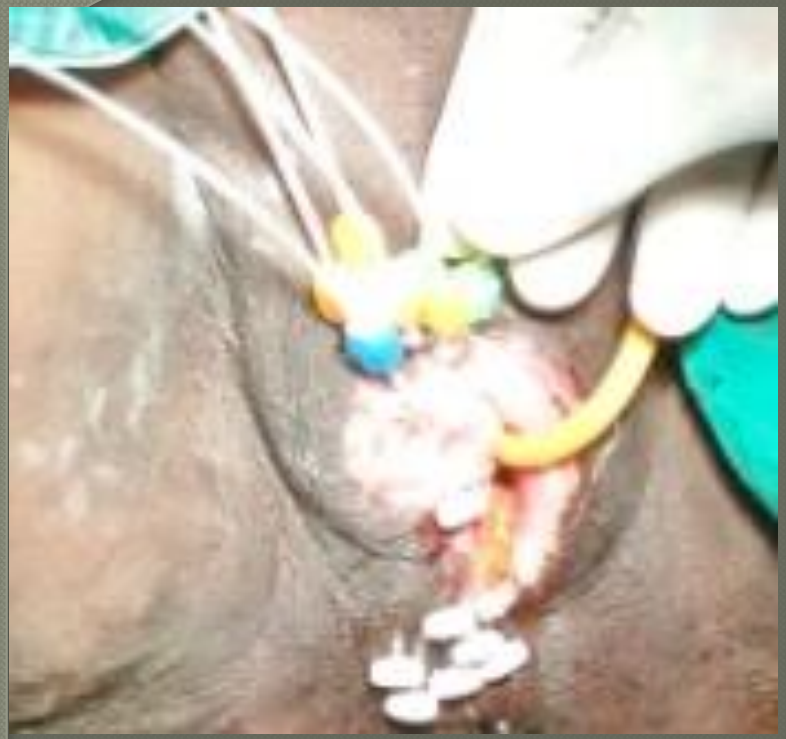


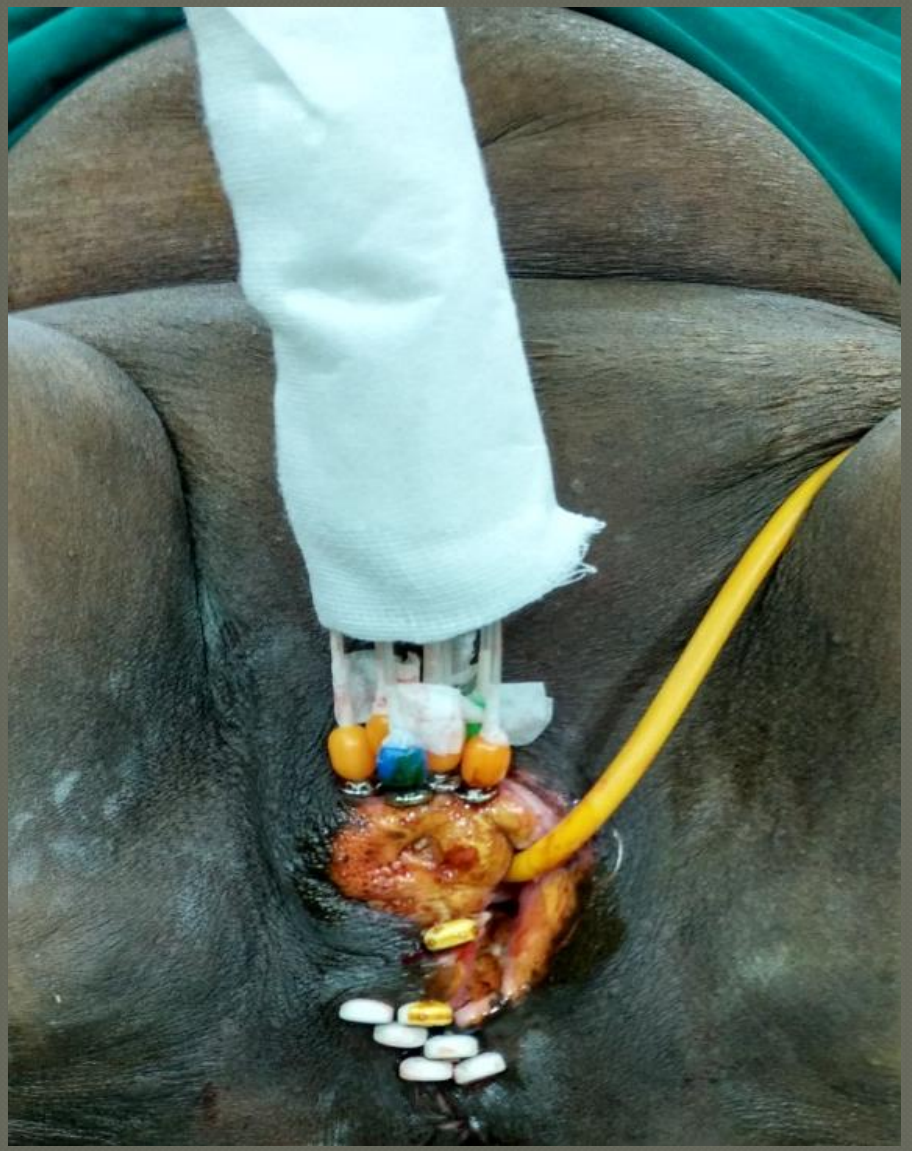




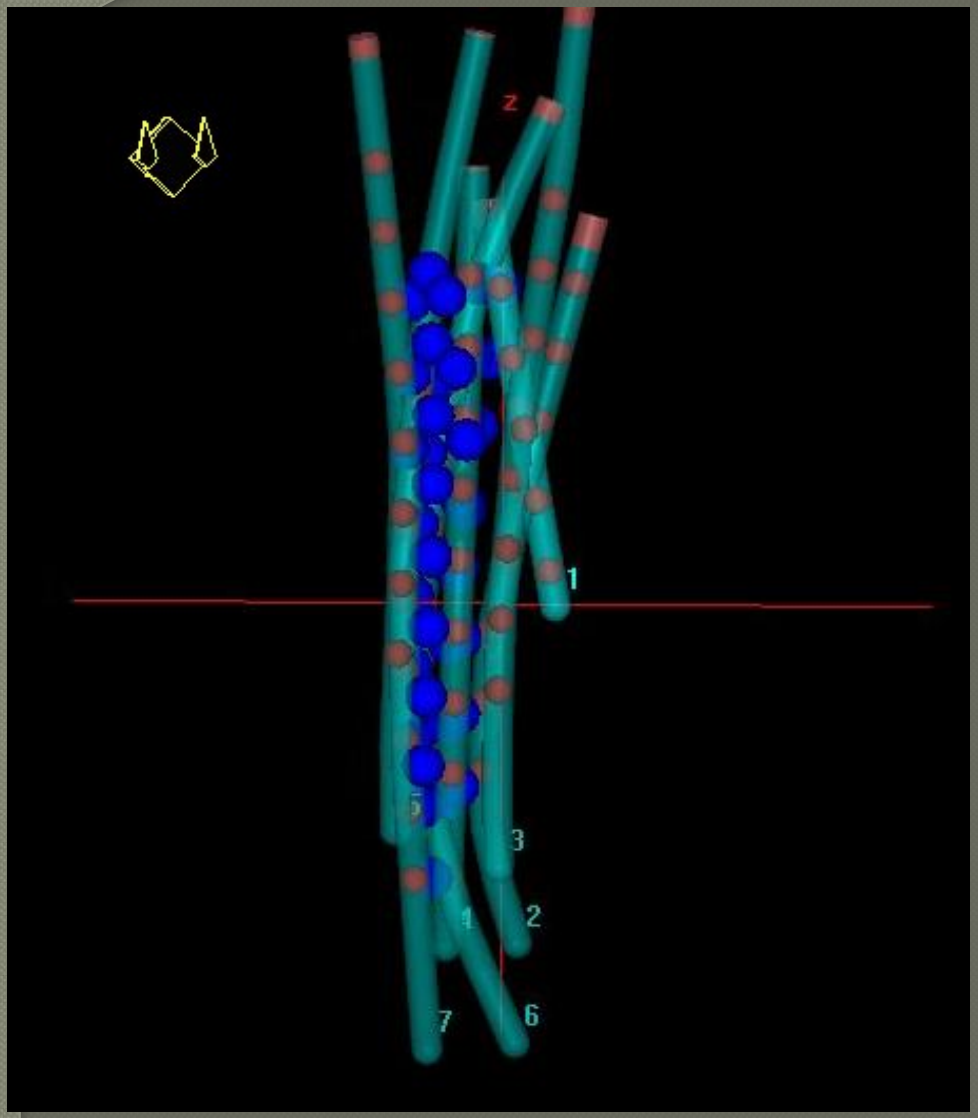








3 SUPERFICIAL TUBES
4 DEEP TUBES


Z
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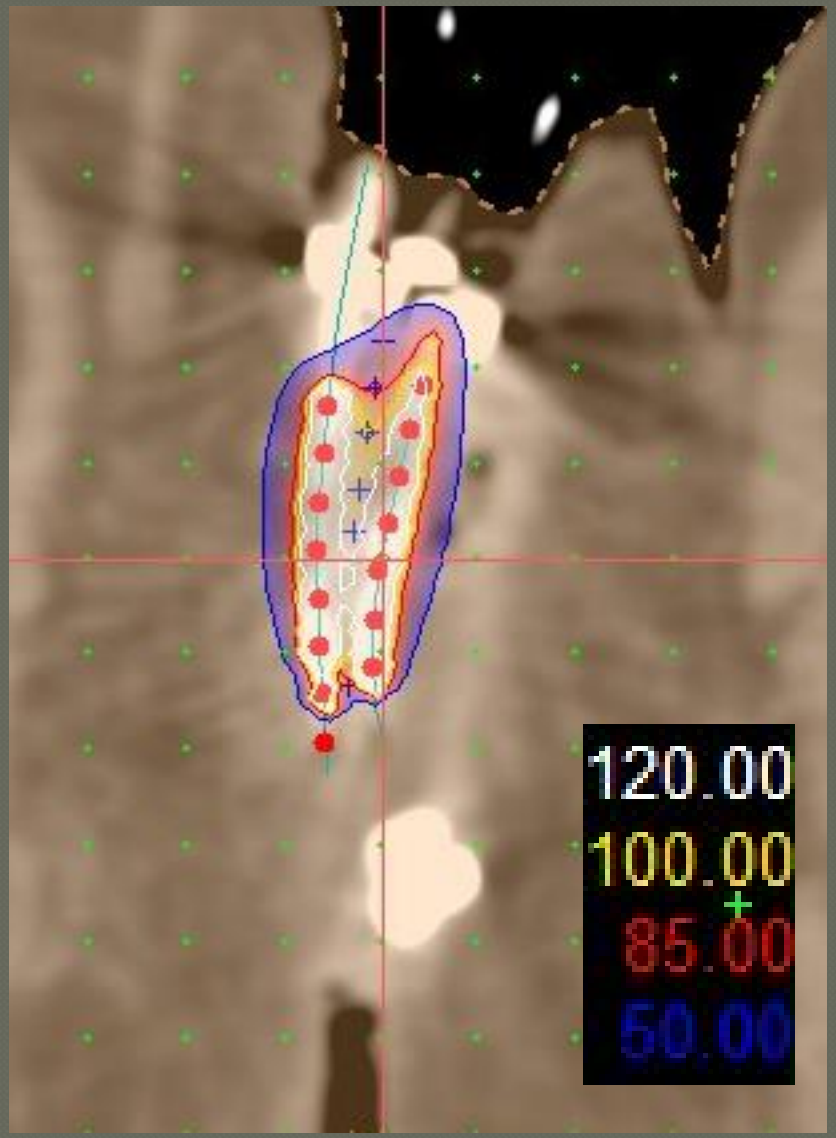
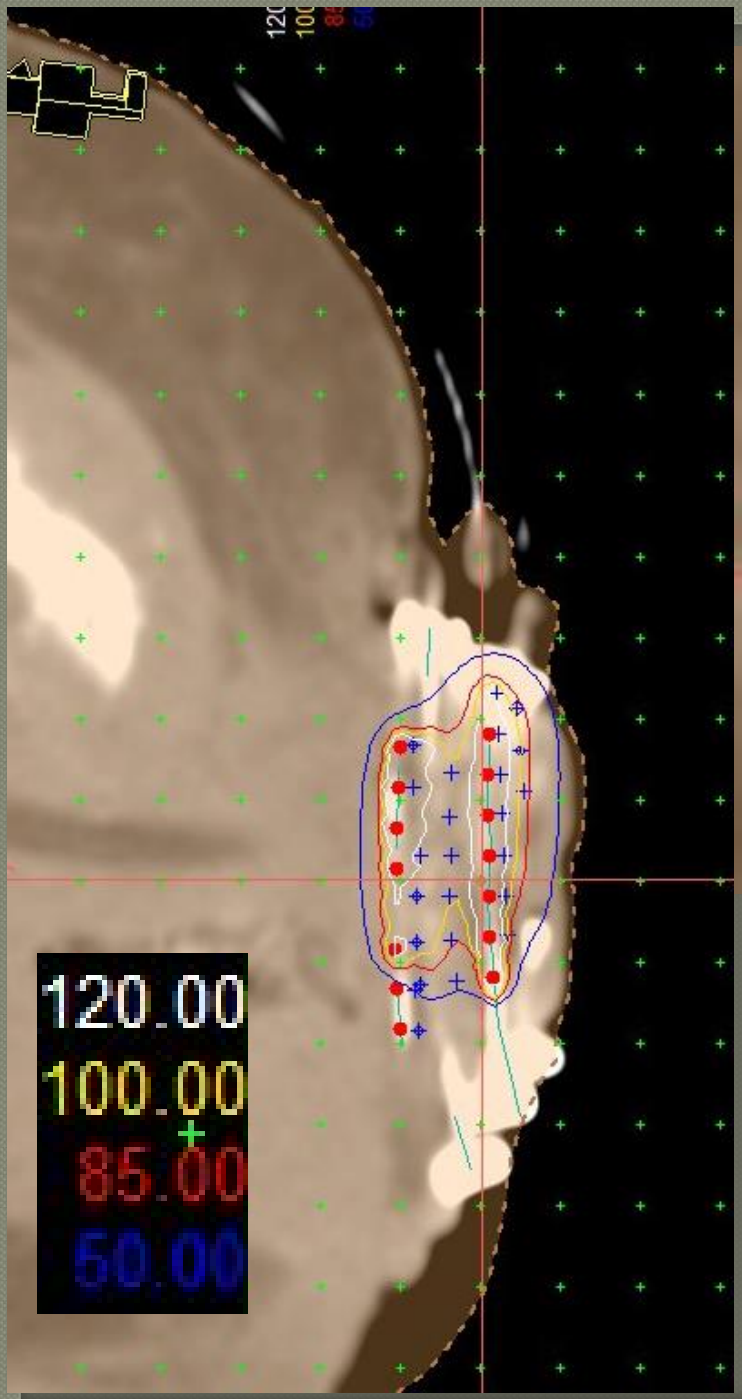
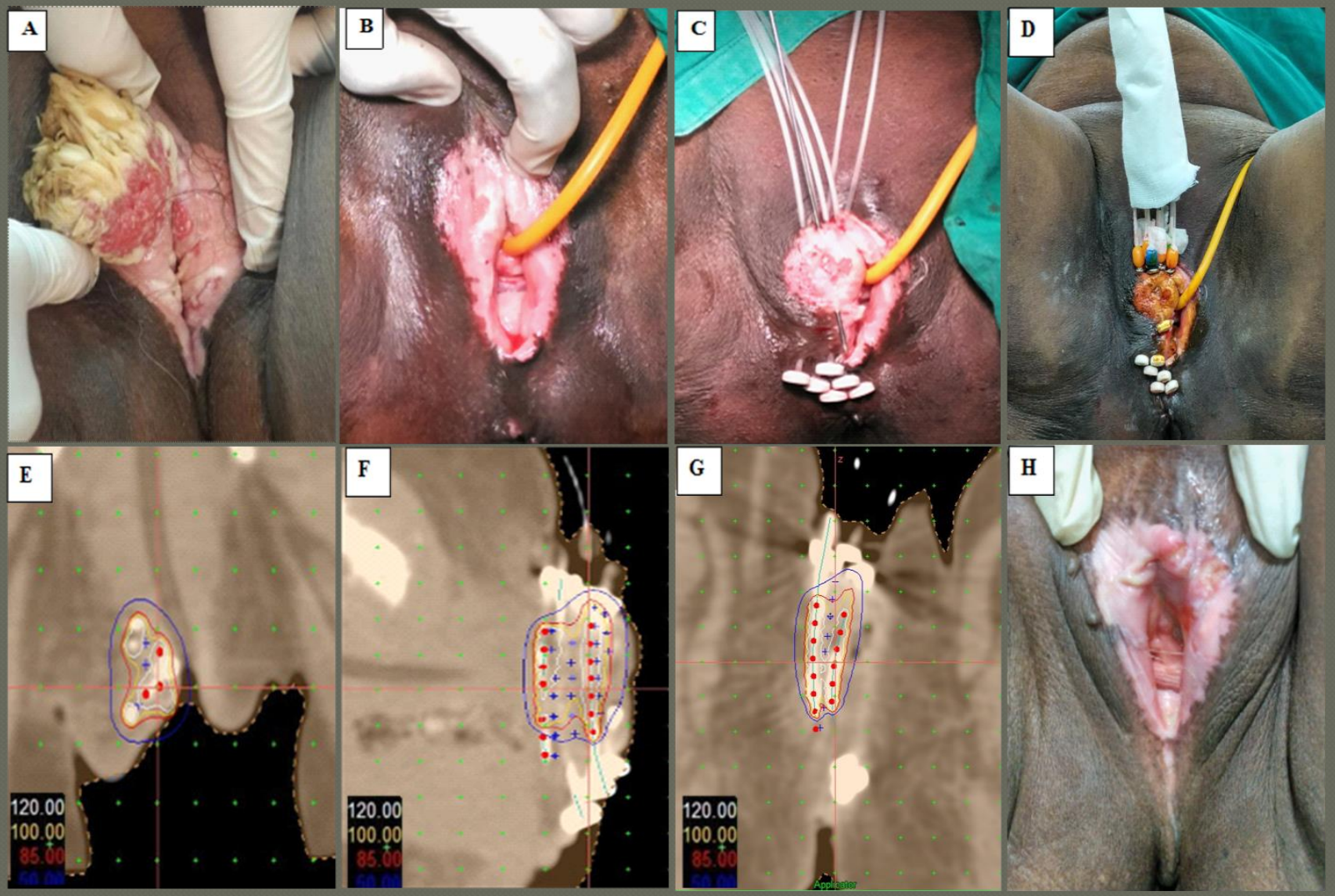

120.00
100.00
85.00
50.00



- 4 GY /# WITH 2# per day 6 hours apart
- Total EQD 2: 85 Gy EQD2

Freehand technique



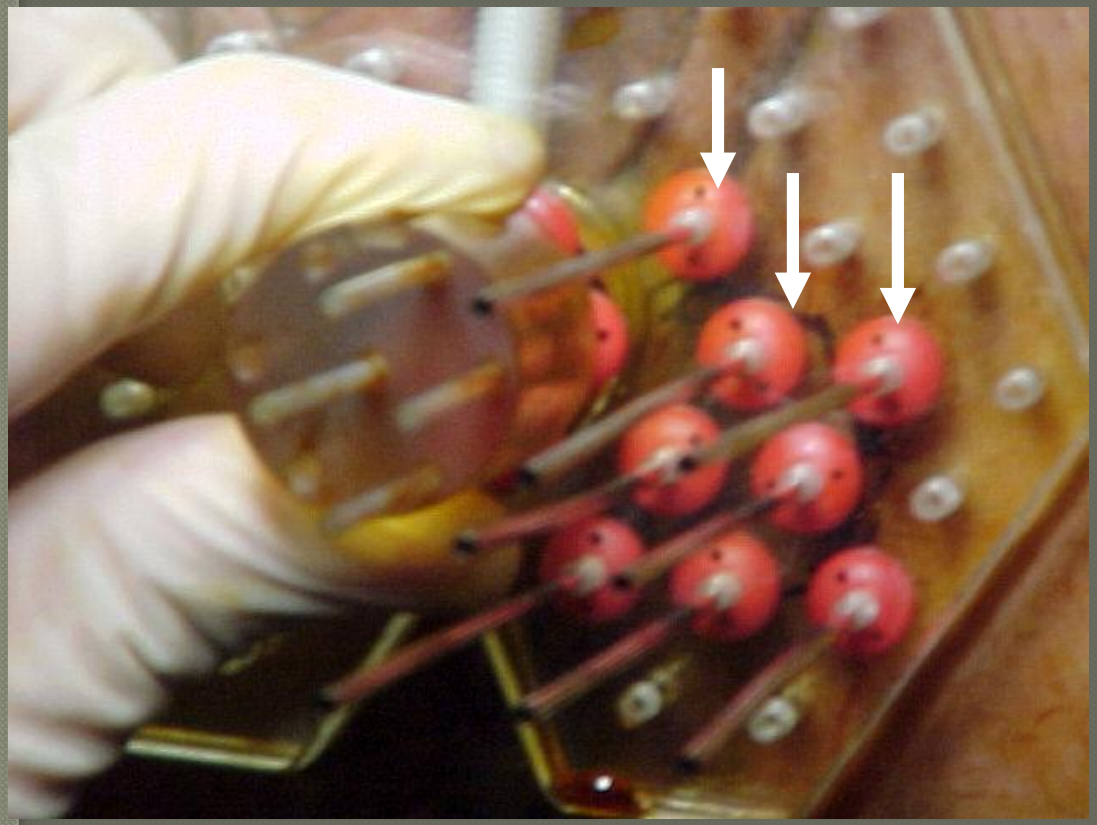
A: At presentation, B: Post EBRT, C & D: Catheter placements, E, F &G: Representative coronal , sagittal & axial CT Images with Isodose distributions, H: Post Tx 3 mn.

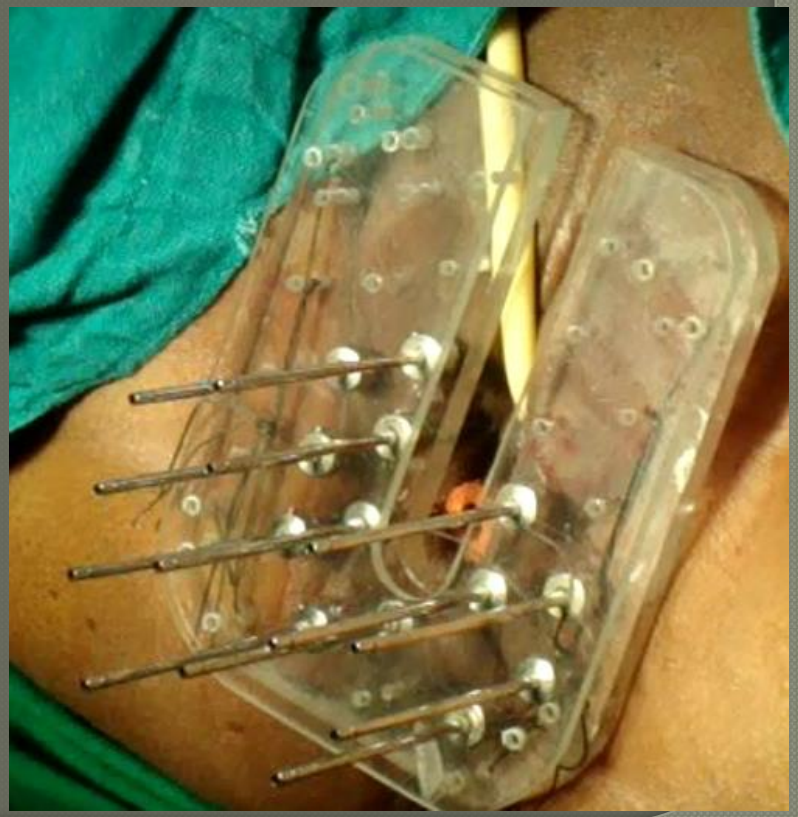
Tumour spread and techniques

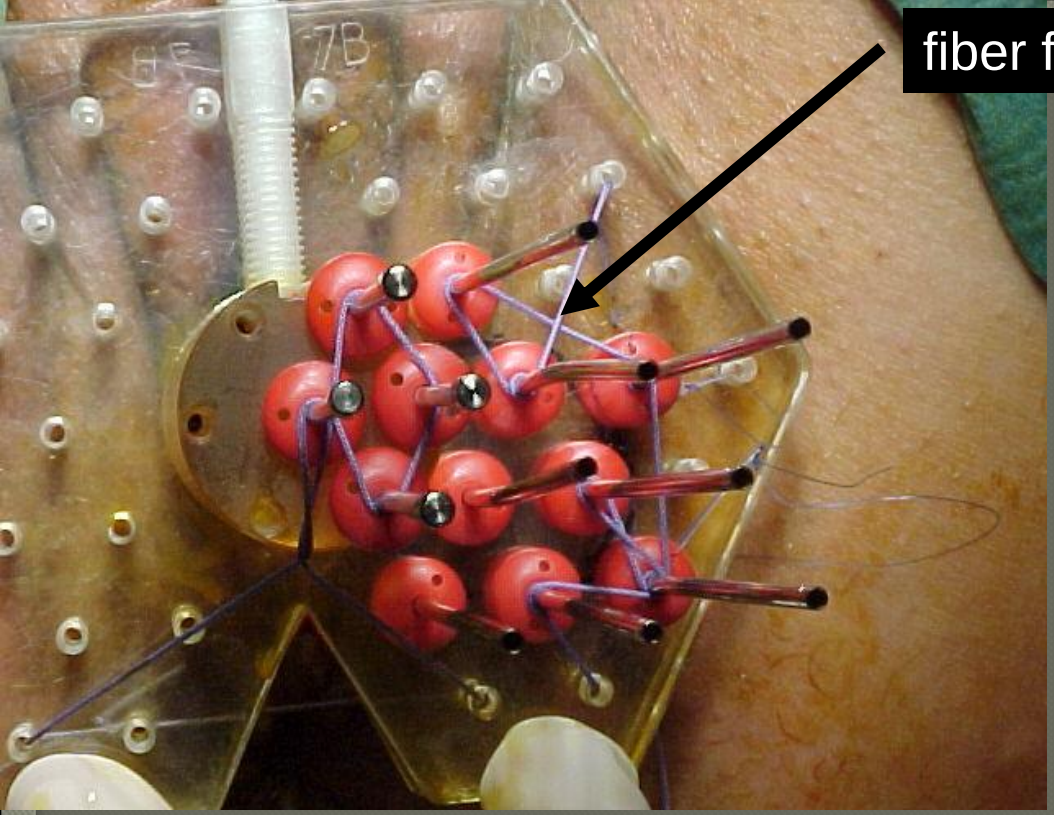
deep tumour extension (vagina, urethra, paraurethral, paravaginal)

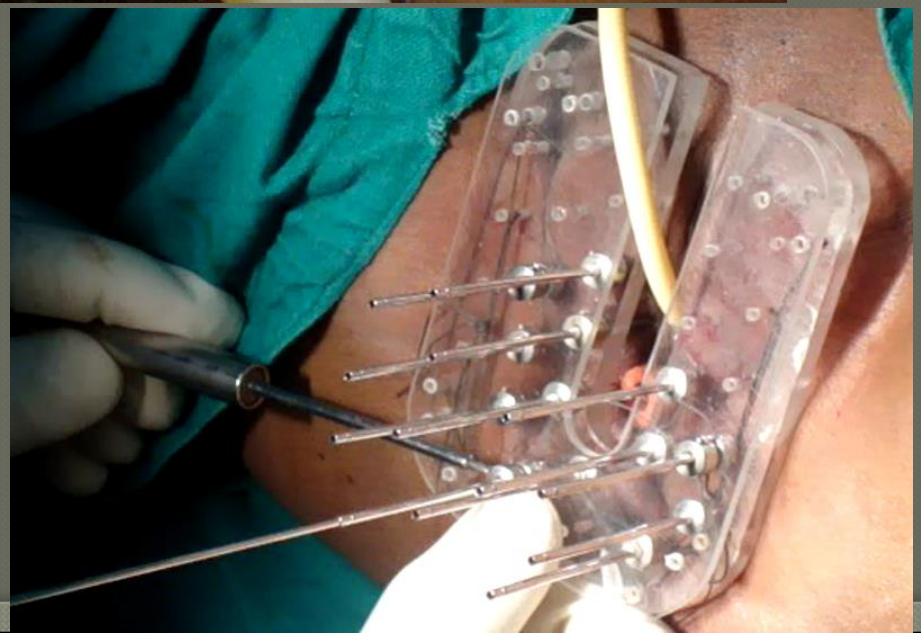
cylinder + template guided needle technique

Cylinder element and buttons for needle fixation

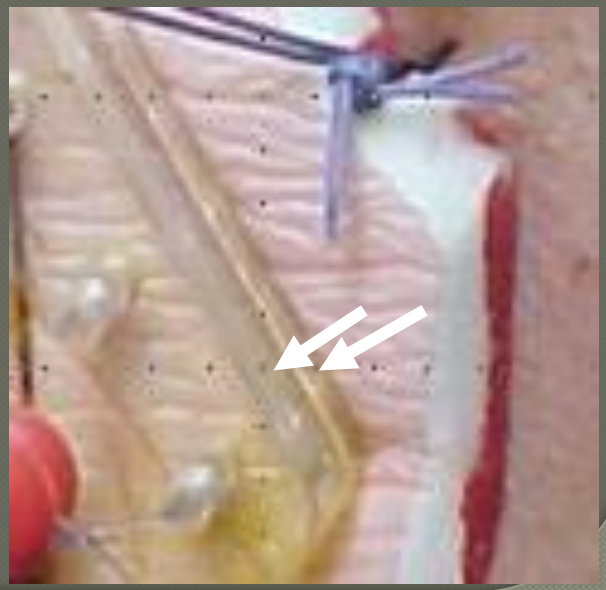








Double template

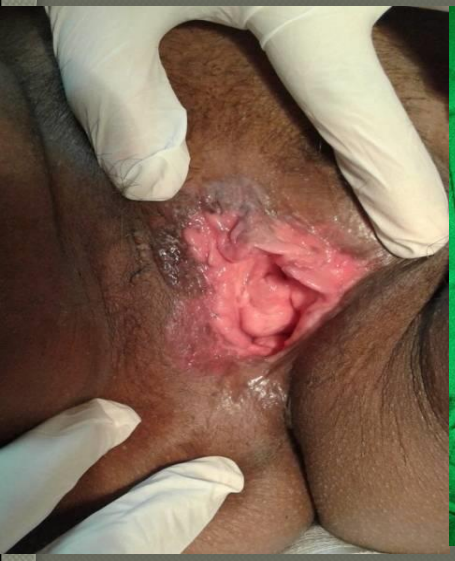
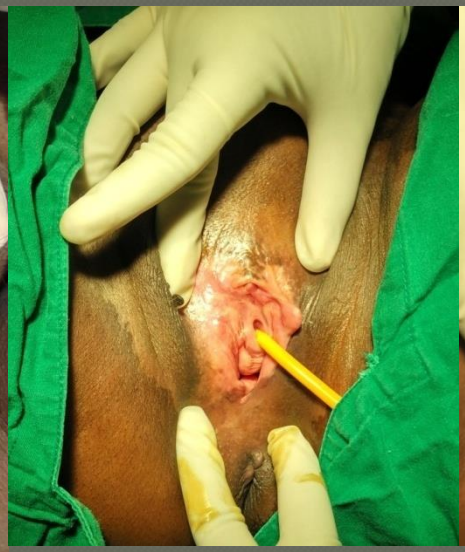
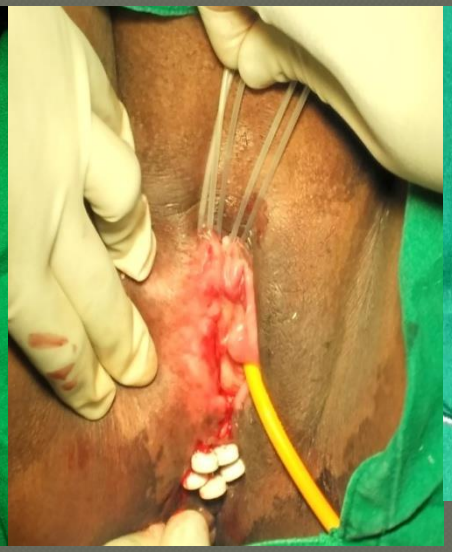


Tumour spread and techniques

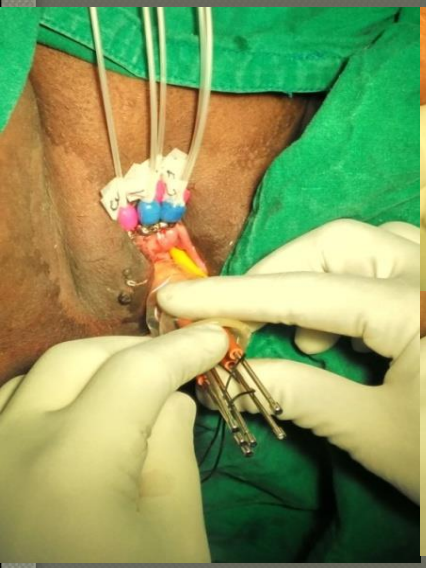
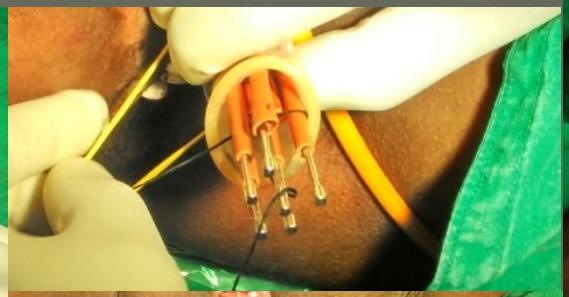
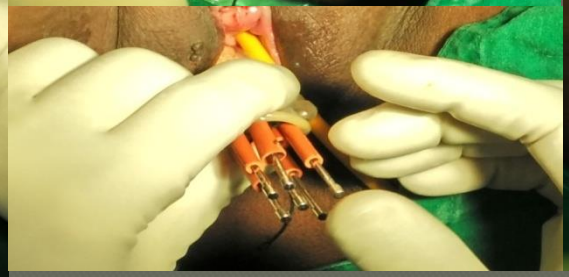
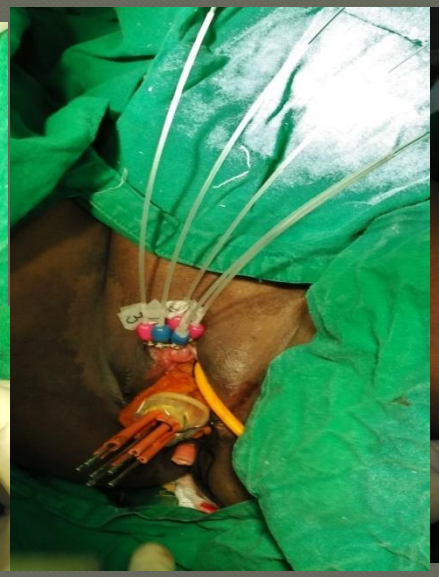
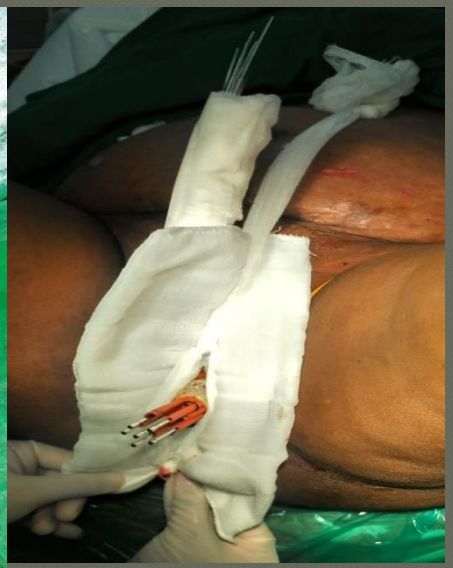
Extensive superficial and deep tumour extension

Complex combined technique

Freehand and customized technique

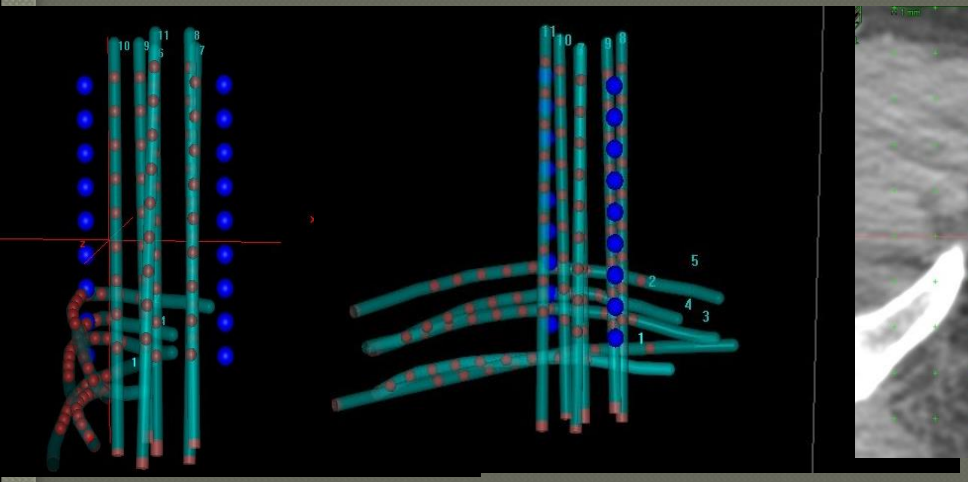




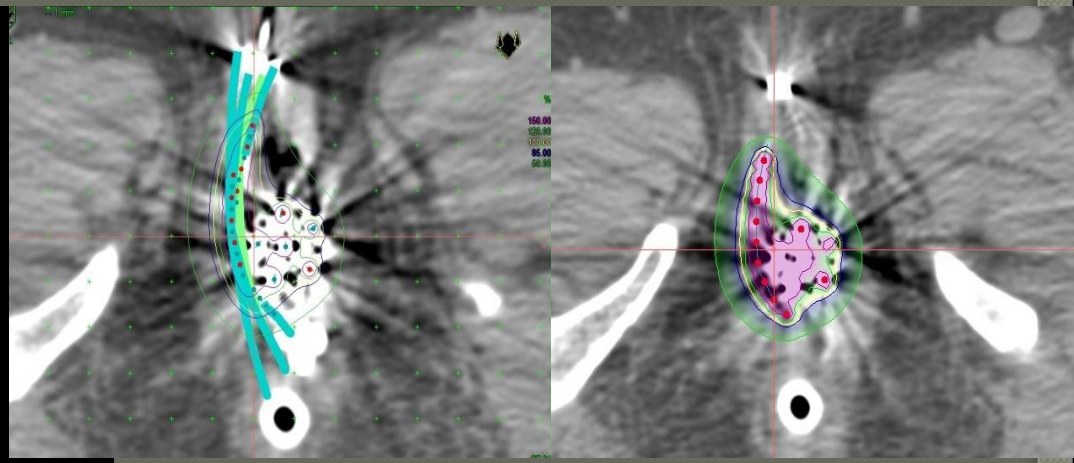


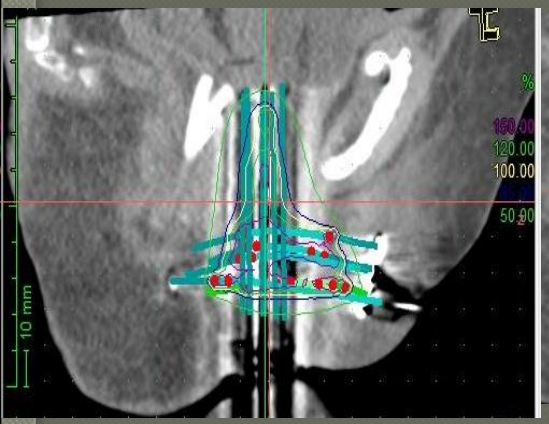






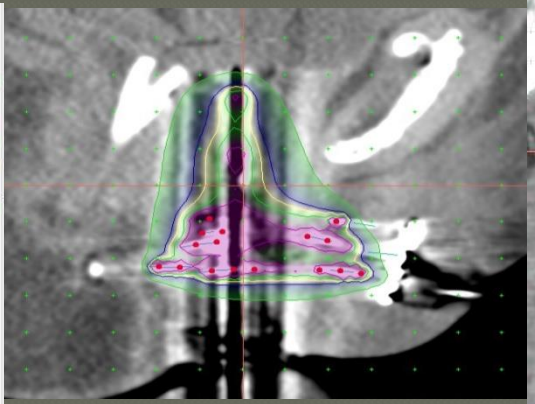
A: At presentation, B: Post EBRT, C & D: Catheter placements,

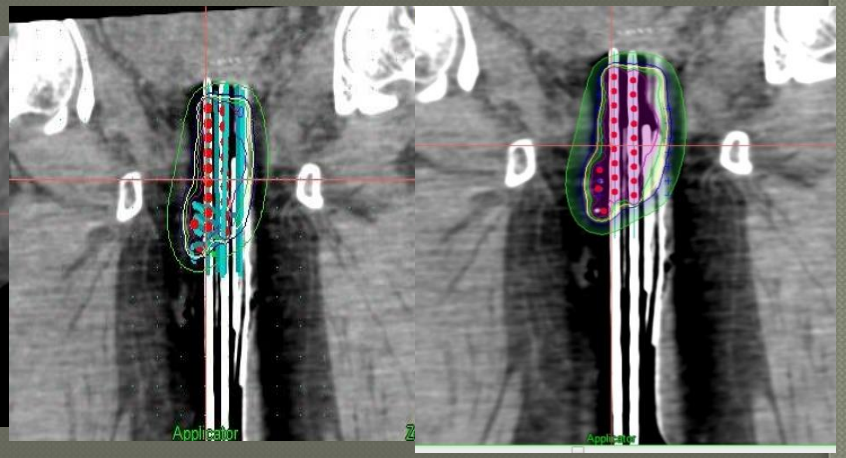
Freehand and customized technique





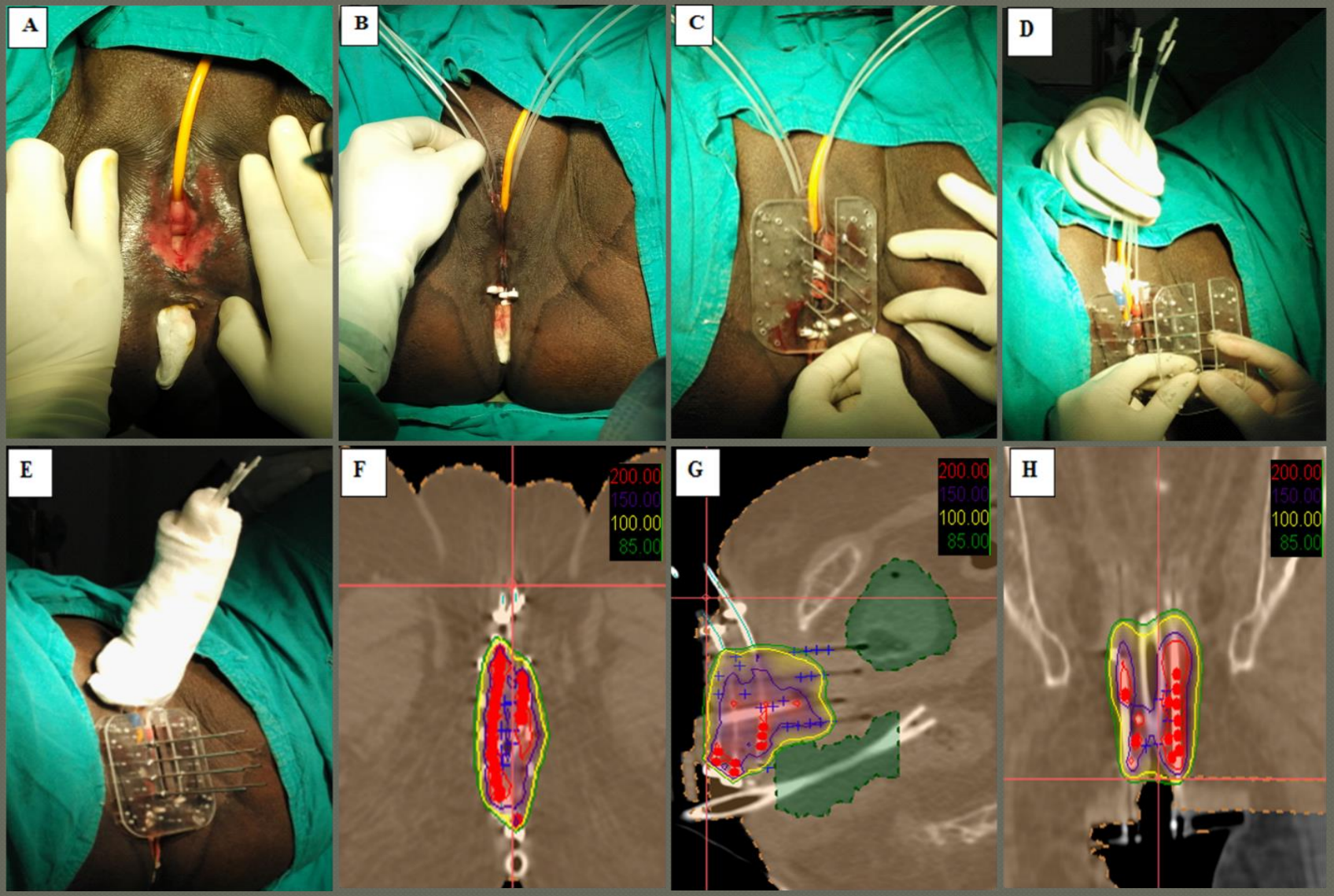






Planning images

Combined freehand & template technique



A-E: Procedure details, F, G & H: Representative axial, sagittal and coronal CT Images with Isodose distributions.

Tata Memorial Hospital Experience
Period : 2000 - 2010

Mahantshetty et al ; Brachytherapy 2017

	Radical Brachy (n=6)	EBRT + Brachy (n=11)
Brachy Dose	**Median 38Gy**	**Median 20Gy**
EBRT dose	**NA**	**Median 50Gy**
HDR Brachy (2#/day)	**3.4 - 4 Gy/# for 8 – 12 #**	**3.4 - 4 Gy/# for 4 – 5 #**
Median OS (mnths)	**62 (12 – 102 mths)**	**33 (10 – 122 mths)**

- Median age : 59 years (Range: 33 to 77)
- Brachytherapy techniques:
  - Needle + plastic tube : 8 pts [Median tubes: 8 (4 - 12)]
  - Template Based : 7 pts [Median tubes:13 (11 - 20)]
- 4 Patients received treatment after radical surgery
- Status at last follow up: 2 pts necrotic ulcer at post. fouchette (disease)
  - 1 pt expired
  - 3 patients alive with disease (status of others not known)

Conclusions - I

- Staging and Mulitdisciplinary Approach
- Radiation : Adjuvant / Definitive / BT
- Disease mapping (Pre Rx & Post XRT) and Pre-planning
- Choice of technique dependent on tumour location & knowledge of local tumor spread
- Combined techniques for tailoring dose distribution
- Adequate fixation & tailor made templates: Important
- Improved needle positioning by guidance (applicable only for deep tumours)

Conclusions - II

- Target volume concept may be extrapolated
- Target volumes : guided predominantly by clincial exam / MR
- Adjustment of needle distribution to target as delineated
- Brachytherapy : PDR / HDR
- No established guidelines and DVH parameters available
- Posterior fouchette : Dose limiting structure for brachy
- Brachythearpy Team work: Learning Curve

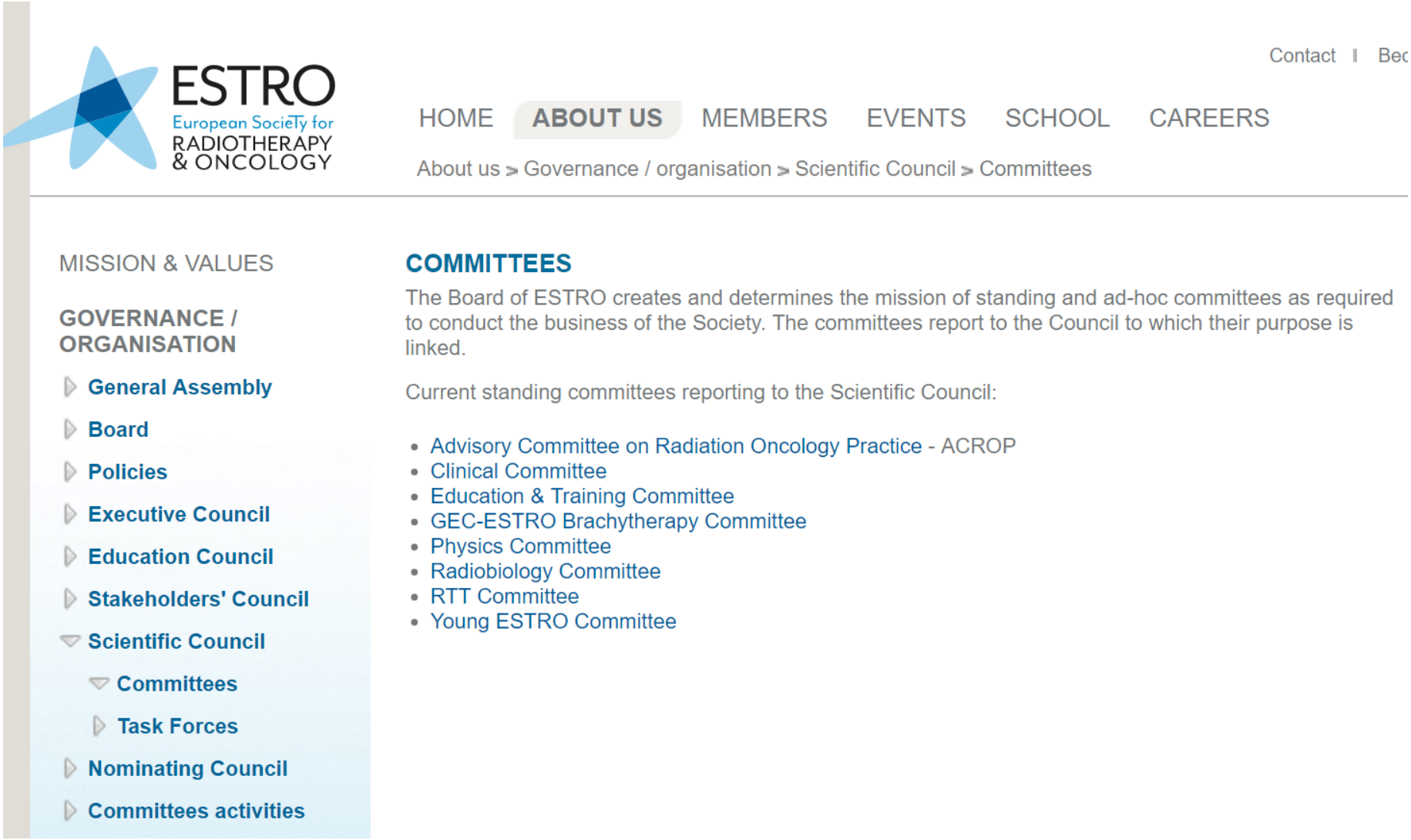
GEC ESTRO gyn network and EMBRACE studies

ESTRO Teaching Course
Image-guided radiotherapy & chemotherapy in gynaecological cancer - with a special focus on adaptive brachytherapy

Madrid 2018

Richard Pötter
Kari Tanderup

ESTRO committee structure



GEC ESTRO working groups

ESTRO
European Society for
RADIOTHERAPY
& ONCOLOGY

Contact | Becor

HOME | ABOUT US | MEMBERS | EVENTS | SCHOOL | CAREERS

About us > Governance / organisation > Committees activities > GEC-ESTRO Brachytherapy Committee

MISSION & VALUES

GOVERNANCE / ORGANISATION

- General Assembly
- Board
- Policies
- Executive Council
- Education Council
- Stakeholders' Council
- Scientific Council
- Nominating Council
- Committees activities

HISTORY

AWARDS

HERO

EU PROJECTS

NATIONAL SOCIETIES

GEC-ESTRO BRACHYTHERAPY COMMITTEE

Over the years, GEC-ESTRO has substantially increased its work, initiating new activities such as organ-related working groups, an executive committee, teaching courses and publications and it is now an integral part of ESTRO. Further information on these activities can be found here.

Working groups

There are six brachytherapy working groups. Please click on the links below or on the right hand side of this page for further information about the activities of the group.

GEC-ESTRO Breast - Chair: Vratislav Strnad
GEC-ESTRO Head and Neck - Chair: György Kovacs
GEC-ESTRO Urology - Chair: Peter Hoskin
GEC-ESTRO Gynaecology - Chair: Kari Tanderup
GEC-ESTRO BRAPHYQS - Chair: Frank-André Sieber
GEC-ESTRO Anal - Chair: Arthur Sun Myint

Brachytherapy publications

GEC ESTRO Handbook of Brachytherapy

The GEC ESTRO Handbook of Brachytherapy is aimed at clinicians, physicists and radiotherapy technologists worldwide, this textbook covers the basics of brachytherapy, including the physics and radiobiology and also describes in detail all aspects of clinical practice.

First published in 2002, this valuable handbook is currently under review. The new version of the GEC ESTRO Handbook of brachytherapy will be included in DOVE, the current version of the book can be found here.

Guidelines and recommendations

Brachytherapy guidelines and recommedations issued by ESTRO and other organisations can be found through the search portal. These comprehensive books present a full review of the state of the art of brachytherapy and clinical radiobiology and are widely regarded as essential reading for all those involved in the delivery of radiation oncology therapies.

GEC ESTRO gyn working group and network

Working group and network chairs:
2000-2005 (Working group): Christine Haie-Meder

2005-2007: Richard Pötter and Christian Kirisits

2007-ongoing: Kari Tanderup and Richard Pötter

GEC ESTRO gyn network core institutions:

Participation and contact:
The GEC ESTRO gyn network is an open network, and we welcome all colleagues who have specific interest in gyneacological brachytherapy. Please email Kari Tanderup (karitand@rm.dk) if you are interested in joining the network.

Past meetings and workshops
Ressources:

- Reporting spreadsheet from Vienna (HDR) and Aarhus (PDR)
- www.EMBRACESTUDY.dk
- ICRU report 89 (www.ICRU.org; **http://jicru.oxfordjournals.org**)

Selection of publications from the Gyn GEC ESTRO network and EMBRACE

GEC ESTRO workshop Brussels 2018

5TH GEC-ESTRO WORKSHOP

30 November-01 December, 2017
Rome, Italy

Venue

Faculty of Medicine and Surgery "A. Gemelli"
Centro Congressi Europa (Conference Center)
Largo Francesco Vito no. 1
00168 Rome
Italy

"The Strength of Brachytherapy"

In November 2016 the GEC-ESTRO Workshop was successfully held for the fourth time in Poznań, Poland. Planned by the GEC-ESTRO Committee and organised by the ESTRO Office, this event has become a hallmark platform for networking with the seven GEC-ESTRO working groups:

GYN network meeting:

- November 30, 2018
- Sign-up: Kari Tanderup

GEC ESTRO gyn network
Step by step process - over the last 20 years...

- Pioneering experiences: from 1998
- Recom I: Target concepts (RO 2005)
- Recom II: Reporting (RO 2006)
- Recom III: Applicator reconstruction (RO 2010)
- Recom IV: Requirements for imaging (RO 2012)
- ICRU report 89 (2016)
- Uncertainties in contouring, treatment planning, treatment delivery: 15 papers (RO vol 107, 2013)
- Retrospective and prospective multicenter clinical studies (2008→)
- Clinical outcome of IGABT (RO vol 120, 2016)

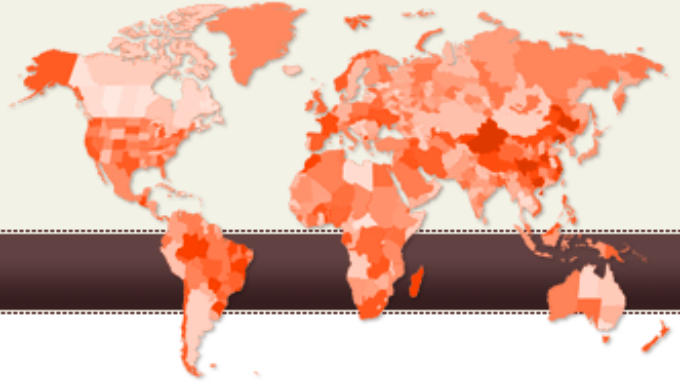
- ESTRO teaching course since 2004 (>2300 participants)
- Annual hands-on workshops (education of >100 institutions)
- Web-based contouring teaching

Current task groups

- **Task groups**
  - **CT contouring in cervix cancer - recommendations (Umesh Mahantshetty)**
  - **Treatment planning recommendations (Kari Tanderup)**
  - **Vaginal brachytherapy and recurrences (Remi Nout)**
  - **Image registation (Jamema Swamidas)**
  - **Definitive endometrium (Angeles Rovirosa)**
  - **Vulva brachytherapy (Cyrus Chargari)**

EMBRACE

{ An intErnational study on MRI-guided BRachytherapy in locally Advanced CErvical cancer }



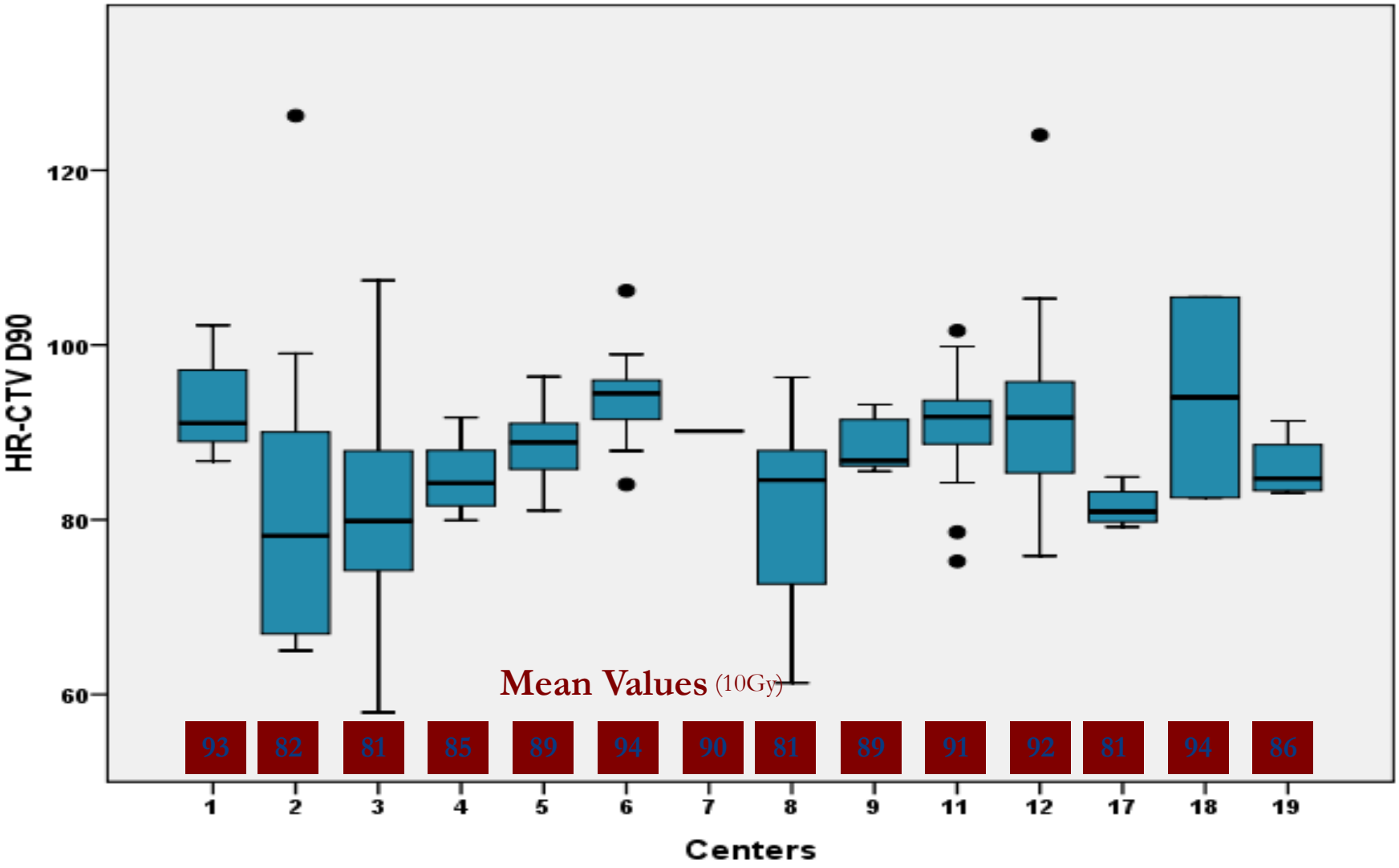
About Embrace | Contacts | Participation | Login

- **EMBRACE - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer**
- **A prospective observational multi-centre trial**
- **Contouring and reporting according to GEC ESTRO recommendations**
- **Fractionation, planning and prescription according to institutional practice**
- **Enrollment of patients in 2008-2015, 1419 pts accrued**

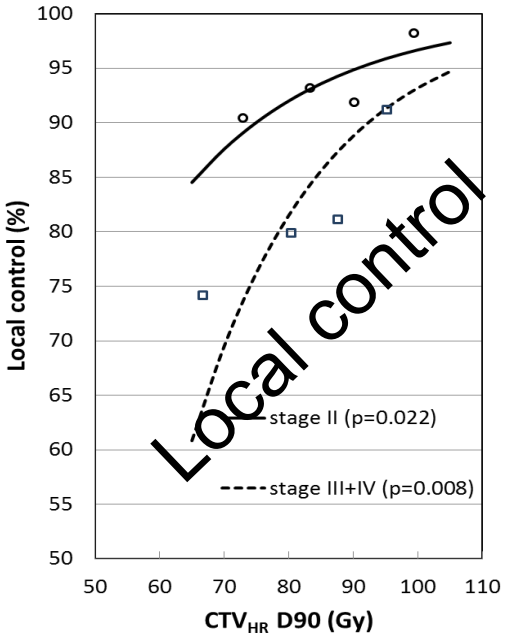
VARIAN medical systems | A partner for life

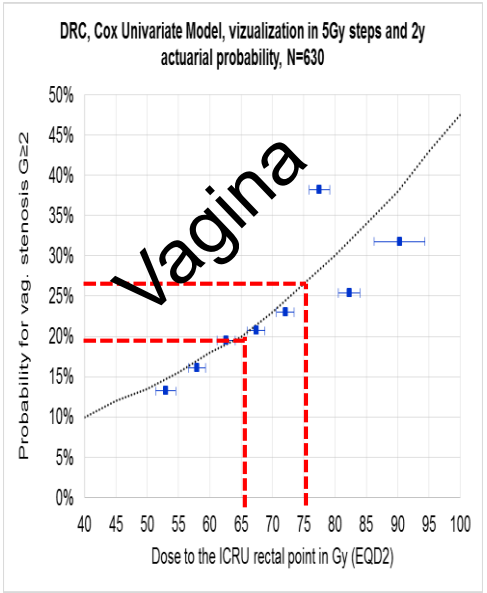
Nucletron Improving patient care

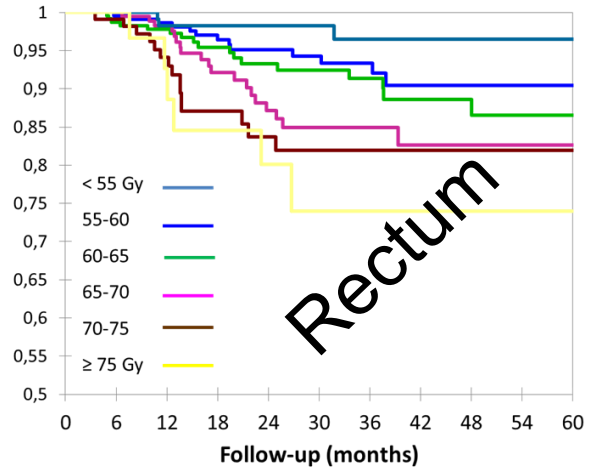
Heterogeneity of dose prescription: HRCTV D90

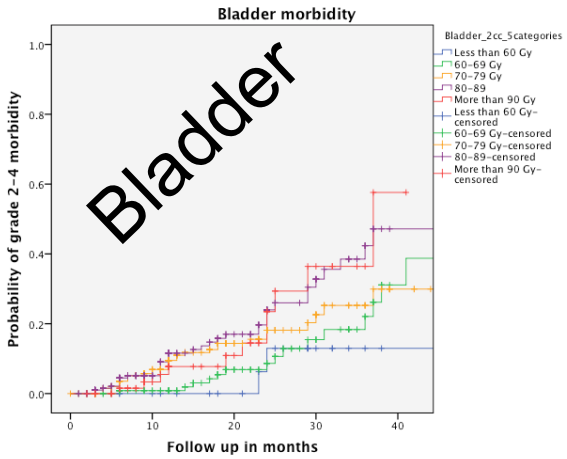


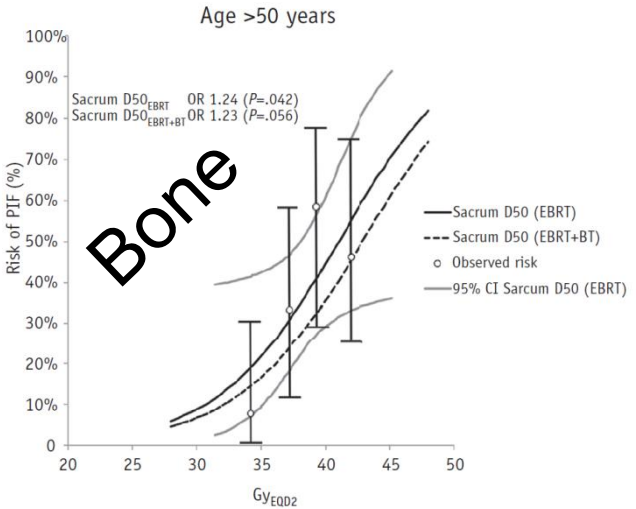
Evidence of dose and effect





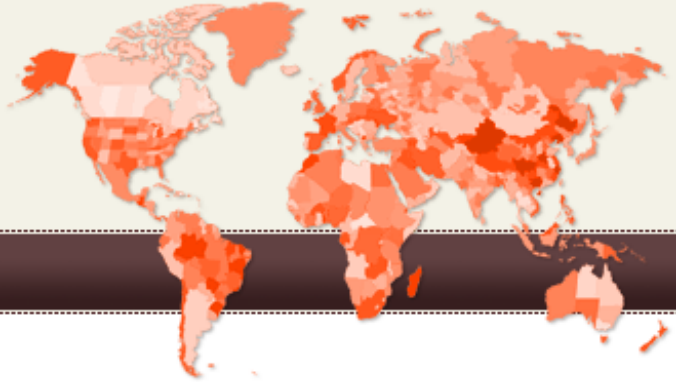


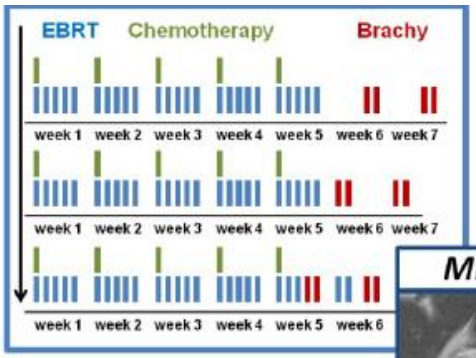


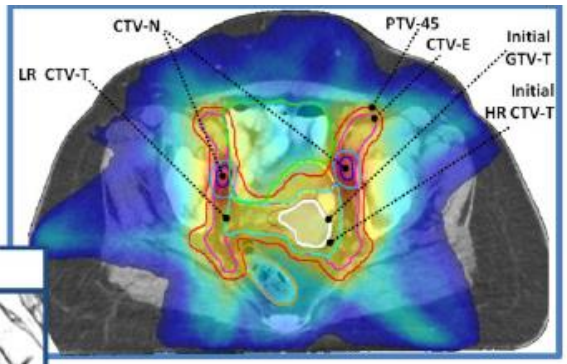


EMBRACE II

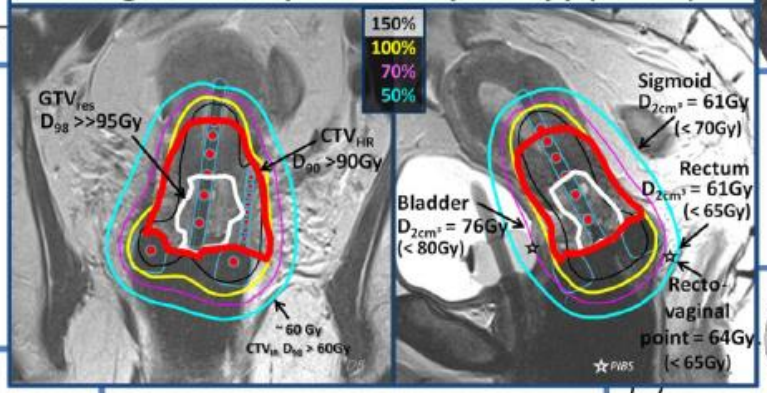
An intErnational study
on MRI-guided BRachytherapy
in locally Advanced CErvical cancer

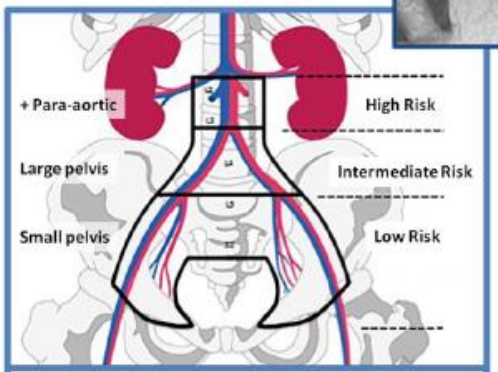




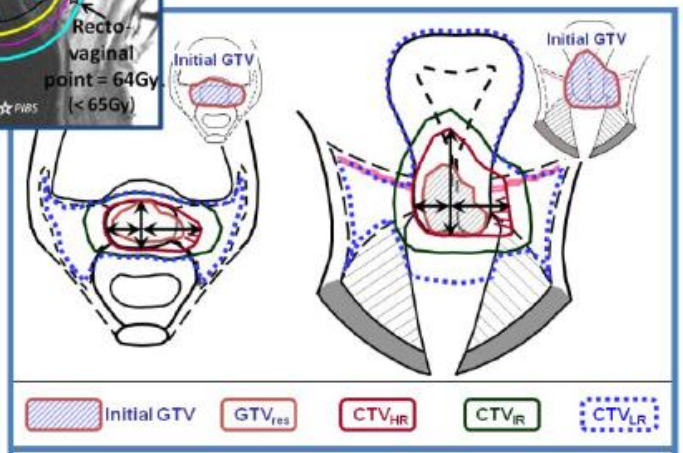


MRI guided adaptive brachytherapy (IGABT)





Nodal CTV-E based on Risk Group



Residual GTV-T, Adaptive HR CTV-T, IR CTV-T

EMBRACE II design

- **Prospective interventional and observational study**
- **Multiple endpoints**
- **Multicenter: >25 centers**
  - **~ 15 current EMBRACE centers and ~20 new centers**
- **1000 patients in 4 years and follow up for 5 years**
- **245 patients accrued since 2016**

- **Substudies on**
  - **Vaginal morbidity**
  - **Imaging**
  - **Translational research**

EMBRACE II interventions

- **Increased use of IC/IS technique in BT:**
  - **HR CTV >30cm3: utilisation of IC/IS of >70% patients and CTV_{HR}>85Gy in 80% of patients (63% in EMBRACE I))**
- **Reduction of vaginal source loading**
- **Systematic utilisation of IMRT**
- **Utilisation of daily IGRT (set-up according to bony structures)**
- **EBRT target concept related to the primary tumour; concepts for OAR contouring**
- **EBRT dose prescription (45Gy/25fx) and reporting**
- **Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence**
- **Systematic application of simultaneous chemotherapy**
- **Reduction of overall treatment time**

EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading: <33% of total loading (51% in EMBRACE I)
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

EMBRACE II interventions

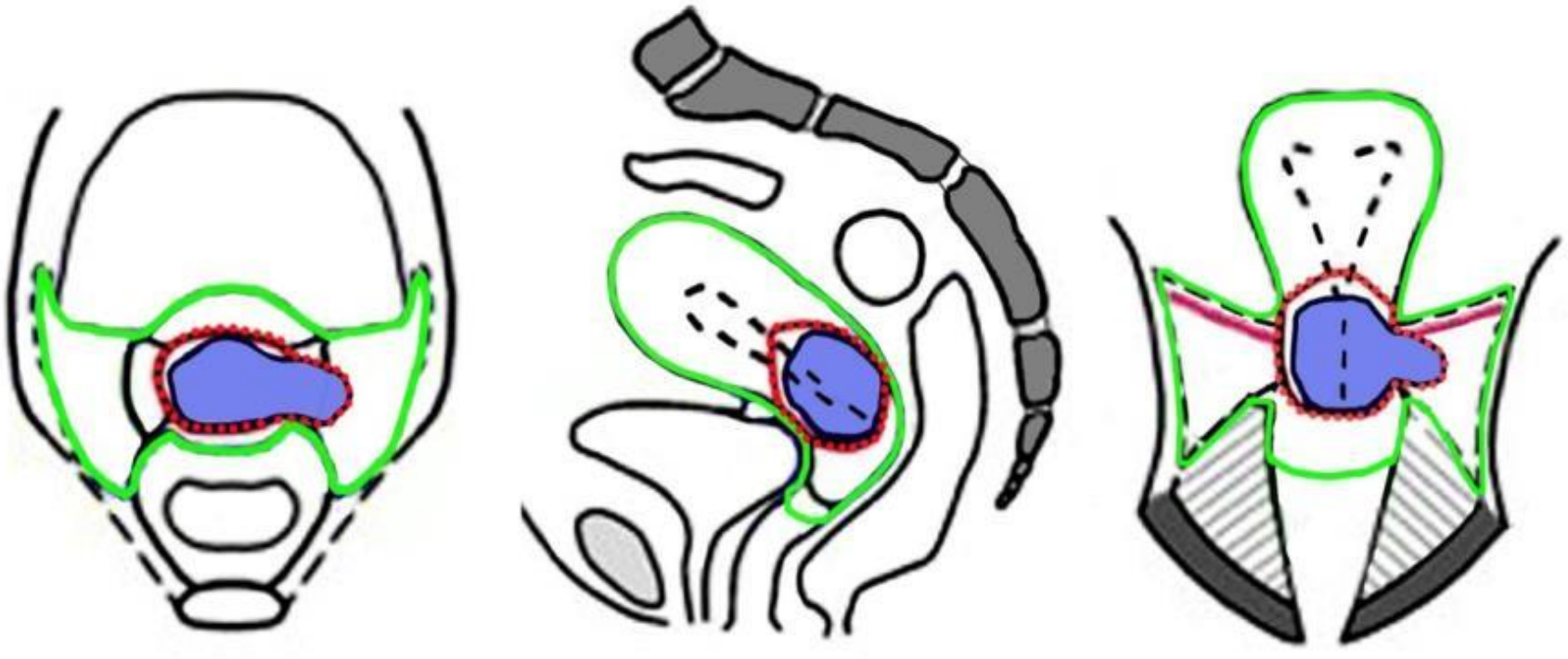
- **Increased use of IC/IS technique in BT**
- **Reduction of vaginal source loading**
- **Systematic utilisation of IMRT + Utilisation of daily IGRT (reduction of V43Gy by 1000cm3 (from 2500cm3 to 1500cm3 pelvis)**
- **EBRT target concept related to the primary tumour; concepts for OAR contouring**
- **EBRT dose prescription (45Gy/25fx) and reporting**
- **Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence**
- **Systematic application of simultaneous chemotherapy**
- **Reduction of overall treatment time**

EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour (adapted to risk) and concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

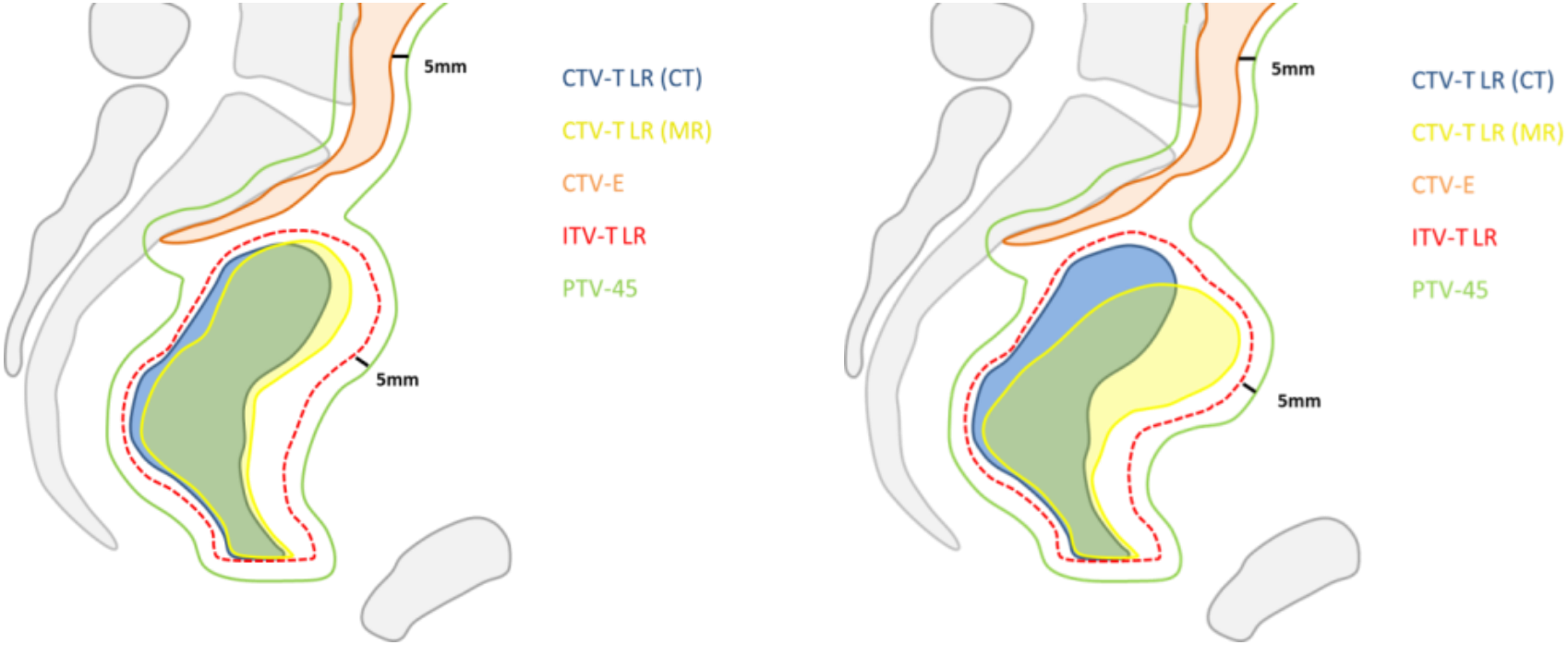
Target concept related to primary tumour

- **Initial GTV (blue)**
- **Initial HR CTV-T (red): GTV+cervix**
- **LR CTV-T (green): HR CTV + uterus + parametria + vagina**



Internal target volume

- **Combined appearance on CT and MRI**
- **Taking organ motion into account**



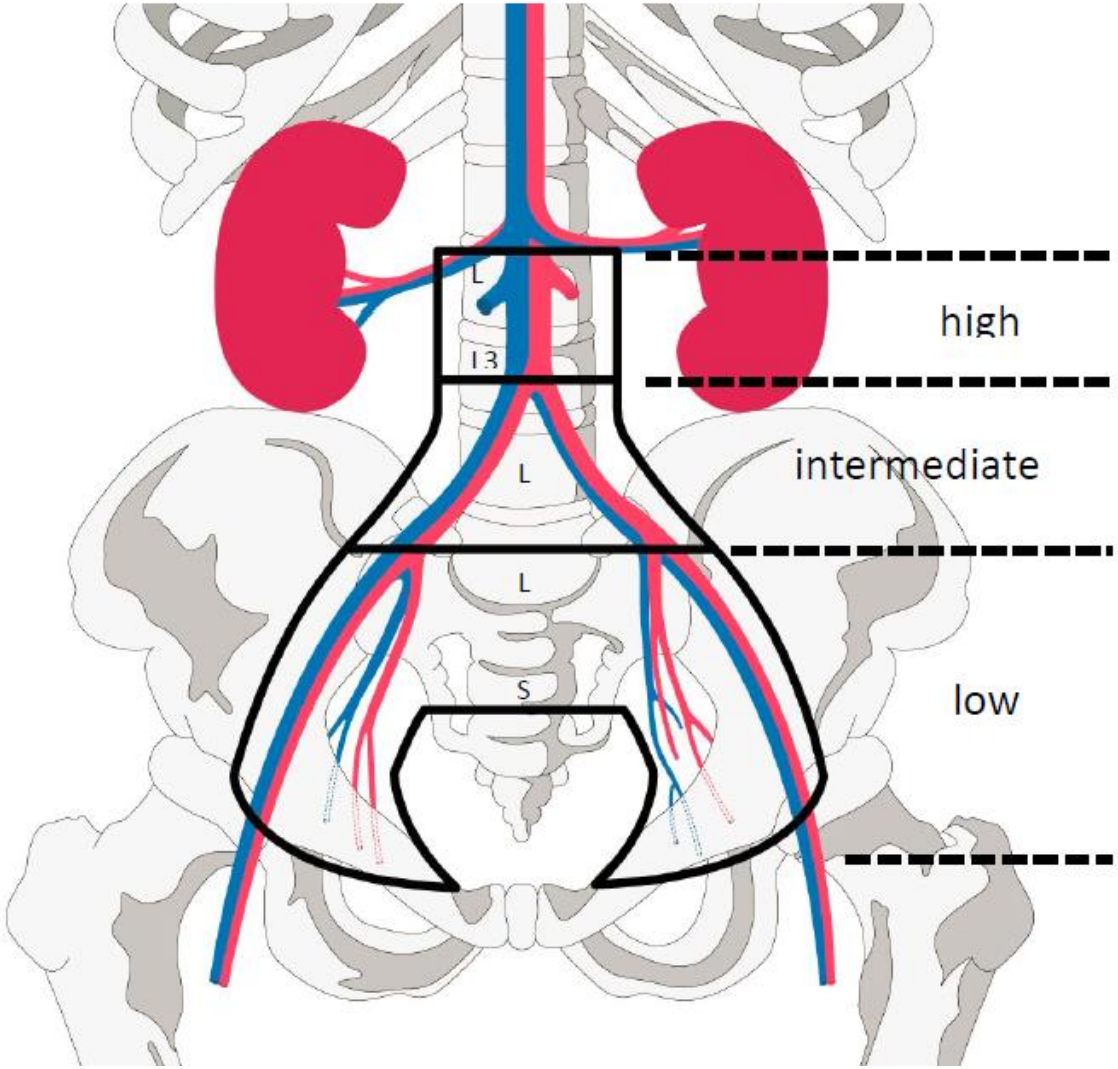
EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription and reporting (45Gy/25 fx in all fractions (30% patients with >45Gy in EMBRACE I)
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence: application of PAN irradiation in 55% of N+ patients (25% in EMBRACE I)
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

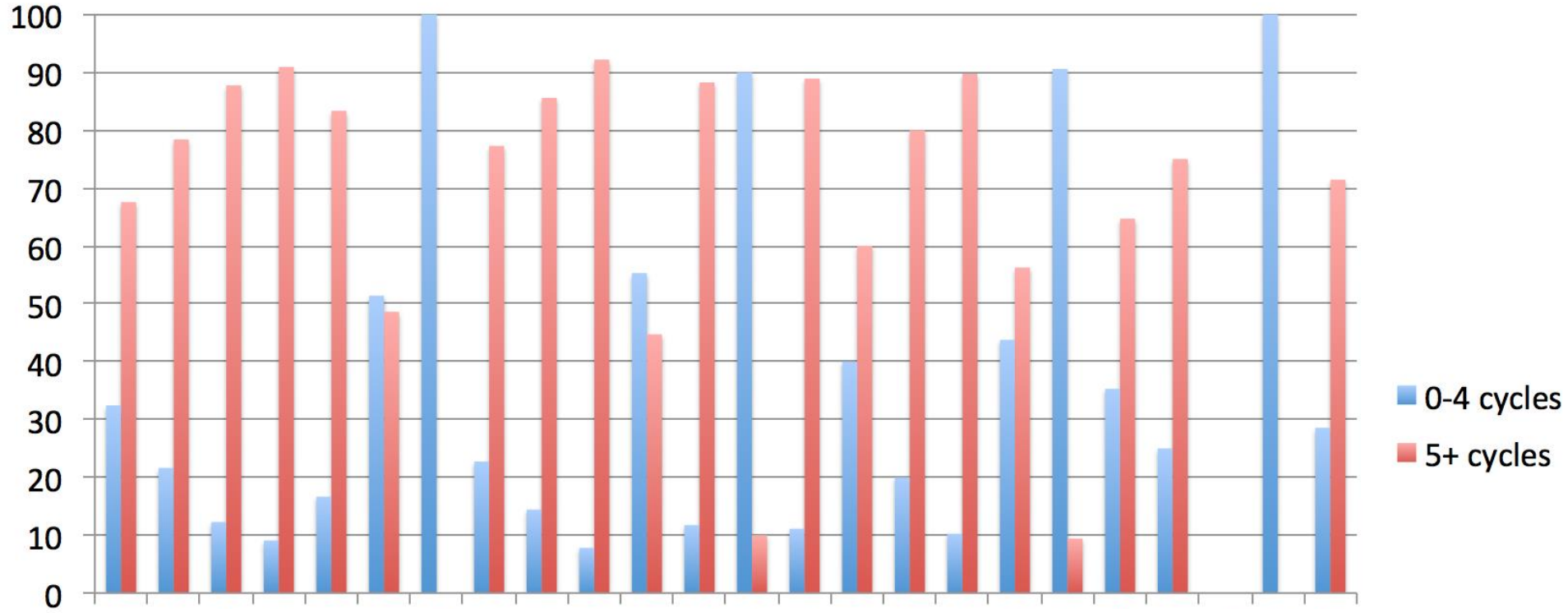
Target concept related to elective lymph nodes



EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy (administration of 5 cycles in 80% of patients (69% in EMBRACE I)
- Reduction of overall treatment time

Administration of chemotherapy in EMBRACE I



EMBRACE II interventions

- **Increased use of IC/IS technique in BT**
- **Reduction of vaginal source loading**
- **Systematic utilisation of IMRT**
- **Utilisation of daily IGRT (set-up according to bony structures)**
- **EBRT target concept related to the primary tumour; concepts for OAR contouring**
- **EBRT dose prescription (45Gy/25fx) and reporting**
- **Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence**
- **Systematic application of simultaneous chemotherapy**
- **Reduction of overall treatment time (OTT<50 days in 80% of patients)**

Accreditation and dummy run for new centers

- **Documentation of compliance (web based)**
  - **Treatment of >10 pts per year qualifying for accrual to EMBRACE II**
  - **Both EBRT and BT performed in the center**
  - **Routine use of IMRT or VMAT**
  - **Routine use of daily IGRT with bony fusion**
  - **Routine use of MRI guided IGABT**
  - **Routine use of combined IC/IS (>20-50% of pts)**

Accreditation and dummy run for new centers

- **Dummy run**
  - **Contouring training for EBRT and BT (self-assessment)**
  - **EBRT planning exercise (self assessment)**
  - **Registration of 5 patient in registration database**
  - **Submission of EBRT and BT contours**
  - **Submission of EBRT and BT treatment plan**

EMBRACE consortium

- **EMBRACE II**
  - **16 EMBRACE I centers**
  - **Accreditation of ~35 new centers**

- **EMBRACE registration study**
  - **Under development**
  - **Possibility to register patient and treatment characteristics as well as treatment outcome**
  - **Possibility to receive feedback on practice and outcome**

Carcinoma Cervix IIIB (FIGO)

MR compatible Tandem and Ring with Interstitial needles (VIENNA - II applicator)

PRACTICAL EXAMPLE

TMH-33422-CN(SD)

Overview

- *Initial findings*
  - Initial clinical findings
  - Initial MRI findings
  - Other
- *EBRT, chemotherapy*
- *Findings at BRACHYTHERAPY (BT)*
  - Clinical findings at BT
  - MRI findings at BT
- *Delineation of GTV, CTV and Organs At Risk (OAR)*

Initial findings

Patient & Tumour

Patient:

41 years old, Pre menopausal

No comorbidities

Tumour:

Histological type: SCC

FIGO Stage: III B, N1

Initial clinical findings:

Portio:

7x5 cm Large endophytic growth

Vagina: Upper 1cm

Fornices: Right and posterior involved

Parametria:

Right: up to LPW

Left: Medial half

Cystoscopy: Normal

MRI Pelvis:

Cervical mass lesion extending into vaginal cavity and lower uterine body.

Bilateral parametria involved.

Enlarged right obturator node (10mm)

(Images in subsequent slides)

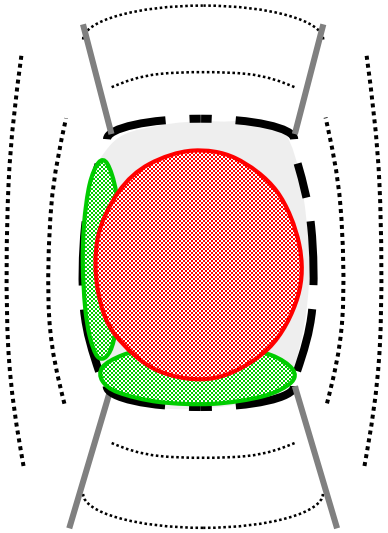
Details: see *Initial Clinical Drawings* (next slide)

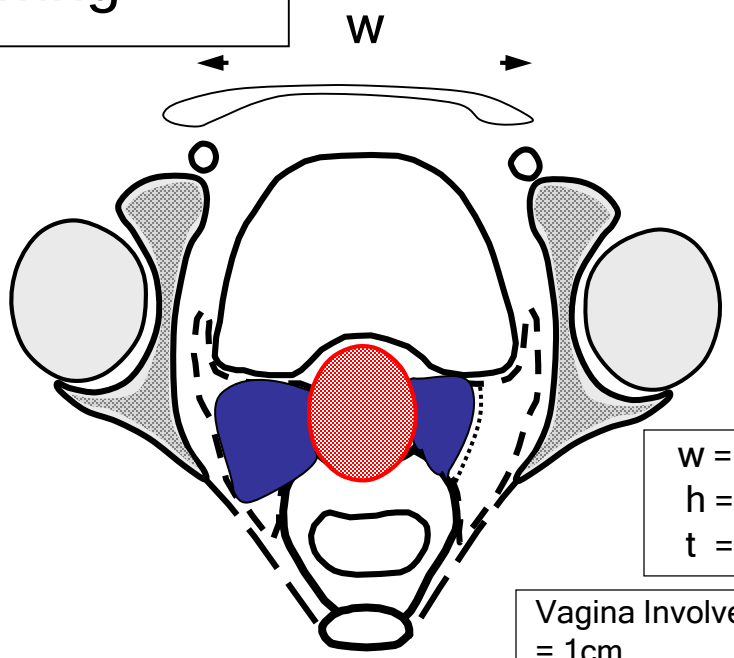
Study ID: TMH-33422-CN(SD)

Clinical Drawing

At Diagnosis

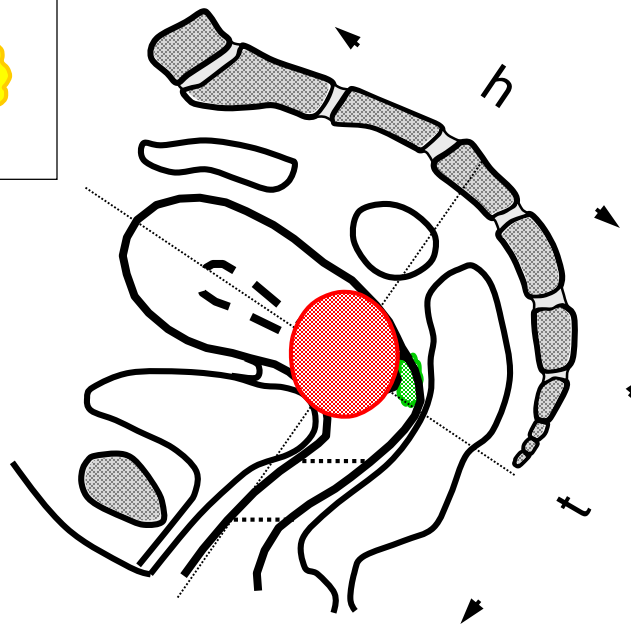
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

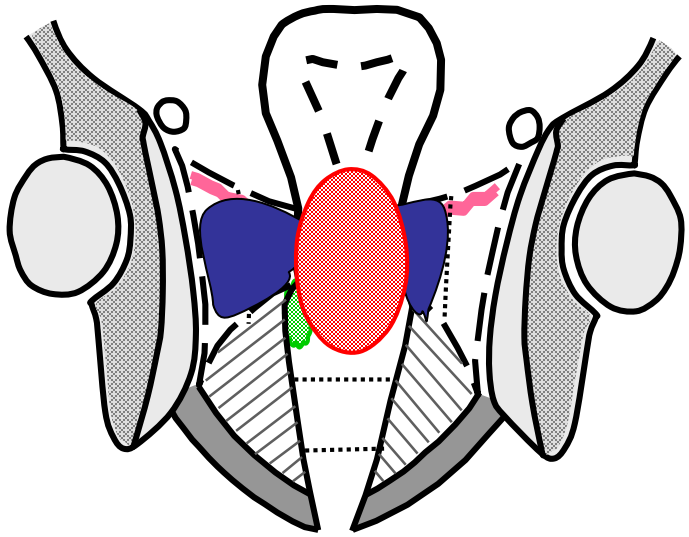




w = 7 cm
h = 5 cm
t = 5 cm

Vagina Involvement = 1cm





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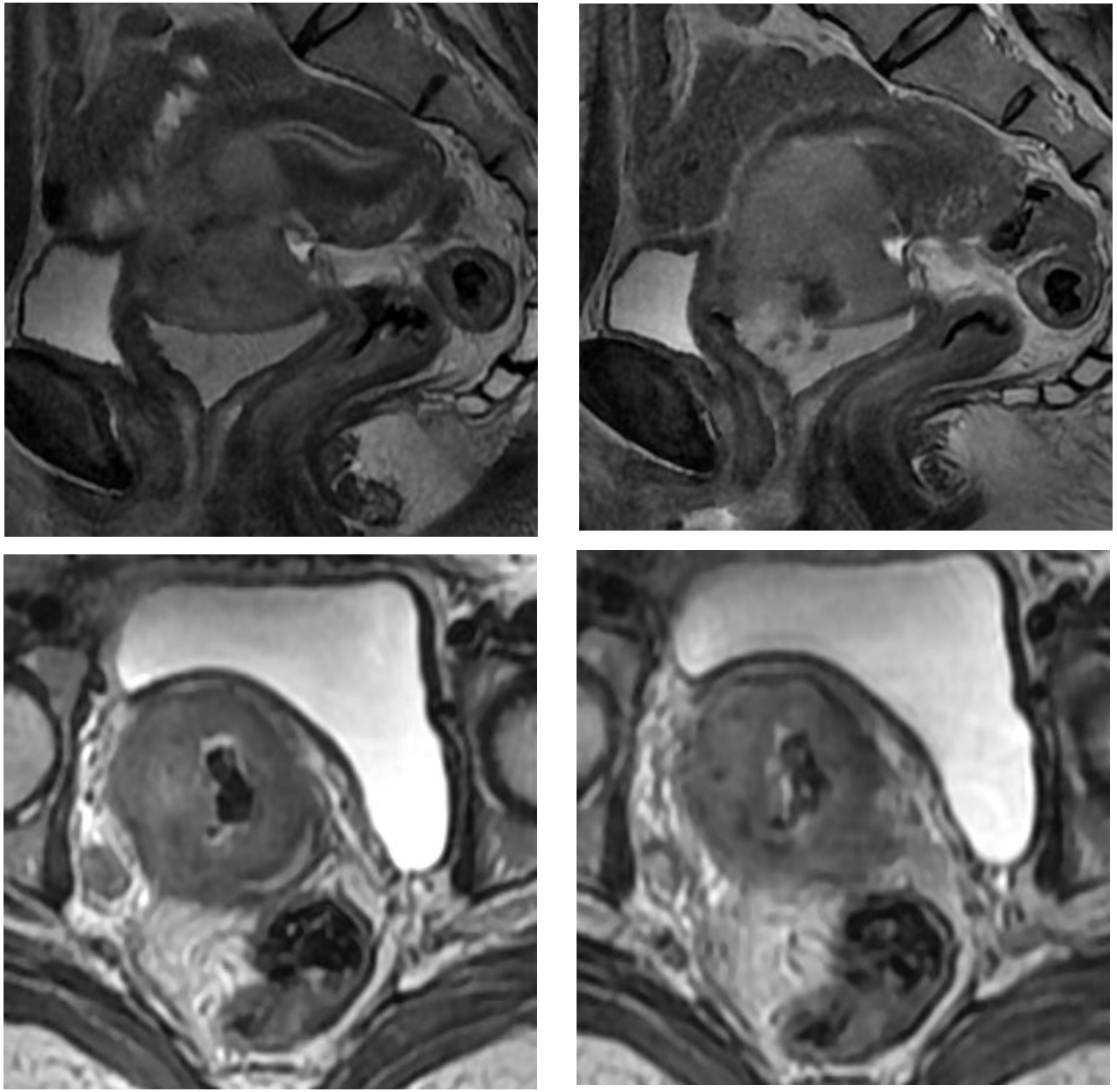
07.11.2016

Dr Umesh
Signature

Study ID: TMH-33422-CN(SD)

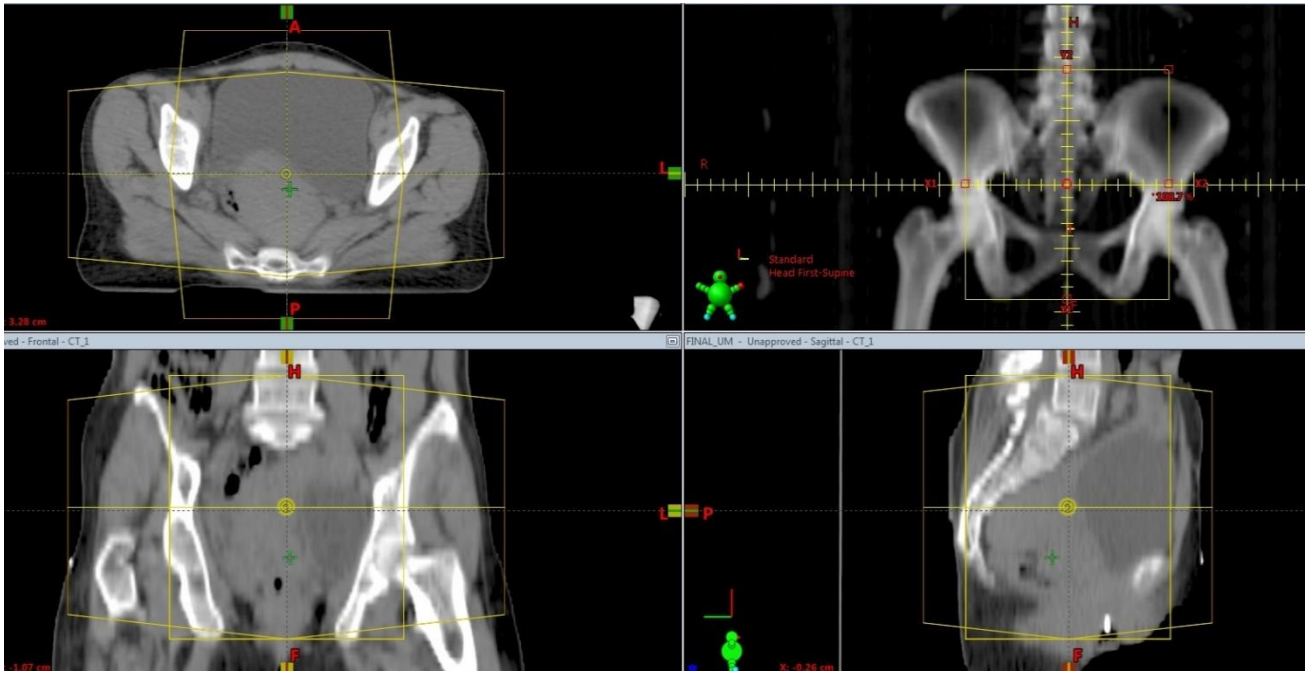
Initial



EBRT, Chemotherapy

EBRT & Chemotherapy

EBRT Technique: Conventional - Box fields
TD: 50 Gy
Dose per fraction: 2 Gy
Boost: no



Concomitant chemotherapy:
Cisplatin 40 mg/m2 weekly, 4 cycles

Findings at brachytherapy (immediately following EBRT)

Clinical findings at BT

Portio:

Residual endophytic growth eroding both lips of cervix

Vagina:

Right and posterior fornices involved.

Parametria:

Rt para involved up to LPW,

Lt para supple.

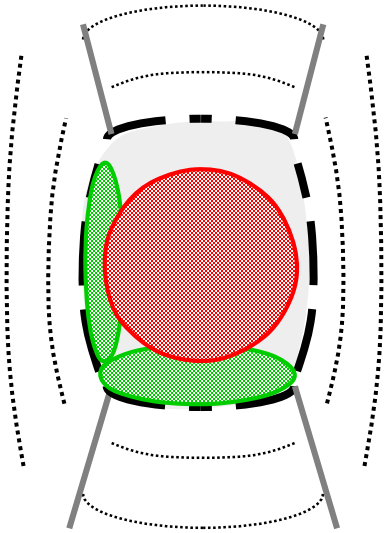
Details: see *Clinical Drawings at BT* (next slide)

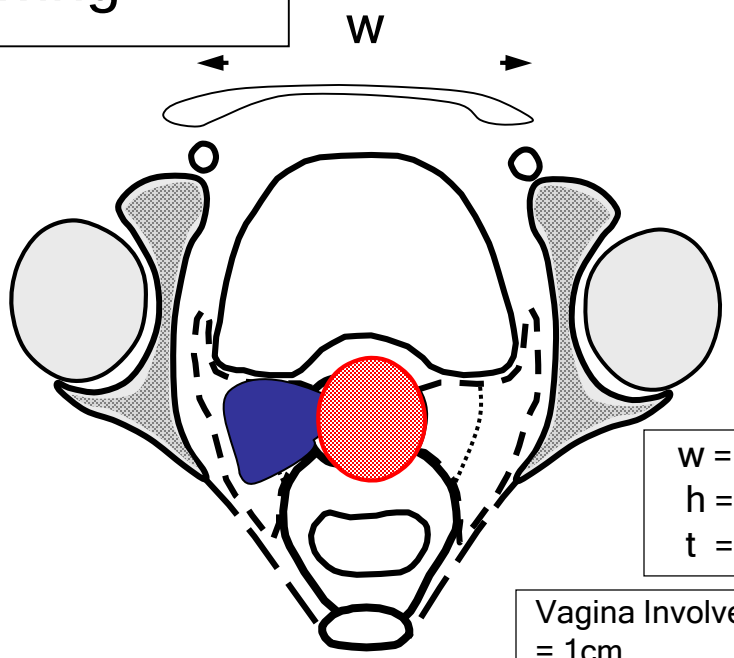
Study ID: TMH-33422-CN(SD)

Clinical Drawing

At Brachytherapy

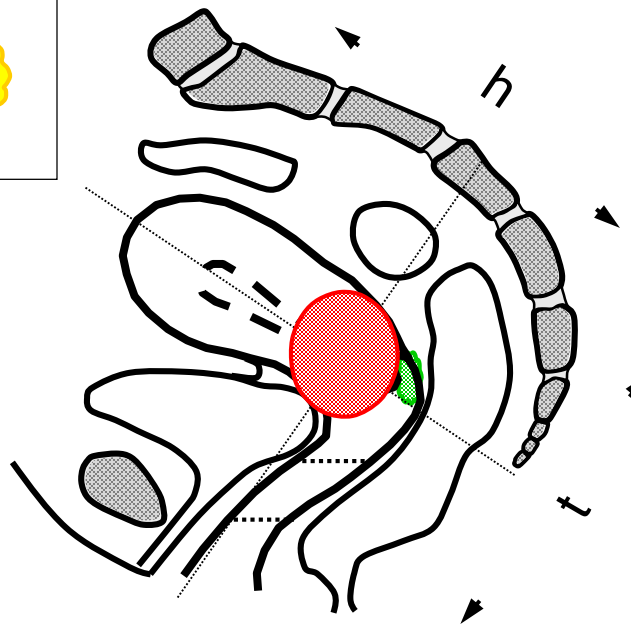
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

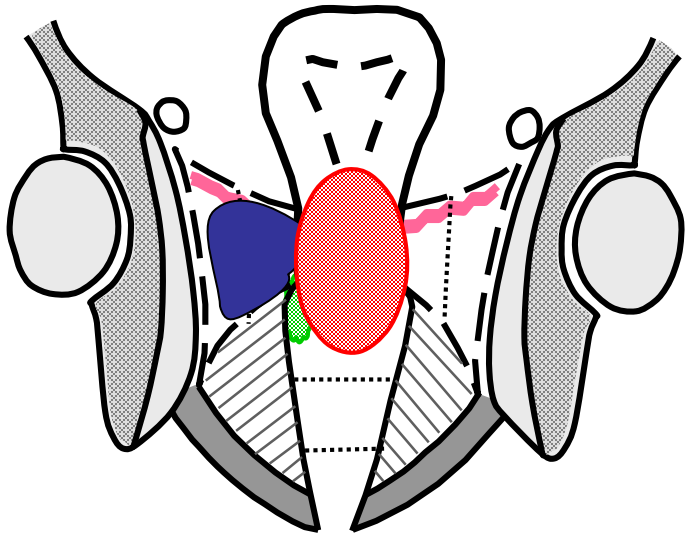




w = 5 cm
h = 3 cm
t = 3 cm

Vagina Involvement = 1cm





dd/mm/yy
27.12.2016

Dr Umesh
Signature

Insertion & imaging

Anaesthesia: General

Application:

Intracavitary component:

- Tandem length: 60 mm
- Tandem angle: 45º
- Ring diameter: 26 mm
- Material: plastic
- Comments: Water-filled plastic tube inside ring & tandem.

Interstitial component:

- N° of needles: 6 (3 straight + 3 divergent) in Rt parametrium
- Insertion depth: 5 cm
- Material: Titanium

Vaginal packing:

- Gauze impregnated with betadine

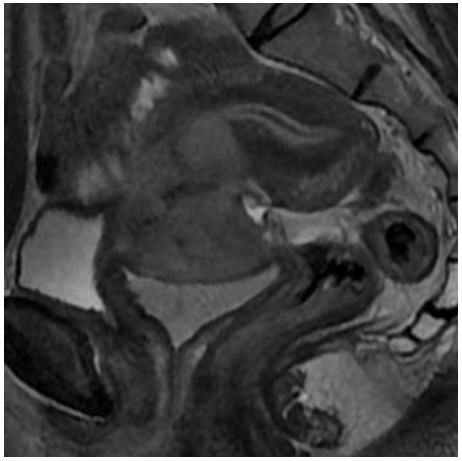
Imaging:

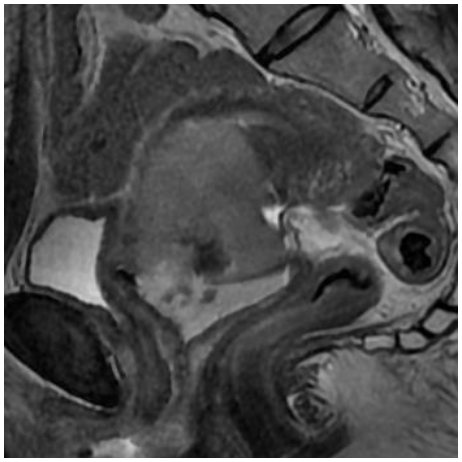
- MRI field strength: 1.5 T
- MRI configuration: closed
- Sequence(s): T2-weighted
- Imaging planes: transverse, sagittal, coronal
- Comments: Before imaging- Empty the bladder using Asepto syringe
  Inject 20cc saline in bladder

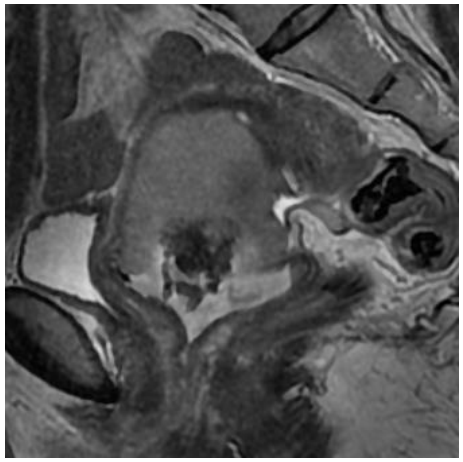
Study ID: TMH-33422-CN(SD)

Initial

Sag







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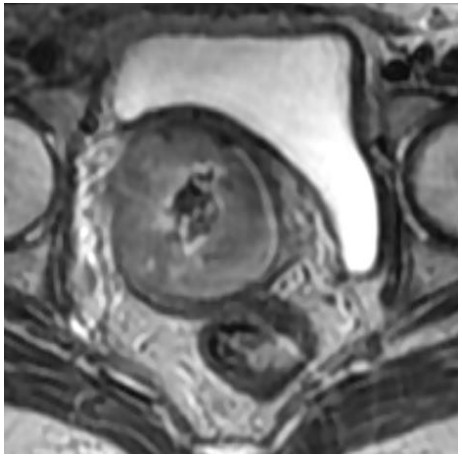

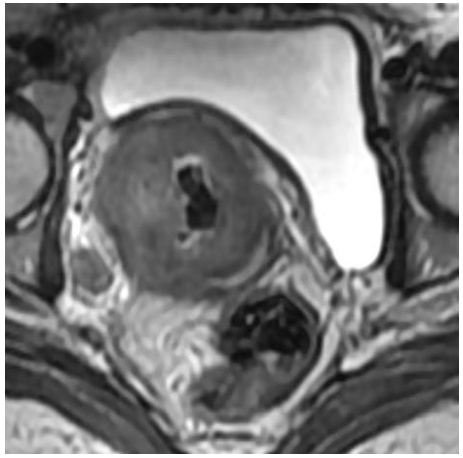

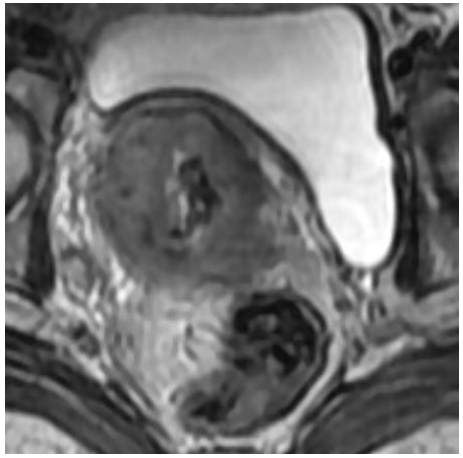

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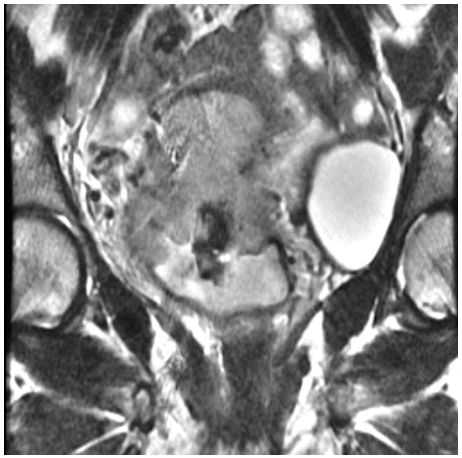

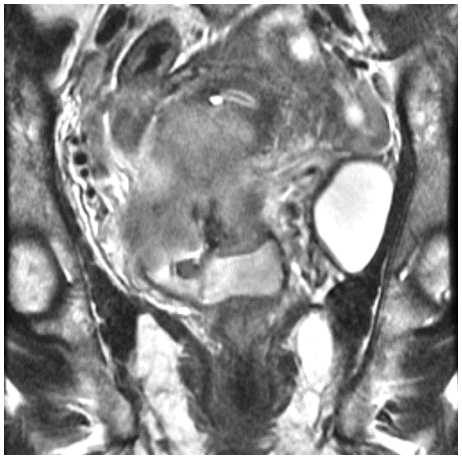

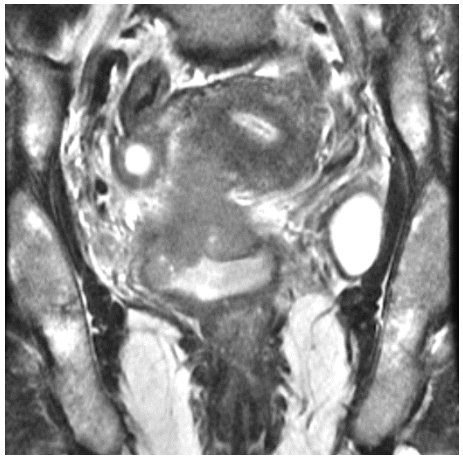

Study ID: TMH-33422-CN(SD)

At Brachy

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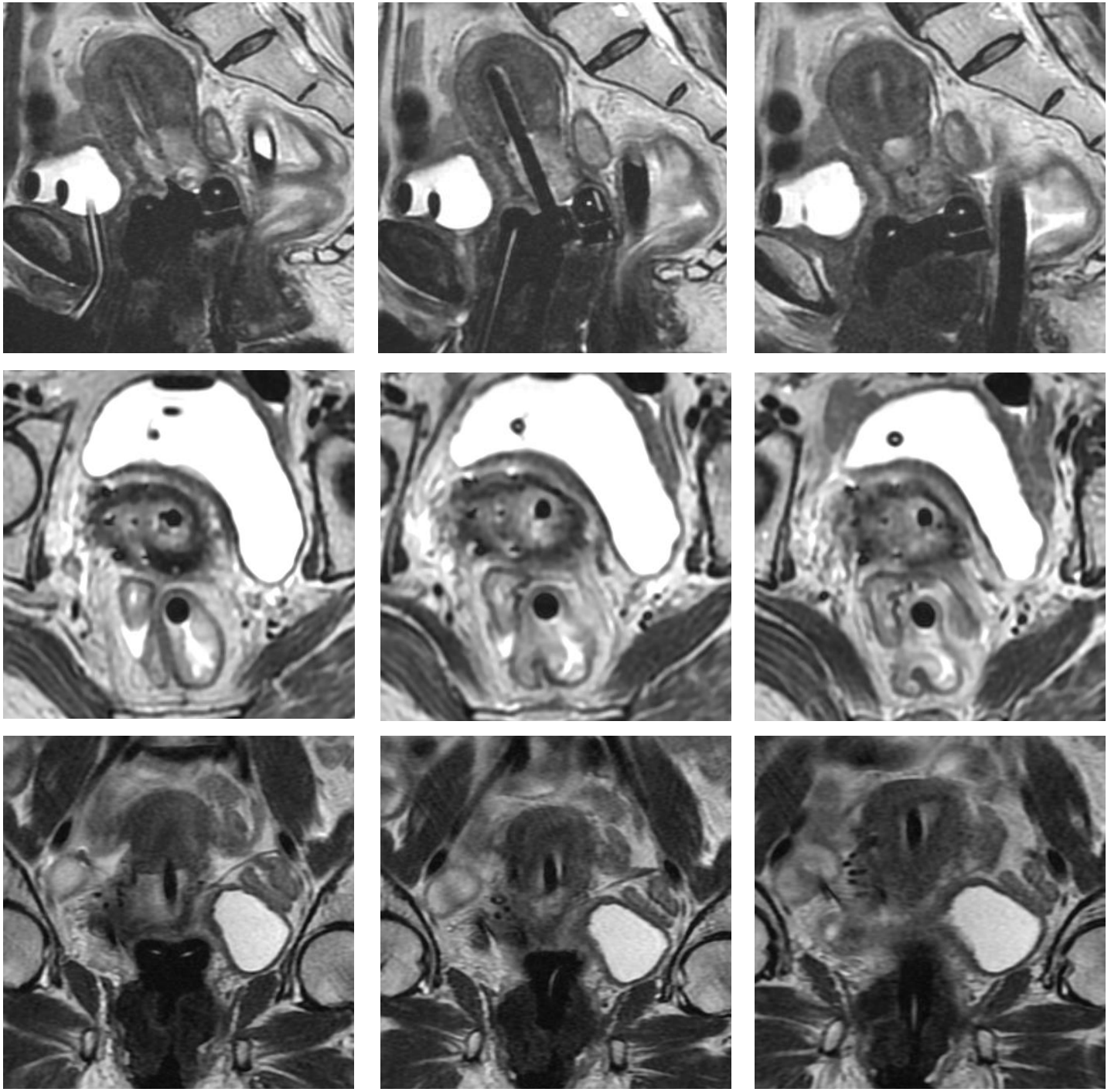
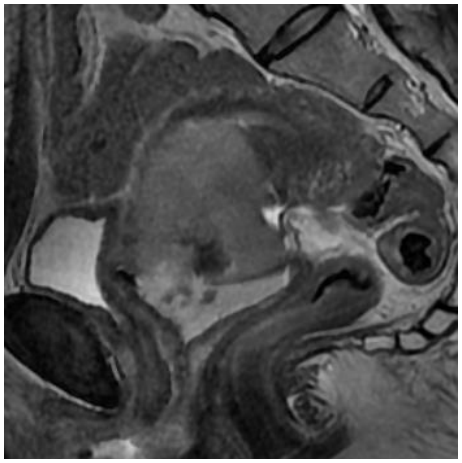
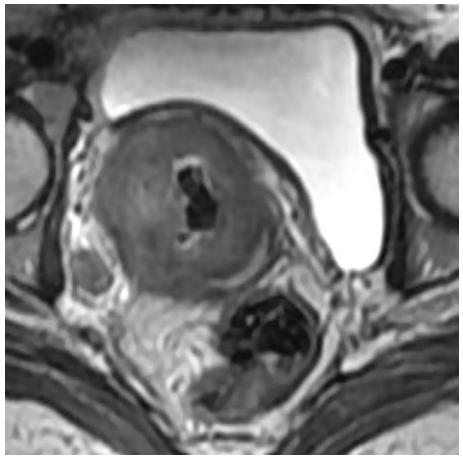
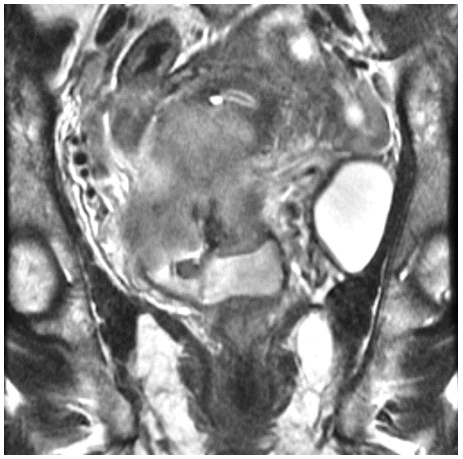
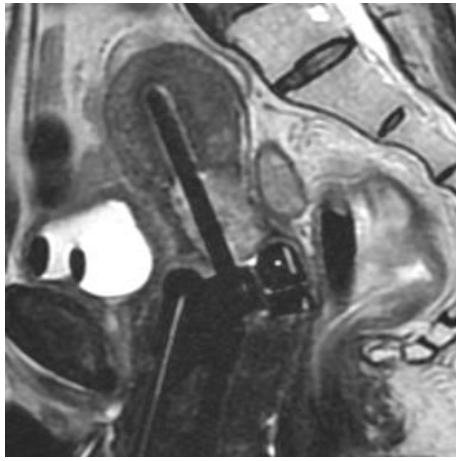
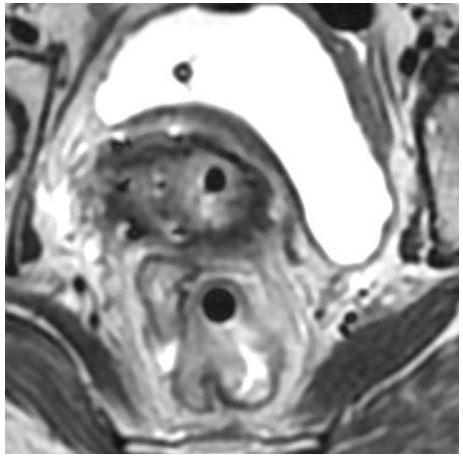
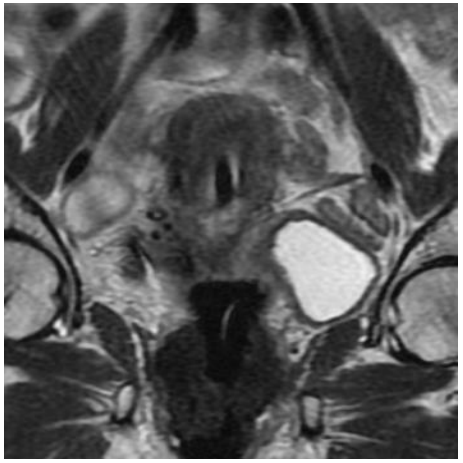


Study ID: TMH-33422-CN(SD)

Initial

At Brachy

Overview

- *Initial findings*
  - Initial clinical findings
  - Initial MRI findings
  - Other
- *EBRT, chemotherapy*
- *Findings at BRACHYTHERAPY (BT)*
  - Clinical findings at BT
  - MRI findings at BT
- *Delineation of GTV_{res}, HRCTV-(CTV- T_{HR}) IRCTV (CTV- T_{IR}) and Organs At Risk (OAR)*

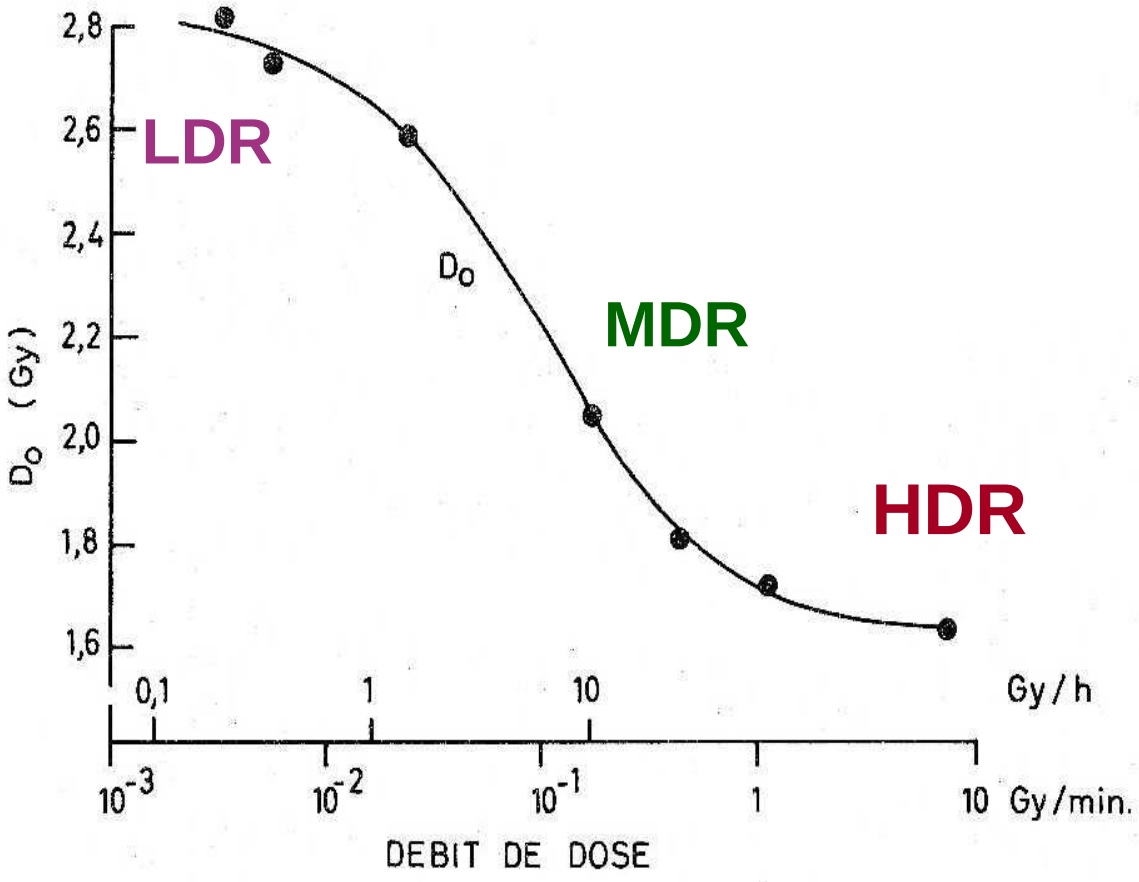
Radiobiological Models to combine dose from External Beam and Brachytherapy (HDR,PDR)

presented by Daniel Berger

General Hospital of Vienna, City of Vienna,
Medical University of Vienna, Department of Radiotherapy

Dose Rates in Brachytherapy

Doses are only comparable for a specified dose rate



ICRU Report 38
dose rate definitions

LDR 0.4 - 2 Gy/h (± 10 Gy/d)

MDR 2 Gy - 12 Gy/h (± 10 Gy/h)

HDR ≥ 12 Gy/h
≥ 0.2 Gy/min (± 10 Gy/min)

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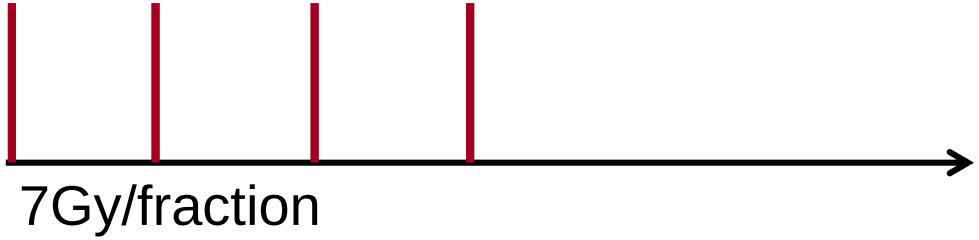
Different Fractionation Schedules

Conventional Therapy (EBRT):

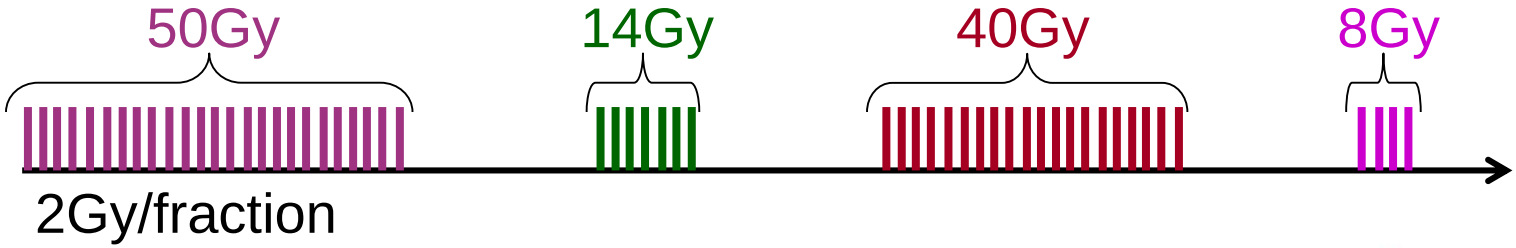
Continuous Low Dose Rate BT:

High Dose Rate BT:



Pulsed Dose Rate BT:

EQD2 - Dose



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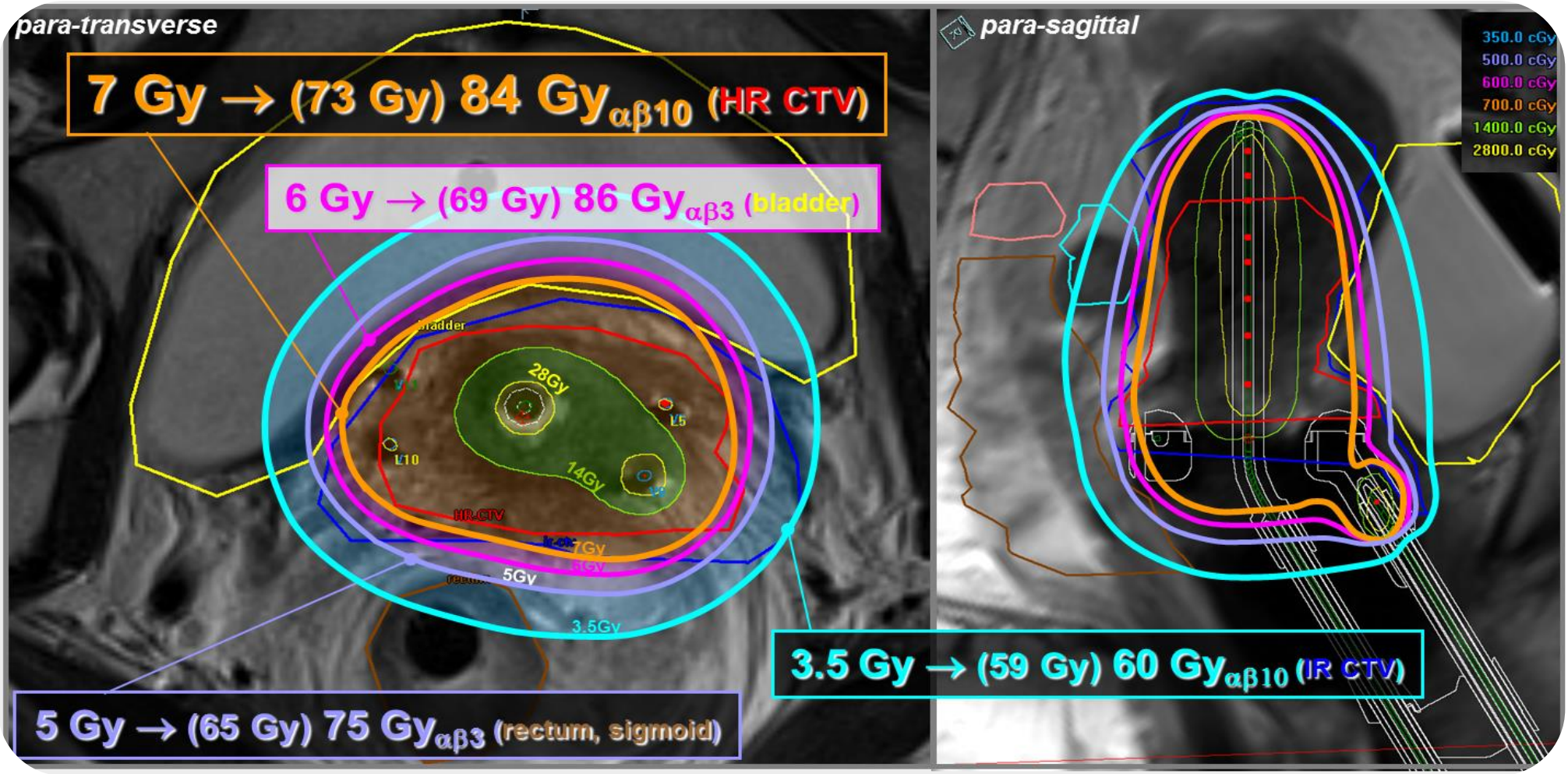
See what you will get



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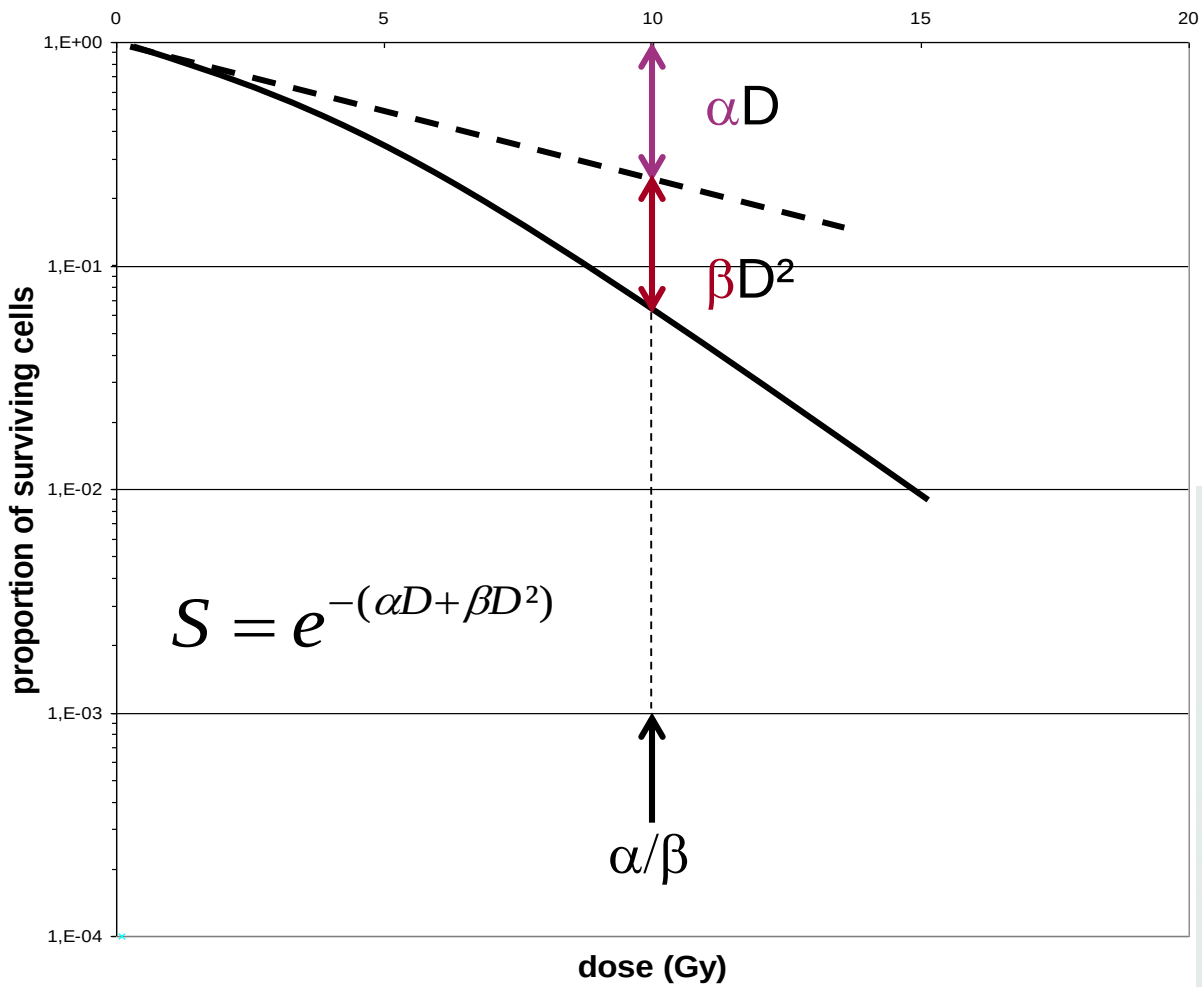
4 R's of radiobiology

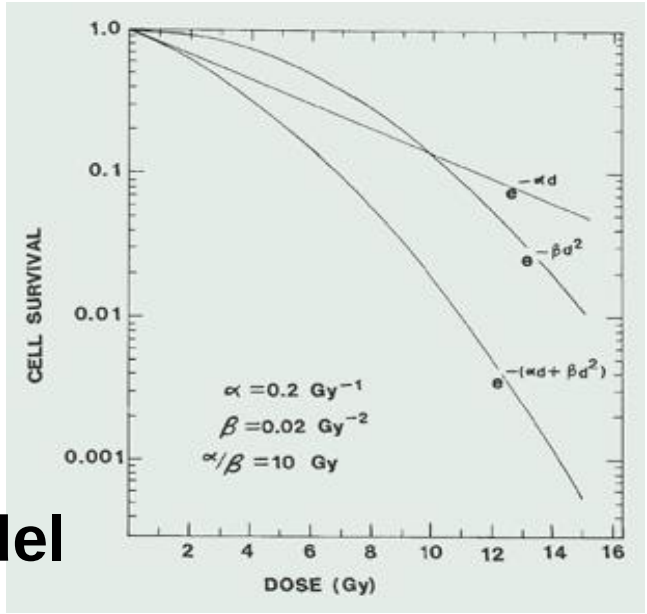
- **R**epair
  - Repair of sub-lethal DNA damage
- **R**edistribution
  - Radiosensitivity depends on phase in the cell cycle → redistribution changes radiosensitivity
- **R**epopulation
  - Cell divide during a radiotherapy treatment
- **R**eoxygenation
  - Radiosensitivity changes due to change in oxygenation

Linear-Quadratic Model



-> Lethal damage

-> Sublethal damage



Survival curve according to the LQ-model

remember survival curve by Puck and Marcus 1956

This can be used to fit a continuously bending curve to cell survival data

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Values of biological parameters

- **Tumour and early reacting normal tissue:**

α/β	~ 10 Gy	7 – 20 Gy for most tumours 9 – 10 Gy for cervix carcinoma
$T_{1/2}$	~ 1.5 hours	0.5 – 1.5 hours

- **Late reacting normal tissue:**

α/β	~ 3 Gy	0.5 – 6 Gy 3 – 4 Gy for bladder, rectum, sigmoid
$T_{1/2}$	~ 1.5 hours	1 – 2 hours

Clinical and experimental experience

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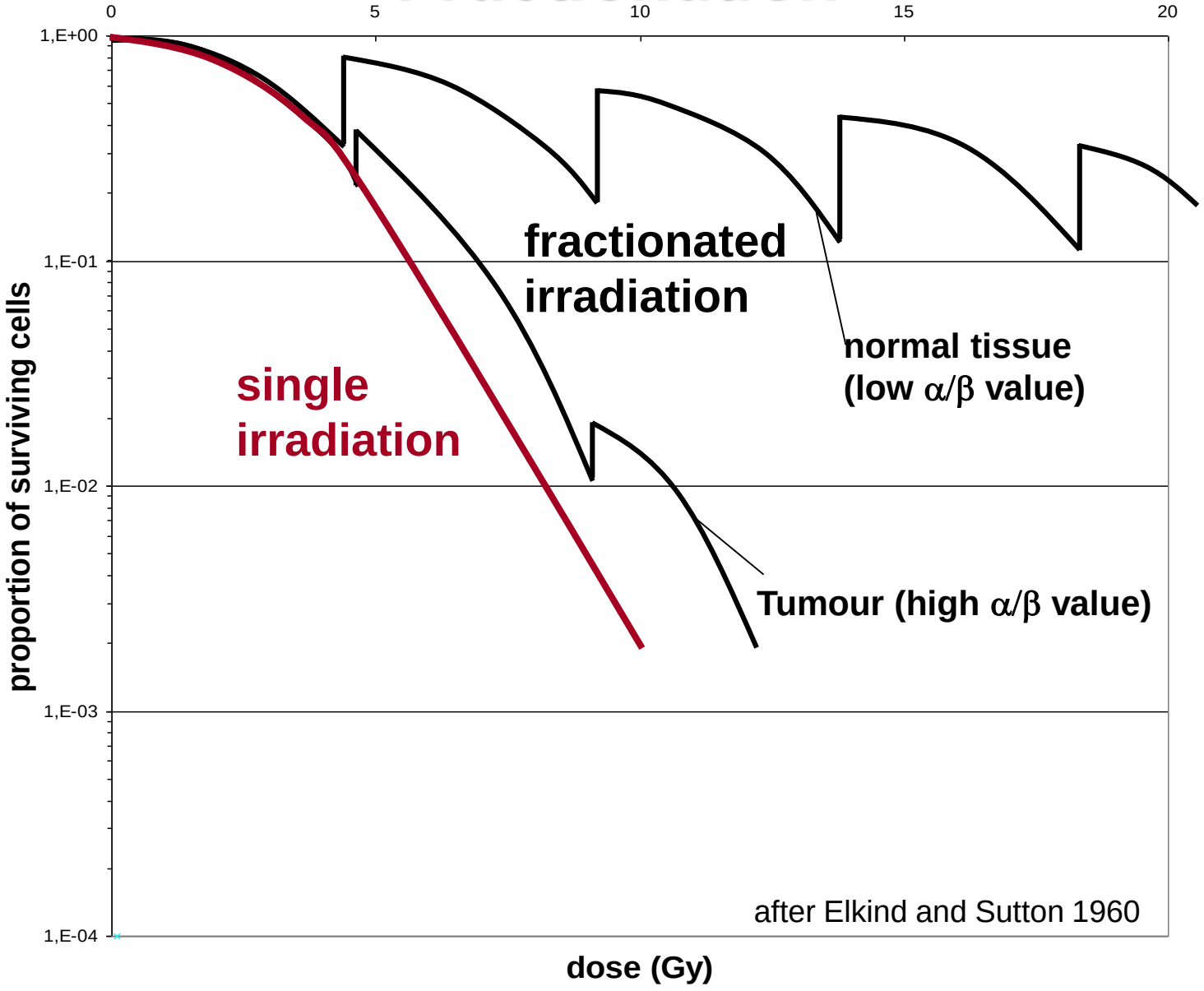
Fractionation



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Limitation

4 Rs of Radiobiology

- **Recovery or Repair (half-time ~1hour)**

- ~~**Redistribution**~~

- ~~**Repopulation (< 1 day)**~~

- ~~**Reoxygenation**~~

Considered in the mathematical description (“equation”)

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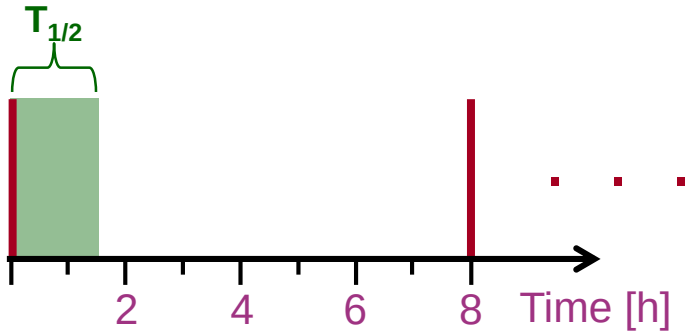
Mathematical Description / Repair Function

➢ External beam radiotherapy and HDR brachytherapy :

no repair during irradiation (min)
repair function g = 1

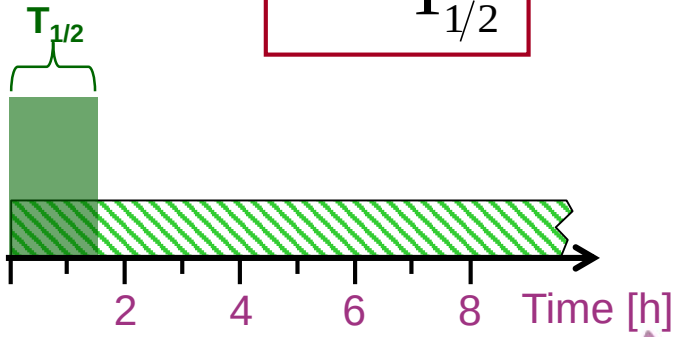


➢ LDR, MDR brachytherapy :

repair during irradiation (hours - days) is significant

$$g(LDR, MDR) = \frac{2}{\mu t}\left[1 - \frac{1 - e^{-\mu t}}{\mu t}\right]$$

$$\mu = \frac{\ln 2}{T_{1/2}}$$



μ … repair rate
$T_{1/2}$ … half time for repair
t … irradiation time

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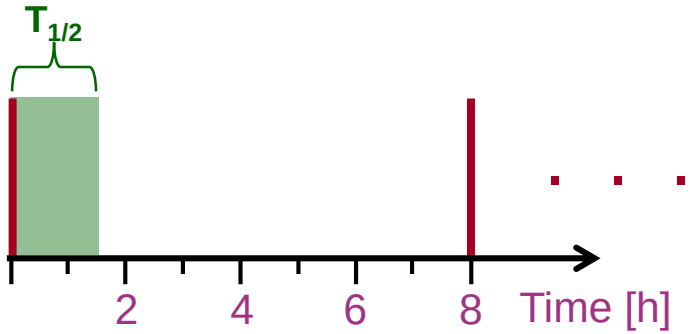
Mathematical Description / Repair Function

➢ External Beam RadioTherapy and HDR BrachyTherapy :

no repair during irradiation (min)

repair function **g = 1**



➢ PDR BrachyTherapy :

repair between successive pulses (hours) and during the whole fraction (hours - days) is significant

$$g(PDR) = \frac{2}{\mu t}\left[1 - \frac{ny - sy^2}{n\mu t}\right]$$

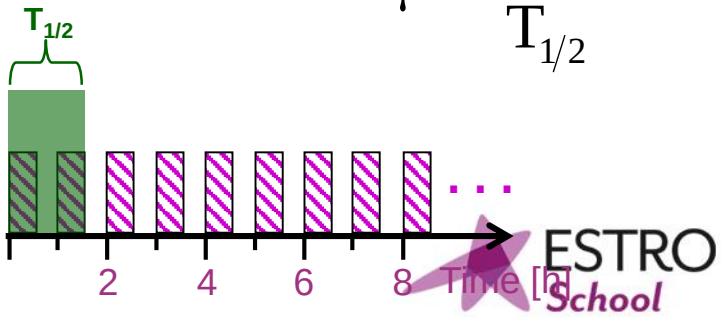
$$s = \frac{nk - k - nk^2 e^{-\mu t} + k^{n+1} e^{-\mu nt}}{\left(1 - ke^{-\mu t}\right)^2}$$

$$y = 1 - e^{-\mu t}$$

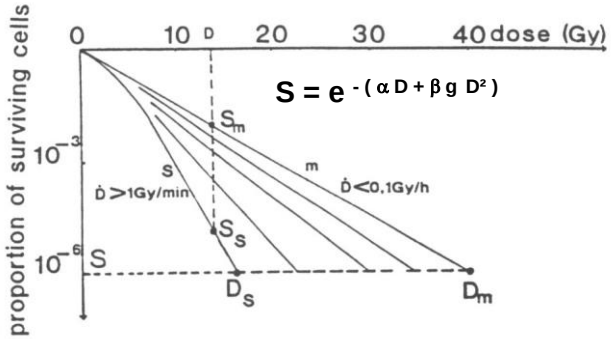
$$k = e^{-\mu x}$$

$$\mu = \frac{\ln 2}{T_{1/2}}$$

- **μ …** repair rate
- **$T_{1/2}$ …** half time for repair
- **t …** irradiation time for each pulse
- **x …** time between pulses without irradiation
- **n …** number of equal pulses



- **Biologically Effective Dose:**



The Role of Dose Rate in Brachytherapy (J. Dutreix) In: A Practical Manual of Brachytherapy (Pierquin / Marinello, Medical Physics Publishing)

1

$$BED = nd\,[\,1 + g\,d\,/\,(\alpha/\beta)\,]$$

- **BED ... virtual dose value that produces the same biological effect as the physical dose with an infinite low dose rate**

Calculated BED values are normalized to conventional EBRT with 2 Gy / fraction (reference schedule) :

2

"isoeffective dose" = "equivalent dose in 2 Gy fractions"

$$BED = D_{IsoE}\,[\,1 + 2\,/\,(\alpha/\beta)\,]$$

g=1
HDR or EBRT

$$D_{isoE} = \frac{nd \cdot \left(1 + \frac{g\,d}{(\alpha/\beta)}\right)}{1 + \frac{2}{(\alpha/\beta)}}$$

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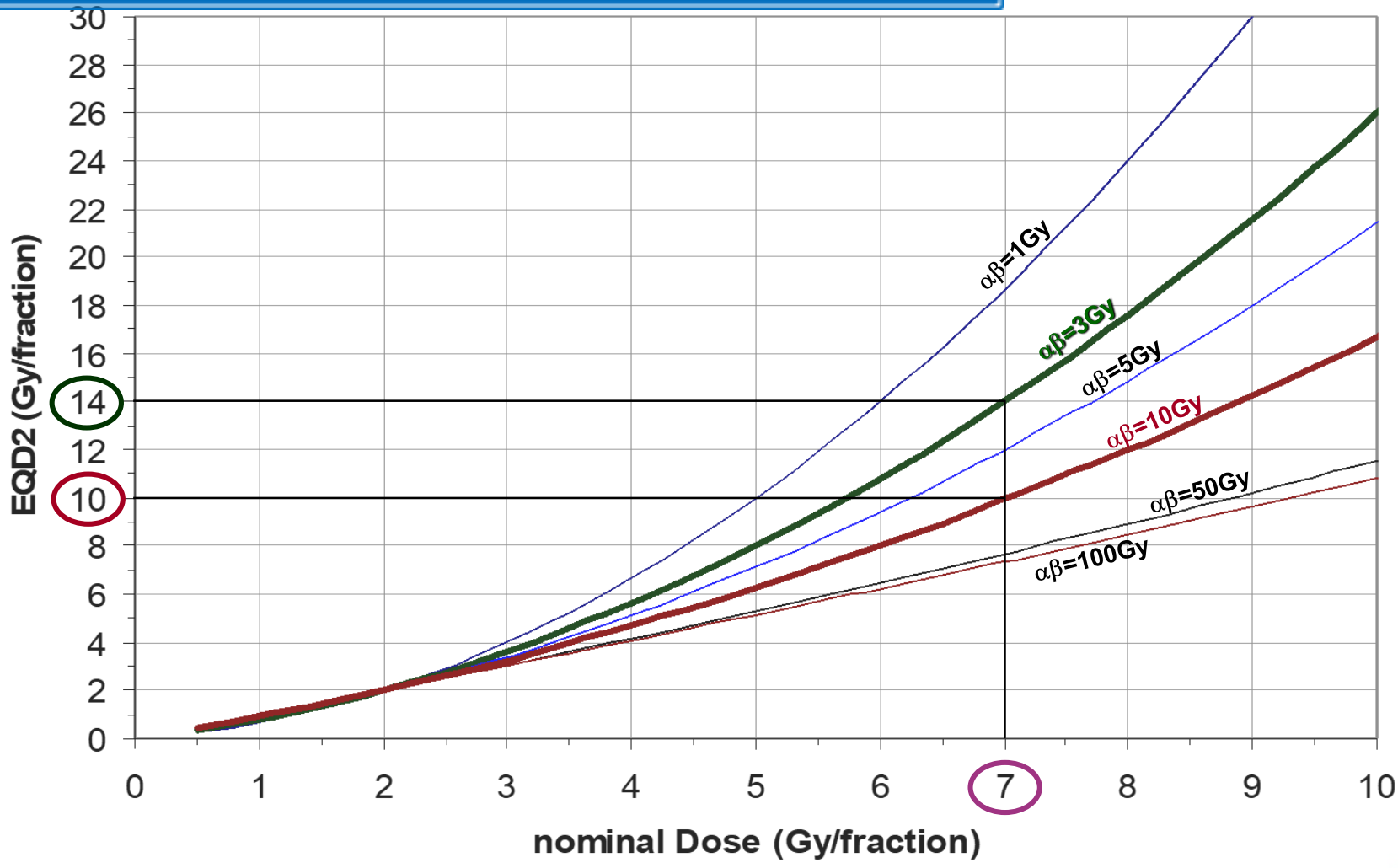
$$D_{isoE} = \frac{nd \cdot (1 + \frac{d}{(a/\beta)})}{1 + \frac{2}{(\alpha/\beta)}}$$

From physical dose to EQD2 dose



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Limitation

4 Rs of Radiobiology

- **Recovery or Repair (half-time ~1hour)**
- ~~**Redistribution**~~
- **Repopulation (< 1 day)**
- ~~**Reoxygenation**~~

Repopulation
– changing the overall treatment time -

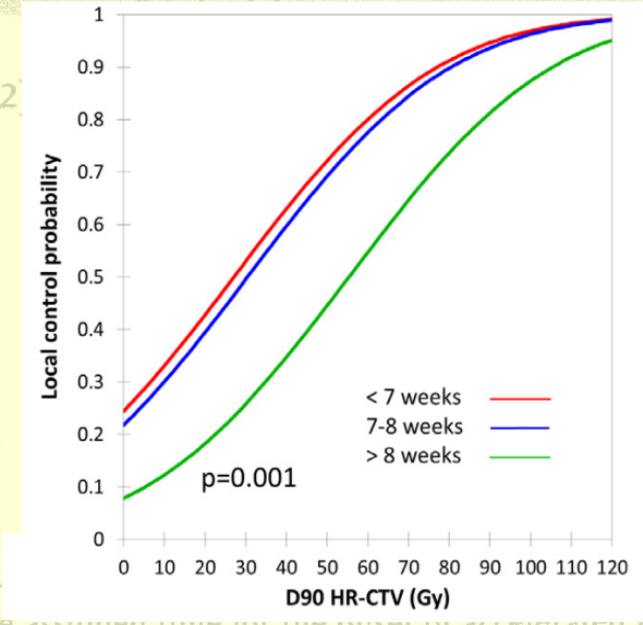
Influencing the local control rate

$$EQD_{2,T} = EQD_{2,t} - (T - t)D_{prolif}$$

- Increasing OTT by one week is equivalent to a loss of 5 Gy in CTV_{HR} D90

Tanderup et al Radiother Oncol, 2016

- Timing of the BT boost?



EBRT ⟷ BT

Mazeron et al, Radiother Oncol 2015

„Per day delay in overall treatment time results in loss of ~ 0.3 – 0.8 Gy/day“

Repopulation
– changing the overall treatment time -

Per day delay in overall treatment time
will results in ~1% loss of local control

Therefore try to ***stay within 50 days*** (OTT) **or**
compensate by
increasing the dose

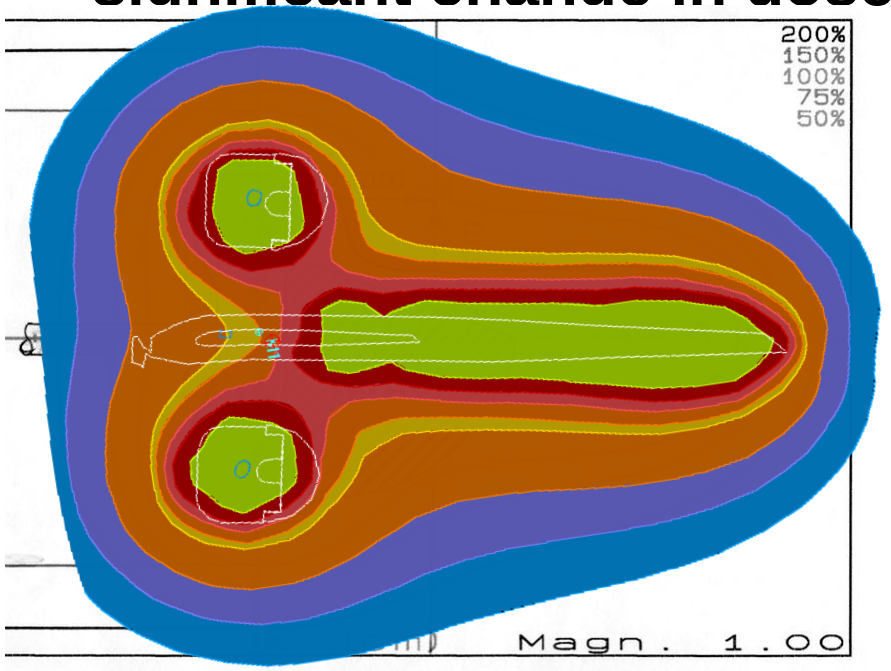
„***Clinical experience*** is more important“ !

* Pooled estimate from a review of studies in the literature. ** T_k is the assumed time for the onset of accelerated proliferation.
Reference details are available from Søren Bentzen and Michael Baumann.

„Per day delay in overall treatment time results in loss of ~ 0.3 – 0.8 Gy/day“

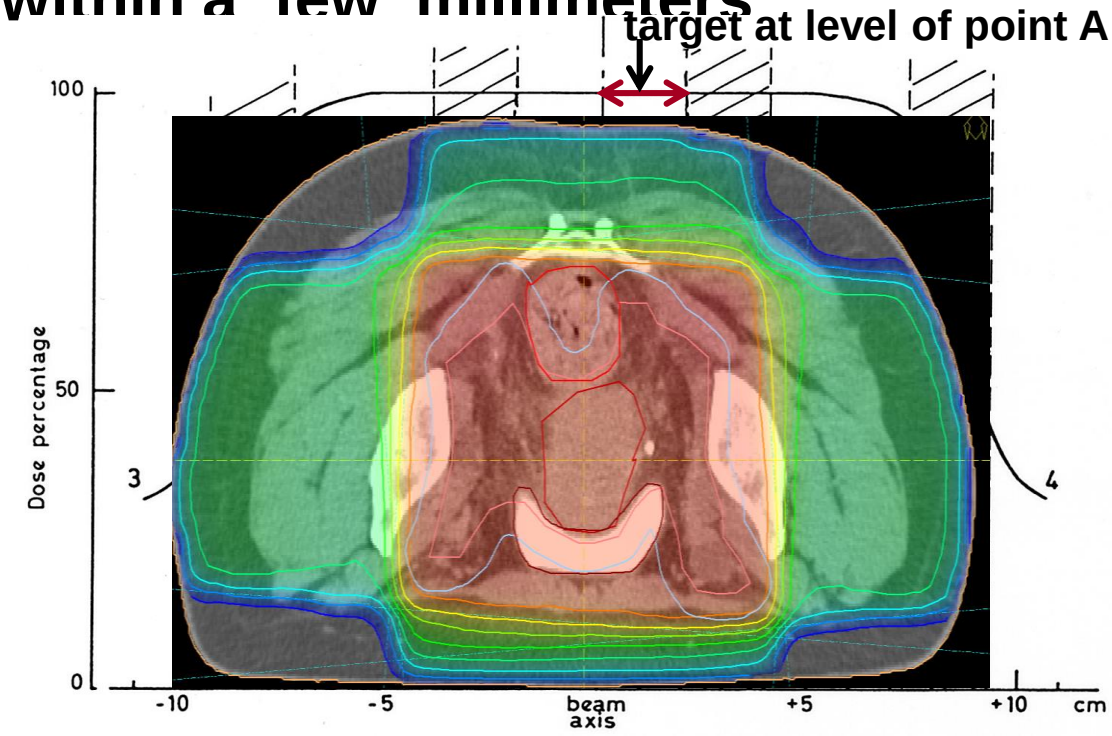
Volume Effect of Intracavitary Brachytherapy

- With intracavitary brachytherapy a very heterogenous dose is applied to target and organs at risk (steep dose gradient)
- significant change in dose within a few millimeters



taken from GEC ESTRO Handbook of Brachytherapy

Standard dose distribution with a tandem-ring applicator



taken from ICRU Report 38

Variation of dose along the lateral axis of EBRT (full line) vs. intracavitary BT (dotted line)

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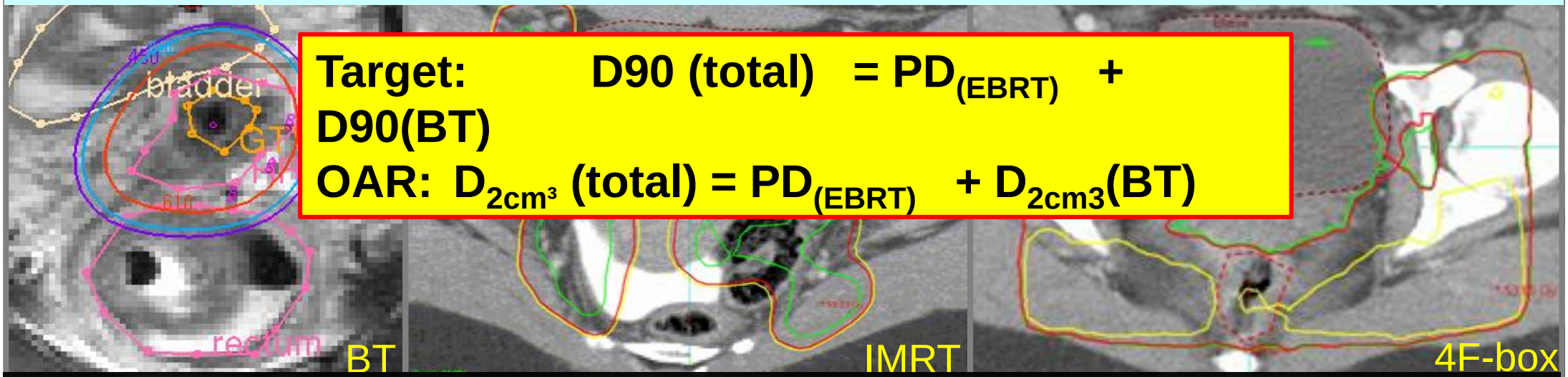
Compare the Position of the Most Exposed D_{xcc} Areas in EBRT and BT



Target: D90 (total) = $PD_{(EBRT)}$ + D90(BT)

OAR: D_{2cm^3} (total) = $PD_{(EBRT)}$ + D_{2cm3}(BT)

So it is deserving to compute for OARs in BT dose planning in this way: **they had received approximately the PD of the external beam treatment.**

- bladder: not the same volume receives the highest dose in IMRT than in 4F-box treatments
- rectum: sometimes the close same division
- sigmoid: always the close same

OAR	IMRT	4F	p
bladder	-1.6	1.4	0.03
rectum	2.9	2.6	>0.05
sigmoid	5.2	0.0	0.0001

The dose of ***BT*** in the most exposed 2 ccm in ***IMRT*** and ***4F*** plans [$D_{EBRT-BT}$ (% - PD)

Provided by G. Fröhlich, Budapest, Hungary

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Application of Biological Model to Clinical Situation

- **Assumptions:**
- **Time between fractions is long enough to enable full sublethal damage repair (min. ~ 8 - 12 hours)**
- **All investigated points and volumes from BT receive full EBRT dose**
- **In fractionated treatments the investigated points or volumes represent the same anatomical position throughout the whole treatment (worst case assumption)**
- **The same absorbed dose and time dose pattern of EBRT and BT produces the same biological effect**
- **ATTENTION: dose and dose rate inhomogeneity within BT volume**

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Limitations of the EQD2 model for BT

- **Chemotherapy is not taken into account**
- **Uncertainty increases for single fraction dose values >10Gy**
- **Only cell repair is considered**
- **α/β values and $T_{1/2}$ are under discussion (E.g. tumour type prostate, OAR etc.)**
- **dose and dose rate inhomogeneity within BT volume is not considered**
- **Overall uncertainty of the biological dose calculation (values) in the range of ~10% -> Reasonable rounding of values**

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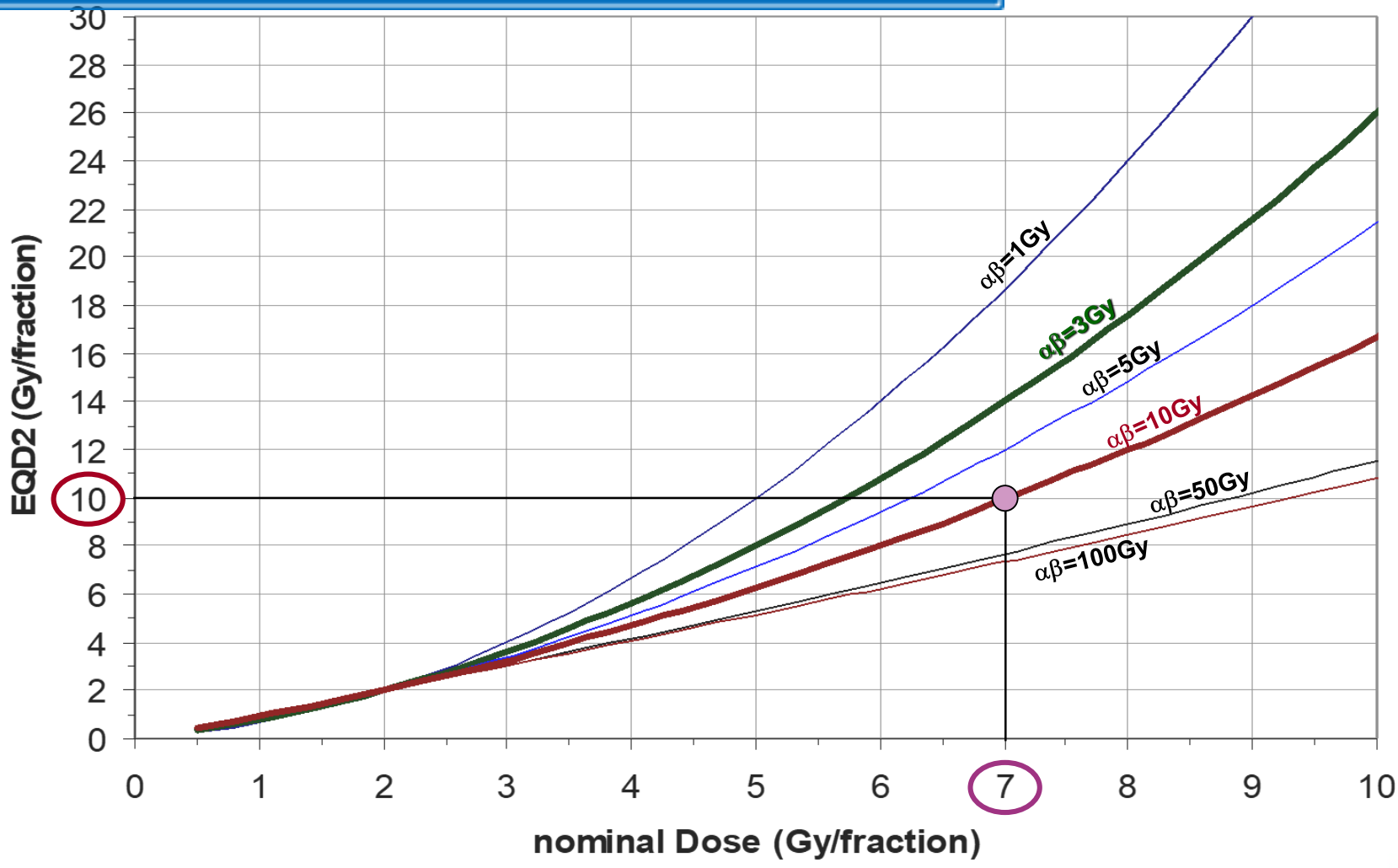
$$D_{isoE} = \frac{nd \cdot \left(1 + \frac{d}{(a/\beta)}\right)}{1 + \frac{2}{(\alpha/\beta)}}$$

From physical dose to EQD2 dose



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Medical aspects of treatment planning and dose constraints: focus on BT

Clinical evidence for dose-effects

ESTRO Teaching Course

Image guided radiotherapy and chemotherapy in gynaecological cancer - with a special focus on adaptive brachytherapy

Madrid September 2018

Richard Pötter

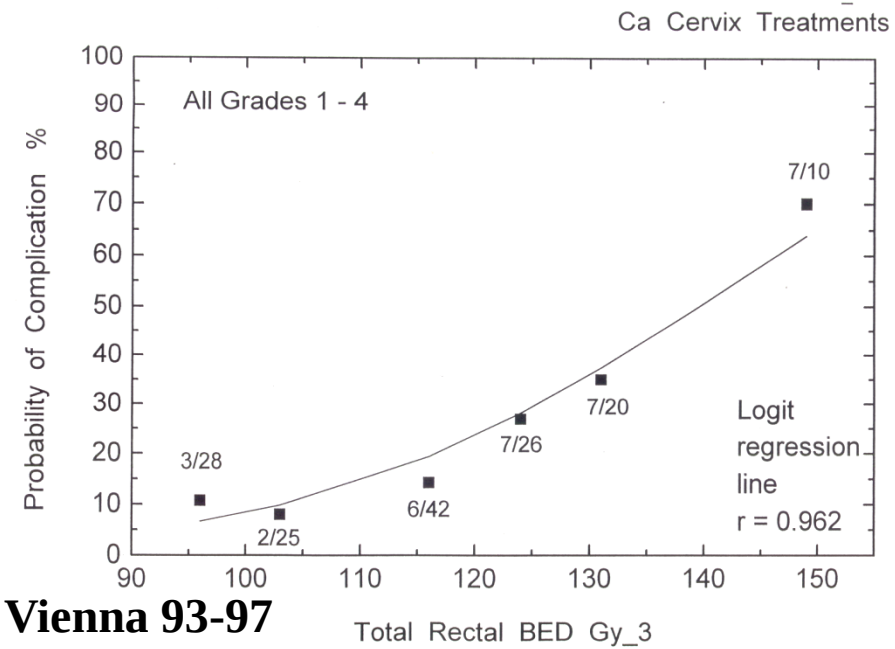
Kari Tanderup

DOSE EFFECT RELATIONSHIP POINT A

N=1499		Dose pt A	Pelvic failure
Stage IB and IIA	(<2 cm)	70-80 Gy	<10%
	(>2 cm)	up to 85-90 Gy	25-37%
Stage IIB		70 Gy	50%
	nonbulky	>80 Gy	20%
	bulky	>80 Gy	30%
Stage III unilateral		up to 70 Gy	50%
		>70 Gy	35%
Stage III bilateral/bulky		< 70 Gy	60%
		>70 Gy	50%
		>85 Gy	35%

„Refinements in brachytherapy techniques are necessary to improve the present results“ (Perez et al IJROBP 1998)

Dose Effect relationship for late rectum side effects based on points (ICRU reference points)

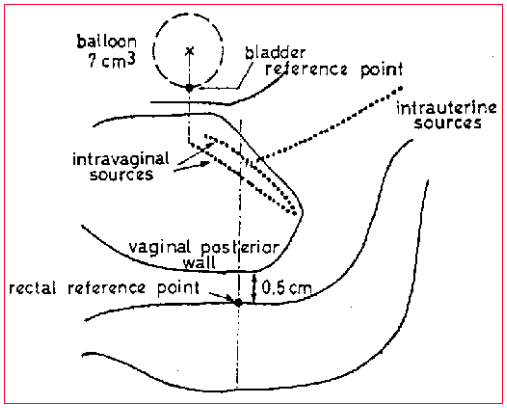


Vienna 93-97

J. Fowler, Knocke, Pötter 1998 unpublished

32 „events“ in 151 patients

Actuarial rate 3y: 24%



BED ~120-130 Gy_3 „cut-off level“ in recent experience

Iso-effective dose in 2Gy/fr ~ 70-80 Gy $_{\alpha\beta 3,2Gyfr}$

no clear dose effect relations bladder, sigmoid, vagina

Clinical Evidence in IGABT Cervix Cancer dose volume effects (dve)

Upcoming Evidence

- Mono-instititutional cohorts (ongoing, publicat. since 2007)
- Multi-center cohorts with retrospective evaluation
  RetroEMBRACE (publications since 2016)
- Prospective Trials
  STIC: comparative 2D vs. 3D (published 2012)
  EMBRACE I: observational, 08/2008 - 12/2015
  EMBRACE II: interventional, from 03/2016

Mono-institutional cohorts dose volume effects (retrospective)

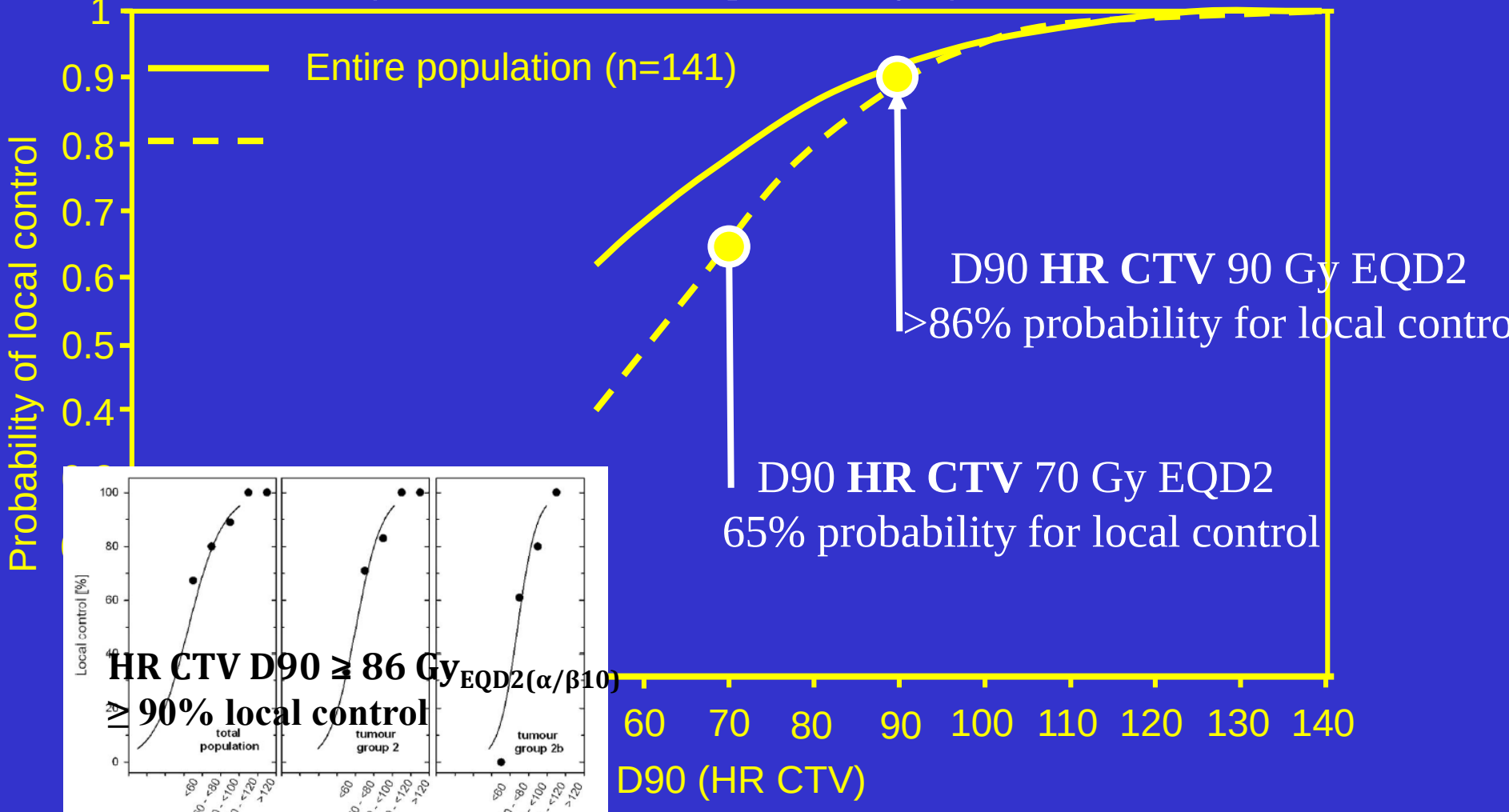
- **Vienna** (Dimopoulos 2008, 2010, Georg 2009,2011(Pötter 2007, 2011))
- **Seoul** (Kim et al. 2008)
- **Paris** (Mazeron 2014, 2015 (Castelnaud-Marchand 2015, Haie-Meder))
- **Aarhus** (Lindegaard, Tanderup 2014)
- **Leuven** (Ribeiro, Limbergen 2016)

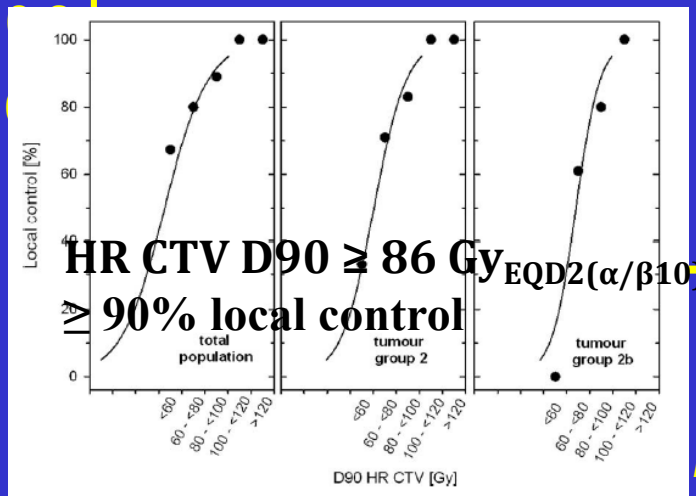
Linking DVH-parameters to clinical outcome

HR CTV/Tumour

Analysis (n=141, FIGO: IB-IVA, median follow-up=51 months)

D90 for the HR-CTV and probability of local control



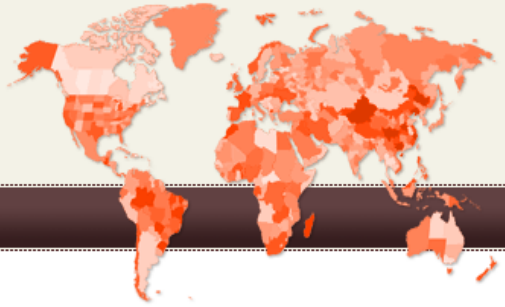


HR CTV D90 ≥ 86 Gy$_{EQD2(\alpha/\beta10)}$
≥ 90% local control

Dimopoulos et al., R&O 2010 *Dimopoulos et al. IJROBP 2008*

RETRO EMBRACE

An intErnational study on MRI-guided BRachytherapy in locally Advanced CErvical cancer



About Retro-Embrace | Contacts | Login

- **Web-based database with a retrospective multicentre collection of data on 3D RT plus IGABT in cervical cancer**
- **780 pts**
- **Eligibility criteria:**
  - **Diagnosis of cervical cancer and treatment with curative intent by IGABT**
  - **Reporting according to GEC ESTRO recommendations**

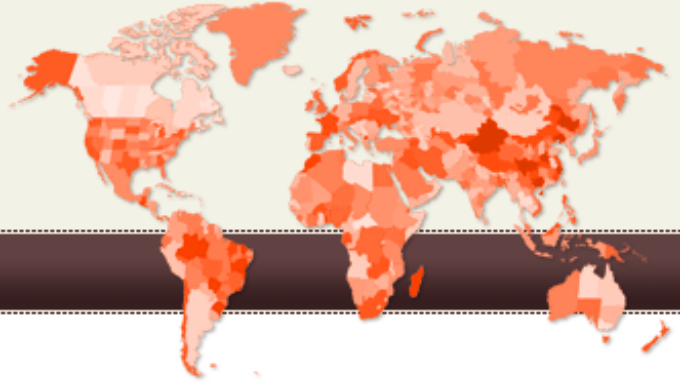
Overall outcome published by Sturdza et al. Radioth Oncol 2016

VARIAN medical systems | A partner for life

Nucletron Improving patient care

EMBRACE

An intErnational study
on MRI-guided BRachytherapy
in locally Advanced CErvical cancer



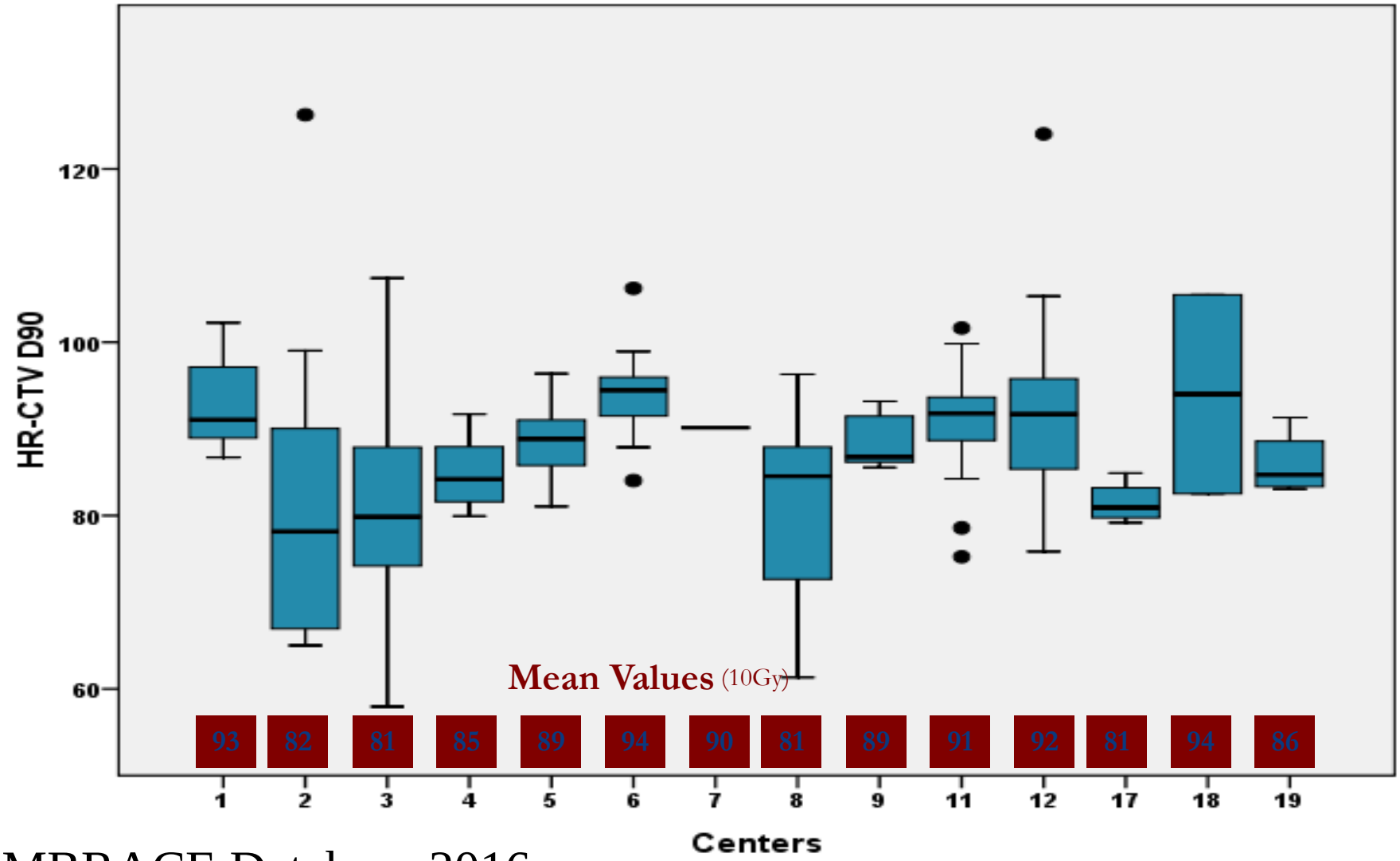
About Embrace | Contacts | Participation | Login

- **EMBRACE - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer**
- **A prospective observational multi-centre trial**
- **Major endpoint: local control;**
- **multiple hypthese on dose volume effects**
- **Enrollment of patients 7/2008-12/2015, 1419 pts accrued**

VARIAN medical systems | A partner for life

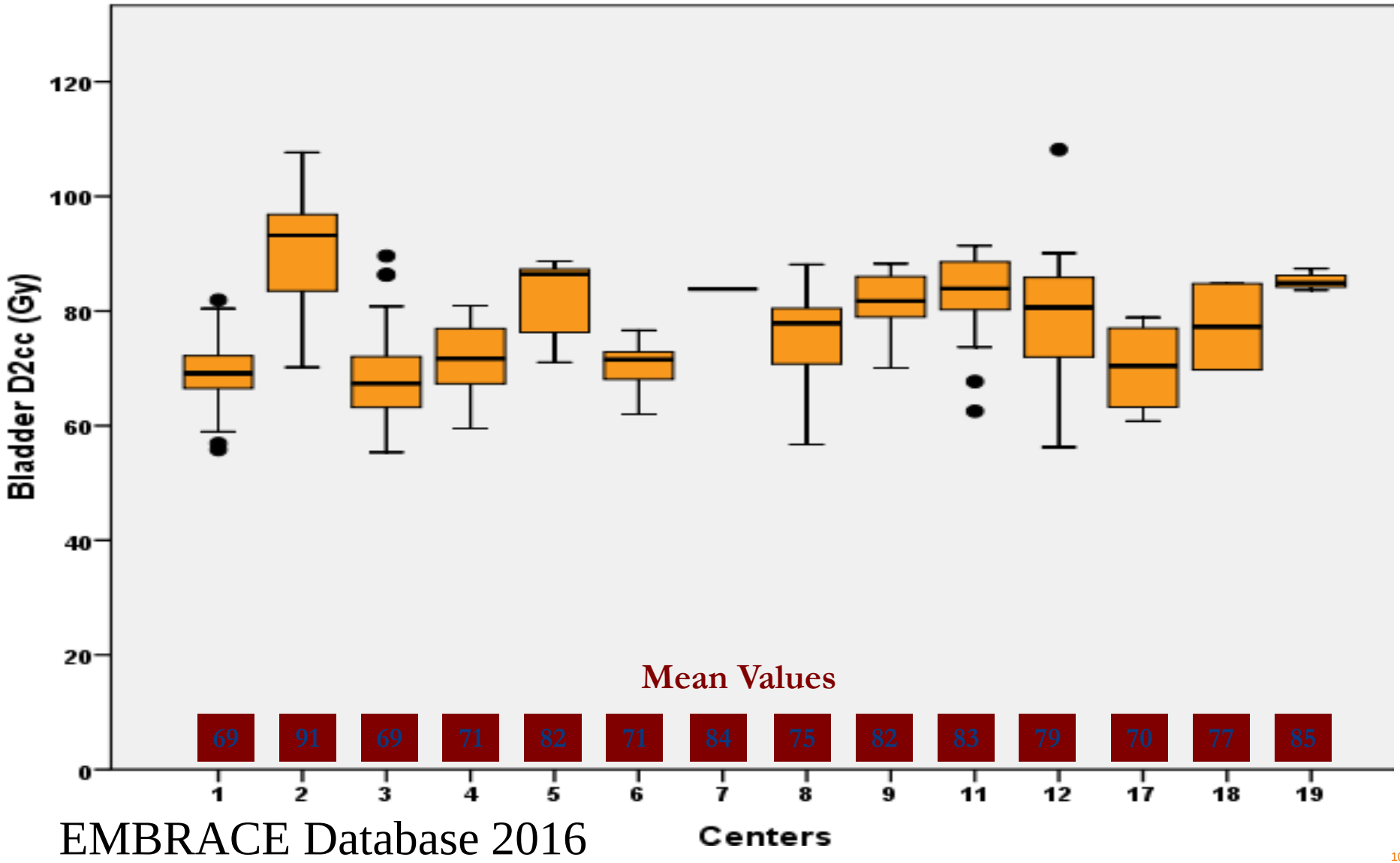
Nucletron Improving patient care

Heterogeneity of dose prescription: HRCTV D90



EMBRACE Database 2016

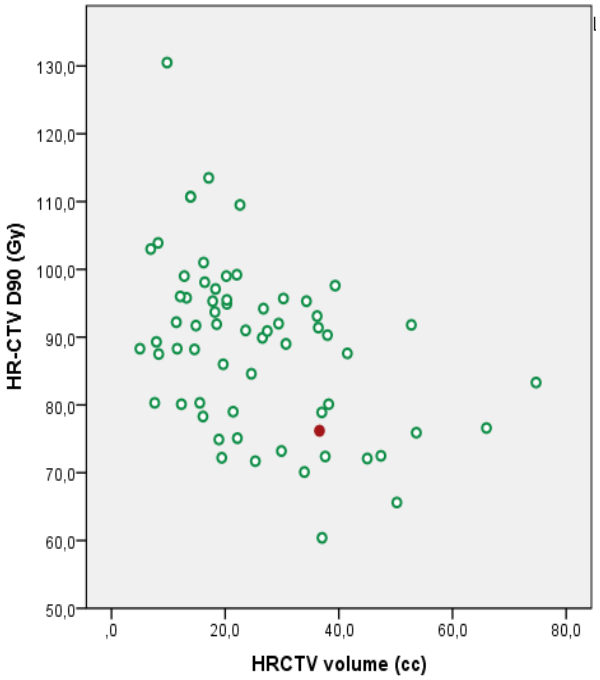
Heterogeneity of dose prescription: Bladder D2cc



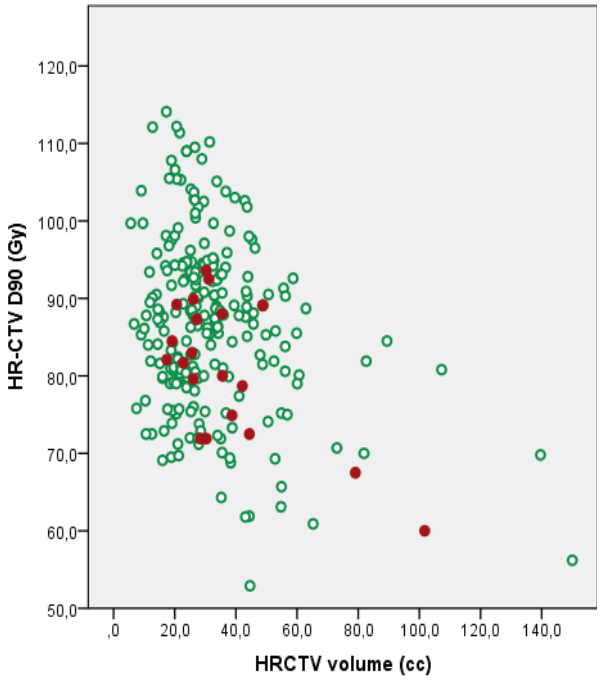
EMBRACE Database 2016

Recurrences according to dose and volume

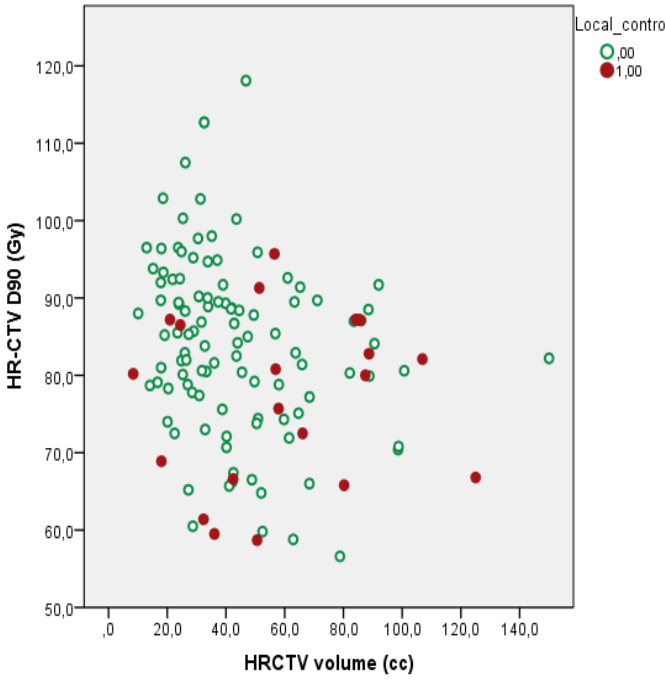
Stage I



Stage II



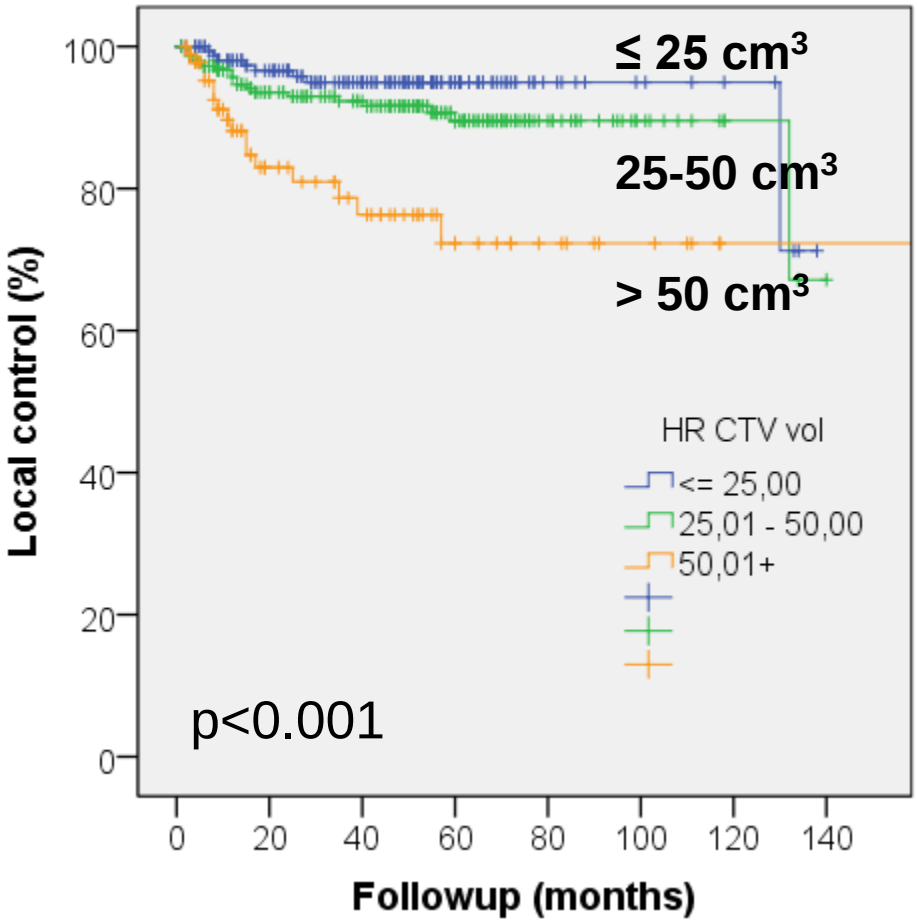
Stage III+IV



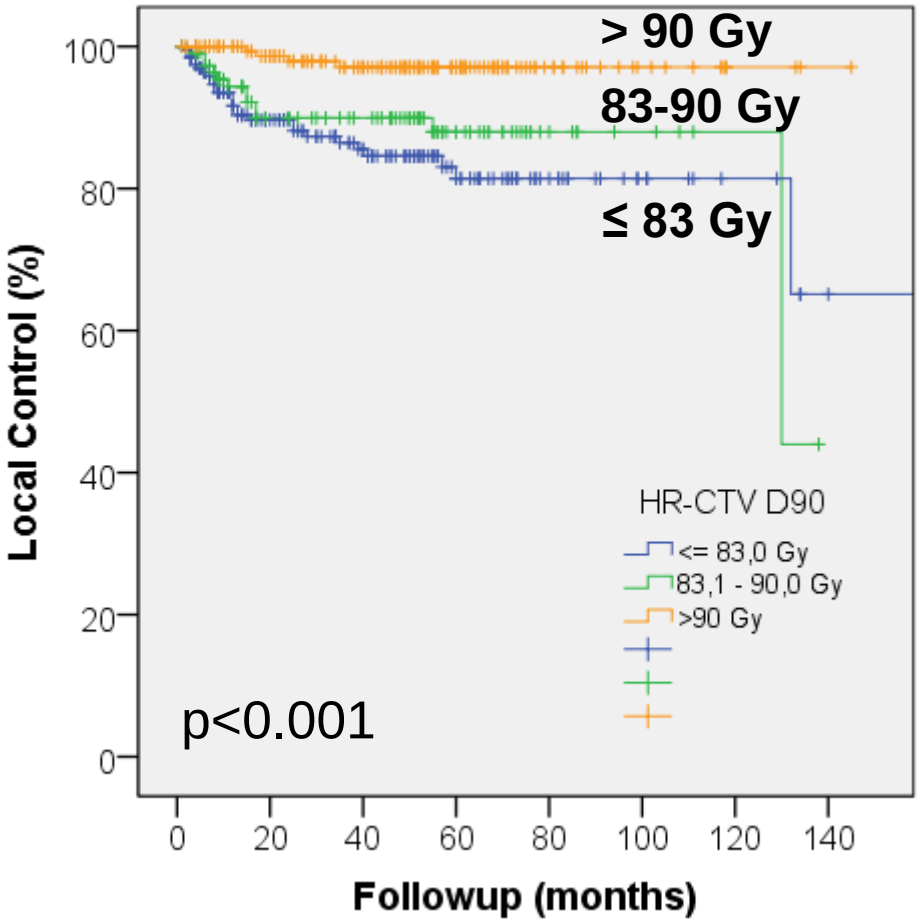
Tanderup et al. Radiotherapy and Oncology 2016

Actuarial local control: univariate analysis separate for HR CTV volume and dose

CTV_{HR} volume



CTV_{HR} dose



Tanderup et al 2015

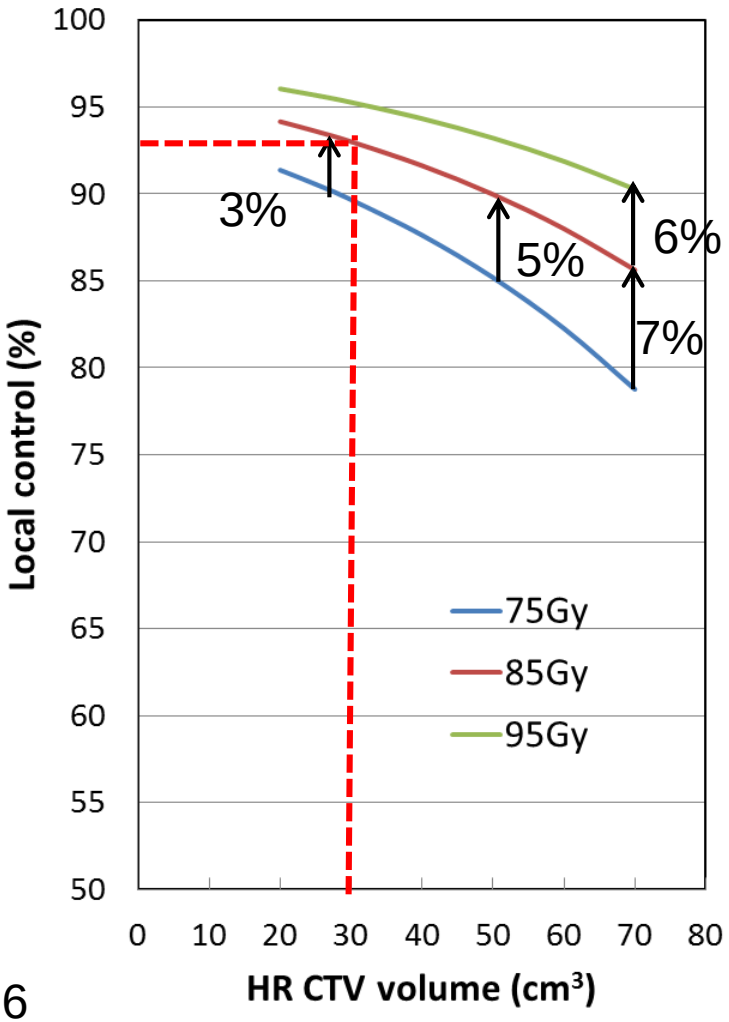
Dose, volume, and time effect

Effect of dose, volume and time:

Dose: 10Gy → 5% LC
Time: 7 days ~ 5Gy
Volume $10cm^3$ ~ 5Gy

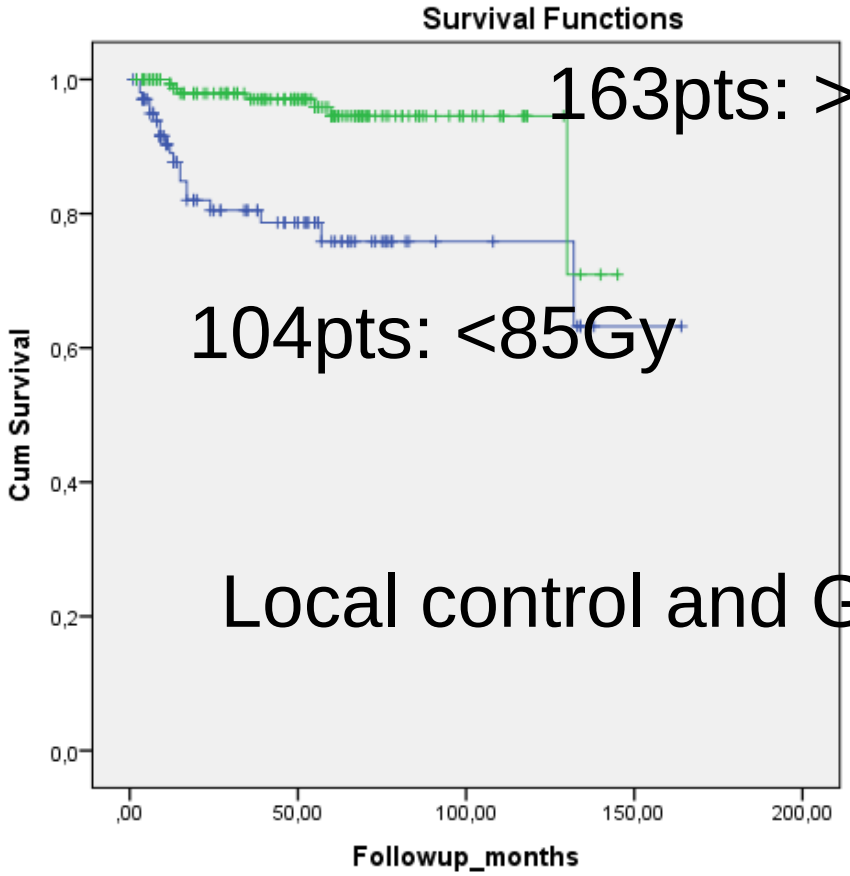
85Gy for $30cm^3$ CTV_{HR}: 93% LC

Local control at 3 years



Tanderup et al, Radiotherapy and Oncology 2016

Dose volume response for GTV

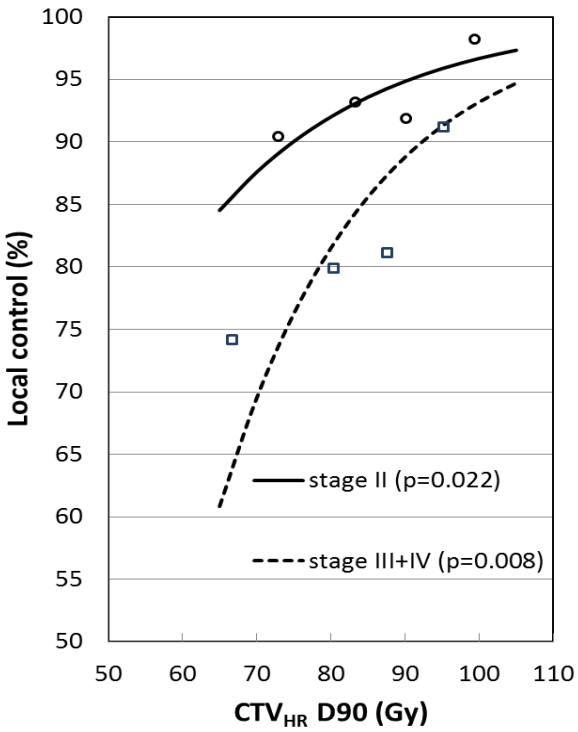


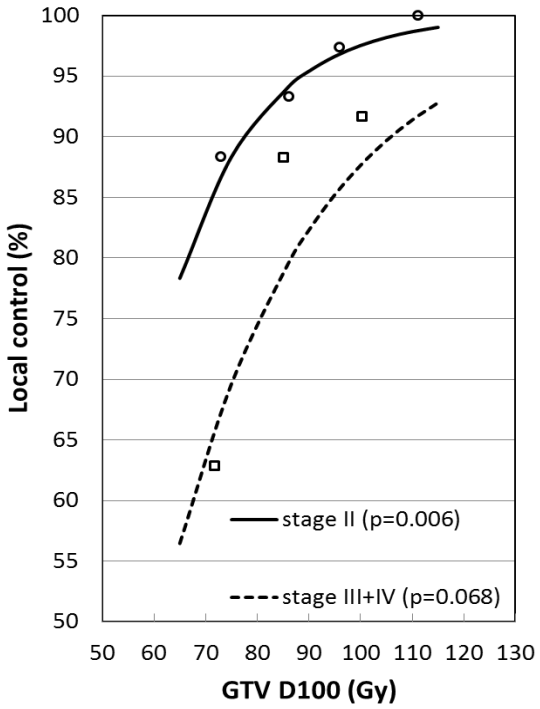
Local control and GTV dose

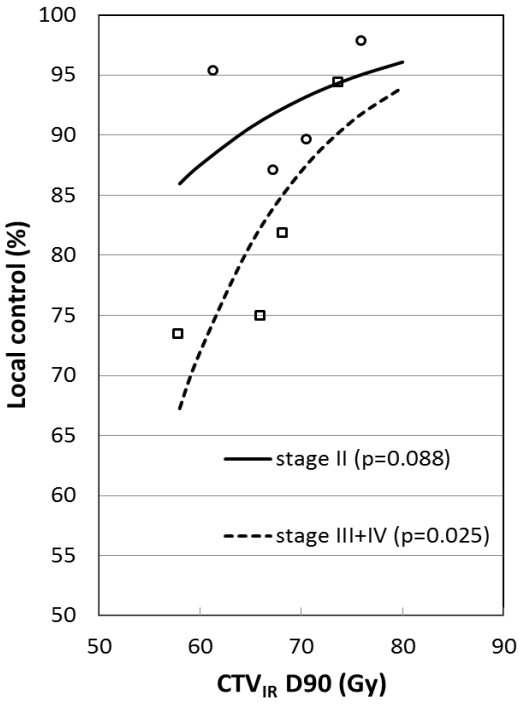
Tanderup 2015
Preparation for EMBRACE II

Dose effect GTV, CTV_{HR} and CTV_{IR}

Stage-related analysis

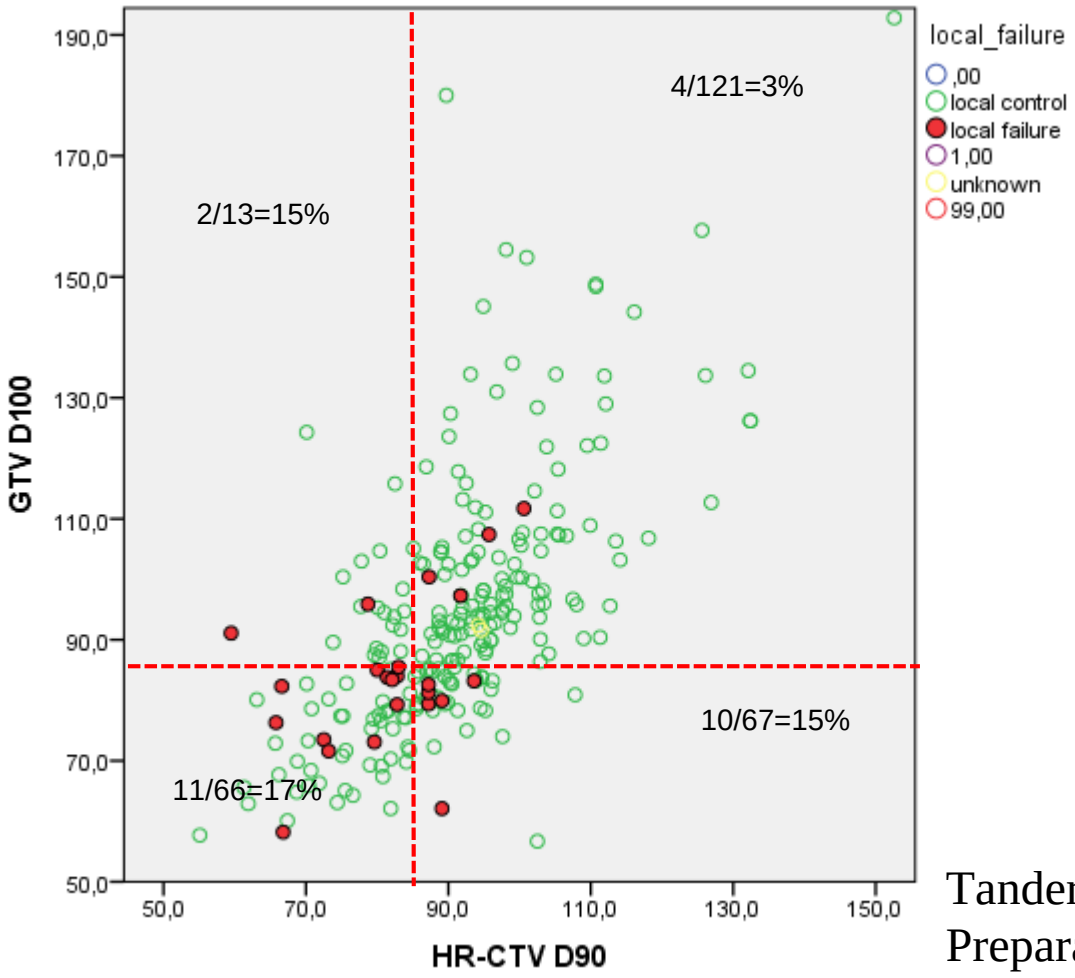






Tanderup et al. Radiotherapy and Oncology 2016

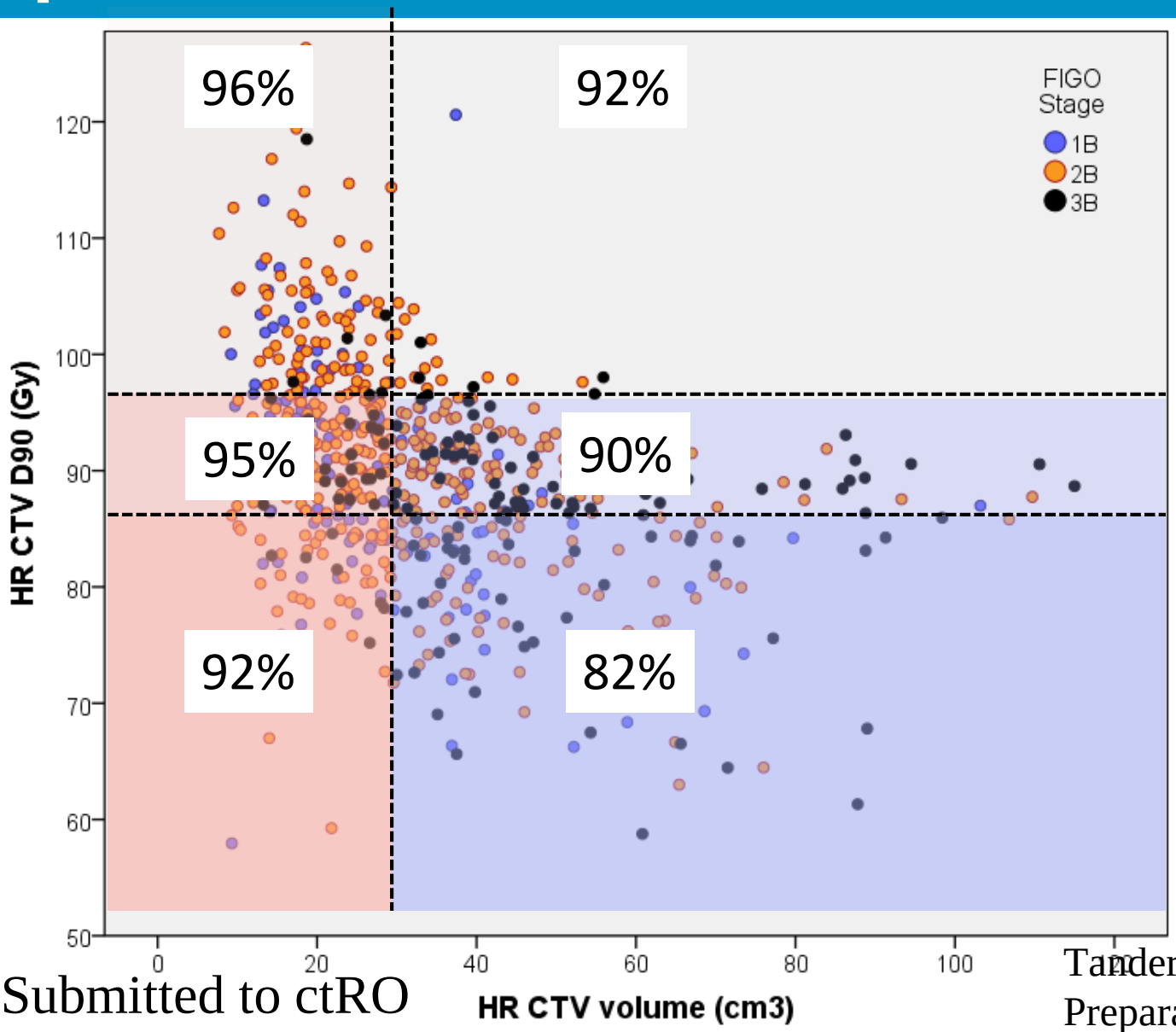
Combined constraints for GTV and CTV_{HR}



Tanderup 2015
Preparation for EMBRACE II

Practice in EMBRACE I and predicted local control from RetroEMBRACE

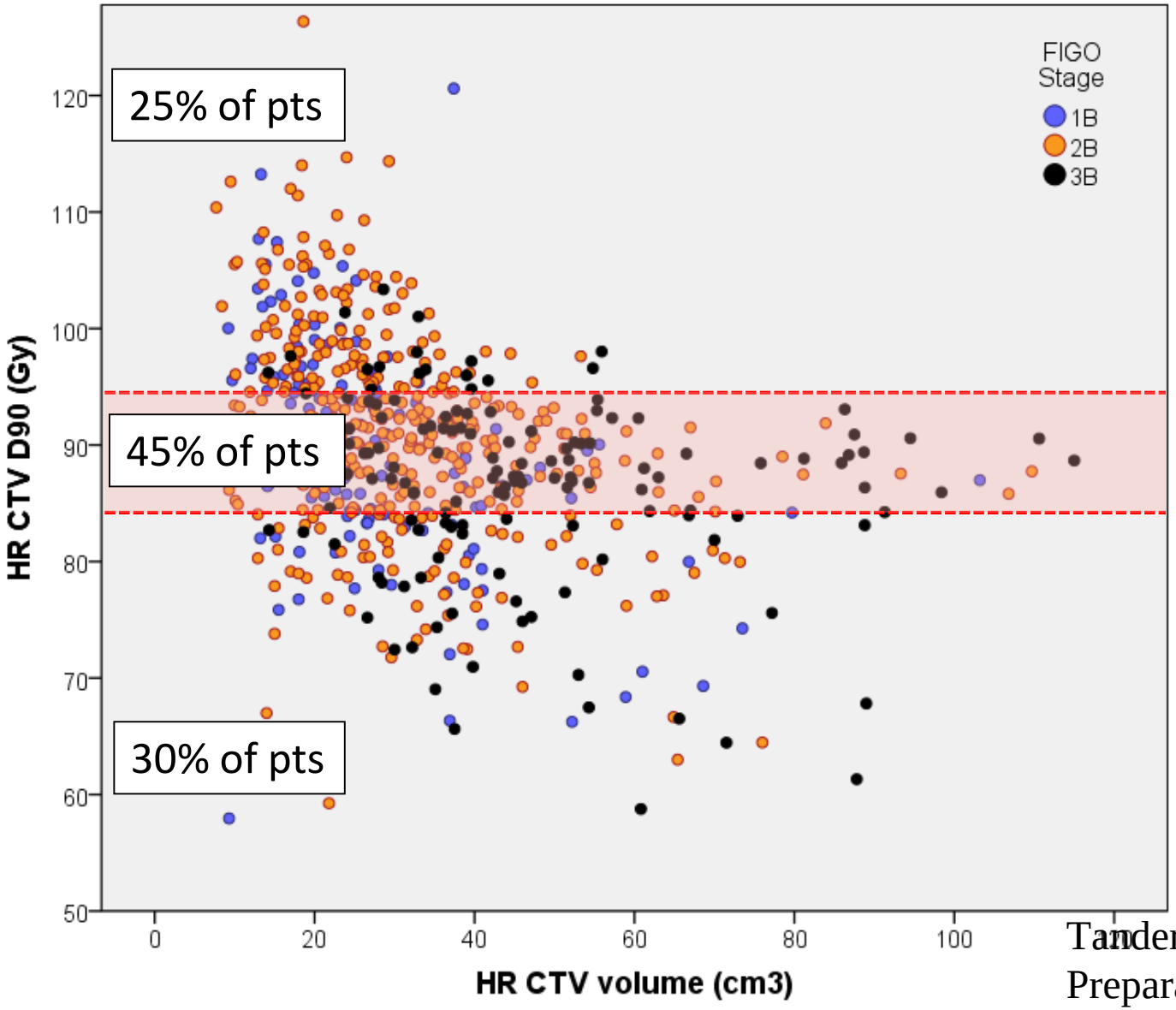
769 pts EMBRACE



Submitted to ctRO

Tanderup 2015
Preparation for EMBRACE II

EMBRACE I practice

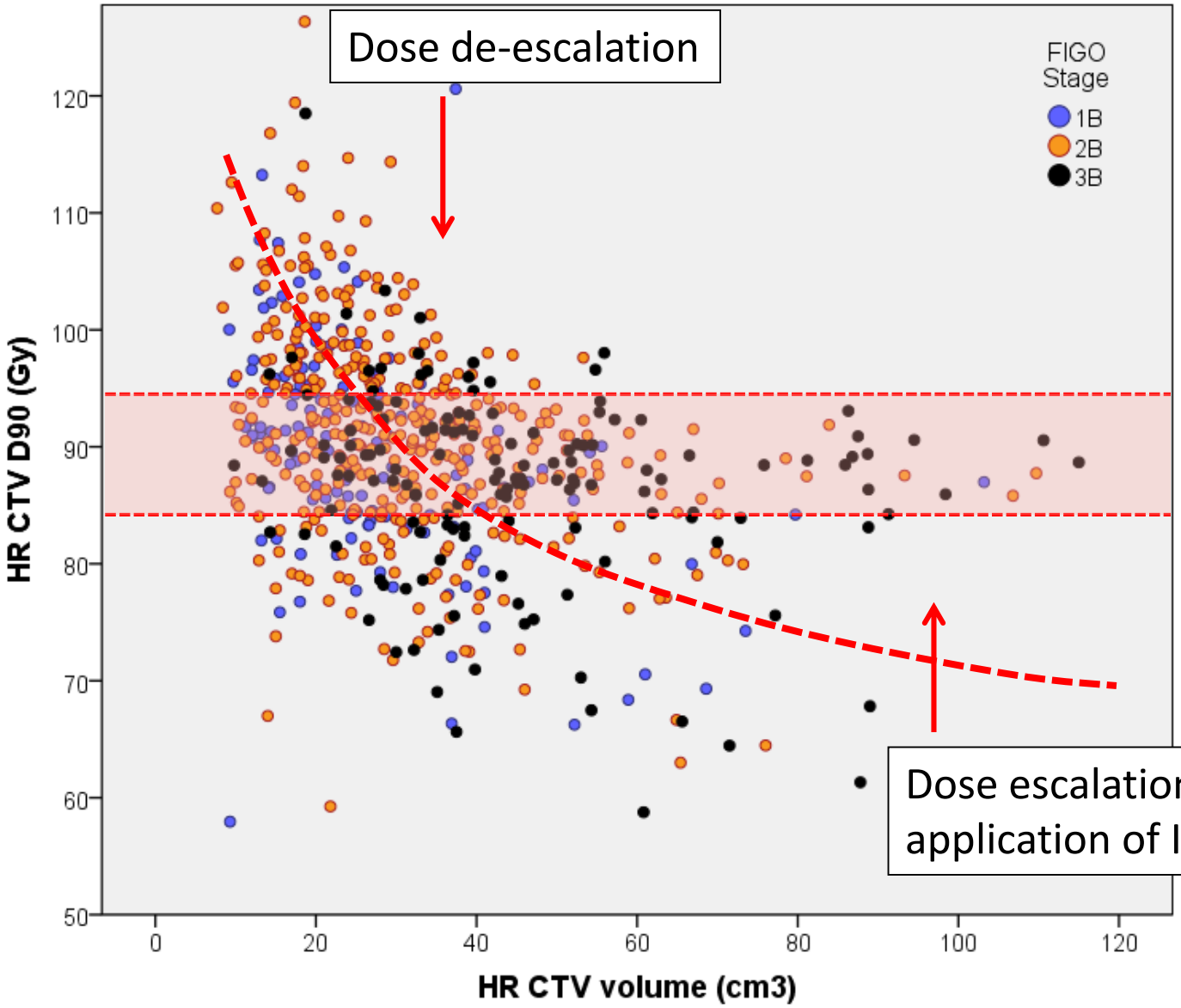


769 pts EMBRACE

HR CTV D90 85-95Gy

Tanderup 2015
Preparation for EMBRACE II

EMBRACE II dose prescription



769 pts EMBRACE

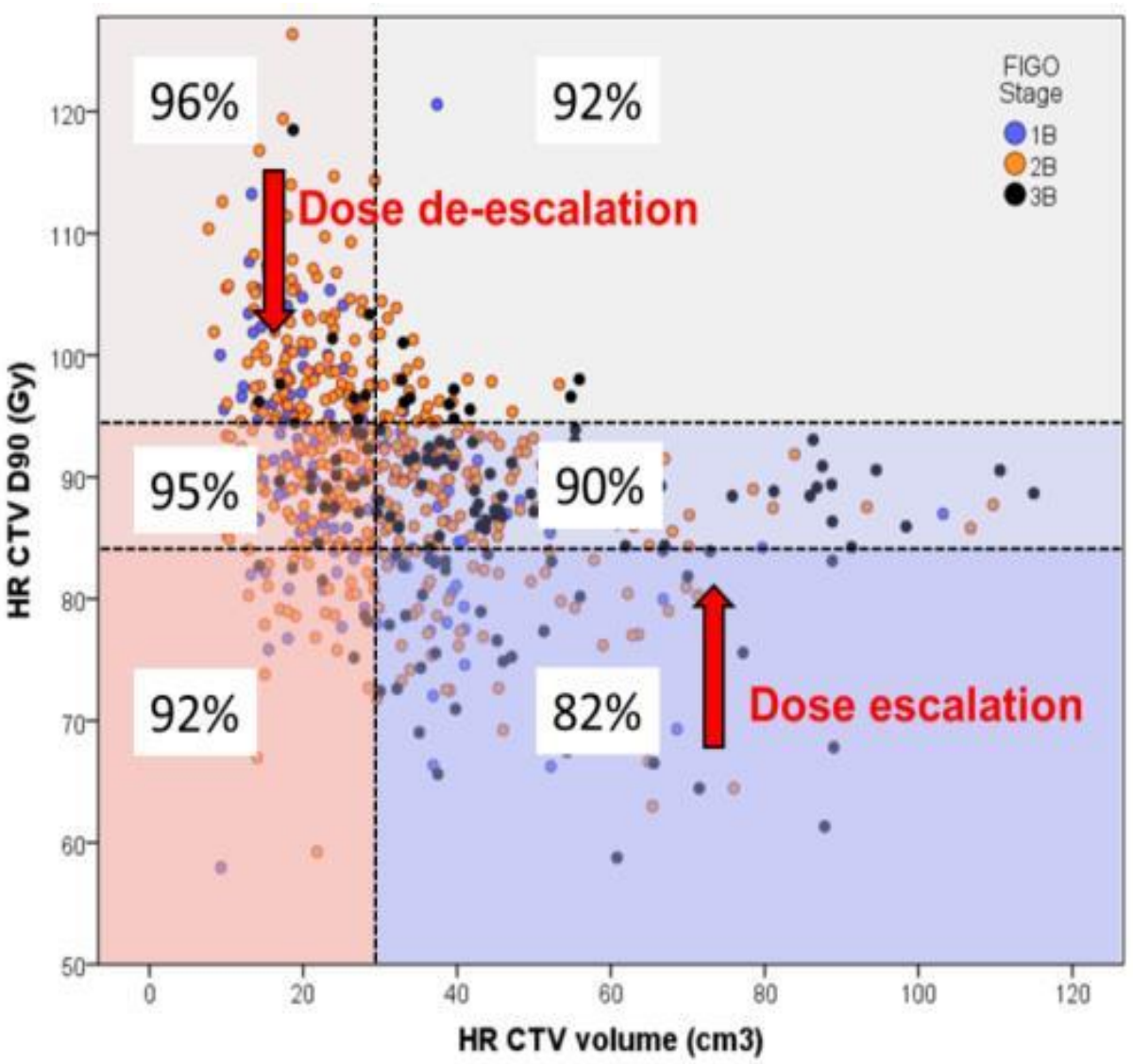
HR CTV D90 85-95Gy

Tanderup 2015

Beach boy approach – Barcelona 2013

EMBRACE II Planning AIMS and Limits for Prescription

OTT < 50 Days	D90 CTV_{HR} $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy
Limits for Prescribed Dose	> 85 Gy

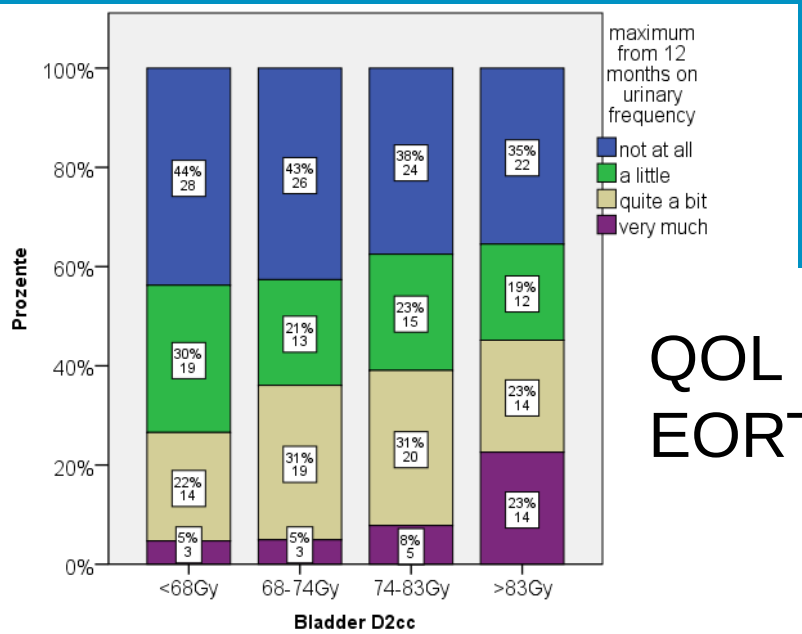


EMBRACE II (2016) cervix cancer: D90, 98 CTV_{HR}, Pt A protocol for planning aims and dose prescription

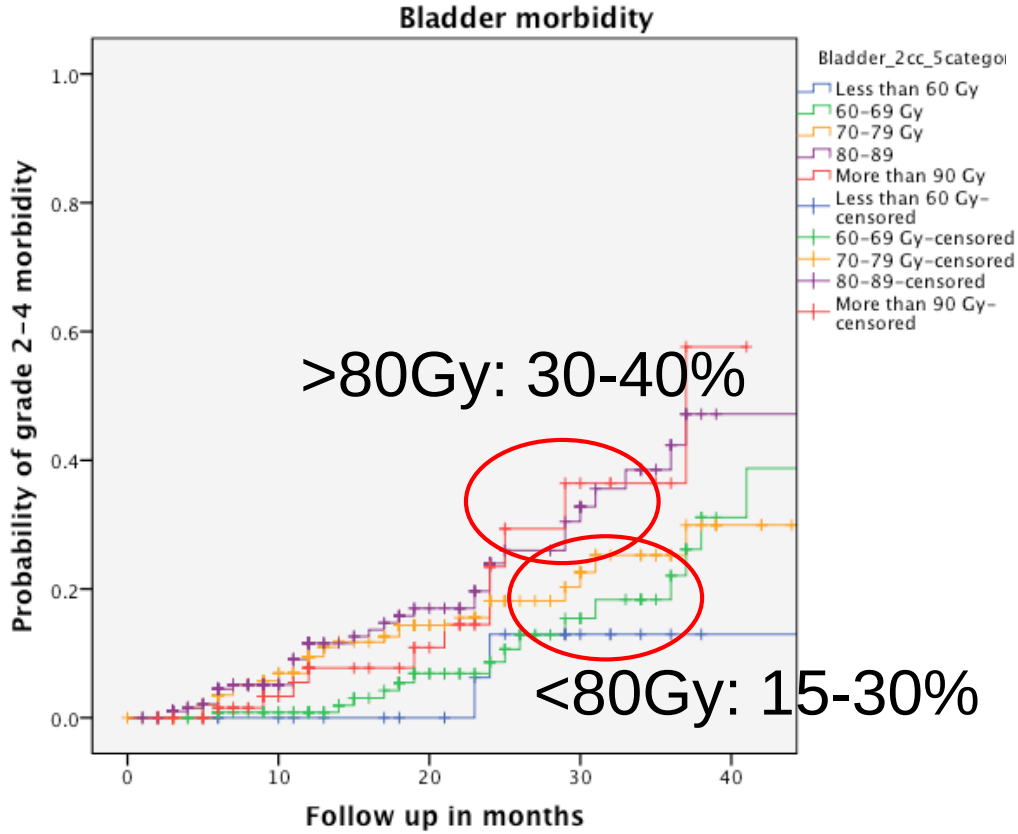
	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV $EQD2_{10}$	D98 CTV_{IR} $EQD2_{10}$	Point A $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy	> 75 Gy	>95 Gy	> 60 Gy	> 65 Gy
Limits for Prescribed Dose	> 85 Gy	-	>90 Gy	-	-

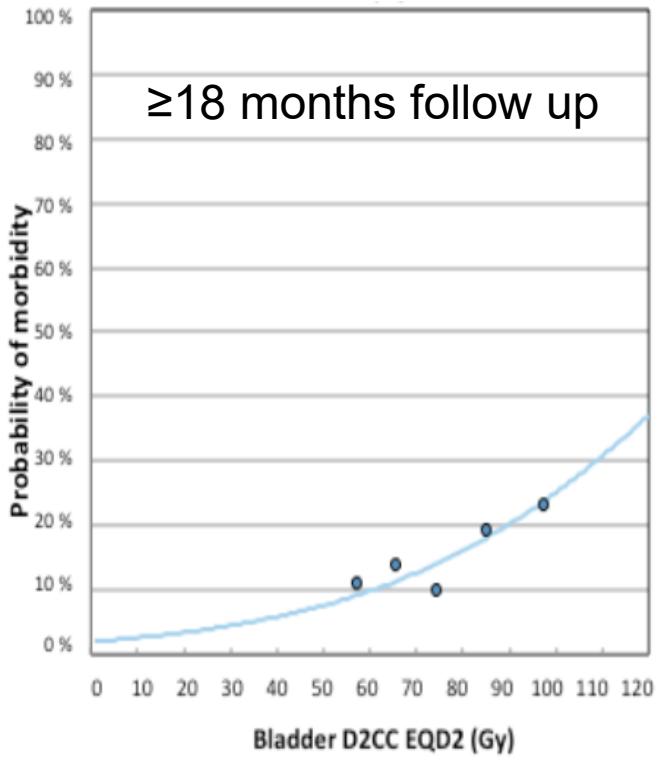
Bladder D_{2cm3}

- **EMBRACE CTCAE**
- **All endpoints except ureter stenosis G≥2**



QOL EORTC

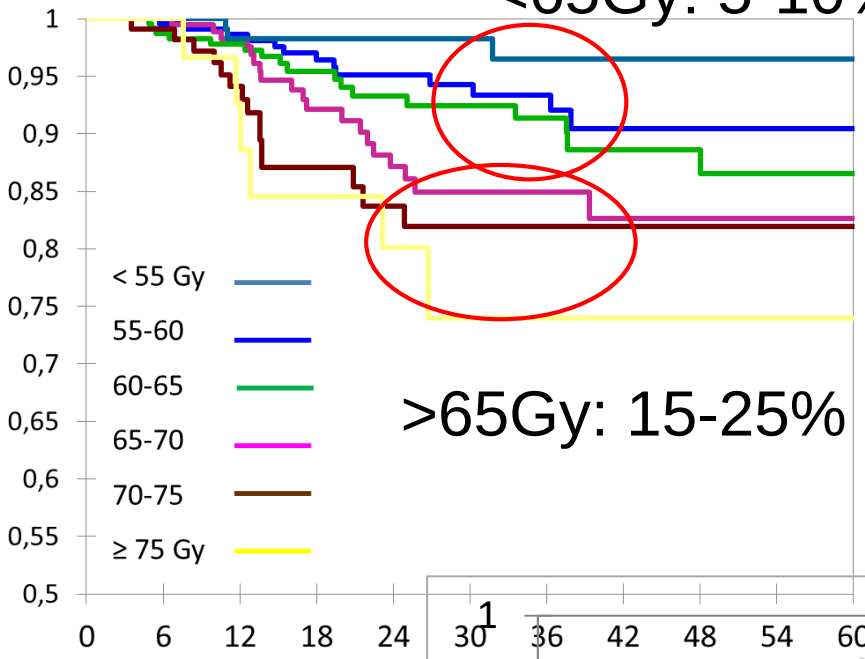




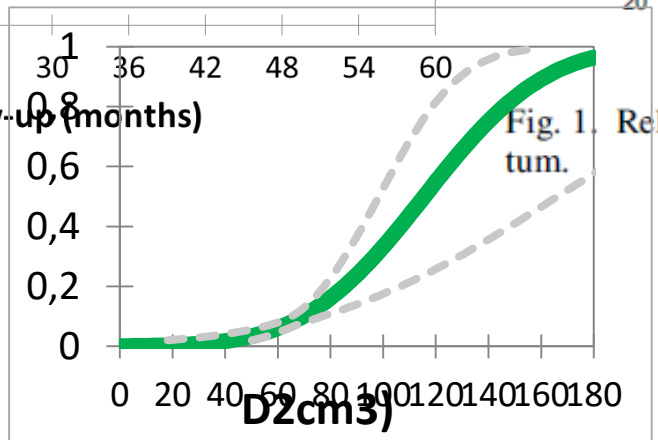
Fokdal et al work in progress

Rectal dose volume effects ($2cm^3$)

≥G2 rectal morbidity
(EMBRACE cohort, n=960)



Mazeron et al.,
RadOnc 2016



≥G2 rectal morbidity (bleeding)
(Vienna cohort, n=145)

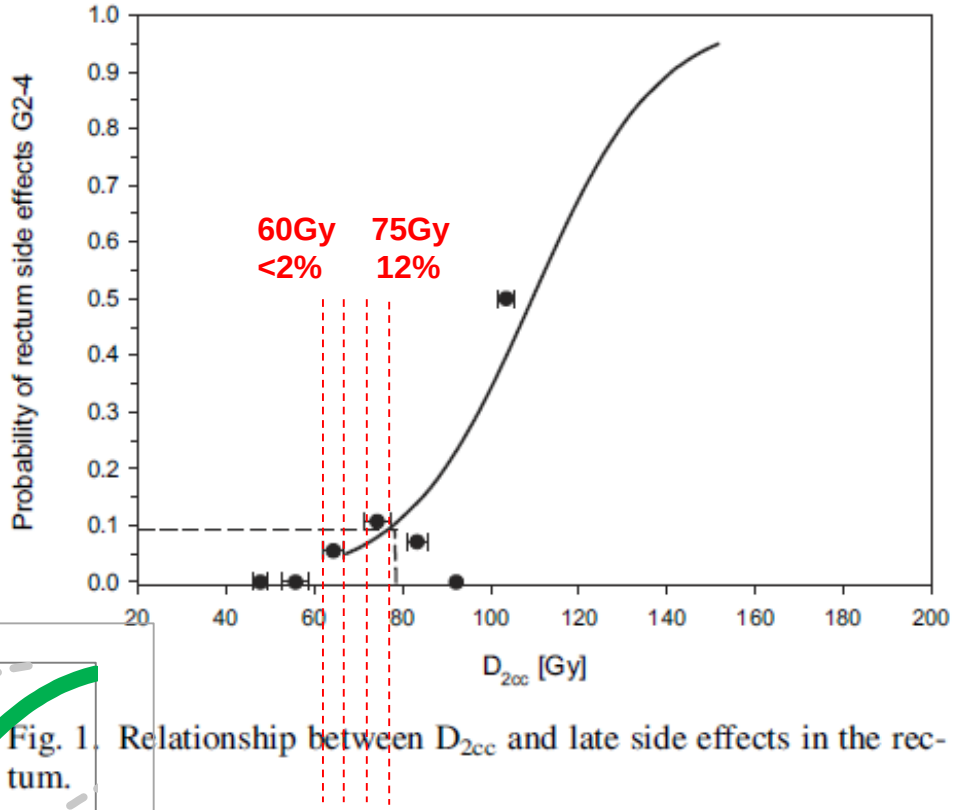
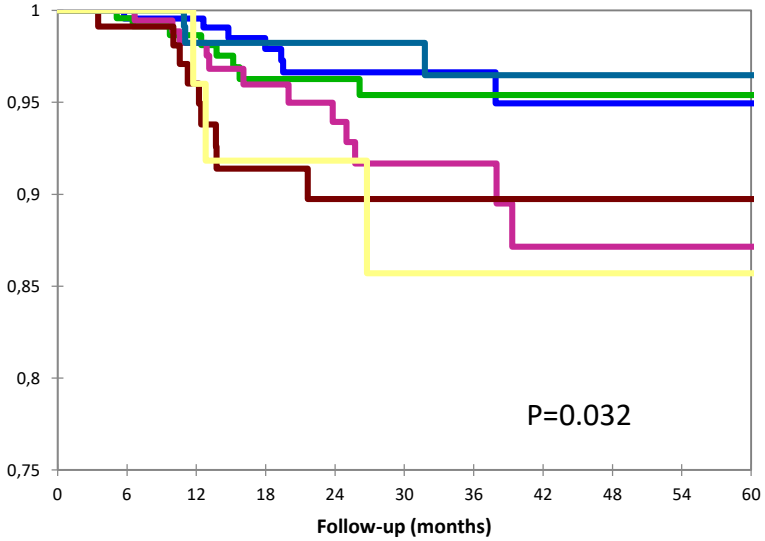


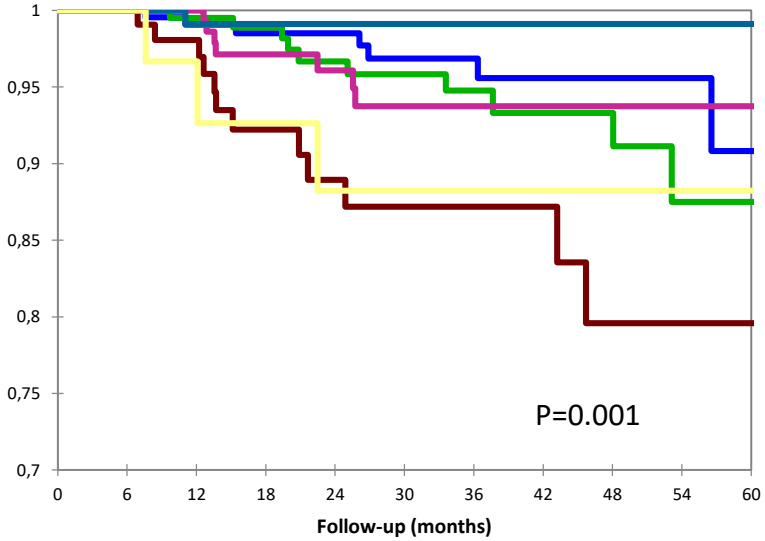
Fig. 1. Relationship between D_{2cc} and late side effects in the rectum.

P. Georg et al.,
IJROBP 2011 (Vienna cohort)

Proctitis



Bleeding



dose effects for different endpoints for rectal morbidity EMBRACE (n=960)

< 55 Gy

55-60

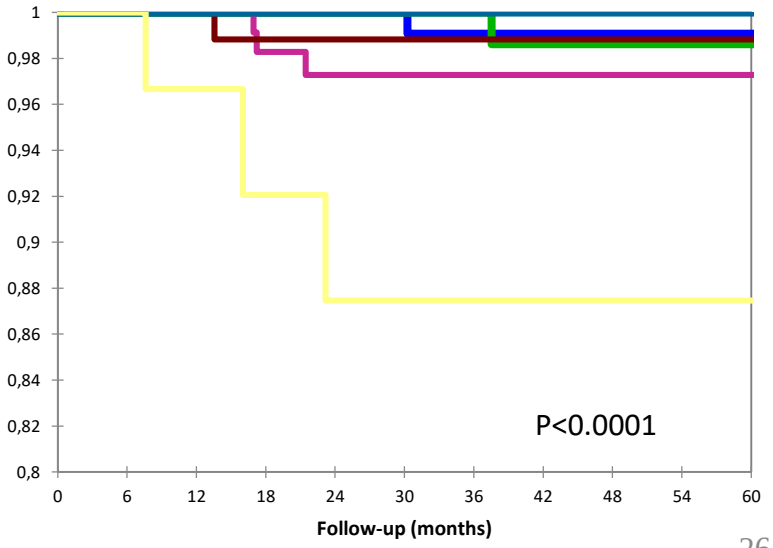
60-65

65-70

70-75

≥ 75 Gy

Fistula

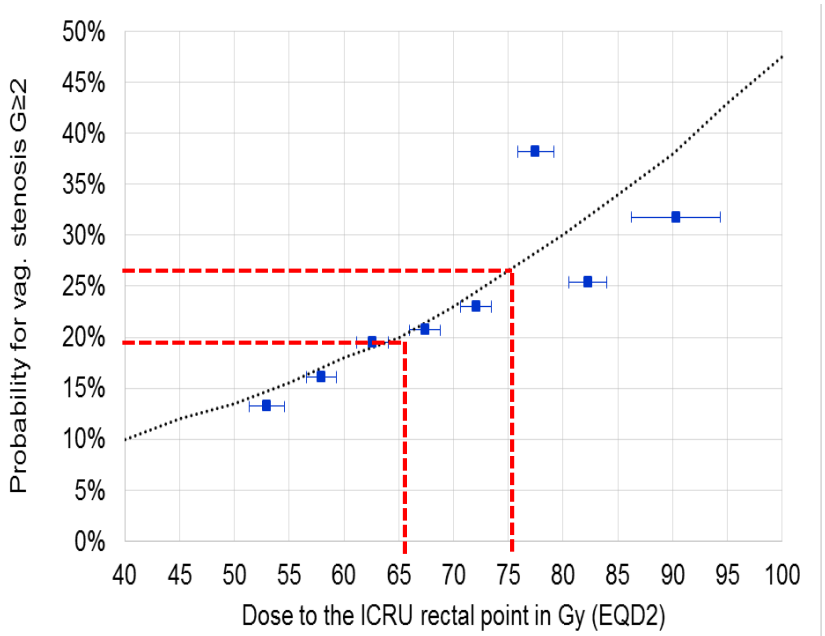


Mazeron et al, RadiothOncol 2016

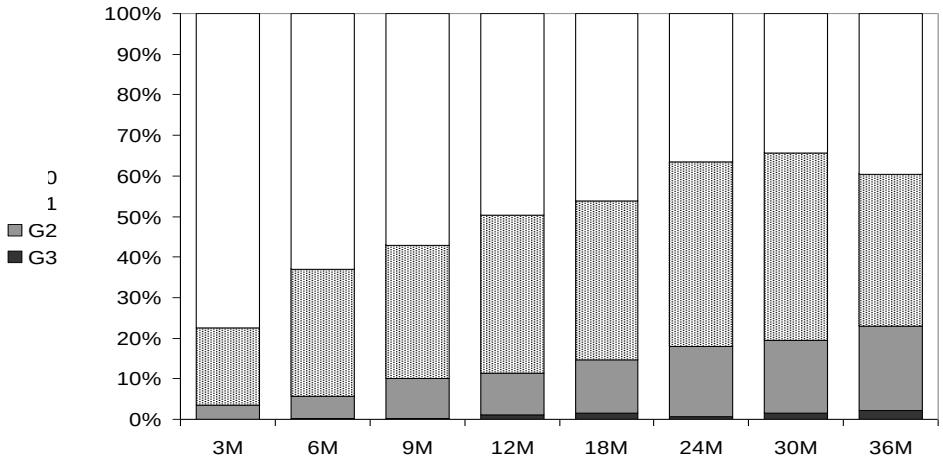
Vaginal stenosis and ICRU recto-vaginal point (630 pts)

Cox-regression, 2 year actuarial risk of ≥G2 stenosis

- Significant impact of EBRT dose (45Gy versus 50Gy)
- Significant impact of BT ICRU recto-vaginal dose



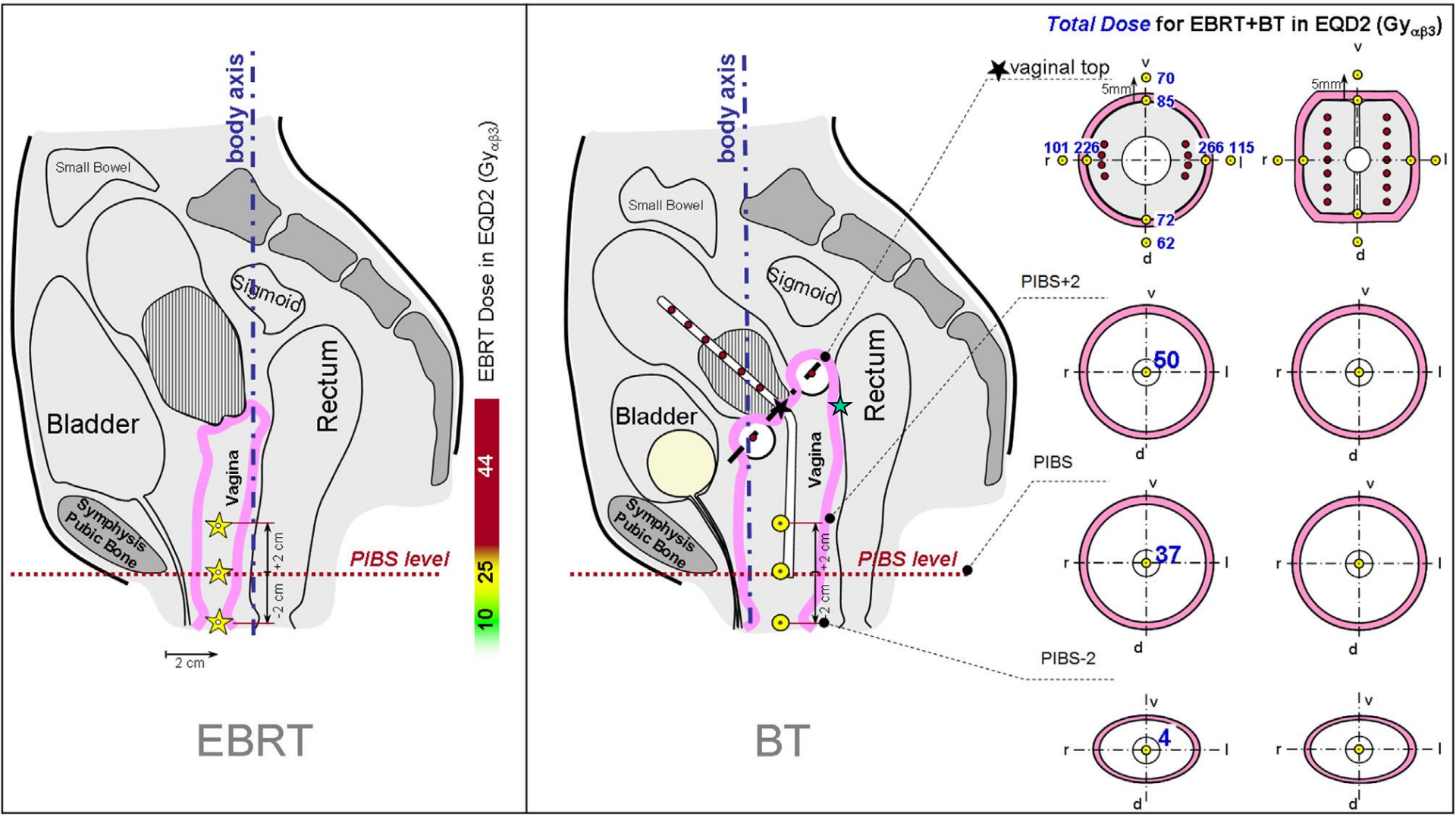
Prevalence vaginal stenosis



Kirchheiner K et al.Manifestation pattern of early-late vaginal morbidity. IJROBP 2014 May 1;89(1):88-95

K Kirchheiner et al, EMBRACE data MUW/AUH, RadiothOncol 2016

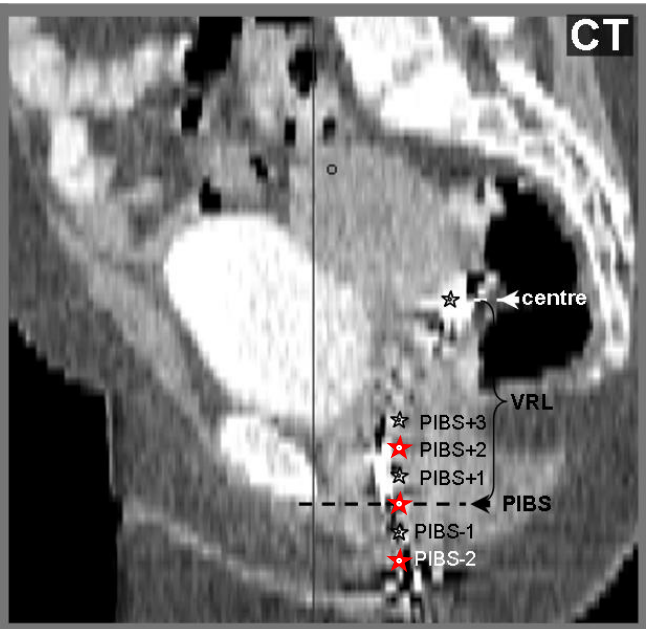
Vaginal Dose Points: PIBS, PIBS+2, PIBS-2: no clinical evidence (too early): contribution from BT and EBRT

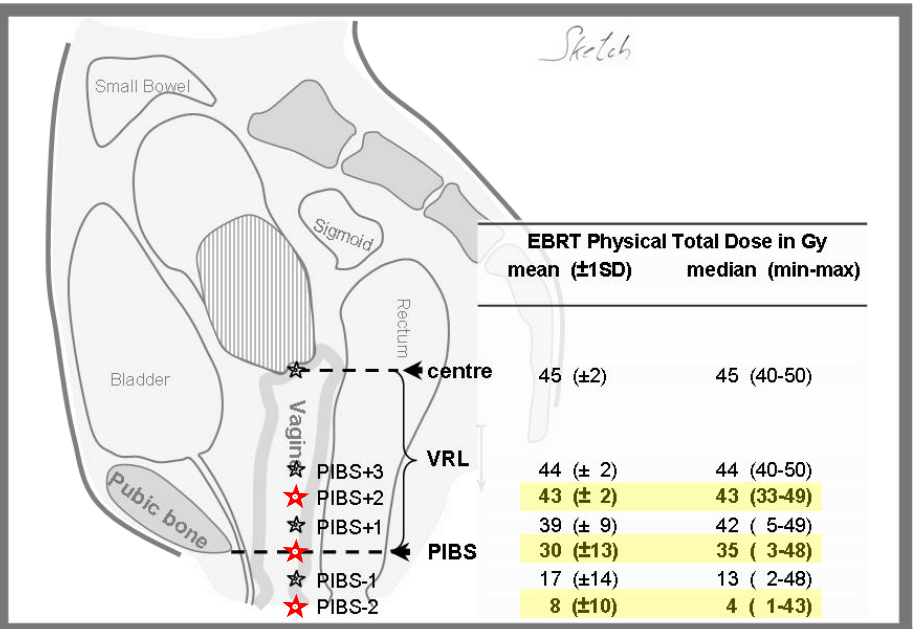


Westerveld et al. RadiothOncol 2013

Vaginal Dose Points (dose values based on Vienna cohort, n=59)

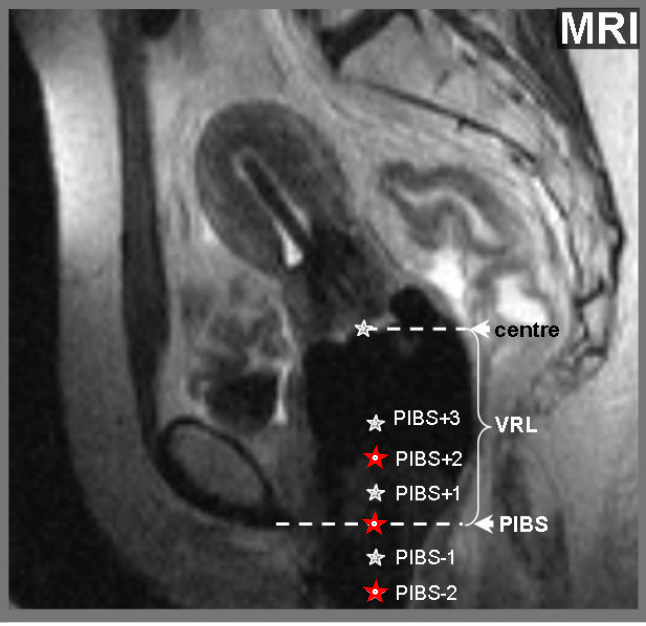
EBRT

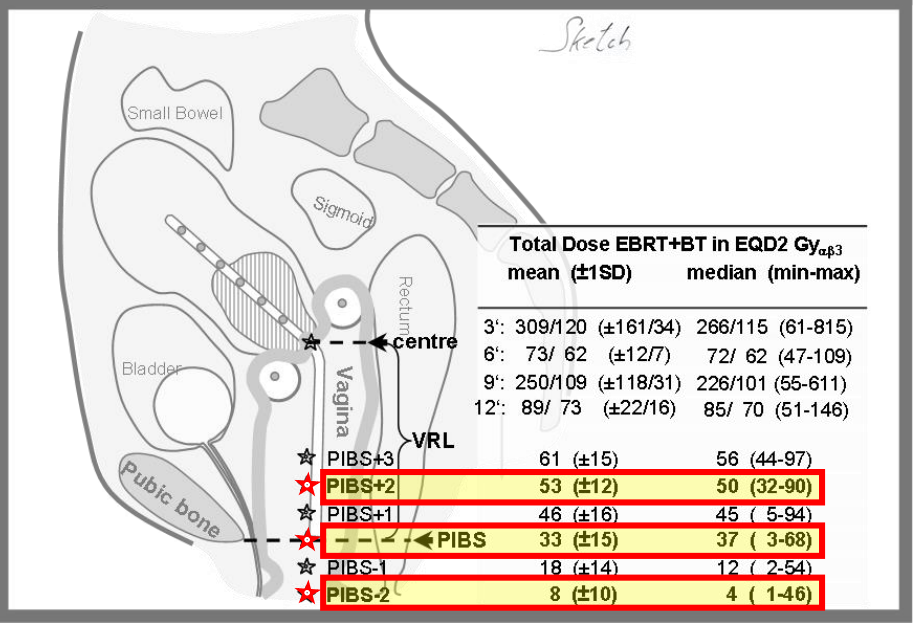




EBRT Physical Total Dose in Gy	mean (±1SD)	median (min-max)
centre	45 (±2)	45 (40-50)
PIBS+3	44 (± 2)	44 (40-50)
PIBS+2	43 (± 2)	43 (33-49)
PIBS+1	39 (± 9)	42 (5-49)
PIBS	30 (±13)	35 (3-48)
PIBS-1	17 (±14)	13 (2-48)
PIBS-2	8 (±10)	4 (1-43)

BT





Total Dose EBRT+BT in EQD2 $Gy_{\alpha\beta 3}$	mean (±1SD)	median (min-max)
3':	309/120 (±161/34)	266/115 (61-815)
6':	73/ 62 (±12/7)	72/ 62 (47-109)
9':	250/109 (±118/31)	226/101 (55-611)
12':	89/ 73 (±22/16)	85/ 70 (51-146)
centre		
PIBS+3	61 (±15)	56 (44-97)
PIBS+2	53 (±12)	50 (32-90)
PIBS+1	46 (±16)	45 (5-94)
PIBS	33 (±15)	37 (3-68)
PIBS-1	18 (±14)	12 (2-54)
PIBS-2	8 (±10)	4 (1-46)

Westerveld et al. Radiotherapy and Oncology 2013

Image guided brachytherapy in cervical cancer

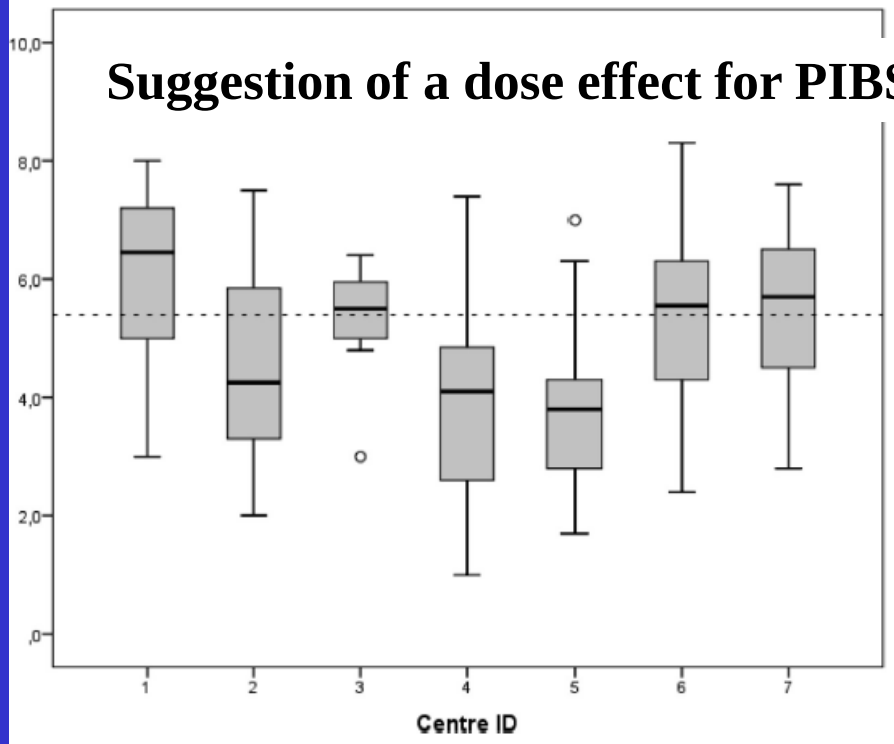
Multicentre evaluation of a novel vaginal dose reporting method in 153 cervical cancer patients

Henrike Westerveld [a,b,*], Astrid de Leeuw [c], Kathrin Kirchheiner [b], Pittaya Dankulchai [d], Bernard Oosterveld [e], Arun Oinam [f], Robert Hudej [g], Jamema Swamidas [h], Jacob Lindegaard [i], Kari Tanderup [i], Richard Pötter [b,j], Christian Kirisits [b,j], the EMBRACE Collaborative Group

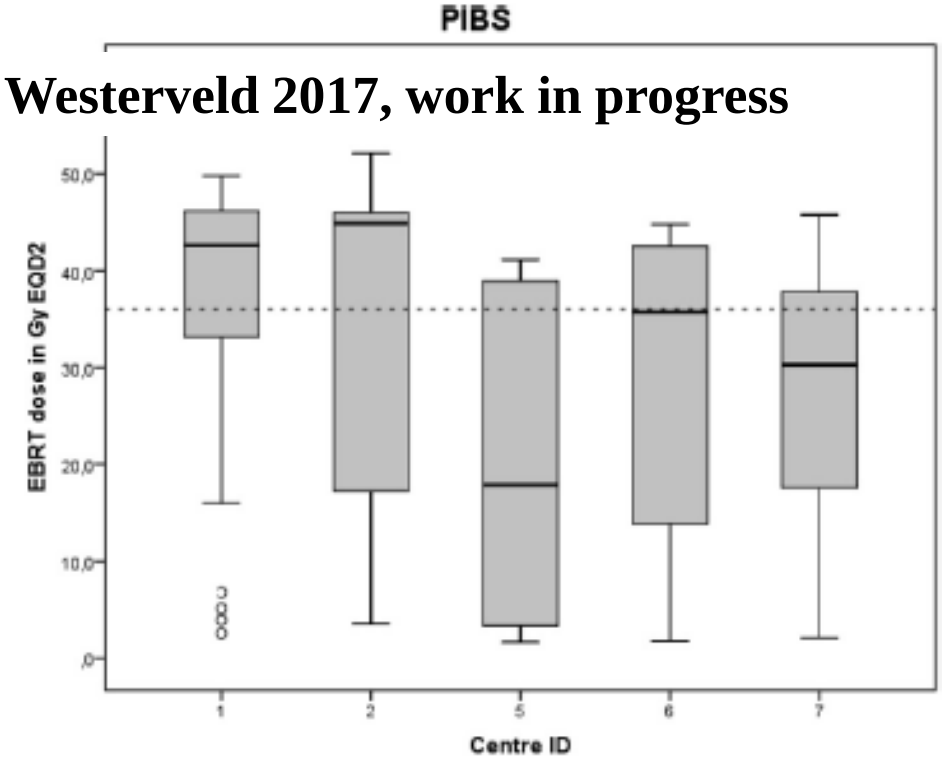
[a] Department of Radiotherapy, Academic Medical Centre, University of Amsterdam, The Netherlands; [b] Department of Radiation Oncology, Comprehensive Cancer Centre, Medical University of Vienna, Austria; [c] Department of Radiation Oncology, University Medical Centre Utrecht, The Netherlands; [d] Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [e] Department of Radiation Oncology, Radiotherapiegroep, Arnhem, The Netherlands; [f] Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [g] Department of Radiotherapy, Institute of Oncology Ljubljana, Slovenia; [h] Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India; [i] Department of Oncology, Aarhus University Hospital, Denmark; and [j] Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Austria

Radioth and Oncol 2016

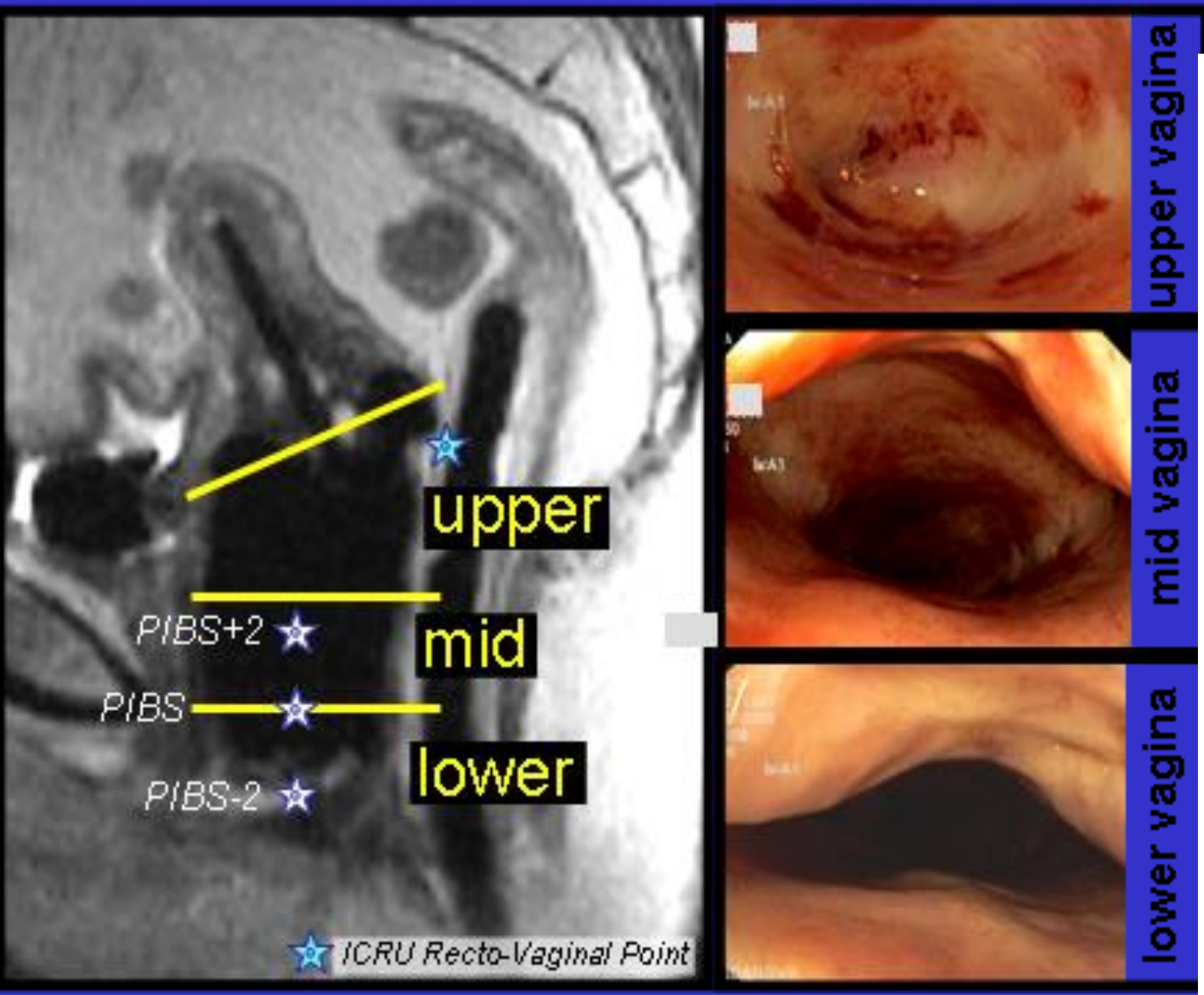
Suggestion of a dose effect for PIBS, Westerveld 2017, work in progress

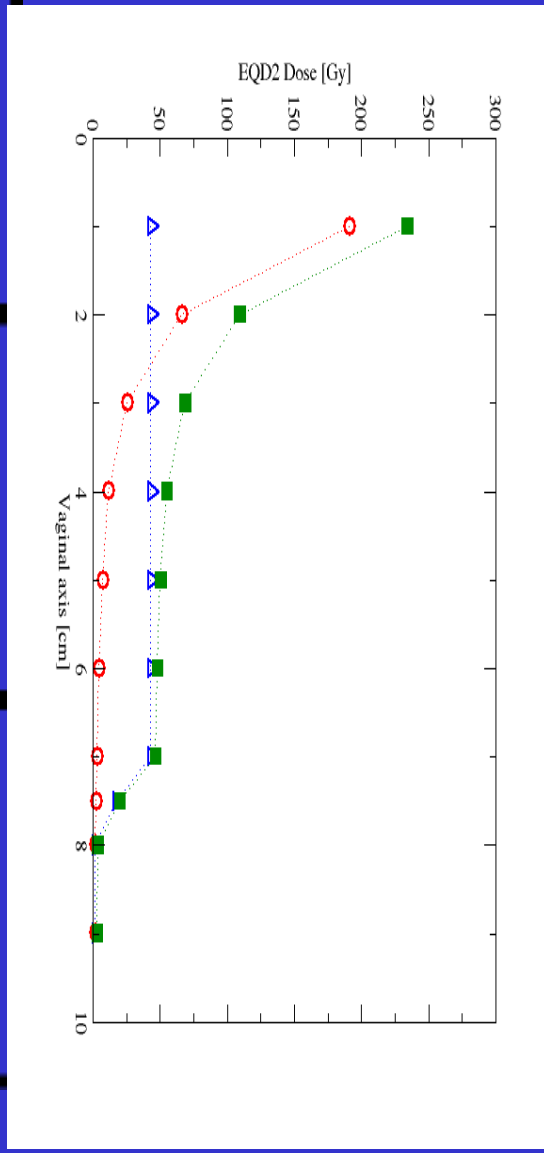


ginal reference length (VRL) in cm per centre. The dotted line represents the median length of the entire cohort.



Vaginal morbidity and radiation doses



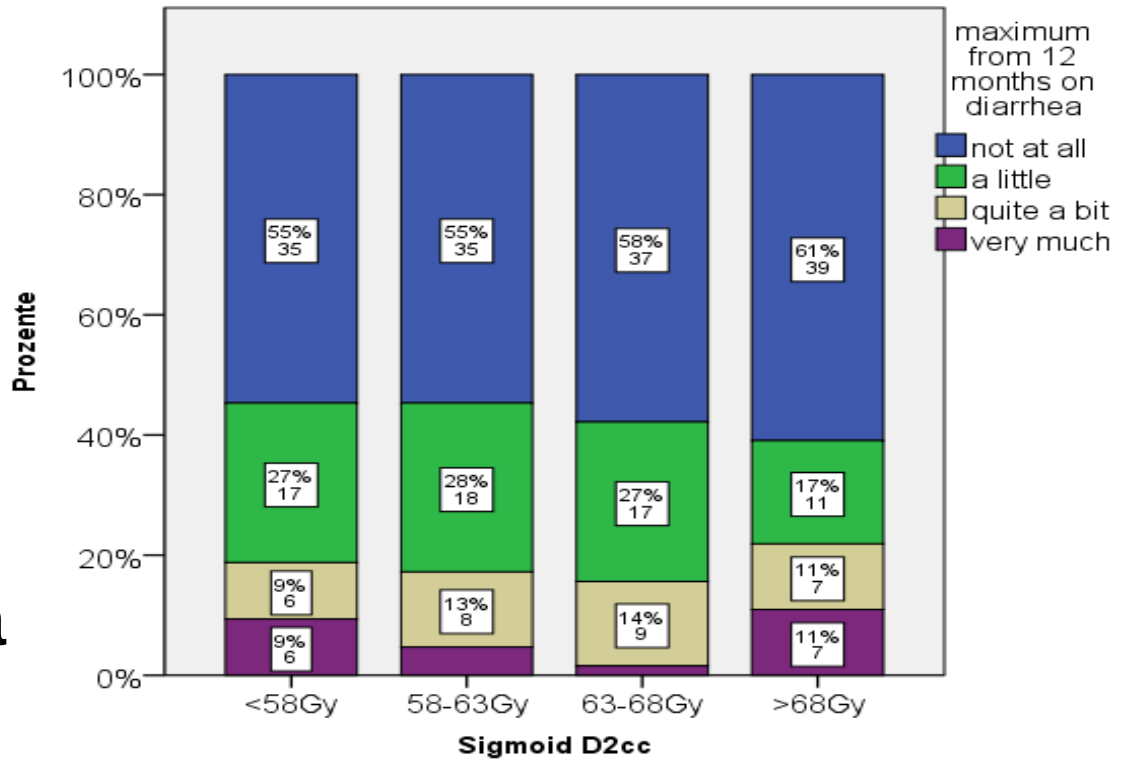


ICRU/GEC ESTRO Report 89 Fig. 6.1/Fig. 8.11

Sigmoid D_{2cm3}, preliminary data (2015)

- **No dose effect established – (so far)**

Diarrhea

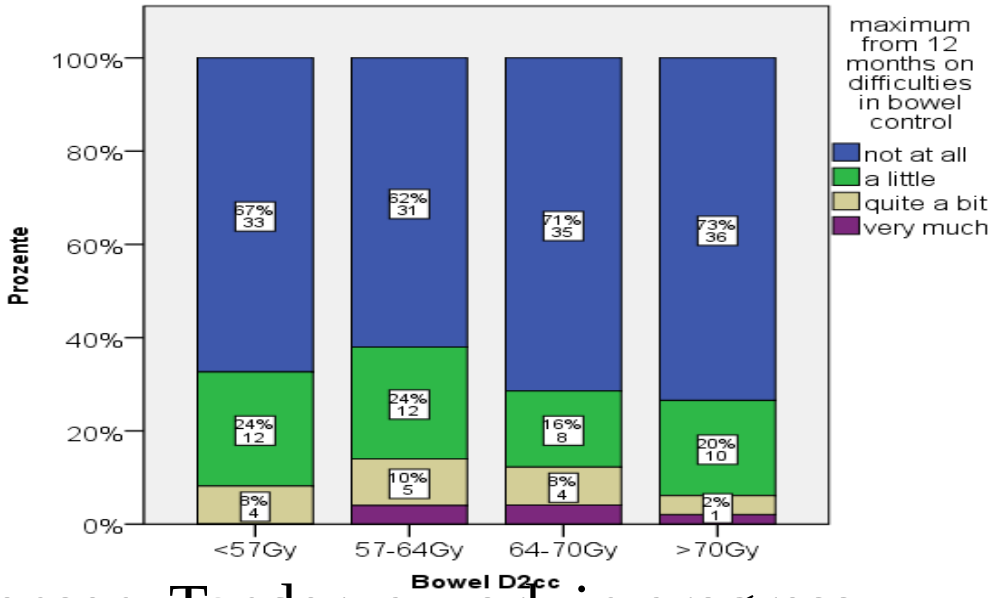


Bowel D_{2cm3}, and EBRT preliminary data

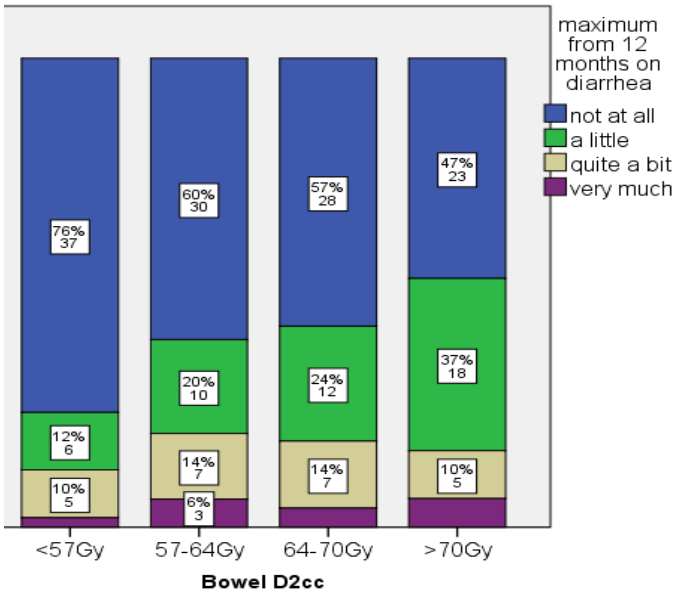
- **dose effect likely to become established for diarrhea**

2 cm^3 (BT) and EBRT: dose (45/50Gy), LN boost, PA RT

Bowel control



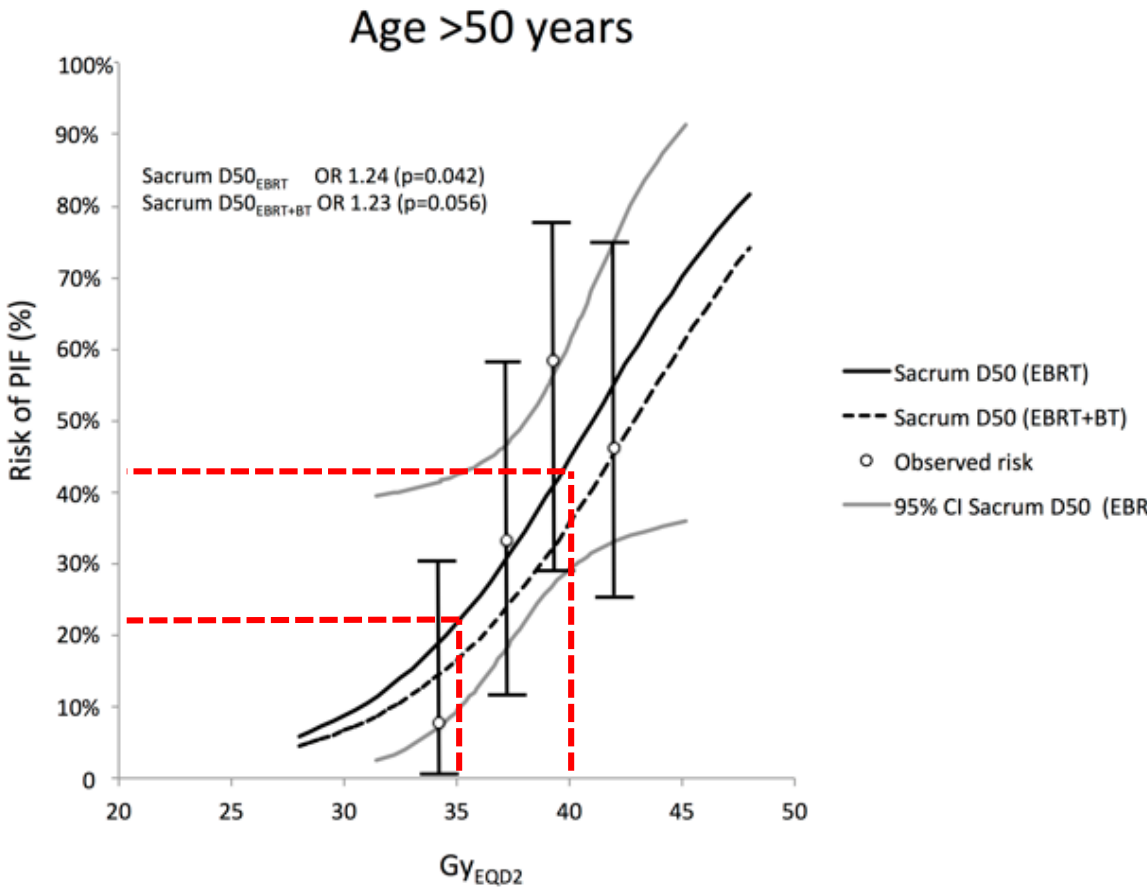
Diarrhea



Jensen, Tanderup work in progress

Pelvic insufficiency fractures

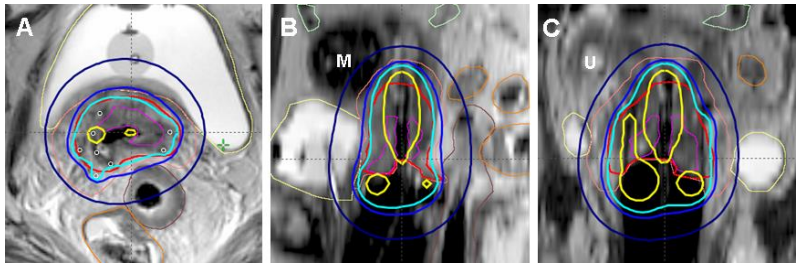
- **Retrospective analysis in 101 patients**
- **Endpoint: Fractures identified on MRI**
- **MRI at 3 and 12 months + on indication**
- **Incidence:**
  - **<50 years 4%**
  - **>50 years 37%**
- **In group with age >50 years: strong impact of sacrum dose**



Ramlov et al, IJROBP, Volume 97 Number 5 2017

Planning aim and prescription dose

- **Planning aim: what you want to obtain**
- **Prescribed dose: what you decide to treat**



Example 1

Structure	Dose-volume parameter	Planning aim, Gy	Prescribed dose Gy
CTV_{HR}	$EQD2_{10}$ D_{90}	≥ 85	88.9
Bladder	$EQD2_3$ D_{2cm^3}	≤ 90	71.1
Rectum	$EQD2_3$ D_{2cm^3}	≤ 70	65.6
Sigmoid	$EQD2_3$ D_{2cm^3}	≤ 70	57.4
Bowel	$EQD2_3$ D_{2cm^3}	≤ 70	53.3

Conclusion dose effect BT (I)

- **Dose effect demonstrated for:**
  - **Residual GTV D100 (98), adaptive CTV_{HR} D90, and CTV_{IR} D90 (98)**
  - **Bladder D 2cm^3**
  - **Rectum D 2cm^3**
  - **Vagina (recto-vaginal point)**

- **Upcoming evidence:** **Bowel D 2cm^3 + EBRT dose/volume**
  Vagina PIBS (+2): EBRT + BT
  Bladder (frequency, continence): ICRU Pt

- **Dose effect not demonstrated for**
  - **Sigmoid**

Conclusion dose effect BT (II)

- **Future Perspective (EMBRACE II)**
- **prospective protocol:**

  planning aims and limits for miminum prescribed dose

  ”soft constraints” and ”hard constraints”

  taking into account multiple parameters:

  - **Target dose $CTV_{HR,}$ (CTV_{IR} GTV_{res})**
  - **Target volume $CTV_{HR,}$ (CTV_{IR} GTV_{res})**
  - **Overall treatment time <50 days**
  - **OARs $D2cm^3$ and dose points (vagina, rectum)**

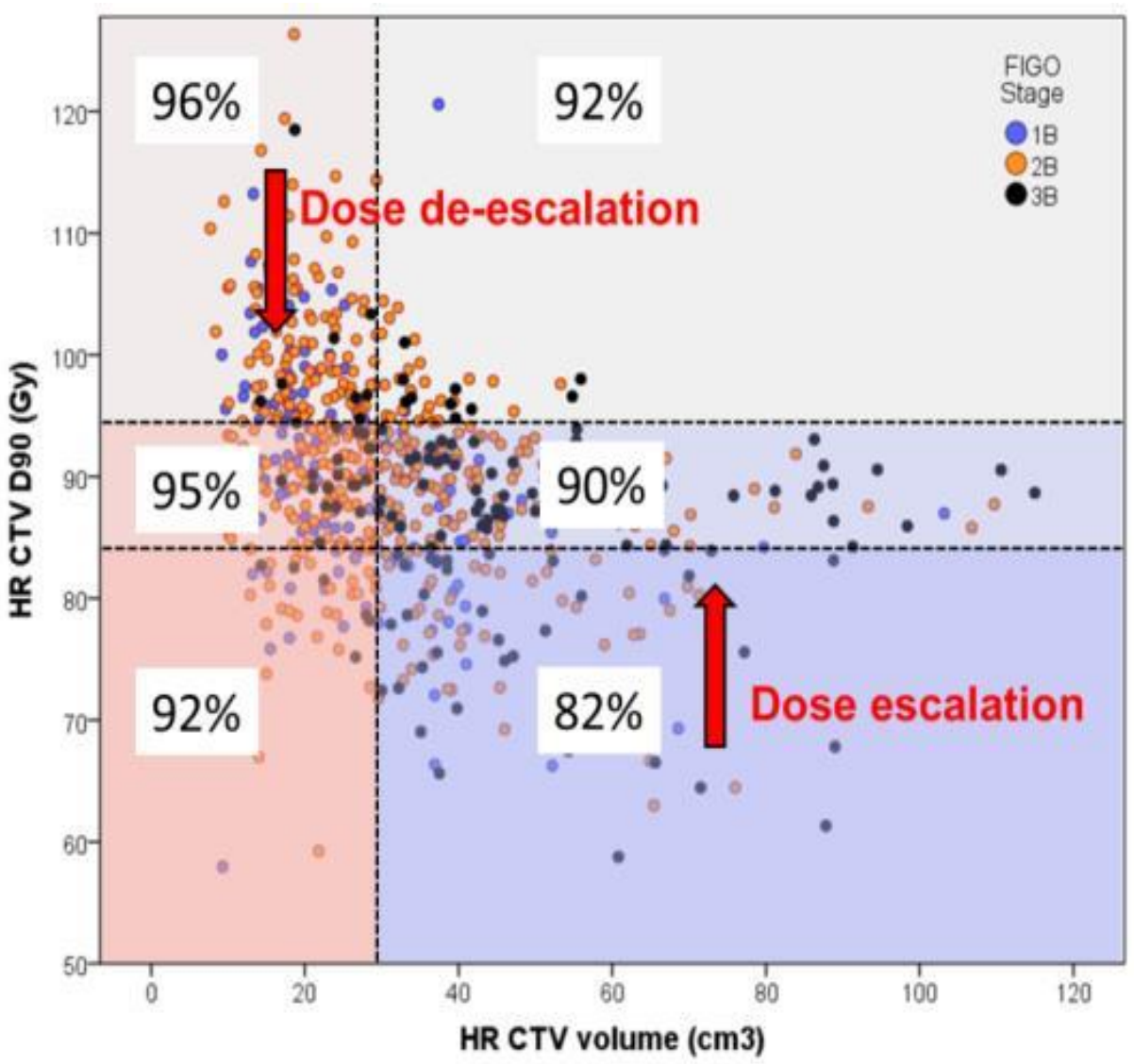
EMBRACE II (2016) cervix cancer: $D2cm^3$ for OARs protocol for planning aims and dose prescription

	Bladder D_{2cm^3} $EQD2_3$	Rectum D_{2cm^3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid/ Bowel D_{2cm^3} $EQD2_3$
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy*
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*

Beach Boys Madrid 2018

EMBRACE II Planning AIMS and Limits for Prescription

OTT < 50 Days	D90 CTV_{HR} $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy
Limits for Prescribed Dose	> 85 Gy
OAR	Bladder D_{2cm^3} $EQD2_3$
Planning Aims	< 80 Gy
Limits for Prescribed Dose	< 90 Gy



CONCLUSIONS AND LIMITATIONS (IGABT)

Linking DVH parameters to clinical outcome

- D90 HR CTV, GTV 100 and local control: strong link
- 2/0.1 ccm for rectal morbidity: strong link

- 2 ccm for bladder morbidity: link
  improvement by location assessment ? (bladder point)
- 2 ccm for sigmoid/b owelmorbidity: weak link
  improvement by movement assessment?
- *Any DVH parameter for vaginal morbidity:* *no link so far*
  ICRU rectovaginal Point: strong link

Limitations: prospective study data only upcoming multicenter study: RetroEMBRACE/EMBRACE

ESTRO School

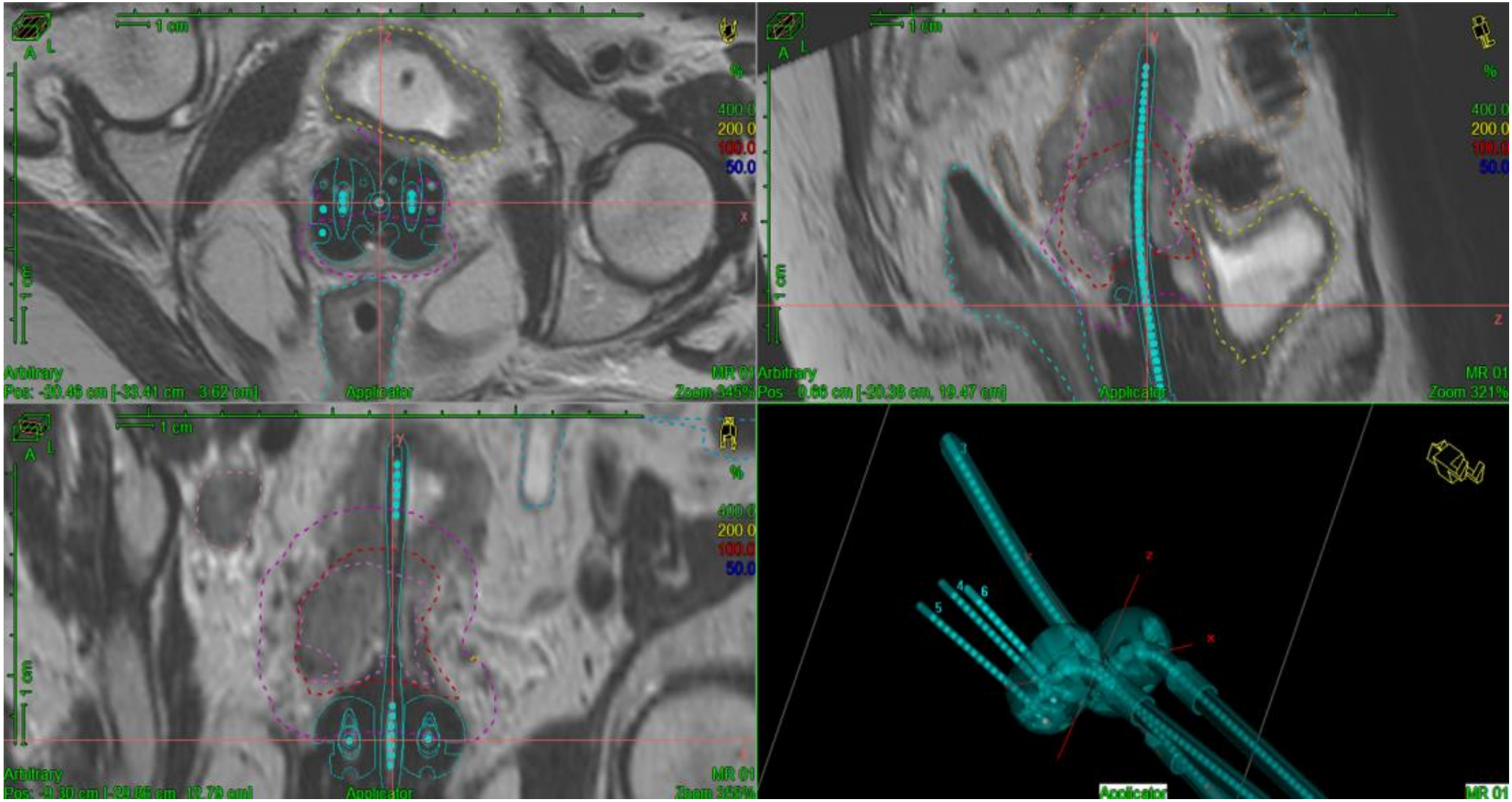
Brachytherapy Planning

Thank you soooo much !

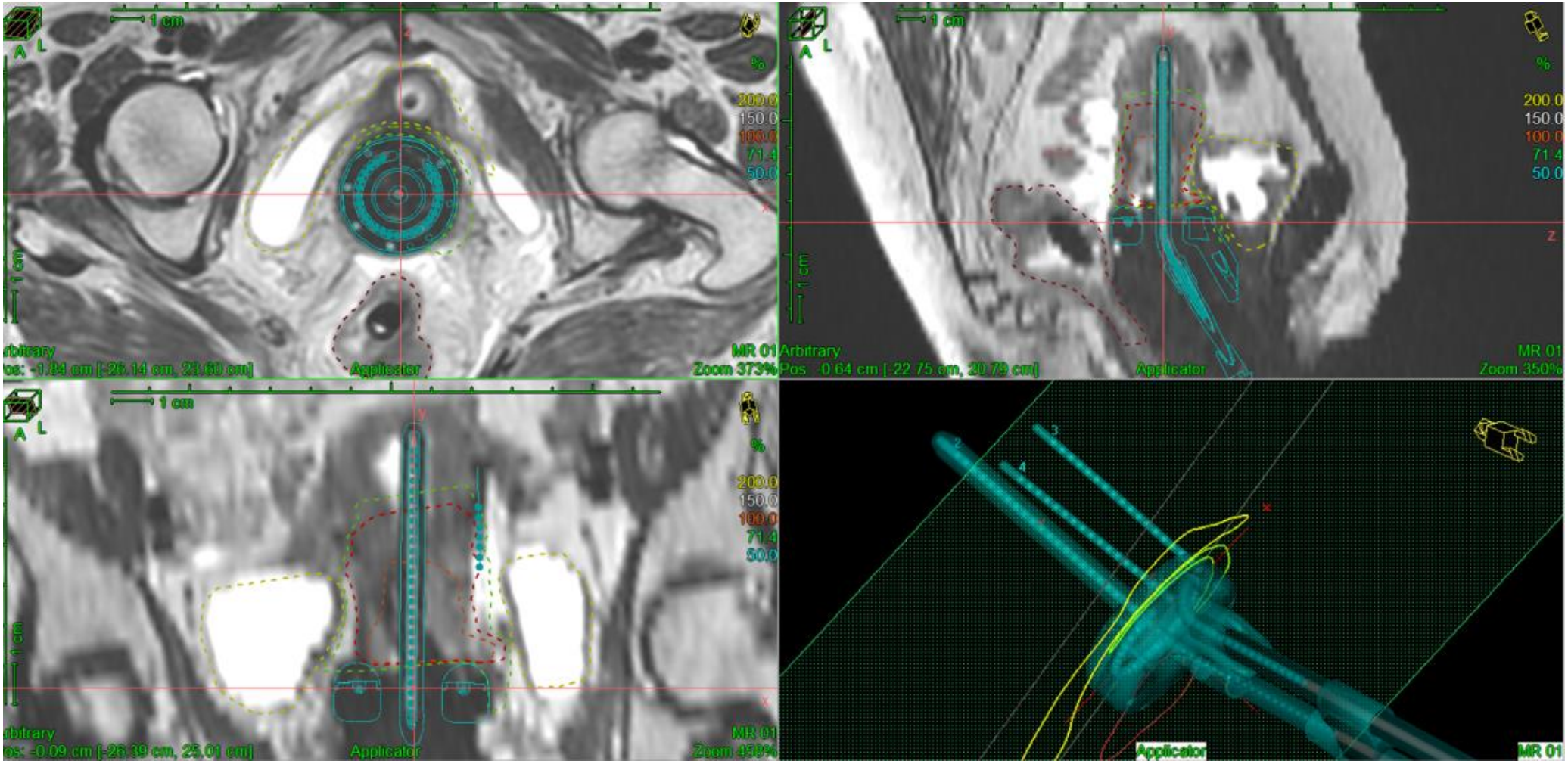
7 Physicists have submitted 9 plans

ESTRO School

Case: UTR076 Applicator: Utrecht applicator + 3 needles (offset 10mm) right side



Case: Tata03 Applicator: Vienna Ring r26i60 + 2 needles left side



EMBRACE II Planning aims + dose limits

Dose volume parameters used for real-time data monitoring:

Target	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV_{res} $EQD2_{10}$	D98 CTV_{IR} $EQD2_{10}$	Point A $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy	> 75 Gy	>95 Gy	> 60 Gy	> 65 Gy
Limits for Prescribed Dose	> 85 Gy	-	>90 Gy	-	-

OAR	Bladder D_{2cm^3} $EQD2_3$	Rectum D_{2cm^3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid D_{2cm^3} $EQD2_3$	Bowel D_{2cm^3} $EQD2_3$
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy*	< 70 Gy*
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*	< 75 Gy*

Hard constraints

Soft constraints

Hard constraints: require comment by center if violated

Brachytherapy Planning HOMEWORK

Target	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV_{res} $EQD2_{10}$	D98 CTV_{IR} $EQD2_{10}$	Point A $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy	> 75 Gy	>95 Gy	> 60 Gy	> 65 Gy
Limits for Prescribed Dose	> 85 Gy	-	>90 Gy	-	-

OAR	Bladder D_{2cm^3} $EQD2_3$	Rectum D_{2cm^3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid D_{2cm^3} $EQD2_3$	Bowel D_{2cm^3} $EQD2_3$
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy*	< 70 Gy*
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*	< 75 Gy*

IU	V	IS	HR-CTV D90	HR-CTV D98	GTV D98	IR-CTV D98	Point A	B D2cc	R D2cc	ICRU (RV)	S D2cc	Bow D2cc	Phy#
52%	27%	20%	91.1	76.5	103.6	60.2	76.9	91.6	56.5	66.1	52.0	46.0	1
31%	0%	69%	*93.8*	76.6	93.8	57.3	114.2	71.9	64.5	43.2	83.2	47.3	2
39%	33%	28%	97.9	86.6	114.3	66.5	75.3	71.9	60.3	79.4	50.4	43.2	2
n.a	n.a	n.a	68.0	63.4	66.4	55.7	72.0	82.6	68.3	43.2	72.2	50.1	3
49%	28%	23%	*87.2*	77.7	85.5	62.7	70.9	81.3	72.2	43.2	76.7	51.8	4
32%	52%	17%	84.2	75.7	97.7	59.3	66.7	86.0	53.9	43.2	48.4	43.2	4
31%	9%	60%	103.3	90.2	116.7	62.4	89.6	82.4	66.3	87.4	83.5	48.0	5
63%	37%	0%	100.3	88.8	94.9	62.3	86.8	93.9	75.2	43.2	54.8	43.2	6
42%	31%	28%	87.2	77.7	86.5	61.4	78.2	81.4	66.5	47.9	77.0	77.0	7

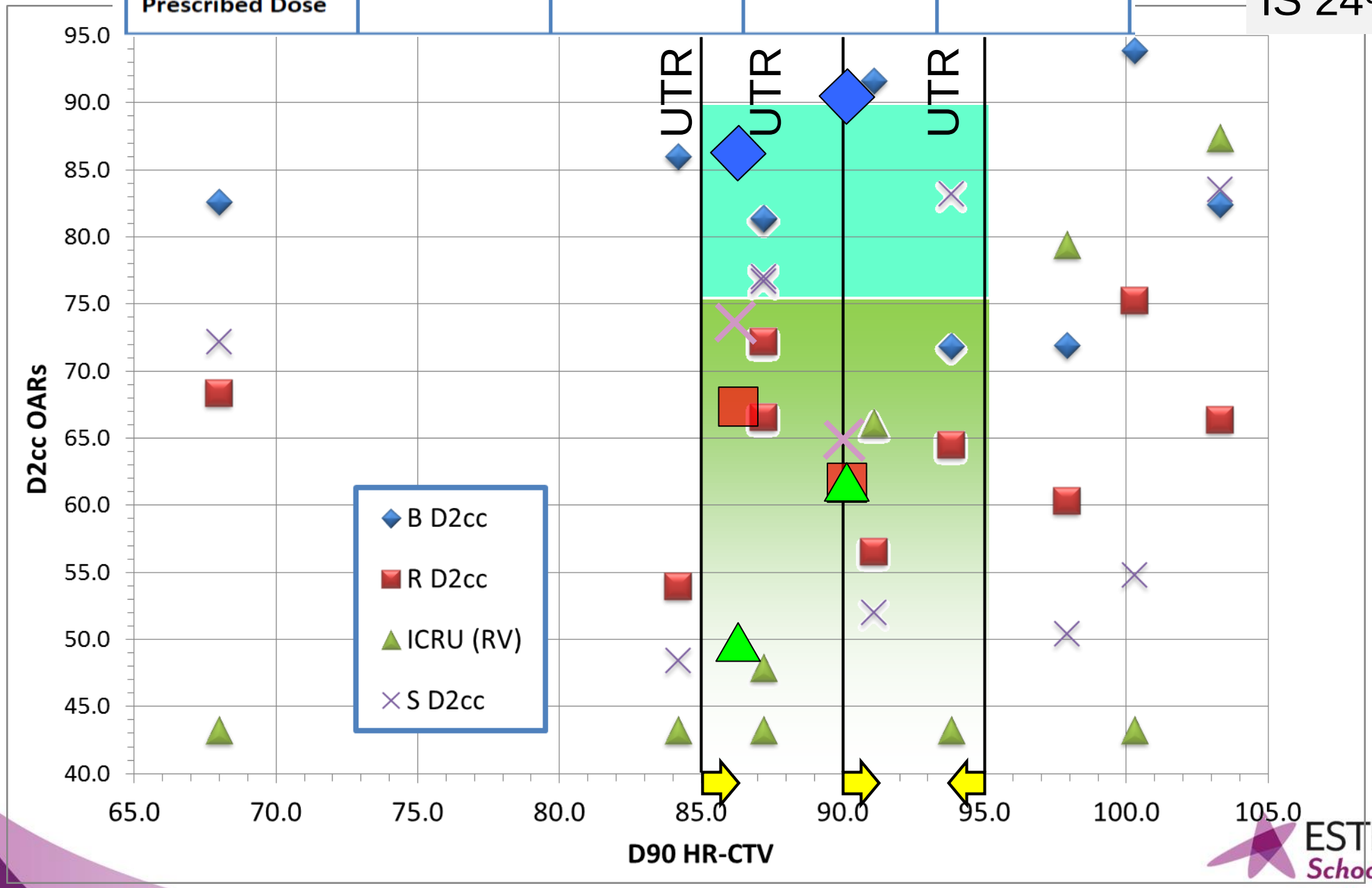
UTR case

manual graph man/graph IPSA

Individual planning aim D90 achieved in all except 1 case*

OAR	Bladder D_{2cm^3} ◆ B D2cc	Rectum D_{2cm^3} ■ R D2cc	Recto-vaginal ▲ ICRU (RV)	Sigmoid D_{2cm^3} × S D2cc
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy*
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*

UTR-plan
IU 39%
V 37%
IS 24%



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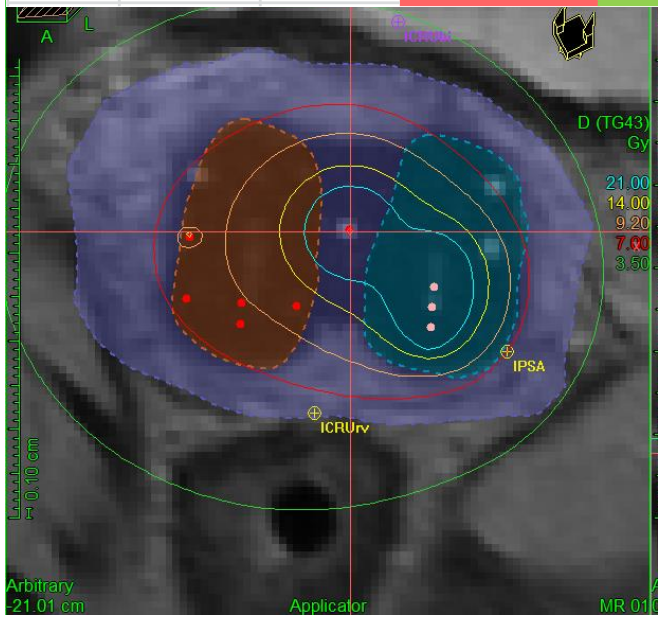
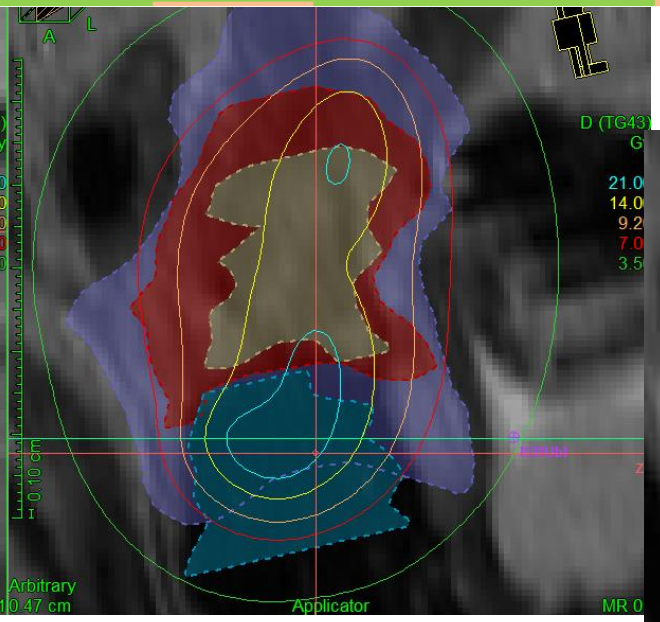
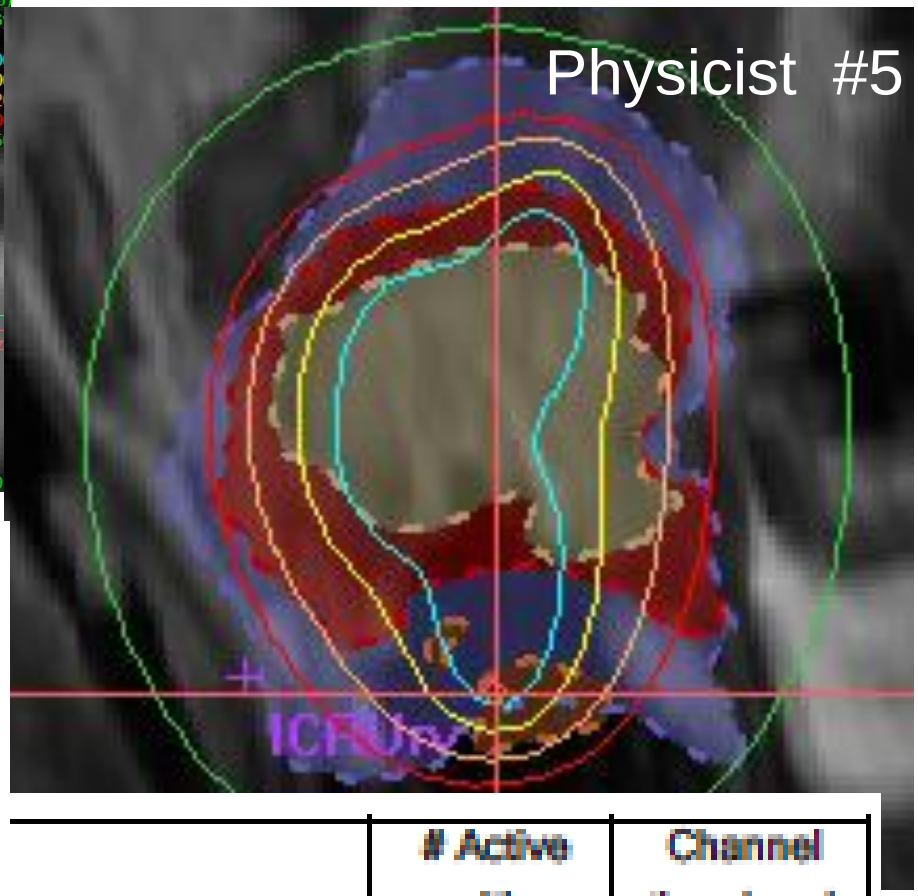
Dose Normalization, Optimization and Prescription

IU	V	IS	HR-CTV D90	HR-CTV D98	GTV D98	IR-CTV D98	Point A	B D2cc	R D2cc	ICRU (RV)	S D2cc	Bow D2cc	Phy#
31%	9%	60%	103.3	90.2	116.7	62.4	89.6	82.4	66.3	87.4	83.5	48.0	5





Optimization type: IPSA
Prescription dose per fraction/pulse (Gy): 7.0000
Total Reference Air Kerma per fraction/pulse at 1 m (Gy): 0.00422

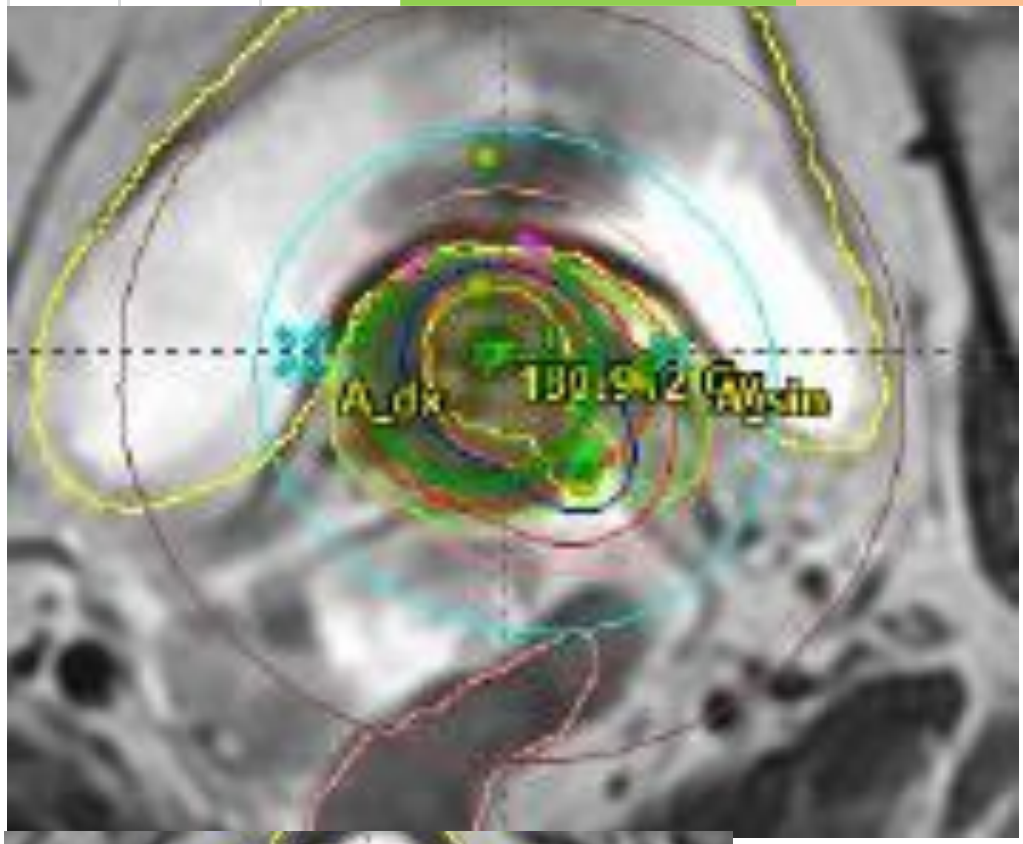


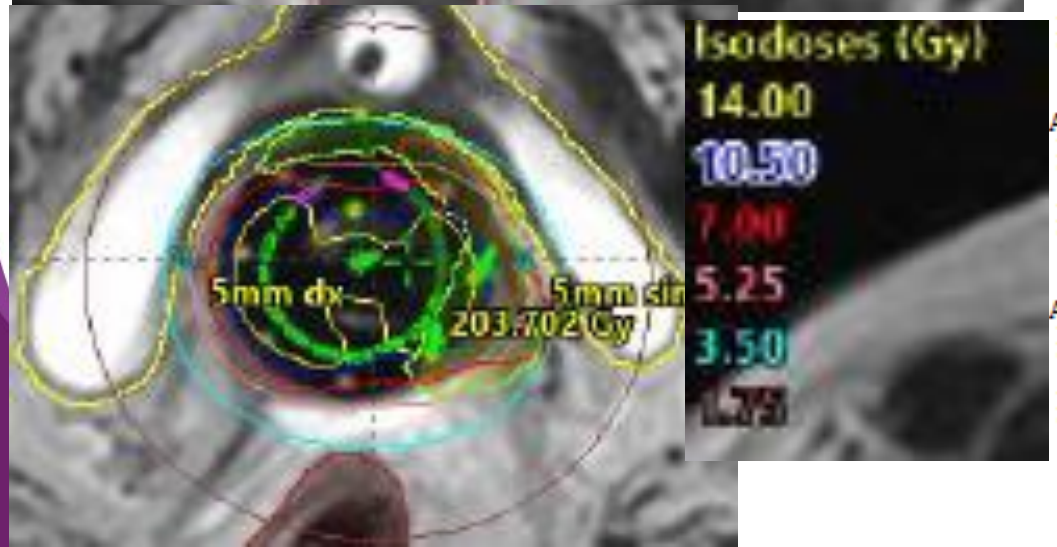
(channel)		(indexer length)	1 5 9 13 17 21 25 (pos)
1 (1)	O1	150.00 (cm)	. . .
2 (2)	O2	150.00 (cm)	AAAA
3 (3)	IU	150.00 (cm)	. . . . . .AAAAAAAAAA..AAAAAAAA
4 (4)	nld6	129.40 (cm)	AAAAAAAAAA..AA
5 (5)	nld7	129.40 (cm)	AAAA. . . . . A
6 (6)	nld8	129.40 (cm)	AAAAAAAAA

		# Active positions	Channel time (sec.)
1 (1)	O1 (Model)	0	0.0
2 (2)	O2 (Model)	4	30.9
3 (3)	IU (Model)	18	104.5
4 (4)	nld6 (Manual)	12	113.7
5 (5)	nld7 (Manual)	5	1.2
6 (6)	nld8 (Manual)	9	88.2

Physicist #1

IU	V	IS	HR-CTV D90	HR-CTV D98	GTV D98	IR-CTV D98	Point A	B D2cc	R D2cc	ICRU (RV)	S D2cc	Bow D2cc	Phy#
52%	27%	20%	91.1	76.5	103.6	60.2	76.9	91.6	56.5	66.1	52.0	46.0	1





Brief Report for "PS2"

Varian Medical Syste

Software version: Brachytherapy Planning 13.6.32

Patient Sex:	Bestämning ej gjord
Total prescription:	7.0 Gy in 1 fractions. Dwell times are displayed for a single fraction.
Treatment site:	CTV-HR
Dose Calculation:	Homogeneous
PDR pulse interval:	-
Plan Created:	den 9 augusti 2018 12:44:33
Last Saved:	den 9 augusti 2018 15:27:53
Source wire serial number:	24-05-6304-003-042618-12166-97
Source nominal activity:	10000.00 mCi
Source treatment activity:	10000.00 mCi (nominal)
Source nominal activity date:	den 16 maj 2018 00:00:00
Treatment date:	den 6 augusti 2018 00:00:00
Total air kerma strength:	3144.07 cGy cm² (nominal)
Total Curie seconds:	2781.00 (nominal)
Total treatment time:	278.10 s
Total time per PDR pulse:	-
PDR number of pulses:	-

TATA

Applicator: Ring, Channel: 1, Source Model: GMP Ir-192 HDR, Tx Strength: 40700.00 cGy cm² / h (nominal),

Position [cm]	130.00	129.50	129.00	128.50	128.00	127.50	127.00	126.50	126.00	125.50
Time [s]	0.0	4.6	9.8	10.1	10.4	5.7	4.0	0.7	0.4	5.4
Position [cm]	125.00	124.50	124.00	123.50	123.00					
Time [s]	10.3	8.3	4.9	1.2	0.0					

Applicator: IU, Channel: 3, Source Model: GMP Ir-192 HDR, Tx Strength: 40700.00 cGy cm² / h (nominal),

Position [cm]	130.00	129.50	129.00	128.50	128.00	127.50	127.00	126.50	126.00	125.50
Time [s]	4.2	7.5	13.2	19.5	18.3	17.1	15.6	12.6	10.9	8.7
Position [cm]	125.00	124.50								
Time [s]	8.9	9.4								

Applicator: needle1, Channel: 4, Source Model: GMP Ir-192 HDR, Tx Strength: 40700.00 cGy cm² / h (nominal),

Position [cm]	130.00	129.50	129.00	128.50	128.00	127.50	127.00	126.50	126.00	125.50
Time [s]	0.1	0.9	1.8	2.0	1.4	0.3	0.0	0.4	2.6	4.4
Position [cm]										
Time [s]										

Applicator: needle2, Channel: 5, Source Model: GMP Ir-192 HDR, Tx Strength: 40700.00 cGy cm² / h (nominal),

Position [cm]	130.00	129.50	129.00	128.50	128.00	127.50	127.00	126.50	126.00	125.50
Time [s]	0.3	2.9	4.5	4.5	5.2	5.0	4.2	4.7	5.1	6.1
Position [cm]										
Time [s]										

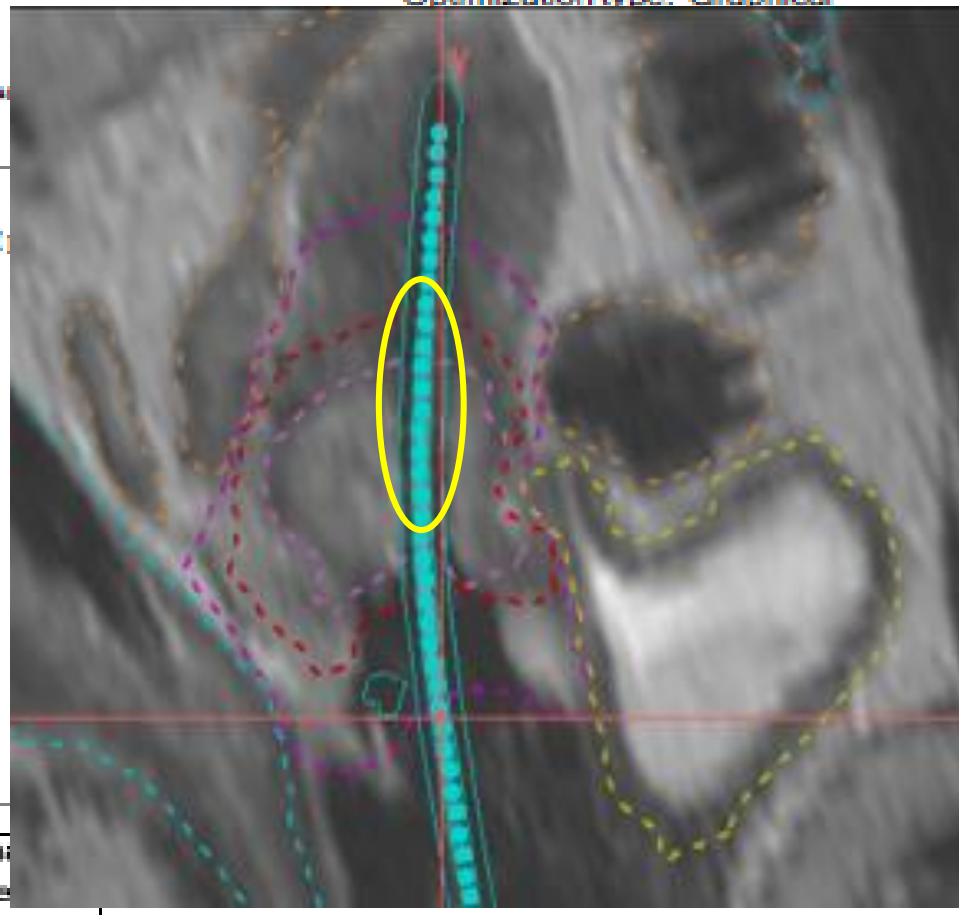
Physicist #7

UTR

Dose Normalization, Optimization and Prescription

IU	V	IS	HR-CTV D90	HR-CTV D98	GTV D98	IR-CTV D98	Point A	B D2cc	R D2cc	ICRU (RV)	S D2cc	Bow D2cc	Phy#
42%	31%	28%	87.2	77.7	86.5	61.4	78.2	81.4	66.5	47.9	77.0	77.0	7

Optimization type: Graphical



Total Refere

Source Positions

Catheter (channel)	Name	Channel length (indexer length)
1 (1)	O1	130.00 (cm)
2 (3)	O2	130.00 (cm)
3 (5)	IU	130.00 (cm)
4 (6)	RAnt	128.90 (cm)
5 (7)	RPost	128.90 (cm)
6 (8)	RMed	128.90 (cm)

300 295 290 285 280 275 270 265 260 255

30.0 29.5 29.0 28.5 28.0 27.5 27.0 26.5 26.0 25.5

Source position separation (cm): 0.10

Catheter (channel) Times

Catheter (channel)	Name	# Active positions	Cha time
1 (1)	O1 (Model)	6	90.0
2 (3)	O2 (Model)	6	123.0
3 (5)	IU (Model)	11	295.0
4 (6)	RAnt (Manual)	9	35.0
5 (7)	RPost (Manual)	9	45.0
6 (8)	RMed (Manual)	14	113.0

Total treatment time (sec.): 338.5

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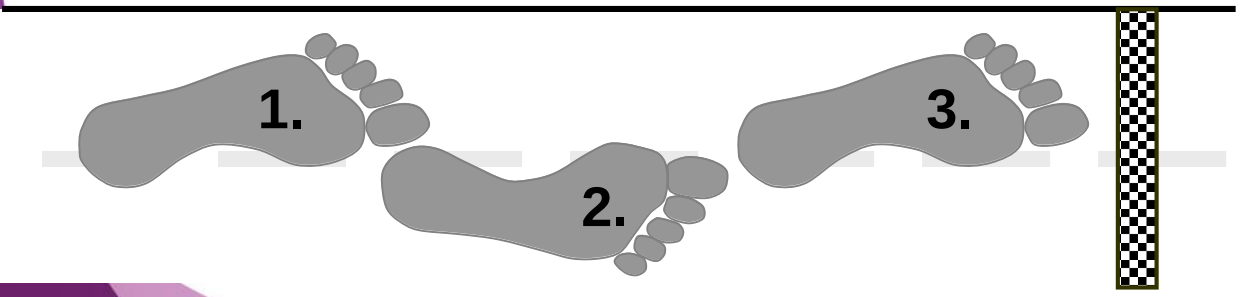
Keep in mind - Daniel's 3 easy steps in manual Treatment Planning Optimization

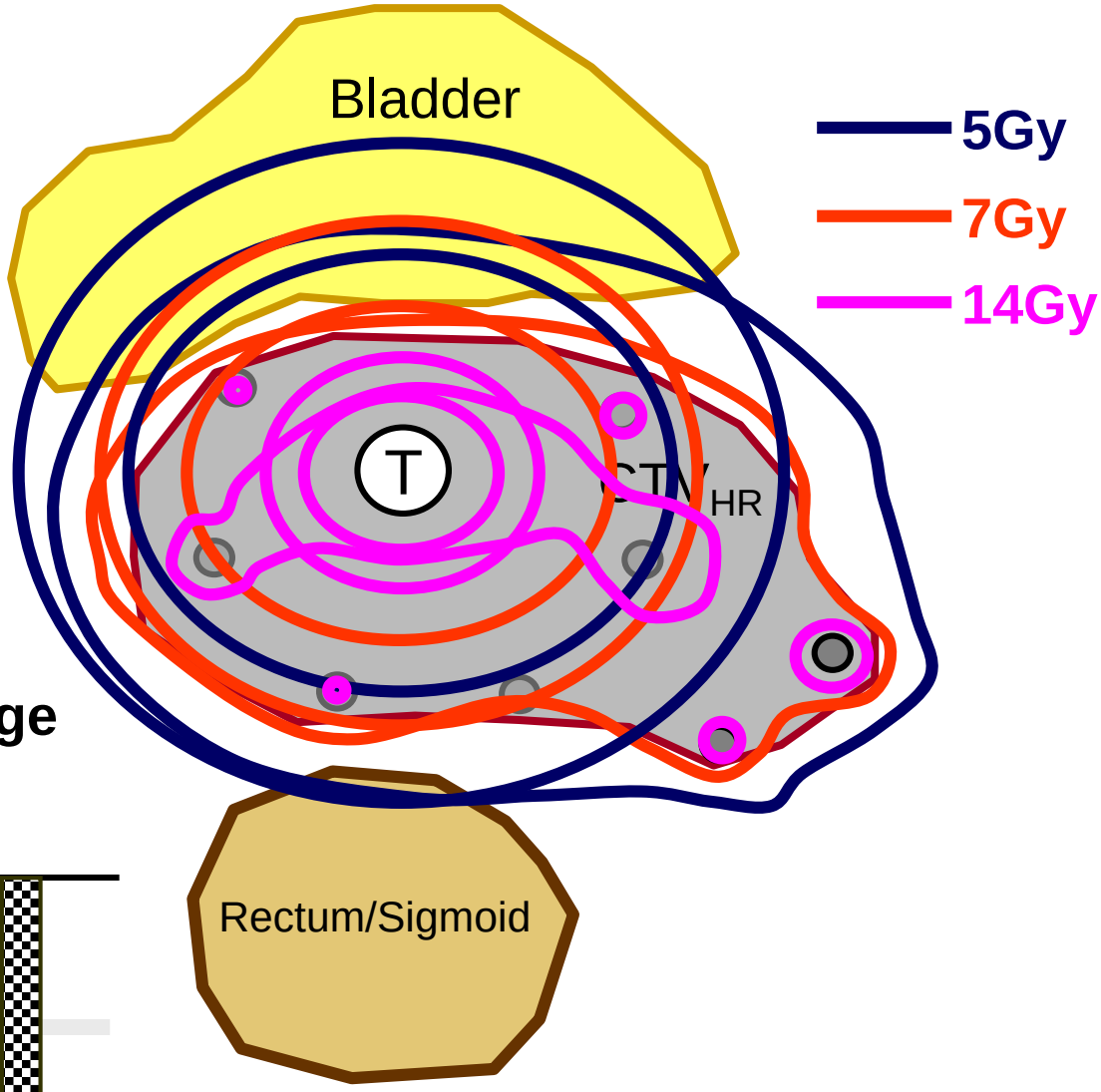
1: Apply (institutional) Standard Loading Pattern and normalize to Point A

2: Optimize the Intracavitary applicator (T/R, T/O) based on OARs *(~10-20% of the dose limit)*

3: Add the interstitial components (Needles) to increase the target coverage

<Dwell-time is 10-20% of Intracavitary>





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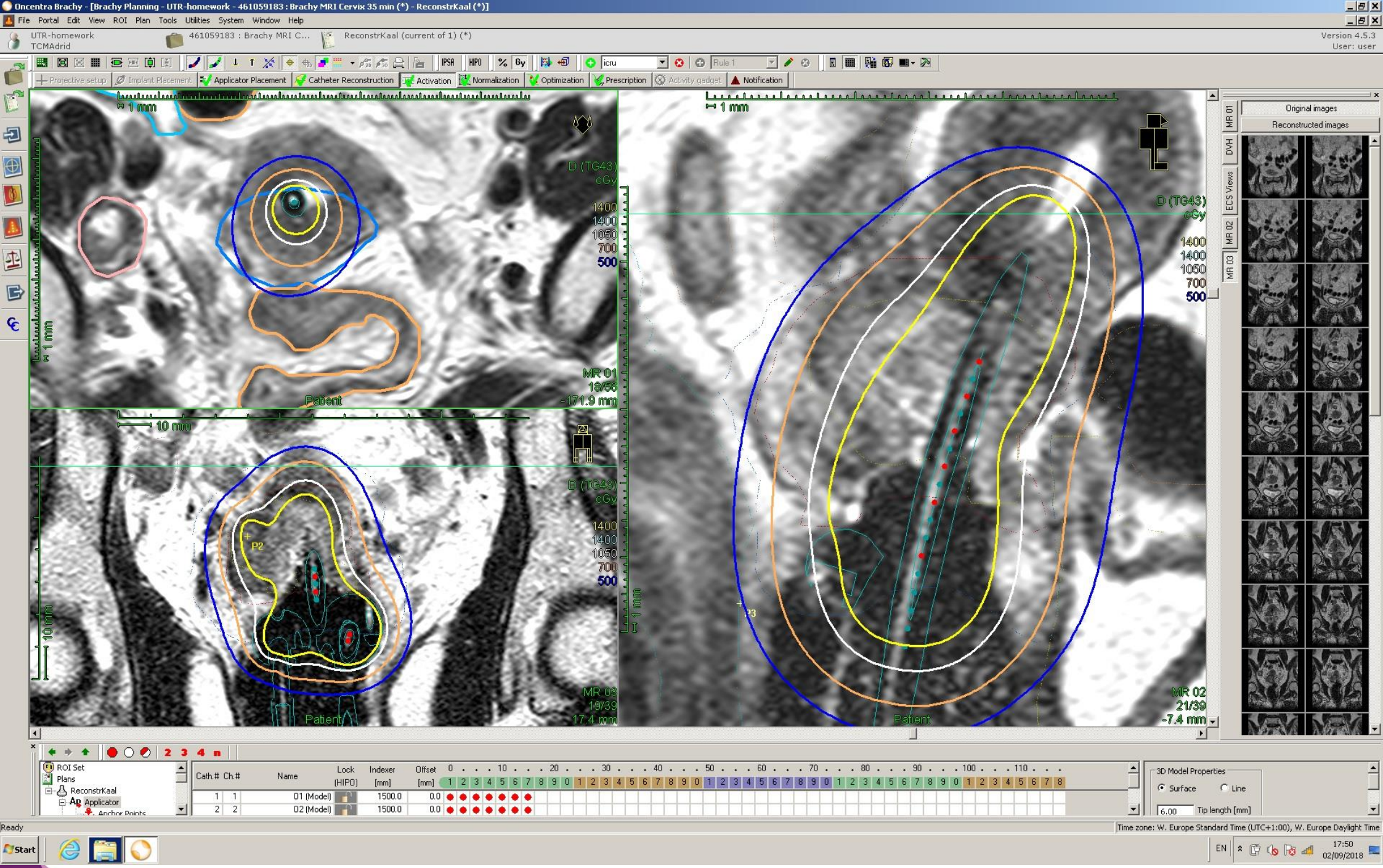

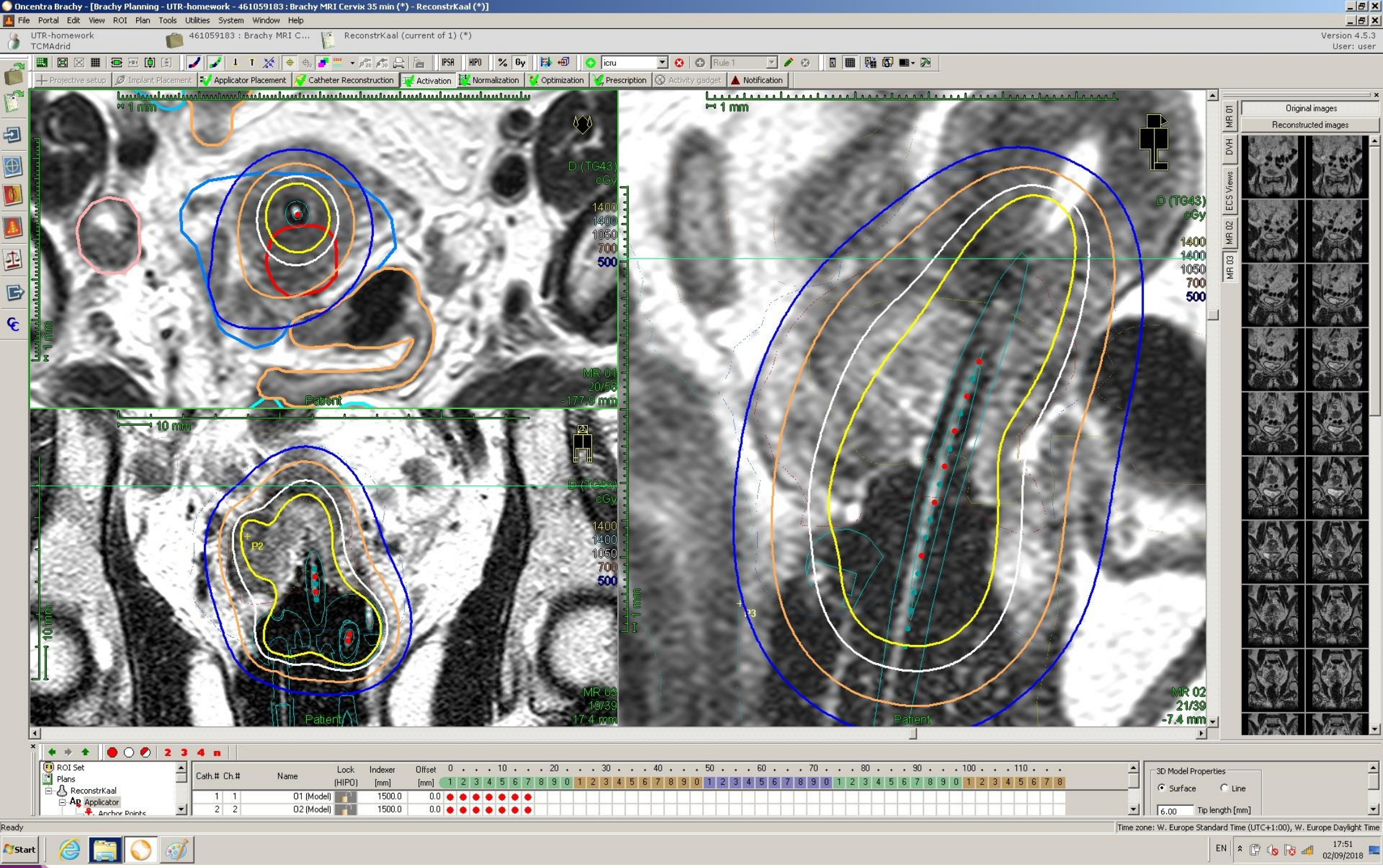

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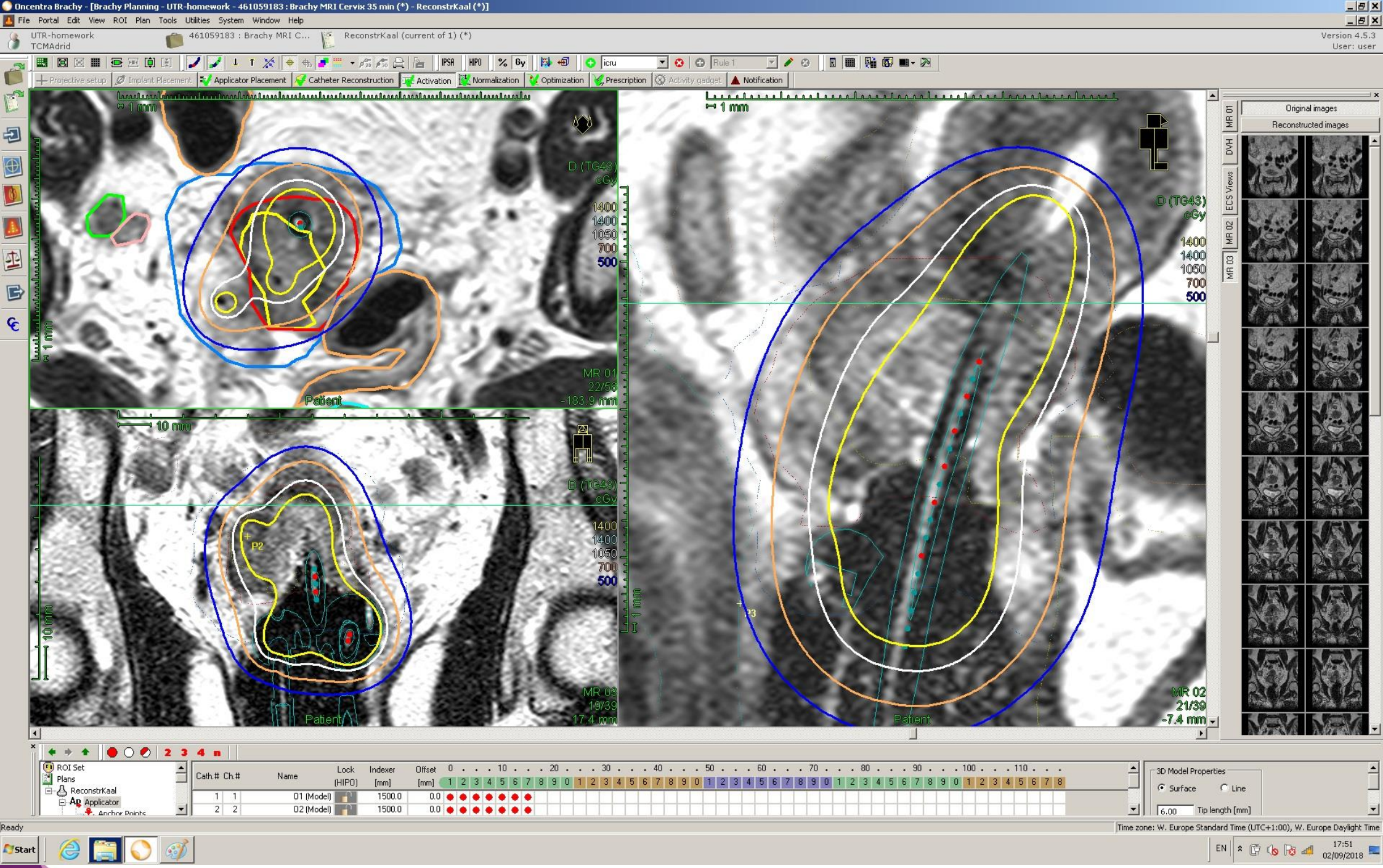

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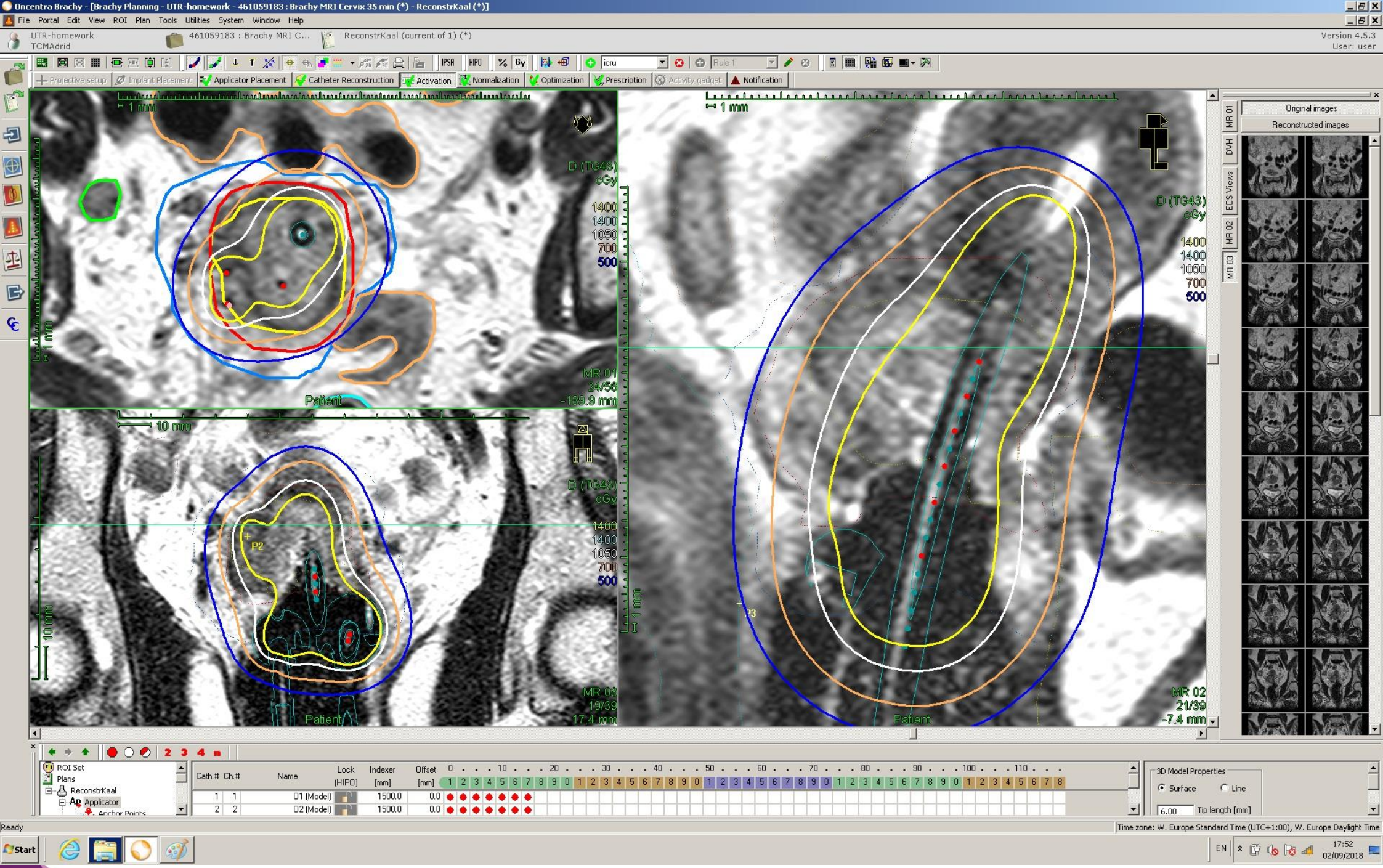

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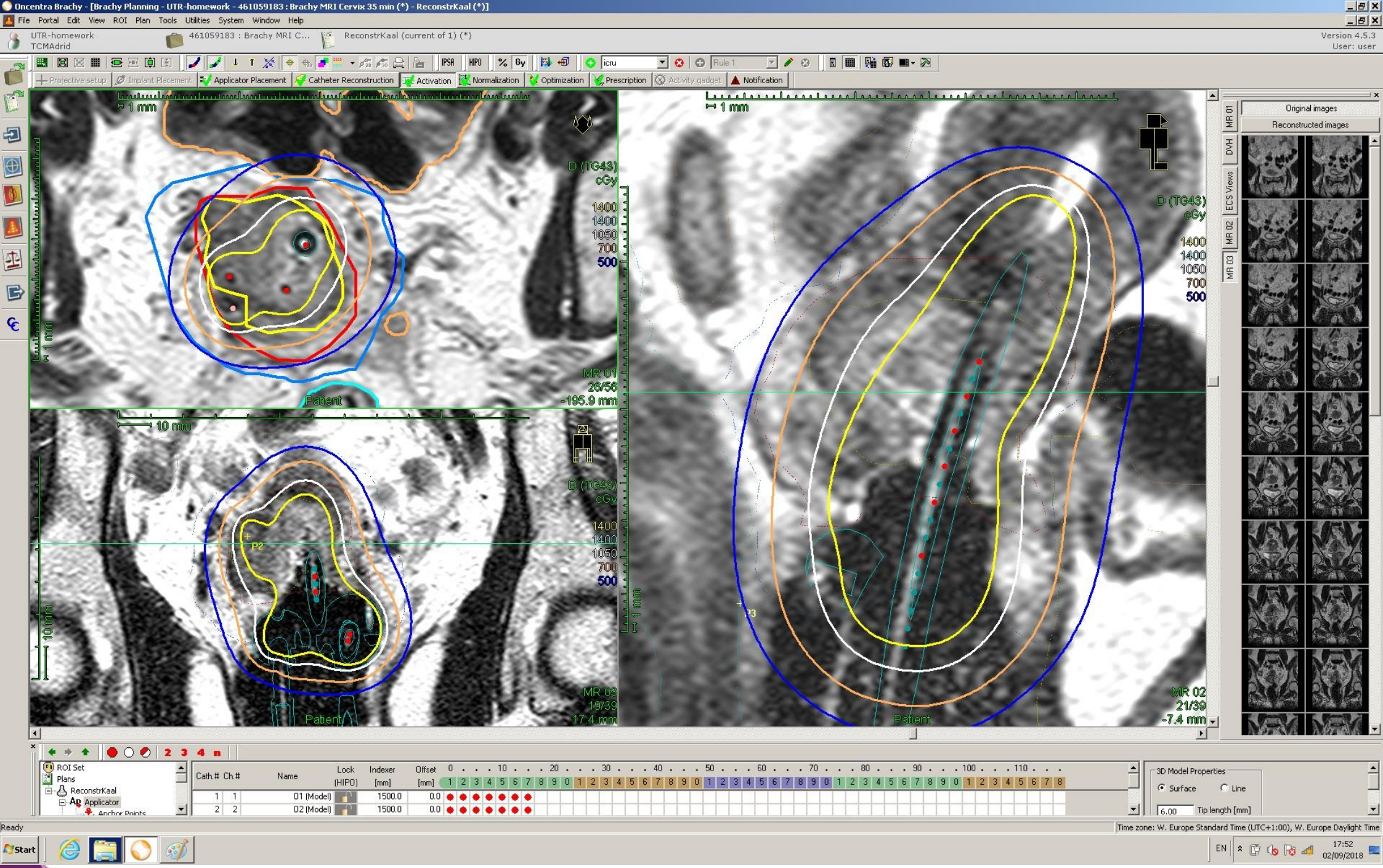
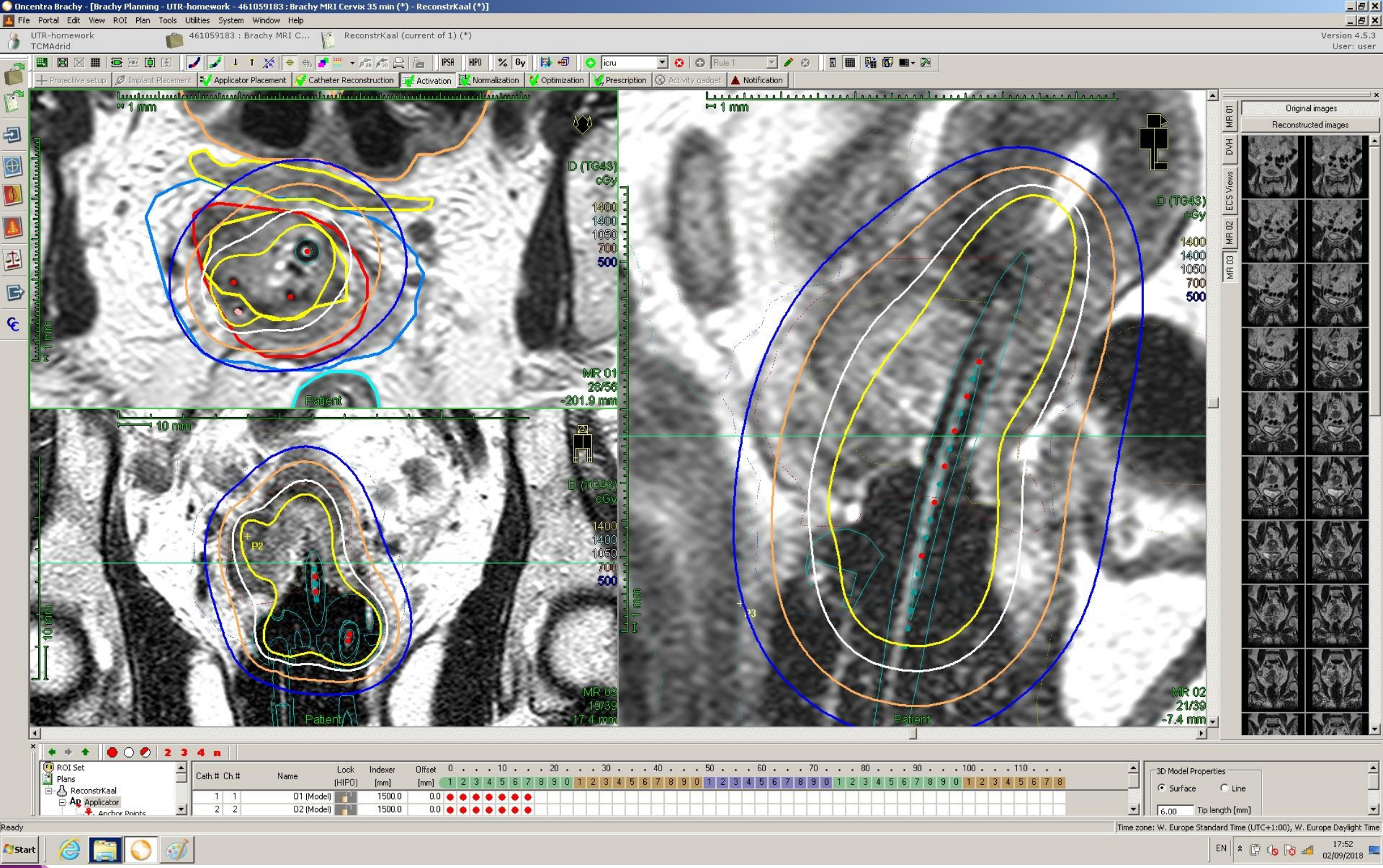
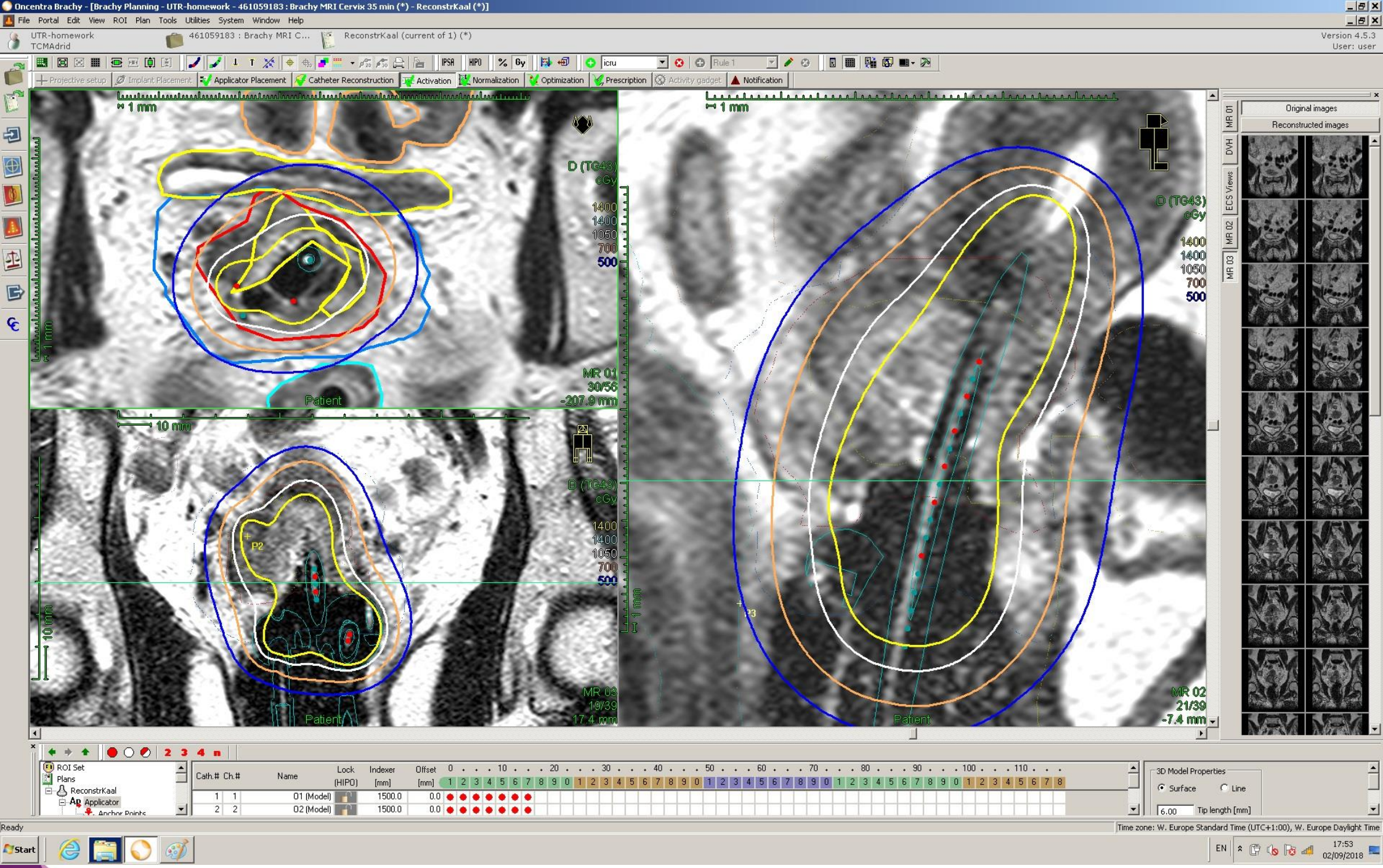


ESTRO School



ESTRO School



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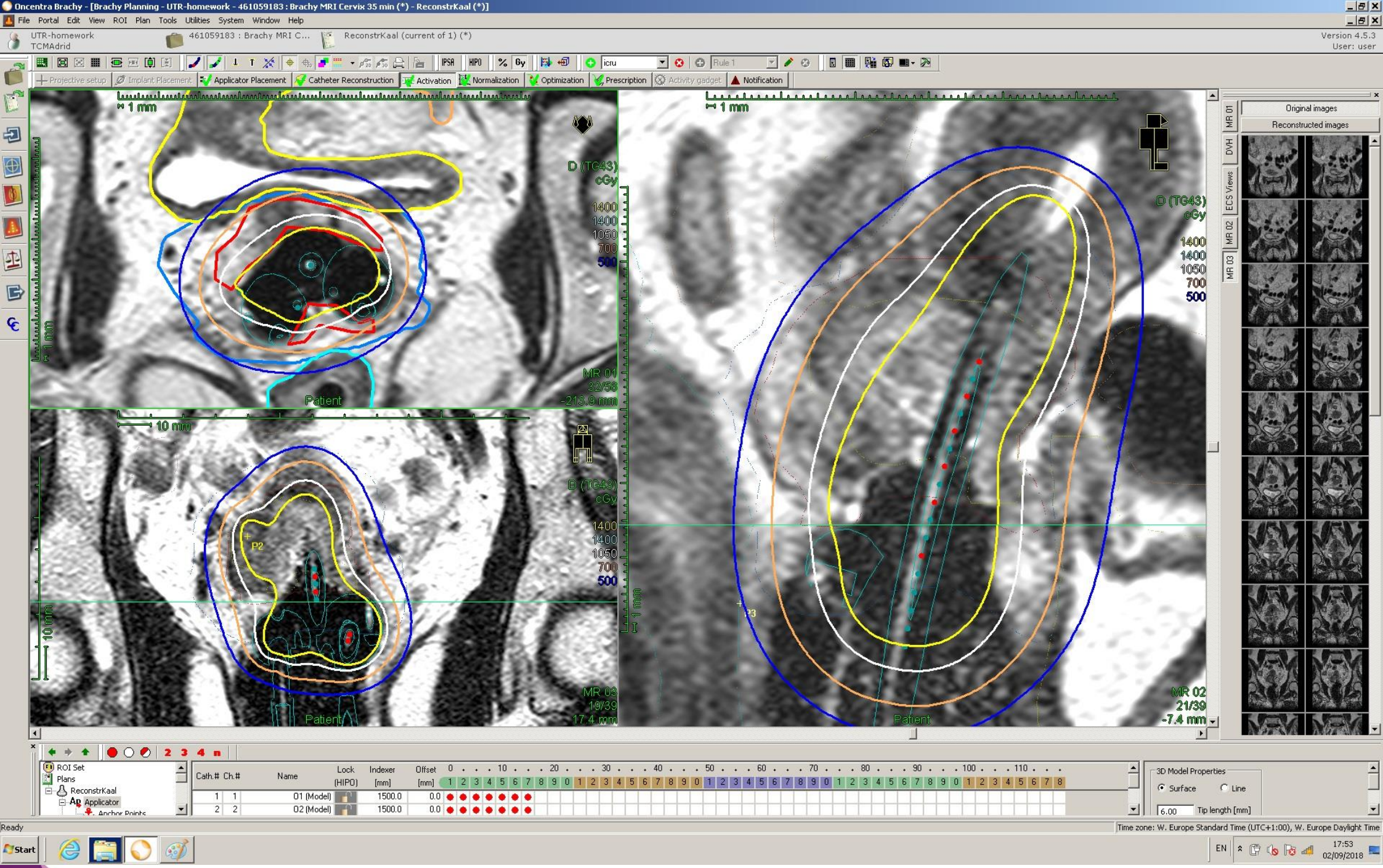

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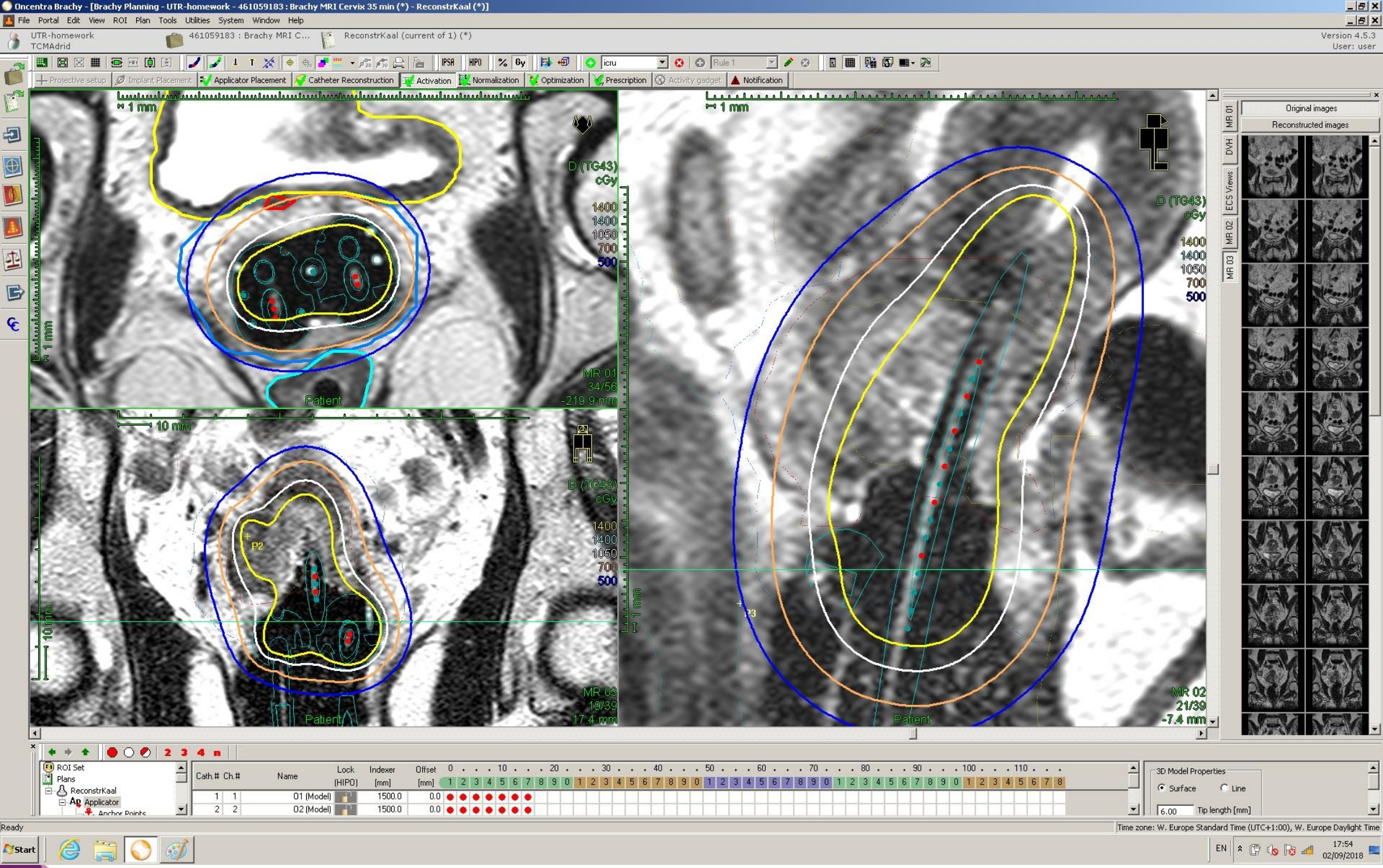

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Physics aspects of treatment planning intracavitary +/- interstitial techniques in cervix cancer

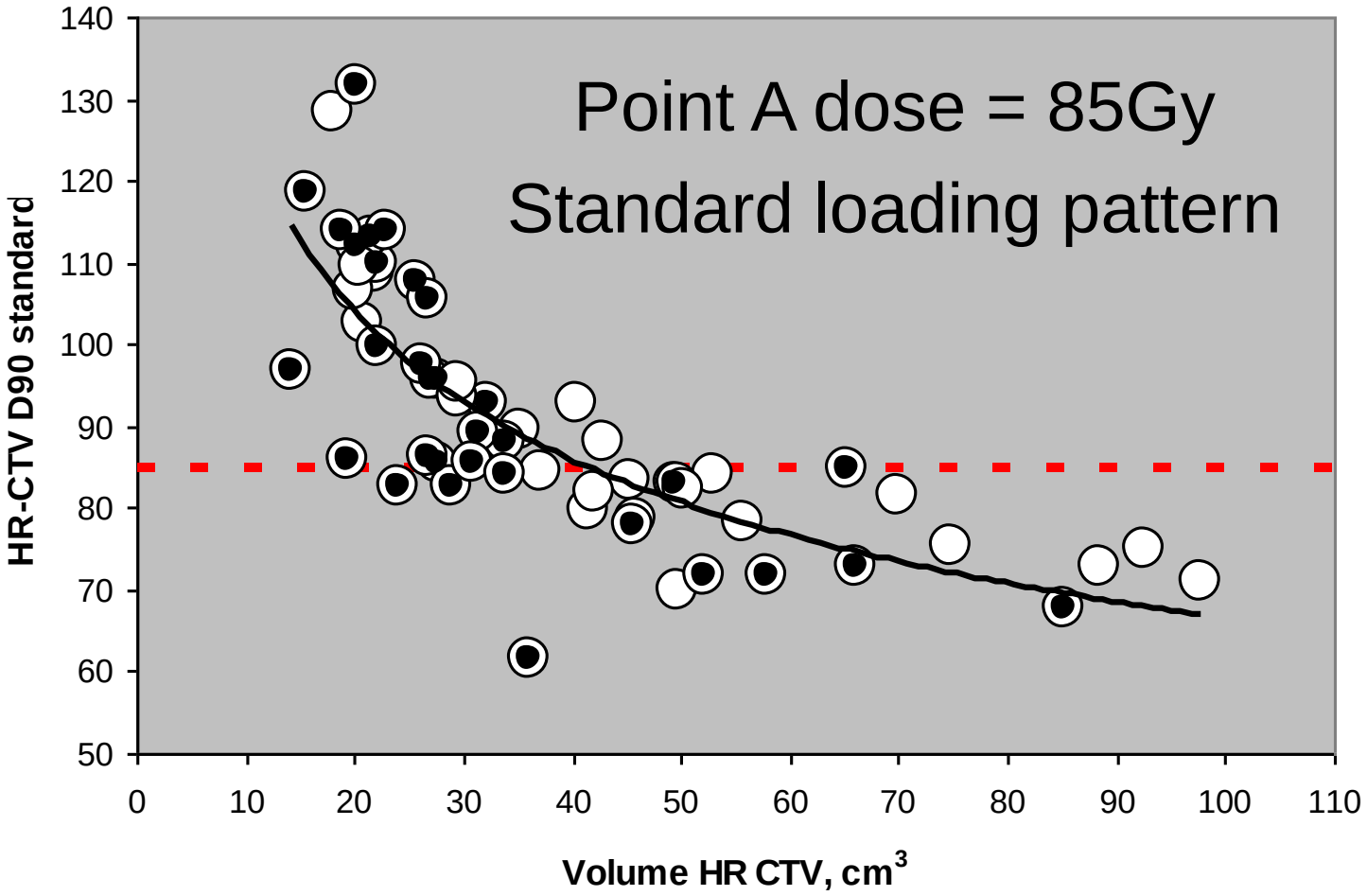
ESTRO Teaching Course
Image-guided radiotherapy & chemotherapy in gynaecological cancer - with a special focus on adaptive brachytherapy

Madrid 2018

Kari Tanderup, PhD

Aarhus University Hospital

Paradox of standard point A dose prescription



◉ Violation of OAR constraint

K Tanderup et al, Radiother Oncol 2010

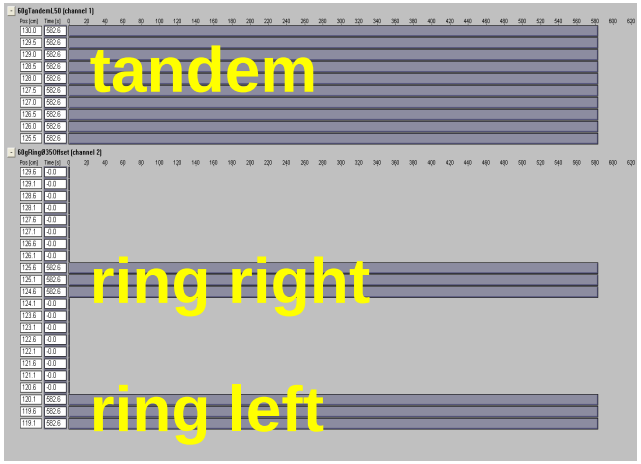
Tools for dose optimisation

- **Manual dose optimisation**
- **Graphical optimization / Dose shaper**
- **Inverse planning**

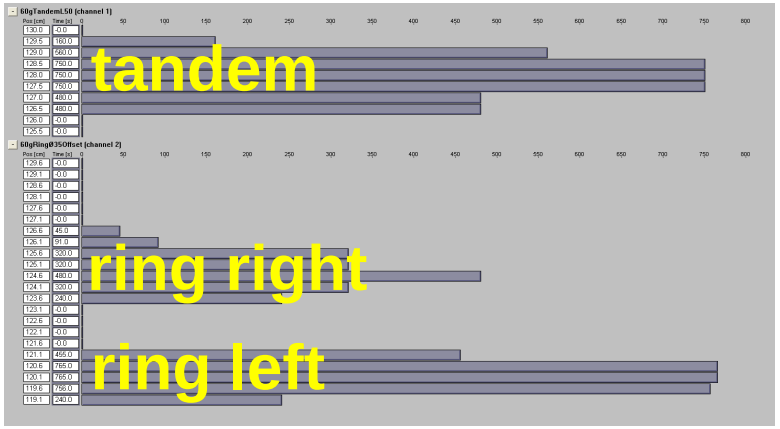
Manual optimisation

Dwell times

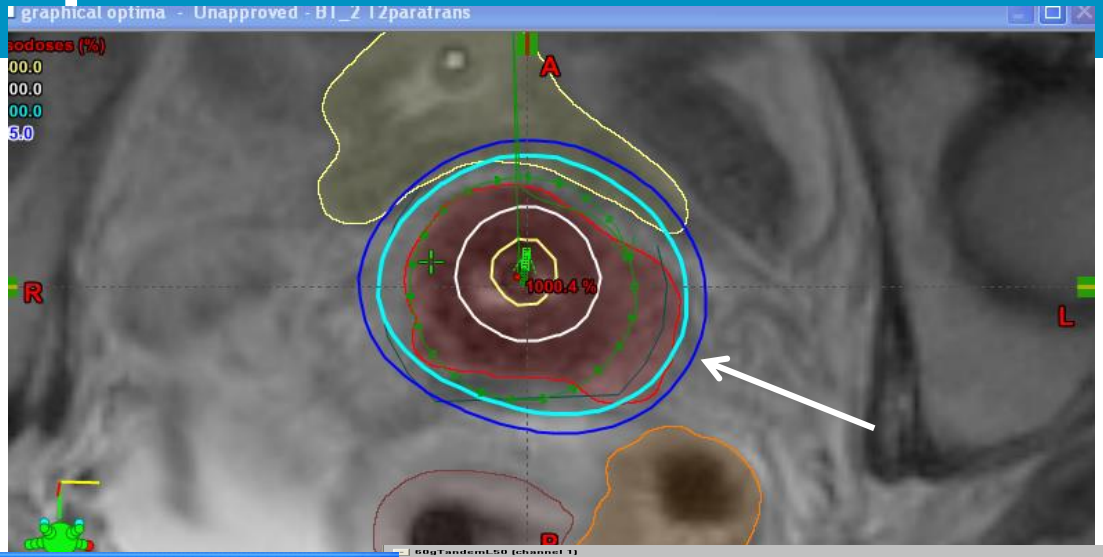
Standard

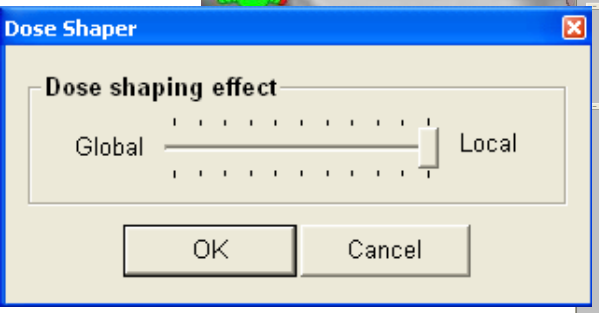


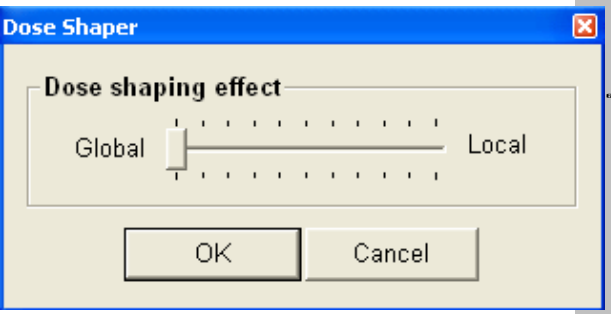
Manually optimised

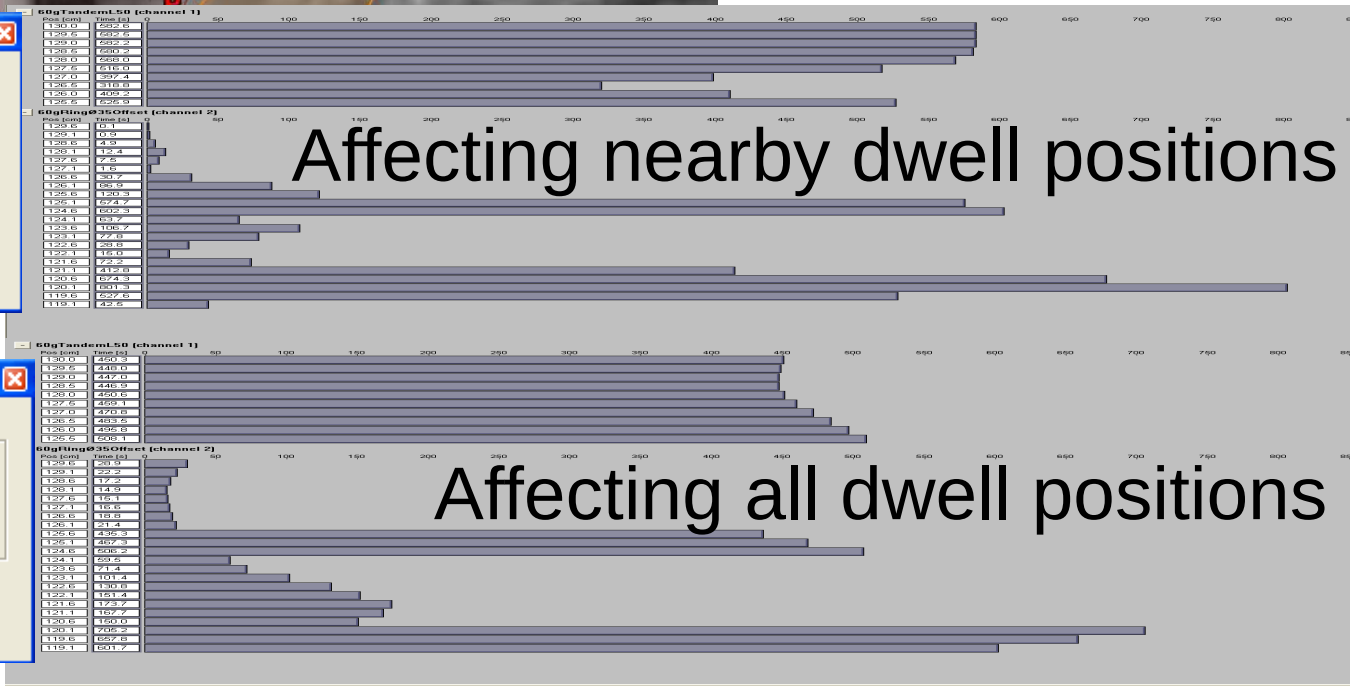


Graphical dose optimisation – “drag and drop”



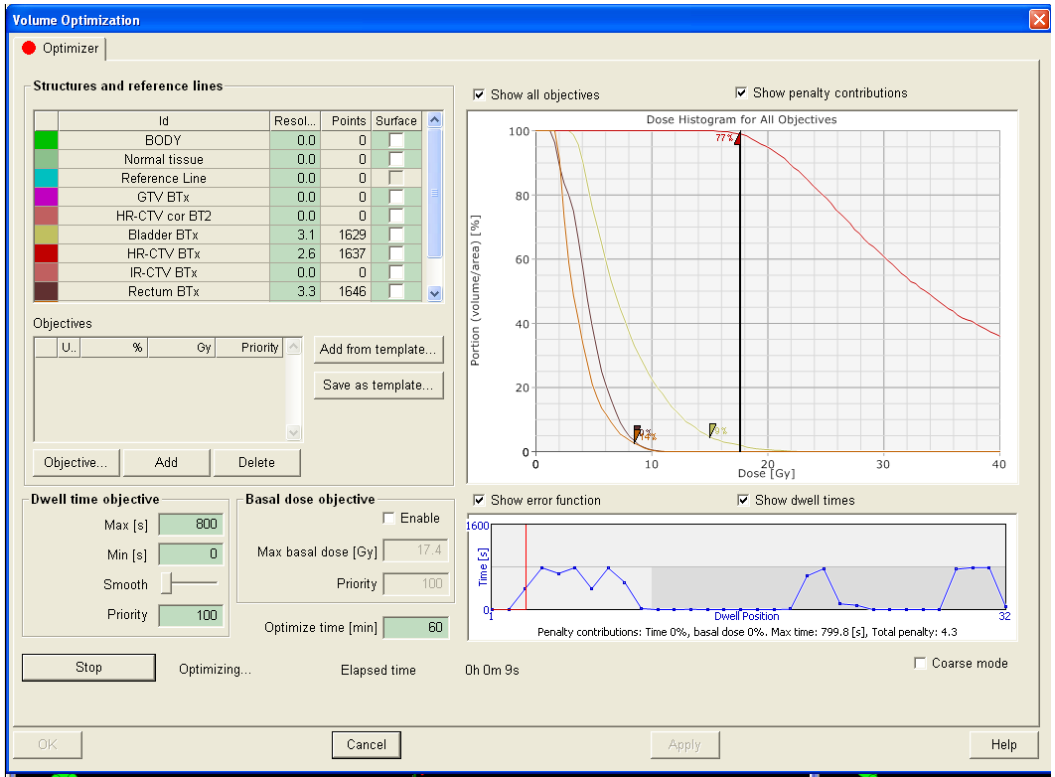






Inverse dose optimisation

- **Controlled by DVH constraints**
- **Weighting factors for different structures**

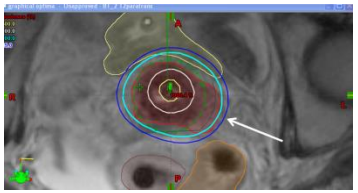


Which type do you prefer?

1. From scratch: manual

COOKED FROM SCRATCH

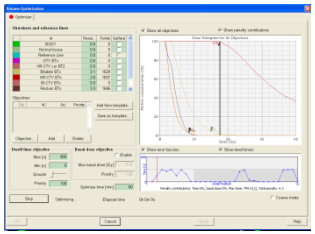
2. Elegant: drag and drop

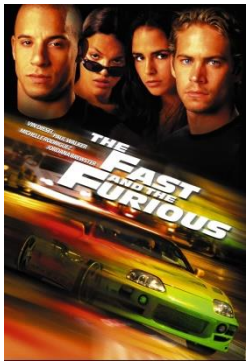


ELEGANT WOMAN

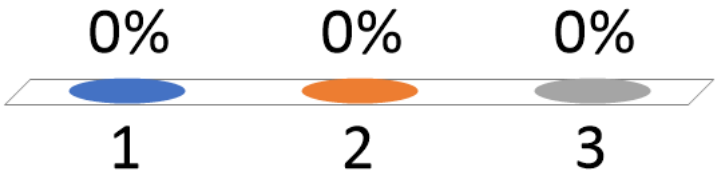
TIMELESS GRACE AND POISE FOR THE EVERYDAY WOMAN

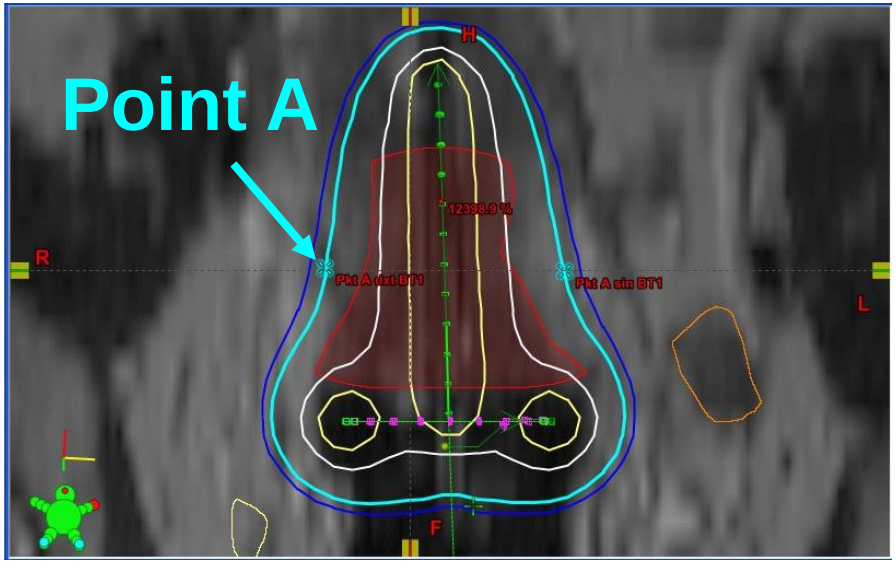
3. Fast and furious: inverse

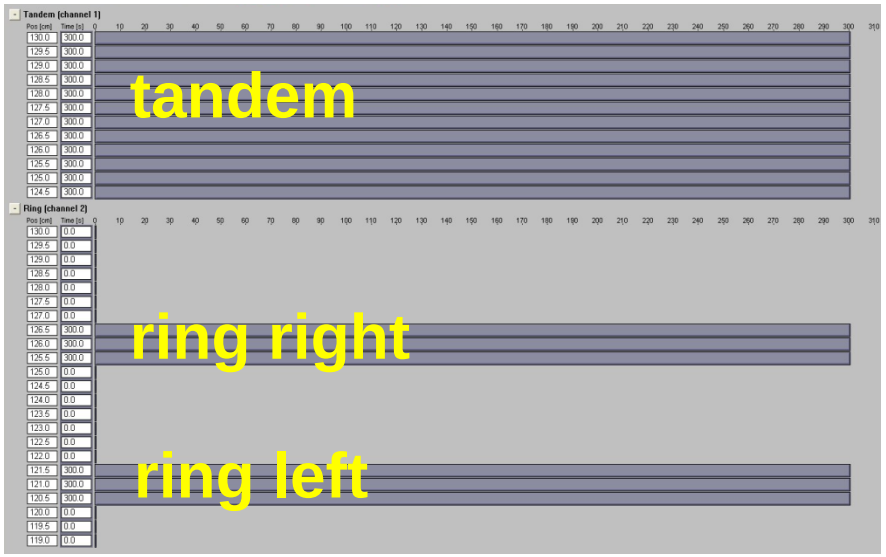




A. 1
B. 2
C. 3







Always start optimisation

with

Standard loading pattern

Standard prescription

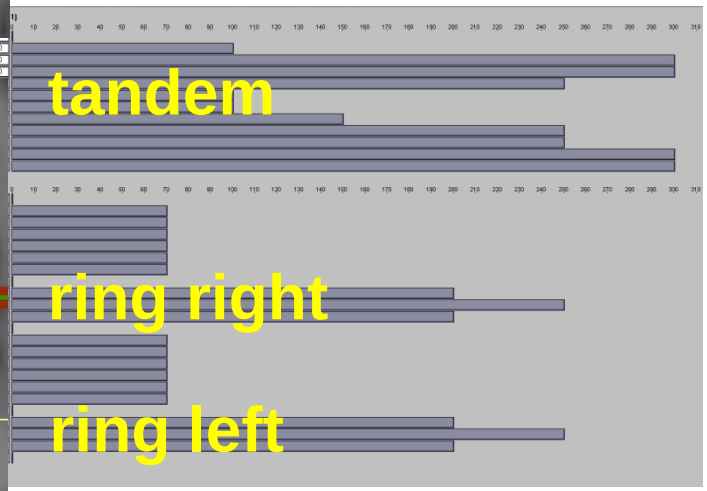
Example 1
Manual dose optimisation

Dose **Dwell times**

Standard

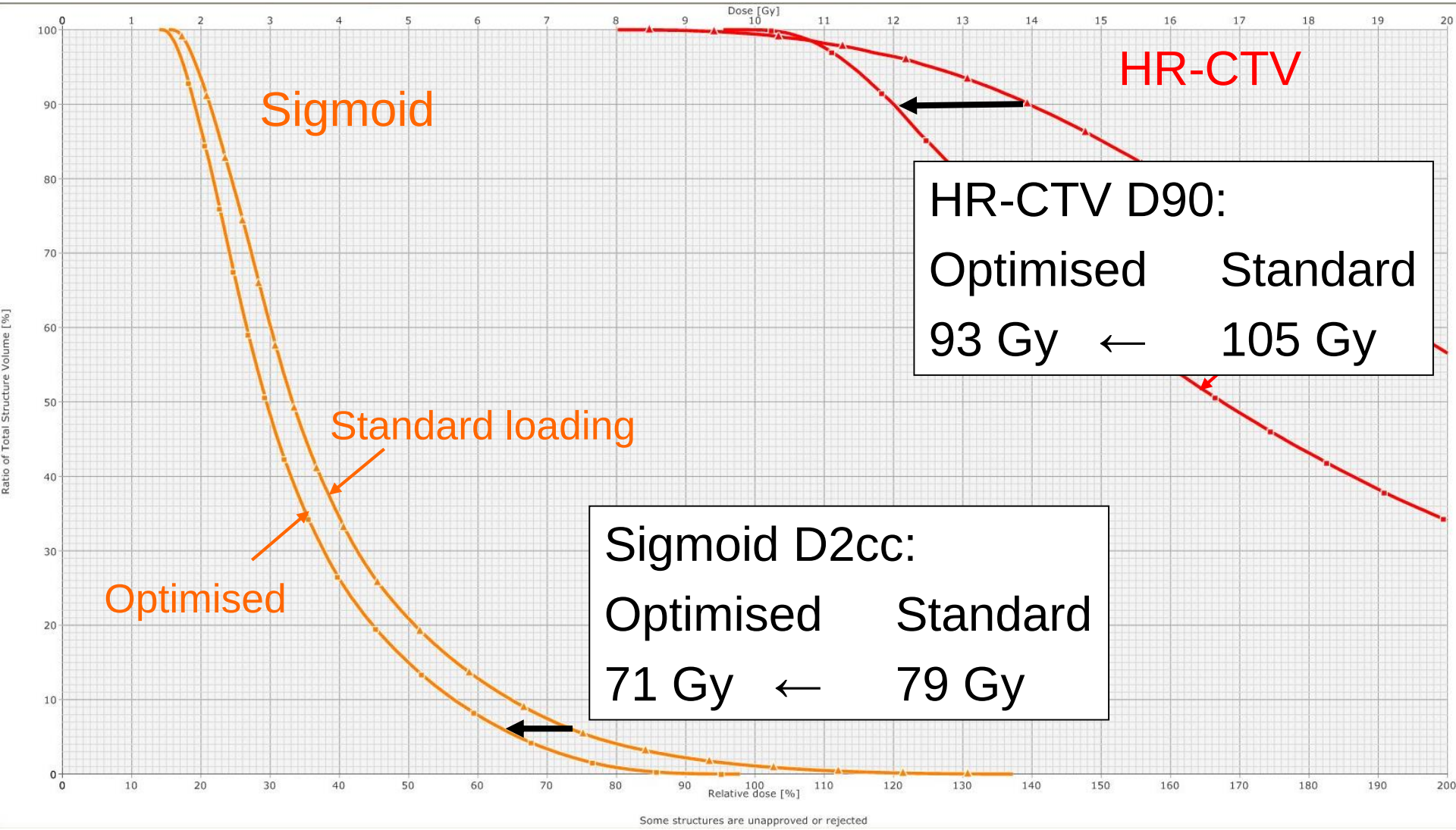
Point A = 7.1Gy ~ 84Gy EQD2
TRAK = 4*0.50 cGy

Manual optimisation

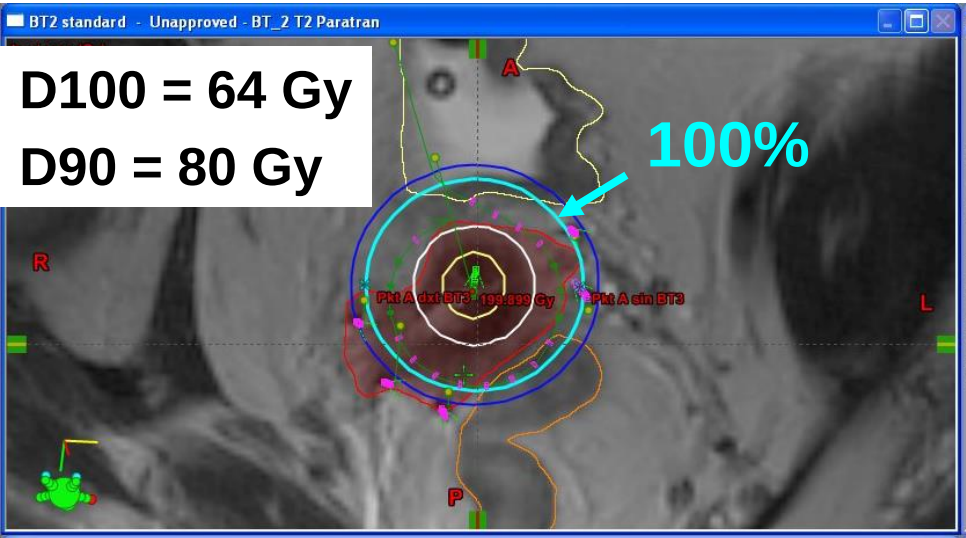


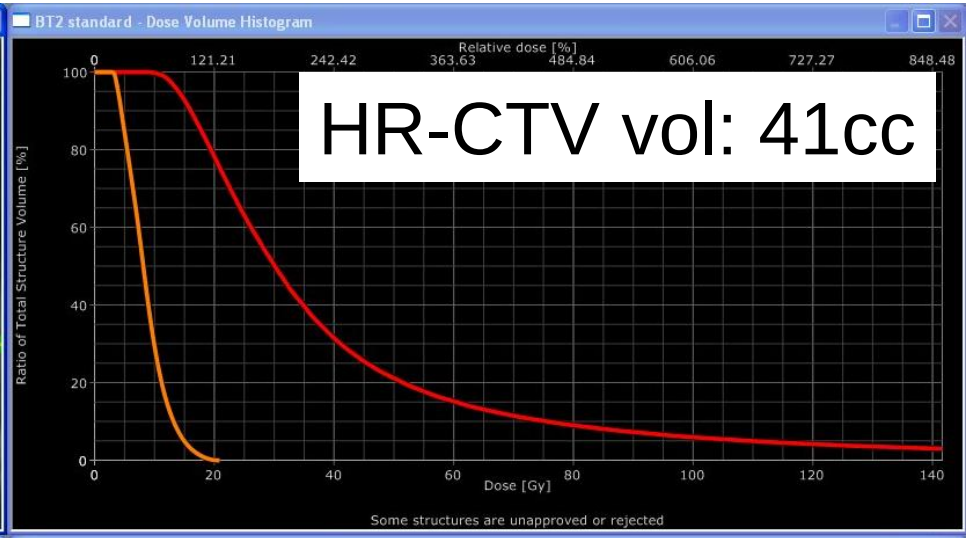
Point A = 5.3Gy ~ 71Gy EQD2
TRAK = 4*0.38 cGy
Reduction: 25%

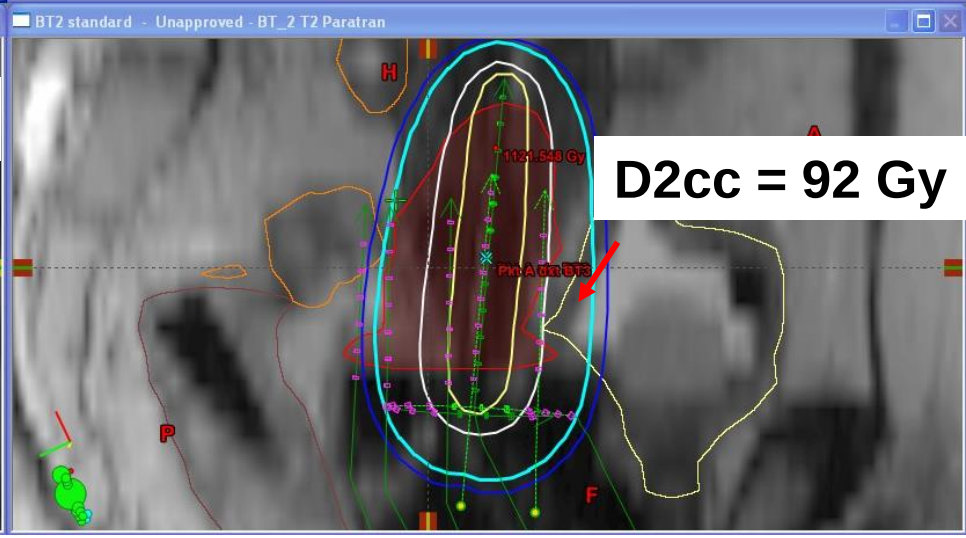
Example 1, DVH



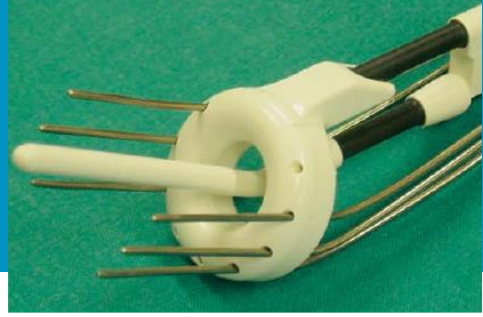
Example 2, Stage IIIB
Standard dose plan







Example 2
Manually optimised plan



Dose **Dwell times**

Standard

TRAK = 4 x 0.50 cGy

Manual optimisation

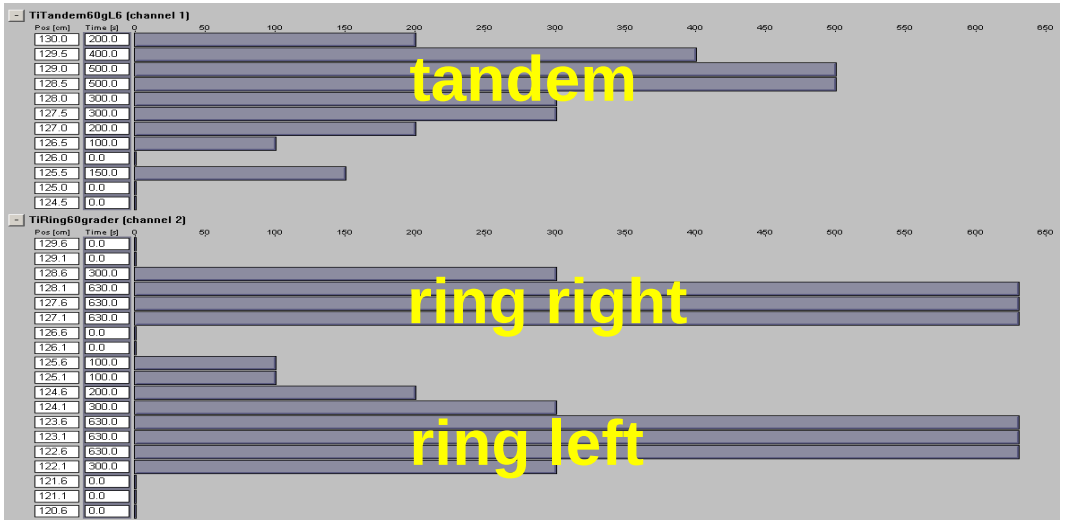
TRAK = 4 x 0.54cGy

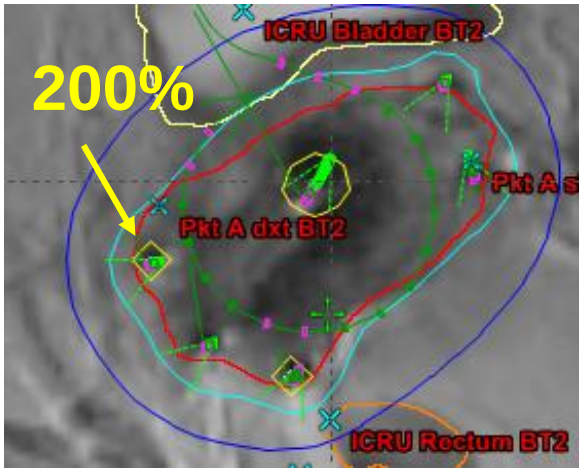
Increase: 7%

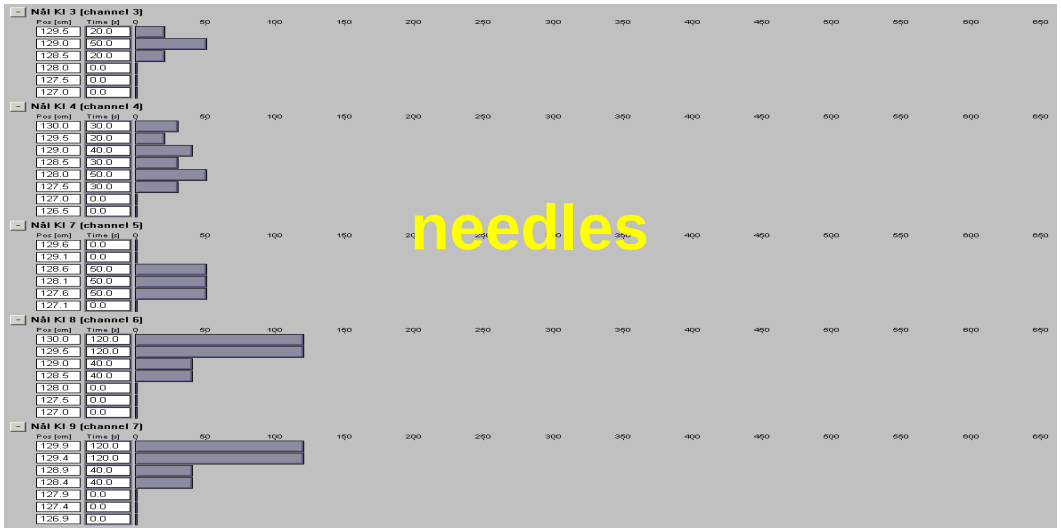
Loading of needles: dwell times and isodoses

Dwell times needles:

- **10-20% of dwell time in tandem/ring**
- **May be >20% if needle is placed directly in the GTV**

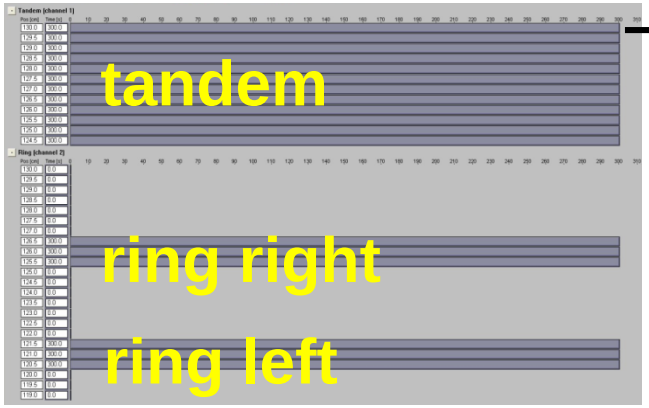






Dwell time threshold for needle loading

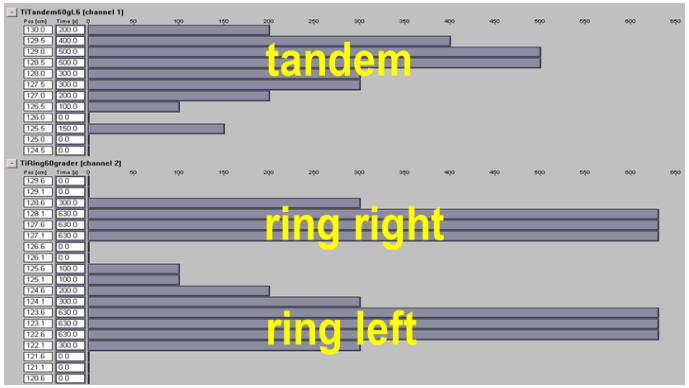
Standard plan

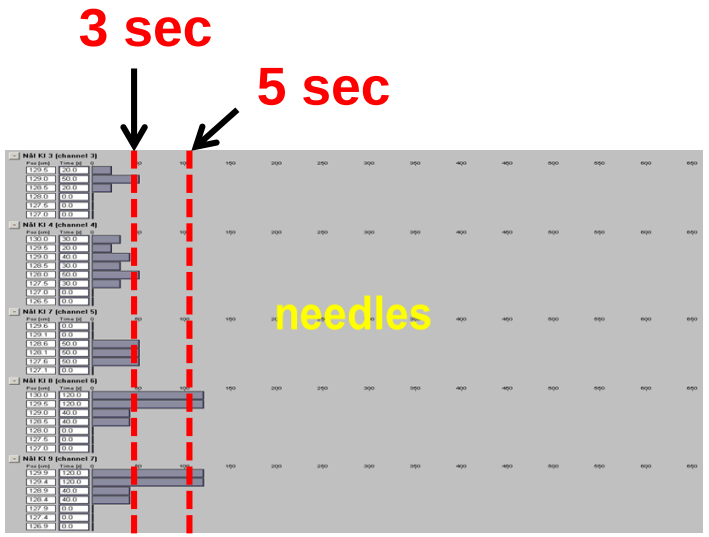


25 sec per dwell position in tandem

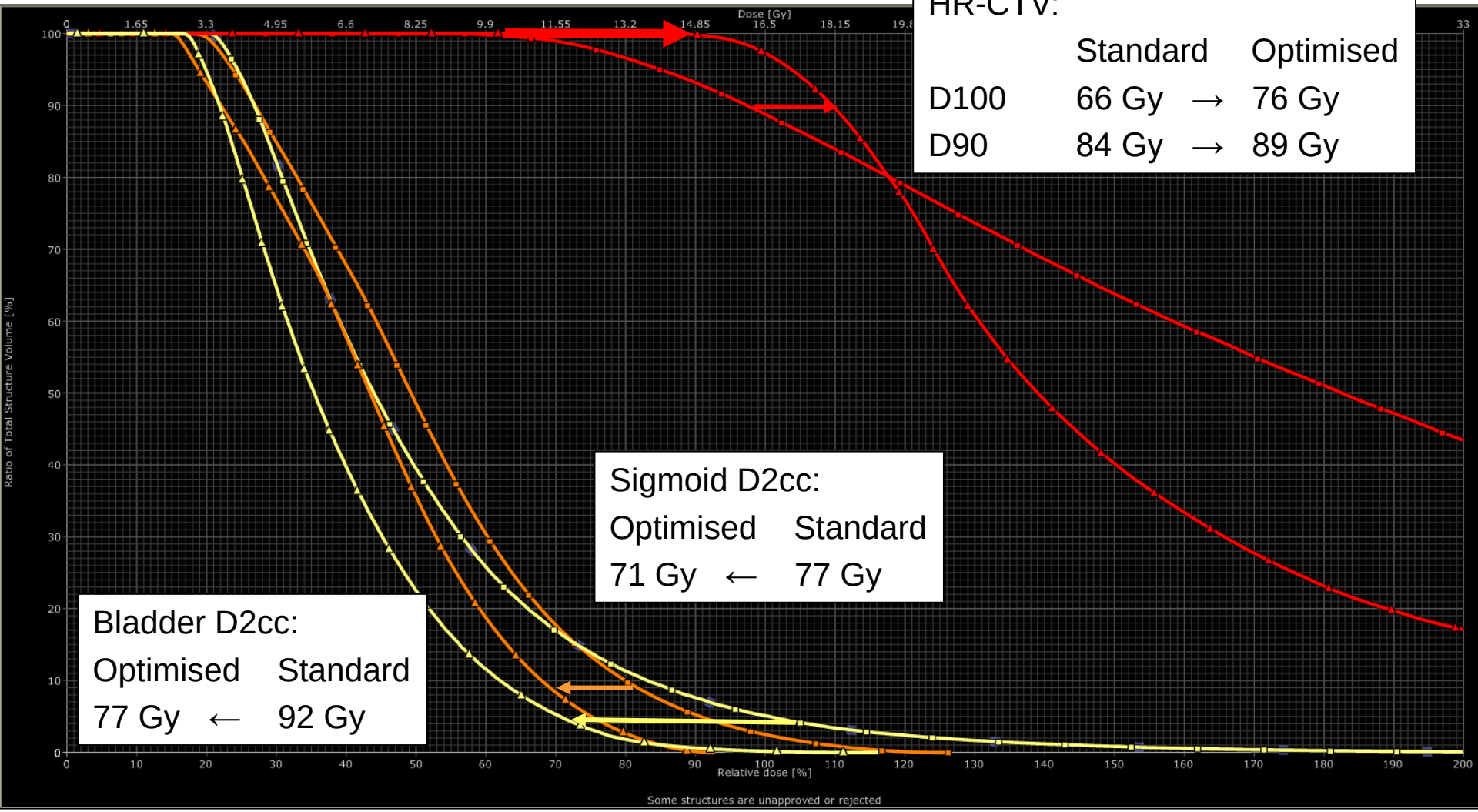
10-20% of 20 sec = 3-5 sec per dwell position in needle

Optimised plan

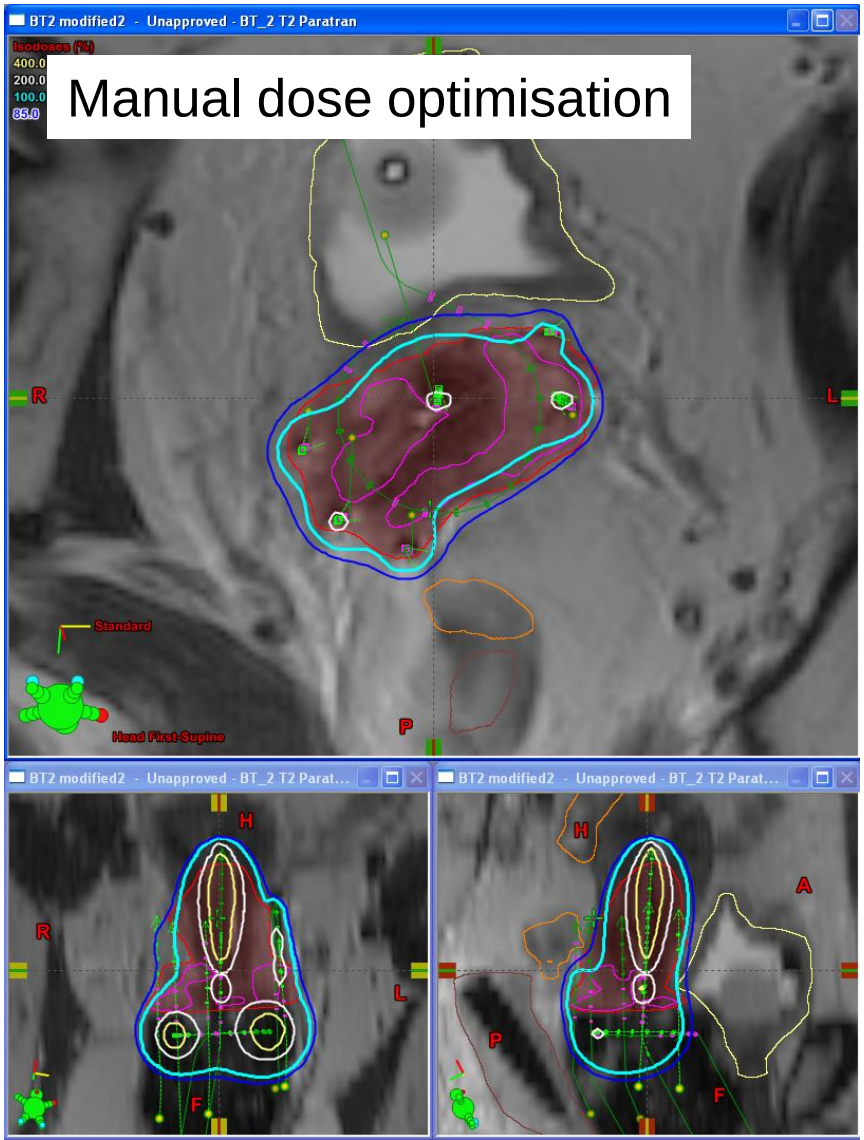


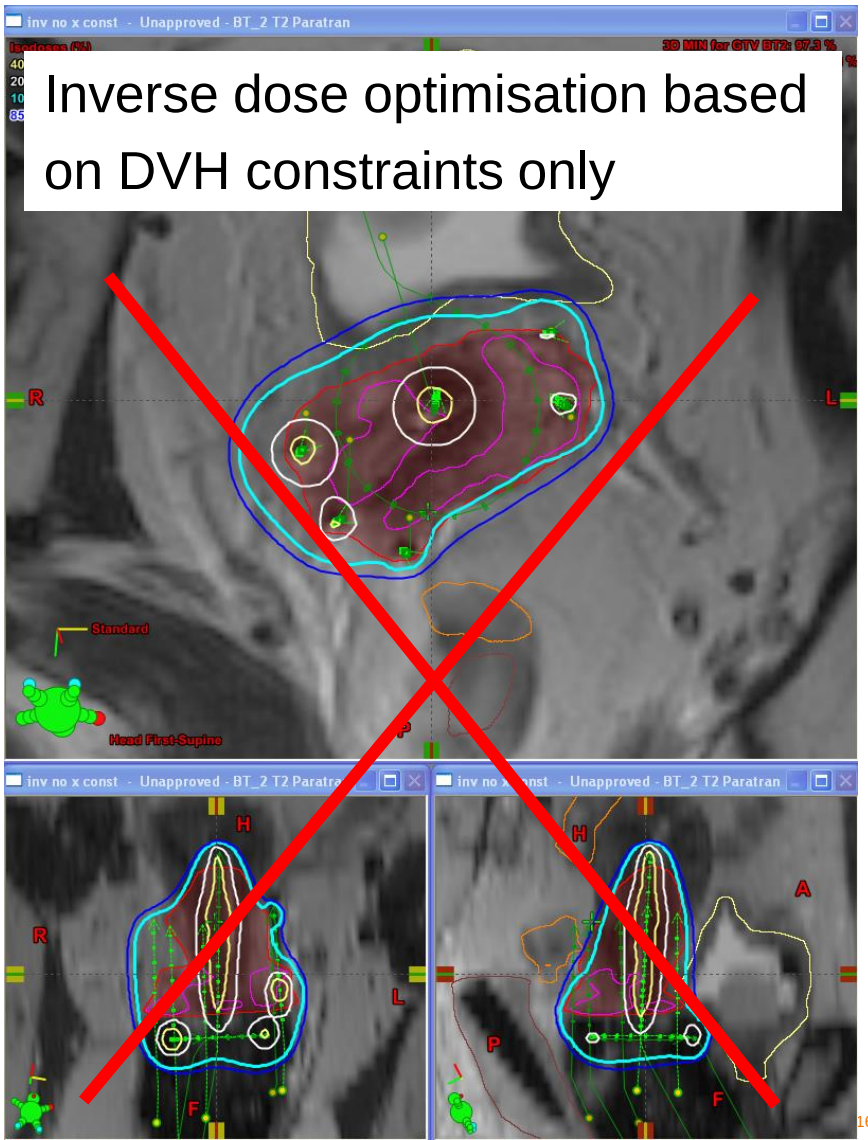


Example 2, DVH

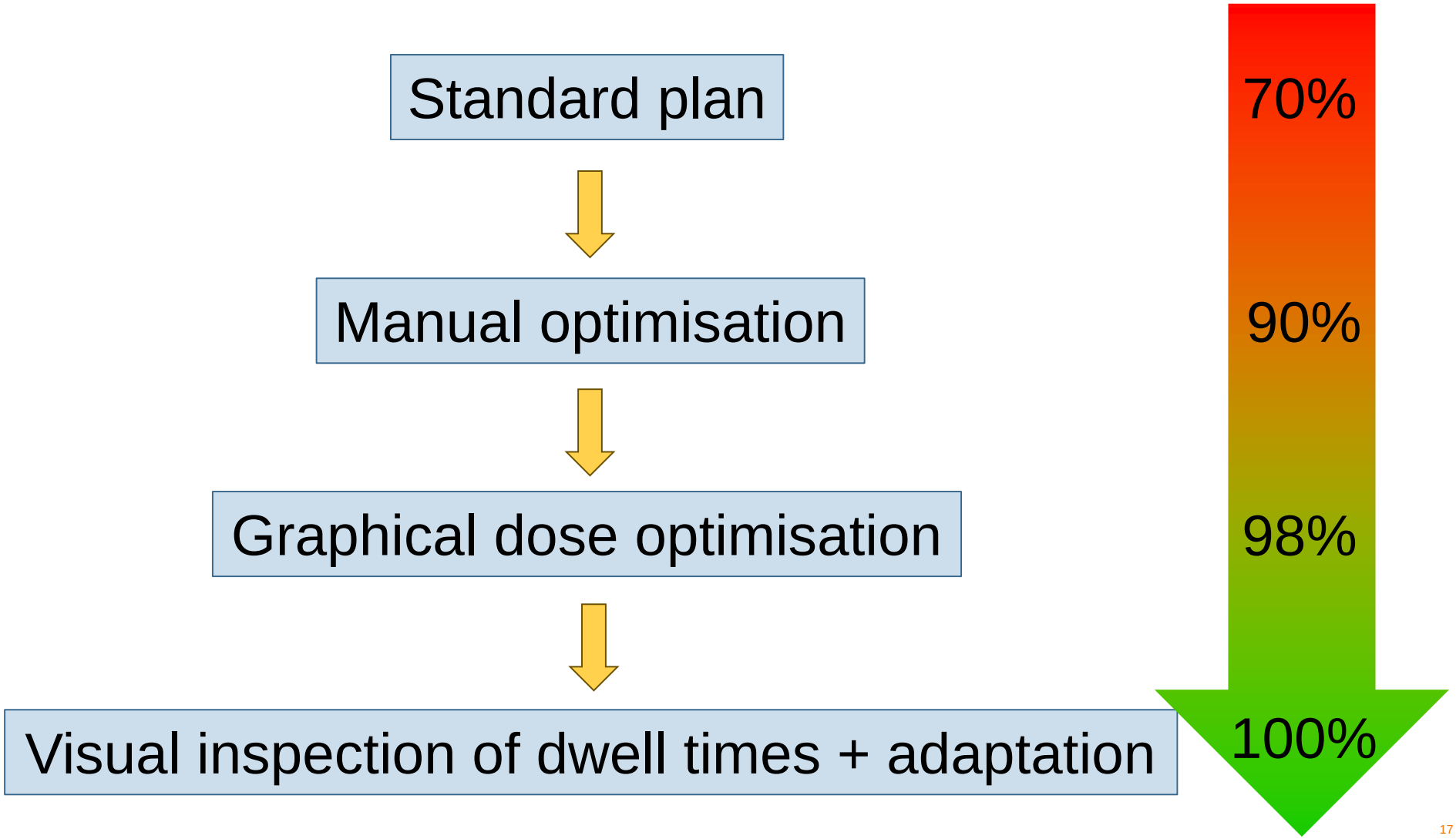


Example 2, inverse planning

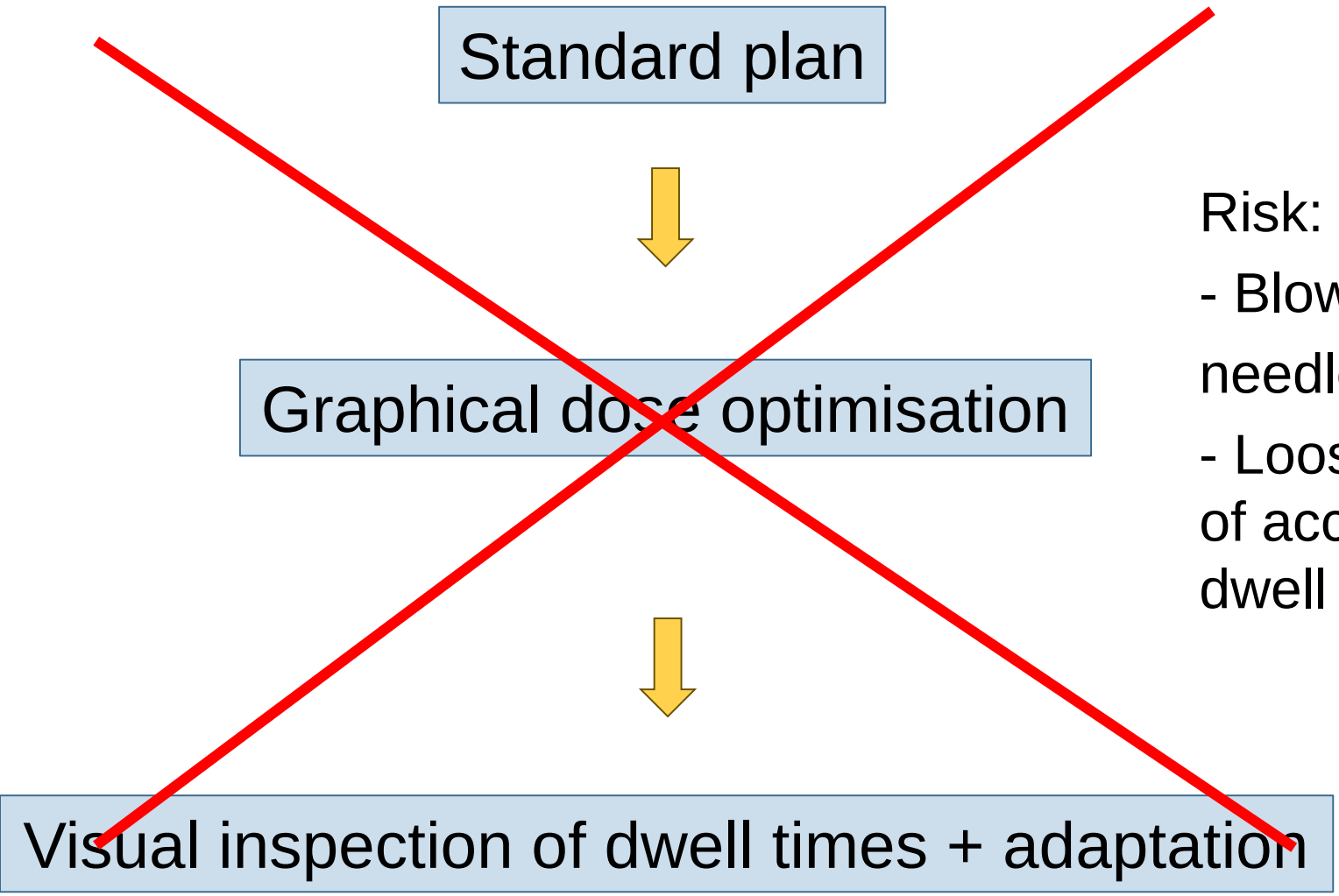




When to use graphical dose optimisation (dose shaper)?



When to use graphical dose optimisation (dose shaper)?

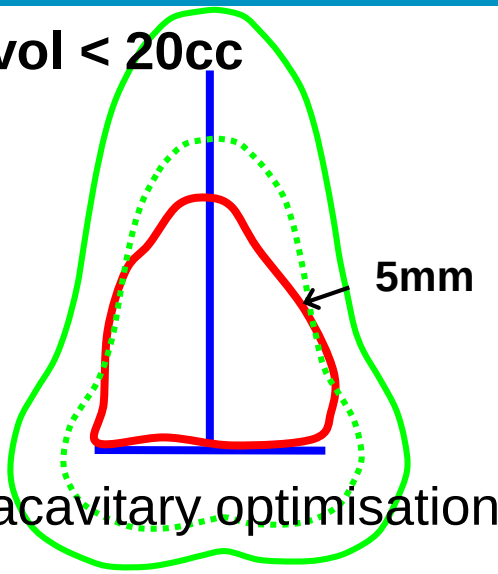


Risk:

- Blowing up needle loading
- Loosing intuition of acceptable dwell times

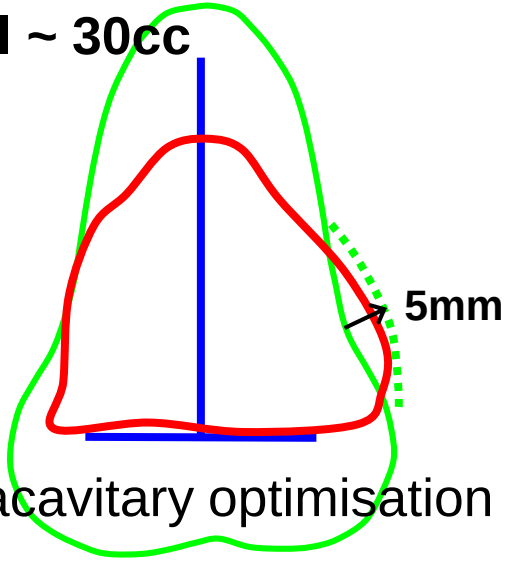
Typical scenarios of dose optimisation

HR-CTV vol < 20cc



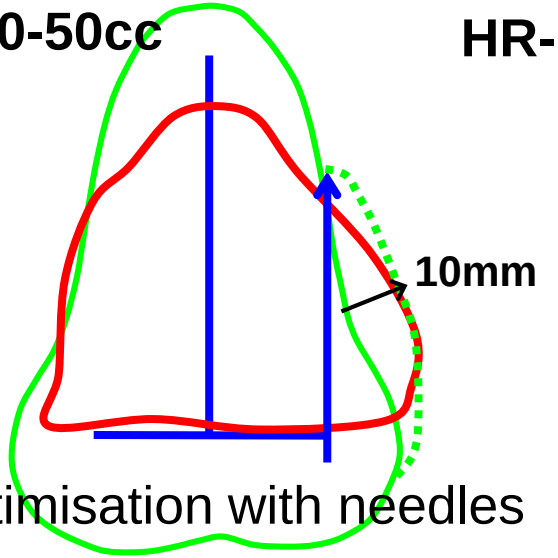
Intracavitary optimisation

HR-CTV vol ~ 30cc



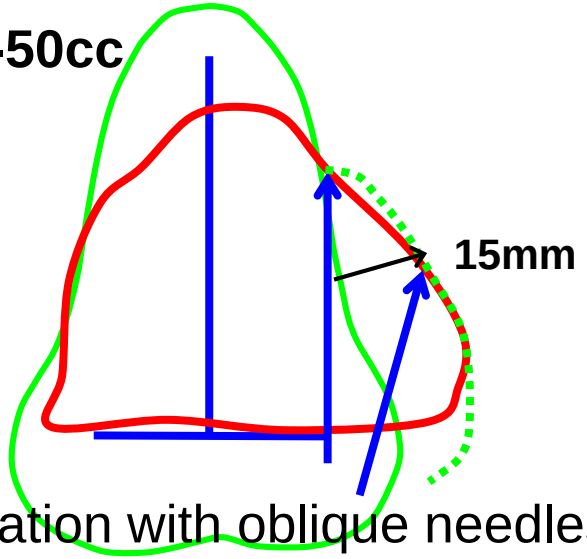
Intracavitary optimisation

HR-CTV vol > 40-50cc



Optimisation with needles

HR-CTV vol > 40-50cc



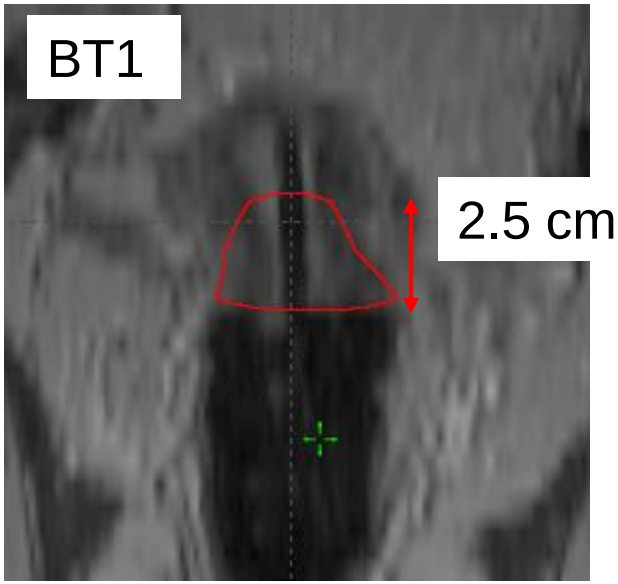
Optimisation with oblique needles

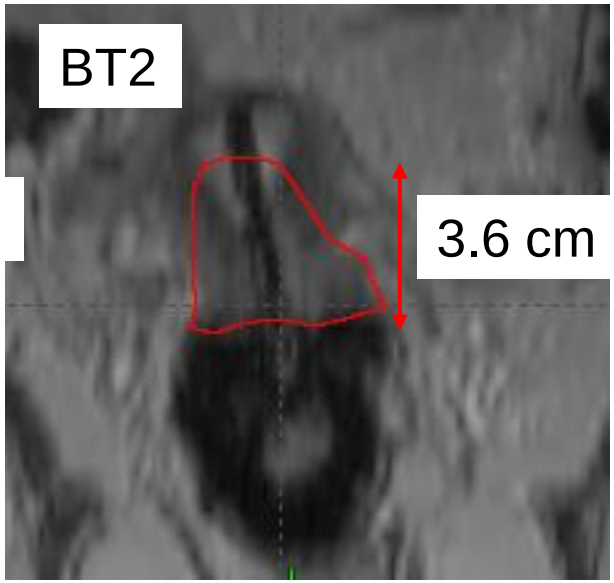
Conclusion – optimisation techniques

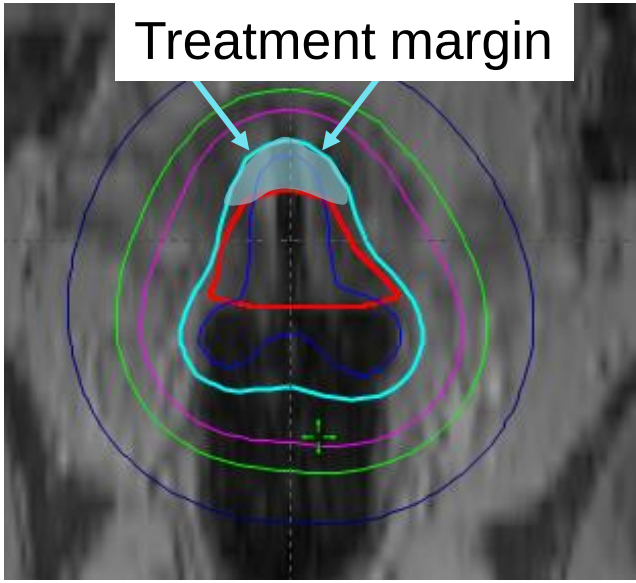
Manual	Conservative and “safe” Iterative procedure Dependent on experience of dose planner
Graphical	Fast for small adaptations and fine tuning after manual opt Beware of: -dwell times -deviations from standard loading
Inverse	Fast Requires extra contouring + manual adaptations Beware of: -dwell times -high dose regions -dose to non-contoured tissue -deviations from standard loading

PTV???
Example contouring uncertainty

- **Variation in cranial border of HR-CTV**
- **Intra-observer variation!**
- **<u>Load the tandem above the CTV_{HR} when feasible</u>**

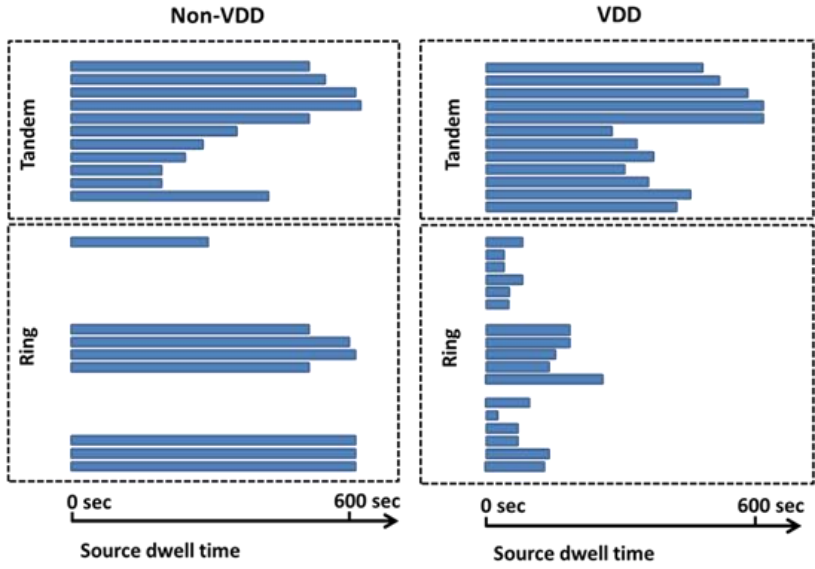


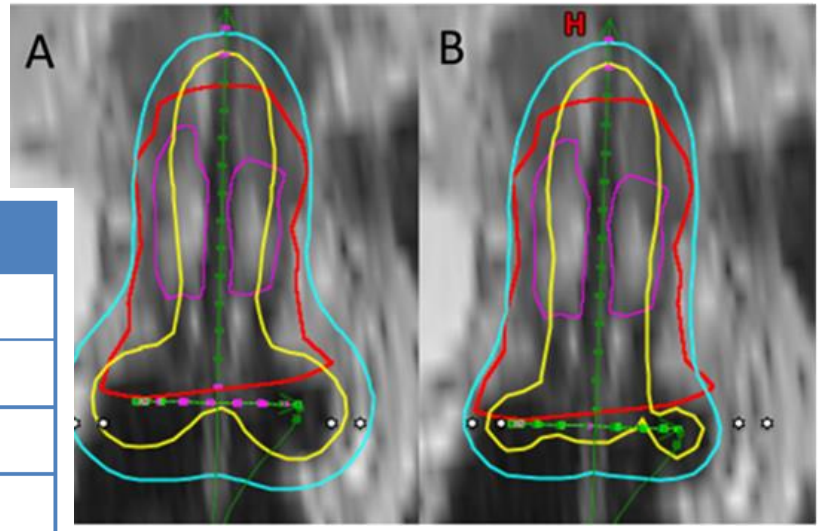




Vaginal dose de-escalation

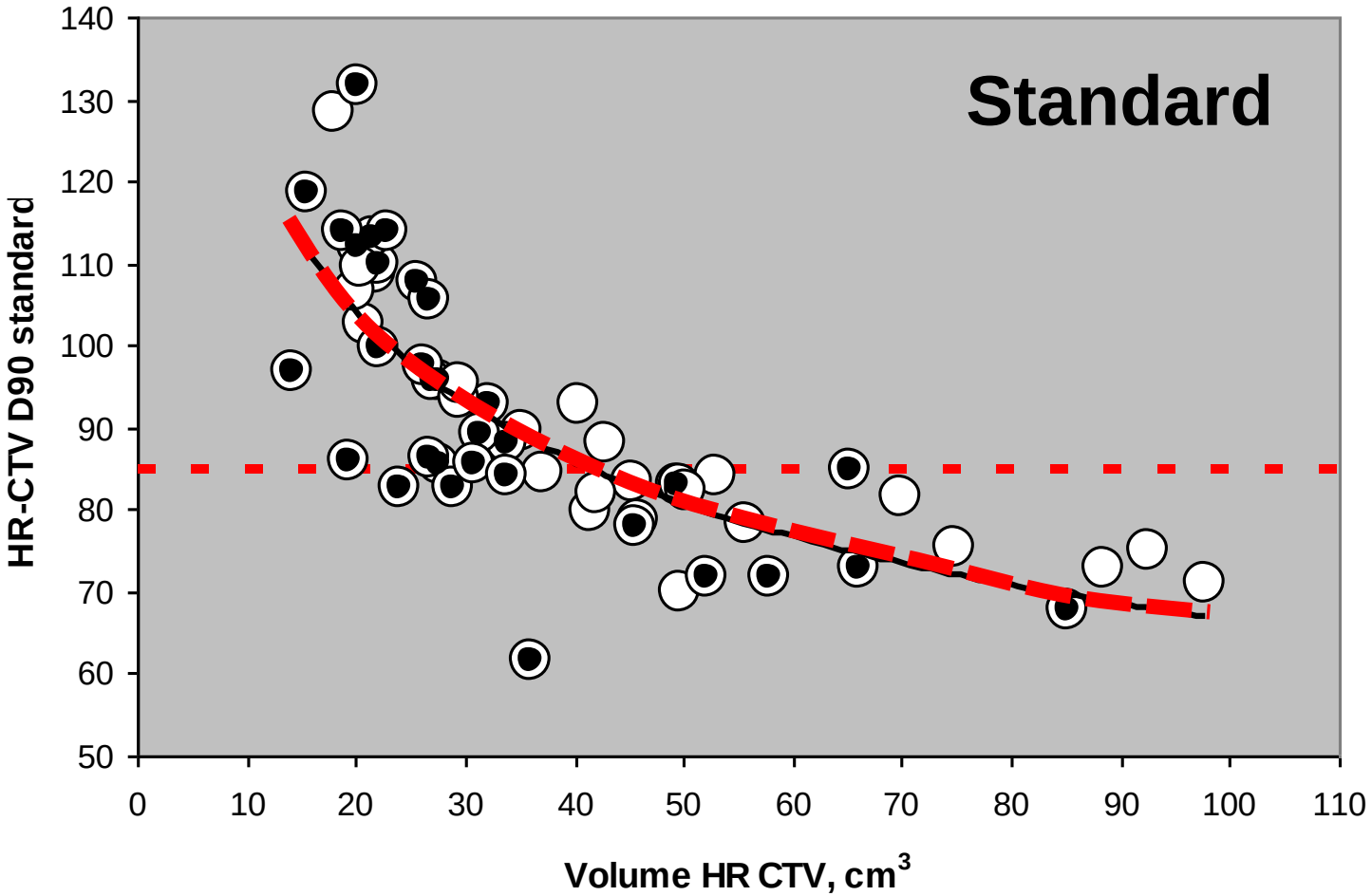
- **Change of loading pattern:**
  - **Shift of dwell time from vaginal sources to tandem/needles**
  - **Aim for 140% isodose out of vaginal mucosa**
  - **Aim for <30-40% loading in ring/ovoids**





	Aim	Priority
ICRU recto-vaginal point dose	<65Gy EQD2 (EBRT+BT)	Primary
The ratio of vaginal TRAK and total TRAK	<30-40%	Secondary
Vaginal lateral dose points at 5mm	<85Gy EQD2 (EBRT+BT)	Secondary
Visual inspection of the 140% isodose	Intruding as little as possible into vaginal tissue, and preferentially located within the applicator	Secondary

From standard to…



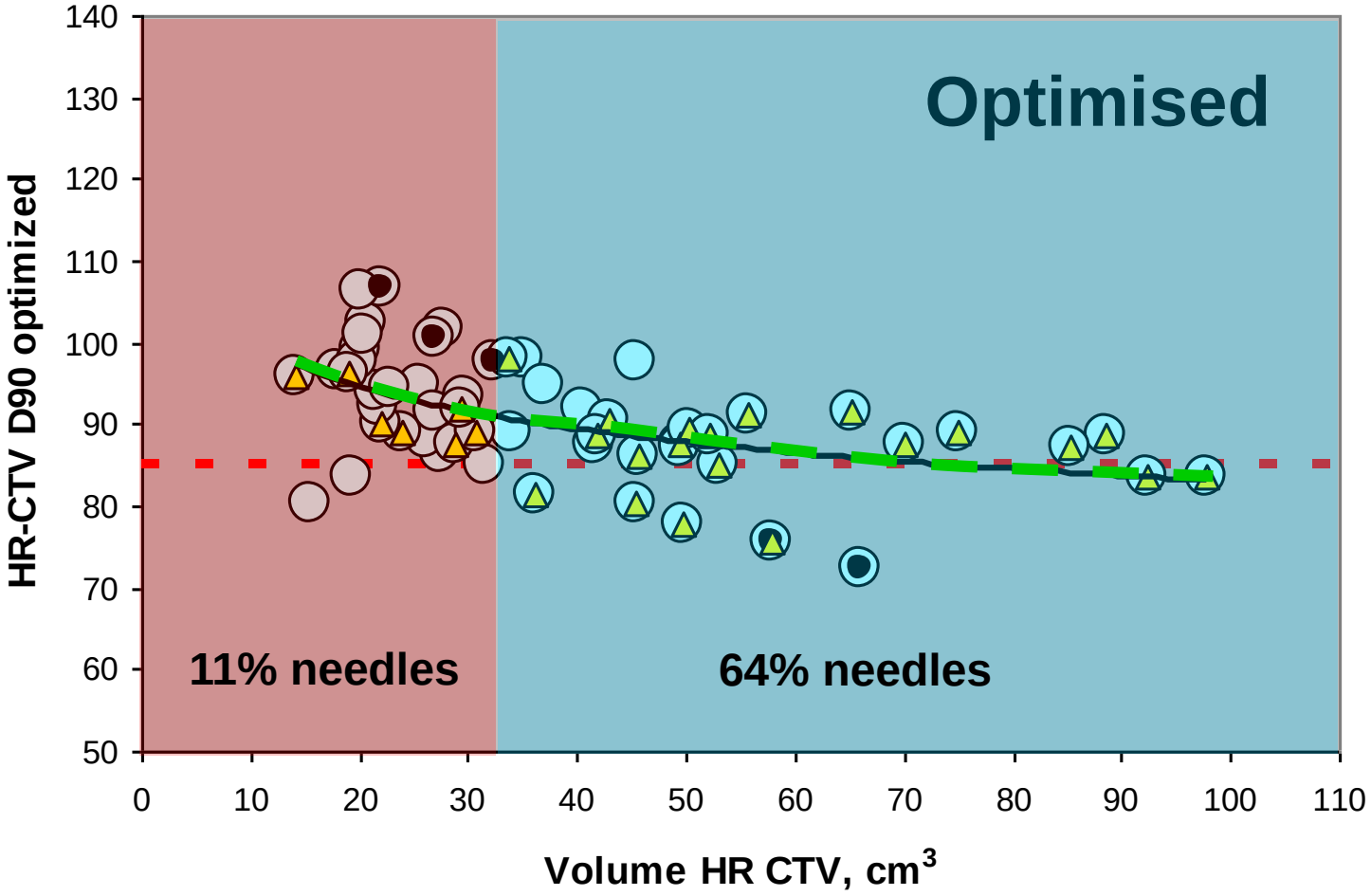
◉ Violation of OAR constraint

K Tanderup et al, Radiother Oncol 2010

From beach-boys to…

From standard to optimised

K Tanderup et al, Radiother Oncol 2010



Violation of OAR constraint

Application of needles

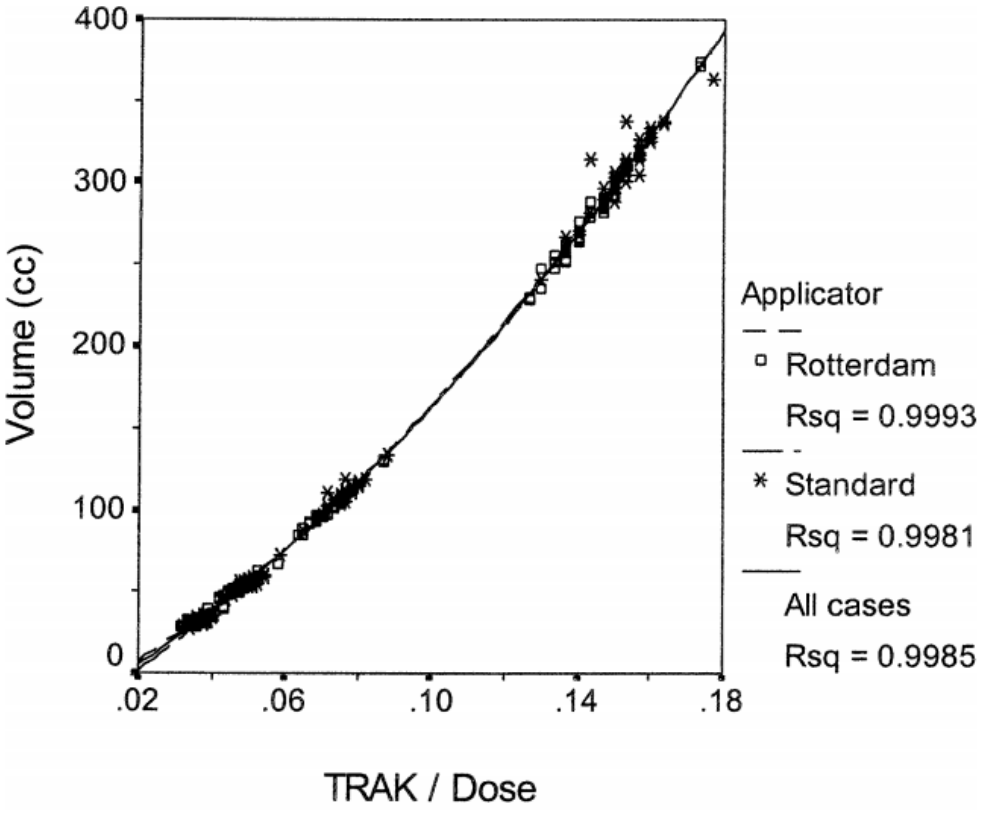
From beach-boys to bar-boys

Keep track of your TRAK!
Total Reference Air Kerma

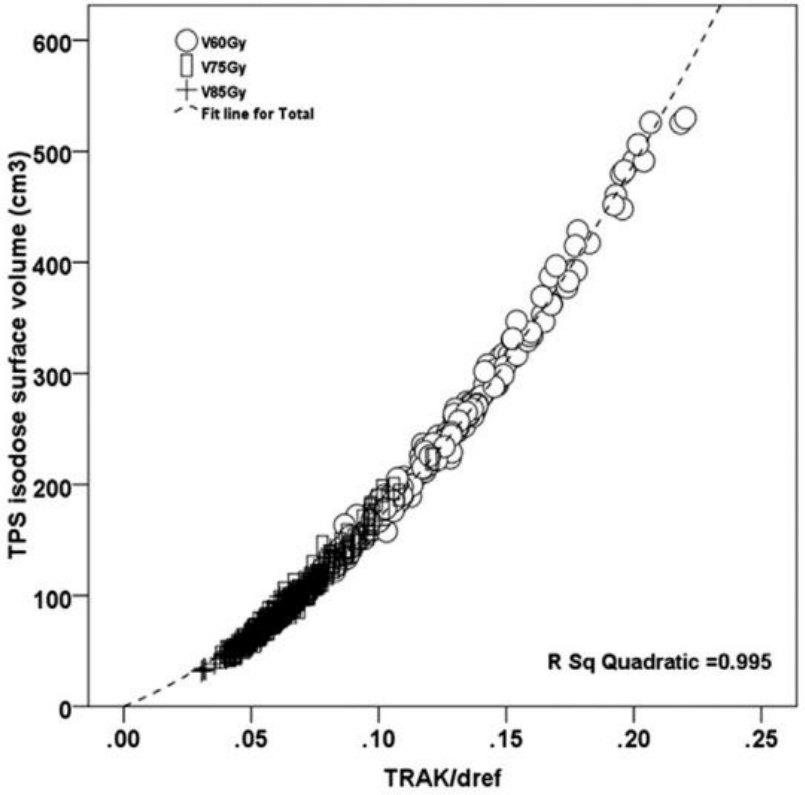
TRAK = $\sum t_i$ * RAKR

RAKR = 4.07 cGy/s (10Ci Ir-192)

$$Vref = 4965\left(\frac{TRAK}{d_{ref}}\right)^{3/2} + \left(\frac{TRAK}{d_{ref}}\right) - 1.5$$

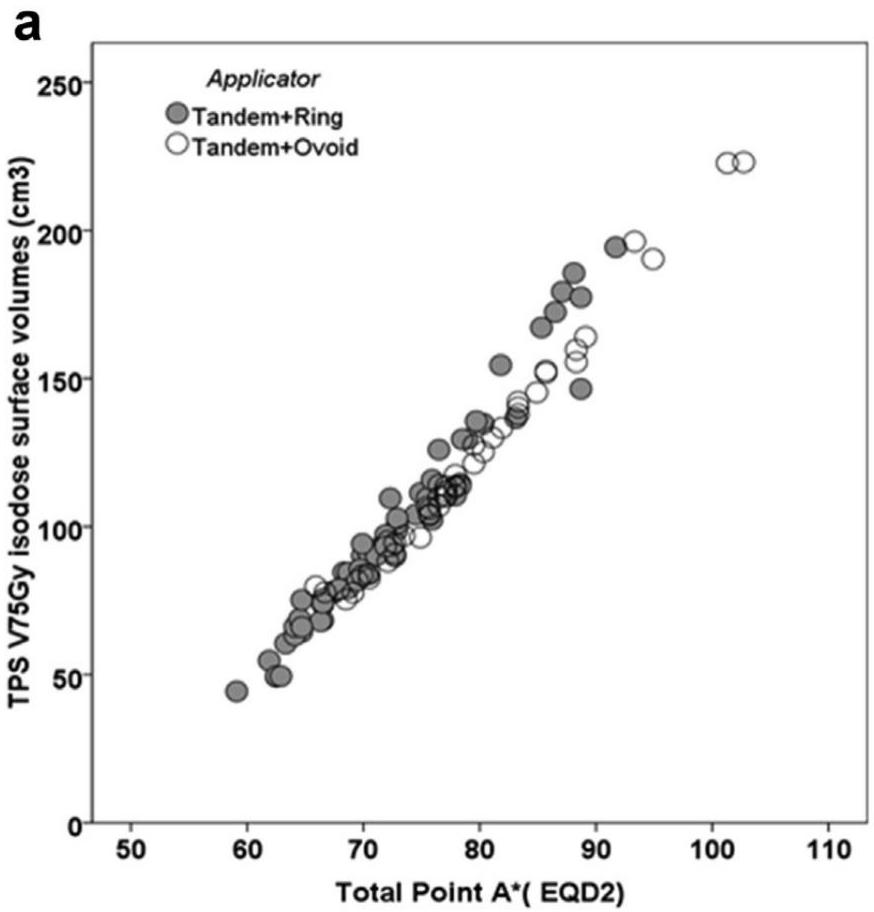


Datta et al, Brachytherapy 2:91–97, 2013



Nkiwane et al, Brachytherapy 16(6):1184-1191, 2017

Why is point A still important in 3D image based brachytherapy?

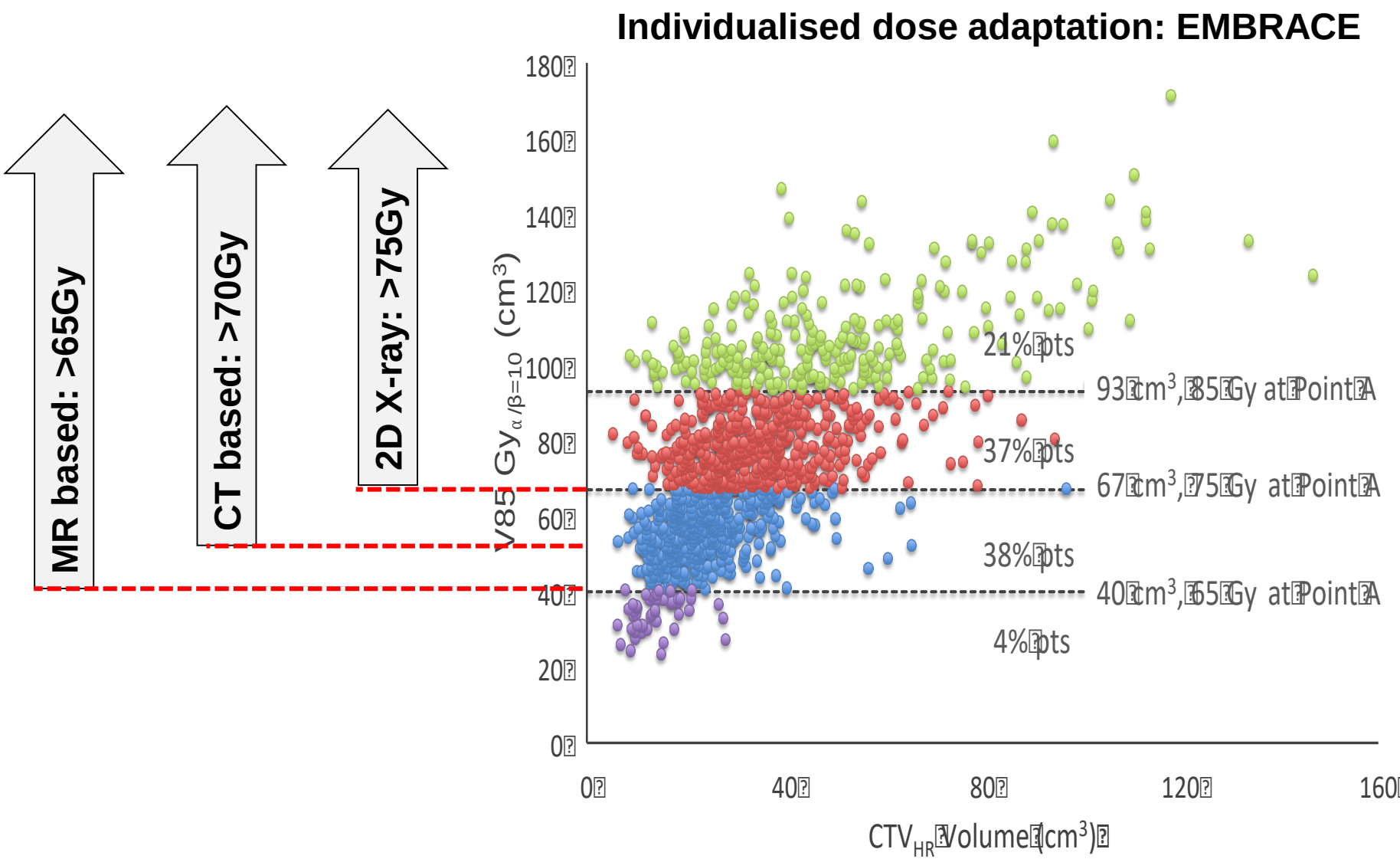


Point A dose is a surrogate of irradiated volume

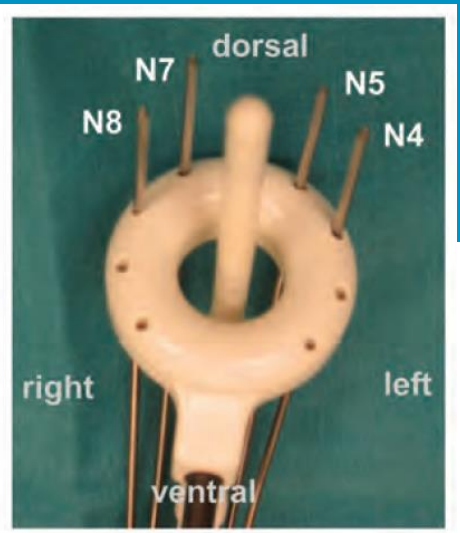
Point A* = 14*TRAK (can be used for IC/IS)

Nkiwane KS et al. Total reference air kerma can accurately predict isodose surface volumes in cervix cancer brachytherapy. A multicenter study. Brachytherapy. 2017; 16(6):1184-1191

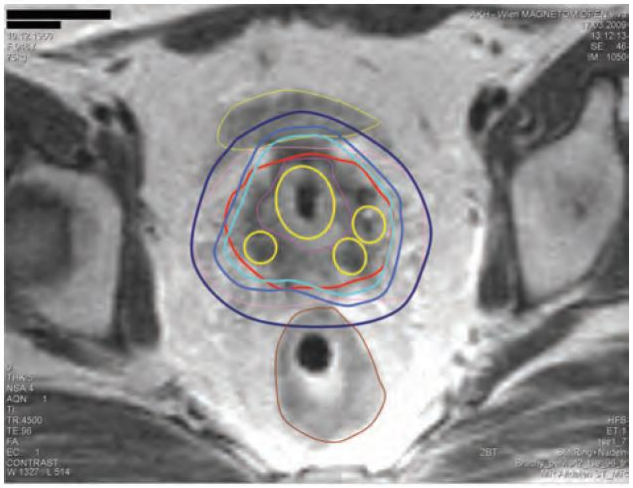
Volumes treated to 85Gy
Be Careful:Thresholds of point A dose



Example IIB (ICRU89)



- CTV_{HR} volume $43cm^3$
- 45Gy EBRT + 4 fx BT
- TRAK 0.43cGy (x4)
- V85Gy = $85cm^3$



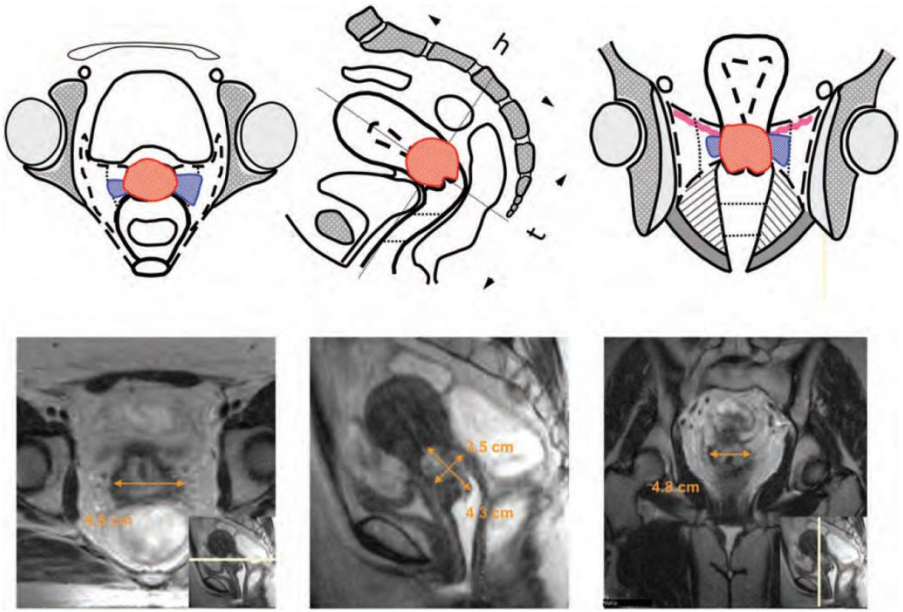
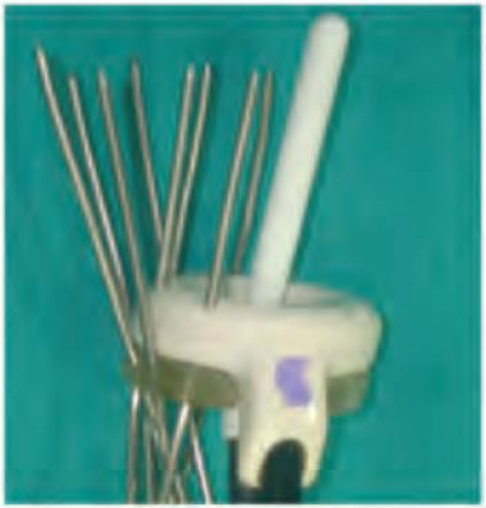
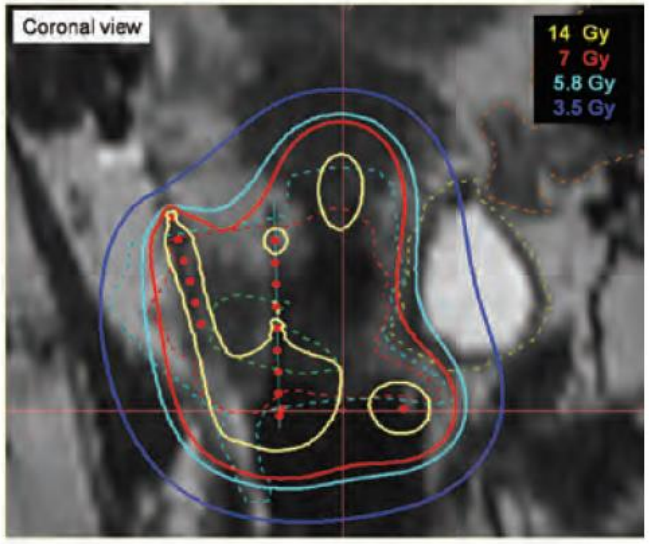


Figure A.5.4. Residual GTV and residual pathological tissue at the time of first brachytherapy: clinical drawings (upper) and corresponding MRI images (lower) at the time of first brachytherapy without applicator in place.

Example IIIB (ICRU89)

- CTV_{HR} volume 66cm^3
- 45Gy EBRT + 4 fx BT
- TRAK 0.50cGy (x4)
- V85Gy = 70cm^3





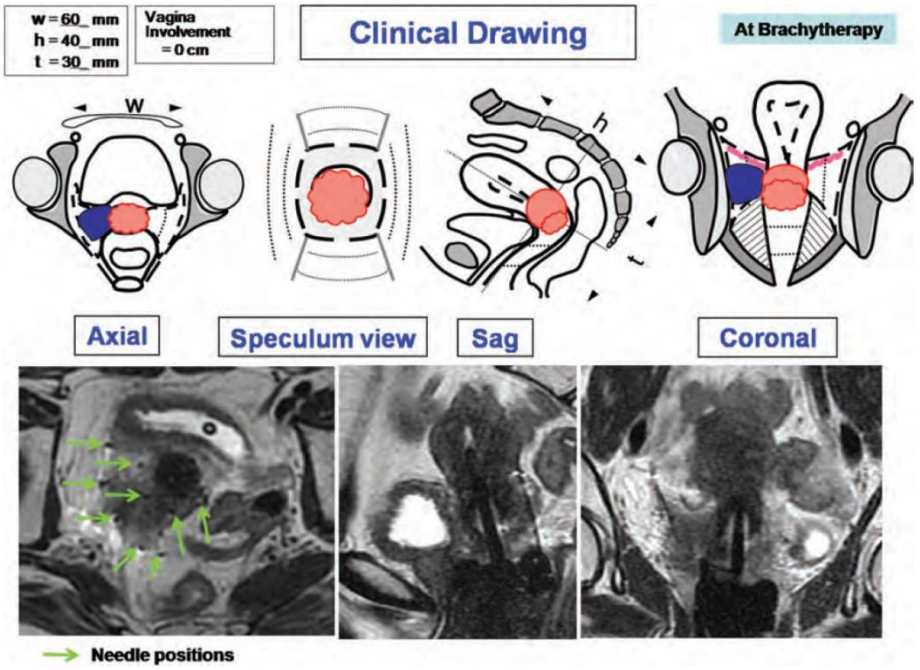


Figure A.8.4. Residual GTV and residual pathological tissue at the time of first brachytherapy: Clinical drawings (upper) and corresponding MRI images (lower) at the time of brachytherapy with applicator in place.

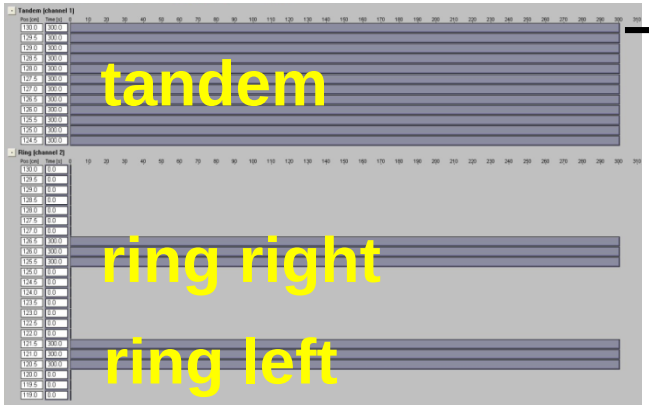
Take home message – dose optimisation

- **Always start dose optimisation with standard loading pattern**
- **Use manual dose optimisation for major changes**
- **Use graphical optimisation for minor adaptation**
- **Needle loading: start with 10-20% per dwell position**

- **Application of combined intracavitary-interstitial applicator: increased therapeutic window by ~10Gy**

Dwell time threshold for needle loading

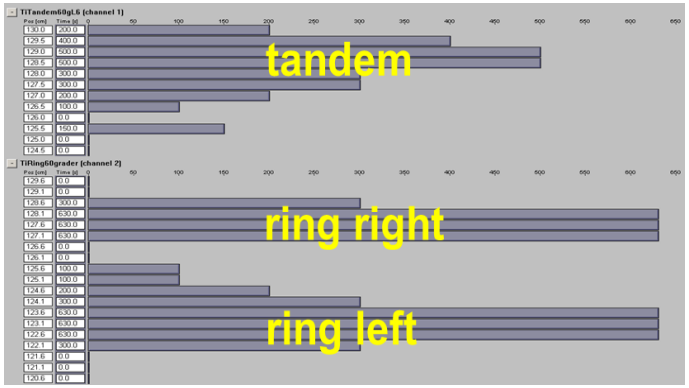
Standard plan

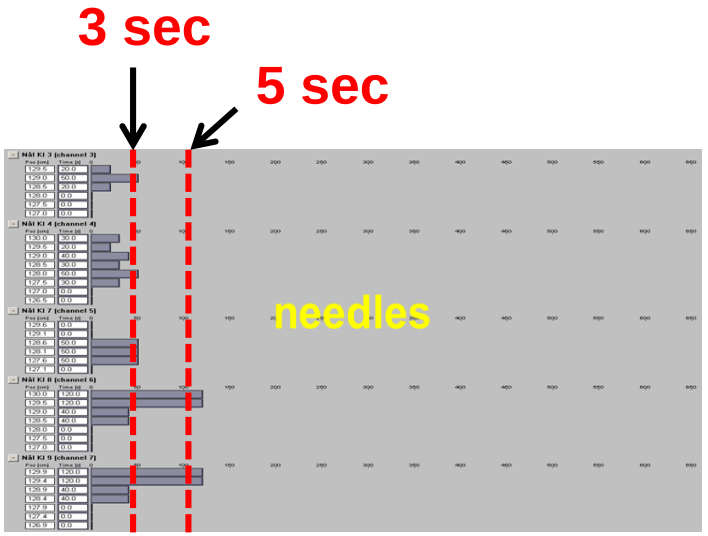


25 sec per dwell position in tandem

10-20% of 20 sec = 3-5 sec per dwell position in needle

Optimised plan



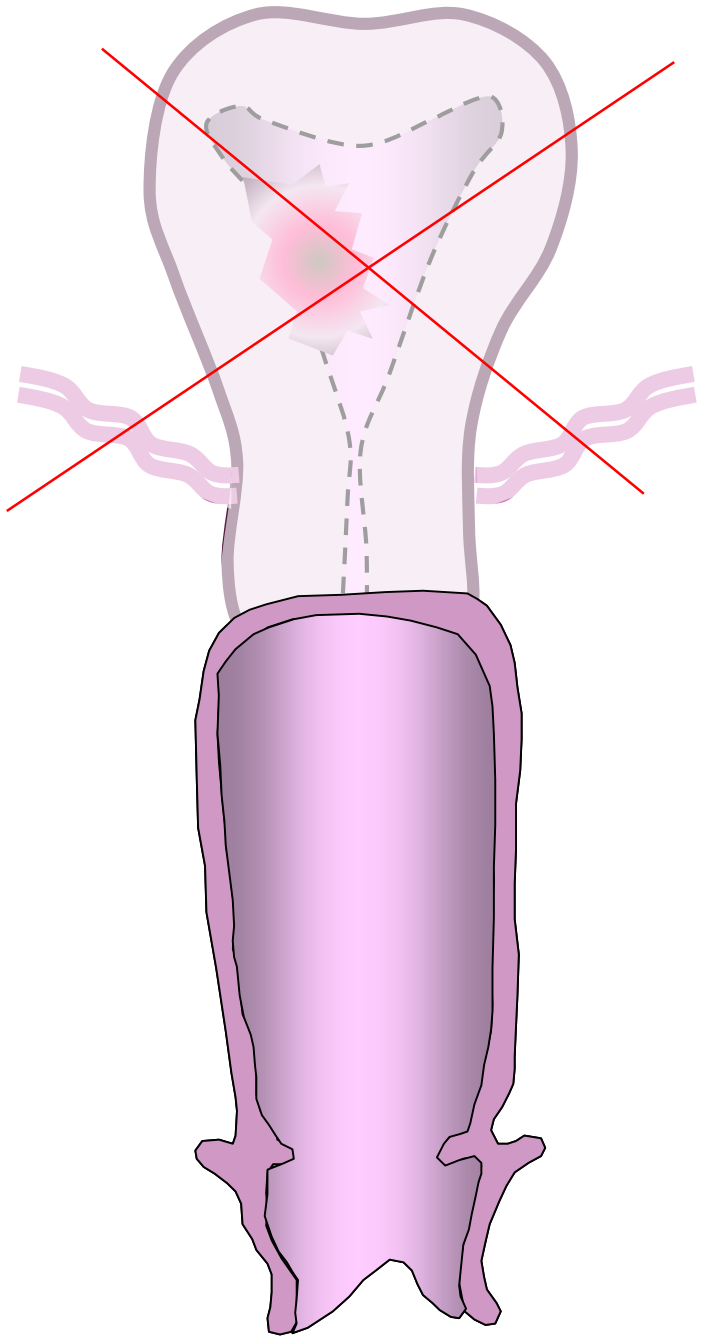


Physics aspects of treatment planning in endometrium cancer

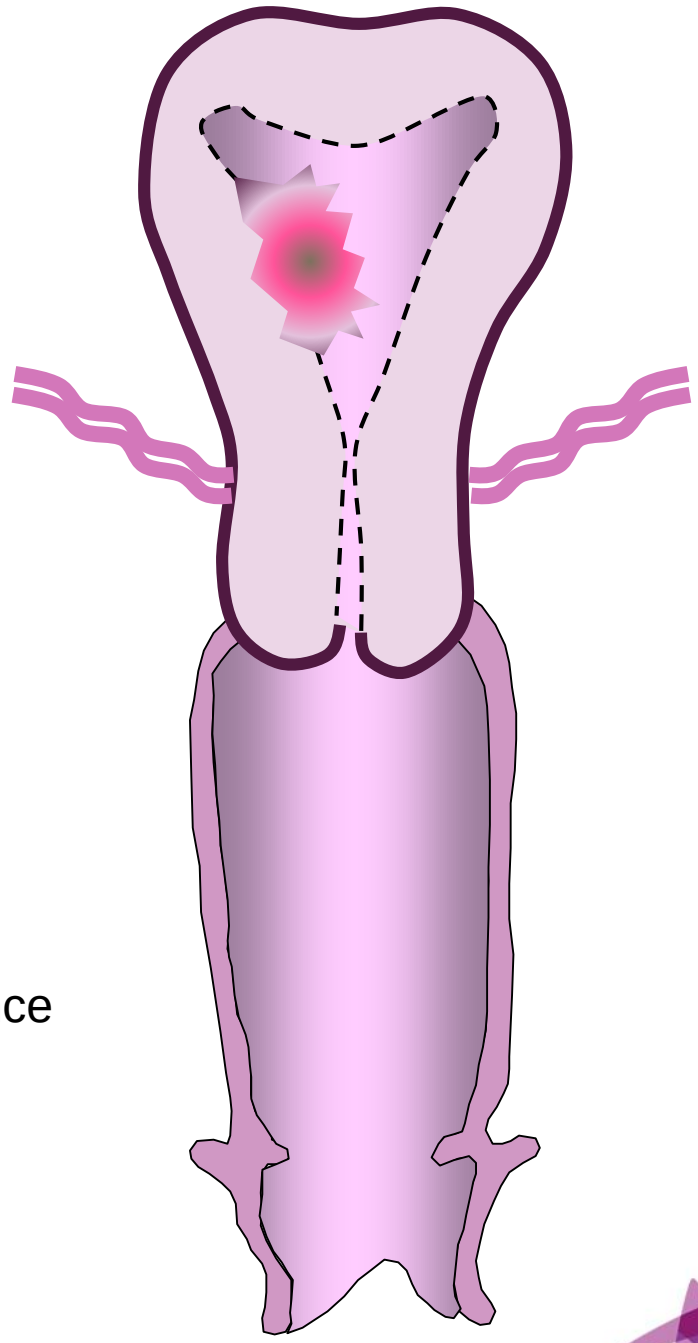
presented by Daniel Berger

General Hospital of Vienna, City of Vienna,
Medical University of Vienna, Department of Radiotherapy

1) post-hysterectomy

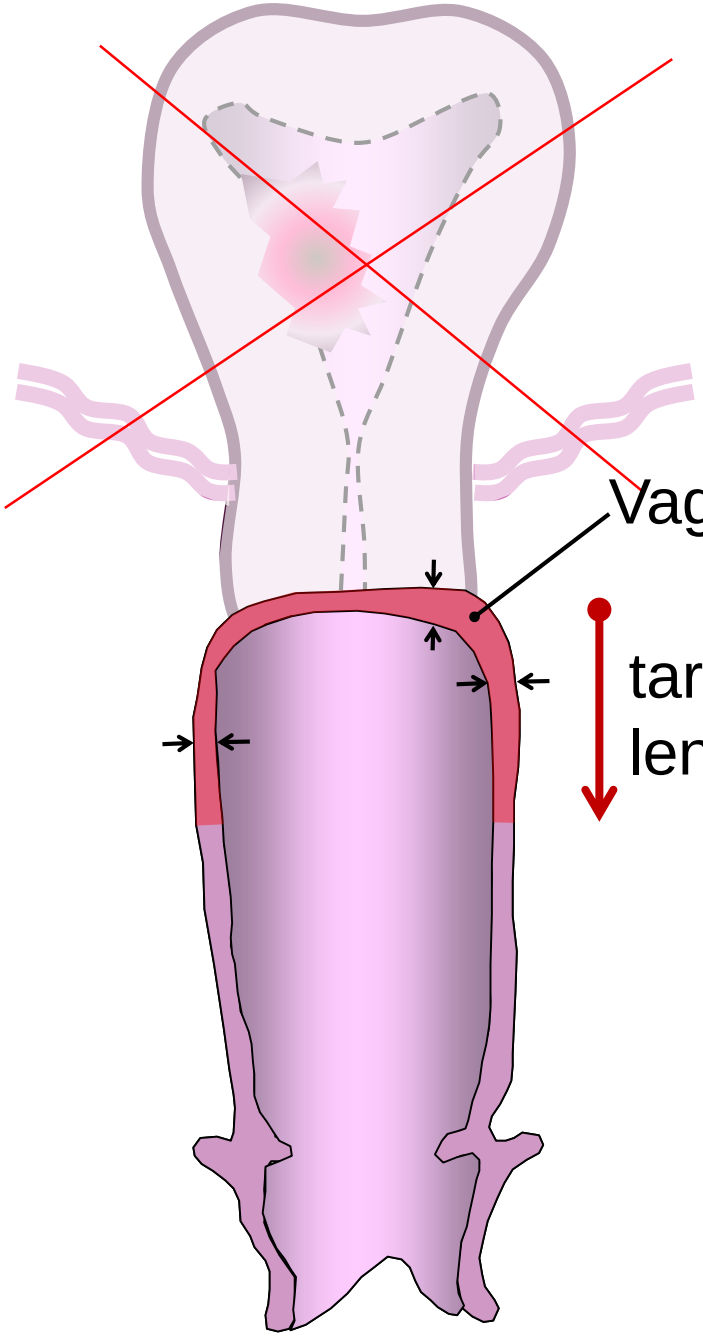


2) patient unfit for hysterectomy



3) recurrence

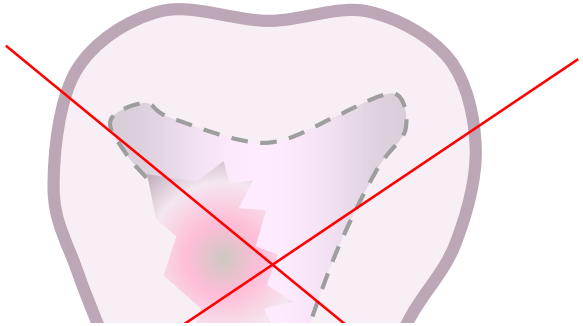
Clinical Target Volume (CTV)



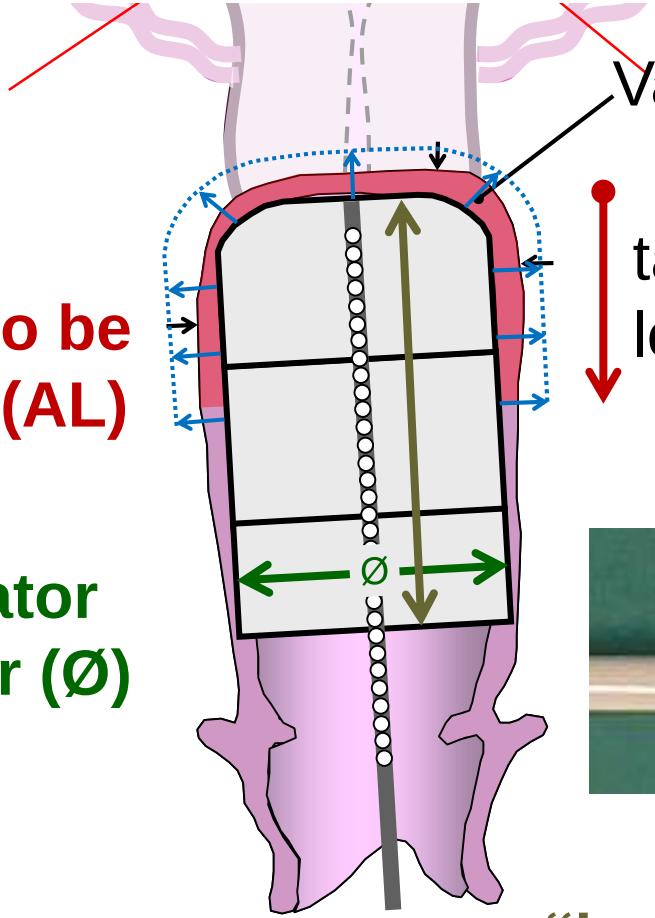
Vaginal wall thickness ~ 2 - 8mm

target length = upper third (1/3) !

Clinical Target Volume (CTV)



Reference Depth 5 mm or individualized depth for dose prescription



= upper third (1/3) !

Length to be treated (AL)

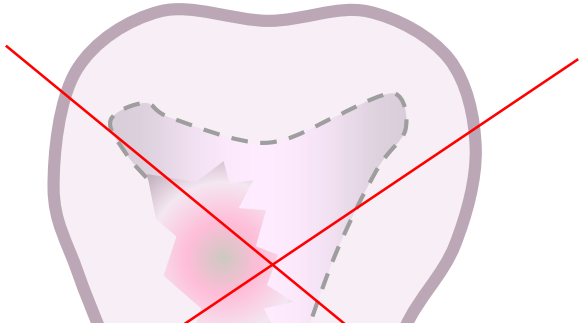
Applicator Diameter (Ø)

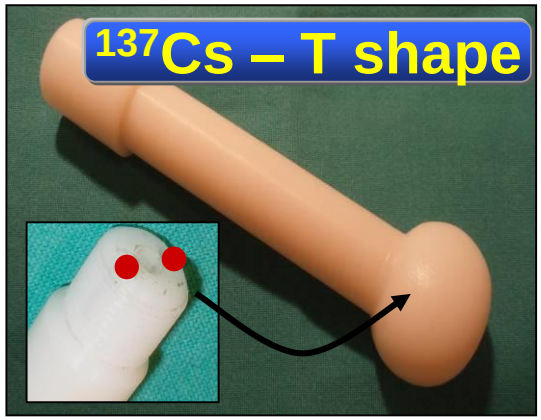
Shape of distal applicator part!

Applicator "insertion" length

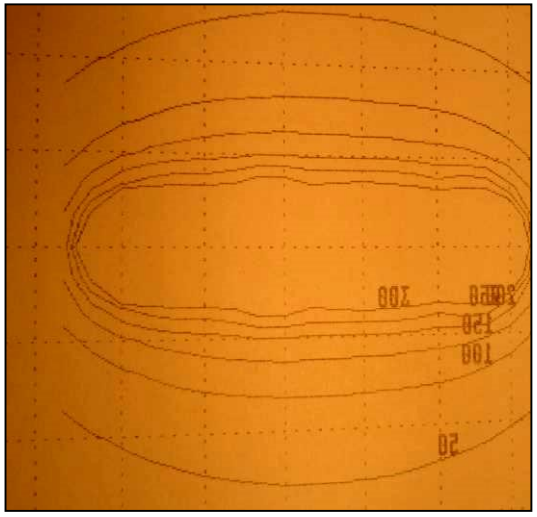
ESTRO School

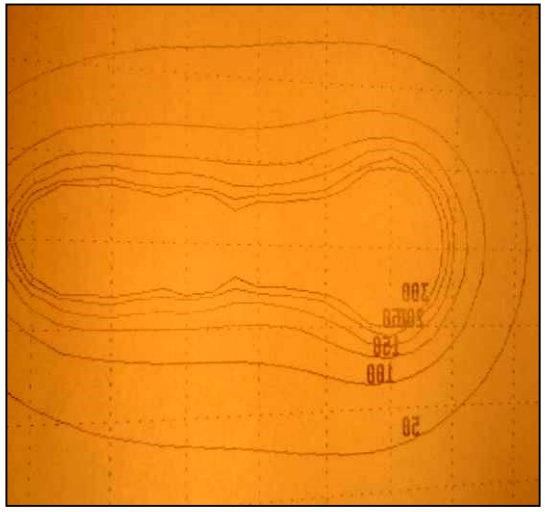
Clinical Tar

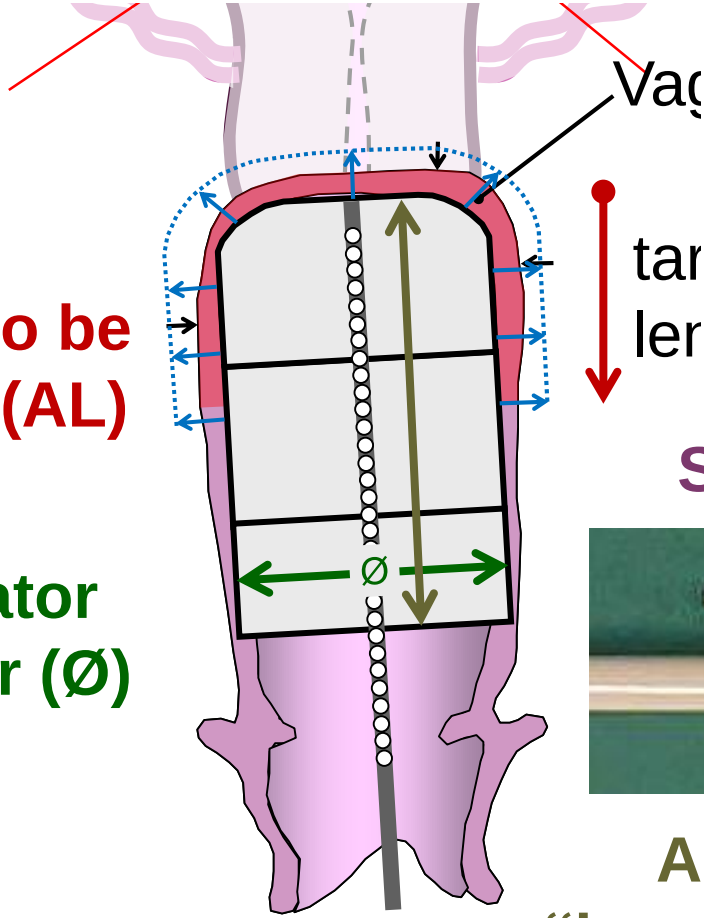




Reference Depth 5 mm or ind





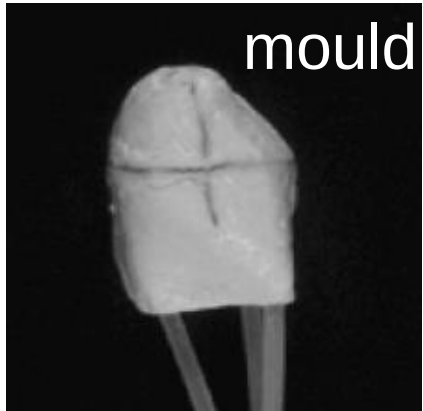


Length to be treated (AL)

Applicator Diameter (Ø)

Shape of distal applicator part!

Applicator "insertion" length



Dose prescription and reporting recommendations for vaginal vault brachytherapy

CONVENTIONAL CLINICAL PRESCRIPTION BASED ON DOSE POINTS; DOSE REPORTING IS IDENTICAL TO PRESCRIPTION

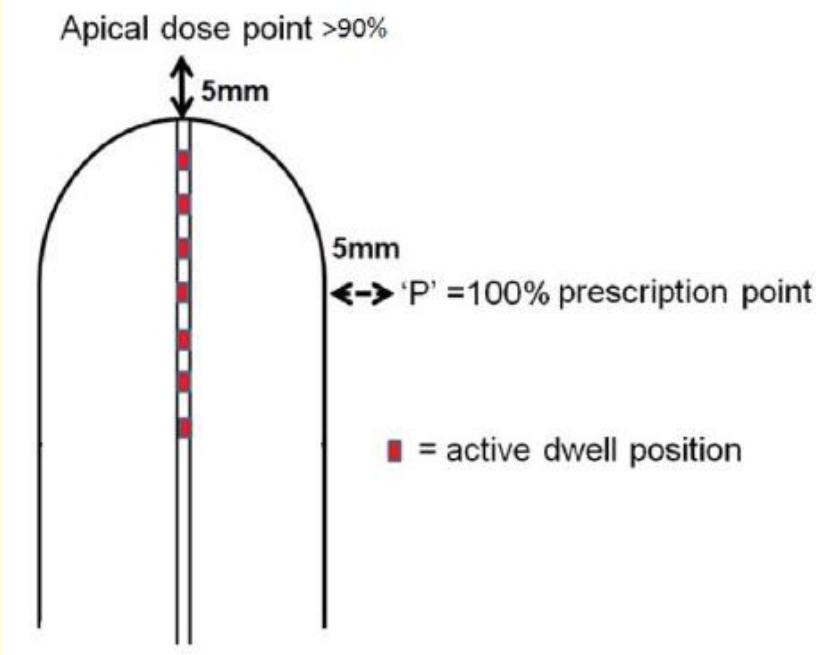
Points at 5 mm from the applicator surface
Prescription point: at the mid-point of active source length 100%
Cylinder: Central apical point..... >90%
Ovoids: apex 5mm from ovoid surface..... >90%
Additional points at other positions along the applicator 100%
(may be used for **dose optimization** avoiding the Havanna cigar effect…)

Clinical reporting
Applicator diameter
Treated length
Treatment time
Optional: vaginal length

Dose to prescription point
In case prescription defined above is not used, the reference dose at 5 mm from the surface

Surface dose at prescription point
Optional: doses at other points

Dose to rectum (ICRU point or D2cc)
Dose to bladder (ICRU point or D2cc)



In addition the physics parameters (e.g. type of source, source activity, dose rate, AI system) have to be reported

Example: VagCyl.Ø30mm,VL=10cm TL=35cm, 2.5 mm step-size

DosePoints

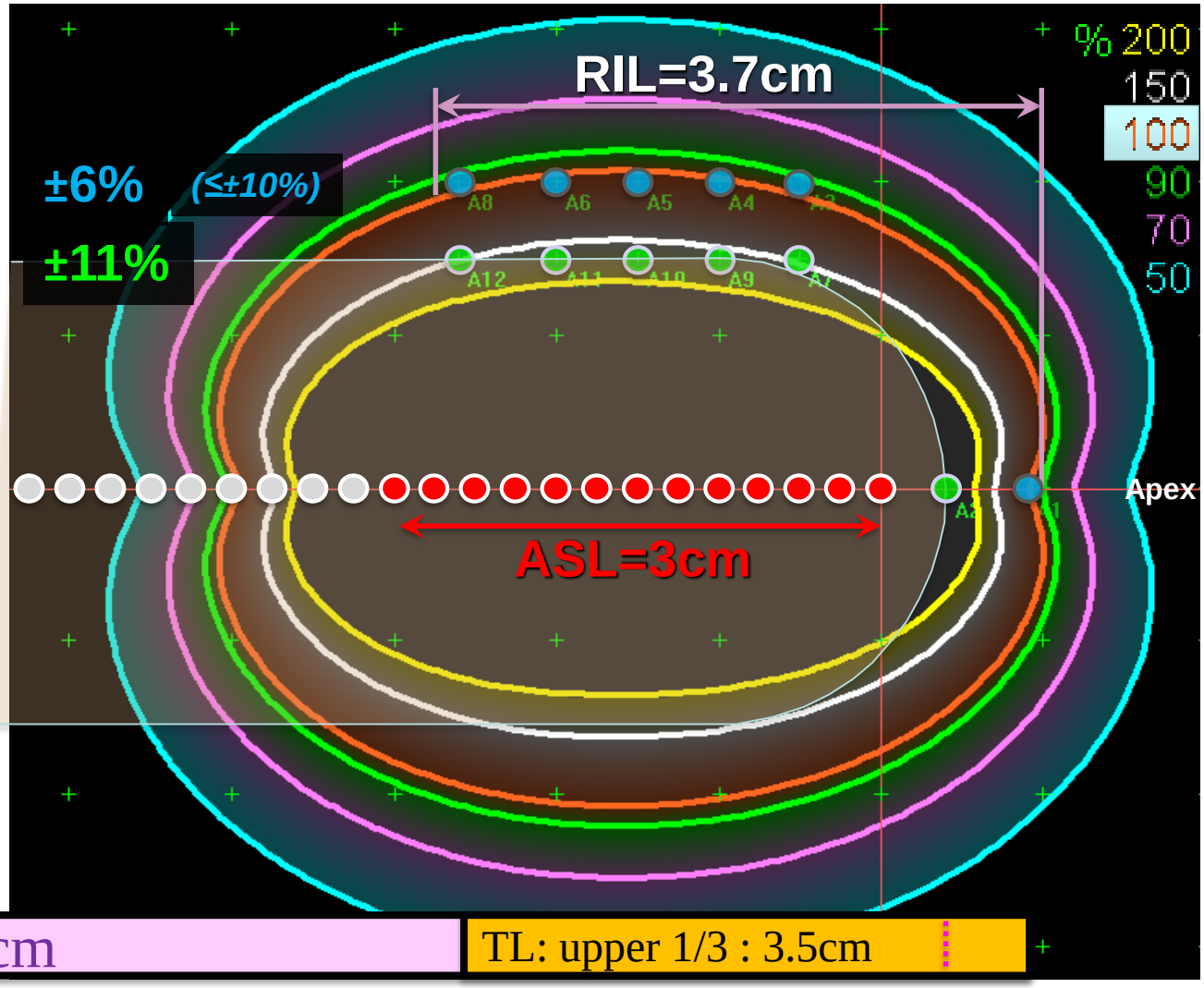
2.5mm step-size	
Apex DP [%]	
0mm	5mm
354,49	101,32
Lateral DP [%]	
0mm	5mm
143,98	92,66
161,30	101,82
168,74	105,76
165,98	104,04
147,87	94,40

Dwells

Active Dwell	
Pos	time [s]
1	14,20
2	14,60
3	14,92
4	14,91
5	14,95
6	14,55
7	14,91
8	14,81
9	15,62
10	16,19
11	17,05
12	17,69
13	18,09

Σ202,5s

TRAK= 0.23 cGy@1m



Inactive Active source pos.

Lat. dose points on applicator surface : 158% ±11% *Apex surface : 355%*

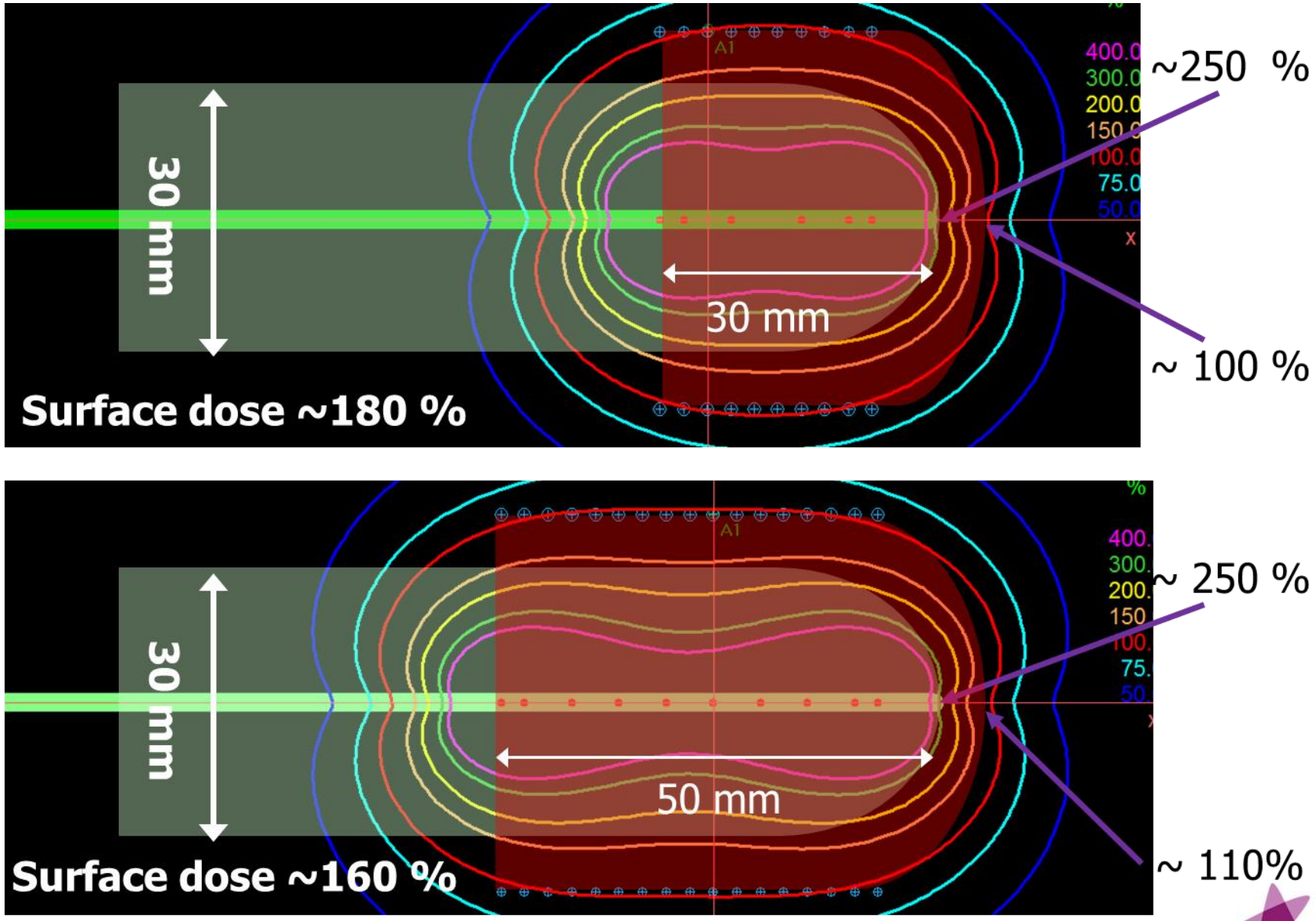
Lat. dose points in 5mm tissue depth : 100% ±6% *Apex 5mm : 101%*

The dose distribution in CTV will depend on

- Length to be treated
- Applicator diameter
- Prescription depth
- Distal part of the applicator

- distance from the first dwell position to the tip of the applicator (→ applicator reconstruction lecture)

length to be treated (3-5 cm)



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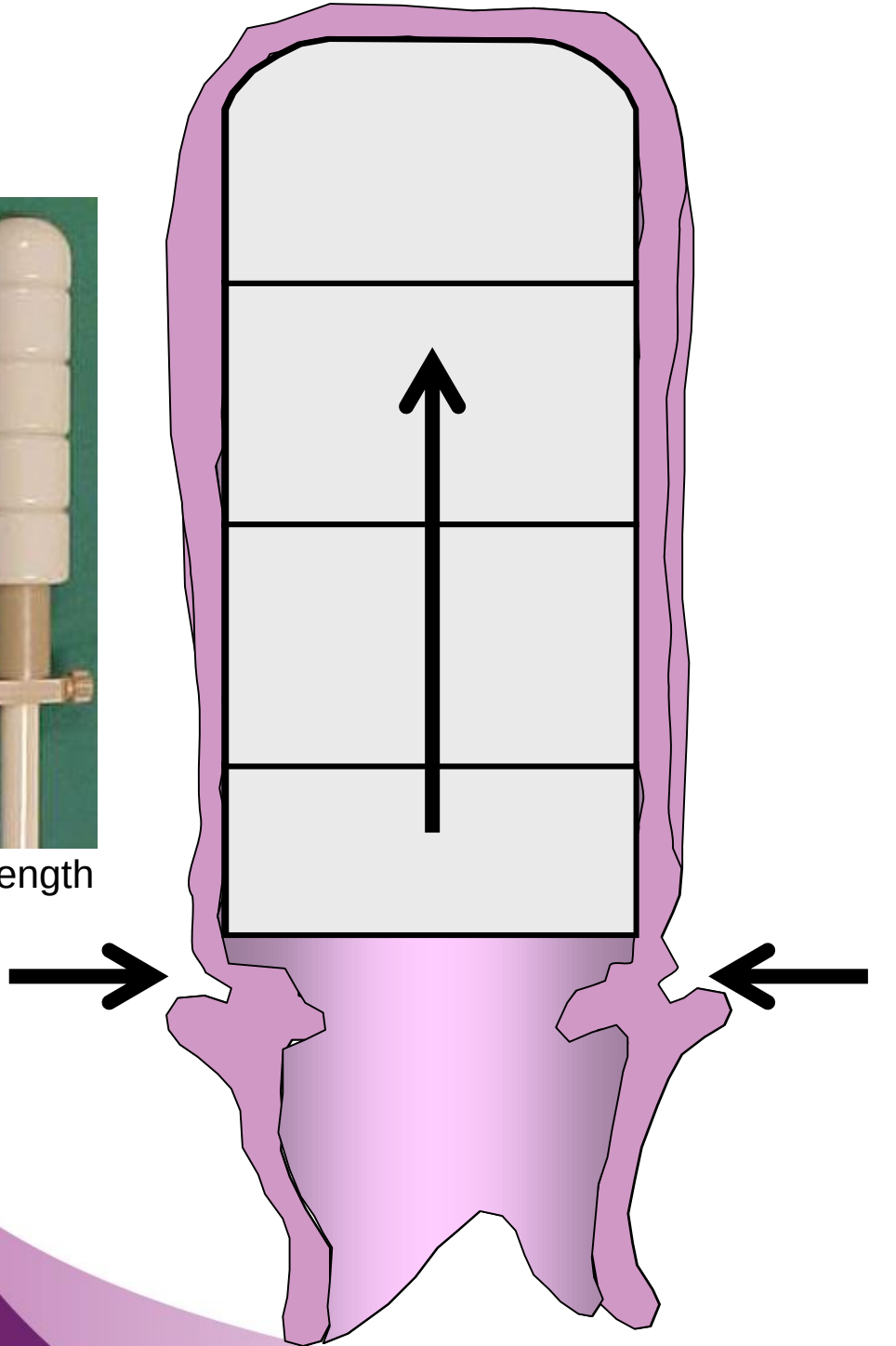
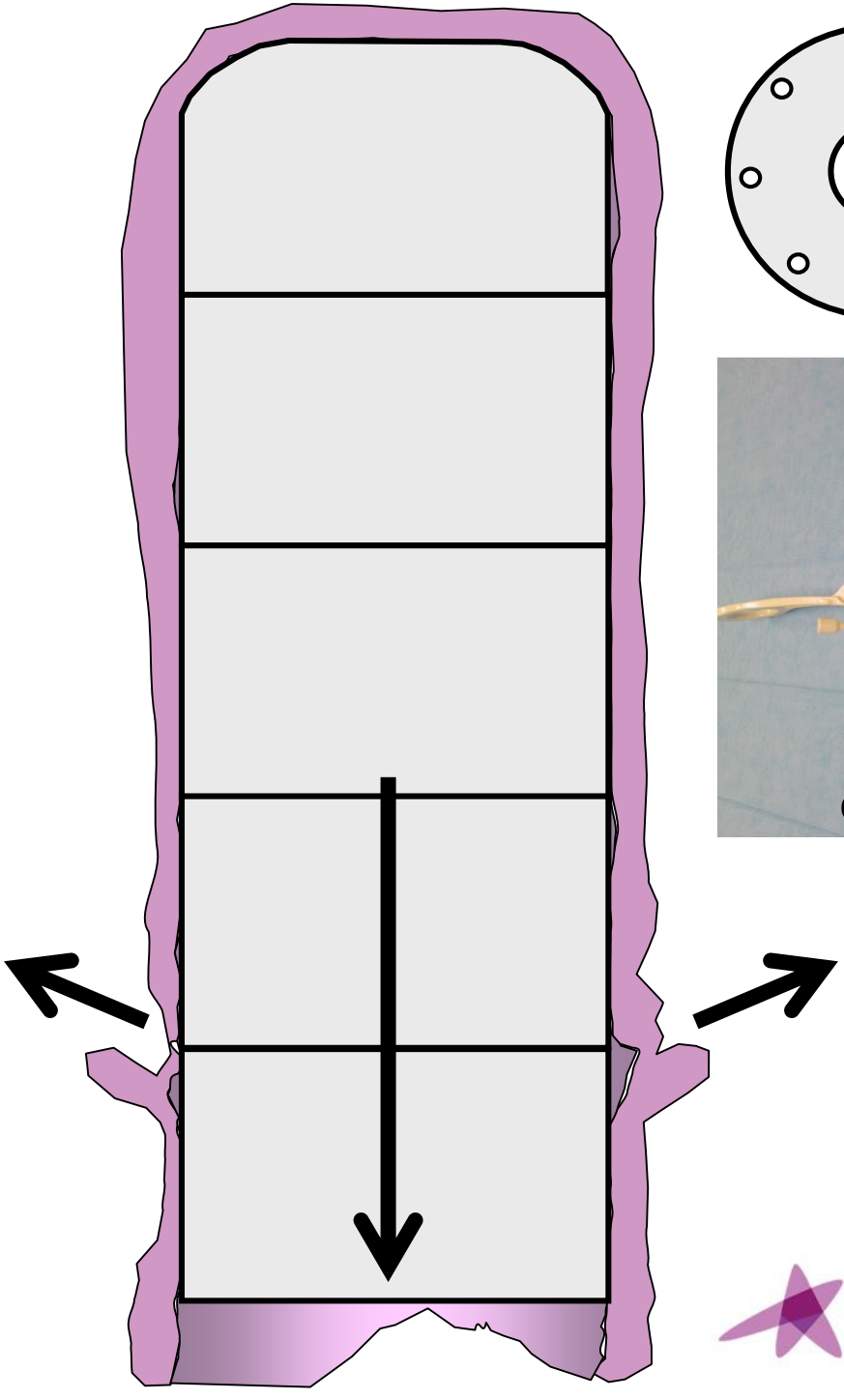
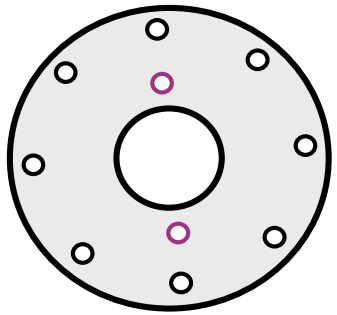
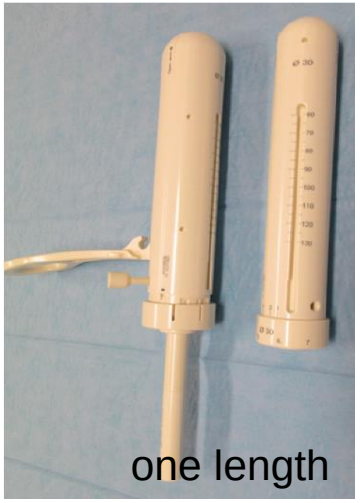
Select the length of the vaginal cylinder to fit into the vagina

flex. length









one length

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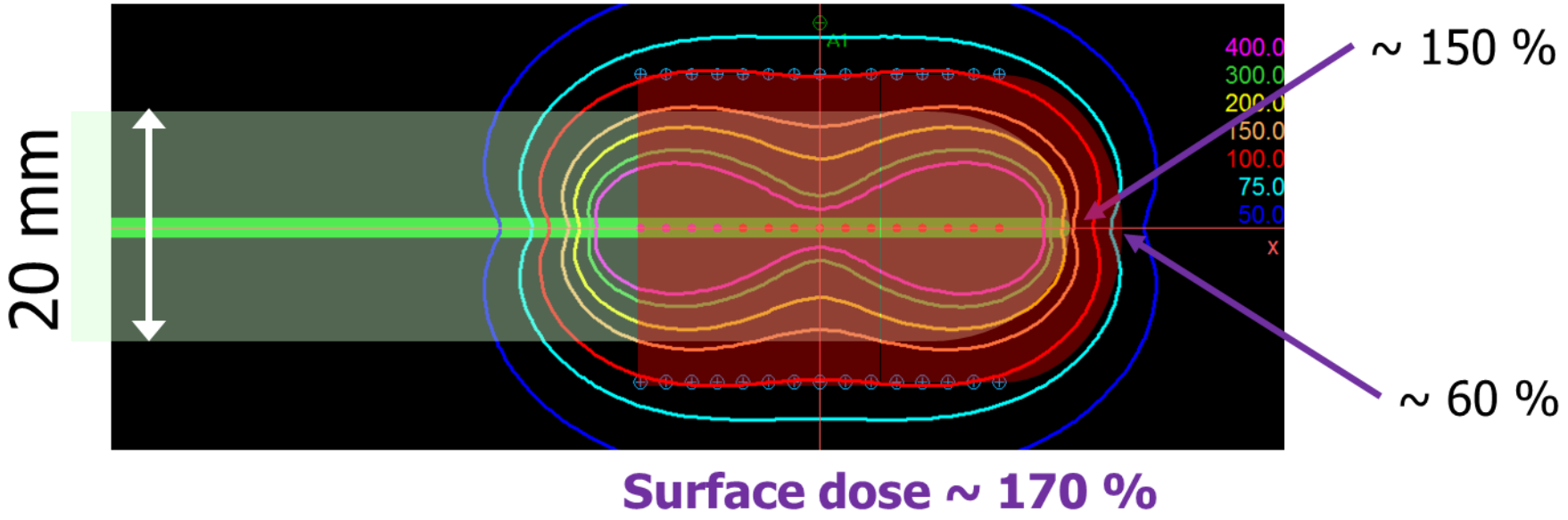
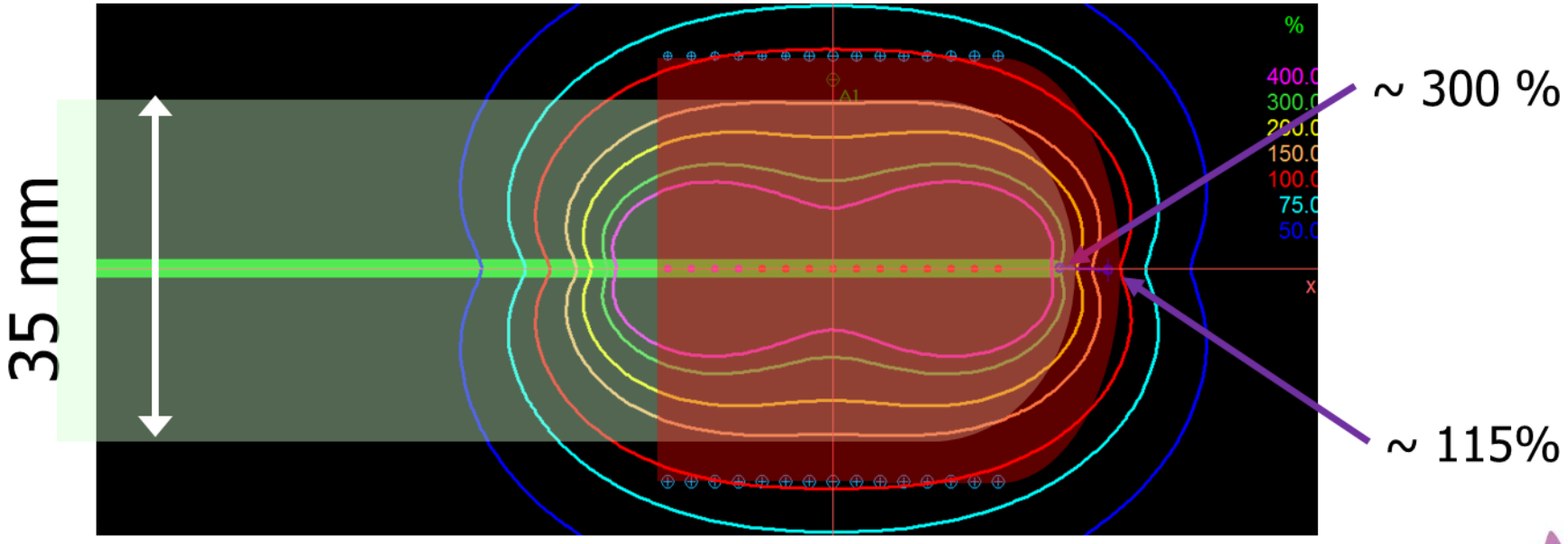
Applicator diameter



Surface dose ~ 170 %



Surface dose ~ 150%

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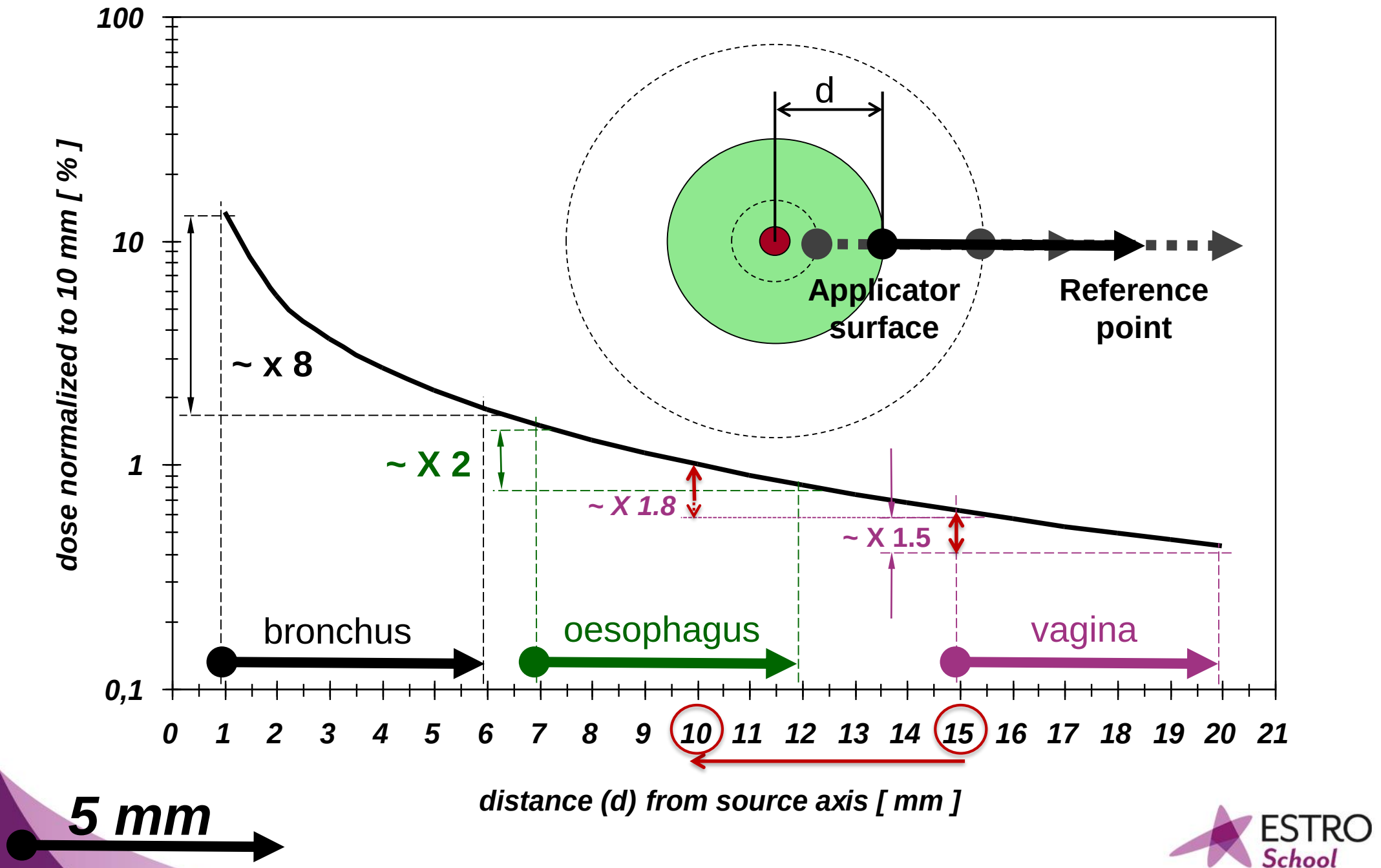
Dose on Applicator Surface and at Reference Depth !



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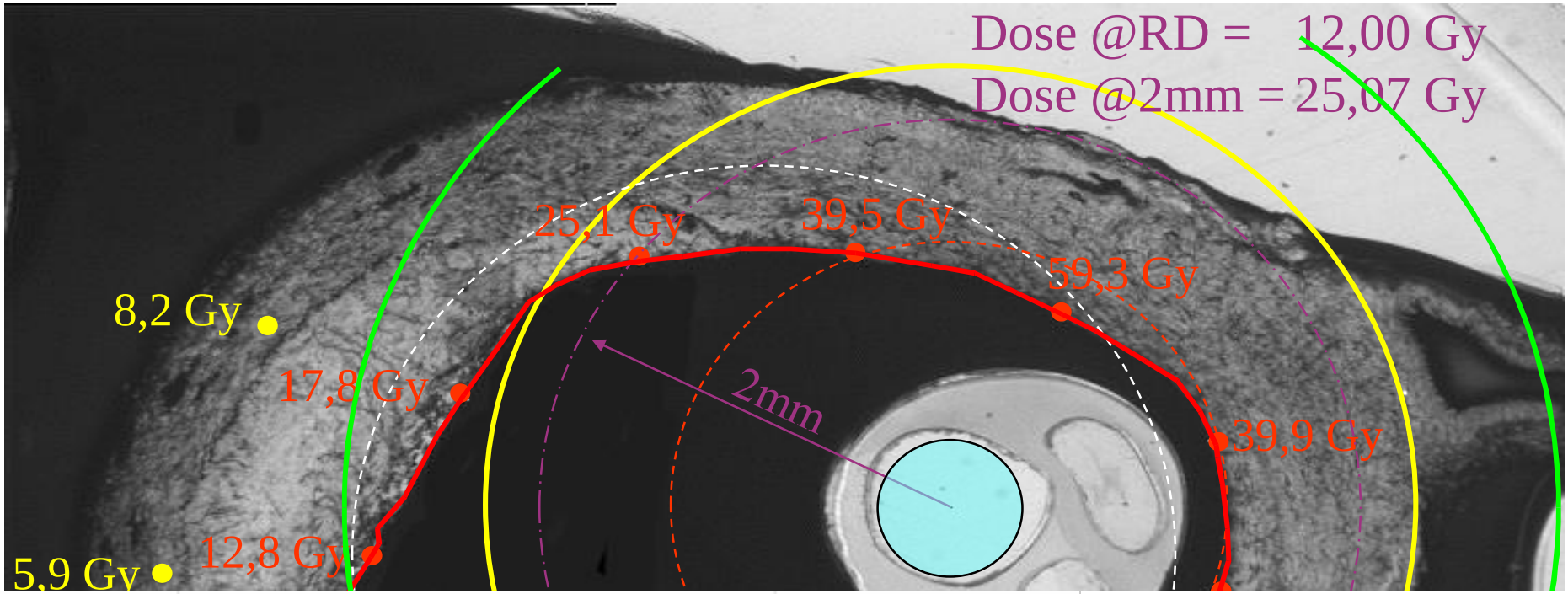
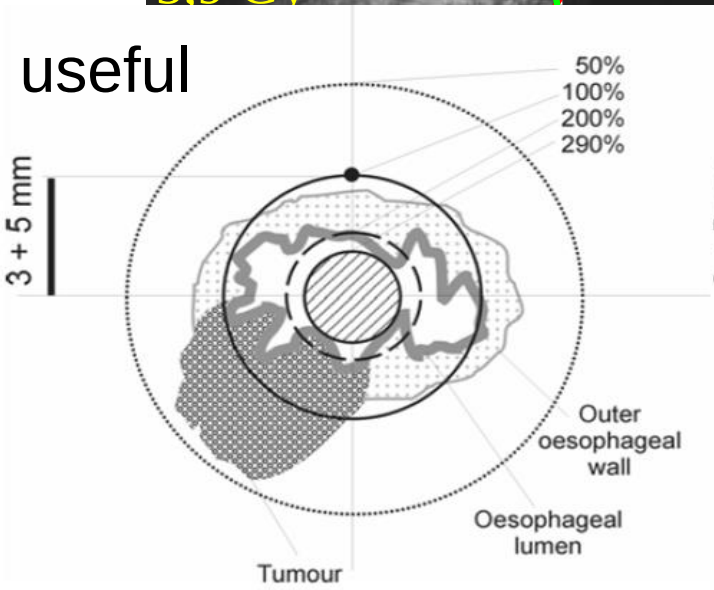
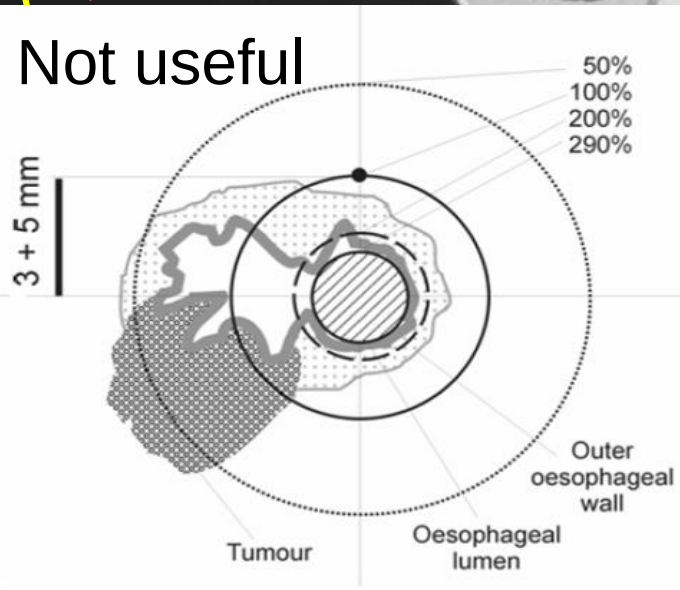
The right size of the brachytherapy applicator !



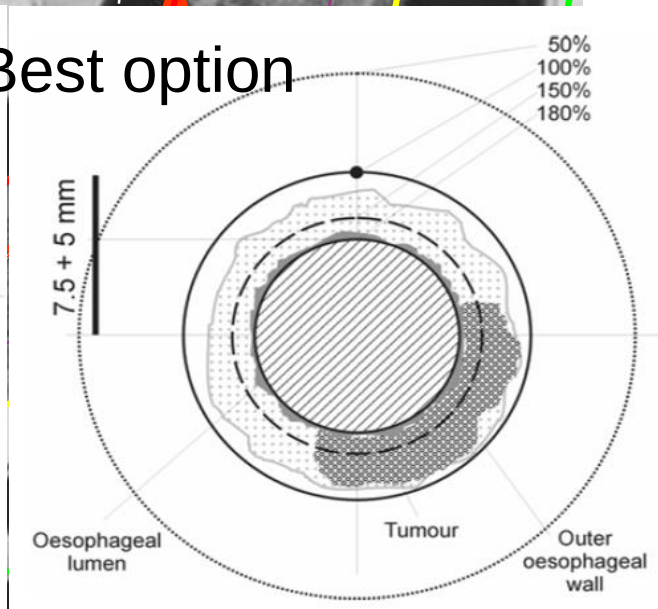
useful



Not useful



Best option



tissue with non-centerd Endoluminar Source

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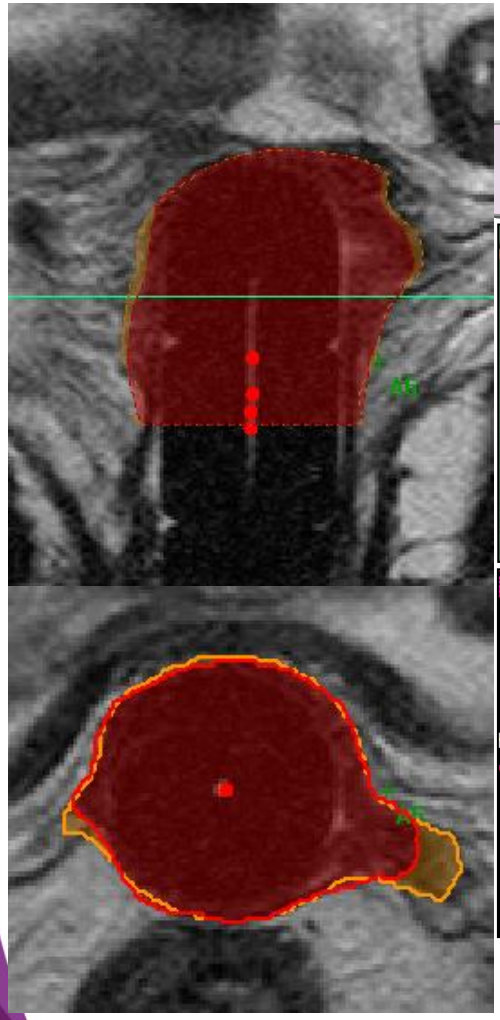
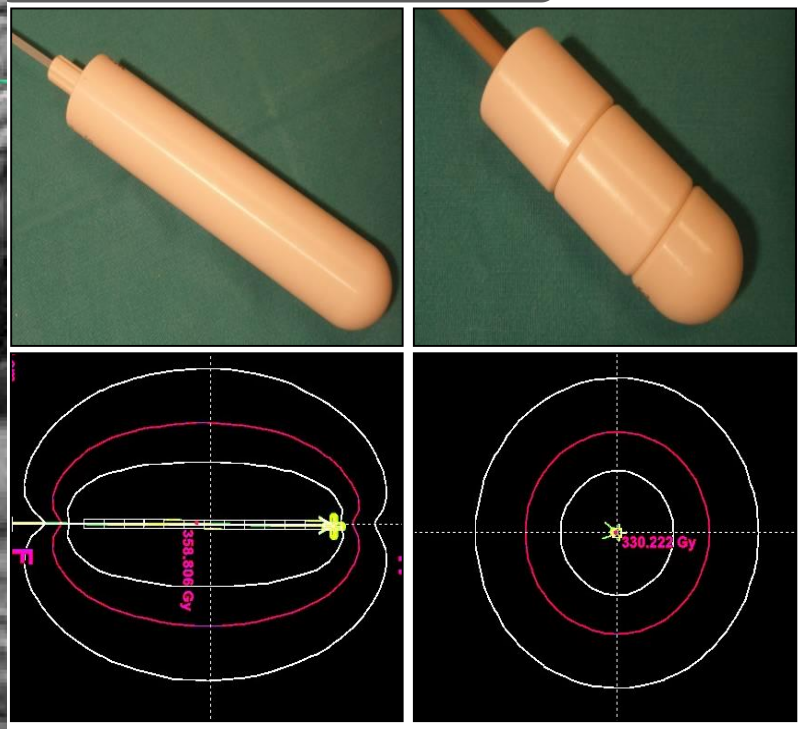
Distal part of the applicator

The “ears”

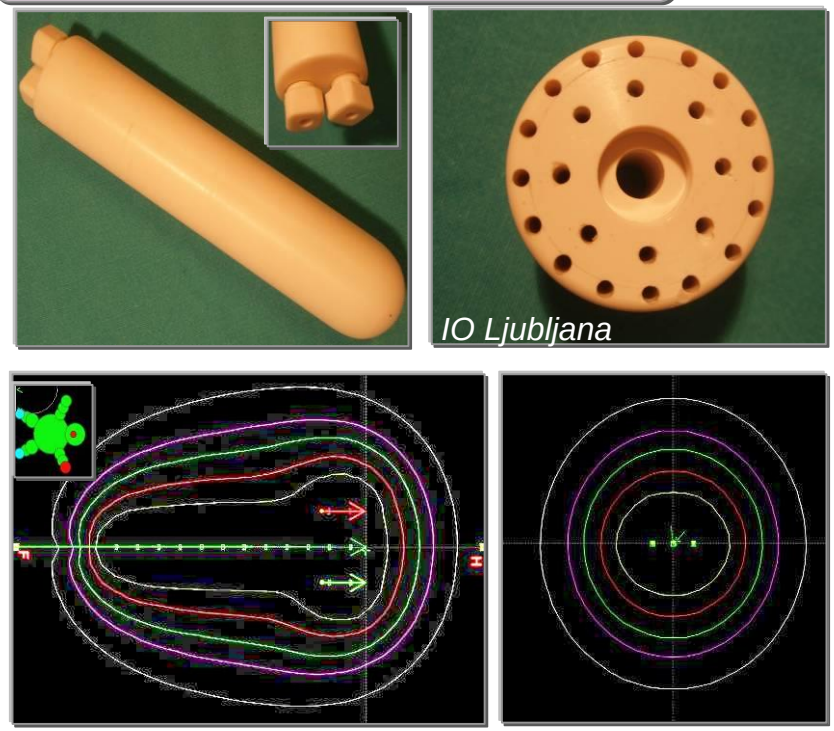


Optimization with multi-channel applicators

^{192}Ir – one channel



^{192}Ir – multi channel



Adapt standard technique → **Individualize treatment**

Courtesy P. Petric

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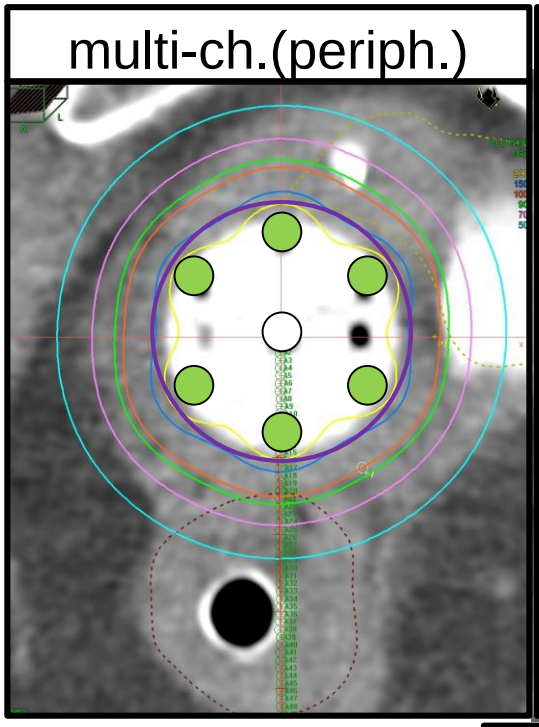
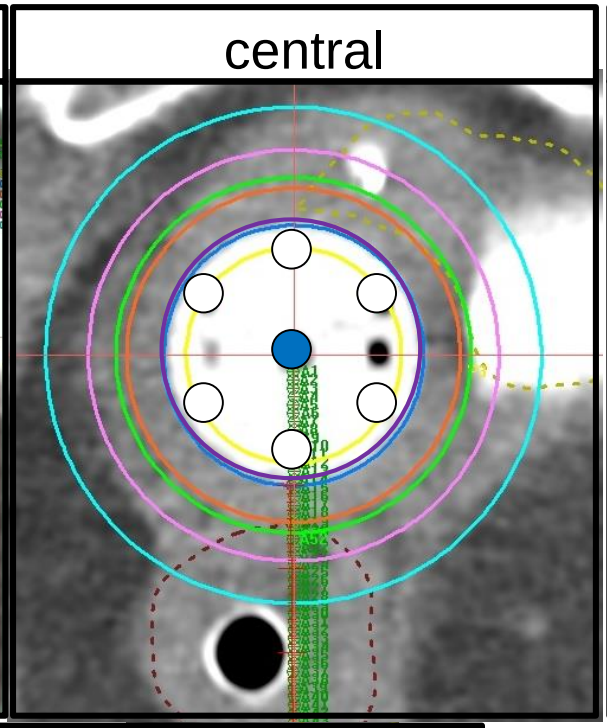
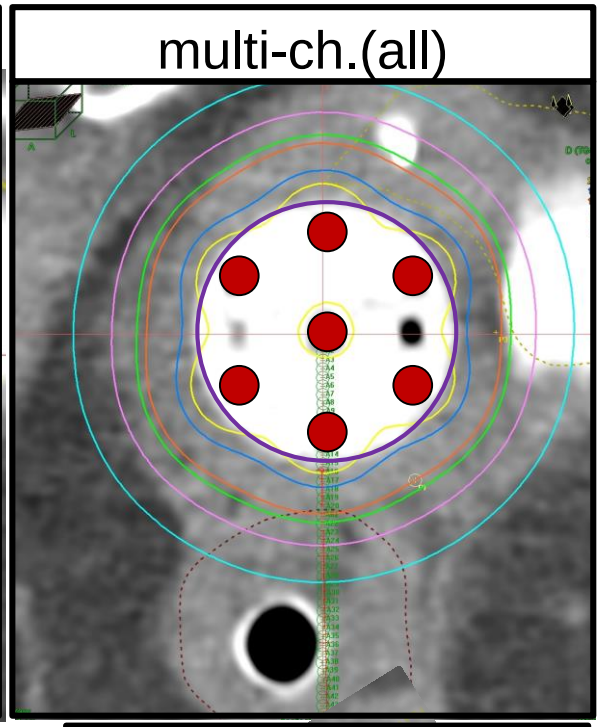
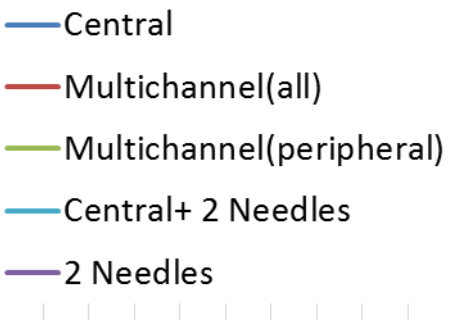
The change of Dose Gradient single - multi-channel

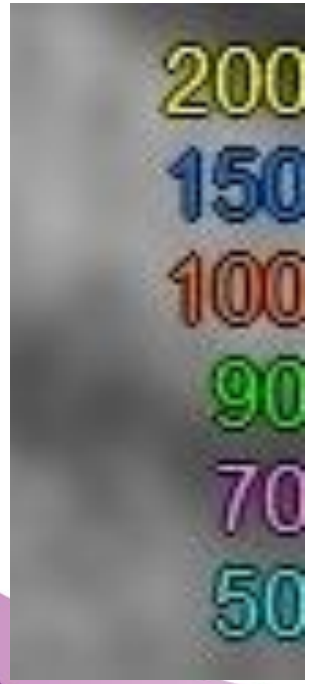


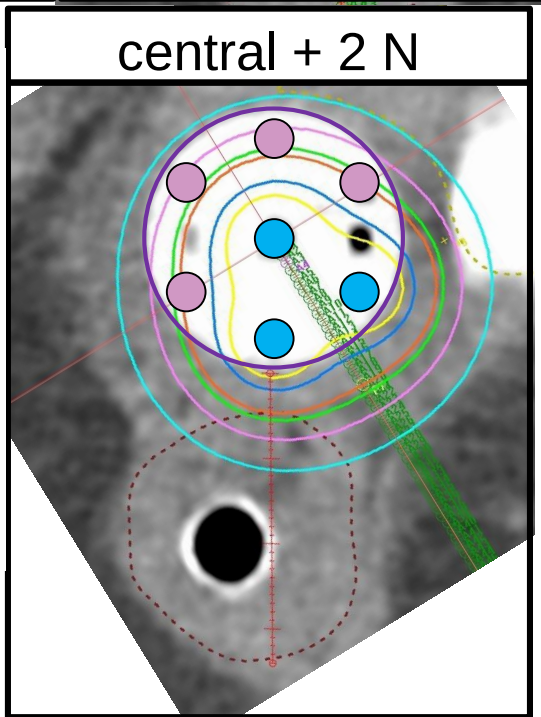


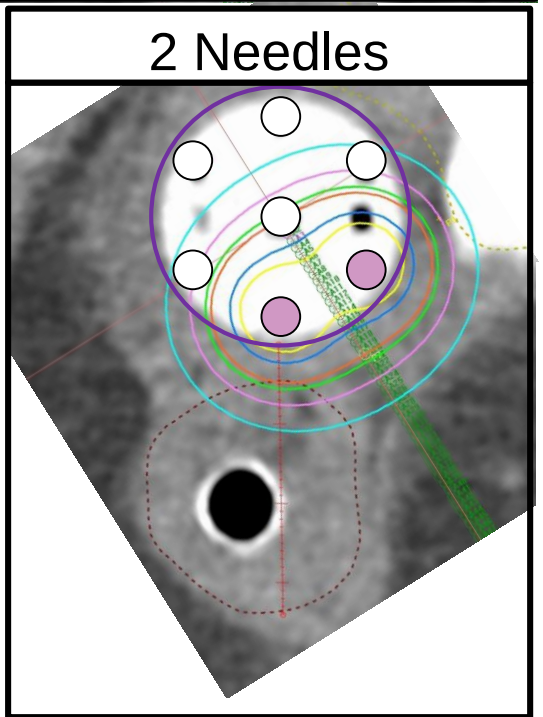




normalized at 5mm from Cyl.Surface







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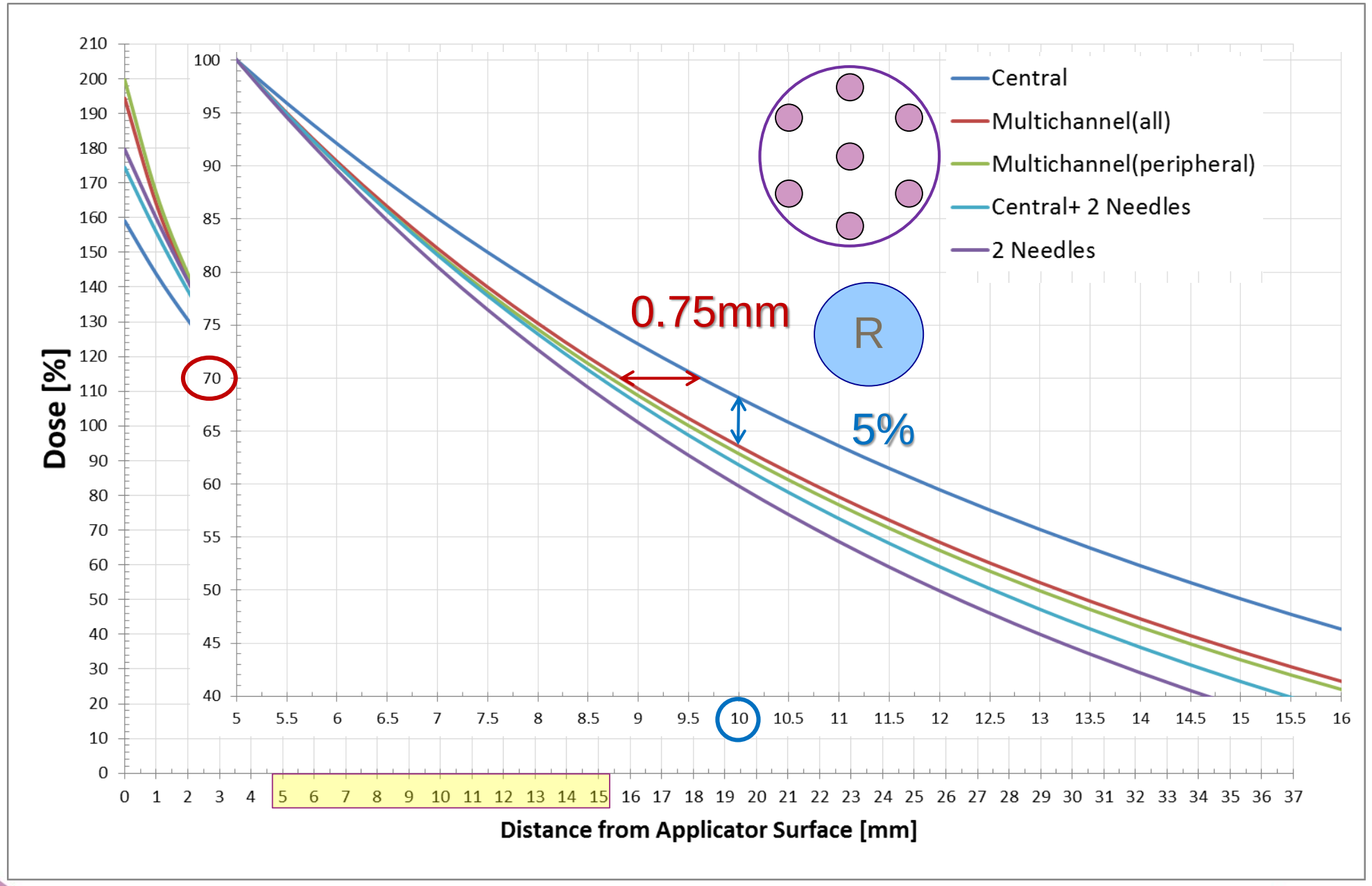
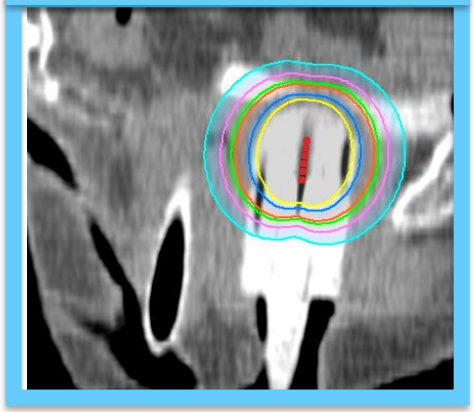
Dose Gradient single / multi-channel

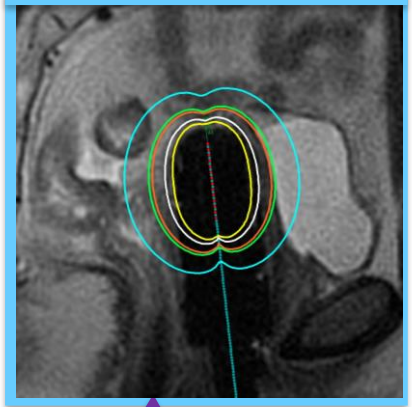


Treatment planning for Vaginal Cylinder

CT - sag

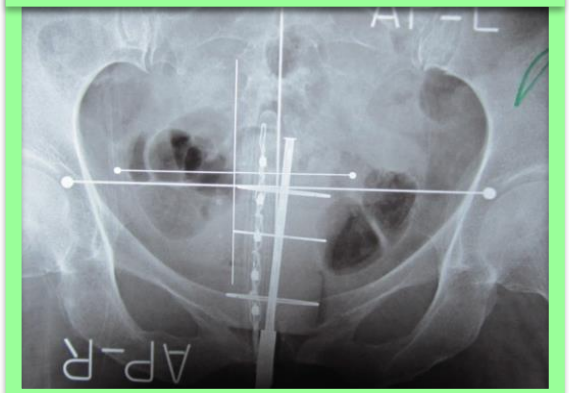


MRI - sag

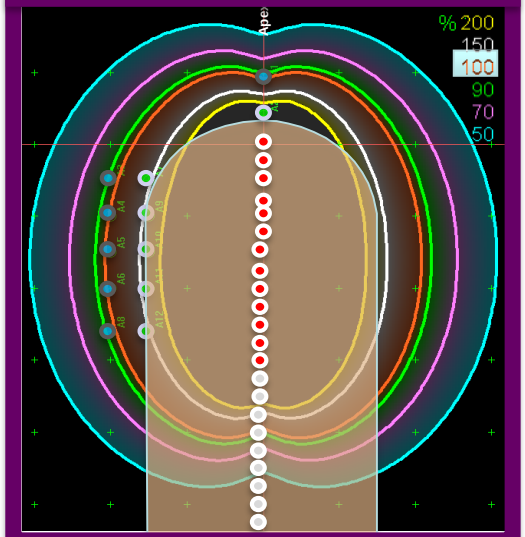


with or without imaging ?

AP -radiograph



Template based



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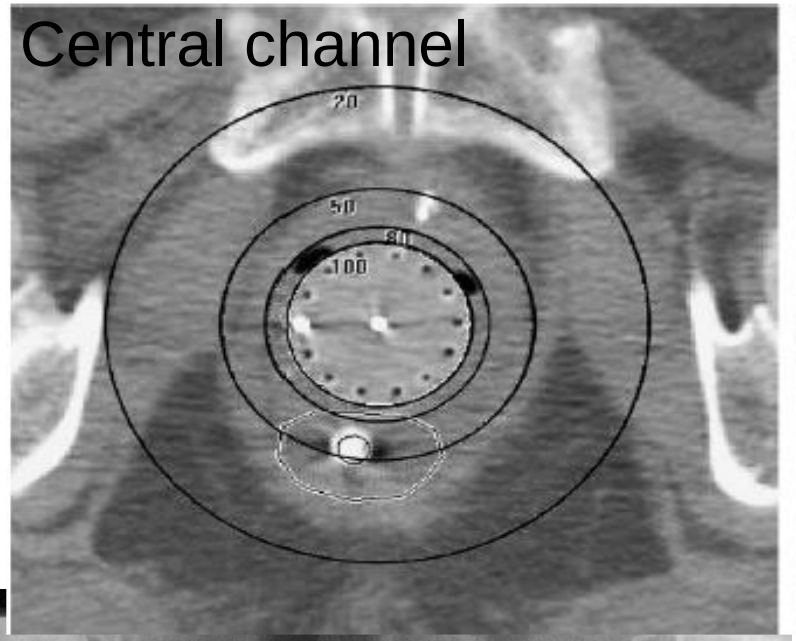
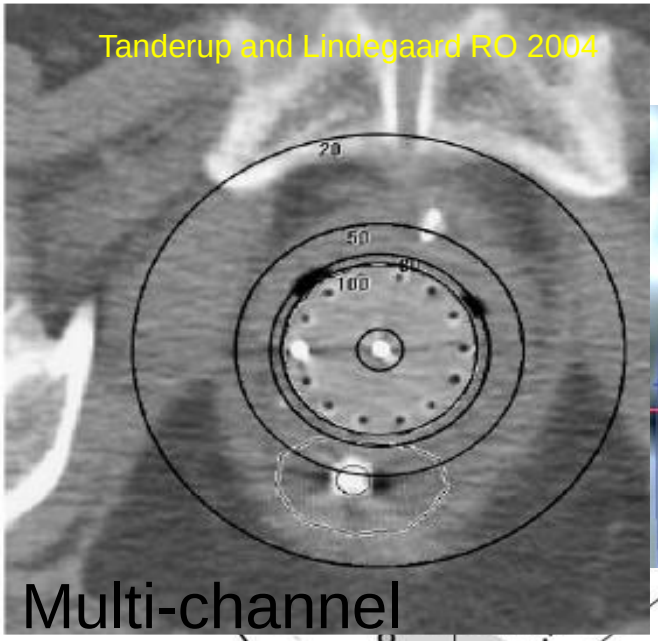
ABS survey regarding postopreative treatment for endometrium cancer

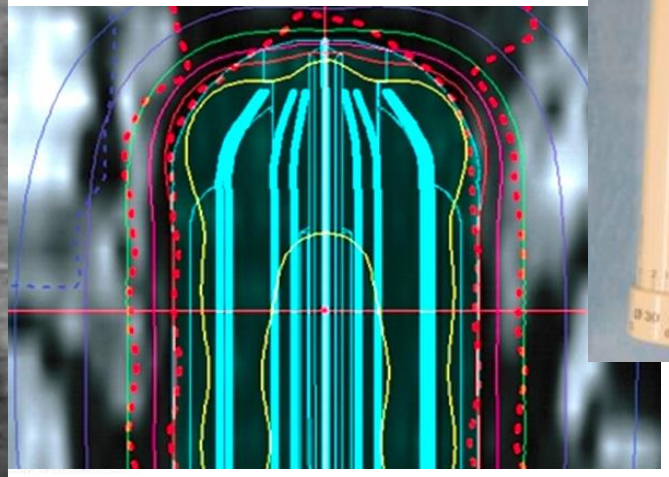
Applicator type	%*
Single channel vaginal cylinder	90.6
Shielded vaginal cylinder	13.0
Multichannel vaginal cylinder	10.9
Fletcher style colpostats	10.6
Henschke style colpostats	1.5
Other	2.1

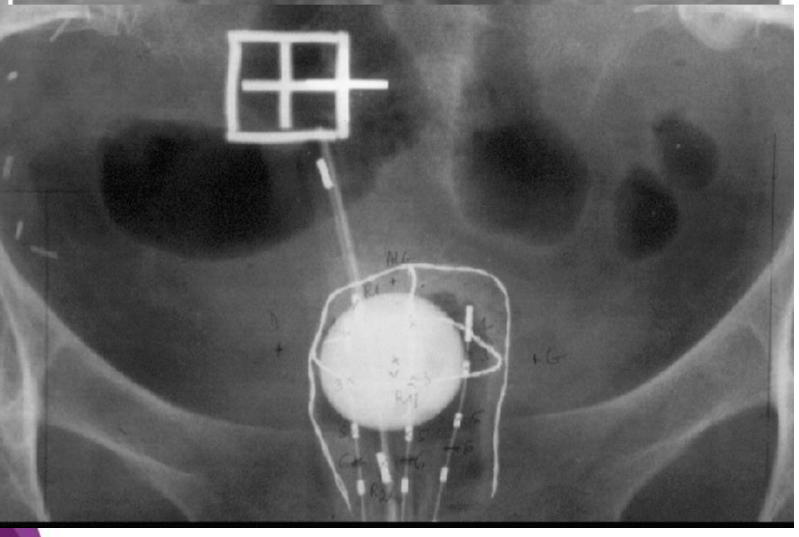
Small et al IJROBP 2005

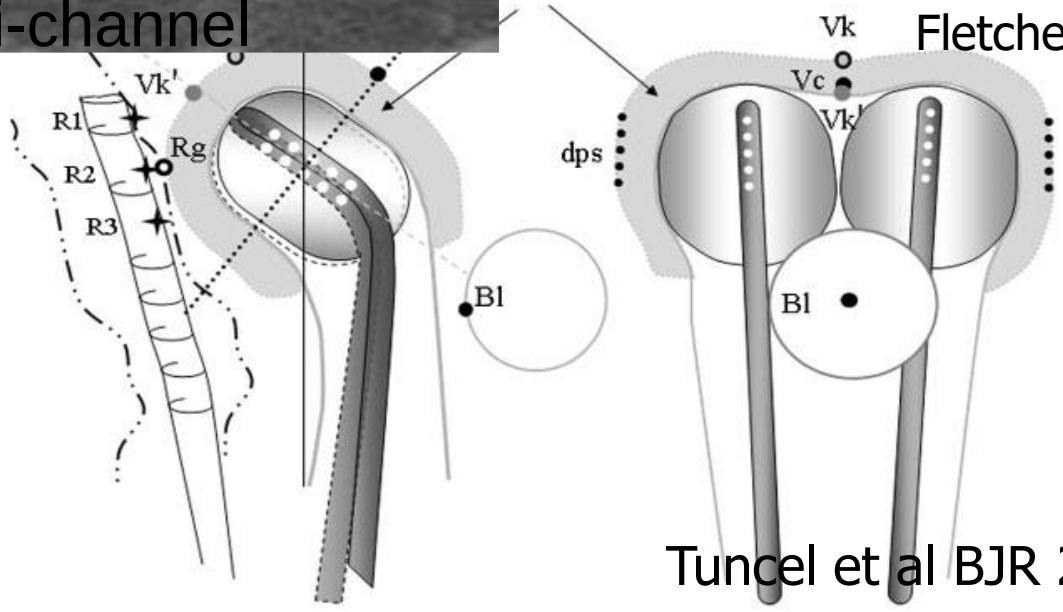
Other applicators









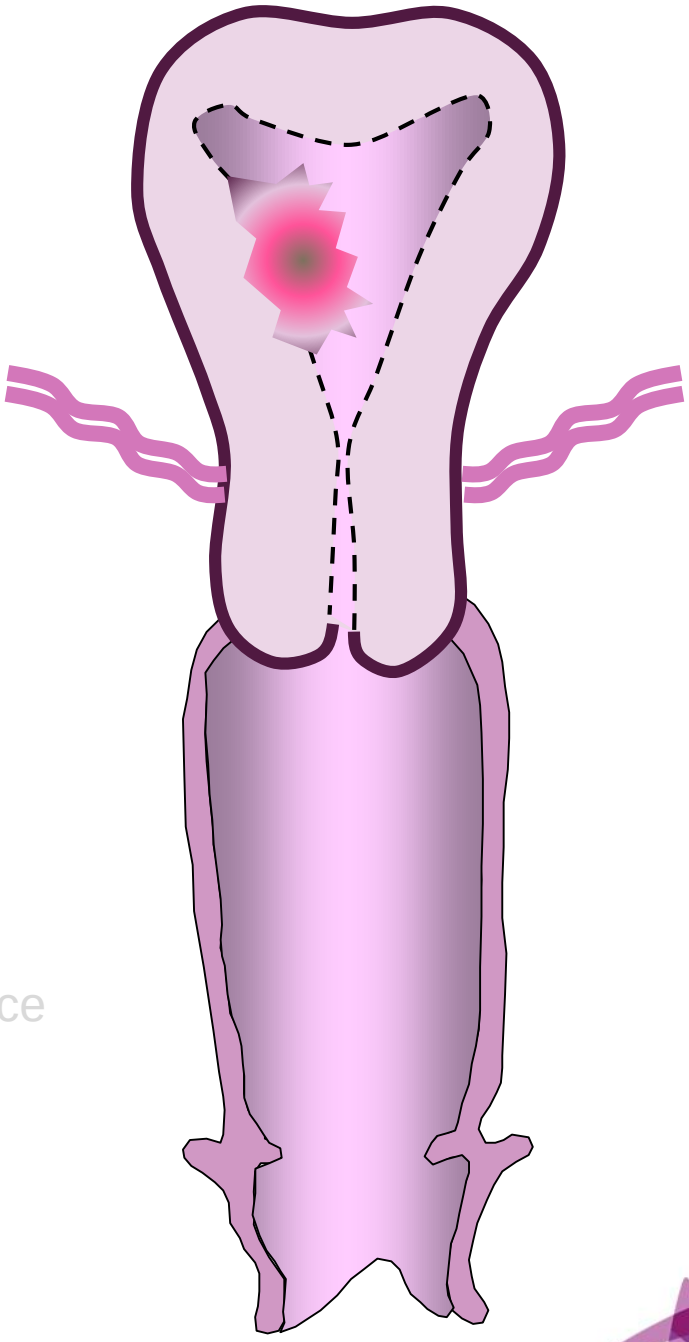


No. fractions	Gy surface	Gy 5mm	Gy3 surface	Gy3 5 mm	Gy10 surface	Gy10 5 mm	% Late morbidity	% Vault control
2-7	24-100	15-67	88-1118	38-438	43-452	15-177	0-29	95-100

Treatment planning for definitive endometrium technique

1) post-hysterectomy

2) patient unfit for hysterectomy



3) recurrence

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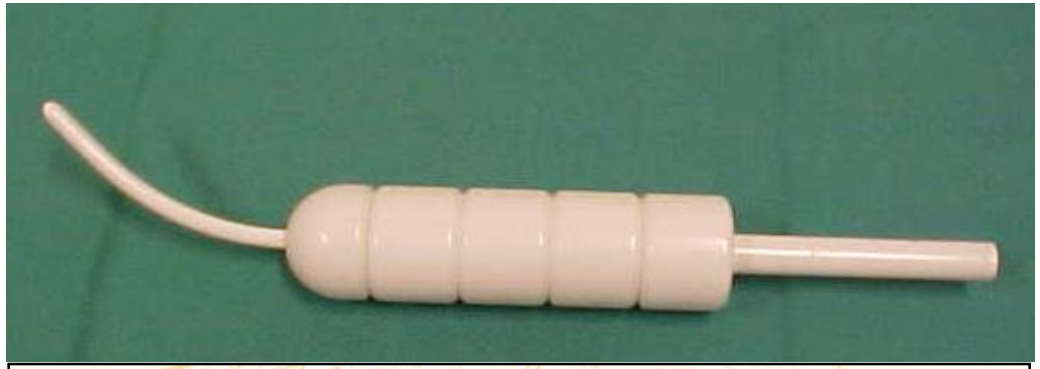
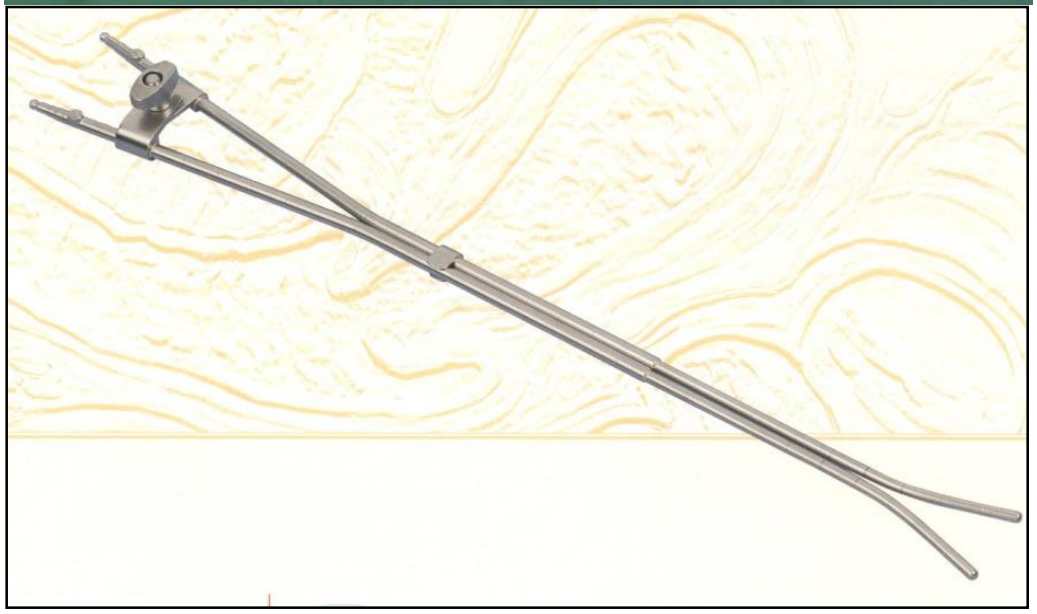
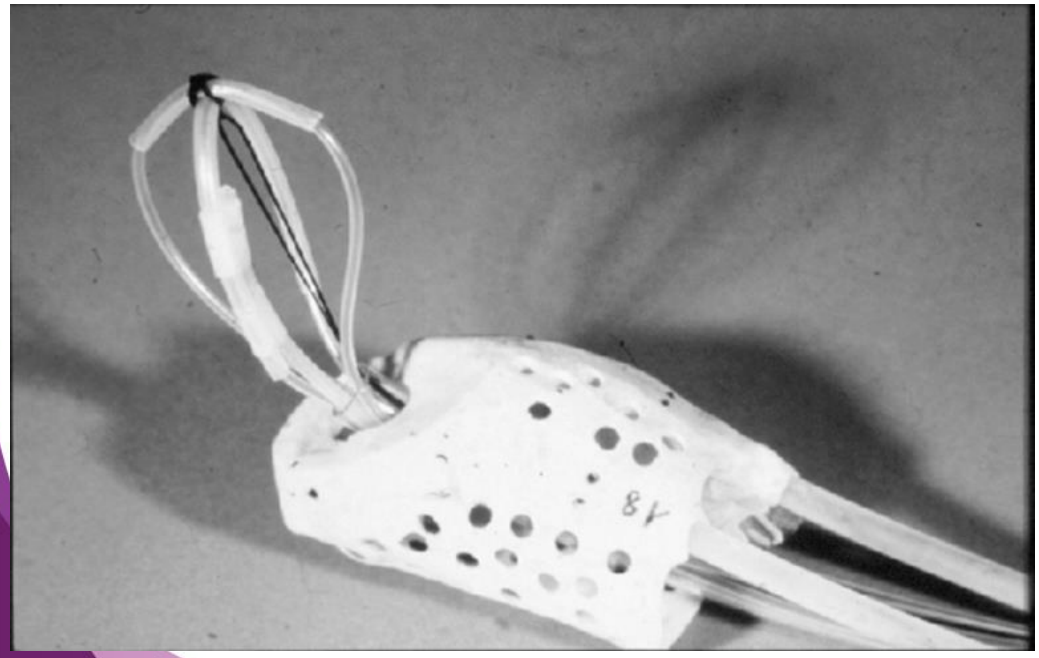
The planning procedure

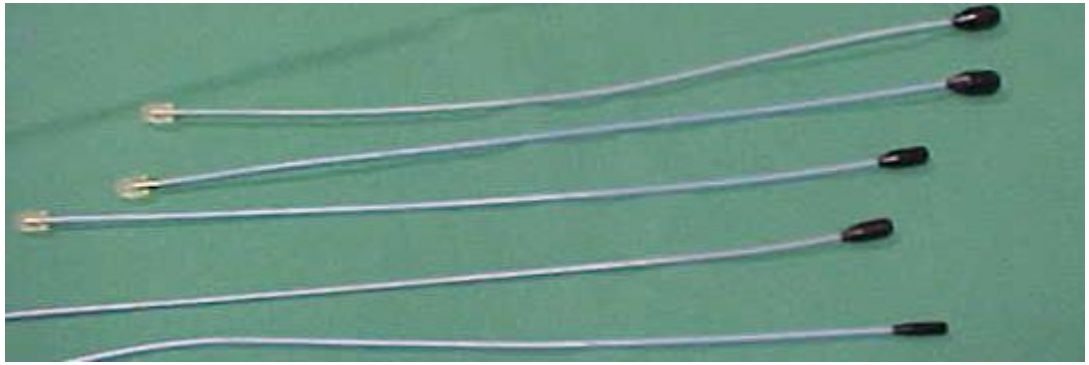
is depending on the applicator type

- one channel applicator
- two channel applicator
- Modified Heyman packing
- Norman-Simon-applicators
- Pernot umbrella technique









Treatment Planning

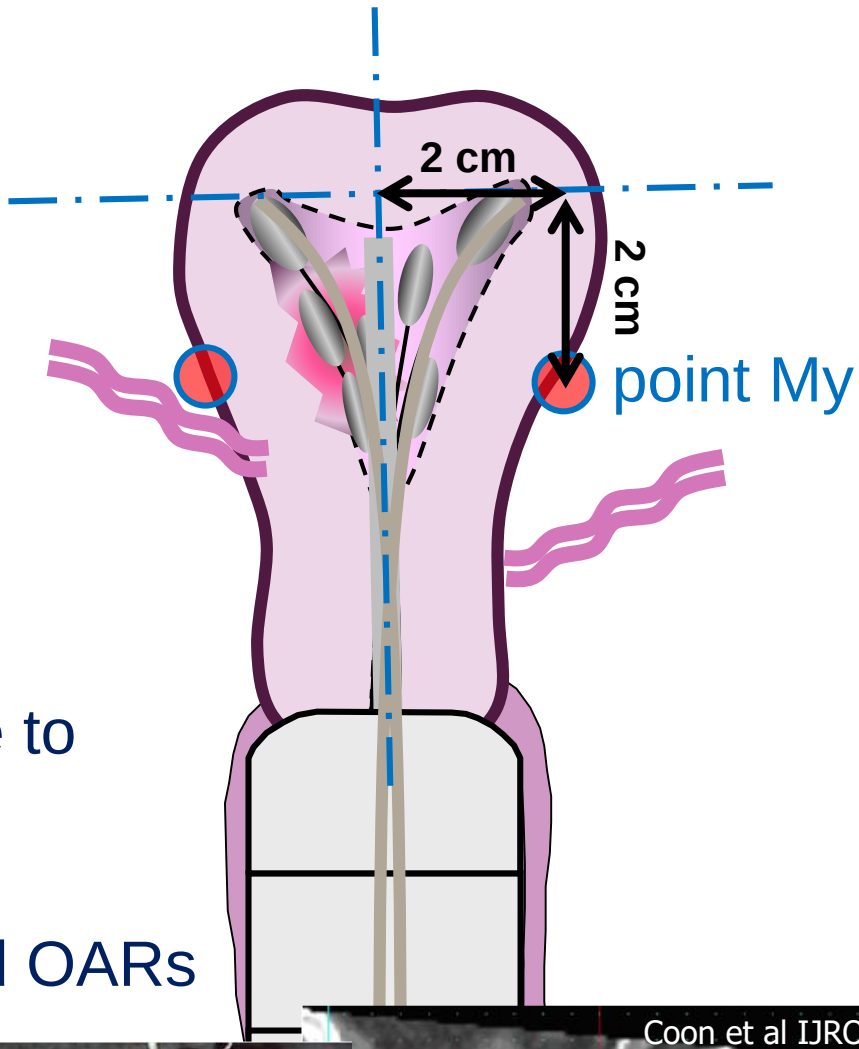
Applicator Reconstruction

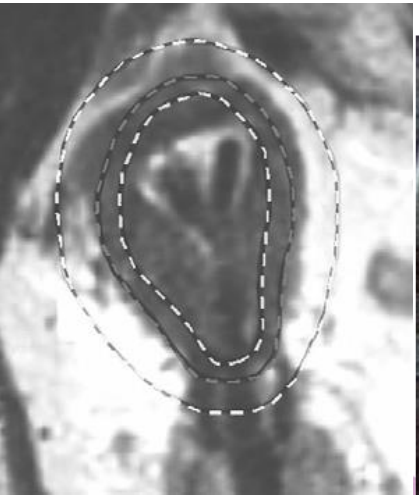
- Heyman
- One-channel
- two-channel or other

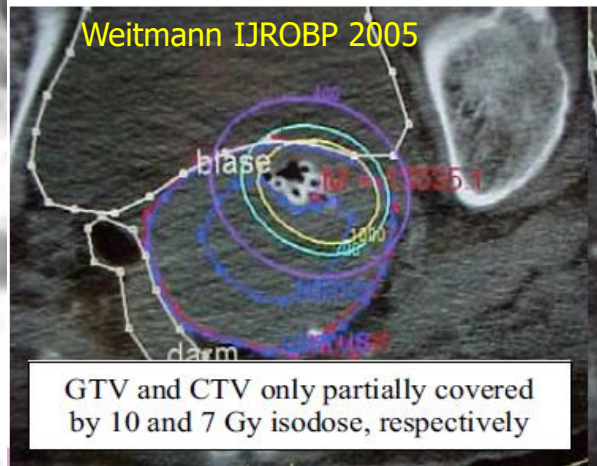
Define point My (Starting point)

Activate Source position and Normalize to point(s) My

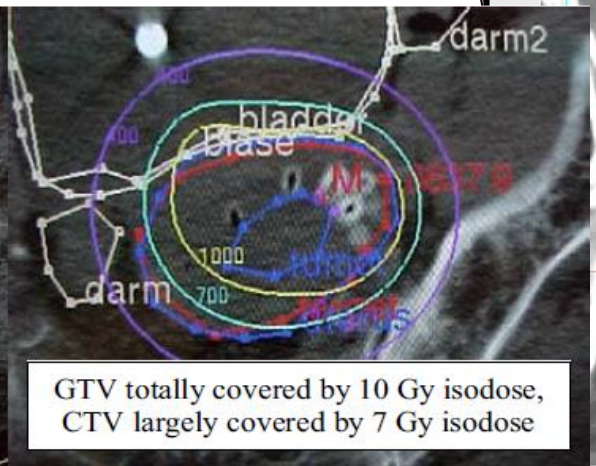
Optimize dwells according to target and OARs



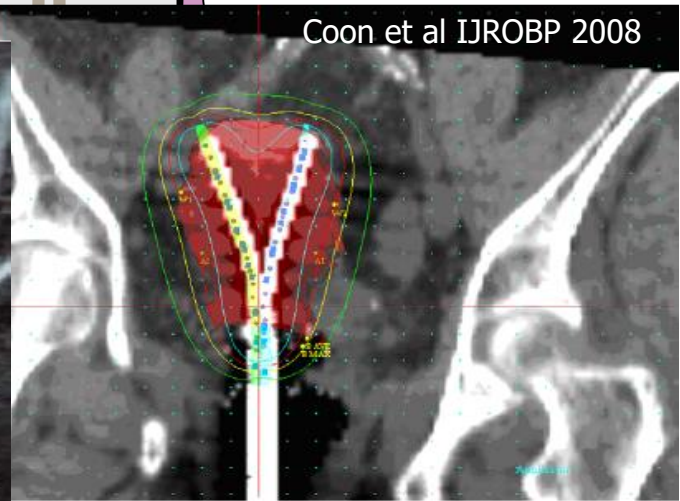




GTV and CTV only partially covered by 10 and 7 Gy isodose, respectively



GTV totally covered by 10 Gy isodose, CTV largely covered by 7 Gy isodose



Applic

Hey

On

two

Define

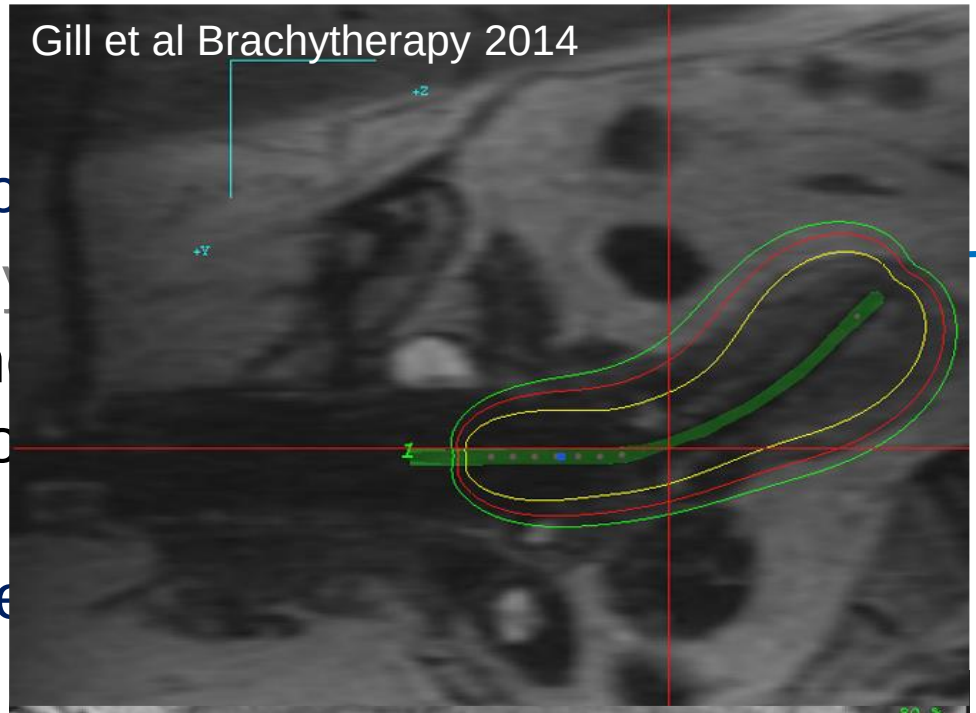
Activa

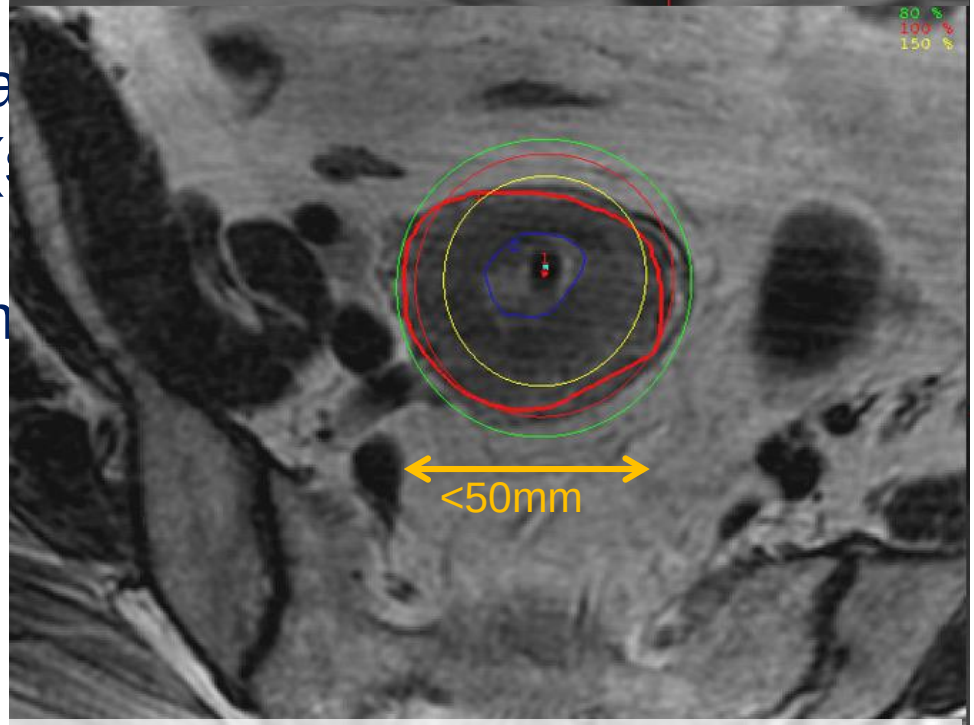
point(

Optim

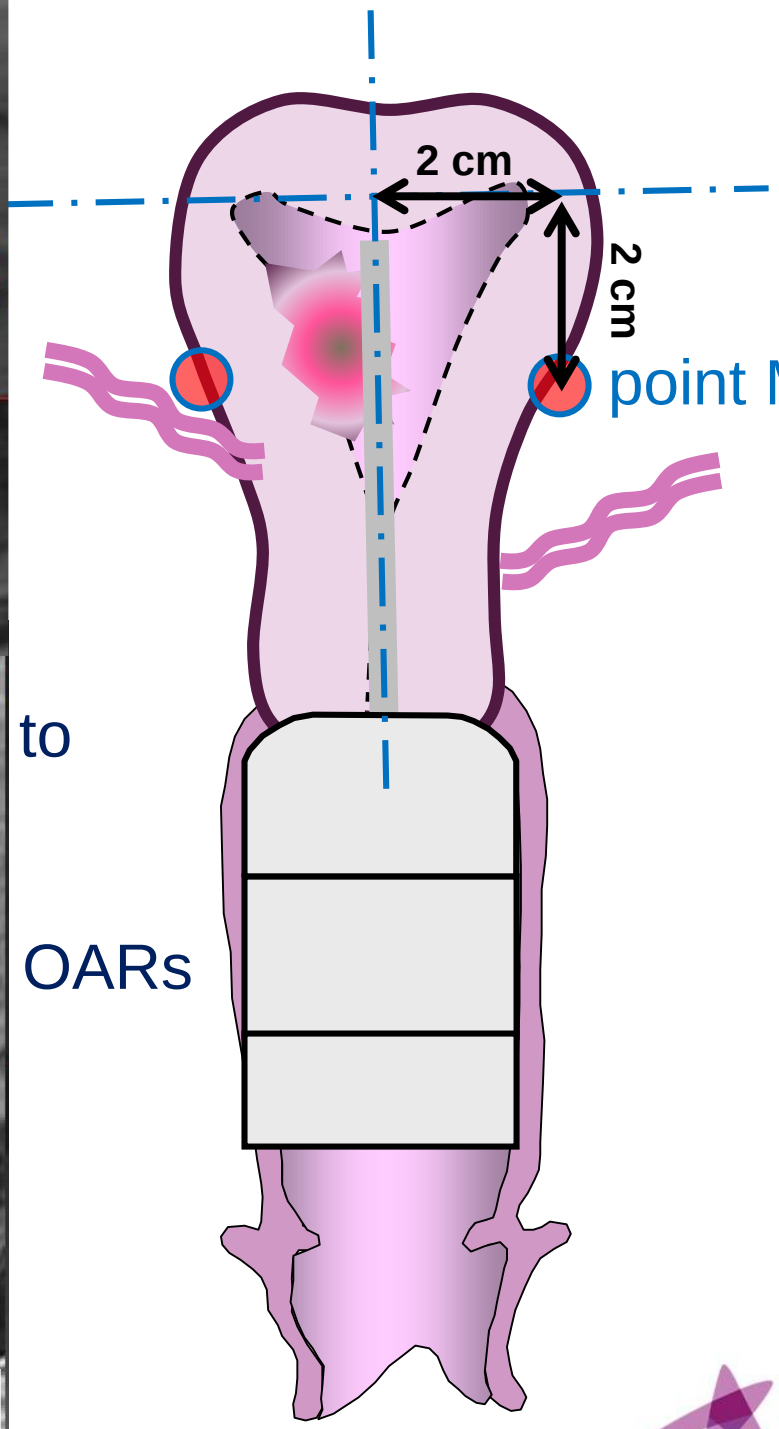
to

OARs





Single channel applicator used for uterus with max with < 5 cm



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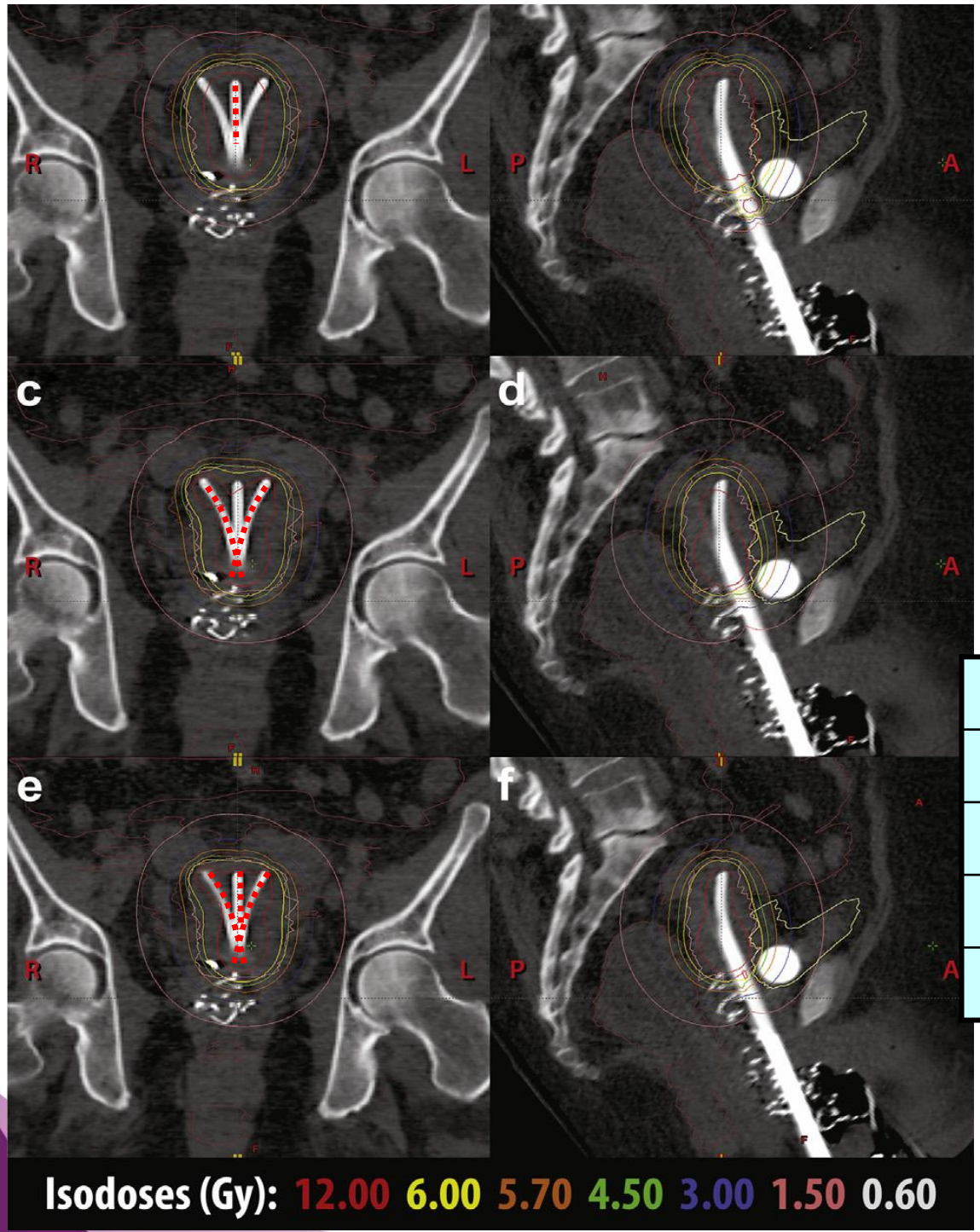
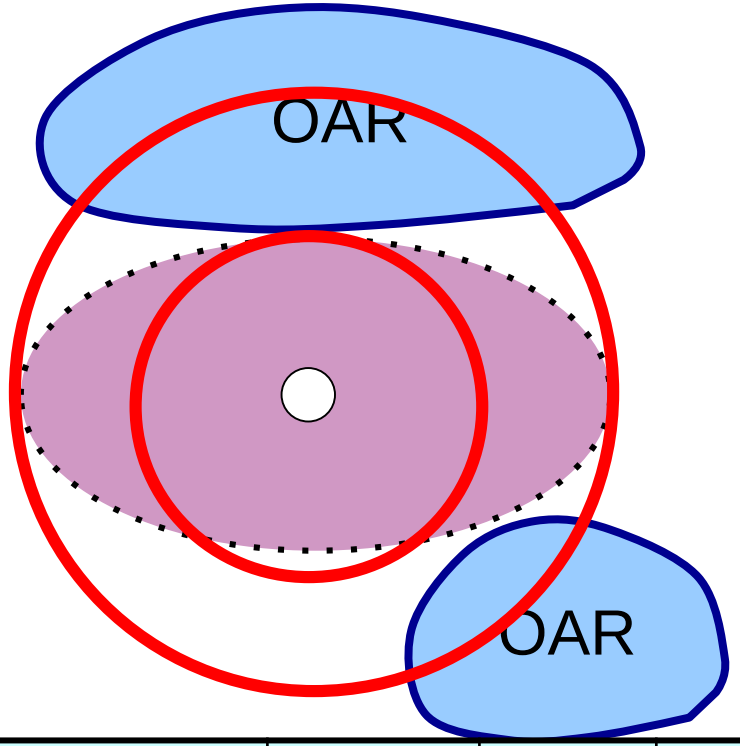
Single, dual and triple channel applicator

Single

Dual

Triple





Dose [Gy]	Single	Dual	Triple
CTV D90	95.0	95.0	95.0
Bladder D2cm^3	8.5	5.7	5.6
Rectum D2cm^3	3.6	3.9	3.9
Sigmoid D2cm^3	6.9	4.9	4.8

Johnsen et al Brachytherapy 2014

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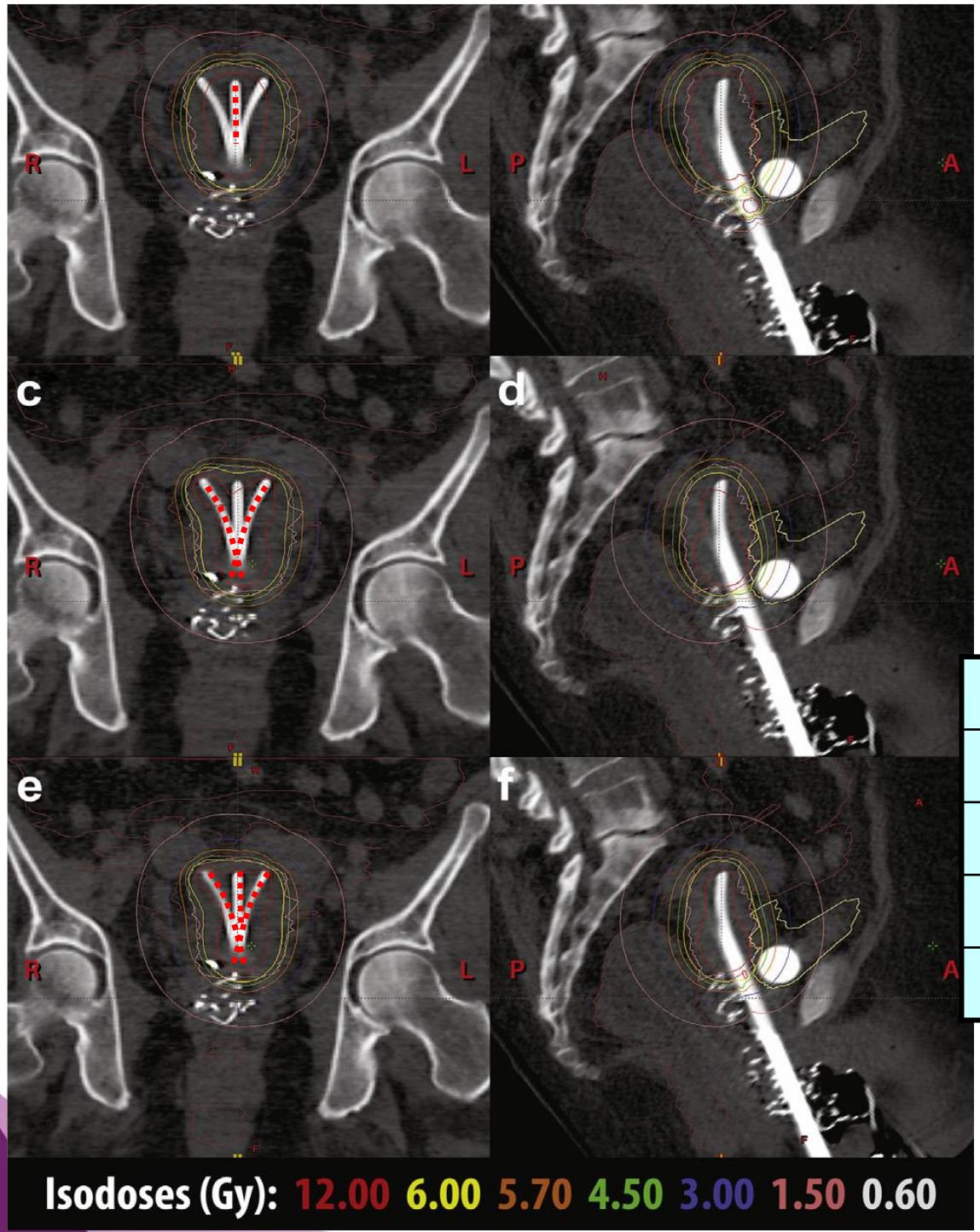
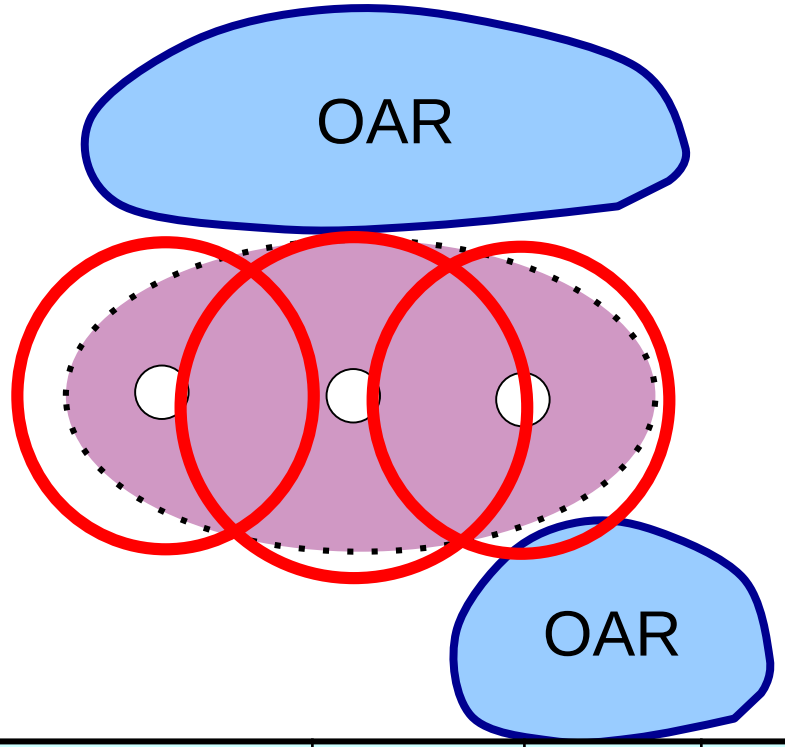
Single, dual and triple channel applicator

Single

Dual

Triple





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Johnsen et al Brachytherapy 2014

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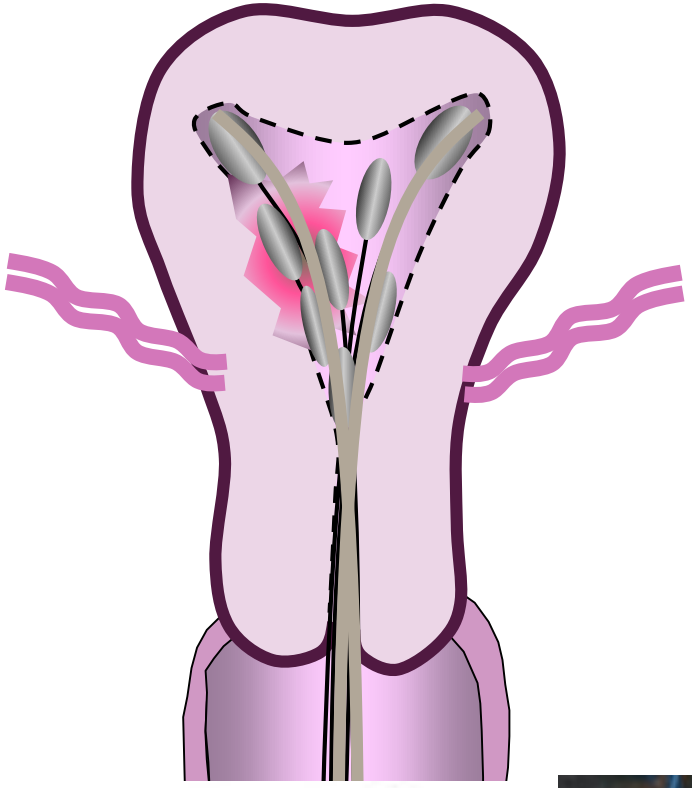
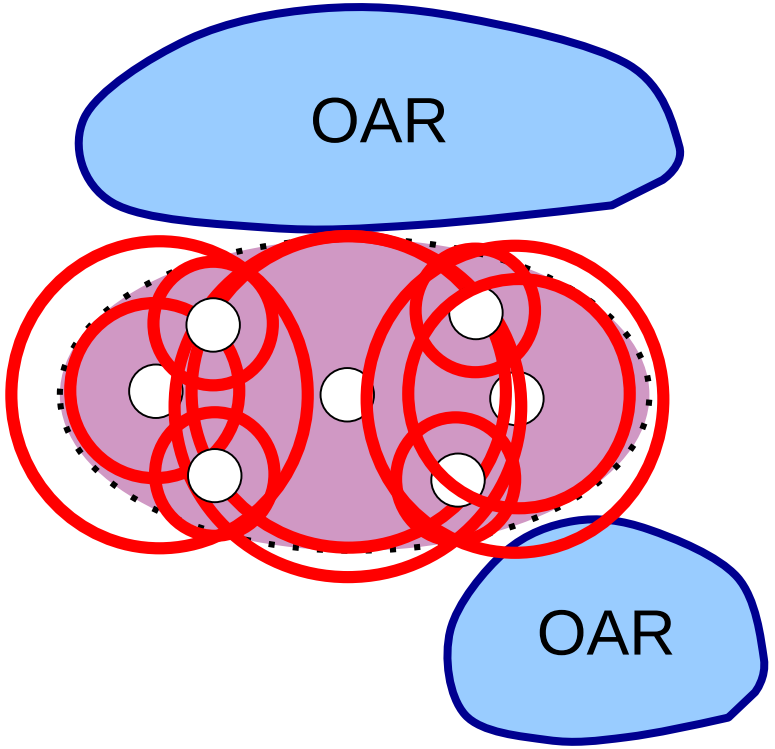
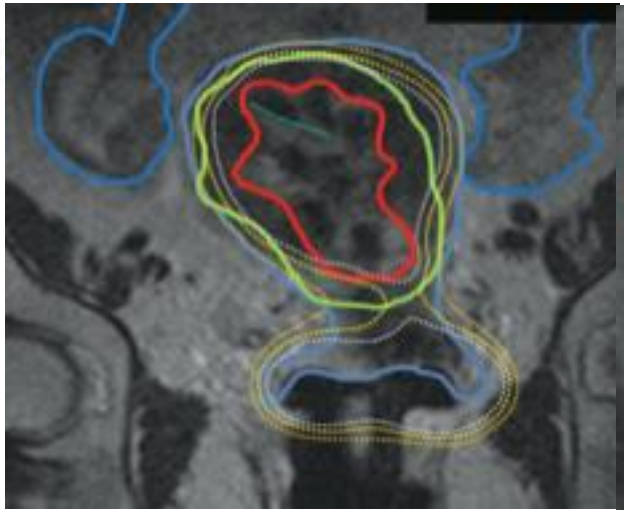
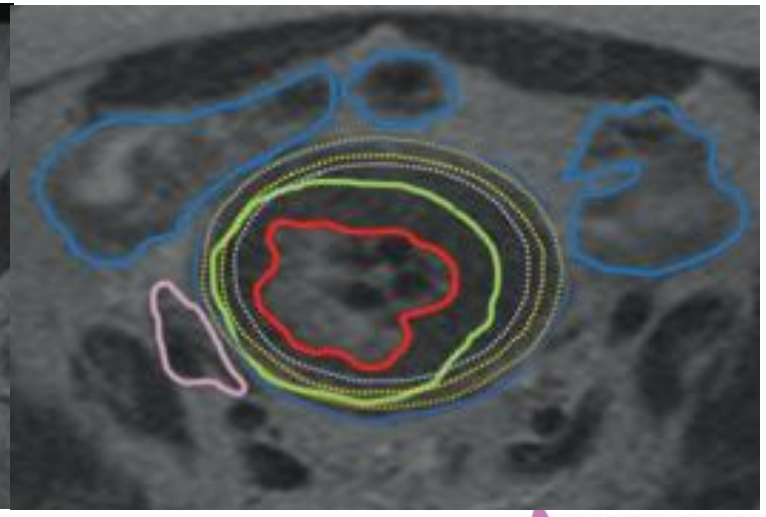
Better applicators





TRAK		59.4 mGy h^{-1} at 1 m
GTV	(34 cm^3), D_{98}:	116.3 Gy $EQD2_{4.5}$
HR CTV	(131 cm^3), D_{90}:	83.1 Gy $EQD2_{4.5}$
LR CTV	(243 cm^3), D_{90}:	59.7 Gy $EQD2_{4.5}$
Sigmoid	D_{2cm^3}:	48 Gy $EQD2_3$
Bowel	D_{2cm^3}:	45 Gy $EQD2_3$
rectum	D_{2cm^3}:	20 Gy $EQD2_3$
bladder	D_{2cm^3}:	53 Gy $EQD2_3$





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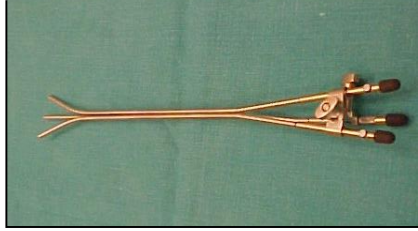
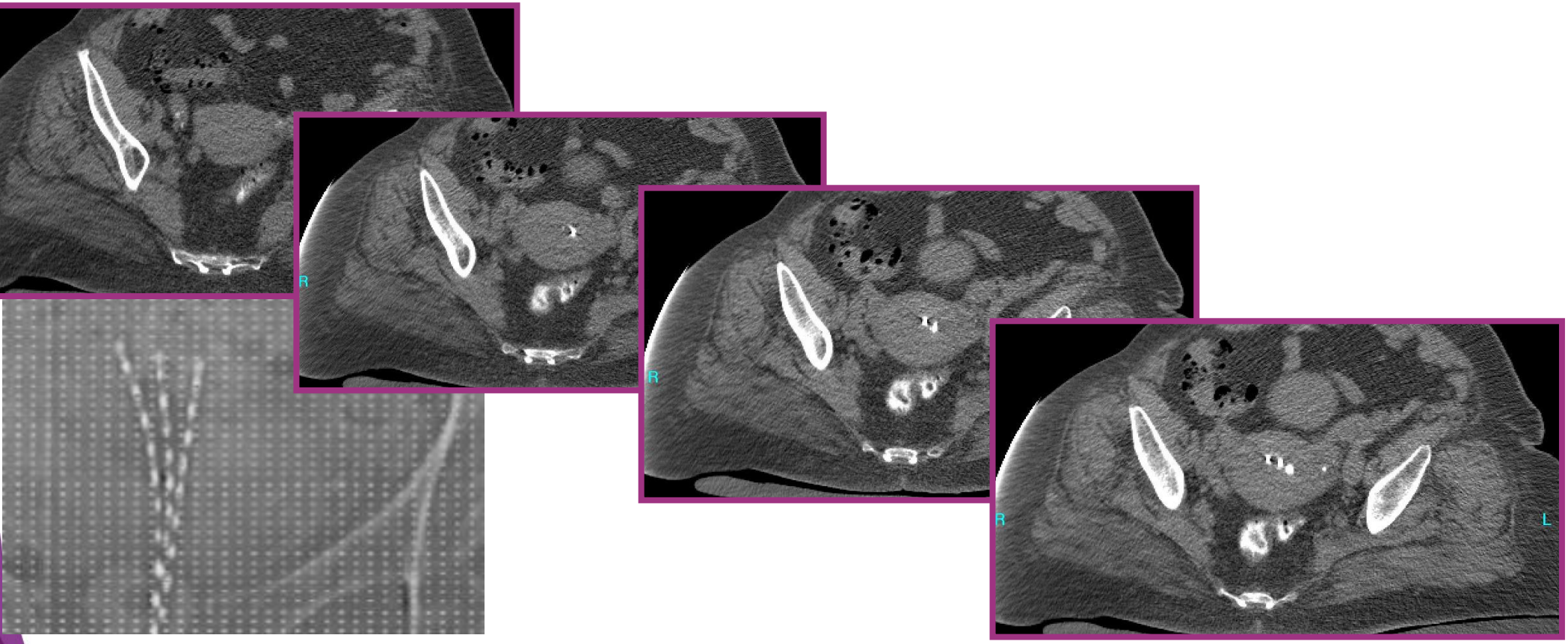
Reconstructing the applicator



- Rigid one-, two- or three channel applicator – follow direct reconstruction procedure



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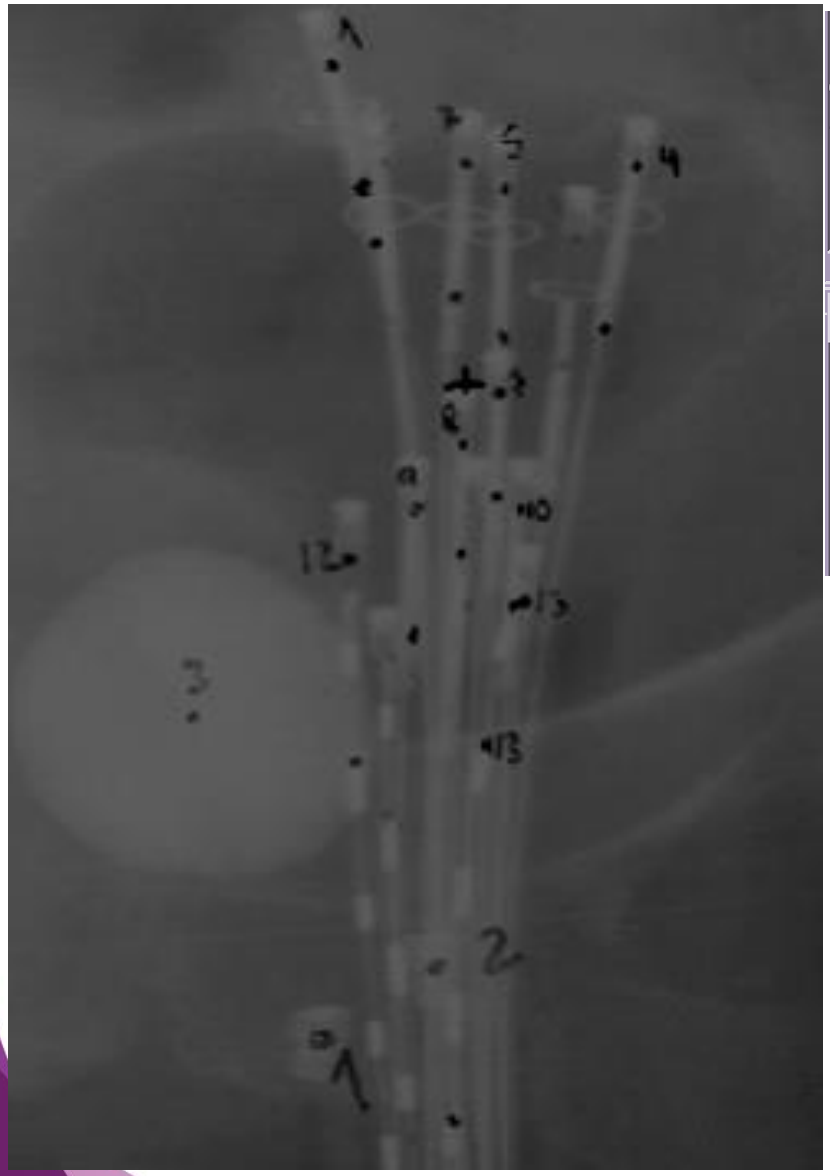
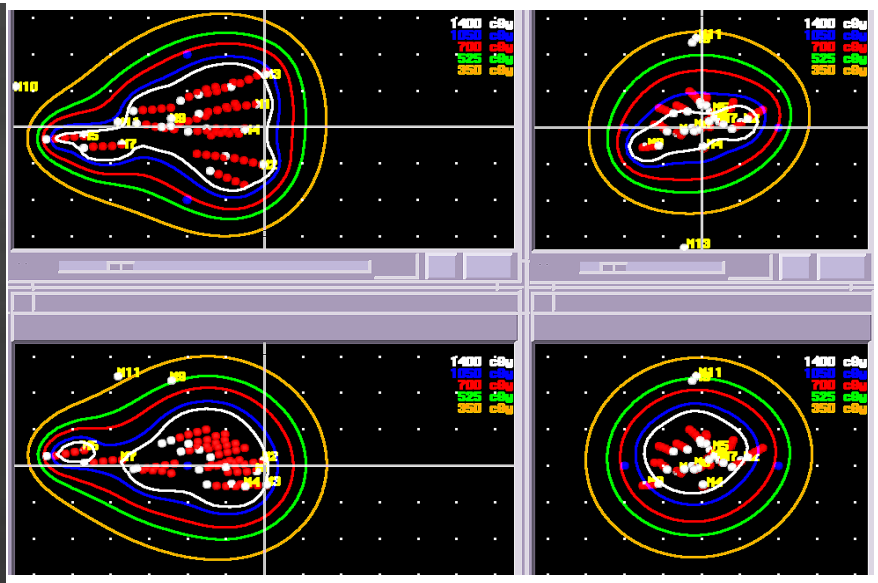
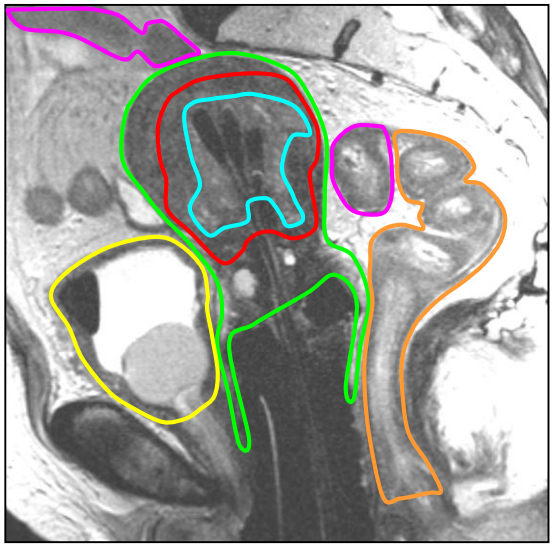
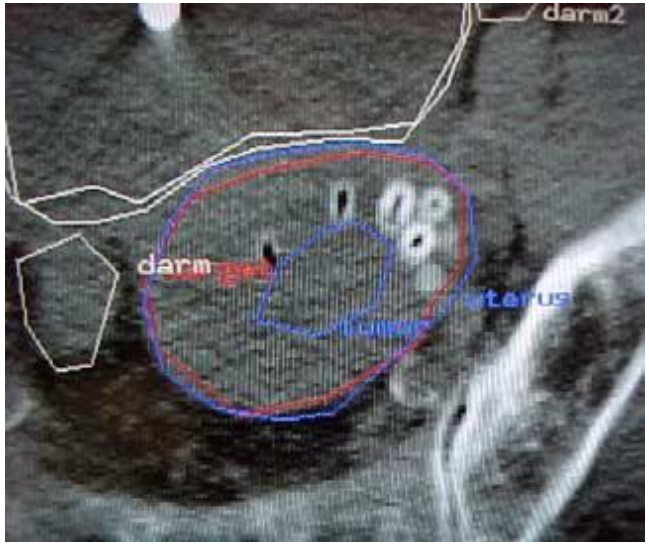
Reconstructing the applicator

- NS-applicators or Heyman packing – with many applicators it could be a complex procedure.









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THANK YOU !

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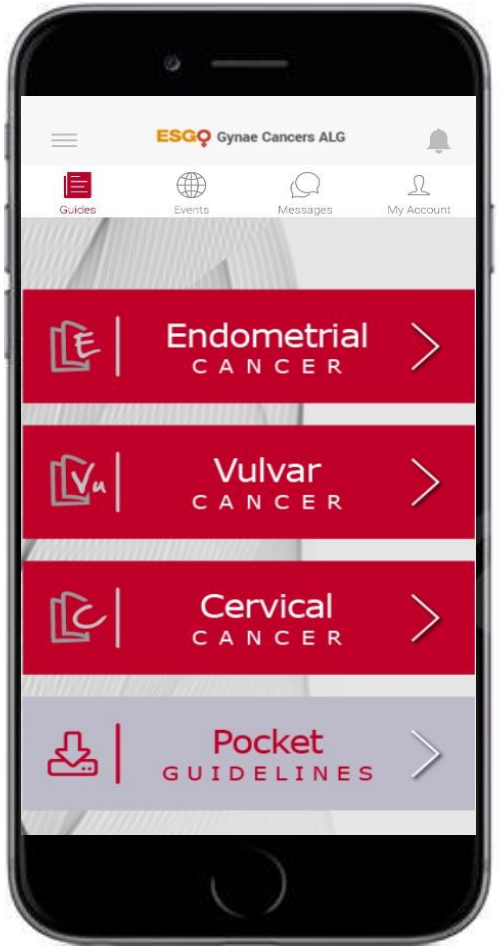

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Physics aspects of treatment planning for interstitial techniques in vagina and vulva cancer

Jamema Swamidas

Daniel Berger

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Learning Objectives

- Review of Treatment planning aspects of Vaginal and Vulval applications
  - Intracavitary
  - Intracavitary and interstitial
  - Interstitial
- Reconstruction, Source activation, Dose points, normalization/optimization.
- Clinical examples of each type

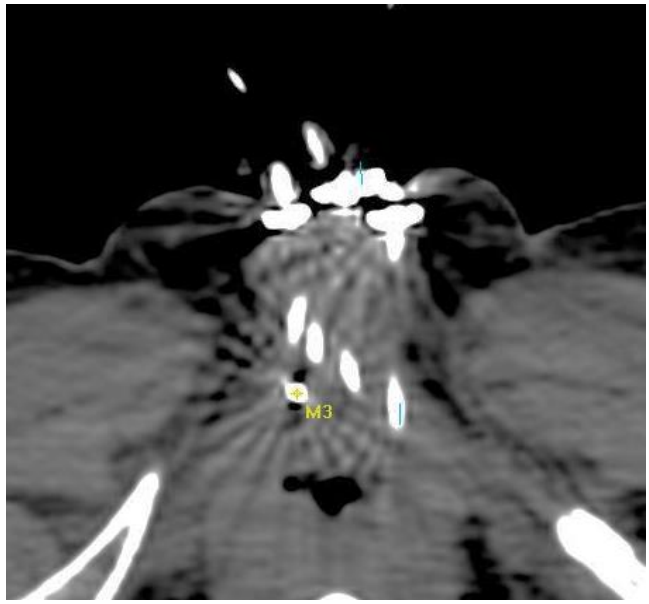
Vaginal and Vulval applications

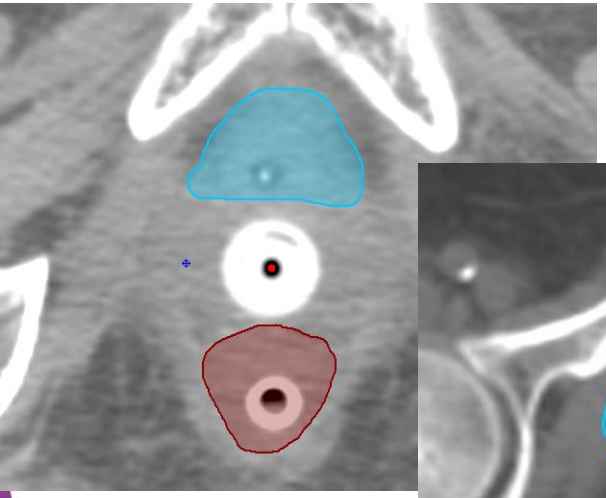
Vagina

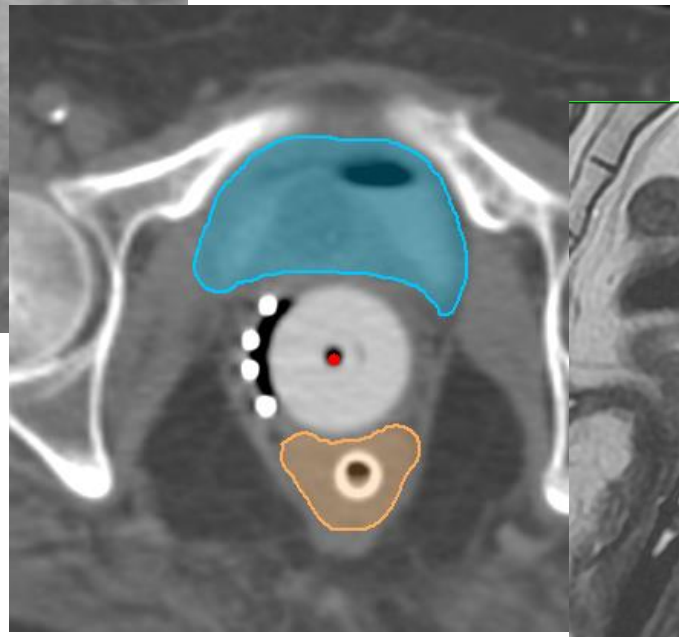
- Cylinder
- Cylinder + Needles
- Cylinder + Tandem + Needles
- MUPIT

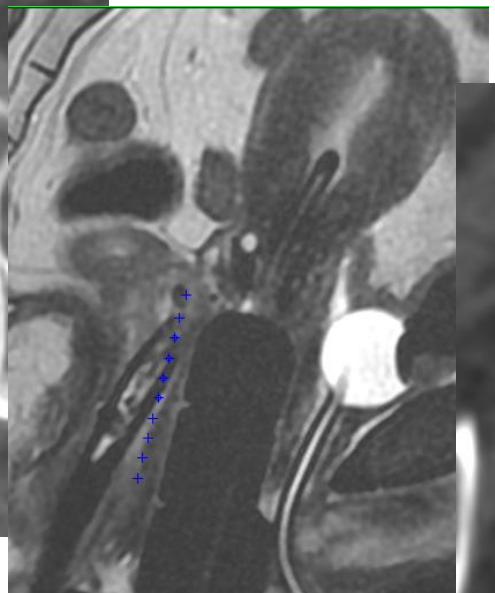
Vulva

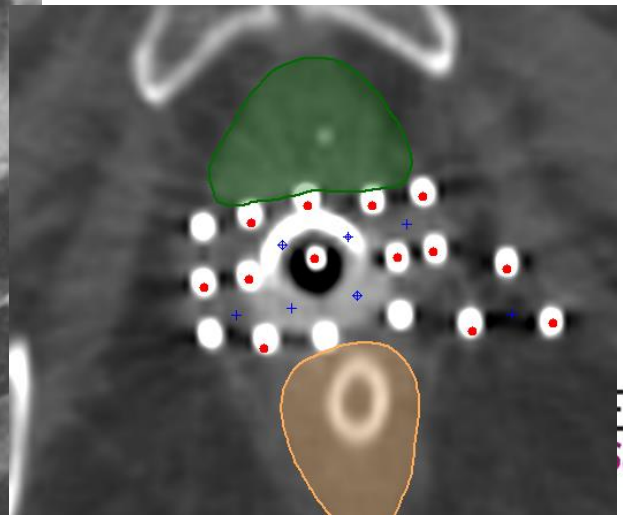
- Free Hand Implant











Vaginal and Vulval implants

	Cylinder	Cylinder + N	Cylinder+T+N	MUPIT	Free Hand Vulval Implant
Implant Type	IC	IC+IS		IS	
Reconstruction	Central Tandem, Needles (offset), numbering of needles is important.			Needles, same length, numbering important.	Plastic Catheters, Crowded, color code the catheters
Source activation	MRI - CTV is delineated, CT - Markers as surrogates / Clinical Examination				
Dose points	Catheter based points from the applicator surface			Basal points	
Optimization	Dose Point Optimization			Geometric Optimization	
Evaluation	Uniformity not an issue, Caution: Hyper dose sleeve should be within the cylinder, and just around the needles, not compromising the target coverage.			DHI > 0.75-0.8	
Tips				Template – Geometry not an issue	Free Hand, Geometry will be an issue. Caution.

« Intracavitary » versus Interstitial treatment planning approach

achieved by Weighting/dwell times (and Normalization point)

determined by location and target

⊗ Normalization/Reference point(s)

High dose region

The Paris system defines the high dose region (hyper dose sleeve) as the volume of tissue immediately surrounding the source which receives a dose equal or greater than twice the reference dose (see for example Fig 2.6 and Fig 2.14).

The clinical experience of those who developed the Paris system indicates that complications (e.g., necrosis) occur when the diameter of this region exceeds 8 - 10 mm (Pierquin et. al. (31)). This constraint will limit the separation between sources.

Taken from the GEC ESTRO Handbook

Dominant weighting in catheter 3
Dose normalized to Reference point
(“reference” distance from applicator surface)

Balanced weighting between catheters 1-12
Dose normalized to ~85% basal dose (MCD)

Slide Courtesy: Daniel Berger, Vienna

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Normalization Point – where to define the Reference point?

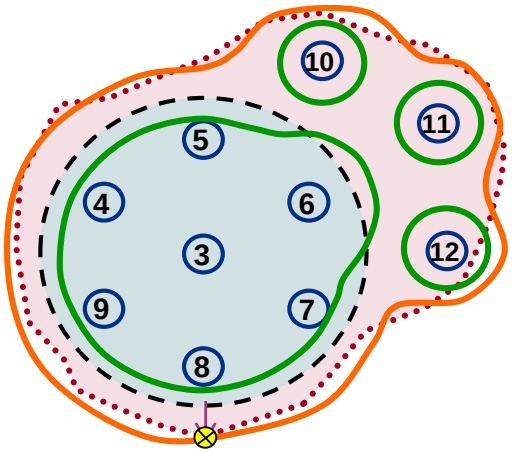
Target

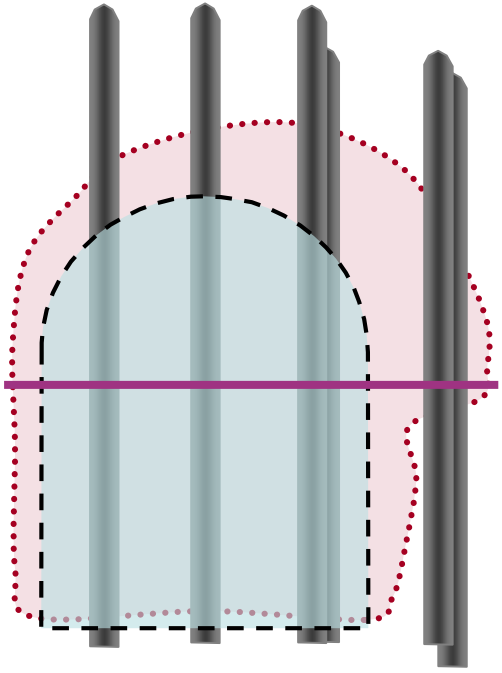
⊗ Normalization/Reference point(s)

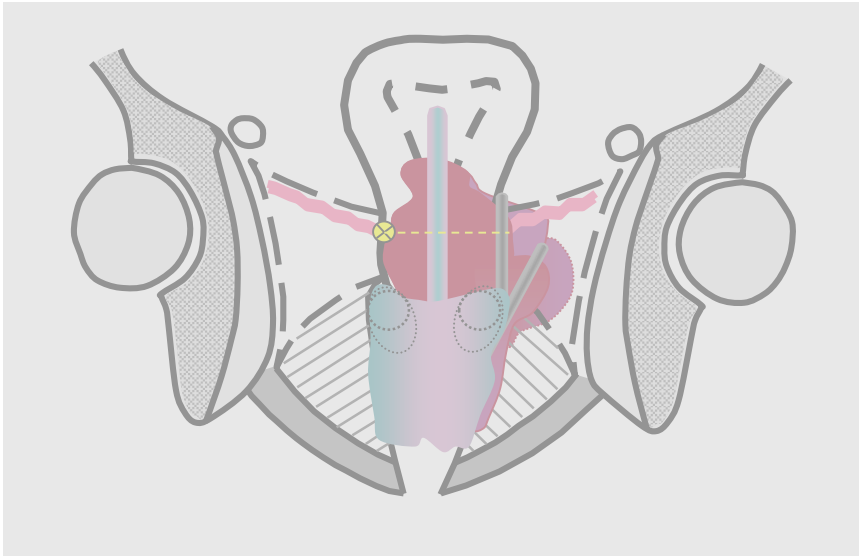
Nr Catheter Nr._

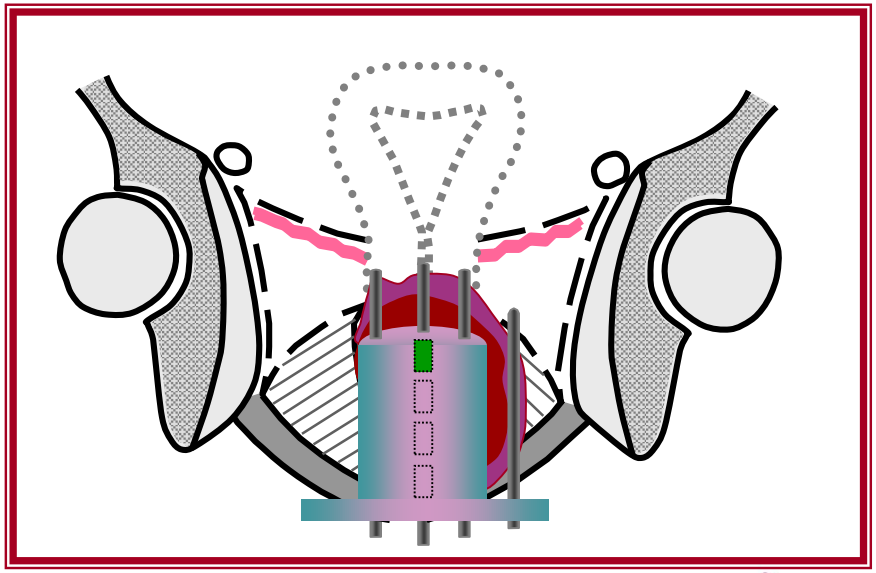
100% (=PD)

200%









☒ Intracavitary ☐ Interstitial

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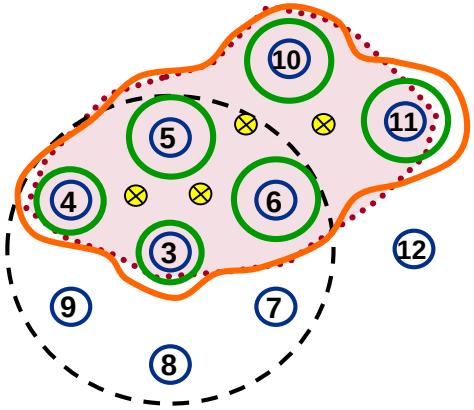
Target

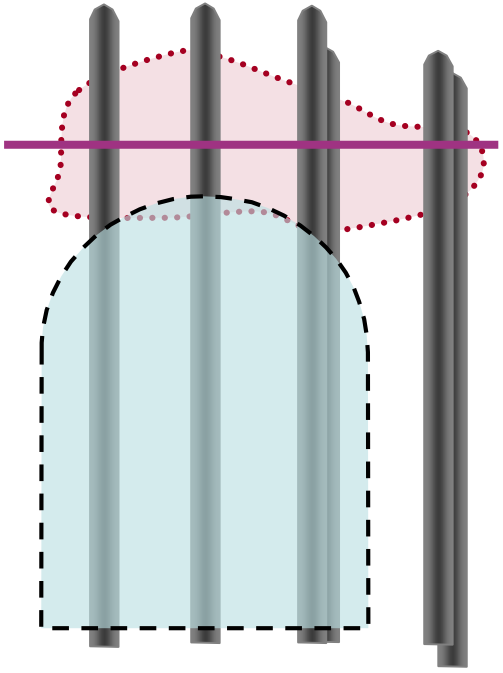
⊗ Normalization/Reference point(s)

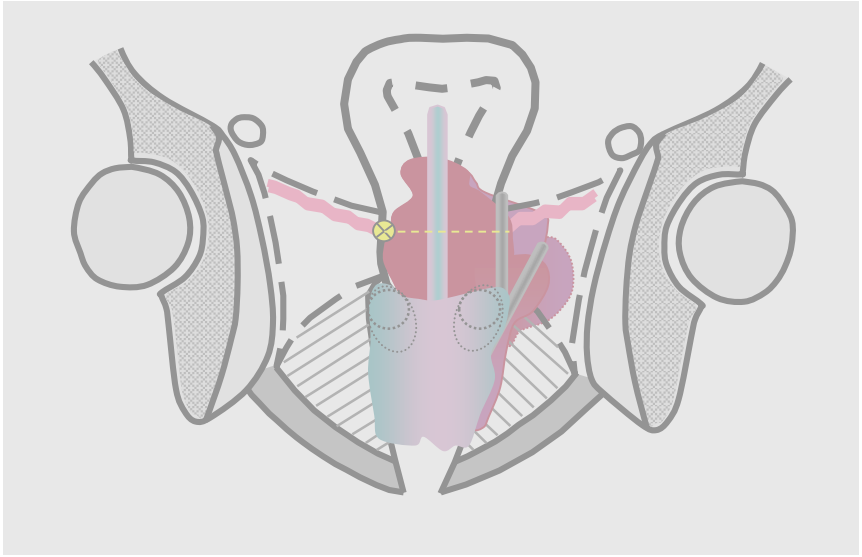
Nr. Catheter Nr._

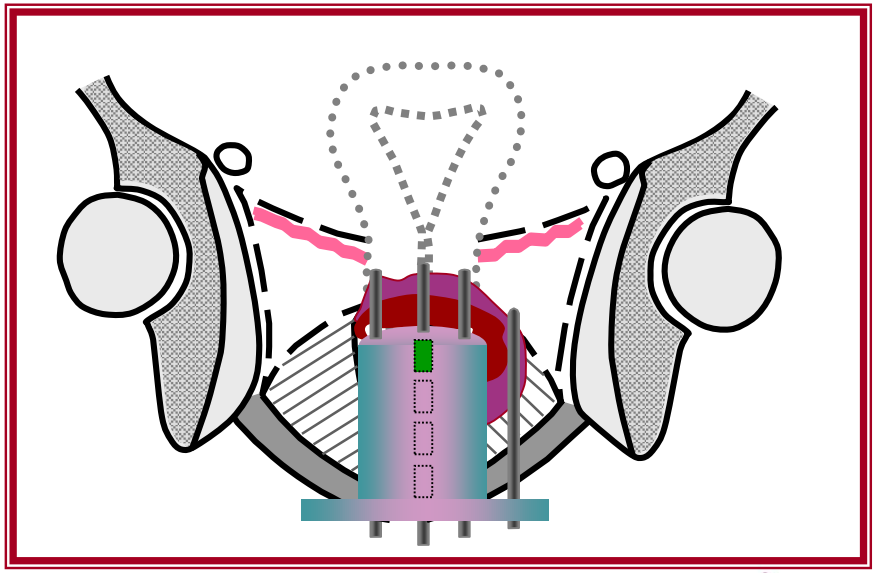
100% (=PD)

200%









☐ Intracavitary ☒ Interstitial

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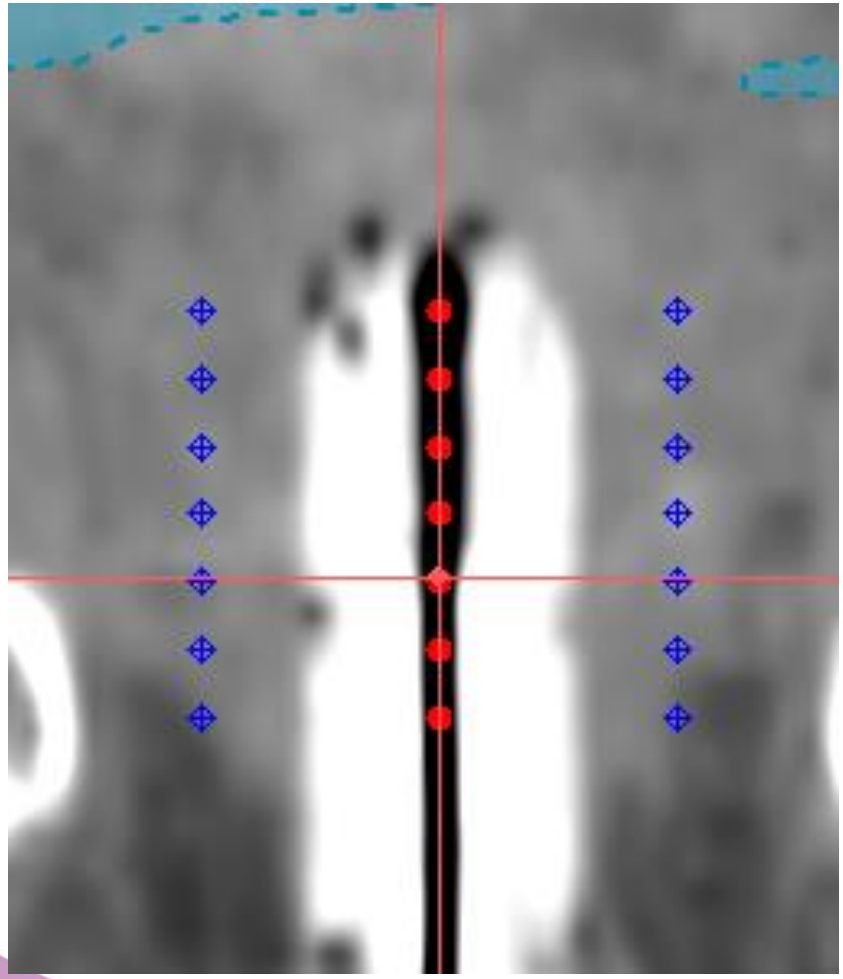
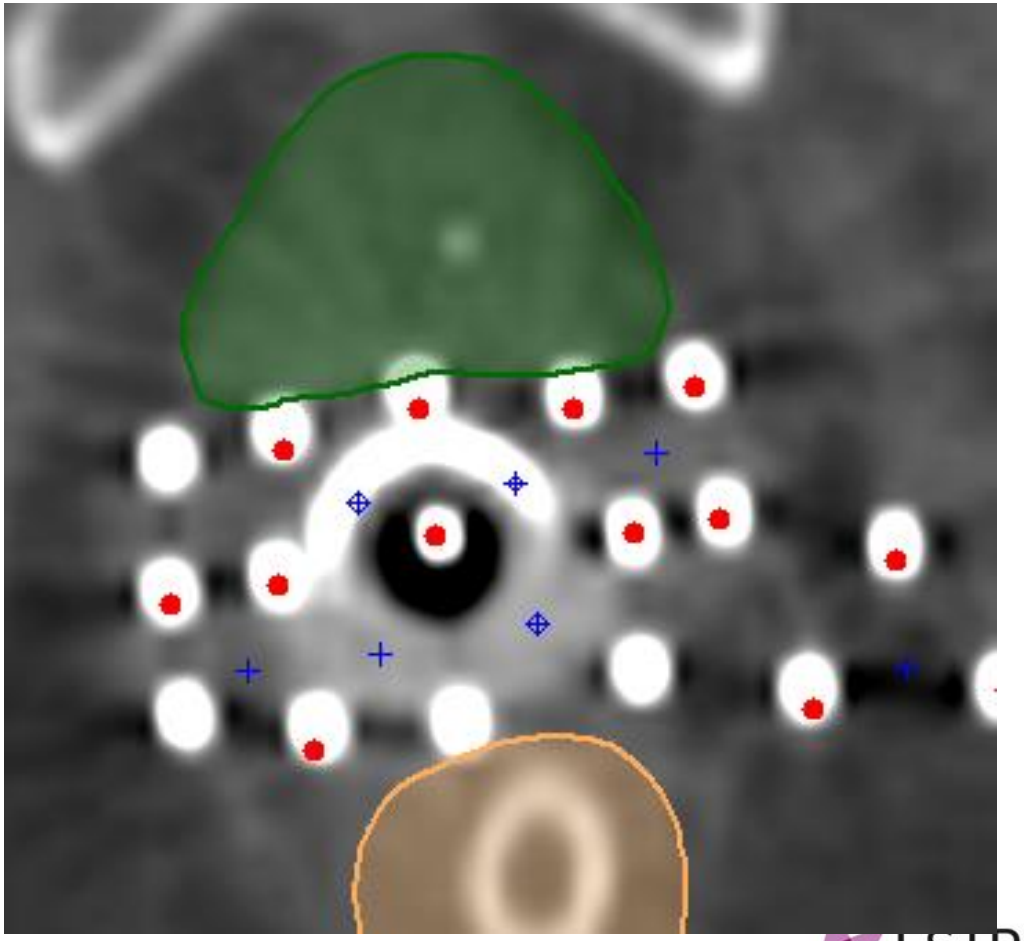
Dose Point vs Geometric Optimization

Desired dose at a number of dose points at a certain distance from the catheter are defined



The dwell locations themselves act as dose points. Aims for dose uniformity between the sources.



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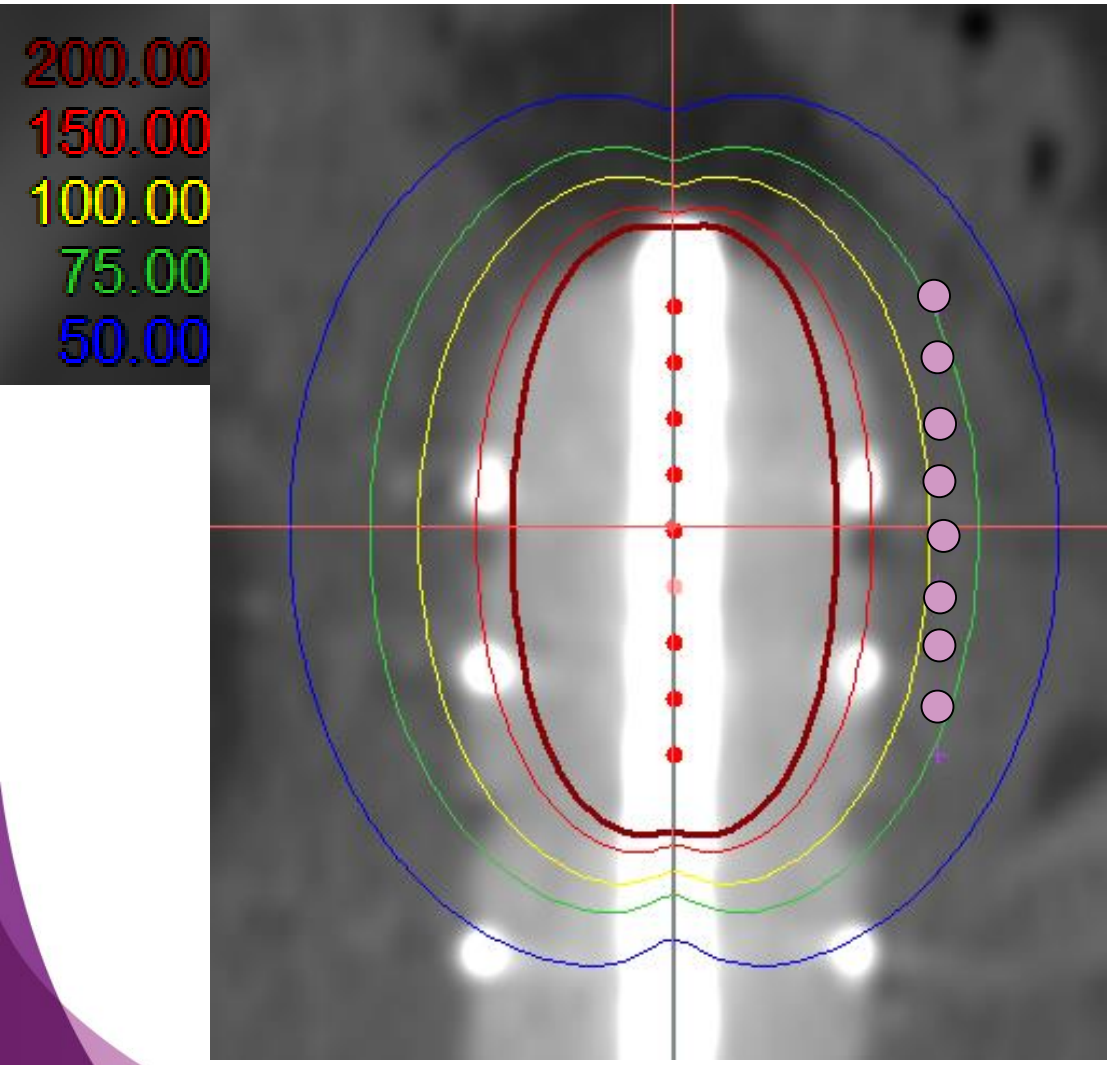
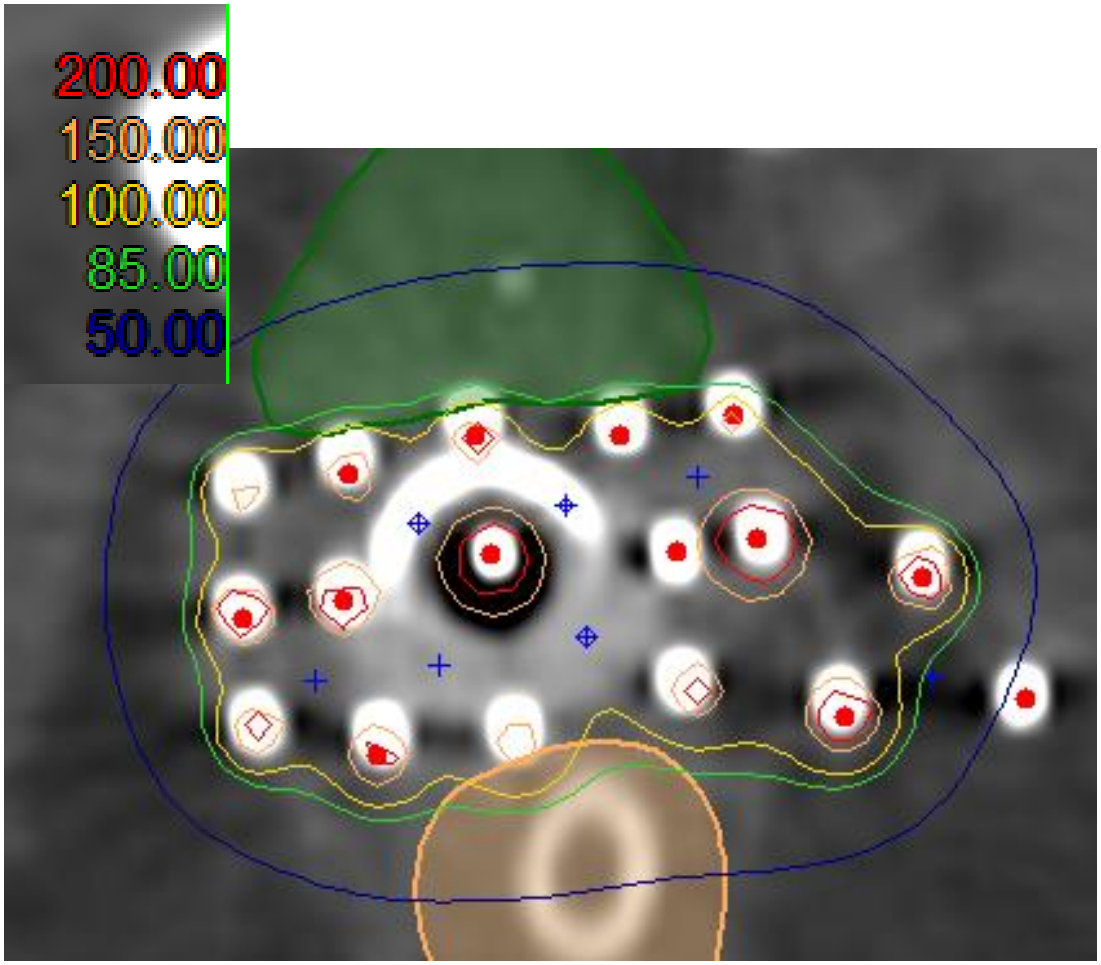
Dose Point vs Geometric Optimization



Eg: STS, Surface mould



Eg: APBI, HN

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DVH Analysis

Coverage Index $CI = \frac{CTV(100\%)}{V(CTV)}$

Homogeneity index (>0.75) $\mathbf{HI = \frac{CTV(100\%)-CTV(150\%)}{CTV(100\%)}}$

Over dose volume Index $OI = \frac{CTV(200\%)}{V(CTV)}$

External volume Index $EI = \frac{NTV(100\%)- CTV(100\%)}{V(CTV)}$

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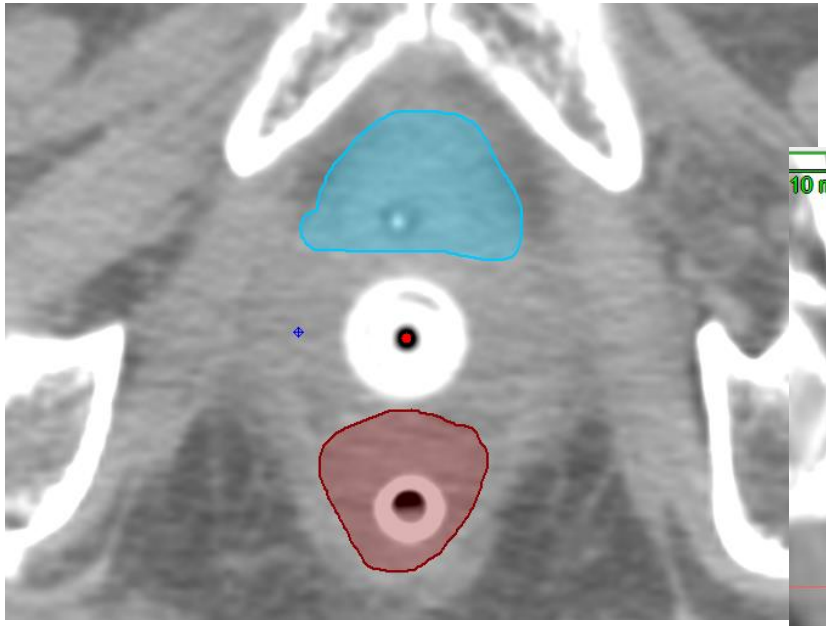
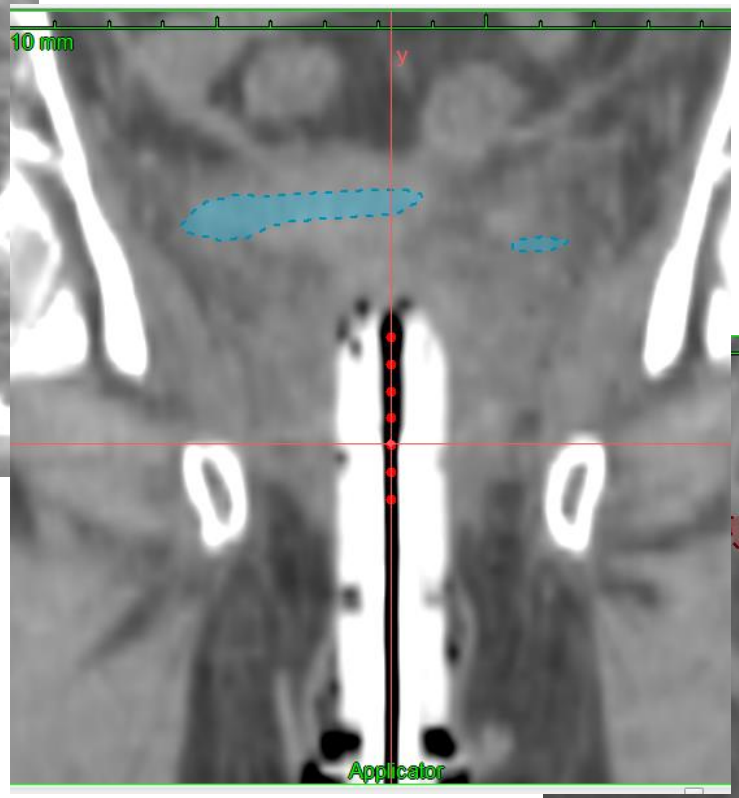
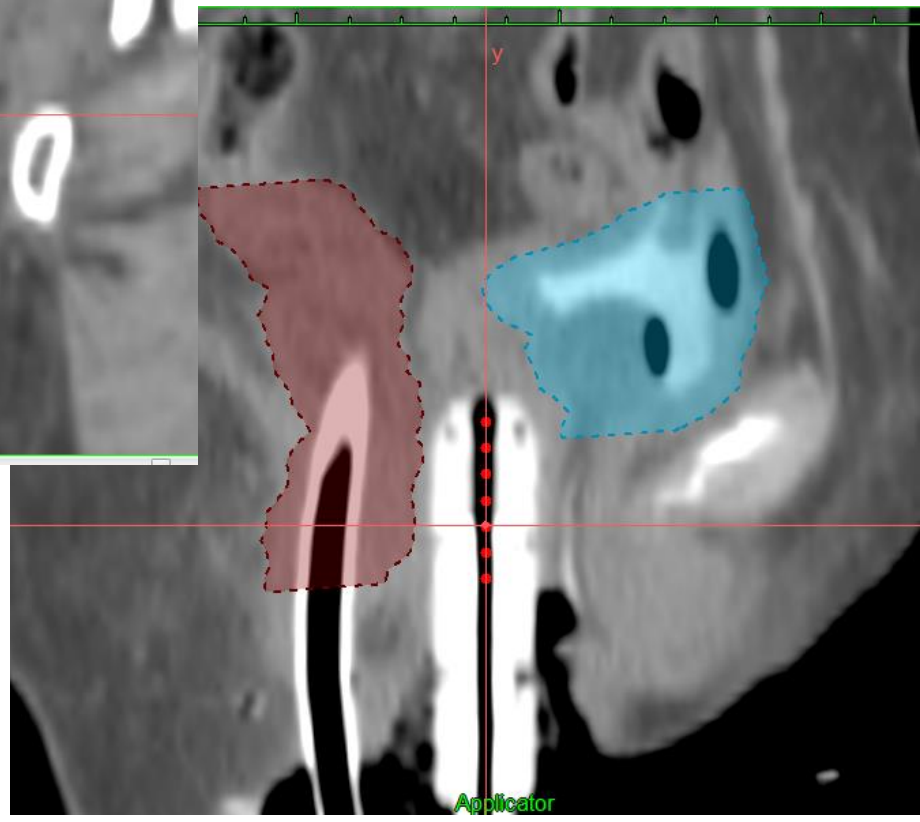
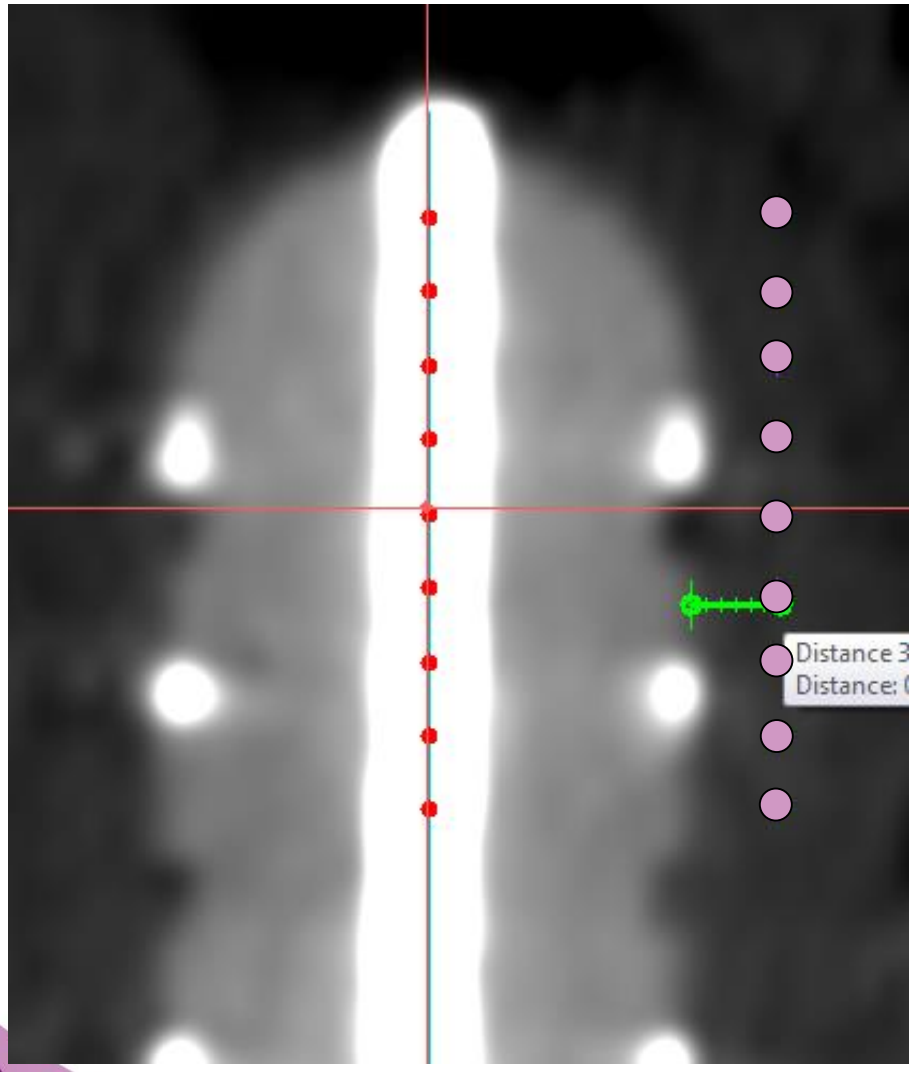
Example 1: Vaginal Cylinder







Vaginal cylinder – Dose points



5-8 mm from the applicator surface, which represent the dose to the vaginal mucosa

Dose to the OAR such as rectum and bladder to be considered while choosing the dose points

Dose: 50 Gy EBRT + 6 Gy x2

Total EQD2 dose = 67 Gy

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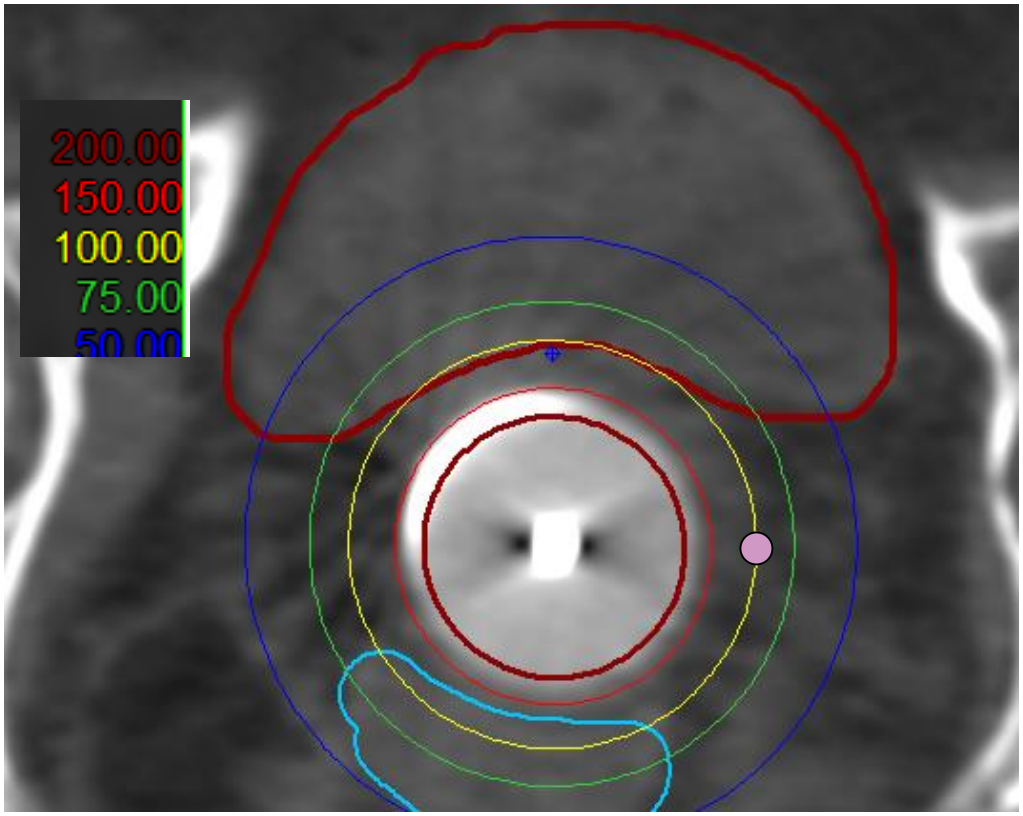
Vaginal cylinder

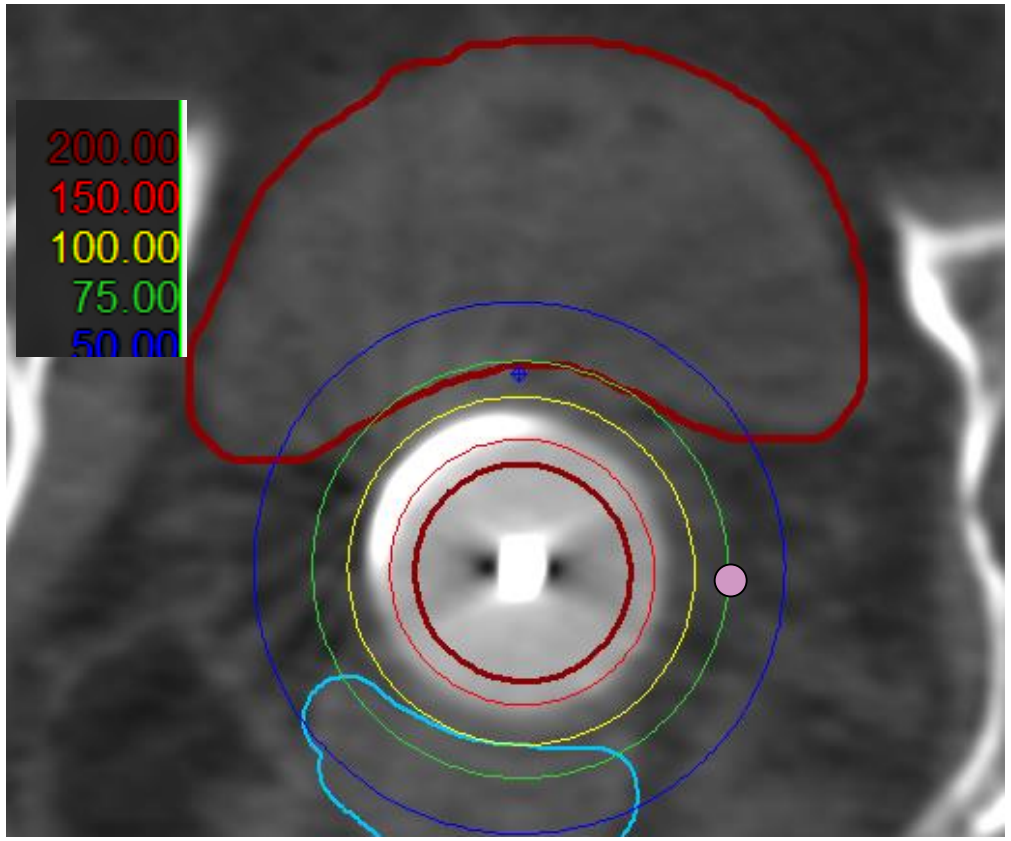
Normalized to Dose points



Rectum = 102 Gy
Bladder = 90 Gy

TRAK = 0.33

Manually Optimized for Rectum



Rectum = 76 Gy
Bladder = 85 Gy

TRAK =0. 0.29

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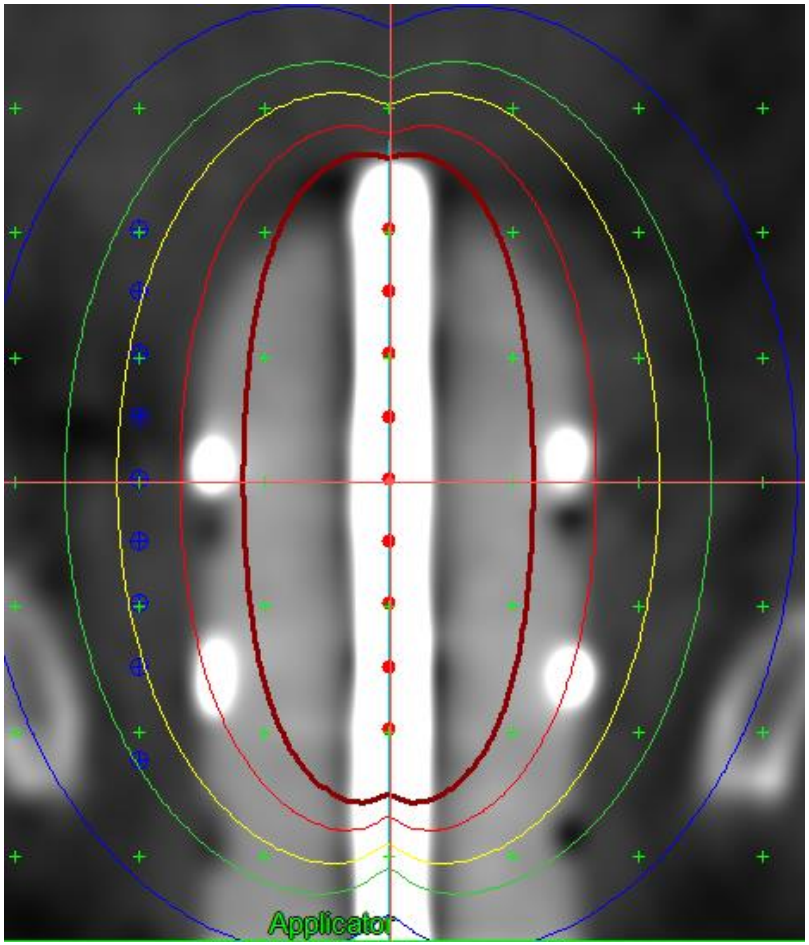
Vaginal Cylinder

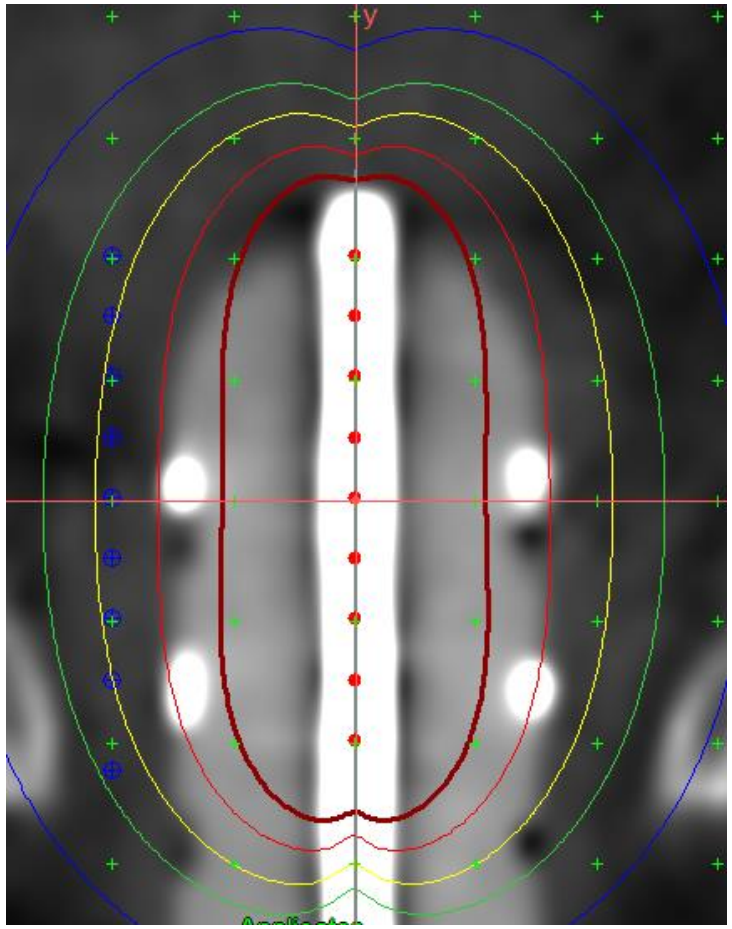
Not Optimized



Rectum = 6.3 Gy
Bladder = 6.4 Gy
TRAK = 0.325

Dose Point Optimized

High doses at the boundaries - Clinical significance?



Rectum = 6.3 Gy
Bladder = 6.6 Gy
TRAK = 0.332

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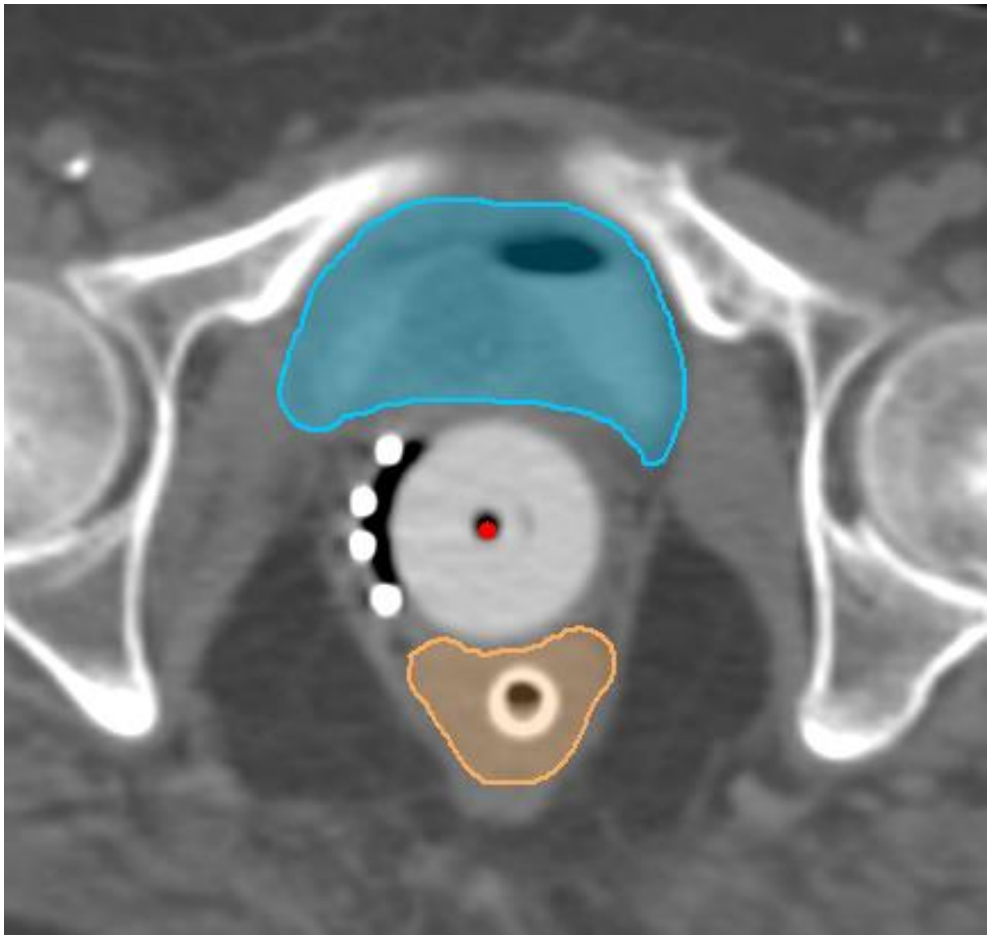
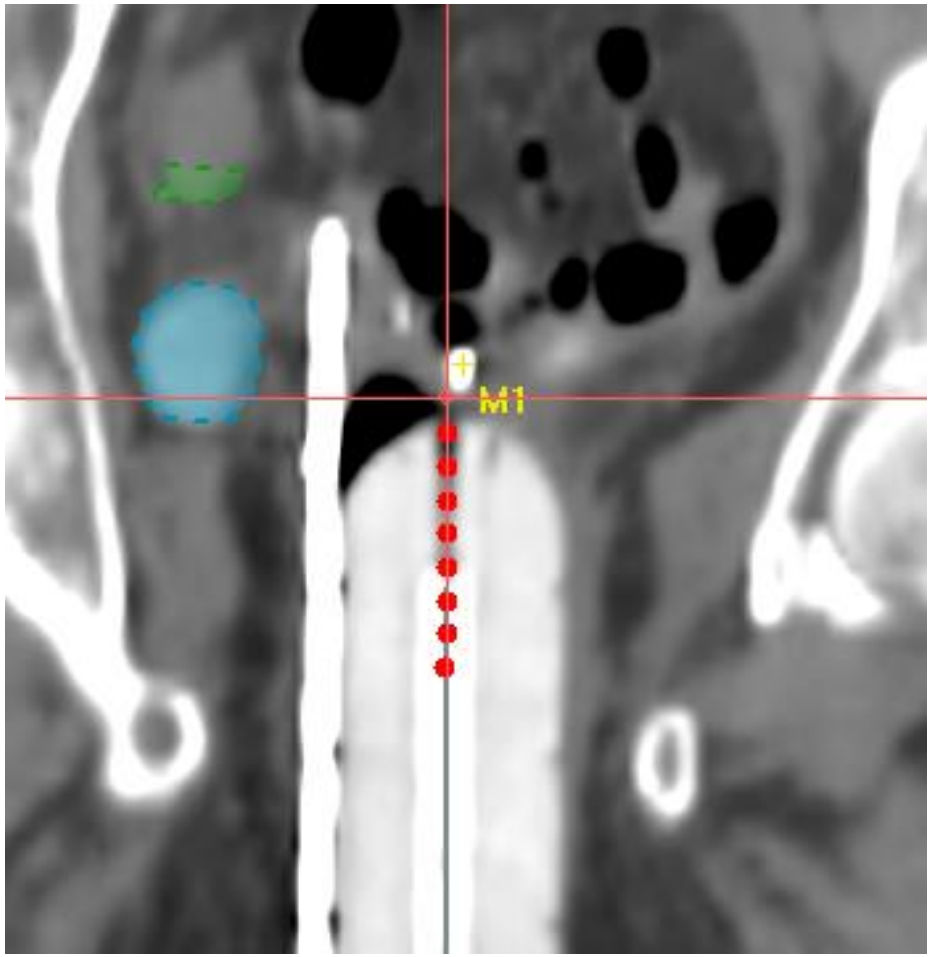
Example 2: Vaginal Cylinder +Needles





Vaginal Cylinder +Needles

IC – Normalized

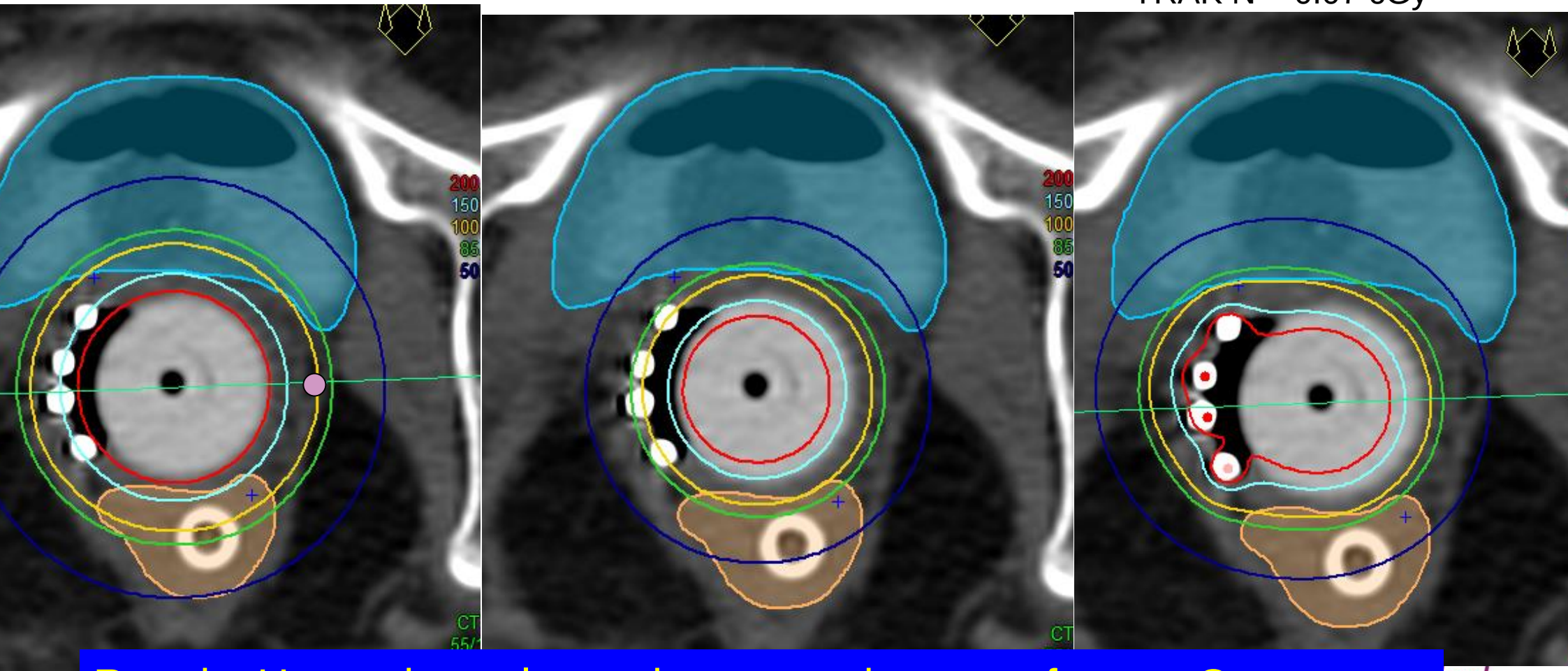
Rectum = 95 Gy
Bladder = 103 Gy
M1 = 85 Gy
TRAK = 0.3 cGy

IC Optimized

Rectum = 74 Gy
Bladder = 81 Gy
M1 = 75 Gy
TRAK = 0.21 cGy

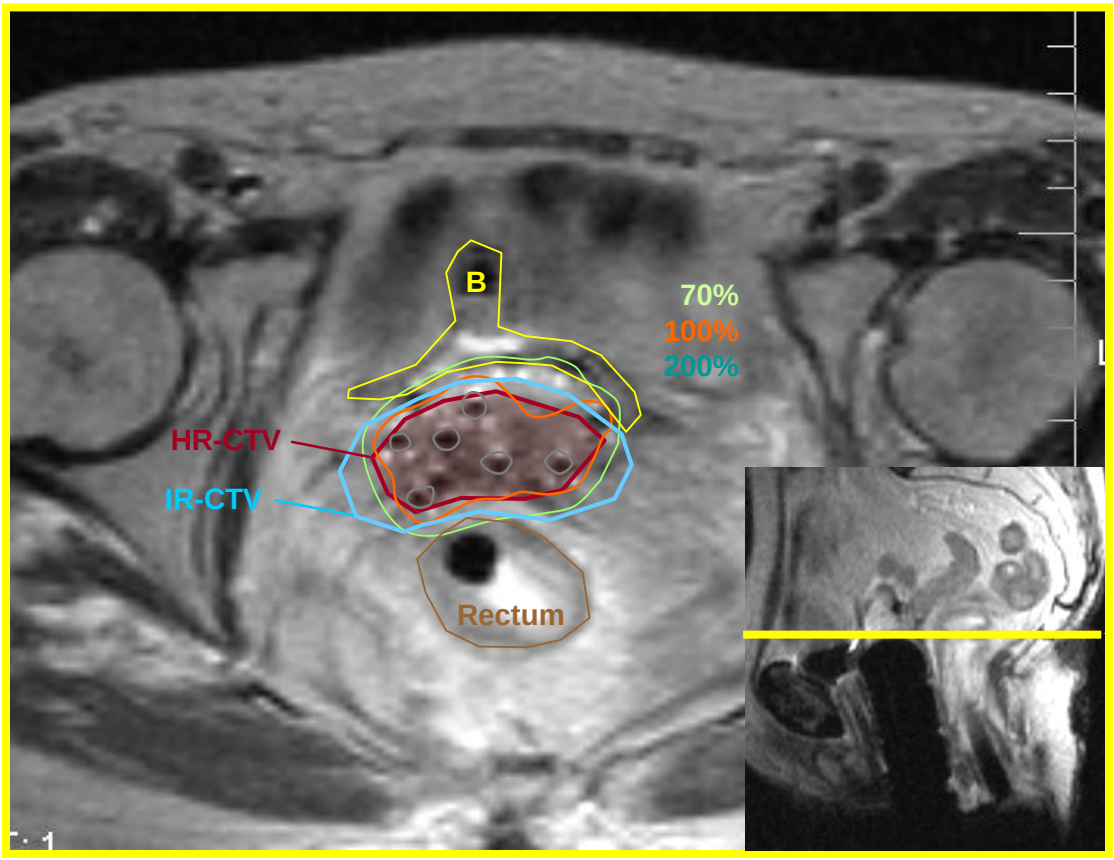
IC + IS

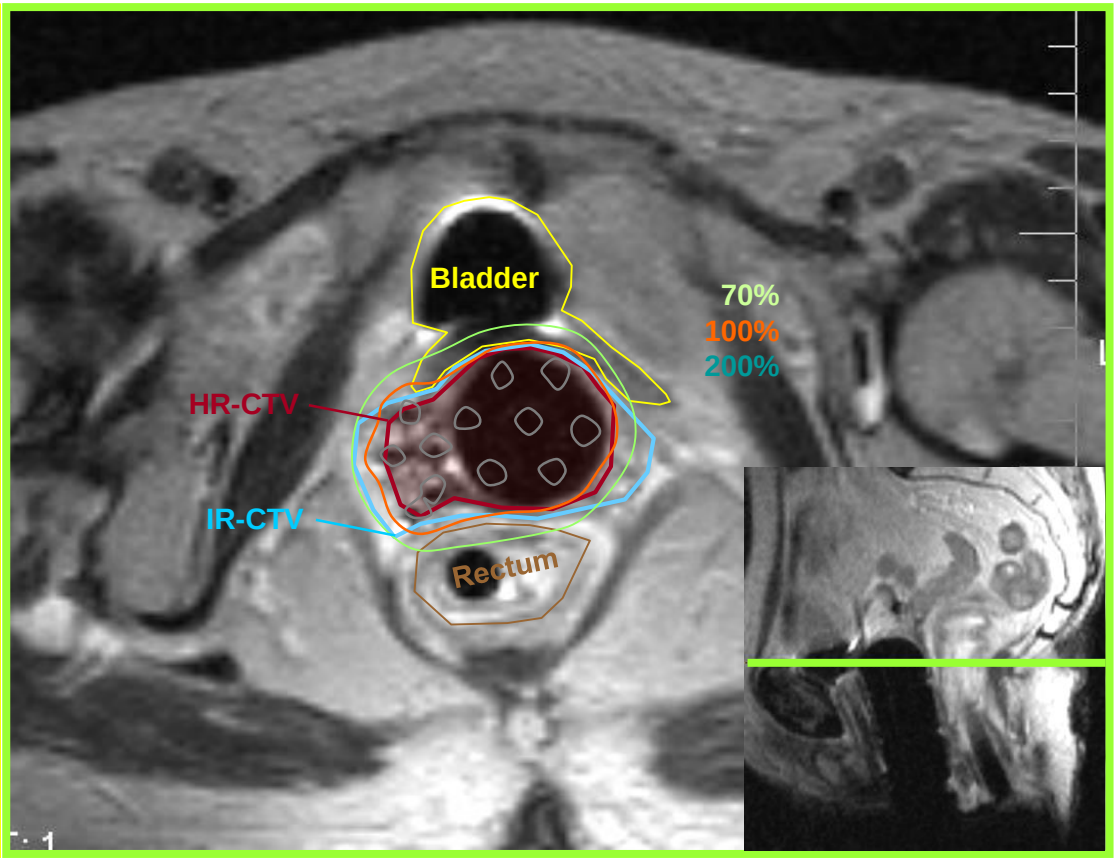
Rectum = 72 Gy
Bladder = 84 Gy
M1 = 88 Gy
Total TRAK = 0.27 cGy
TRAK N = 0.07 cGy



Restrict Hyper dose sleeve, but not at the cost of target Coverage

Example 3: Vaginal Cylinder+ needles





☐ **Intracavitary** ☒ **Interstitial**

Slide Courtesy: Daniel Berger

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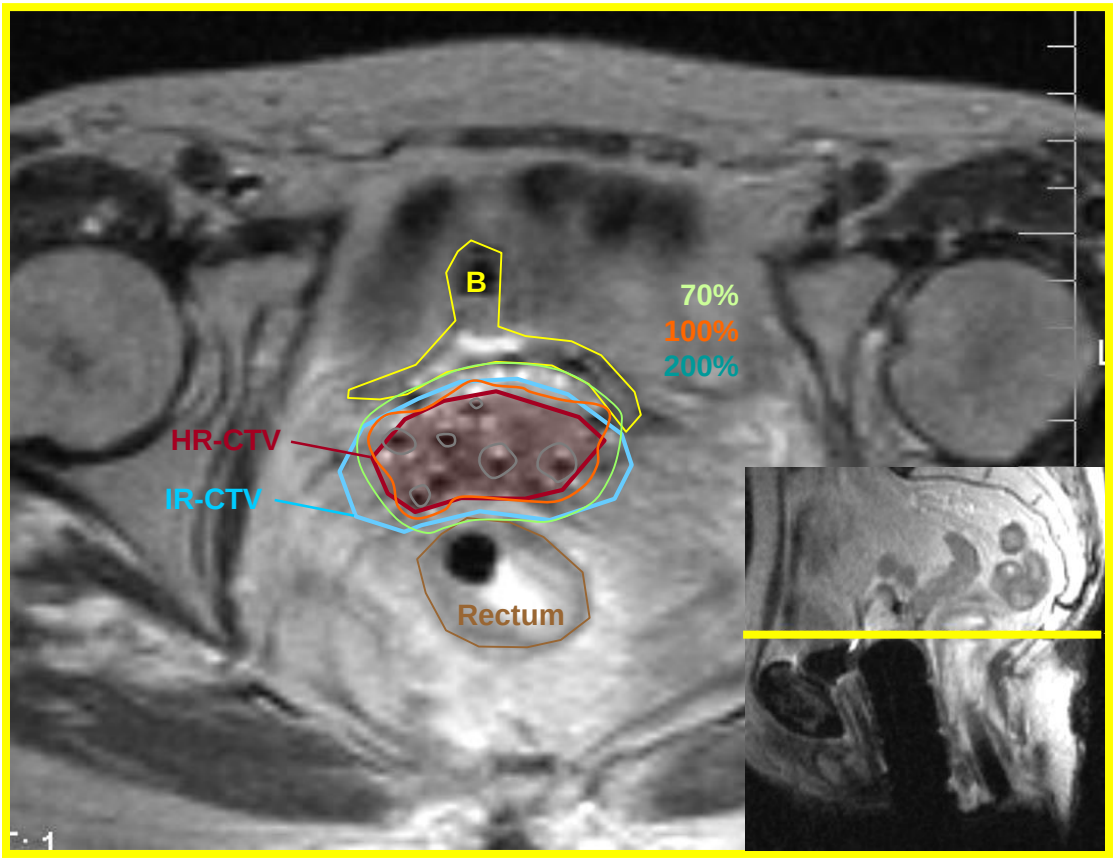

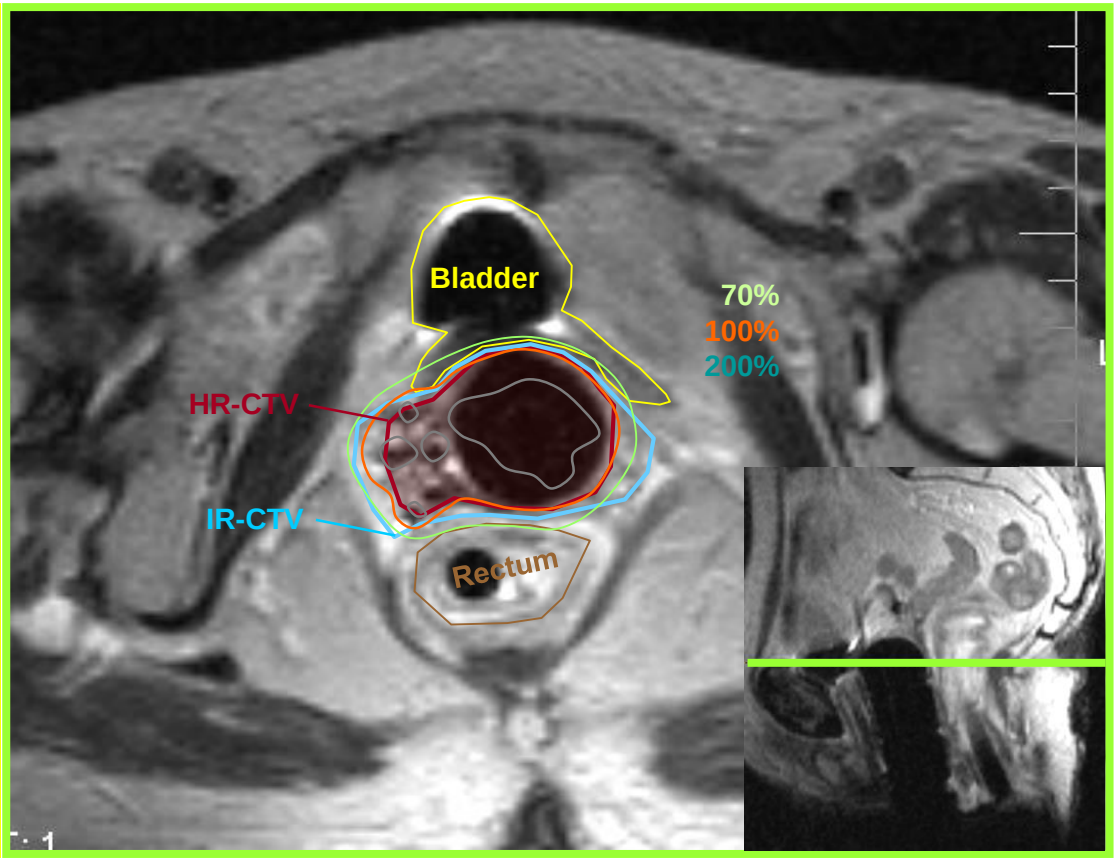

HR-CTV D90 = 88 $Gy_{\alpha\beta10}$

IR-CTV D90 = 70 $Gy_{\alpha\beta10}$

Bladder D_{2cc} = 70 $Gy_{\alpha\beta3}$

Rectum D_{2cc} = 67 $Gy_{\alpha\beta3}$

Sigmoid D_{2cc} = 55 $Gy_{\alpha\beta3}$

☒ **Intracavitary** ☒ **Interstitial**

Slide Courtesy: Daniel Berger

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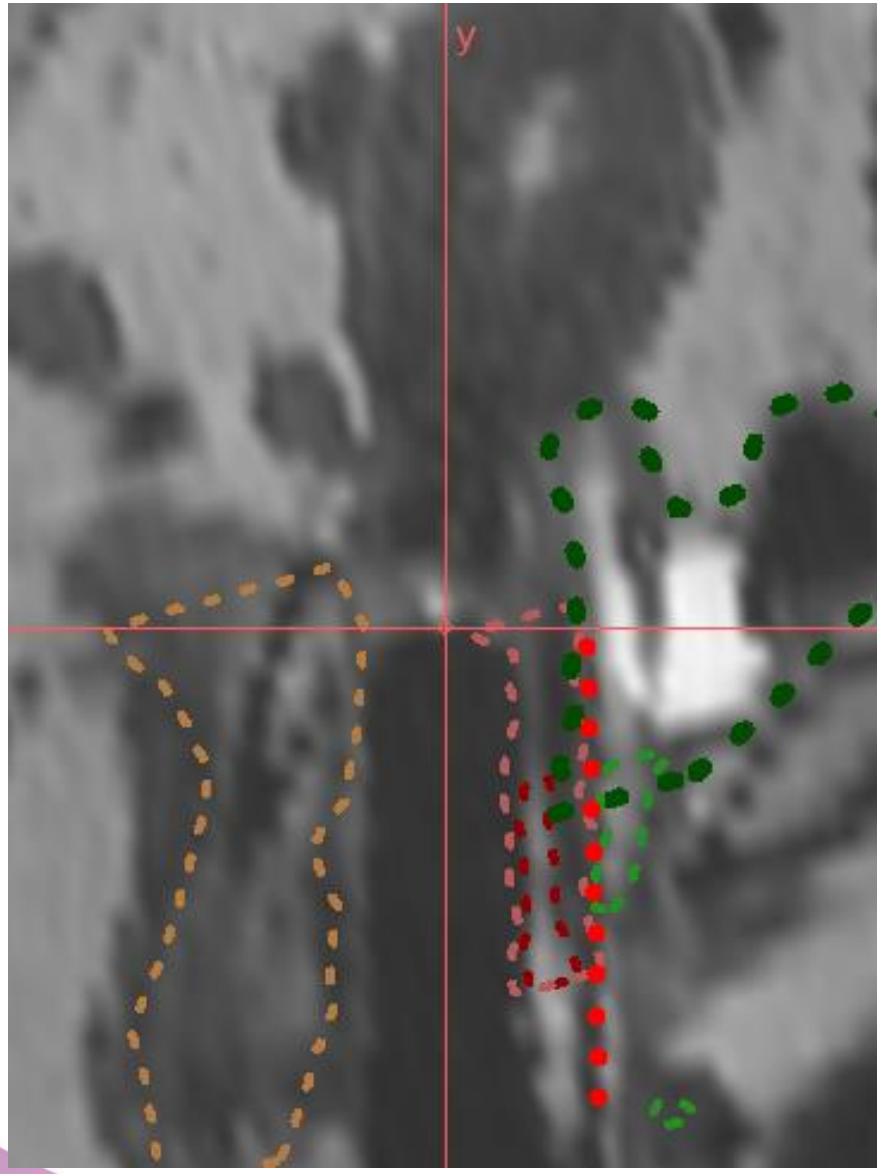
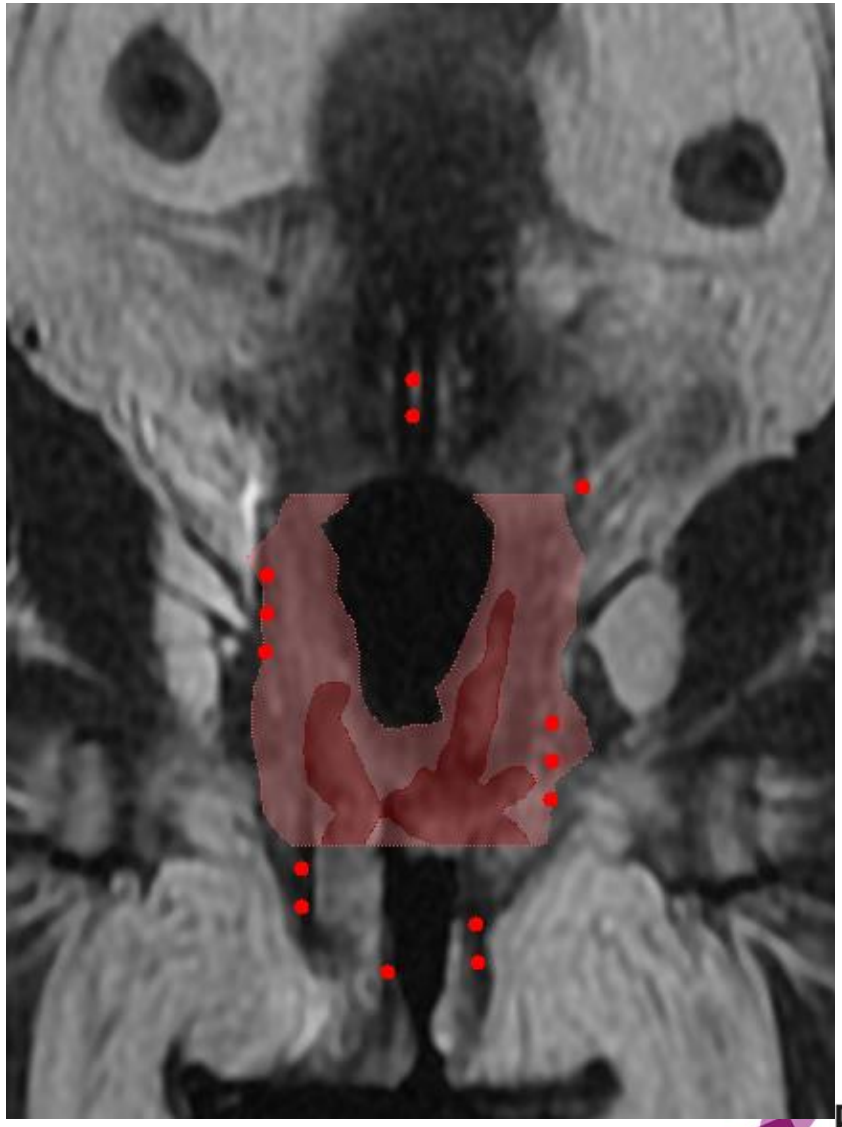
Example 4: Vaginal Cylinder + Needles +Tandem





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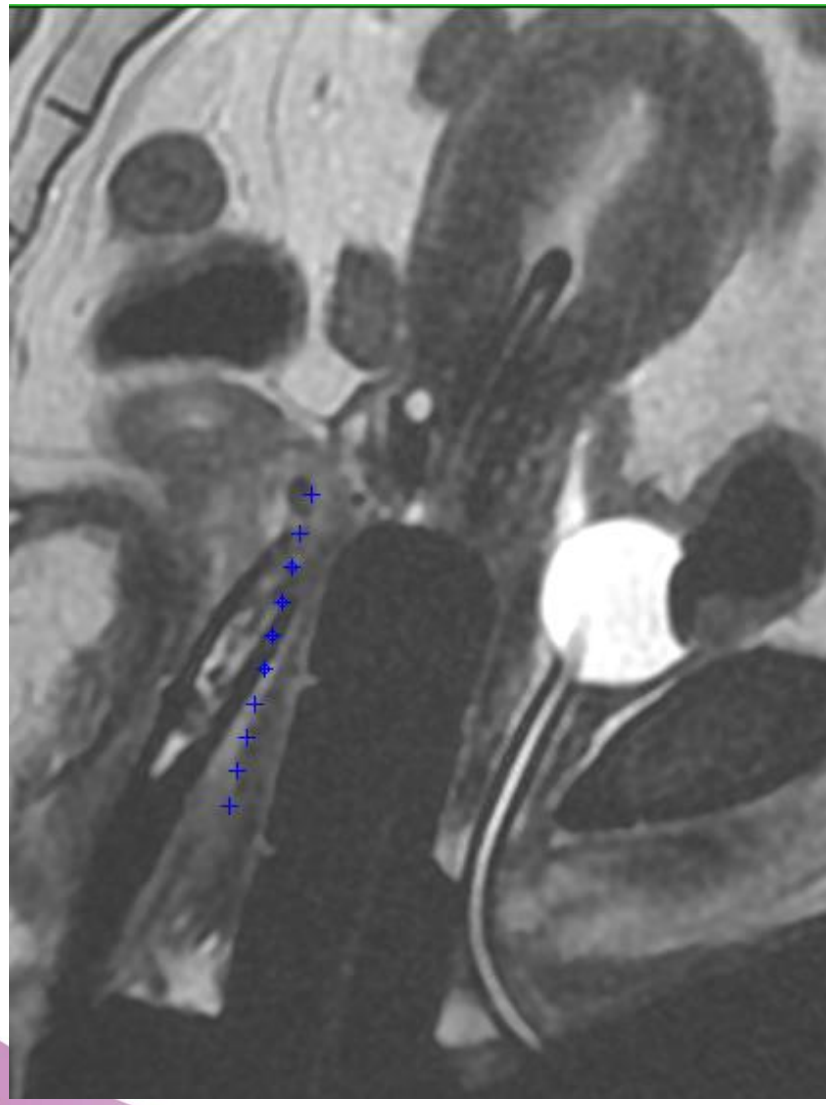
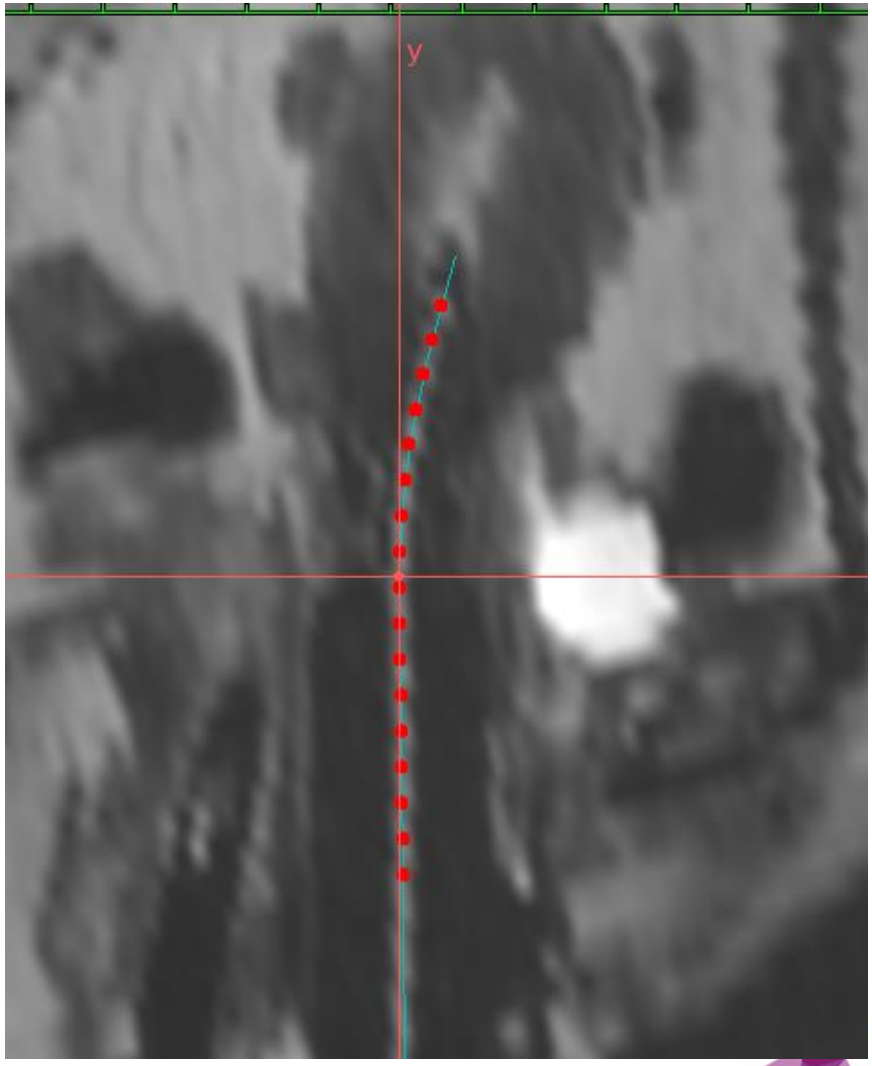
Example 4: Vaginal Cylinder + Needles +Tandem

Dose Points from applicator Surface



Source activation: based on HR CTV / clinical examination



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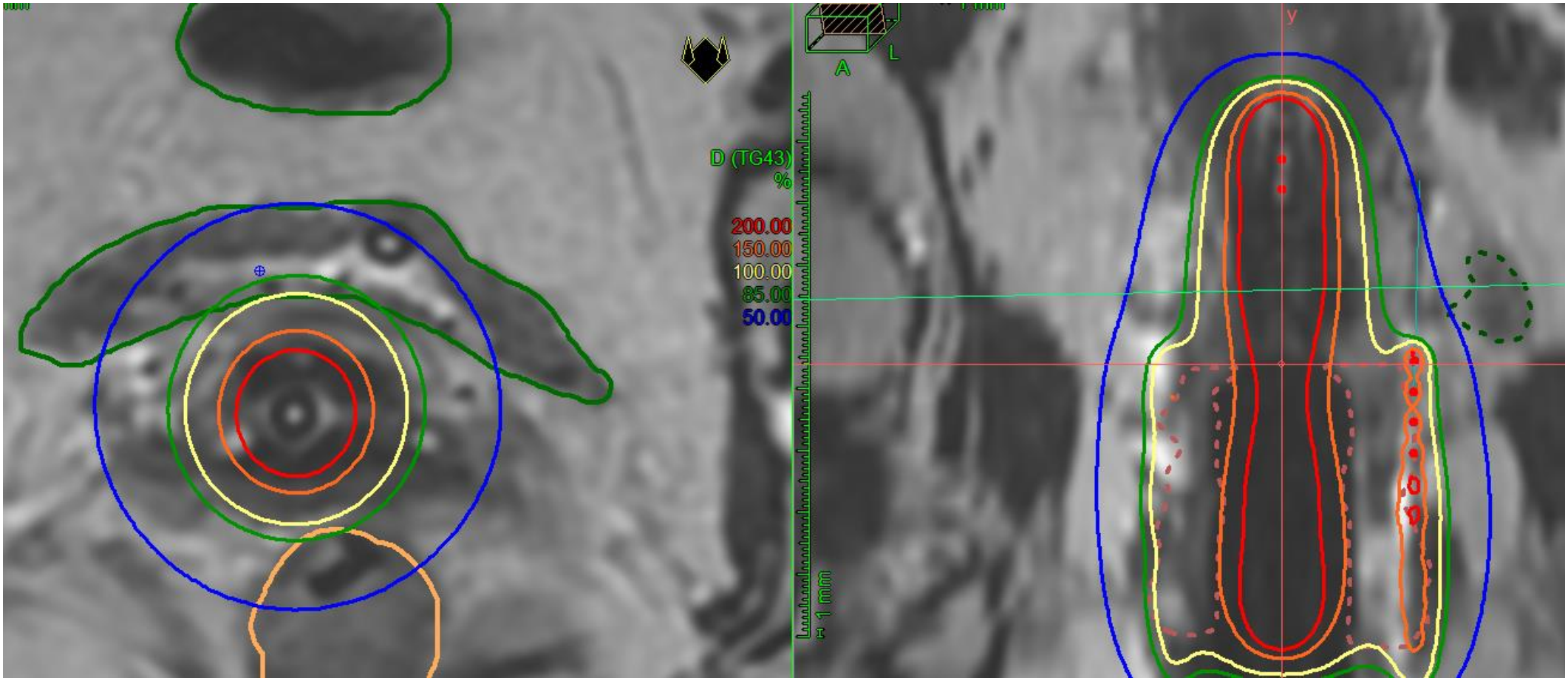
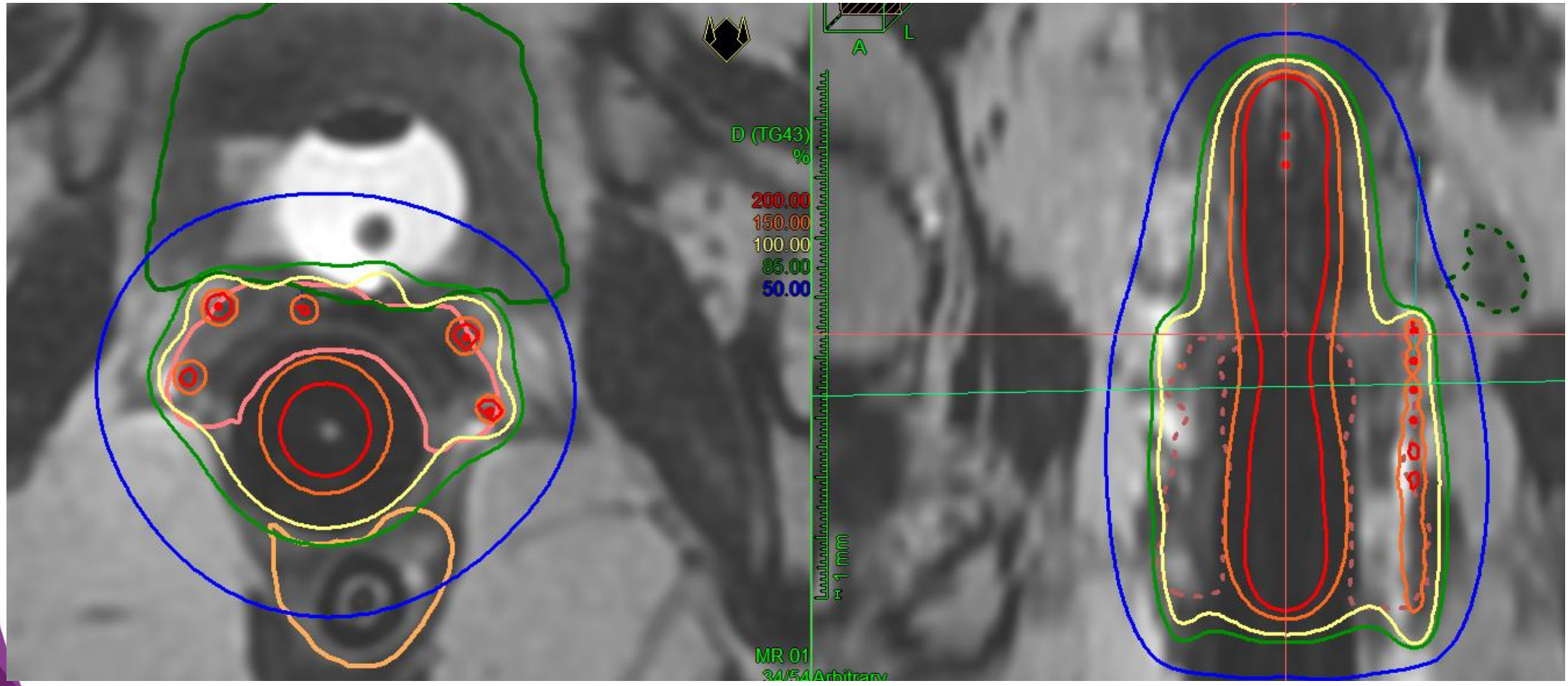
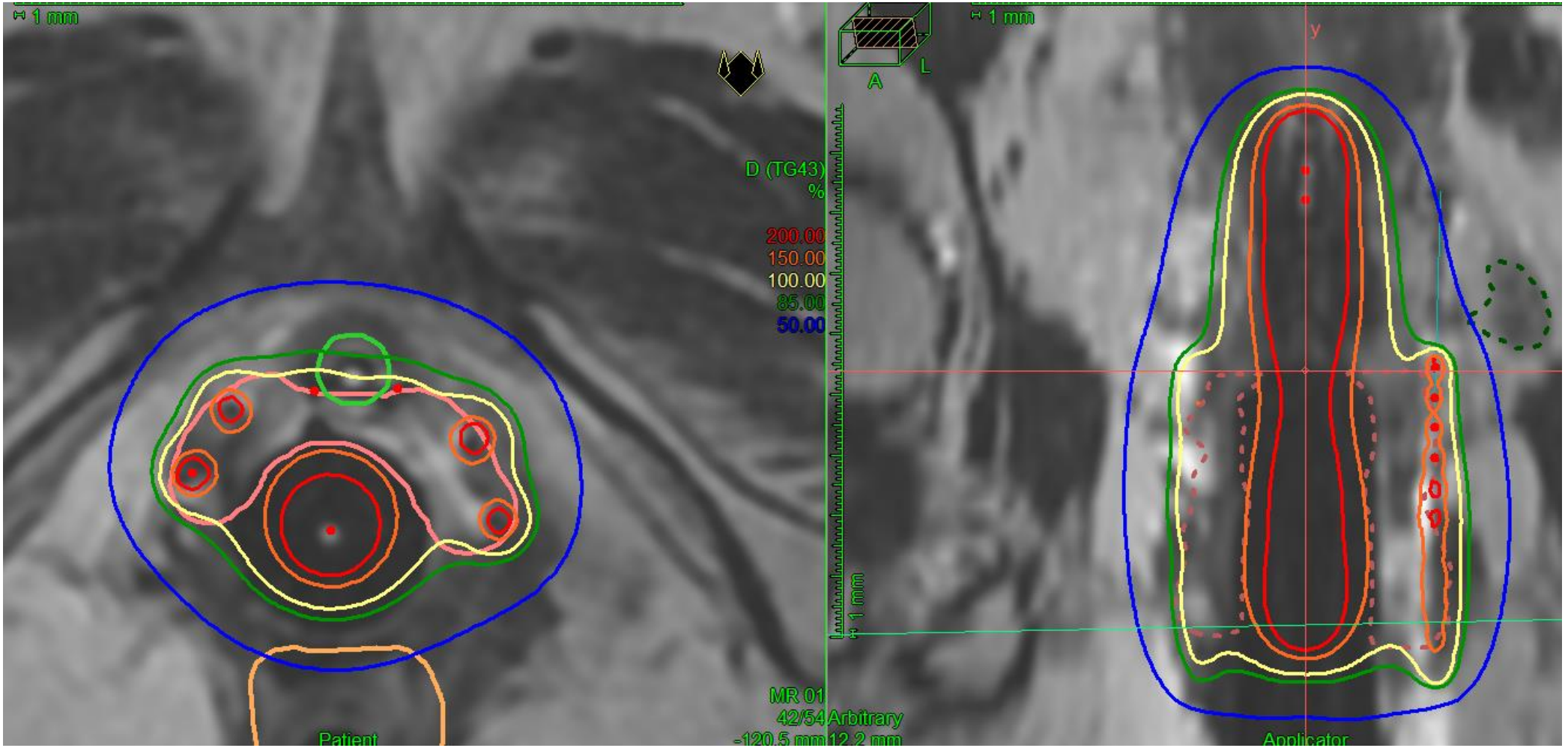
Example 4: Vaginal Cylinder + Needles +Tandem Intracavitary – Uterus level



Example 4: Vaginal Cylinder + Needles +Tandem Interstitial – Upper vagina



Example 4: Vaginal Cylinder + Needles +Tandem Interstitial – Lower vagina



Rectum D2cc = 75 Gy
Bladder D2cc = 88 Gy
Urethra D2cc = 69 Gy
D90 HRCTV = 88 Gy

Total TRAK = 0.4 Gy
TRAK C = 0.28 Gy
TRAK N = 0.12 Gy

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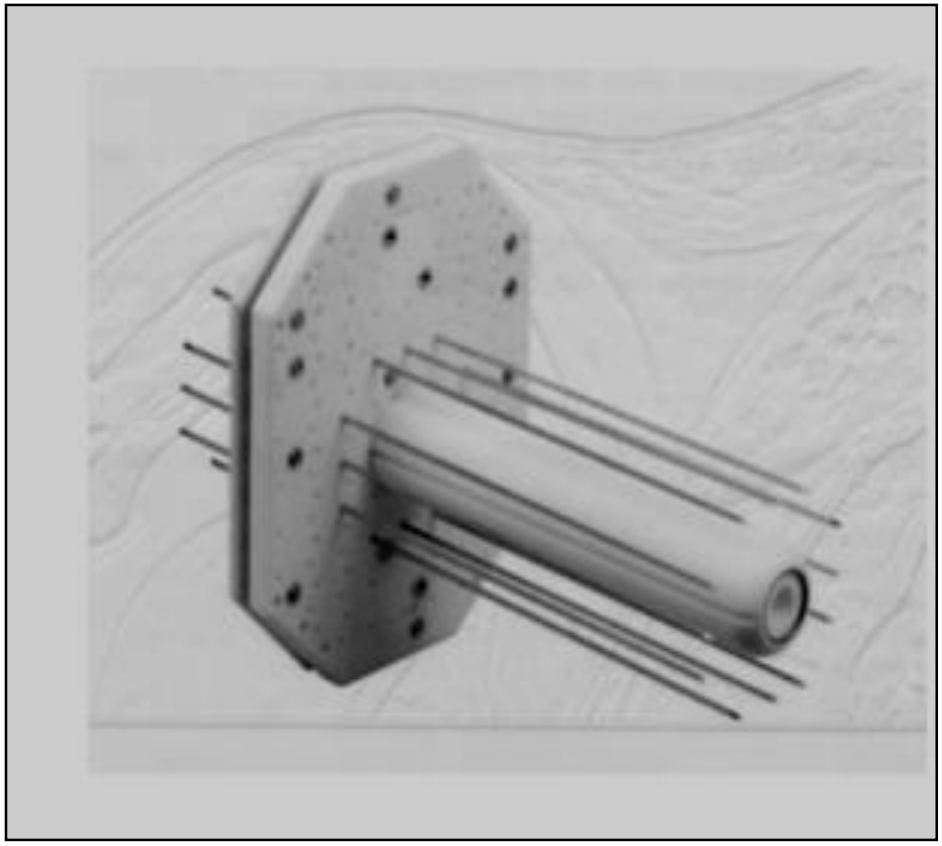
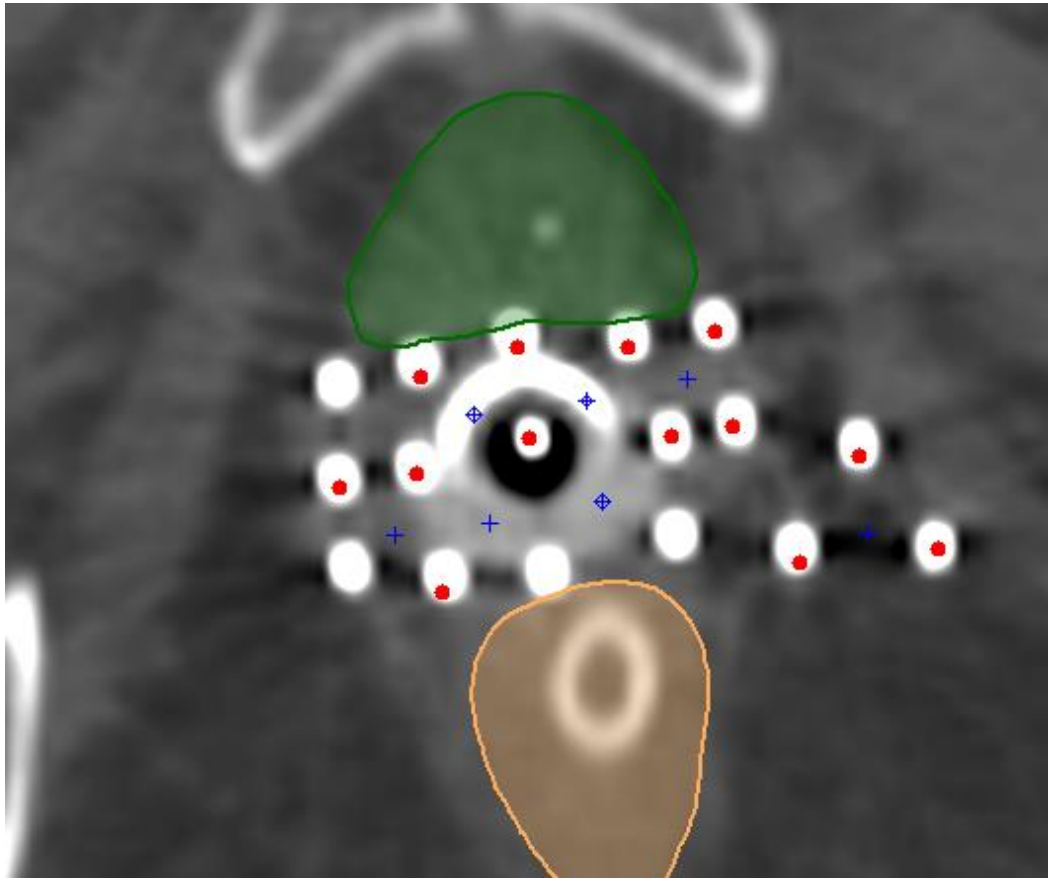
Example 5 : MUPIT

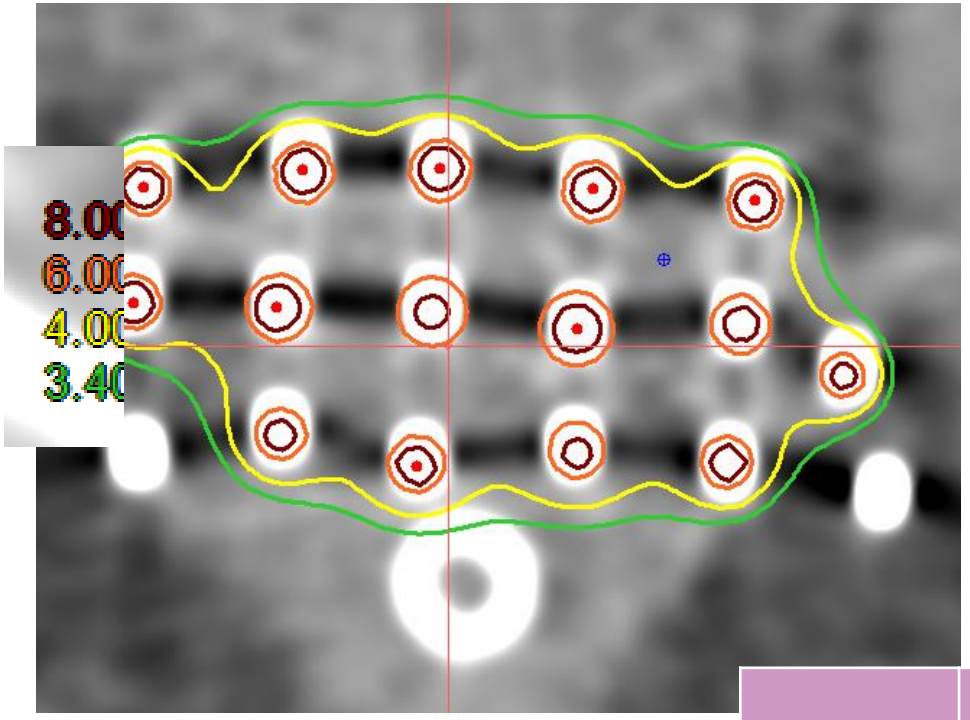


Picture: From Google

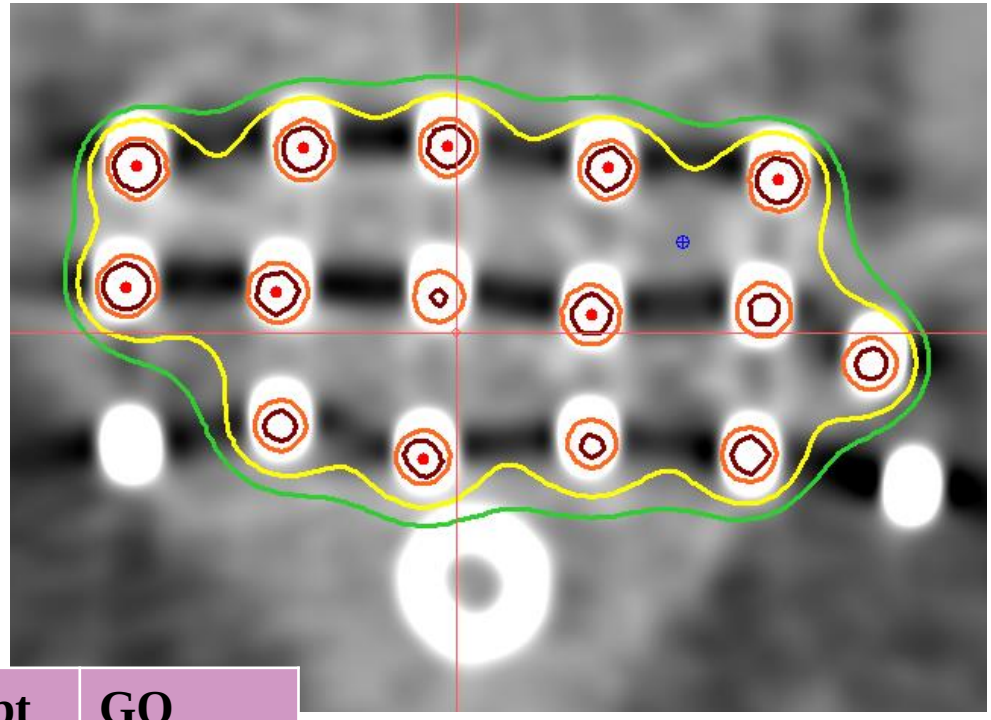


MUPIT

No optimization – Normalized



Geometrically optimized



	No Opt	GO
200%	4.3	4.0
150%	**12**	**9.0**
100%	45	44.7
85%	57.4	57.7
TRAK	0.17	0.17
DHI	**0.73**	**0.8**

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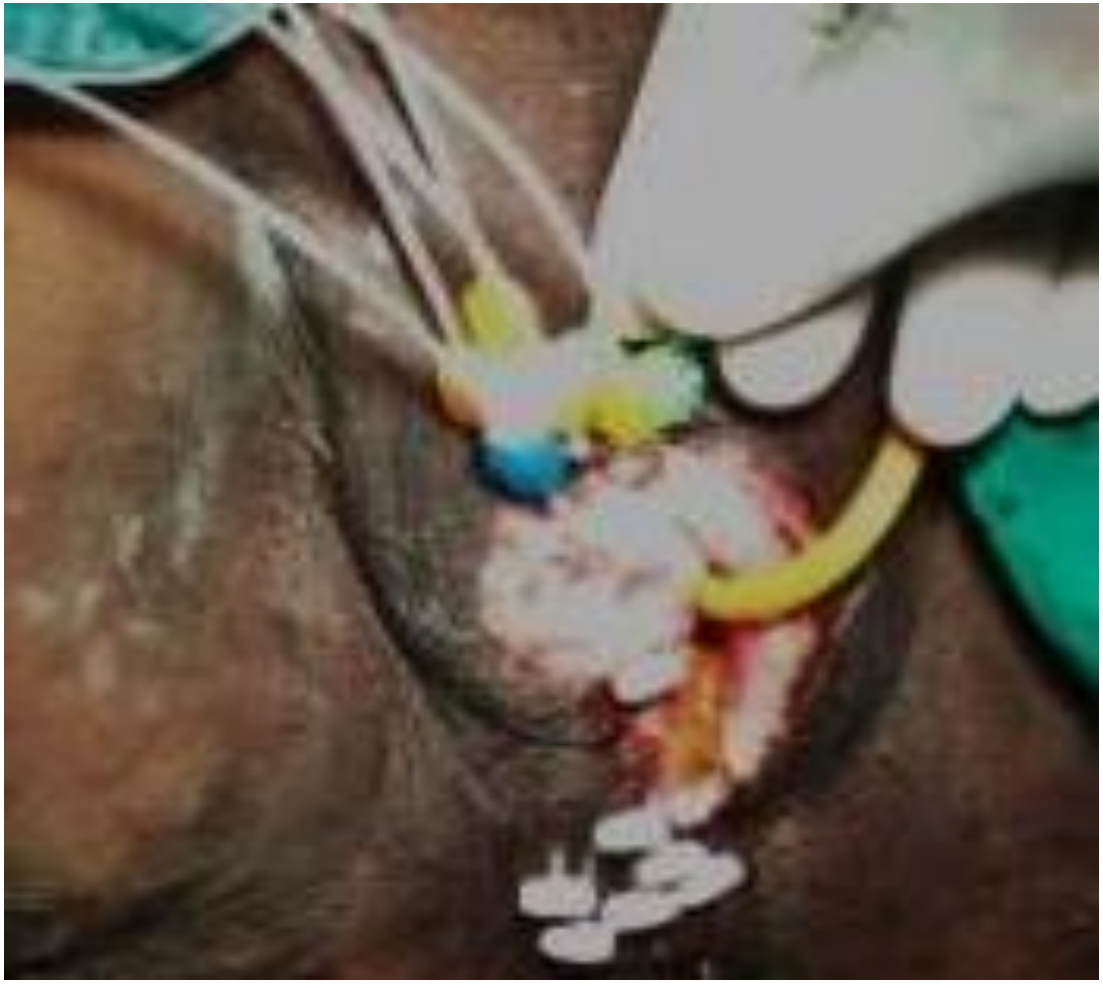
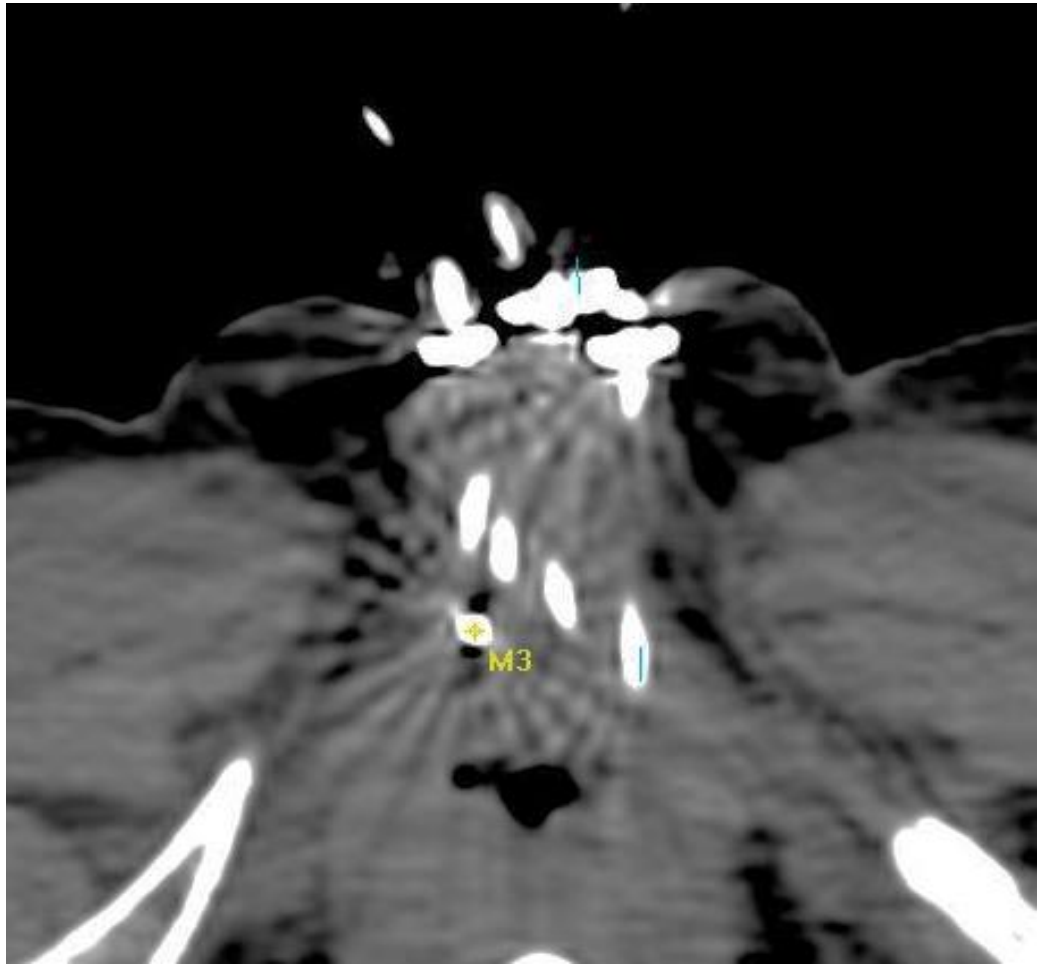
Example 6: Vulval Implant





- Crowded catheters.
- Close to the skin (Skin reactions – if not reconstructed correctly)
- Identification of planes using color coded plastic beads,
- Marker as surrogates for tumor margin

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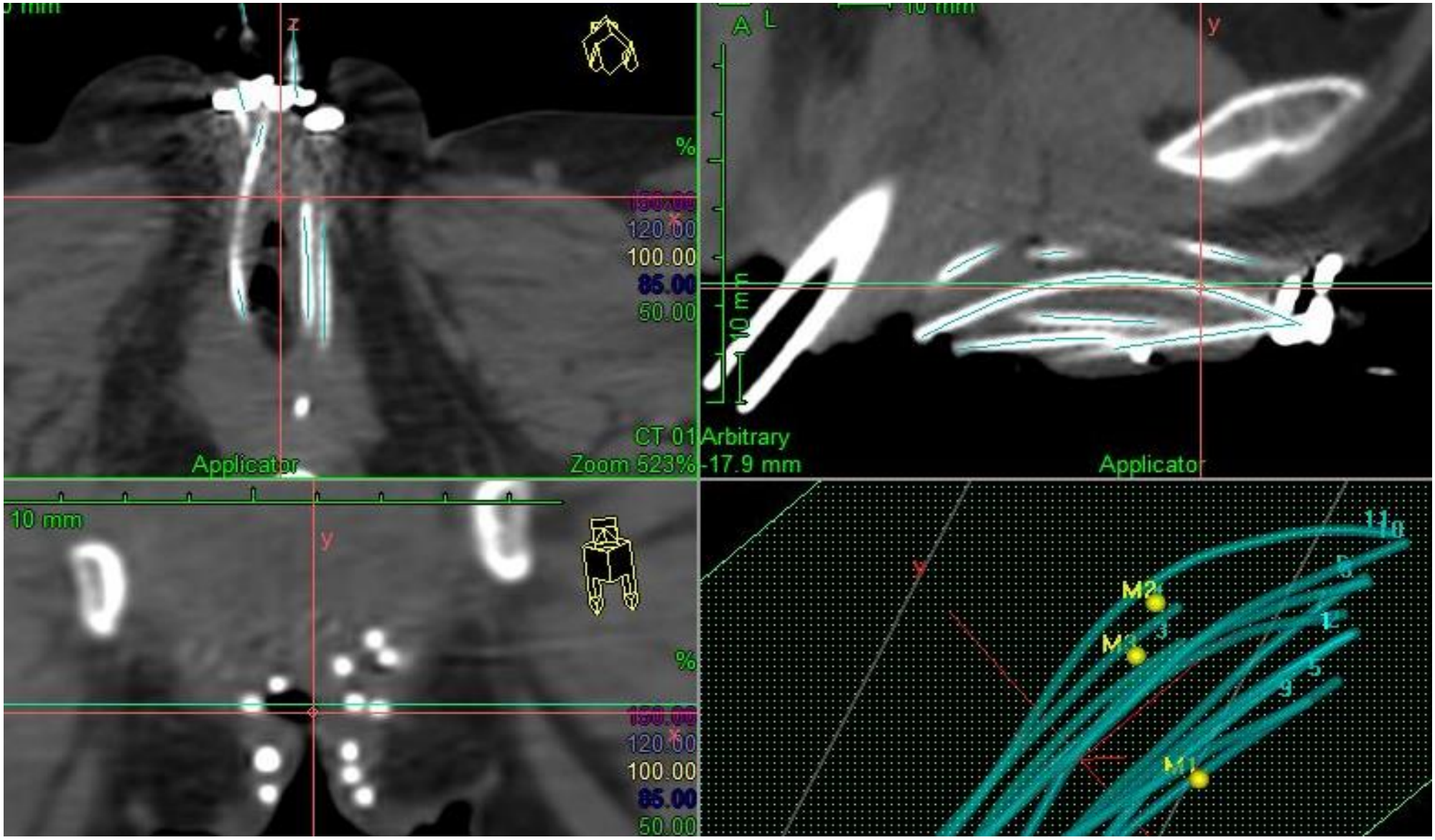
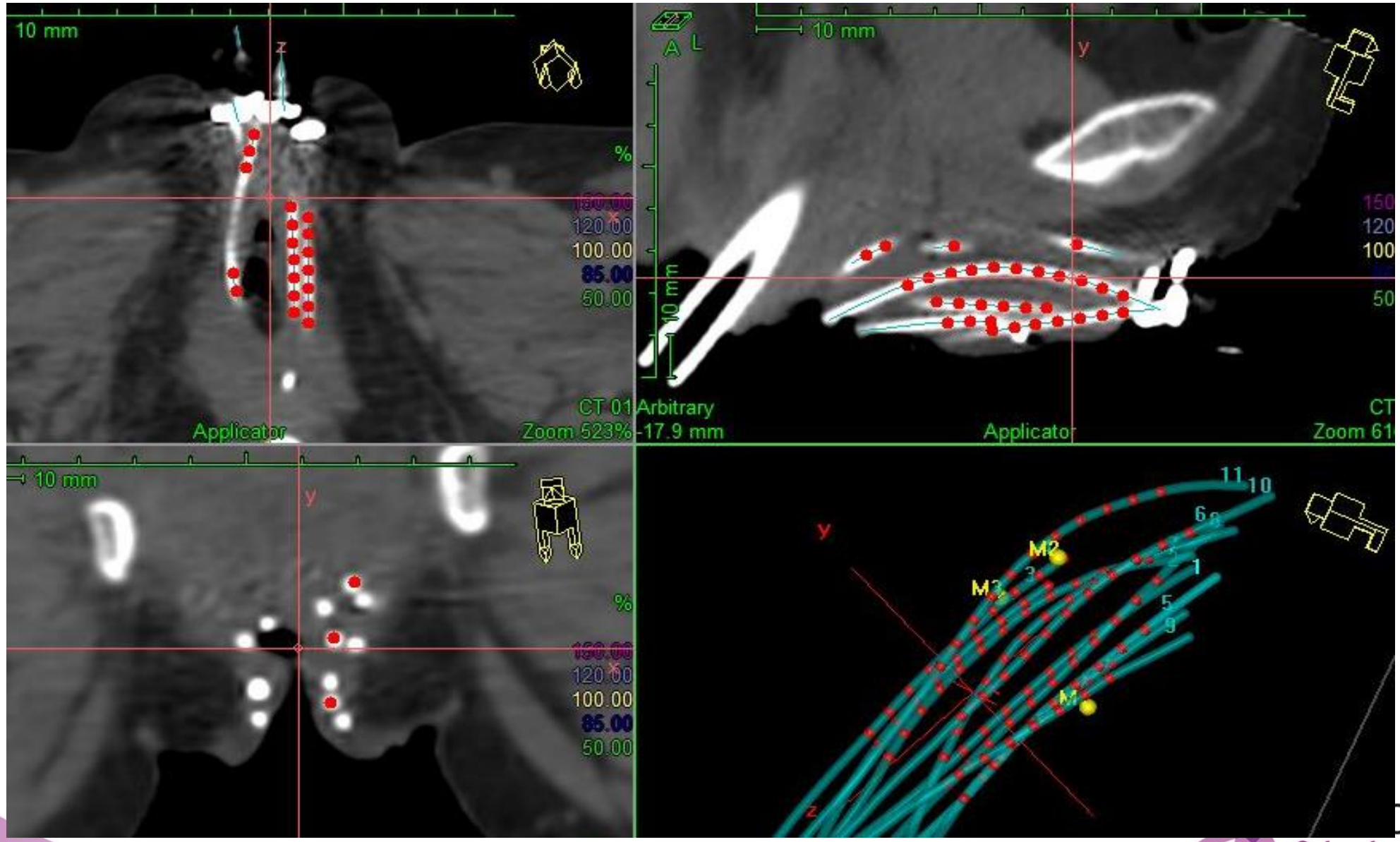
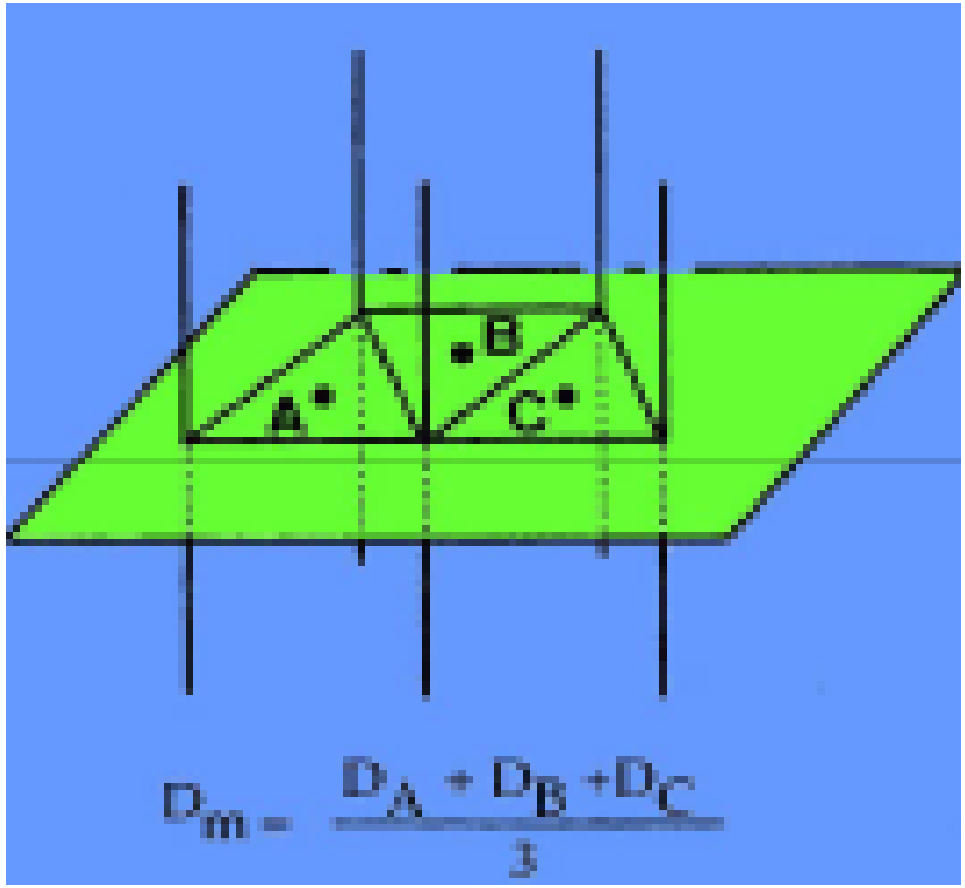
Vulval Implant Reconstruction

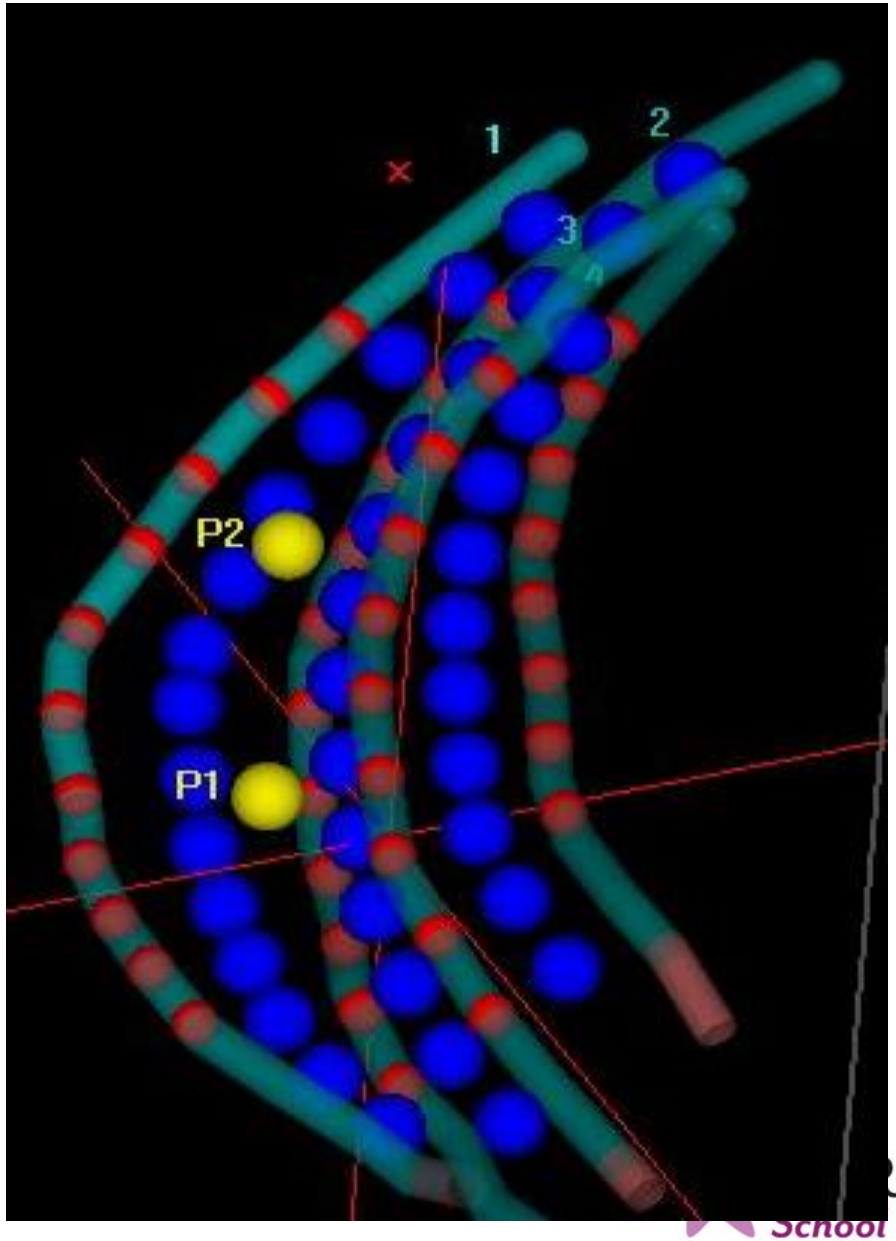


Vulval – Source activation



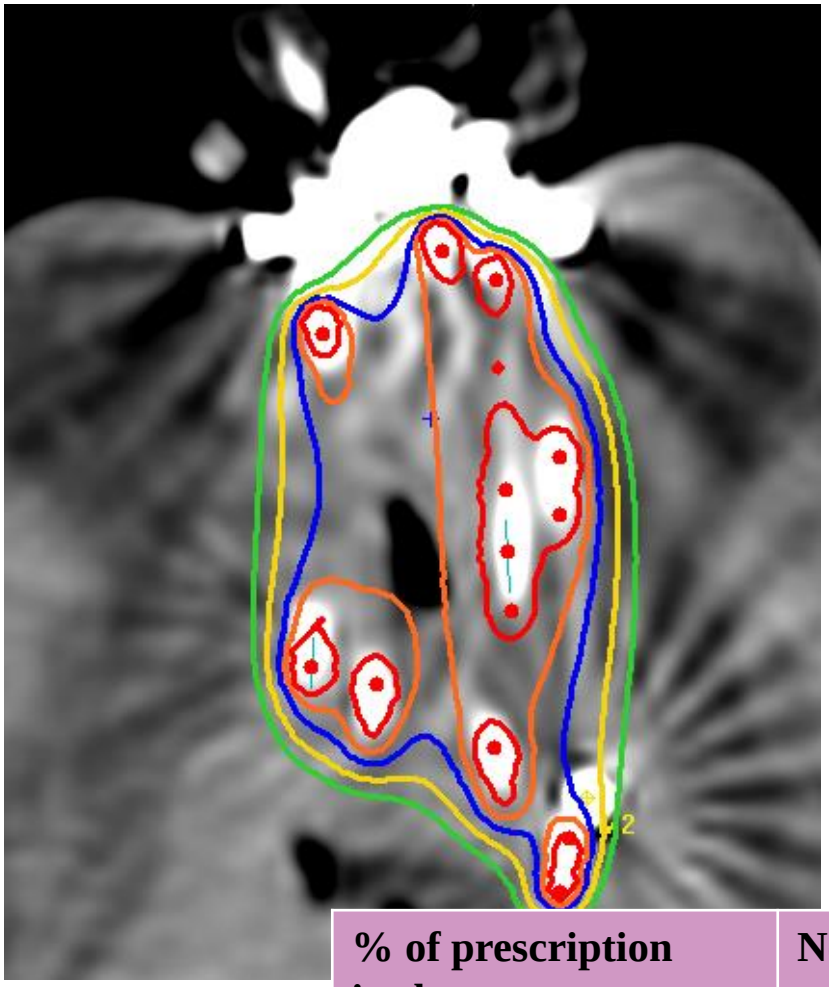
Vulval Implant - Dose / Normalization points



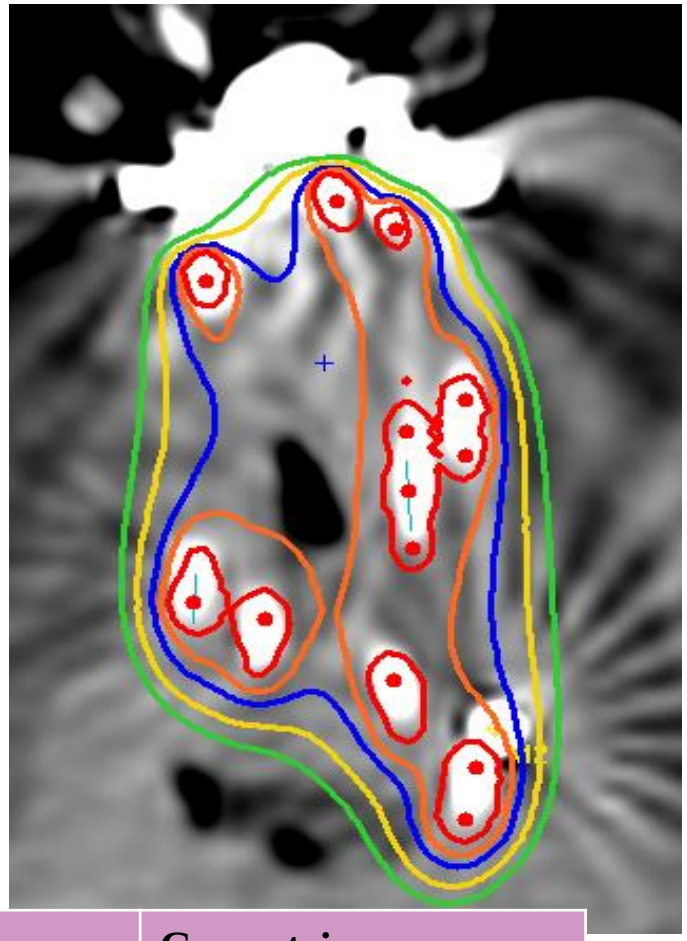


Optimization

No Optimization



Geometric optimization



% of prescription isodose	No optimization	Geometric Optimization
200	5	6
150	13	14
100	29	33
85	37	41
DHI	0.55	0.58

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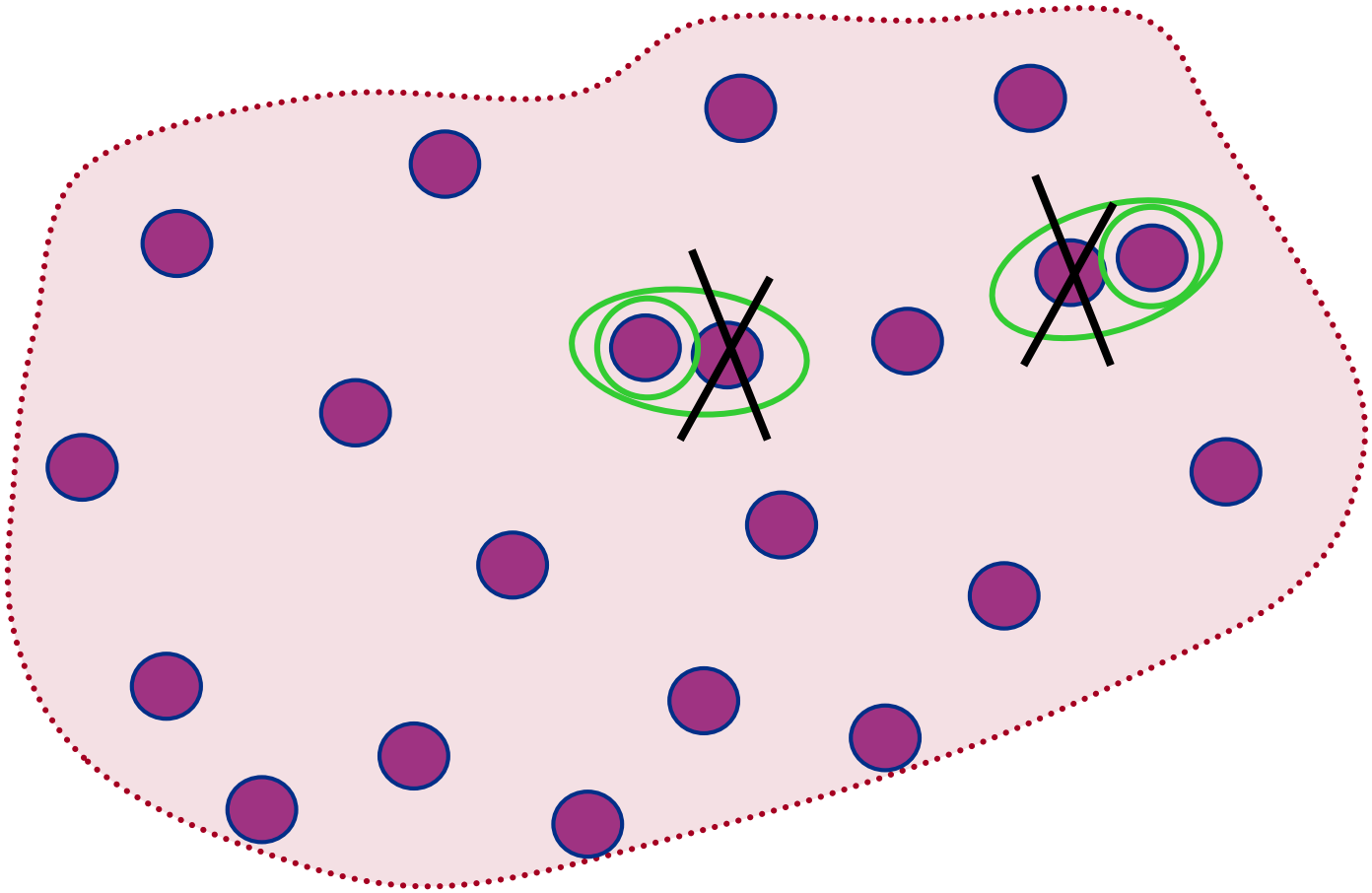
Target

Needels

200%



Slide Courtesy: Daniel Berger, Vienna

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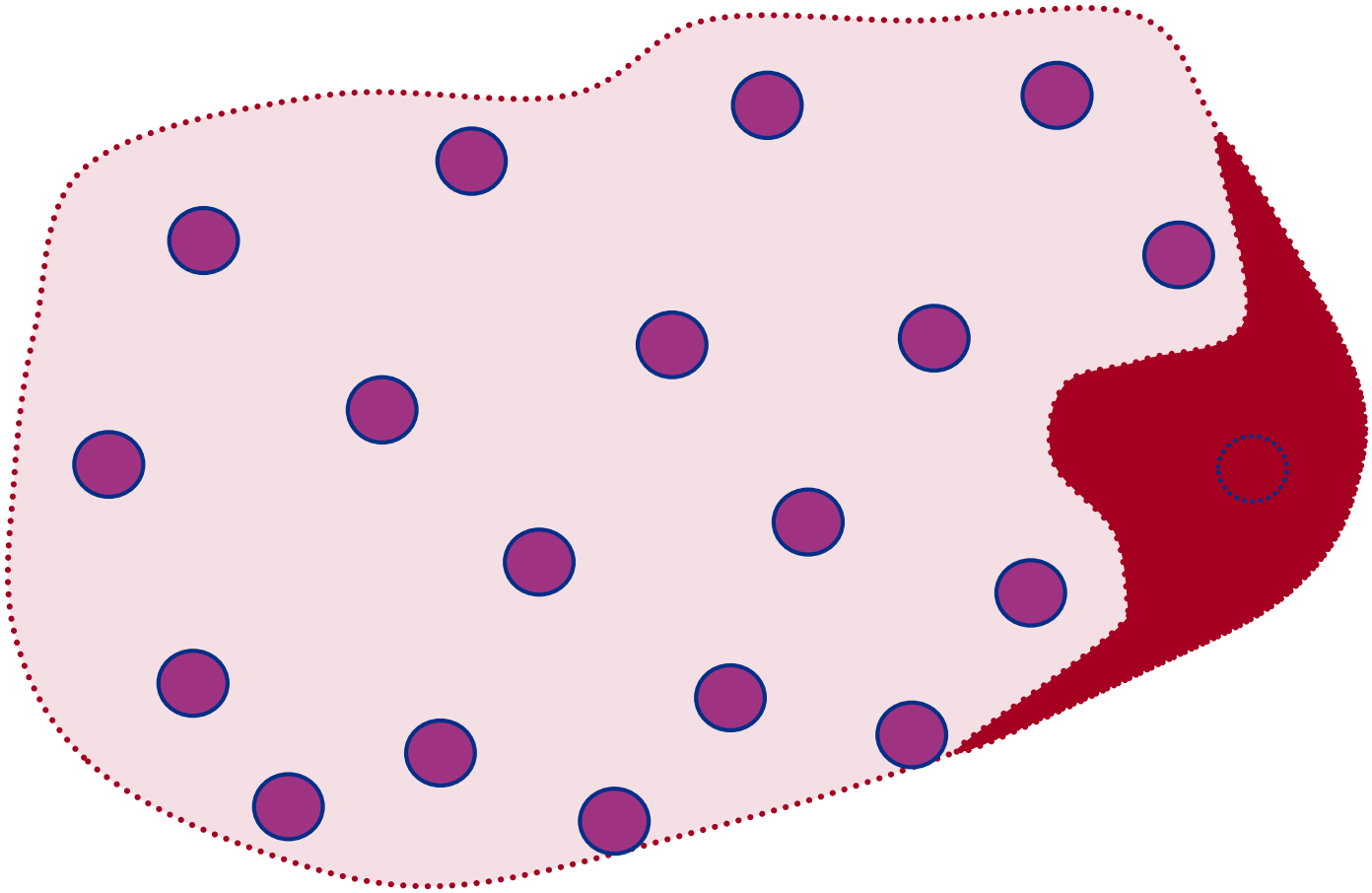
Target

Needels



Slide Courtesy: Daniel Berger, Vienna

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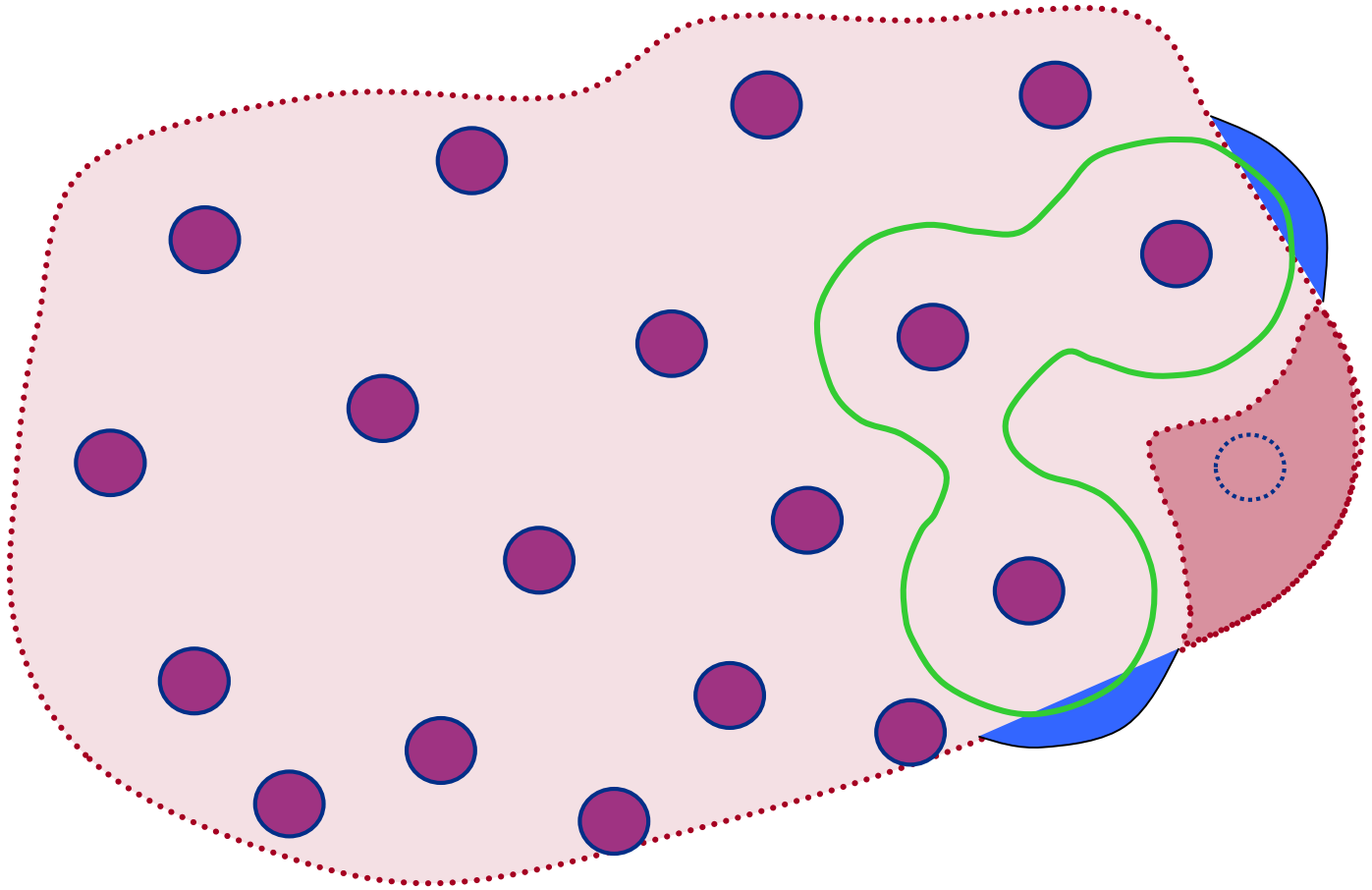
Target

Needels

200%



Slide Courtesy: Daniel Berger, Vienna

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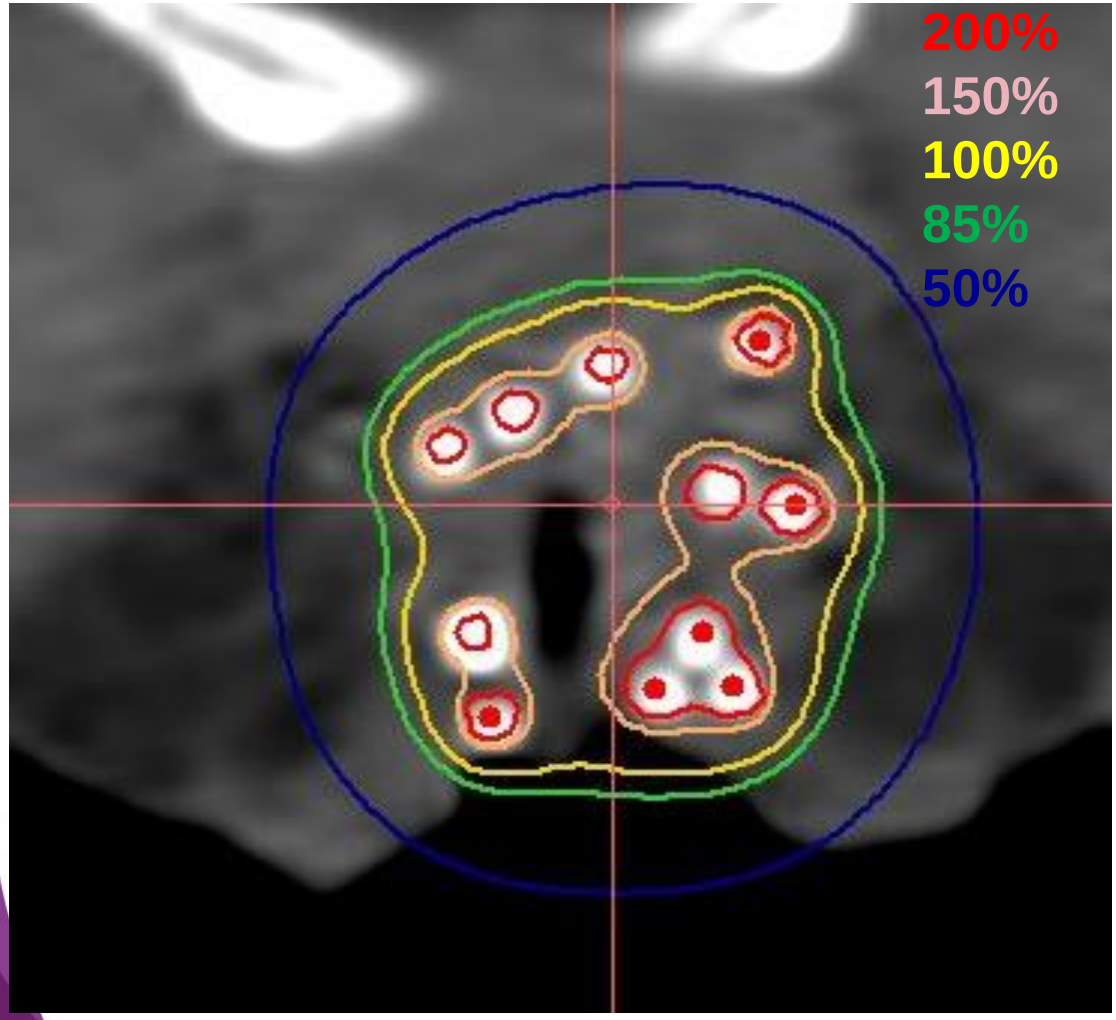
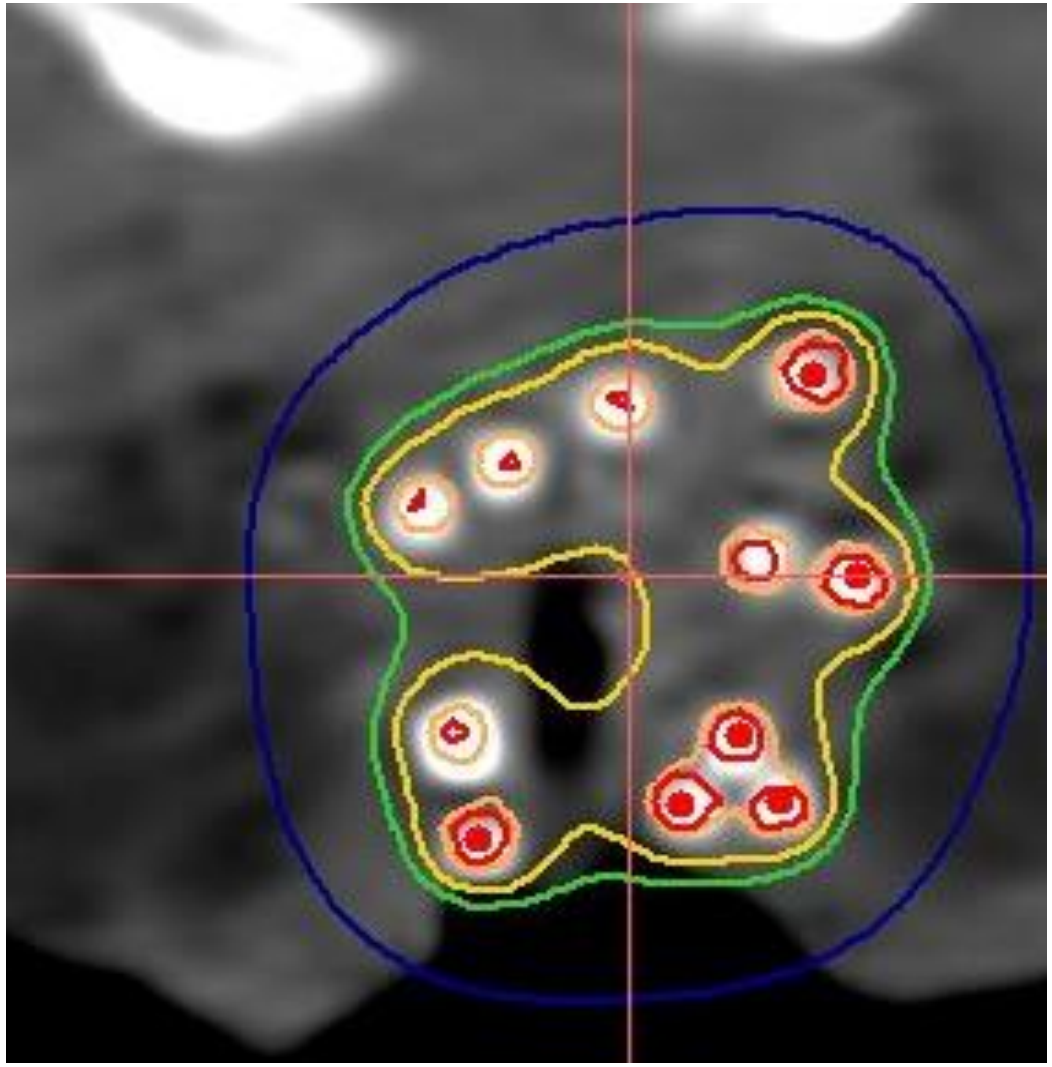
Summary : Vaginal and Vulval implants

	Cylinder	Cylinder + N	Cylinder+T+N	MUPIT	Free Hand Vulval Implant
Implant Type	IC	IC+IS		IS	
Reconstruction	Central Tandem, Needles (offset), numbering of needles is important.			Needles, same length, numbering important.	Plastic Catheters, Crowded, color code the catheters
Source activation	MRI - CTV is delineated, CT - Markers as surrogates / Clinical Examination				
Dose points	Catheter based points from the applicator surface			Basal points	
Optimization	Dose Point Optimization			Geometric Optimization	
Evaluation	Uniformity not an issue, Caution: Hyper dose sleeve should be within the cylinder, and just around the needles, not compromising the target coverage.			DHI > 0.75-0.8	
Tips				Template – Geometry not an issue	Free Hand, Geometry will be an issue. Caution.

Geometric Optimization





DHI =

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Combinations of images and use of image registration in Brachytherapy

presented by Daniel Berger

General Hospital of Vienna, City of Vienna,
Medical University of Vienna, Department of Radiotherapy

Courtesy N Nesvacil, K Tanderup, Ch Kirisits

Techniques for rigid registration in RadioTherapy

- **Identity (DICOM)**

  automatic registration based on DICOM coordinate system
  - PET-CT, PET-MRI
  - **BT:** multiplanar MRI
- **Mutual information**

  automatic registration (CT, MRI-CT)
  - in EBRT: bony anatomy, external contour
  - in **BT**: head: bony anatomy, pelvis: BT applicator (≠ bony anatomy)
  - delineated structures
- **Landmark-based**

  manual definition of landmarks for registration
  - external markers, implanted markers, clips
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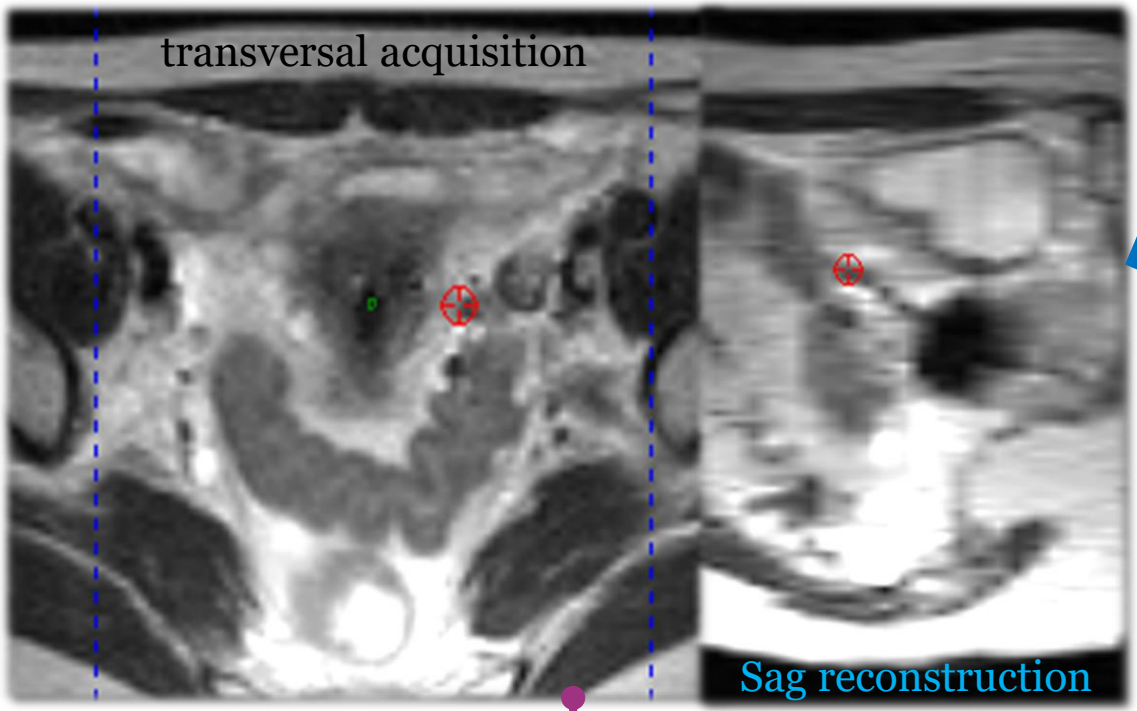
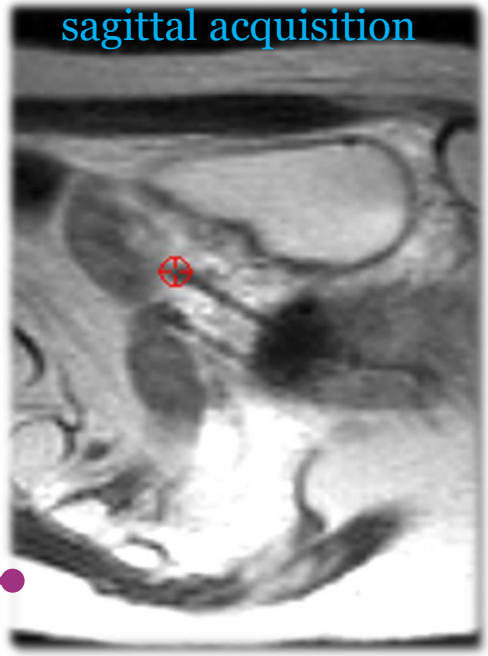
DICOM Identity-based registration of multiplanar MRI:
applicator reconstruction, needle depth verification



Mark/reconstruct needle tip in tr. MRI
verify with registered sag. MRI



DICOM

\+ Improved reconstruction precision for large MRI slice thickness available in TPS and/or DICOM viewers

▲ Uncertainty dominated by patient movement during acquisition (long scan times, anaesthesia)

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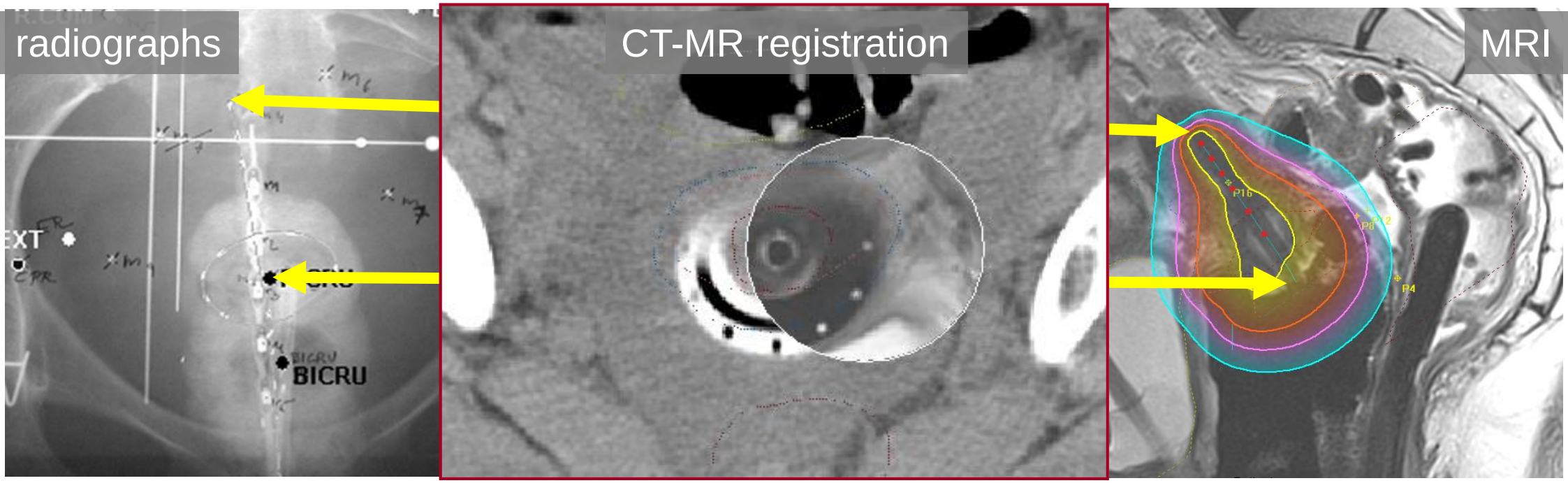
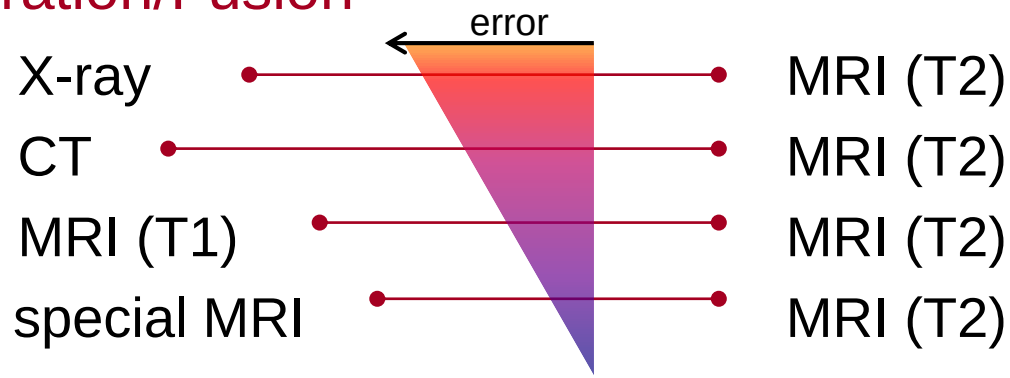
Minimized or No Registration Error ?

Registration/Fusion ERROR!



Registration/Fusion



If you register different images (CT-MRI) use “**applicator based” registration**

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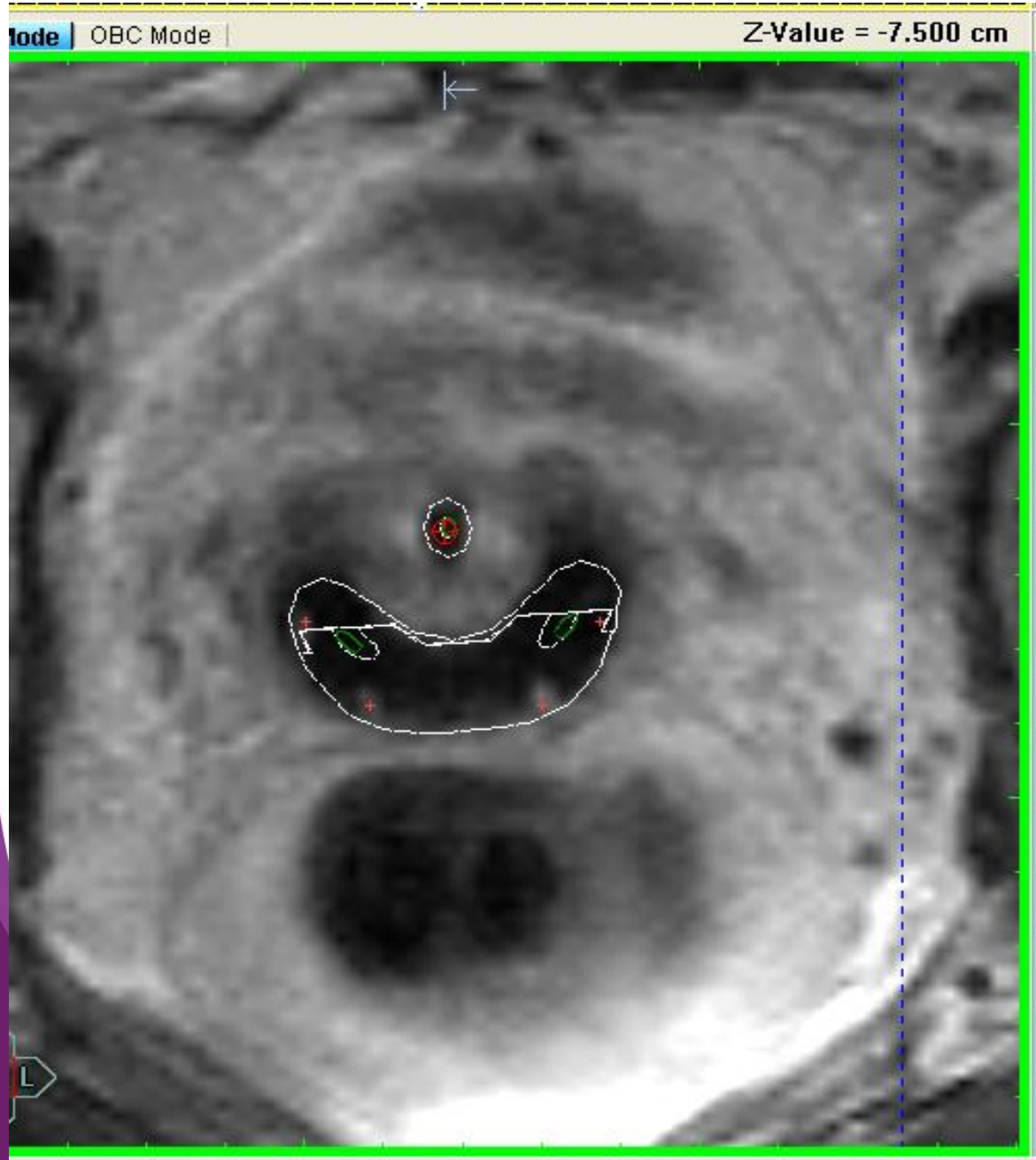
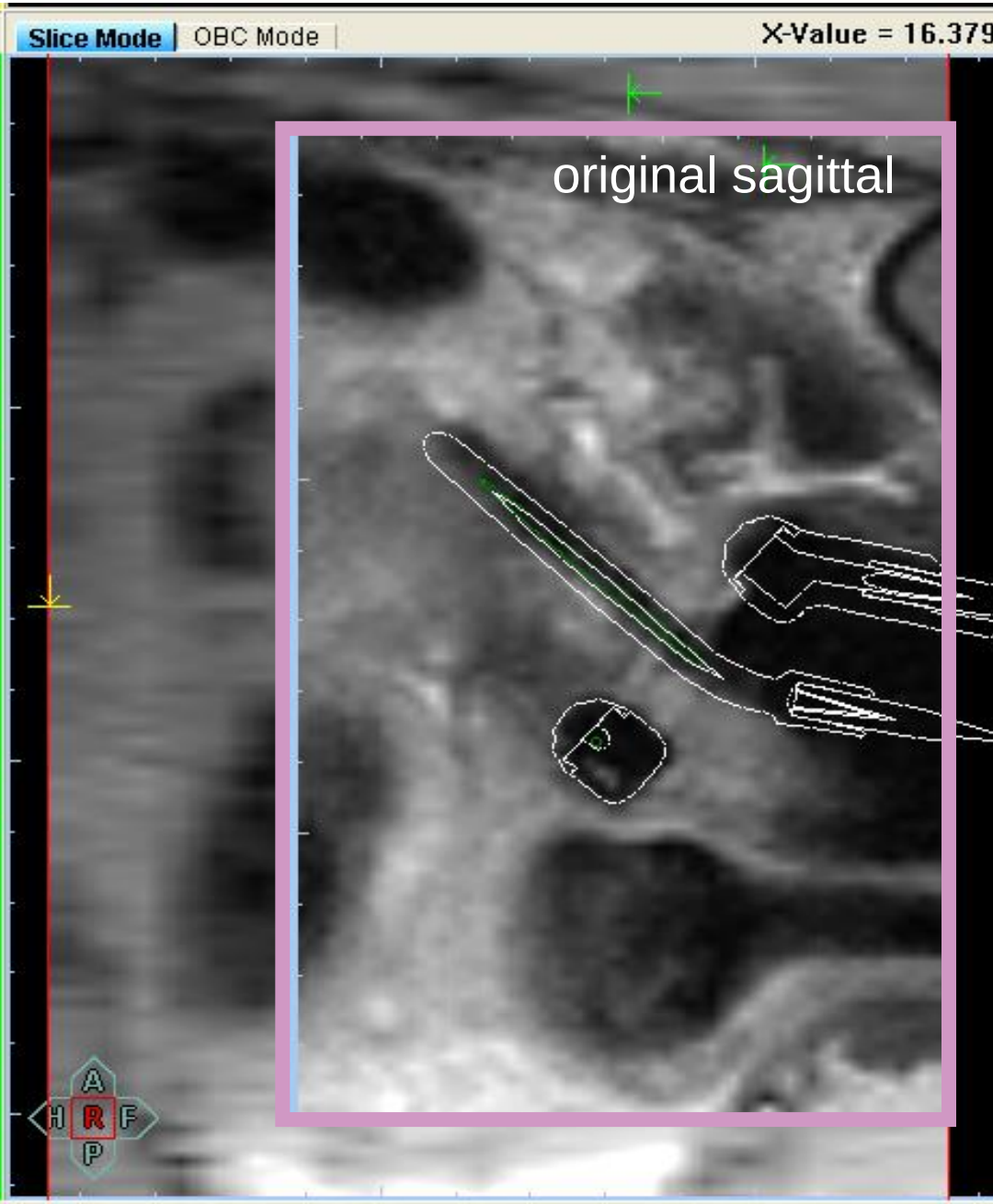
Image registration for applicator recon. between MRIs (using DICOM coordinates)





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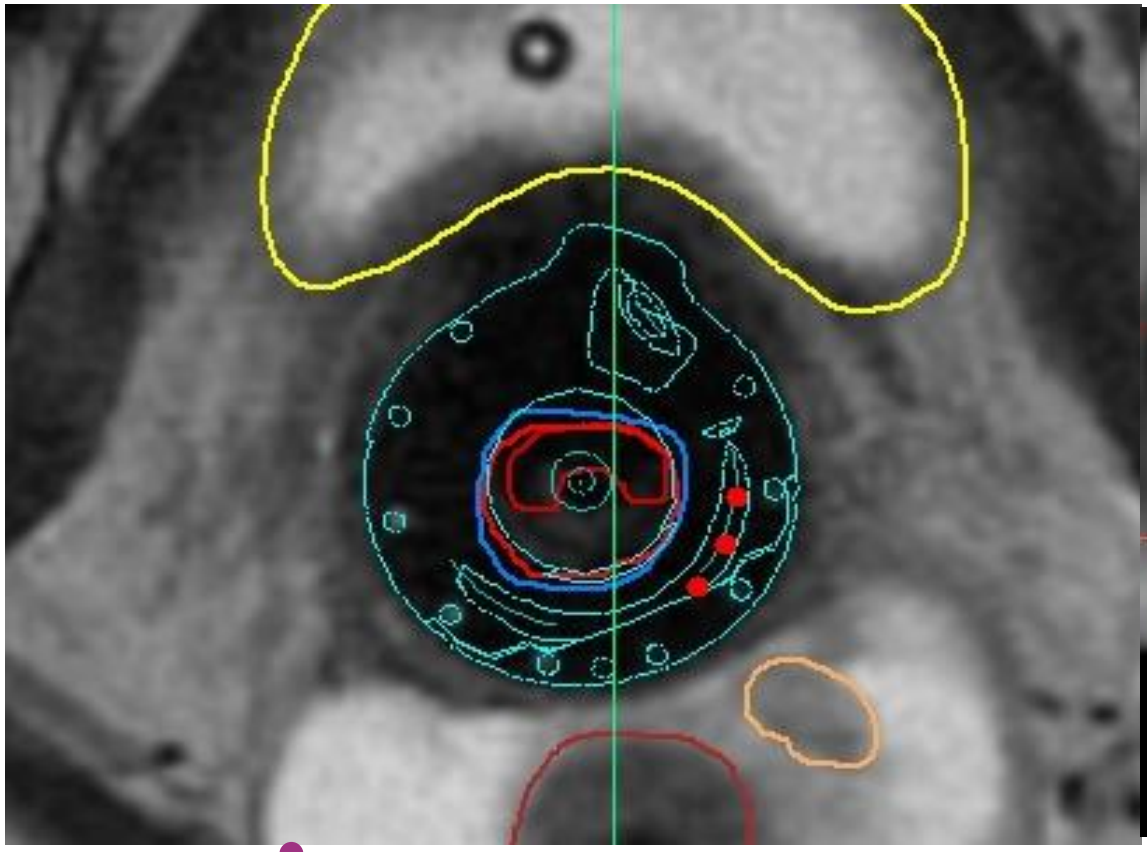
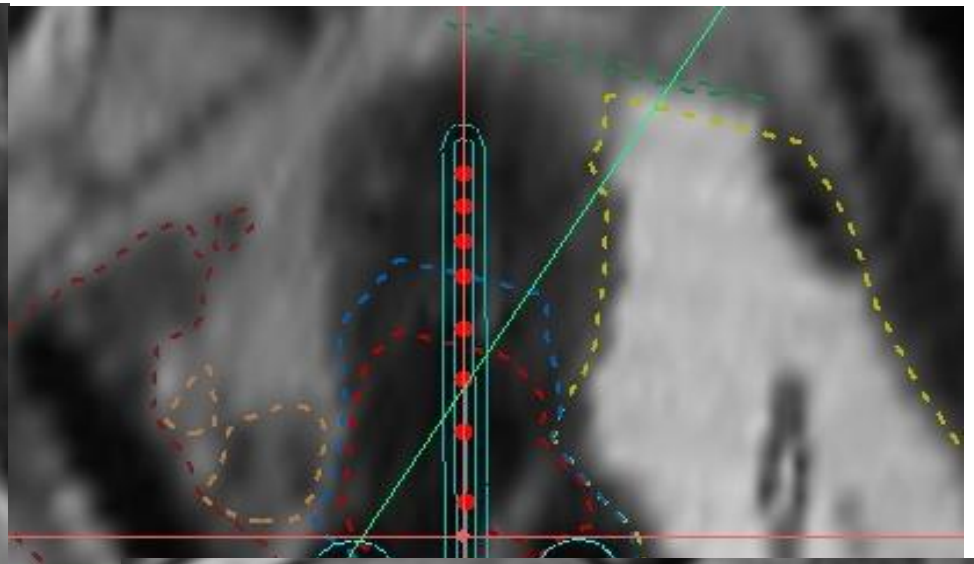
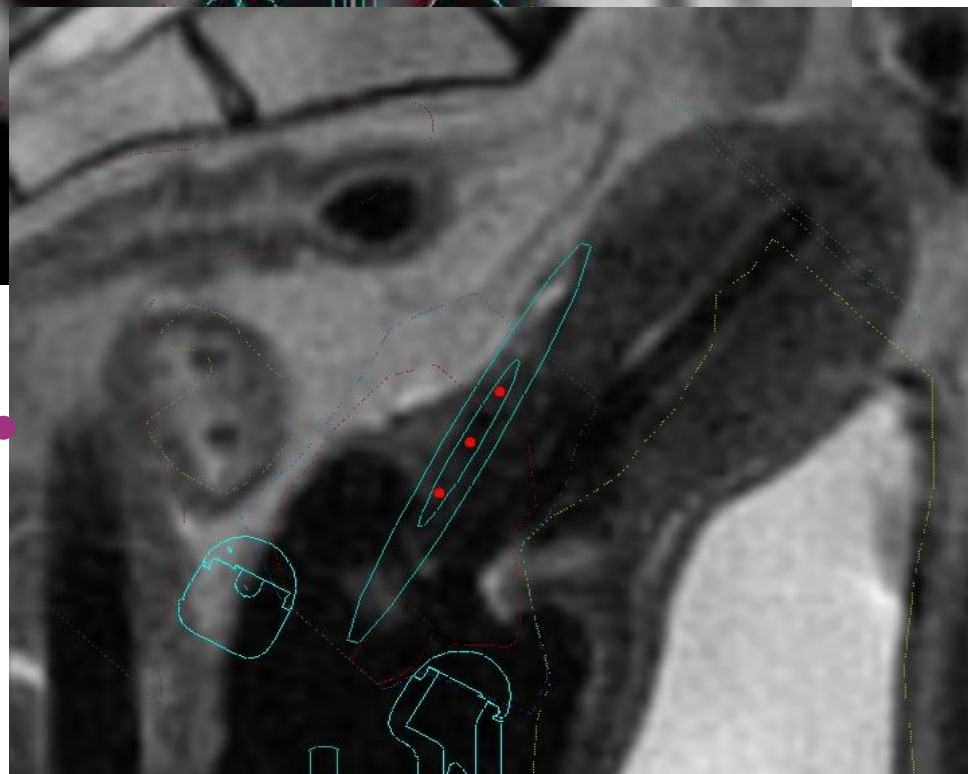




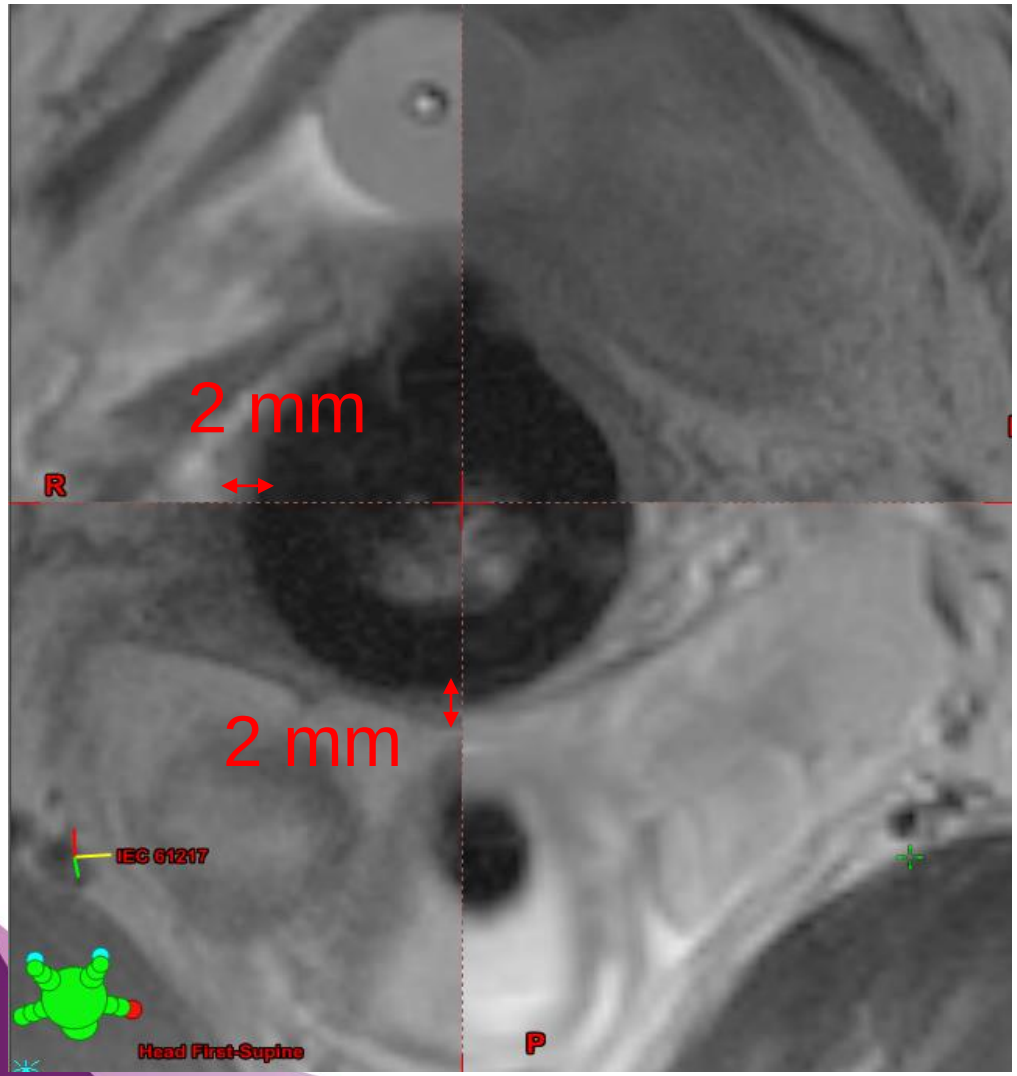


DICOM

Registration uncertainties!

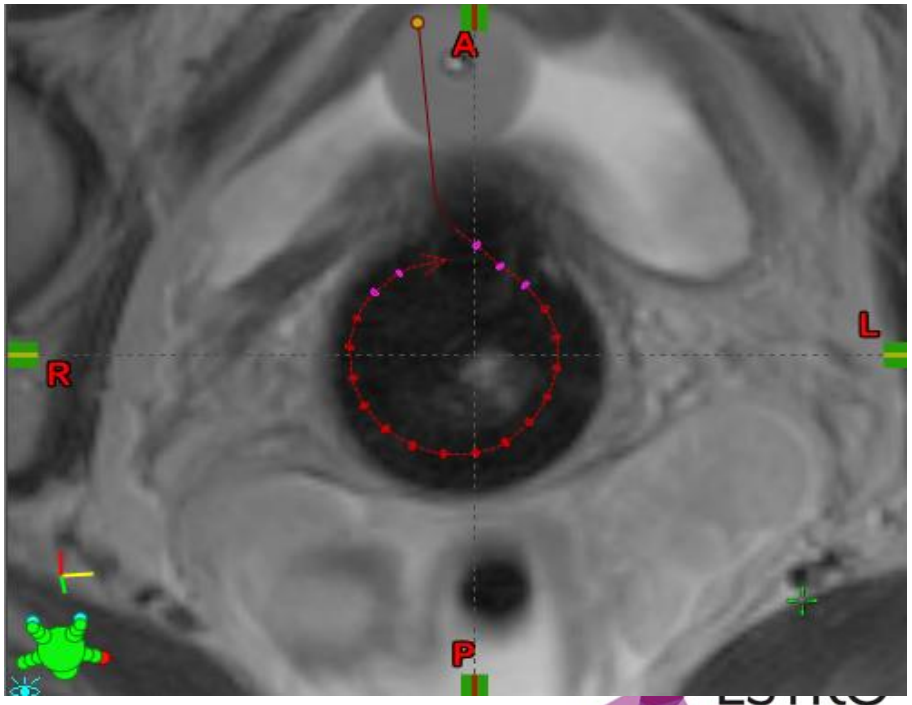
DICOM

Registration between T1 and T2 Images during reconstruction



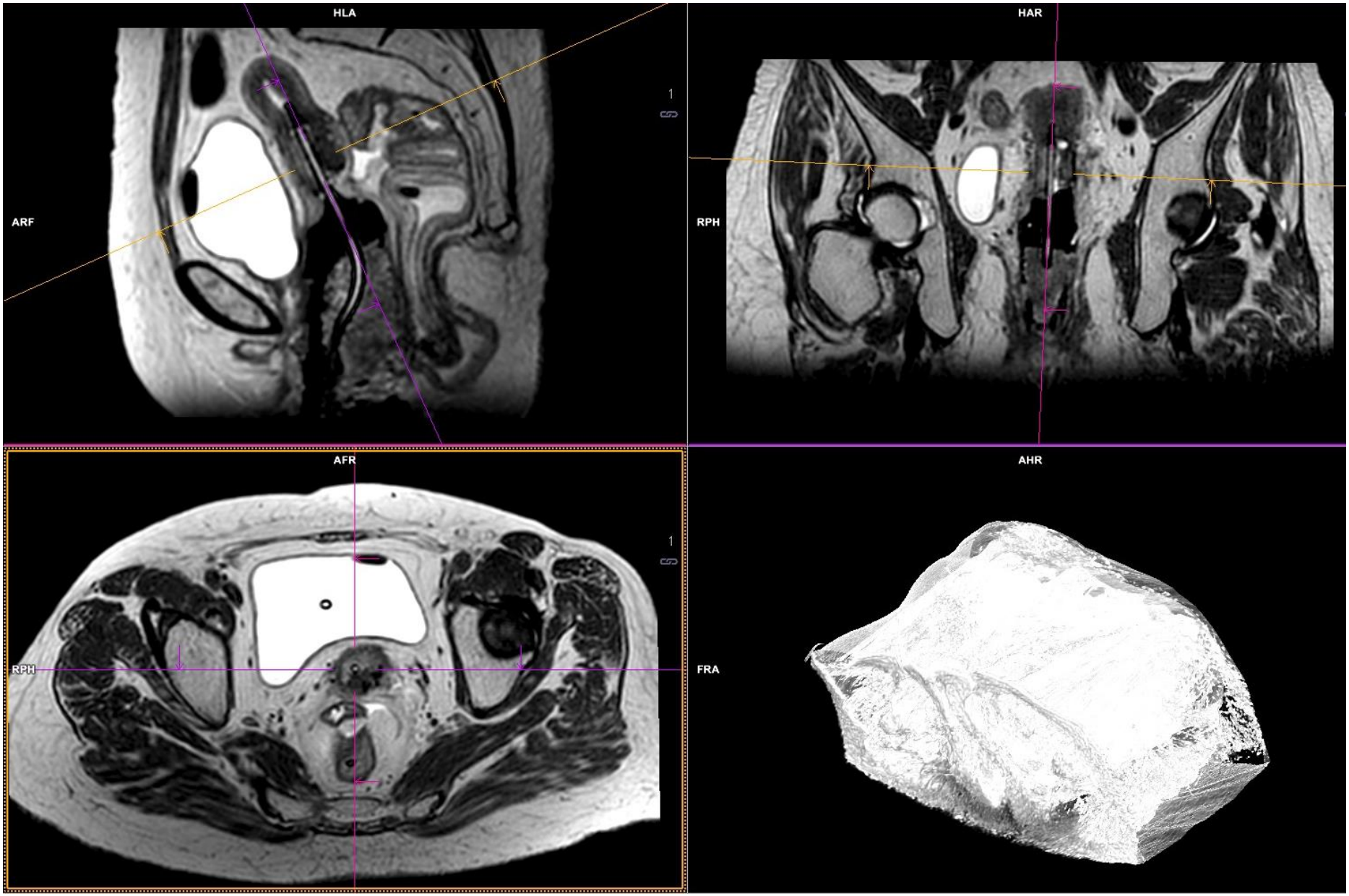
Impact on DVH parameters:
HR CTV: 7% (underestimation)
Bladder: 10% (overestimation)
Rectum: 13% (underestimation)

Reconstruction on T2



Courtesy of K. Tanderup

3D MRI Sequence



Courtesy J. Maximenko (Offenbach)

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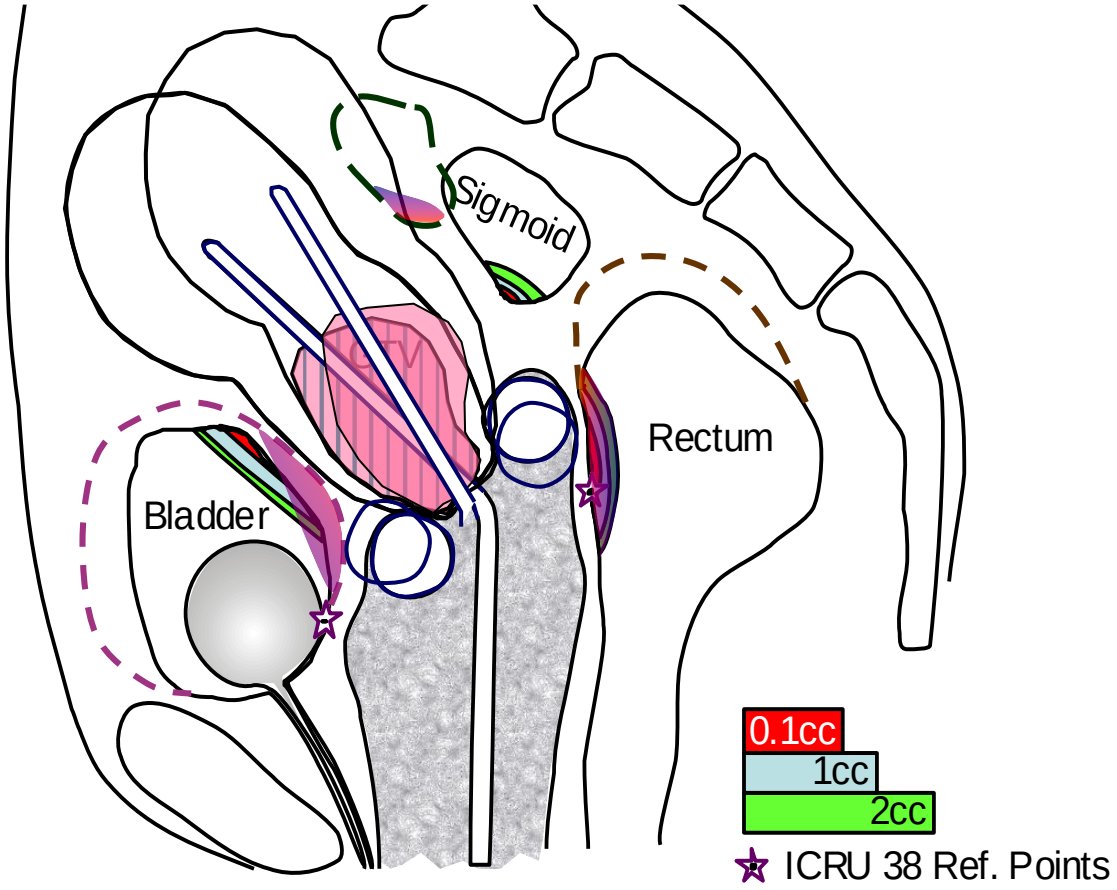
Inter-/intra-fraction variations

Target
fixed to applicator

Rectum:
change of position or
filling with gas

Bladder:
change of filling
(use of bladder filling
protocol)

Sigmoid:
might change
its location



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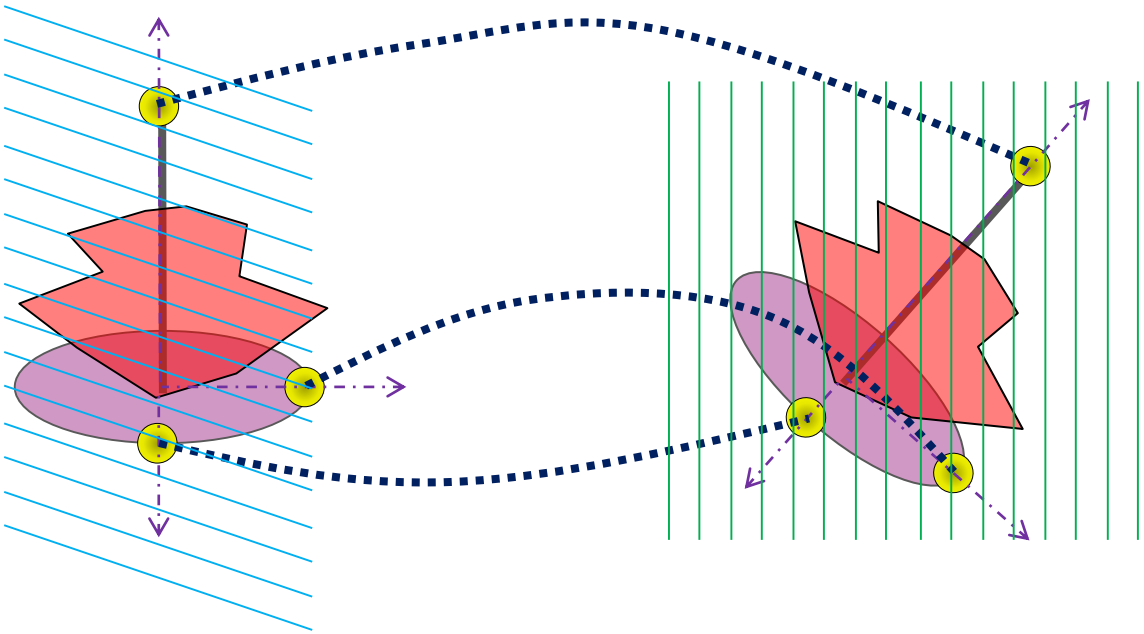
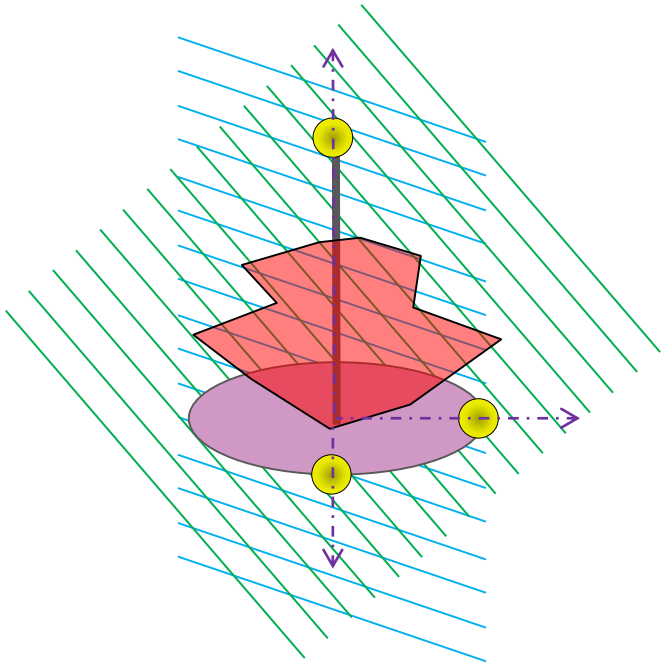
Applicator-based registration (tandem-ring)

manual: landmark definition based on applicator points

automatic: volumetric images with reconstructed applicators (3D models)

Image set A + **Image set B** → **Image set A+B**





If we know where the applicator is, we can define reproducible image registration points using the **applicator** as a **reference coordinate system** in all kinds of images!

Example of manual method:
Align coordinate system according to applicator model and digitize 3 defined points

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Applicator-based

Applicator-based registration (tandem-ring)

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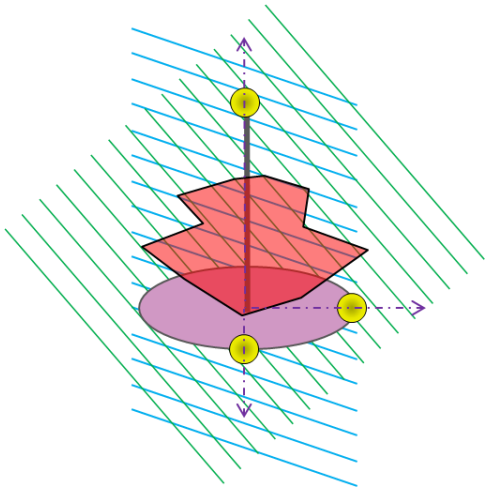
Example of manual method:
Align the coordinate system according to applicator model and digitize **3 defined points**



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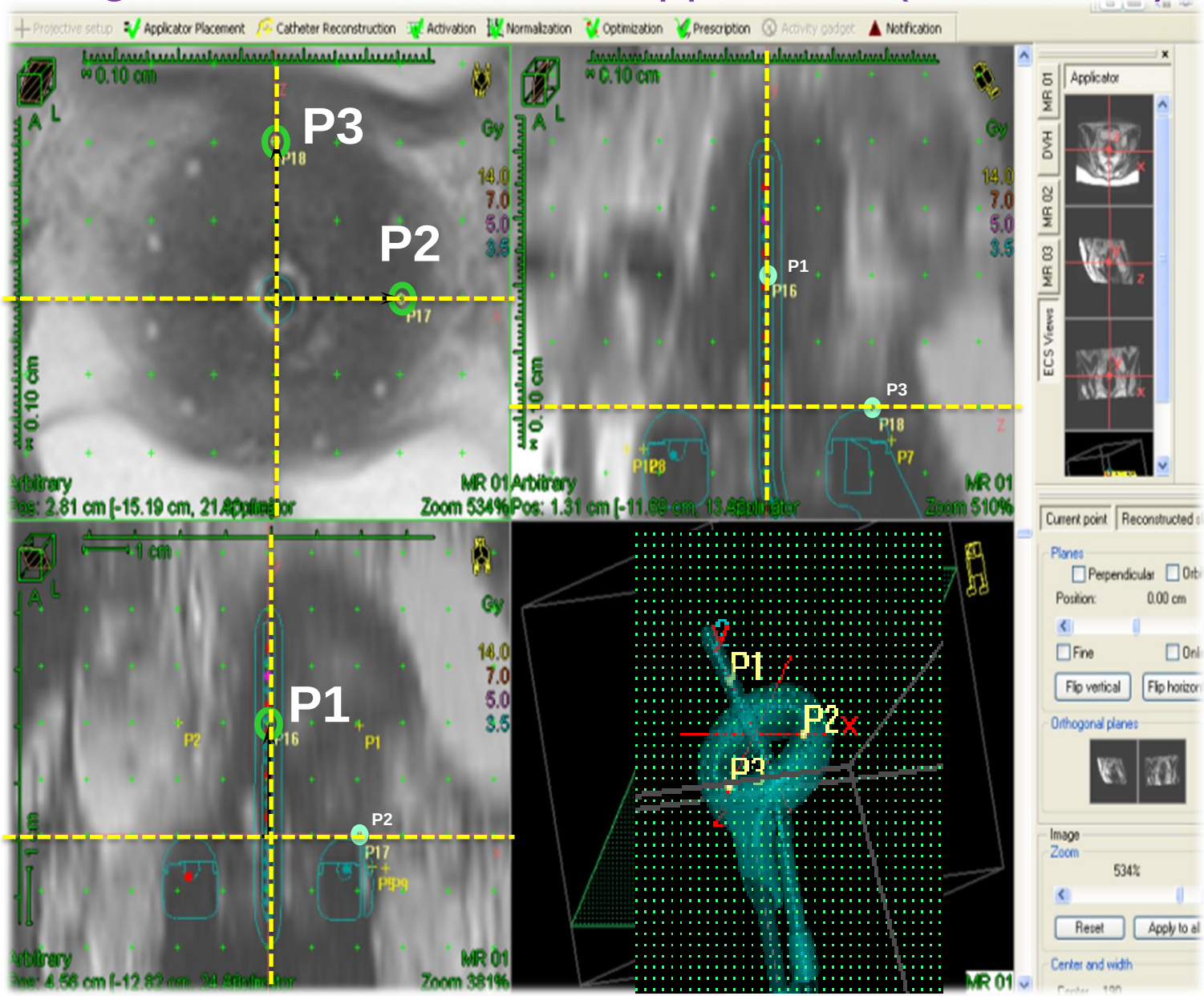

Solutions for 3D image guided adaptive planning

Is access to MRI with applicator in place available ?

Yes, for each fraction/application

MRI for each HDR fraction
MRI for each application, CT before each fraction for OAR verification,…

Yes, but only for first application

MRI for first application, CT for subsequent fractions (re-using MRI target from first fraction): software-based target transfer to avoid interobserver contouring uncertainties

No, not at all

pre-BT MRI for target delineation on CT with applicator in situ at BT

or even: volumetric US scan after applicator insertion for target definition, and CT scan for OAR delineation (registration via applicator)

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Image Modality ?

Increasing uncertainty

Fusion

CT

MR

CT

CT

CT

MR

CT

CT

Gold Standard

MR

MR

MR

MR

Pre-BT

1BT

2BT

3BT

....

Image Modality ?

Increasing uncertainty

Fusion

CT

MR

CT

CT

CT

MR

CT

CT

Gold Standard

MR

MR

MR

MR

Pre-BT

1BT

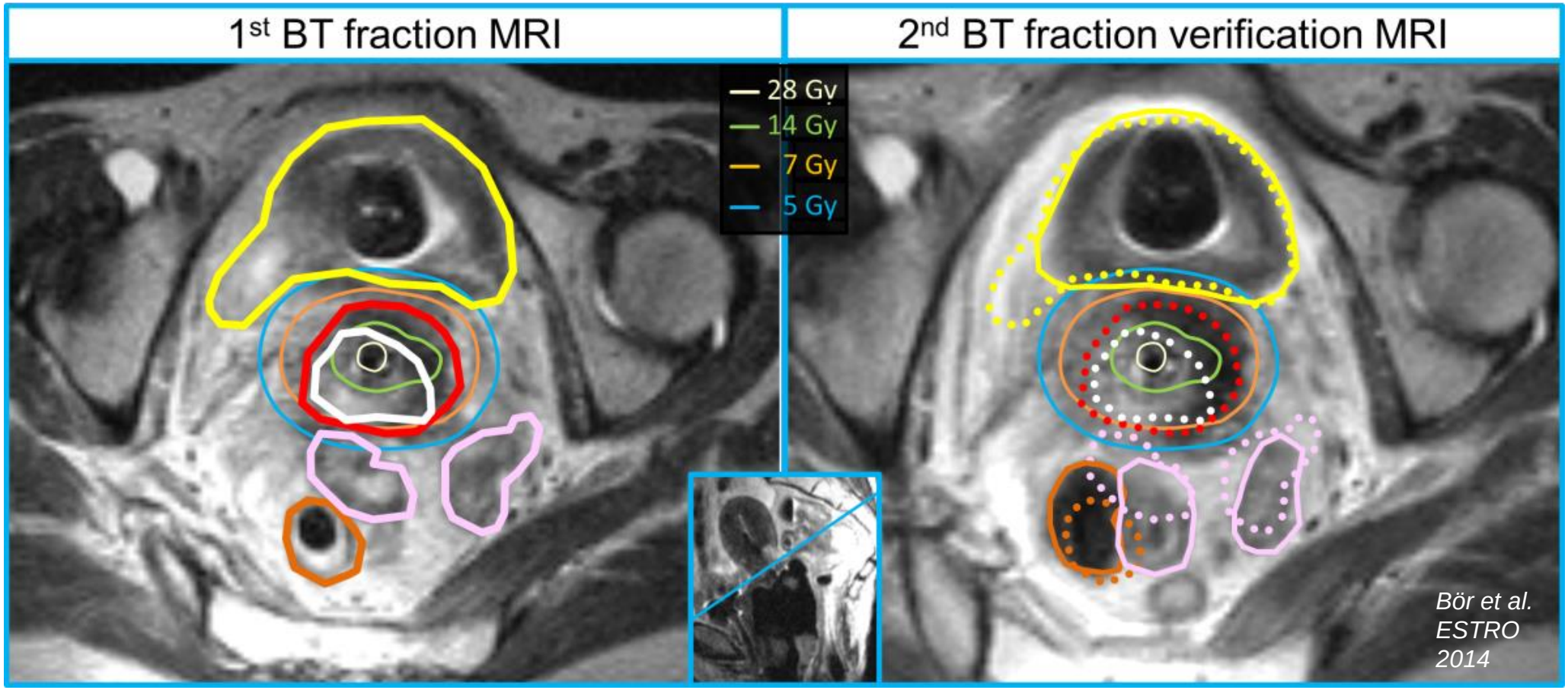
2BT

3BT

....

Applicator-based

Example from Vienna: day 1 – day 2 comparison



Fast registration of MRI F1 and F2 via applicator coordinate system to

- check implant stability (relative position of applicators/needles and target)
- check organ variation
- decide to ☐ treat ☐ adapt organ filling ☐ recontour re-evaluate

REPLAN ? ☐ yes ☐ no

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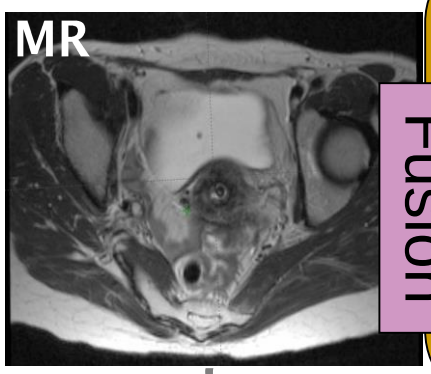
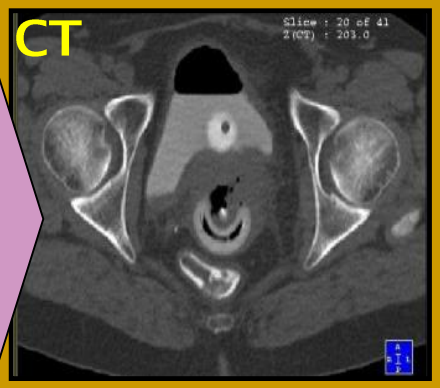
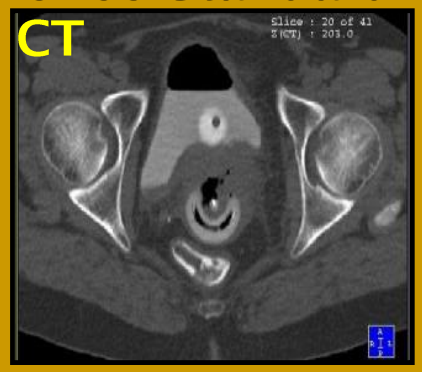
Image Modality ?

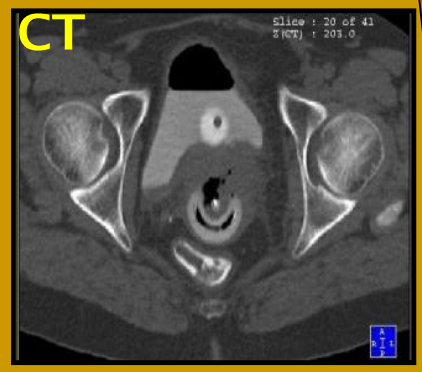


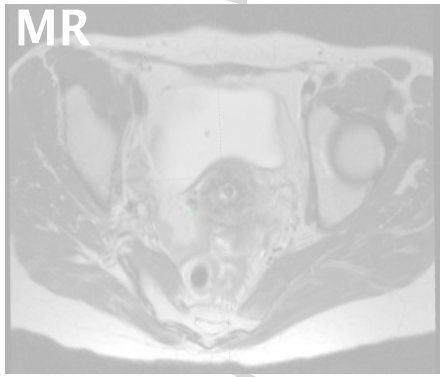
Fusion

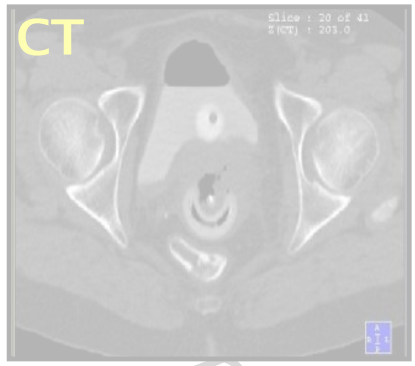
Bronce Standard

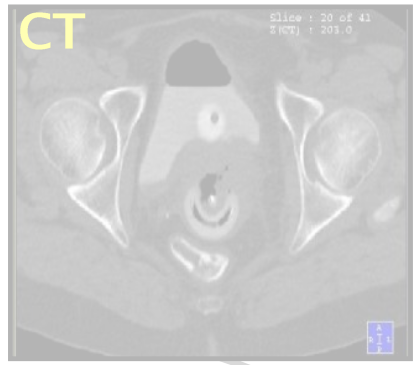


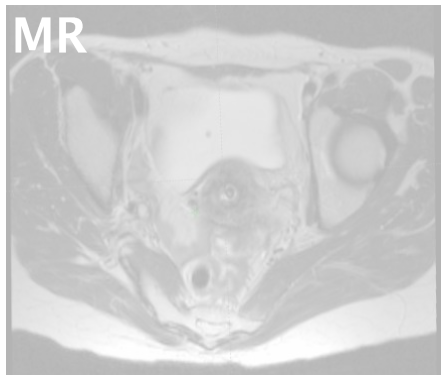


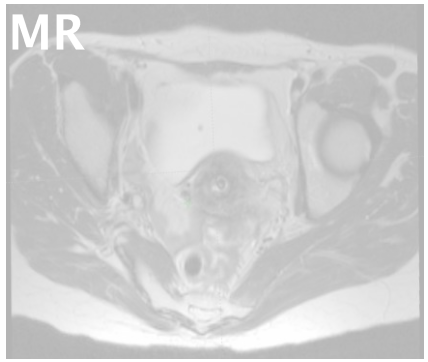


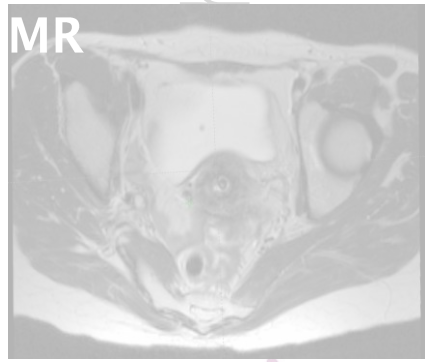












Pre-Brachyther

Increasing uncertainty

Pre-BT

1BT

2BT

3BT

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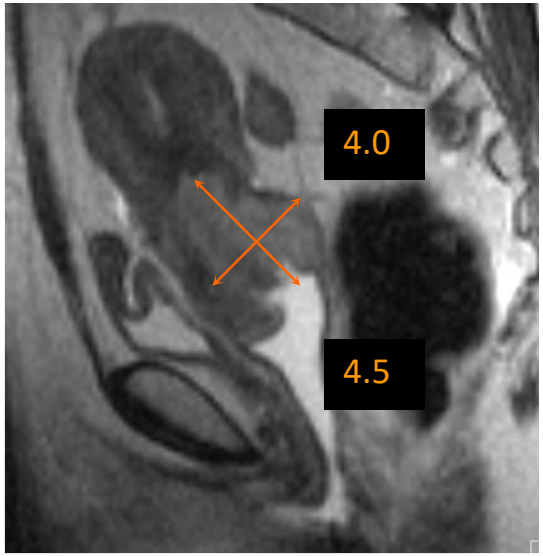
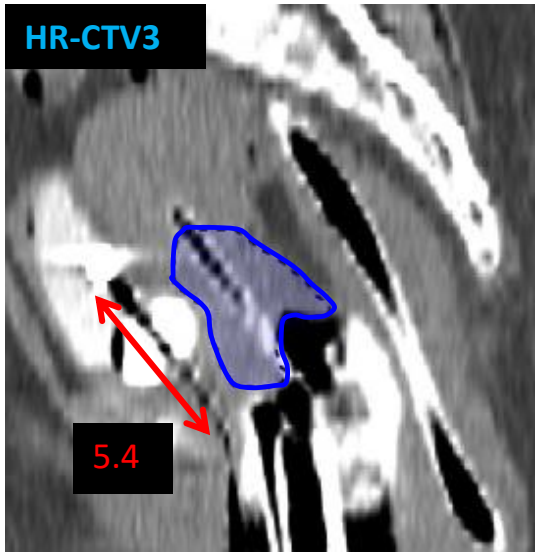
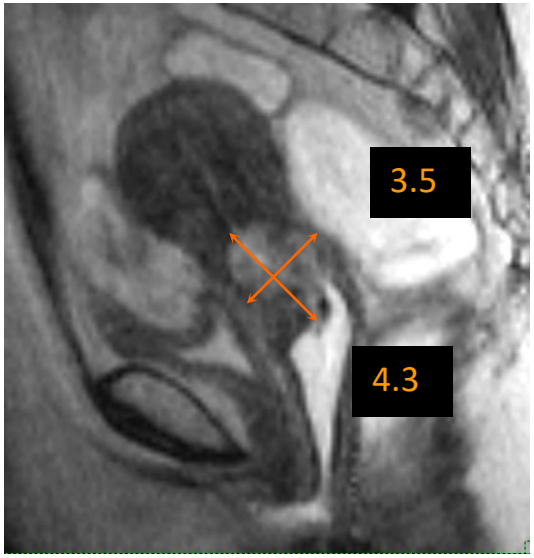
Example: CTV_{HR} „pre-BT MRI“ (CTV_{HR} 3)

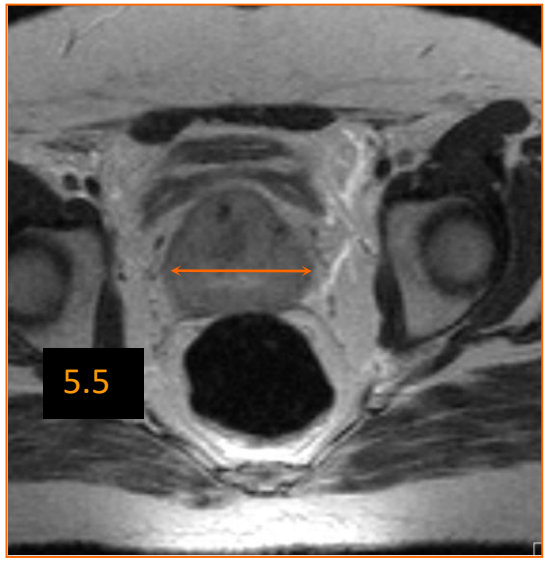
PreBrachy MRI

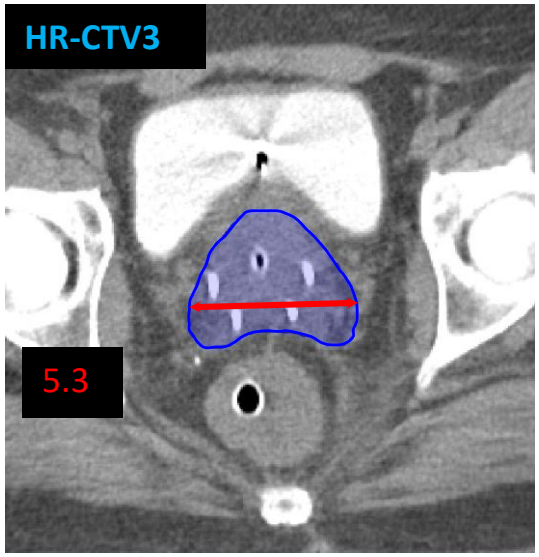
1st Brachytherapy

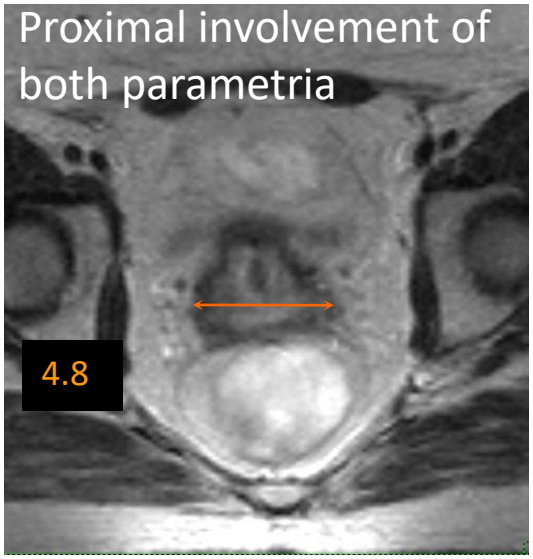












Courtesy of M. Federico

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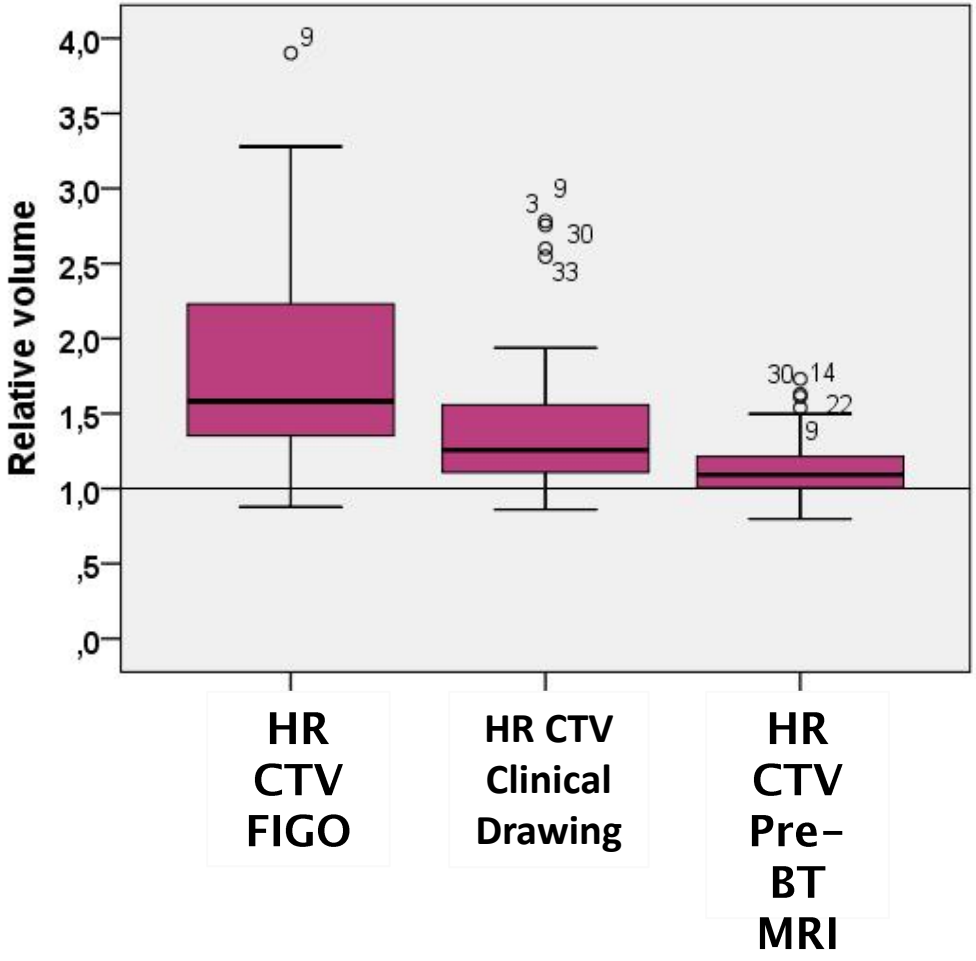
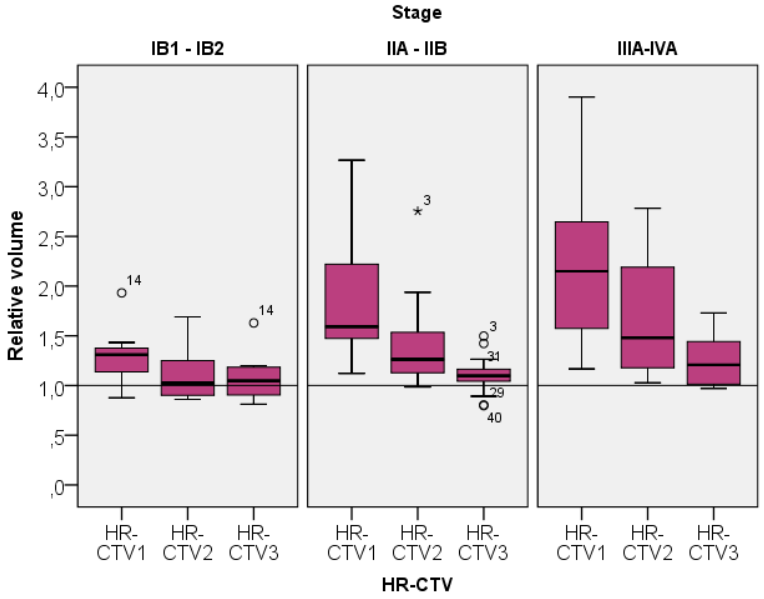
Delineation on CT according to three principles



Three increasingly comprehensive principles for delineation on CT:

FIGO only
FIGO + clinical drawing
FIGO + clinical drawing + pre-BT MRI



Courtesy of M. Federico

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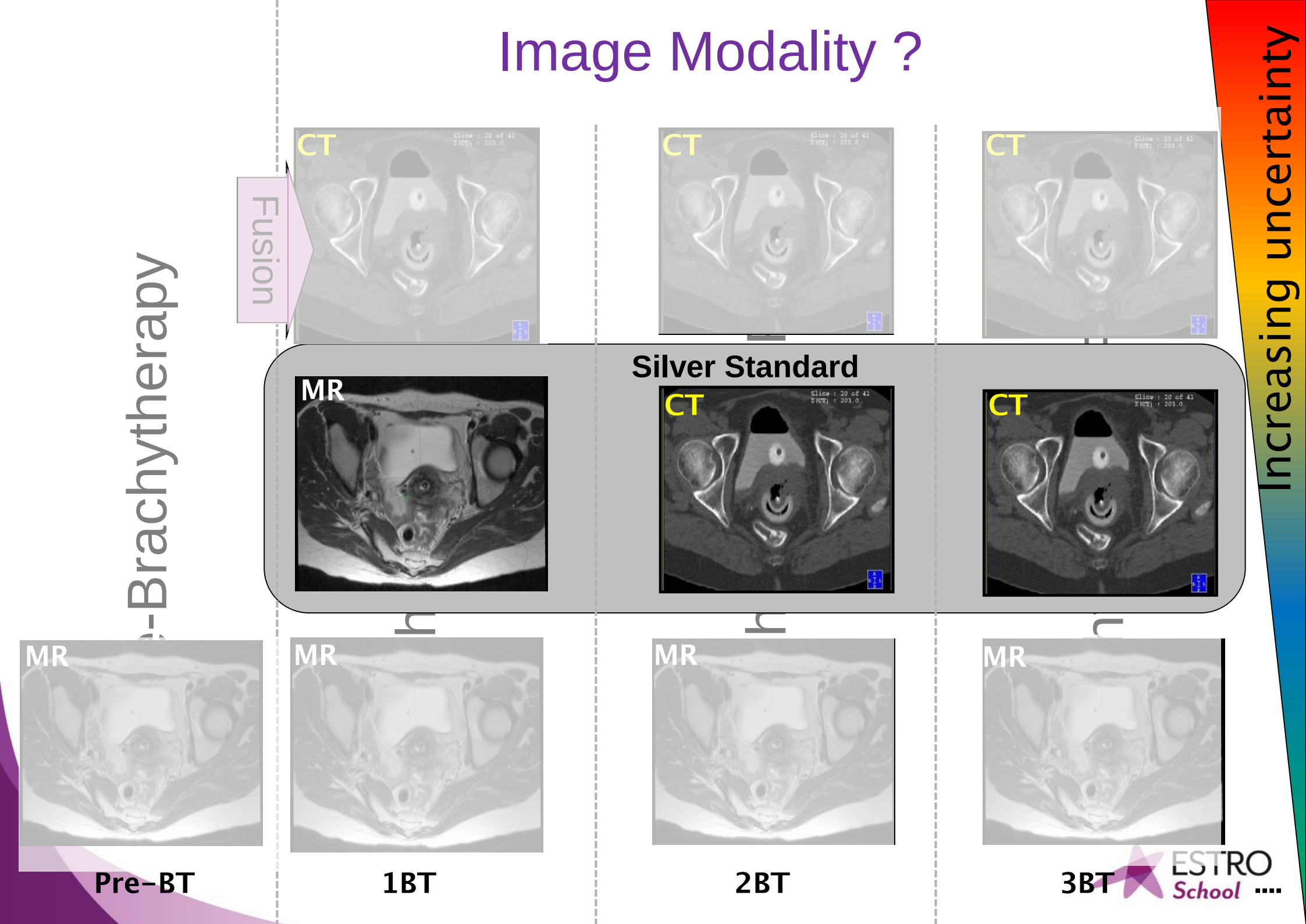
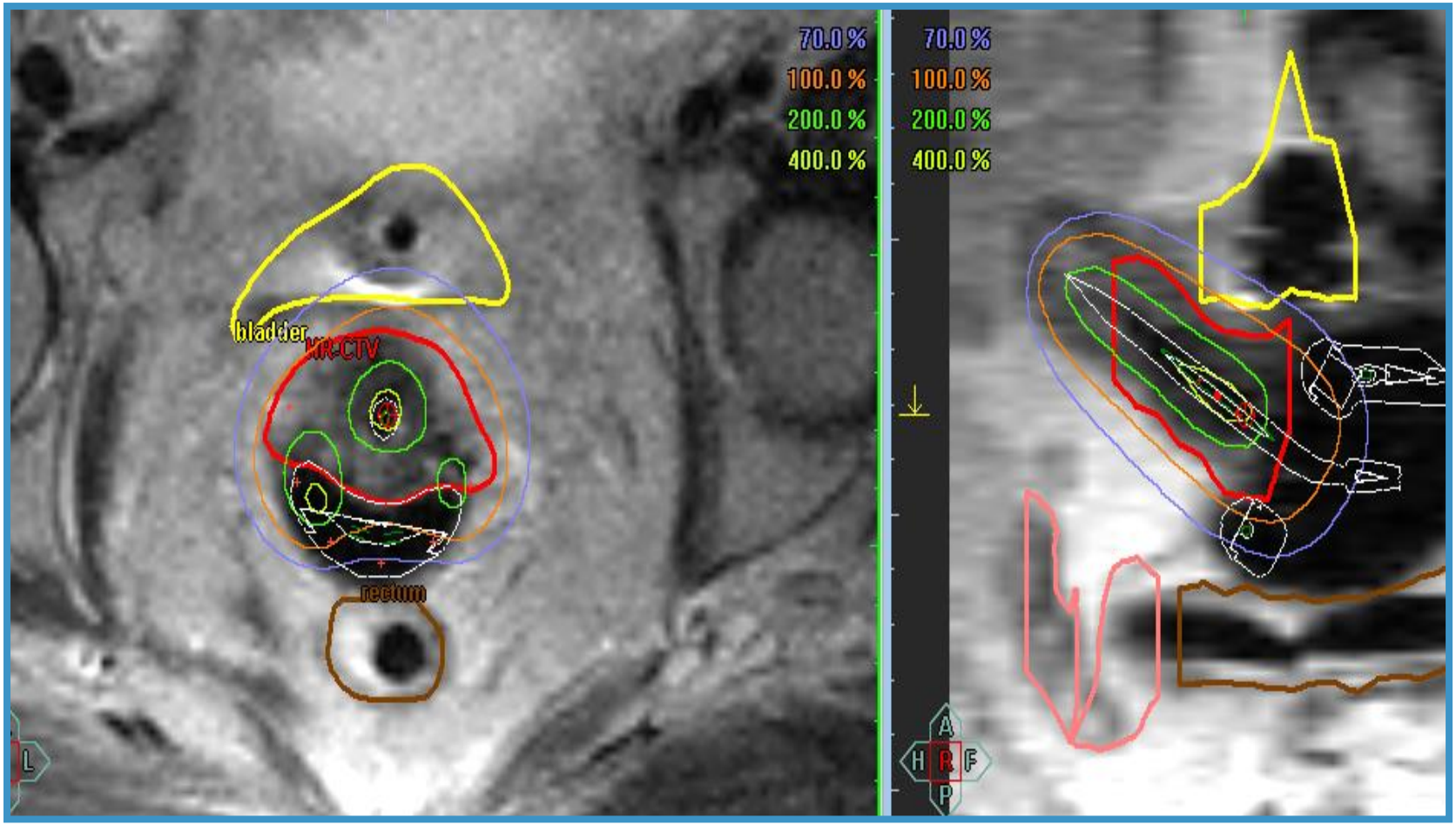
Image Modality ?



1st application: MRI

Applicator, target (HR CTV), OAR (rectum, bladder, sigmoid)
Dose planning and optimization on target+organ contours



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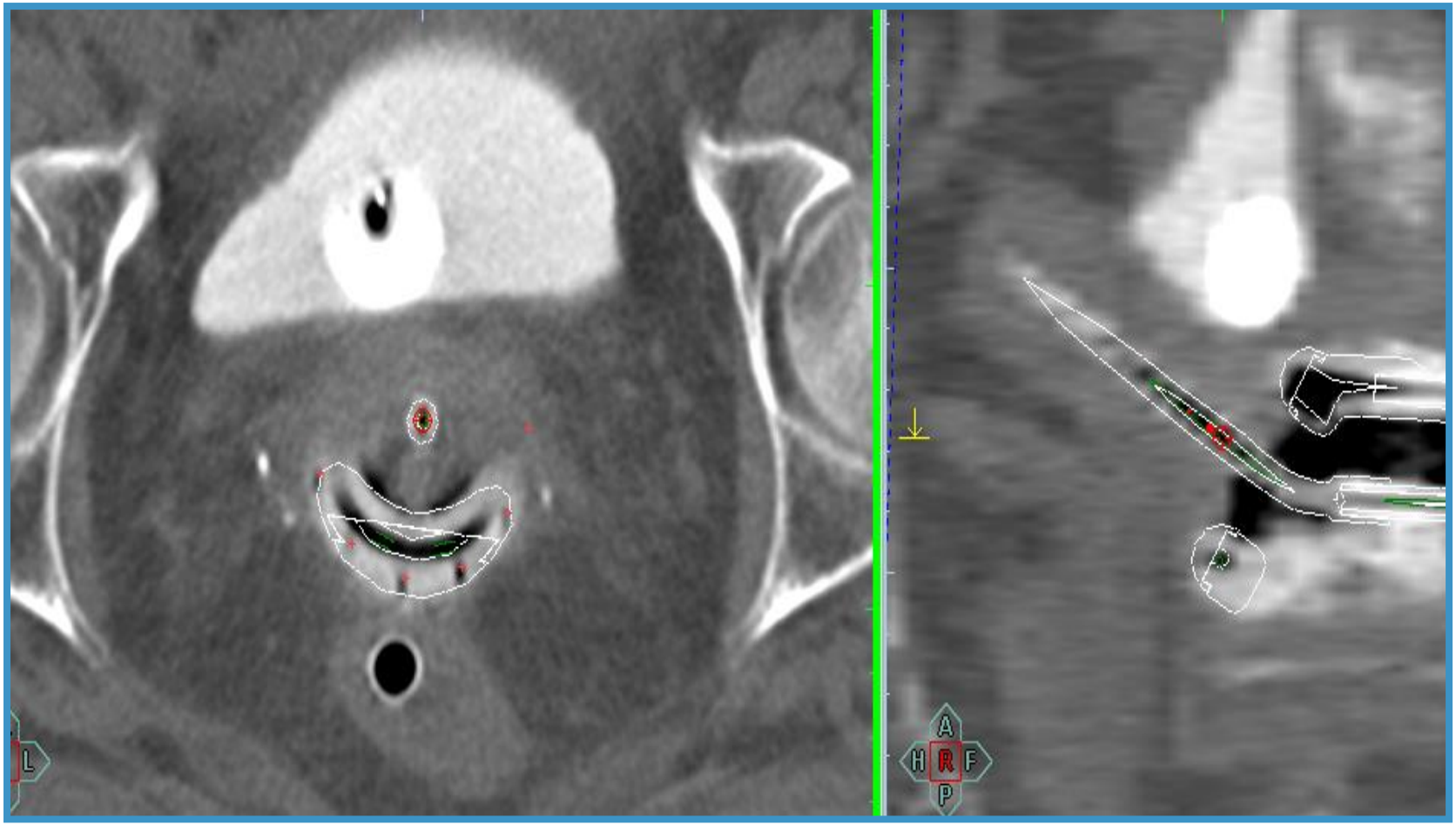
2nd application: CT

3D applicator reconstruction



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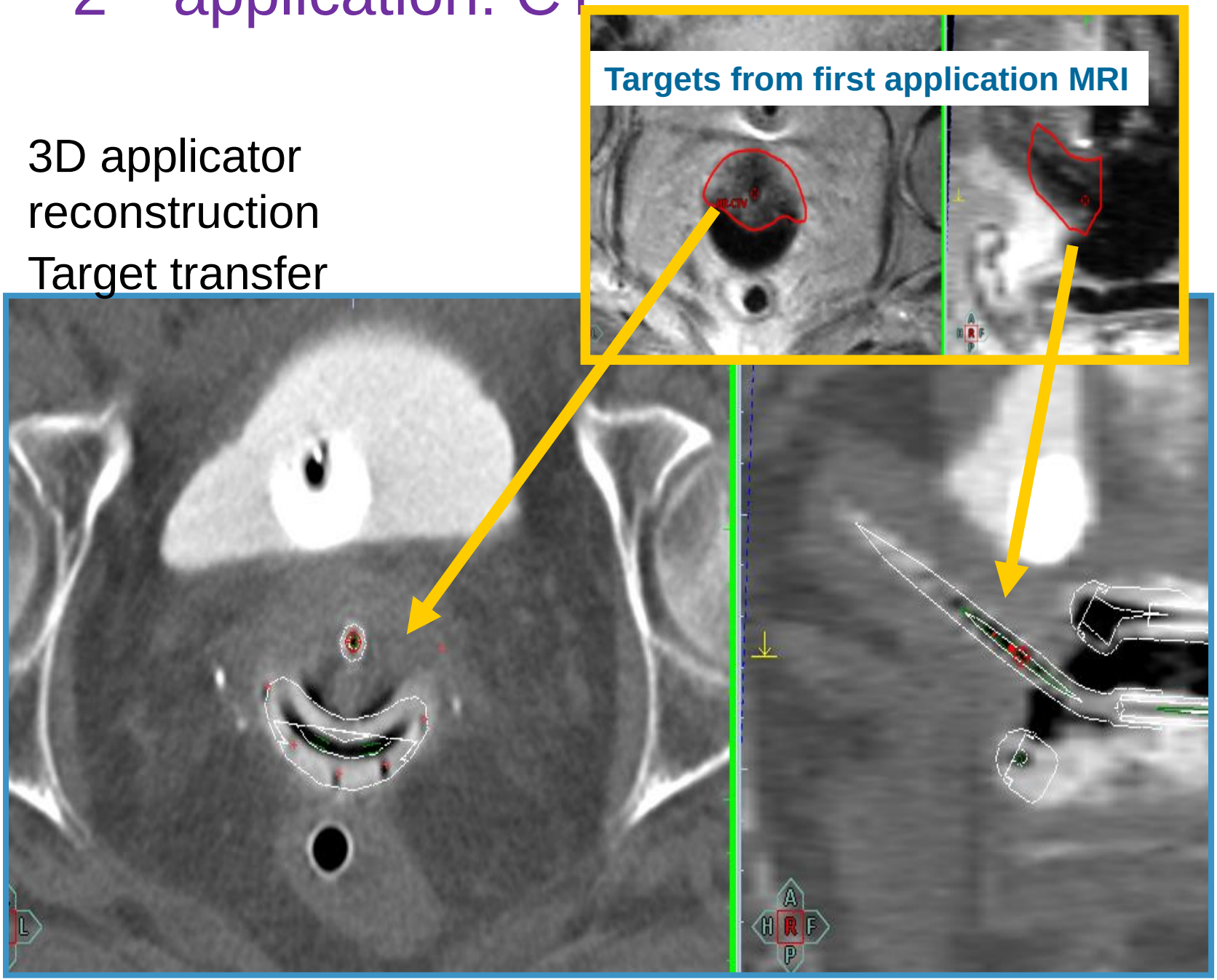
2nd application: CT

3D applicator reconstruction

Target transfer



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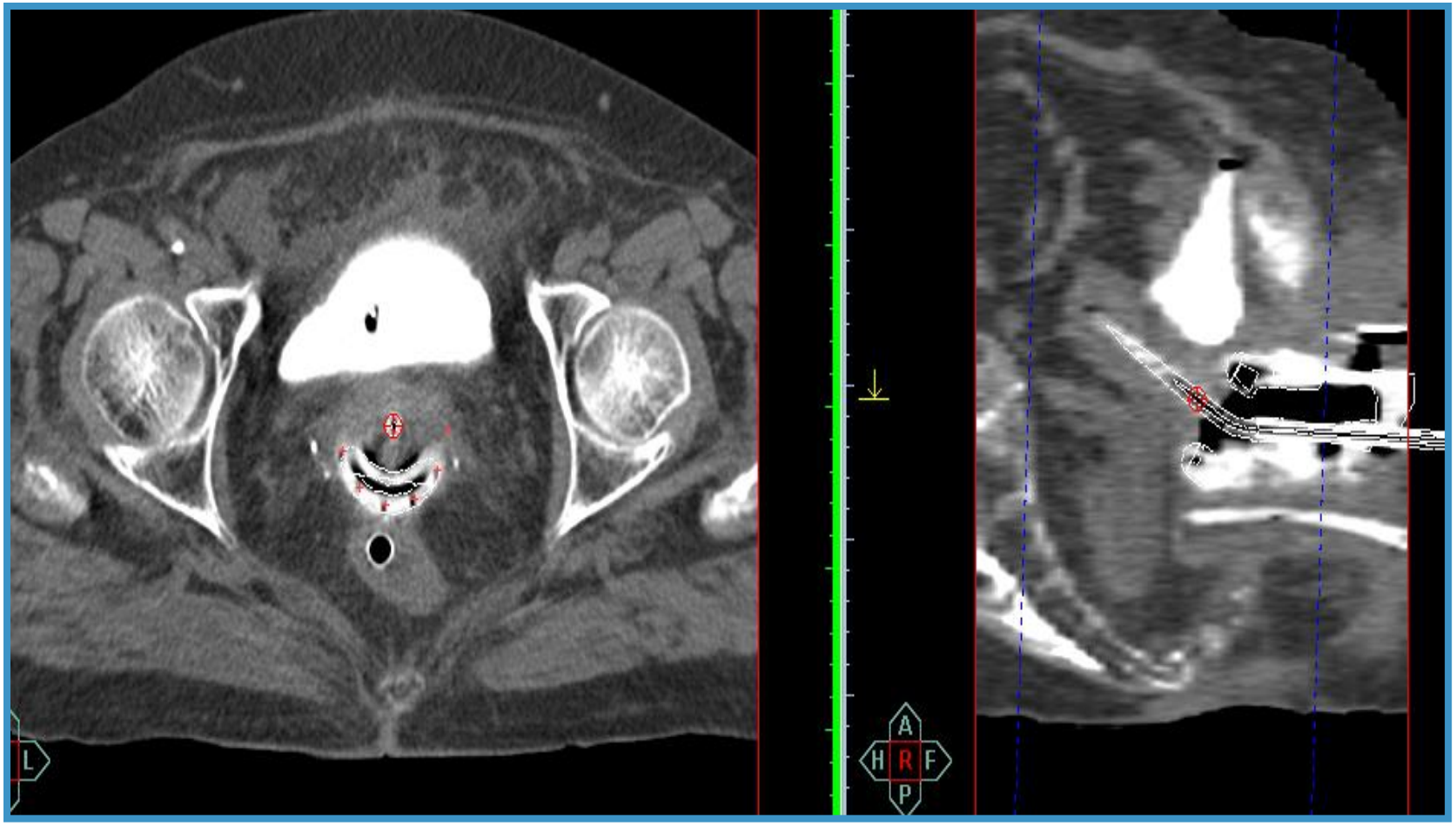
2nd application: CT

Rigid image registration based on 3D applicator model



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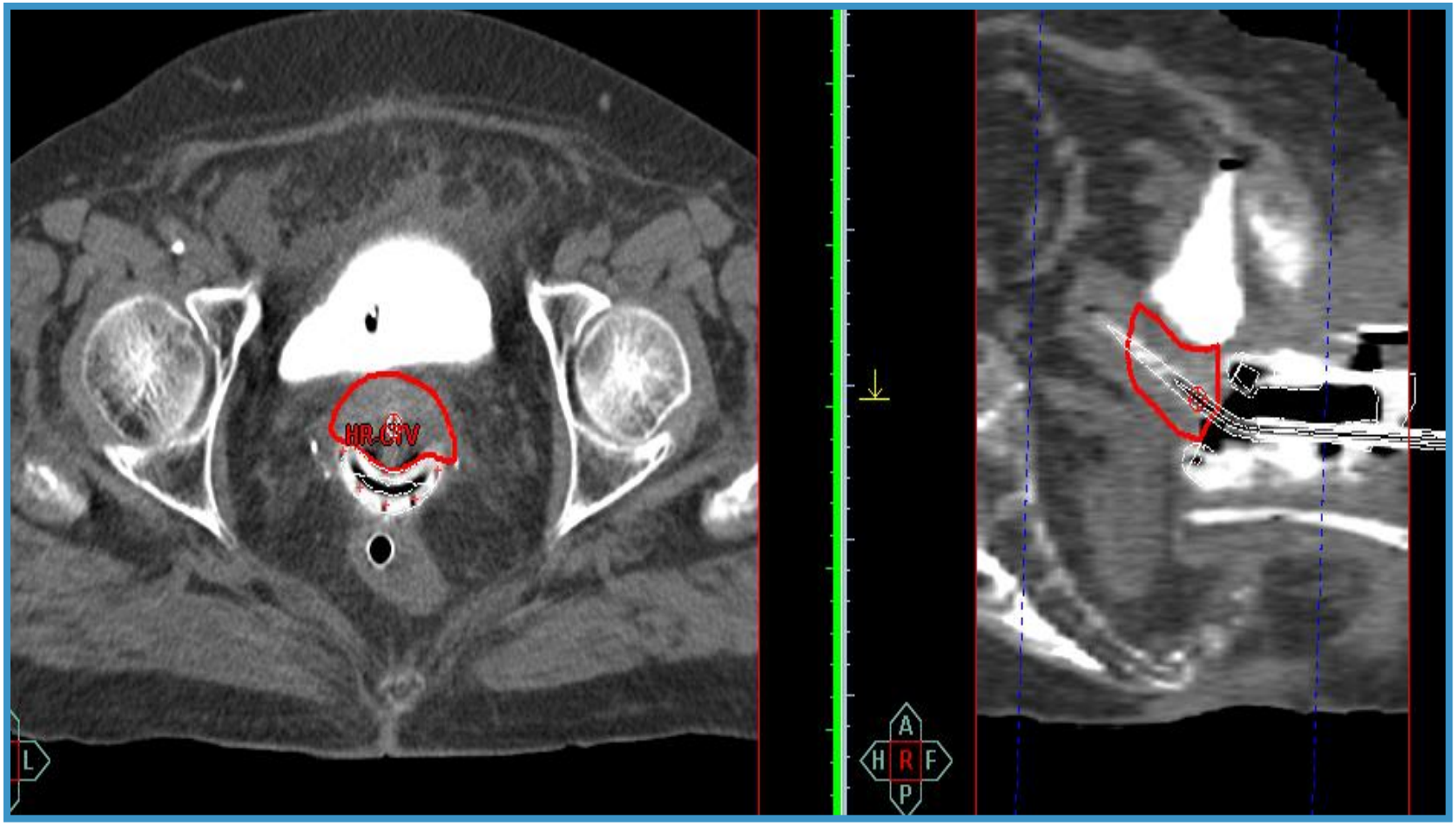
2nd application: CT

Automatic target transfer from MRI to CT with applicator as reference system



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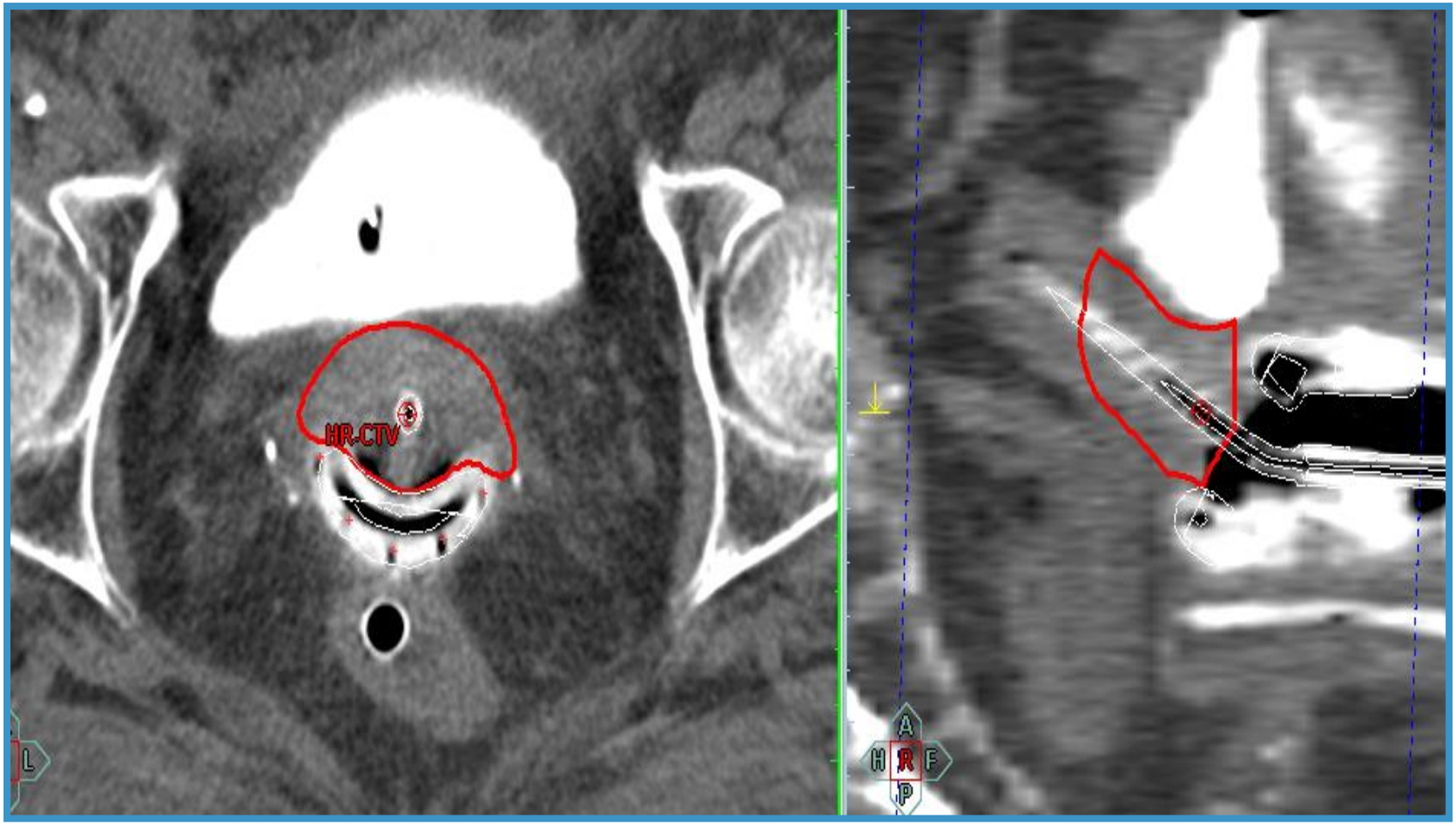
2nd application: CT

Contouring OAR on CT



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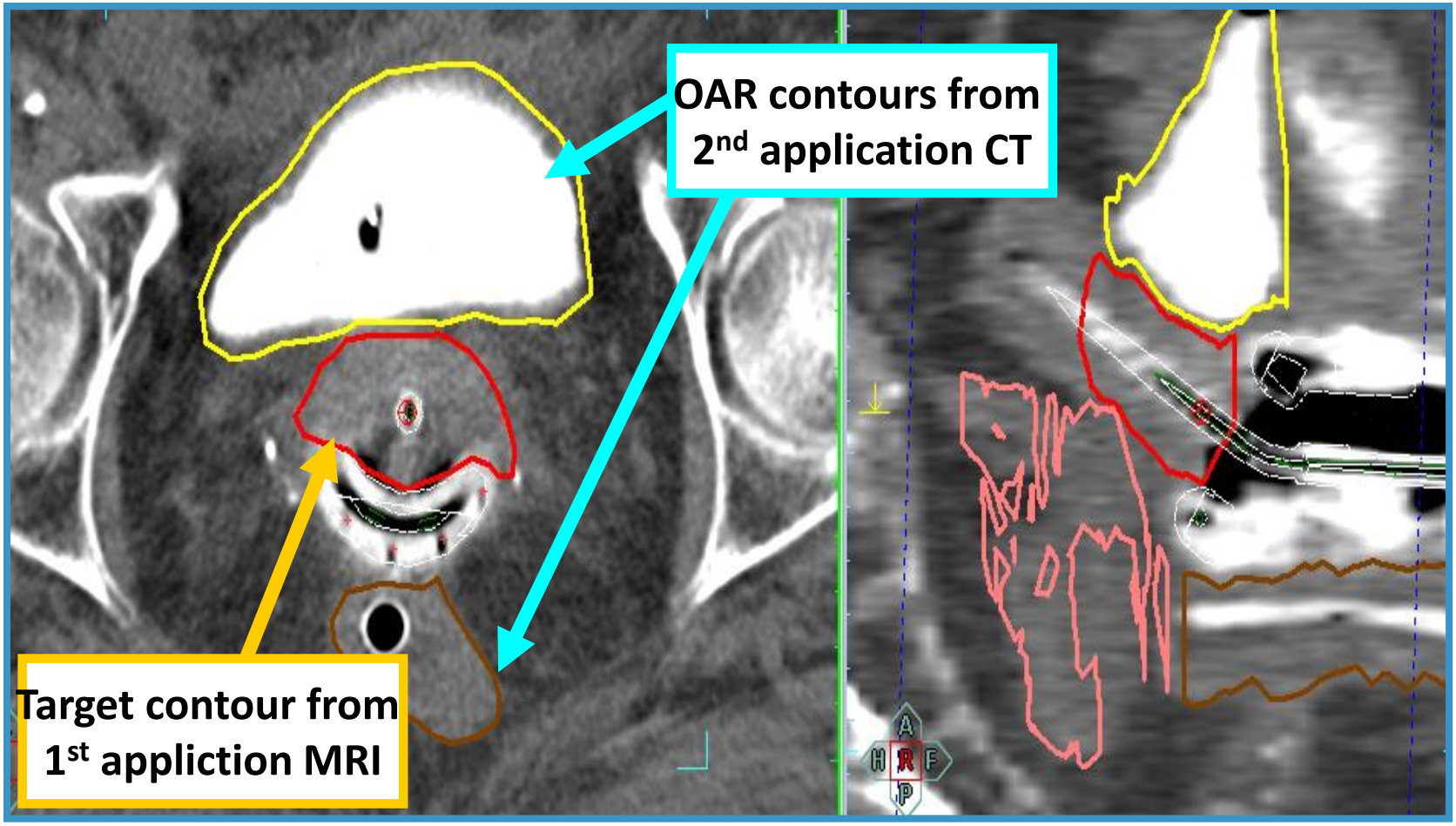
2nd application: CT

Contouring **OAR on CT**



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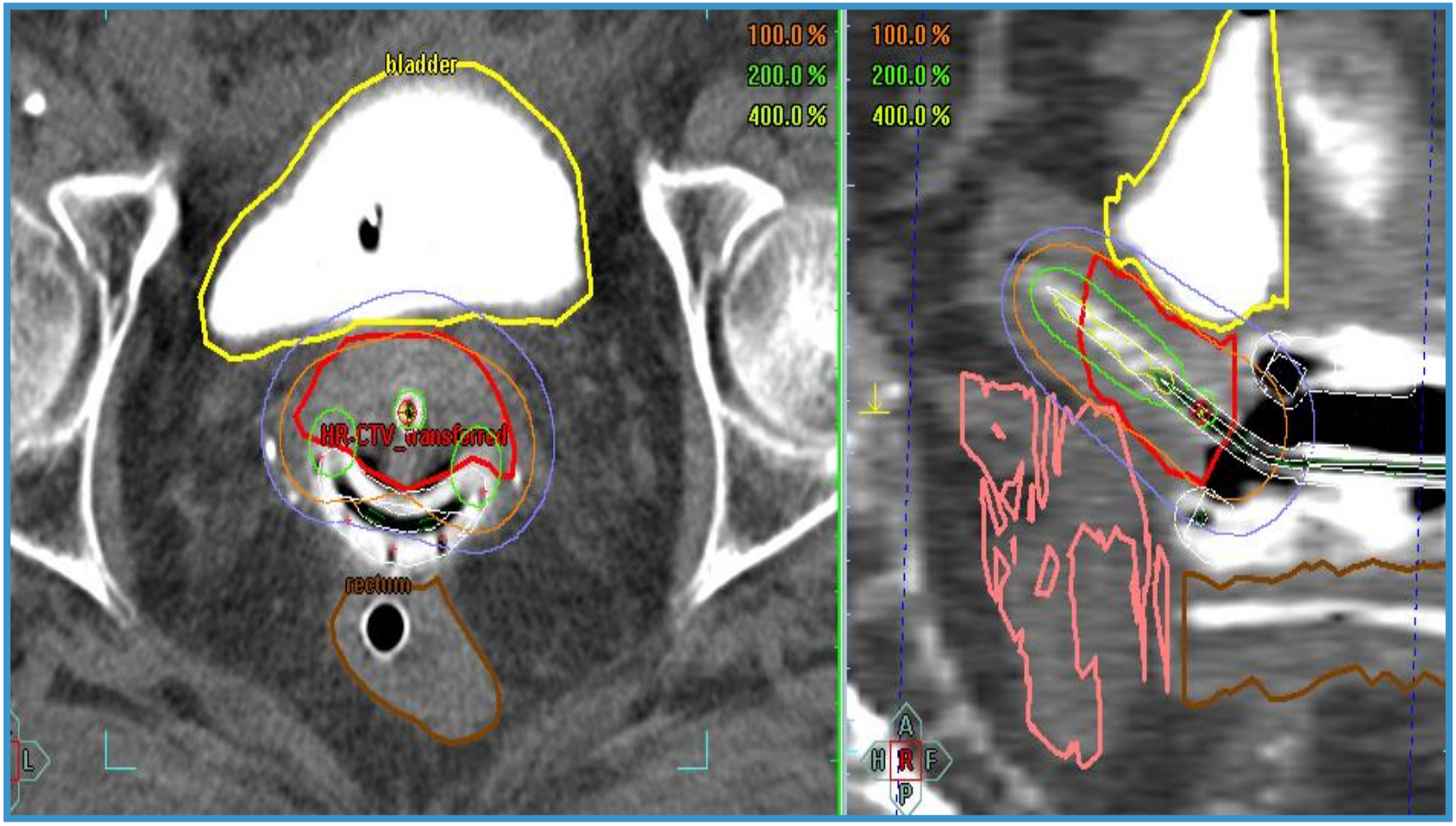
2nd application: CT

Dose planning and optimization based on copied target and individual OAR contours. All dose constraints for targets and OAR have to be achieved.



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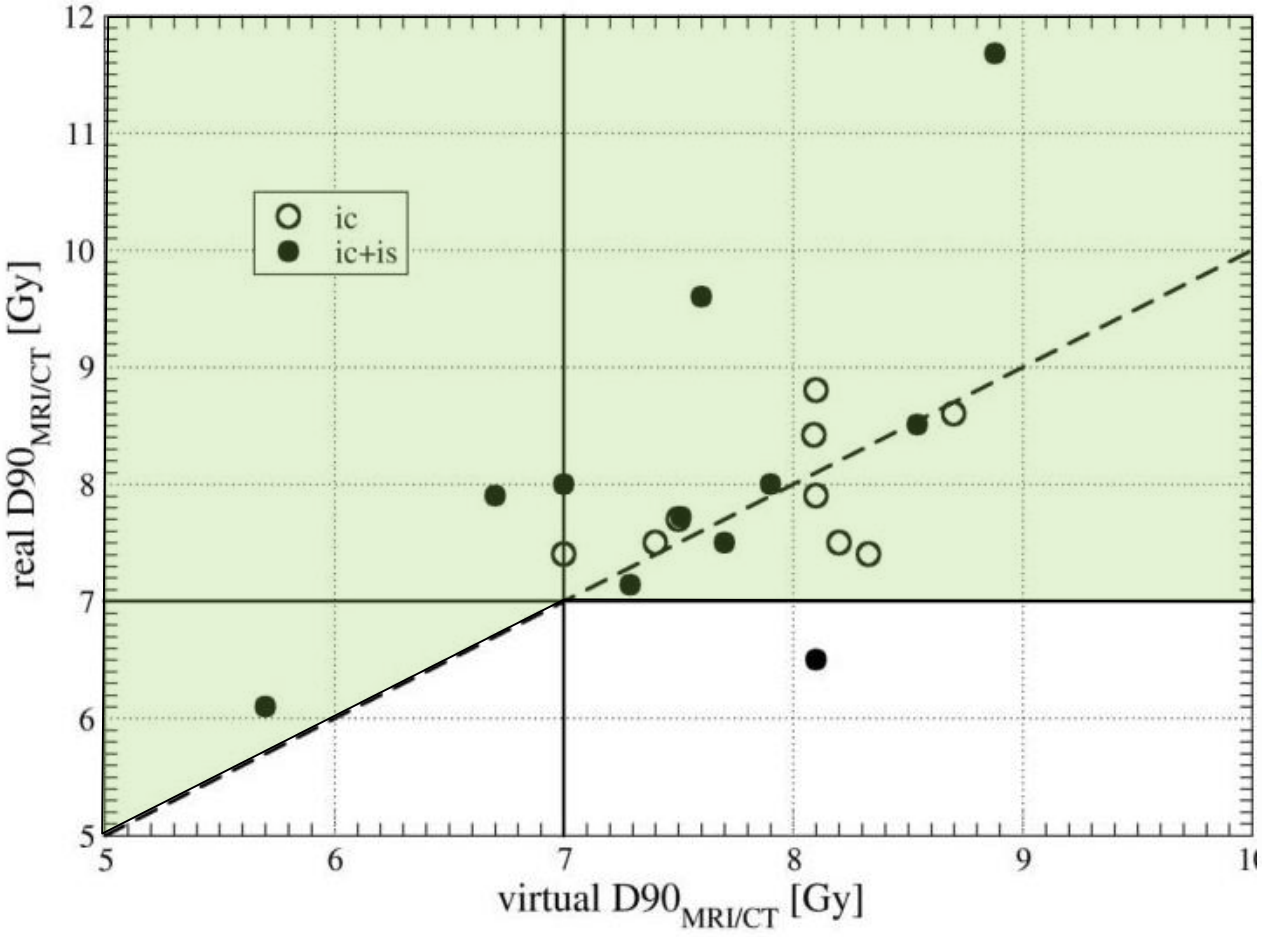
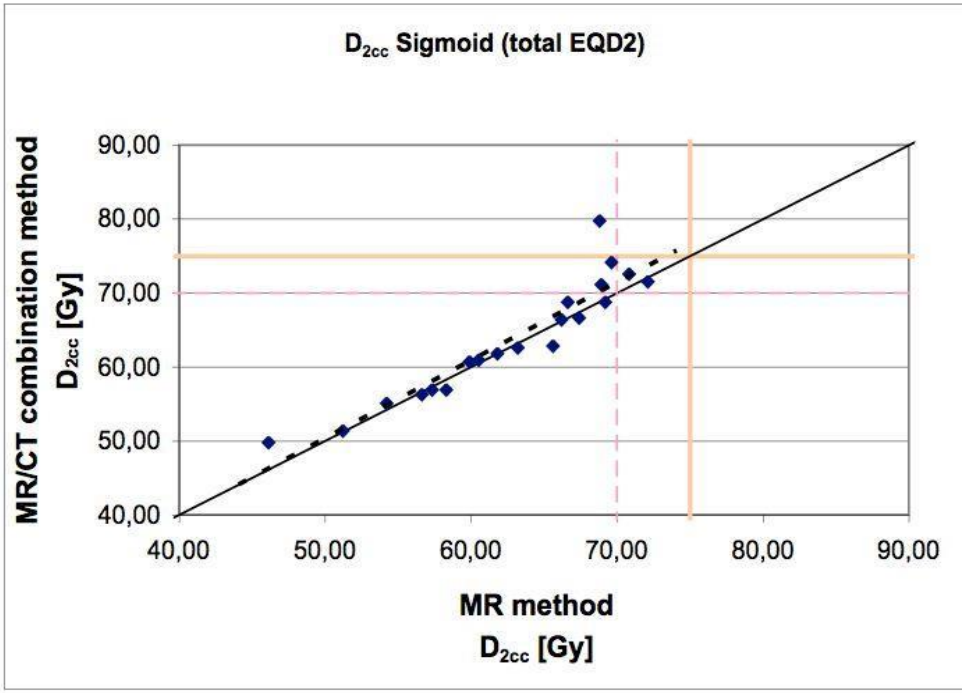
Results: D_{90} CTV_{HR}, D_{2cm^3} sigmoid



Planning aim D_{90} CTV_{HR}>7Gy per fraction was reached in all but one cases
(applicator position was different on MRI and CT)



Planning aim D_{2cm^3} sigmoid<80Gy EQD2(α/β=3Gy)
In total was reached in all but one cases (intrafractionorgan motion, contouring uncertainties)

Nesvacil et al. R&O 2013

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Solutions for 3D image guided adaptive planning

Is access to MRI with applicator in place available ?

Yes, for each fraction/application

MRI for each HDR fraction
MRI for each application, CT before each fraction for OAR verification,…

Yes, but only for first application

MRI for first application, CT for subsequent fractions (re-using MRI target from first fraction): software-based target transfer to avoid interobserver contouring uncertainties

No, not at all

pre-BT MRI for target delineation on CT with applicator in situ at BT

or even: volumetric US scan after applicator insertion for target definition, and CT scan for OAR delineation (registration via applicator)

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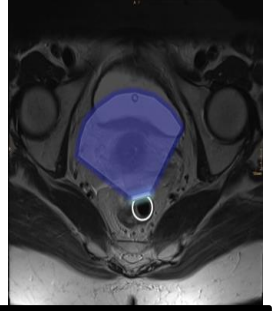
No MRI? Use of transrectal US for target visualisation in cervix BT?



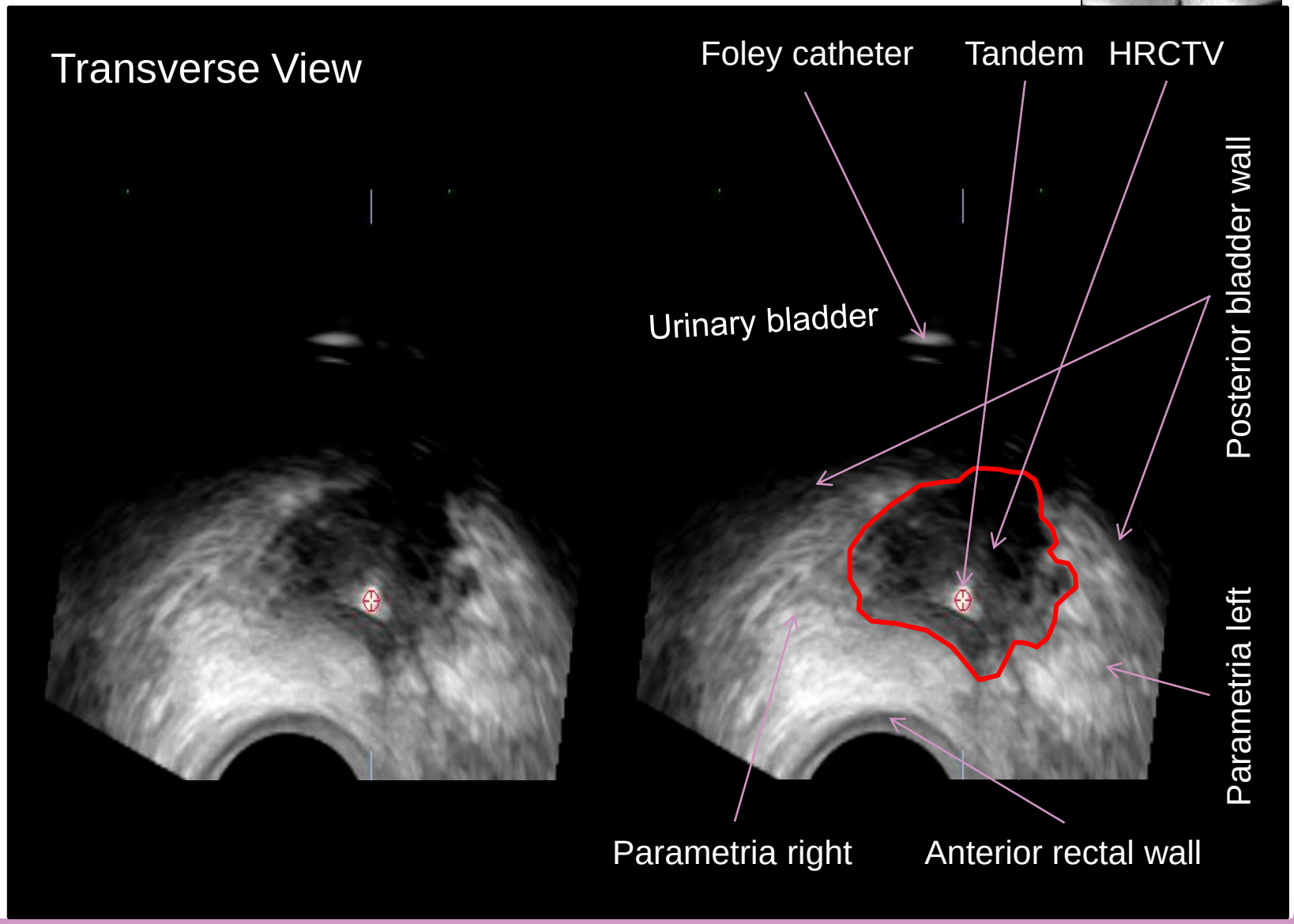
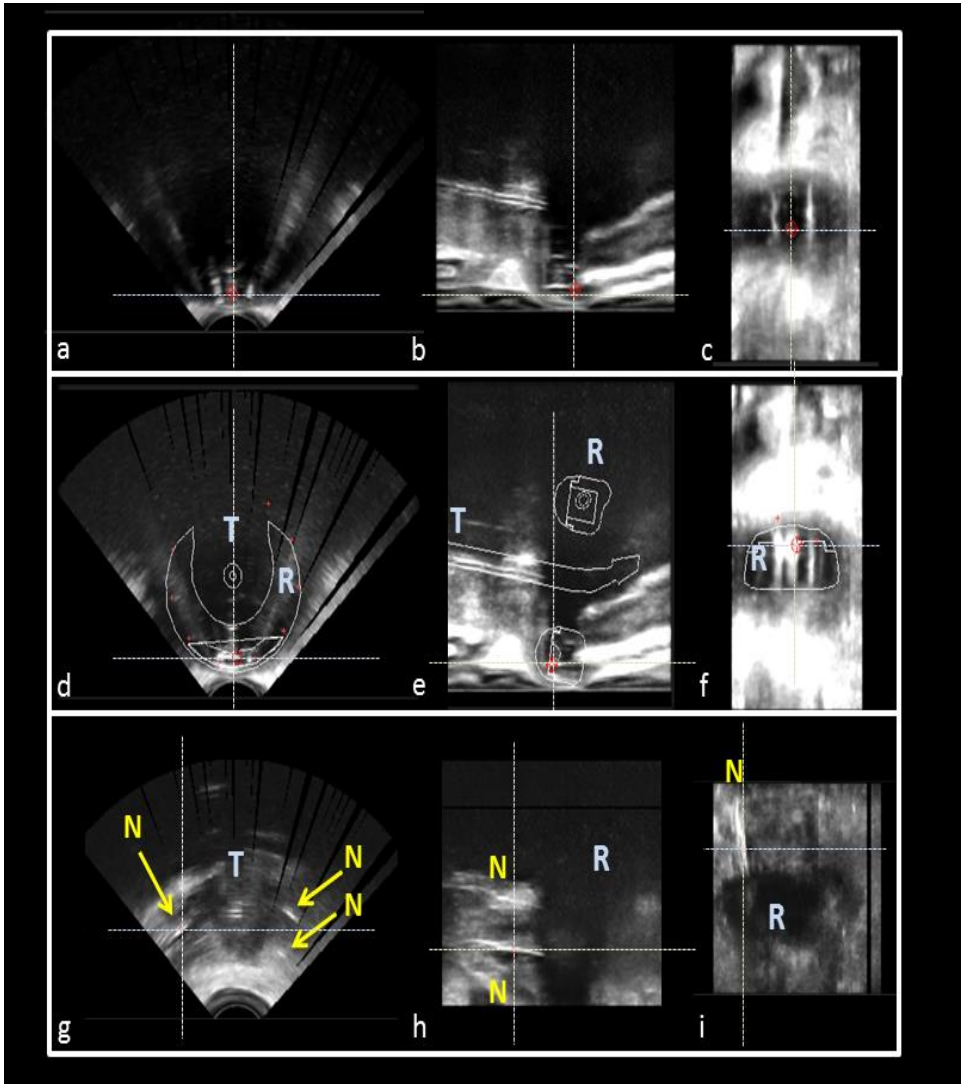


Image quality: TRUS-preBT: 2.9, TRUS-BT: 2.3, MRI-preBT: 2.9, MRI-BT: 2.7, CT-BT: 2.1

Direct applicator reconstruction on TRUS – large uncertainties



transversal sagittal coronal

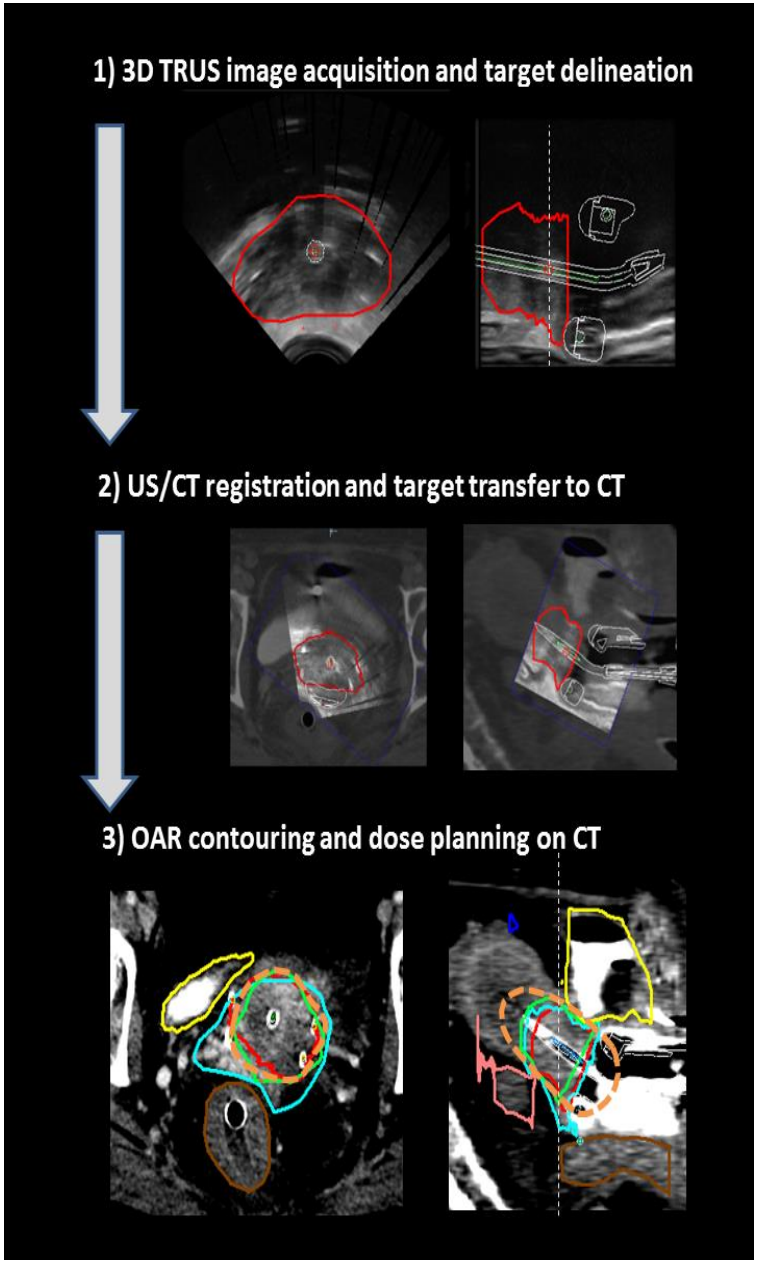
Ring applicator only partly visible

Tandem tip beyond FOV (probe dimensions optimized for prostate imaging)

Needle depiction quality as high as for prostate BT

Possible solution: TRUS acquisition + online applicator tracking

Nesvacil et al, Brachytherapy 2016,



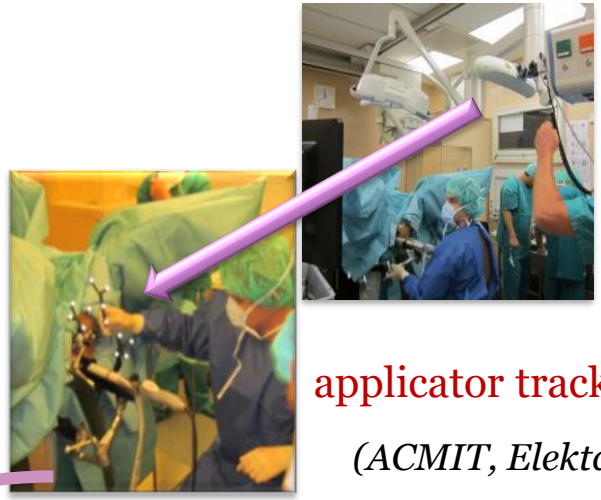
- Workflow for combination of TRUS and CT for treatment planning under investigation
  - Applicator reconstruction (automatic)
  - Fusion with CT
  - Delineation of target on TRUS/CT
  - OARs delineation on CT
- Method is expected to produce dose distributions that are more comparable with MRI-only, than the CT-only method.

Target volume comparison: blue (CT), green (MRI), red (TRUS)

Transrectal ultrasound for target definition in CT-based cervix cancer IGABT (no access to MRI @BT)

pre-implant scan, TRUS guidance of implantation

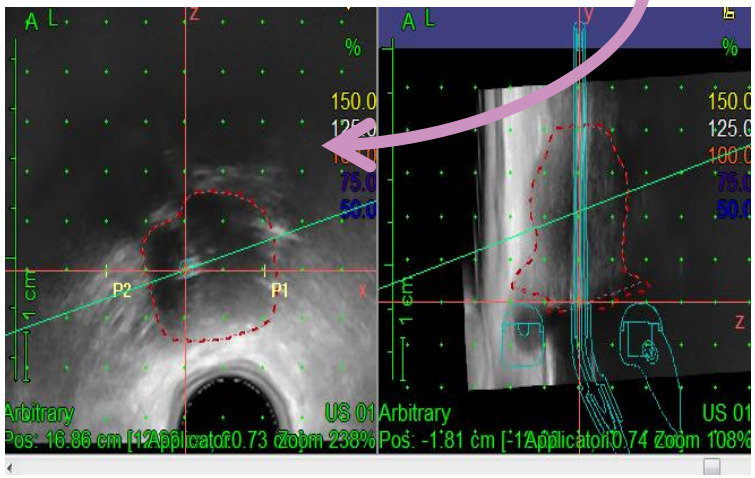
volumetric post-implant scan



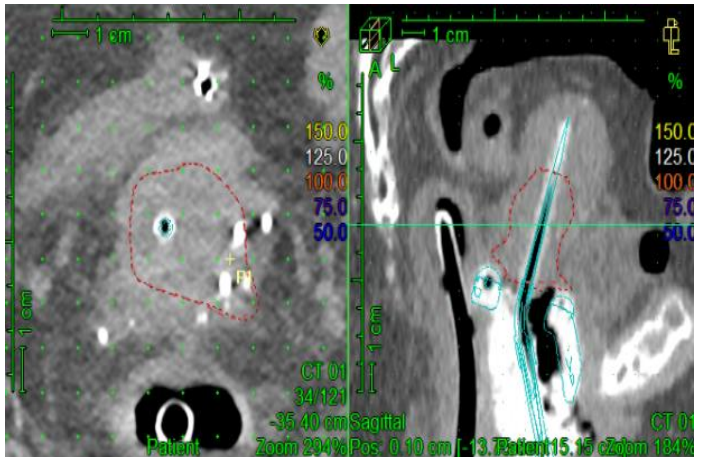
applicator tracking

(ACMIT, Elekta)

TRUS target delineation



TRUS-CT registration via applicator



- main uncertainty: tracking, QA

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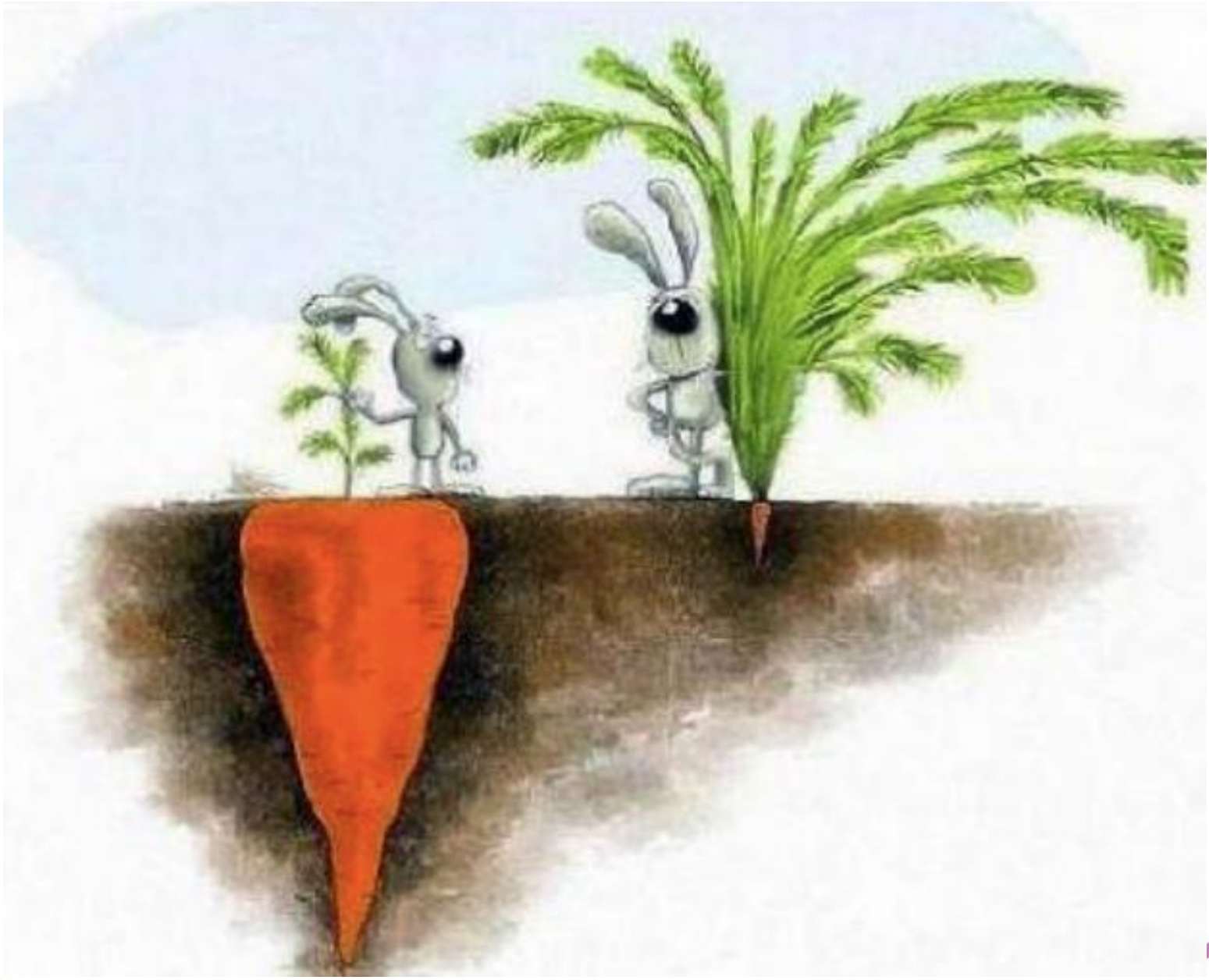
“**Fusion** leads to Con**fusion**”



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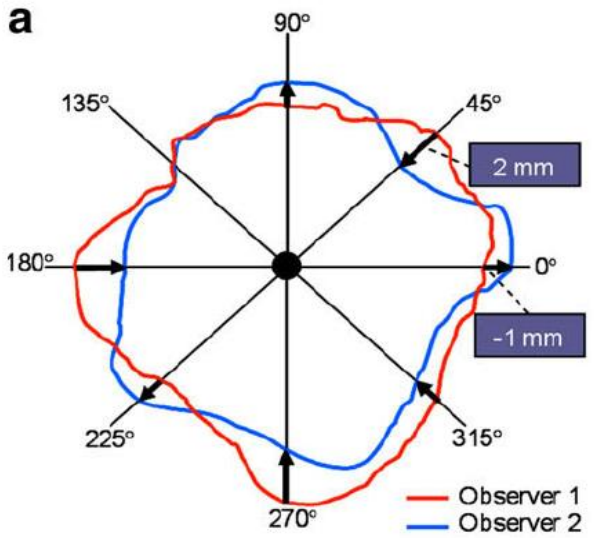
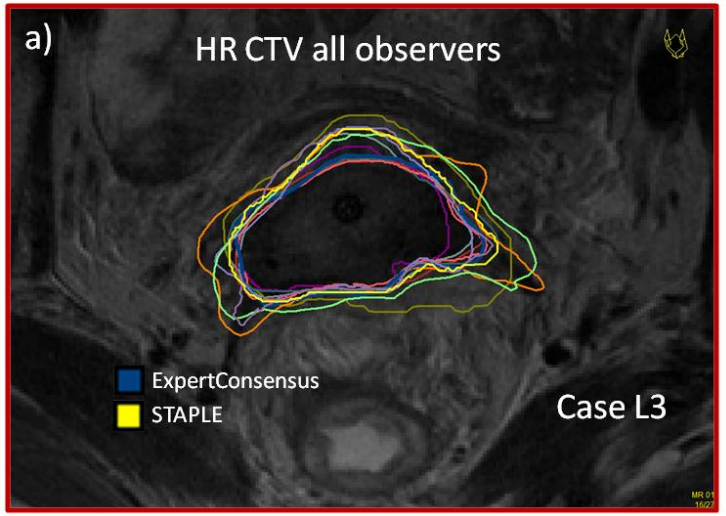
Inter- and intra-fraction uncertainties and in brachytherapy

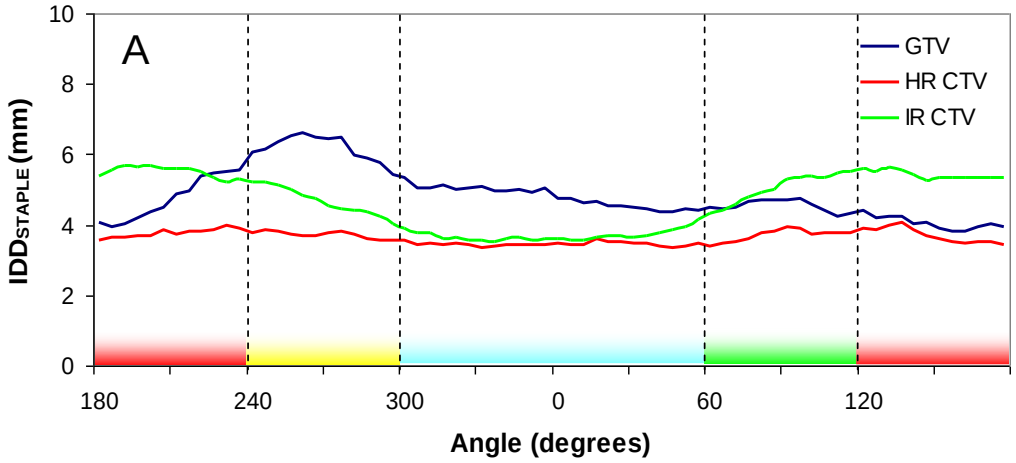
Kari Tanderup and Nicole Nesvacil

Contouring uncertainties CTV_{HR} on MRI

- CTV_{HR}:
  - Mean deviation <4mm
- GTV, CTV_{IR}:
  - Mean deviation <6–7mm



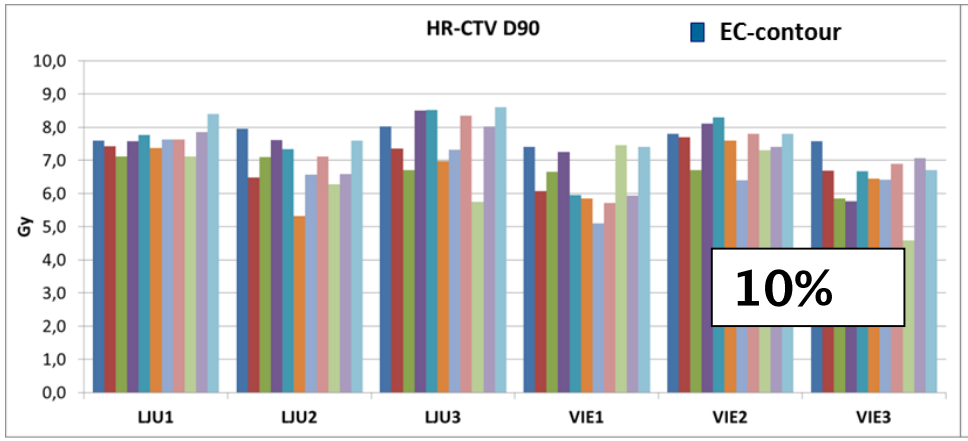


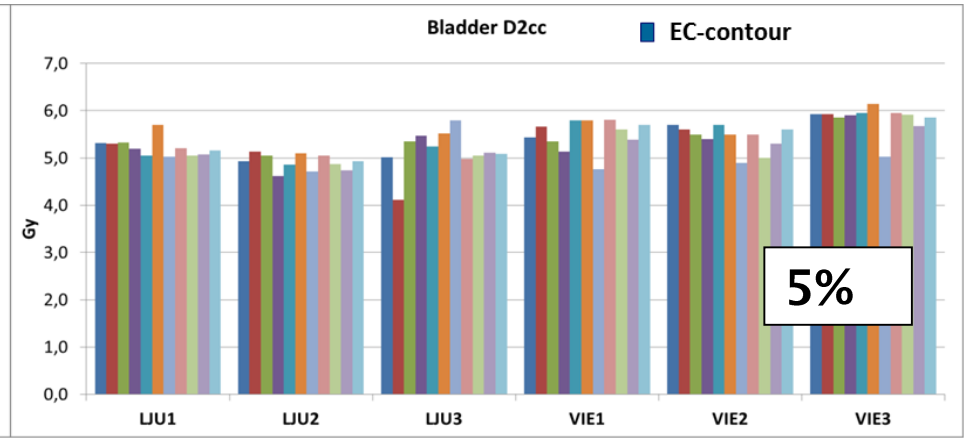


Petric et al, R&O 2008

Petric et al. Radiother Oncol. 2013 Apr;107(1):6-12

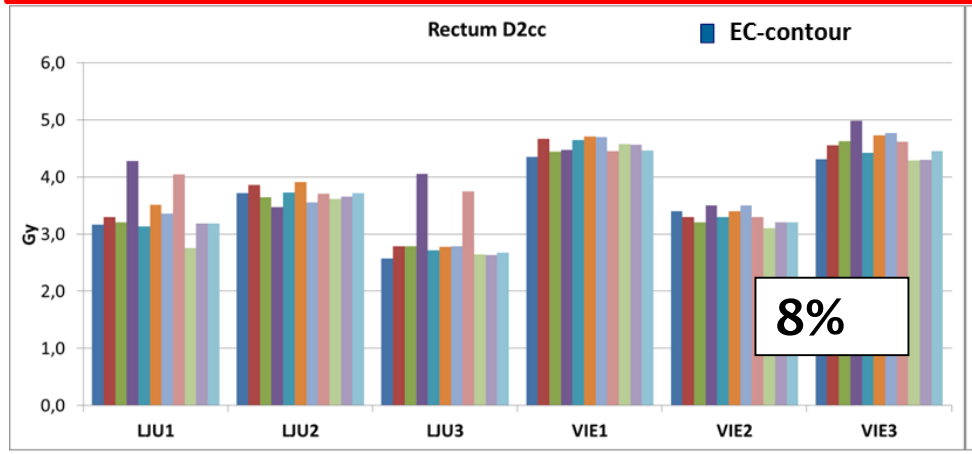
Impact of contouring uncertainties on dose

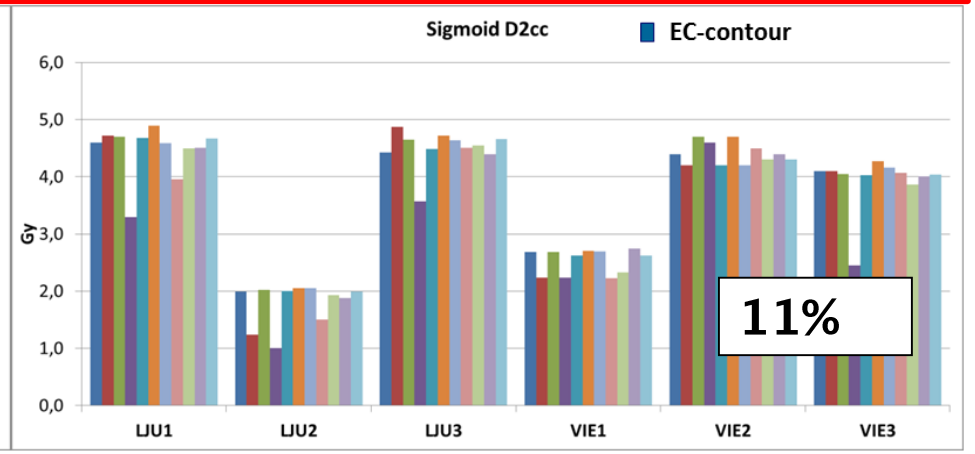




Mean (Gy)	7,59	6,80	7,61	6,34	7,51	6,31
SD (Gy)	0,38	0,70	0,95	0,81	0,59	0,74
Rel.SD (%)	5,0	10,3	12,5	12,7	7,9	11,7

Mean (Gy)	5,21	4,91	5,17	5,5	5,4	5,82
SD (Gy)	0,20	0,18	0,45	0,34	0,26	0,30
Rel.SD (%)	3,9	3,6	8,7	6,2	4,9	5,2





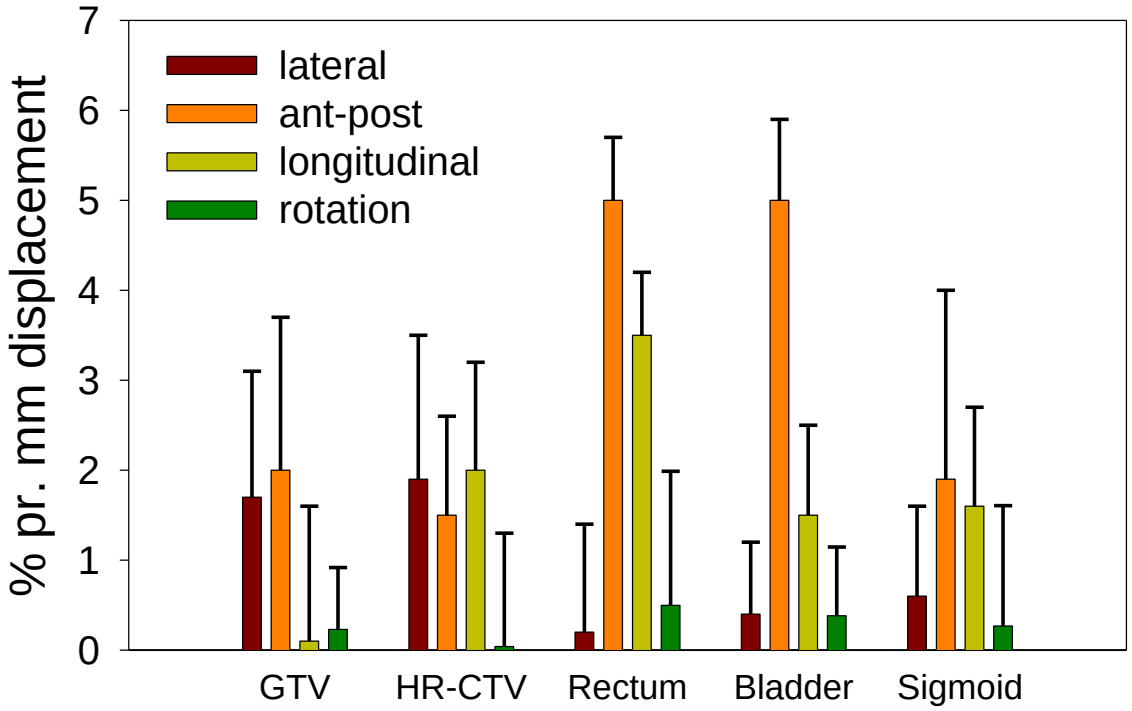
Mean (Gy)	3,39	3,68	2,96	4,57	3,30	4,57
SD (Gy)	0,45	0,13	0,51	0,11	0,13	0,22
Rel.SD (%)	13,3	3,6	17,1	2,4	4,0	4,8

Mean (Gy)	4,45	1,77	4,51	2,51	4,41	3,91
SD (Gy)	0,47	0,38	0,35	0,22	0,20	0,52
Rel.SD (%)	10,6	21,6	7,9	8,9	4,6	13,4

Hellebust et al, Radiother Oncol. 2013 Apr;107(1):13-9

Reconstruction uncertainties

- Evaluation of the impact of reconstruction uncertainties on DVH parameters (mean and standard deviation)

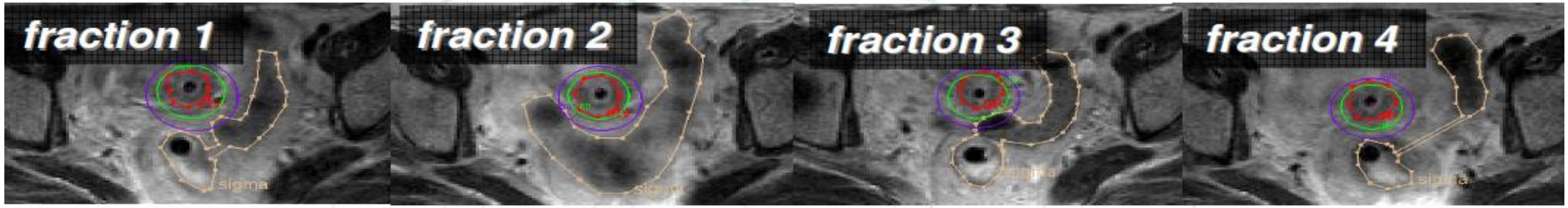


Tanderup et al, Radiother Oncol. 2008 Nov;89(2):156-63

Random dosimetric variations during Brachtherapy

Same plan used for 4 fractions, anatomical changes between irradiations may lead to large random dosimetric uncertainties

Lang et al. 2013, Radiother Oncol



Results of a multicentre study between 6 centres with different treatment/ application techniques (Nesvacil et al. 2013, Radiother Oncol 107 and references therein) :

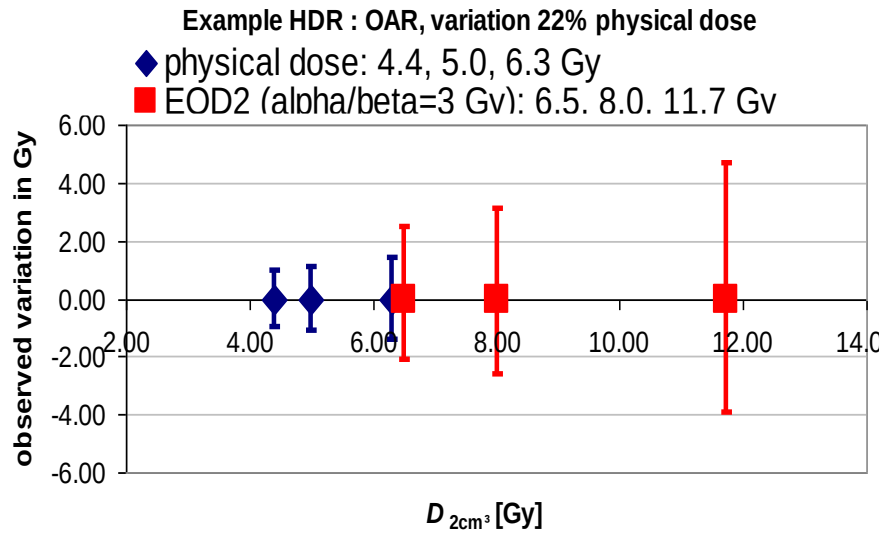
De Leeuw et al.; Hellebust et al.; Anderson et al.; Mohamed et al.; Lang et al.; Jamema et al.

			Bladder SD D2cc			Rectum SD D2cc			Sigmoid SD D2cc			HR CTV SD D90
total	2.7	1.5	**20.3%**	4.5	4.1	**22.0%**	1.6	-0.9	**26.8%**	-1.1	-1.7	**13.1%**
Intraaplication	1.3	1.5	17.7	3.8	2.3	20.5	-2.3	-3.7	23.5	-2.5	-4.3	10.8
interapplication	3.9	0.0	22.3	5.8	5.2	23.2	6.8	3.7	30.2	0.4	-0.8	15.1

Note: Changes correspond to physical dose change between 2 time points during course of BT. Effect on total EQD2 (EBRT+BT) depends on fractionation schedule (PDR, HDR, …)

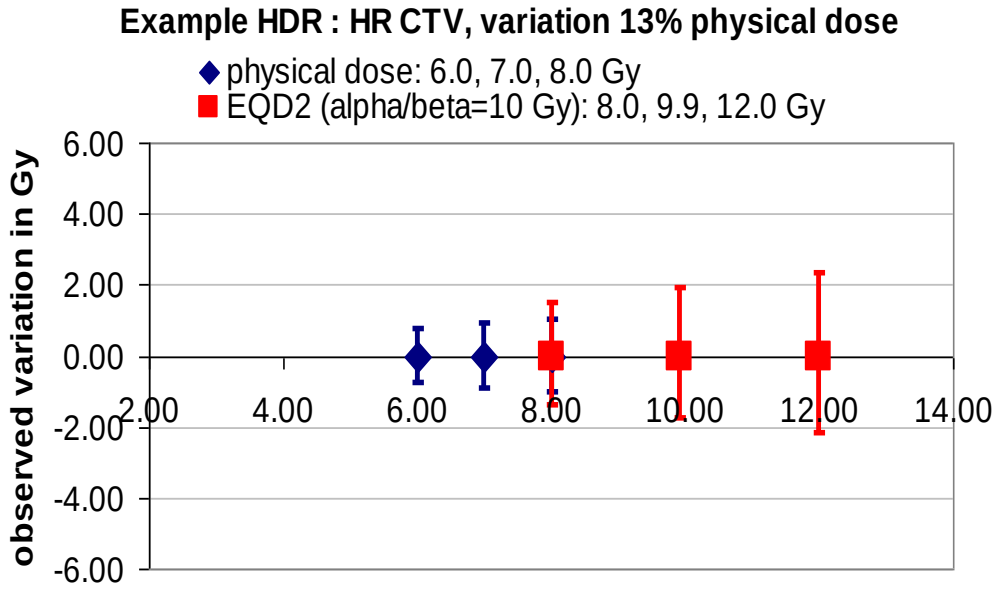
Nesvacil et al, Radiother Oncol. 2013 Apr;107(1):20-5

Translating random uncertainties to EQD2: single fraction dose



OAR
(SD 22%)

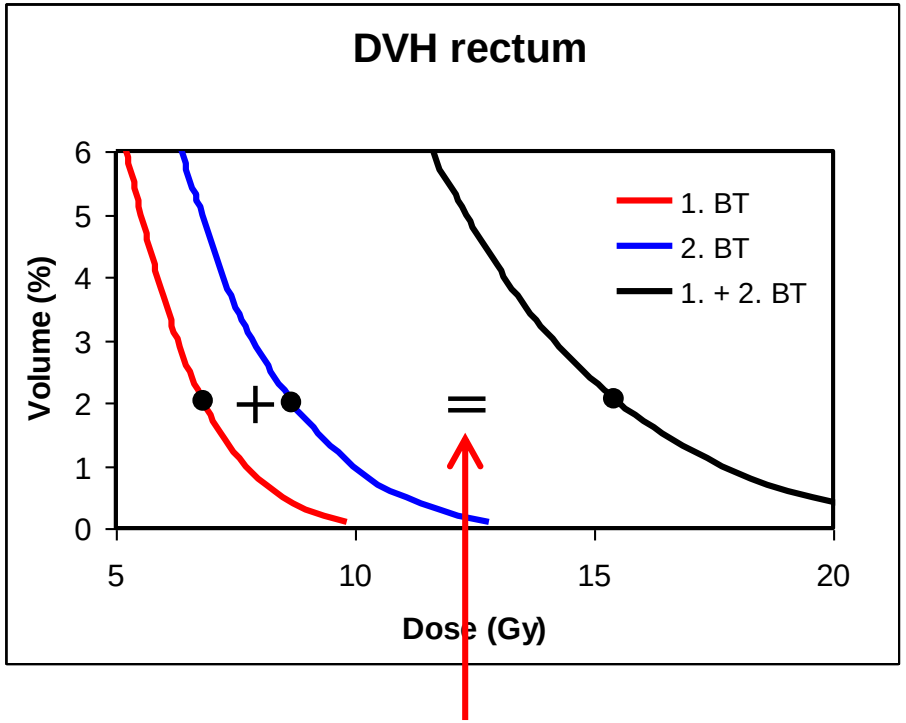
At higher EQD2 doses error bars become asymmetrical!



HR CTV
(SD 13%)

The impact of uncertainty on the total treatment dose depends on the fractionation scheme!

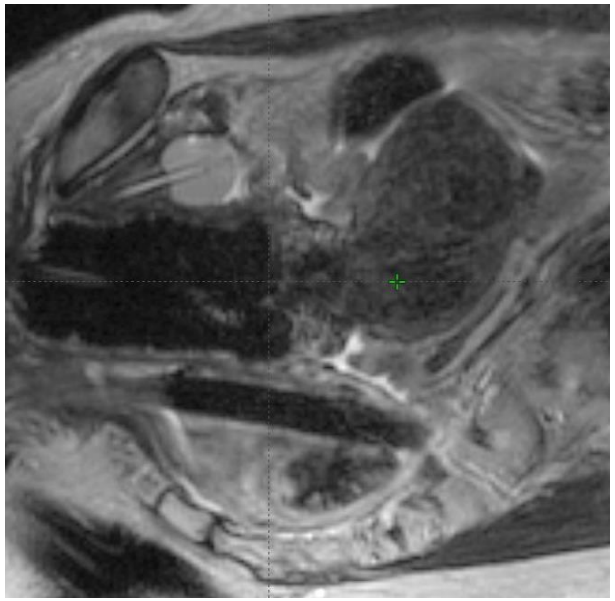
”Worst case assumption”
Calculation of DVH for several fractions

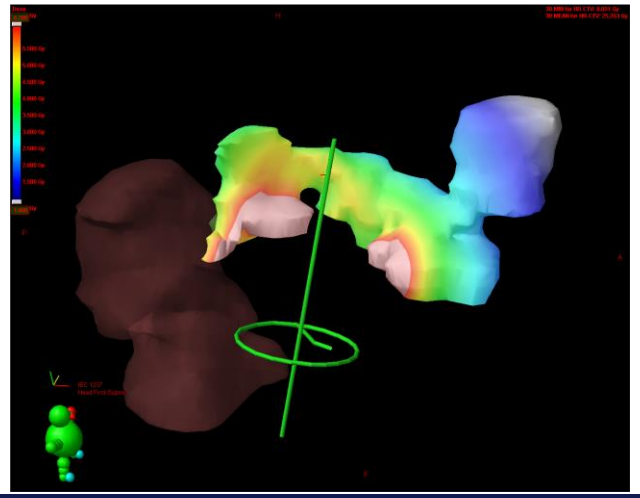


Approximation
”Worst case assumption” or DVH addition

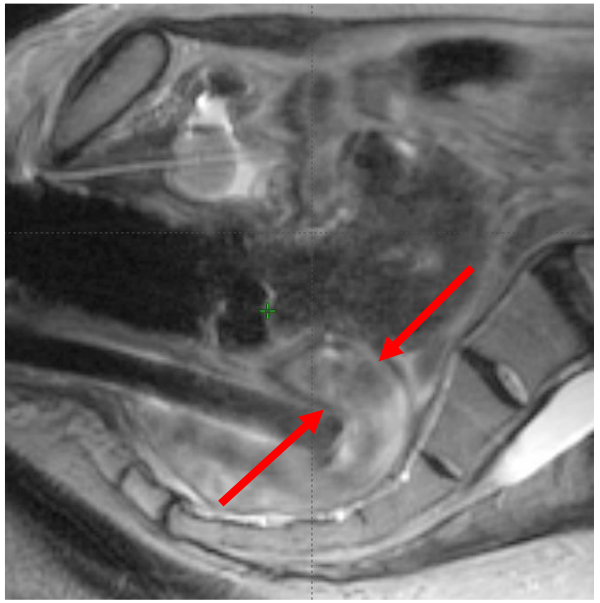
Different location of hotspots

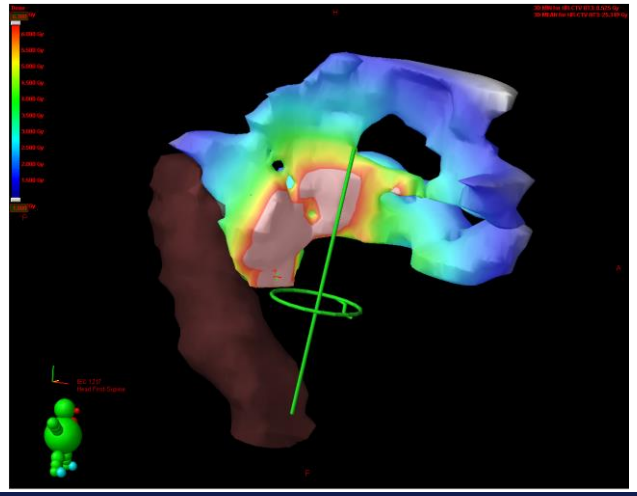
1. BT





2. BT





Influence of organ deformation

- Sigmoid
  - Highly mobile
  - DVH calculation conservative
- Rectum and bladder
  - Less mobile

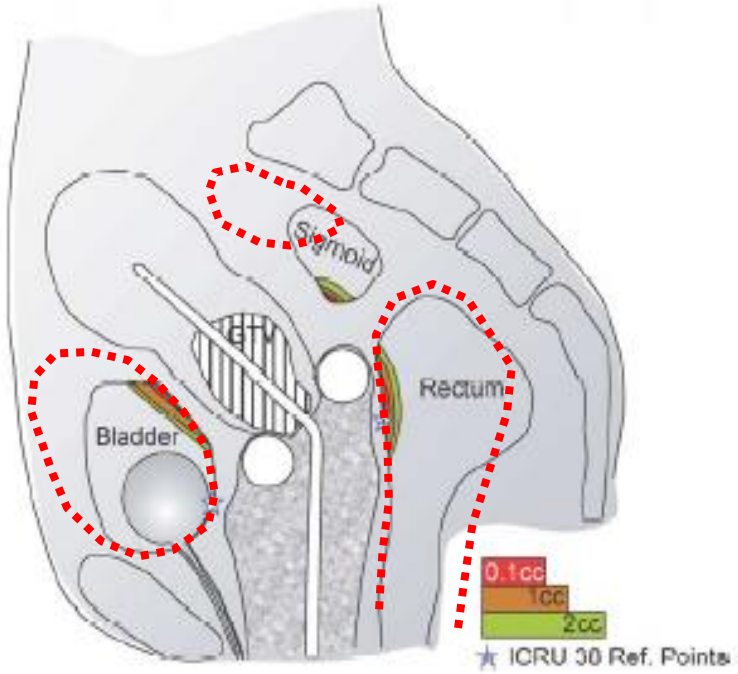


Table 2
Summary of results of spatial location of D_{2cm^3} hot spot region for each of the OAR.

Categories	Rectum ($n = 27$)	Bladder ($n = 27$)	Sigmoid ($n = 27$)
1. Overlapping region >50%	16	8	3
2. Overlapping region 10–50%	7	14	9
3. Overlapping region <10%/no overlap	4	5	15

Jamema S et al, Radiother Oncol. 2013 Apr;107(1):58–

DVH addition

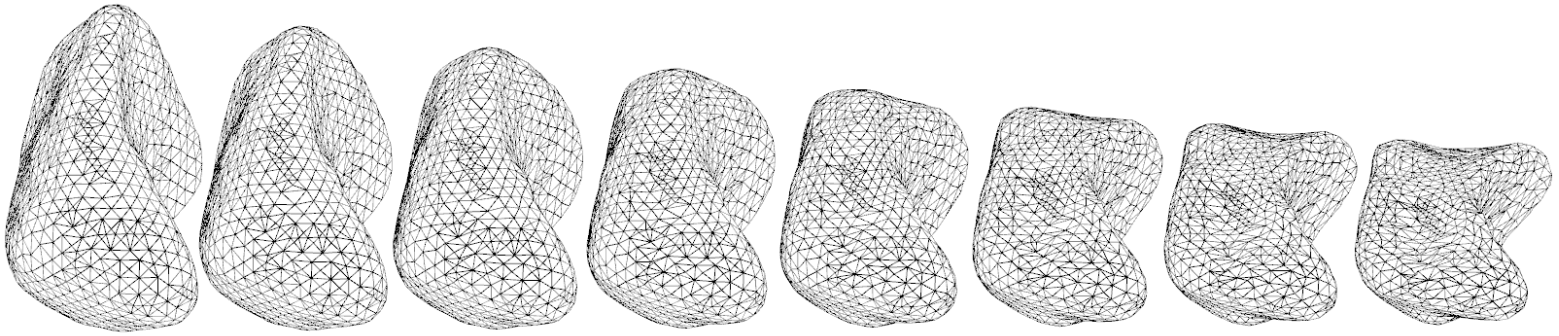
- Bladder and rectum dose:

$$BT_{total} = BT1 + BT2 + BT3 + BT4$$

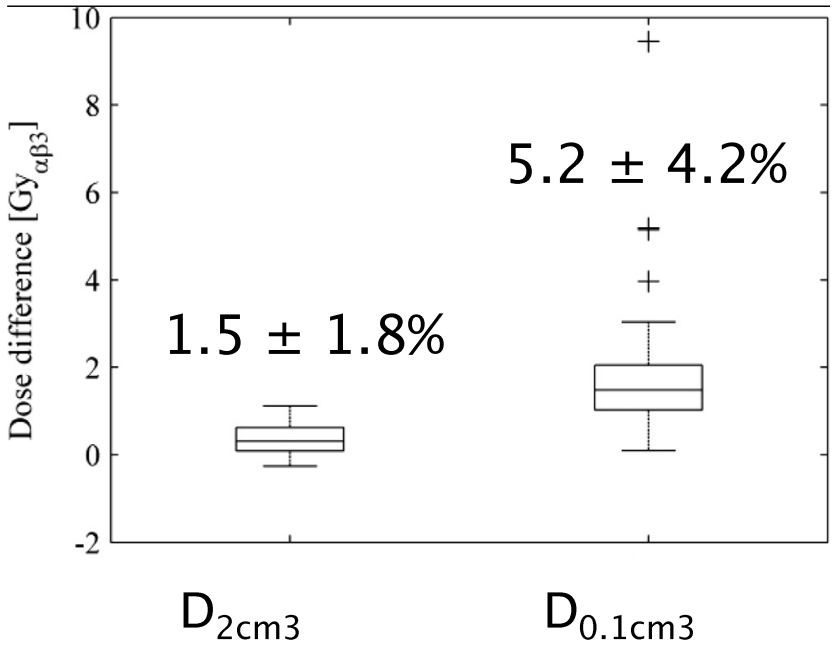
- Sigmoid dose potential over-estimation of dose:

$$BT_{total} < BT1 + BT2 + BT3 + BT4$$

Bladder dose accumulation with deformable registration (biomechanical)



Difference between DVH addition and 3D dose accumulation:

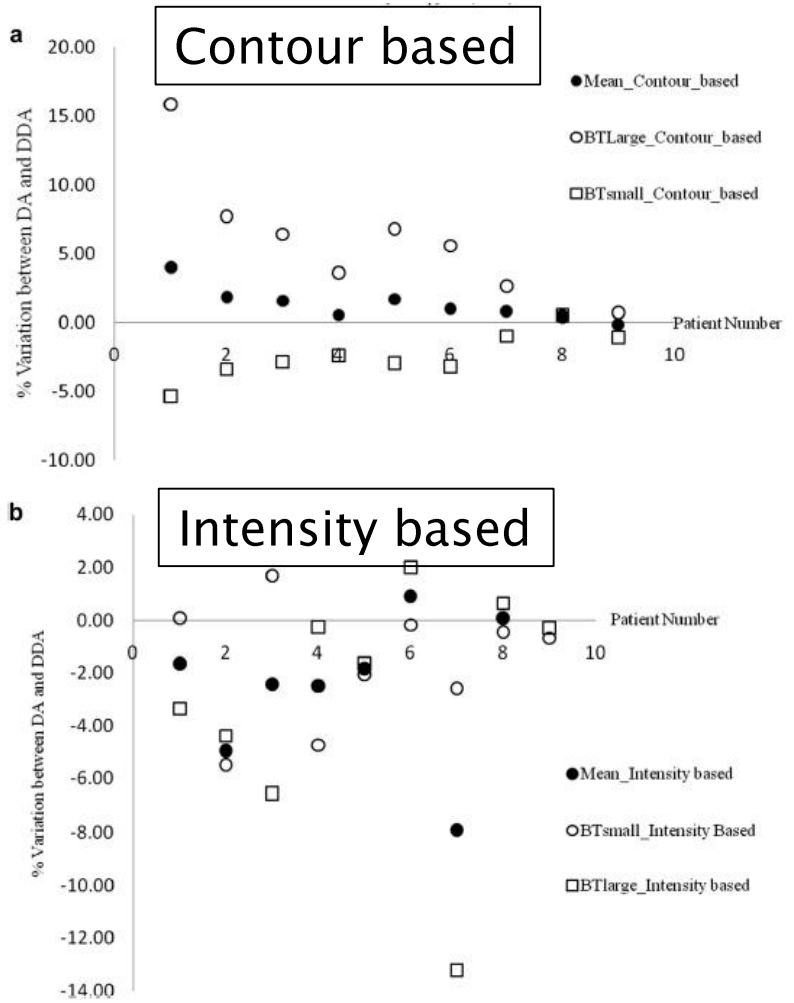


Andersen et al, Radiother Oncol. 2013 Apr;107(1):52

Pitfalls DIR based dose accumulation: Consistency of results

- Dose accumulation with intensity based DIR may not be consistent

- In-consistent DIR may systematically underestimate dose



-> DIR has currently very high, unknown uncertainties.
Clinically not advised to use it for decision making!!!!

Jamema et al, Brachytherapy. 2015 Nov-Dec;14(6):953

The total uncertainty budget

- Radiotherapy and Oncology vol 107(1), 2013
- 19 papers on brachytherapy and mainly on uncertainties

Table 1
Uncertainty budget (SD) for one intracavitary brachytherapy fraction. The overall uncertainty for the entire treatment course is depending on the fractionation schedule and level of verification.

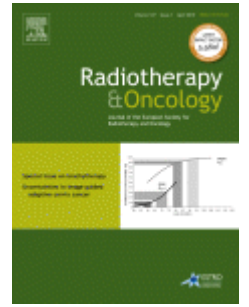
	Target (HR CTV D90)	OARs (D_{2cm^3})
Source strength	2%	2%
Dose and DVH calculation	3%	3%
Dwell position uncertainty (reconstruction and source positioning)	4%	4%
DVH addition across fractions (previously called "worst case assumption")	NA	1%[a]–?%
Contouring (inter-observer)	9%	5–11%
Intra- and inter-fraction (intra-application) uncertainties[b] (5)	11%	20–25%
Total[c]	12%	21–26%

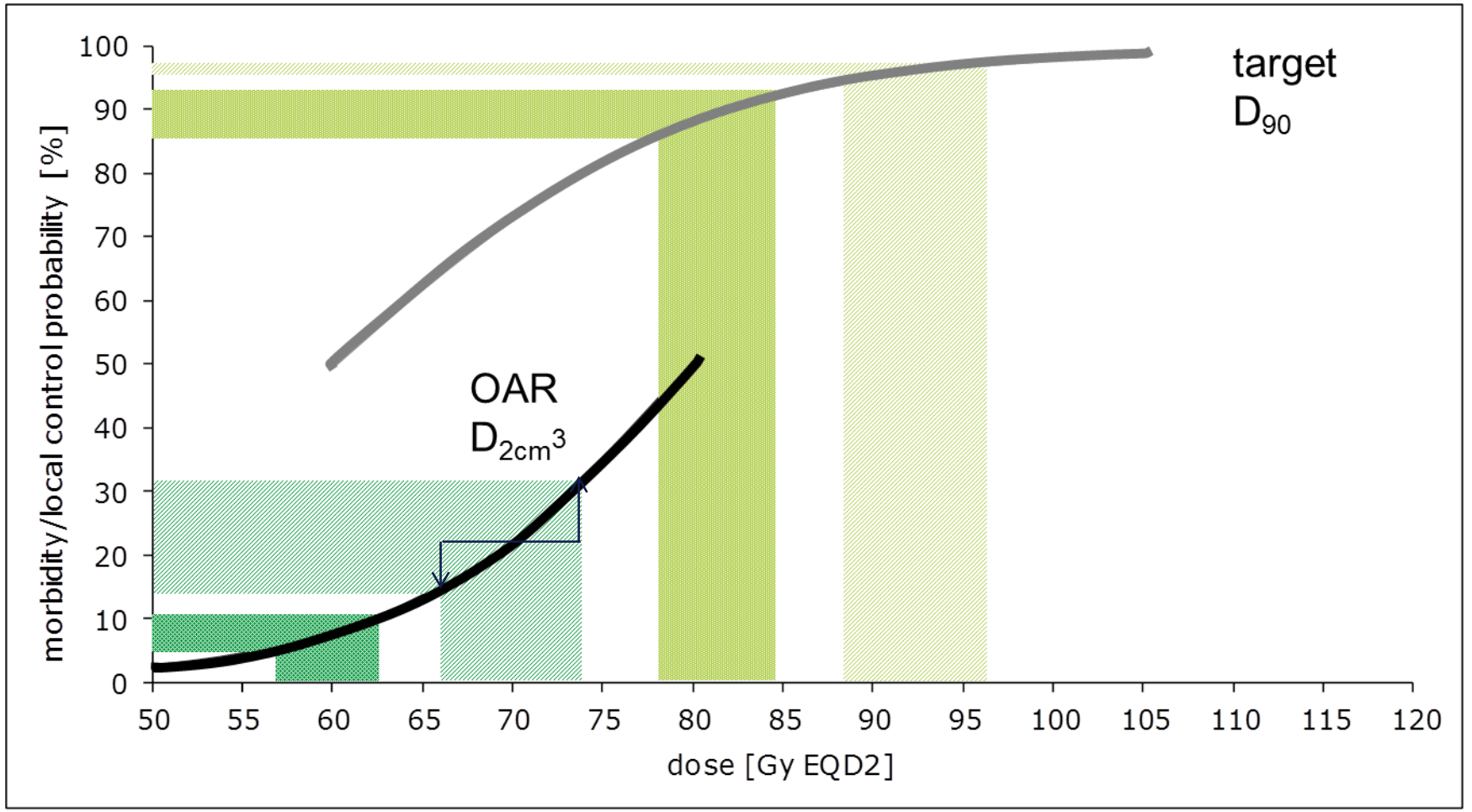
[a] For the bladder and likely rectum, whereas it has not been evaluated for sigmoid.
[b] Per se including intra-and inter-observer contouring variations.
[c] Contouring uncertainties included through intra- and inter-fraction uncertainties.

Examples total dose and uncertainty

- HR CTV: D90 = 90 ± 4Gy
- Bladder: D_{2cm3} = 85 ± 7Gy
- Rectum: D_{2cm3} = 70 ± 4Gy
- Sigmoid: D_{2cm3} = 70 ± 7Gy

Dosimetric uncertainties and dose-response relationships





Schematic illustration of the effect of dosimetric uncertainties of prescribed vs. delivered dose on response probabilities.

Summary, Conclusion, Take Home Message

- Systematic uncertainties can be minimized by refining our clinical protocols for
  - Applicator reconstruction,
  - organ filling,
  - image acquisition (optimal image quality for applicator reconstruction and delineation at the same time)

- Random inter-/intra-fraction uncertainties are a dominant factor for the total uncertainty budget in gyn BT. They can be large and can be monitored by use of repetitive imaging workflows.

PRACTICAL EXAMPLE
VIE003JR

Large tumour, bad response to EBRT

LARGE TUMOUR, BAD RESPONSE

Overview

- *Initial findings*
  - Initial clinical findings
  - Initial MRI findings
  - Other
- *EBRT, chemotherapy*
- *Findings at BRACHYTHERAPY (BT)*
  - Clinical findings at BT
  - MRI findings at BT
- *Delineation of GTV, CTV and Organs At Risk (OAR)*

LARGE TUMOUR, BAD RESPONSE

Initial findings

Patient &Tumour

Patient:

41 years old

lap. LN-Staging:pN0

Tumour:

Histological type: SCC

FIGO stage: 2b

Initial clinical findings:

Portio:

Exo-/Endophytic tumour

Vagina:

not involved

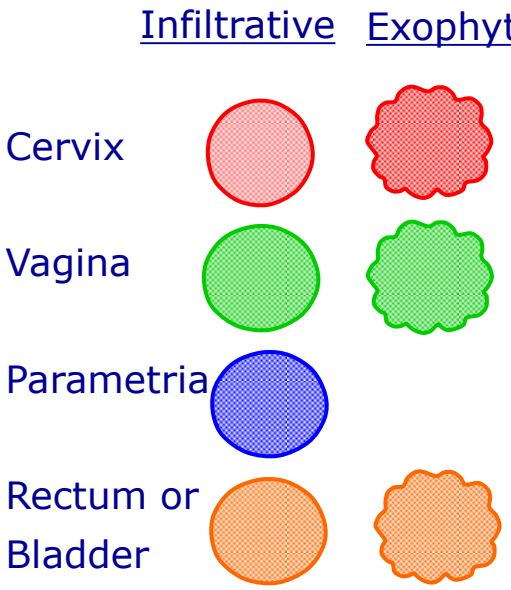
Parametria:

Right: proximal infiltration

Left: distal infiltration

Details: see *Initial Clinical Drawings* (next slide)

Clinical drawings at diagnosis



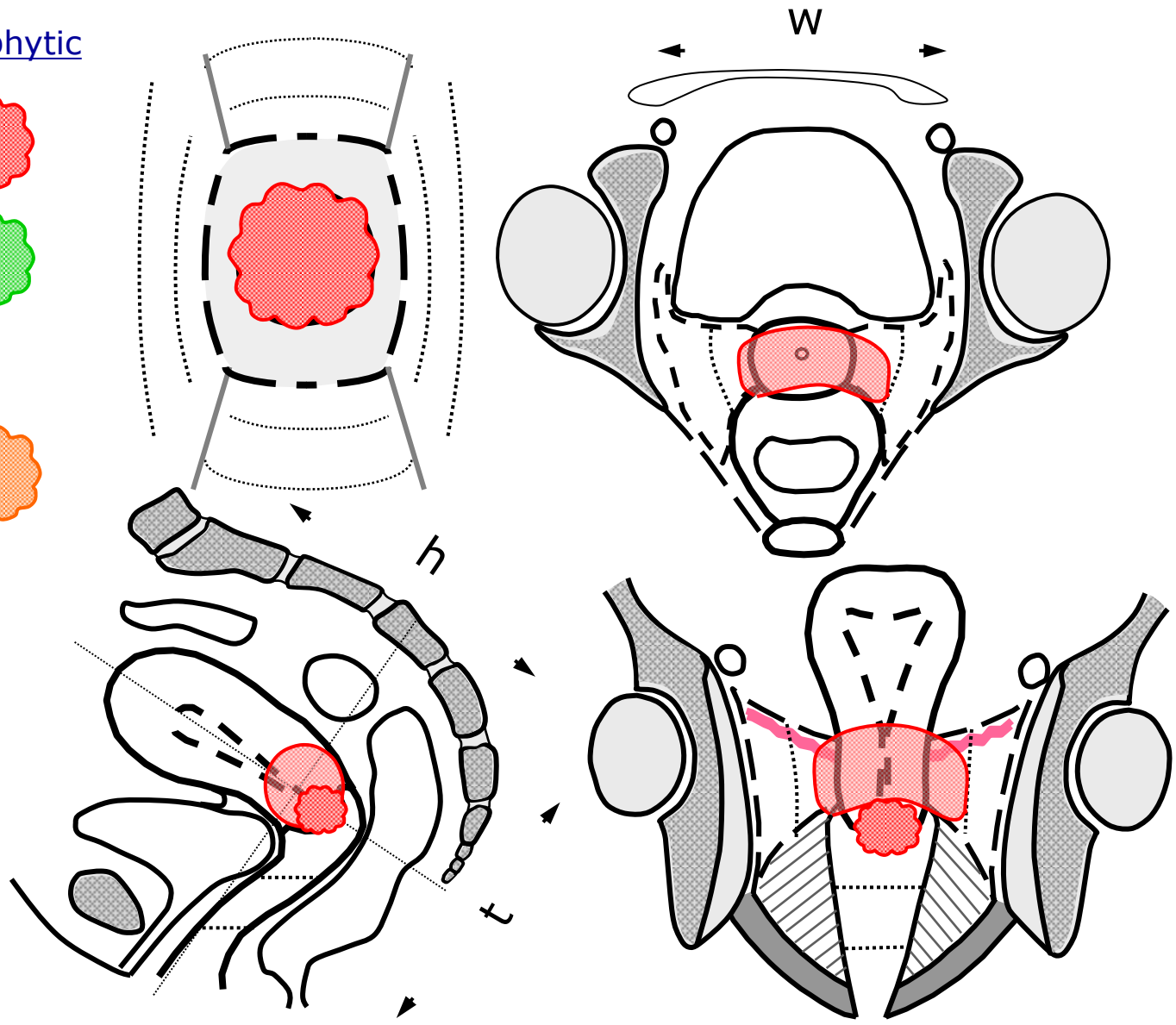
Tumour size:

Width: 5 cm

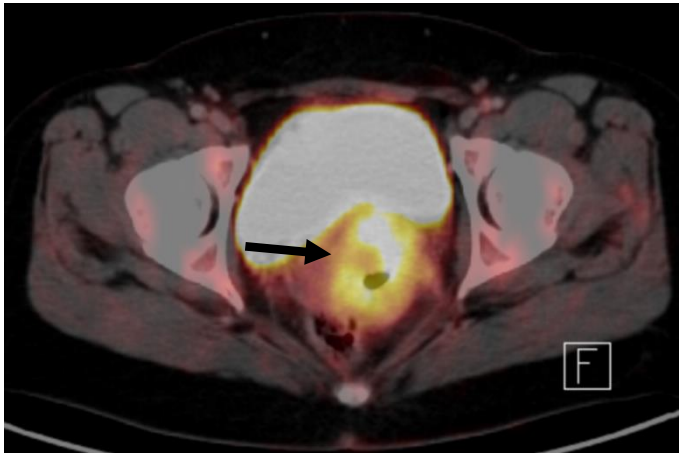
Thickness: 4 cm

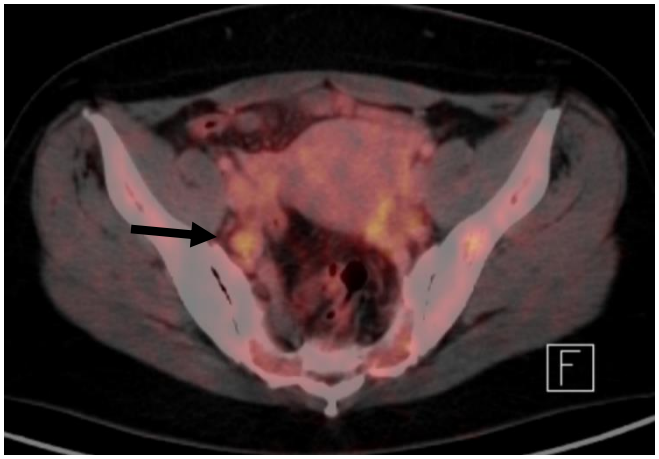
Height: 5 cm

Vaginal inv.: 0 cm



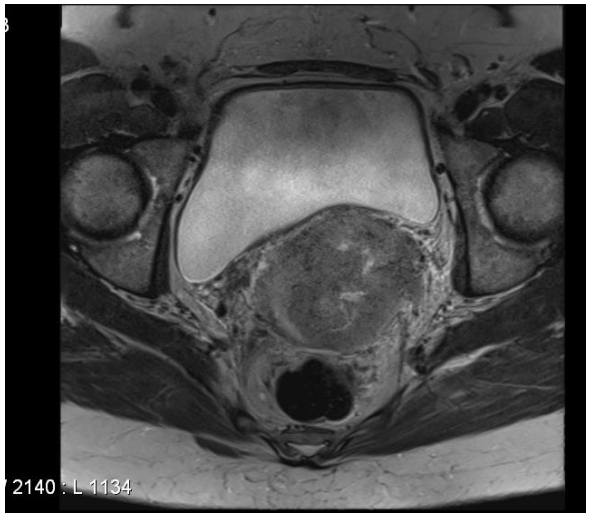
PET-CT findings at diagnosis

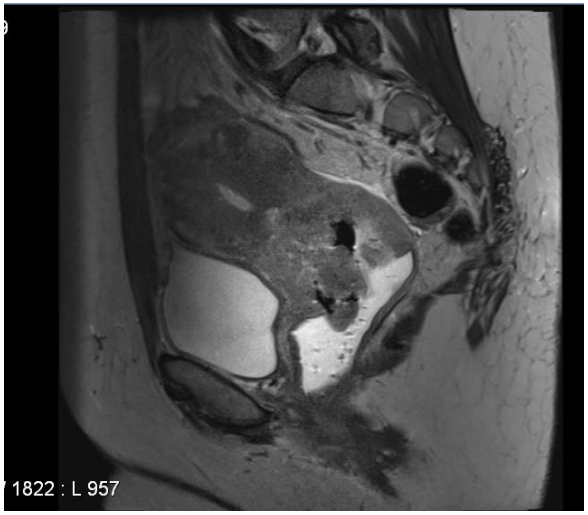


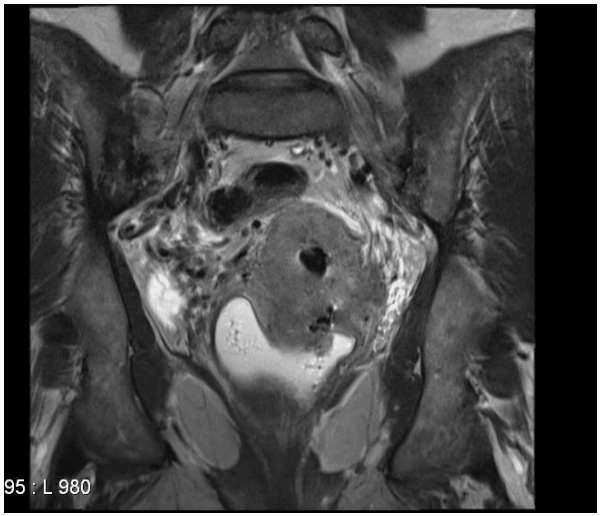


lap. Lymph node staging: 0/22 pos lymph nodes

MRI findings at diagnosis



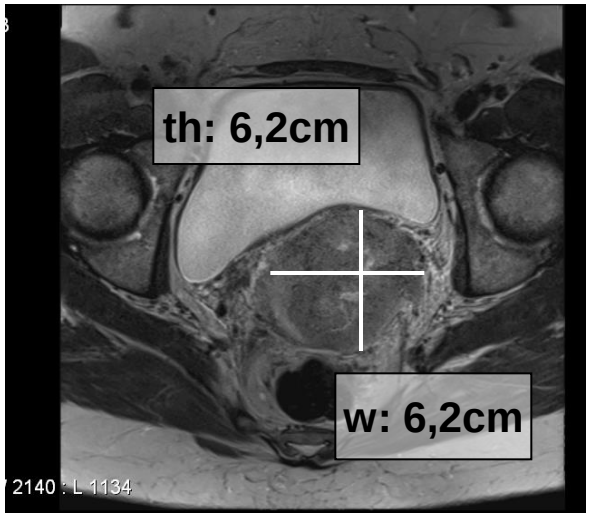


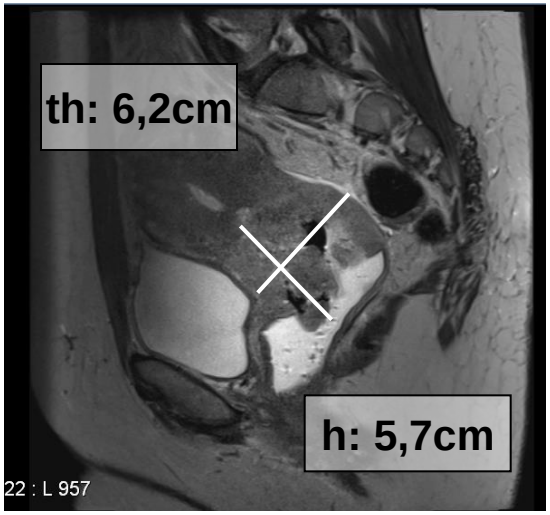


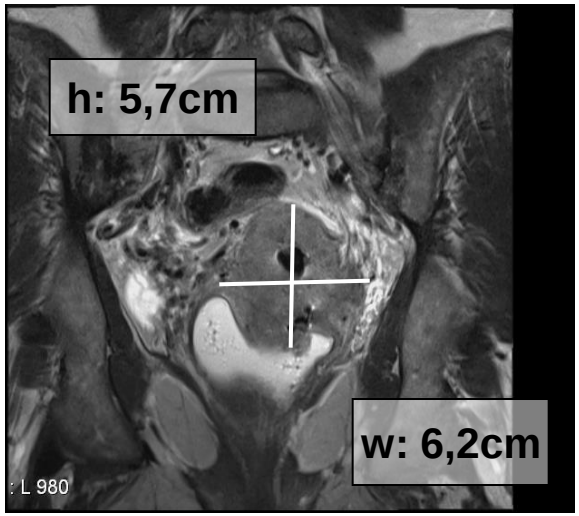
EBRT Treatment

EBRT: IMRT; pelvis
TD: 45 Gy
Concurrent cisplatin 40 mg/m², 5 cycles

MRI findings at diagnosis



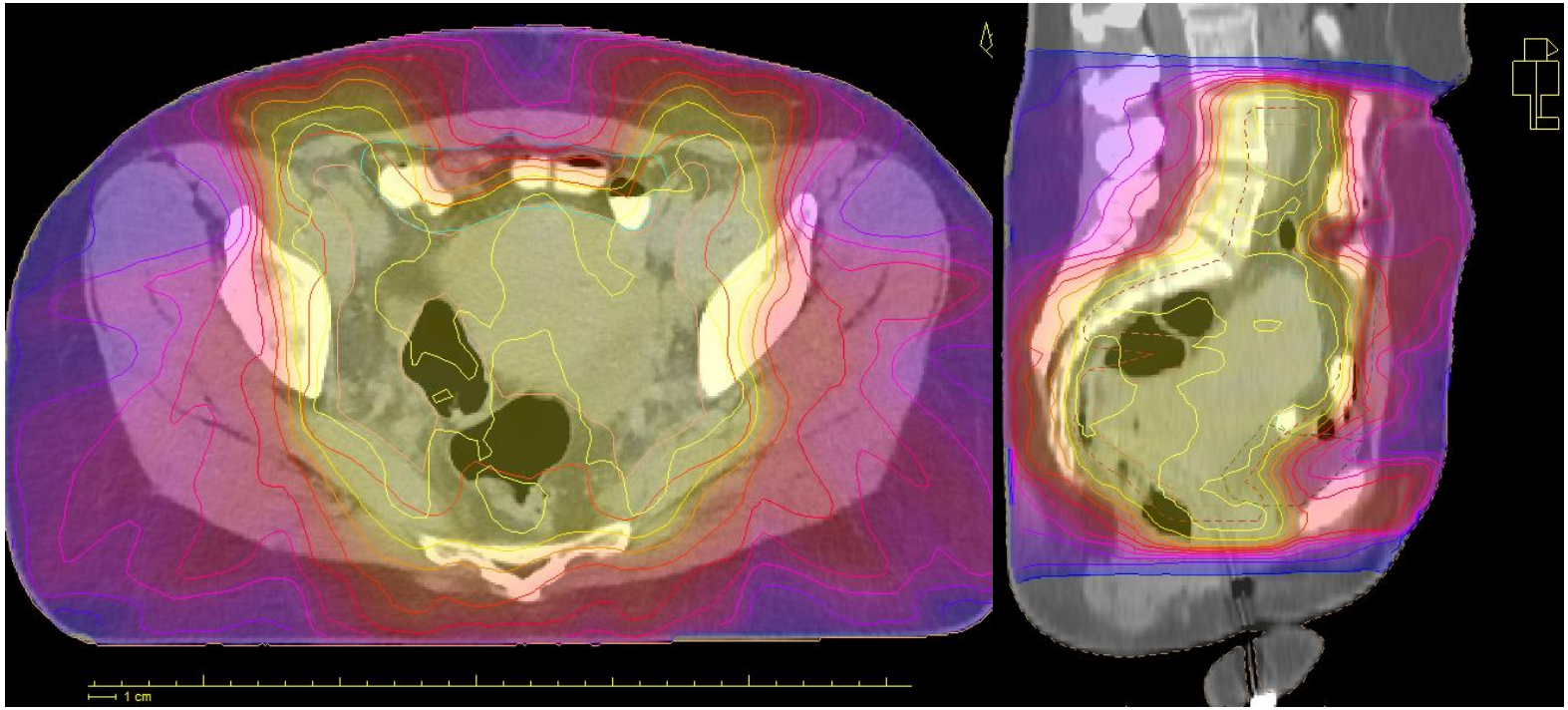




V=110cm³

Treatment

EBRT: IMRT; pelvis
TD: 45 Gy; 1.8Gy per fraction
Concurrent cisplatin 40 mg/m², 5 cycles
MRI-based adaptive BT: 7 Gy x 4 fractions – EQD2 > 85 Gy



LARGE TUMOUR, BAD RESPONSE

Findings at brachytherapy

(immediately following EBRT)

Clinical findings at BT

Portio:

minimal regression of exophytic part

Vagina:

≅ diameter (implications for selecting applicator diameter): Large

Involvement with tumour: No

Parametria:

Right: Proximal residuum

Left: Distal residuum

Details: see *Clinical Drawings at BT* (next slide)

Clinical drawings at BT

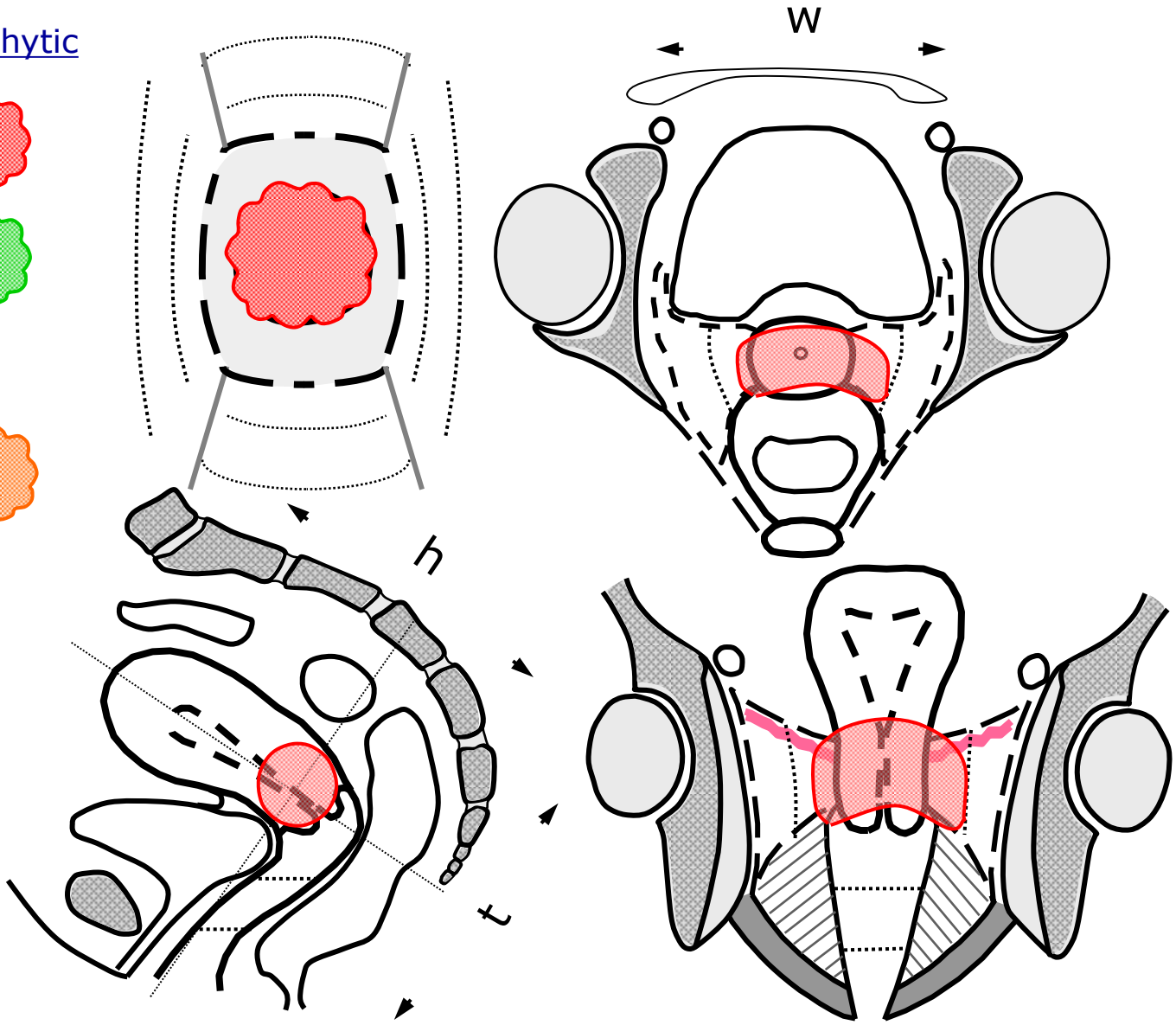
Infiltrative Exophytic

Cervix

Vagina

Parametria

Rectum or Bladder



Tumour size:

Width: 5 cm

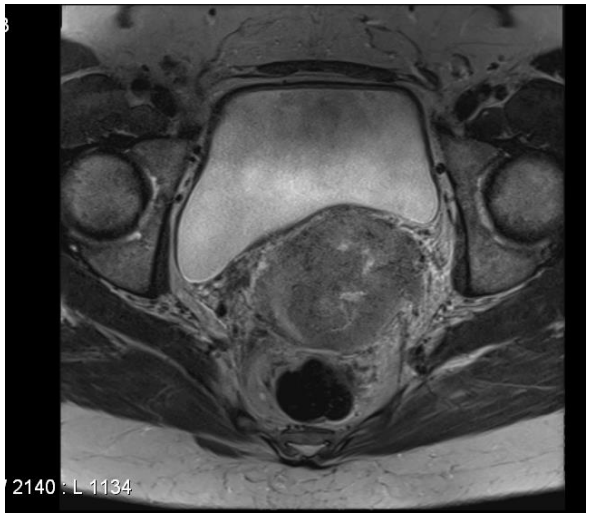
Thickness: 4 cm

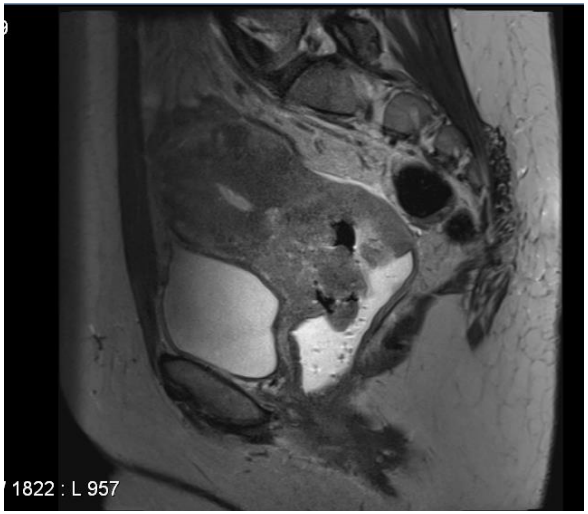
Height: 5 cm

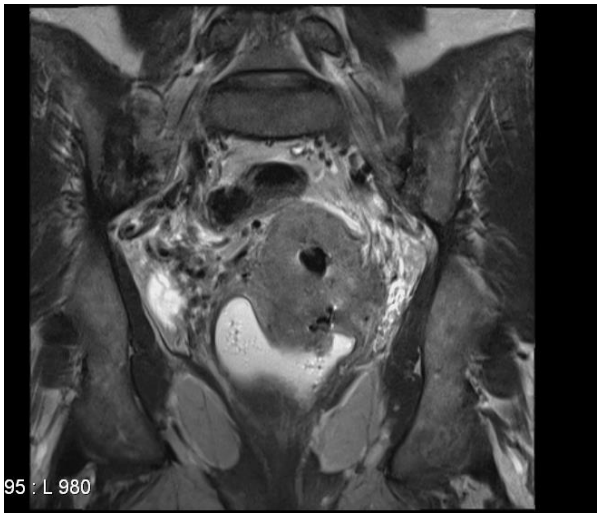
Vaginal inv.: 0 cm

MRI findings

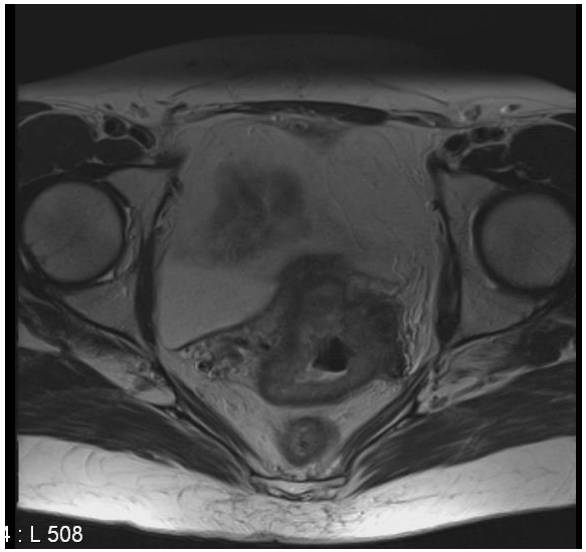
Diagnosis

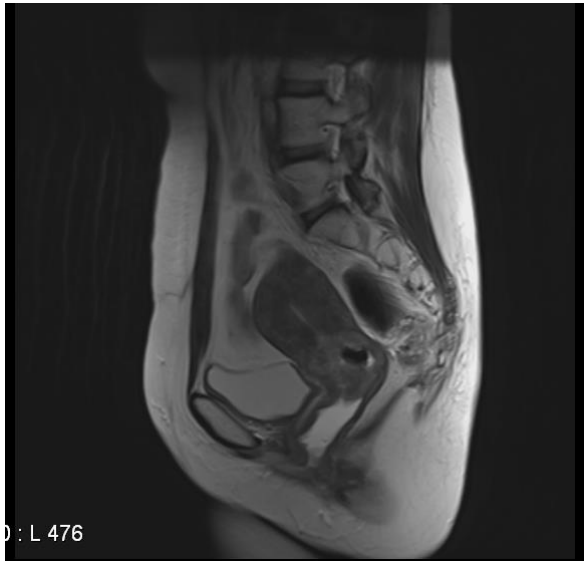


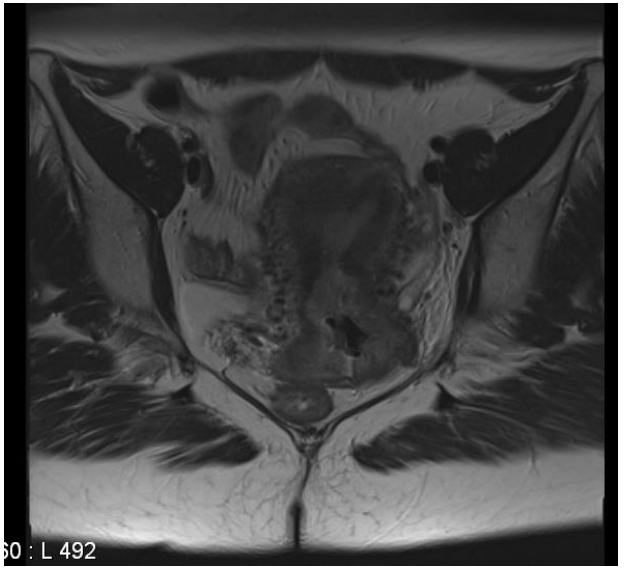




Before BT EBRT Dose 34.2Gy

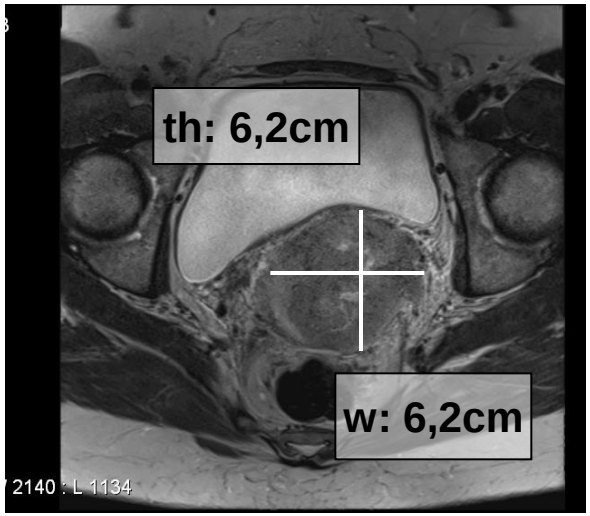


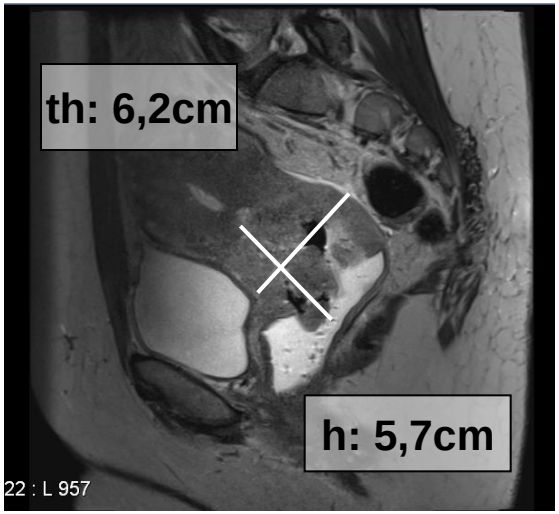


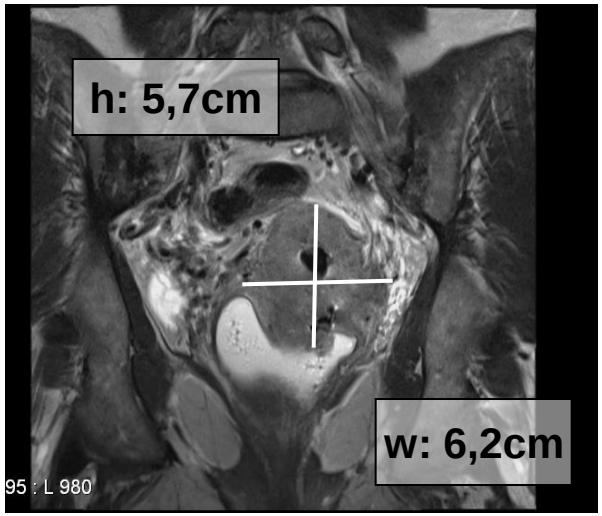


MRI findings

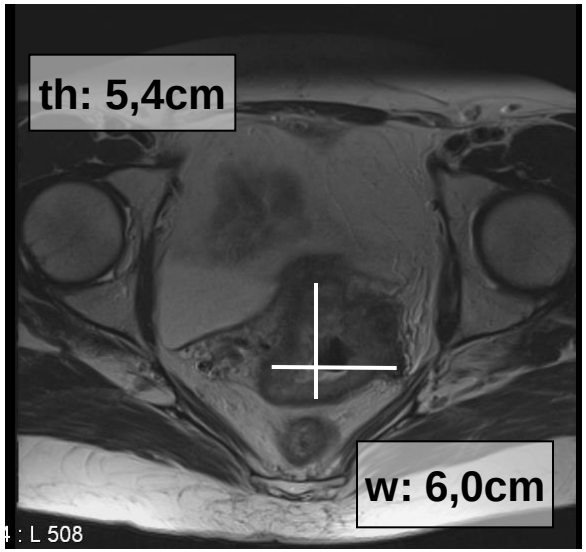
Diagnosis $V=110cm^3$

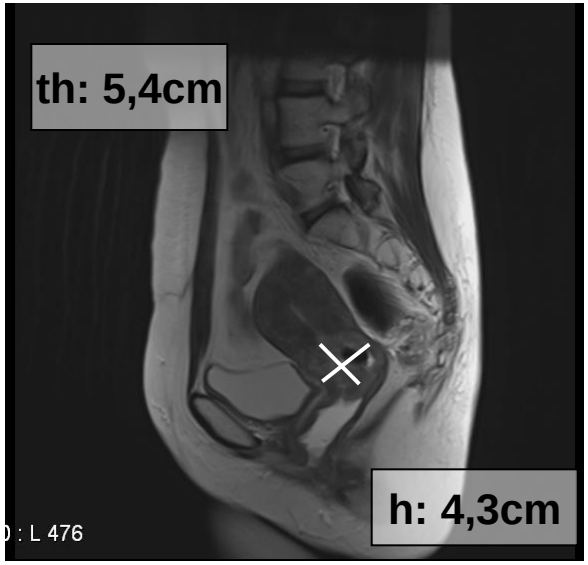


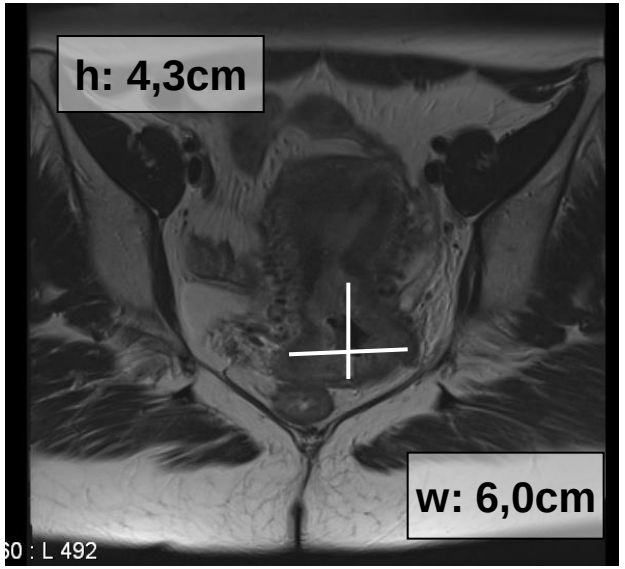




Before BT $V=70cm^3$







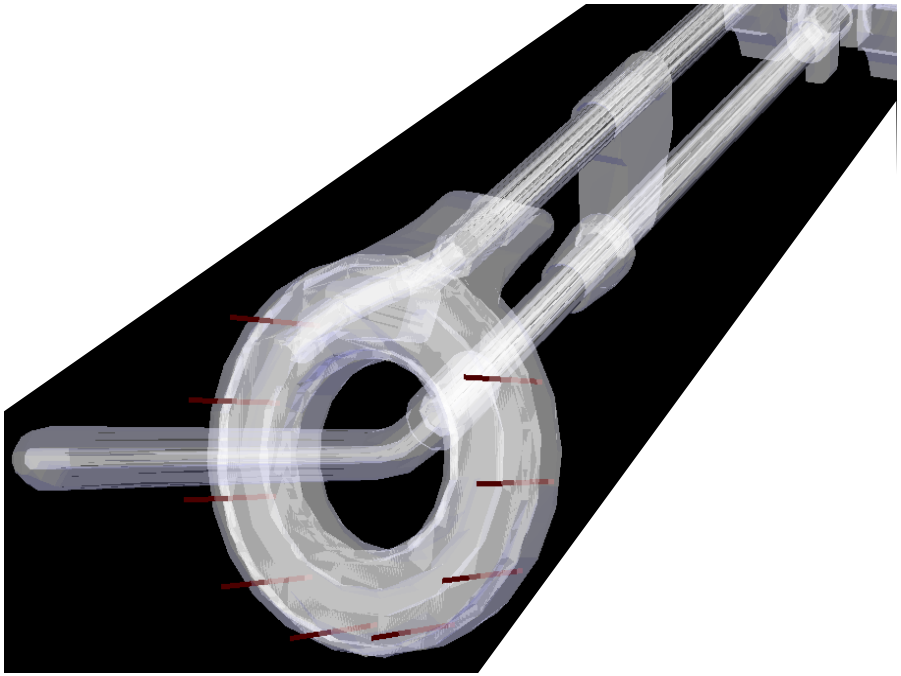
Insertion & imaging

Anaesthesia: epidural

Application:

Intracavitary component:

- Tandem length: 60 mm
- Tandem angle: 60º
- Ring diameter: 34 mm
- Material: plastic
- Comments: Vienna II.



Interstitial component:

- N° of needles:7+5
- Insertion depth:
- Material: Titanium

Vaginal packing:

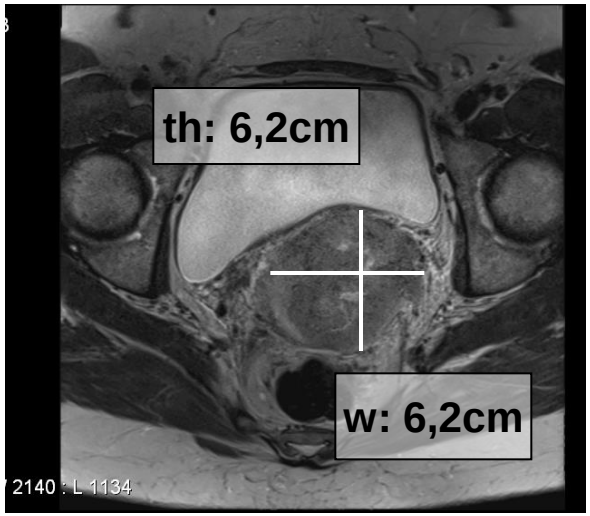
- Gauze impregnated with gadolinium

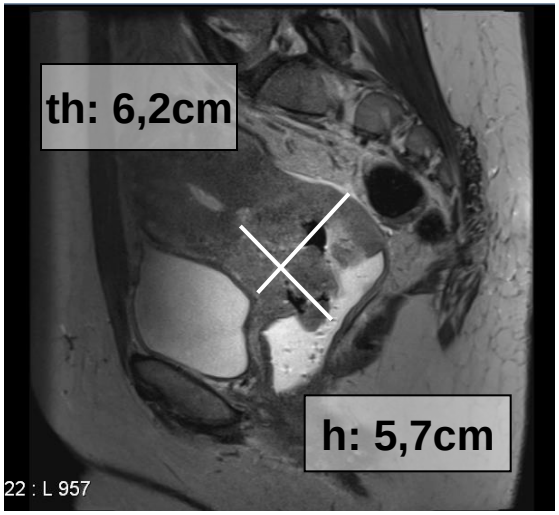
Imaging:

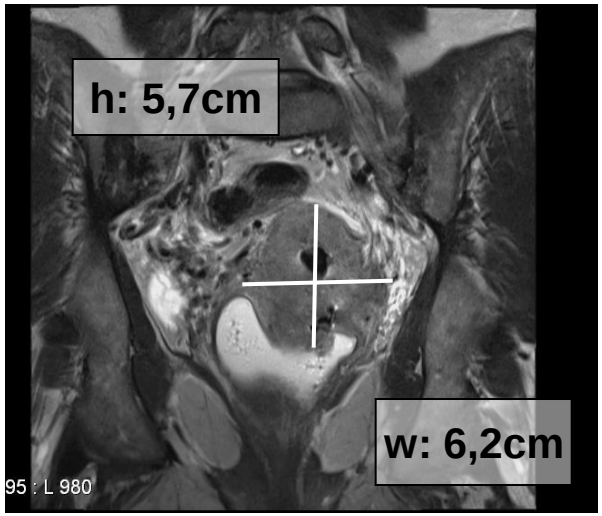
- MRI field strength: 1.5 T
- MRI configuration:
- Sequence(s): T2-weighted
- Imaging planes: para-transverse, para-sagittal, para coronal
- Comments regarding protocol: No contrast; Foley catheter open

MRI findings

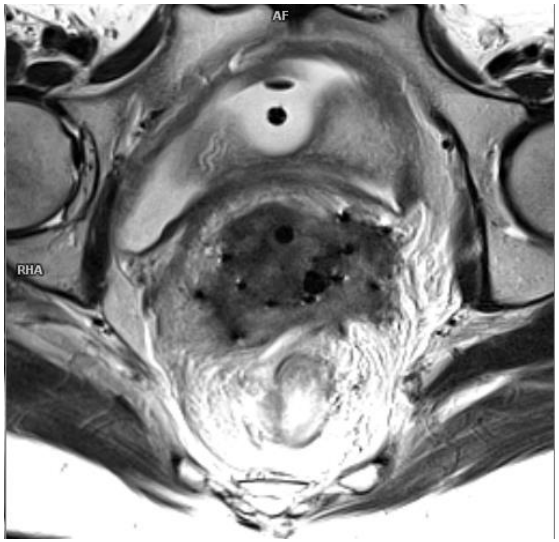
Diagnosis *V=110cm³*

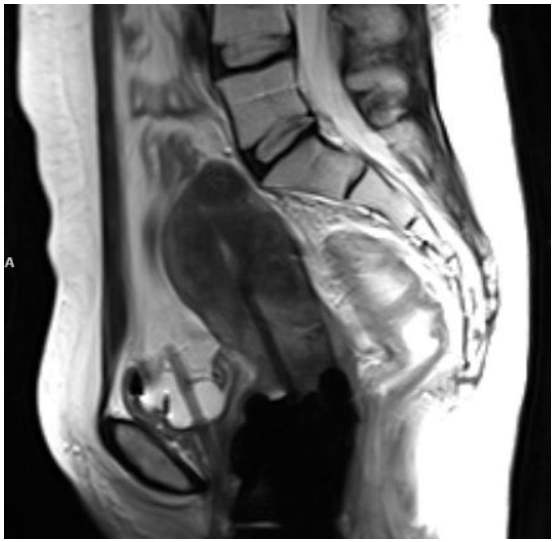


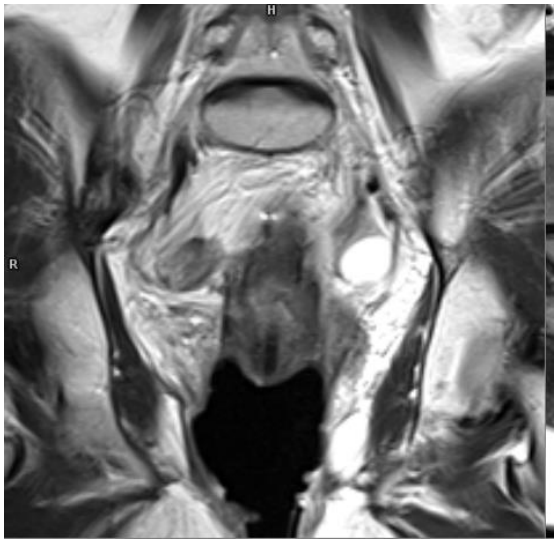




At BT (last week of EBRT dose 39.6Gy *V=30cm³*







Time dose fractionation for EBRT + HDR BT

ESTRO Teaching Course
Image-guided radiotherapy & chemotherapy in gynaecological cancer - with a special focus on adaptive brachytherapy

Madrid 2018

Kari Tanderup
Richard Pötter

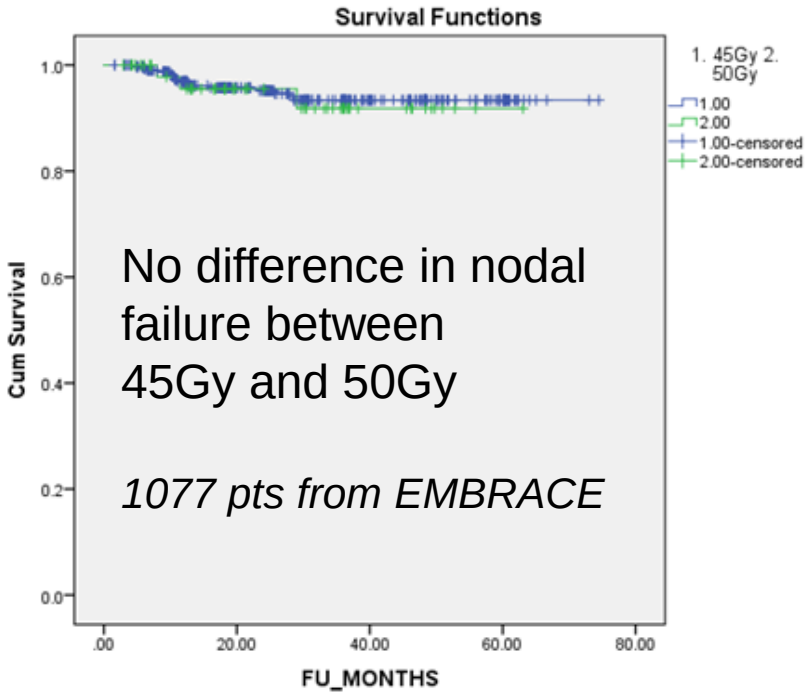
Aarhus University Hospital

Combination of EBRT and BT

- EBRT dose and fractionation
- BT dose and fractionation
- Timing of BT boost
- Overall treatment time

What do we know about dose to the elective target volume?

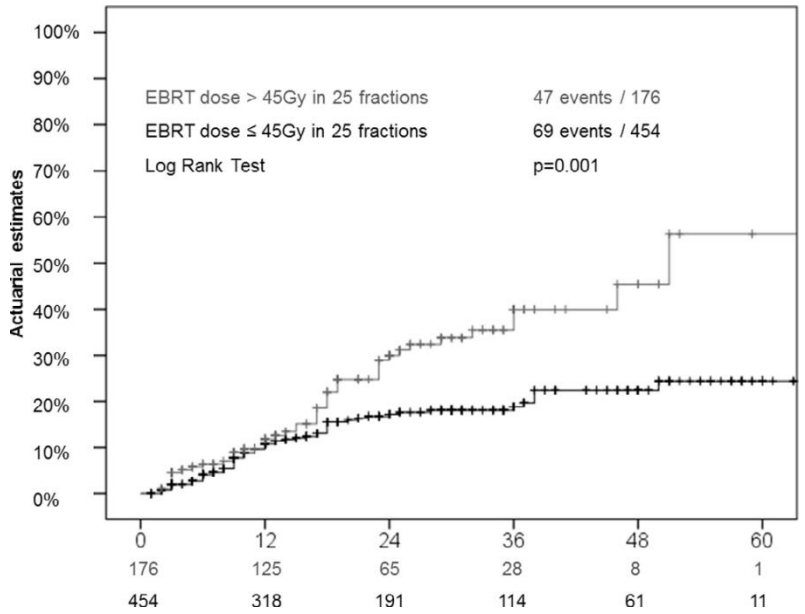
- **Do we need 45Gy or 50Gy for control of microscopic disease in lymph nodes with chemoradiation?**



C Nomden, A de Leeuw, IM Jürgenliemk- Schultz, UMCU

- **Difference in morbidity between 45Gy and 50Gy?**

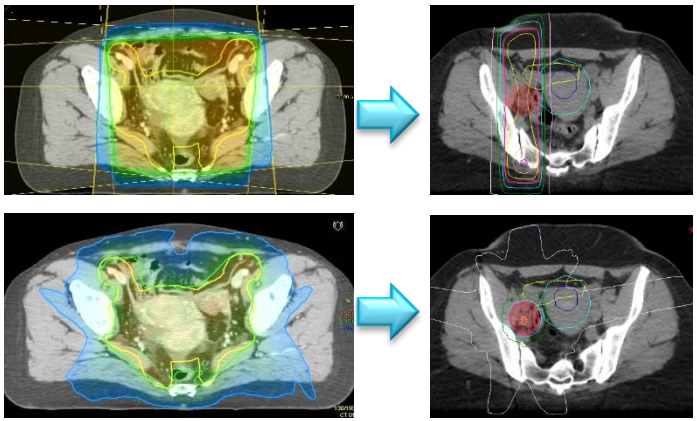
Vaginal stenosis
630 pts from EMBRACE



Kirchheiner et al, RO 118 160–166, 2016

Timing of Nodal Boost

Sequential Boost



i.e.:

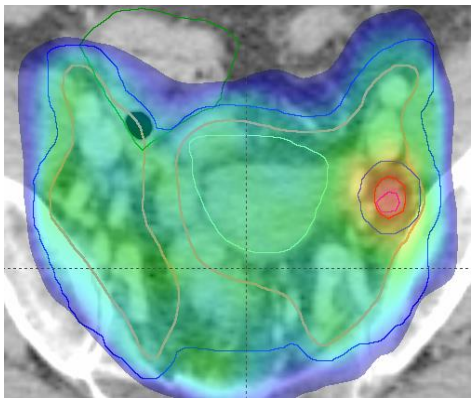
PTV-E:
45 Gy in 25 fx

→ PTV-N:
16 Gy in 8 fx

+ GTV Regression can be considered

− ↑ Totally delivered D (“waste D”)

Simultaneous Integrated Boost



i.e.: *(EMBRACE 2 Study protocol)*

PTV-E: 45 Gy in 25 fx
PTV-N: 55 Gy in 25 fx (True pelvis)
57.5 Gy in 25 fx (Outside True p.)

+ ↓ Overall Treatment Time

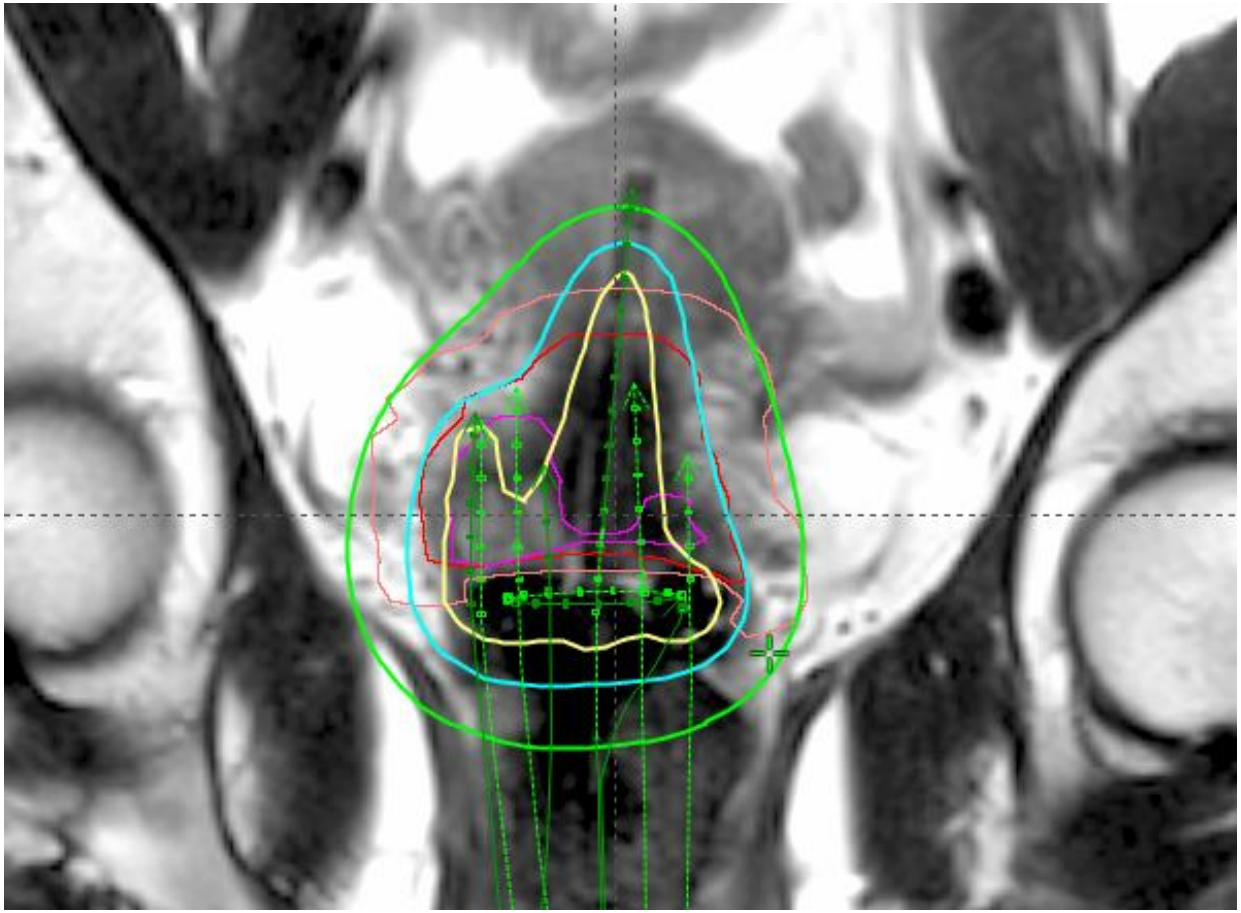
+ ↓ Totally administered D

− CTV-T & CTV-N move differently

− Nodes shrink- Replanning

Courtesy Primoz Petric

Time, dose and fractionation primary tumour



EQD2 for some common schedules

EBRT dose	EBRT #fx	BT fraction dose	BT fractions	Total EQD2
50Gy	25 fx	7Gy	3 fx	80Gy
50Gy	25 fx	8Gy	3 fx	86Gy
50Gy	25 fx	9Gy	2 fx	79Gy
45Gy	25 fx	7Gy	4 fx	85Gy

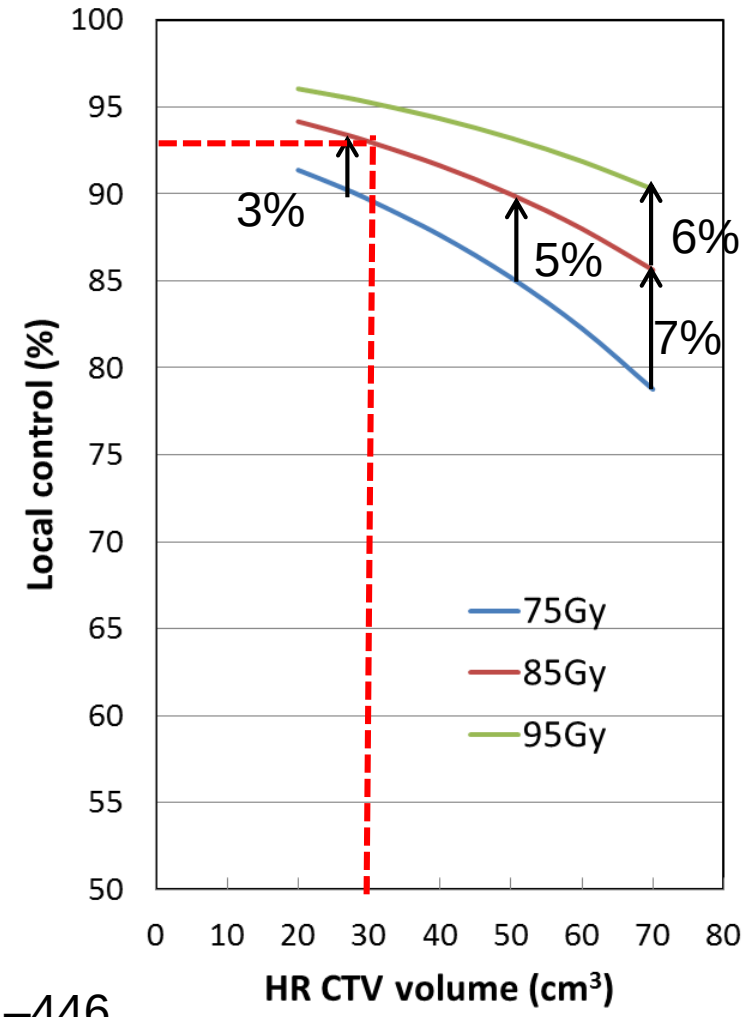
What do we know about dose and local control for CTV_{HR}?

Effect of dose, volume and time:

Dose:	10Gy → 5% LC
Time:	7 days ~ 5Gy
Volume	$10cm^3$ ~ 5Gy

85Gy for $30cm^3$ CTV_{HR}: 93% LC

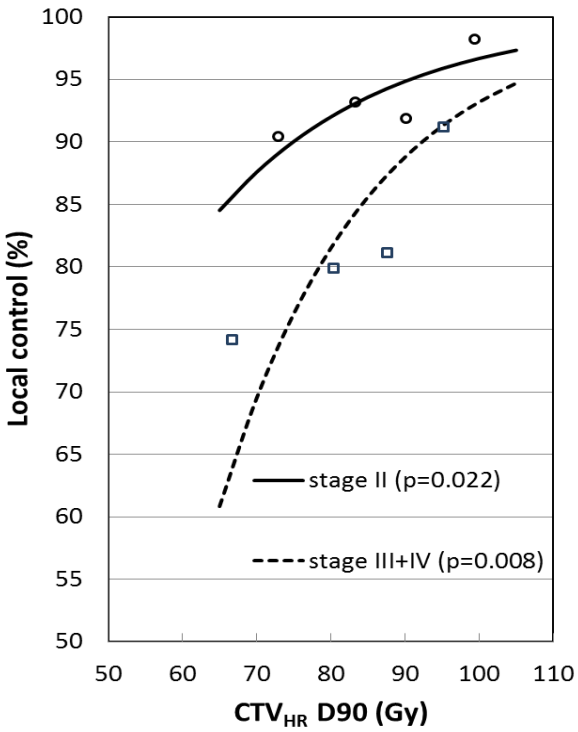
Local control at 3 years

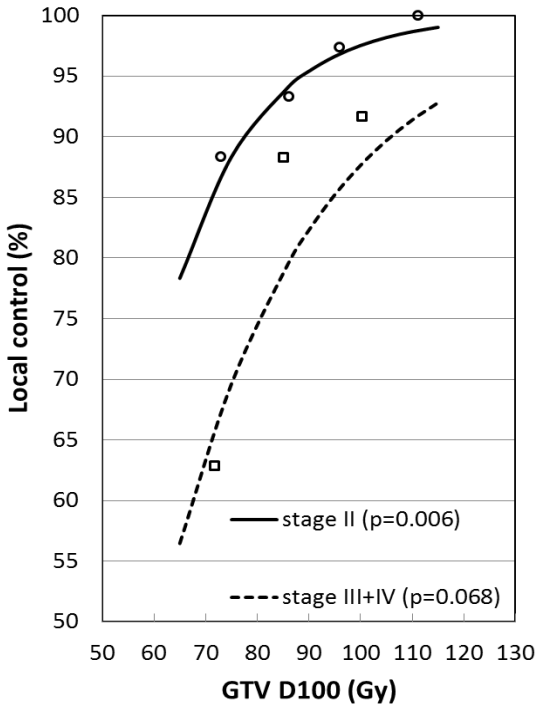


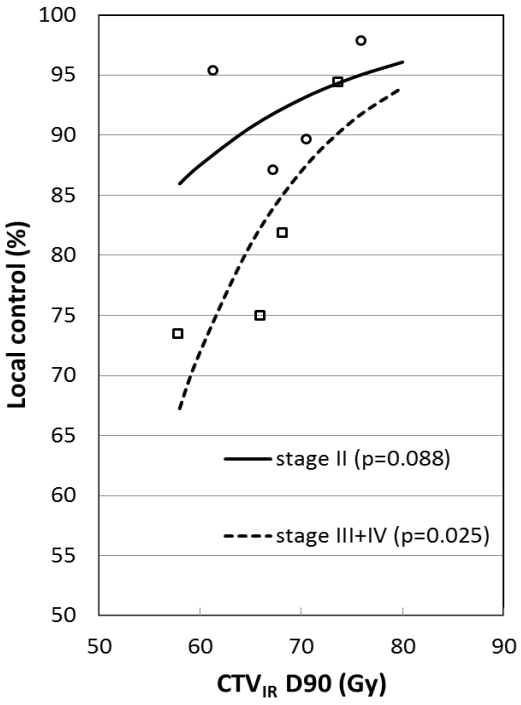
Tanderup et al, Radiother Oncol 120 (2016) 441–446

Dose effect GTV, CTV_{HR} and CTV_{IR}

Analysis according to stage





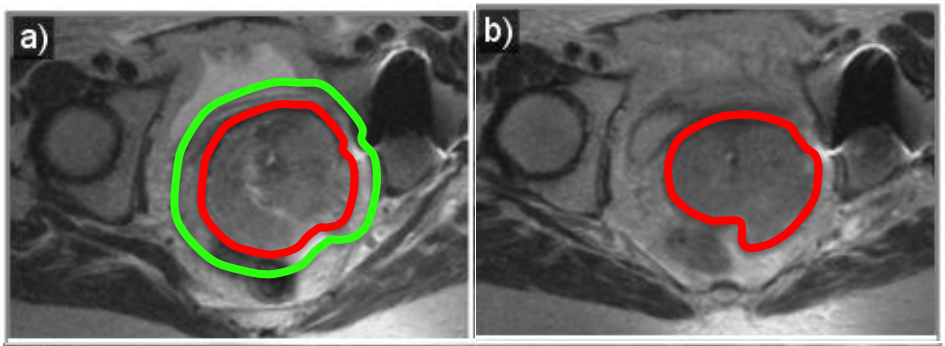


Tanderup et al, Radiother Oncol 120 (2016) 441–446

Example: cervical cancer, FIGO IIIB: total dose 90 Gy EQD2

EBRT dose

0 Gy



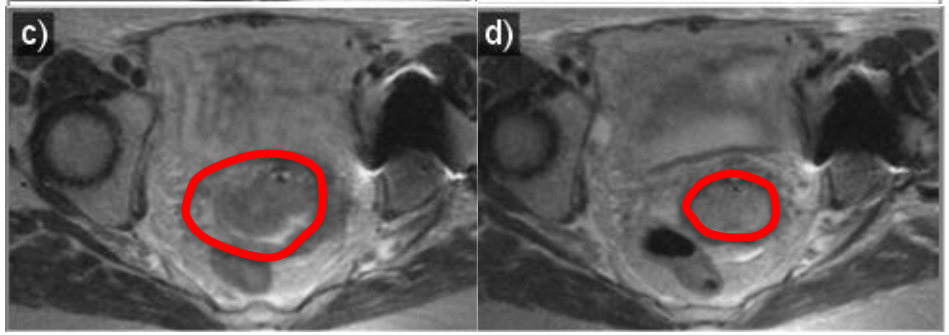
EBRT dose

9 Gy

Cisplatin (40 mg/m^2) x1

18 Gy

Cisplatin (40 mg/m^2) x2

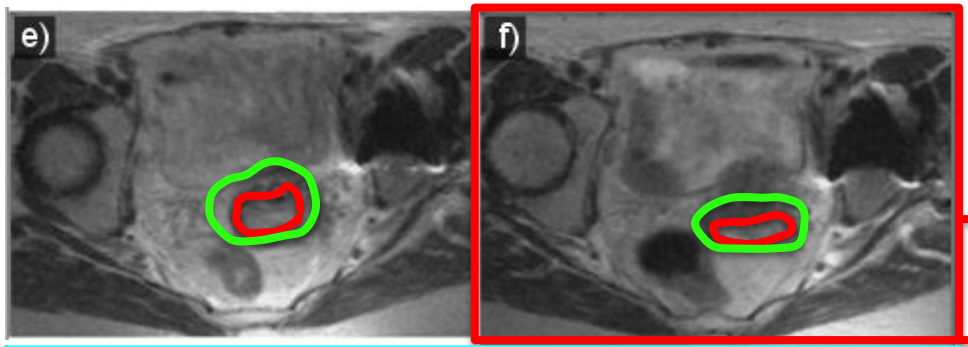


27 Gy

Cisplatin (40 mg/m^2) x3

36 Gy

Cisplatin (40 mg/m^2) x4

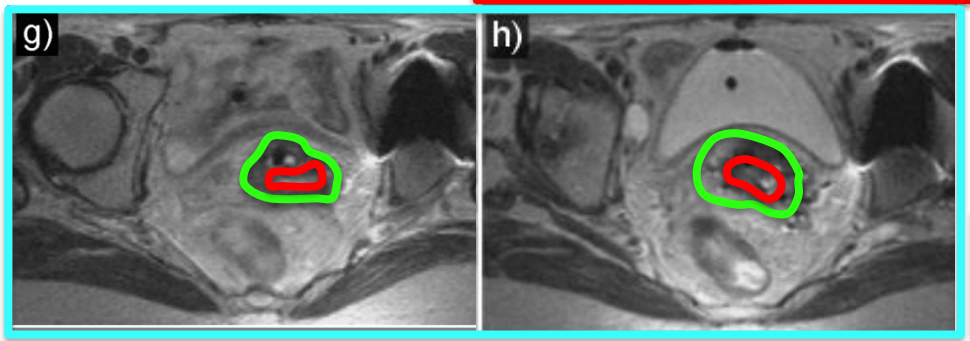


45 Gy

Pre-brachytherapy

EBRT45 Gy

Cisplatin (40 mg/m^2) x5



IGABT 45 Gy

Brachytherapy

GTV

CTV

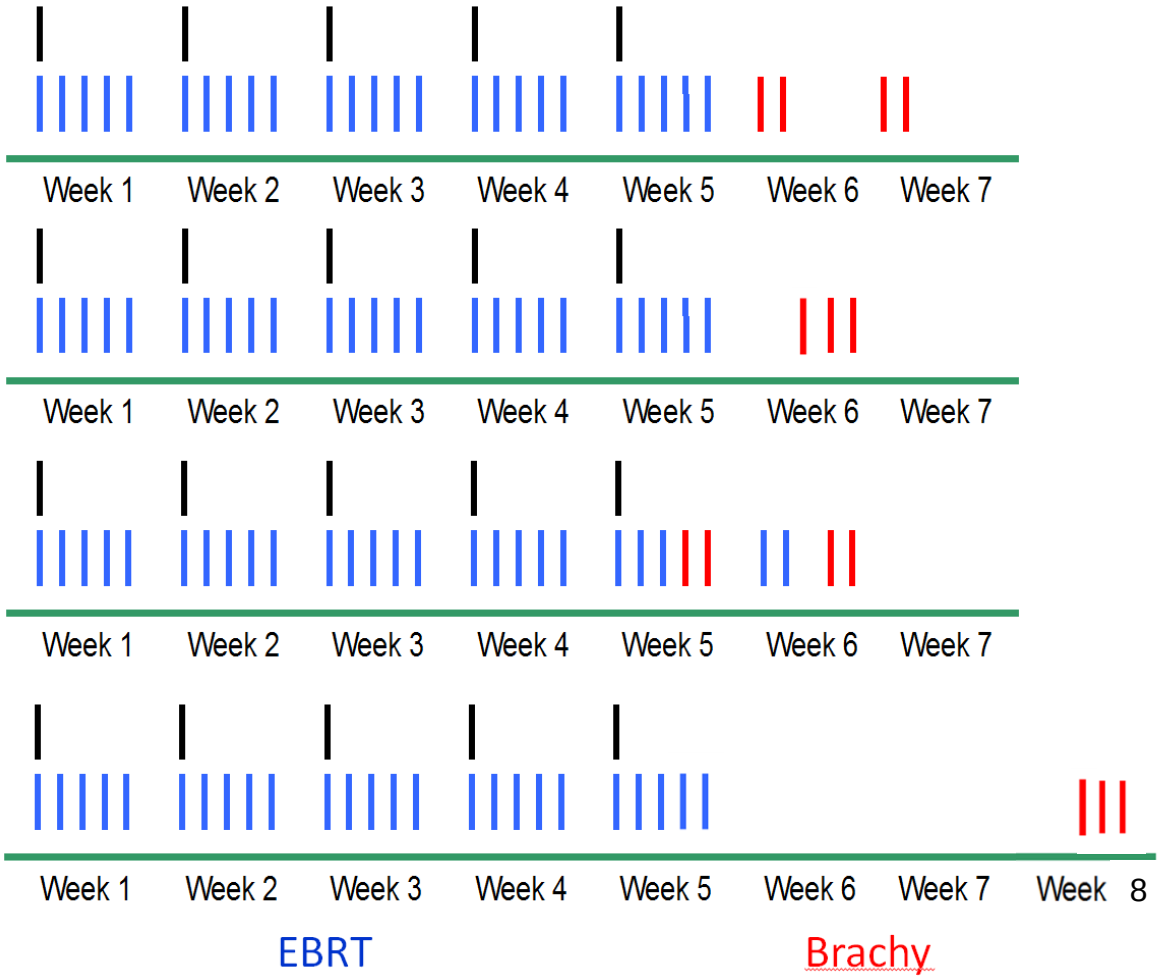
Impact of overall treatment time

1 week extra OTT ~ 5Gy less to CTV_{HR}

1 week extra OTT ~ loss of 2.5% local control

- **How to keep overall treatment time limited?**
- **Primary tumour:**
  - **Start BT towards the end of EBRT or immediately after end of EBRT**
  - **With the help of IC/IS it is not necessary to wait further for tumour shrinkage**
- **Pathological lymph nodes**
  - **Simultaneously integrated boost**

Equieffective dose and impact of overall treatment time



	EQD2	OTT correction
45Gy/25 fx EBRT 7Gy x 4 fx HDR BT	85Gy	+2Gy
50Gy/25 fx EBRT 7Gy x 3 fx HDR BT	80Gy	+5Gy
45Gy/25 fx EBRT 7Gy x 4 fx HDR BT	85Gy	+5Gy
50Gy/25 fx EBRT 7Gy x 3 fx HDR BT	80Gy	-5Gy

Take home messages

- **Elective lymph node target: 45-50Gy EBRT**
  - **Perspective of reducing morbidity with 45Gy**
- **Pathological lymph nodes: 55-60Gy EBRT**
  - **Balance between tumour control and morbidity**
- **Primary tumour (CTV_{HR}): >85-90Gy EBRT+BT**
  - **Balance between EBRT and BT**
  - **With more IC/IS BT it is possible to reduce EBRT dose to 45Gy**
- **Overall treatment time: <50 days**

Common dose planning aims for target structures

	EBRT dose	BT dose EQD2	Total EQD2 EBRT+BT
Elective lymph node target: CTV-E	45-50Gy	-	45-50Gy
Pathological lymph nodes	55-60Gy	0-4Gy	60Gy
Intermediate Risk CTV: CTV_{IR}	45-50Gy	15-20Gy	60-70Gy
High Risk CTV: CTV_{HR}	45-50Gy	35-45Gy	85-90Gy
GTV	45-50Gy	50-55Gy	95-100Gy
Point A	45-50Gy	25-40Gy	70-85Gy

Morbidity and QoL after IGABT for cervical cancer: Rectum, Sigmiod, Bladder, Vagina

ESTRO GYN teaching course, Madrid 2018

Remi Nout
Leiden University Medical Center

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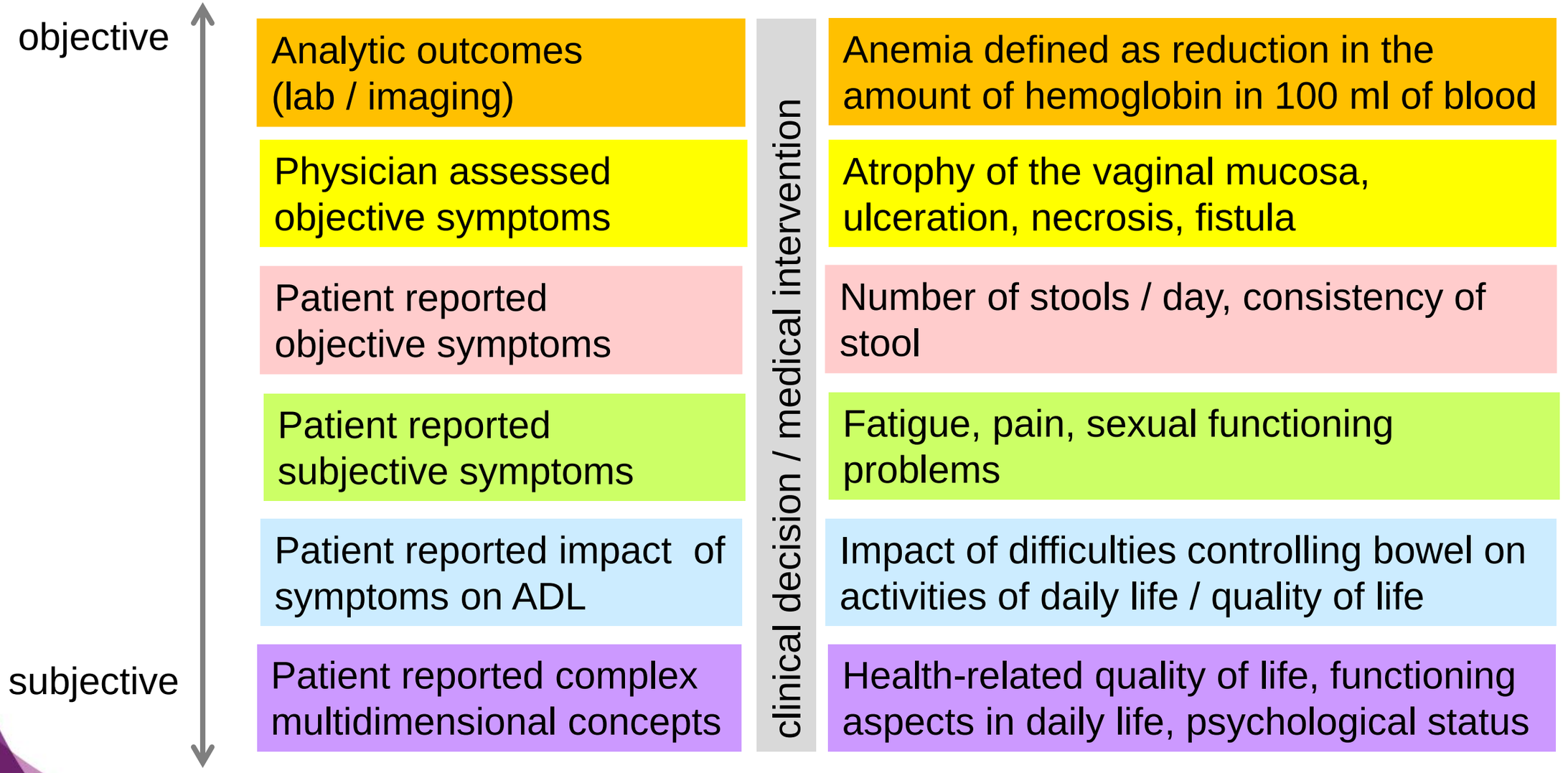
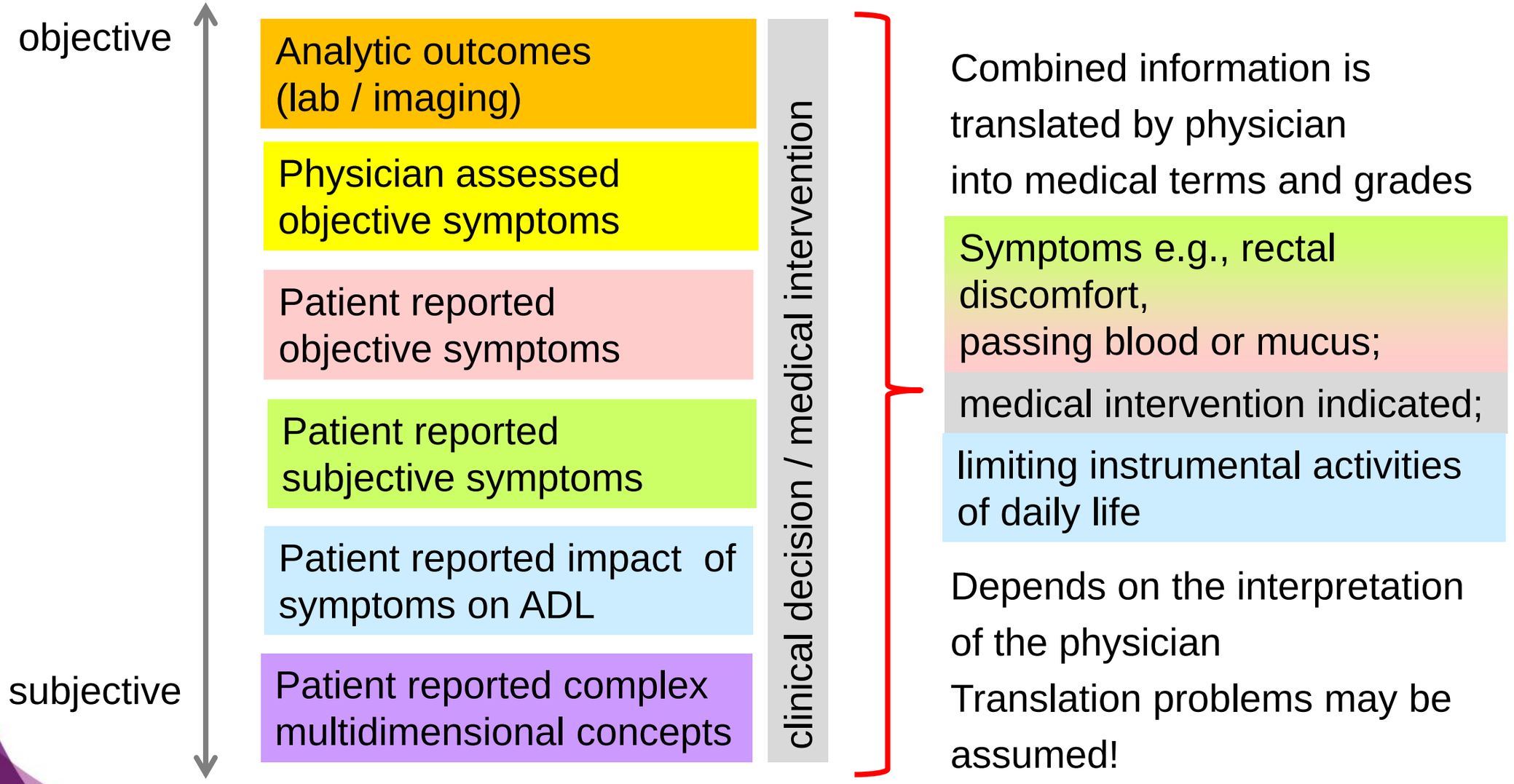
Learning Objectives

- Late morbidity patterns for rectum, bladder, bowel and vagina
- Mid & long-term impairments in quality of life (functional aspects in daily life and patient reported symptoms)
- Differential value of physician assessed morbidity and patient reported outcomes (symptoms and QoL).

Morbidity assessment in clinical trials



Physician assessed morbidity
Common Toxicity Criteria of AE



Inter-rater reliability of CTCAE morbidity assessment

Atkinson et al. Qual Life Res 2012

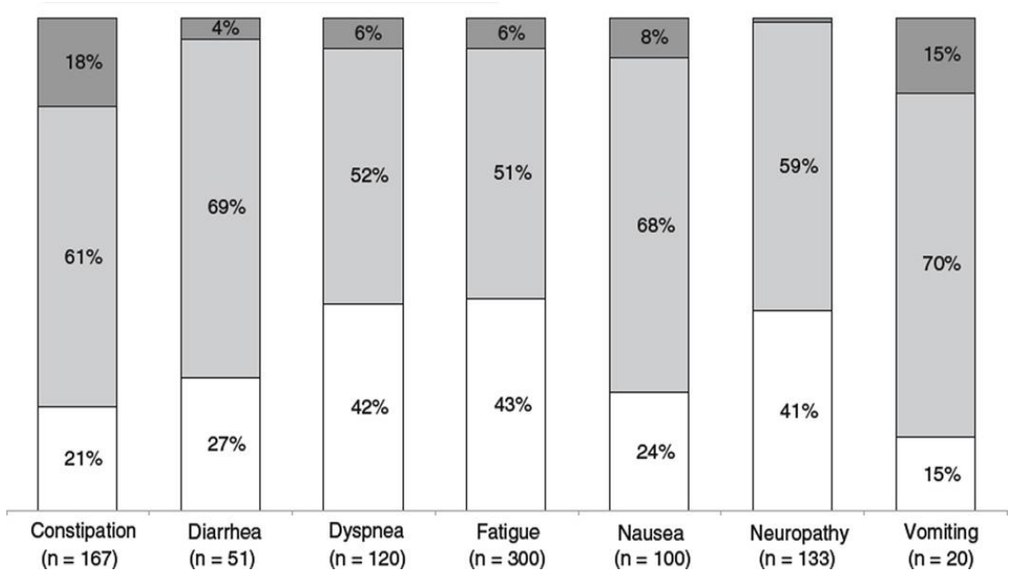
N=393 patients, mixed cancer type

CTCAE assessed by 2 independent physicians within ~1h

Results in symptomatic patients

- 15-43% agreement
- 51-70% 1 grade differences
- 1-18% 2 grades differences

CTCAE agreement between
2 physicians is moderate at best!



The lower the CTCAE grading, the more variation between physicians is observed.

Disagreement mainly between G0/G1/G2.

Chinnachamy et al. Jpn J Clin Oncol

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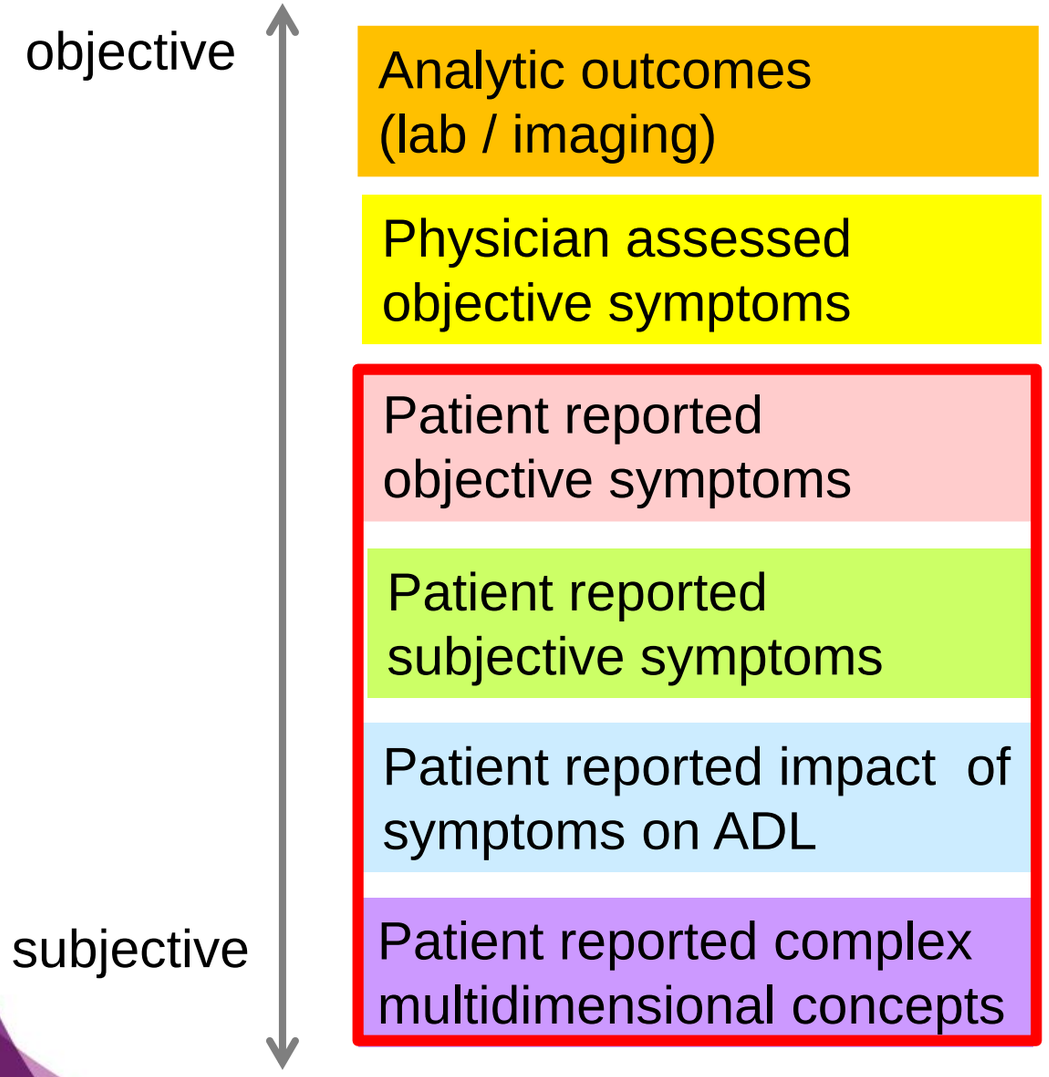
Patient Reported Outcomes (PRO)



PRO considered as Gold standard

"…any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." Final

FDA PRO Guidance, Dec 2009

Objectifying the subjective experience
by questionnaires
with predefined response categories
and robust psychometric properties

Health-related quality of life assessment

EORTC QLQ C30
European Organization of Research and Treatment of Cancer Quality of Life Questionnaires
(Aaronson et al.) *Europe*

FACT-G
Functional Assessment of Cancer Therapy
(Cella et al.) *US*

SF 36
Short Form Health Survey 36
(Ware et al.) *beyond oncology*

Basic module and different disease- and treatment related modules available

Assessment

1. Overall quality of life
2. Aspects of functioning in daily life
   physical, social, emotional, role, cognitive functioning
3. Patient reported symptoms

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EORTC / FACT QoL

Answer categories
- ❑ not at all
- ❑ a little
- ❑ (somewhat)
- ❑ quite a bit
- ❑ very much

Widely used for PRO symptom assessment

Answer categories not precise

No linear association with CTCAE grading

PRO-CTCAE

PRO assessment tool of the future

Compatible with CTCAE v4, covers 78 symptoms

Currently under development and validation

Frequency
- ❑ never
- ❑ rarely
- ❑ occasionally
- ❑ frequently
- ❑ almost constantly

Severity of symptoms
- ❑ none
- ❑ mild
- ❑ moderate
- ❑ severe
- ❑ very severe

Interference with usual activities
- ❑ not at all
- ❑ a little
- ❑ somewhat
- ❑ quite a bit
- ❑ very much

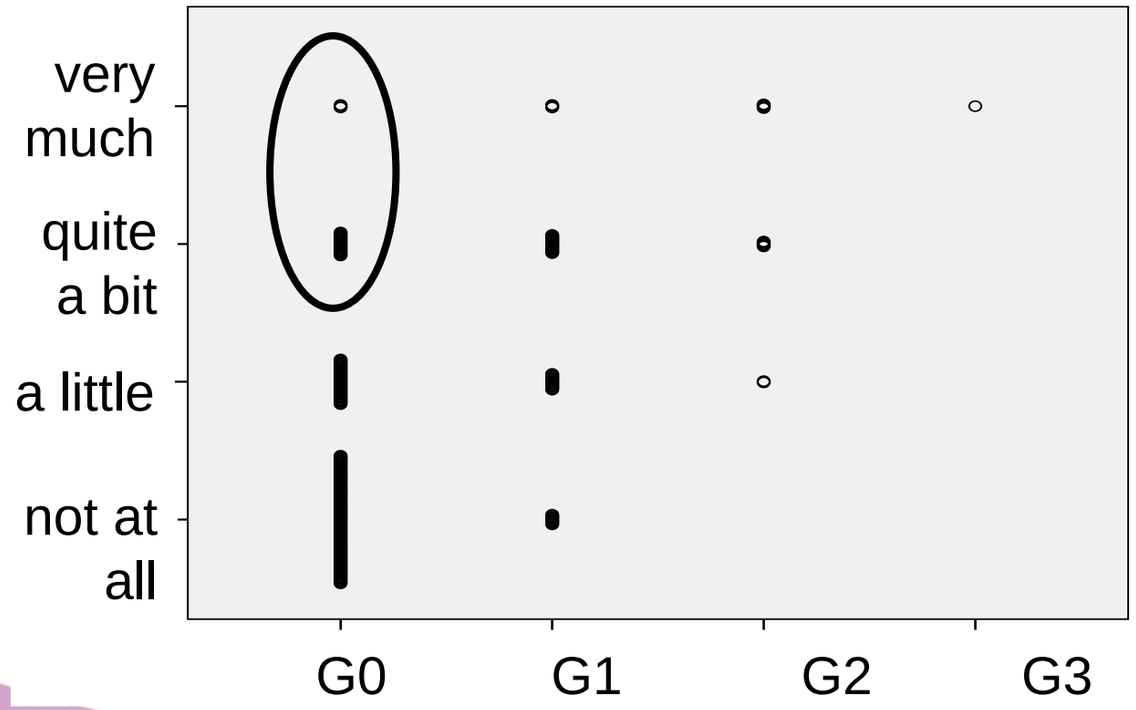
Agreement physician assessed vs. Patient reported symptoms

Kirchheiner et al. SUON 2012

N=223 cervical cancer, CTCAE v3 vs. EORTC C30 + CX24

3 months after end of definitive radiochemotherapy

EORTC : Did you pass water / urine frequently?



Discrepancy:

Patient reported symptom “quite a bit” to ”very much” in EORTC QLQ

→ CTCAE grading 0

CTCAE Urinary frequency

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12 overlapping symptoms CTCAE & EORTC QLQ	nr.of “quite a bit” or “very much” problems reported	nr.of discrepancies (CTCAE G0)
diarrhea	27	13
anal incontinence	17	15
bleeding hemorrhage GI	1	1
urinary frequency	52	23
urinary incontinence	15	7
bleeding hemorrhage GU	2	1
limb edema	21	10
fatigue	53	22
insomnia	53	26
hot flashes	73	19
vaginal dryness*	22	11
vaginal stenosis*	24	11
N=223 patients at 3 months FUP	In total 360 substantial problems reported	159 (44%) of substantial problems not recognized by physician assessed CTCAE

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Possible explanations

Patients

- tendency to “please the doctor”, based on gratitude
- certain symptoms too embarrassing to report
- level of distress caused by the symptoms is rated (highly subjective)
- psychological coping strategies (dissimulating / aggravating symptoms)

Physicians

- more emphasis on identifying severe G3/G4 morbidity than milder morbidity
- limited time to fully explore symptoms (general questions about any symptoms vs. systematical assessment of each symptom)
- continuum of severity along which a patient is put into context

Kirchheiner et al. 2012
Vistad et al. 2008
Atkinson et al. 2012

Summary I

- Technical developments in RT → less severe G3/G4 morbidity
  Focus to milder and moderate G1/G2 morbidity and impact on QoL, PRO are especially sensitive

- Physician assessed CTCAE morbidity has a wide range of interpretation and therefore a low inter-rater reliability
  (especially in mild to moderate morbidity)

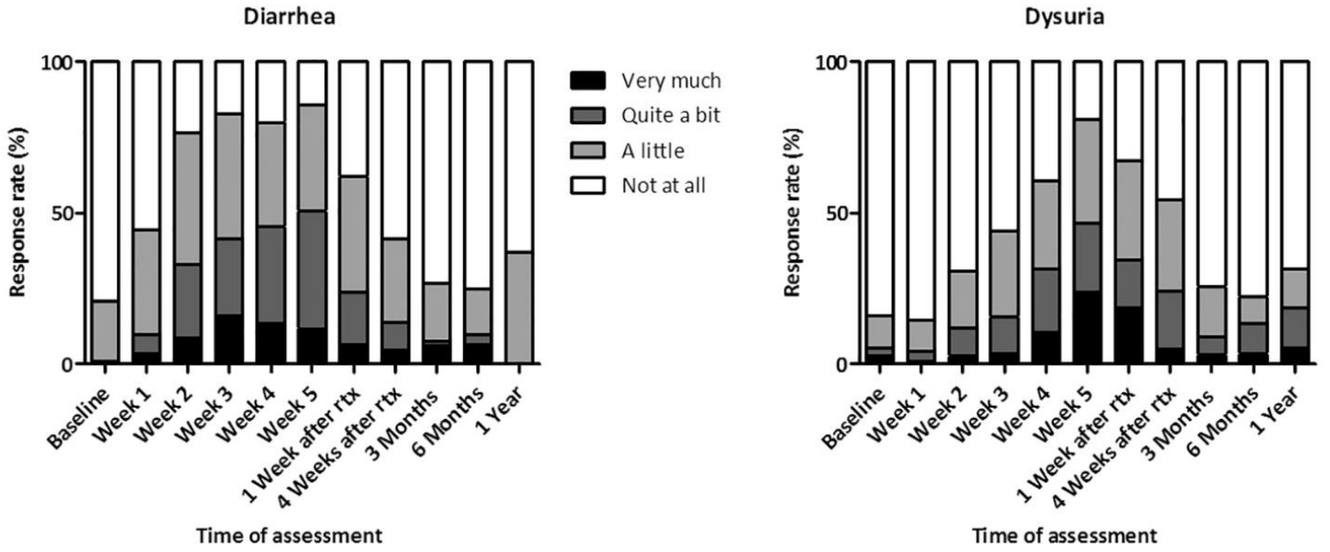
- Low associations between physician assessed and patient reported morbidity are consistently described in literature

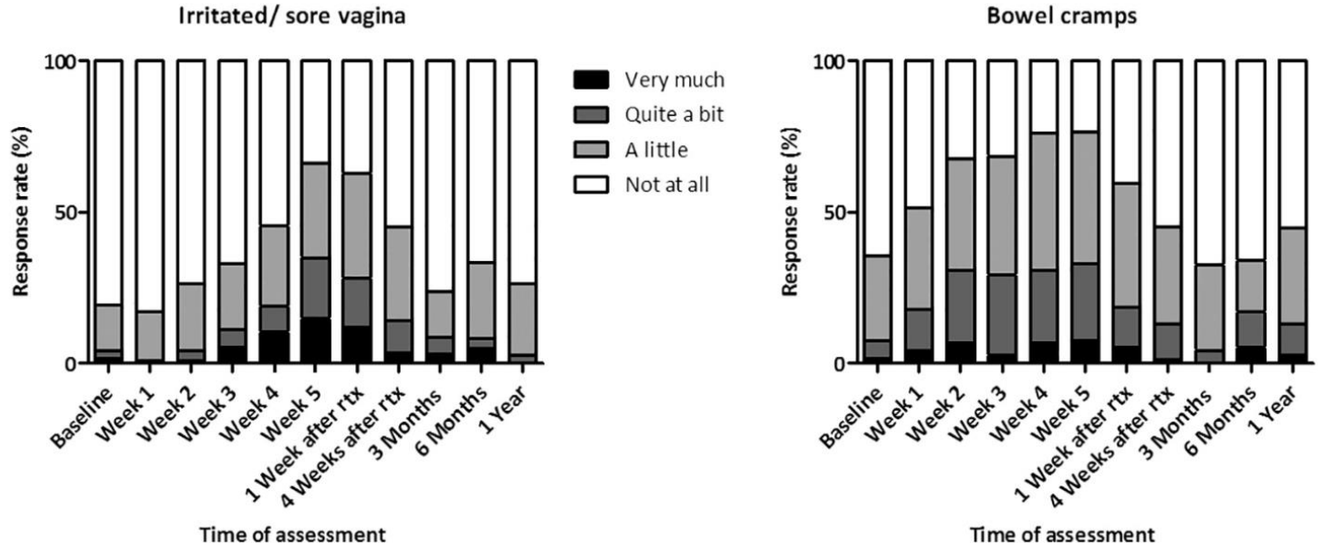
- Both provide valuable information → combined reports or a collaborative approach provide a more accurate understanding of morbidity

Learning Objectives

- Late morbidity patterns for rectum, bladder, bowel and vagina
- Mid & long-term impairments in quality of life (functional aspects in daily life and patient reported symptoms)
- Differential value of physician assessed morbidity and patient reported outcomes (symptoms and QoL).

Most frequently reported symptoms during and shortly after treatment





- EORTC-C30 and CX24
- 137 patients
- Prospective weekly assessment

Heijkoop et al. Gyn Onc 2017

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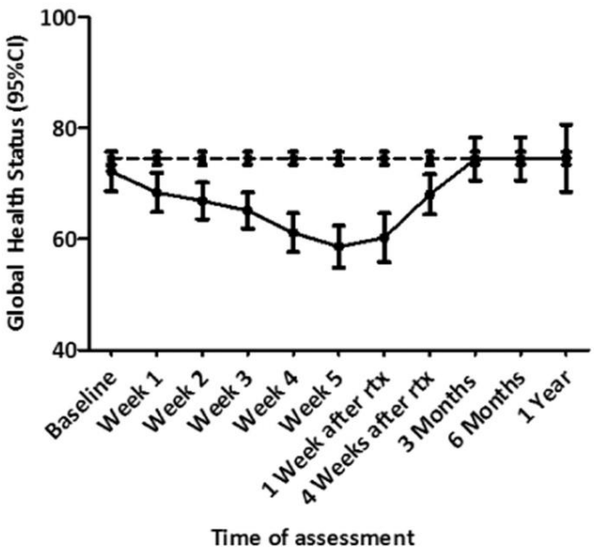
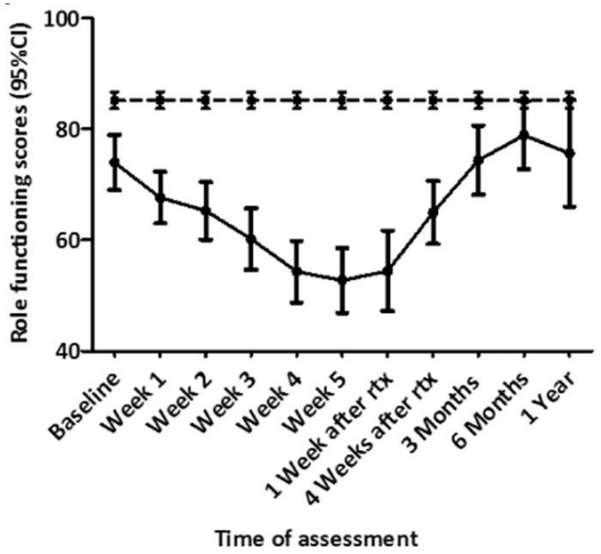
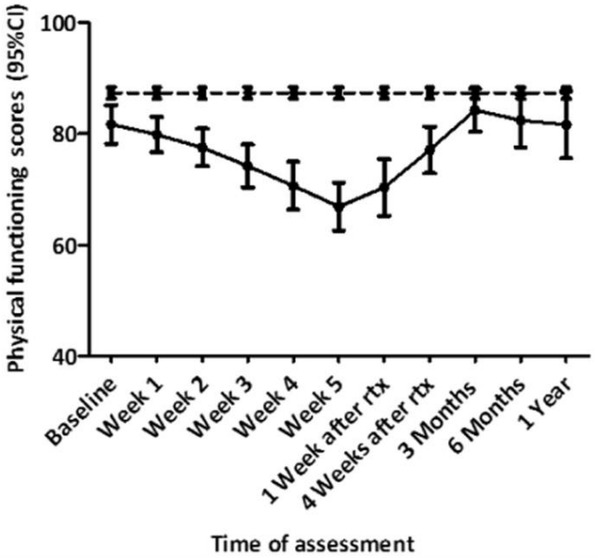
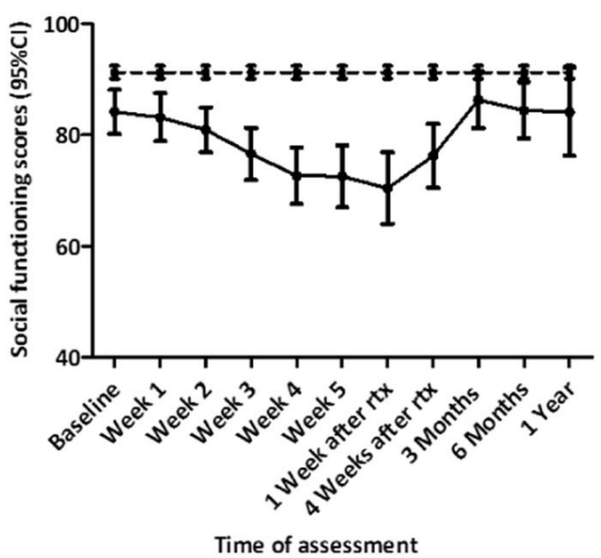
Most frequently reported symptoms during and shortly after treatment









- EORTC-C30 and CX24
- 137 patients
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Heijkoop et al. Gyn Onc 2017

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EMBRACE

An intErnational study on MRI-guided BRachytherapy in locally Advanced CErvical cancer

Median follow up 27 months (1-83)

1416 pts. in database

Exclusion:
-protocol violations (n = 61)
-suspicion/evidence of disease at 3 months (n = 69)
-missing baseline and/or any follow-up (n = 110)

1176 pts. with:
Baseline AND
≥3 months follow-up

- CTCAE v3.0
- EORTC-C30 and CX24
- Prospective assessment

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Bladder

Radiotherapy and Oncology 127 (2018) 423–430

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

EMBRACE

Physician assessed and patient reported urinary morbidity after radio-chemotherapy and image guided adaptive brachytherapy for locally advanced cervical cancer

Lars Fokdal [a,*], Richard Pötter [b], Kathrin Kirchheiner [b], Jacob Chr. Lindegaard [a], Nina Boje Kibsgaard Jensen [a], Christian Kirisits [b], Cyrus Chargari [c], Umesh Mahantshetty [d], Ina Maria Jürgenliemk-Schulz [e], Barbara Segedin [f], Peter Hoskin [g], Kari Tanderup [a]

Descriptive

crude incidence

actuarial incidence

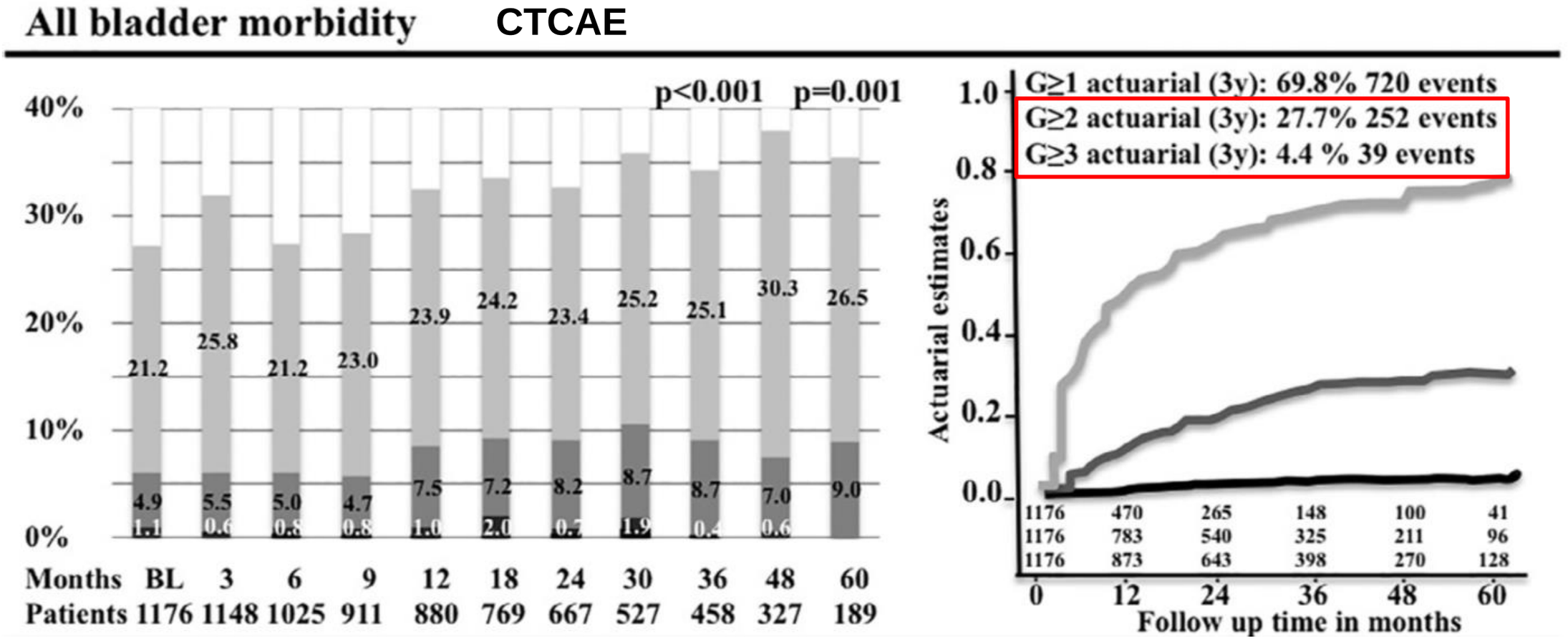
prevalence

EMBRACE I. CTCAE v3
Urinary frequency/urgency
Incontinence, urinary
Cystitis
Bladder spasm
Bleeding (Hemorrhage GU) – bladder, ureter, urethra
Stenosis/stricture – bladder, ureter, urethra
Fistula – bladder, ureter, urethra
Bladder other

Bladder

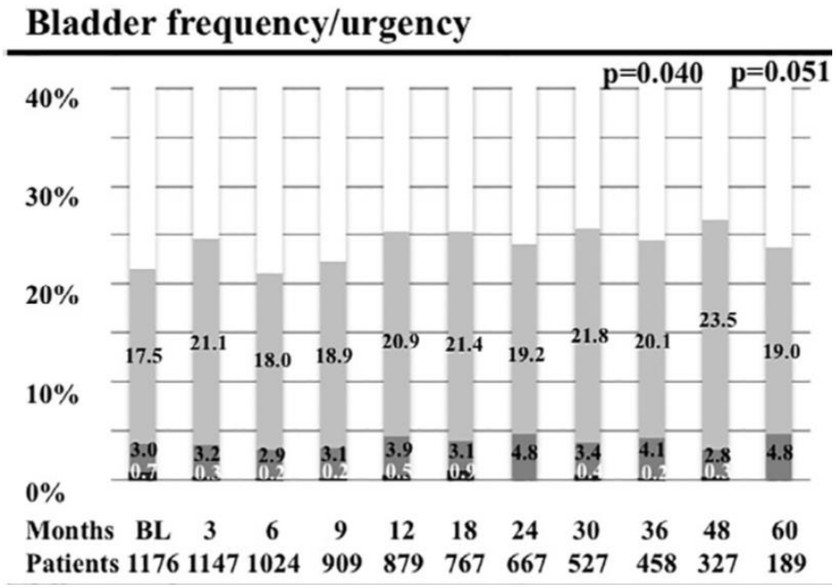
N = 1176	Frequency/ urgency	Incontinence	Spasm	Bladder stenosis	Cystitis	Bleeding	Fistula[a]		Ureteral stricture[b]	
							All	No bladder invasion	All	No baseline hydronephrosis
Grade 0	569 (48.4%)	784 (66.7%)	1081 (91.9%)	1166 (99.1%)	958 (81.5%)	1098 (93.4%)	1157 (98.4%)	1102 (99.1%)	1125 (95.7%)	1067 (97.6%)
Grade 1	470 (40.0%)	267 (22.7%)	75 (6.4%)	7 (0.6%)	132 (11.2%)	55 (4.7%)	4 (0.3%)	3 (0.3%)	15 (1.3%)	13 (1.2%)
Grade 2	123 (10.4%)	106 (9.0%)	19 (1.6%)	3 (0.3%)	75 (6.4%)	19 (1.6)	3 (0.3%)	2 (0.2%)	12 (1.0%)	5 (0.5%)
Grade 3	14 (1.2%)	14 (1.2%)	1 (0.1%)	0 (0%)	10 (0.9%)	4 (0.3%)	7 (5)[c] (0.6%)	2 (0.2%)	22 (18)[c] (1.9%)	8 (0.7%)
Grade 4		5 (0.4%)	0 (0.1%)	0 (0%)	1 (0.1%)	0 (0%)	5 (4)[c] (0.4%)	3 (0.3%)	2 (1)[c] (0.2%)	0 (0%)

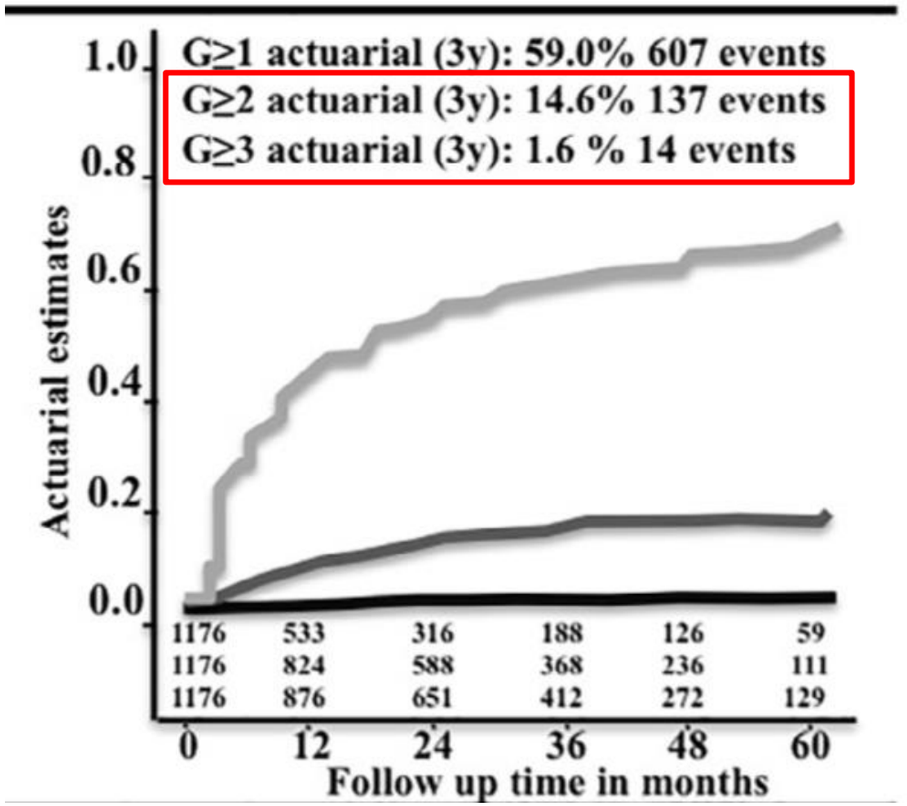
Bladder


All bladder morbidity
CTCAE
p<0.001
p=0.001
40%
30%
20%
10%
0%
21.2
25.8
21.2
23.0
23.9
24.2
23.4
25.2
25.1
30.3
26.5
4.9
5.5
5.0
4.7
7.5
7.2
8.2
8.7
8.7
7.0
9.0
Months BL 3 6 9 12 18 24 30 36 48 60
Patients 1176 1148 1025 911 880 769 667 527 458 327 189
G≥1 actuarial (3y): 69.8% 720 events
G≥2 actuarial (3y): 27.7% 252 events
G≥3 actuarial (3y): 4.4 % 39 events
Actuarial estimates
1.0
0.8
0.6
0.4
0.2
0.0
1176 470 265 148 100 41
1176 783 540 325 211 96
1176 873 643 398 270 128
0 12 24 36 48 60
Follow up time in months

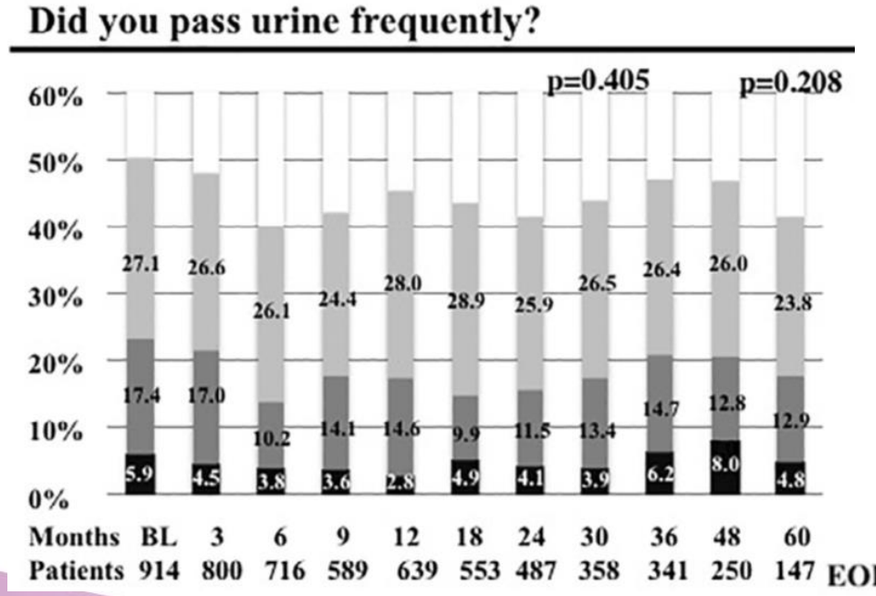
Bladder frequency/urgency

CTCAE





EORTC



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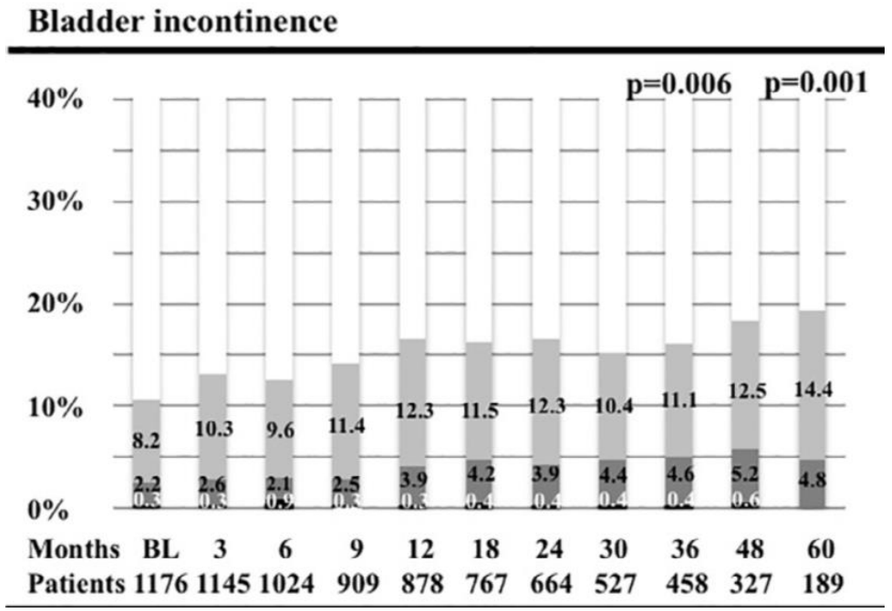
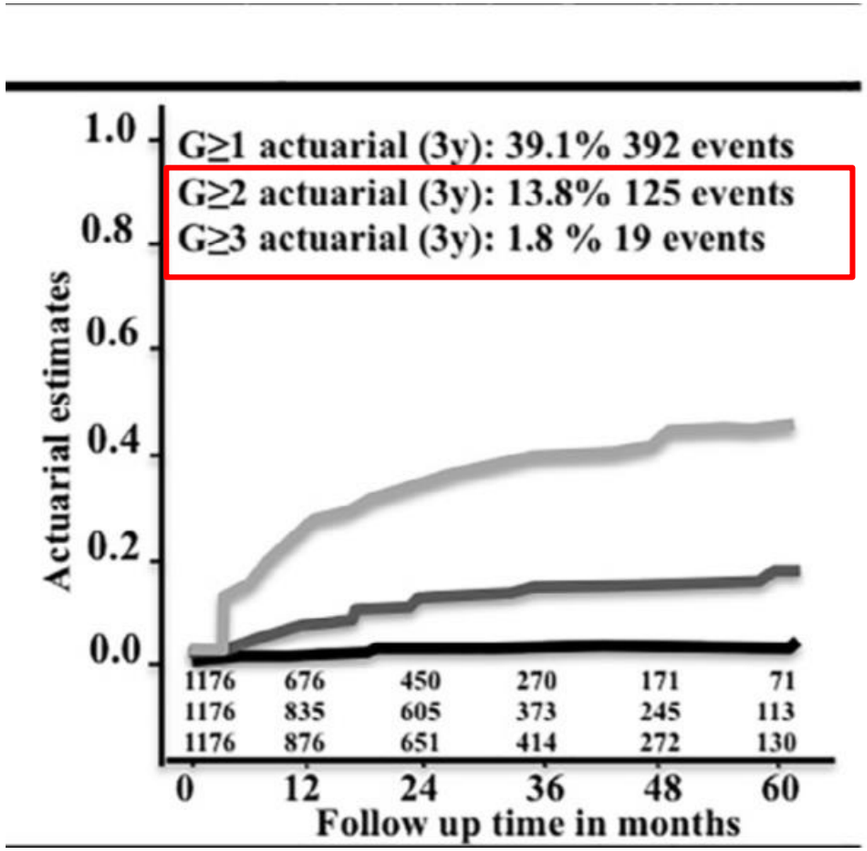
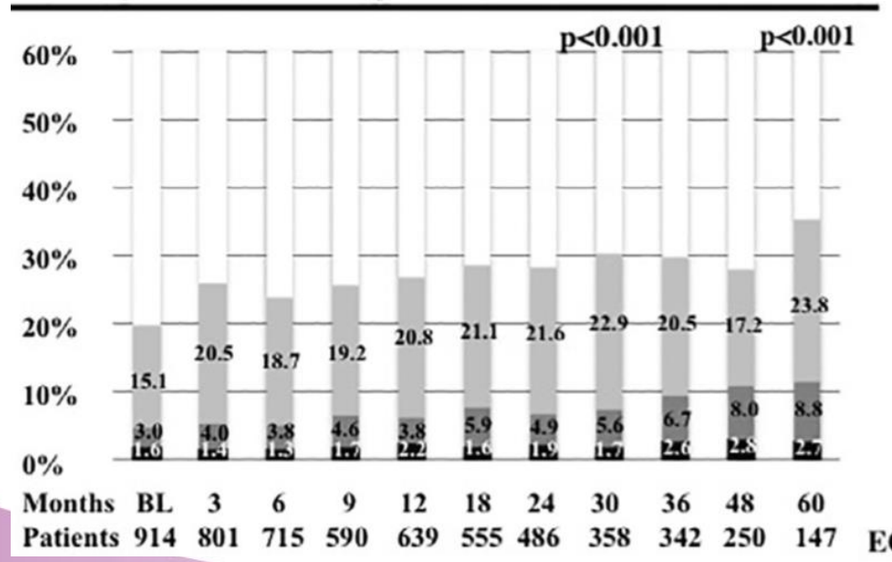
Bladder incontinence

CTCAE





EORTC



EORTC categories Not at all A little Quite a bit Very much

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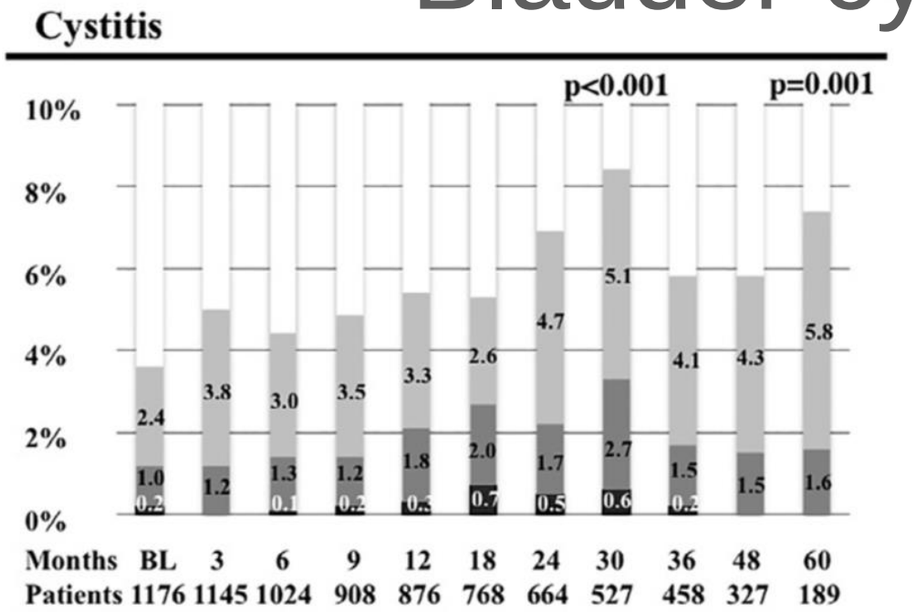
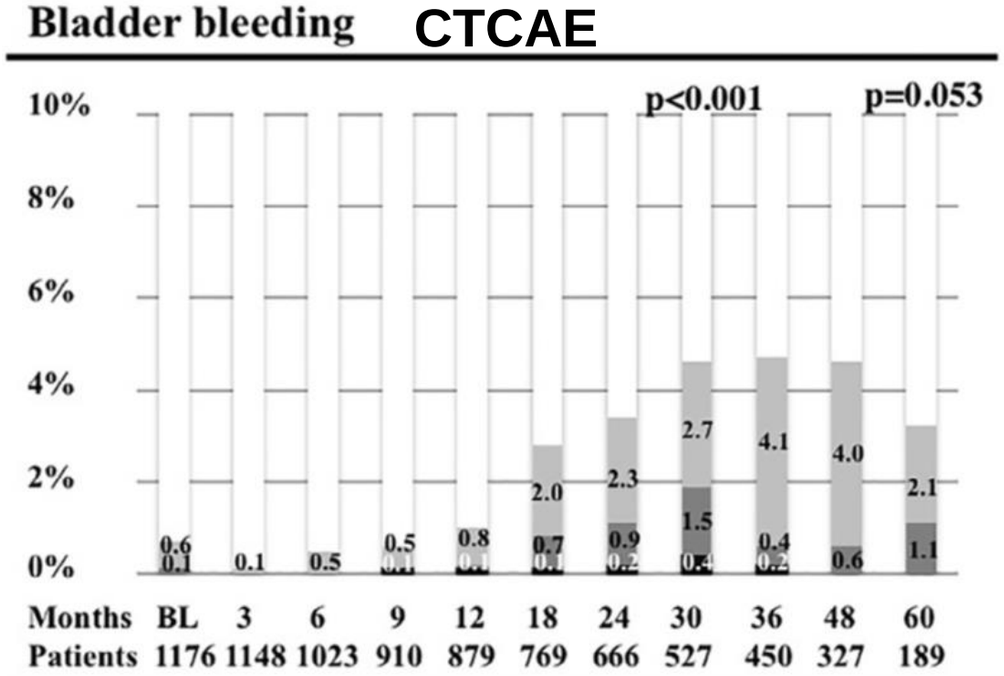
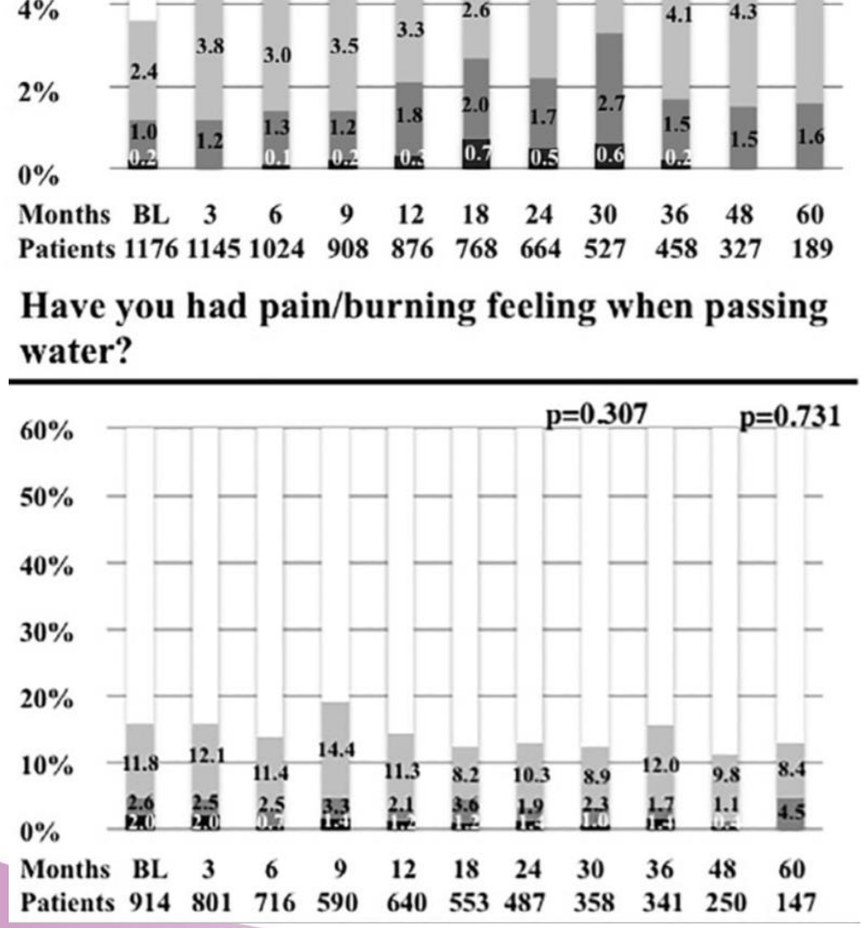
Bladder cystitis and bleeding

CTCAE





EORTC



EORTC categories Not at all A little Quite a bit Very much

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Morbidity: GI, Rectum, Bowel

Radiotherapy and Oncology 120 (2016) 412–419

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Image guided brachytherapy in cervical cancer

Dose–volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study ☆

Renaud Mazeron [a,*], Lars U. Fokdal [b], Kathrin Kirchheiner [c], Petra Georg [c], Noha Jastaniyah [c], Barbara Šegedin [d], Umesh Mahantshetty [e], Peter Hoskin [f], Ina Jürgenliemk-Schulz [g], Christian Kirisits [c], Jacob C. Lindegaard [b], Wolfgang Dörr [c], Christine Haie-Meder [a], Kari Tanderup [b], Richard Pötter [c], on behalf of the EMBRACE collaborative group[1]

EMBRACE I. CTCAE v3
Diarrhea
Flatulence
Incontinence (anal)
Proctitis
Bleeding (hemorrhage GI, anus, rectum, sigmoid, colon, small bowel)
Stricture / stenosis (anus, rectum, sigmoid, colon, small bowel)
Fistula (anus, rectum, sigmoid, colon, small bowel)
Gastro-intestinal other

Rectum (CTCAE overview)

	Proctitis		Bleeding		Stenosis		Fistula		ALL	
	N	%	N	%	N	%	N	%	N	%
Grade 0	782	81.5	805	83.8	949	98.9	951	99.1	694	72.3
Grade 1	135	14.1	114	12.0	5	0.5	0	0	193	20.1
Grade 2	39	4.1	31	3.2	6	0.6	5	0.5	58	6.0
Grade 3	4	0.4	10	1.0	0	0	3	0.3	14	1.6
Grade 4	0	0	0	0	0	0	1	0.1	1	0.1

Median Follow-up: 25.4 months

Times to onset
From 1st fraction

Grade 1-4	16.8+/-12.7
Grade 2-4	17.5+/-9.5
Grade 3-4	[25] 15.8+/-5.3

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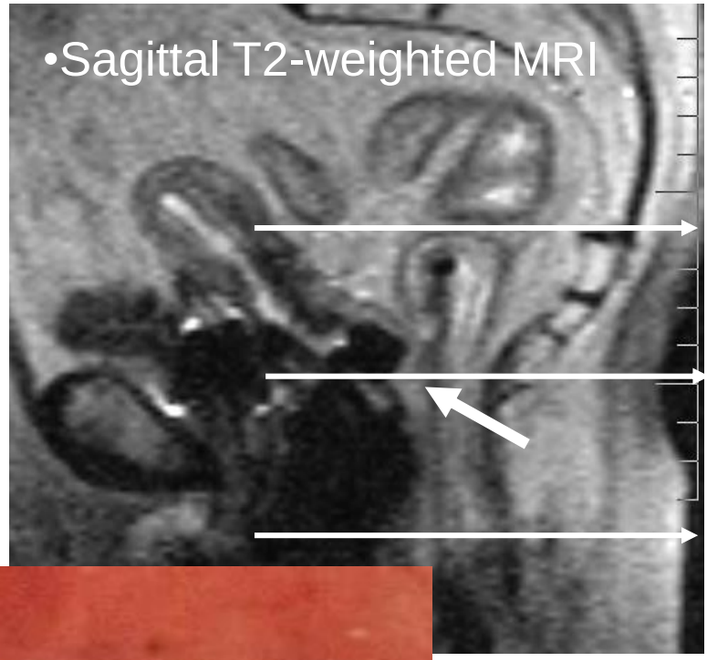
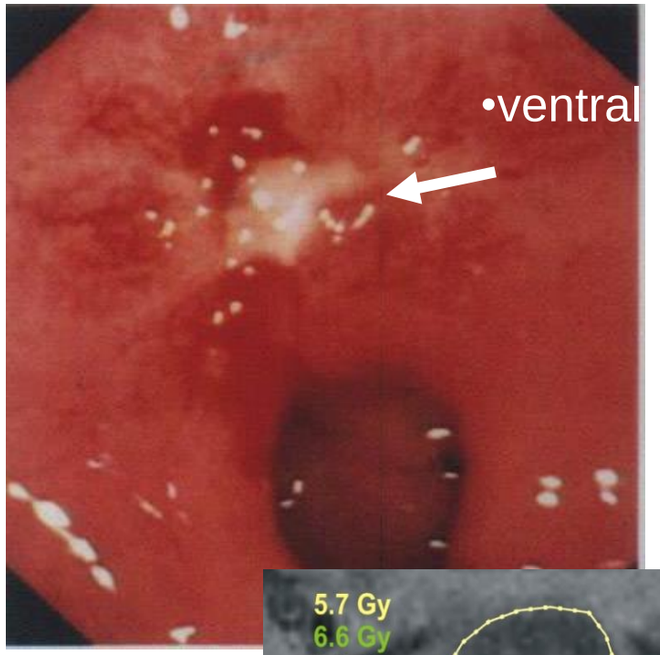
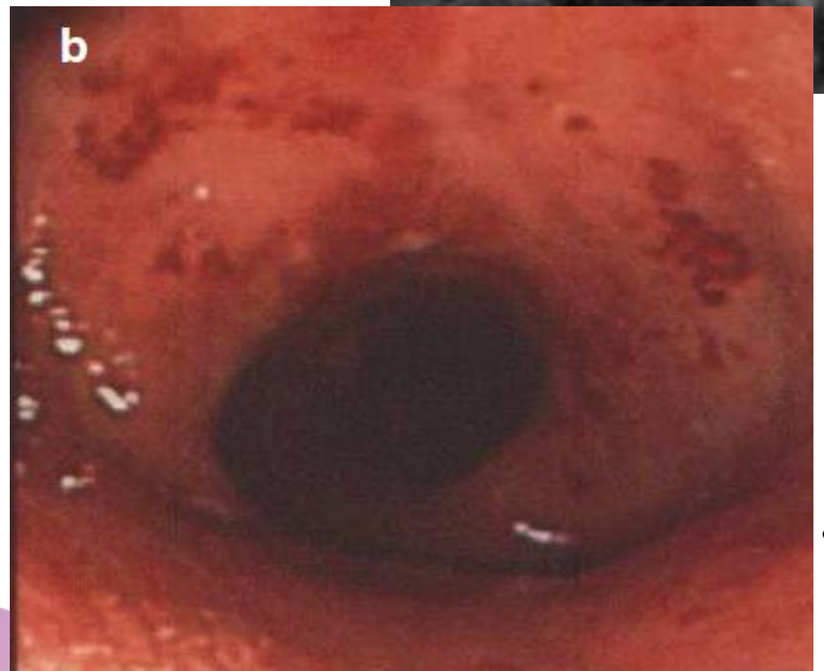
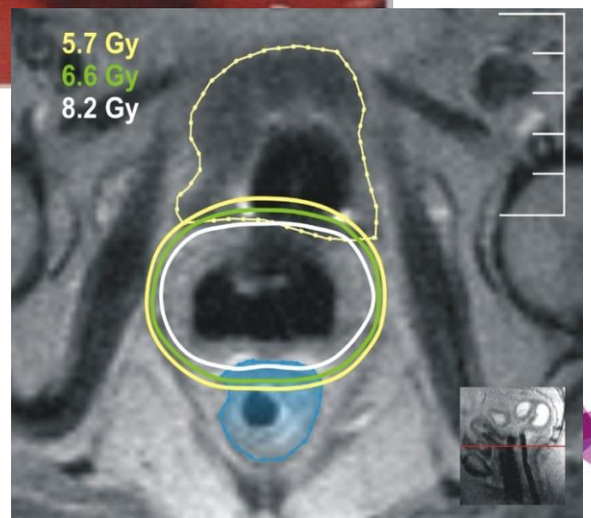
Rectum: Late telangiectasia and micro-ulceration



Endoscopy







•*Georg P et al. R&O 2009*

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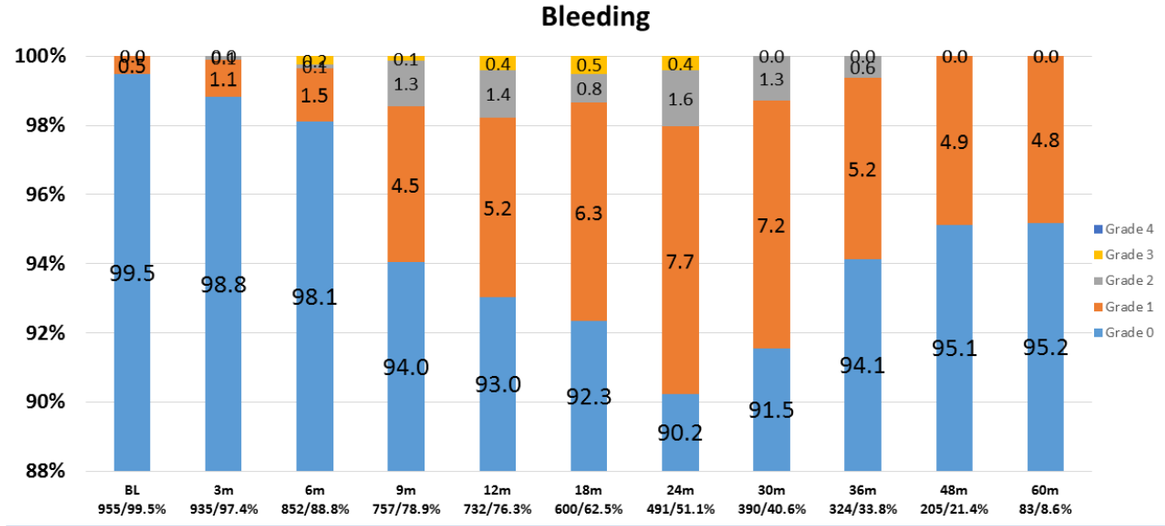
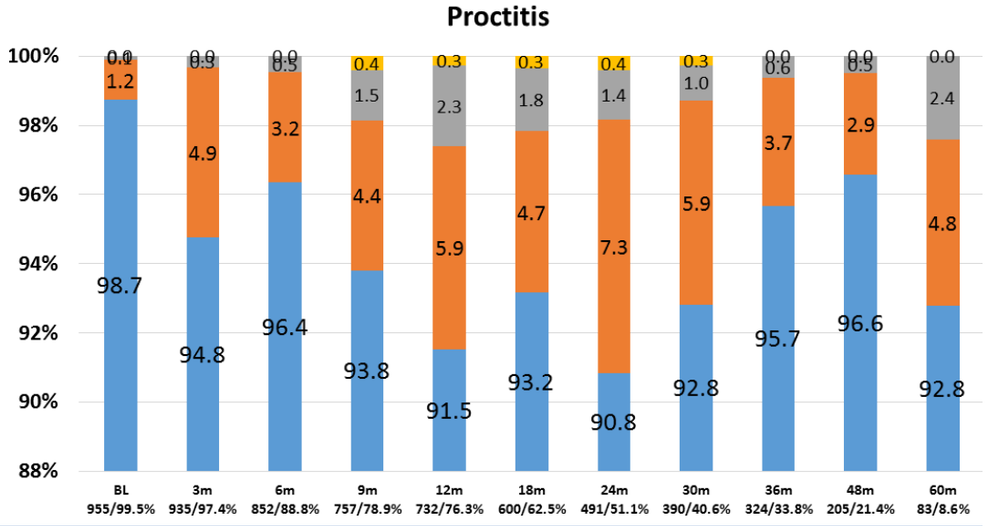
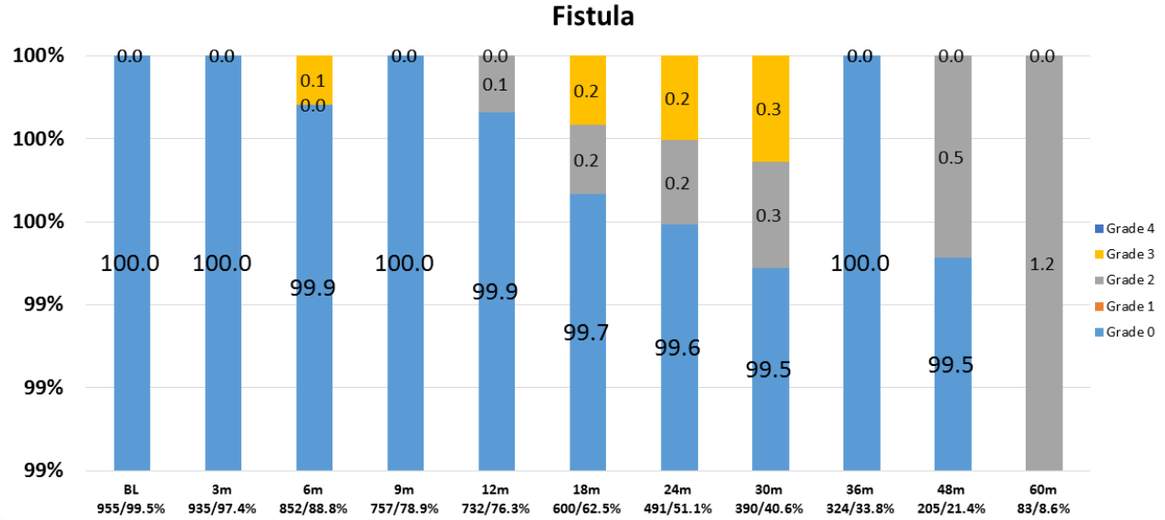
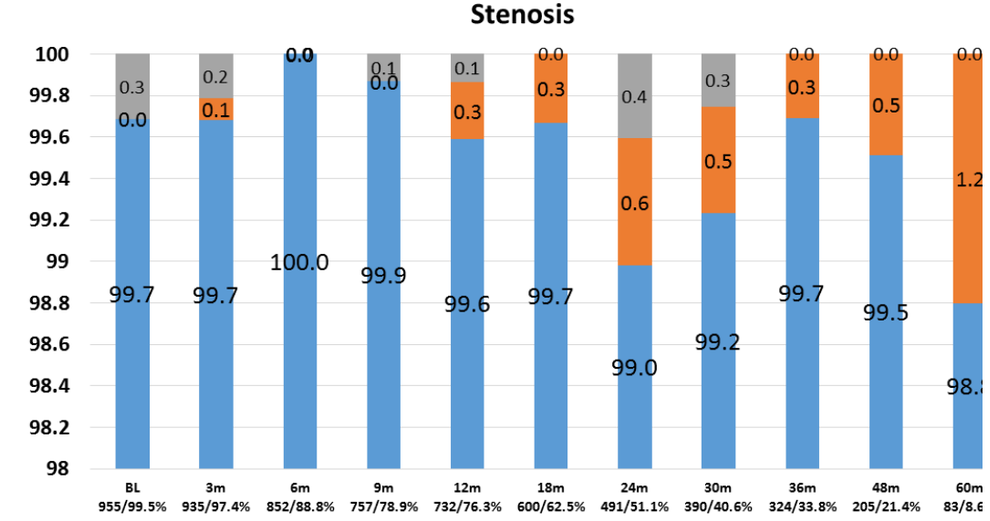
Rectum prevalence: bleeding, proctitis, fistula, stenosis



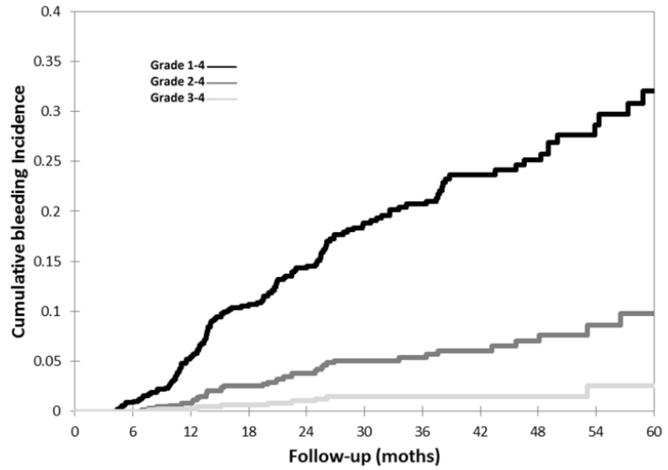






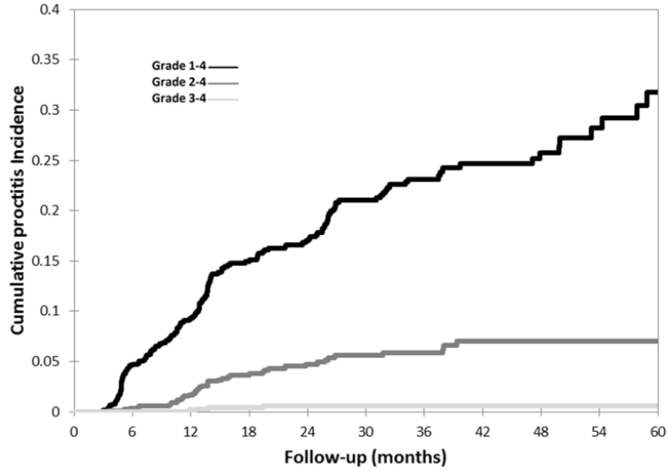
Actuarial estimate of bleeding, proctitis, stenosis, fistula

A



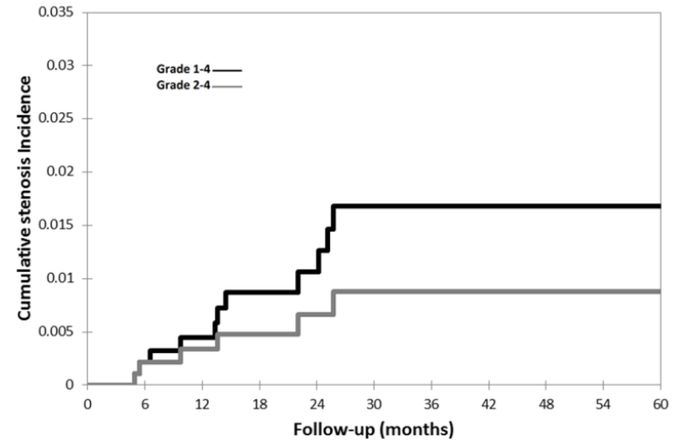
Number at risk						N events	Inc. at 3-y
Grade 1-4	960	722	436	260	137	155	20.7%
Grade 2-4	960	755	489	311	169	41	5.4%
Grade 3-4	960	759	501	319	175	10	0.6%

B



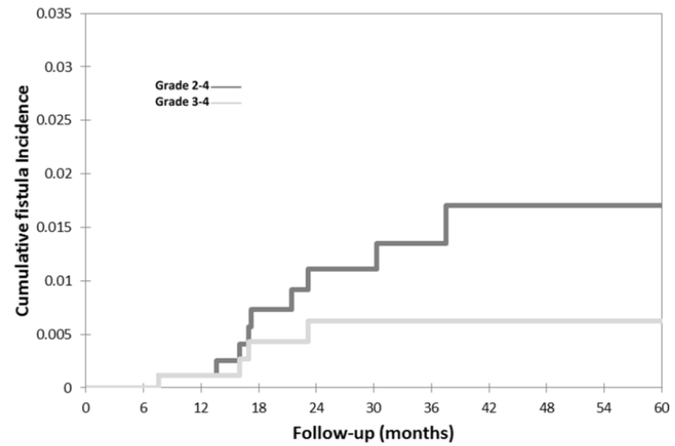
Number at risk						N events	Inc. at 3-y
Grade 1-4	960	695	426	257	136	175	23.1%
Grade 2-4	960	747	482	305	163	43	5.8%
Grade 3-4	960	760	504	322	177	4	0.6%

C



Number at risk						N events	Inc. at 3-y
Grade 1-4	960	760	503	319	174	11	1.7%
Grade 2-4	960	760	504	321	176	6	0.9%
Grade 3-4	960	761	507	324	179	0	0%

D



Number at risk						N events	Inc. at 3-y
Grade 1-4	960	760	503	322	178	9	1.4%
Grade 2-4	960	760	503	322	178	9	1.4%
Grade 3-4	960	760	504	322	178	4	0.6%

ESTRO School

Morbidity: GI, Rectum, Bowel

Radiotherapy and Oncology 127 (2018) 431–439

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

EMBRACE

Bowel morbidity following radiochemotherapy and image-guided adaptive brachytherapy for cervical cancer: Physician- and patient reported outcome from the EMBRACE study

Nina Boje Kibsgaard Jensen [a,*], Richard Pötter [b], Kathrin Kirchheiner [b], Lars Fokdal [a], Jacob Christian Lindegaard [a], Christian Kirisits [b], Renaud Mazeron [c], Umesh Mahantshetty [d], Ina Maria Jürgenliemk-Schulz [e], Barbara Segedin [f], Peter Hoskin [g], Kari Tanderup [a], EMBRACE Collaborative Group [1]

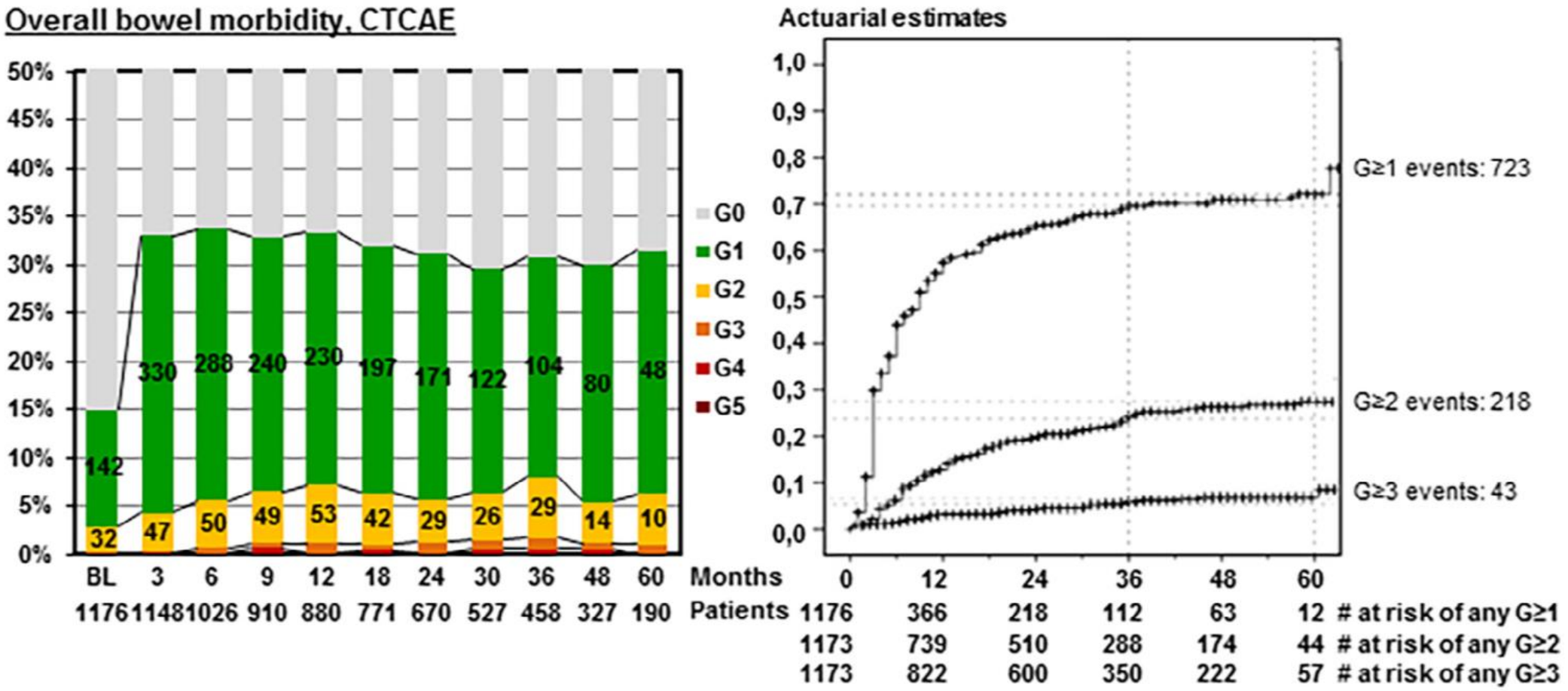
EMBRACE I. CTCAE v3
Diarrhea
Flatulence
Incontinence (anal)
Proctitis
Bleeding (hemorrhage GI, anus, rectum, sigmoid, colon, small bowel)
Stricture / stenosis (anus, rectum, sigmoid, colon, small bowel)
Fistula (anus, rectum, sigmoid, colon, small bowel)
Gastro-intestinal other

Bowel morbidity overview

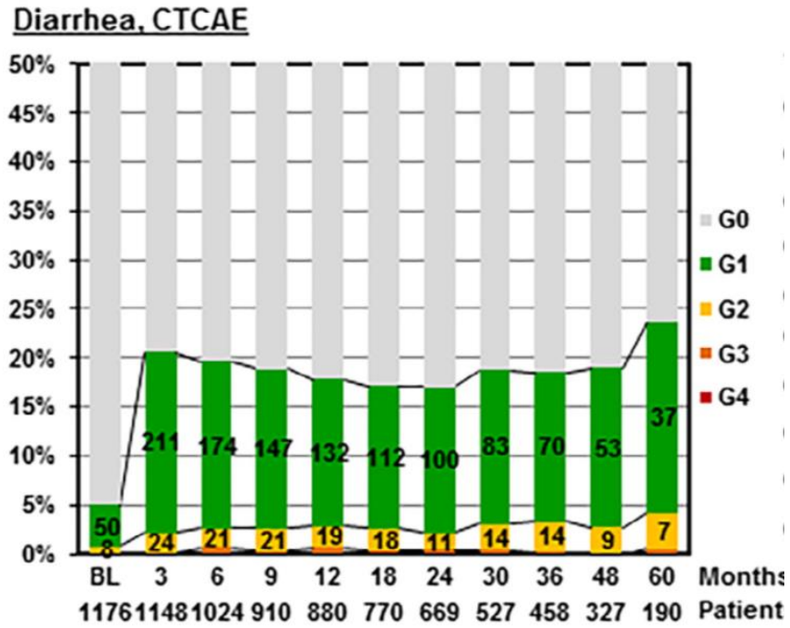
CTCAE v. 3.0	Diarrhea		Flatulence		Incontinence		Stenosis/stricture		Fistula		Overall bowel morbidity	
Grade	BL	FUP	BL	FUP	BL	FUP	BL	FUP	BL	FUP	BL*	FUP*
Grade 0	1117 (95.0%)	679 (57.7%)	1082 (92.0%)	694 (59.2%)	1164 (99.0%)	1018 (86.6%)	1175 (99.9%)	1144 (97.6%)	1174 (99.8%)	1165 (99.1%)	1000 (85.0%)	453 (38.5%)
Grade 1	50 (4.3%)	395 (33.6%)	78 (6.6%)	382 (32.6%)	12 (1.0%)	131 (11.1%)	1 (0.01%)	13 (1.1%)	2 (0.2%)	5 (0.4%)	142 (12.1%)	505 (42.9%)
Grade 2	8 (0.7%)	85 (7.2%)	16 (1.4%)	97 (8.2%)	0	23 (2.0%)	0	4 (0.3%)	0	1 (0.1%)	32 (2.7%)	175 (14.9%)
Grade 3	1 (0.1%)	16 (1.4%)	N.A.	N.A.	0	2 (0.2%)	0	7 (0.6%)	0	2 (0.2%)	1 (0.1%)	27 (2.3%)
Grade 4	0	1 (0.1%)	N.A.	N.A.	0	2 (0.2%)	0	5 (0.4%)	0	3 (0.2%)	1 (0.1%)	15 (1.3%)
Grade 5	0	0	N.A.	N.A.	0	0	0	0	0	0	0	1 (0.1%)
Total	1176	1176	1176	1173	1176	1176	1176	1173	1176	1176	1176	1176

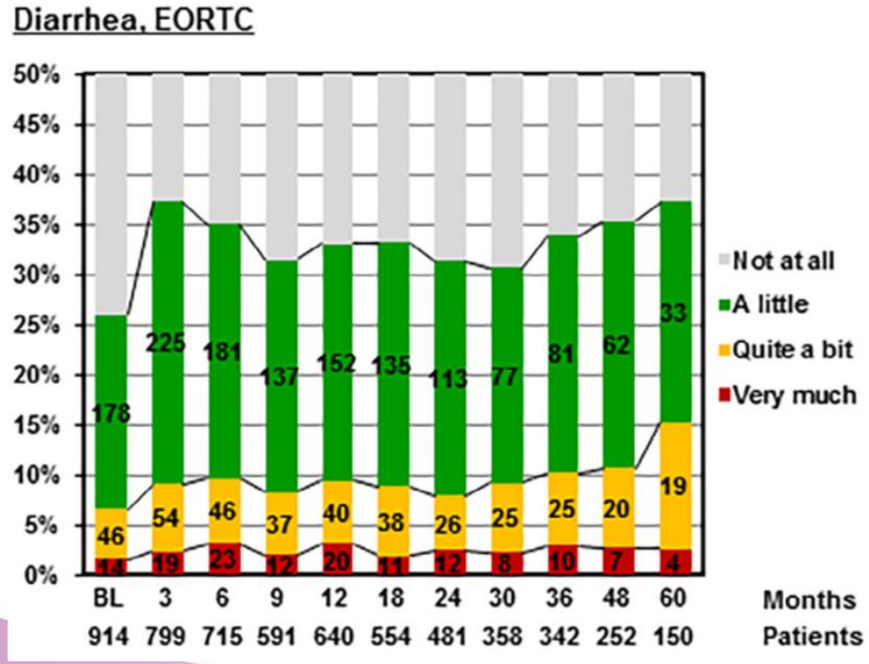
EORTC C30/CX24 reporting	Have you had diarrhea		Have you been constipated		Have you had cramps in your abdomen		Have you had difficulty controlling your bowel	
	BL	FUP	BL	FUP	BL	FUP	BL	FUP
"Not at all"	676 (74.0%)	329 (36.0%)	625 (68.4%)	524 (57.4%)	554 (60.6%)	339 (37.1%)	814 (89.0%)	443 (48.5%)
"A little"	178 (19.5%)	355 (38.9%)	184 (20.1%)	263 (28.7%)	245 (26.8%)	353 (38.6%)	83 (9.1%)	313 (34.2%)
"Quite a bit"	46 (5.0%)	161 (17.6%)	78 (8.5%)	88 (9.6%)	83 (9.1%)	157 (17.2%)	16 (1.8%)	111 (12.1%)
"Very much"	14 (1.5%)	68 (7.4%)	27 (3.0%)	39 (4.3%)	32 (3.5%)	65 (7.1%)	1 (0.1%)	47 (5.2%)
Total	914	913	914	914	914	914	914	914

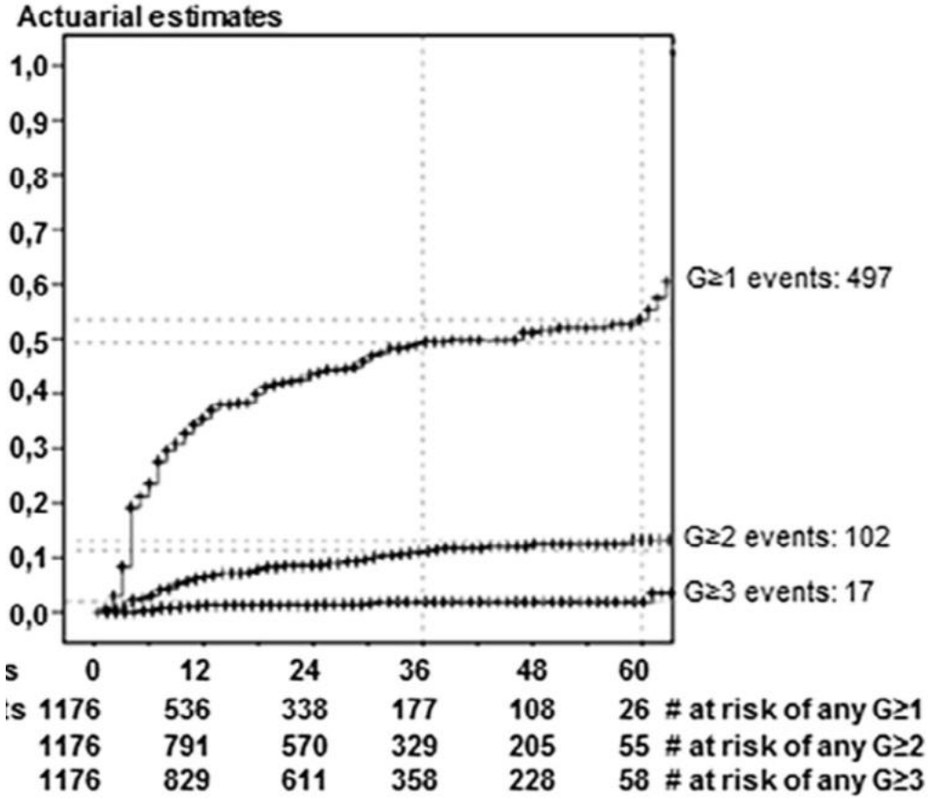
Bowel morbidiy overall



Diarrhea







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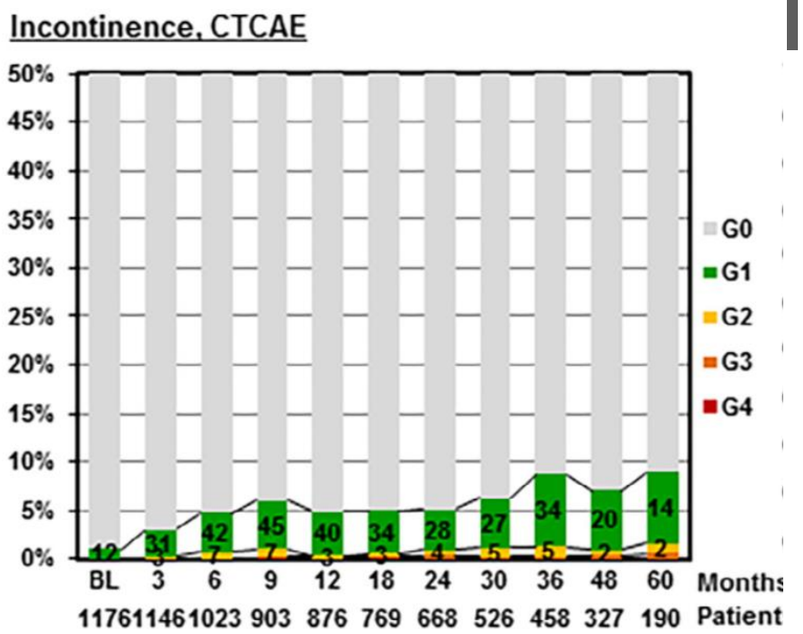
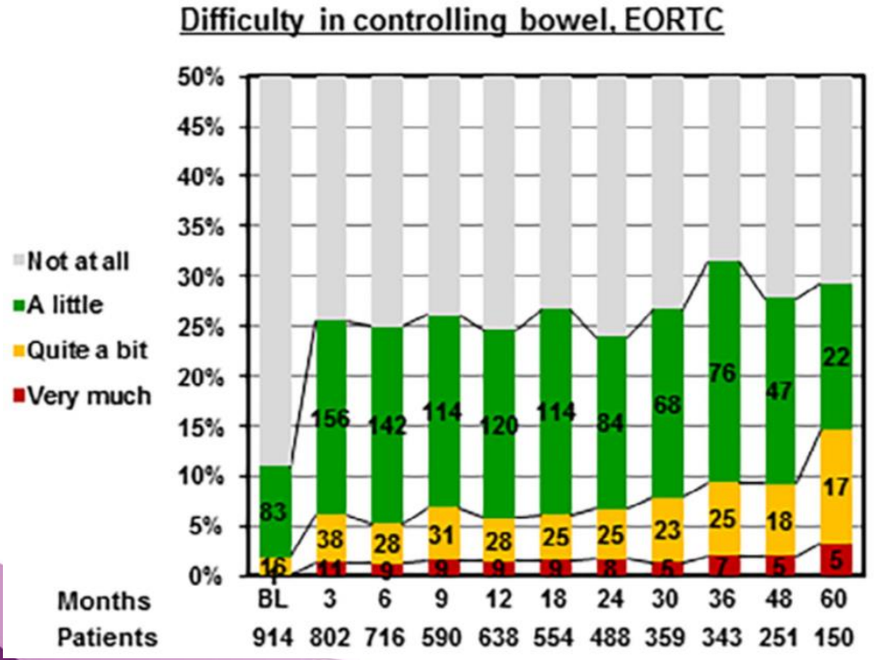
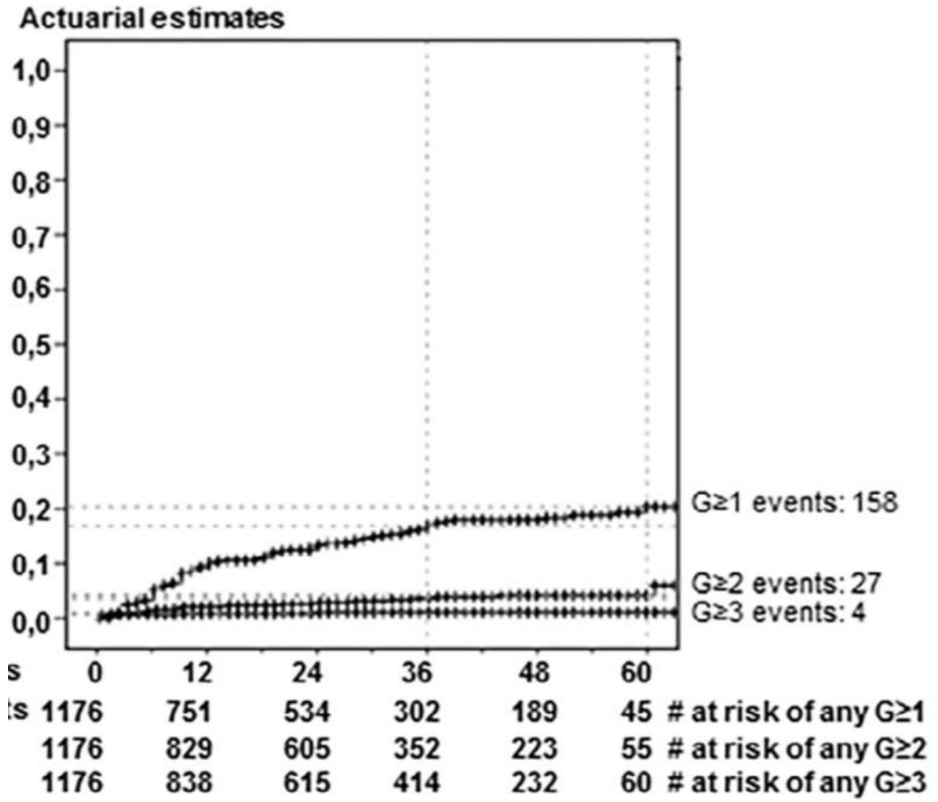
Incontinence







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Vaginal morbidity

International Journal of Radiation Oncology biology • physics

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Clinical Investigation: Gynecologic Tumor

Manifestation Pattern of Early-Late Vaginal Morbidity After Definitive Radiation (Chemo)Therapy and Image-Guided Adaptive Brachytherapy for Locally Advanced Cervical Cancer: An Analysis From the EMBRACE Study

Kathrin Kirchheiner, MSc,*,† Remi A. Nout, MD, PhD,‡ Kari Tanderup, PhD,§ Jacob C. Lindegaard, MD, DMSc,§ Henrike Westerveld, MD, PhD,‖ Christine Haie-Meder, MD,¶ Primož Petrič, MD, PhD,#,** Umesh Mahantshetty, DMRT, MD, DNB,†† Wolfgang Dörr, DVM, PhD,*,† and Richard Pötter, MD, PhD*,†

EMBRACE I. CTCAE v3
Vaginal dryness
Vaginal stenosis/length
Vaginal mucositis
Bleeding (hemorrhage GU)
Fistula (Vagina cont.)
Vaginal other
Hormonal therapy
Regular vaginal dilatation

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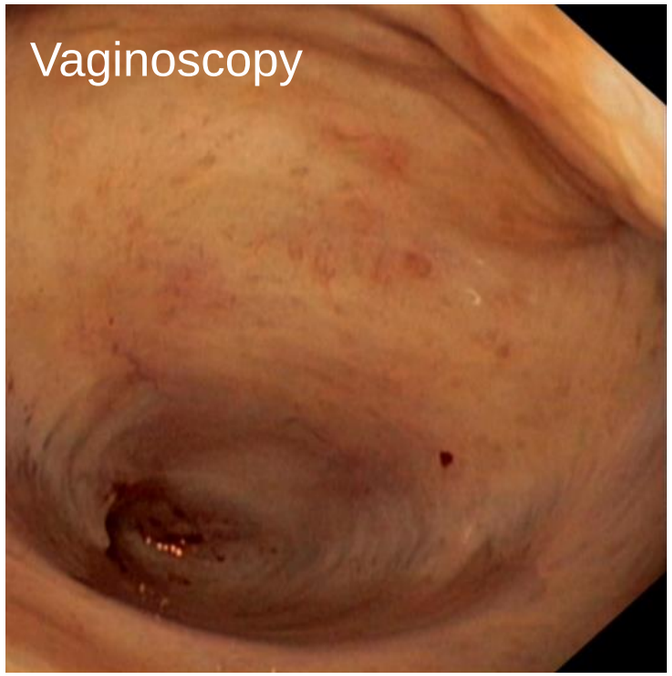
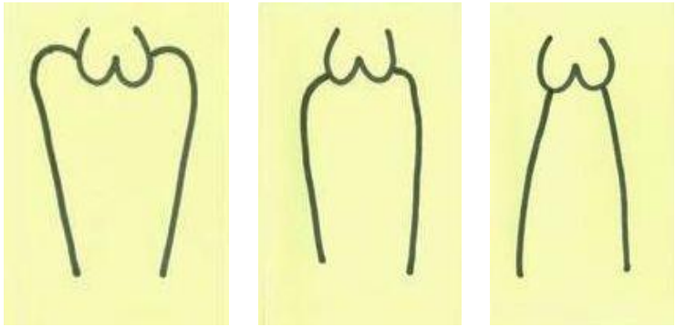
Vaginal stenosis

Flattening of the fornices → „conical appearance“





Impact on sexuality:

Feeling of vaginal shortening

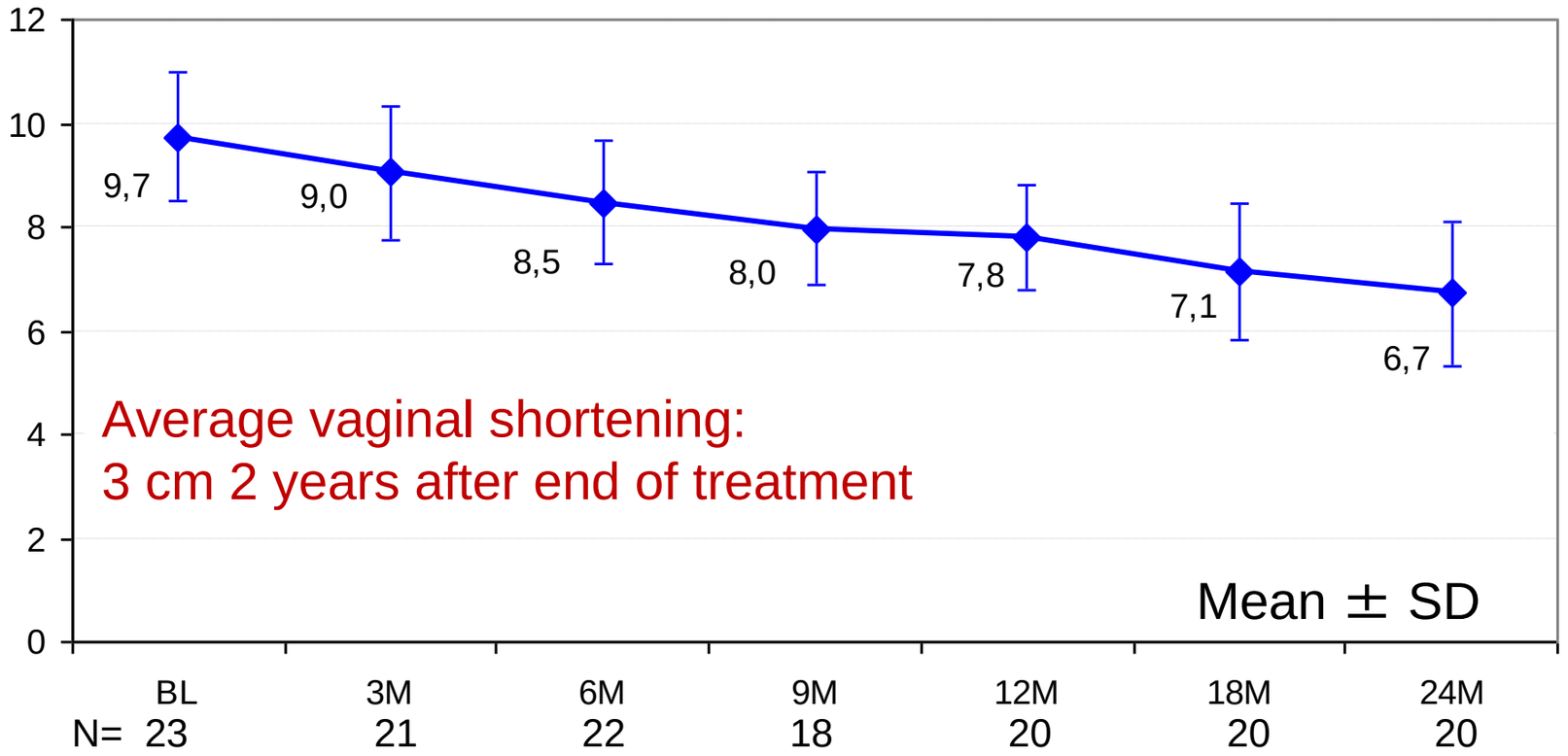
Feeling of vaginal tightening, esp. at the introitus

→ Pain during intercourse (dyspareunia)

Kirchheiner et. al. SUON 2012

Vaginal length reduction

Fibrosis, loss of elasticity



Kirchheiner et al. abstract ESSM 2016

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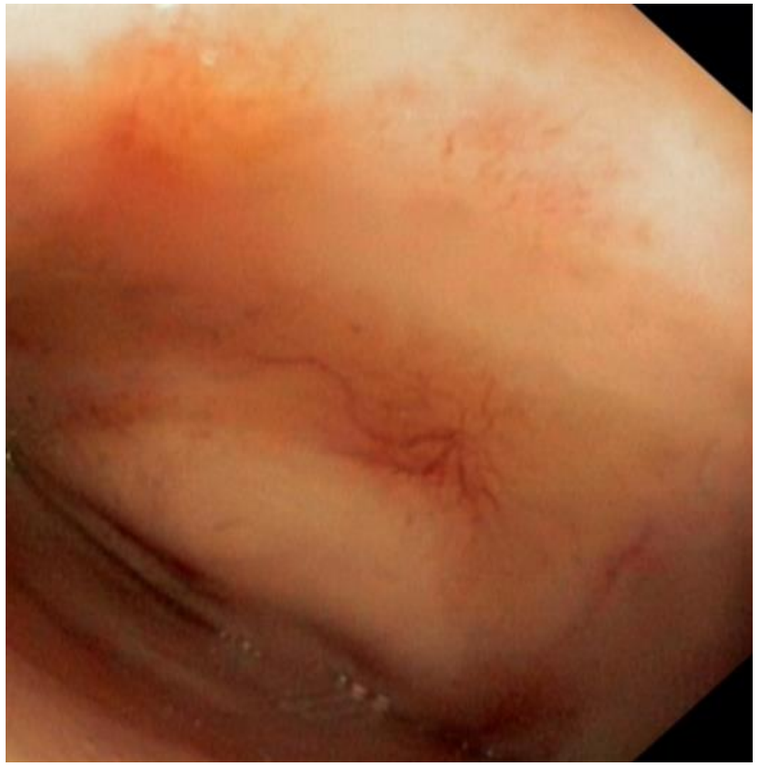
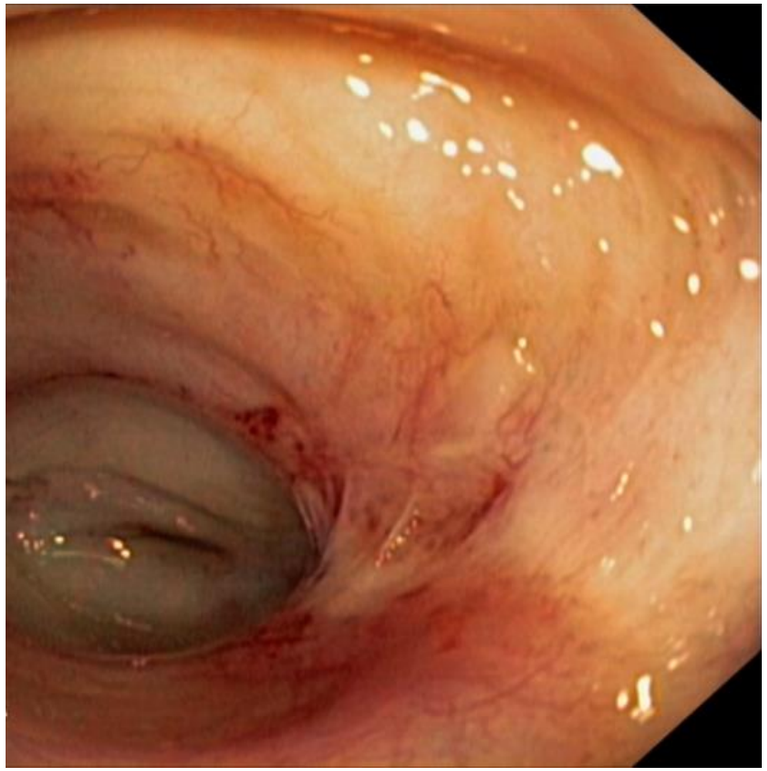
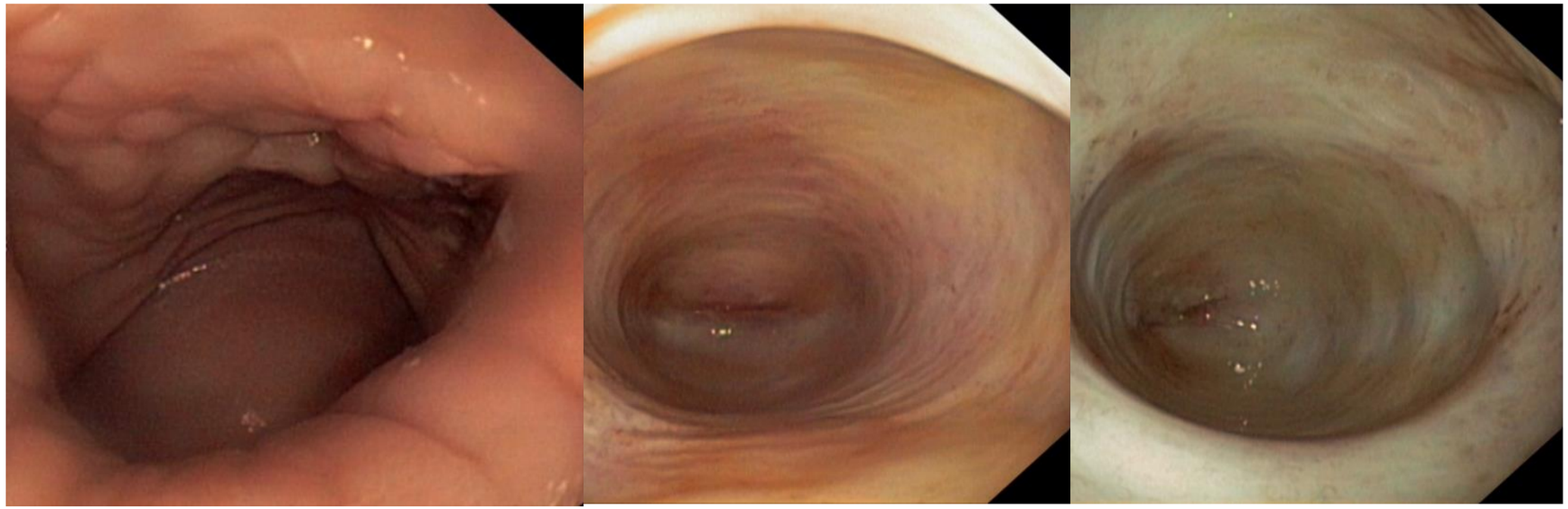
Telangiectasia





Impact on sexuality:
Contact bleeding during or after intercourse
(causes fear of recurrence)

Atrophy of the mucosa



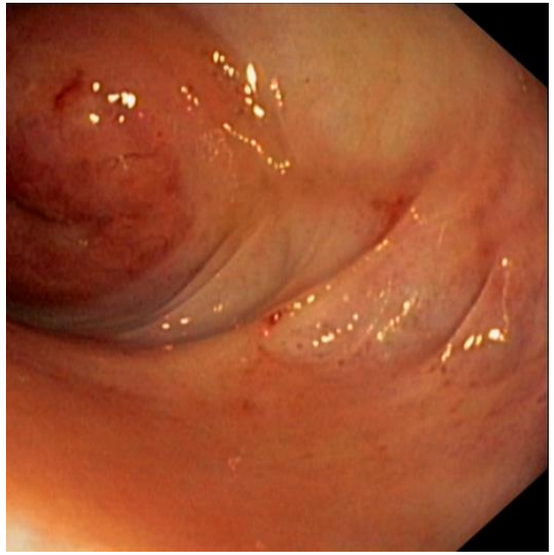
Impact on sexuality

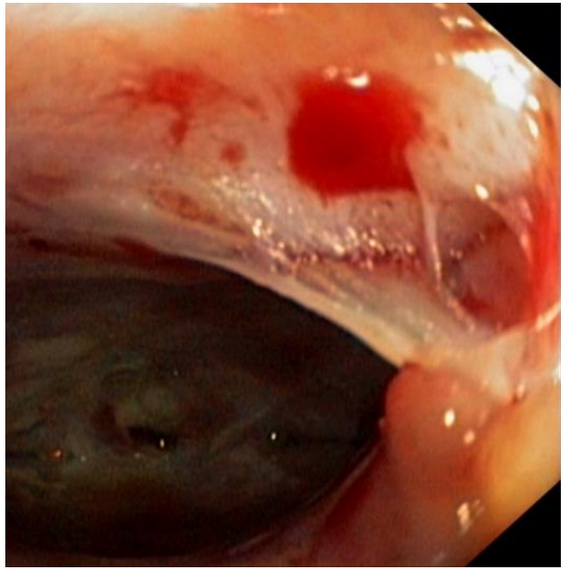
Reduced lubrication despite sexual arrousal

→ painful friction and irritation of the mucosa,

Feeling of soreness, itching, burning

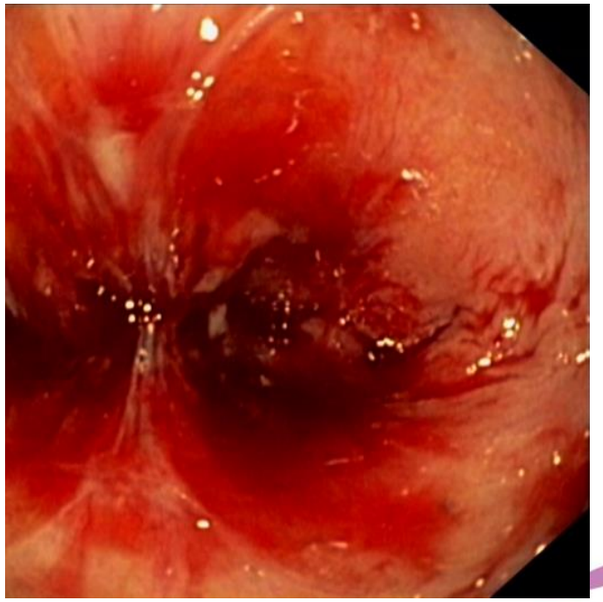
Adhesions





Resolvement during examination often painful

Impact on sexuality:
Rupture of adhesion during intercourse causes pain and bleeding



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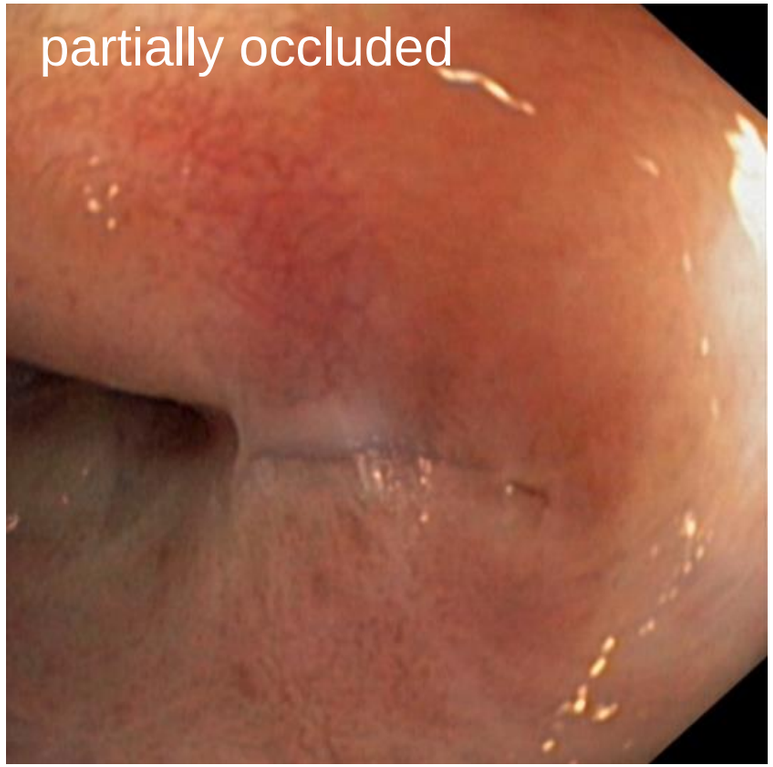
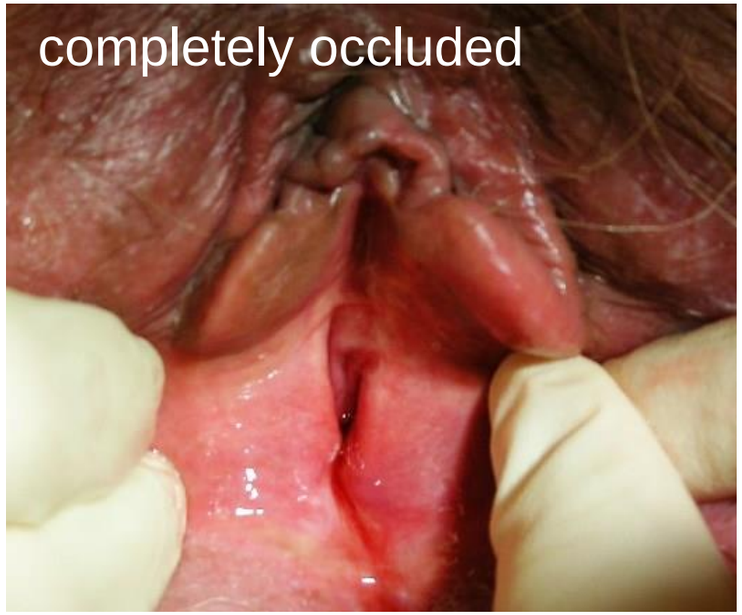
Vaginal occlusion





Prevention:
Regular dilation
and / or intercourse

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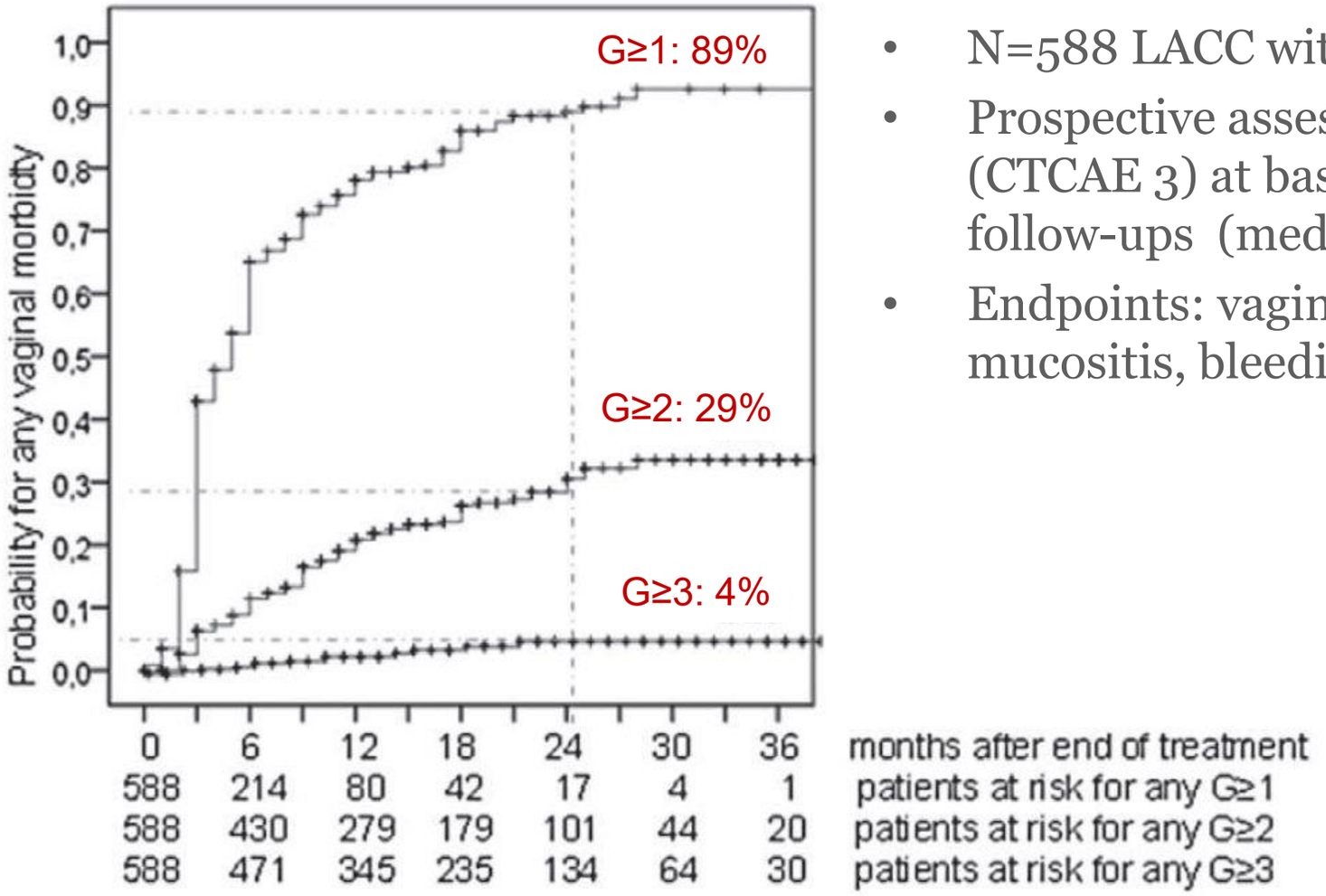
Vaginal morbidity overview



- N=588 LACC within EMBRACE study
- Prospective assessment of morbidity (CTCAE 3) at baseline and regular follow-ups (median 15 months)
- Endpoints: vaginal stenosis, dryness, mucositis, bleeding, fistula

Kirchheiner et al.
IJROBP 2014

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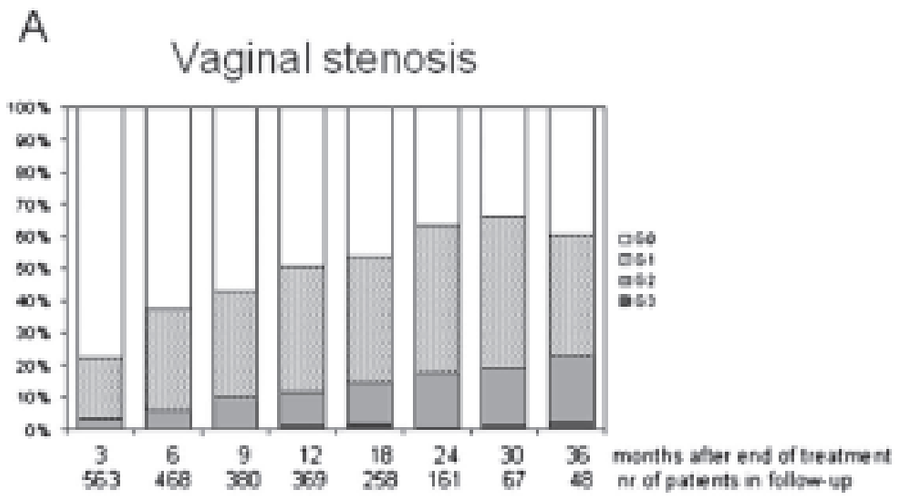
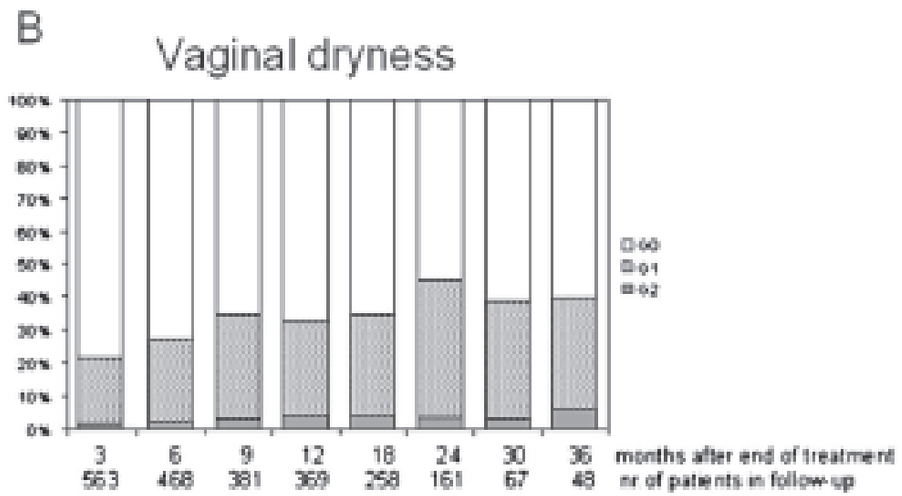
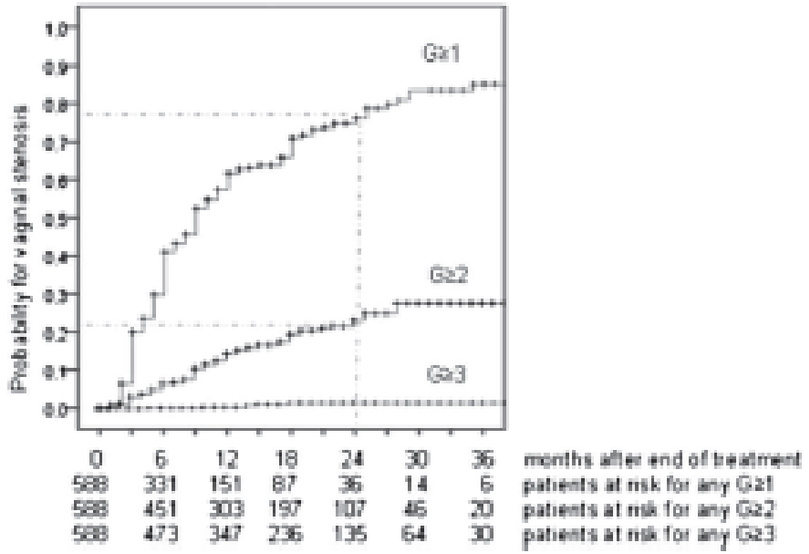
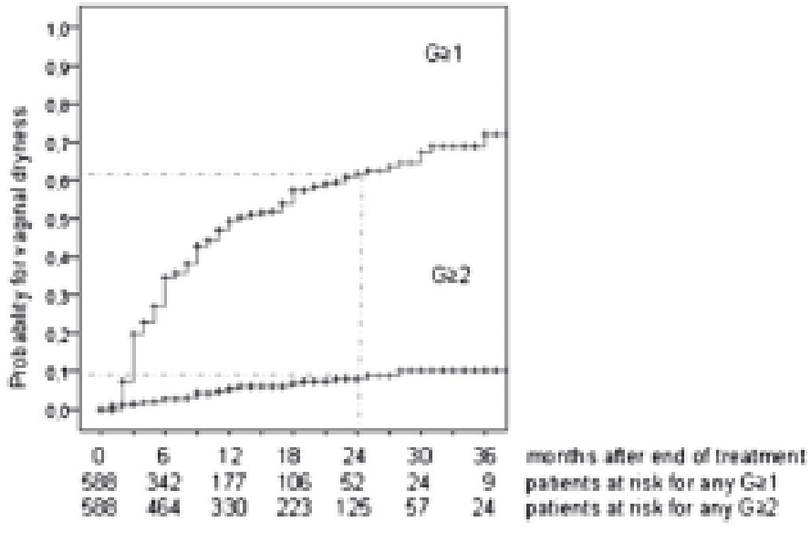
Vaginal stenosis and dryness









Kirchheiner et al.
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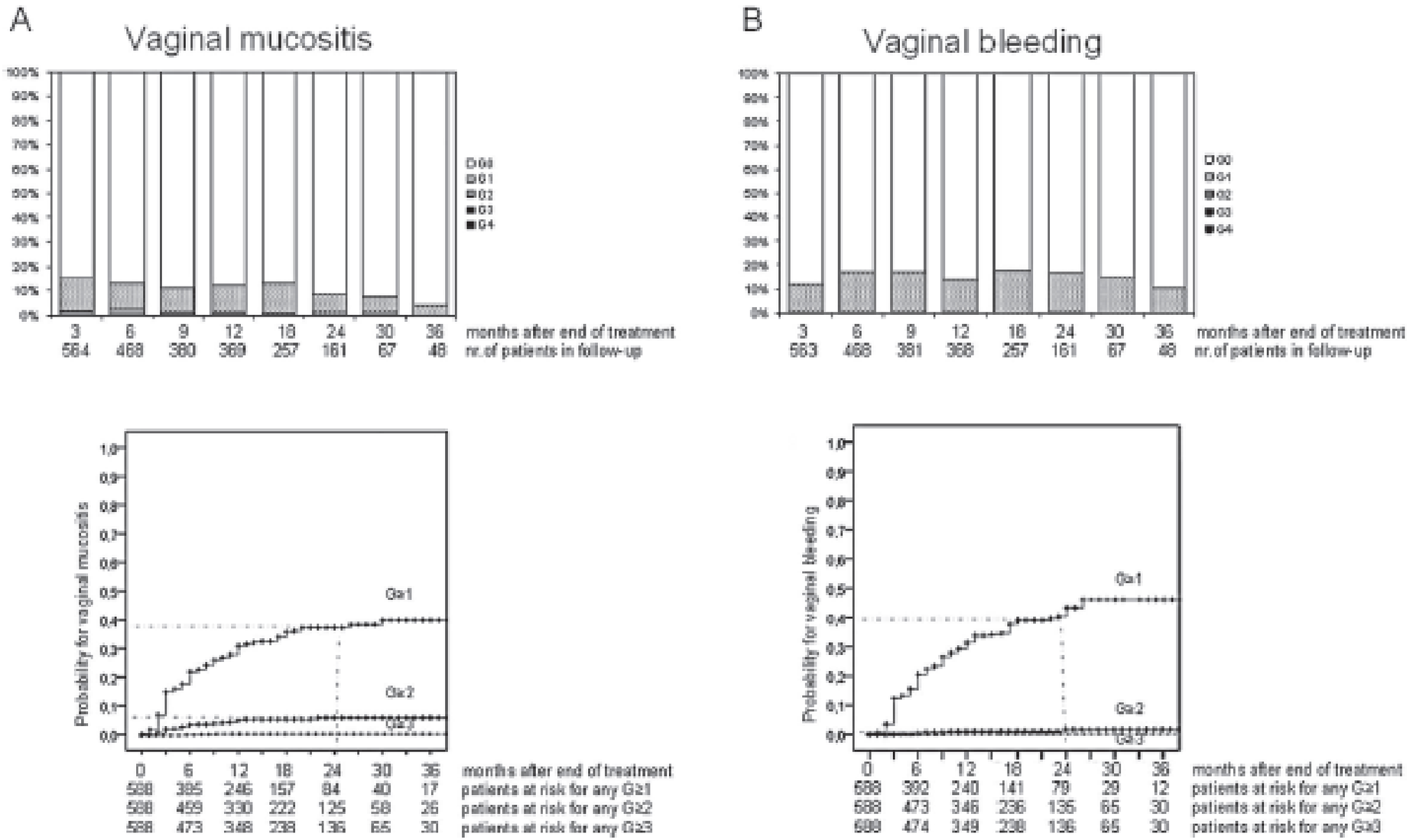
Vaginal mucositis and bleeding



Kirchheiner et al.
IJROBP 2014

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Table 3 Crude incidences of treatment-related individual vaginal symptoms and overall vaginal morbidity in 588 patients with a median follow-up time of 15 months

Grade	Vaginal stenosis	Vaginal dryness	Vaginal mucositis	Vaginal bleeding	Vaginal fistula	Other vaginal symptoms	Overall vaginal morbidity
G0	241 (41%)	312 (53%)	415 (71%)	407 (69%)	582 (99%)	523 (89%)	155 (26%)
G1	256 (43%)	244 (42%)	146 (25%)	175 (30%)	2	47 (8%)	309 (53%)
G2	86 (15%)	32 (5%)	23 (4%)	5 (1%)	0	14 (2%)	111 (19%)
G3	5 (1%)	N.A.	3	1	4 (1%)	4 (1%)	12 (2%)
G4	N.A.	N.A.	1	0	0	0	1
G5	N.A.	N.A.	0	0	0	0	0

Abbreviation: N.A. = not applicable.

Crude incidence, rates for single vaginal endpoints

Summary

At two years, actuarial probability of severe vaginal morbidity (G≥3) was 3.6%.

However, mild and moderate vaginal symptoms were still pronounced (G≥1: 89%, G≥2: 29%), of which the majority developed within 6 months.

Stenosis was most frequently observed, followed by vaginal dryness. Vaginal bleeding and mucositis was mainly mild and infrequently reported.

Kirchheiner et al.
IJROBP 2014

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Impact on sexuality

International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Health-Related Quality of Life in Locally Advanced Cervical Cancer Patients After Definitive Chemoradiation Therapy Including Image Guided Adaptive Brachytherapy: An Analysis From the EMBRACE Study

Kathrin Kirchheiner, MSc, PhD,* Richard Pötter, MD,*,† Kari Tanderup, PhD,‡ Jacob C. Lindegaard, MD, DMSc,‡ Christine Haie-Meder, MD,§ Primož Petrič, MSc, MD,‖,¶ Umesh Mahantshetty, DMRT, MD, DNB,# Ina M. Jürgenliemk-Schulz, MD, PhD,** Bhavana Rai, MD, DNB,†† Rachel Cooper, FRCR,‡‡ Wolfgang Dörr, DVM, PhD,*,† and Remi A. Nout, MD, PhD§§, for the EMBRACE Collaborative Group

Radiotherapy and Oncology 118 (2016) 160–166

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Radiotherapy and Oncology

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Brachytherapy

Dose–effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study

Kathrin Kirchheiner [a,*], Remi A. Nout [b], Jacob C. Lindegaard [c], Christine Haie-Meder [d], Umesh Mahantshetty [e], Barbara Segedin [f], Ina M. Jürgenliemk-Schulz [g], Peter J. Hoskin [h], Bhavana Rai [i], Wolfgang Dörr [a,j], Christian Kirisits [a], Søren M. Bentzen [k], Richard Pötter [a,j], Kari Tanderup [c], the EMBRACE Collaborative Group[1]

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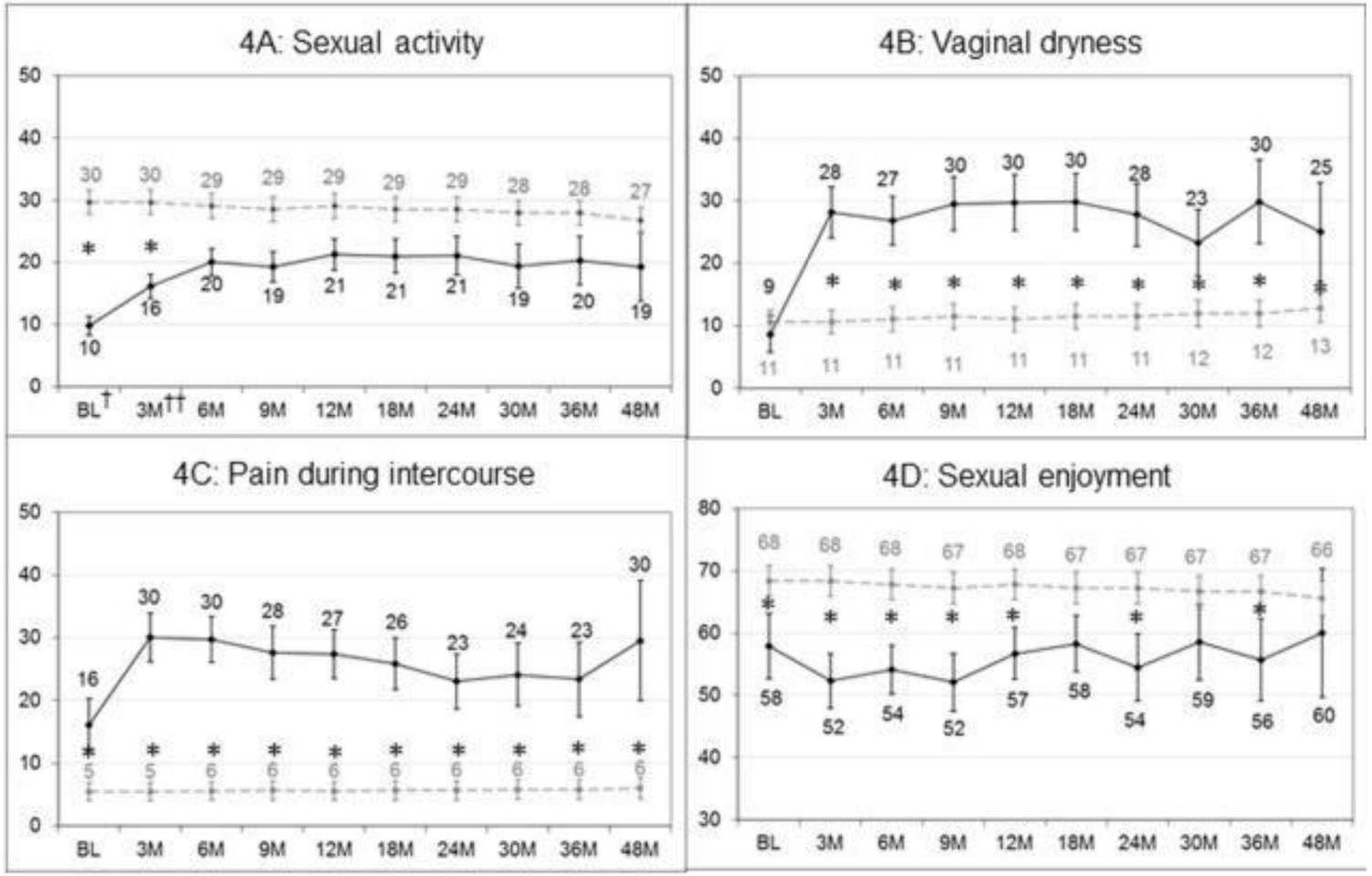
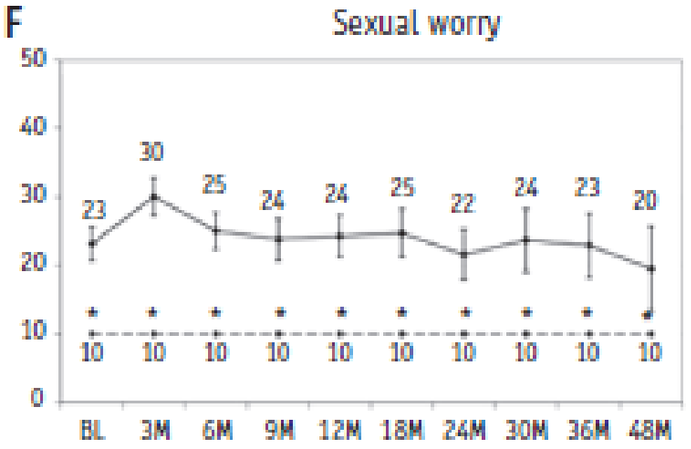
Impact on sexuality



- Comparison with age-matched, female normative reference population (dotted line).



Kirchheiner et al. IJROBP 2016

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Stenosis: ICRU recto-vaginal reference point

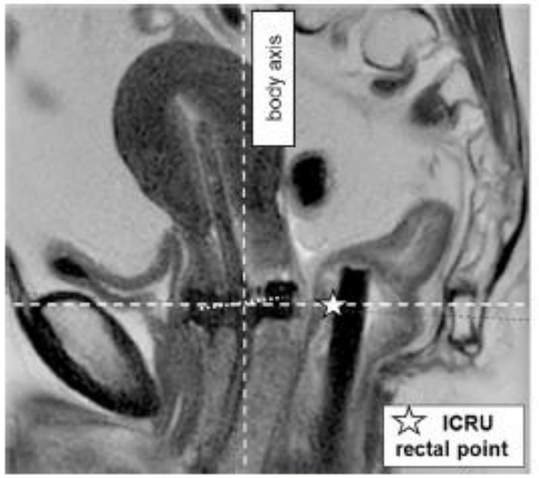

Fig. 1. ICRU rectal point depicted on sagittal T2 MRI, positioned at the intersection level between tandem and the source positions in the ring and 5 mm dorsal of the posterior vaginal wall on the axis perpendicular to the body axis.

With increasing dose to the recto-vaginal reference point, the probability of vaginal stenosis G≥2 increases significantly (p=0.003).

Based on the model curve, the risk was 20% at 65Gy, 27% at 75Gy and 34% at 85Gy (recto-vaginal reference point dose).

Keeping the EBRT dose at 45Gy/25fractions and decreasing the dose contribution of brachytherapy to the vagina decrease the risk of stenosis.

A planning aim of ≤65Gy EQD2 (EBRT+brachytherapy dose) to the recto-vaginal reference point is therefore proposed.

Kirchheiner et al.

RO 2016

Morbidity: others

Radiotherapy and Oncology 127 (2018) 440–448

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EMBRACE

Fatigue, insomnia and hot flashes after definitive radiochemotherapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: An analysis from the EMBRACE study

Stéphanie Smet [a,b], Richard Pötter [a], Christine Haie-Meder [c], Jacob C. Lindegaard [d], Ina Schulz-Juergenliemk [e], Umesh Mahantshetty [f], Barbara Segedin [g], Kjersti Bruheim [h], Peter Hoskin [i], Bhavana Rai [j], Fleur Huang [k], Rachel Cooper [l], Erik van Limbergen [b], Kari Tanderup [d], Kathrin Kirchheiner [b,*], the EMBRACE Collaborative Group [1]

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EMBRACE

Physician assessed and patient reported lower limb edema after definitive radio(chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: A report from the EMBRACE study

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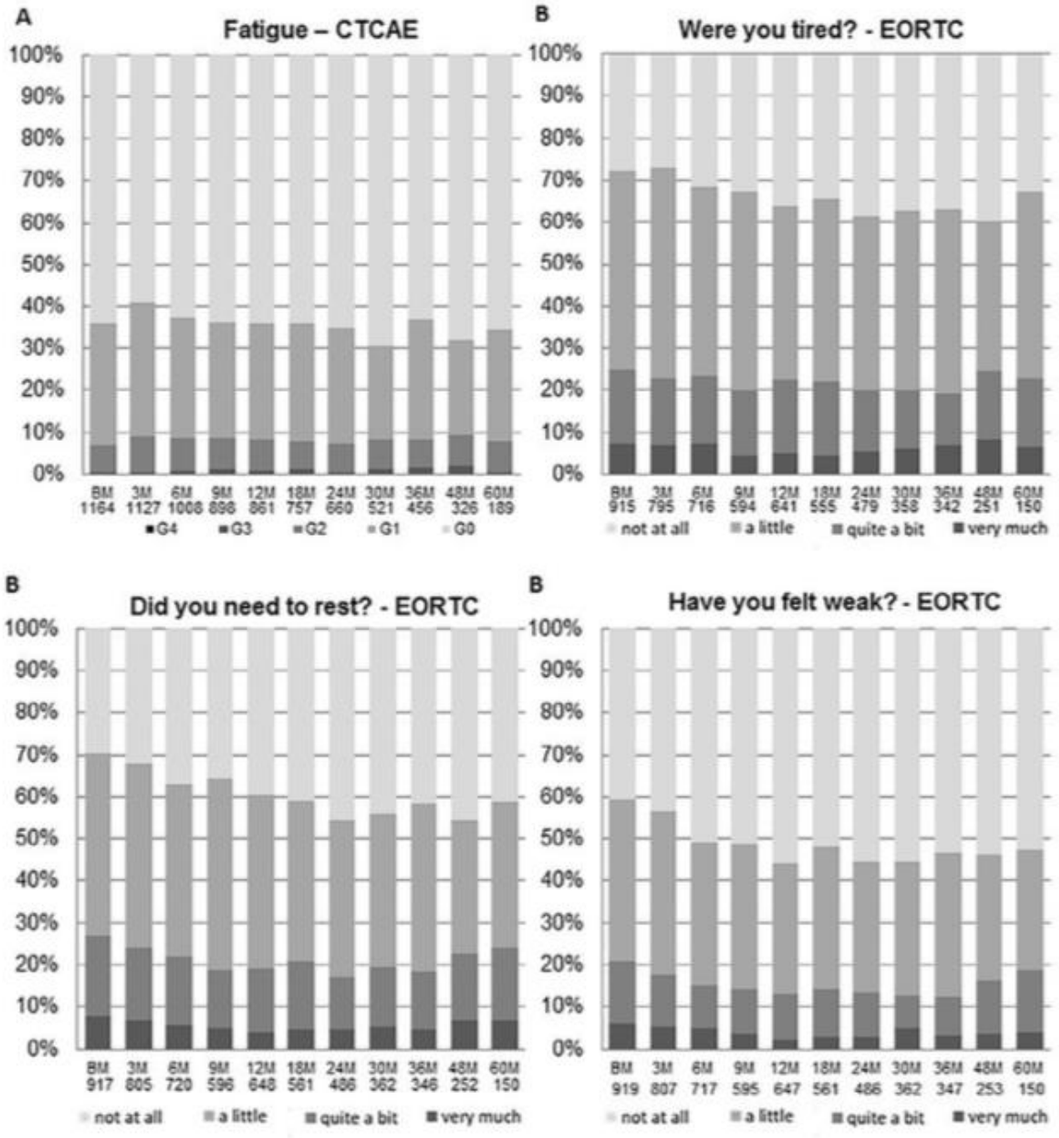
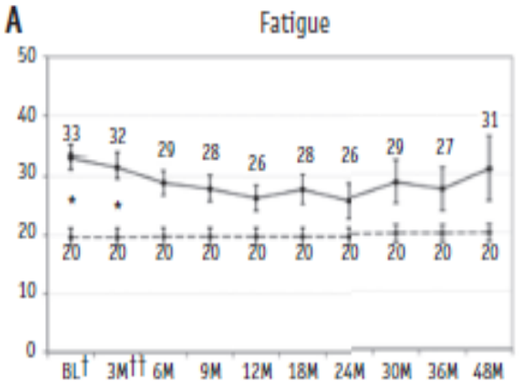
EMBRACE I. CTCAE v3
Fibrosis – deep connective tissue (pelvis right / left)
Fracture – insufficiency (Pelvic ring / Femoral head)
Muscle/soft tissue/bone other
Edema: limb
Edema: trunk/genital
Fatigue
Insomnia
Hot flashes
Other, specify category and grade

Fatigue





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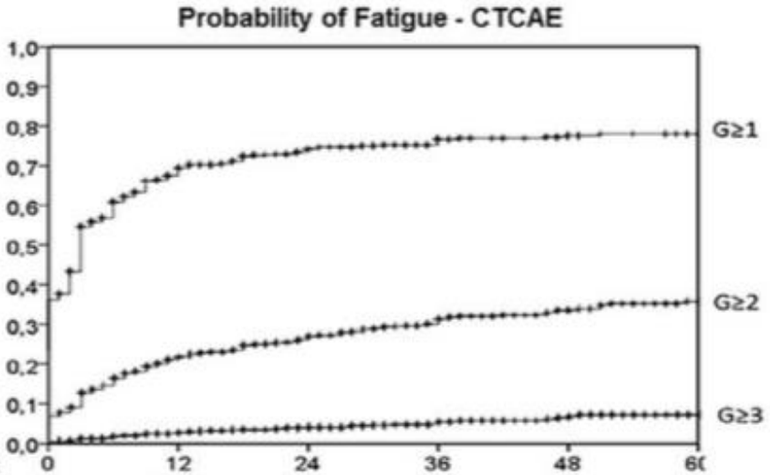

Months after treatment	0	12	24	36	48	60
Pts at risk for any G≥1	1164	295	178	105	64	33
Pts at risk for any G≥2	1164	706	502	307	198	93
Pts at risk for any G≥3	1164	853	635	403	264	123

	events	total	BM	1y	3y	5y
G≥1	841	1164	36%	69%	77%	78%
G≥2	314	1164	6.8%	22%	31%	36%
G≥3	52	1164	0.6%	2.7%	5.5%	7.2%

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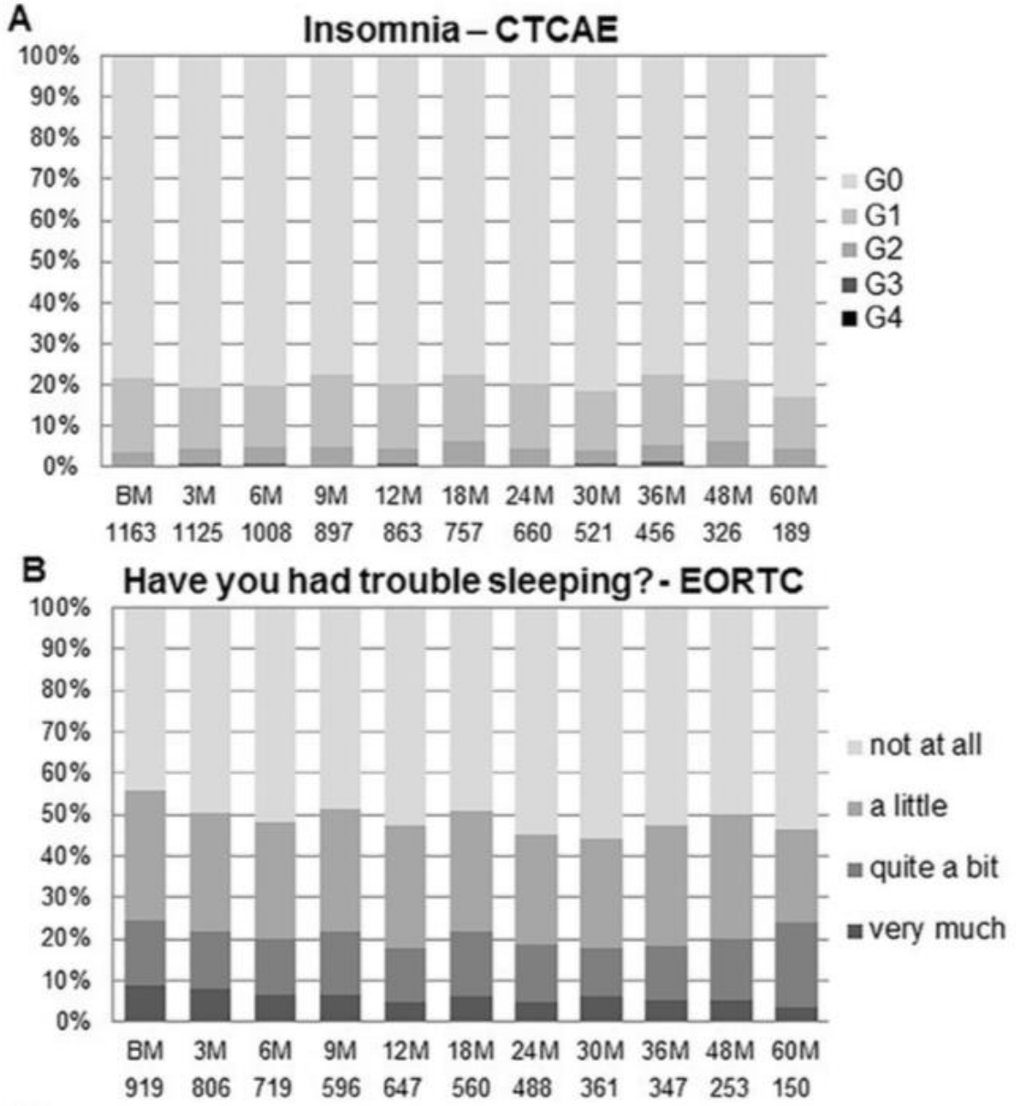
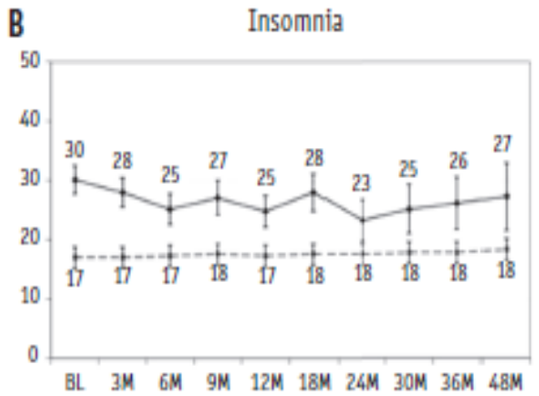
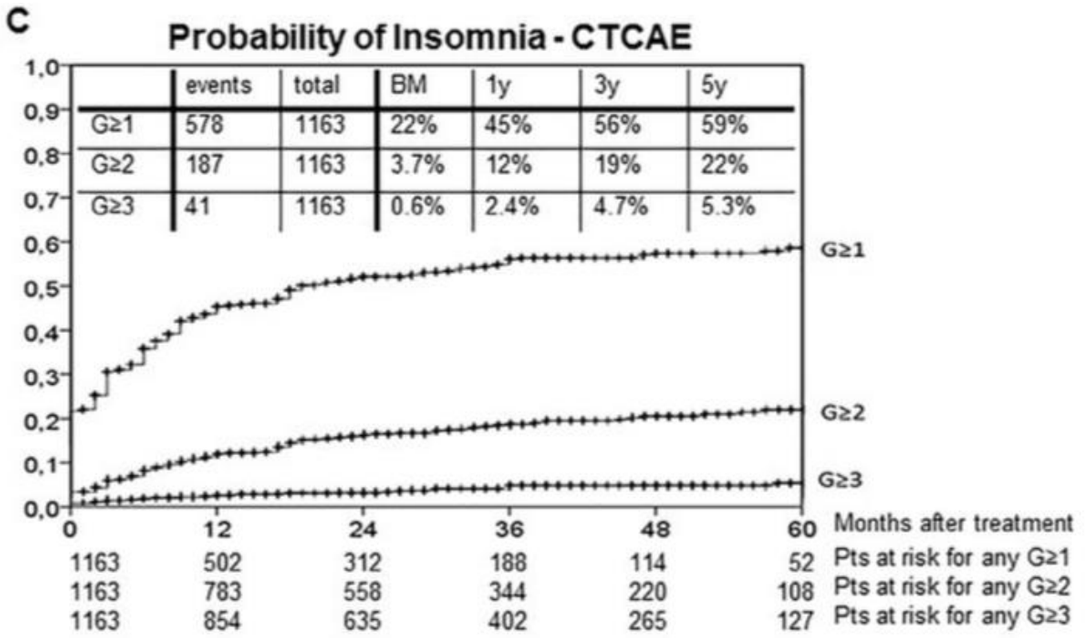
Insomnia







	events	total	BM	1y	3y	5y
G≥1	578	1163	22%	45%	56%	59%
G≥2	187	1163	3.7%	12%	19%	22%
G≥3	41	1163	0.6%	2.4%	4.7%	5.3%

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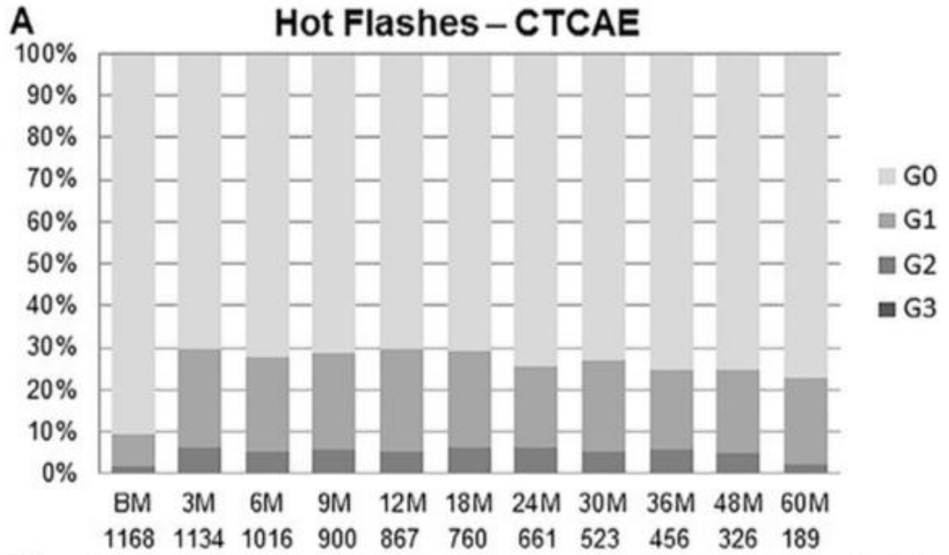
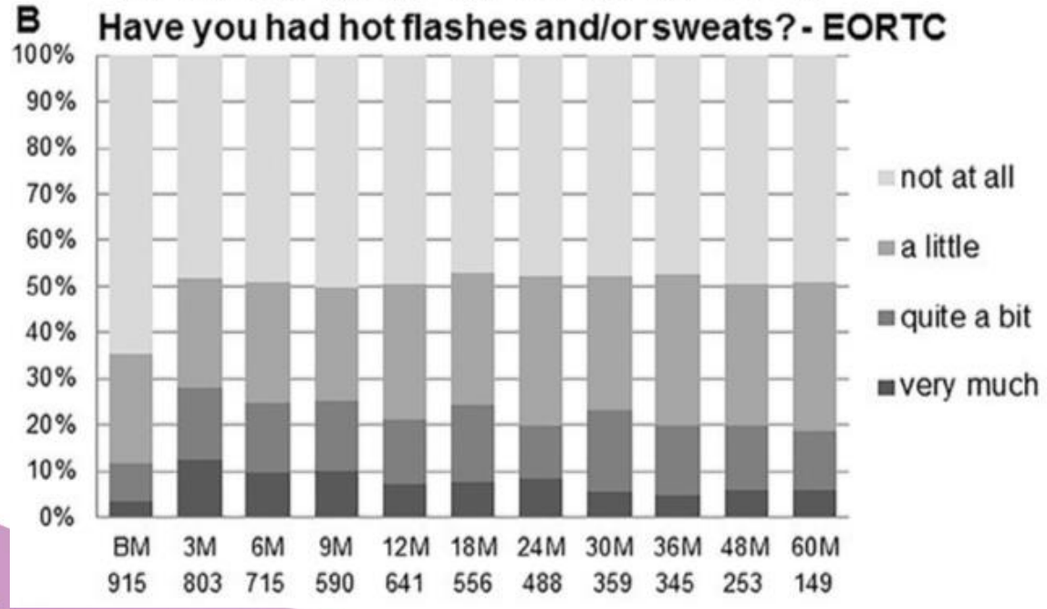
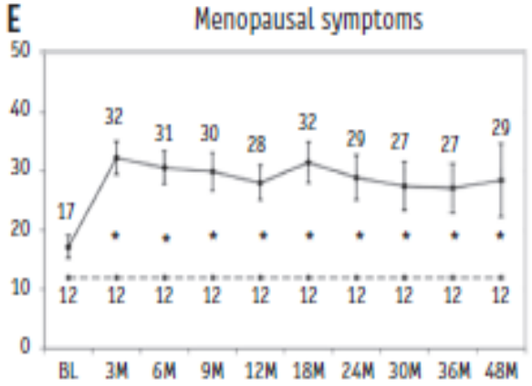
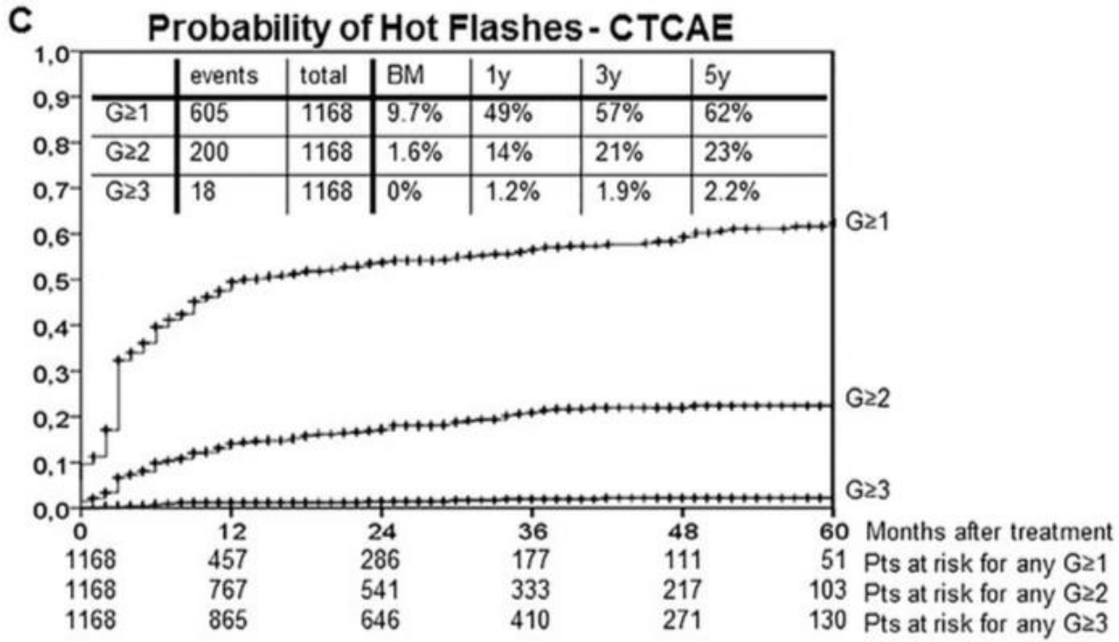
Hot flashes









	events	total	BM	1y	3y	5y
G≥1	605	1168	9.7%	49%	57%	62%
G≥2	200	1168	1.6%	14%	21%	23%
G≥3	18	1168	0%	1.2%	1.9%	2.2%

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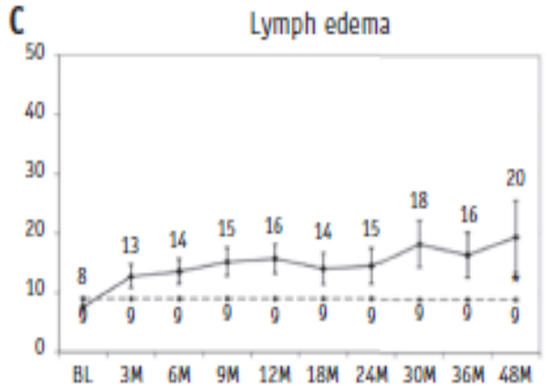
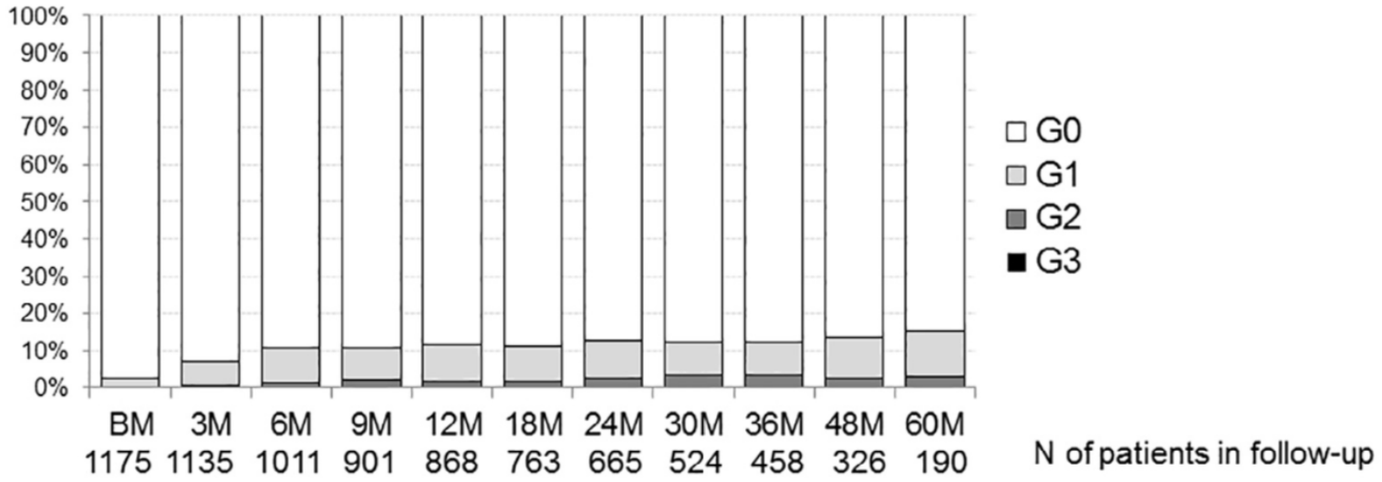
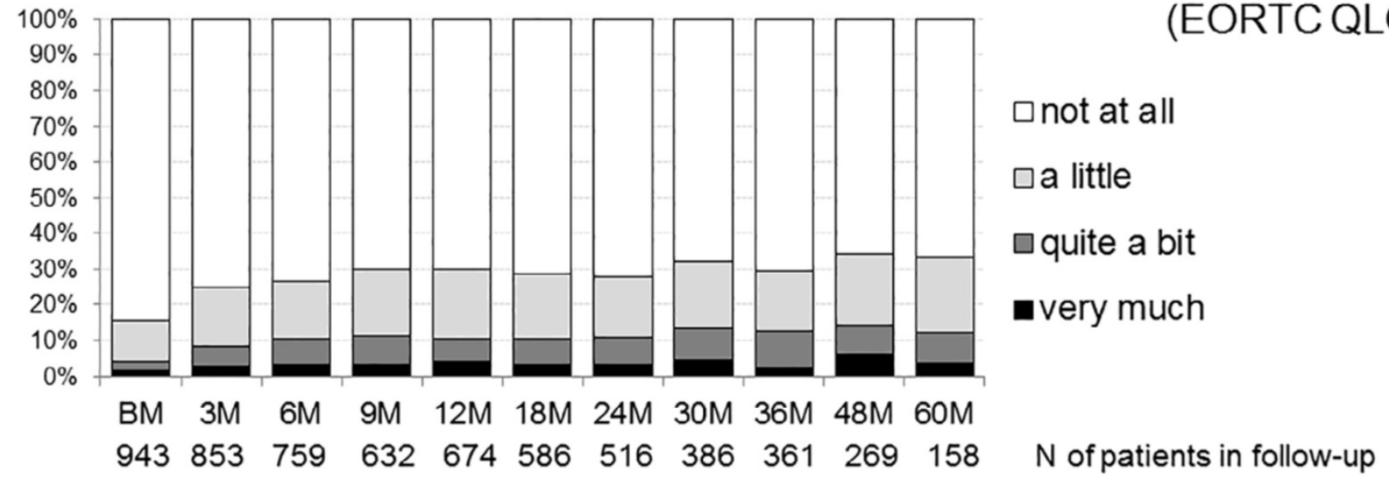
Lower limb edema

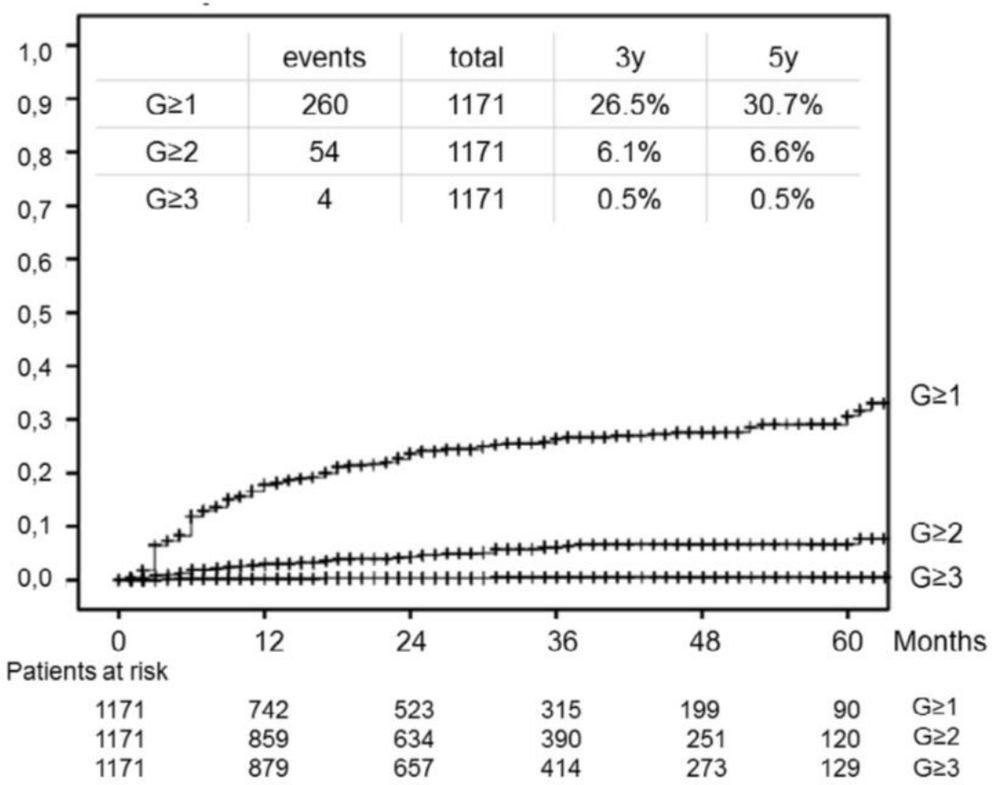


A: Prevalence rates of physician assessed lower limb edema (CTCAE v.3)



B: Prevalence rates of patient reported swelling in one or both legs (EORTC QLQ)





	events	total	3y	5y
G≥1	260	1171	26.5%	30.7%
G≥2	54	1171	6.1%	6.6%
G≥3	4	1171	0.5%	0.5%

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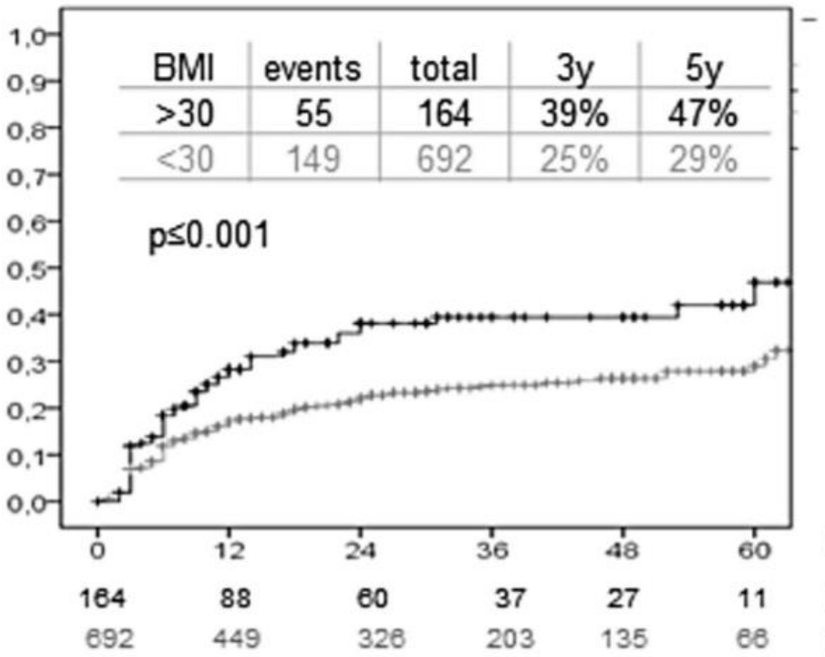
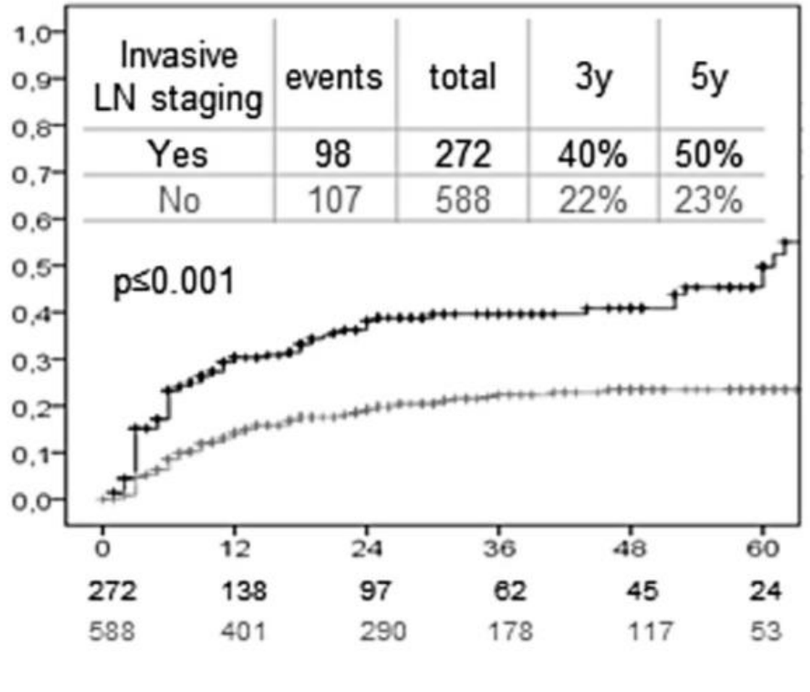
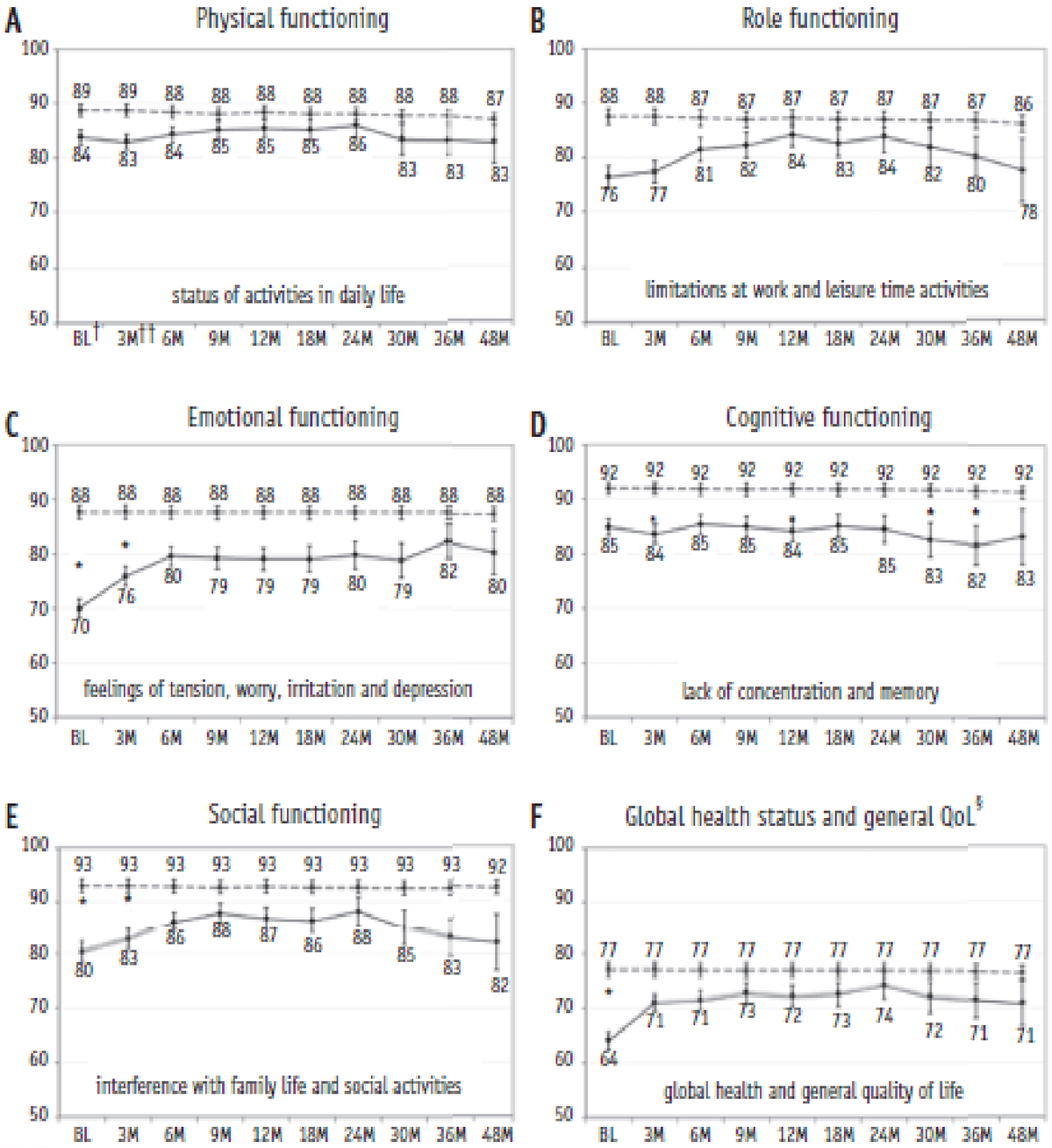
Lower limb edema: risk factors







LONG-TERM QUALITY OF LIFE

- 744, multi-institutional LACC patients (EMBRACE study)
- Prospective QoL assessment with EORTC-QLQ-C30+CX24
- Median follow-up 21 months
- Higher score represent better functioning and QoL
- Comparison with age-matched, female normative reference population (dotted line).

Kirchheiner et al. IJROBP 2016

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Reported severe morbidity IGABT

RetroEMBRACE: Late toxicity recorded in 610/731 patients.

Actuarial rates of severe (G3-G5) at 5 years were:

- Bladder 5%
- GI-tract 7%
- Vagina 5%

Monocentric series MRI guided IGABT >100 patients (Vienna, Aarhus, Paris) report: 5.6% - 7% severe (G3-G5) morbidity

Summary II

- Retrospectively reported severe late morbidity 5-7% with MRI guided IGABT. However, mild and moderate are more frequent and may negatively affect QoL.

- EMBRACE prospective analysis confirms ~5% severe late morbidity
- QoL analysis provides valuable information on impact of mild morbidity

- Most frequently reported symptoms include:

- Bladder: frequency, incontinence
- Rectum: proctitis
- Bowel: diarrea, bowel cramps
- Vaginal: stenosis, dryness
- Other: hot flushes

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Thank you!

Patterns of recurrence after IGABT

Li Tee Tan

ESTRO GYN teaching course
Madrid 2018

Cambridge University Hospitals NHS
NHS Foundation Trust

Outline

- Retro-EMBRACE (ESTRO 37)
- EMBRACE
- EMBRACE-II

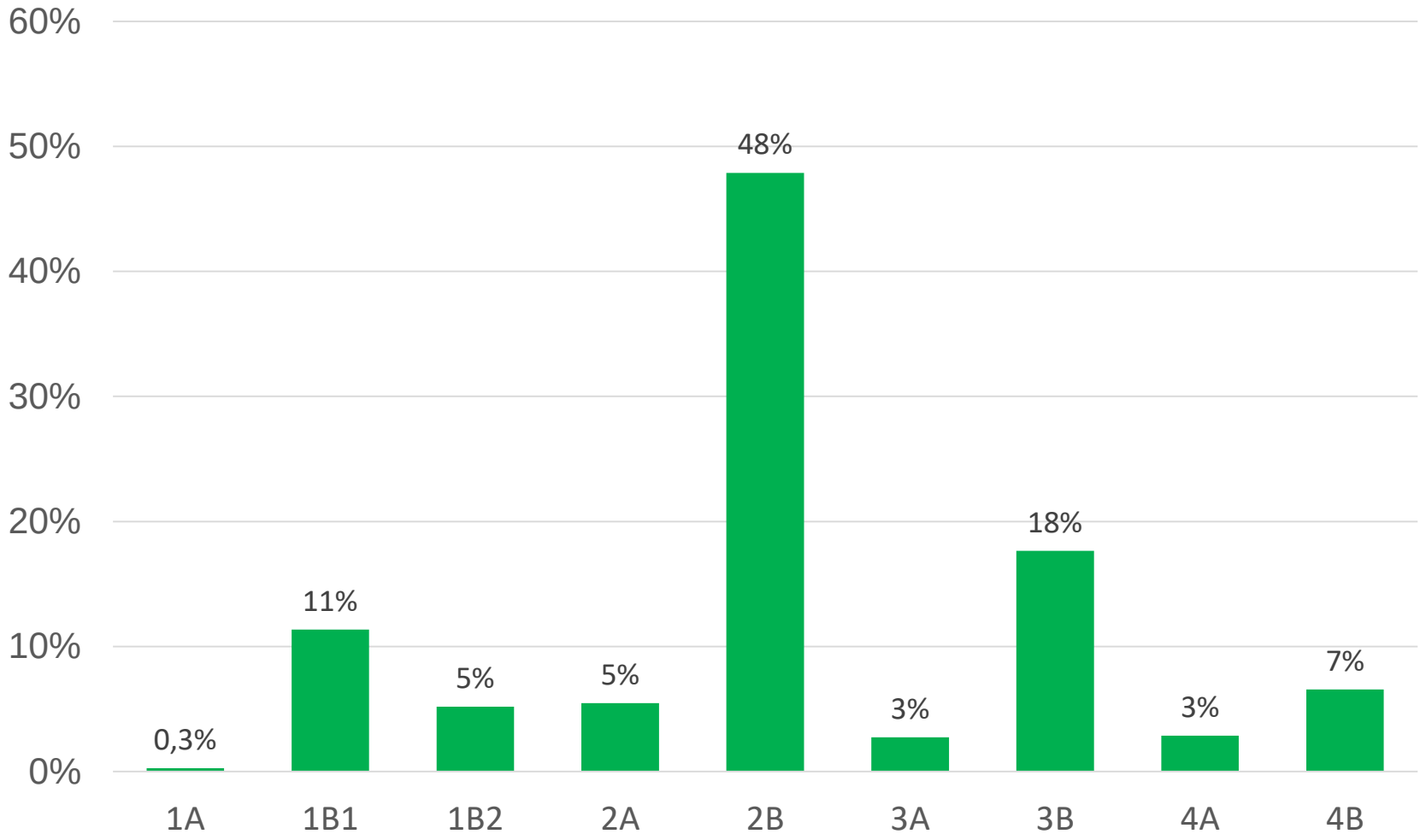
Retro-EMBRACE

- 731 patients from 12 institutions worldwide
- Treated between January 1998 and August 2012
- (Chemo)-RT + MRI/CT-based IGABT
- Median follow-up = 53 months (range: 2-169)

Patients

- Median age = 53 years (range: 23-91)
- Histology
  - Squamous cell 85%
  - Adeno 10%
- Positive nodes
  - Pelvic 40%
  - Paraaortic 7%
- MRI width ≥5 cm 45%

T(NM) stage



Treatment

- EBRT
  - Pelvis 84%
  - Pelvis + PAN 16%
  - Chemotherapy 77%
- Brachytherapy
  - MRI 81%
  - CT 19%
  - Combined IC+IT 23%

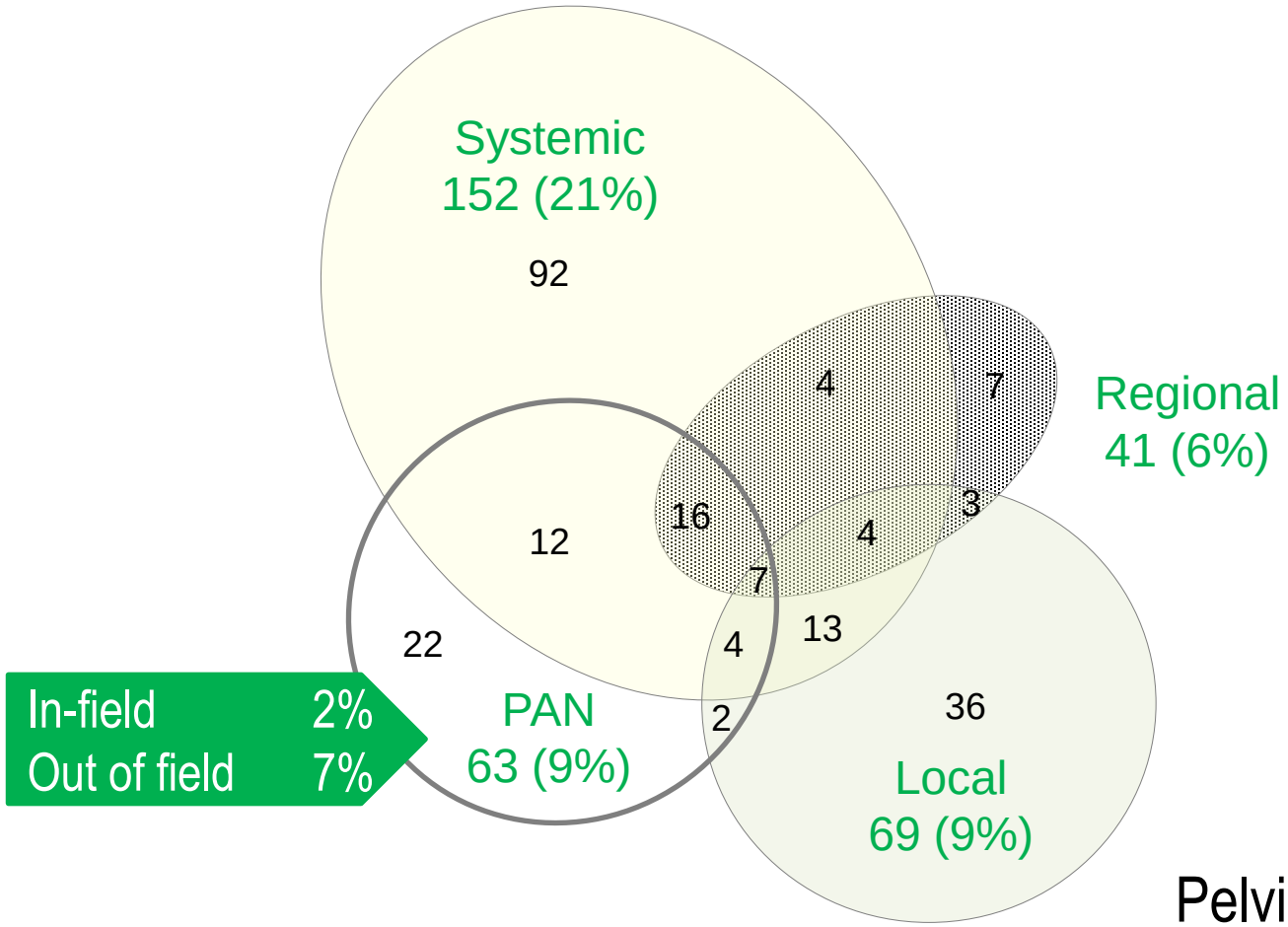
Treatment failures

- Local (cervix, upper vagina and/or parametria)
- Regional (pelvic nodes)
- Pelvic (local and/or regional)
- Systemic (excluding PAN relapse)
- Distant (including PAN relapse)

Failures at first relapse

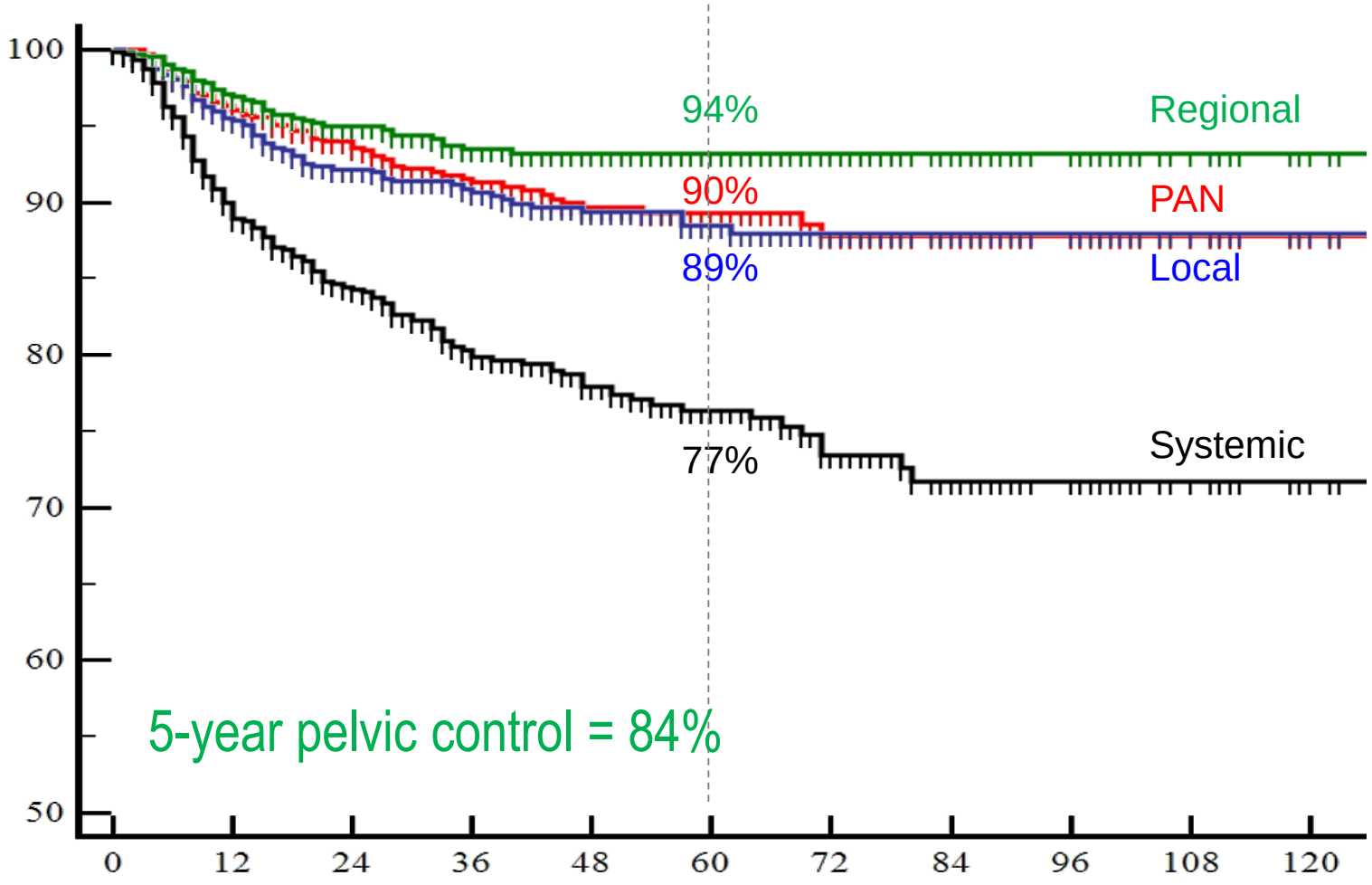
- 222 patients (30%), 325 events
  - Single type 71%
  - Two types 15%
  - Three or more types 14%

Crude failures

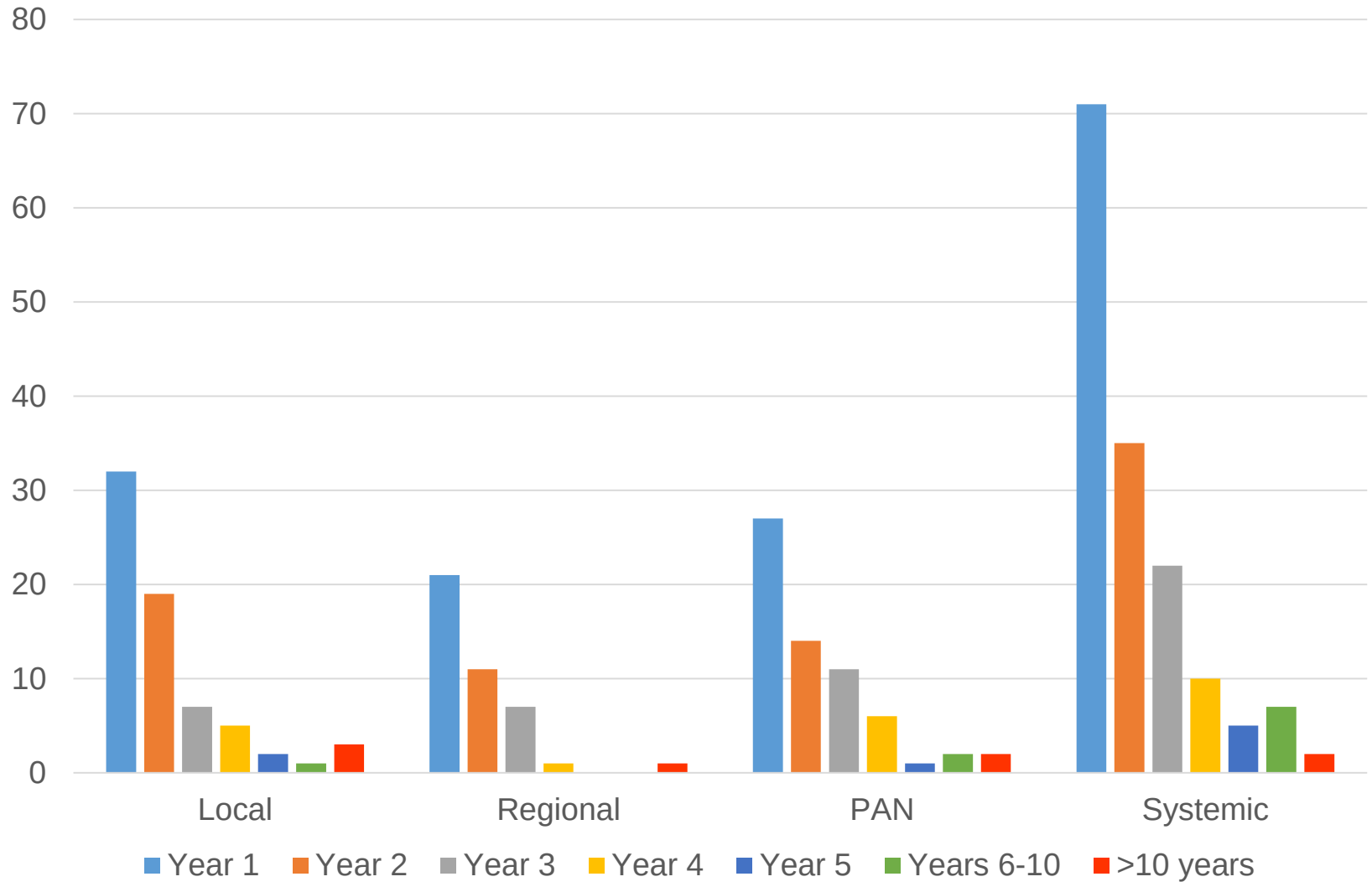


Pelvic (L + R) 13%
Distant (S + P) 24%

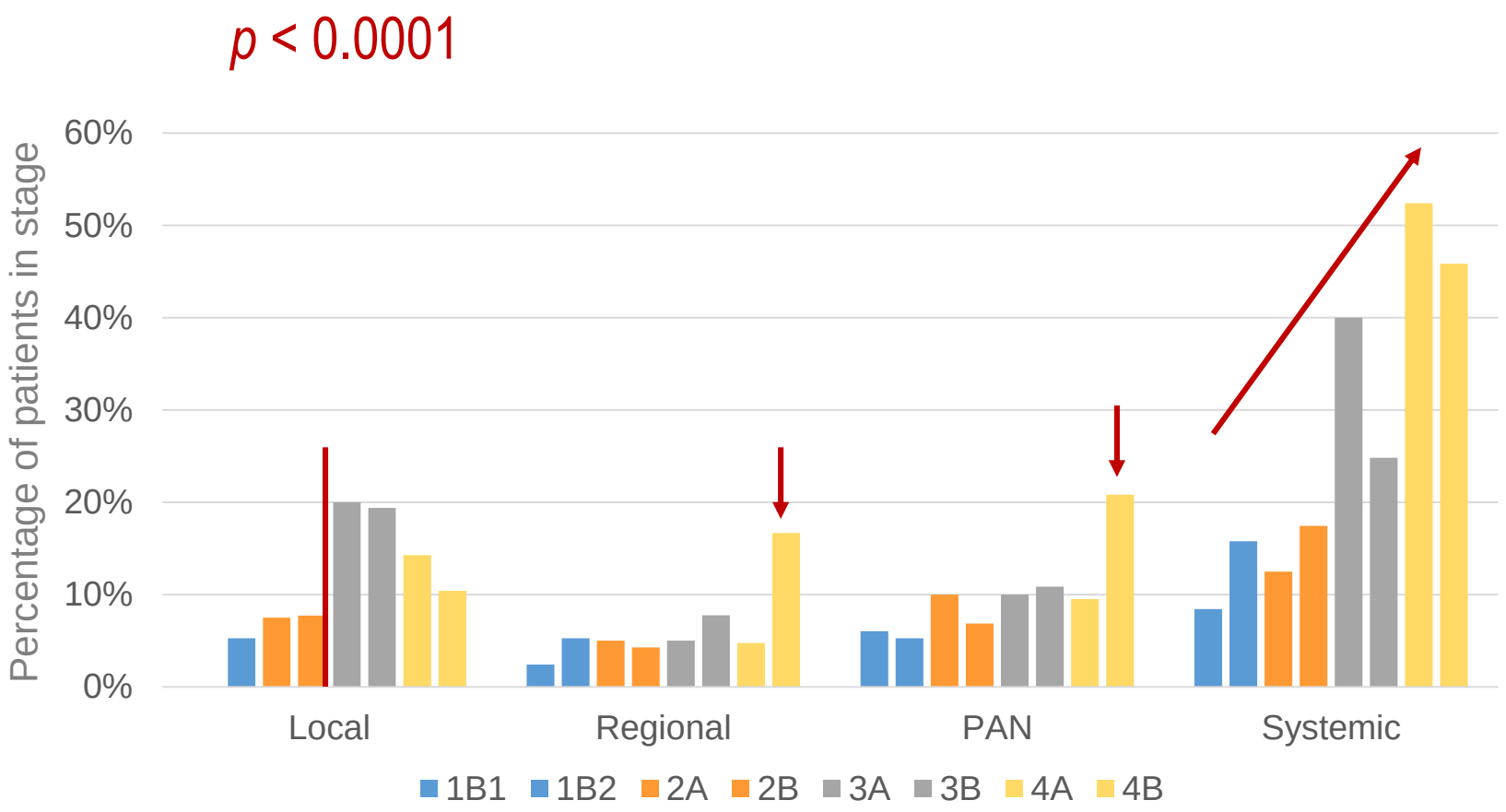
Actuarial failures



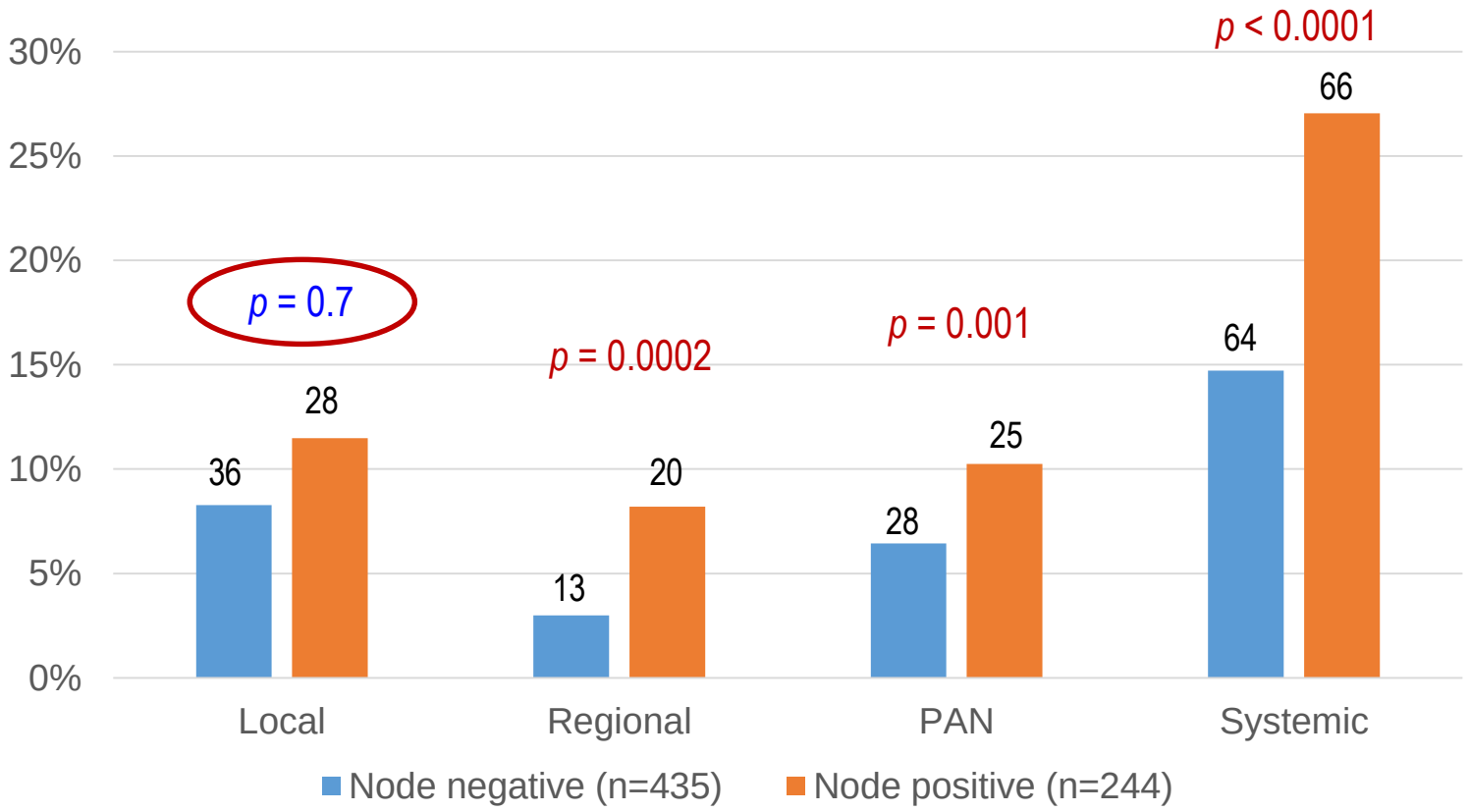
Time to first event(s)



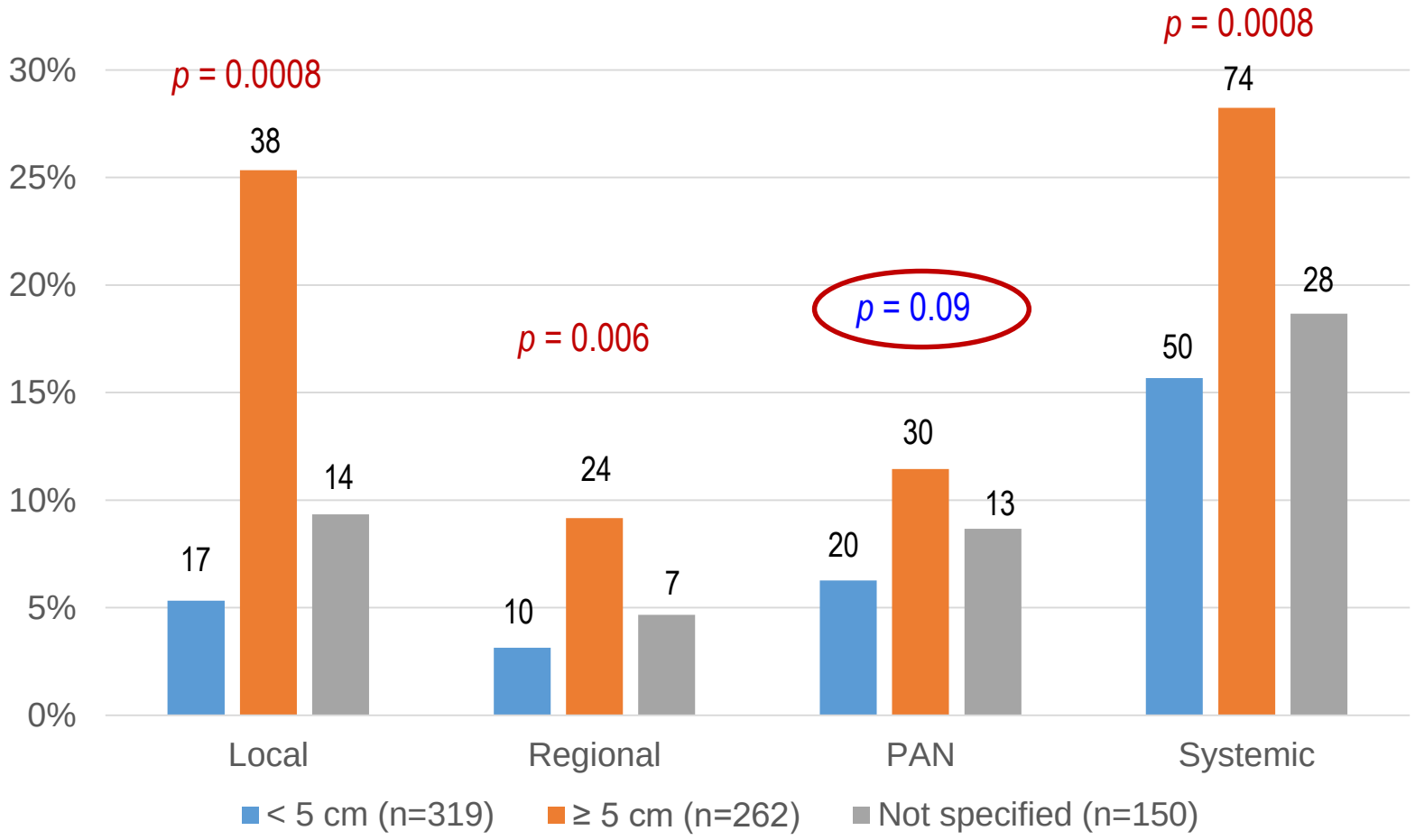
Failure by T(NM) stage



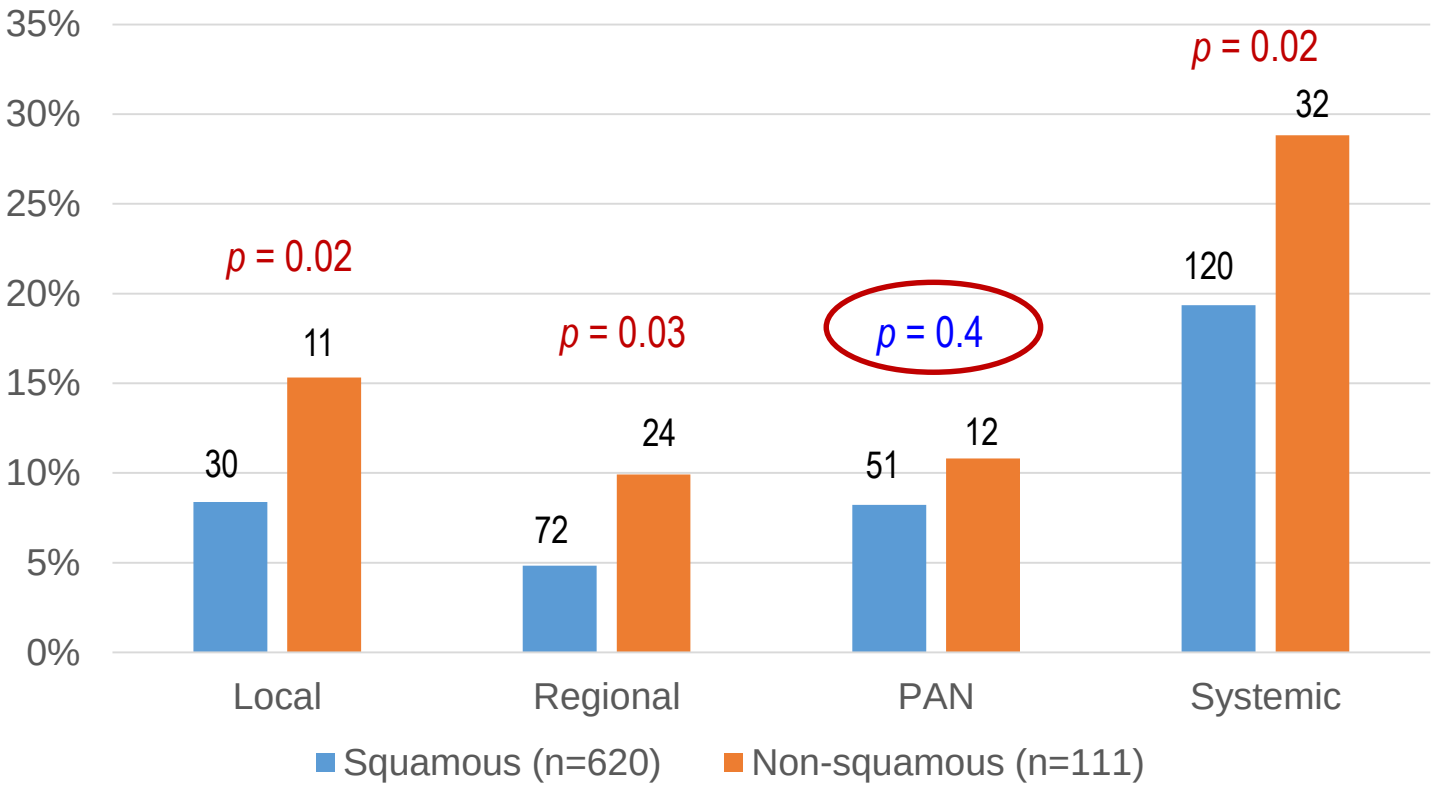
Failure by nodal status



Failure by MRI width



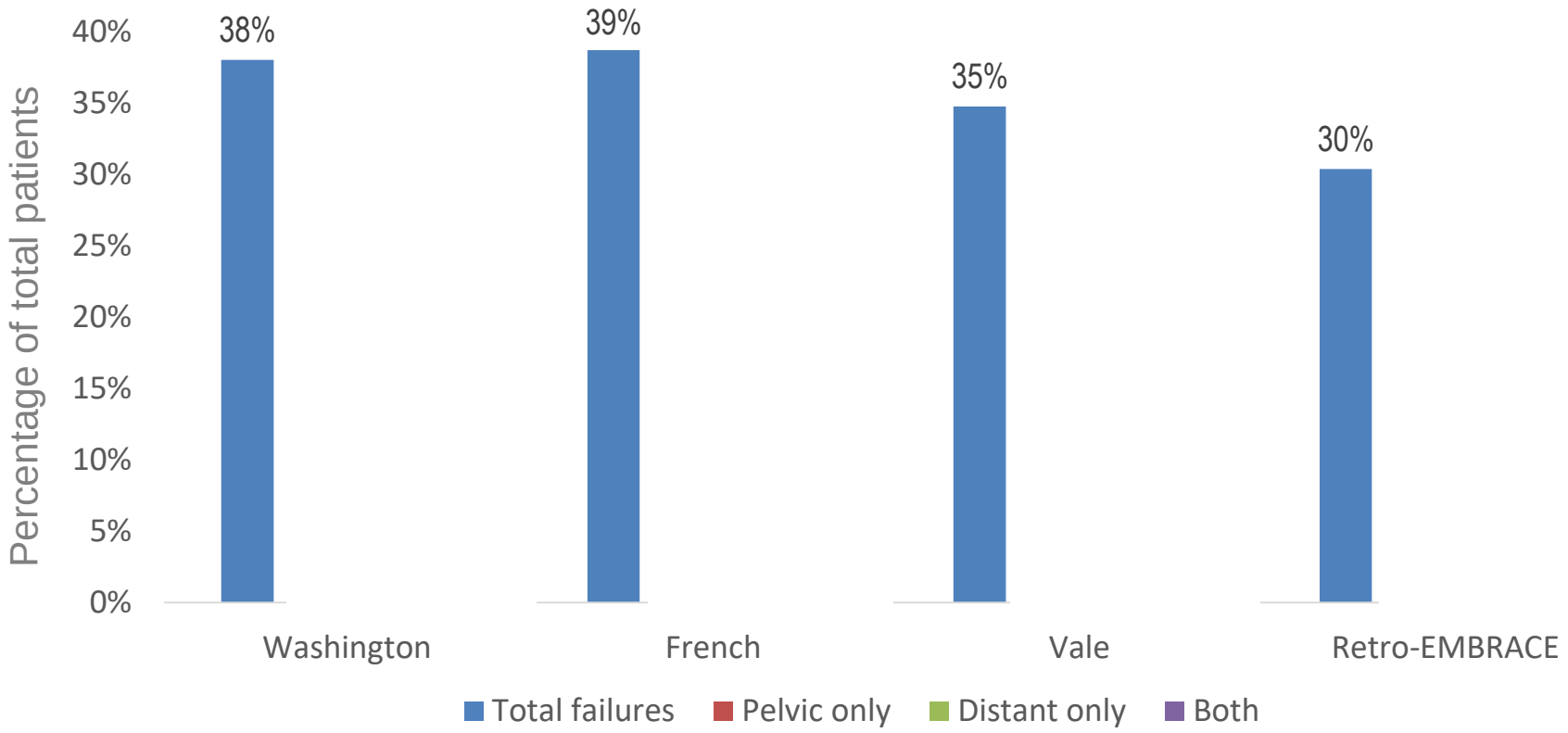
Failure by histology



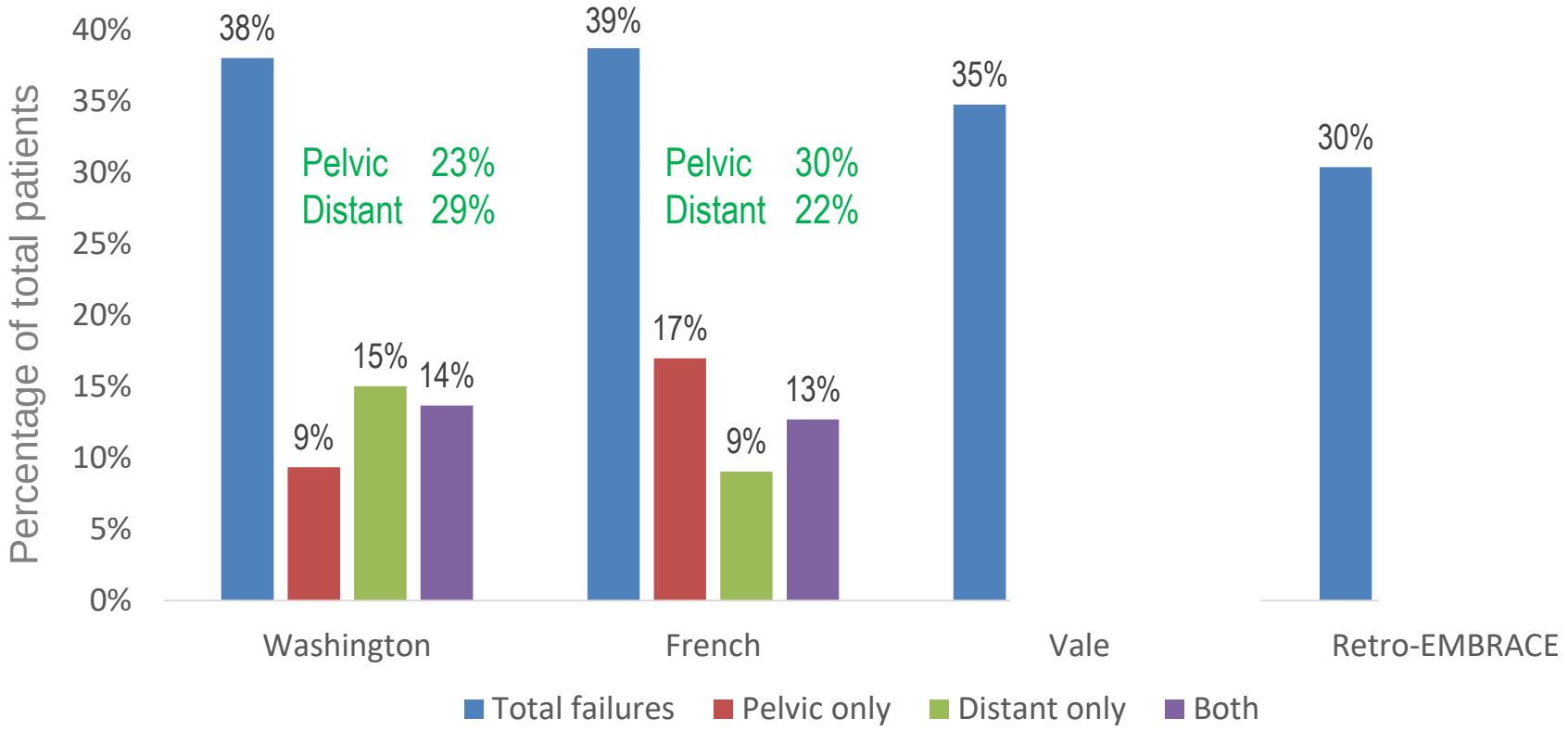
Historical comparisons

- Perez (Washington University) - RT alone
  - 1499 patients (1959 – 1993)
- French cooperative study - RT alone
  - 1875 patients (1970 – 1993)
- Vale Chemoradiotherapy Meta-Analysis
  - 3128 patients, 13 randomised trials

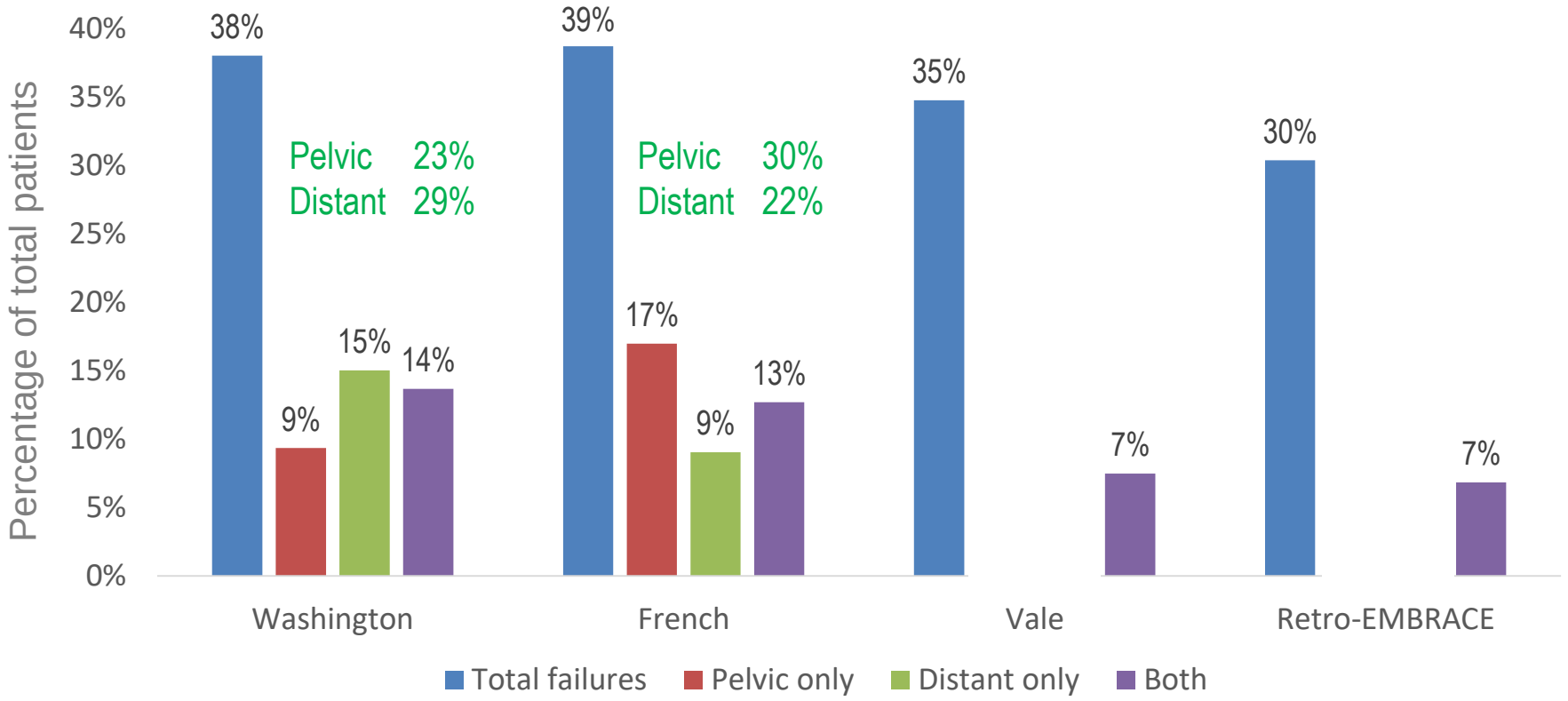
Historical comparisons



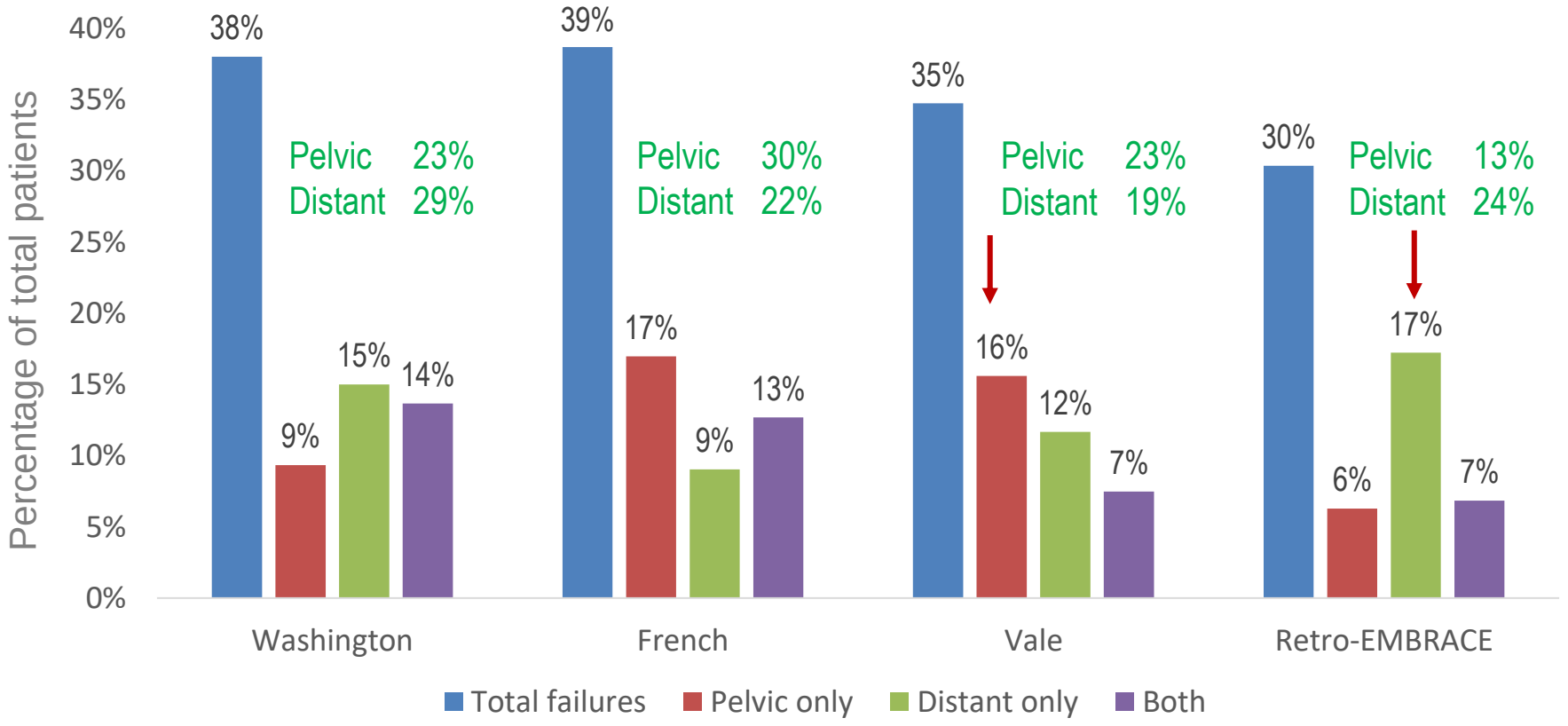
Historical comparisons



Historical comparisons



Historical comparisons

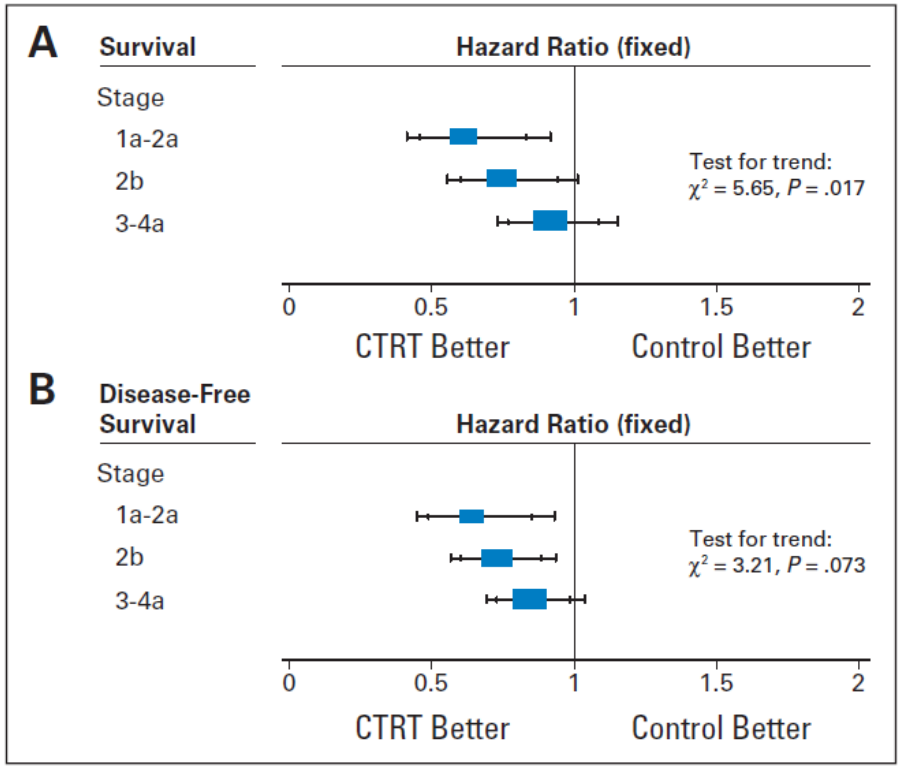


Shifting challenge

- RT alone era
  - Suboptimal loco-regional + systemic control (except for small tumours with low propensity for metastatic spread)

Shifting challenge

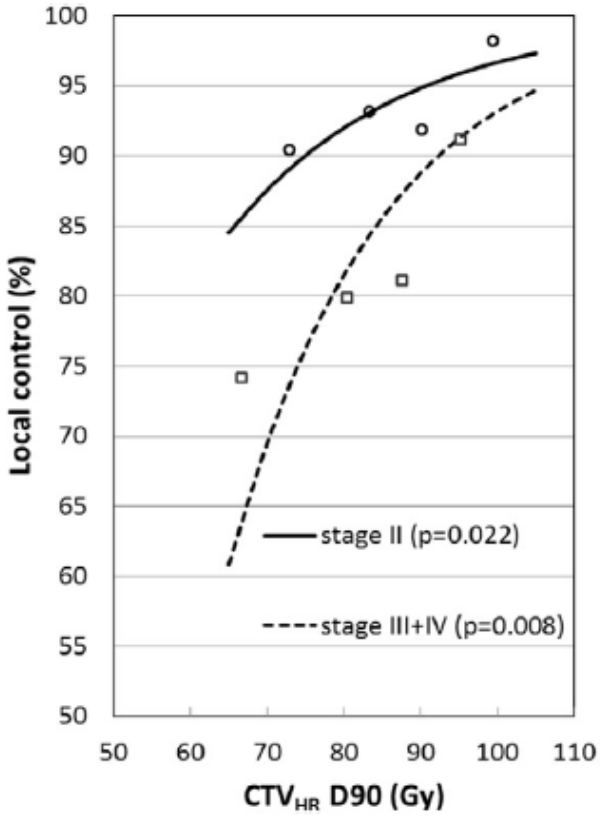
- Chemo-RT era
  - Suboptimal loco-regional control of advanced stage tumours

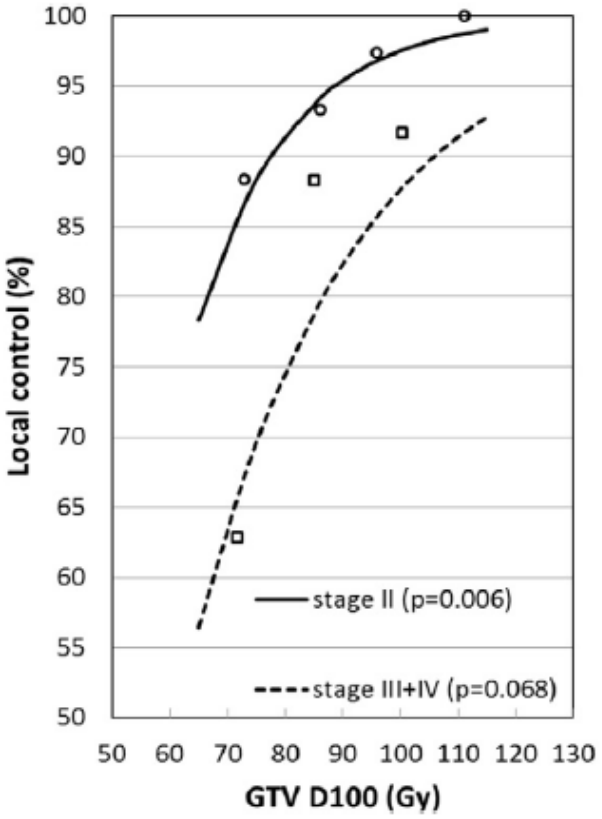


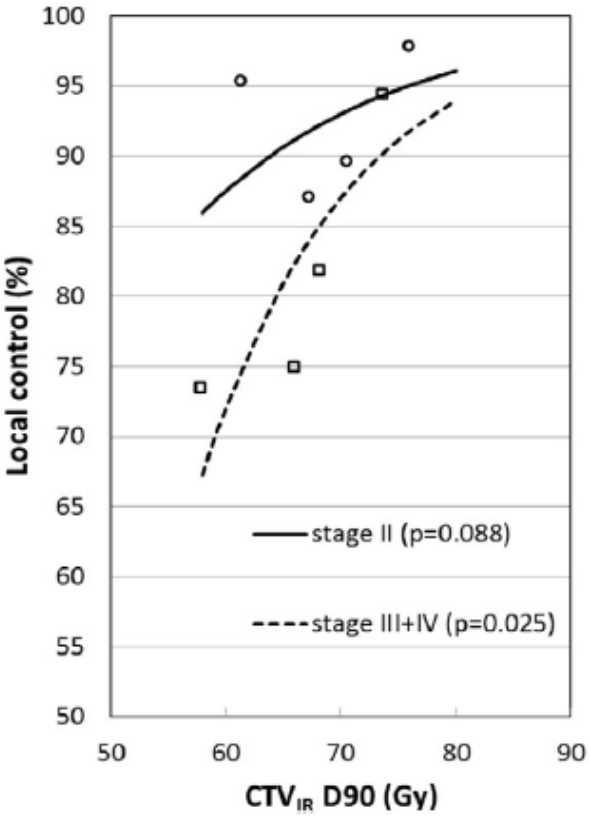
Shifting challenge

- IGBT era
  - Optimal loco-regional control for all stages
  - Suboptimal systemic control

Dose







Tanderup et al., RetroEMBRACE, 2016, RadiothOncol

Dose

- CTV-HR dose ≥85 Gy (D90) delivered in 7 weeks provide 3 year LC rates of
  - >94% in limited size (20 cc)
  - >93% in intermediate size (30 cc)
  - >86% in large size (70 cc)
- Doses of 90–95 Gy add 1–4% to local control, depending on tumour volume.
- Increased CTV-HR volume by 10 cc requires additional 5 Gy for equivalent local control.

Tanderup et al., RetroEMBRACE, 2016, RadiothOncol

Dose

- Similar levels of local control obtained with
  - GTV_{res} doses ≥95 Gy (D98)
  - CTV-IR doses of ≥60 Gy (D98)

Target	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV_{res} $EQD2_{10}$	D98 CTV_{IR} $EQD2_{10}$	Point A $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy	> 75 Gy	>95 Gy	> 60 Gy	> 65 Gy
Limits for Prescribed Dose	> 85 Gy	-	>90 Gy	-	-

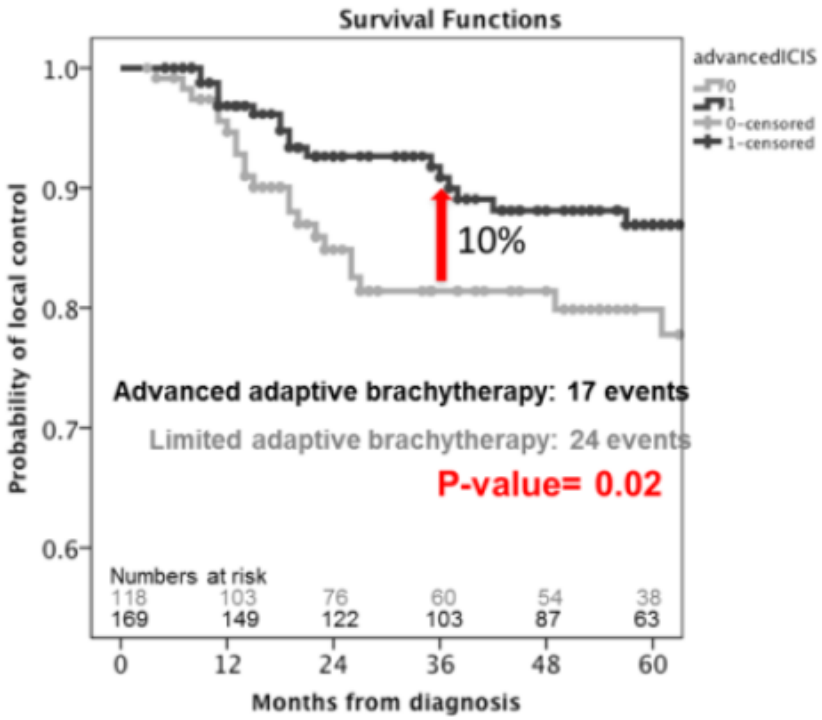
Tanderup et al., RetroEMBRACE, 2016, RadiothOncol

	45 Gy in 25# + 7 Gy x 4#				45 Gy in 25# + 7 Gy x 3#	
D90	greater than 90 Gy_{10}	84 Gy_{10}			greater than 87 Gy_{10}	80 Gy_{10}
per #	greater than 7.8 Gy	7 Gy			greater than 9 Gy	8 Gy
D2cc bladder	less than 90 Gy_3	95 Gy_3			less than 85 Gy_3	90 Gy_3
per #	less than 6.3 Gy	6.7 Gy			less than 7 Gy	7.5 Gy
D2cc rectum/sigmoid	less than 70 Gy_3	75 Gy_3			less than 65 Gy_3	70 Gy_3
per #	less than 4.5 Gy	5 Gy			less than 4.7 Gy	5.4 Gy
D2cc small bowel	less than 65 Gy_3	75 Gy_3			less than 65 Gy_3	70 Gy_3
per #	less than 4 Gy	5 Gy			less than 4.7 Gy	5.4 Gy
for clinician ref only: Point A	80 Gy_{10}	75 Gy_{10}				70 Gy_{10}
per #	6.5 Gy	5.9 Gy				6.4 Gy

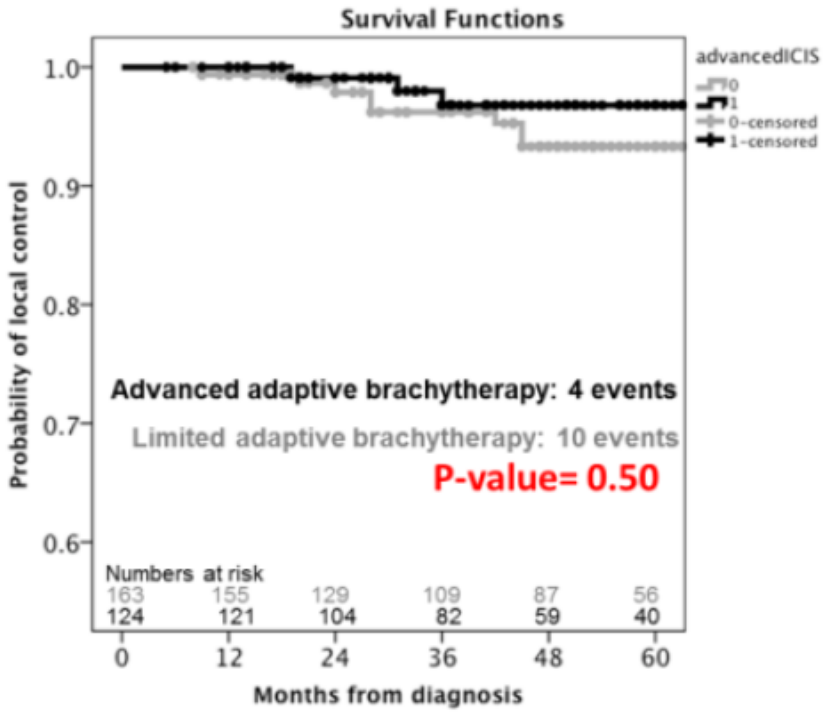
Number of fractions	4										
	F 1	clinician accepted	F 2	clinician accepted?	F 3	clinician accepted?	F 4	clinician accepted?			clinician accepted?
Date	3/9/18		4/9/18							dose values in Gy	
Plan lock time	17:24:07		11:11:38						TOTAL BT	TOTAL BT + EBT	
Standard plan (T/M)	No		No								
Number of needles loaded	4		4								
TRAK [Gy at 1m]	0.00553		0.00552								
Ring dwell time (secs)	173.6		197.6								
IU dwell time (secs)	173.6		172.9								
Needle dwell time (secs)	199.80		181.20		0.00		0.00				
Total dwell time (secs)	547.00		551.7								
Bladder filling (ml)	60ml		60ml								
Norm Pt Dose A(lt/rt) / A(an	7.7		7.9								
PD;$_{\alpha/\beta}$[α/β-10Gy]	11.4		11.7		0.0		0.0		23.0	67.3	
dose to A right "	12.6		12.0						*quote A(lt/rt) when prescribed to A(a		
A_{right} - D;$_{\alpha/\beta}$[α/β-10Gy]	23.8		21.9		0.0		0.0		45.8	90.0	
dose to - A left "	15.2		15.2						*quote A(lt/rt) when prescribed to A(ant/part)		
A_{left} - D;$_{\alpha/\beta}$[α/β-10Gy]	32.1		31.8		0.0		0.0		63.9	108.1	
HR-CTV [cm^3]	73.2		73.0								
HR-CTV D 100	5.2		5.2								
HR-CTV D 98	6.3		6.6								
D 98;$_{\alpha/\beta}$[α/β-10Gy]	8.6		9.0		0.0		0.0		17.6	61.9	
HR-CTV D 90	7.8		8.1								
D 90;$_{\alpha/\beta}$[α/β-10Gy]	11.6		12.1		0.0		0.0		23.8	68.0	
HR-CTV D 50	12.9		13.3								
HR-CTV V100 - volume of PD [%]	90.9		91.4								
HR-CTV V7Gy [%]	95.0		96.3								
IR-CTV [cm3]	206.3		208.9								
IR-CTV D 98	3.0		3.4								
IRCTV D 98;$_{\alpha/\beta}$[α/β-10Gy]	3.3		3.7		0.0		0.0		7.0	51.3	
GTV [cm3]	21.5		21.4								
GTV D98	6.8		7.5								
GTV D 98;$_{\alpha/\beta}$[α/β-10Gy]	9.5		11.0		0.0		0.0		20.5	64.8	
SIGMOID 2cm^3 - dose	4.4		3.9								
2cm^3 - D;$_{\alpha/\beta}$[α/β-3Gy]	6.6		5.3		0.0		0.0		11.9	55.1	
SIGMOID 0.1cm^3 - dose	7.4		5.1								
BLADDER [cm3]	235.2		131.7								
BLADDER ICRU B1 - dose	2.6		2.6								
BLADDER 2cm^3 - dose	6.4		5.0								
2cm^3 - D;$_{\alpha/\beta}$[α/β-3Gy]	12.1		8.1		0.0		0.0		20.2	63.4	
BLADDER 0.1cm^3 - dose	7.7		5.8								
EMBRACE vaginal-rectal poi	3.7		5.6								
ICRU rectal dose - Dicu [α/β-3Gy]	5.0		9.6		0.0		0.0		14.6	57.8	
RECTUM 2cm^3 - dose	4.8		5.1								
2cm^3 - D;$_{\alpha/\beta}$[α/β-3Gy]	7.6		8.2		0.0		0.0		15.8	59.0	
RECTUM 0.1cm^3 - dose	7.8		6.2								
SMALL BOWEL 2cm^3 - dose	1.4		2.6								
2cm^3 - D;$_{\alpha/\beta}$[α/β-3Gy]	1.3		2.9		0.0		0.0		4.2	47.4	

Technique

CTVHR $\geq$ 30 cm^3



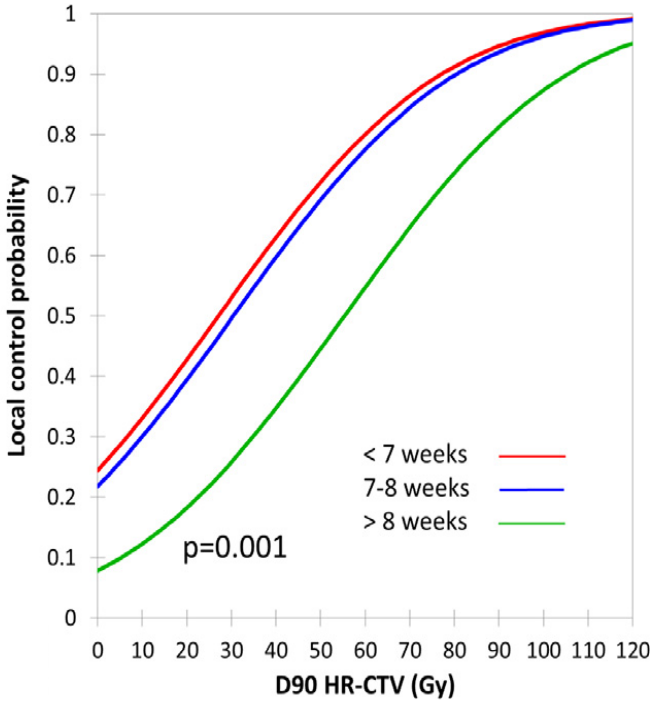
CTVHR < 30 cm^3



Fokdal L, et al. Radiother Oncol. 2016 Sep;120(3):434-440

Overall treatment time

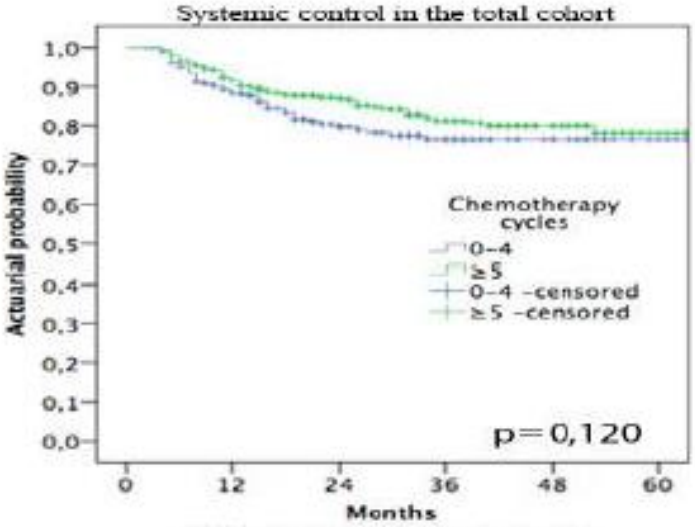
- Increasing OTT by one week is equivalent to a loss of 5 Gy in CTV_{HR} D90

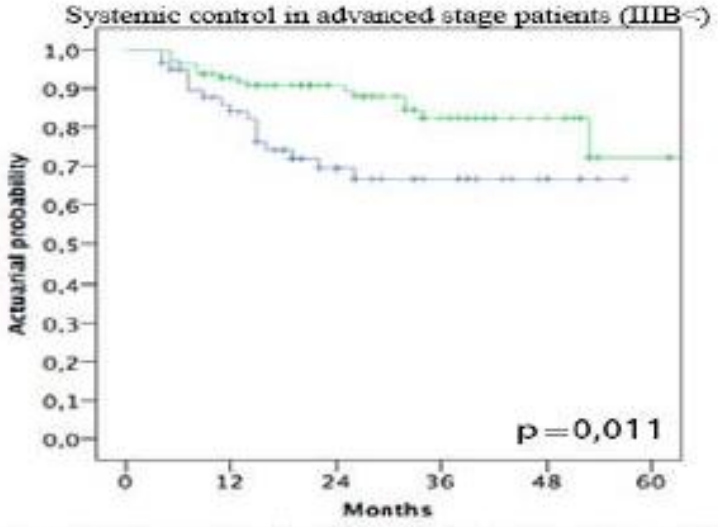


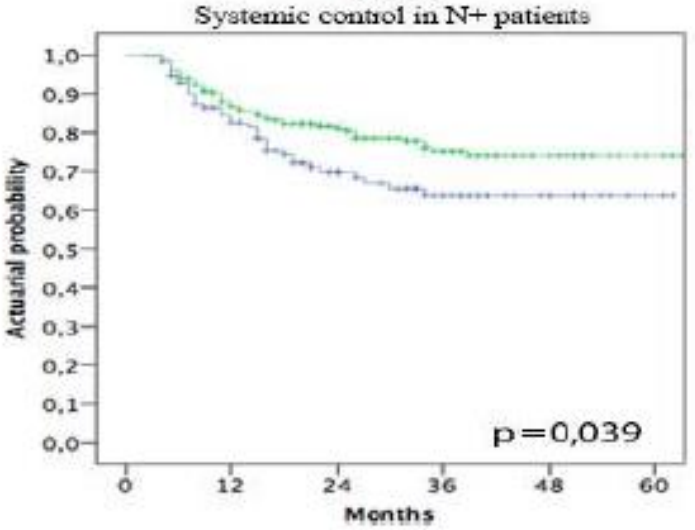
Mazeron et al, Paris data, Radiother Oncol 2015

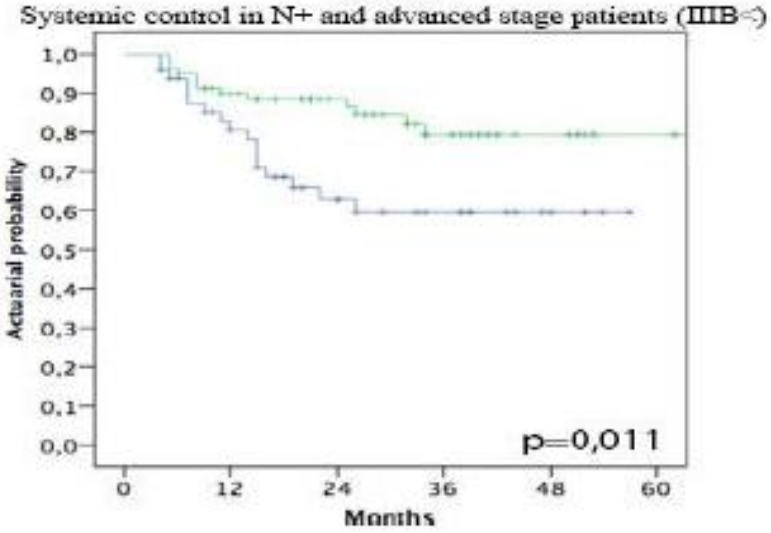
Tanderup et al., RetroEMBRACE, 2016, RadiothOncol

Chemotherapy cycles







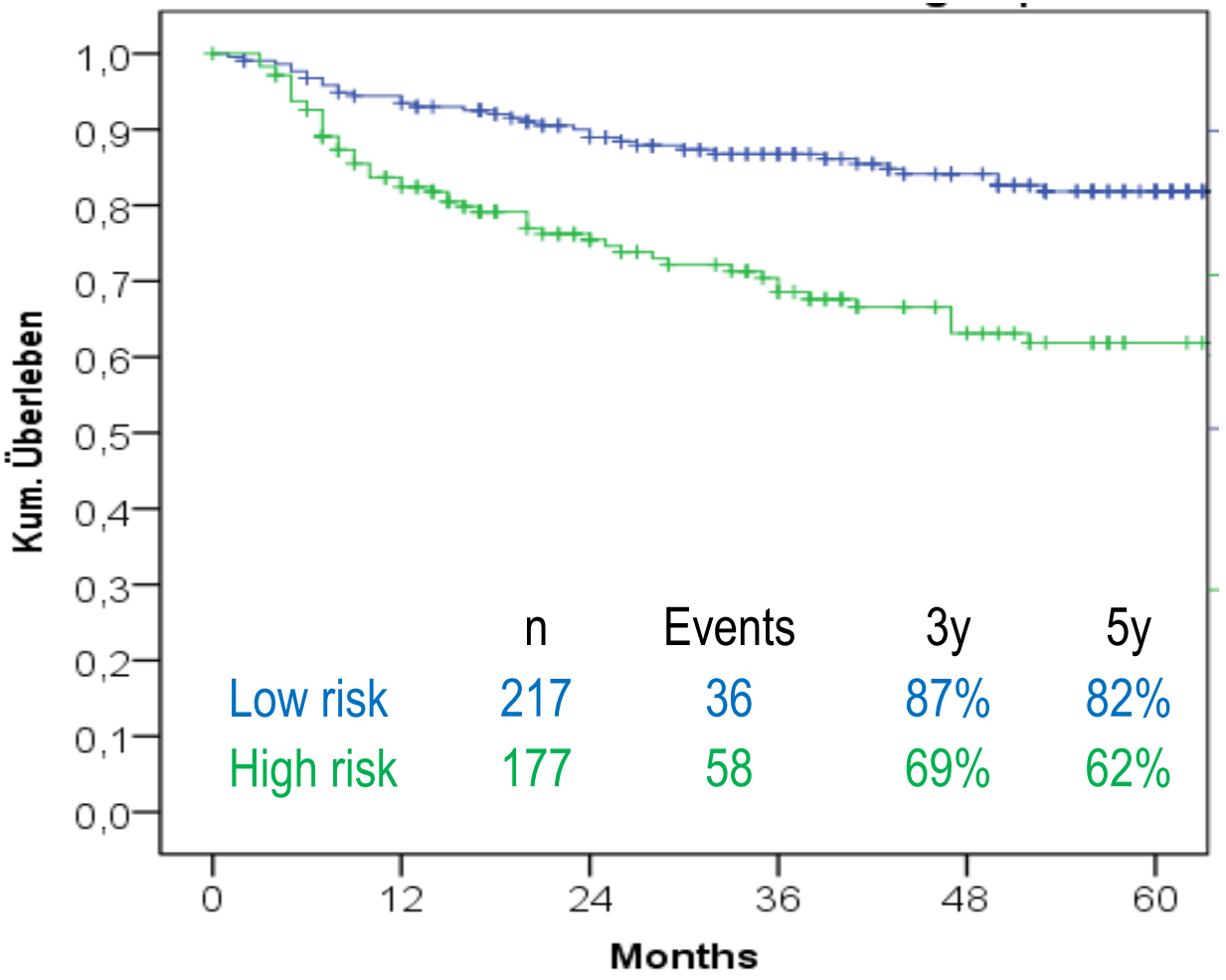


Fortin I. et al. Abstract ASTRO 2015.

Risk groups (systemic control)

- 394 consecutive patients from 7 centres
  - 5 centers enrolled selected patients
- Two risk groups on univariate analysis
  - Low risk
    - 1B, 2A, 2B, 3A and N0
    - 1BN+
  - High risk
    - 2A-2B and N+
    - Any 3B or 4A

Risk groups (systemic control)



Sturdza et al. 2015 (unpublished)

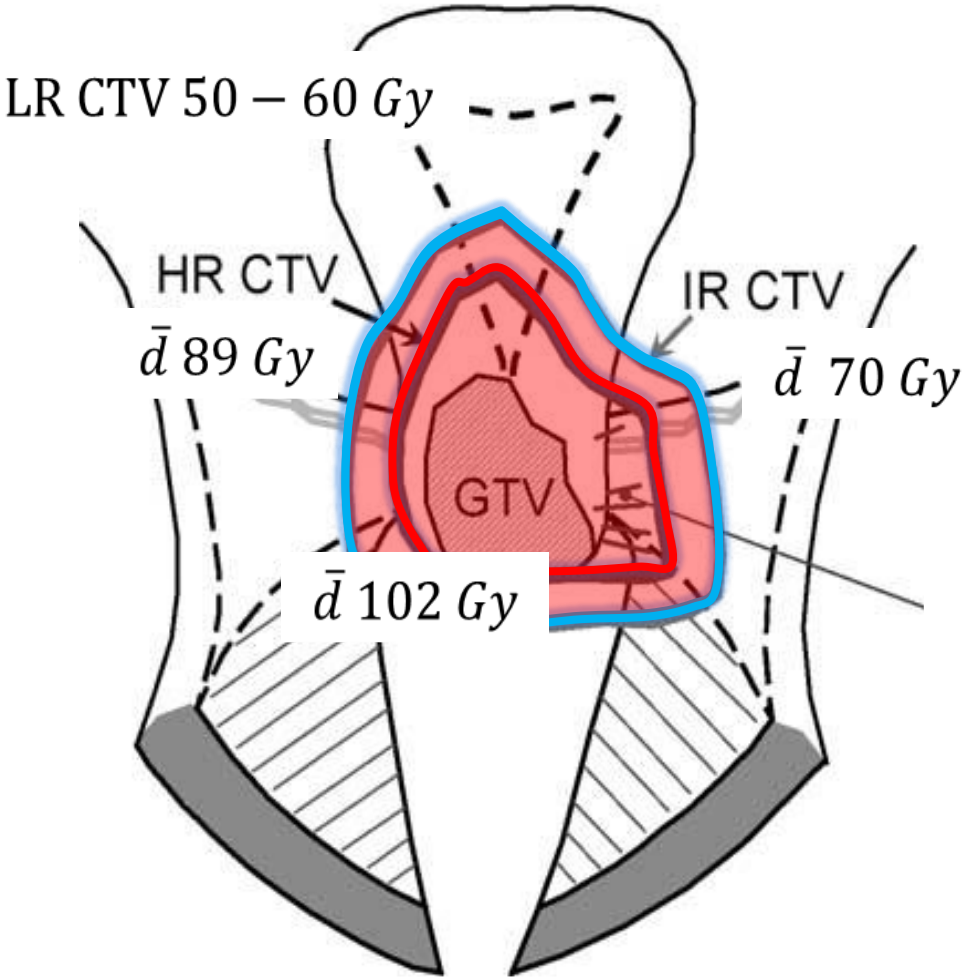
Outline

- Retro-EMBRACE (ESTRO 37)
- EMBRACE
- EMBRACE-II

Large variations in volumes

Name	Mean (cc)
Initial CTV-T LR	230
Initial GTV-T	55
Adaptive CTV-T LR	78
Adaptive CTV-T HR	33
Residual GTV	9

Variation in dose



Crude failures*
(n=1416, median FU 2 years)

			rEMB
• Local	6.5%	(80/1230) (Schmid *et al.* 2017)	9%
• Nodal	8%	(86/1077) (Nomden *et al.* 2017)	6%
• Distant	18%	(133/753) (Fortin *et al.* 2015)	30%
• ~50% of failures synchronous			29%

** Preliminary data Jun 2017*

Local control (n=1230)

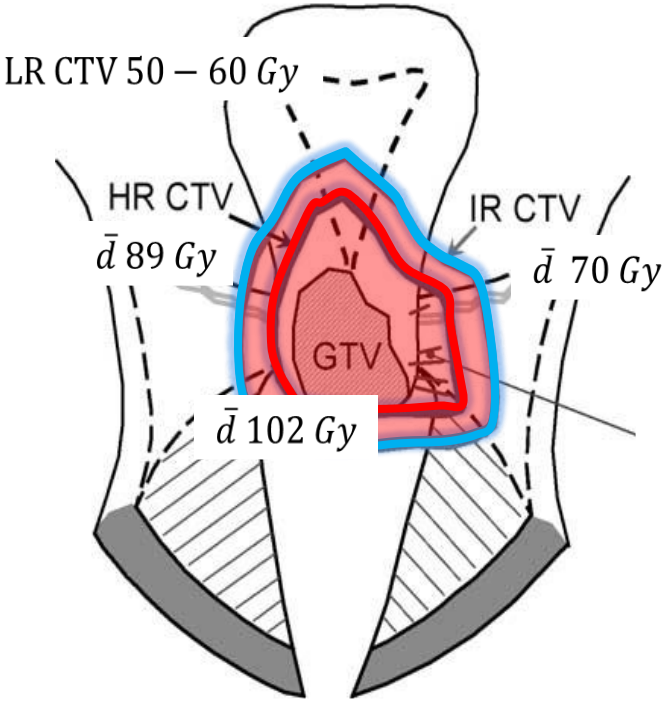
- 24 incomplete remissions (IR)
  - 72 IR at 3 months, 48 resolved at 6-9 months
  - 98% complete remission rate
- 56 local recurrences (LR) (median FU 25 months)
  - Median time to LR = 11.5 months
  - 86% of LR occured within 24 months
- 80 local failures (IR+LR) (6.5%) (Schmid *et al.* 2017)
  - 42 (52%) synchronous nodal or distant failures

Location of local failures (63/80)

- 108 locations
  - Cervix + uterus: 80% (n=50)
  - Proximal parametria: 13% (n=8)
  - Distal parametrium/pelvic wall: 29% (n=18)
  - Vagina: 29% (n=18)
  - Bladder: 19% (n=12)
  - Rectum: 3% (n=2)

Local failures wrt BT volumes

- In HR CTV alone 51% (n=27)
- In IR CTV alone 17% (n=9)
- In both 30% (n=16)
- Ouside both 2% (n=1)



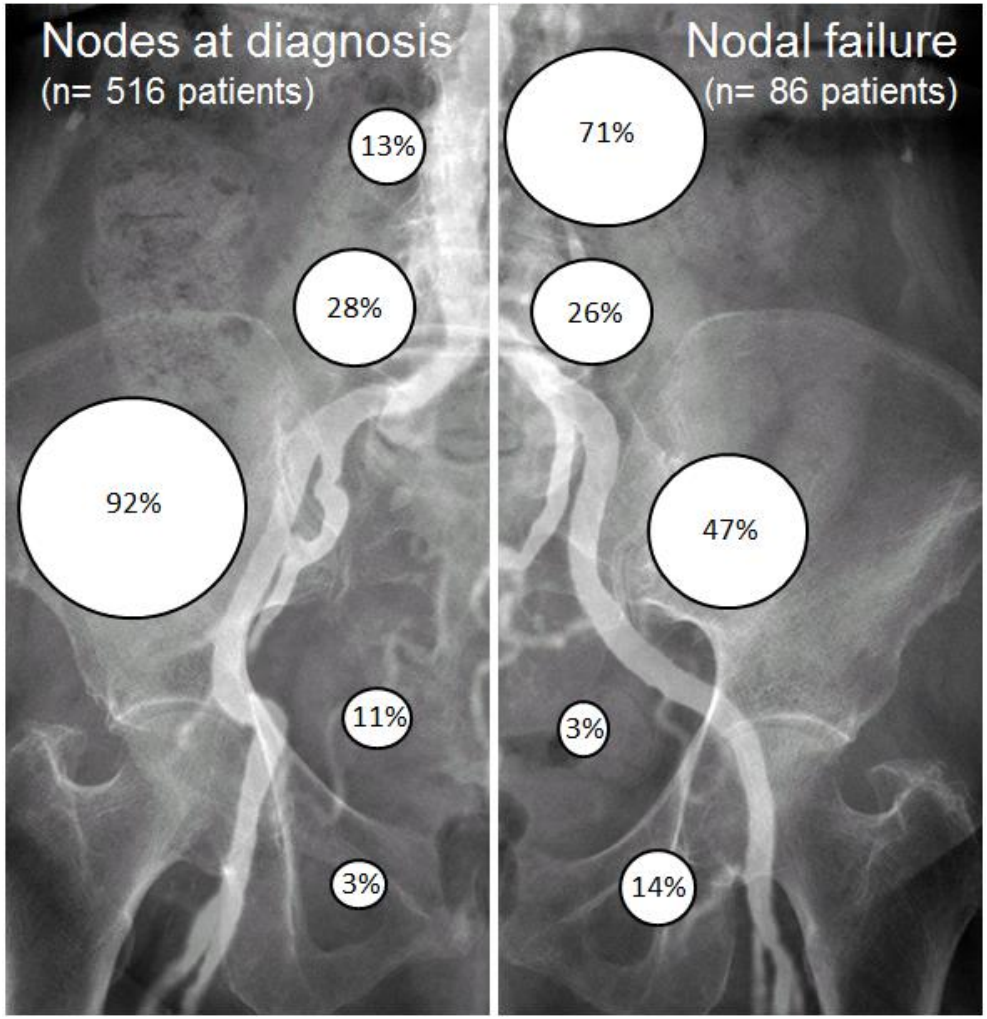
Nodal failures

- Total patients = 1077
  - Nodal failures = 86 (8%)
- N+ at diagnosis = 516
  - Nodal failures = 60* (12%)
- N- at diagnosis = 561
  - Nodal failures = 25* (5%)

* For one patient with nodal failure, nodal status at diagnosis unknown

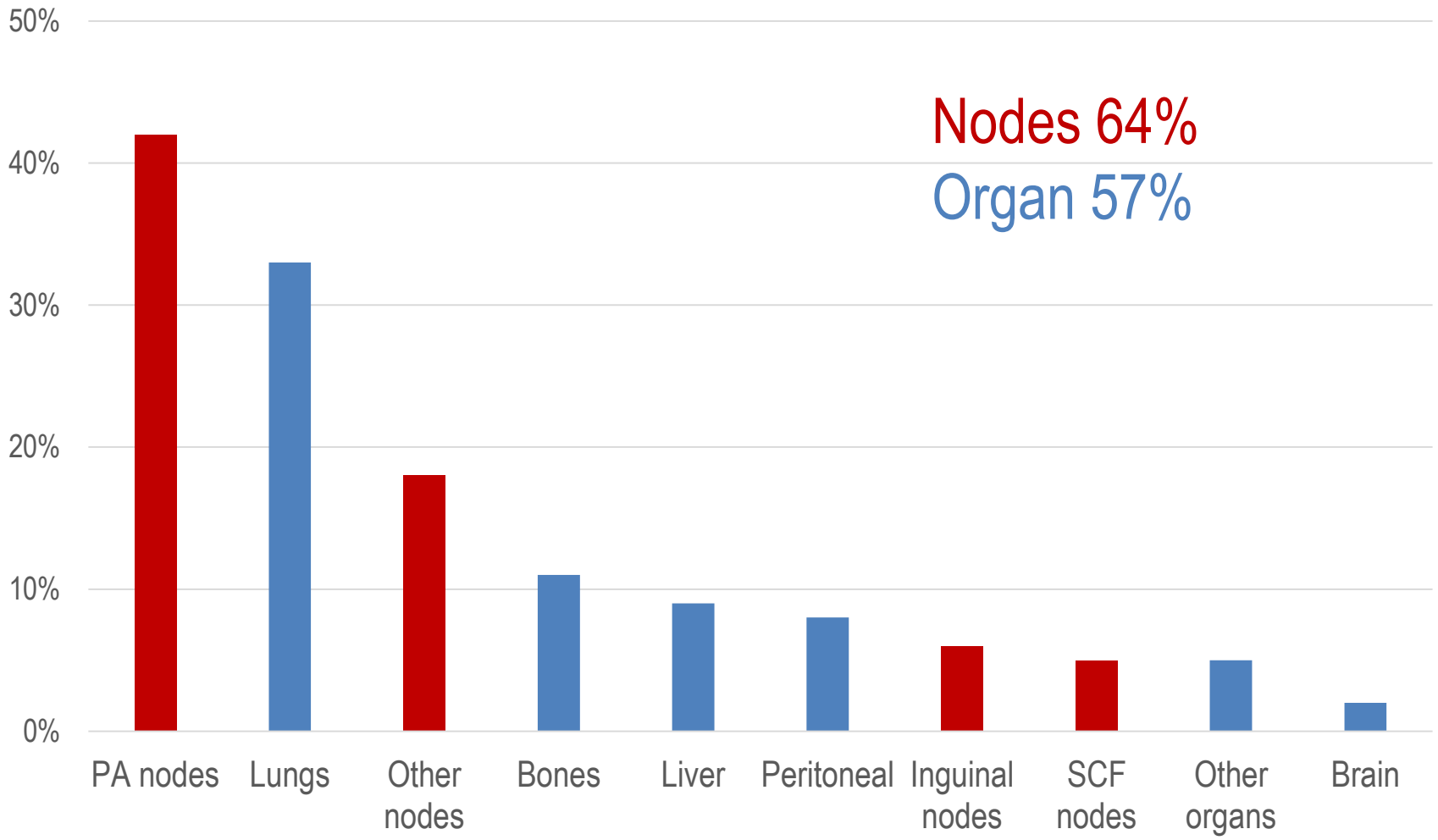
Nomden et al. under submission

Pattern of nodal recurrence



Nomden et al. under submission

Distant recurrence



Fortin et al. ASTRO 2015

Outline

- Retro-EMBRACE (ESTRO 37)
- EMBRACE
- EMBRACE-II

EMBRACE-II interventions – tumour control

- Increased use of IC/IS BT
  - CTV-HR >30cc, >70%
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time (≤ 50 days)

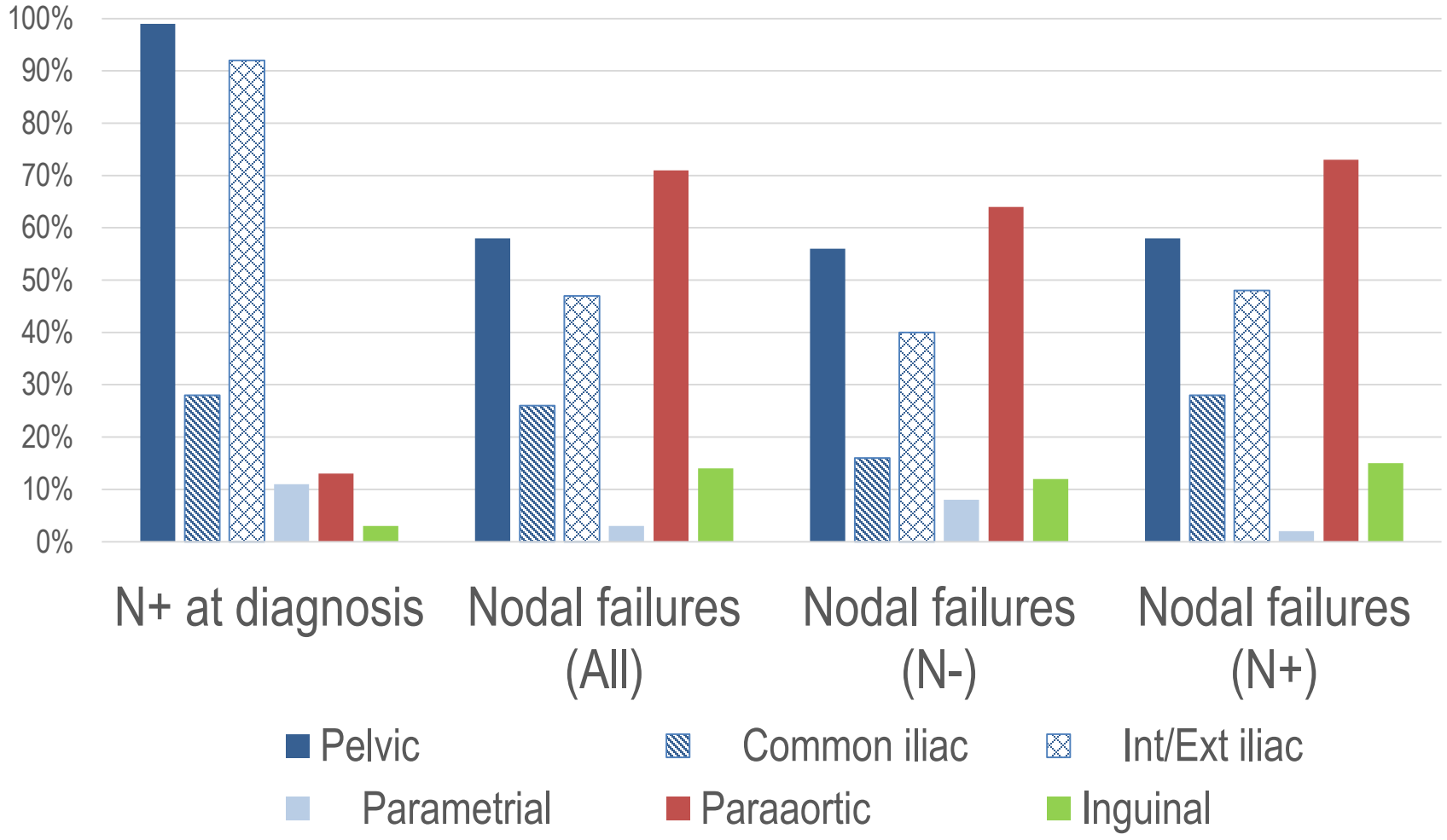
Personalised strategies

Local	Regional	PAN	Systemic
• Combined intracavitary & interstitial BT	• Nodal boost	• Prophylactic PAN RT • Adjuvant chemo	• Adjuvant chemo

Improved predictive markers

ARCHIVED

Location



Nomden et al. under submission

Implementation of IMRT/VMAT and image-guided brachytherapy in Spain

Elena Villafranca

Complejo Hospitalario de Navarra

IMAGE-GUIDED RADIOTHERAPY & CHEMOTHERAPY IN GYNAECOLOGICAL CANCER - WITH A SPECIAL FOCUS ON ADAPTIVE BRACHYTHERAPY

Madrid, Spain - 2-6 September 2018

ESTRO School

Index

1. Guidelines in IMRT and RM-IGBT in cérvix cancer
2. Experience in the Complejo Hospitalario de Navarra
3. Experience in Spain.

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 2, pp. 348–355, 2011

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2009.10.075

CLINICAL INVESTIGATION **Cervix**

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY FOR THE DEFINITIVE TREATMENT OF CERVIX CANCER

KAREN LIM, M.B.B.S.,* WILLIAM SMALL, JR., M.D.,† LORRAINE PORTELANCE, M.D.,‡ CARIEN CREUTZBERG, M.D., PH.D.,§ INA M. JÜRGENLIEMK-SCHULZ, M.D., PH.D.,‖ ARNO MUNDT, M.D.,¶ LOREN K. MELL, M.D.,¶ NINA MAYR, M.D.,** AKILA VISWANATHAN, M.D.,†† ANUJA JHINGRAN, M.D.,‡‡ BETH ERICKSON, M.D.,§§ JENNIFER DE LOS SANTOS, M.D.,‖‖ DAVID GAFFNEY, M.D., PH.D.,¶¶ CATHERYN YASHAR, M.D.,¶ SUSHIL BERIWAL, M.D.,*** AARON WOLFSON, M.D.,††† ALEXANDRA TAYLOR, F.R.C.R.,‡‡‡ WALTER BOSCH, PH.D.,§§§ ISSAM EL NAQA, PH.D.,§§§ AND ANTHONY FYLES, M.D. * FOR THE GYN IMRT CONSORTIUM.

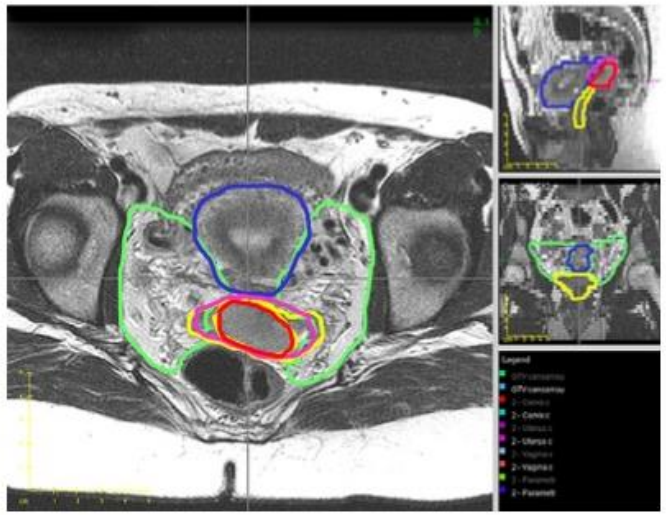


Fig. 2. Axial and reconstructed sagittal and coronal views of T_2-weighted MR images from a clinical contouring case showing 95% agreement contours for GTV (red), cervix (pink), vagina (yellow), parametria (green), and uterus (blue).

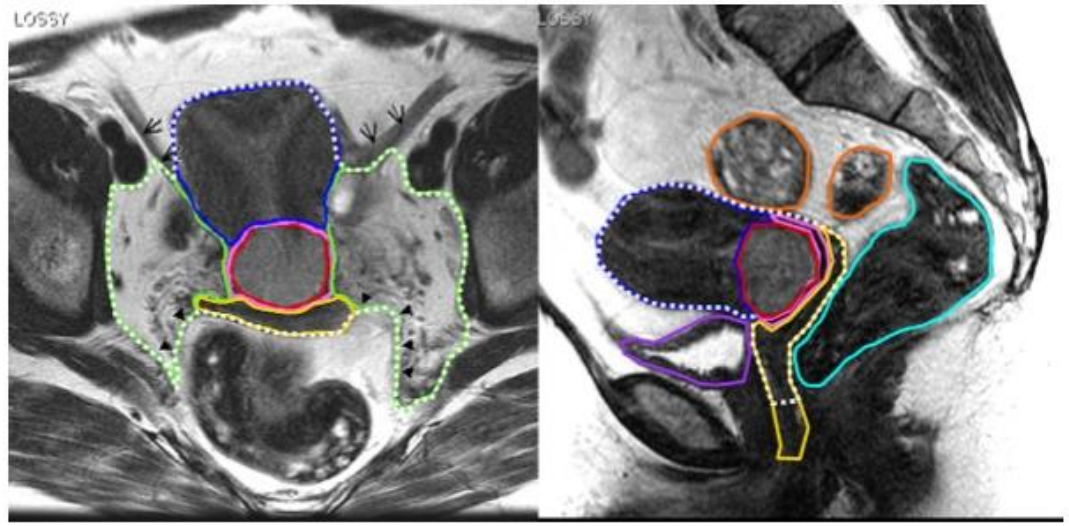


Fig. 3. T_2-weighted MR axial (left) and sagittal (right) images of one patient demonstrating GTV (red), cervix (pink), uterus (blue), vagina (yellow), parametrium (green), bladder (purple), rectum (light blue), and sigmoid (orange). Arrow heads refer to uterosacral ligaments and mesorectal fascia. Arrows refer to the broad ligament and top of the fallopian tube. Dashed white lines represent the CTV.

Table 2. CTV components

GTV	Entire GTV; intermediate/high signal seen on T_2-weighted MR images
Cervix	Entire cervix; if not already included within GTV contour
Uterus	Entire uterus
Parametrium	Entire parametrium, including ovaries; include entire mesorectum if uterosacral ligament involved
Vagina	Minimal or no vaginal extension: upper half of the vagina
	Upper vaginal involvement: upper two-thirds of the vagina
	Extensive vaginal involvement: entire vagina

Table 3. Anatomical boundaries of parametria

Location	Anatomic structures
Anteriorly	Posterior wall of bladder or posterior border of external iliac vessel
Posteriorly	Uterosacral ligaments and mesorectal fascia
Laterally	Medial edge of internal obturator muscle/ ischial ramus bilaterally
Superiorly	Top of fallopian tube/ broad ligament. Depending on degree of uterus flexion, this may also form the anterior boundary of parametrial tissue.
Inferiorly	Urogenital diaphragm

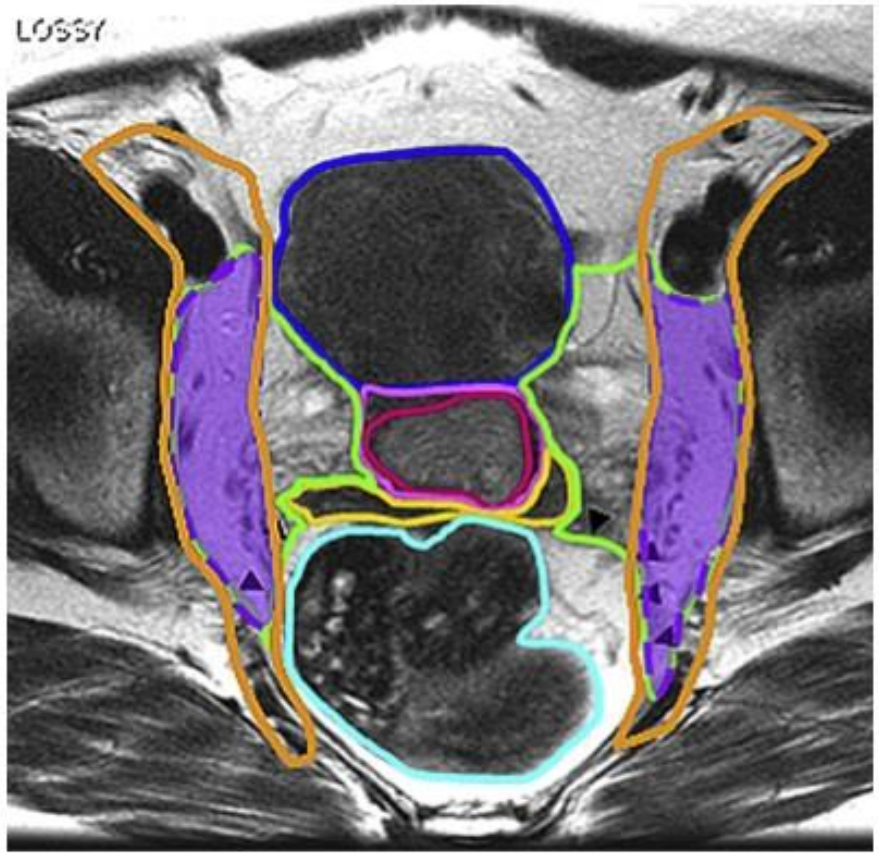


Fig. 6. Axial T_2-weighted MR image showing overlap (purple-shaded region) between nodal clinical target volume (orange contour) and lateral portion of parametrial volume (green contour).

Nodal CTV

The nodal CTV must include involved nodes and relevant draining nodal groups (common, internal, and external iliac and obturator and presacral lymph nodes). Inclusion of para-aortic lymph nodes will depend on the extent of disease and results of staging investigations. Details of nodal CTV delineation will not be addressed in this document as a number of guidelines already exist (9, 30, 31).

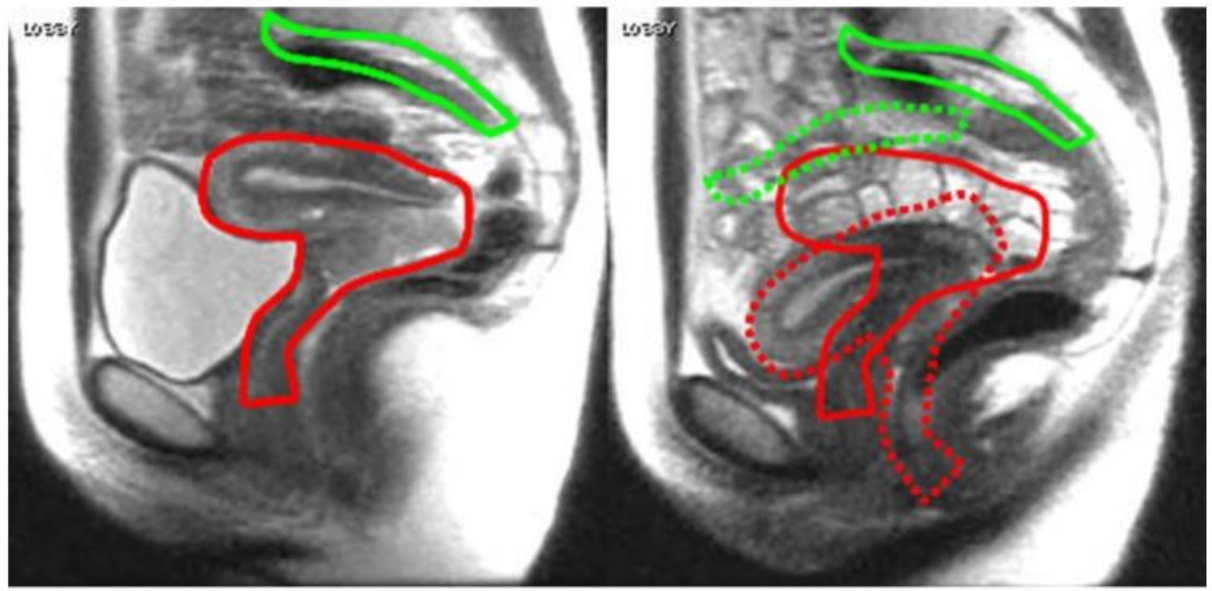


Fig. 7. Sagittal T_2-weighted MR images obtained 1 week apart from the same patient, demonstrating the marked difference between uterus and cervix positions, with altered bladder filling. Primary tumor CTV (red contour) and nodal CTV (green) contours overlaid. Solid lines represent targets at week 1, dashed lines represent the targets at week 2 if a direct translational shift is made to compensate for the change in the primary tumor CTV position. Nodal CTV and portions of tumor CTV in week 2 are missed.

PTV margins and image guidance

The survey of patterns of practice indicated that PTV margins varied among Consortium members, largely as a function of data available for organ motion for this site. A number of groups have published CTV-PTV margin recommendations which have ranged from 0.6 to 4 cm, depending on their methodology for assessing organ motion (11, 12, 14, 18, 32, 33). The combination of unpredictable organ motion and substantial tumor regression resulted in conservative margin recommendations by the Consortium. Margins of 1.5 to 2 cm around the CTV were recommended if good quality daily soft tissue verification was available during treatment. A PTV margin of 7 mm around the nodal CTV was agreed upon in line with previous recommendations in the postoperative cervix cancer setting (*e.g.*, RTOG protocol 0418). If bone matching alone was being used, more generous margins would be necessary, due to the uncertainty of tumor CTV position in relation to nodal CTV position. The use of IMRT without any form of daily soft tissue verification risks geographical target miss and should be approached with caution. Even the use of fiducial markers is not always reliable as they may shift over the course of treatment.

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Radiotherapy and Oncology 74 (2005) 235–245

www.elsevier.com/locate/radonline

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group☆ (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV

Christine Haie-Meder[a,*], Richard Pötter[b], Erik Van Limbergen[c], Edith Briot[a], Marisol De Brabandere[c], Johannes Dimopoulos[b], Isabelle Dumas[a], Taran Paulsen Hellebust[d], Christian Kirisits[b], Stefan Lang[b], Sabine Muschitz[b], Juliana Nevinson[e], An Nulens[c], Peter Petrow[f], Natascha Wachter-Gerstner[b]

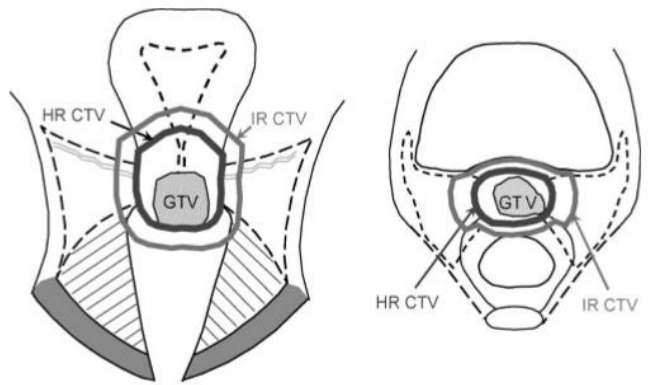

Fig. 5. Schematic diagram for cervix cancer, limited disease, with GTV, high risk CTV and intermediate risk CTV for definitive treatment: coronal and transversal view.

Radiotherapy and Oncology 78 (2006) 67–77
www.thegreenjournal.com

ESTRO project

Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology

Richard Pötter[a,*], Christine Haie-Meder[b], Erik Van Limbergen[c], Isabelle Barillot[d], Marisol De Brabandere[c], Johannes Dimopoulos[a], Isabelle Dumas[b], Beth Erickson[e], Stefan Lang[a], An Nulens[c], Peter Petrow[f], Jason Rownd[e], Christian Kirisits[a]

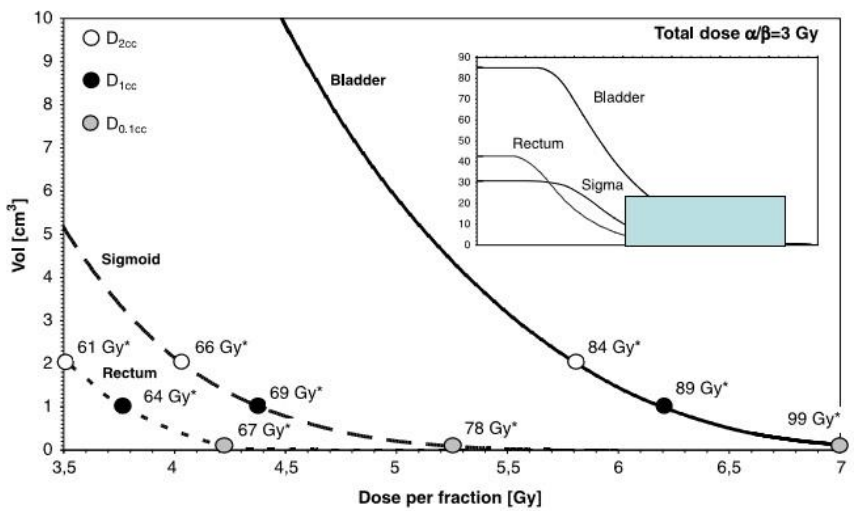

Fig. 5. Cumulative dose volume histograms of bladder, rectum and sigmoid (patient, Figs. 1, 3, 4 and 6) based on organ contouring indicating the minimum dose in the most irradiated tissue volume adjacent to the applicator ($D_{0.1cc}$, D_{1cc}, D_{2cc} for 0.1, 1, and 2 cm^3). *Total EQD2 dose values for these OAR are given assuming four identical HDR fractions with an α/β of 3 Gy. Treatment planning, for this example, was based on dose constraints for D_{2cc} (bladder: 90 Gy_{EQD2}; rectum, sigma: 70 Gy_{EQD2}). 90 Gy_{EQD2} is reached with four HDR fractions of 6.3 Gy (25.2 Gy), which is corresponding to 48 PDR pulses with 77 cGy/puls, 1 puls/h (37 Gy) and to LDR with 77 cGy/h in 48 h (37 Gy). For 70 Gy_{EQD2} the dose per HDR fraction is 4.5 Gy (18 Gy). The same dose is reached with 48 PDR pulses with 54 cGy/puls, 1 puls/h (26 Gy), and LDR with 54 cGy/h in 48 h (26 Gy).

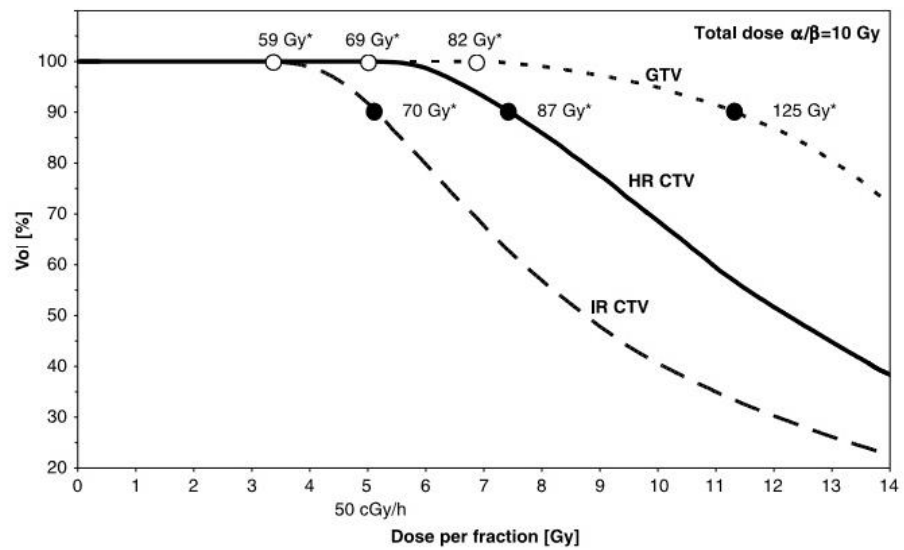

Fig. 4. Dose volume histograms of GTV, HR CTV, and IR CTV for one fraction of HDR intracavitary brachytherapy (patients Figs. 1, 3, 5 and 6). Prescribed dose is 25×1.8 Gy external beam therapy to ICRU point plus 40 Gy_{EQD2} (4×7 Gy) brachytherapy to HR CTV, which gives a total of 84 Gy_{EQD2} (α/β=10 Gy). *Total EQD2 values are given based on four identical fractions. In general, similar DVH curves are obtained for LDR or PDR treatments, but with different total EQD2 doses, e.g. 48 h LDR treatment with 50 cGy/h for D90 of IR CTV gives 69 Gy_{EQD2}, but 83 Gy_{EQD2} (74 cGy/h) for D90 of HR CTV and 110 Gy_{EQD2} (113 cGy/h) for D90 of GTV.

Radiotherapy and Oncology 96 (2010) 153–160

Contents lists available at ScienceDirect

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journal homepage: www.thegreenjournal.com

GEC-ESTRO Recommendations

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group: Considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer brachytherapy

Taran Paulsen Hellebust [a,*], Christian Kirisits [b], Daniel Berger [b], José Pérez-Calatayud [c], Marisol De Brabandere [d], Astrid De Leeuw [e], Isabelle Dumas [f], Robert Hudej [g], Gerry Lowe [h], Rachel Wills [h], Kari Tanderup [i]

Radiotherapy and Oncology 103 (2012) 113–122

Contents lists available at SciVerse ScienceDirect

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GEC-ESTRO Recommendations

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy

Johannes C.A. Dimopoulos [a], Peter Petrow [b], Kari Tanderup [c], Primoz Petric [d], Daniel Berger [e], Christian Kirisits [e], Erik M. Pedersen [c], Erik van Limbergen [f], Christine Haie-Meder [g], Richard Pötter [e,*]

[a] *Metropolitan Hospital, Athens, Greece;* [b] *Institut Curie, Paris, France;* [c] *Aarhus University Hospital, Denmark;* [d] *Institute of Oncology Ljubljana, Slovenia;* [e] *Comprehensive Cancer Center, Medical University of Vienna, Austria;* [f] *Universitaire Ziekenhuis Gasthuisberg Leuven, Belgium;* [g] *Institut Gustave Roussy, Villejuif, France*

Image-guided brachytherapy in cervical cancer: experience in the Complejo Hospitalario de Navarra

Elena Villafranca[1], Paola Navarrete[1], Amaya Sola[1], Juan Carlos Muruzabal[2], Sara Aguirre[2], Santiago Ostiz[3], Carmen Sanchez[3], Rosa Guarch[4], Nuria Lainez[5], Marta Barrado[1].

Department of Radiation Oncology[1], Gynaecology[2], Radiology[3], Pathological Anatomy[4] and Medical Oncology[5]

Complejo Hospitalario de Navarra

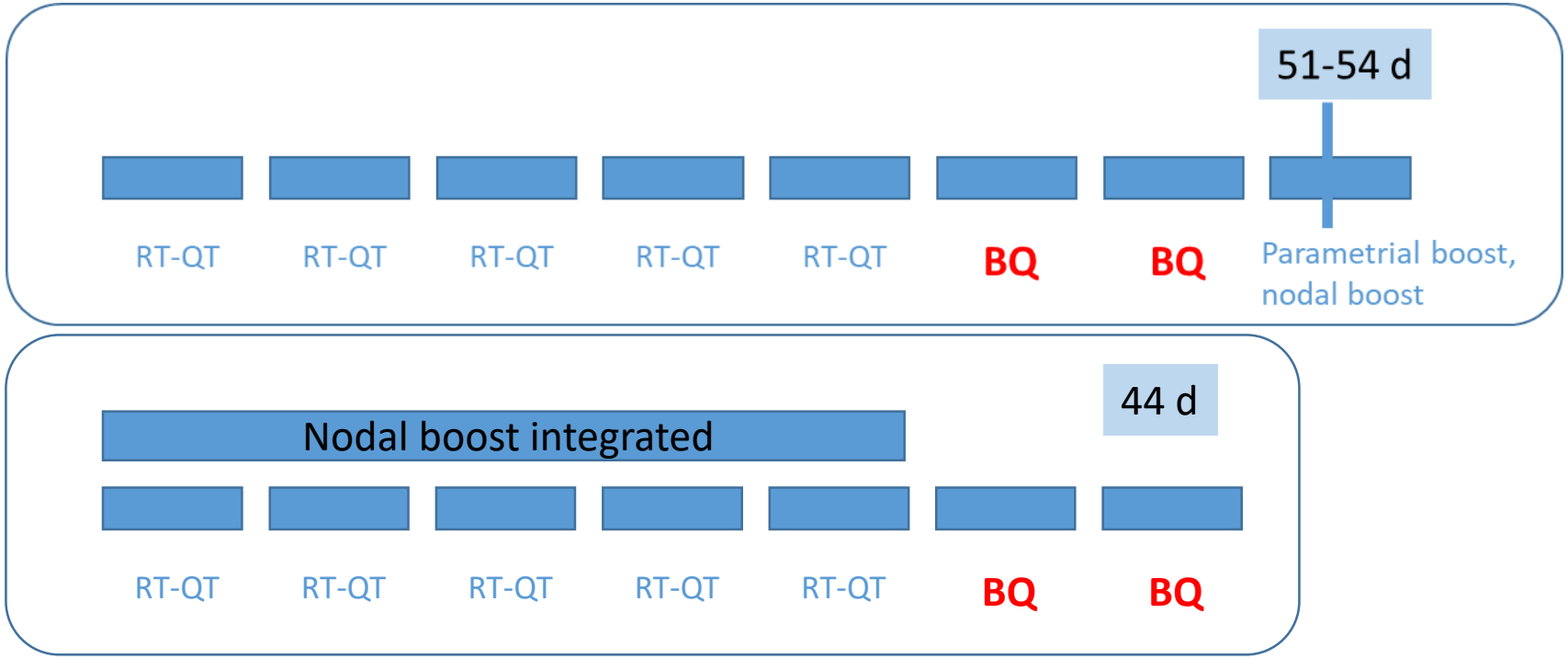
Pamplona. Spain

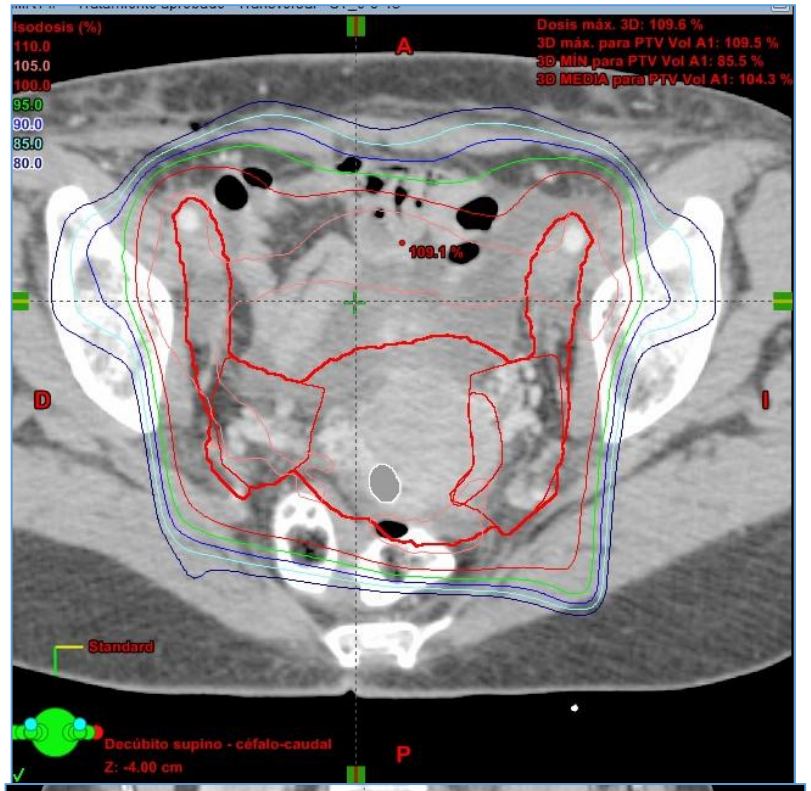
RPOR in press

Material and Methods

- Evaluation: All cases with locally advanced cervical tumours are evaluated by the Committee of Gynaecological Tumours. Patients undergo computerized tomography (CT), MRI and, in some cases, positron emission tomography-CT (PET-CT) studies, and pelvic-paraaortic lymphadenectomy is performed for staging.
- Chemotherapy involved the use of cisplatin 40 mg/m2, 1 day/week during 5 weeks.

- External beam radiotherapy (EBRT) was initially 3D but since 2011 IMRT is performed. All the cases received 45 Gy over 5 weeks.
  - In cases with lymph node remanents following lymphadenectomy or findings of extracapsular extension in some lymph nodes, a lymph node boost to 56-60 Gy was carried out after brachytherapy. Patients included in the EMBRACE II study received an integrated boost at a dose of 55-57 Gy according to the pelvic or paraaortic localization, respectively.
  - Before the availability of combined intracavitary-interstitial applicators, patients with macroscopic residual parametrial disease received a parametrial dose to achieve 60 Gy after brachytherapy, taking into account the parametrial doses of the brachytherapy.

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100.0
95.0
90.0
85.0
80.0
Dosis máx. 3D: 109.6 %
3D máx. para PTV Vol A1: 109.5 %
3D MIN para PTV Vol A1: 85.5 %
3D MEDIA para PTV Vol A1: 104.3 %
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103.1 %
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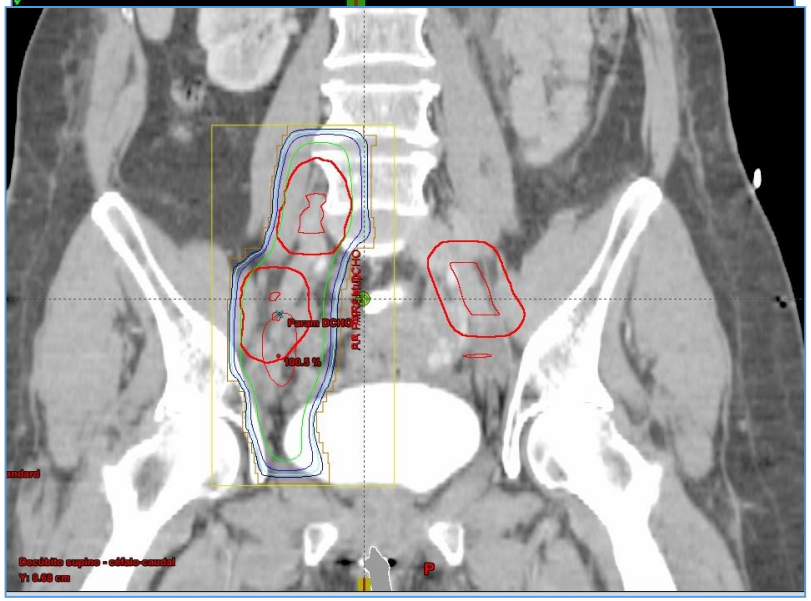
Z: -4.00 cm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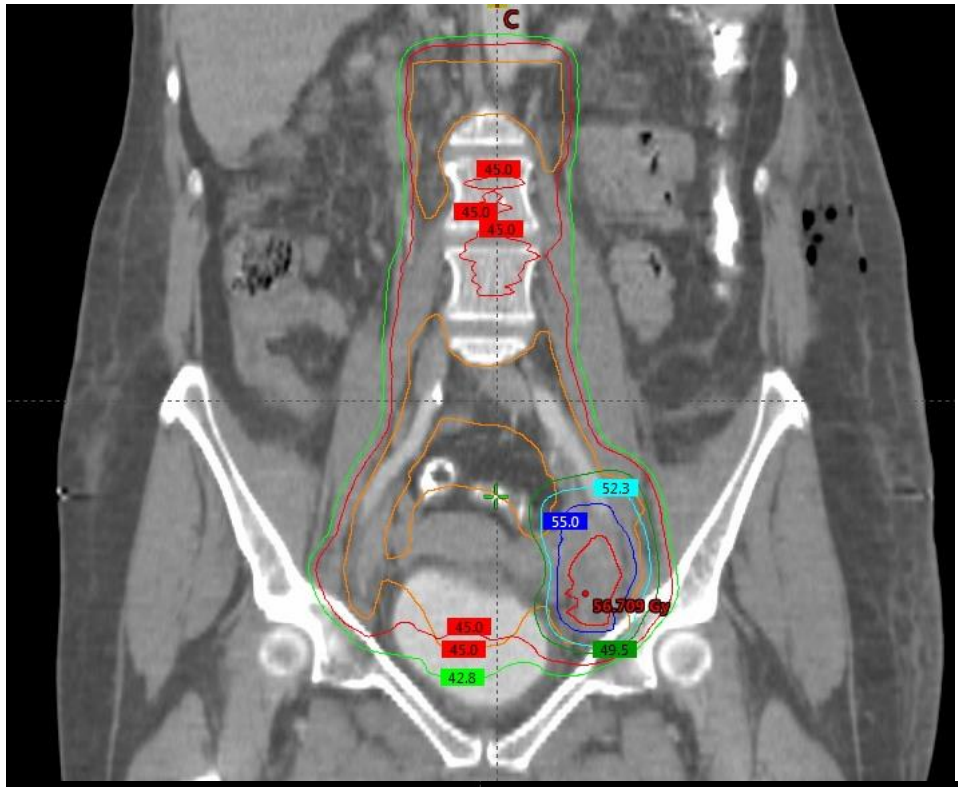
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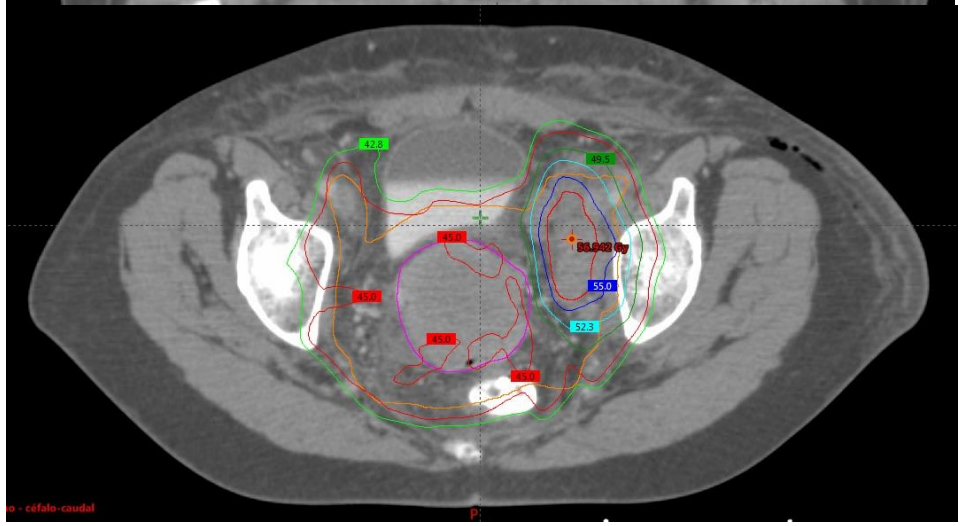
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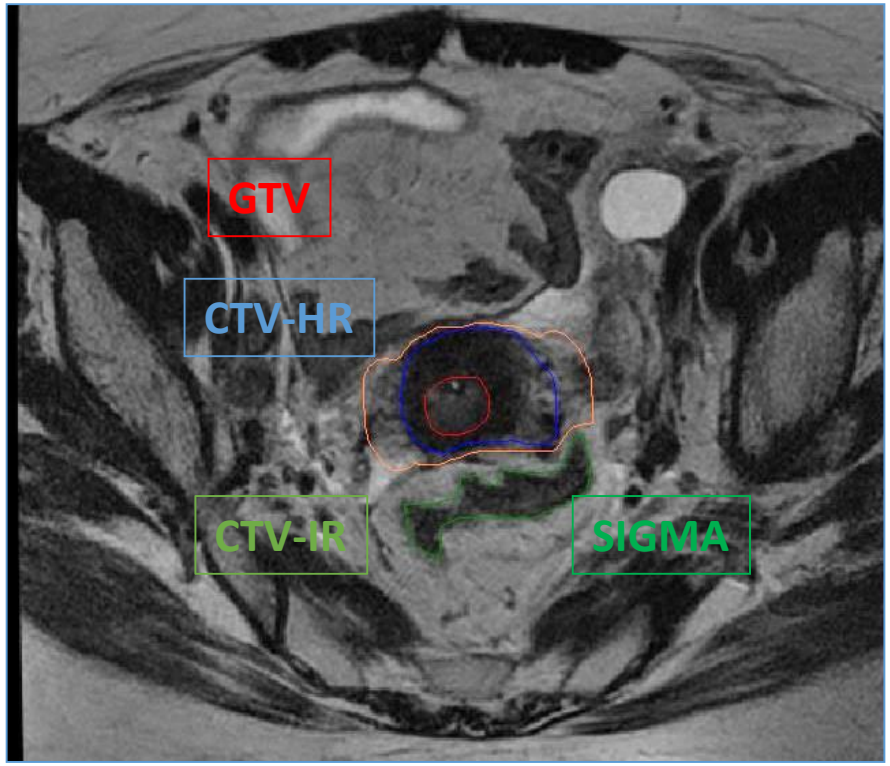
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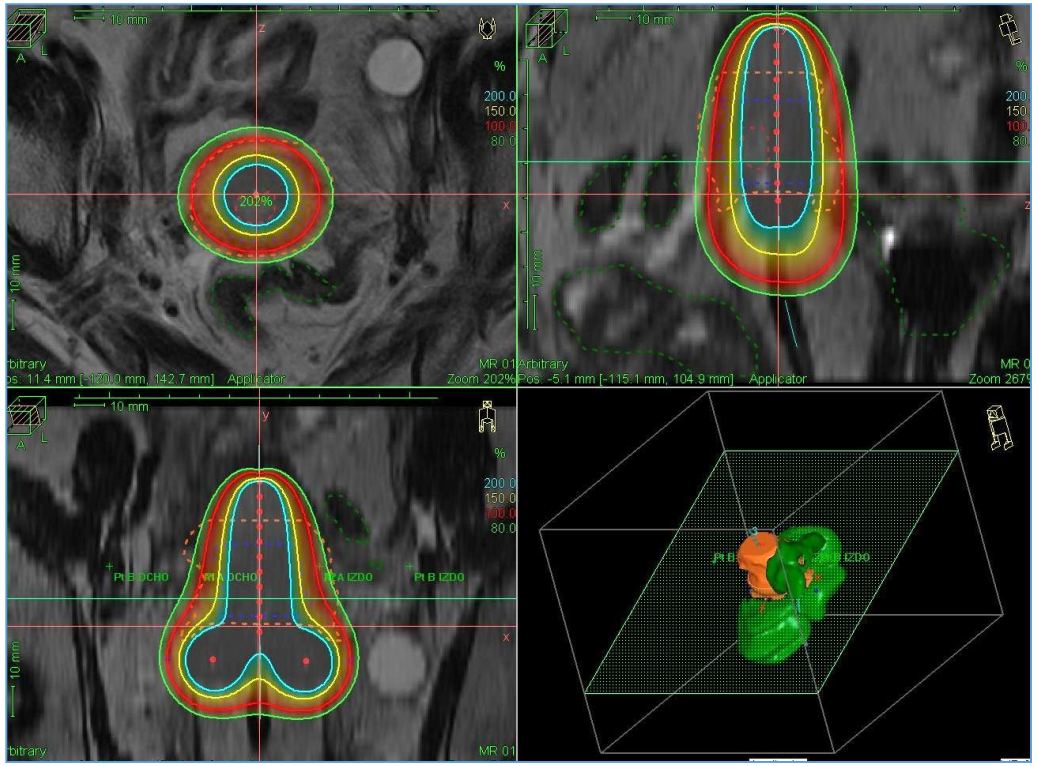
CTV-HR
CTV-IR
SIGMA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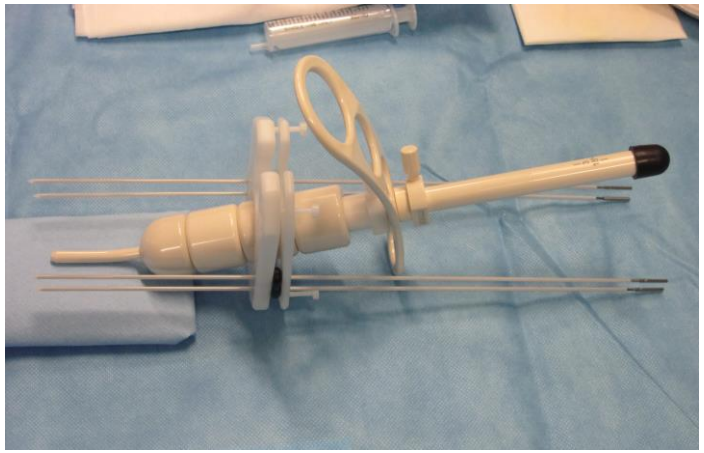

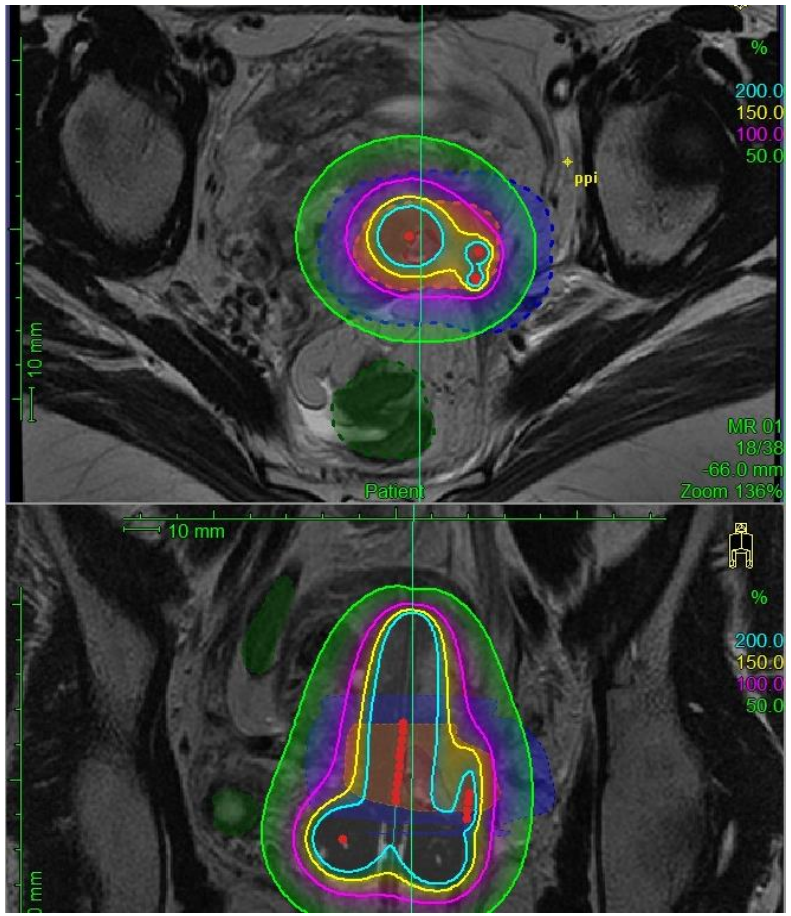
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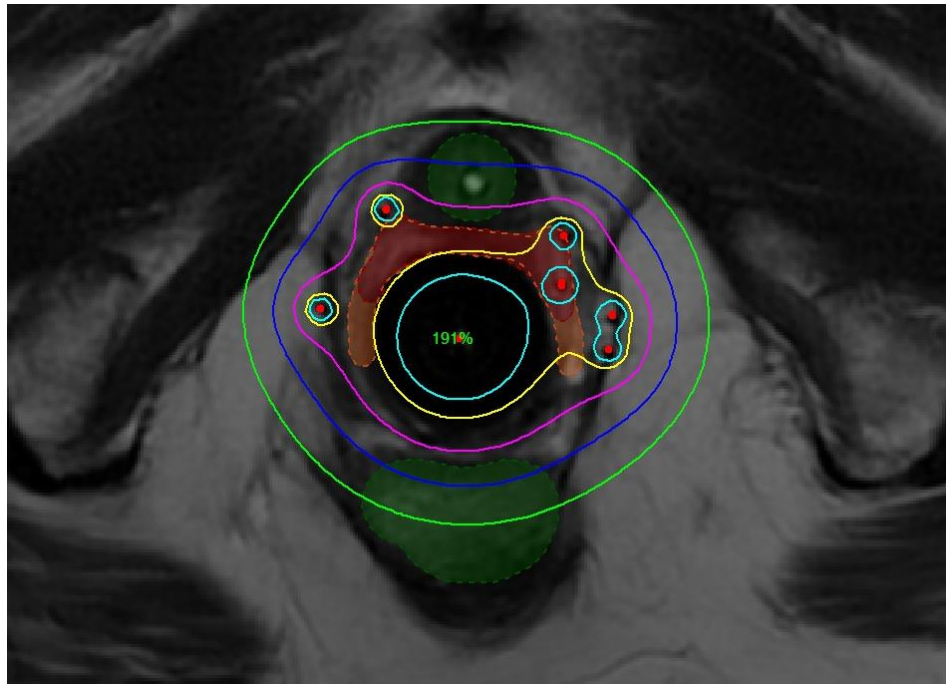

191%

- At week 5 of EBRT, all patients underwent MRI to evaluate response and to choose the applicator for brachytherapy. Brachytherapy was then done at weeks 6 and 7; first with 5 fractions of 6 Gy in 2 implants, and then with 4 fractions of 7 Gy after entry in the EMBRACE study in 2011. In both protocols MRI was performed after each implant for treatment planning. The objective was to carry out all the treatment in less than 55 days.
- The GEC-ESTRO guidelines were followed for the delimitation of volumes in MRI-GBT. Taking into account the dose of EBRT, the dosimetric objectives were to achieve D90 HR-CTV > 100% of the prescription dose, D90 IR-CTV > 60 Gy EQD2, D2cc rectum and sigma < 75 Gy EQD2 and D2cc < 85 Gy EQD2.

Doses recomendations

- **D90 CTV-HR > 85 -90 Gy**
- D98 GTV> 95 Gy
- D90 CTV-IR > 60 Gy

- **Rectum: D2cc < 75 Gy less fistula, D2cc < 65 Gy less proctitis**
- ***Vagina: Punto Recto-vaginal < 75 Gy.***
- Vejiga: D2cc < 80-85 Gy.
- Sigma: D2cc <70-75 Gy

- Follow-up: The patients were followed every 3 months during the first two years. The follow-up study always included physical examination, cytology every 6 months, MR every 6 months and CT annually. From years 3 to 5 the consultations were made every 6 months, with MR every year. After year 5 the follow-ups were carried out annually. The visits were alternated between the Gynaecology Department and the Brachytherapy Unit.
- Statistical analysis : General digestive, urinary and rectal toxicity were reported according to the Common Terminology Criteria for Adverse Events (CTCAE) v4 scale. T de Student was used to compare median of doses between groups of toxicity grade 0-1 versus grade 2-3. Kaplan-Meier test was used to calculate survival curves. Log rank test was used to compare prediction factors in survival

Table 1. Characteristics of the series

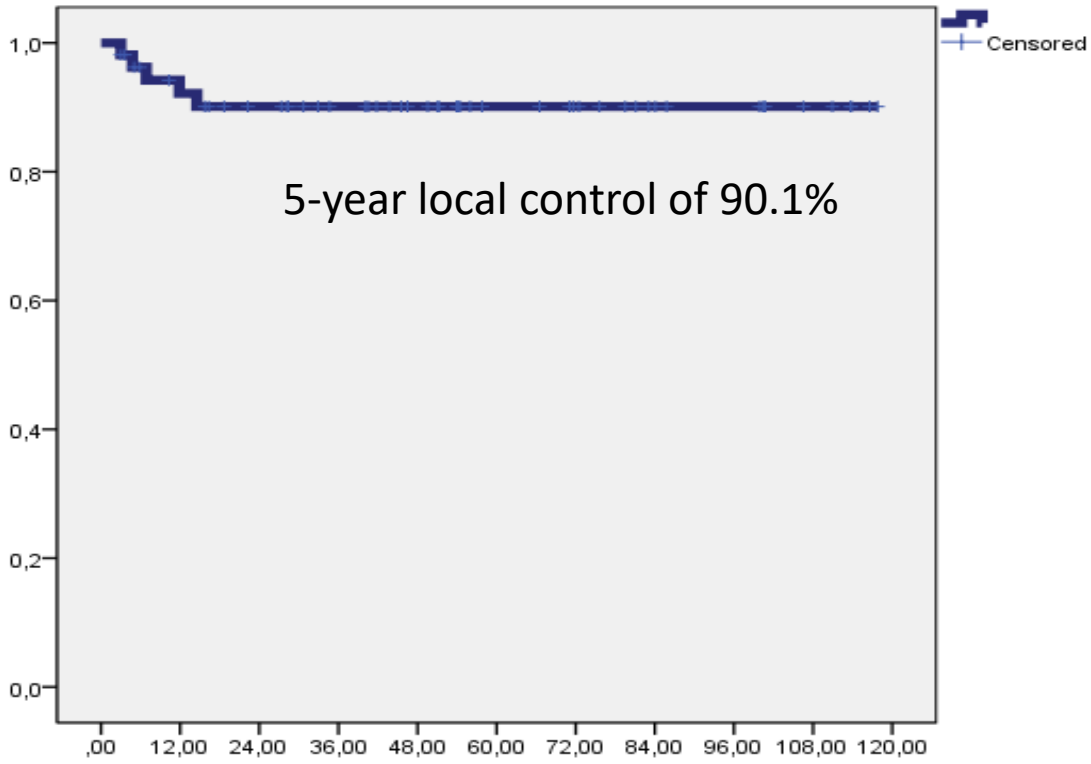
		N	%
Age	Median	51.2	27-85
Stage T	T1b2	3	5.3
	T2a2	1	1.8
	T2b	41	71.9
	T3a	2	3.5
	T3b	8	14
	T4a	2	3.5
Stage pN	N0	32	56.1
	N1	21	36.8
	No lymphadenectomy	4	7
Histologic type	squamous	45	78.9
	adenocarcinoma	12	21.1
Grade	Grade I	9	15.8
	Grade II	29	59.9
	Grade III	10	17.5
	nr	9	15.8

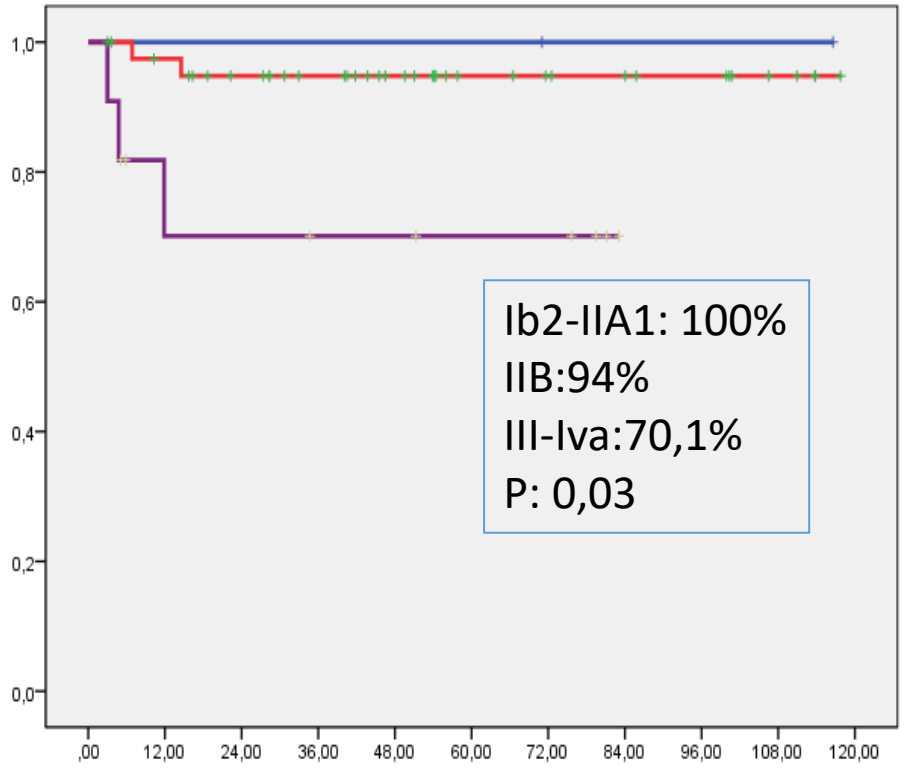
From November 2007 to July 2016 a total of 58 patients with a mean age of 52 years (range: 27 to 85 years)

Table2. Description of the treatment: external radiotherapy (ERT) and RMI guide-brachytherapy (IGBT)

		N	%
Radiotherapy			
	3D	27	47.4
	IMRT	30	52.6
Brachytherapy	Intracavitary	42	73.7
	Interstitial	13	22.8
	Intraoperative	2	3.5
Doses EQD2		Median	Range
	GTV D100	103.7	53-345
	CTV-HR D100	77.7	46-103
	CTV-HR D90	94.4	50-131
	D2cc bladder	83.5	55-103
	D2cc rectum	69.1	54-92
	D2cc sigmoid	64.7	48.7-81.7

Fig 1: Local control

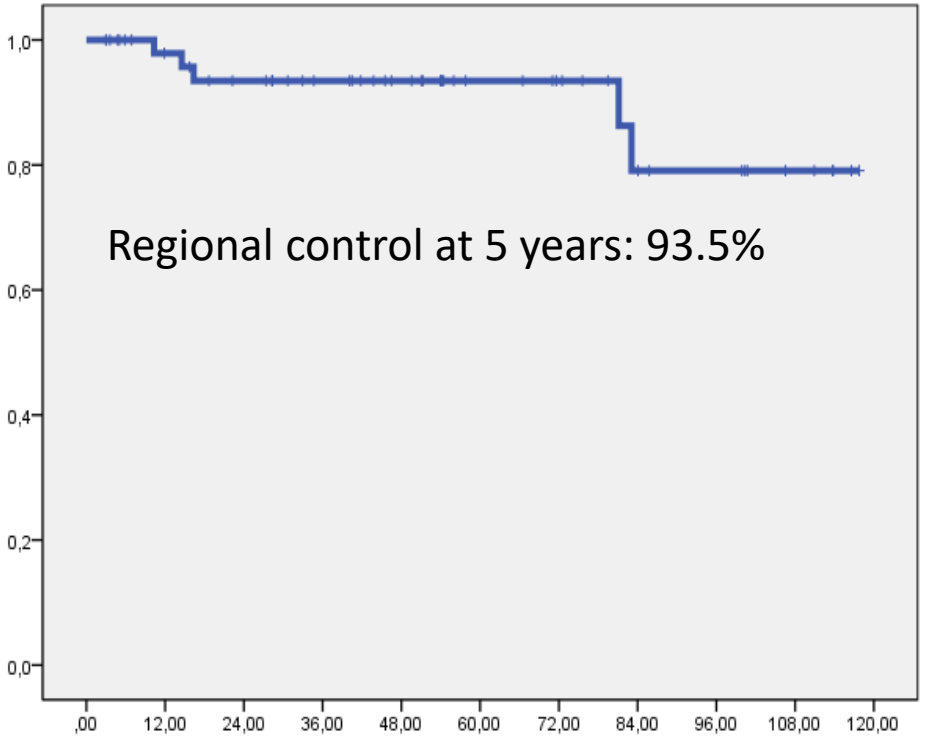




At a median follow up of 74.6 months (range: 16-122 m): 5p local recurrences (2p IIB, 2p IIIB, 1p Iva), 6p node recurrence and 9 p metastatic disease.

		Local control	p
Histologic type	Scamous	95%	0,001
	Adenocarcinoma	72,2%	
Node status afther lymphadenectomy	N0	100%	0,002
	N+	76,7%	
Brachytherapy	Intracavitary	100%	0,007
	Interstitial	78,6%	
D90 CTV-HR	< 85 Gy	91%	ns
	> 85 Gy	93%	
CTV-HR volumen	< 30 cc	93%	ns
	> 30 cc	92%	

Fig 2: regional control



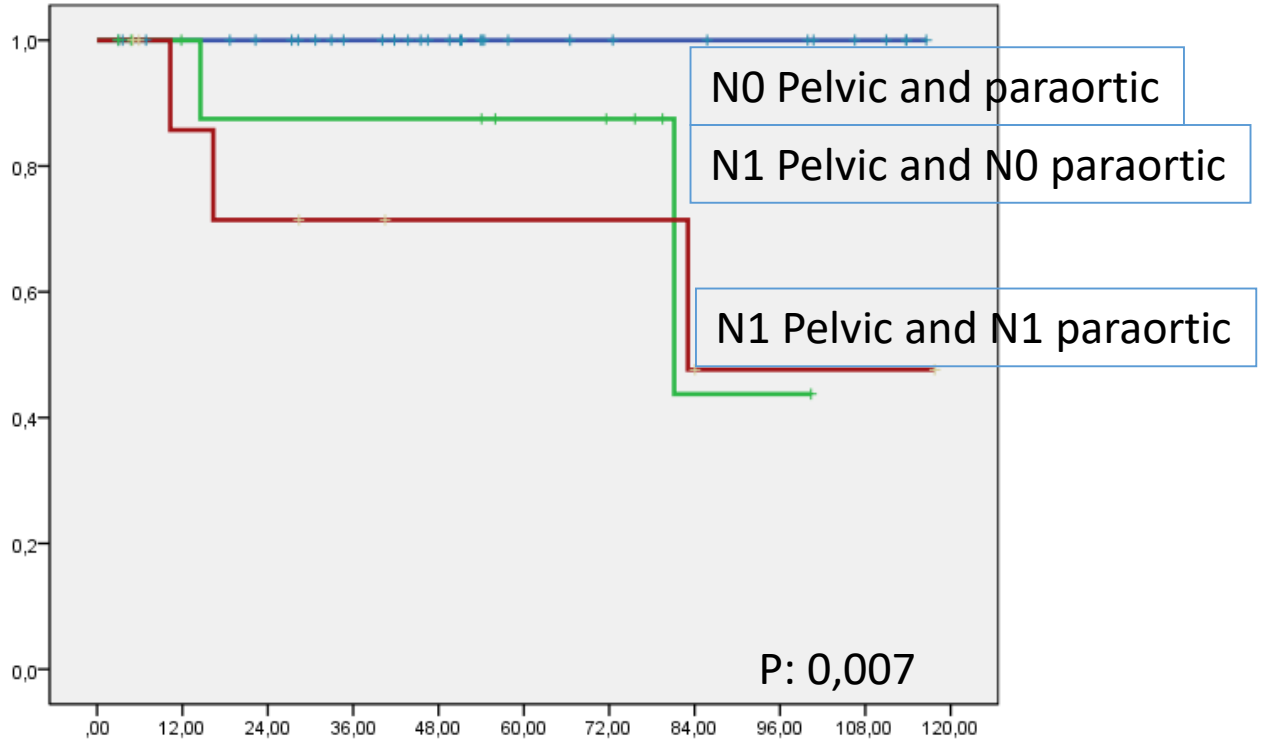
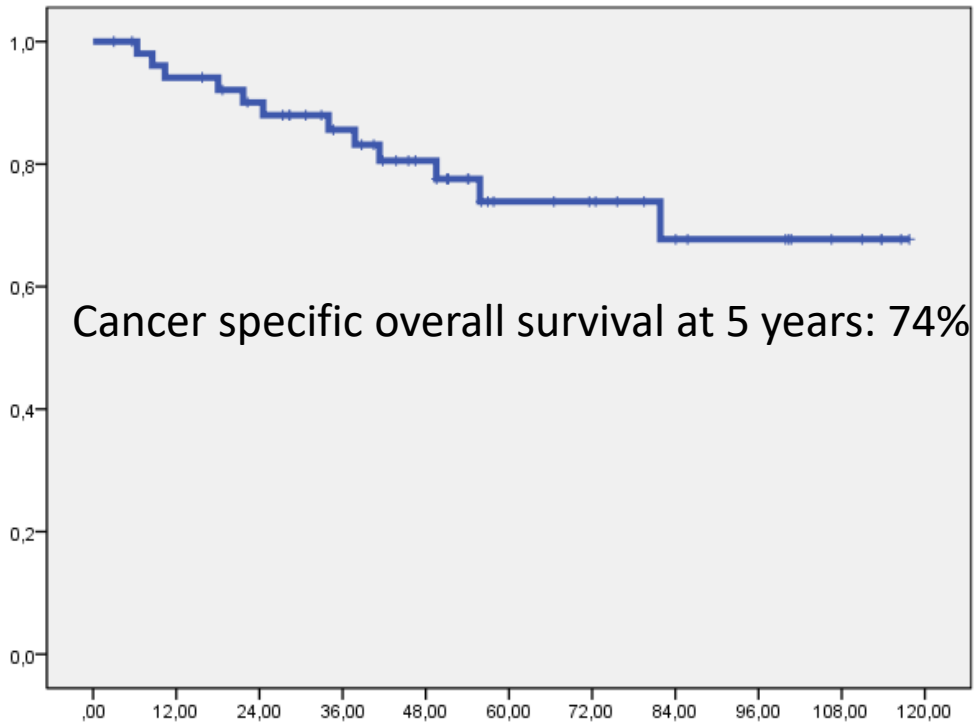


Figure 3: Cancer specific overall survival.



		CEOS	p
Stage	Ib2-IIB	83%	0,001
	III-Iva	41%	
Histology	squamous	78%	ns
	adenocarcinoma	59,7%	
Lymph node involvement	N0	85	0,01
	Npelvic-paraortic+	72	
	Npelvic+paraortic+	35	
ERT	3D	66.5%	ns
	IMRT	75,3%	
CTV-HR dose	<85 Gy	77%	ns
	>85 Gy	82,5&	
CTV-HR volumen	< 30 cc	81,8%	ns
	>30 cc	67%	

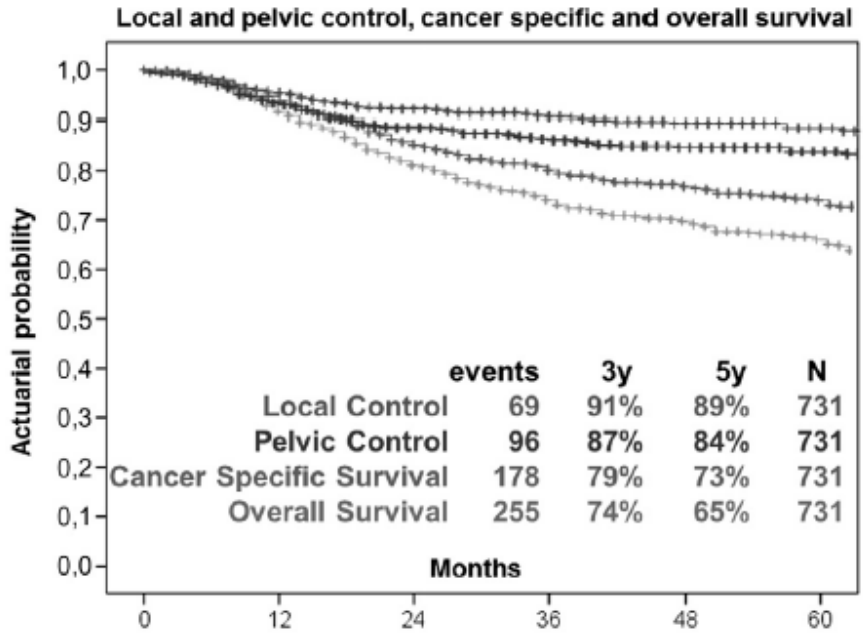
Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study

Alina Sturdza [a], Richard Pötter [a,*], Lars Ulrik Fokdal [b], Christine Haie-Meder [c], Li Tee Tan [d], Renaud Mazeron [c], Primoz Petric [e], Barbara Šegedin [e], Ina Maria Jurgenliemk-Schulz [f], Christel Nomden [f], Charles Gillham [g], Orla McArdle [g], Erik Van Limbergen [h], Hilde Janssen [h], Peter Hoskin [i], Gerry Lowe [i], Ekkasit Tharavichitkul [j], Elena Villafranca [k], Umesh Mahantshetty [l], Petra Georg [a], Kathrin Kirchheiner [a], Christian Kirisits [a], Kari Tanderup [b], Jacob Christian Lindegaard [b]

Radiotherapy and Oncology 120 (2016) 428–433

Patient and tumour characteristics.

Variable		No of patients *n*/%
Median age (years)	53 (23–91)	731
FIGO stage	1B	123 (16.8%)
	2A	42 (5.6%)
	2B	368 (50.3%)
	3A	23 (3.1%)
	3B	145 (19.8%)
	4A	23 (3.1%)
Histology	Squamous cell Ca	591 (84.7%)
	Adenocarcinoma	9.3%
	Others	6%
Median tumour width at diagnosis	Clinically: 50 mm	MRT: 46 mm
Nodal status	N+	40%
	N–	60%
CHT	Yes: 566 (76.5%)	No: 165 (22.5%)



Actuarial g3-g5 Morbidity was 5%, 7%, 5% for bladder, gastrointestinal and vagina

FIGO stage	Number of patients	Actuarial local control at 3/5 years	Actuarial pelvic control at 3/5 years	Actuarial overall survival at 3/5 years	Actuarial cancer specific survival at 3/5 years
1A	2	100%	100%	100%	100%
1B	123	98%/98%	96%/96%	88%/83%	93%/90%
2A	42	97%/94%	95%/92%	83%/80%	87%/84%
2B	368	93%/91%	89%/87%	78%/70%	83%/77%
3A	23	71%/71%	66%/66%	54%/42%	54%/48%
3B	145	79%/75%	73%/67%	56%/42%	65%/53%
4A	23	76%/76%	76%/76%	43%/32%	53%/ 40%
4B	5	–	–	–	
Total	731	91%/89%	87%/84%	74%/65%	79%/73%

Toxicity

Acute grade 2-3 toxicity was : rectal 15.7%, intestinal 15.7% and vesical 15.5%.

No patient presented grade 4 toxicity, but **late grade 2-3 toxicity** was observed: rectal 8.6%, intestinal 8.6%, and vesical 15.5%. The latter type of toxicity was due to an increase in frequency in 6 cases; 2 for hydronephrosis and 1 vesicovaginal fistula in 1 patient after rescue surgery for suspicion of tumour persistence.

Late rectal and urinary morbidity in relation to the dosimetric parameters: appearance of late toxicity grade 2-3 according to the EBRT received with the following results: rectal: 15% 3D vs. 10.5% IMRT (p: ns X2 Pearson), urinary: 22% 3D, 21% IMRT (p: ns). According to the bracthytherapy:

Cronic toxicity		D2cc (Gy)	p (T Student)
Rectal toxicity	G0-1	67,7	ns
	G2-3	72,4	
Urinary toxicity	G0-1	83,2	ns
	G2-3	80,4	

Cronic toxicity	D2cc (Gy)		p (X^2 Pearson)
Rectal toxicity	< 75 Gy	10%	ns
	> 75 Gy	14%	
Urinary toxicity	< 85 Gy	13,7%	ns
	> 85 GY	26,7%	

Original article

Physician assessed and patient reported urinary morbidity after radio-chemotherapy and image guided adaptive brachytherapy for locally advanced cervical cancer

Lars Fokdal [a,*], Richard Pötter [b], Kathrin Kirchheiner [b], Jacob Chr. Lindegaard [a], Nina Boje Kibsgaard Jensen [a], Christian Kirisits [b], Cyrus Chargari [c], Umesh Mahantshetty [d], Ina Maria Jürgenliemk-Schulz [e], Barbara Segedin [f], Peter Hoskin [g], Kari Tanderup [a]

[a] Department of Oncology, Aarhus University Hospital, Denmark; [b] Department of Radiation Oncology, Medical University of Vienna, Austria; [c] Department of Radiotherapy, Gustave-Roussy, France; [d] Department of Radiation Oncology, Tata Memorial Centre, HBNI, Mumbai, India; [e] Department of Radiation Oncology, Utrecht University, Netherlands; [f] Department of Oncology, Institute of Oncology Ljubljana, Slovenia; and [g] Mount Vernon Cancer Centre, United Kingdom

Table 2
Crude maximum incidence of individual bladder endpoints and ureteral stricture according to CTCAE v 3.0 and total number of patients with bladder symptoms (all individual bladder endpoints analysed together) or urinary symptoms (all individual bladder endpoints and ureteral stricture analysed together).

N = 1176	Frequency/ urgency	Incontinence	Spasm	Bladder stenosis	Cystitis	Bleeding	Fistula[a]		Ureteral stricture[b]		Patients with bladder morbidity	Patients with urinary morbidity
							All	No bladder invasion	All	No baseline hydronephrosis		
Grade 0	569 (48.4%)	784 (66.7%)	1081 (91.9%)	1166 (99.1%)	958 (81.5%)	1098 (93.4%)	1157 (98.4%)	1102 (99.1%)	1125 (95.7%)	1067 (97.6%)	454 (38.6%)	440 (37.4%)
Grade 1	470 (40.0%)	267 (22.7%)	75 (6.4%)	7 (0.6%)	132 (11.2%)	55 (4.7%)	4 (0.3%)	3 (0.3%)	15 (1.3%)	13 (1.2%)	469 (39.9%)	466 (39.6%)
Grade 2	123 (10.4%)	106 (9.0%)	19 (1.6%)	3 (0.3%)	75 (6.4%)	19 (1.6)	3 (0.3%)	2 (0.2%)	12 (1.0%)	5 (0.5%)	211 (17.7)	210 (17.9%)
Grade 3	14 (1.2%)	14 (1.2%)	1 (0.1%)	0 (0%)	10 (0.9%)	4 (0.3%)	7 (5)[c] (0.6%)	2 (0.2%)	22 (18)[c] (1.9%)	8 (0.7%)	33 (31)[c] (2.8%)	49 (44)[c] (4.2%)
Grade 4		5 (0.4%)	0 (0.1%)	0 (0%)	1 (0.1%)	0 (0%)	5 (4)[c] (0.4%)	3 (0.3%)	2 (1)[c] (0.2%)	0 (0%)	9 (8)[c] (0.8%)	11 (9)[c] (0.9%)

[a] Fistulas have been analysed in all patients and in the subgroup of patients without bladder invasion on MRI at baseline.
[b] Ureteral stricture has been analysed in all patients and in the subgroup of patients without baseline hydronephrosis.
[c] The numbers in parenthesis show the crude maximum incidence with subtraction of those patients with morbidity that persists from baseline.

Please cite this article in press as: Fokdal L et al. Physician assessed and patient reported urinary morbidity after radio-chemotherapy and image guided adaptive brachytherapy for locally advanced cervical cancer. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.05.002

Dose–volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study ☆

Renaud Mazeron [a,*], Lars U. Fokdal [b], Kathrin Kirchheiner [c], Petra Georg [c], Noha Jastaniyah [c], Barbara Šegedin [d], Umesh Mahantshetty [e], Peter Hoskin [f], Ina Jürgenliemk-Schulz [g], Christian Kirisits [c], Jacob C. Lindegaard [b], Wolfgang Dörr [c], Christine Haie-Meder [a], Kari Tanderup [b], Richard Pötter [c], on behalf of the EMBRACE collaborative group[1]

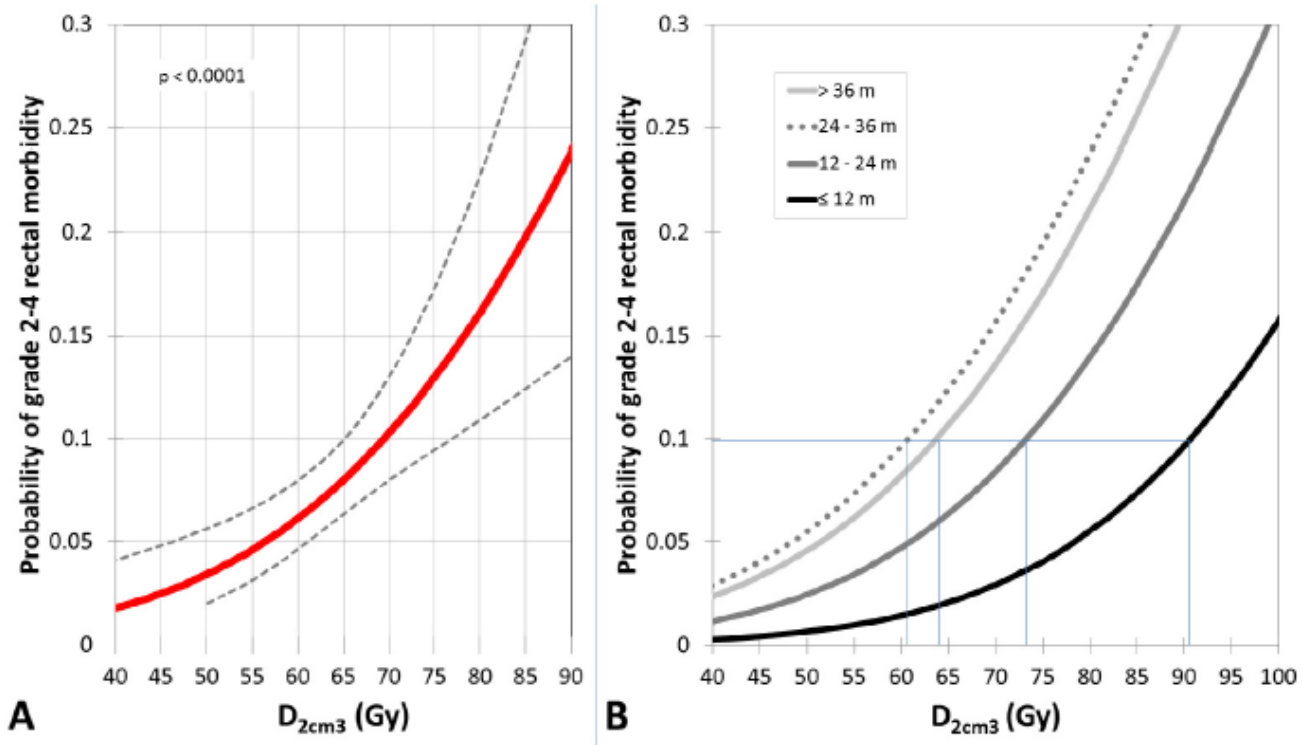


Fig. 3. Dose–volume effects for grade 2–4 overall rectum morbidity (A) and impact of follow-up on the relationships (B). Figure A focuses on the common prescription range of D_{2cm^3}. The full plot is provided as an additional material (Additional Fig. 2). Gray dashes: 95% confidence interval.

CONCLUSION

- In the present study the results obtained with the use of MRI-GBT in all the women with cervical cancer are comparable to those of the most important multicentre studies reported to date, with scarce, albeit manageable, late toxicity.
- The future is leading in the direction of the EMBRACE II study which is aimed at reducing toxicity in women showing good response after radiochemotherapy and intensification of brachytherapy treatment, especially with interstitial brachytherapy in order to improve local control and survival in patients with advanced tumours and poor initial response.

Orchis purpurea
Oteiza. Navarra

Experience in Spain

- Other hospitals with RM-IGBT: H. La Fe, C. Benidorm, H Clinico Madrid, I Catalan de Oncologia, H Marques de Valdecilla….
- Two meeting of Spanish Group of Brachytherapy.
  - 2009: Santander.

  2015 Pamplona.
- I workshop of interstitial brachytherapy in cervix cancer". Pamplona Jun 2018

VII Reunión de Consenso del grupo de Braquiterapia de la SEOR

"Planificación 3D en braquiterapia ginecológica"

Palacio de la Magdalena de Santander

Santander, 6 de Marzo de 2009

SEOR

Sociedad Española de Oncología Radioterápica

Santander
6 Marzo 2009

Clin Transl Oncol (2010) 12:000-000
DOI

EDUCATIONAL SERIES Yellow Series*

ADVANCES IN CLINICAL MANAGEMENT AND THERAPY OF CANCER

Consensus on 3D treatment planning in gynaecologic brachytherapy of the Radiation Oncology Spanish Society (SEOR) Brachytherapy Group

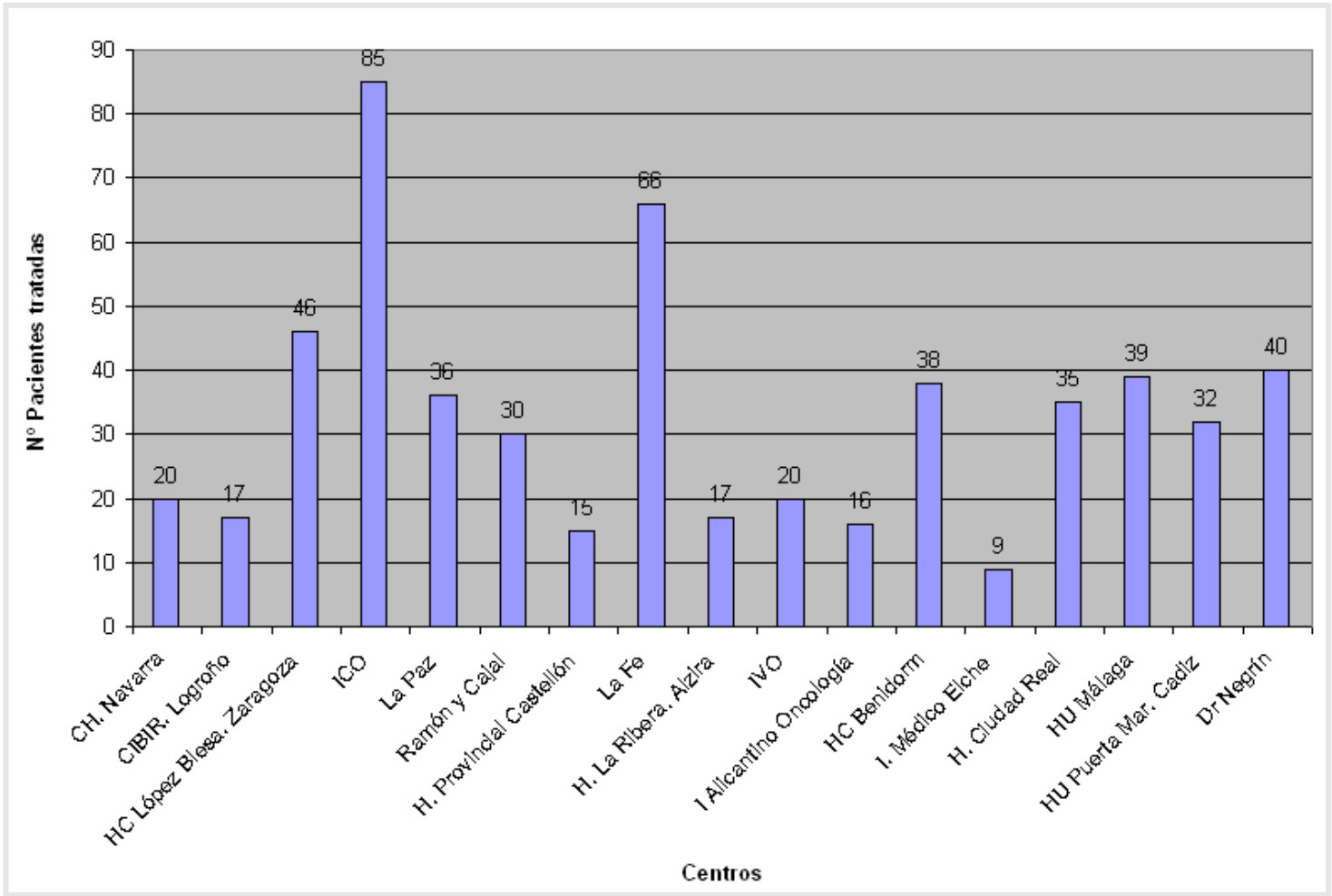
José Luis Guinot · José Pérez-Calatayud · Silvia Rodríguez · Alejandro Tormo · Vicente Crispín · Juan Carlos Menéndez on behalf of the Brachytherapy Spanish Group

Jornada de Braquiterapia GEB.
Cáncer de cérvix: Braquiterapia guiada por imagen intersticial-endocavitaria

Results of the spanish cuestionary. Pamplona 2015

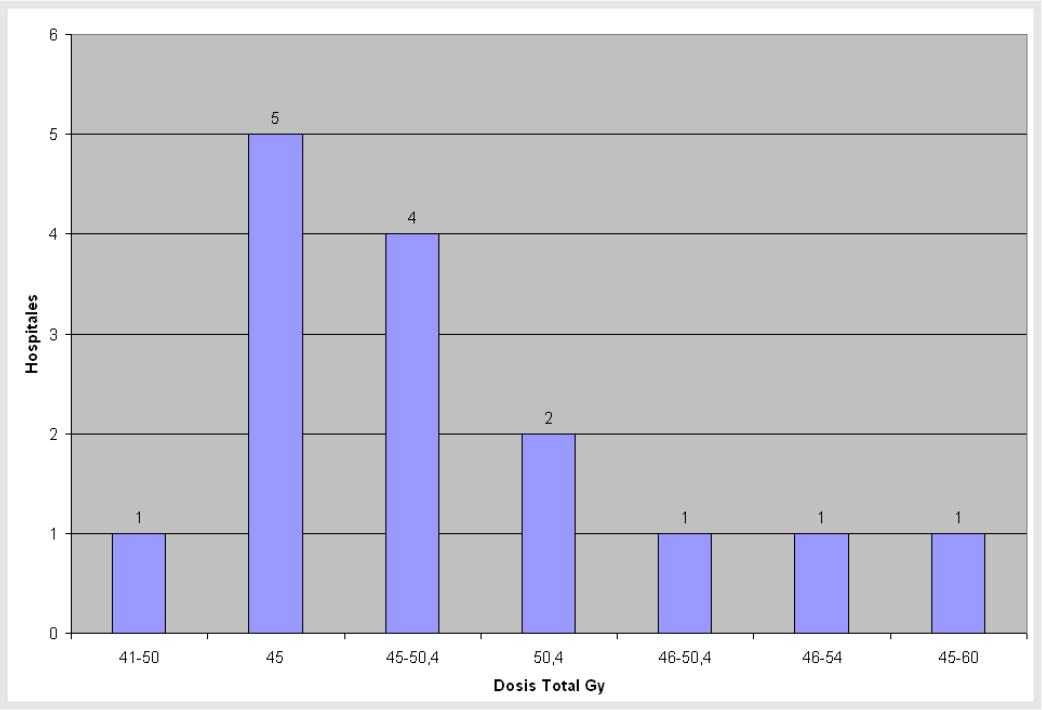
Dra. Amaya Sola Galarza.
Médico Adjunto Svo Oncología RT.
Complejo Hospitalario de Navarra

- GEB: started in1999.
- 128 doctors of 54 Hospitals.
- 17 have answered the cuestionary: 31.48 %



- Median patients treated between 2013-2014: 33 p

External radiotherapy

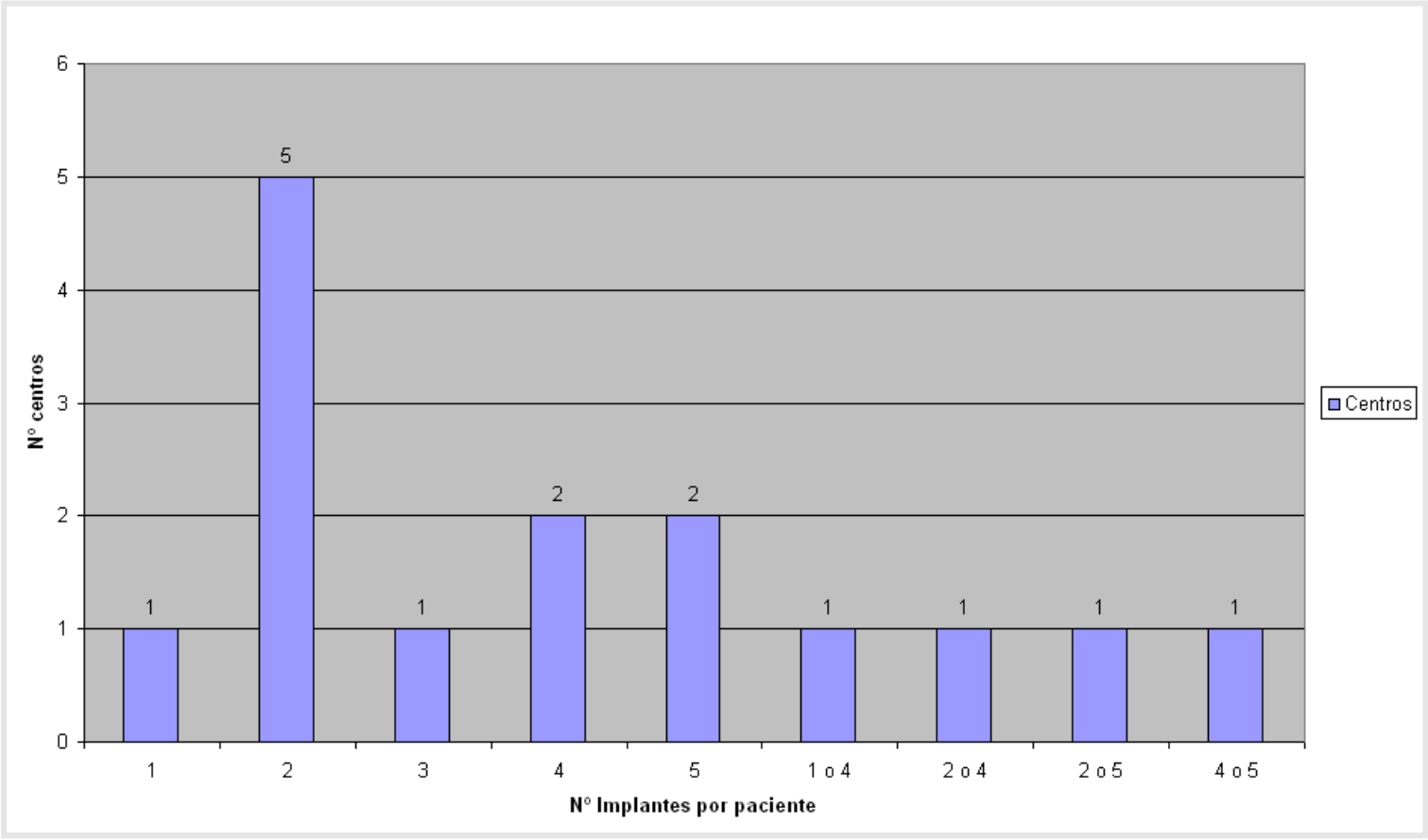


- Technic : 81.25 % have the 3 (IMRT, IGRT, 3D). 68.75 % IMRT and IGRT
- Most centers (68.75%) : 45-50.4 Gy
- Dose per fration: 1.8-2 Gy, 25-28 .
- QT (87.5% centers 14/16) : CDDP 40 mg/m2/weekly.

Dosimetric criteria

- PTV: D95>95 % DP
- Rectum: V 45 <50%, V50 < 50%.
- Bladder: V45 < 60%, V50 < 50%.
- Sigmoid: V60 < 30%
- Bowell: V 45 < 195 cc, V 40 < 150cc
- Femur heads: V 45 < 5% V 50 < 5-10%.

Brachytherapy



- 16 centers
- Unique implant (PDR: 2 h), 33 % 2 implants, 13 % 4 implants, 13% 5 implants, others

Interstitial brachytherapy for locally advanced cancer

- 7 centers don’t have aplicattors.
- 10 centers: only 7 hospitals do interstitial brachytherapy regulary.

OBJETIVOS DOCENTES

1. Conocer recomendaciones de braquiterapia guiada por imagen de resonancia de GEC-ESTRO, GEB y GBFM, ICRU 89.

2. Reconocer beneficios de braquiterapia intersticial en tumores avanzados.

3. Facilitar la formación in situ con aplicadores intersticiales y planificación con casos clínicos.

PROFESORES

Silvia Rodríguez. Oncóloga Radioterápica. Clínica Benidorm.

José Pérez Calatayud. Físico médico. Hospital La Fe Valencia.

Inés Álvarez de Eulate. Radióloga. CHN.

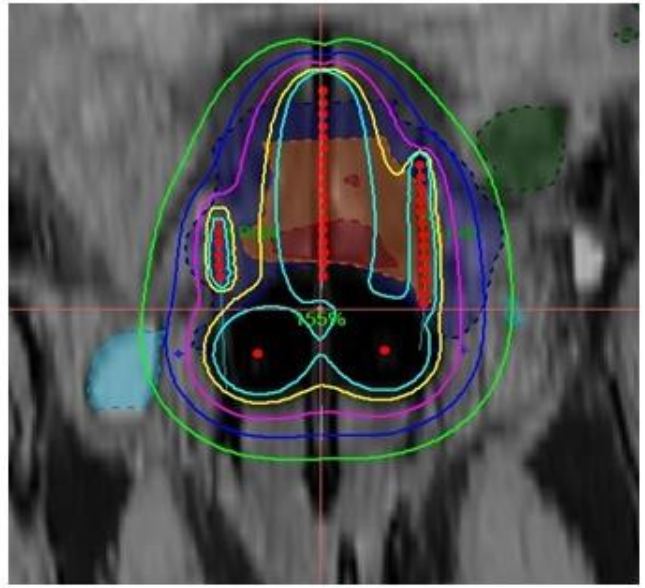
Santiago Pellejero. Físico médico. CHN.

Elena Villafranca. Oncóloga Radioterápica. CHN.

Acreditación docente: 1.41 créditos

Inscripción: contactar con Elekta: elekta.spain@elekta.com

Colaboración:



"I Workshop en Braquiterapia intersticial en el cáncer de cérvix"

Directores del Curso: Elena Villafranca. Santiago Pellejero

Destinado: Especialistas en Oncología radioterápica y Radiofísica, con Unidad de Braquiterapia.

Fecha: 15 y 16 de Junio de 2018.

Lugar: Complejo Hospitalario de Navarra. Edificio de Radioterapia. Pabellón J.

Unit of brachytherapy:

Doctors:

- Amaya Sola
- Paola Navarrete
- Marta Barrado
- Elena Villafranca

Physicists:

- Santiago Pellejero
- Nahiara Fuentemilla

Nurses:

- Marivi Hurtado
- Pilar Almeida
- Ines Villafranca
- Ana Cea

Dactylorhiza insularis

Erreniega. Navarra

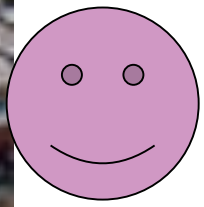
ESTRO School

WWW.ESTRO.ORG/SCHOOL

Hospital Clinico San Carlos.

Madrid. Spain

Sofía Cordoba Largo. Radiation Oncologist



ESTRO School

Brachytherapy Unit.
Radiation Department Overview

- 7 radiation oncologists
- 4 radiation physicists

- Number of staff involved in brachytherapy.
  - number of radiation oncologists: 3. (2 gynecol tumors. 2 prostate) (1 per day)
  - number of radiation physicists: 4 (1 per day)
  - Nurse: 2
  - Technician: 1

ESTRO School

Brachytherapy Overview

- Disease indications/patient types:
  - Cervical cancer: BTE after EBRT (concomitant chemotherapy)
  - Endometrial cancer: adyuvant BTE alone or combined with EBRT
  - Prostate cancer: Low , Intermediate and high risk
  - Breast cancer: Boost

- number of patients treated with brachytherapy per year: 2017: 198patients

  - Cervical cancer: patients
  - Endometrial cáncer: patients
  - Vaginal cancer: 2 patients
  - Vulvar cáncer: 8 patients +

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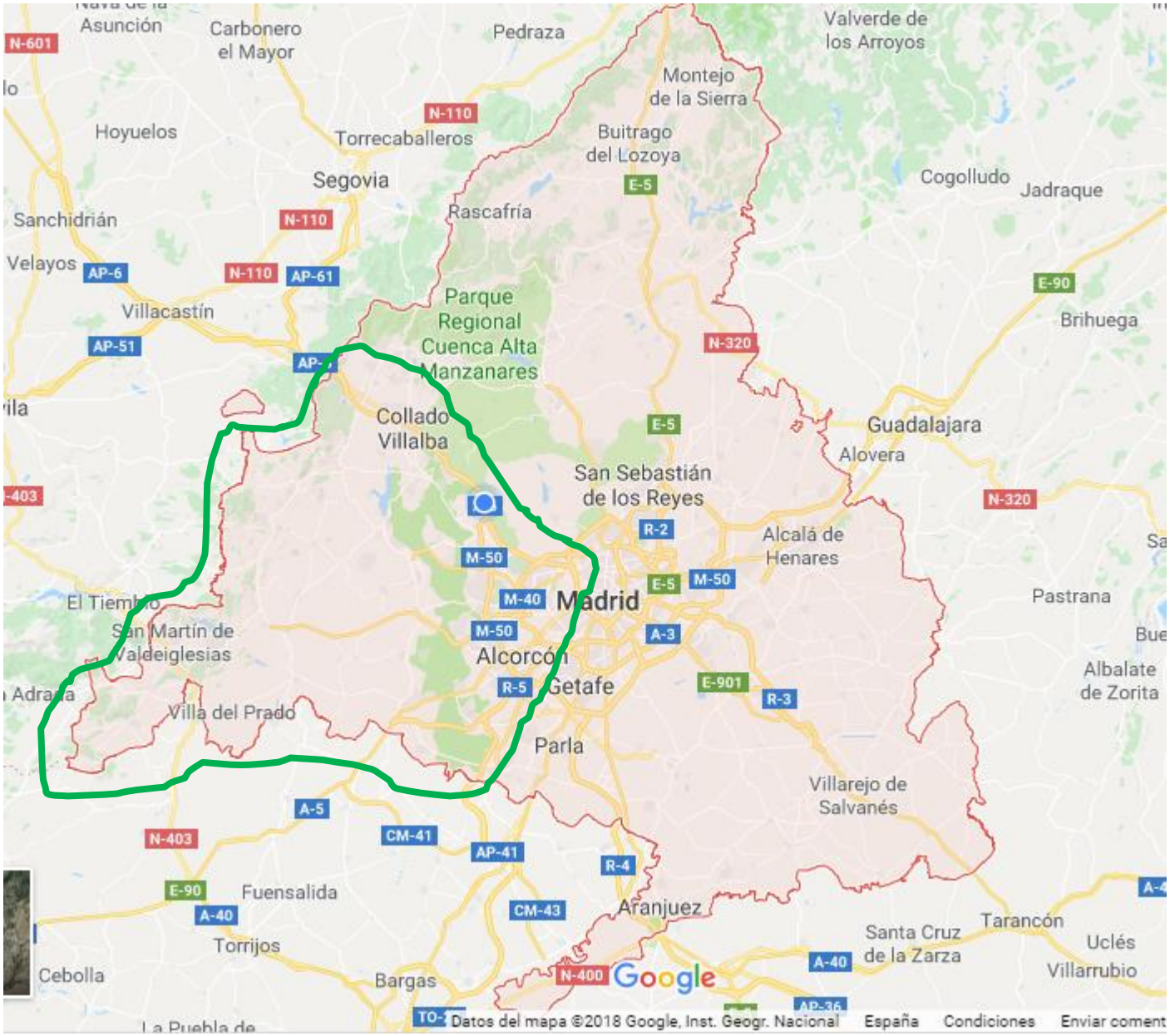
Asunción
Carbonero el Mayor
Pedraza
Valverde de los Arroyos
Montejo de la Sierra
Hoyuelos
Torrecaballeros
Buitrago del Lozoya
Segovia
Cogolludo
Jadraque
Rascafría
Sanchidrián
Velayos
Villacastín
Parque Regional Cuenca Alta Manzanares
Brihuega
Collado Villalba
Guadalajara
Alovera
San Sebastián de los Reyes
Alcalá de Henares
Madrid
Pastrana
El Tiemblo
San Martín de Valdeiglesias
Alcorcón
Getafe
Albalate de Zorita
Villa del Prado
Parla
Villarejo de Salvanés
Fuensalida
Aranjuez
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Tarancón
Uclés
Villarrubio
Torrijos
Cebolla
Bargas
Google
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España
Condiciones
Enviar coment

Brachytherapy Overview

- Brachytherapy infrastructure:
  - Imaging facilities: CT, MRI (Radiologist department)

This is not a problem¡¡¡¡¡

  - Equipment:
  - applicator type(s) : Utrech
  - Afterloader: microselectron
    - planning system: Oncentra planning system

EBRT:

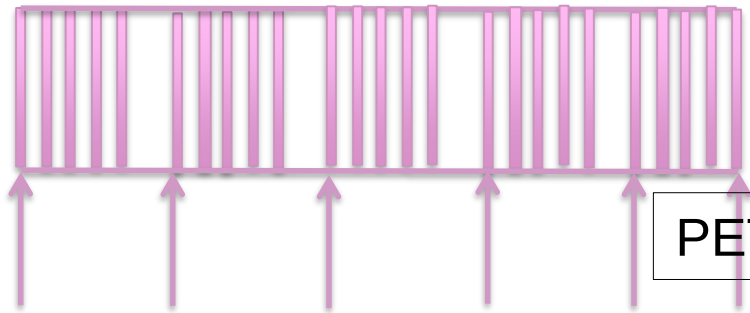
MRI

PET-TC

3D-RTE/VMAT/TOMO-
Daily IGRT

PTV45: 45/25

PTV55: 55/25



Cisplatin 40 mg/m2

Cervical cancer:

– Cervical cancer: IGBT after EBRT

IGBT: 4 x7Gy (D90), EQD2>90Gy

1º IMPLANT

MRI

CT

1º Aplication

INGRESO

CT

2º Aplication

2º IMPLANT

MRI

CT

3º Aplication

INGRESO

CT

4º Aplication

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IGBT (MRI) SINCE 2014

BUT

- Contouring
- Reconstruction
- Dosimetry……
- Dose and treatment……..

XIII
REUNION DE CONSENSO EN BRAQUITERAPIA

BRAQUITERAPIA 3D E INTERSTICIAL EN GINECOLOGÍA

Hospital de Navarra

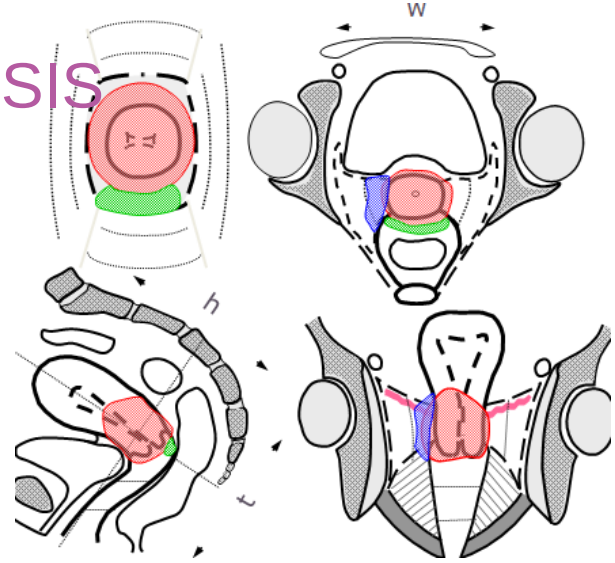
PAMPLONA

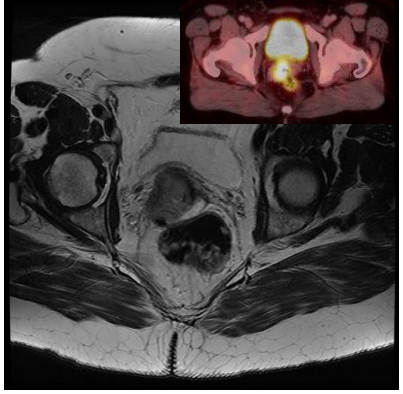
3 de OCTUBRE de 2015

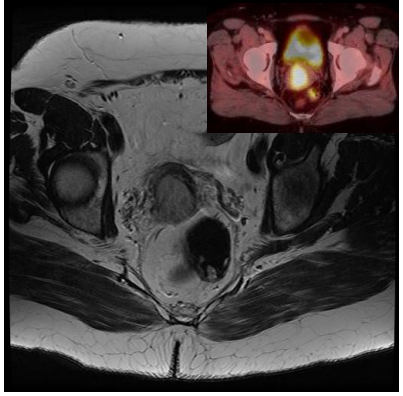
November 2015……

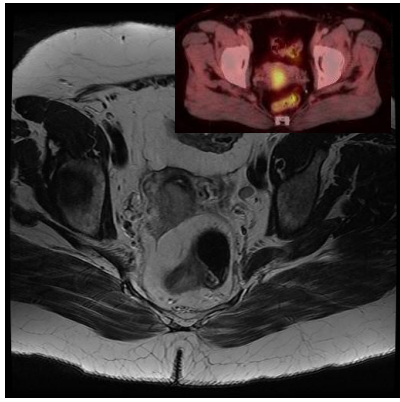
- Future goals: quality improvement and better trazability to good practices.
- Objectives and specific issues you would like to see addressed in this workshop:
  - clinical dosimetry, good practice
  - MR/CT fusion
  - ROI delineation
  - Tricks, etc

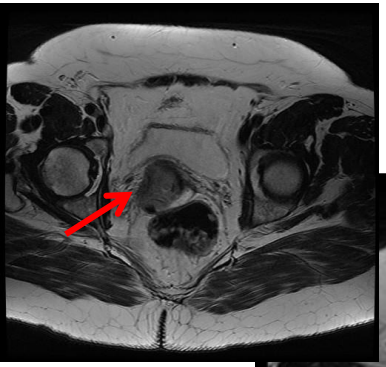
AT DIAGNOSIS

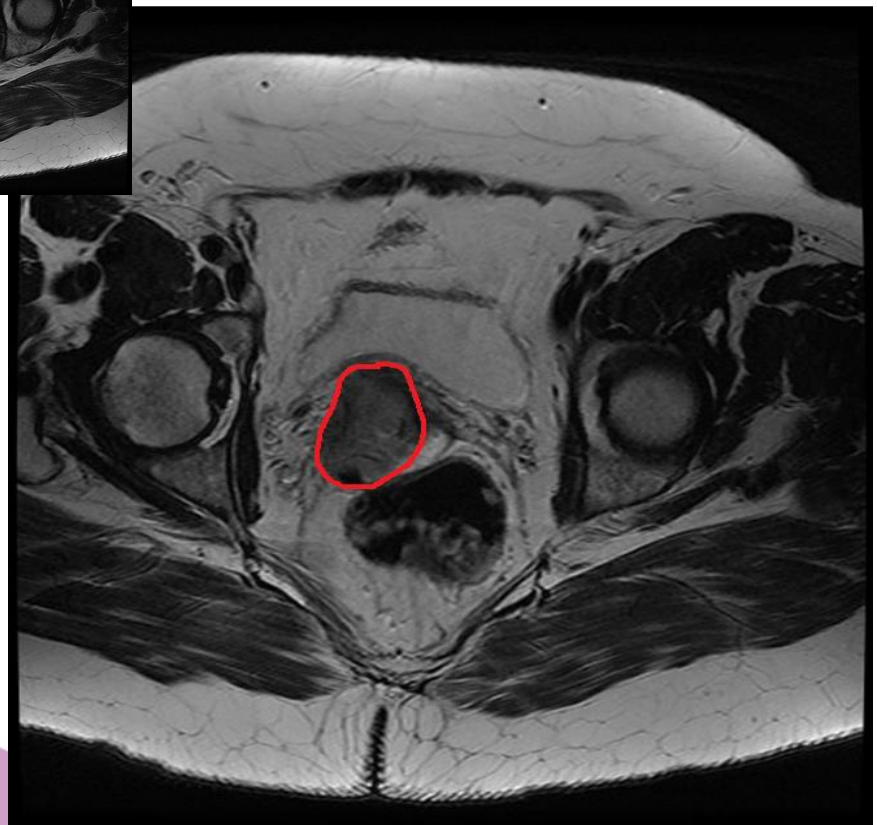


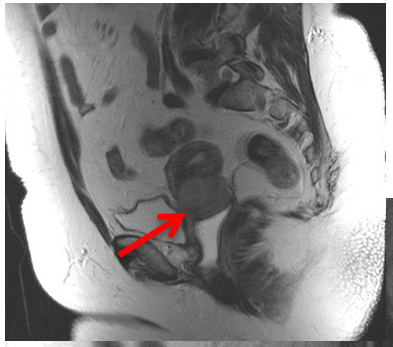


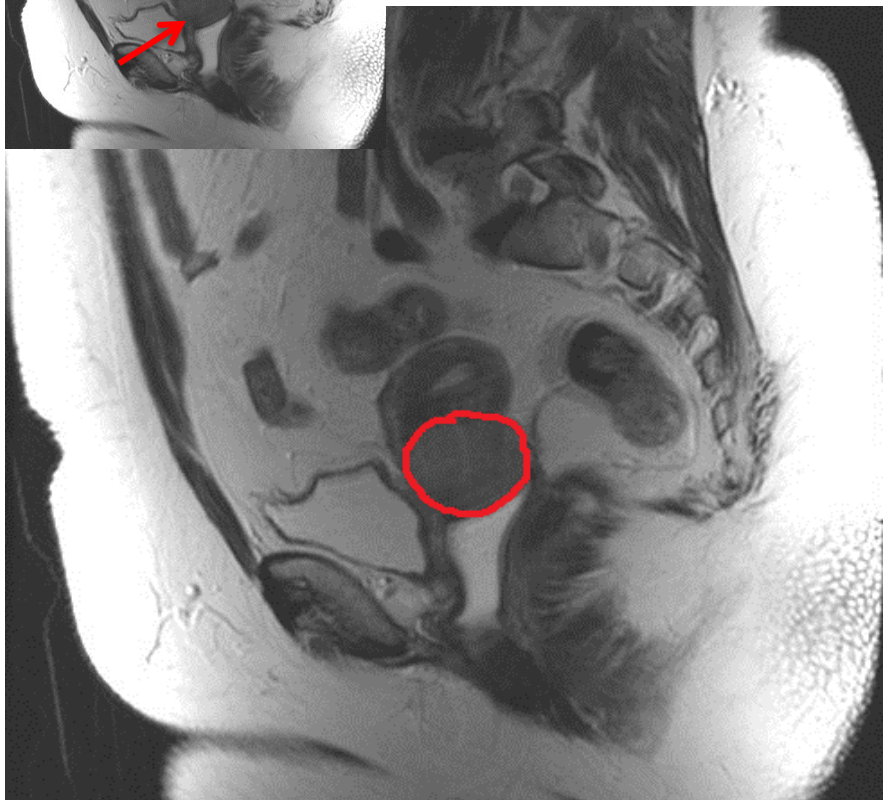




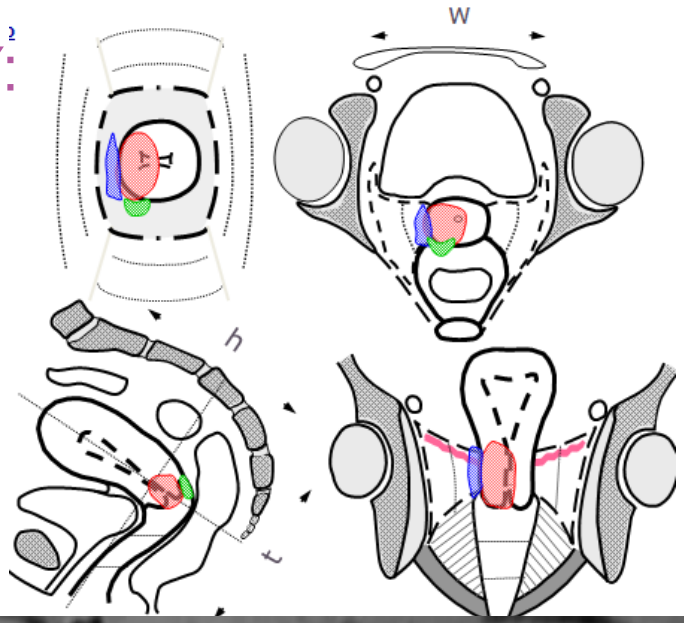


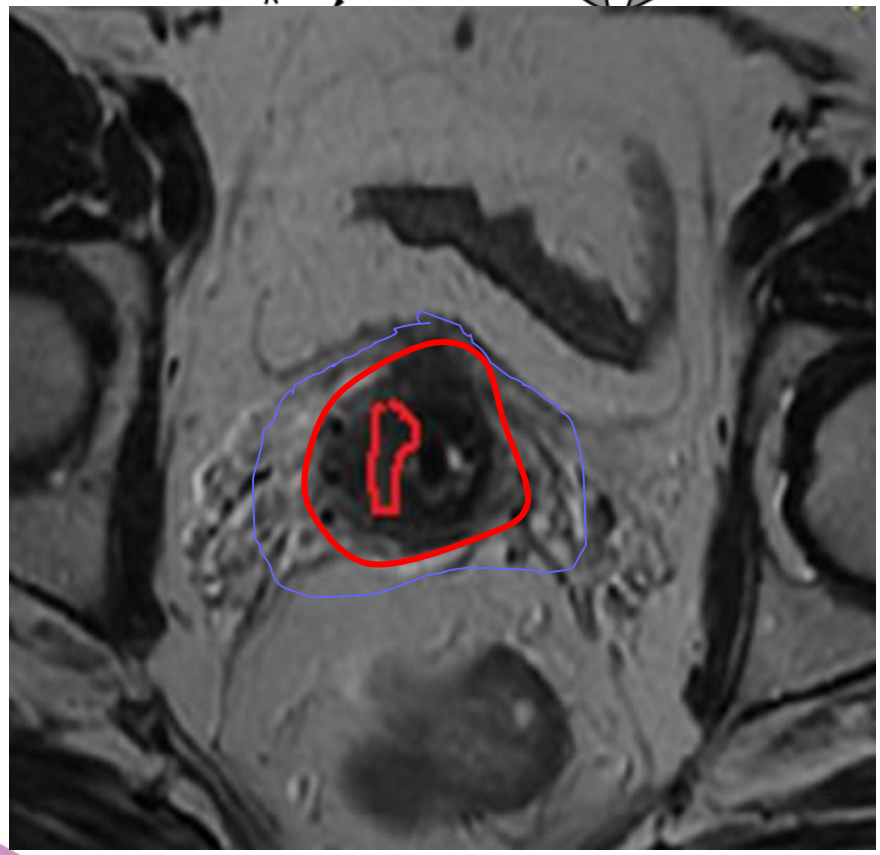


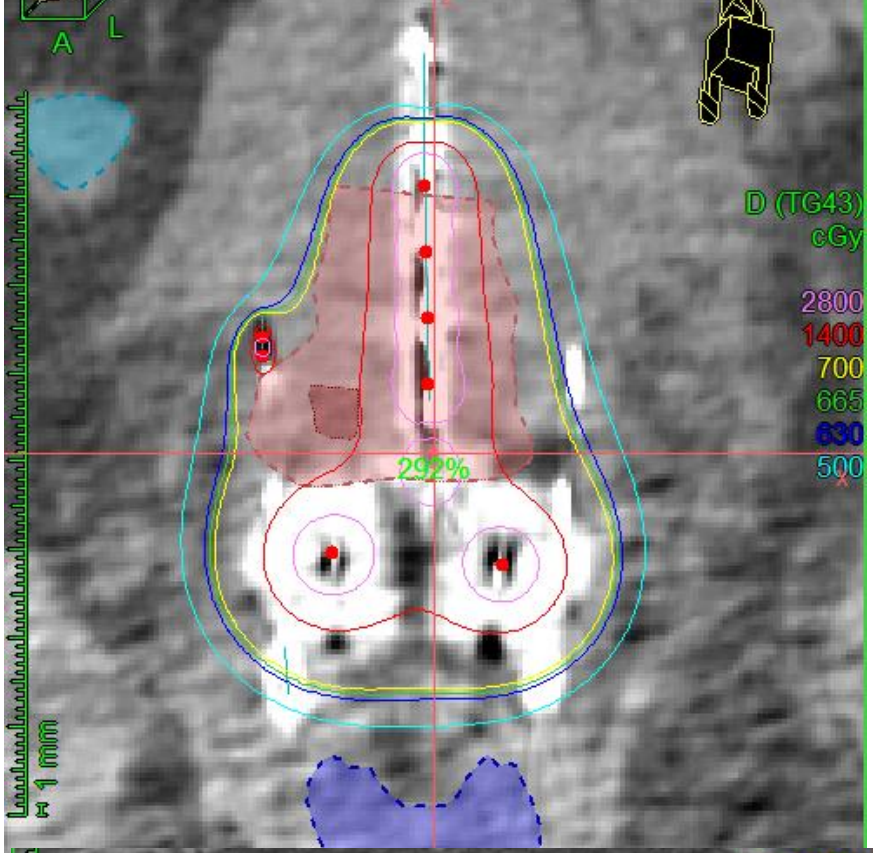


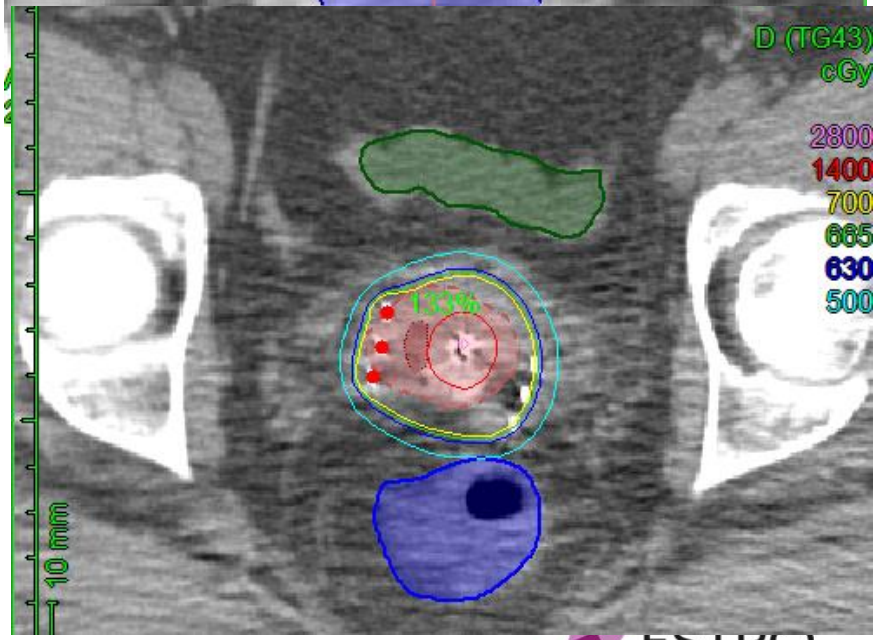


BRACHY:









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α/β_Tumor(Gy):	10								
α/β_OAR (Gy):	3								
		EBRT	HDR_1	HDR_2	HDR_3	HDR_4	HDR_5	HDR_6	TOTAL
DOSIS/SESIÓN (Gy):		1.8	7.0	7.0	7.0	7.0			
N° DE SESIONES:		25	1.0	1.0	1.0	1.0	1.0	1.0	
DOSIS TARGET (Gy):		45.0	7.0	7.0	7.0	7.0	0.0	0.0	73.0
	D90	45.0	8.76	8.01	8.43	8.65			
	D98	45.0	7.53	6.97	7.34	7.50			
	Gy (2cc pinnacle)								
DMF_RECTO:	45.00	1.0	0.62	0.38	0.60	0.53			
DMF_VEJIGA:	45.00	1.0	0.67	0.75	0.66	0.65			
DMF_SIGMA:	45.00	1.0	0.00	0.17	0.24	0.25			
DMF_INTESTINO:	45.00	1.0	0.32	0.17	0.20	0.24			
BED_TARGET(Gy):		53.1	13.2	11.8	12.7	13.1	0.0	0.0	104.0
BED_TARGET(Gy)_D90:		53.1	16.4	14.4	15.5	16.1	0.0	0.0	115.6
BED_TARGET(Gy)_D98:		53.1	13.2	11.8	12.7	13.1	0.0	0.0	104.0
BED_RECTO (Gy):		72.0	10.6	5.0	10.1	8.3	0.0	0.0	106.0
BED_VEJIGA (Gy):		72.0	12.0	14.4	11.7	11.5	0.0	0.0	121.6
BED_SIGMA (Gy):		72.0	0.0	1.7	2.6	2.8	0.0	0.0	79.1
BED_INTESTINO (Gy):		72.0	3.9	1.7	2.1	2.6	0.0	0.0	82.2
D2Gy_TARGET(Gy):		44.3	11.0	9.9	10.6	10.9	0.0	0.0	86.7
D2Gy_TARGET(Gy)_D90:		44.3	13.7	12.0	12.9	13.4	0.0	0.0	96.4
D2Gy_TARGET(Gy)_D98:		44.3	11.0	9.9	10.6	10.9	0.0	0.0	86.7
D2Gy_RECTO_2cc(Gy):		43.2	6.4	3.0	6.0	5.0	0.0	0.0	63.6
D2Gy_VEJIGA_2cc(Gy):		43.2	7.2	8.7	7.0	6.9	0.0	0.0	73.0
D2Gy_SIGMA_2cc(Gy):		43.2	0.0	1.0	1.6	1.7	0.0	0.0	47.4
D2Gy_INTESTINO_2cc(Gy):		43.2	2.3	1.0	1.2	1.6	0.0	0.0	49.3

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II Edición
REVISIONES EN ONCOLOGÍA CLÍNICA

MADRID 5-8 JUNIO 2018

MARTES 5	CÁNCER DE PRÓSTATA / CÁNCER DE MAMA
MIÉRCOLES 6	TUMORES CEREBRALES / BRAQUITERAPIA
JUEVES 7	CABEZA Y CUELLO / TUMORES GINECOLÓGICOS
VIERNES 8	TUMORES DIGESTIVOS / CÁNCER DE PULMÓN

ORGANIZAN

SEOR
SOCIEDAD ESPAÑOLA DE ONCOLOGÍA RADIOTERÁPICA

CAMPUS UNIVERSITARIO ONCOLOGÍA

ESTRO School

OBJETIVOS DOCENTES

1. Conocer recomendaciones de braquiterapia guiada por imagen de resonancia de GEC-ESTRO, GEB y GBFM, ICRU 89.

2. Reconocer beneficios de braquiterapia intersticial en tumores avanzados.

3. Facilitar la formación in situ con aplicadores intersticiales y planificación con casos clínicos.

PROFESORES

Silvia Rodríguez. Oncóloga Radioterápica. Clínica Benidorm.

José Pérez Calatayud. Físico médico. Hospital La Fe Valencia.

Inés Álvarez de Eulate. Radióloga. CHN.

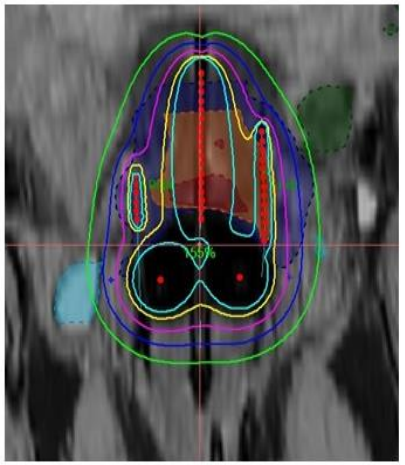
Santiago Pellejero. Físico médico. CHN.

Elena Villafranca. Oncóloga Radioterápica. CHN.

Acreditación docente: 1.41 créditos

Inscripción: contactar con Elekta: elekta.spain@elekta.com

Colaboración:



"I Workshop en Braquiterapia intersticial en el cáncer de cérvix"

Directores del Curso: Elena Villafranca. Santiago Pellejero

Destinado: Especialistas en Oncología radioterápica y Radiofísica, con Unidad de Braquiterapia.

Fecha: 15 y 16 de Junio de 2018.

Lugar: Complejo Hospitalario de Navarra. Edificio de Radioterapia. Pabellón J.

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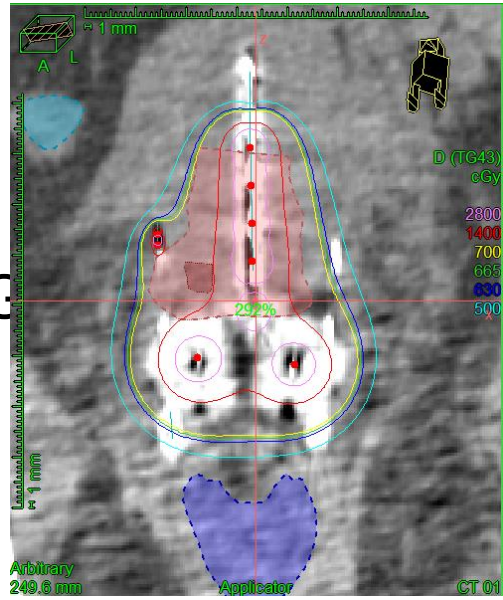
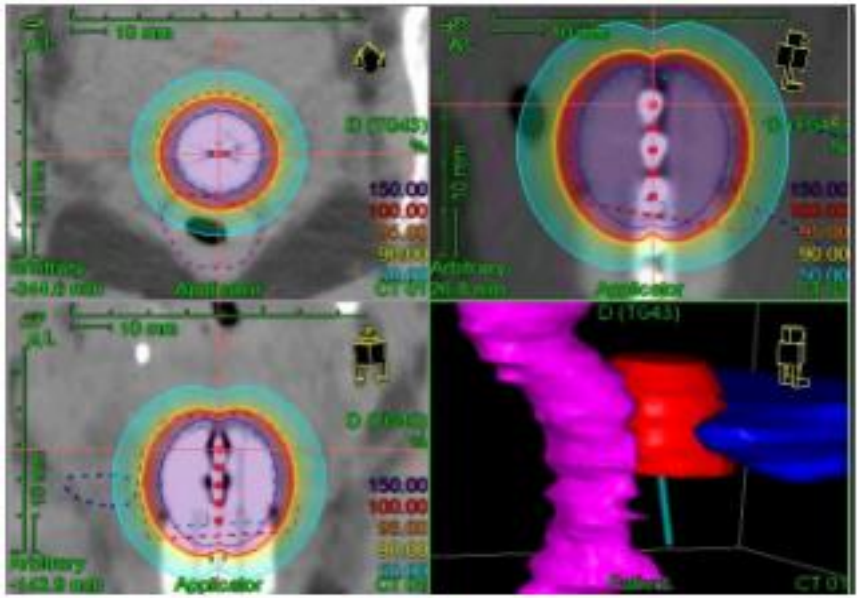
NEW ITEMS, (no so new……..¡¡¡¡¡¡)

EMBRACE II:

- New Dose specificactions: D90, D98 (HRCTV and G
- Keep in mind vaginal dose and toxicity
- New dose tolerance: planning aims and limits for prescribed dose for OAR
- TRAK



EMBRACE registration study: REGISTER MY PATIENTS AND TREATMET CHARACTERISTICS, AND TREATMENT OTCOME



XVIII REUNION DE CONSENSO EN BRAQUITERAPIA VAGINAL POSTOPERATORIA.

Salón de Actos.

Hospital Universitario Rey Juan Carlos

Dirección: Calle Gladiolo, s/n, 28933 Móstoles, Madrid

Comité Organizador

Dra. Pilar Samper Ots y Dr. Ramón Polo del Hospital Universitario Rey Juan Carlos. Móstoles.

Dra. Angels Rovirosa Casino y Dr. Antonio Herreros del Hospital Clinic de Barcelona.

Avalado por:

SEOR
SOCIEDAD ESPAÑOLA DE ONCOLOGÍA RADIOTERÁPICA

sefm Sociedad Española de Física Médica

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MUCHAS GRACIAS

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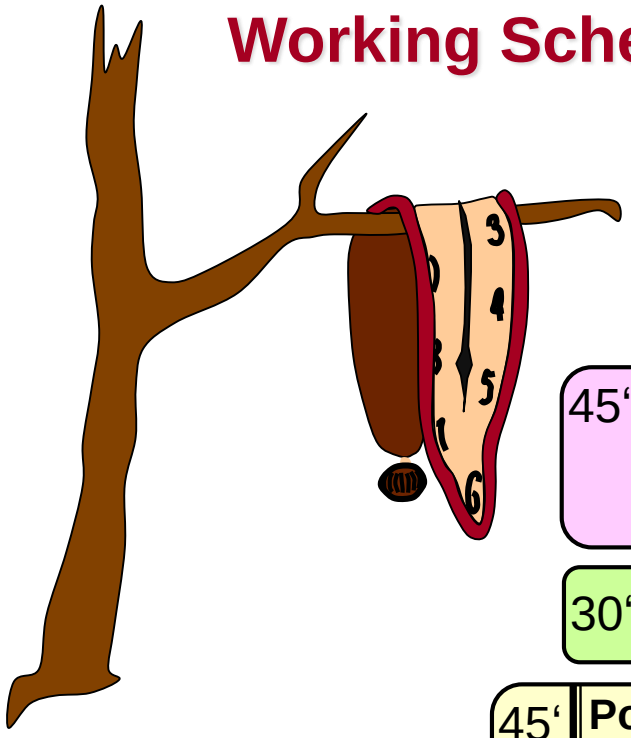
ESTRO Teaching Course on
Image-guided radiotherapy & Chemotherapy in Gynaecological Cancer
- with a special focus on adaptive BT-

Tips and Tricks

Working Schedule Brachytherapy of Cervix Cancer



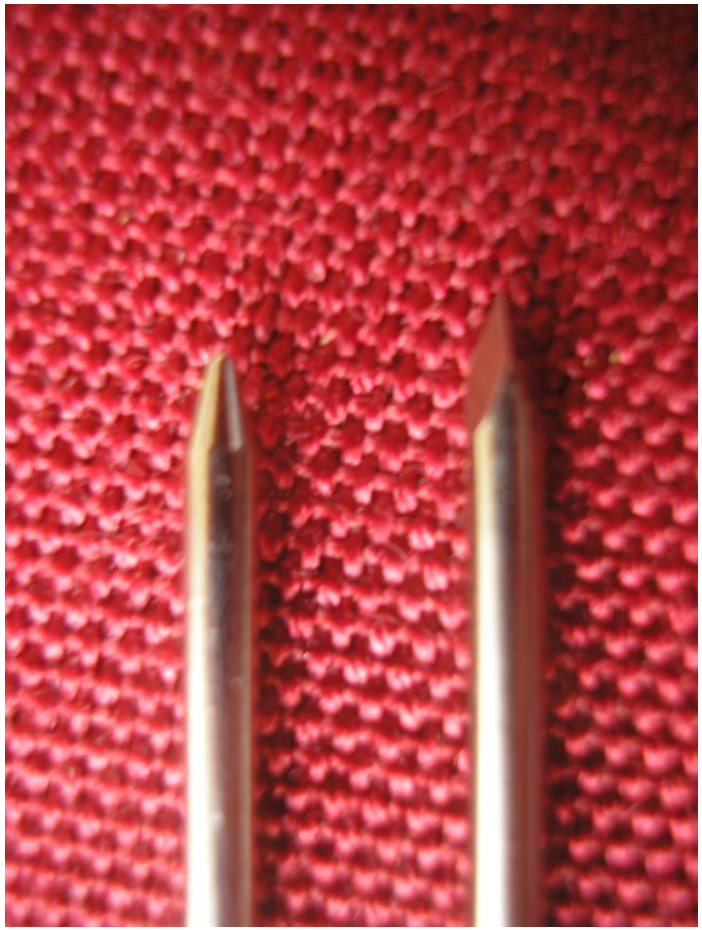
Multidisciplinary Team approach

15‘	**Preparation** Patient med.tech. Documents DVH pre-planning	 Surgical-nurse /Physician RTT Physician and Physicist
45‘	**Anaesthesia** Spinal/Epidural or General	 Anaesthetist / Anaesthesia-nurse
30‘	**Application IC±IS (TRUS)**	Physician / surg.-nurse/RTT
45‘	**Post Intervention Imaging** MR / CT supervision + discussion	 RTT (diagnostic) Physician and Physicist
30‘	**Contouring** Organs at Risk Target Volume	 RTT / Physician Physician
45‘	**Treatment Planning** Reconstruction / Constraints Discussion and Validation	 RTT / Physicist Physicist and Physician
15‘	**Radiation Treatment**	RTT

Total Time 3h 45min

PRE-REQUISITES

- Check list
- Dummy run
- Workflow and various processes
- Applicators
- Treatment planning principles
- Analgesics
- Removal of application
- Manage the bleeding after removal
- Do not use sharp needles
- Optimization tools
- Learning Curve



Preconditions - Management

- *Peri-operative Management (bowel preparation, measurements against thrombosis and infection, iv. hydration)*
- *Pain management - anaesthesia (spinal / epidural / general)*
- *Sectional imaging (CT / MRI)*
  -at diagnosis and before brachytherapy (alternative 1)
  -at diagnosis and at first brachytherapy (alternative 2)
  -at diagnosis and at every brachytherapy (alternative 3)
- *Equipment (appropriate set of applicators)*
- *Learning curve*

Teaching Courses!

Hands on

Workshops!

Cadeveric

workshops!