Welcome to
1st AROI - ESTRO GYN Teaching Course

Transition from

"Conventional 2D to 3D Radiotherapy"

with a special emphasis

on

"Brachytherapy in Cervical Cancers"

ESTRO School

MOU – Torino Italy

ESTRO – AROI : April 2016

AROI - ESTRO GYN TEACHING COURSES IN INDIA 2017- 2019

- **1st year (2017): Theme: "Transition from 2D to 3D BT in Cervical Cancers In 2017"** Principles of Advanced EBRT and Conventional BT planning including procedure details preferably by *cadaveric hands-on workshop*, commissioning and quality assurance, planning and plan evaluation, reporting and introduction to Concepts of Image Based BT and protocols in Cervical Cancers.

- **2nd year (2018): Theme: "Image Based BT in Cervical Cancers with emphasis on GEC-ESTRO ICRU 89 Reporting"** Principles of 3D Image Based BT in cervical cancers including various imaging modalities, target concepts, planning details, plan evaluation and reporting. Preliminary discussion on protocol development.

- **3rd year (2019): Theme: "Evaluation & Finalization of Protocol for BT in Cervical Cancers"** Principles of Advanced EBRT including IMRT /IGRT, 3D Image Based BT and systemic therapy in current era, development of a template for future Indian courses and finalization on research protocol.

- **Participants:** A team of physician and physicist from each institution who are actively involved in treating cervical cancers including BT. **Limited number of teams: 40 - 45 teams approximately.**

TEAM OF RADIATON ONCOLOGIST & MEDICAL PHYSICIST POTENTIALLY INTERESTED IN IMPLEMENTING AND ENHANCING EXISITING GYN BT PRACTICE IN THE INSTITUTION

Transition from Conventional 2D to 3D Radiotherapy with a special emphasis on Brachytherapy in Cervical Cancers

Ist ESTRO-AROI GYN Teaching Course

8-11 March 2017
Bengaluru, India

ROADMAP

RADIOTHERAPY TREATMENT PLANNING AND DELIVERY

RADIATION ONCOLOGIST, MEDICAL PHYSICIST, RADIATION THERAPIST, OTHER SPECIALIST

FACULTY

ESTRO COURSE DIRECTORS
- Richard Pötter, *Radiation Oncologist, Medical University Hospital, Vienna (AT)*
- Kari Tanderup, *Medical Physicist, University Hospital, Aarhus (DK)*

AROI COURSE DIRECTORS
- Umesh Mahantshetty, *Radiation Oncologist, Tata Memorial Hospital, Mumbai (IN)*
- Jamema Swamidas, *Medical Physicist, ACTREC, Tata Memorial Centre, Mumbai (IN)*

TEACHERS
- Christine Haie Meder, *Radiation Oncologist, Institut Gustave Roussy, Villejuif (FR)*
- D. N. Sharma, *Radiation Oncologist, AIIMS, Delhi (IN)*

LOCAL ORGANISERS
- M G Janaki, *Radiation Oncologist, MS Ramiah Medical College, Bengaluru*
- Revathi, *Medical Physicist, MS Ramiah Medical College, Bengaluru*

ESTRO COURSES : So far!
Image-guided cervix radiotherapy – with a special focus on adaptive brachytherapy

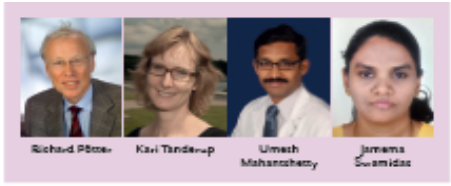
In the ESTRO school for more than 10 years:

- 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 Bengaluru (6th Itern) 03 2017: 80 parti. AROI ESTRO**

In total ~ 2000 participants


Discussion of Course Directors


Discussion of Course Directors

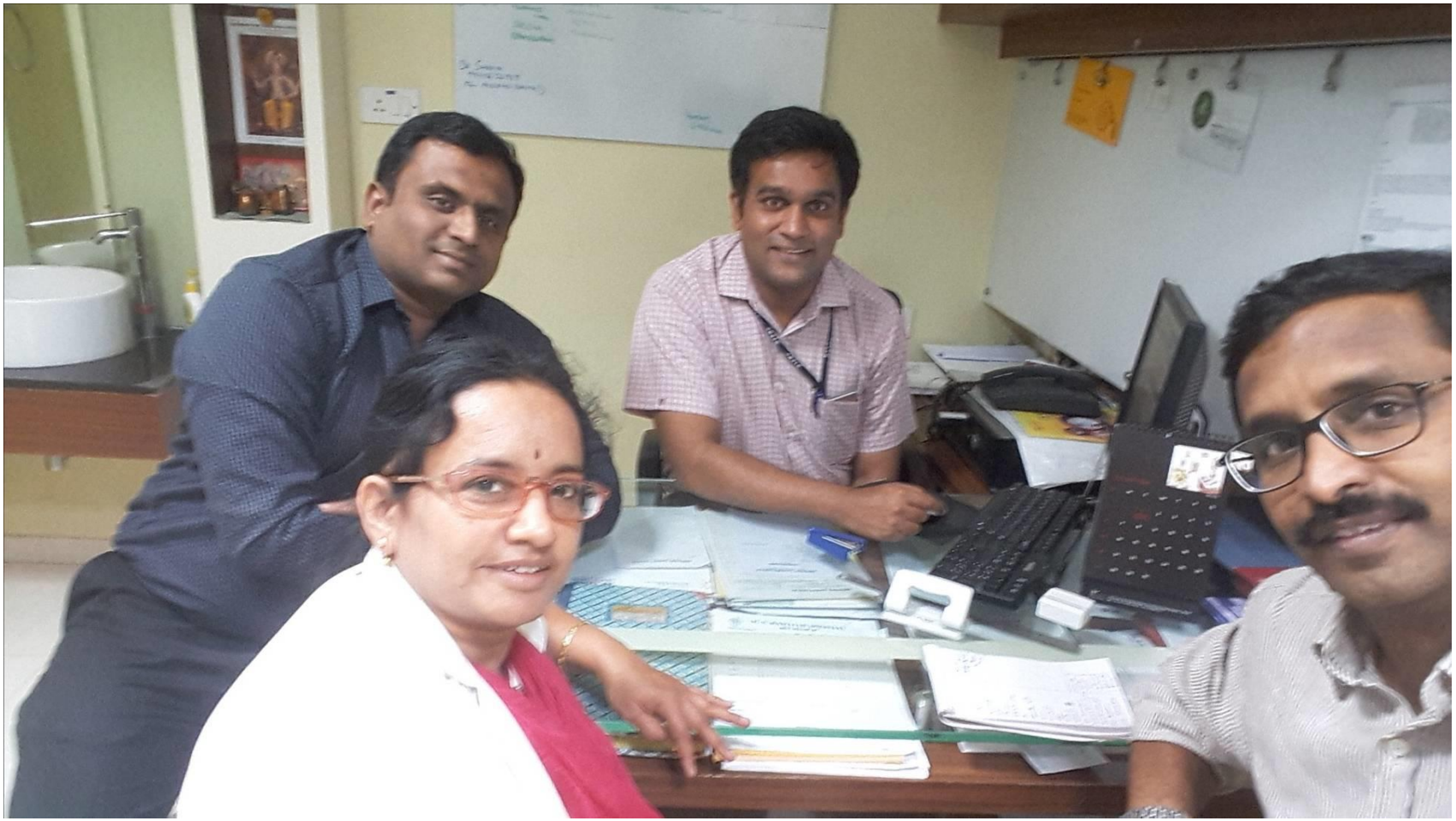


WORLD CONGRESS OF BRACHYTHERAPY

San Francisco
June 2016

MEETING AT STARBUCK'S CORNER

MS Ramaiah Medical College Nov. 2016



Visit to the site and discussion with local organizers

Poznan Dec. 2016

Discussion on the program & logistics!

Tata Memorial Hospital Mumbai
Feb. 2017

Preparation for commissioning of the workshop at TMH!

7th March 2017 at the Venue

ESTRO Course Directors:

- Richard Pötter, Radiation Oncologist, Medical University Hospital, Vienna (AUT)
- Kari Tanderup, Physicist, University Hospital, Åarhus (DEN)

AROI Course Directors:

- Umesh Mahantshetty, Radiation Oncologist, Tata Memorial Centre, Mumbai (IND)
- Jamema SV, Medical Physicist, ACTREC, Tata Memorial Centre, Mumbai (IND)

ESTRO & AROI Teaching Faculty:

- Christine Haie Meder, IGR, Villejuif, (FRA)
- D N Sharma, Radiation Onclogist, AIIMS, Delhi (IND)

LOCAL ORGANISER

- **M G Janaki, Radiation Oncologist, MS Ramaiah Medical College, Bengaluru, (IND)**
- **Revathi, Medical Physicist, MS Ramaiah Medical College, Bengaluru, (IND)**

PROJECT MANAGER

- **Melissa Vanderijst, ESTRO**

Program Highlights

Transition from 2D to 3 D Radiotherapy for Cervical Cancer

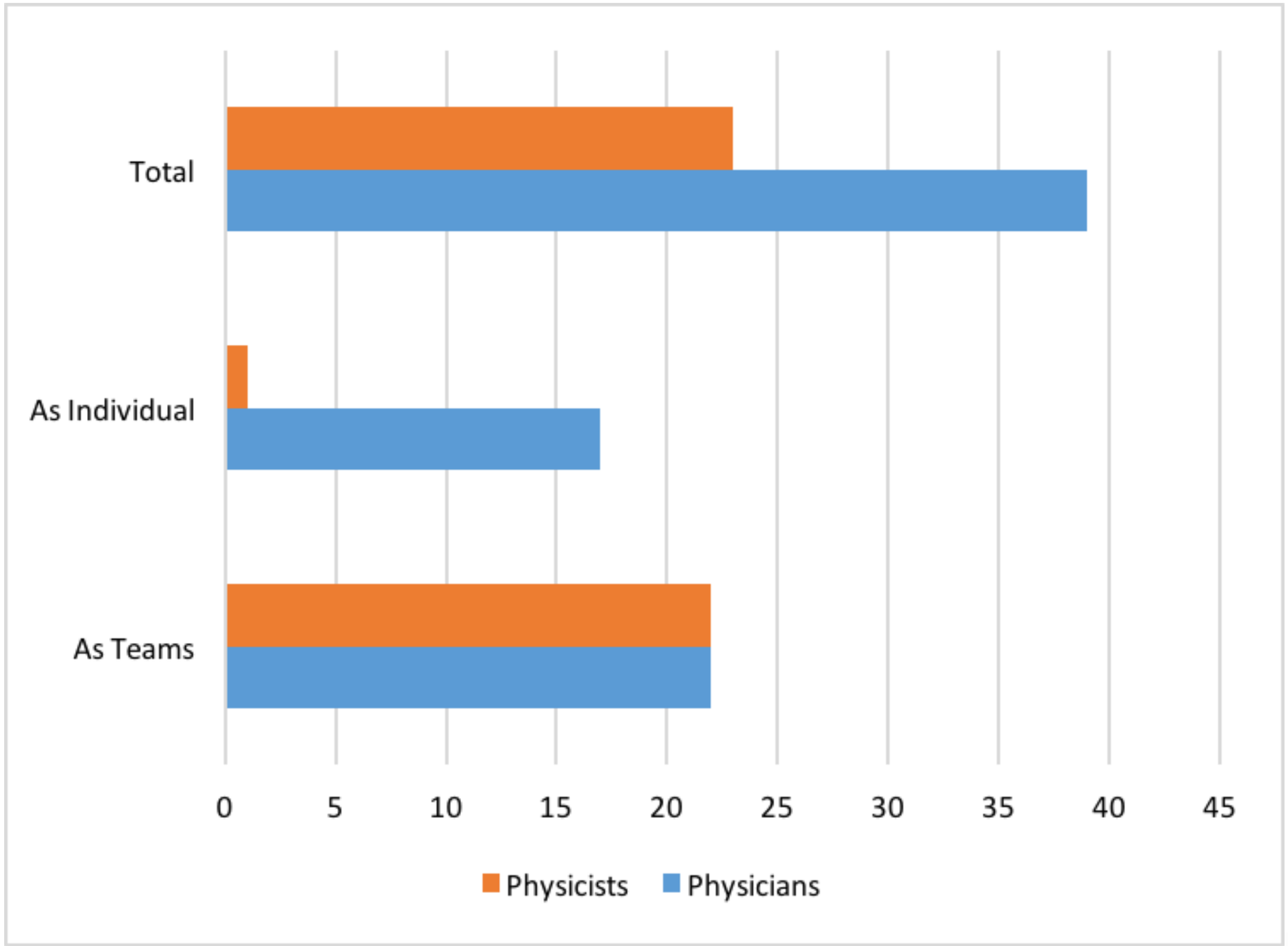
- **Day 1:**
  - External Beam RT : 2D to State of the art RT
  - EBRT Contouring and Planning Workshop
- **Day 2:**
  - Basics of cervical brachytherapy
  - Hands on Workshop of BT Application on Cadevers
  - BT Commissioning Workshop
- **Day 3:**
  - Transition form 2D to 3D BT
  - Principles of BT planning
  - BT Contouring and Applicator Reconstruction workshop
- **Day 4:**
  - Treatment planning workshop
  - Practical implementation
  - Setting goals

- *On behlaf of AROI and ESTRO,*
  - *The Advanced learning Center, MSRMC Staff*
  - *The Volunteers who donated their body for Research*
  - *The Enthusiastic Teaching Staff*
  - *The Enthusiastic participants*
  - *The Sponsors*

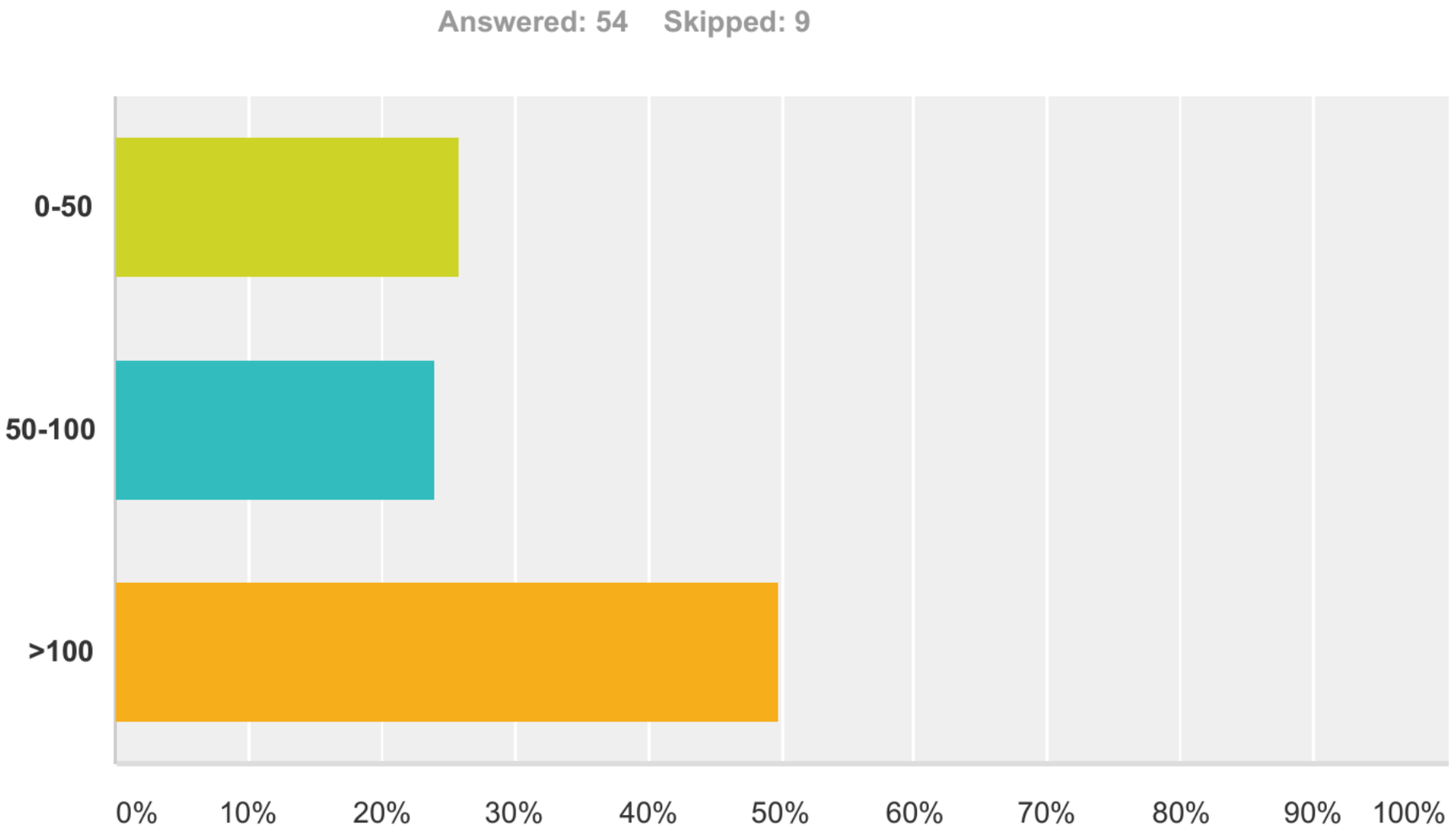
Pre course questionnaire analysis...

Dr Manur Gururajachar Janaki
Professor
Department of Radiotherapy
Ramaiah Medical College
Bengaluru

Participants of the course.....
Total....63



Burden of cervical cancer……



Type of set up...

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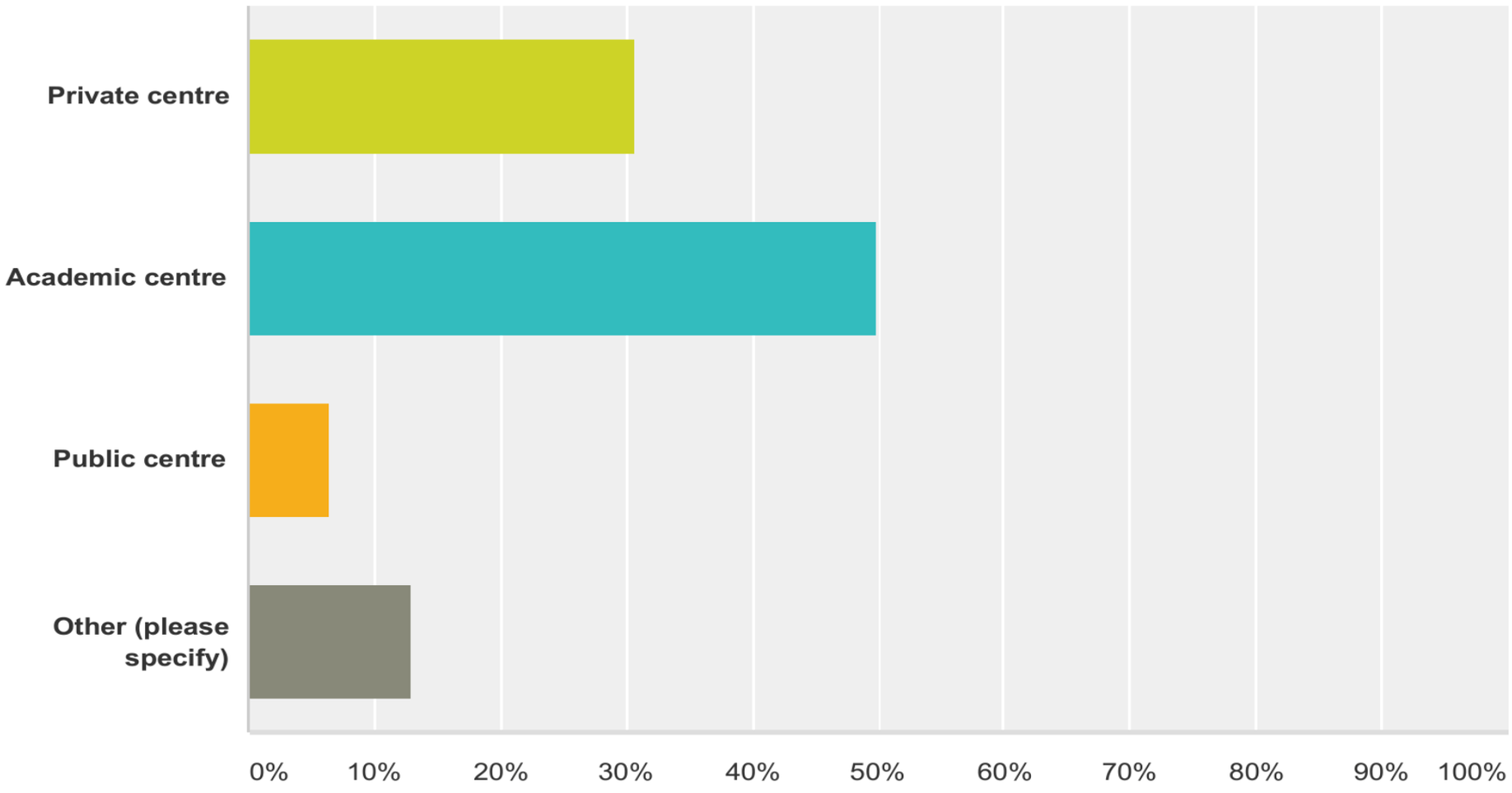
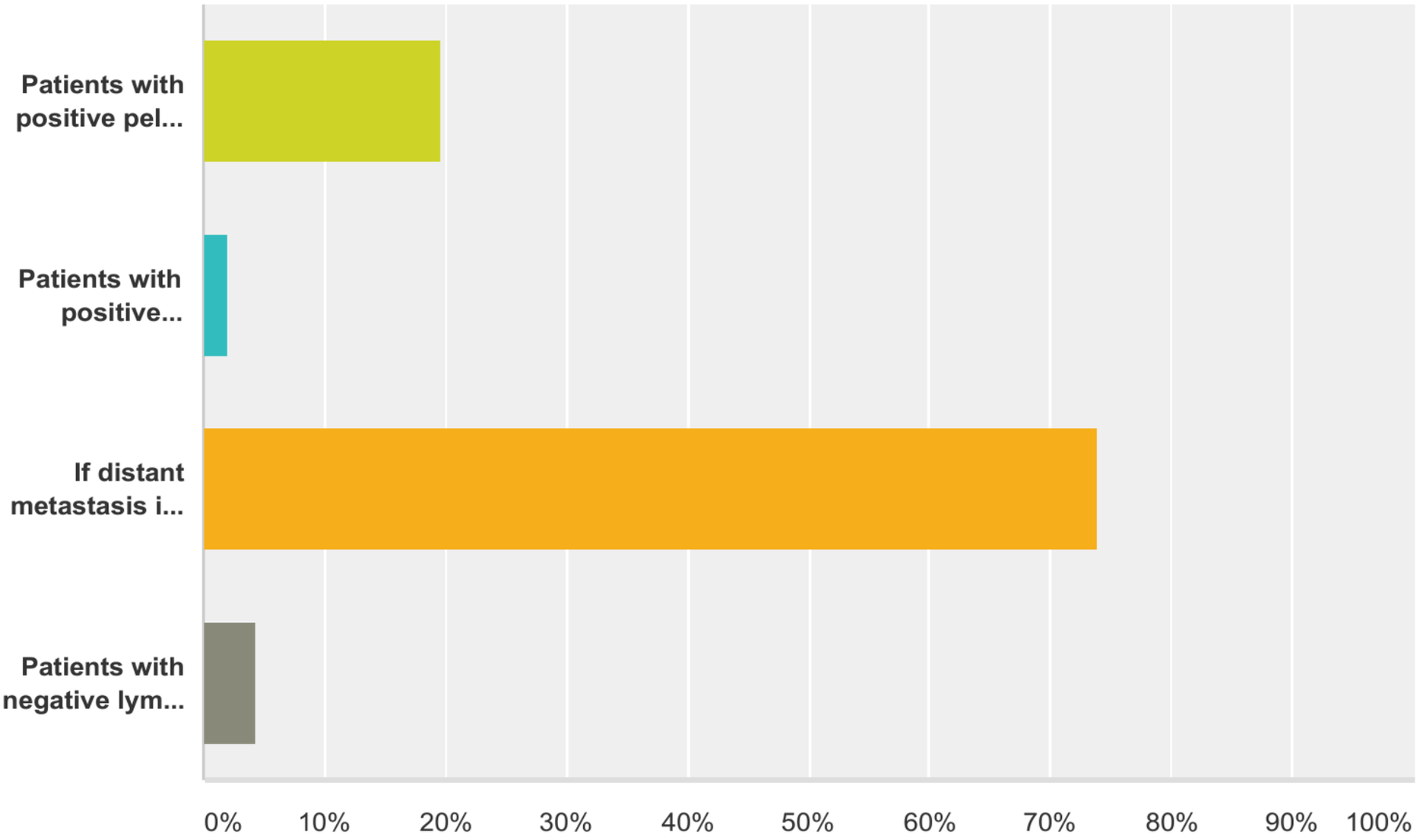
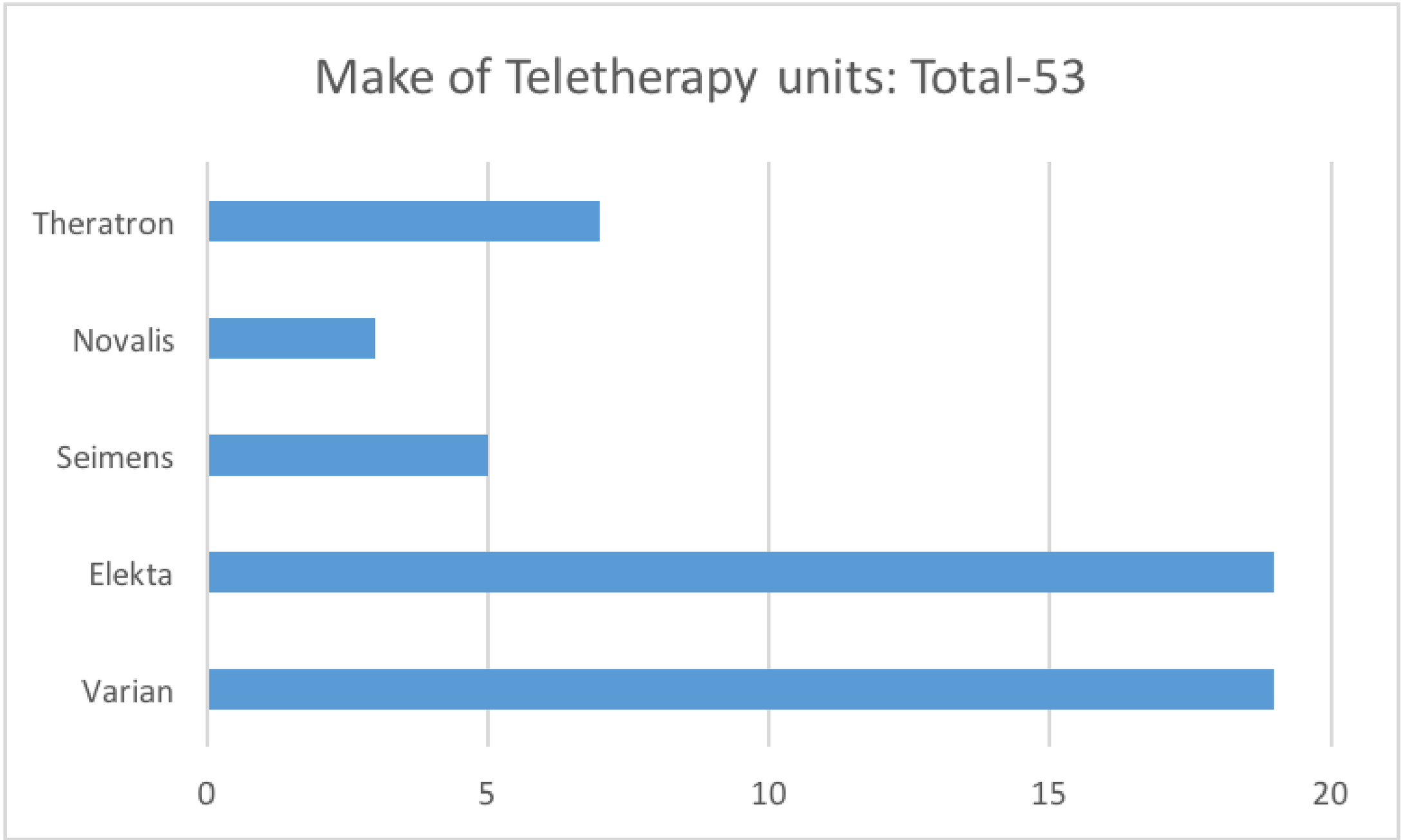
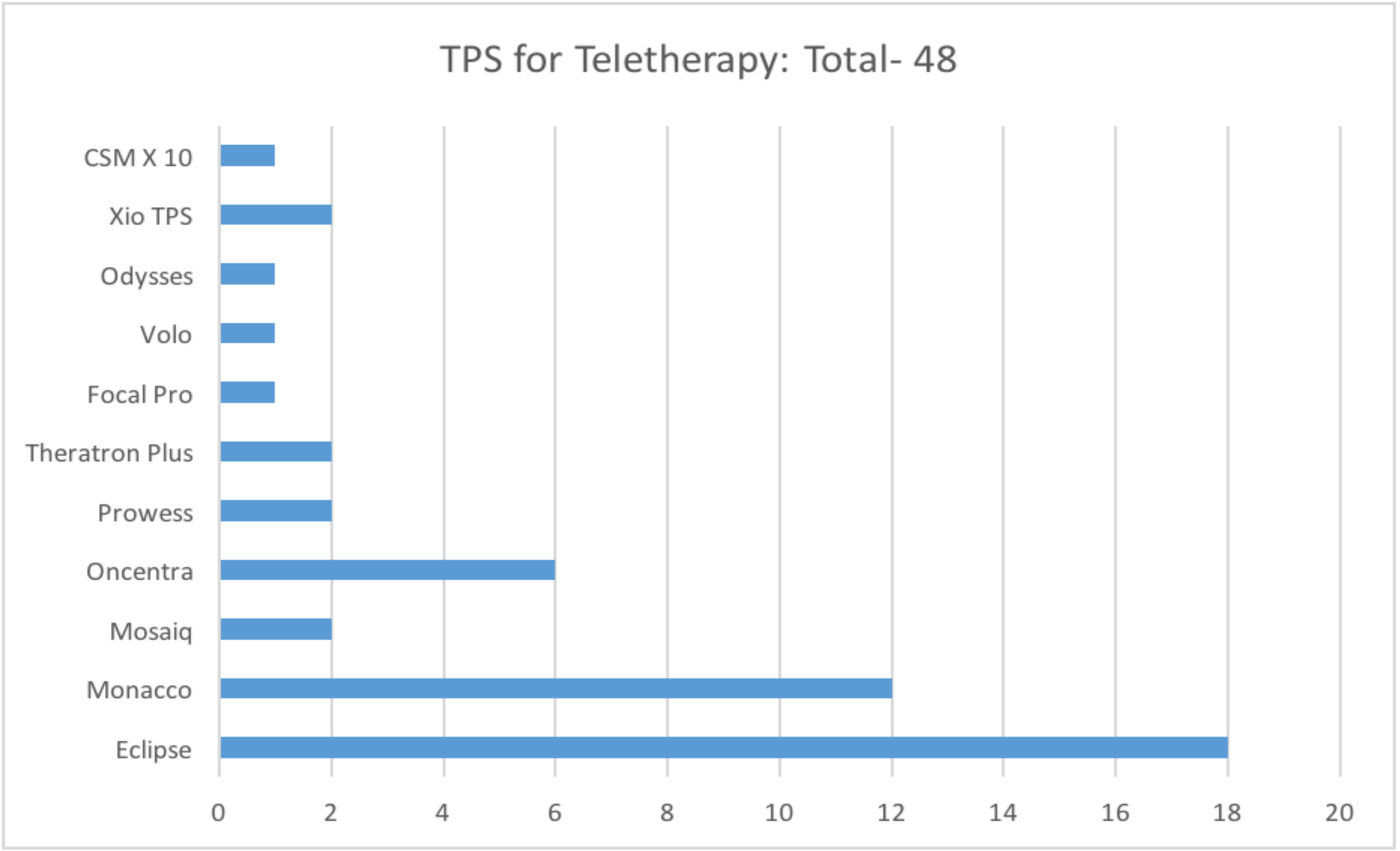


When is CTRT used?

Answered: 46 Skipped: 17

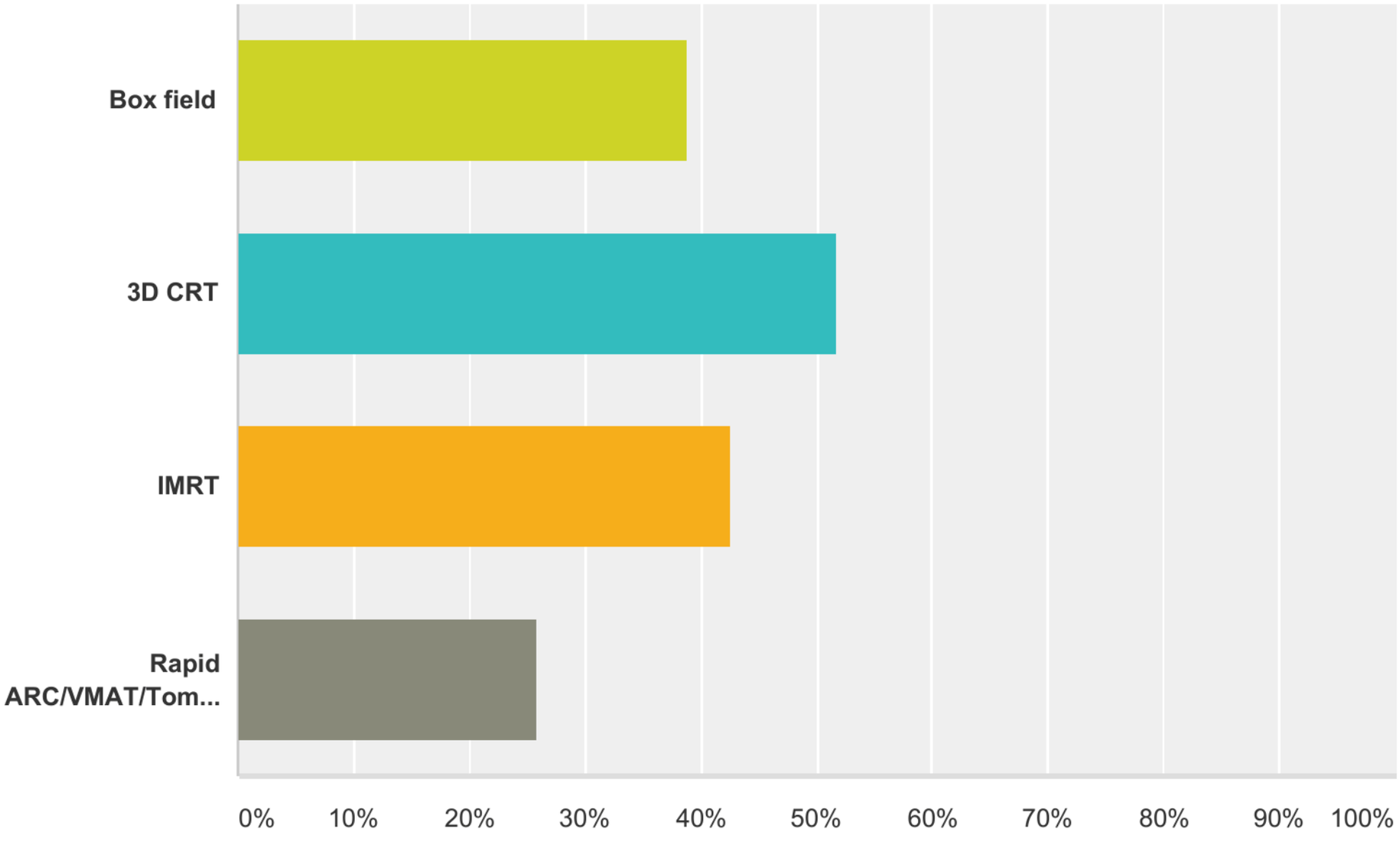



Make of Teletherapy units: Total-53
Theratron
Novalis
Seimens
Elekta
Varian
0
5
10
15
20


TPS for Teletherapy: Total- 48
CSM X 10
Xio TPS
Odysses
Volo
Focal Pro
Theratron Plus
Prowess
Oncentra
Mosaiq
Monacco
Eclipse
0
2
4
6
8
10
12
14
16
18
20

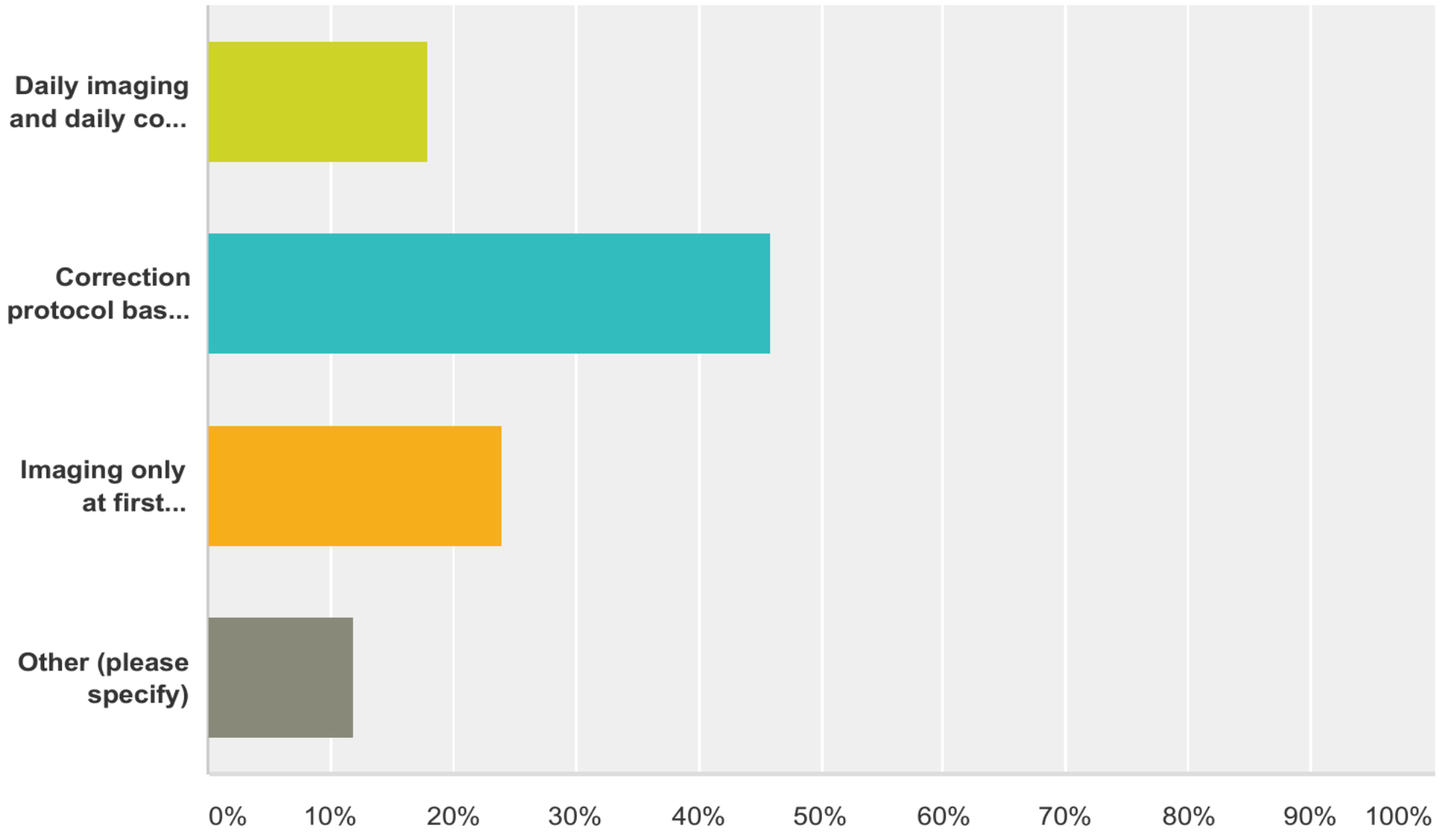
Technique of EBRT

Answered: 54 Skipped: 9



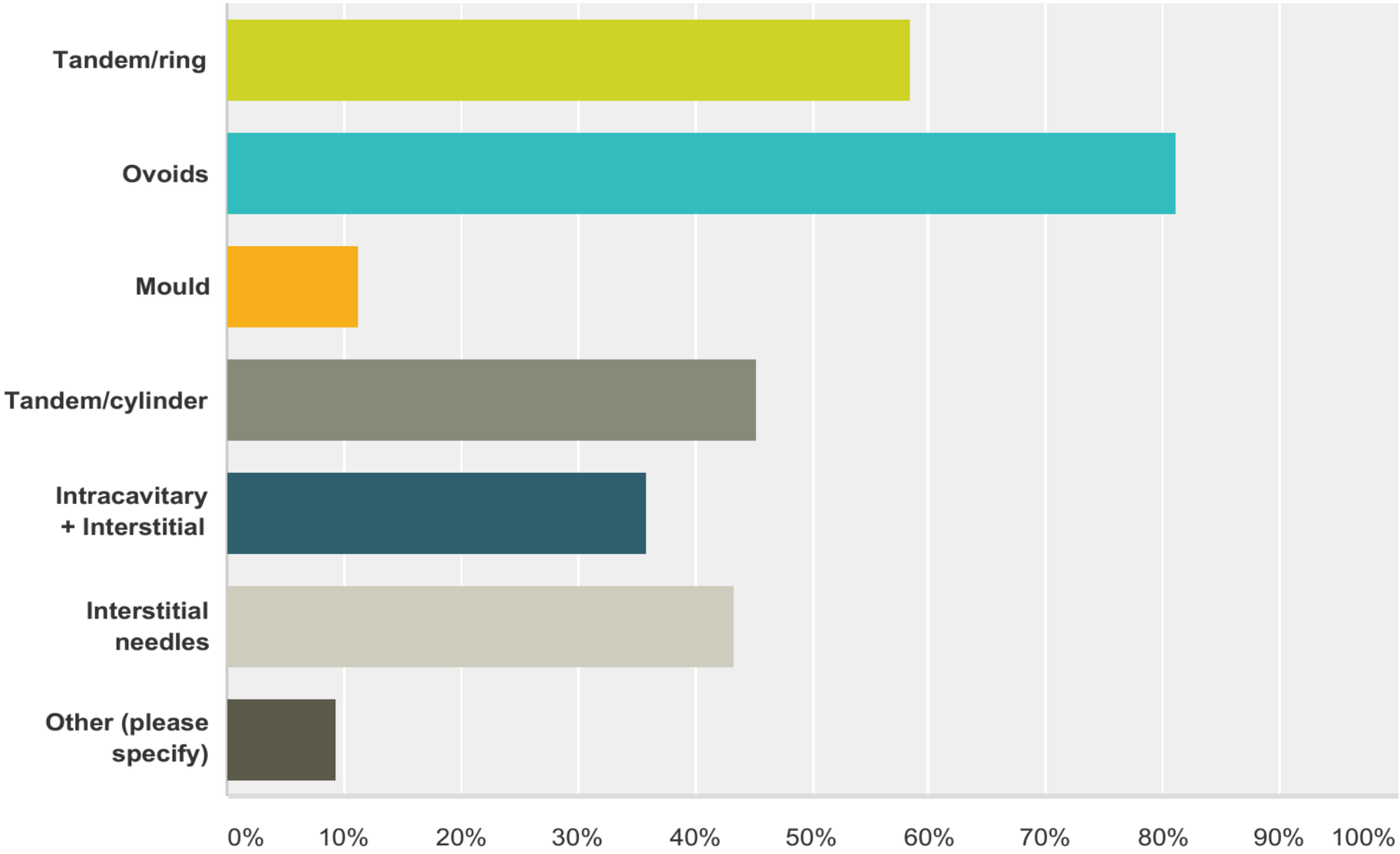
Verification during EBRT..

Answered: 50 Skipped: 13



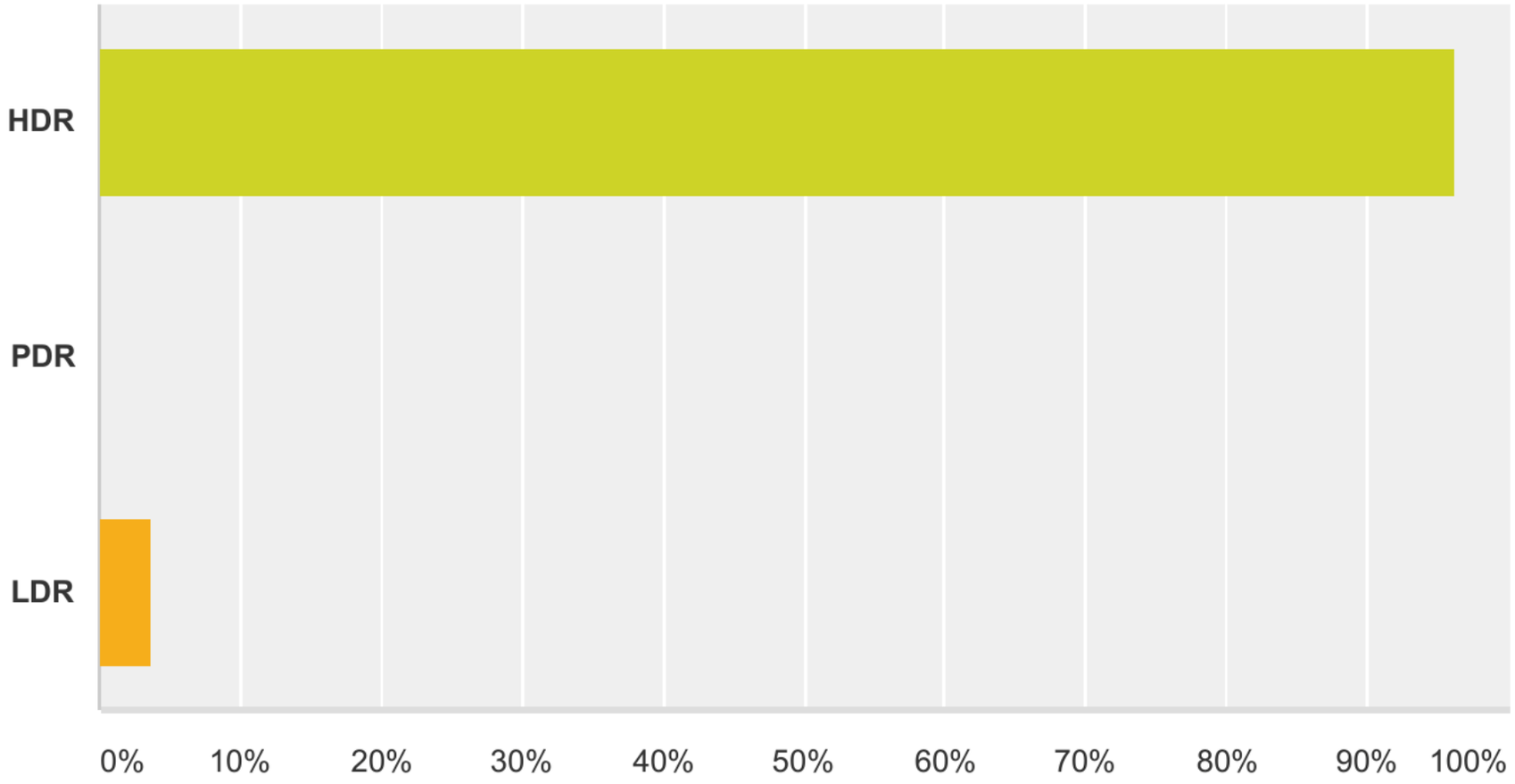
Brachy applicator used....

Answered: 53 Skipped: 10



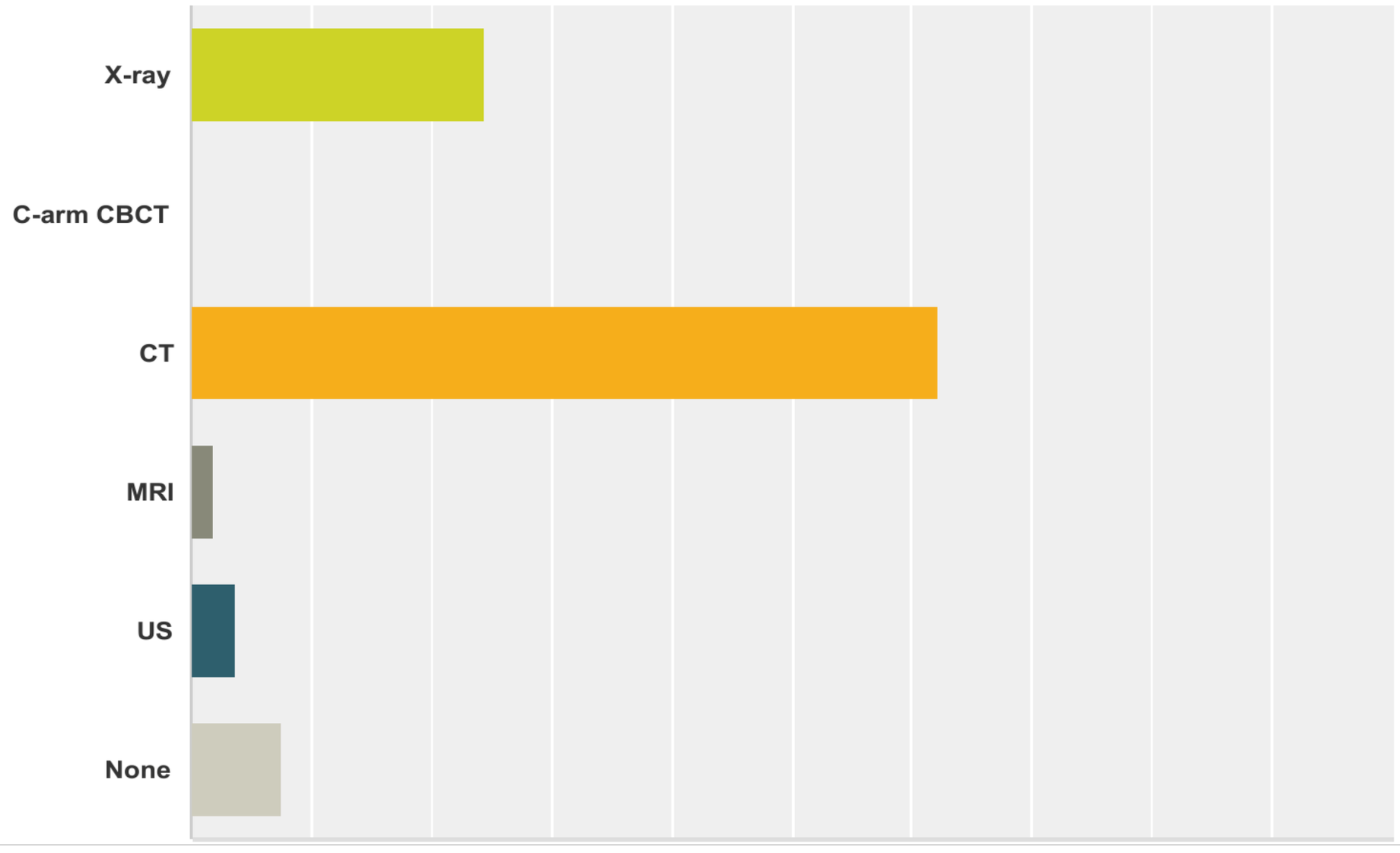
Dose rate used.....

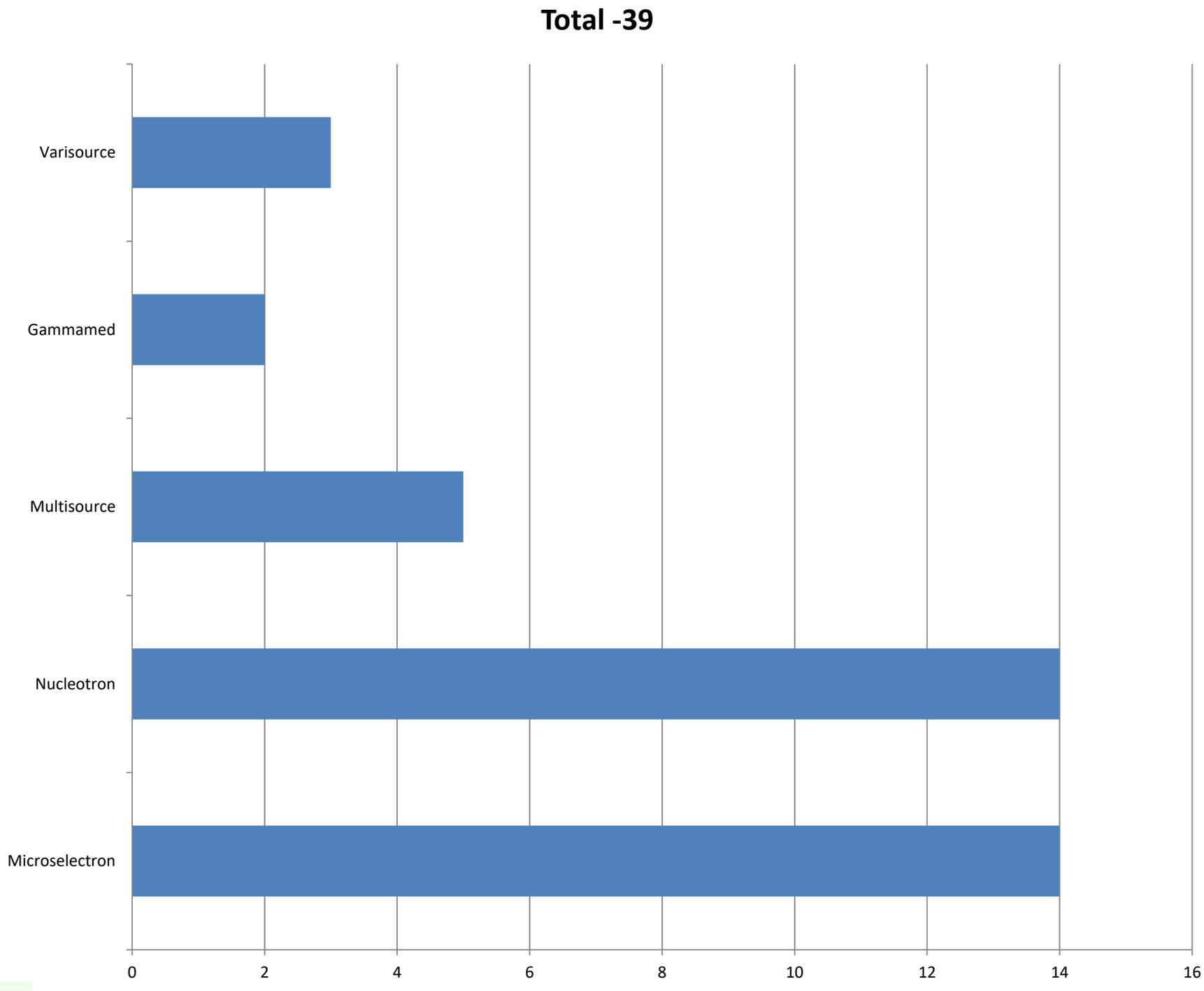
Answered: 53 Skipped: 10



Imaging for brachytherapy....

Answered: 53 Skipped: 10





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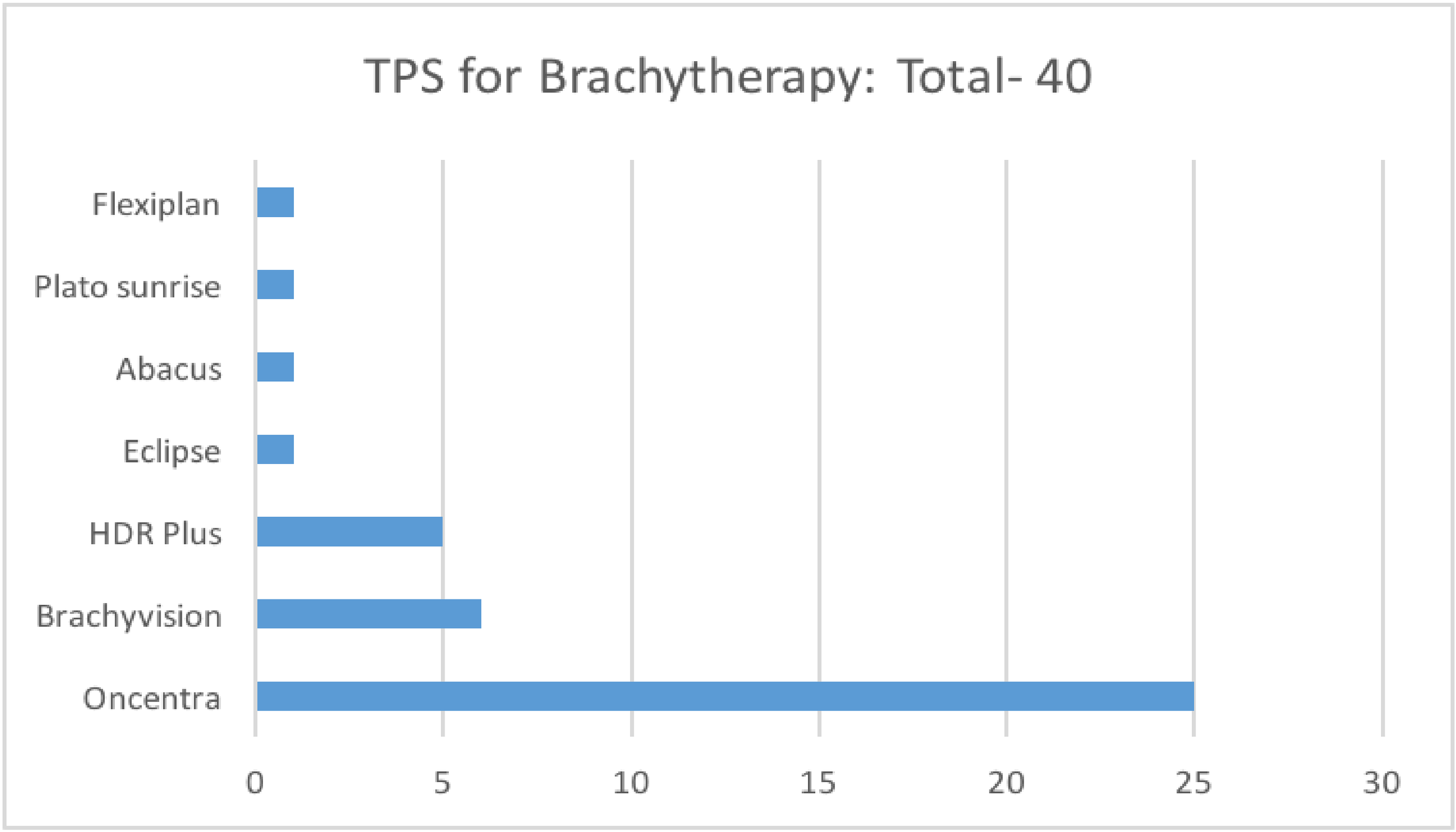
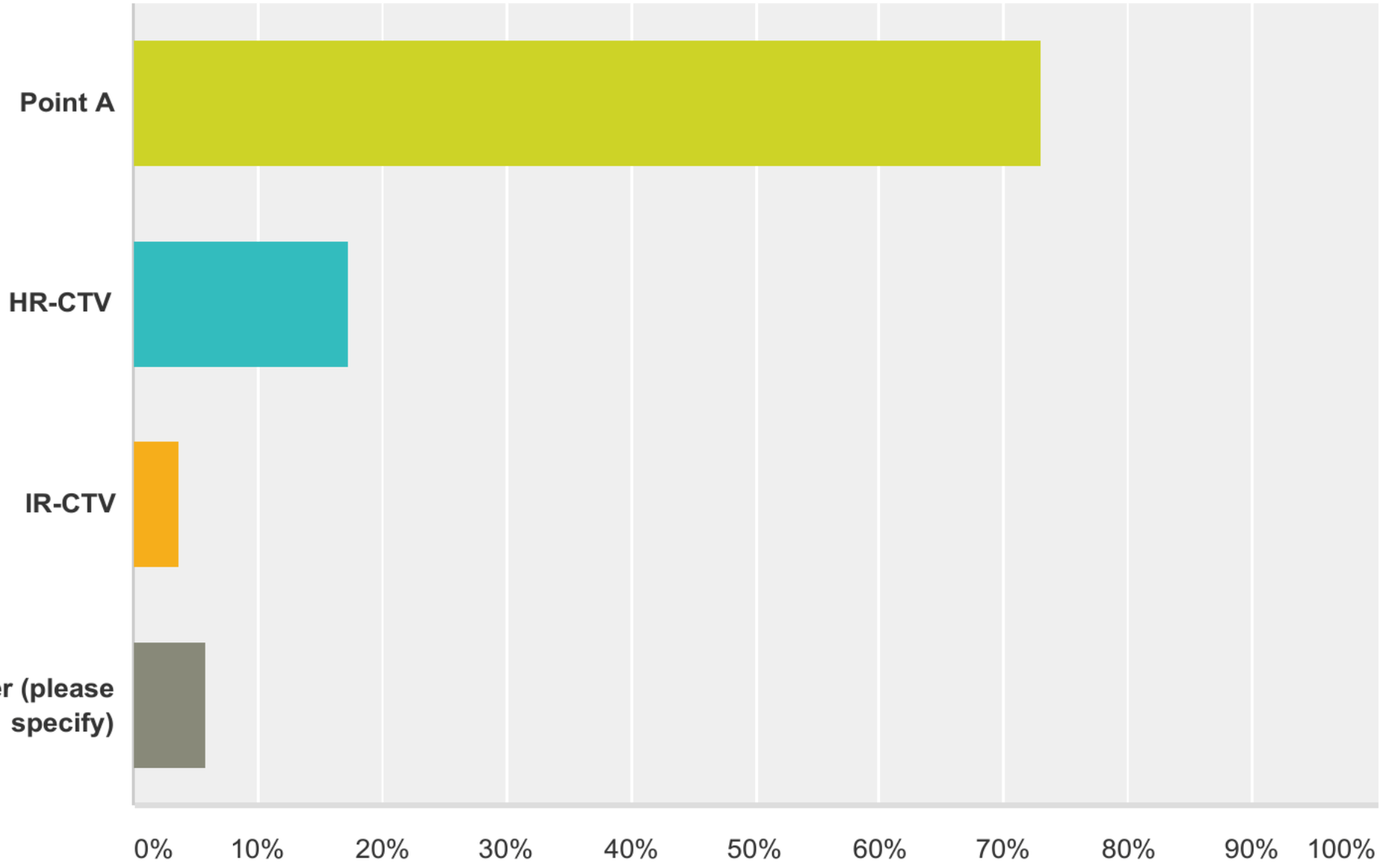

TPS for Brachytherapy: Total- 40
Flexiplan
Plato sunrise
Abacus
Eclipse
HDR Plus
Brachyvision
Oncentra
0
5
10
15
20
25
30

Prescription to...

Answered: 52 Skipped: 11



Most commonly used schedules.....

1. Dose....7 Gy (4 to 9)
2. Fractions...3 Fr (1to 5 Fr)
3. Gap between fractions..a week (6 hrs to a week)
4. Total dose....21 Gy (16 - 30)

Likely to start 3D imaging .....

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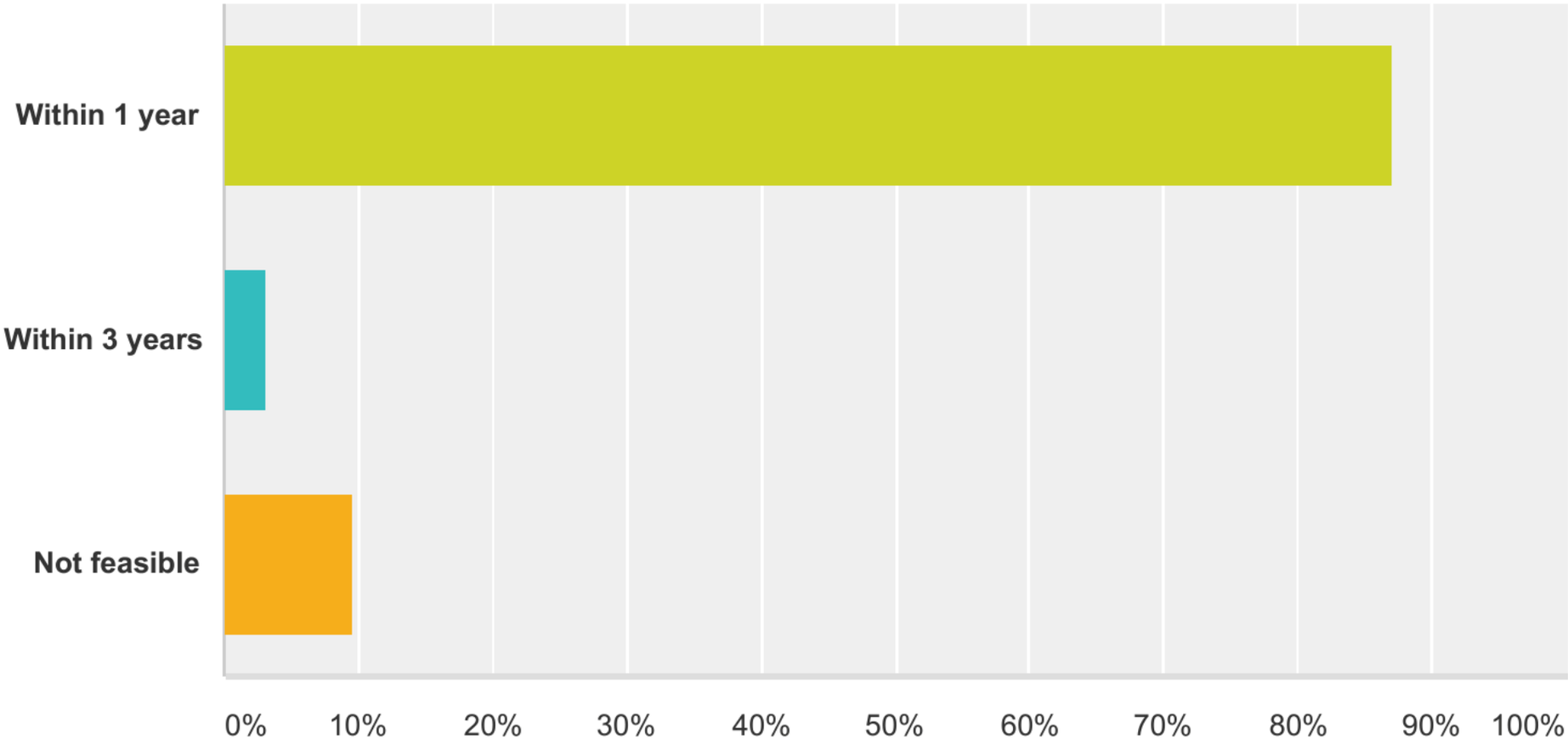


Thank You.
Have a great academic feast and interaction!!

ESTRO School

Anatomical considerations
Role of clinical gynaecological examination
Staging

C. Haie-Meder
Brachytherapy Unit

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

GUSTAVE ROUSSY
COMPREHENSIVE CANCER CENTER

Cervix cancer : generalities

- 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 and -18 = the most prevalent of the oncogenic types

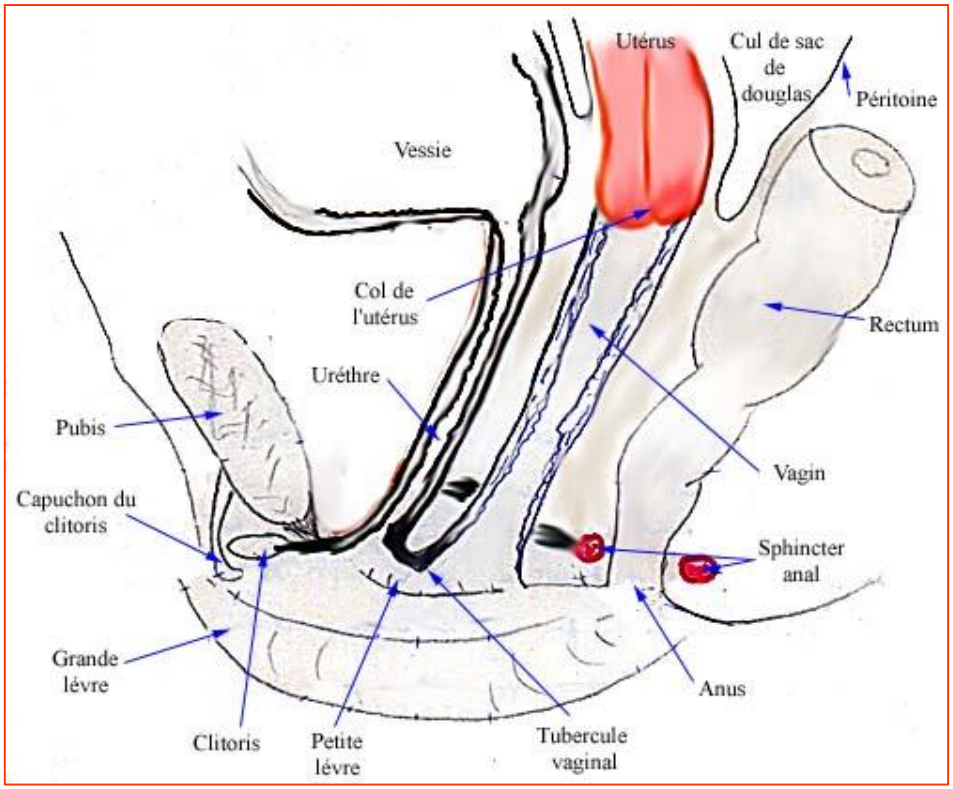
Cervix cancer : generalities

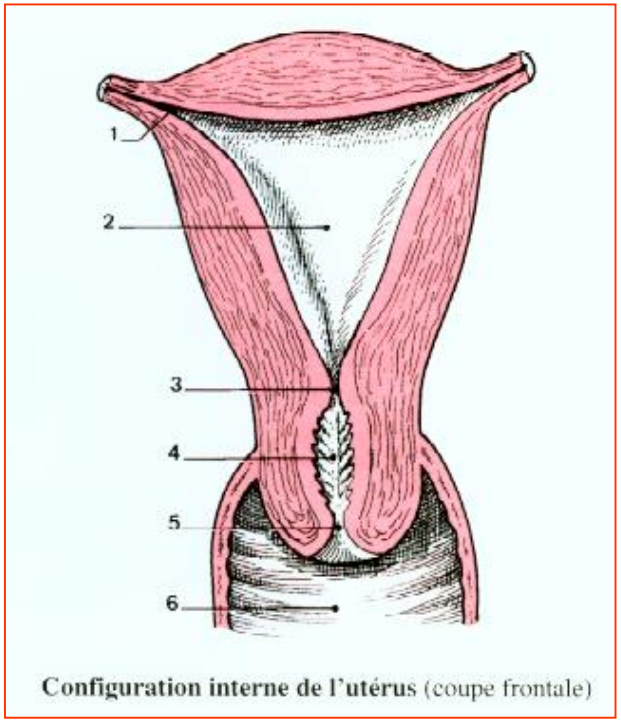
- Curable disease

Local Control	Survival
IA: 95–100%	IA: 95–100%
IB1: 90–95%	IB1: 85–90%
IB2: 60–80%	IB2: 60–70%
IIA: 80–85%	IIA: 75%
IIB: 60–80%	IIB: 60–65%
IIIA: 60%	IIIA: 25–50%
IIIB: 50–60%	IIIB: 25–50%
IVA: 30%	IVA: 15–30%
	IVB: <10%

Anatomical considerations

Uterus





Configuration interne de l'utérus (coupe frontale)

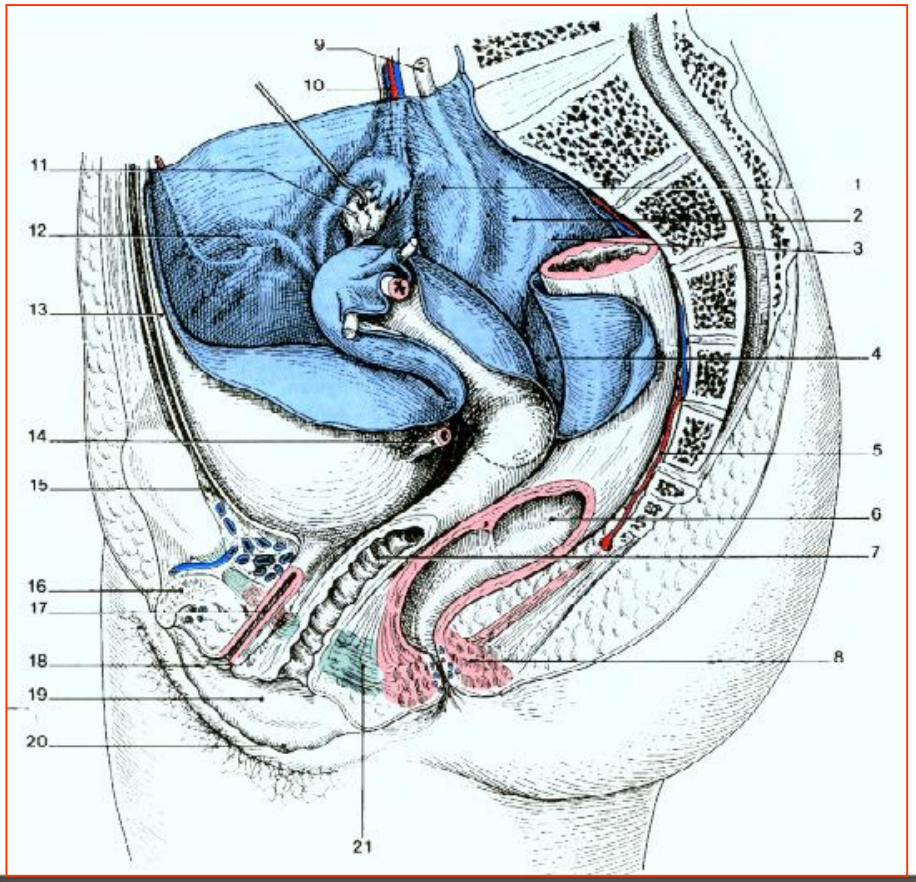
Hollow muscle

weight : 50 g (nulliparous)
70 g (multiparous)

Anatomical considerations

Uterus

Supravaginal part
Bladder and rectum faces covered with peritoneum

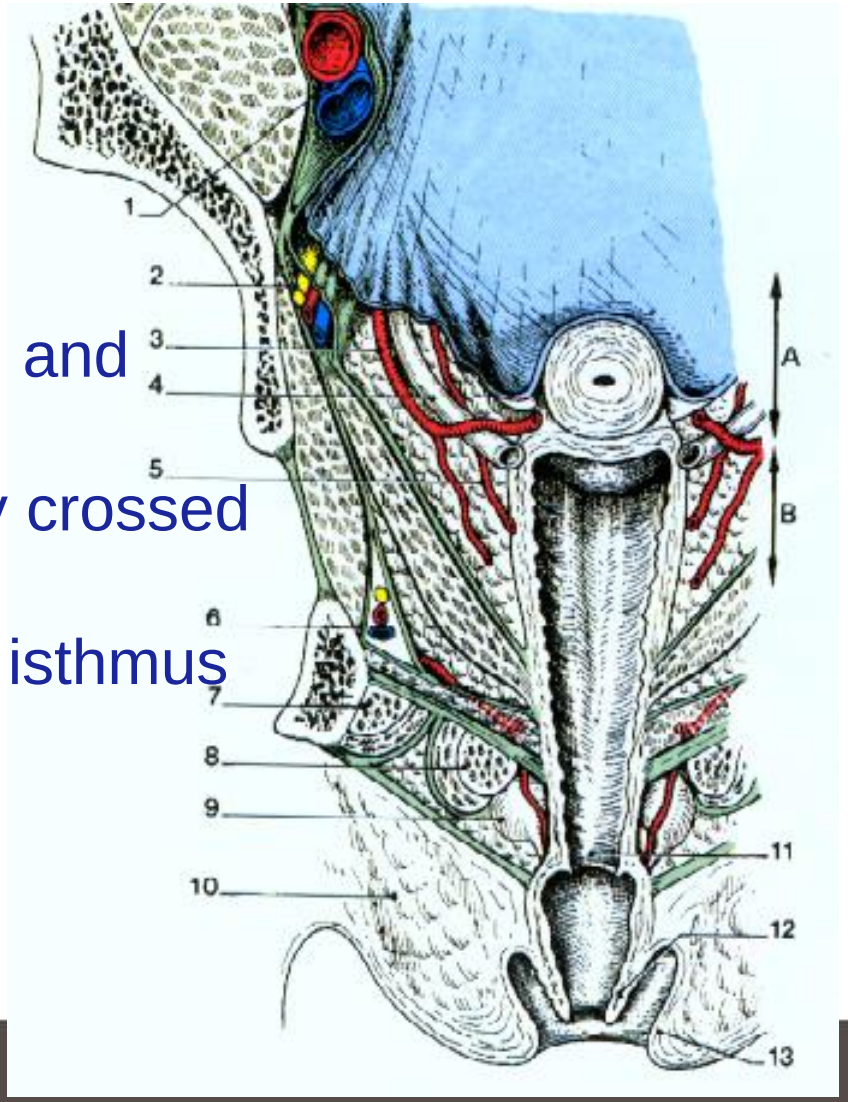


Vaginal part
Separated from the vagina
by vaginal fornices

Anatomical considerations

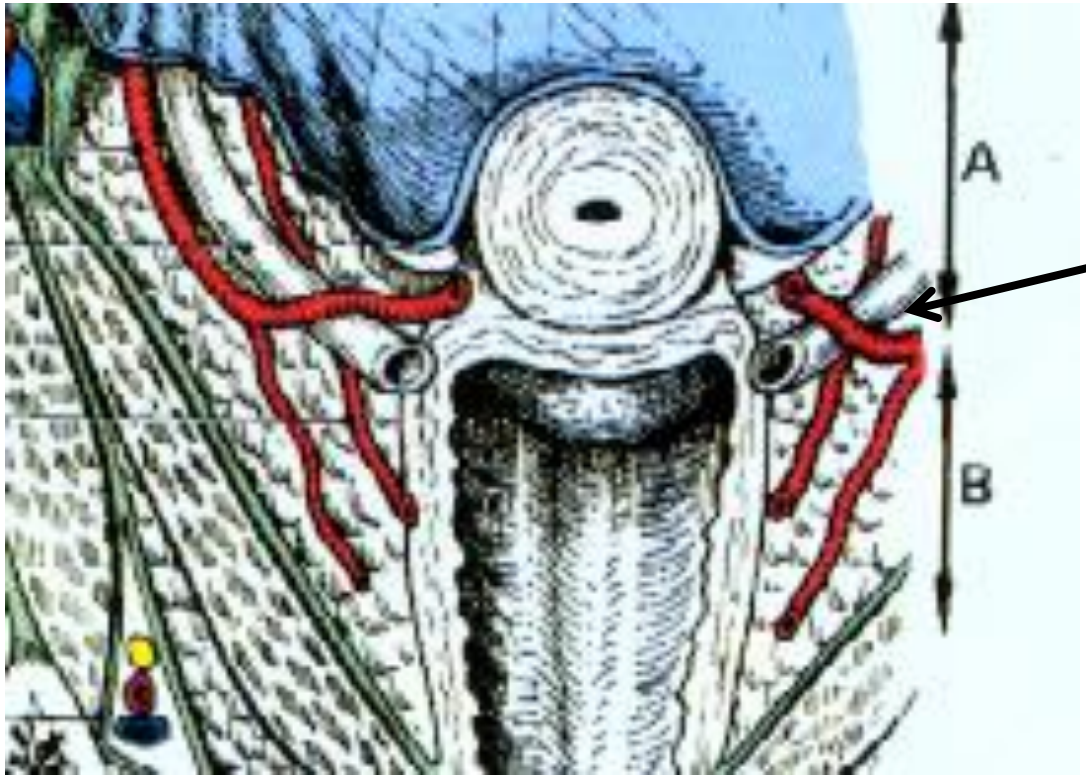
Uterus

- **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



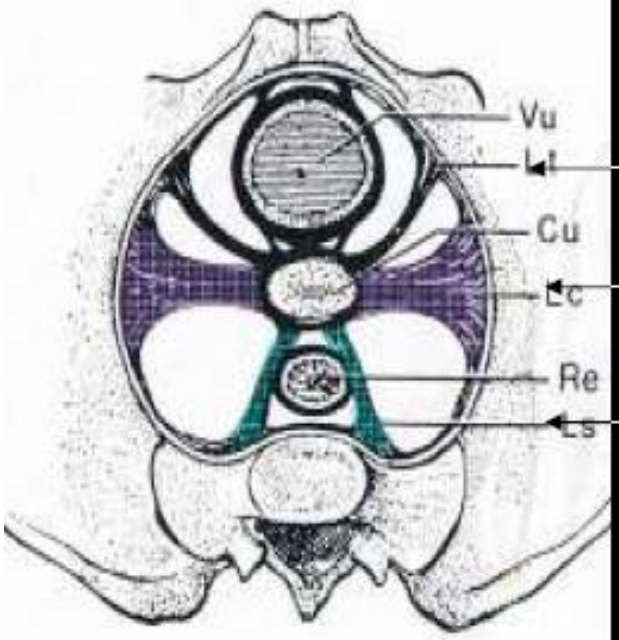
Anatomical considerations

Uterus



Anatomical considerations

Uterus



Transverse cervical ligament

Broad ligament

Uterosacral ligament

Anatomical considerations

Uterus

Parametrial Limits:

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

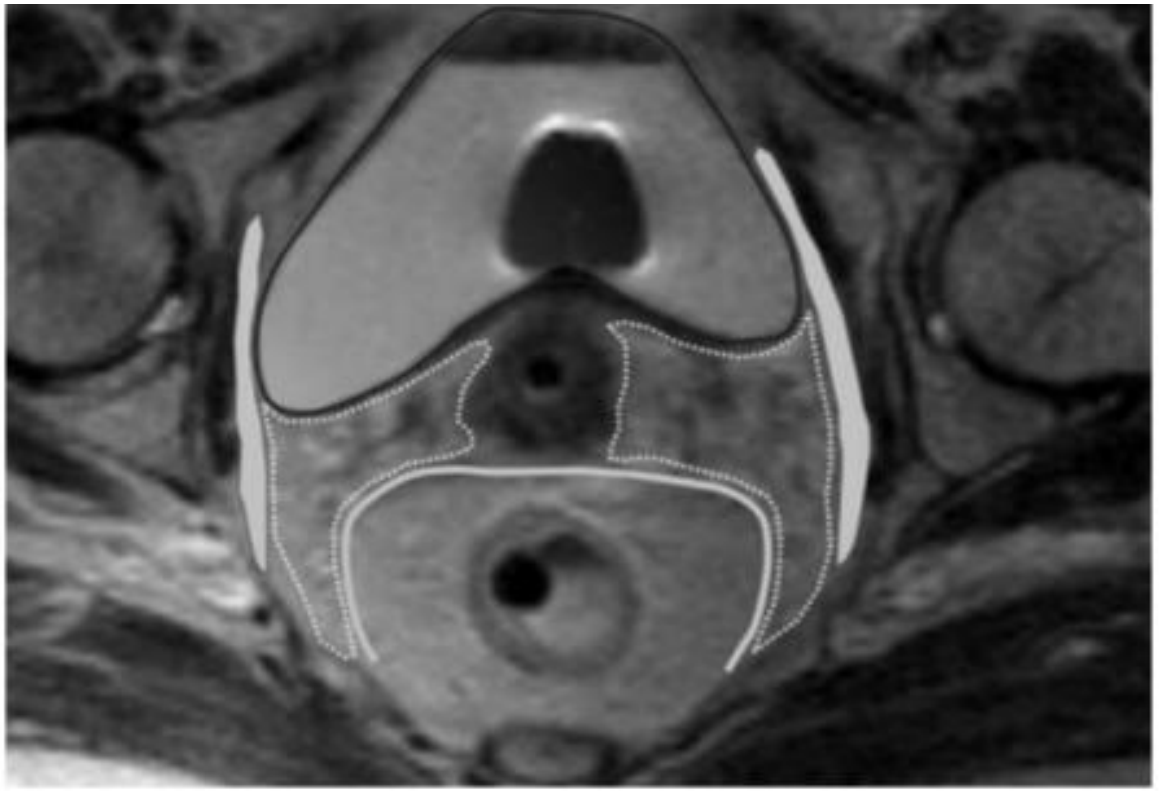


Fig. 2. Definition of parametria according to visible and reproducible radiologic criteria at its borders: ventral = bladder, dorsal = perirectal fascia, medial = tumor/cervical rim, lateral = pelvic wall (PW). At the PW, the space that contains vessels and lymph nodes is particularly indicated. For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

Dimopoulous et al IJROBP 64(5):1380-1388, 2006

Anatomical considerations

Classification of radical hysterectomy

Denis Querleu, C Paul Morrow

Lancet Oncol 2008; 9: 297–303

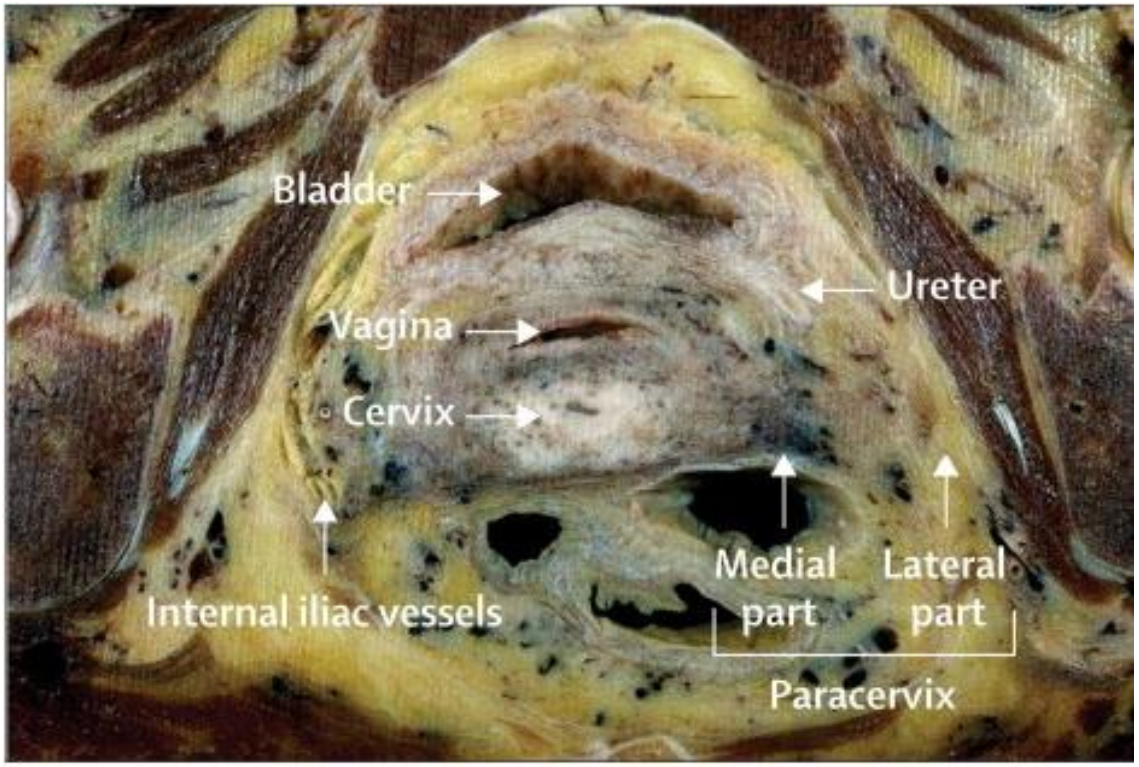


Figure 1

Transverse section of pelvis

Anatomical considerations

Classification of radical hysterectomy

Denis Querleu, C Paul Morrow

Lancet Oncol 2008; 9: 297–303

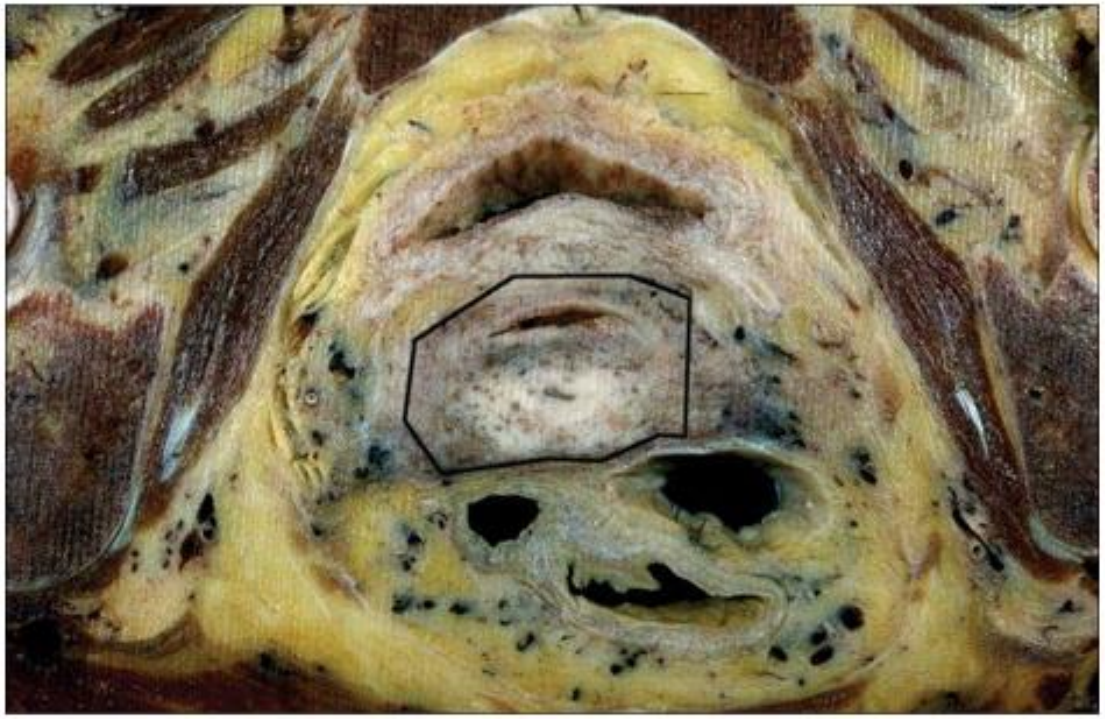


Figure 4

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.

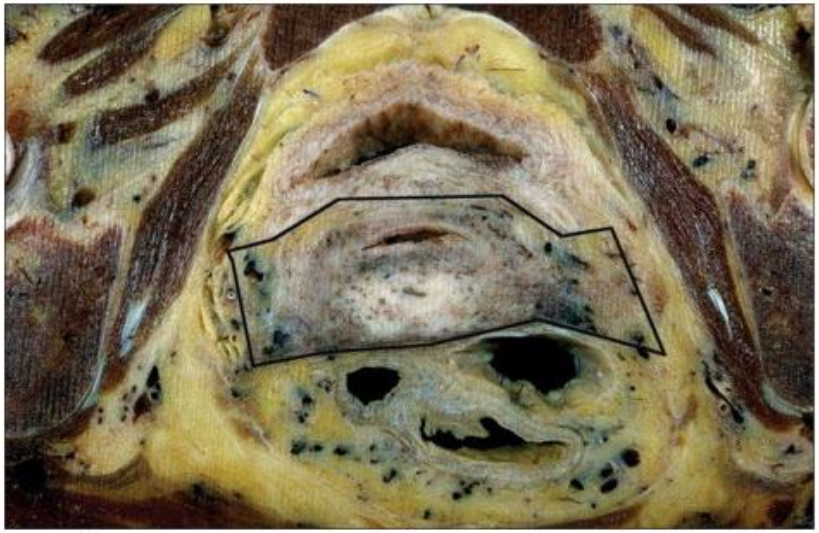


Figure 6

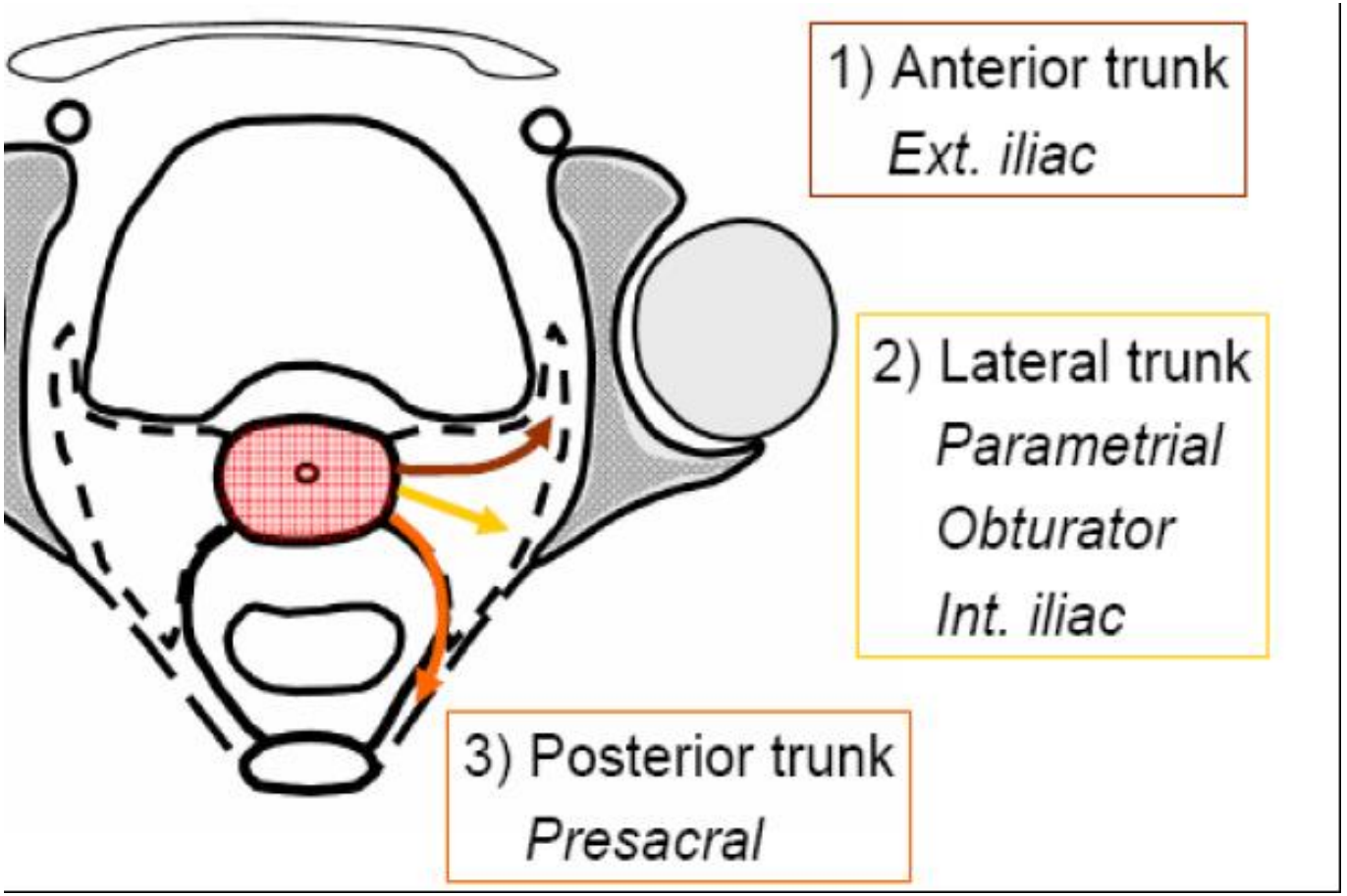
Type C2 radical hysterectomy

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

Anatomical considerations

Lymphatic drainage

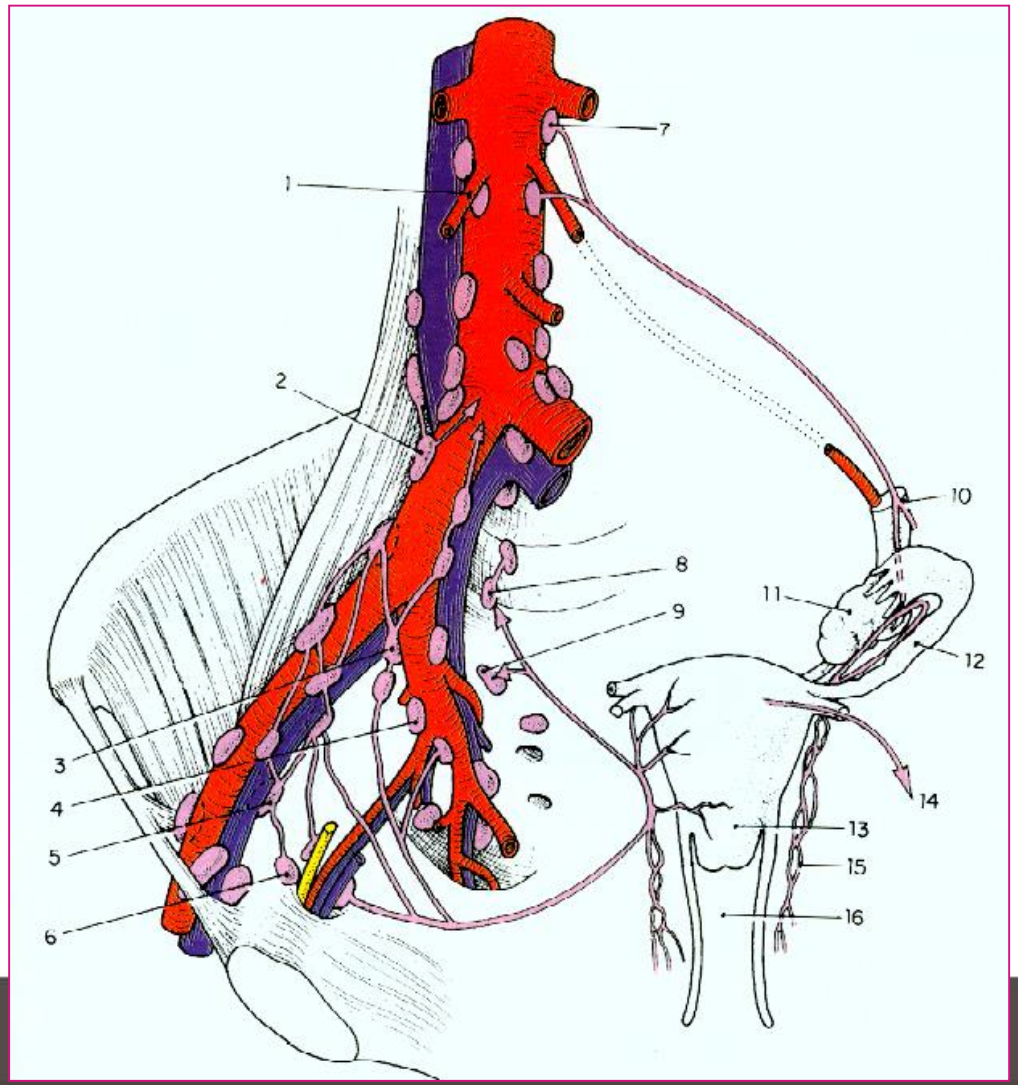
Uterus



Anatomical considerations

Lymphatic drainage

Uterus



Lymph nodes	Anatomical boundaries					
	Cranial	Caudal	Medial	Lateral	Anterior	Posterior
Common iliac nodes	Bifurcation of abdominal aorta (at the inferior border of L4)	Bifurcation of the common iliac vessels (at the inferior border of L5, at the level of the superior border of the ala of sacrum)	Loose cellular tissue	Psoas muscle	Loose cellular tissue anterior to the common iliac vessels	Body of L5
Internal iliac nodes	Bifurcation of common iliac vessels (at the inferior border of L5)	Plane through superior border of the head of femurs at the level of the superior border of the coccyx	Loose cellular tissue	Piriformis muscle	Posterior border of the external iliac lymph nodes and loose cellular tissue	Loose cellular tissue
External iliac nodes	Bifurcation of common iliac vessels (at the inferior border of L5)	Femoral artery	Loose cellular tissue	Iliopsoas muscle	Loose cellular tissue	Anterior border of the internal iliac lymph nodes and loose cellular tissue
Obturator nodes	Plane through the acetabulum	Superior border of the neck of femurs, at the small ischiadic foramen	Loose cellular tissue	Internal obturator muscle (intrapelvic portion)	Loose cellular tissue	Loose cellular tissue
Presacral nodes	Intervertebral space of L5–S1 (sacral promontory)	Superior border of the 1st coccygeal vertebra	–	Piriformis muscle	Loose cellular tissue	Anterior aspect of sacrum
Inguinal nodes	Superior limit of the neck of femurs	Bifurcation of the femoral artery into its superficial and deep branches	Adductor muscles	For superficial inguinal nodes: the adipose and loose connective tissue and the sartorius muscle; for deep inguinal nodes: the femoral vessels	Subcutaneous adipose tissue	Pectineal muscle

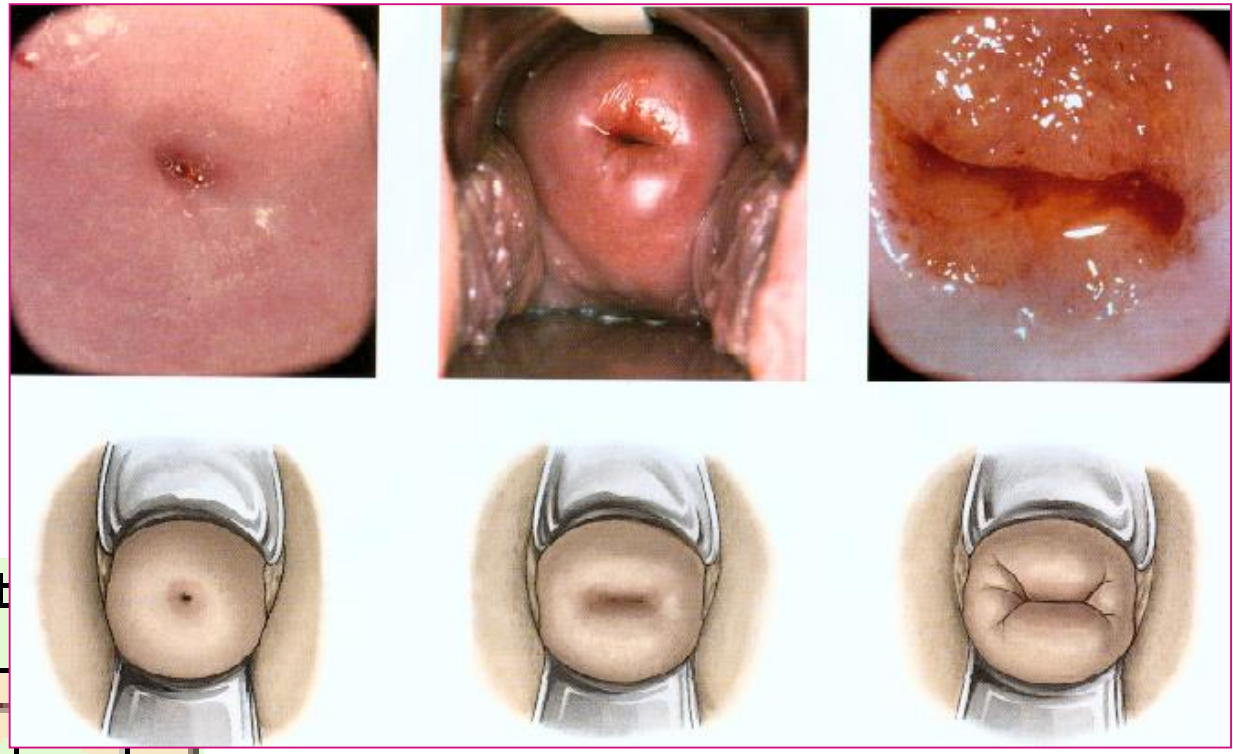
Role of clinical examination

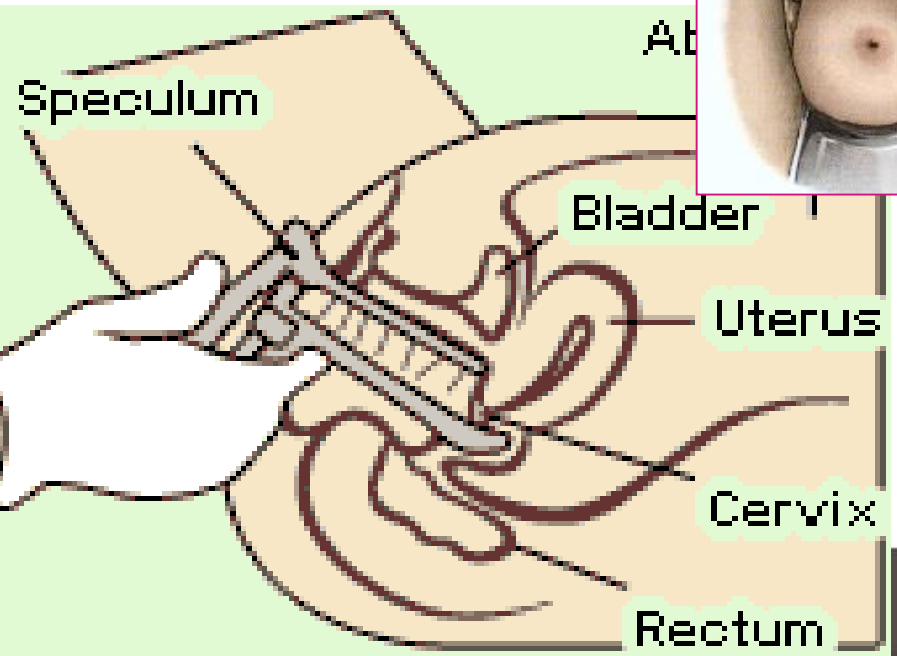
- Accurate tumor characteristics
- Staging
- General condition and fitness for radical treatment

Do you do gynaecological examination under general anaesthesia?

1. Yes
2. No

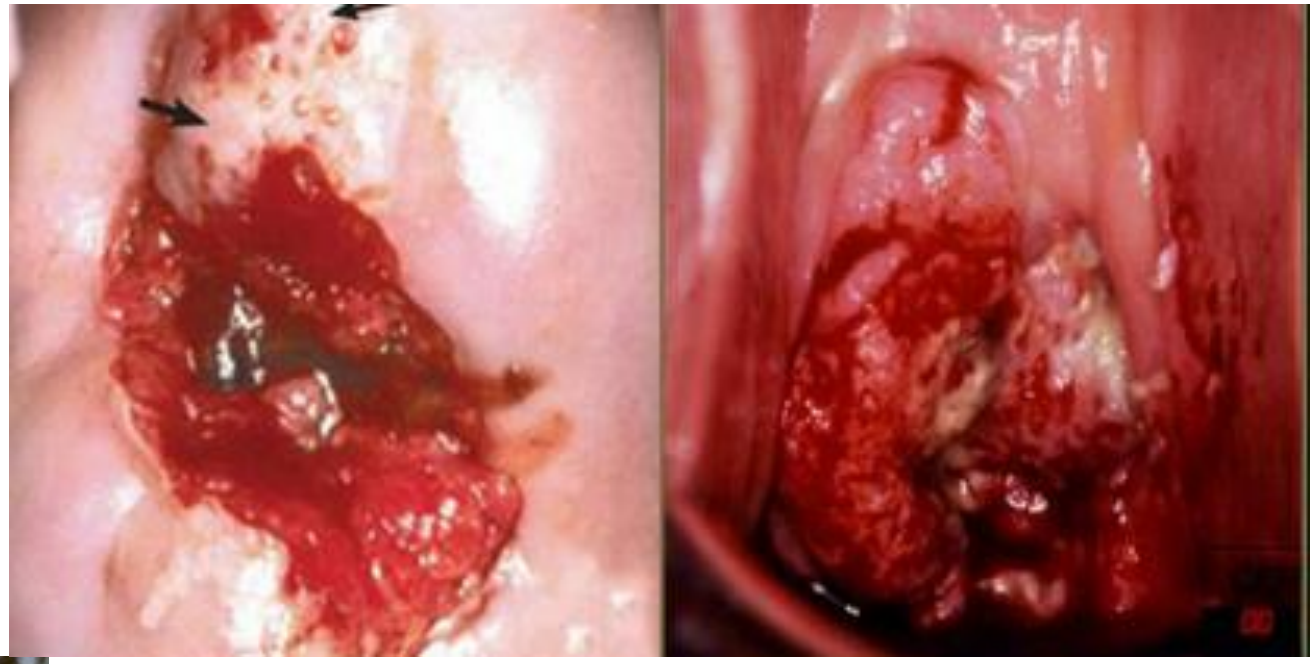
Clinical examination

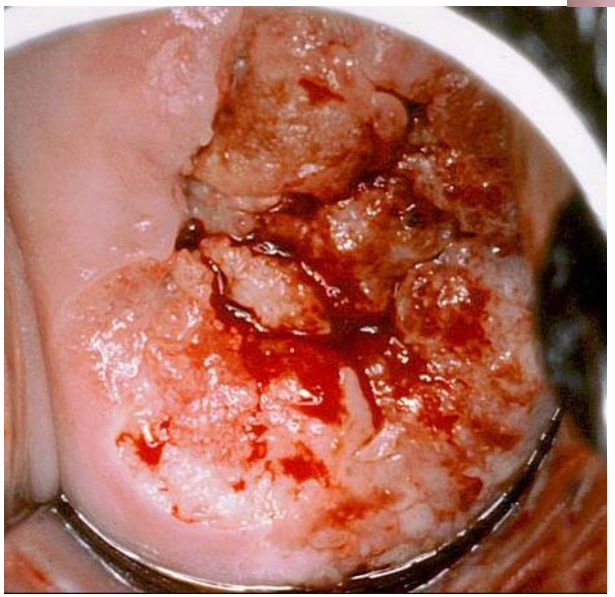


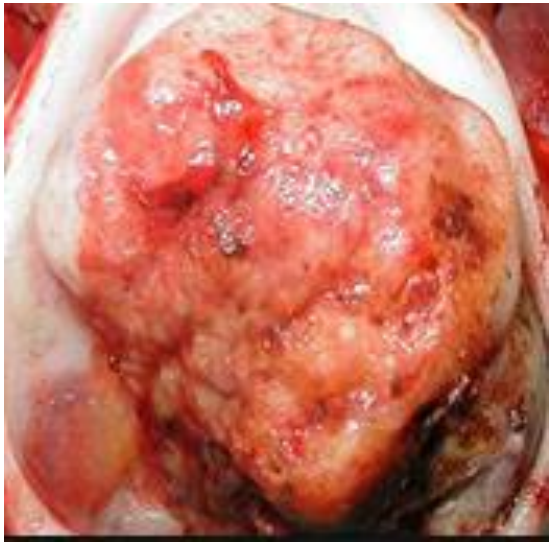


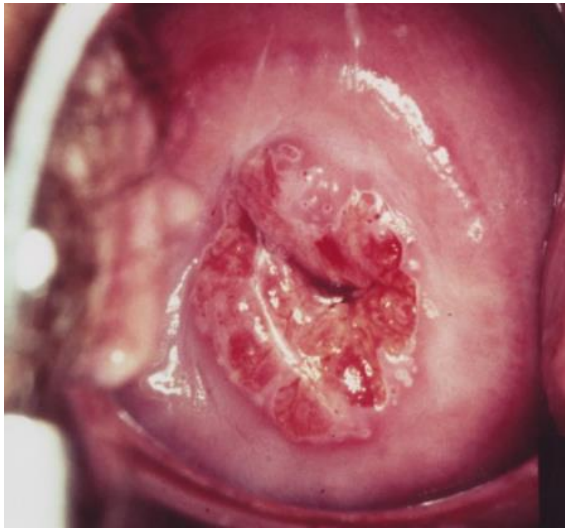
GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

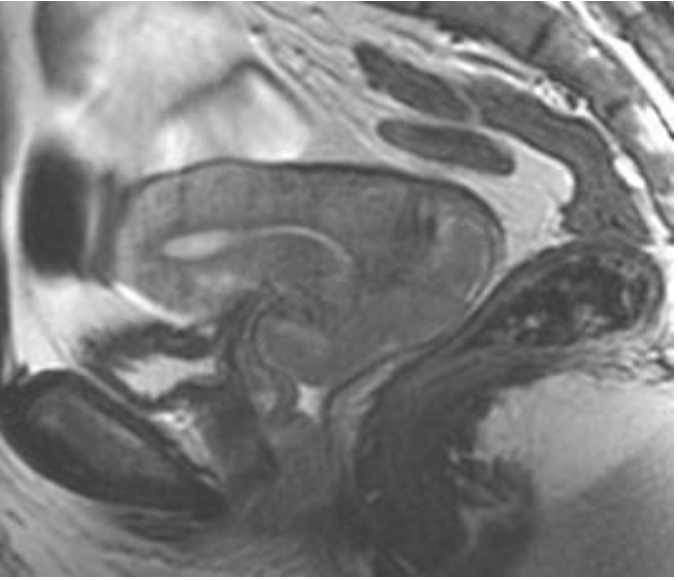
ESTRO School











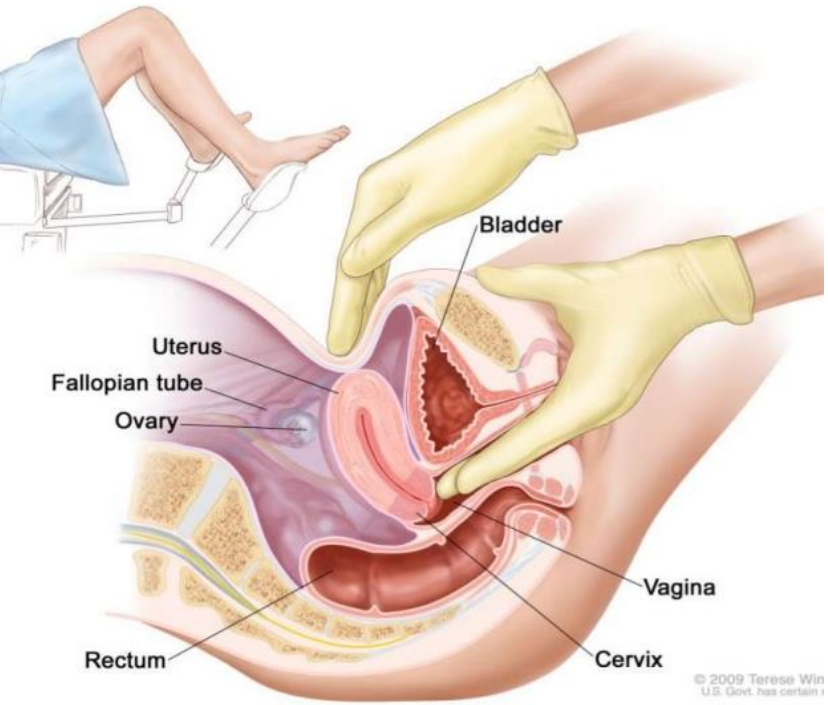
Clinical examination

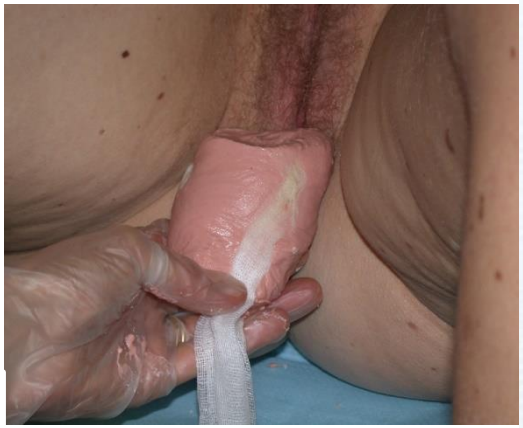
Tumor measurement

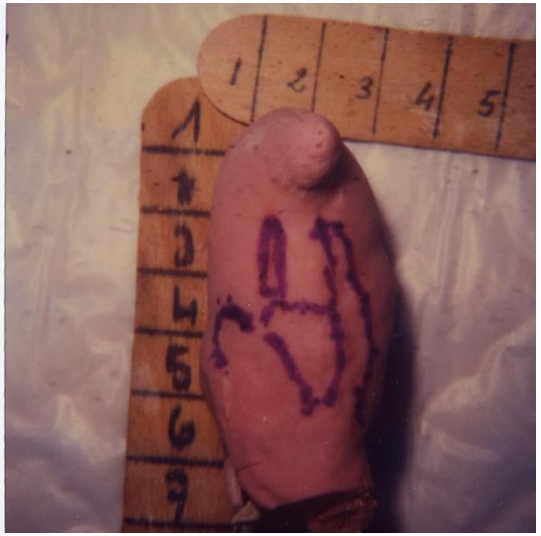
Tumor extension:

vagina (vaginal impression)

parametrium







Staging

Which staging do you use?

1. **FIGO**
2. **TNM classification**

Seminars in Diagnostic Pathology (2012) 29, 167-173

ELSEVIER

Seminars in
Diagnostic
Pathology

Issues and inconsistencies in the revised gynecologic staging systems

Lisa Cole, MD, Mark H. Stoler, MD

- Lymphovascular invasion
- Extension to the uterine corpus
- Nodal status

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%

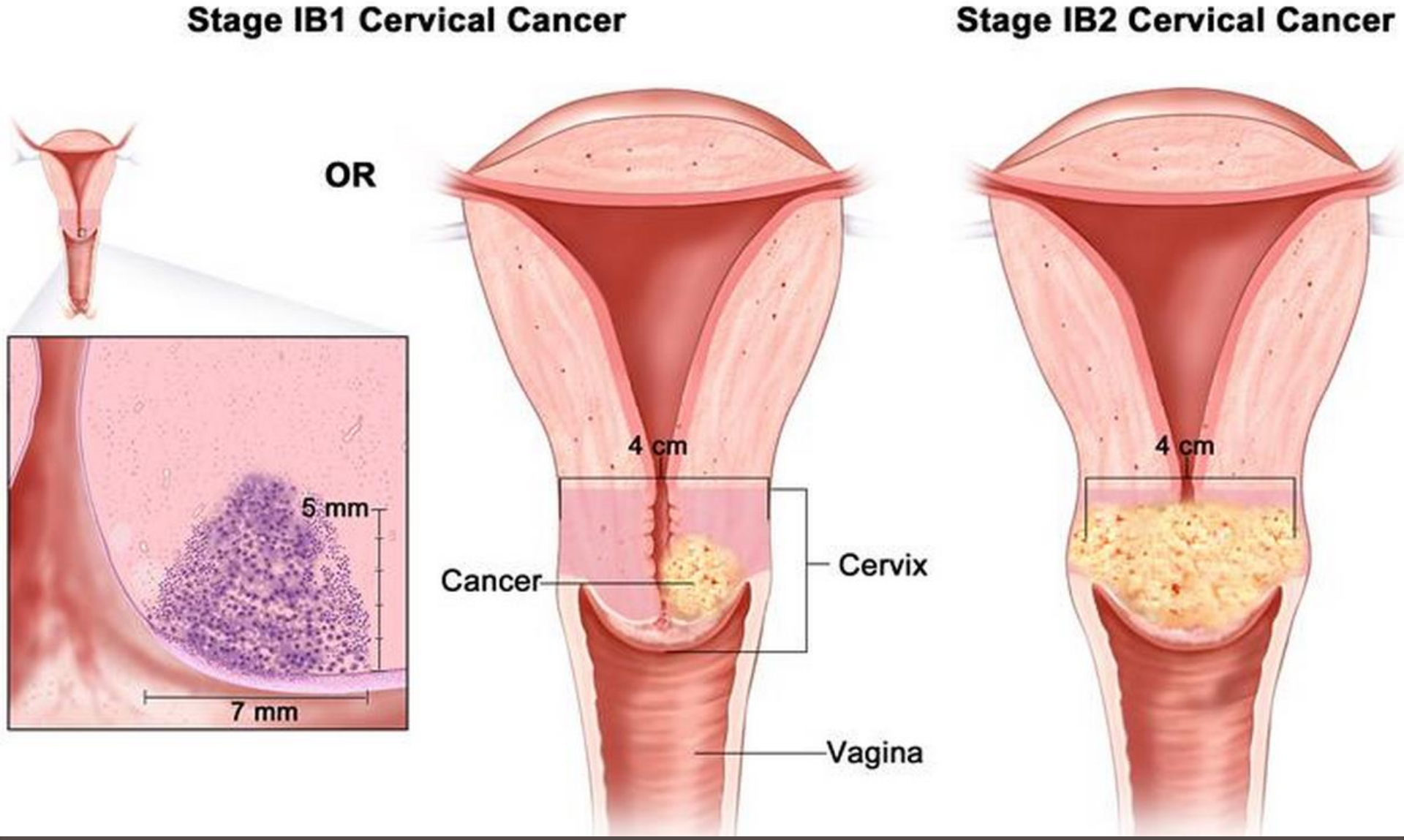
5-year survival : 75.7%

- **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

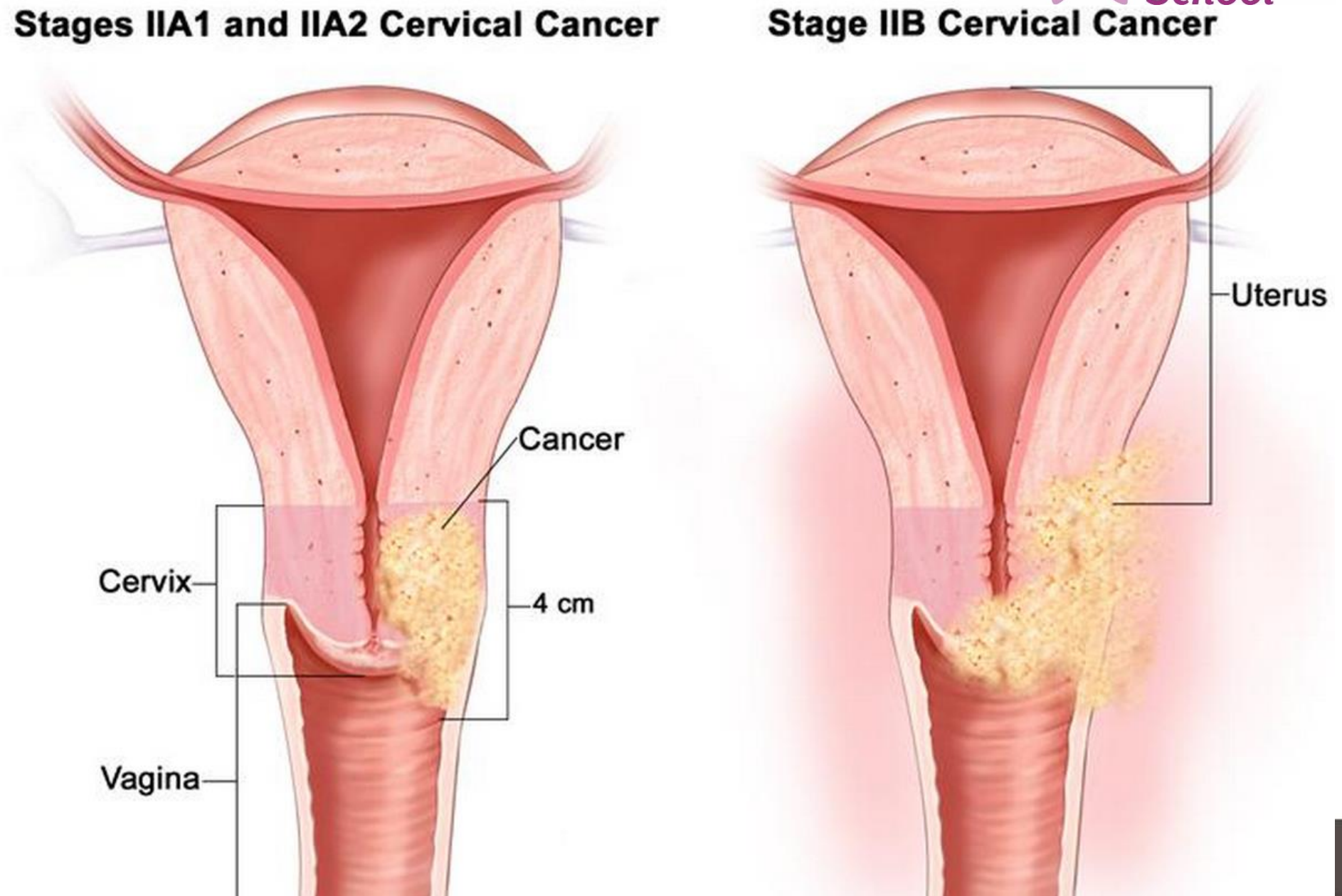
- **Stage III: tumour extends to pelvic sidewall and/or lower third of vagina or causes hydronephrosis or non-functioning kidney**
  - IIIa: lower third of vagina, no pelvic side wall extension
  - IIIb: involving pelvic side wall or causing hydronephrosis

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

FIGO stage I 2008

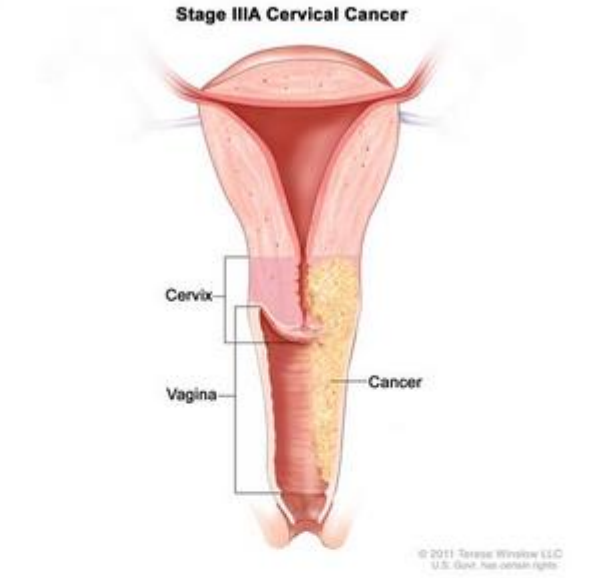


FIGO stage II 2008



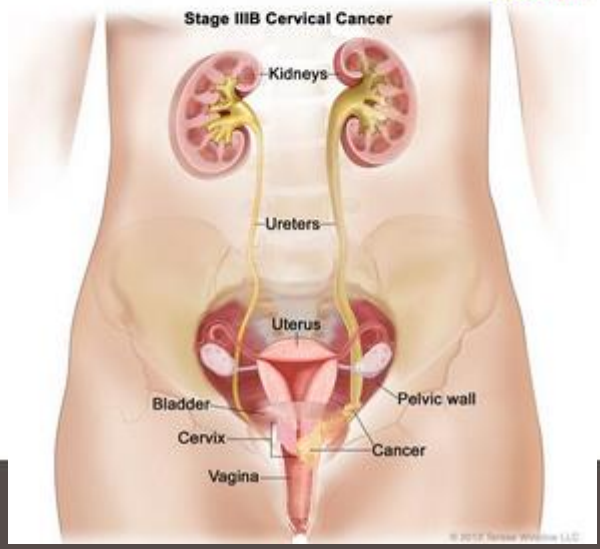
FIGO stage III/IV 2008

Enlarge



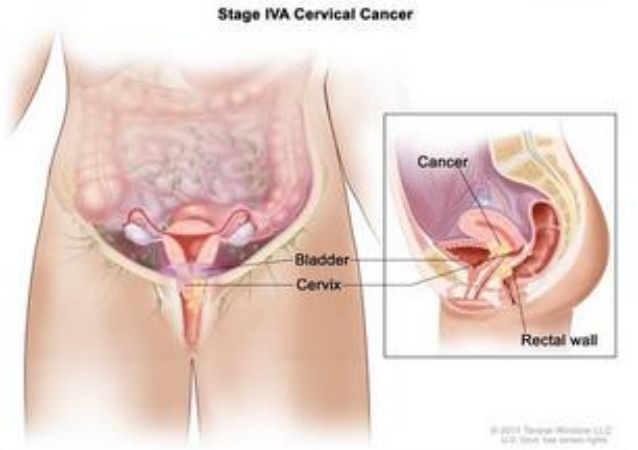
IIIA

Enlarge



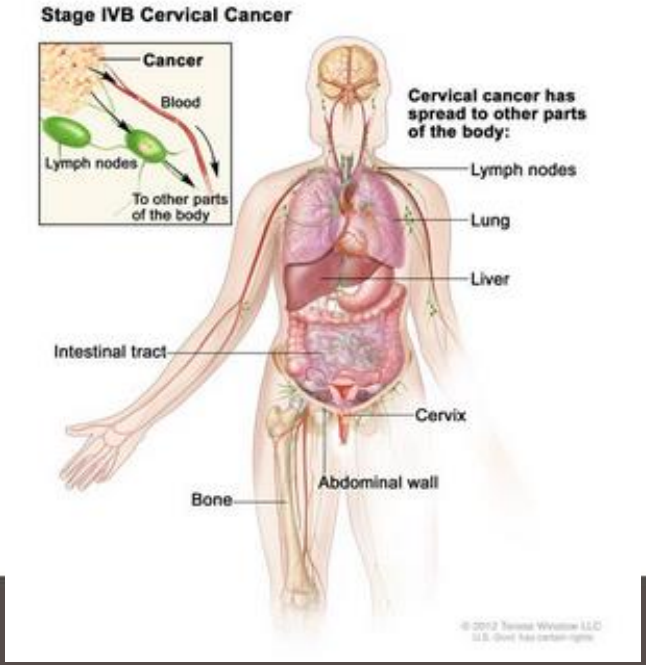
IIIB

Enlarge



IVA

Enlarge



IVB

FIGO staging / TNM classification

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

Conclusion

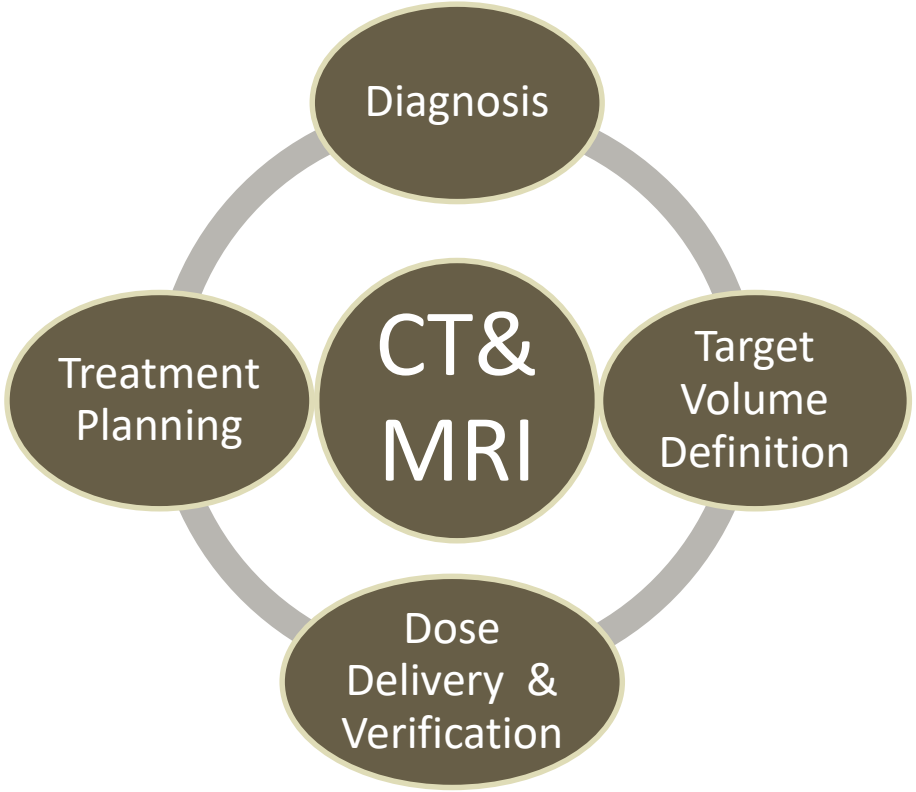
- Importance of clinical examination
- Knowledge of lymphatic drainage
- FIGO classification ⟶ therapy

IMAGING : NORMAL PELVIC ANATOMY

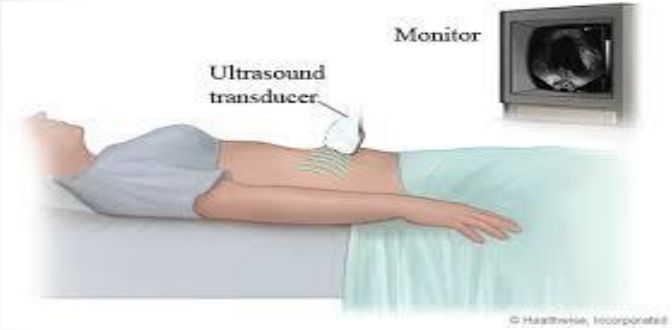
UTERUS,PARAMETRIA,ORGANS AT RISK & NODES : ON USG, CT & MRI

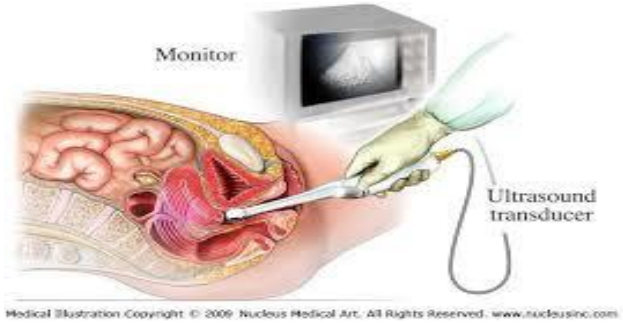
Dr Aditi Jain
Department of Radiodiagnosis
M.S. Ramaiah Medical College & Hospitals.

Role of Imaging



ULTRASONOGRAPHY (USG)





TAS

- Frequency of USG probe - 3.5 to 5 MHz
- Full Bladder
- + Larger field of view

TVS

- Frequency of USG probe - 5 to 7.5 MHz
- Empty Bladder, Better Resolution, Obese patient, Retroverted Uterus
- Limited field of view

ULTRASONOGRAPHY (USG)

Advantages

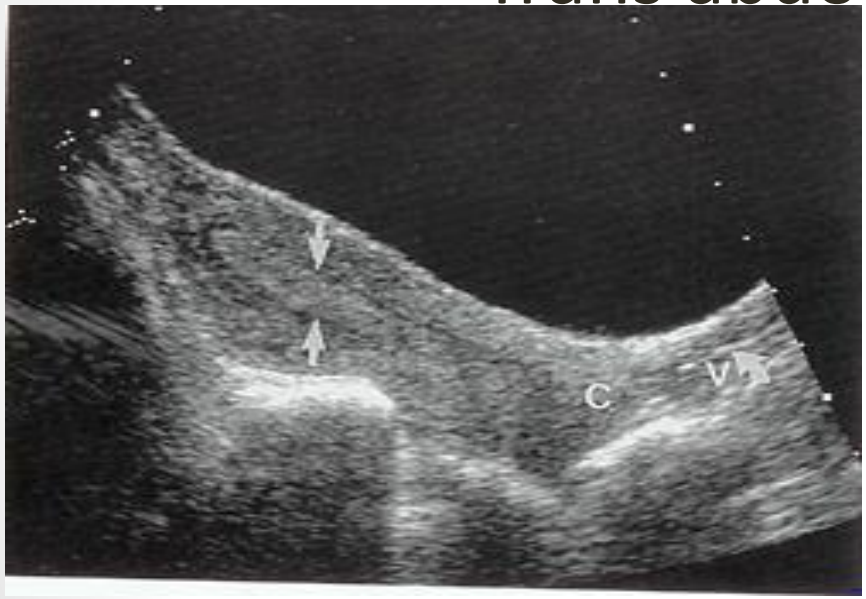
- First line imaging investigation
- Non invasive
- Widely available & inexpensive
- No ionizing radiation
- Detection of primary tumours
- Hydronephrosis

Limitations

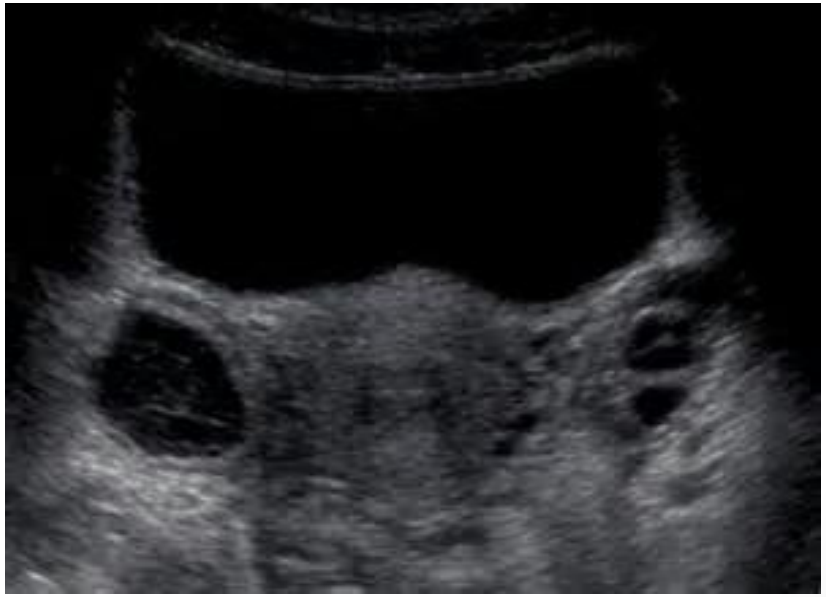
- User dependent
- Non-reproducible results
- Obscuration of details by bowel gases
- Primary tumour
- Pelvic lymph nodes and pelvic side walls, peritoneal disease
- Parametrial spread
- Bladder invasion

Normal Sonographic Anatomy: Uterus

Trans abdominal Scan

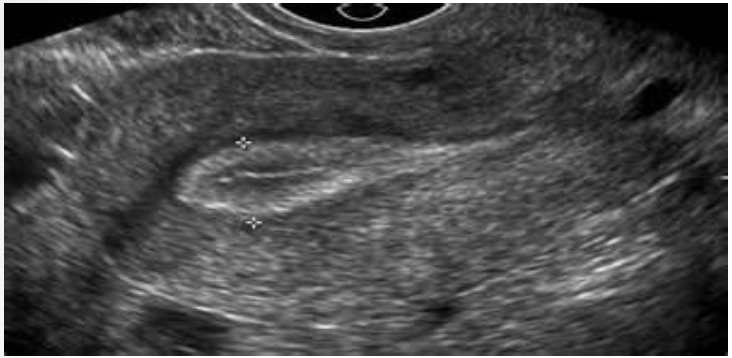


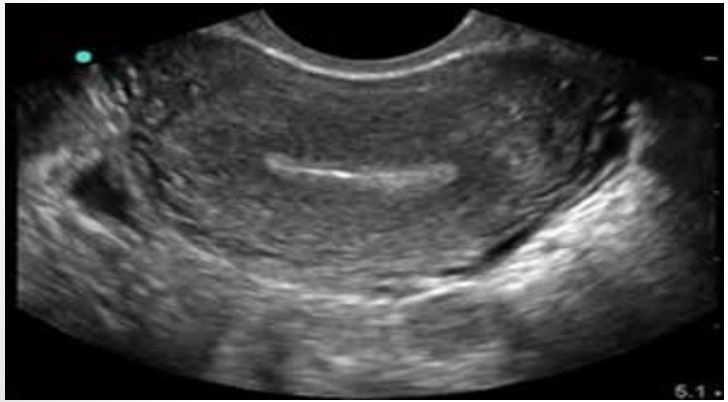
Sagittal



Axial

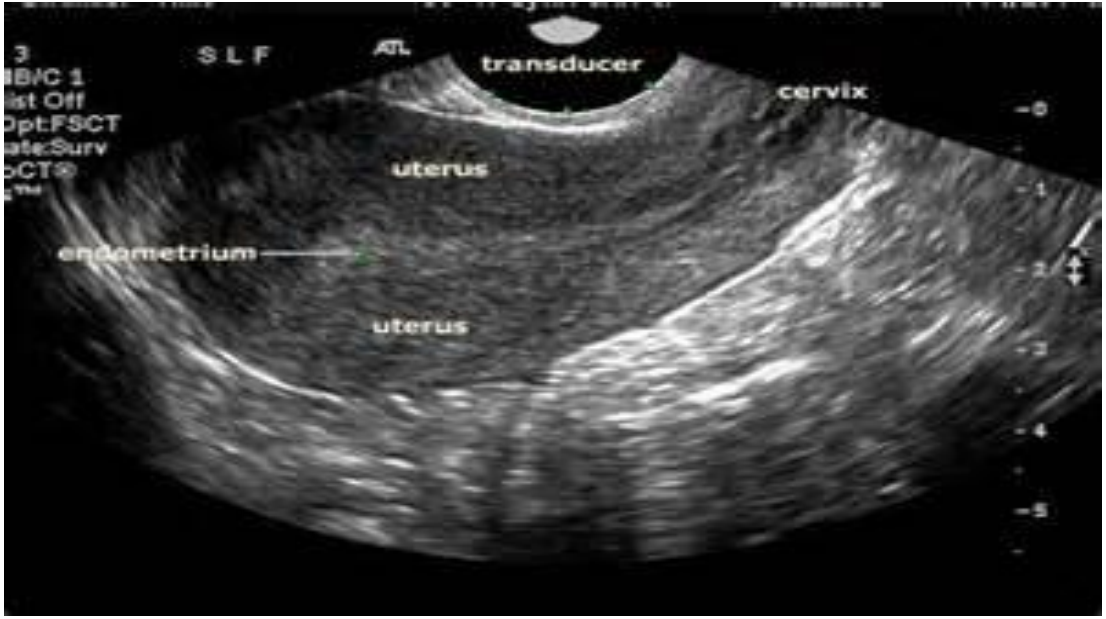
TVS: Uterus





- The **Perimetrium** : not visible on ultrasound examination.
- The **myometrium** has three layers:
  - Inner myometrium appears as a thin hypoechoic area surrounding the echogenic endometrium.
  - The Intermediate layer is the thickest and has a uniformly homogeneous low to moderate echogenicity.
  - The thin outer layer is less echogenic
- **Endometrial cavity** : seen as a central echogenic line, thickness varies during the menstrual cycle.

TVS: Cervix

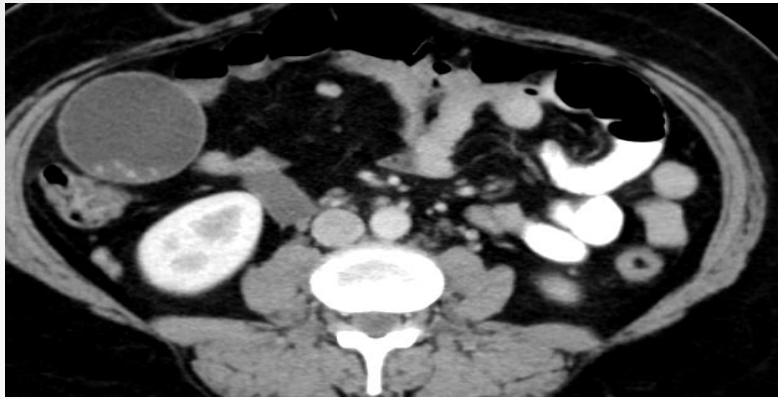


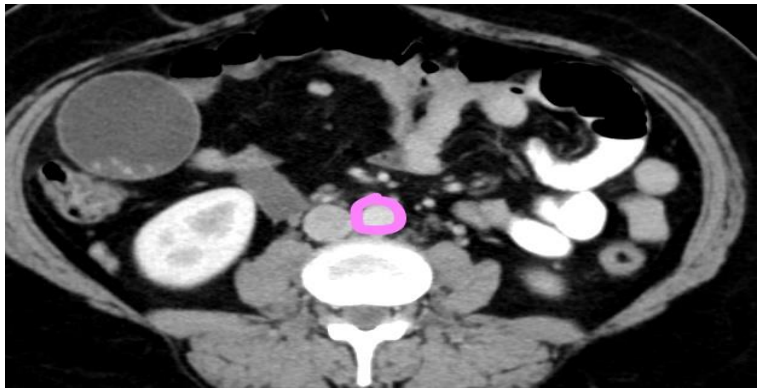
A tubular structure of homogeneous echogenicity. The endocervical canal appears as an echogenic interface

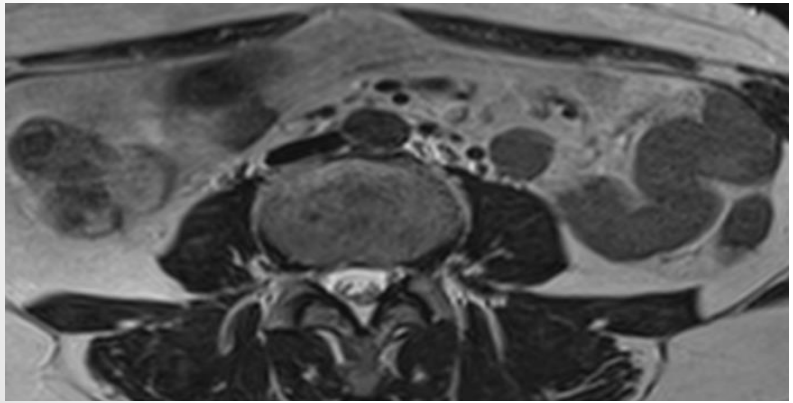
CROSS SECTIONAL IMAGING ANATOMY : CT &MRI

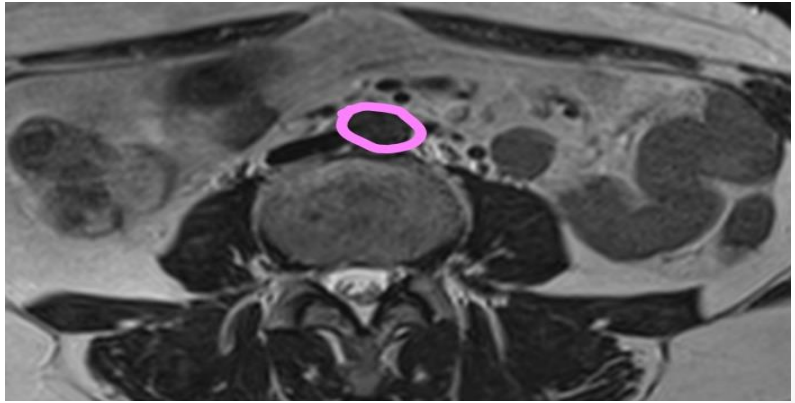
Axial, Coronal, Sagittal
& Post Contrast

Aorta

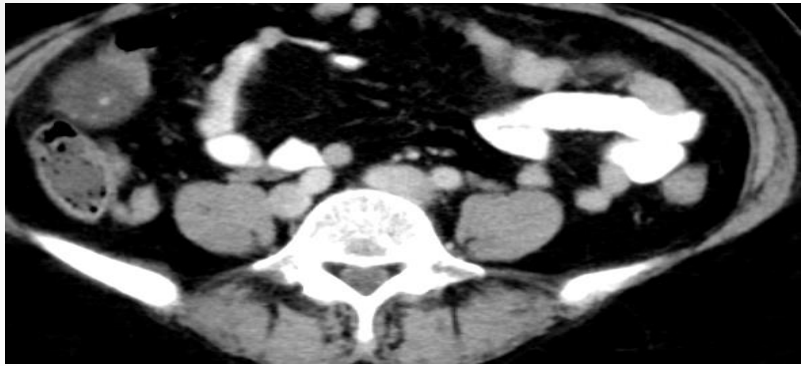


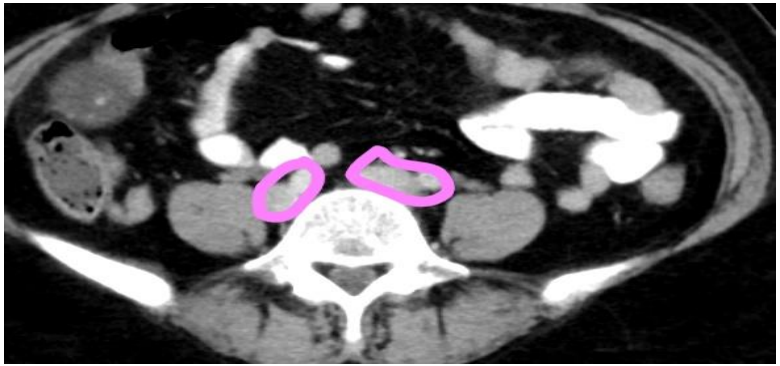


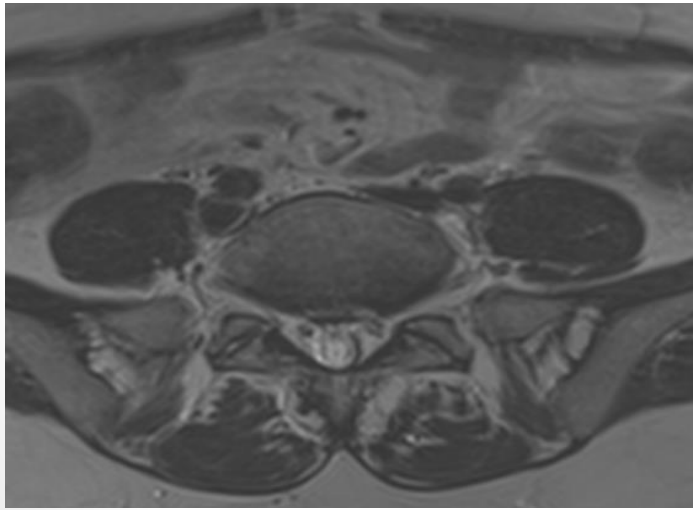


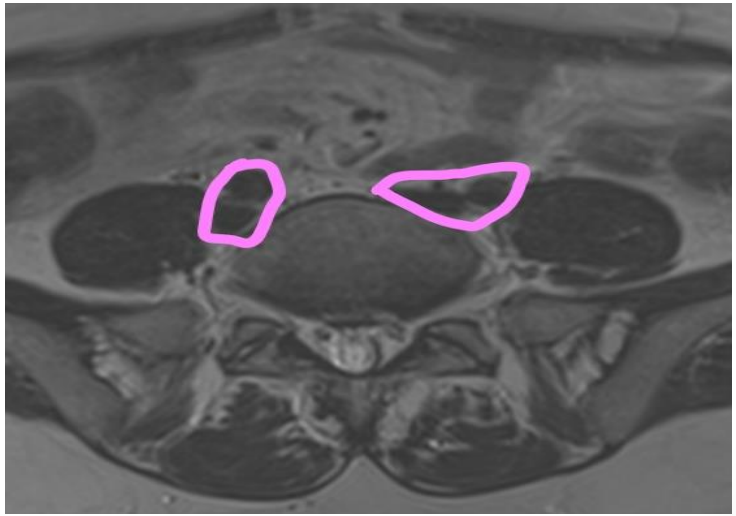


Common Iliac vessels

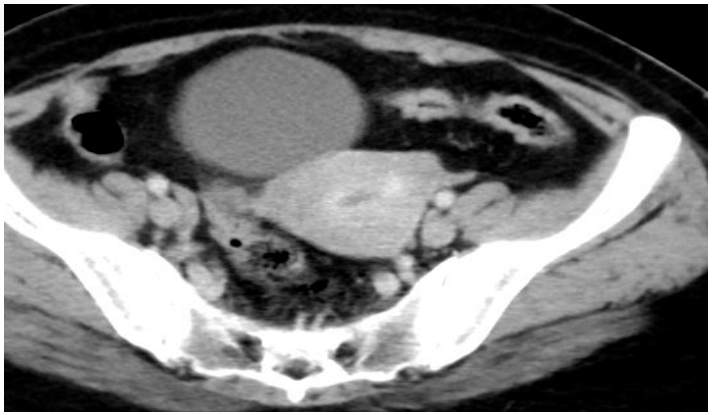


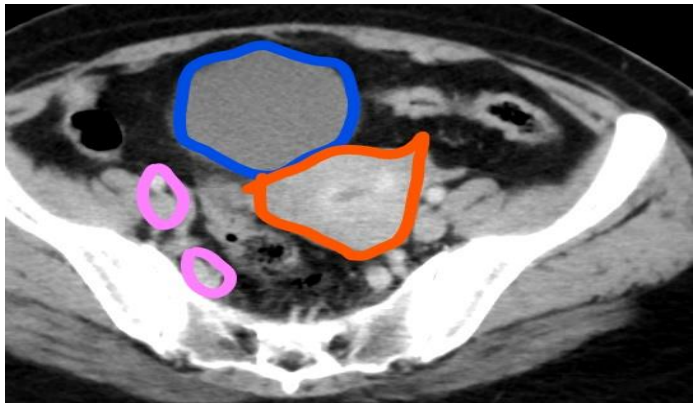


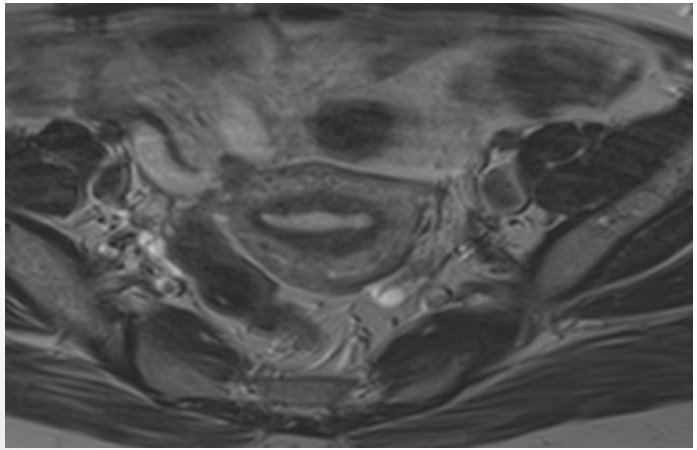


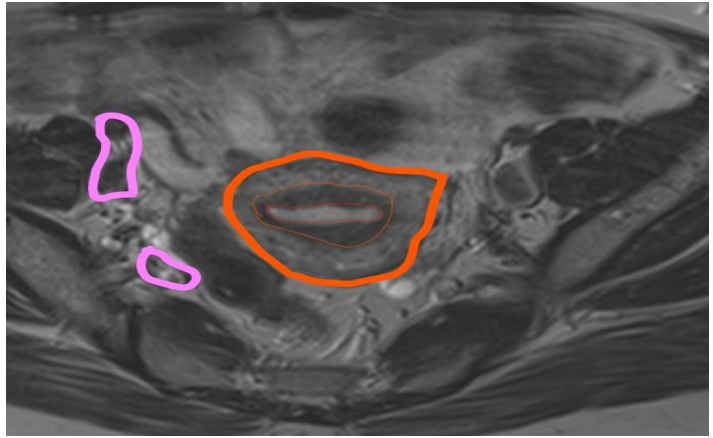


Uterus & Iliac vessels

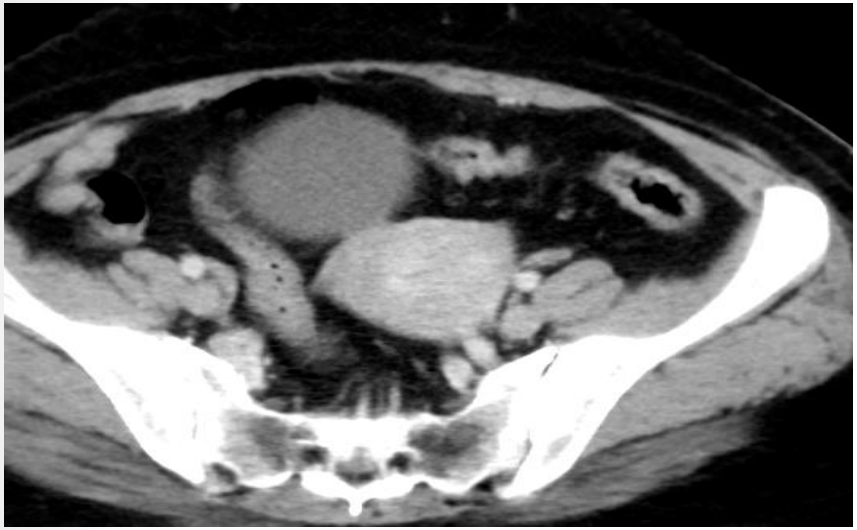


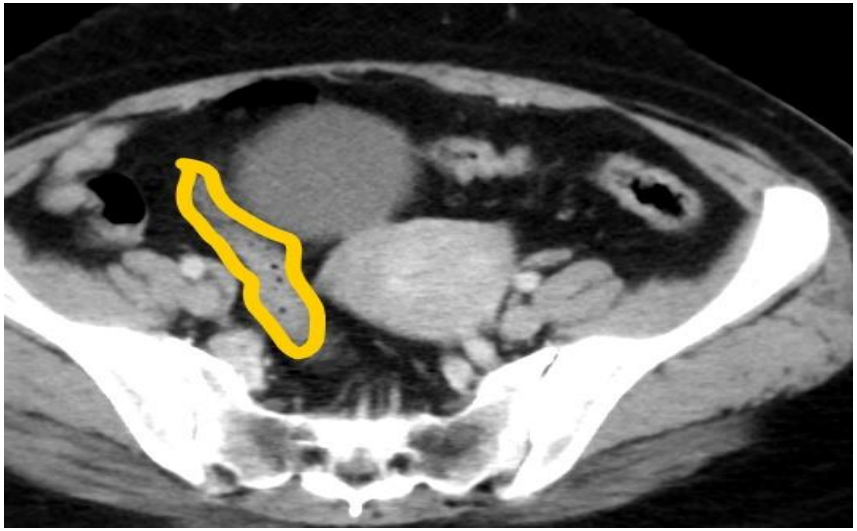




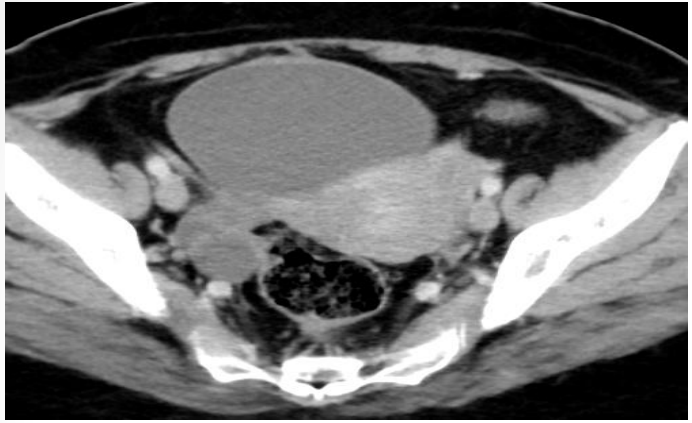


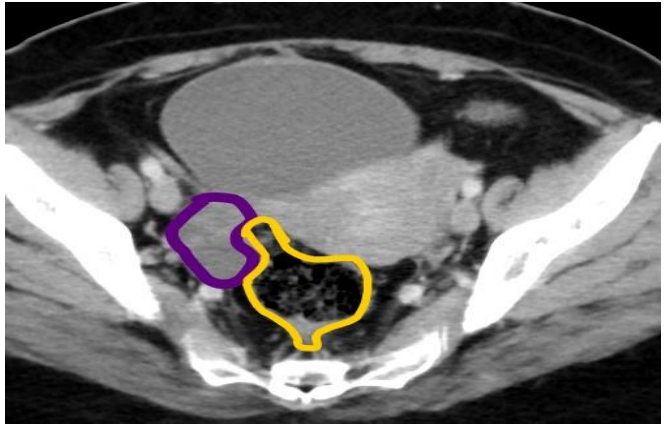
Sigmoid Colon

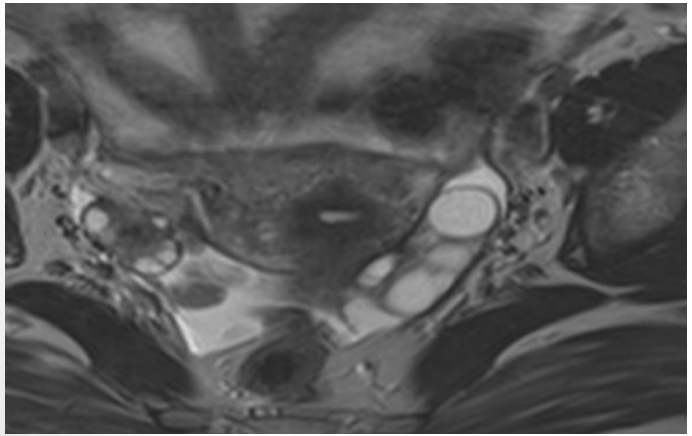


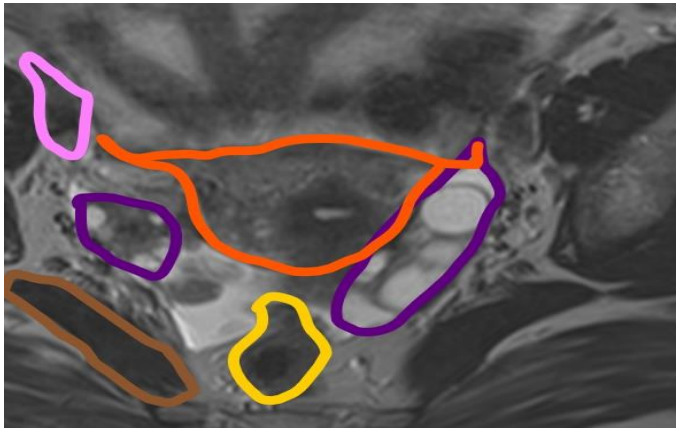


Pelvic side walls & Ovaries

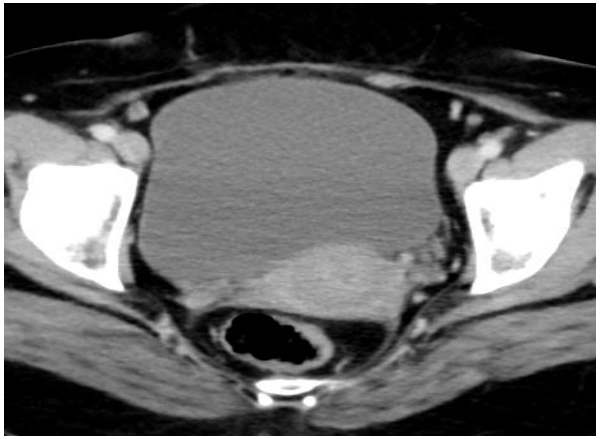


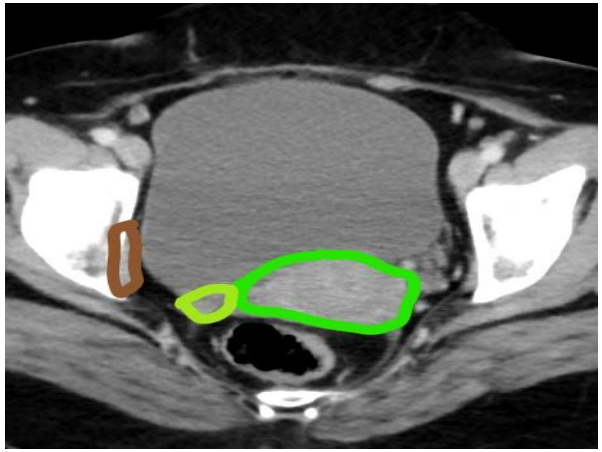


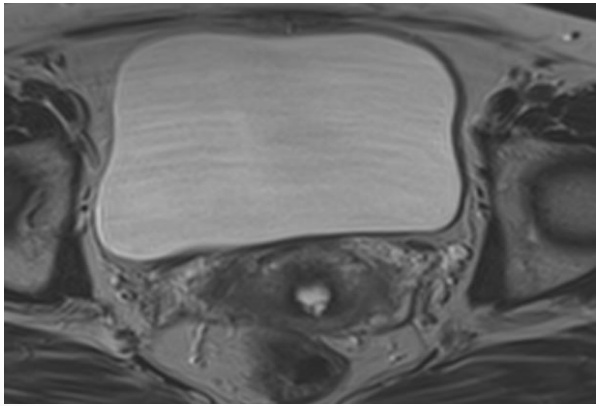


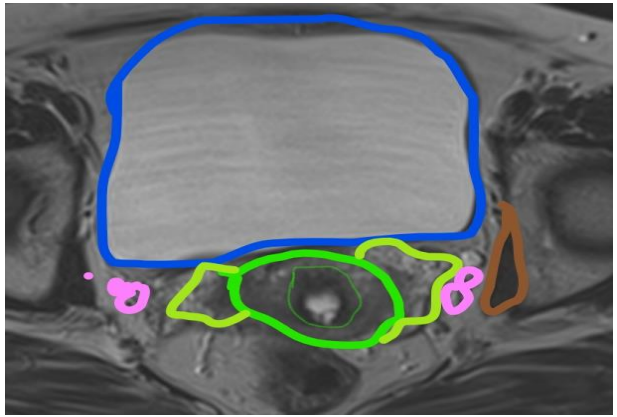


Cervix & Parametria

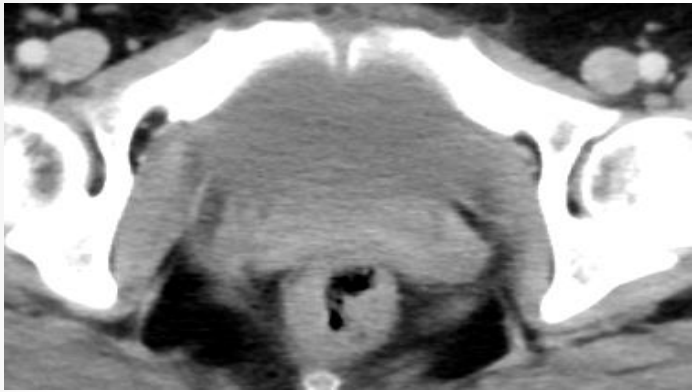


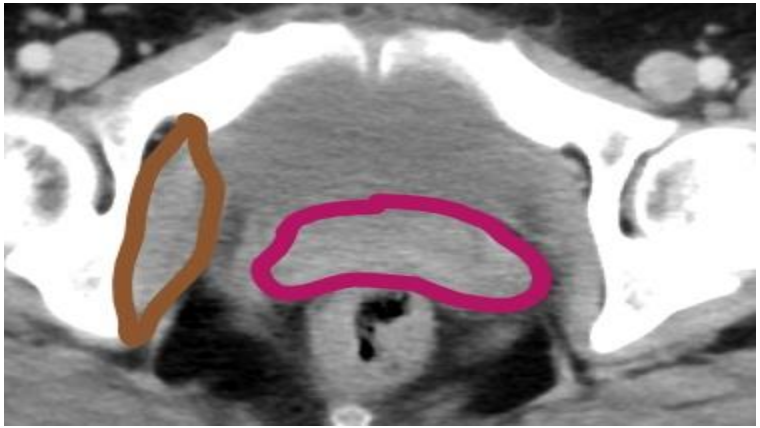


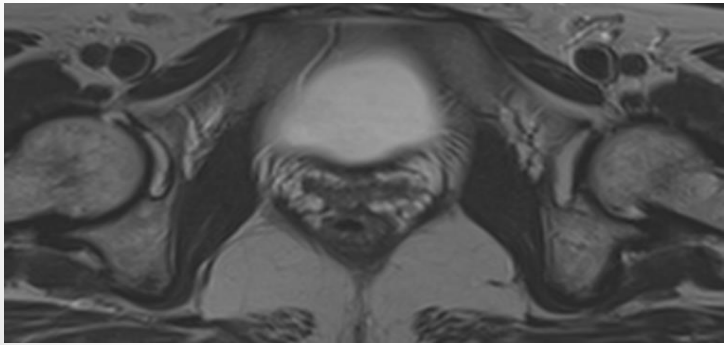


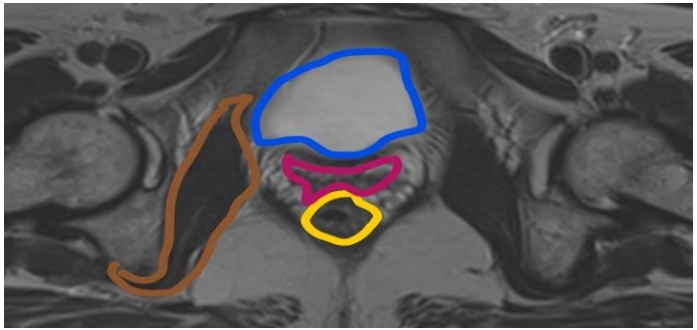


Vagina

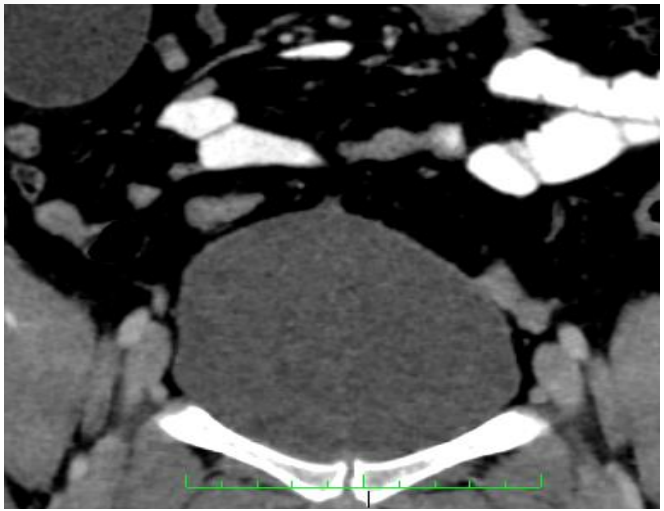


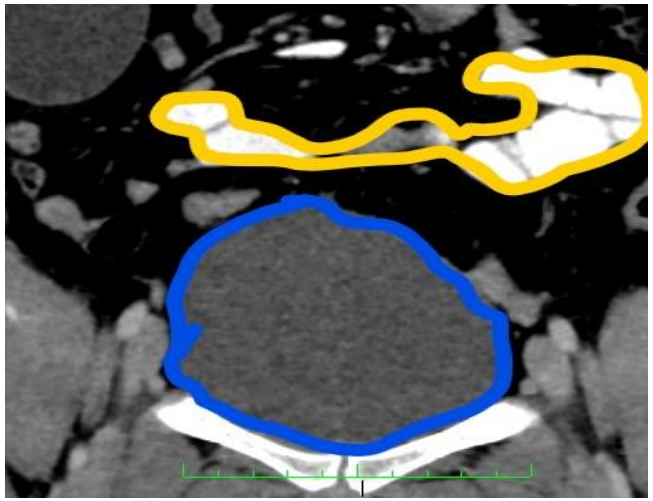


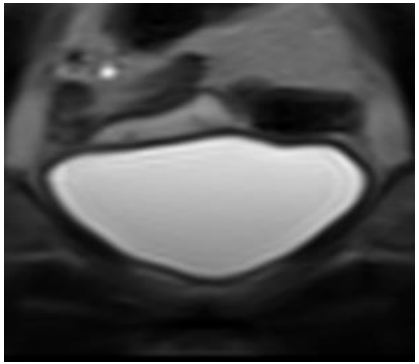




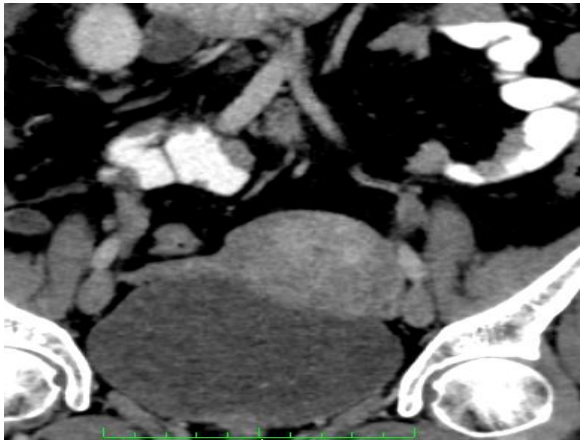
Bladder: Coronal

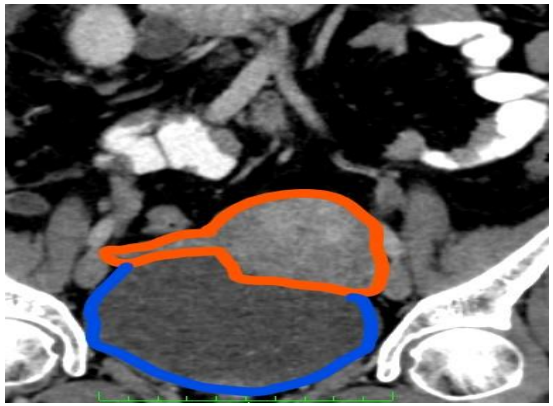


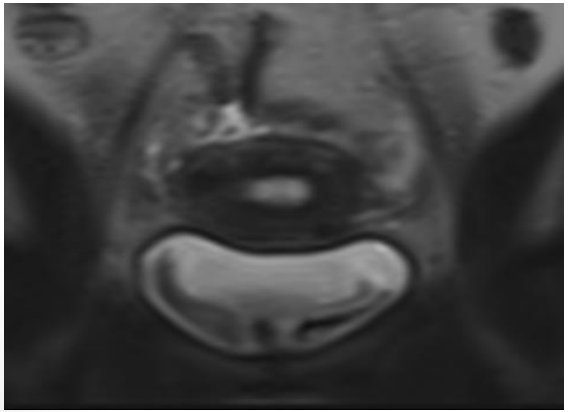


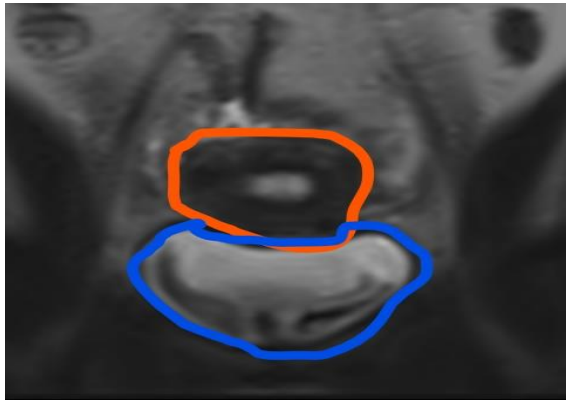


Uterus

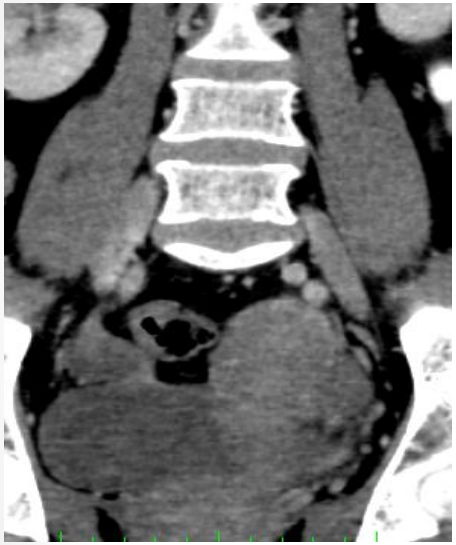


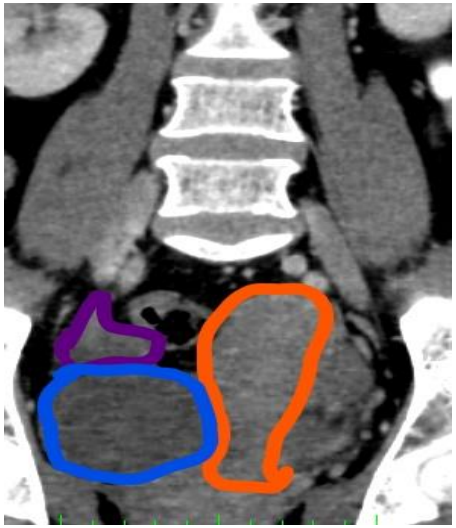


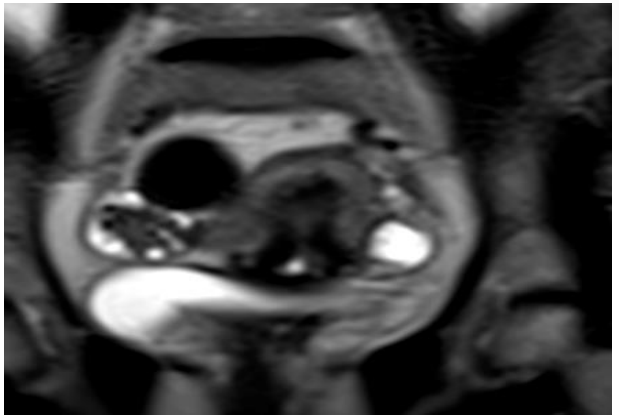


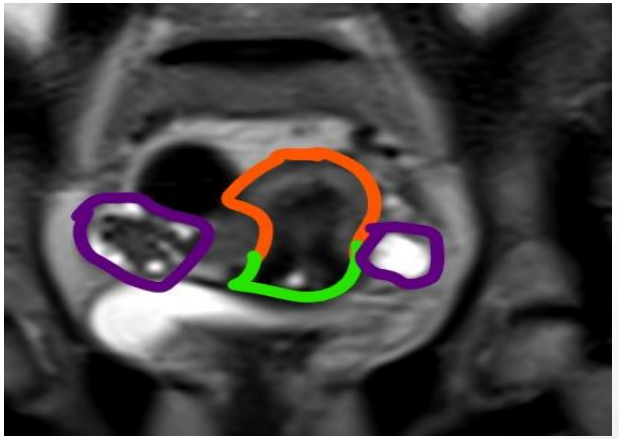


Ovaries

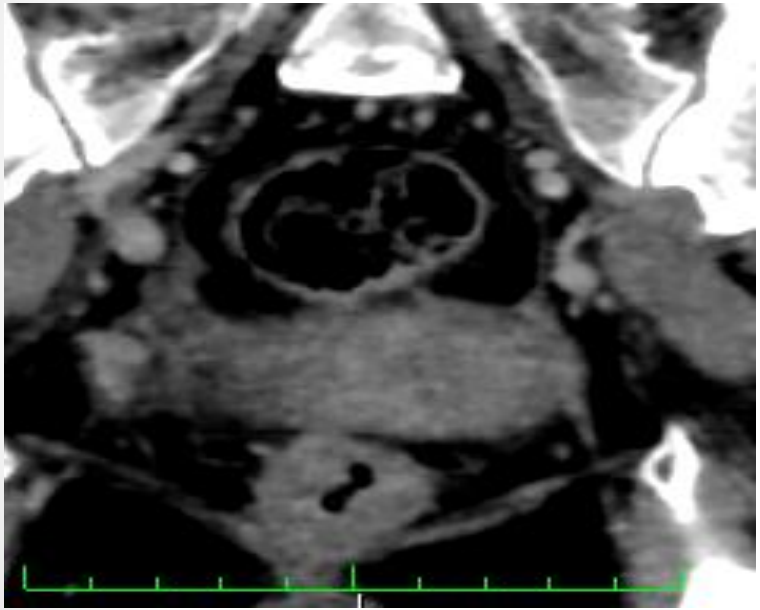


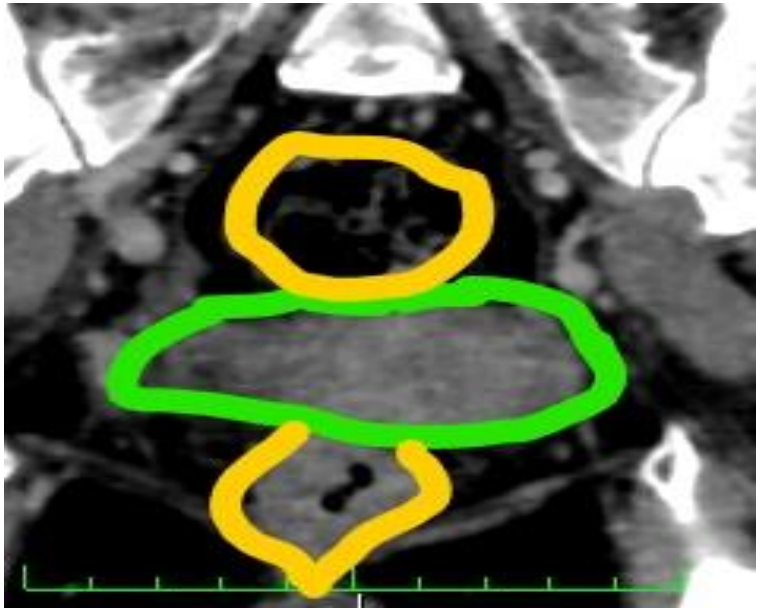




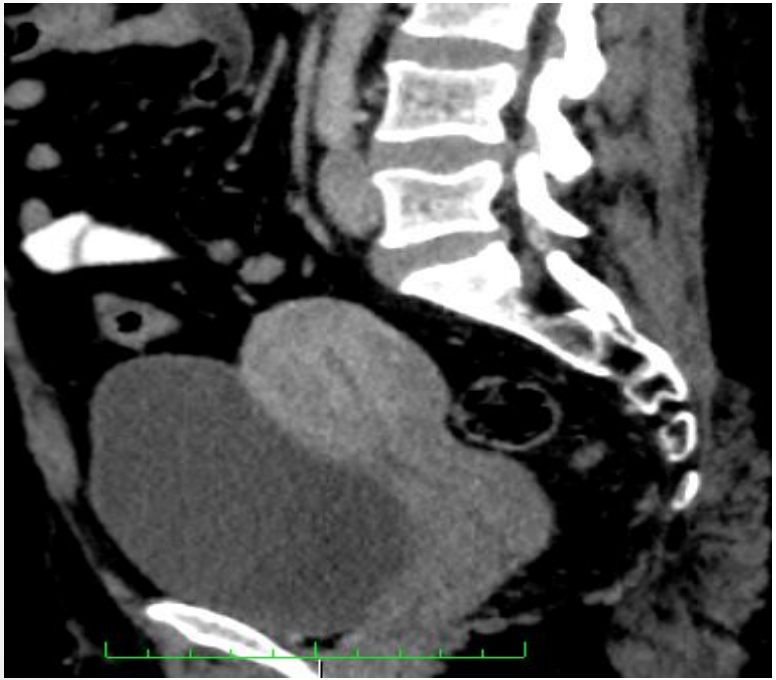


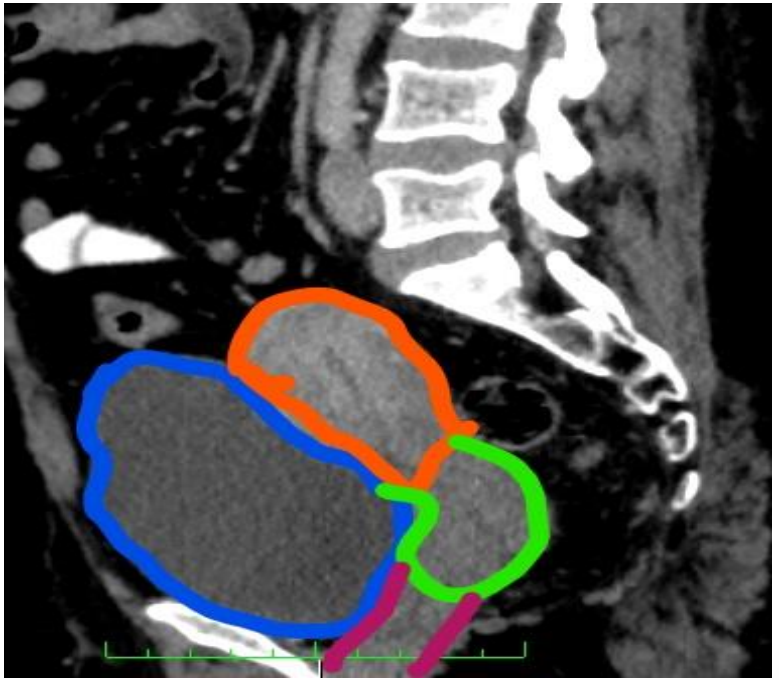
Cervix & Colon



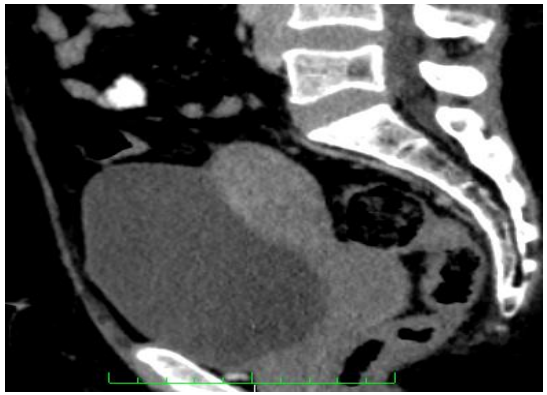


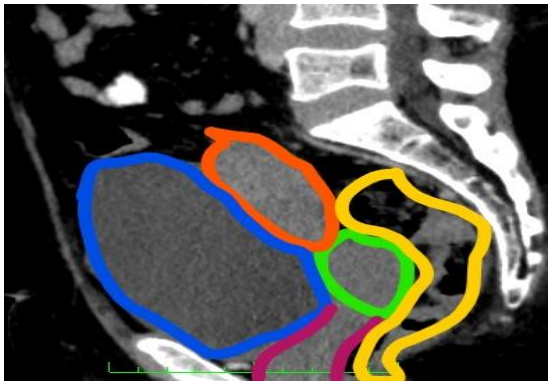
Cervix and Uterus: Sagittal

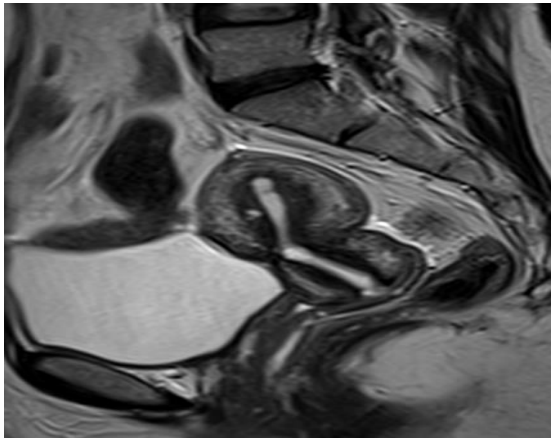


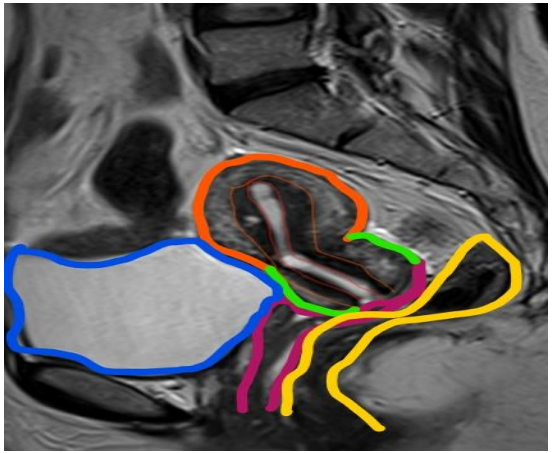


Uterus & Rectum









Zonal Anatomy: Uterus

re

o

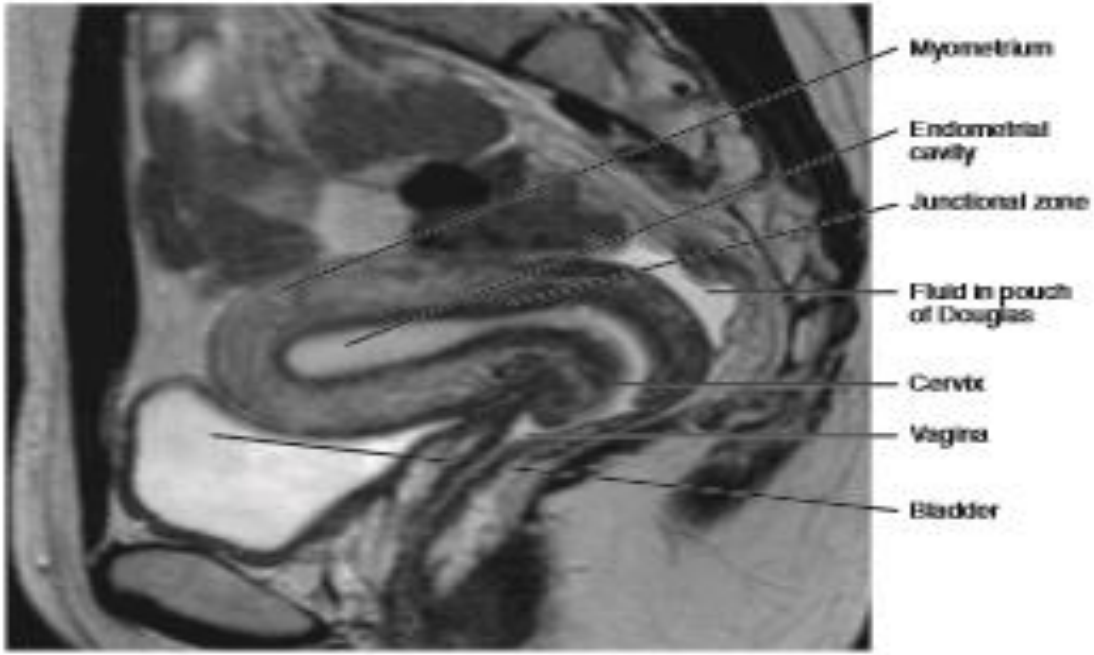
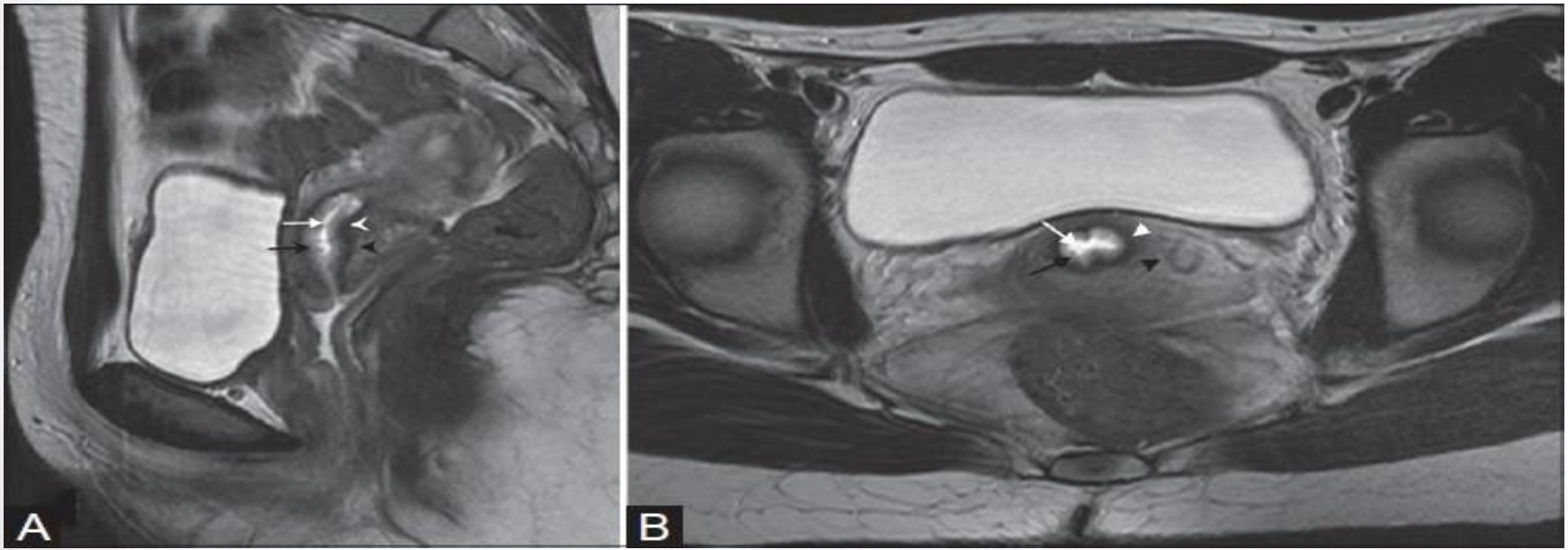


Fig. 14.44 Sagittal T2-weighted sequence through the female pelvis showing the anatomical relations of the uterus.

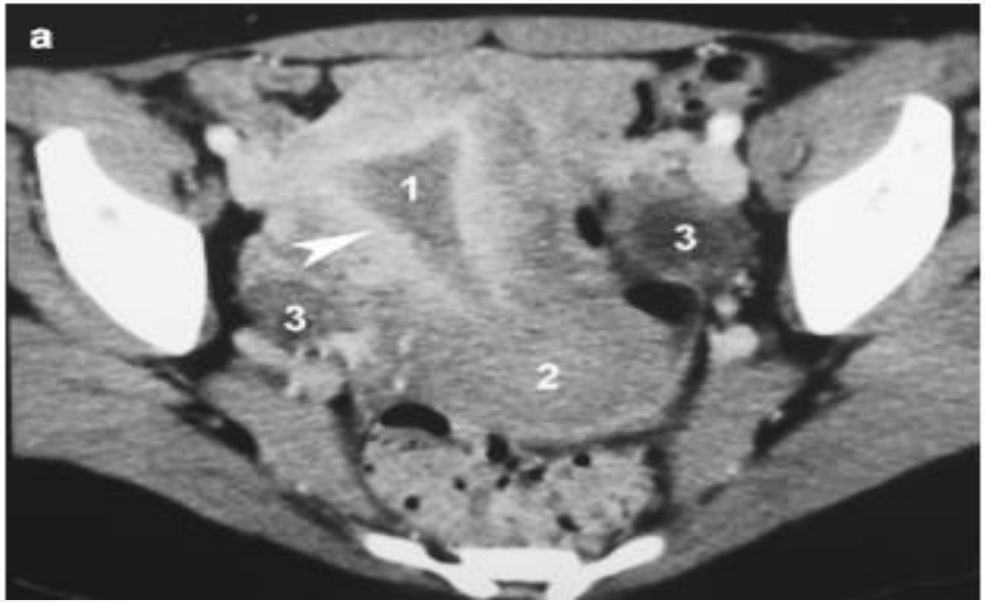
Zonal Anatomy: Cervix

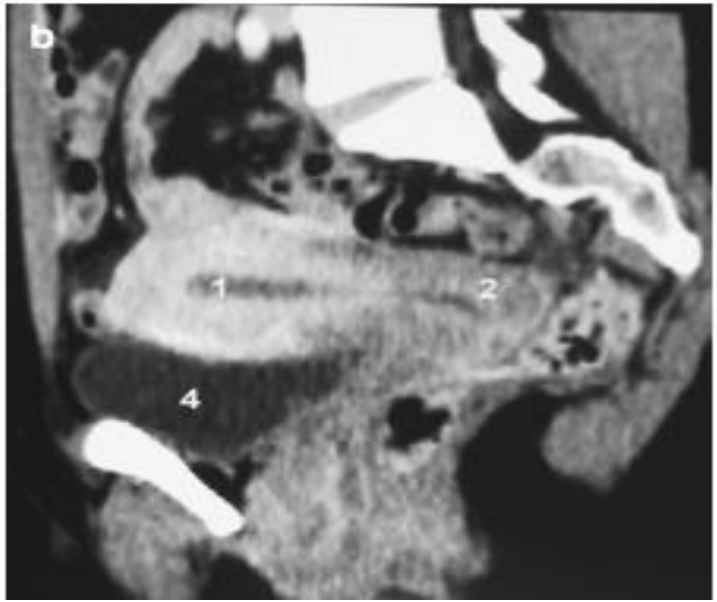


Sagittal

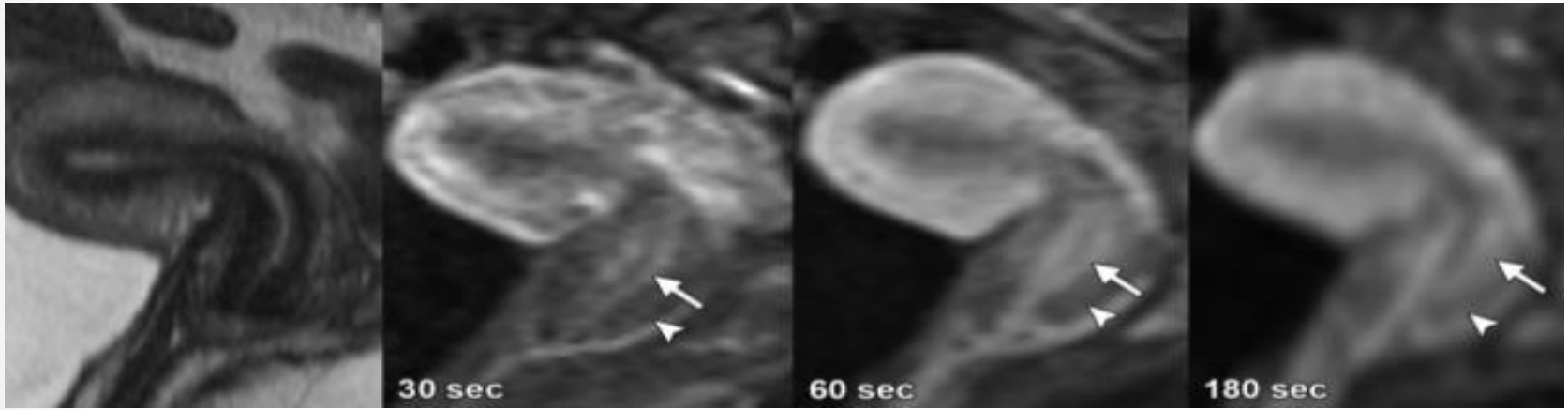
Axial

Post Contrast CT

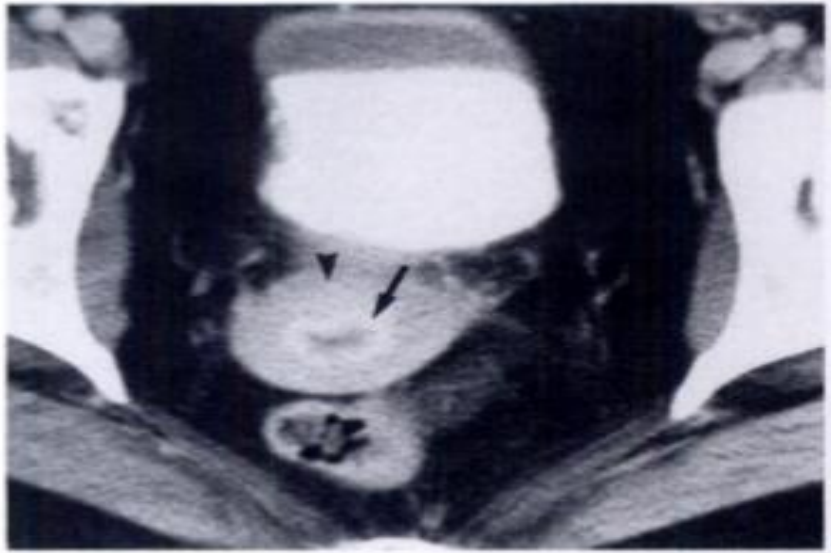


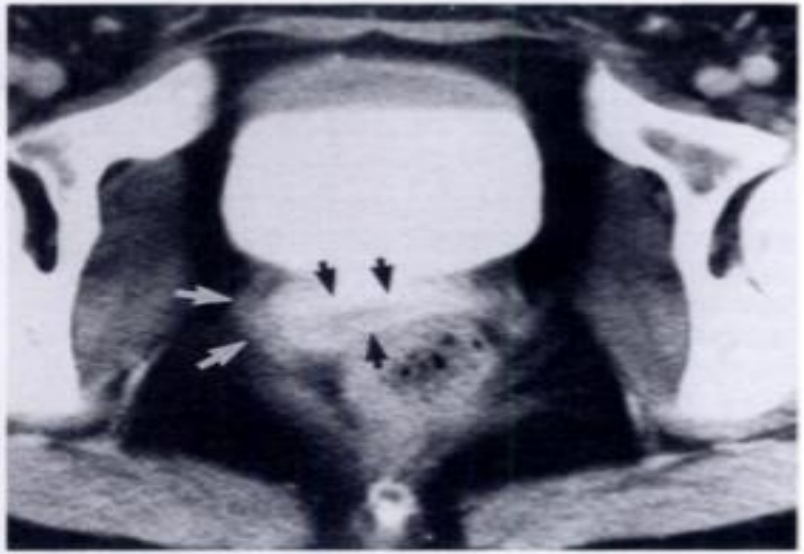


Dynamic Post contrast MRI



Post contrast CT

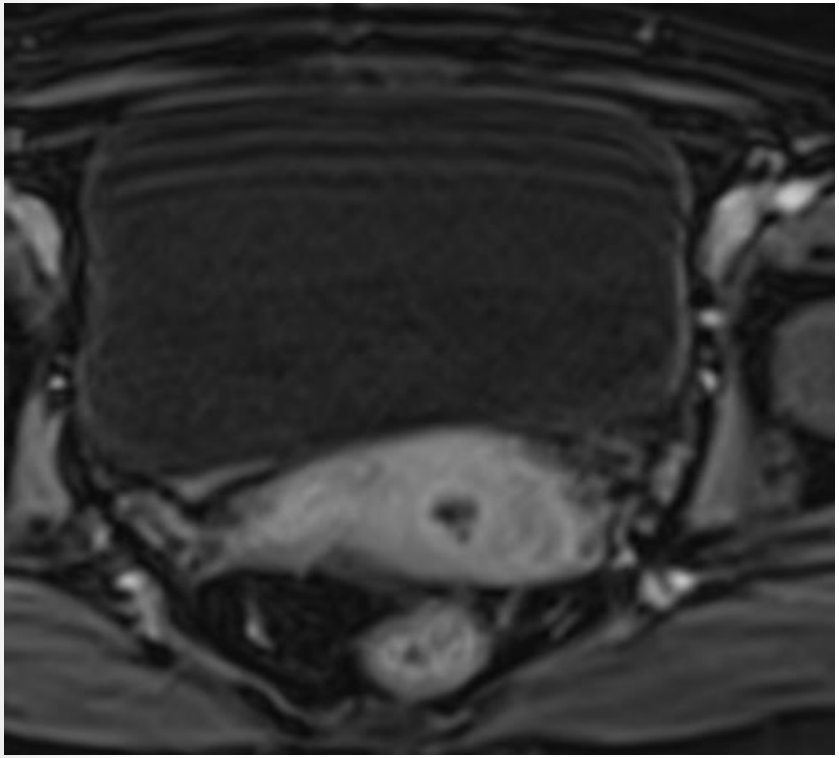




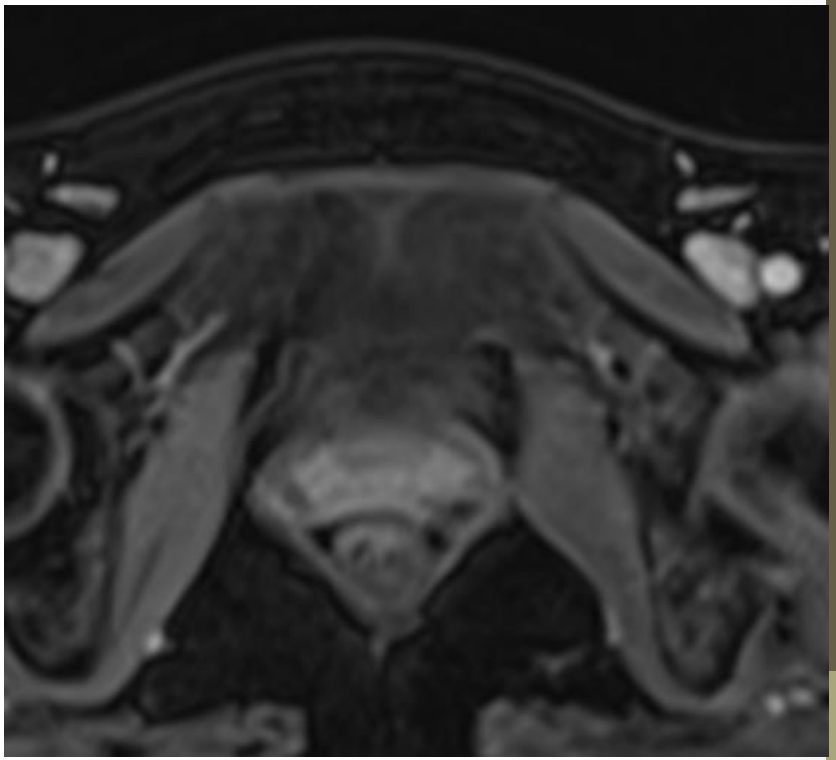
Cervix

Vagina

Post contrast MRI

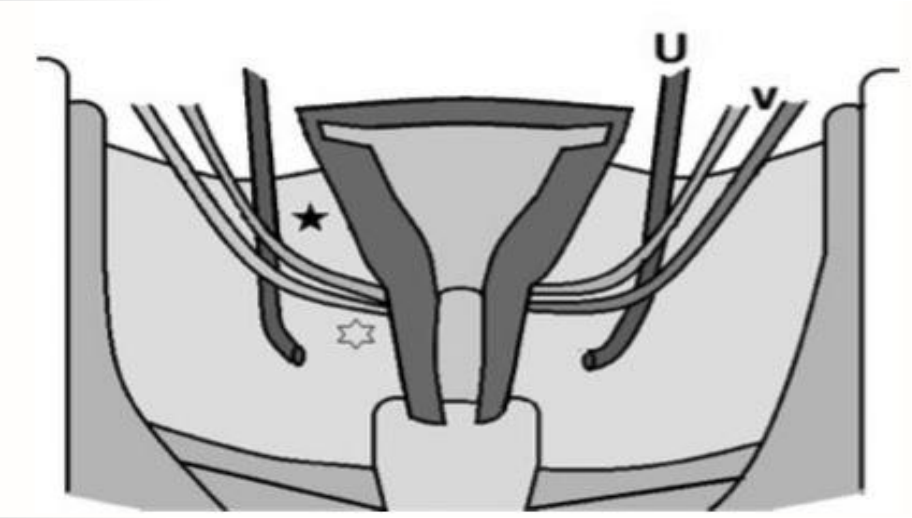


Cervix



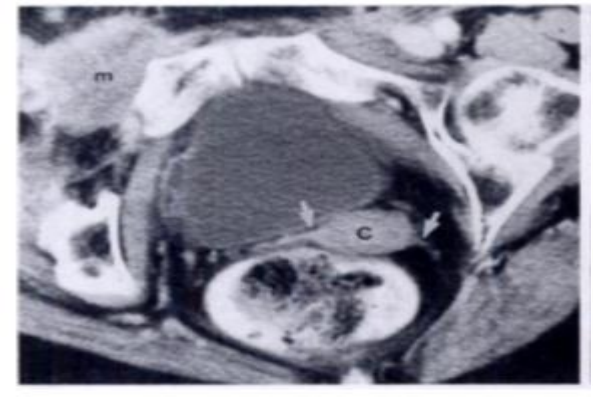
Vagina

PARAMETRIA

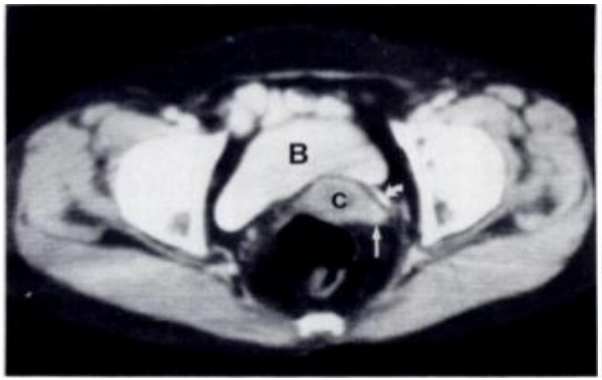


- Cellular connective tissue located between the leaves of the broad Ligament.
- Contents :Uterine artery ,ovarian ligament ,parauterine blood vessels and/or nerves, lymphatics, and fibrous tissue.
- The distal ureter is in the parametrium
- Seen as predominately fat density regions that outline the lateral margins of the uterus, cervix, and upper vagina and extend laterally toward the pelvic sidewalls

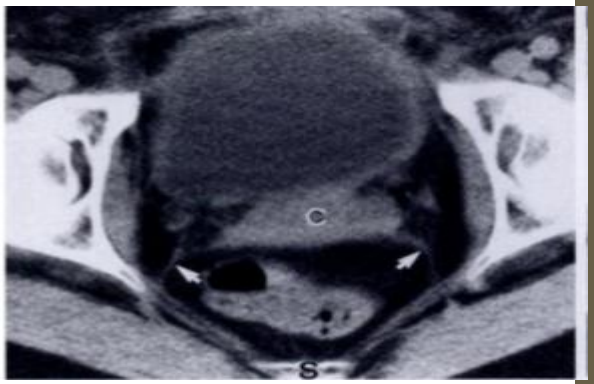
Parametrium: CT



Cardinal ligament

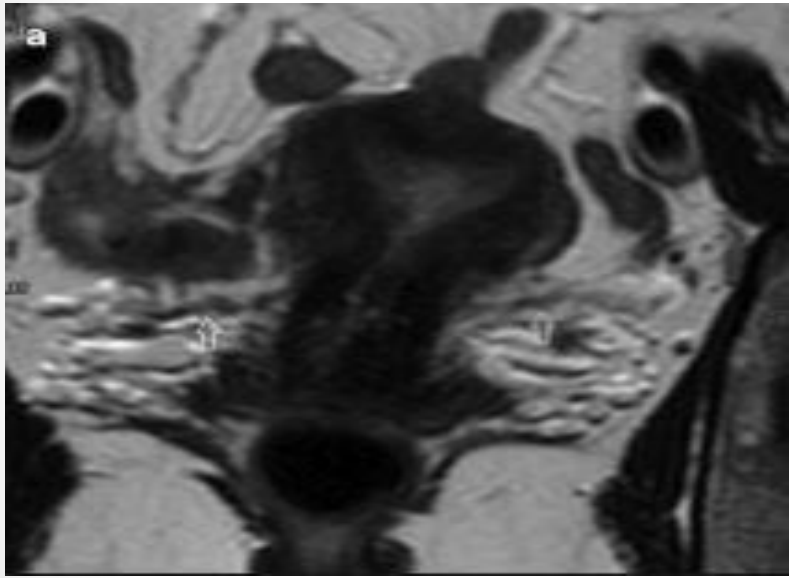


Ureter

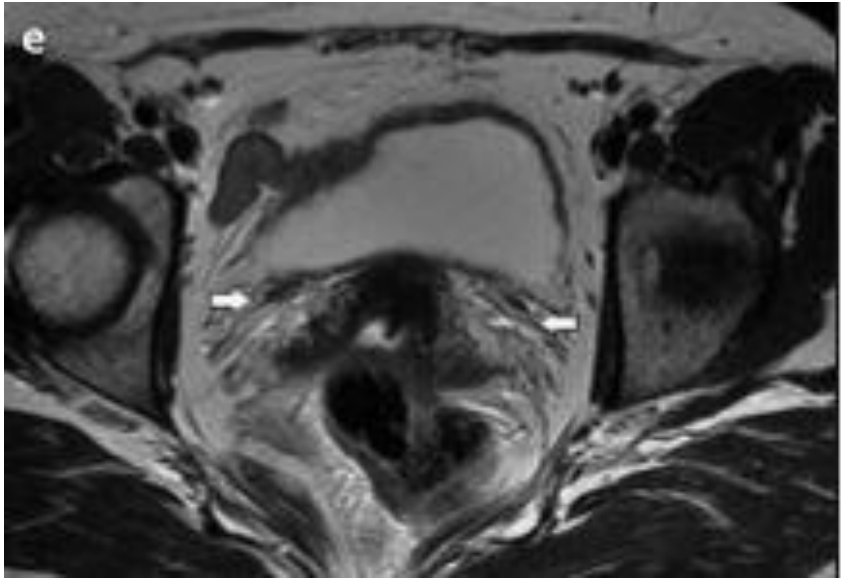


Uterosacral ligament

Parametrium: MRI



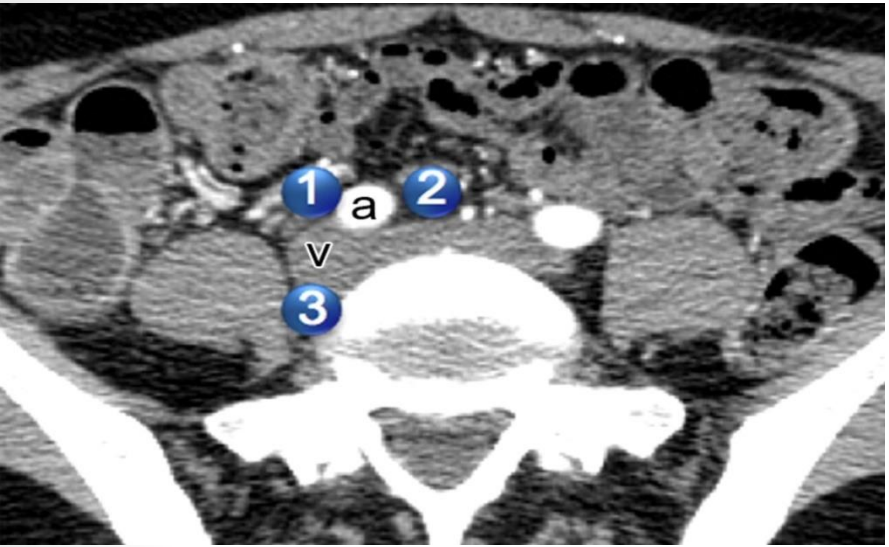
Coronal

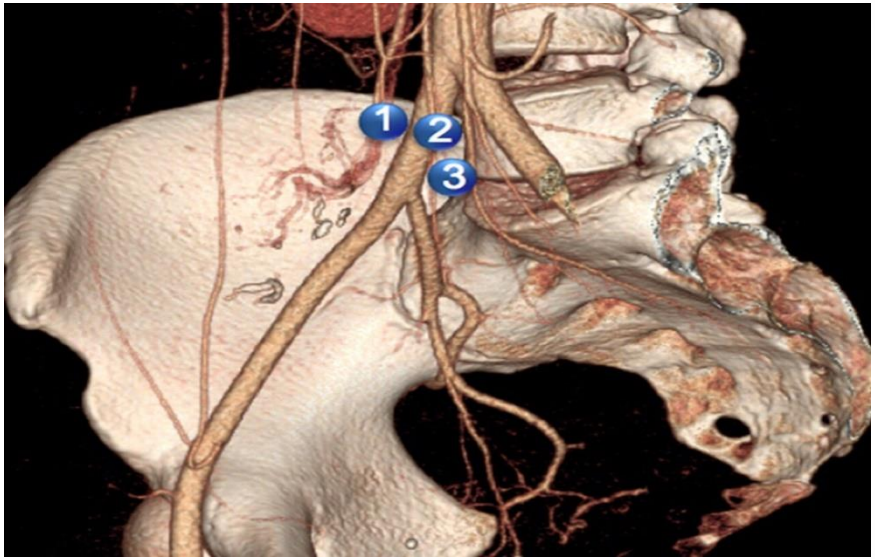


Axial

Nodal Anatomy

Common Iliac nodes

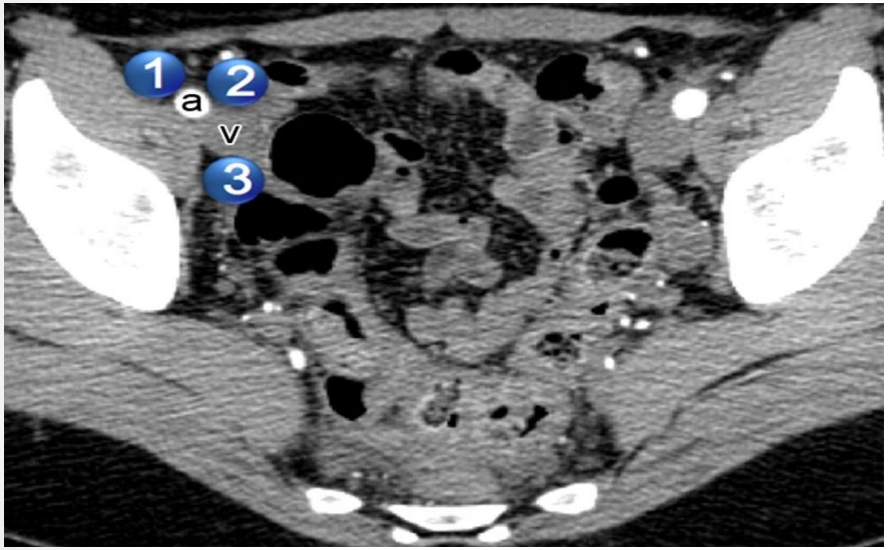




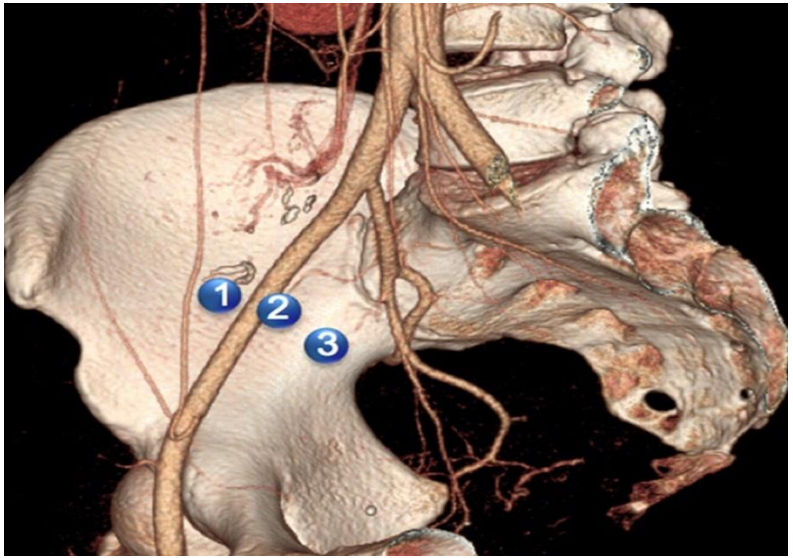
Axial CT

Volume rendered reformatted CT

External Iliac nodes

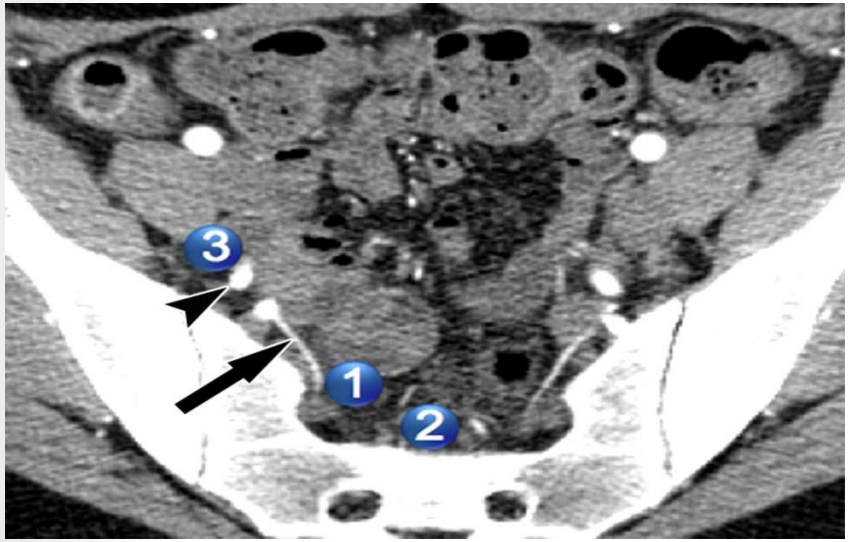


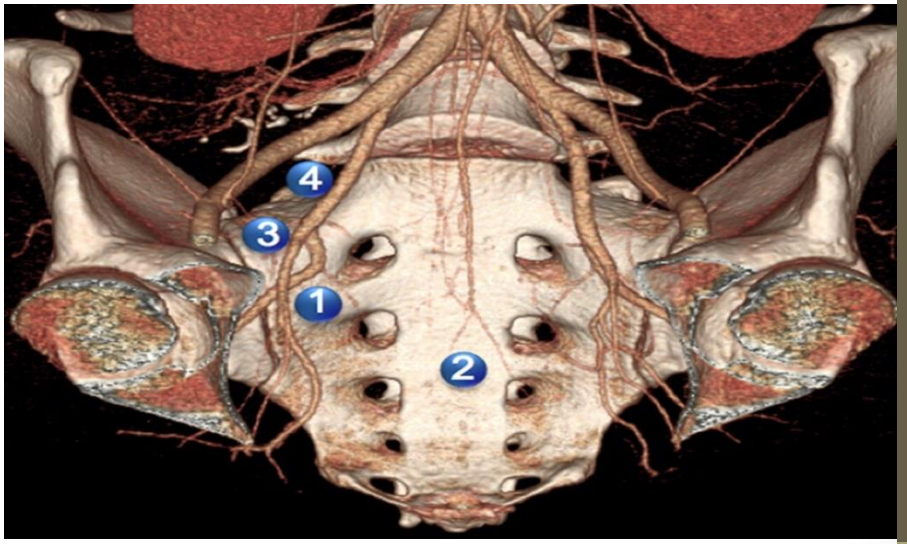
Axial CT



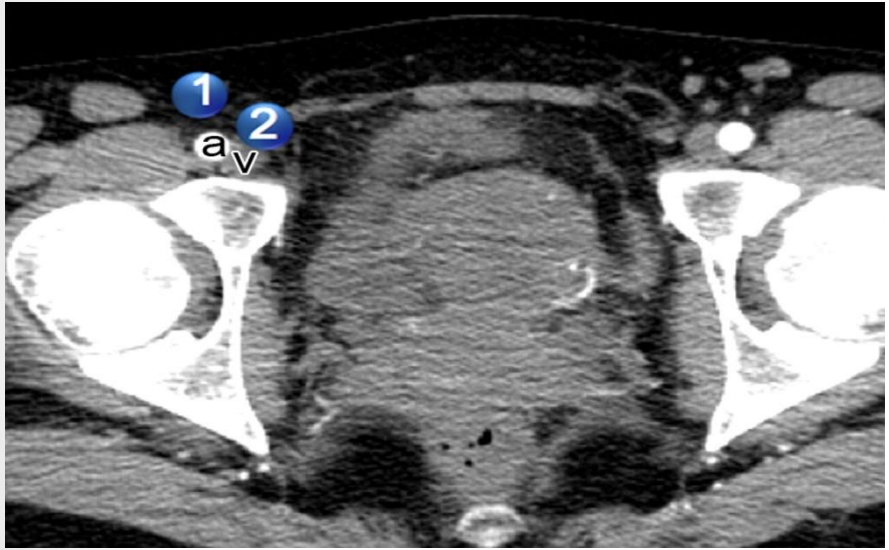
Volume rendered reformatted CT

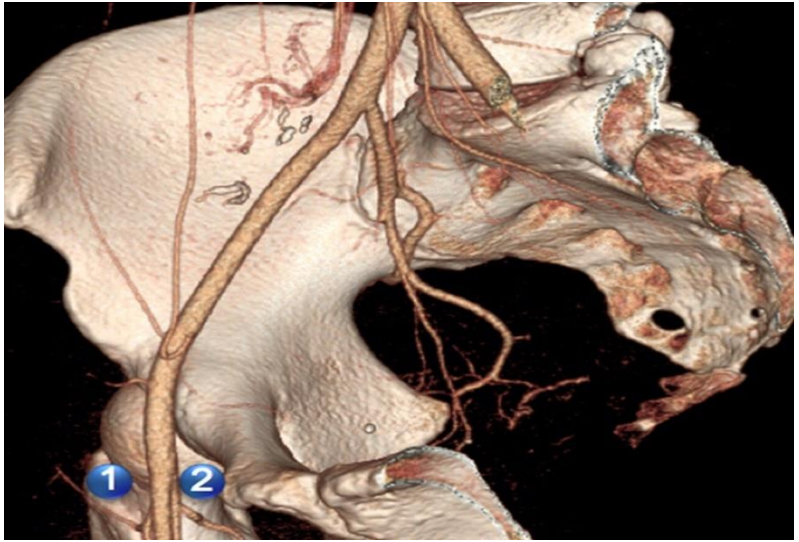
Internal Iliac nodes



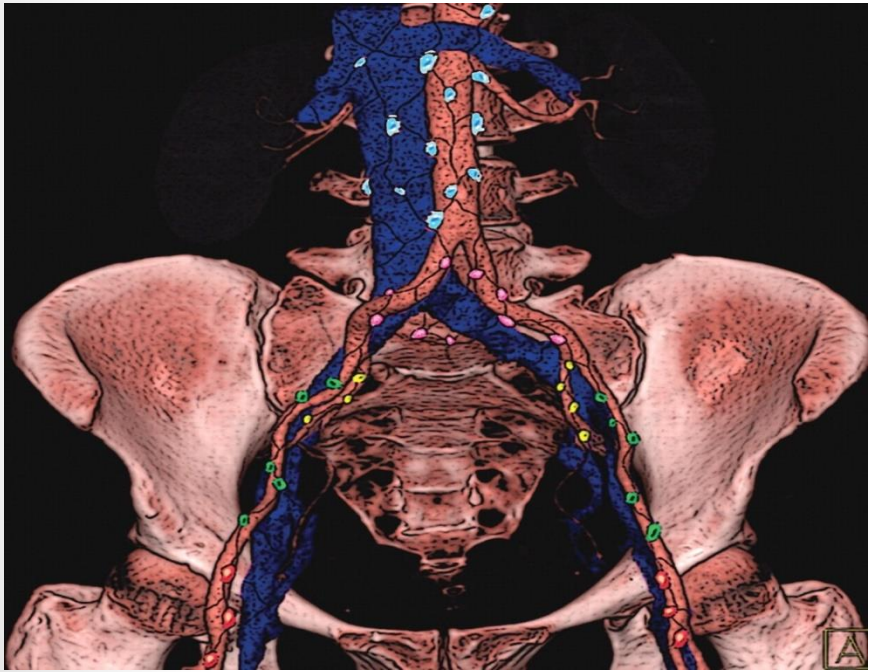


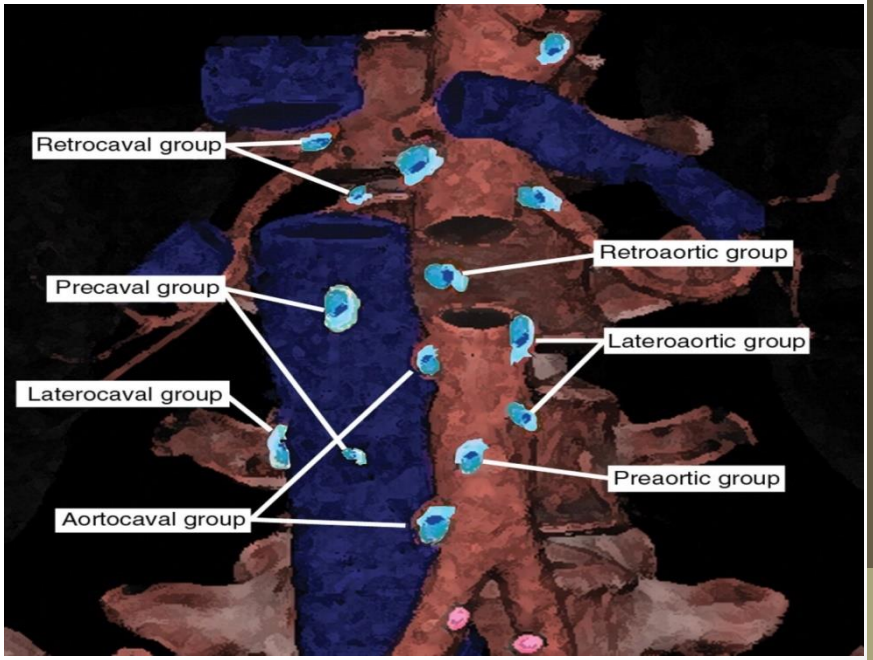
Inguinal nodes



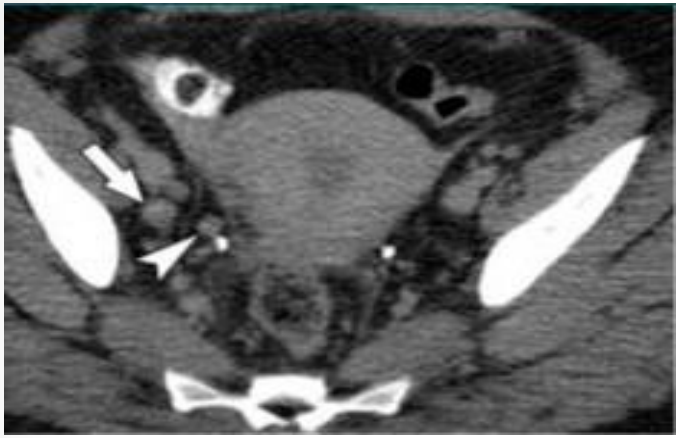


Pelvic & Para-aortic nodes

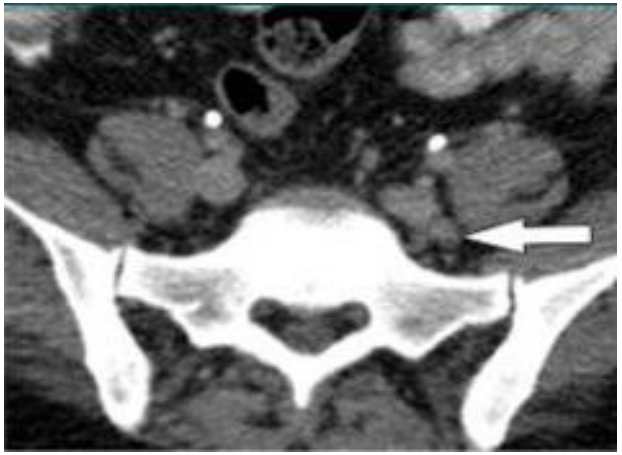




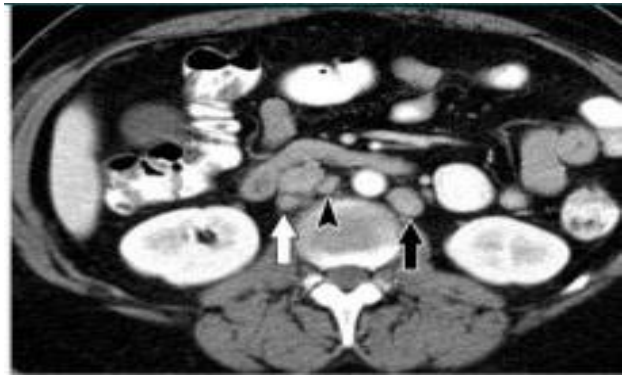
Enlarged Nodes: CT



Obturator & Parametrial

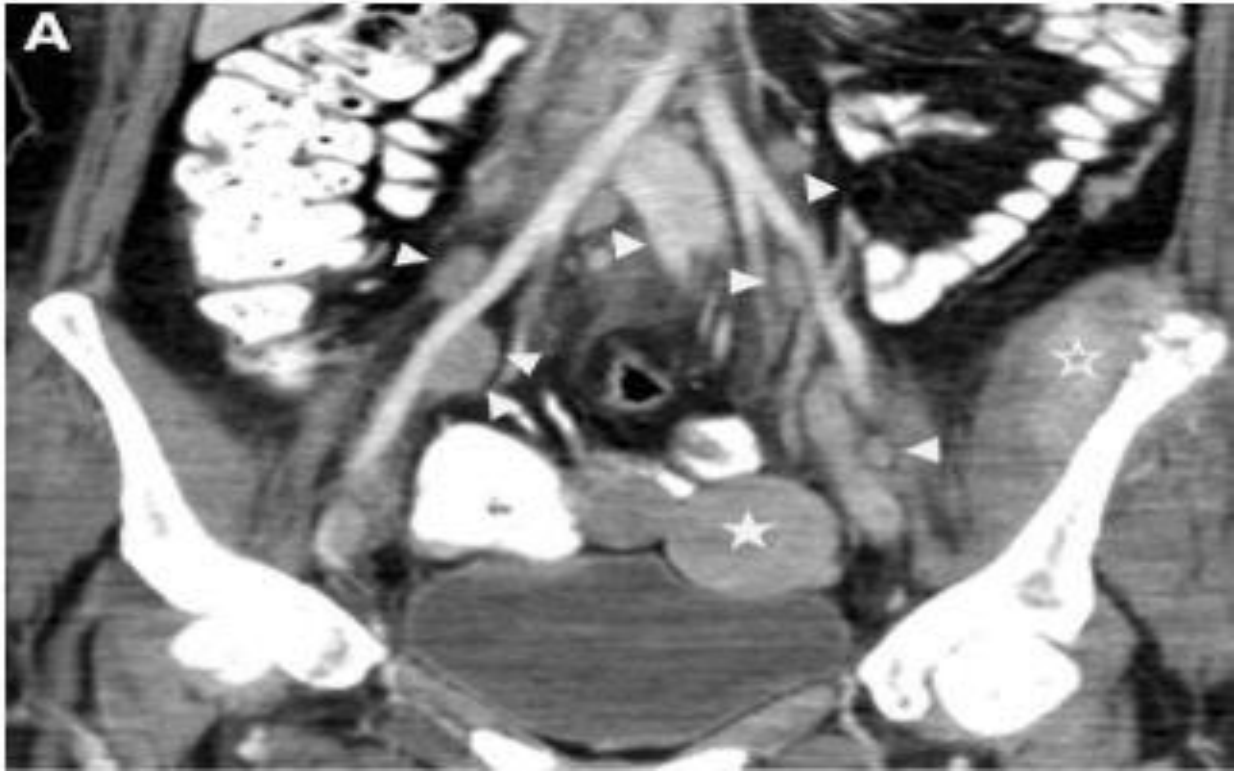


Middle common Iliac

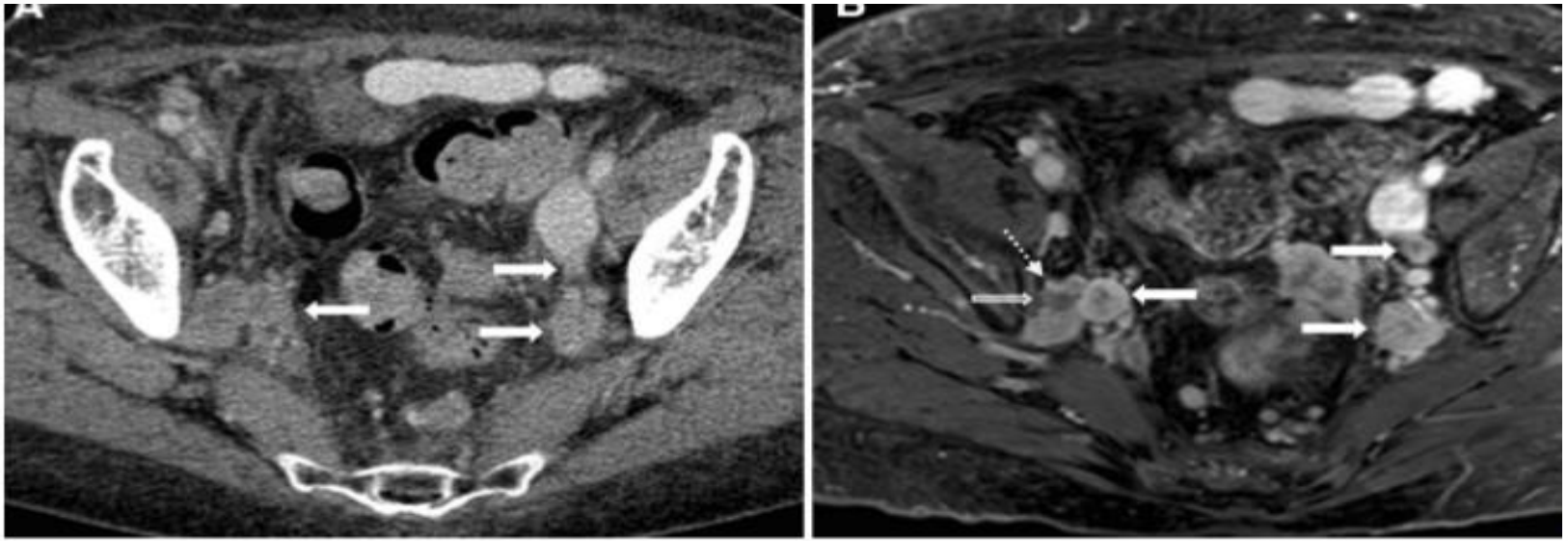


Para-aortic

Coronal CT: Nodes vs Vessels



MRI: Nodal architecture



CT

Advantages

- Adenopathy
- Defining Advanced disease
- Monitoring Distant metastases
- Planning placement of radiation ports
- Guiding percutaneous biopsies
- Electron density of tissues for dose calculation algorithms
- Image acquisition of less than 1 min in multislice CT
- Spatial relationship between brachytherapy , uterus and other organs visible.
- Organs at risk: CT and MRI equal

Limitations

- Ionizing radiation
- Normal organ contours, borders between organs and uterine parts not clearly visible even after oral, rectal, i.v contrast
- Tumour detection
- Overestimation of early parametrial spread
- Early involvement of bladder wall and vagina not reliable
- Radiation changes
- Cervix and residual disease
- Target volumes based contouring overestimated the contour width.

MRI

Advantages

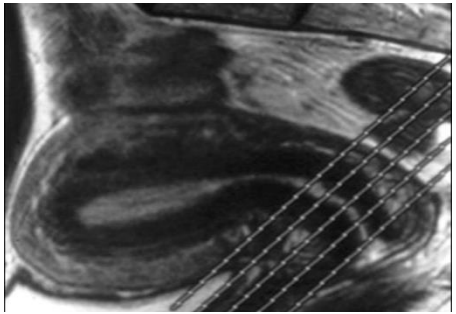
- Single best modality for evaluation of cervical cancer
- For staging, treatment planning and follow-up of cervical cancer
- High contrast resolution.
- Multiplanar capability
- Easy orientation for clinicians
- Tumor regression during radiotherapy

Limitations

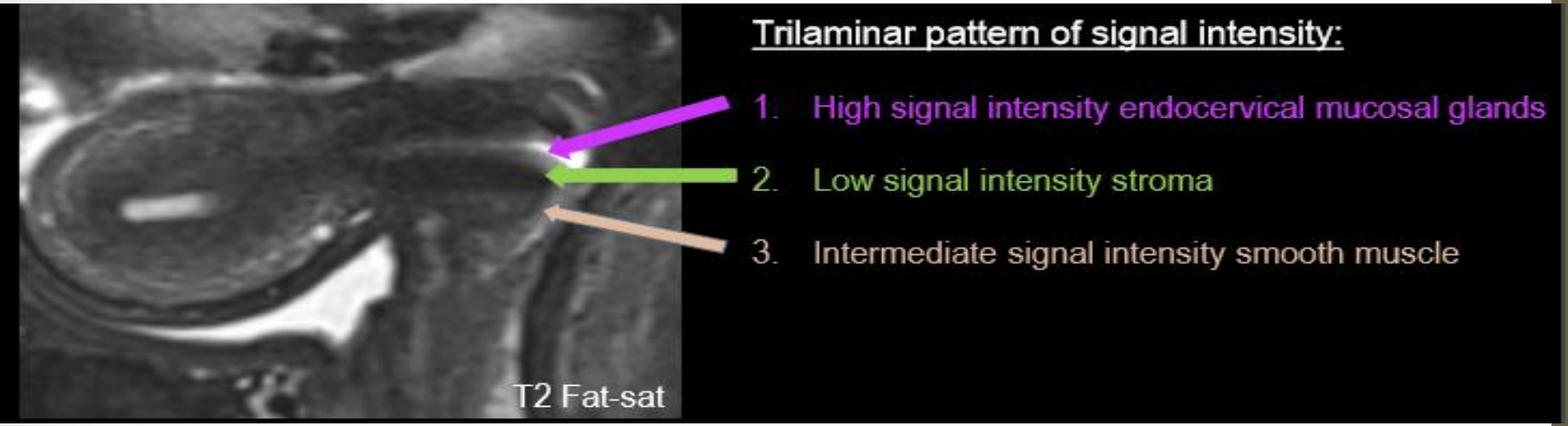
- Intrinsic spatial image distortion
- Missing electron density information
- Manual tissue attenuation coefficient to be put or presumption of homogeneous attenuation throughout

Technical considerations: MRI

- **High resolution T2-weighted imaging: mainstay for tumor detection**
- Oblique axial T2W images : perpendicular to the cervical long axis: Fat-suppressed sequences : evaluation of parametrial involvement.
- Complementary sequences : Post contrast T1 weighted , Diffusion weighted imaging
- Role of IV contrast :
  - Detection of small tumors
  - Improves accuracy of diagnosing bladder and rectal invasion.
  - Post-treatment : differentiate residual or recurrent tumor from radiation fibrosis.
  - Delineate complications of treatment, such as fistula

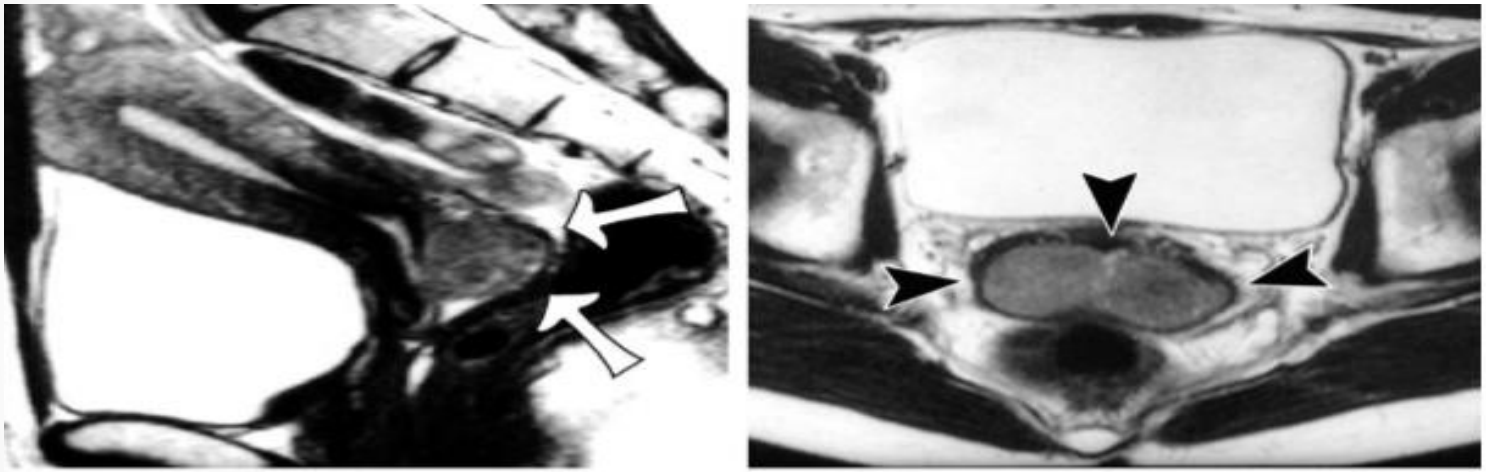


Zonal Anatomy: Cervix



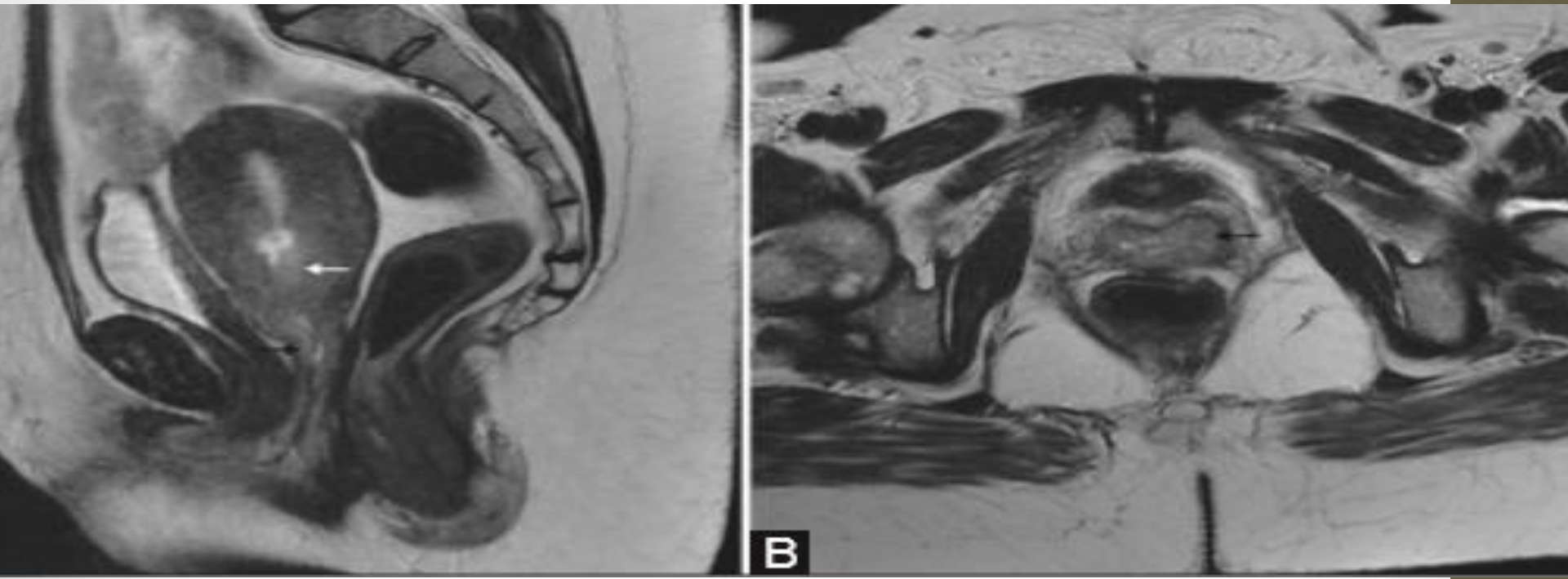
Cervical Cancer Staging: CT&MRI

Stage IB

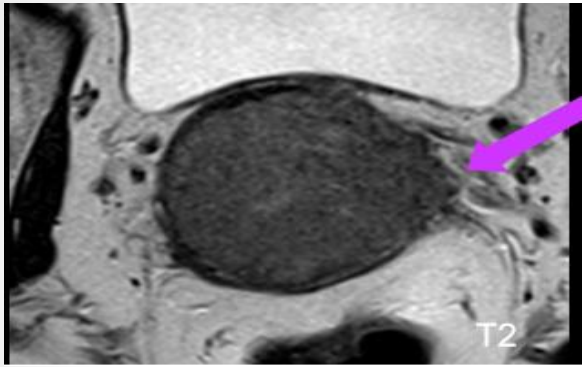


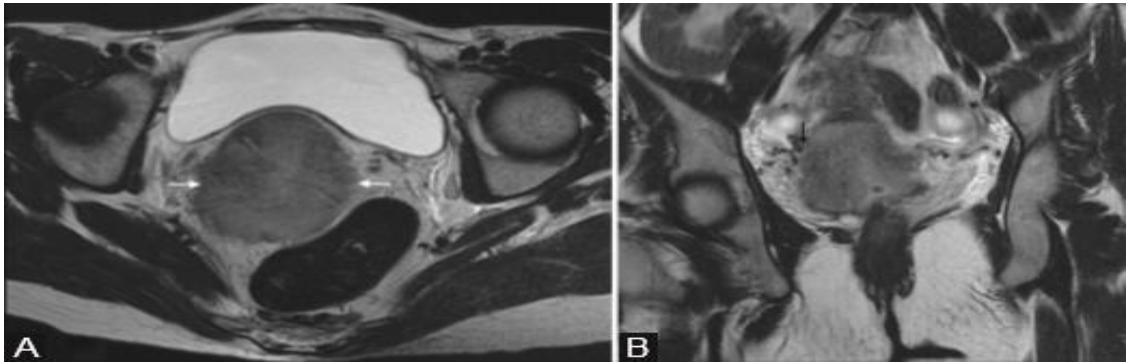
On T2-weighted images, cervical cancer : a relatively hyper-intense mass easily distinguishable from low signal-intensity cervical stroma.

Stage IIA



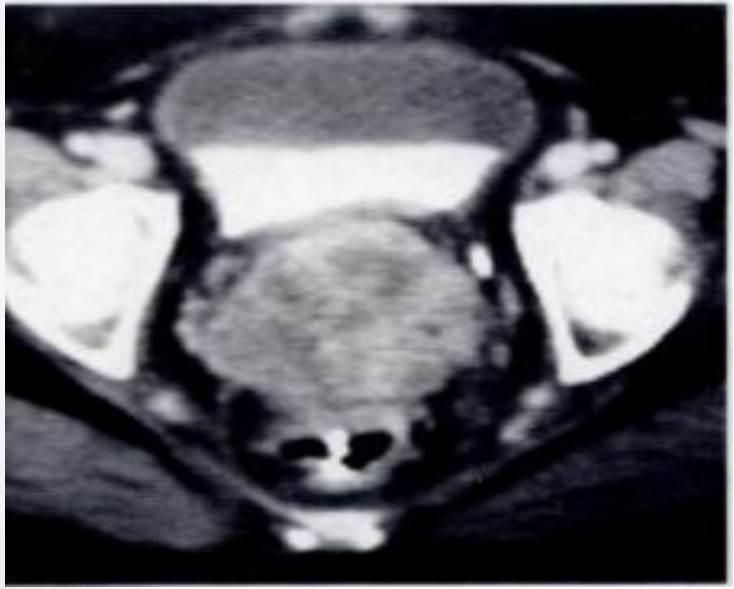
Stage IIB: MRI

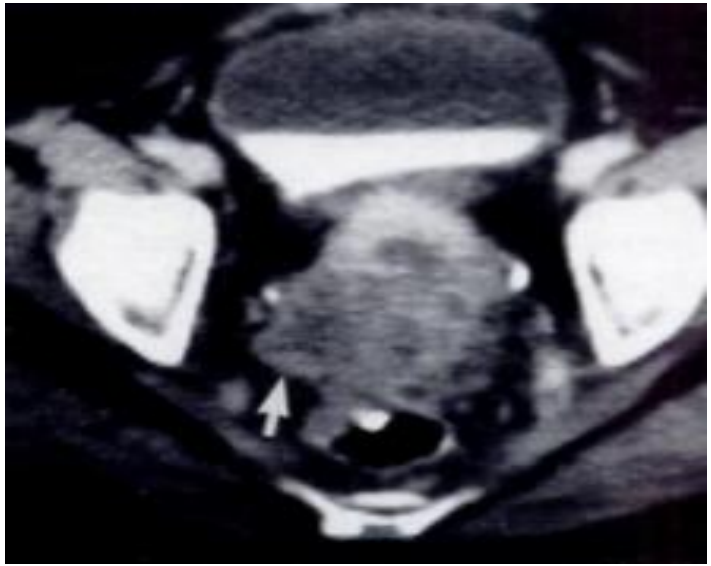




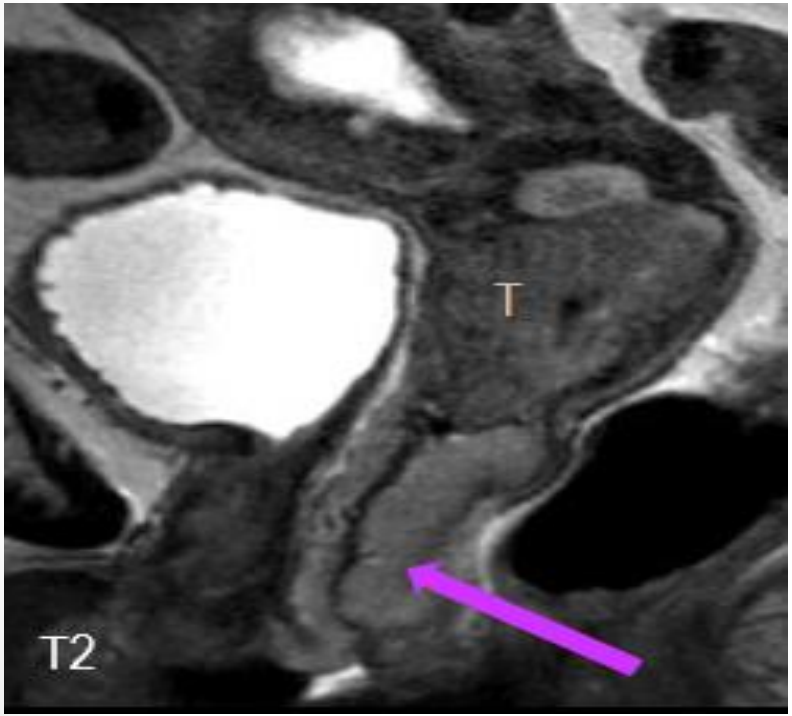
Complete disruption of the cervical stroma with nodular or irregular tumor signal intensity extending into the parametrium is a reliable sign of invasion

Stage IIB: CT



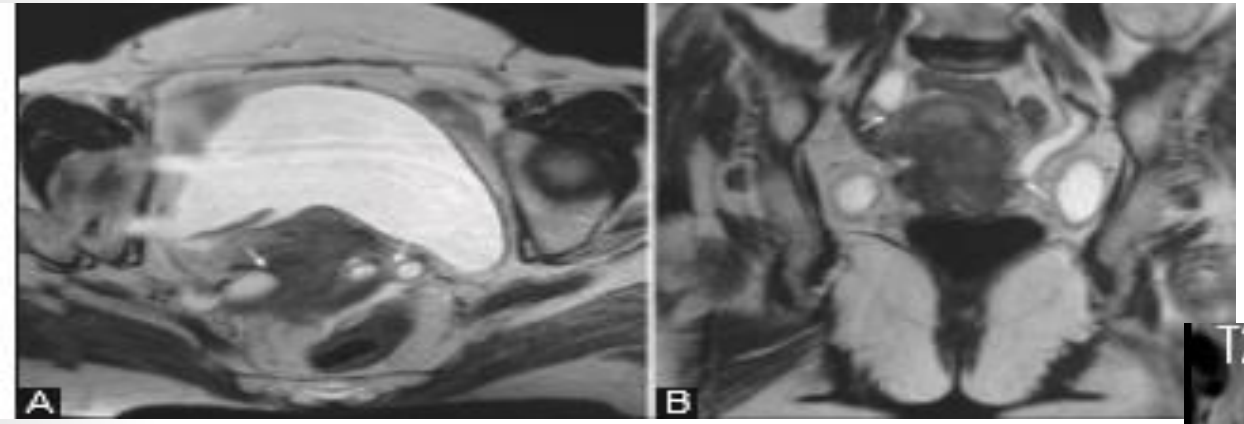


Stage III A

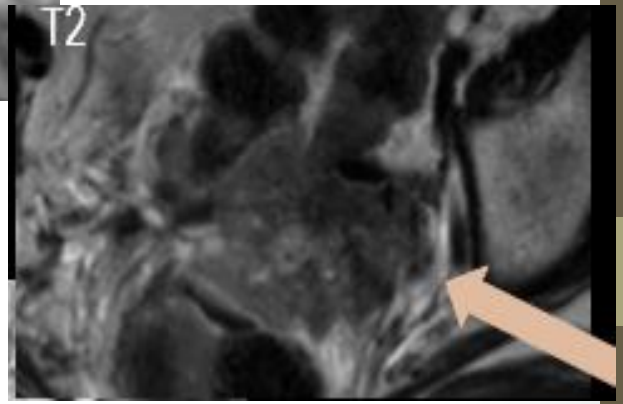


T2 sagittal image demonstrates cervical tumor (T) with invasion of the lower one-third of the vagina (arrow).

Stage IIIB

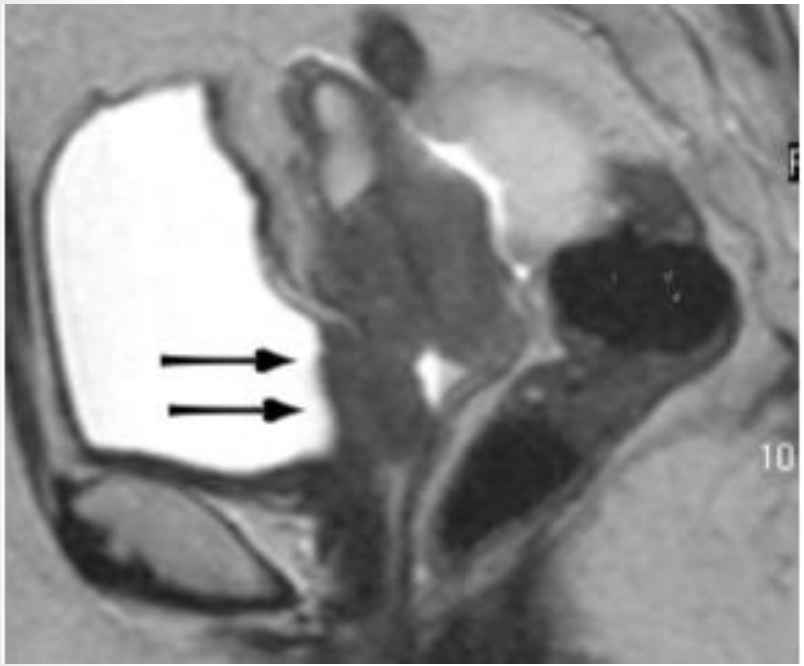


Ureter involvement



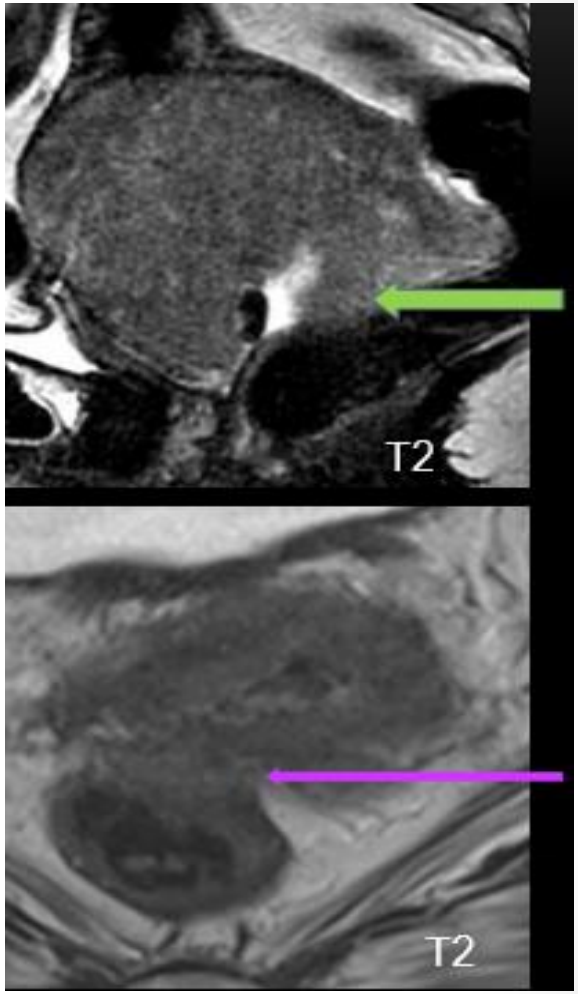
Side wall involvement

STAGE IV A

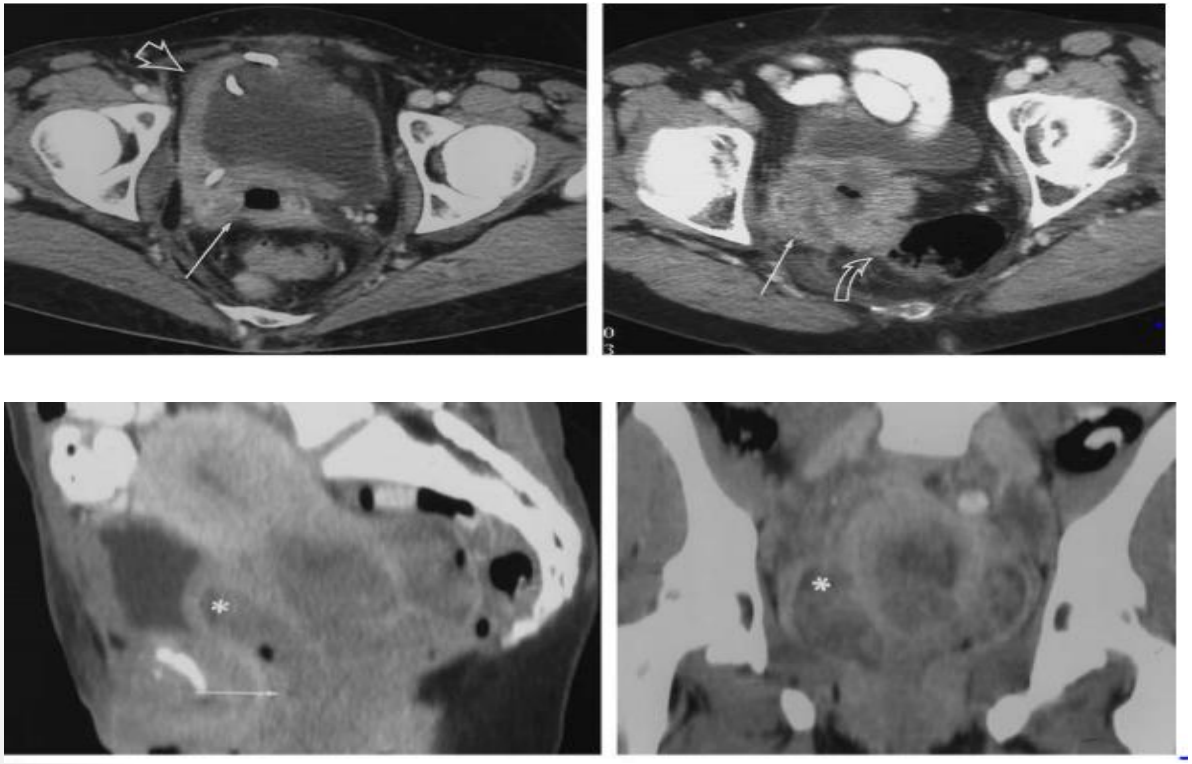


Bladder invasion

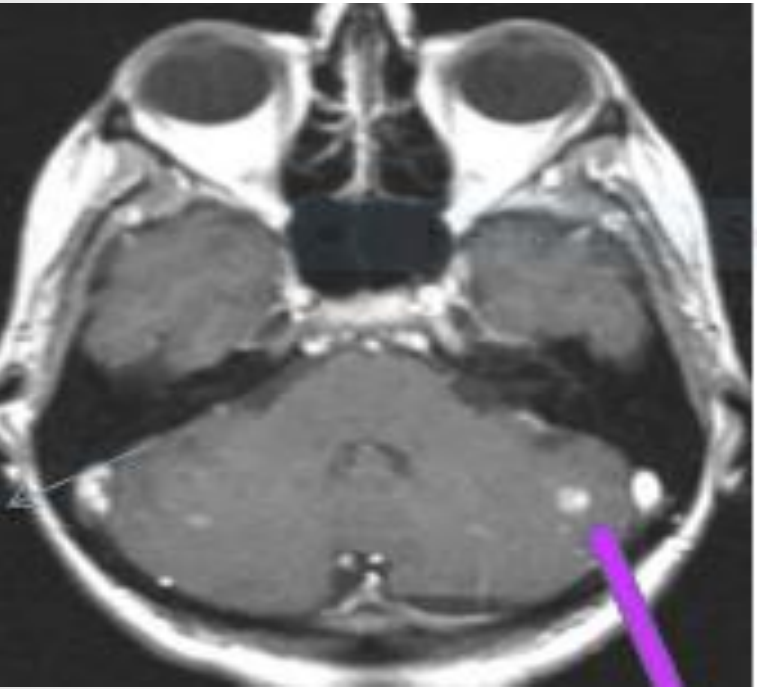
Rectal invasion



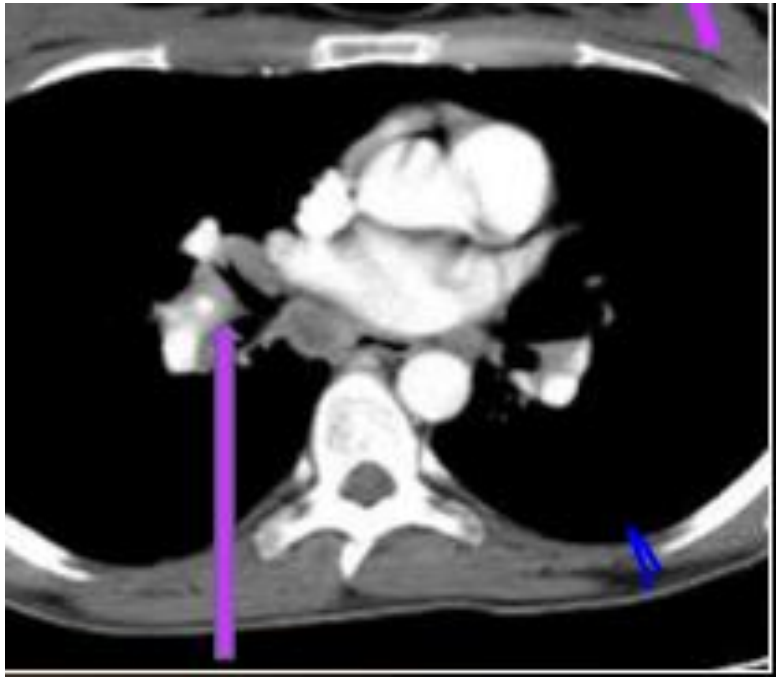
Stage III & IV :CT



Stage IVB



Brain metastases



Mediastinal Nodes

CT VS MRI

	General characteristics					
	Soft tissue depiction	Image acquisition	Contrast media	Multiplanar imaging	Radiation exposure	Scanning time
MRI	Superior quality on T2-weighted sequences	Specific protocols required	Not obligatory needed	without reconstruction	No	Long
CT	Inferior quality	Specific protocols required	Recommended	only with reconstruction	Yes	Short

	Diagnostic scan					
	Tumor detection	Parametrial invasion	Invasion of organs	Invasion of vagina	LN status	Recurrence detection
MRI	Estimation of dimensions within 0.5 cm compared to pathology specimen. Detection of endocervical growth and uterine corpus invasion is possible	High accuracy for: –Distinction between stromal and parametrial invasion –Estimation of degree of parametrial invasion	High accuracy in prediction of infiltration of surrounding organs	High accuracy in predicting vaginal invasion, if vaginal contrast is used (e.g., ultrasound gel)	CT and MRI have similar inaccuracy in detecting LN metastases	Dynamic contrast-enhanced MRI enables differentiating tumor recurrence from radiation fibrosis
CT	Inaccurate estimation of tumor dimensions even with contrast enhancement and inability to detect uterine corpus invasion	Low accuracy in distinction between parametrial tumor spread and normal parametrial tissue	Early invasion of bladder and rectum is not reliably detectable	Low accuracy in predicting vaginal infiltration, especially at early stages	CT and MRI have similar accuracy in detecting LN metastases	CT is of low predictive value for differentiation between radiation fibrosis and recurrence

Thank you

IMAGING PATHOLOGY OF CERVICAL CANCER

Clinical drawings, US, CT, MRI, PET-CT..

At the time of Diagnosis/ Brachytherapy

Umesh Mahantshetty

Professor,

Department of Radiation Oncology

&

GYN Disease Management Group Member

Tata Memorial Hospital, Mumbai, India

IMAGING PATHOLOGY OF CERVICAL CANCER

RADIATION ONCOLOGIST'S PERSPECTIVE

- Clinical Examination
- US
- CT
- MR
- PET-CT

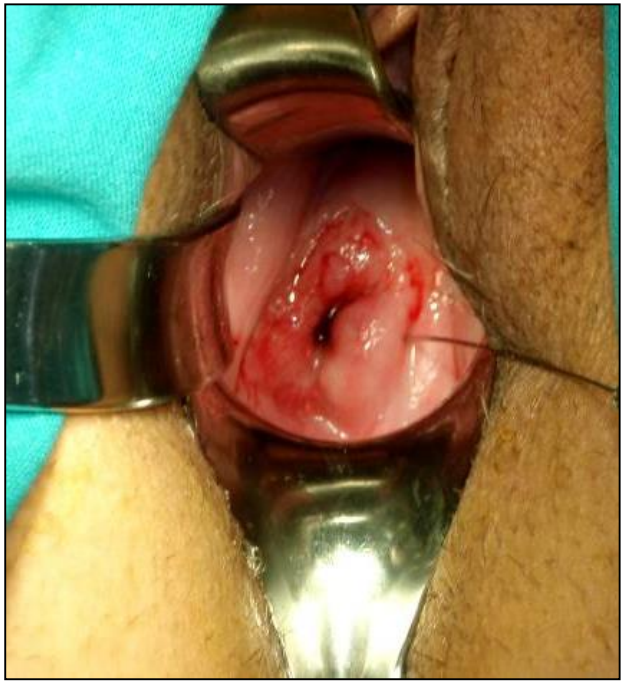
At Brachytherapy ……. Prof. Richard Poetter

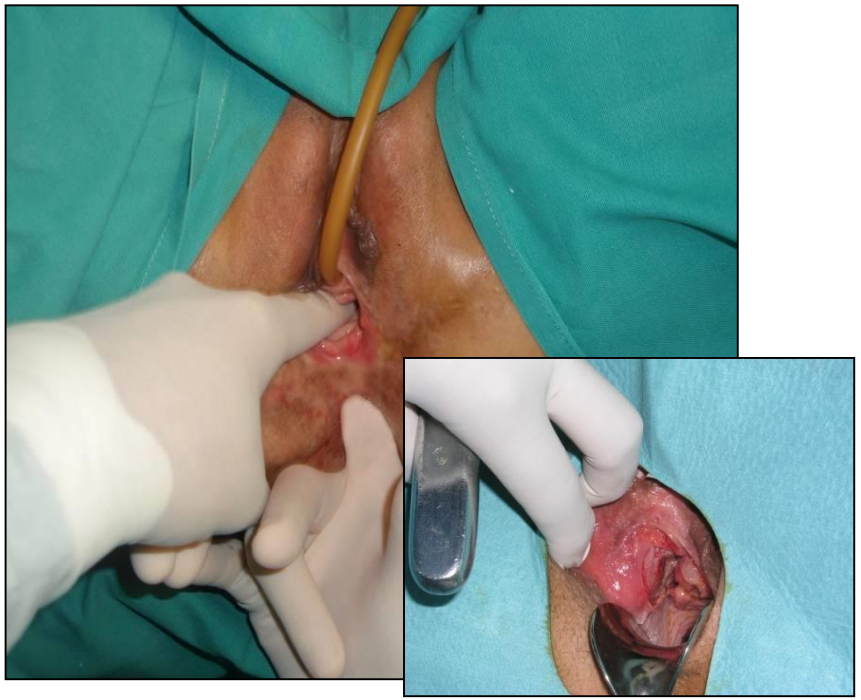
Basic imaging level

Clinical Examination : Inspection & Palpation

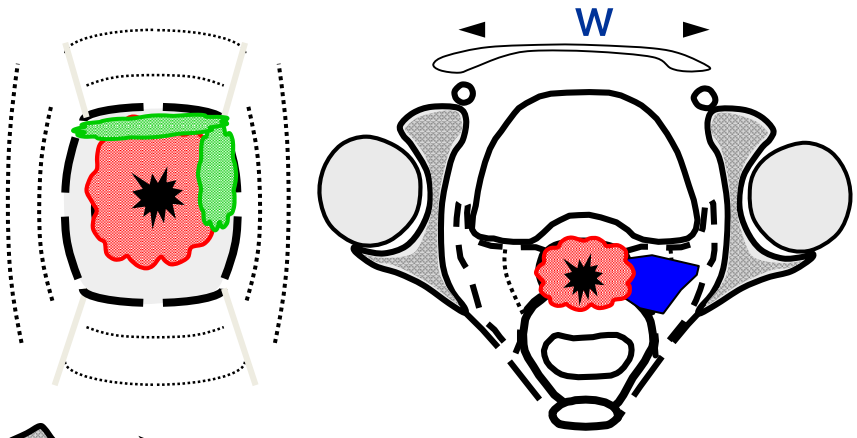
Imaging device: Eye & Finger

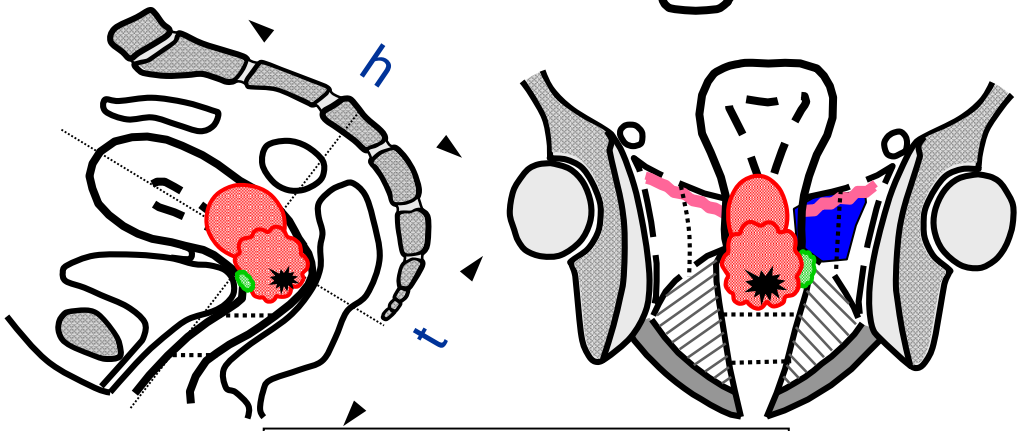
- *Technology widely available*
- *Low cost*
- *Largest amount of experience accumulated*
- *Superior to US, CT, MRI, PET CT for portio, vagina, vulva, skin...*





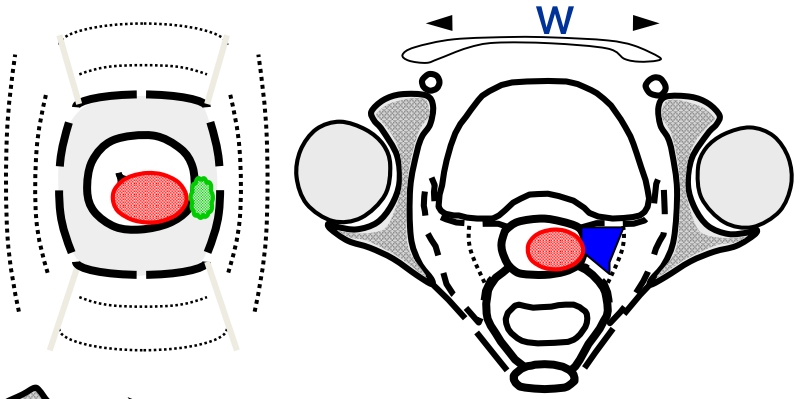
Documentation by Clinical Drawings

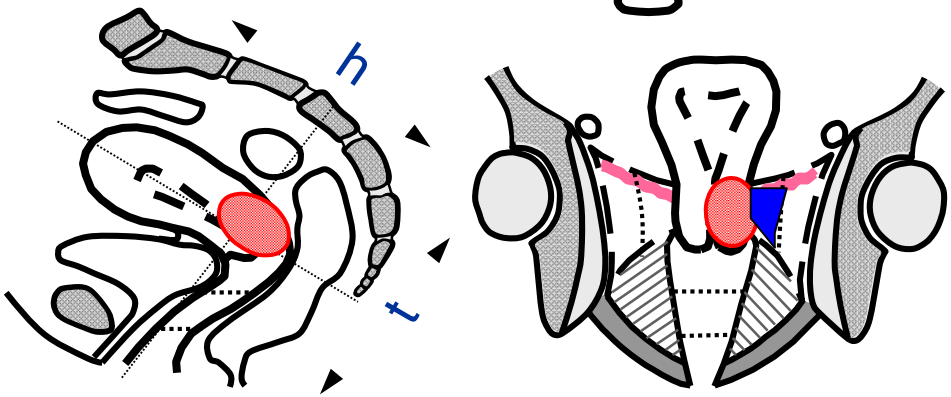




At Diagnosis

At Brachytherapy





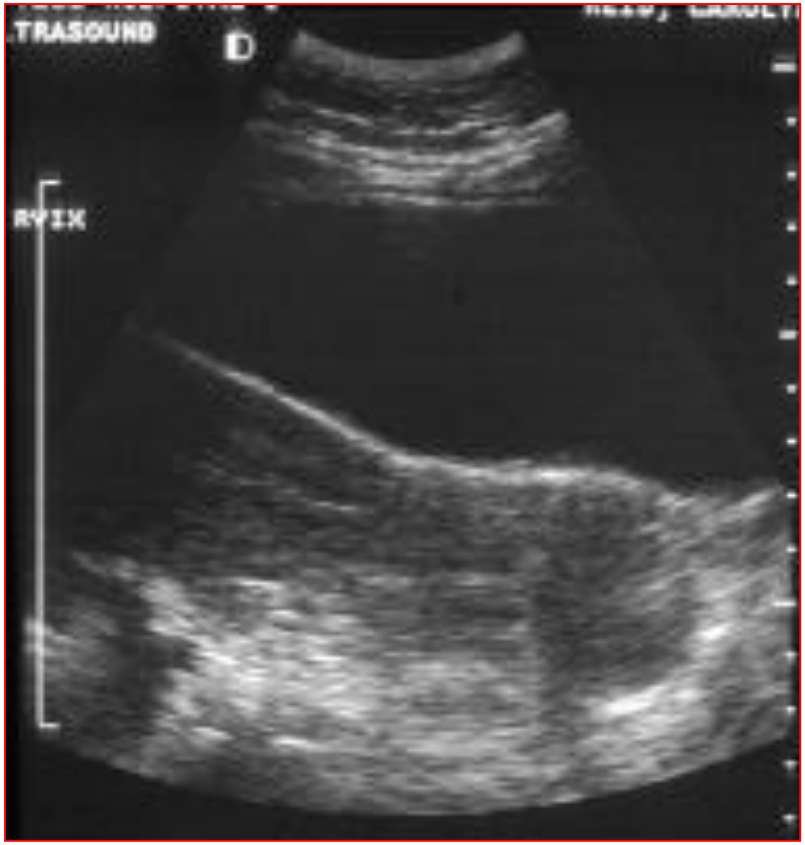
- Complimentary to other imaging modalities

Ultrasonography (US)
Trans-abdominal, trans-vaginal & trans-rectal US

- Early tumors (stage- I & II) not detected by US

Signs

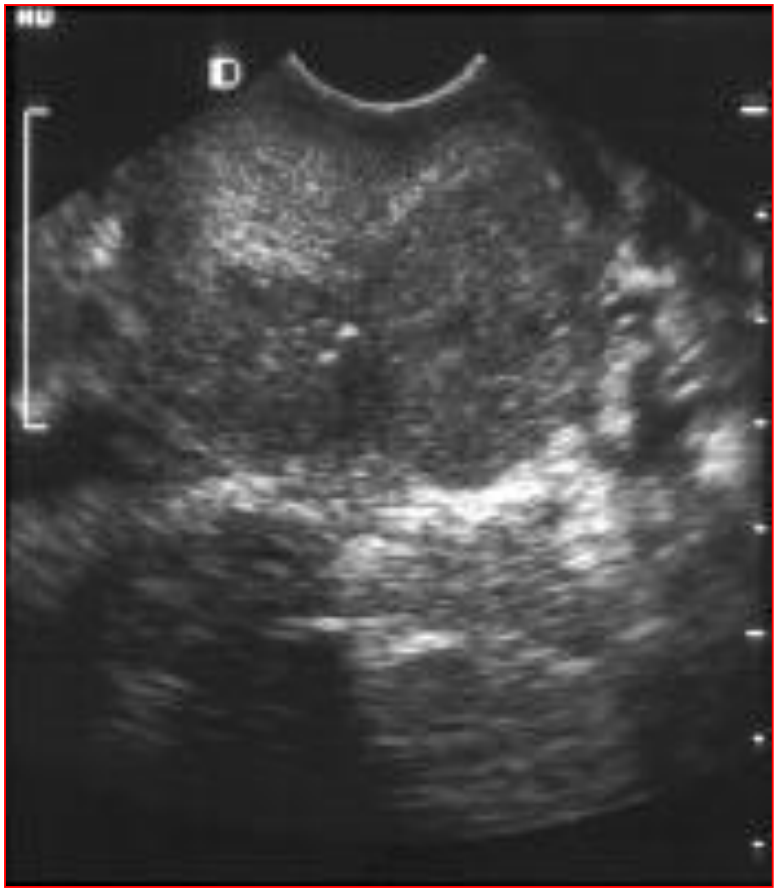
- Enlargement of cervix
- Irregularity of cervical outline
- Haemato/ Pyometra
- Hydroureteronephrosis / bladder invasion



LIMITATIONS OF US

- OPERATOR DEPENDENT

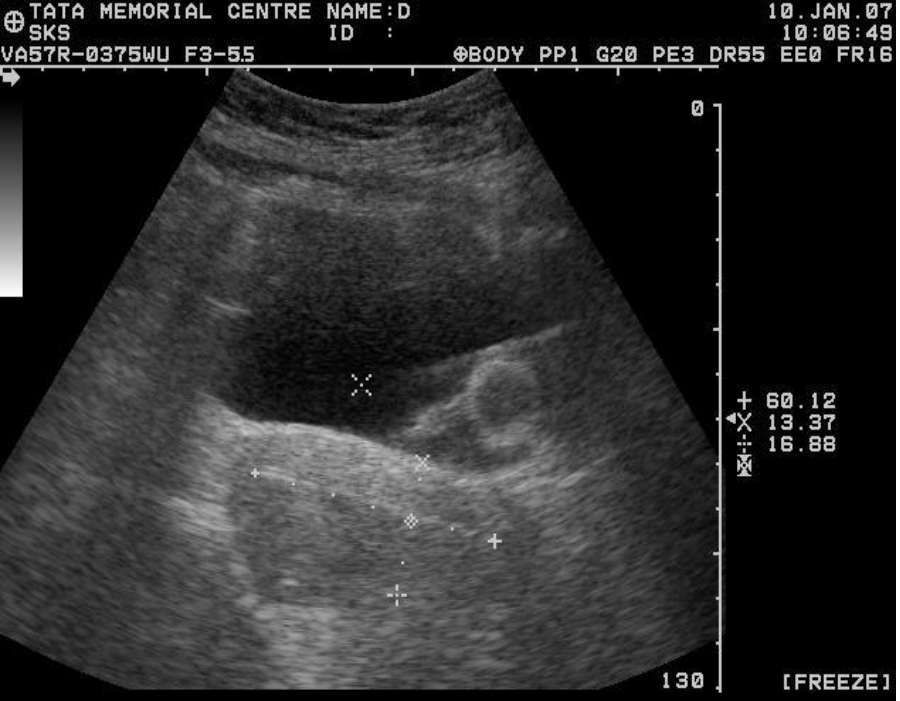
- INTER OBSERVER VARIATION

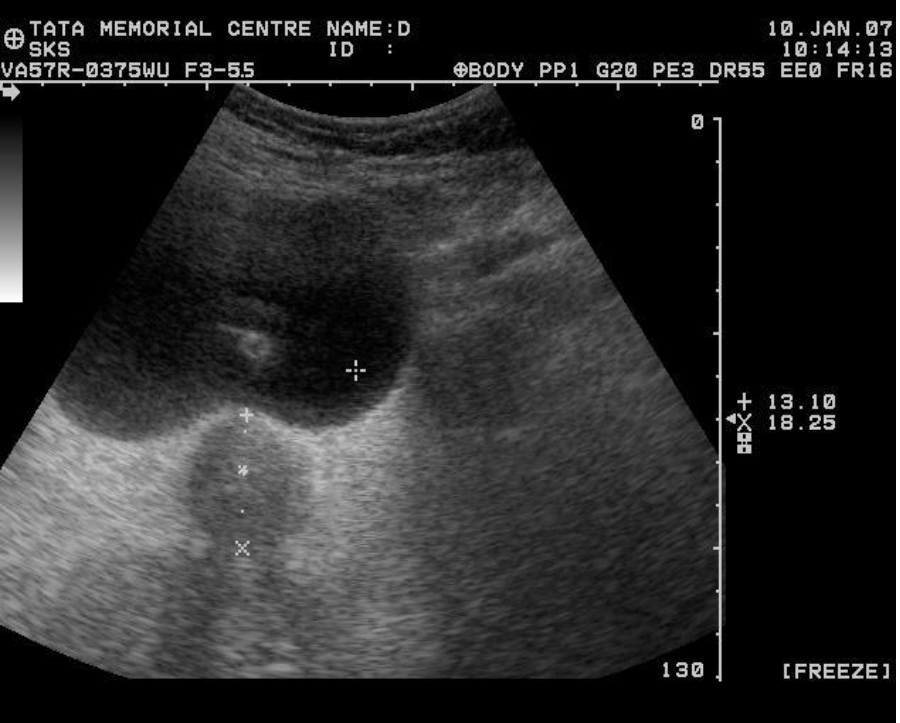


US IN BT

- REAL TIME IMAGING TO PREVENT PERFORATIONS

- GUIDE BT APPLICATION



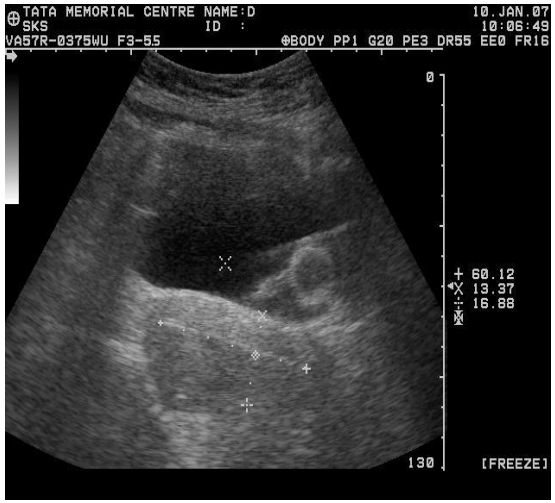


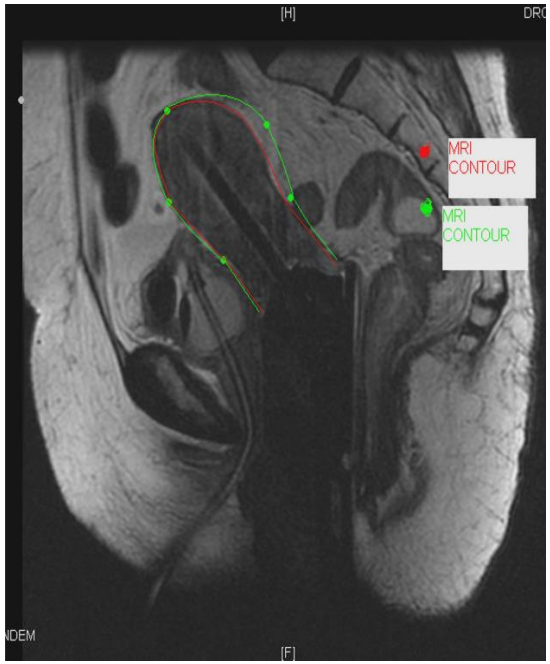
US in Cx Brachytherapy

- Ultrasound guided insertion of central tandem
  - Tandem length
  - Retroverted uterus
  - False passage
- Ultrasound based planning
  - Uterine wall thickness
  - Bladder points
  - Rectal points
- Drawbacks
  - Coronal imaging not available
  - Posterior uterine surface not visible well

TAUS and MRI correlation (TMH data)

- 32 Applications with MRI Compatible Applicator
- Anterior Reference Points : 96 %
- Posterior Reference Points : 72 %
- Magnitude of Variation (>15%) : < 8%





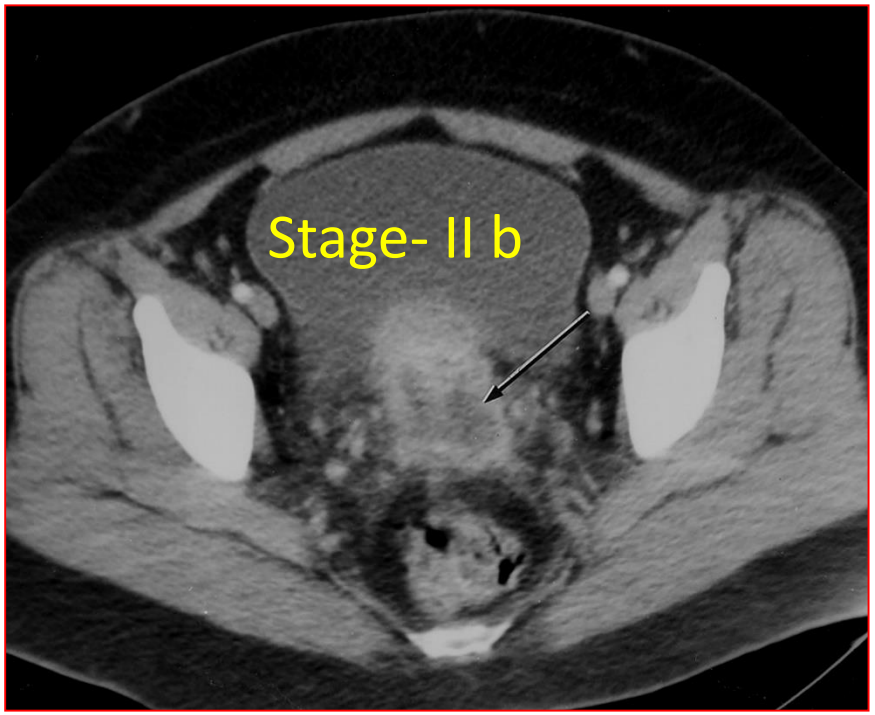
Significant Correlation between the USG and MRI Reference Points

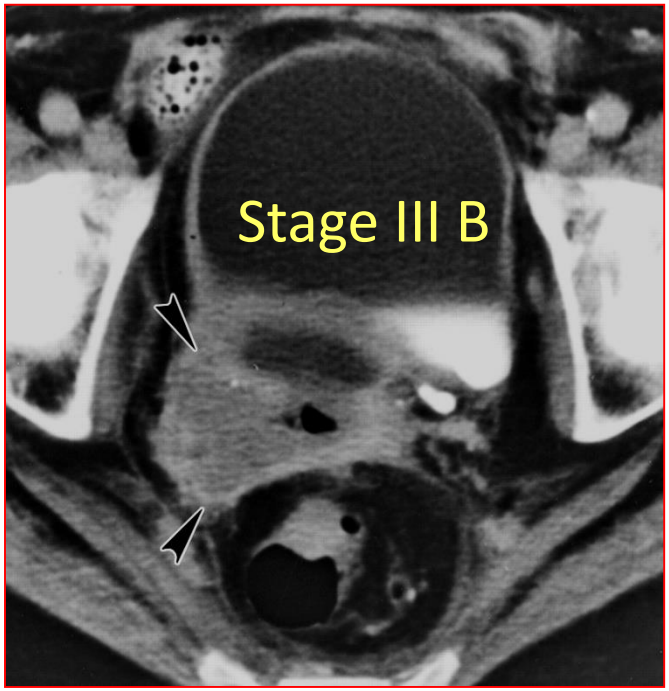
Suggest : Use of USG for ICA Planning (21/2 D Planning)

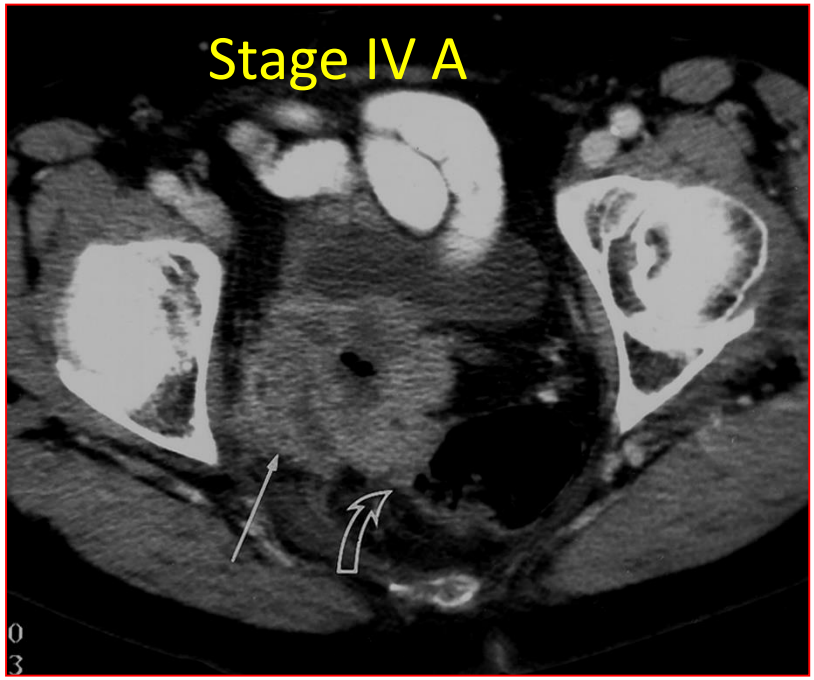
Mahantshetty et al. Rad. Onc. Aug. 2011

CT

- Visualization of small primary tumor limited
- Currently used in staging of advanced disease (MR superior)
- Guide biopsy of nodes
- Plan RT ports

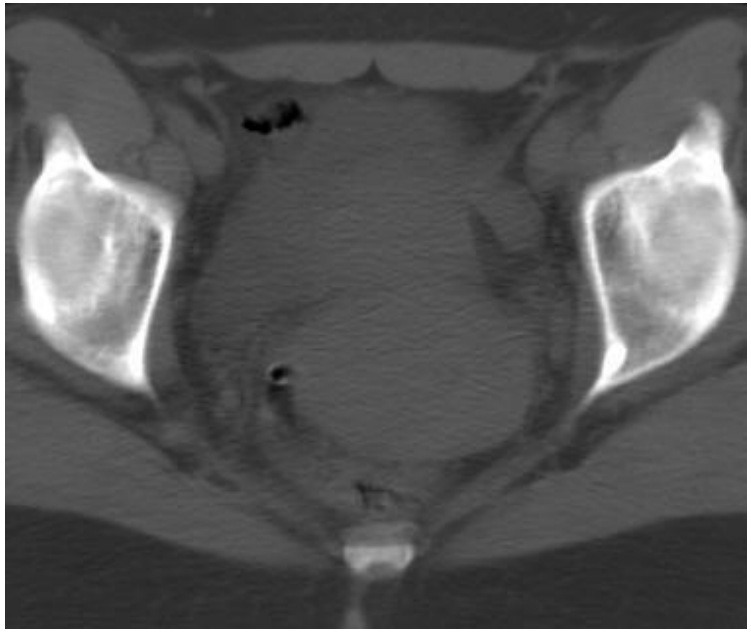

Stage- II b


Stage III B


Stage IV A

Computed Tomography

Non-enhanced CT simulator images



Advantages

- Availability
- Cost
- Good depiction: organs at risk
- Infrastructure & personnel: less demanding than MRI

Limitations

- Low soft tissue depiction quality
- Poor GTV & CTV depiction

CT for EBRT- Image acquisition

What are the key issues for image acquisition when using CT?

- Administration of IV contrast

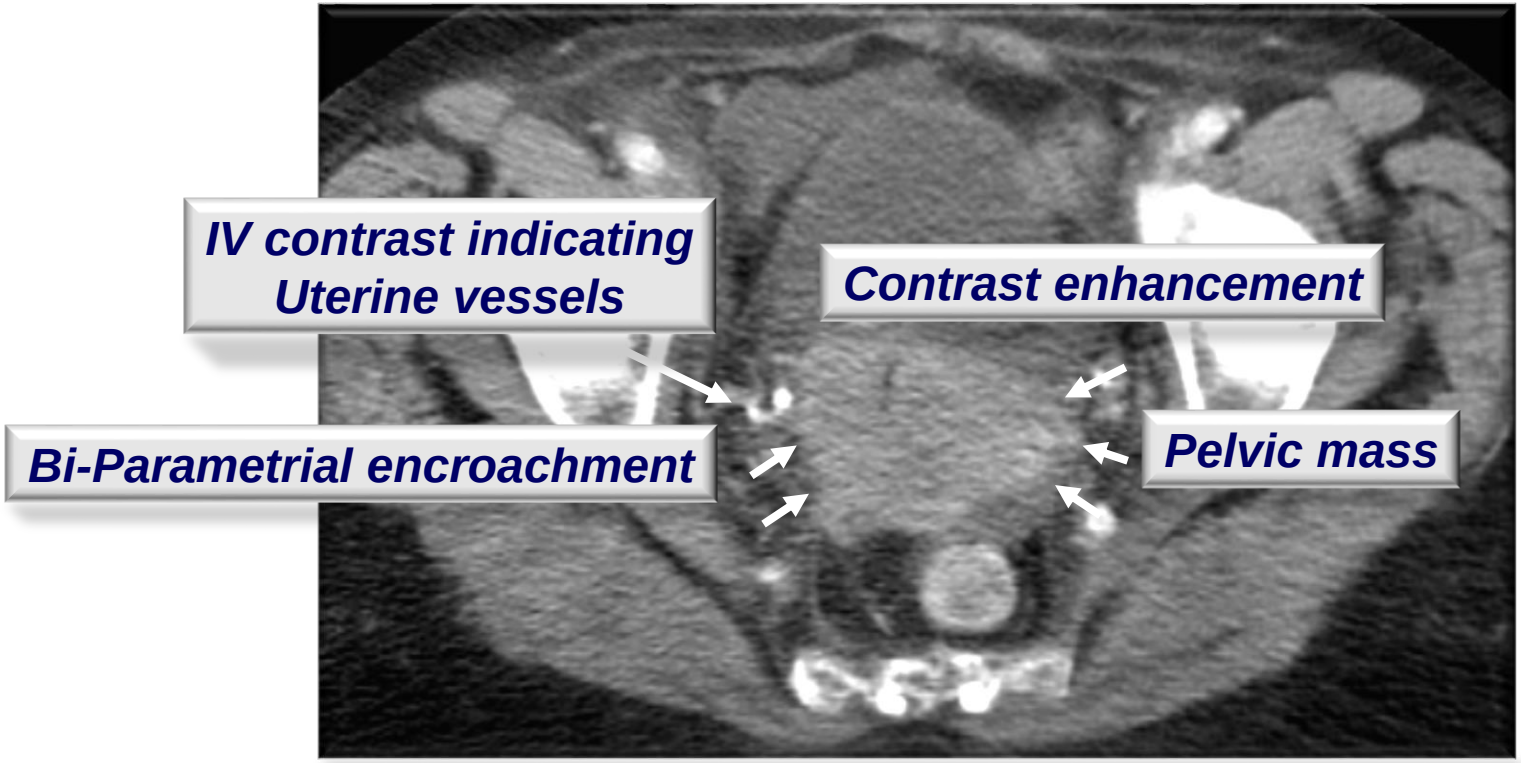
- Delayed image acquisition for bladder visualisation

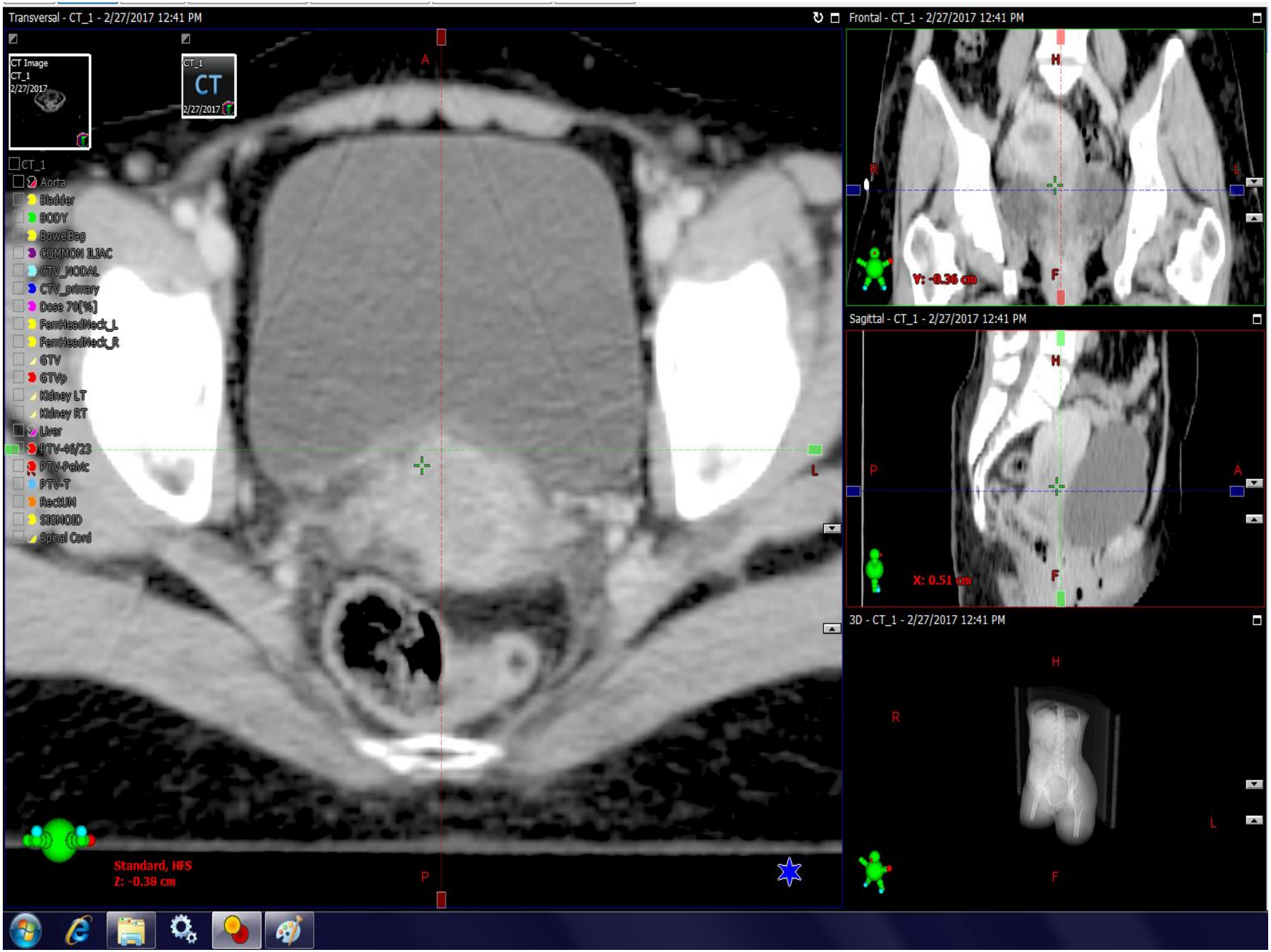
- Administration of oral iodine based contrast

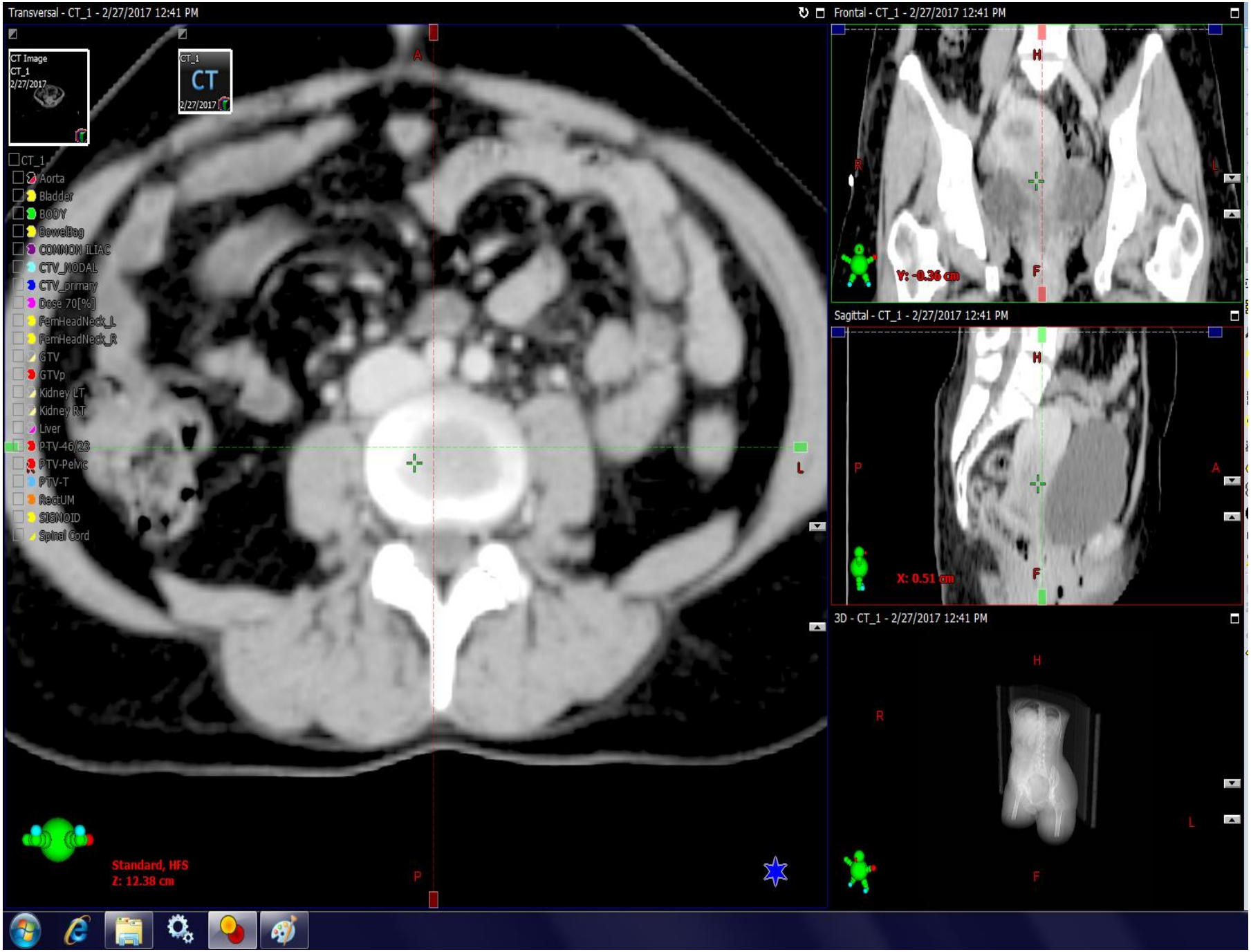
- Patient positioning

- Organ filing : Bladder & Rectum

CT: IV contrast for EBRT imaging




Transversal - CT_1 - 2/27/2017 12:41 PM
CT Image
CT_1
2/27/2017
CT_1
CT
2/27/2017
CT_1
Aorta
Bladder
BODY
BowelBag
COMMON ILIAC
CTV_NODAL
CTV_primary
Dose 70[%]
FemHeadNeck_L
FemHeadNeck_R
GTV
GTVp
Kidney LT
Kidney RT
Liver
PTV-46/23
PTV-Pelvic
PTV-T
RectUM
SIGMOID
Spinal Cord
A
L
P
Standard, HFS
Z: -0.38 cm
Frontal - CT_1 - 2/27/2017 12:41 PM
H
R
L
F
Y: -0.36 cm
Sagittal - CT_1 - 2/27/2017 12:41 PM
H
P
A
F
X: 0.51 cm
3D - CT_1 - 2/27/2017 12:41 PM
H
R
L
F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CT Image
CT_1
2/27/2017
CT_1
CT
2/27/2017
CT_1
Aorta
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FemHeadNeck_L
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Spinal Cord
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P
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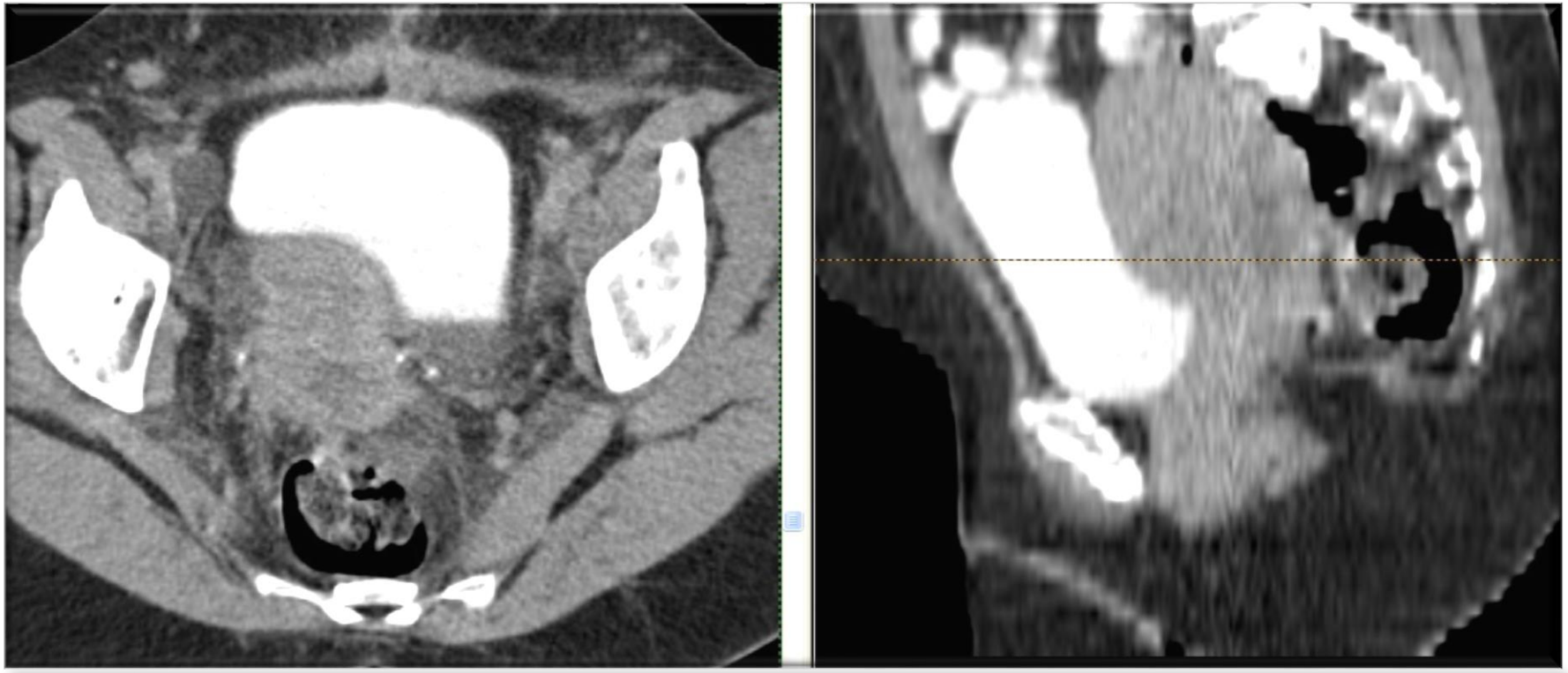
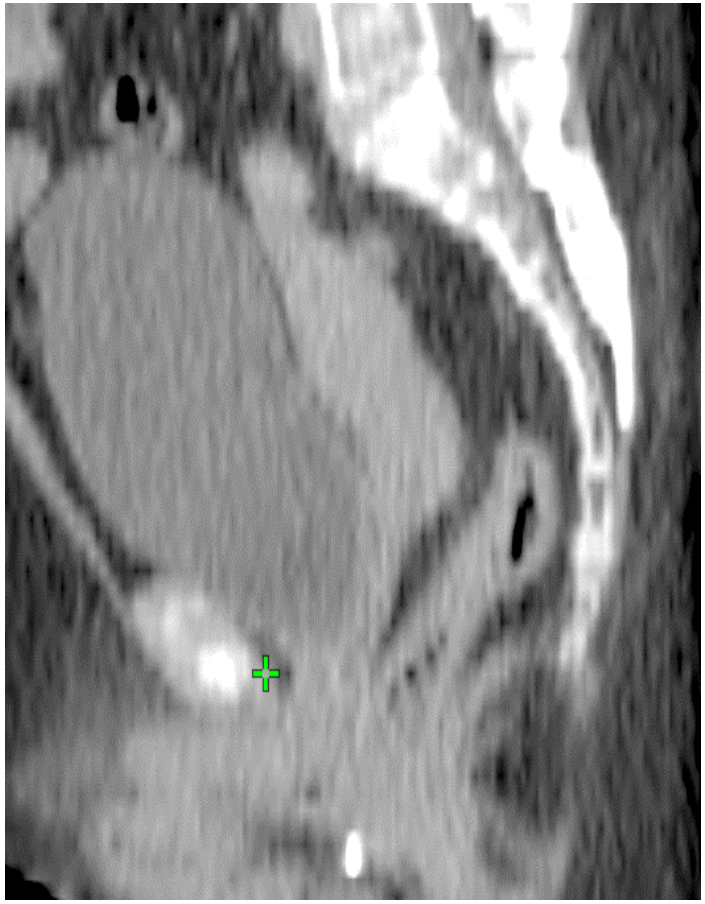
Z: 12.38 cm
Frontal - CT_1 - 2/27/2017 12:41 PM
H
R
L
F
Y: -0.36 cm
Sagittal - CT_1 - 2/27/2017 12:41 PM
H
P
A
F
X: 0.51 cm
3D - CT_1 - 2/27/2017 12:41 PM
H
R
L
F

CT: IV contrast delayed image acquisition

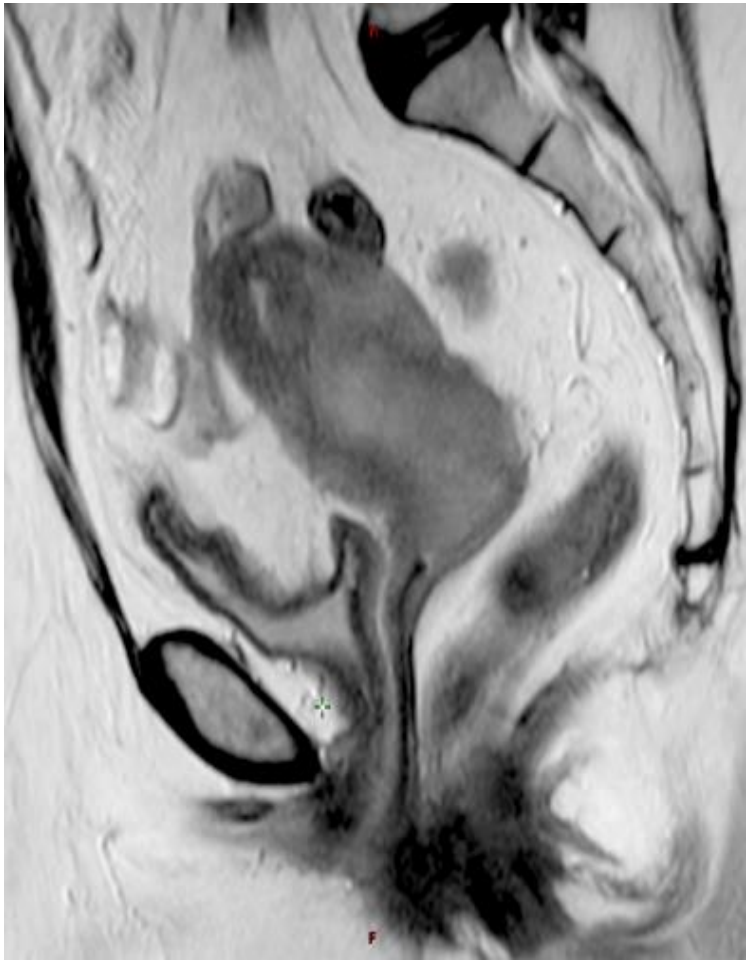
IV contrast – delayed image acquisition for bladder



Endometrial invasion of cervical disease

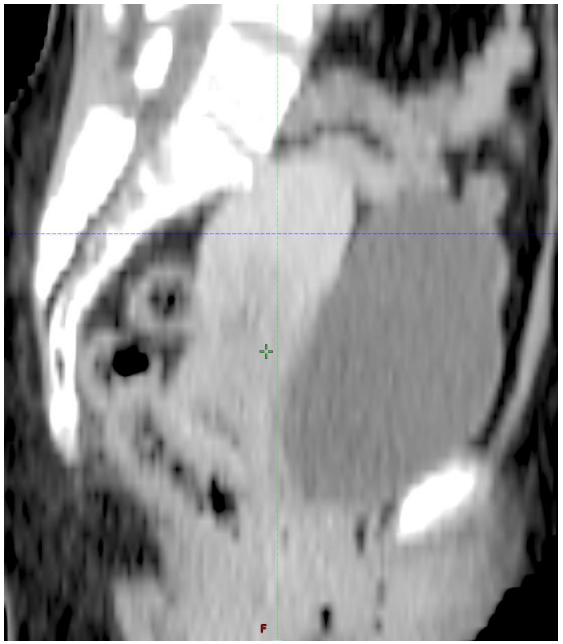
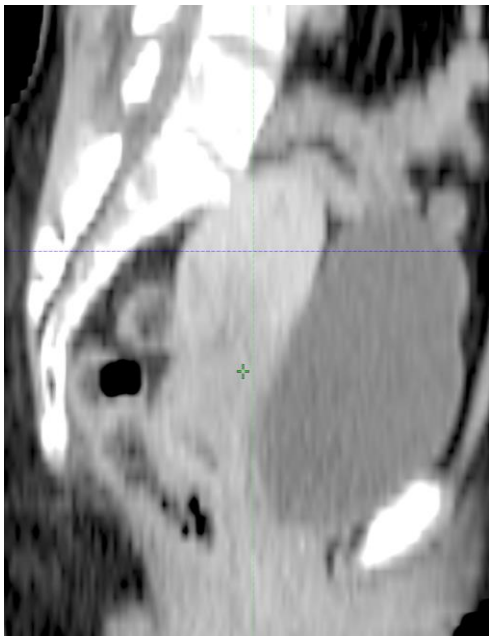
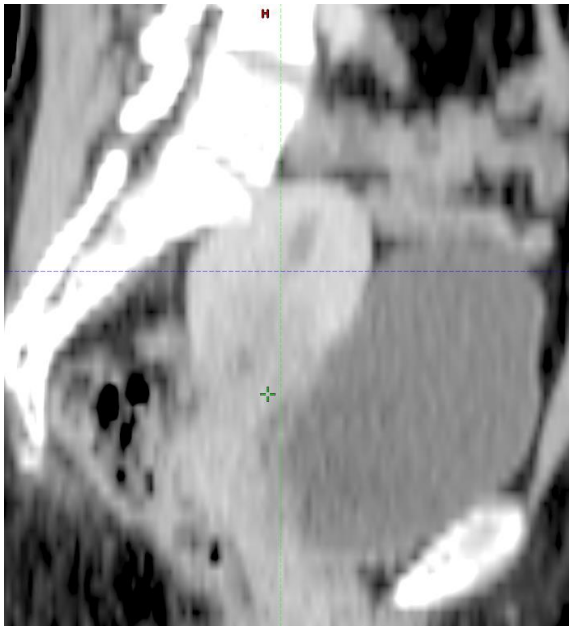
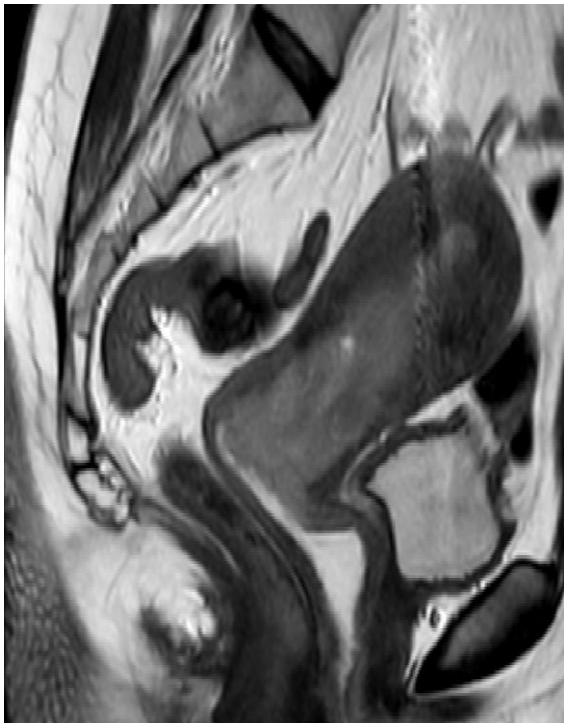
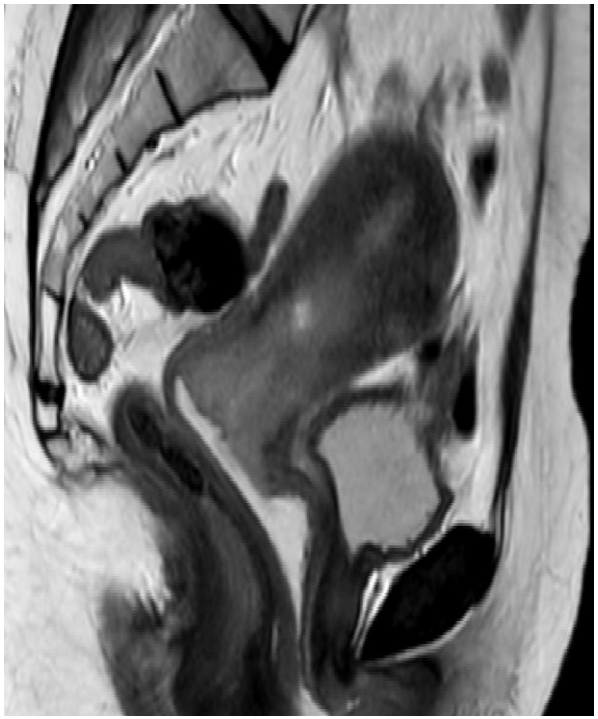


Vs



CT

MRI

Imaging protocols MRI and CT

	General characteristics					
	Soft tissue depiction	Image acquisition	Contrast media	Multiplanar imaging	Radiation exposure	Scanning time
MRI	Superior quality on T2-weighted sequences	Specific protocols required	Not obligatory needed	without reconstruction	No	Long
CT	Inferior quality	Specific protocols required	Recommended	only with reconstruction	Yes	Short

	Diagnostic scan					
	Tumor detection	Parametrial invasion	Invasion of organs	Invasion of vagina	LN status	Recurrence detection
MRI	Estimation of dimensions within 0.5 cm compared to pathology specimen. Detection of endocervical growth and uterine corpus invasion is possible	High accuracy for: –Distinction between stromal and parametrial invasion –Estimation of degree of parametrial invasion	High accuracy in prediction of infiltration of surrounding organs	High accuracy in predicting vaginal invasion, if vaginal contrast is used (e.g., ultrasound gel)	CT and MRI have similar inaccuracy in detecting LN metastases	Dynamic contrast-enhanced MRI enables differentiating tumor recurrence from radiation fibrosis
CT	Inaccurate estimation of tumor dimensions even with contrast enhancement and inability to detect uterine corpus invasion	Low accuracy in distinction between parametrial tumor spread and normal parametrial tissue	Early invasion of bladder and rectum is not reliably detectable	Low accuracy in predicting vaginal infiltration, especially at early stages	CT and MRI have similar accuracy in detecting LN metastases	CT is of low predictive value for differentiation between radiation fibrosis and recurrence

Dimopoulos J, Fidarova E: The use of sectional imaging for image-guided radiotherapy. In: Viswanathan AN et al eds. Gynecologic Radiotherapy. Springer 2011

MR Imaging

Gold standard for evaluation of cervical cancer

Indications for MRI in cervical cancer

- Diagnosis
- Local staging of disease
- Nodal Disease: Pelvic and para-aortic
- RT Planning
- Evaluation of response to treatment
- Recurrent disease/ fibrosis
- Prediction of response to treatment

Advantages of MRI

- Multiplanar- axial, coronal, sagittal
- Superior soft tissue contrast
- No radiation hazards
- Suitable alternative for patients with contra-indications for iodinated CT contrast media such as allergy.
- Morphological as well as functional information (Diffusion weighted imaging, dynamic contrast enhanced MRI)

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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

A B S T R A C T

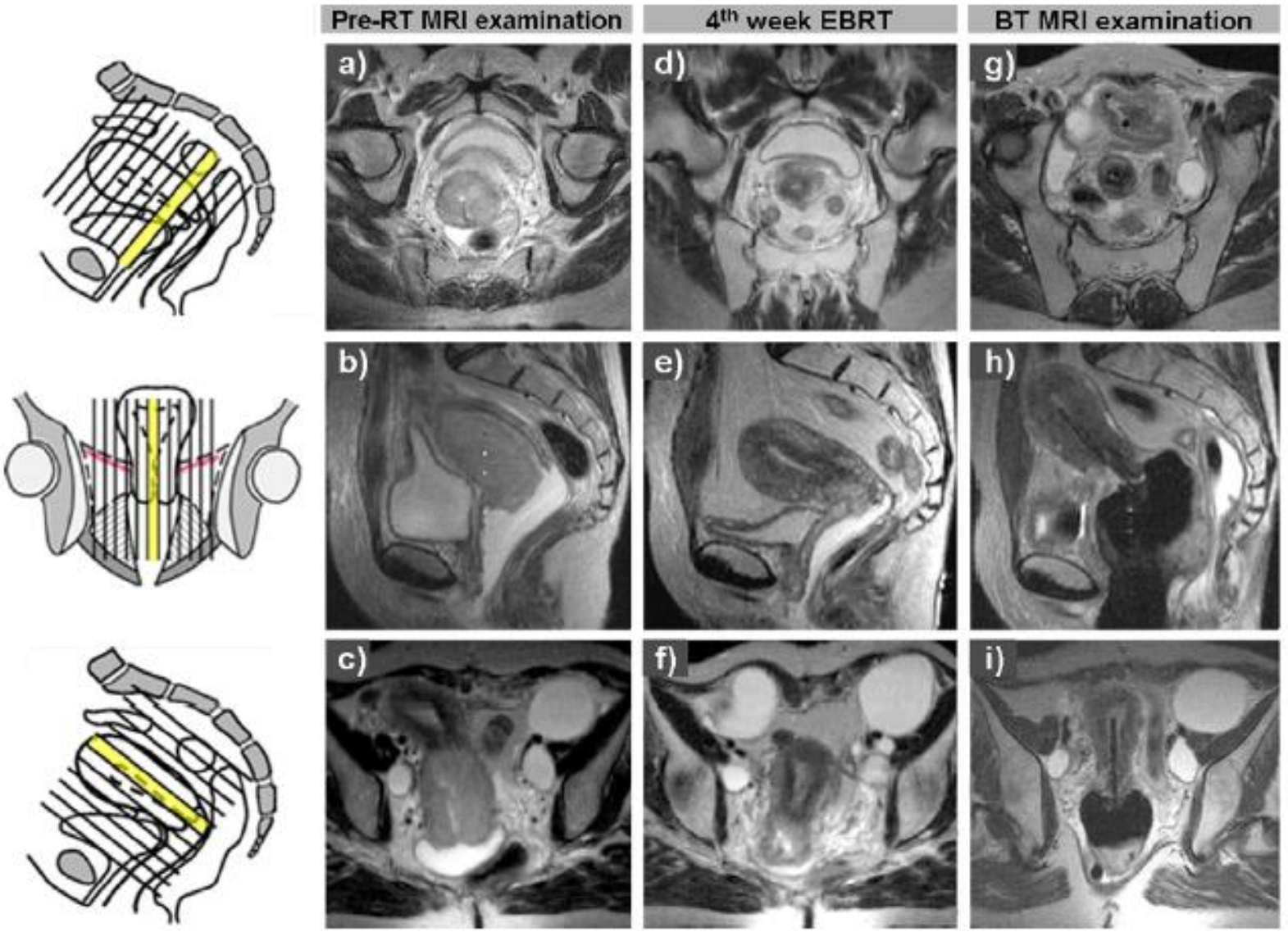
The GYN GEC-ESTRO working group issued three parts of recommendations and highlighted the pivotal role of MRI for the successful implementation of 3D image-based cervical cancer brachytherapy (BT). The main advantage of MRI as an imaging modality is its superior soft tissue depiction quality. To exploit the full potential of MRI for the better ability of the radiation oncologist to make the appropriate choice for the BT application technique and to accurately define the target volumes and the organs at risk, certain MR imaging criteria have to be fulfilled. Technical requirements, patient preparation, as well as image acquisition protocols have to be tailored to the needs of 3D image-based BT. The present recommendation is focused on the general principles of MR imaging for 3D image-based BT.

Methods and parameters have been developed and progressively validated from clinical experience from different institutions (IGR, Universities of Vienna, Leuven, Aarhus and Ljubljana) and successfully applied during expert meetings, contouring workshops, as well as within clinical and interobserver studies.

It is useful to perform pelvic MRI scanning prior to radiotherapy ("*Pre-RT-MRI examination*") and at the time of BT ("*BT MRI examination*") with one MR imager. Both low and high-field imagers, as well as both open and close magnet configurations conform to the requirements of 3D image-based cervical cancer BT. Multiplanar (transversal, sagittal, coronal and oblique image orientation) T2-weighted images obtained with pelvic surface coils are considered as the golden standard for visualisation of the tumour and the critical organs. The use of complementary MRI sequences (e.g. contrast-enhanced T1-weighted or 3D isotropic MRI sequences) is optional. Patient preparation has to be adapted to the needs of BT intervention and MR imaging. It is recommended to visualise and interpret the MR images on dedicated DICOM-viewer workstations, which should also assist the contouring procedure. Choice of imaging parameters and BT equipment is made after taking into account aspects of interaction between imaging and applicator reconstruction, as well as those between imaging, geometry and dose calculation.

In a prospective clinical context, to implement 3D image-based cervical cancer brachytherapy and to take advantage of its full potential, it is essential to successfully meet the MR imaging criteria described in the present recommendations of the GYN GEC-ESTRO working group.

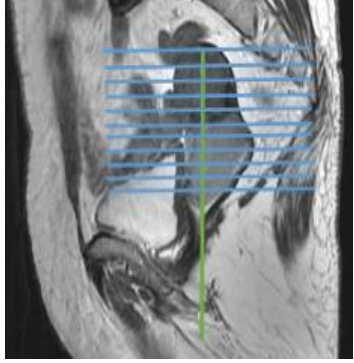
IMAGE PLANE, ORIENTATION AND COVERAGE



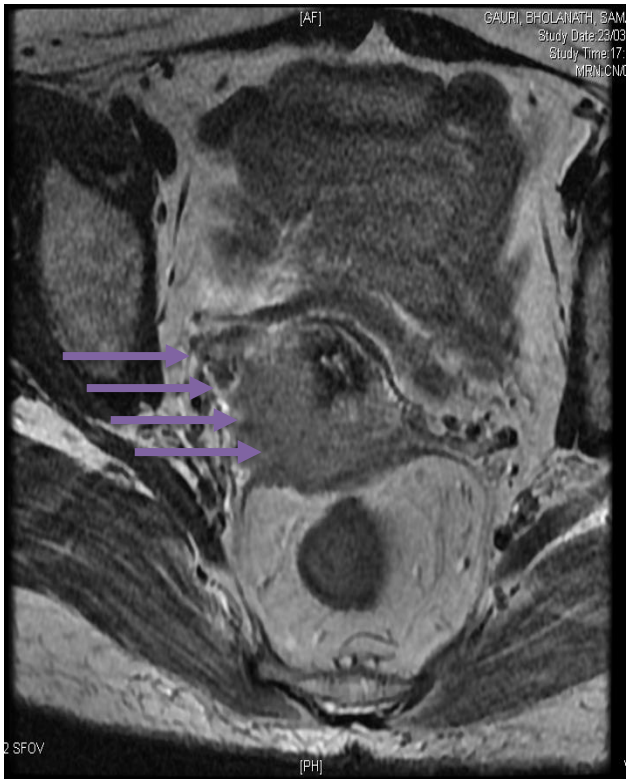
Para – transverse , para-coronal, para-saggital

RO 2012; GEC-ESTRO RECOMMENDATION-IV

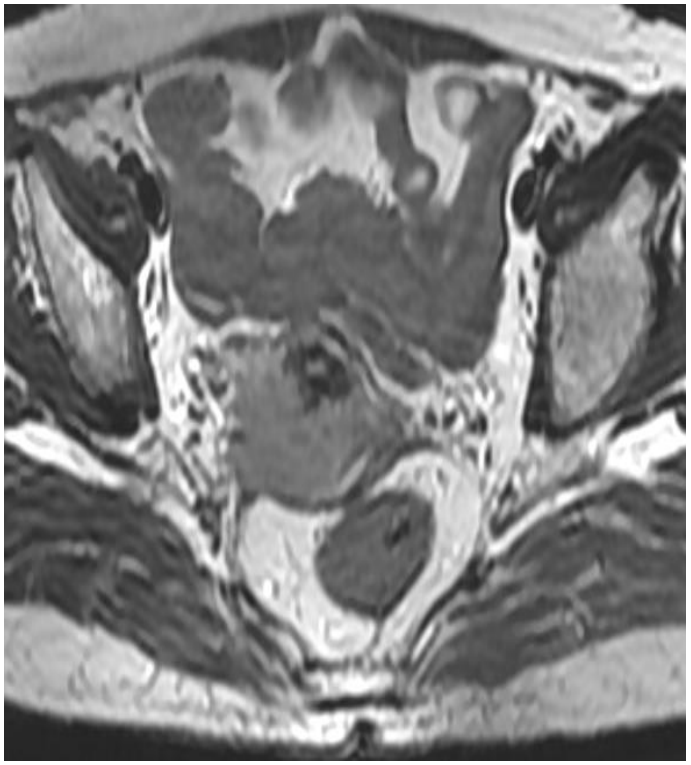
Right parametrial invasion



Para-axial



True-axial



Technical Requirements:

1. **Magnetic Field Strength:**

   - 0.2 – 1.5T for both Pre-Rx and BT MR series

   - 3T for Pre Rx MR (Experience growing)

   - 3T for BT : limited experience due to Image distortion, artefacts and heating effects of BT applicator

2. **Magnet Configuration:** Open or Closed

3. **Coils:** Pelvic coil

4. **Patient Preparation:**

   - Bowel preparation and reduction in bowel movements

   - Reduce ant. ABD motion by elastic bands and Anterior Pre-Saturation bands : to reduce signals form skin and sub-cut tissues

   - US jelly in the vagina for vaginal mucosal disease (Pre Rx MR)

   - Vaginal packing with dilute gado (0.2 T) and no contrast for (1.5T)

   - Bladder filling protocol : reproducible during BT MR and Rx delivery

   - Rectal dosimeters - optional

RO 2012; GEC-ESTRO RECOMMENDATION-IV

Table 2
Image acquisition protocols for pre-RT MRI scan and BT MRI scan. This table summarises the important information regarding sequence parameters for each of the different MRI sequences. The numbering of sequences is the same as in Table 1.

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]
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	35 × 20	512	256	2	3–4	Yes
	4		No	2000–5000	90–120	4–20	35 × 40	512	256	2	5	Yes
	5	TSE	Optional	500–700	10–20	NA	35 × 20	512	256	2	5–7	Yes
		3D GRE[i]	Optional	5–10	2–5	[i]	37 × 30	[i]	[i]	[i]	1–4	[i]
	6	TSE	Optional	500–700	10–20	NA	35 × 20	256	256	2	3–5	Yes
	7	TSE	Optional	500–700	10–20	NA	35 × 20	256	256	2	3–5	Yes
		3D GRE[i]	Optional	5–10	2–5	[i]	37 × 30	[i]	[i]	[i]	1–4	[i]
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									

[a] TR = time of repetition.
[b] E = time of echo.
[c] ETL = echo train length or turbo factor.
[d] FOV = minimum field of view.
[e] M = matrix: (f) = frequency, (p) = phase.
[f] Nex = number of excitations.
[g] SW = slice width.
[h] NPW = no phase wrap.
[i] Exact parameters depending on vendor, gradient performance, and parallel imaging abilities, GRE = gradient echo.

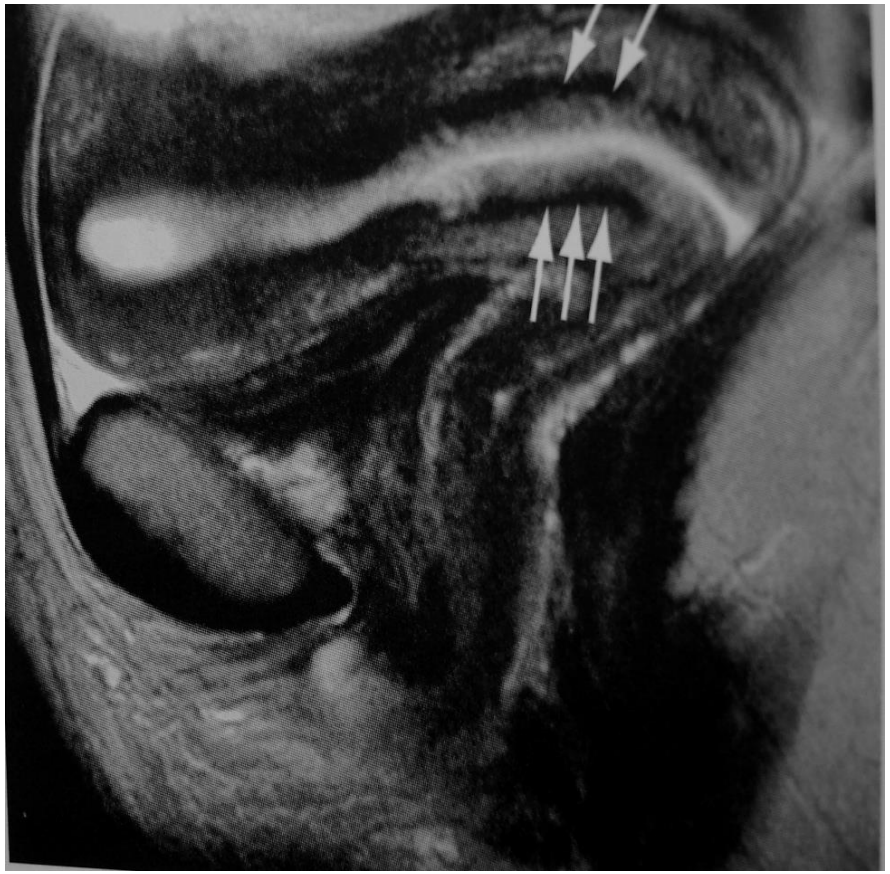
Interaction with Radiologist, Radiology and Brachytherapy

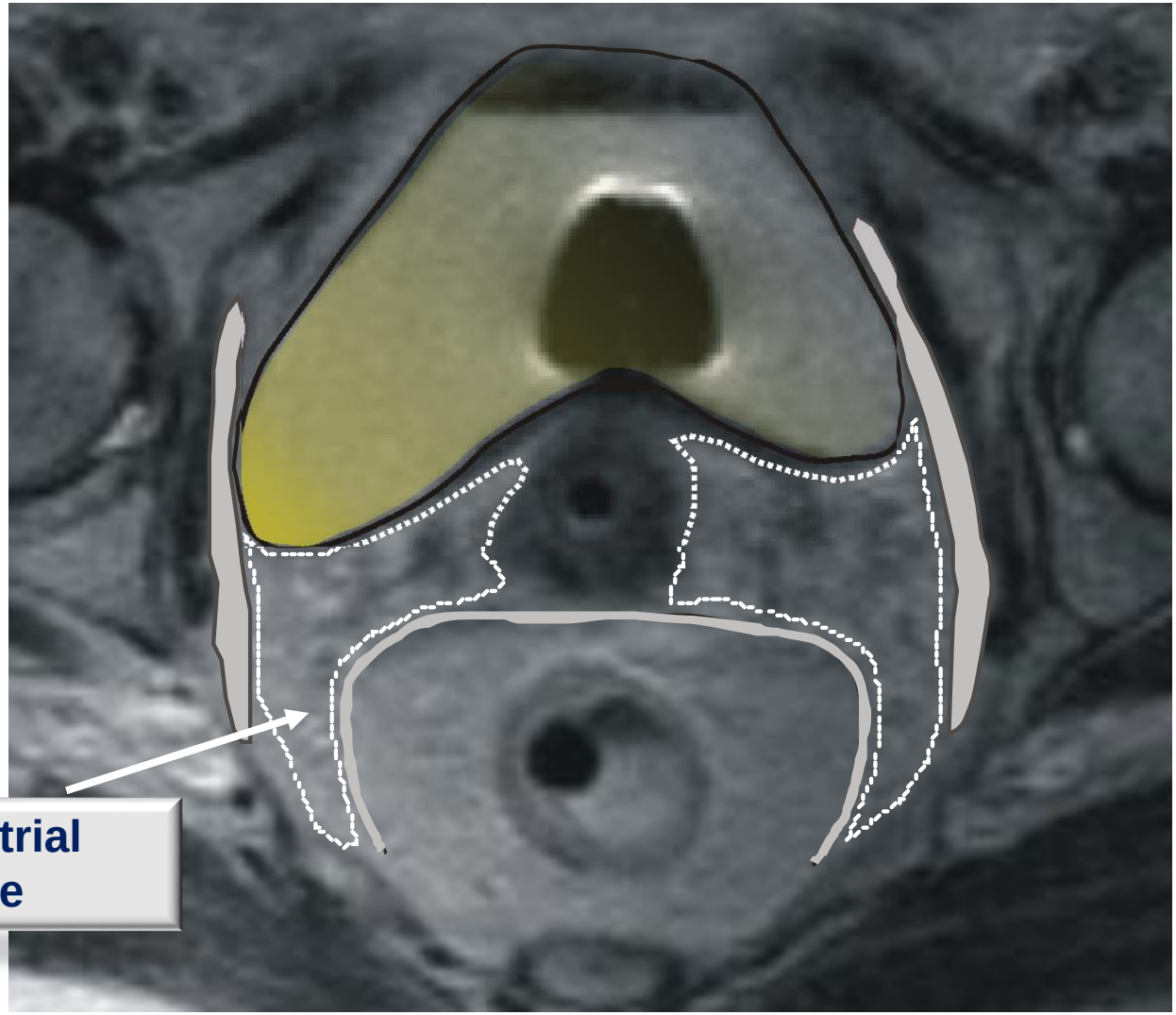
Technologist

Standardize a protocol for your MR

RO 2012; GEC-ESTRO RECOMMENDATION-IV

Normal Anatomy





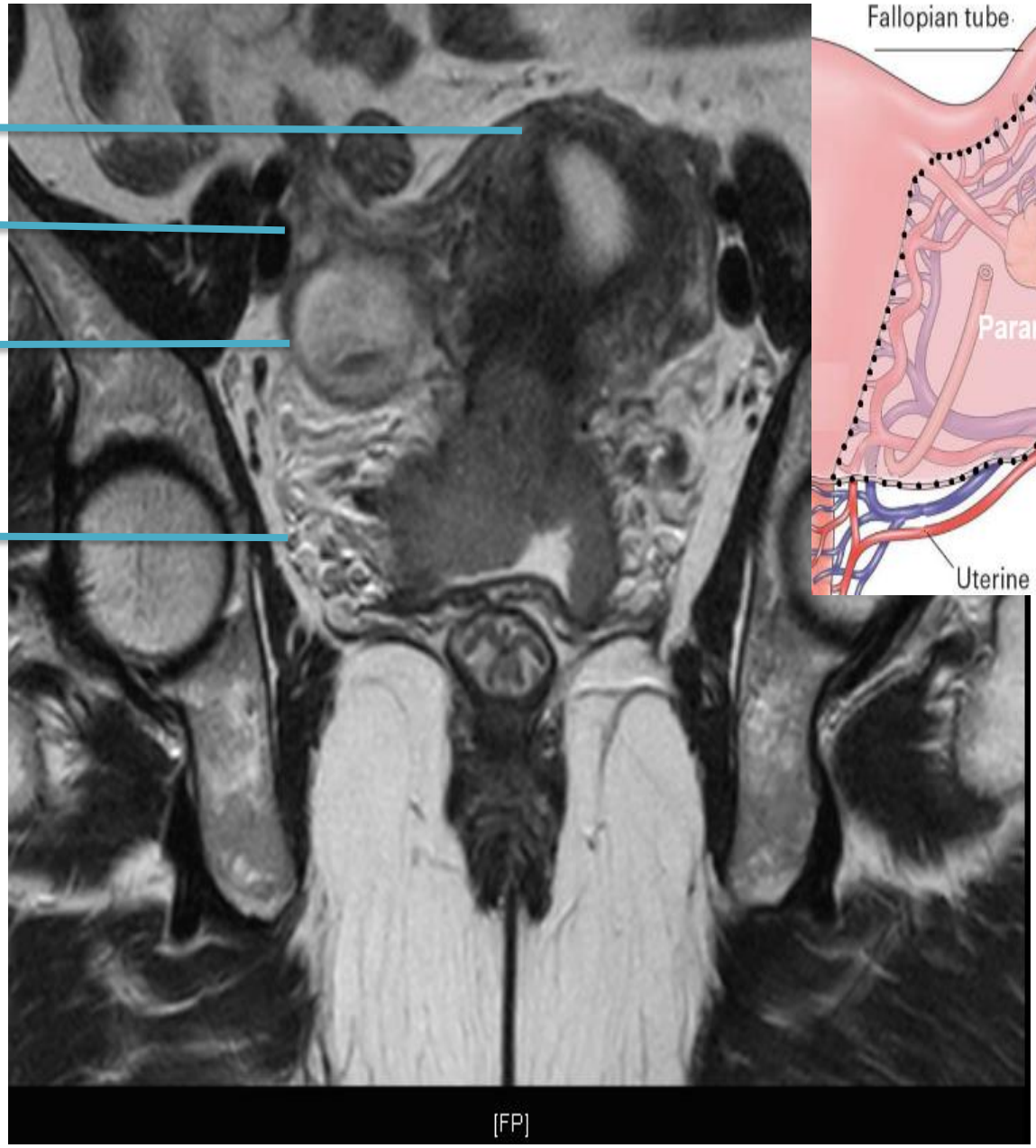
Dimopoulos et al. IJROBP 2006

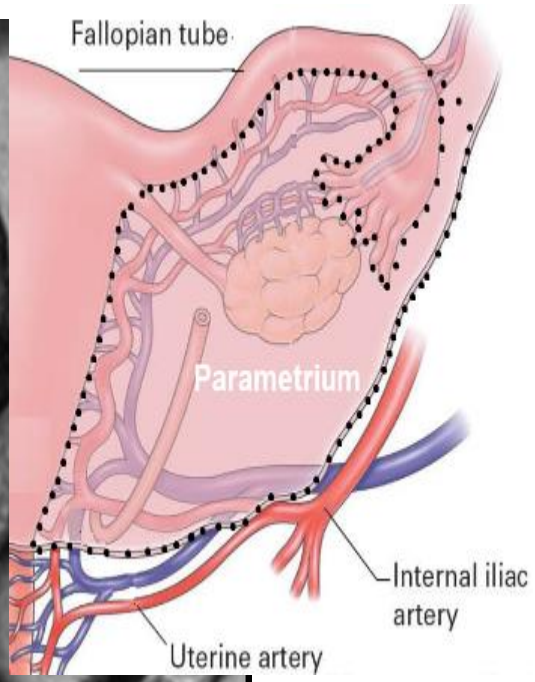
Fundus

Fallopian tube

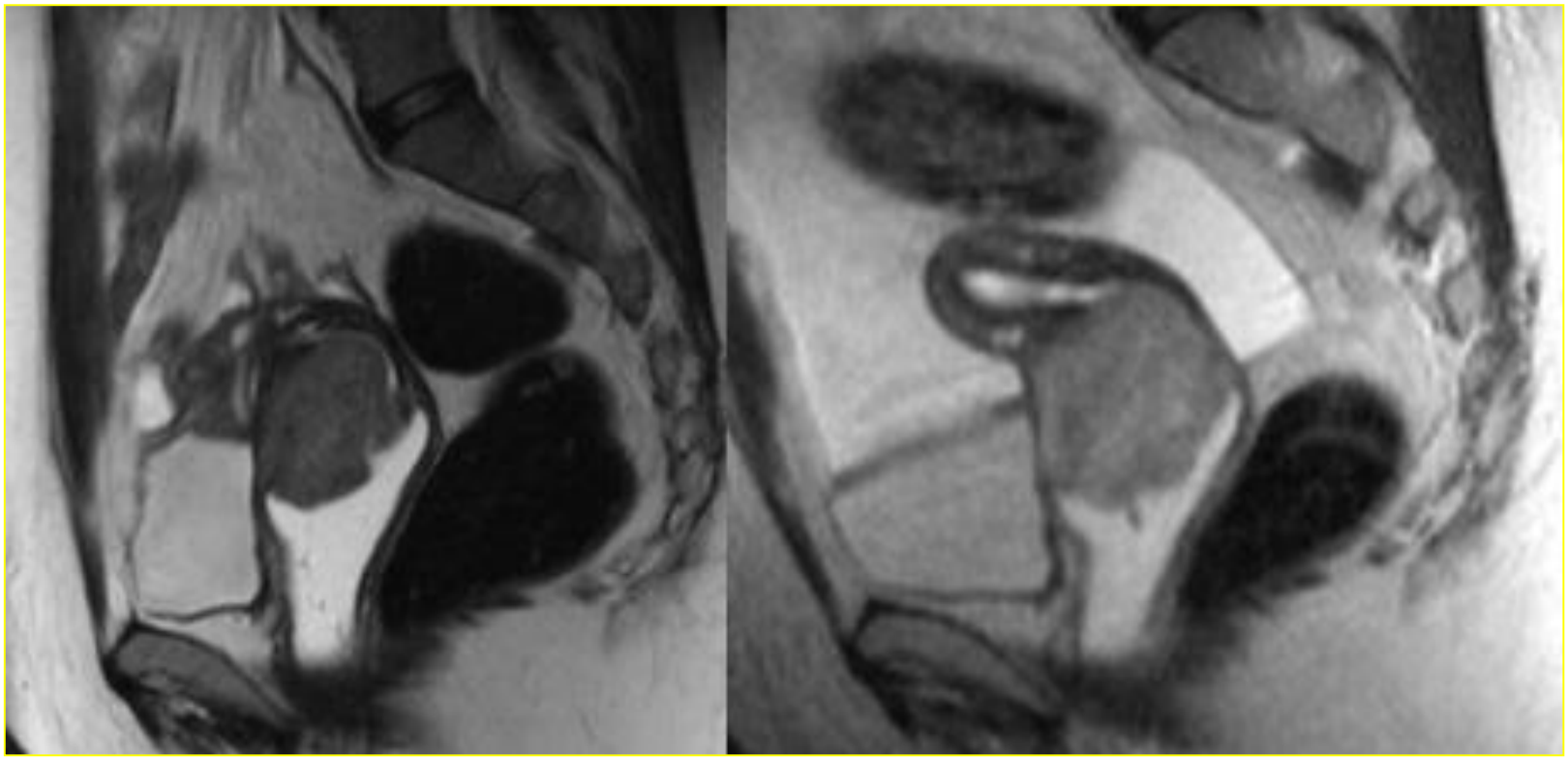
Ovary

Parametrium





MR FIELD STRENGTH

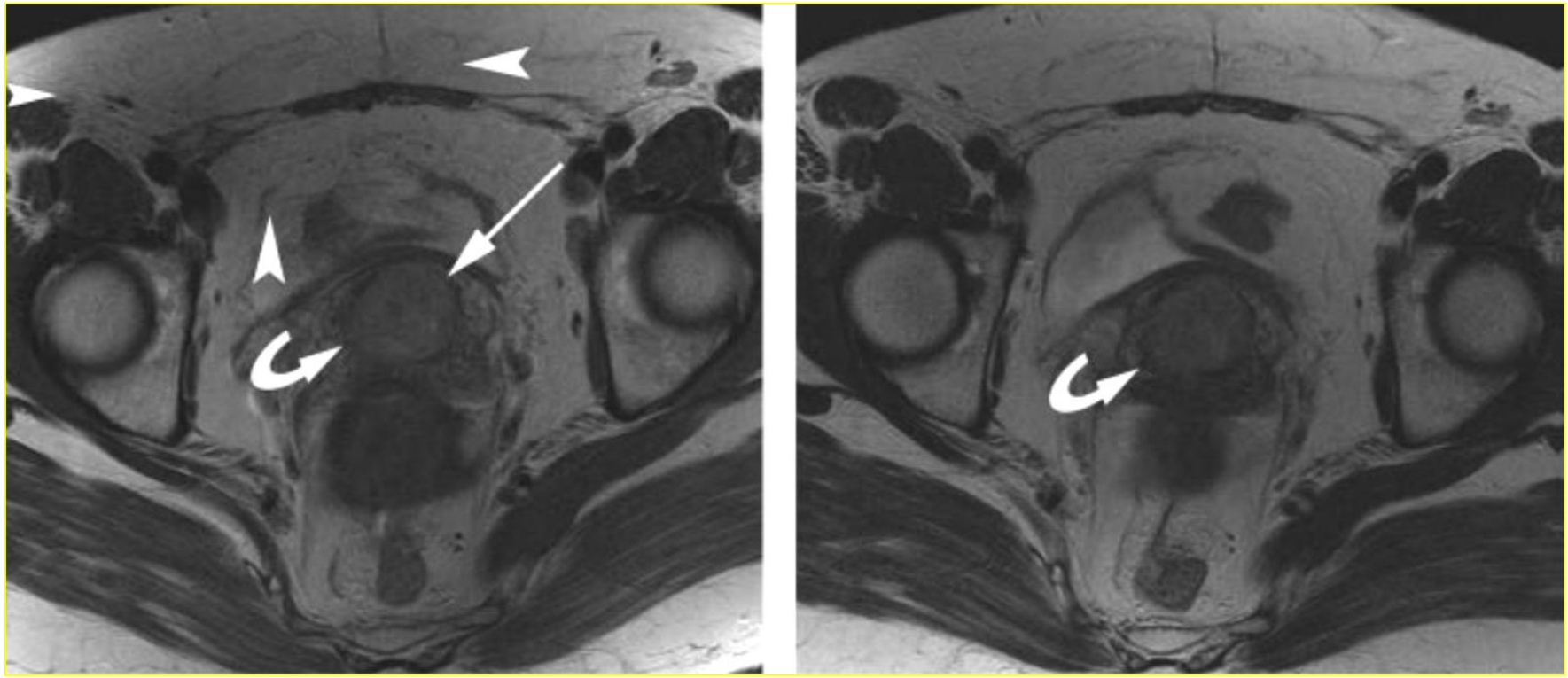


1.5 T

0.23 T

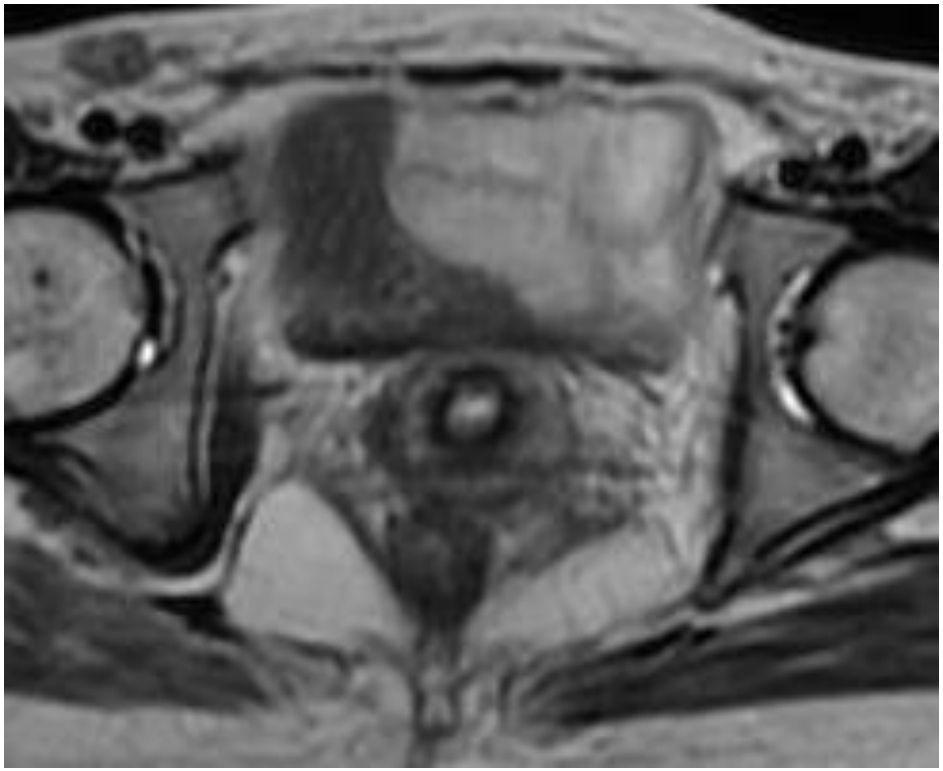
MR IMAGING : GYN GEC ESTRO RECOMMENDATIONS

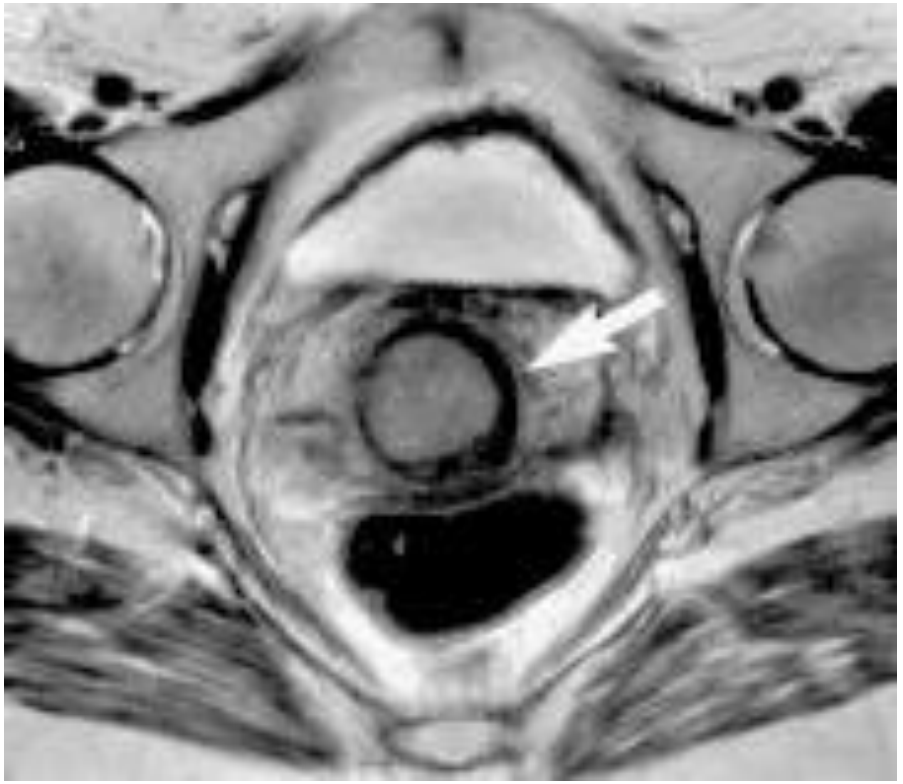
FIELD STRENGTH



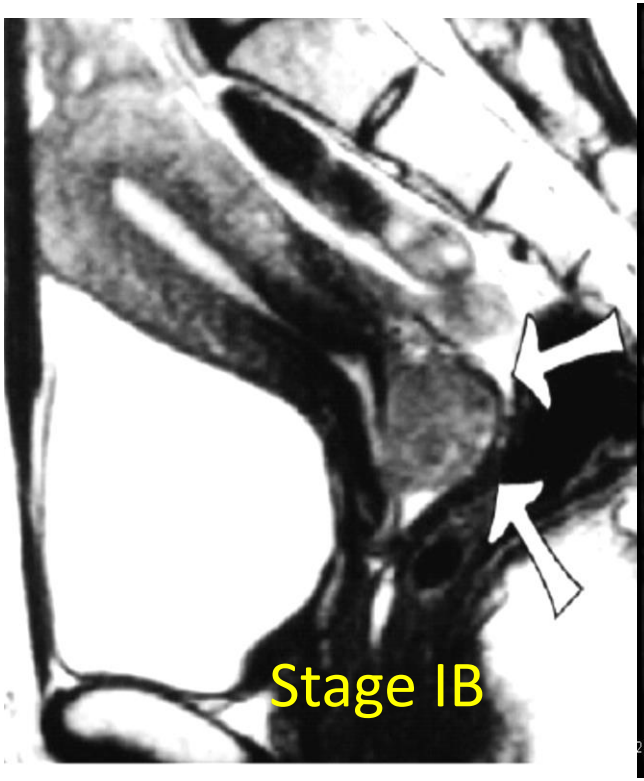
3 T **1.5 T**

Masatoshi et al Radiology 2009





Preservation of a hypo-intense fibrous stromal ring - rules out parametrial invasion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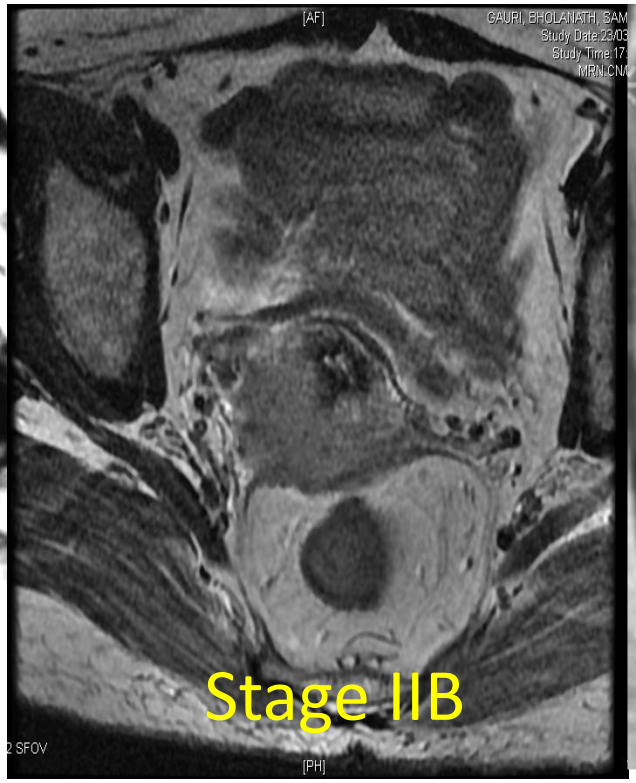
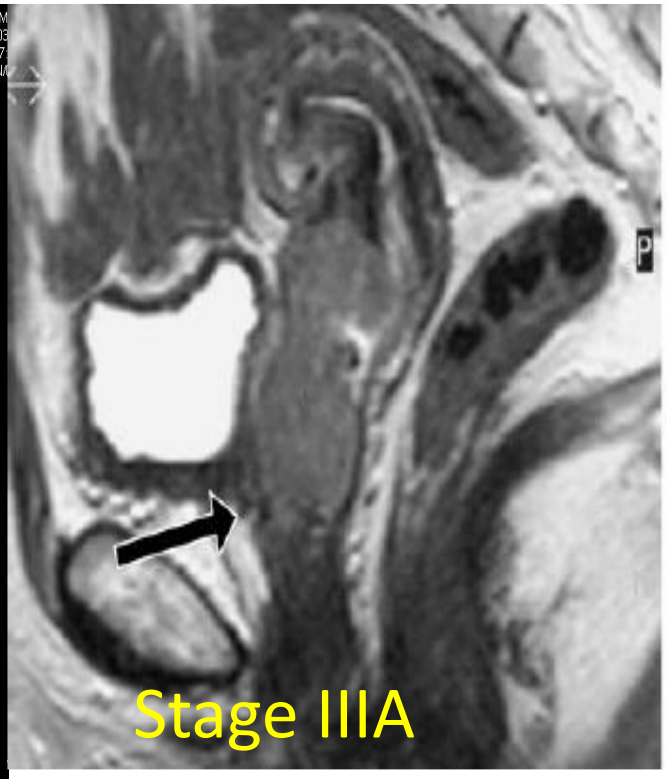
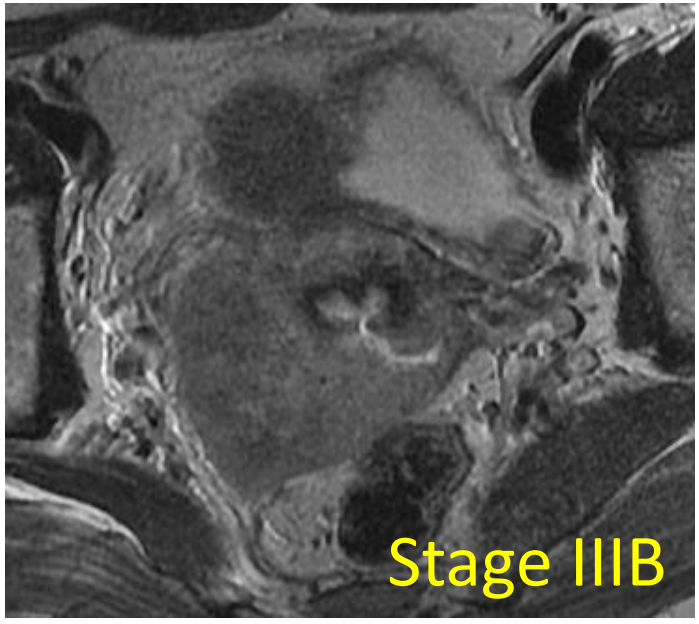
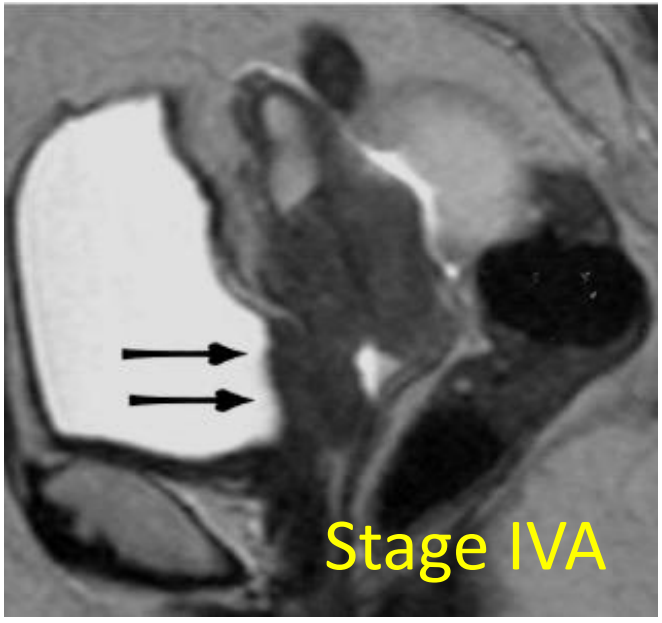

[AF]
[PH]
Stage IIB


Stage IIIA


Stage IIIB


Stage IVA

MR Imaging Primary tumor characteristics and its implications for image-guided radiotherapy

expansive with spiculae

→ no remnants in PM

expansive with spiculae + infiltrating parts

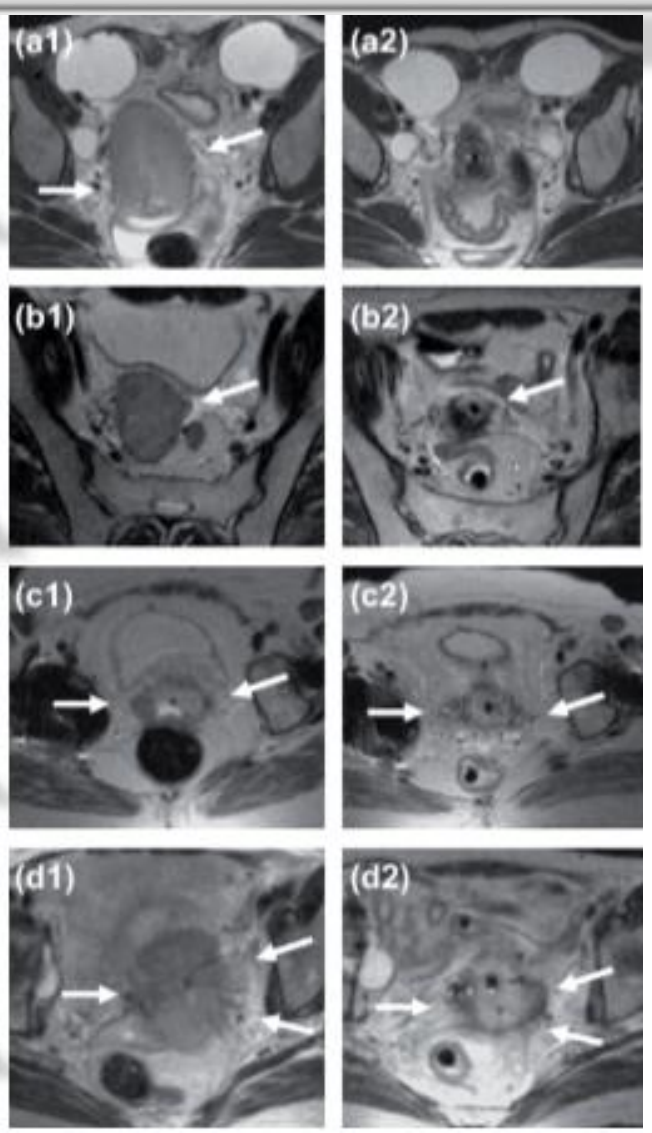
→ grey zones in the PM

infiltrative parts in both PM

→ grey and bright zones

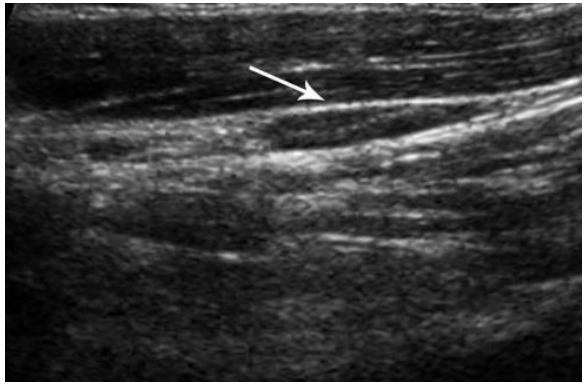
infiltrative parts in both PM

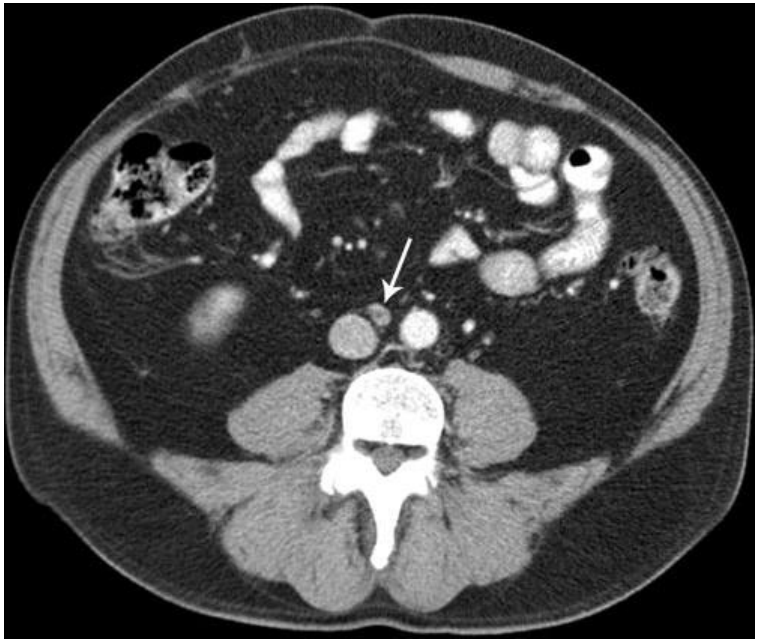
→ grey and bright zones

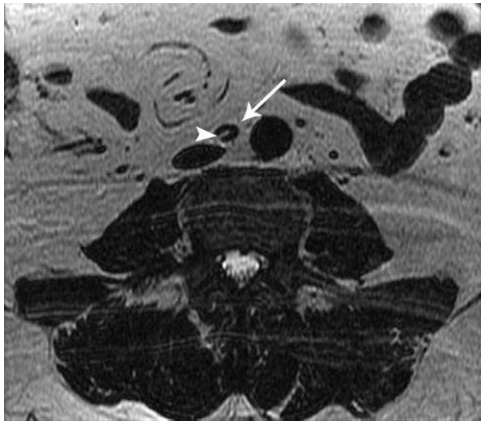


Schmid et al. Acta Oncologica 2013

ASSESSMENT OF NODAL PATHOLOGY







Torabi M, J Nucl Med 2004 ; 45 : 1509-18

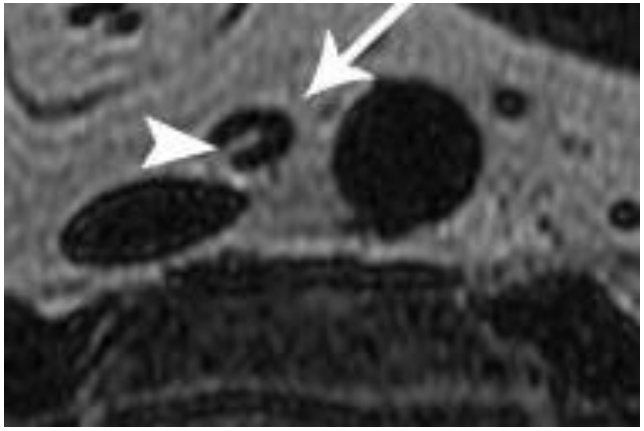
ASSESSMENT OF NODAL PATHOLOGY

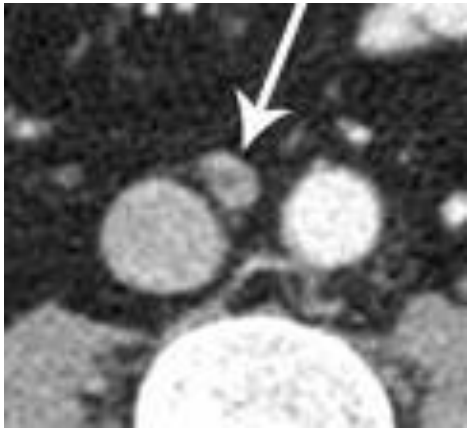
Normal nodes

Size : < 10 mm in short axis
- Smooth, regular borders
- Uniform SI / density
- fatty hilum
- oval shape

Abnormal nodes

Size : > 10 mm in short axis
- Irregular borders
- Non Uniform SI / density
- hilar necrosis
- round shape





Torabi M, J Nucl Med 2004 ; 45 : 1509-18

FDG PET- CT

BIOLOGICAL & ANATOMICAL DATA

FDG Uptake in Pelvic Organs

Normal Pelvic Organs & Benign Lesions

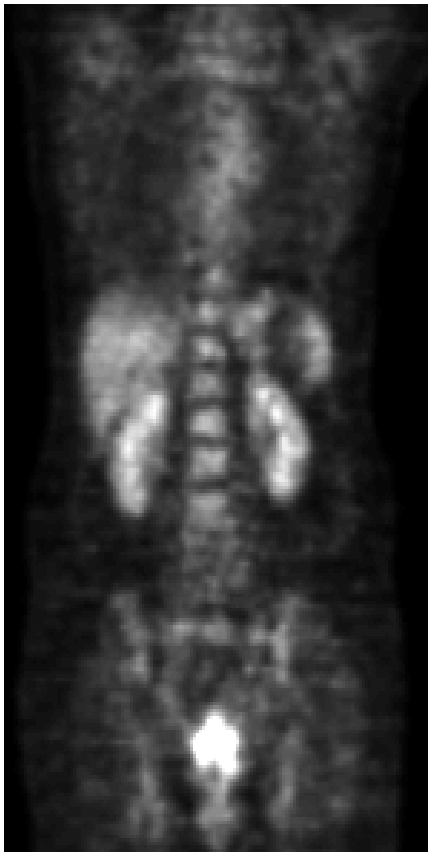
1. Urinary tract
2. Menstruating
3. Ovarian follicular cysts
4. Cystadenoma
5. Endometriosis
6. Leiomyoma
7. Infection/inflammation

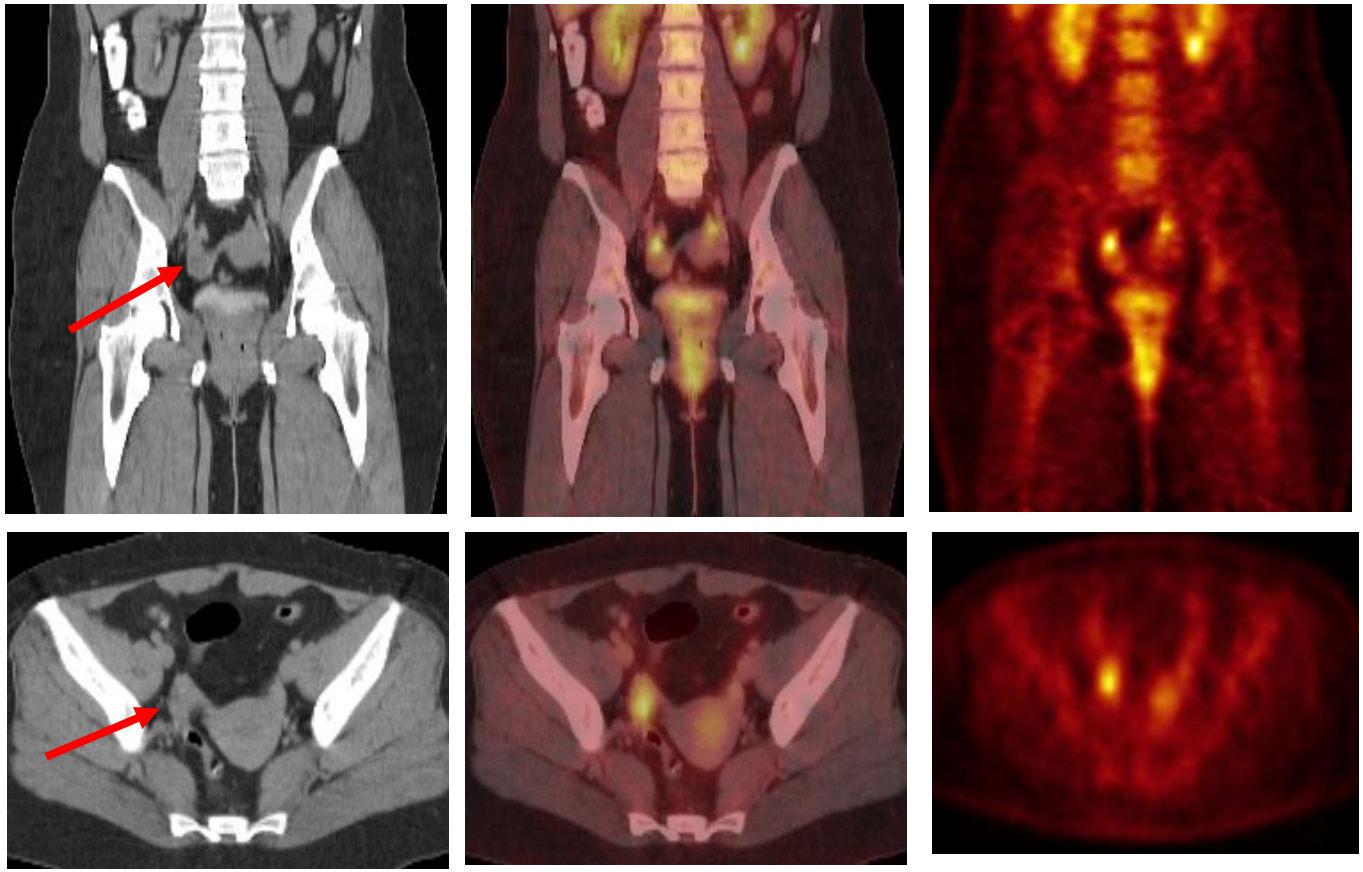
PET in Gynecologic Cancer

- Cervical Cancer
- Ovarian Cancer
- Endometrial Cancer
- Vaginal Cancer
- Vulvar Cancer

FDG-PET

FDG-PET/CT





PET and Cervical Cancers

NEWLY DIAGNOSED

➢ Early Stage (I-IIA)

- ➢ Surgery / RT
- ➢ >50 % require Adj. Rx
- ➢ 20-30 % pelvic node +ve
- ➢ CT/MRI limitations
- ➢ Can PET identify these 20-30 % patients?
- ➢ Avoid morbidity of multi-modality Rx

➢ Advanced Stage (IIB-IIIB)

- ➢ Radical RT + CT
- ➢ Pelvic Radiation
- ➢ 30-45% para aortic node+ve
- ➢ CT/MRI limitations
- ➢ Can PET identify at least 30%
- ➢ Tailor multi-modality treatment Rx

Knowledge of natural history of GYN Cancers and Lymph Nodal Spread : Vital

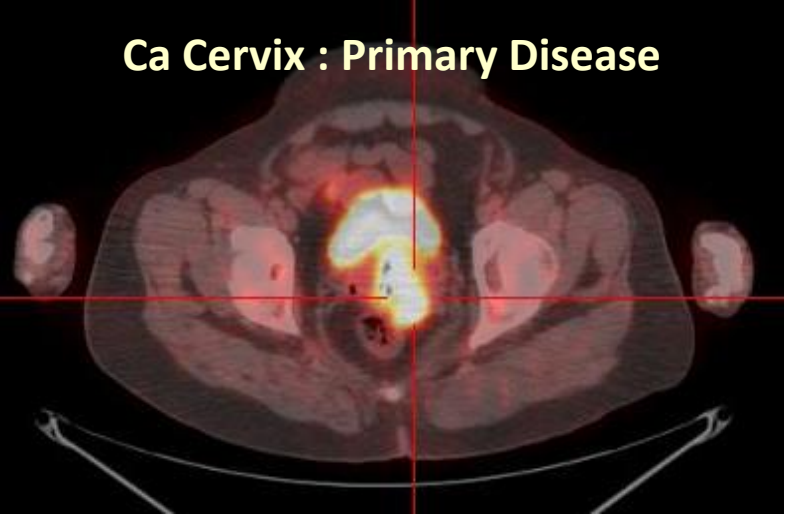
PET and Cervical Cancers

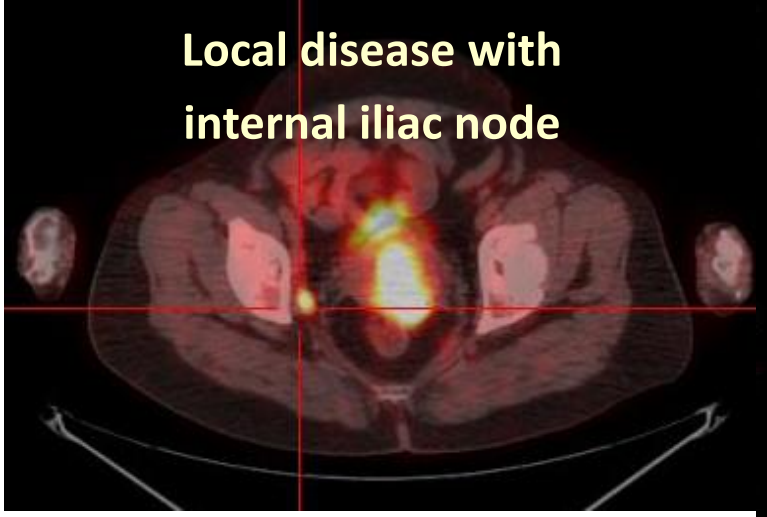
- **Primary Tumor Staging**
- **Lymph Nodal Staging : Early Vs Advance Stages**
- **Pre-treatment Prognostic Value**
- **Treatment Plan Optimization : Single modality, Aggressive Rx …**
- **Post-therapy Surveillance**

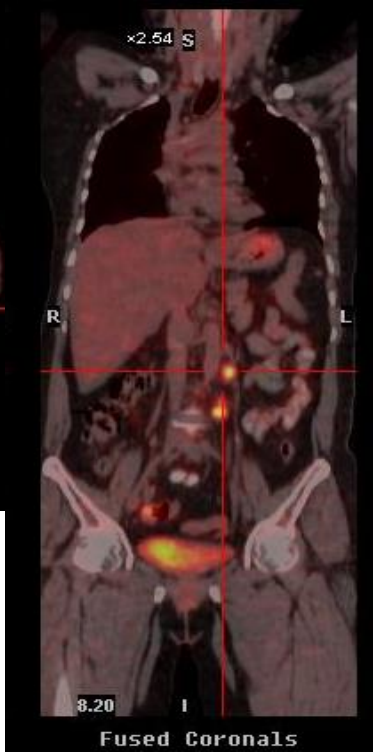
  - Local

  - Regional (Pelvic / Para-aortic)

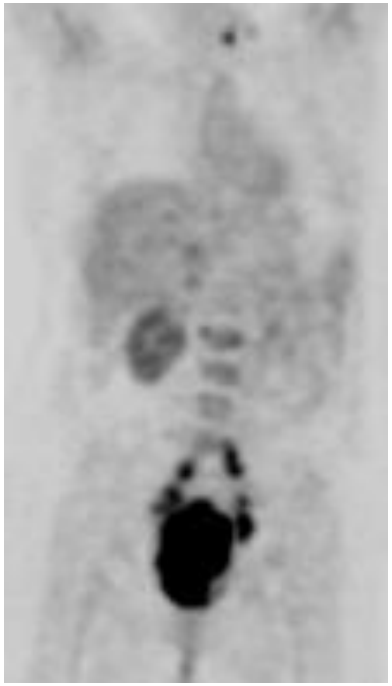
  - Distant Metastasis



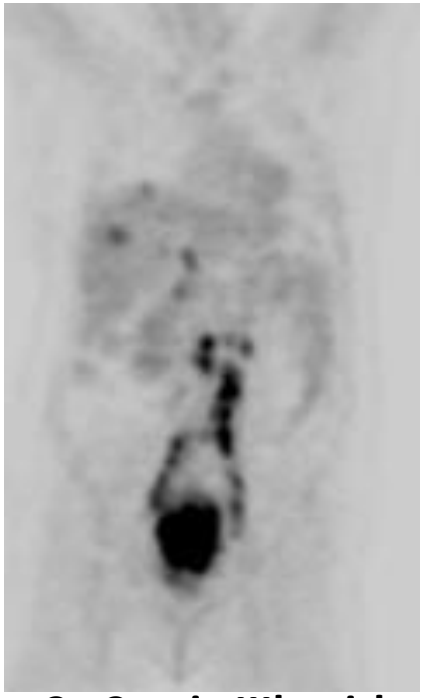




PET and Cervical Cancers



Ca Cervix IIIb with
SCF node

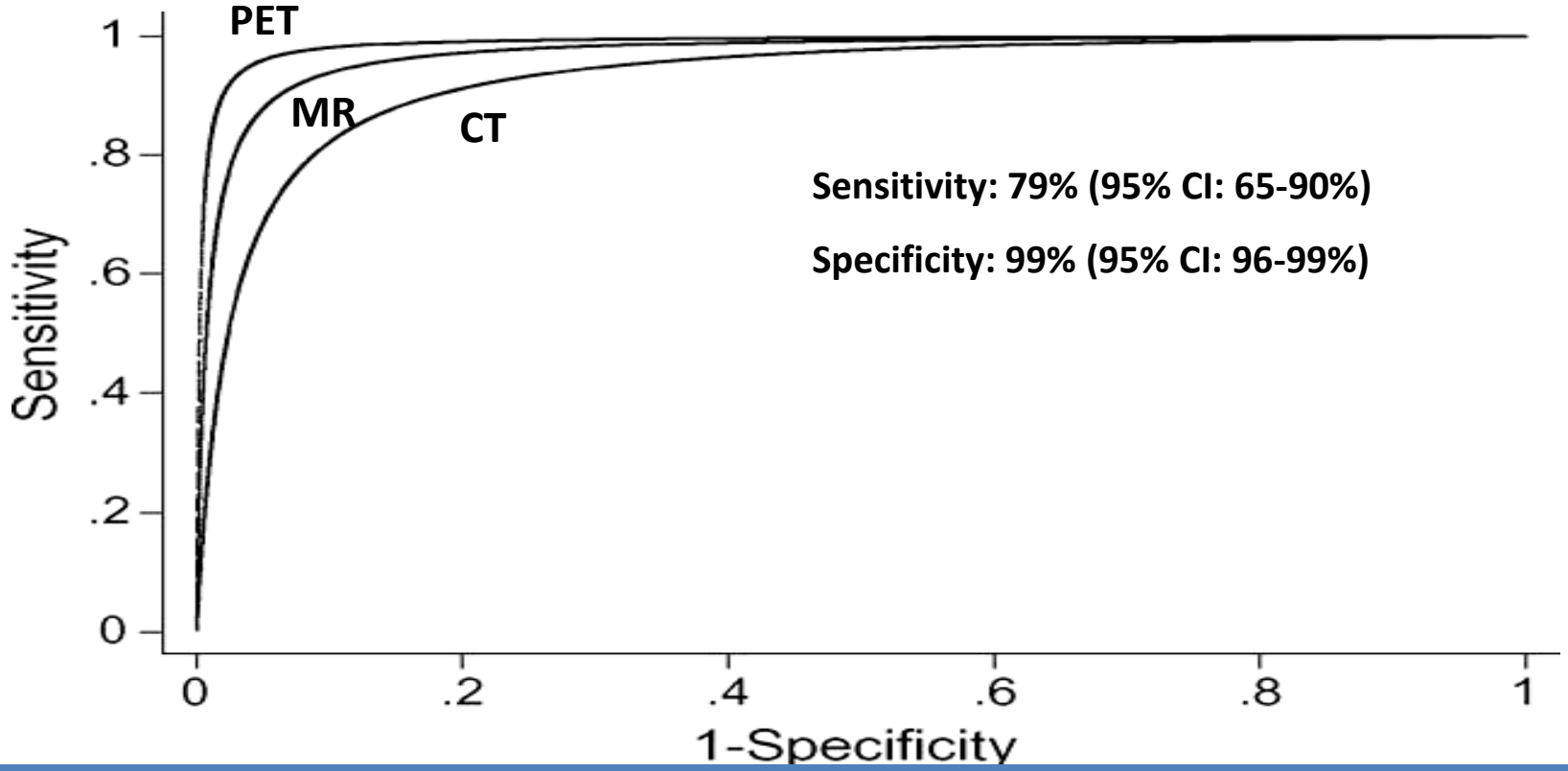


Ca Cervix IIIb with
Liver Metastasis

PET / PET-CT and Cancer Cervix

Lymph Nodal Staging

ROC curve for PET to detect pelvic nodal metastasis in newly diagnosed cervical cancer, with 95% confidence intervals (Area under curve = 0.970).



Sensitivity: 79% (95% CI: 65-90%)

Specificity: 99% (95% CI: 96-99%)

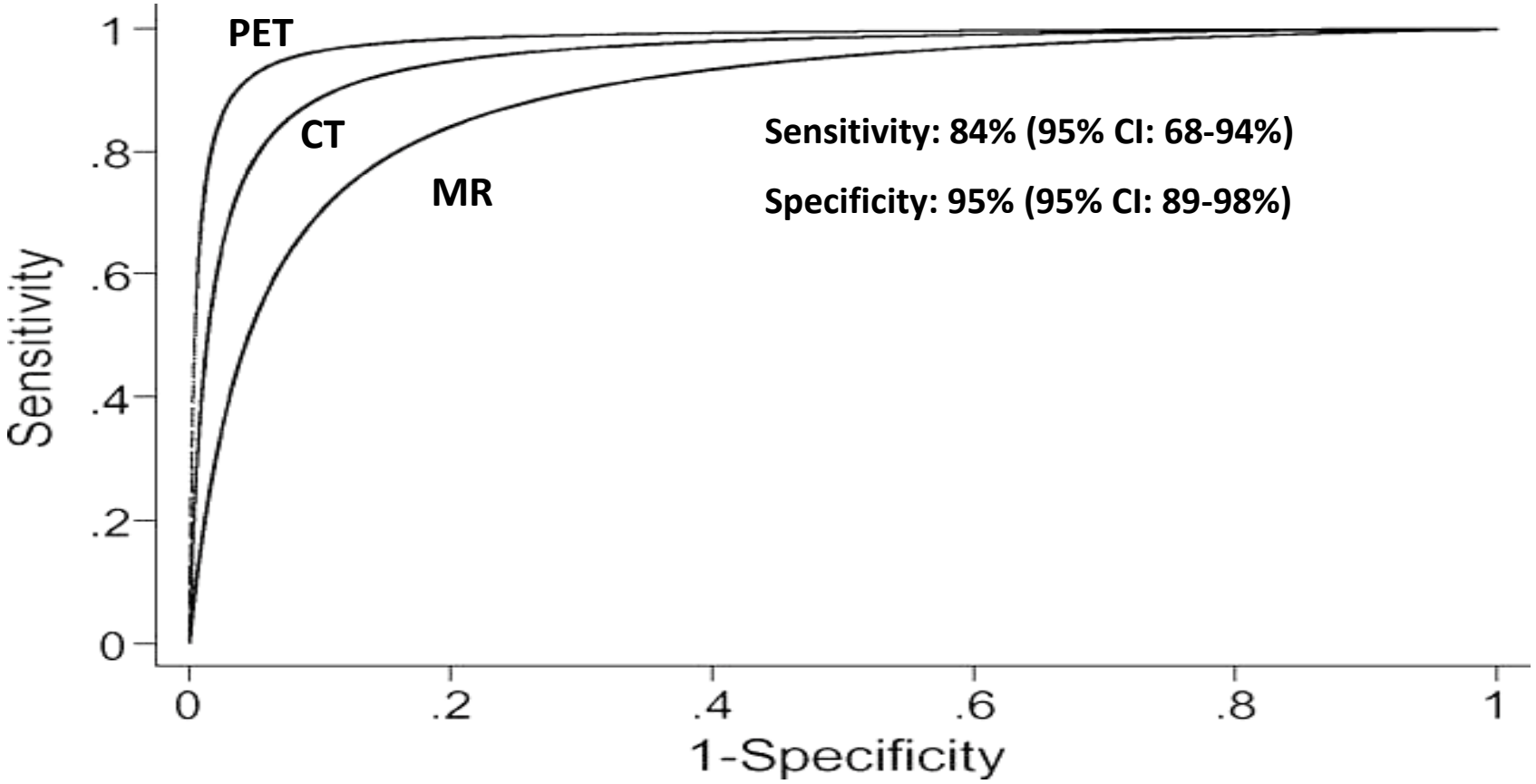
No enough evidence exists for detection of nodal disease in early Cx cancer and cannot replace lymph nodal dissection

L.J. Havrilesky et al. / G O 2005

PET / PET-CT and Cancer Cervix

Para-aortic Lymph Nodal Staging

ROC curve for PET to detect aortic nodal metastasis in newly diagnosed cervical cancer, with 95% confidence intervals (Area under curve = 0.952).



L.J. Havrilesky et al. / Gynecologic Oncology 97 (2005) 183–191

PET / PET-CT and Cancer Cervix

Post Therapy Surveillance

- **30 - 45% develop recurrences within 2 - 3 years Post Rx**
- **Response Evaluation : Important Predictor for recurrence & survivals**
- **Local Disease : Response and Detection of Early Local Recurrence**
- **Pelvic and / or Para-aortic Nodal Disease**
- **Other Sites of Distant Metastasis : Lung, Mediastinal Nodes, Bone,**

PET / PET-CT and Cancer Cervix

Response and Outcome

- Mean 3 months post therapy PET scan Evaluation
- Retrospective study in 152 pts

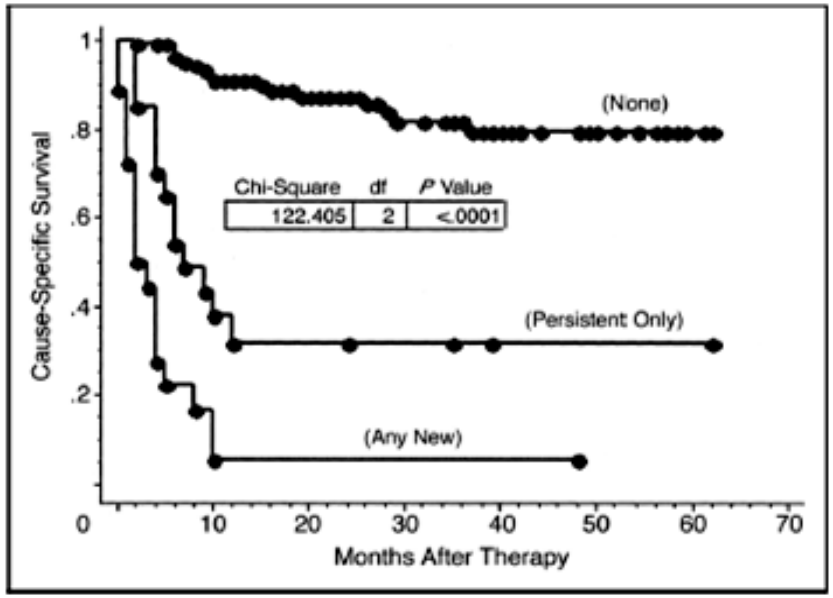


Fig 1. Cause-specific survival.

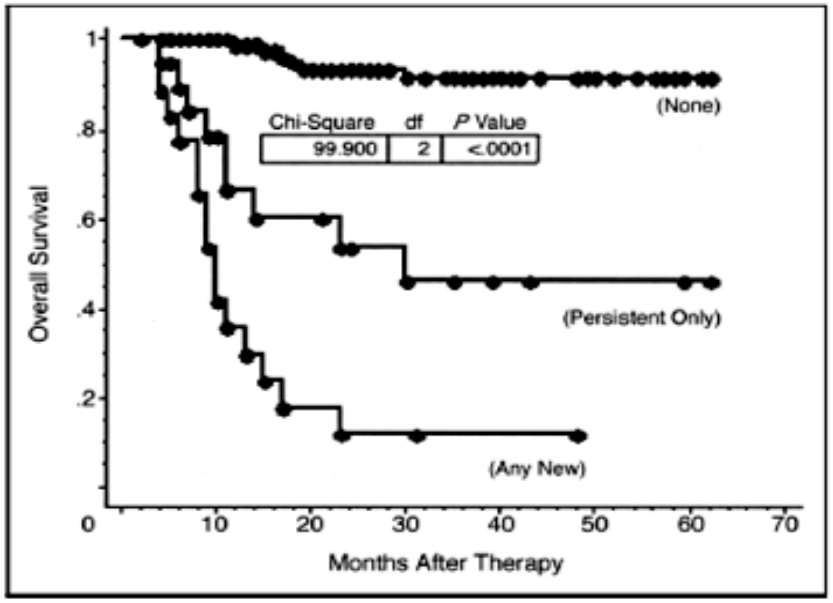


Fig 2. Overall survival.

Grigsby et al JCO 2004

- **PET has limitations to detect microscopic lesions <1cc**
- **Post Rx Pelvic inflammation might persists for months : false positivity high**
- **Need for further research to document treatment response**

SUMMARY

- Clinical Examination and objective documentation
- CT Imaging : Minimum in locally advanced Cervical cancer
- MR Imaging : Gold Standard
  - Understanding and Reading MR : Essential
- PET-CT : As an alternative to CT Imaging

THANK YOU

Acknowledgement s

ESTRO Teaching Material

GYN ESTRO Teaching Faculty

GYN Unit, TMH

Imaging Pathology of Cervix Cancer Clinical Drawings, CT, US, PET CT, MRI At time of Brachytherapy

Primoz Petric, MD, Msc
Senior Consultant

Department of Radiation Oncology
NCCCR, HMC
Doha, Qatar

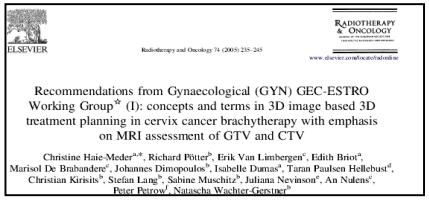
Adapted and Presented by

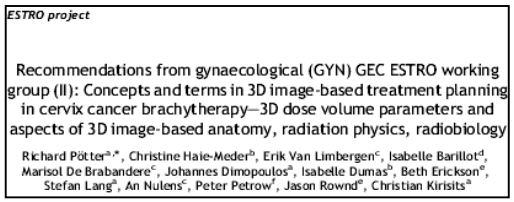
Richard Pötter, Medical University Vienna

Gold standard I : T2W MRI

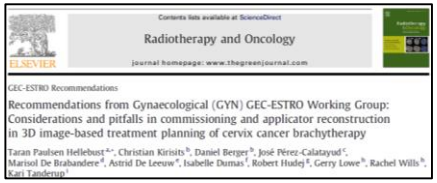
Magnetic Resonance Imaging

- 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

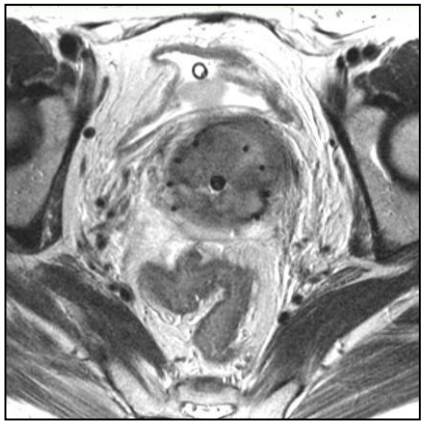
GEC-ESTRO Recommendations

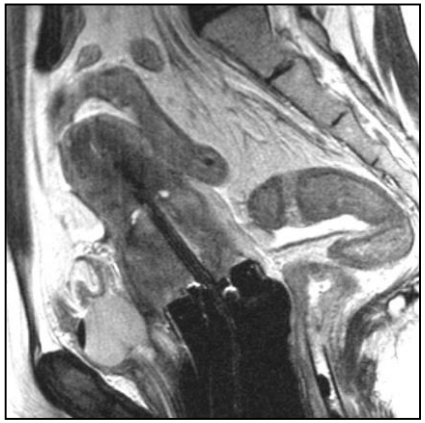
Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group: Considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer brachytherapy

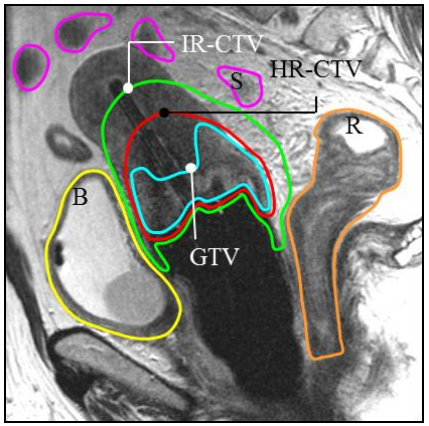

Radiotherapy and Oncology

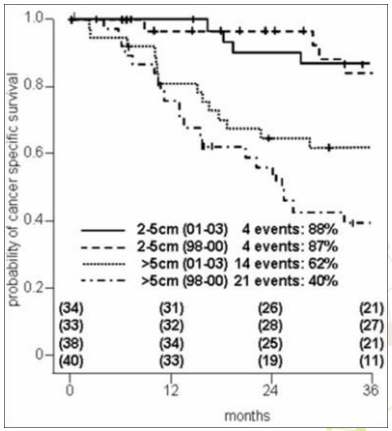
GEC-ESTRO Recommendations

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

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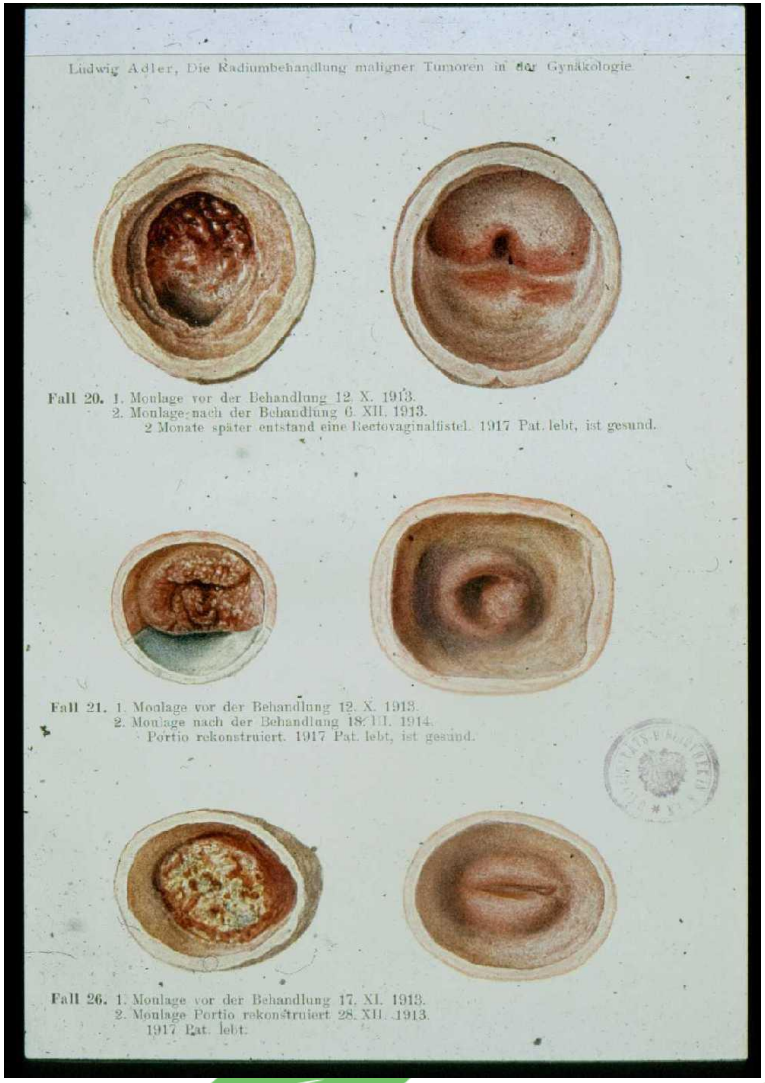
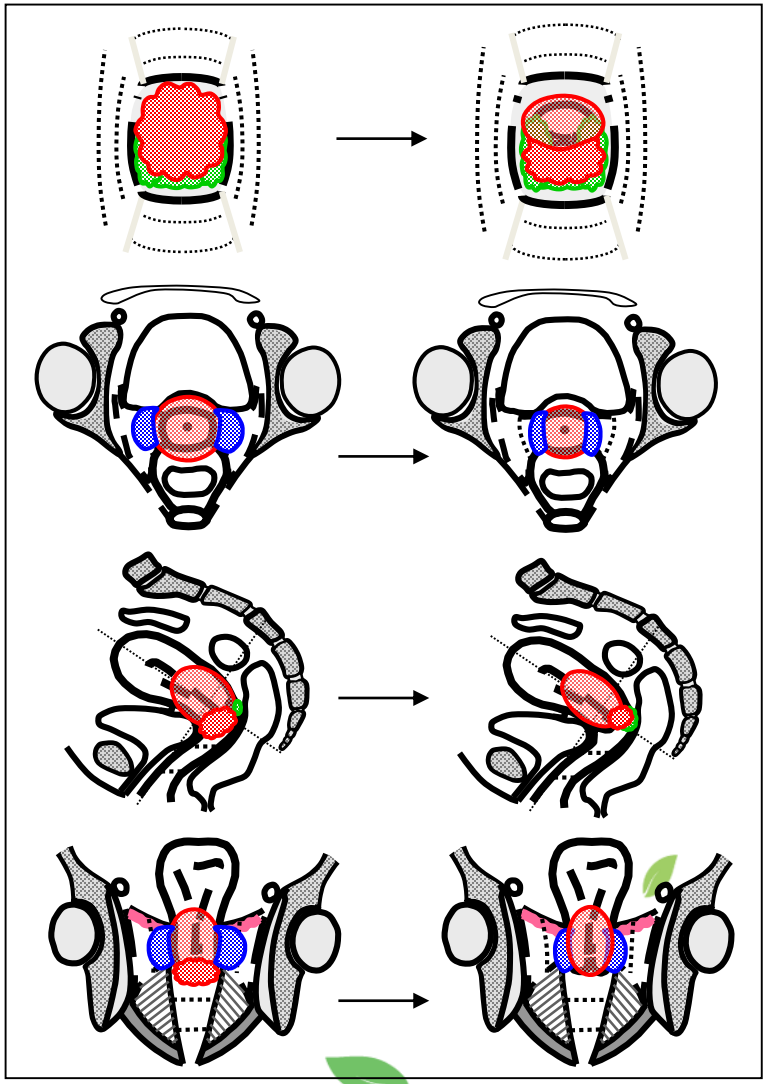
Sala E. Radiology 2006
Yu KK. Radiology 1999

Gold Standard II: Clinical examination: Inspection & Palpation & 3D/4D documentation

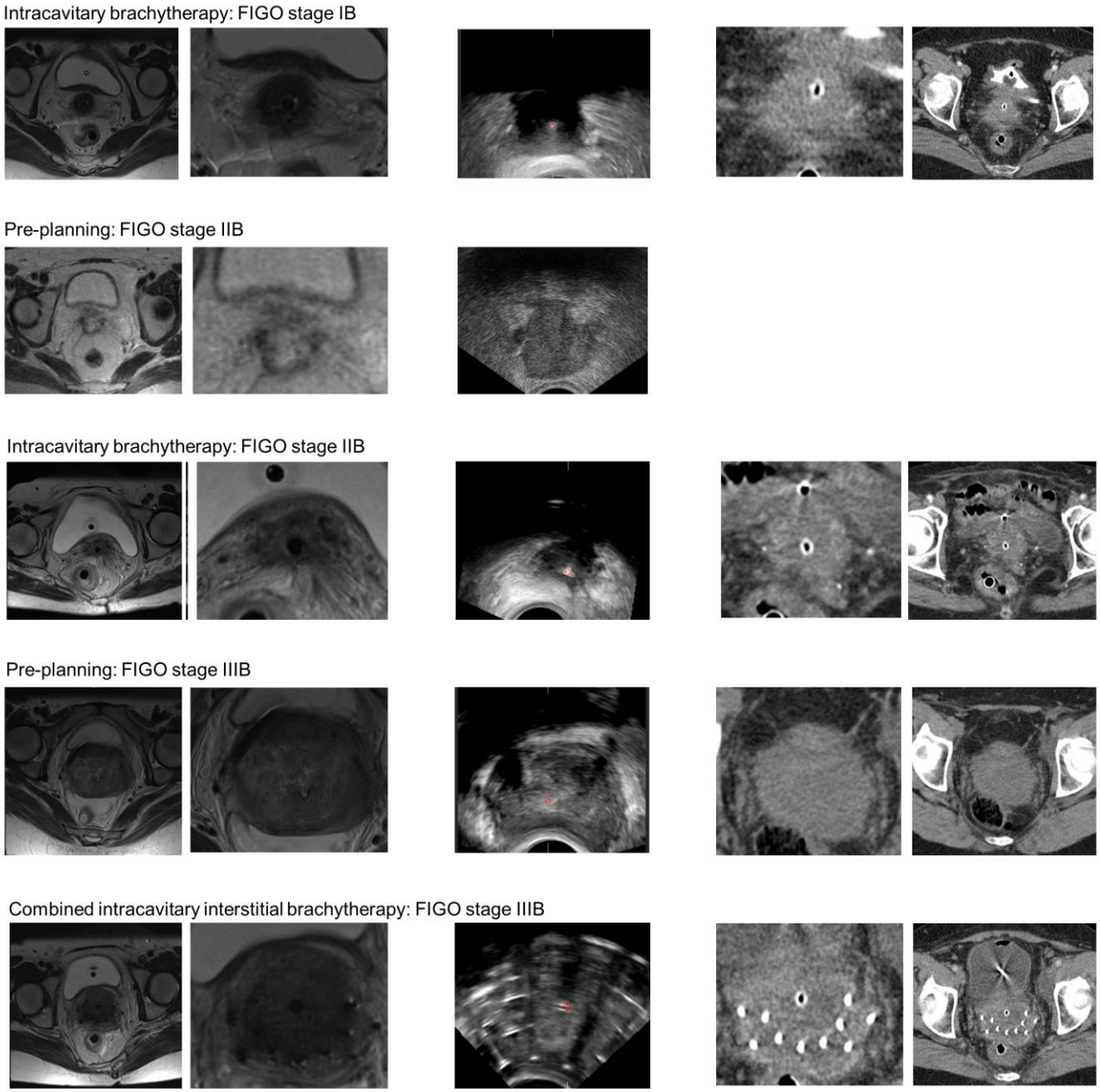
Adler: Strahlentherapie, 1918



EMBRACE study protocol, 2011



Courtesy: R. Pötter, MUW



M. Schmid, Vienna, ongoing clinical study

Imaging at BT

MRI (gold)

US (silver+)

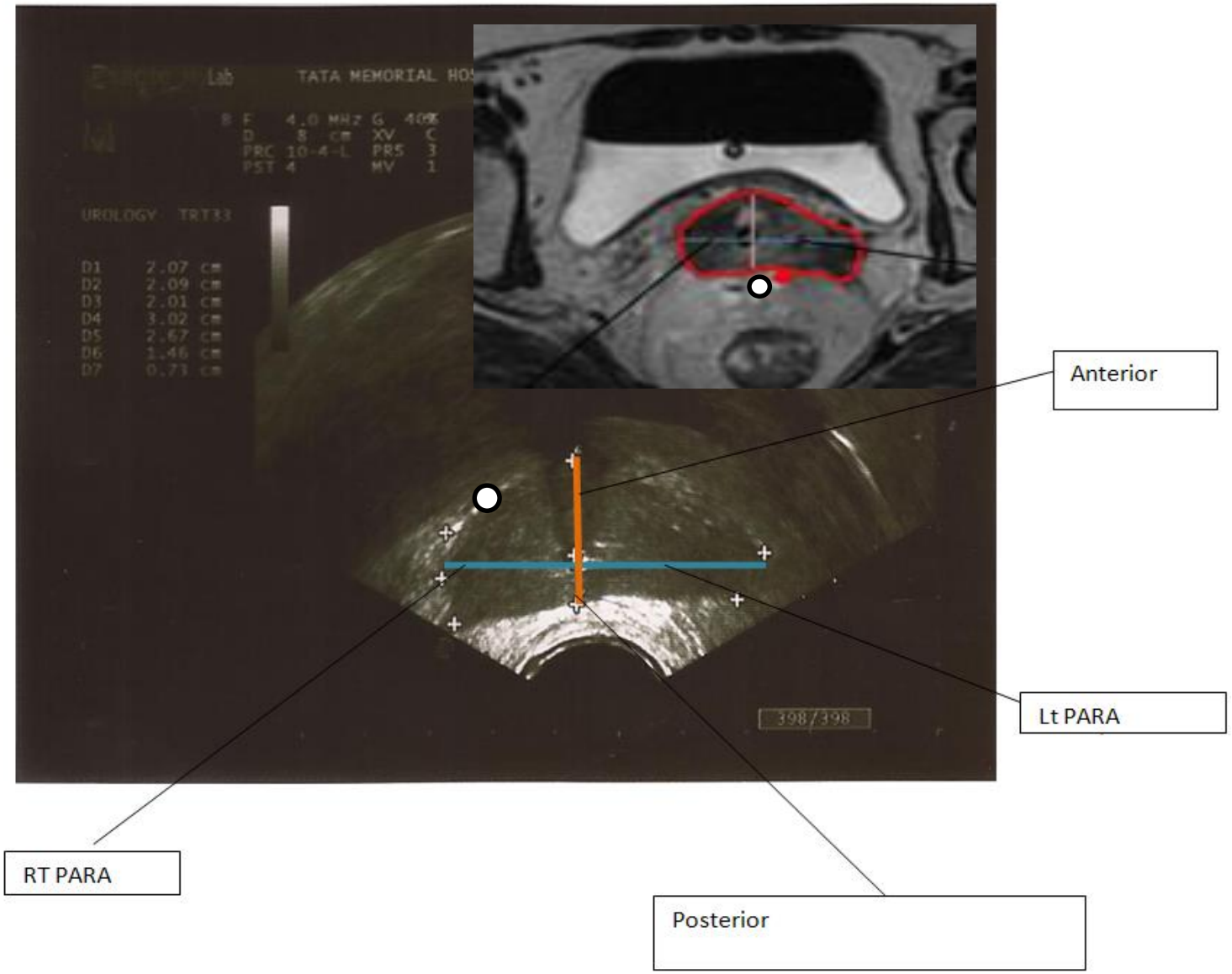
CT (bronze)

Clinical drawing (gold)

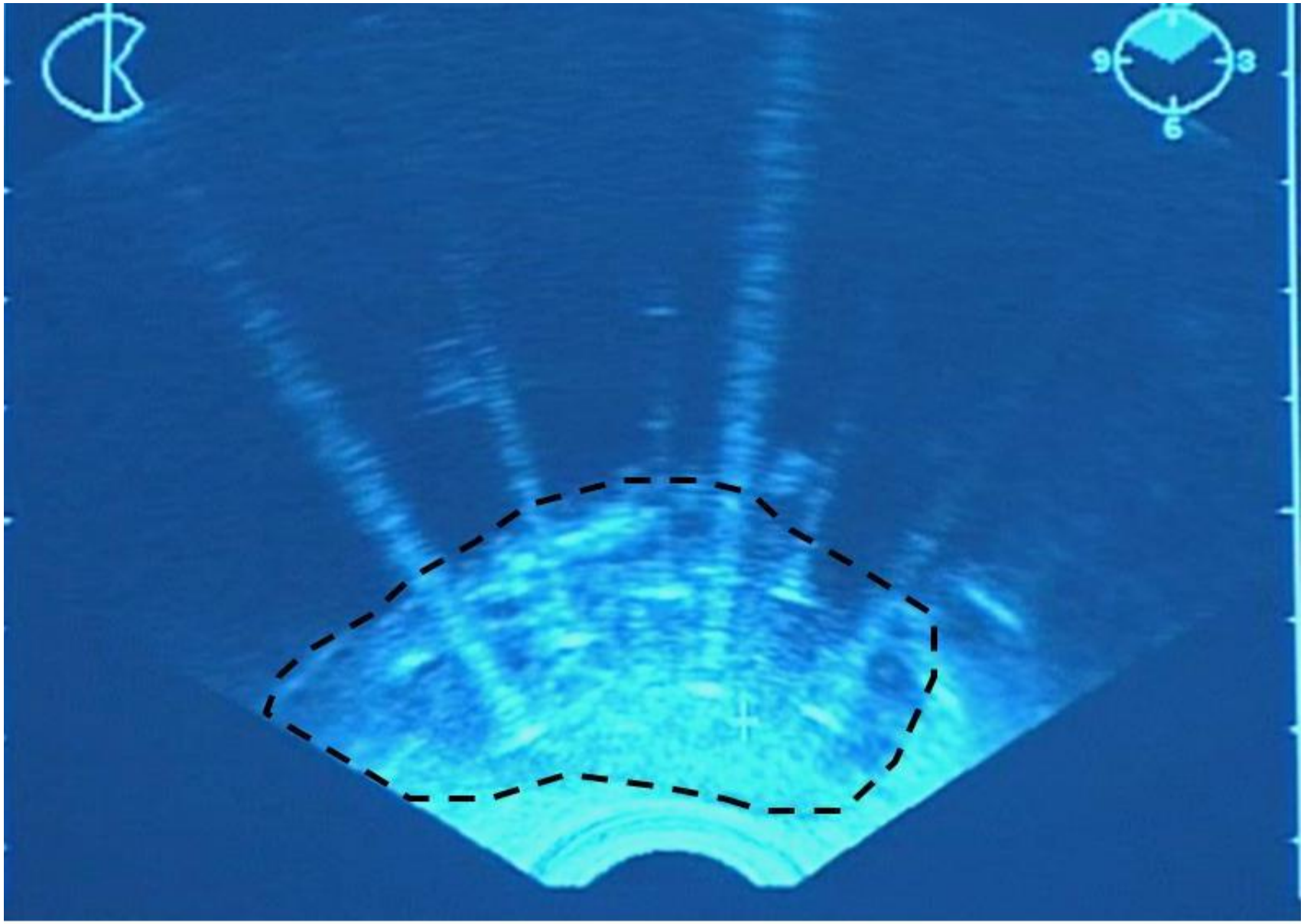
RESEARCH : TRUS Guided Target Volume Definition

TMH STUDY: ONGOING RESEARCH (N=27 pts so far)

MRI-TRUS Correlation



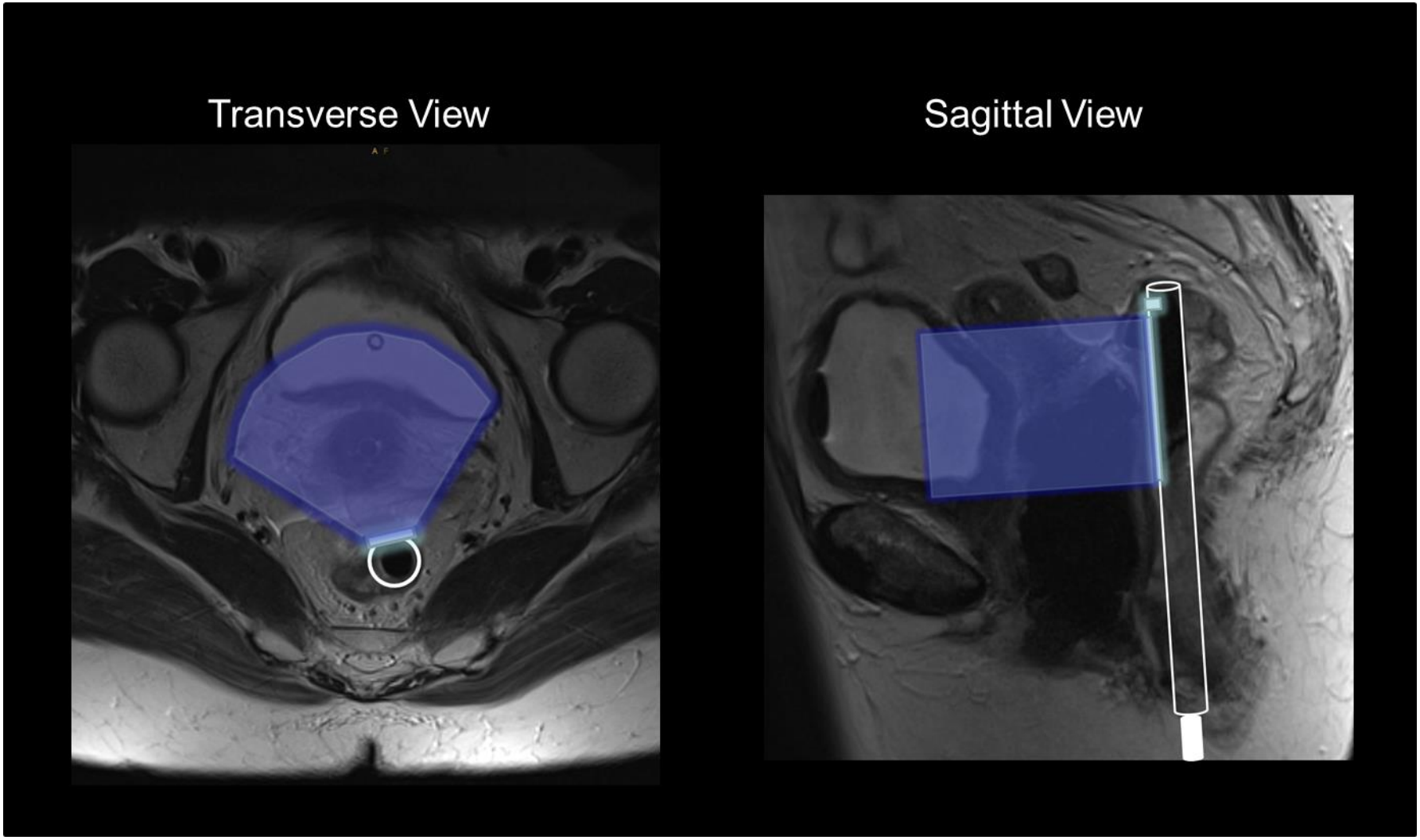
TRUS image showing IBT needles in cervical cancer



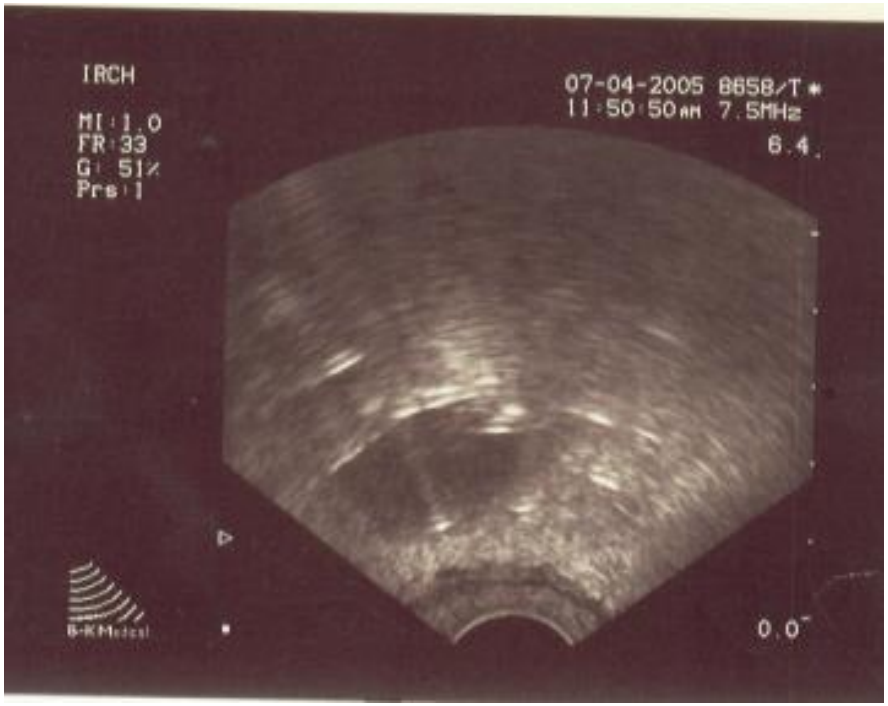
By courtesy of D. Sharma

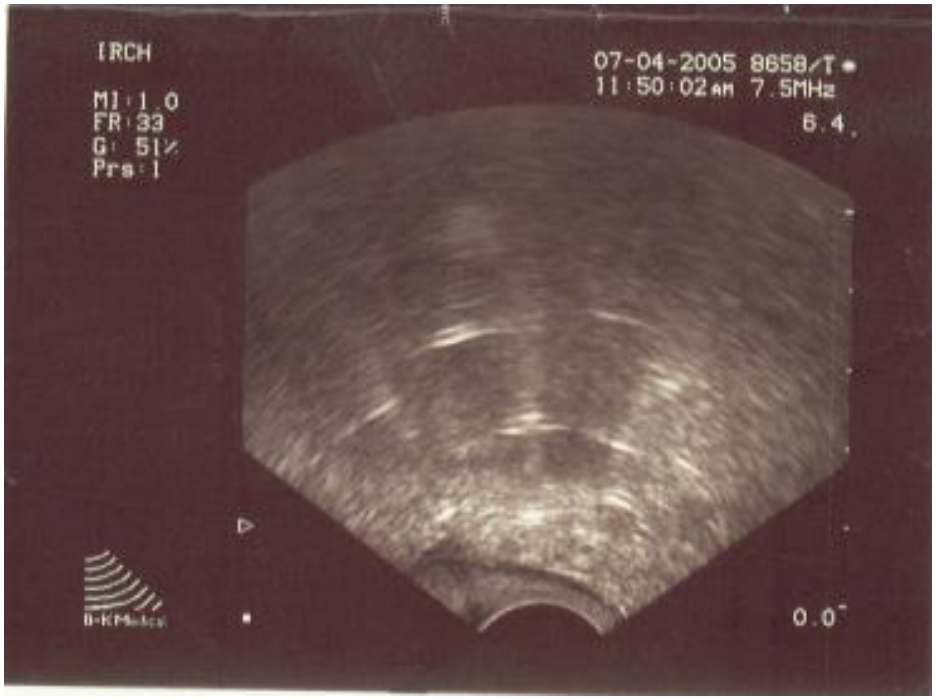
Transrectal Ultrasound

Echo is orthogonal to the probe



(In vaginal US: echo is in direction of the probe)





J Gynecol Oncol Vol. 21, No. 1:12-17, March 2010 DOI:10.3802/jgo.2010.21.1.12

Original Article

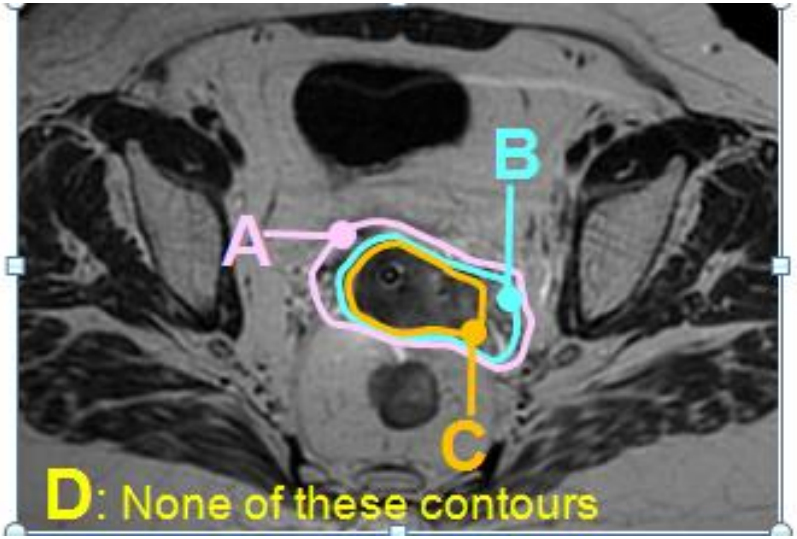
Use of transrectal ultrasound for high dose rate interstitial brachytherapy for patients of carcinoma of uterine cervix

Daya Nand Sharma[1], Goura Kisor Rath[1], Sanjay Thulkar[2], Sunesh Kumar[3], Vellaiyan Subramani[1], Parmod Kumar Julka[1]

Departments of [1]Radiation Oncology, [2]Radiodiagnosis, [3]Gynecology and Obstetrics, All India Institute of Medical Sciences, New Delhi, India

Interpretation of imaging findings at BT

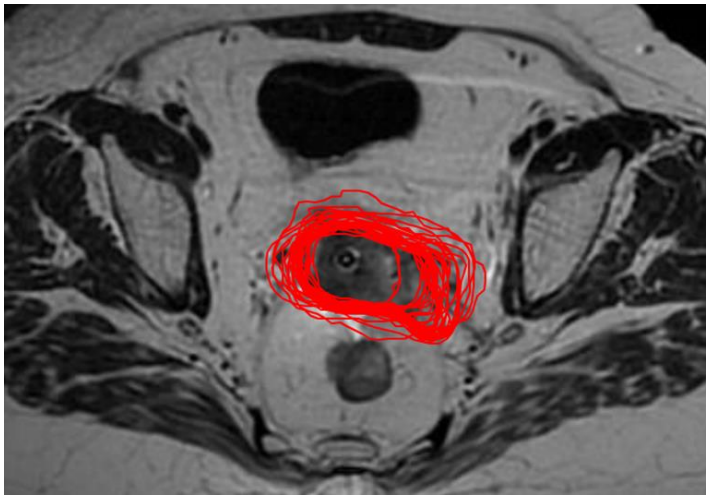
What is the High Risk CTV on this slice? (your best guess)

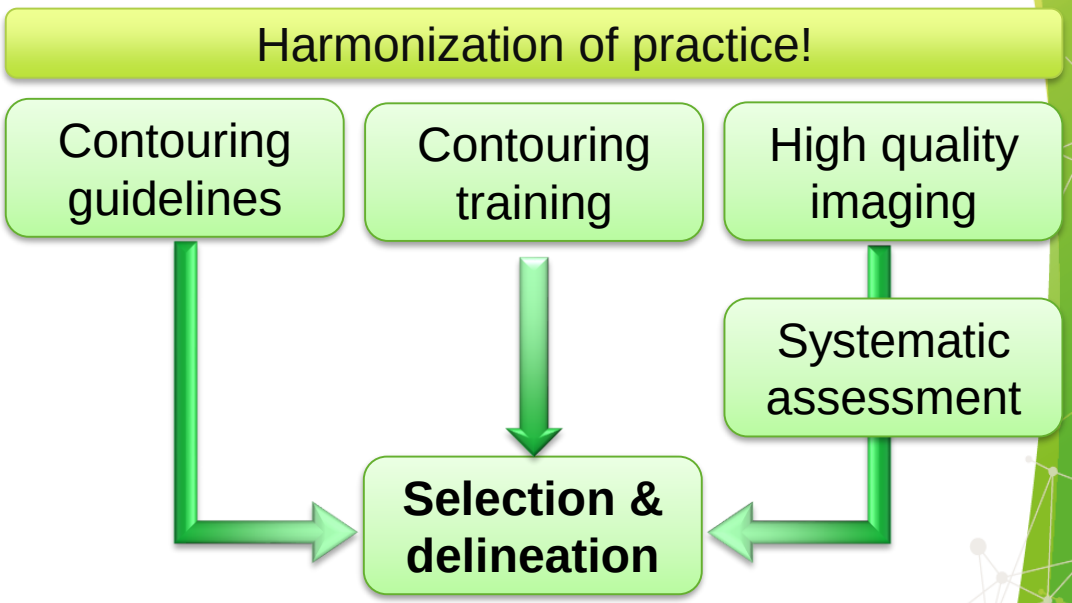


A. A
B. B
C. C
D. D

Interpretation of imaging findings at BT

Contouring uncertainties: weakest link in Image guided BT?



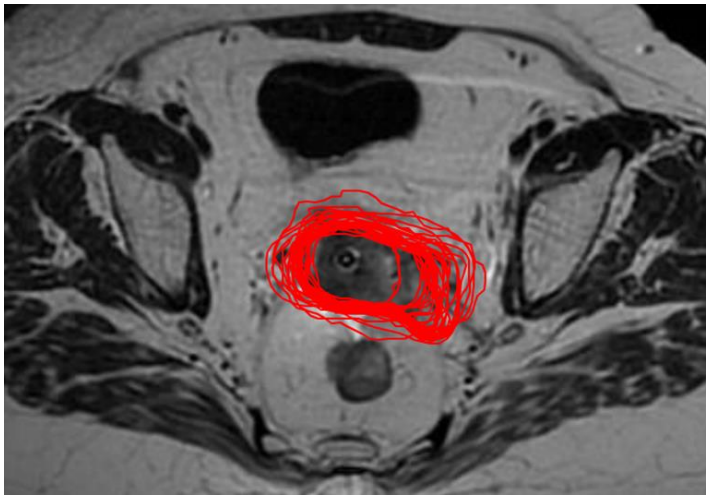


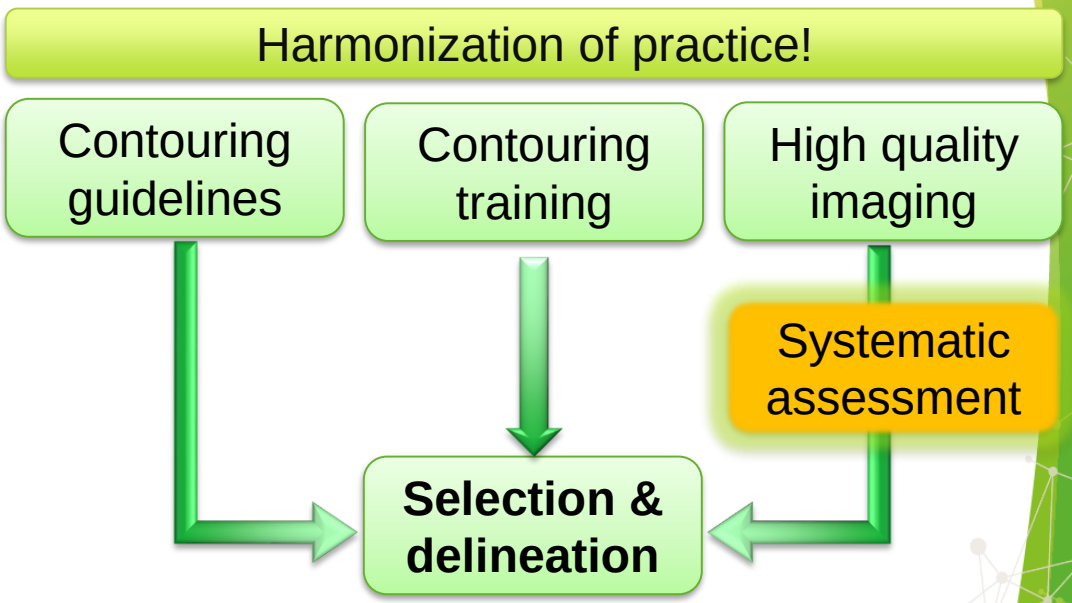
MRI and/or CT/US with clinical drawings

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

Interpretation of imaging findings at BT

Contouring uncertainties: weakest link in Image guided BT?



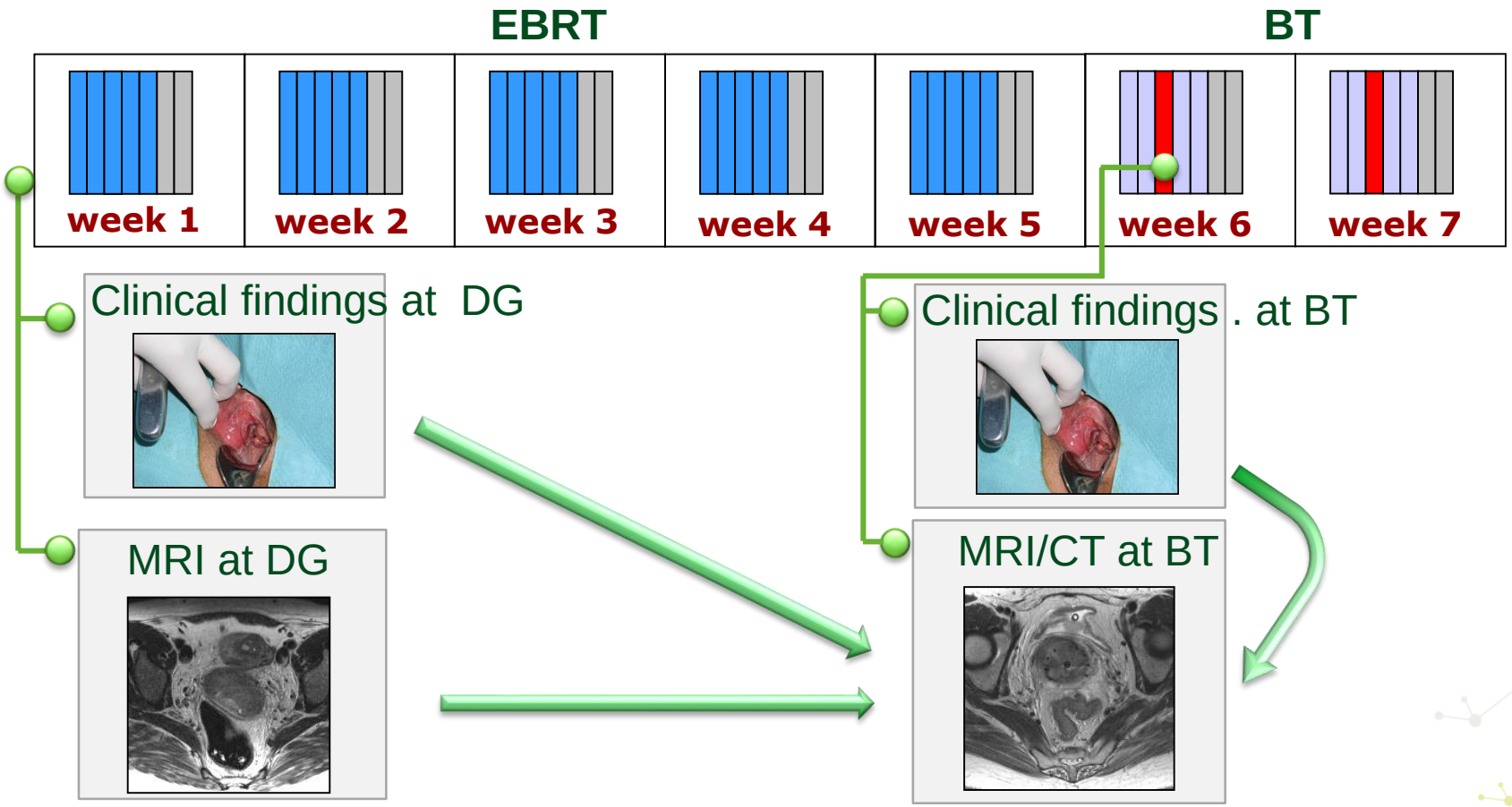


MRI and/or CT/US with clinical drawings

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

Assessment of sectional imaging at time of BT

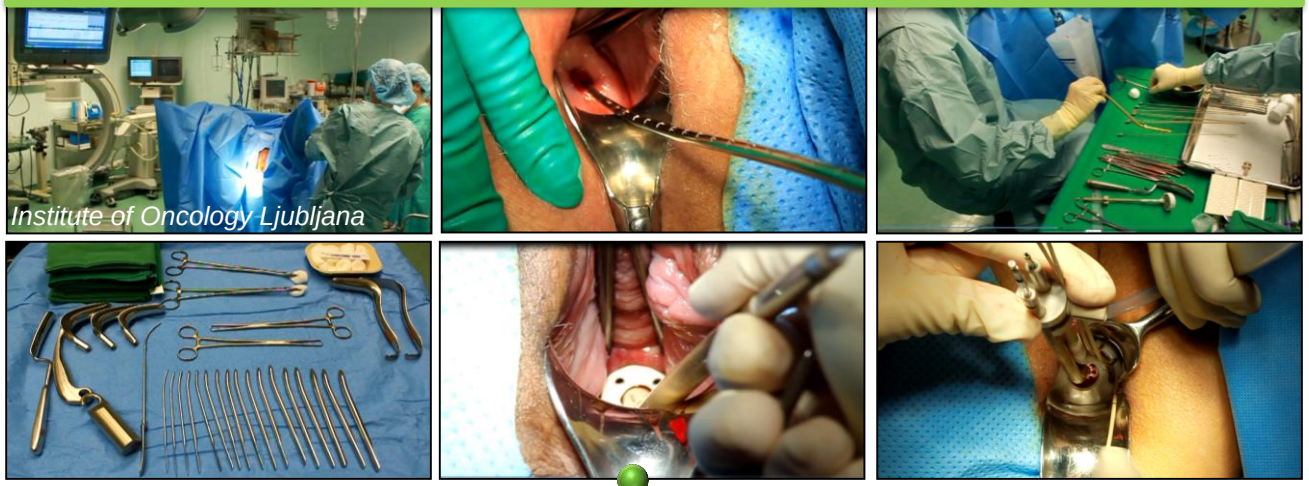
General principles



MRI and/or CT/US with clinical drawings

STEPS of Assessment of MRI/CT at BT

THEATRE

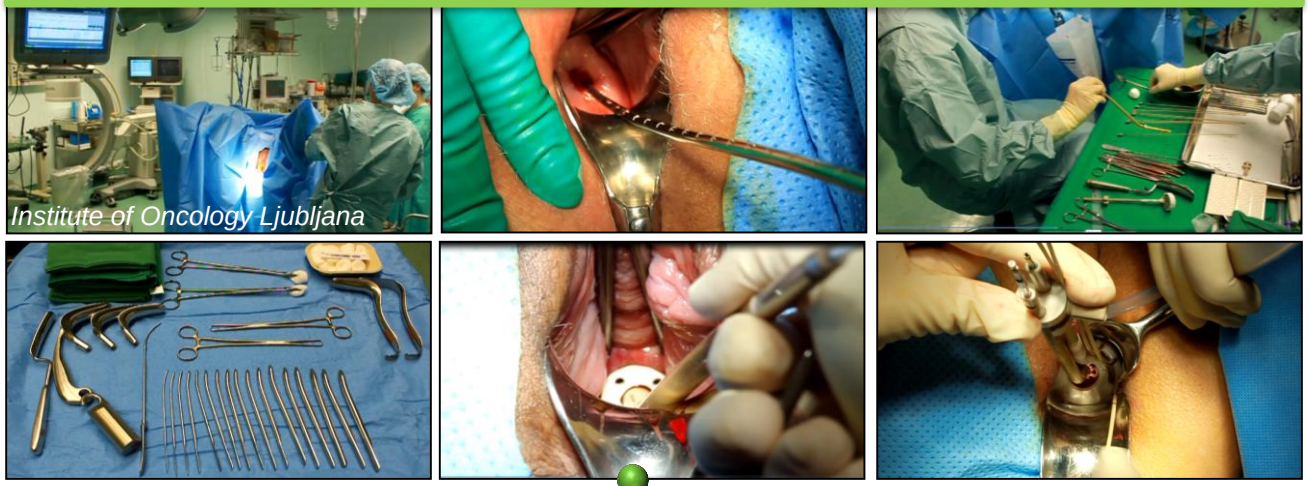


MRI and/or CT/US with clinical drawings

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

STEPS of Assessment of MRI/CT at BT

THEATRE



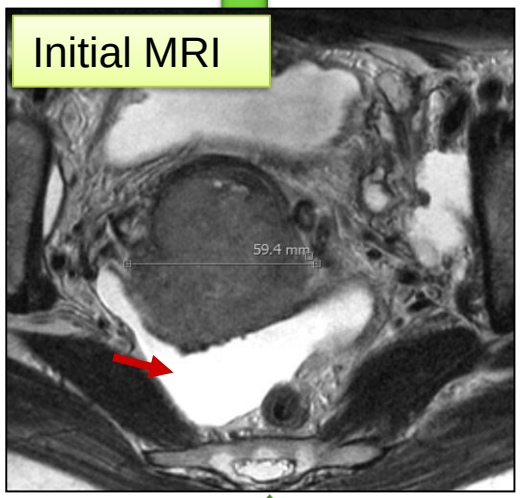
MRI and/or CT/US with clinical drawings

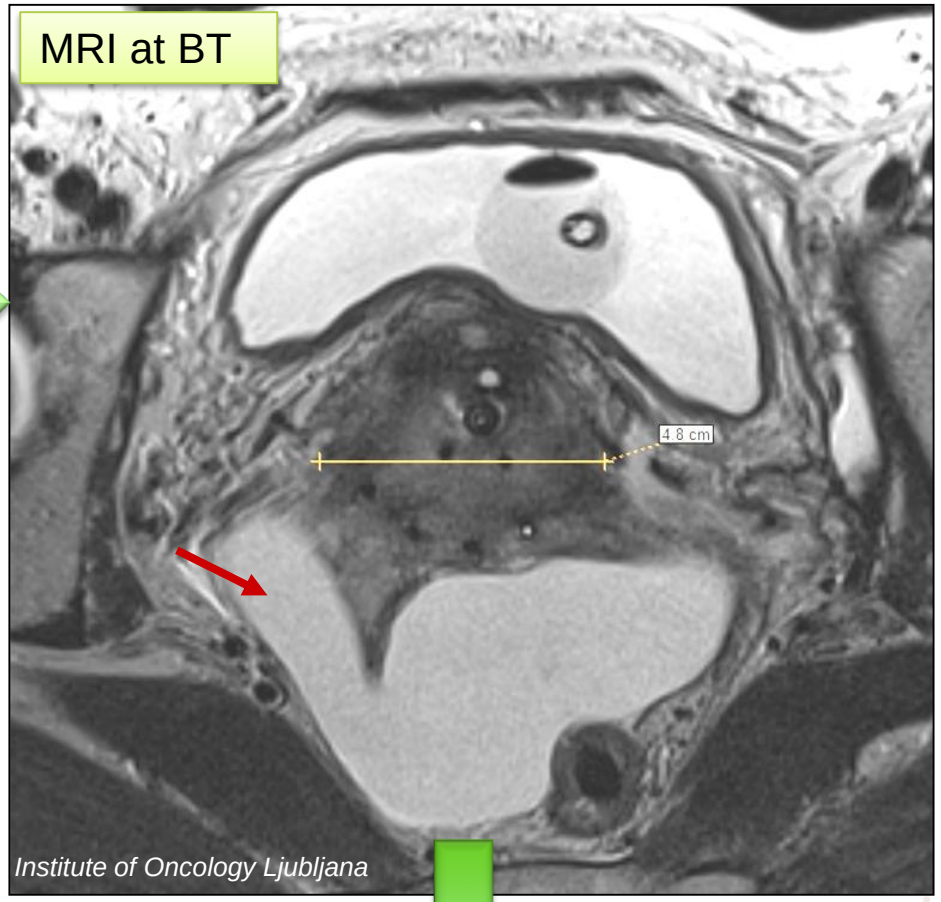
1. Rule out ***FLOP*** → 2. Set the ***STAGE*** for contouring

1. Rule out **FLOP**

FL **FL**uid in abdomen?

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



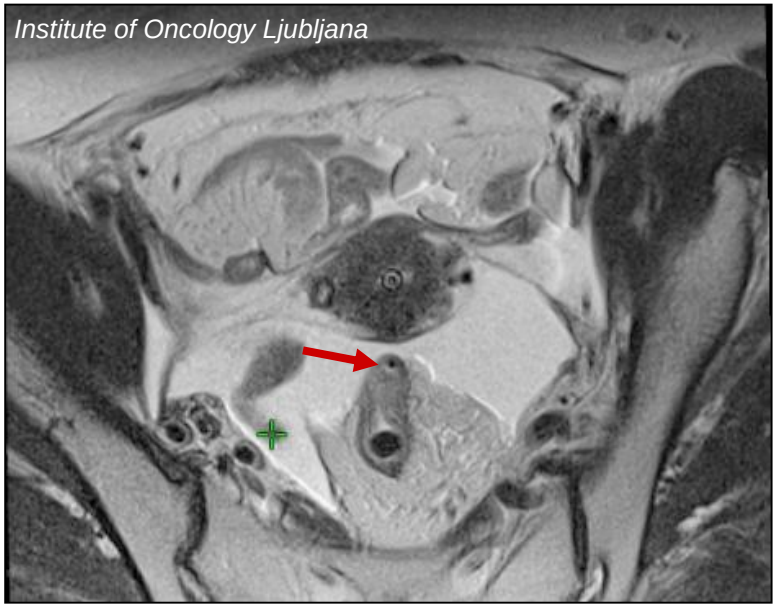


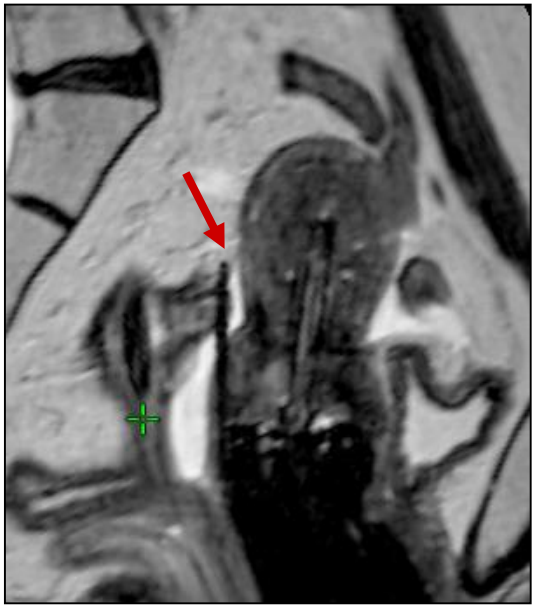
Compare with initial findings!

1. Rule out **FLOP**

FL **FL**uid in abdomen?

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





Action? ⇨ Have institutional policies and protocols ready!

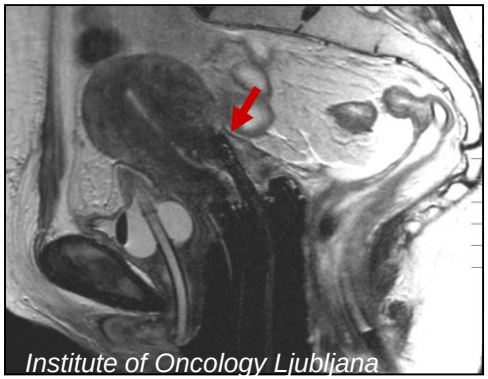
1. Rule out **FLOP**

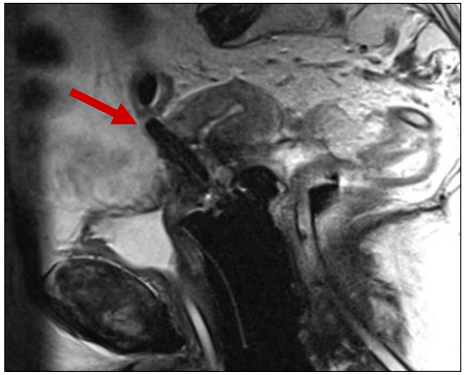
FL **FL**uid in abdomen?

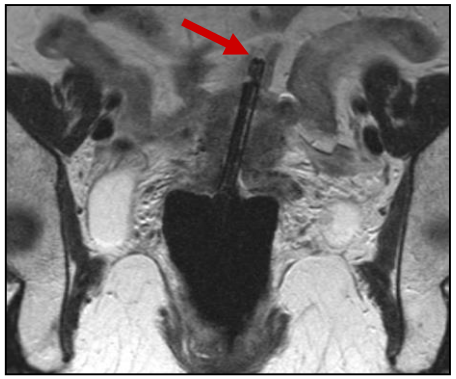
OP **O**rgan **P**erforation?

Uterine perforations

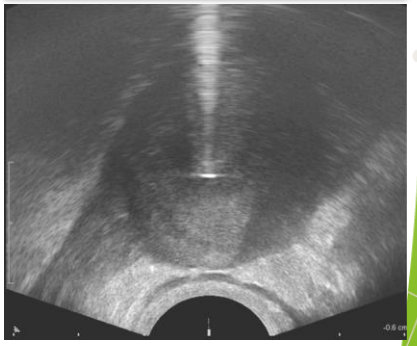
Up to ≈ 5-10 %!







US guidance!



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

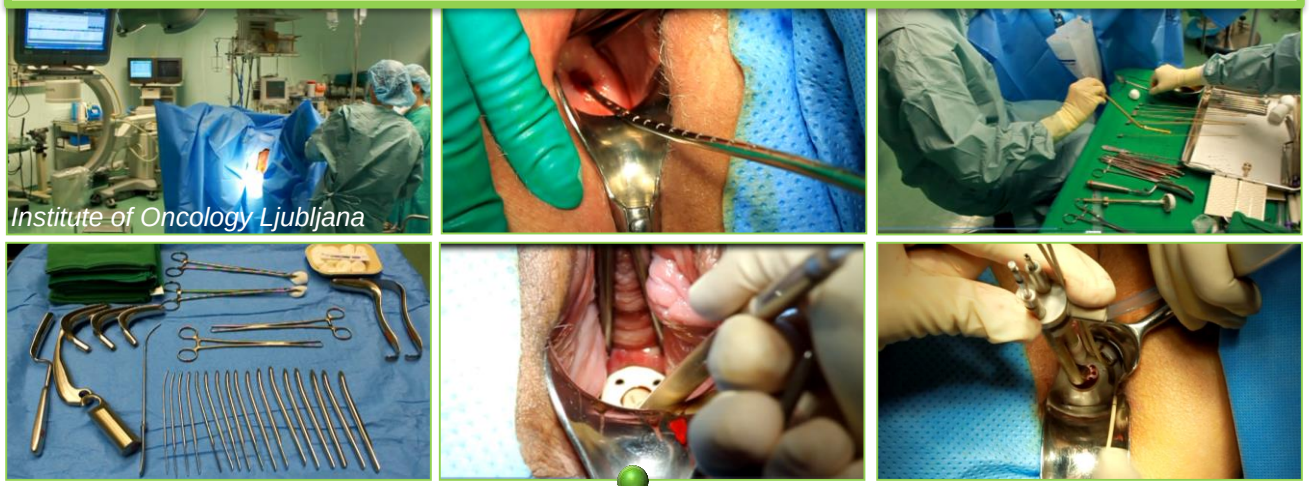
Jhingran A, Eifel PJ. IJROBP 2000
Barnes EA, et al. Int J Gynecol Cancer 2007
Lanciano R, et al. IJROBP 1994

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

Systematic Assessment of MRI/CT at BT

THEATRE



MRI and/or CT/US with clinical drawings

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

Set the **STAGE** for contouring

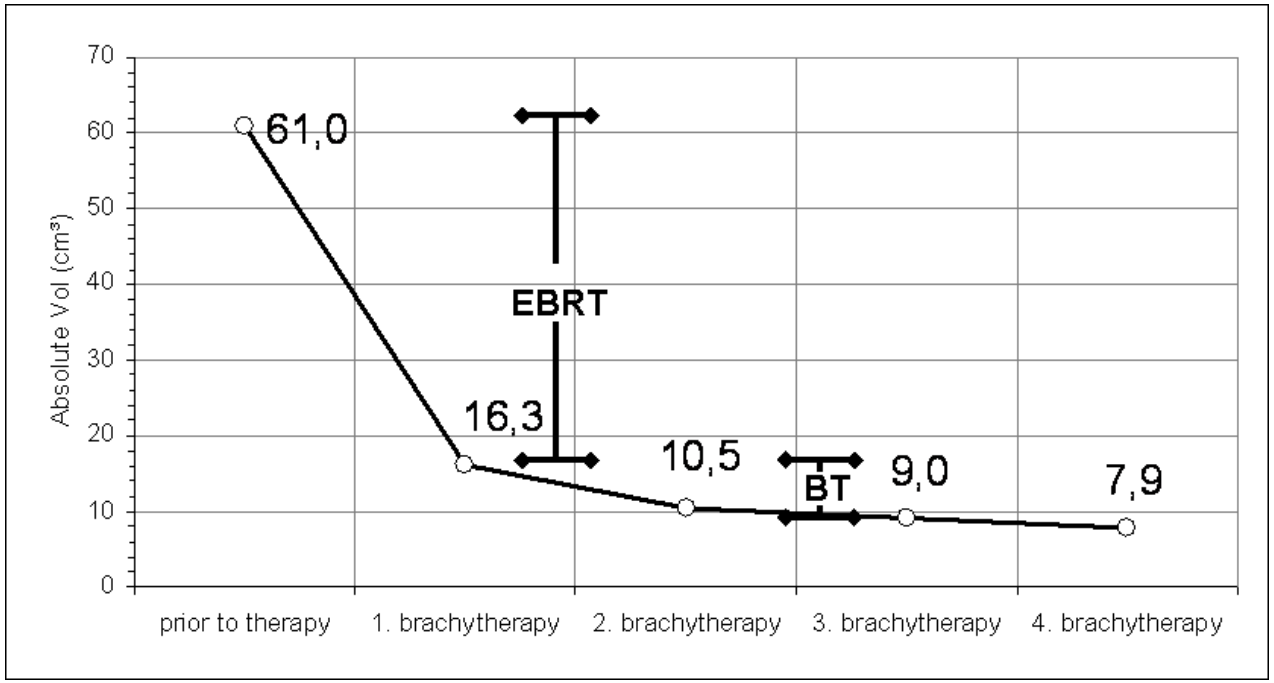
- **S**ize of the residual tumor?
- **T**opography of the target Volume?
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

Set the **STAGE** for contouring

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

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%

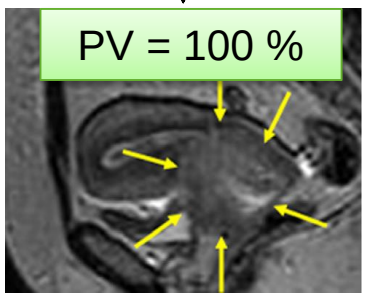
Size of the tumor at Brachytherapy

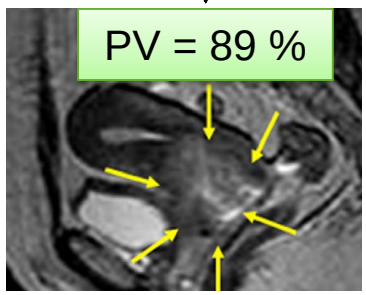
Volume change during treatment

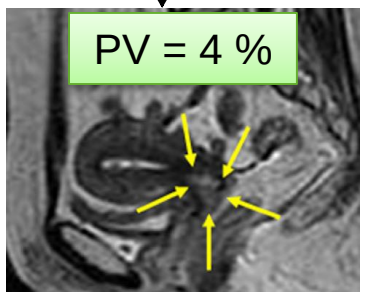
N= 115
stage IB2 - IVA

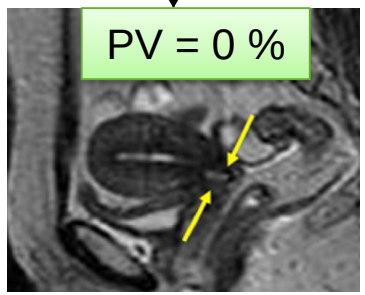
EBRT BT

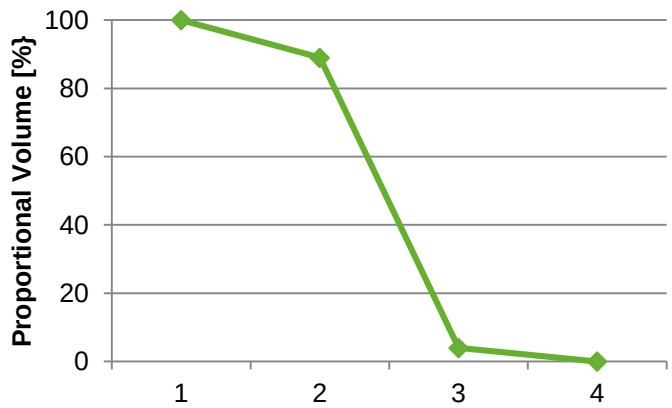
V_1 V_2 V_3 V_4











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

→ Alive & well at 7 y

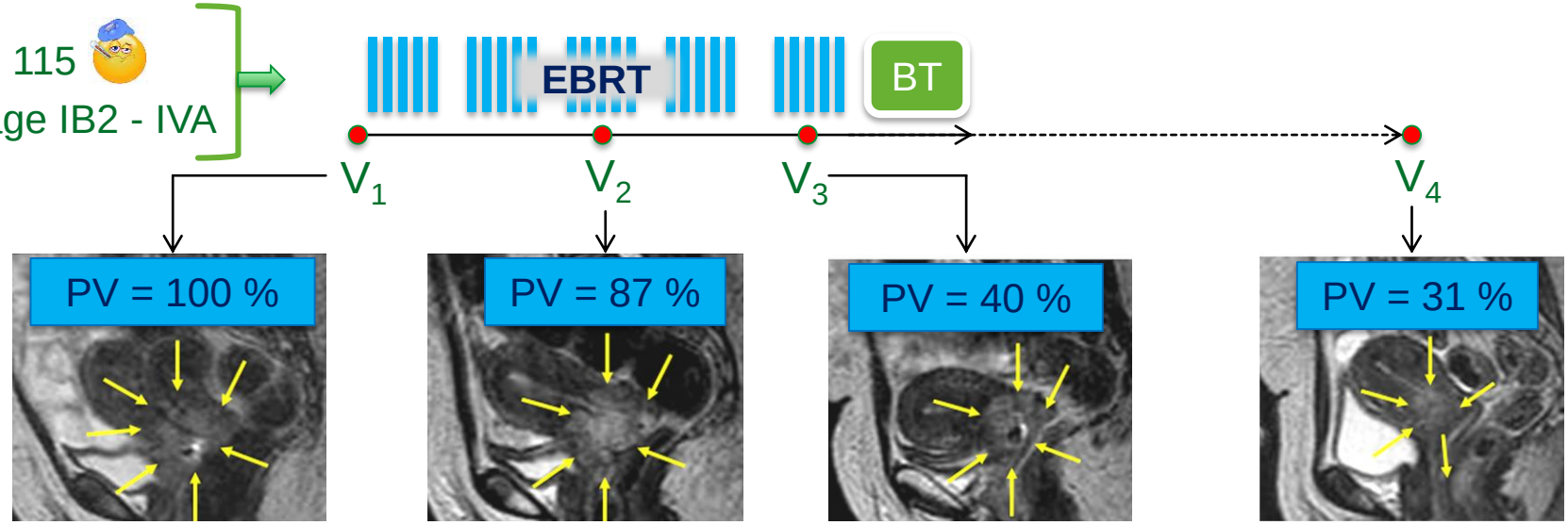
Mayr NA, et al. Int J Radiat Oncol Biol Phys 2010
Wang JZ, et al. Cancer 2010

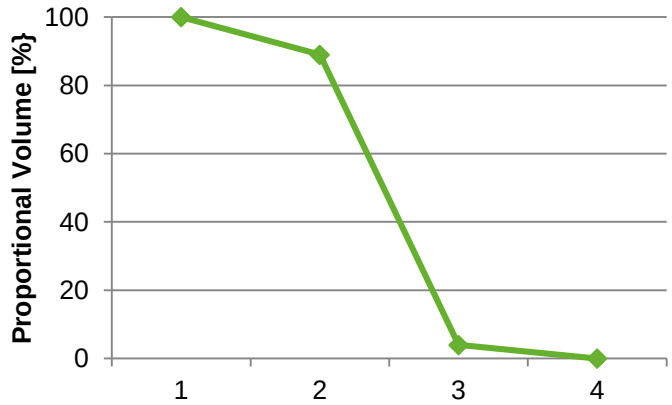
Size of the tumor at Brachytherapy

Volume change during treatment

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

N= 115
stage IB2 - IVA





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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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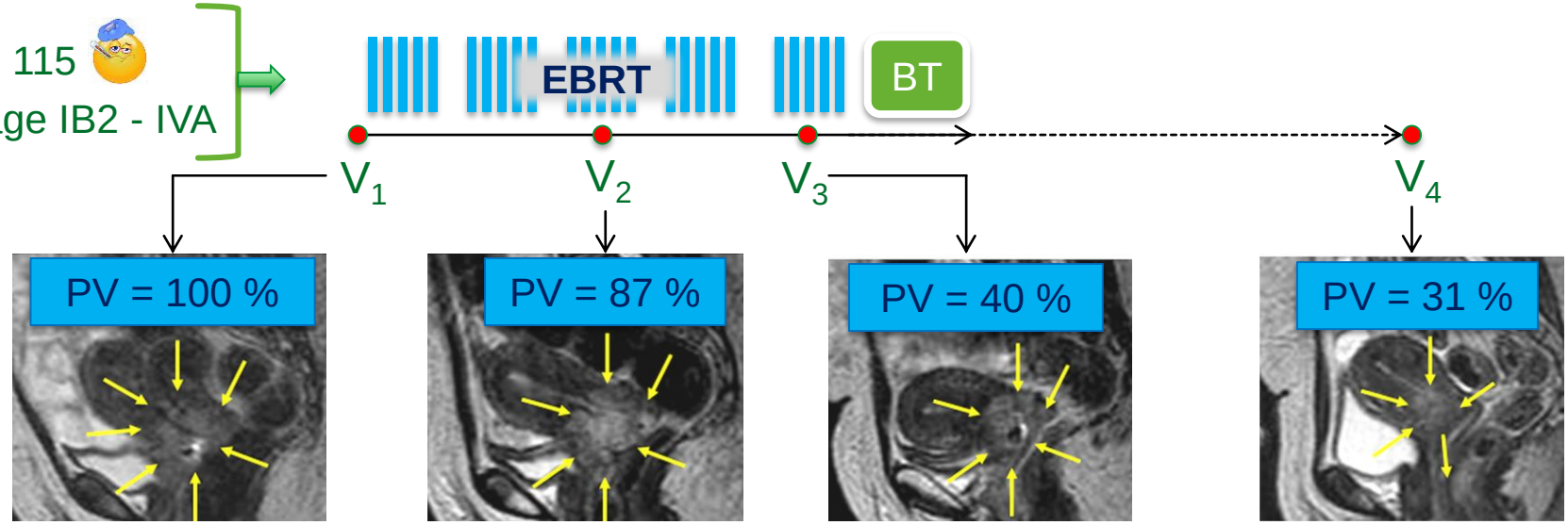
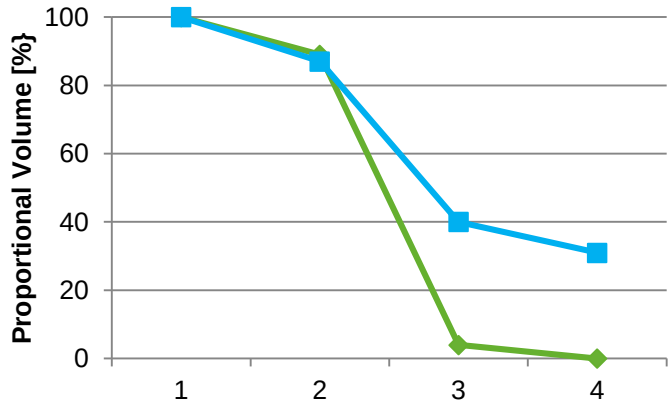
stage IB2 - IVA





- 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 %)

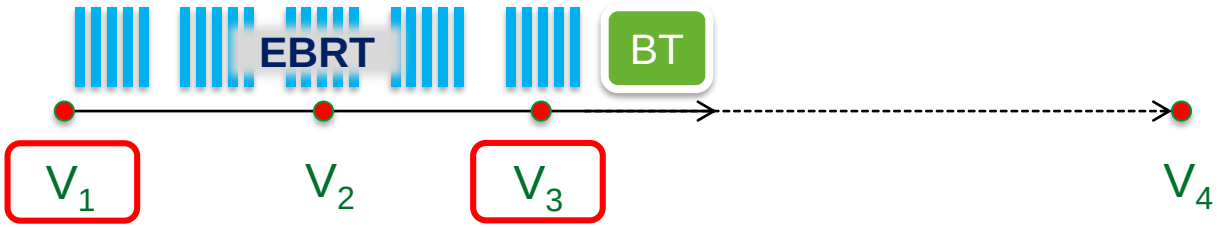
→ LR at 1 y
Death at 2 y

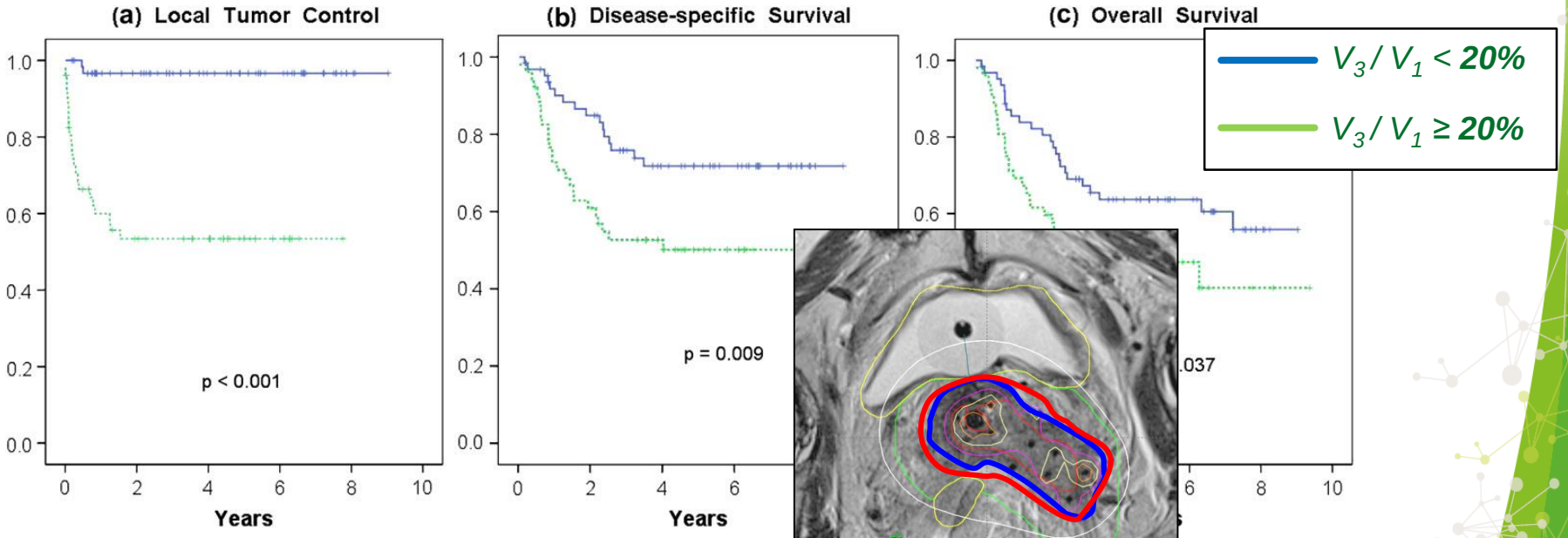
Mayr NA, et al. Int J Radiat Oncol Biol Phys 2010
Wang JZ, et al. Cancer 2010

Size of the tumor at Brachytherapy

Volume change as outcome predictor

N= 115
stage IB2 - IVA



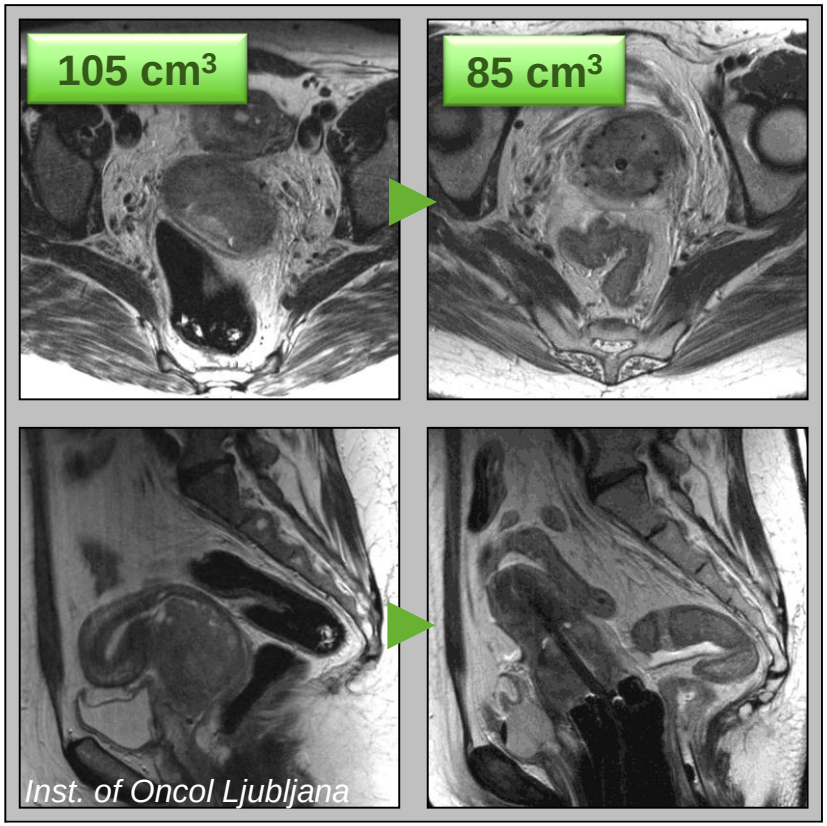
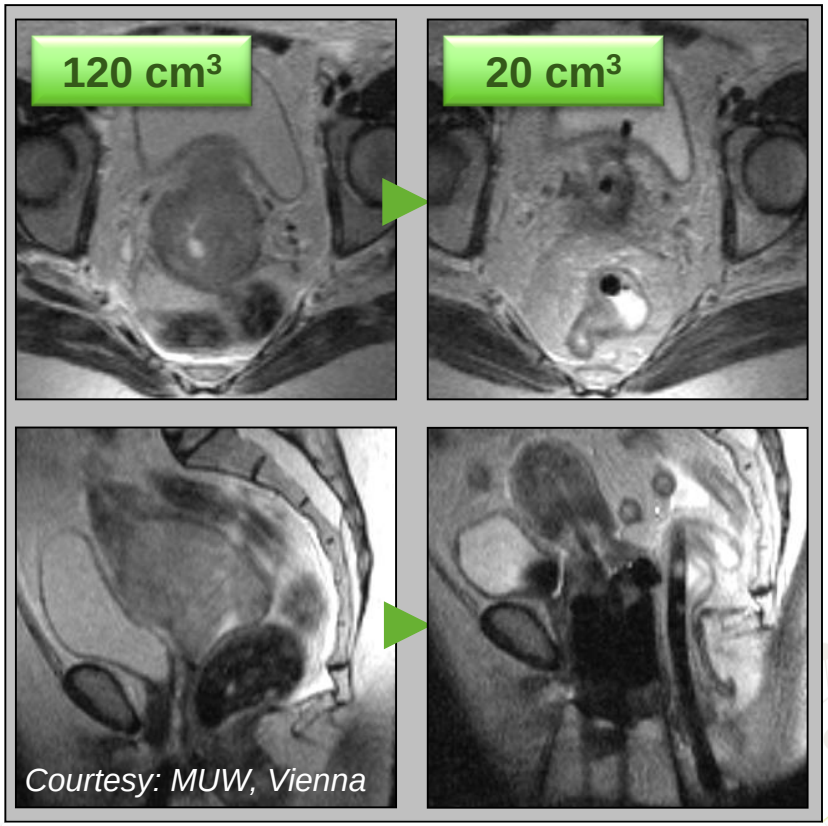


Mayr NA, et al. Int J Radiat Oncol Biol Pl
Wang JZ, et al. Cancer 2010

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

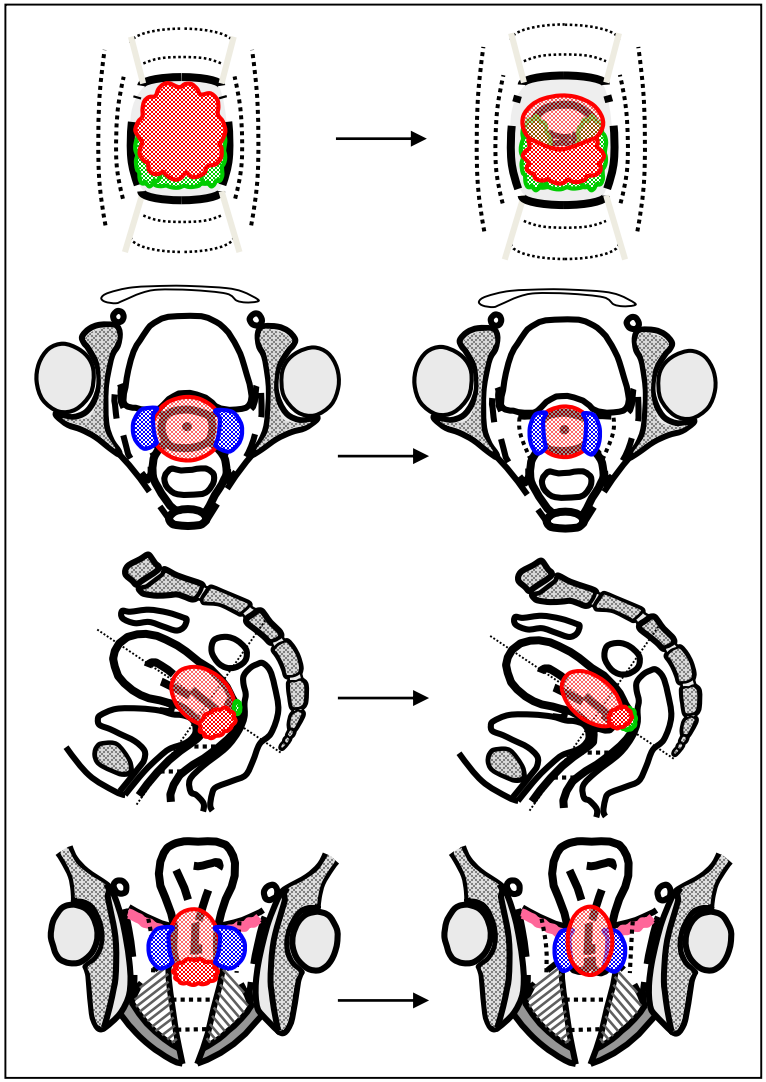
Size of the tumor at Brachytherapy

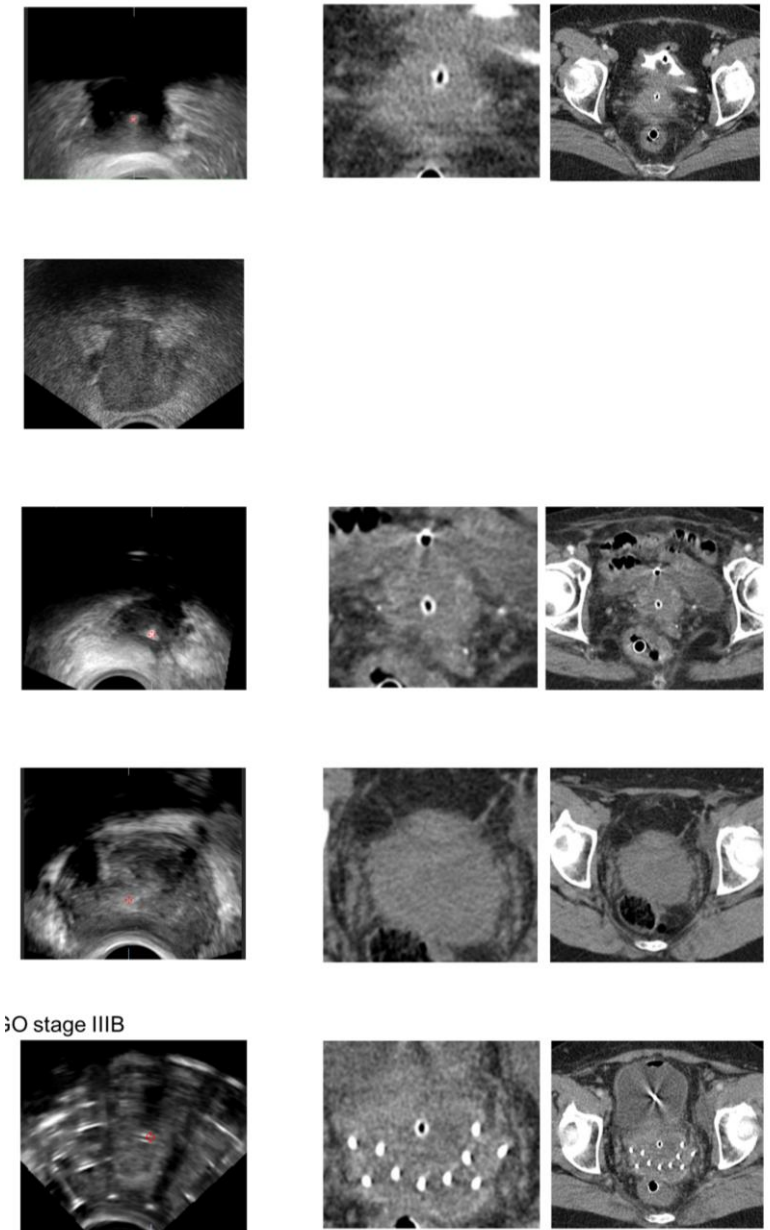
Qualitative vs. quantitative

Bad response	Good response
	
81 %	17 %

The Challenge of no MRI at BT: CT and/or US and clinical examination with documentation

EMBRACE study protocol, 2011



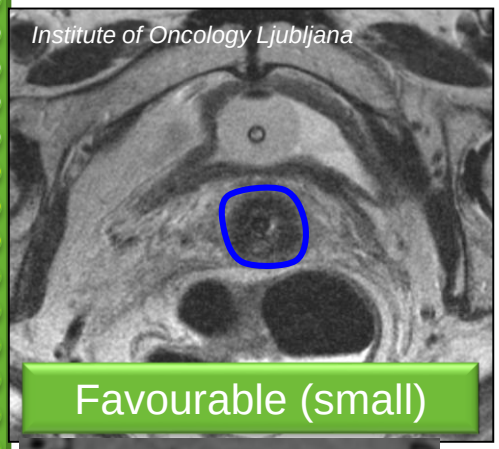


Set the **STAGE** before contouring

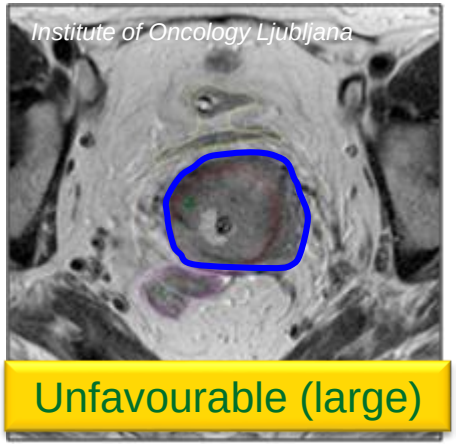
- **S**ize of the residual tumor?
- **T**opography of the target V?
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

Topography of the tumour

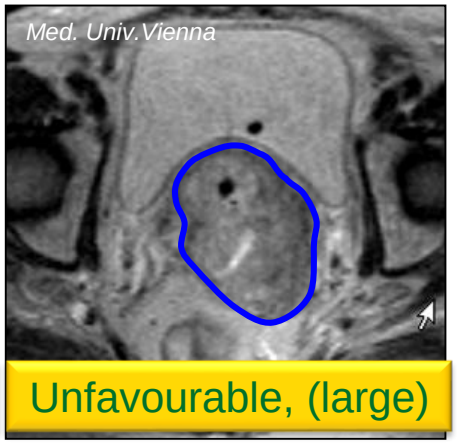
Tumour and Target shape and extent



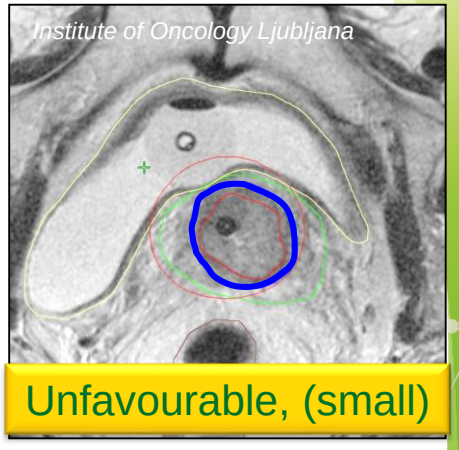
Favourable (small)



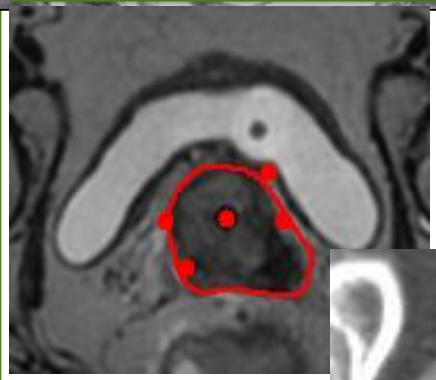
Unfavourable (large)

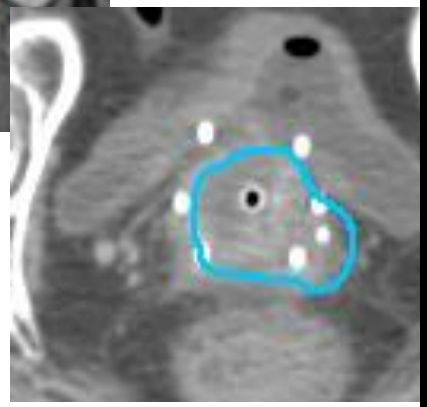


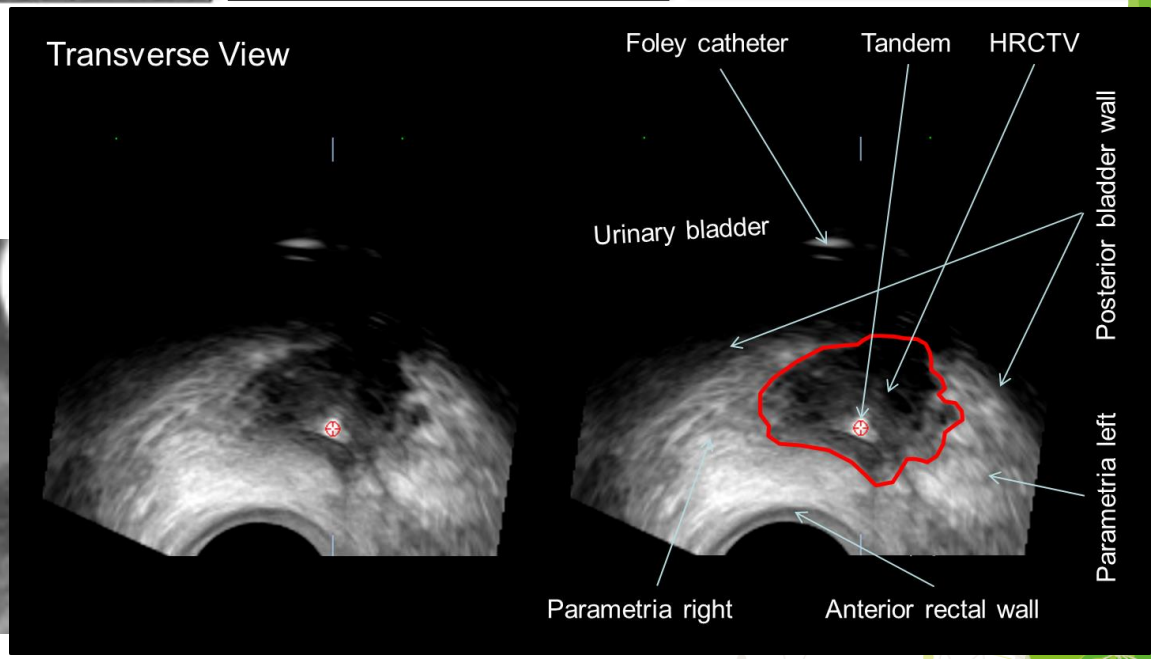
Unfavourable, (large)



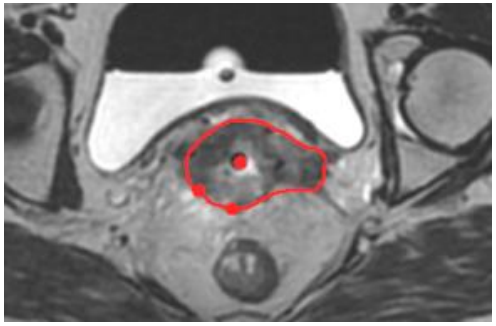
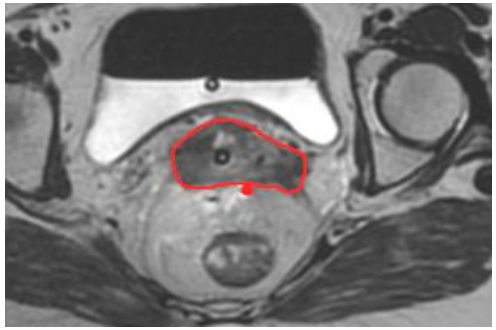
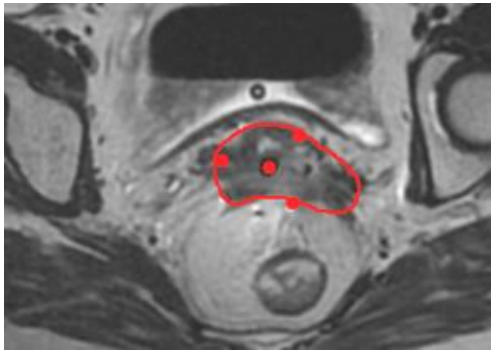
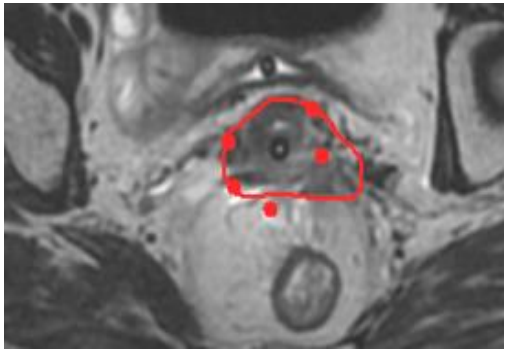
Unfavourable, (small)

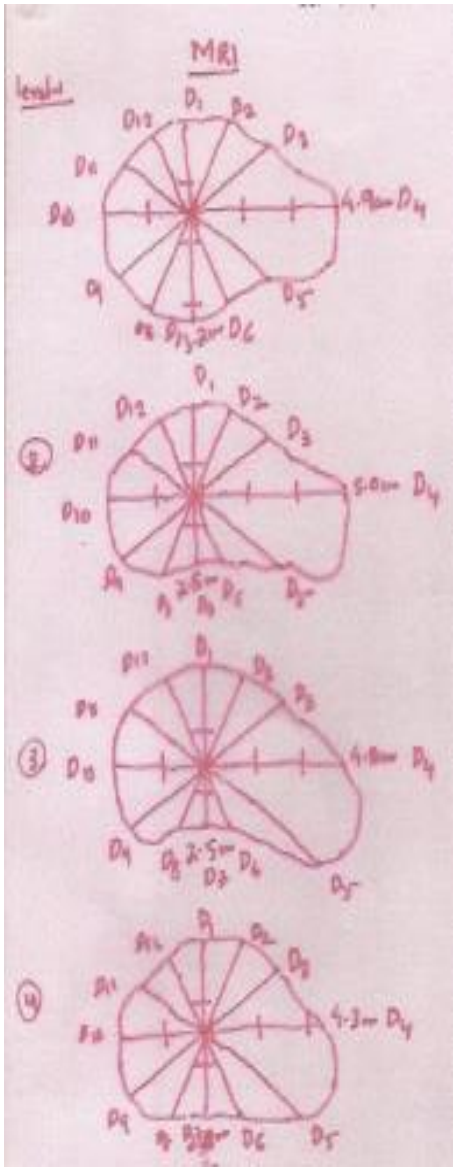


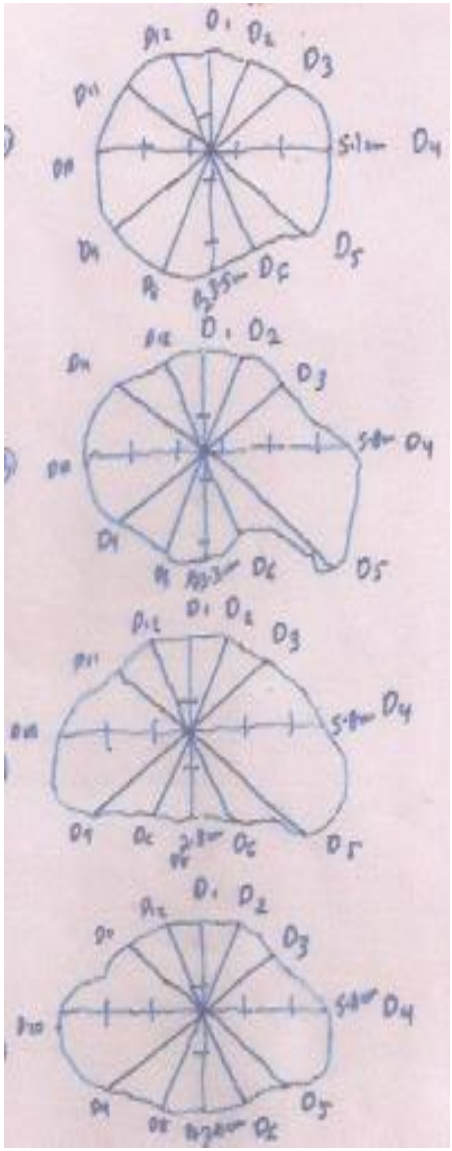


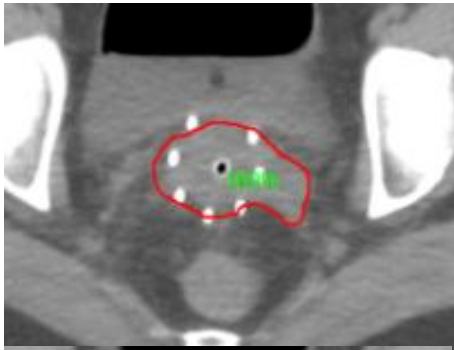
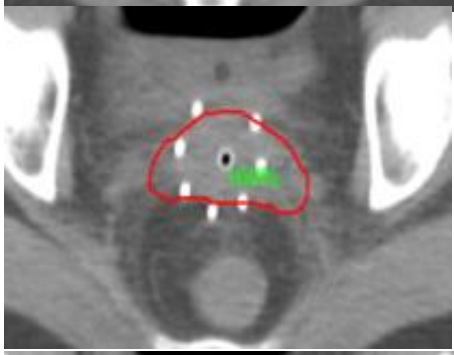
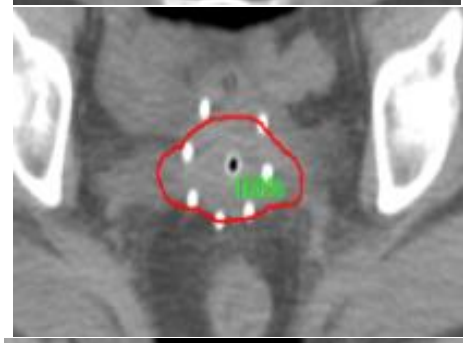
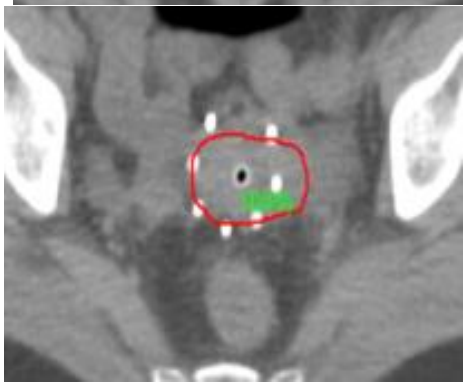


Ca Cervix-IIIB,
HRCTV includes para involved at BT





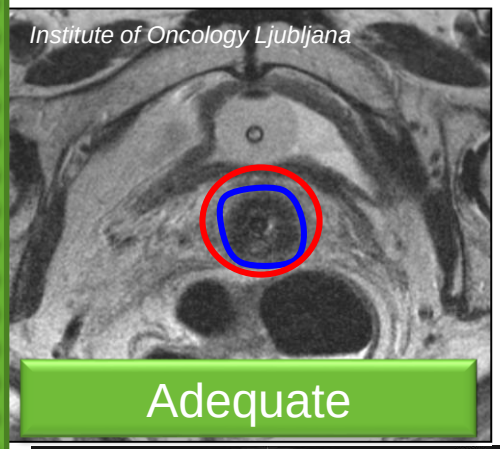
Ongoing TMH Clinical Study

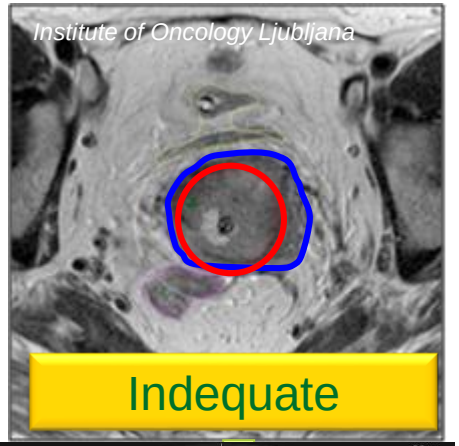
Set the **STAGE** before contouring

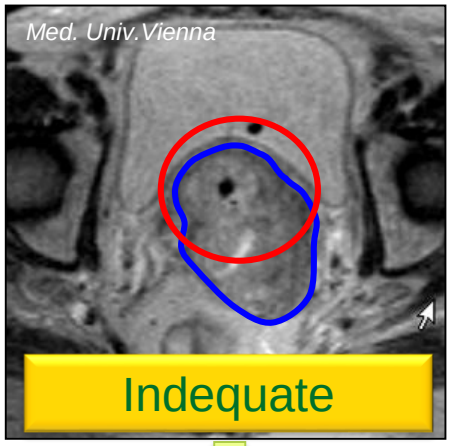
- **S**ize of the residual tumor?
- **T**opography of the target V?
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

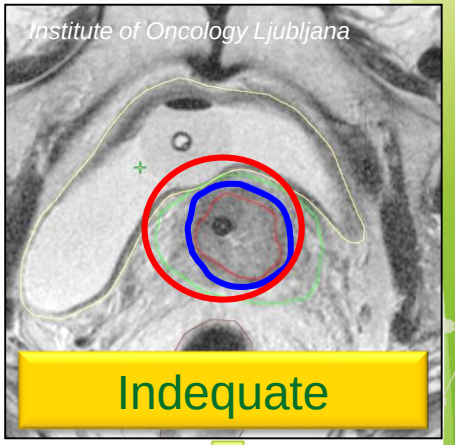
Adequacy of the implant

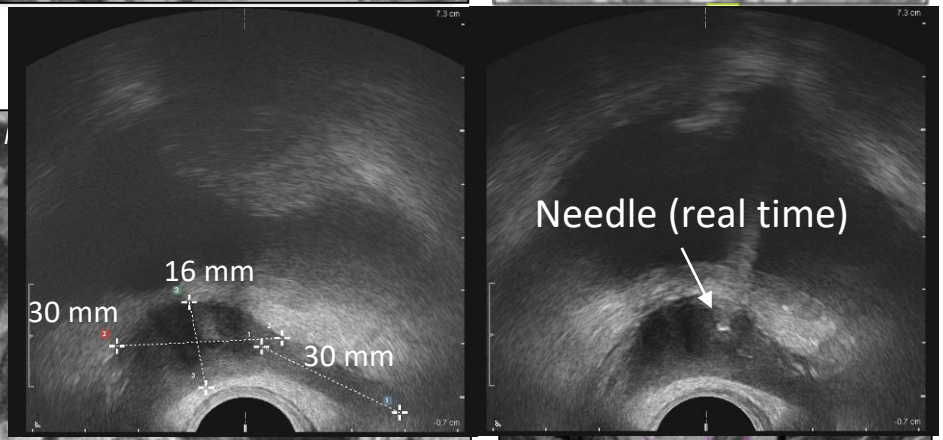
Relation: Applicator(s) - Target V - Organs

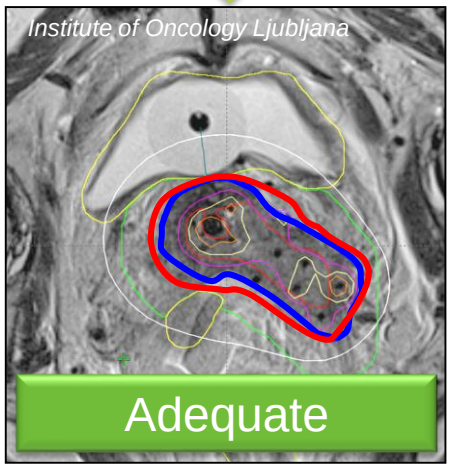


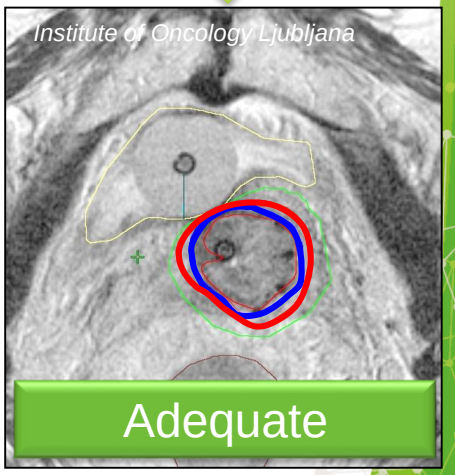












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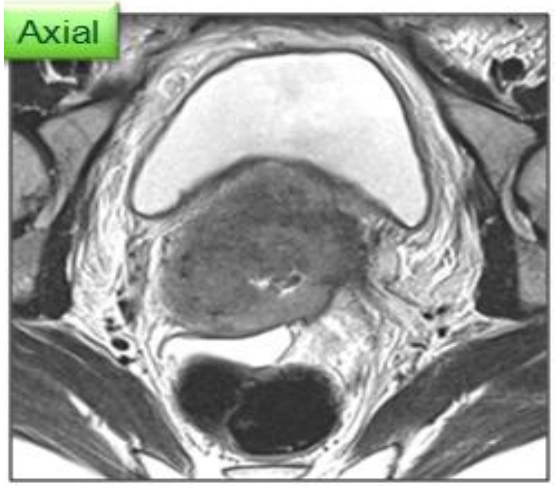
- **E**xtra findings?

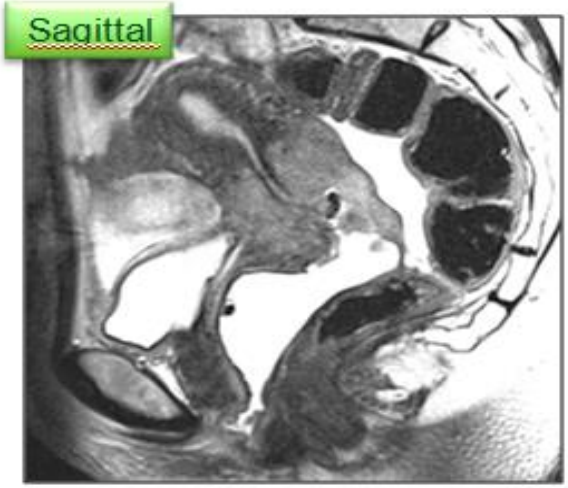
Grey zones

Grey zones at BT correlate with *Initial spread*

Axial



Sagittal



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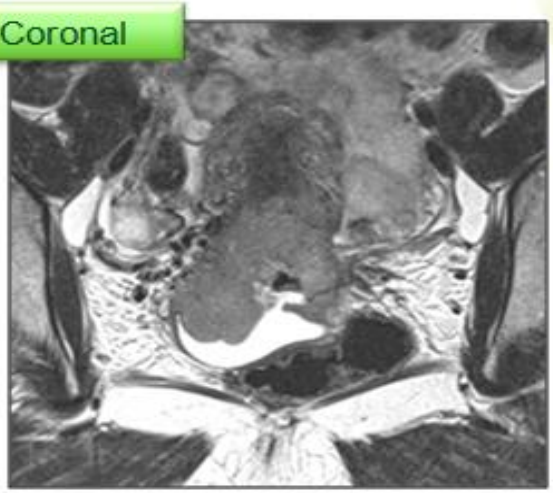

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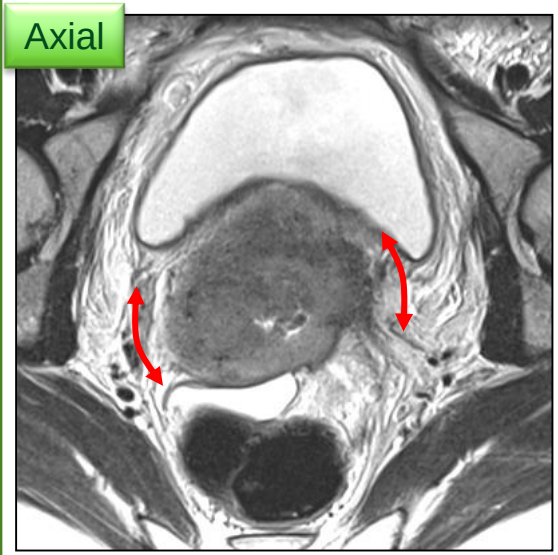

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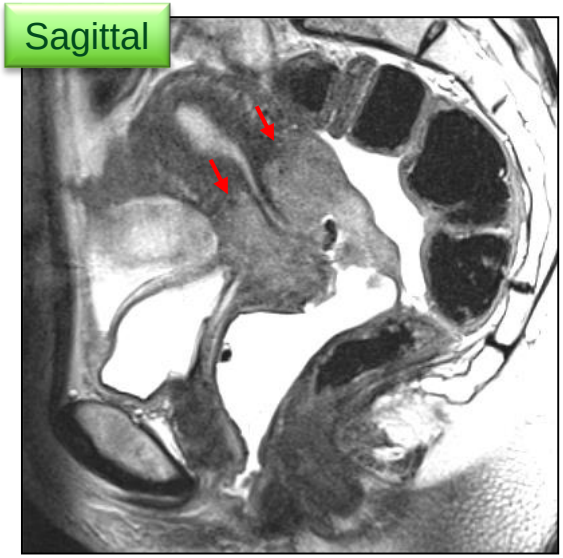

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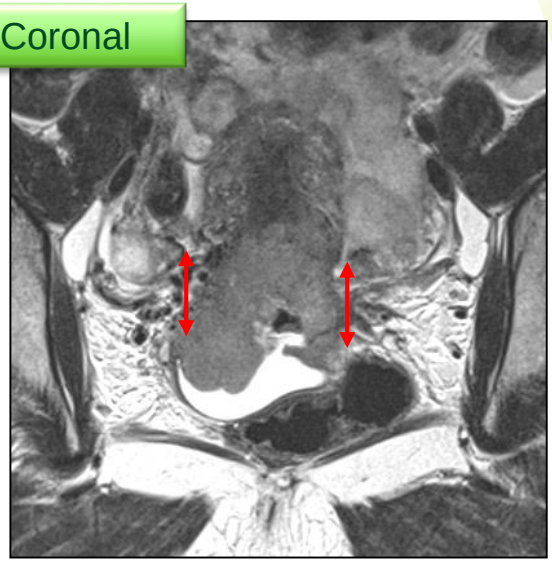

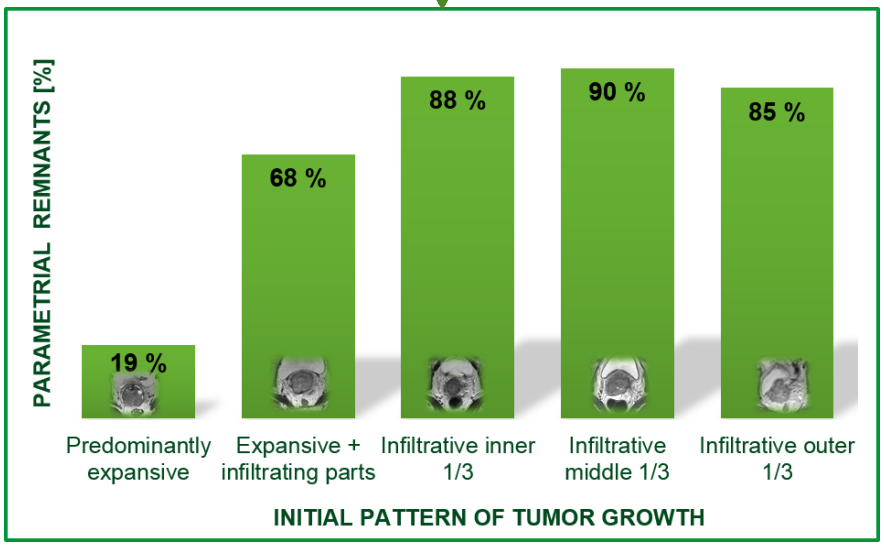

Schmid MP, et al. Acta Oncol 2013
Yoshida K, et al. IJROBP 2016

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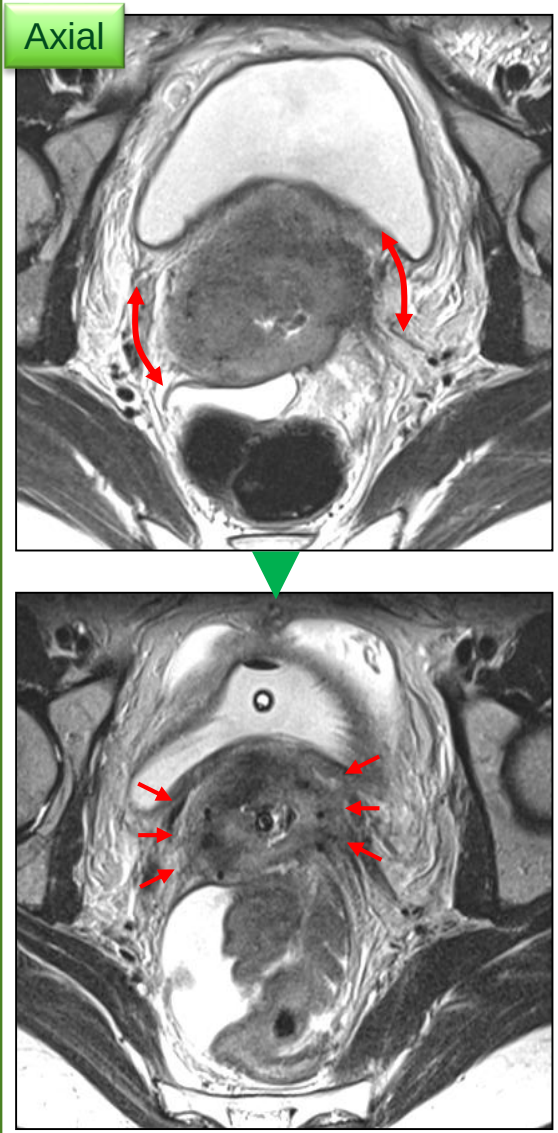

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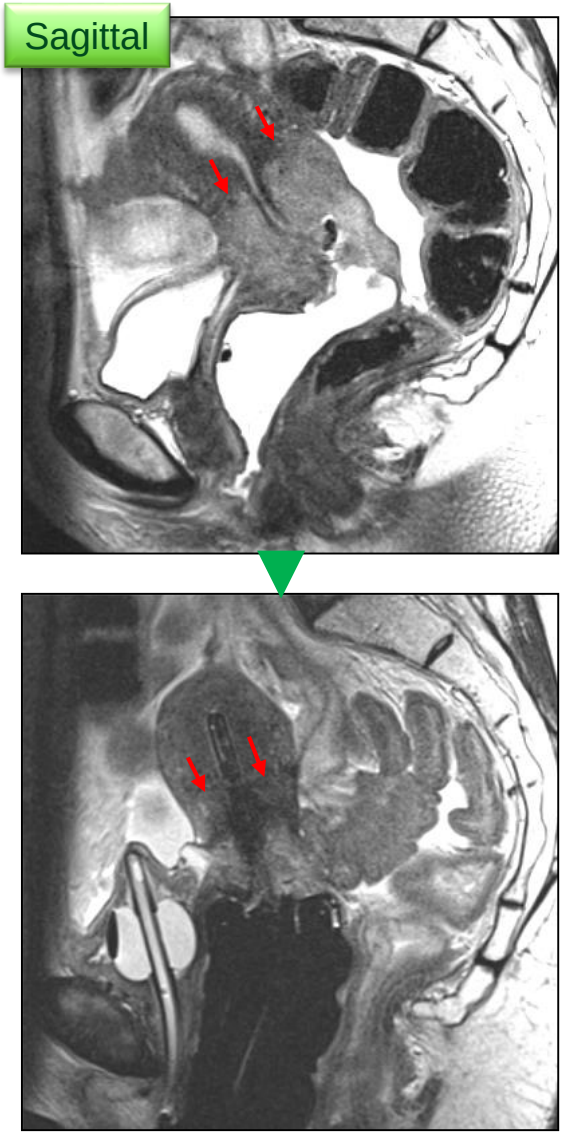

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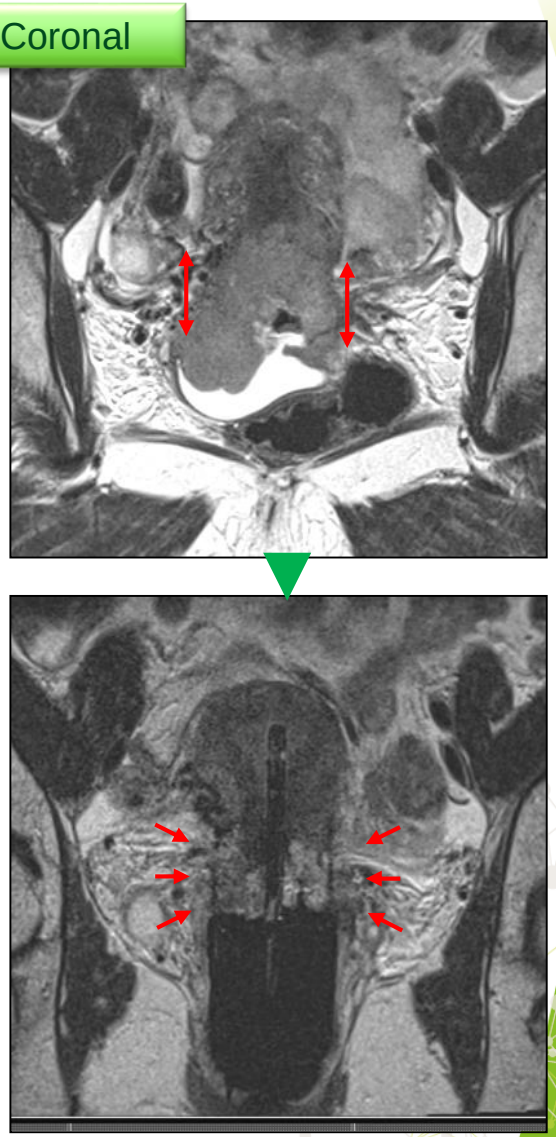

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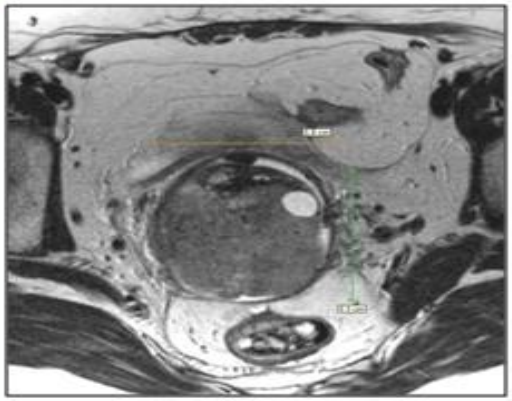
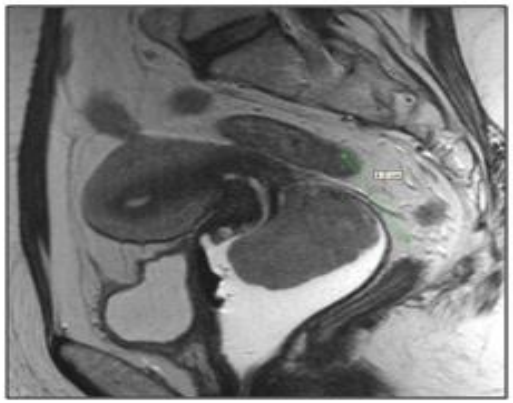
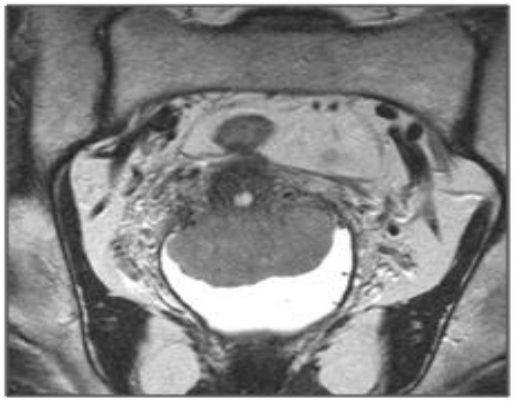


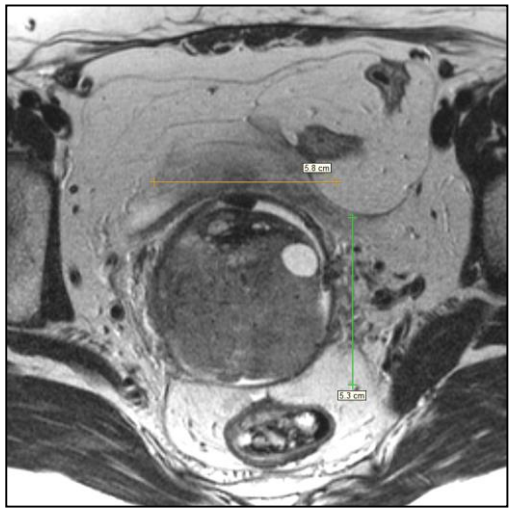


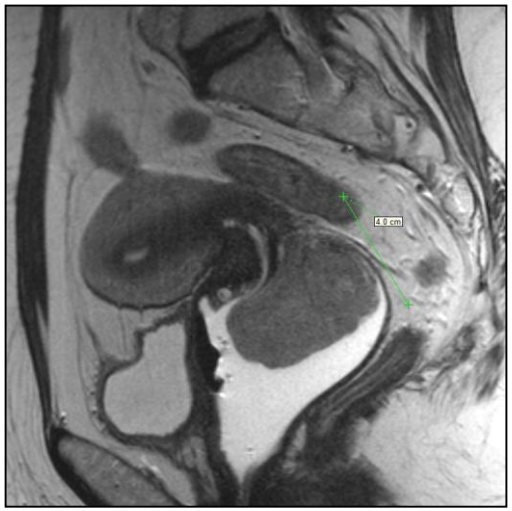


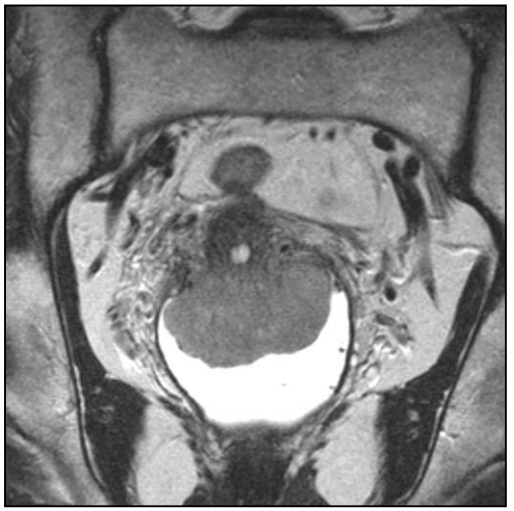
Estimate probability for residual pathological tissues in parametria after EBRT for this patient:

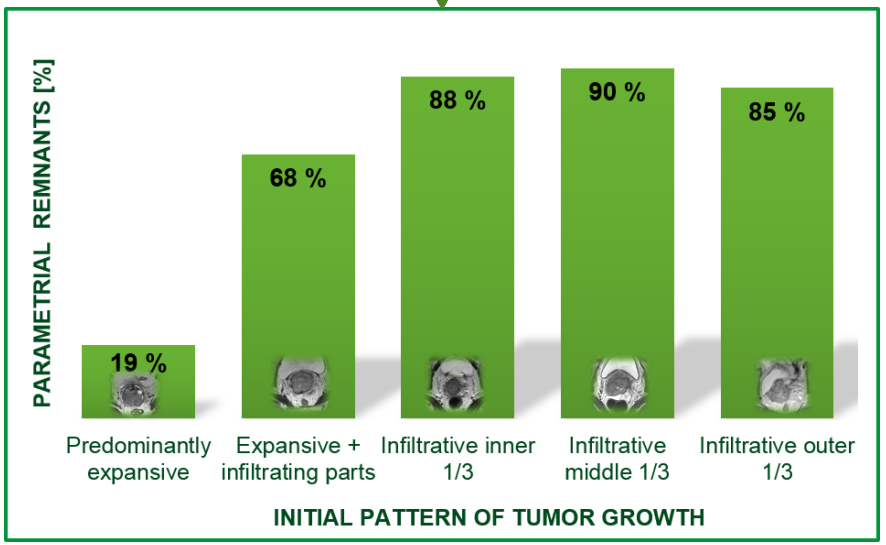
Grey zones

Grey zones at BT correlate with *Initial spread*









Schmid MP, et al. Acta Oncol 2013
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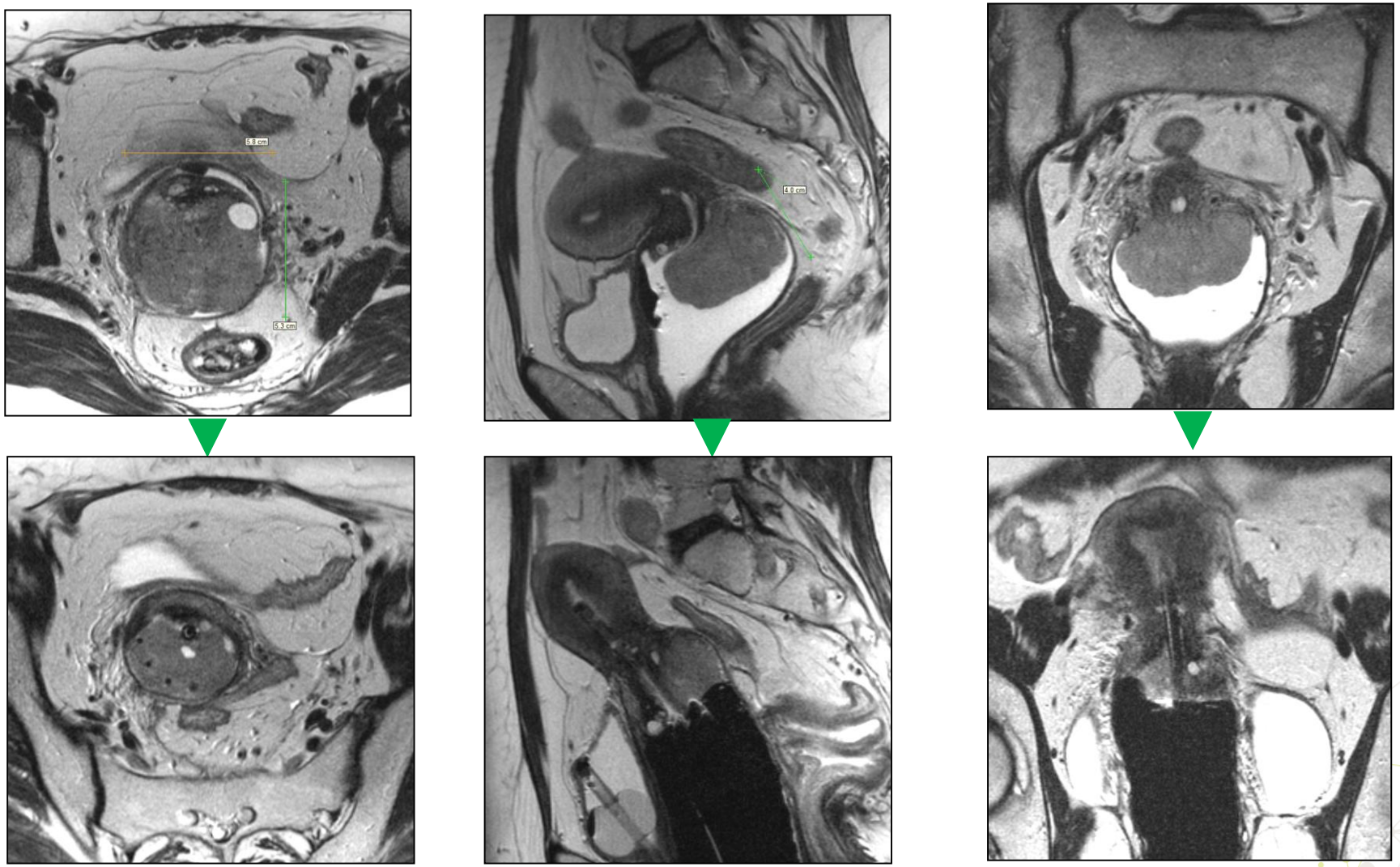


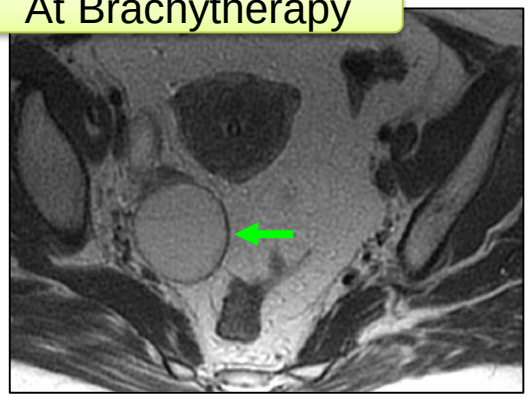
Set the **STAGE** before contouring

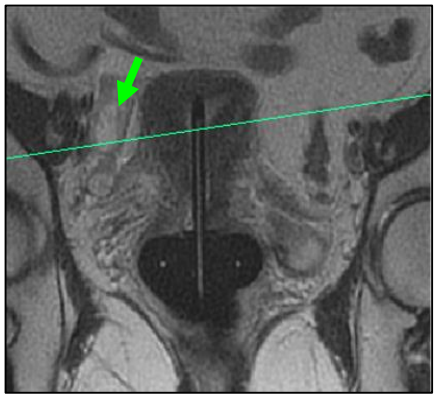
- **S**ize of the residual tumor?
- **T**opography of the target V?
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

“Extra” findings?

Practical Example

At Brachytherapy





- Images kept in BT department
- 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!
- Challenge: *radiation oncologist’s* vs. *radiologist’s* perspective!

SUMMARY – EXAMPLE T2W MRI at BT from Rad. Onc. Perspective (gold standard)

Rule out **FLOP**

Set the **STAGE** for contourig

MRI and/or CT/US with clinical drawings

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

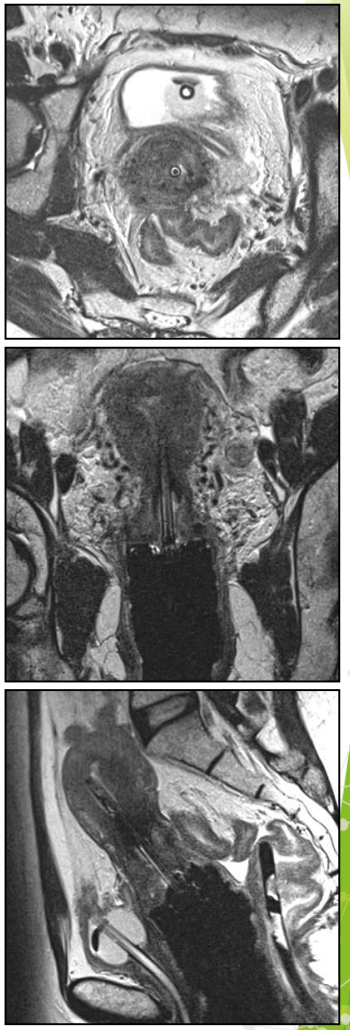
1. **S**ize of the tumor:
   - 8 cm^3 (ellipsoid formula)
   - Regression to Proportional V: PV = 20 % initial V

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. (fibrosis in clin exam)

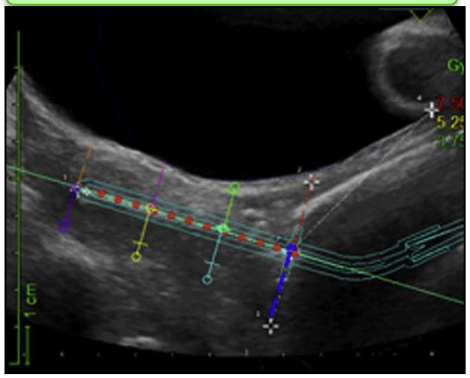
5. "**E**xtra":
   1. No necrosis.
   2. *BT-related primary tumour findings reported.*
   3. *Lymph nodes and other details not assessed.*



Choice of imaging modality for IGABT

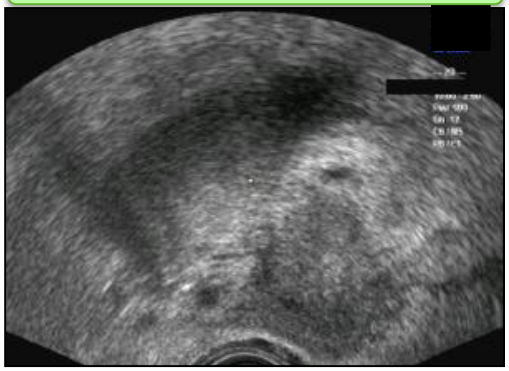
ULTRASOUND

Transabdominal



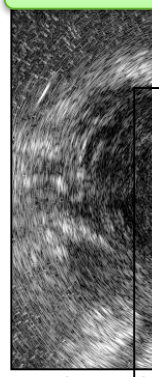
Van Dyk et al. Brachytherapy 2015

Transrectal



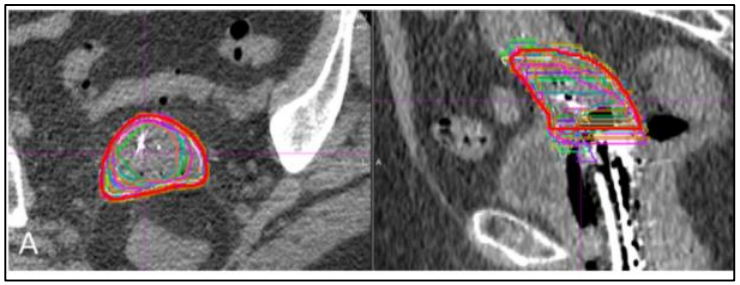
Schmid MP, et al. Radiother Oncol 2016

Rotatin

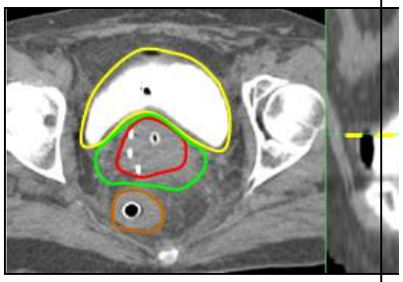


Petric P, Kir

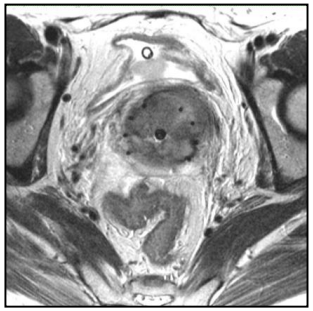
CT

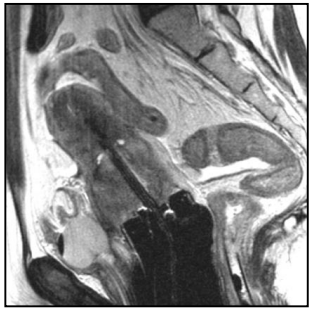


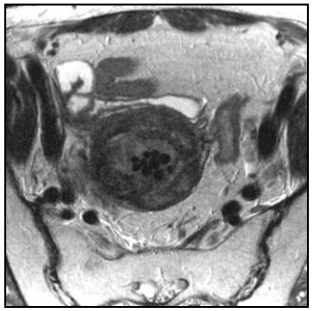
Viswanathan AN, et al Int J Radiat Oncol Biol Phys 2014



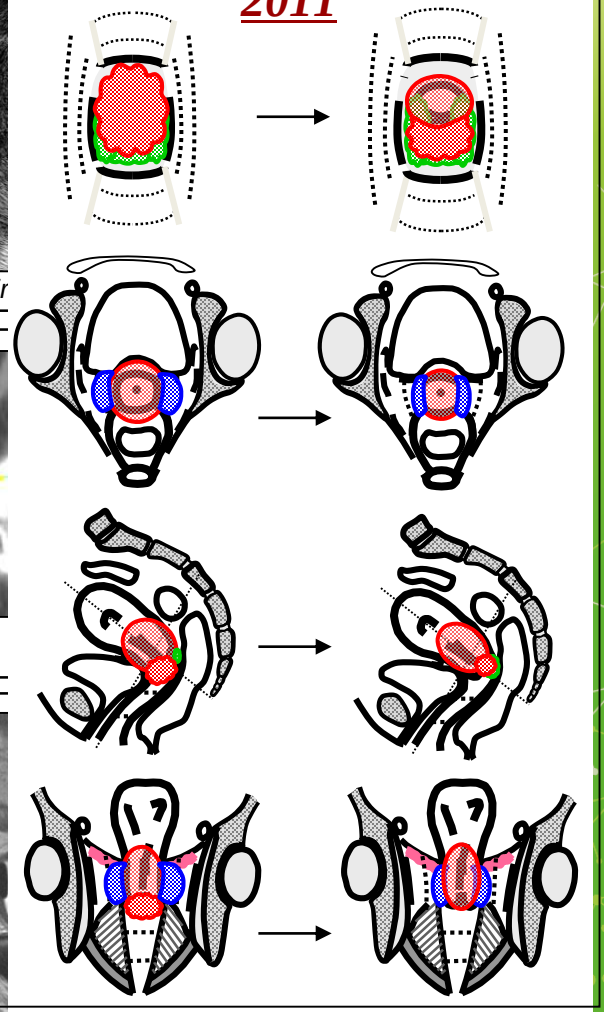
MRI







EMBRACE study protocol, 2011



Patient Preparation for Treatment Planning

EBRT

Immobilization, Organ Filling / Reproducibility

Umesh Mahantshetty

Professor, Department of Radiation Oncology

Tata Memorial Hospital, Mumbai, India

- **Counseling and preparation**
- **Pre-planning Audit**
- **Consent**
- **Positioning**
- **Immobilization**
- **Organ filling: Bladder, Rectum etc.. & Reproducibility**

Counseling & Patient preparation Instructions

- Counseling about radiation, anticipated side effects etc..
- Obtain written Informed Consent
- Patient Preparation:

  - preparation of the parts (perineum)

- Dietary instructions & Rx of constipation

Pre-planning Audit

- Review history, clinical findings and staging
- Imaging findings: primary, nodal and normal anatomical variations
- Planning Aims:

  - Radical / Postoperative / Palliative

  - Radiation technique: 3D CRT / IMRT / VMAT etc..

Q. During external beam radiation therapy, following position is given for patients with cervical cancer

A. Supine
B. Prone
C. Prone with belly board
D. Lithotomy

Positioning & Immobilization

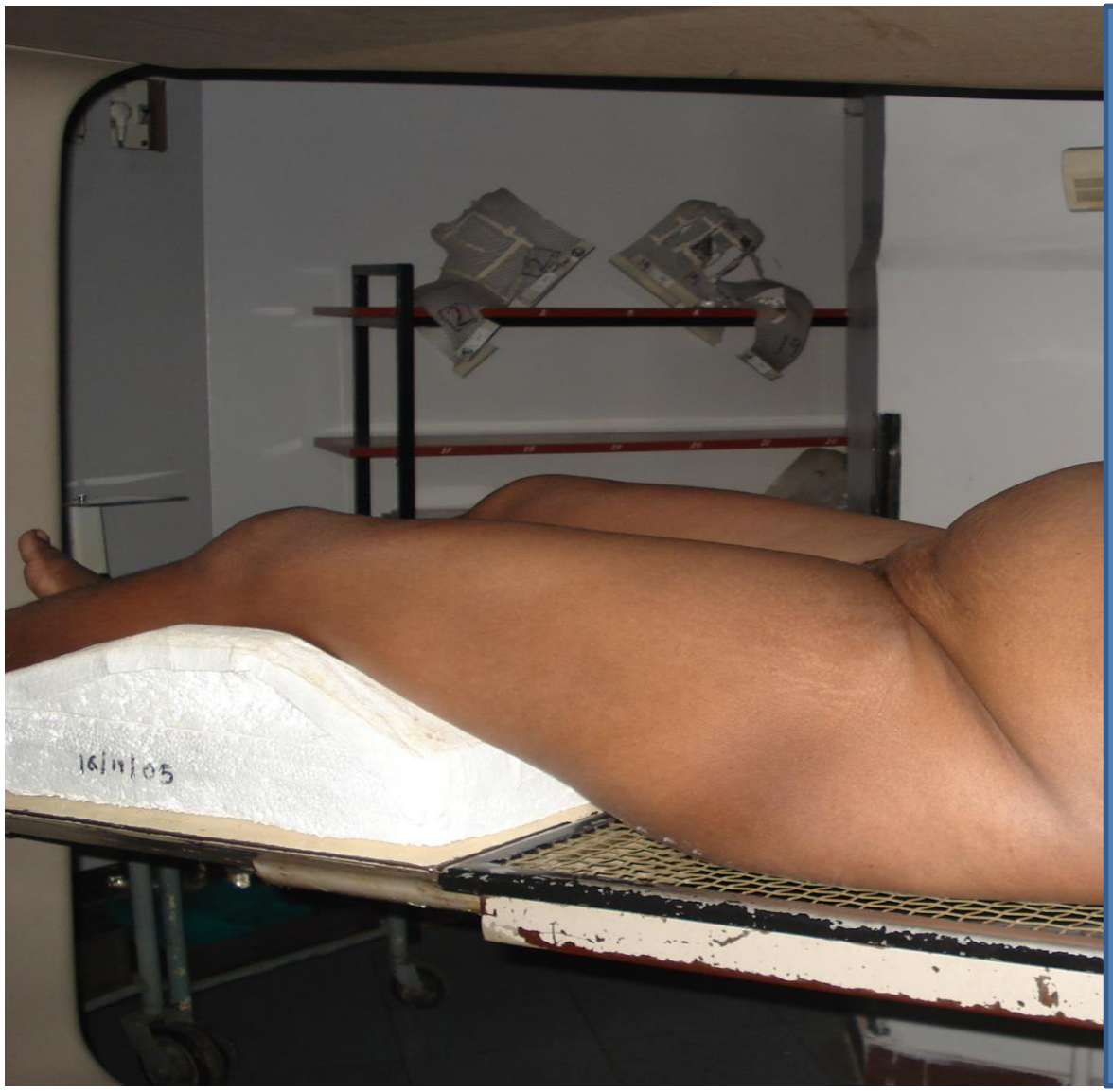
- AIM:- Comfortable and a Reproducible position through out the treatment

SUPINE POSITION

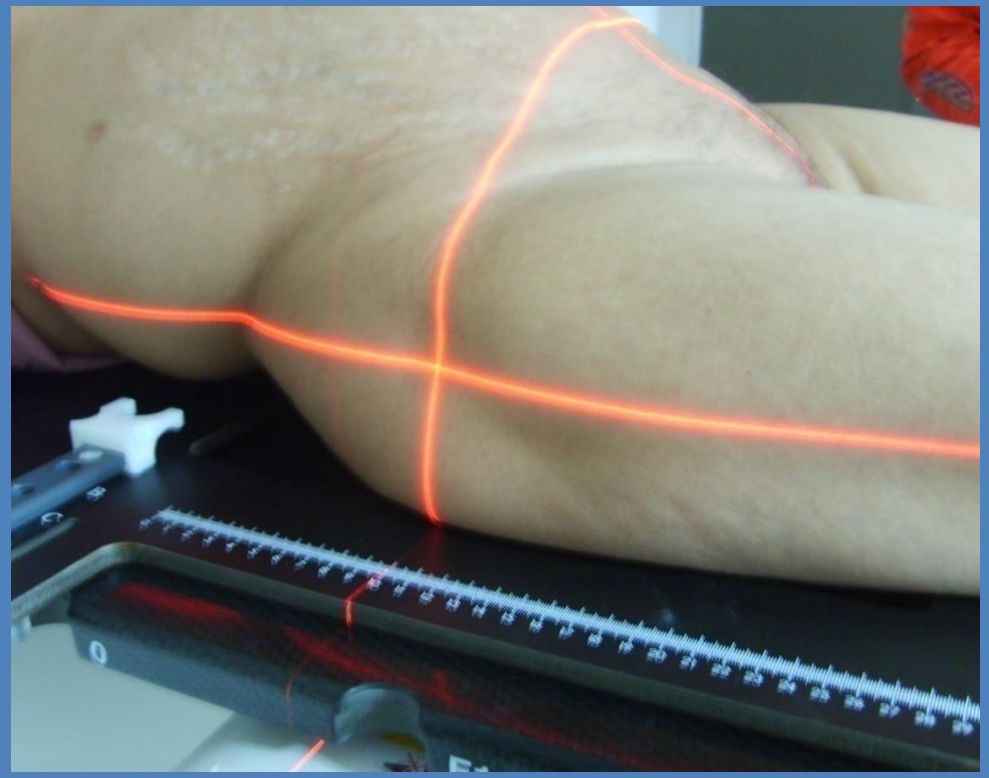
- Commonest position
- Hands on chest , legs straight with heels together

FROG leg position:- groin skin folds, low 1/3 vaginal tumors / inguinal regions

SUPINE WITH KNEE REST & ALIGNMENT



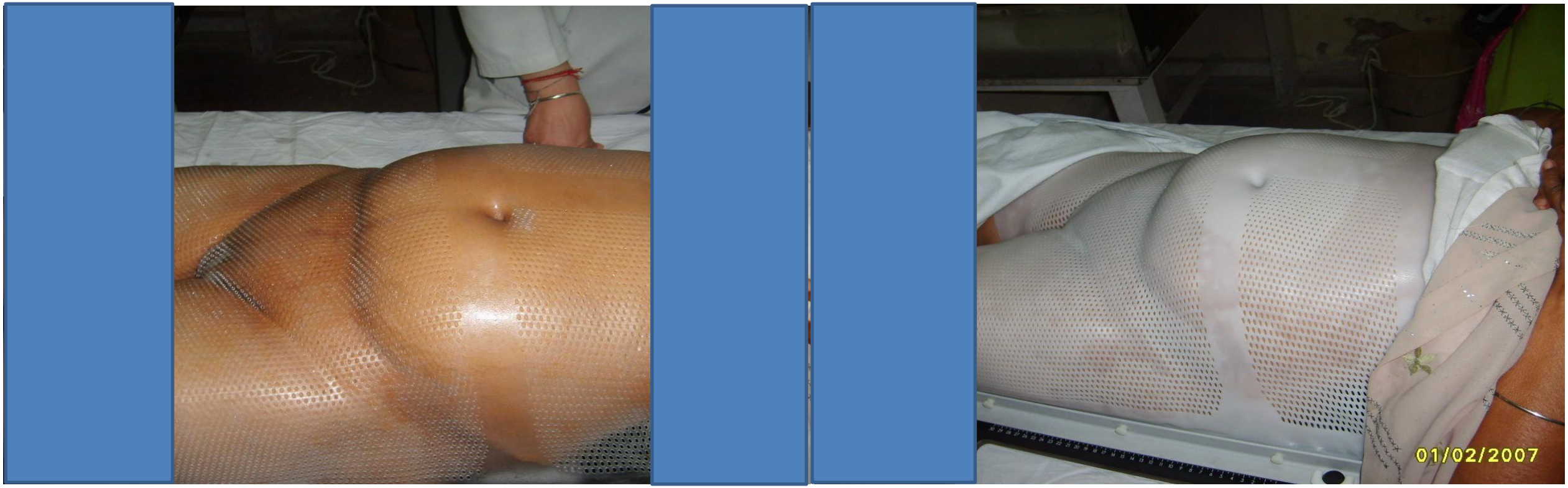
LASER ALIGNMENT



Immobilisation

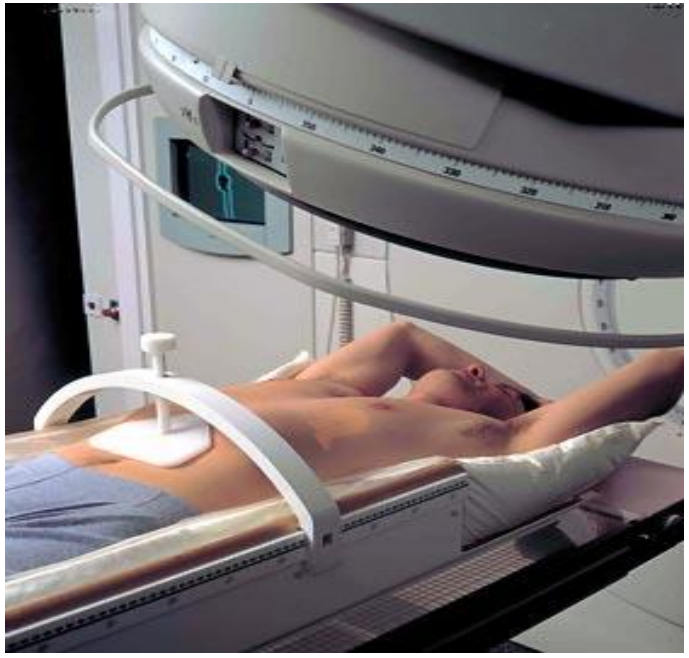
1. Knee Rest- comfortable, relaxes back against flat couch, relieves lumbar lordosis
2. Ankle rest-change in foot-change/rotation bony reference points
3. Belly board with prone position
4. Vacloks / Body fix/ frame

Thermoplastic molds



- Fixation of lower thoracic cage and the pelvis after alignment
- Challenging in Obese patients
- Reproducibility : weight loss / shrinkage etc…

Immobilization: Other methods



Elekta Body Frame

Body Fix system with Vacloks

Prone Versus Supine

Prone vs. supine position in endometrial cancer IMRT

47 patients; adjuvant RT

- 21 pts: prone
- 26 pts: supine

Small Bowel dosimetric and clinical results:

	V10Gy	V20Gy	V30Gy	V40Gy	V45	V50 Gy	p-value
Prone	89%	69%	33%	12%	5%	0%	NS
Supine	87%	63%	26%	8%	4%	0%	

	Acute G1	Acute G2	Late G1	Late G3
Prone	7 pts	14 pts	7 pts	1 pts
Supine	6 pts	19 pts	5 pts	0 pts

Conclusion: no difference in dose and toxicity.

Beriwal S, et al. 2007, IJROBP

Prone versus supine

Systematic review

Systematic review of the role of a belly board device in radiotherapy delivery in patients with pelvic malignancies

Esther M. Wiesendanger-Wittmer, Nanna M. Sijtsema *, Christina T. Muijs, Jannet C. Beukema

Department of Radiation Oncology, University of Groningen, The Netherlands

- 33 publications
- Prone position: lower irradiated small bowel V
- Prone on a belly board: more significant small bowel V reduction
- Possible effect on reduction of GI morbidity

Conclusion: prone positioning on a belly board can reduce the small bowel dose. Dose reduction depends on the IMRT technique used.

Wiesendanger-Wittmer EM, et al. Radiother Oncol 2012

Positioning & Immobilization - Summary

- Supine with mild flexion at knees with knee rest & alignment
- Vacloks or Bodyfix

  - Are now generally used and provide excellent reproducibility

  - Comfortable to patient

  - Cost Issues
- Immobilization device and Reproducibility should be adopted depending on the clinical environment especially the image guidance techniques (EPID/CBCT etc.) by each Institution

ORGAN FILING PROTOCOLS

- **Bladder filing**

  - Some bladder filing protocol

  - Various protocols utilized (500 – 1000 ml)

- **Rectal filing**

  - Empty bowels daily before planning / treatment

  - If gaseous distension of rectum / sigmoid at planning : Repeat planning after emptying

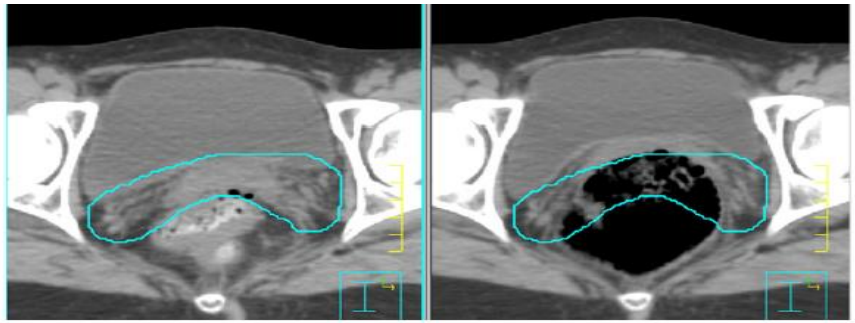


Fig. 2. Effect of rectal filling comparing the planning scan (left) to pretreatment scan (right). Cyan contour represents the CTV. (CTV - clinical target volume).

Organ filing: Bladder

Jhingran A, et al. IJROBP 2012

- 24 patients
- Post-histerectomy pelvic IMRT
- Simulation with full and empty bladder
- Bladder filling instructions (full bladder on treatment)
- Rescanning twice weekly during IMRT
- Bladder volumes varied: Median difference (max-min V): 247 cm3 (95-585)
- Rectal V variation less pronounced
- Vaginal fiducial markers movement:
    - 0.6 cm in lateral direction (0-0.9 cm)
    - 1.5 cm in AP direction (0.8-2.8 cm)
    - 1.2 cm in sup.-inf. direction (0.6-2.1)
- Large rectal/bladder V correlated with significant vaginal apex displacement
- **Conclusion:** even with detailed instructions, patients are unable to maintain consistent bladder filling.

Jhingran A, et al. IJROBP 2012

Organ filling

Chang JS, et al. Radiat Oncol 2013

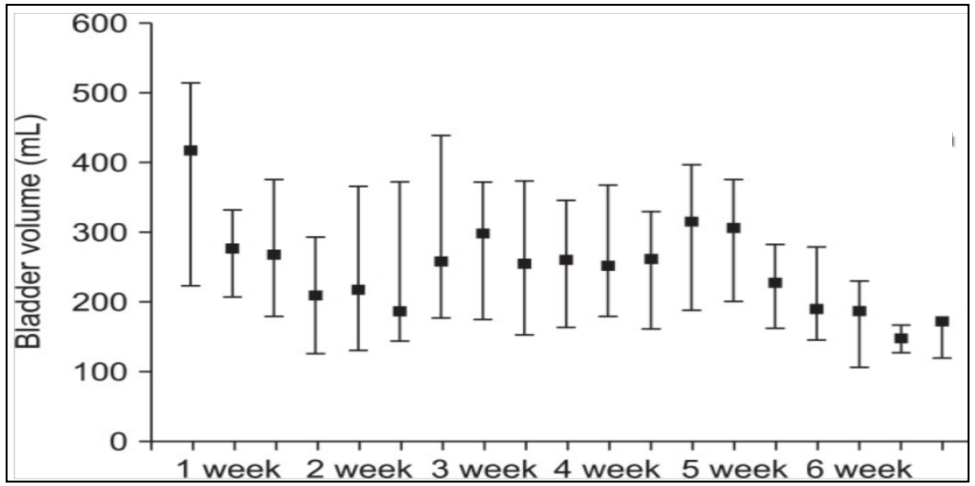
20 rectal cancer patients

5 US – based measurements of bladder V before and during treatment

Initial V: 417 (147 – 1.245) ml

Week 6 V: 157 ml (60 % reduction)

Average reduction per week: 161 ml (38 %)

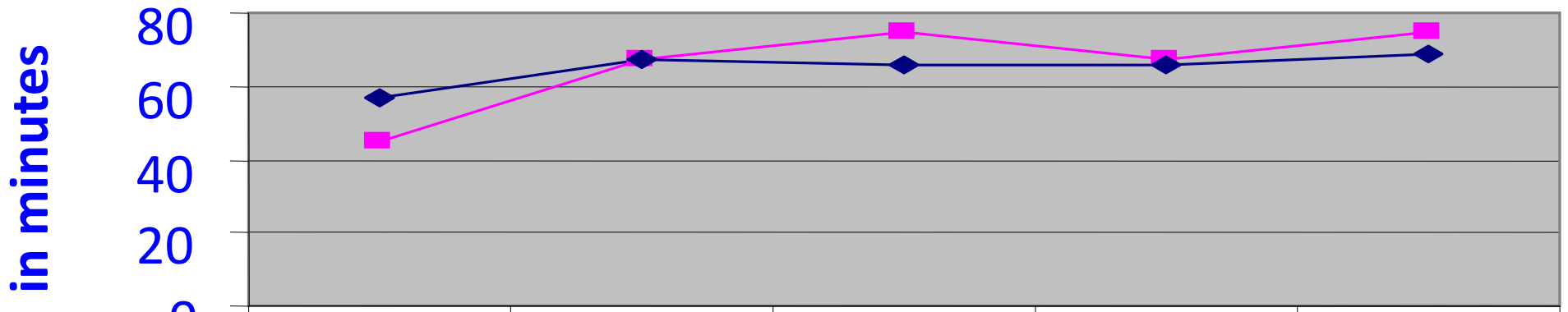


TMH Study (N = 46 patients)

Protocol for Bladder filling : Oral Intake of 750-1000 ml over 15-20 minutes after emptying the bladder

Bladder filling (upto 300 +/- 50 ml) time after 30 minutes repeated every 15 min.

Methodology : Volume assessed by serial Trans-Abdominal US

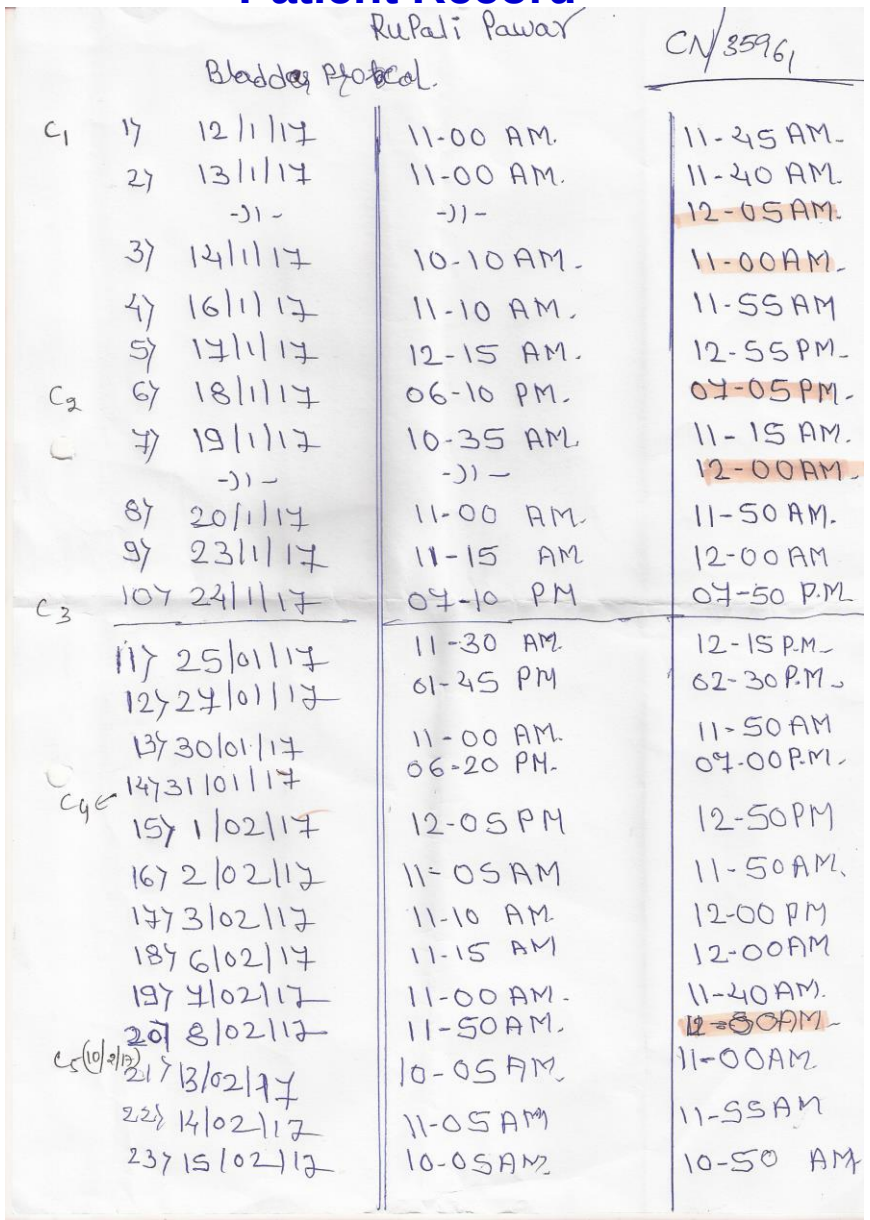


	wk1	wk2	wk3	wk4	wk5
Median filling time	45	67.5	75	67.5	75
Mean filling time	57	67	66	66	69

Mahantshetty et al ; TCRT 2017 (under review)

Bladder protocol Compliance: Quick Assessment

Patient Record



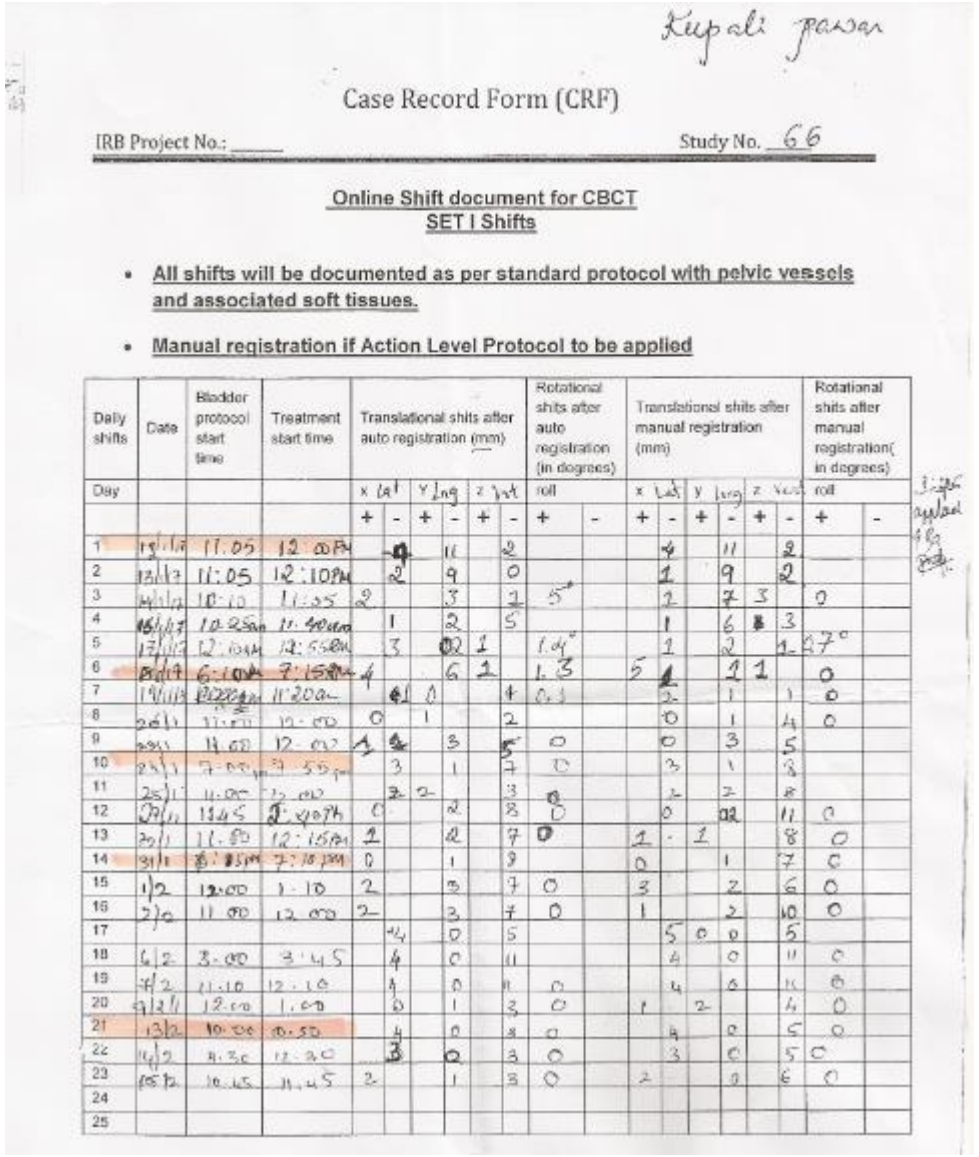
Rupali Pawar

CN/35961

Bladder Protocol.

C_1	1)	12/1/17	11-00 AM.	11-45 AM.
	2)	13/1/17	11-00 AM.	11-40 AM.
		-)1-	-)1-	12-05 AM.
	3)	14/1/17	10-10 AM.	11-00 AM.
	4)	16/1/17	11-10 AM.	11-55 AM
	5)	17/1/17	12-15 AM.	12-55 PM.
C_2	6)	18/1/17	06-10 PM.	07-05 PM.
	7)	19/1/17	10-35 AM.	11-15 AM.
		-)1-	-)1-	12-00 AM.
	8)	20/1/17	11-00 AM.	11-50 AM.
	9)	23/1/17	11-15 AM	12-00 AM
	10)	24/1/17	07-10 PM	07-50 P.M.
C_3	11)	25/01/17	11-30 AM.	12-15 P.M.
	12)	27/01/17	01-45 PM	02-30 P.M.
	13)	30/01/17	11-00 AM.	11-50 AM
	14)	31/01/17	06-20 PM.	07-00 P.M.
C_4	15)	1/02/17	12-05 PM	12-50 PM
	16)	2/02/17	11-05 AM	11-50 AM.
	17)	3/02/17	11-10 AM	12-00 PM
	18)	6/02/17	11-15 AM	12-00 AM
	19)	7/02/17	11-00 AM.	11-40 AM.
	20)	8/02/17	11-50 AM.	12-30 PM.
C_5 (10/2/17)	21)	13/02/17	10-05 AM.	11-00 AM.
	22)	14/02/17	11-05 AM	11-55 AM
	23)	15/02/17	10-05 AM.	10-50 AM

Technologist Record



Rupali pawar

Case Record Form (CRF)

IRB Project No.: _____ Study No. 66

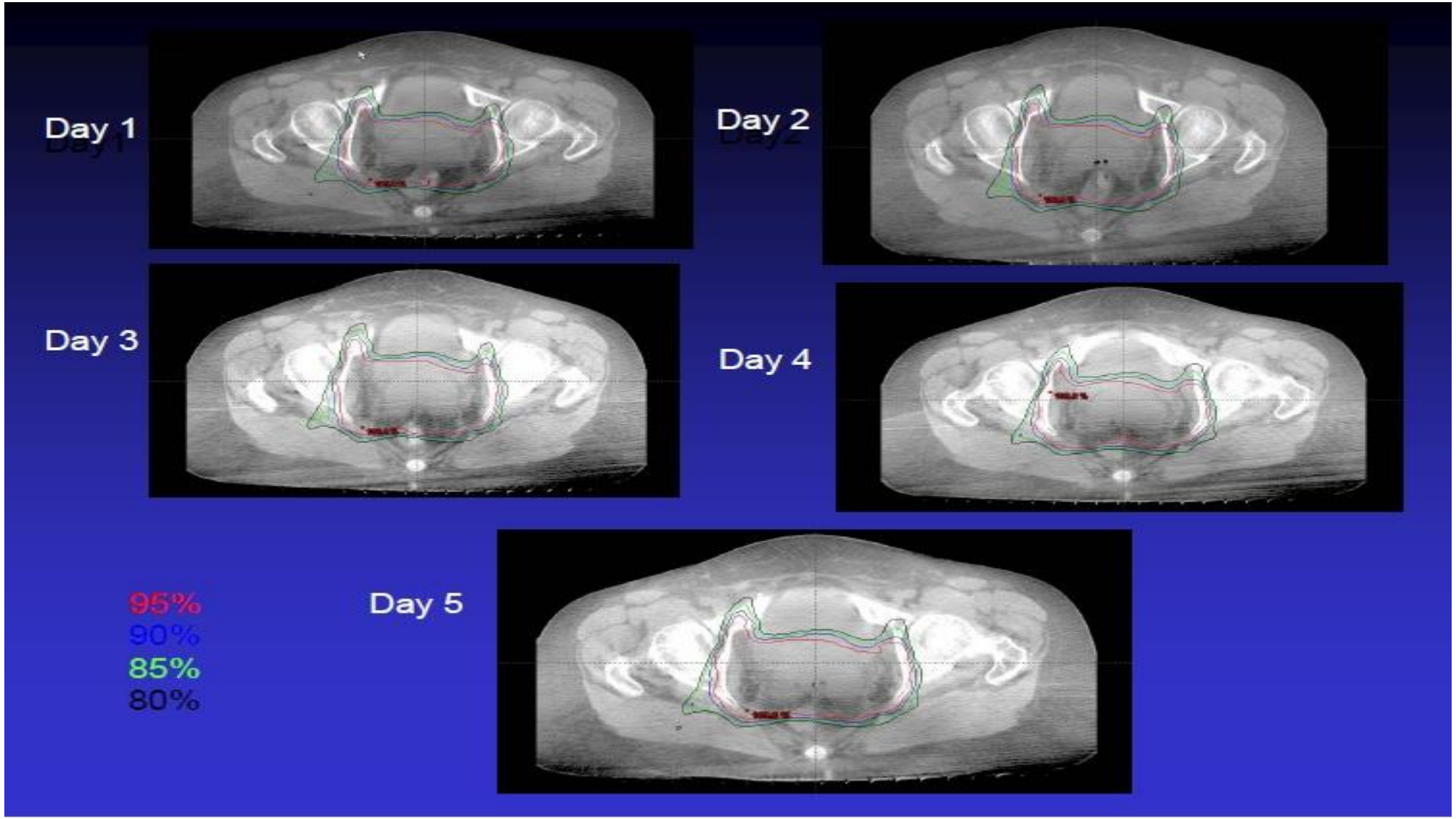
Online Shift document for CBCT
SET I Shifts

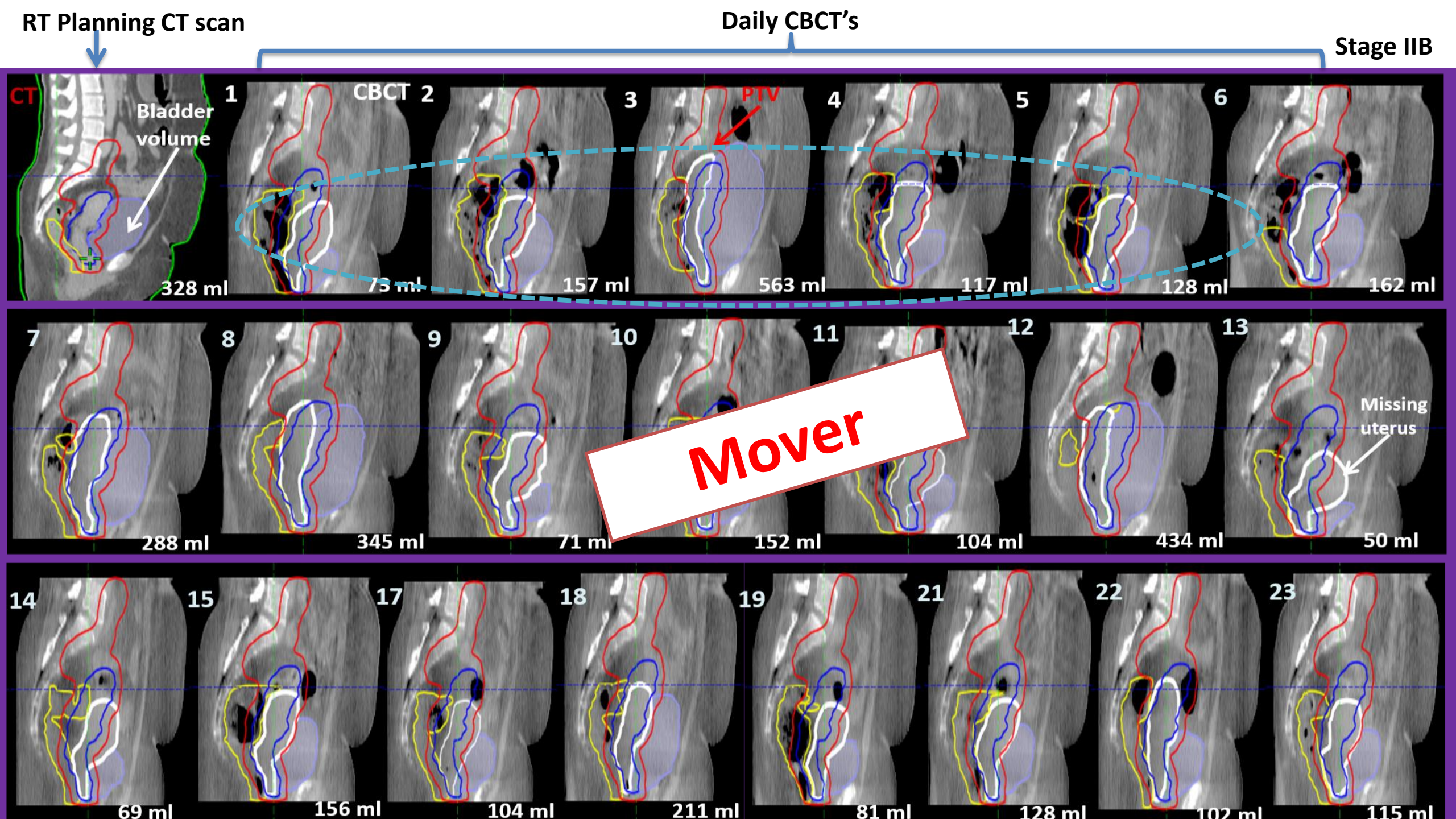
- **All shifts will be documented as per standard protocol with pelvic vessels and associated soft tissues.**
- **Manual registration if Action Level Protocol to be applied**

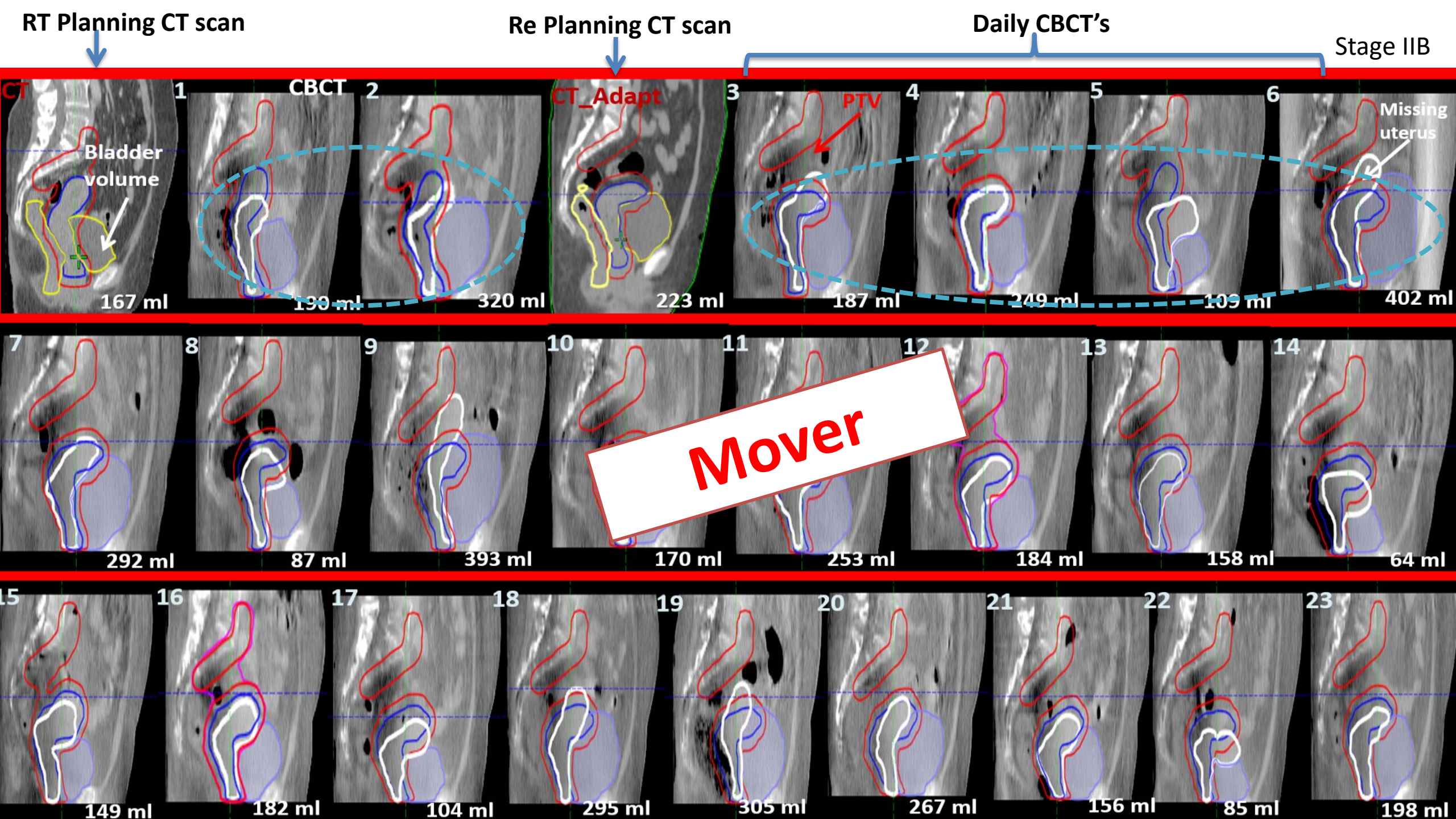
Daily shifts	Date	Bladder protocol start time	Treatment start time	Translational shifts after auto registration (mm)						Rotational shifts after auto registration (in degrees)		Translational shifts after manual registration (mm)						Rotational shifts after manual registration(in degrees)	
Day				x Lat		y Long		z Vert		roll		x Lat		y Long		z Vert		roll	
				+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
1	12/1/17	11:05	12:00PM		4		11		2				4		11		2		
2	13/1/17	11:05	12:10PM		2		9		0				1		9		2		
3	14/1/17	10:10	11:05	2			3		3	5°			2		7	3		0	
4	16/1/17	10:25am	11:40am		1		2		5				1		6		3		
5	17/1/17	12:10PM	12:55PM		3		02	1		1.4°			1		2		1	37°	
6	18/1/17	6:10PM	7:15PM	4			6	1		1.3		5			1	1		0	
7	19/1/17	10:20am	11:20a		01	0			4	0.1			2		1		1	0	
8	20/1/17	11:00	12:00	0		1			2				0		1		4	0	
9	23/1/17	11:00	12:00	1	5		3		5	0			0		3		5		
10	24/1/17	7:00pm	7:55pm		3		1		7	0			3		1		3		
11	25/1/17	11:00	12:00		2	2			3	0			2		2		8		
12	27/1/17	11:45	12:40PM	0			2		8	0			0		02		11	0	
13	30/1/17	11:50	12:15PM	1			2		7	0		1		1			8	0	
14	31/1/17	6:05PM	7:10PM	0			1		9			0		1			7	0	
15	1/2/17	12:00	1:10	2			3		7	0		3			2		6	0	
16	2/2/17	11:00	12:00	2			3		7	0		1			2		10	0	
17					4		0		5				5	0	0		5		
18	6/2/17	3:00	3:45		4		0		11				4		0		11	0	
19	7/2/17	11:10	12:10		1		0		11	0			4		0		11	0	
20	9/2/17	12:00	1:00		0		1		3	0		1		2			4	0	
21	13/2/17	10:00	10:50		4		0		8	0			4		0		5	0	
22	14/2/17	9:30	12:30		3		0		8	0			3		0		5	0	
23	15/2/17	10:45	11:45	2			1		8	0		2			0		6	0	
24																			
25																			

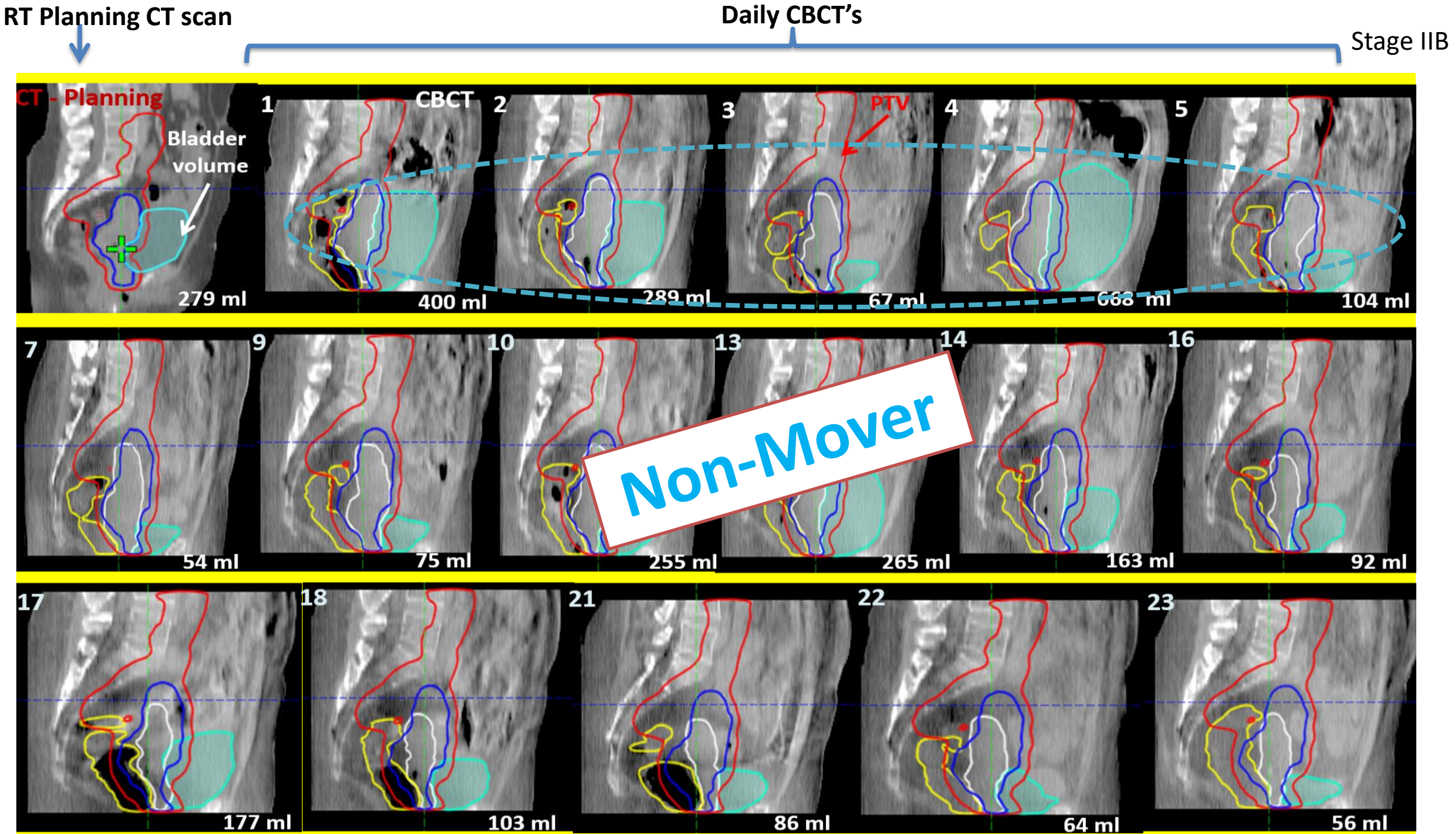
An example of Image Guided Radiation therapy (IGRT)

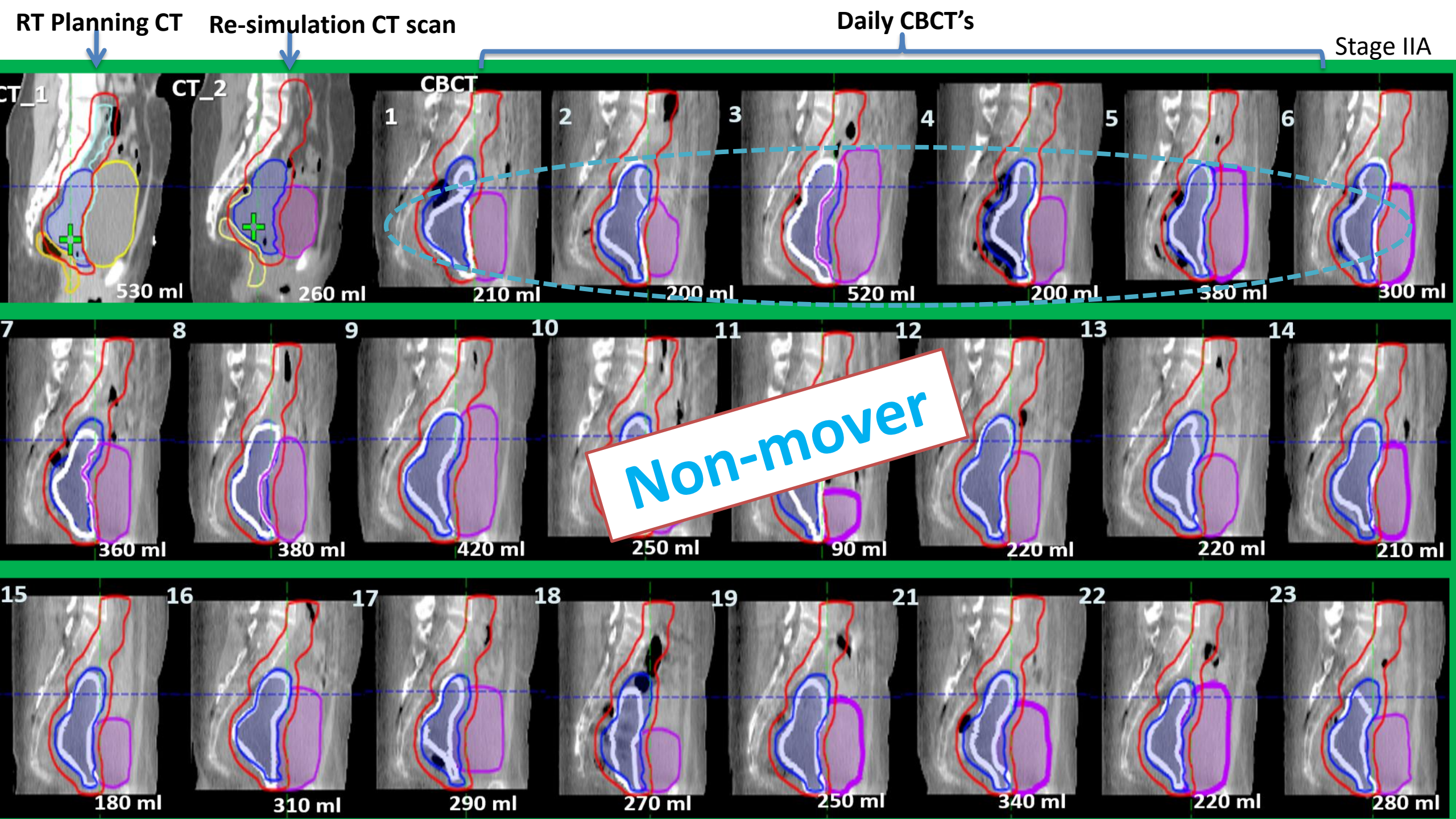
Bladder Filling Status

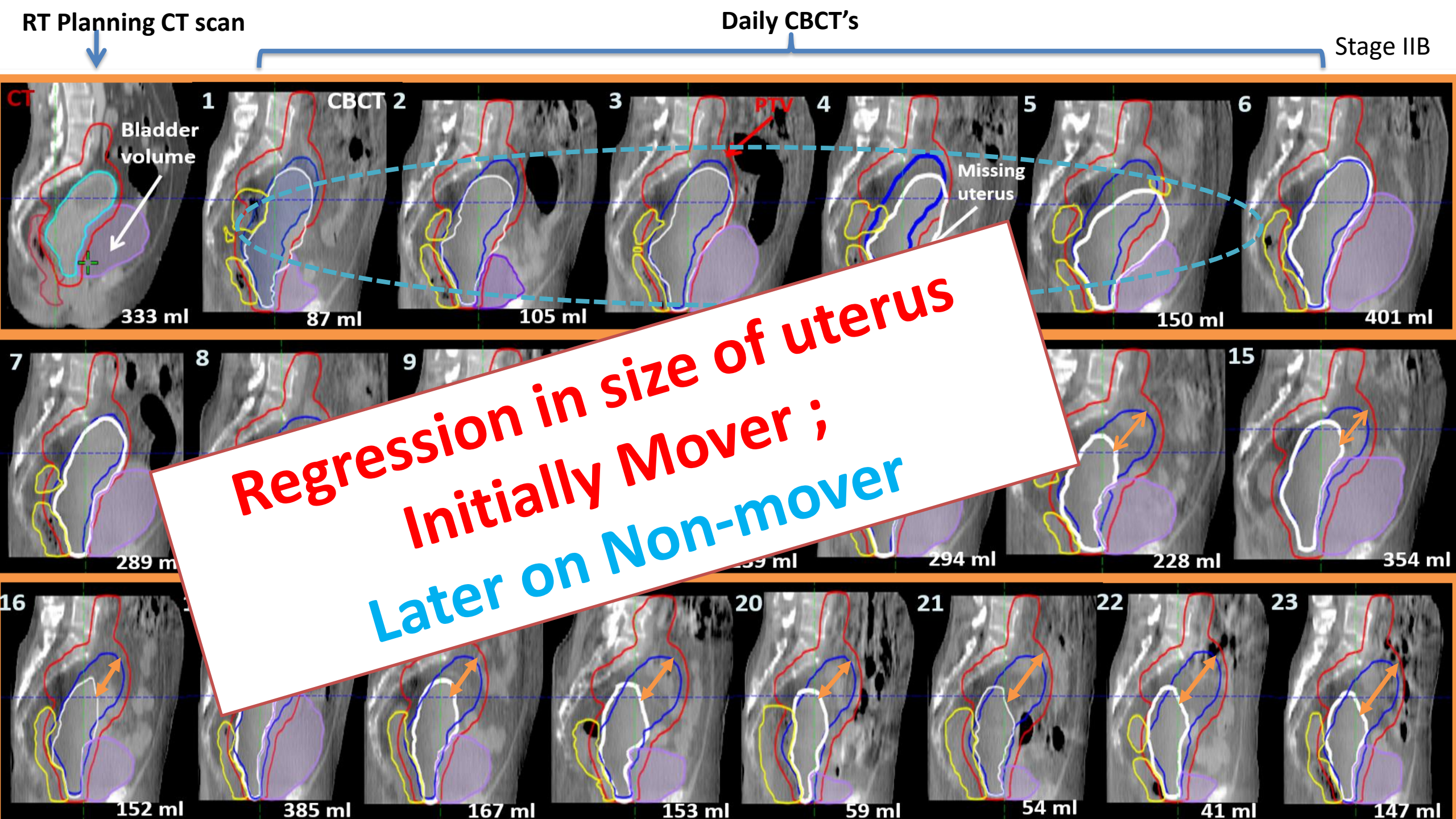



RT Planning CT scan
Daily CBCT's
Stage IIB
CT
Bladder volume
328 ml
1
CBCT 2
3
PTV
4
5
6
73 ml
157 ml
563 ml
117 ml
128 ml
162 ml
7
8
9
10
11
12
13
Mover
Missing uterus
288 ml
345 ml
71 ml
152 ml
104 ml
434 ml
50 ml
14
15
17
18
19
21
22
23
69 ml
156 ml
104 ml
211 ml
81 ml
128 ml
102 ml
115 ml


RT Planning CT scan
Re Planning CT scan
Daily CBCT's
Stage IIB
CT
Bladder volume
167 ml
1
CBCT
190 ml
2
320 ml
CT_Adapt
223 ml
3
PTV
187 ml
4
249 ml
5
109 ml
6
Missing uterus
402 ml
7
292 ml
8
87 ml
9
393 ml
10
170 ml
11
253 ml
12
184 ml
13
158 ml
14
64 ml
Mover
15
149 ml
16
182 ml
17
104 ml
18
295 ml
19
305 ml
20
267 ml
21
156 ml
22
85 ml
23
198 ml


RT Planning CT scan
Daily CBCT's
Stage IIB
CT - Planning
Bladder volume
279 ml
1
CBCT
400 ml
2
289 ml
3
PTV
67 ml
4
668 ml
5
104 ml
7
54 ml
9
75 ml
10
255 ml
13
265 ml
14
163 ml
16
92 ml
Non-Mover
17
177 ml
18
103 ml
21
86 ml
22
64 ml
23
56 ml

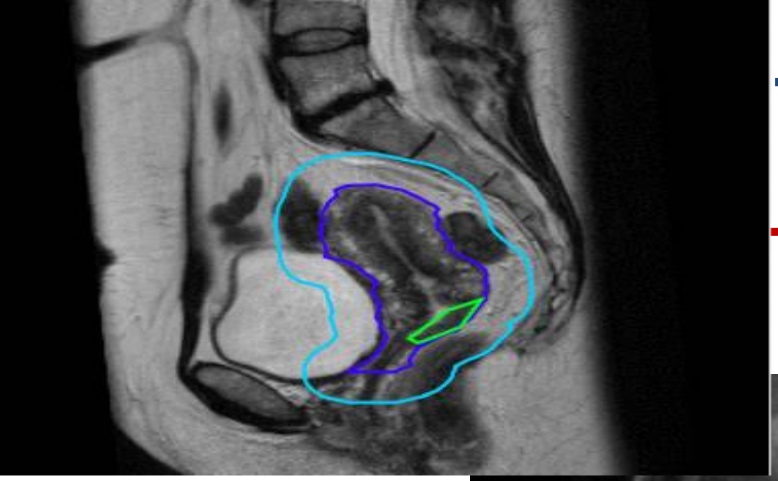

RT Planning CT
Re-simulation CT scan
Daily CBCT's
Stage IIA
CT_1
CT_2
CBCT
1
2
3
4
5
6
530 ml
260 ml
210 ml
200 ml
520 ml
200 ml
380 ml
300 ml
7
8
9
10
11
12
13
14
360 ml
380 ml
420 ml
250 ml
90 ml
220 ml
220 ml
210 ml
Non-mover
15
16
17
18
19
21
22
23
180 ml
310 ml
290 ml
270 ml
250 ml
340 ml
220 ml
280 ml


RT Planning CT scan
Daily CBCT's
Stage IIB
CT
Bladder volume
333 ml
1
CBCT 2
87 ml
105 ml
3
PTV
4
Missing uterus
5
150 ml
6
401 ml
7
289 ml
8
9
294 ml
15
228 ml
354 ml
16
152 ml
385 ml
167 ml
20
153 ml
21
59 ml
54 ml
22
41 ml
23
147 ml
Regression in size of uterus
Initially Mover ;
Later on Non-mover

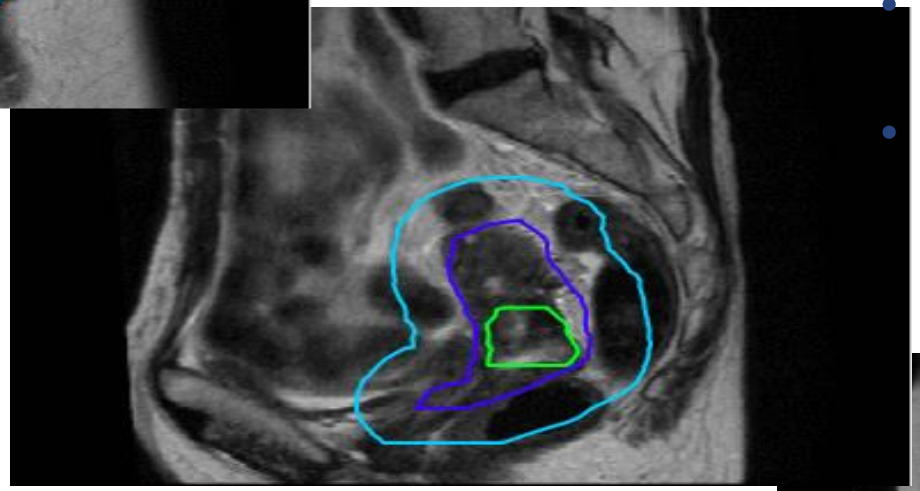
Target motion & Bladder filing effect during EBRT

Van de Bunt et al 2008

- 5 consecutive MRI's during EBRT
- Impact of changes in bladder and bowel filling on position changes of uterus
- Not only one organ is responsible



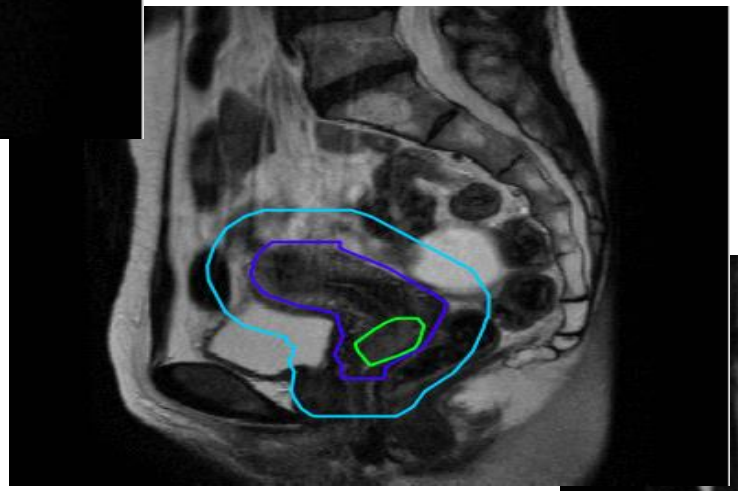
Low impact



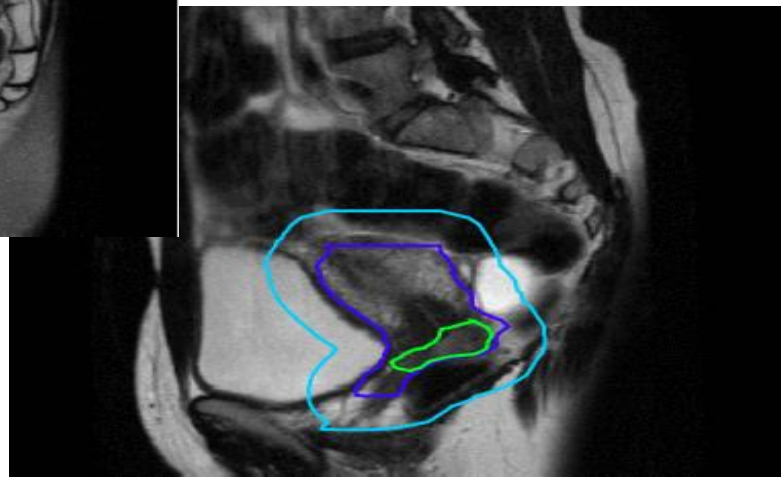
Low impact

GTV
CTV
PTV

High impact of bladder and bowel

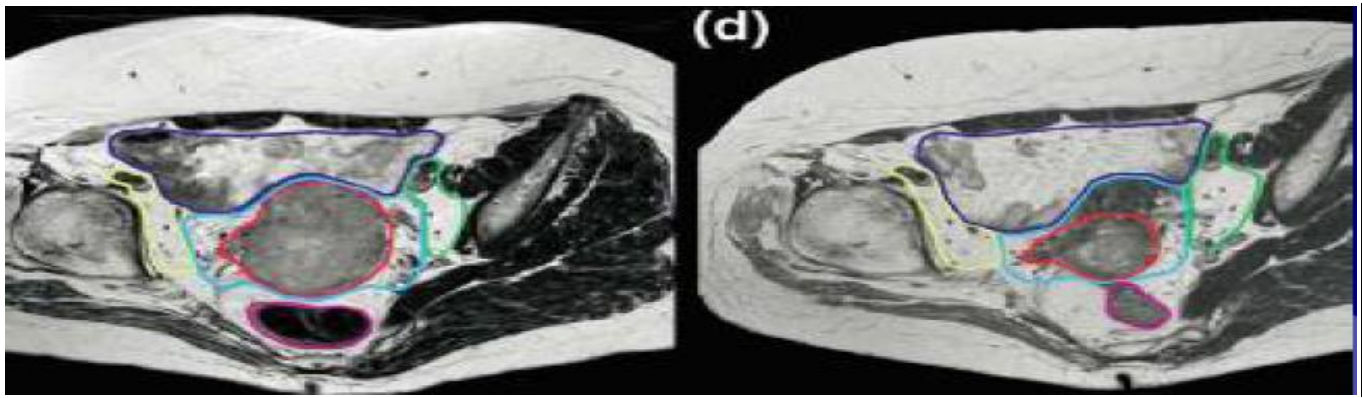


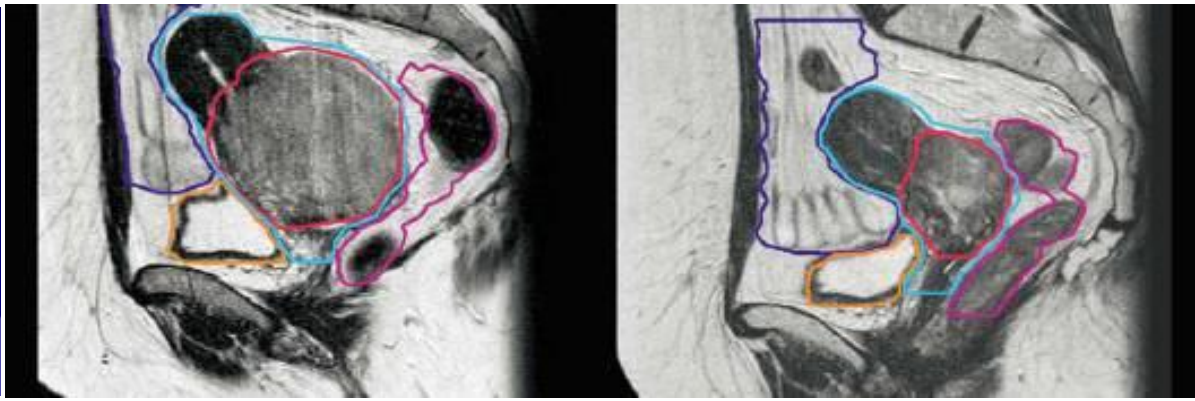
High impact of bladder



Courtesy : Ina Schulz, Utrecht

TUMOR REGRESSION DURING EXTERNAL RADIATION THERAPY





- Significant changes in tumor volumes occur during EBRT
- Tumors shrink & often quite quickly with CTRT
- Shrinkage is a double-edged sword

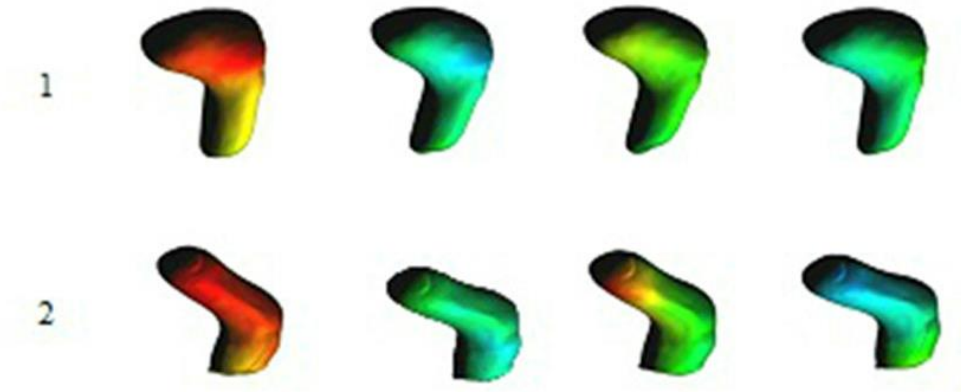
➢ University of Utah used physical exam measurements and found by 30.8 Gy tumors reduced by 50%

➢ MD Anderson used weekly conventional CT & noted a mean reduction of 64%

Lee et al. Red Journal 2005;58:625
Beadle et al. ASTRO 2006
Mayr et al. Am J Roentgenol 2006;187:65
Van de Bunt et al. Red Journal 2006;64:189

Organ Motion: Intrafraction

- 7 studies N= 92 patients
- Cinematic-MRI, VB/MVCT and portal imaging before and after each fraction.
- Mean range of 0.1-3.0 mm.
- Displacements greater than 5 mm occurred less than 3% of the time
- No predominance in direction



The overall mean (M), systematic error (Σ), and random error (σ) of the intra-fraction changes in patient setup over the entire patient group.

Patient motion	LR (mm)	CC (mm)	AP (mm)
M	−0.1	0.4	1.1
Σ	1.3	0.4	0.6
σ	1.4	1.0	1.1

Heijkoop, Sabrina T., et al. "Quantification of intra-fraction changes during radiotherapy of cervical cancer assessed with pre-and post-fraction Cone Beam CT scans." *Radiotherapy and Oncology* (2015).

SUMMARY

- Patient Position & Immobilization:

  - Supine with Knee rest and laser alignment

  - Whole body vacloks / body fix: as an alternative

- Organ filing:

  - Rectum: Preferably empty through out the planning and Rx

  - Bladder: Minimize the variation by adopting some bladder filing protocol

Imaging Protocols for Radiation Planning:
Fluoroscopic simulation, CT, Virtual simulation

Dr. D.N. Sharma

Professor,

Department of Radiation Oncology,

All India Institute of Medical Sciences, New Delhi

Outline

- X-ray/Fluoroscopy simulation:
  (Conventional Simulation)
- CT Simulation
- Virtual Simulation

I will not discuss

- Patient preparation, immobilisation
- MRI, PET-CT simulation
- Treatment verification

Patient preparation, Immobilization,

Imaging, Simulation etc.

Target /OAR delineation

DRR, Beam placement, Plan generation, Evaluation

Treatment verification, Treatment delivery

Role of Simulation in RT process

- The simulation belongs to the most important st
of whole treatment process
- Mimic the radiation t
diverg

Target coverage & OAR sparing

e beam

of the treatment field to optimize coverage
of target & minimize irradiation of normal tissue

Simulation Team

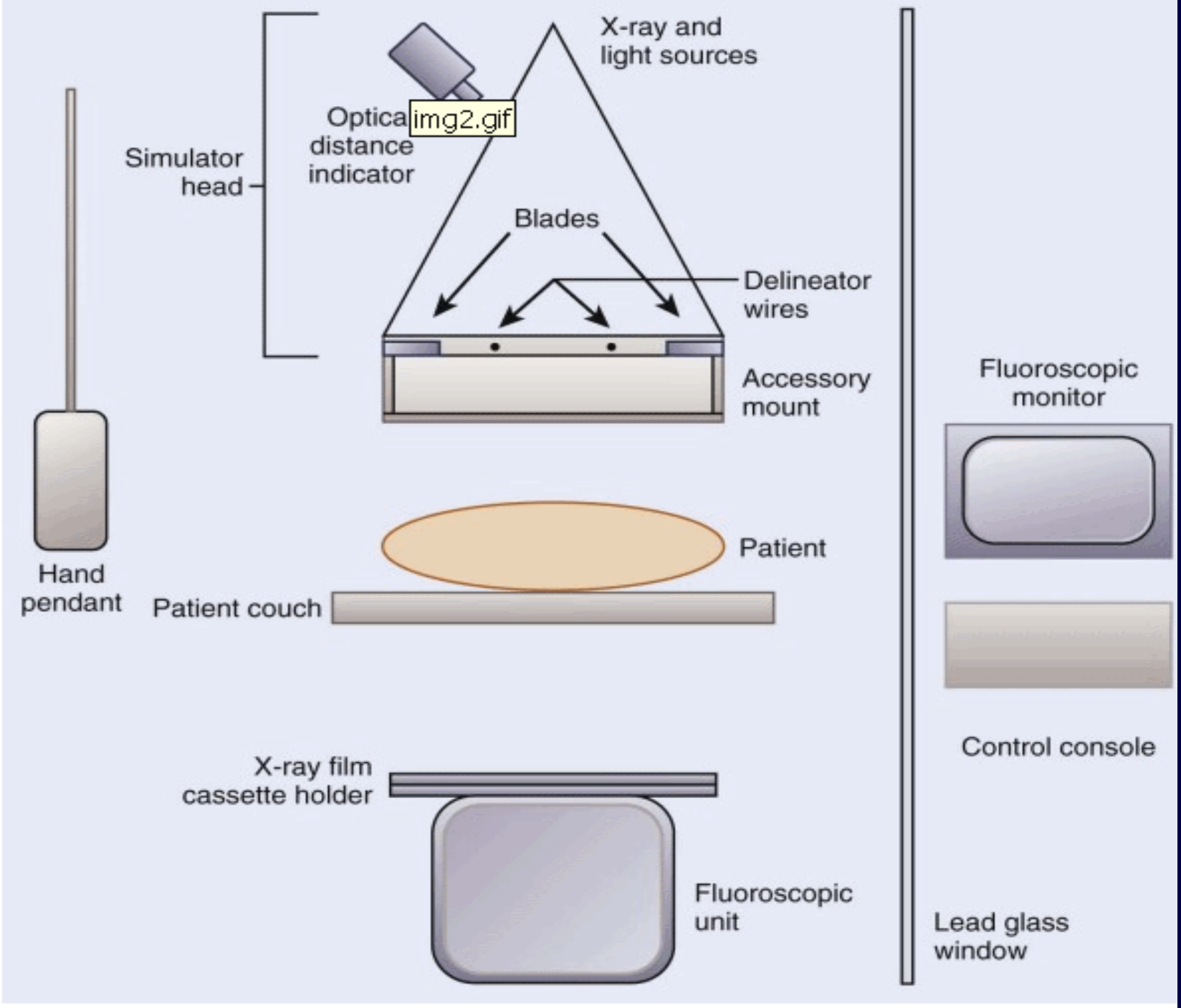
- Radiation Oncologist
- Medical physicist
- Radiation Therapist
- Radiation Staff nurse
- Maintenance Engineer

- Radiologist

Conventional Fluoroscopic Simulator

- It consists of diagnostic X-ray tube mounted on a rotating gantry,

- Mimics all the mechanical features and geometric field arrangement of various machines ranging from Cobalt-60 to high energy LINAC

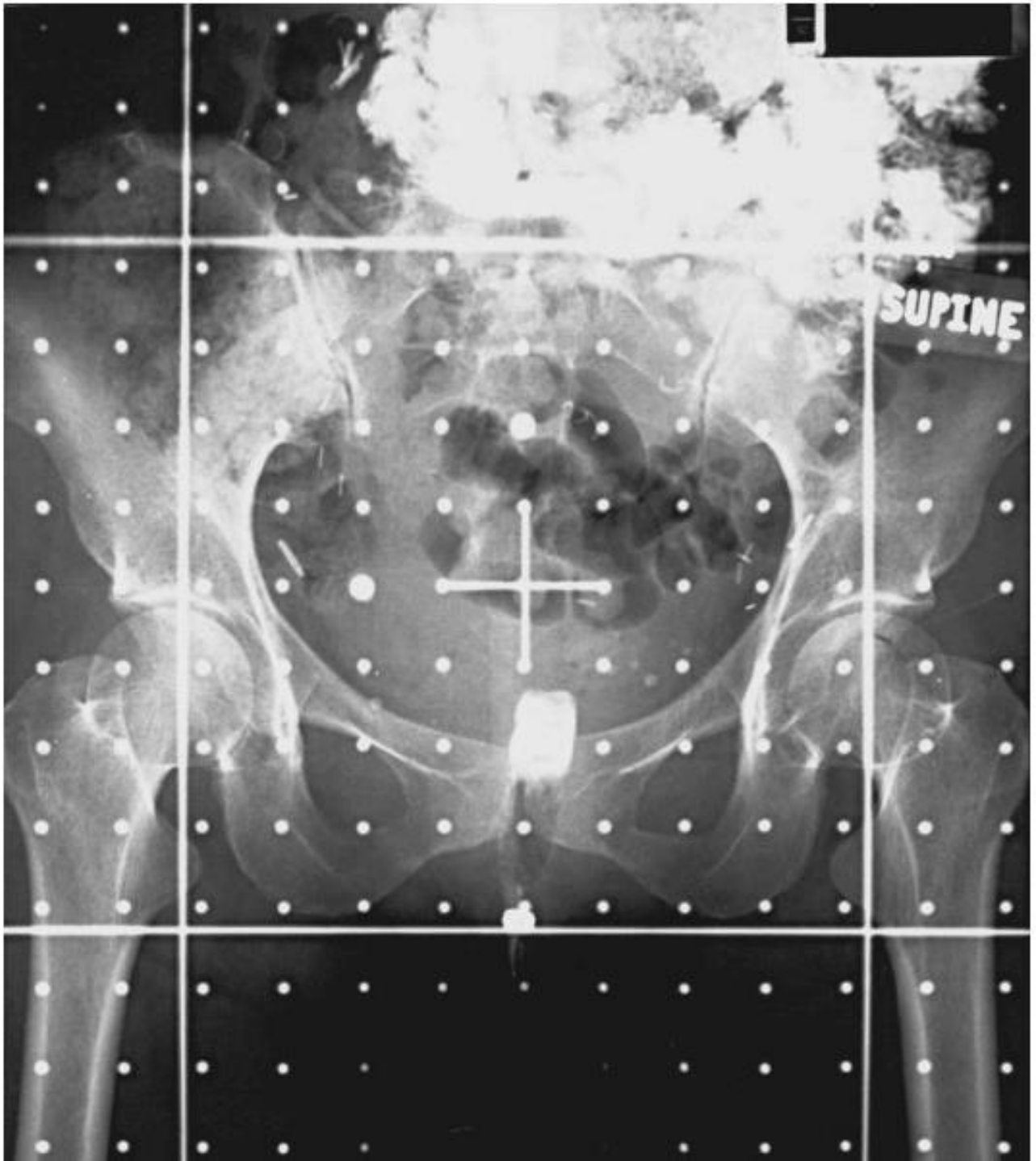

X-ray and
light sources
Optical
distance
indicator
img2.gif
Simulator
head
Blades
Delineator
wires
Accessory
mount
Fluoroscopic
monitor
Hand
pendant
Patient
Patient couch
Control console
X-ray film
cassette holder
Fluoroscopic
unit
Lead glass
window

Conventional Simulator

- Main simulation machine in the peripheral centers
- Provides live or real time X-ray imaging
- Useful for palliative and routine plannings
- Suits the busy centers with high patient load
- Easy availability and low cost
- Image quality: bony landmarks, contrast, markers
- Target and OAR not visible
- Only 2D image and therefore not for 3D-CRT

Procedure

- Supine position with immobilization device
- Set kV and mA
- Consistent Bladder filling protocol
- Oral and rectal contrast for bowel and rectum
- Marker in the vagina, seeds, titanium clips
- AP and lateral films, L2 to 3 cm below tuberosities
- FAD as per the treatment unit
- Keep image intensifier close to table
- Keep exposure ALARA

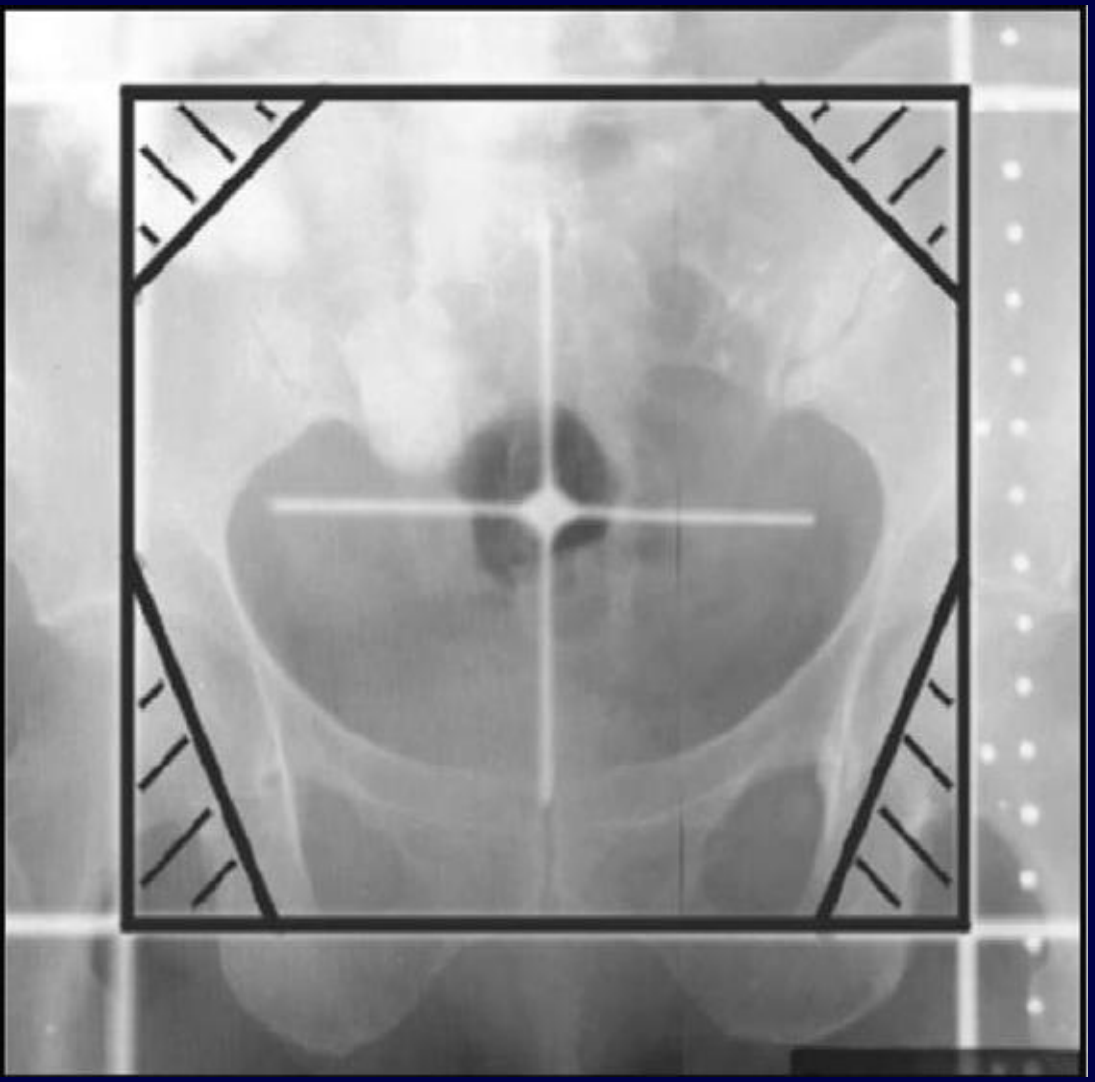

SUPINE

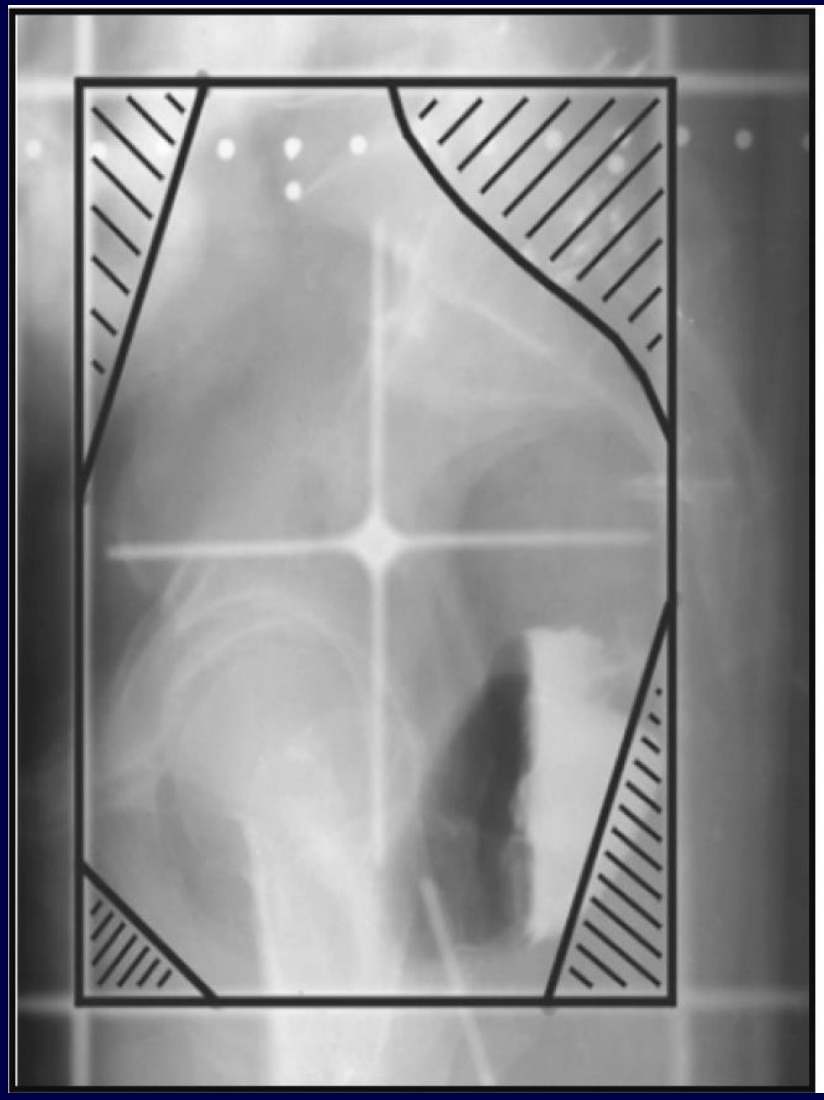
Field borders [AP-PA field]

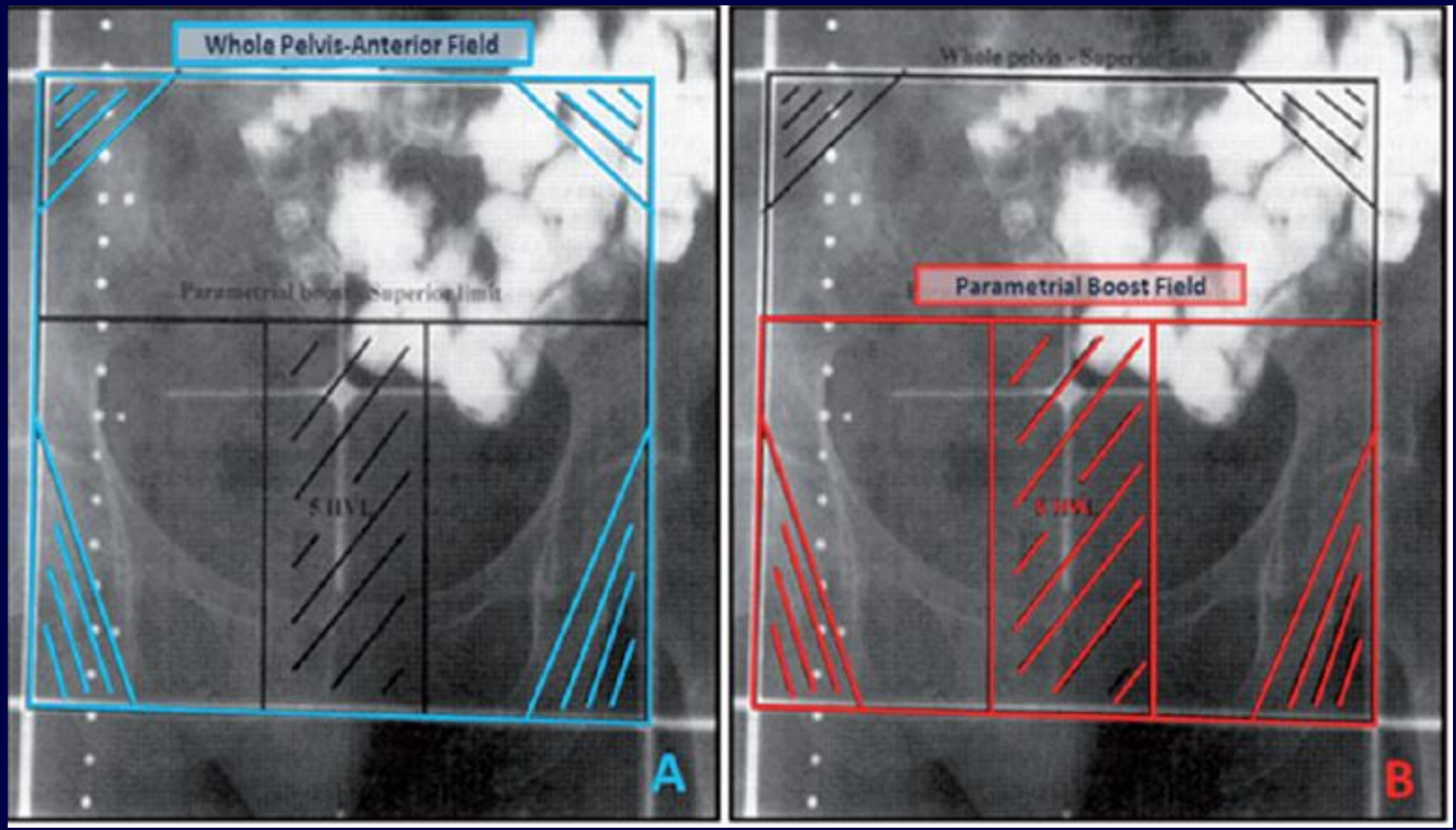
- Superior border- L4-L5 junction (to encompass the common iliac node)
- Lateral border- 1.5 cm from the widest pelvic part of the pelvic brim
- Inferior-no vaginal wall involved- lower border of the obturator foramen.
- If they are then – 2cm below the lower most point of disease

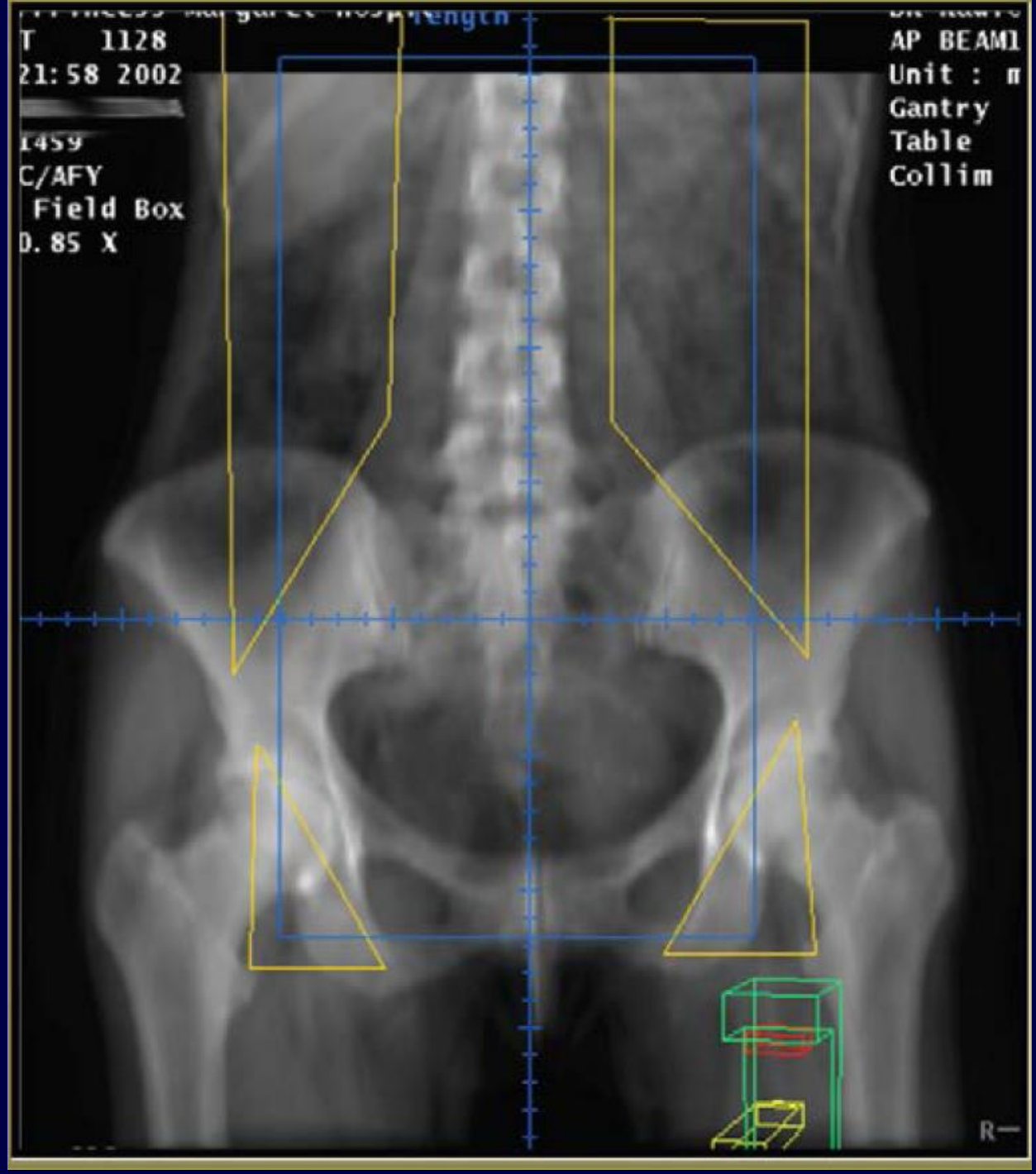
Lateral fields

- Superior and inferior would be corresponding to the AP-PA fields
- Anterior –vertical line to the anterior edge of pubic symphysis
- Posterior-to encompass the sacral hallow (junction S2-S3)






Whole Pelvis-Anterior Field
A
Parametrial Boost Field
B


T 1128
21:58 2002
1459
C/AFY
Field Box
0.85 X
AP BEAM1
Unit : n
Gantry
Table
Collim
R

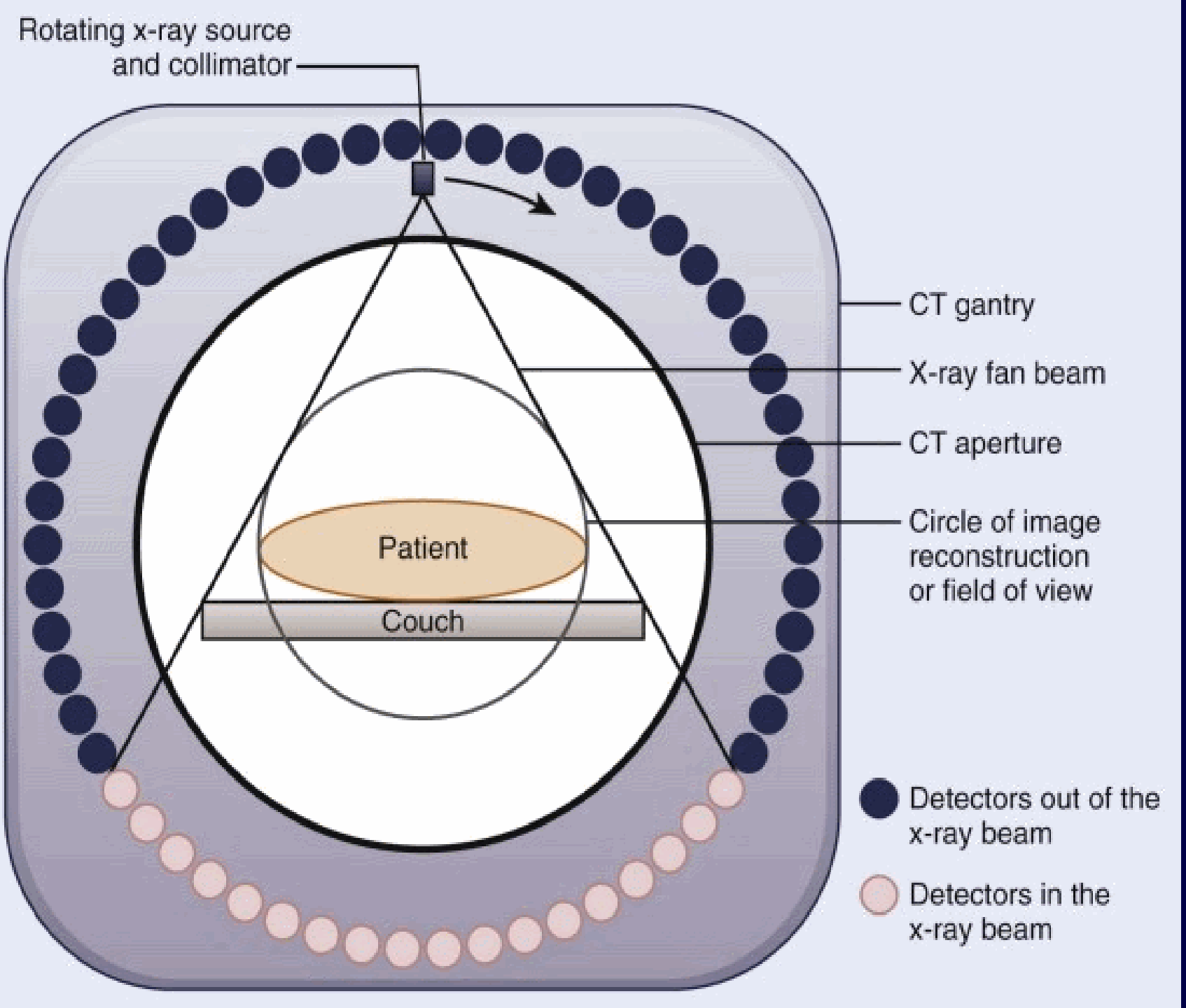
CT simulation

- The CT scanner is used to acquire a volumetric CT-Scan of a patients which represents the “virtual “or digital patients

- The CT-simulation software provides virtual representation of the geometric capabilities of a treatment machine

CT Simulator Components

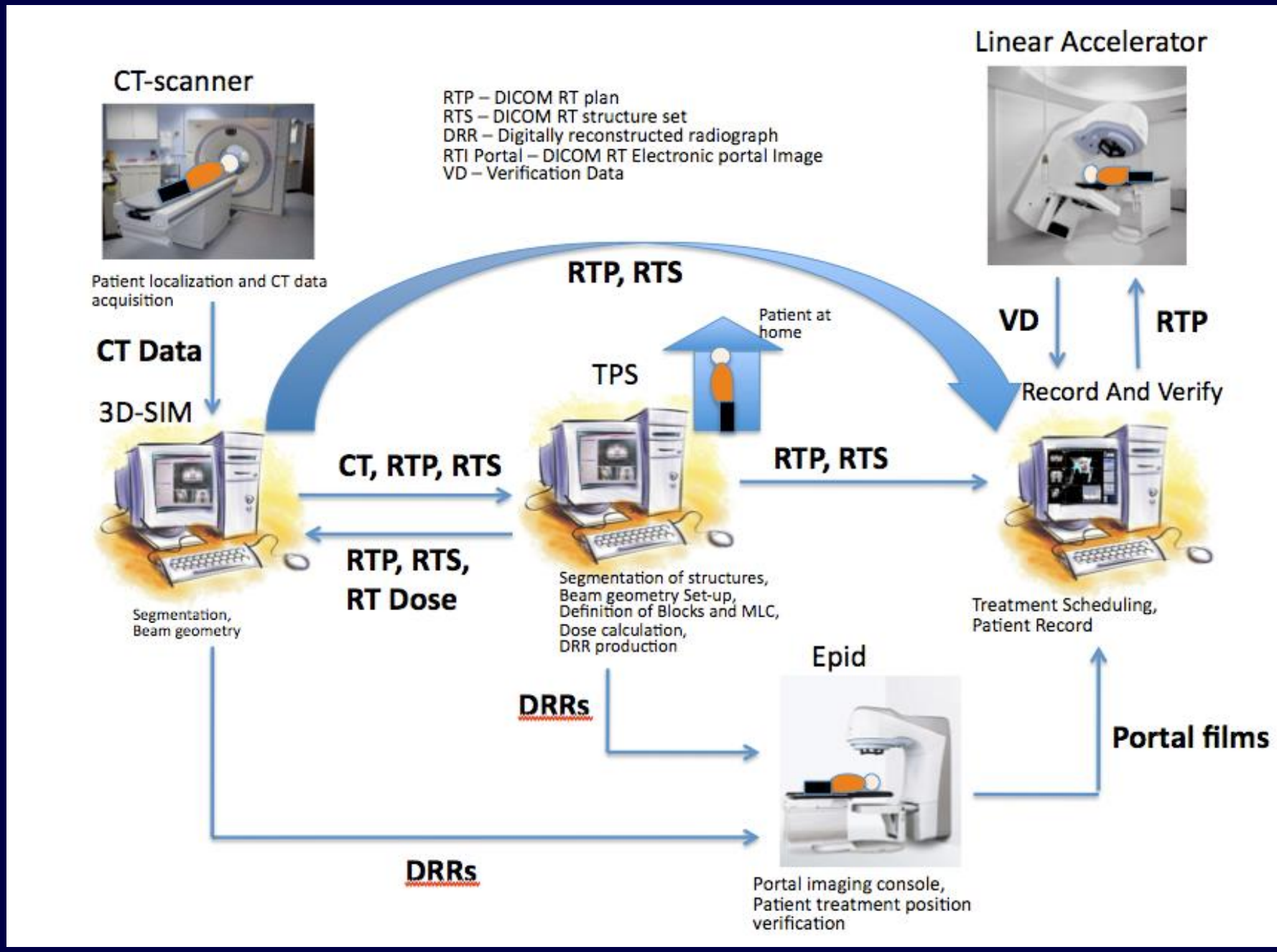
- X-ray tube
- Large bore CT-scanner with opening of up to 85cm
- Detectors systems
- Collimators and attenuator
- Patients couch
- Laser
- Computer and work station
- Control console


Rotating x-ray source
and collimator
CT gantry
X-ray fan beam
CT aperture
Circle of image
reconstruction
or field of view
Patient
Couch
Detectors out of the
x-ray beam
Detectors in the
x-ray beam


28 1:24PM

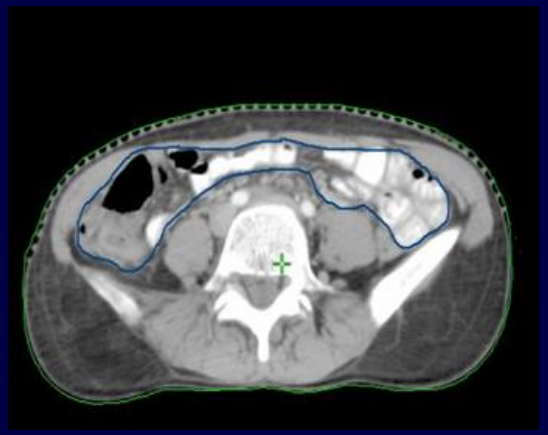
Features of Multislice CT scanner

- Faster scan times
- Lower tube heat loading
- Longer volume covered per rotation
- Improved temporal resolution - faster scan times
- Improved spatial resolution – thinner slices
- Decreased image noise – more mA available


Linear Accelerator
CT-scanner
RTP – DICOM RT plan
RTS – DICOM RT structure set
DRR – Digitally reconstructed radiograph
RTI Portal – DICOM RT Electronic portal Image
VD – Verification Data
RTP, RTS
Patient localization and CT data acquisition
Patient at home
VD
RTP
CT Data
TPS
Record And Verify
3D-SIM
CT, RTP, RTS
RTP, RTS
RTP, RTS,
RT Dose
Segmentation of structures,
Beam geometry Set-up,
Definition of Blocks and MLC,
Dose calculation,
DRR production
Segmentation,
Beam geometry
Treatment Scheduling,
Patient Record
Epid
DRRs
Portal films
DRRs
Portal imaging console,
Patient treatment position
verification

CT Simulation

- **Standard Bladder protocol**
- **Contrast materials**:
  - Intravenous contrast (Inj. Omnipaque/Iomerol @ 2cc/kg) preferably via an automatic timed contrast injector), unless medically contraindicated or patients had history of contrast allergy.
  - An oral contrast may be used to opacify bowel
  - Per-rectal barium for localizing the rectum



CT Simulation

- **Field of view: Large (80-85 cm)**
  - Pelvic RT: Upper border of T12 Vertebrae to 5cm below ischial tuberosity
- Slice thickness: (2.5-5 mm) ≤ 5 mm
- No interslice gap
- Table increments: 3mm
- Flat table couch

Virtual Simulation

- It is the process in which simulation is carried out using software created on patient CT data set.

- It simulates all the parameters of the actual treatment machine (Gantry angle, couch position, Radiation field).

- The presence of patient physically is not required, while doing treatment simulation planning.

- Thus it also called as Virtual simulation

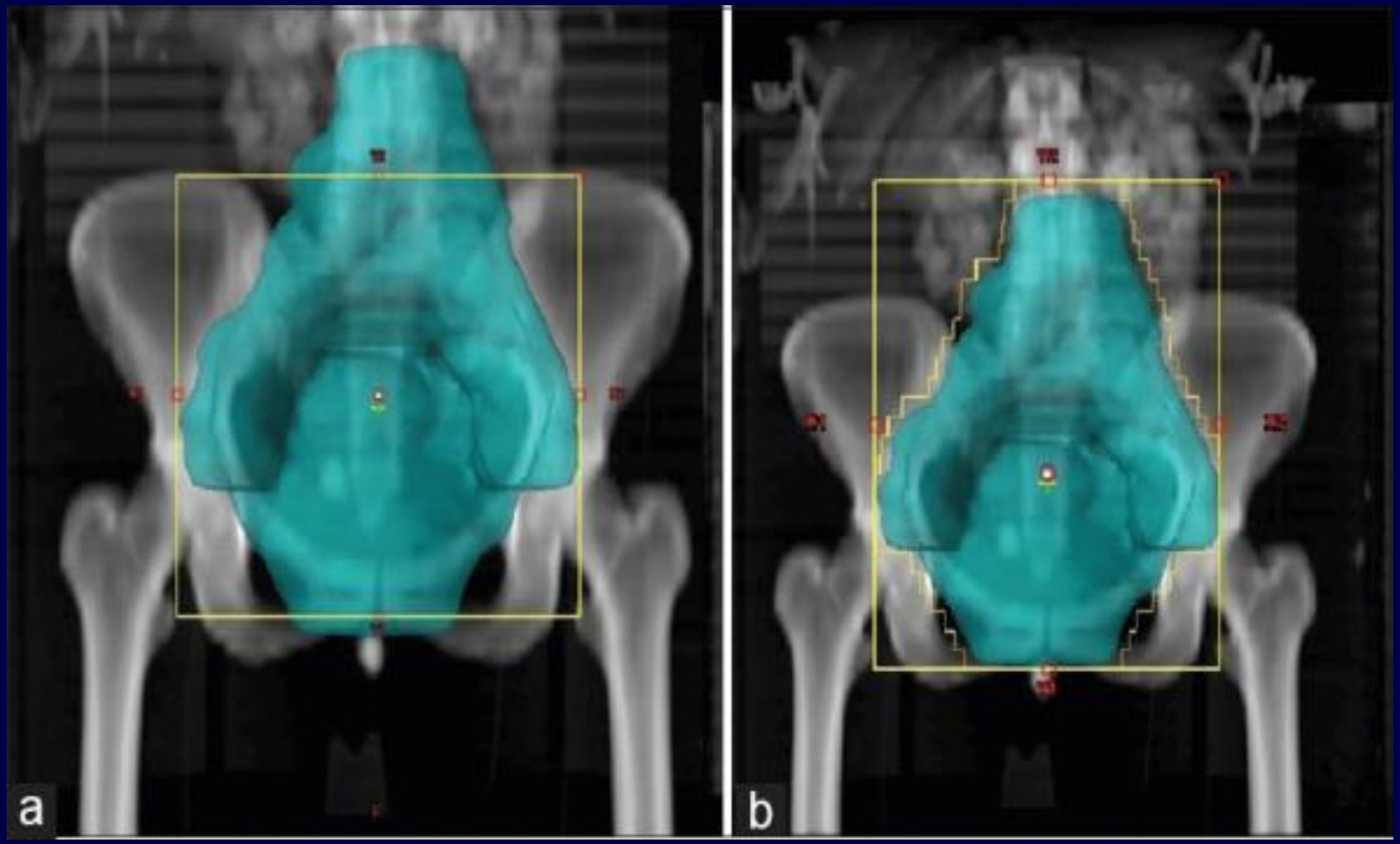
George W. Sherouse, PhD, DABR, FAAPM, Univ North Carolina

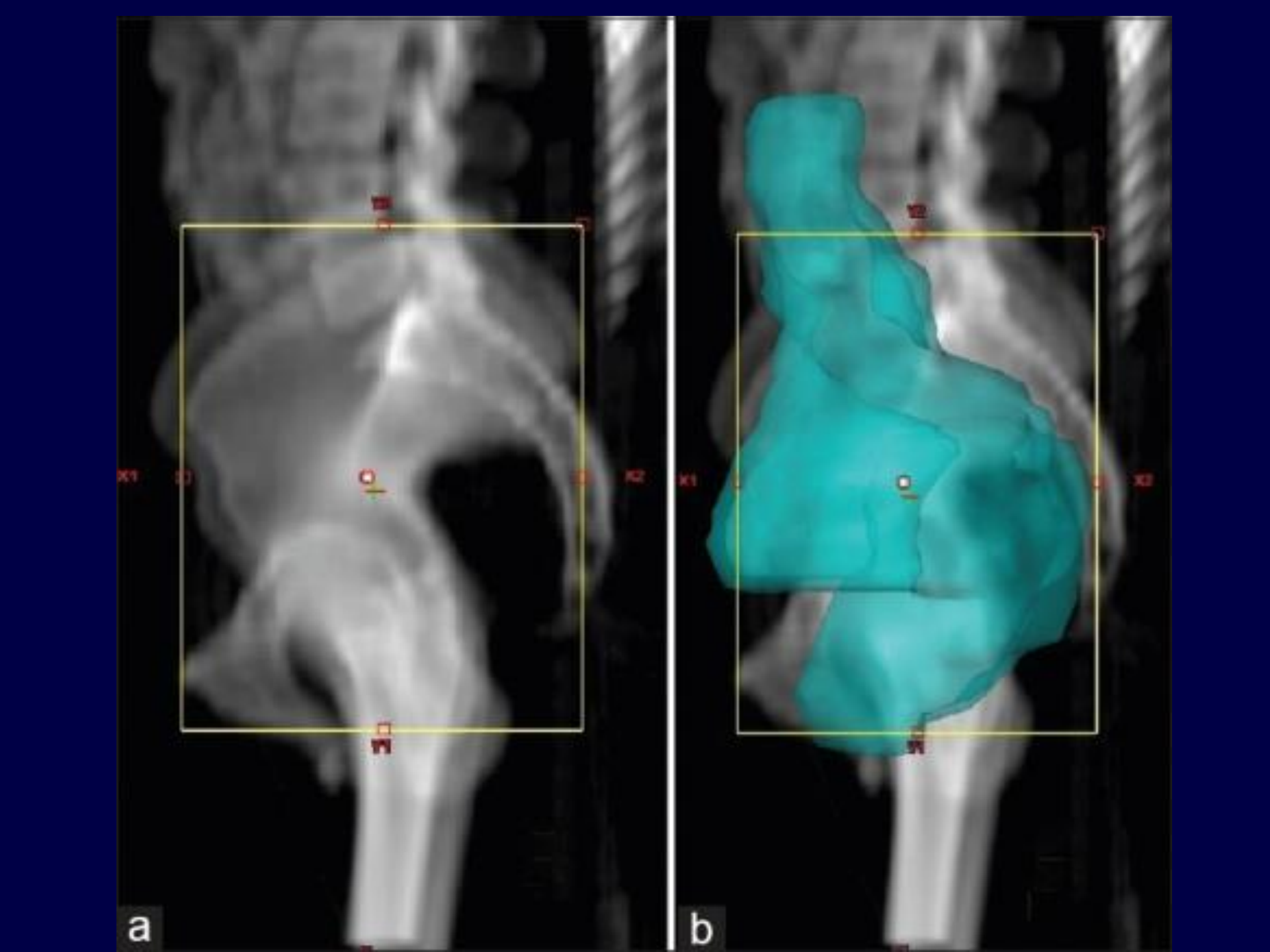
Virtual Simulation: Workflow

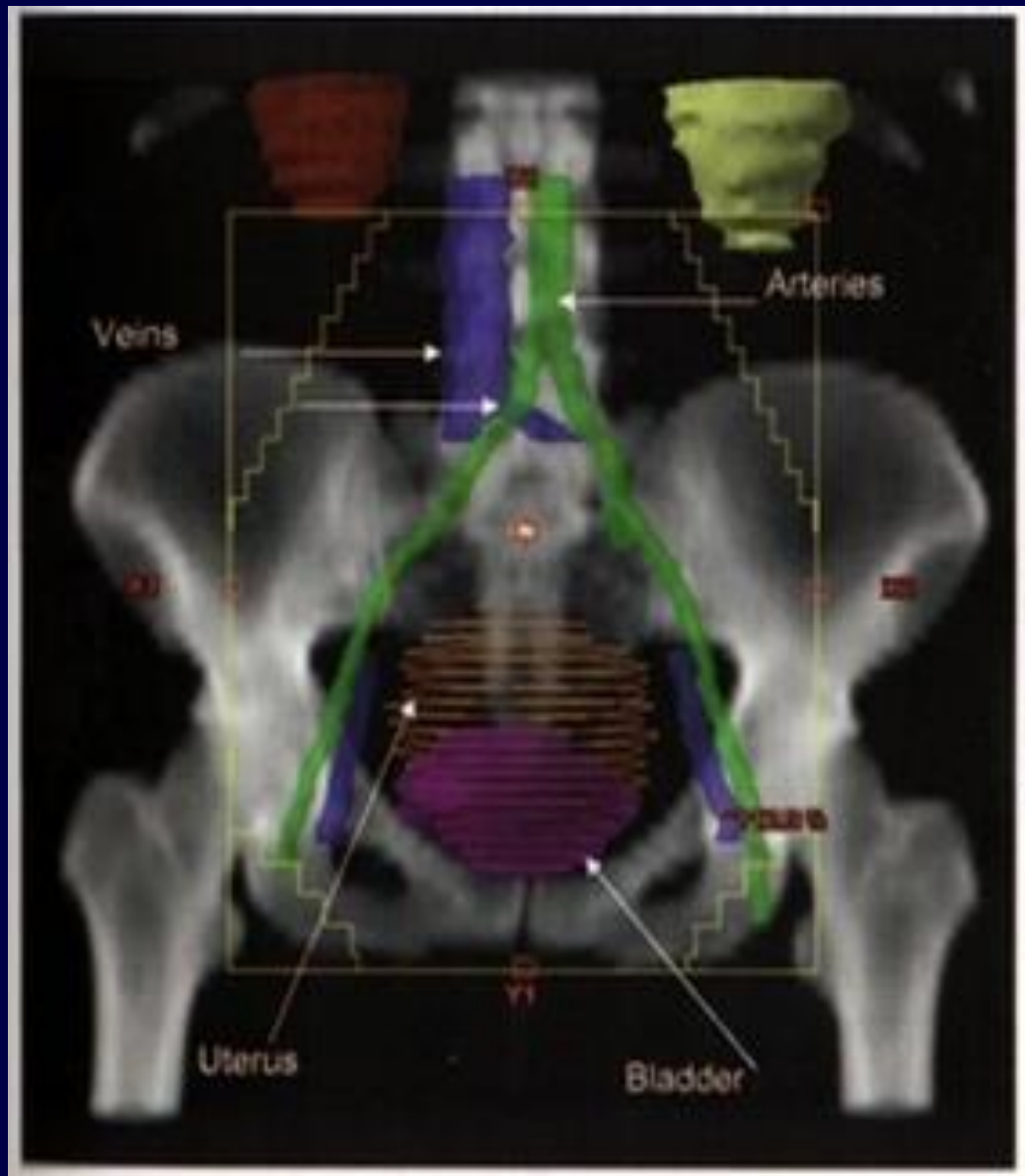
- Software to perform virtual simulation
- DRR
- Target definition
- Treatment planning
- Dose planning

Advantages of Virtual-Simulation

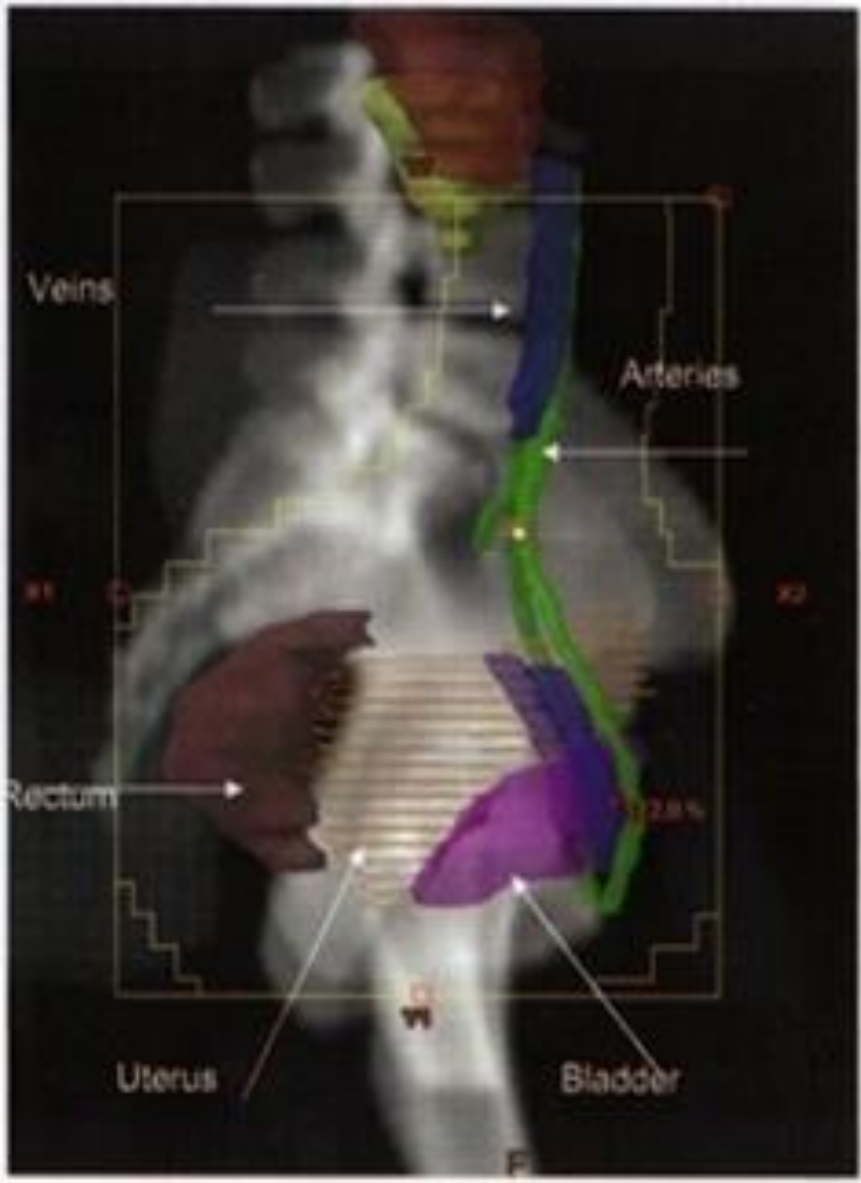
- Patient throughput is more
- Non coplanar simulation is possible
- 3D data set is available, resulting in better visualization of tumor and nodal involvement, leads to reduction in side effect
- Full 3D allowing unique verification of beam coverage and avoidance in three dimensions
- Beams can be simulated and verified that are not possible with conventional simulation


a
b


a
b

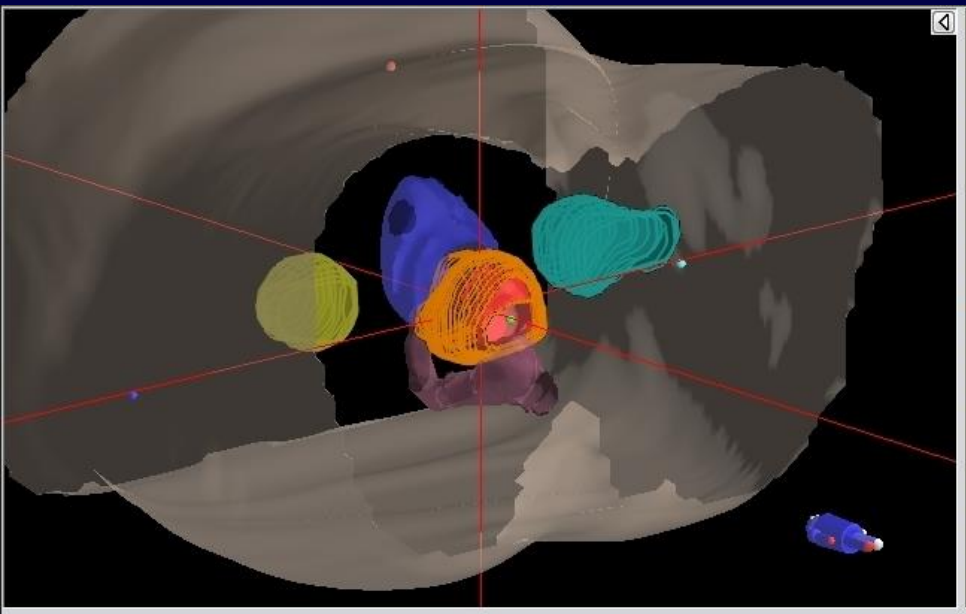


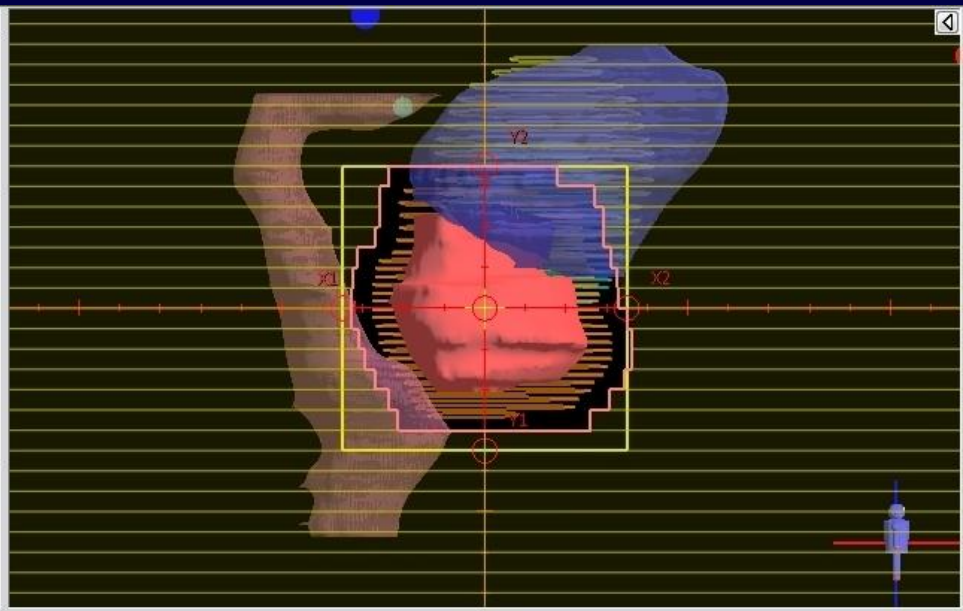
DDR – Anterior beam

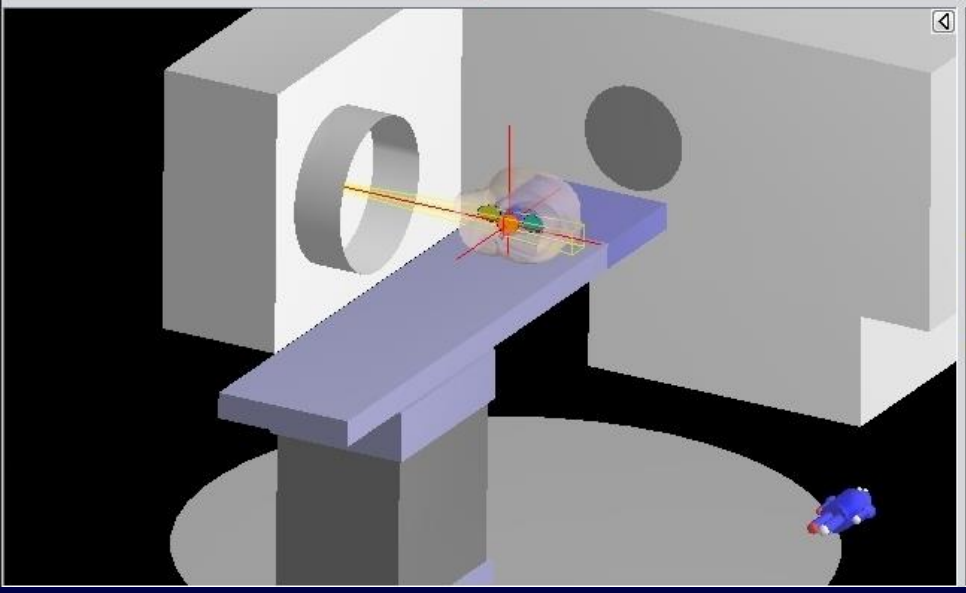


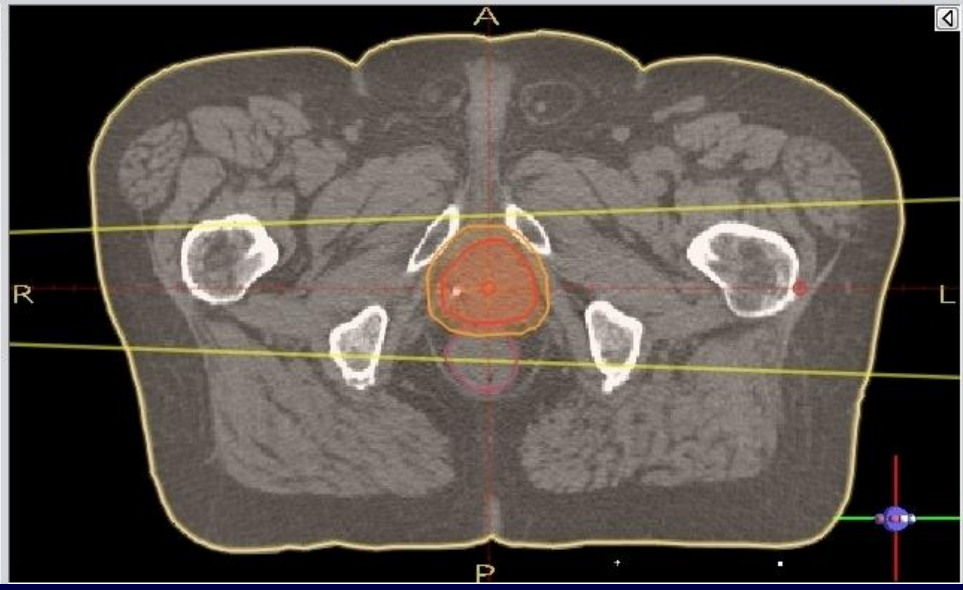
DDR – Right Lateral beam

BEV and REV: Virtual Simulation









Thank you

UMC Utrecht

مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH • EDUCATION • RESEARCH صحة • تعليم • بحوث

CTV delineation
For External Beam RadioTherapy (EBRT)

Ina Jürgenliemk-Schulz

University Medical Centre Utrecht, The Netherlands

Primoz Petric

National Center for Cancer Care and Research, Doha, Qatar

Modified and Presented by

Richard Pötter,

Medical University of Vienna

1st ESTRO AROI Gyn teaching course

Transition for Conventional 2D to 3D Radiotherapy

With special emphasis on brachytherapy in cervical cancer

Bengaluru, India, March 2017

Definitions *(upcoming definitions in the frame of adaptive thinking)*

GTV = Gross Tumor Volume

- Macroscopic tumor, visible clinically and with imaging

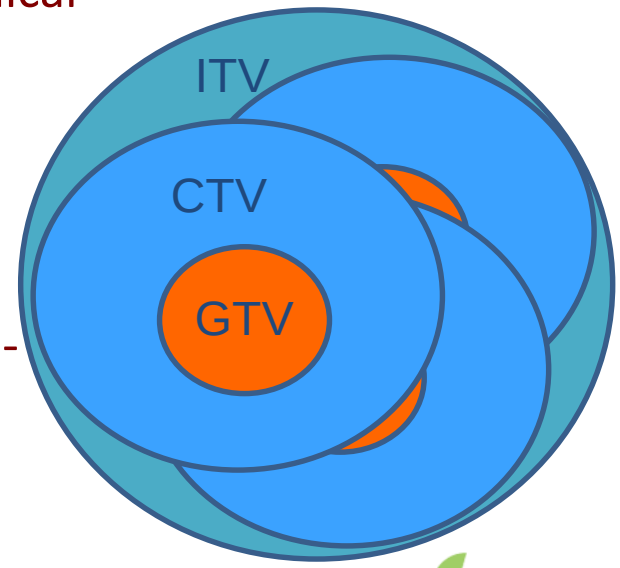
ICRU reports 50-83

CTV = Clinical Target Volume

- Tissue volume that contains a GTV and/or subclinical microscopic malignant disease, which has to be eliminated

ITV = Internal target volume

- Volume that accounts for internal inter- and intra-fraction motion and deformation of the CTV



Valid for the primary tumor: GTV-T, CTV-T
for lymph nodes: no GTV-N, CTV-E (elective nodal CTV)
GTV-N, CTV-N

The overall CTV of the primary tumor for EBRT always includes ?

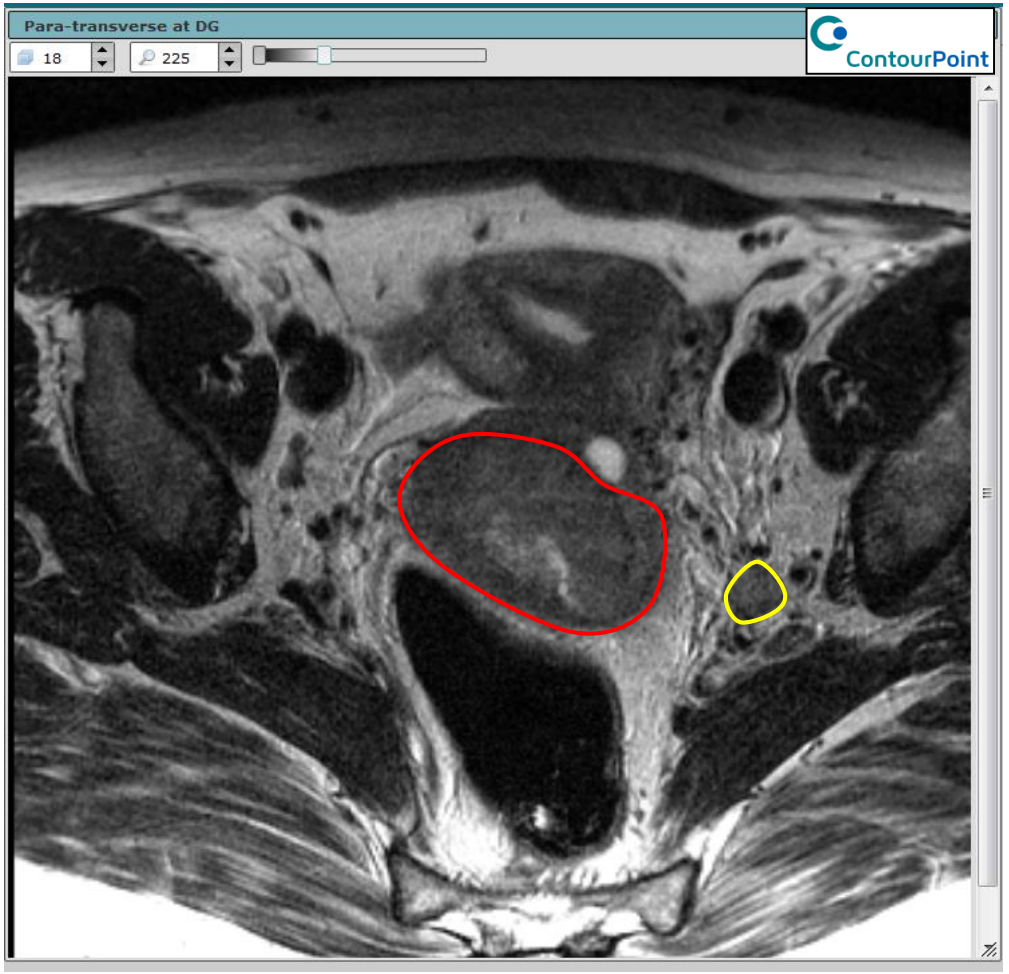
A. GTV +Cervix+Uterus +Parametria+upper vagina
B. GTV + cervix only
C. GTV, Cervix + Parametria only
D. GTV + whole Uterus only
E. GTV + cervix + Upper Vagina only
F. Adjacent organs
G. Ovaries

GTV-T *(GTV initial)*

GTV is in principal composed of:

- Primary tumor GTV-T
- macroscopic lymph node metastases GTV-N

High signal intensity on T2 weighted MRI

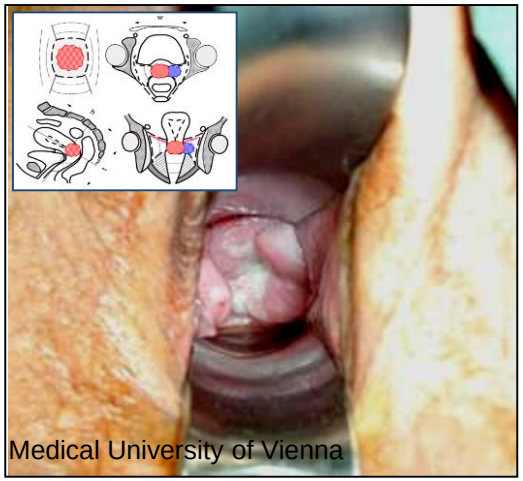


GTV

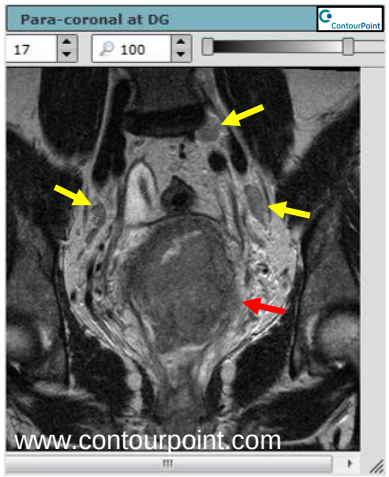
Consists of *Primary* and *Nodal* GTV *(GTV-T initial and GTV-N initial)*

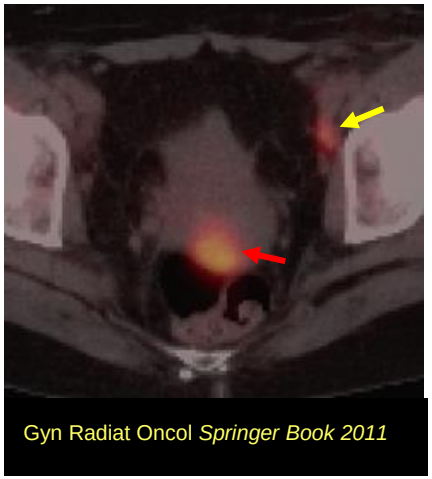
Investigation modality needs to be reported

Clinical Examination

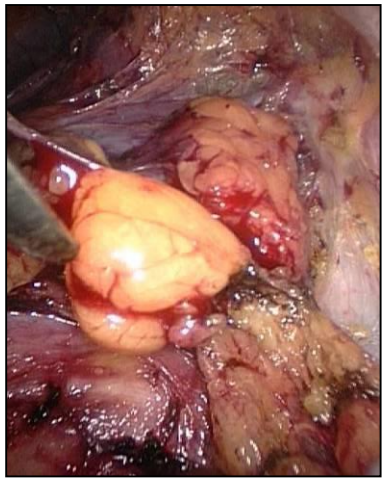


Imaging (MRI, CT, PET CT, US)

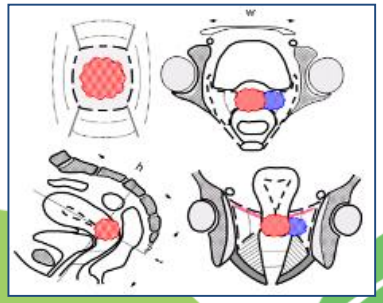




Invasive



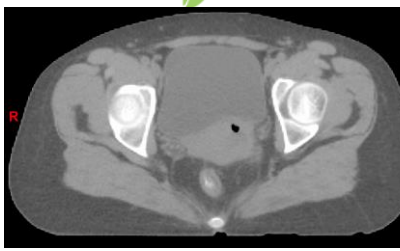
GTV contouring: combine information from different modalities



In case of GTV-T and CT only available,

clinical examination

is essential plus full documentation

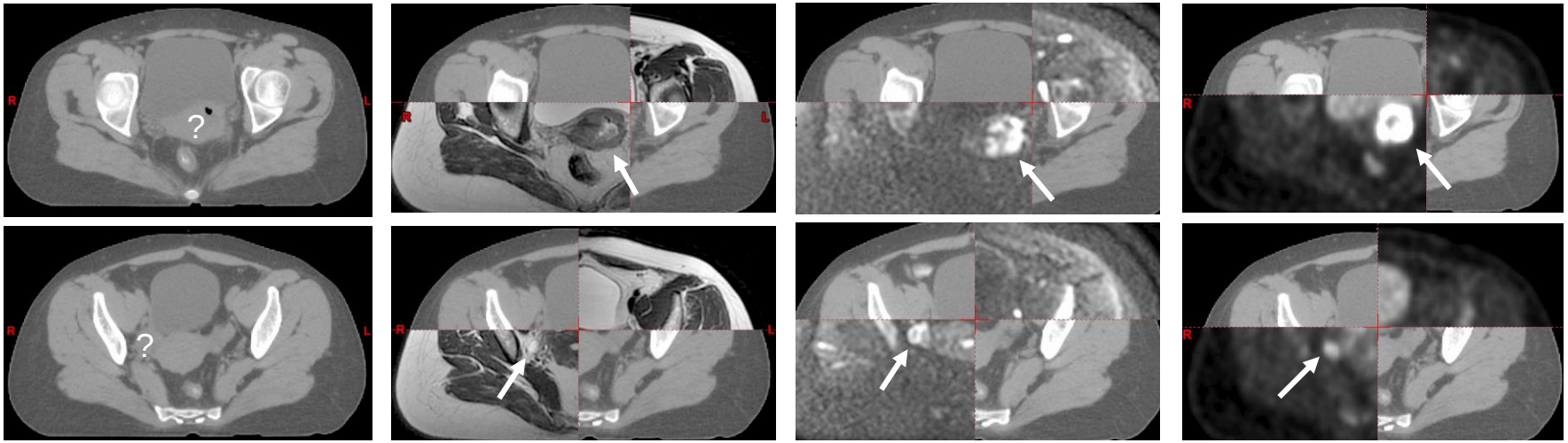


Initial GTV-T contouring (composite GTV)

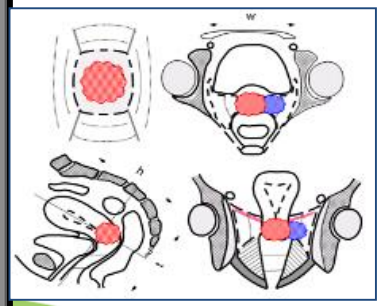
Co-registration of different imaging modalities?

Imaging in *same (treatment) position:* CT, MRI, PET-CT simulator

CT simulator | CT + T2w MRI | CT + DW MRI | CT + PET



Example; NCCCR, Doha, Qatar



Combined imaging answers many questions, but opens some new ones...

Clinical judgement remains essential in the era of imaging epidemics!

CTV contouring (Tumor and Nodes related)

Consists of *Primary CTV(high and low risk)* and *Nodal* CTV*(elective)*

Initial CTV-T:

- GTV
- Remaining unaffected cervix

} *HR-CTV-T initial*

- Parametria
- Uterus
- Vagina
- Involved organs (FIGO IVA)

} *LR-CTV-T initial*

Nodal CTV: *CTV-Elective and CTV-N*

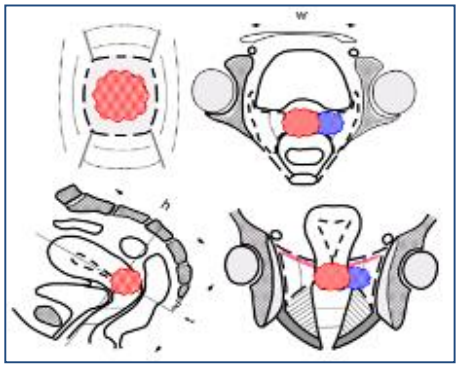
- Lymph node regions at risk (vessel orientated)
- Affected lymph-nodes: CTV-N

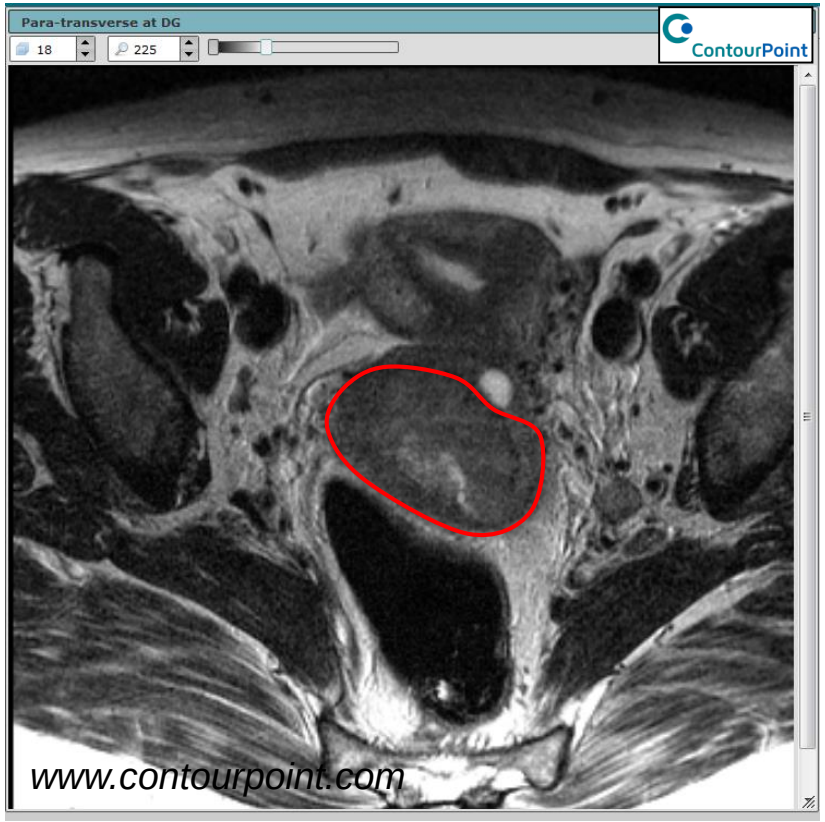
Initial CTV-T

- GTV
- Cervix
- Parametria
- Uterus
- Upper Vagina
- Involved organs (FIGO IVA)

Initial CTV-T

- GTV *(GTV-T initial)*
- Cervix
- Parametria
- Uterus
- Upper Vagina
- Involved organs (FIGO IVA)



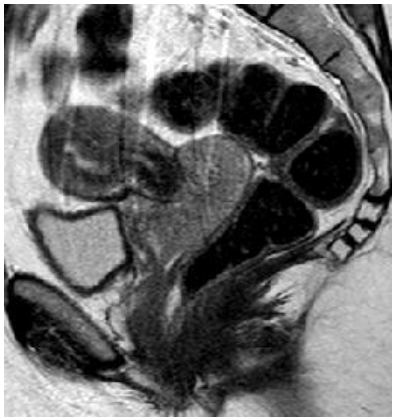


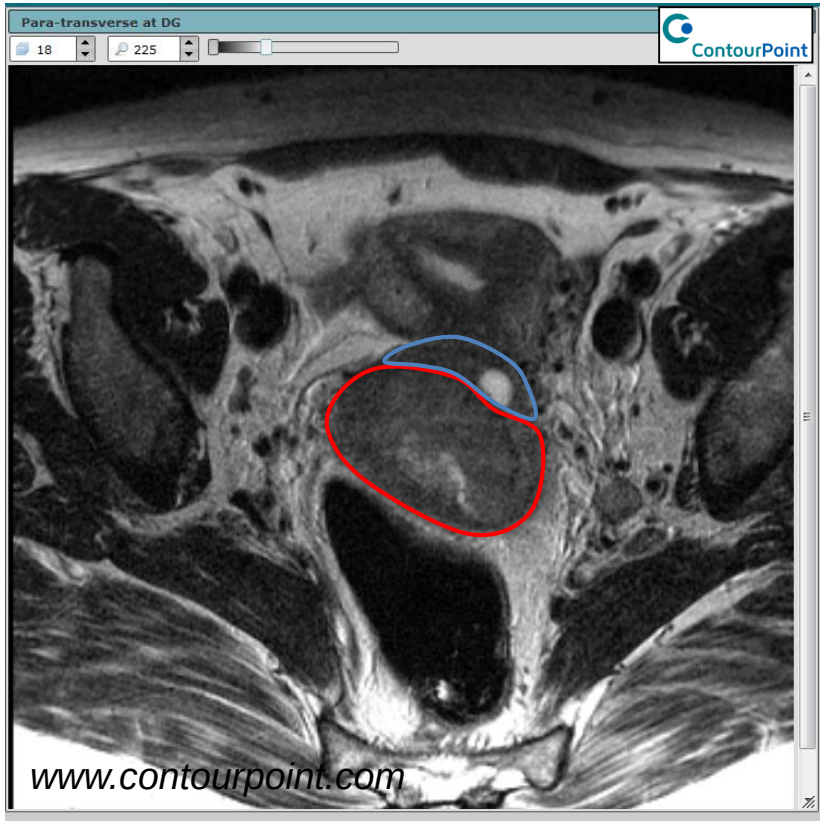
Initial CTV-T: HR CTV-T$_{initial}$

- GTV
- Cervix

} *HR-CTV-T initial*

- Parametria
- Uterus
- Upper Vagina
- Involved organs (FIGO IVA)

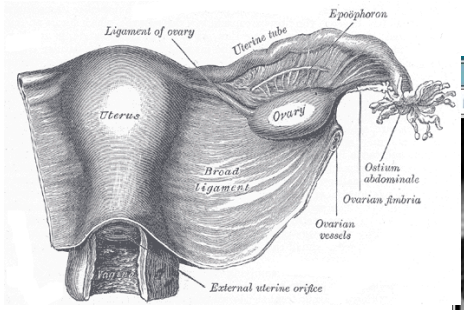


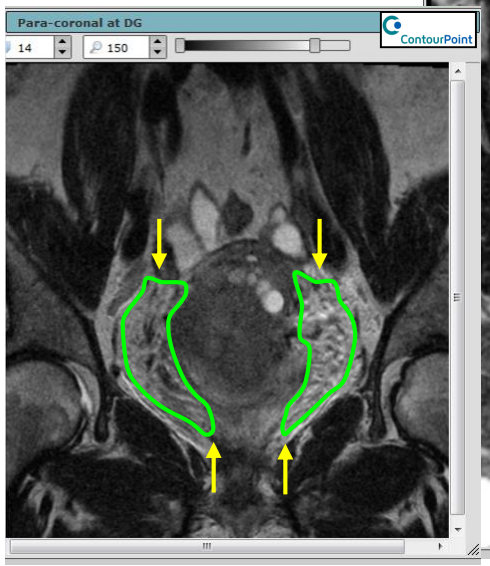


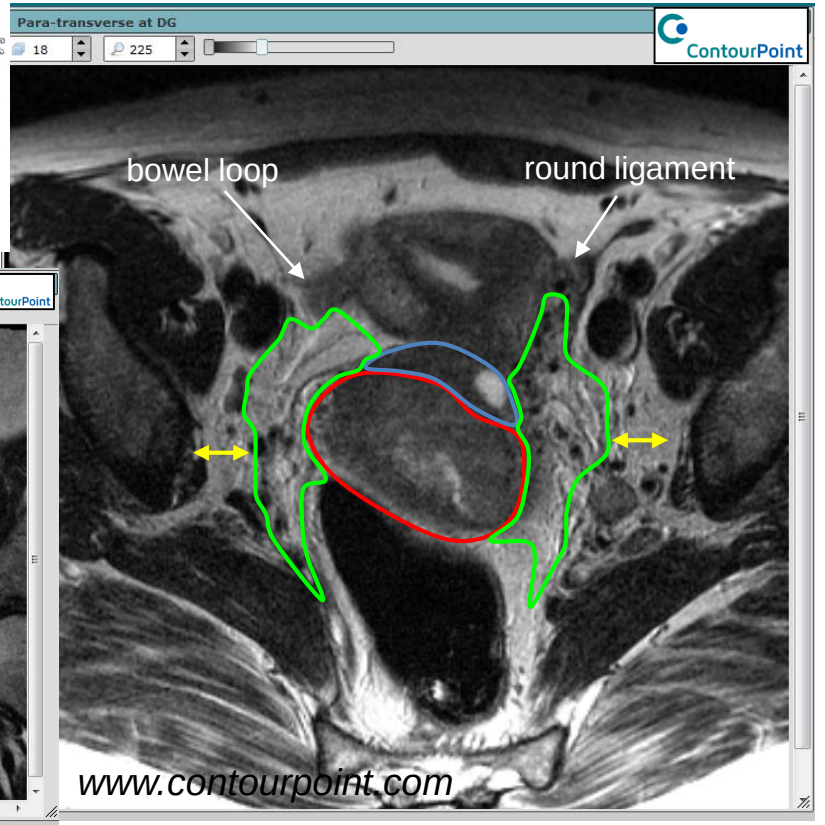
Initial CTV-T: LR CTV-T$_{initial}$

Parametrium = the lateral extension of the uterine subserous connective tissue into the broad ligament

- GTV
- Cervix
- Parametria
- Uterus
- Upper Vagina
- Involved organs



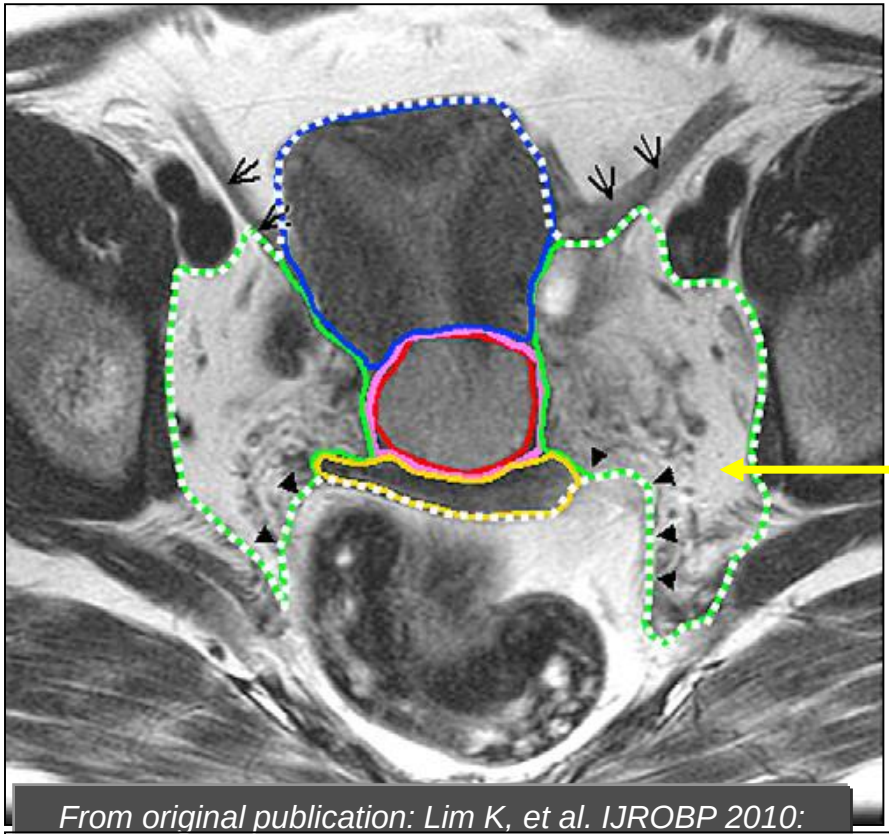


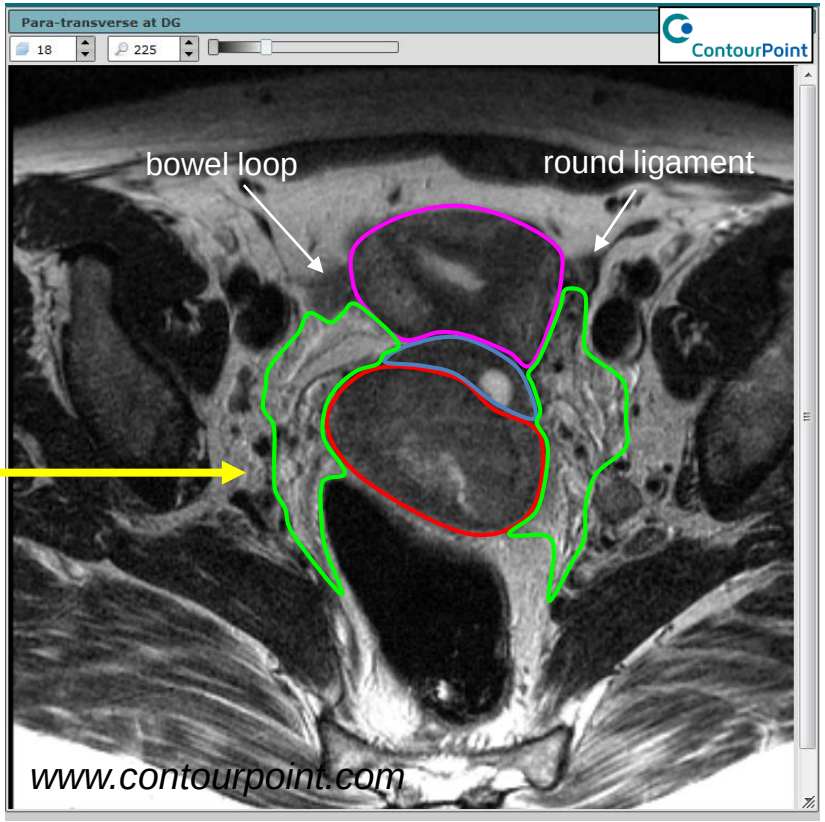


Anatomical boundaries

Anteriorly	*Posterior wall of bladder/bowel loops or posterior border of external iliac vessel*
Posteriorly	*Uterosacral ligaments and mesorectal fascia*
Laterally	*Medial border of internal obturator muscle/ pelvic sidewall*
Superiorly	*Top of fallopian tube/ broad ligament*
Inferiorly	*Depending on vaginal tumor extension, pelvic floor*

Initial CTV-T: LR CTV-T$_{initial}$

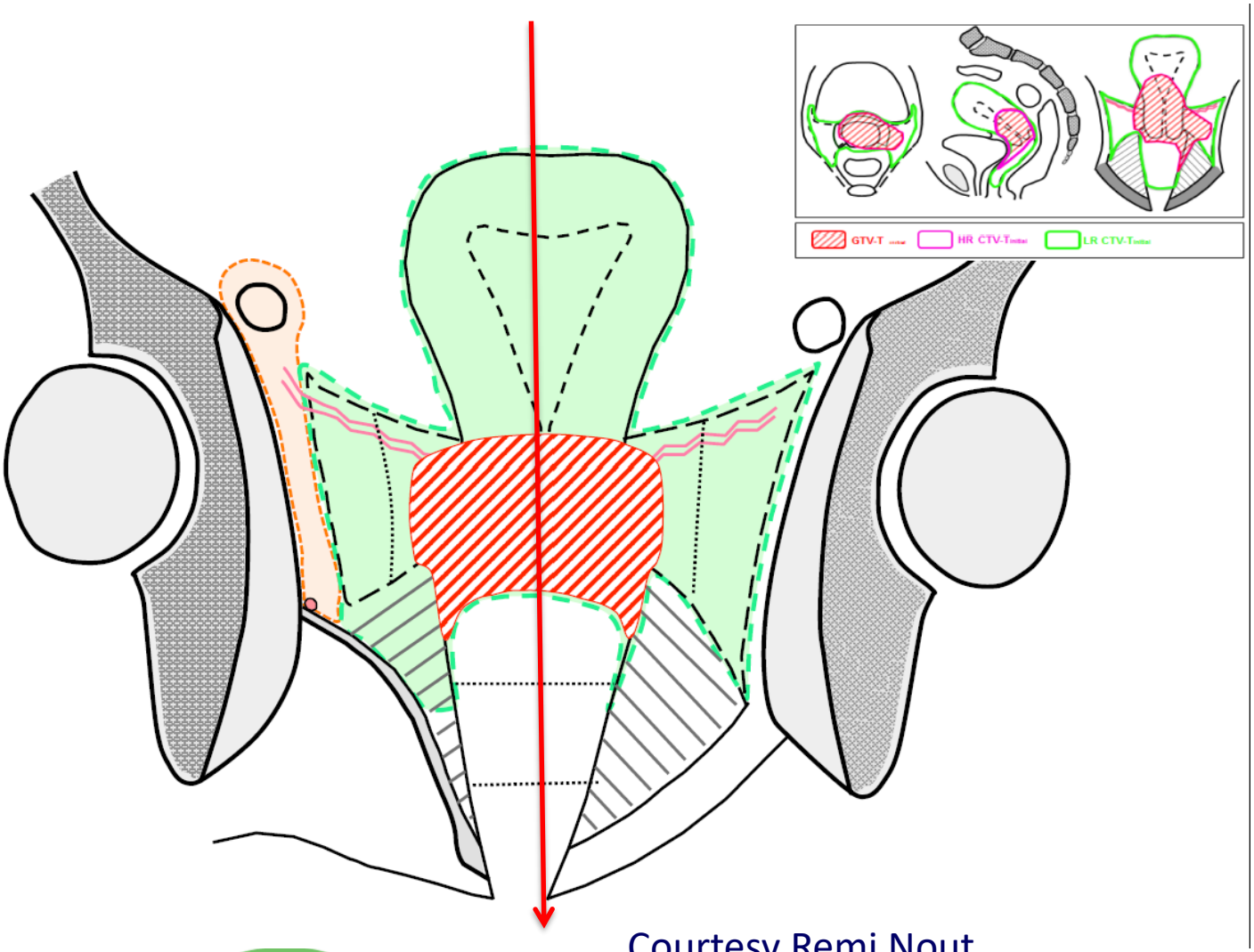




From original publication: Lim K, et al. IJROBP 2010:

metrial volume. Laterally, the parametrial volume should extend to the pelvic sidewall (excluding bone and muscle). It is acknowledged that there would be some overlap of this volume with the nodal CTV, particularly along the obturator strip. The pelvic sidewall was considered a more consistent

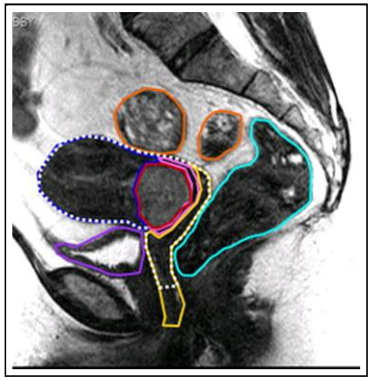
Future LR-CTV-T$_{initial}$ and CTV-T-E

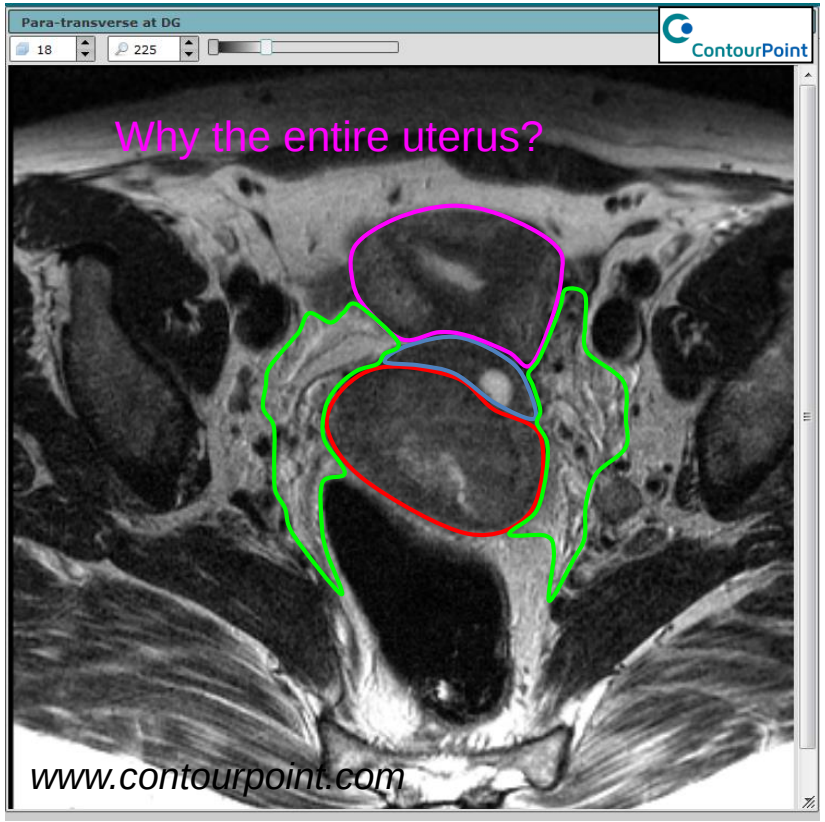


Courtesy Remi Nout

Initial CTV-T: LR CTV-$T_{initial}$

- GTV
- Cervix
- Parametria
- Uterus
- Upper Vagina
- Involved organs (FIGO IVA)



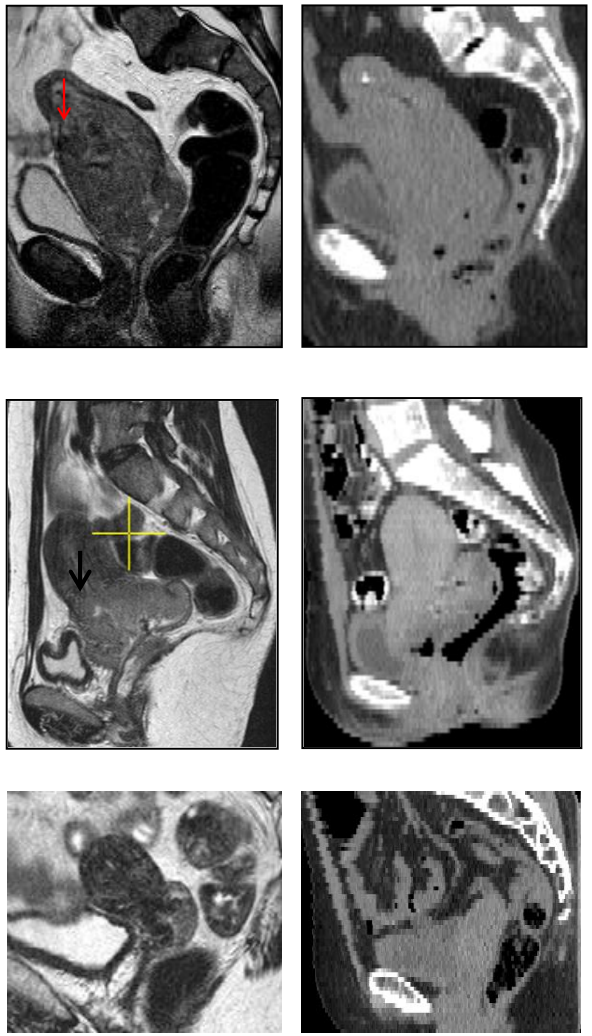


Lim K, et al. IJROBP 2010

Why the entire uterus?

Rationale

- Uterus & cervix: embryological one unit
  - –interconnected lymphatics
  - –no separating fascial plane
- Challenging to determine myometrial invasion
- Trachelectomy, early stage disease[a]:
  - Local recurrence < 5 %, Mortality < 3%
  - Uterine recurrences[b,c,d] 2 %
- Trachelectomy, tumor > 2 cm or lymphovascular invasion[a,e]:
  - Local recurrence up to 10 %



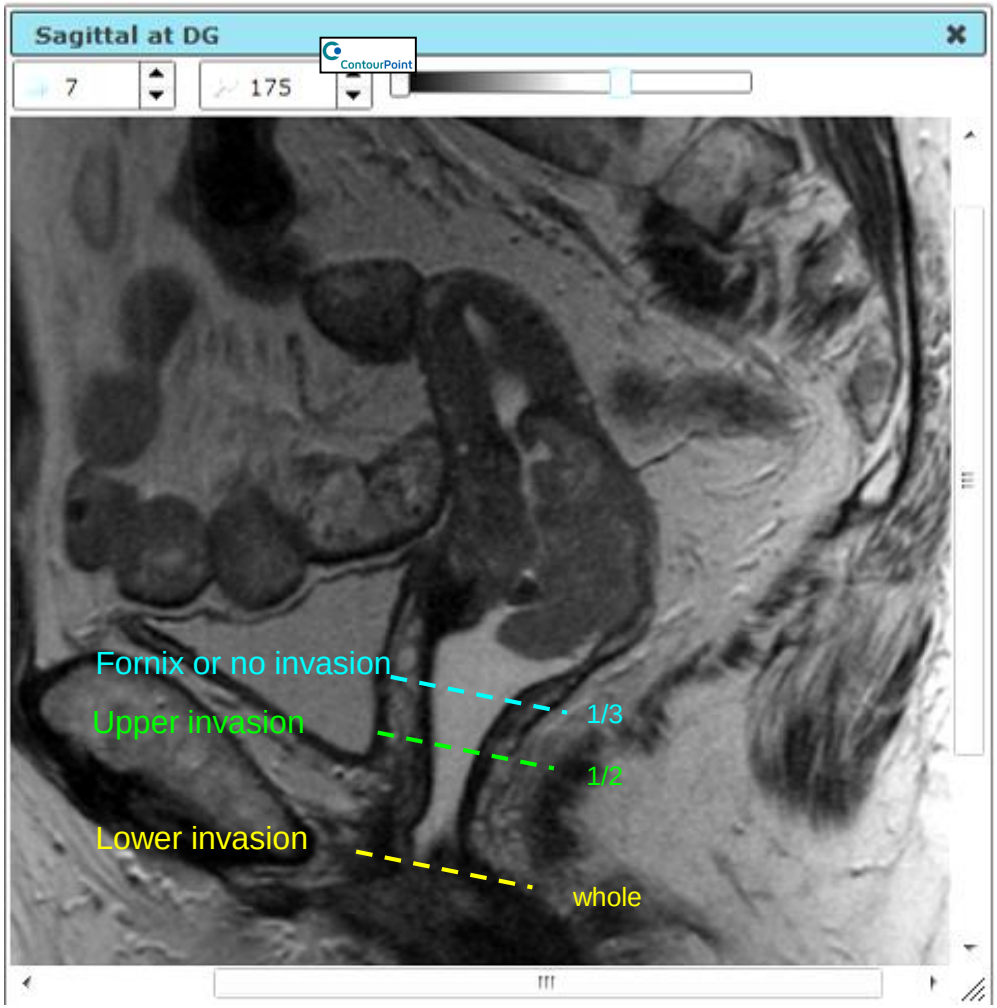
- Allowing for some dose reduction to the fundus in cases without uterine infiltration will be investigated in future

Lim K, et al. IJROBP 2010
[a]Plante M. Gynecol Oncol 2008
[b]Bali A, et al. Gynecol Oncol 2008
[c]Diaz JP, et al. Gynecol Oncol 2008
[d]Hertel H, et al. Gynecol Oncol 2006
[e]Nishio H, et al. Gynecol Oncol 2009

Primary CTV: LR CTV-$T_{initial}$

Amount of vagina selected for target delineation is depending on vaginal tumor extension in any case: at least 2 cm caudal to vaginal extension of GTV

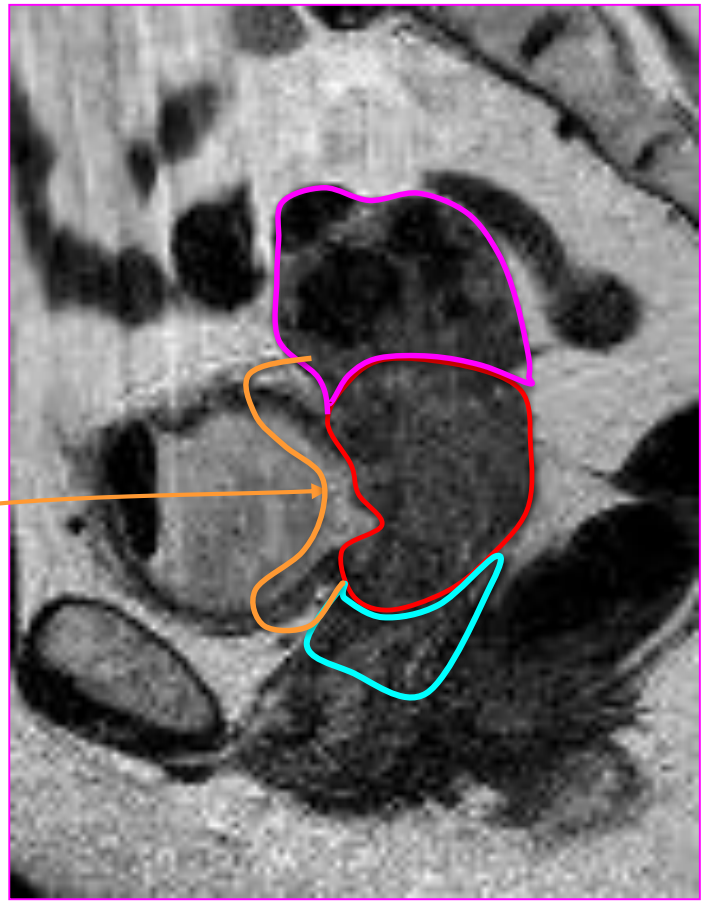
- GTV
- Cervix
- Parametria
- Uterus
- Varying Vaginal length
- Involved organs (FIGO IVA)



Primary CTV: LR CTV-$T_{initial}$

In case of infiltration into bladder, rectum, mesorectum, sacro-uterine ligaments :
2 cm margin into unaffected tissue

- GTV
- Cervix
- Parametria
- Uterus
- Upper Vagina
- Involved organs (FIGO IVA)



Primary CTV: LR CTV-T$_{initial}$

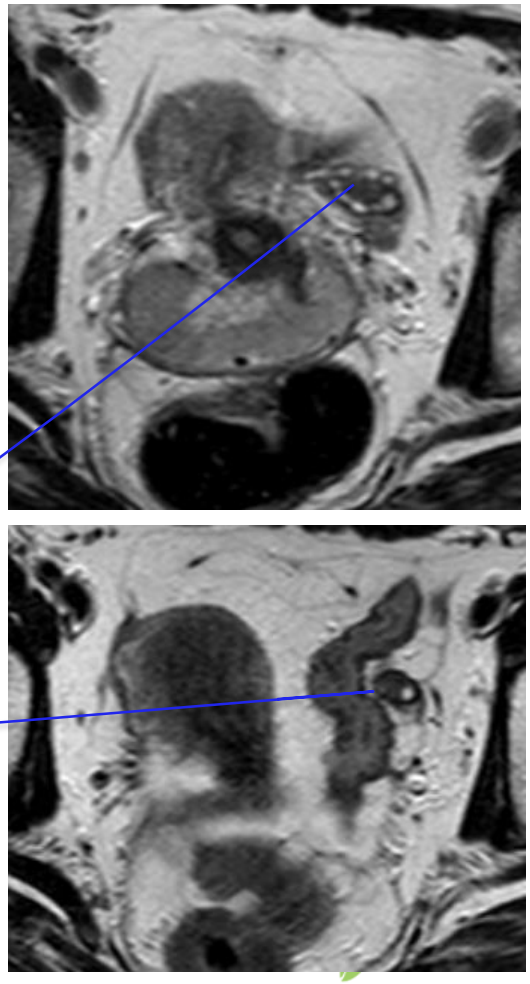
Overall risk of ovarian metastases is small, increased risk reported for:

- adeno/adenosquamous histology, even micro-invasive
- high grade and LVSI
- extension into the uterine corpus
- ovaries can be highly mobile !

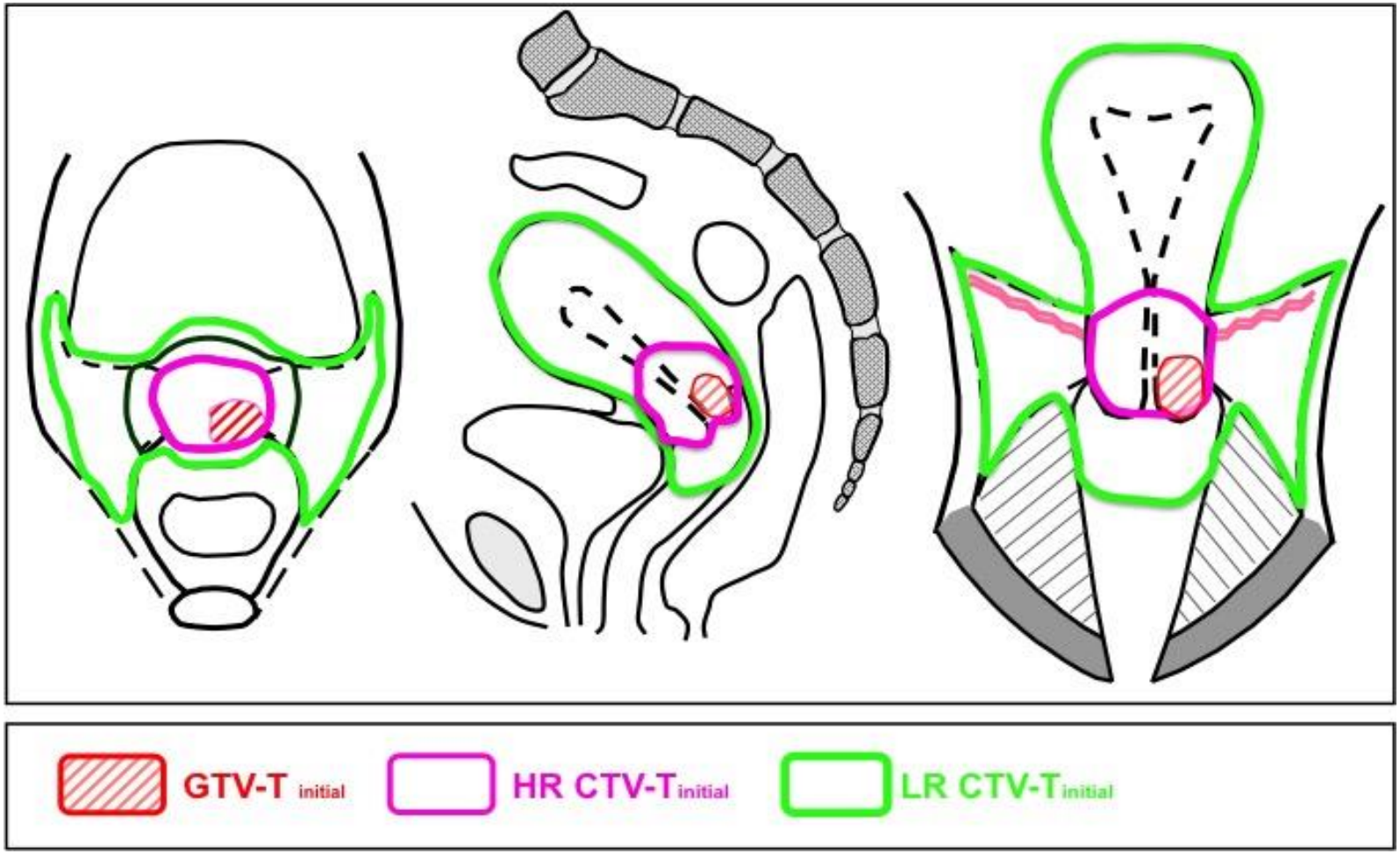
- GTV
- Cervix
- Parametria
- Uterus
- Vagina
- Involved organs (FIGO IVA)

LR-CTV-T initial

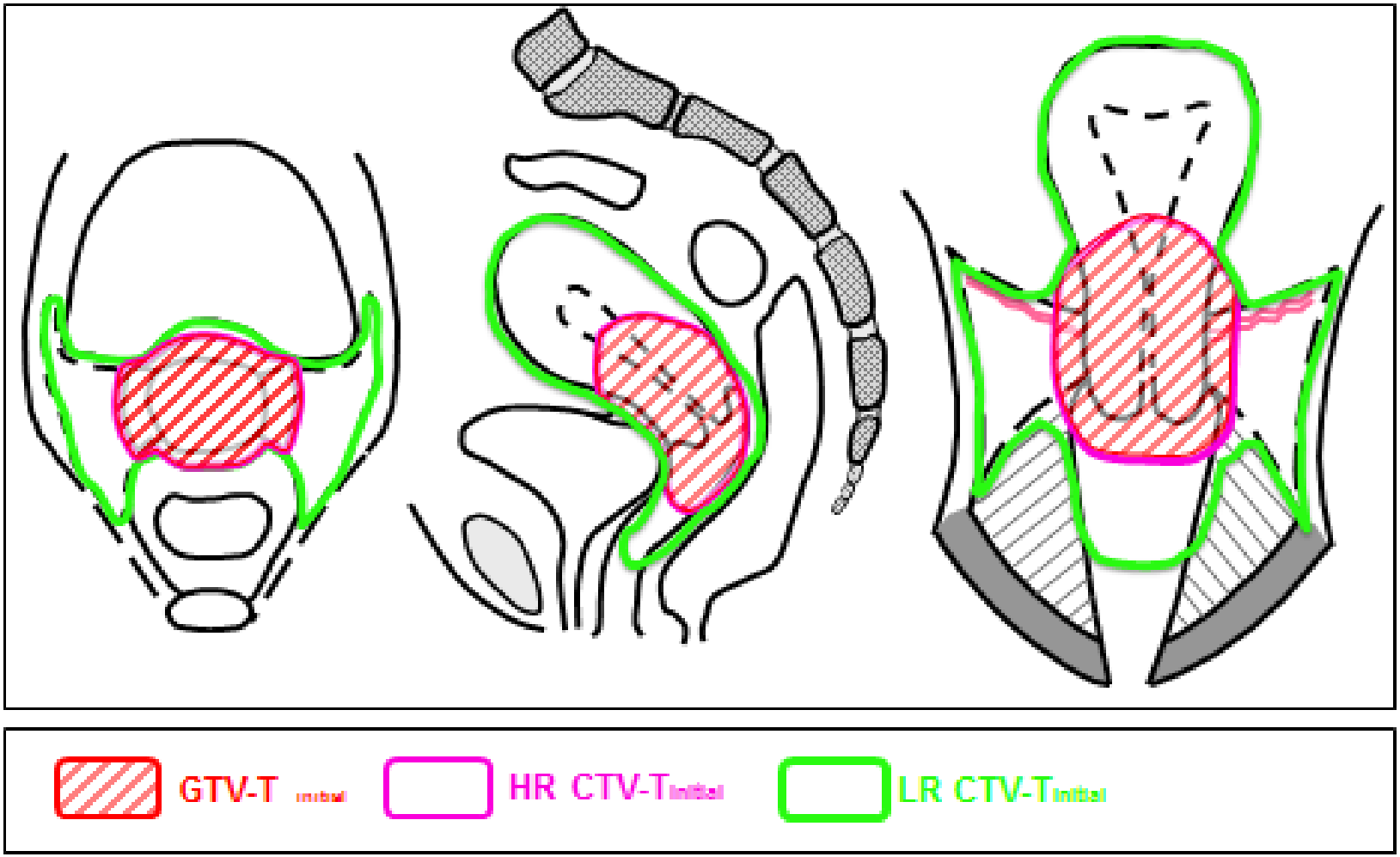
- Ovaries ?



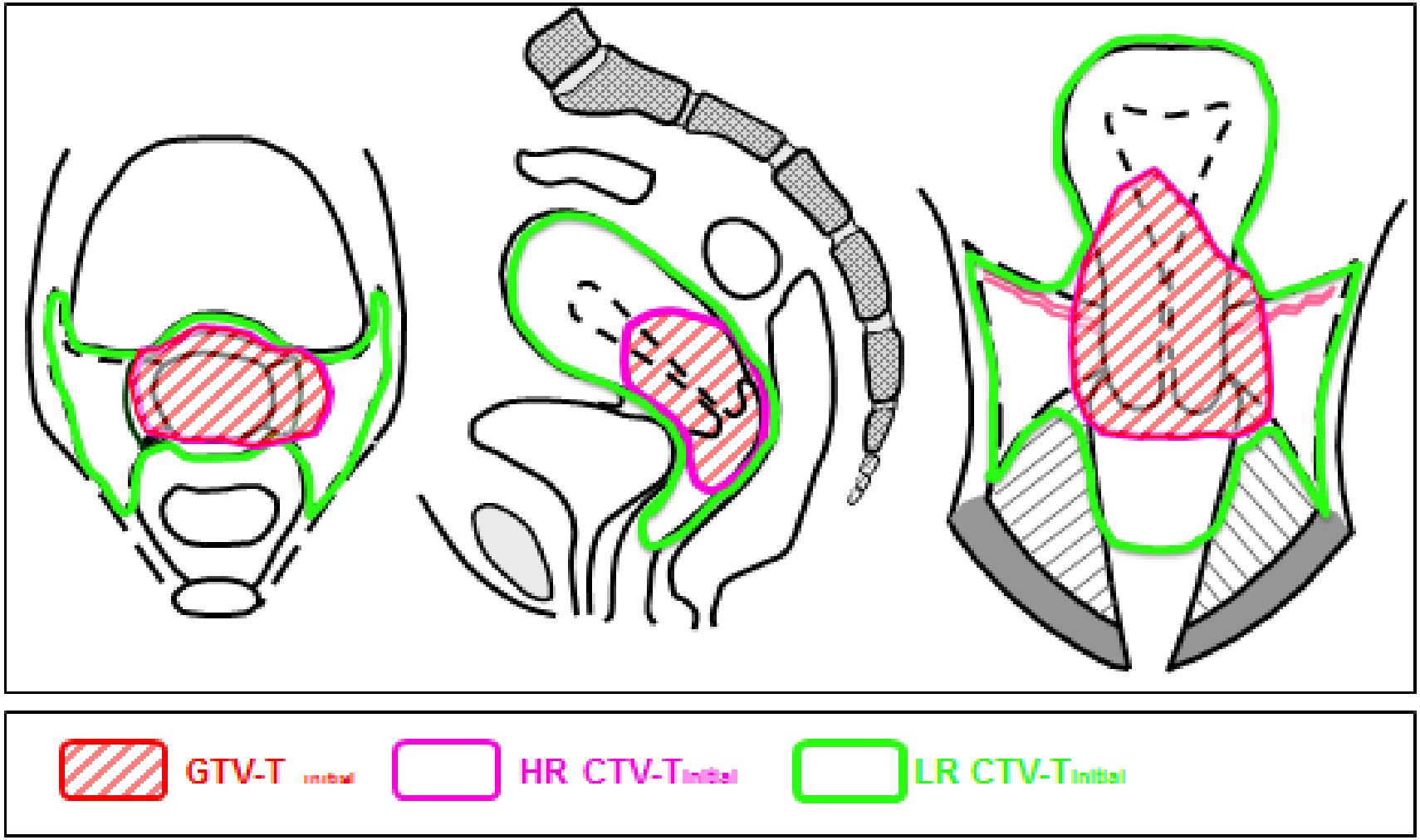
EMBRACE II: CTV-T: initial GTV, HR CTV, LR CTV: Stage IB1



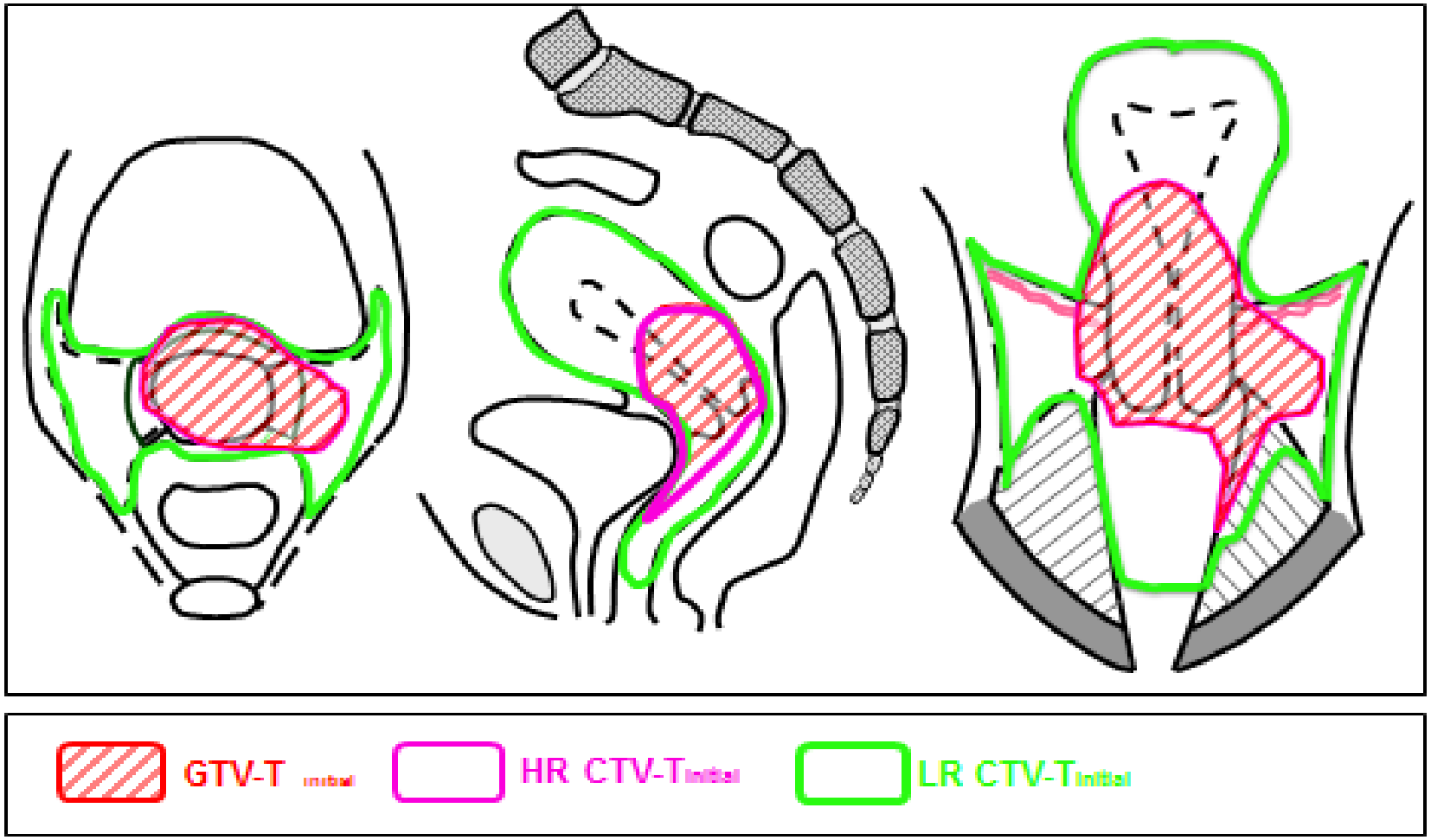
EMBRACE II: CTV-T: initial GTV, HR CTV, LR CTV: Stage IB2



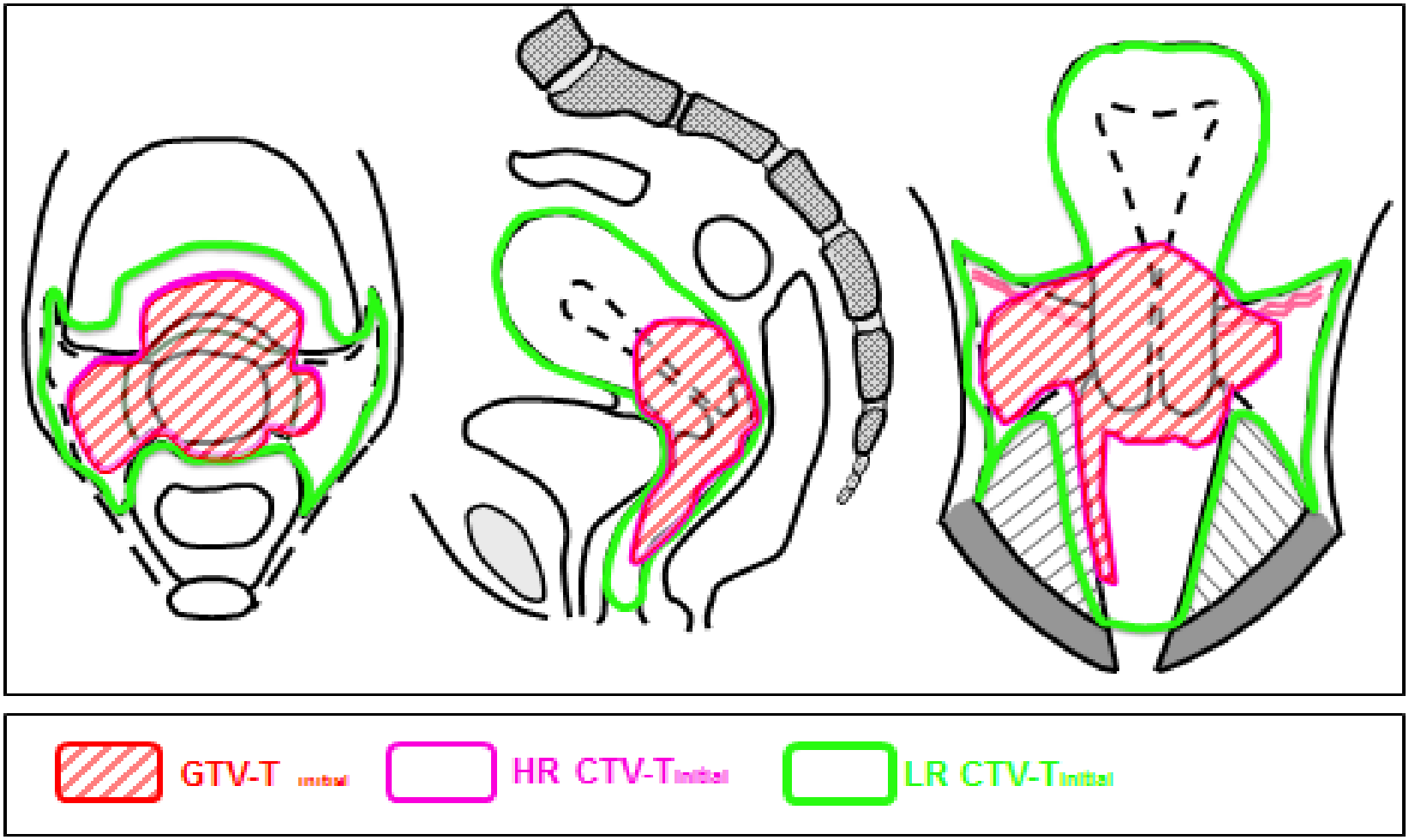
EMBRACE II: CTV-T: initial GTV, HR CTV, LR CTV: stage IIB



EMBRACE II: CTV-T: initial GTV, HR CTV, LR CTV: stage IIIB



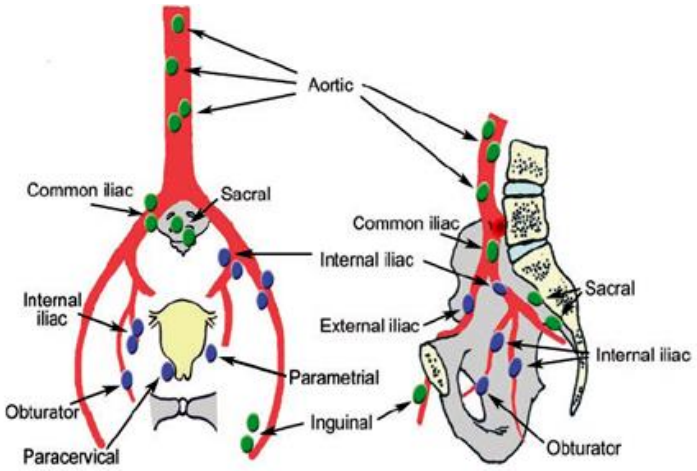
EMBRACE II: CTV-T: initial GTV, HR CTV, LR CTV: stage IVA



Nodal CTV *(CTV-E, no macroscopic nodal involvement)*

Lymph nodes are located around vessels

- Paraaortic
- Common iliac
- External iliac
- Internal iliac
- Obturator
- Presacral
- Inguinal (in stage IIIa)



Nodal CTV contouring = Delineation of vessels with margins

Which margin/s are necessary ?

The margin needed to include 99% of detectable lymph nodes is?

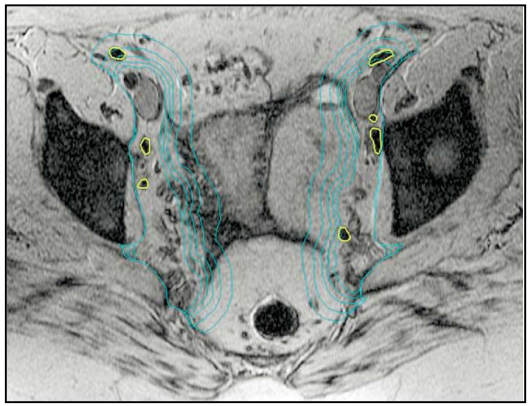
A. 5 mm
B. 7 mm
C. 10 mm
D. 5 mm with small adaptations
E. 7 mm with small adaptations
F. 10 mm with small adaptations

Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

- 20 patients, gynae cancer
- USPIO administered
- All nodes outlined
  - 61 nodes / patient
  - 1 to 12 mm short axis
- Muscle and bone excluded



	3D margin around vessels (mm)				
	3	5	**7**	10	15
Nodal coverage	56 %	76 %	**88 %**	94 %	99 %
Bowel V in PTV	-	-	**147 cm^3**	190 cm^3	266 cm^3

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

Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol 63.no.5, 1604-1612, 2005.

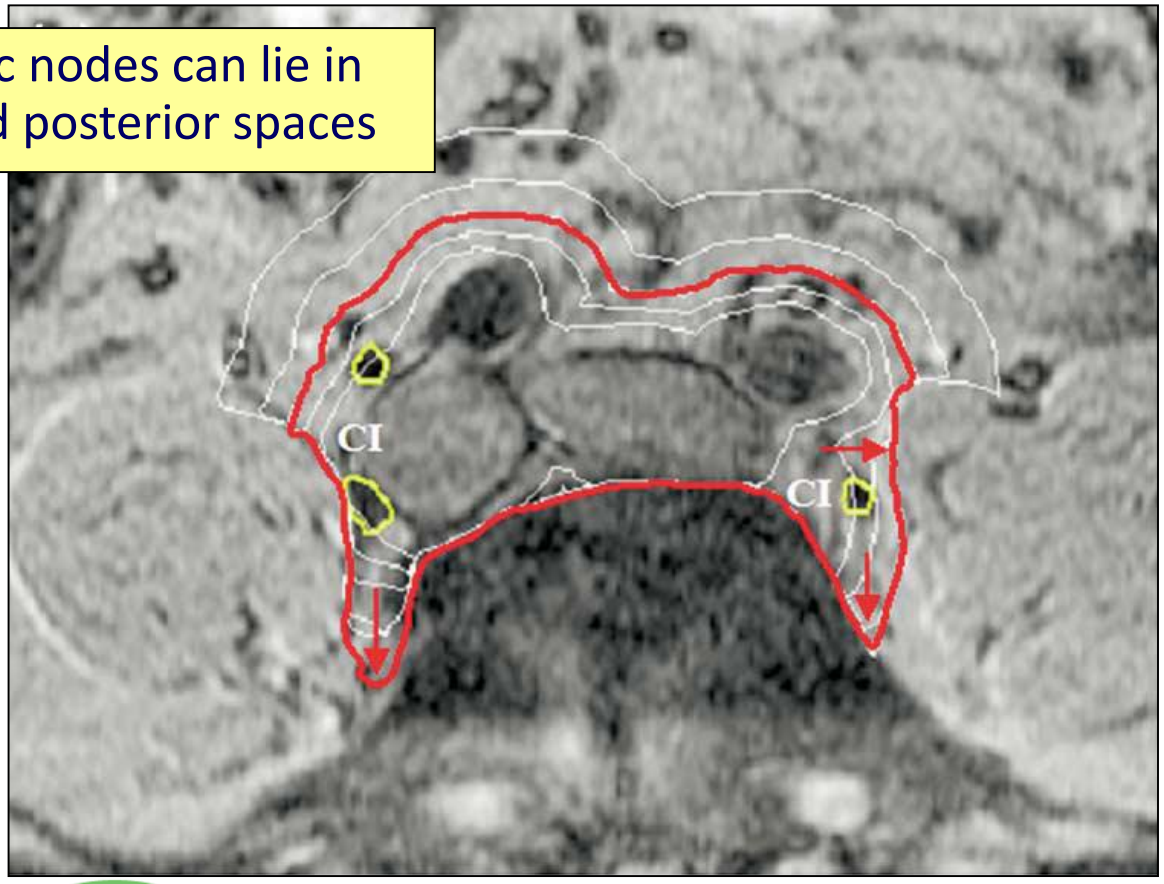
Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

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

Common iliac nodes can lie in lateral and posterior spaces



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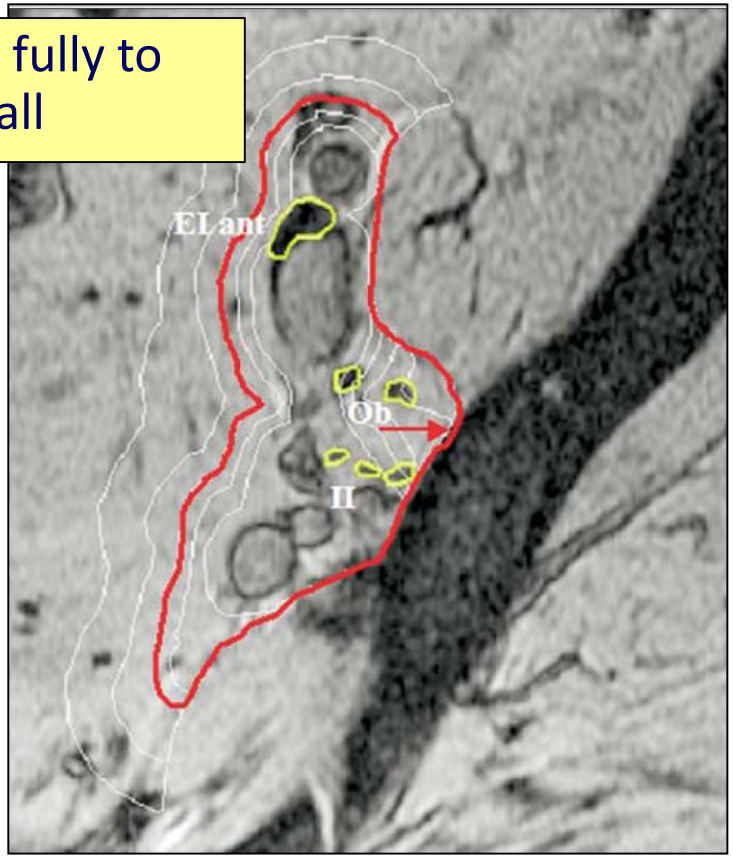
Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

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

Contour must extend fully to pelvic sidewall



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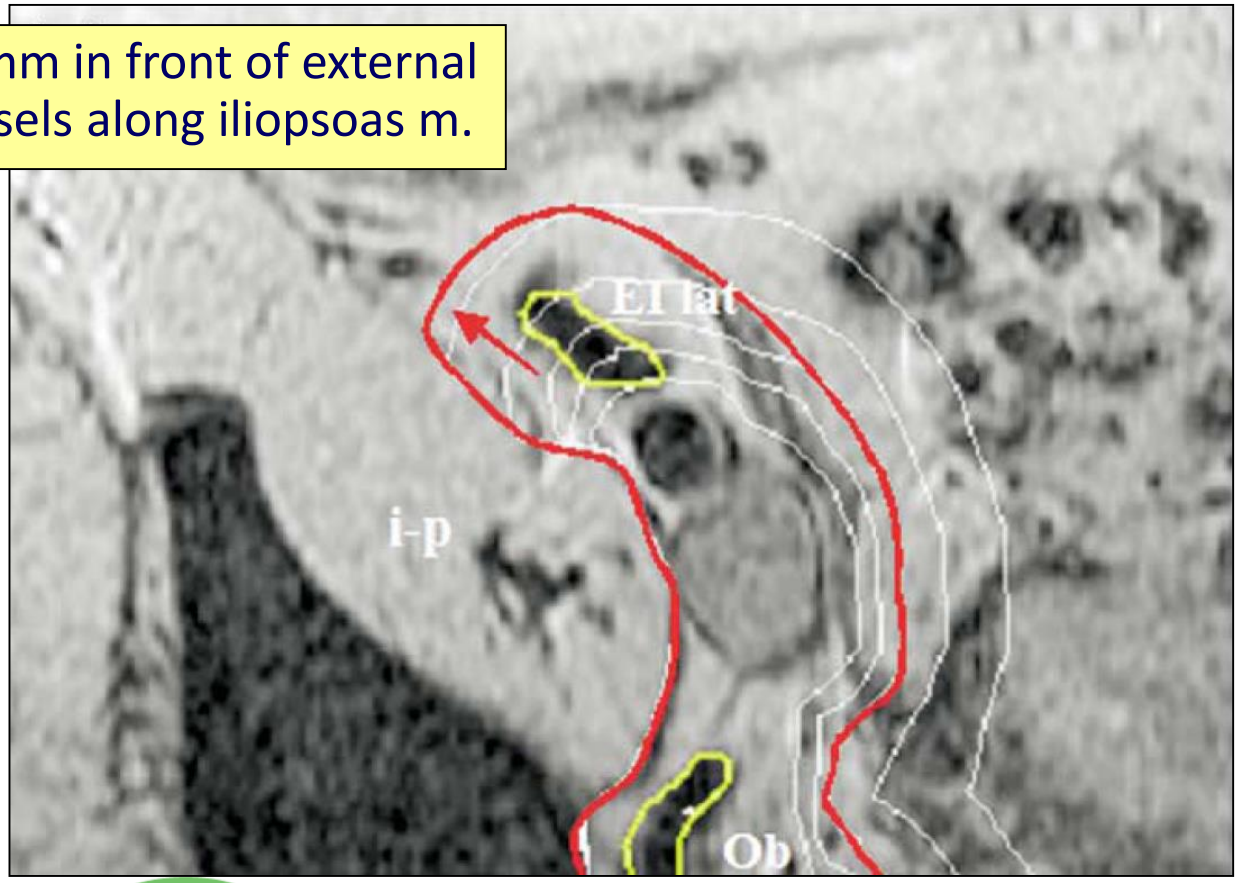
Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

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

Extend 10 mm in front of external iliac vessels along iliopsoas m.



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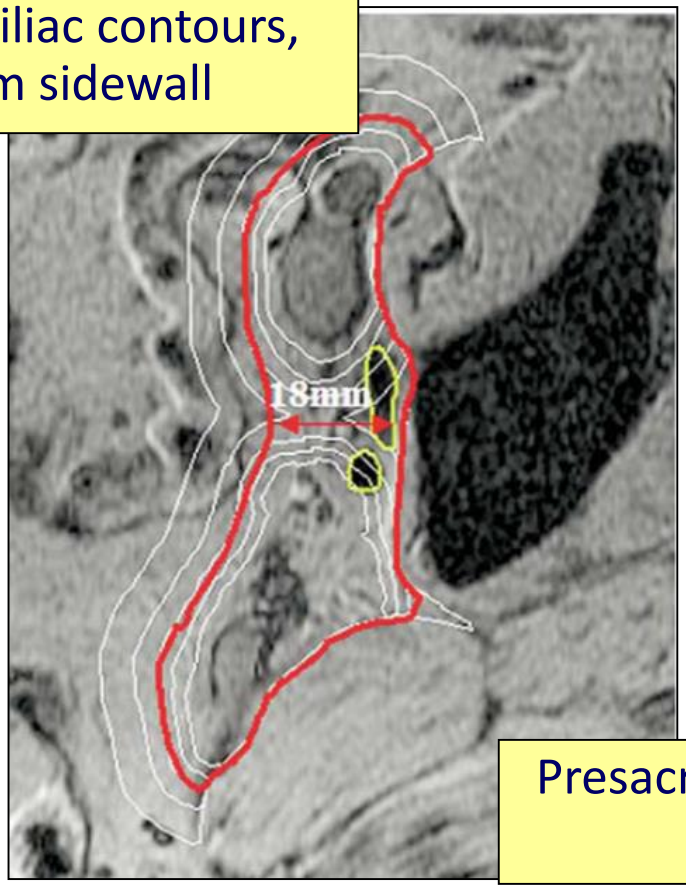
Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

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

Join external & internal iliac contours, keep 18 mm from sidewall



Presacral nodes: keep 10 mm in front of sacrum

Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol 63.no.5, 1604-1612, 2005.

Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

Recommendations for pelvic nodal CTV delineation

Uniformly draw a contour around the pelvic blood vessels by 7 mm.

Include all visible nodes and exclude muscle and bone from the volume.

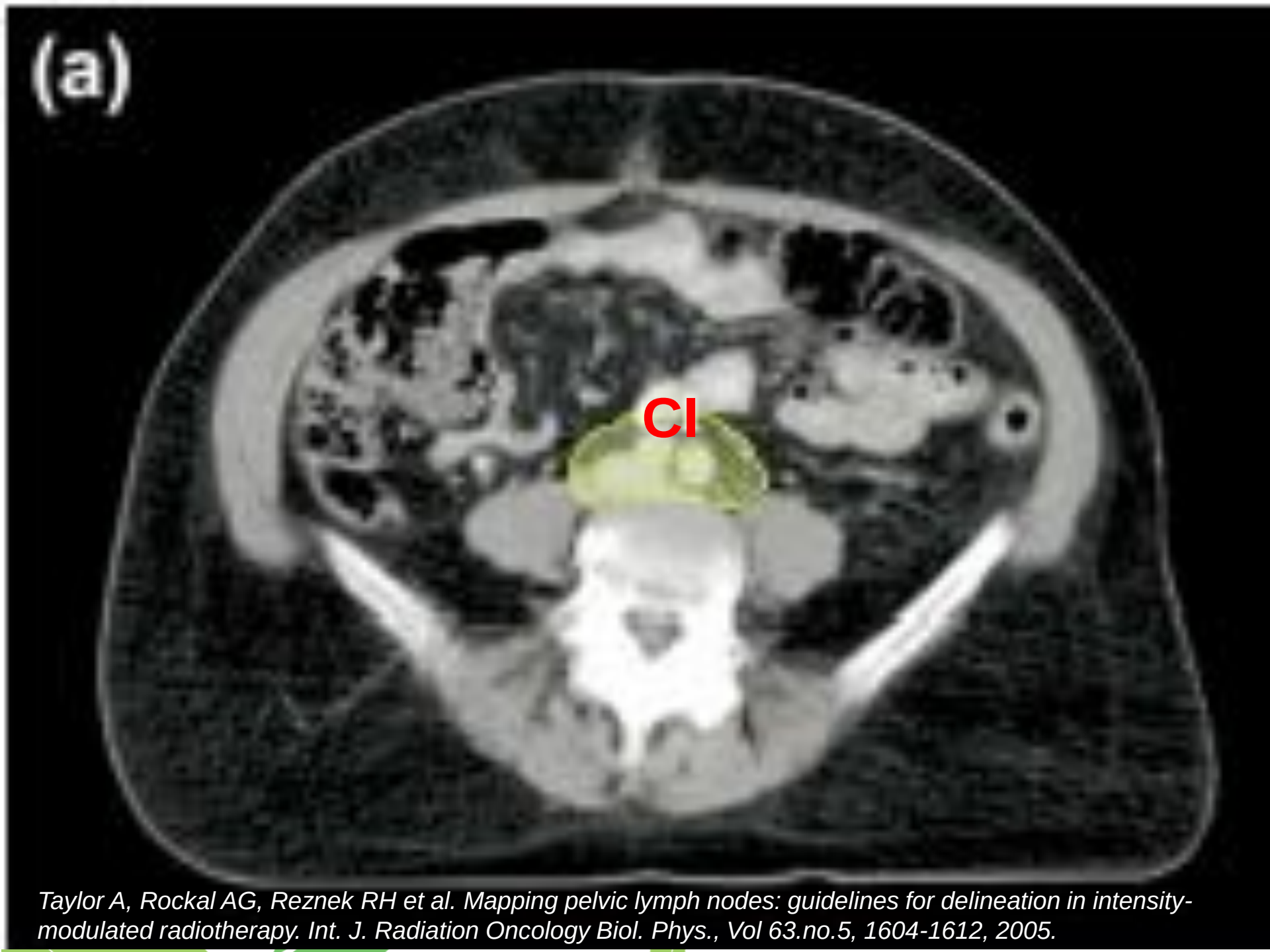
Ensure the lateral border of the volume extends to the psoas muscle and pelvic sidewall.

Continue the medial border around the external iliac vessels posteriorly, parallel to the sidewall, until it joins the medial contour of the internal iliac vessels to encompass the obturator region. This creates a strip medial to the pelvic sidewall that should be at least 18 mm wide.

To include all the lateral external iliac nodes, extend the contour around the external iliac artery anterolaterally along the iliopsoas muscle by an additional 10 mm.

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)

Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol 63.no.5, 1604-1612, 2005.



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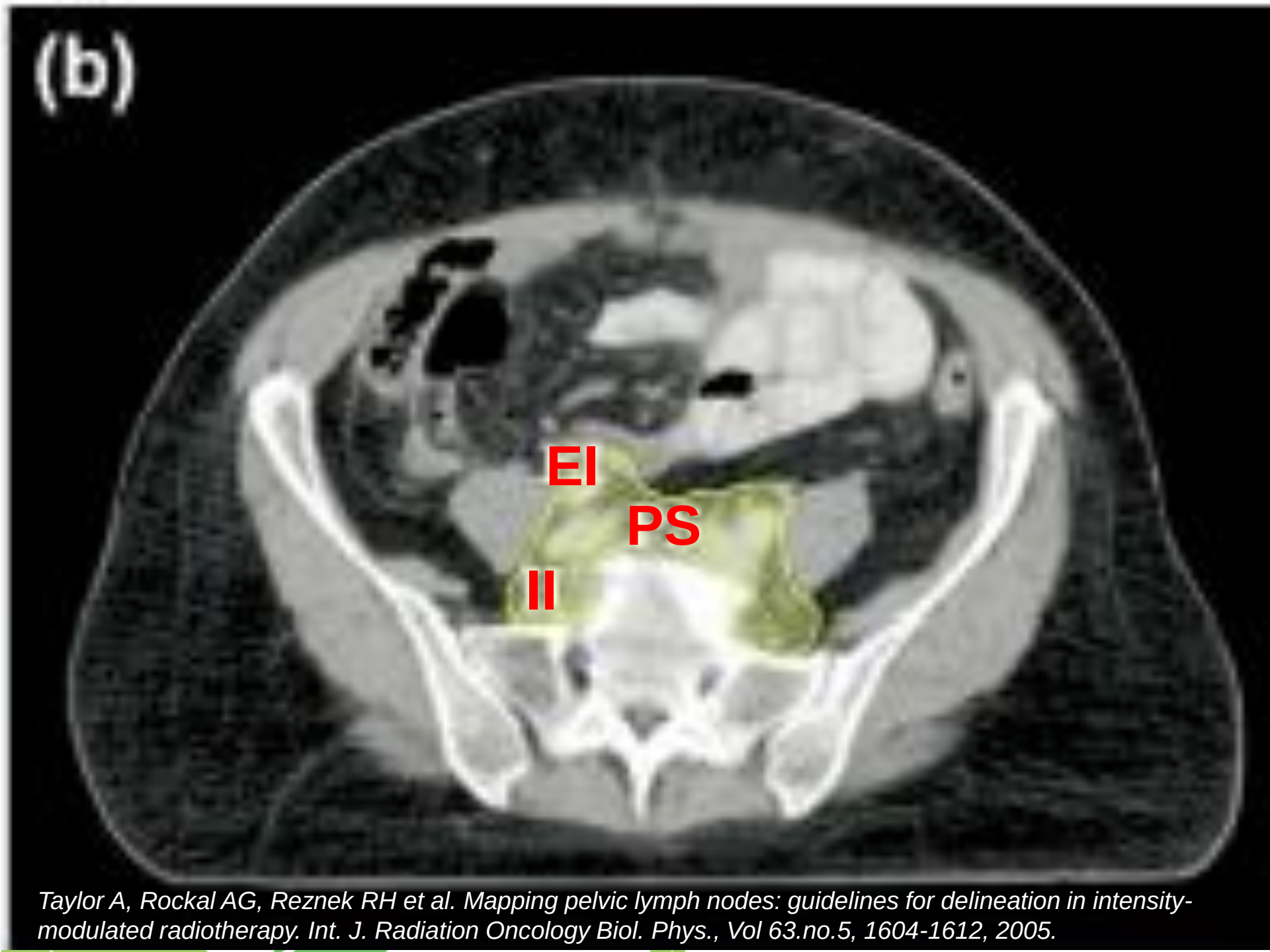

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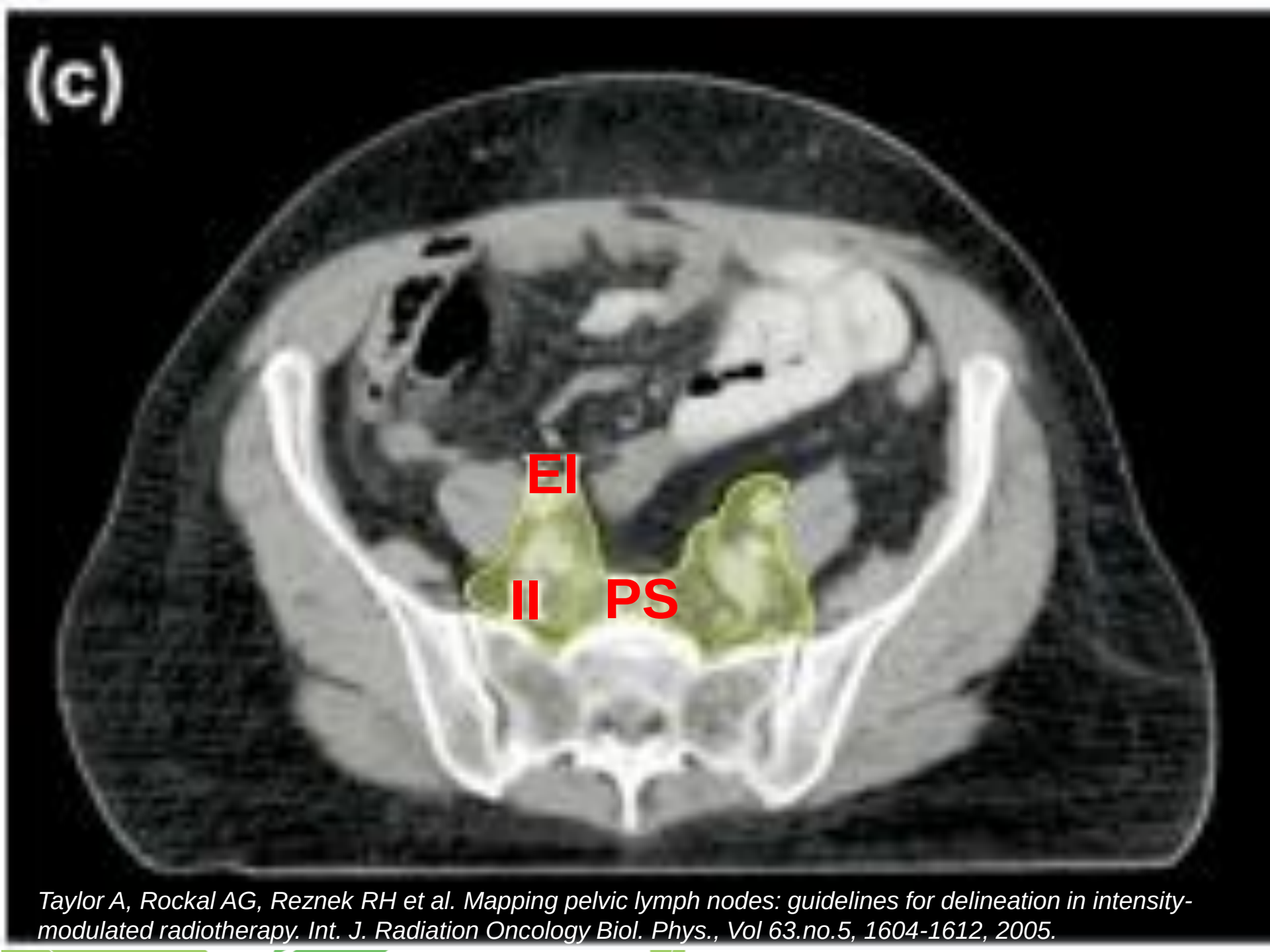

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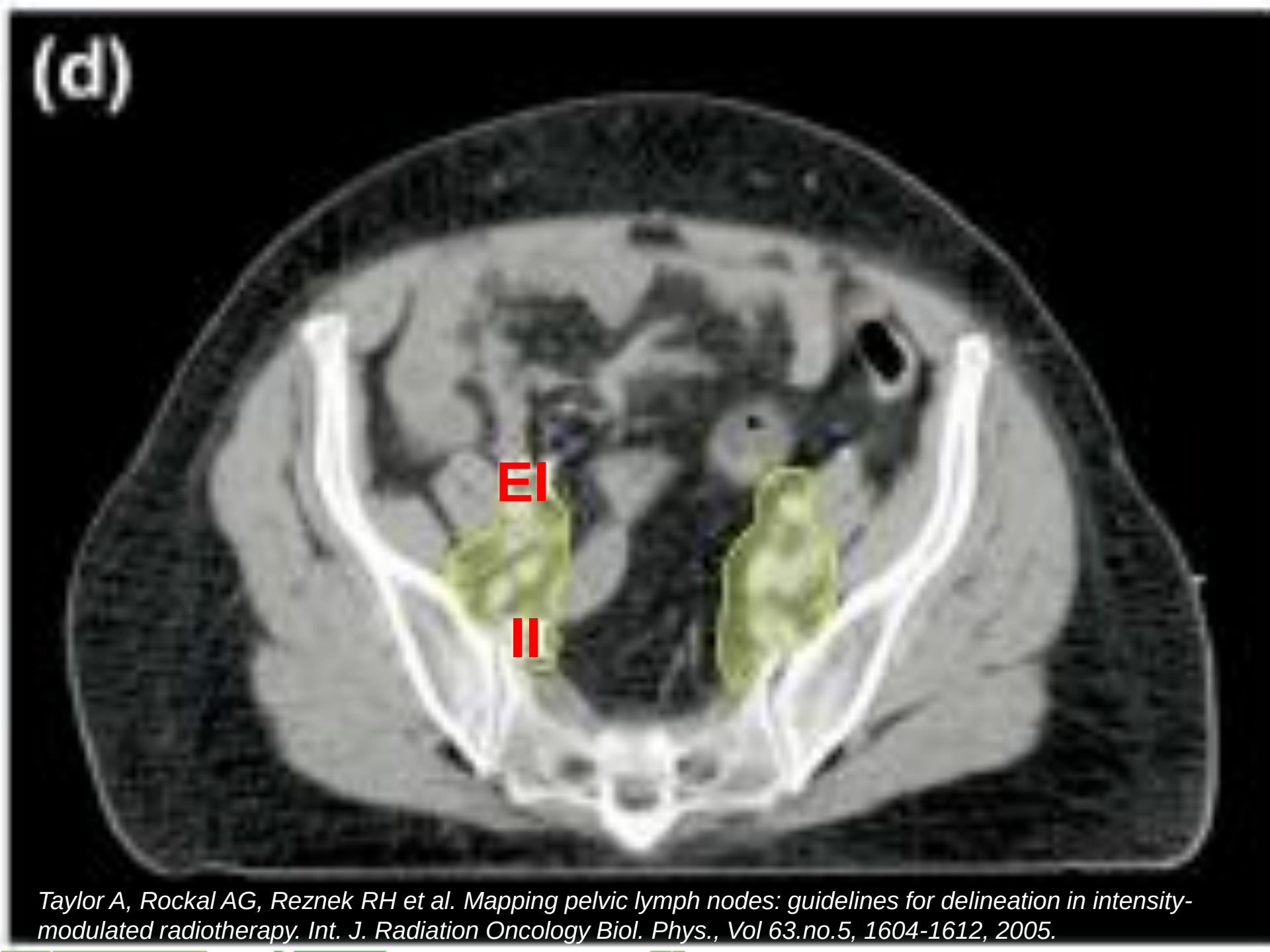

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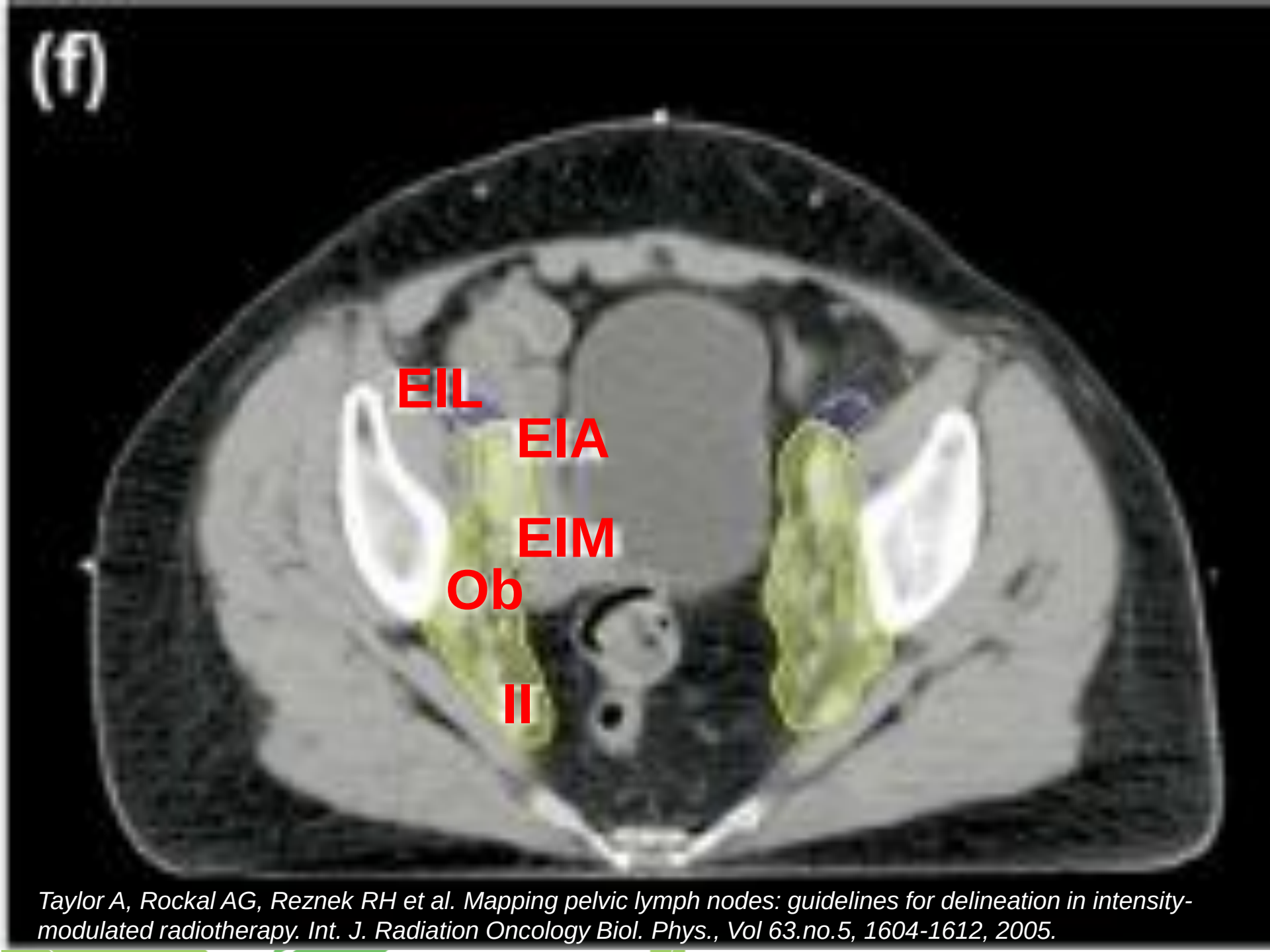

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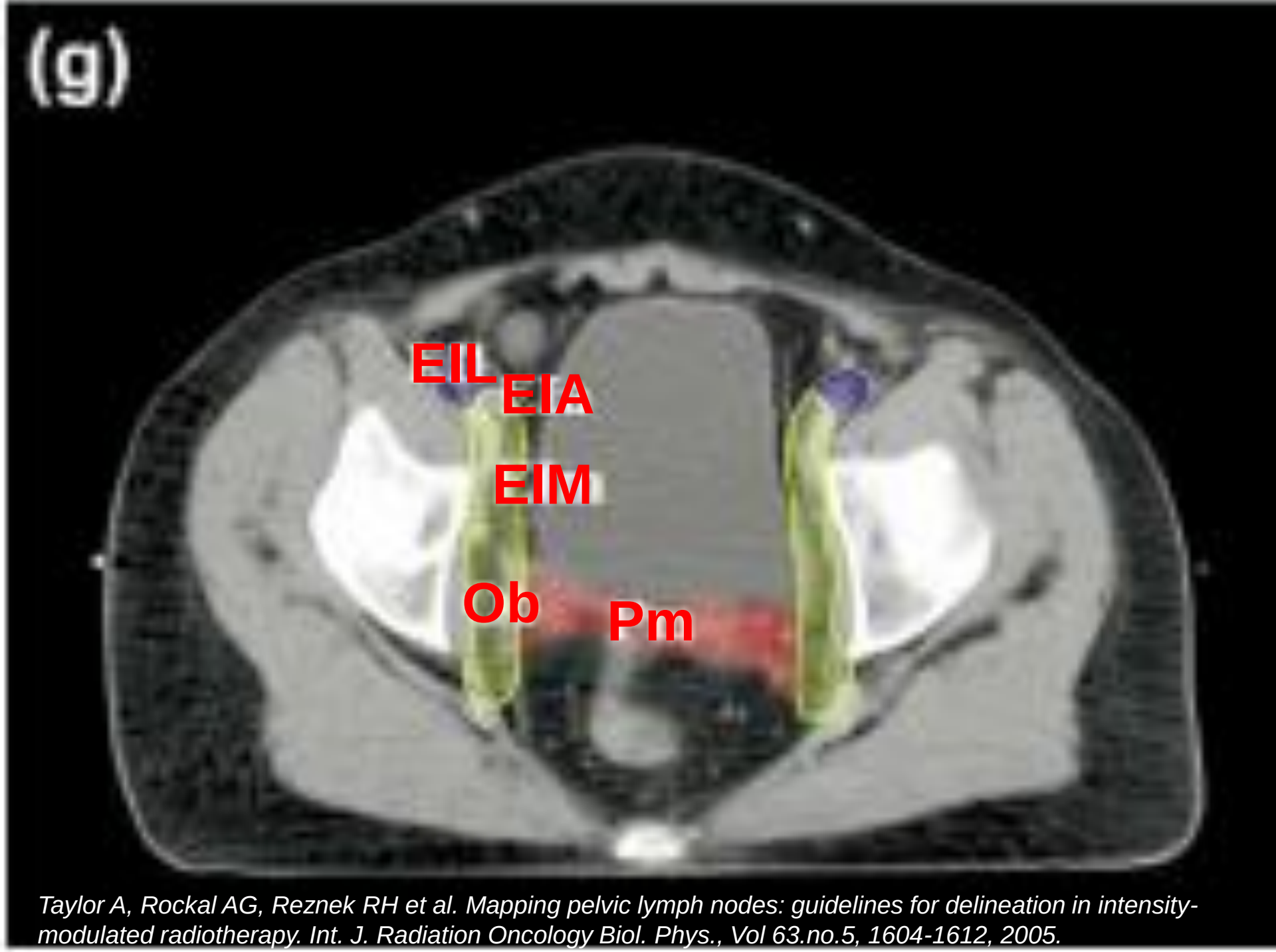

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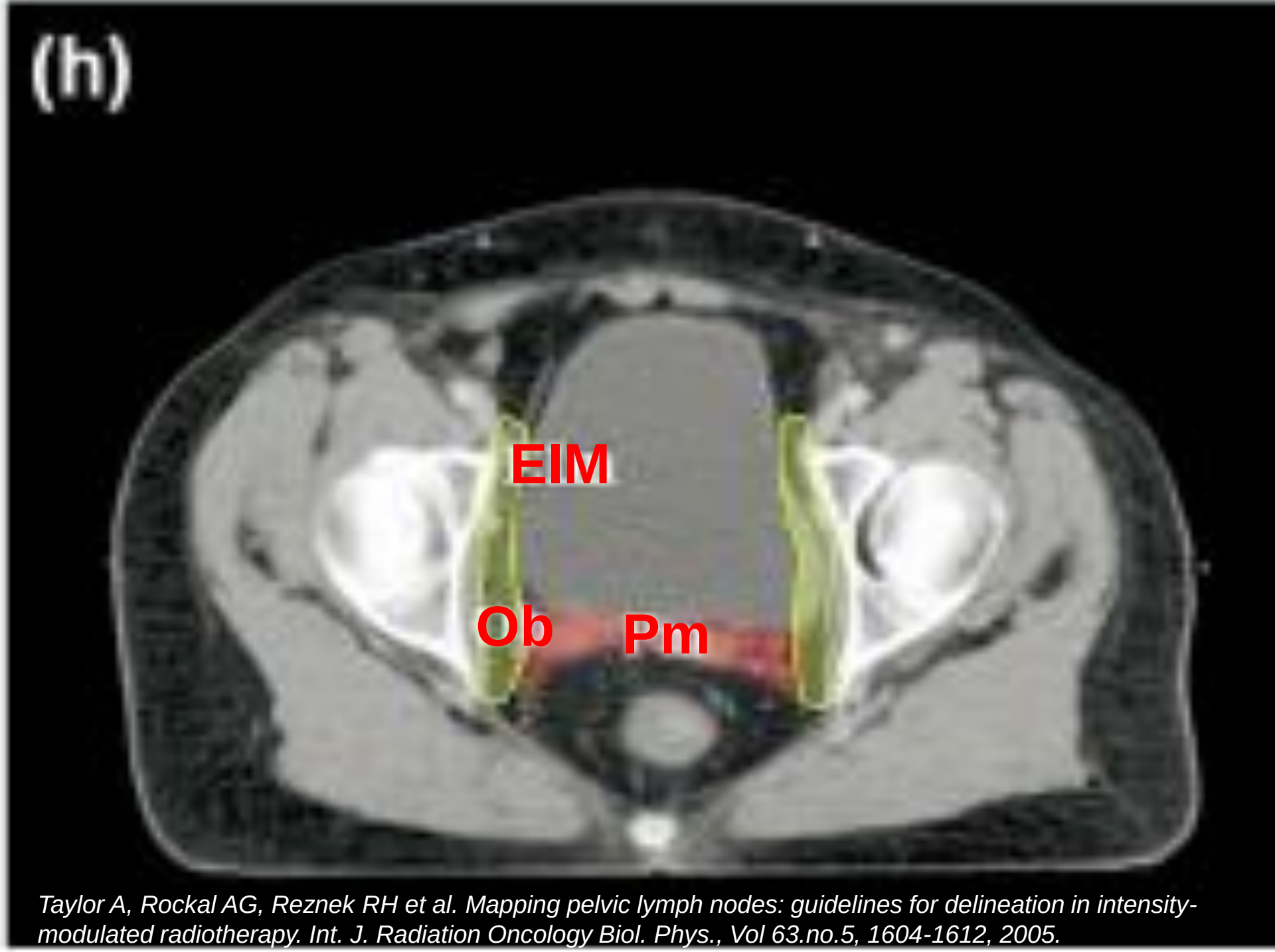


Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol 63.no.5, 1604-1612, 2005.

RTOG, GOG, NCIC, ESTRO, ACRIN Consensus

Small W, et al. IJROBP, 2008

(postoperative setting)

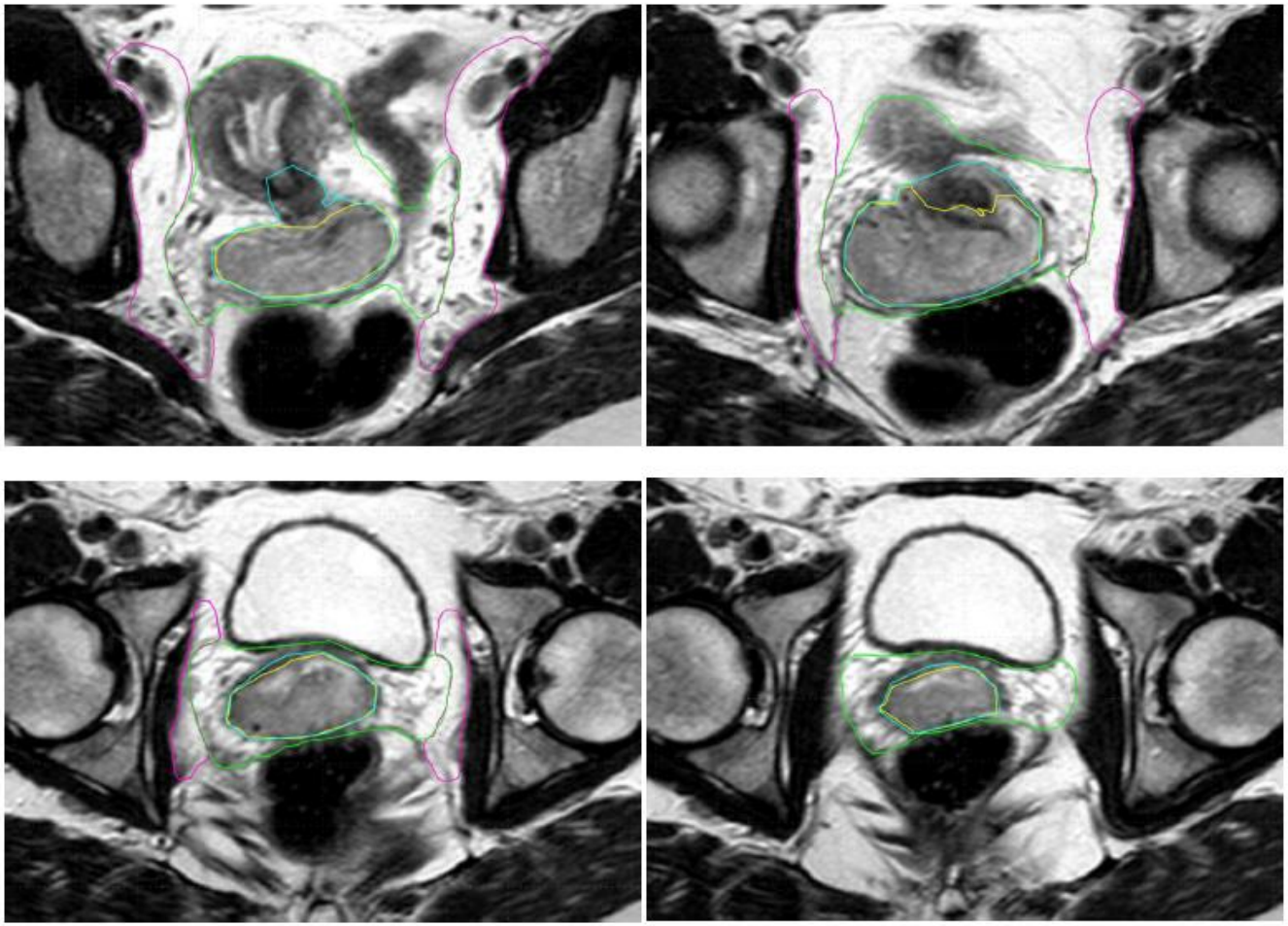
Pelvic nodal groups for cervix and endometrial cancer contouring:

- Common iliac
- External iliac
- Internal iliac
- Presacral
  - in cervix cancer
  - endometrial cancer with cervical invasion

Small W, Mell LK, Anderson P et al. Consensus guidelines for deineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int. J. Radiation Oncology Biol. Phys., vol 71, No.2, 428-434, 2008

Elective nodal CTV: Caudal extension

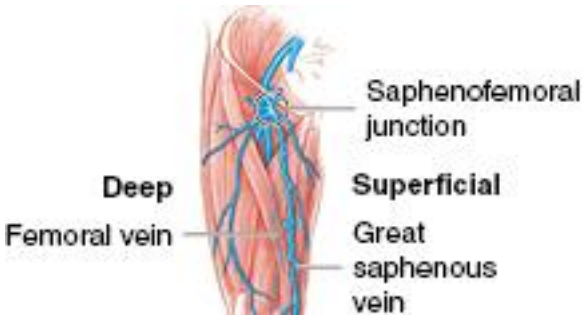
- Transition zone goes down to the pelvic floor (usually at the upper part of the obturator foramen, below femoral head, were internal iliac vessels enter or leave the true pelvis)

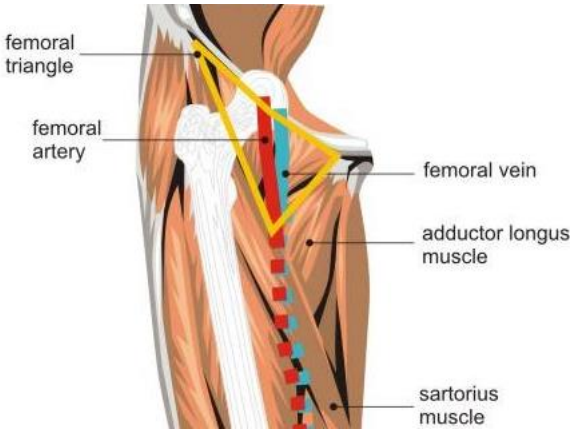


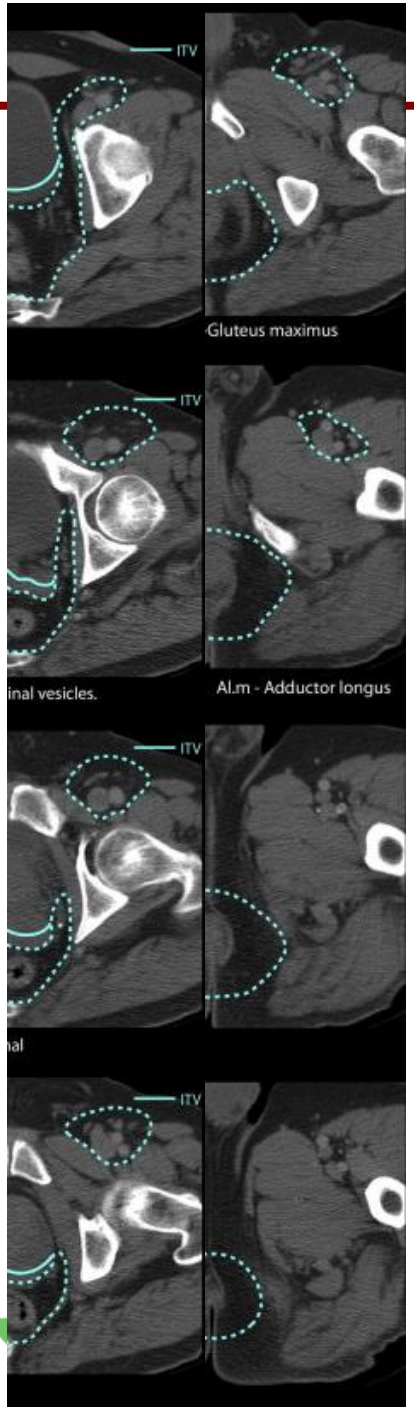
From EMBRACE II protocol

Elective nodal CTV: Caudal extension

- In case of distal one third vaginal involvement
- Include inguinal nodes continuously from the external iliac nodes at least 2 cm caudal to the saphenous/femoral junction/upper edge of trochanter minor





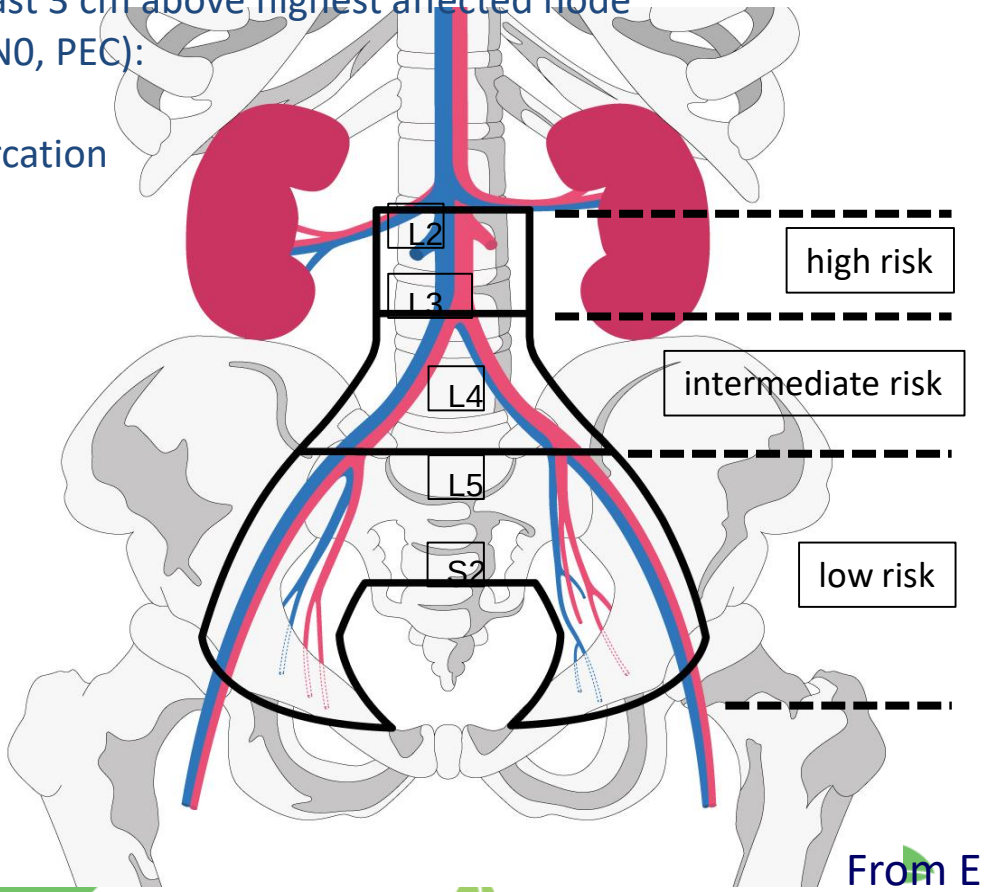


Ng et al., Australasian Gastrointestinal Trials Group (AGITG) Contouring Atlas and Planning Guidelines for Intensity-Modulated Radiotherapy in Anal Cancer, Int. J. Radiation Oncology Biol. Phys., Vol 83, 1455-1462, 2005.

Elective nodal CTV: Cranial extension

Ongoing investigations and discussion (EMBRACE II)

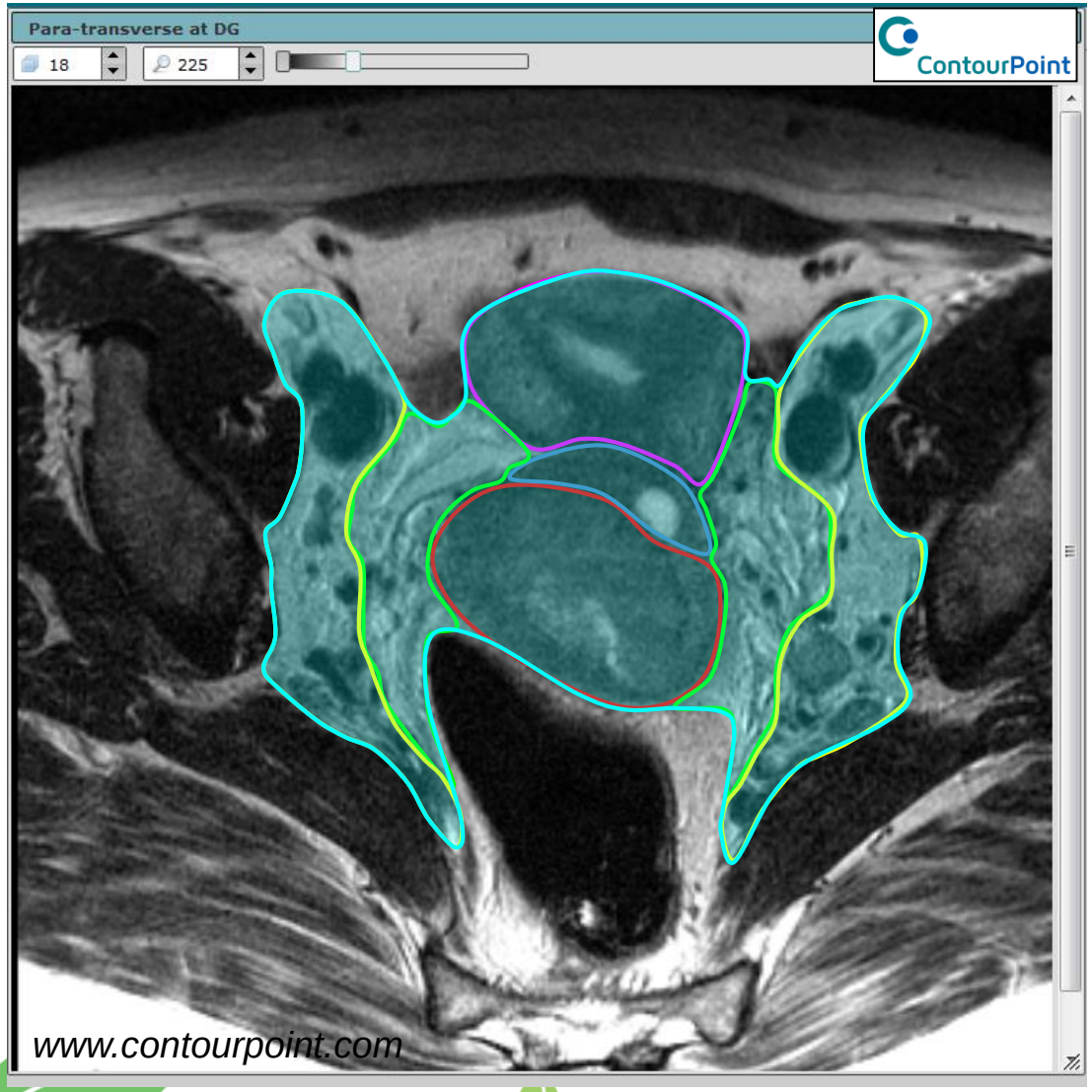
- Intermediate risk: upper border level of aortic bifurcation or defined by bony anatomy (L3/34)
- High risk: Depending on extension of nodal disease into common iliac region consider or ≥ 3 pelvic nodes:
  inclusion of low PAO region up to renal vessels (L2),
  extension of at least 3 cm above highest affected node
- Low risk (stage IB1, N0, PEC):
  Upper border:
  common iliac bifurcation



From EMBRACE II protocol

Total CTV for definitive cervix cancer EBRT

Initial CTV-T + Nodal CTV (CTV-E)

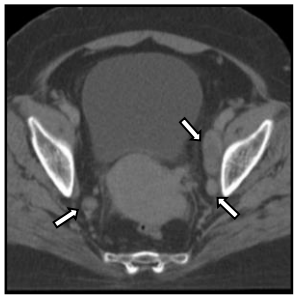


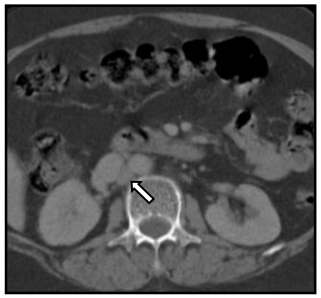
The margin needed to include 99% of detectable lymph nodes is?

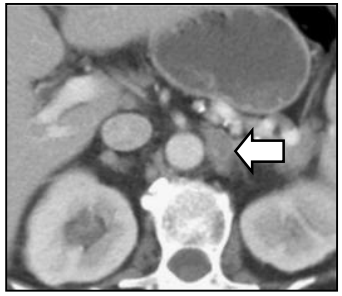
A. 5 mm
B. 7 mm
C. 10 mm
D. 5 mm with small adaptations
E. 7 mm with small adaptations
F. 10 mm with small adaptations

GTV for nodal RT boost

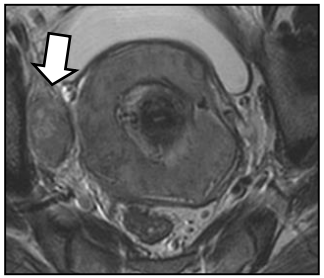
Imaging: indirect proof, (morphological & functional characteristics)

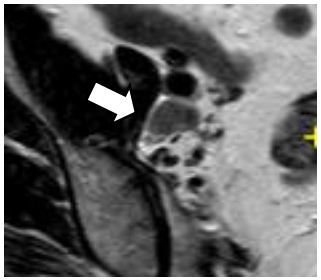


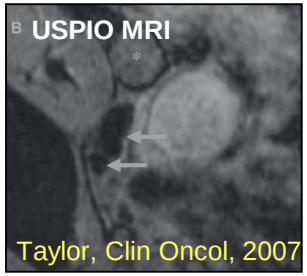




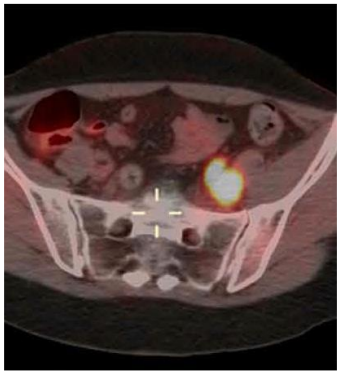
Sensitivity	Specificity	
21-73 %	82-93 %	

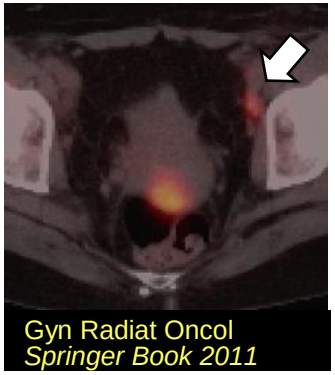


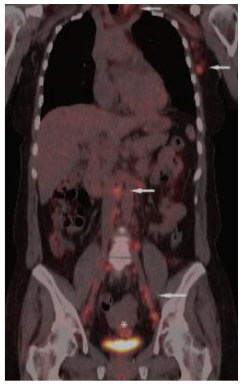




53 - 87 %	92 - 98 %	







68 - 94 %	95 %	Pelvis
95 - 100 %	95 - 99 %	PAO

MRI and PET-CT preferable over CT

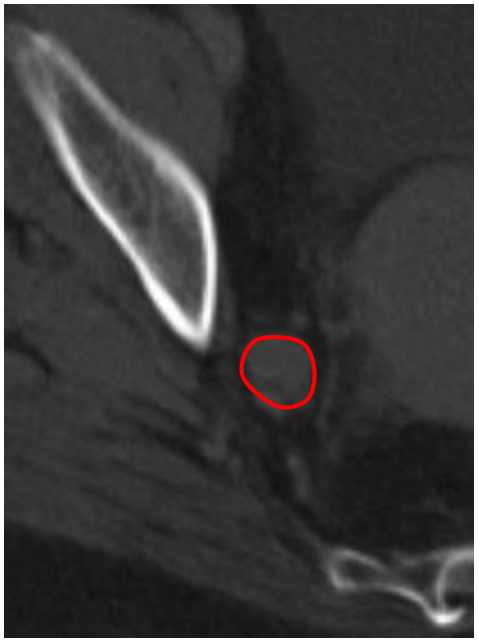
New contrast agents and tracers....

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

From GTV to CTV

CTV-N: in principal no margin around the nodal GTV

In case of extracapsular extension, add some margin, e.g up to 5 mm

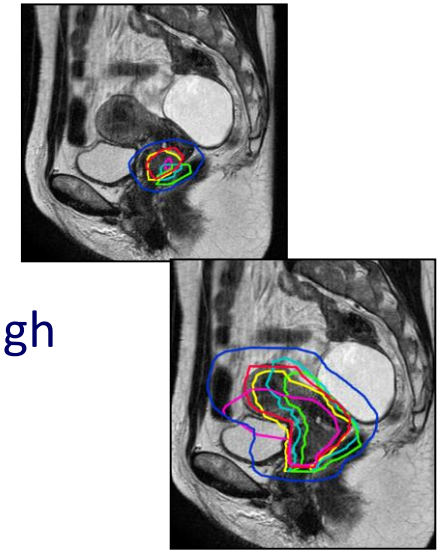


EMBRACE II protocol

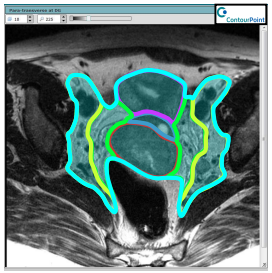
PTV-margin to be discussed

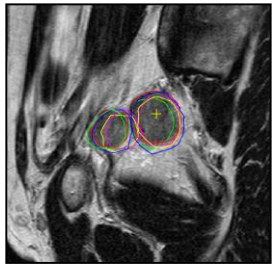
Conclusions

- **Concept of initial GTV-T is recommended**
- **Concept of initial CTV-T is recommended**
  with initial HR CTV-T and LR CTV-T
- (tumor and uterus moving is taken into account through the concept of Internal Target Volume (ITV-T)
  presentation Kari Tanderup on ITV and PTV



- **Concept of target for nodal region CTV-E is recommended**
  for pot. microscopic spread, vessels + 7mm: **CTV-E**
- Concept of Nodal boost target CTV-N is recommended
- (no ITV for CTV-E and CTV-N is recommended!)





Management and treatment planning of paraaortic node area

Christine Haie-Meder
Brachytherapy Unit
Gustave Roussy Cancer Center
Villejuif
France

Paraaortic (PAo) node involvement

Locally advanced disease : 36% - 50% of all tumors

Early stage tumors :
FIGO IA1 with lymph vascular space involvement, IA2, or IB1 with proven positive pelvic nodes :
3% to 5.5% risk of PAo node positivity

FIGO IB2-IVA : **15% - 35%** risk of involved PAo node

Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group

C. Haie[1], M.H. Pejovic[2], A. Gerbaulet[1], J.C. Horiot[3], H. Pourquier[4], J. Delouche[5], J.F. Heinz[6], D. Brune[7], J. Fenton[8], G. Pizzi[9], P. Bey[10], R. Brossel[11], P. Pillement[12], F. Volterrani[13] and D. Chassagne[1]

Radiother Oncol 11 (1988) 101-12

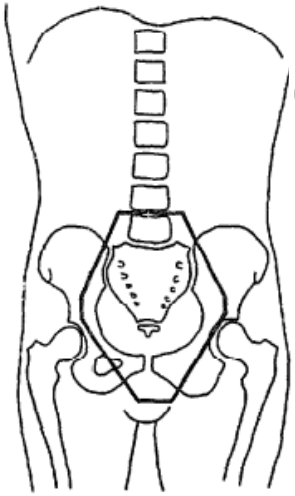


Fig. 1. Pelvic irradiation.

441 patients
Early stage IB-IIA1 with positive pelvic node
Advanced stage IIA2-IIIB whatever pelvic status
All with negative PAo nodes (lymphangiogram)

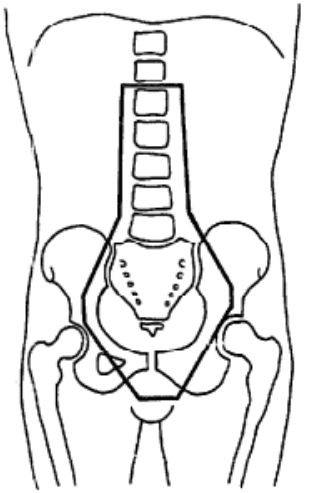


Fig. 2. Pelvic and para-aortic irradiation.

Observed (O) and expected (E) number of critical events.

	Randomized irradiation						
	Pelvis			Pelvis + para-aortic nodes			*p*
	O	E	O/E[a]	O	E	O/E[a]	
Pelvic failure	66	70.7	0.9	71	66.3	1.1	NS
Para-aortic node metastasis	29	19.8	1.5	10	19.1	0.5	<0.01
Other distant metastasis	42	40.4	1.0	31	38.6	0.8	NS

13%

[a] The O/E is the ratio of the number of events observed in a subgroup to the number of events expected in this subgroup assuming that the event rate of this subgroup is the same among all subgroups.

VOLUME 22 · NUMBER 5 · MARCH 1 2004

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Pelvic Irradiation With Concurrent Chemotherapy Versus Pelvic and Para-Aortic Irradiation for High-Risk Cervical Cancer: An Update of Radiation Therapy Oncology Group Trial (RTOG) 90-01

Patricia J. Eifel, Kathryn Winter, Mitchell Morris, Charles Levenback, Perry W. Grigsby, Jay Cooper, Marvin Rotman, David Gershenson, and David G. Mutch

Table 3. Survival and Recurrence Rates

Outcome	Pelvic RT + Chemotherapy (n = 194) %	95% CI	Pelvic + Para-Aortic RT (n = 195) %	95% CI	Relative Risk* Valve	95% CI	P
Overall survival					0.48	0.35 to 0.67	< .0001
5 years	73	67% to 80%	52	45% to 59%			
8 years	67	60% to 75%	41	33% to 49%			
No. of patients at risk beyond 8 years	48		26				
Disease-free survival					0.49	0.36 to 0.66	< .0001
5 years	68	62% to 75%	43	36% to 50%			
8 years	61	53% to 68%	36	29% to 44%			
Patients at risk beyond 8 years	44		22				
Locoregional failure					0.42	0.28 to 0.64	< .0001
5 years	18	12% to 23%	34	28% to 41%			
8 years	18	12% to 23%	35	28% to 42%			
Para-aortic failure					1.65	0.70 to 3.90	.15
5 years	7	3% to 11%	4	1% to 7%			
8 years	9	4% to 13%	4	1% to 7%			
Distant metastasis (excluding para-aortic failure)					0.48	0.32 to 0.73	.0013
5 years	18	13% to 24%	31	25% to 38%			
8 years	20	14% to 26%	35	28% to 42%			
Cause-specific failure†					0.45	0.32 to 0.64	.00012
5 years	24	17% to 29%	41	34% to 48%			
8 years	26	19% to 32%	47	39% to 55%			

Abbreviation: RT, radiotherapy.
*A value less than 1 indicates an advantage for pelvic RT and chemotherapy.
†Failure is death as a result of treated cancer, complications of protocol treatment, or unknown causes.

The Oncologist®

Gynecologic Oncology

Adaptive 3D Image-Guided Brachytherapy: A Strong Argument in the Debate on Systematic Radical Hysterectomy for Locally Advanced Cervical Cancer

The Oncologist 2013;18:415–22

Renaud Mazeron,[a] Jennifer Gilmore,[a] Isabelle Dumas,[b] Jérôme Champoudry,[b] Jennifer Goulart,[a] Ben Vanneste,[a] Anne Tailleur,[a] Philippe Morice,[c] Christine Haie-Meder[a]

163 patients

11% had paraaortic failure

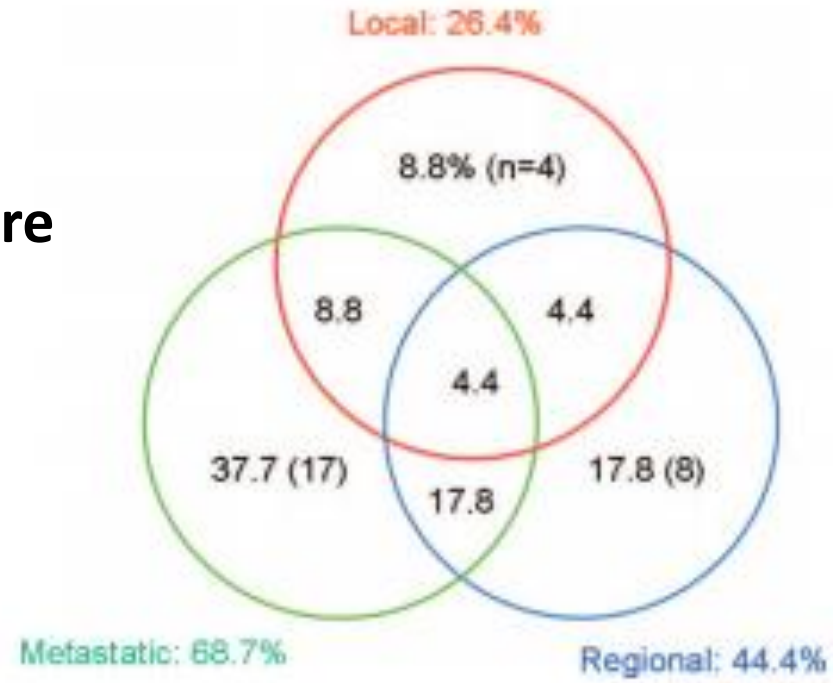
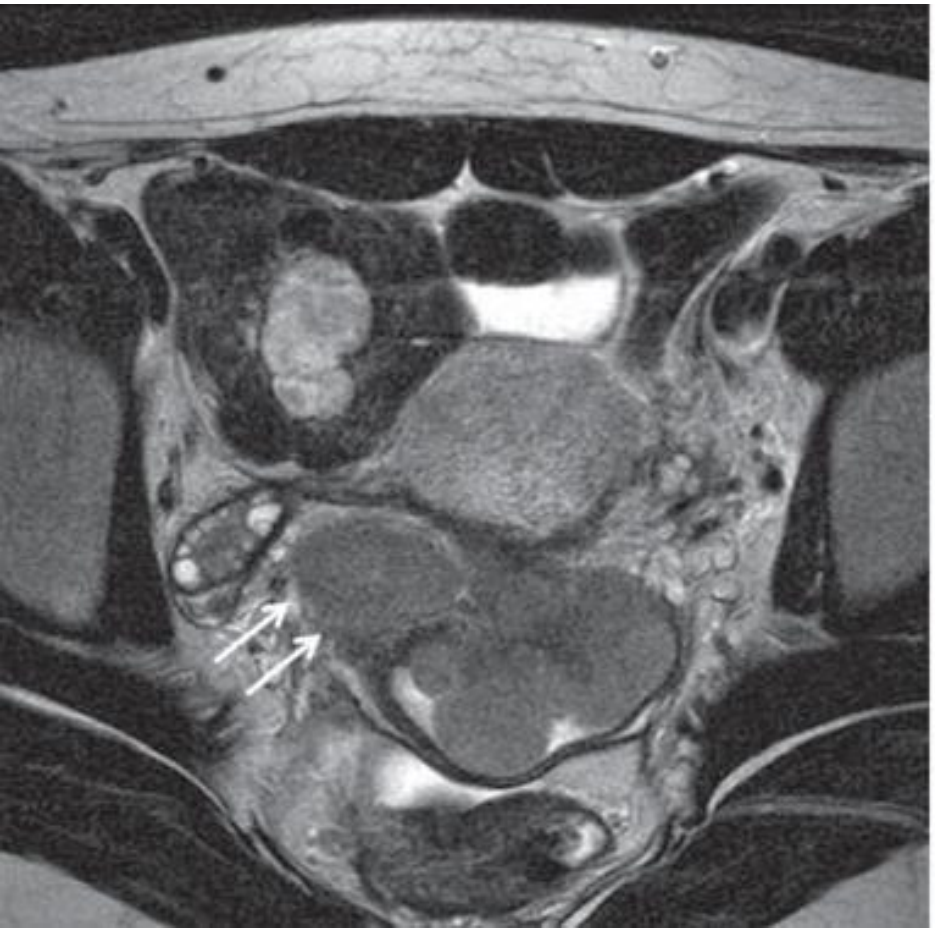


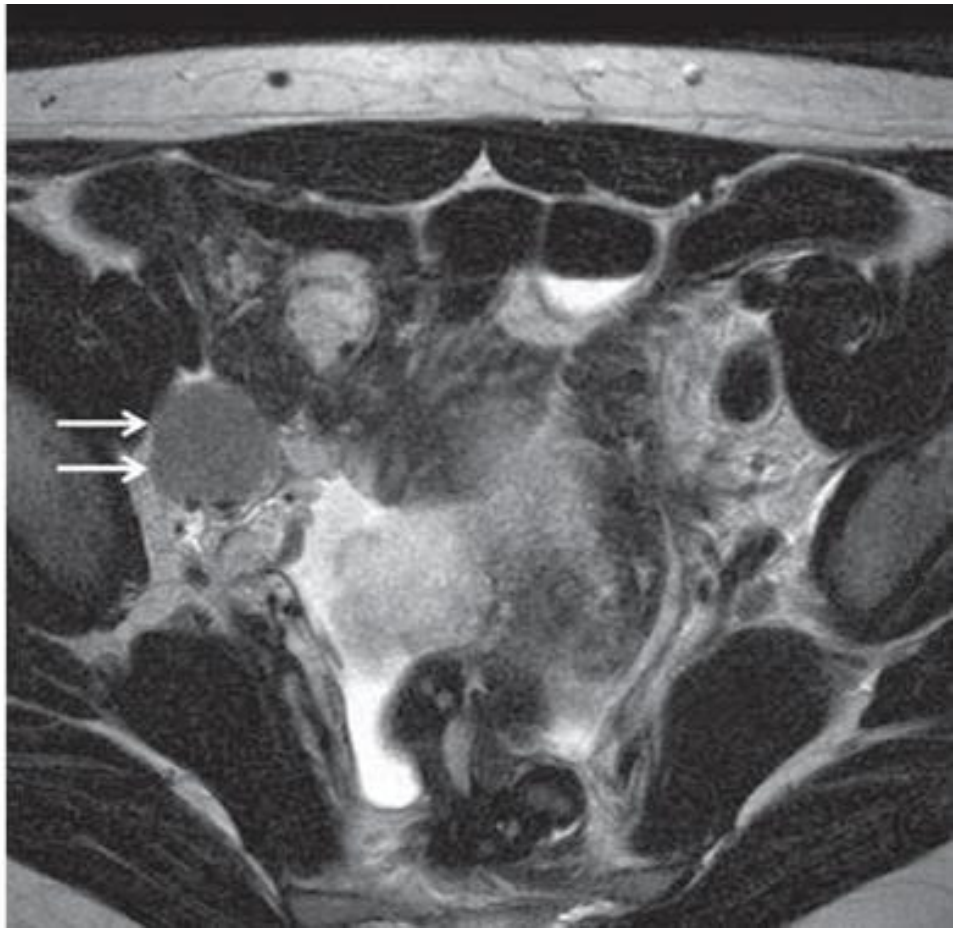
Figure 1. Pattern of relapses.

How can one better assess paraaortic node status?

Nodal assessment

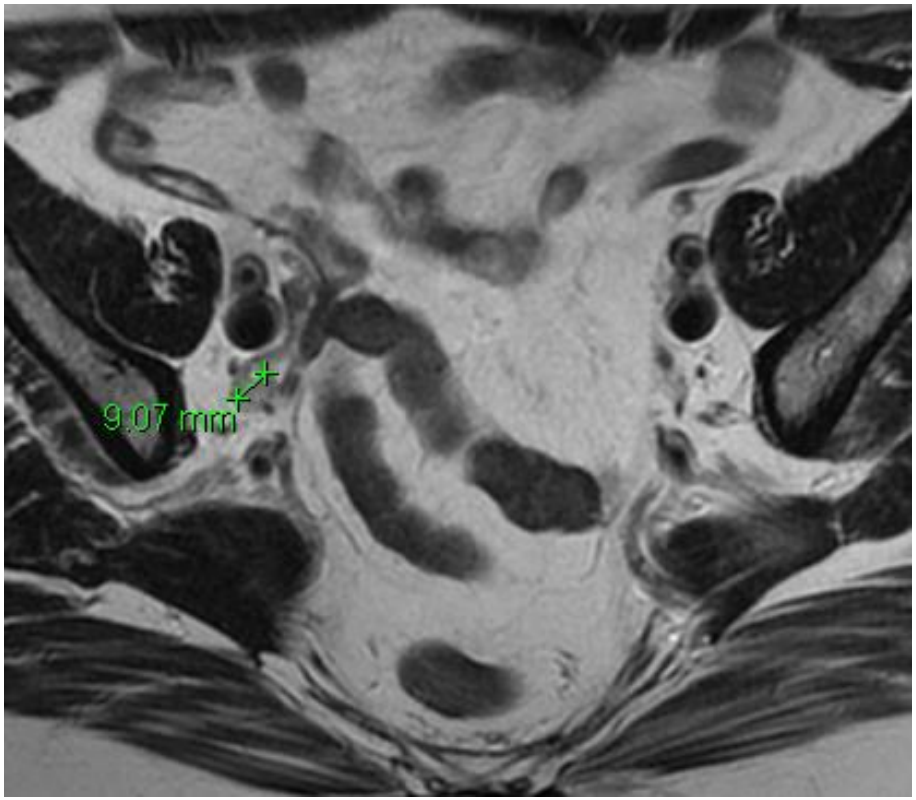
MRI ≥ CT-scanning for nodal involvement assessment

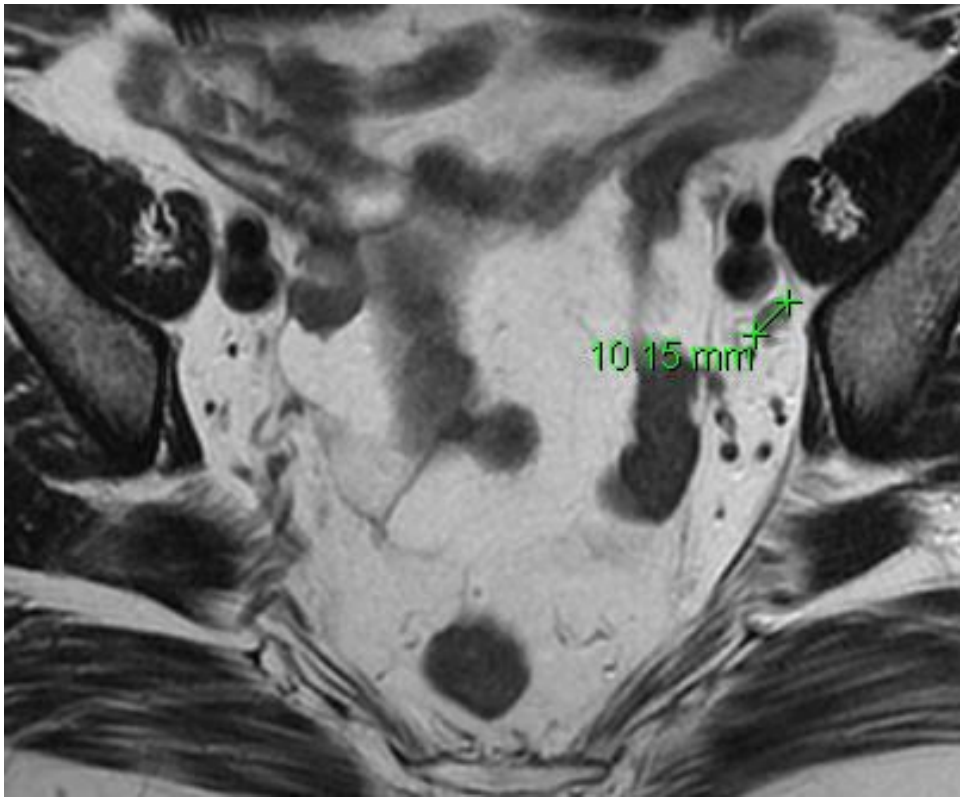




Nodal assessment

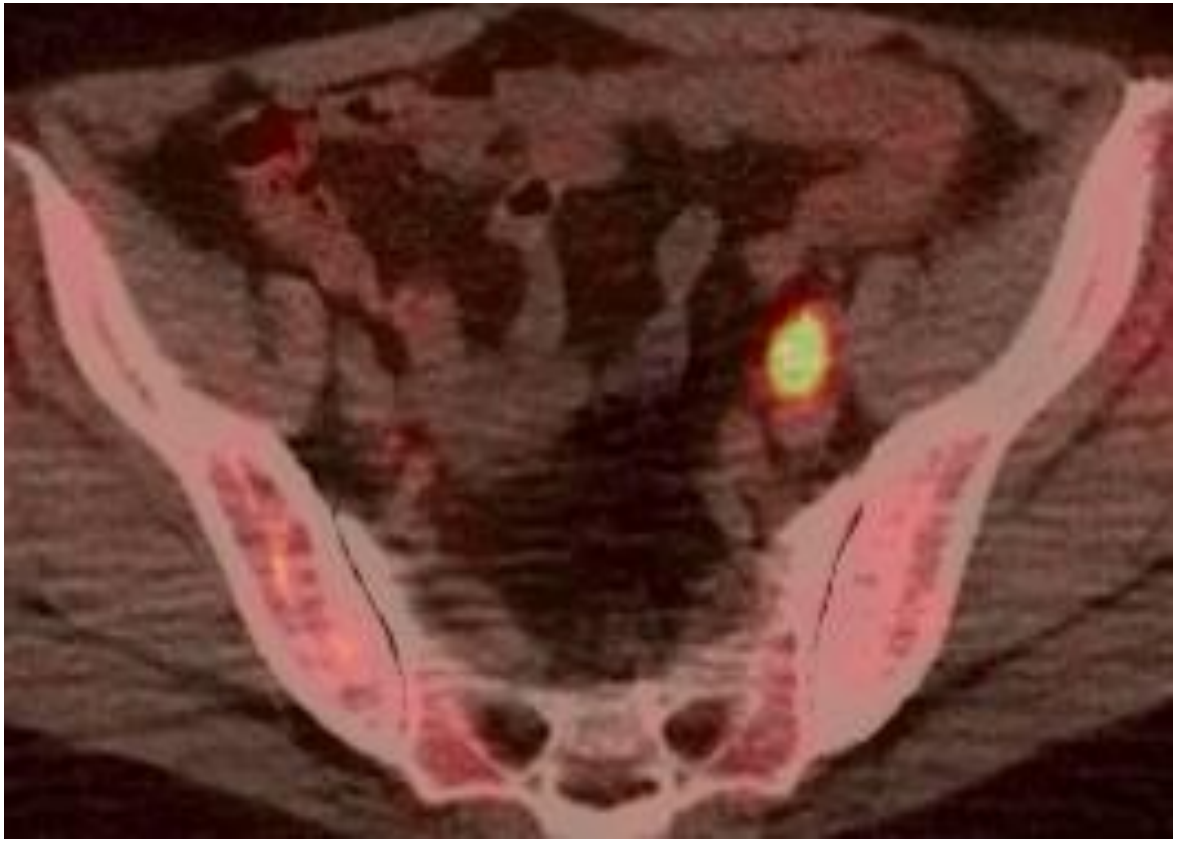
MRI ≥ CT-scanning for nodal involvement assessment





Nodal assessment

Role of PET-CT



Role of PET-CT advanced stage

New trends in the evaluation and treatment of cervix cancer: The role of FDG–PET

Nicolas Magné [a,*], Cyrus Chargari [a], Lisa Vicenzi [a], Norman Gillion [a], Taha Messai [a], Jacques Magné [b], Gérald Bonardel [c], Christine Haie-Meder [a]

Cancer Treatment Reviews (2008) 34, 671–681

Table 2 FDG–PET for initial lymph node staging in advanced-stage disease

	n	Study	FIGO stages	Imaging modality	LN	Se	Sp	Nodal status confirmation
Sugawara et al.[9]	21	P	IB-IVA	PET *vs* CT	Overall	0.86	1.00	LND/follow-up
					Overall	0.57	1.00	
Rose et al.[25]	32	P	IIB-IVA	PET	PALN	0.75	0.92	LND
					PELN	1.00	1.00	
Yildirim et al.[50]	16	R	IIB-IVA	PET	PALN	0.50	0.83	LND
Grigsby et al.[78]	152	R	IB-IV	PET	Overall	0.67	0.93	Follow-up
Narayan et al.[41]	7	R	IB-IVB	PET	PELN	0.80	0.92	LND
Yeh et al.[42]	42	P	IB-IVA	PET	PALN	0.83	0.97	LND
Lin et al.[8]	50	P	IB-IVA	PET	PALN	0.86	0.87	LND
Yen et al.[43]	135	P	IB2-IVB + recurrence	PET	PELN	0.88	1.00	LND/follow-up
					PALN	0.95	1.00	
Choi et al.[46]	22	P	IB-IVA	PET–CT	PELN	0.77	0.55	LND
Amit et al.[45]	75	P	I-IV	PET–CT	PELN	0.60	0.94	LND/follow-up
Loft et al.[51]	119	P	IB1-IVA	PET–CT	PELN	0.96	0.75	LND/follow-up
					PALN	1.00	0.95	

Se: sensitivity, Sp: specificity, R: retrospective, P: prospective, SLN: sentinel lymph node, CPR: centropelvic relapse, PELN: pelvic lymph node, PALN: para-aortic lymph node, histo: histological examination.

Prognostic value of PET-CT

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

July 2000-March 2009 560 patients **J Clin Oncol 2010;28:2108-13**

Table 1. Frequency and Level of Lymph Node Metastasis Observed on FDG-PET by FIGO Stage of Cervical Cancer

FIGO Stage	Total No. of Patients	No. of Lymph Nodes		Lymph Node Type					
				Pelvic		Para-Aortic		Supraclavicular	
		No.	%	No.	%	No.	%	No.	%
IA1	1	1	100	0		0		0	
IA2	11	10	91	1	9	0		0	
IB1	148	118	91	29	19	3	2	0	
IB2	91	40	49	41	51	7	9	1	1
IIA	14	7	50	7	50	3	21	1	7
IIB	161	74	46	87	54	27	17	6	4
IIIA	4	2	50	2	50	1	25	1	25
IIIB	111	36	32	75	68	37	33	12	11
IVA	11	5	45	6	55	3	27	0	
IVB	20	3	15	17	85	12	60	10	50
All	560	189	34	264	47	93	17	31	6

Prognostic value of PET-CT

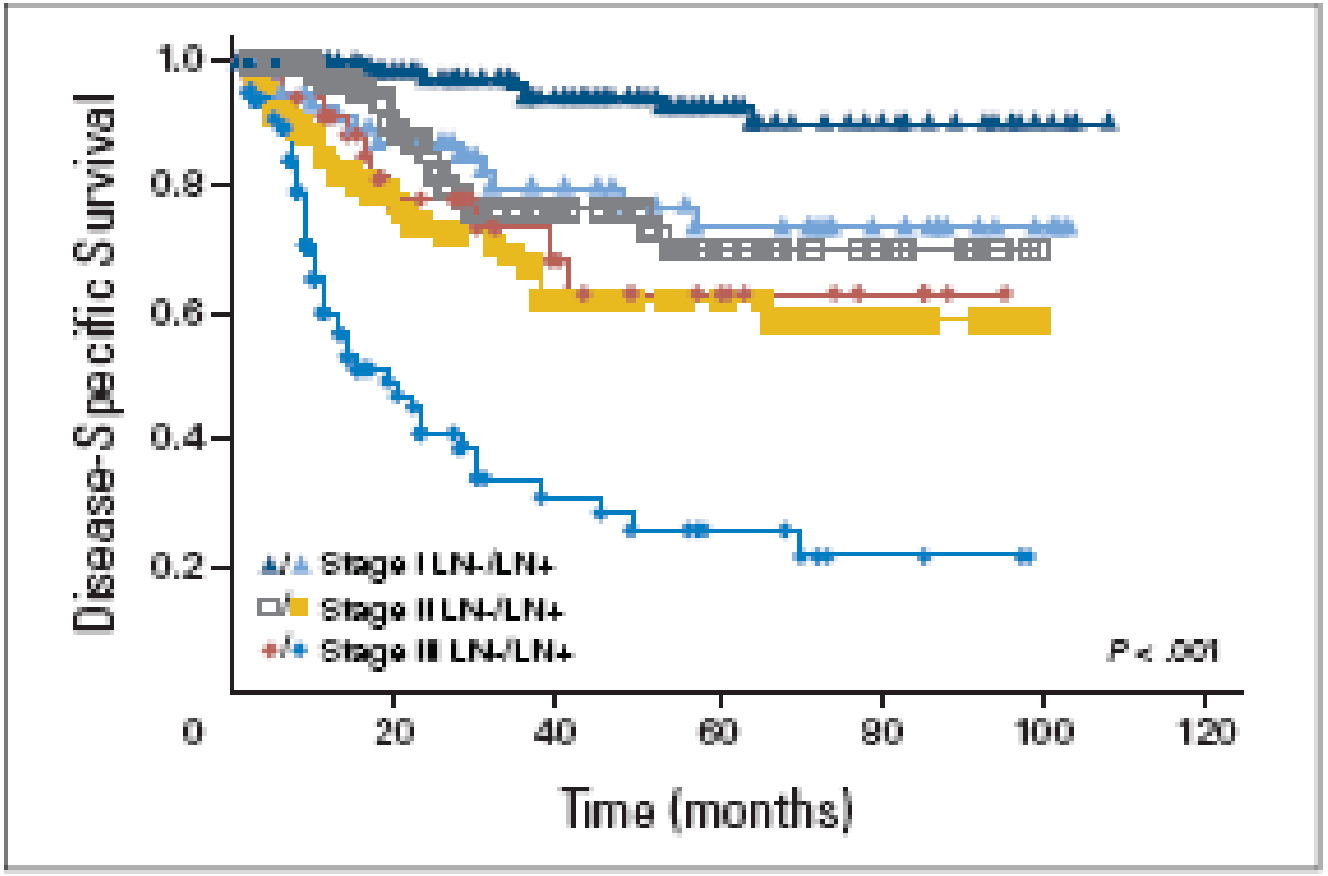


Fig 1. Kaplan-Meier disease-specific survival divided by International Federation of Gynecology and Obstetrics stage and positron emission tomography (PET) lymph node (LN) status: stage I, PET negative (dark blue triangle); stage I, PET positive (light blue triangle); stage II, PET negative (gray square); stage II, PET positive (gold square); stage III, PET negative (red circle); and stage III, PET positive (blue circle).

Nodal-staging surgery for locally advanced cervical cancer in the era of PET

Sebastien Gouy, Philippe Morice, Fabrice Narducci, Catherine Uzan, Jennifer Gilmore, Hélène Kolesnikov-Gauthier, Denis Querleu, Christine Haie-Meder, Eric Leblanc

Lancet Oncol 2012; 13: e212–

	N (n)*	Stage	Para-aortic nodes removed (median)	Technique	Negative para-aortic PET status and positive histological para-aortic nodal status			Positive para-aortic PET status and positive histological para-aortic nodal status		
					Total	Negative pelvic node PET status	Positive pelvic node PET status	Total	Negative pelvic node PET status	Positive pelvic node PET status
Uzan (2011)[19]	114 (114)	IB2–IVA	14	PET/CT	10% (11/114)	5% (4/80)	20% (7/34)	..	..	..
Leblanc (2011)[20]	195 (182)	IB2–IVA	18	PET/CT	14% (25/182)	12% (18/149)	21% (7/33)	54% (7/13)	40% (2/5)	63% (5/8)
Ramirez (2011)[21]	60 (53)	IB2/IVA	11	PET/CT	17% (9/53)	12% (3/26)	22% (6/27)	71% (5/7)	0	71% (5/7)
Mortier (2008)[22]	44 (41)	IB2–IIIB	6†	PET and PET/CT	12% (5/41)	..	..	100% (3/3)	..	..
Yildirim (2008)[23]	16 (12)	IIB–IIIB	17	PET/CT	16% (2/12)	..	..	50% (2/4)	..	..
Loft (2007)[24]	15‡	IB1–IVA	..	PET/CT	..	..	..	100% (15/15)§	100% (2/2)	100% (13/13)
Lin (2003)[25]	50 (36)	IIB–IVA	†	PET	5% (2/36)	..	..	86% (12/14)	..	..
Rose (1999)[26]	32 (24)	IIB–IVA	†	PET/CT	8% (2/24)	0% (0/16)	25% (2/8)	75% (6/8)	0	75% (6/8)
Total	..	..	..	..	12% (56/462)	9% (25/271)	22% (22/102)	78% (50/64)	..	..

*Number of patients in the series (number with negative para-aortic PET status). †Lymphadenectomy to the level of the inferior mesenteric artery. ‡Number with positive para-aortic PET status. §12 were confirmed by histological examination and three by other modalities or follow-up.

Table 2: Studies of PET or PET-CT for detection of para-aortic node metastasis in locally advanced cervical cancer

Lancet Oncol 2012 13:212-20

VOLUME 31 · NUMBER 24 · AUGUST 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prospective Multicenter Study Evaluating the Survival of Patients With Locally Advanced Cervical Cancer Undergoing Laparoscopic Para-Aortic Lymphadenectomy Before Chemoradiotherapy in the Era of Positron Emission Tomography Imaging

Sebastien Gouy, Philippe Morice, Fabrice Narducci, Catherine Uzan, Alejandra Martinez, Annie Rey, Enrica Bentivegna, Patricia Pautier, Desiree Deandreis, Denis Querleu, Christine Haie-Meder, and Eric Leblanc

- 3 French centers : 237 patients
- Institut Gustave Roussy, Villejuif
- Oscar Lambret, Lille
- Centre Claudius Regaud, Toulouse

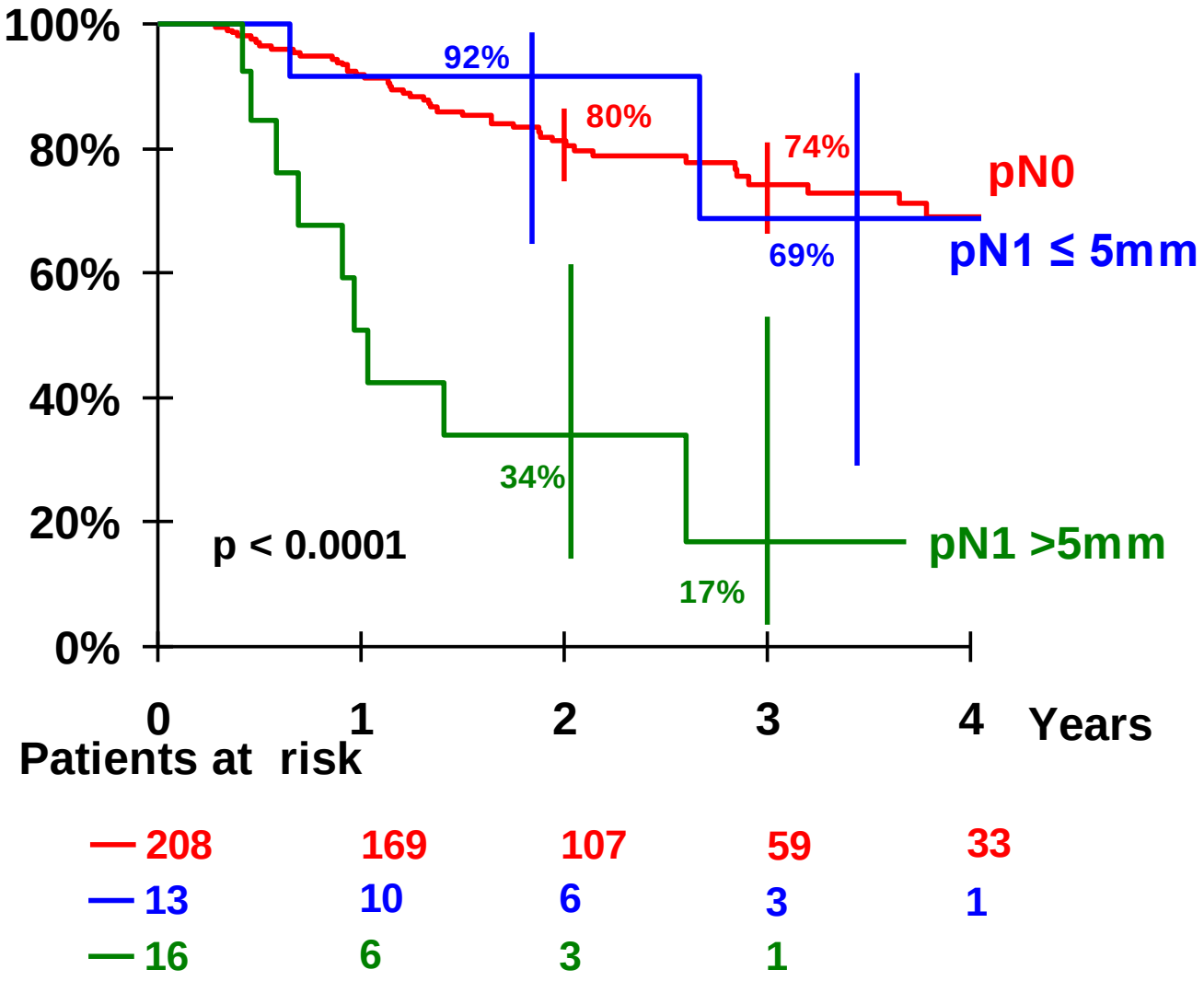
Patient characteristics

Characteristics	Number of patients (%)
Median age (years-range)	46 (10-74)
Tumor stage (1987 FIGO classification)	
IB2	79 (33%)
IIA	10 (5%)
IIB	121 (50%)
IIIA	6 (3%)
IIIB	16 (7%)
IVA	5 (2%)
Histologic subtype	
Squamous Cell Carcinoma	199 (84%)
Adenocarcinoma	35 (15%)
Adenosquamous	1
Clear cell adenocarcinoma	1
Glassy cell adenocarcinoma	1
Pelvic node uptake(s) during PET imaging	
No	187 (79%)
Yes	50 (21%)
Size of the biggest para-aortic nodes involved	
≤ 5 mm	13
> 5 mm	16
Duration of the CRT (including brachytherapy)*	
≤ 55 days	161 (68%)
> 55 days	75 (32%)
Median delay between procedures (days-range)	14 (1-49)
PET/CT-para-aortic surgery**	35 (6-76)
PET/CT-Chemoradition therapy**	27 (3-60)
Surgery-Chemoradiation therapy***	

88 %

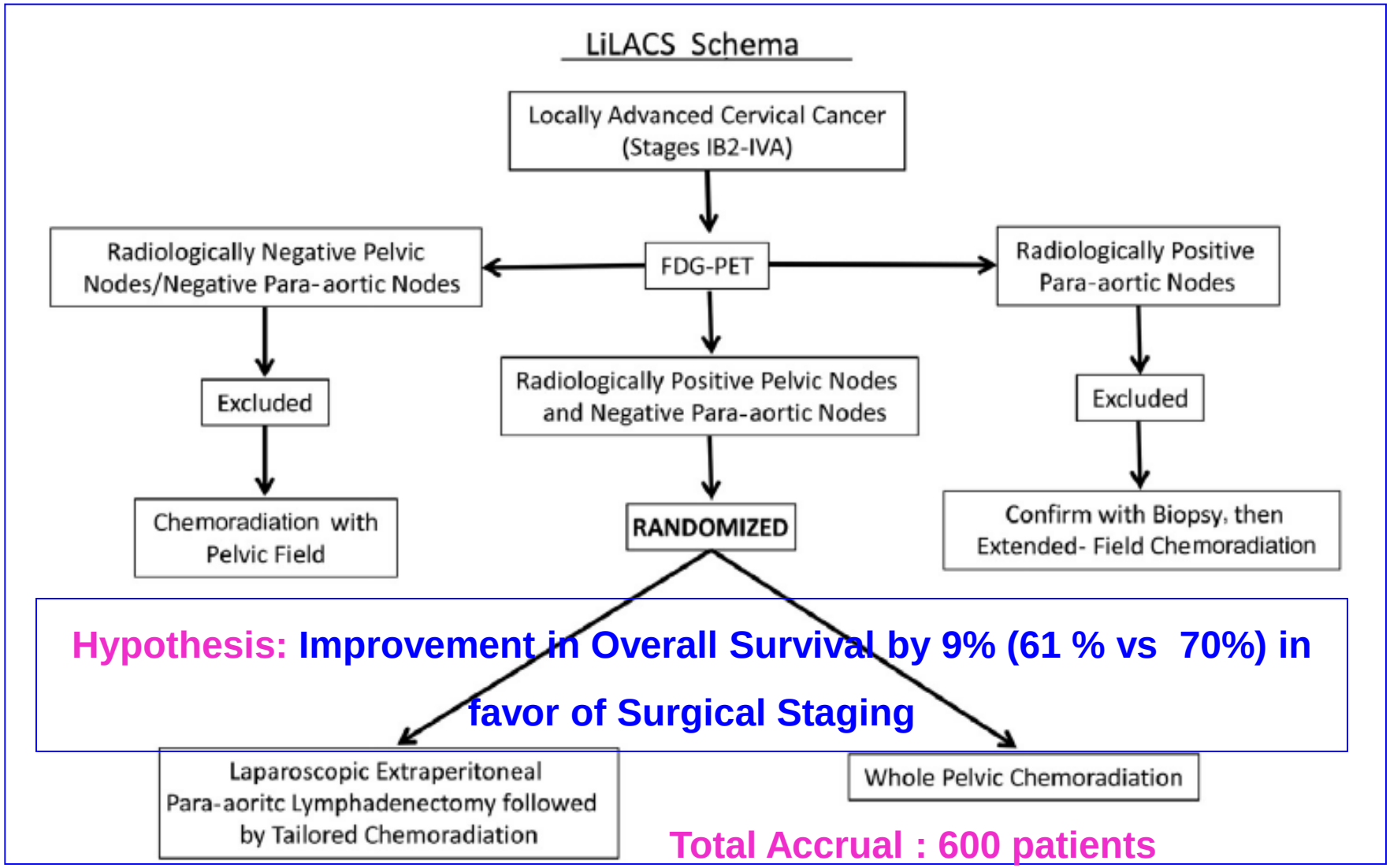
29 (11%) PA+ : False negative rate

EFS according to the size of + PA nodes



Lymphadenectomy in Locally Advanced Cervical Cancer Study (LiLACS): A Phase III Clinical Trial comparing surgical with radiological staging in patients with Stages IB2 - IVA Cervical Cancer

Journal of Minimally Invasive Gynecology (2014) 21, 3–8 © 2014



Up to which level should PAo lymph node dissection be performed?

Should Systematic Infrarenal Para-aortic Dissection Be the Rule in the Pretherapeutic Staging of Primary or Recurrent Locally Advanced Cervix Cancer Patients With a Negative Preoperative Para-aortic PET Imaging?

Eric Leblanc, MD, Ninad Katdare, MD,* Fabrice Narducci, MD,* Lucie Bresson, MD,* Sebastien Gouy, MD,† Philippe Morice, MD, PhD,† Gwenael Ferron, MD,‡ Denis Querleu, MD, PhD,‡ and Alejandra Martinez, MD‡*

Int J Gynecol Cancer 2016;26: 169-75

- **Incidence of skip metastases above the level of the inferior mesenteric artery (IMA)?**
- **Extraperitoneal PA retroperitoneal lymph node dissection**
- **All nodes were removed from both common iliac bifurcations up to the left renal vein**
- **Nodes resected from both common iliac bifurcation up to the origin of the IMA, called the inframesenteric group, and those from the IMA up to the left renal vein, called the supramesenteric group, were extracted separately in endoscopic bags**
- **Pathological examination of the supramesenteric and inframesenteric nodes separately**
- **Record of postoperative complications**

Should Systematic Infrarenal Para-aortic Dissection Be the Rule in the Pretherapeutic Staging of Primary or Recurrent Locally Advanced Cervix Cancer Patients With a Negative Preoperative Para-aortic PET Imaging?

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Int J Gynecol Cancer 2016;26: 169-75

- January 2010-December 2013 : 196 stage IB1 with pelvic pN1, IB2, to IVA LACC
- 30 patients (15%) PA Pn1
- Only 1 patient only with positive nodes exclusively located above the IMA (3.3% of the pN1 group; 95% confidence interval : 0%-9.7%)
- Complications : 15 (7.6%) patients
- **Conclusion:** Given the very low rate of skip metastases above the IMA and the potential additional morbidity of a systematic extended dissection, a **bilateral ilioinframesenteric dissection seems to be** an acceptable pattern of PA lymphadenectomy in LACC patients

PAo irradiation :
Which technique?
Which dose?

Extended field radiation with PAo node inclusion

Previous studies of irradiation to paraaortic metastasis[a]

Authors	No. of patients	Radiation technique	Dose (Gy)	Median survival (months)	5 year survival rate (%)	Major (≥ G3) complications (%)
Piver [25,26]	31	2P + Rot	44–60	–	9.6	–
Komaki [15]	22	2P or 4P	40–58	–	40	–
Nori [21]	27	2P	50–52	–	29	–
Jolles [12]	11	2P	45–50	–	–	36
Feuer [8]	5	–	45	–	16.7	0
Crawford [4]	29	2P or 4P or Rot	42–50	20	–	0
Malfetano [16]	13	–	45	–	–	0
Cunningham [5]	21	2P	40–50	–	48	–
Vigliotti [33]	43	2P or 4P	39.6–60	–	32	19
Hicks [11]	11	2P	45	30	–	27
Kodaira [14]	41	4P	40–70	–	32.2	0
Grigsby [10]	43	2P	30.6–55	26	32	5
Grigsby [9]	30	4P	7.2–60	–	29 (4 years)	40
Present study	29	Dyn or Dyn + 2P	50–63.4	15	29 (2 years)	0

[a] 2P, anteroposterior–posteroanterior opposed portals; 4P, four portals; Rot, rotational technique; Dyn, dynamic arc conformal technique.

- Disease limited to PAo nodes = reasonable outcome with field extension to the PAo area +/- CT
- Conv. RT techniques & CT = higher toxicities

Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB & bulky IB and IIA cervical carcinomas

Ten-year treatment results of RTOG 79-20. JAMA 1995

- 10 yr OS - 44% Vs 55%
- DFS – similar 40 Vs 42%;
- LRF similar - 35% Vs 31%
- Better Survival following first failure
- Higher G 4 & 5 toxicities at 10 yrs 4% vs 8%
- Death due to RT complications 1% vs 2%

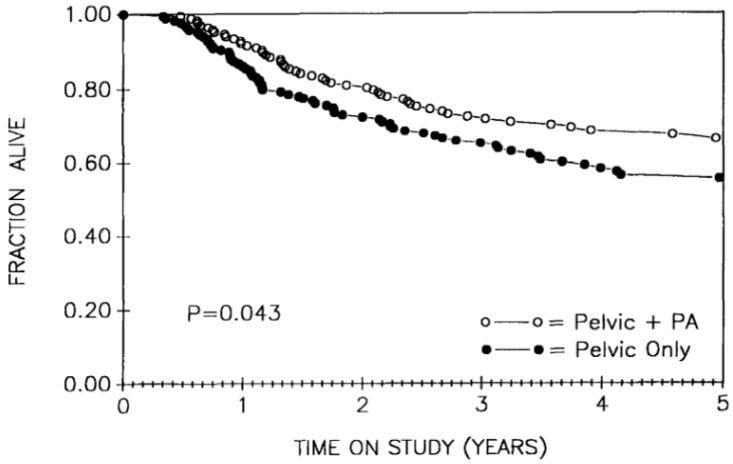
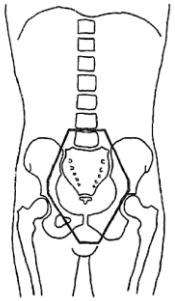
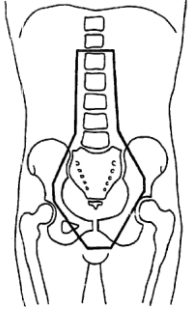


Fig. 1. RTOG 79-20 survival by assigned treatment (Kaplan-Meier).



Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group

C. Haie[1], M.H. Pejovic[2], A. Gerbaulet[1], J.C. Horiot[3], H. Pourquier[4], J. Delouche[5], J.F. Heinz[6],



- No difference in local control, distant metastases and DFS.
- Incidence of para-aortic metastases & distant metastases without tumour at pelvic sites was significantly higher in patients receiving pelvic RT.
- Higher GI complications in PAo RT group (3.5% vs 8% at 4 years : p= 0.005)

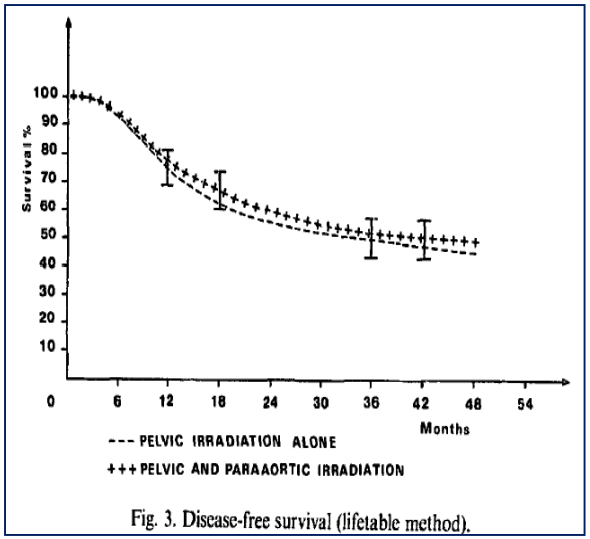


Fig. 3. Disease-free survival (lifetable method).

Conclusions:

- Routine para-aortic RT for all high risk patients with cervical carcinoma is of limited value.
- Patients with a high probability of local control can benefit from extended field irradiation, despite an increase in severe digestive complications.

Role of IMRT

IMRT for PAo RT

	Number of patients and study type	Dose of radiation therapy	Feasibility and toxic effects	Survival effect
Chen (2011)[73]	Retrospective study: 109 patients treated with IMRT and concomitant cisplatin-based chemotherapy; 13 had involved para-aortic nodes and underwent extended field radiation therapy	CTV received 45–48 Gy; GTV received 50·4–54 Gy; nodal GTV received 54–60 Gy with concomitant boost	Patients with para-aortic disease were not assessed separately; acute gastrointestinal and haematological toxic effects grade ≥3 of 2·7% and 23·9%; long-term gastrointestinal and genitourinary toxicity grade ≥3 of 4·6% and 6·4%	Patients with para-aortic disease were not assessed separately; 3-year overall and disease-free survival was 78·2% and 67·6%, respectively
Ahmed (2004)[75]	Planning study: planning techniques compared in 5 patients to assess dose reduction to organs at risk with IMRT; AP/PA to pelvis and para-aortic area, four-field box pelvis and para-aortic area and four-field box pelvis/IMRT in para-aortic area	45 Gy to the pelvis; dose to para-aortic gross nodal disease was 54–57 Gy with conventional radiation therapy and 60 Gy for IMRT	Feasibility of dose escalation with reduction of dose to the organs at risk by IMRT	--
Esthappan (2008)[76]	Planning study: IMRT plans generated for 10 patients with involved para-aortic nodes; PET-CT simulation	MTV nodal planned to 60 Gy; nodal PTVs planned to 50 Gy; MTV cervix planned to 20 Gy to be followed by brachytherapy	IMRT to pelvis and para-aortic feasible; volume of bowel receiving 45 Gy can be reduced to <15%	--
Gerszten (2006)[77]	Feasibility study: 21 patients treated with extended field IMRT and concurrent cisplatin	45 Gy with simultaneous integrated boost to 55 Gy to involved nodes with concurrent cisplatin followed by 5×5 Gy HDR brachytherapy	Well tolerated with no grade 3 or 4 genitourinary or gastrointestinal toxic effects; 19% grade 3 haematological toxic effects	--
Kidd (2010)[78]	Prospective study: 135 patients treated with IMRT, 317 with 3-dimensional radiation therapy; of those, 23 in IMRT group and 36 in non-IMRT group had extendedfield radiation therapy for PET-positive para-aortic nodes; PET-CT simulation	50·4 Gy to the pelvic volume and 20 Gy to the cervical volume followed by 6×6·5 Gy HDR brachytherapy	No separation of results for extended field vs pelvis alone; overall IMRT was better tolerated with 6% vs 17% rate of grade 3 bowel toxic effects (p=0·0017)	Improved overall and cause-specific survival in IMRT group (p=0·0001)
Mutic (2003)[79]	Planning study: four patients with para-aortic involved nodes; AP/PA to pelvic area and IMRT in para-aortic area; PET-CT simulation	Pelvis treated with AP/PA fields to 50·4 Gy with a midline shield at 16·2 Gy to be followed by brachytherapy; para-aortic area planned with IMRT to 50·4 Gy to PTV1 and 59·4 Gy to PTV2	IMRT in para-aortic region is feasible and reduces dose to organs at risk	--

AP/PA=anteroposterior/posteroanterior. CTV=clinical target volume. GTV=gross tumour volume. HDR=high dose rate. IMRT=intensity-modulated radiation therapy. MTV=metabolic target volume. PTV=planning target volume.

Table 6: **Published data on para-aortic IMRT**

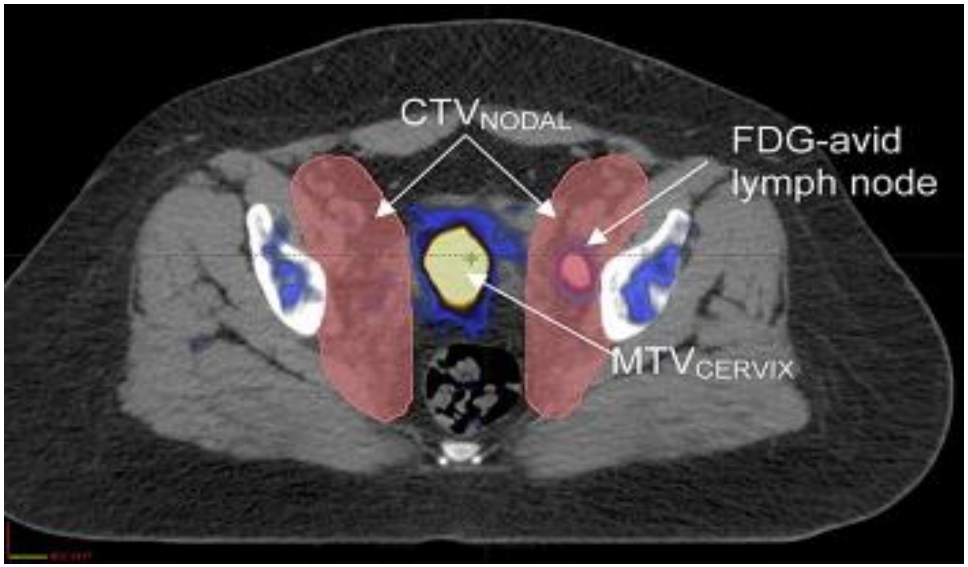
Gouy Lancet Oncol 2012;13: 212-20

PET- CT Based IMRT

Characteristic	135 pts IMRT	317 pts Non-IMRT	Total	*p* Value
Mean age at diagnosis (y)	52	52	52	
Chemotherapy	120 (89%)	262 (83%)	449	0.2238
Stage				0.7003
Ia2	0 (0%)	2 (0.7%)	2	
Ib1	20 (14.8%)	33 (10.4%)	53	
Ib2	21 (15.6%)	56 (17.7%)	77	
IIa	3 (2.2%)	7 (2.2%)	10	
IIb	58 (43.0%)	126 (39.7%)	184	
IIIa	2 (1.5%)	2 (0.6%)	4	
IIIb	29 (21.5%)	82 (25.9%)	111	
IVa	2 (1.5%)	7 (2.2%)	9	
IVb	0 (0%)	2 (0.6%)	2	
Histology				0.3710
Adenocarcinoma	13 (9.6%)	17 (5.4%)	30	
Adenosquamous	2 (1.5%)	9 (2.8%)	11	
Squamous	117 (86.7%)	286 (90.2%)	403	
Other	3 (2.2%)	5 (1.6%)	8	
Lymph nodes				0.0309
None	68 (50.4%)	131 (41.3%)	199	
Pelvic only	41 (30.4%)	140 (44.2%)	181	
Para-aortic	23 (17.0%)	36 (11.4%)	59	
Supraclavicular	3 (2.2%)	10 (3.2%)	13	

Kidd et al., IJROBP 2010

PET-CT Based IMRT: Outcome



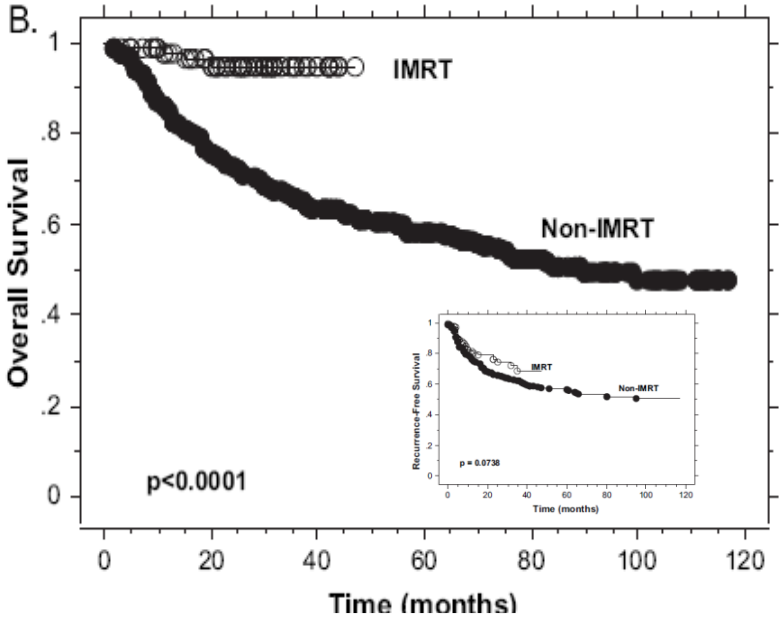


Table 2. Distribution of recurrences for the IMRT, non-IMRT, and total groups

Recurrence	IMRT	Non-IMRT	Total	*p* Value
Overall	39 (28.9%)	139 (43.8%)	178	0.036
Pelvic	11 (8.1%)	33 (10.4%)	44	
Distant	21 (15.6%)	78 (24.6%)	99	
Both	7 (5.2%)	28 (8.8%)	35	

Kidd et al., IJROBP 2010

PET-CT Based IMRT: Toxicities

ACUTE toxicities

Toxicity	G1	G2	G3	G4
GI	8 (38.1%)	2 (9.5%)	0	0
GU	5 (23.8%)	2 (9.5%)	0	0
Skin	1 (4.8%)	2 (9.5%)	0	0
Hematologic toxicity	6 (28.6%)	3 (14.3%)	4 (19.0%)	0

LATE toxicities: Grade 3 or more GI and GU toxicities

Complication	IMRT group	Non-IMRT group	Total
Rectovaginal fistula	2	12	14
Vesicovaginal fistula	0	11	11
Small bowel obstruction	2	7	9
Large bowel obstruction	2	5	7
Cystitis, Grade 4	1	5	6
Rectal ulcer	1	5	6
Ureteral stricture	0	4	4
Rectal stricture	0	2	2
Proctitis, Grade 4	0	2	2
Ischemic colitis	0	1	1

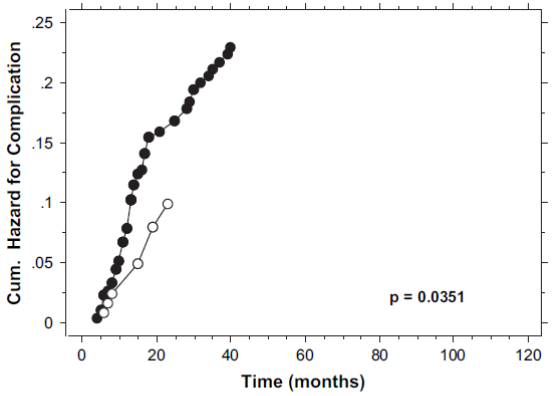
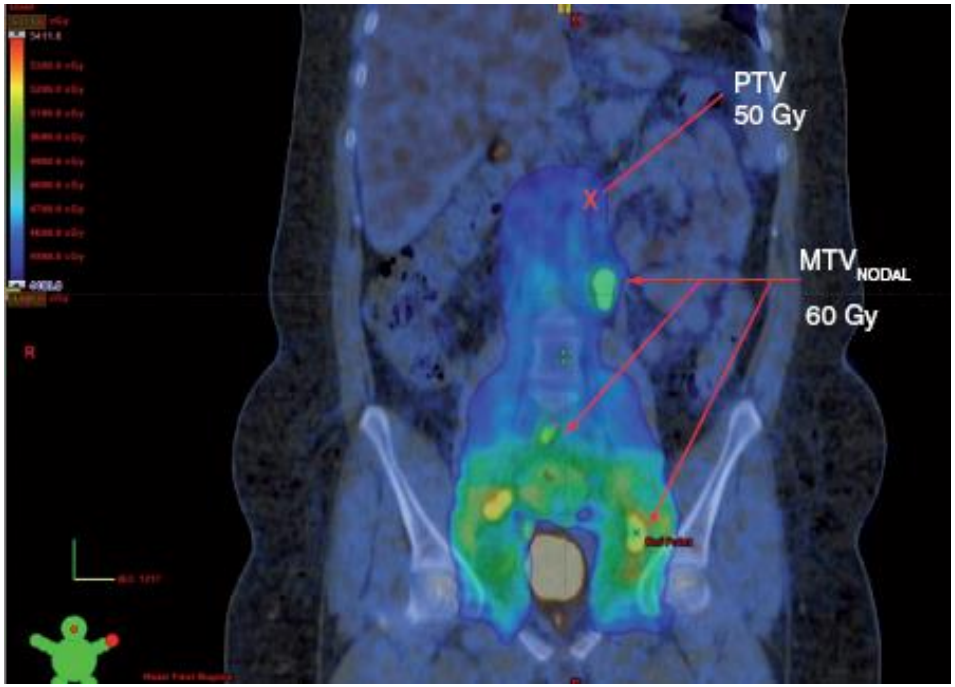


Fig. 4. Cumulative hazard function rates of bowel or bladder complication for the intensity-modulated radiation therapy (IMRT) (○) and non-IMRT (●) groups.

Conclusion: Cervical cancer patients treated with FDG-PET/CT-guided IMRT have improved survival and less treatment-related toxicity compared with patients treated with non-IMRT radiotherapy

Grigsby et al., IJROBP 2010

Which dose to the PAo nodes?



Which dose according to nodal size?
Which nodes require more than 45-50Gy?

Which dose to the PAo nodes?

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.*§

208 patients

Table 2. Para-aortic lymph nodes

Lymph node status	Patients (no.)	Mean lymph node dose (Gy)	Paraaortic lymph node failure
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

Int J Radiat Oncol Biol Phys 2004;59:706-12

Which dose to the PAo nodes?

Lymph node as the only failure rate <2%

Table 4. Pelvic lymph nodes

Lymph node status	Patients (no.)	Failure sites: Cervix	Failure sites: Distant	Failure sites: Both
PET negative	76	7	7	1
PET positive/CT ≤1 cm	89	7	17	3
PET positive/CT >1 cm to ≤2 cm	21	1	5	1
PET positive/CT >2 cm to ≤3 cm	15	3	3	2
PET positive/CT >3 cm to ≤4 cm	5	0	3	0
PET positive/CT >4 cm to ≤5 cm	2	0	1	0
Total	208	18	36	7

29/132 (22%) with PET pelvic + at diagnosis will have distant metastases

Table 5. Paraaortic lymph nodes

Lymph node status	Patients (no.)	Failure sites: Cervix	Failure sites: Distant	Failure sites: Both
PET negative	175	17	20	5
PET positive/CT ≤1 cm	24	1	12	1
PET positive/CT >1 cm to ≤2 cm	5	0	3	0
PET positive/CT >2 cm to ≤3 cm	4	0	1	1
Total	208	18	36	7

16/33 (48%) with PET PAo + at diagnosis will have distant metastases

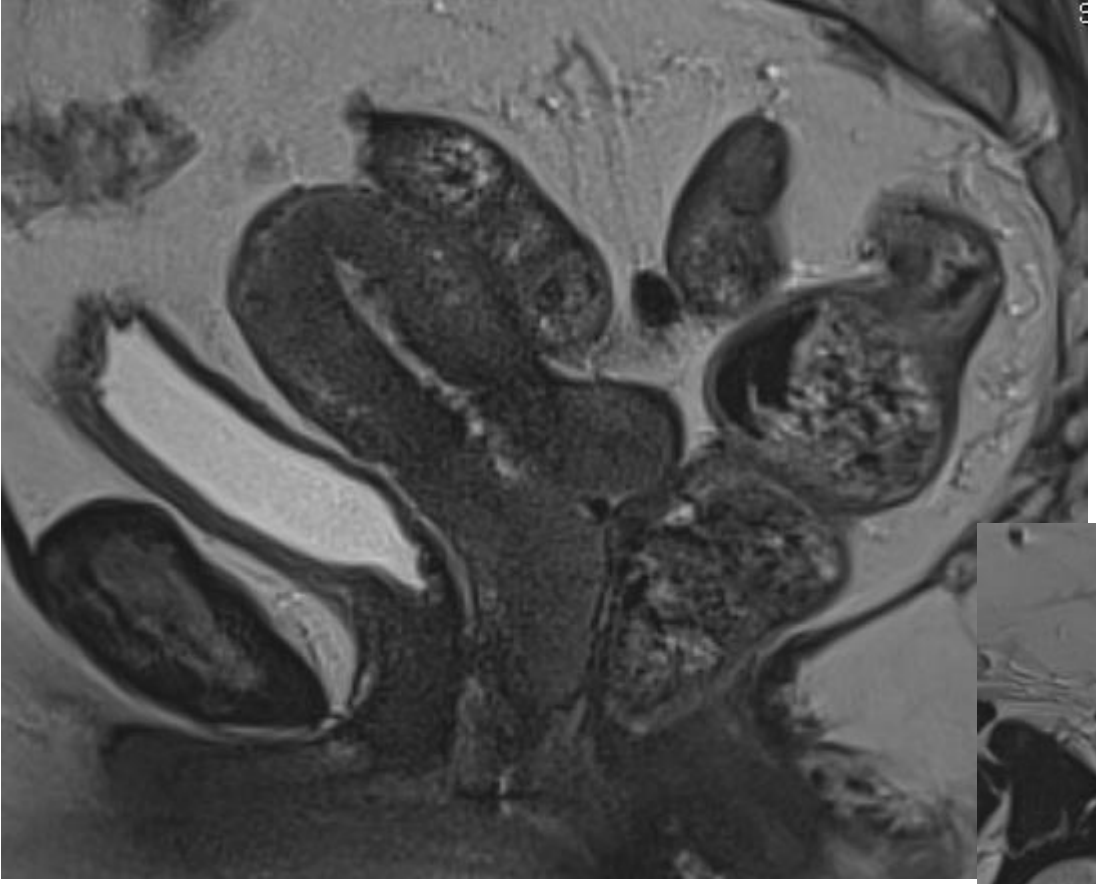
Int J Radiat Oncol Biol Phys 2004;59:706-12

Which dose to the PAo nodes if macroscopic disease?

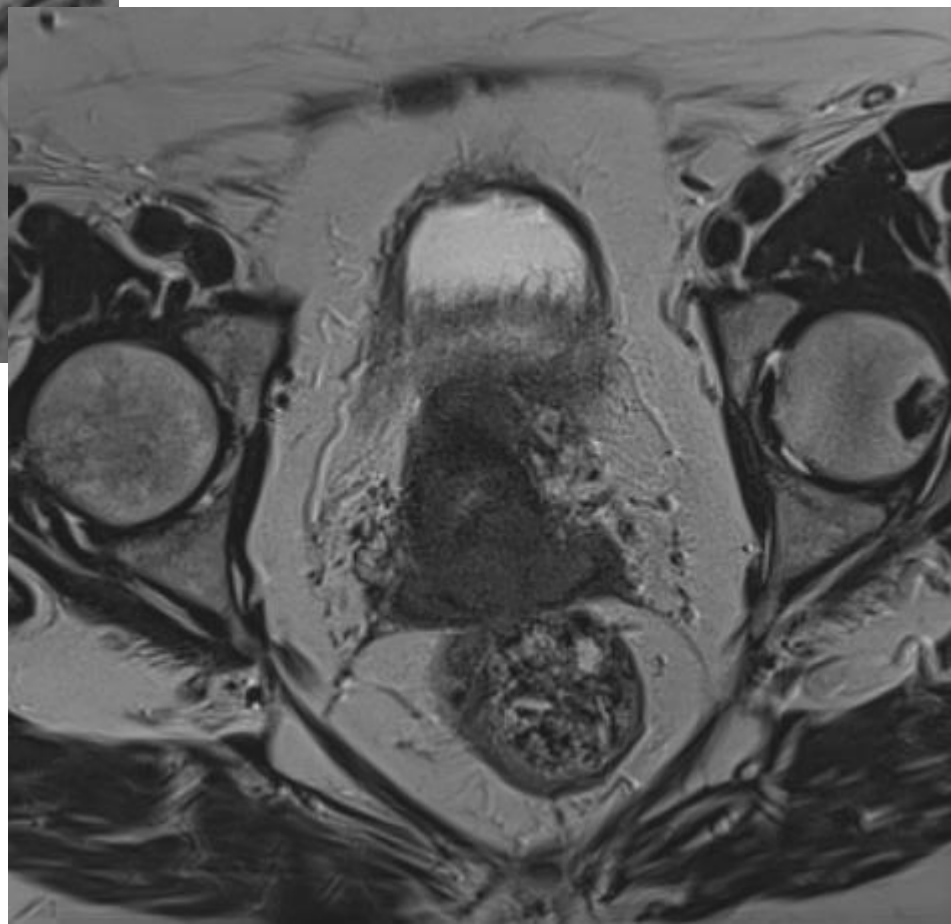
- No clear consensus
- Escalation up to 55Gy (SIB IMRT)
- Risk of distant metastases
- Adjuvant chemotherapy?

Nodal assessment in advanced cervix cancer : Conclusions

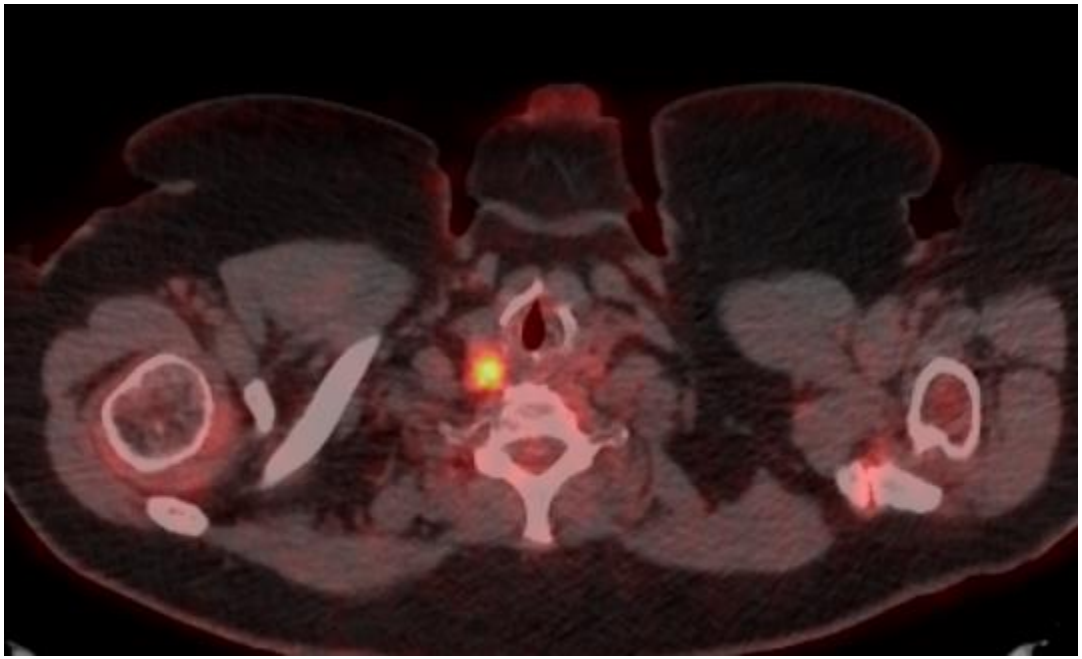
- Role of PET-CT
- Importance of pretherapeutic PAo laparoscopic lymph node dissection
- Patients with PAo node ≤ 5 mm, treated by extended field CRT, have a disease free survival similar to the survival of patients with negative PA nodes
- No clear recommendations for dose if macroscopic PAo nodes



35 year old patient
Stage IIB
No lymph node at MRI

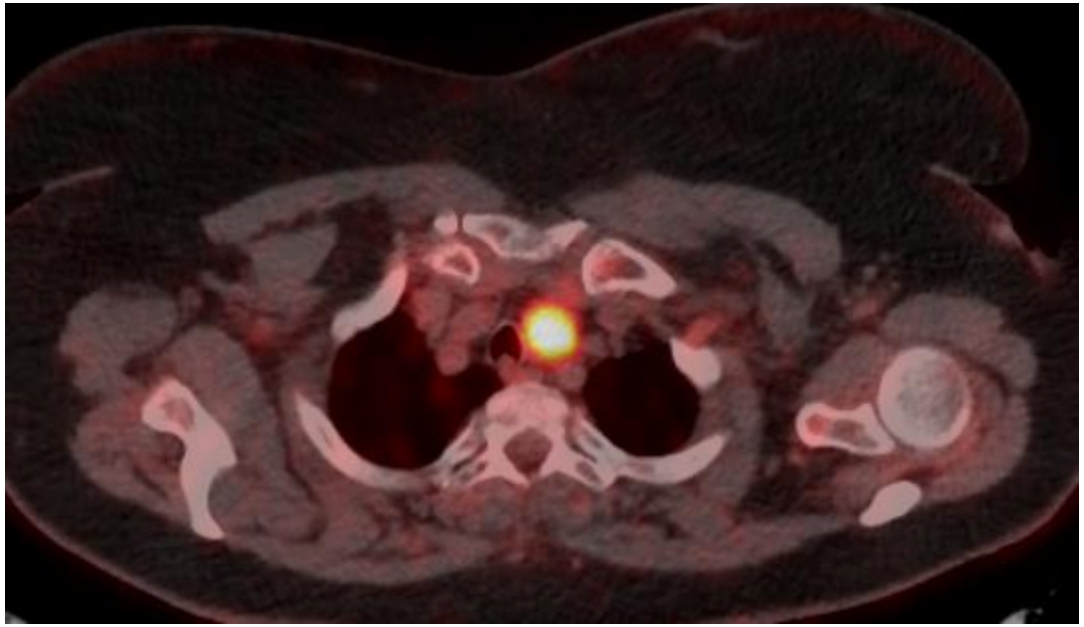


Mind PET-CT conclusions



Bilateral supra-clavicular lymph nodes

Mind PET-CT conclusions




giverny.

Image guidance, organ motion and ITV/PTV

ESTRO-AROI Teaching Course
Transition from conventional 2D to 3D radiotherapy with a special emphasis on brachytherapy in cervical cancers

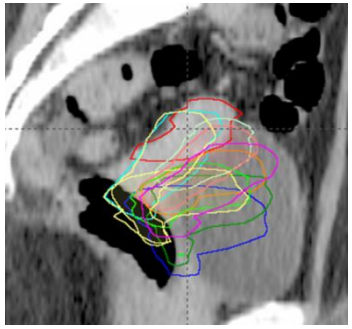
Bengaluru 2017

Prof Kari Tanderup
Prof Richard Pötter

Aarhus University Hospital

ITV and PTV

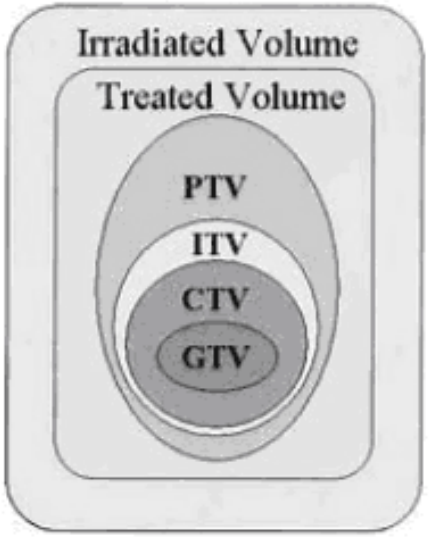
- **ITV: Internal variations**
  - **Position, size and shape of CTV**
    - **Tumour shrinkage**
    - **Organ movement**
    - **Organ deformation**

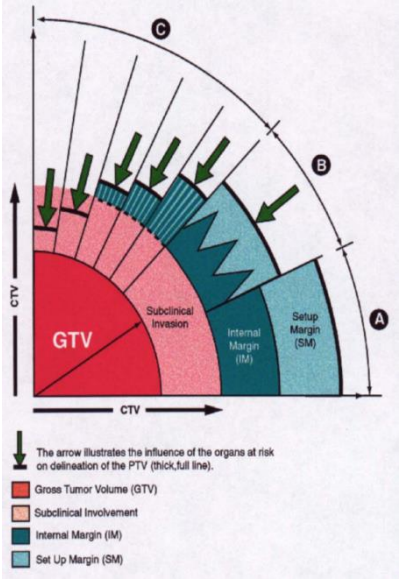


- **PTV: External variations**
  - **Beam positioning**
  - **Patient set-up (e.g. uncertainties when setting up according to skin marks)**

- **If no considerable internal variations are present**
  - **Expansion may be performed directly from CTV to PTV**

- **ITV and PTV margins are not directly “additive”**





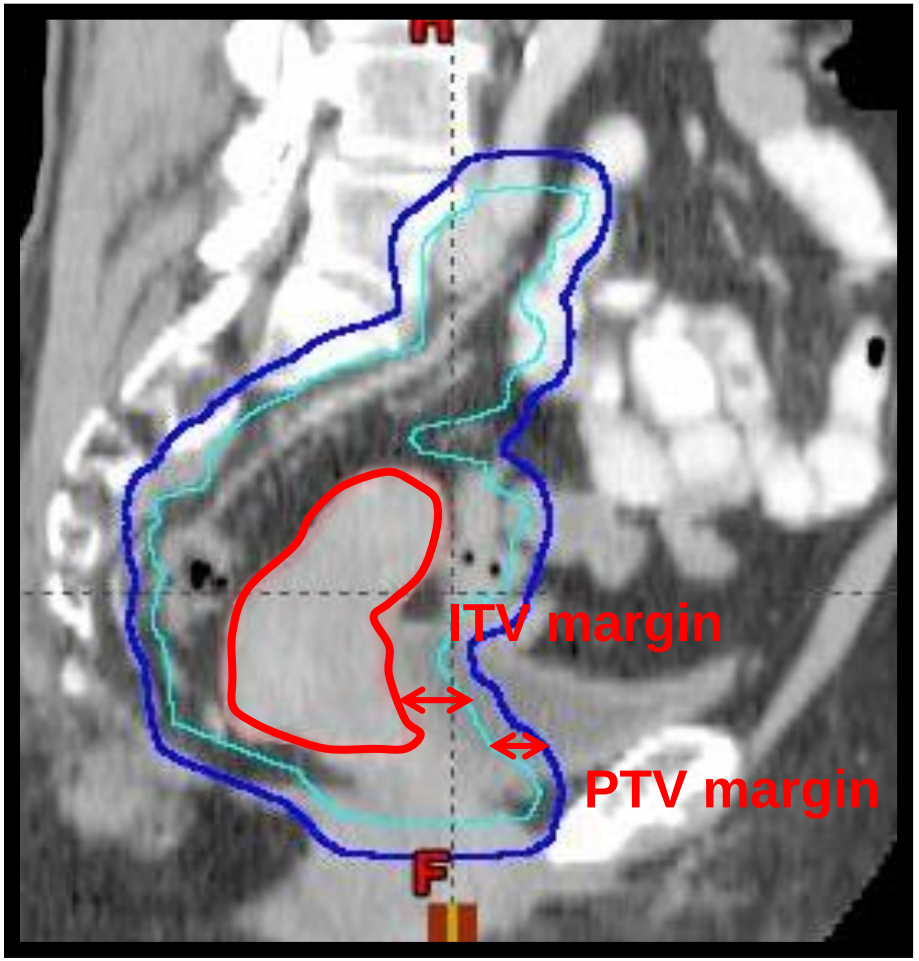
On which target volumes should we add ITV margin?

A. Uterus
B. GTV and cervix (initial CTV_{HR})
C. Pathologic lymph nodes
D. Elective lymph node target

Margins in cervix cancer

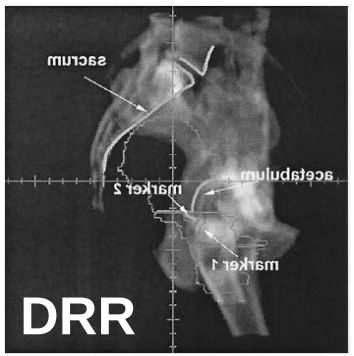
- Primary CTV
  - ITV margin
  - PTV margin
- Pathologic nodes
  - PTV margin
- Elective CTV
  - PTV margin

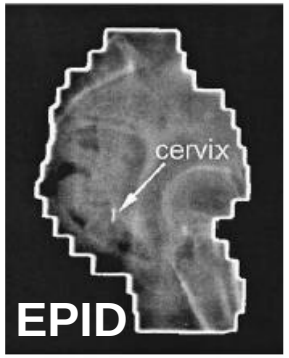
- Role of on-board imaging?



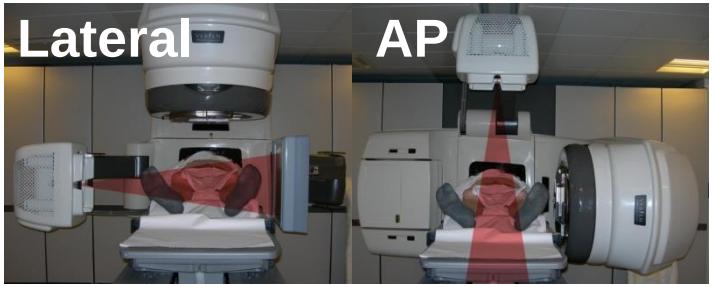
IGRT methods

- **EPID (Electronic Portal Imaging Device)**
  - **MV**
  - **2D**

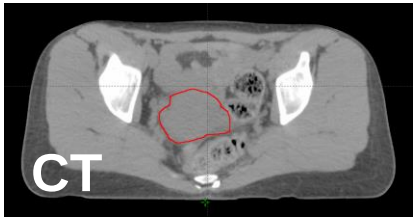


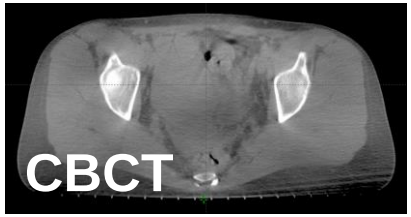


- **kV imaging (OBI – On Board Imaging)**
  - **kV**
  - **2D**



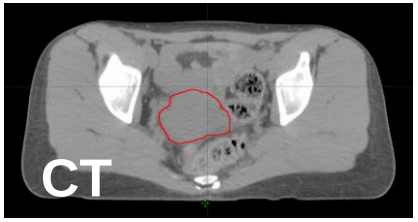
- **CBCT (Cone Beam CT) imaging**
  - **kV**
  - **3D**

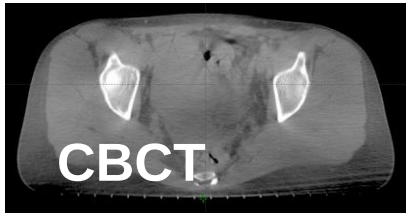




How to fuse CT planning scan to on-board imaging (CBCT, kV, EPID)?

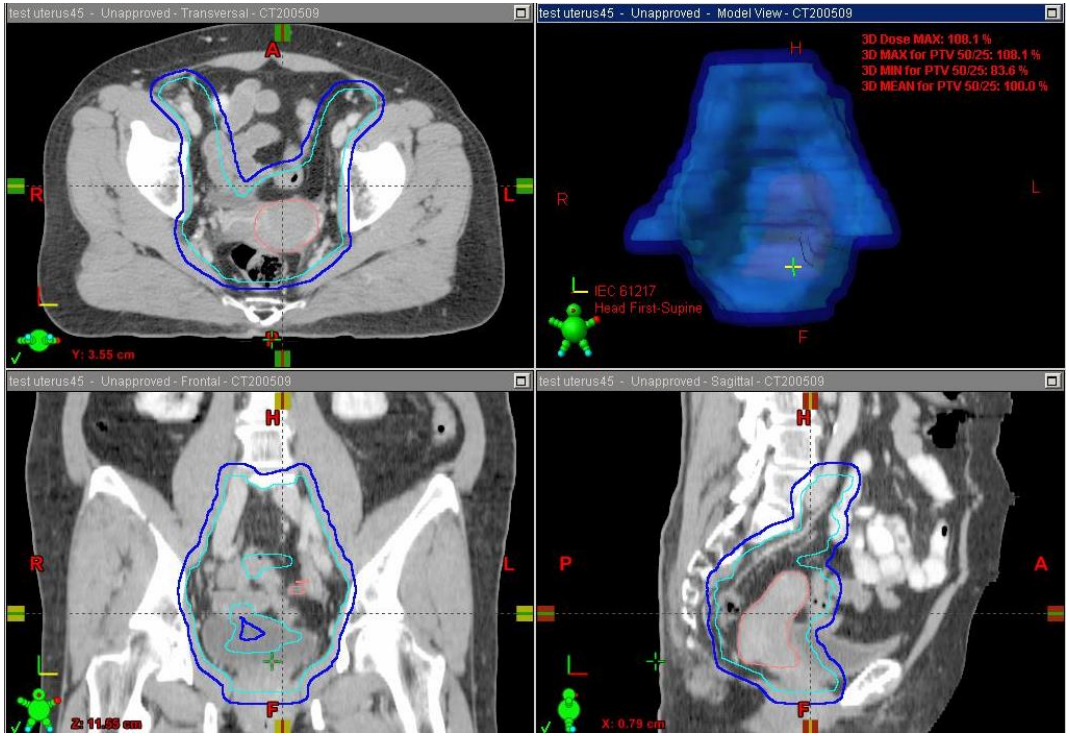
A. **Bony fusion**
B. **Fusion on cervix**
C. **Fusion on markers in cervix**





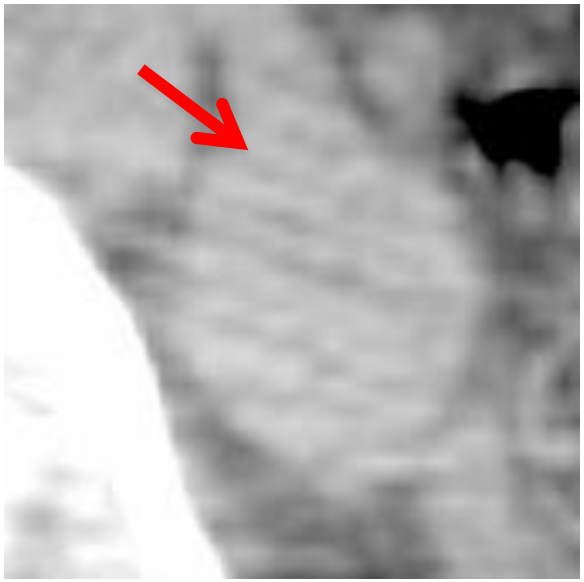
PTV elective target volume

- **Assumption:**
  - **Lymph nodes are in a fixed relation to bony anatomy**
  - **Bony registration aligns elective lymph node target**

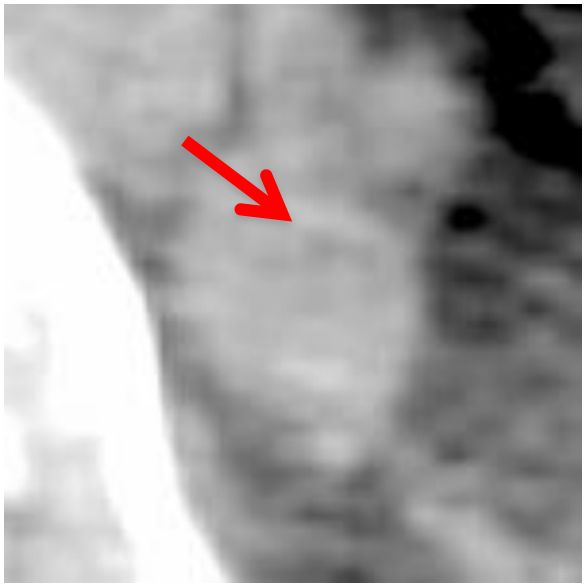


PTV pathological lymph nodes

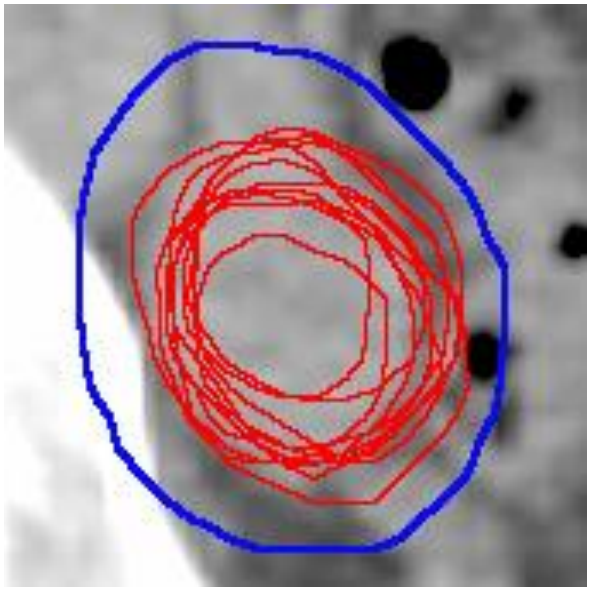
- **Assumption:**
  - **Lymph nodes are in a fixed relation to bony anatomy**
  - **Bony registration aligns pathological lymph node target**
- **Most often pathological lymph nodes shrink during RT**



CBCT 1st treatment



CBCT 24th treatment

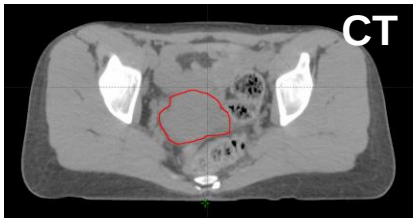


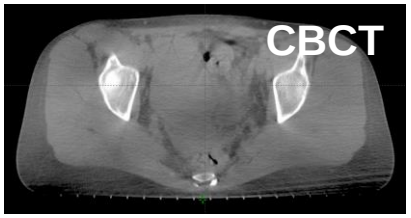
PTV (blue)
GTV on 10 CBCT (red)

Anne Ramlov, Radiother Oncol, in press

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

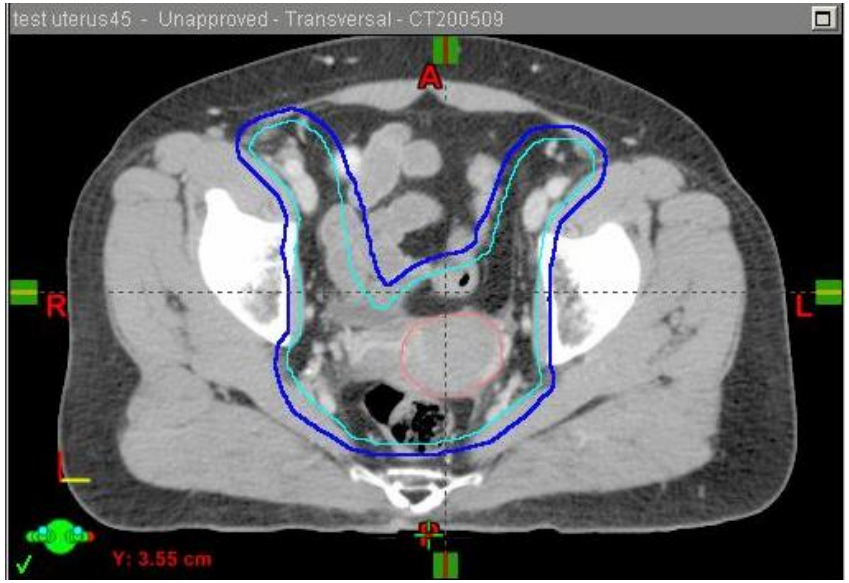
Variable	Vertical [mm]	Lateral [mm]	Longitudinal [mm]
Mean (M)	0,4	2,7	0,4
Σ	3,6	2,9	2,6
σ	3,6	3,2	2,4
Margin*	11,6	9,6	8,2

*Van Herk formalism: ***2,5*Σ+0,7*σ***
Semin Radiat Oncol 2004; 14:52-64

L.Laursen, RO 105 (2012) 220–225

Which PTV margin do you apply for CTV-E?

A. ≤5 mm
B. 6-9 mm
C. ≥10 mm



Do you think it is worthwhile to implement daily IGRT and decrease margin from 7-10mm to 5mm?

A. It is too many ressources to implement daily IGRT
B. It will not have impact on morbidity
C. 5mm PTV margin is not safe for target coverage
D. PTV margin reduction to 5mm is worthwhile

Why does the margin matter?

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

r

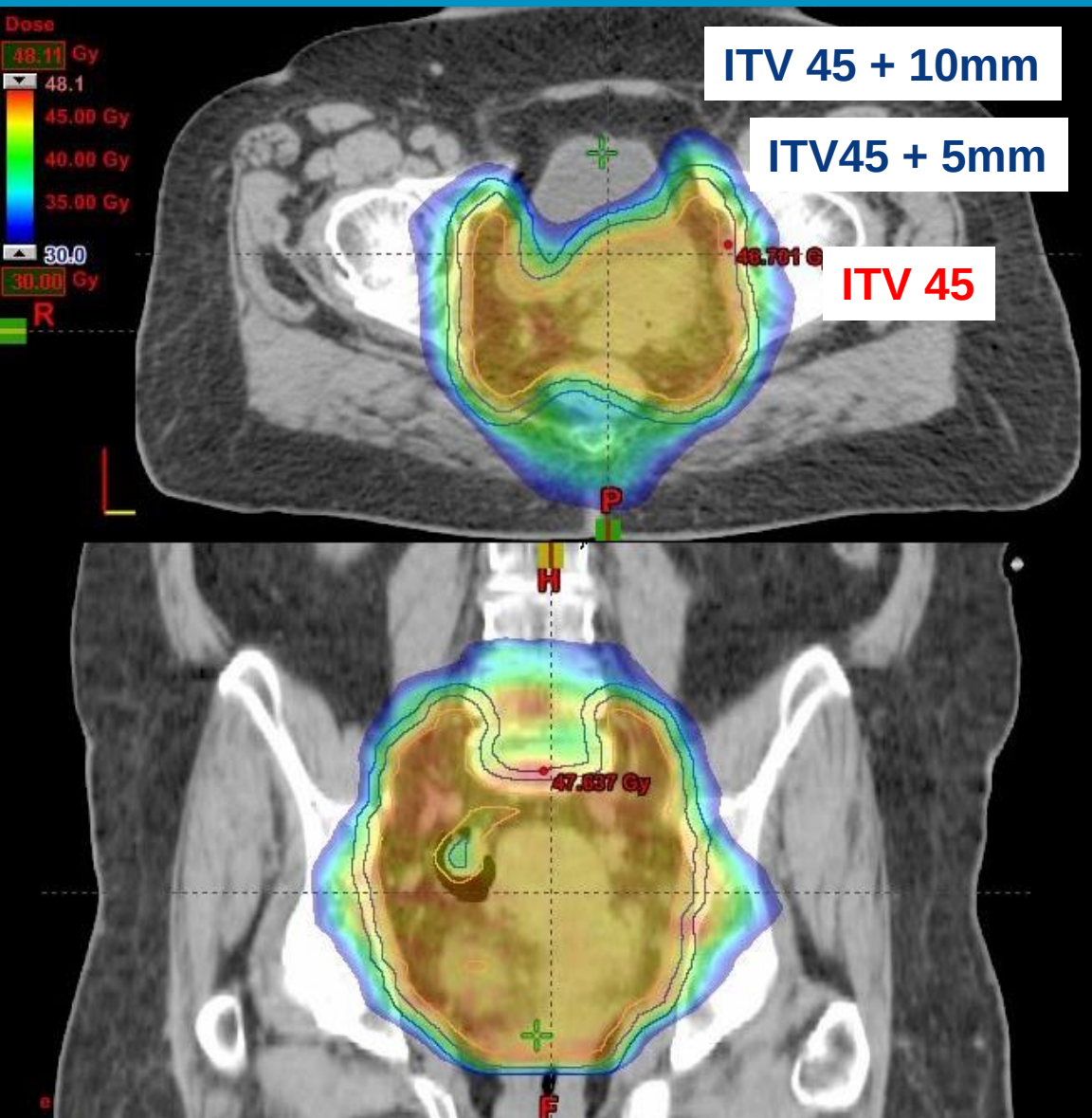
$\downarrow$

πr^2

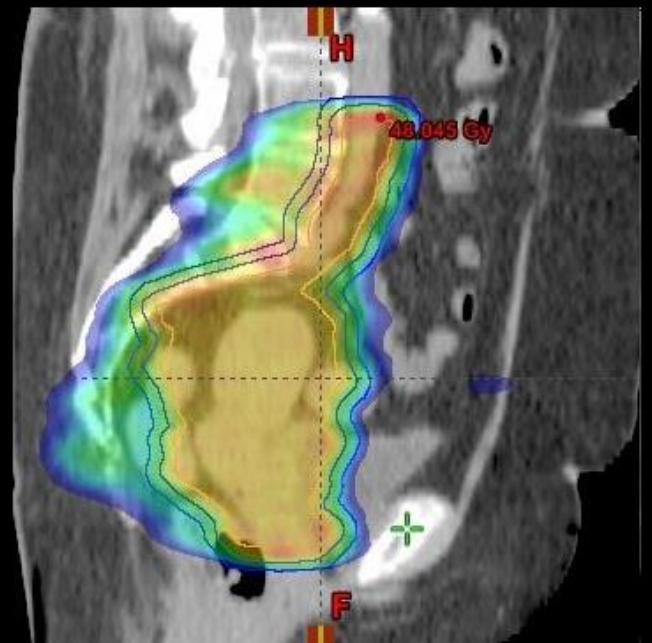
$\downarrow$

$4/3\pi r^3$

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

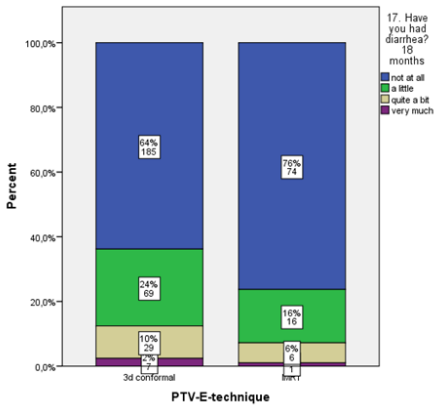


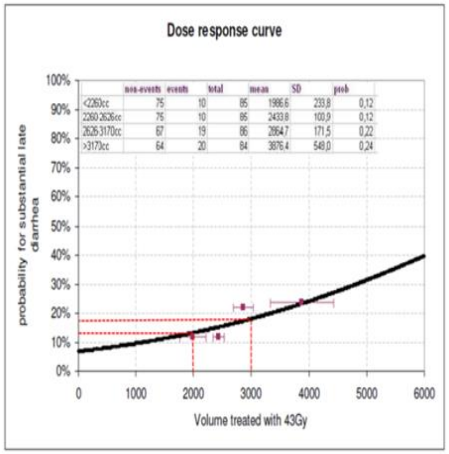
ITV 45	ITV 45 + 5mm	ITV 45 + 10mm
1000 cc	1500 cc	2000 cc



Is it important to reduce irradiated volume?

- **Evidence that bowel irradiation is related with acute morbidity**
- **Evidence that bowel irradiation is related with late morbidity**





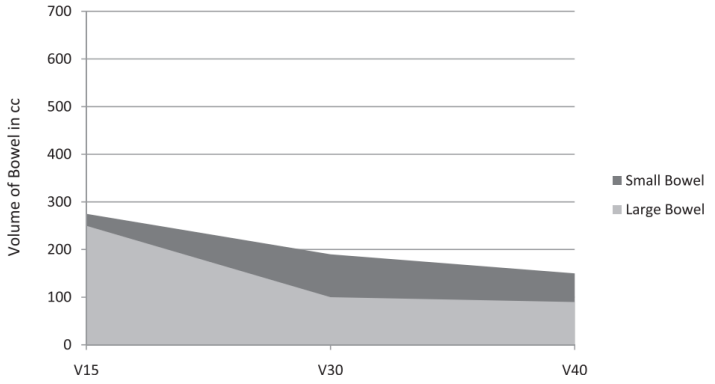
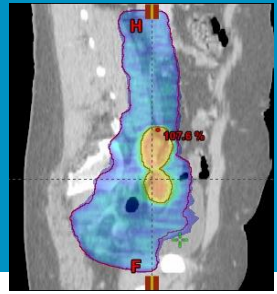


Fig. 1. Recommended dose–volume histogram. Restricting small bowel and large bowel volume doses within the recommended area under curve can restrict late bowel toxicity to within 5%.

Preliminary EMBRACE data

Chopra S, IJROBP, 88, 630-635, 2014

EMBRACE I, EMBRACE II and AROI practice: EBRT volume (V43Gy)



Elective irrad.	Pelvic	Para-aortic
V43 (cc) EMBRACE I	~ 2500 cm^3	~ 3000 cm^3
CTV vol (cc)	~ 1000 cm^3	~ 1500 cm^3
PTV vol (cc) 5mm margin	~ 1500 cm^3	~ 2000 cm^3
V43Gy (cc) EMBRACE II	~ 1500 cm^3	~ 2000 cm^3

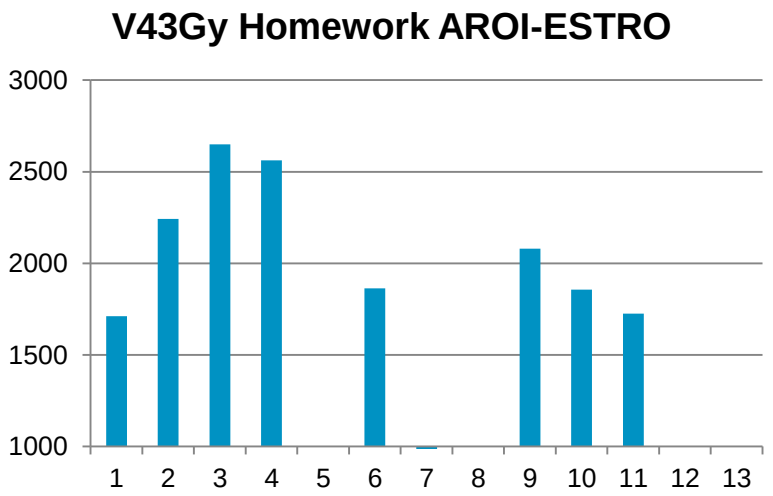
Nodal boost	Pelvic
V57 (cc) EMBRACE I	160 cm^3
CTV-N vol (cc)	10cc per node
PTV-N vol (cc) 5mm margin	30cc per node
V50Gy (cc) EMBRACE II	120 cm^3

Change of practice: EMBRACE I → EMBRACE II

CRT → IMRT : ↘ 500cm^3 (V43)

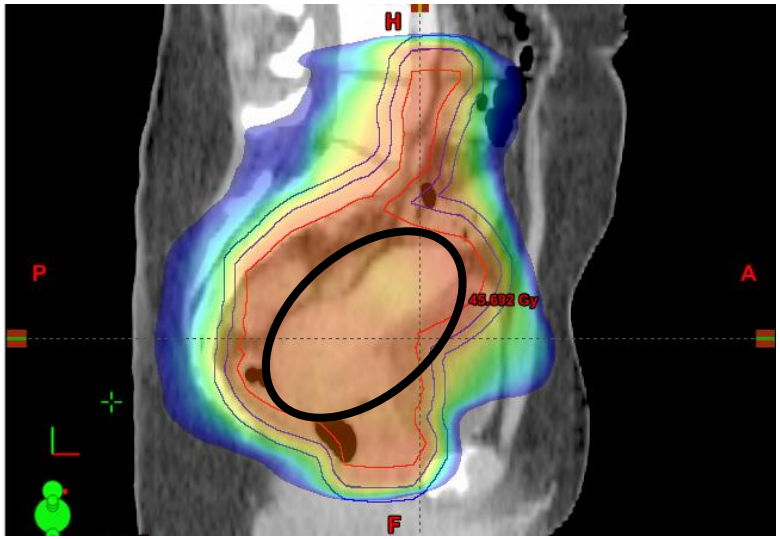
50Gy → 45Gy : ↘ 400cm^3 (V43)

xmm → 5mm : ↘ x cm^3 (V43)



Which total margin (ITV+PTV) is appropriate for the mobile primary tumour related CTV (GTV+cervix+uterus)?

A. 5 mm
B. 10 mm
C. 15 mm
D. 20mm
E. >20mm



Motion and dose – primary target

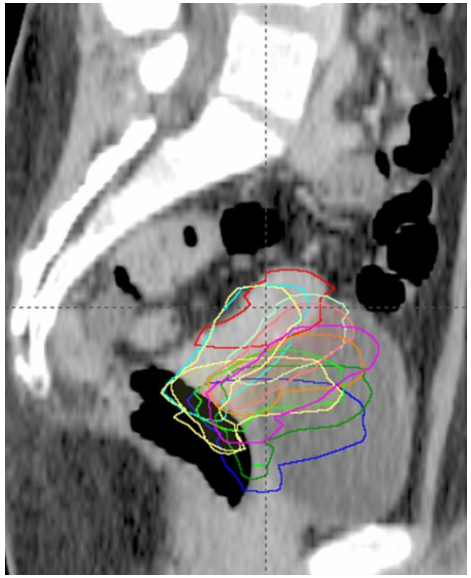
- **Jadon et al. A systematic review of organ motion and image-guided strategies in external beam radiotherapy for cervical cancer. Clin Oncol (R Coll Radiol). 2014 Apr;26(4):185-96**
  - **39 relevant studies**
  - **Patient specific motion: 5-40mm**
  - **Population based margins would be large (up to 40mm)**

- **Most studies evaluate geometry**
- **Few studies evaluate coverage (e.g. V95%)**
- **1 study evaluates dosimetric impact (D98)**

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

Patient case:

- 45/25fx EBRT
- 1.5cm CTV-PTV margin
- 50% of fractions: uterus outside PTV
- 40Gy EQD2 BT prescribed to CTV_{HR}



A. 20Gy

B. 30Gy

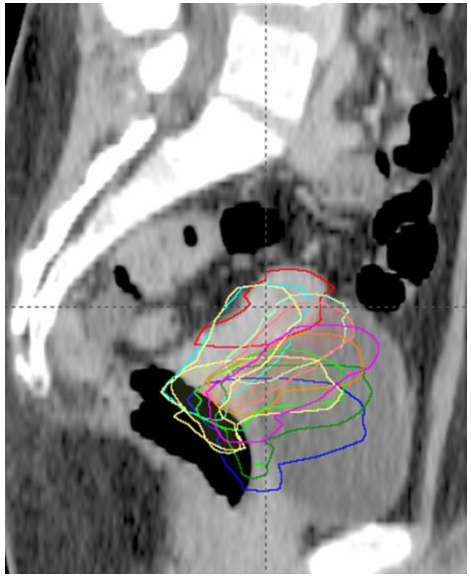
C. 35Gy

D. >40Gy

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

Accumulated doses

- Daily image guidance
- IMRT PTV margins of
  - 5mm
  - 20mm
- Shortcomings:
  - Uterus dose? (CTV includes upper uterus only in case of myometrium invasion)
  - Only 20 patients

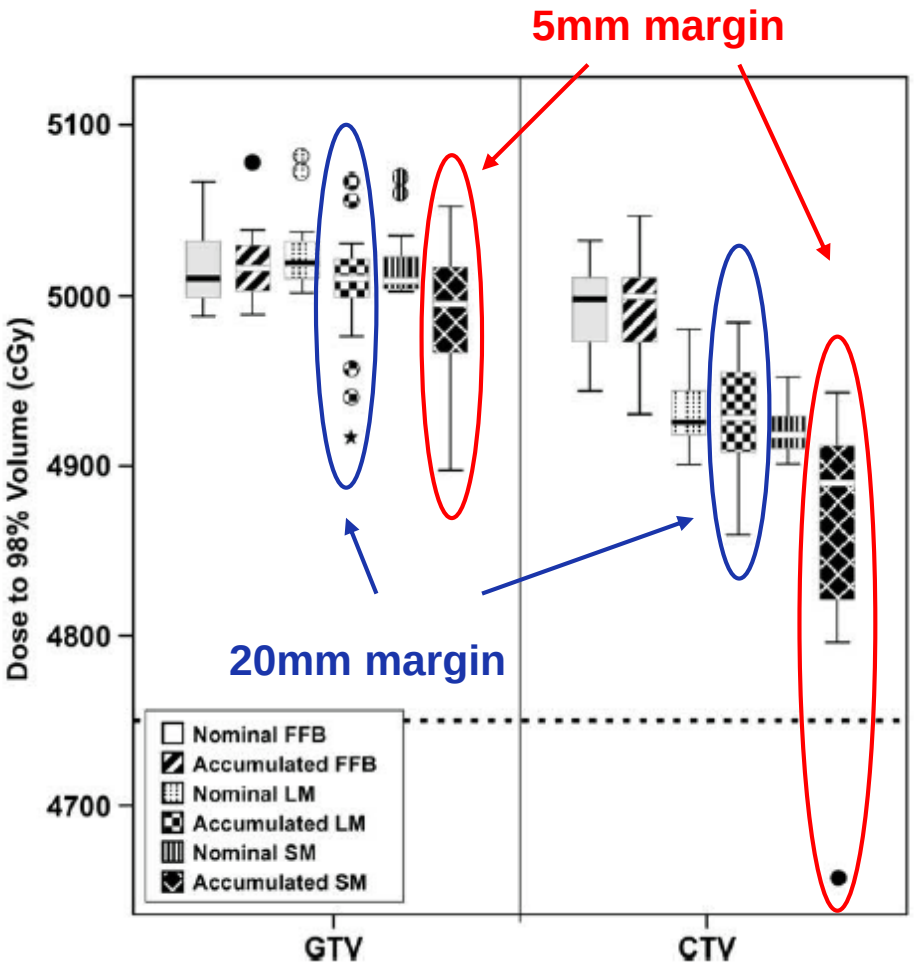
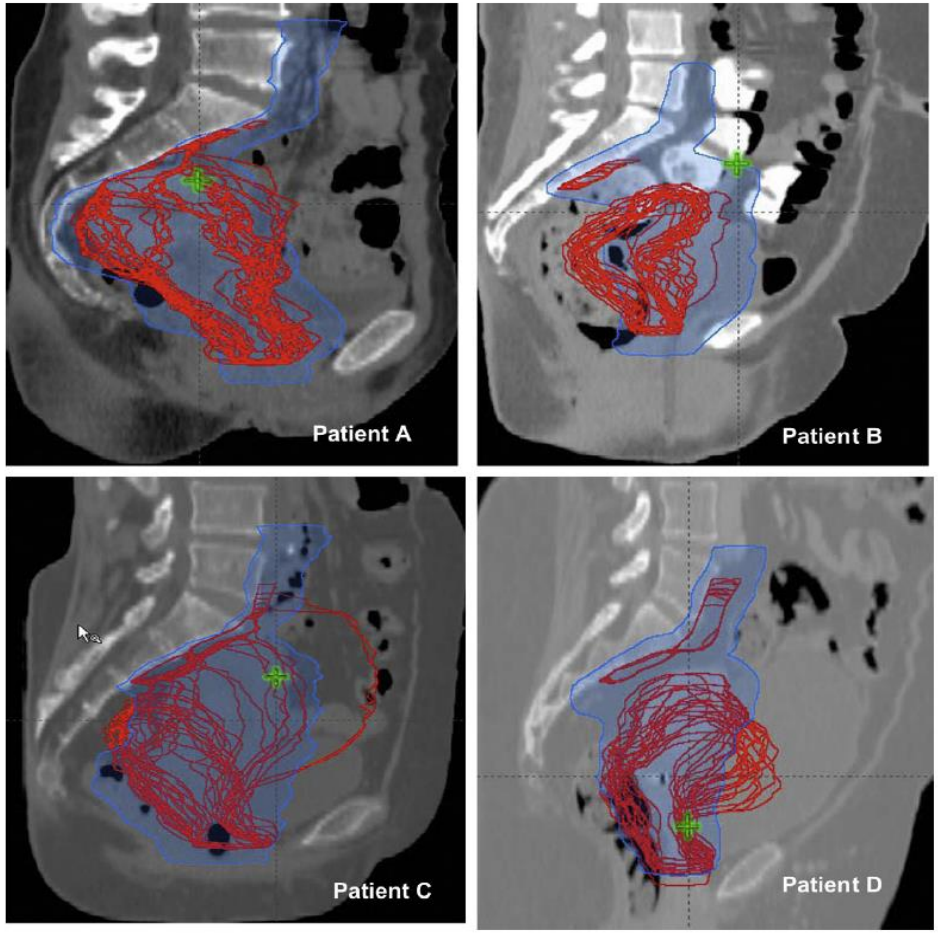


Fig. 4. Box plots of nominal and accumulated dose to 98% of gross tumor volume and primary tumor clinical target volume for four-field box (FFB), large-margin (LM), and small-margin (SM) plans.

Lim et al, Pelvic radiotherapy for cancer of the cervix: Is what you plan actually what you deliver?, IJROBP 2009

Which of these motion patterns are of most concern for local control?



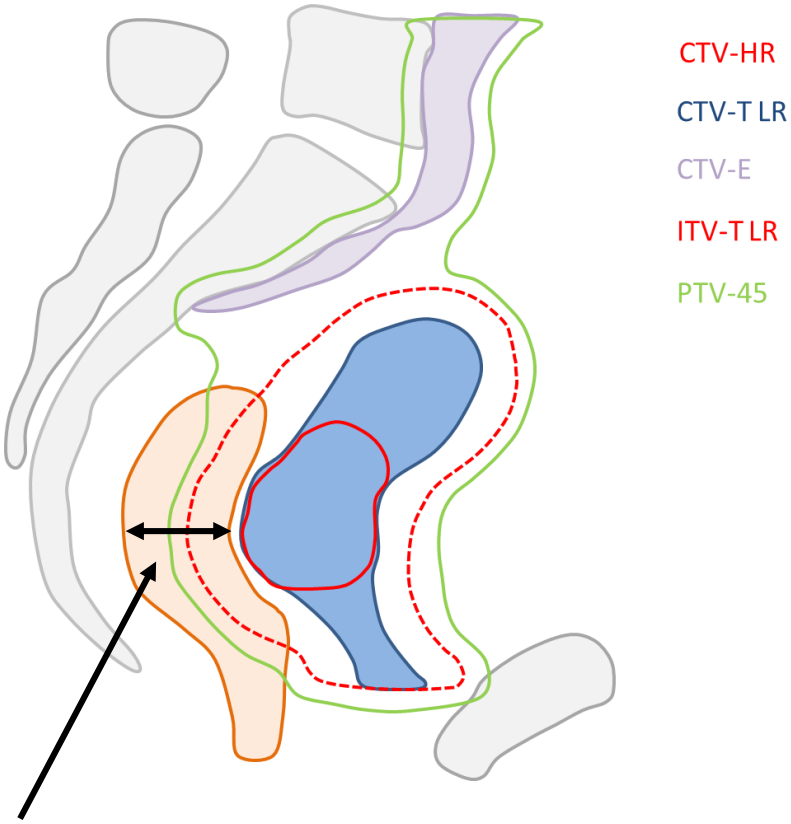
A. A
B. B
C. C
D. D

Tyagi et al, DAILY ONLINE CONE BEAM COMPUTED TOMOGRAPHY TO ASSESS INTERFRACTIONAL MOTION IN PATIENTS WITH INTACT CERVICAL CANCER, IJROBP 2011

ITV-T LR and PTV-T LR

Standard:

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



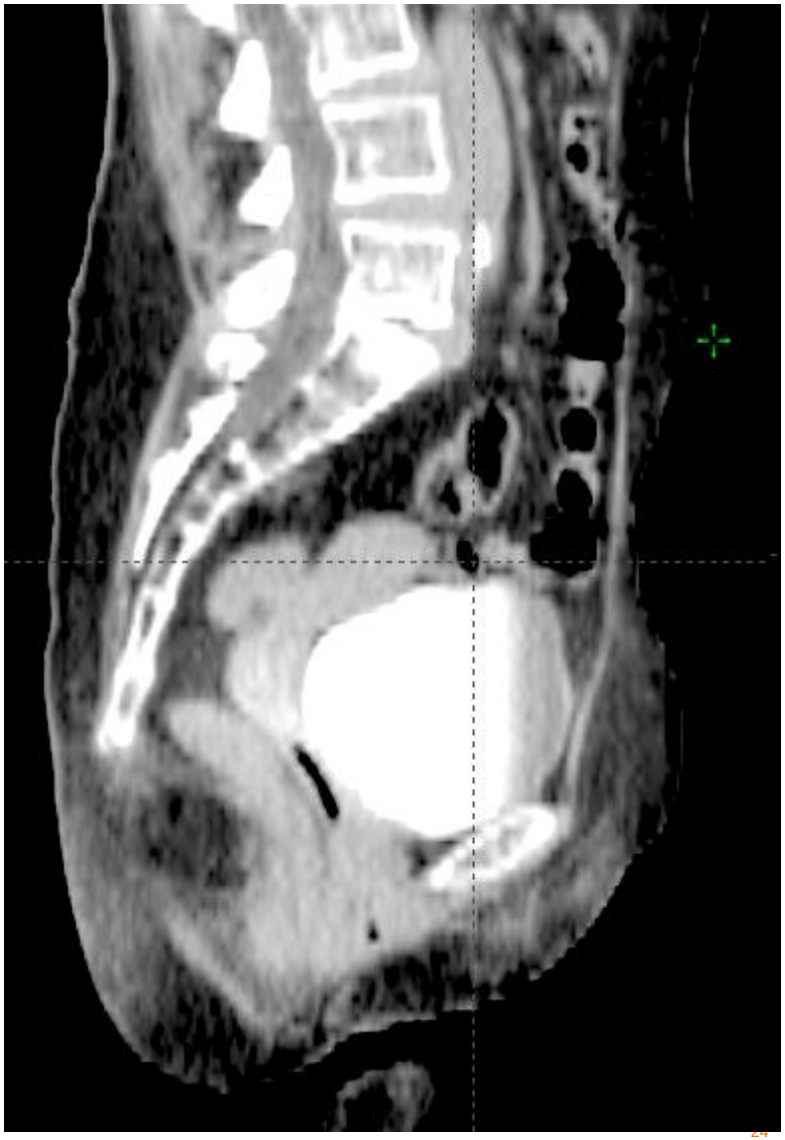
Maximum rectal filling at treatment planning scan: 40mm

Bladder filling strategy in your department?

A. No bladder filling protocol
B. Patient to void before each fraction for reproducible bladder filling
C. Instruct patients to keep full bladder at treatment
D. Specific drinking protocol

Bladder filling and bowel volume

- **Full bladder versus empty bladder decreases volume of bowel irradiated to a significant dose**
- **Examples drinking protocol:**
  - **Instruction of patients to keep full bladder**
  - **Aarhus University Hospital: 450-500ml 1 hour prior to planning CT scan and to each treatment**
  - **Tata Memorial: 750-1000ml 30 minutes prior to planning CT and to each treatment**
- **Reproducibility of bladder filling?**
  - **Significant variation**
  - **Main purpose is to push bowel away!**

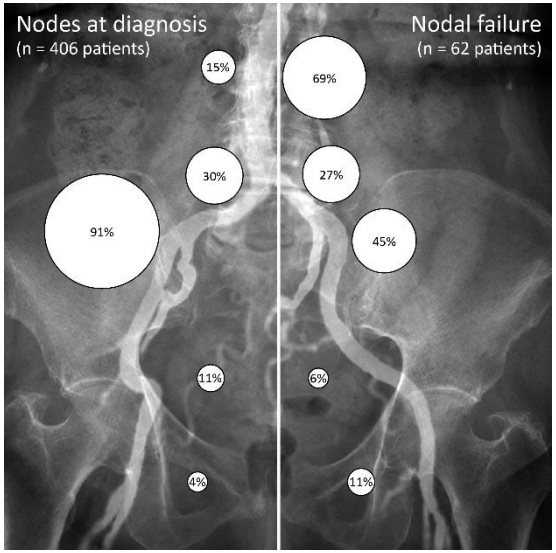


What has most impact on bowel dose?

A. **Bladder filling protocol**
B. **Reduction from 10 to 5mm CTV-E margin**
C. **Re-planning during radiotherapy to address tumour shinkage**

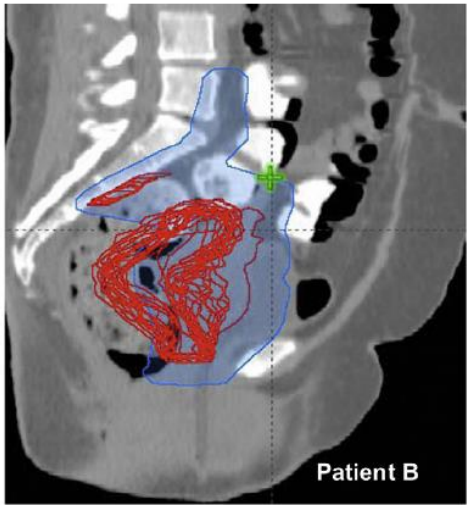
Take home message: nodal CTV

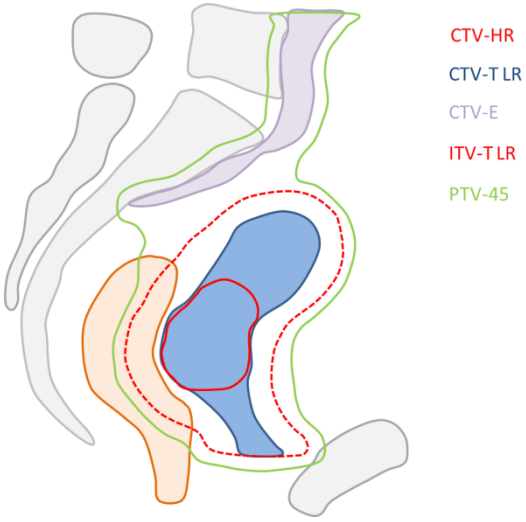
- **Margins add to considerable irradiation of normal tissue**
- **PTV margin for elective target volume:**
  - **7-10mm margin without daily image guidance**
  - **5mm margin with daily image guidance and bony fusion**
- **Potential in pelvic elective radiotherapy to reduce irradiated volume by 40%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



Take home message: primary CTV

- **Significant inter-fraction variations have been reported: 5-40mm**
- **Uninvolved uterus is not the most critical target**
- **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.**





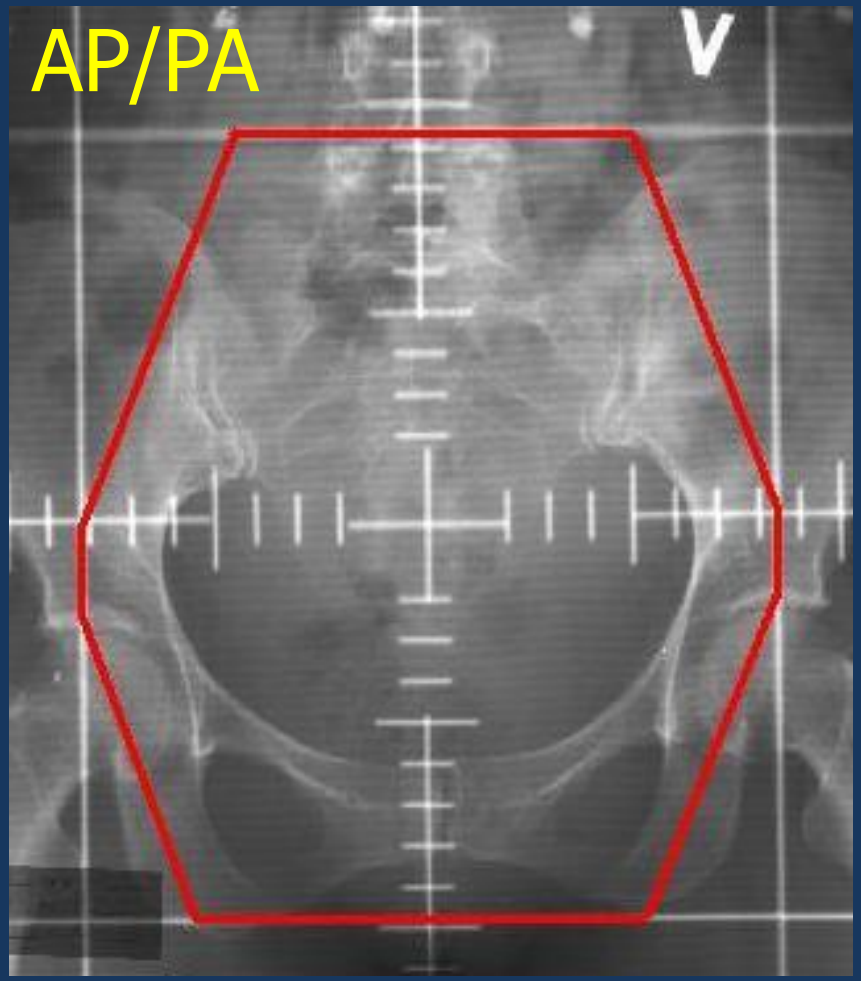
Treatment Techniques of EBRT for Cervical Cancer – physics aspects

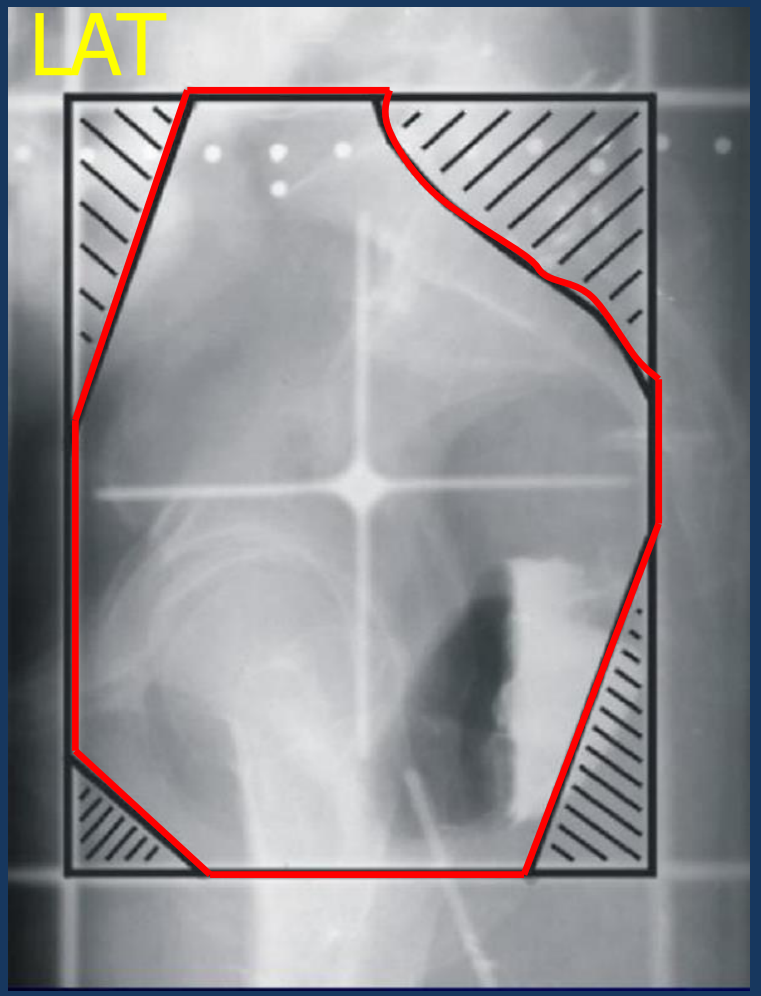
Jamema Swamidas
Medical physicist
Tata Memorial Hospital, Mumbai,
India

What kind of techniques do we have?

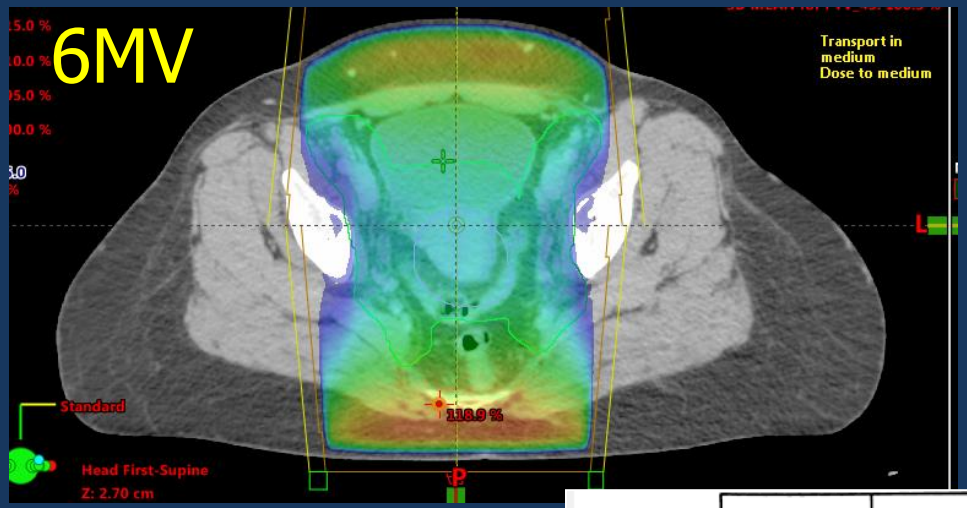
- AP-PA fields
- Four-field box techniques, X-ray based / CT based
- 3DCRT – 3 Dimensional Conformal Radiotherapy
- IMRT
- Rotational technique (VMAT) - FF and FFF
- Proton Therapy

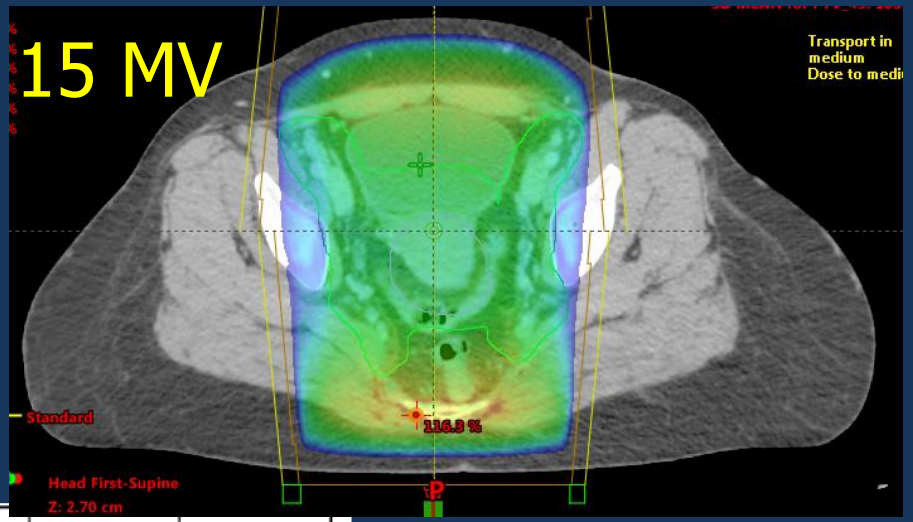
Based on X-ray imaging

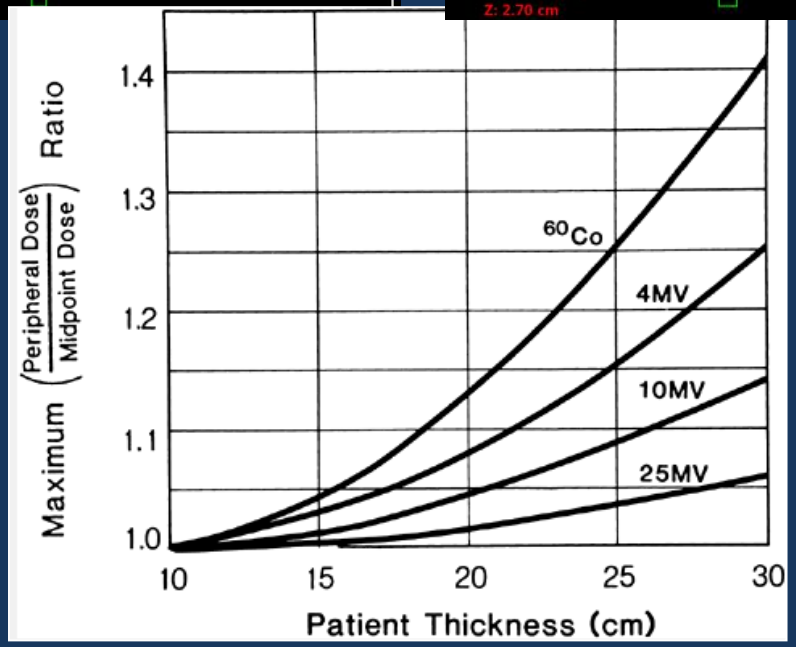




AP/PA 6 MV vs 15MV

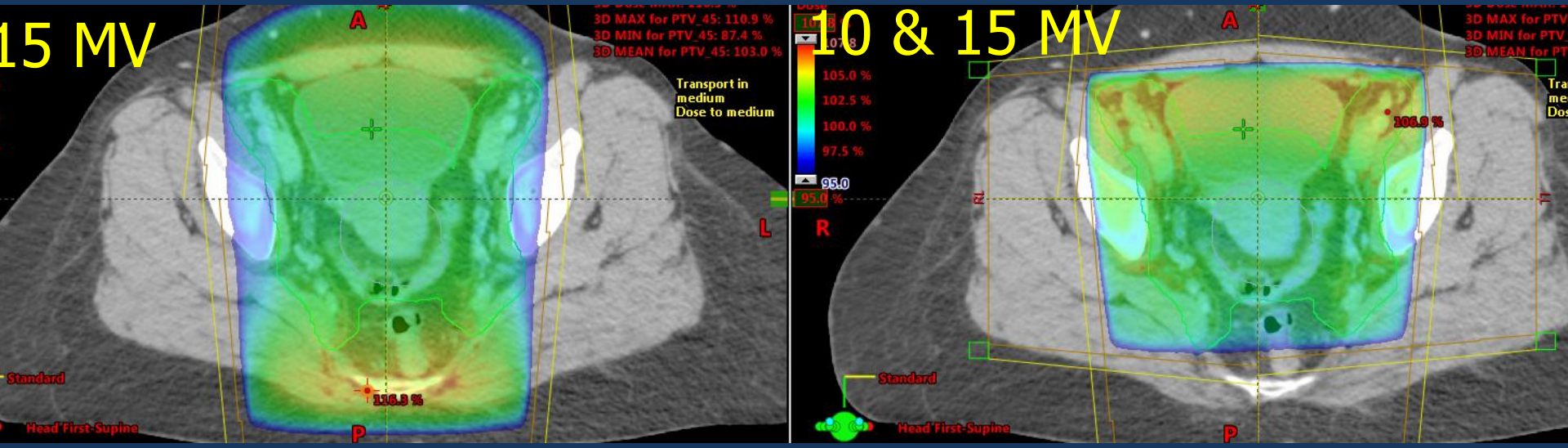






Khan 1994

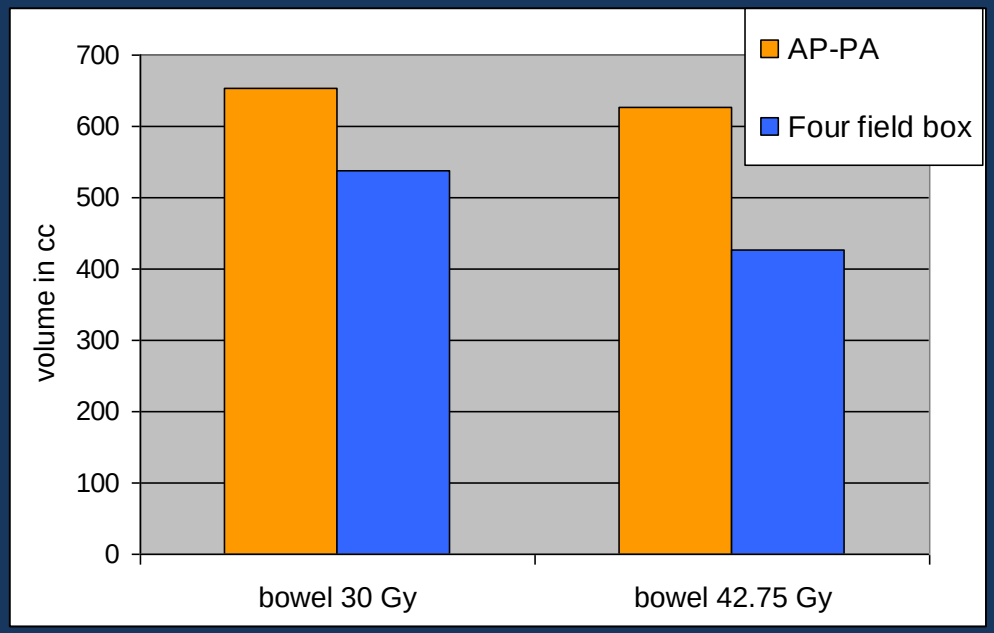
AP/PA vs 4F BOX (3DCRT)

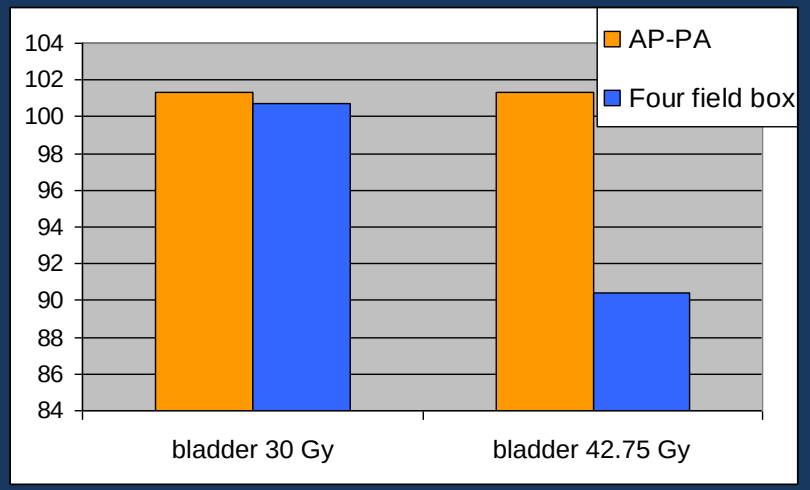


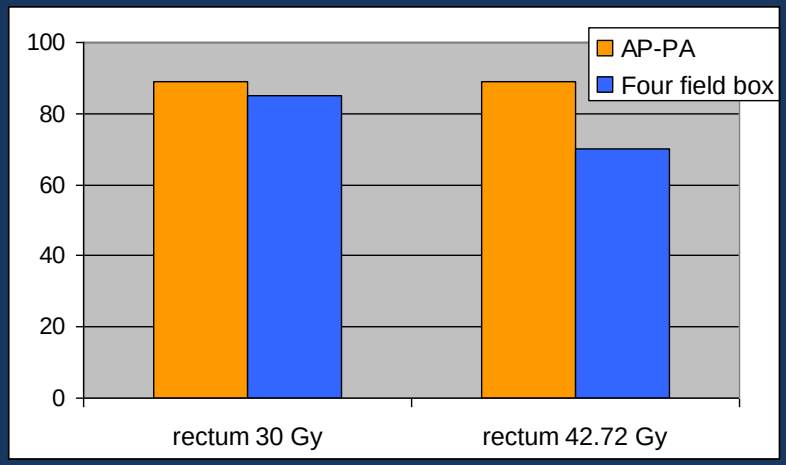
- Significant Organ sparing
- Improved conformity

AP/PA vs 4F BOX (3DCRT)

10 MV

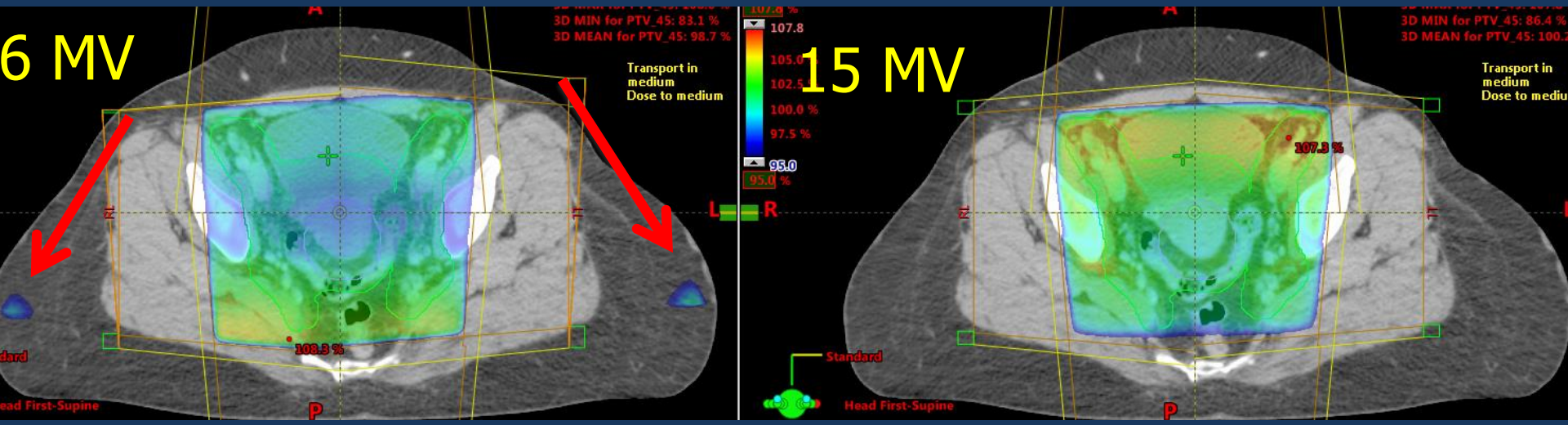






Van de Bunt et al 2006

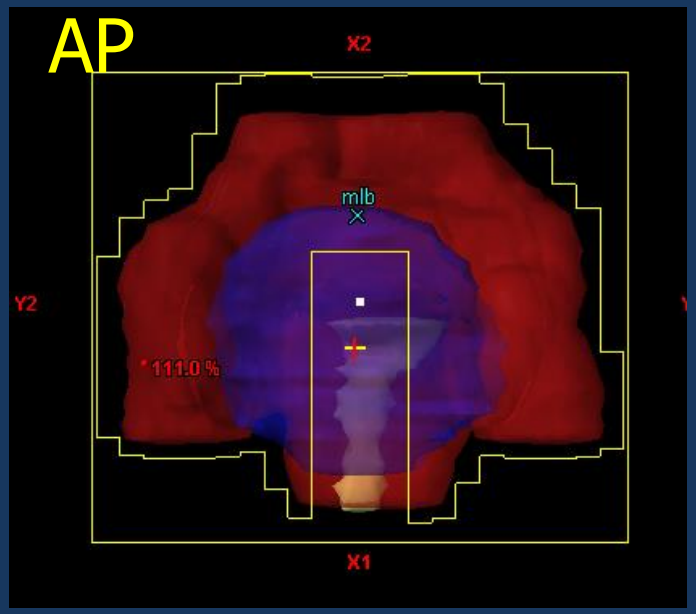
4F Box 6MV vs 15MV

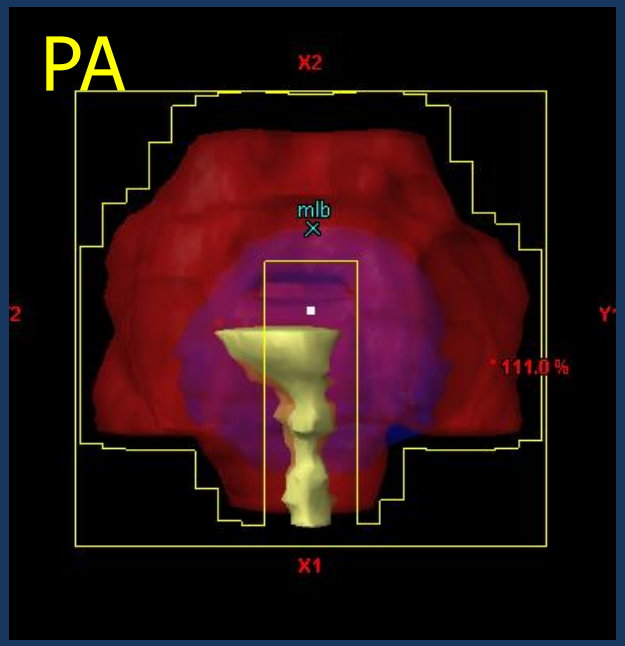


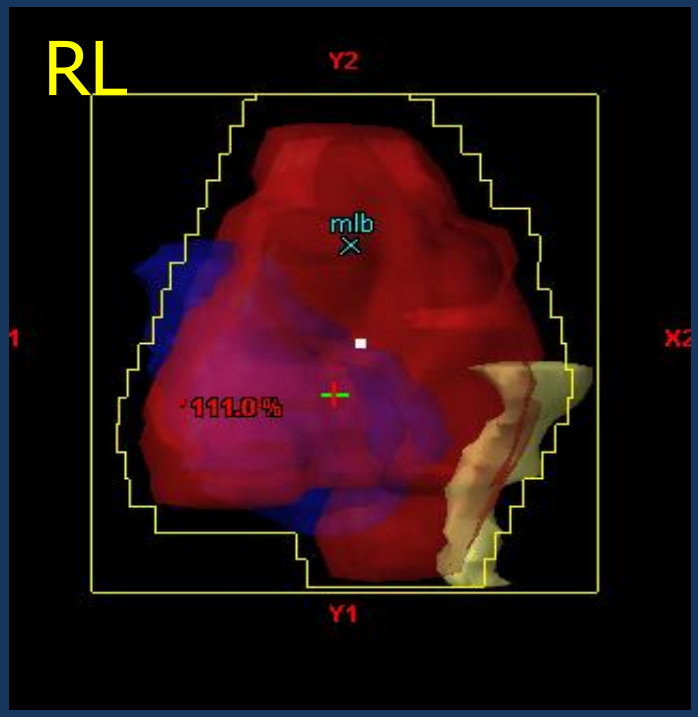
- Homogeneity in higher energy
- Dose (95%) spilling in muscles

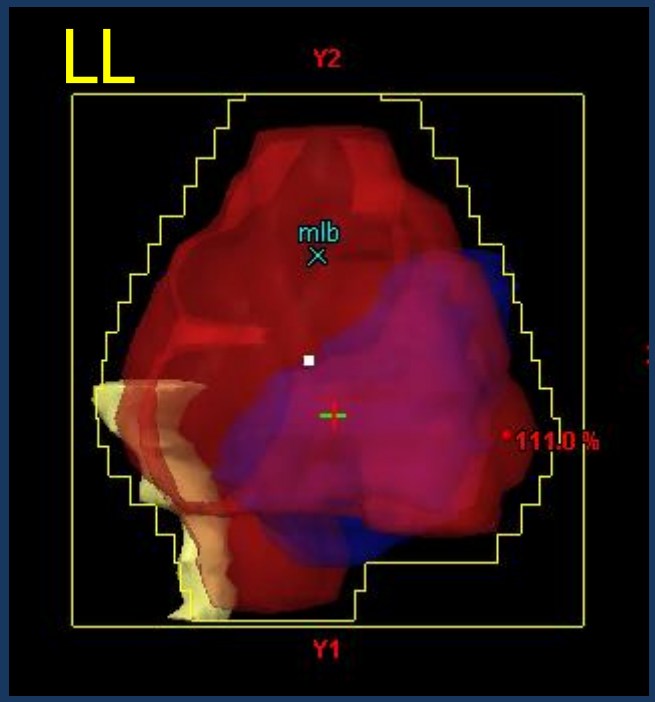
MLB (midline block) 3DCRT

- Central rectangular portion with an area 10 × 4 cm at isocenter
- Homogeneity around target for teletherapy and brachytherapy
- Thickness of 5.5 HVL
- The fall-off of dose between point A and point B is estimated by normalizing the point A dose value to 100%.


AP
X2
mlb
Y2
111.0 %
X1


PA
X2
mlb
111.0 %
X1


RL
Y2
mlb
111.0 %
Y1


LL
Y2
mlb
111.0 %
Y1

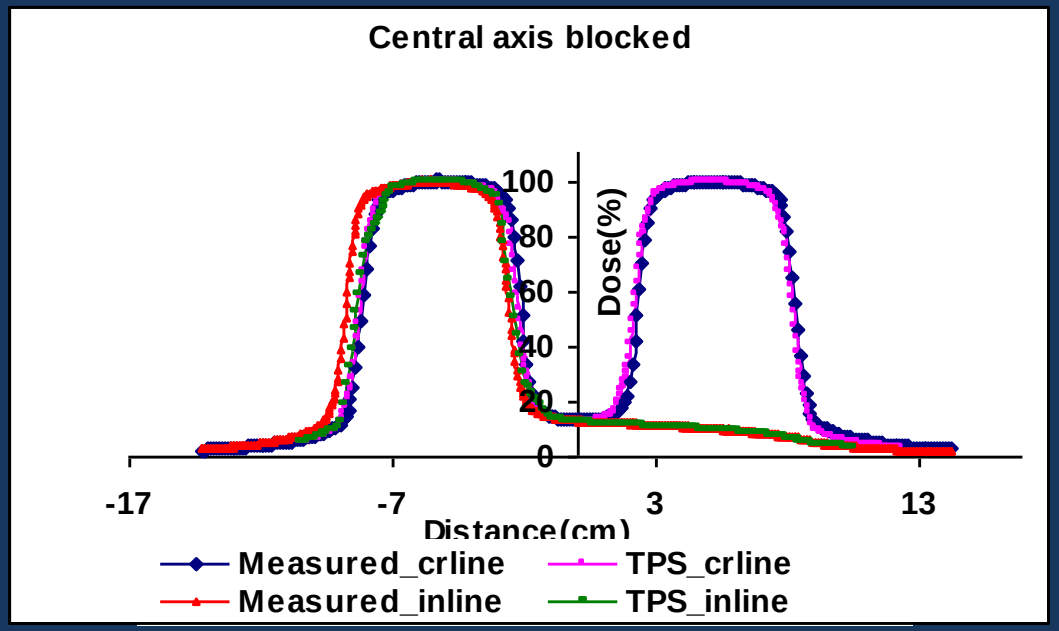
Mid Line Block

Normalization

- For corner shielding, normalization at the isocentre
- For Midline block- at a reference point

TPS modelling

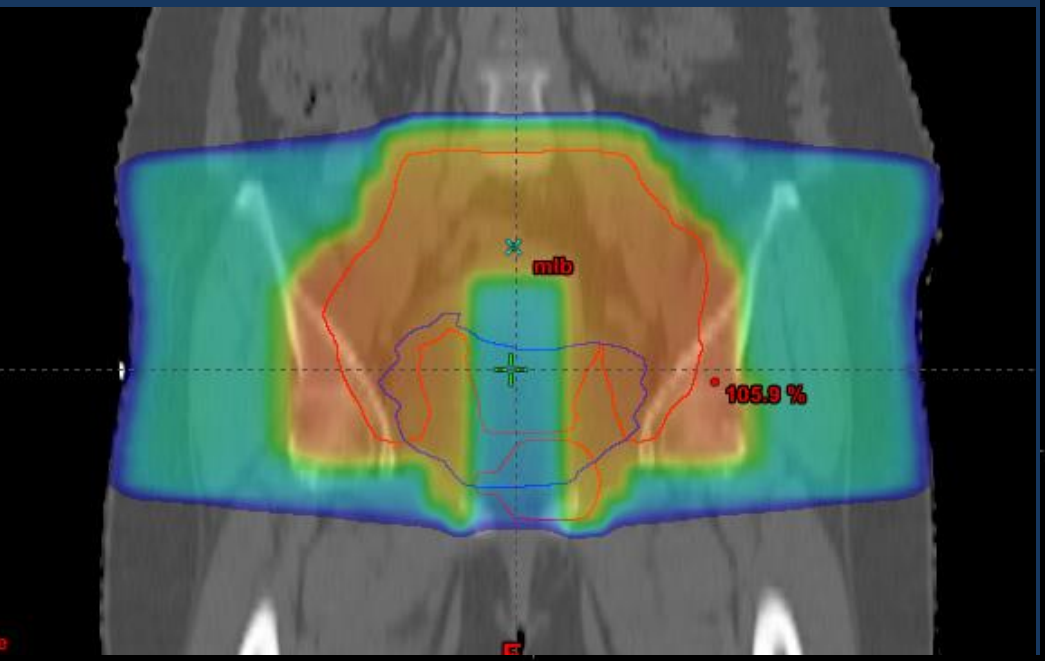
- Accurate modeling in TPS
- Central axis is blocked

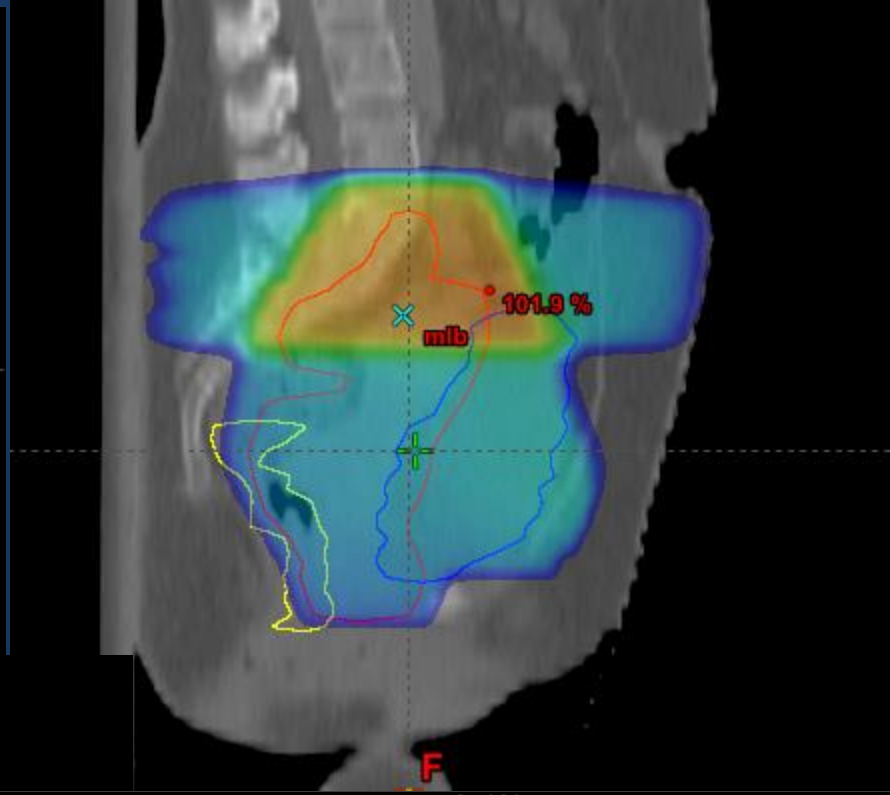


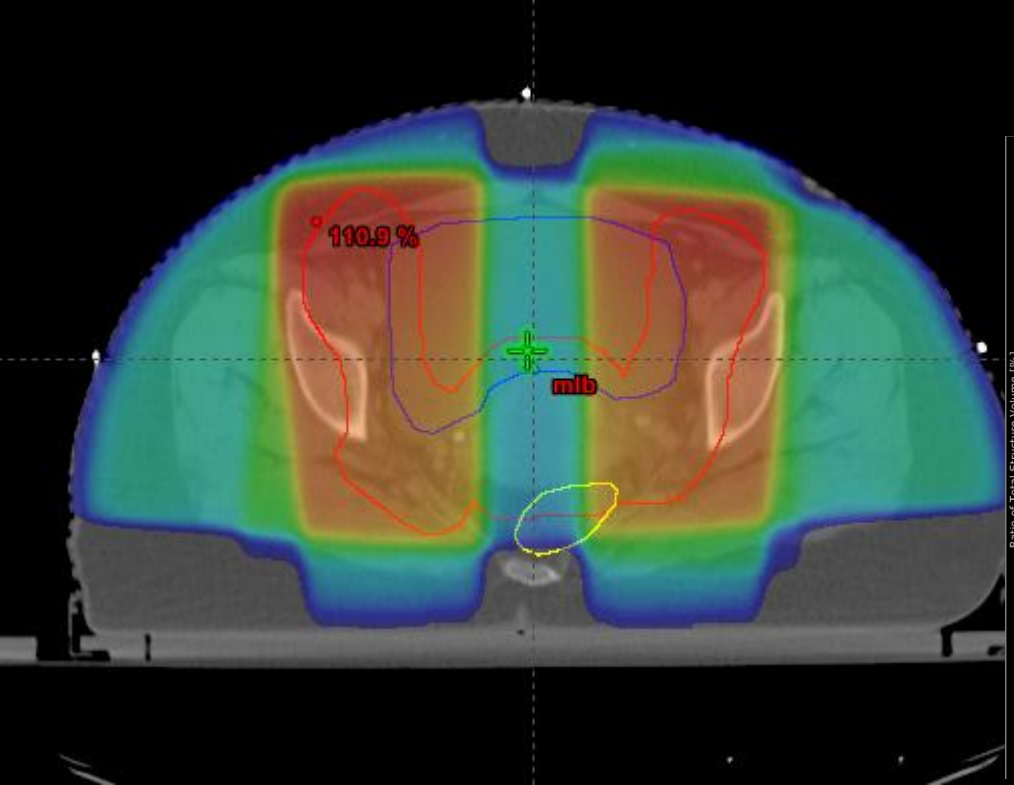
Swamidas et al, ACPSEM 2009

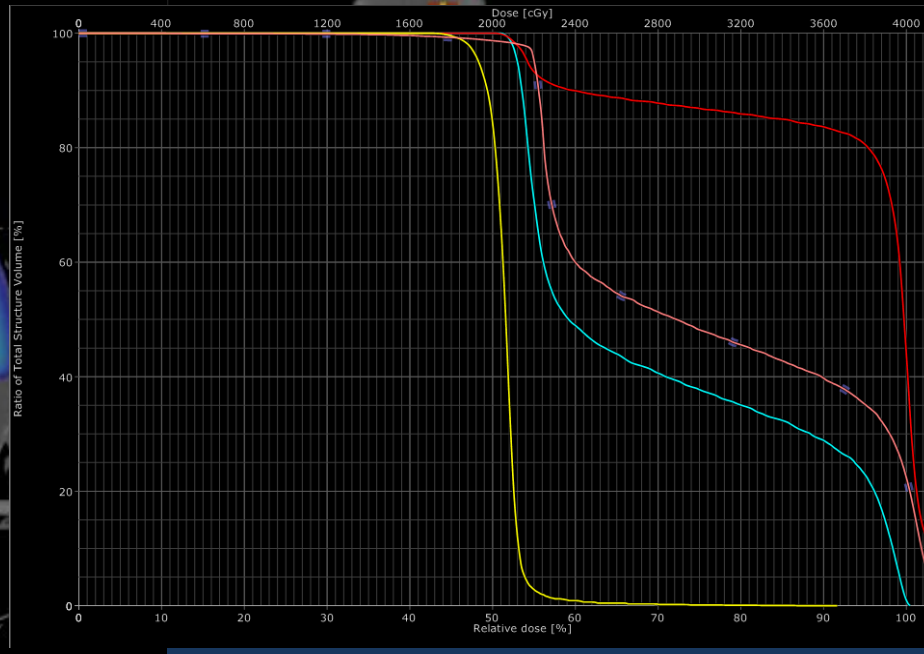
Normalization

Field	Normalized at Ref point	Normalized at isocentre (blocked)	% deviation
AP	53	97	**83%**
PA	65	118	**82%**
RT LAT	53	96	**81%**
LT LAT	64	116	**81%**

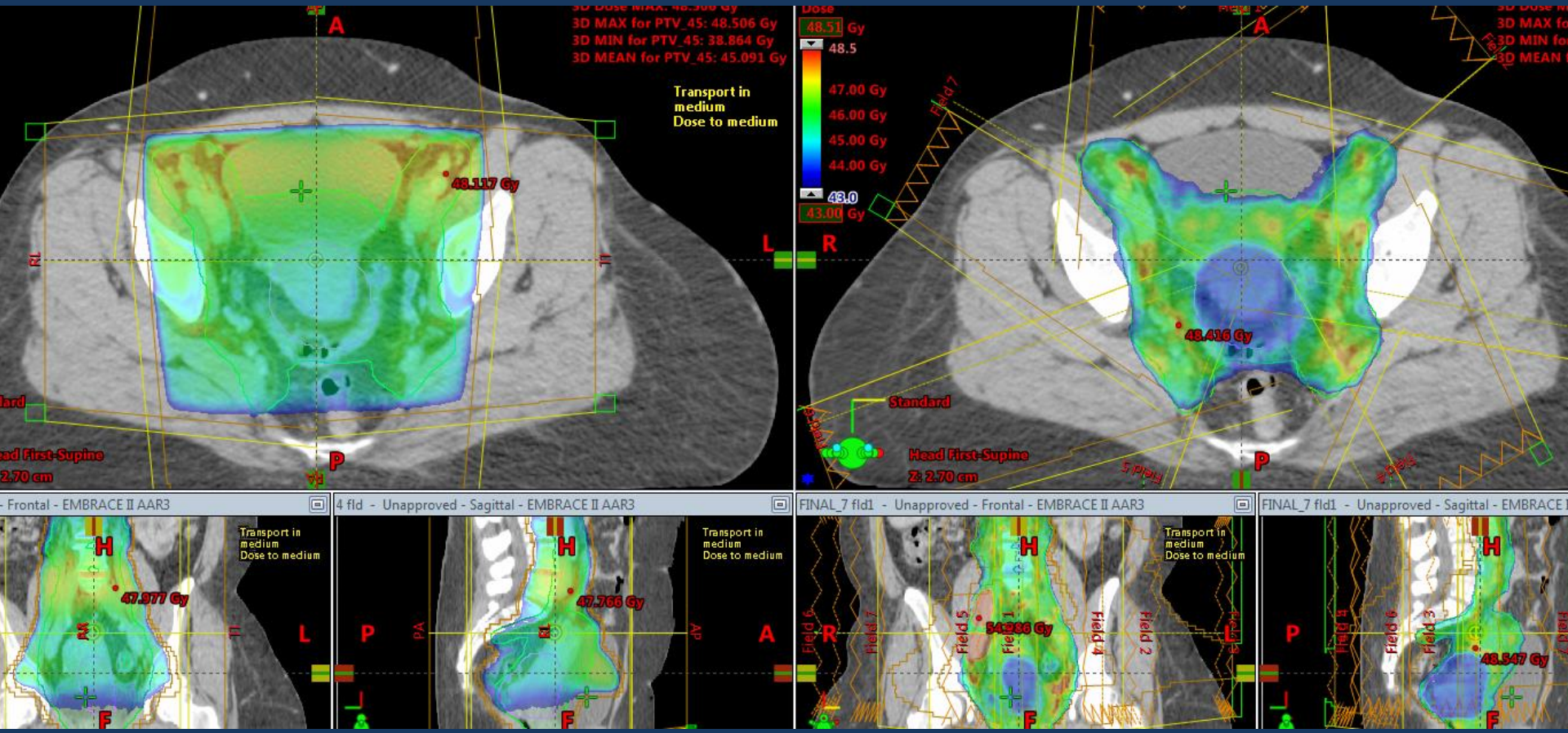

mlb
105.9 %


101.8 %
mlb
F


110.9 %
mlb

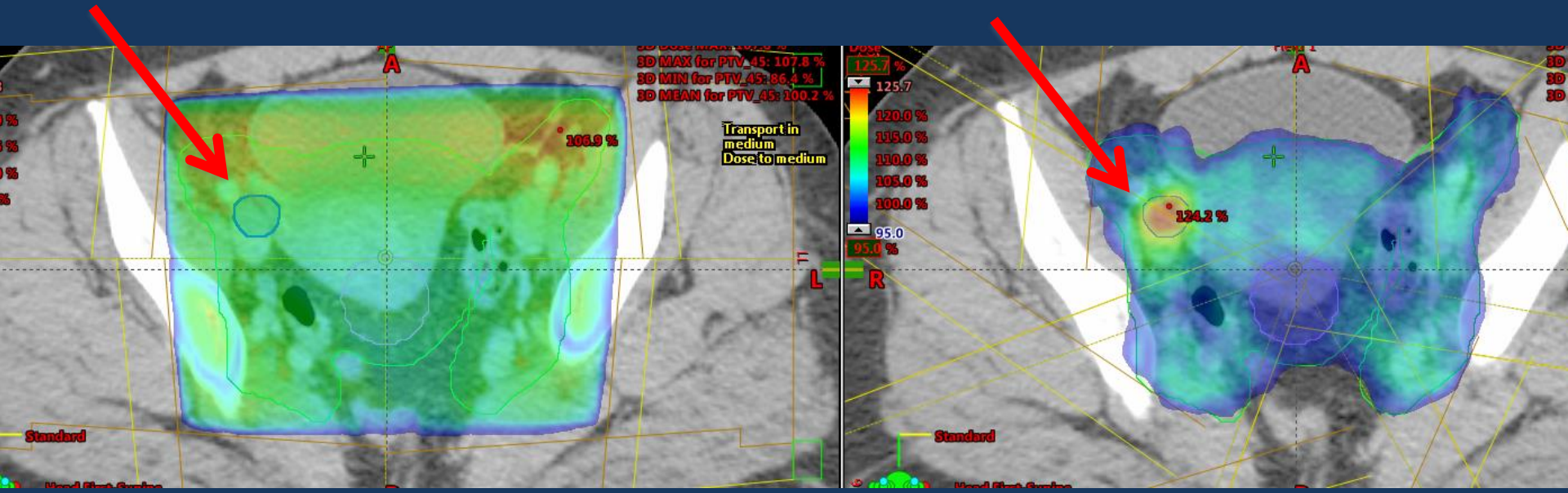

Dose [cGy]
0
400
800
1200
1600
2000
2400
2800
3200
3600
4000
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
Relative dose [%]

3DCRT vs IMRT



Significant Organ sparing

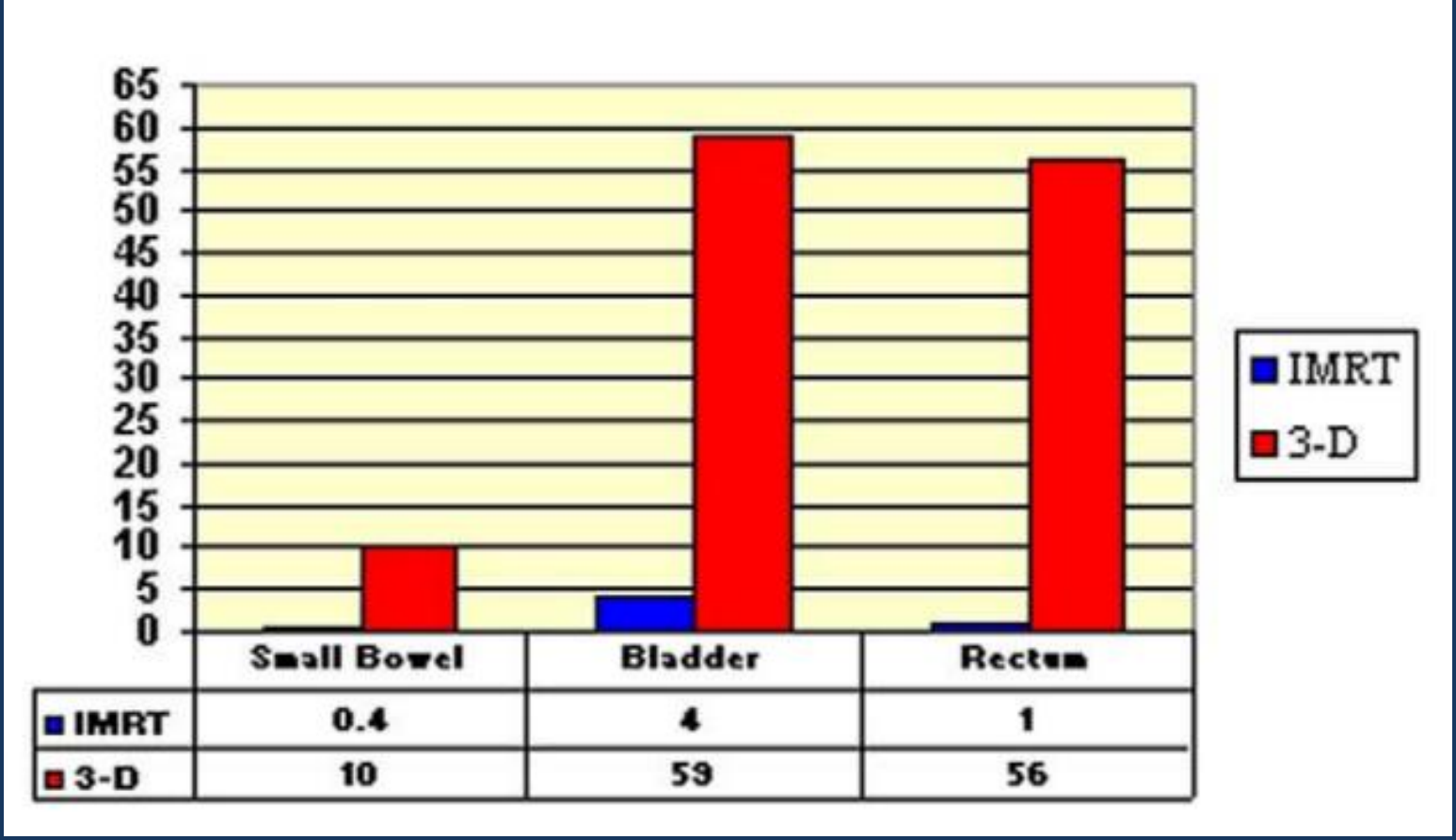
3DCRT vs IMRT



Simultaneous Integrated Boost

3D CRT vs IMRT

Percentage volume of tissues receiving doses 45 Gy.

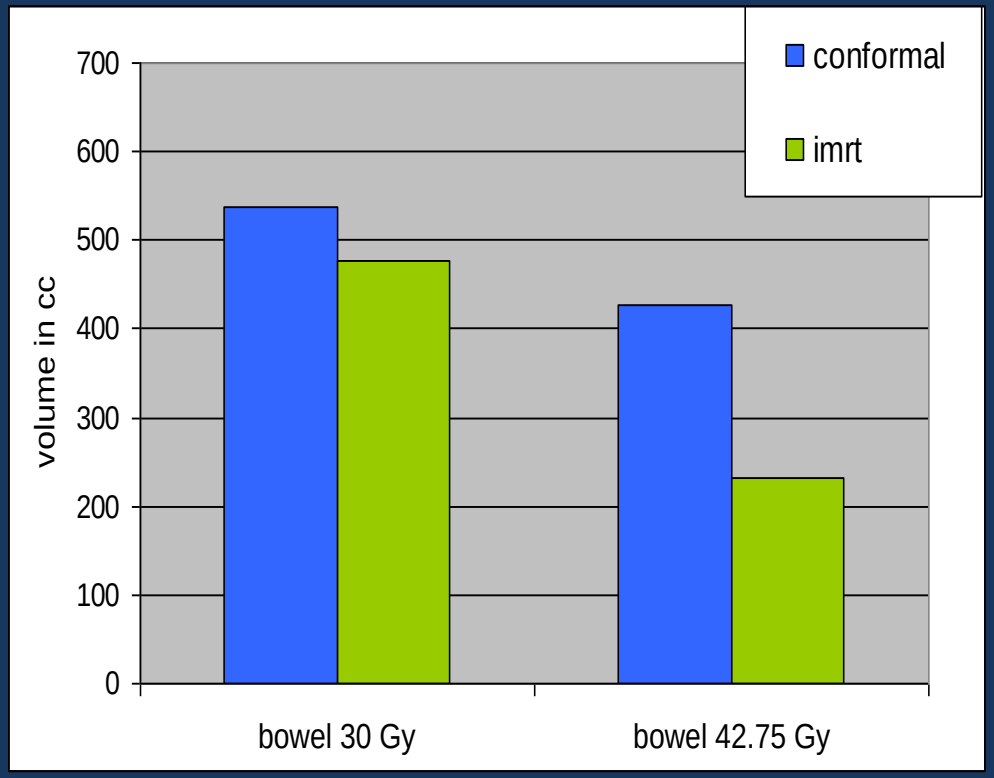


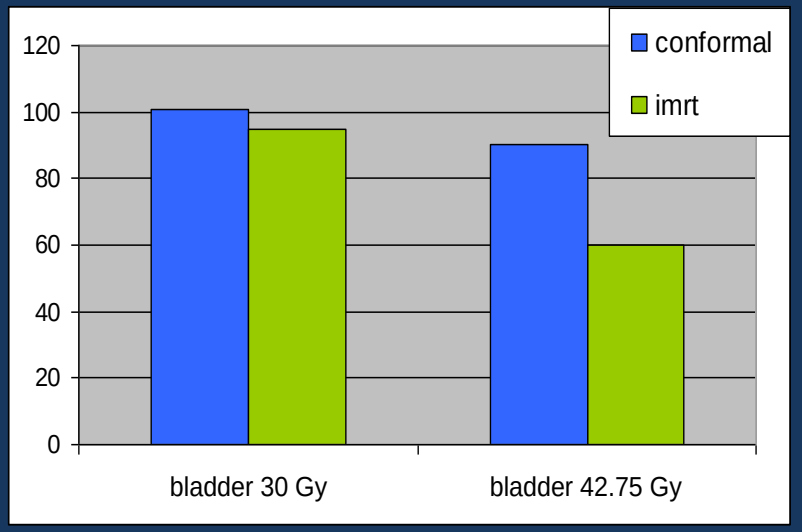
	Small Bowel	Bladder	Rectum
IMRT	0.4	4	1
3-D	10	59	56

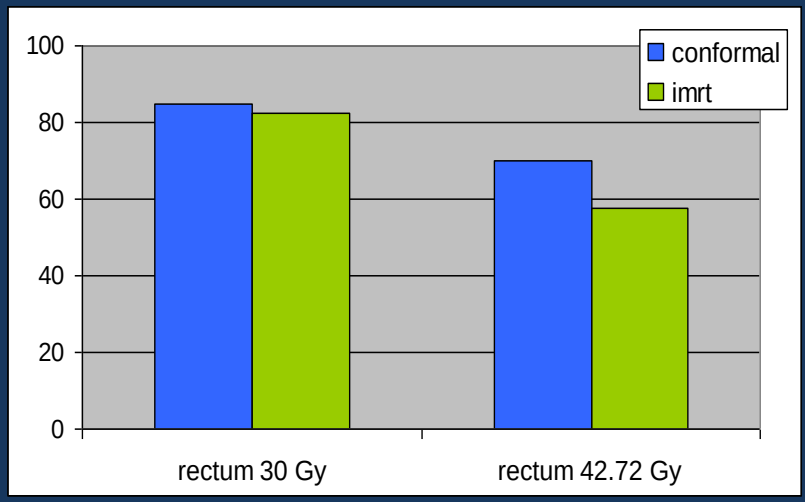
Heron et al, Gynaecologic oncology, 2002

3D CRT vs IMRT

14 patients with cervical cancer, IMRT: 7 beams, 10 MV





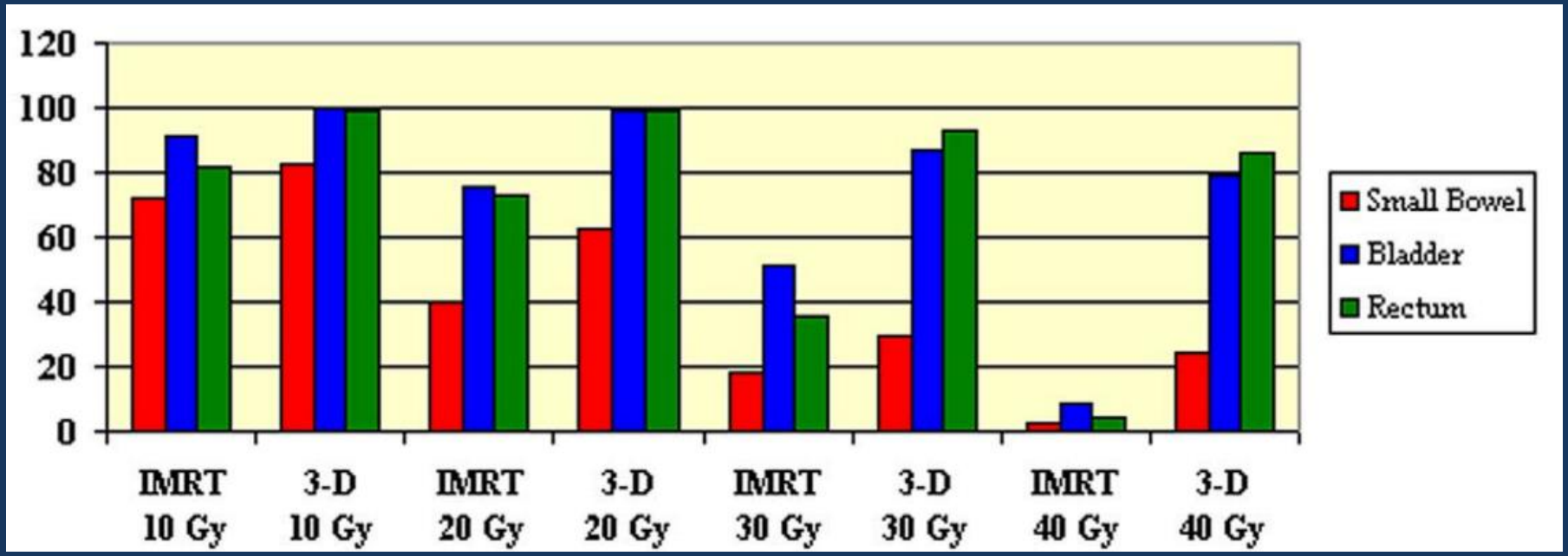


Gain of IMRT is organ sparing!

Portelance et al 2001, Van de Bunt et al 2006, Lukovich et al

3D CRT vs IMRT

Mean percentage volume of tissue irradiated as a function of dose

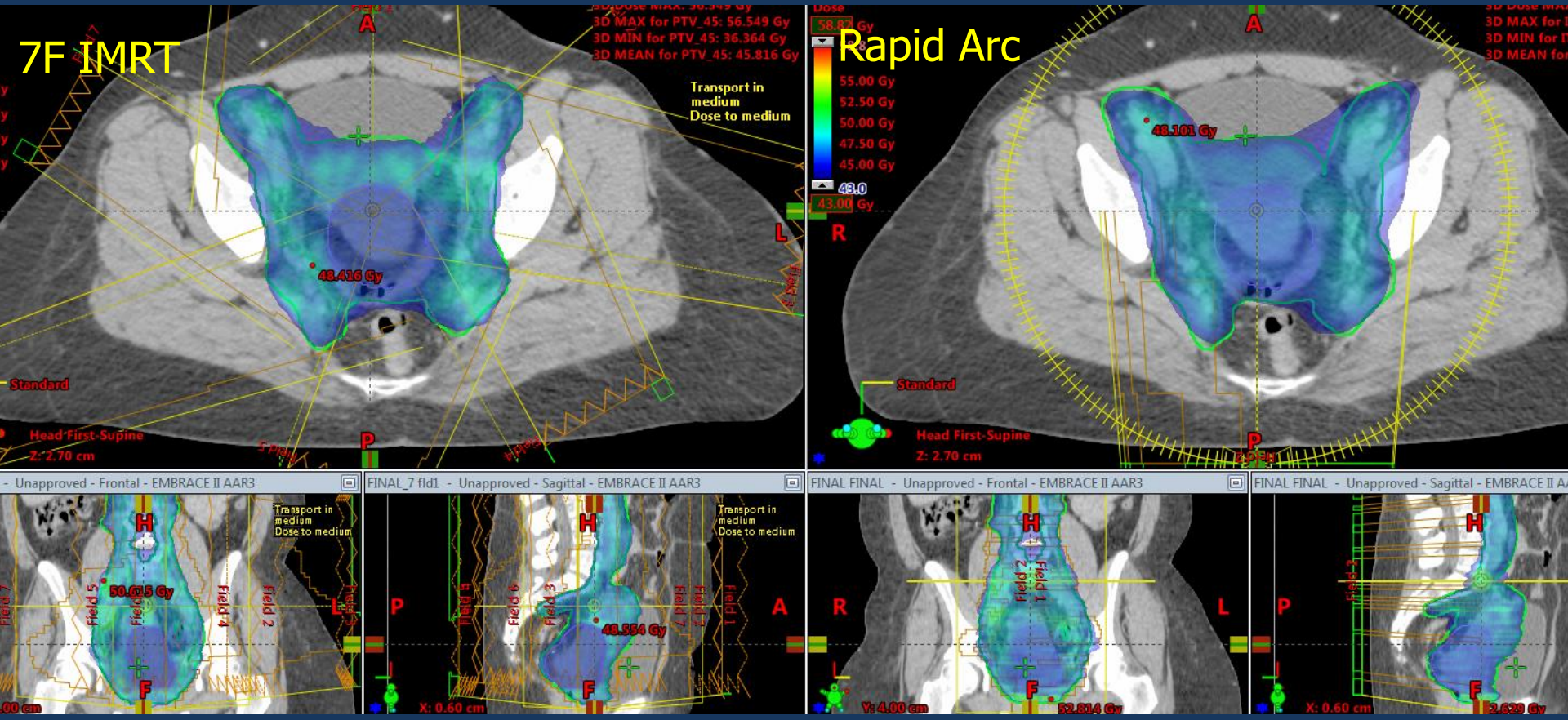


Heron et al, Gynaecologic oncology, 2002

3D CRT vs IMRT

- Significant OAR sparing (Reduction of High and intermediate dose volumes)
- SIB
- Low dose volume increased ? in IMRT

IMRT vs VMAT


7F IMRT
Rapid Arc
3D MAX for PTV_45: 56.549 Gy
3D MIN for PTV_45: 36.364 Gy
3D MEAN for PTV_45: 45.816 Gy
Transport in medium
Dose to medium
48.416 Gy
48.101 Gy
55.00 Gy
52.50 Gy
50.00 Gy
47.50 Gy
45.00 Gy
Standard
Head First-Supine
Z: 2.70 cm
- Unapproved - Frontal - EMBRACE II AAR3
FINAL_7 fld1 - Unapproved - Sagittal - EMBRACE II AAR3
FINAL FINAL - Unapproved - Frontal - EMBRACE II AAR3
FINAL FINAL - Unapproved - Sagittal - EMBRACE II AA
48.554 Gy
X: 0.60 cm
Y: 4.00 cm

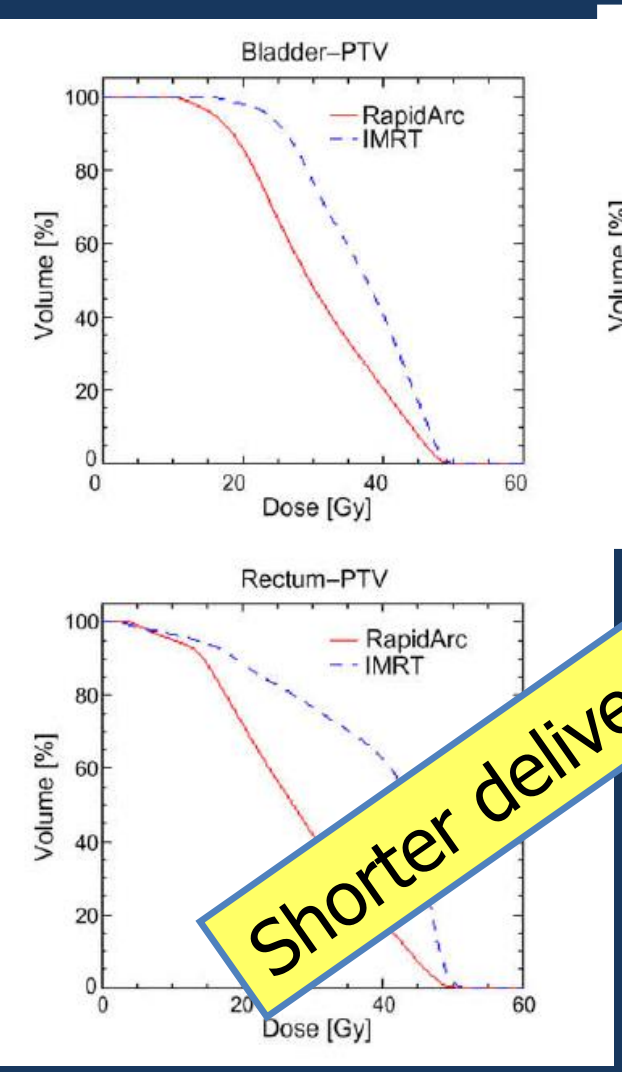
VMAT vs IMRT

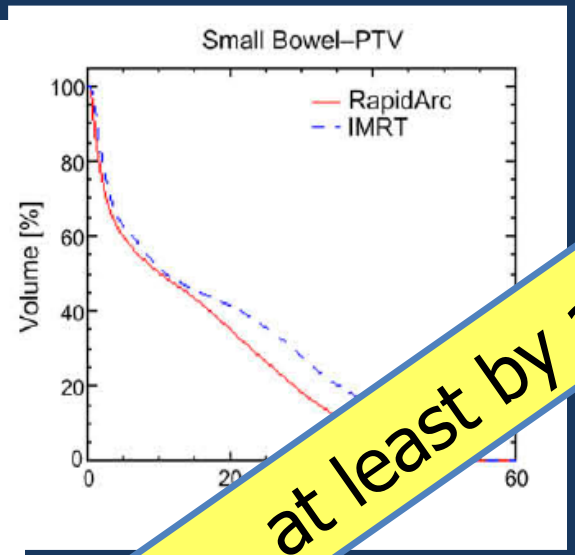
- Target:
  - VMAT showed a slightly improved target coverage in terms of D2% (not significant) .
  - No sig diff in min dose, same HI
  - Conformity is superior in VMAT
- OARs:
  - VMAT reduced irradiated high dose levels (V40 and V50) particularly for the bladder (not significant?).
- integral dose significantly lower ?.
- Reduced treatment time and MU in VMAT.

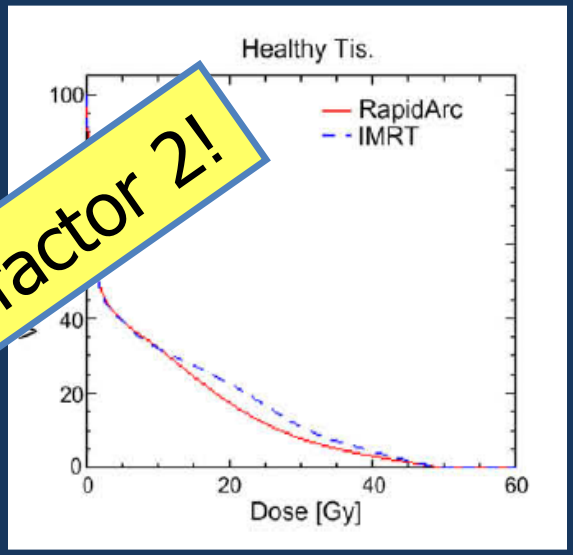
Cozzi et al R&O 2008

IMRT vs VMAT (RapidArc)

8 patients with ca. cervix





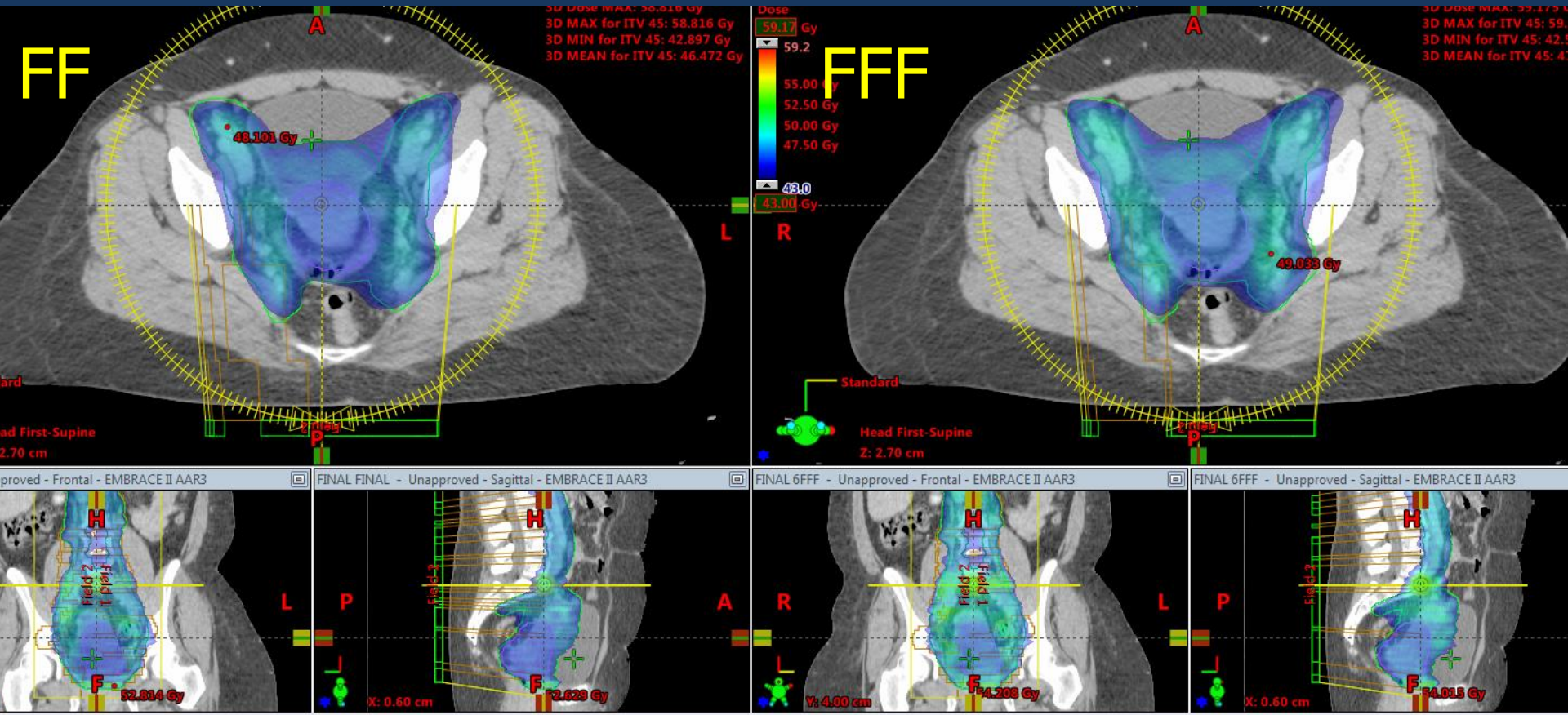


Shorter delivery time, at least by a factor 2!

	Parameter	Objectives	IMRT	RapidArc	p
Rectum-PTV	Mean (Gy)	<45	42.5	36.3	0.02
	V_{40Gy}(%)	Minimise	78.7	51.5	0.03
	$D_{2\%}$(Gy)	<47.5	50.9	51.1	0.65
	$D_{50\%}$(Gy)	<30	44.1	38.0	0.02
Bladder-PTV	Mean (Gy)	<42	36.6	30.3	0.001
	V_{40Gy}(%)	Minimise	40.5	20.2	0.01
	$D_{2\%}$(Gy)	<47.5	47.8	46.9	0.04
	$D_{50\%}$(Gy)	<35	36.6	29.0	0.002

Cozzi et al R&O 2008, Qiao L 2016 et al

VMAT FF vs FFF



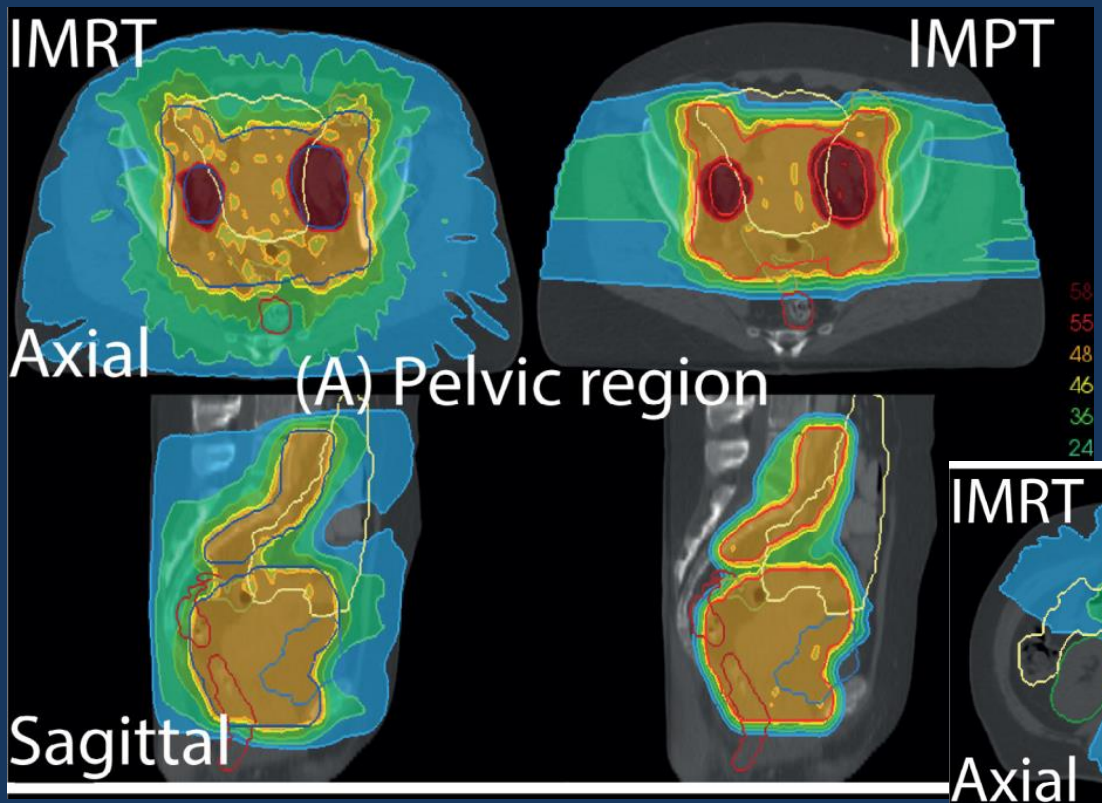
VMAT FF vs FFF

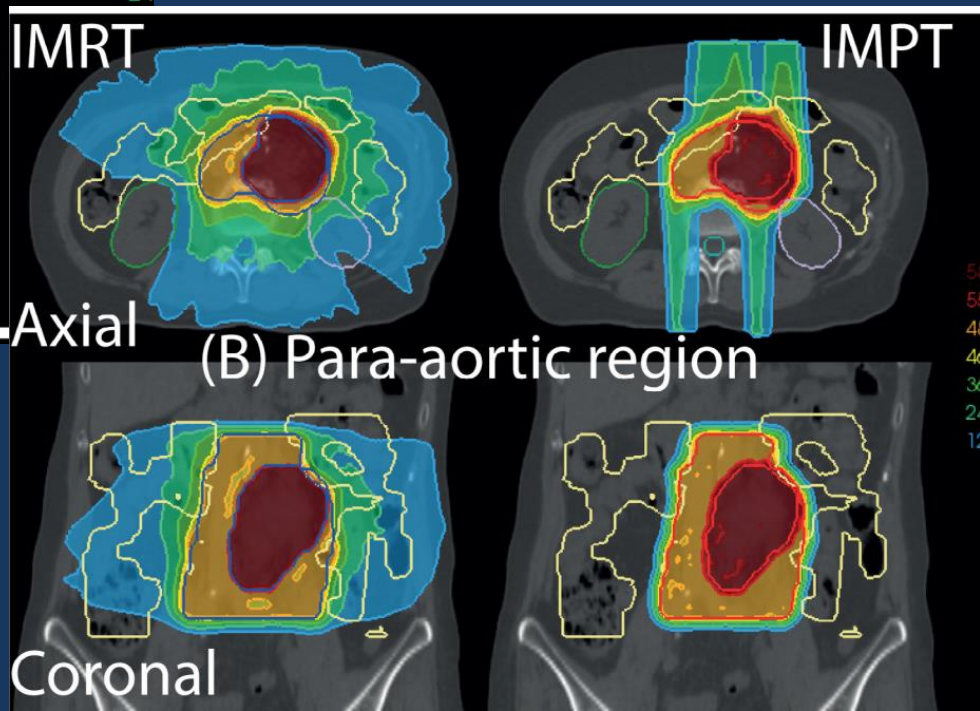
- No differences in dose distribution between FFF-VMAT and FF-VMAT for OARs and target.
- Reduction of beam-on time
- 11% less for 6FFF-VMAT and 16% less for 10FFF - VMAT

Fuli Zhang et al. Oncology and Translational Medicine August 2016, Qiao et al

.

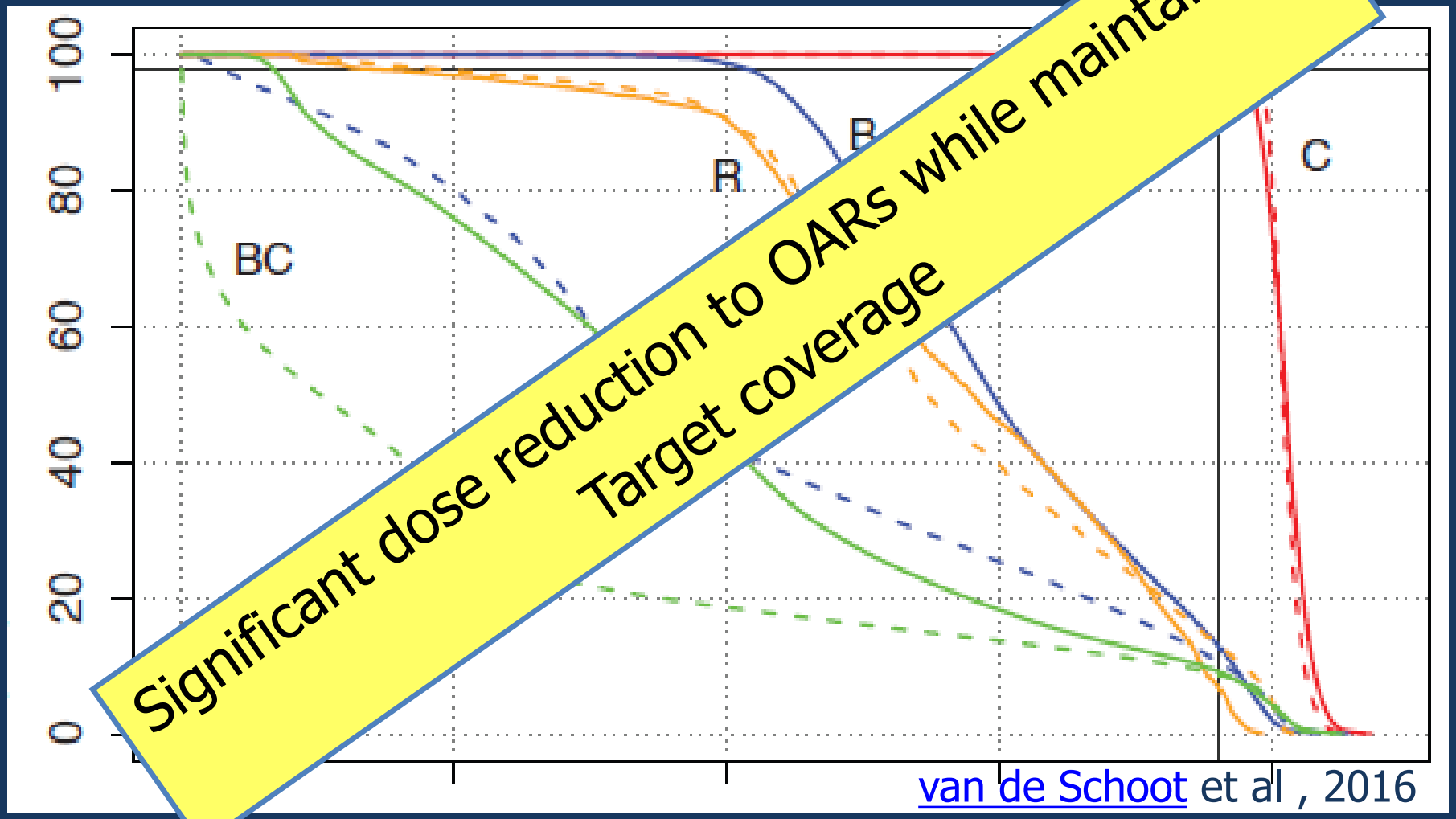
IMRT vs IMPT





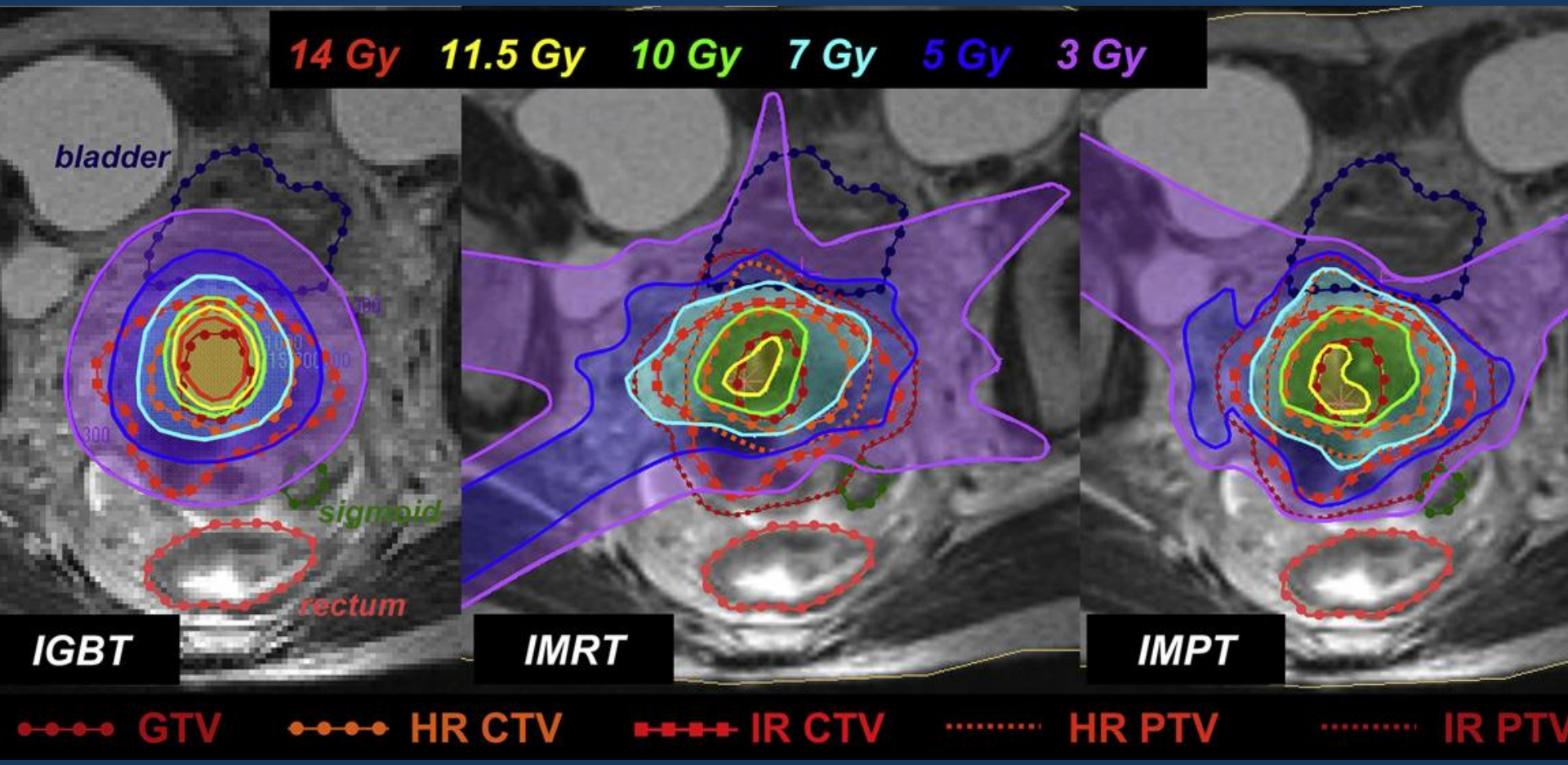
Vande san de et al, 2016

VMAT vs IMPT



van de Schoot et al , 2016

IGBT vs IMRT vs IMPT

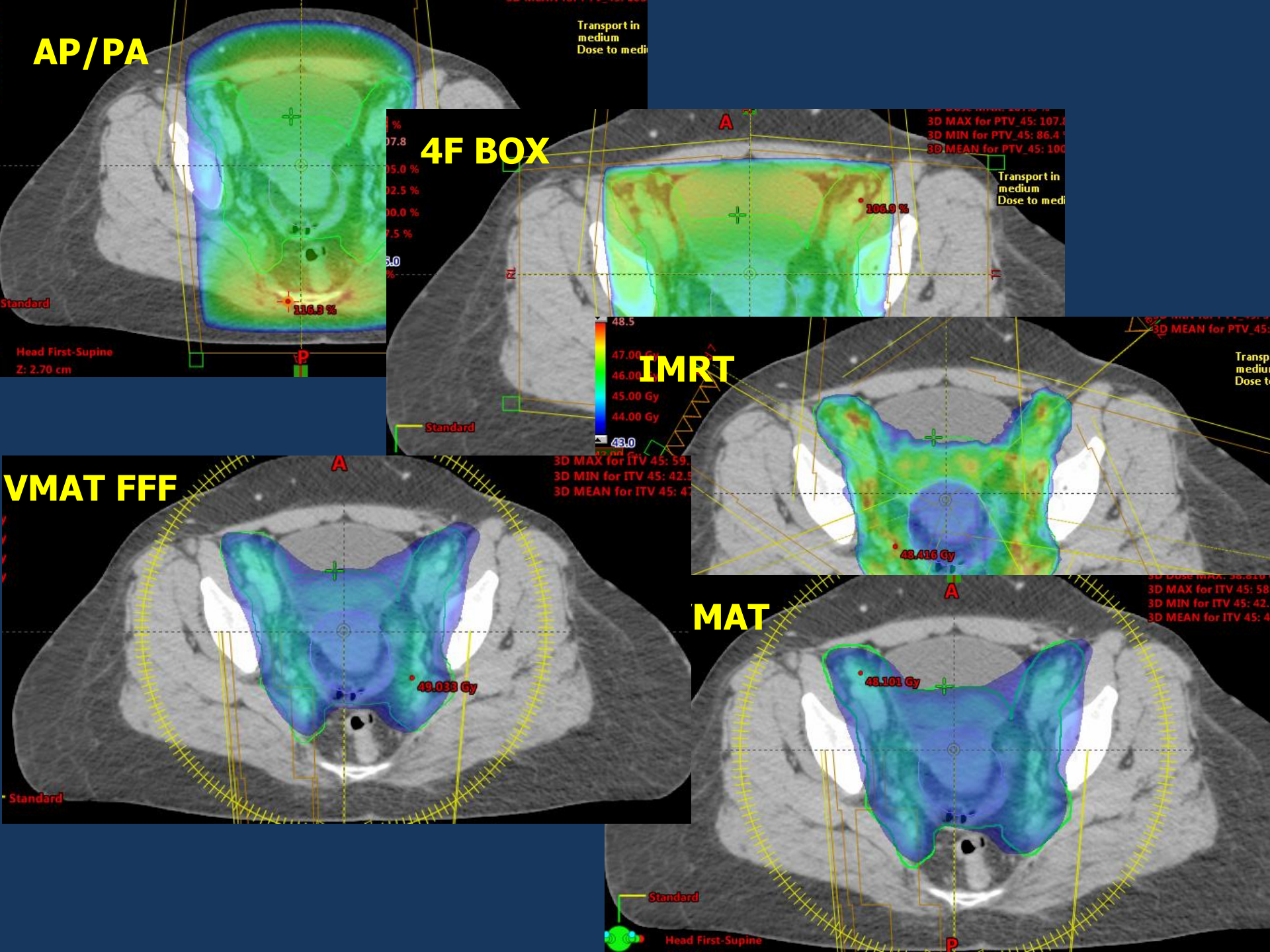


George et al, 2008

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


AP/PA
Transport in medium
Dose to medi
Standard
116.3 %
Head First-Supine
Z: 2.70 cm
4F BOX
A
3D MAX for PTV_45: 107.
3D MIN for PTV_45: 86.4
3D MEAN for PTV_45: 100
Transport in medium
Dose to medi
106.9 %
Standard
IMRT
48.5
47.00 Gy
46.00
45.00 Gy
44.00 Gy
43.0
3D MEAN for PTV_45
Transp
mediu
Dose t
48.416 Gy
VMAT FFF
A
3D MAX for ITV 45: 59.
3D MIN for ITV 45: 42.5
3D MEAN for ITV 45: 47
49.038 Gy
Standard
MAT
A
3D MAX for ITV 45: 58
3D MIN for ITV 45: 42.
3D MEAN for ITV 45: 4
48.101 Gy
Standard
Head First-Supine
P

Conclusion

- Conventional simulator radiograph based planning is still prevalent
- Choice of energy
- MLB – normalization, T odeling
- 3DCRT vs IMRT – icant organ sparing
- IMRT vs VM gnificant reduction of MU
- VMAT F FF – Marginal Reduction of time
- VMAT vs IMPT – Significant reduction of dose to OARs

Advanced BT is superior than IMRT

Acknowledgements

- Prof. Taran Paulsen Hellebust, Norway
- Prof. Kari Tanderup, Aarhus

Clinical Evidence for EBRT Techniques & Medical Dose Constraints including DVH parameters

Umesh Mahantshetty

Outline

- Dosimetric Evidence for IMRT
- Pelvic IMRT : Post-op & Intact Uterus
- PA IMRT
- Incorporation on Newer Imaging Modalities
- Newer XRT Techniques Vs BT

Dosimetric meta-analysis

First author, [Reference]	Country	Prescribed dose, Gy	Sample size		Organs at risk	Level of the dose, Gy
			IMRT*	3D-CRT+		
Heron DE [26]	USA	45	10	10	Rectum, Small bowel, Bladder	10, 20, 30, 40, 45
Chen MF [36]	Taiwan	50.4	33	35	Rectum, Small bowel, Bladder, Bone marrow	5, 10, 15, 20, 25, 30, 35, 40, 45
Mell LK [30]	USA	45	7	7	Rectum, Small bowel, Bladder, Bone marrow	5, 10, 20, 30, 40, 45
Igdem S [31]	Turkey	45 or 50.4	10	10	Rectum, Small bowel, Bladder, Bone marrow	5, 10, 15, 20, 25, 30, 40, 45
Roeske JC [37]	USA	45	10	10	Rectum, Small bowel, Bladder	5, 10, 15, 20, 25, 30, 35, 40, 45
Portelance L [17]	USA	45	10	10	Rectum, Small bowel, Bladder	45
Lujan AE [38]	USA	45	10	10	Bone marrow	5, 10, 15, 20, 25, 30, 35, 40, 45
Brixey CJ [39]	USA	45	36	88	Iliac crest, Lumbar spine, Sacrum	5, 10, 15, 20, 25, 30, 35, 40, 45
Ahmed RS [27]	USA	45	5	5	Bone marrow	5, 10, 15, 20, 25, 30, 35, 40, 45
Mell LK [37]	USA	45	37	0	Bone marrow	10, 20, 30, 40
Mundt AJ [38]	USA	45	36	30	Small bowel	5, 10, 15, 20, 25, 30, 35, 40, 45
Salama JK [40]	USA	45	13	13	Rectum, Small bowel	5, 10, 15, 20, 25, 30, 35, 40, 45
Georg D [41]	Austria	50.4	5	5	Rectum, Small bowel, Bladder	5, 10, 15, 20, 25, 30, 35, 40, 45

* intensity modulated radiotherapy; + three-dimensional conformal radiotherapy.

Yang Radiation Oncology 2012, 7:197

Dosimetric meta-analysis Summary

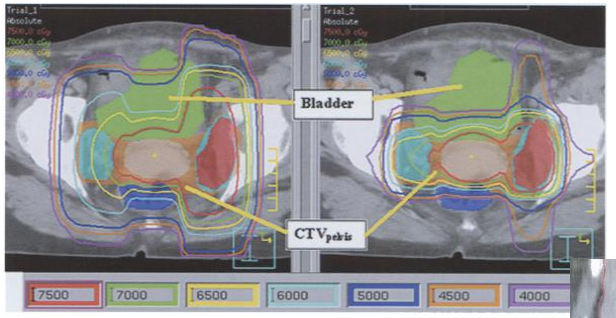
OAR	25 Gy	30 Gy	35 Gy	40 Gy	45 Gy
Rectum	no	- 26.4%	- 27.0%	- 37.3%	-39.5%
Bowel	no	no	no	-17.8%	-17.3%
Bladder	no	no	no	no	no

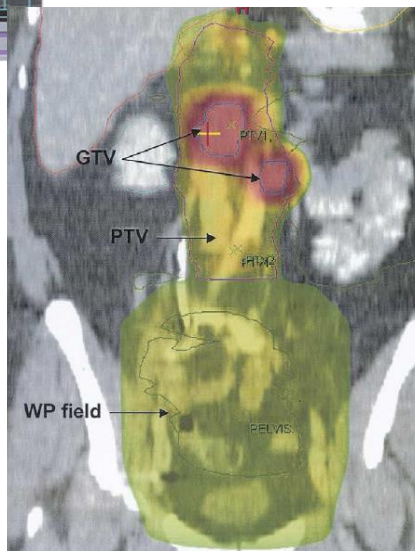
Pooled averages

Yang Radiation Oncology 2012,7:197

Use of IMRT Techniques in GYN Cancers- Clinical Evidence

- Optimize dose to normal tissue
  - Decrease the normal tissue toxicities
- Optimize more dose to tumor (Boost: Sequential/Simultaneous)
  - Increase tumor control rates
- Expansion of Indications
  - Extended field radiation
  - Salvage Re-irradiation





Sem Rad Oncol. 2002

Yang Radiation Oncology 2012, 7:197

Review

Gynecol Oncol 130:229–36;2013

Intensity modulated radiotherapy in gynecologic cancers: Hope, hype or hyperbole?

Aaron Wagner [a], Anuja Jhingran [b], David Gaffney [a,*]

- In **postoperative cases**, IMRT use **should be considered**. To demonstrate preferred patient reported outcomes, participation on the RTOG/GOG 1203 TIME-C trial is encouraged.

- In **intact cases**, the use of IMRT should be **limited to IRB-approved protocols** secondary to additional planning concerns.

- **Consensus guidelines** exist as to contouring both postoperative and intact cases, and should be utilized. However, **changes are in progress**, secondary to concerns as noted above, and appropriate care should be taken during treatment planning, which may require patient **specific adjustments**.

- **IGRT** should be utilized when IMRT is implemented secondary to the significant inter-fraction variability that can occur.

Q: What percentage of cervical cancer patients with intact uterus undergo IMRT/VMAT treatment at your centre?

A. 10%

B. 25%

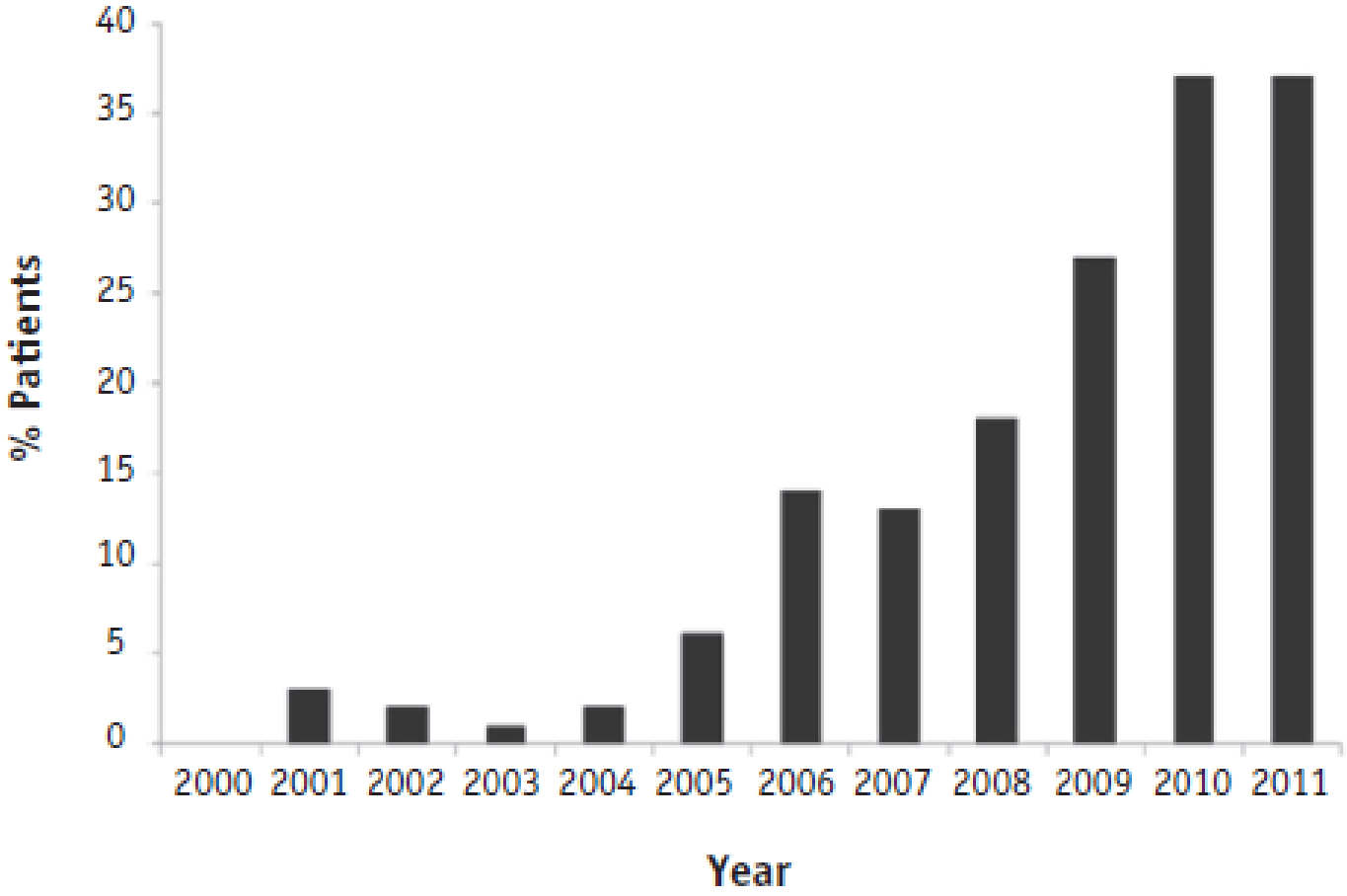
C. 85%

D. None

Trends in Quality of Treatment in patients with Intact Uterus in US:

1999-2011

Utilization of IMRT
N = 1508 patients



Smith et al: IJROBP 2015; 92: 260-7

AIIMS INDIA STUDY

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

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)

Gandhi A et al; IJROBP ; 87:542-8;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

Significant reduction in V40 for Rectum, bladder and small bowel

Gandhi A et al; IJROBP ; 87:542-8;2013

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

GI Chronic toxicity

	WP-CRT arm	WP-IMRT arm	p value
Overall	50%	13.6%	.011
Grade 1	27.3%	9%	
Grade 2	13.6%	4.5%	

CONCLUSION: WP-IMRT is associated with significantly less toxicity compared with WP-CRT and has a comparable clinical outcome. Further studies with larger sample sizes and longer follow-up times are warranted to justify its use in routine clinical practice.

Gandhi A et al; IJROBP ; 87:542-8;2013

A Phase II Randomized Trial Comparing Intensity Modulated Radiation Therapy (IMRT) with Conventional Radiation Therapy in Stage IIB Carcinoma Cervix

(NCT00193804/TMH/158/2004): November 2004

Carcinoma Cervix Stage IIB (SQ / Adeno CA)

100 patients

Conventional External RT (40 Gy /20#)

+ ICA – HDR (7 Gy x 5#)

with Concomitant Chemo-radiation

100 patients

IMRT Pelvis (50 Gy/25#)

+ ICA – HDR (7 Gy x 5#)

with Concomitant Chemo-radiation

HYPOTHESIS:

- Reduction in Acute and Late RT toxicity's by:15-25%
- Accrual Period: 5 years
- Power of detection: 80% (alpha error: 0.05)

Final Analyses: Ongoing

TOXICITIES

	Conventional Arm	IMRT Arm
Pts randomized	100	100
Compliance to Rx	95	97
Acute toxicities		
Acute GI		
Gr II	15	12
Gr III	03	02
Acute GU		
Gr II/ Gr III	06	05
Acute hematological		
Thrombocytopenia (Gr II/III)	05	03
Neutropenia (Gr II/III)	08	03
Anemia Gr I	16	22
Anemia Gr II/ III	04	04
Late Toxicities		
RT Proctitis Gr II	02	09
Gr III / IV	03	08
RT Cystitis Gr II	03	06
Gr III	01	03

SK Shrivastava et. al. ICARO & ASTRO 2009

IMPLEMENTATION OF IGRT IN AN IMRT ENVIRONMENT : PRE-REQUISTE TO SUCCESS

Target delineation

Imaging protocol

Contouring Consensus

Immobilization

Type of IGRT

Set up / IGRT

Organ motion (interfraction/ intrafraction)

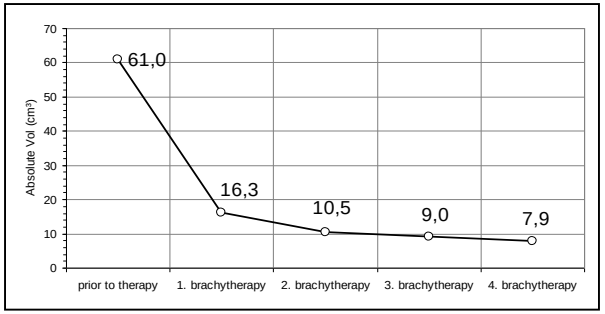
Bladder filling

Rectal filling

TUMOR Regression

Adaptive Plan

- **Mid RT Replan**
- **Plan of the Day Approach**

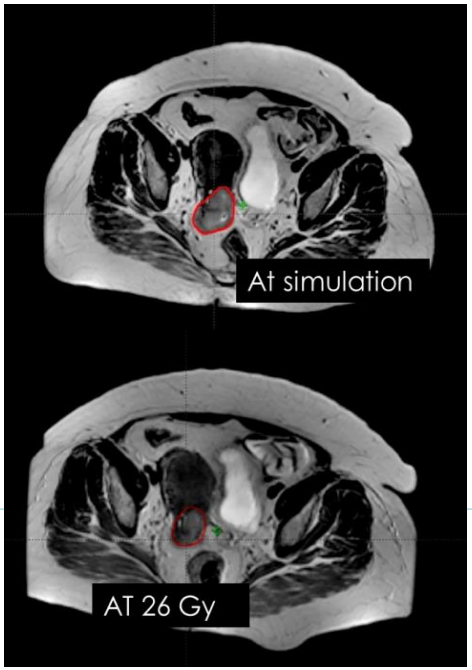


IGRT PROTOCOL : INSTITUTIONAL

A Study to Evaluate CTV to PTV Margins for Pelvic Nodal Region and CTV to ITV Margins for Utero-cervical Complex During Cervical Cancer Radiation Therapy

U.M. Mahantshetty,[1] A. Nachankar,[1] Y. Ghadi,[1] S. Chaudhari,[1] S. Jamema,[1] R. Engineer,[1] S. Chopra,[2] D.D. Deshpande,[1] and S. Shrivastava[3]; [1]*Tata Memorial Centre, Mumbai, India,* [2]*ACTREC,*

TMH Study; ASTRO 2014



- Cervical cancer with intact Uterus
- N = 40 patients with FIGO IIB-IIIB

- Daily CBCT IGRT
- Nodal CTV matching
- Mid RT Tumor Regression with MRI
- Tumor regression: the mean cervical tumor volume reduced from 58.4 cc at diagnosis to 28.3 cc) at mid treatment

	Surrogate for Organ Motion : Online – Offline matching (Intrafraction)		
	Mean X Lateral (mm)	Mean Y ANT-POST (mm)	Mean Z SUP-INF (mm)
Day 5	5.3	7.9	6.4
Day 10	4.9	7.8	7.6
Day 15	4.7	8.8	7.2
Day 20	6.4	7.5	8.7
Day 25	4.7	7	9.6

Parameter	Error (in mm) measured along		
	X-Axis (RT – LT)	Y-axis (ANT-POST)	Z-axis (SUP-INF)
SD of Random error (σ)	4.3	5.8	6.6
SD of systematic error (ξ)	2.2	2.6	3.4

Post Operative IMRT in GYN Cancers

I. J. Radiation Oncology ● Biology ● Physics Volume 52, Number 5, 2002

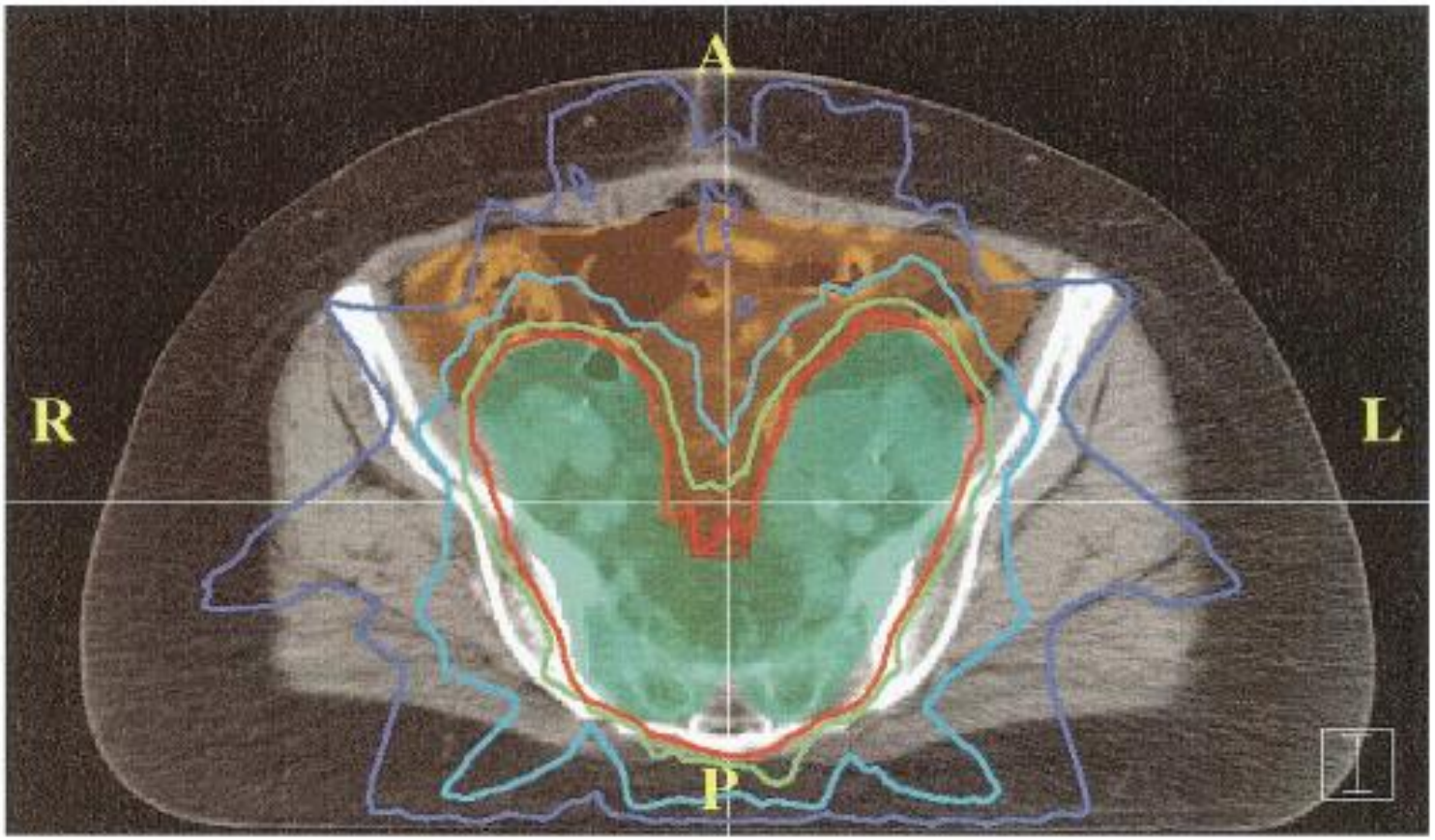


Fig. 2. Isodose curves from an IM-WPRT plan superimposed on an axial CT slice through the upper pelvis. The small bowel and PTV are shaded in orange and green, respectively. Highlighted are the 100% (red), 90% (green), 70% (light blue), and 50% (dark blue) isodose curves.

RTOG 0418

A phase II study of post op IMRT in gynecological cancer

- 83 patients (43 pts endometrial ; 40 pts cervical cancer)
- RT 50.4Gy with weekly CDDP (40mg/m^2)
- 90% patients received 4 cycles of CDDP
- Pelvic IMRT with emphasis on small bowel & BM sparing technique

IJROBP 2013

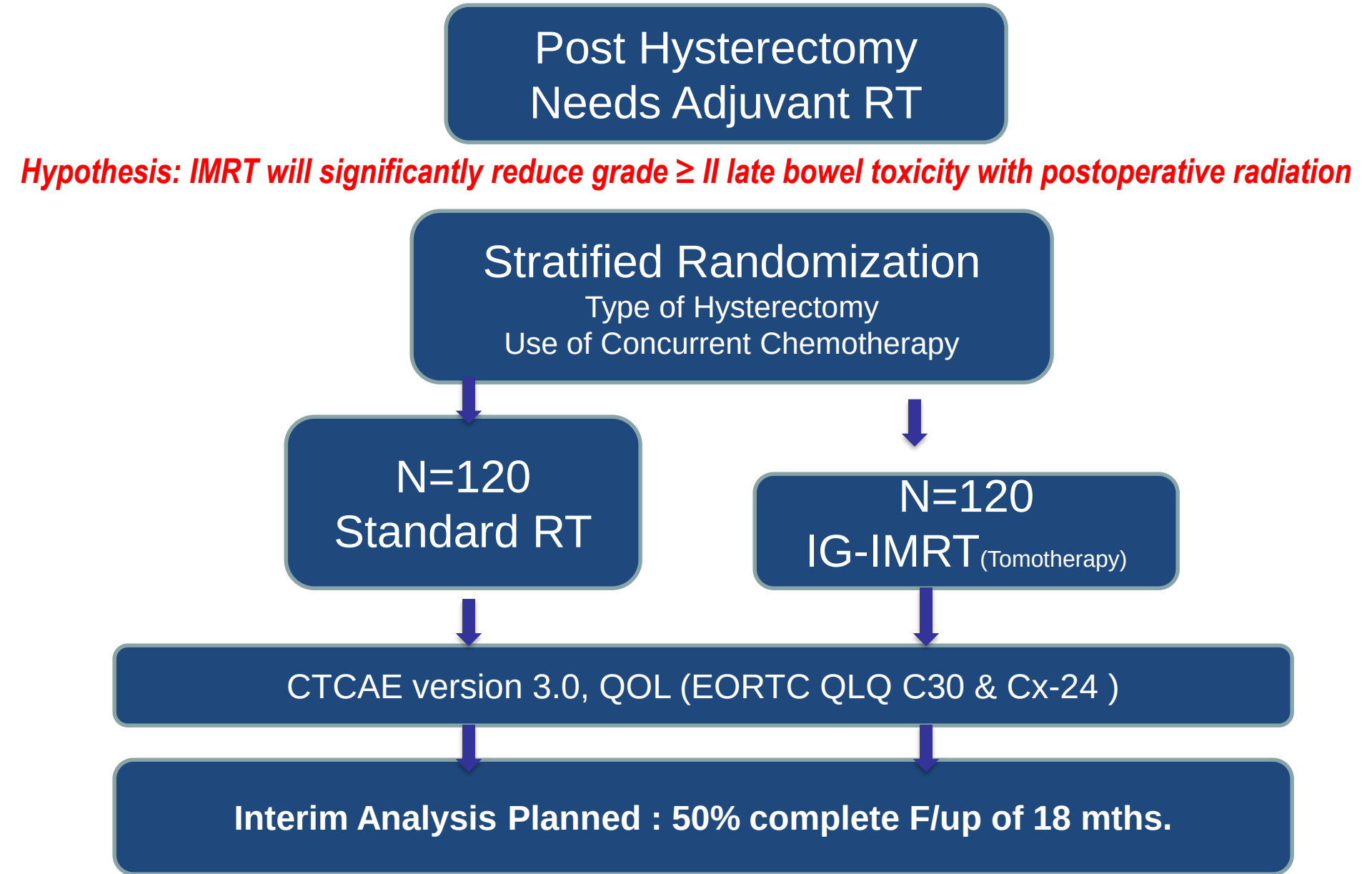
- Hematological toxicities in CRT pts
  - Gr 1 : 23%
  - Gr 2 : 33%
  - Gr 3 : 25% (Vs 31% RTOG 9708 p = NS)
- Median V 10 : 96%; V20: 84%
- Median V 30 : 61%; V40: 37%
- V40 >37% : 75% had Gr≥2 Vs 40%
- Grade 4 toxicity : 0% Vs 13% (RTOG 9708)

Conclusions: Pelvic IMRT with weekly cisplatin is associated with low rates of HT and high rates of weekly cisplatin use. The volume of bone marrow receiving 40 Gy and the median dose to bone marrow correlated with higher rates of grade 2 toxicity among patients receiving weekly cisplatin (cervical cancer patients). Evaluation and limitation of the volume in patients receiving concurrent

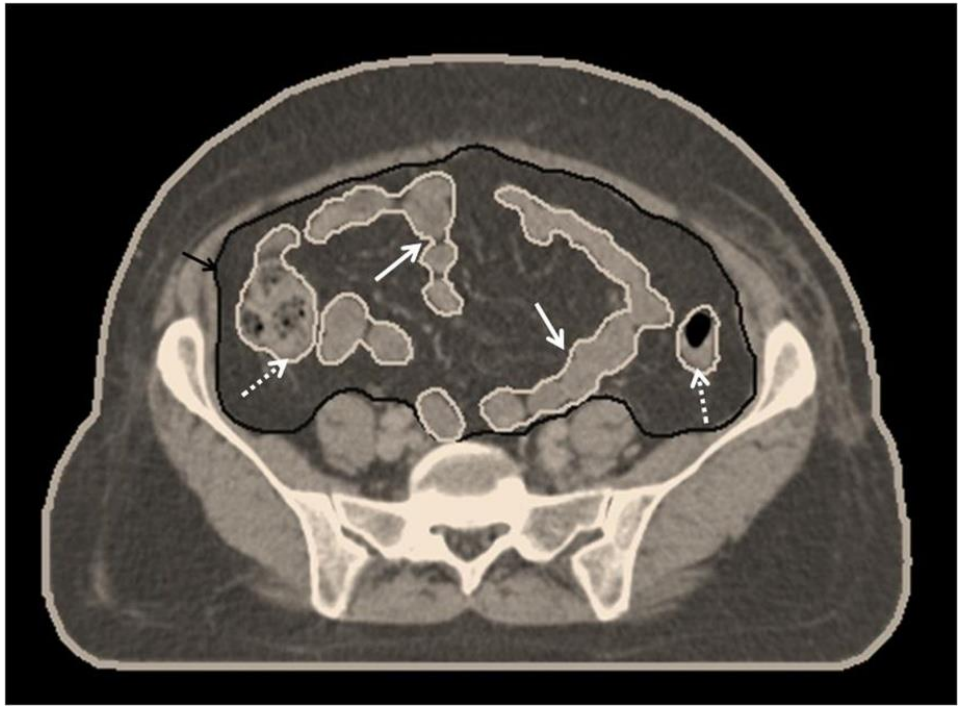
V 40 Gy > 40% correlated with ≥ grade 2 HT toxicity
Mahantshetty et al; IJGC 2012

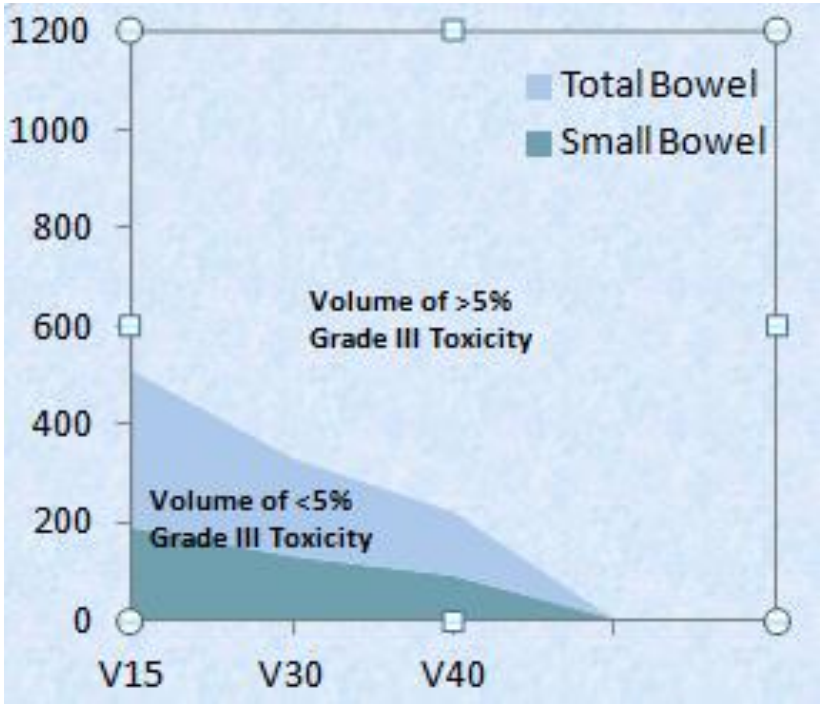
IJROBP 2013

Phase III RCT of Postoperative Adjuvant Conventional Radiation (3DCRT) Vs. Image Guided Intensity Modulated Radiotherapy (IG-IMRT) for Reducing Late Bowel Toxicity in Cervical Cancer (PARCER): Interim Analysis (Tata Memorial Centre)



OAR Contouring & Dose Constraints





Small & Large Bowel

Peritoneal Cavity

Rectum, Bladder

Hard Constraints:
V15 SB <190 cc, V40 SB <100 cc

Soft Constraints:
Rectum <60% vol >/= 30 Gy
<35% Bladder >/=45 Gy

Bowel Doses : 3DCRT vs. IMRT

Bowel Dose	IMRT	3DCRT	P value
V15 Small Bowel ≥ 275 cc	8 (13.1%)	25 (44.6%)	<0.0001
V40Small Bowel ≥ 150 cc	1 (1.6%)	26 (46.4%)	<0.0001
V15 Peritoneal Cavity ≥ 1200 cc	15 (24.5%)	24 (42.8%)	0.06
V40 Peritoneal Cavity ≥ 750 cc	1 (1.6%)	20 (35.7%)	<0.0001

IMRT led to significant reduction in Bowel and PC doses

S Chopra et al; ASTRO 2015

Primary Endpoint

	IG-IMRT	3DCRT	p value
Late Grade ≥ II toxicity (Primary Endpoint)	11.4%	25%	0.13
Late Grade ≥ III toxicity (Exploratory Endpoint)	3.2%	17.8%	0.02

Median Follow Up = 20 months

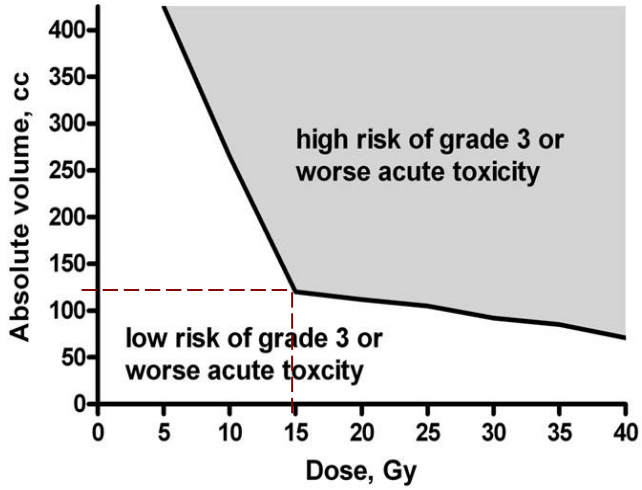
14% absolute difference; statistically insignificant at interim analysis

S Chopra et al; ASTRO 2015

Dose constraints depend on contouring approach

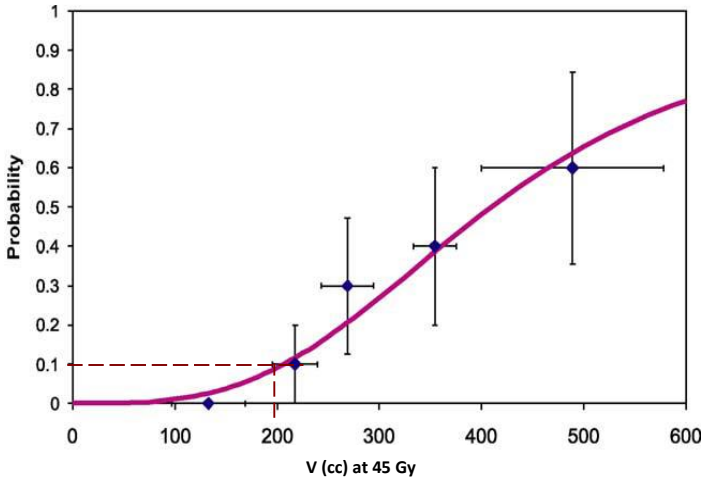
Treshold – based risk models

Baglan – Robertson, IJROBP 2002



Based on delineation of Bowel Loops

Roeske, Radiother Oncol 2003



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)

Dose Constraints : Literature

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%**	**V40< 40 - 50%**	

Bowel Bag :V45 < 200 cc for <10% probability for ≥ Gr 3 toxicity

Table shows studies regarding toxicity with IMRT for cervical and endometrial cancer

	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

Gynecol Oncol 130:229–36;2013

RTOG 1203 protocol: A Randomized Phase III Study Of Standard Vs. IMRT Pelvic Radiation For Post-Operative Treatment Of Endometrial And Cervical Cancer (TIME-C)--RTOG CCOP Study

TIME-C Trial

- Conventional RT Vs Pelvic IMRT
- End Point: 20% (90% to 70%) reduction in Acute Grade 2+ GI toxicity
- Accrual Status: 289 patients accrual completed:2015
- Final Report : Awaited

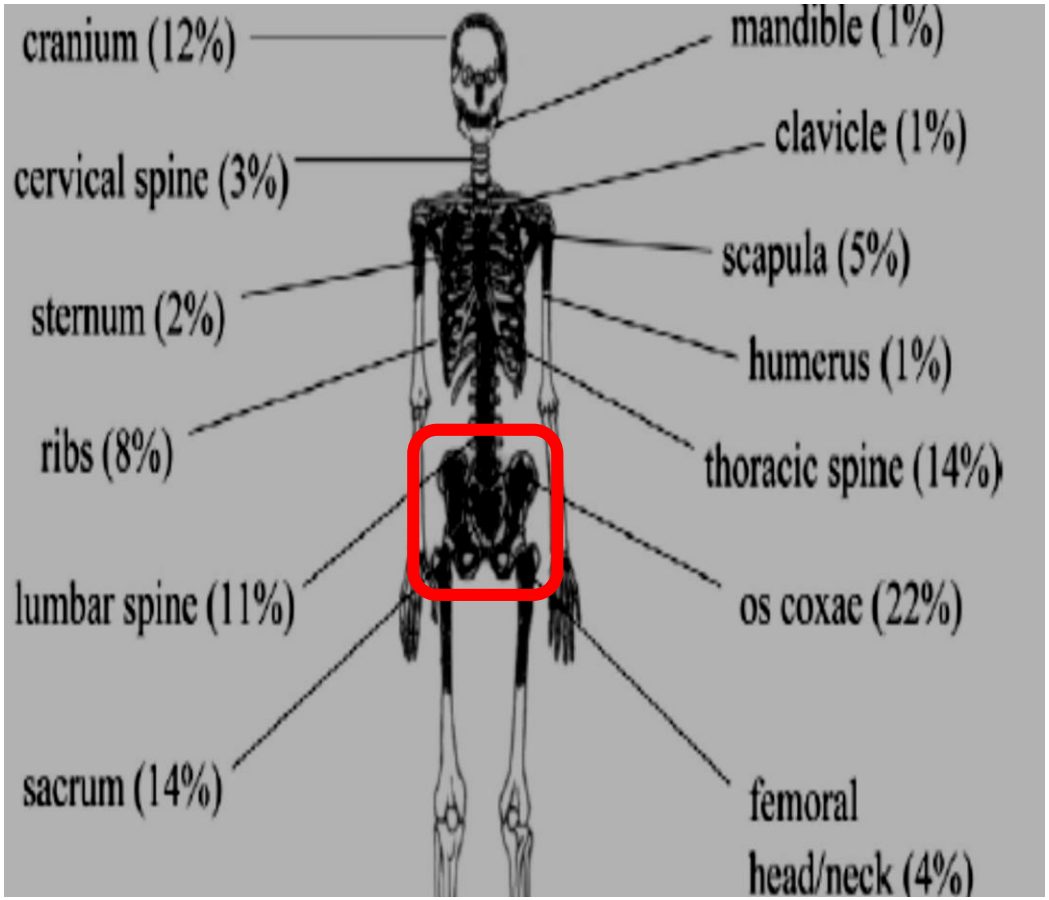
EMBRACE II Protocol CONSTRAINTS

		Hard dose constraints	Soft dose constraints
Targets	PTV45	V95% > 95% Dmax<107%*	
	ITV45	Dmin> 95%	
	PTV-N(#)	D98% > 90% of prescribed LN dose Dmax < 107% of prescribed LN dose	
	CTV-N(#)	D98% > 100% of prescribed LN dose	D50% > 102%
Help contour	CTV-HR +10mm		Dmax < 103%
OARs	Bowel	Dmax < 105% (47.3Gy)*	When no lymph node boost: • V40Gy < 100cm3** • V30Gy < 350cm3** When lymph node boost or para-aortic irradiation: • V40Gy < 250cm3** • V30Gy < 500cm3** Dmax < 57.5Gy
	Sigmoid	Dmax < 105% (47.3Gy)*	Dmax < 57.5Gy
	Bladder	Dmax < 105% (47.3Gy)*	V40Gy < 75%** V30Gy < 85%** Dmax < 57.5Gy
	Rectum	Dmax < 105% (47.3Gy)*	V40Gy < 85%** V30Gy < 95%** Dmax < 57.5Gy
	Spinal cord	Dmax < 48Gy	
	Femoral heads	Dmax < 50Gy	
	Kidney	Dmean < 15Gy	Dmean < 10Gy
	Body	Dmax < 107%*	
	Vagina PIBS-2cm		When vagina not involved: $D_{PIBS-2cm}$<5Gy
Optional	Ovaries	<5-8 Gy	
	Duodenum***	V55<15cm^3	

PET-CT Based Active Bone Marrow as a potential OAR

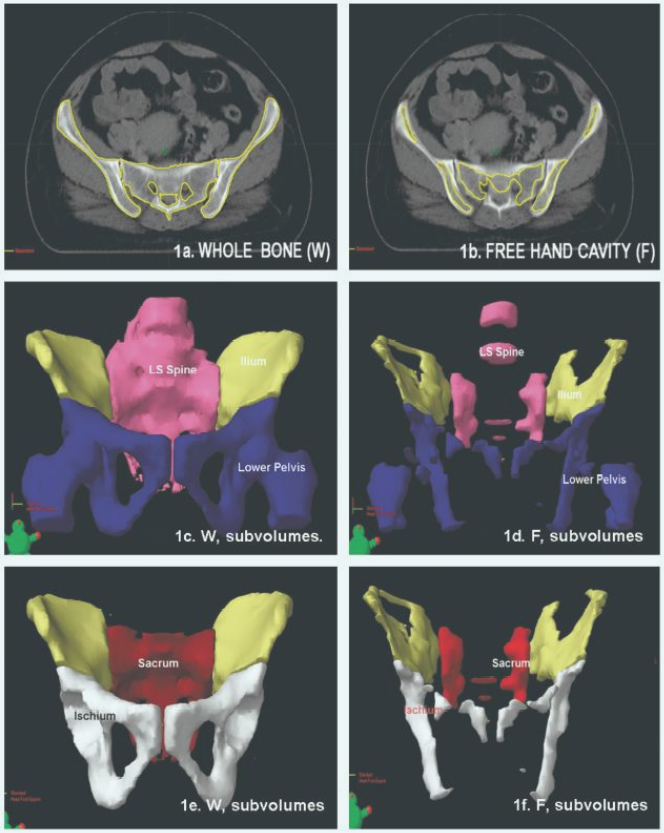
Bone marrow : Organ at risk for haematological toxicities

Adult: Haematopoietic Tissue Distribution

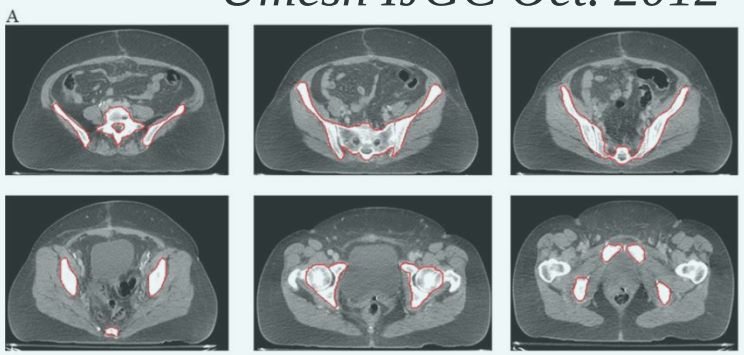


- **Approx. 45-50% of active marrow in pelvic field**
- **Constitutes critical mass for toxicities**

CT Based

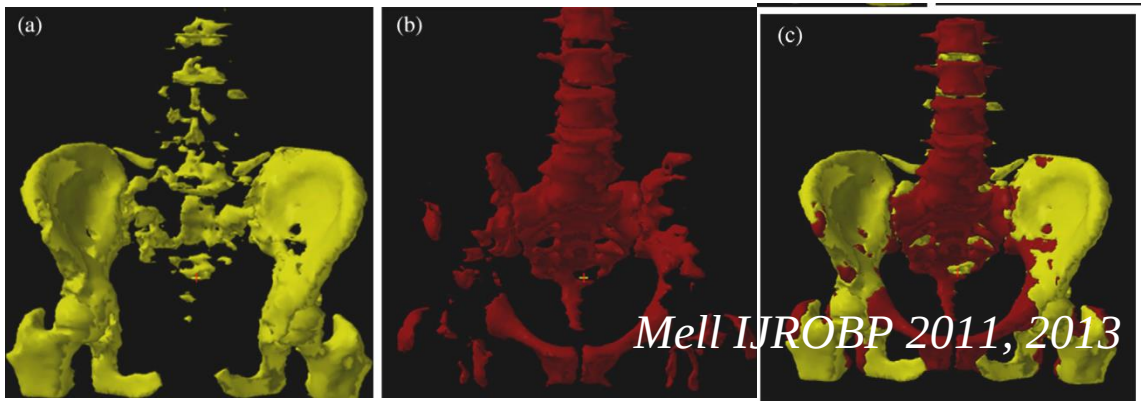


Umesh IJGC Oct. 2012

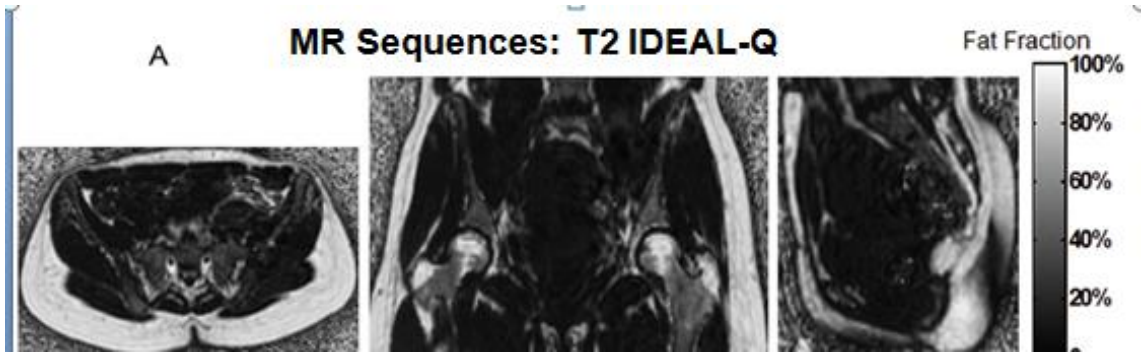


IJROBP 2013

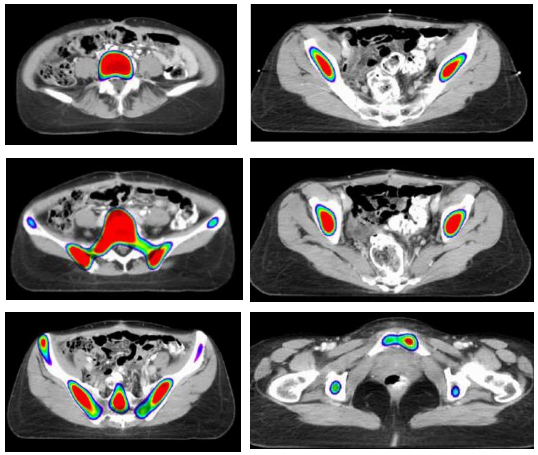
FDG PET: SUV > Mean corrected for body weight



Mell IJROBP 2011, 2013

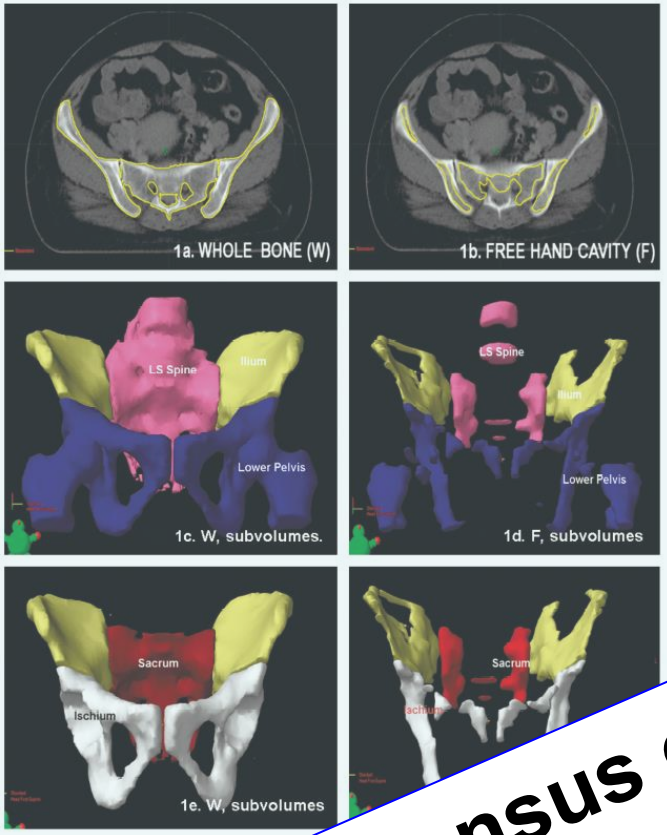


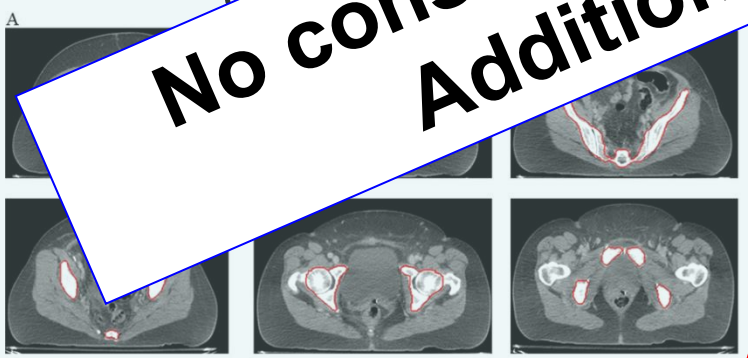
SPECT-CT: Tc 99m sulphur colloid defined hot-spots



Roeske et al; Rad. Oncol 2005

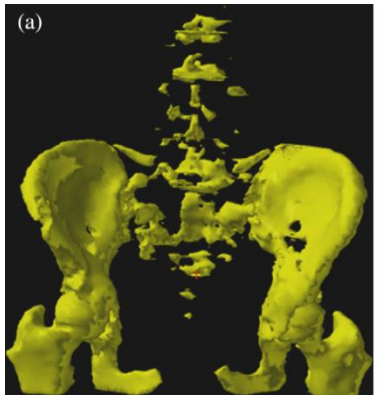
CT Based

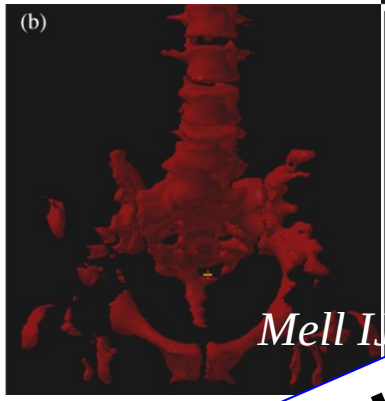


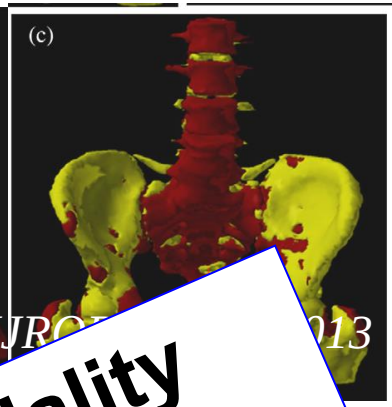


IJROBP 2013

FDG PET: SUV > Mean corrected for body weight



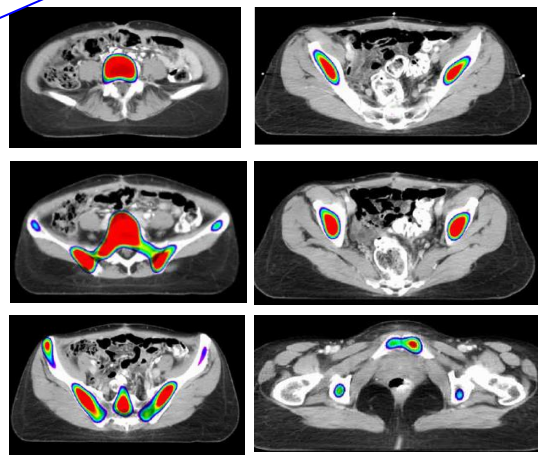




Mell IJRO 2013

No consensus on optimal single modality
Additional Research Required

Tc 99m sulphur colloid defined hot-spots



Roeske et al; Rad. Oncol 2005

Comparison of various studies

	SPECT IMRT	Anal Ca Mell	Cervix Mell	TMH Whole bone	TMH Free hand
Whole pelvis					
V10	**100**	**85(15)**	**91(3.6)**	88(5.18)	**86.5 (6.8)**
V20	88	75(17)	74(6.1)	79.6(5.2)	77.5 (6.2)
V30	66	56(19)	53(7.5)	62.9(6.5)	62.5 (6.5)
V40	23	32(17)	28(10.3)	40(0.45)	**40.5 (8.4)**

Dose Constraints: BM Sparing IMRT (Grade 2 HT toxicity)

- No definite constraints available
- V10 < 90% *(INTERTECC)*
- V40 < 37- 40% *(RTOG; TMH)*

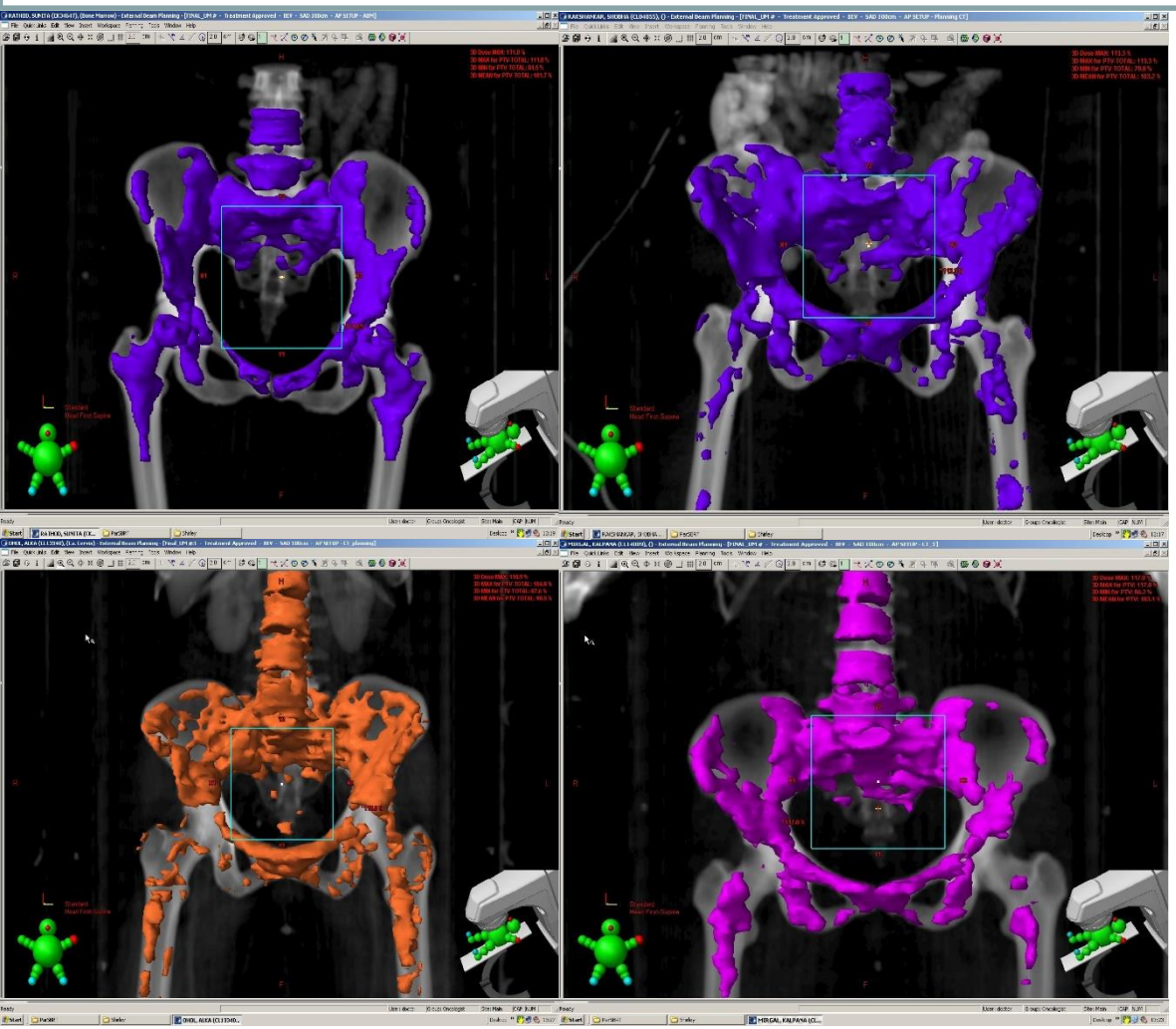
International Evaluation of Radiotherapy Technology Effectiveness in Cervical Cancer (INTERTECC): Phase II/III Trial of Intensity Modulated Radiotherapy

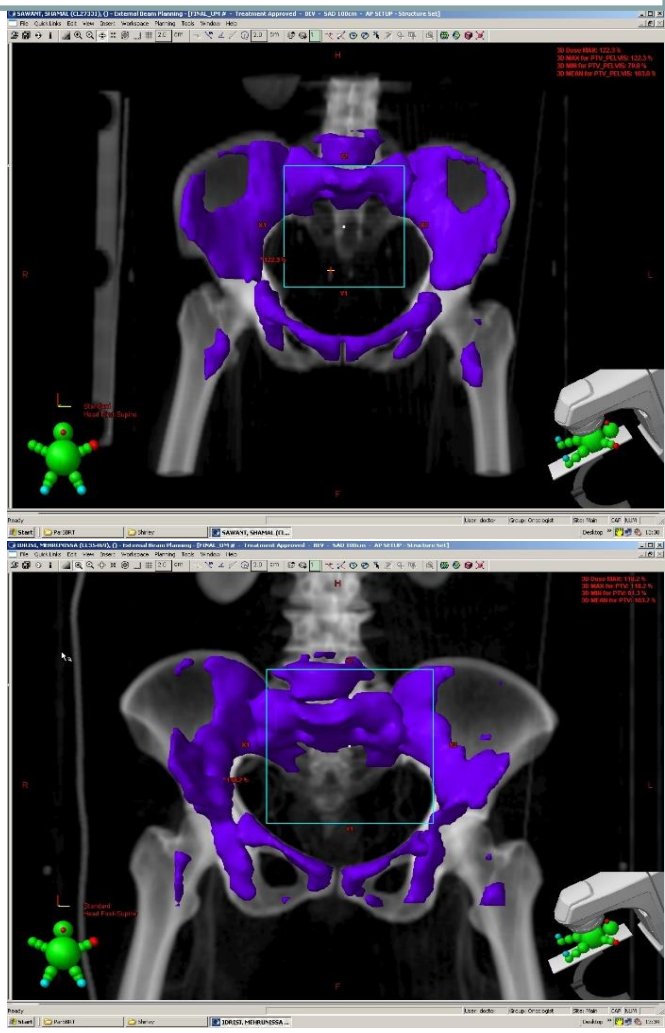
UC San Diego
RADIATION ONCOLOGY

CART UCSD CENTER FOR ADVANCED RADIOTHERAPY TECHNOLOGIES

INTERTECC Trial: Multi-centric International Study

- Phase II/III Trial of IMRT (45-50.4 Gy) with Cisplatin CT
- Stage I-IVA, Post-op or Intact
- Primary Endpoint: Acute G3 Heme + G2 GI Toxicity
- Target Accrual: 91 (Phase II) + 334 (Phase III) = 425
- Phase II: Single Arm (Lead-In)
- Translational Sub-Studies:
  - Phase II Trial of Image-Guided BM-Sparing IMRT
  - Validation of High-Dimensional Model of BM Toxicity
  - Validation of Shape Model using Daily kV CBCT
- Phase III: Randomized Trial of BM sparing IMRT Vs. IMRT/ 3D CRT
- Central IMRT QA (MDA and Wash U.)





FDG PET based contouring

FLT PET based contouring

TMH Experience : 9 pts recruited in phase II study

	Baseline	Wk 1	2	3	4	5	Vol of FBM (cc)	V10Gy (<90% -Mell et al)	V40Gy (< 40% - RTOG 0418)	Mean Dose FBM (<25Gy)
Pt 1	0	0	0	0	0	Gr 1	**425**	74.2 %	25.6 %	24.9 Gy
Pt 2	0	0	0	0	0	Gr 1	**482**	83.9 %	34.9 %	29.0 Gy
Pt 3	0	0	0	Gr 1	Gr 1	Gr 2	**446**	79.7 %	35.9 %	27.5 Gy
Pt 4	0	0	0	Gr 1	Gr 1	Gr 2	**702**	69.3 %	13.2 %	21.9 Gy
Pt 5	0	0	0	0	0	Gr 1	**409**	83.1 %	18.3 %	24.4 Gy
Pt 6	**0**	**0**	**Gr 4 ***	**Gr 2**	**0**	**0**	**272**	**95.3 %**	**28.9 %**	**28.8 Gy**

- **Baseline Active BM reserves were low**
- **Dose constraints not achieved**
- **Grade 4 HT toxicity**

INTERTECC Preliminary Data: Jan 2015

	All (N=61)
Treated within 60 days, n (%)	57 (93%)
Completed 5 cycles cisplatin, n (%)	50 (82%)
Achieved Hard Bowel Constraint (V45<250cc), n (%)	55 (90%)
Achieved Soft Bowel Constraint (V45<200cc), n (%)	45 (74%)
Achieved Bone Marrow Constraints (V10<90%, V20<75%), n (%)	57 (93%)
Active Bone Marrow Sparing, n (%)	30 (43%)
FDG-PET, n (%)	15 (21%)
FLT-PET, n (%)	15 (21%)
Bowel V45 (cc) (mean, s.d.)	147 ± 89
Bone Marrow V10 (mean, s.d.)	84% ± 6.3%
Bone Marrow V20 (mean, s.d.)	65% ± 9.8%
Bone Marrow V30 (mean, s.d.)	42% ± 6.8%
Bone Marrow V40 (mean, s.d.)	19% ± 5.4%
Bone Marrow Mean Dose (Gy) (mean, s.d.)	26.0 ± 2.3
Active Bone Marrow Mean Dose (Gy) (mean, s.d.)	26.0 ± 2.6
Completed both baseline & Follow-up QOL Assessment, n (%)	54 (89%)

Courtesy: Loren Mell UCSD; PI INTERTECC

Int J Radiat Oncol Biol Phys. 2017 Mar 1;97(3):536-545. doi: 10.1016/j.ijrobp.2016.11.027. Epub 2016 Nov 23.

Bone Marrow-sparing Intensity Modulated Radiation Therapy With Concurrent Cisplatin For Stage IB-IVA Cervical Cancer: An International Multicenter Phase II Clinical Trial (INTERTECC-2).

Mell LK[1], Sirák I[2], Wei L[3], Tarnawski R[4], Mahantshetty U[5], Yashar CM[6], McHale MT[7], Xu R[7], Honerkamp-Smith G[7], Carmona R[7], Wright M[7], Williamson CW[6], Kasaová L[2], Li N[6], Kry S[8], Michalski J[9], Bosch W[9], Straube W[9], Schwarz J[10], Lowenstein J[7], Jiang SB[7], Saenz CC[7], Plaxe S[7], Einck J[6], Khorprasert C[11], Koonings P[12], Harrison T[12], Shi M[3], Mundt AJ[6]; INTERTECC Study Group.

RESULTS:

- October 2011 to April 2015, (median follow-up was 26.0 months)
- 83 patients
- The incidence of any primary event was 26.5% (95% [CI] 18.2%-36.9%), significantly lower than the 40% incidence hypothesized a priori from historical data (P=.013)
-
1
-
IM
2

Significant reduction in acute grade 3 neutropenia but not leucopenia with BM sparing IMRT

leukopenia (25.7% vs 41.7%; P=.13) and any grade ≥3 hematologic toxicity (31.4% vs 43.8%; P=.25).

CONCLUSIONS:

IMRT reduces acute hematologic and GI toxicity compared with standard treatment, with promising therapeutic outcomes. Positron emission tomography IG-IMRT reduces the incidence of acute neutropenia.

EVIDENCE

Can High Tech XRT replace BT?

High Tech XRT

Vs

BT (Conventional)

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*

*Departments of *Radiation Oncology and †Gynecologic Oncology, Magee-Womens Hospital of University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; and ‡Department of Gynecologic Oncology, Western Pennsylvania Hospital, Pittsburgh, Pennsylvania*

Int J Radiation Oncol Biol Phys, Vol. 90, No. 5, pp. 1083–1090, 2014

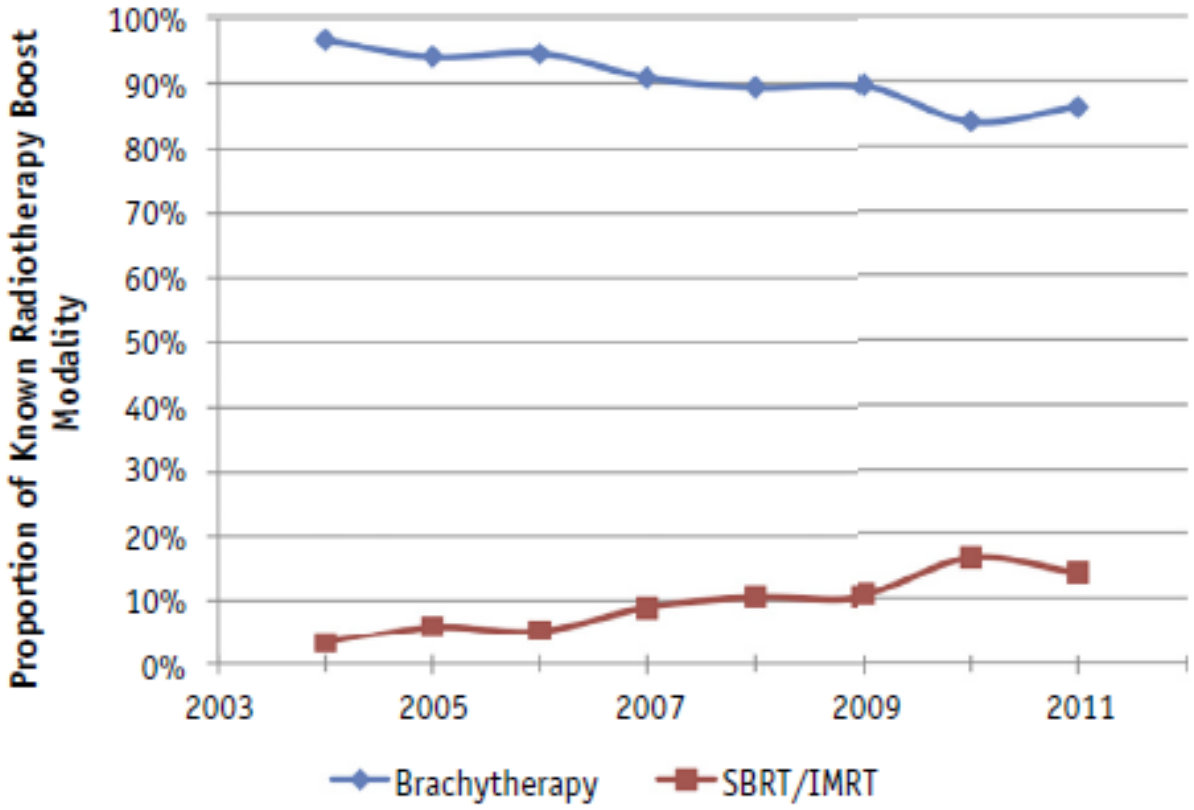


Fig. 1. Changes in radiation therapy boost modality utilization over time from 2004 to 2011. IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation therapy.

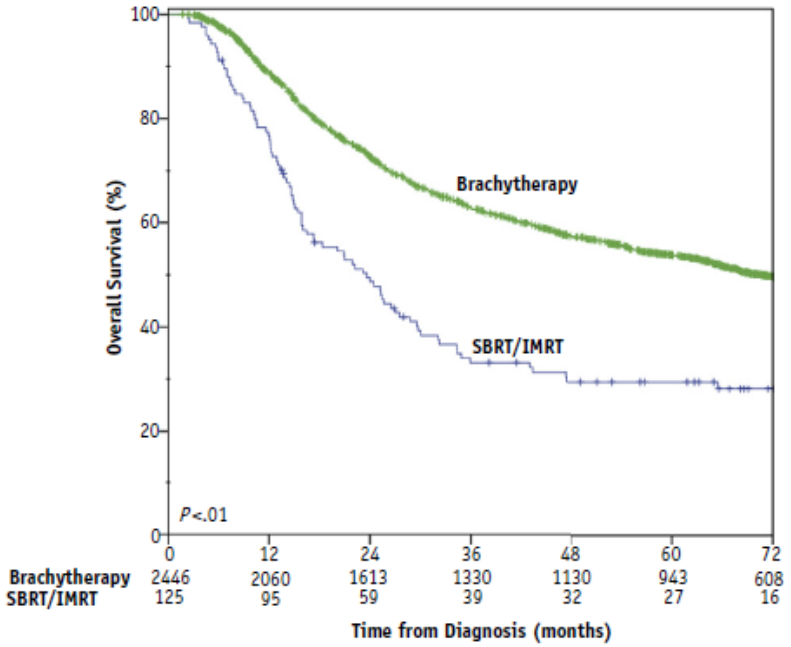


Fig. 2. Kaplan-Meier overall survival estimate stratified by boost modality. IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation therapy.

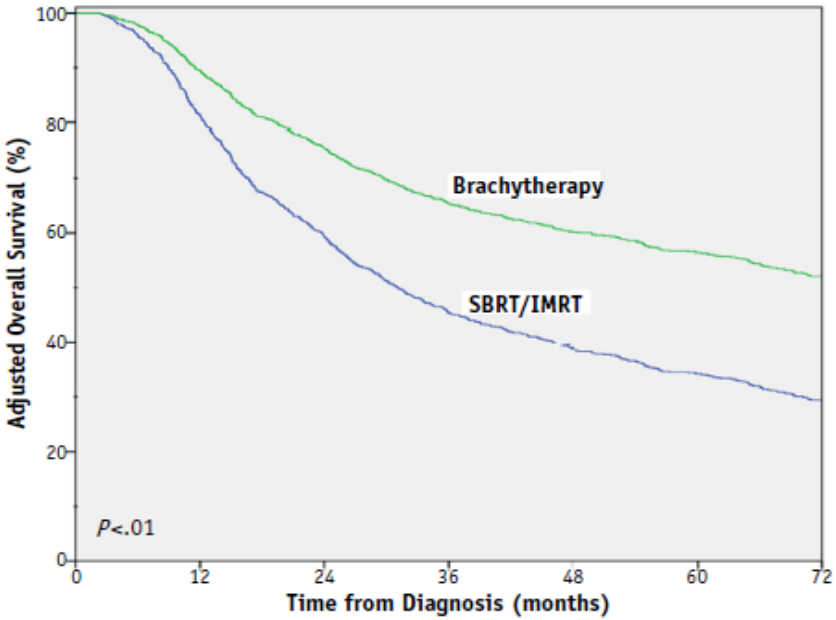


Fig. 3. Adjusted overall survival estimate, stratified by boost modality and corrected for significant variables on multivariable Cox proportional hazard model analysis (age, Charlson/Deyo score, stage, and chemotherapy utilization). IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation therapy.

SUMMARY

- **Pelvic IMRT**

  - IMRT /IGRT reduces toxicities especially in post op pelvic settings

  - Ongoing studies : BM sparing potential for further interventions

- **PA Region IMRT**

  - Potential to reduce toxicities

  - Dose Escalation protocols with PET : promising

- **SBRT – IMRT Vs BT**

  - Use of SBRT results in inferior outcome as compared to 2D BT

Patient preparation and principles of BT Application Counseling, Anesthesia and Procedure

Umesh Mahantshetty, DMRT, MD, DNBR

Professor, Radiation Oncology

TATA MEMORIAL HOSPITAL, MUMBAI, INDIA

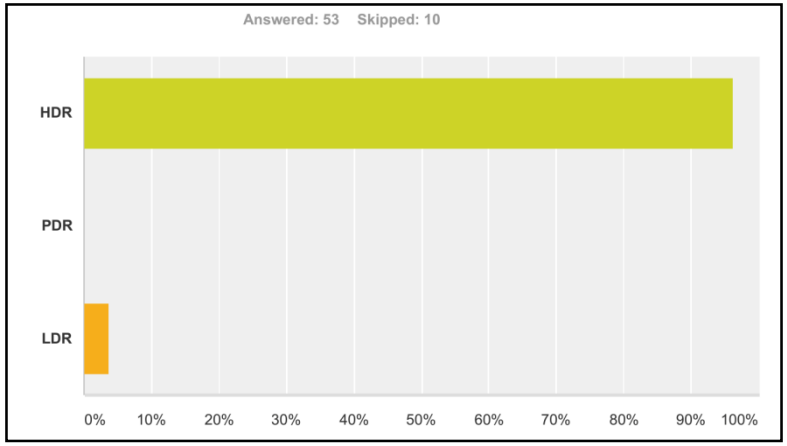
GYN GEC – ESTRO TEACHING FACULTY

OUTLINE

- Patient Selection
- Preplanning
- Pre-procedure Counseling and Preparation
- Principles of BT Application
- Post BT Treatment Care

Patient Selection (1)

- Cervical Cancer patients treated with radical radio (chemo) therapy
- Radical radiation therapy : combination of External & BT
- Brachytherapy: Majority centers practice fractionated High Dose Rate (HDR) System. LDR / PDR are the other systems.
- HDR Brachytherapy: fractionated with 2 - 6 fractions once weekly depending on FIGO Stage



Patient Selection (2)

- Brachytherapy boost is planned towards the end or after completion of external beam radiation therapy
- Pelvic examination to assess suitability for brachytherapy application
- **Brachytherapy Procedure Pre-requisites:**
  - Review for fitness to undergo anesthesia
  - Pelvic anatomy and tumor topography suitable for appropriate applicator placement
- **Pre-planning:** Tumor topography, Imaging & availability of applicators.

Imaging protocols MRI and CT

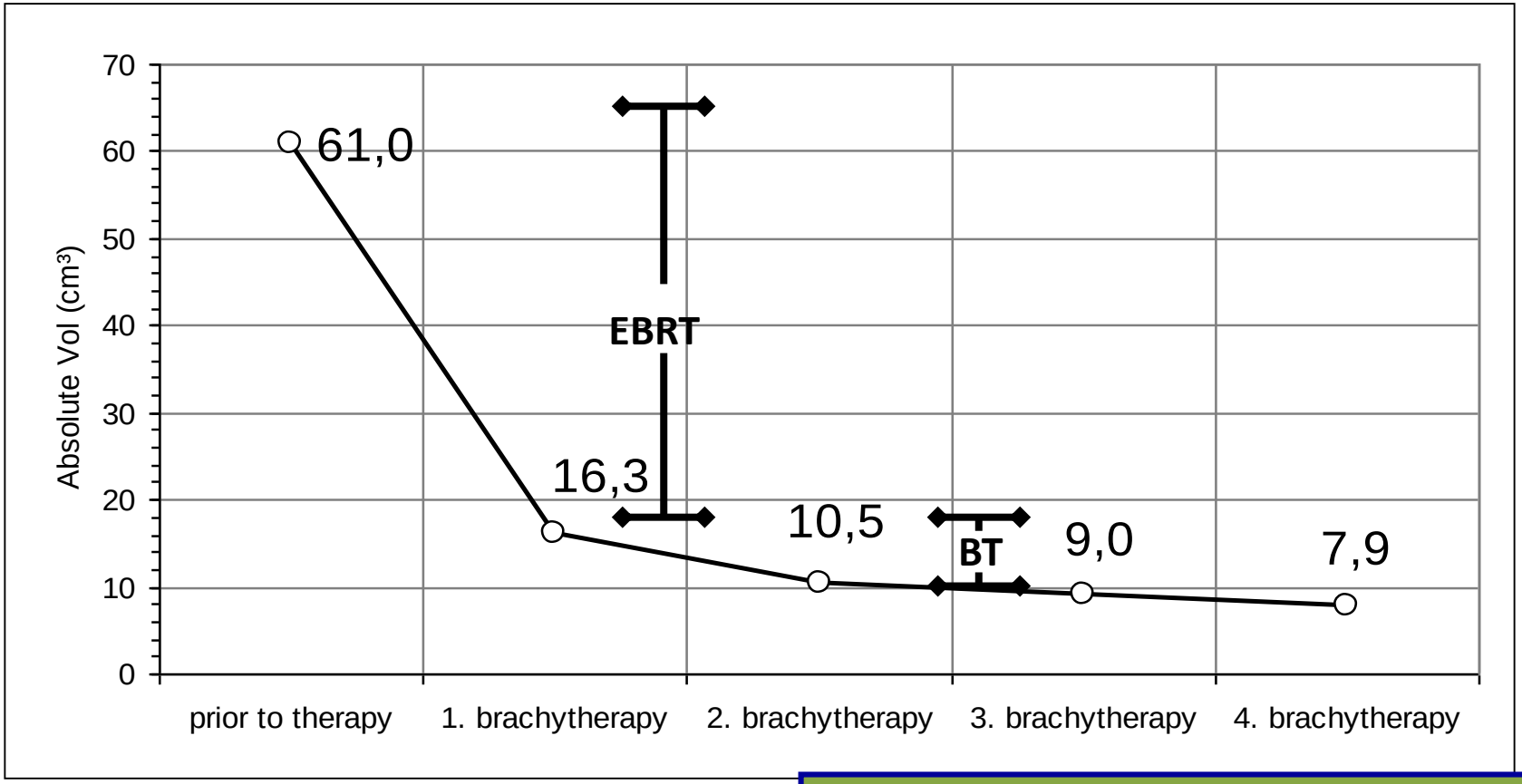
Key issues for image-guided radiotherapy

Quantitative tumor regression

Courtesy : Johannes Dimopoulos

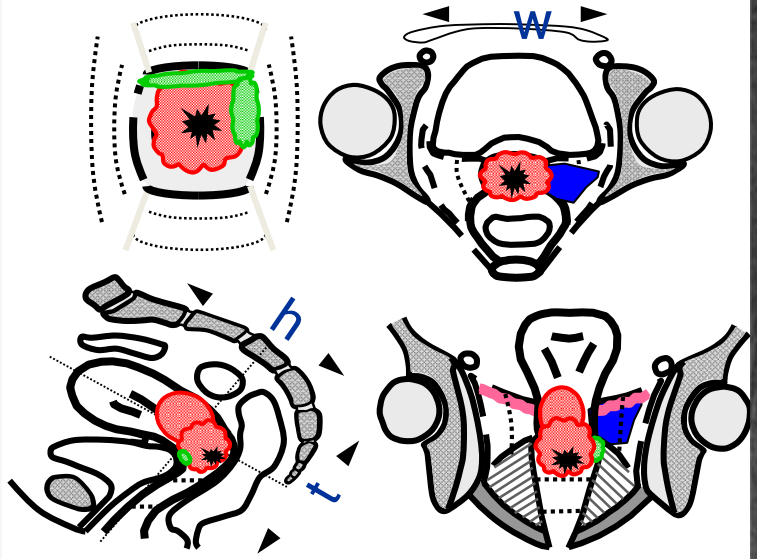
EBRT: tumor regression 75%
Brachytherapy: tumor regression 10%

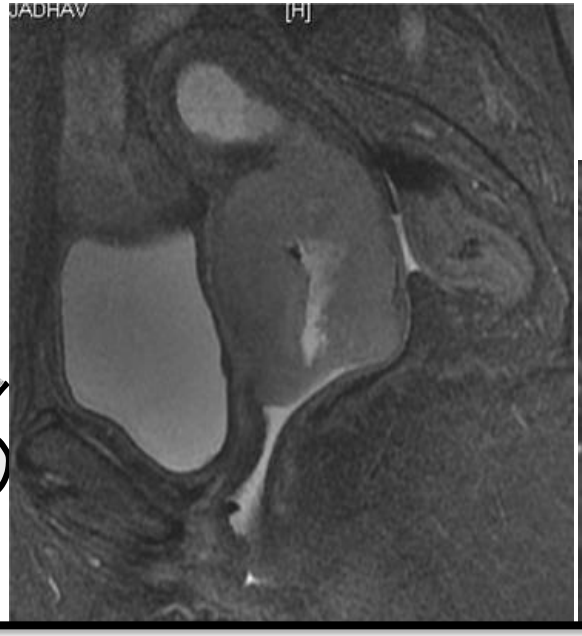
} easy to predict



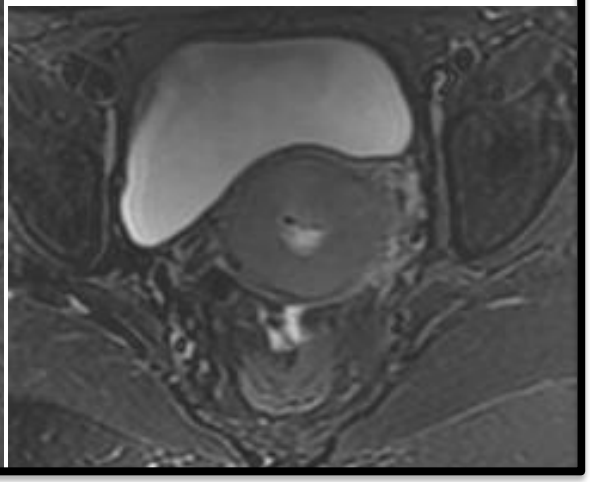
Dimopoulos et al. Strahlenther Onkol 2009

Clinical Drawing

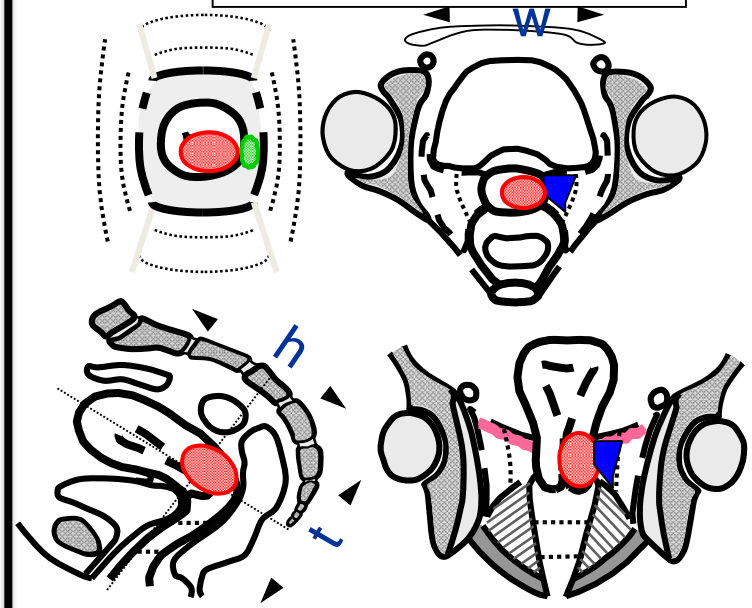


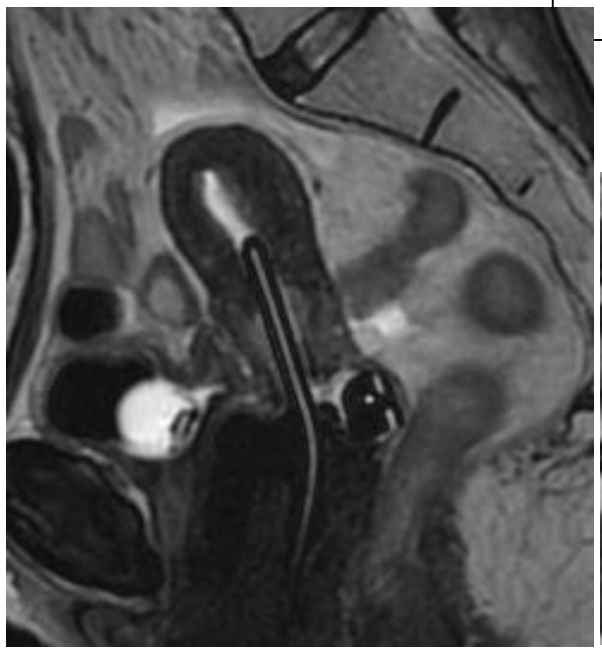


MR at Diagnosis

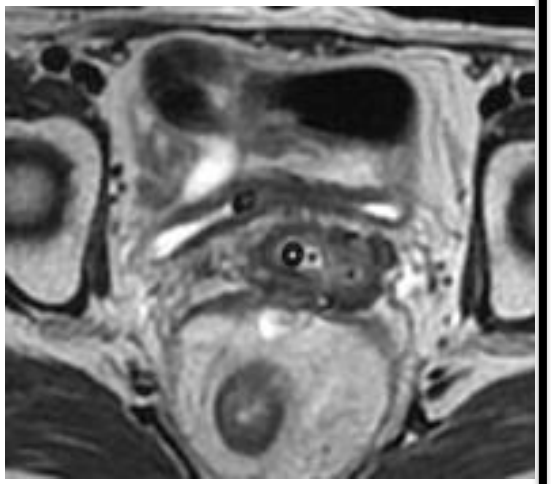


Clinical Drawing





MR at Brachytherapy



PREPLANNING

- ✧ Staging
- ✧ RADIO(CHEMO)THERAPY details
- ✧ Timing : depending upon response to EBRT
- ✧ Anesthesia fitness and type
- ✧ Assessment of response to EBRT
- ✧ Assessment of vagina: size of the ovoid / ring
- ✧ Admission to ward for preparation (Day: -1)

Pre-procedure Counseling, Instructions and Preparation for Brachytherapy Procedure (Day : -1)

- Counseling about the procedure in patients language
- Obtain written Informed Consent
- Pre-operative instructions:
  - Preparation of parts (perineum),
  - Bowel preparation by simple enema
  - Vaginal Douche
  - Nil by mouth at-least 4-6 hours prior to procedure

Pre-operative Counseling, Instructions and Preparation for Brachytherapy Procedure (Day : -1)

- Appropriate medications for existing co-morbidities
- Review latest blood investigations (anemia & electrolyte imbalance) and correction accordingly
- Evaluate patient suitability for Imaging (CT / MR)
- Check for Appropriate Applicators availability

Principles of the BT Procedure - 1

- ✧ Secure intravenous access.
- ✧ Check for the desired Instrumentation before BT procedure starts
- ✧ Short Anesthesia
- ✧ Position patient in lithotomy position.
- ✧ Parts painted and draped.
- ✧ Foley's catheterization and 7 ml of Radio opaque contrast
- ✧ EUA: response to external RT

  determine appropriate ovoid dimension.

Q. Do you do the BT Procedure under anesthesia?

A. Yes

B. No

Q. If yes, which Anesthesia do you routine utilize?

A. Short General Anesthesia
B. Spinal Anesthesia
C. Sedation / Blocks / Analgesics
D. Verbal Anesthesia

Anesthesia for Brachytherapy Procedure

- **Principle: Adequate relaxation for cervical dilatation, vaginal packing and application reproducible esp. in fractionated HDR**
- Short General Anesthesia: preferred for proper application
- Alternatives if patient high risk for general anesthesia:
  - Spinal anesthesia with epidural analgesia
  - Sedation and analgesics
  - Regional Blocks: Obturator blocks
  - Local blocks: Para-cervical blocks

Brachytherapy Techniques (2)

- Choice of appropriate technique depends on:
  - residual tumor topography at brachytherapy
  - availability of brachytherapy applicators
  - availability of expertise
- In General: depending on residual disease at brachytherapy
  - Disease confined to cervix and medial third parametrium: IC alone
  - Extensions beyond medial third parametrium: IC + IS combination
  - Extensive disease not amenable to IC + IS: IS
- Applications can be modified in subsequent fractions (esp. HDR)

Brachytherapy Techniques (1)

- **Intracavitary (IC)**

  - Tandem - Ovoid, Tandem - ring, Tandem - cylinder etc.

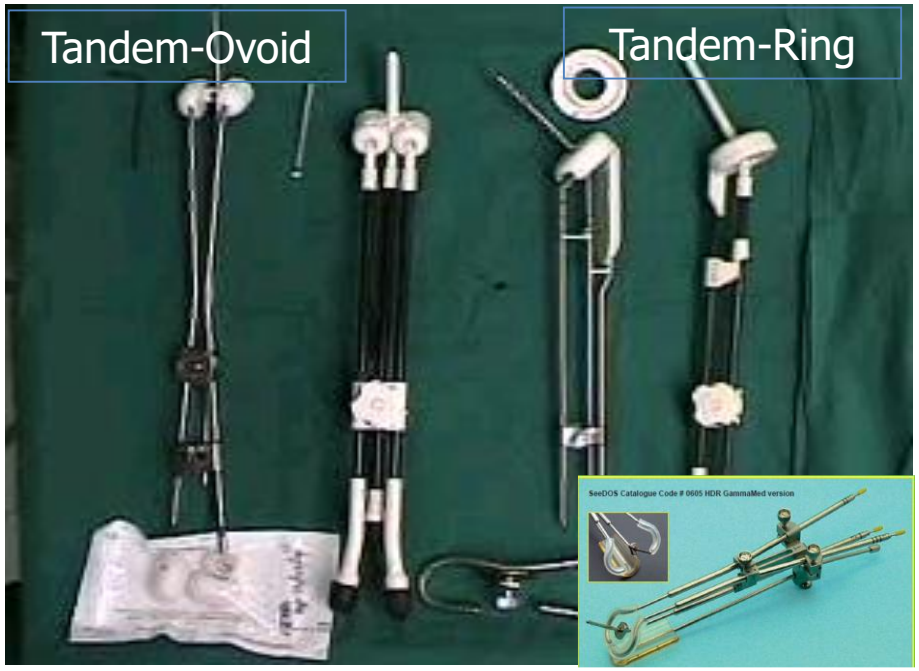
- **Combined Intracavitary and Interstitial (IC + IS)**

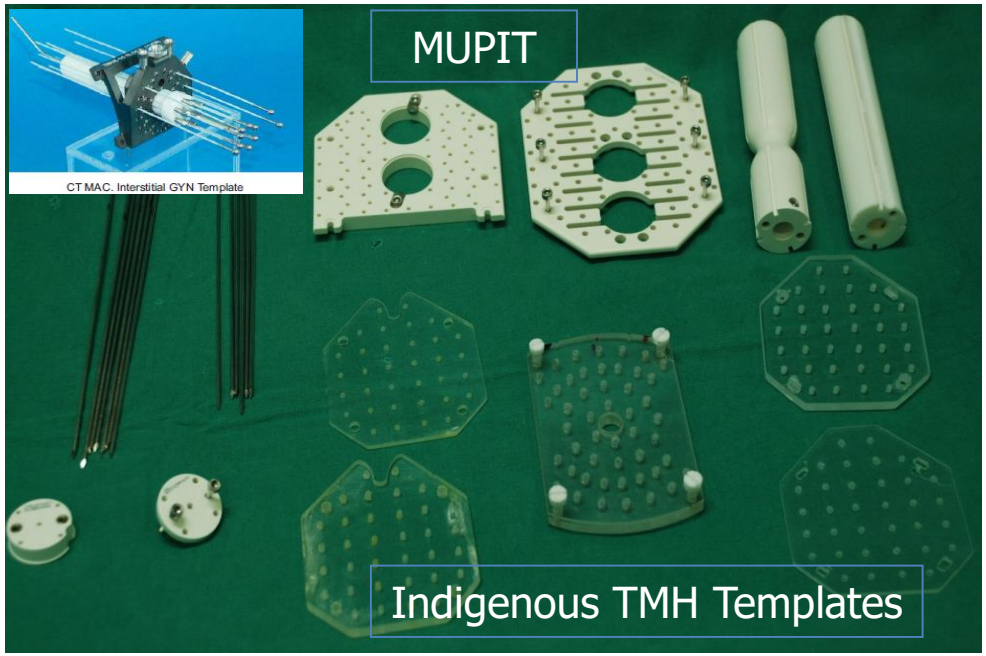
  - Vienna Applicator, Utrecht applicator, etc.

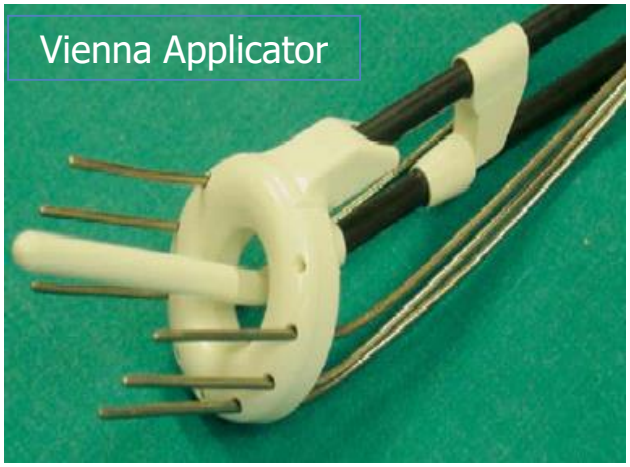
- **Interstitial (IS)**

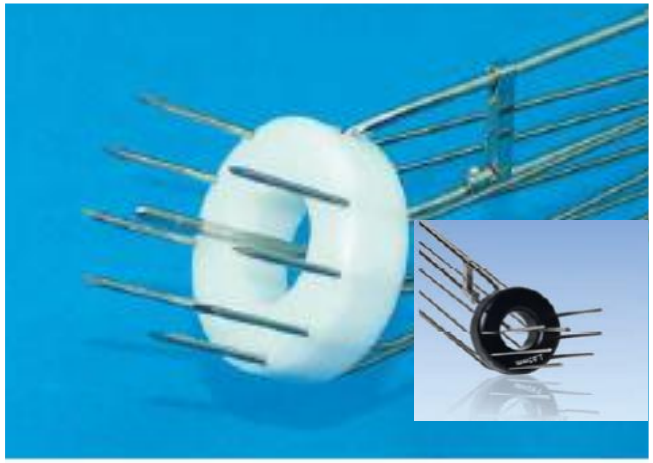
  - MUPIT, Indigenous Templates with needles / tubes

Brachytherapy Applicators for GYN Cancers









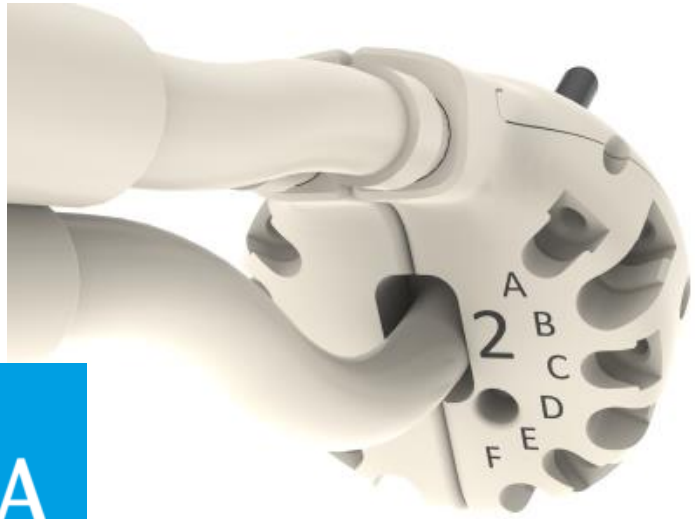
CT Vienna System with Titanium Needles

Tandem - Ring with needles/tubes

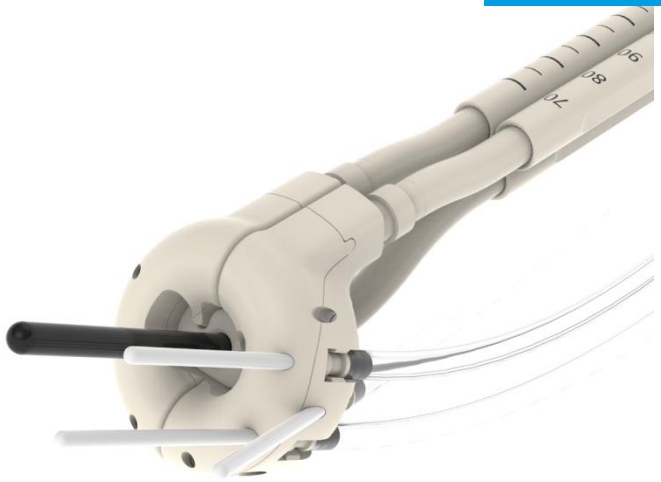
Tandem - Ovoid with tubes

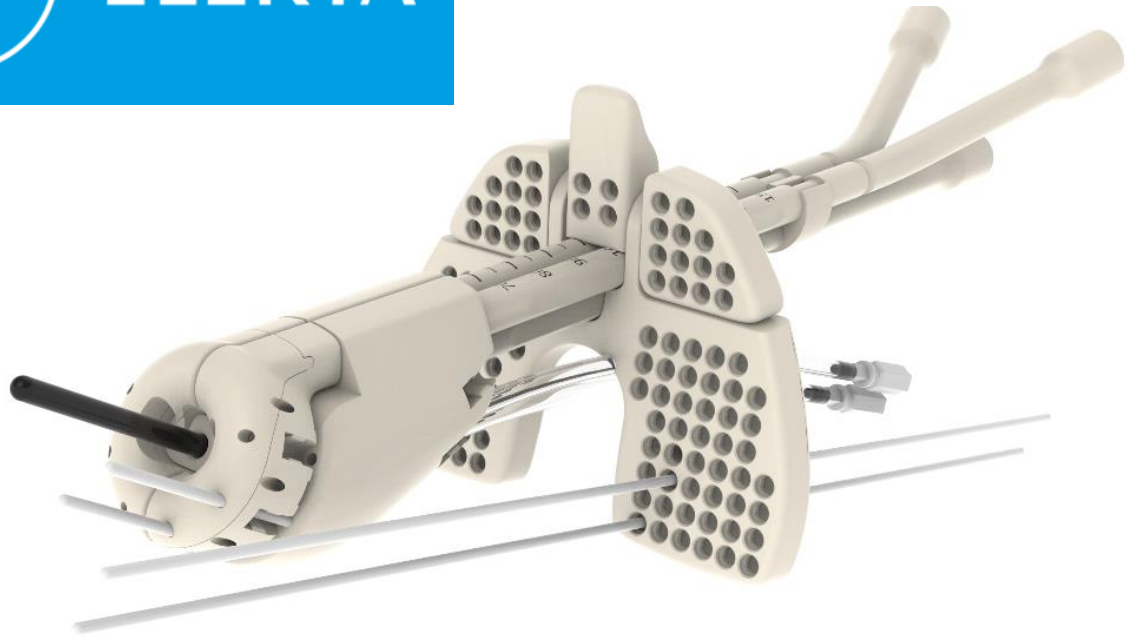
Latest Development in Applicators

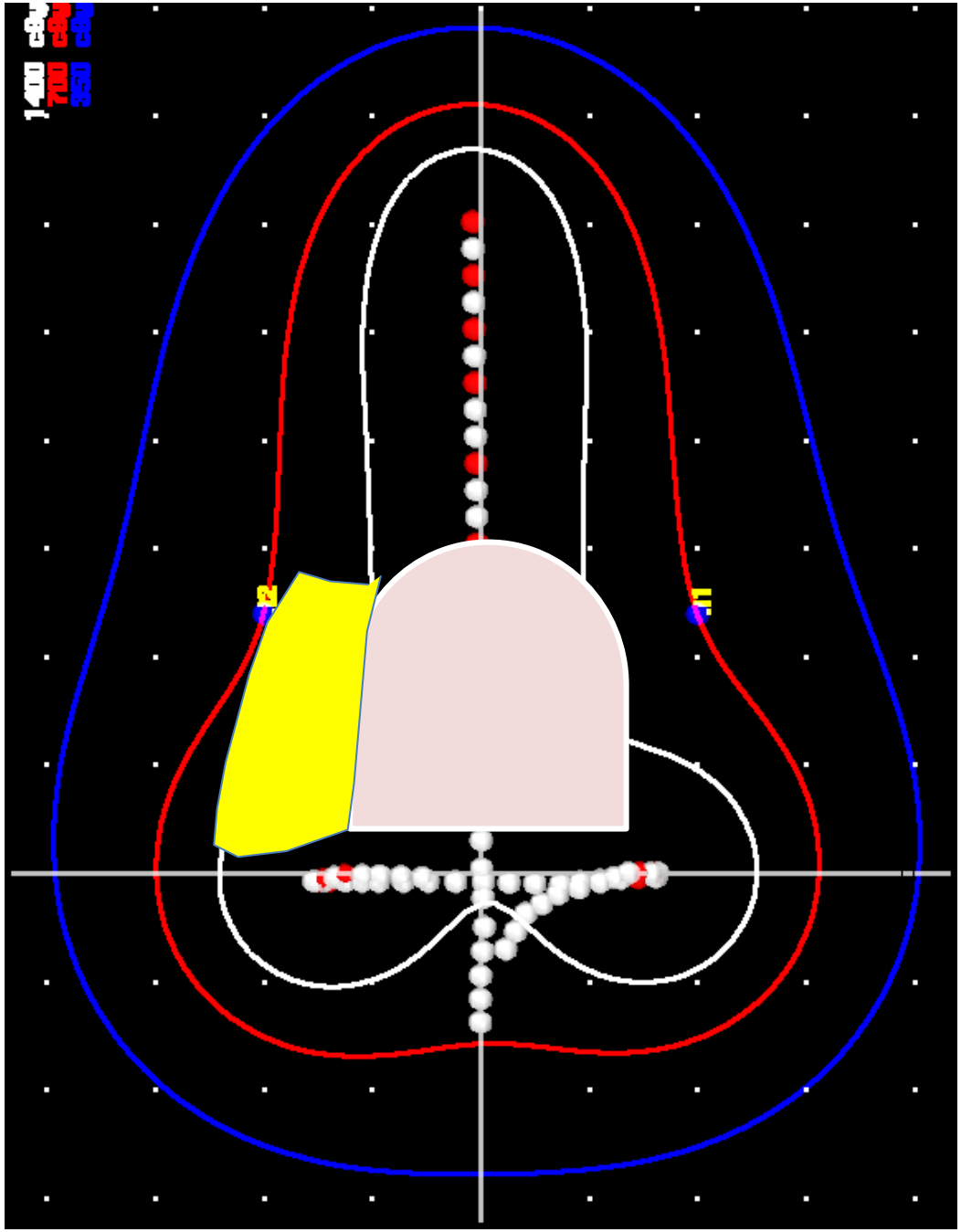
VENEZIA GYN APPLICATOR



ELEKTA






1400
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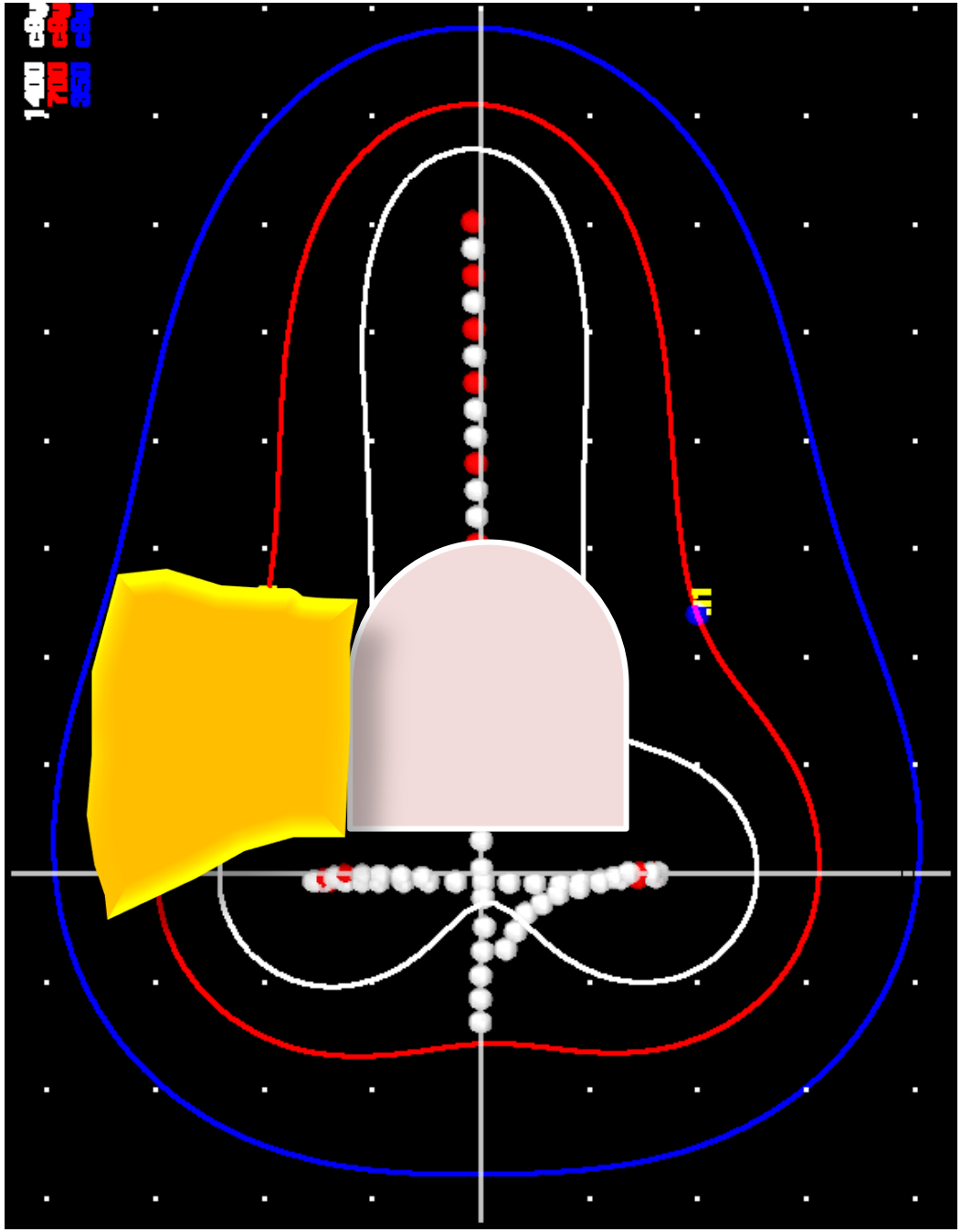


VIDEO PRESENTATION
OF
BT PROCEDURE

Treatment delivery & Care in the Ward

- Removal of the applicators under sedation/ analgesics after treatment delivery
- Shift of patient to the ward from treatment unit
- Follow the post procedure instructions
- Back Care, Bowel Care, Hydration, Catheter care
- Patient Position : to avoid movements / displacement of the applicators
- Medications, (Antibiotics, anti-inflammatory) , Analgesia (epidural)
- Intake – Output charting,
- Regular monitoring of Vital parameters

REMOVAL OF THE APPLICATOR

Intracavitary Alone:

- Unlock the Applicator Assembly
- Each tube / catheter of ICA component is removed separately
- A gentle vaginal examination with local anesthesia jelly is performed to check for bleeding/ vaginal tears

IC + IS

- Unlock the Applicator Assembly
- Uterine tandem is gently pulled out
- The Vienna ring / Ovoid with Needles/ tubes assembly is pulled out gently in total
- Be careful with the bent needles / needle tips not injuring the vagina
- A gentle vaginal examination with local anesthesia jelly is performed to check for bleeding/ vaginal tears

Management of acute bleeding after removal

Do not panic!!!

- Secure the IV access and start IV fluids
- Nurse : TO monitor the vitals Unlock the Applicator Assembly
- At removal : look at the needle / tube tips
- Needles / tubes with fresh blood tinge are usually potential spots
- Bimanual compression with betadine gauze & local anesthetic rolled on your fingers
- Maintain the compression for atleast 7- 10 minutes
- Estimate the Bleeder : Arterial Vs Venous or vaginal tear
- To perform CT pelvis after patient is stable to assess pelvic collection

“Man often becomes what he believes himself to be.

If I keep on saying to myself that I cannot do a certain thing, it is possible that I may end by really becoming incapable of doing it. On the contrary, if I have the belief that I can do it, I shall surely acquire the capacity to do it even if I may not have it at the beginning.” — Mahatma Gandhi

Brachytherapy Skills?

Work hard to Strengthen your skills – technology will follow you !!

THANK YOU

FOR YOUR ATTENTION !

Applicators for intracavitary treatment of cervical cancer

Primoz Petric

National Center for Cancer Care and Research, Doha, Qatar

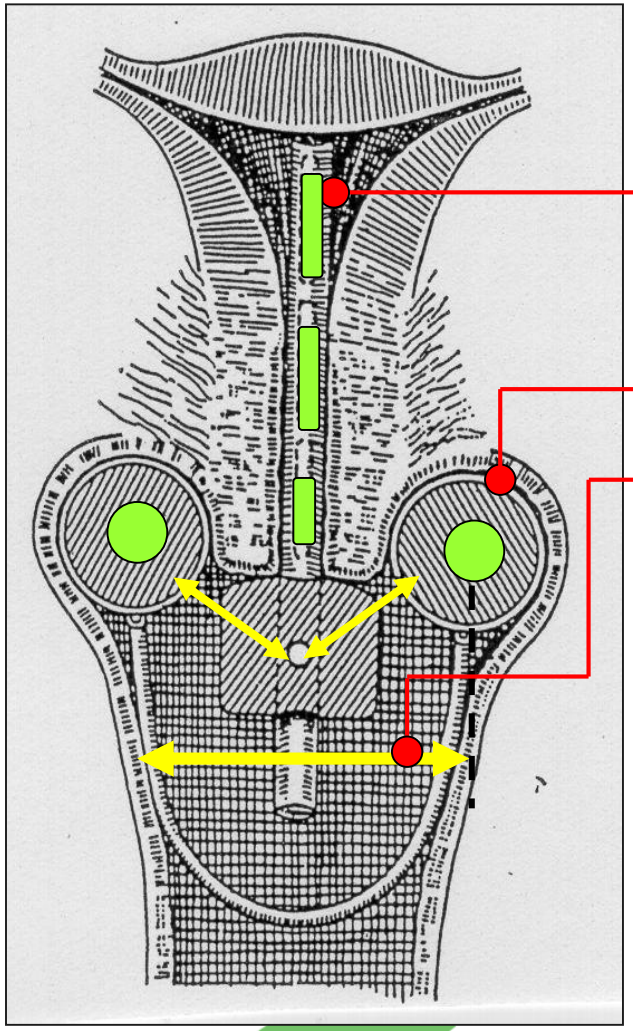
Adapted and Presented by

Richard Pötter, Medical University Vienna

Historical Systems & Techniques

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

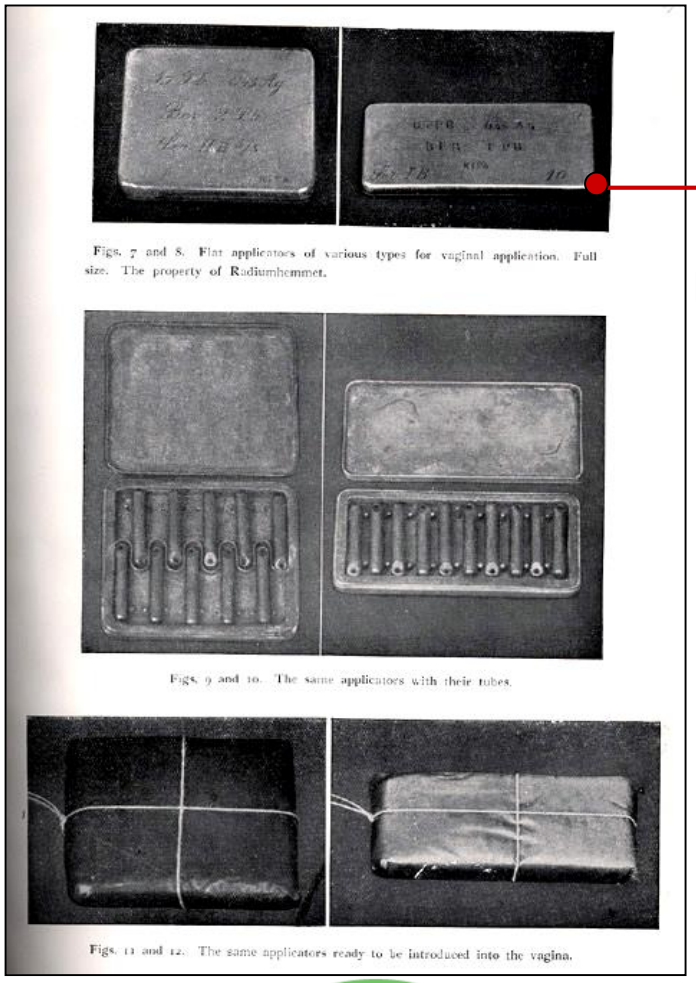
- X mg of ^{226}Ra for Y hours

Typical application

- ≈ 5 days (*120 h*)
- 7000-8000 mgh

Classical Stockholm method

1913-1914: Radiumhemmet, Stockholm, Sweden

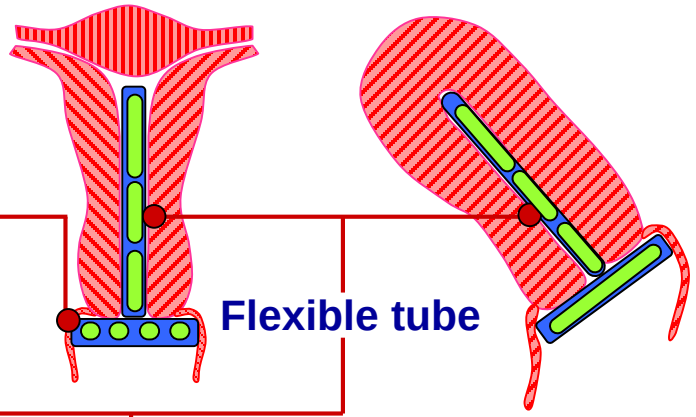


Figs. 7 and 8. Flat applicators of various types for vaginal application. Full size. The property of Radiumhemmet.

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

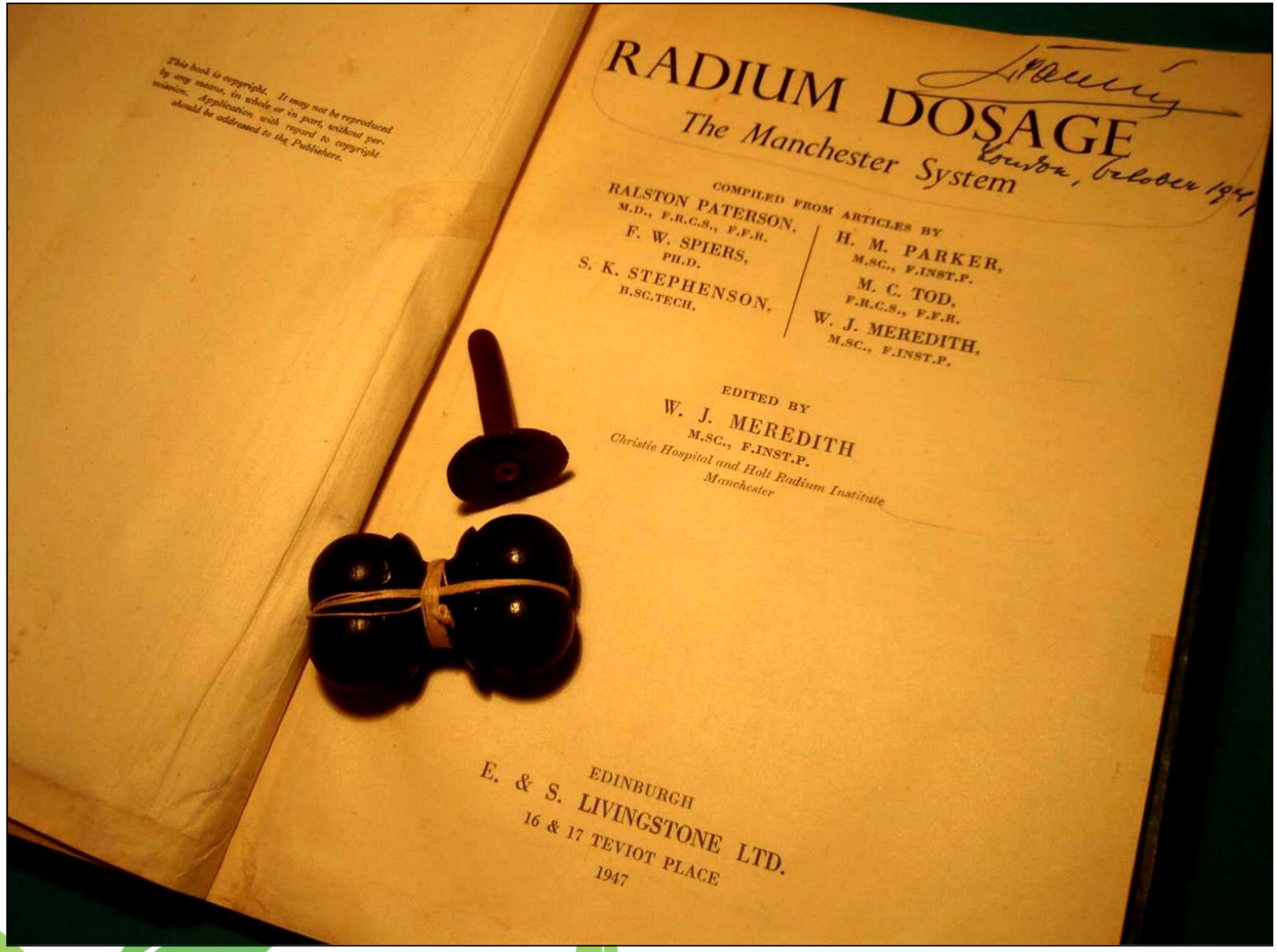
- X mg of ^{226}Ra for Y hours

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

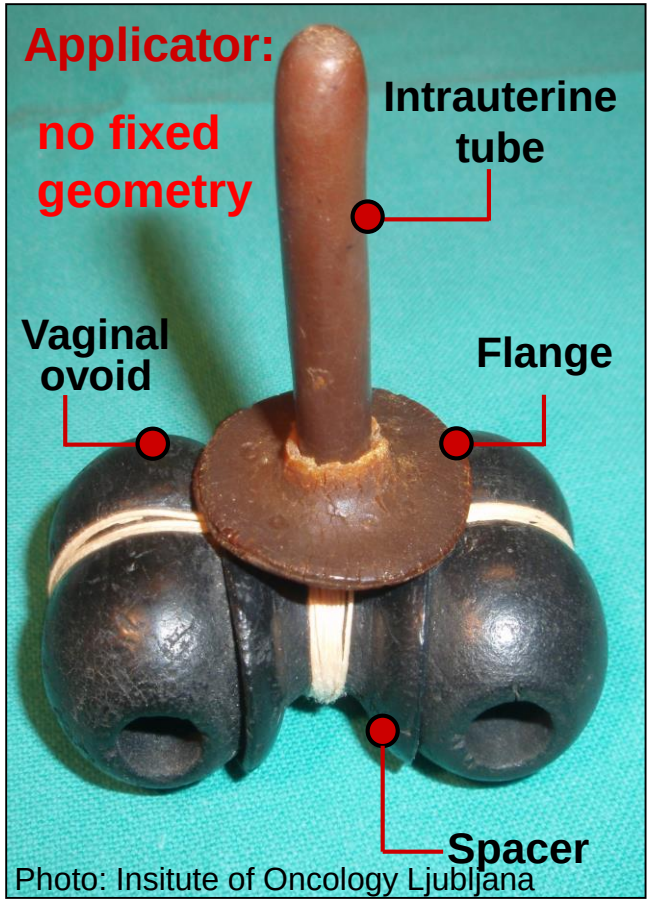
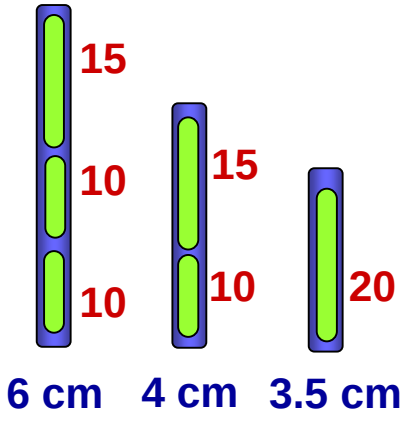
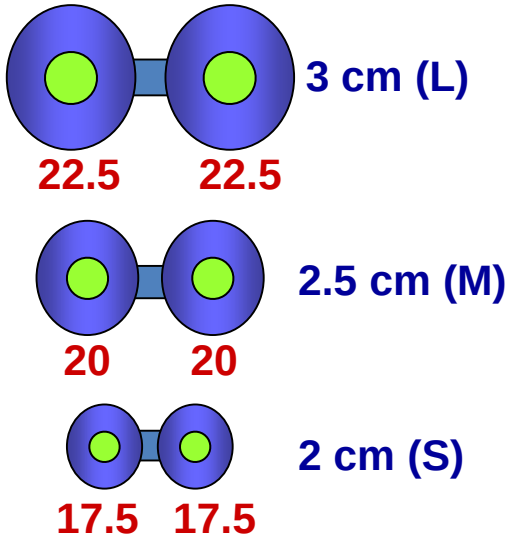


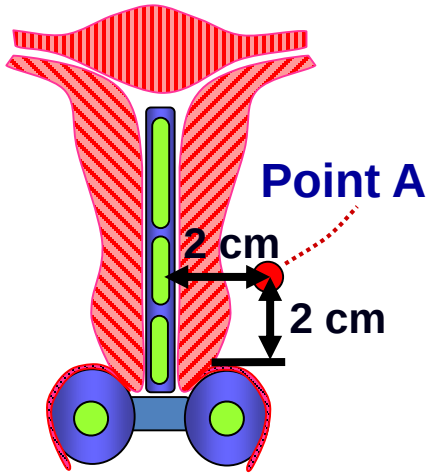
Photo: Insitute of Oncology Ljubljana

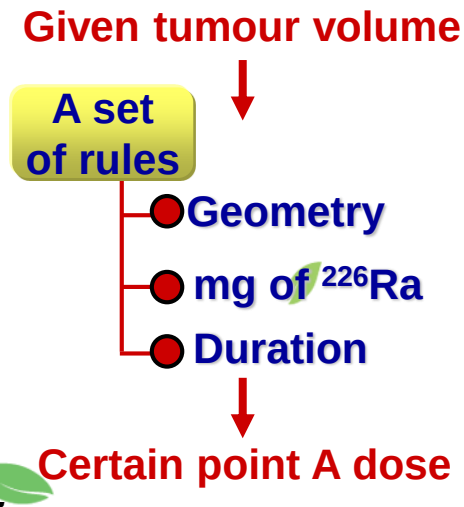
^{226}Ra preloading (mg):





TYPICAL TREATMENT:
140 hours for 7500 R at point A
(dose rate 53 R/h)

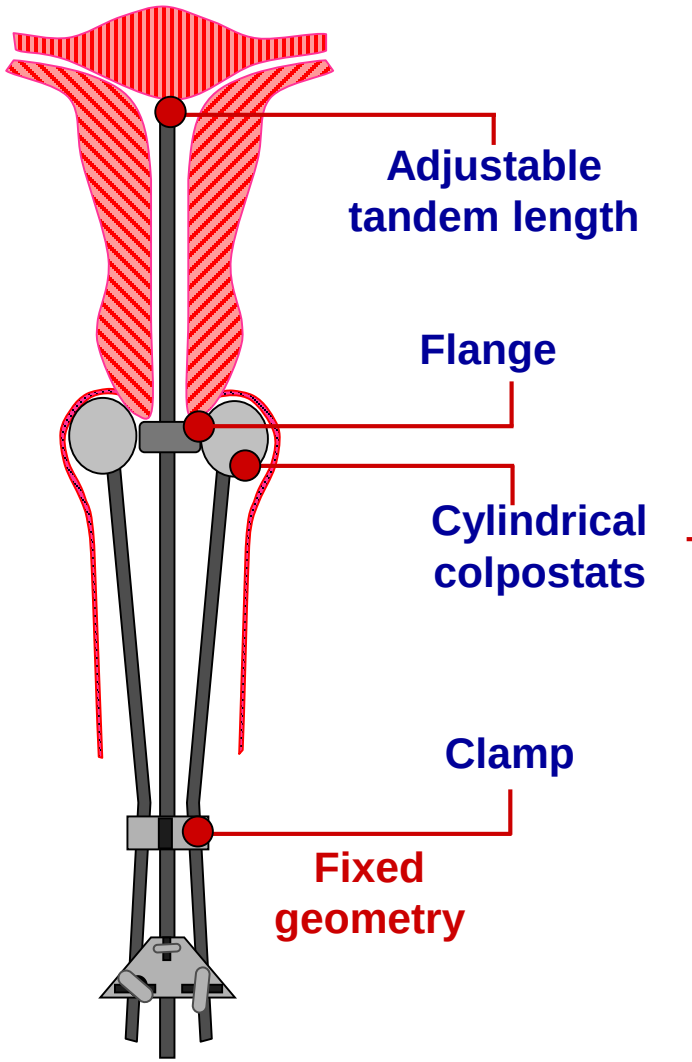


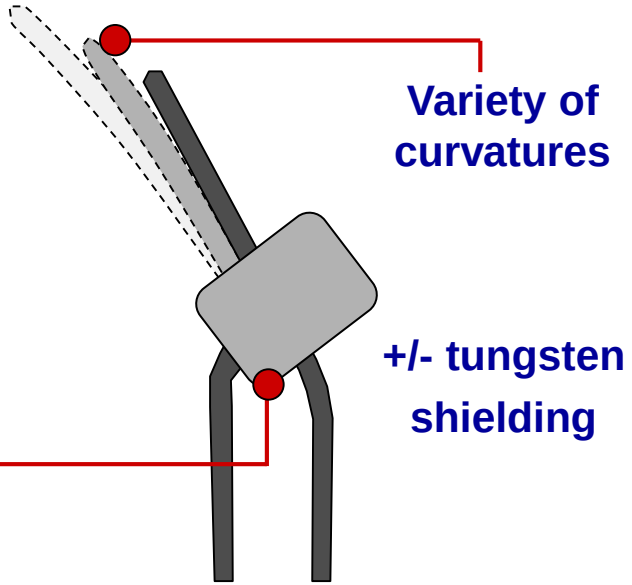


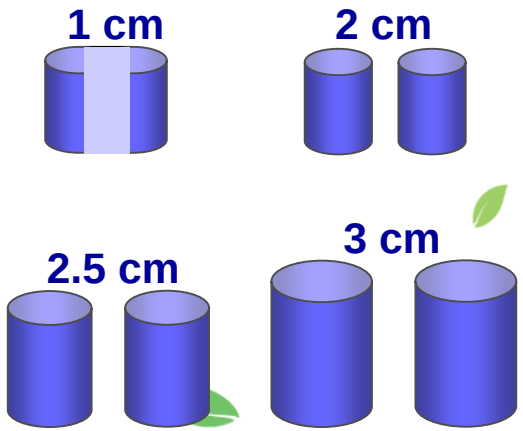
Meredith WJ, ed.. Radium dosage. The Manchester system. Edinburgh;1947.

Fletcher–Suit–Delclos–Horiot Technique

1950's: Fletcher





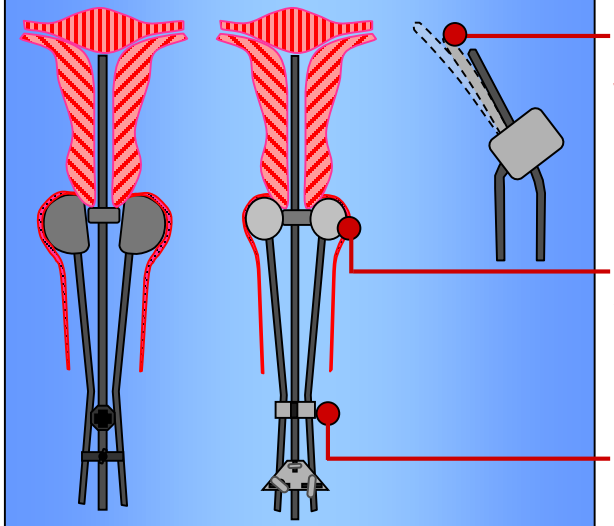


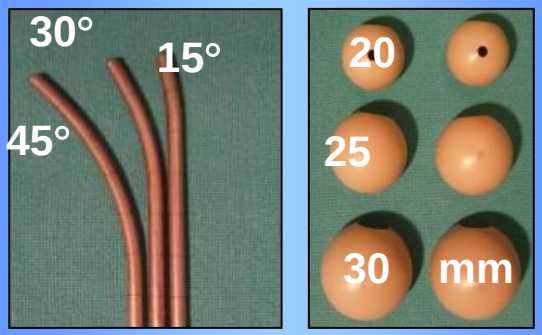
Modern Intracavitary Techniques

Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher tyle

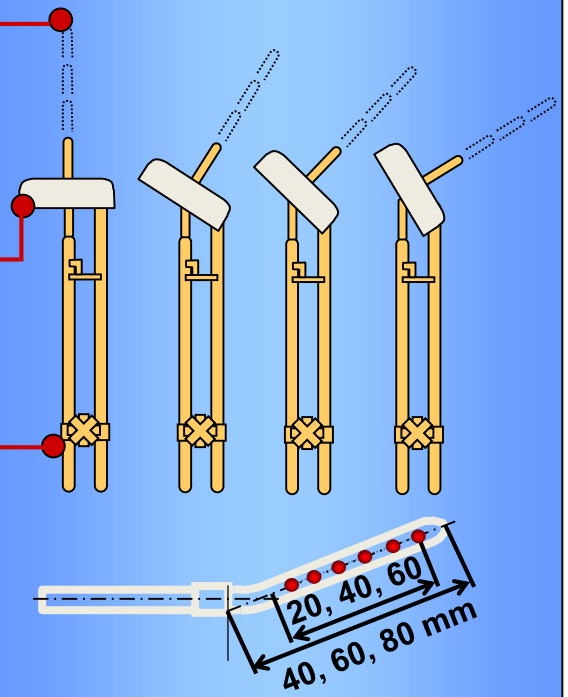


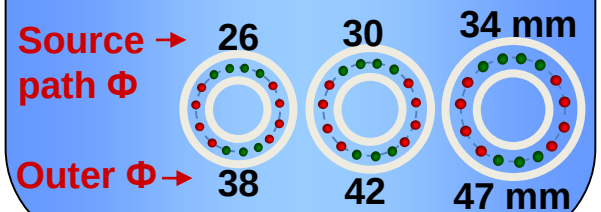


Common features:

- Uterine Tandem: various lengths, angles or curvatures
- Ovoids, cylinders, rings various outer & source path diameters
- Clamp

Stockholm style

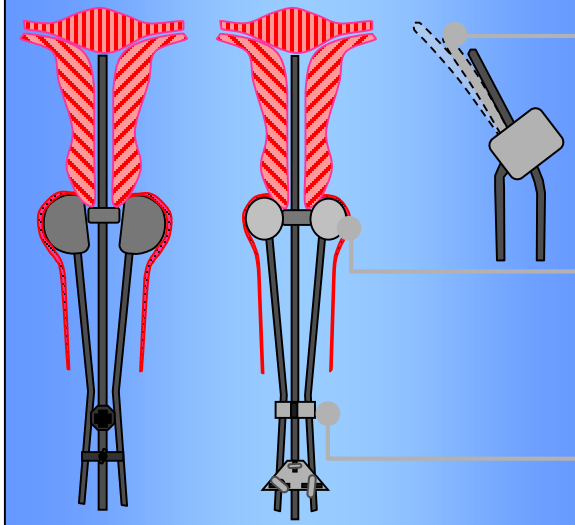




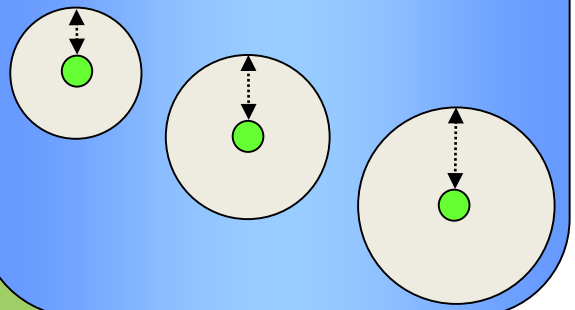
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Varies with diameter



Common features:

Uterine Tandem:
various lengths,
angles or curvatures

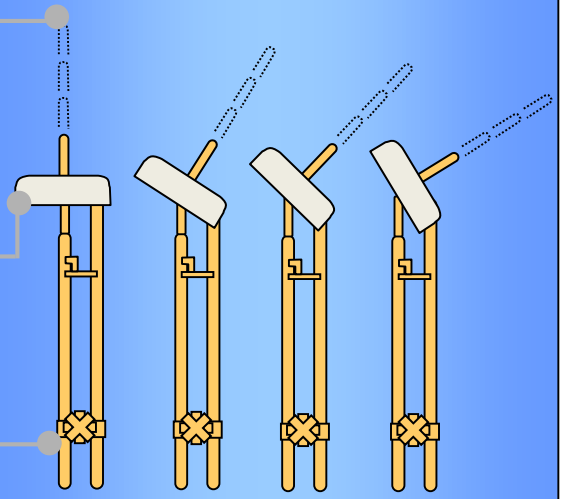
Ovoids, cylinders, rings
various outer & source
path diameters

Clamp

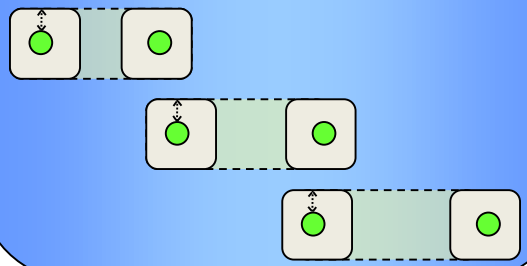
Differences:

Thickness of
ovoids and rings

Stockholm style



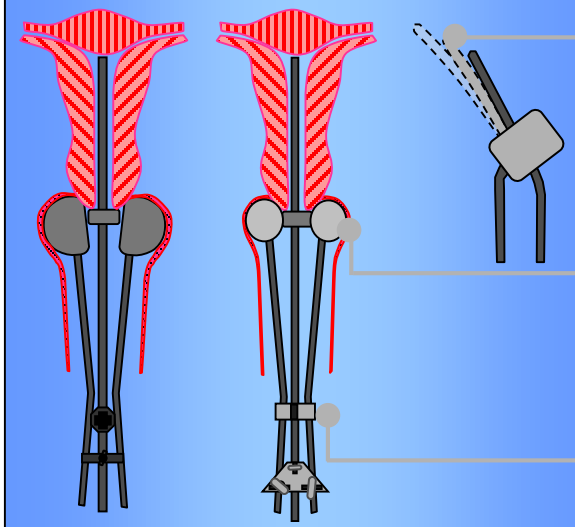
Constant



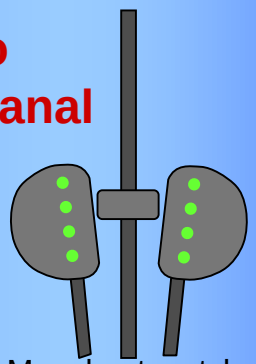
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Parallel to cervical canal



Manchester style

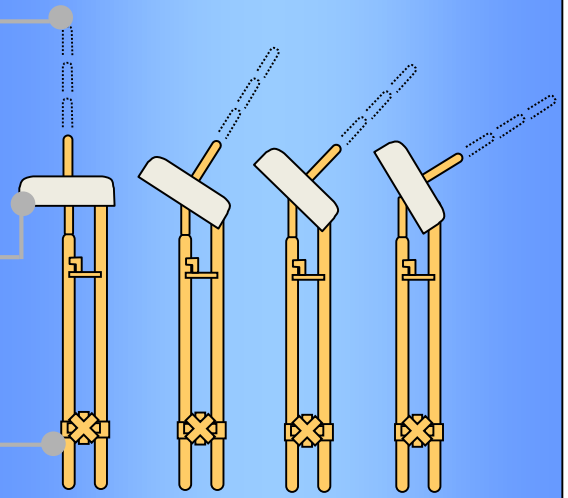
Common features:

- Uterine Tandem: various lengths, angles or curvatures
- Ovoids, cylinders, rings various outer & source path diameters
- Clamp

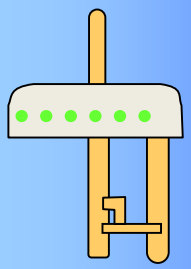
Differences:

Source path orientation

Stockholm style



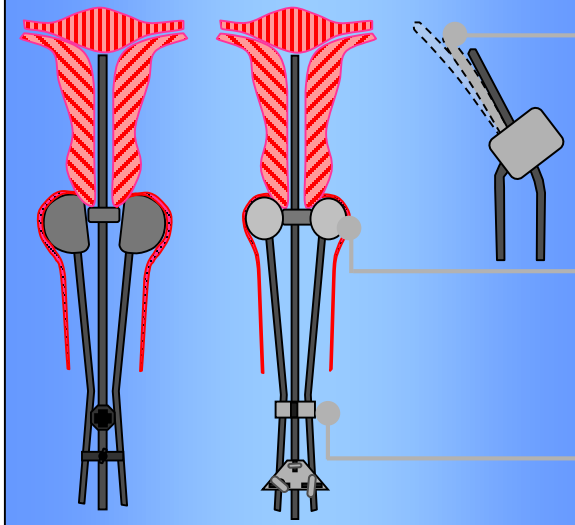
Perpendicular to cervical canal



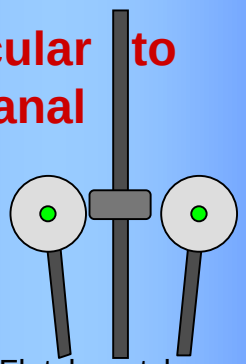
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Perpendicular to cervical canal



Fletcher style

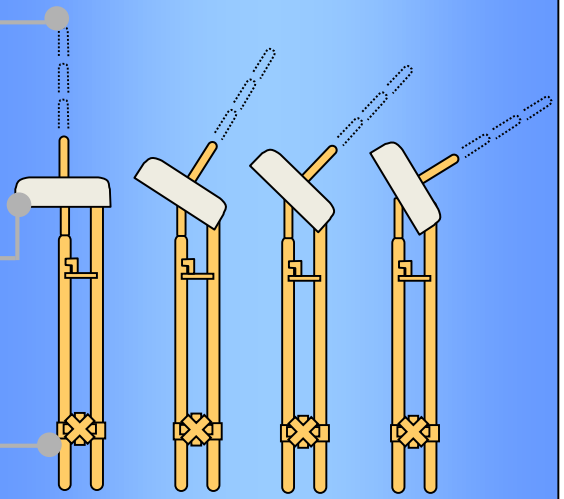
Common features:

- Uterine Tandem: various lengths, angles or curvatures
- Ovoids, cylinders, rings various outer & source path diameters
- Clamp

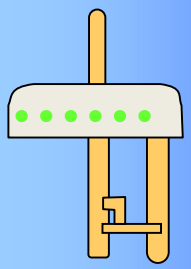
Differences:

Source path orientation

Stockholm style



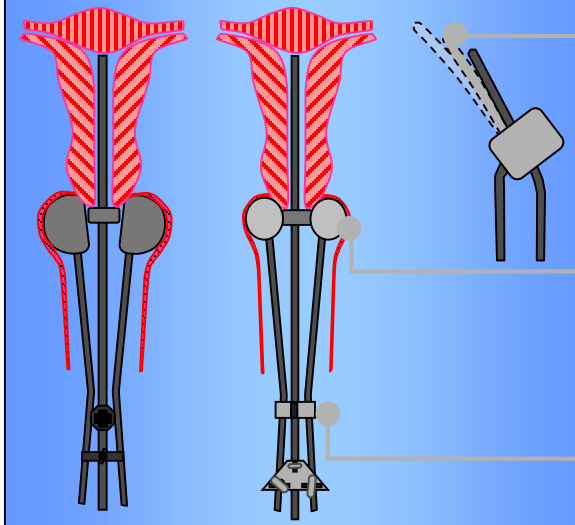
Perpendicular to cervical canal



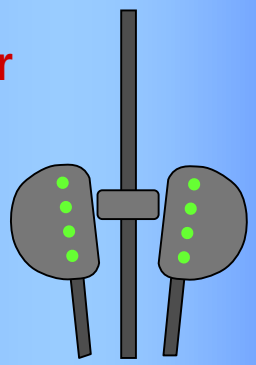
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Lower



Common features:

Uterine Tandem:
various lengths,
angles or curvatures

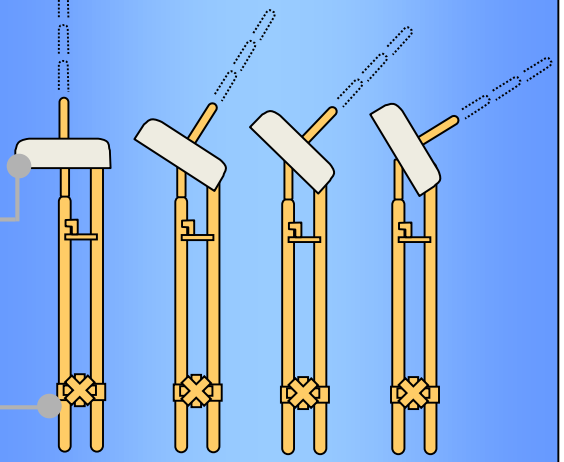
Ovoids, cylinders, rings
various outer & source
path diameters

Clamp

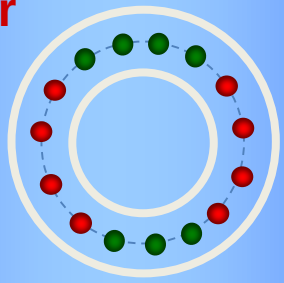
Differences:

Loading flexibility

Stockholm style



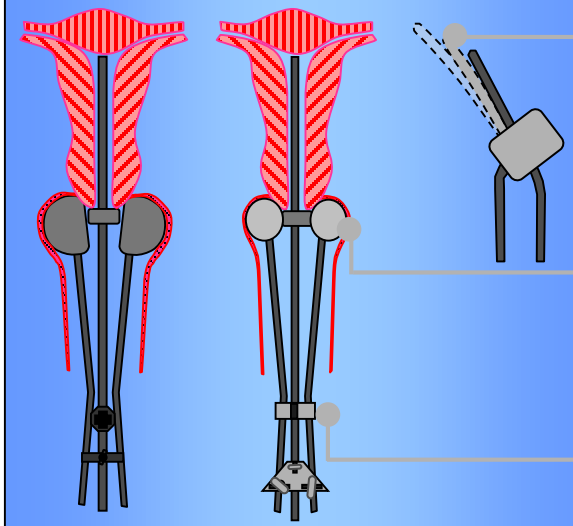
Higher



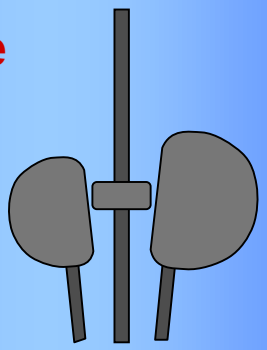
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Possible



Common features:

Uterine Tandem:
various lengths,
angles or curvatures

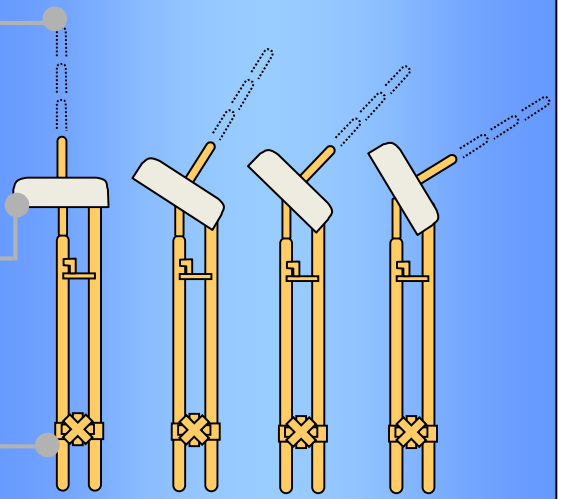
Ovoids, cylinders, rings
various outer & source
path diameters

Clamp

Differences:

Asymetric insertion

Stockholm style

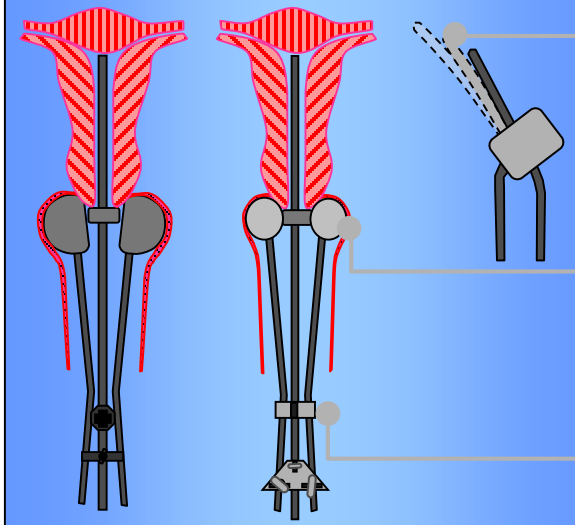


Not applicable

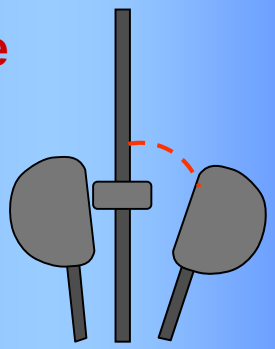
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Possible



Common features:

Uterine Tandem:
various lengths,
angles or curvatures

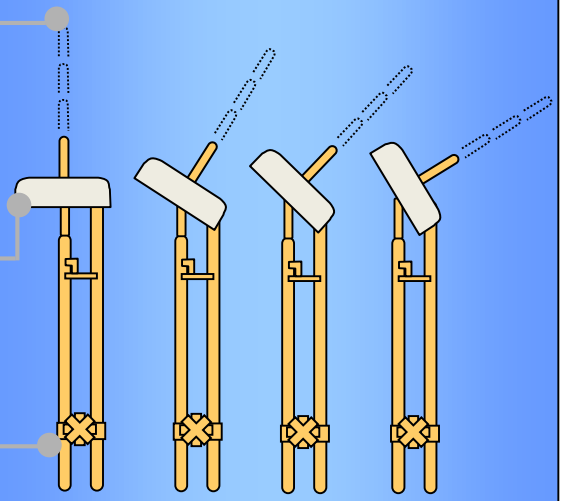
Ovoids, cylinders, rings
various outer & source
path diameters

Clamp

Differences:

Adjustable spacing

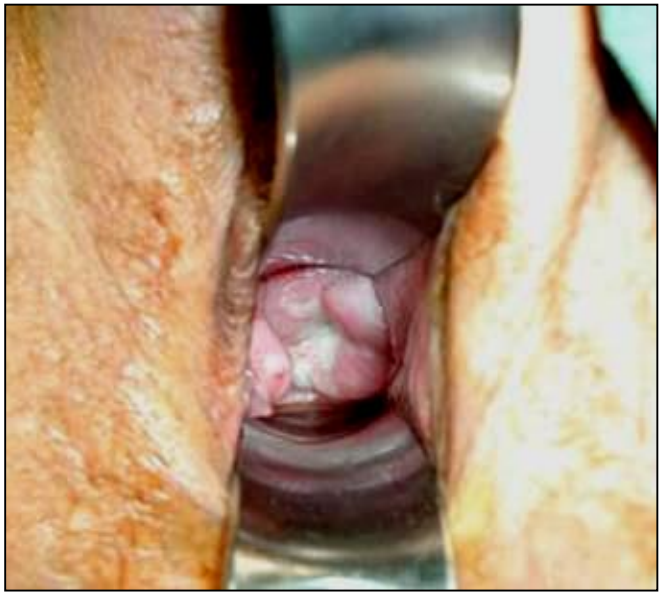
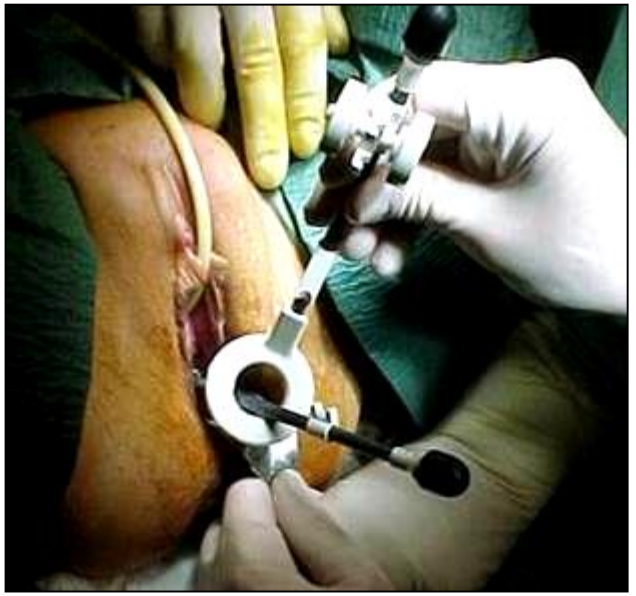
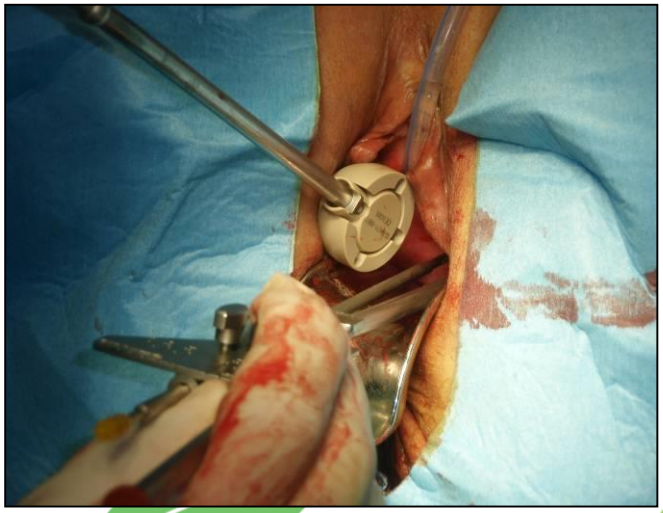
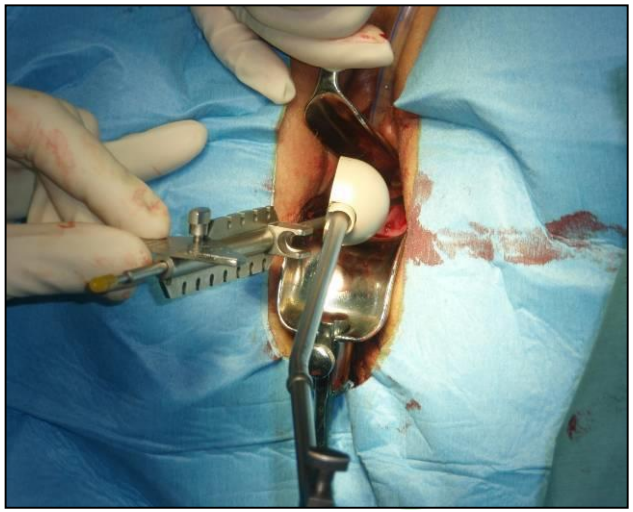
Stockholm style



Not applicable

Modern Intracavitary Techniques

Applicator insertion

Modern Intracavitary Techniques

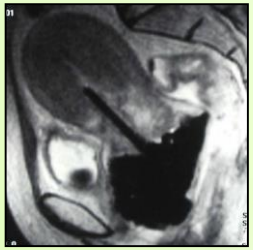

Concept: same as 100 years ago…

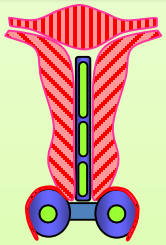
Modern IC techniques

Materials: Imaging…

Channel diameters: Smaller

Loading patterns: Mimicking historical

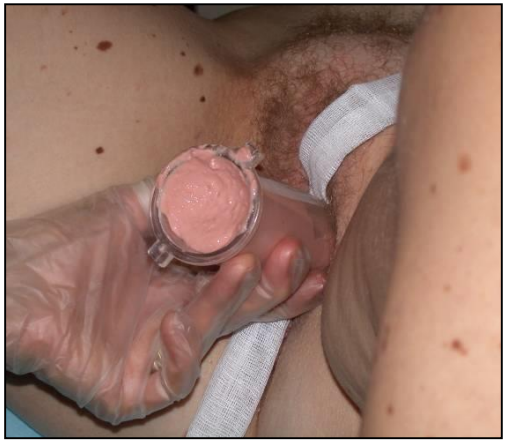


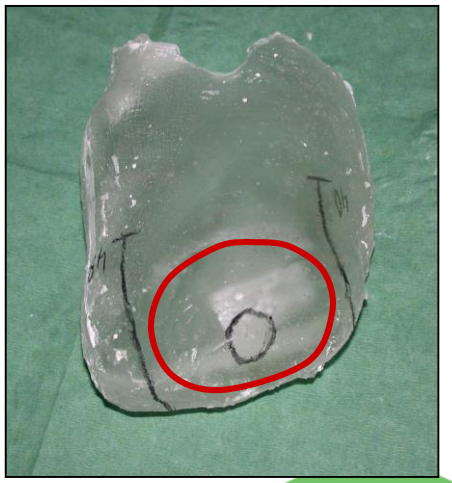


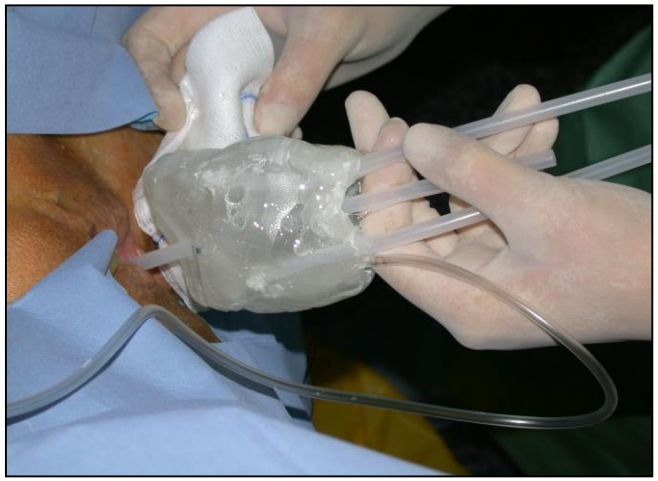
Mould Technique

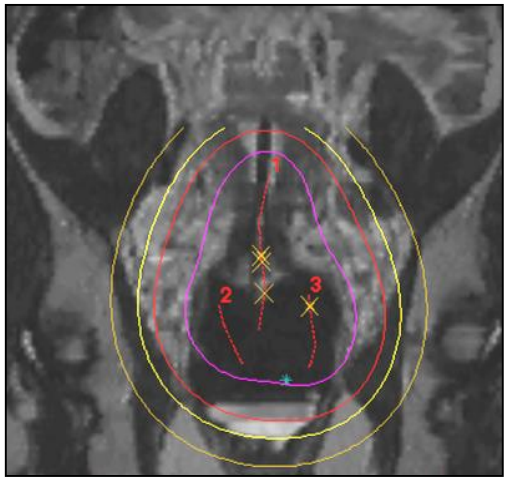
Personalized applicators

- Individually adapted to anatomy & tumour
- Good patient tolerance
- No need for vaginal packing
- MRI compatibility
- Prolonged bed rest avoided





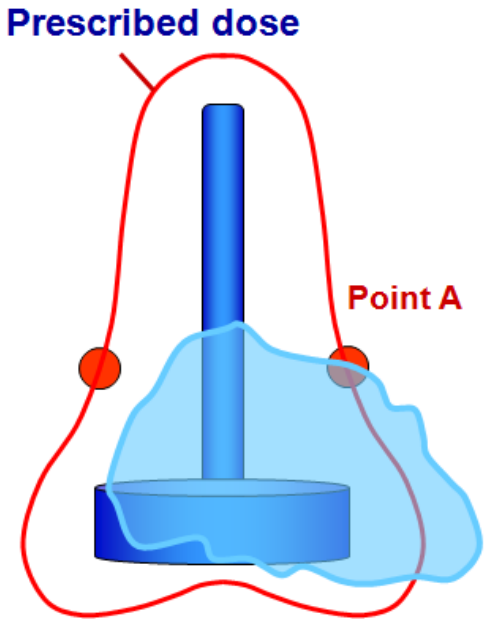




Courtesy: C. Haie-Meder, IGR, Paris, France

Limitations of modern IC applicators

How far from point A can we “push” the prescription isodose?



A. Up to ~1 mm

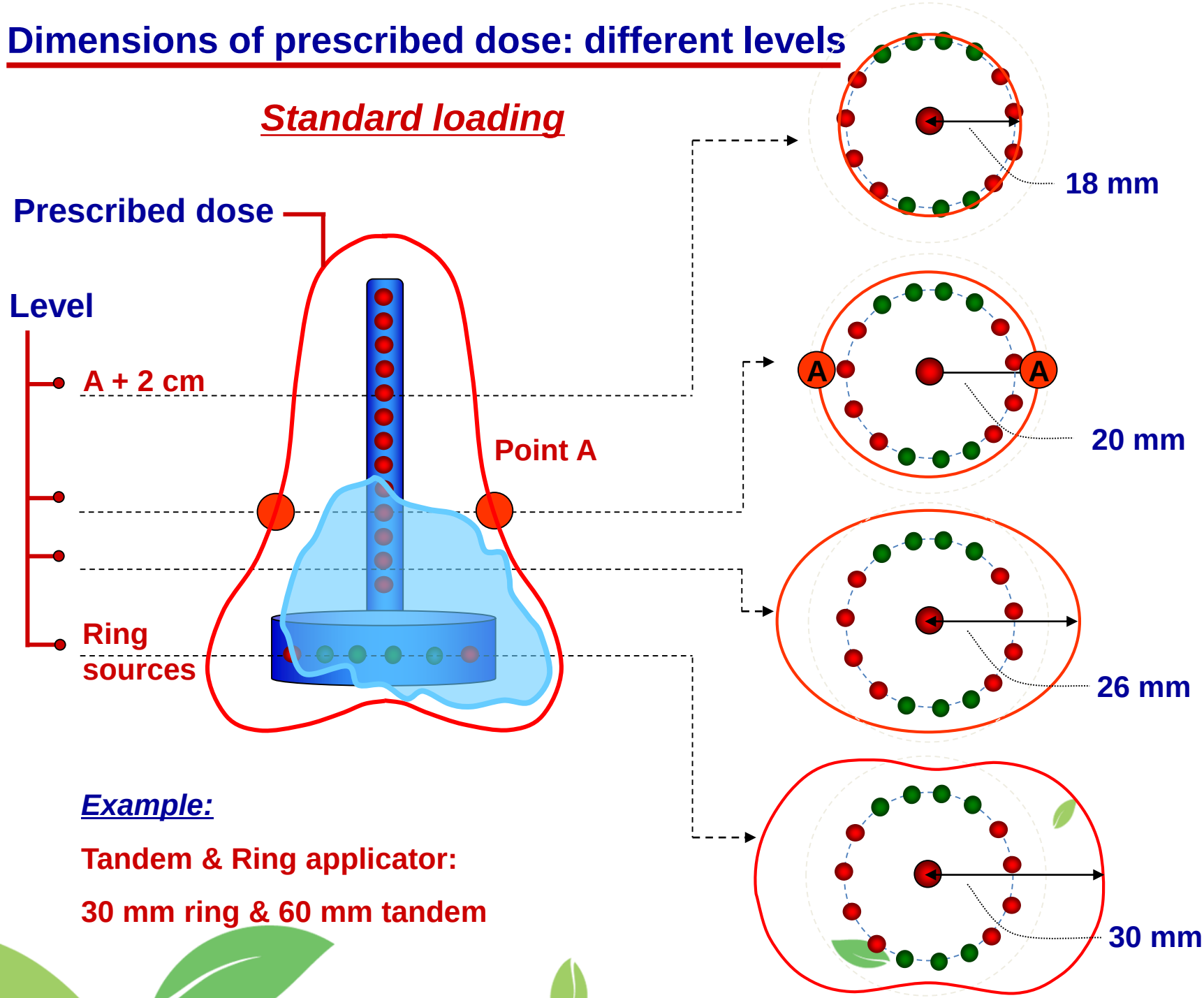
B. Up to ~ 5 mm

C. Up to ~ 10 mm

D. Up to ~ 20 mm

Dimensions of prescribed dose: different levels

Standard loading



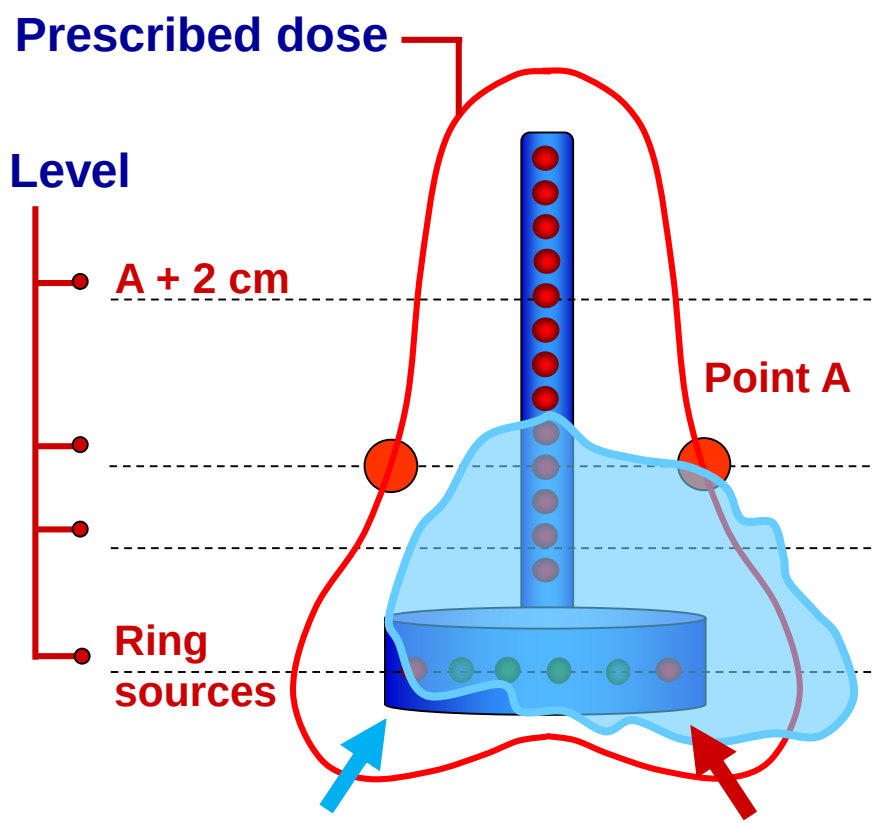
Example:

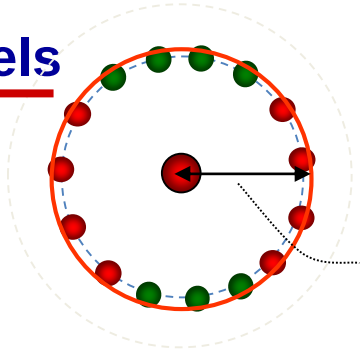
Tandem & Ring applicator:

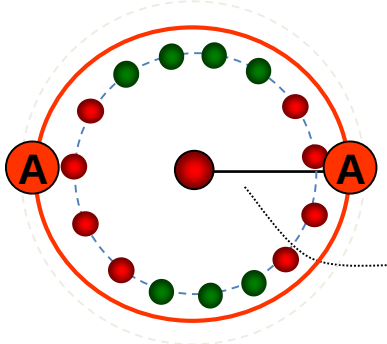
30 mm ring & 60 mm tandem

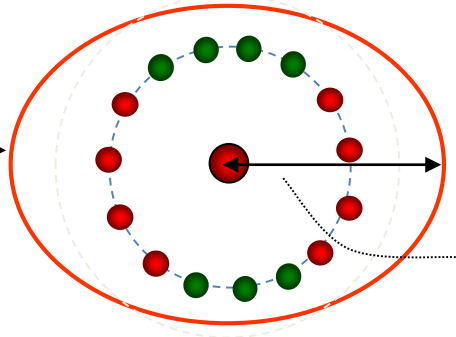
Dimensions of prescribed dose: different levels

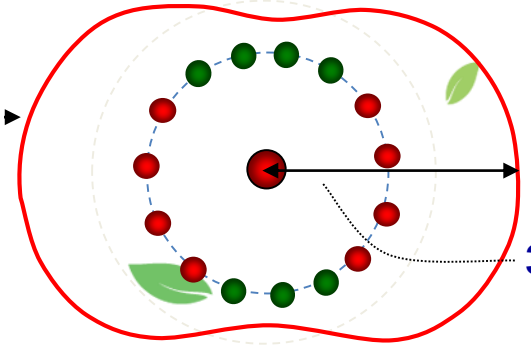
Standard loading











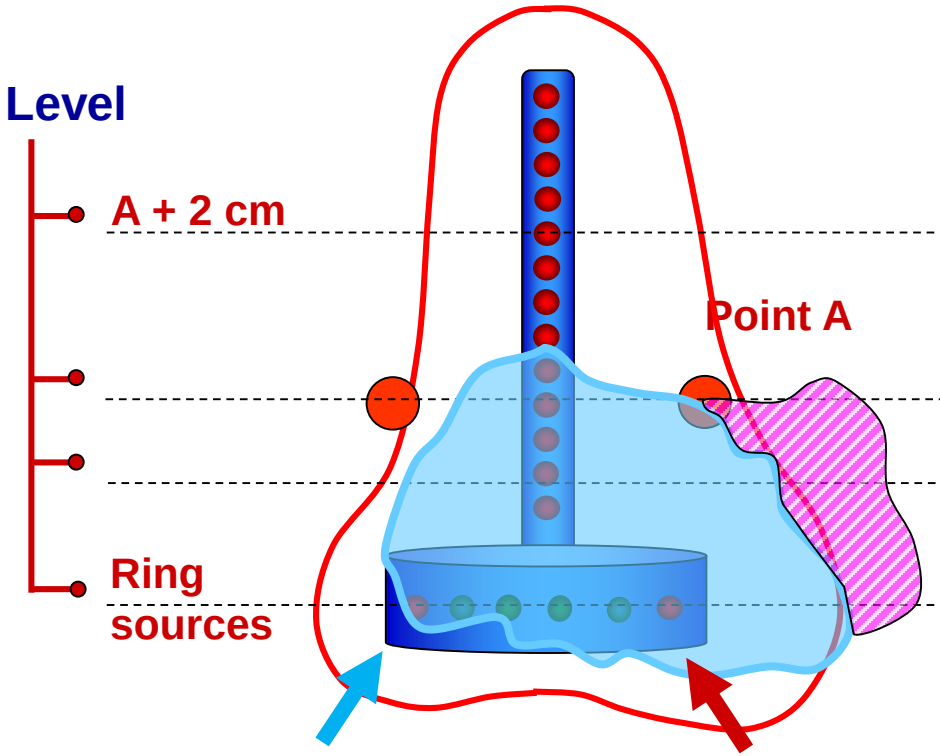
Example:

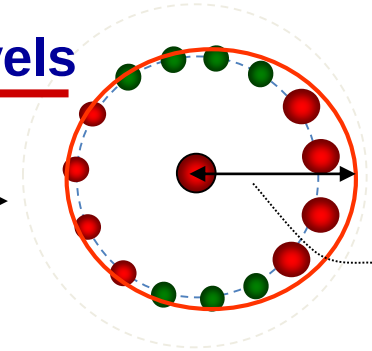
Tandem & Ring applicator:

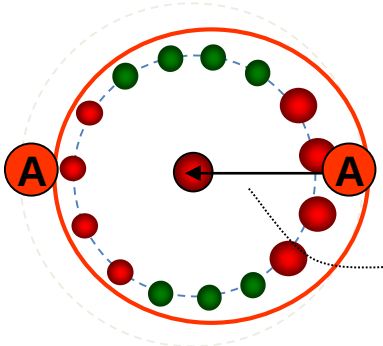
30 mm ring & 60 mm tandem

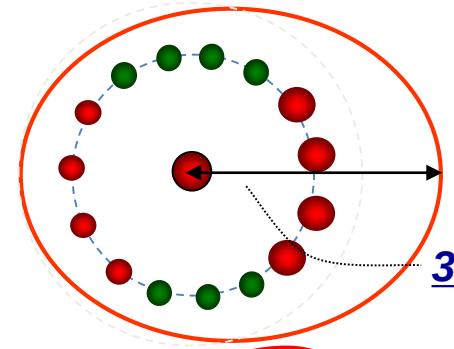
Dimensions of prescribed dose: different levels

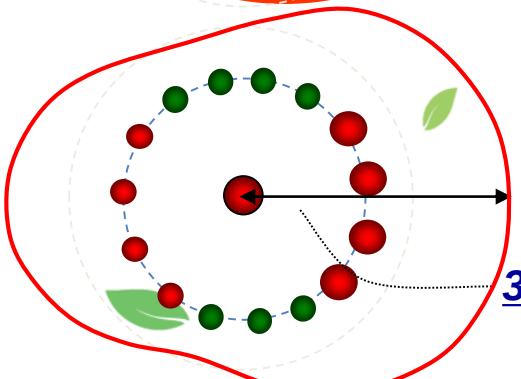
Modified Intracavitary loading



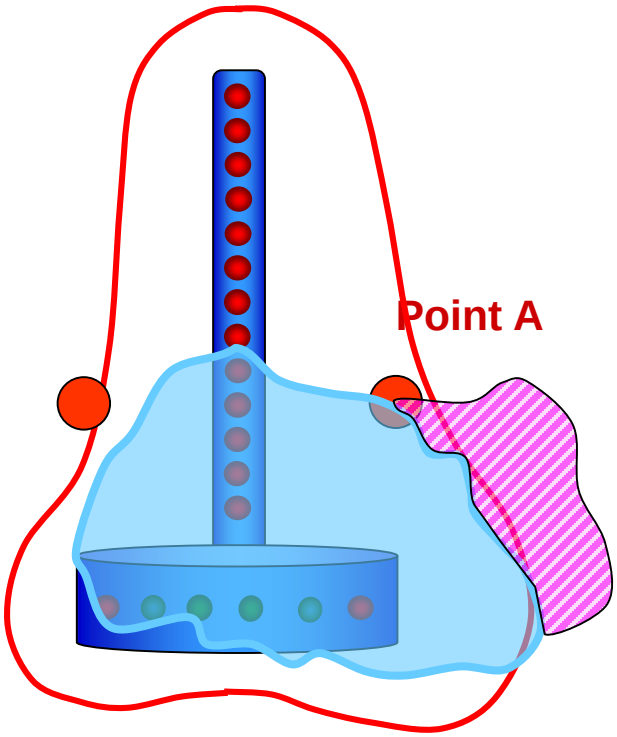






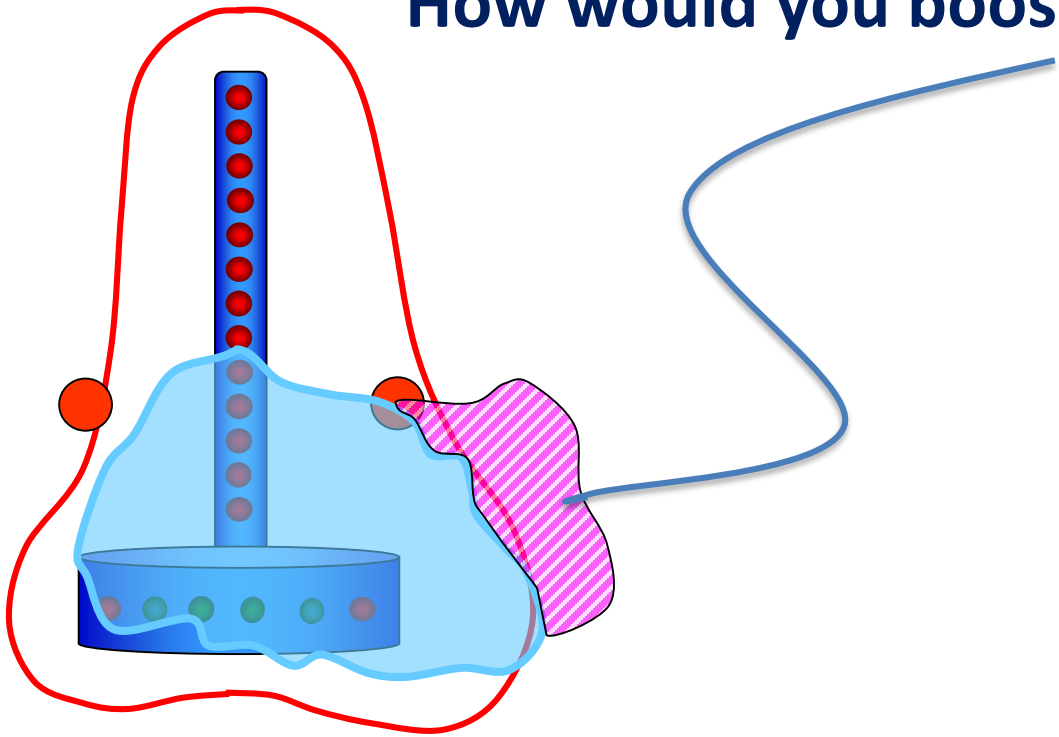


Overcoming limitations of IC applicators



Overcoming limitations of IC applicators

How would you boost this area?



A. By expansion of dose from IC applicator

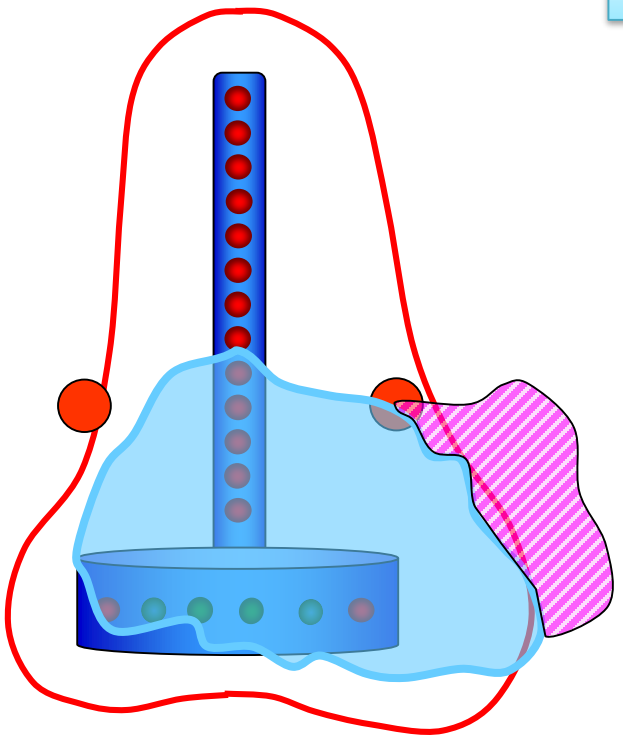
B. By EBRT boost with midline shielding

C. By adding Interstitial to Intracavitary BT

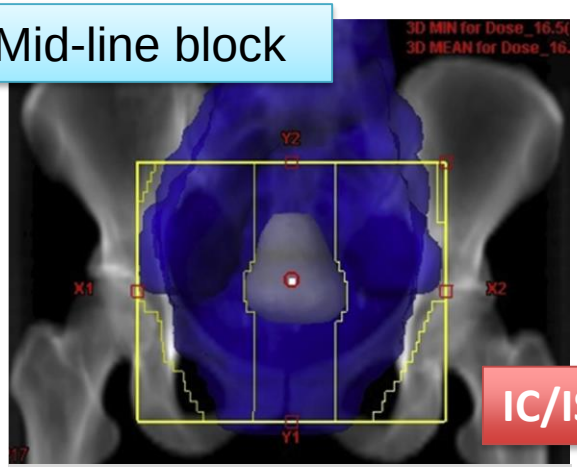
D. Other

Overcoming limitations of IC applicators

External beam boost with midline "shielding"



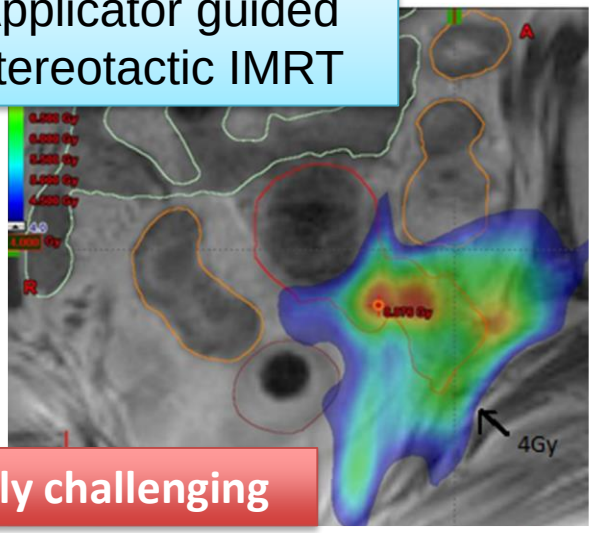
Mid-line block



From: Mohamed S, et al.. Brachytherapy 2015;23-28.
(Comparison of EBRT boost to IC/IS boost)

IC/IS boost > EBRT boost

Applicator guided stereotactic IMRT

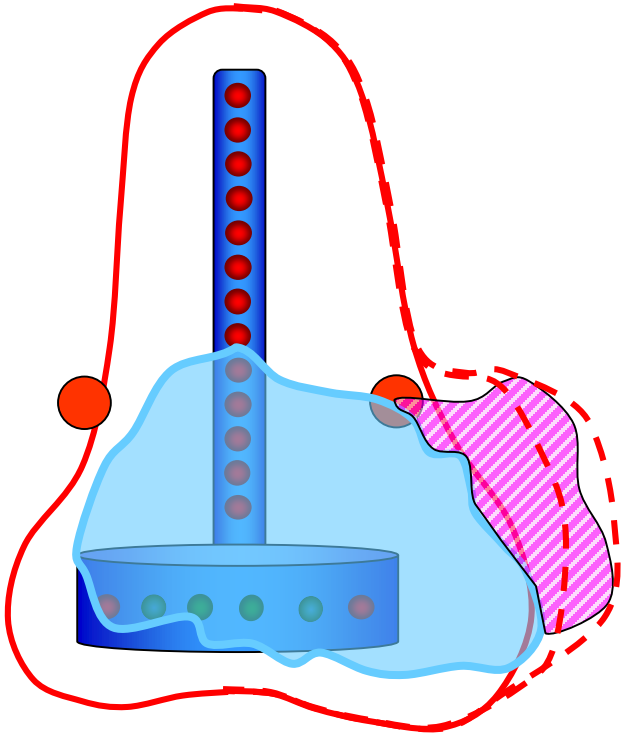


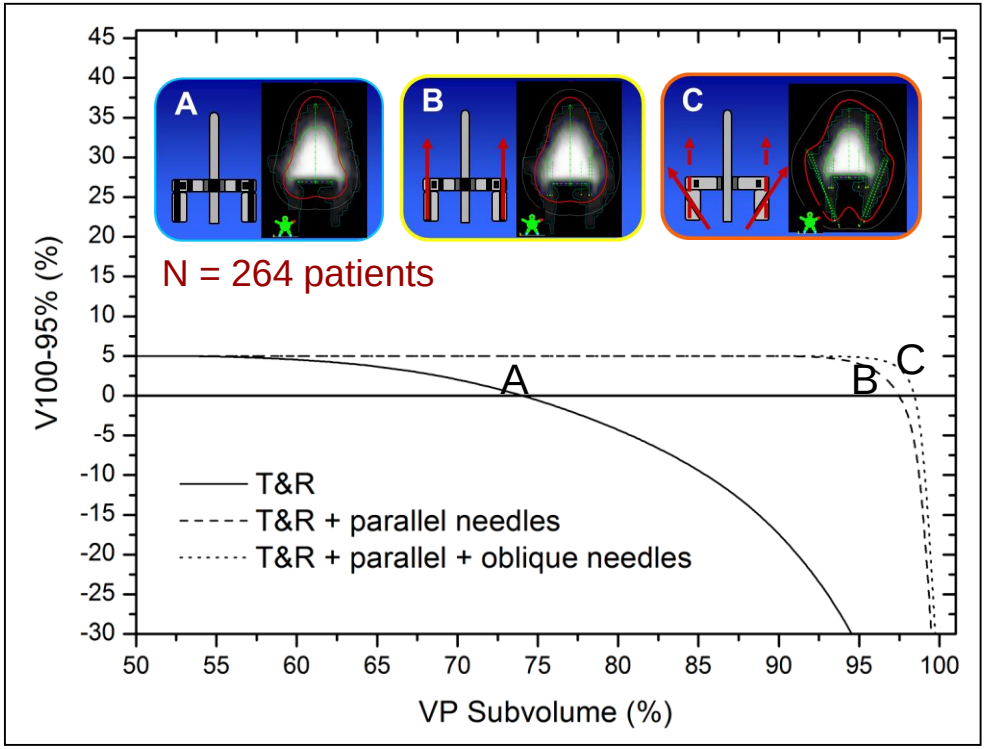
When IC/IS BT is highly challenging

Assenholt MS, et al Brachytherapy 20114

Overcoming limitations of IC applicators

Combined Intracavitary & Interstitial brachytherapy





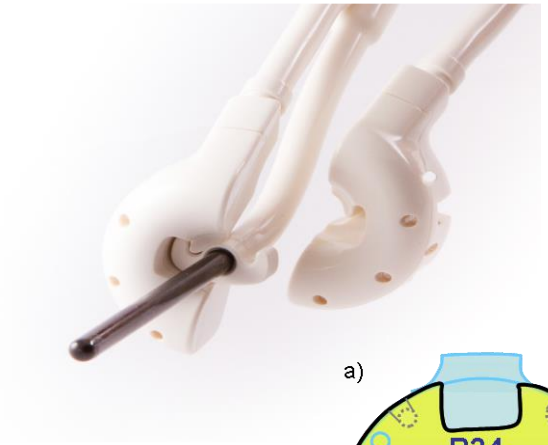
Petric P, et al. Radiother Oncol 2010 (Abstract)

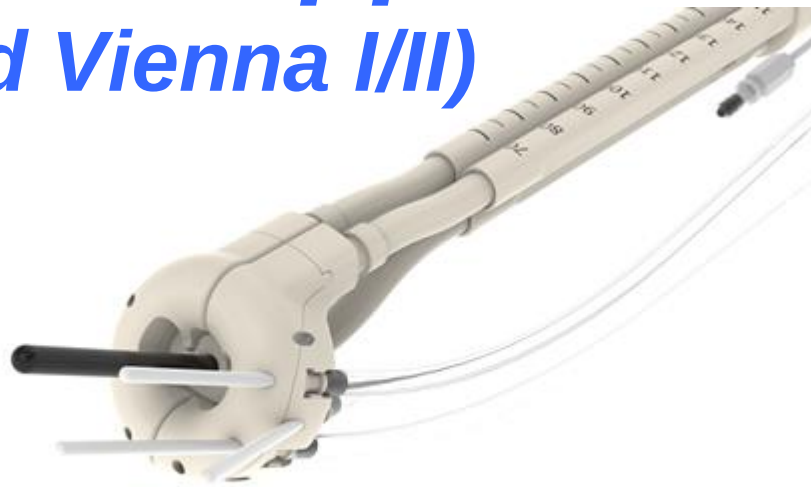
Mohamed S, et al Brachytherapy 2015:

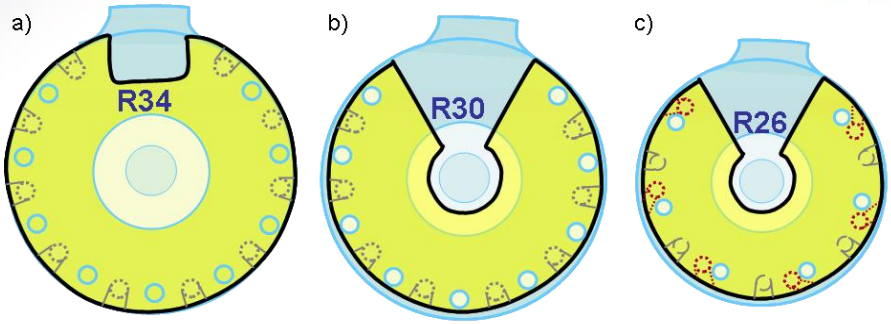
IC/IS boost superior to EBRT boost

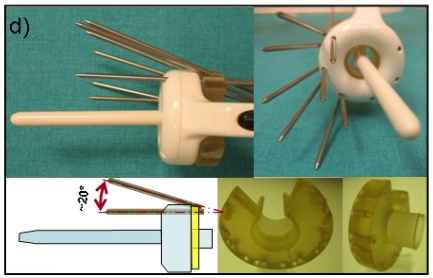
Kirisits C, et al. IJROBP 2006
Dimopoulos JCA, et al. IJROBP 2006
Nomden CN, et l. IJROBP 2012
Berger D, et al. Brachytherapy 2010 (Abstract)

A novel comprehensive applicator
(Venezia, Elekta and Vienna I/II)





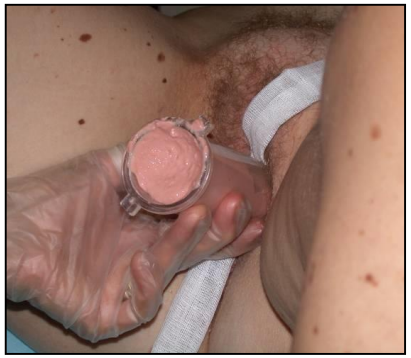


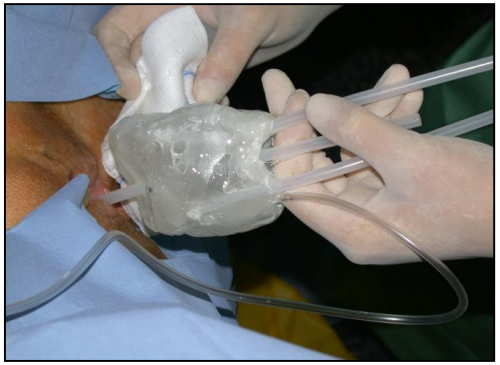


holes for straight needles
holes for divergent needles
additional holes for r26

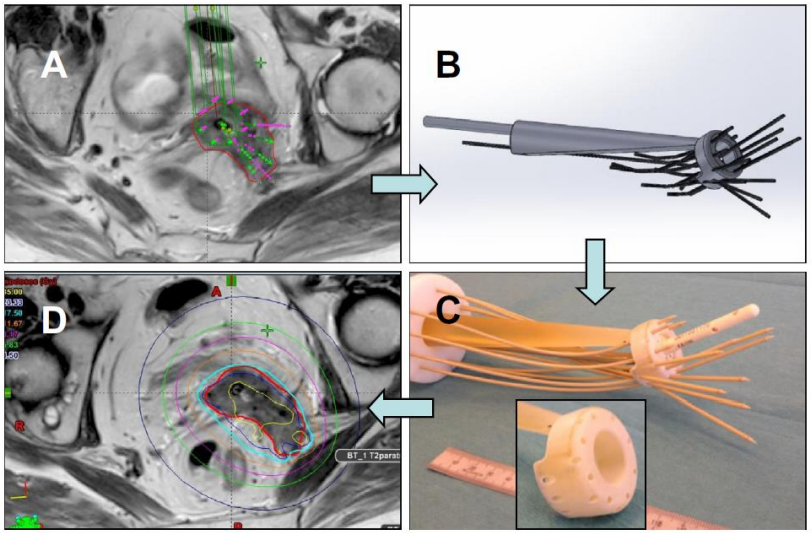
Berger, Kirisits, Mahantshetty et al. . Vienna II, 2016, (submitted to R&O)

3D printing technology (IC or IC/IS)

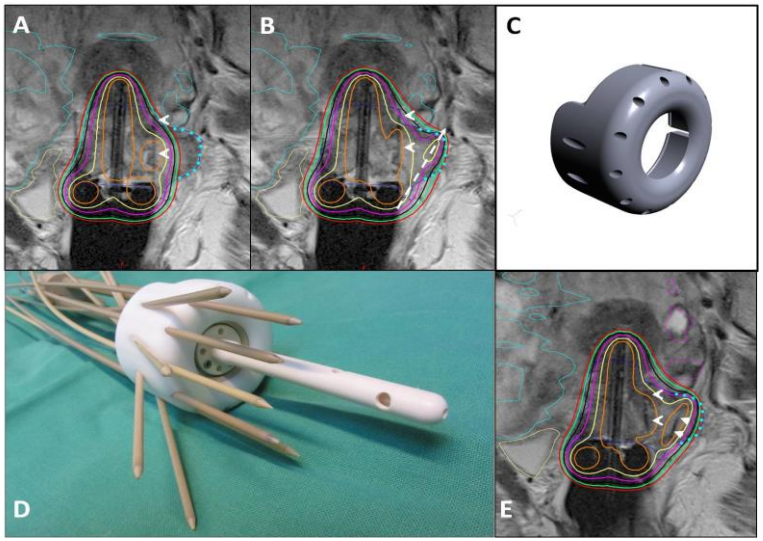




Classic Moulage technique



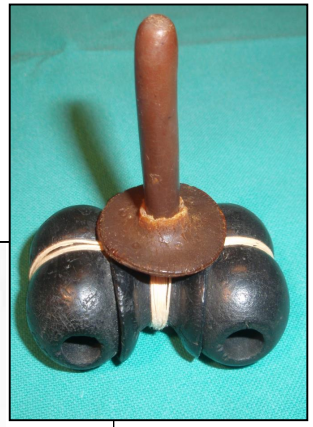
Lindegaard J, et al. Radiother Oncol 2016

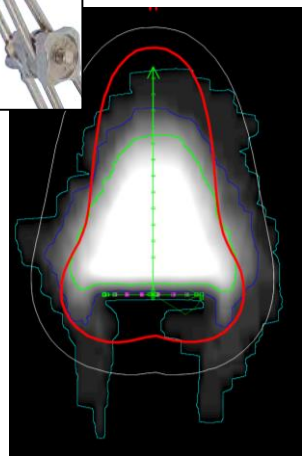


Petric P, et al.. In: Song W, et al. Eds. Taylor & Francis 2016

Summary

- Modern intracavitary applicators
  - Same concept as historical systems; main differences:
    - CT, MRI compatibility, materials
    - Fixed, adjustable components
    - Smaller channel diameters
- Intracavitary technique alone:
  - limited possibility for D adaptation
- Interstitial boost superior to EBRT boost
- Emerging technologies:
  - Comprehensive applicator IC/IS (Vienna II type)
  - 3D printing





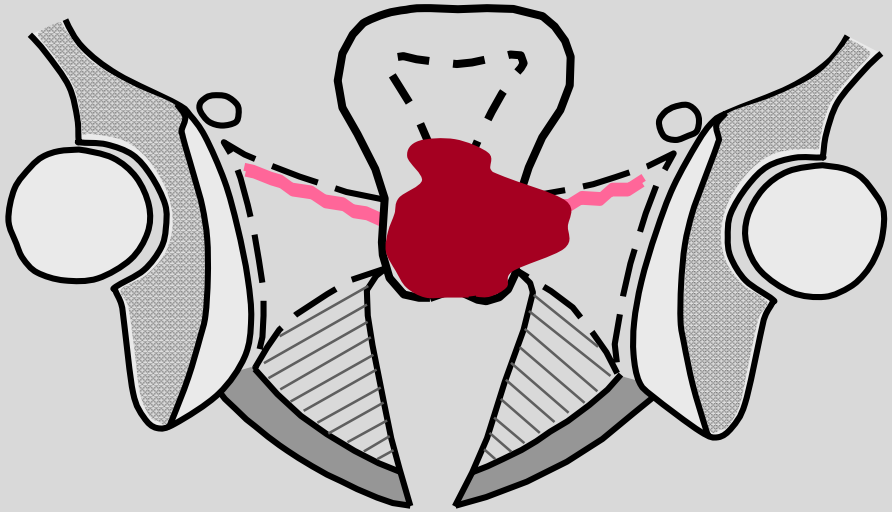
Combined intracavitary-interstitial technique for cervix cancer

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

Johannes C. Athanasios Dimopoulos, Head, Radiation Oncology
Metropolitan Hospital, Athens, Greece

Q: What brachytherapy technique would you do for this tumor topography after external radiation and chemotherapy?

At BT

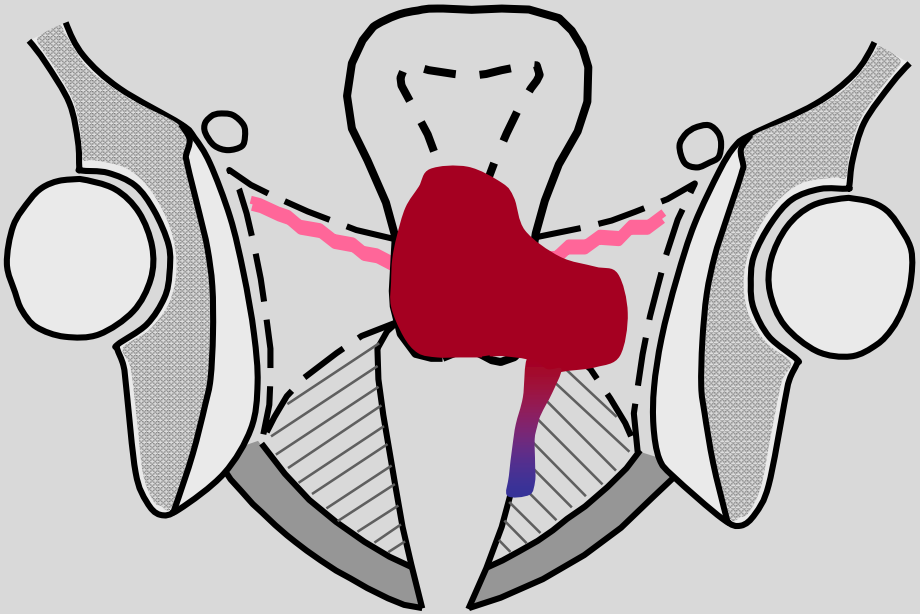


A. Standard Intracavitary
B. Intracavitary + interstitial
C. EBRT boost
D. EBRT boost + Intracavitary

KBD

Q: What brachytherapy technique would you do for this tumor topography after external radiation and chemotherapy?

At BT



A. Standard Intracavitary
B. Intracavitary + interstitial
C. EBRT boost + Intracavitary
D. No further Radiation

KBD

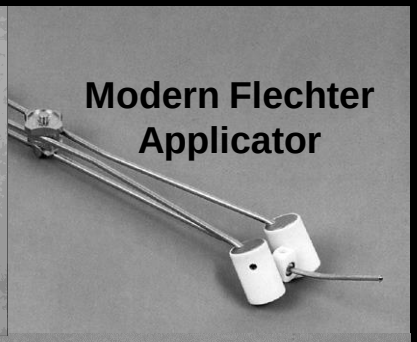
OUTLINE

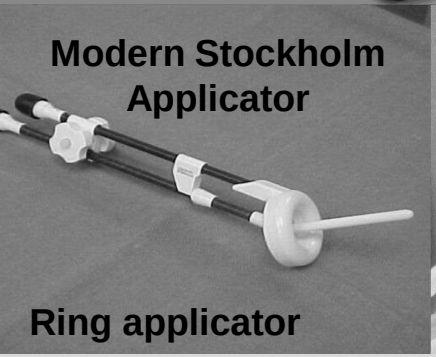
- *Limitations of STD Intracavitary Applicators*
- *Conventional Interstitial Techniques*
- *Modern Intracavitary + Interstitial Techniques*
- *Optimizing Applicator placement by Image guidance*
- *Principles of Selection of Appropriate Technique*

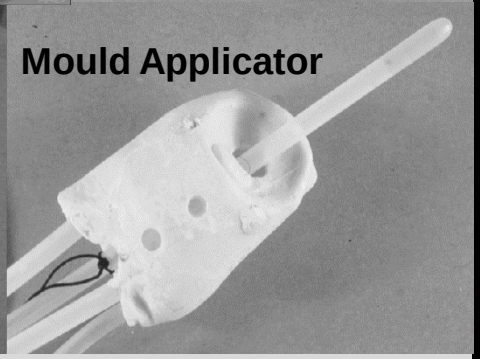
Limitations of pure intracavitary techniques

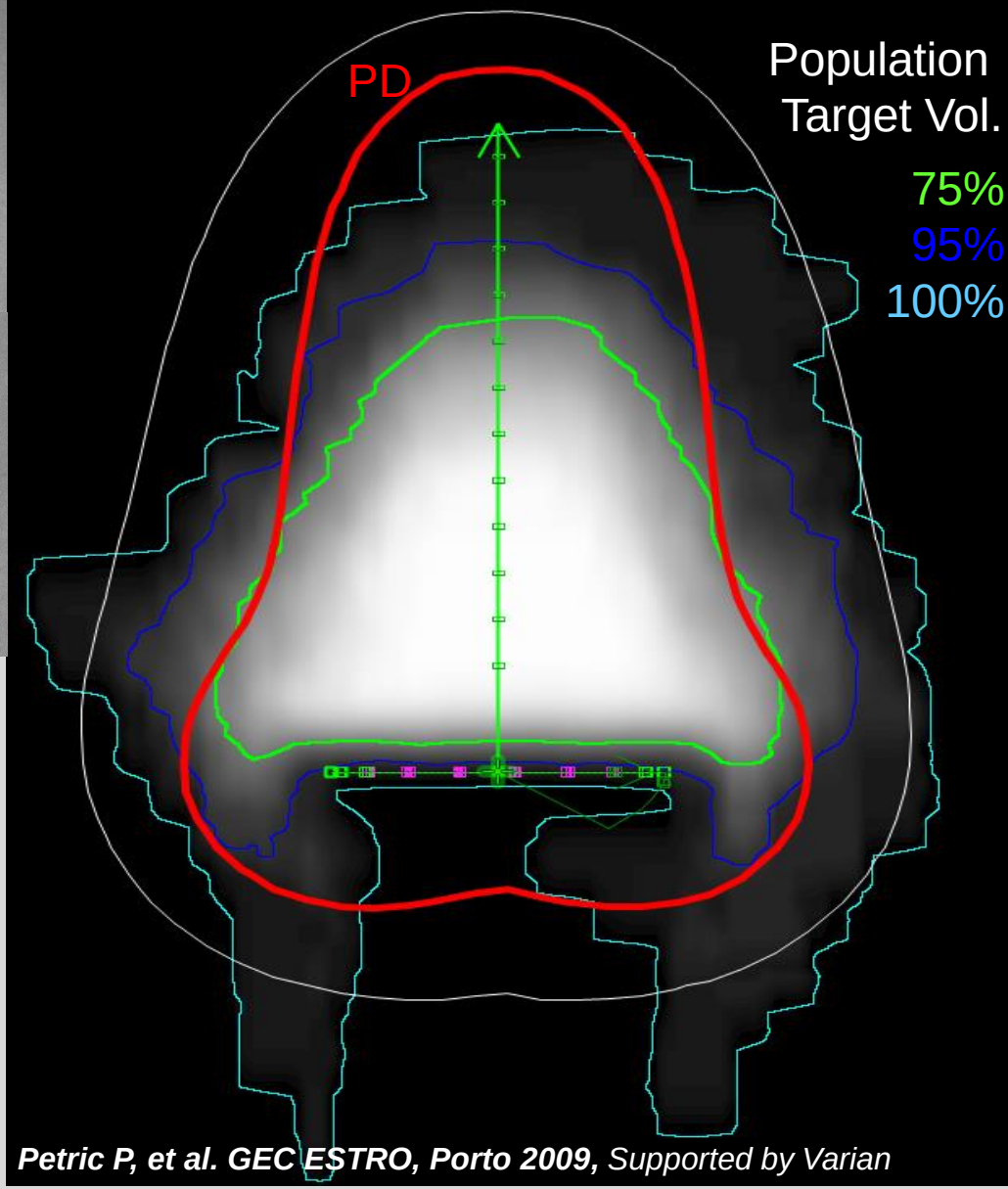
- *middle/distal parametrial tumor extension*
- *unfavourable topography/unfavourable relation to the applicator (e.g. asymmetrical tumors) (depending on applicator position)*
- *2-3 cm distal intravaginal tumor growth*
- *para-vaginal tumor growth*
- *unfavourable topography of organs at risk (not predictable – correction within the frame of subsequent applications)*

264 patients









Petric P, et al. GEC ESTRO, Porto 2009, *Supported by Varian*

Courtesy: P. Petric,D. Berger

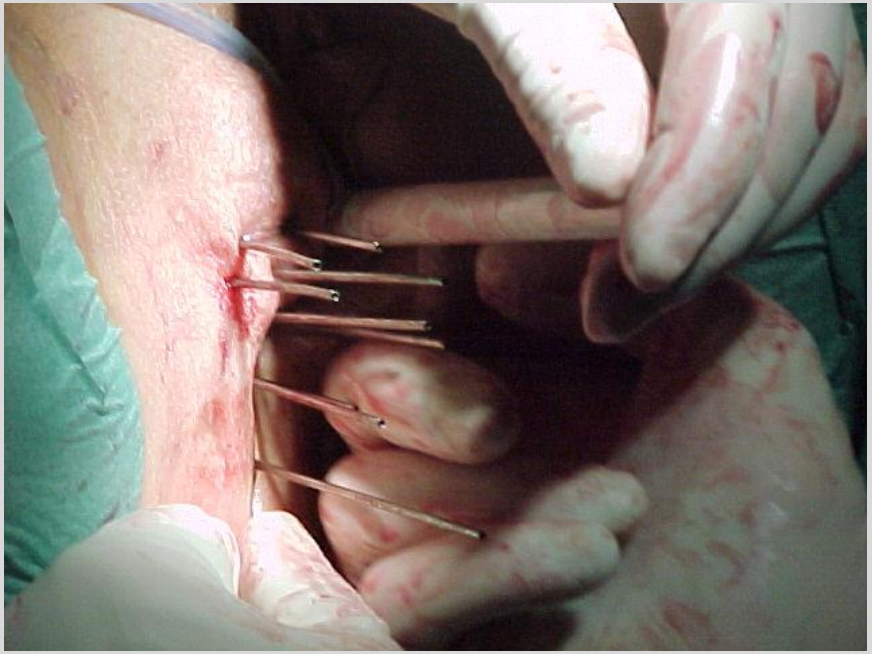
Indications for combined intracavitary/interstitial

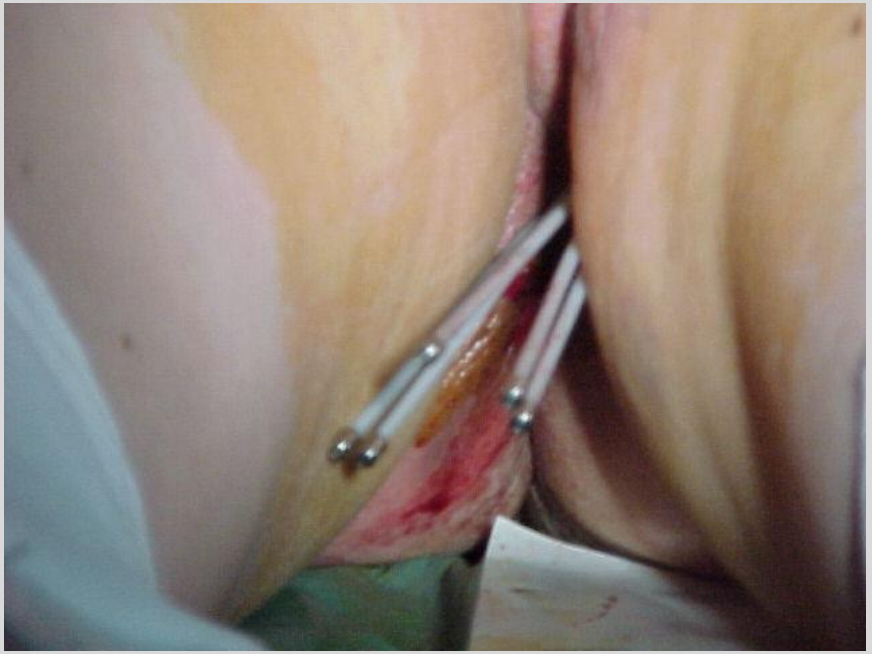
- *middle/distal parametrial tumor extension*
- *unfavourable topography/unfavourable relation to the applicator (e.g. asymmetrical tumors) (depending on applicator position)*
- *distal intravaginal tumor growth*
- *para-vaginal tumor growth*
- *unfavourable topography of organs at risk (not predictable – 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*

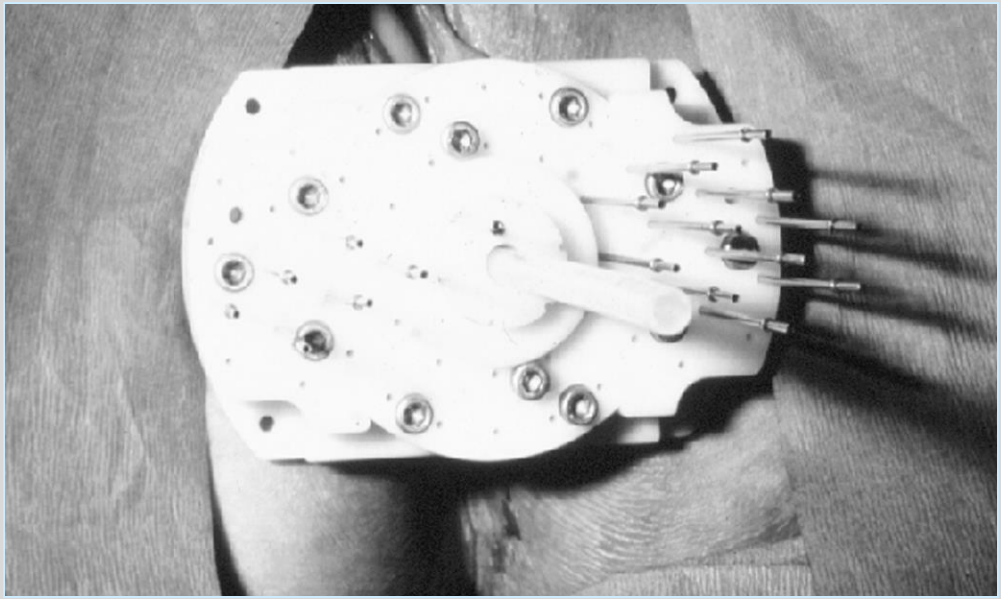
CLASSICAL INTERSTITIAL TECHNIQUES
FREEHAND PLACEMENT



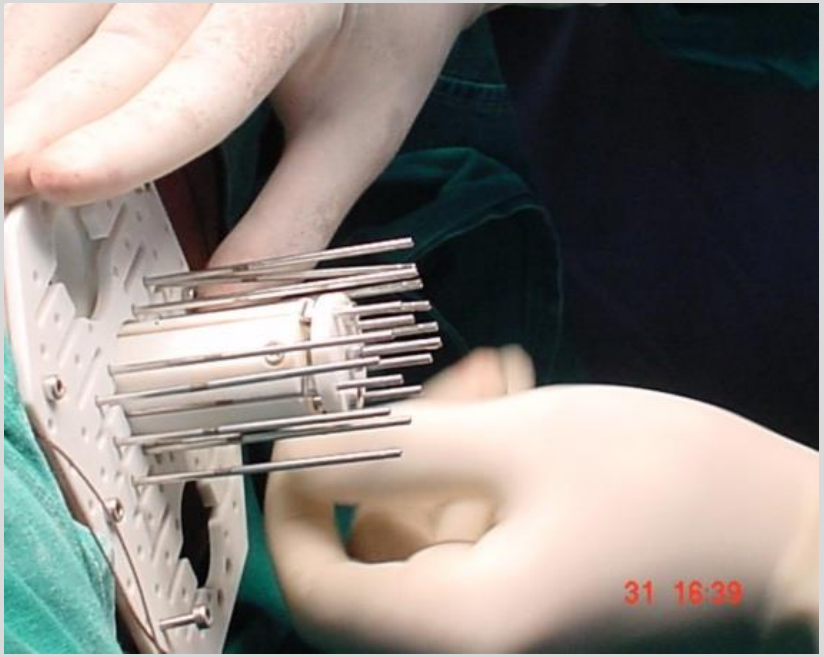


CLASSICAL INTERSTITIAL TECHNIQUES
PERINEAL TEMPLATES

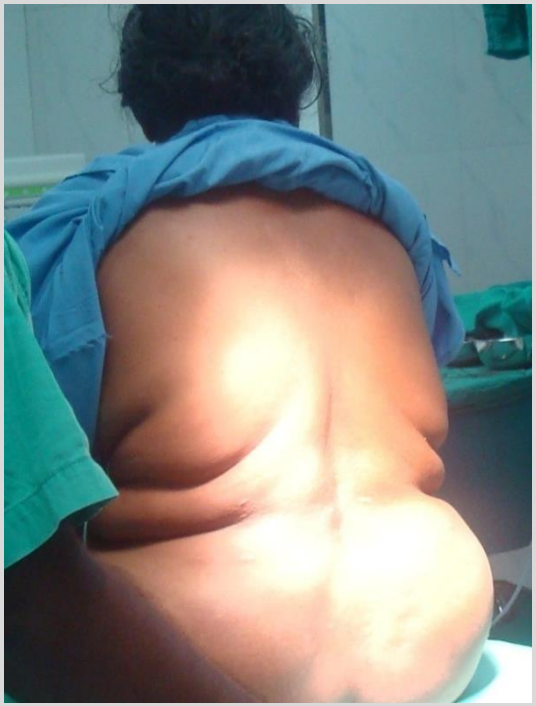
SYED

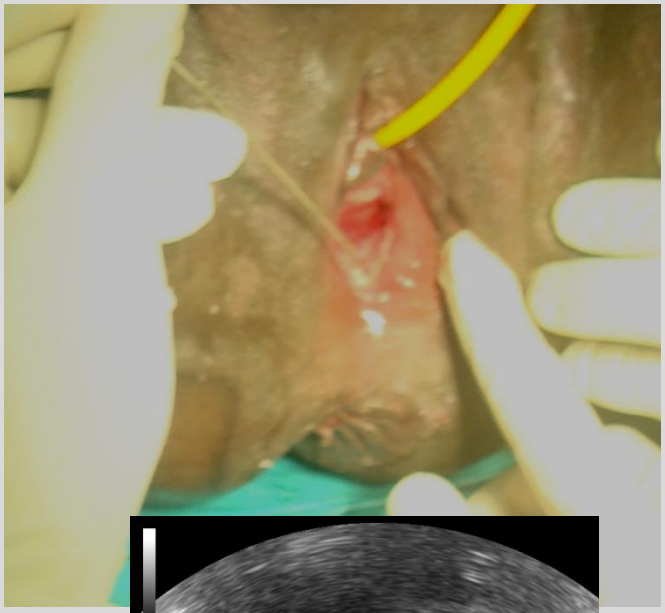


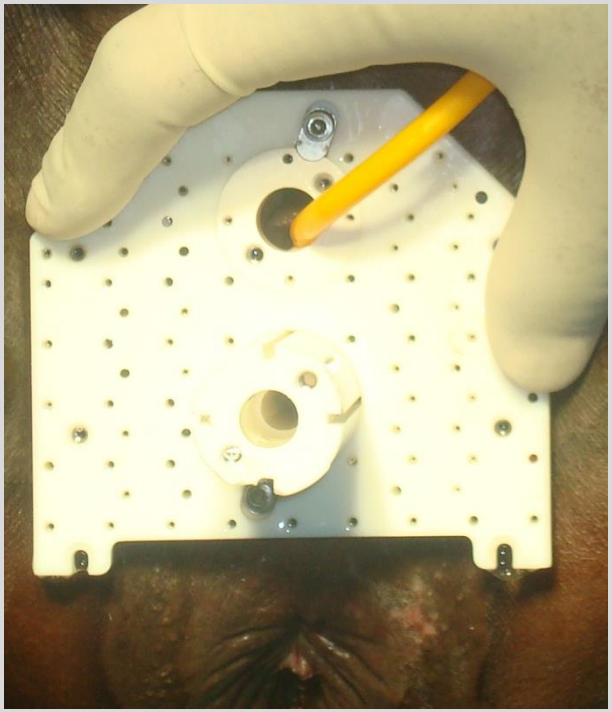
MUPIT

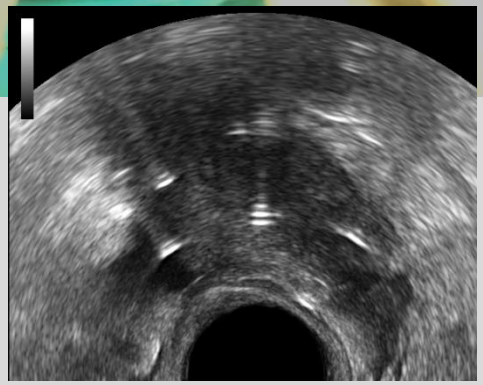


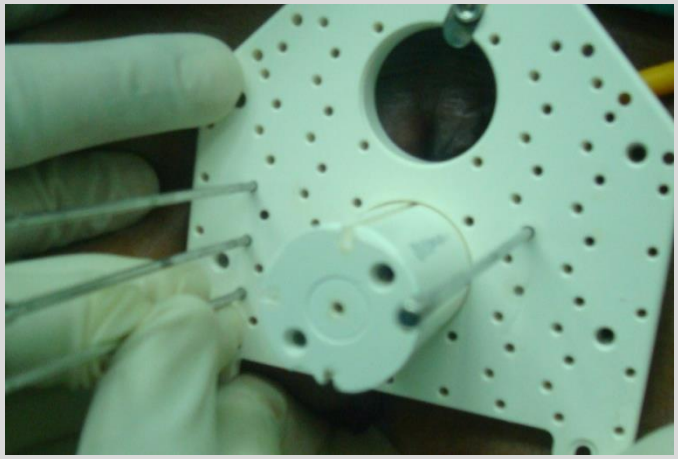
PRINICPLES OF MUPIT PROCEDURE

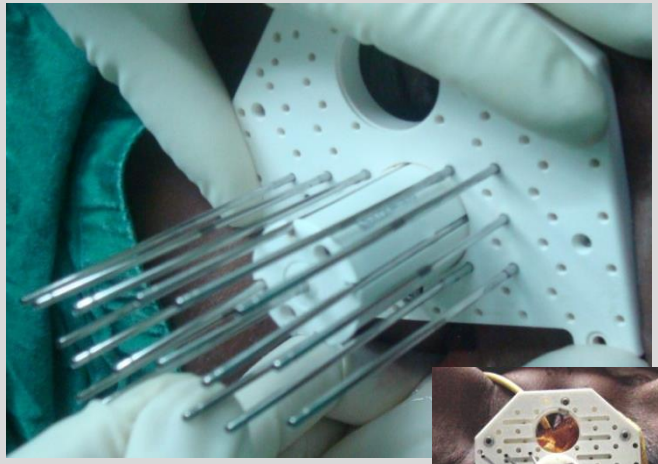


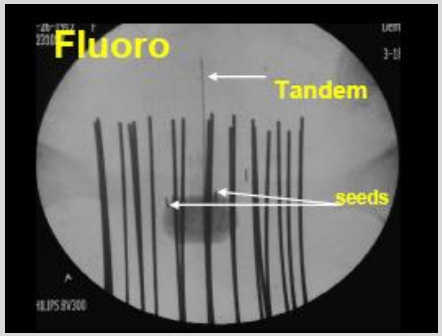


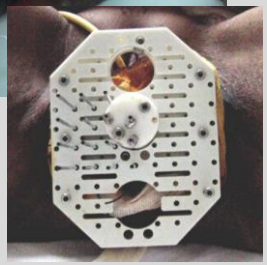






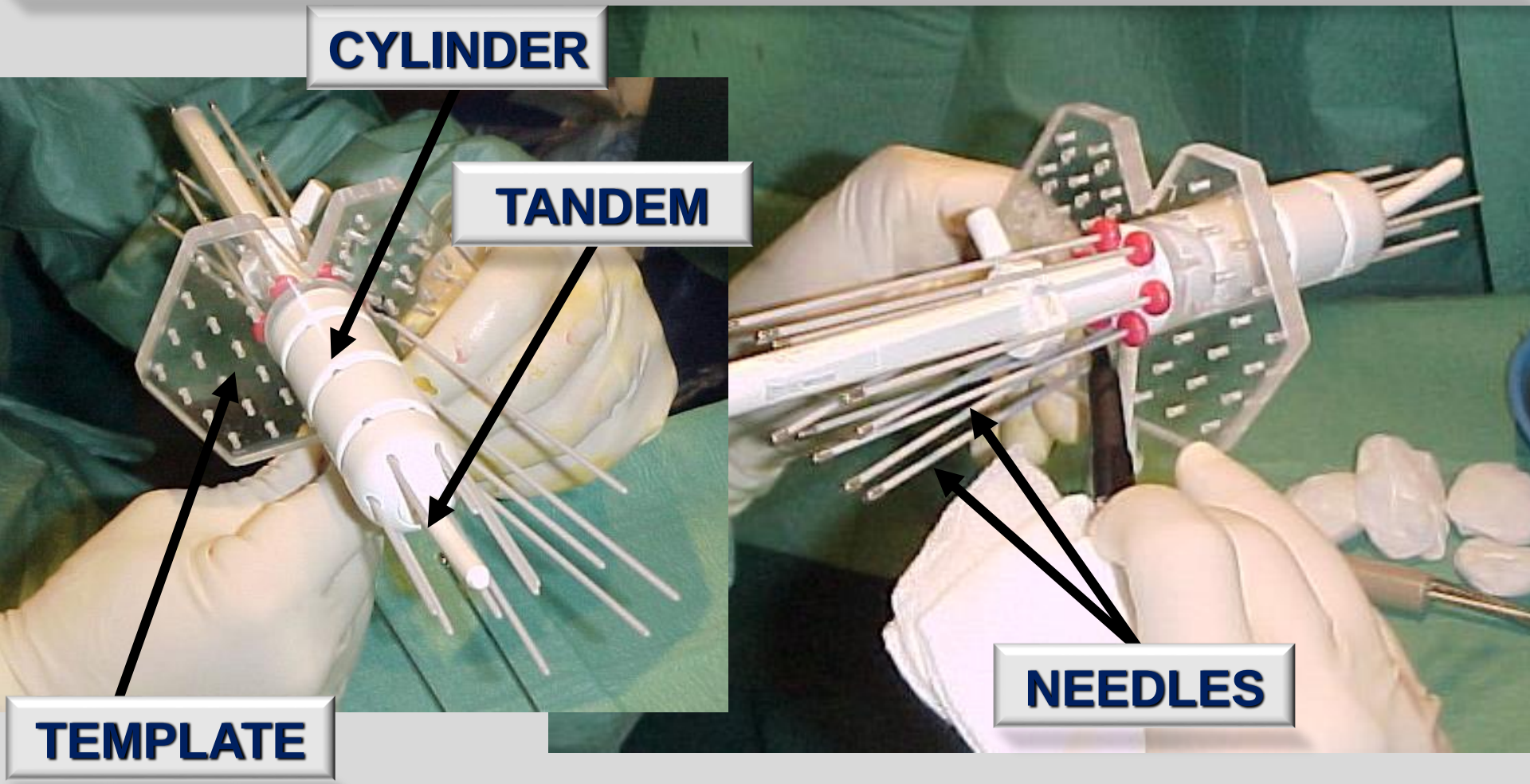


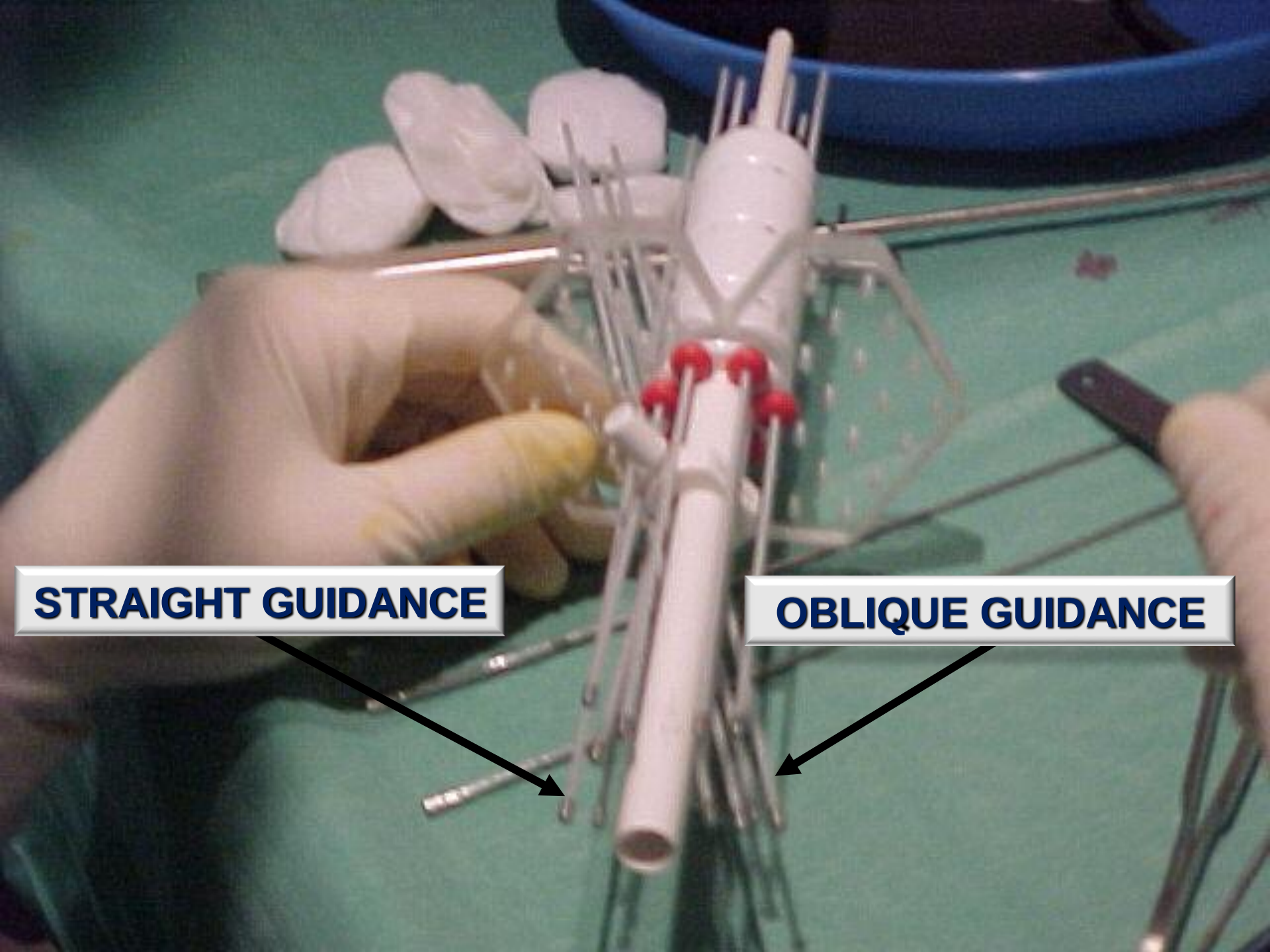




MODIFIED CLASSICAL INTERSTITIAL TECHNIQUES

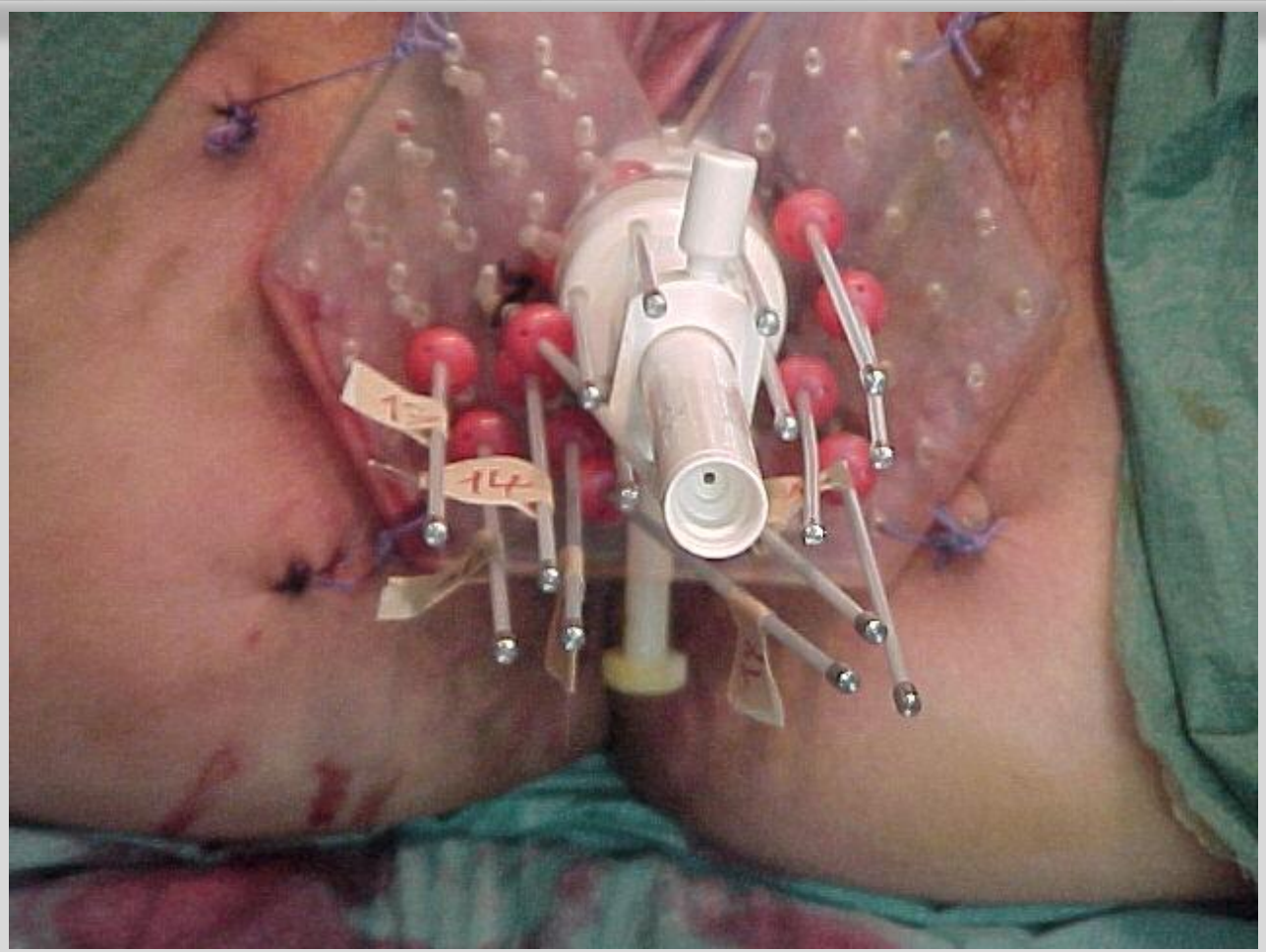
MRI-compatible cylinder + tandem + template




STRAIGHT GUIDANCE
OBLIQUE GUIDANCE

MODIFIED CLASSICAL INTERSTITIAL TECHNIQUES

COMPLETED IMPLANT



CLASSICAL & MODIFIED INTERSTITIAL TECHNIQUES

DRAWBACKS

- *Accurate freehand implantation is difficult*
  - *positioning often inaccurate*
  - *loss of parallelism*
  - *not reproducible*

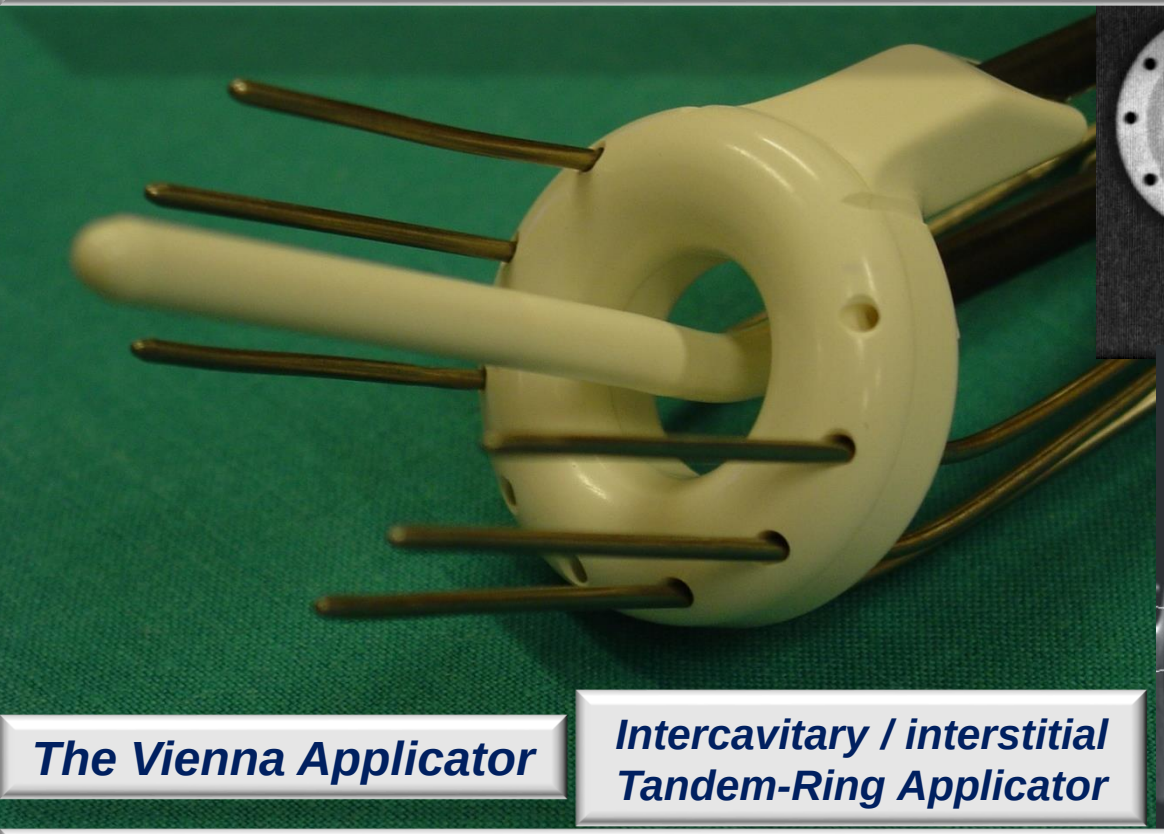
- *Perineal templates (Syed, MUPIT, others)*
  - *high number of needles used*
  - *long distances between template and target (loss of parallelism, inaccurate positioning)*
  - *impediment for general acceptance: considerable risk of serious acute/late complications*

INTRACAVITARY + INTERSTITIAL TECHNIQUES

TASKS

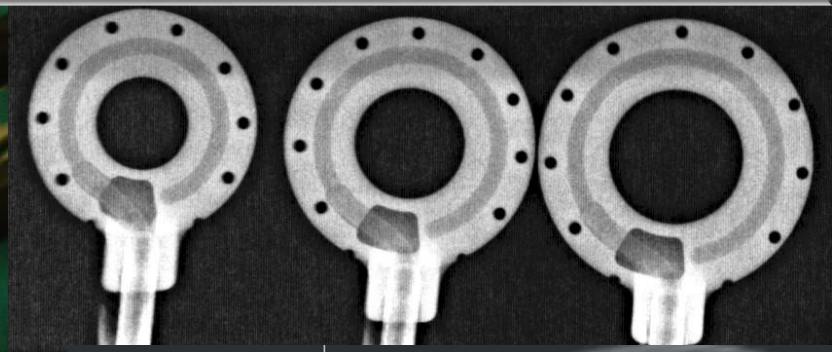
- *improve control over the placement of needles: short distance between template and the target (accurate and reproducible insertion)*
- *lesser number of needles to achieve an adequate target coverage*
- *to be combined with individualised MRI based treatment planning to tailor the dose distribution (improve local control without increasing side effects)*

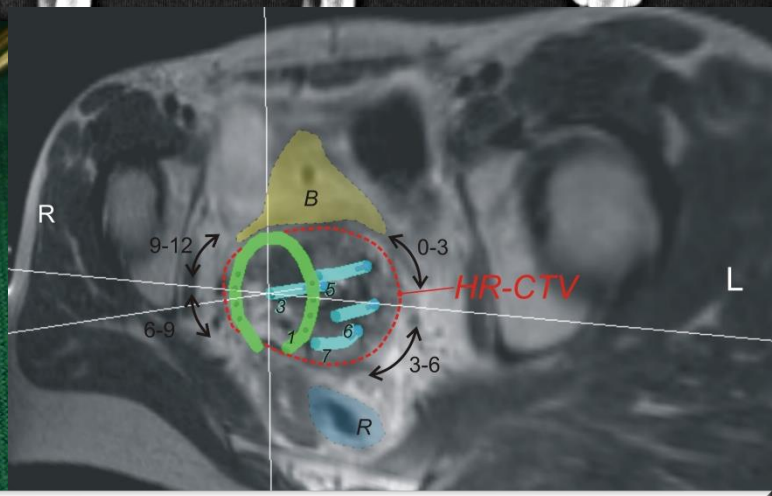
MODERN INTERSTITIAL TECHNIQUES



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)

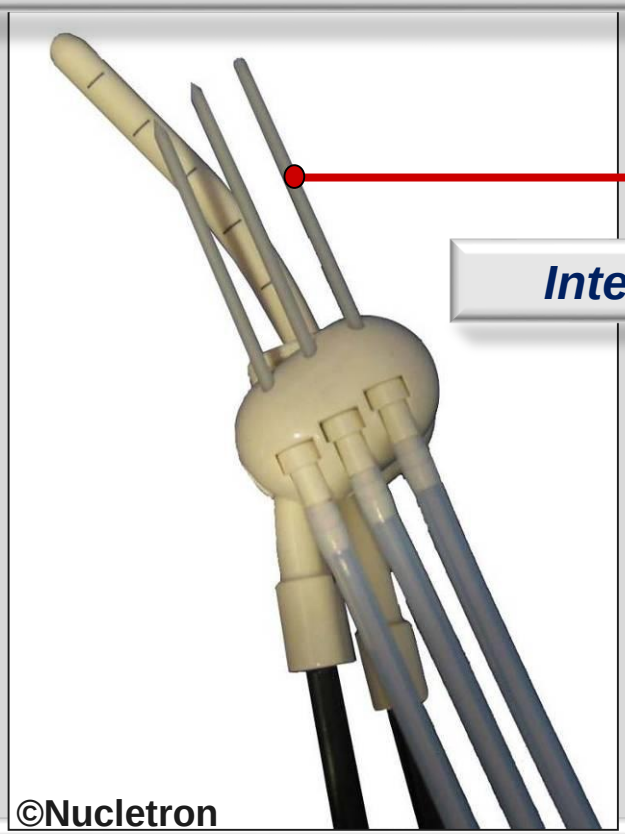
MODERN INTERSTITIAL TECHNIQUES

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

INTRACVITARY +INTERSTITIAL TECHNIQUES

VIDEO PRESENTATIONS

VIENNA APPLICATION AT AKH VIENNA

VIENNA APPLICATION AT TATA

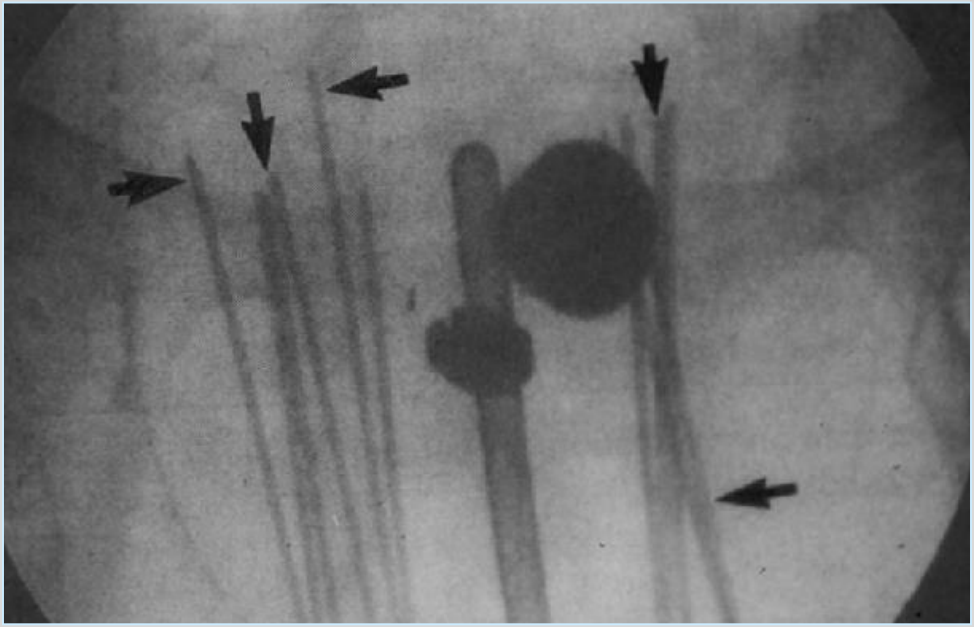
INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

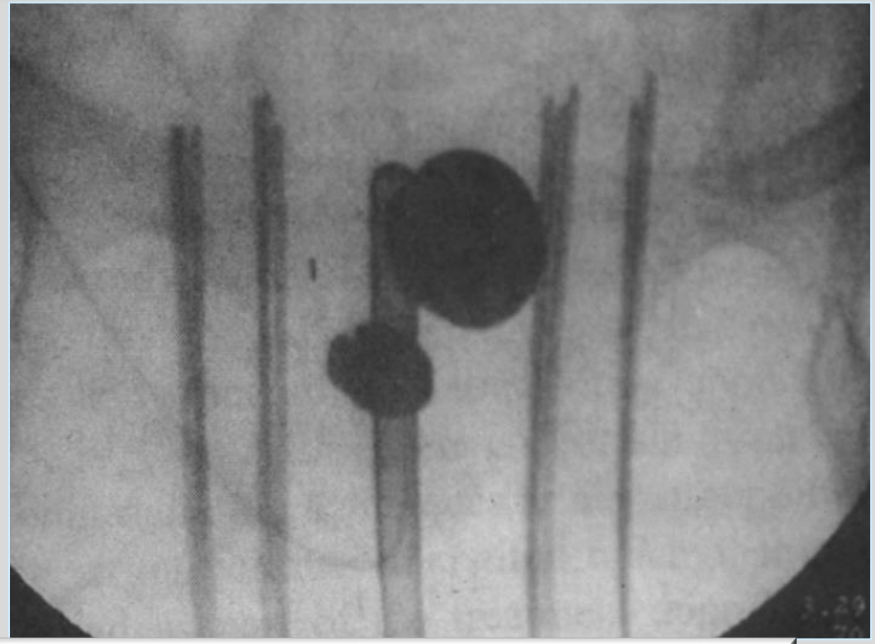
NEEDLE PLACEMENT ACCURACY

- *Fluoroscopy*
- *(Laparotomy guided implants)*
- *Computed tomography*
- *Ultrasound*
- *MRI and open MRI*

INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

NEEDLE PLACEMENT ACCURACY: FLUOROSCOPY





REPOSITIONING: ACCURATE

LIMITATIONS: TARGET VISUALIZATION & COVERAGE

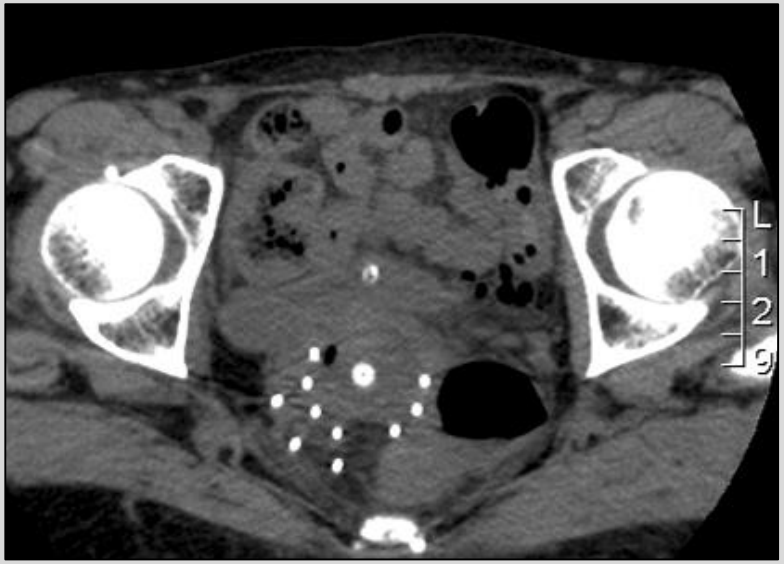
Nag IJROBP 40:415-20;1998

Computed Tomography

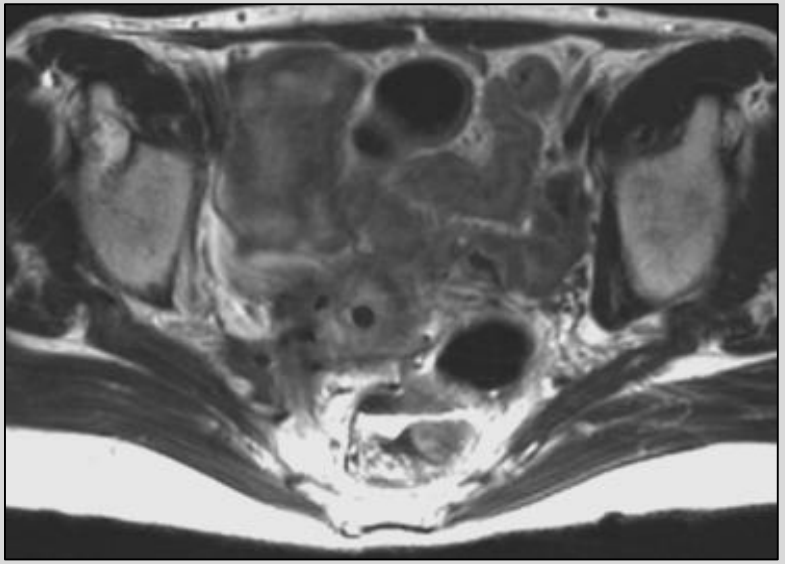
Findings at Brachytherapy

Example: cervix cancer

Assess Tumour size & Topography



Native CT (no contrast)



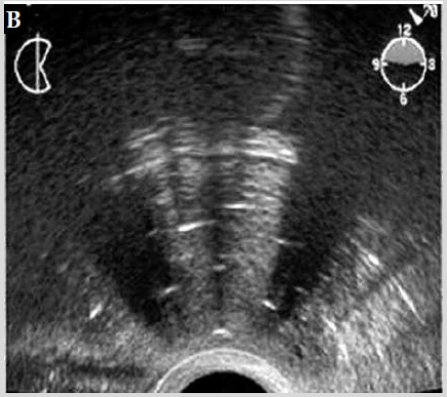
T2W FSE MRI (same patient)

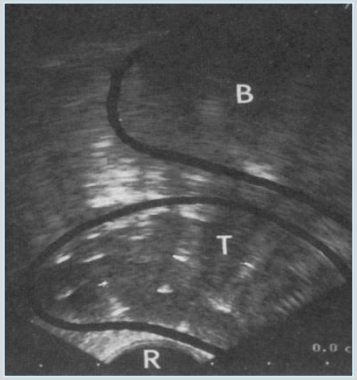
Courtesy; Jacob C Lindegaard, Aarhus University Hospital

INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

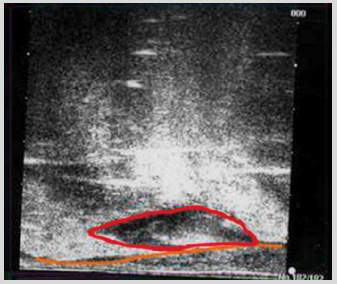
	Ultrasound	MRI
Accessibility in the operating room	High	Low
Real-time image guidance	High	Low
Catheter visualization	High	High
Target visualization	High	High
Volume based evaluation	Low	High
Treatment planning	Low	High
Experience with technique	Low	High
Clinical evidence	Low	High

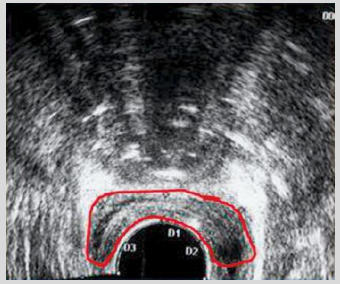
Kamrava M. J Contemp Brachytherapy 2014





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.



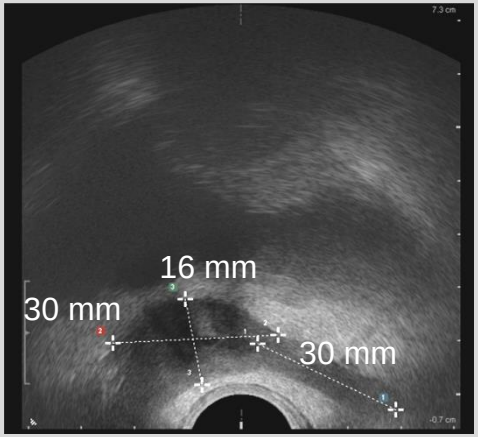


Ultrasound

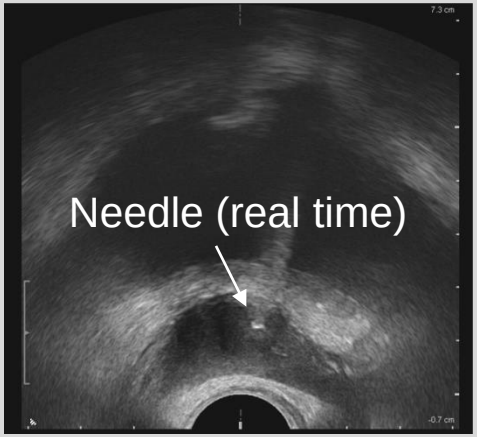
Findings at Brachytherapy

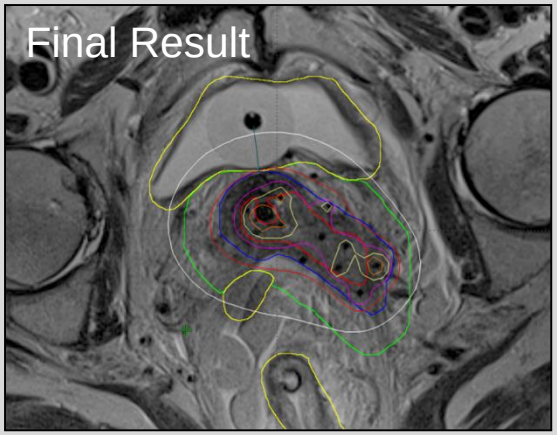
Cervix cancer

Assess Tumour size & Topography



Transrectal Ultrasound



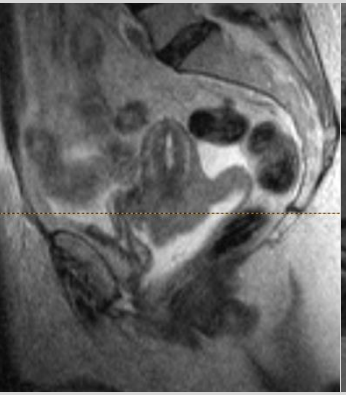
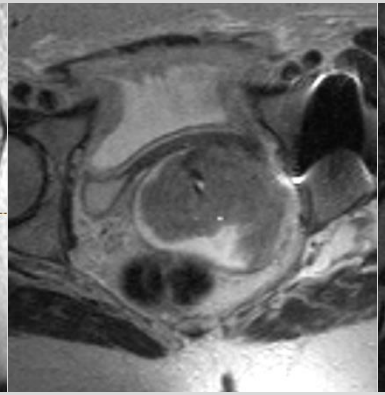
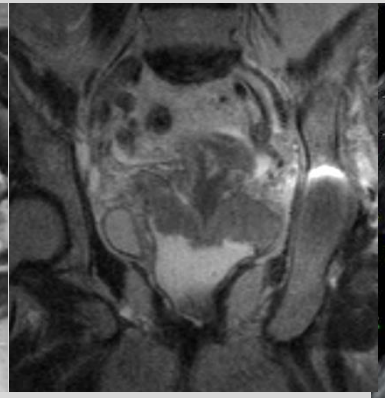
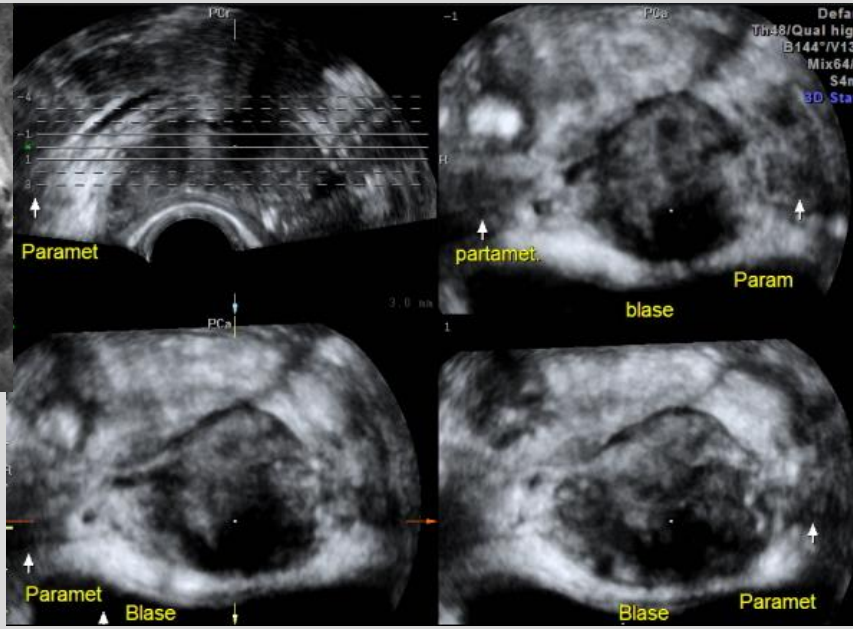


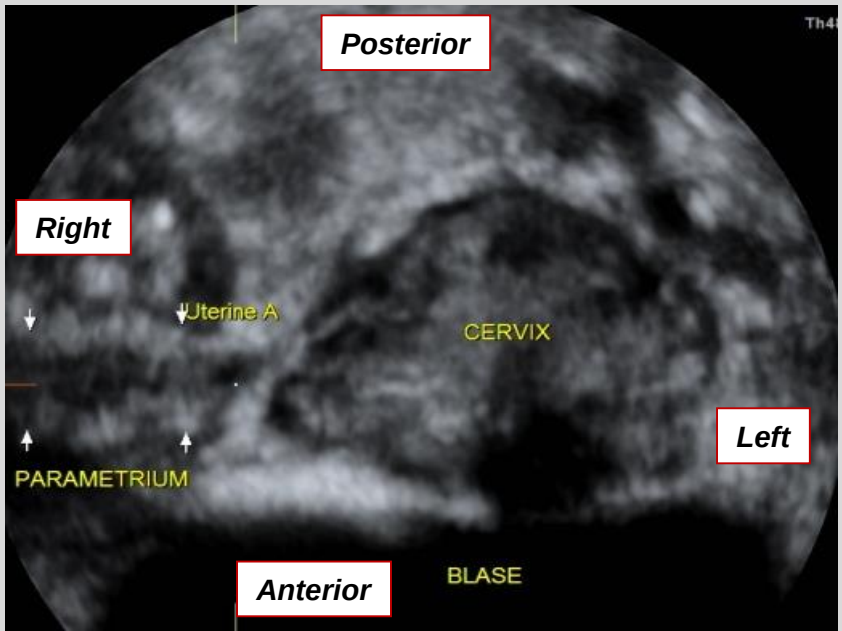
T2W FSE MRI (same patient)

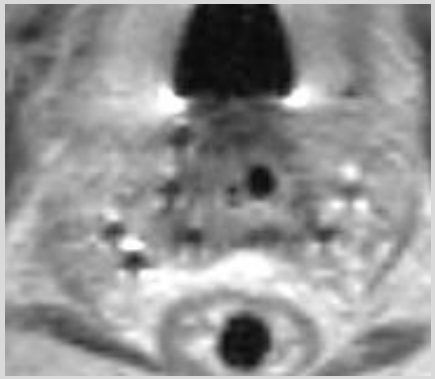
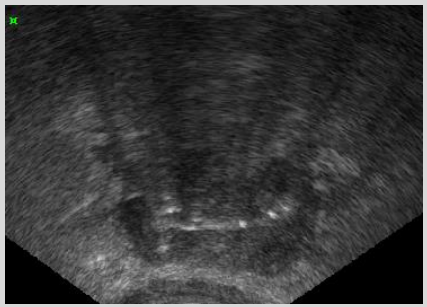
→ *Decide on application technique, Guide insertion, Aid treatment planning*

Source: Institute of Oncology Ljubljana

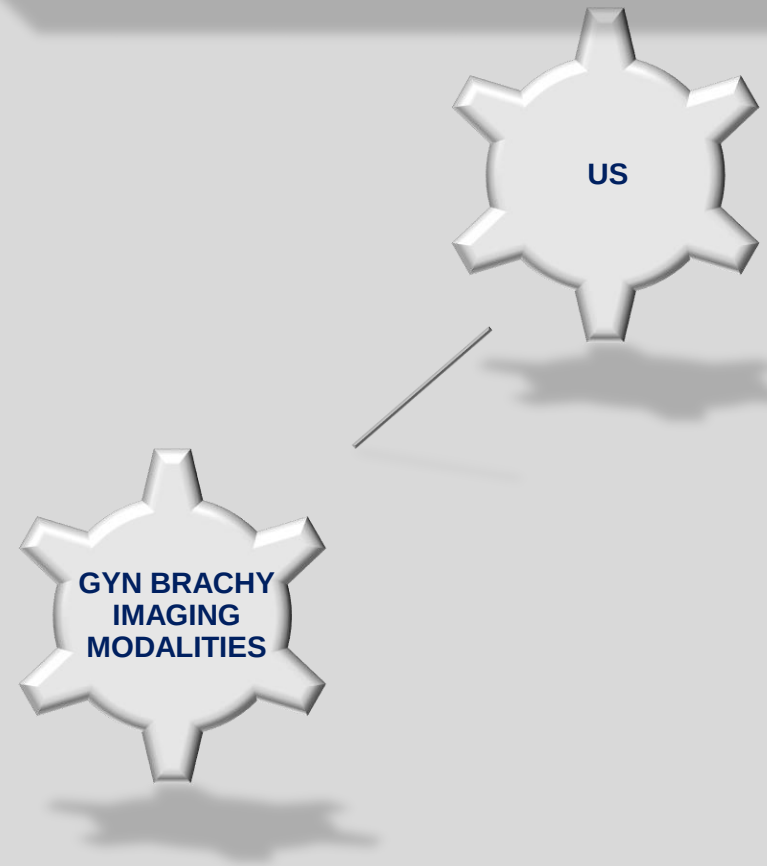
INTERSTITIAL TECHNIQUES
POTENTIAL OF MODERN US TECHNIQUES

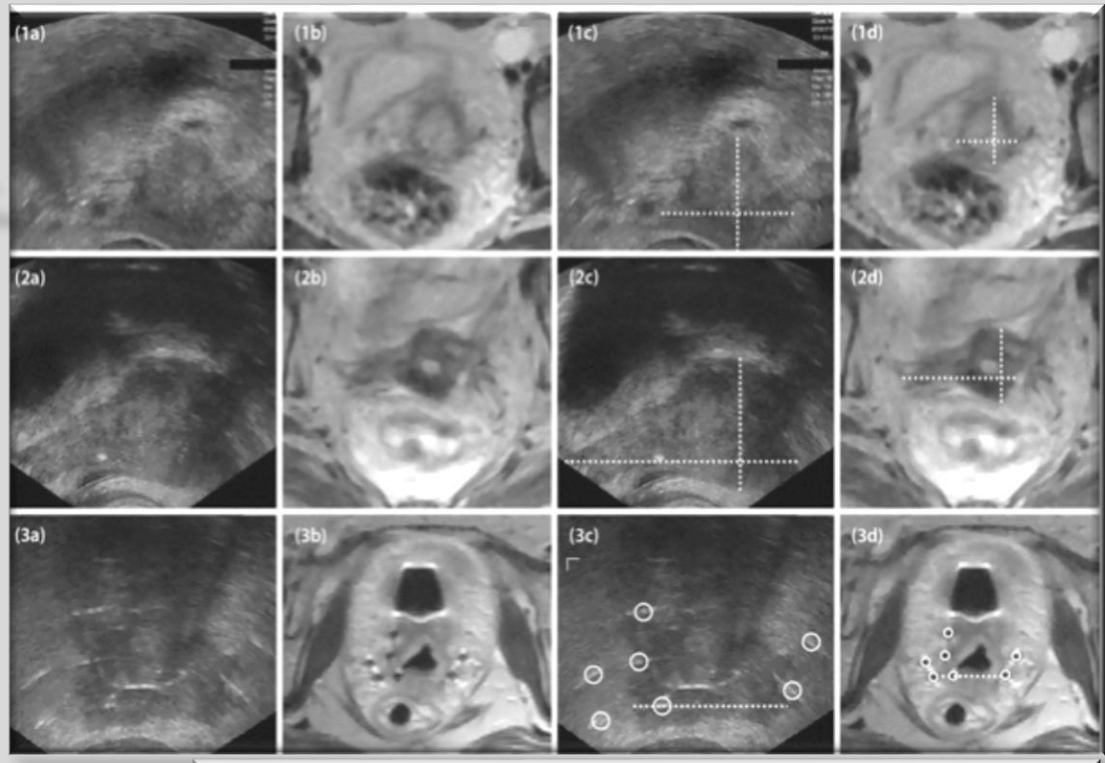







INTERSTITIAL TECHNIQUES
POTENTIAL OF MODERN US TECHNIQUES





Schmid et al. Strahlenther Onkol 2013

Good correlation between US and MRI

INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

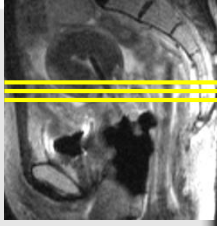
NEEDLE PLACEMENT ACCURACY: OPEN MRI

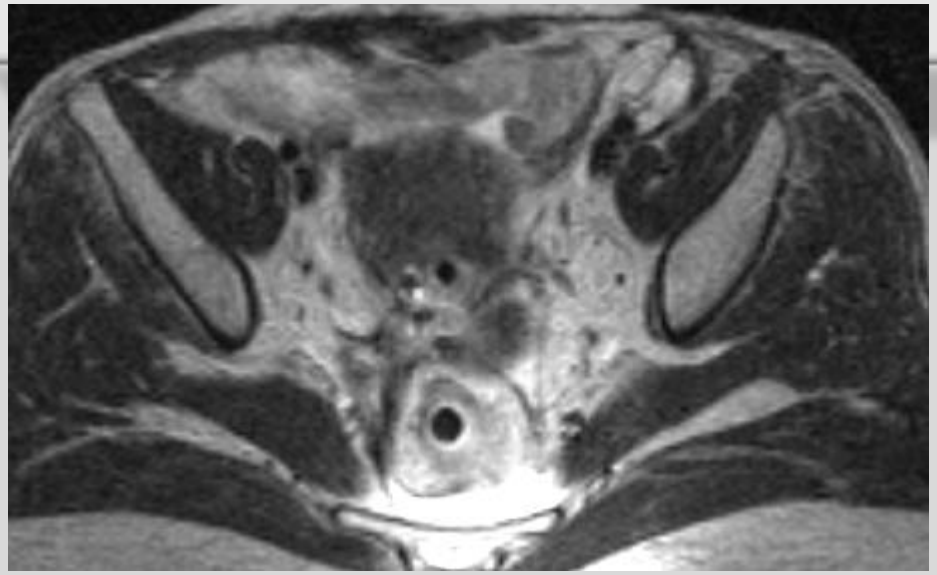
Needle placement accuracy : open MRI with Titanium-Zirconium needles

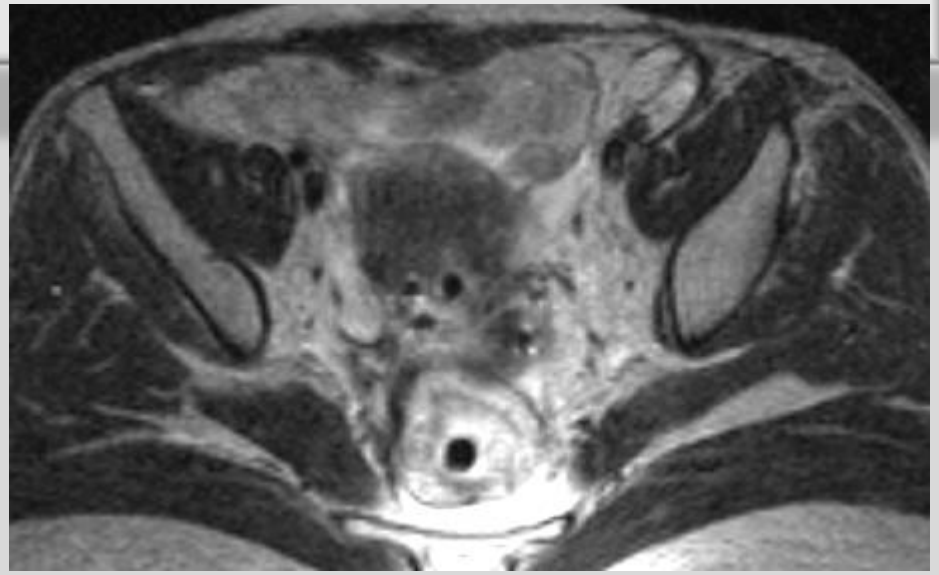
Popowski, IJROBP 47:759-65;2000 6 pts

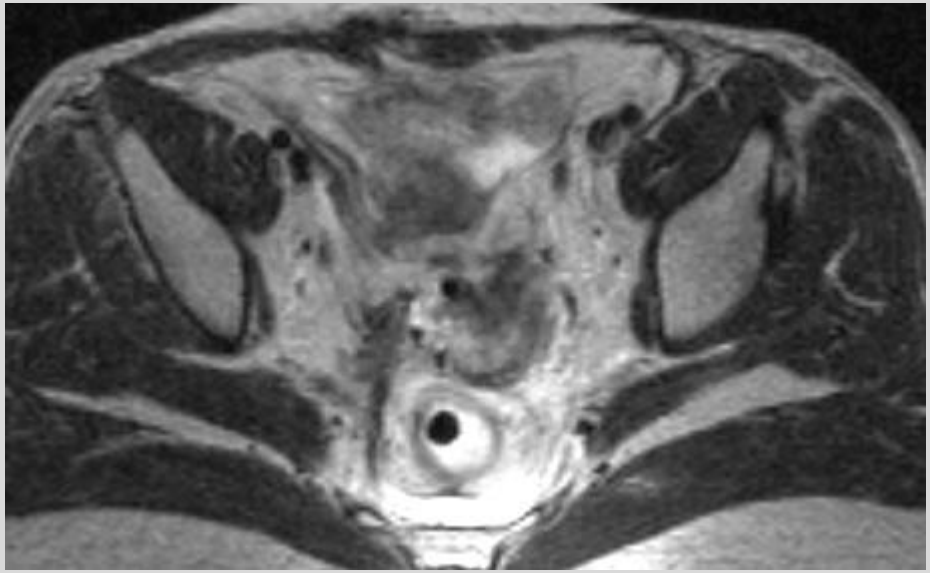
- *Improvement in the treatment quality*
- *Implantation accuracy*
- *Critical organ avoidance*

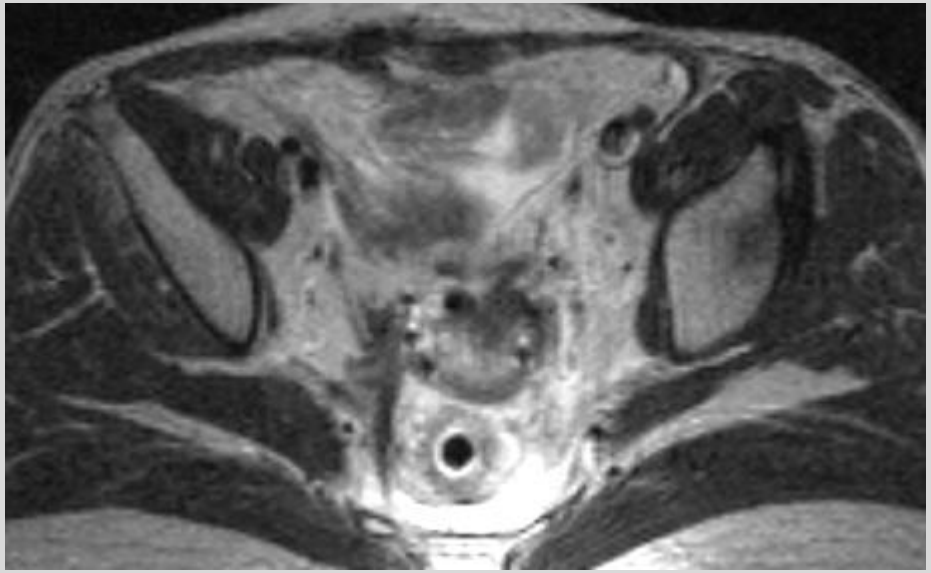
INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT



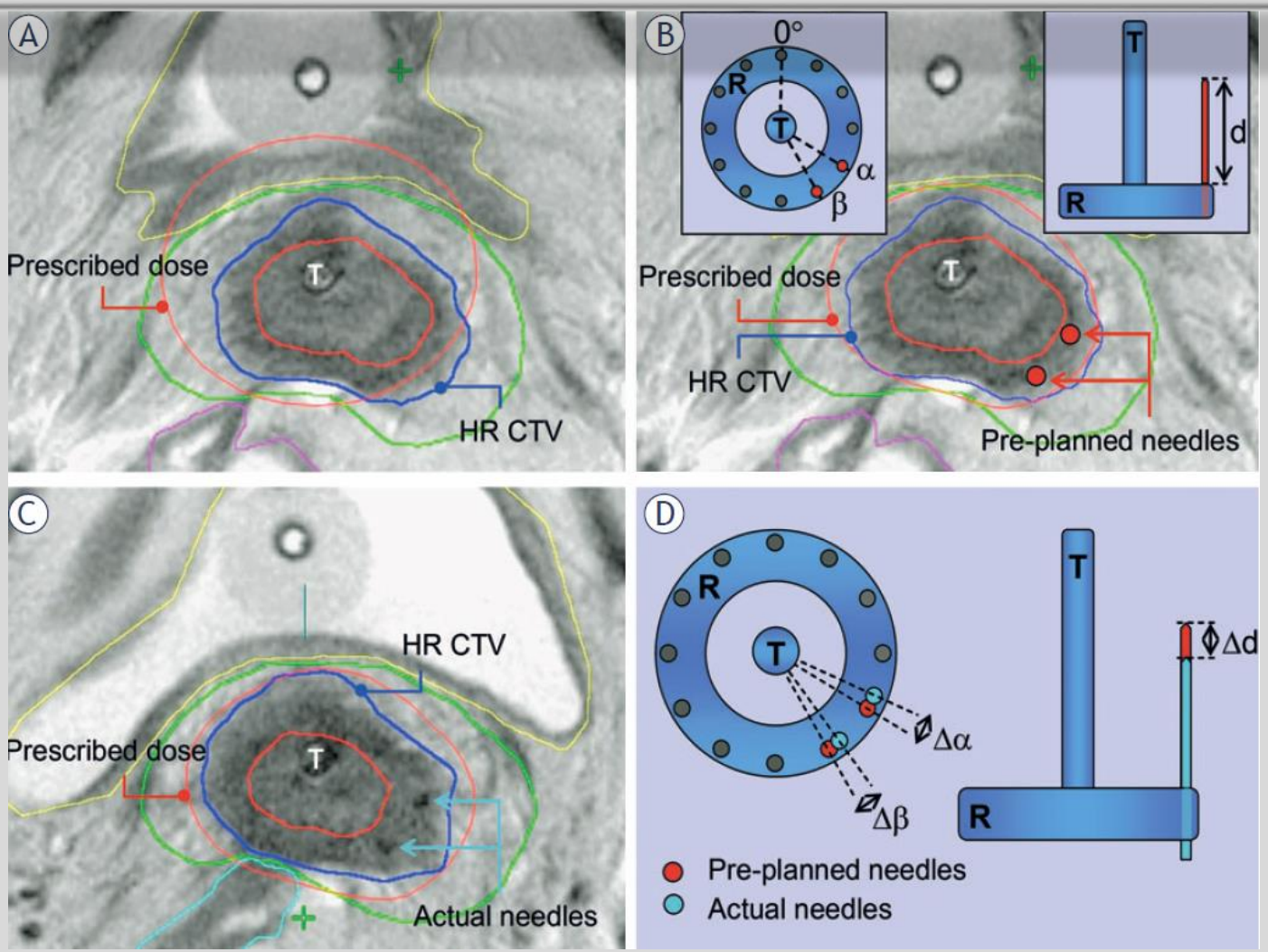








INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT



Petric et al. Radiol Oncol 2014; 48(3): 293-300.

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

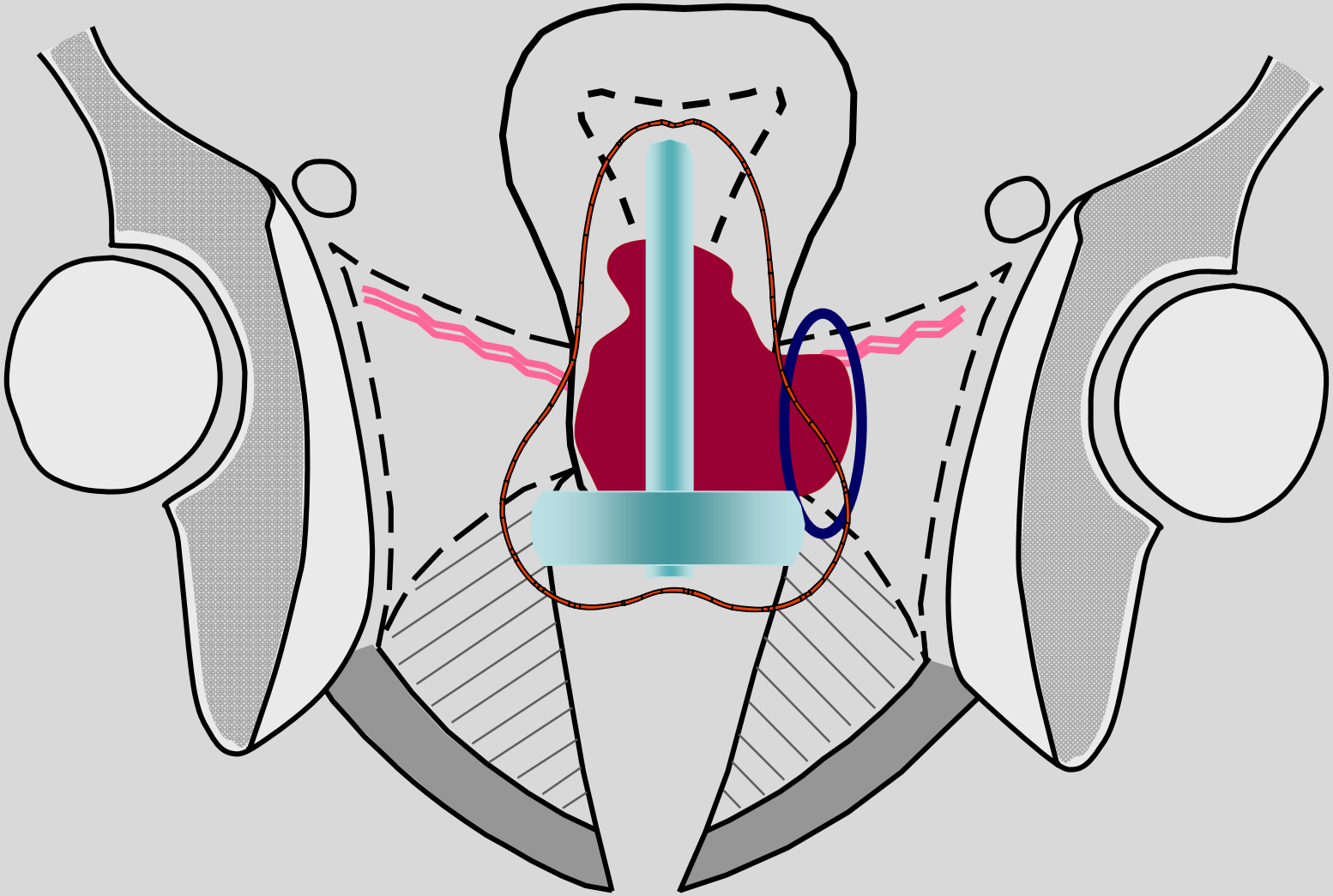
At the time of brachytherapy

-Topography of residual tumor in relation to the applicator

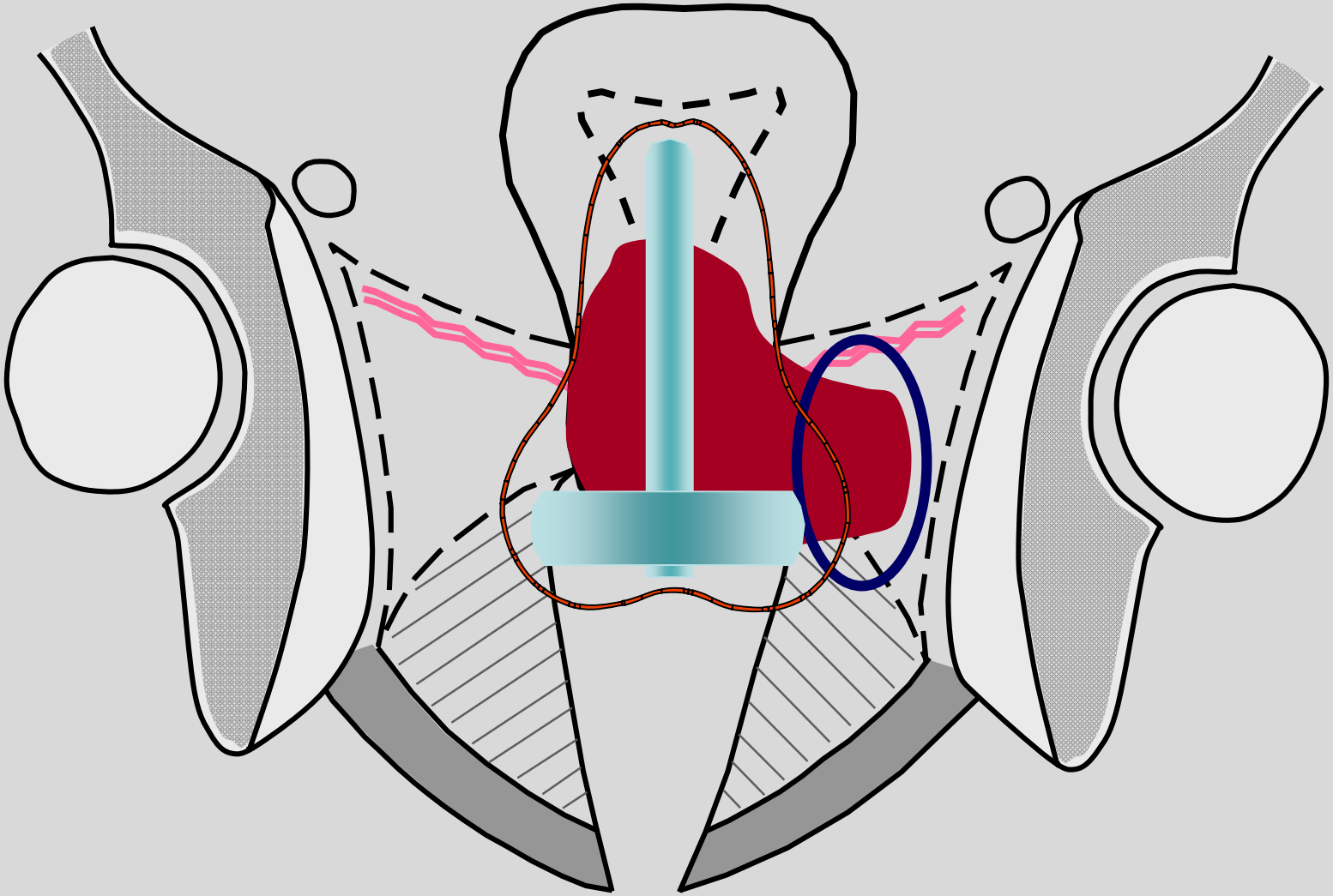
Selection of Brachytherapy Technique

- In General: depending on residual disease at brachytherapy
  - Disease confined to cervix and medial third parametrium: IC alone
  - Extensions beyond medial third parametrium: IC + IS combination
  - Extensive disease not amenable to IC + IS: IS
- Applications can be modified in subsequent fractions (esp. HDR)

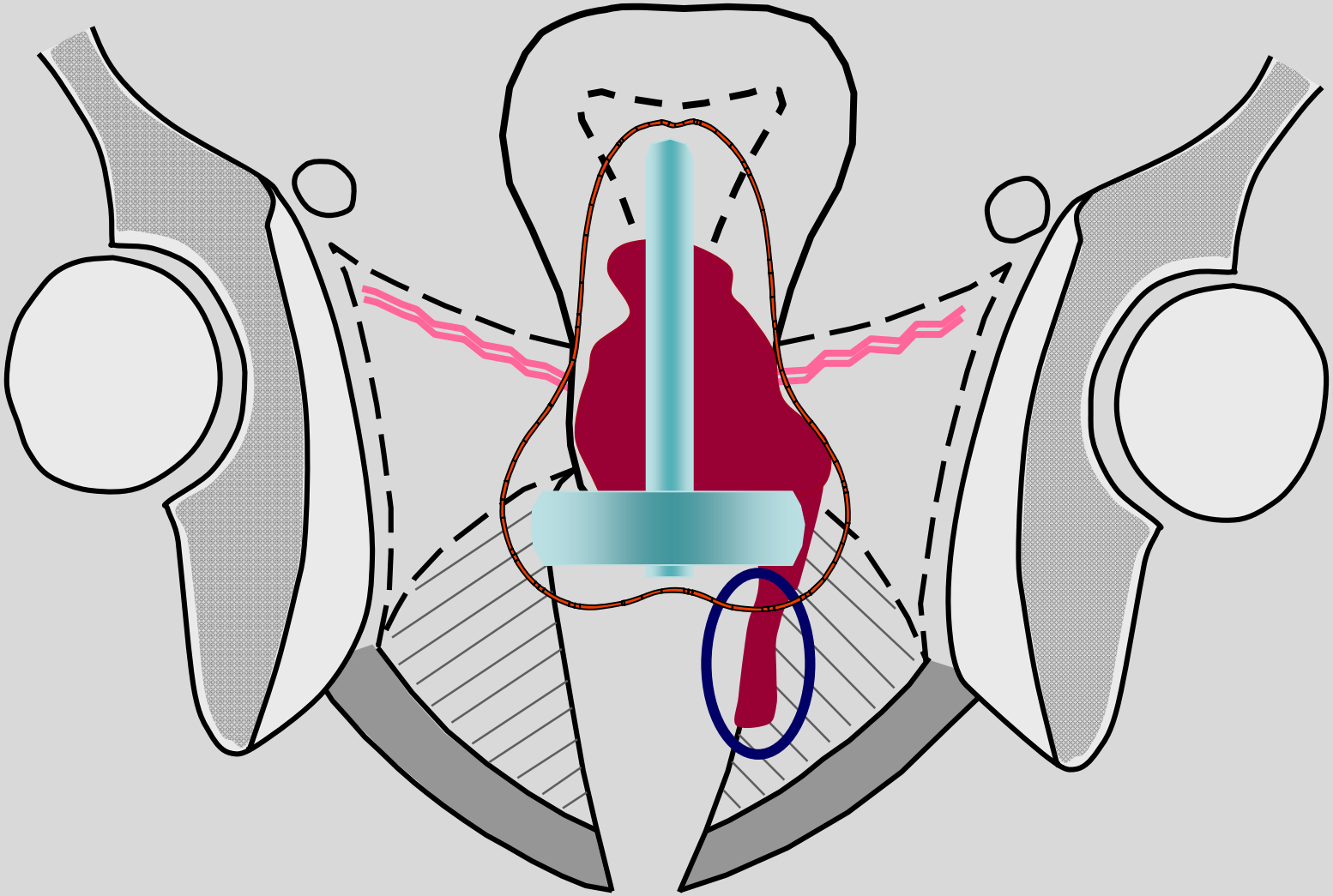
DETECTION OF INAPPROPRIATE COVERAGE: 1



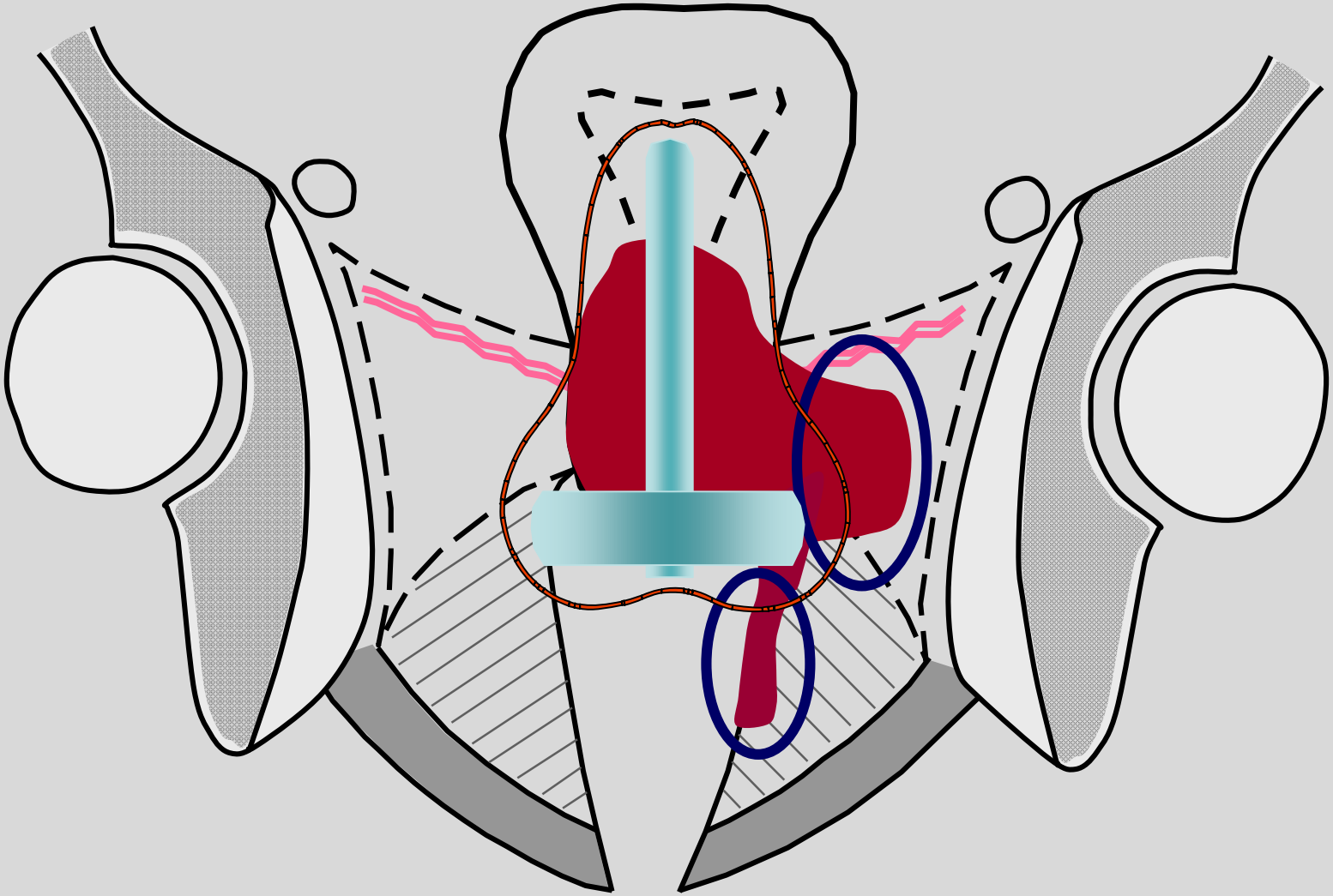
DETECTION OF INAPPROPRIATE COVERAGE: 1A



DETECTION OF INAPPROPRIATE COVERAGE: 2



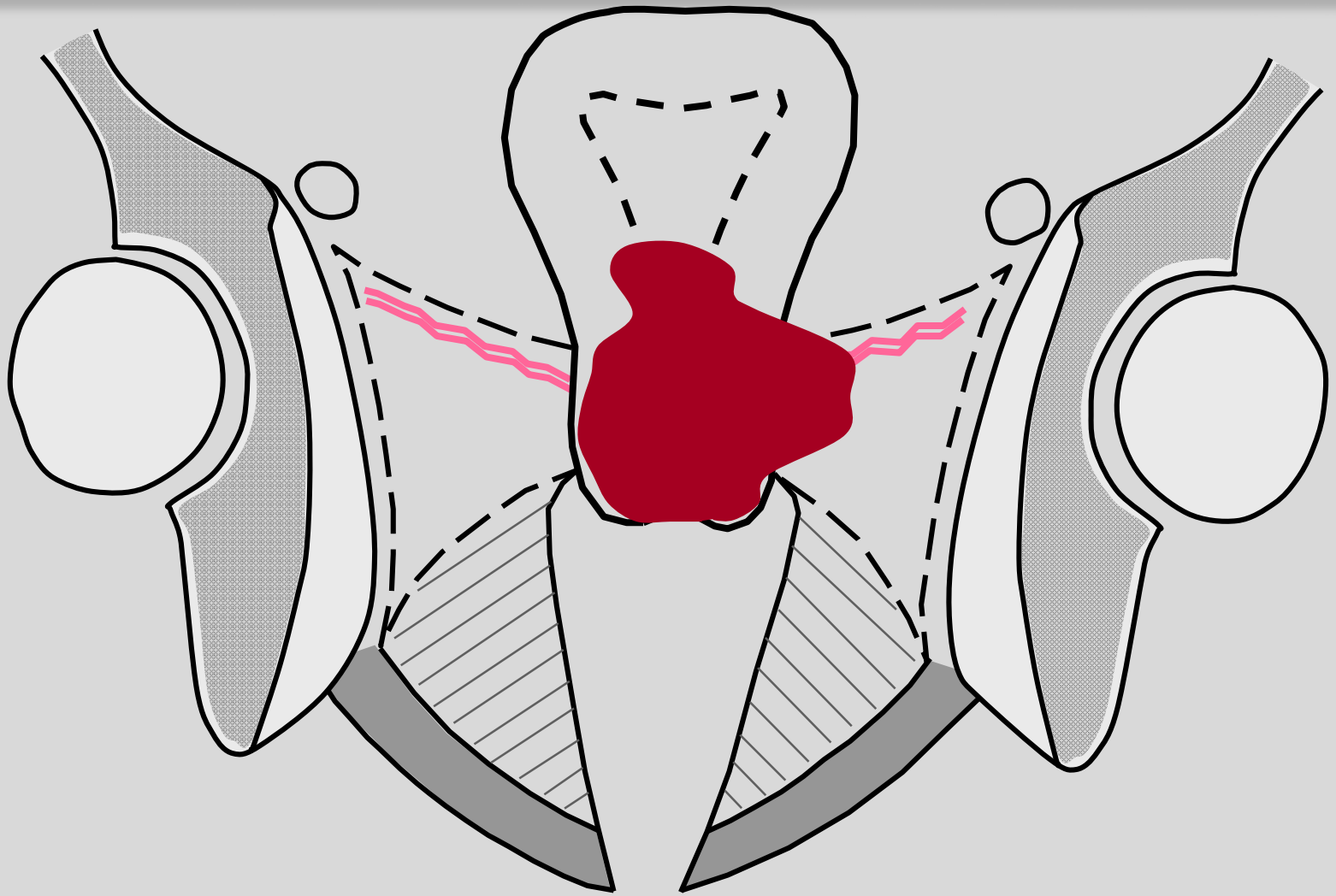
DETECTION OF INAPPROPRIATE COVERAGE: 2A



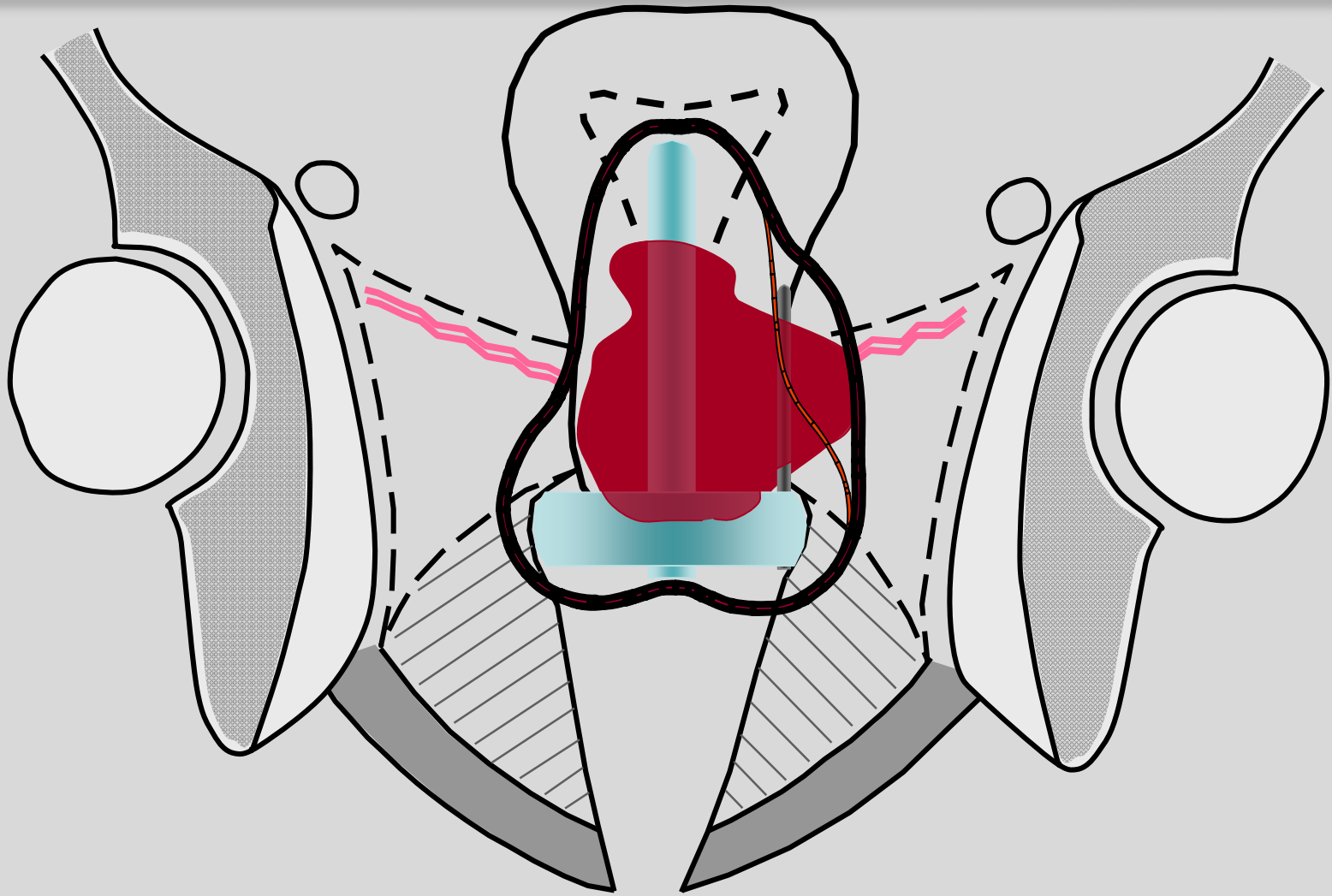
Preconditions - Management

- *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*

Pattern of tumor regression: 1

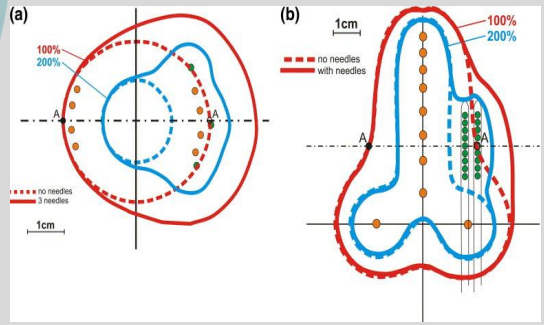


Pattern of tumor regression: 1



The Vienna Applicator

Intercavitary / interstitial
Tandem-Ring Applicator

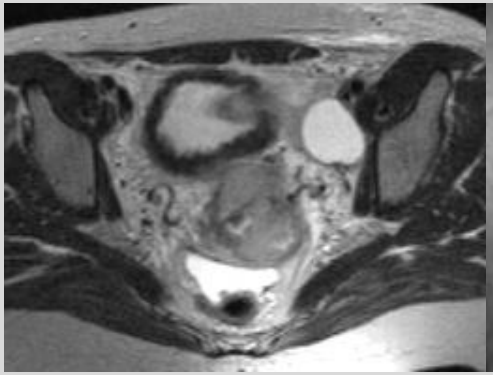
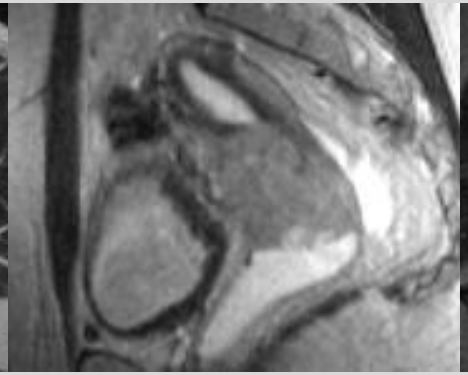
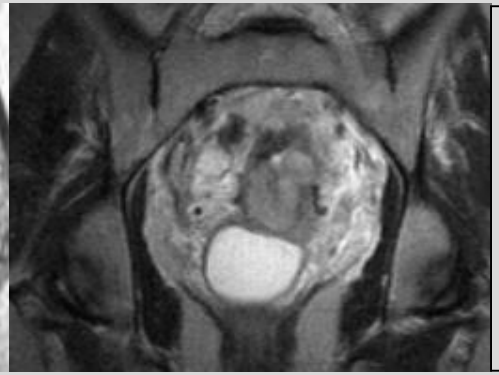
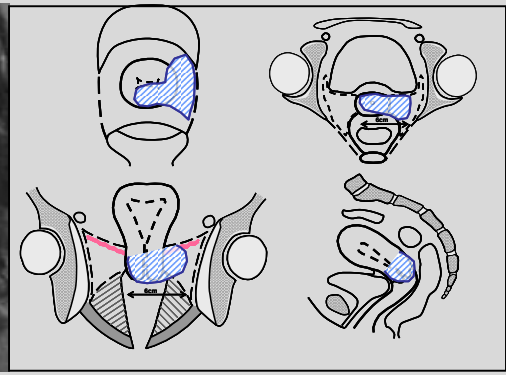


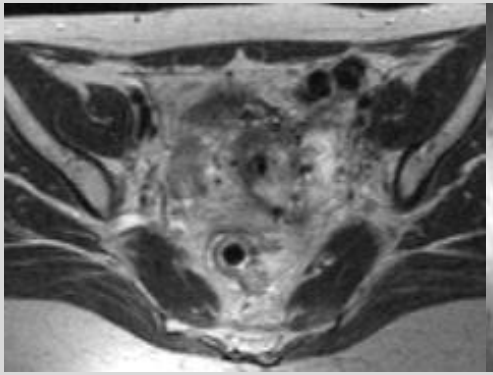
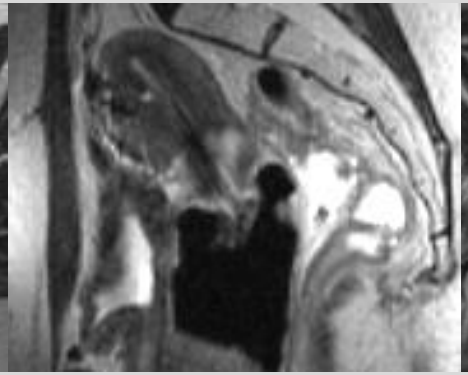
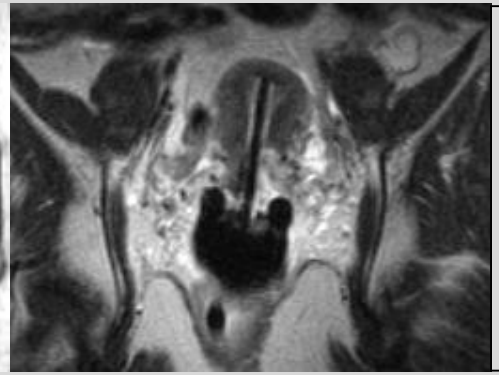
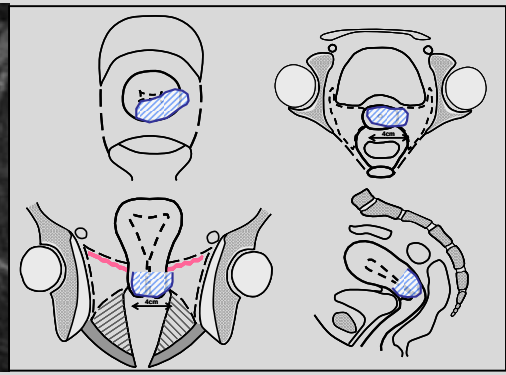
Modified Applicator: drilled holes into ring to insert needles parallel to the Tandem

Kirisits et al. IJROBP 2006 (technical note)

Dimopoulos et al. IJROBP 2006 (clinical results)

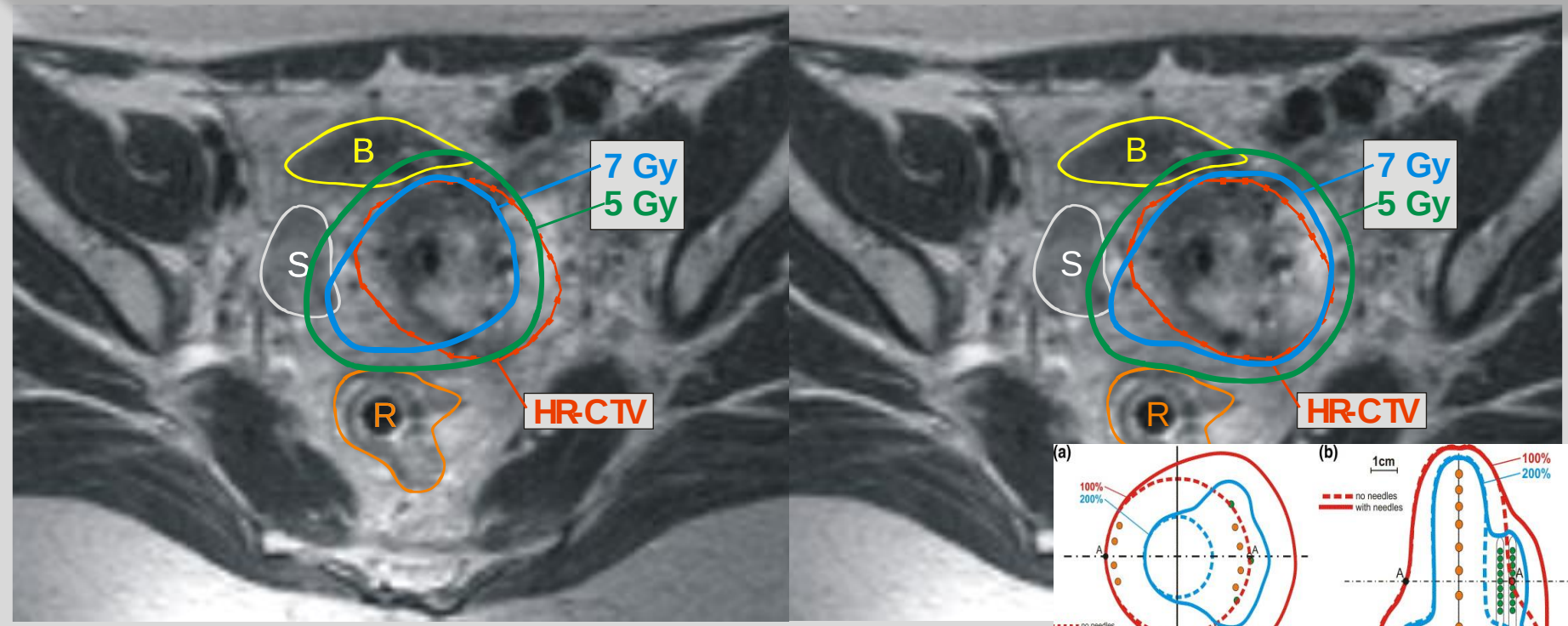
Clinical example
Stage IIB / distal / insufficient response

Clinical example - Interstitial Treatment MRI Based Treatment Planning plus Novel Application Technique

standard treatment plan **optimized interstitial**



INTRACAVITARY PLUS NEEDLES LEFT PARAMETRIUM

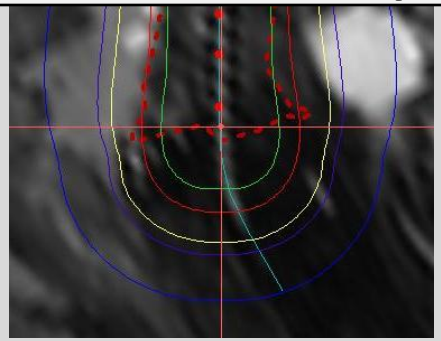
Improved placement control - Low number of needles – Combined with MRI based treatment planning

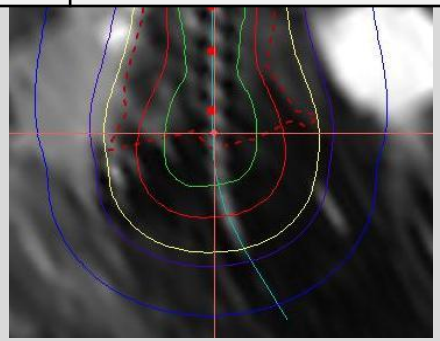
UNFAVORABLE TOPOGRAPHY FOR OAR'S: 1- 2A

STD INTRA-CAVITARY BT

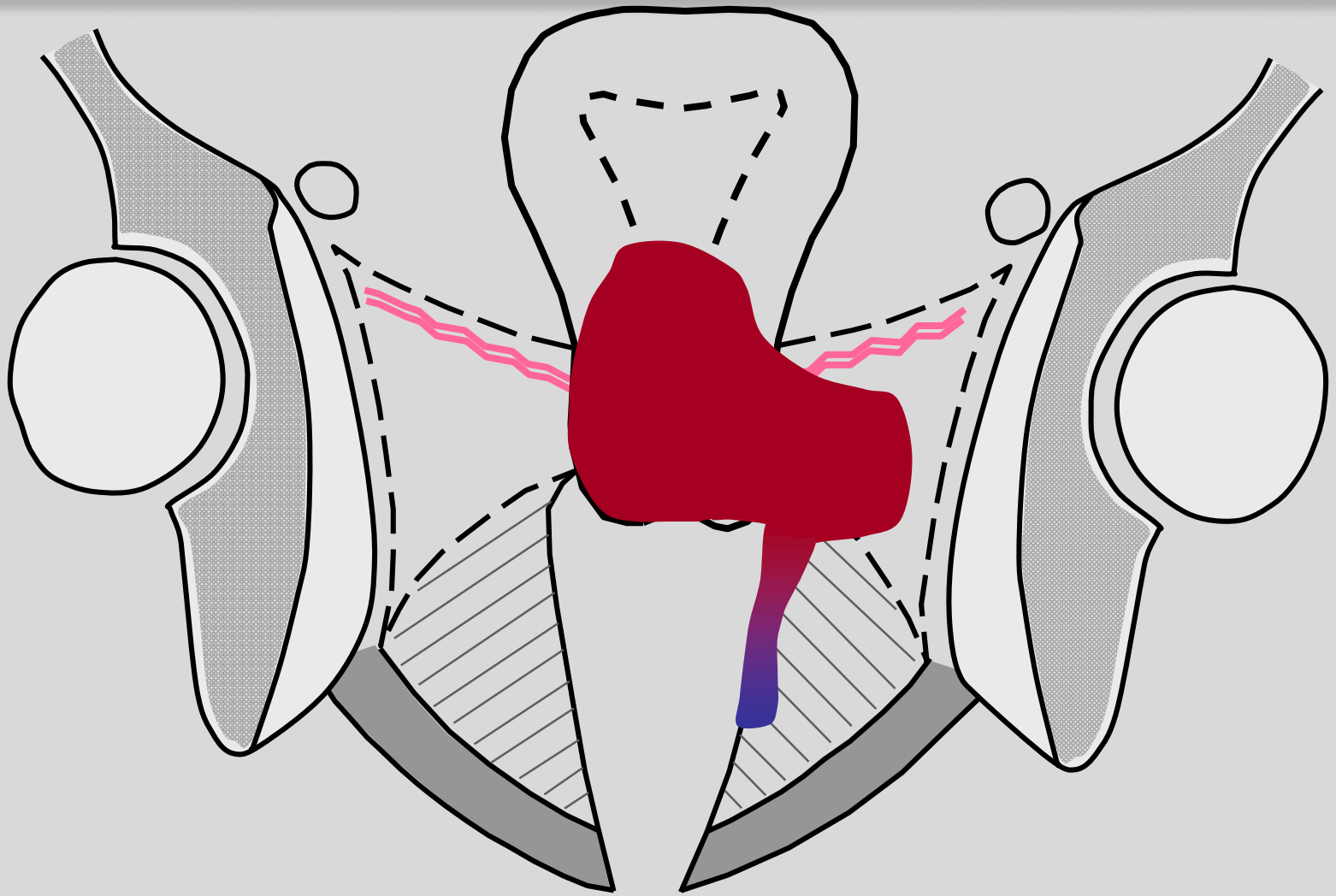
Vienna

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

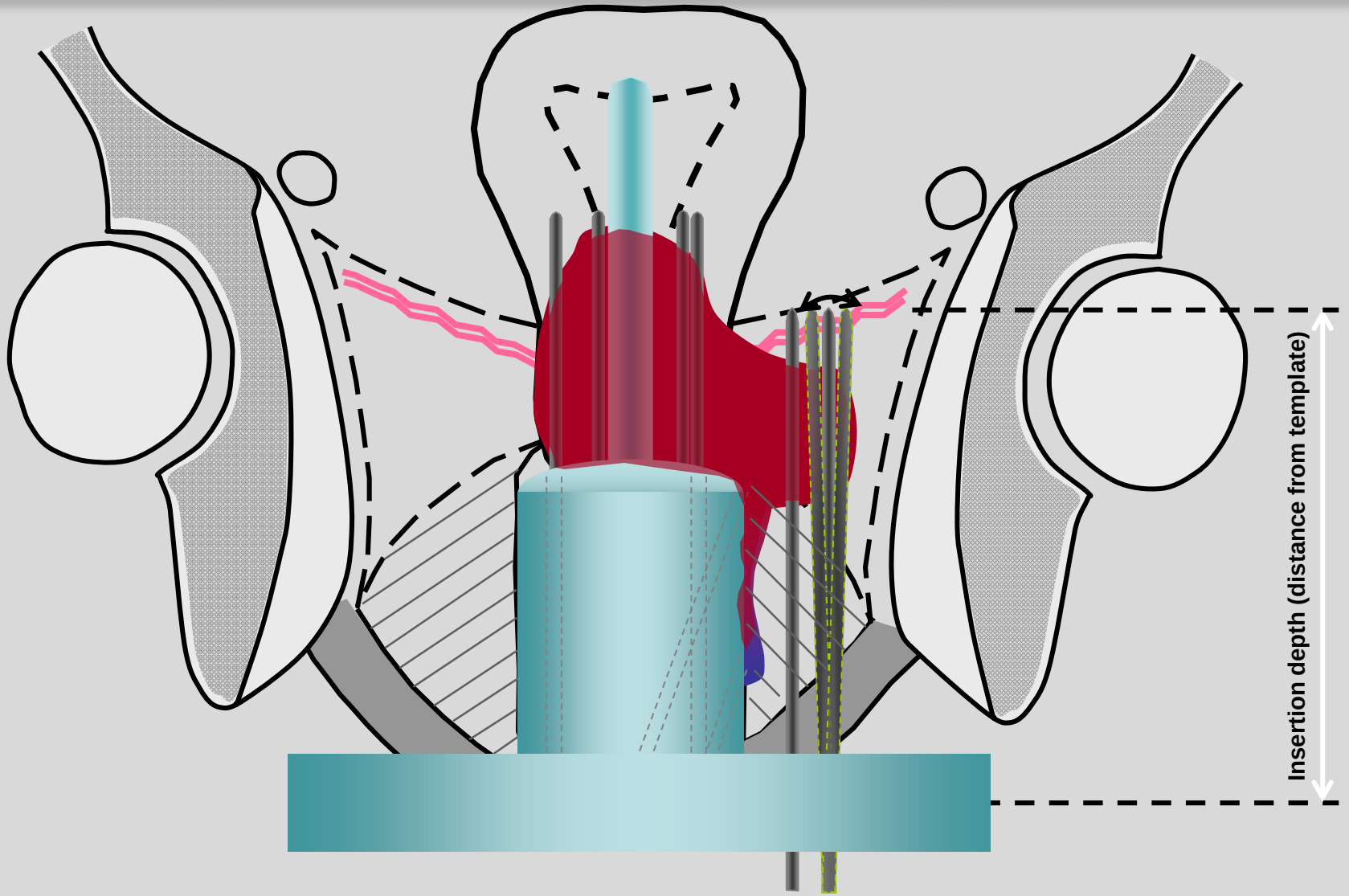




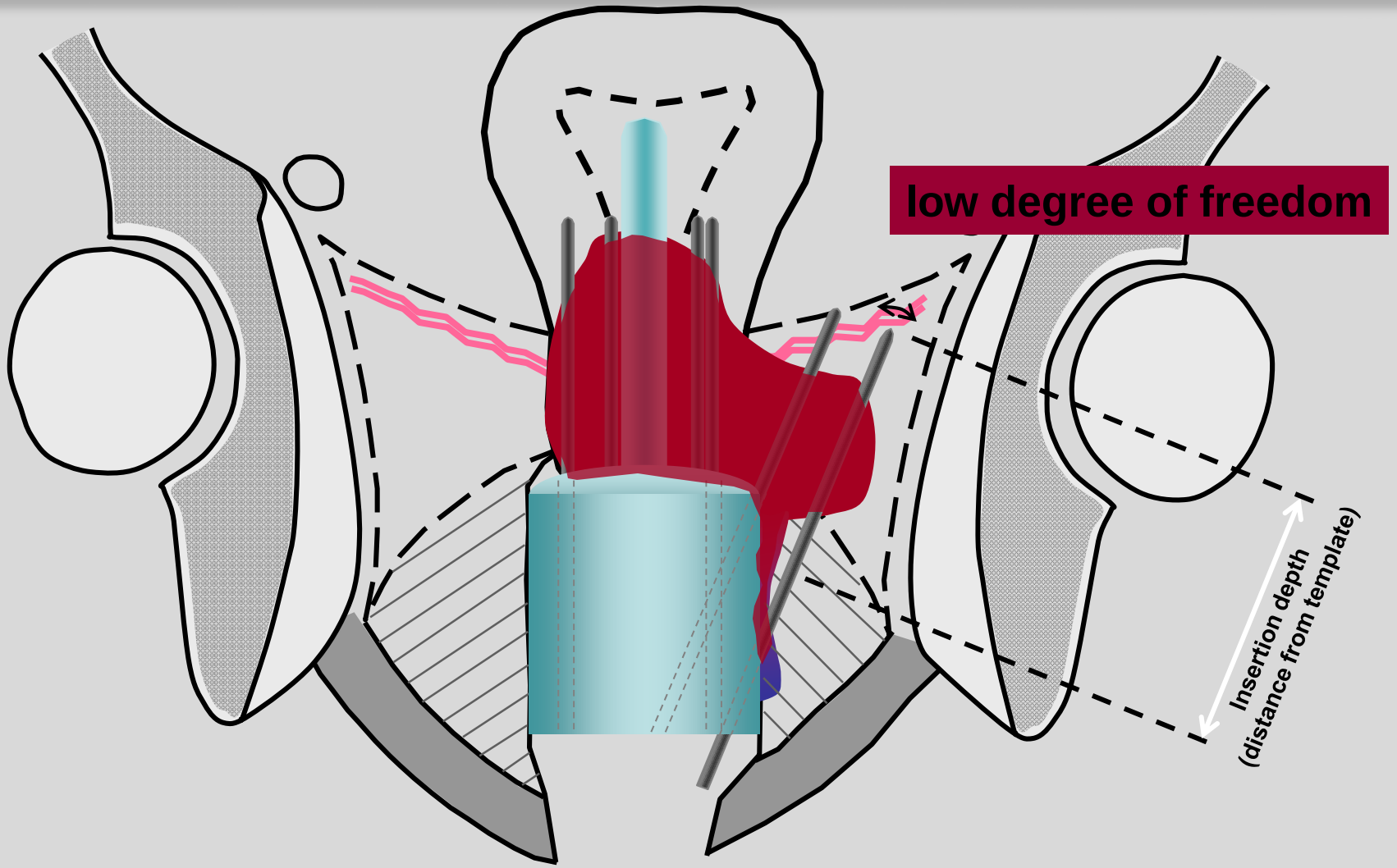
Pattern of tumor regression: 2-2A



Pattern of tumor regression

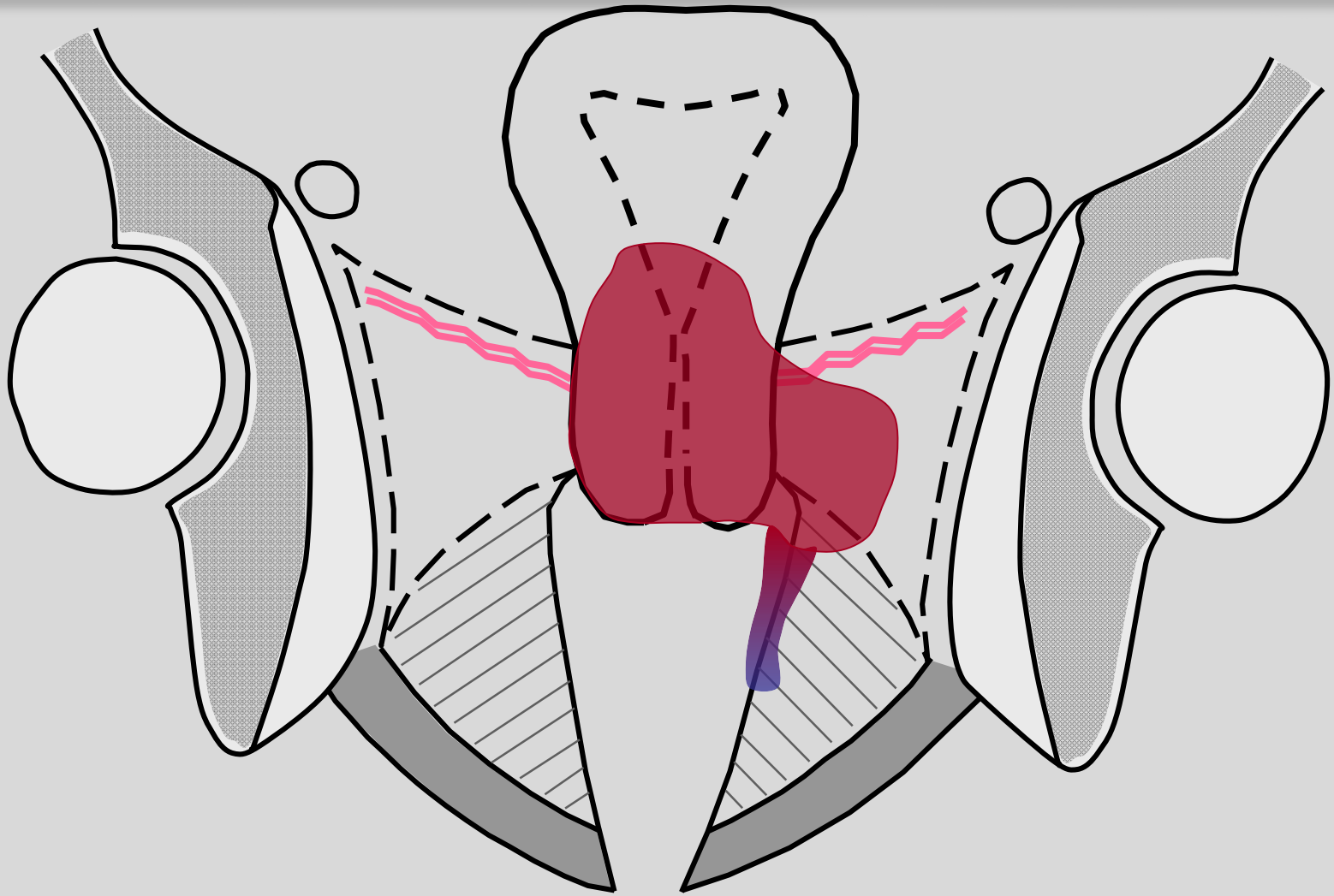


Pattern of tumor regression



Tandem + Cylinder + Needles

Applicator for distal parametrial disease
additional parallel and divergent template guided needles

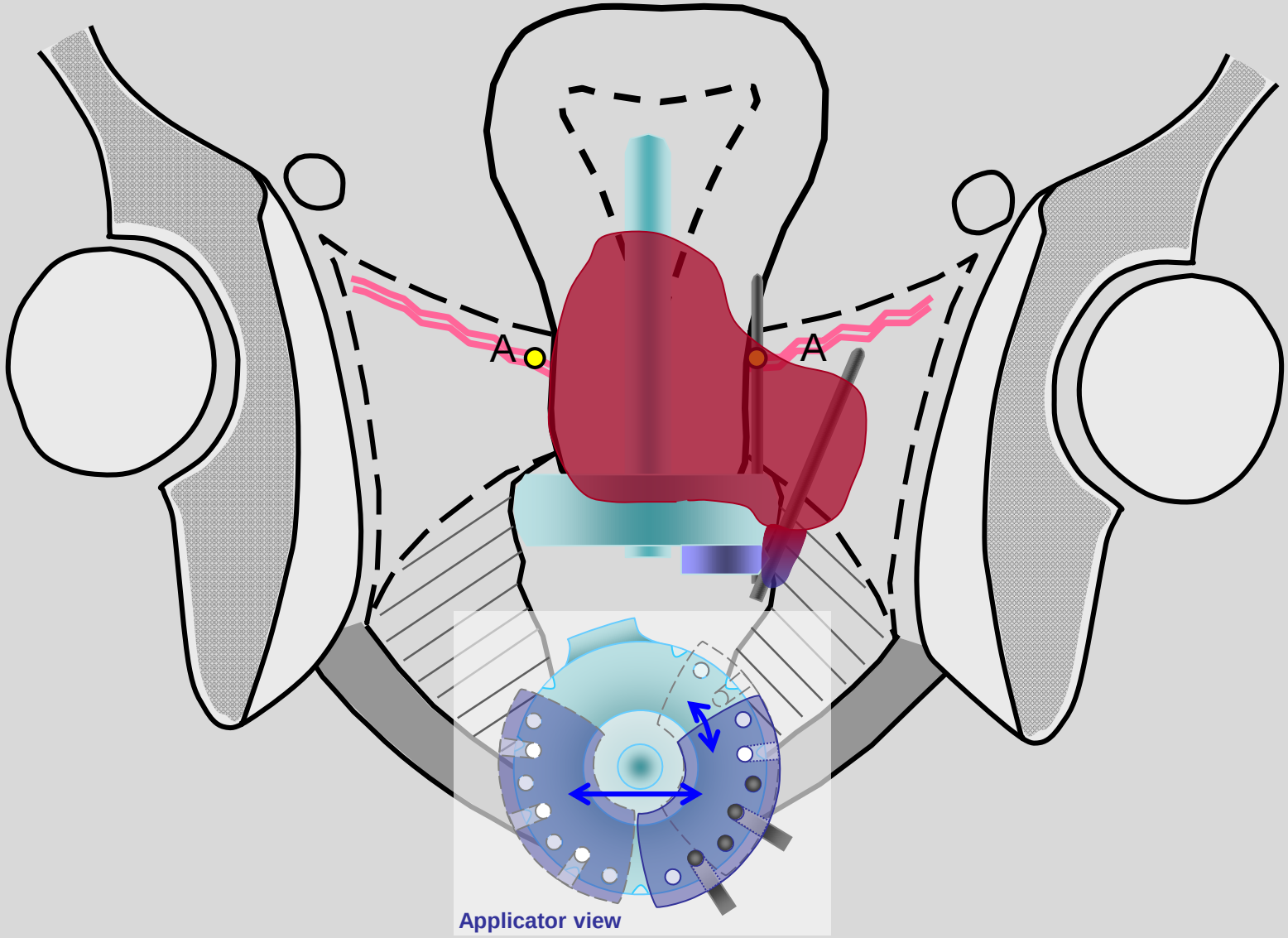


The Vienna II Applicator

Berger et al. ABS 2010

Applicator for distal parametrial disease

additional parallel and divergent template guided needles



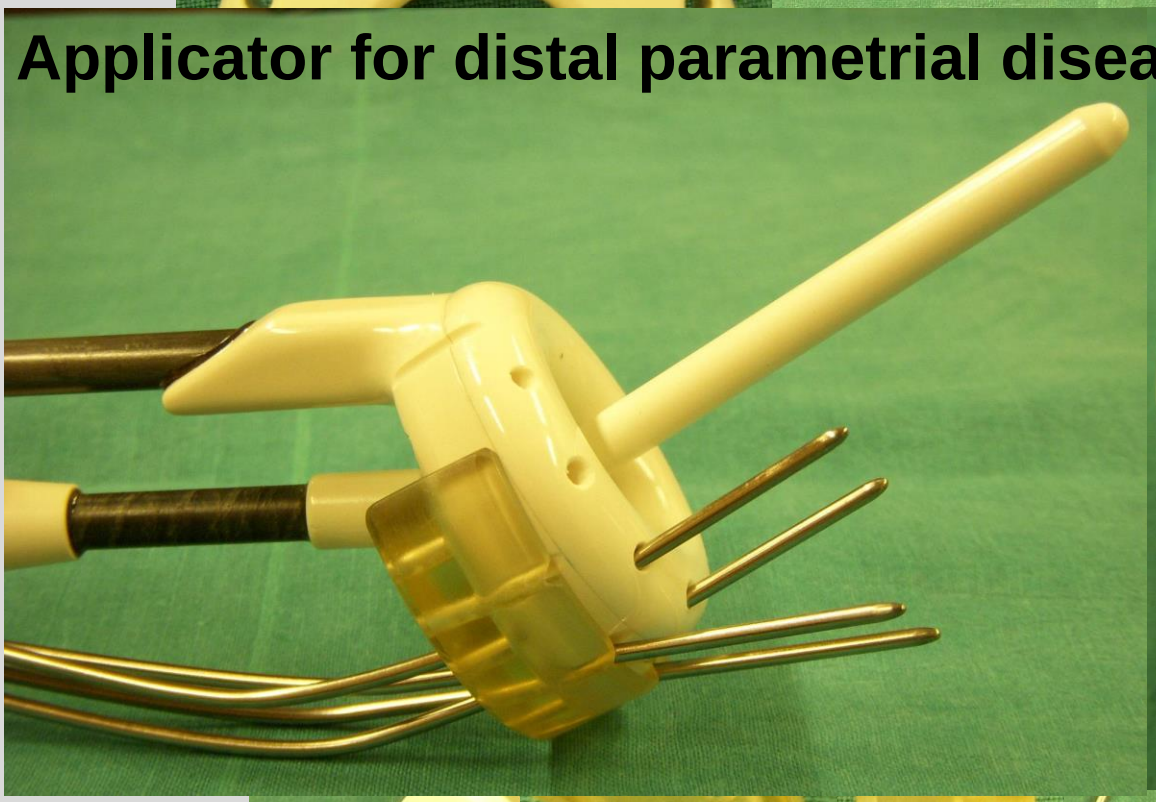
The Vienna II Applicator

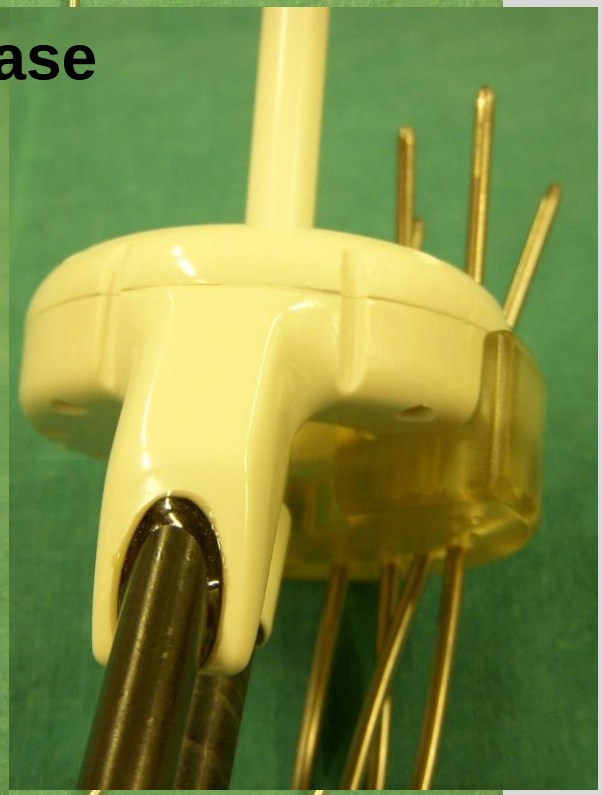
Berger et al. ABS 2010

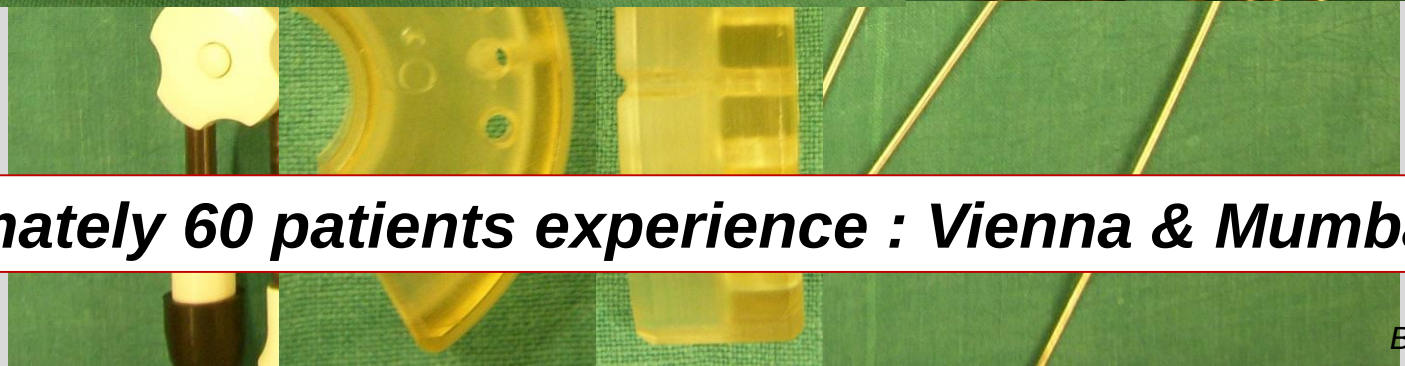
Modified Vienna Ring

Pre-bended needles

Applicator for distal parametrial disease





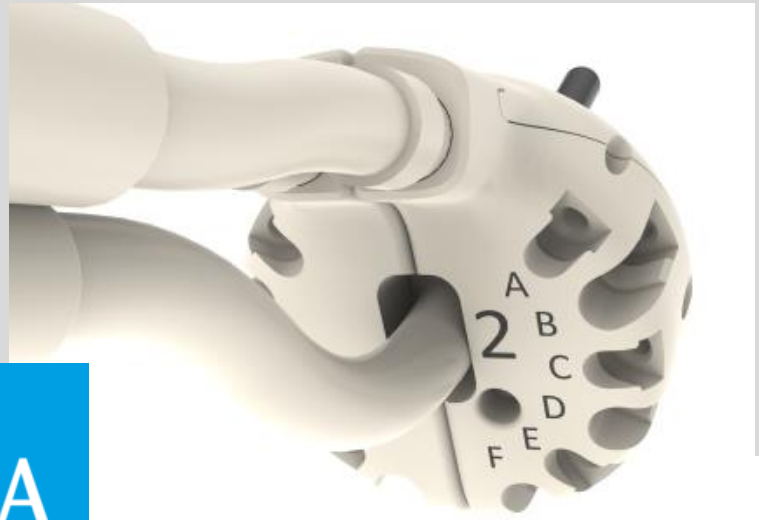


Approximately 60 patients experience : Vienna & Mumbai

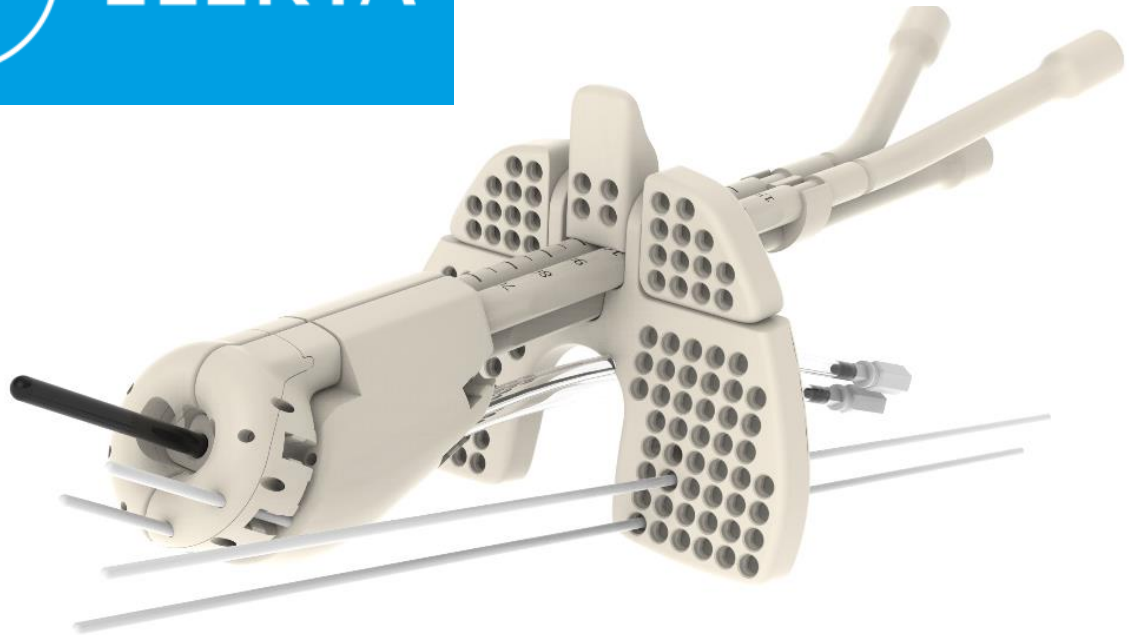
Berger et al.

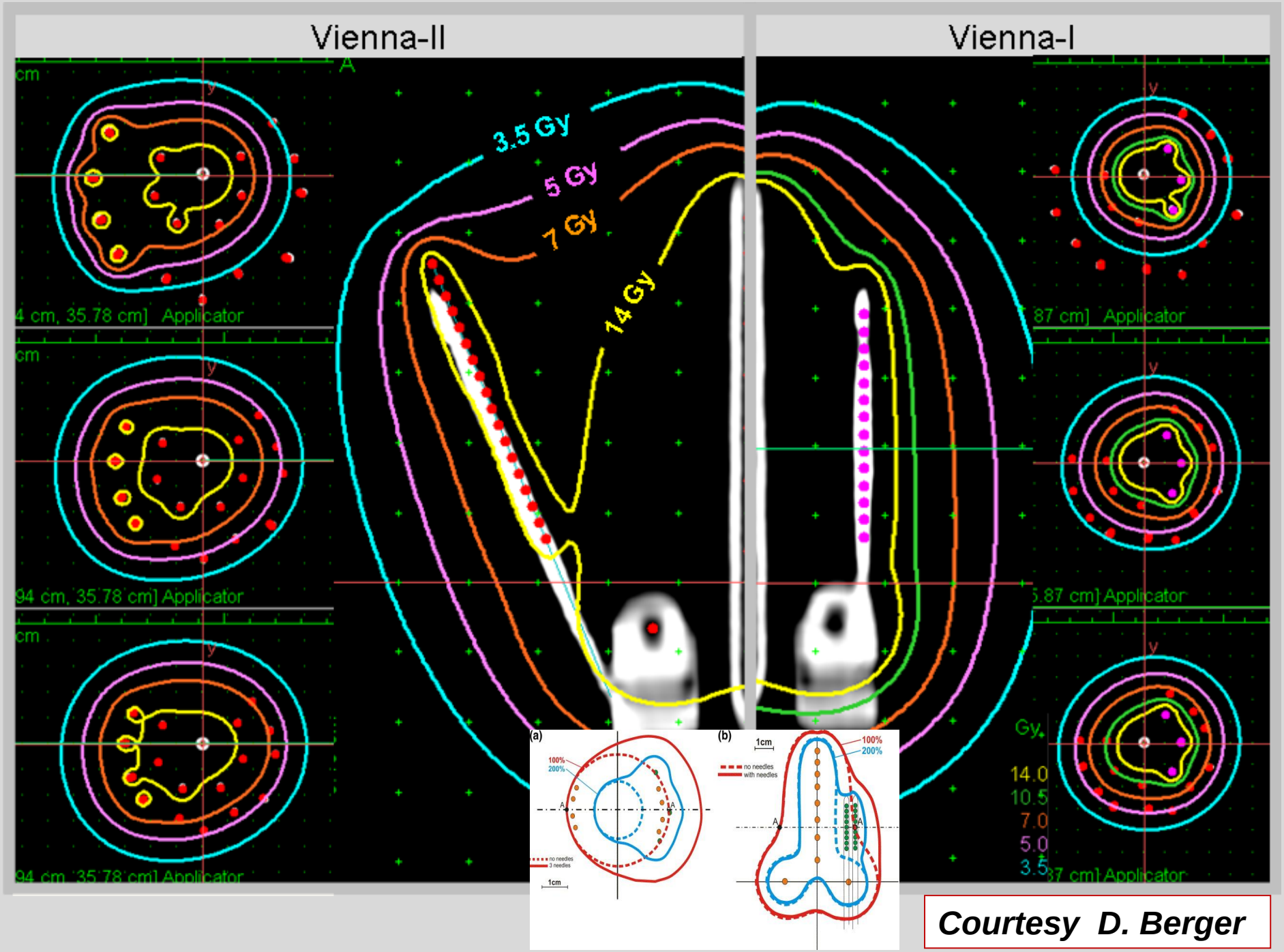
Latest Development in Applicators

VENEZIA GYN APPLICATOR



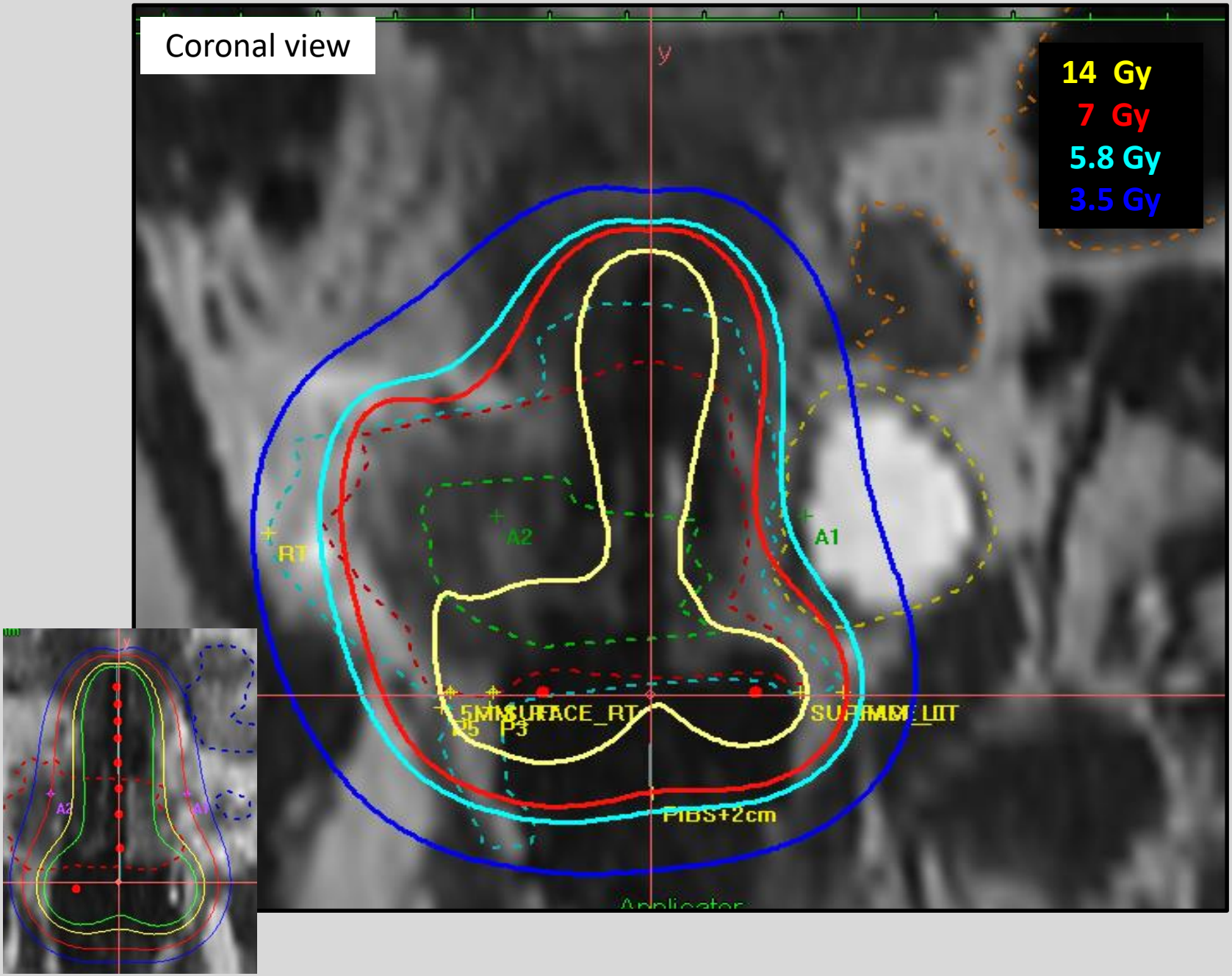
ELEKTA



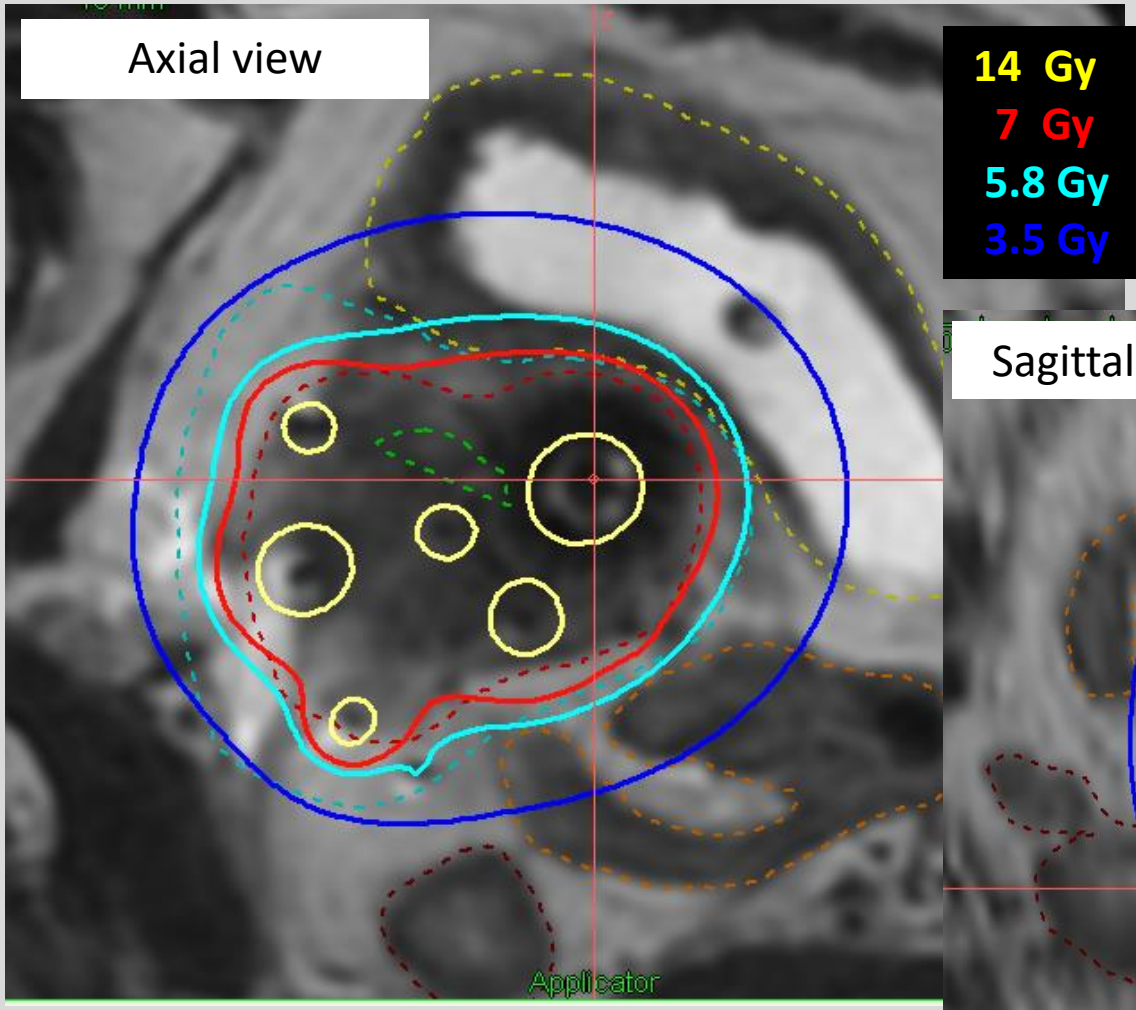


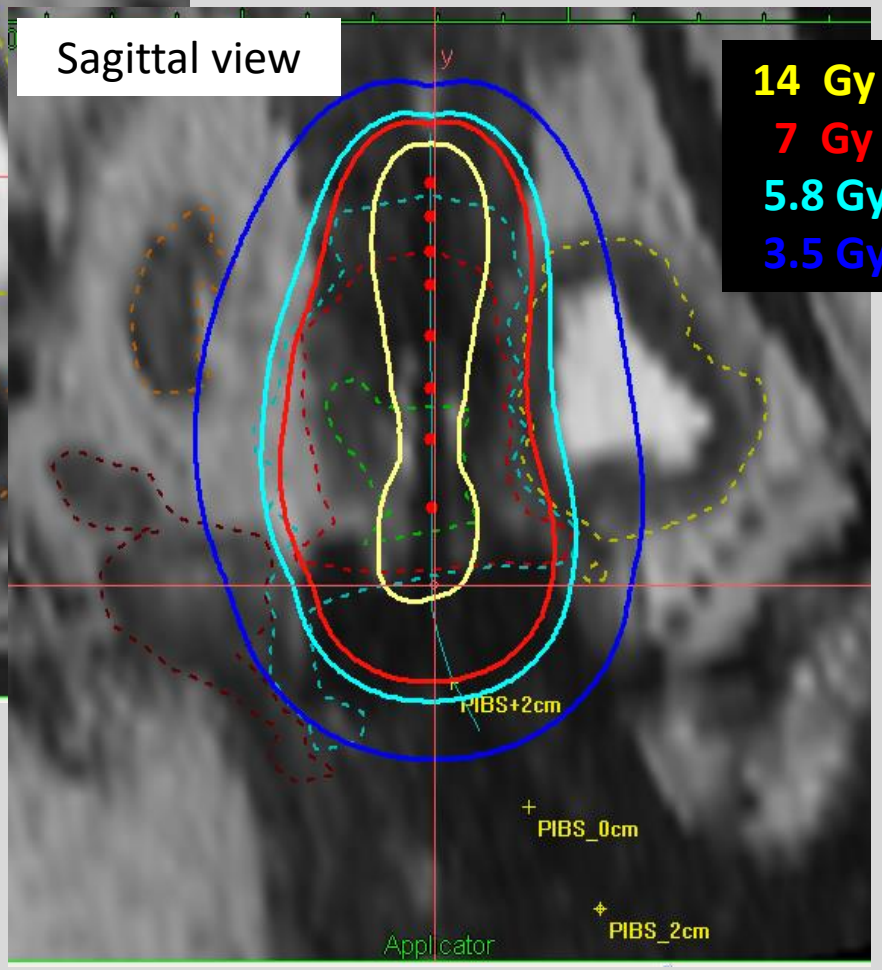
Courtesy D. Berger

PLAN EVALUATION



PLAN EVALUATION





PIBS:Postero-inferior border of pubic symphysis

GEC –ESTRO / ICRU (89)

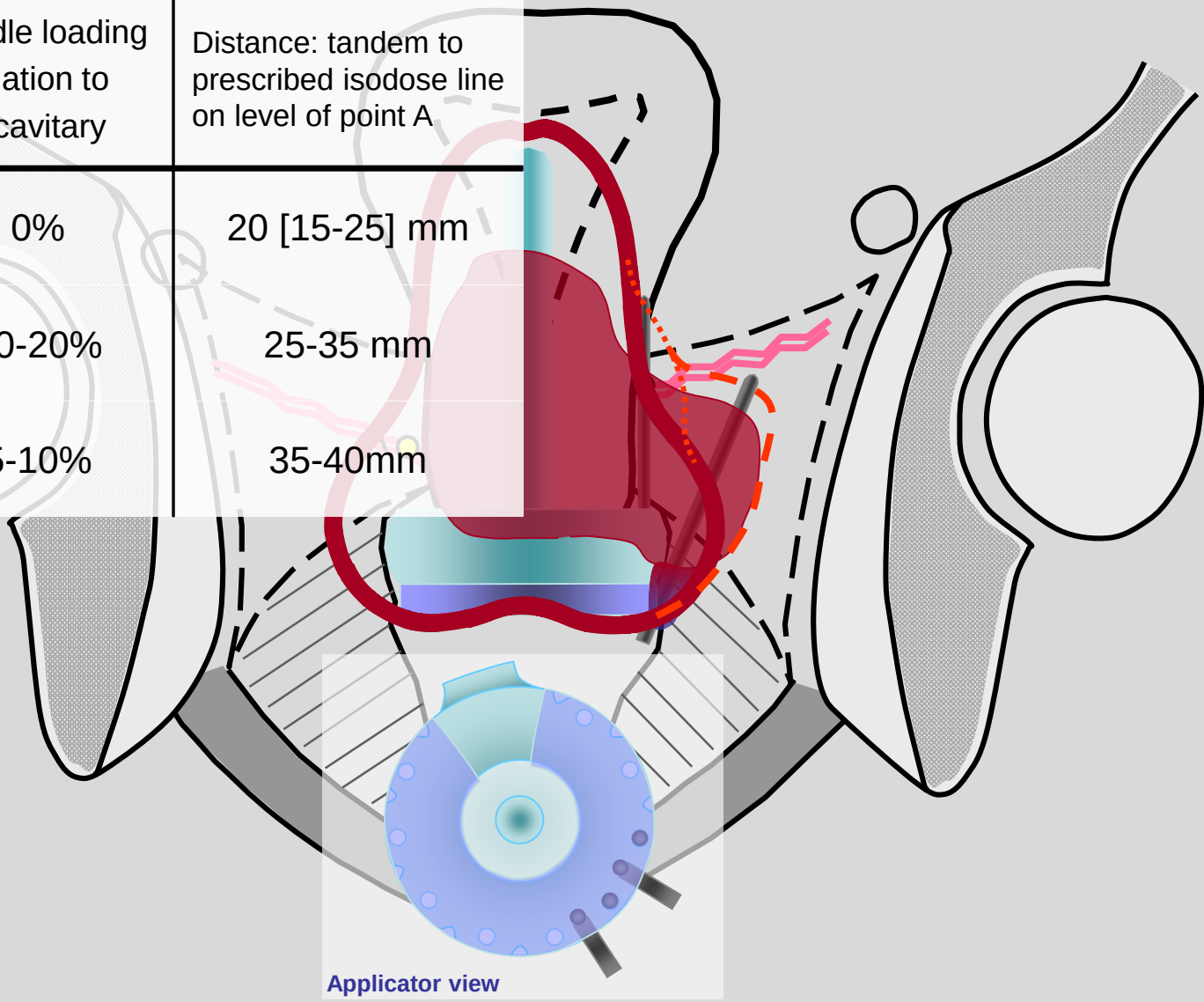
REPORTING OF DOSE VOLUME PARAMETERS

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

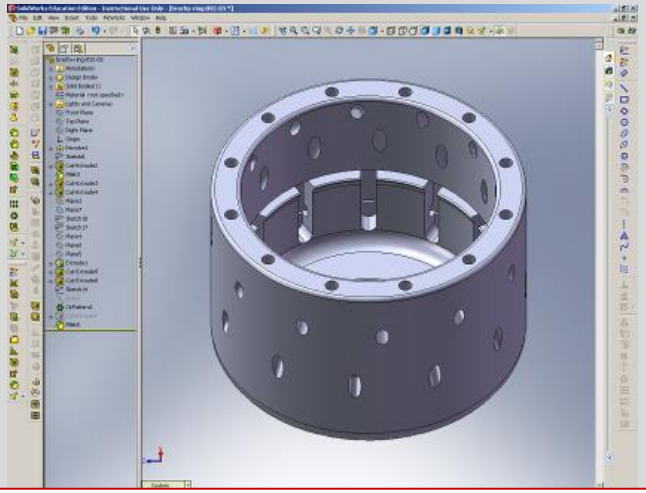


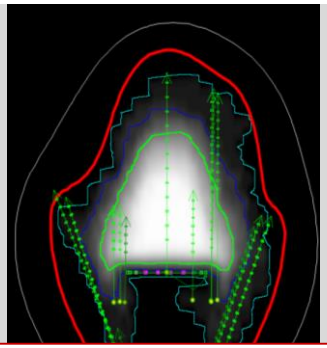
D. Berger et al.

Adaptive BT applicators

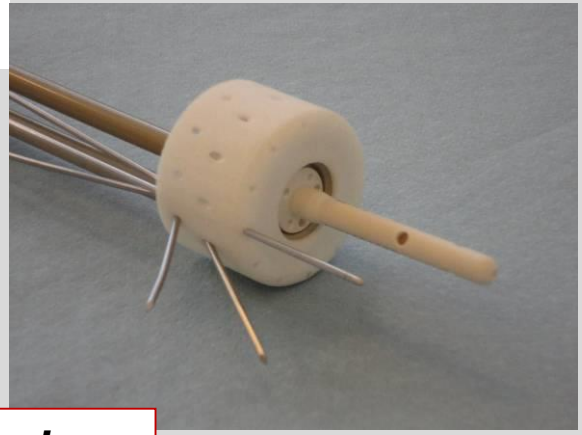
3D Printing

Virtual applicator





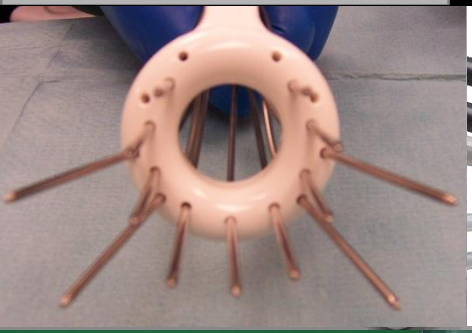
New applicator

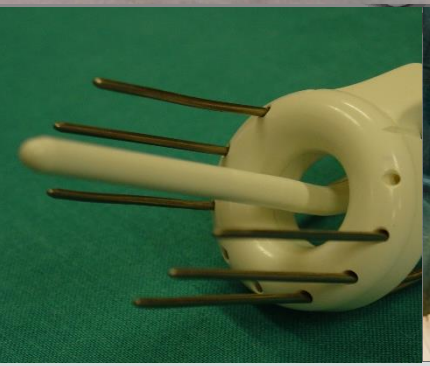


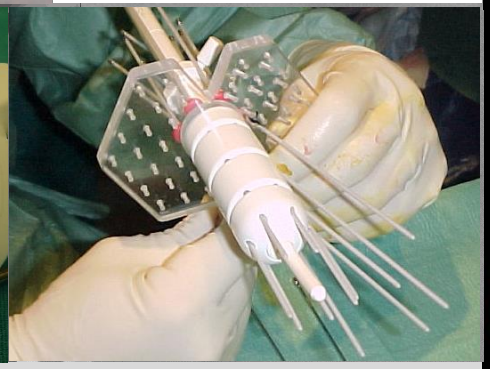
264 patients with tumour mapping Ljubljana, Vienna, Aarhus

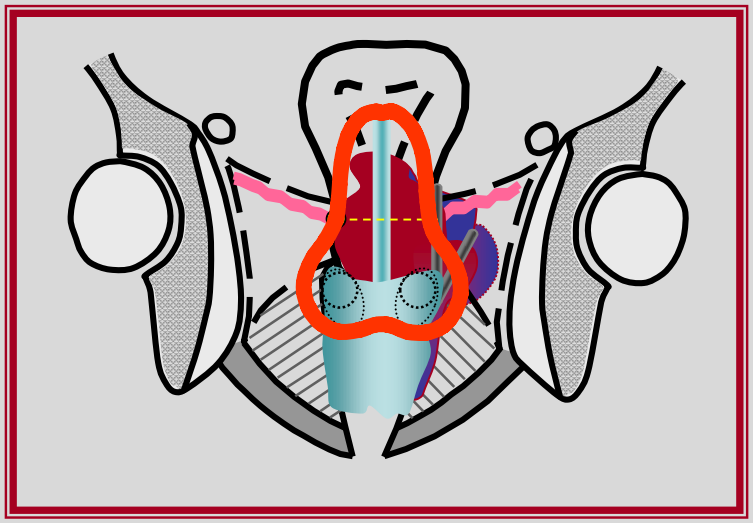
Provided by Primoz Petric and Jacob Lindegaard Ljubljana/Aarhus

Mission

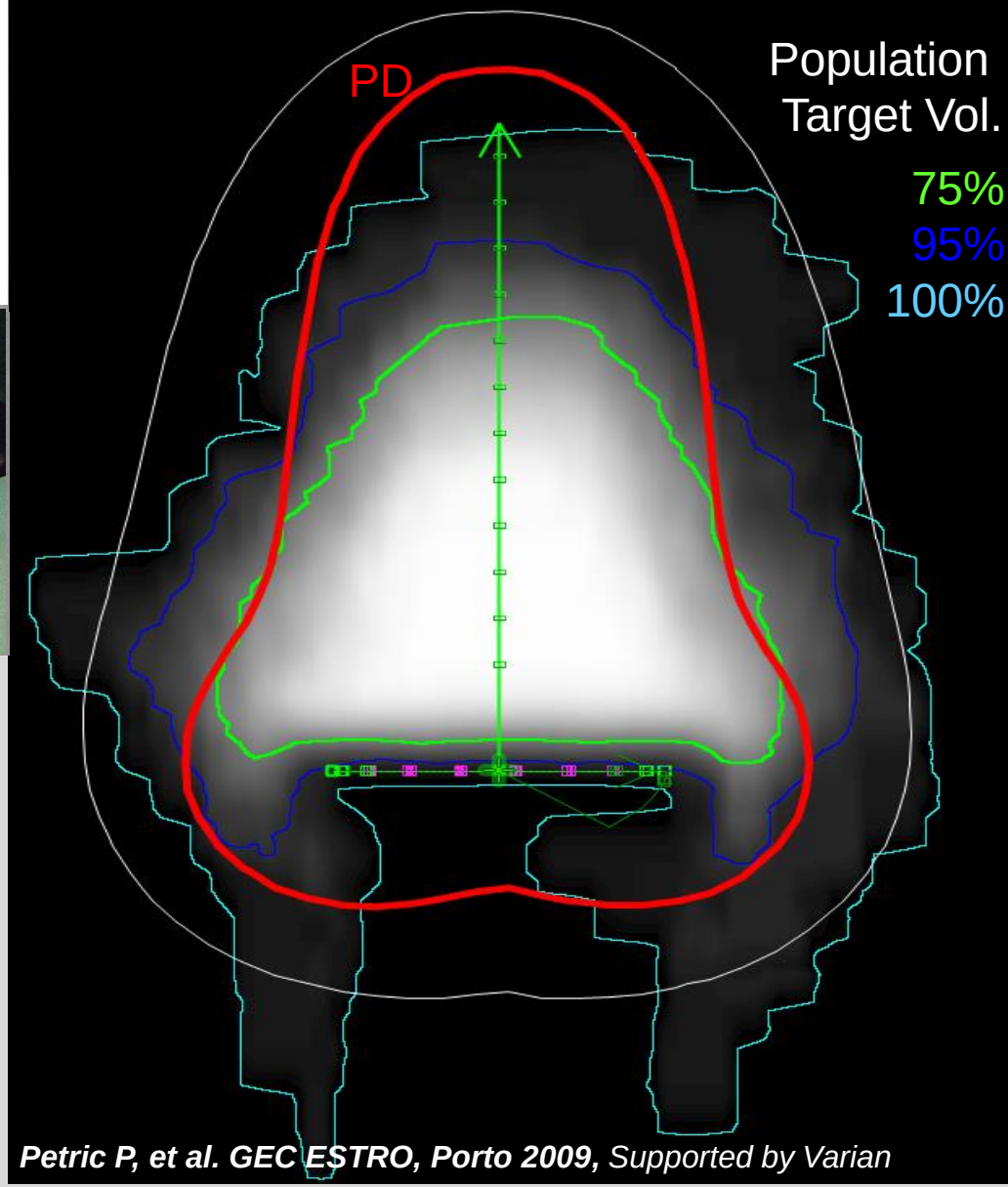








264 patients



Petric P, et al. GEC ESTRO, Porto 2009, *Supported by Varian*

Courtesy: P. Petric,D. Berger

SUMMARY & CONCLUSIONS

- *Conbined Intracavitary & Interstitial techniques when inappropriate coverage (topographic and dosimetric) with pure intracavitary techniques*
- *Several approaches (applicators,guidance) available*
- *Application technique: Various tumor topography at BT*
- *A good portion of cases can be treated with simple techniques*
- *Combined Intracavitary & Interstitial techniques: Associated with a learning curve for accurate placement/few needles/MRI based tuomr topoography*

CLINICAL DIAGRAMS: CERVICAL CANCER

Umesh Mahantshetty

Professor,

Department of Radiation Oncology

&

GYN Disease Management Group Member

Tata Memorial Hospital, Mumbai, India

ESTRO
European Society for Therapeutic Radiology and Oncology

TATA MEMORIAL CENTRE
टाटा स्मारक केंद्र
SERVICE RESEARCH EDUCATION

Q: Clinical drawings aid in

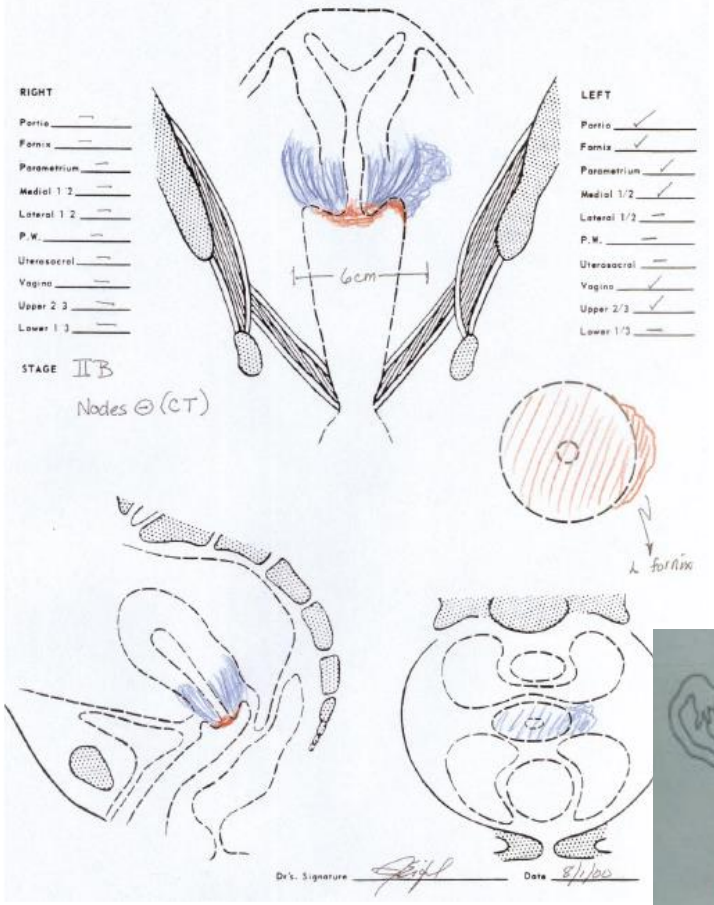
A. 3D Documentation
B. Evaluation of Disease Remission
C. Selection of BT technique
D. All of the above

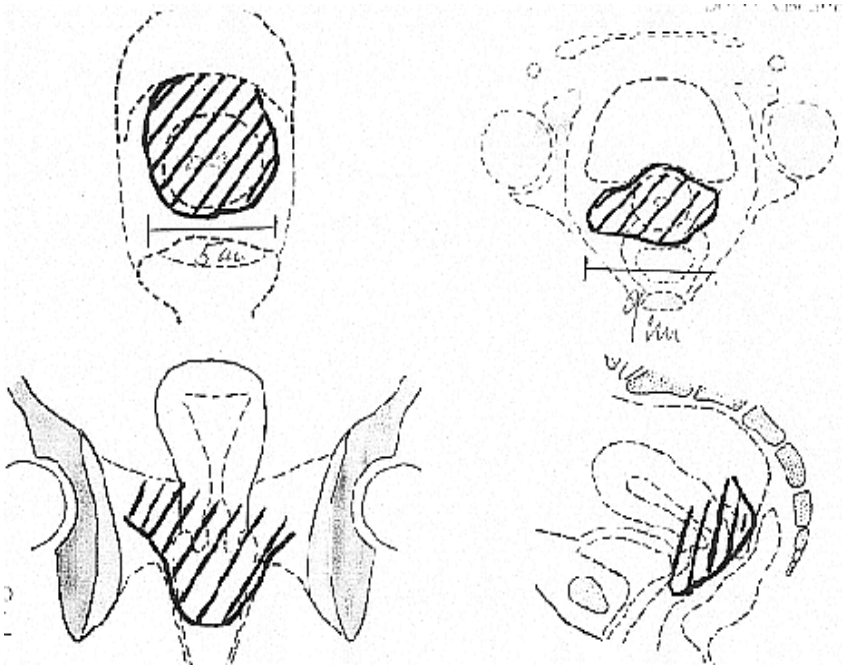
Clinical drawings

Vienna

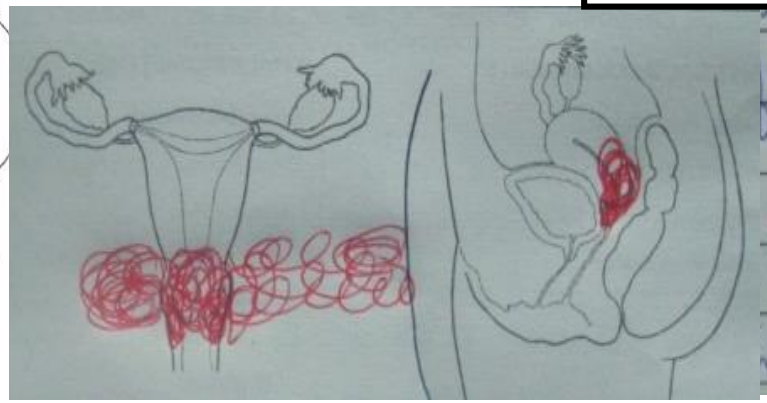
Eifel-Levenback (ed)

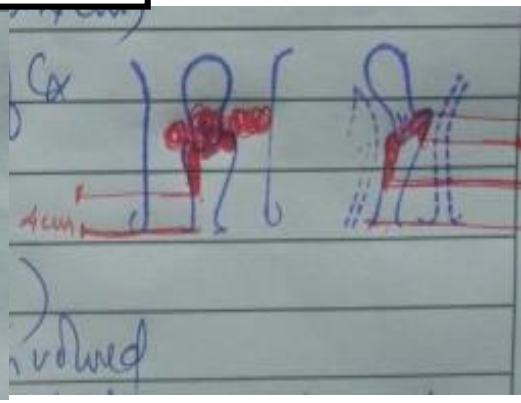
Atlas of clinical oncology 2001





TMH, Mumbai



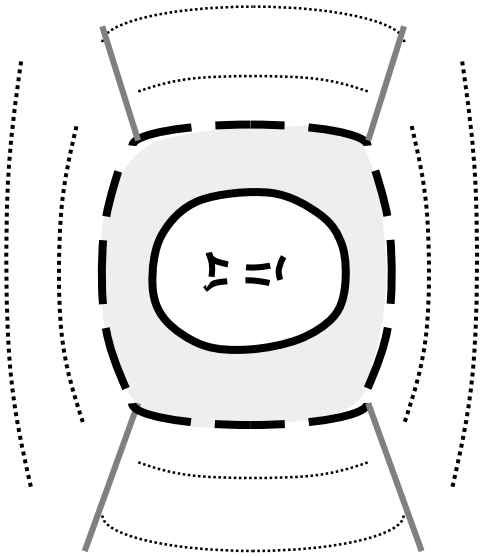


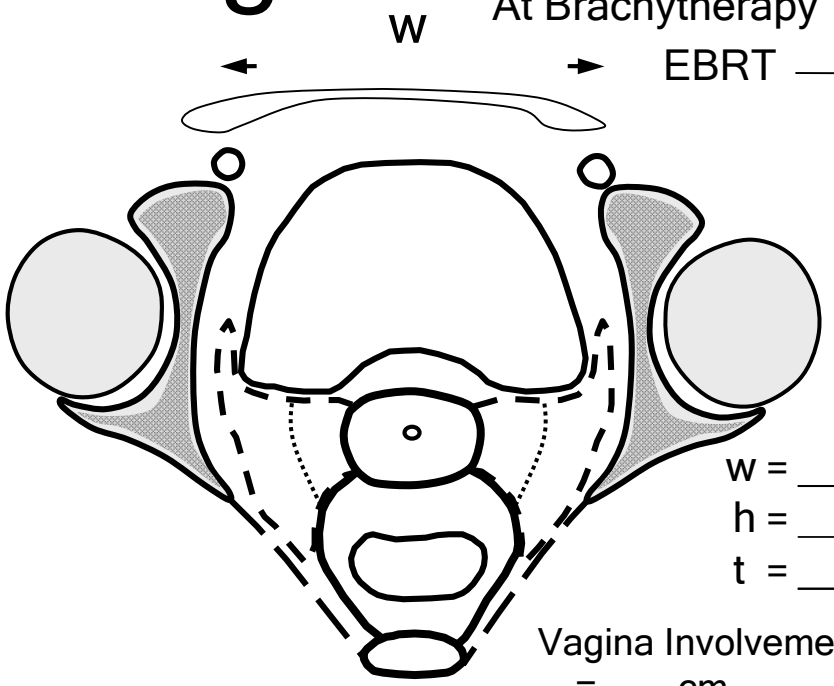
Clinical Mapping of disease extent: Critical for Image based brachytherapy practice

Patient : ABC

Clinical Drawing

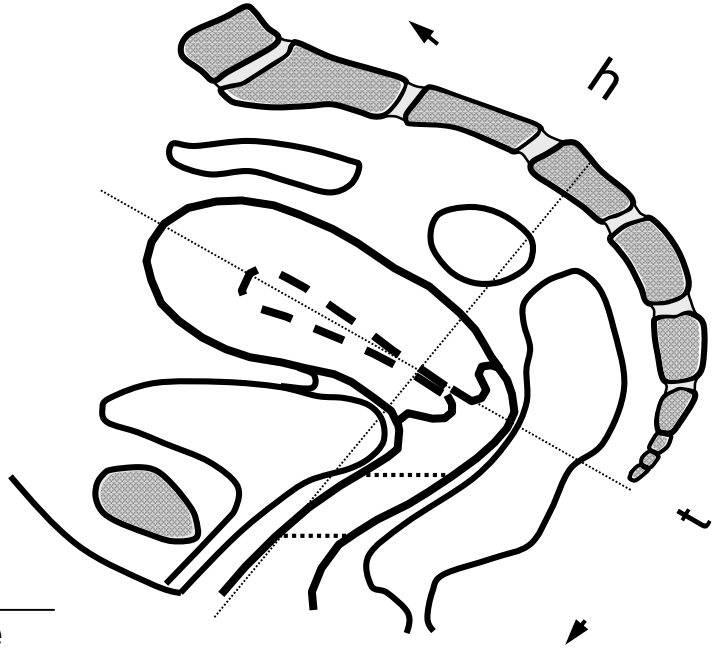
At Diagnosis ☐
At Brachytherapy ☐
EBRT ____ Gy

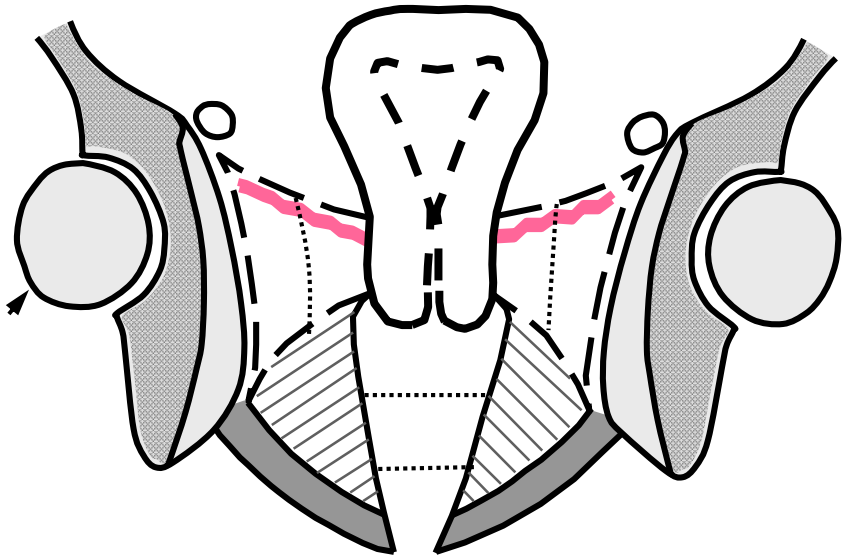




w = ____ cm
h = ____ cm
t = ____ cm

Vagina Involvement
= ____ cm





dd/mm/yy
/ /

Signature

Legend: Option 1

Infiltrative Exophytic

Cervix

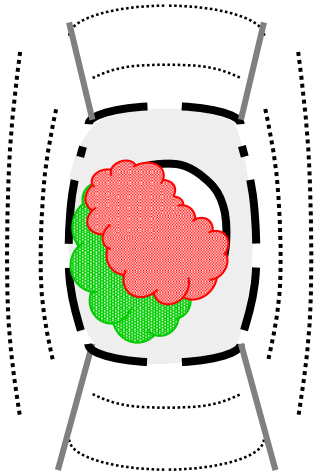
Vagina

Parametria

Rectum or Bladder

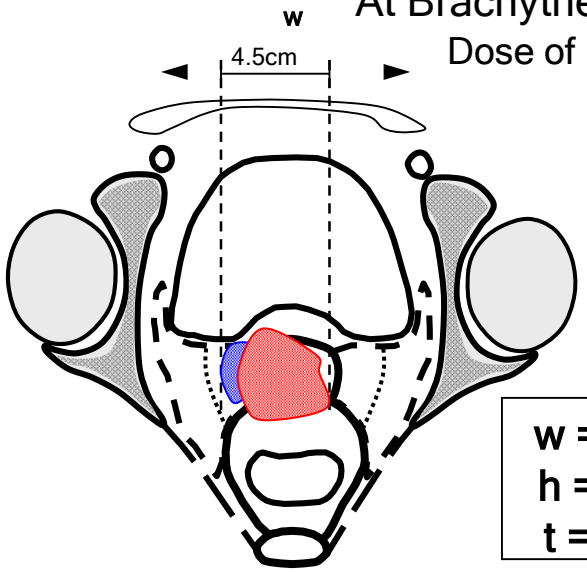
At Diagnosis X

IIB

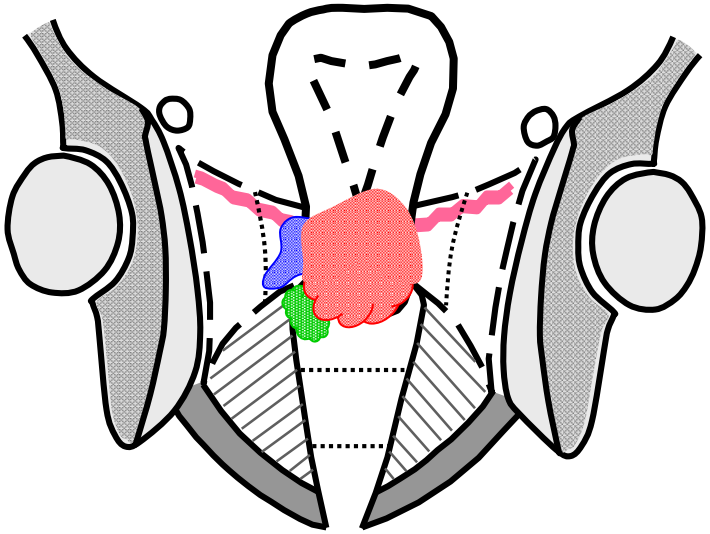


At Brachytherapy ☐

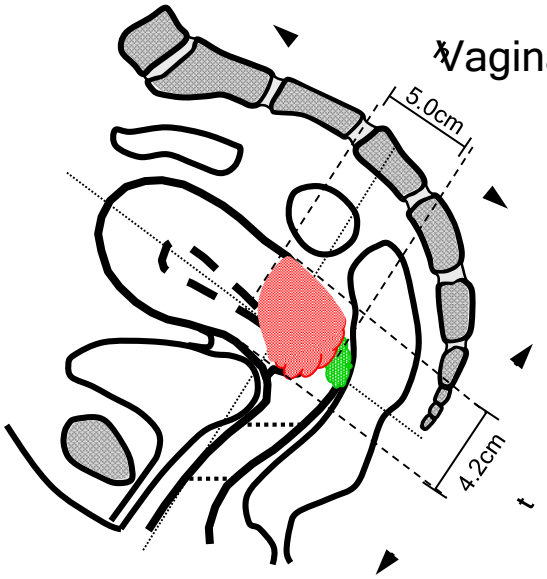
Dose of EBRT ___ Gy



w = 4.5 cm
h = 5.0 cm
t = 4.2 cm



Vagina: 2 cm



dd/mm/yy

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Signature

Legend: Option 2

At Diagnosis X

At Brachytherapy ☐

Dose of EBT ____ Gy

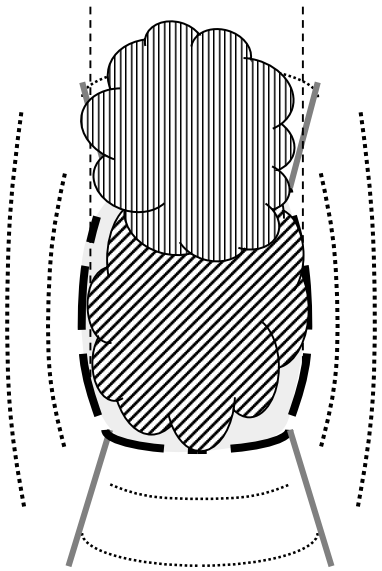
or Cervix

Vagina

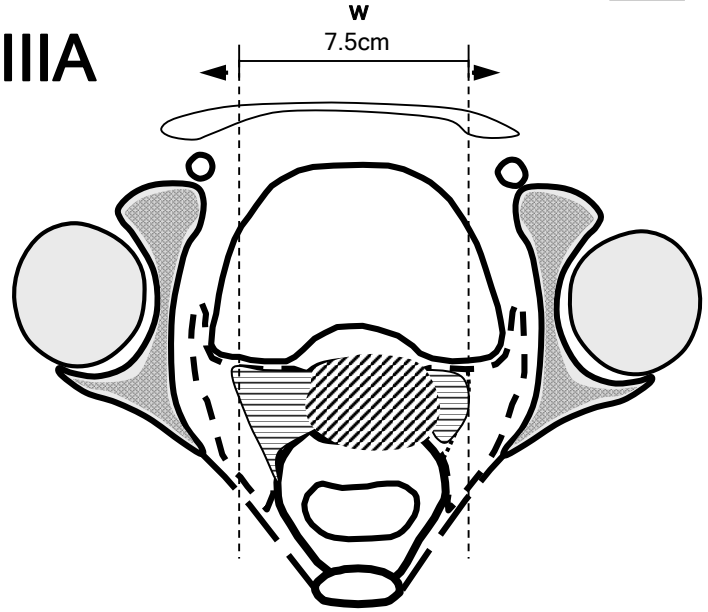
Parametria

Rectum or Bladder Infiltration

Exophytic

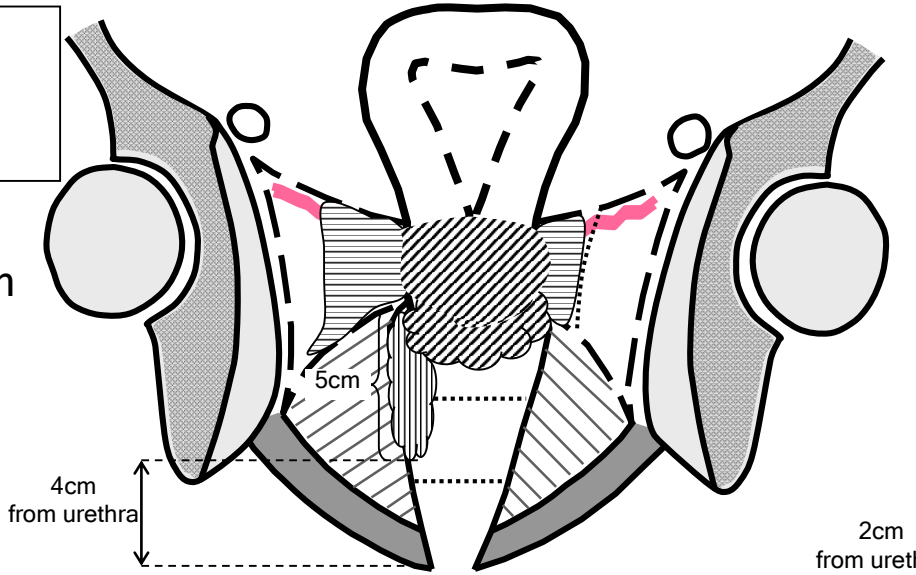


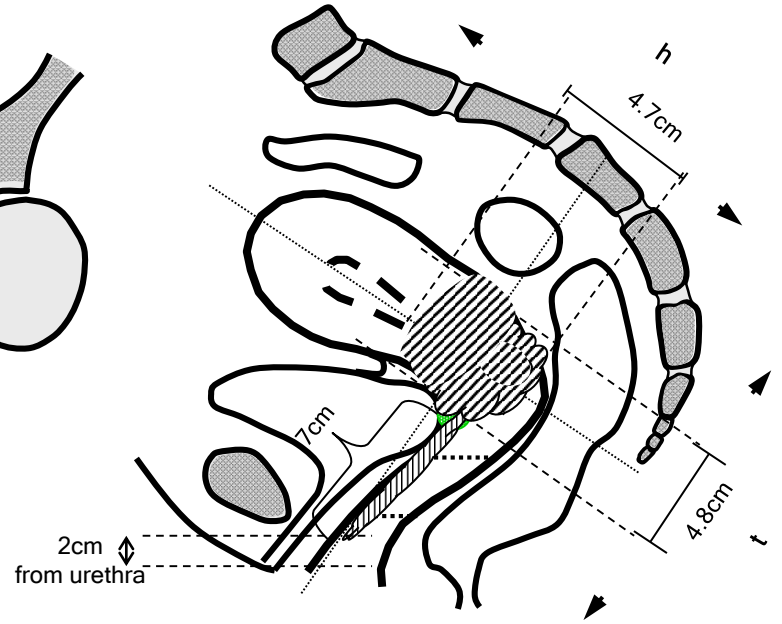
IIIA



w = 7.5 cm
h = 4.7 cm
t = 4.8 cm

Vagina: 7 cm





dd/mm/yy

___/___/___

_____

Signature

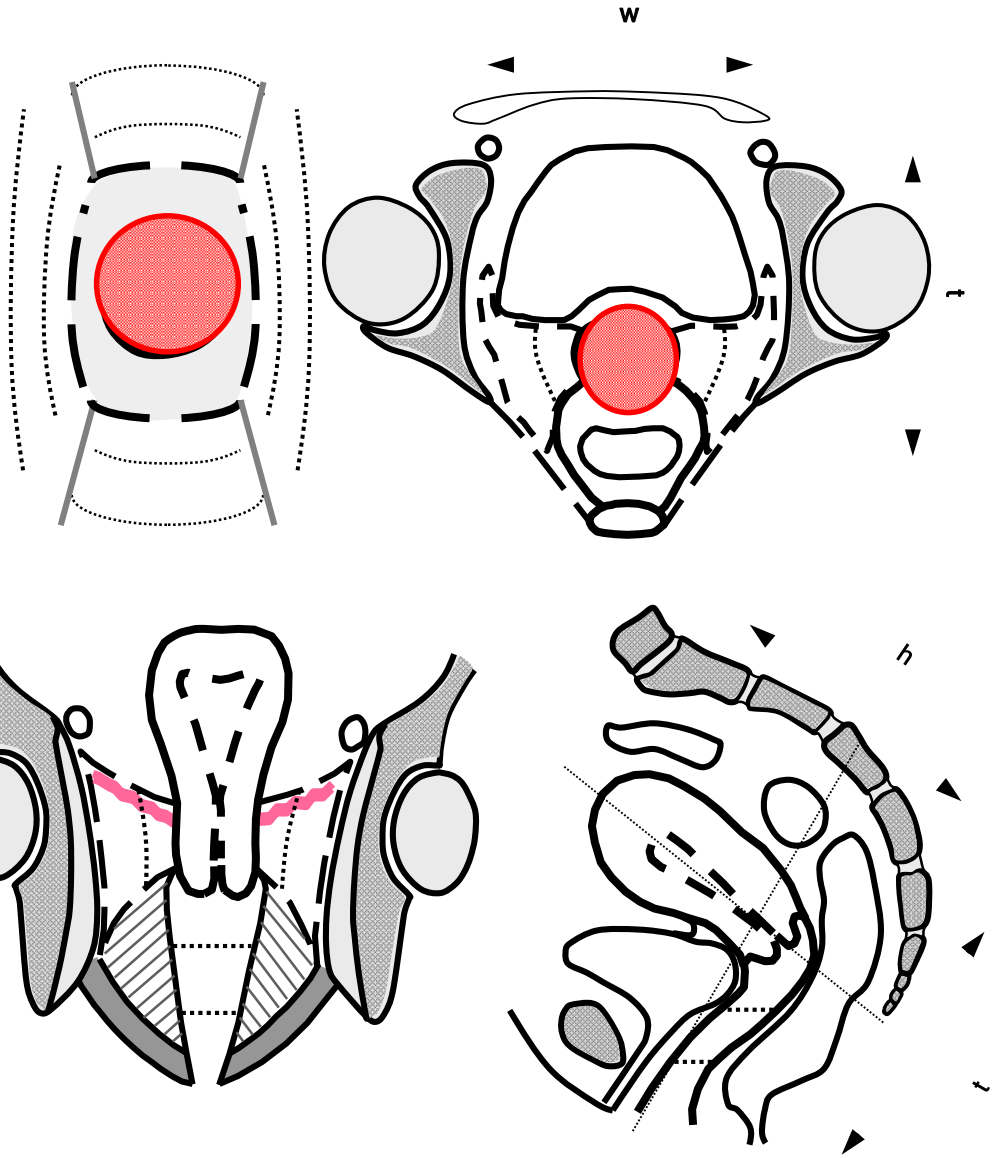
Option 3: Copy and Paste

Cervix

Vagina

Parametria

Rectum or Bladder



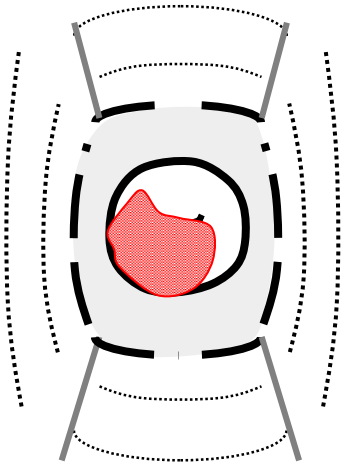
At Diagnosis [X]

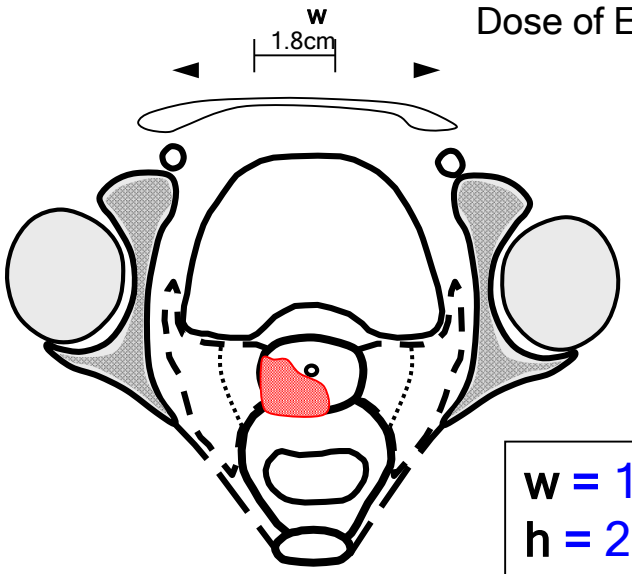
IB1

At Brachytherapy [ ]

Dose of EBRT Gy

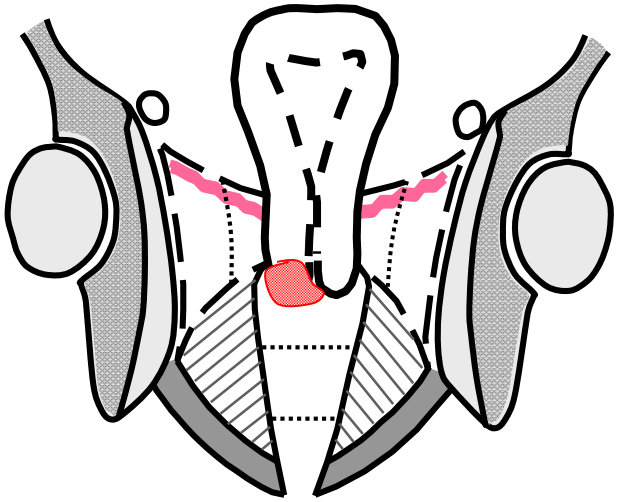
- Cervix: tumour at the posterior and right lip, from 5 to 10h
- Vagina: not involved
- Parametria: not involved

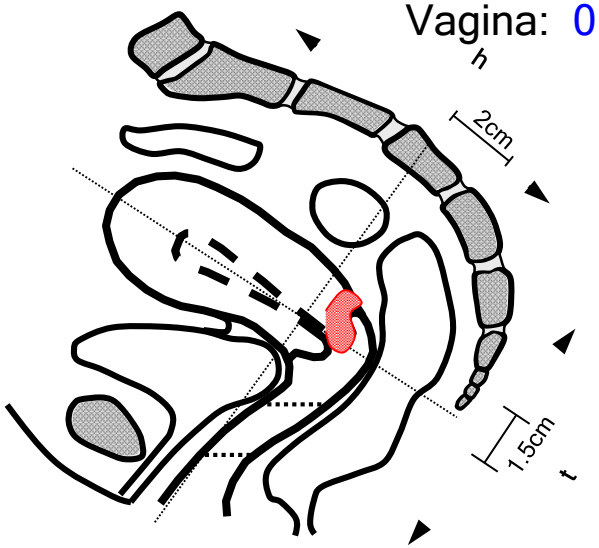




w = 1.8 cm
h = 2.0 cm
t = 1.5 cm

Vagina: 0 cm





dd/mm/yy
__/__/__

Signature

At Diagnosis ☐

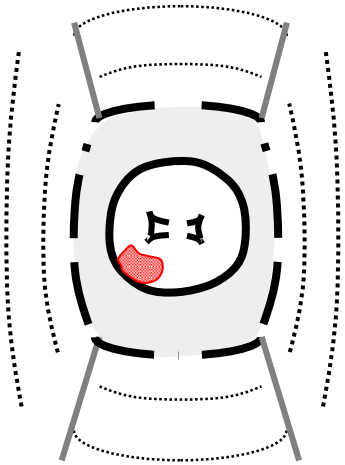
IB1

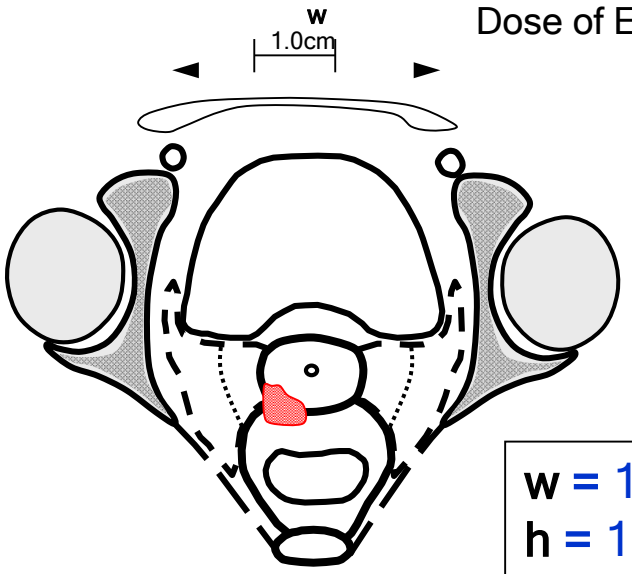
At Brachytherapy ☒

Dose of EBRT Gy

Good response

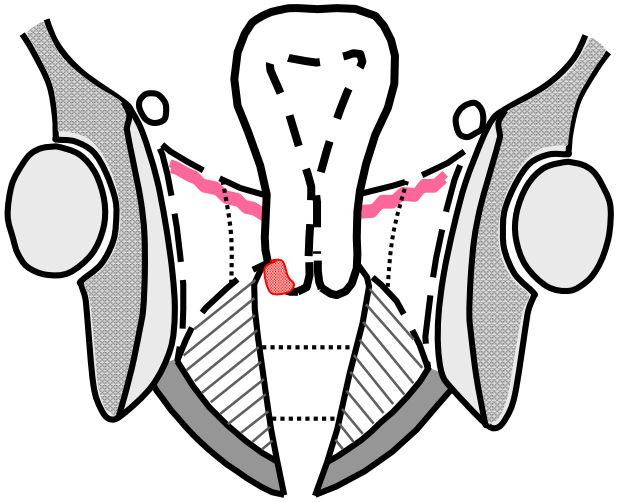
- Cervix: residual tumour from 7 to 9h
- Vagina: not involved
- Parametria: not involved

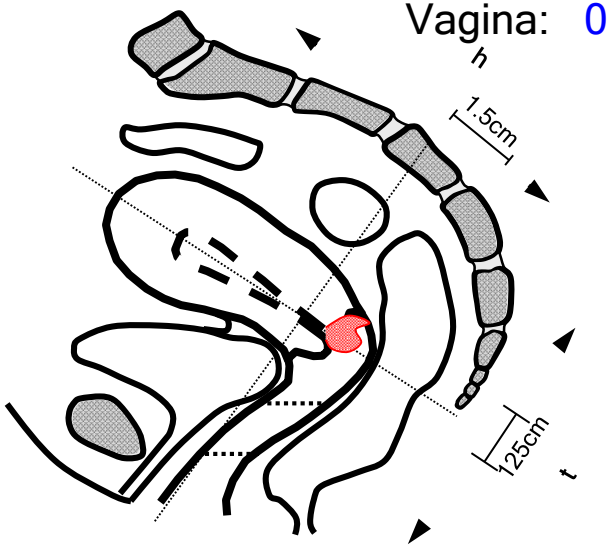




w = 1.0 cm
h = 1.5 cm
t = 1.2 cm

Vagina: 0 cm





dd/mm/yy
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Signature

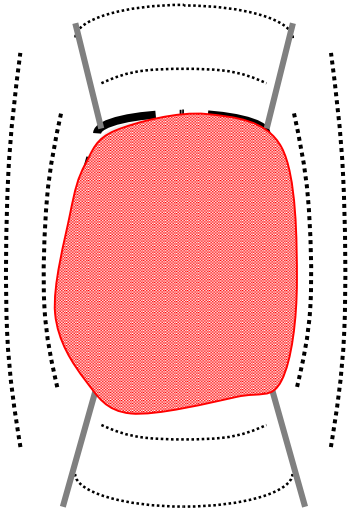
At Diagnosis [X]

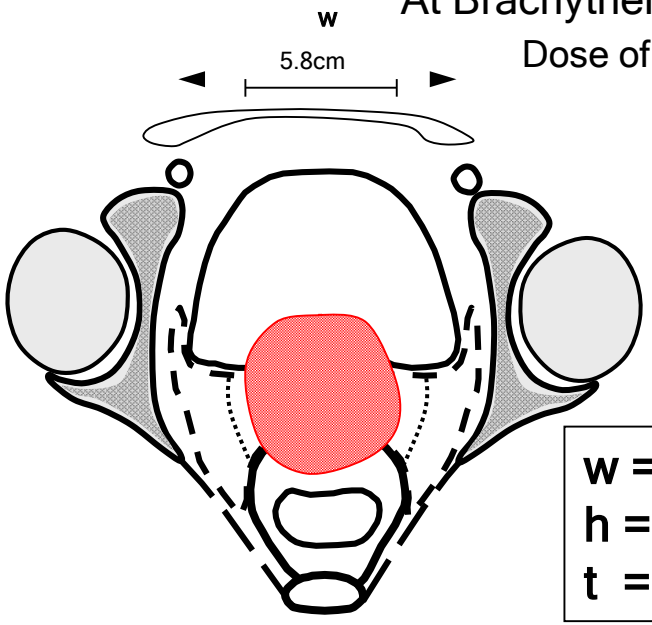
Special Case
IB2 - Bulky

At Brachytherapy [ ]

Dose of EBRT ___ Gy

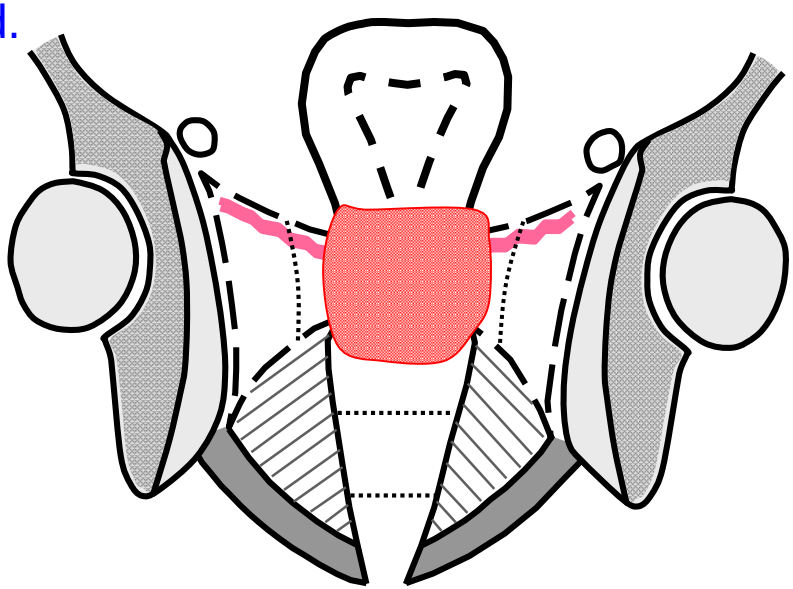
bulky cervical tumour where the tumour bulges towards the vaginal, bladder and rectal walls, but these structures are not involved.

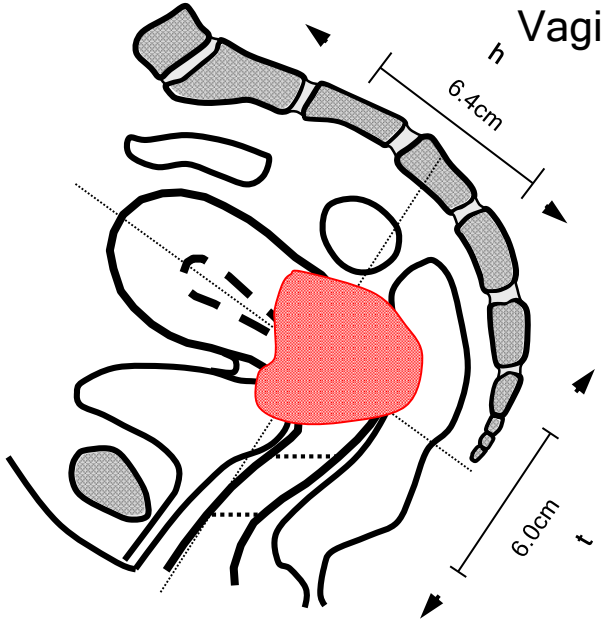




w = 5.8 cm
h = 6.4 cm
t = 6.0 cm

Vagina: 0 cm





dd/mm/yy
___/___/___

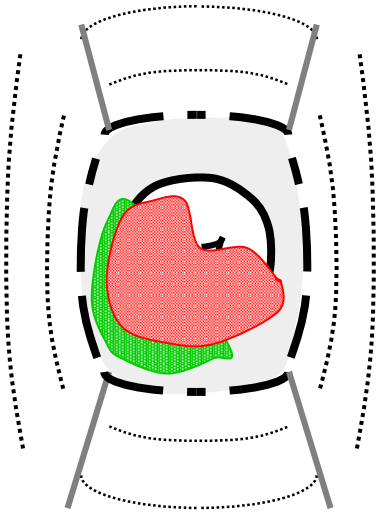
_____
Signature

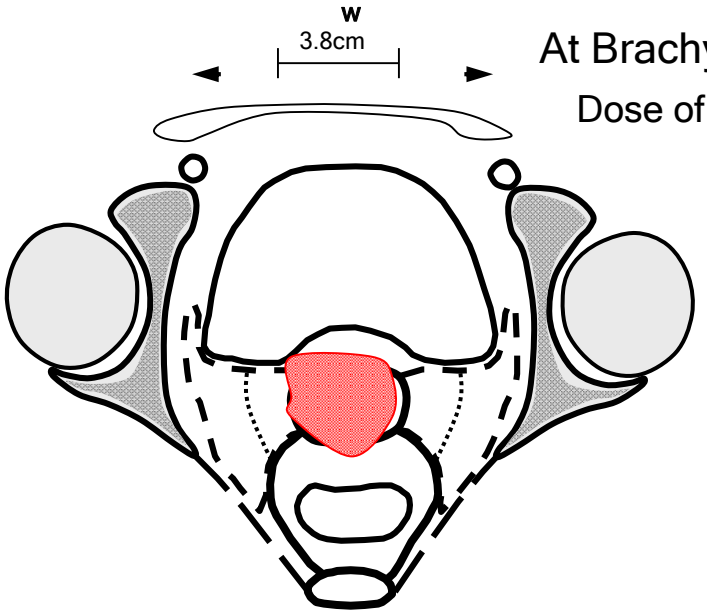
At Diagnosis X

IIA

w = 3.8 cm
h = 2.5 cm
t = 4.0 cm

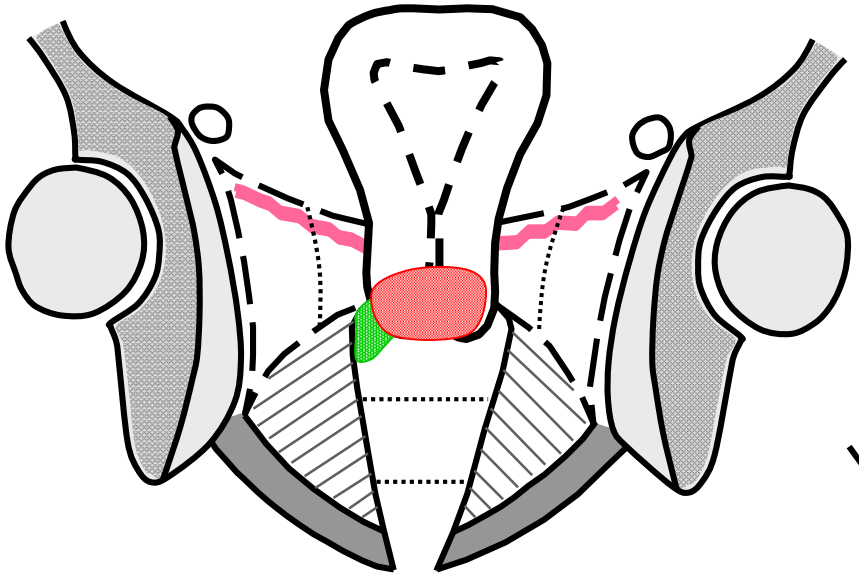
Vagina: 1.5 cm

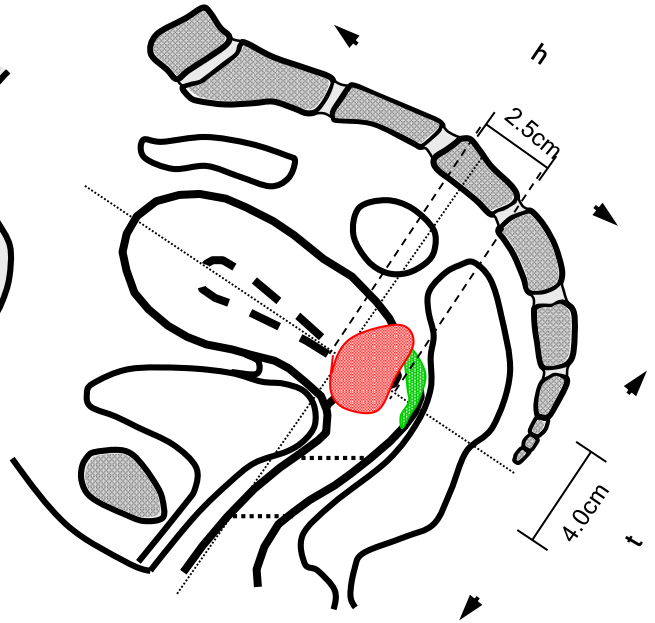




At Brachytherapy ☐

Dose of EBRT____ Gy





dd/mm/yy
__/__/__

Signature

Note: extension of vaginal involvement is specified separately, and should **not** be included in **h**

At Diagnosis ☐

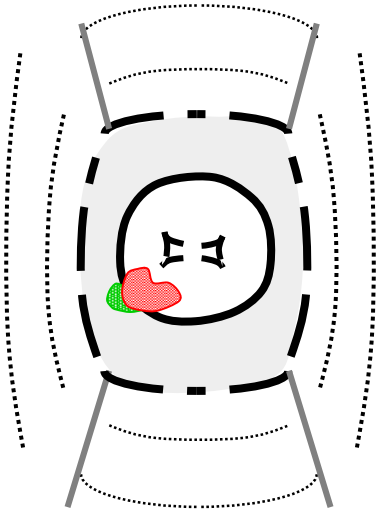
At Brachytherapy ☒

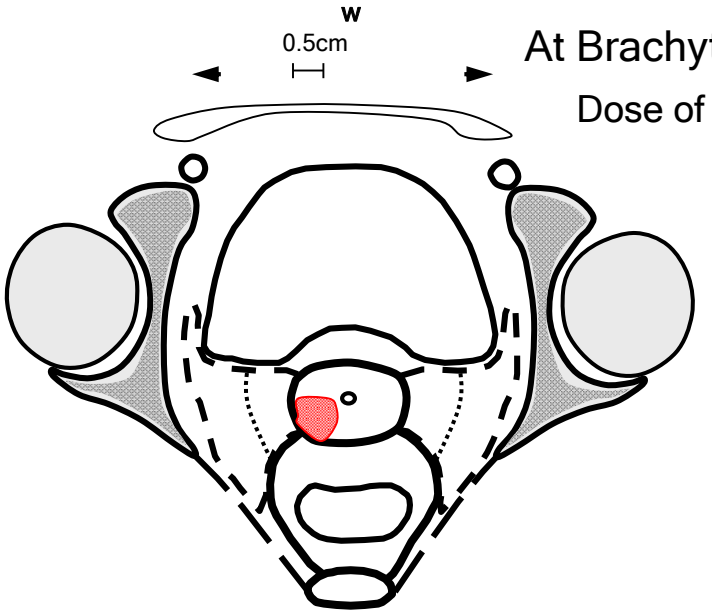
Dose of EBRT 45 Gy

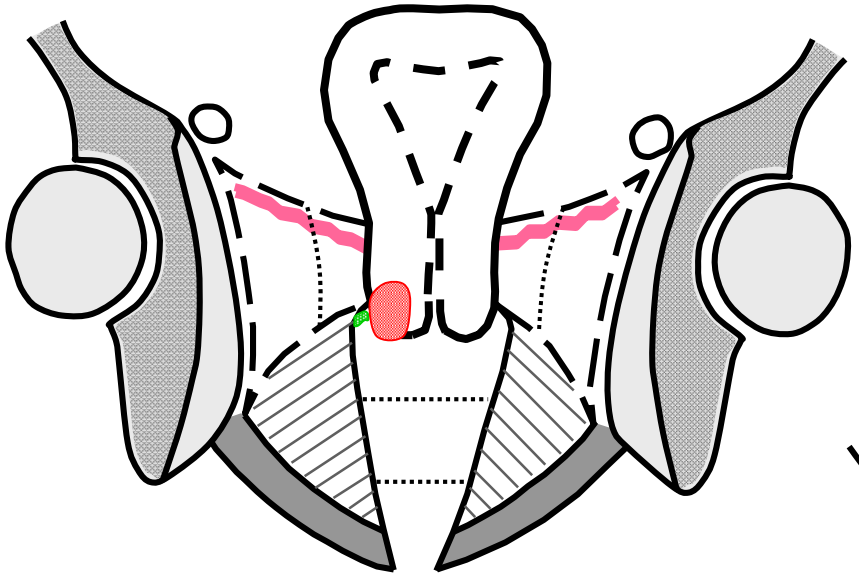
IIA

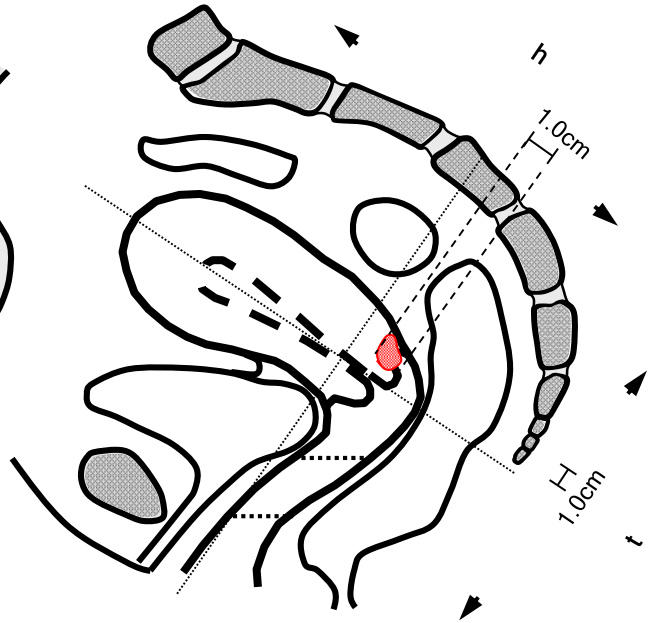
w = 1.0 cm
h = 1.0 cm
t = 1.0 cm

Vagina: 0.3 cm









dd/mm/yy
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Signature

Note: the small extension of vaginal involvement can be measured only on clinical exam. In this case, it can be included in **w**.

At Diagnosis [X]

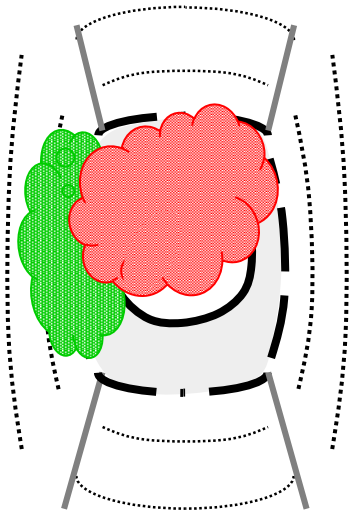
At Brachytherapy [ ]

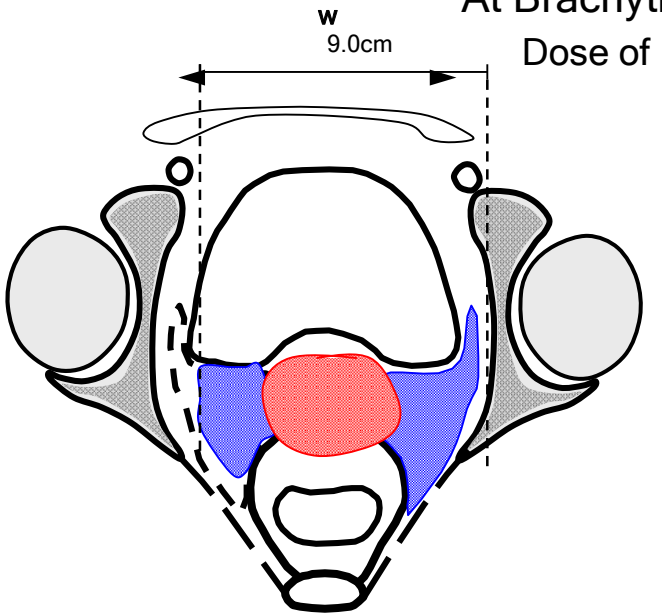
Dose of EBRT ___ Gy

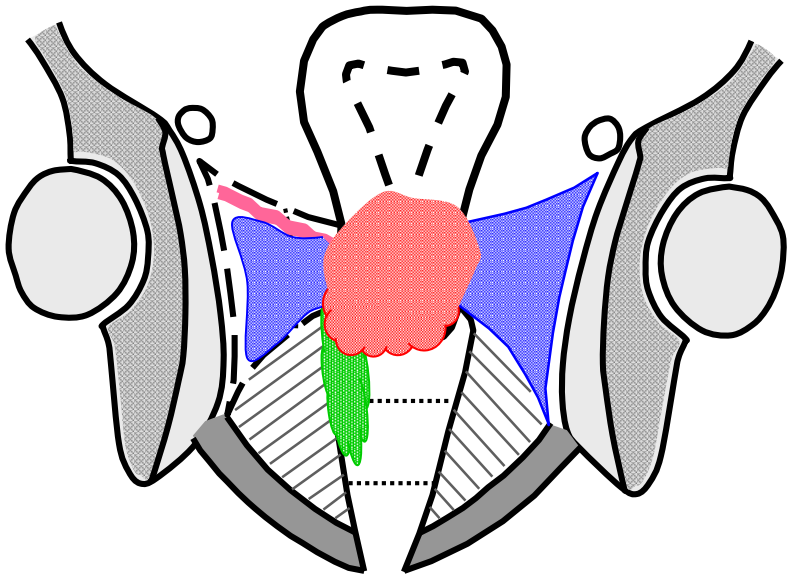
IIIB

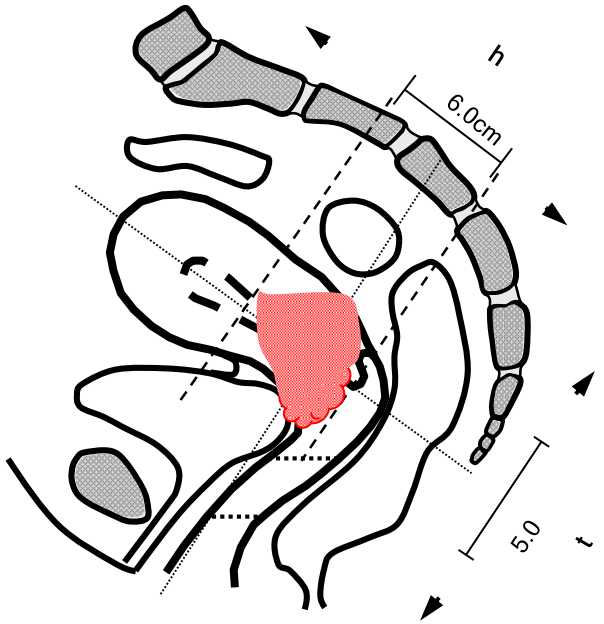
w = 9.0 cm
h = 6.0 cm
t = 5.0 cm

Vagina: 5 cm









dd/mm/yy
__/__/__

Signature

Note: vagina and parametria not included in h

At Diagnosis ☐

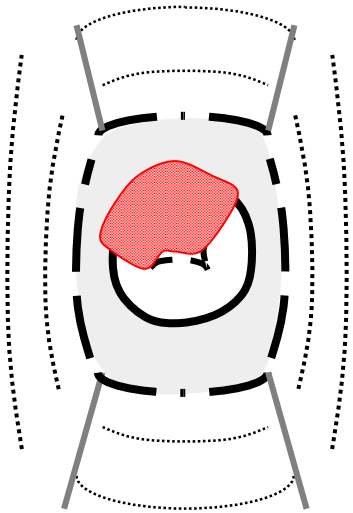
At Brachytherapy ☒

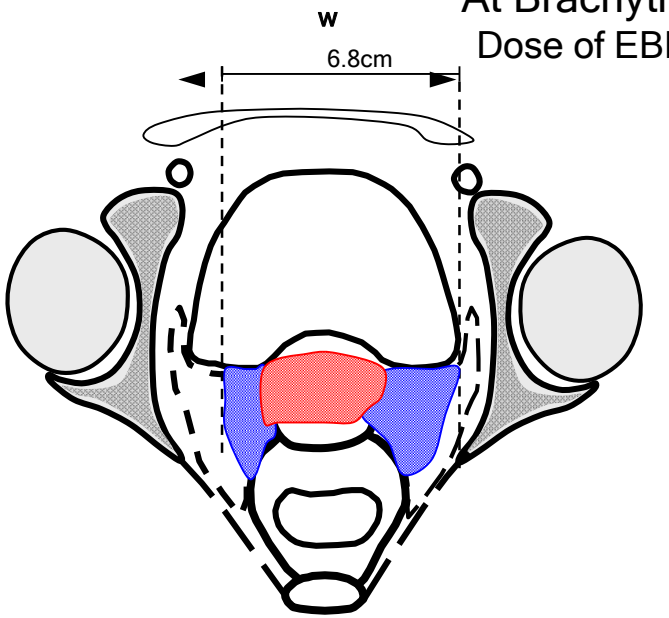
Dose of EBRT 50.4 Gy

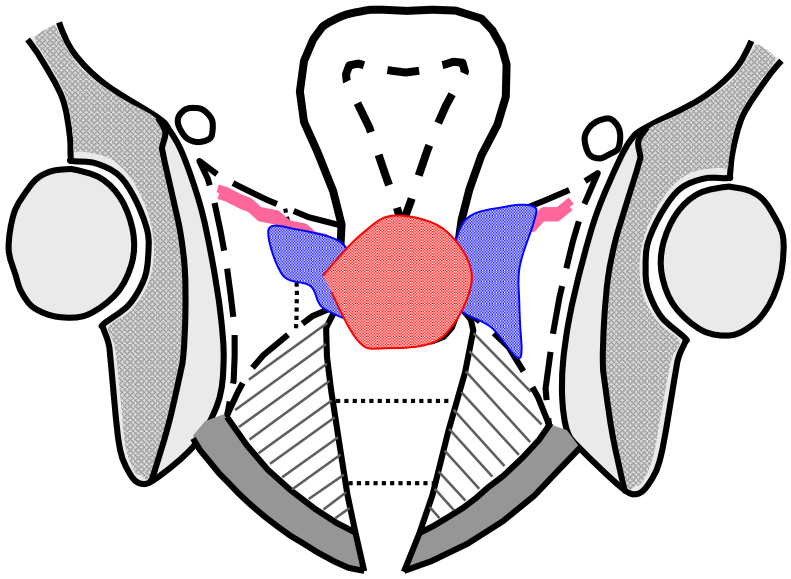
IIIB

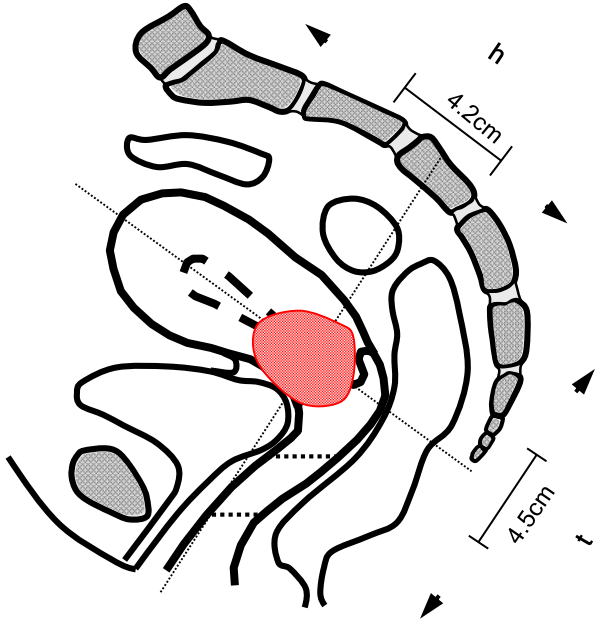
w = 6.8 cm
h = 4.2 cm
t = 4.5 cm

Vagina: 0 cm









dd/mm/yy

/ /

Signature

Note: parametria **not** included in **h**.

At Diagnosis [X]

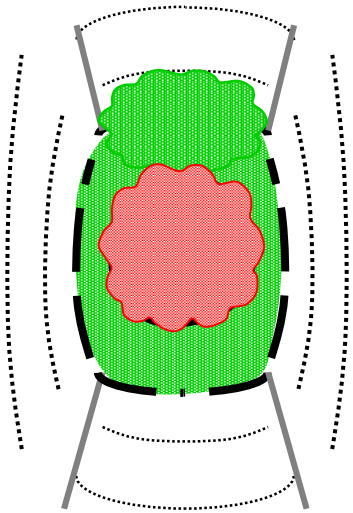
At Brachytherapy [ ]

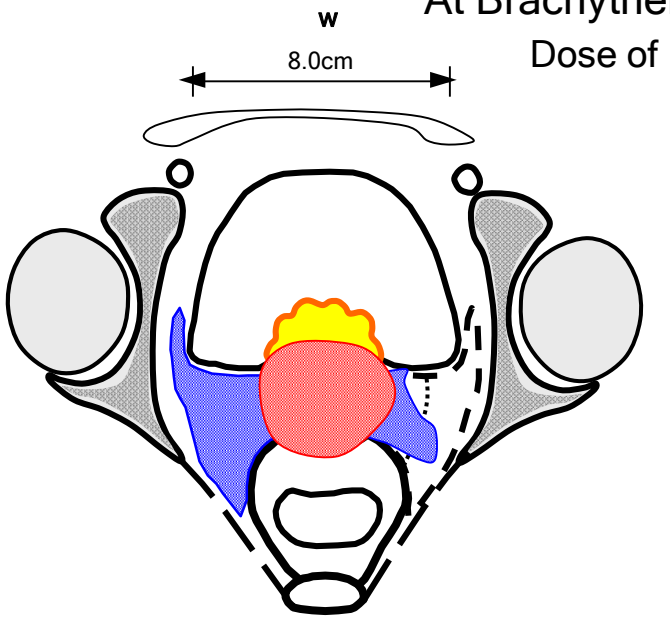
Dose of EBT____ Gy

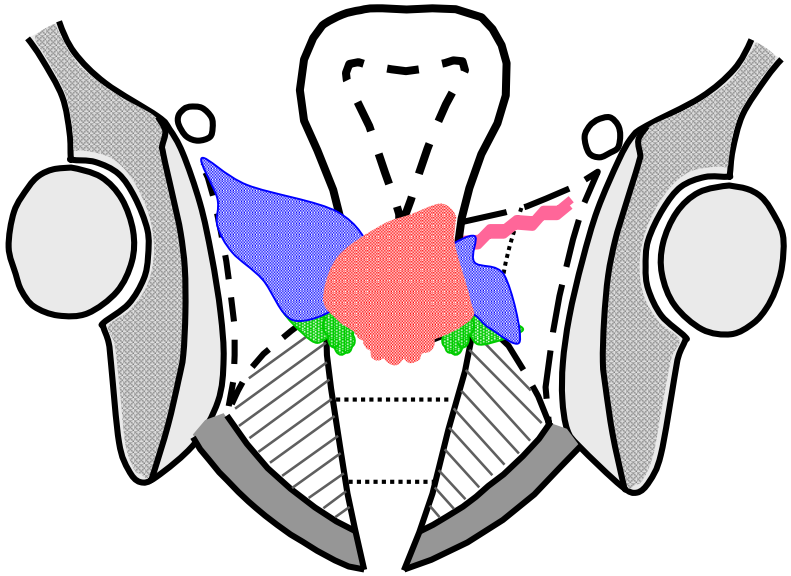
IVA - Bladder

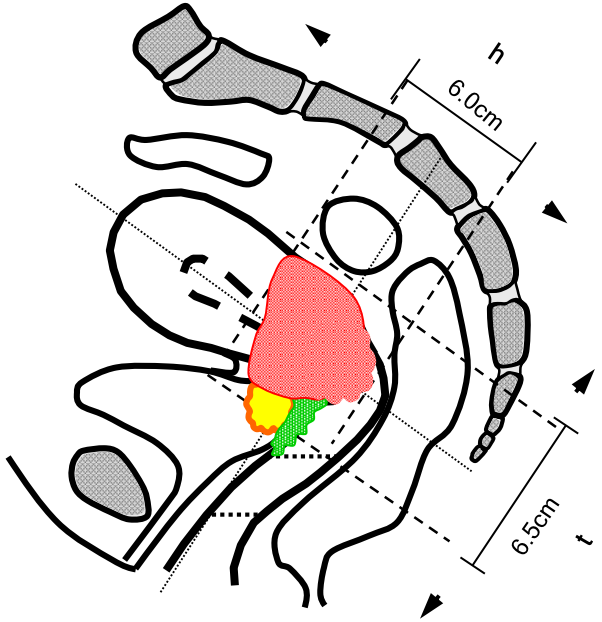
w = 8.0 cm
h = 6.0 cm
t = 6.5 cm

Vagina: 5 cm









dd/mm/yy
__/__/__

_____
Signature

At Diagnosis ☐

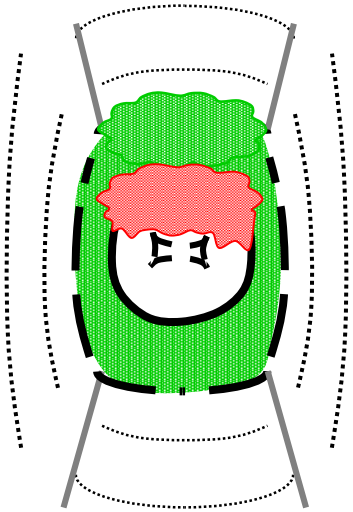
At Brachytherapy ☒

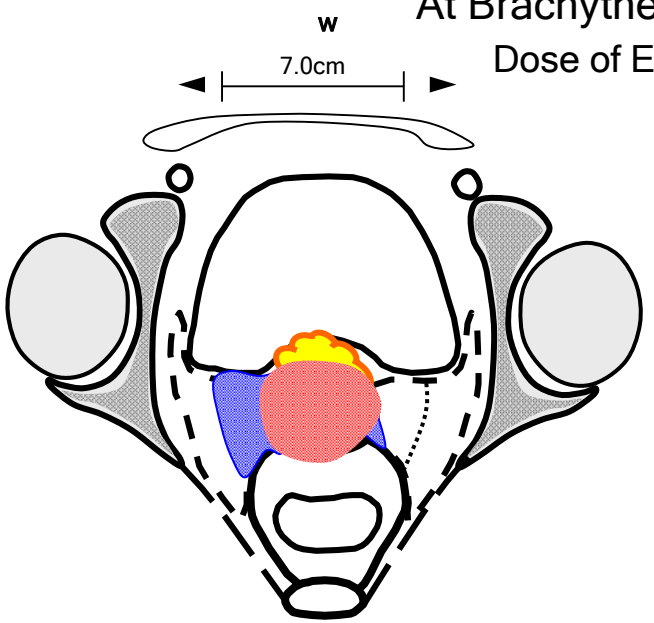
Dose of EBRT 45 Gy

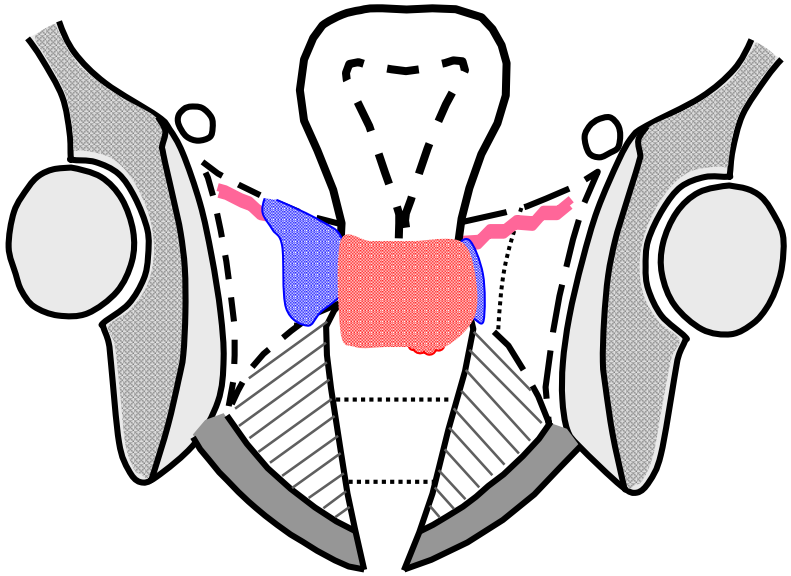
IVA - Bladder

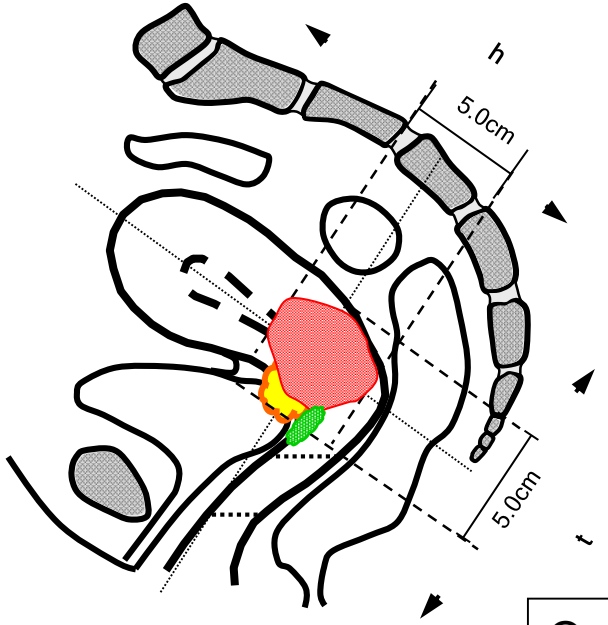
w = 7.0 cm
h = 5.0 cm
t = 5.0 cm

Vagina: 2.5 cm







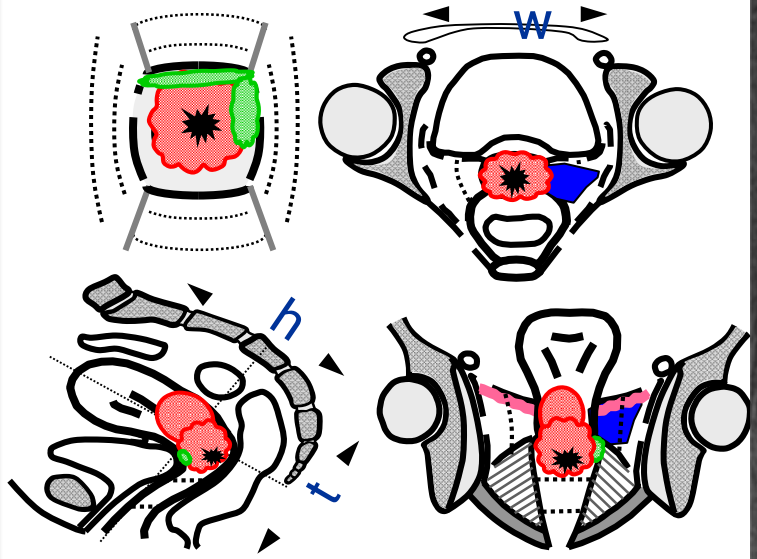


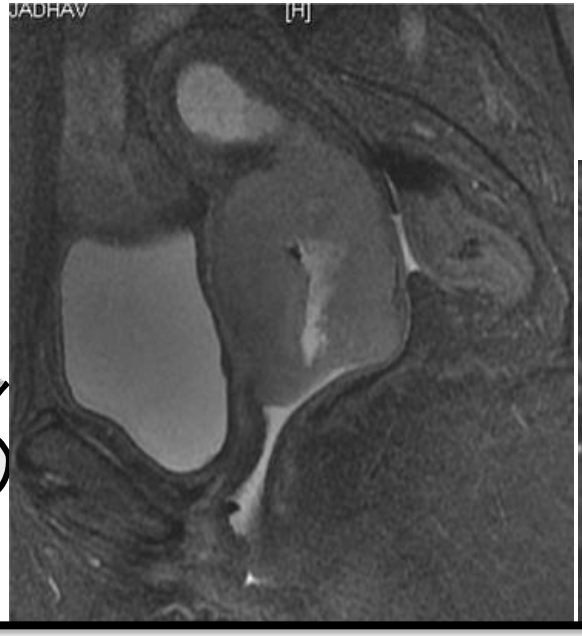
dd/mm/yy
/ /

Signature

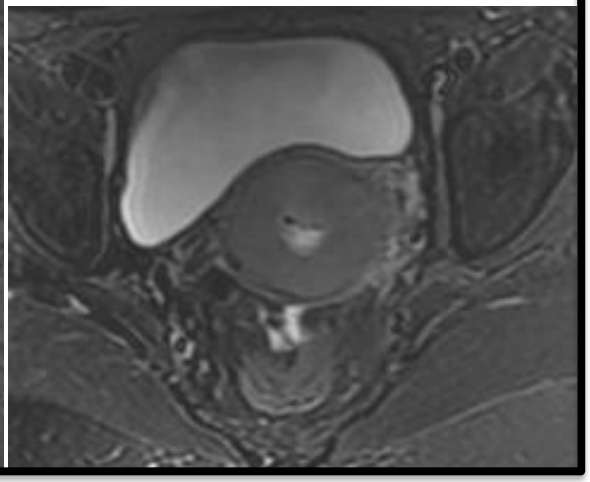
Case V

Clinical Drawing

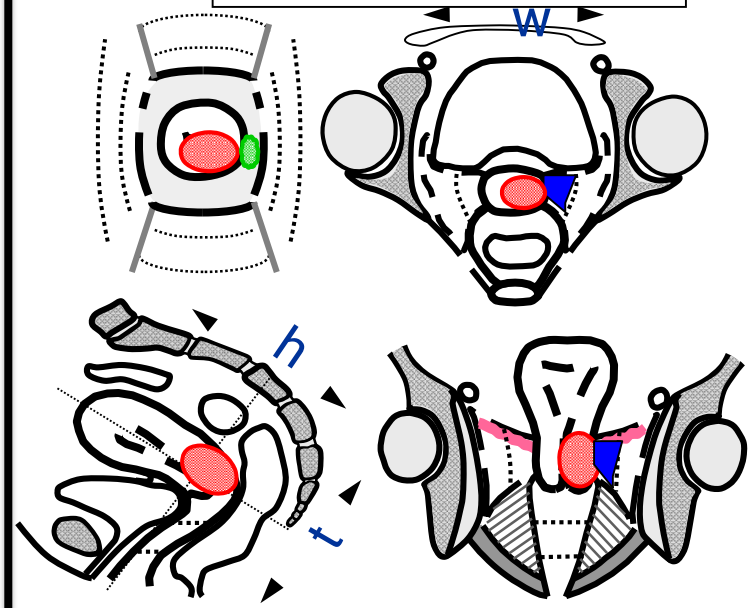




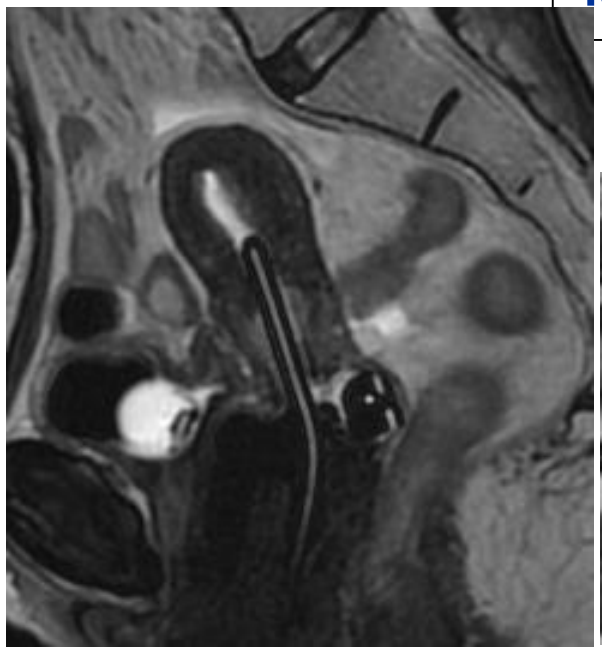
MR at Diagnosis

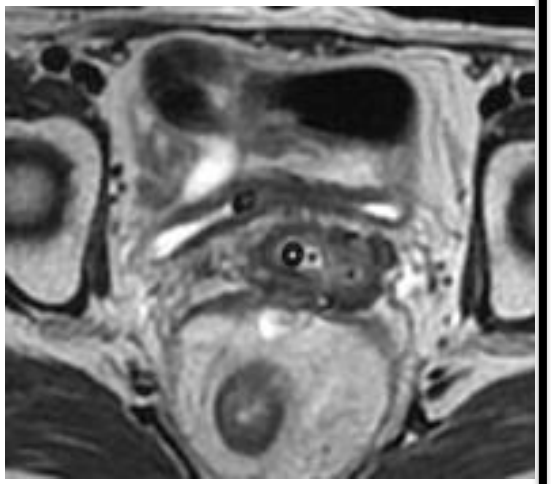


Clinical Drawing



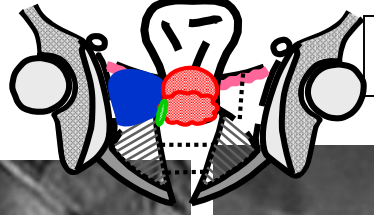
MR at Brachytherapy





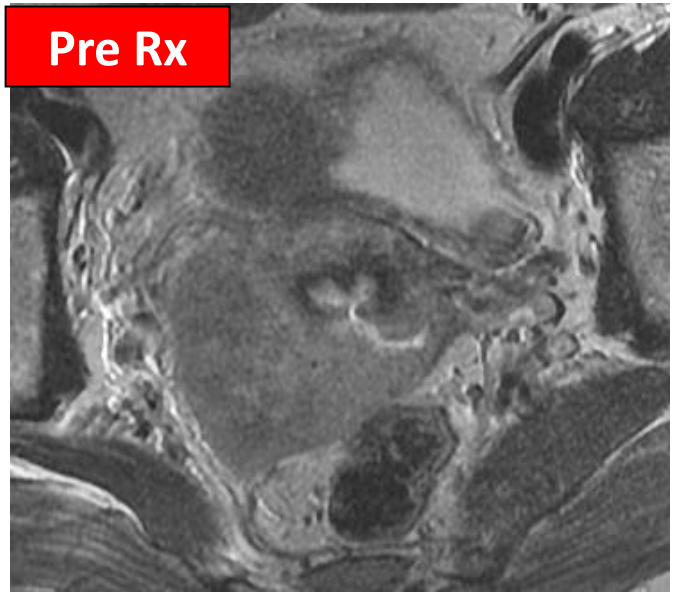
Axial

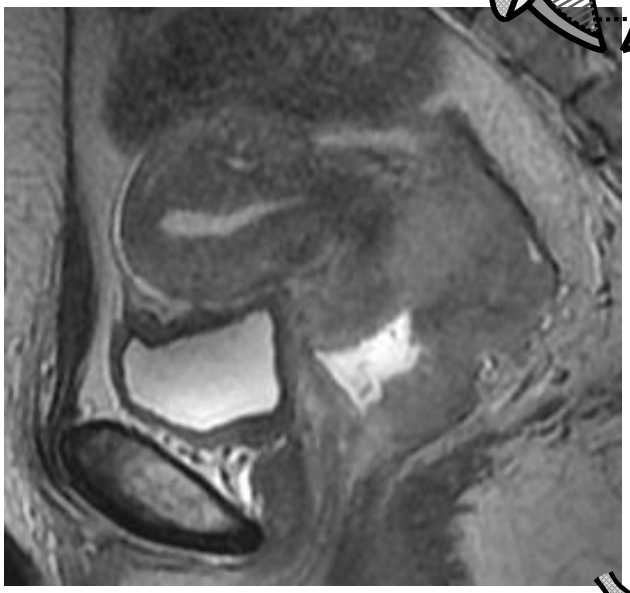
Sag

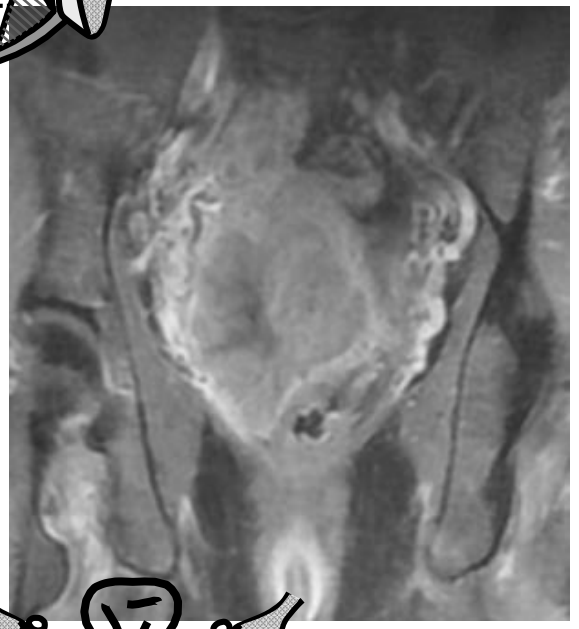


Coronal

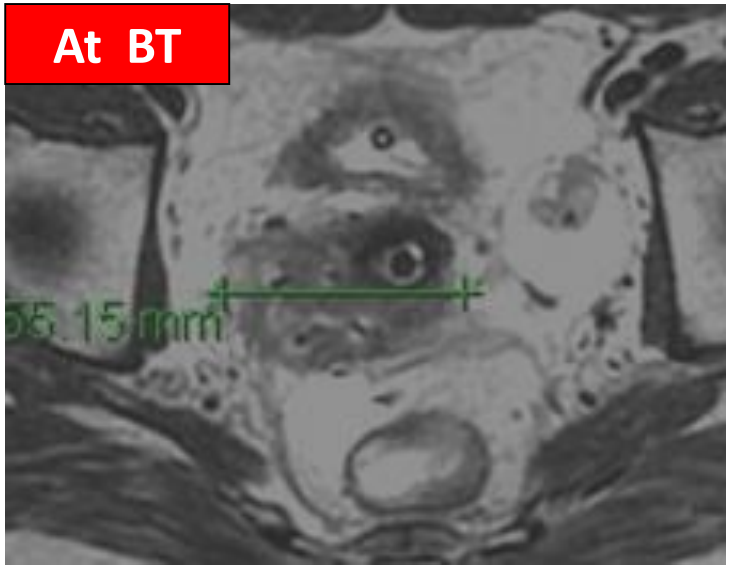
Pre Rx

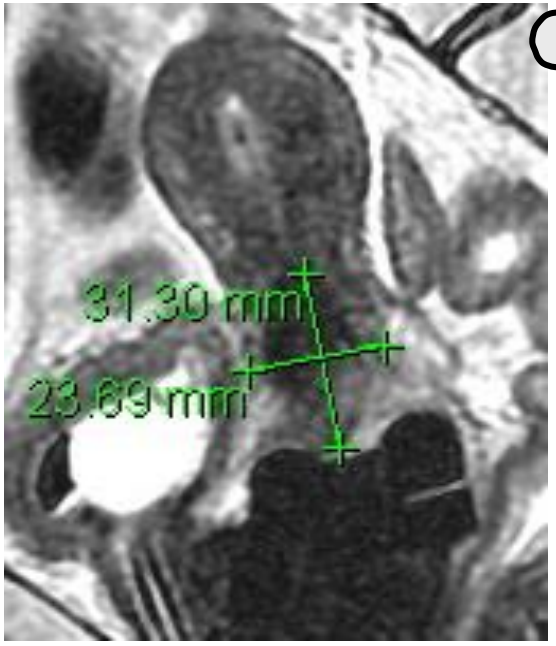


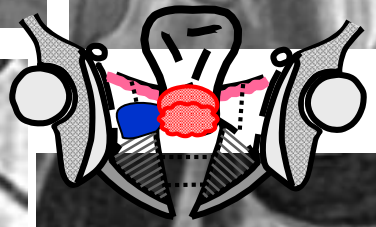


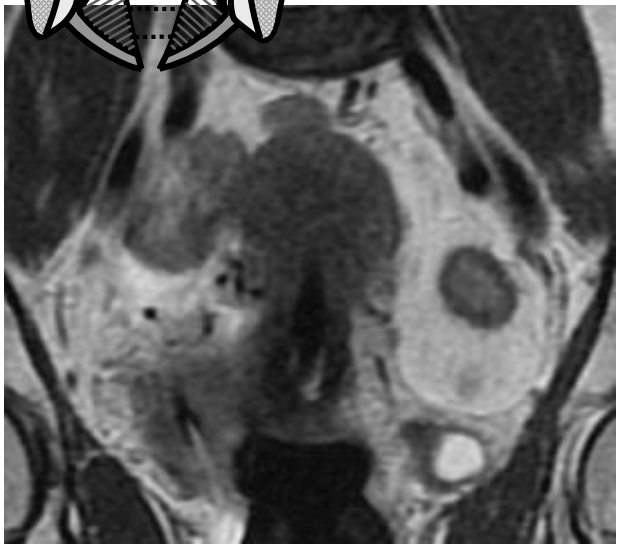


At BT



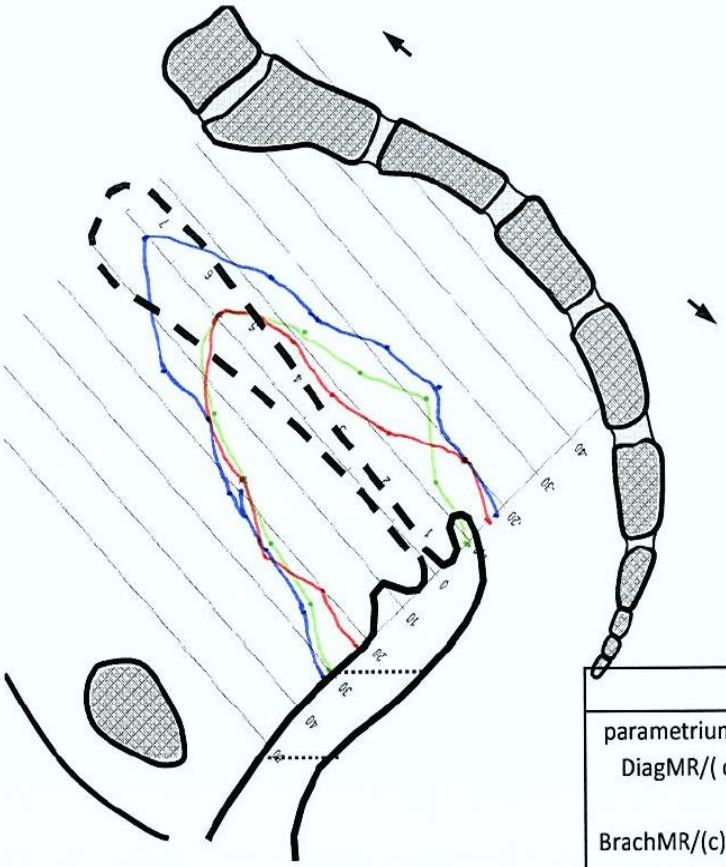


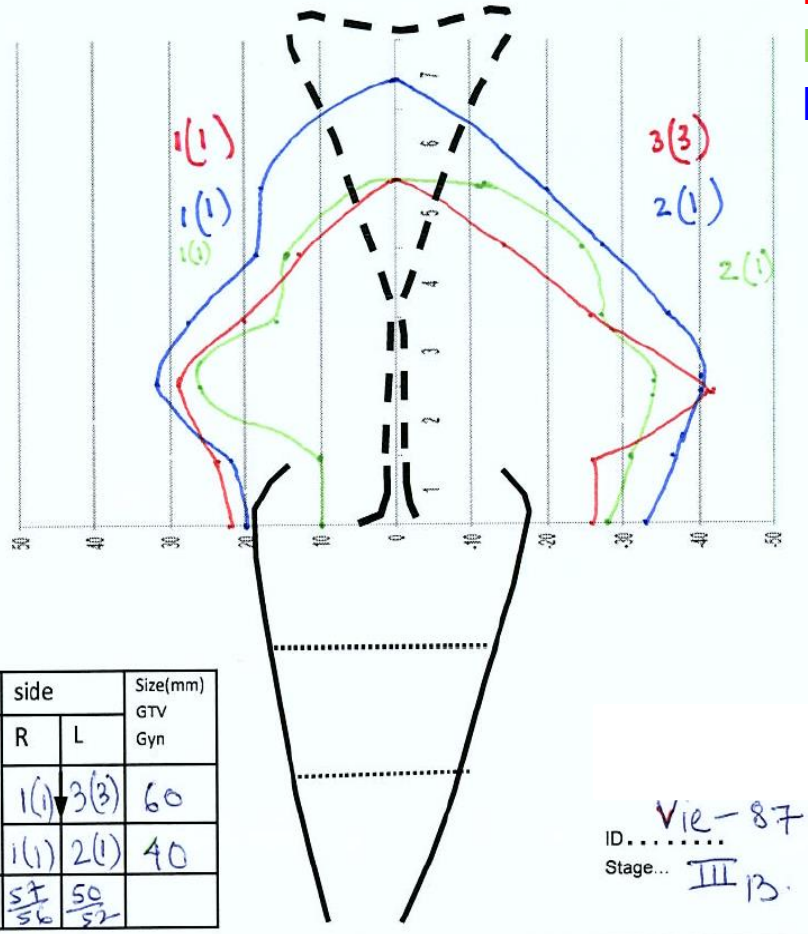




10

MR
HR CTV
IR CTV





	side		Size(mm) GTV Gyn
parametrium DiagMR/(c)	R	L	
	1(1)	3(3)	60
BrachMR/(c)	1(1)	2(1)	40
Distence pelvic Wall Diag/(brachy)	57/56	50/52	

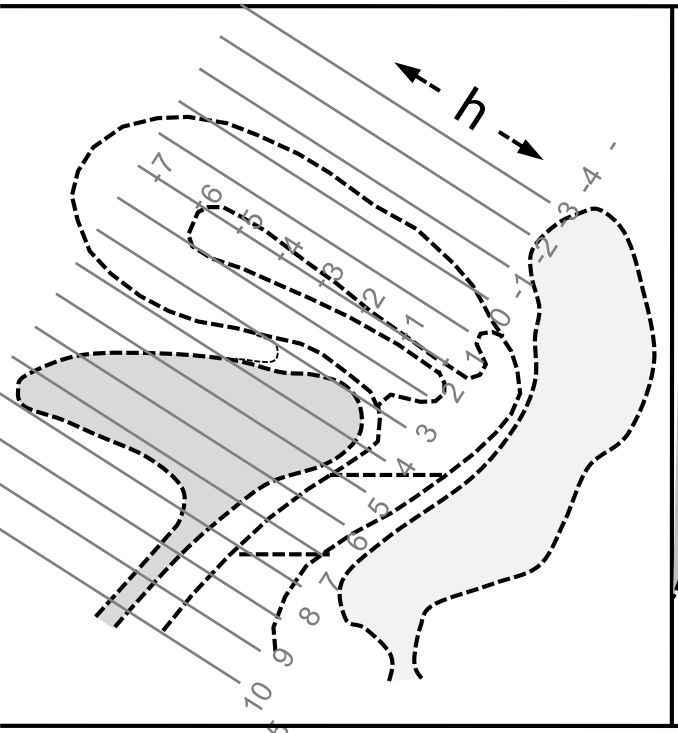
ID..... Vie-87
Stage... III 13.

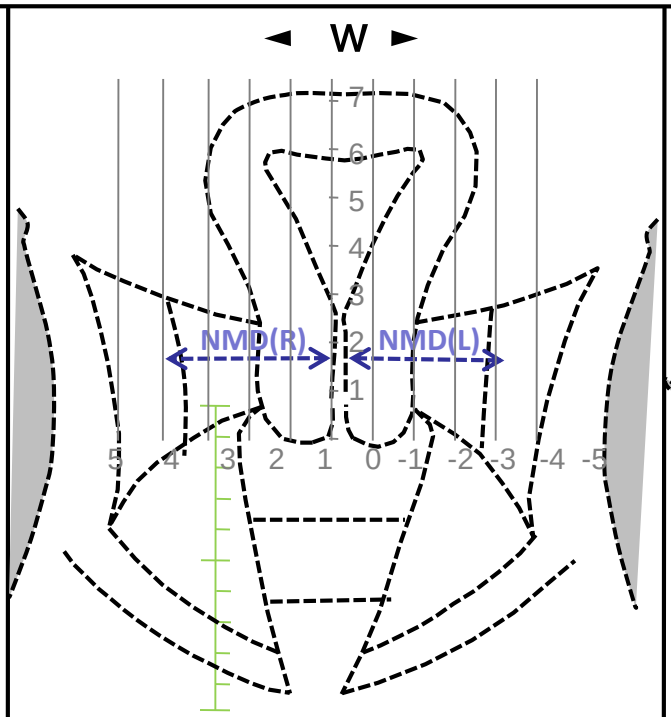
	1 MR	1 HR	1 IR	2 MR	2 HR	2 IR	3 MR	3 HR	3 IR	4 MR	4 HR	4 IR	5 MR	5 HR	5 IR	6 MR	6 HR	6 IR	MAX	Date MR .....
RT	22	10	20	26	10	22	29	26	32	20	16	28	13	14	19	-	~~14~~	18		Date Brachy .....
LT	26	28	33	23	32	37	42	33	40	26	27	37	15	25	27	-	~~12~~	20		
ANT	22	30	30	20	24	26	24	21	23	19	18	21	16	13	15	-	11	16		
POST	15	9	18	20	12	20	11	22	26	08	15	23	08	12	16	-	~~13~~	19		

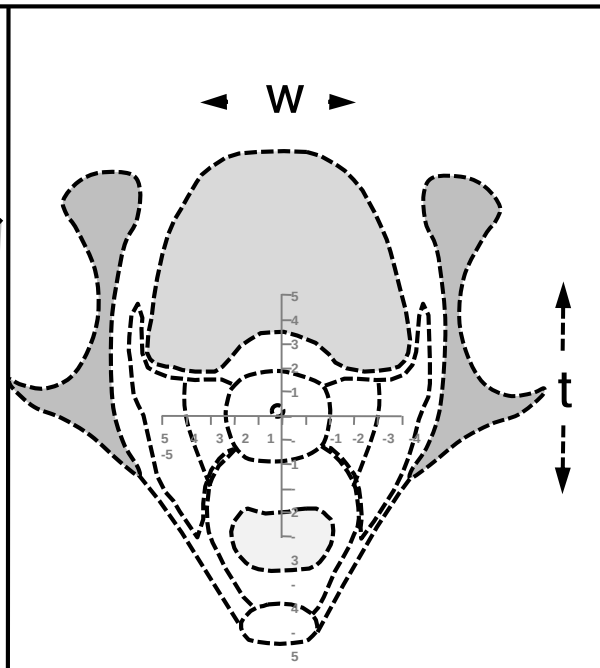
MRI Compared

(c) clinical para status,
Distence of pelvic wall from central canal at the maximum width of disease.

At Diagnosis □ / **At Brachytherapy** □
[Brachytherapy fraction no. __]





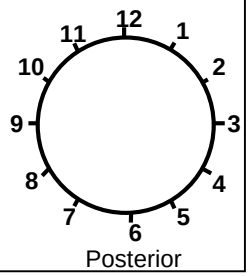


h = ____ cm **t = ____ cm** **w = ____ cm** **NMD (R) =____cm** **NMD (L) =____cm**

[NMD-Near Minimum Distance]

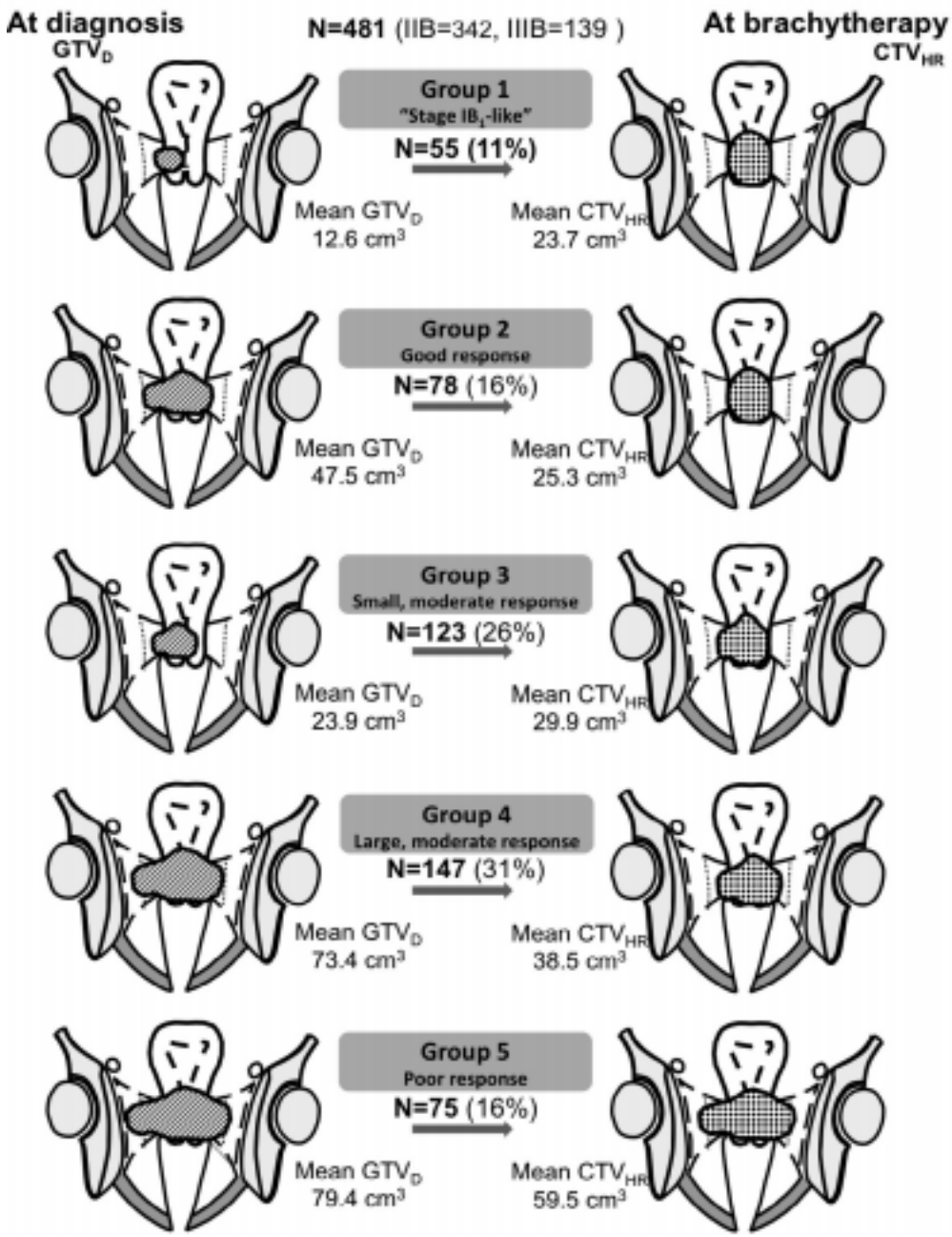
Vaginal Disease

Ant : ___ cm
Post :___ cm
Rt Lat: ___cm
Lt Lat: ___cm



	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

PATTERNS OF DISEASE AT DIAGNOSIS AND HRCTV AT BT



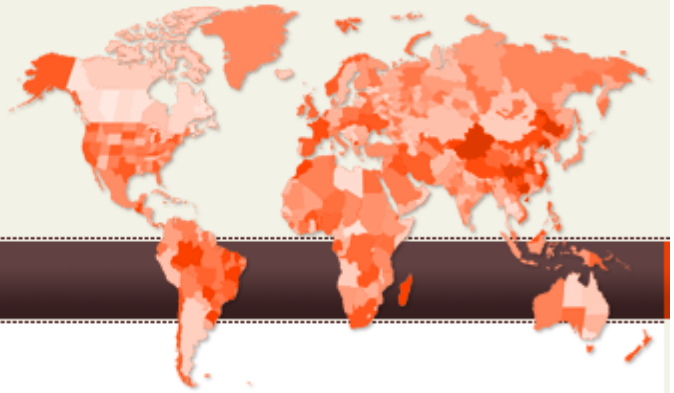
IJROBP 2016

SUMMARY

- Clinical drawings at diagnosis and brachytherapy: Mapping Vital
  - Platform for common language
  - Immediate Response evaluation : More objective
  - Selection of Brachytherapy technique and Applicators
  - Assist in critical analysis of recurrences / late sequelae
- Associated with a small learning curve

EMBRACE

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



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

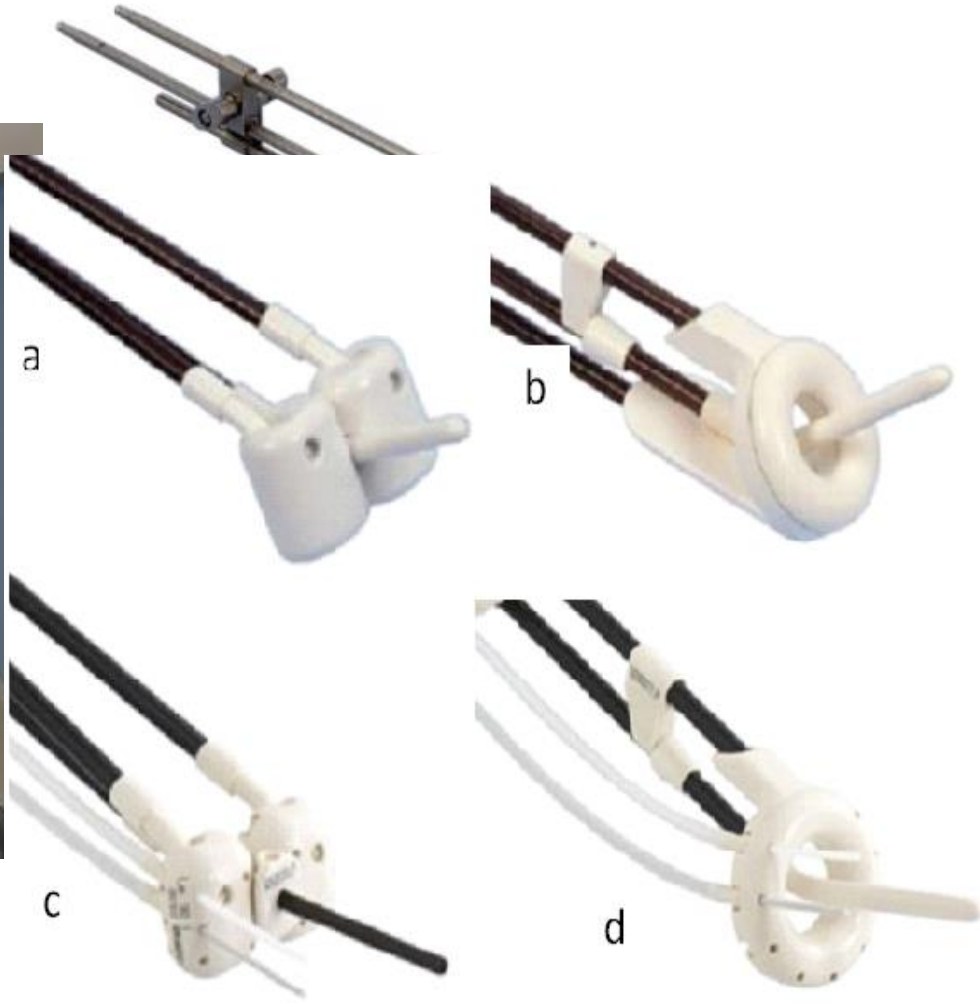
www.embracestudy.dk/AboutAppendix.aspx

Applicator commissioning

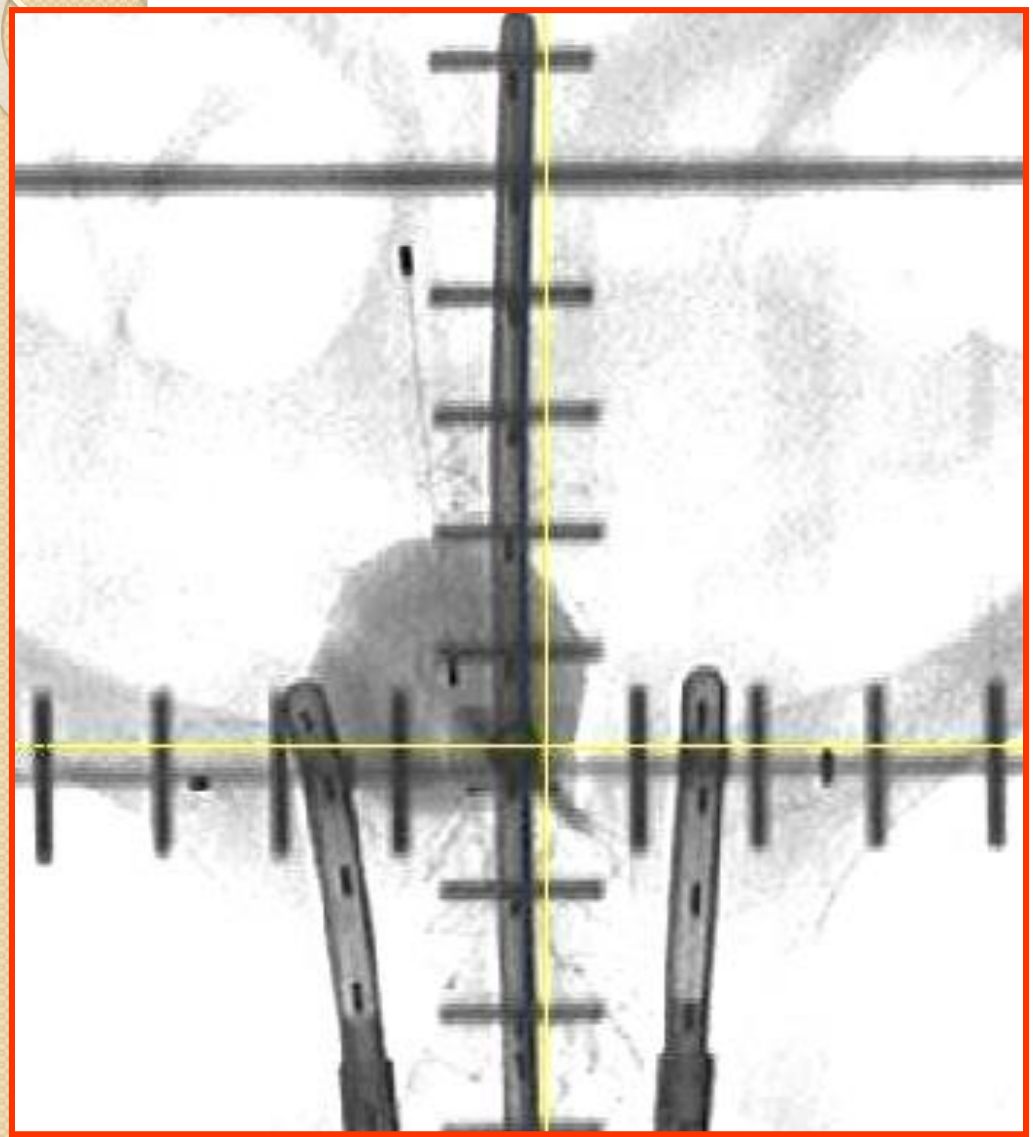
Swamidas V Jamema PhD,

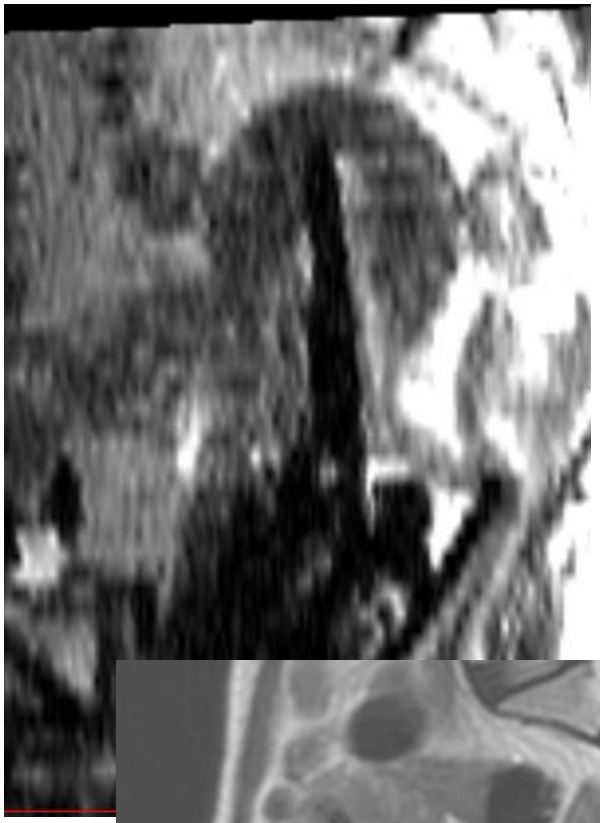
Tata Memorial Hospital, Mumbai, India

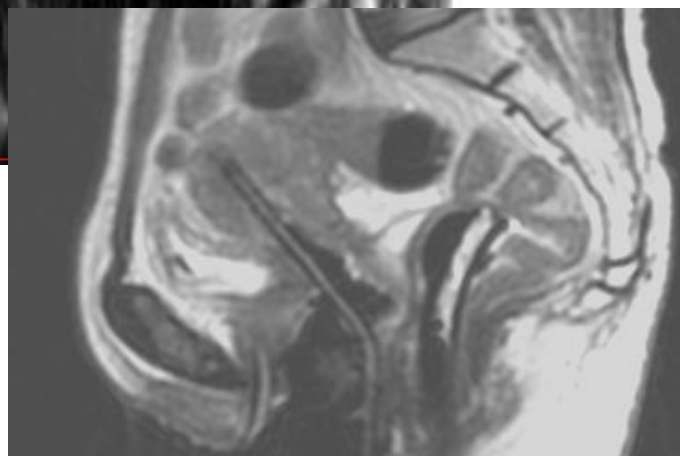
Commissioning



Why so much fuss about Applicator reconstruction in 3D BT

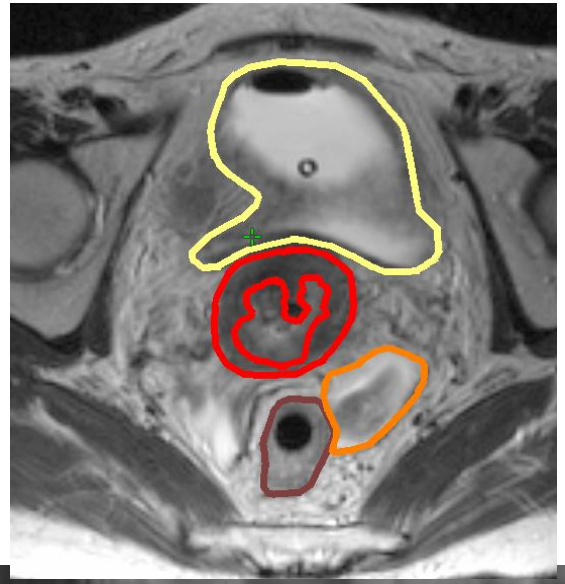


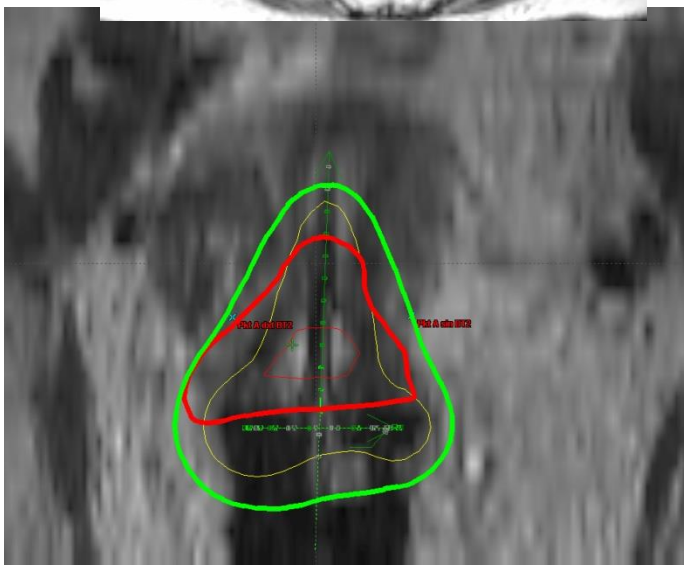




Why applicator reconstruction important: Clinical consequences

- 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



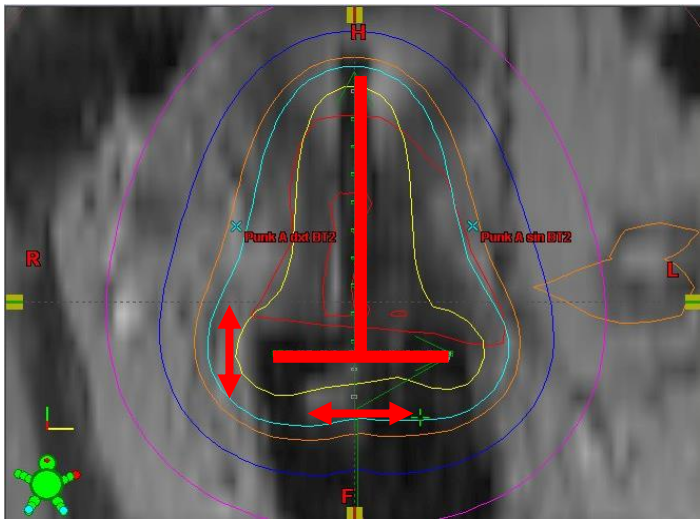


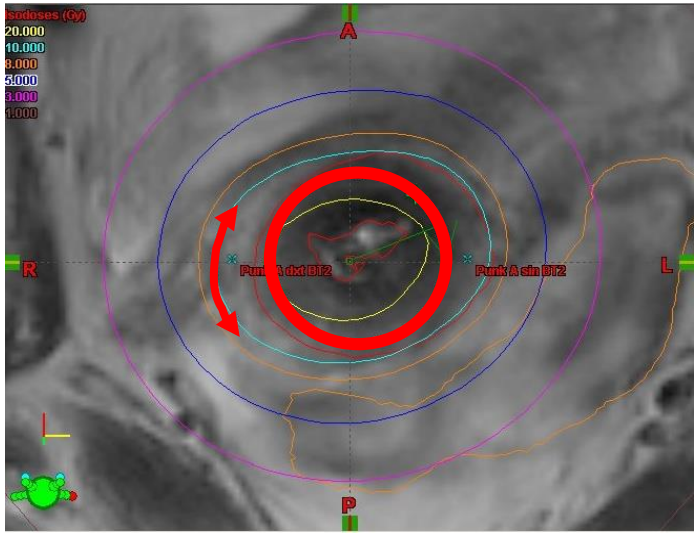
Tanderup et al, R&O 2008

Simulation of uncertainty

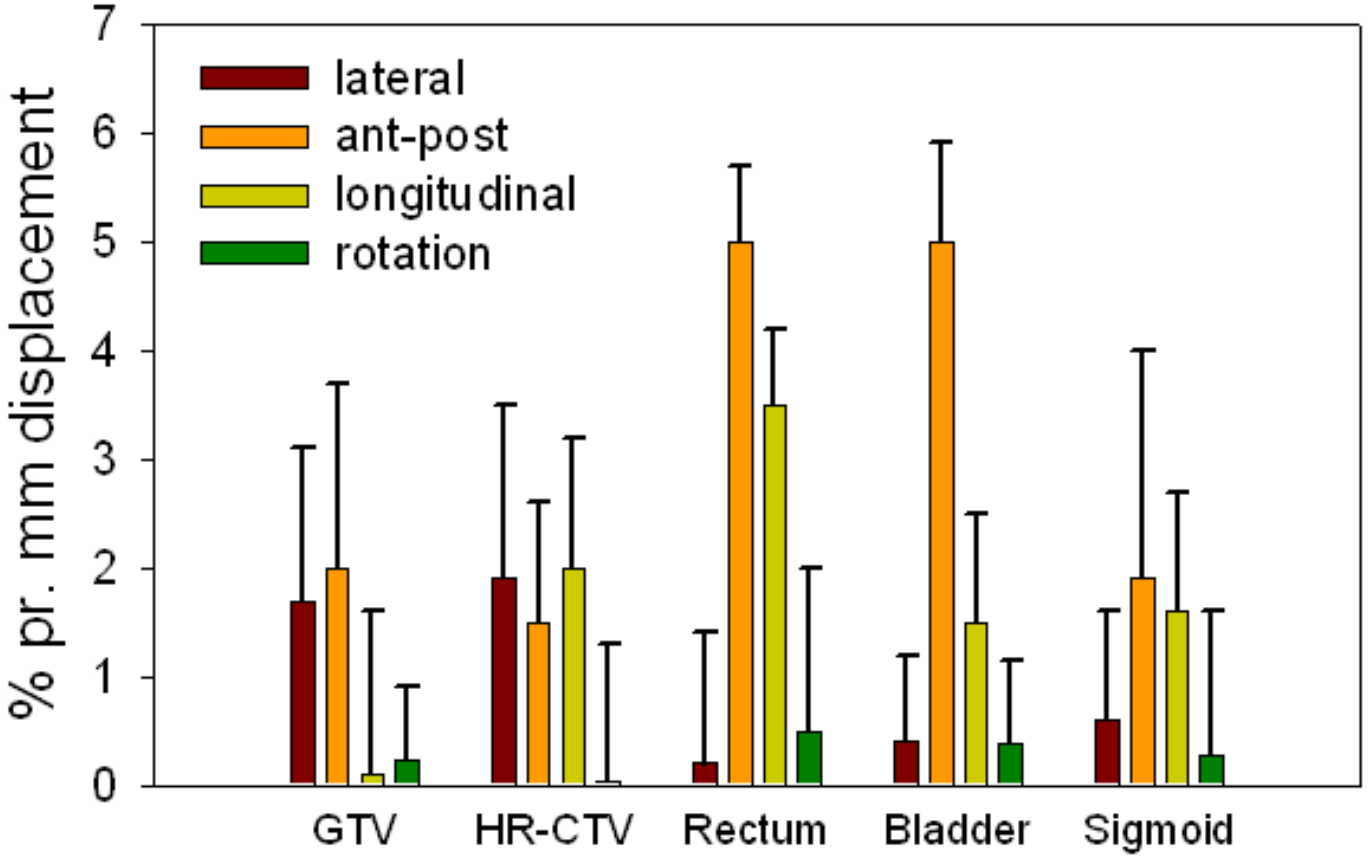
- Displacement in directions:
  - Longitudinal (along tandem):
    - ± 3 mm, ± 5 mm
  - Lateral:
    - ± 3 mm
  - Ant-post
    - ± 3 mm
- Rotation of ring:
  - ± 15 dgr (4 mm)

Tanderup et al, R&O 2008



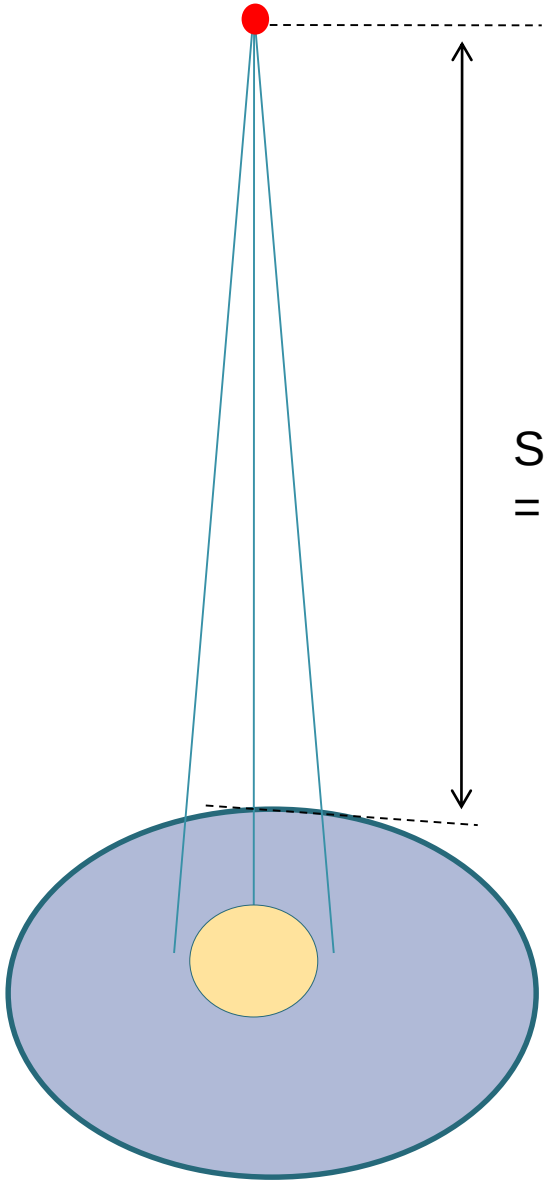


Mean DVH shifts (%) pr mm

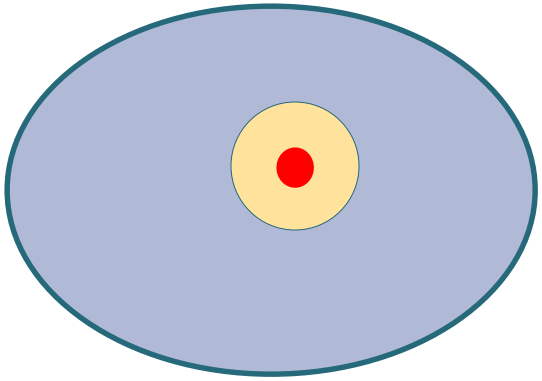


Tanderup et al, R&O 2008

What is Applicator reconstruction in Brachytherapy?



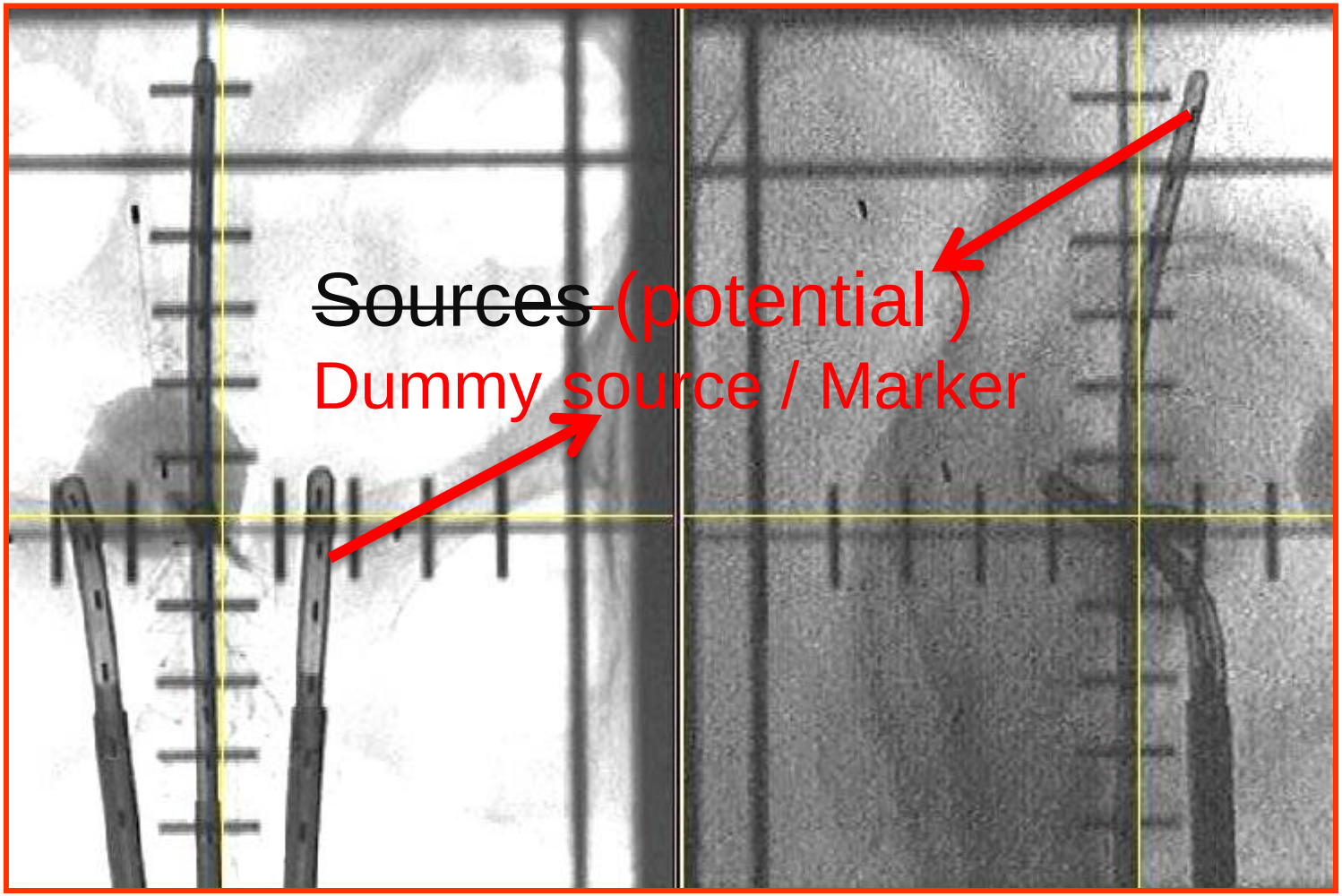
External therapy



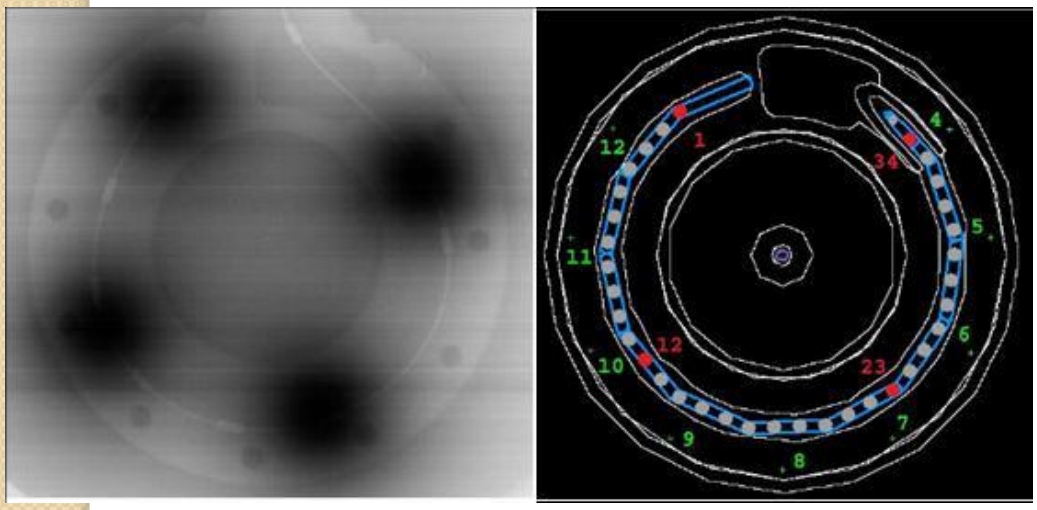
Brachytherapy

defining a source path inside the applicator

What is applicator reconstruction?



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.

Reading material

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

GEC-ESTRO Recommendations

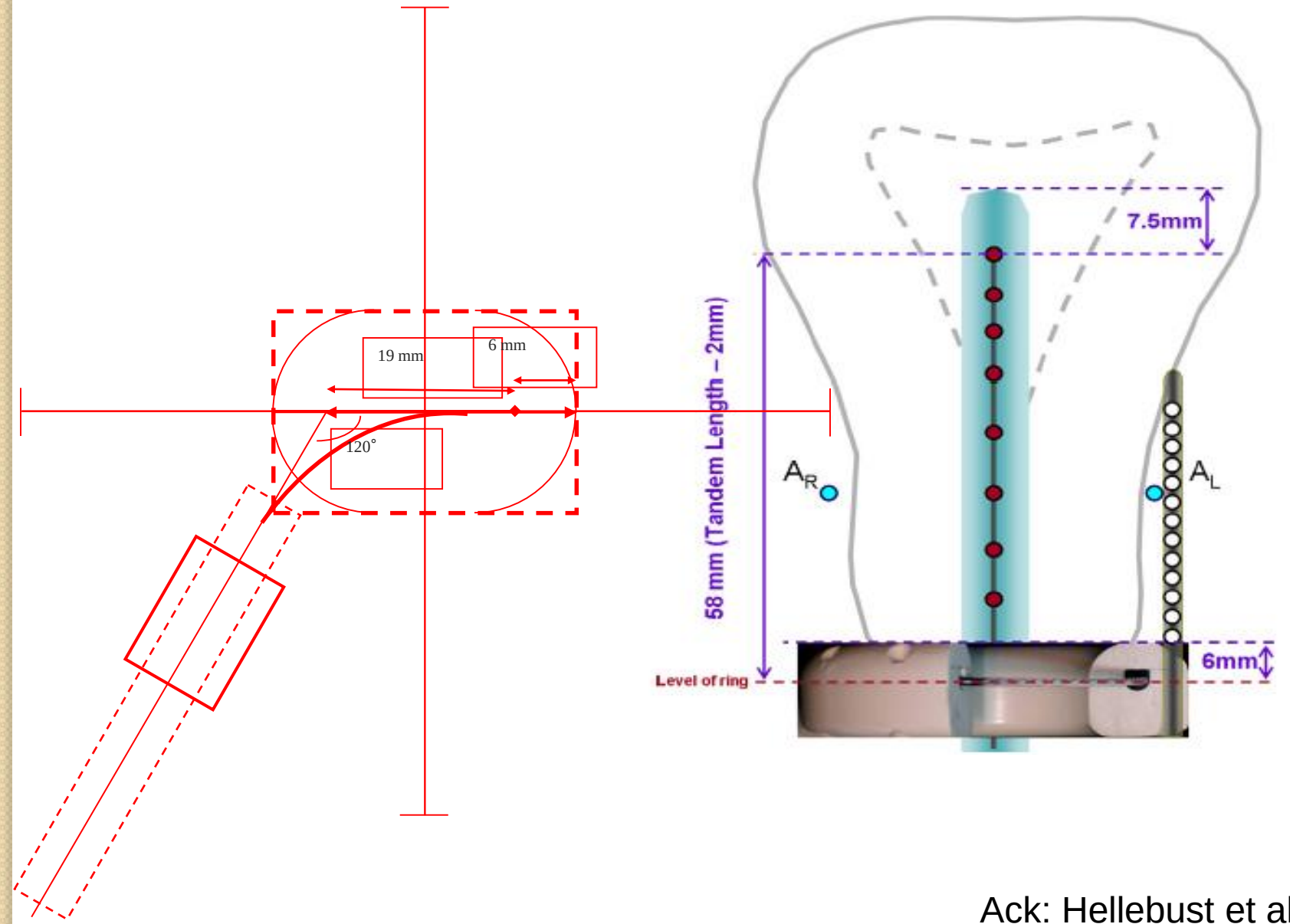
Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group: Considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer brachytherapy

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 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.

Step 1/5: Understand the geometry

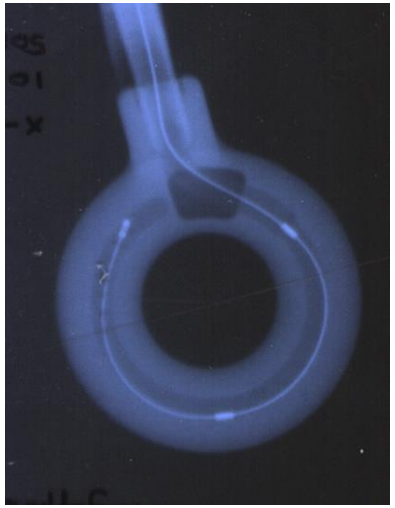


Ack: Hellebust et al

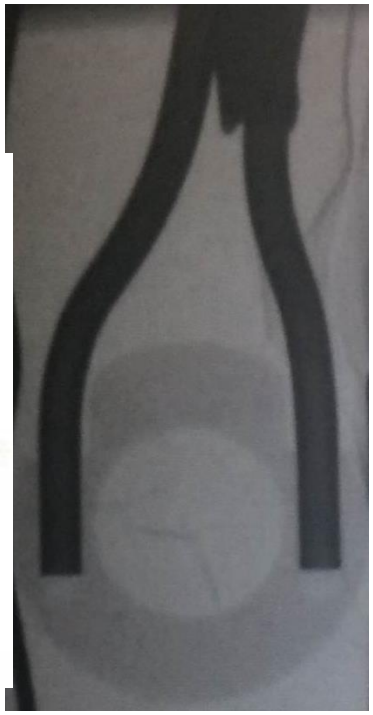
Step 1/5: Understand the geometry

The ring applicator from Bebig vs Elekta

X-ray



X-ray

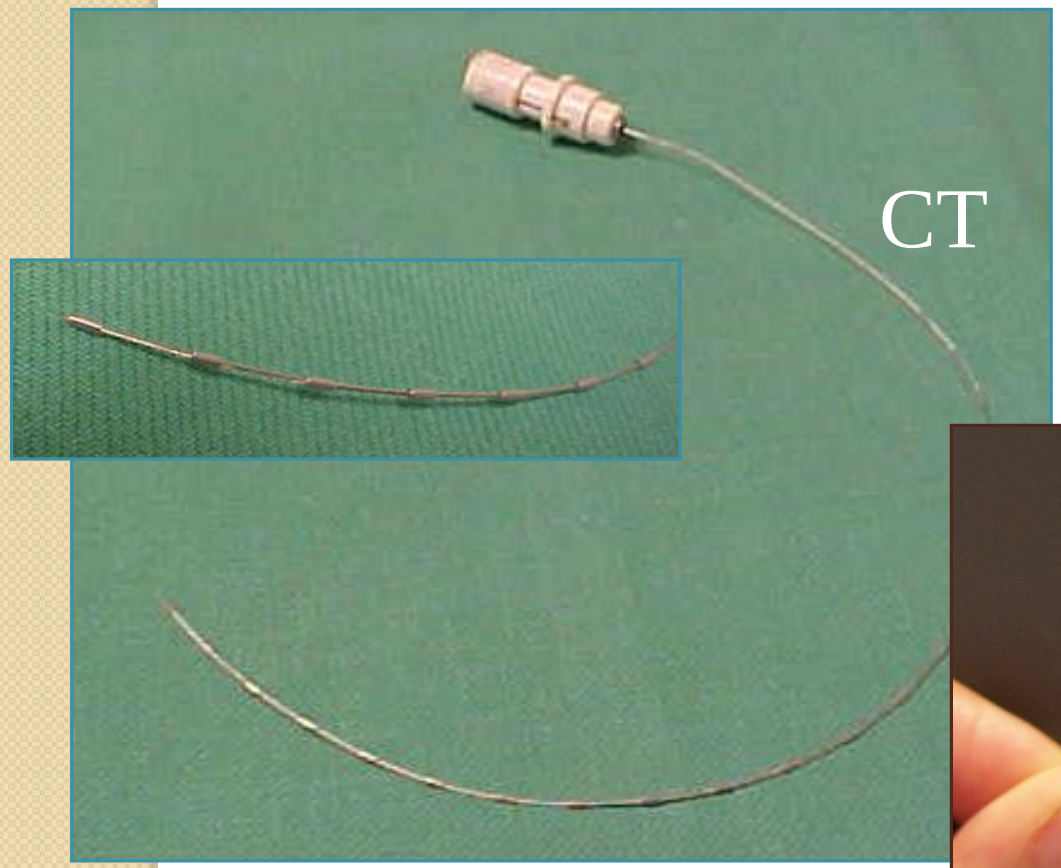


Elekta

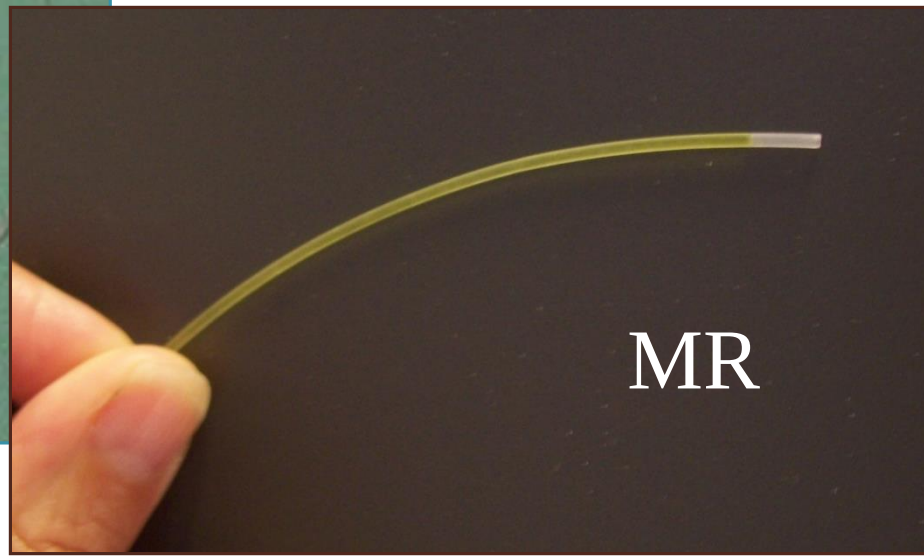
Bebig

Slide courtesy : Hellebust

Step 2/5: Choose the Markers

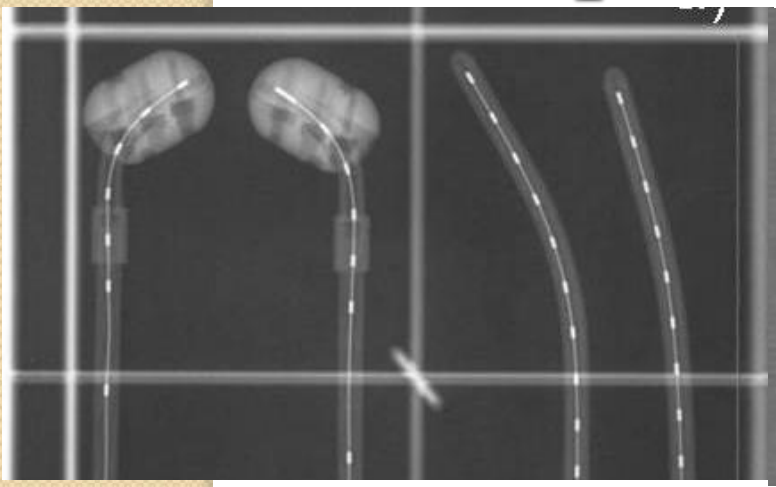


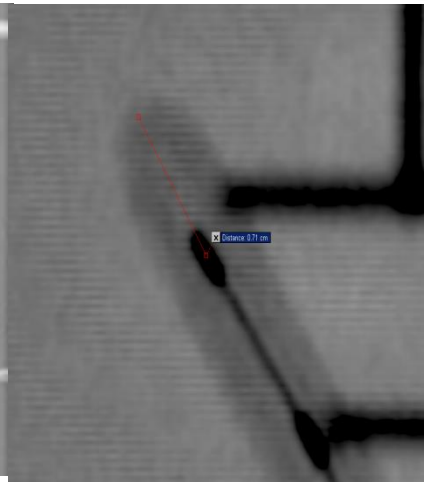
important: Dedicated for each type of applicator, check for locking!!

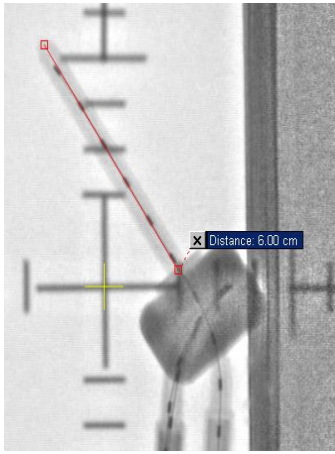


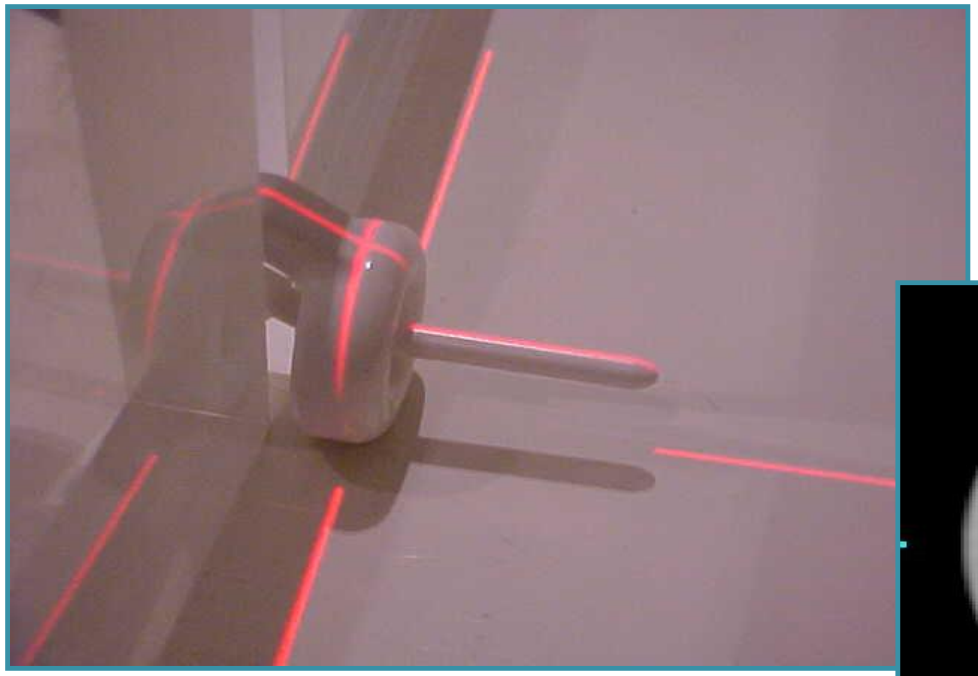
Ack: Hellebust

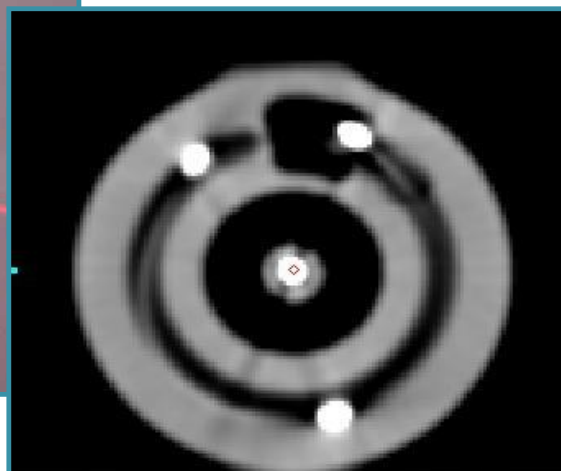
Step 3/5: Radiograph / CT





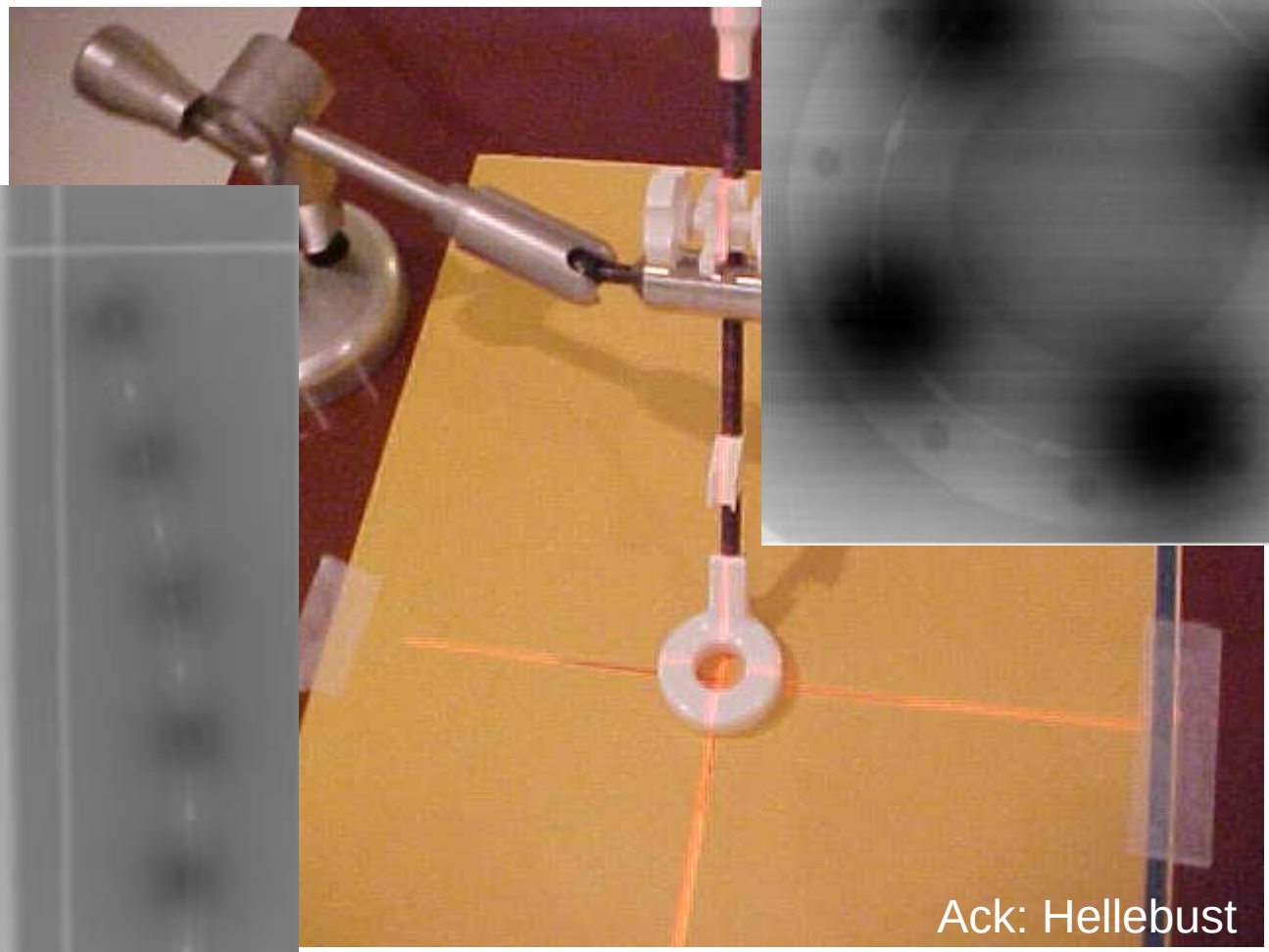


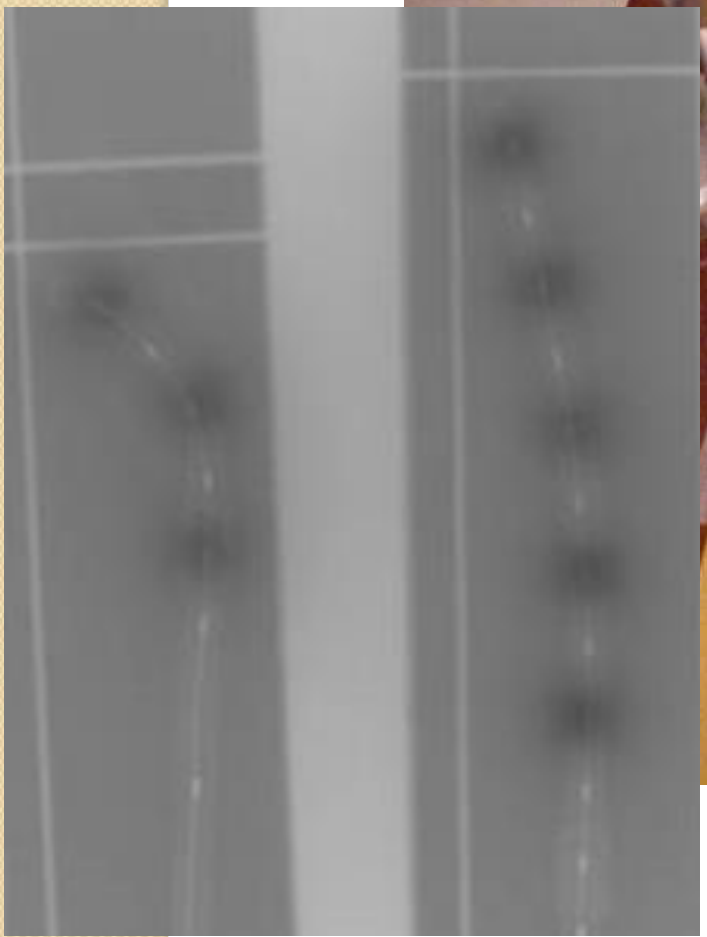




Ack: Hellebust TP

Step 4 /5 : Auto radiograph



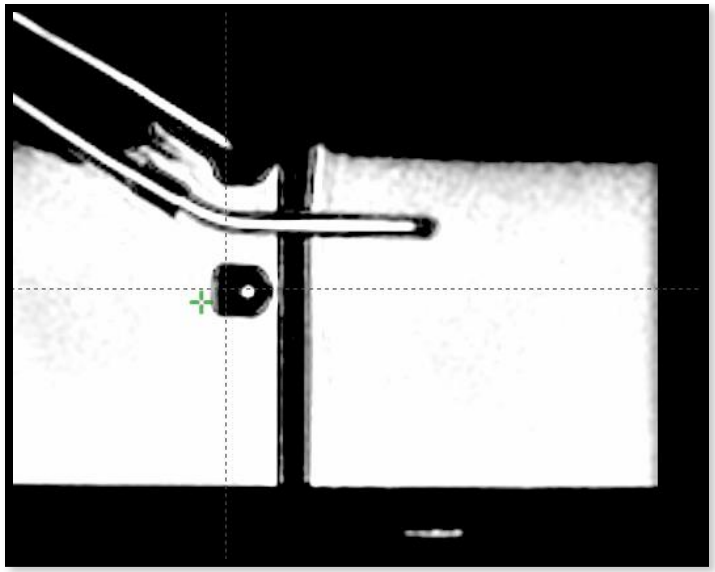


Ack: Hellebust

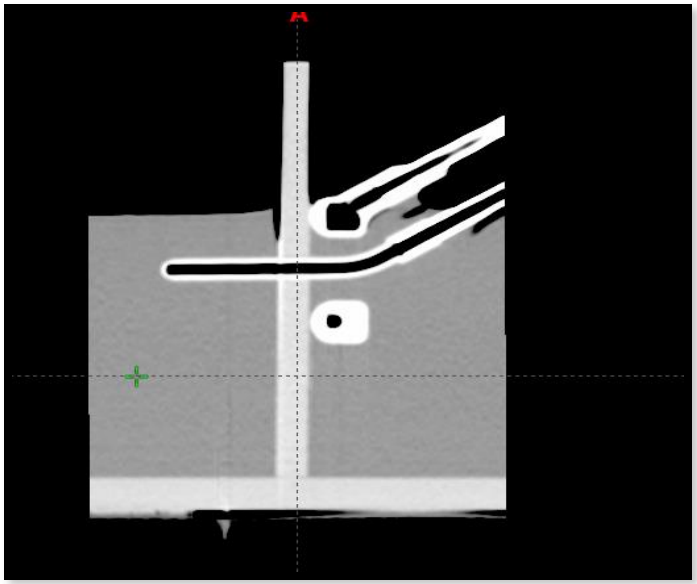
Step 5/5 : Analysis

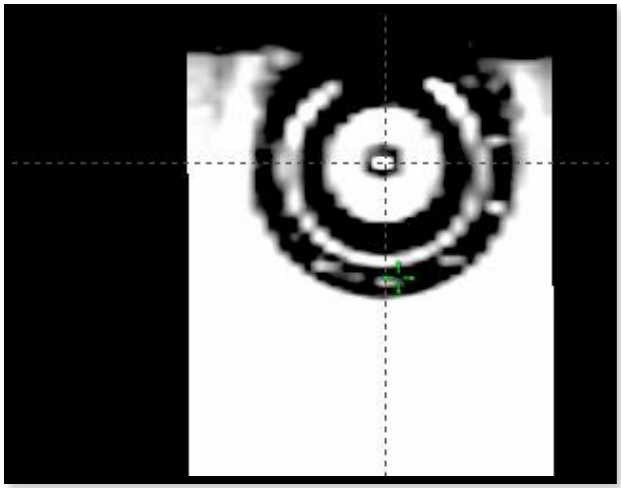
- Compare the auto radiograph with the manufacturer specifications
- Comparing step 1 with 4

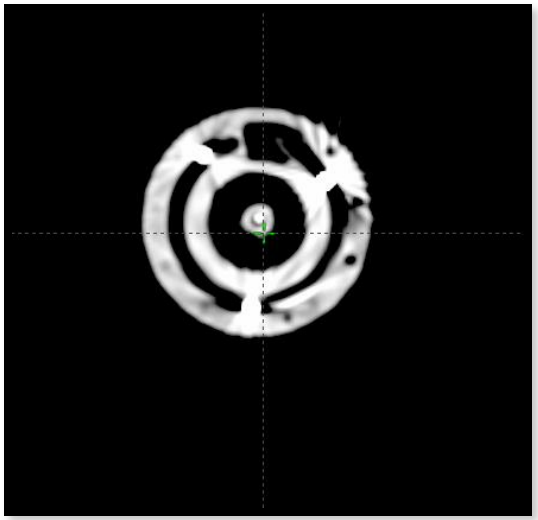
MRI



CT

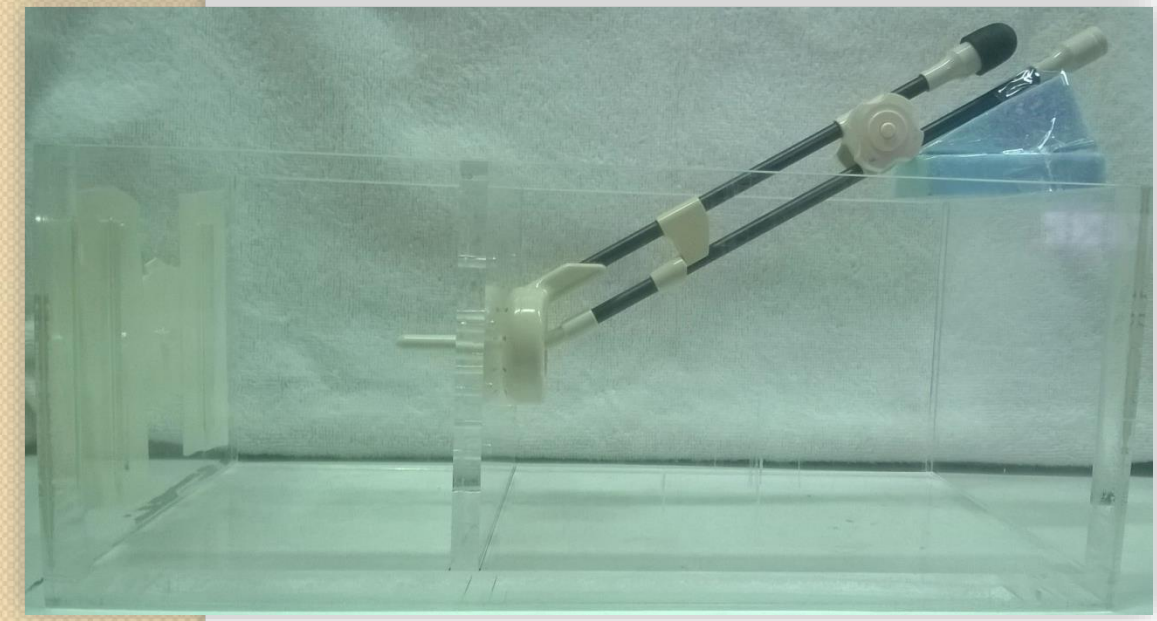




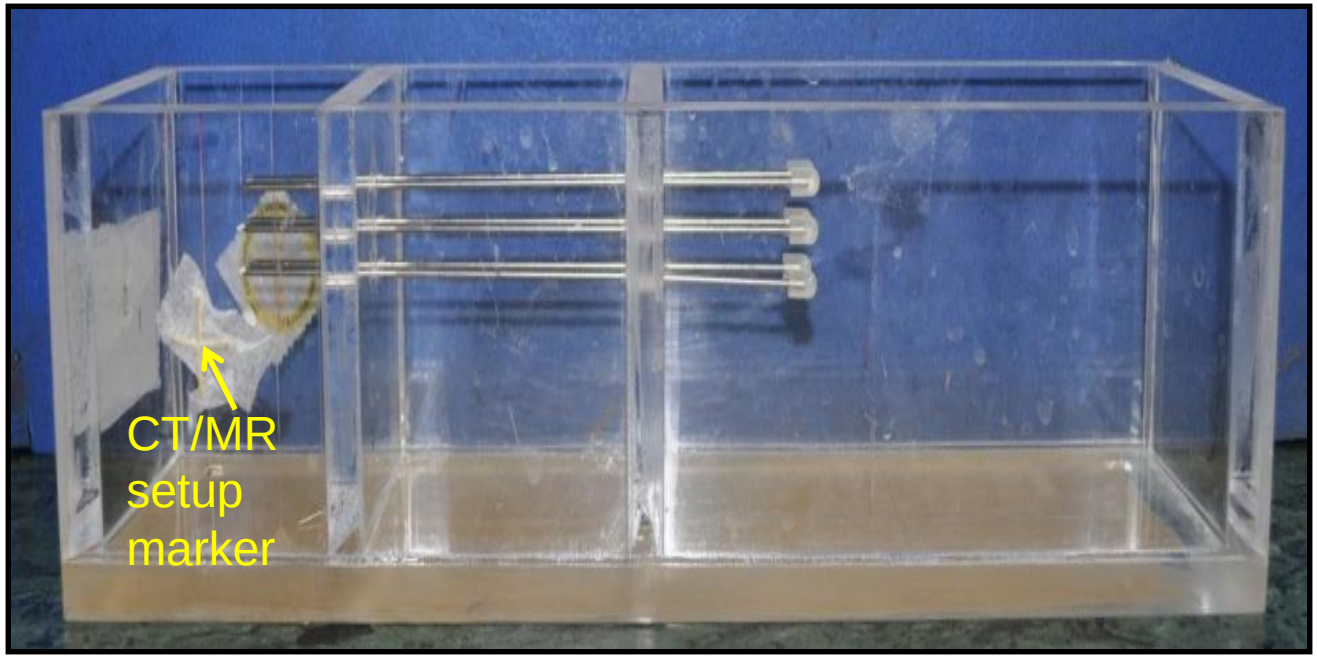


Phantom

- Should facilitate accurate positioning of the applicator
- External setup markers for proper setup during imaging



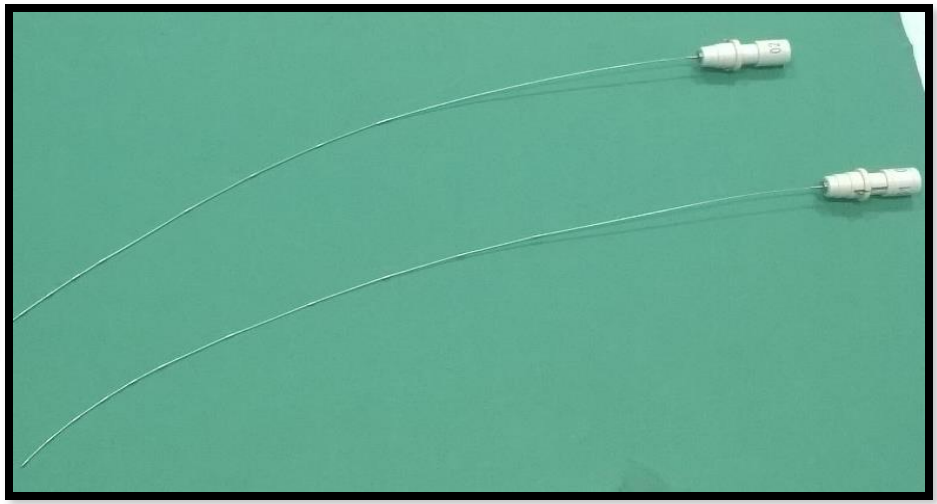
Vienna Applicator



Interstitial Needles

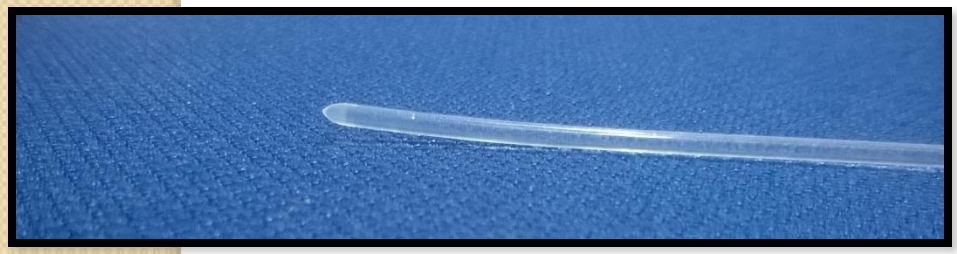
Medium:

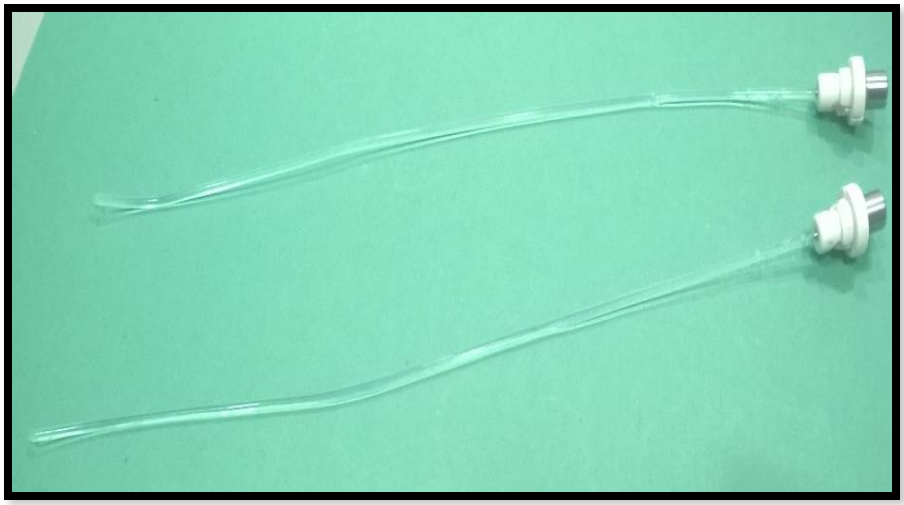
- Preferable if it resembles human tissue imaging qualities.
- Ideal for CT/ MR applicator is Agarose gel (3%) with CuSO4 (1 g/L)



X-ray markers for CT/MR applicator.

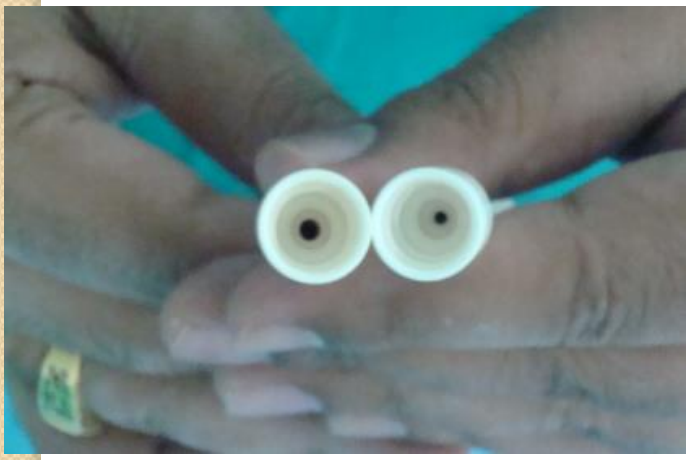
DO NOT USE X-RAY MARKER DURING MRI.

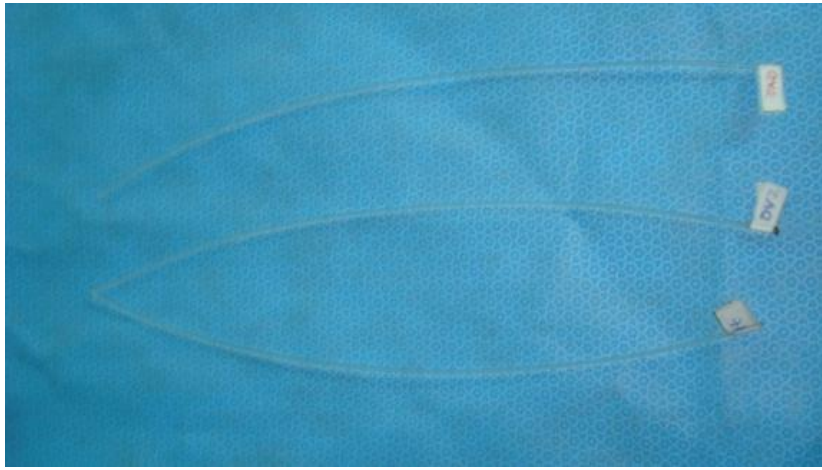


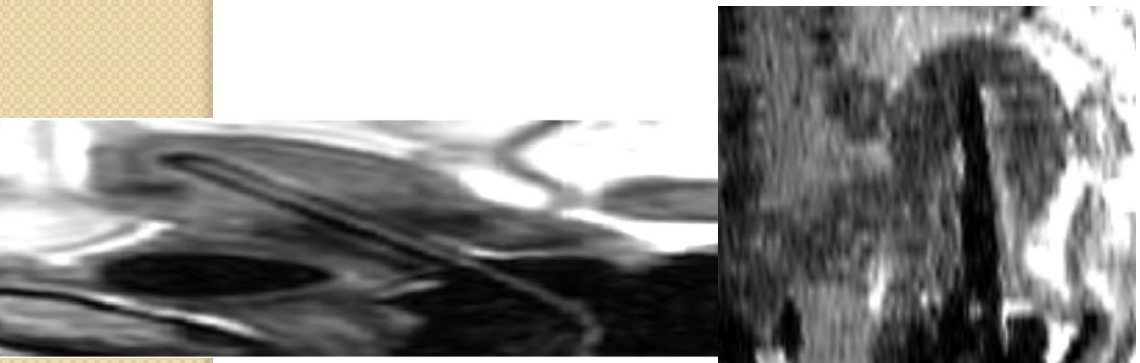


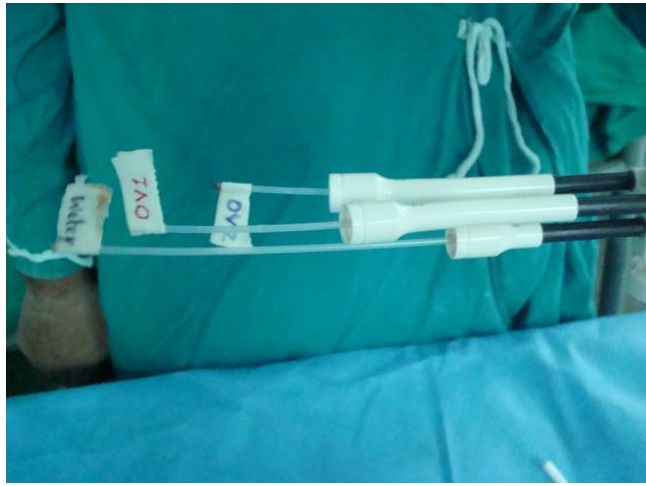
MR markers for CT/MR applicator.
They are filled with water.
$CuSO_4$ can also be used.

Applicator reconstruction using MR images



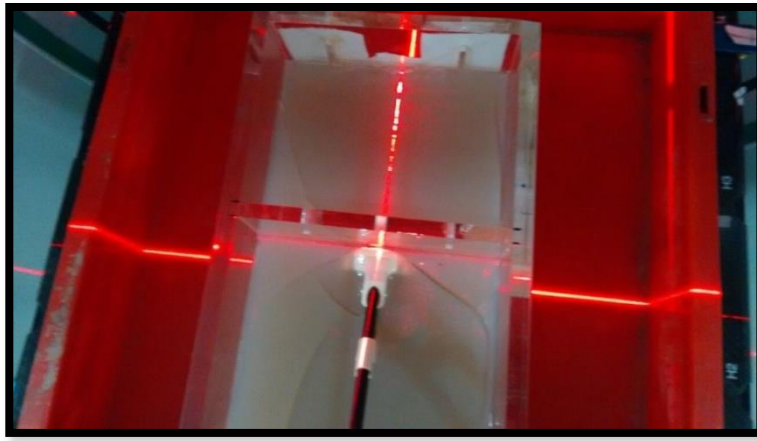






Imaging

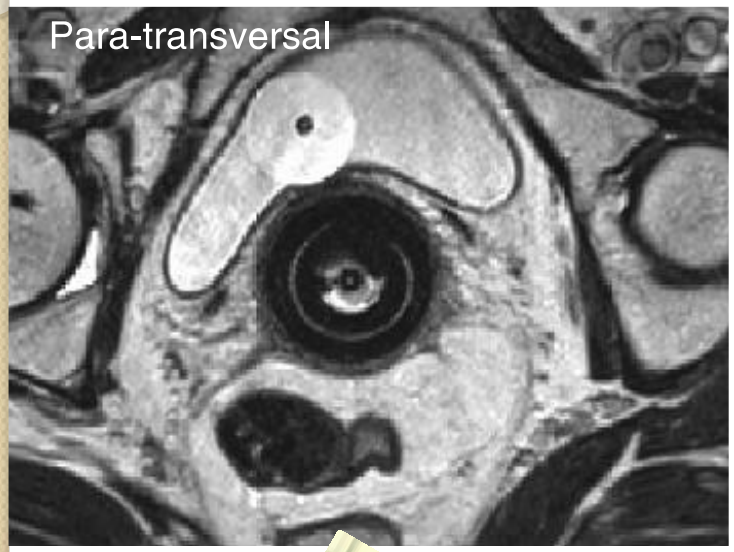
- Setup according to the external markers.
- Align the axis of the applicator along the saggital Laser.

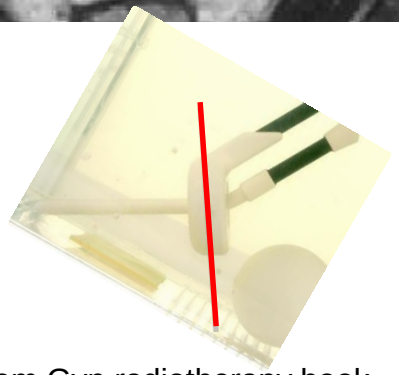


- Imaging Series
  - CT – <1 mm slice thickness
  - MRI – T1, T2 para-axial, para-saggital and para- coronal. 2- 3 mm slice thickness.

Orientation of the imaging sequence

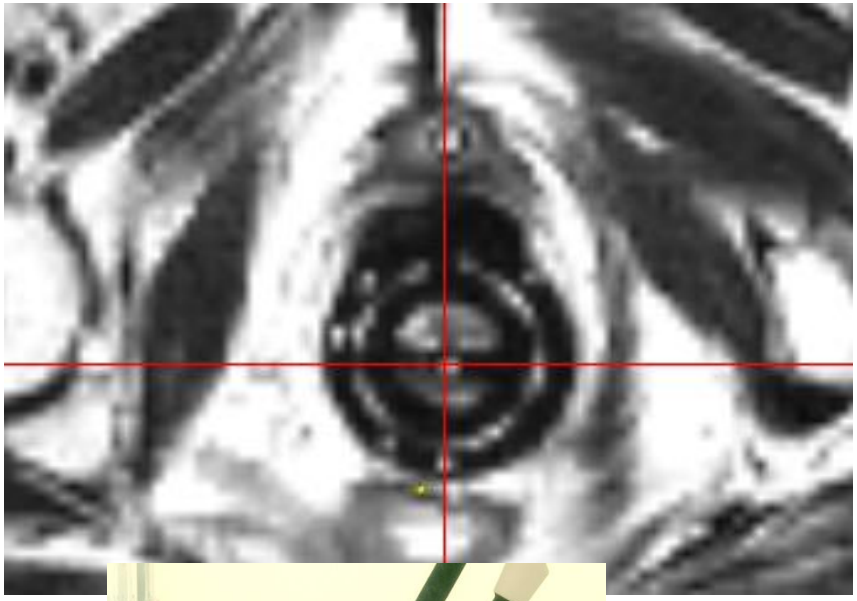
- Para transverse

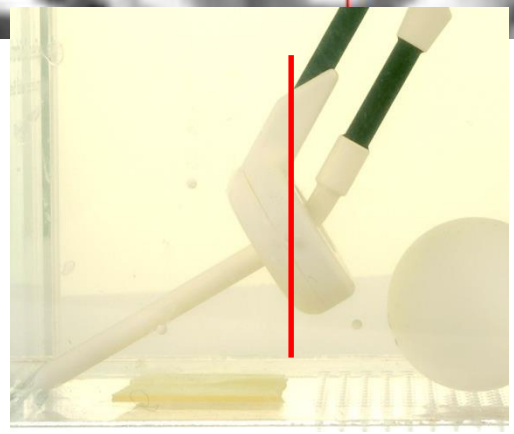




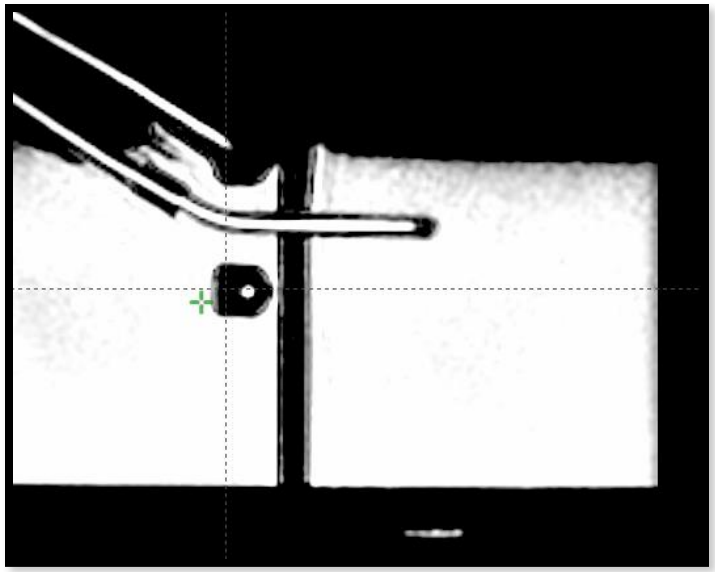
From Gyn radiotherapy book,
Editor: A viswanathan,
Kirisits C, Erickson B, Potter P

- Transverse (MP Reconstructed)

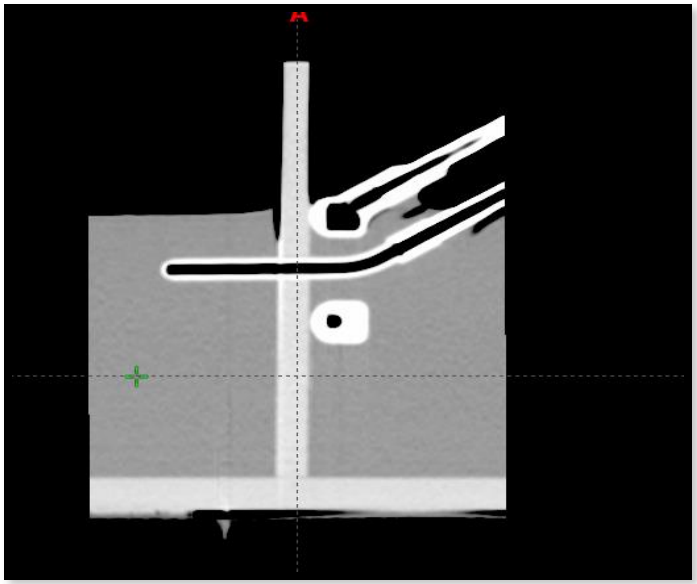


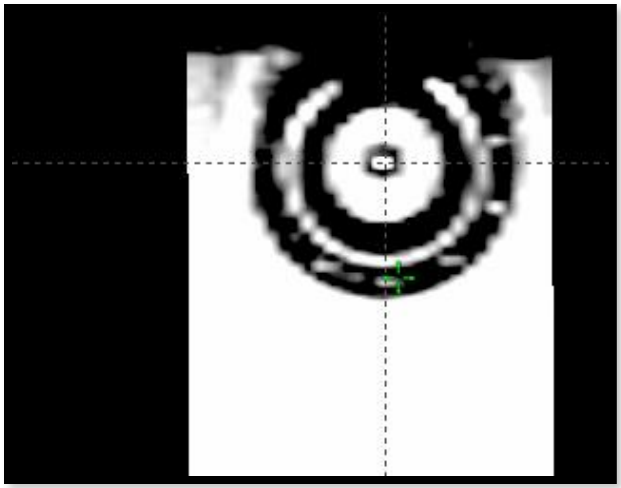


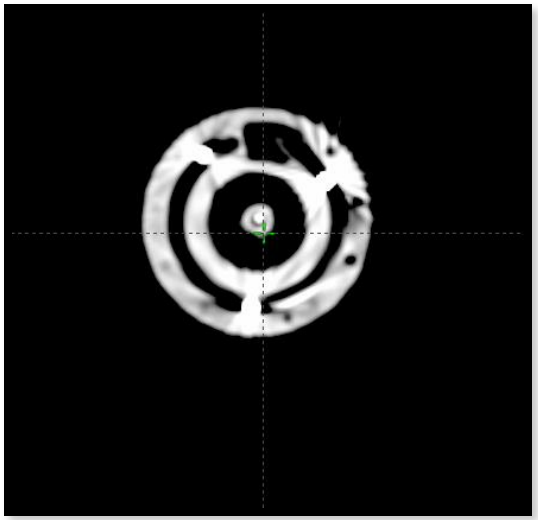
MRI



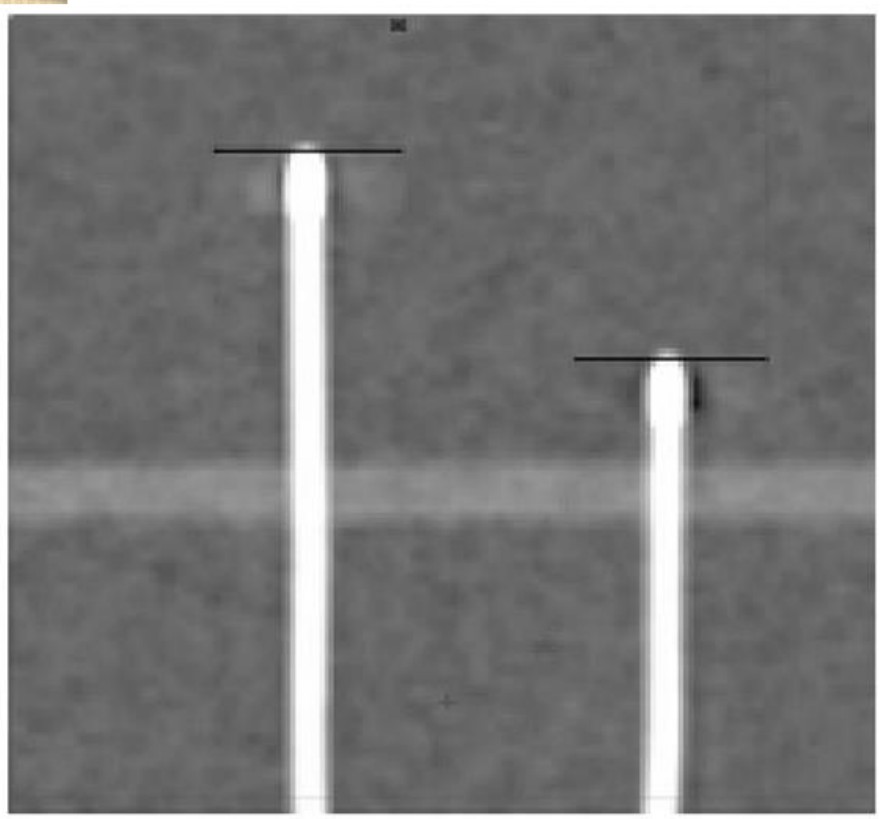
CT



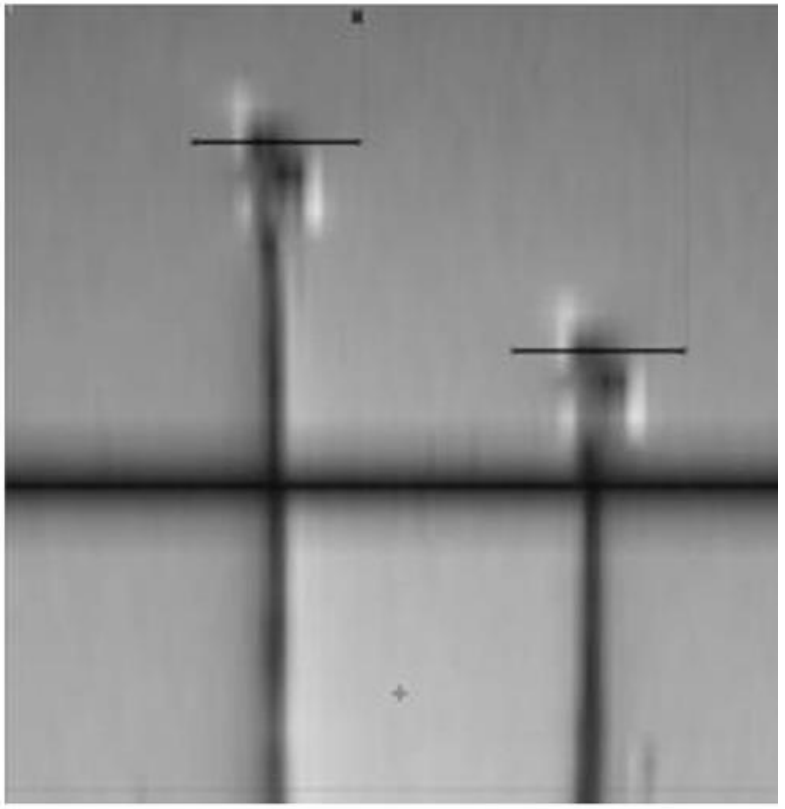




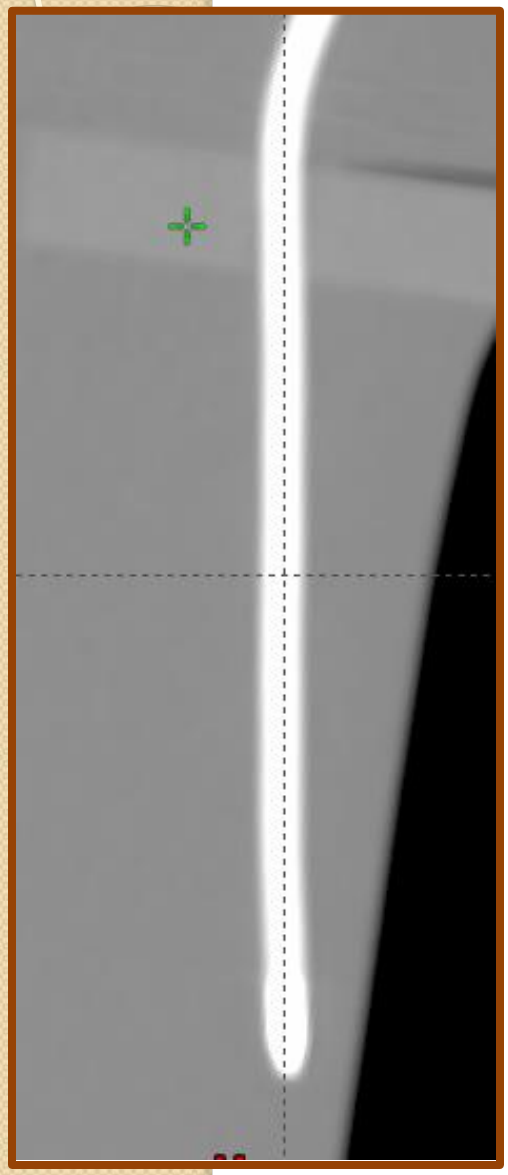
Titanium applicators



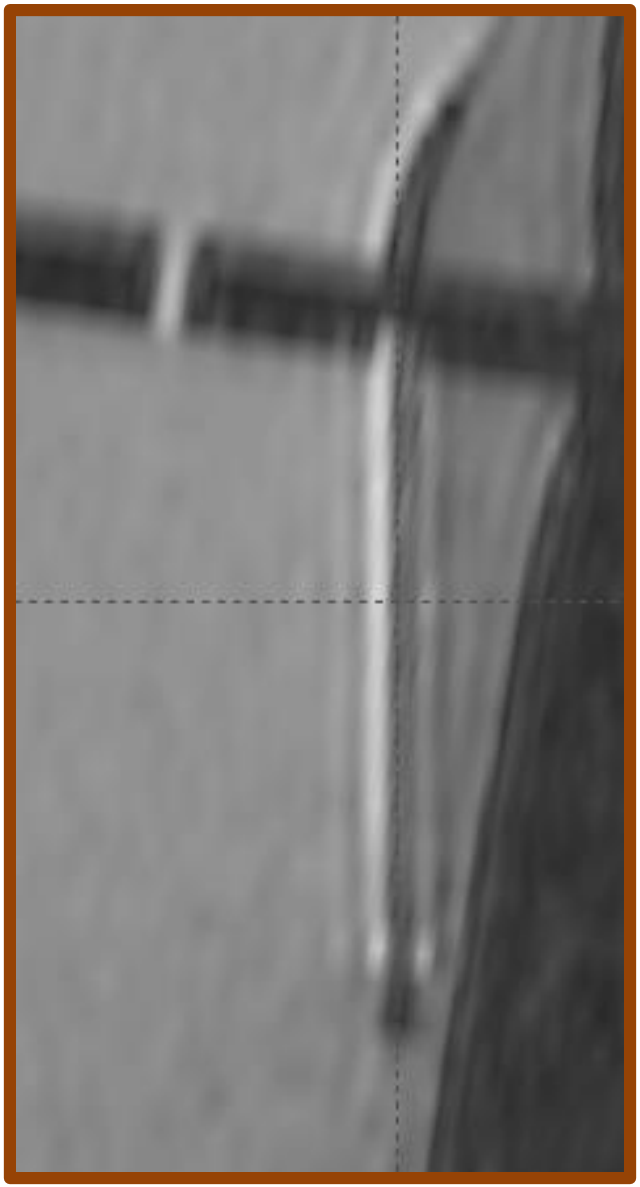
b



CT

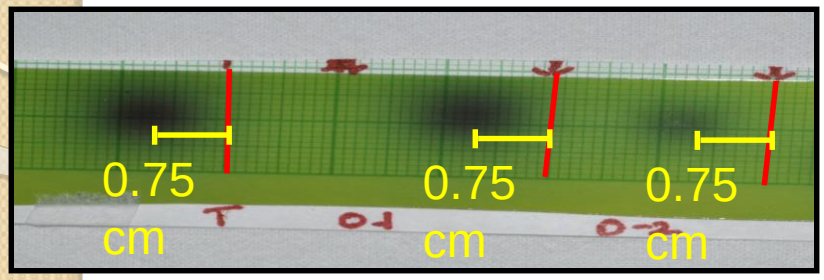


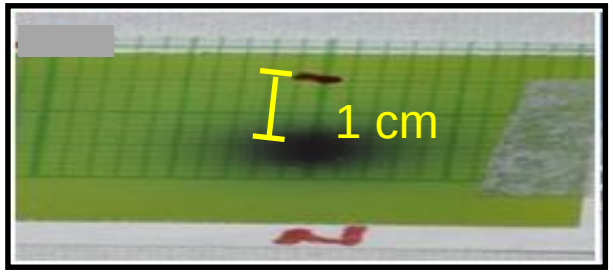
1.5 T



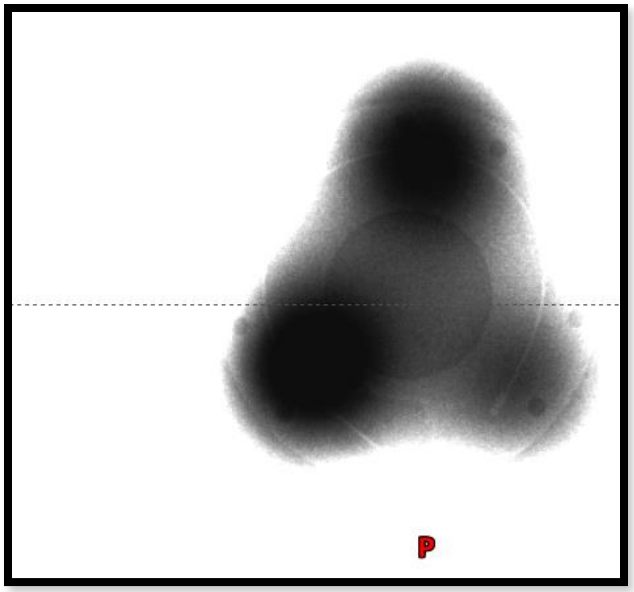
3.0 T

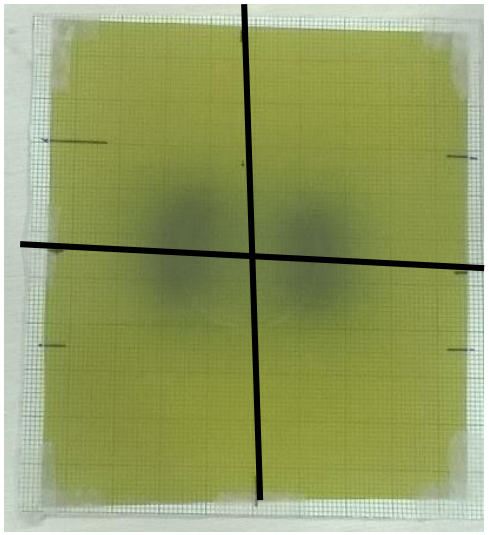
Auto Radiograph



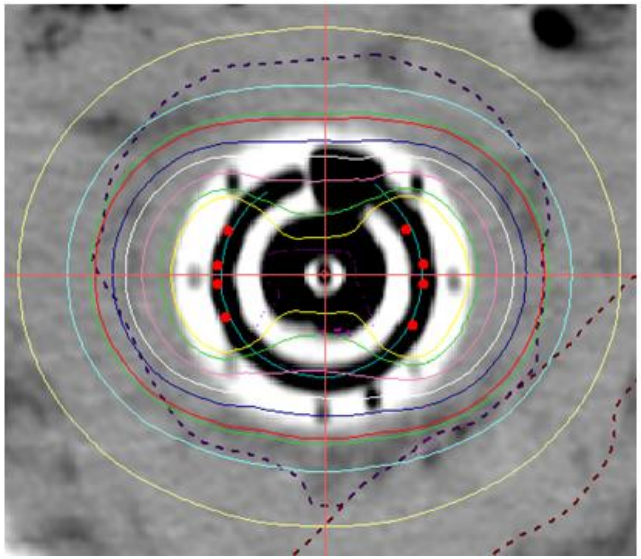


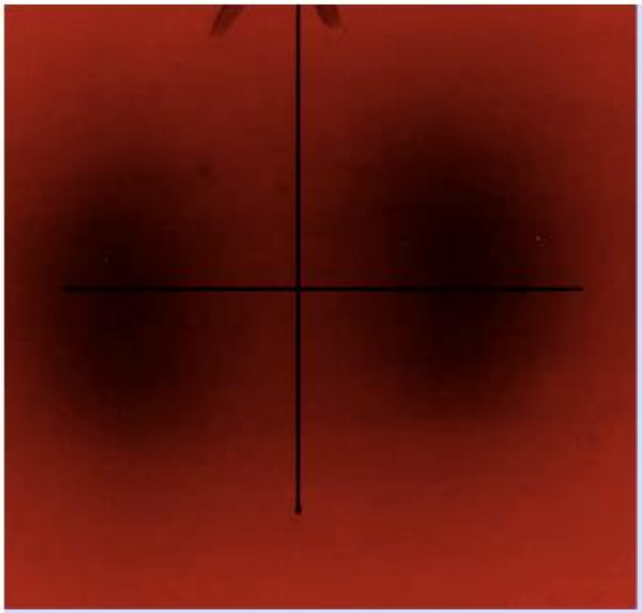
Red line indicates the physical tip

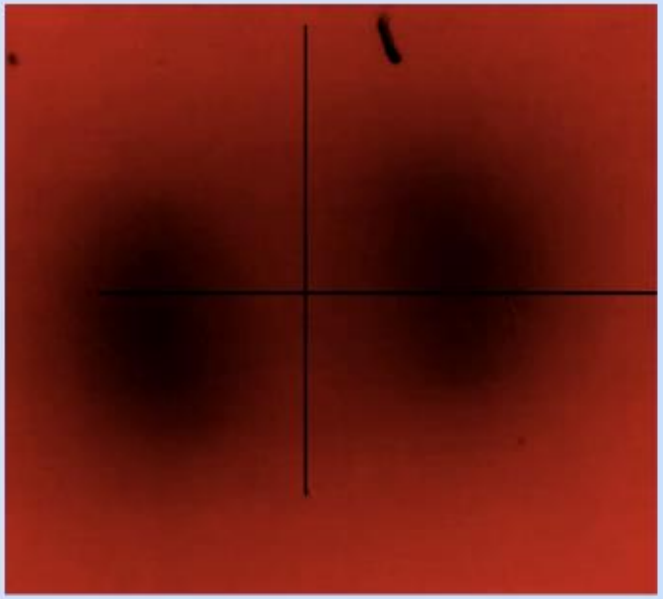




Ring Applicator





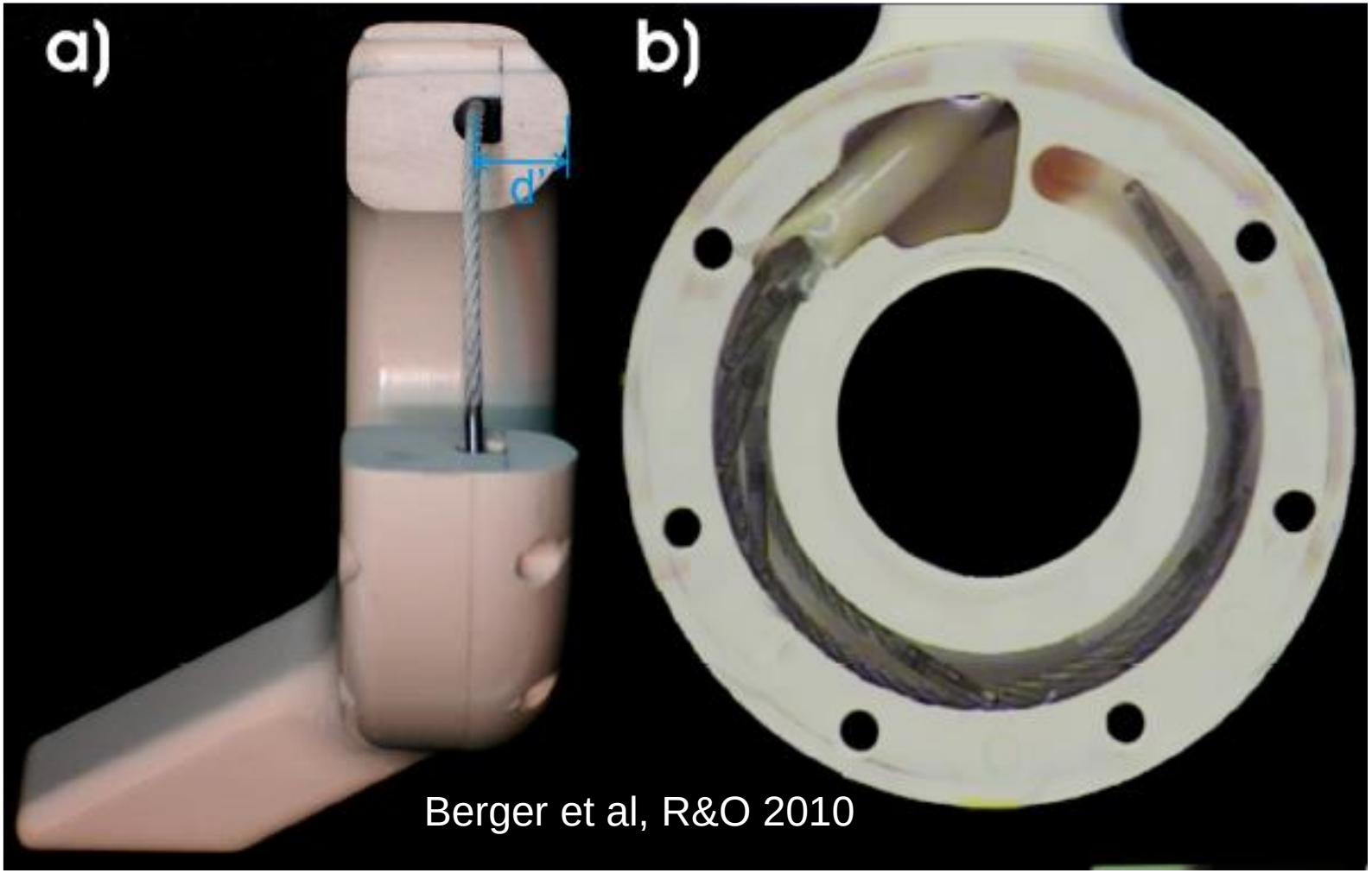


Acceptable

Not Acceptable

Images : Hellebust

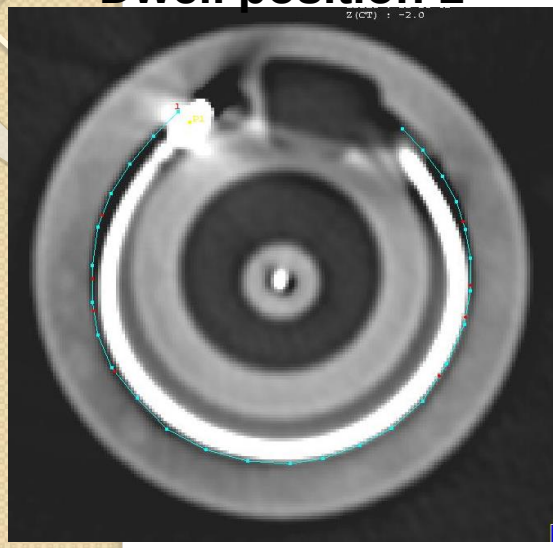
Photo of the ring with the source



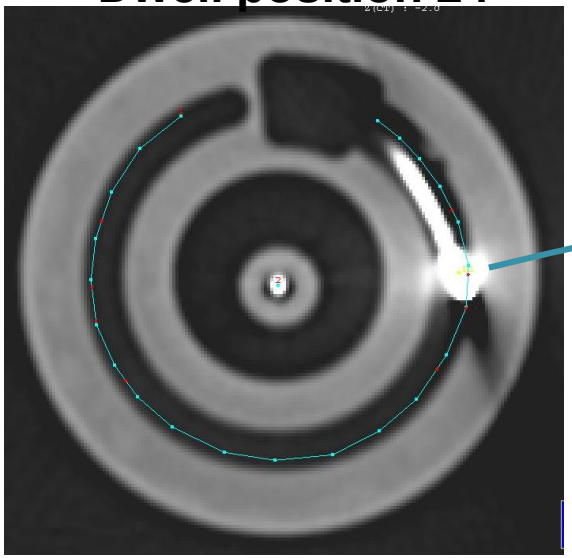
Berger et al, R&O 2010

CT images of the ring with the source

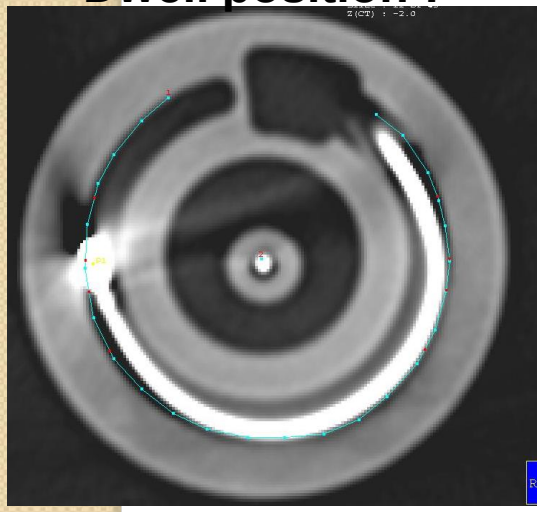
Dwell position 1

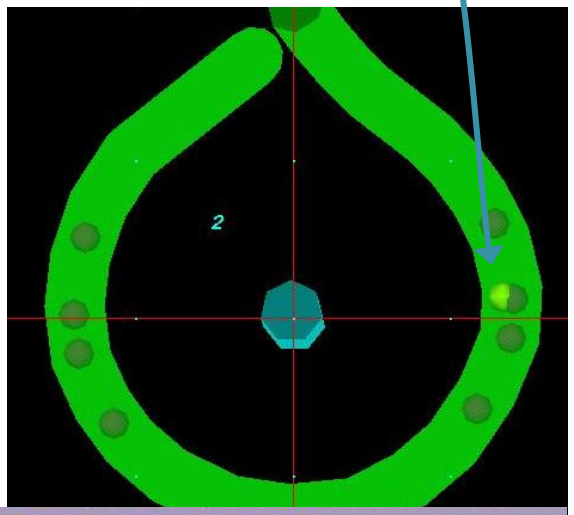


Dwell position 24



Dwell position 7

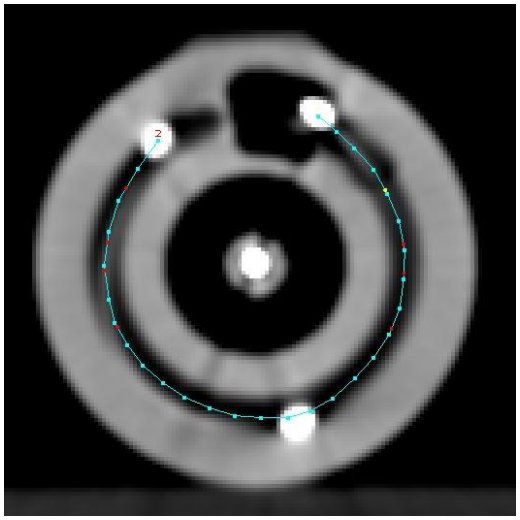


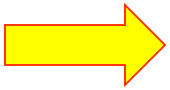


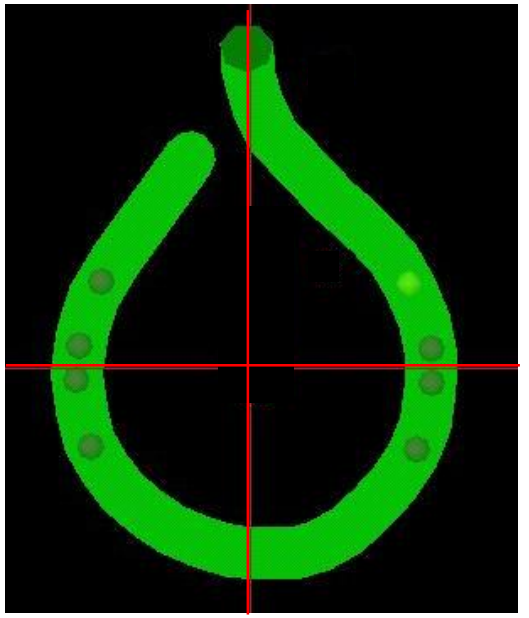
Hellebust et al, PMB 52 (2007)

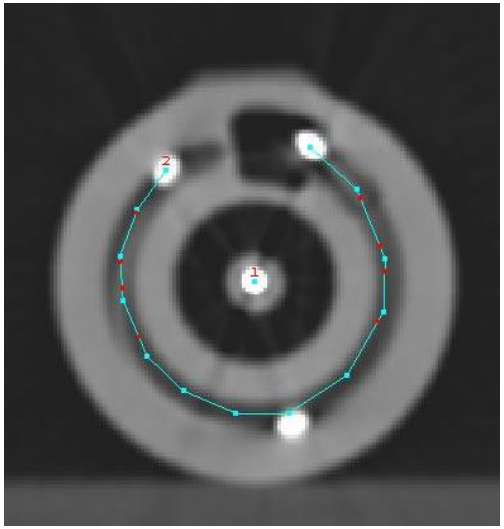
Summary

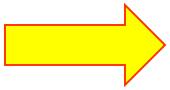
- Applicator commissioning is essential
- Uncertainties in commissioning / applicator reconstruction leads to dose variation in target / OARs
- Consists of simple 5 steps
  - Understand the geometry
  - Choose the markers
  - Radiograph / auto radiograph
  - Analyze the images

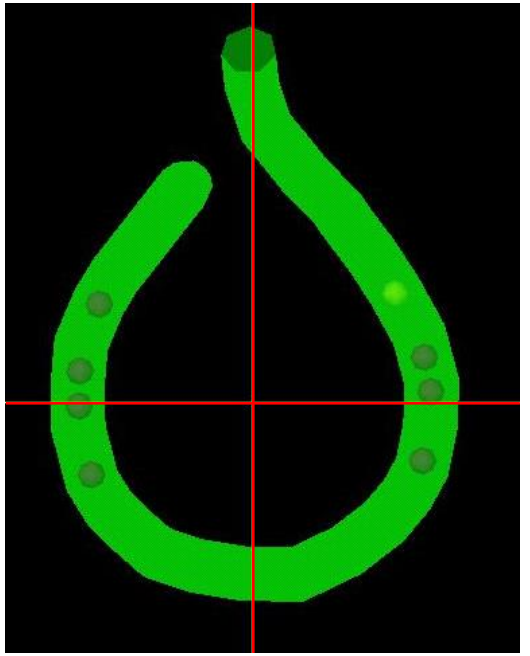








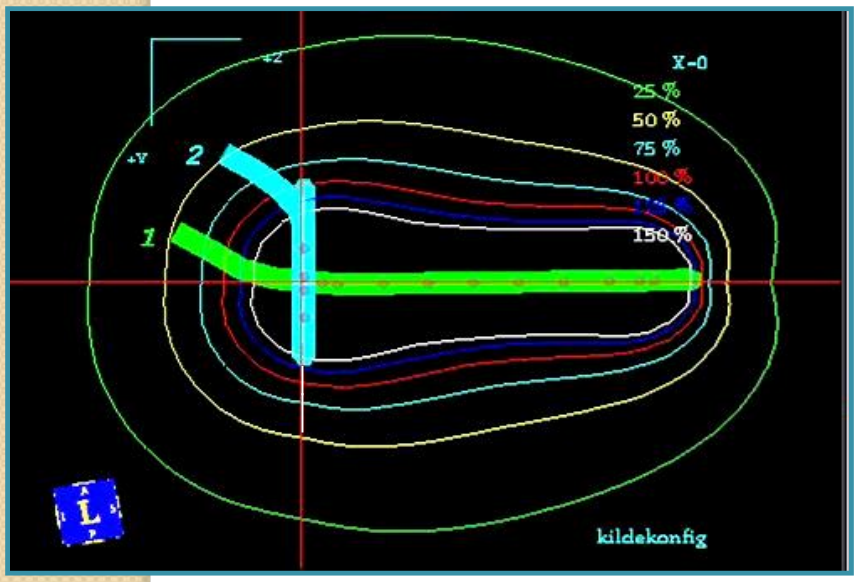




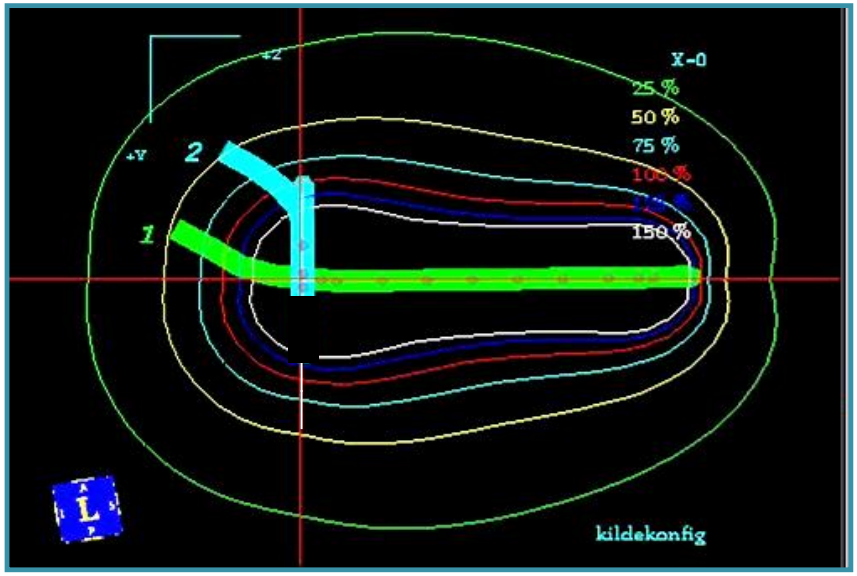
Ack: Hellebust TP

The ring applicator from Bebig vs Elekta lateral view on x-ray (only metal part visible)

Elekta



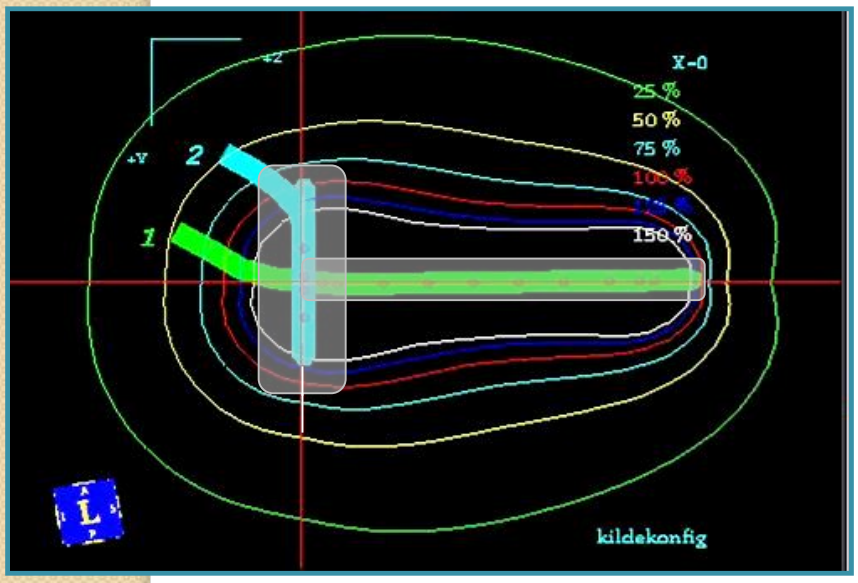
Bebig



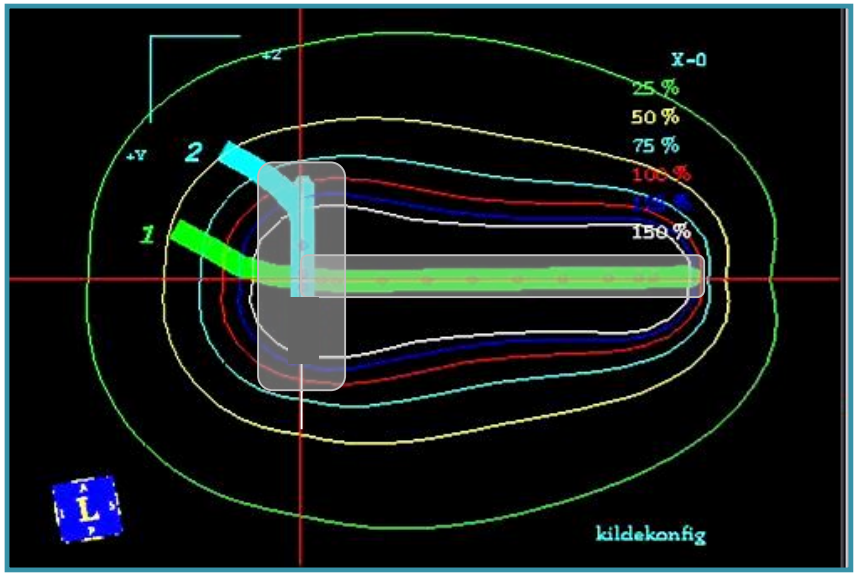
Slide courtesy : TP Hellebust

The ring applicator from Bebig vs Elekta, lateral view including plastic ring important for localization of ICRU rectum point and vaginal points

Elekta



Bebig



Slide courtesy : Hellebust

Hypothetical Case

Cervical Cancer

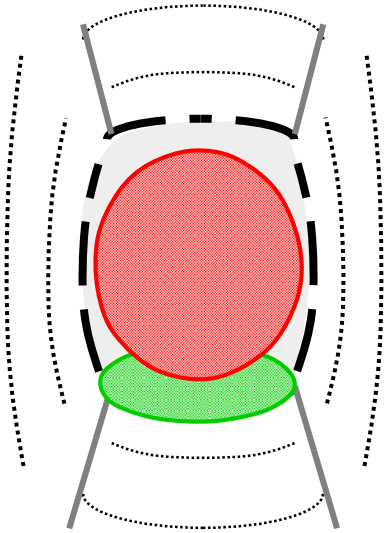
Clinical FIGO IIIB

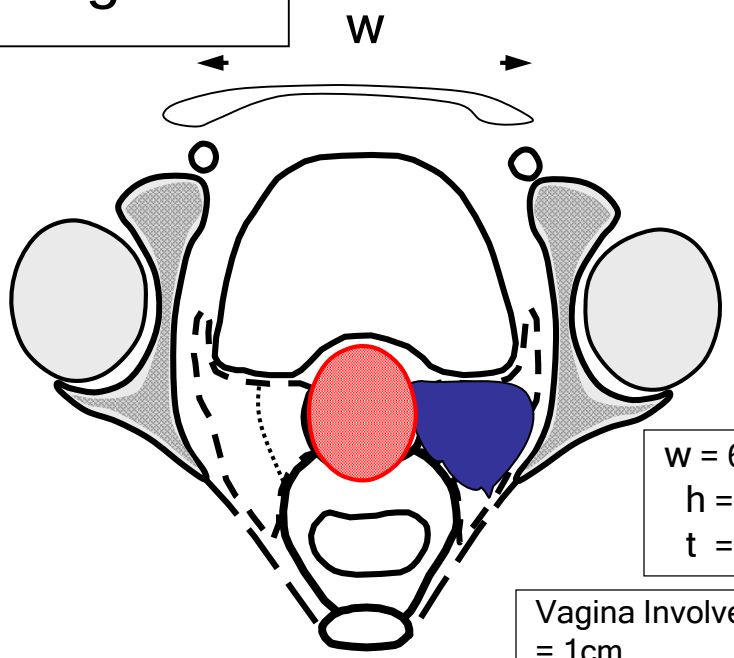
Partial Response to EBRT

Clinical Drawing

At Diagnosis

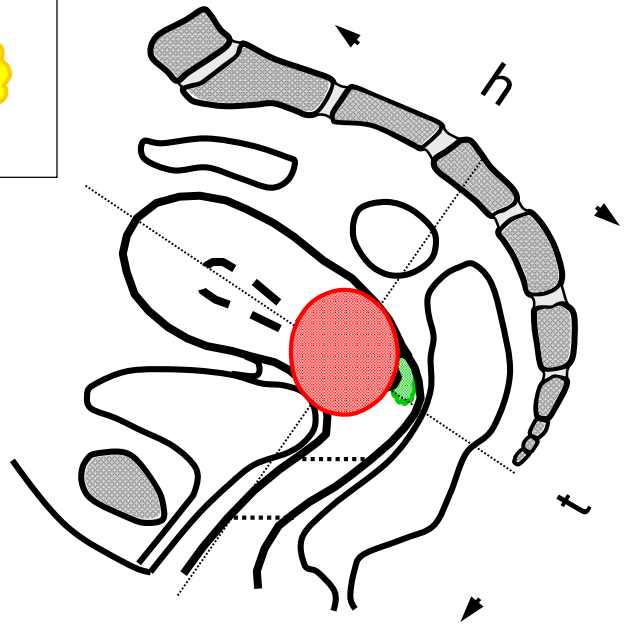
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

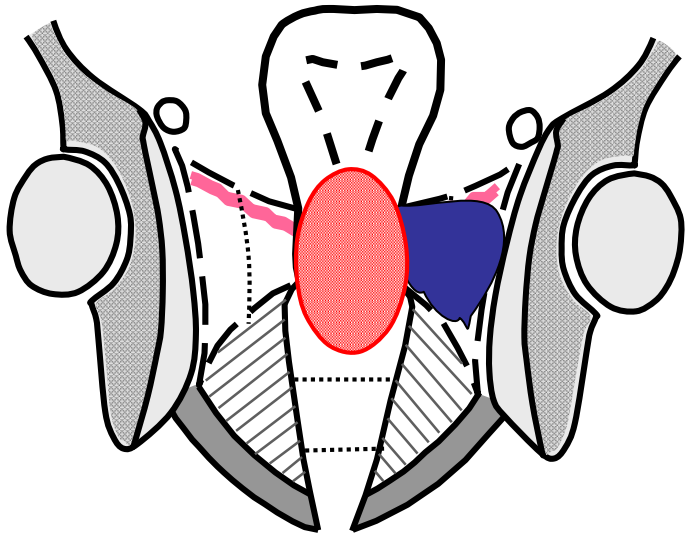




w = 6.5 cm
h = 5 cm
t = 5 cm

Vagina Involvement = 1cm



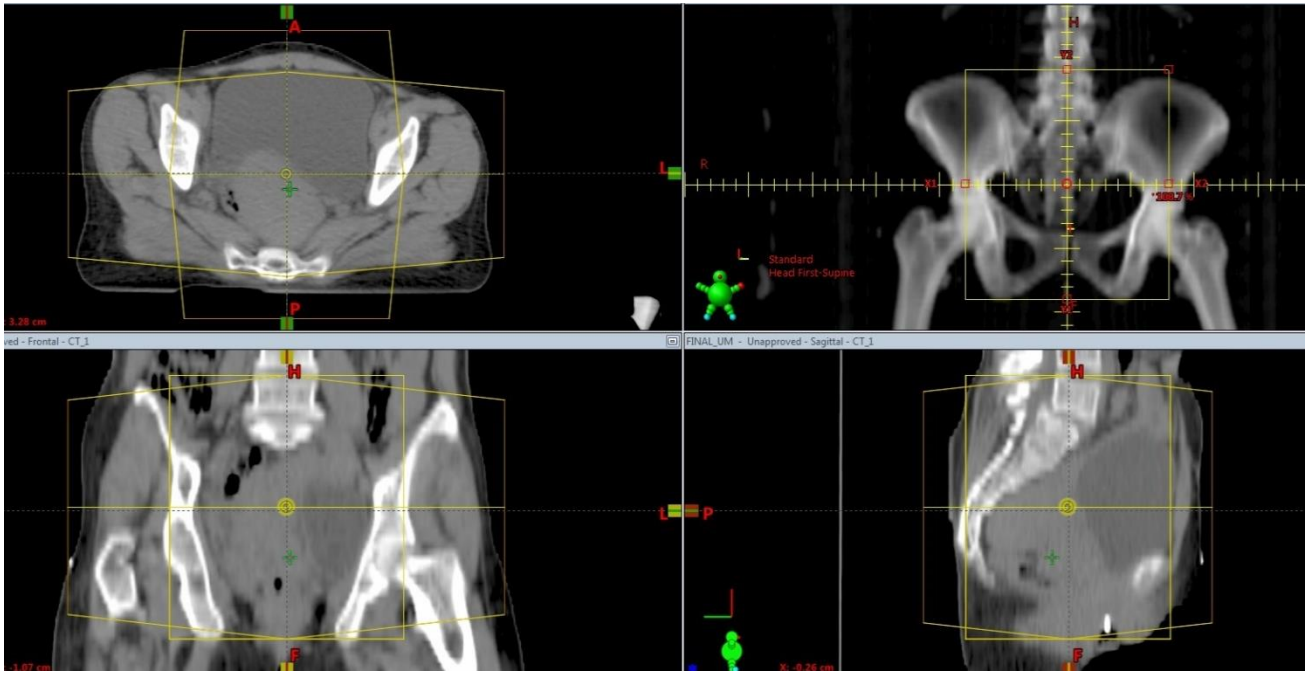


dd/mm/yy
07.11.2016

Dr Umesh
Signature

EBRT & Chemotherapy

EBRT Technique: Conventional - Box fields
TD: 50 Gy
Dose per fraction: 2 Gy
Boost: no

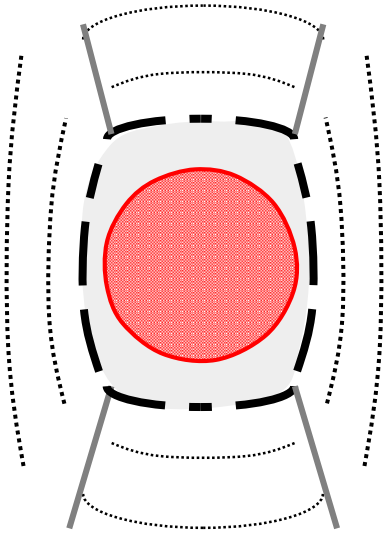


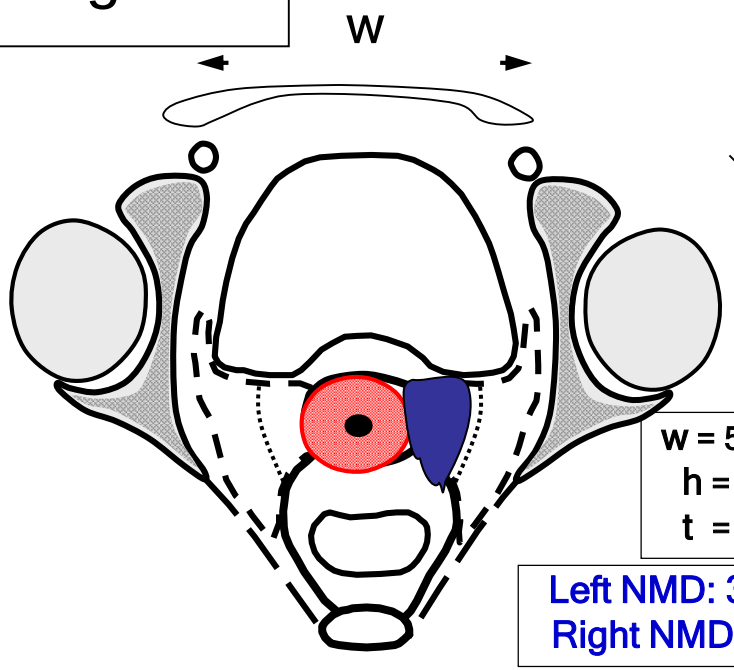
Concomitant chemotherapy:
Cisplatin 40 mg/m2 weekly, 4 cycles

Clinical Drawing

At Brachytherapy

	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

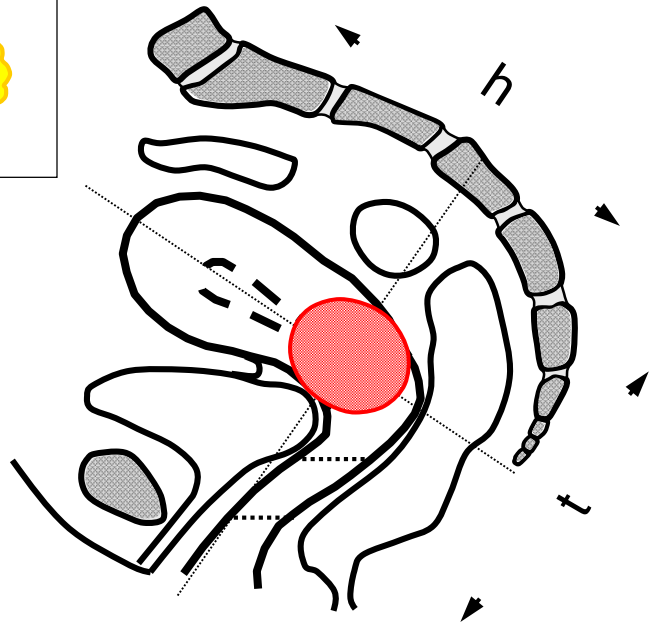


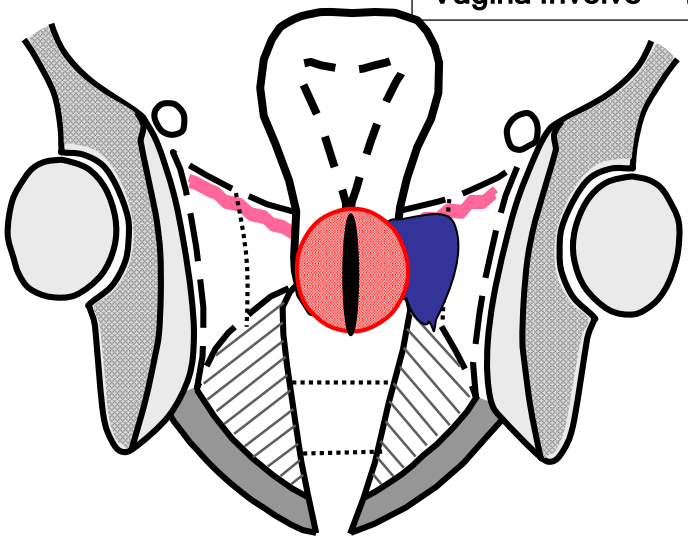


w = 5.5 cm
h = 3 cm
t = 3 cm

Left NMD: 3.5 cm
Right NMD: 2 cm

Vagina Involve = nil





dd/mm/yy
27.12.2016

Dr Umesh
Signature

Q: What are your options for optimum BT Application?

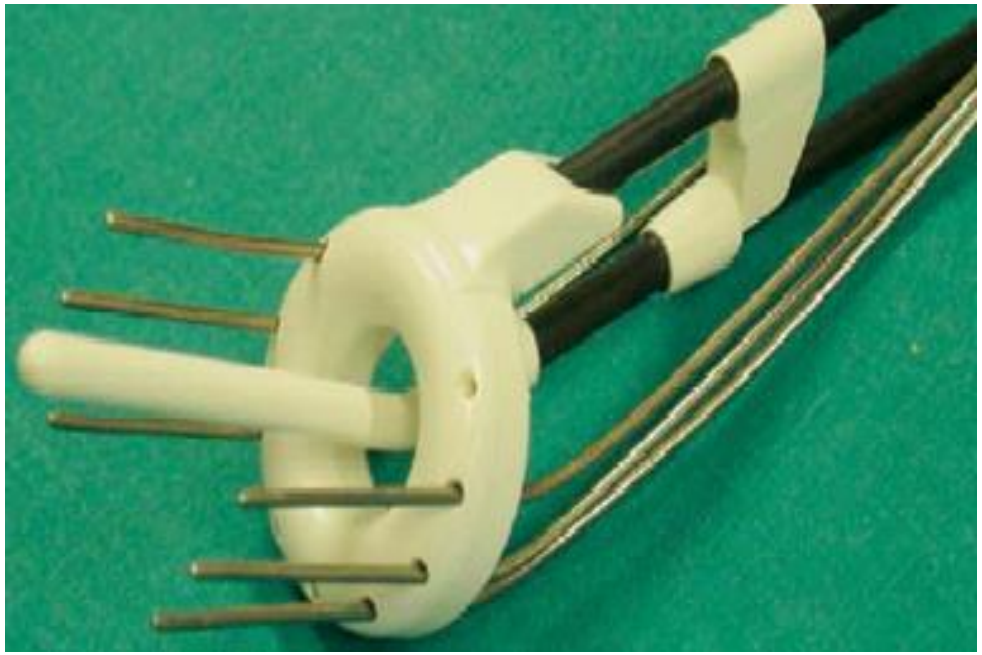
A. Tandem –ring with needles (Vienna)

B. Tandem- Ovoid with needles (Utrecht)

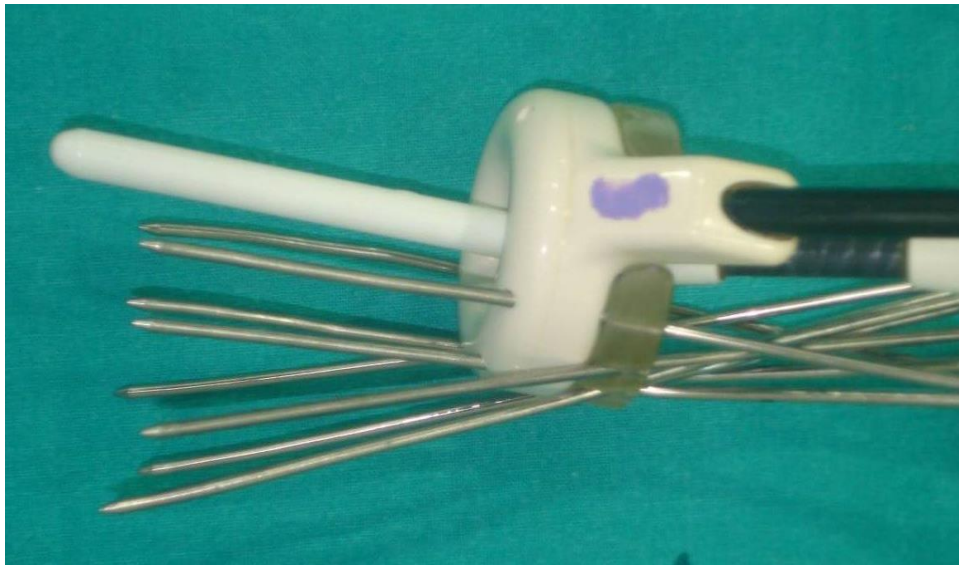
C. Perineal Template

D. Others

Applicators



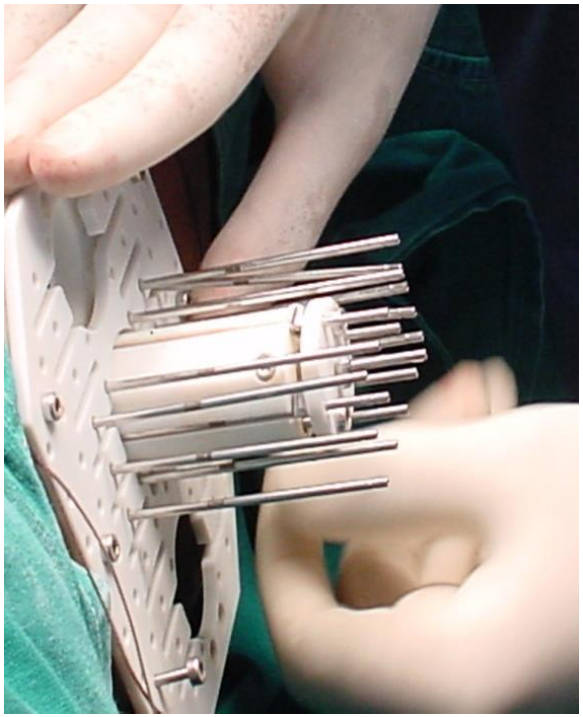
Vienna



Vienna with Additional needles

Tandem - Ovoid with tubes

MUPIT



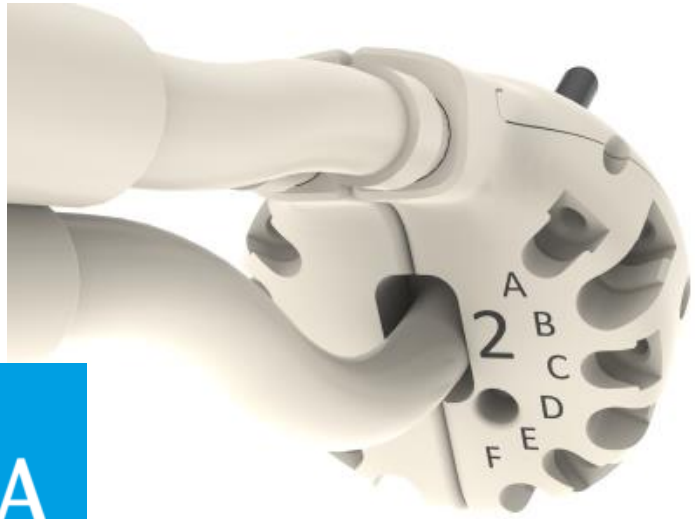
BT APPLICATION PRACTICE

IC + IS APPLICATION

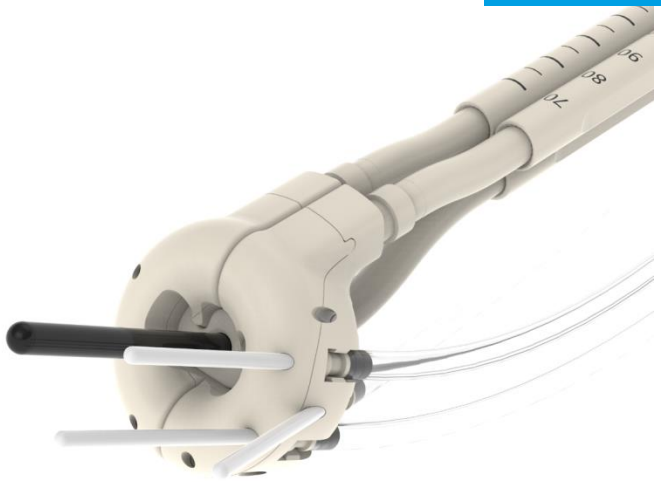
DURATION: 75 MINUTES

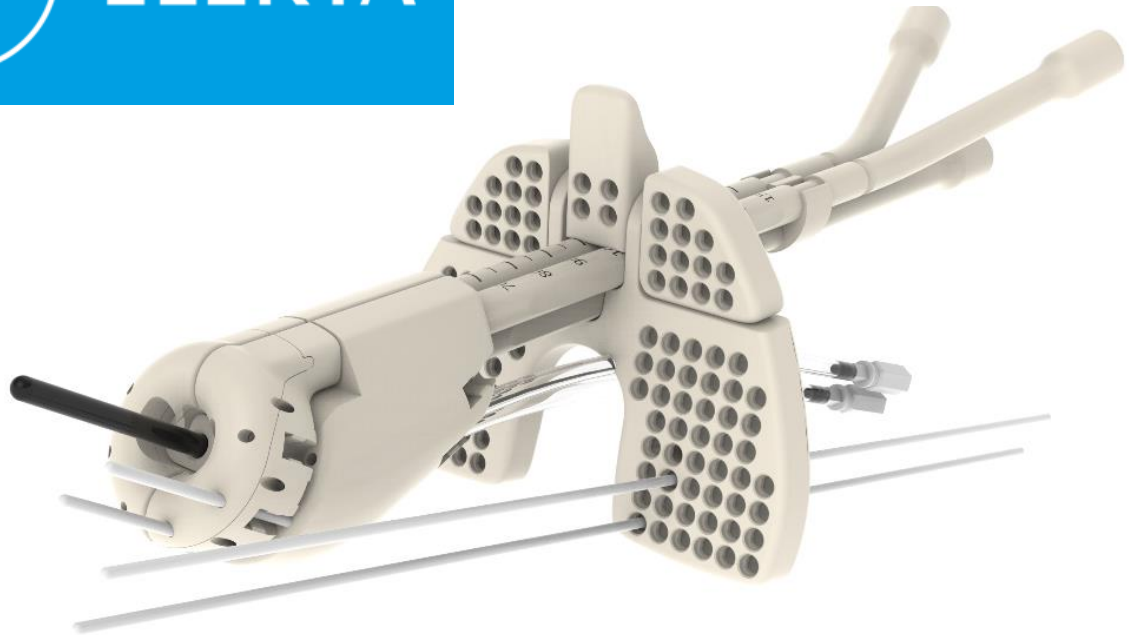
Latest Development in Applicators

VENEZIA GYN APPLICATOR

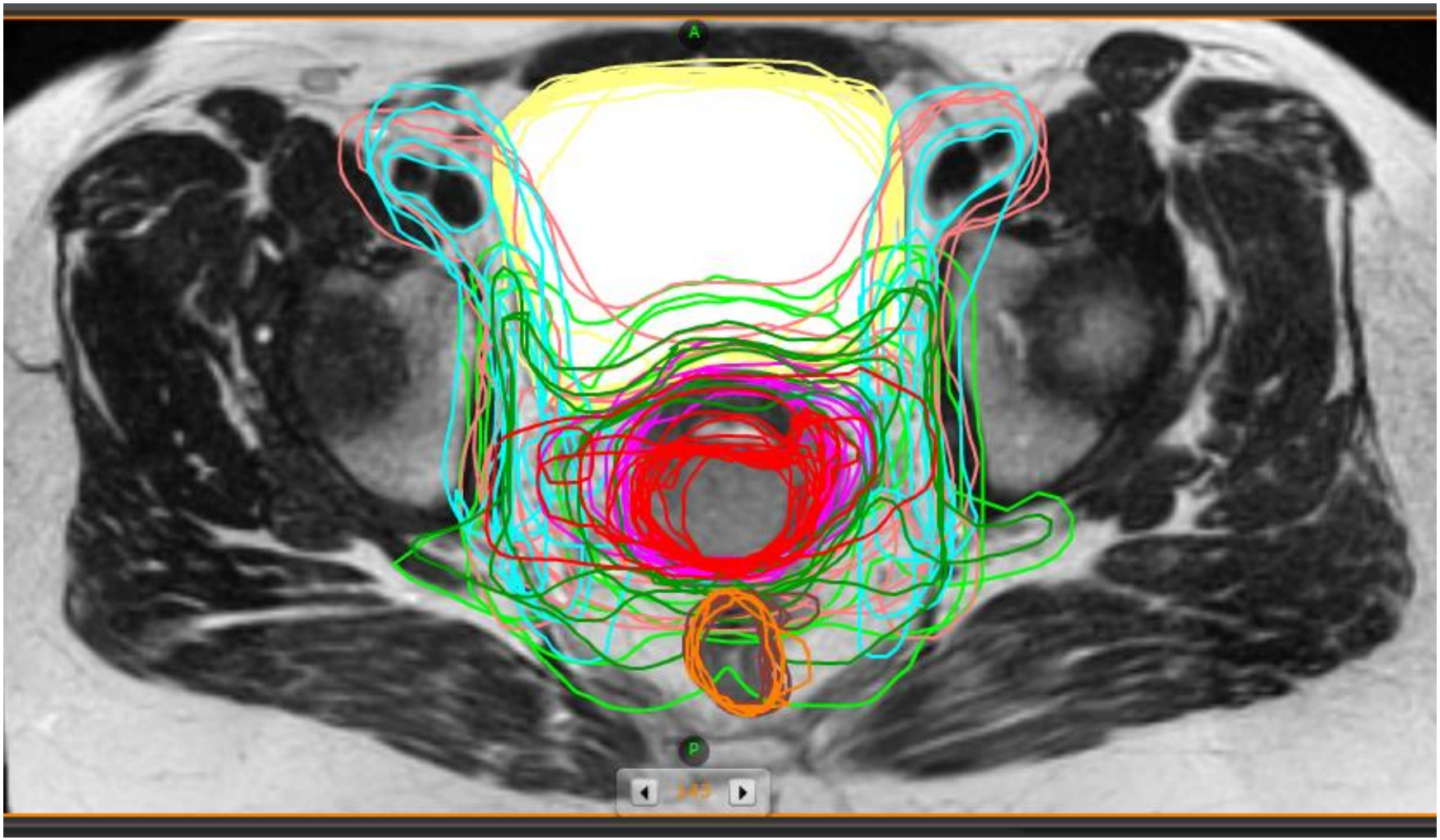


ELEKTA

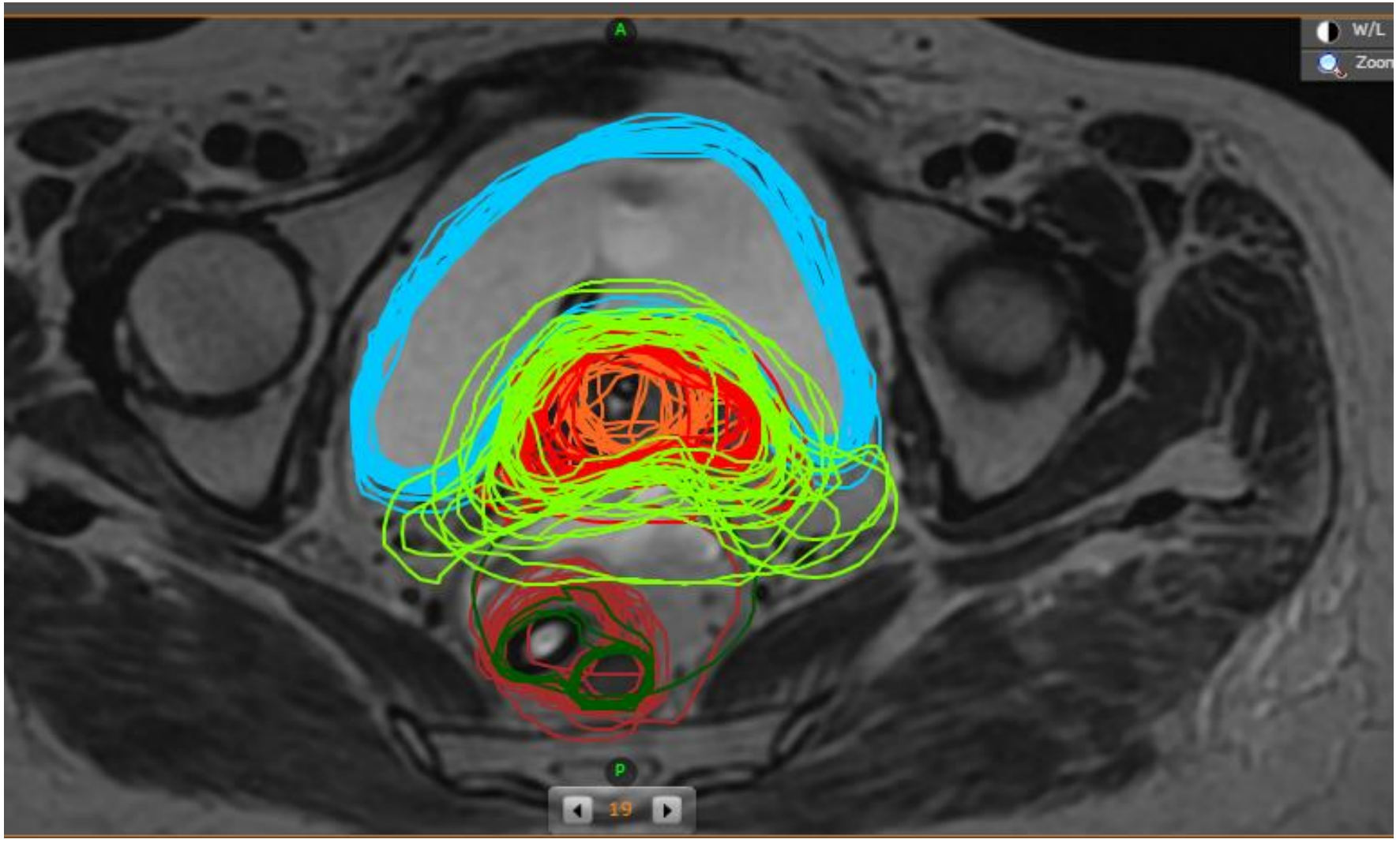




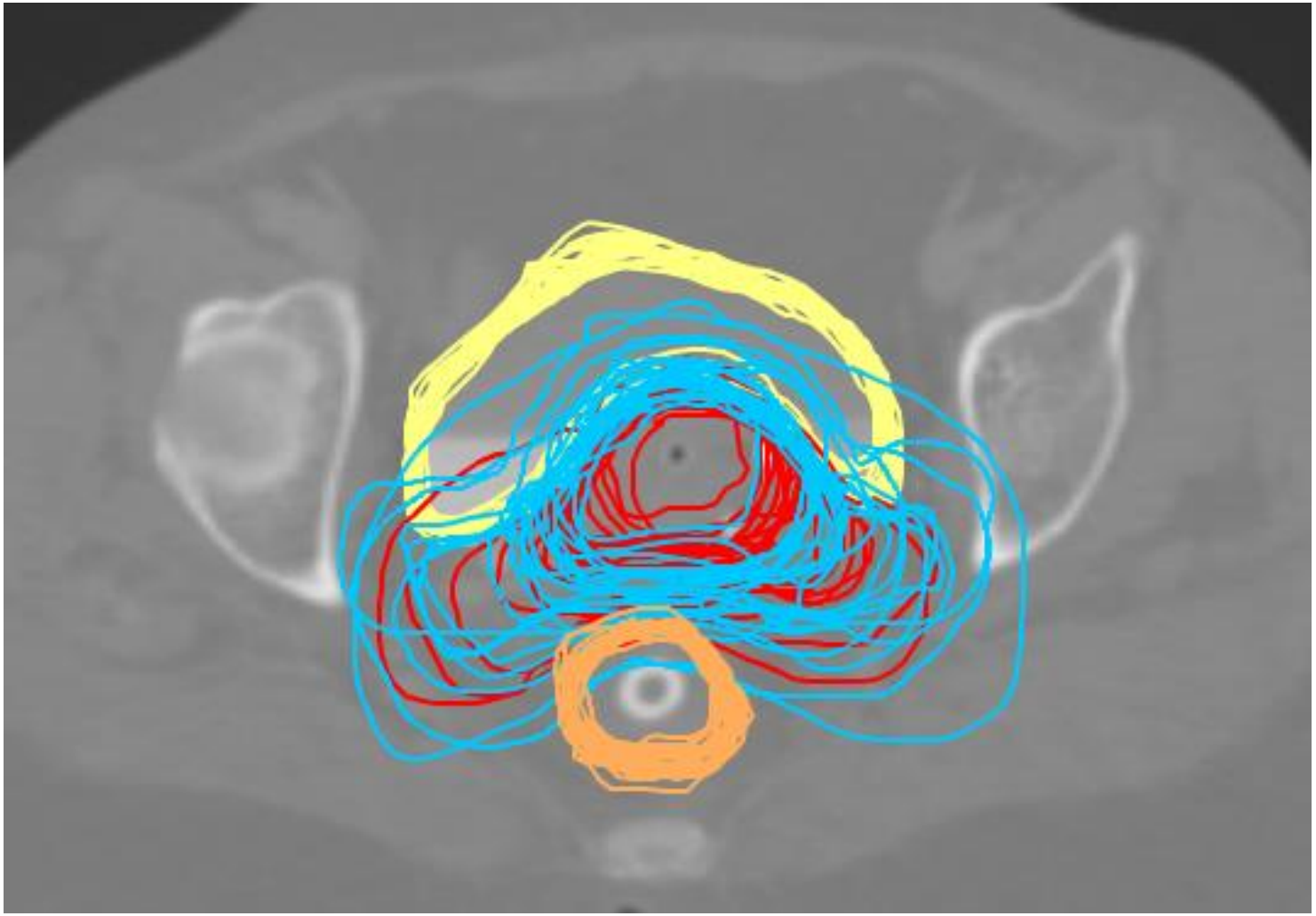
EBRT WORKSHOP
Day 1
20 contours only



Home work
MR Based Contouring
22 contours only



Home work
CT Based Contouring
25 contours only



Gyn GEC ESTRO recommendations

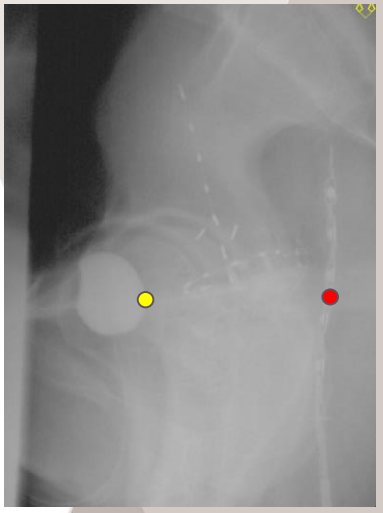
GTV, CTVs :

- at time of diagnosis
- at time of brachytherapy

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Brachytherapy evolution in prescription

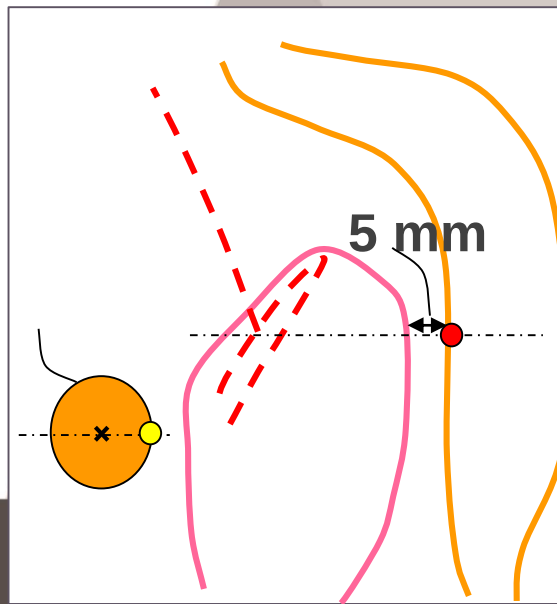
- 2D era : dose prescription based on X-rays and « systems »:
  - mg/h of radium or TRAK
  - mainly to point A
  - or to a reference volume



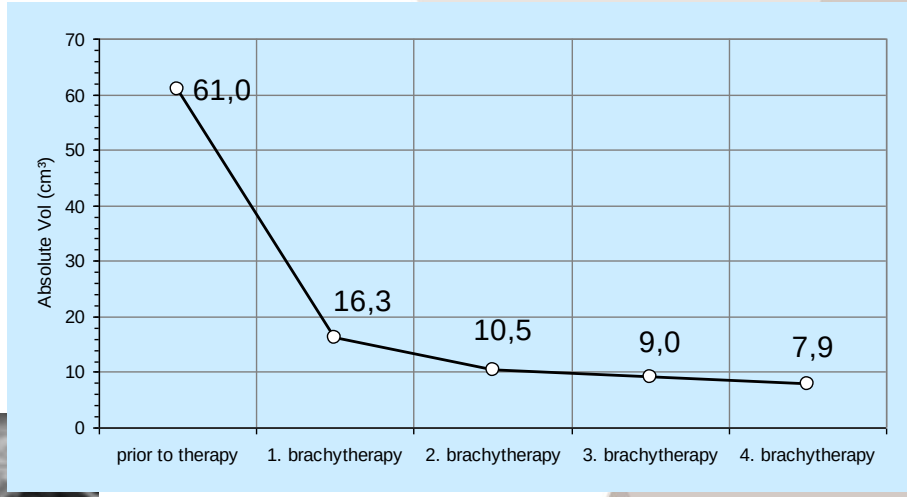
- Introduction of 3D-images
  - prescription to a target volume

To apply to uterovaginal brachytherapy

common language



Adaptive MRI based planning concept



Dimopoulos et al. IJROBP 2006

GEC-ESTRO volume concept

Within GEC-ESTRO, 3 teams coming from different traditions :

- Leuven : ovoid / mould PDR / point A
- Vienna : ring / HDR / point A
- Paris : mould / LDR / PDR / reference / volume

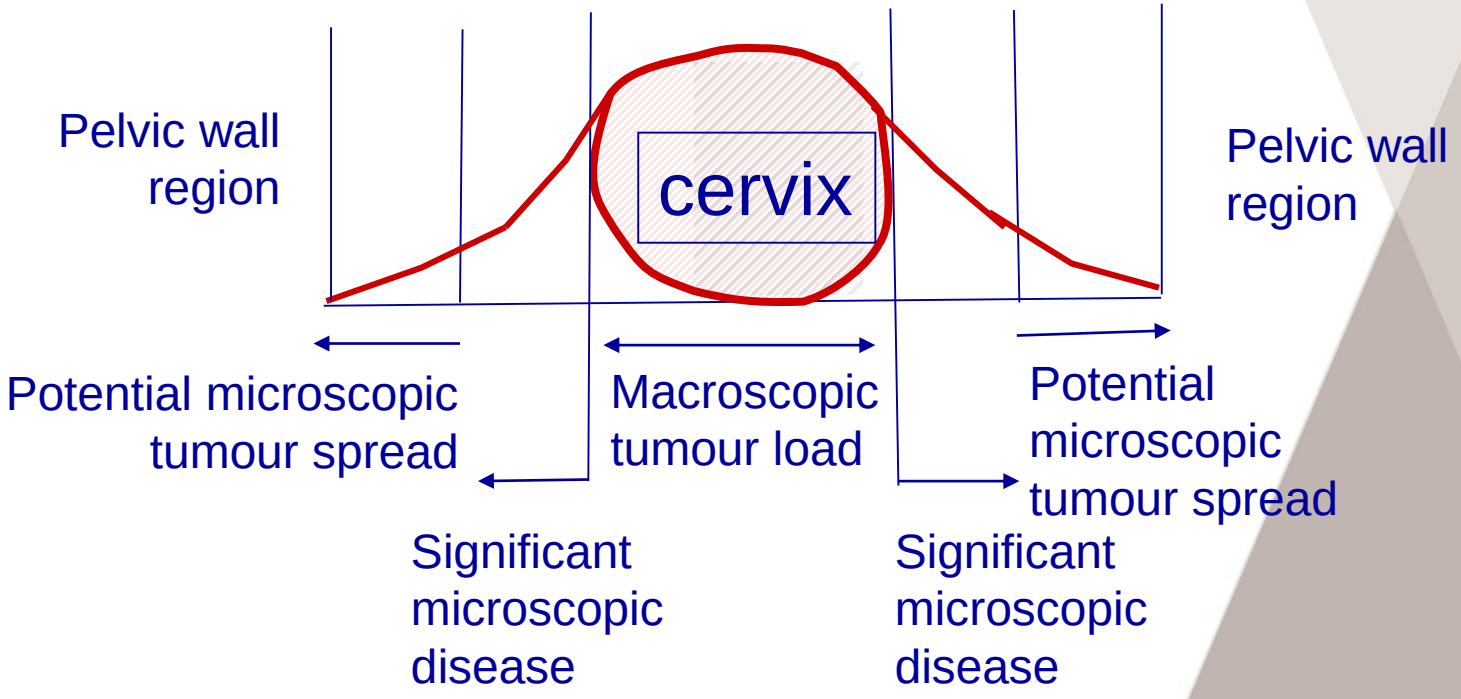
Principles for MRI based Cervix BT

Delineation of GTV, PTV and OAR
in relation to the applicator

- **MRI compatible applicators**
- **Specific investigation protocols**
  - **Quality of images**
- **Image acquisition: orientation**
- **Accuracy of Images (QA)**

Target volume concepts

Cancer cell density
in 3 different target volumes



Target volume concepts

Target definition

2 CTVs

A first target related to the extent of GTV **at time of BT**:
corresponding to residual disease
with a high dose prescribed to this target (80-90 Gy)
High risk CTV

A second target related to the extent of GTV **at diagnosis** :
with an intermediate dose prescribed to this target (60 Gy)
Intermediate risk CTV

Target volume concepts

HR CTV :

- GTV **at the time of BT**
- CTV if complete response : limited to cervix
- CTV if incomplete response : cervix plus adjacent structures with presumed residual disease - assessed by both clinical examination and imaging (~30-60 cc)
- Intent : 85 to 90 + Gy total dose to CTV in definitive radiotherapy in advanced disease
- Dose comparable with dose to point A

Target volume concepts

High Risk CTV :

GTV at time of brachytherapy

In all cases includes:

- Whole cervix
- Presumed tumour extension assessed by:
- Clinical assessment
- Residual grey zones on MRI

NO SAFETY MARGINS

AIM : DOSE HIGH ENOUGH TO STERILIZE MACROSCOPIC TUMOUR

Target volume concepts

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)

Target volume concepts

Intermediate Risk CTV :

GTV at time of diagnosis

In all cases includes:

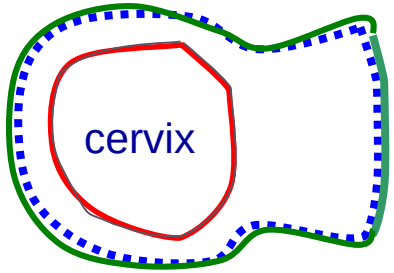
- HR-CTV
- integrates initial CTV

SAFETY MARGINS :
1-1.5 cm cranially
0.5cm antero-posteriorly
1cm laterally

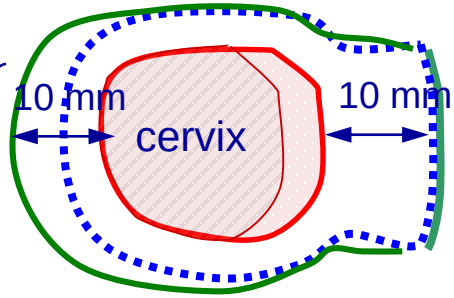
AIM : TO STERILIZE MICROSCOPIC TUMOUR

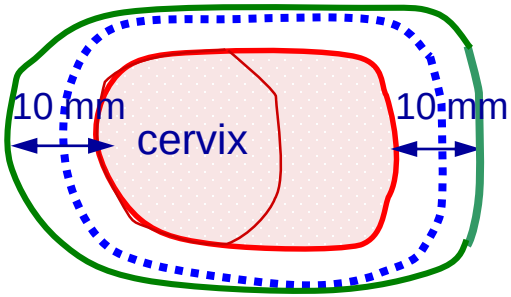
CTV BT

Complete remission

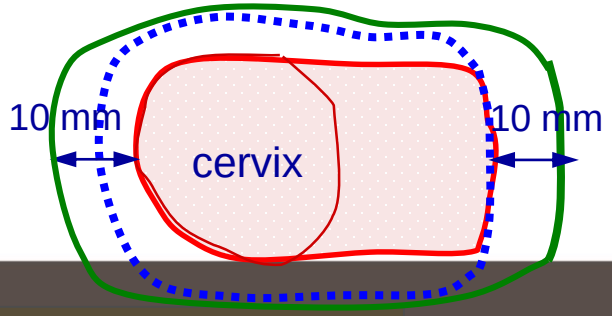


Partial remission





Stable disease



Legend

HR-CTV

IR-CTV

Initial tumour extension (at diagnosis)

Residual disease

Turning point

Question n° 1: HR-CTV includes:

1. at least the whole cervix
2. the whole cervix + safety margins
3. the whole uterus + safety margins
4. the totality of the initial tumor extension

Turning point

Question n° 2 : IR-CTV includes:

1. the initial tumor size and extension plus safety margins
2. the whole uterus + safety margins
3. HR-CTV plus safety margins taking the initial tumor extension into account

Patient n° 1

Mrs Odette TAM…
56 year-old
WHO=0, 70 kg, 1m69

Vaginal bleeding

Biopsy: moderately differentiated squamous cell carcinoma

Stage IB1 : initial clinical examination

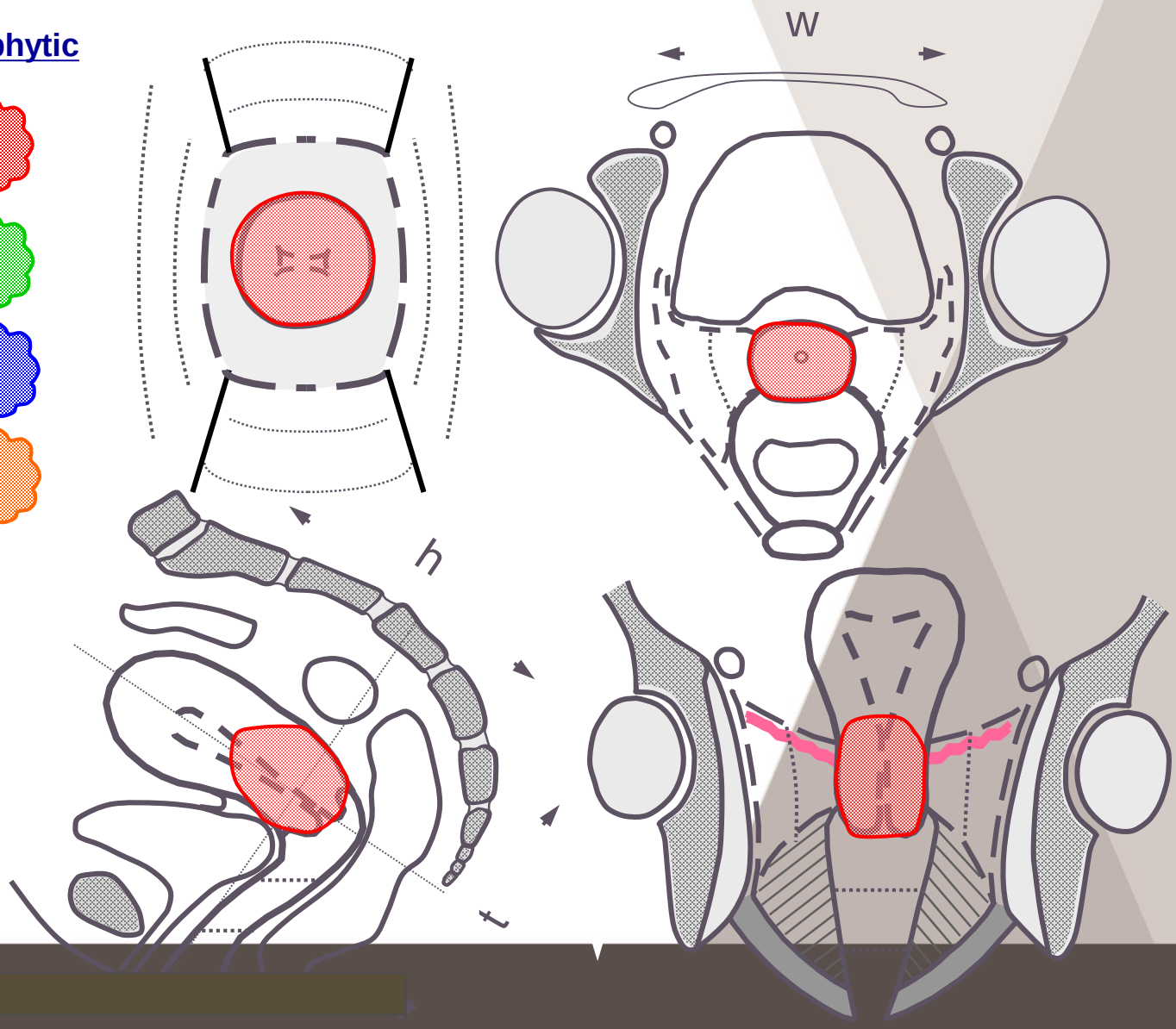
	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

Dimensions (cm):

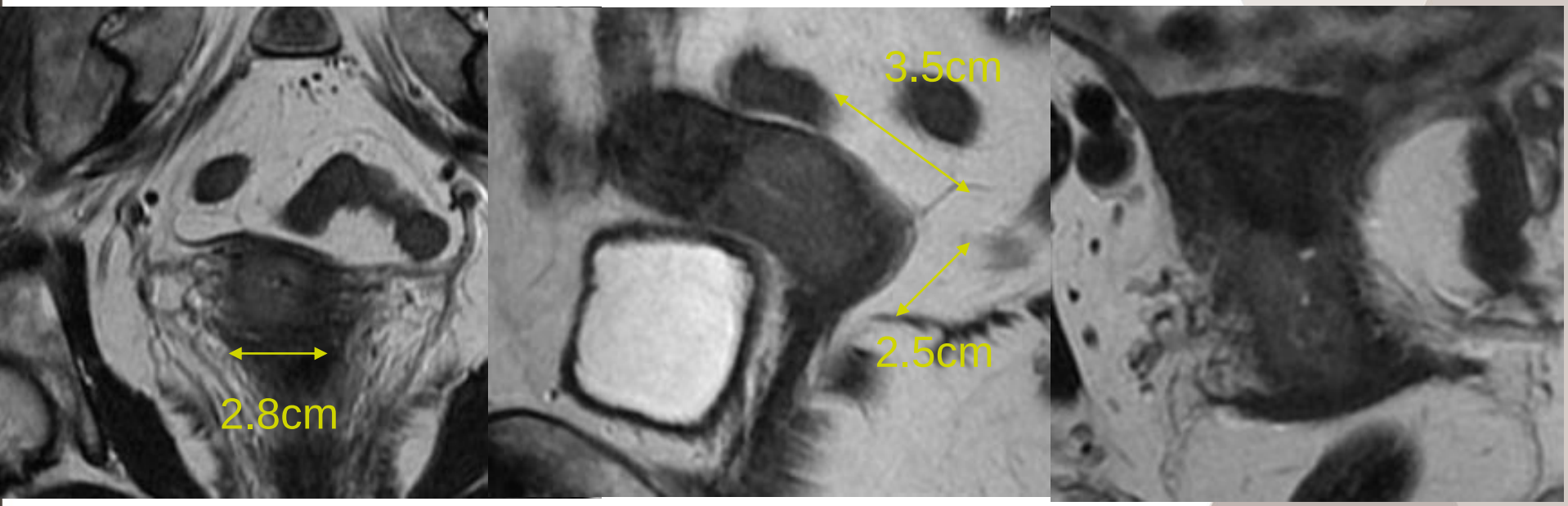
Width : 3

Thickness : 2.5

Height : 3



Stage IB1



Stage IB1 : at the time of brachytherapy

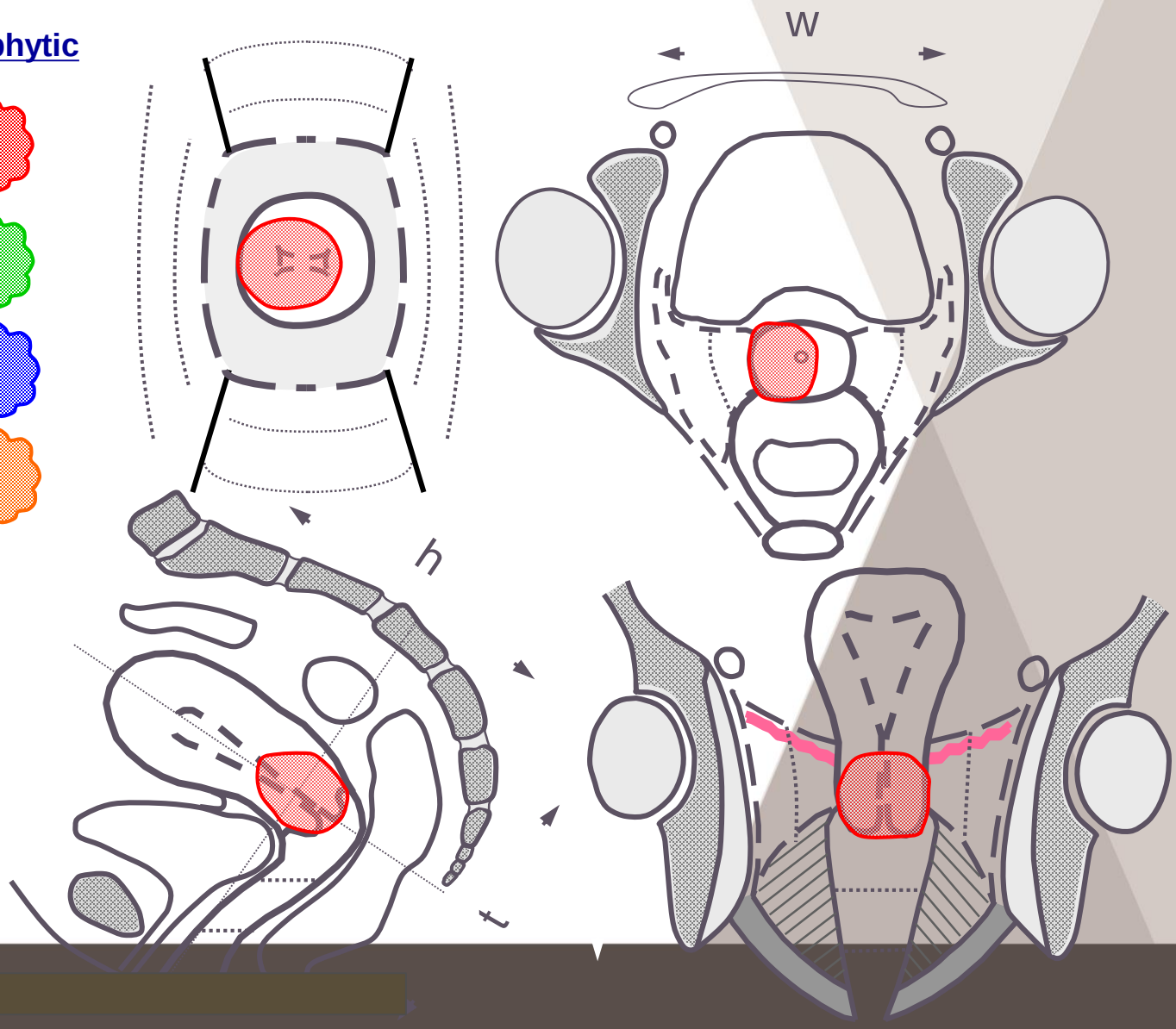
	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

Dimensions (cm):

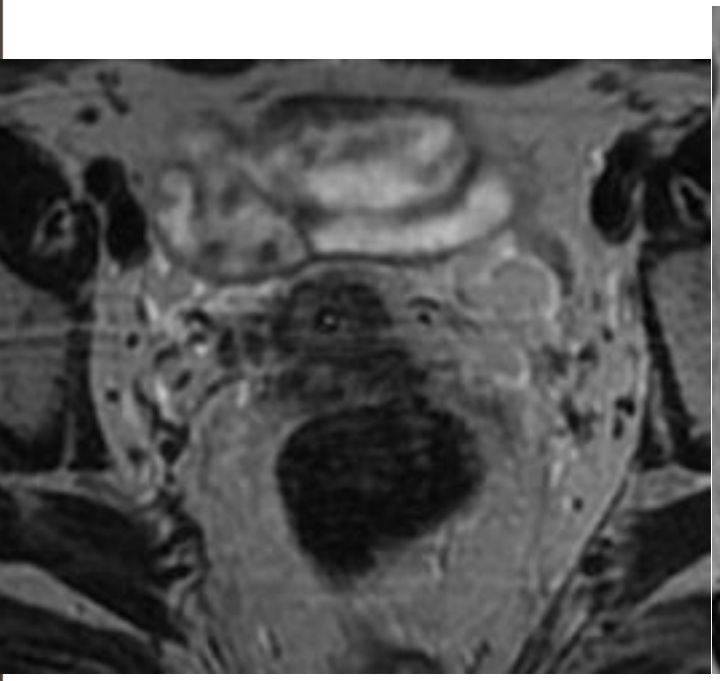
Width : 1.5

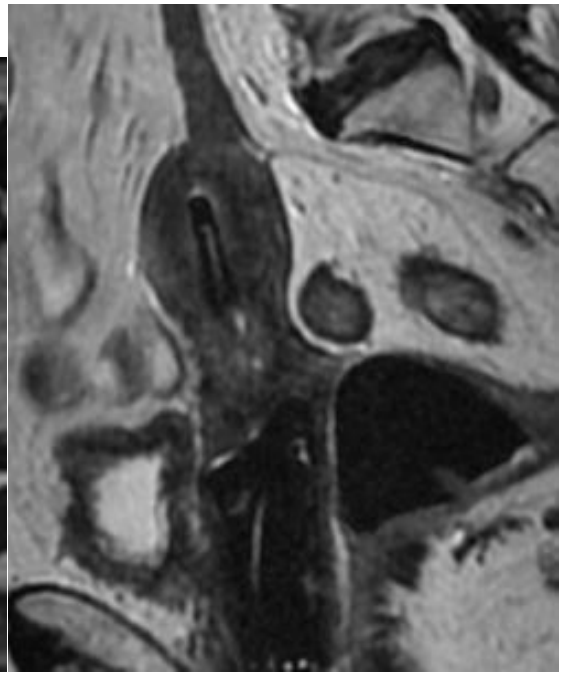
Thickness : 2

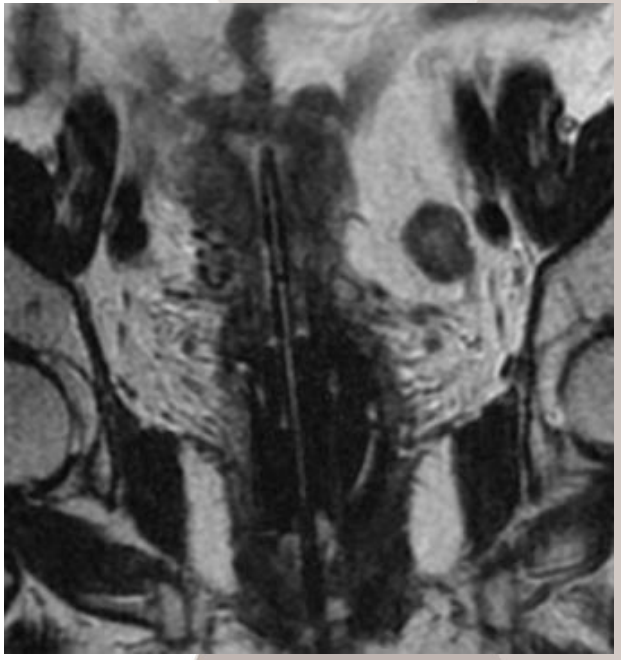
Height : 1.5



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

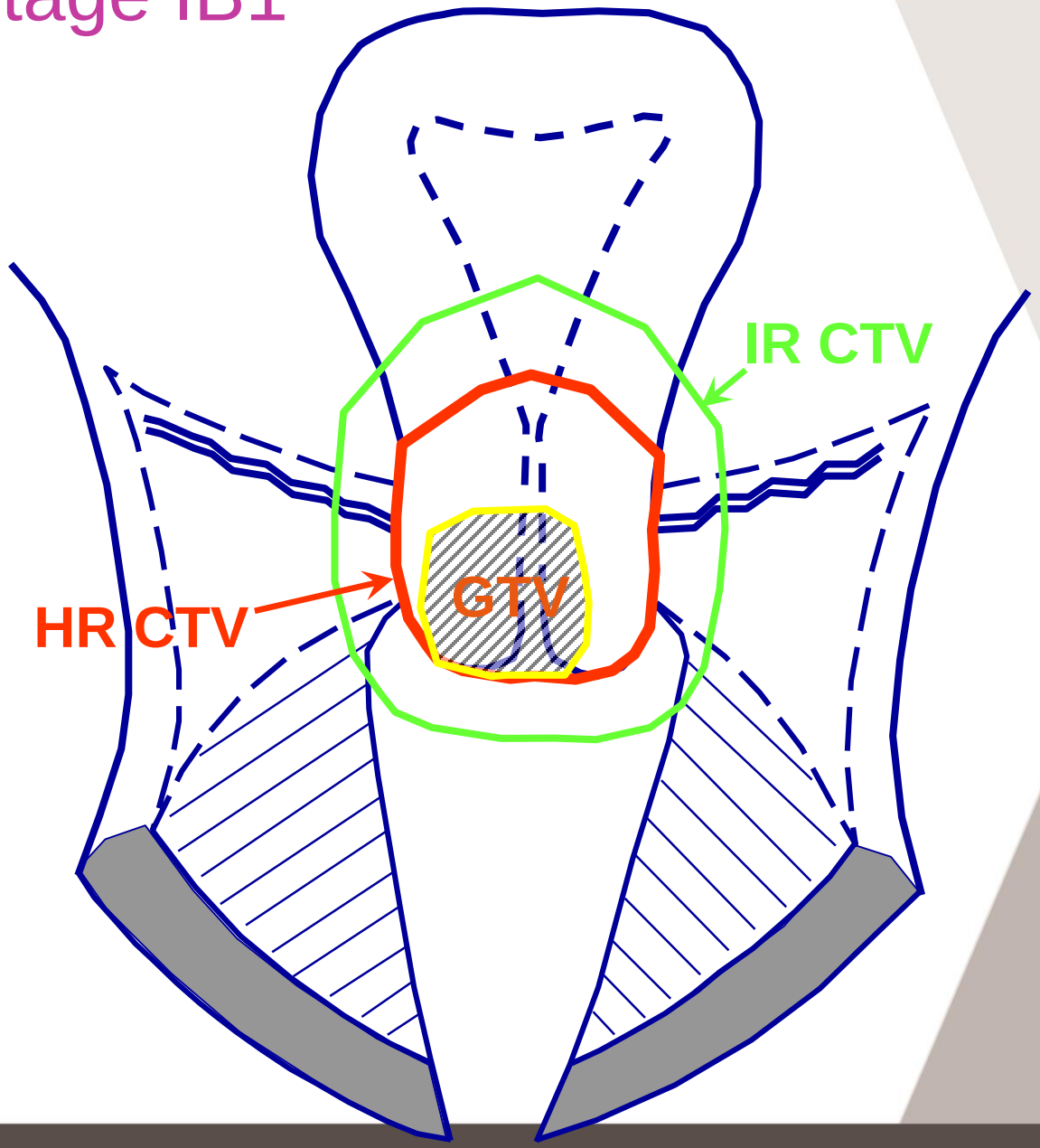
Intermediate Risk CTV :

GTV at time of diagnosis
In all cases includes:

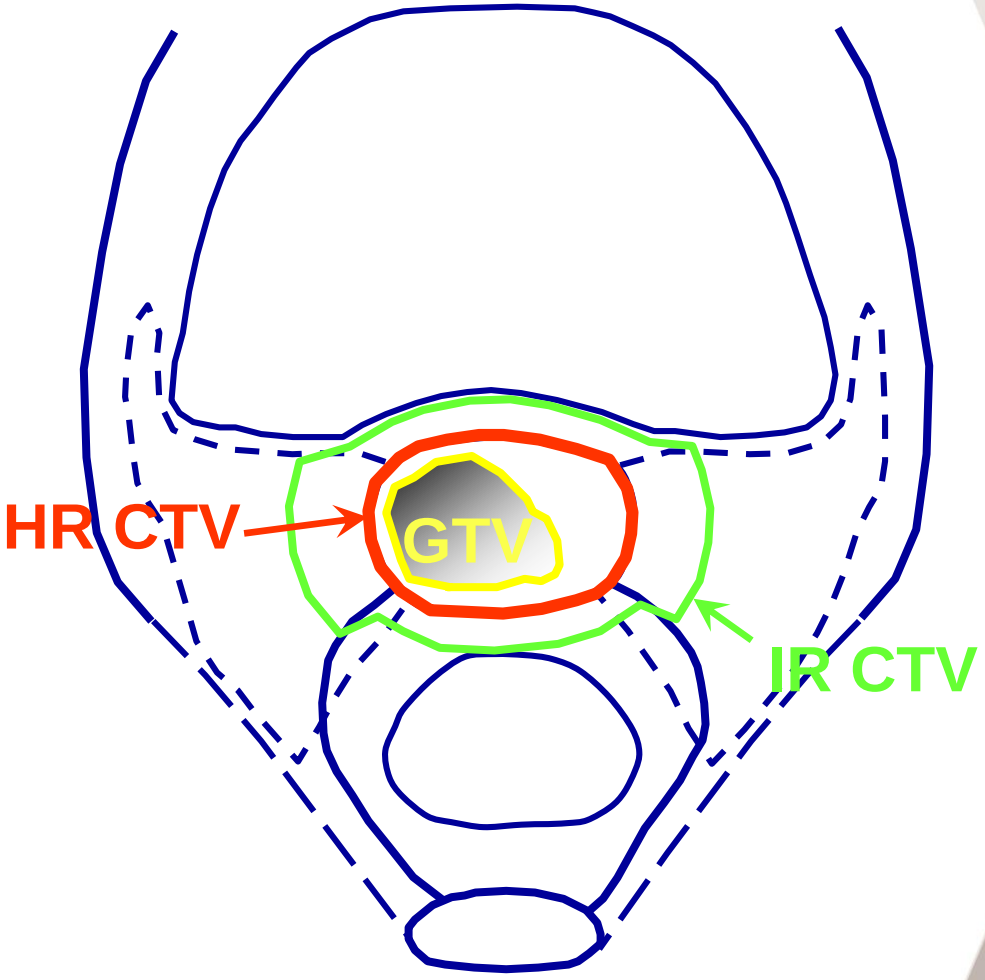
- HR-CTV
- integrates initial CTV

SAFETY MARGINS :
1-1.5 cm cranially
0.5cm antero-posteriorly
1cm laterally

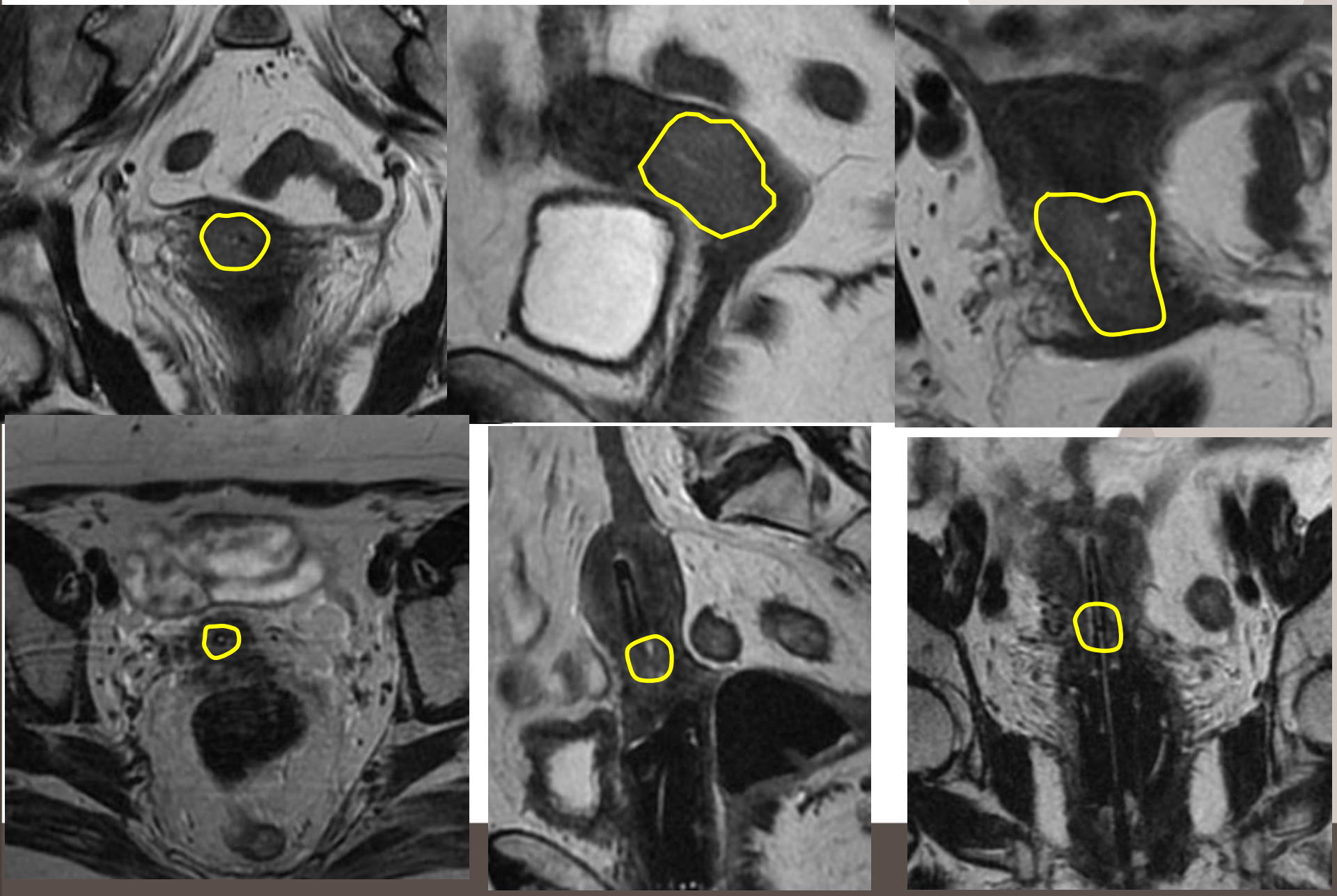
Stage IB1



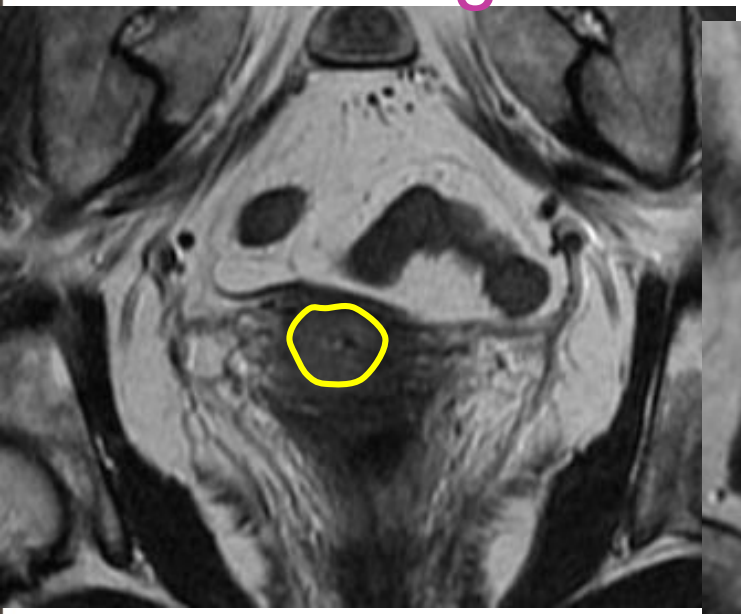
Stage IB1

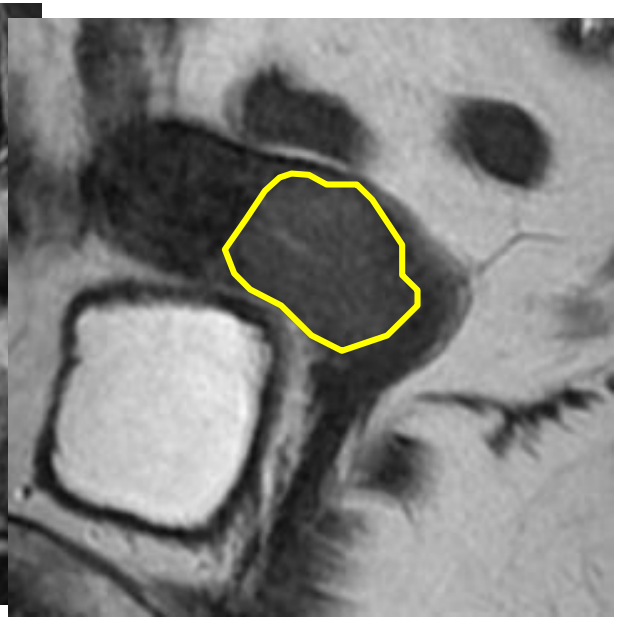


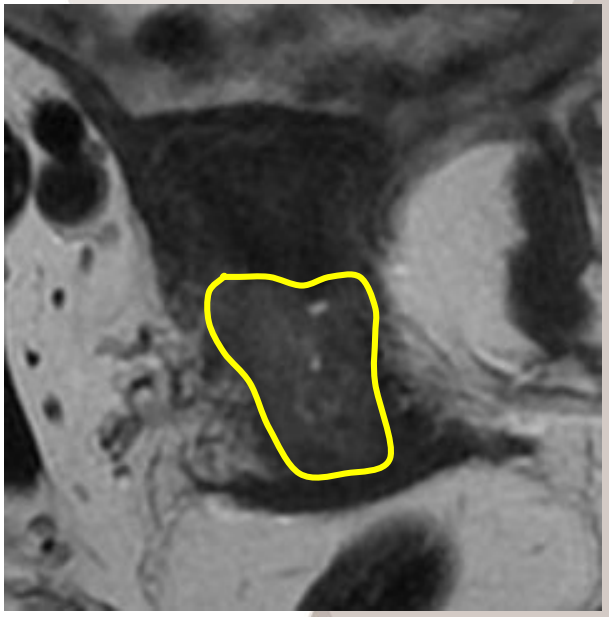
Stage IB1

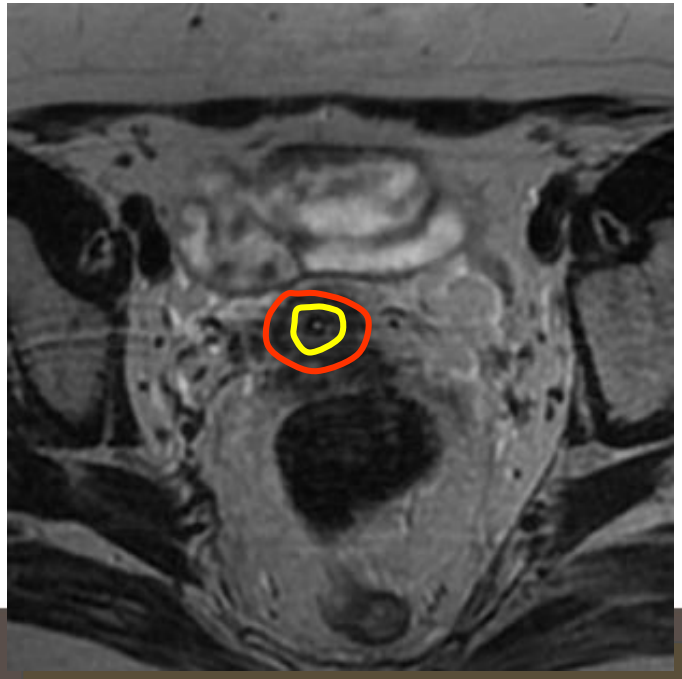


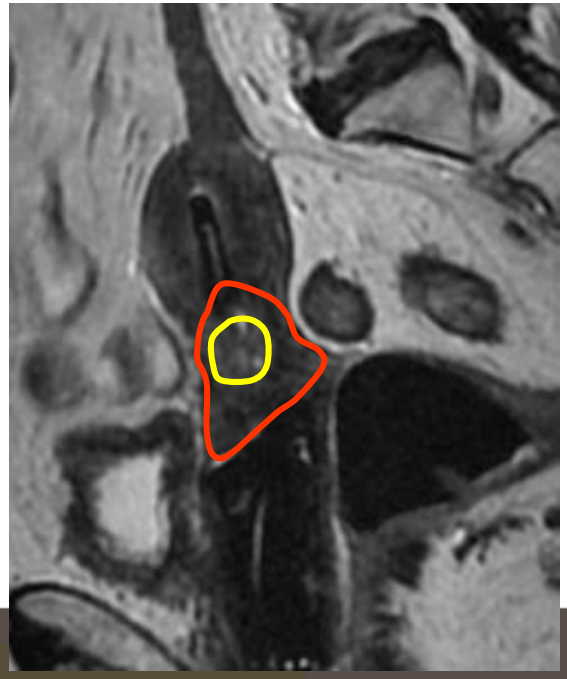
Stage IB1

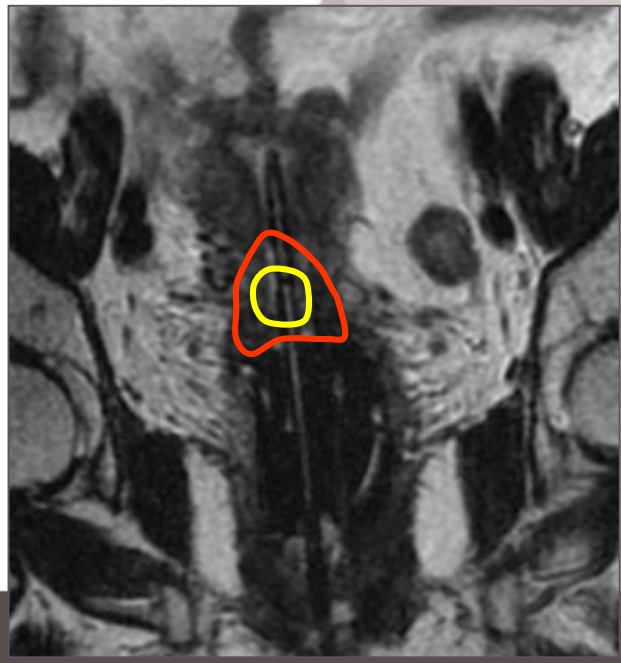




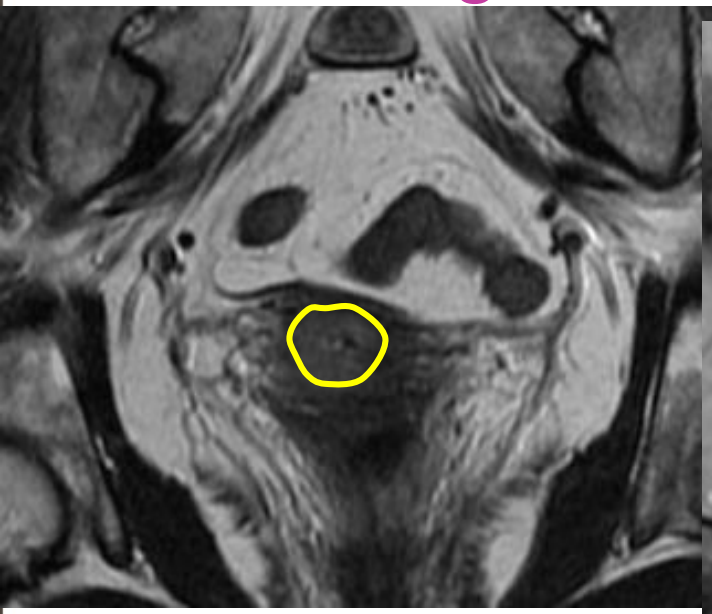


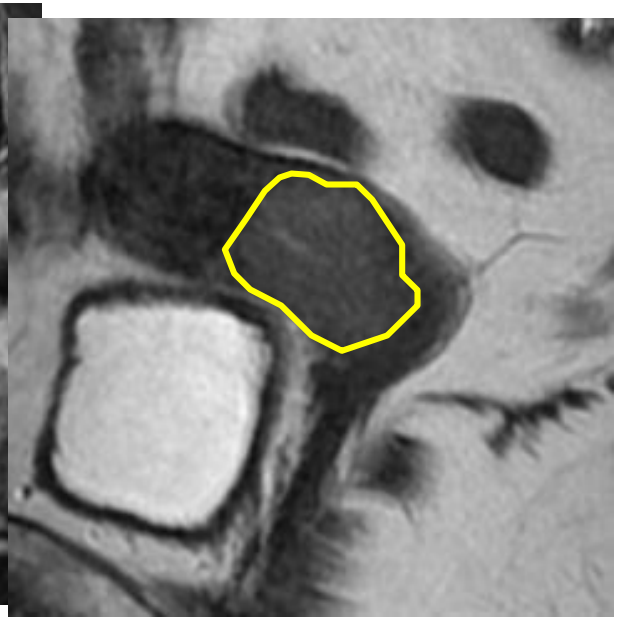


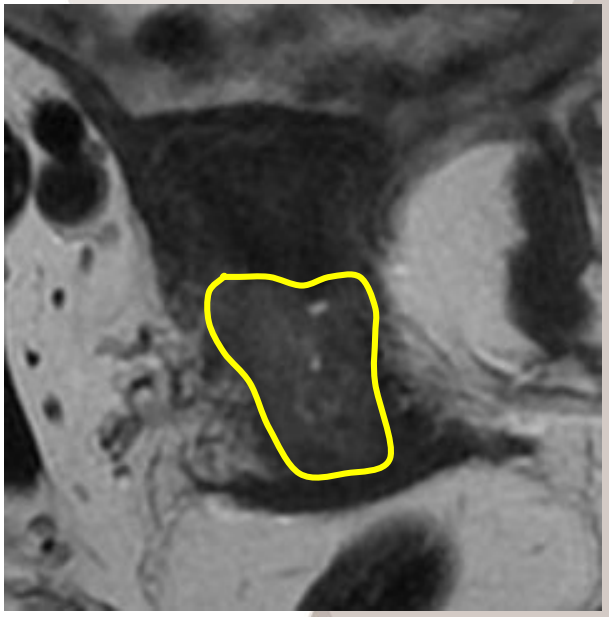


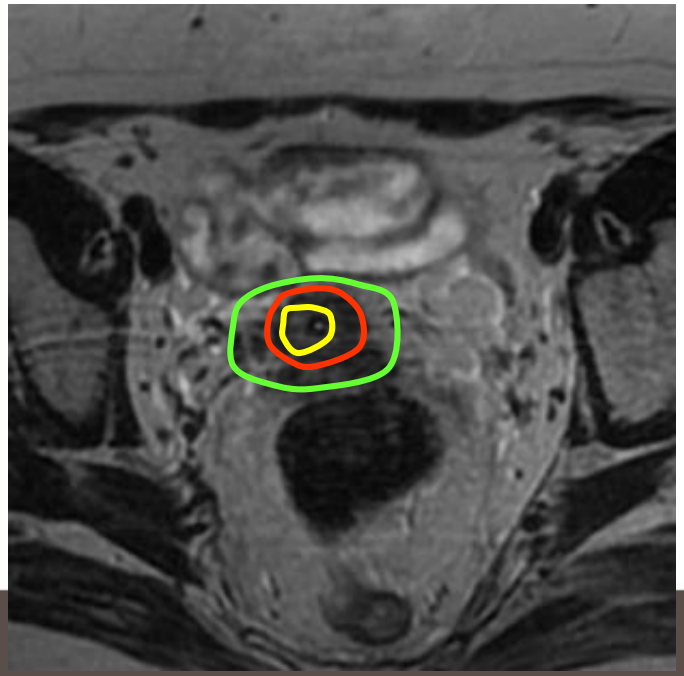


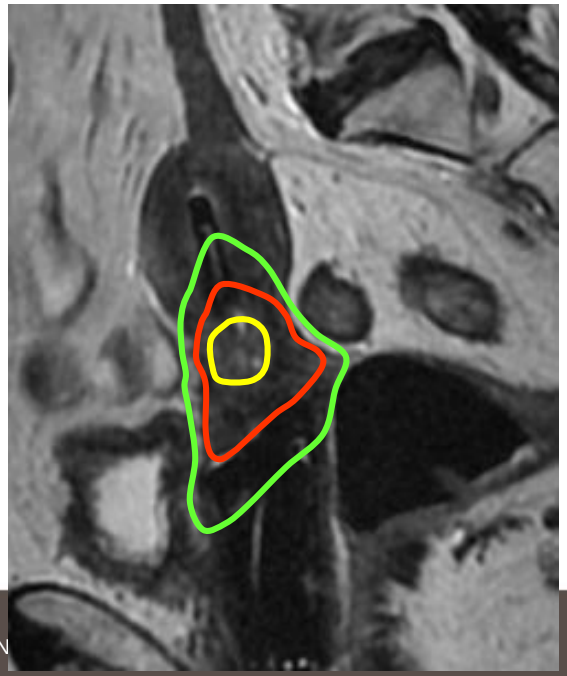
Stage IB1

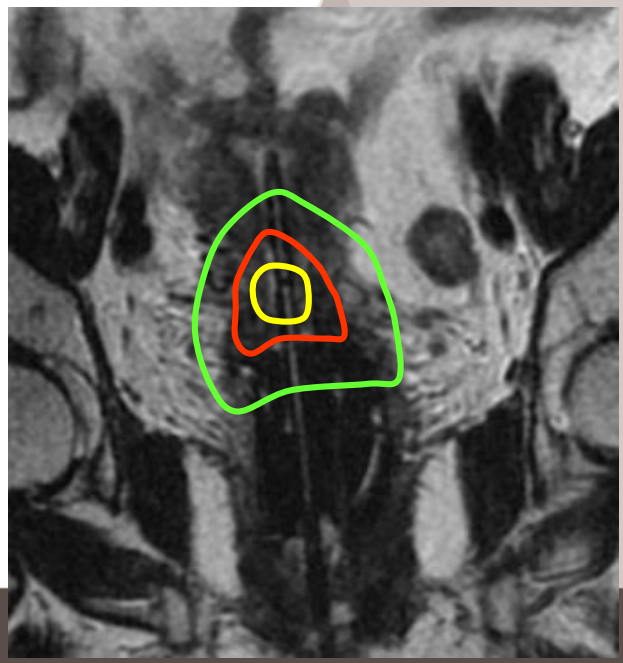












Patient n° 2

Mrs Valérie 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

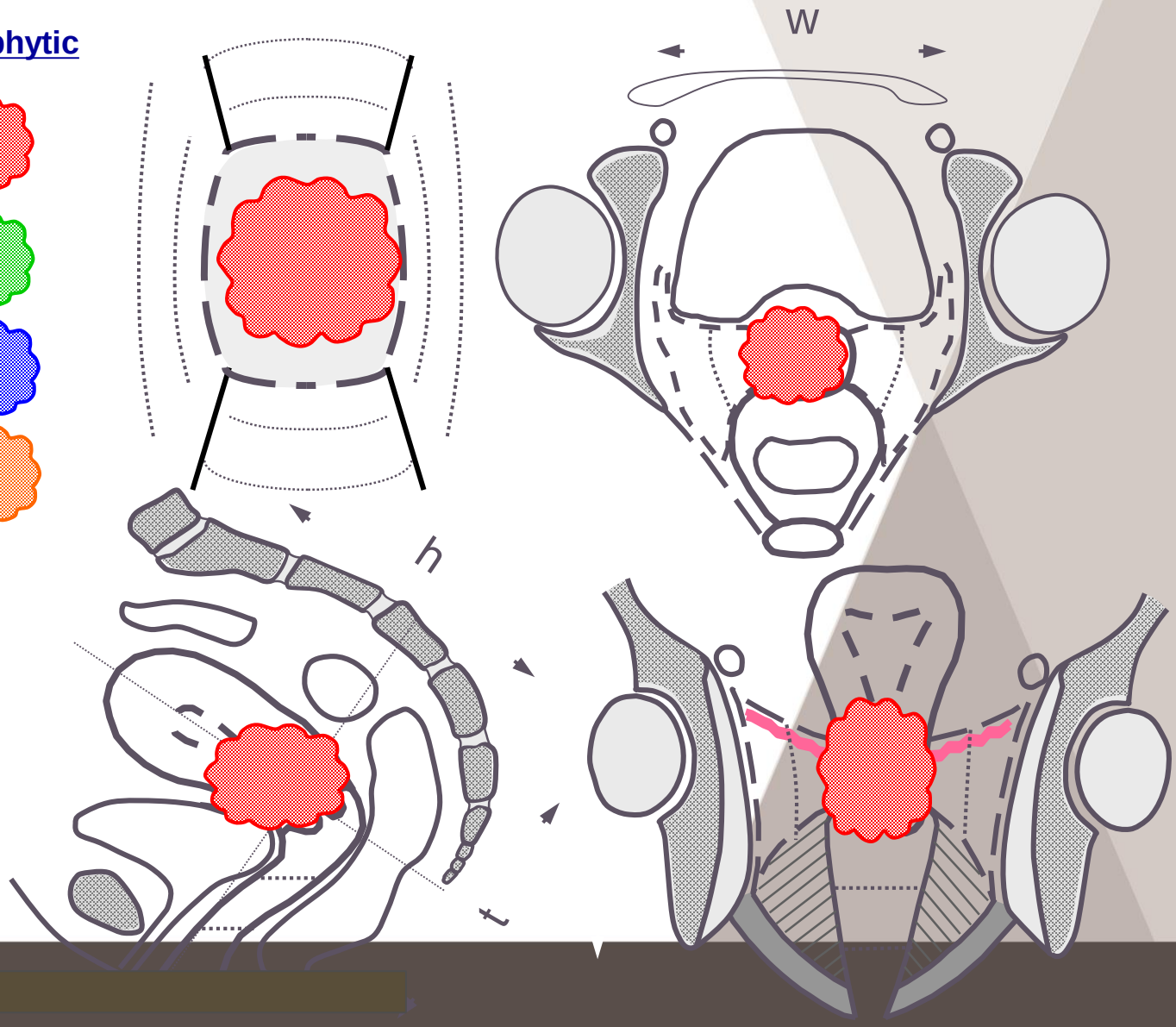
	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

Dimensions (cm):

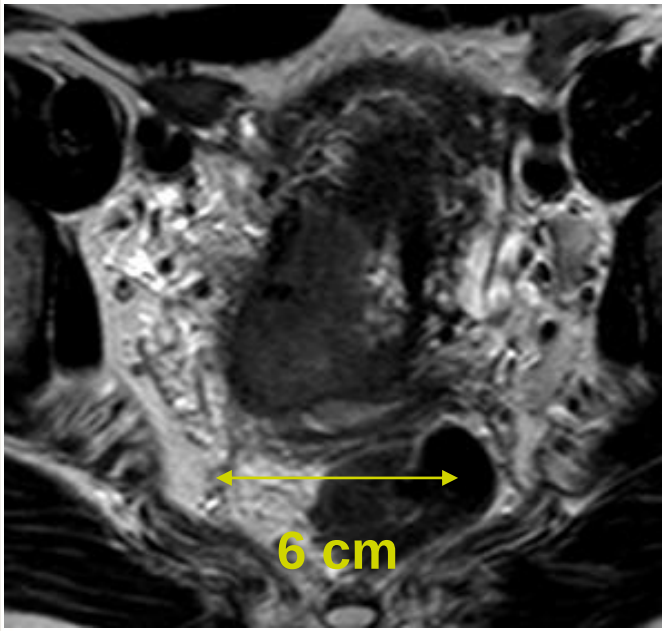
Width : 6

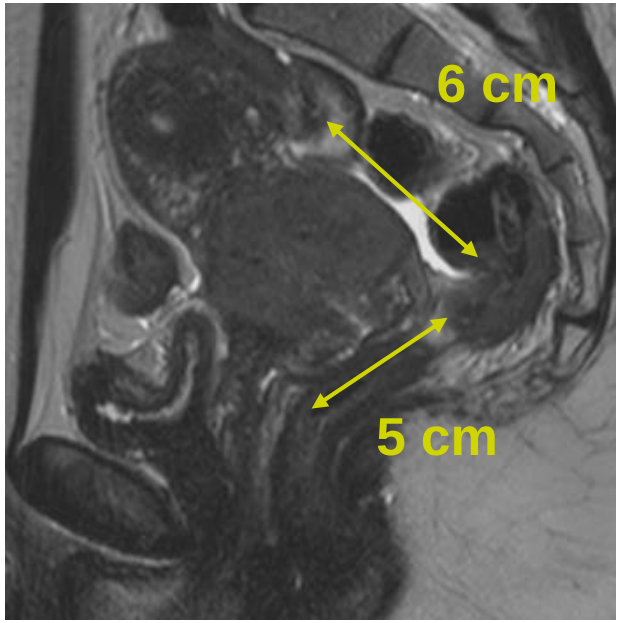
Thickness : 5

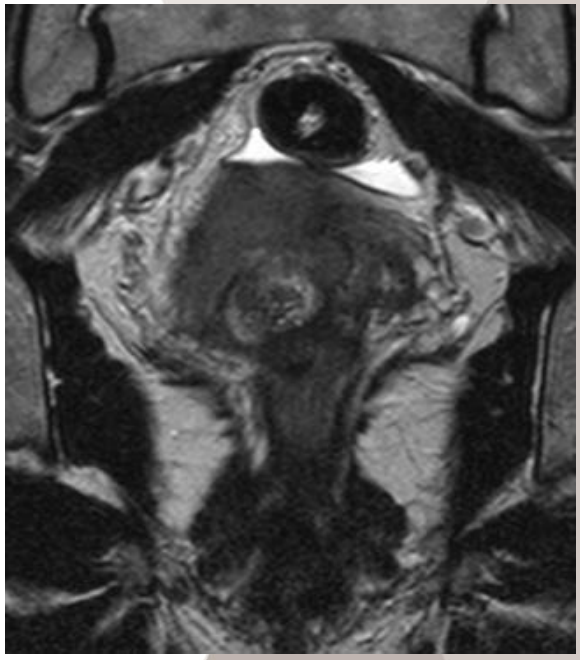
Height : 5



Stage IB2 : initial MRI







Stage IB2 : at the time of brachytherapy

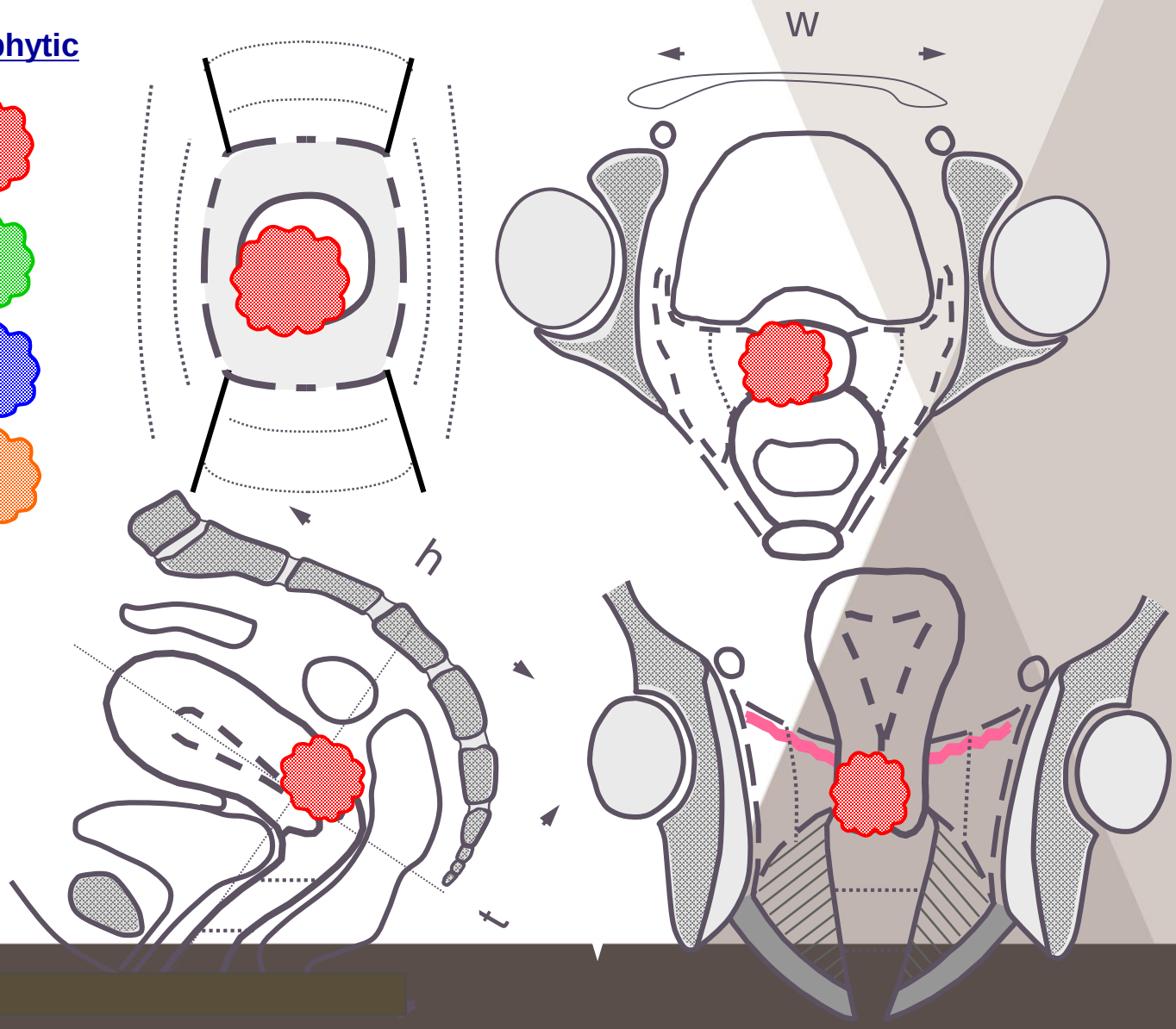
	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

Dimensions (cm):

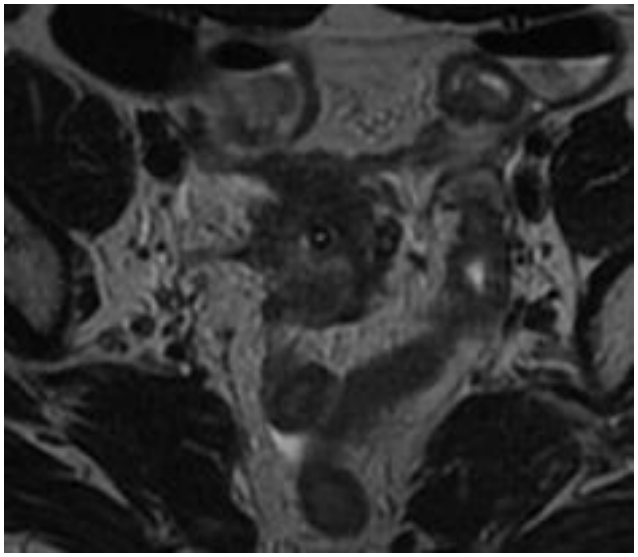
Width : 2.5

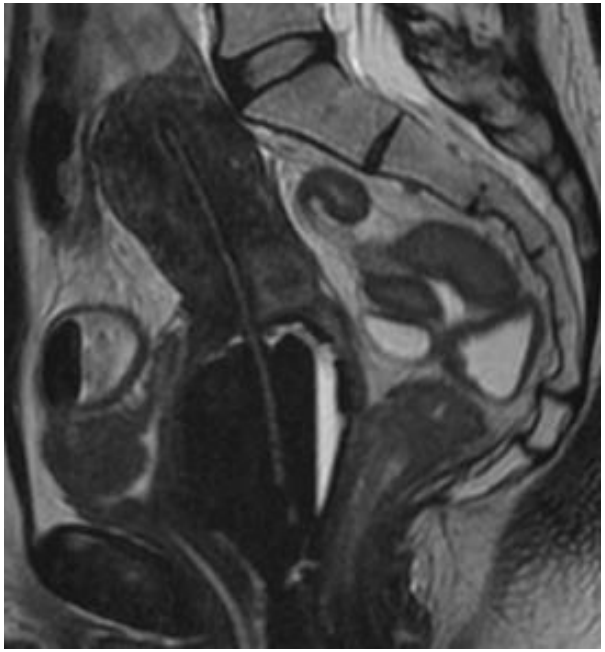
Thickness : 2

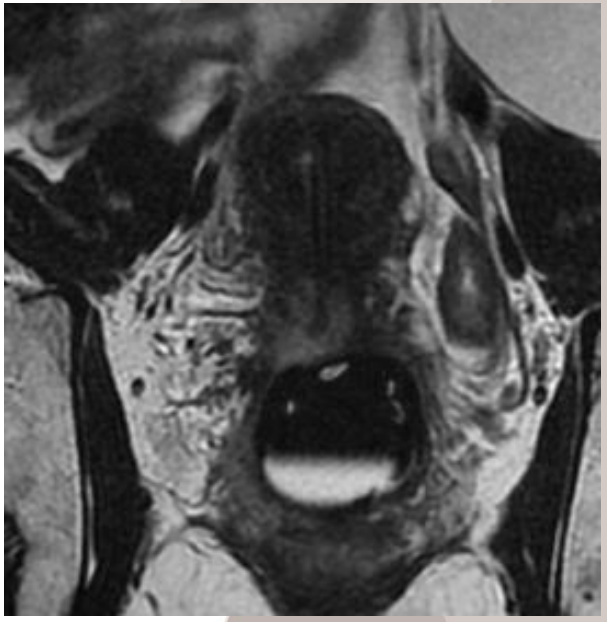
Height : 2.5



Stage IB2 : at the time of brachytherapy







Turning point

Question n° 3: in this patient HR-CTV includes:

1. the initial tumor extension
2. the whole cervix+ safety margins
3. the whole cervix only
4. the whole uterus

Turning point

Question n° 4: in this patient IR-CTV includes:

1. the whole cervix + initial tumor extension
2. the whole cervix + safety margins
3. the whole cervix only
4. the whole uterus

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

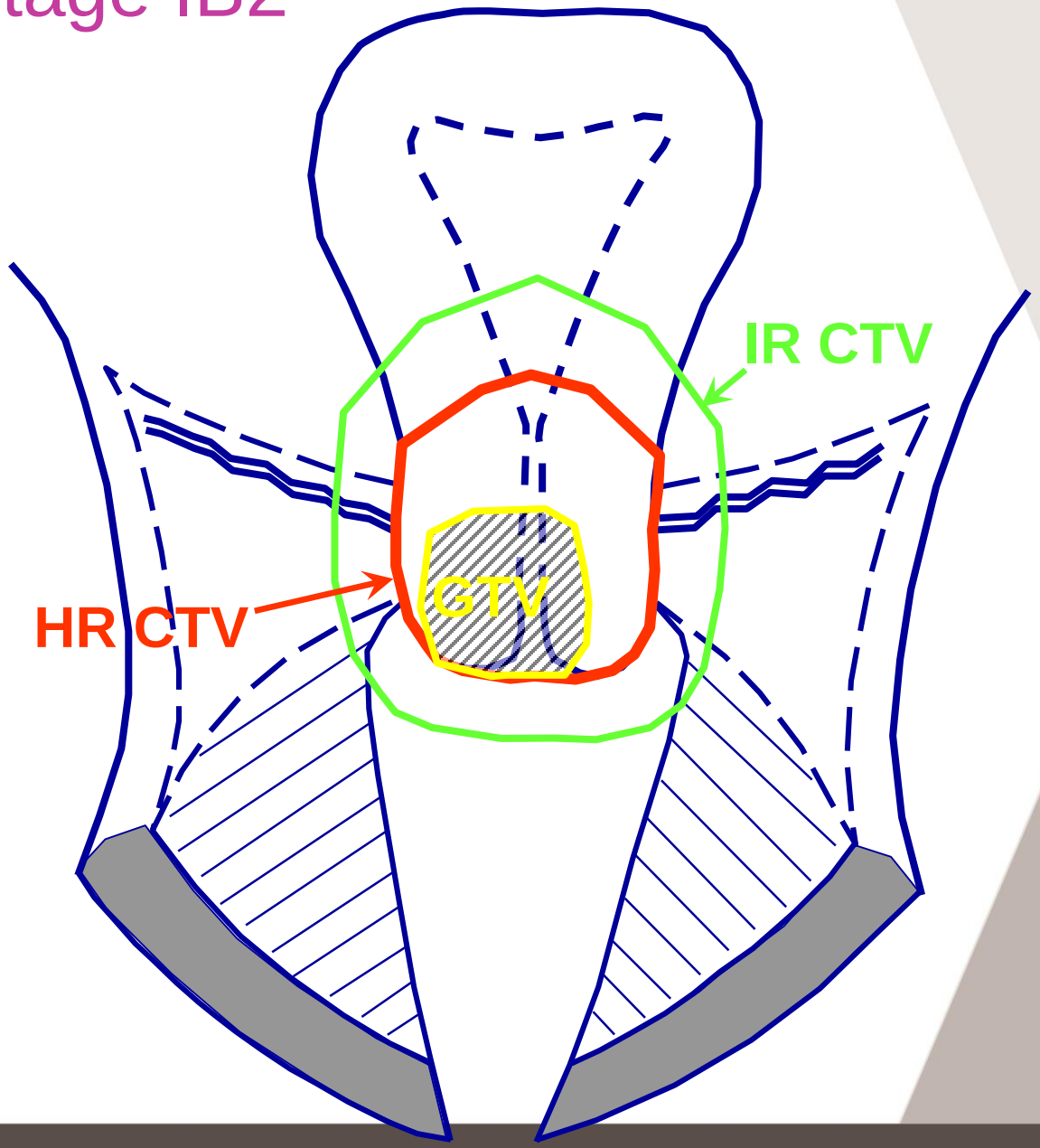
SAFETY MARGINS :

1-1.5 cm cranially

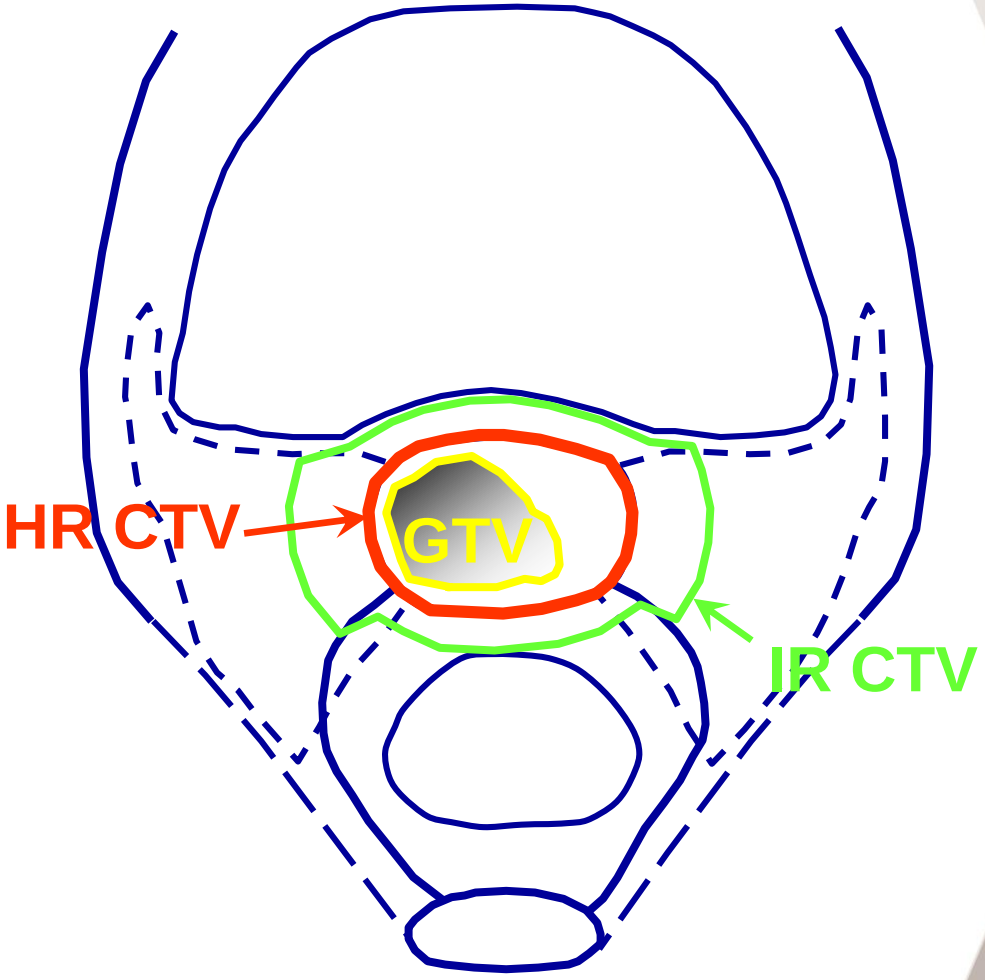
0.5cm antero-posteriorly

1cm laterally

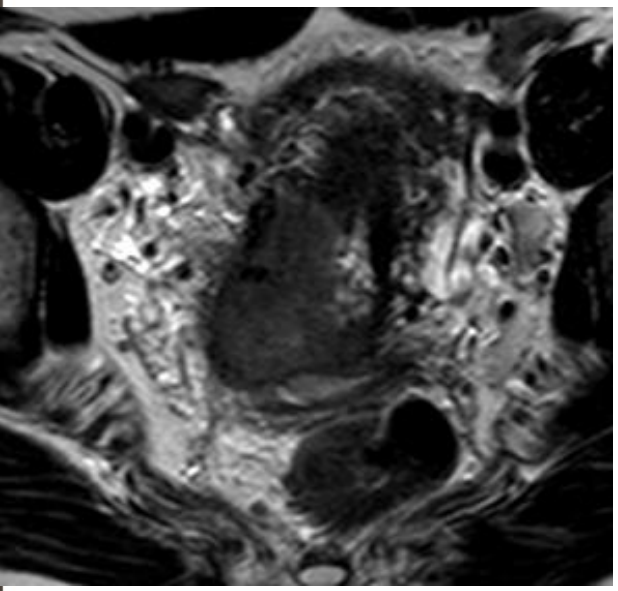
Stage IB2

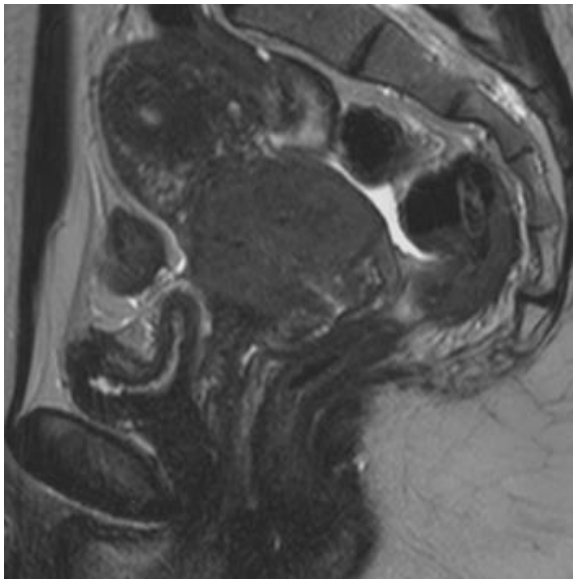


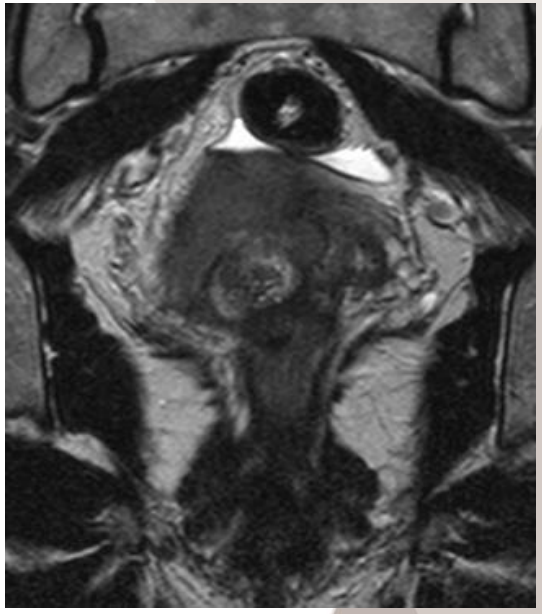
Stage IB2

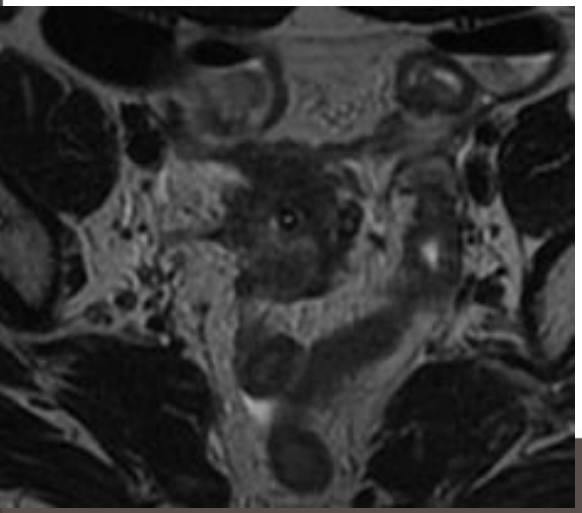


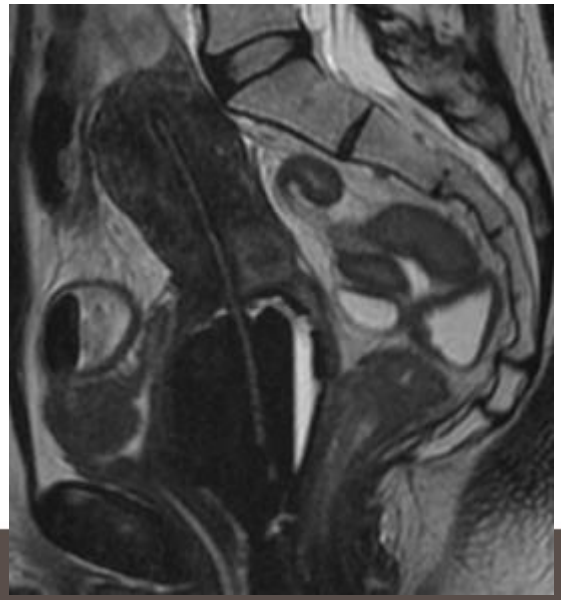
Stage IB2

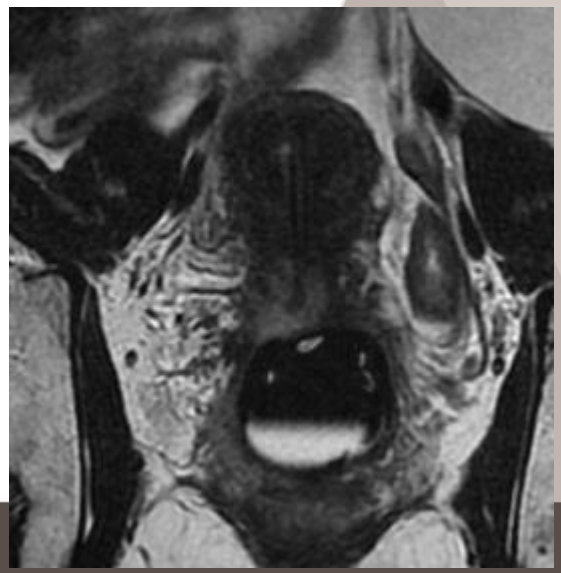




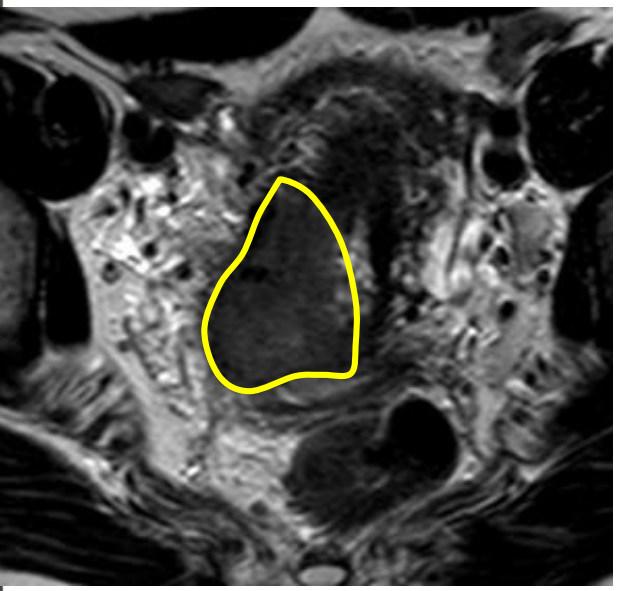


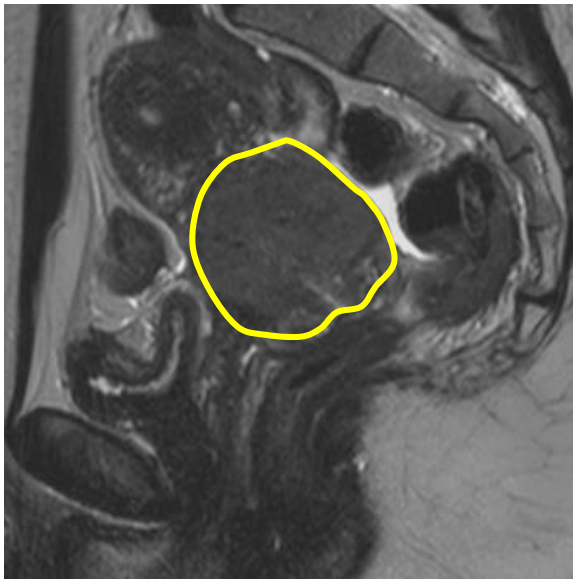


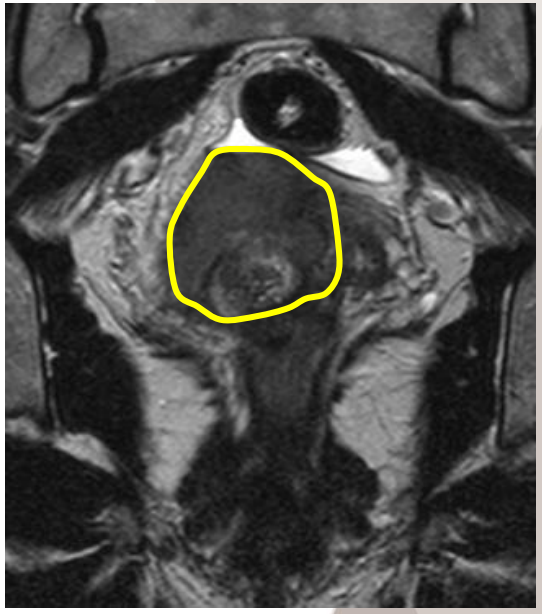


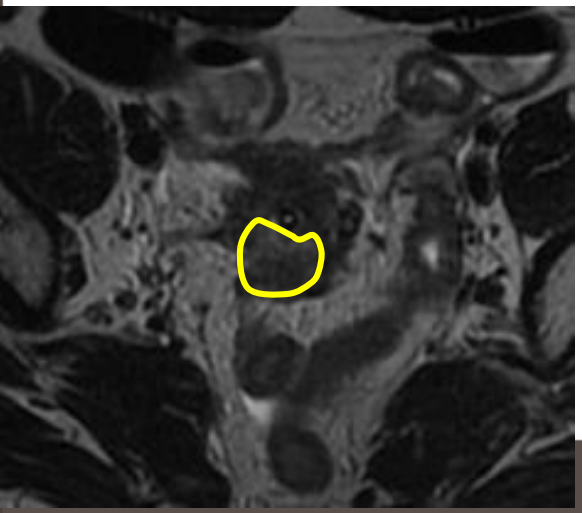


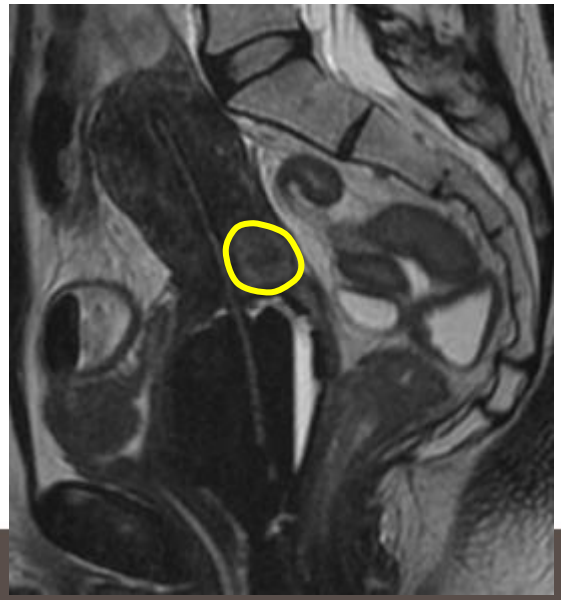
Stage IB2

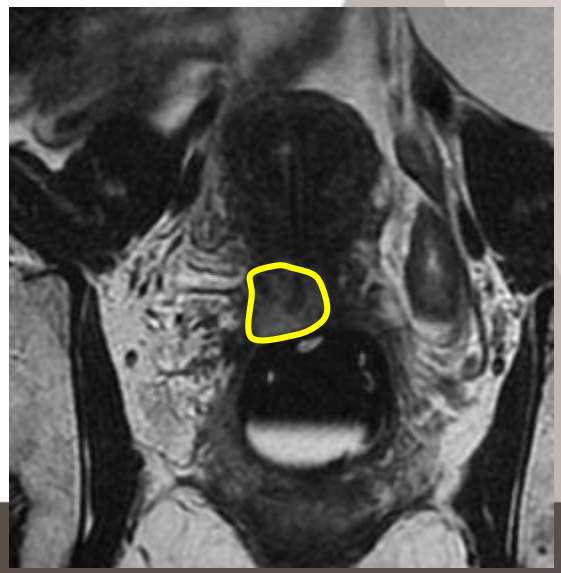




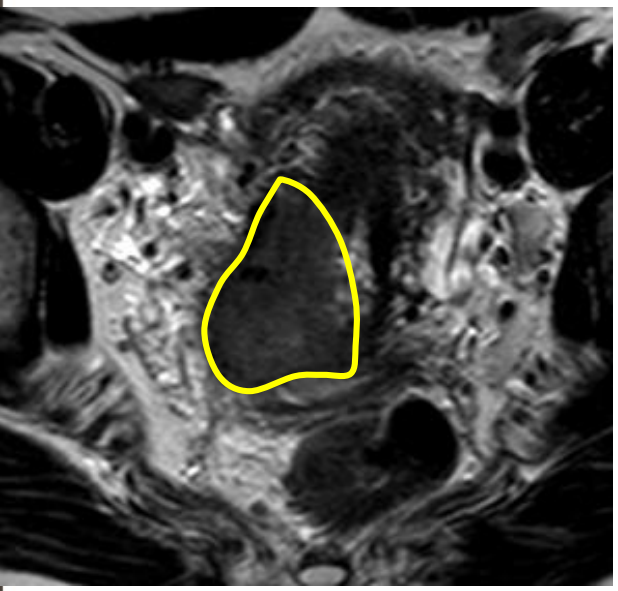


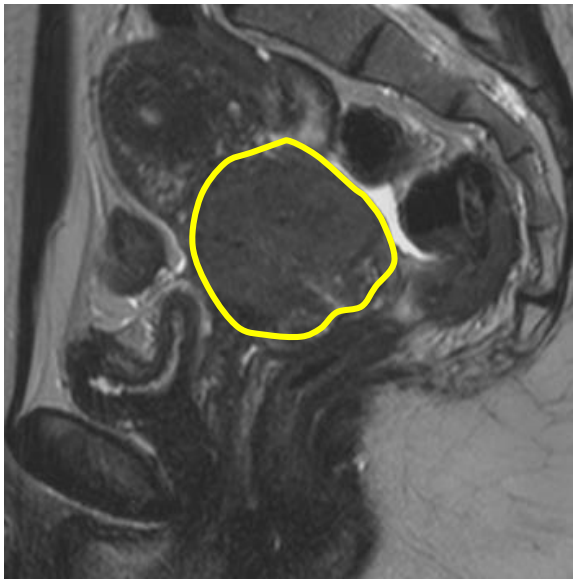


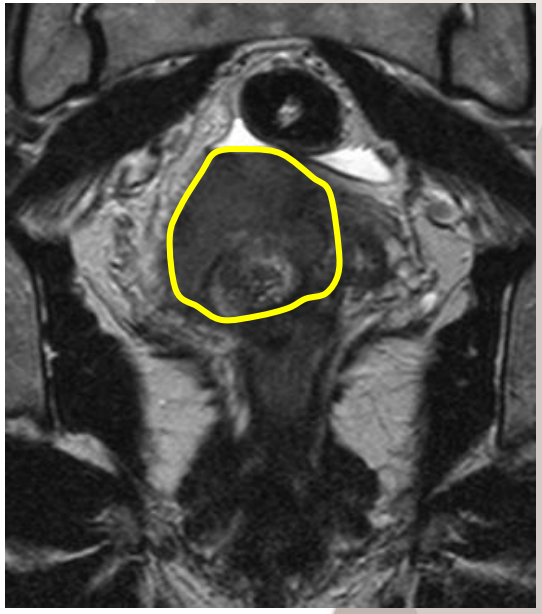


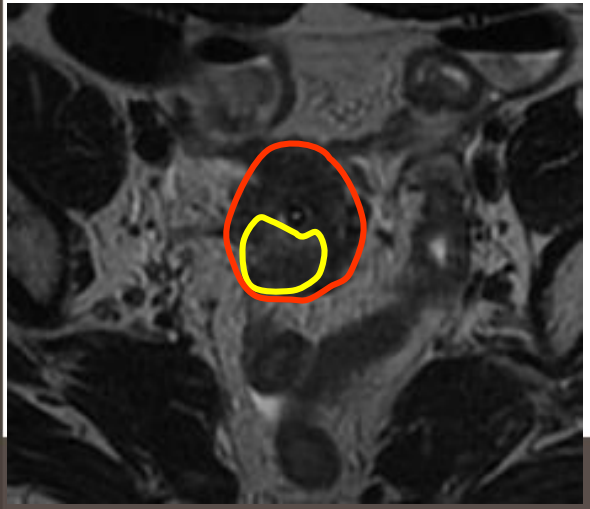


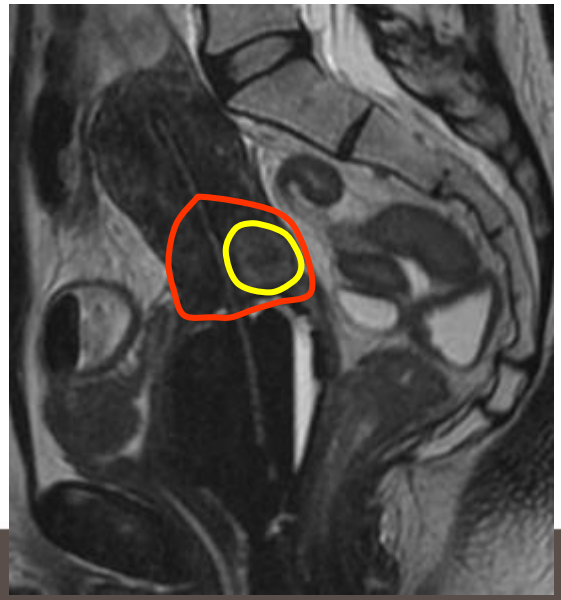
Stage IB2

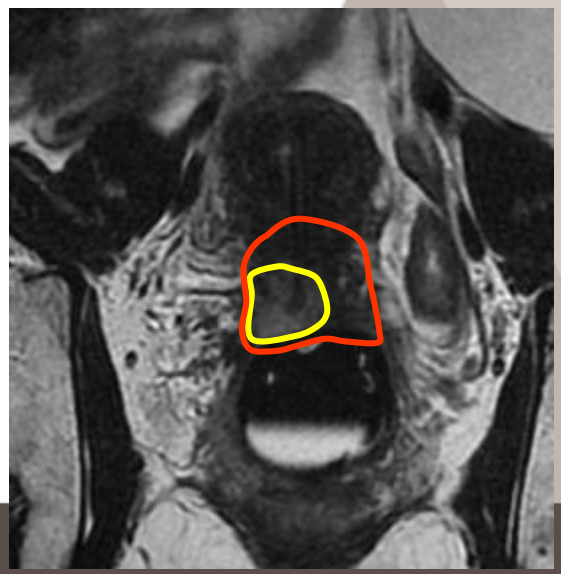




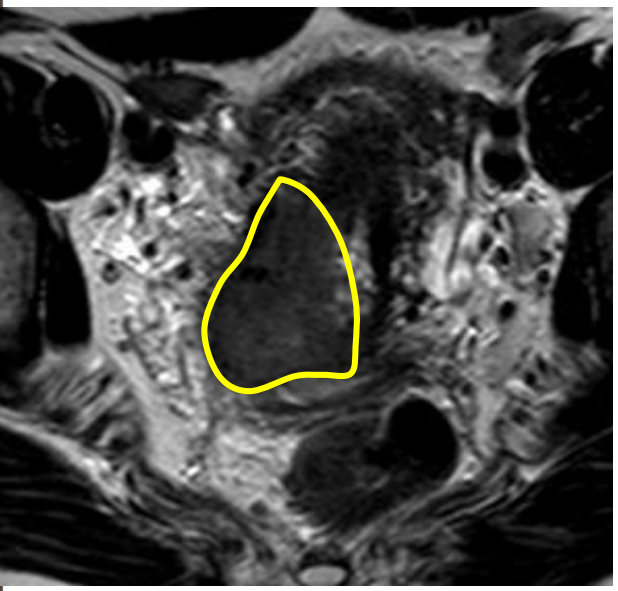


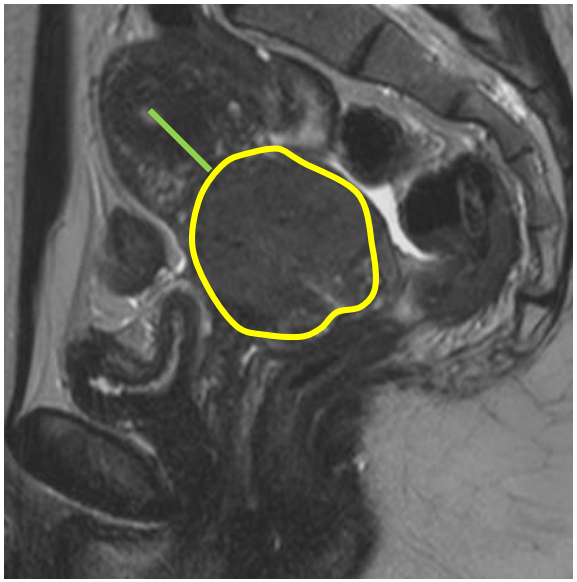


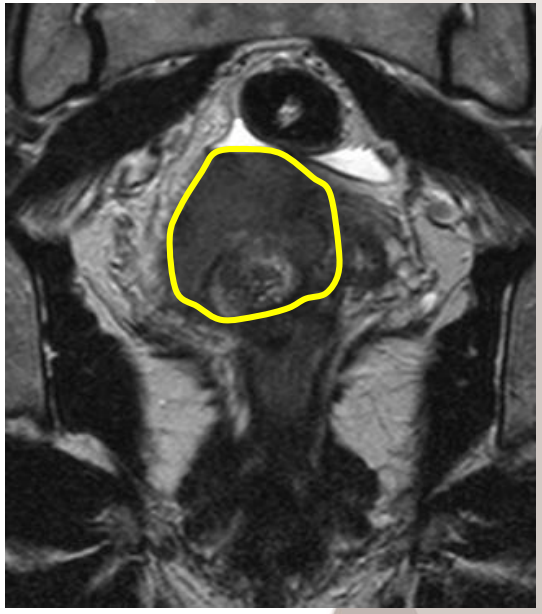


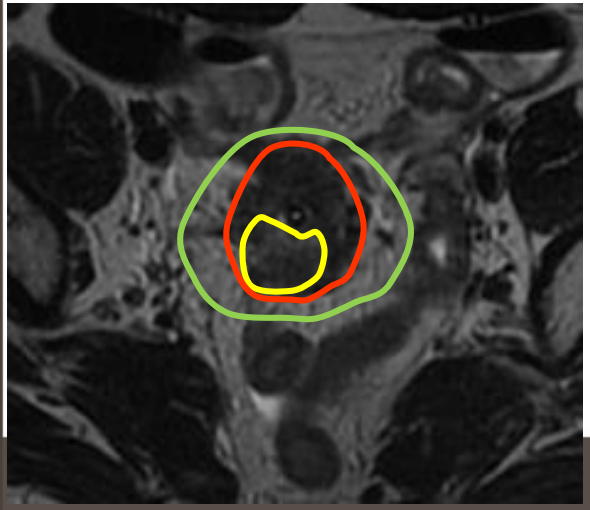


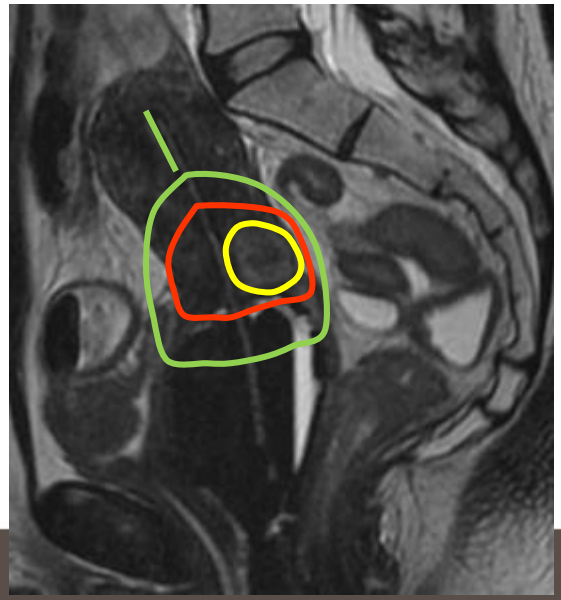
Stage IB2

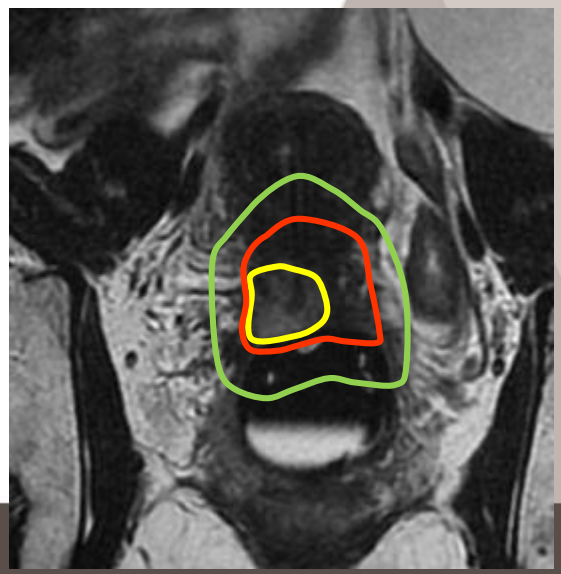












Patient n° 3

Mrs Claire DUP…
36 year-old
WHO=0

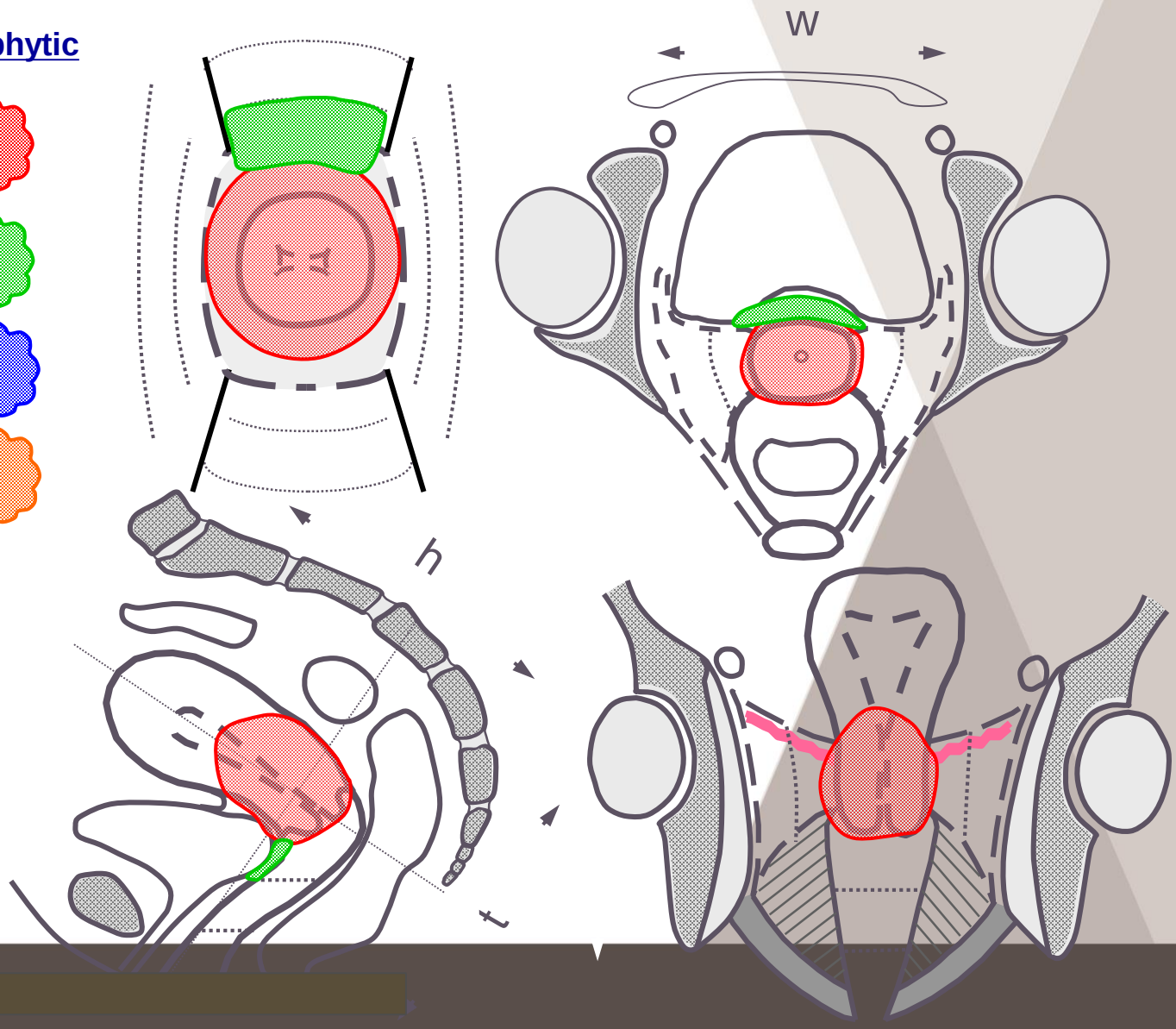
Vaginal bleeding

Biopsy: poorly differentiated squamous cell carcinoma

At clinical examination : cervical tumor predominant in the anterior lip + infiltration of the anterior fornix + infiltration of upper part of the anterior vaginal wall (1.5 cm)

Stage IIA : initial clinical examination

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		



Dimensions (cm):

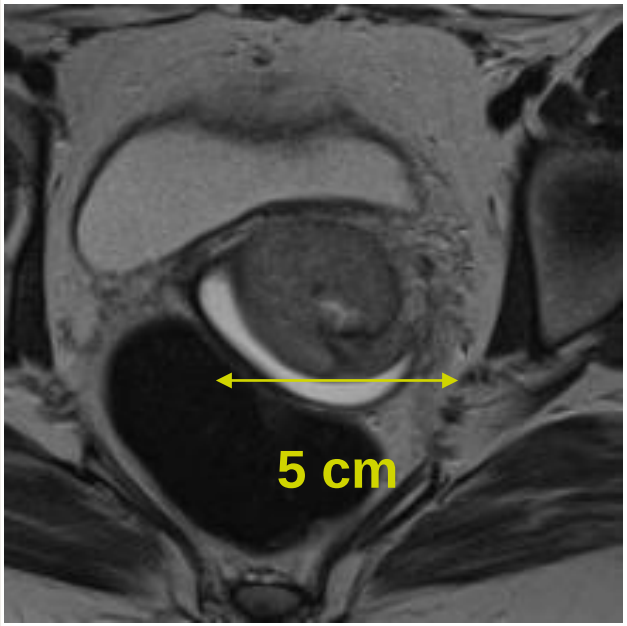
Width : 5

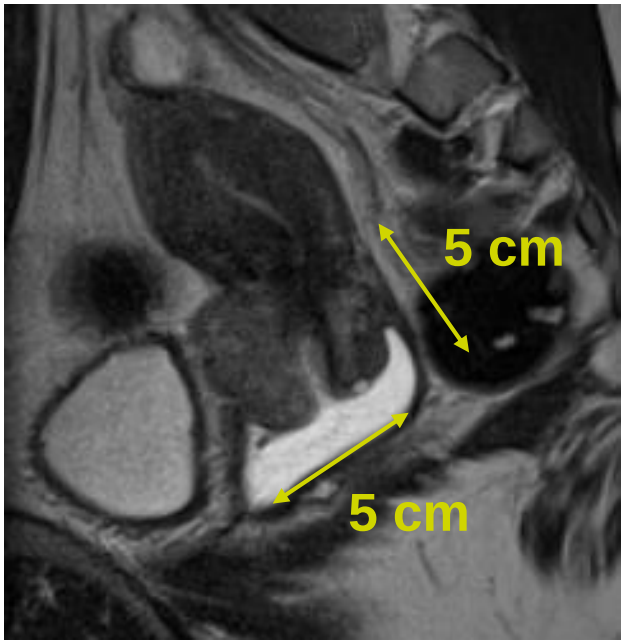
Thickness:4.5

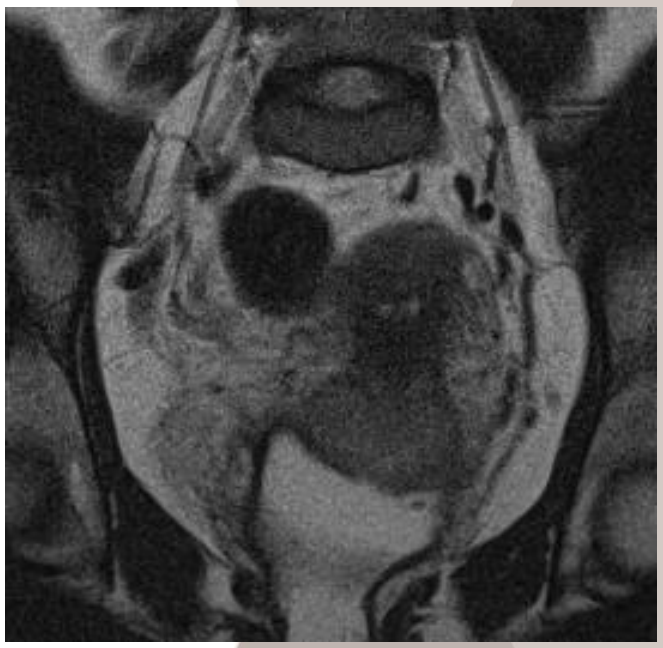
Height : 5

Vaginal involv 1.5

Stage IIA : initial MRI

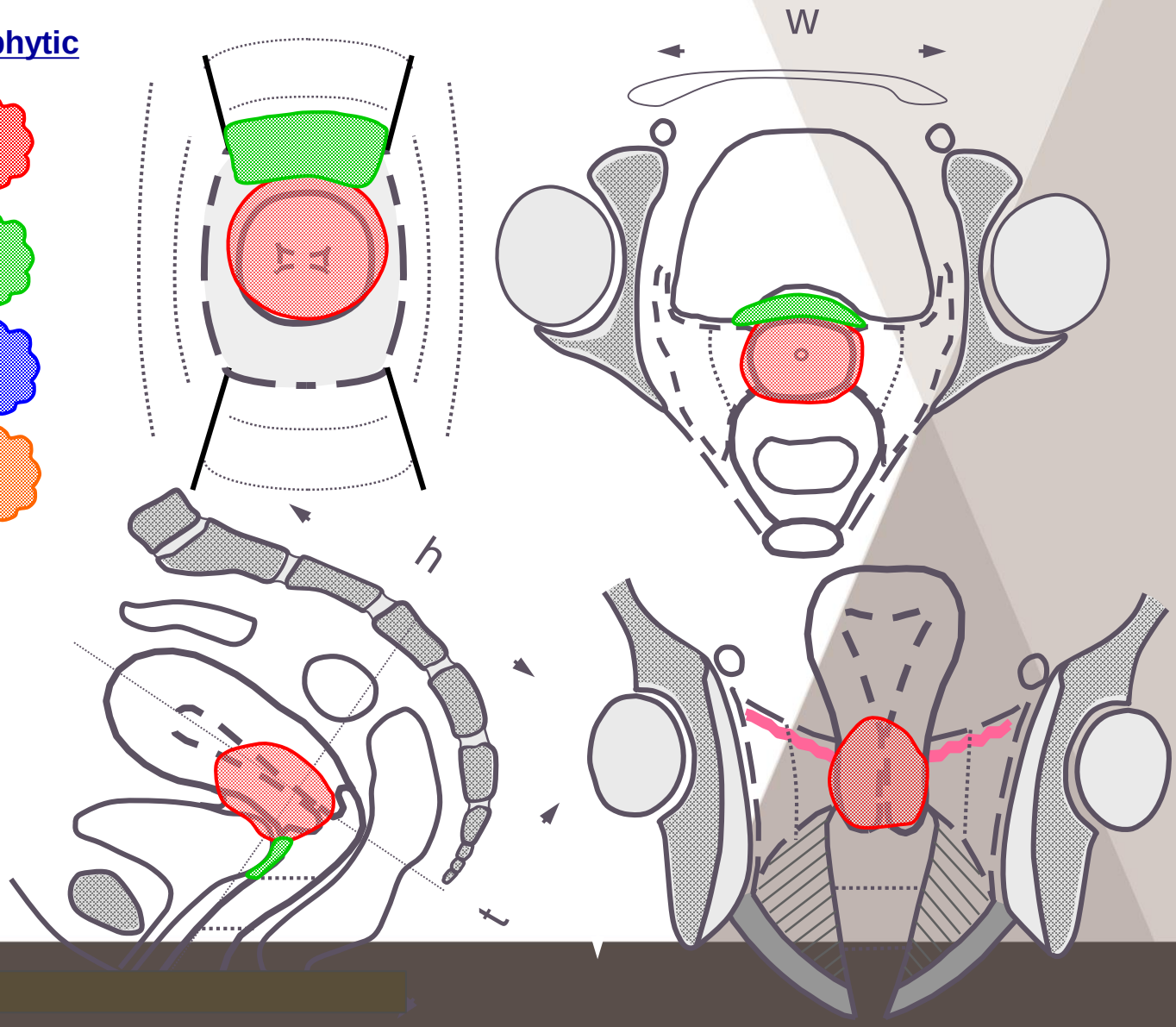






Stage IIA : at time of brachytherapy

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		



Dimensions (cm):

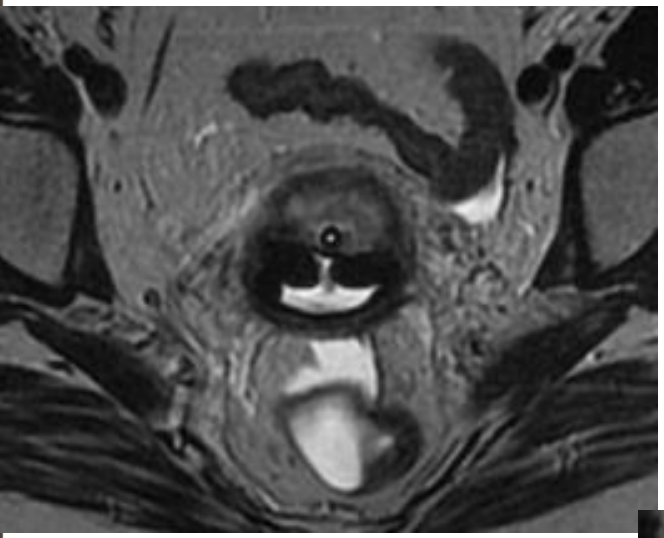
Width : 3.5

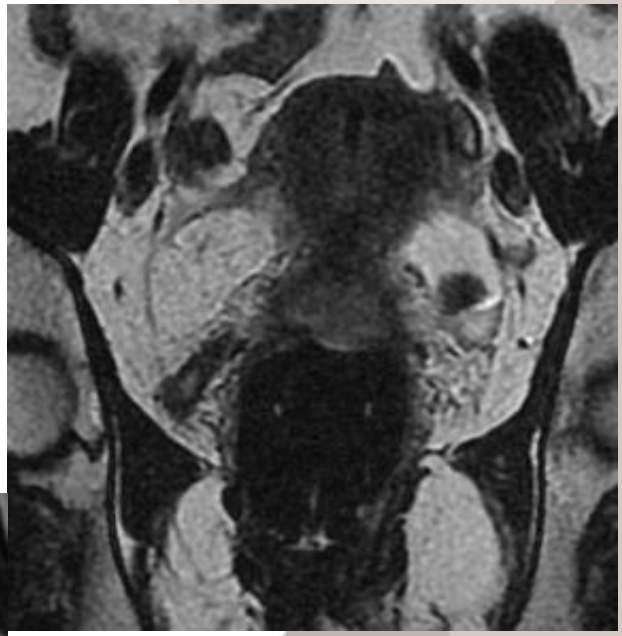
Thickness:3.5

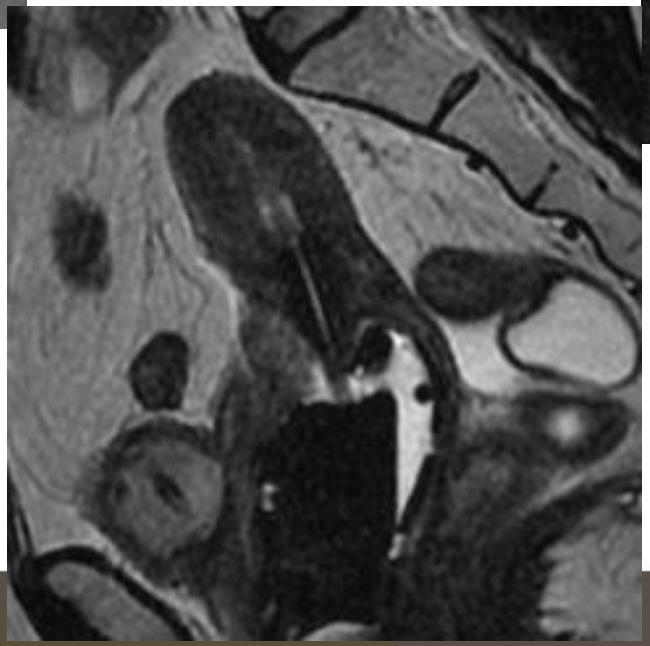
Height : 3

Vaginal involv :1

Stage IIA : MRI at time of brachytherapy







Turning point

Question n° 5: HR-CTV includes:

1. the initial tumor extension
2. the GTV + whole cervix + safety margins
3. the whole cervix only
4. the GTV + whole cervix

Turning point

Question n° 6: IR-CTV includes:

1. the initial tumor extension
2. the GTV + whole cervix + safety margins
3. the whole cervix only
4. the GTV + whole cervix

Target volume concepts

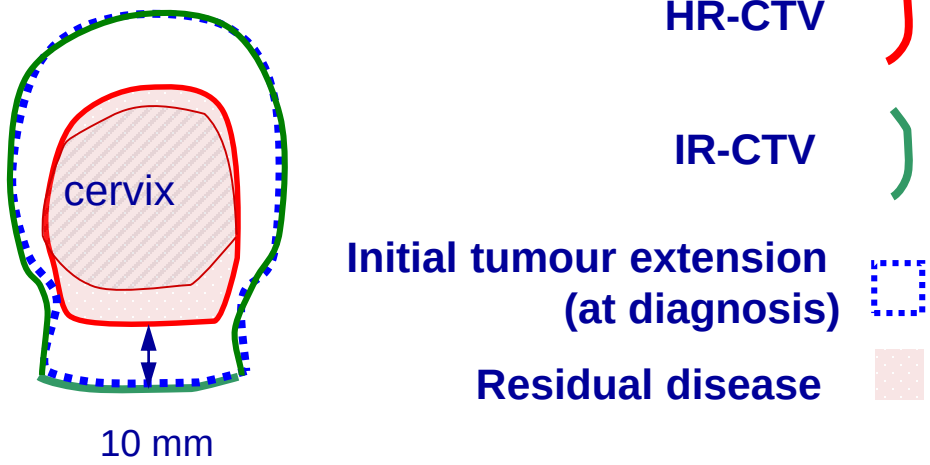
High Risk CTV :

GTV at time of brachytherapy

In all cases includes:

- GTV + whole cervix
- Presumed tumour extension in adjacent tissues
  - **Clinical assessment**

NO SAFETY MARGINS



Intermediate Risk CTV :

GTV at time of diagnosis

In all cases includes:

- HR-CTV
- integrates initial CTV

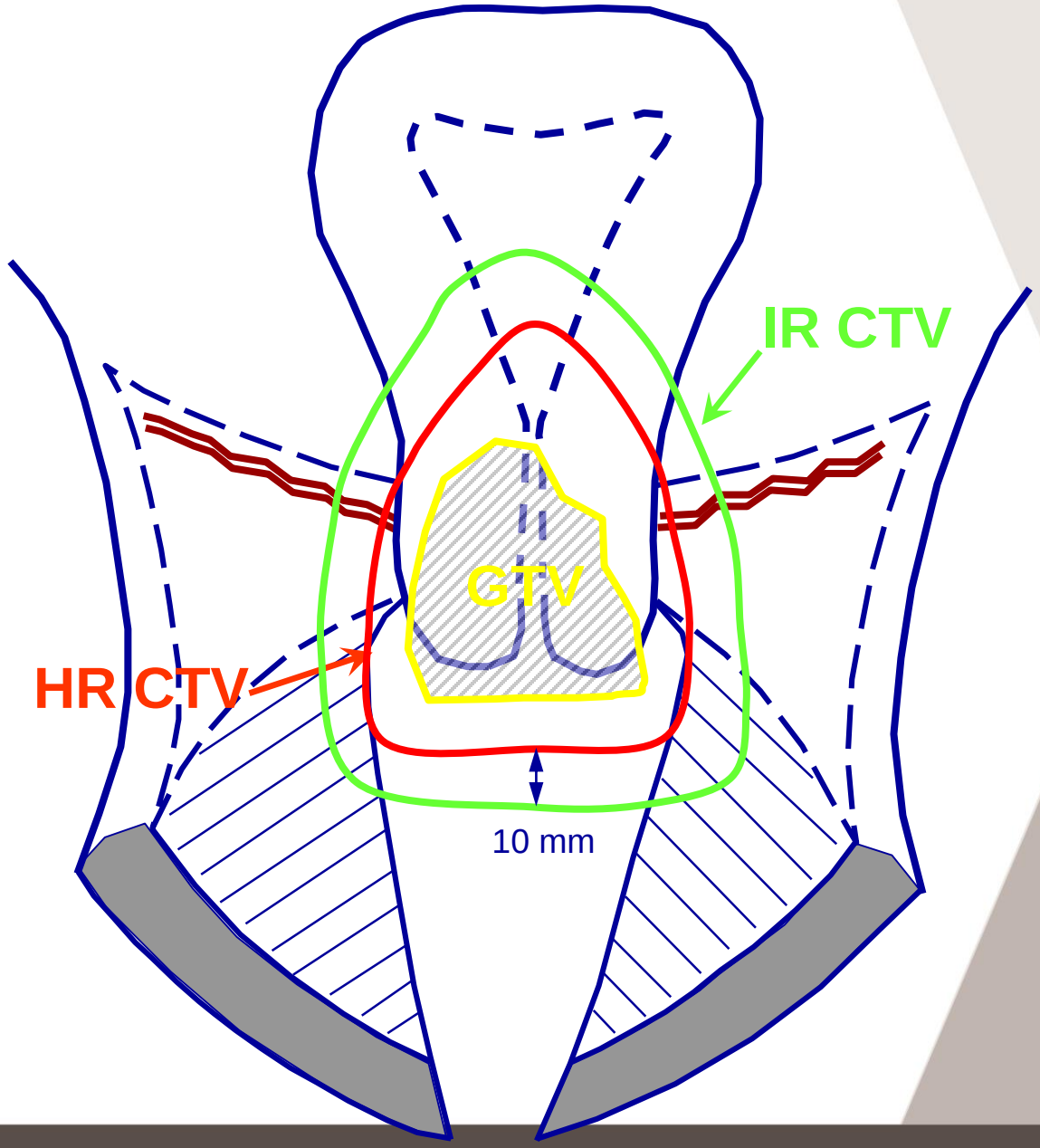
SAFETY MARGINS :

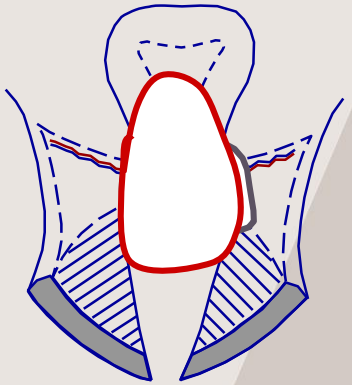
1-1.5 cm cranially

0.5cm antero-posteriorly

1cm laterally

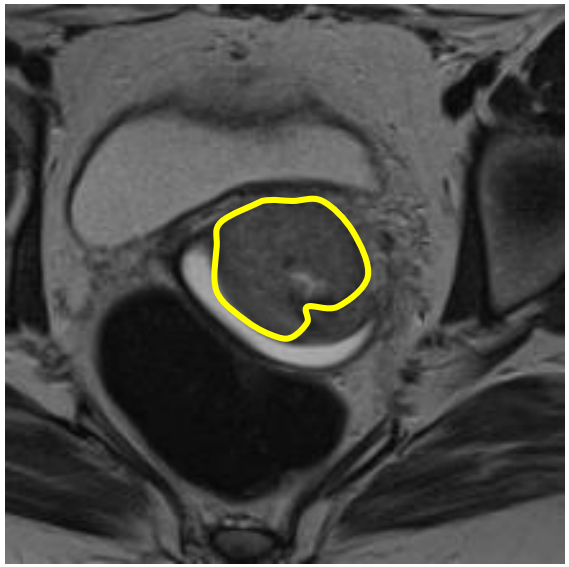
Stage IIA

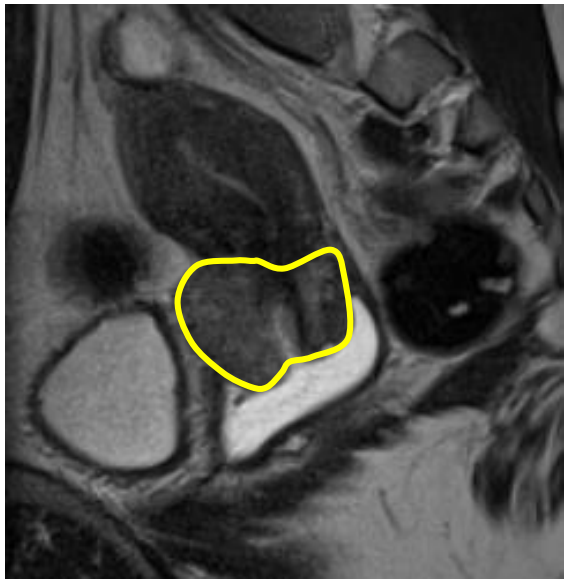


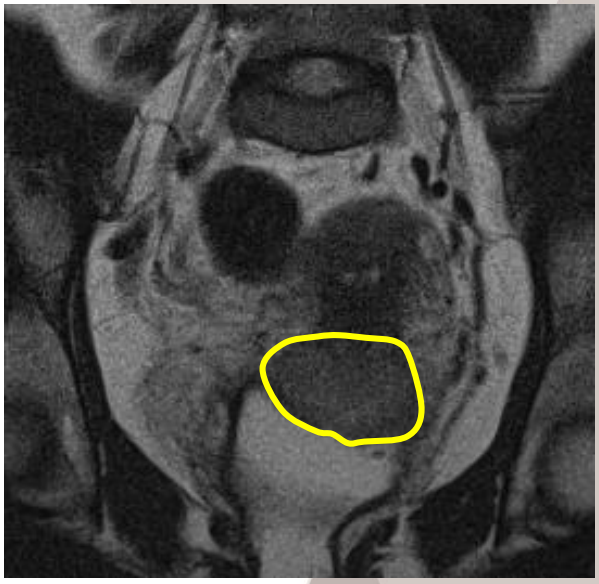


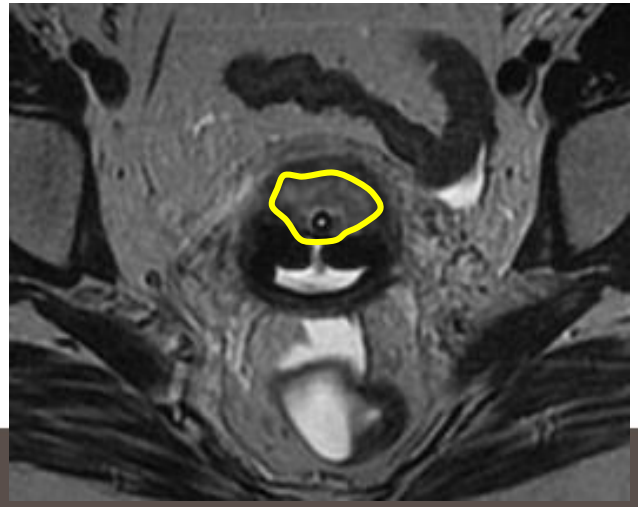
Tumor at time of diagnosis

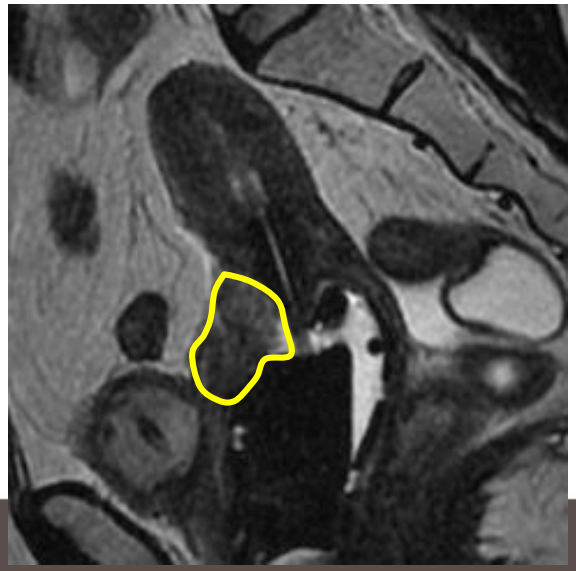
Stage IIA

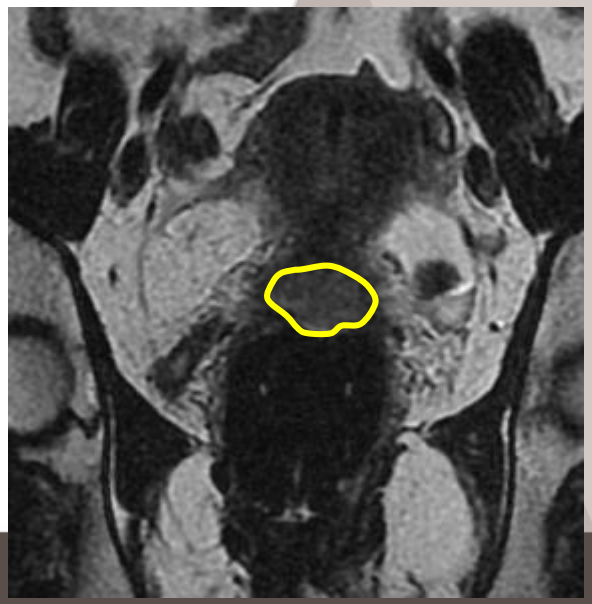




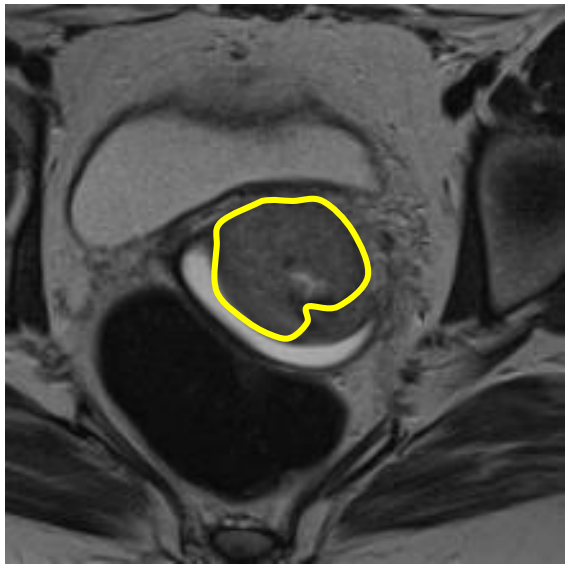


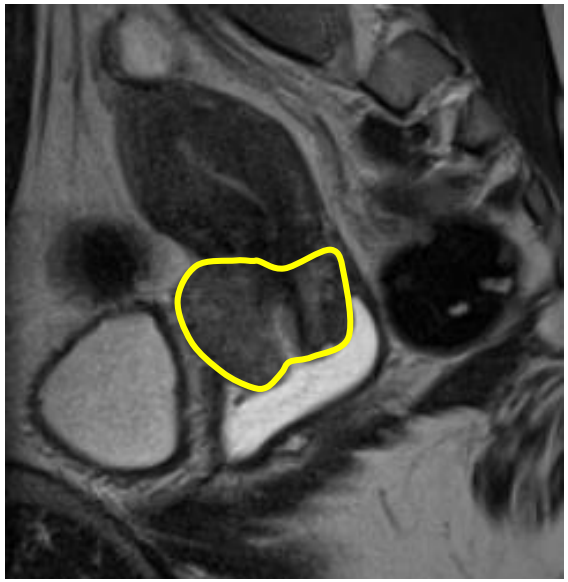


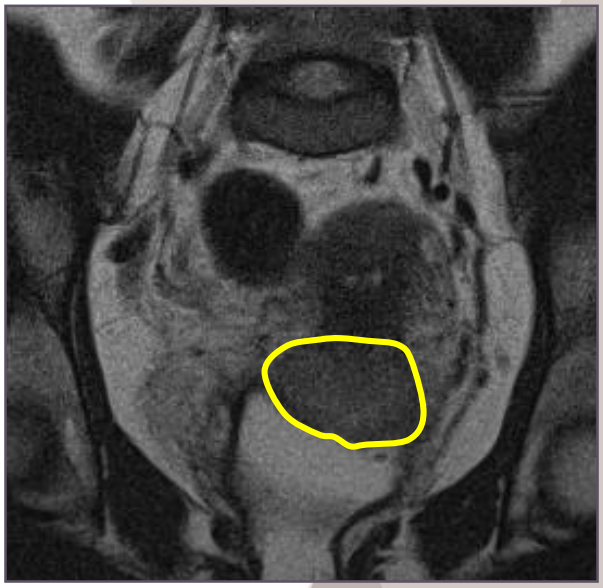


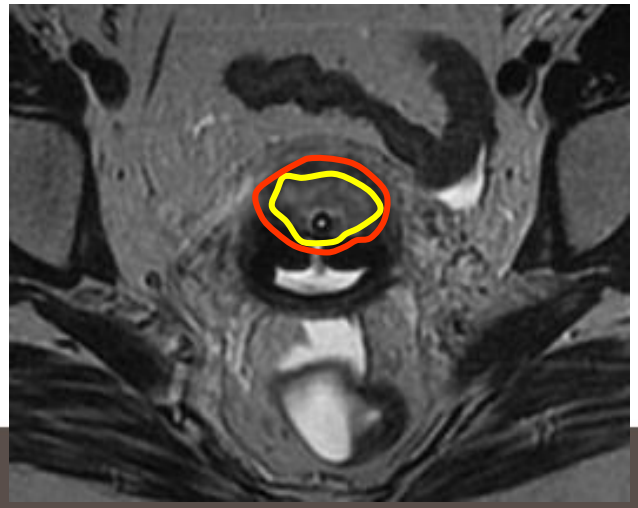


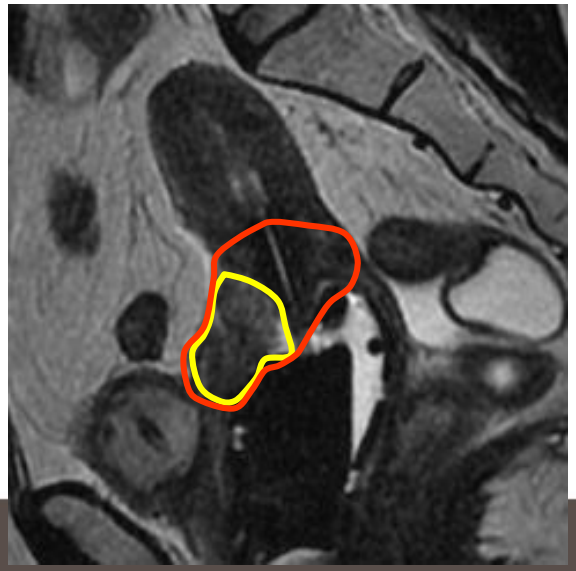
Stage IIA

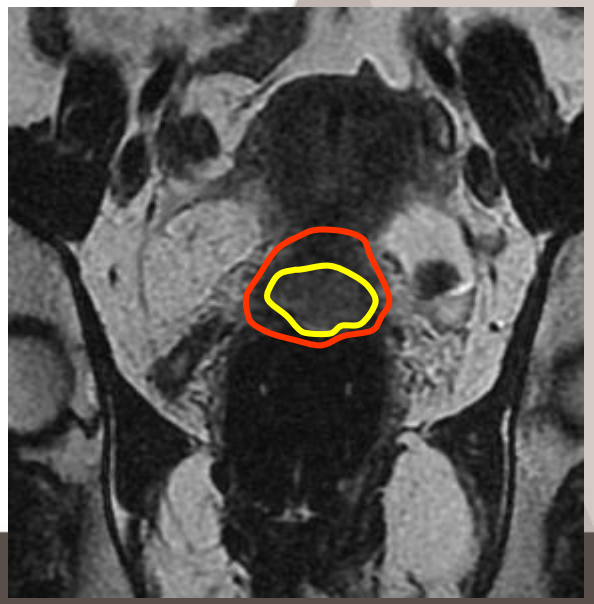




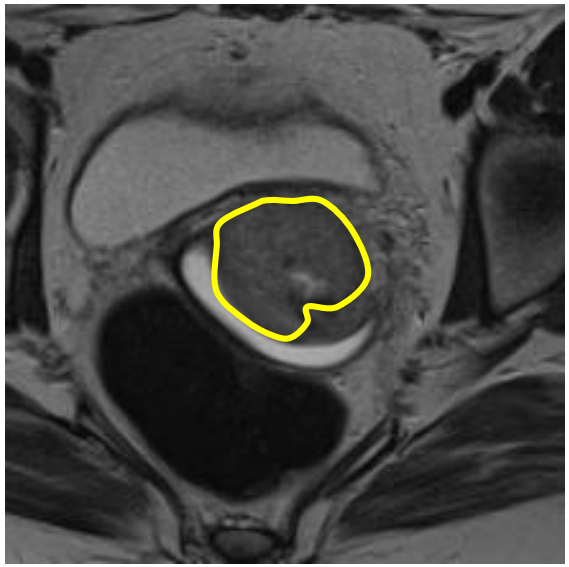


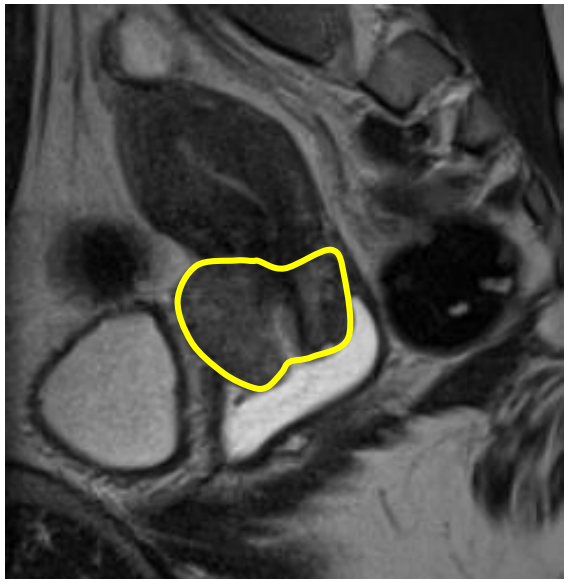


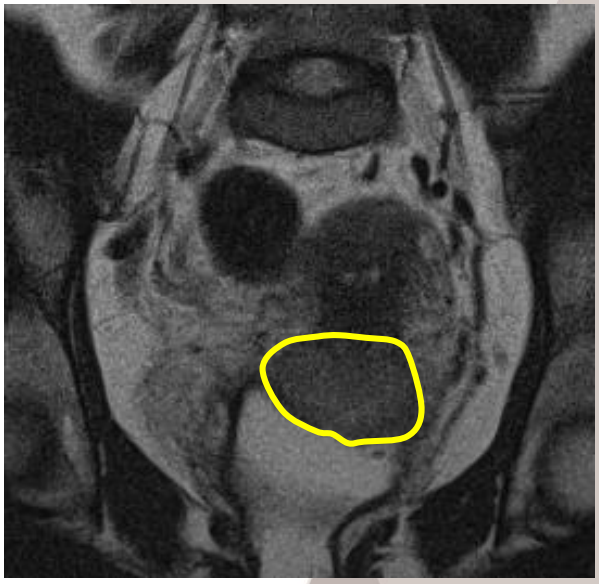


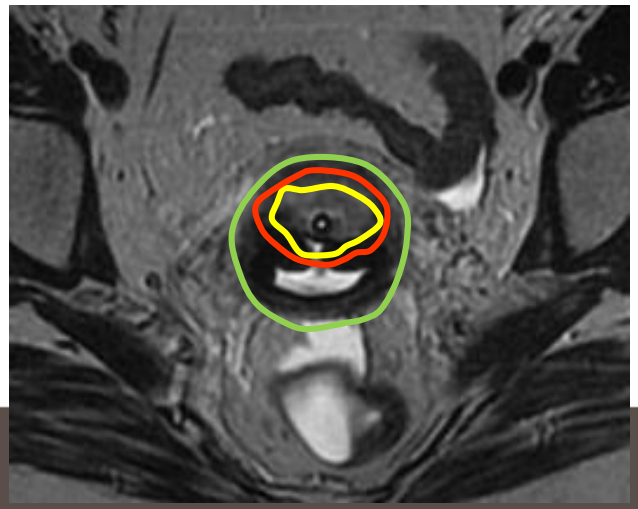


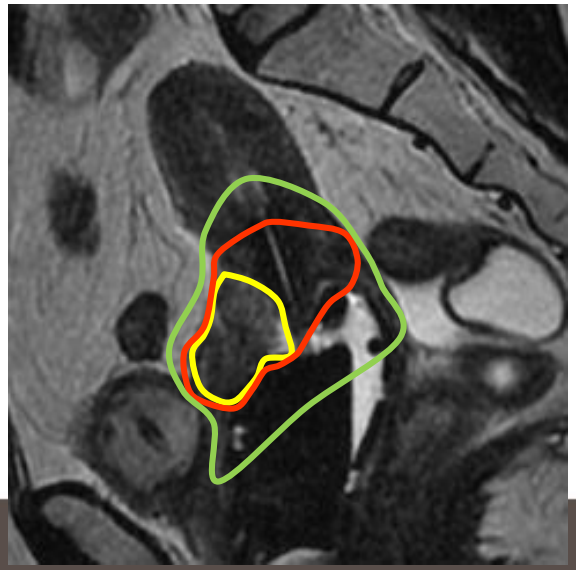
Stage IIA

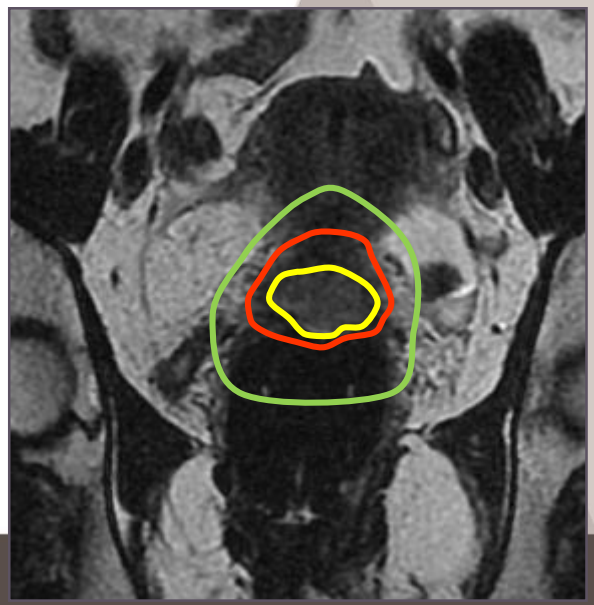












Patient n° 4

Mrs Evelyn 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

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

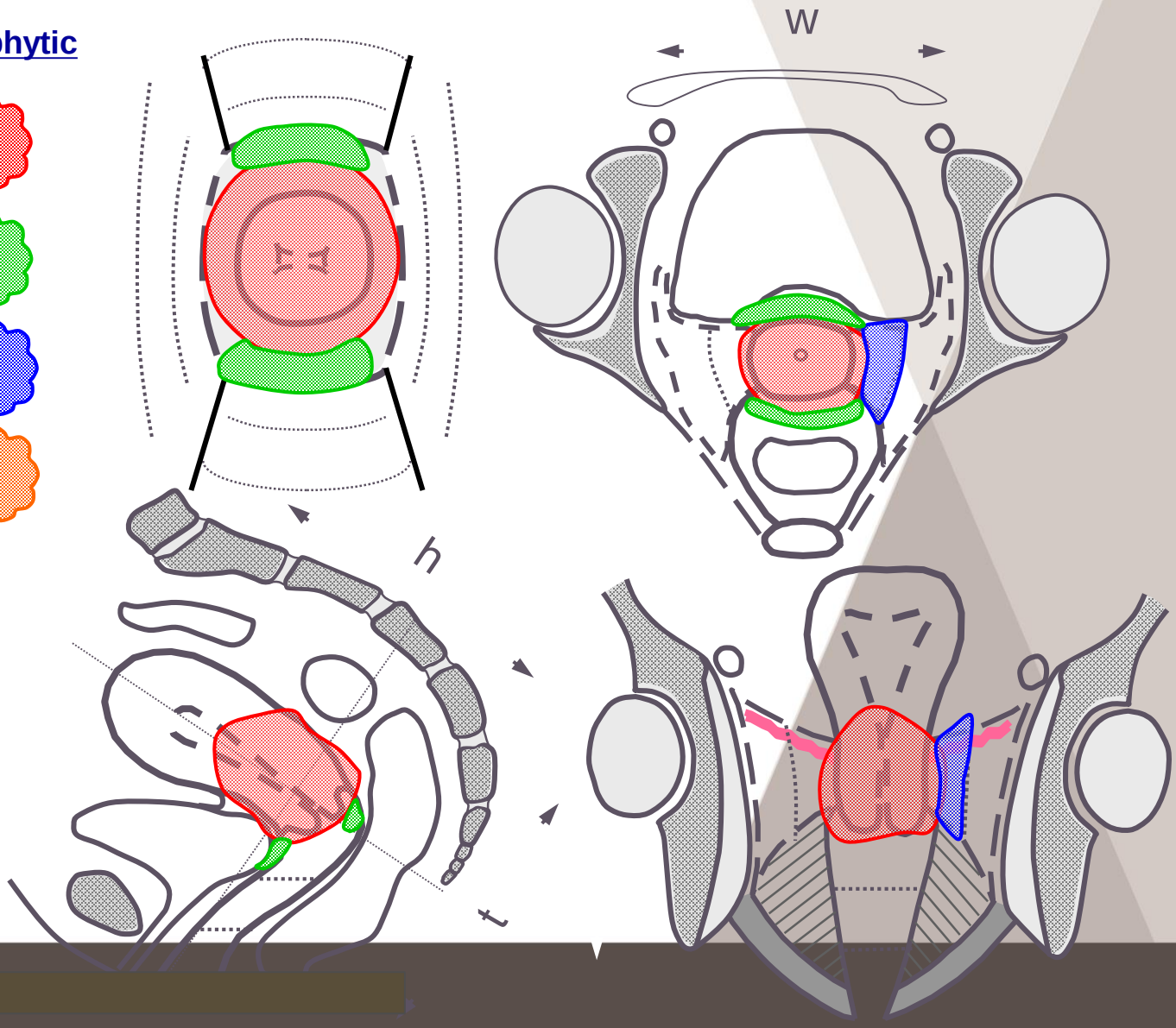
Dimensions (cm):

Width : 5

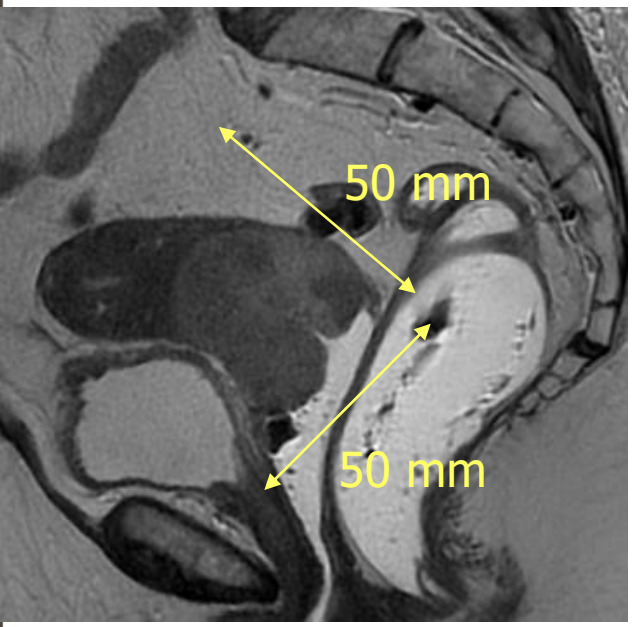
Thickness:5

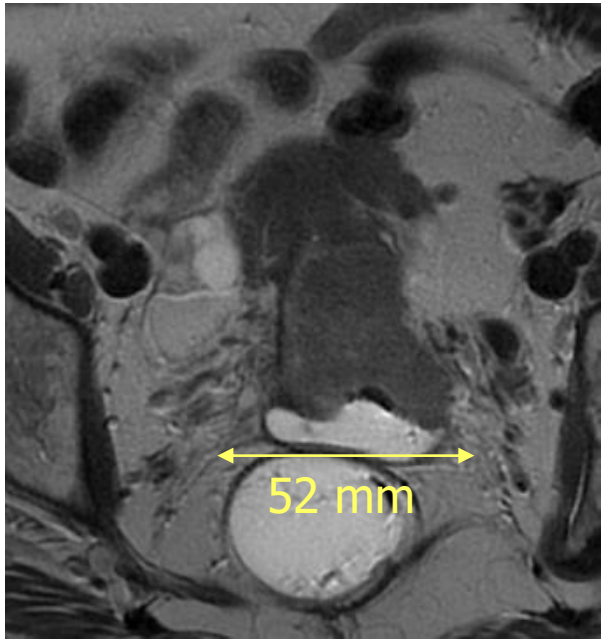
Height : 5

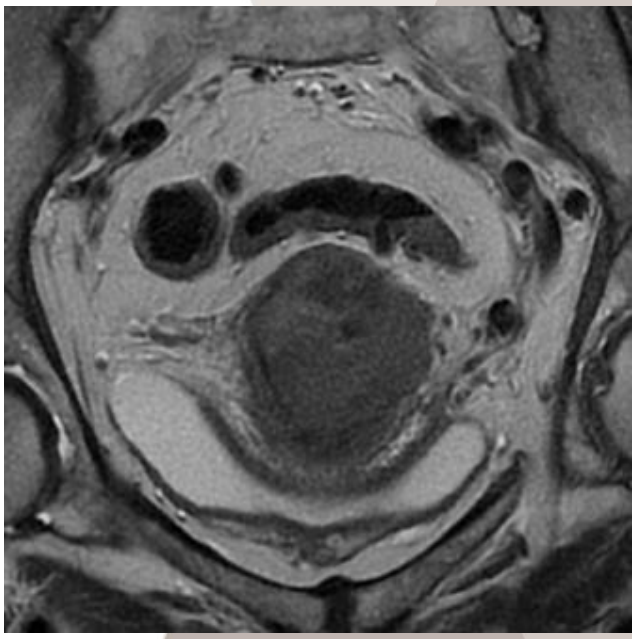
Fornix involv 1



Stage IIB : initial MRI







Stage IIB : at the time of brachytherapy

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

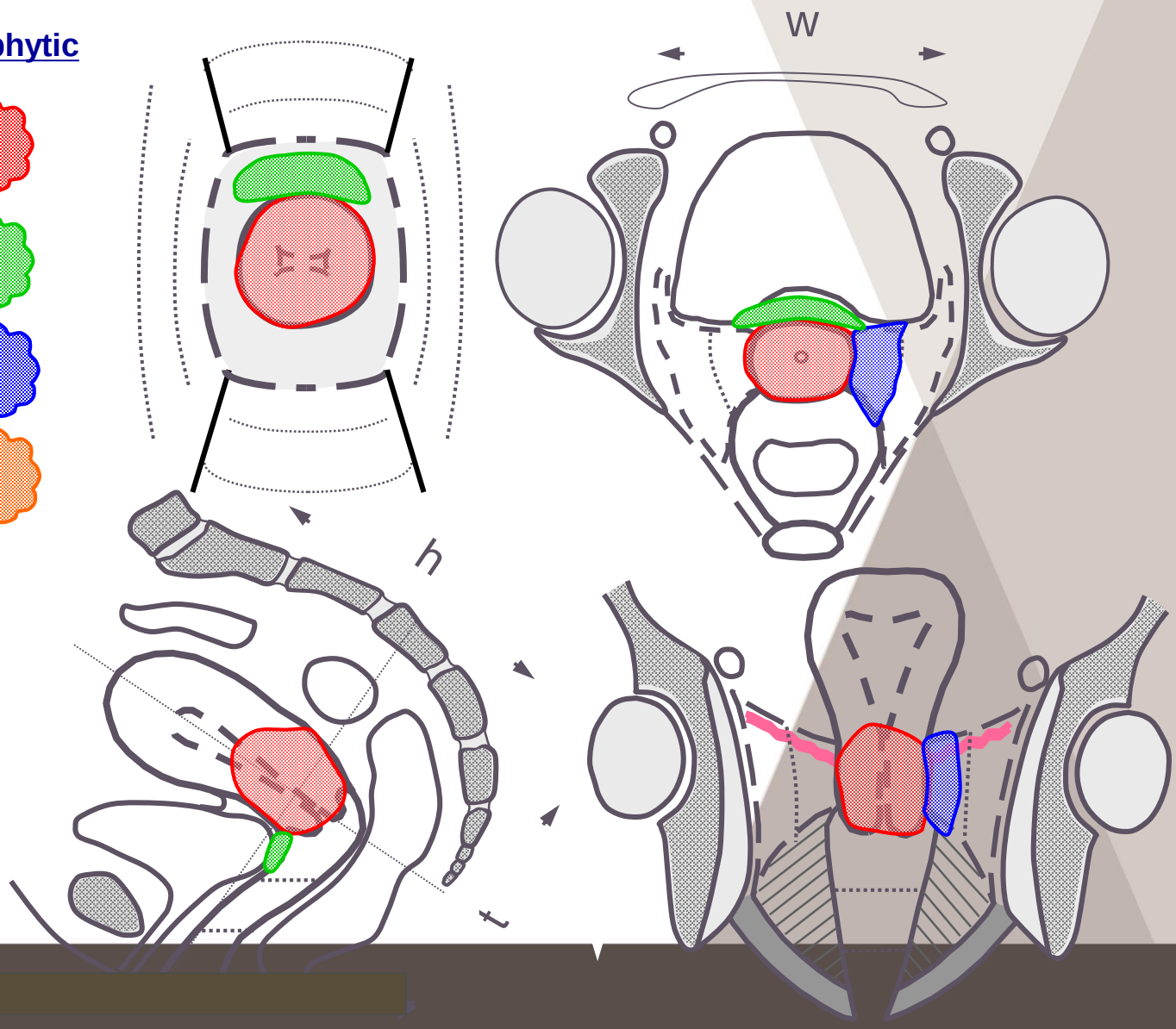
Dimensions (cm):

Largeur : 3

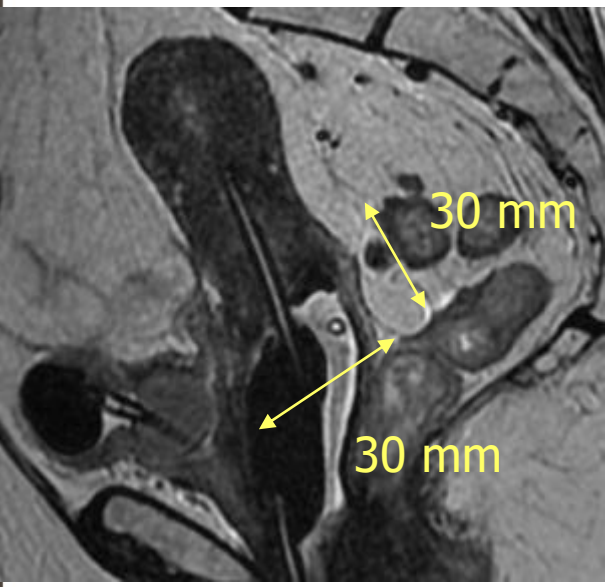
Epaisseur : 3

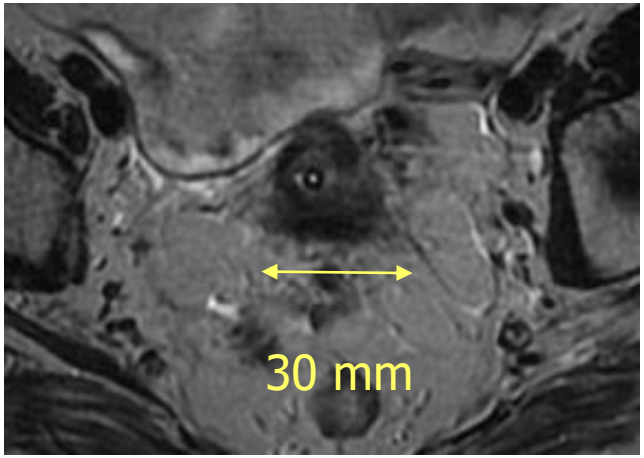
Hauteur : 3

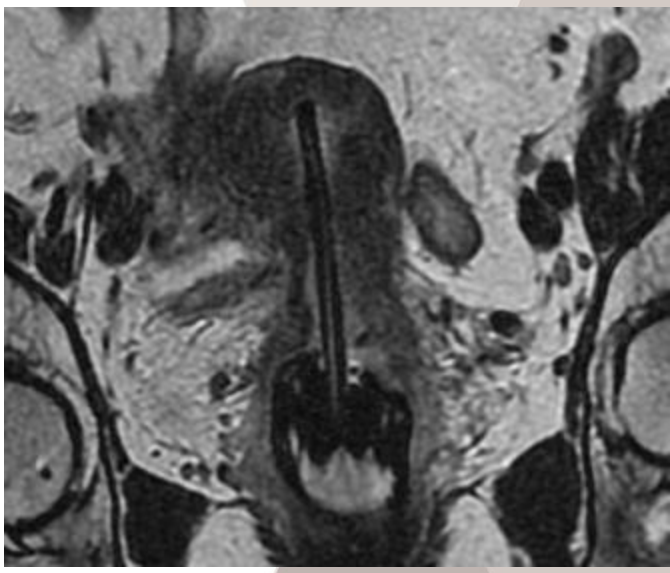
Env. vaginal : 1



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

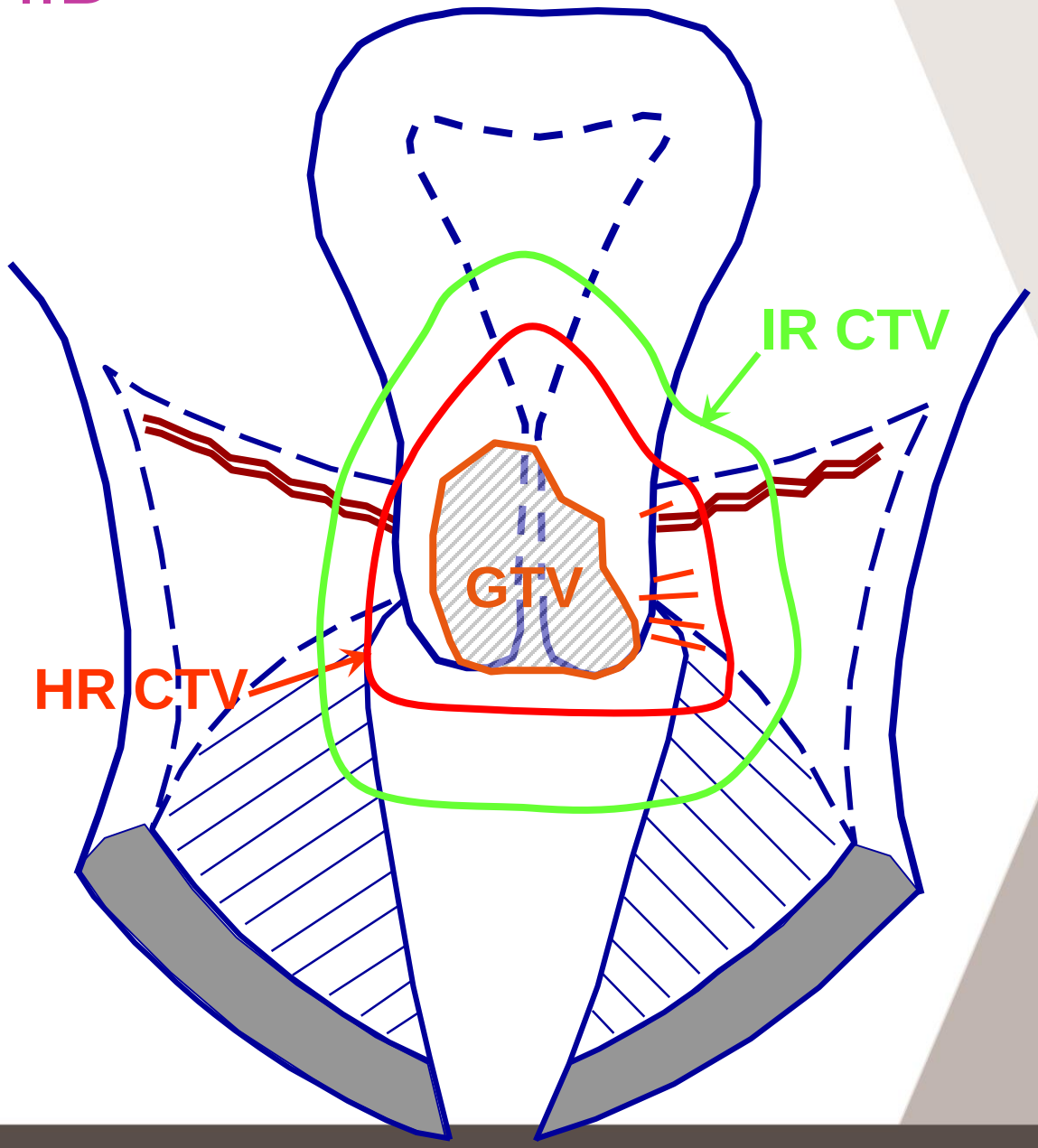
SAFETY MARGINS :

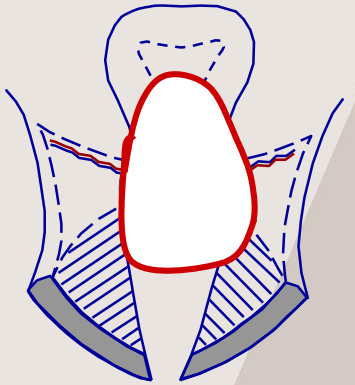
1-1.5 cm cranially

0.5cm antero-posteriorly

1cm laterally

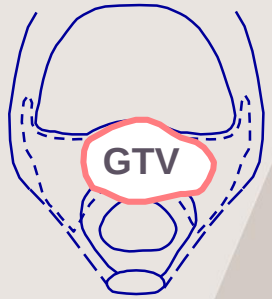
Stage IIB



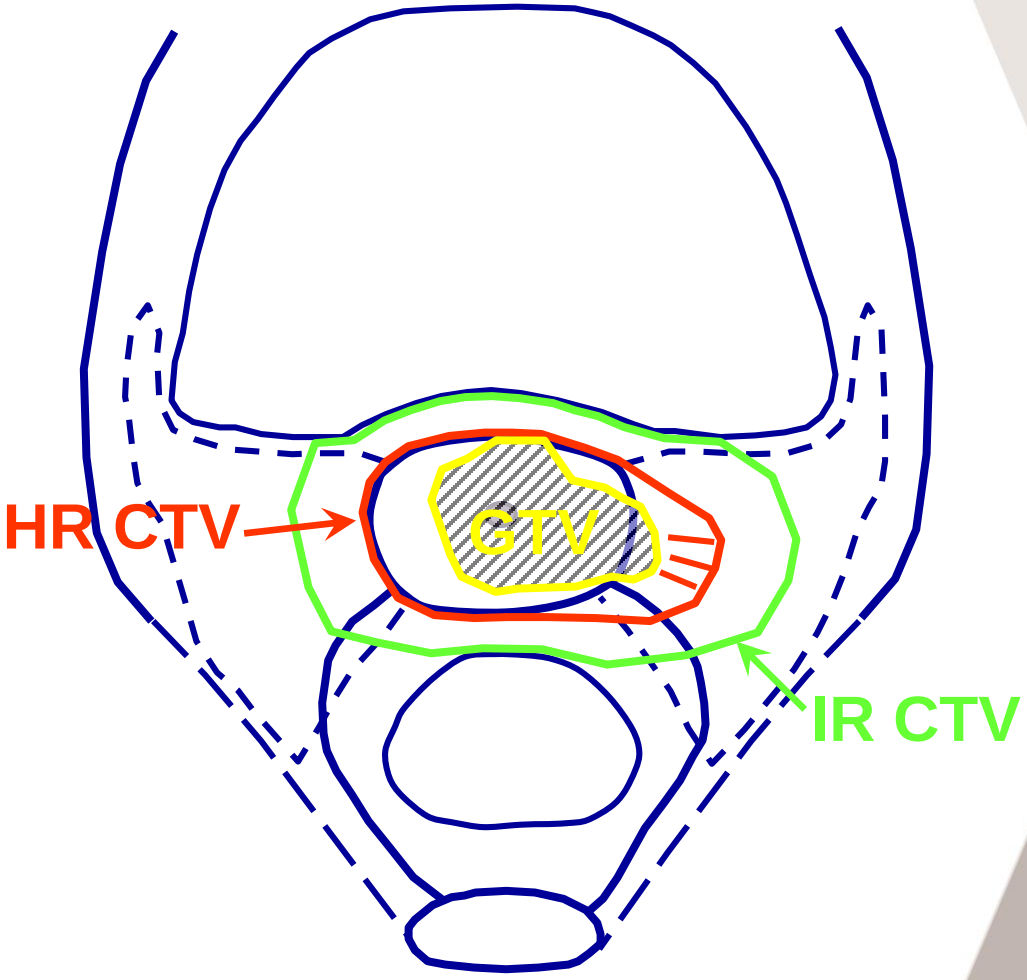


Tumor at time of diagnosis

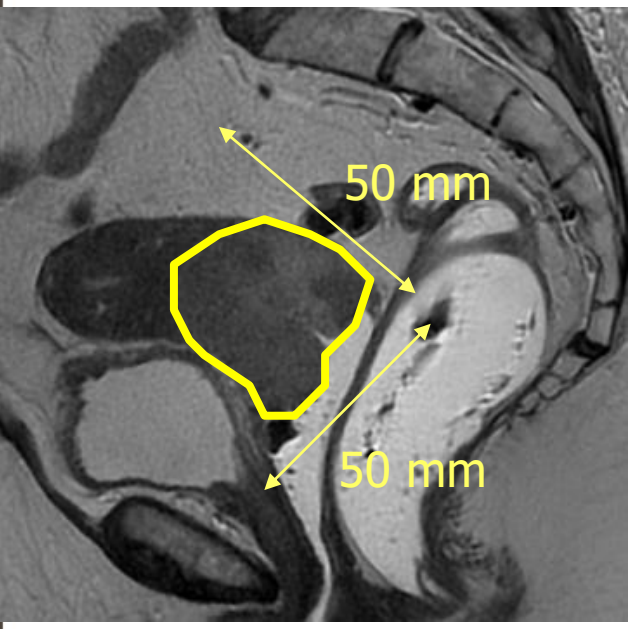
Stage IIB

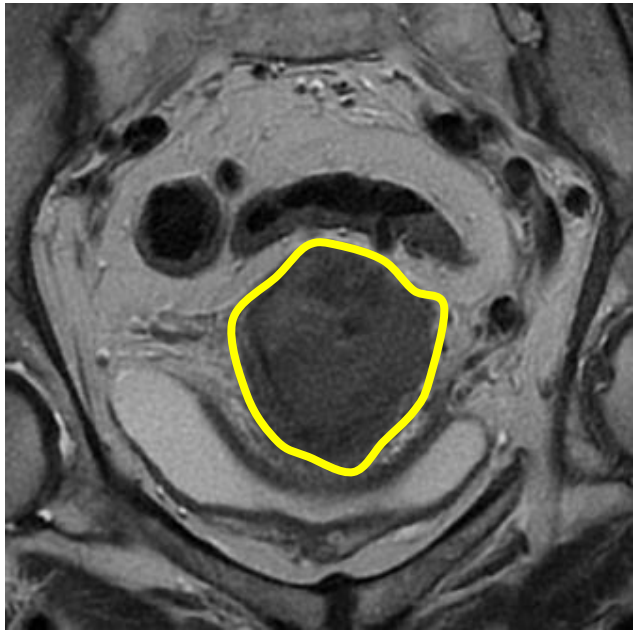


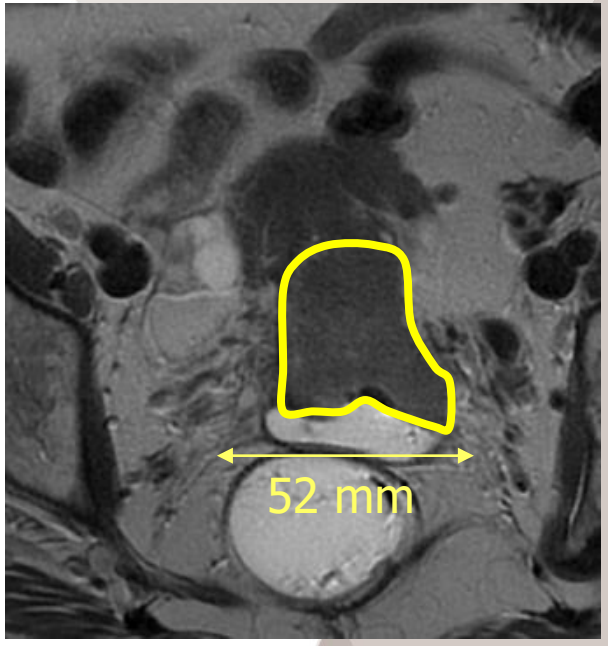
Tumor at time of diagnosis.

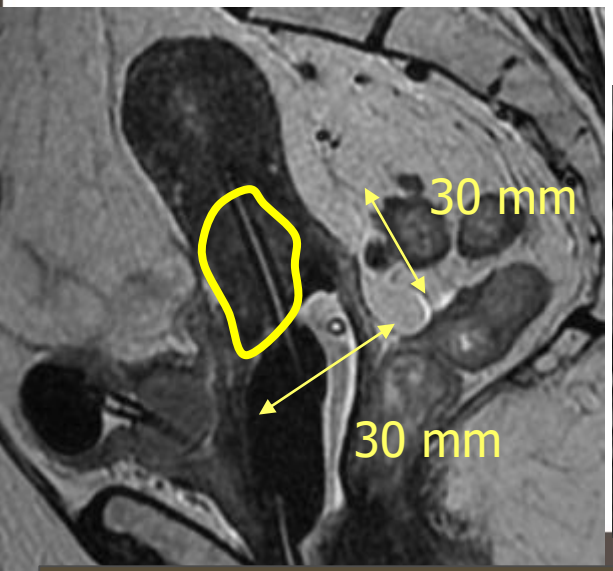


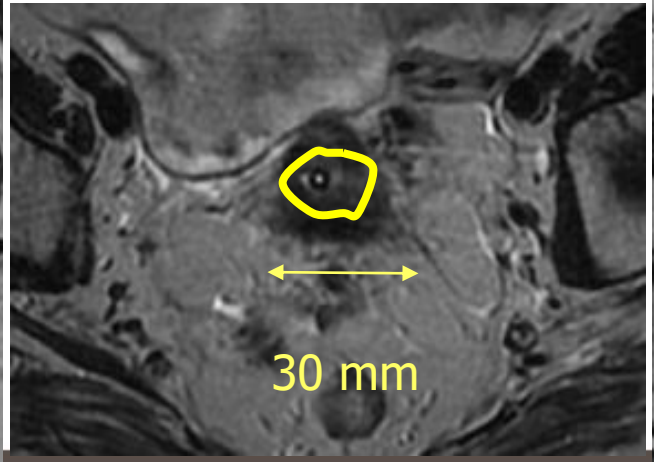
Stage IIB

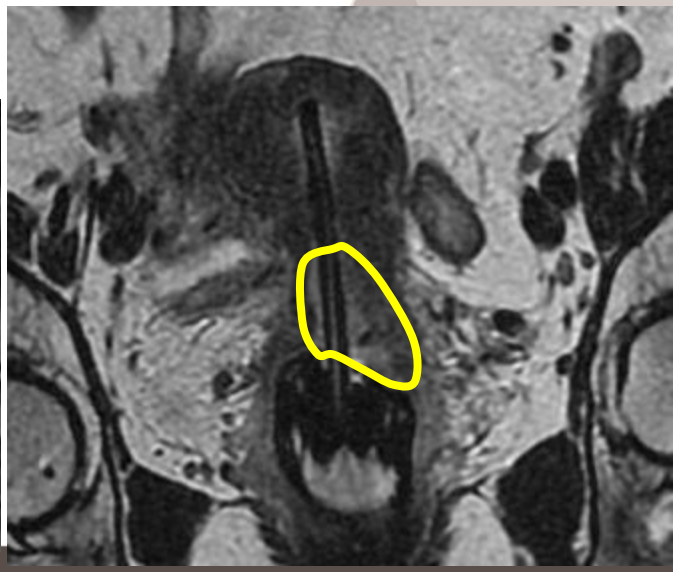




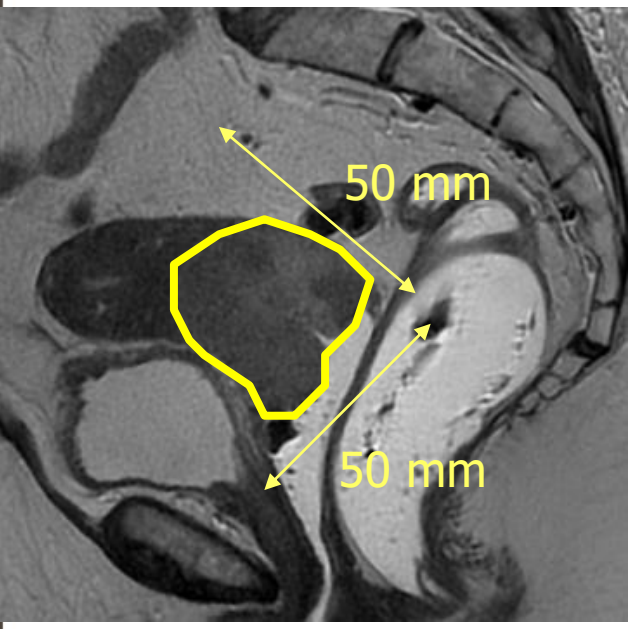


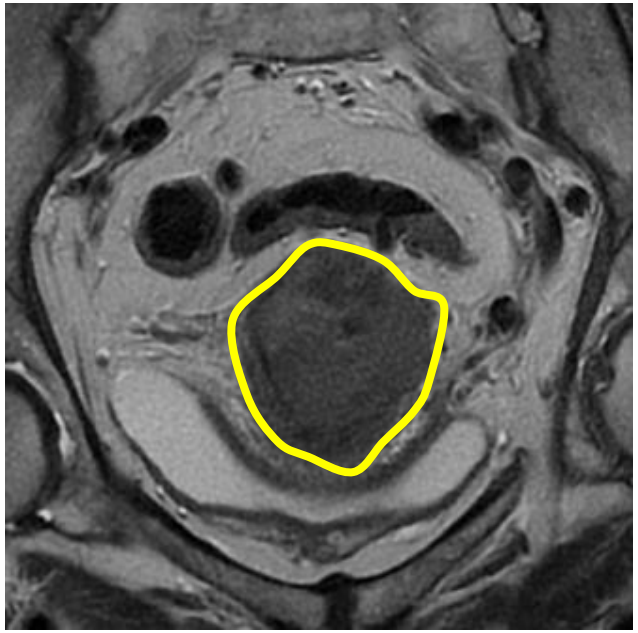


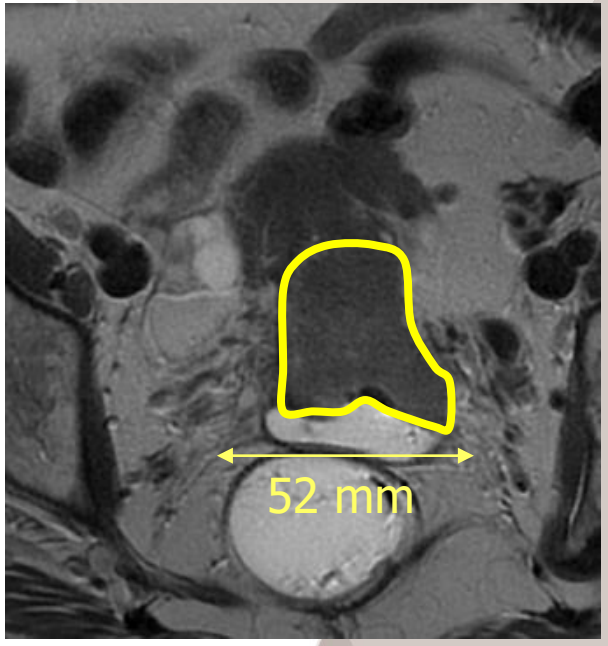


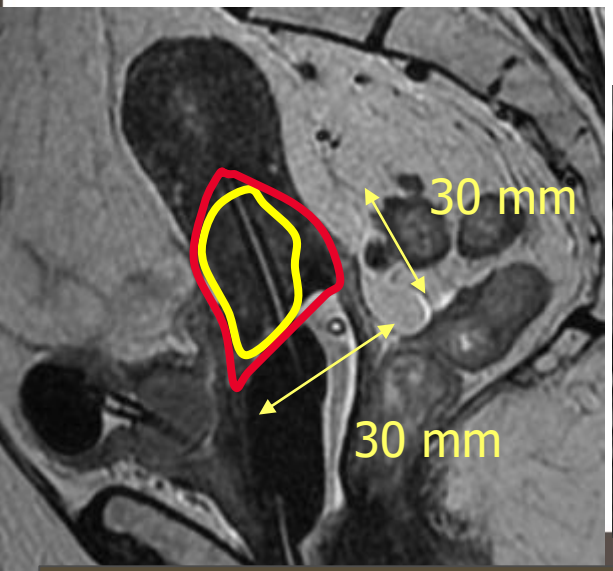


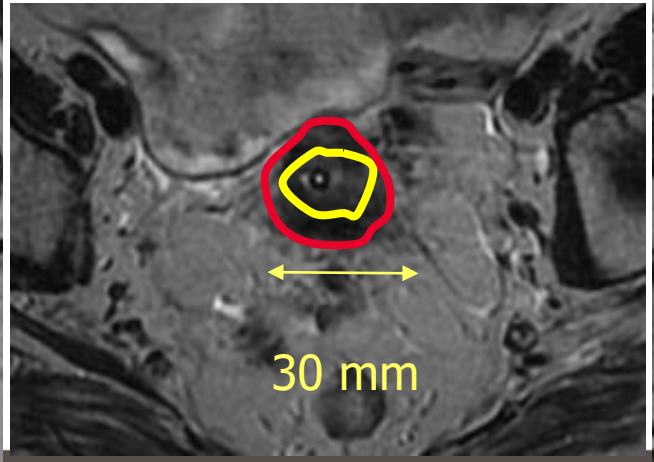
Stage IIB

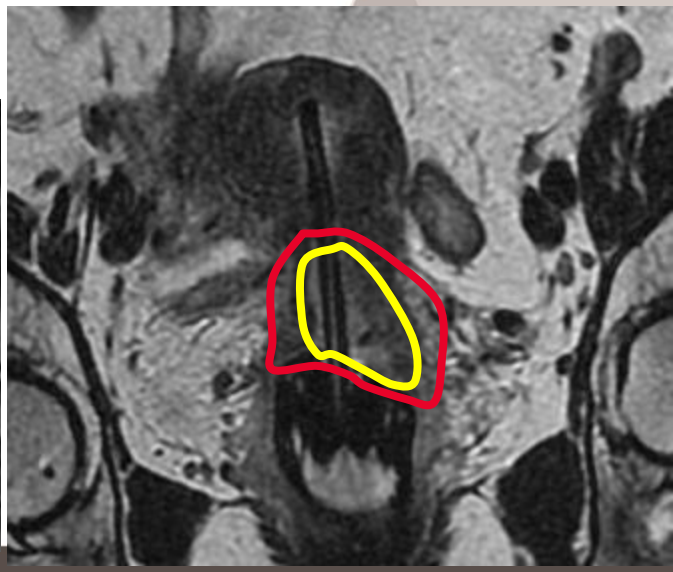




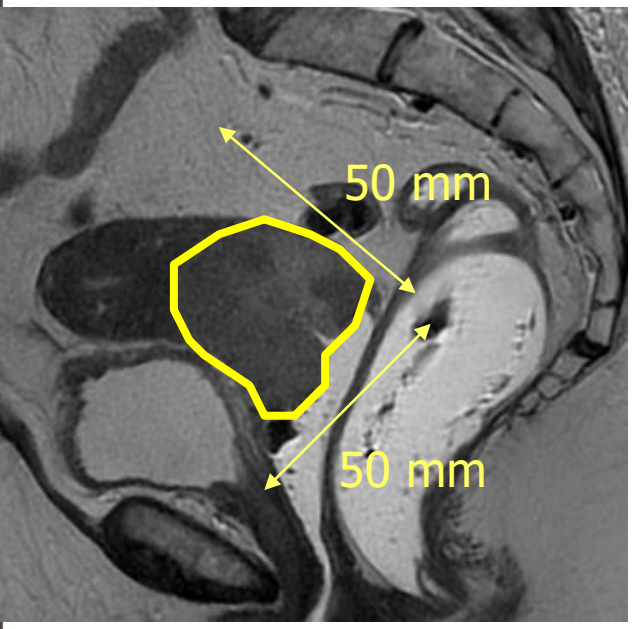


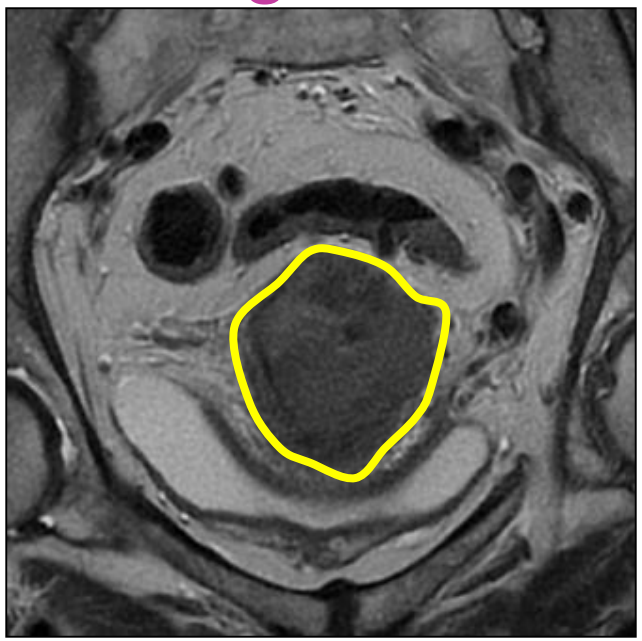


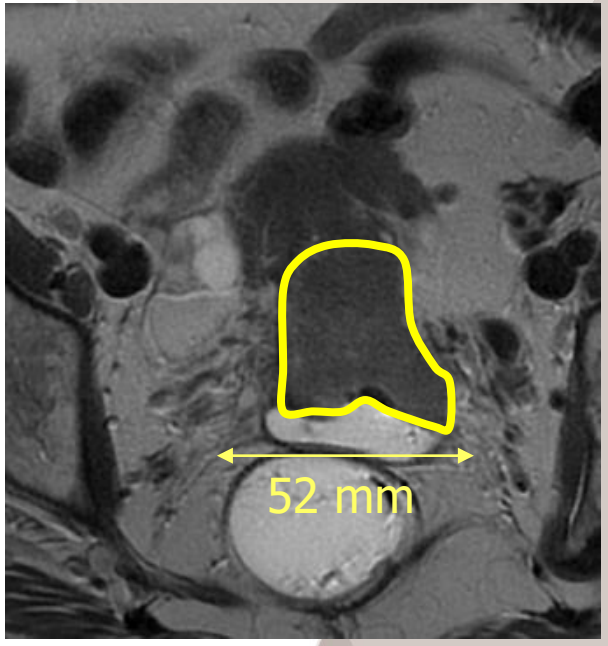


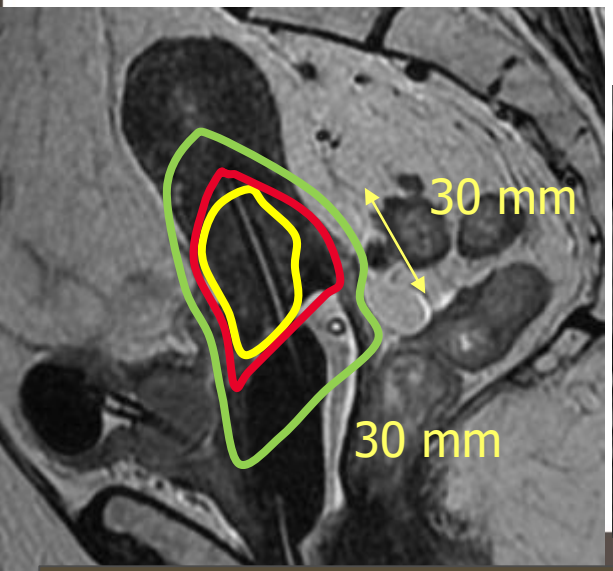


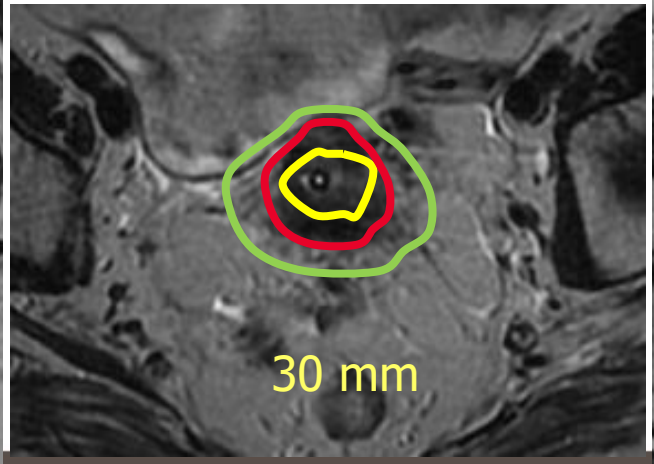
Stage IIB

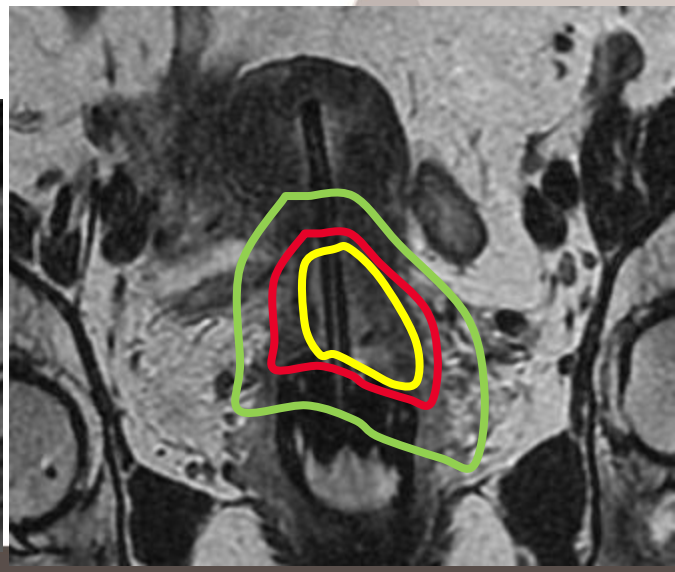












Patient n° 5

Mrs Maria-Christina SIL…
55 year-old

WHO=0, 60 kg, 1m53

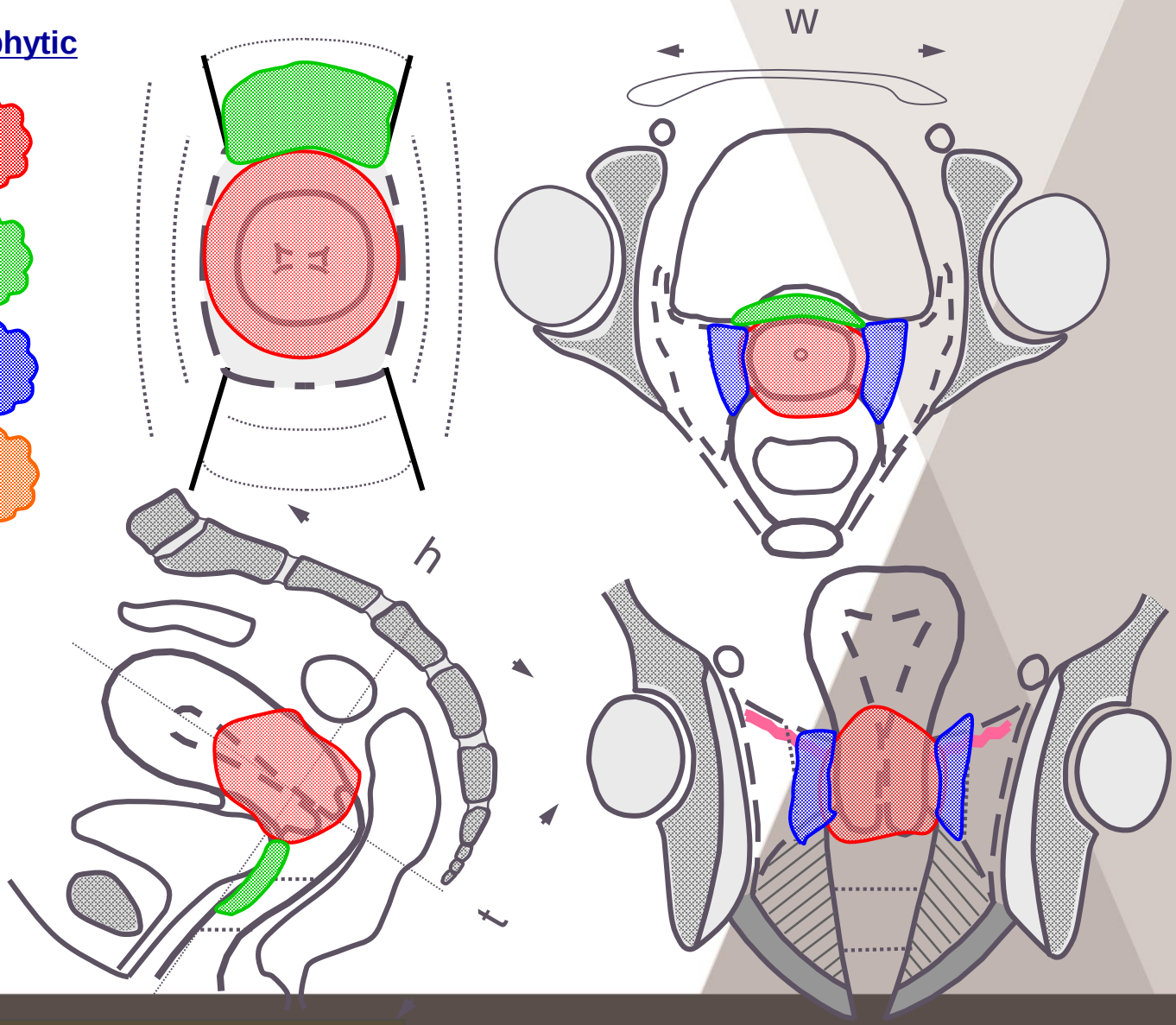
Vaginal bleeding

Biopsy: moderately differentiated SCC

At clinical examination : cervical tumor + infiltration of the ½ upper anterior vaginal wall + proximal infiltration of both parametria

Stage IIB : initial clinical examination

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		



Dimensions (cm):

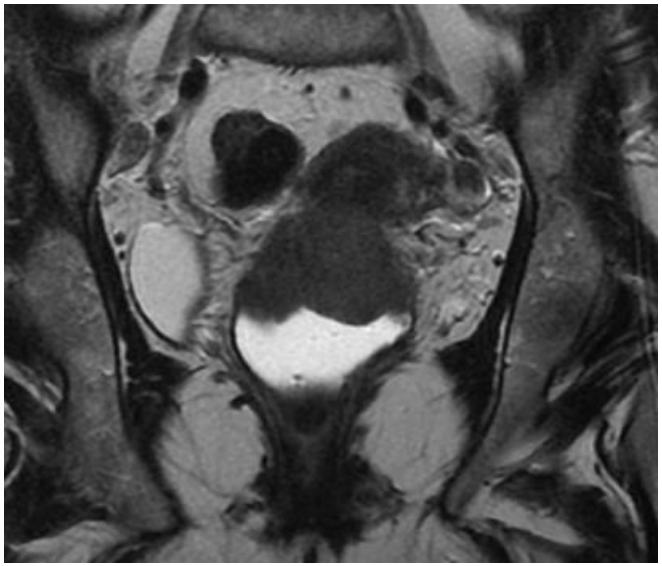
Width : 5

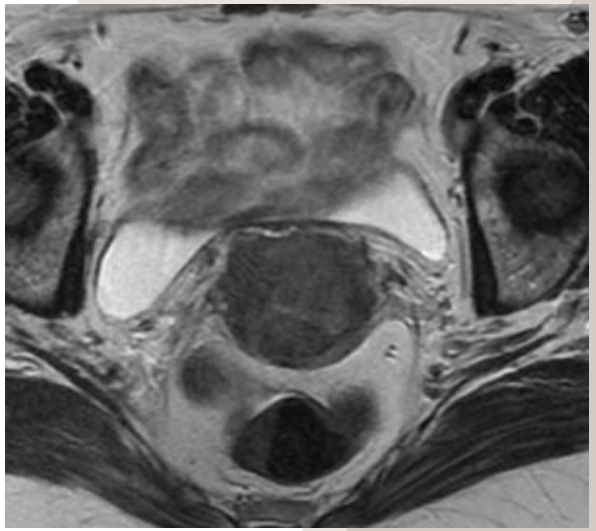
Thickness:5

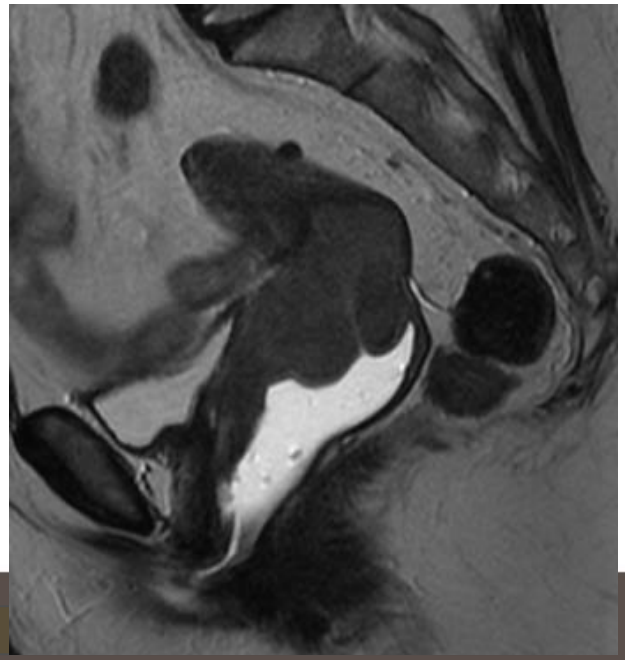
Height : 5

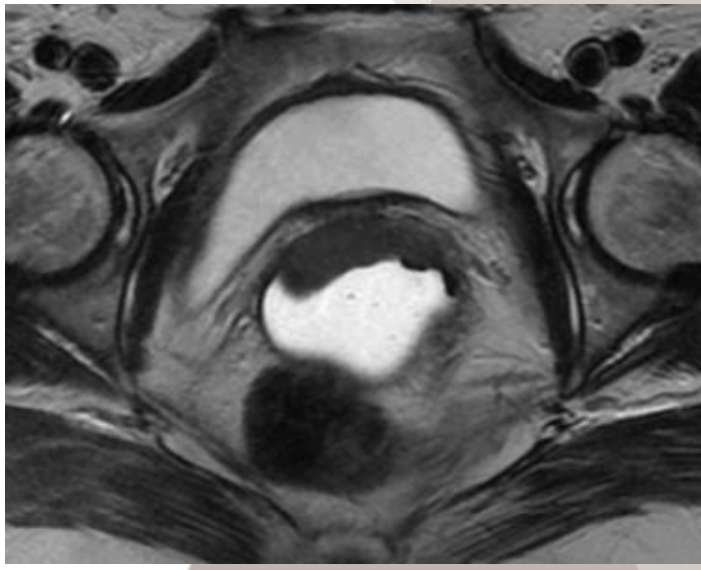
Vag involv 3

Stage IIB : initial MRI



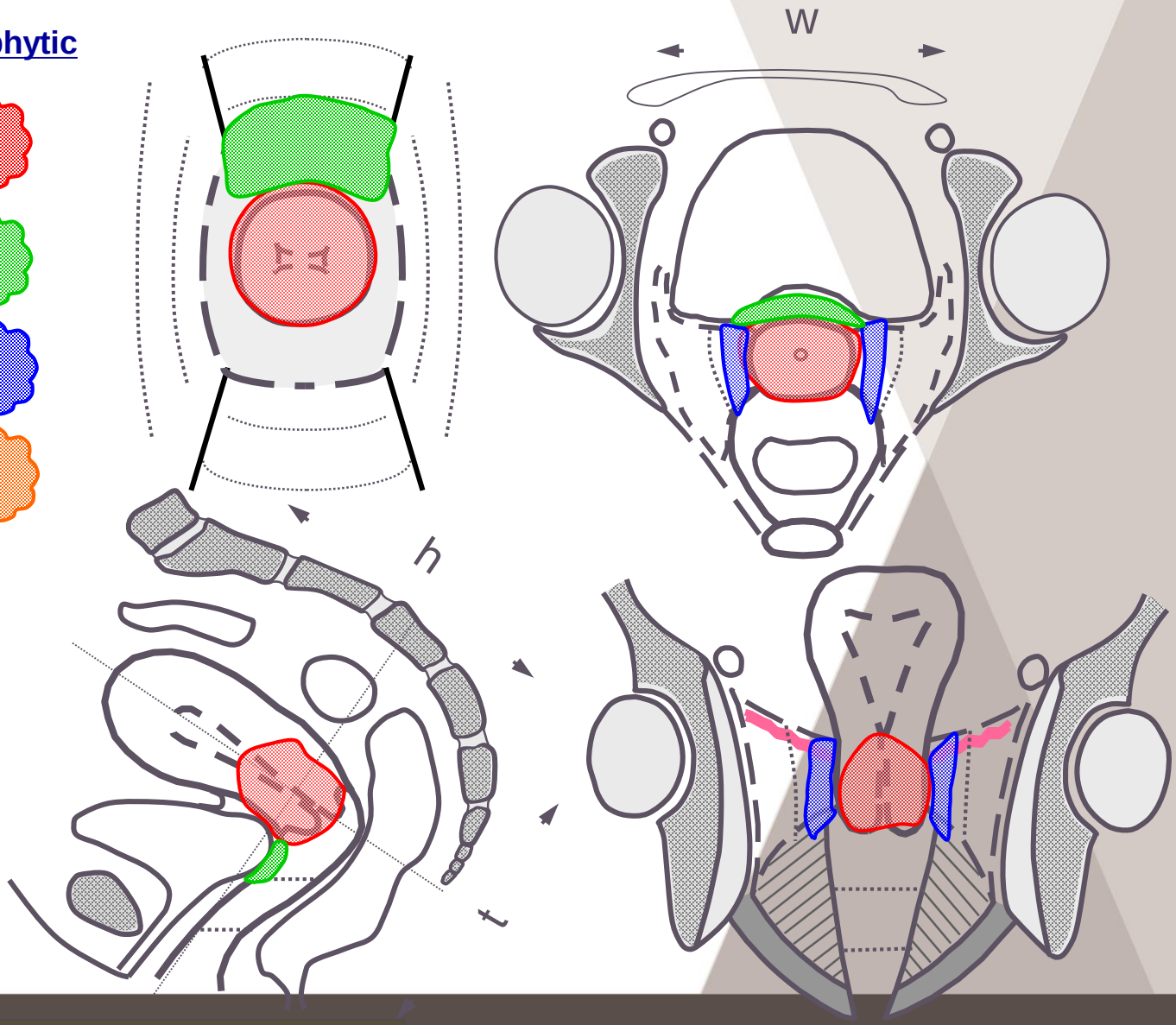






Stage IIB : clinical examination at BT

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		



Dimensions (cm):

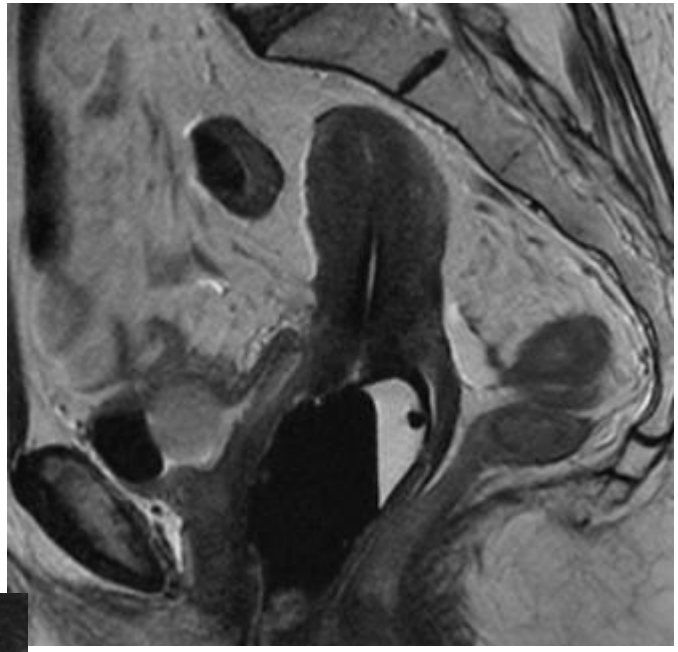
Width : 3.5

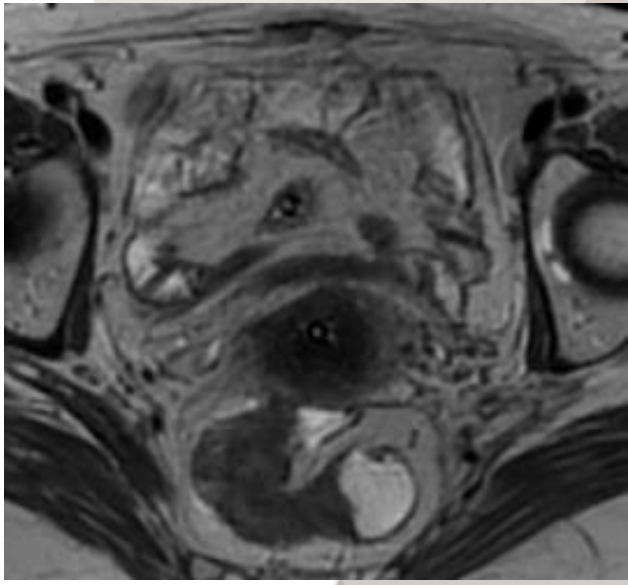
Thickness:3.5

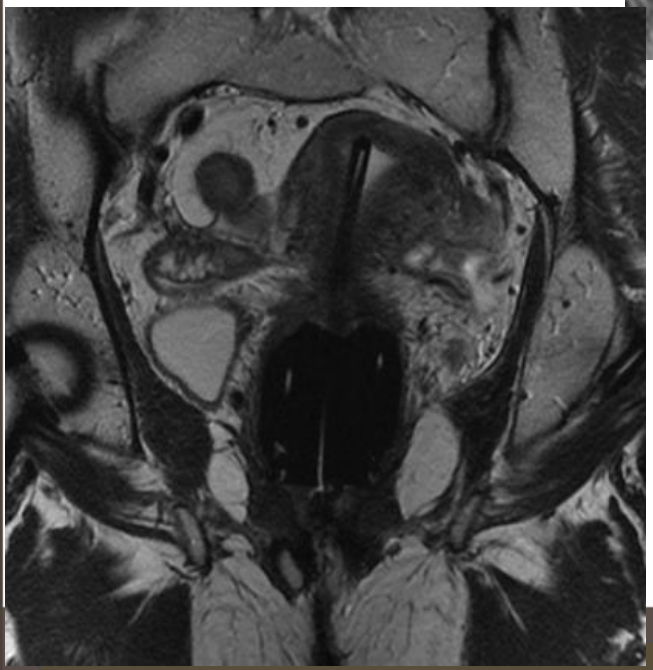
Height : 3

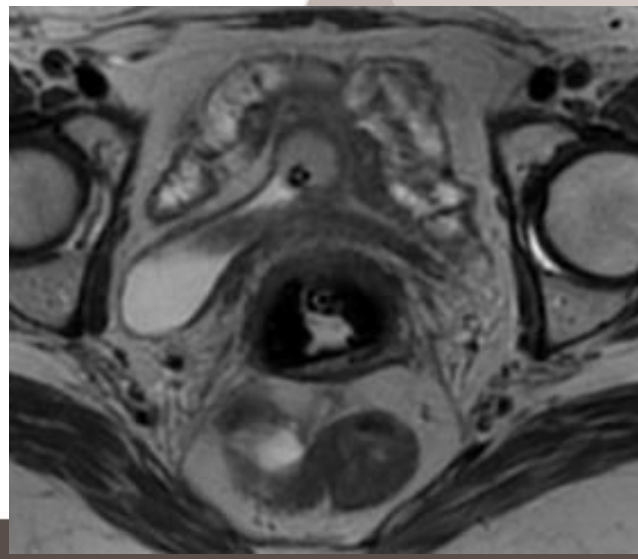
Vag involv 1.5

Stage IIB : MRI at BT

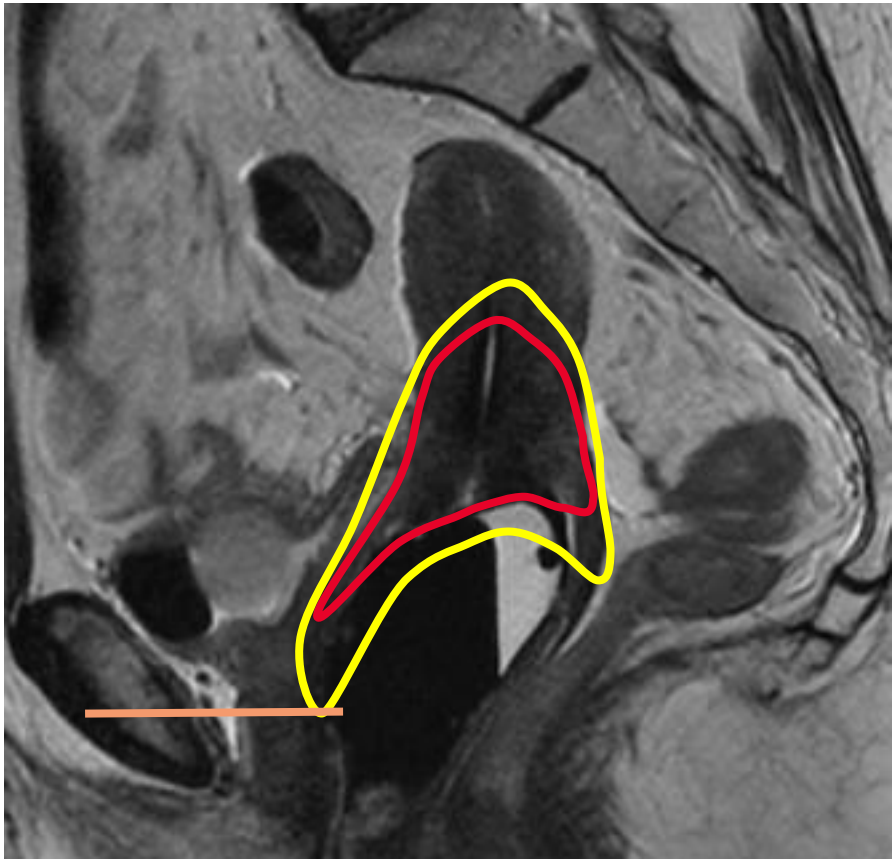


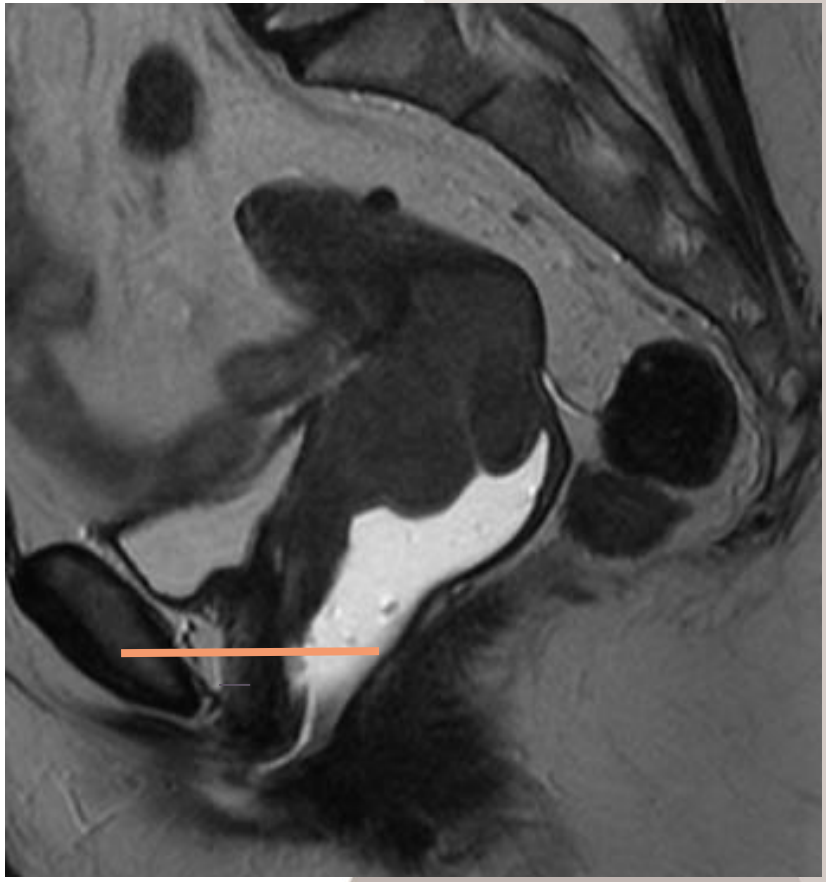






IR-CTV in the vagina





Patient n° 6

Mrs Caroline CUN…
44 year-old

WHO=0, 62 kg, 1m65

Vaginal bleeding for > 1year

Biopsy: well differentiated carcinoma

At clinical examination : cervical tumor + infiltration of the left fornix + infiltration of the left parametrium to the pelvic wall (especially on the posterior part of the parametrium)

Stage IIIB : initial clinical examination

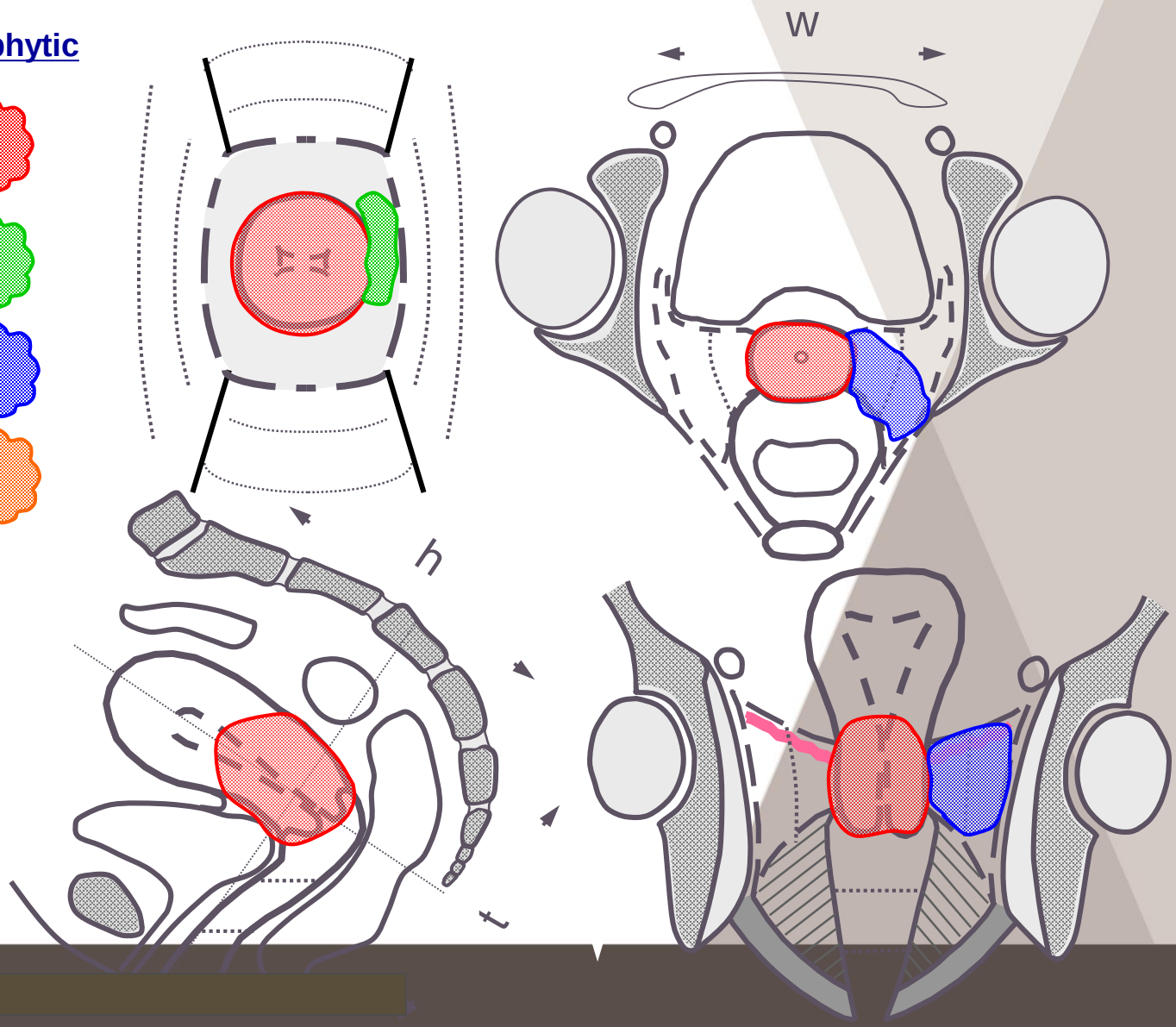
	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

Dimensions (cm):

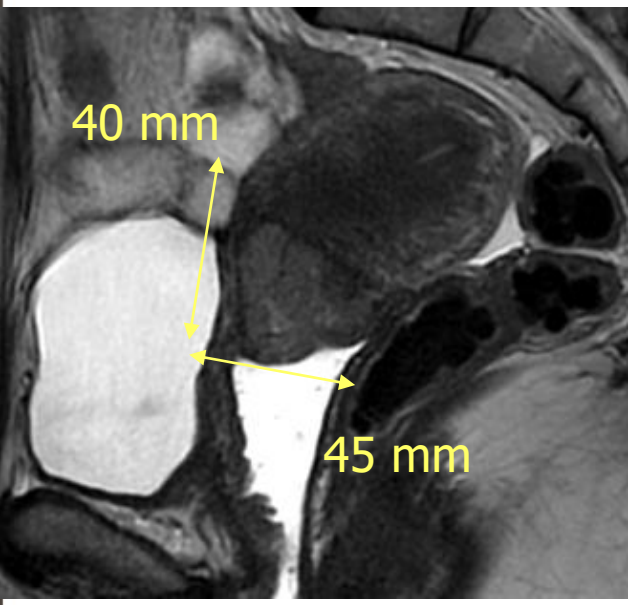
Width : 6

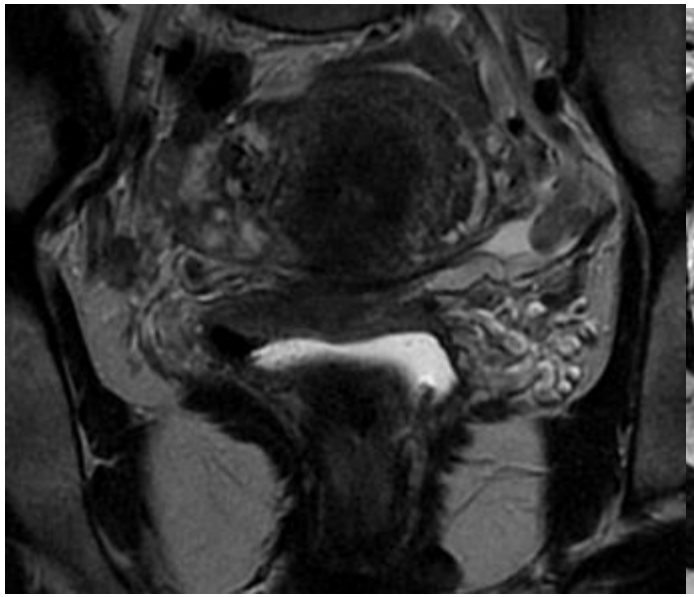
Thickness :4

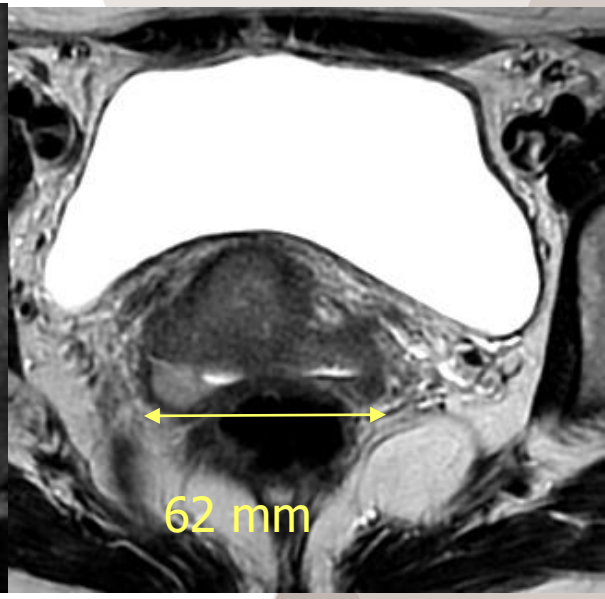
Height : 4

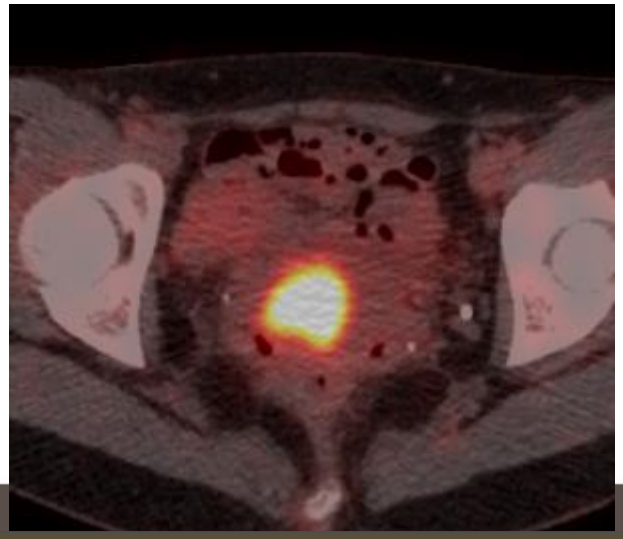


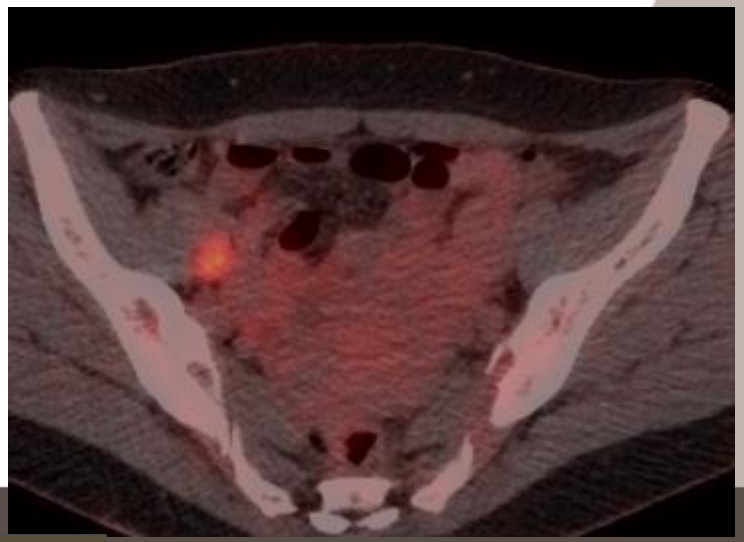
Stage IIIB : initial MRI





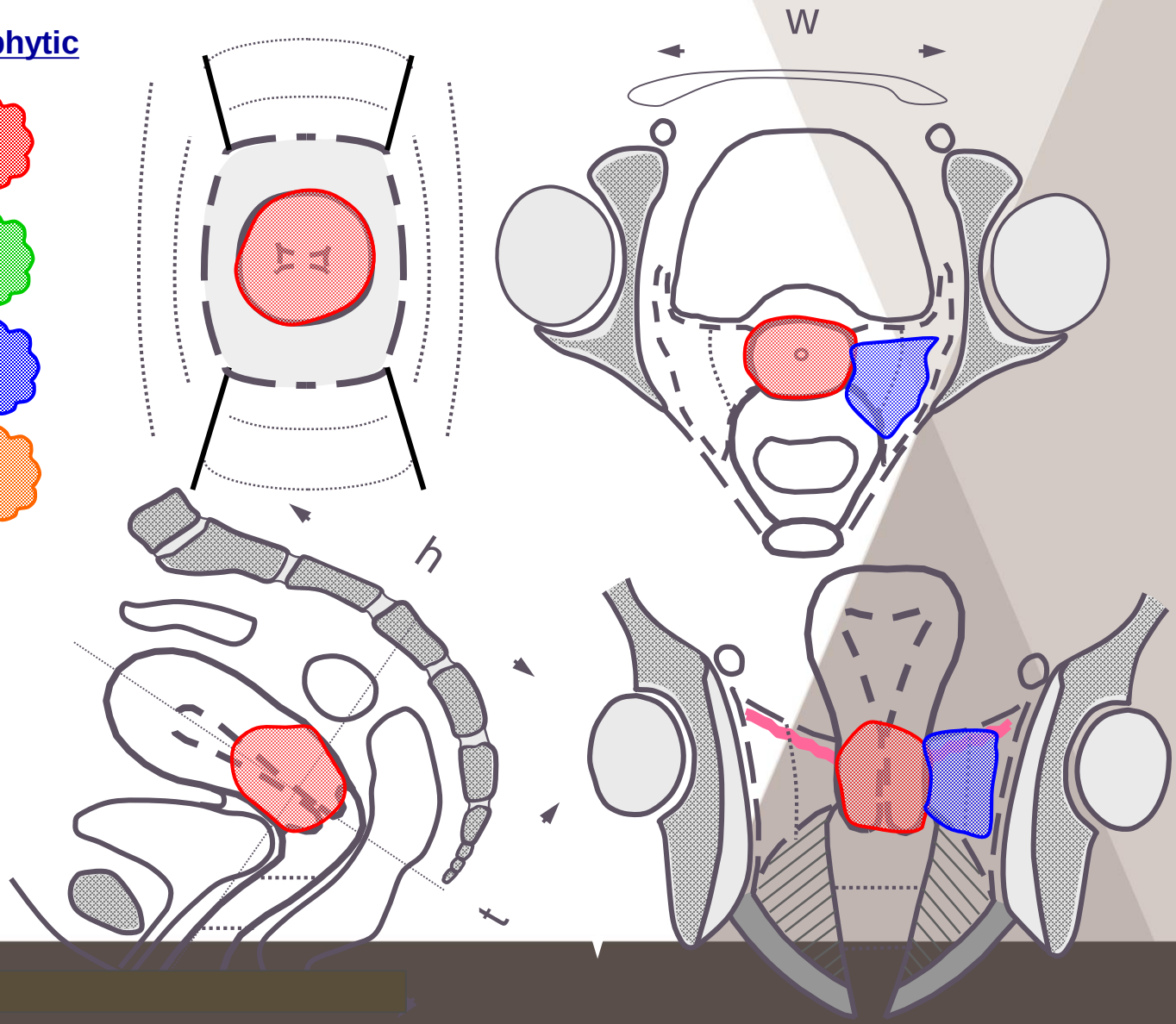






Stage IIIB : at the time of brachytherapy

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		



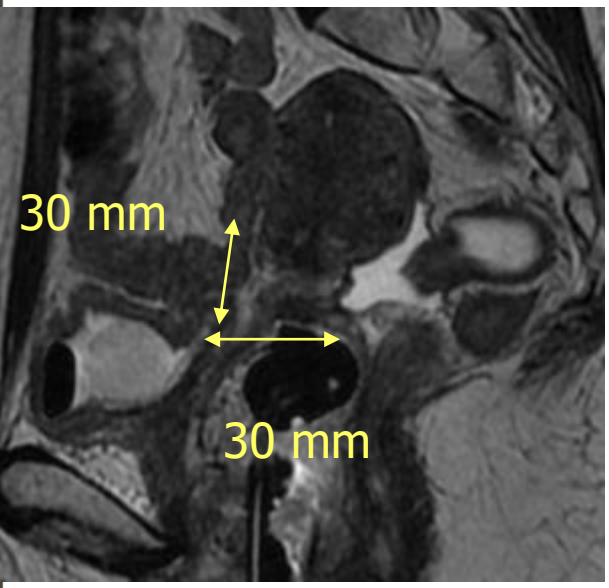
Dimensions (cm):

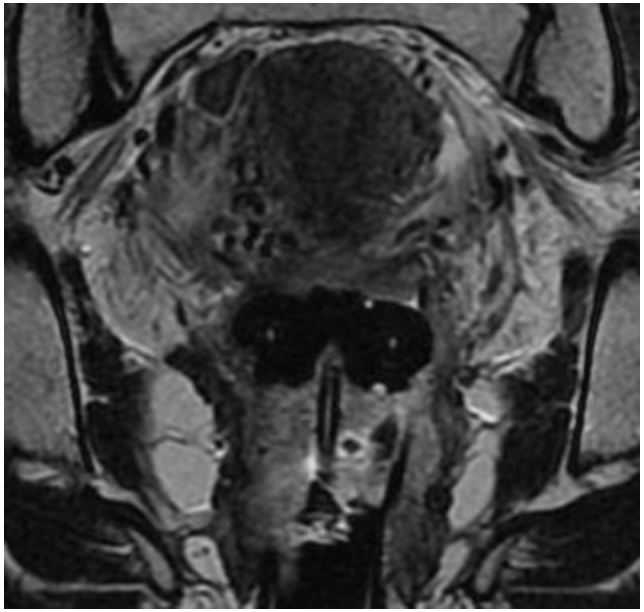
Width: 4.5

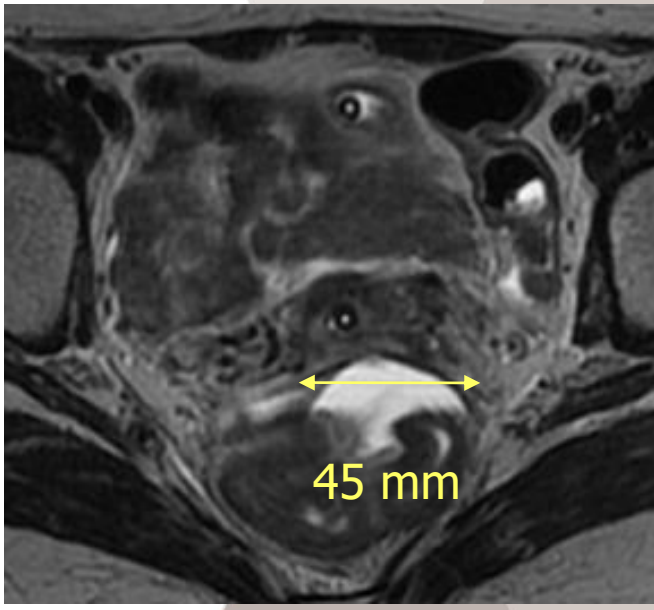
Thickness : 3

Height : 3

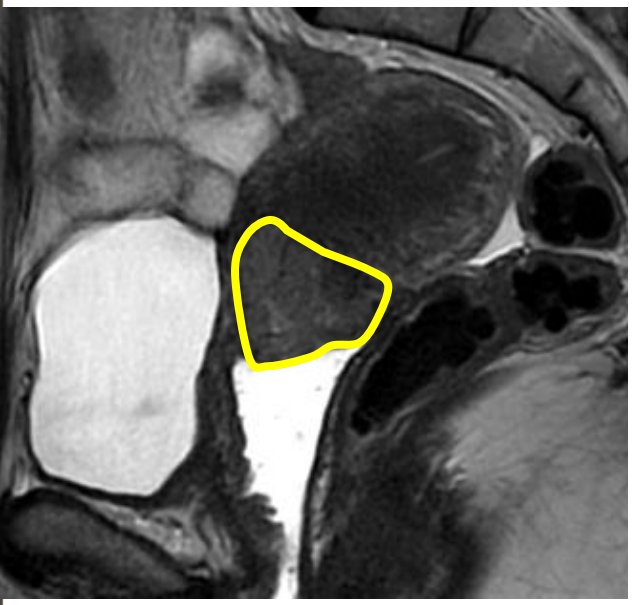
Stage IIIB : MRI at the time of brachytherapy

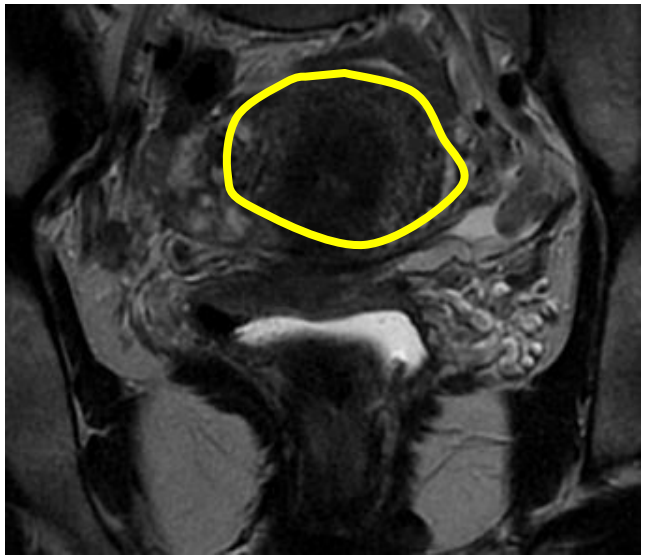


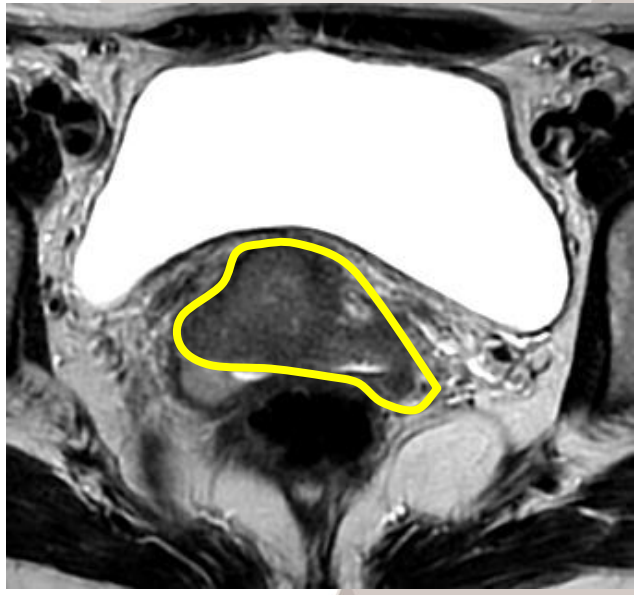


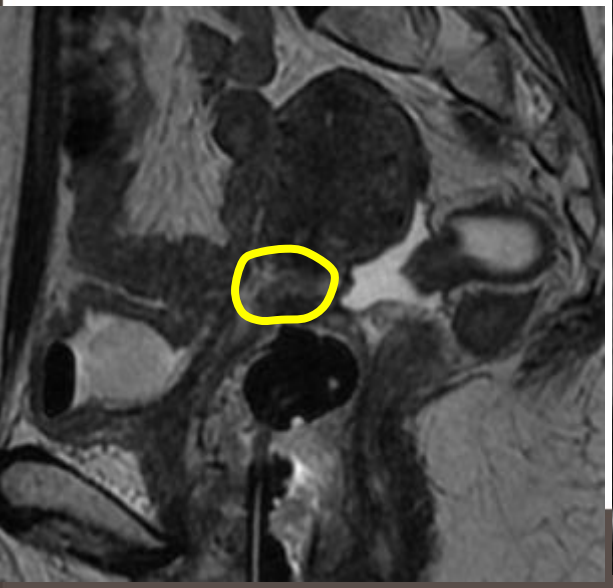


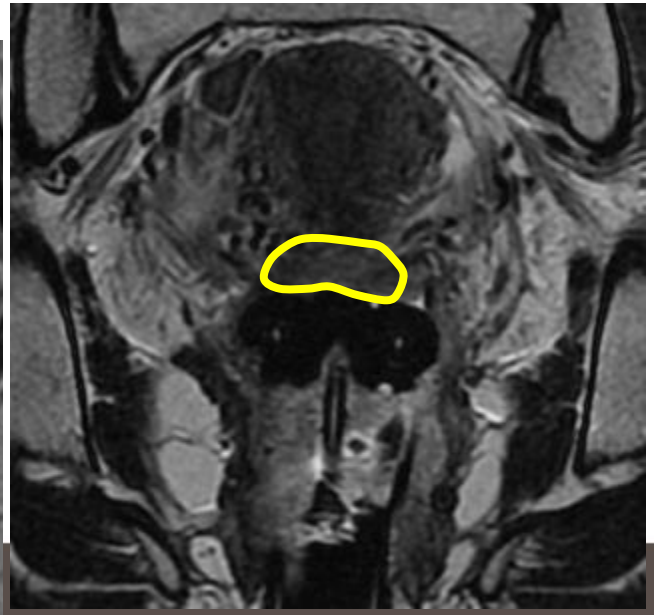
Stage IIIB

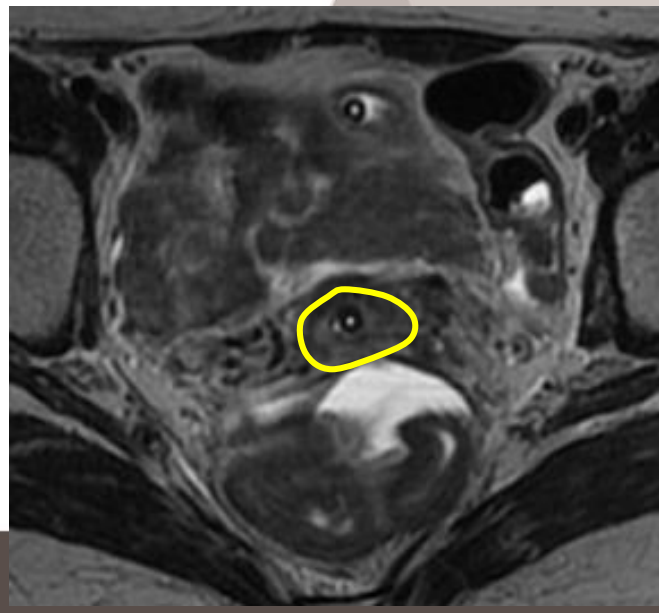




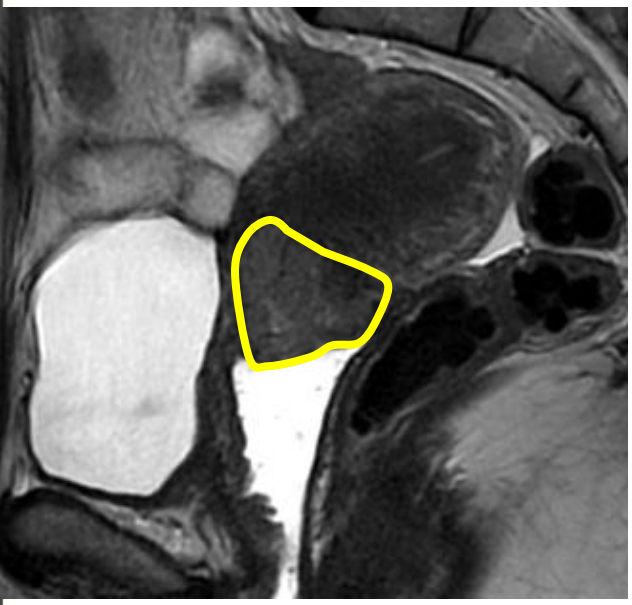


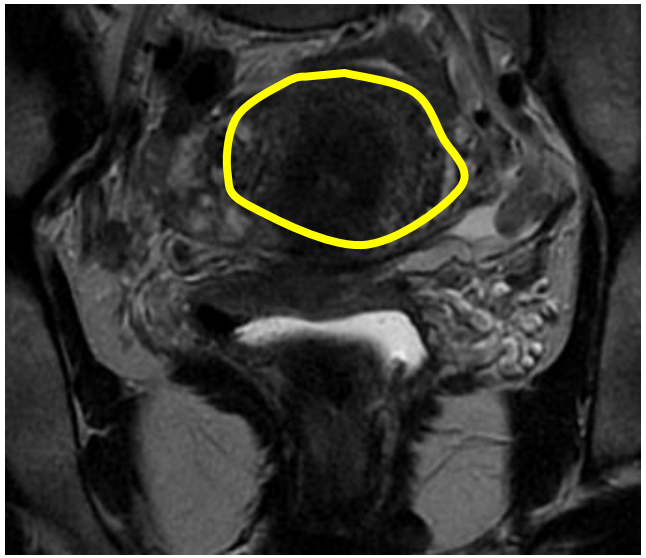


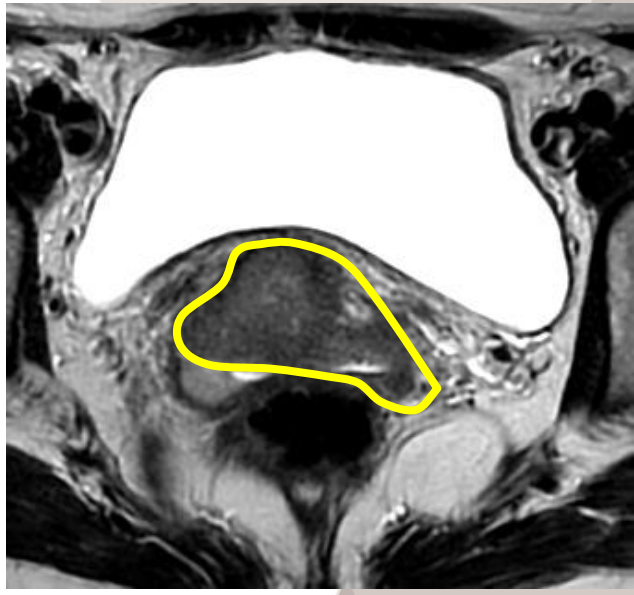


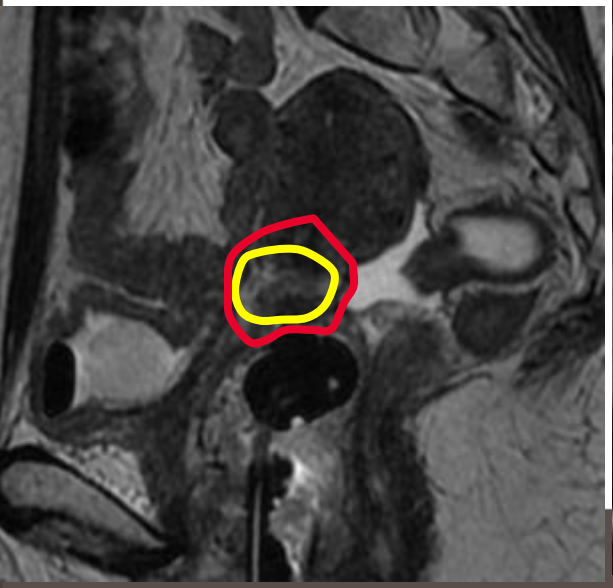


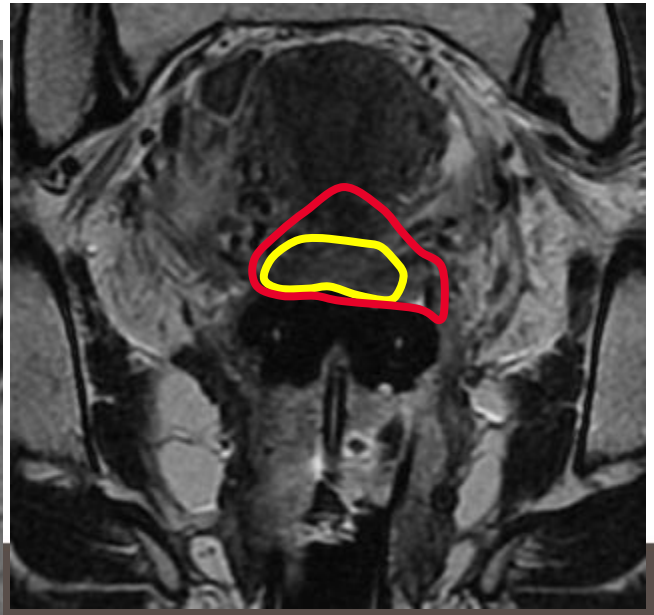
Stage IIIB

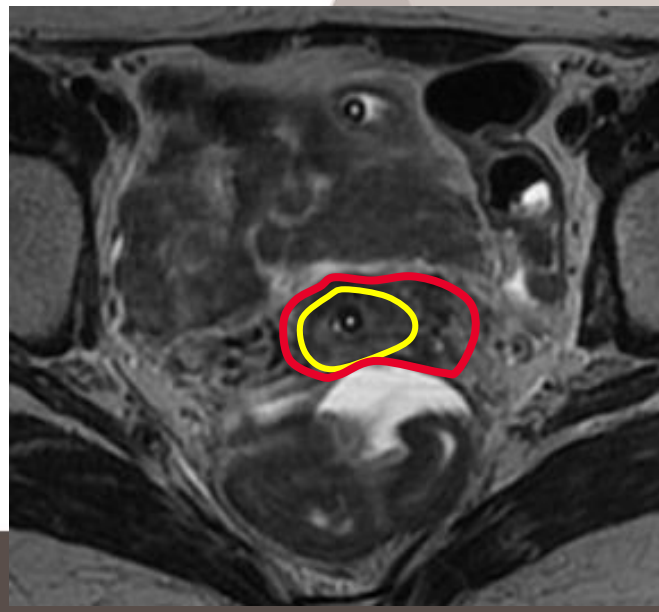




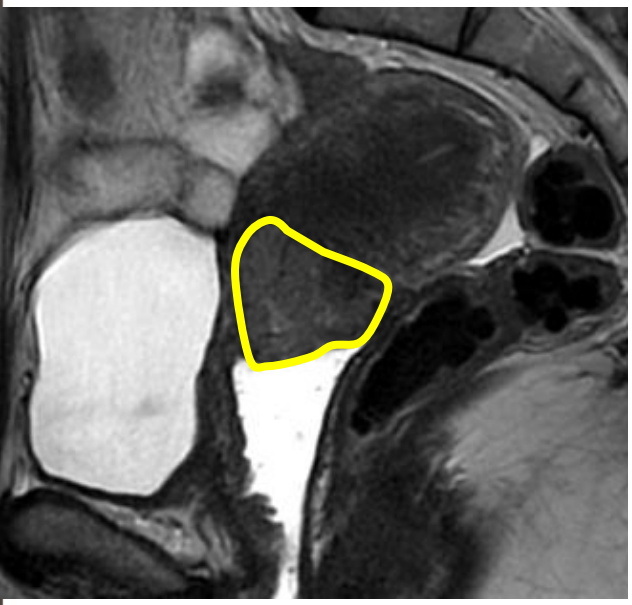


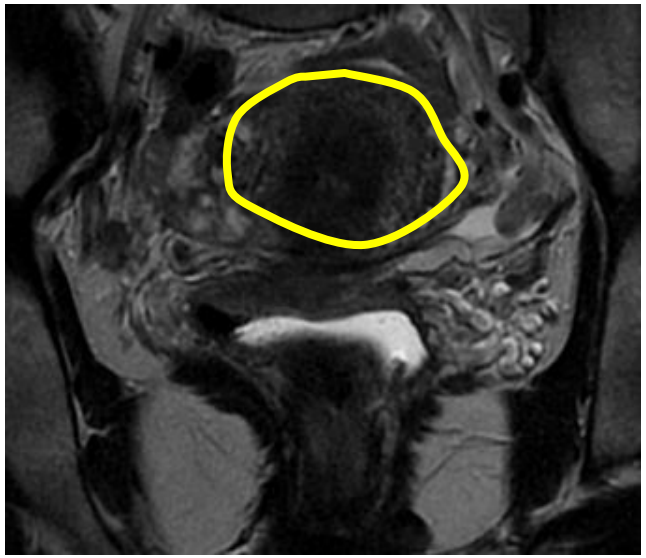


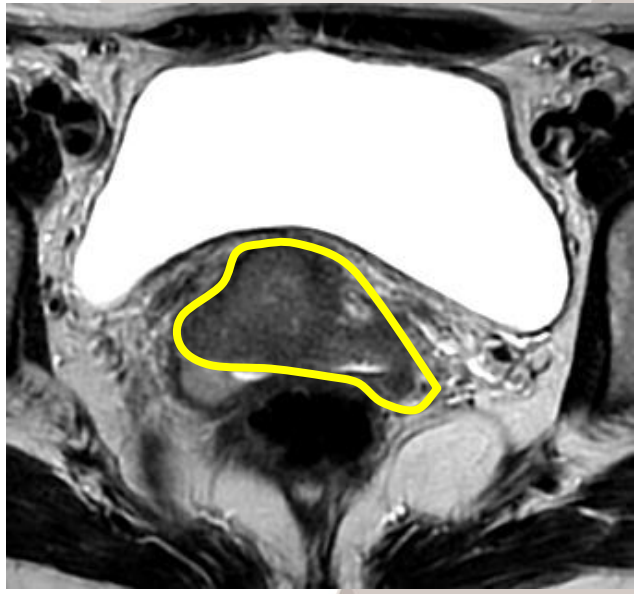


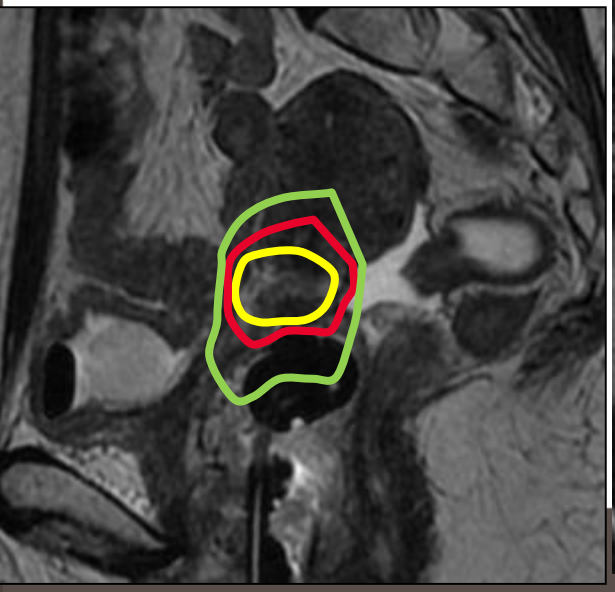


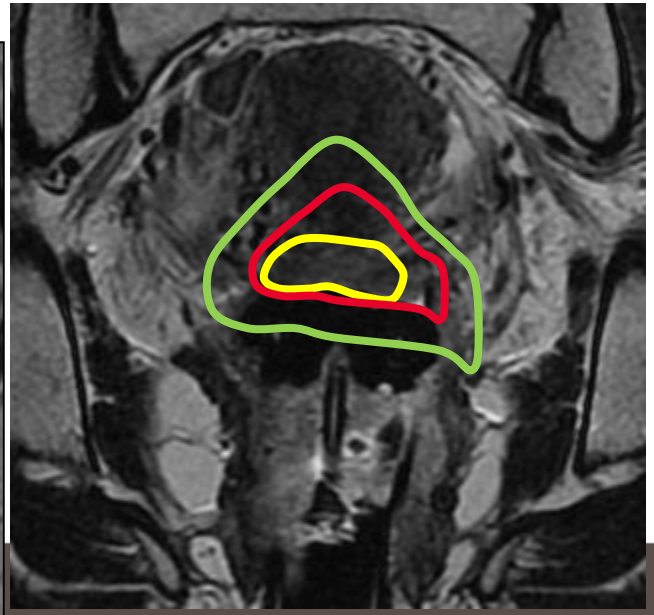
Stage IIIB

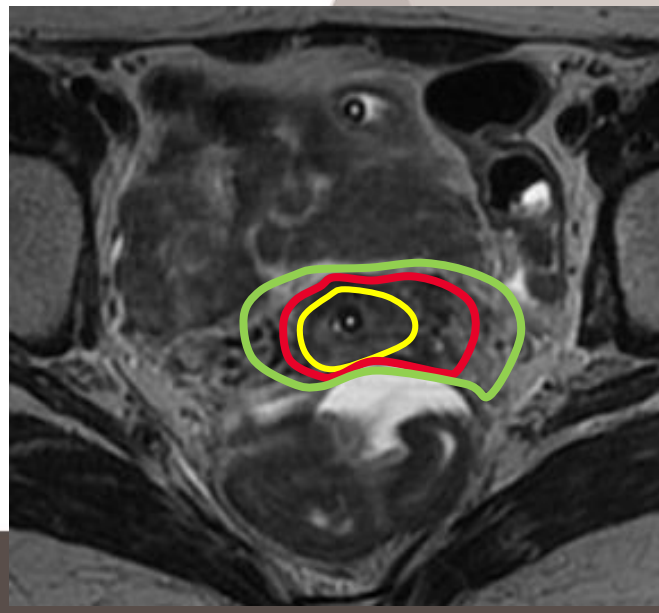




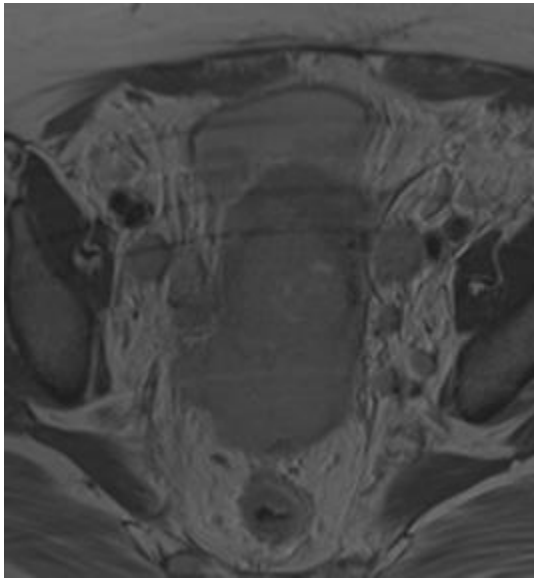


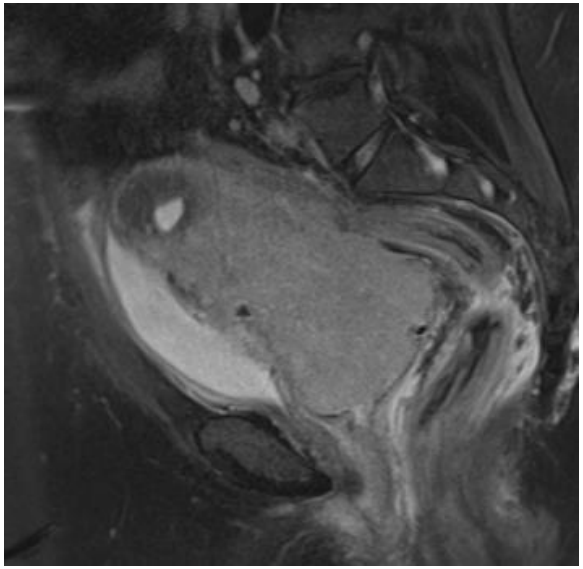


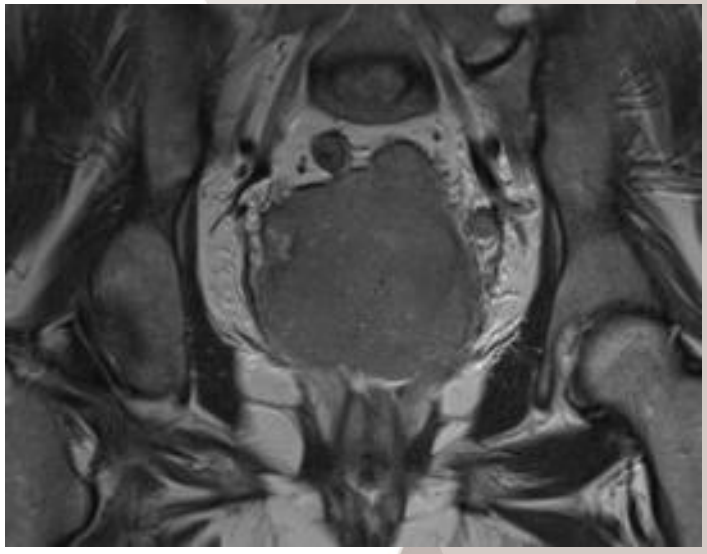


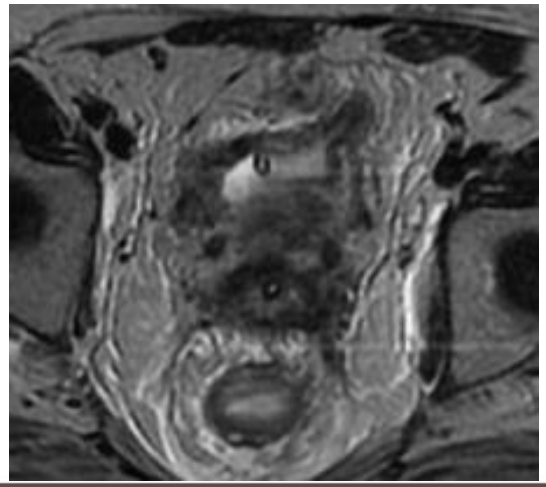


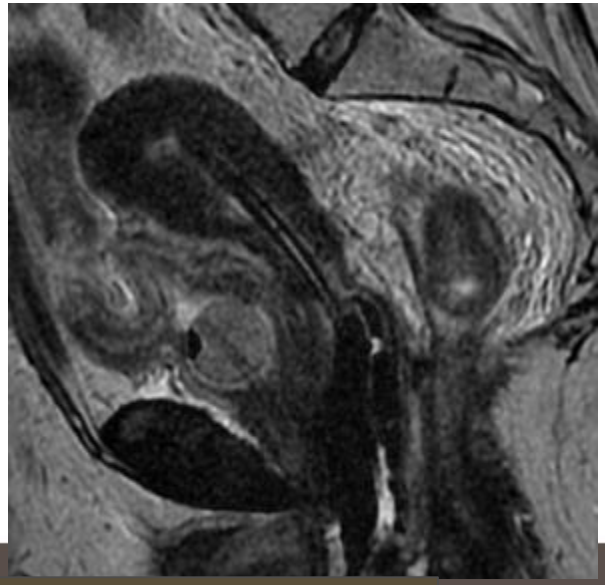
Stage IIIB

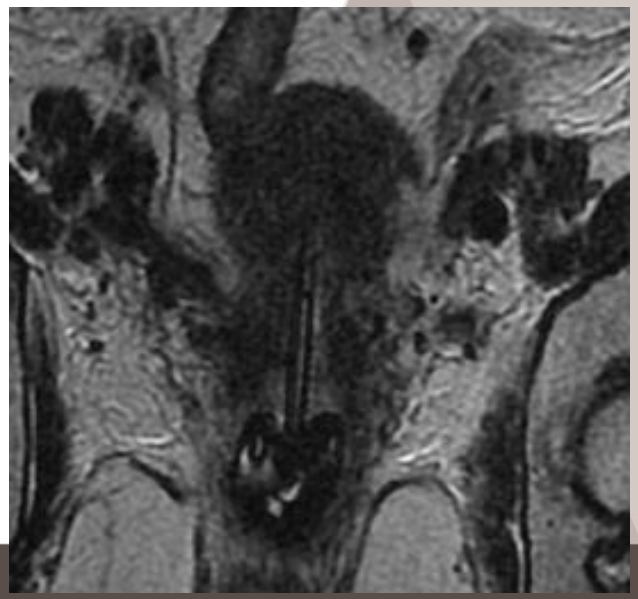




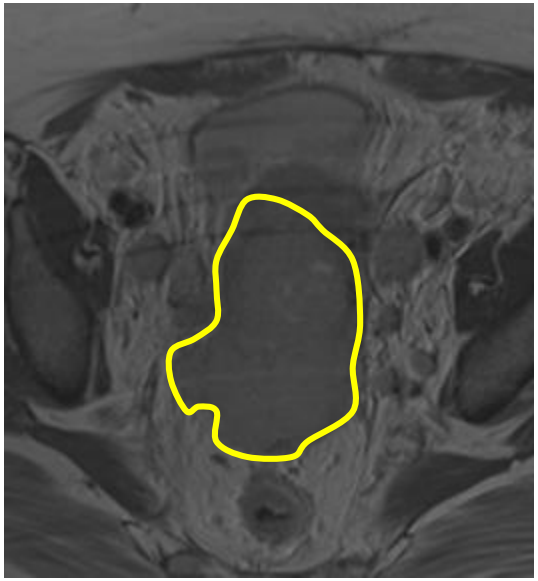


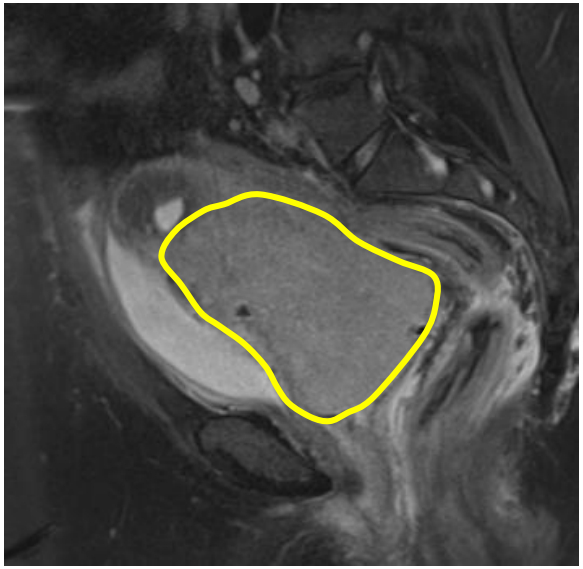


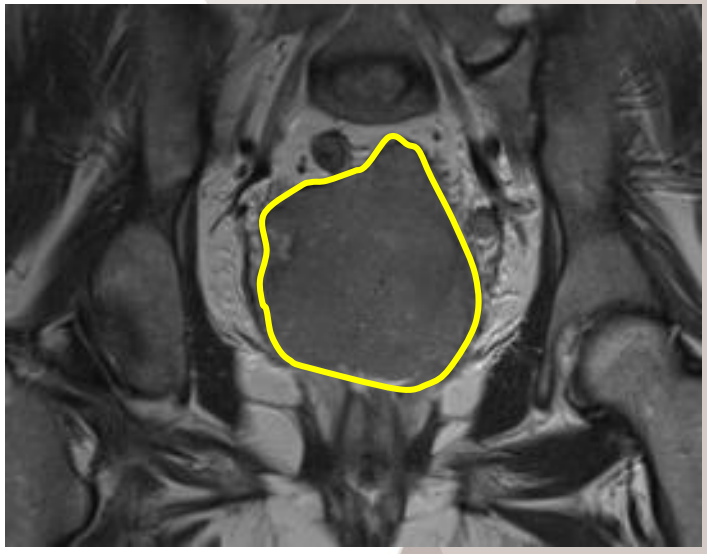


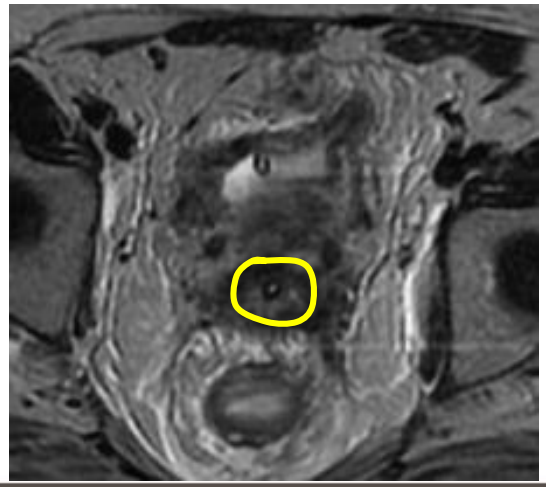


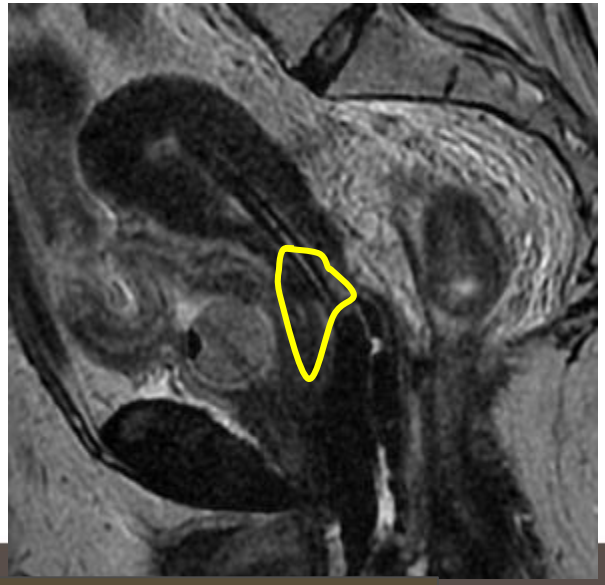
Stage IIIB

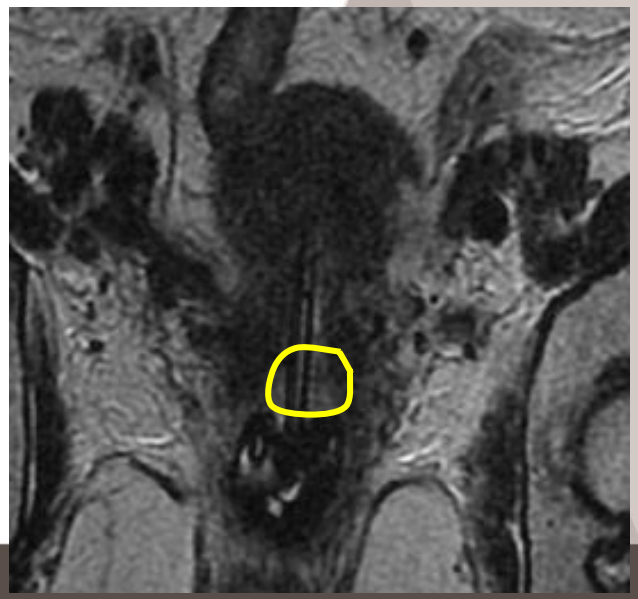




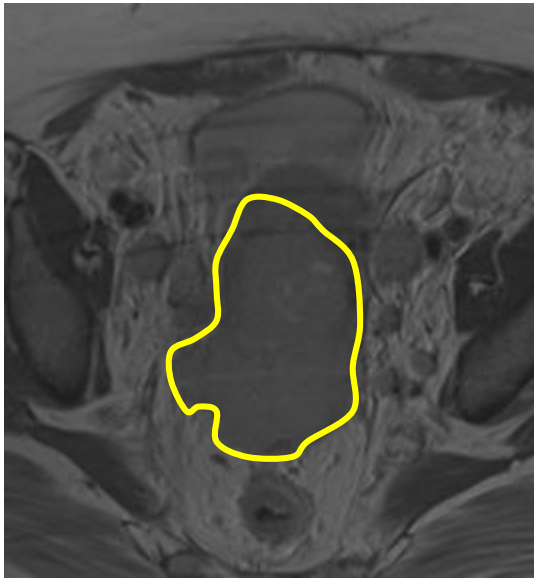


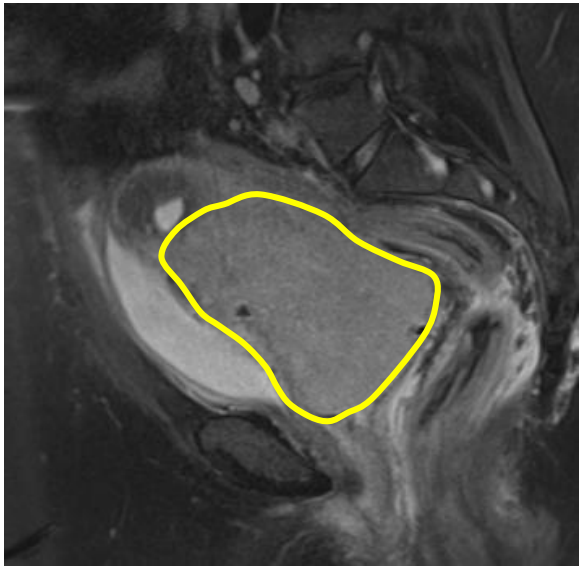


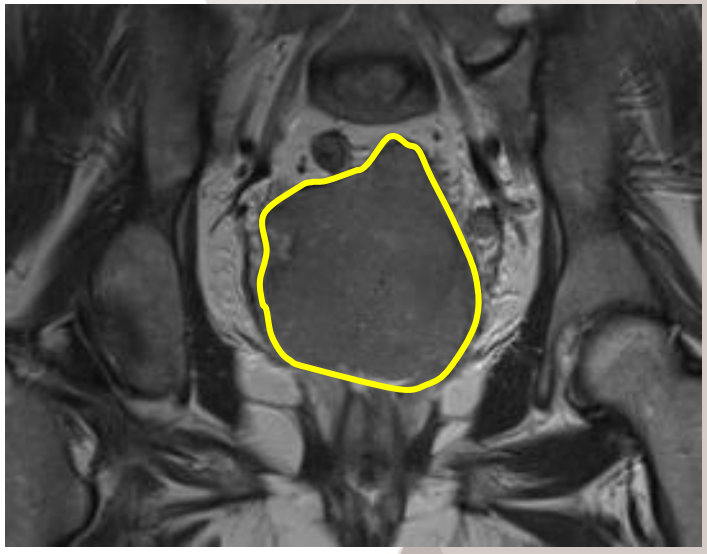


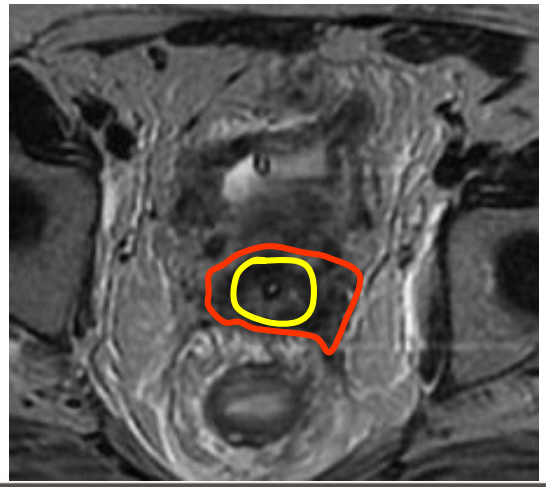


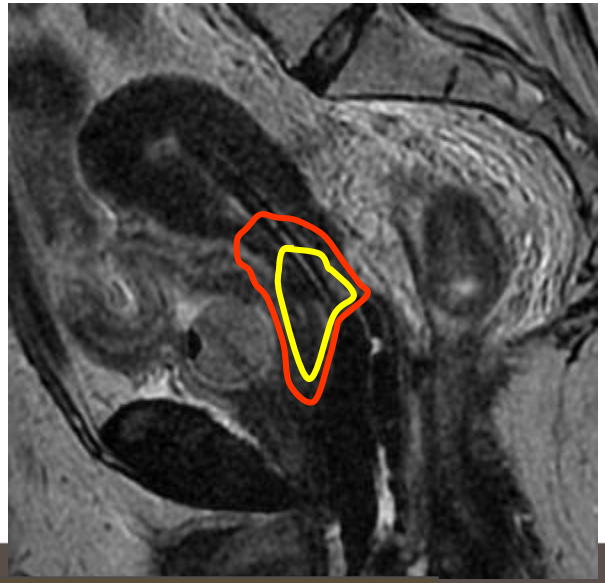
Stage IIIB

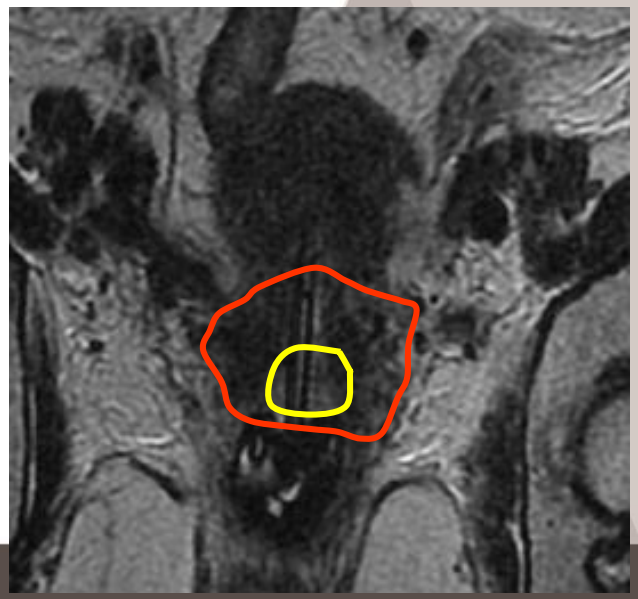




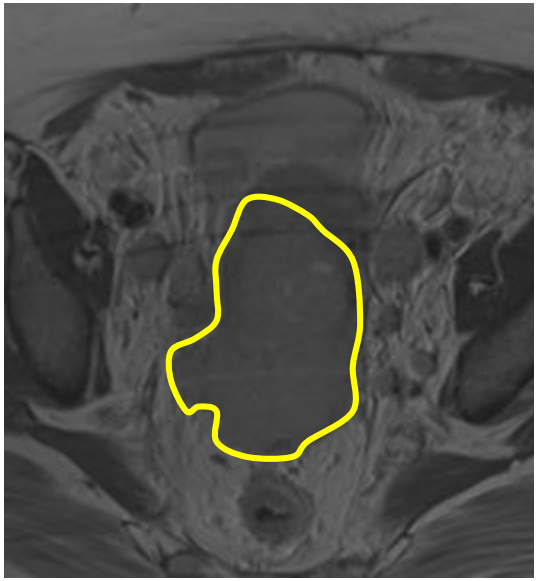


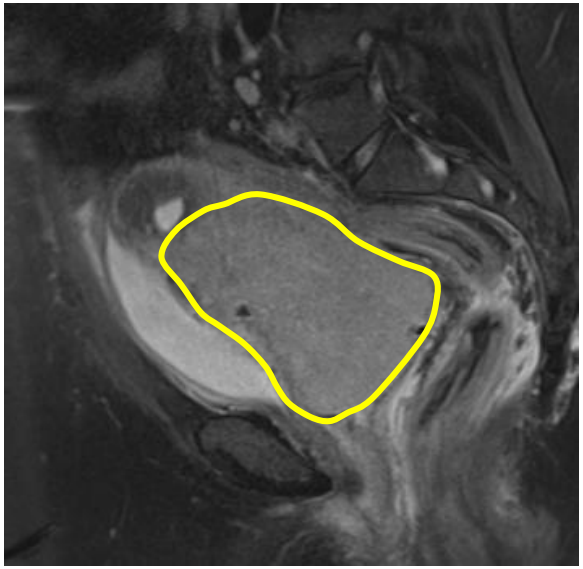


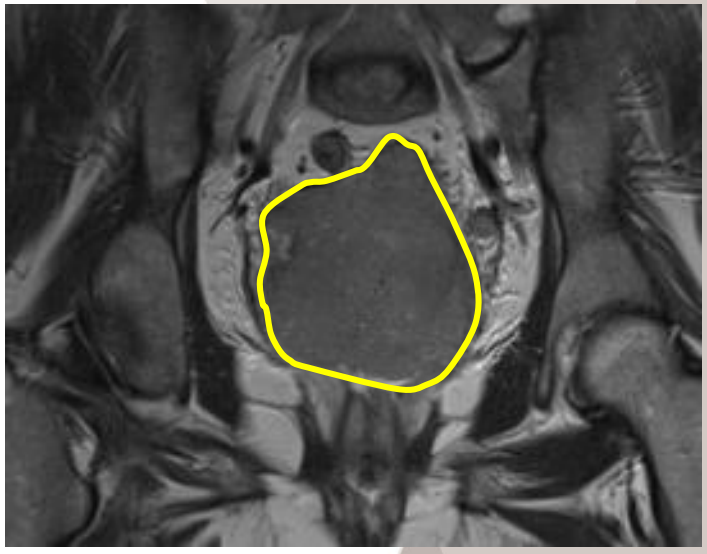


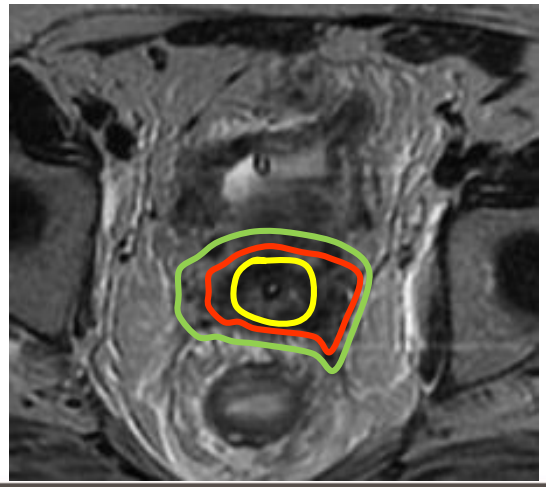


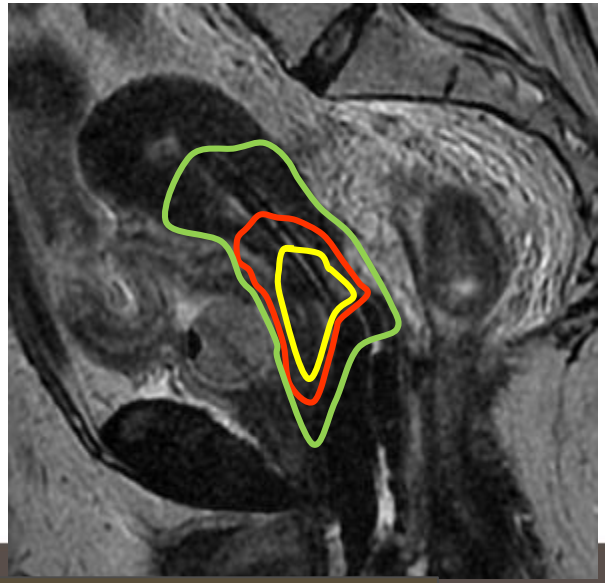
Stage IIIB

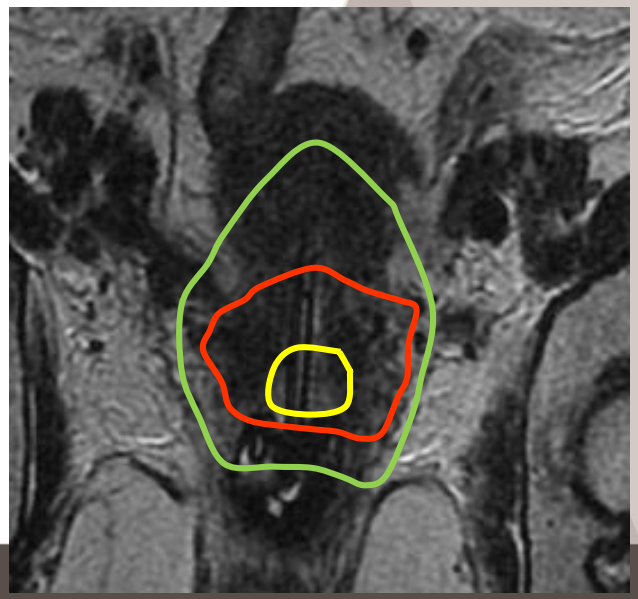












Patient n° 7

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

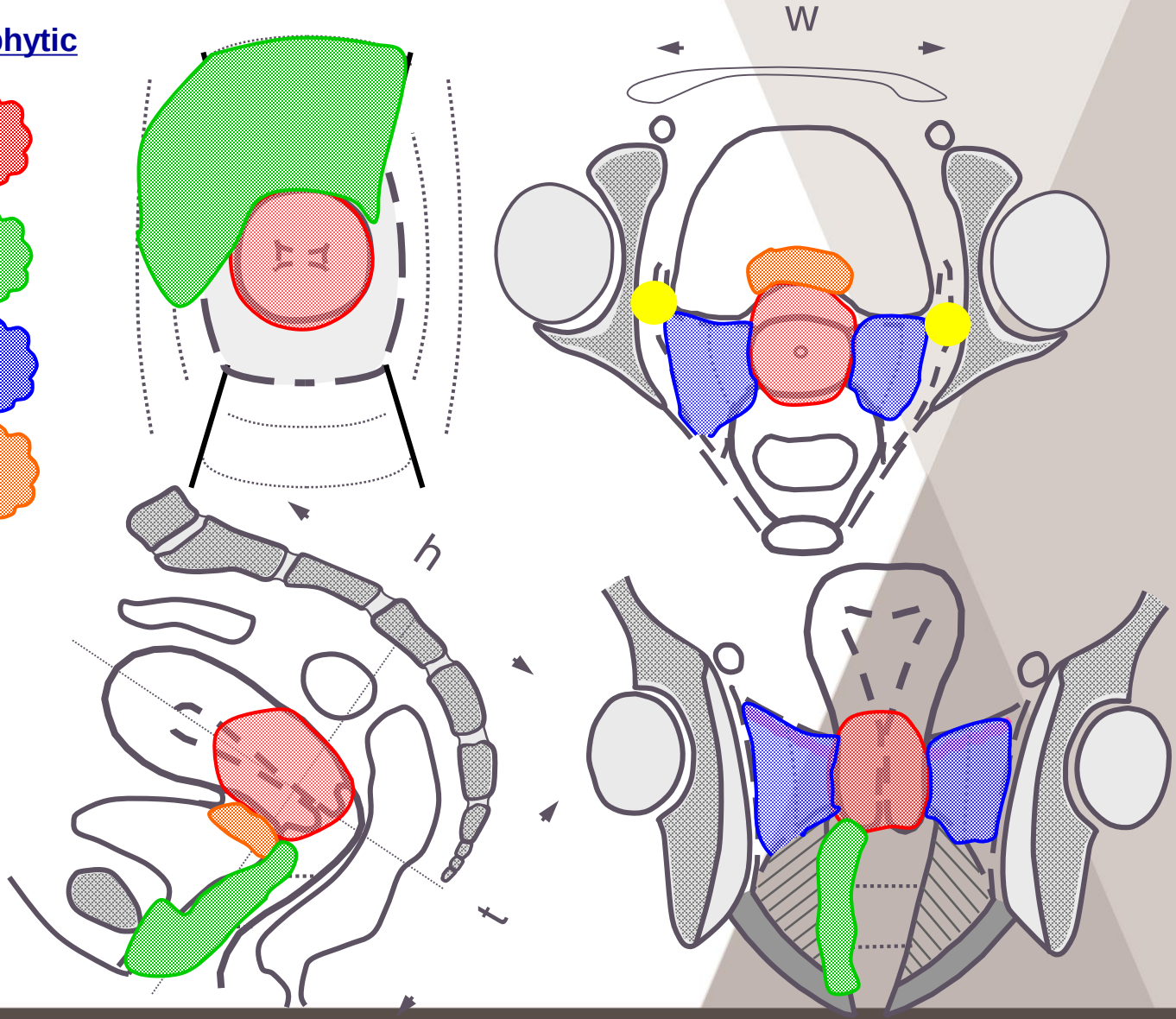
Infiltrating **Exophytic**

Cervix

Vagina

Parametrium

Rectum or Bladder



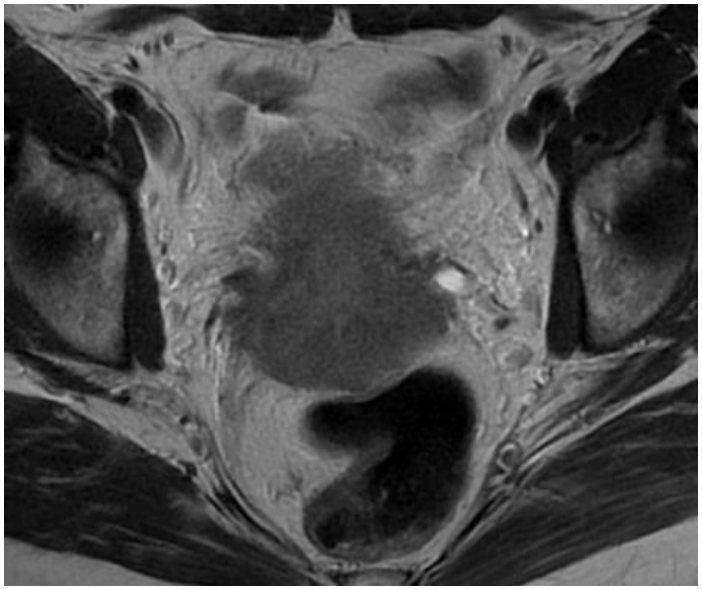
Dimensions (cm):

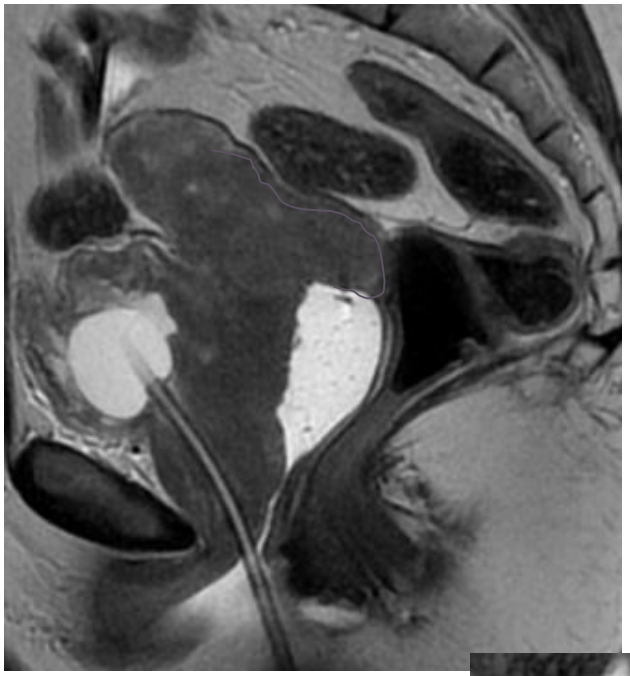
Width : 8

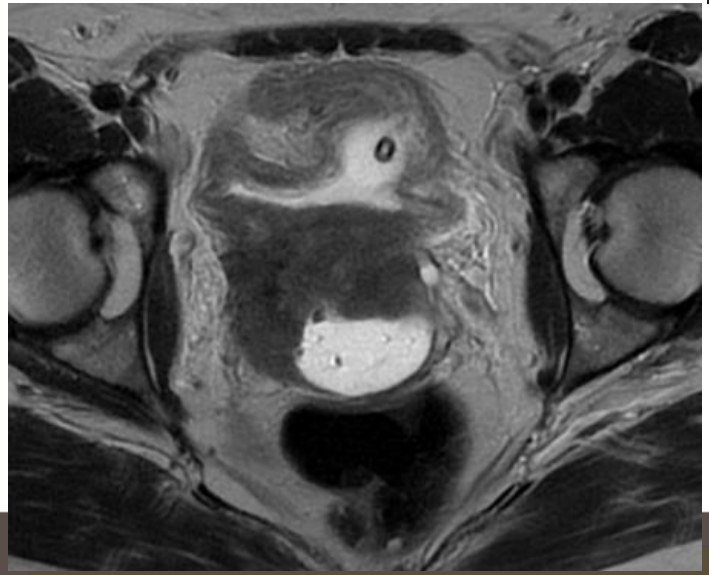
Thickness :6

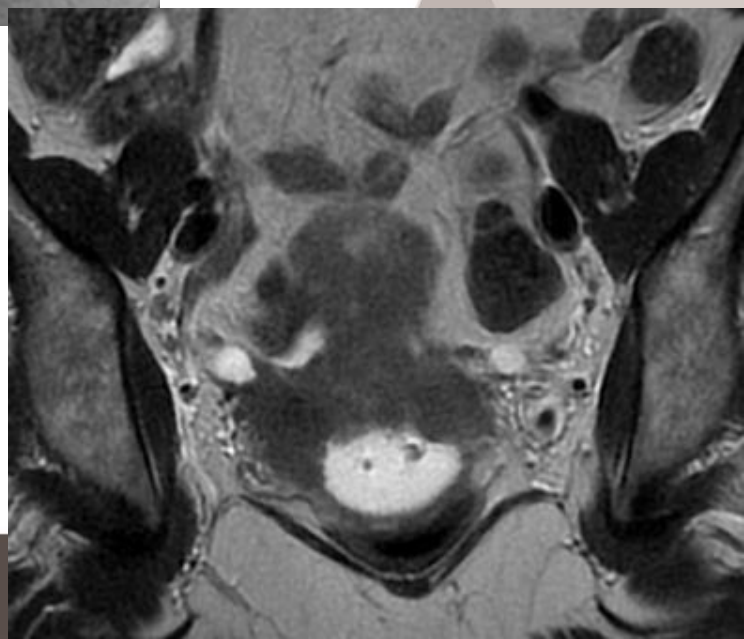
Height : 7

Stage IVA : initial MRI

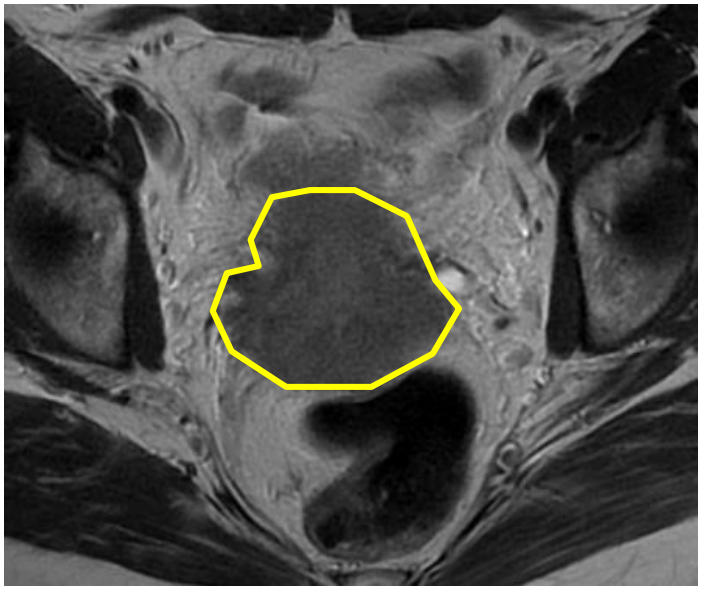


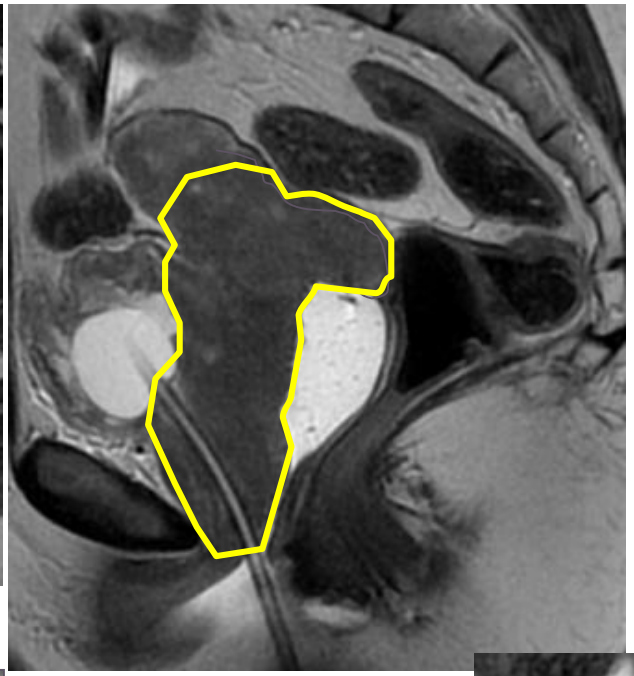


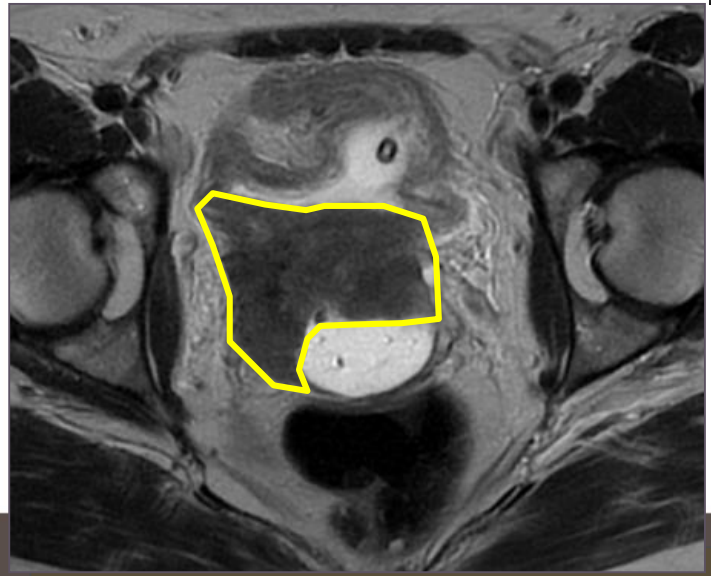


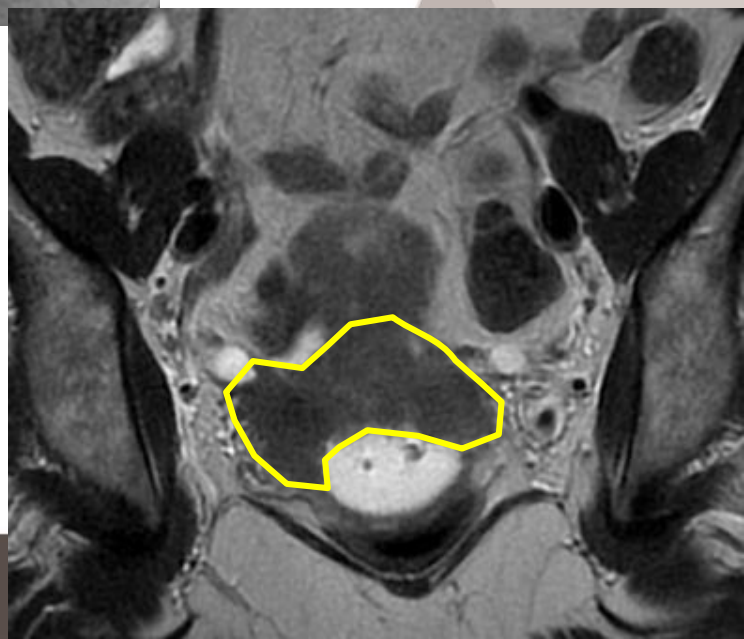


Stage IVA : initial MRI









Stage IVA : at time of brachy

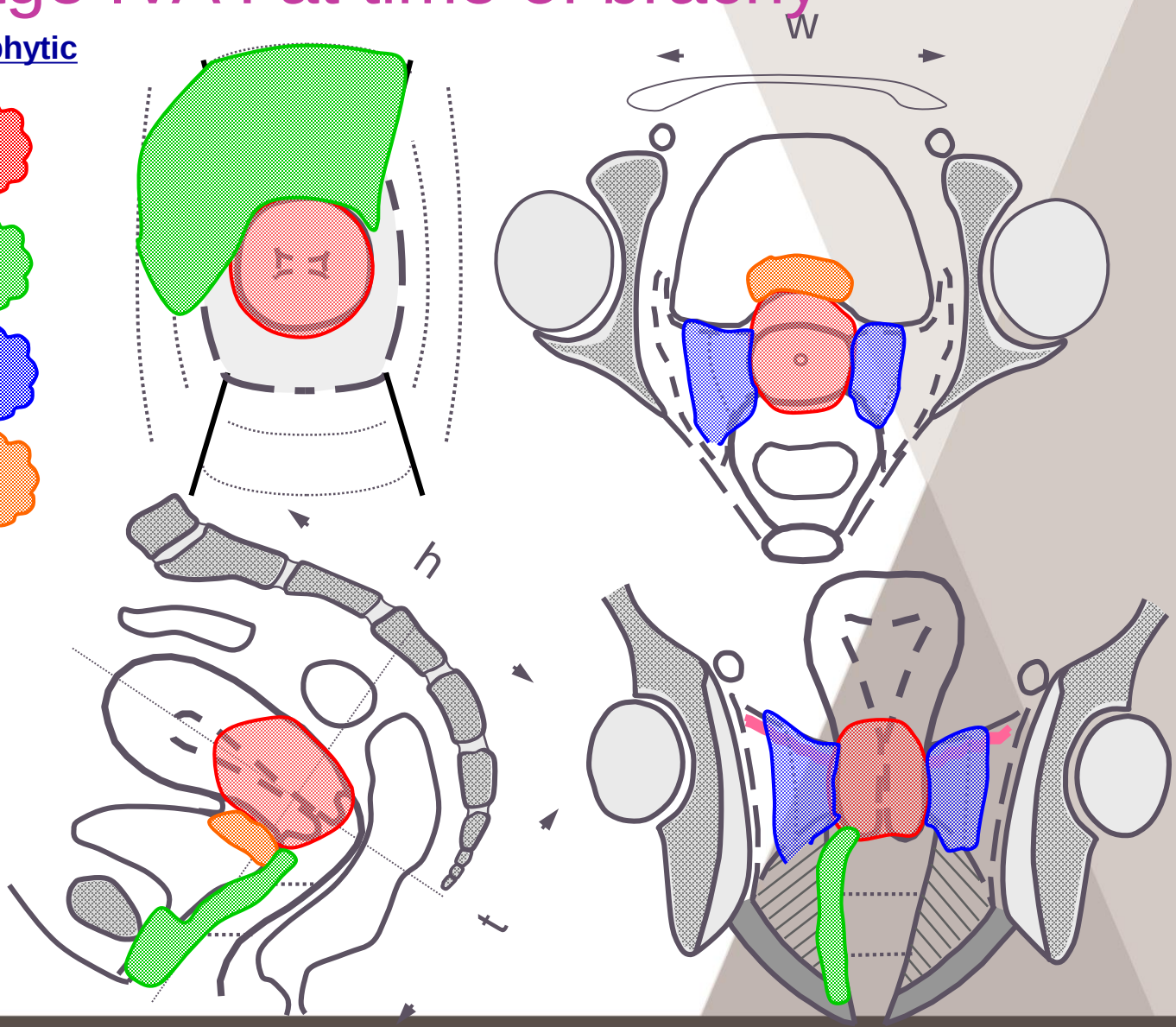
Infiltrating **Exophytic**

Cervix

Vagina

Parametrium

Rectum or Bladder



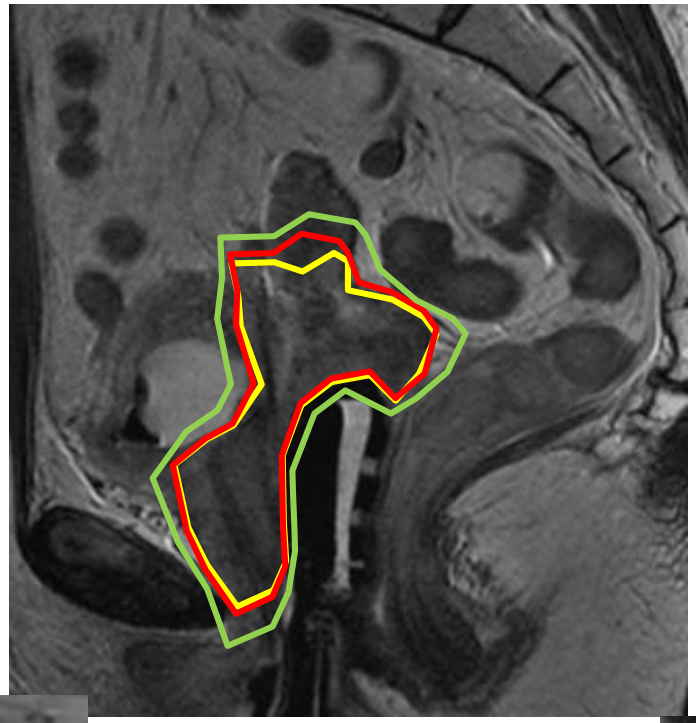
Dimensions (cm):

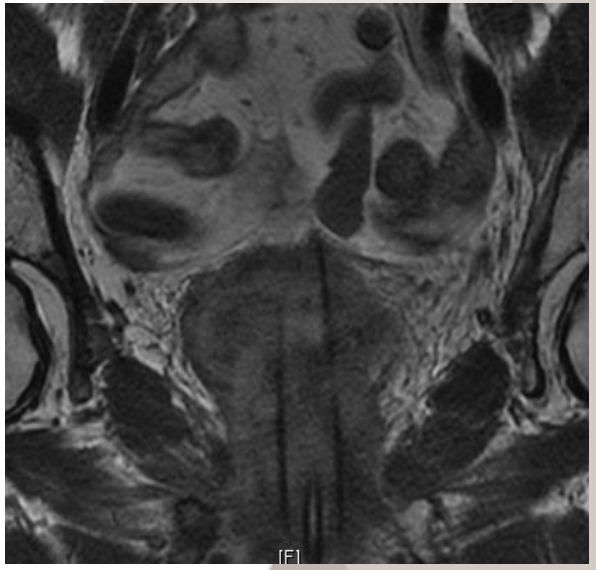
Width : 8

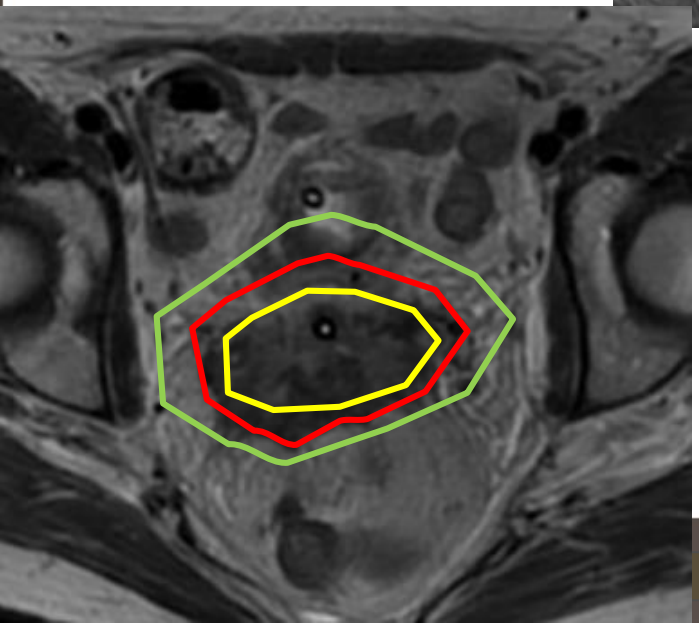
Thickness :6

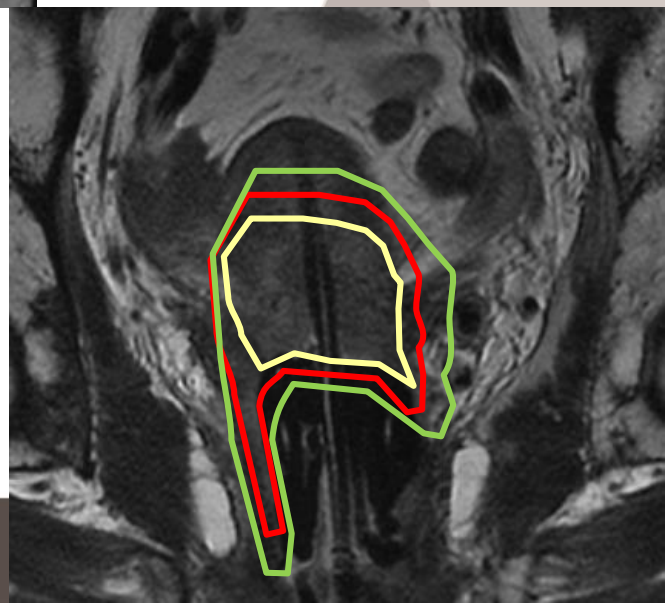
Height : 7

Stage IVA : at time of brachytherapy





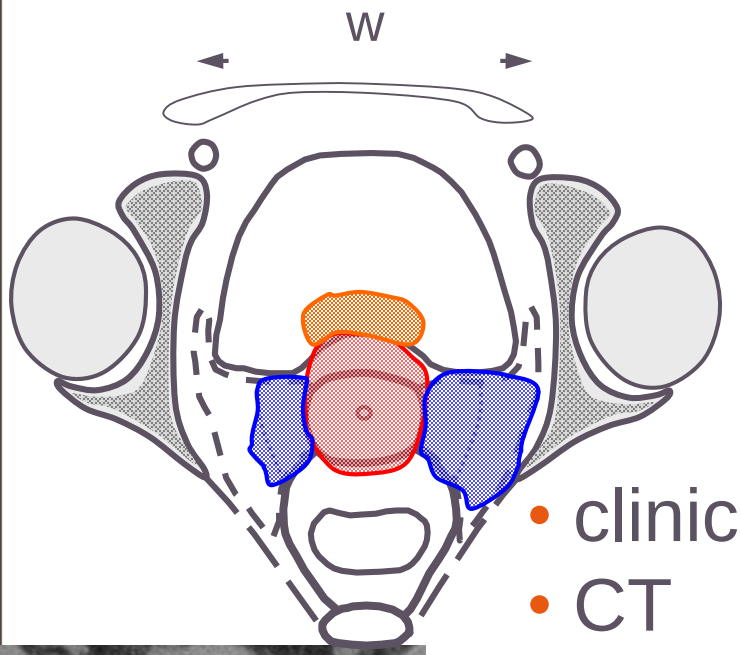




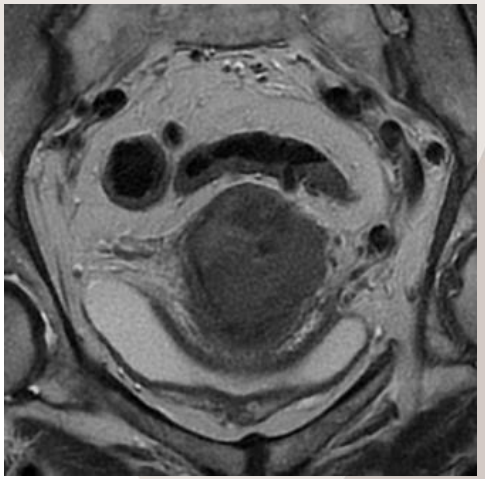
Journal of the ICRU

ICRU REPORT 89

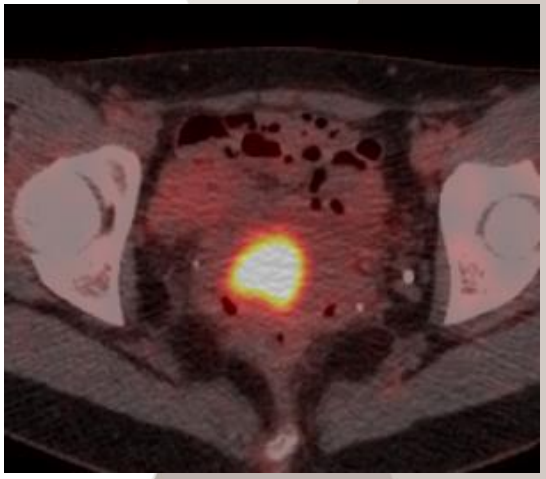
Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix

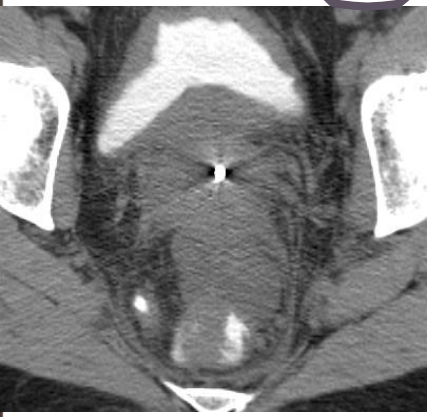


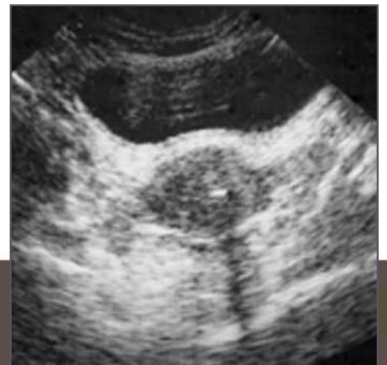
GTV_{init}



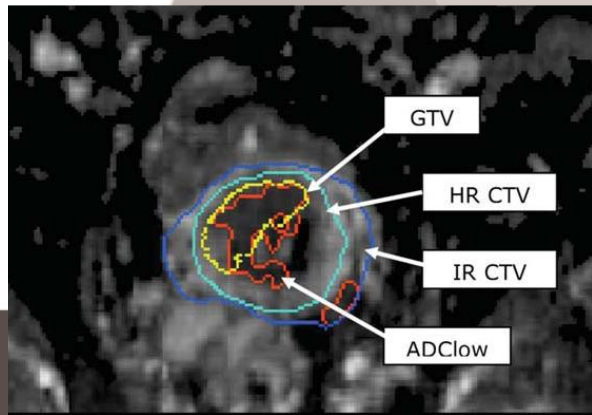
- clinical examination
- CT
- MRI
- PET-CT
- diffusion weighted MRI
- US

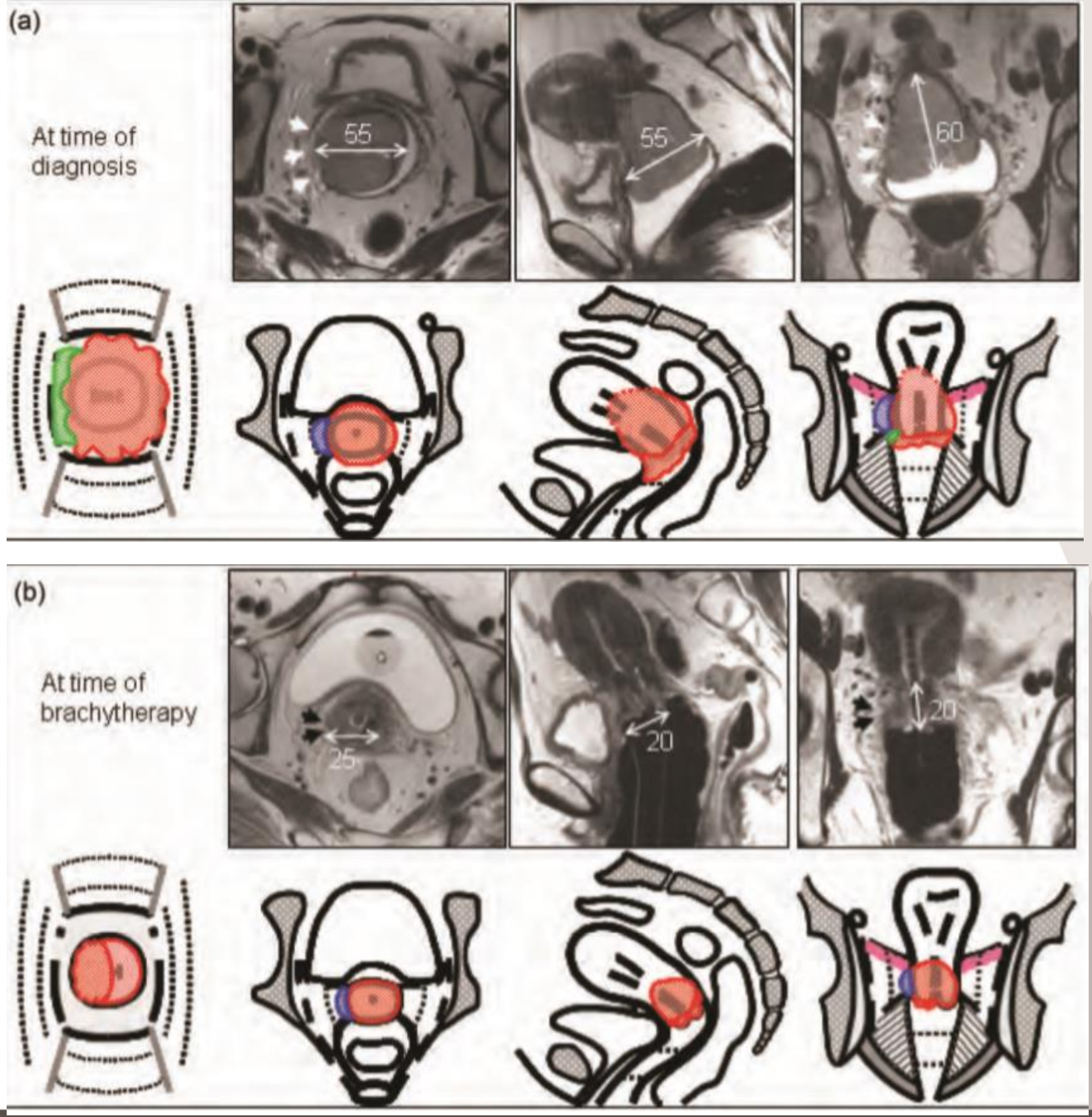


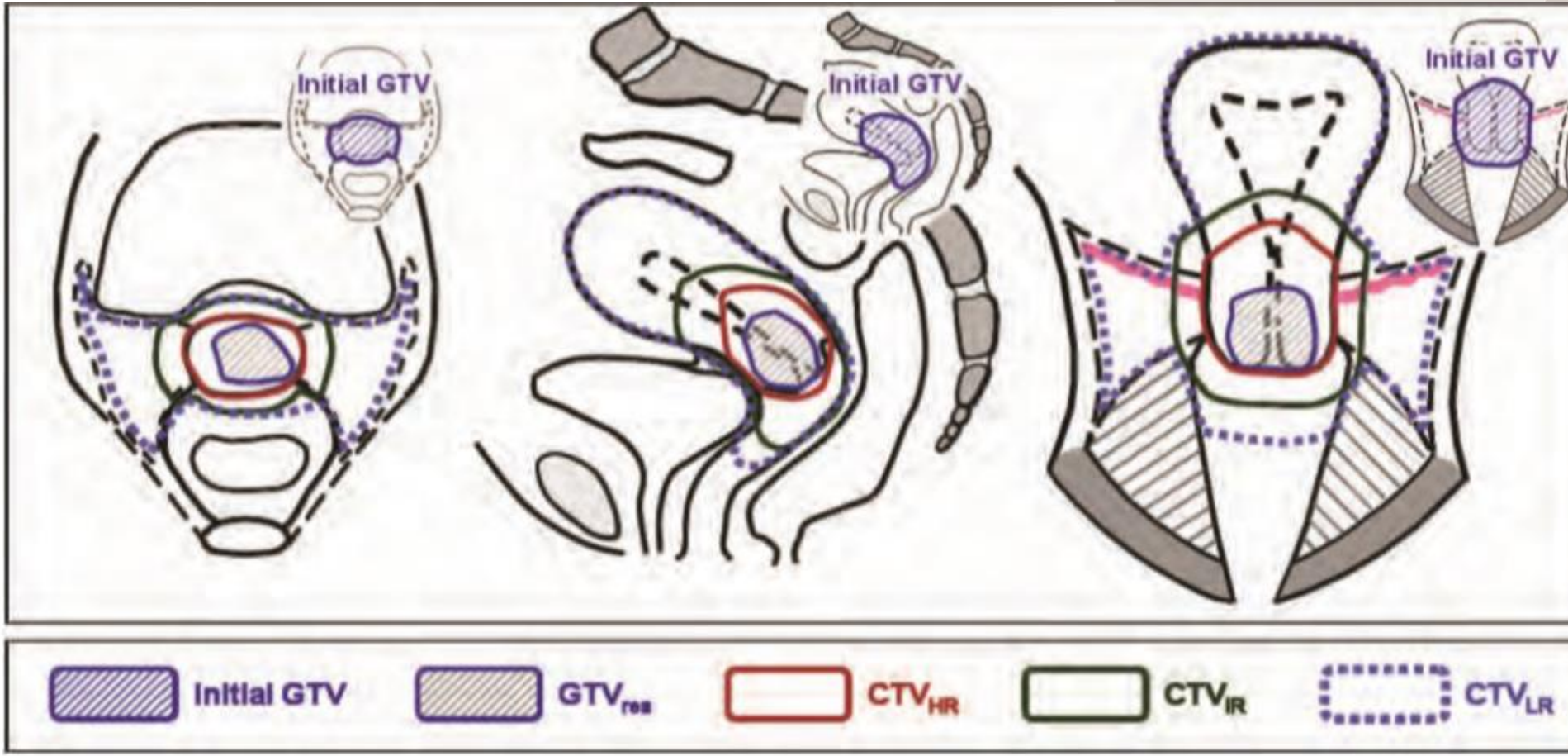




Composite GTV




(a)
At time of diagnosis
55
55
60
(b)
At time of brachytherapy
25
20
20



gure 5.9. Schematic diagram for cervical cancer, Stage IB_2 (bulky disease), good response after chemo-radiotherapy: residual
TV-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 arou
V-T_{HR}), and CTV-T_{LR} for adaptive brachytherapy: coronal, transversal, and sagittal view (see also Appendix Example 2 and 9).

ICRU 88

Oncological volume concepts relevant to radiotherapy

Three-dimensional imaging = selection and delineation of :

- GTV-T : composite GTV
- GTV_{res}
- CTV-T :GTV-T and potential microscopic disease
- CTV_{adapt} : GTV_{res} + residual pathologic tissue
- HR-CTV
- IR-CTV


Café de Flore
CAFE DE FLOR
CAFE DE FLORE

2D and 3D delineation of Organ at Risks

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Professor

Department of Radiation Oncology

All India Institute of Medical Sciences, New Delhi

AROI-ESTRO

Teaching Faculty

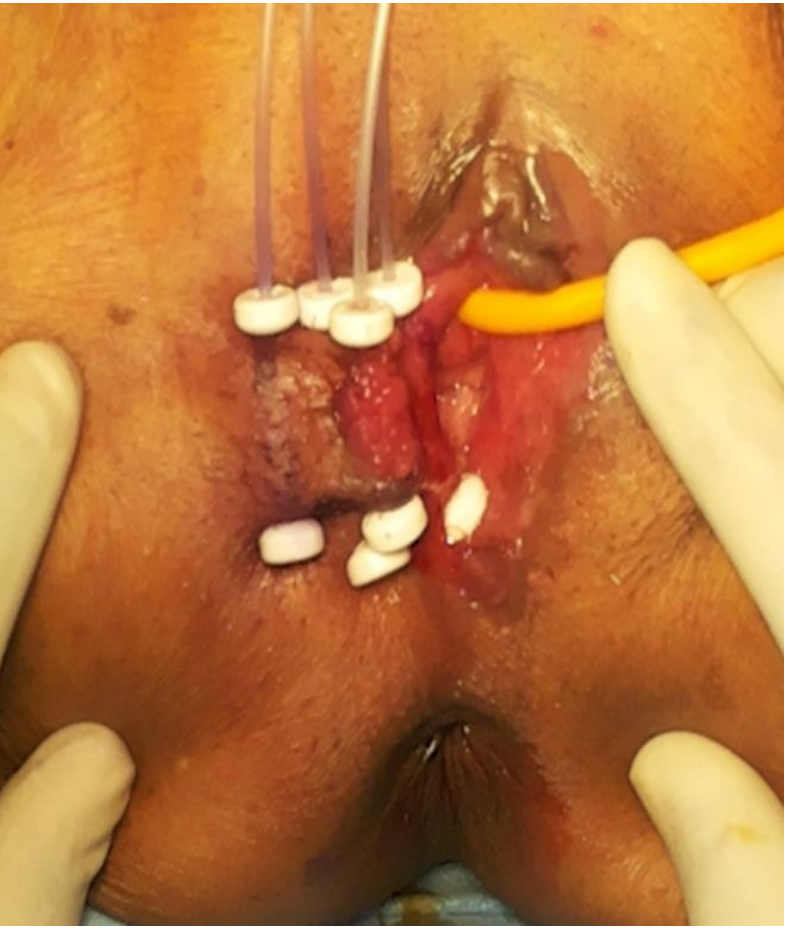
OARs in Brachytherapy

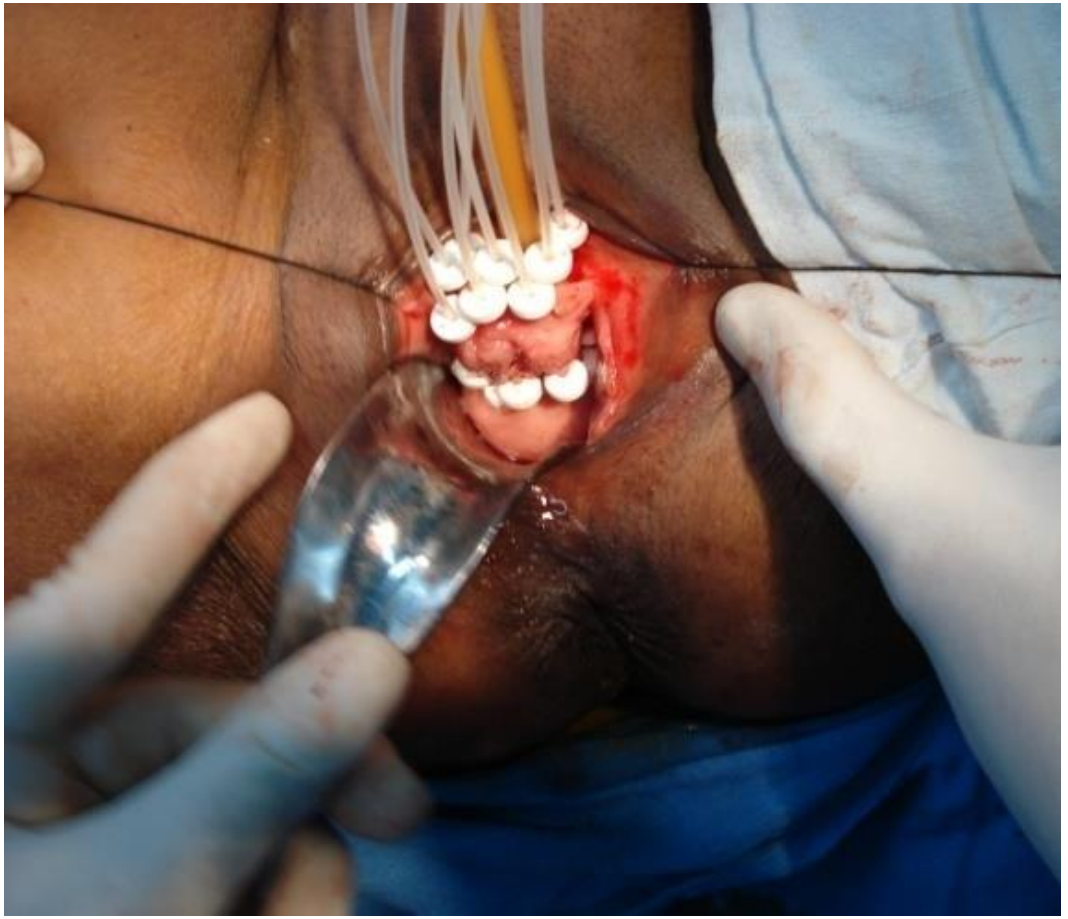
What are the relevant OARs in ICRT ?

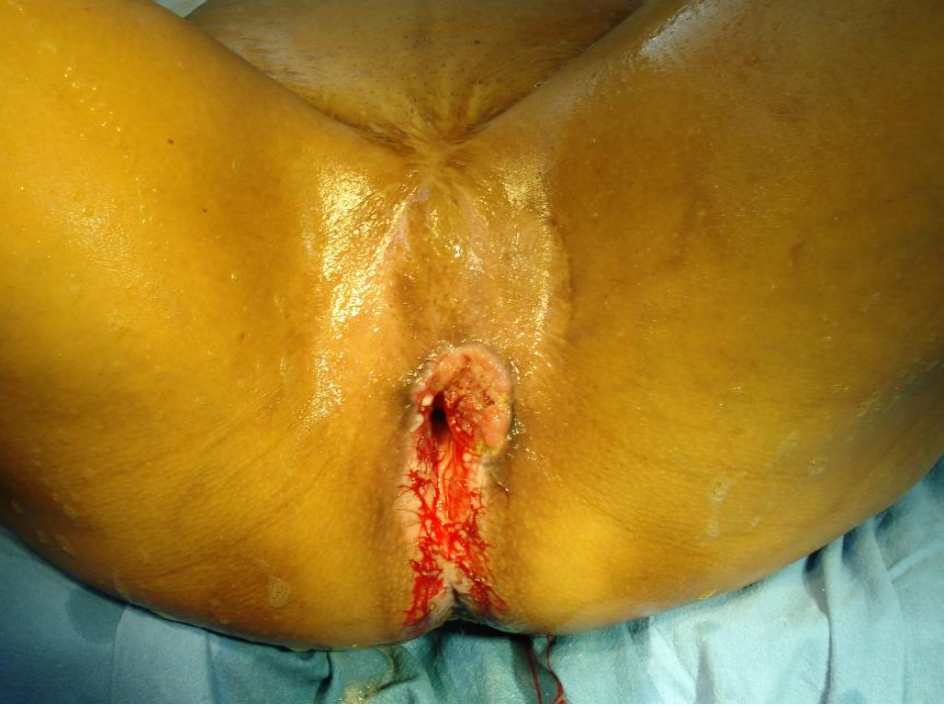
A. A: Bladder, Rectum
B. B: Bladder, Rectum, Sigmoid
C. C: Bladder, Rectum, Sigmoid, Vagina
D. D: Bladder, Rectum, Sigmoid, Vagina, Urethra

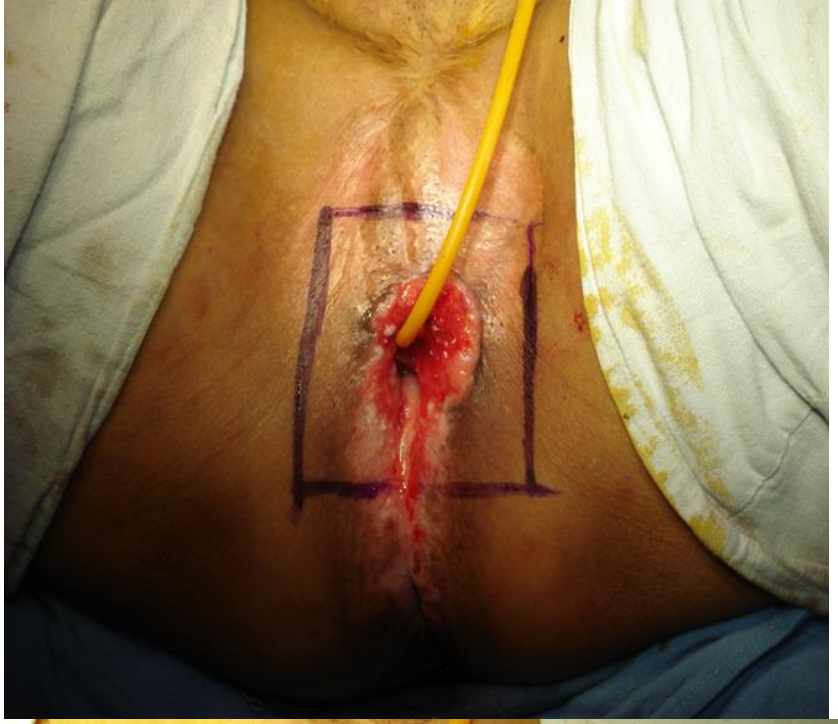
OARs in Brachytherapy

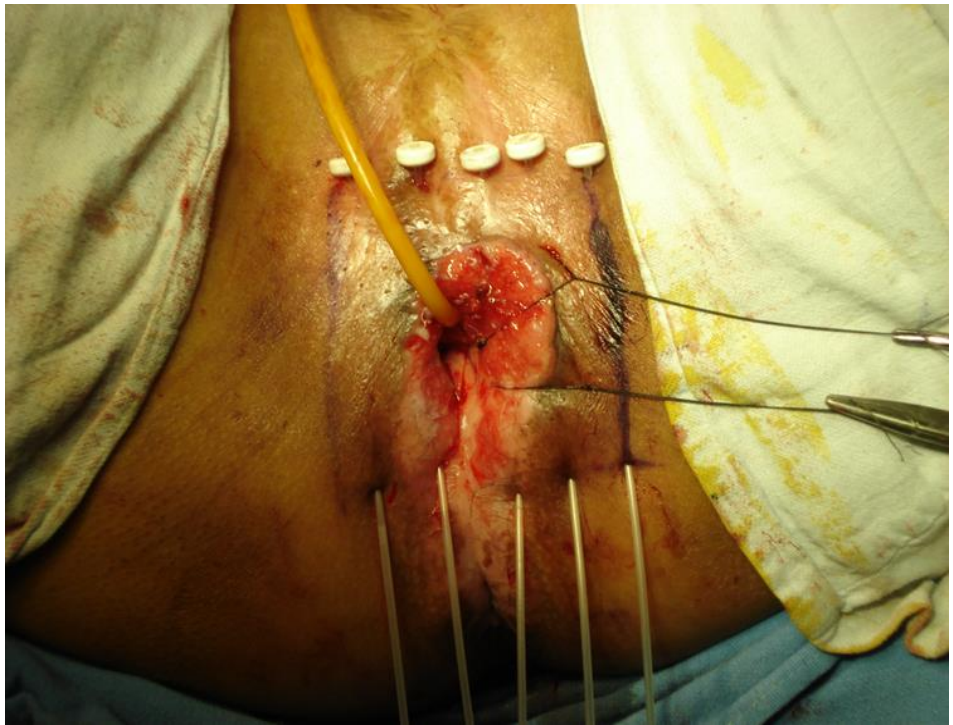
Various brachytherapy procedures

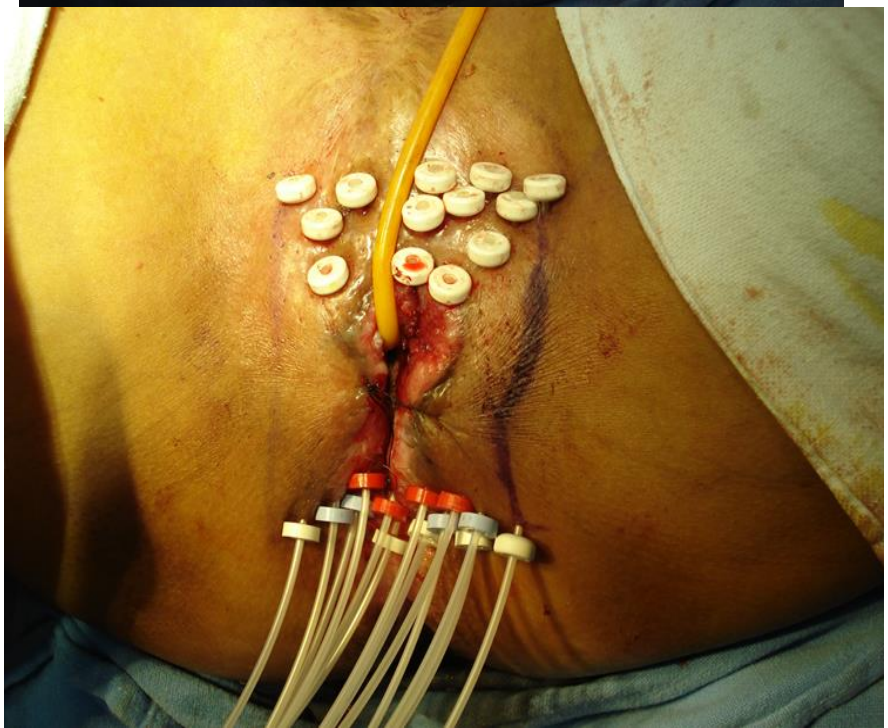






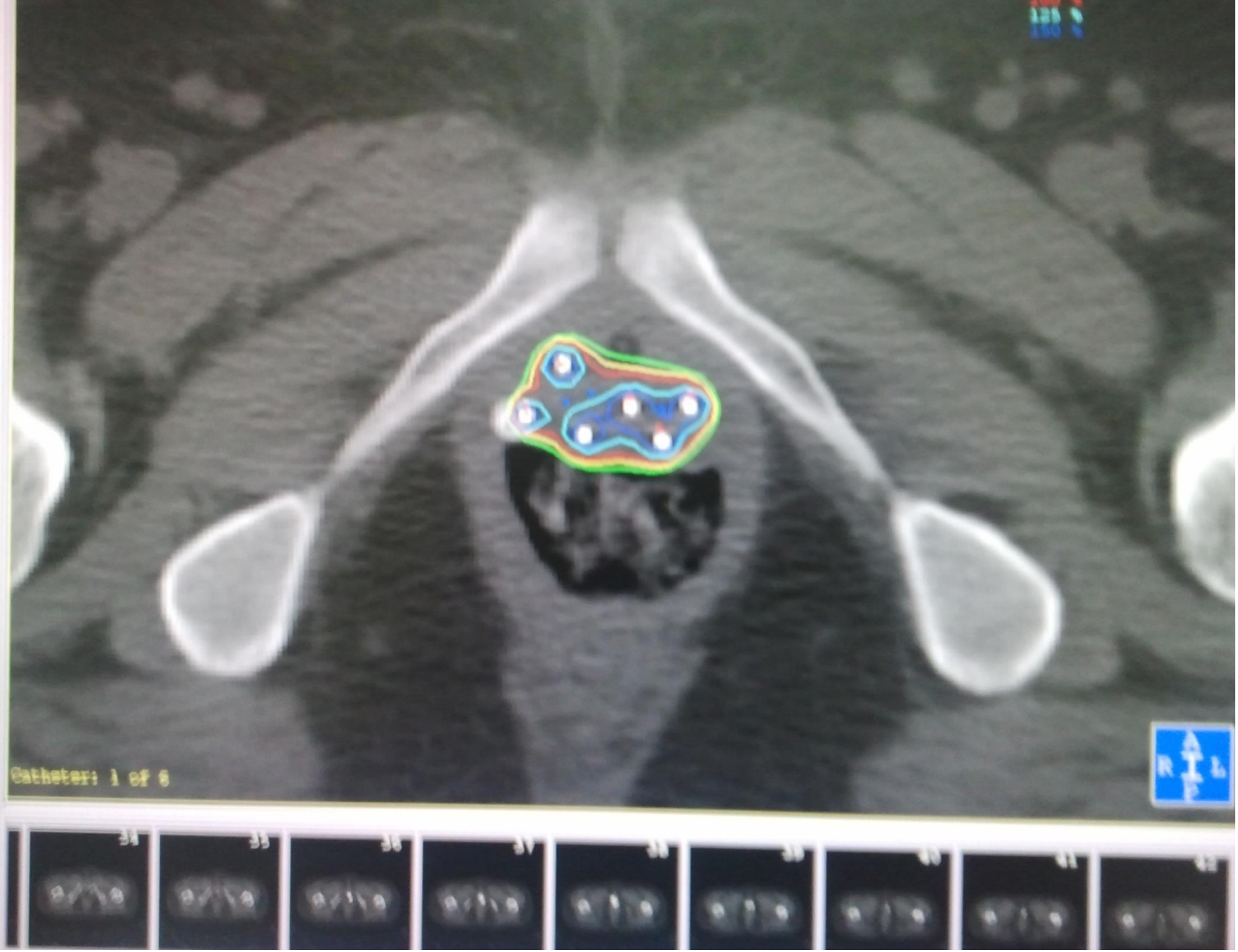


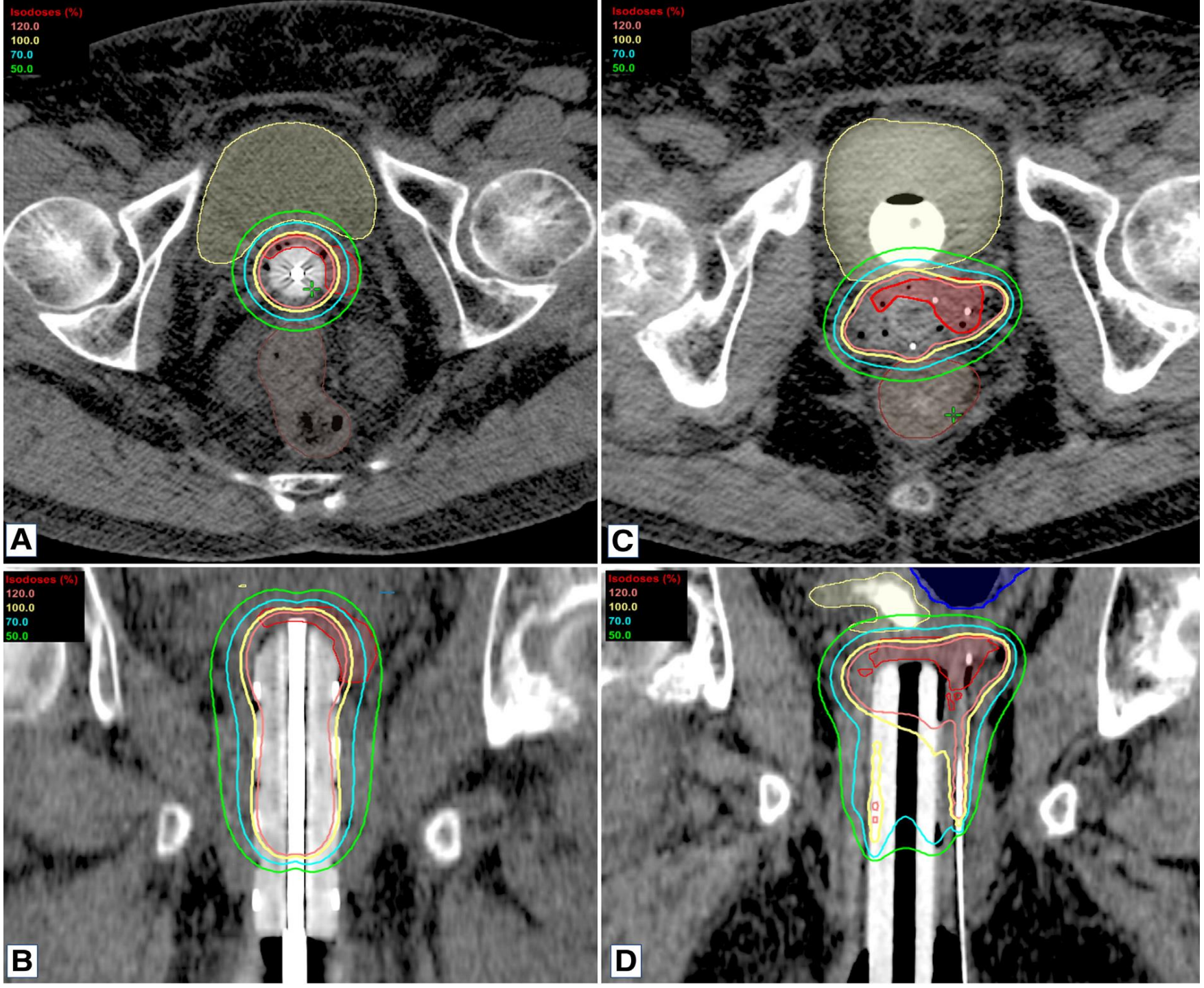




Why are OARs important in Brachytherapy?

- Considerable dose is delivered by brachytherapy (WPRT= 45 Gy + 40-45 by ICRT)
- Almost equal to EBRT dose
- OARs lie very close to the target volumes
- Dose intensity is higher
- Sharp dose fall off


Catheter: 1 of 6


Isodoses (%)
120.0
100.0
70.0
50.0
A
Isodoses (%)
120.0
100.0
70.0
50.0
C
Isodoses (%)
120.0
100.0
70.0
50.0
B
Isodoses (%)
120.0
100.0
70.0
50.0
D

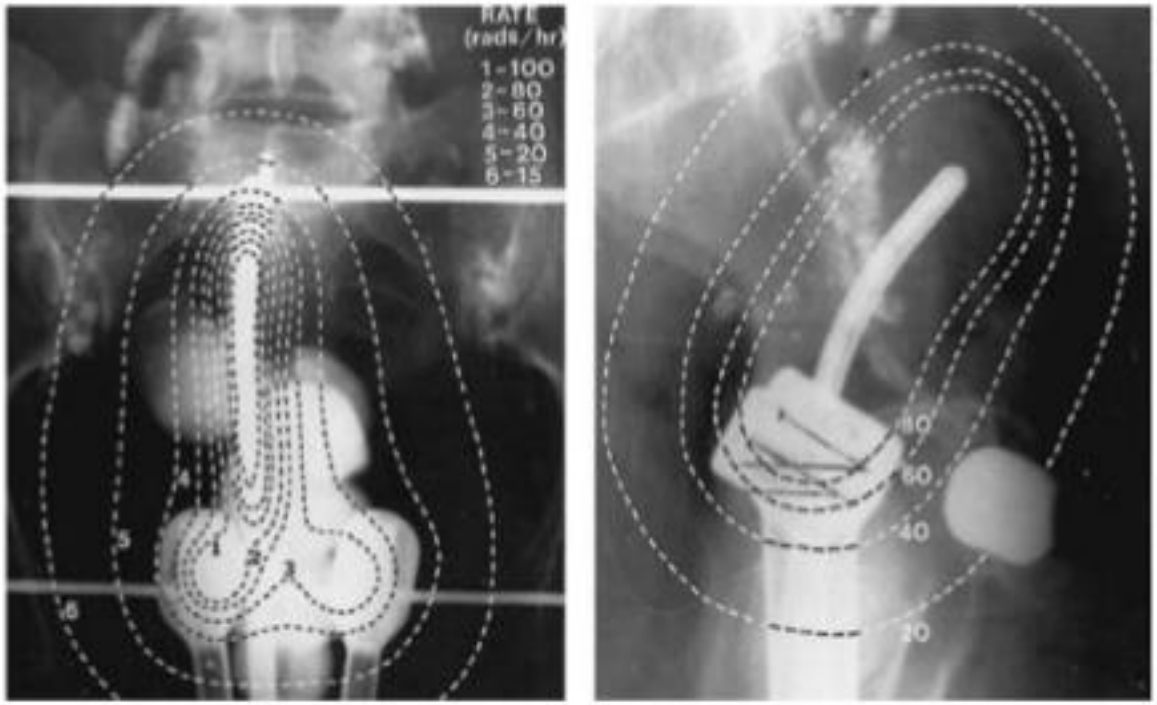
Morbidities and QOL

- Accurate evaluation of morbidities and correlation with doses require:
  - Accurate delineation of OARs
  - Take in to account all potential OARs (possible in 3D not in 2D)

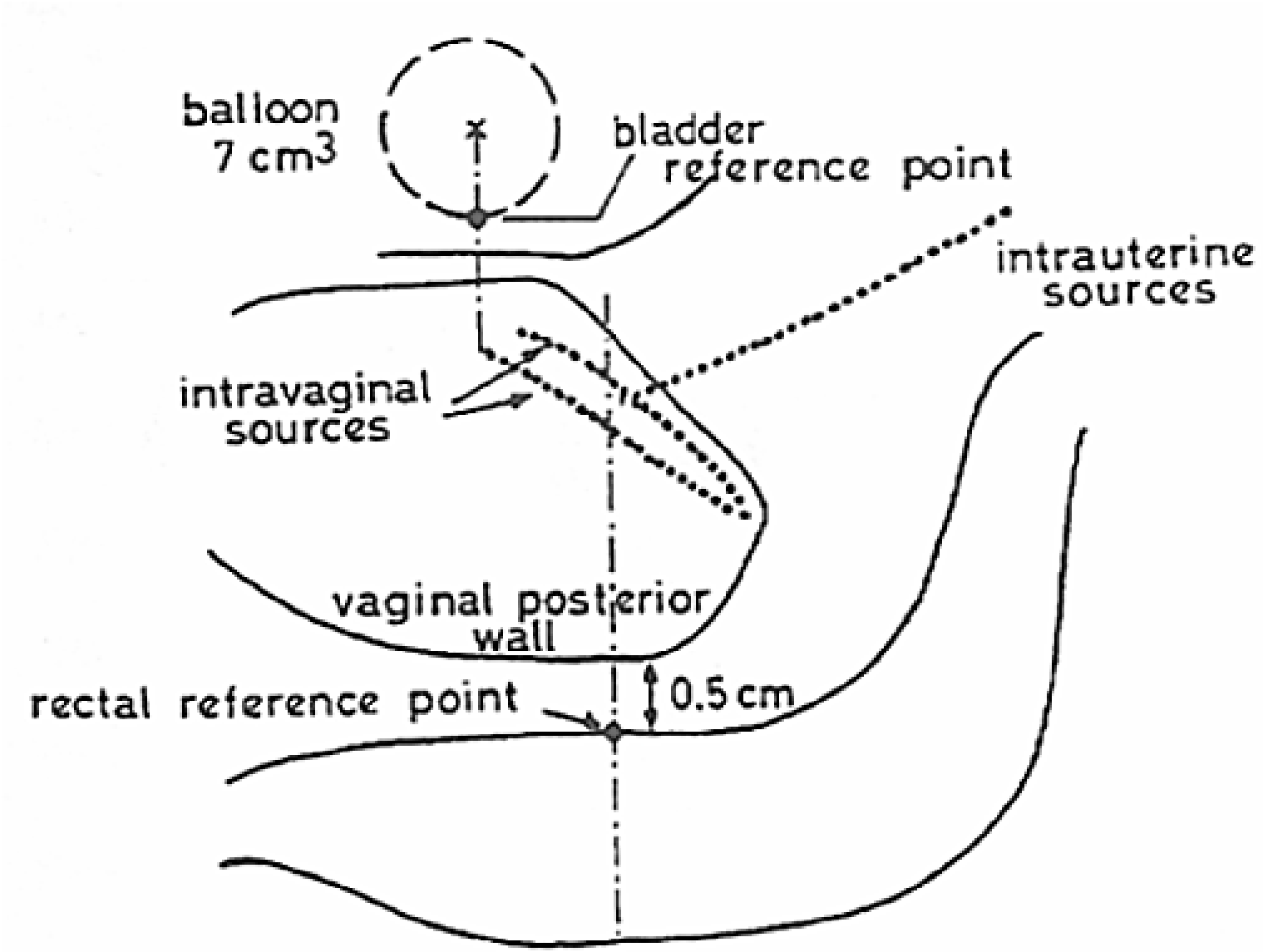
2D delineation of Organ at Risks

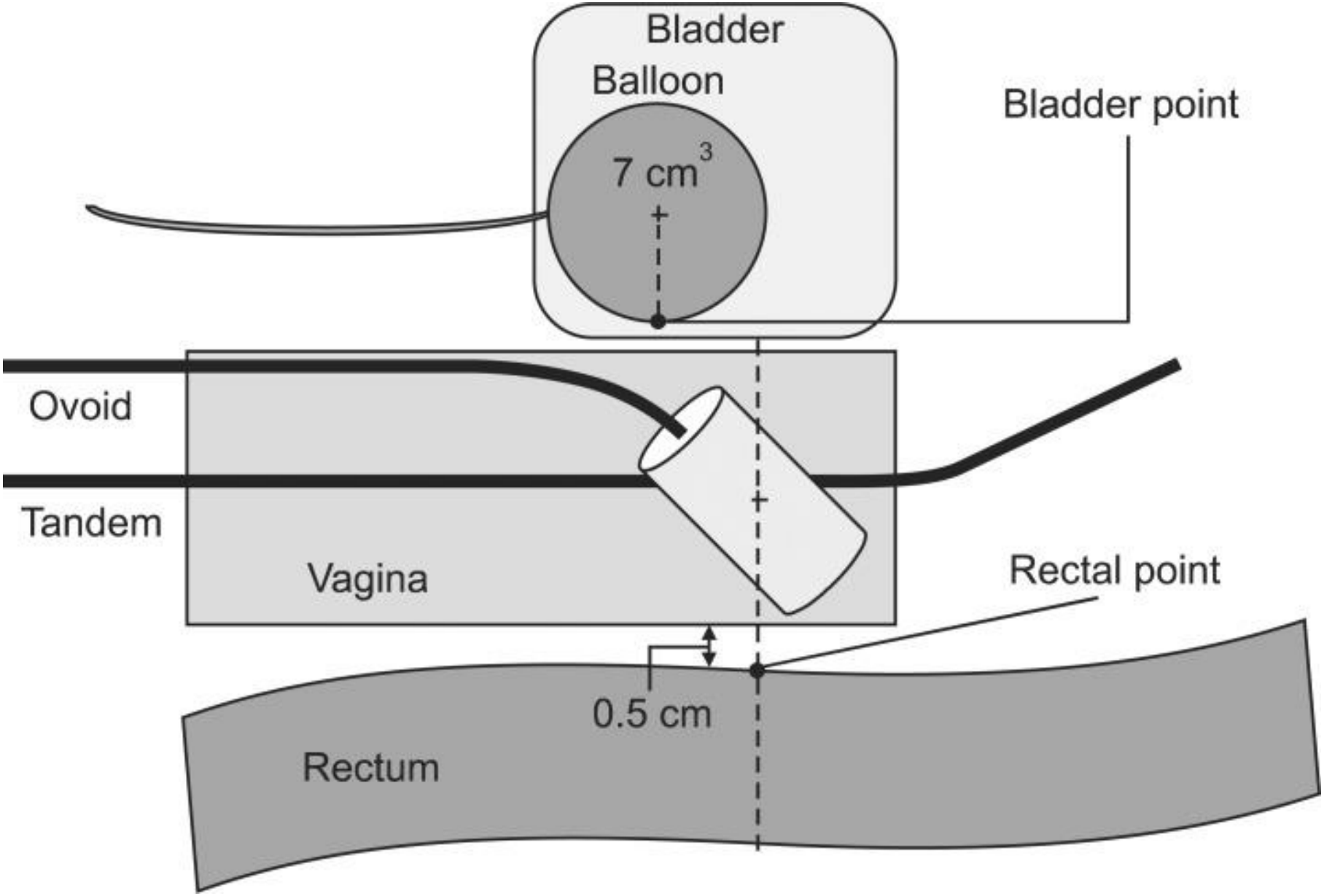
- Based on radiographic imaging
- Most guidelines do not recommend radiographic image
- OARs are localized based on points
- Only few organs are localised
- The toxicity correlation is poor
- If volumetric imaging is not available, X-ray based simulation may be practiced but certainly not encouraged

2D brachytherapy planning



ICRU 38: Bladder and Rectal points



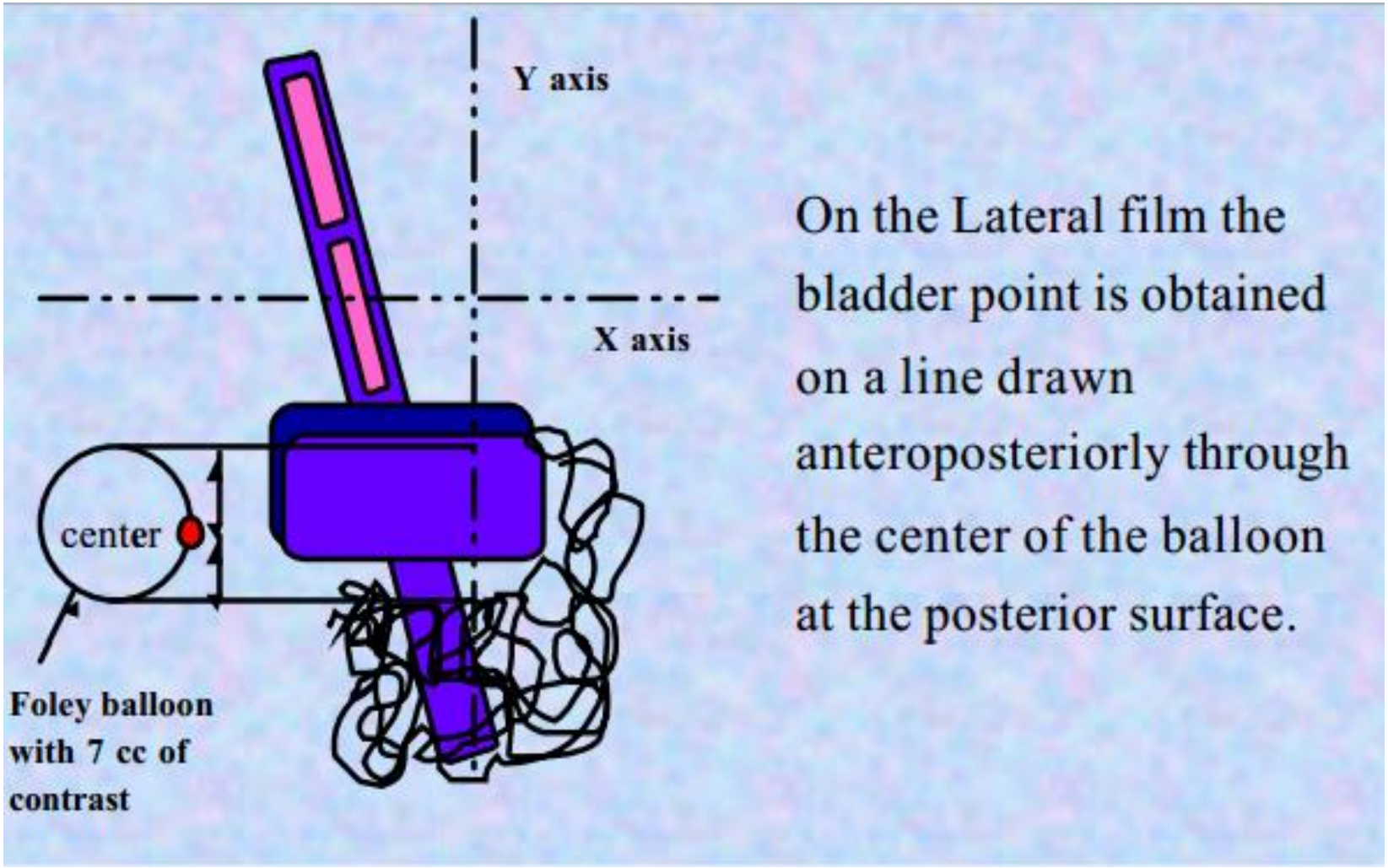

Bladder
Balloon
7 cm3
Bladder point
Ovoid
Tandem
Vagina
Rectal point
0.5 cm
Rectum

Bladder reference point

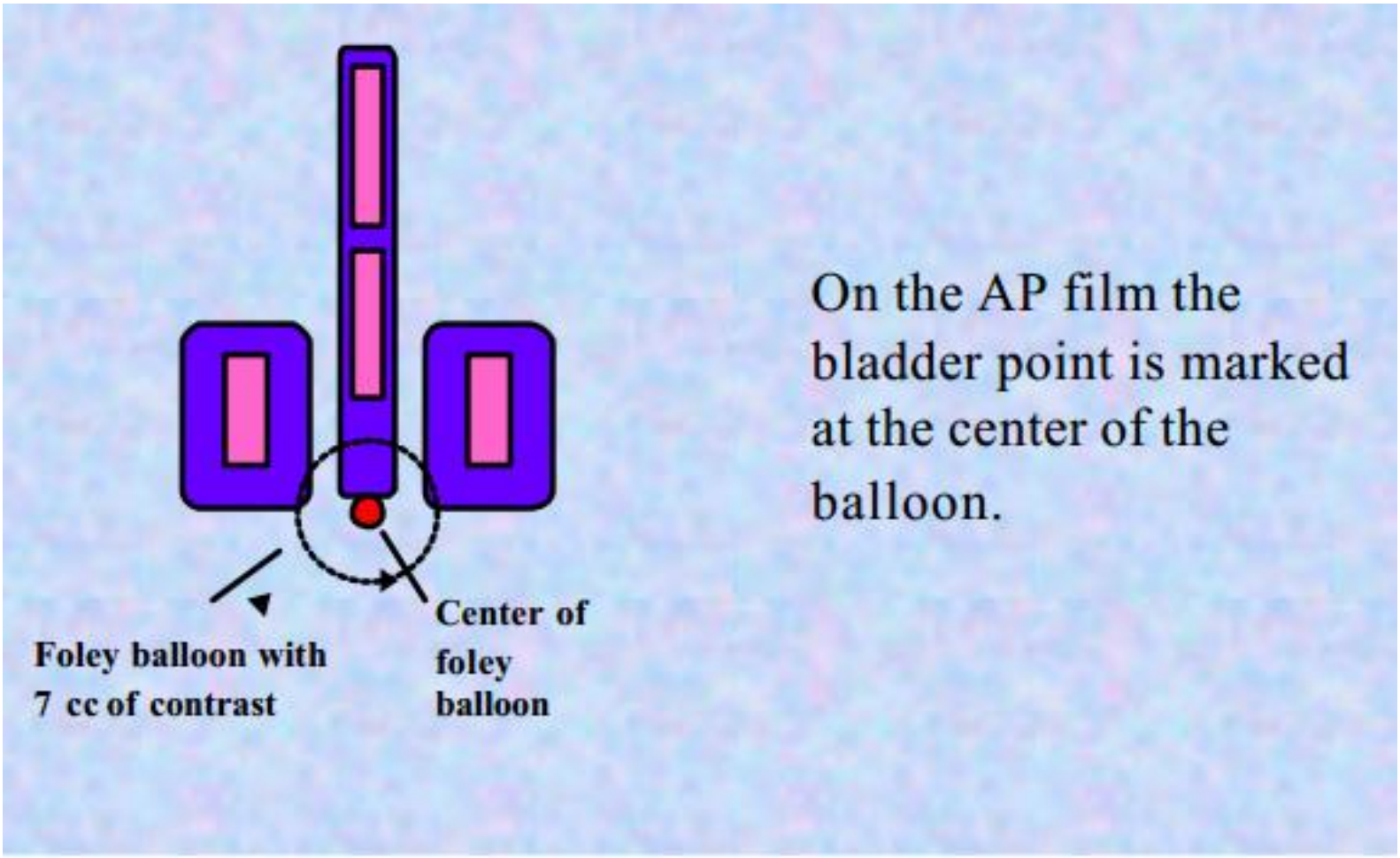
Bladder point is obtained in following way:

- Foley's catheter balloon is filled with 7 cm^3 of radio-opaque fluid
- Catheter is pulled downward to bring the balloon against the urethra
- On lateral radiograph, reference point is at the posterior surface of balloon
- On frontal radiograph reference point is taken at the centre of balloon

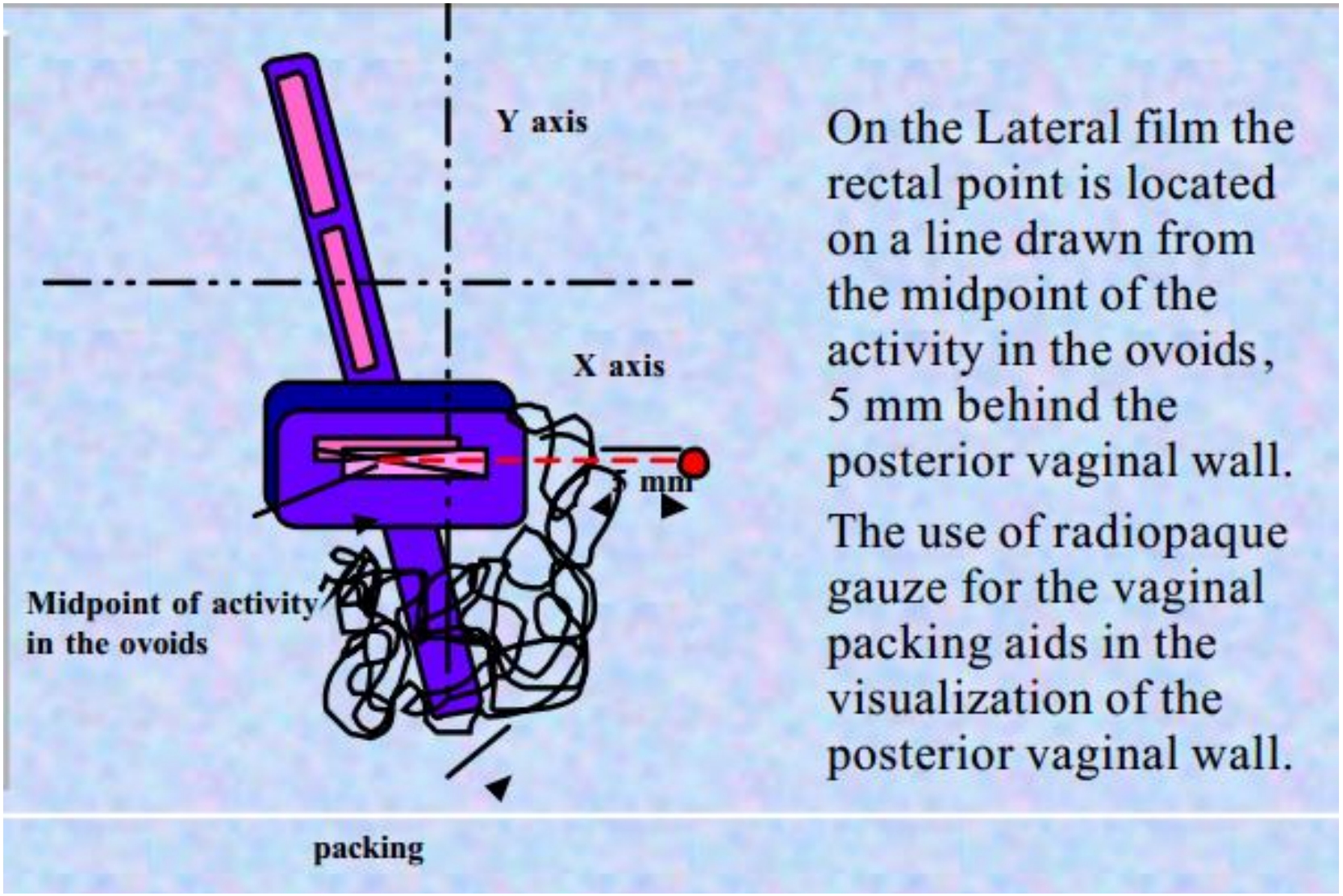
Bladder reference point: Lateral view



Bladder reference point: AP view



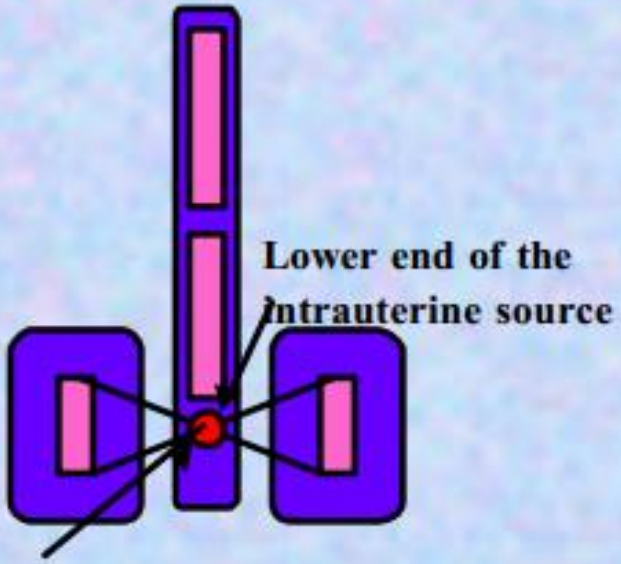
Rectal reference point: Lateral view



On the Lateral film the rectal point is located on a line drawn from the midpoint of the activity in the ovoids, 5 mm behind the posterior vaginal wall.

The use of radiopaque gauze for the vaginal packing aids in the visualization of the posterior vaginal wall.

Rectal reference point: AP view



The rectal point is identified at the midpoint of the activity of the sources in the ovoids or at the lower end of the intrauterine source.

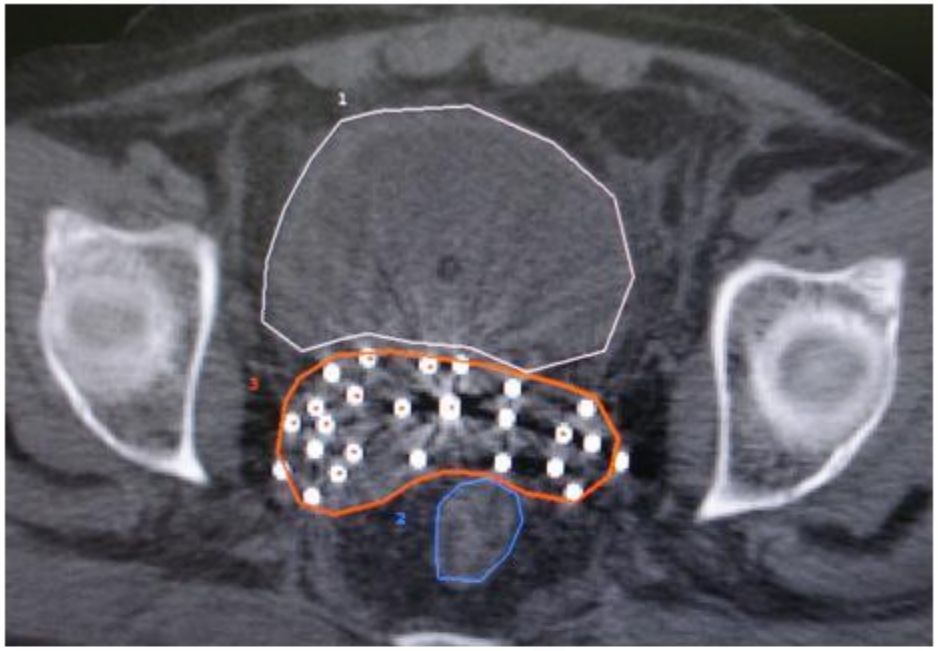
3D delineation of OAR

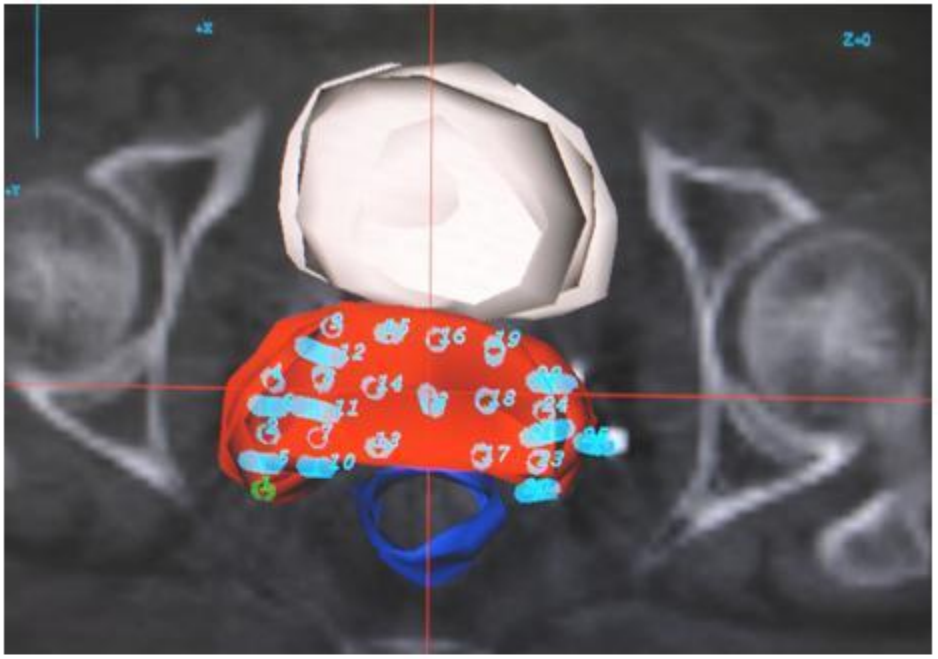
- Based on the volumetric imaging
- Various imaging devices used

- MRI : Standard
- CT Scan : Practical
- USG : Investigational

Delineation of OARs

- **Sigmoid colon:** Should be clearly identified, and the whole structure should be contoured, with specific focus on the areas adjacent to the uterus. Length up to the junction with the descending colon.
- **Rectum :** This implies the entire length from the ano-rectum to the recto-sigmoid junction
- **Bladder:** The whole posterior, posterior-caudal (trigone), and posterior-cranial bladder wall should be included till bladder neck


1
3
2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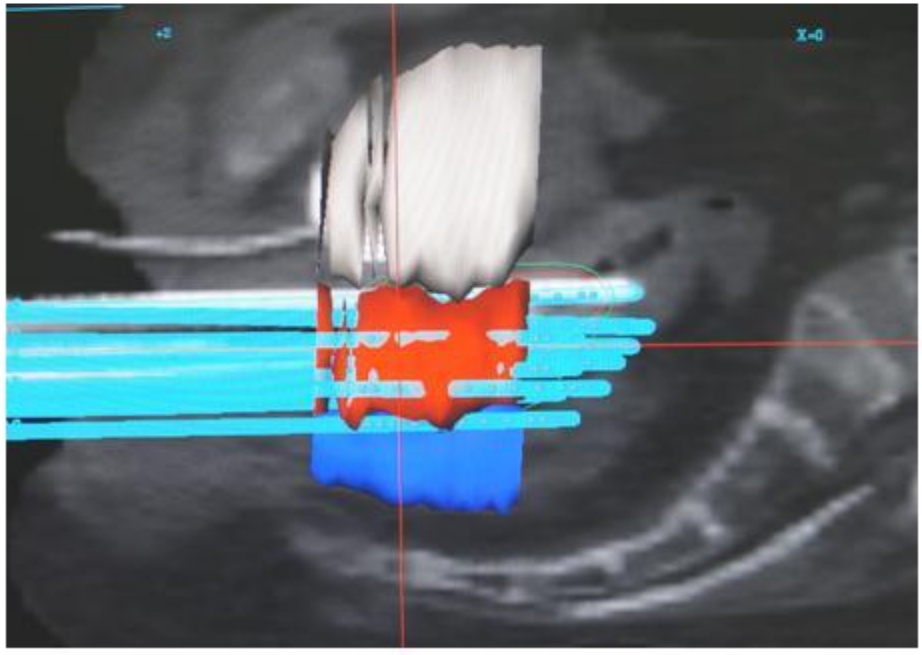
Z=0
+Y
12
6
9
4
8
11
7
3
10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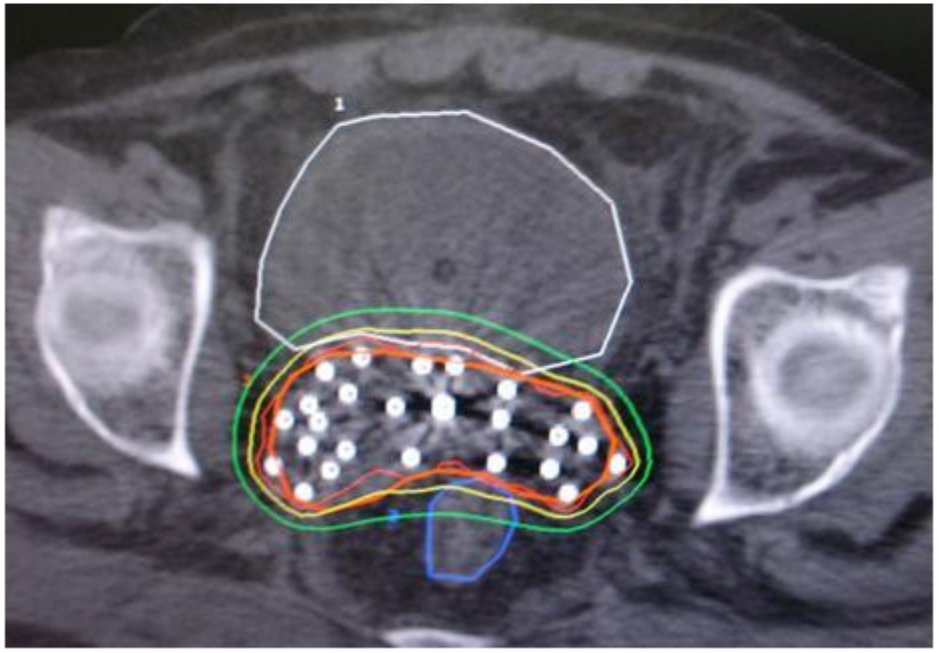
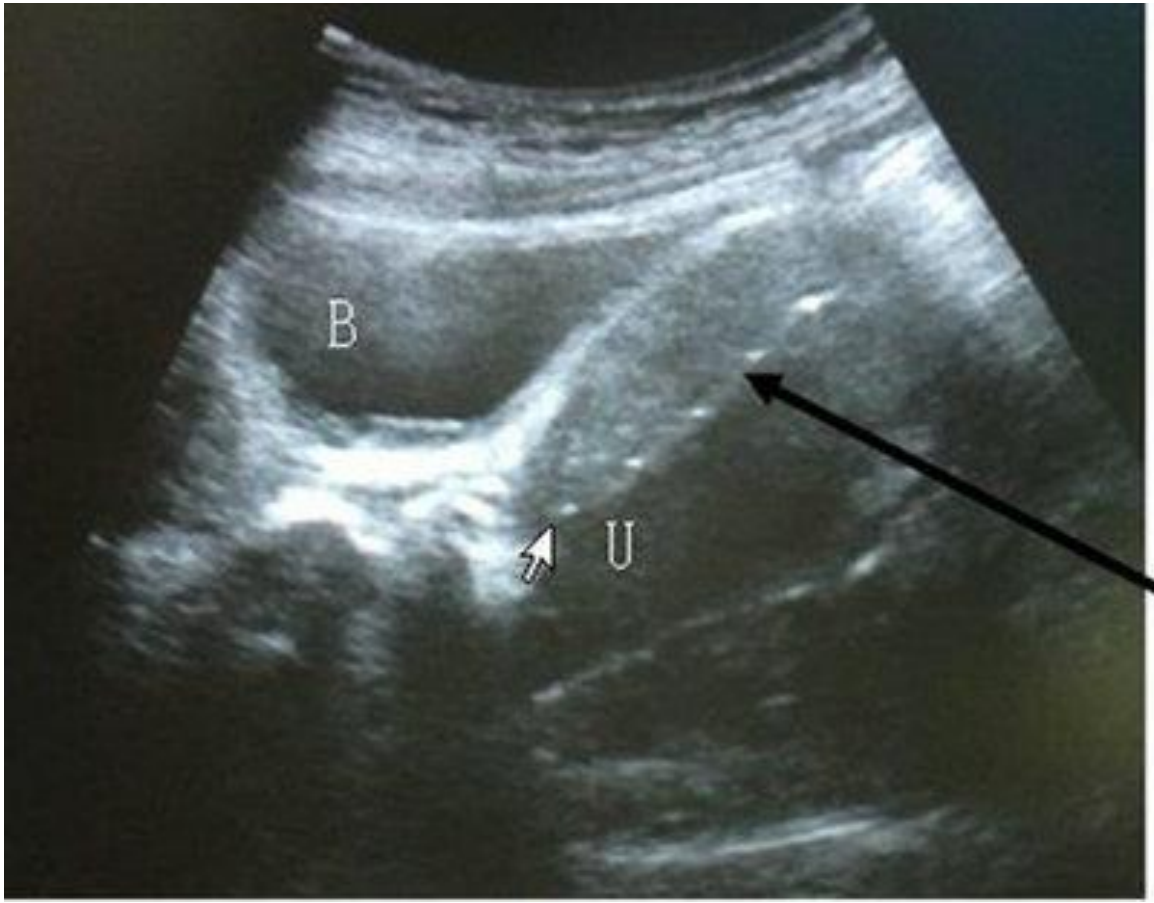

1
3



Uterine tandem

ELSEVIER

CrossMark

BRACHYTHERAPY

Brachytherapy 15 (2016) 839–844

Gynecologic Oncology

Combining transrectal ultrasound and CT for image-guided adaptive brachytherapy of cervical cancer: Proof of concept

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[2]*Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Austria*
[3]*Austrian Center for Medical Innovation and Technology, Wr. Neustadt, Austria*

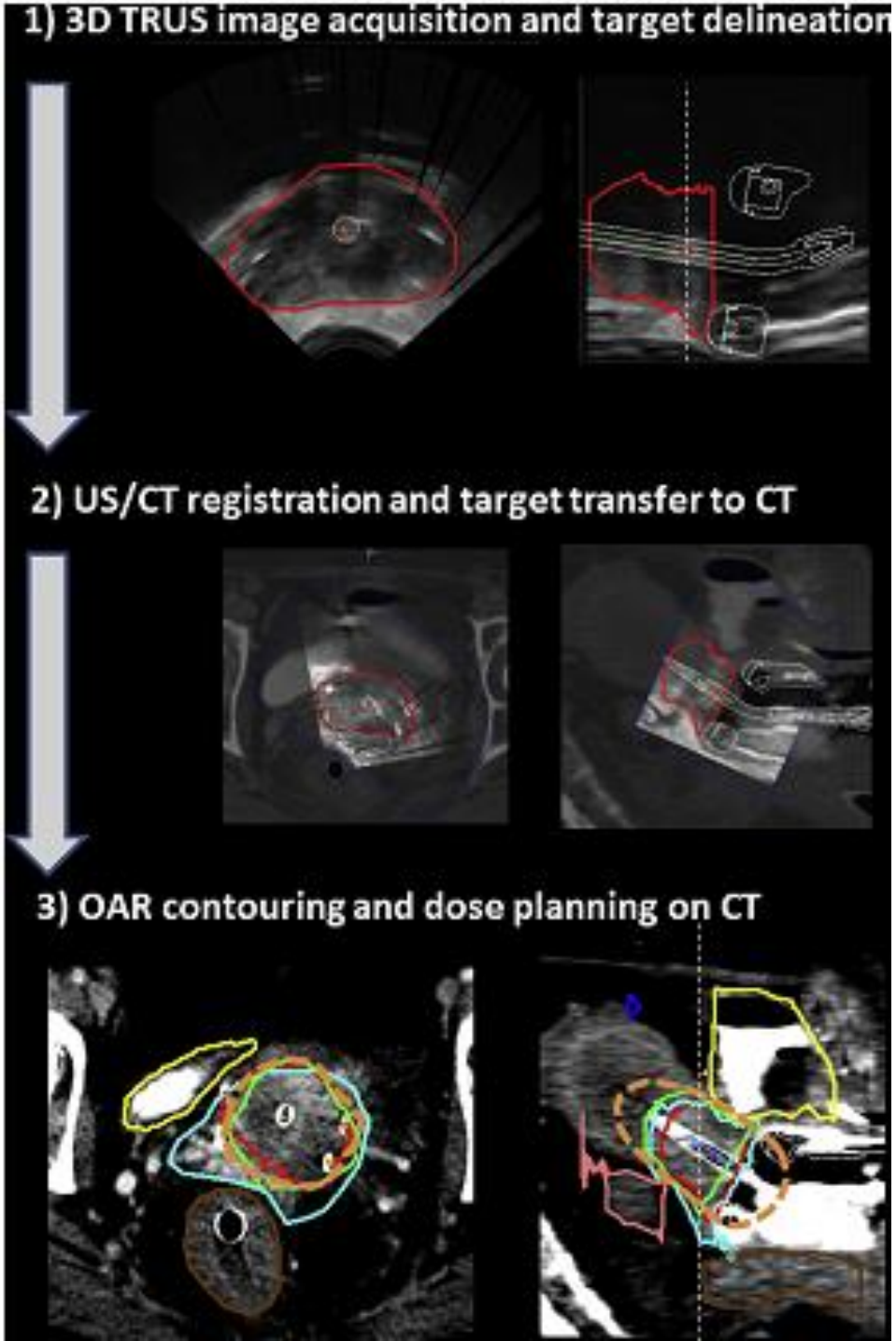
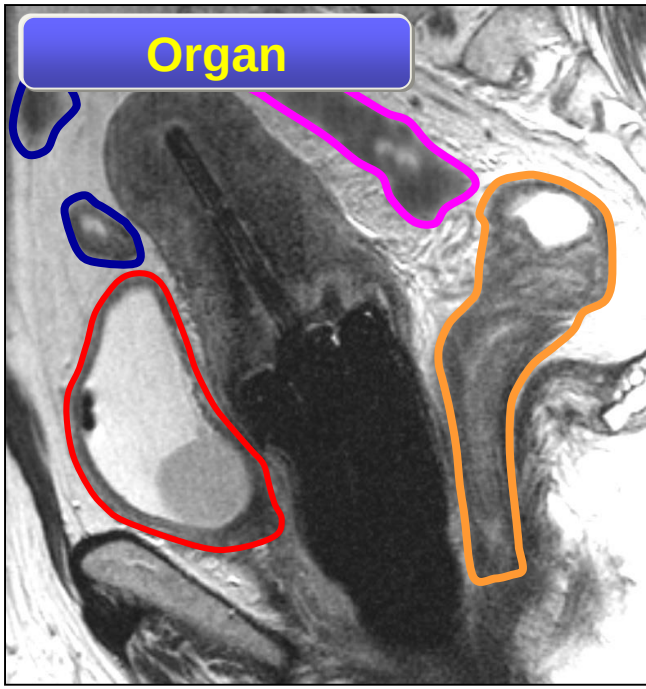

1) 3D TRUS image acquisition and target delineation
2) US/CT registration and target transfer to CT
3) OAR contouring and dose planning on CT

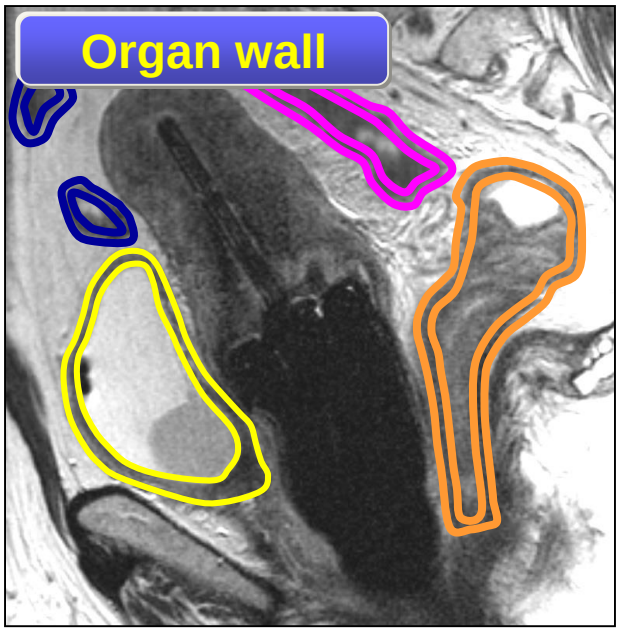
Table 1
Evaluation of the treatment plan optimized for TRUS CTV_{HR} and CT OARs, for three contour sets: TRUS/CT, MRI only, and CT only

Evaluated parameter	TRUS/CT contours	MRI contours	CT contours
CTV_{HR} D_{90} (Gy)	92.3	88.8	69.0
Bladder D_{2cm^3} (Gy)	85.2	84.0	85.2
Rectum D_{2cm^3} (Gy)	63.5	63.7	63.5
Sigmoid D_{2cm^3} (Gy)	66.1	62.9	66.1

Delineate Organ or Organ wall?

- *Wall: More correct*
- *Demanding & time consuming*
- *Prone to uncertainties*

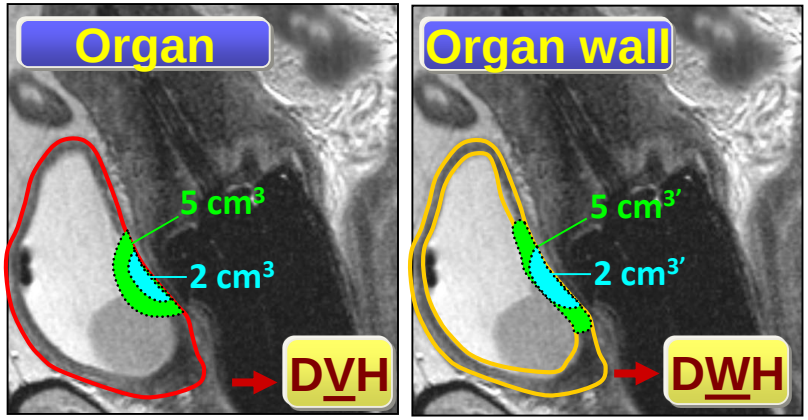




Can we contour organs instead of organ walls?

Delineate Organ or Organ wall?

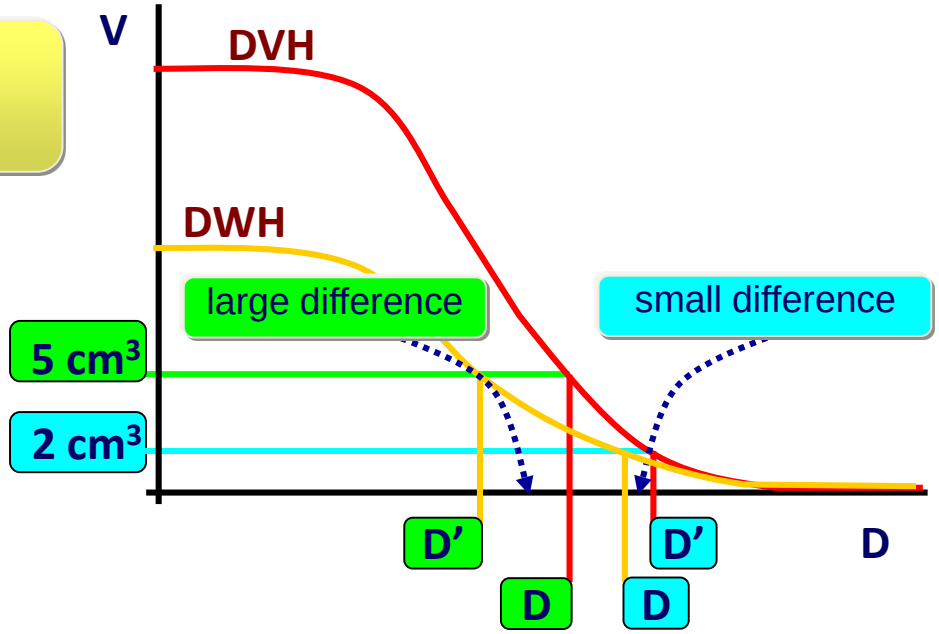
I. Situation in Brachytherapy



Can we contour <u>organs</u> instead of <u>organ walls</u>?

↓

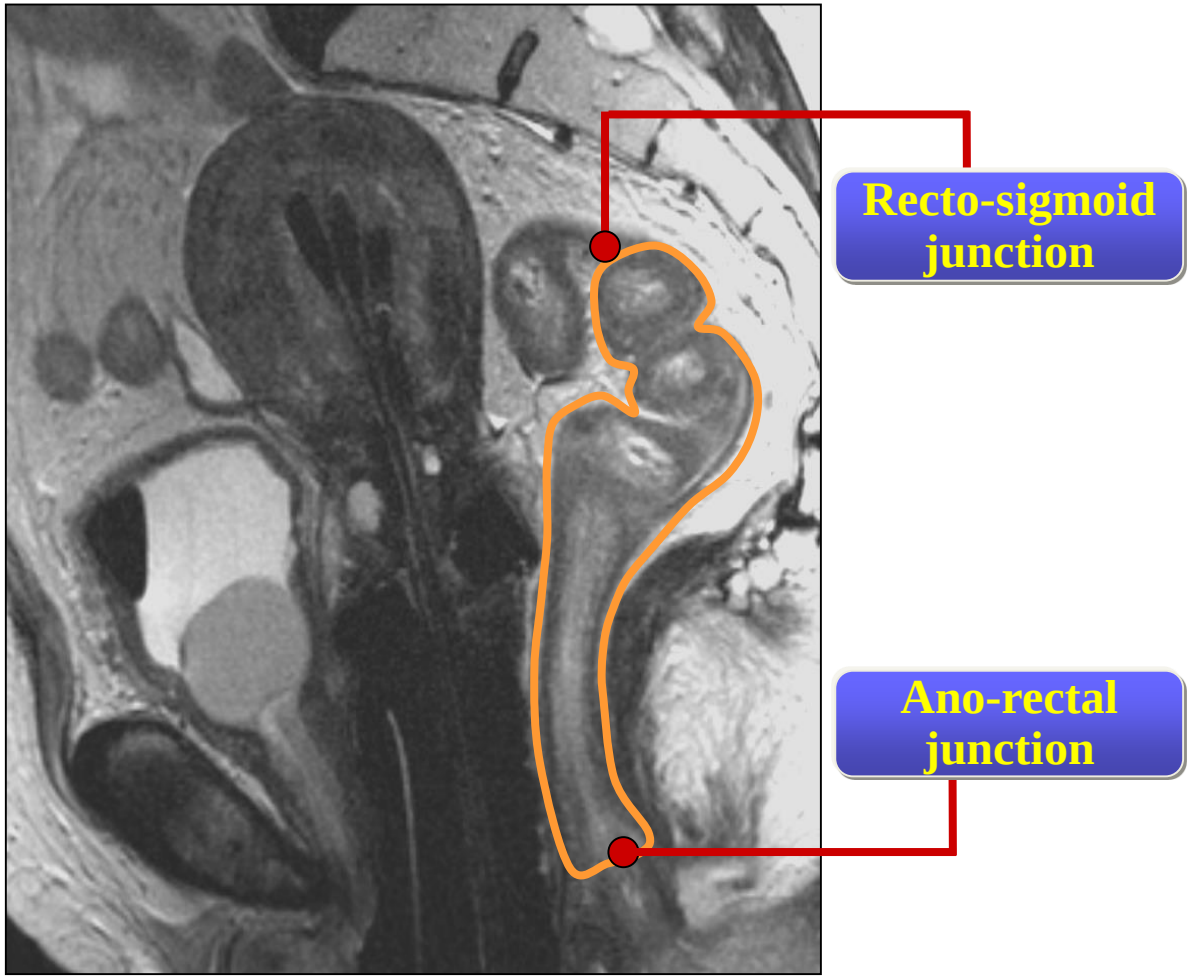
<u>Yes, if</u> doses to 2 cm³ are evaluated.



Olszewska AM. Radiother Oncol 2001;61:83-85

Clear Definitions of Organs at risk

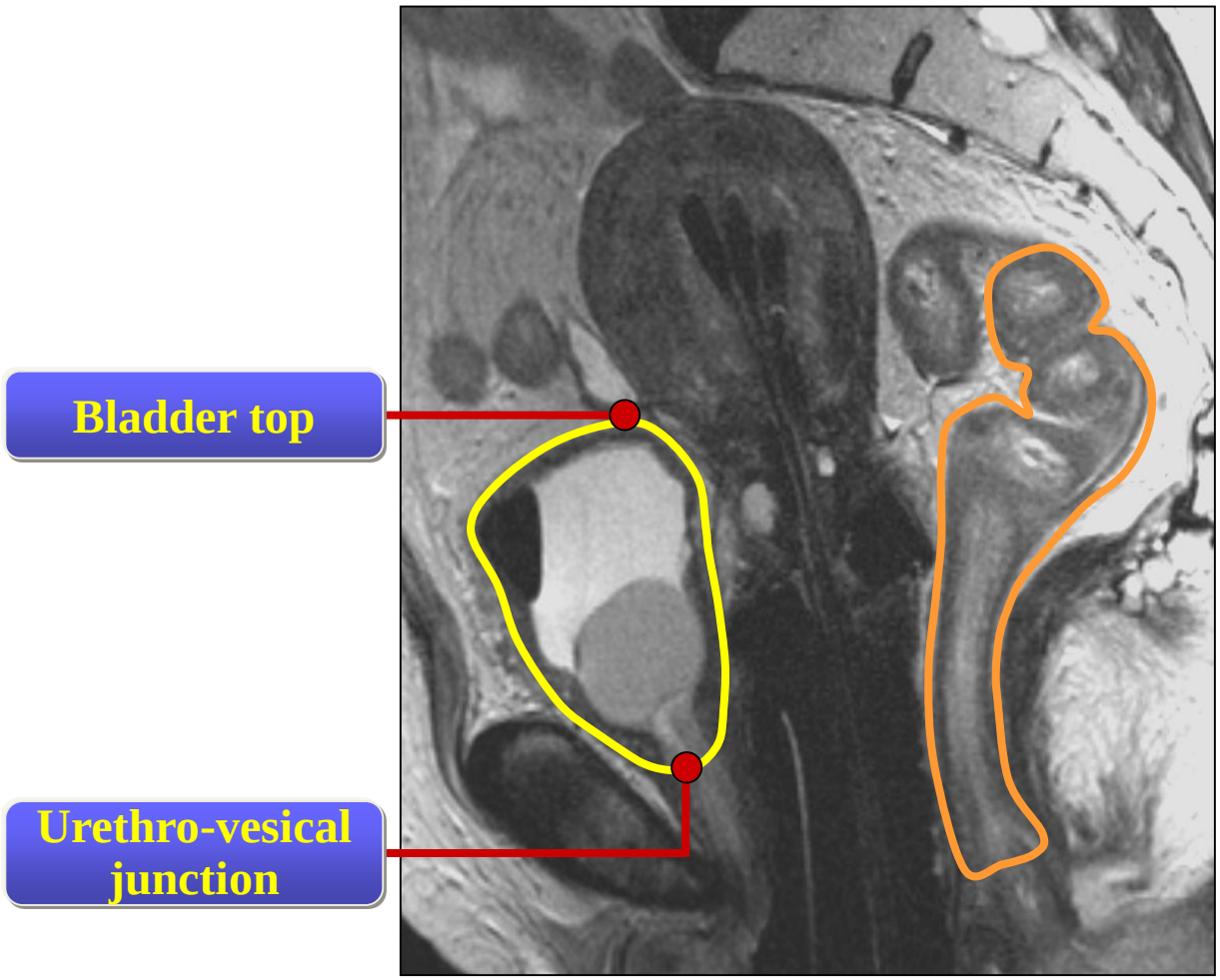
Rectum



Muren LP, et al. Radiother Oncol 2004
Michalski JM, et al. IJROBP 2010

Clear Definitions of Organs at risk

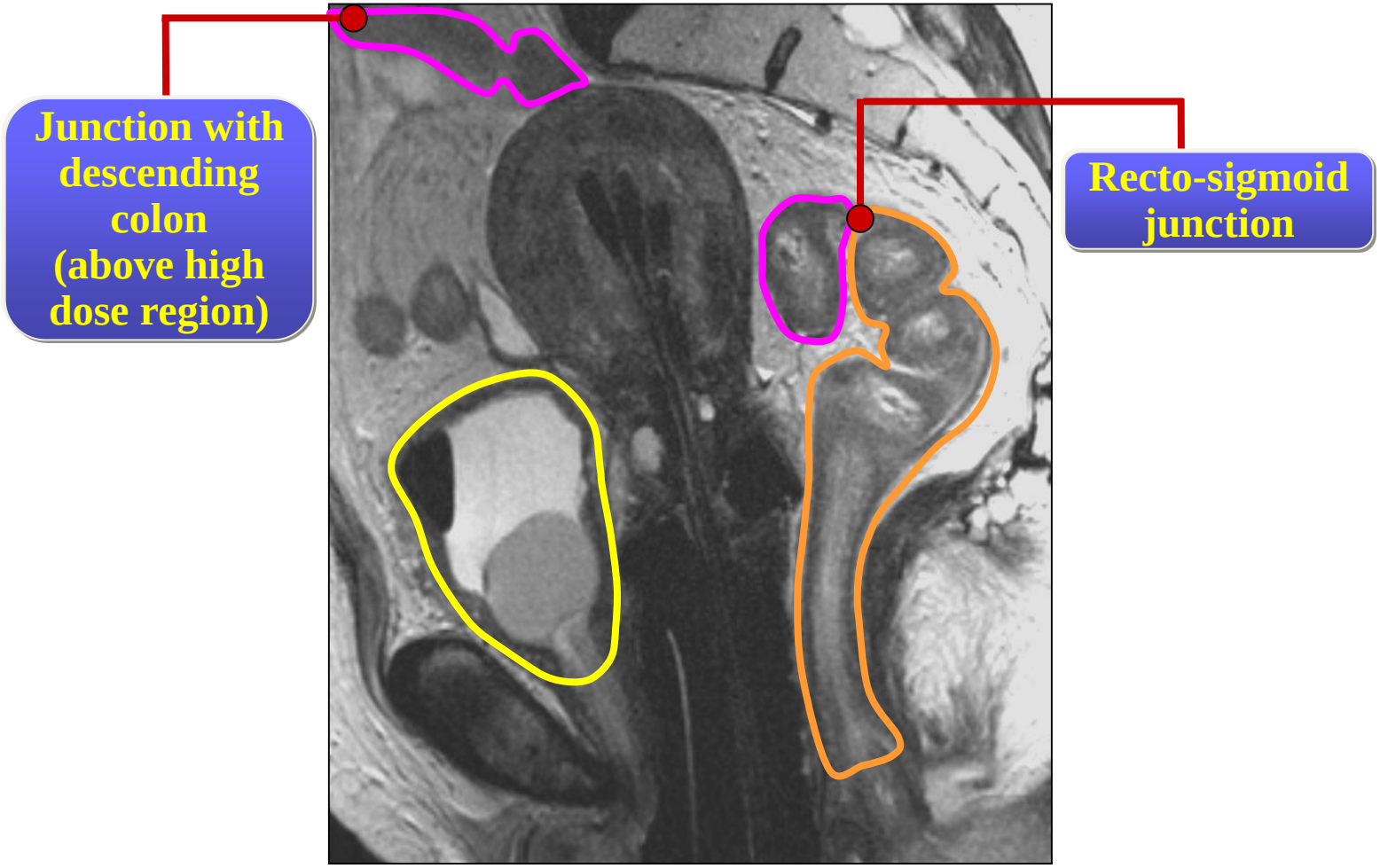
Bladder



Viswanathan AN, et al. IJROBP 2010

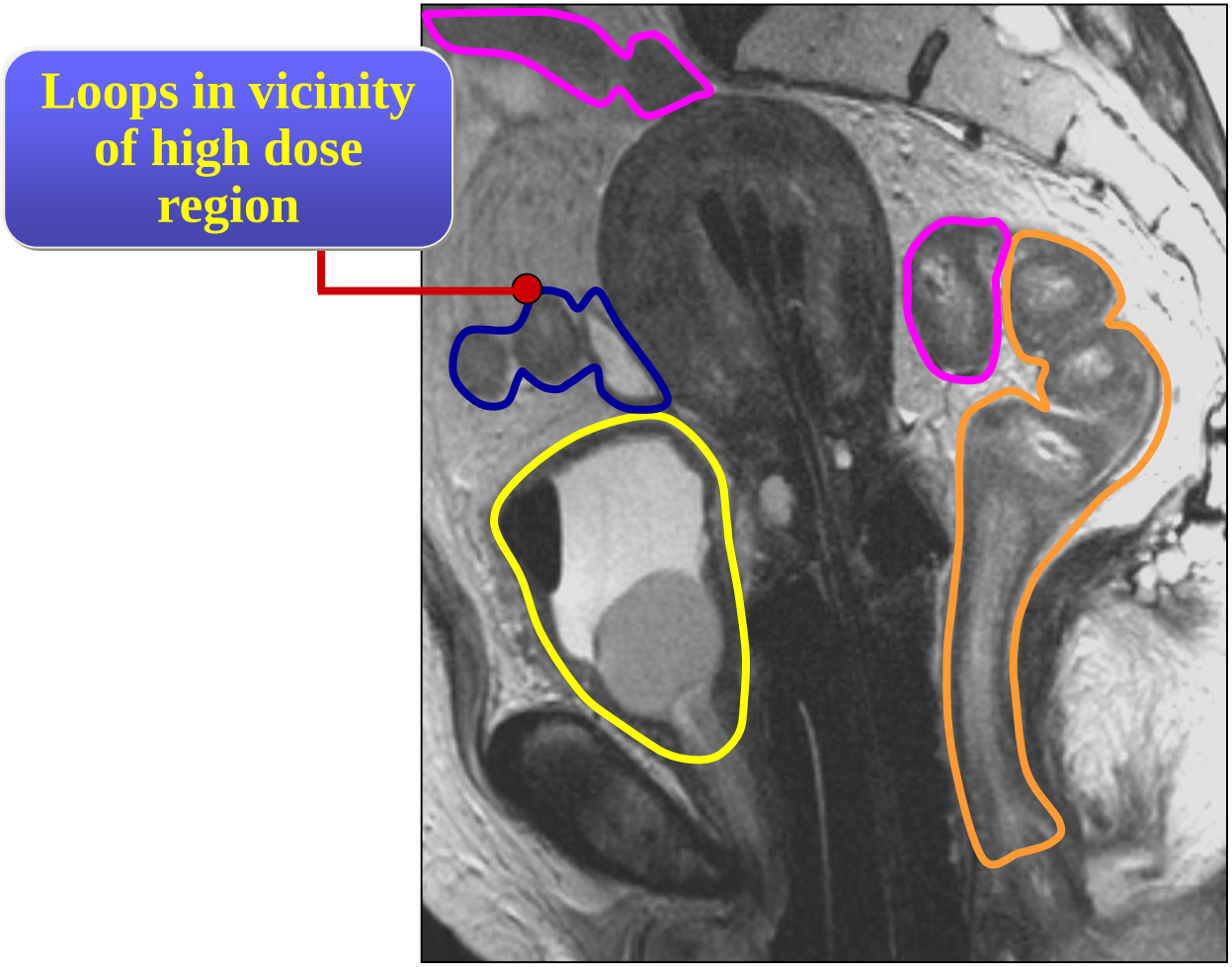
Clear Definitions of Organs at risk

Sigmoid colon



Clear Definitions of Organs at risk

Small bowel



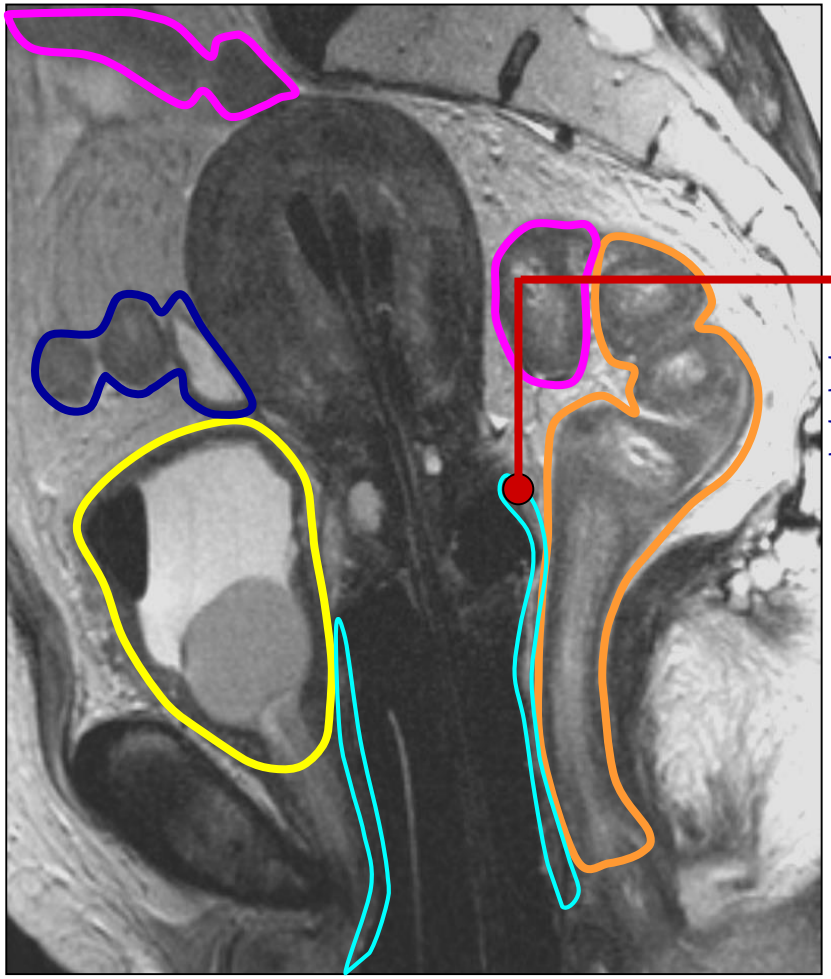
Kavanagh BD, et al. IJROBP 2010
Muren LP. Radiother Oncol 2003

Kvinnsland Y. Radiother Oncol 2005
Hysing LB. Radiother Oncol 2006

Sanguinetti G. Radiother Oncol 2008
Fokdal L. Radiother Oncol 2005

Clear Definitions of Organs at risk

Vagina



Vaginal wall

Delineation, DVH, Reporting:

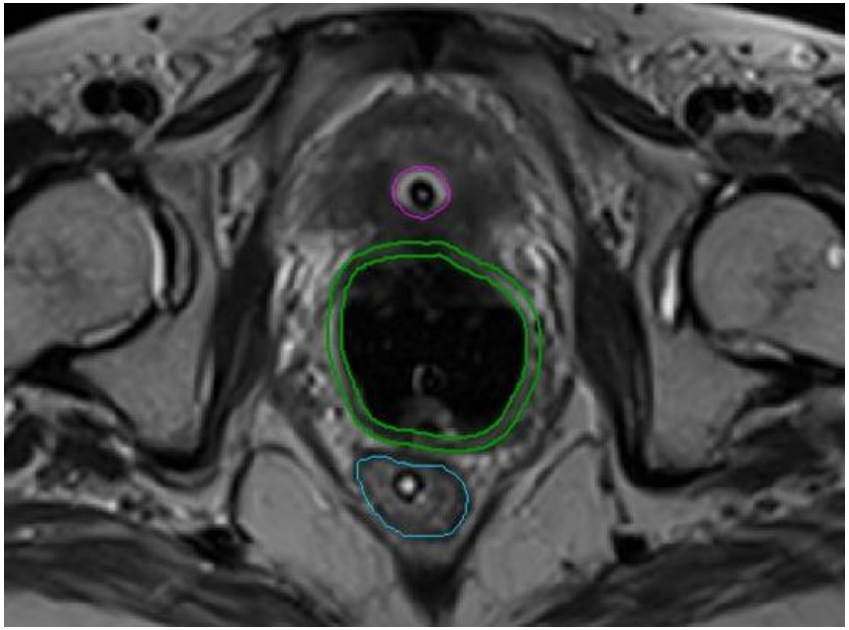
- ↑ uncertainties
- ↓ reproducibility

SUBJECT OF FURTHER STUDIES

Berger D, et al. IJROBP 2007

Vaginal wall Contouring

- Contour vaginal wall according to visible low signal intensity of vaginal wall.
- If not accurately distinguished: Take 3 mm as overall organ wall thickness and contour from fornices till introitus in three parts as per ICRU 89



Other OARs

- **Urethra-** Foleys catheter and surrounding low signal intensity was used for delineating urethra from bladder neck to urethral orifice
- **Uninvolved Uterus-** Whole uterus is contoured. HR CTV was subtracted from whole uterus to obtain volume of uninvolved uterus

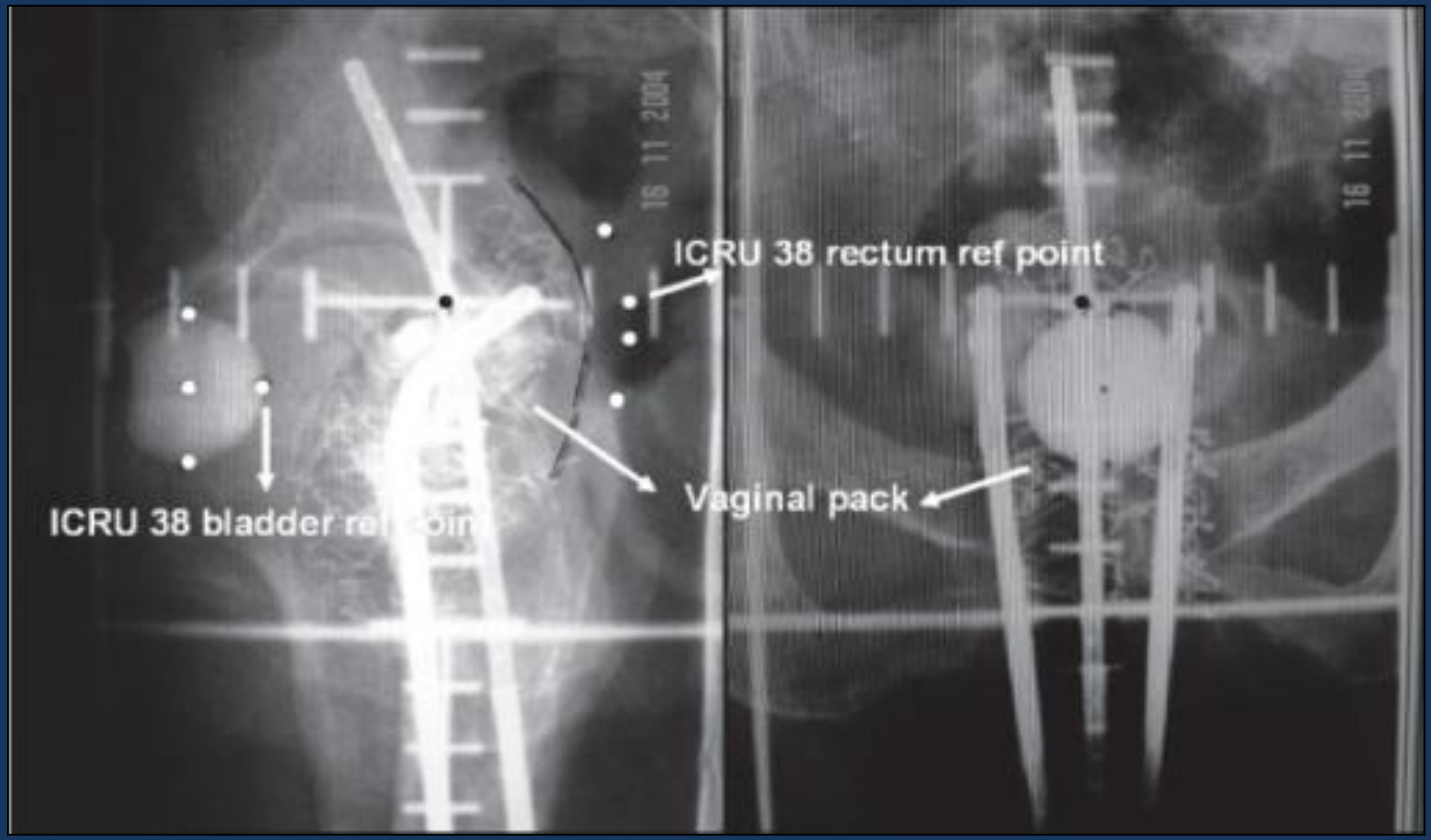
Summary

- OAR delineation in Gyn Brachy is very crucial
- 2D delineation of OAR is not encouraged
- 3D imaging should be preferred
- Though MRI is ideal imaging for OAR delineation, but has practical issues
- CT scan is feasible, practical
- USG is new

Principles of 2D radiographs based planning and CT information

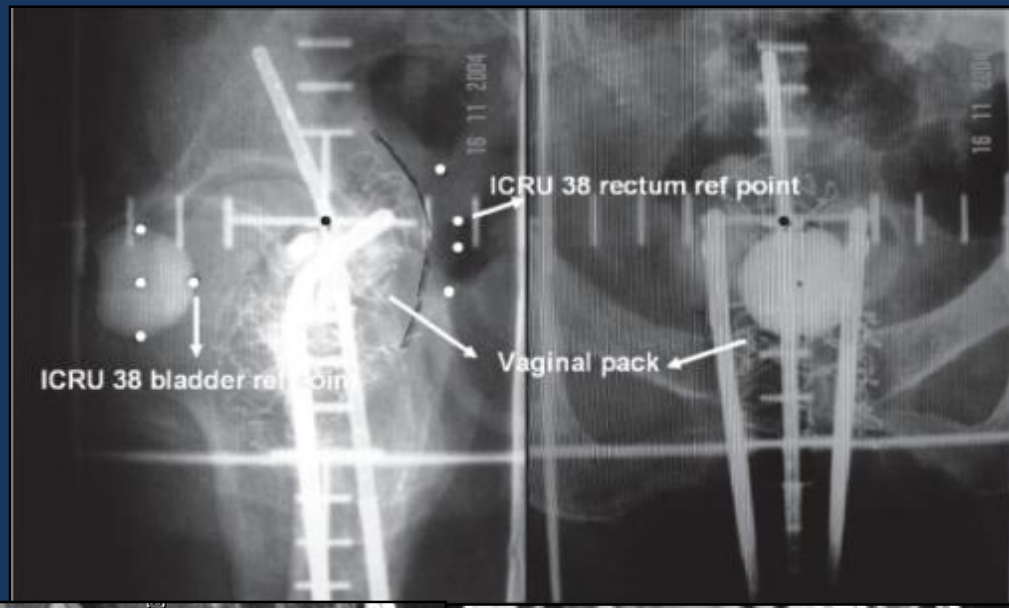
Swamidas V Jamema PhD
Department of Medical Physics
Tata Memorial Hospital
Mumbai

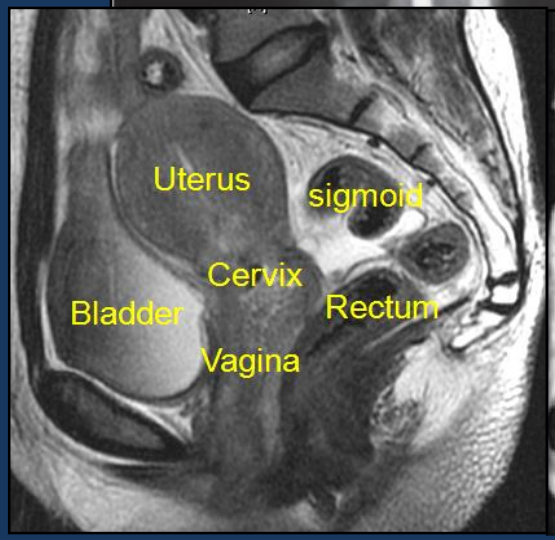
2D Brachytherapy - What we can see

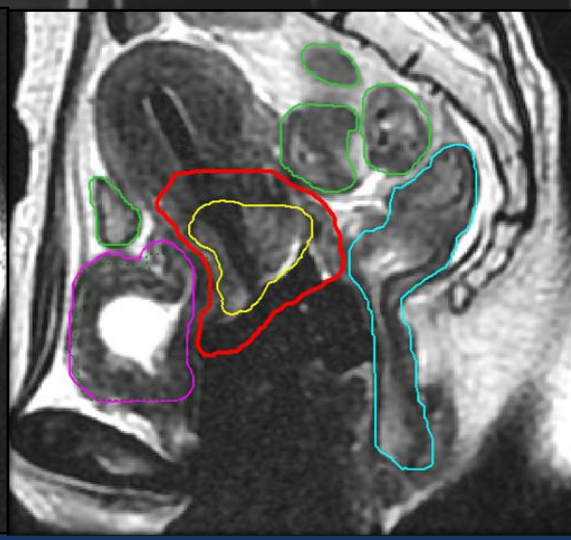


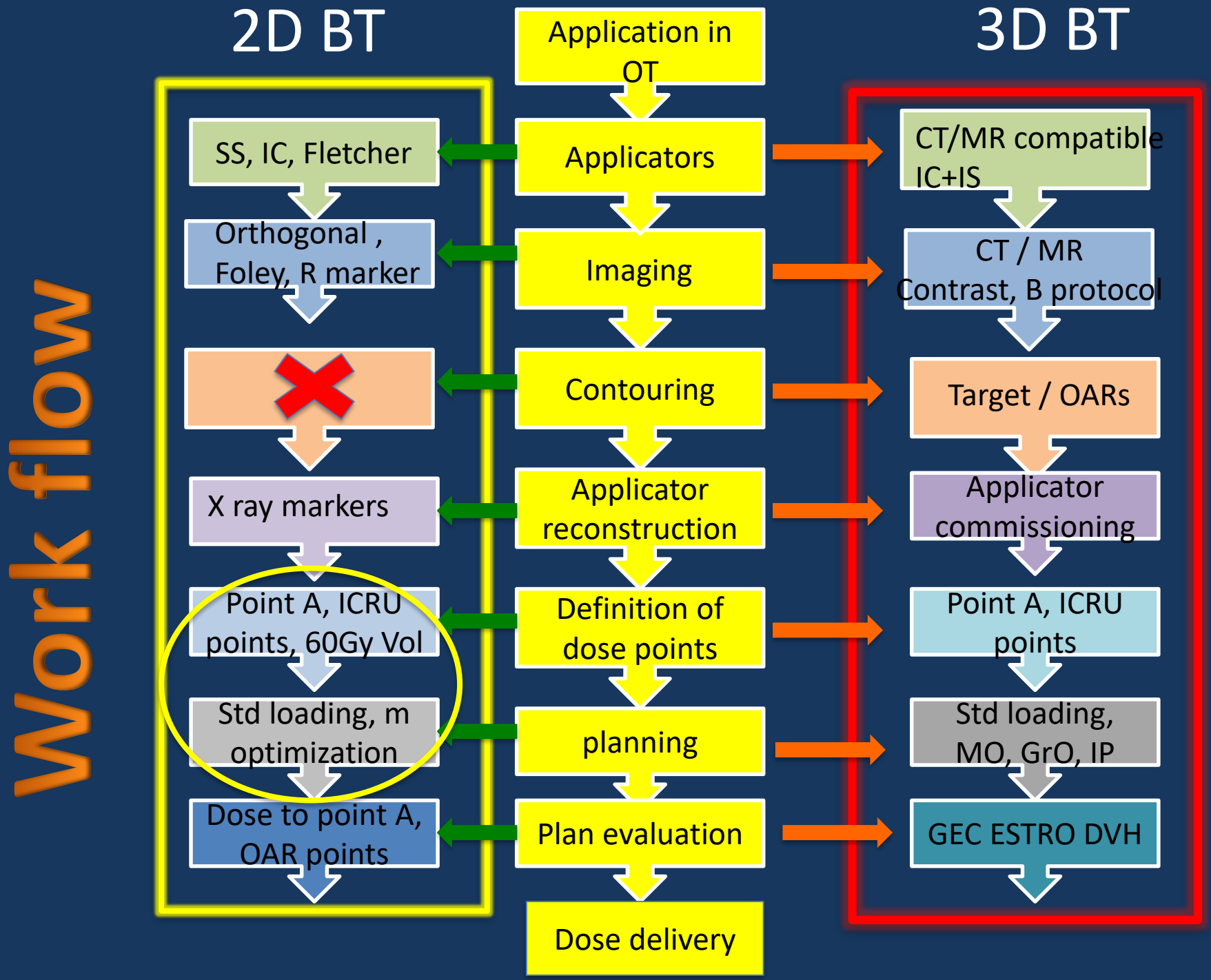
2D Brachytherapy- What we cannot see

- Target / disease at the Cervix and parametrium
- Uterus
- Rectum – posterior wall
- Bladder –Anterior wall
- Sigmoid
- Small bowel



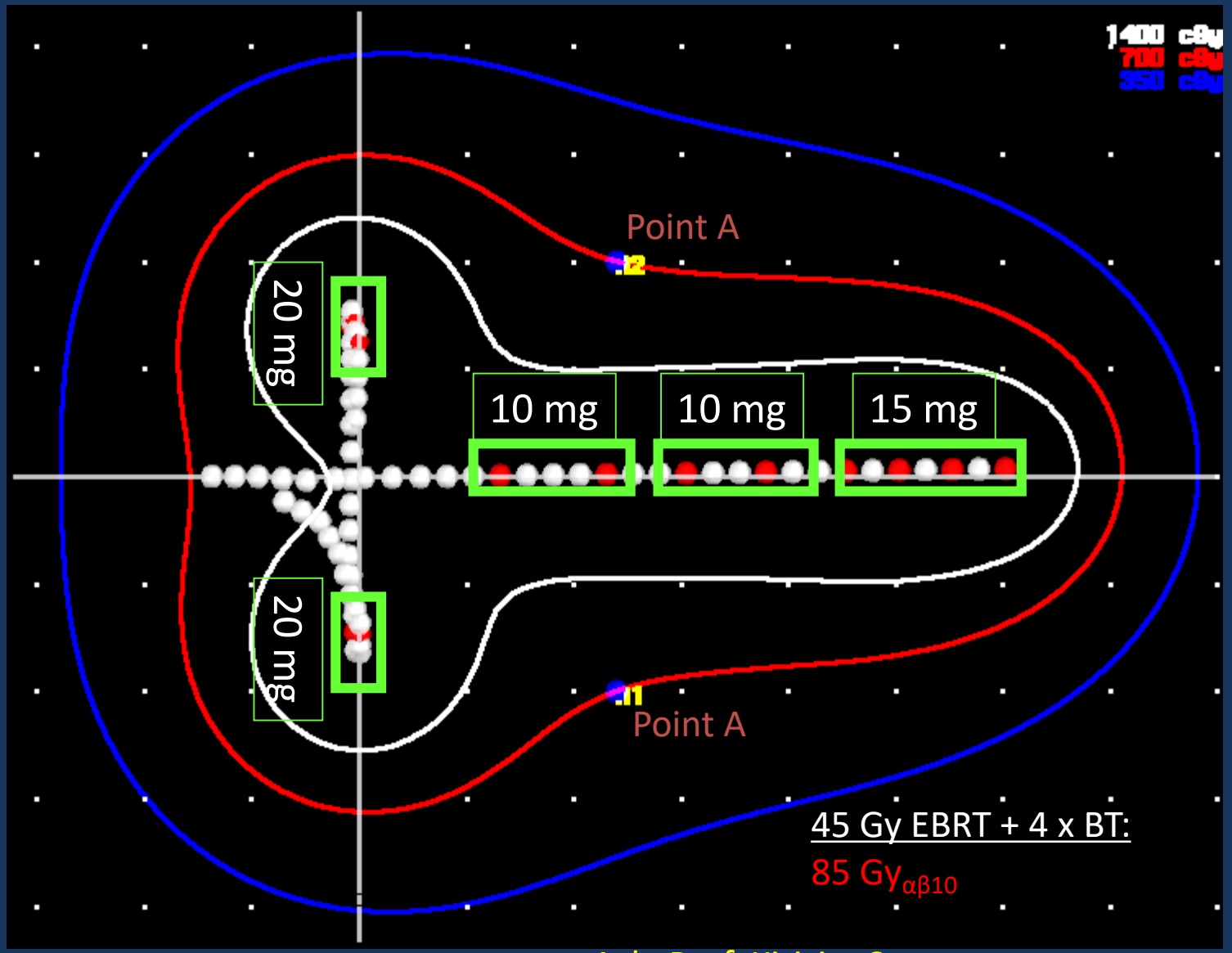





Work flow
2D BT
Application in OT
3D BT
SS, IC, Fletcher
Applicators
CT/MR compatible IC+IS
Orthogonal , Foley, R marker
Imaging
CT / MR Contrast, B protocol
Contouring
Target / OARs
X ray markers
Applicator reconstruction
Applicator commissioning
Point A, ICRU points, 60Gy Vol
Definition of dose points
Point A, ICRU points
Std loading, m optimization
planning
Std loading, MO, GrO, IP
Dose to point A, OAR points
Plan evaluation
GEC ESTRO DVH
Dose delivery

IUT	Loading in terms of units Cx to fundus		Vaginal ovoids	Loading in terms of units In each
Large 6 cm	4-4-6 (10-10-15 mg)		Large 3 cm	9 (22.5 mg)
Medium 4 cm	4-6 (10-15 mg)		Medium 2.5 cm	8 (20 mg)
Short 2 cm	8 -10 (20mg)		Short 2 cm	7 (17.5 mg

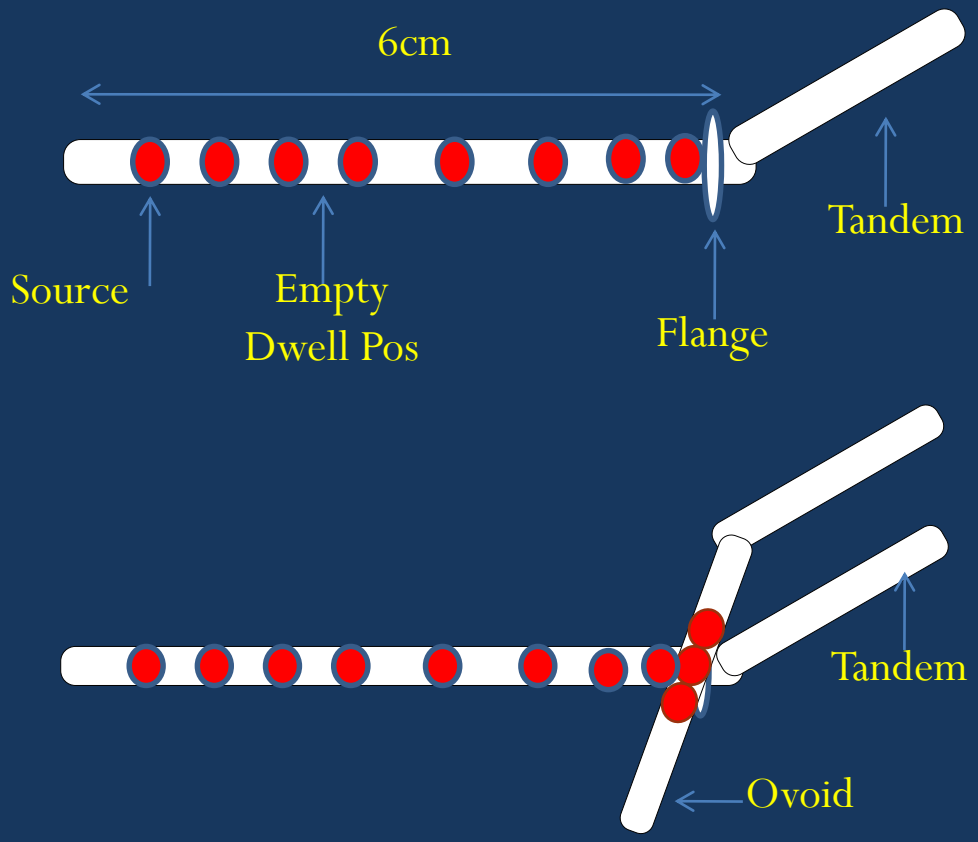
Standard loading Pattern – Radium to LDR, HDR



Ack: Prof. Kirisits C

Standard loading pattern – Tata

Tandem (6cm)	Ovoid (1.5,2.0cm)
1	4
3	5
5	6
7	7**
10	
13*	
16	
20	



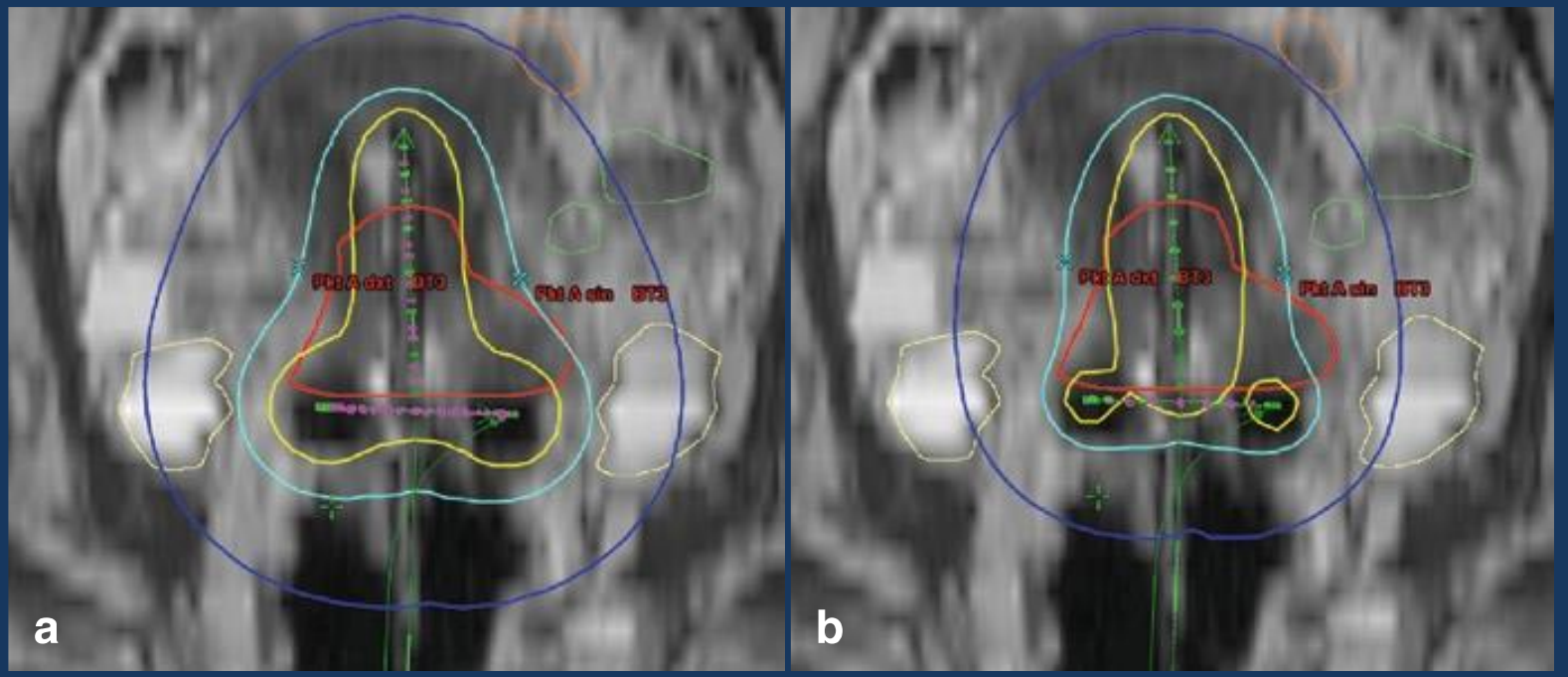
* 4cm tandem

**ovoid dia 2.5cm

Standard loading pattern

Schools	Source loading (V/U)
Stockholm, Paris	1
Fletcher	0.6-1.4
American	0.15-0.25
Other schools	No vaginal loading, Only tandem

Standard loading pattern



- Vienna Loading
- Point A normalization
- V/U = 1
- Width_A(at ring) = 6.2cm

Milwaukee Loading

Point A normalization

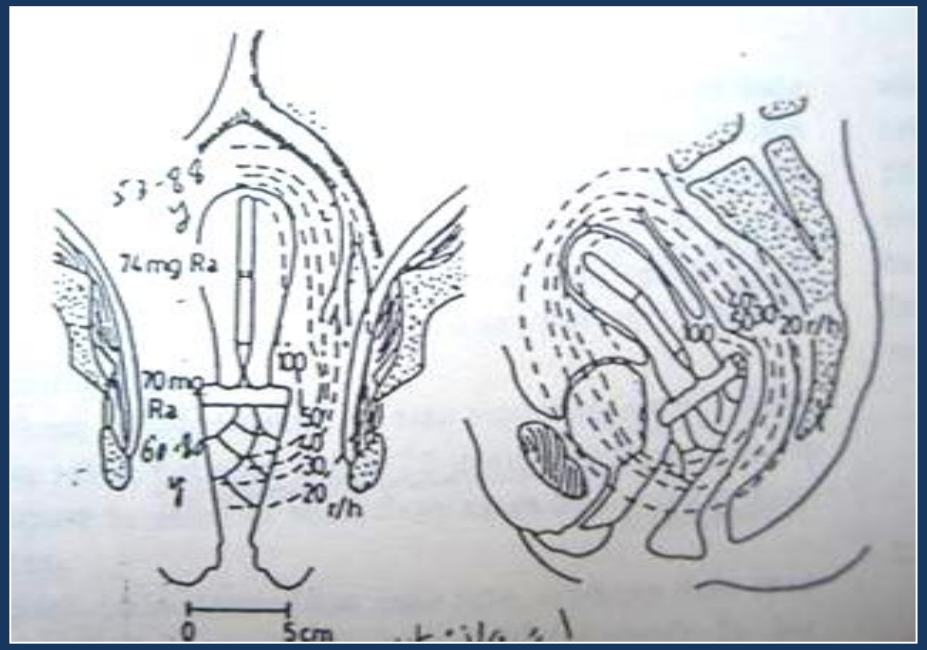
V/U = 0.16

Width_A = 4.3 cm

From Gynaecologic Radiation therapy book,
Edited by A viswanathan,C Kirisits, B Ericson, R Potter

History

- Dosimetry systems
  - Stockholm
  - Paris
  - Fletcher
  - ***Manchester***



Vol. XXVI, No. 305

TREATMENT OF CANCER OF THE CERVIX UTERI—A REVISED "MANCHESTER METHOD"

By Margaret Tod, M.B., Ch.B., F.R.C.S.E., F.F.R., and W. J. Meredith, M.Sc., F.Inst.P.

The Christie Hospital and Holt Radium Institute, Manchester

(Accepted for publication March, 1953)

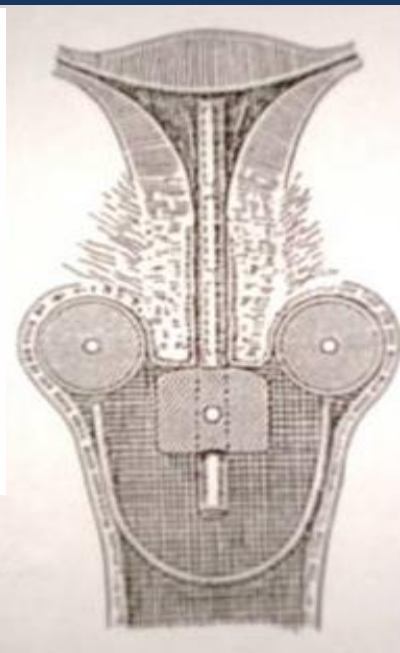
Introduction

...e "Manchester method" technique for the ...dium treatment of cancer of the uterine cervix ...rst described by Tod and Meredith (1938). ...its three main features were:

...The selection and definition of two points, A and ... dosage specification. Point A (*cf.* Fig. 2) was ...d as being "2 cm lateral to the central canal of ...erus and 2 cm up from the mucous membrane ... lateral fornix in the axis of the uterus". Point ... cm lateral to Point A at the same level.

and dimensions have proved to be clinically convenient as well as physically desirable, so no change in the vaginal applicators has become necessary. The flanged, thin rubber intra-uterine tubes, chosen to reduce dilatation to a minimum, and made in various lengths, have also proved to be satisfactory. The applicators are illustrated in Fig. 1.

3. *The use of a system of loading of the intra-uterine tube and vaginal ovoids in terms of simple numbers of "units" of radium such that the dose rate at Point A was fairly constant no matter which combination of applicators was used.* Although it is possible to obtain

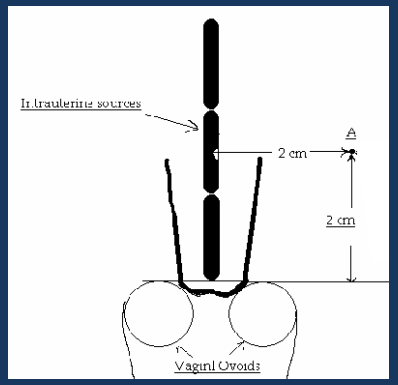


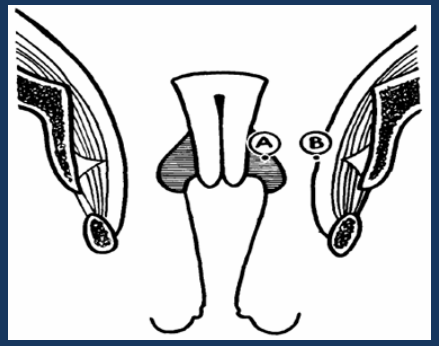
Manchester system – 3 rules

- Rule 1:Define treatment in terms of dose to a ***point*** representative of the target i.e., uterus, more or less reproducible from patient to patient.

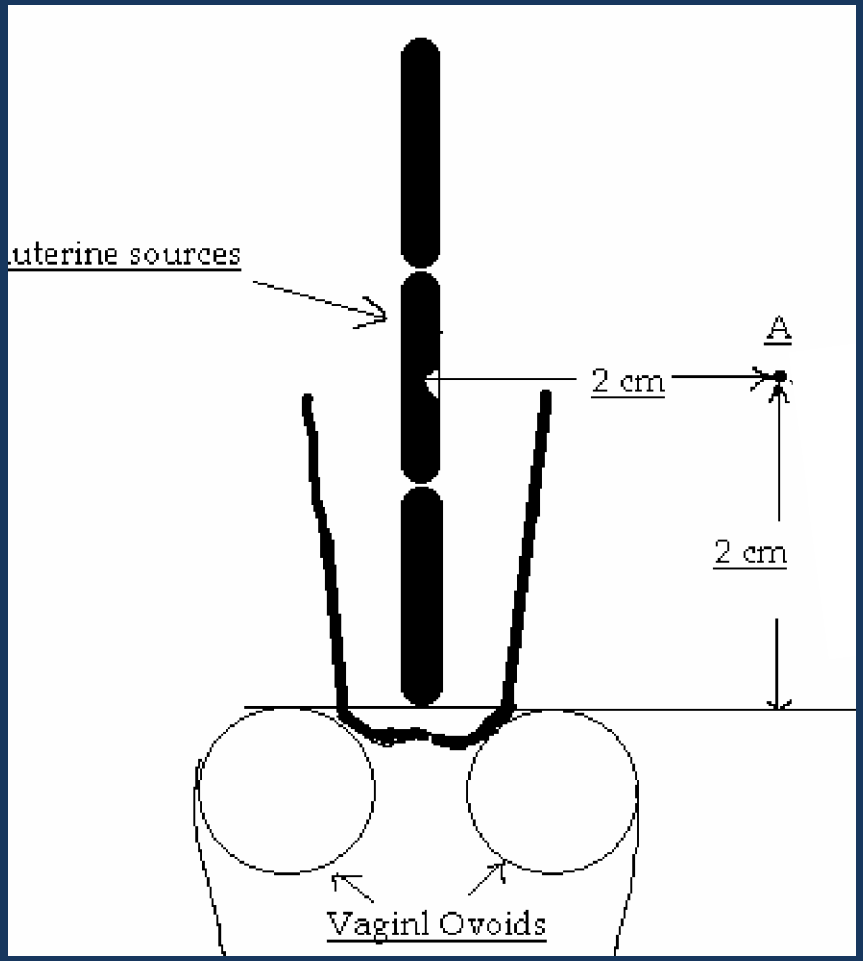
- Rule 2: Design applicators and their loading to enable the same dose-rate to this point 'A' regardless of which combination of applicators is used.

- Rule 3:Define a set of rules dictating the relationship, position, and activity of radium sources in the uterine and vaginal applicators to achieve the consistent dose rates



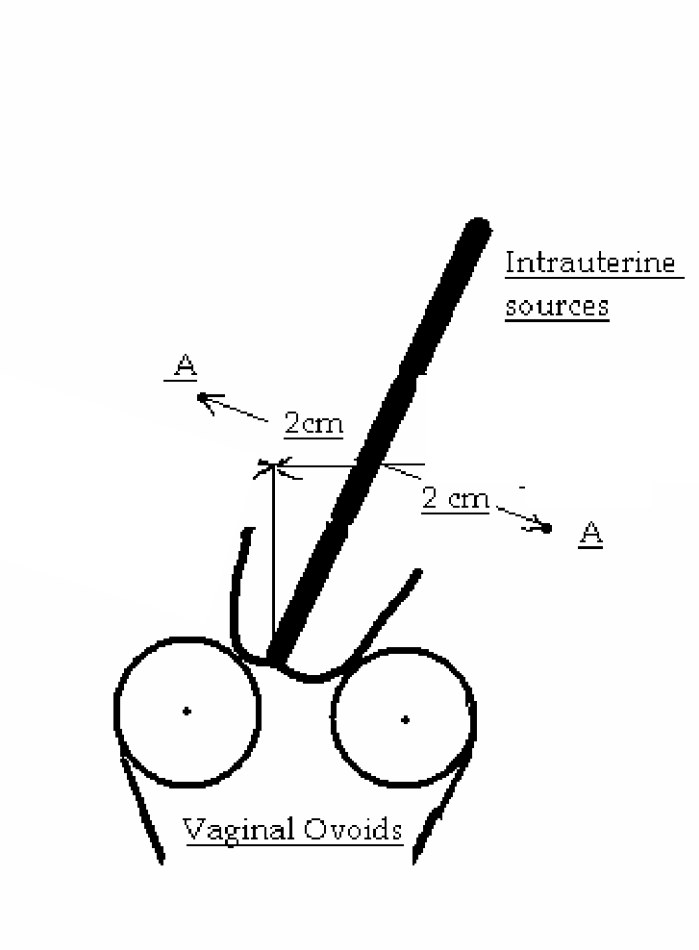


1938 - Original definition of point A



2 cm lateral to the uterine canal and 2 cm from the mucous membrane of the LATERAL SUPERIOR FORNIX of the vagina in the plane of the uterus.

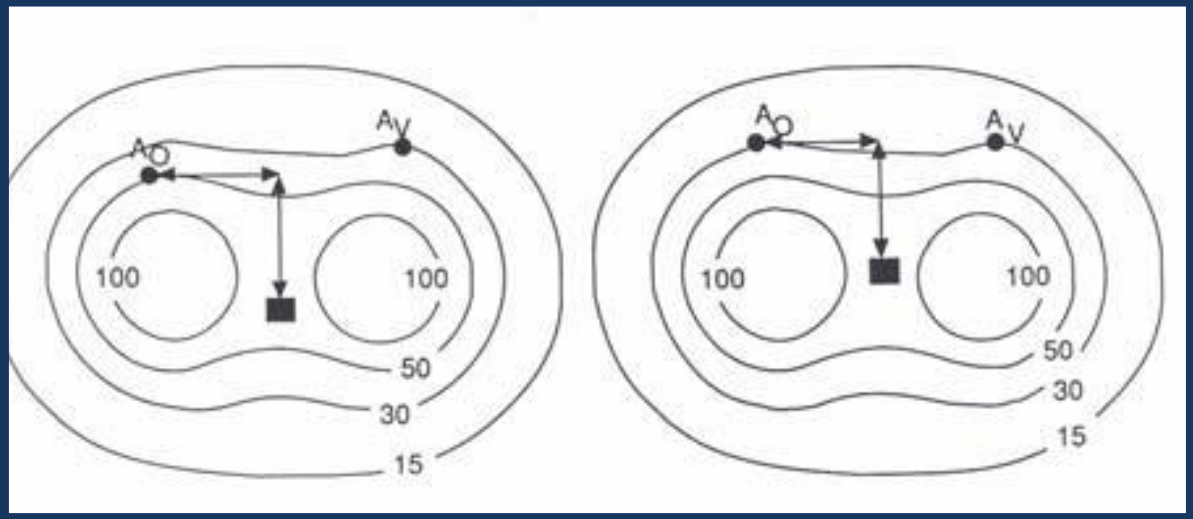
1953 -Modified definition of point A



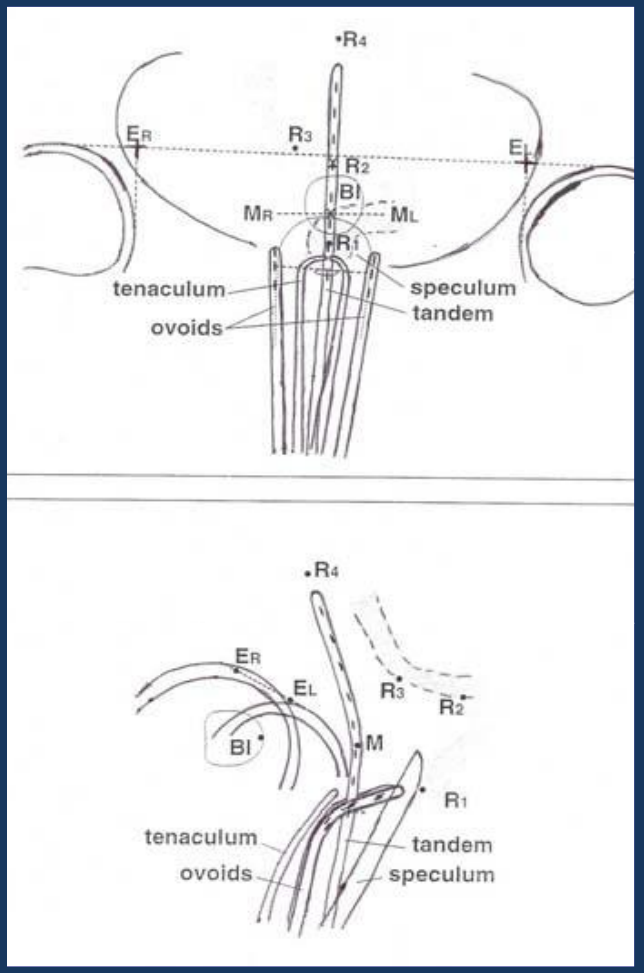
2 cm lateral to the uterine canal and 2 cm from the LOWER END OF THE IUT/OS

Definition - Point A

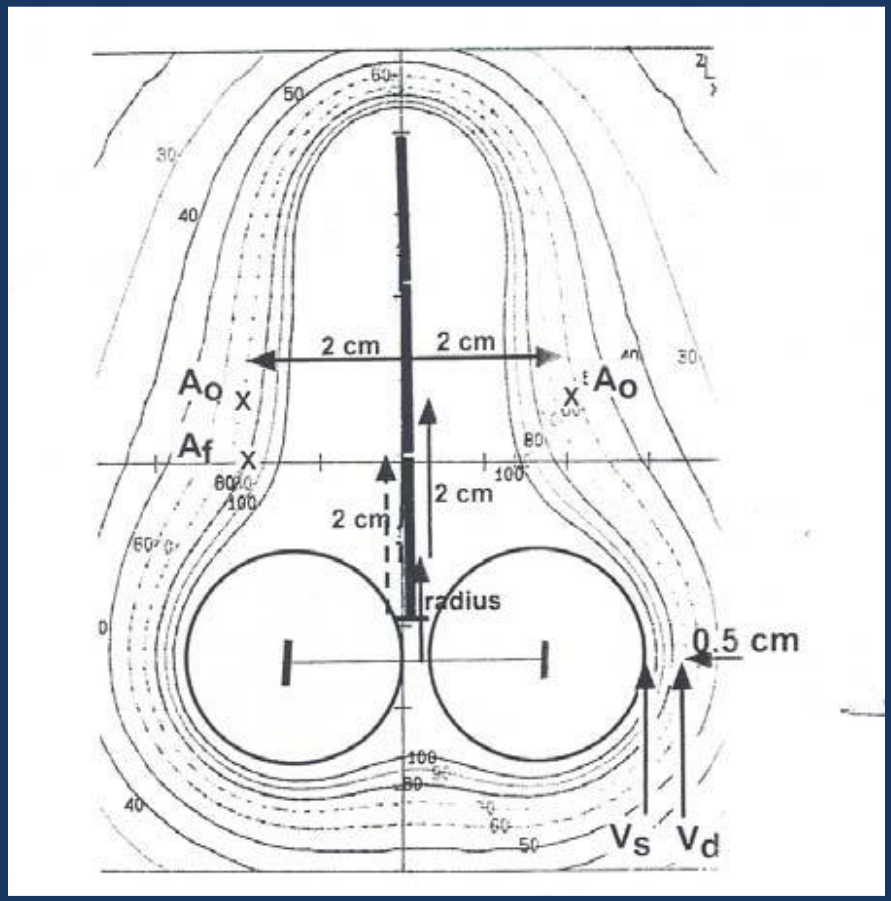
Point Av



Point M



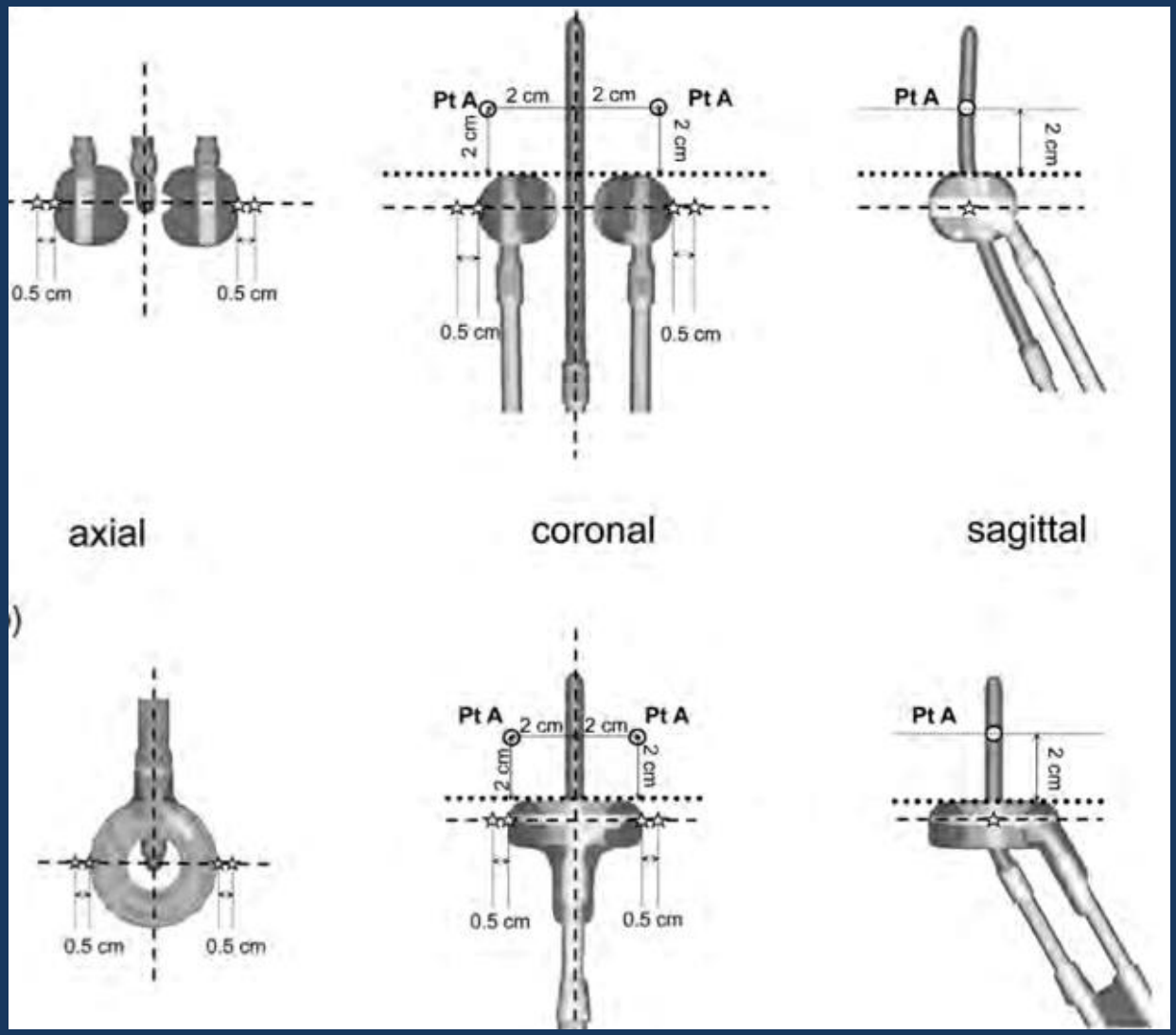
ABS Definition - Point A



- T/O:

Draw a line connecting the middle of the sources in the vaginal ovoids on the AP radiograph and move 2cm (plus radius of the ovoid), superiorly along the tandem from the intersection of this line with the intrauterine source line and then 2 cm lateral on either side of the tandem.

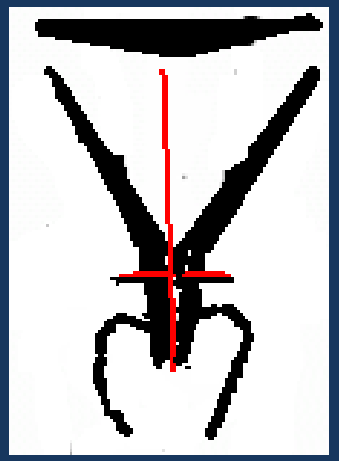
ICRU 89 – Point A



Limitation of Point A

- Different methods of definition provide different values for the calculated dose rate to point A.

- Relates to position of sources and not to specific anatomic structure.
- It is very sensitive to position of ovoid sources relative to tandem which should not be deciding factor in deciding on implant duration.



- Depending on size of cervix point A may be inside or outside of tumor.

ICRU 38 & Point A

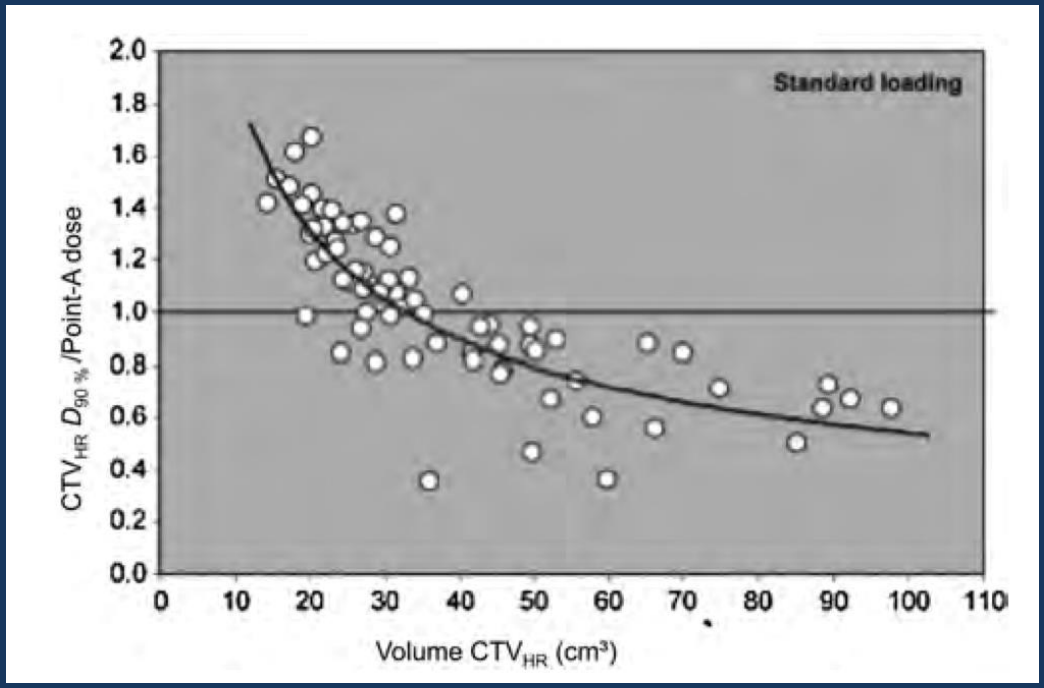
- ICRU 38 discouraged the use of point A and B because the exact meaning and their definitions have not always been interpreted in the same way in different centers and even in the same center over a period of time.

- Encourages the use of target volume for dose prescription and reporting along with the reference volume for 60Gy absorbed dose prescription.

ICRU 89- Point A

- Recommended while reporting treatment regimens.
  - Allows comparison between different approaches.
  - Acts as a link to non- 3D image-based approaches.
  - Serves as a quality assurance parameter along with TRAK.
  - Standard loading point-A normalized plan acts as a perfect starting point for complicated IC+IS plans.

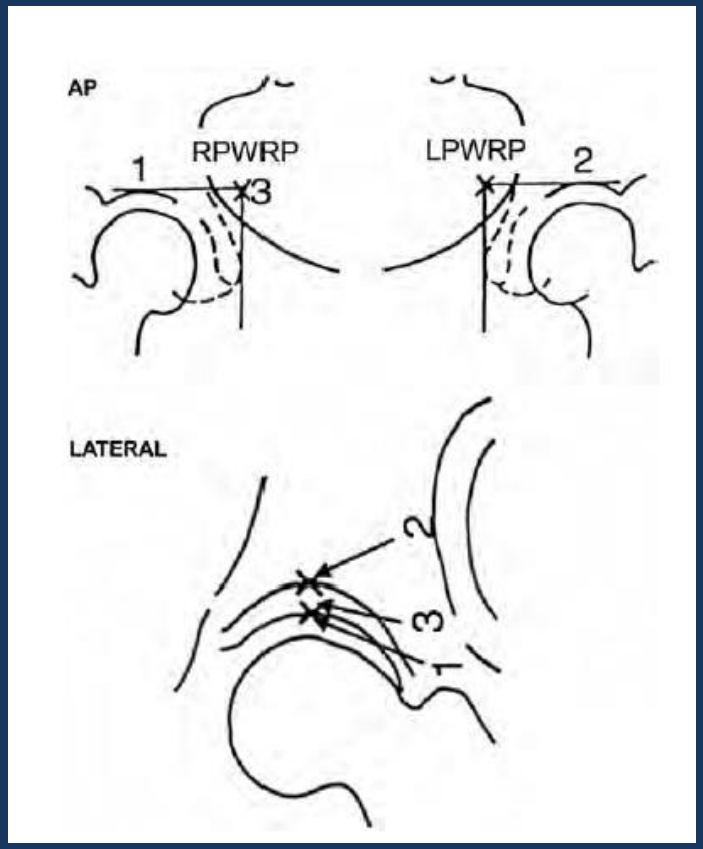
Point A and HR CTV D90



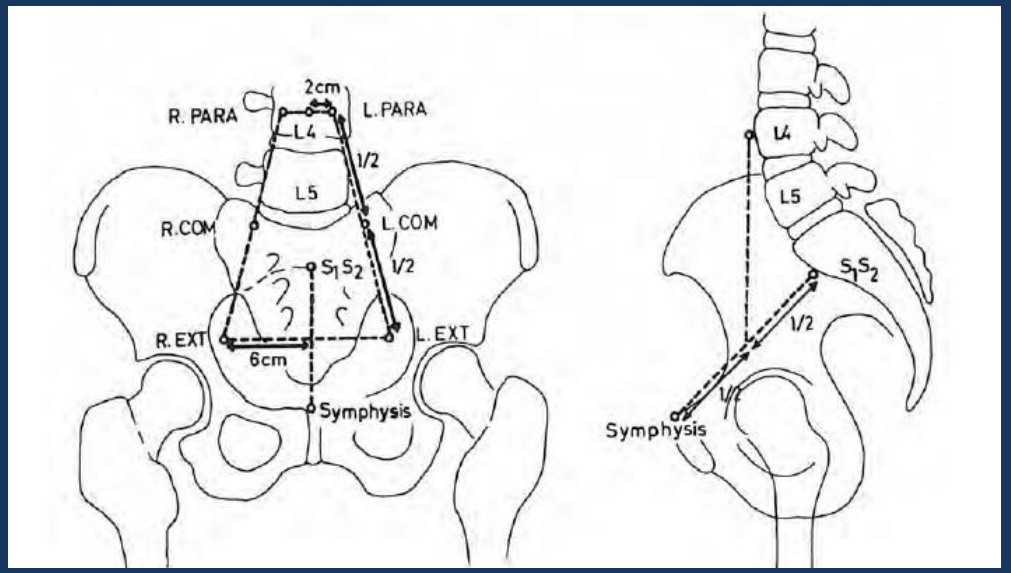
- It provides an estimate of the average CTVHR D90 % for a large patient population with a balanced disease-stage distribution
- Point A is a good representation of “an average position” of the tumor
- Helps in introducing / check for major dose escalation or reduction for such patient population as a whole.

Pelvic wall and lymph node points

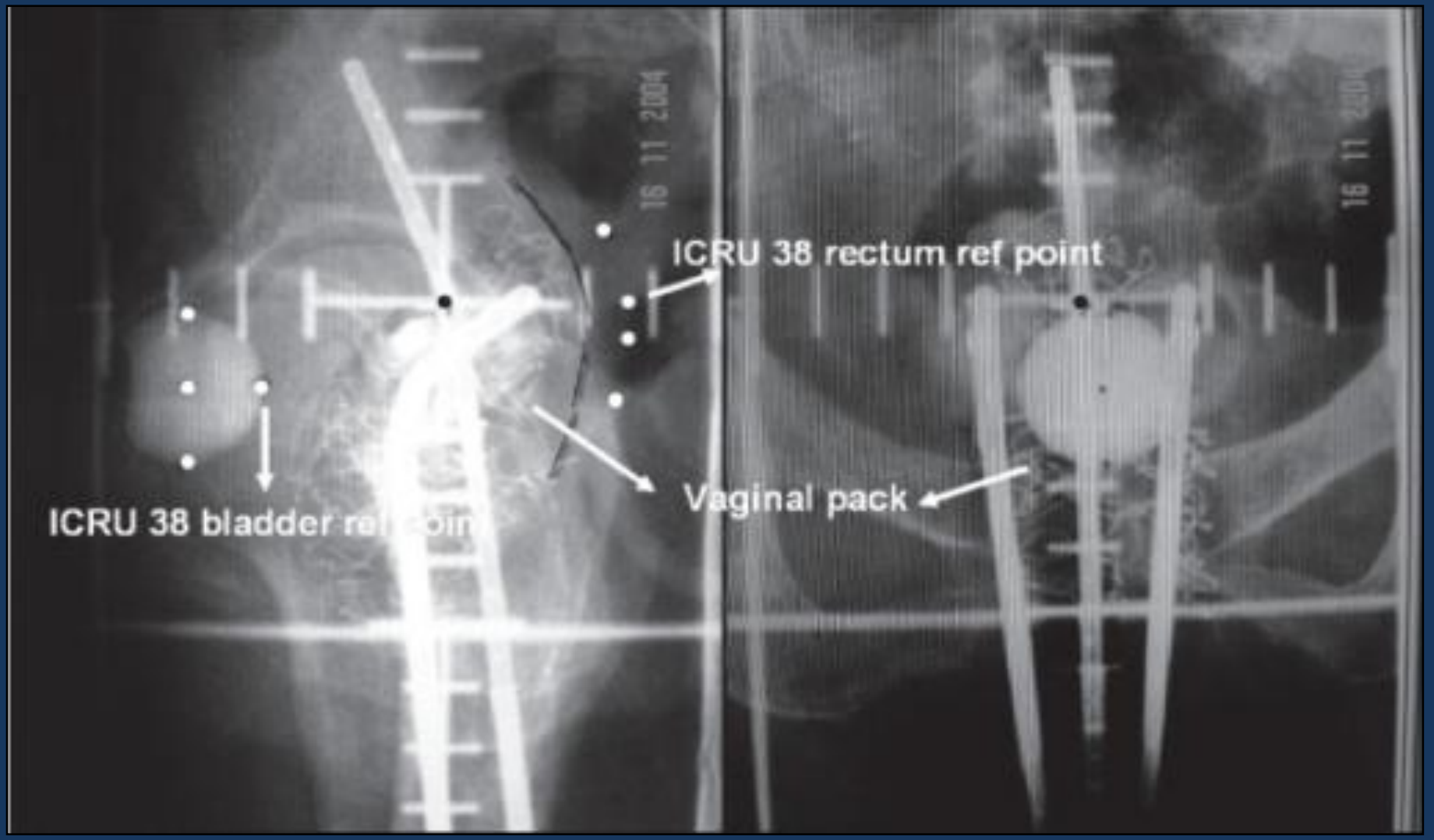
PWRP



Lymphatic trapezoid



OARs – ICRU rectum and bladder point



Correlation of ICRU reference points and D2cc

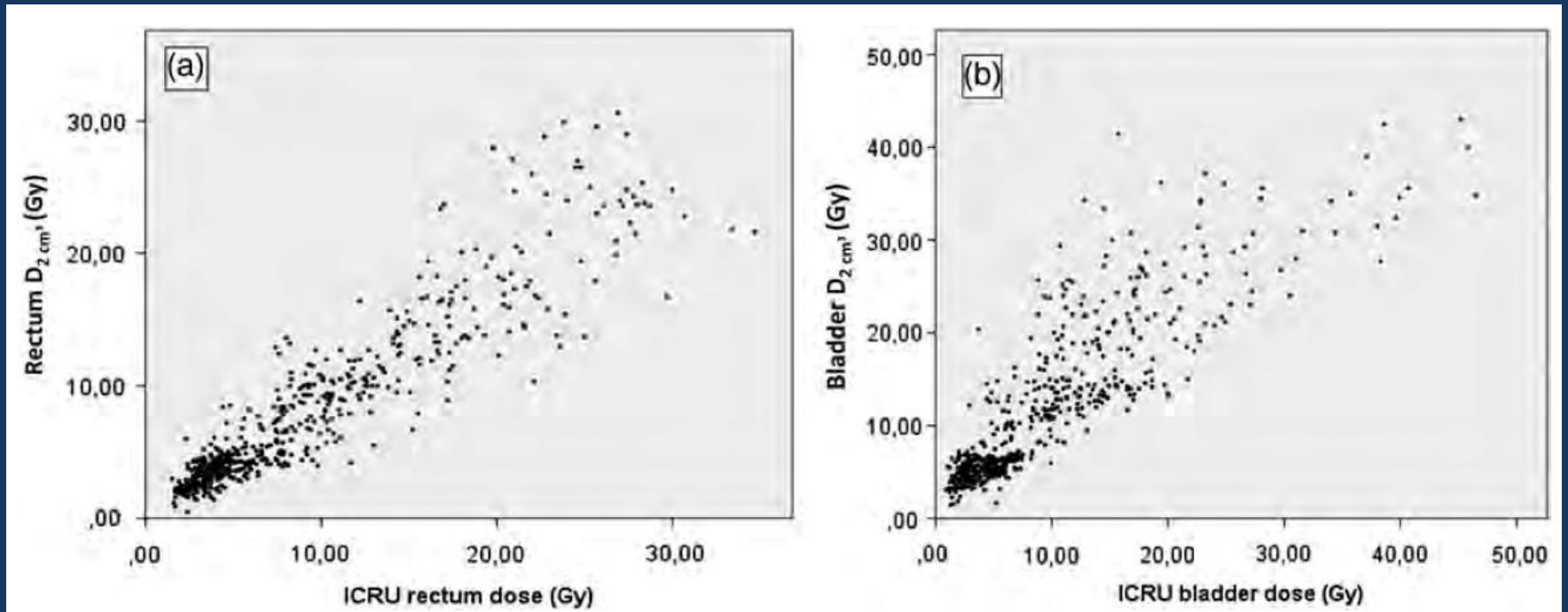
- Rectum: ICRU rectal reference point correlates with the D2cc dose of the organ rectum (Barillot et al., 2000; Crook et al., 1987; Georg et al., 2011; Koom et al., 200
  Perez et al., 1999; Pourquier et al., 1996; Stryker et al., 1988).

- Bladder: ICRU bladder reference point, does not correlate well with bladder complications (ICRU 38 bladder point underestimates the bladder dose) (Stryker et al., 1988).

Correlation of ICRU reference point and D2cc

- Rectum: ICRU point is 20% (sd 40 %) larger than D2cm3
- Bladder: ICRU point is 20% (sd 32 %) smaller than D2cm3

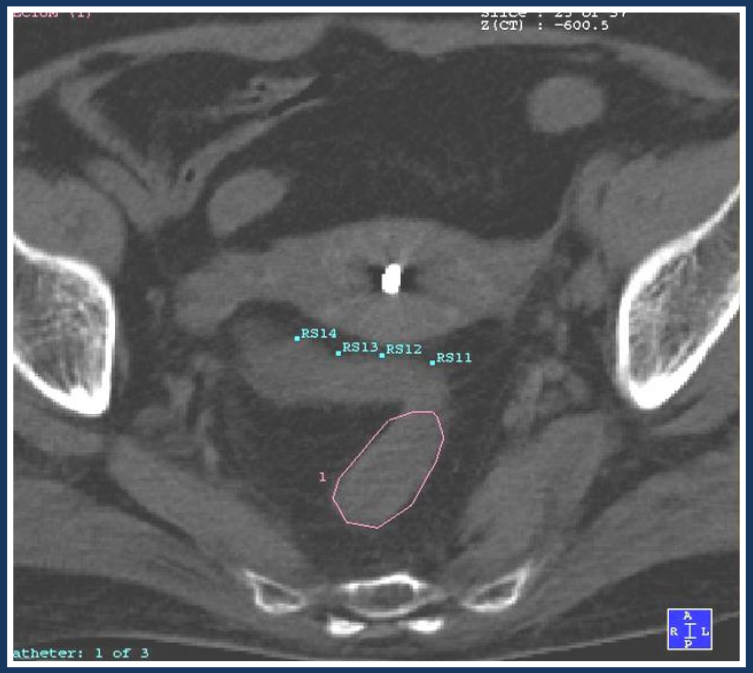
(Kirchheiner et al., 2016).



Sigmoid points on 2D radiographs

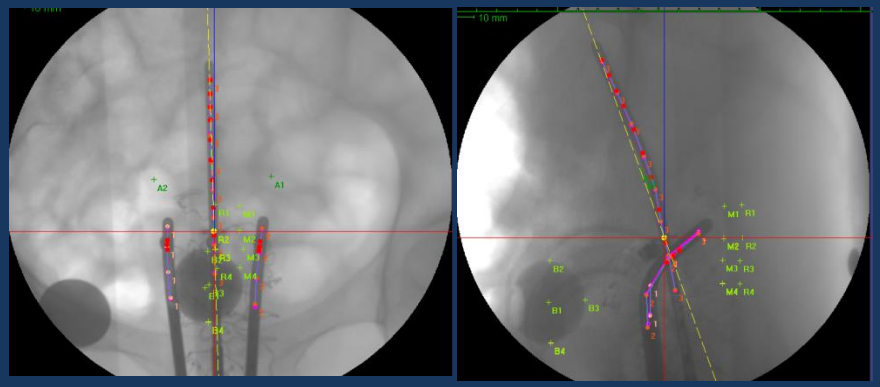
- 27 Patients treated with CT image based dosimetry
- Upper rectal and sigmoid points were marked on CT images
- Searched for a reproducible point with respect to applicator and other points
- No point was found that was reproducible that can act as a surrogate for upper rectal and sigmoid

- Barium contrast inserted and withdrawn that visualizes the sigmoid wall.

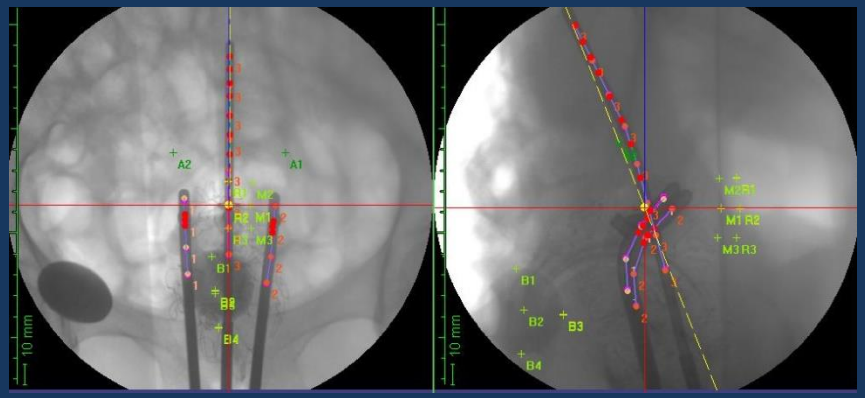


Mahantshetty et al, JCRT 2011

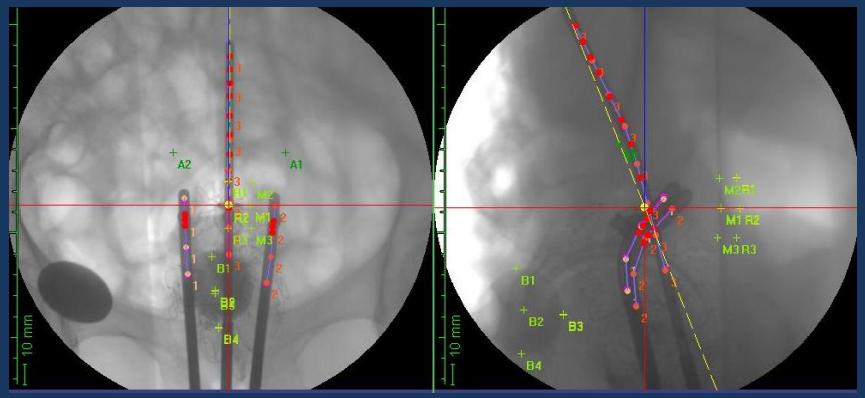
2D Inter application dose variation



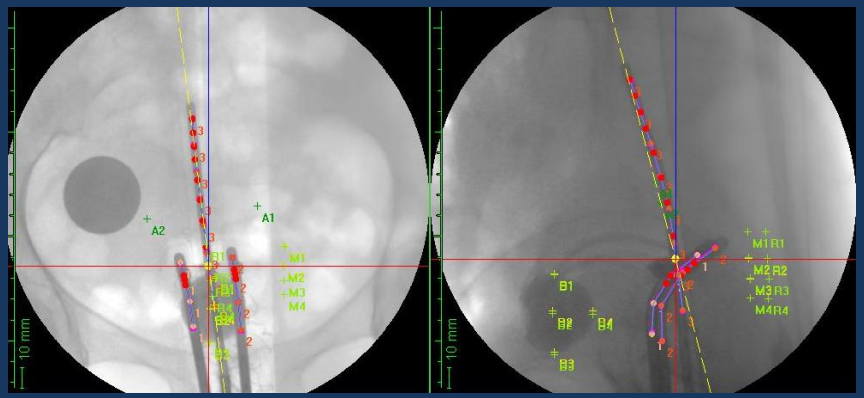
B=49.4%, R= 78.5%



B=39.06%, R=59.03%



B=45.32%, R=64.99%



B=41.32%, R= 67.28%

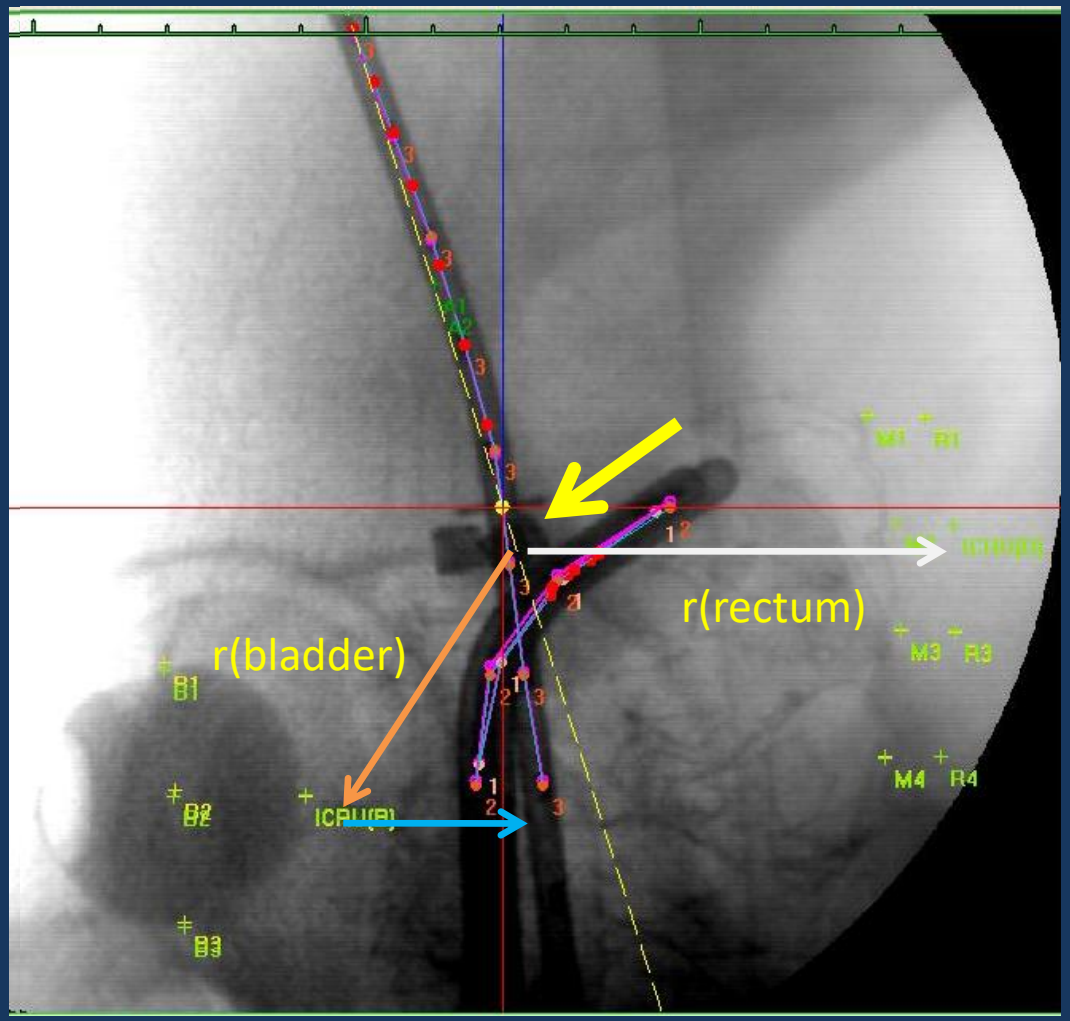
Inter application variation- spatial location

- Flange as the ref point (polar co cordinates)

r(bladder)= distance b/w centre of Flange and ICRU bladder point

r(rectum)= distance b/w centre of Flange and ICRU rectum point

Θ(bladder)=270° - Sin^{-1}ø
where, Sin ø=(a/r) &
a= perpendicular distance b/w ICRU bladder point and vertical axis



RESULTS - Summary

Inter application dose variation

TYPE	BLADDER		RECTUM	
	Mean	St. dev.	Mean	St. dev.
% interapplication dose variation w.r.t. 1st fraction	10.4	7.9	9.1	5.3

Inter application spatial location – OAR points

TYPE	BLADDER		RECTUM	
	Mean	St. dev.	Mean	St. dev.
Mean position in polar coordinates w.r.t. flange(r cm,θ^o)	(2.8,207.5)	(0.4,13.2)	(2.7,0)	(0.3,0)
Variation w.r.t. 1st fractionr cm, θ^o)	(0.4,5.9)	(0.2,5.4)	(0.3,0)	(0.28,0)

2D inter application conclusion

- The inter-fraction dose variation of about 10% is seen in 60% of cases for both rectum and bladder. However , maximum variation for rectum and bladder is within 20% and 30% respectively.

- The variation in ICRU rectal point was less as compared to ICRU Bladder point doses

- Inter-fraction variation in doses and spatial location may be critical if the ICRU bladder and rectal point doses are high at first brachytherapy planning

2D radiograph – Reporting – ICRU 89

Level 1

- TRAK
- Point A
- Recto Vaginal Reference point dose
- Bladder Reference point dose

Level 2

- Estimated dose in the CTVHR (in the CTVIR if used for prescription)
- Pelvic wall point (optional)
- Lymphatic trapezoid (optional)
- OARs
- Vaginal point doses at level of sources (lateral at 5 mm)
- Lower- and mid-vagina doses (PIBS, PIBS +2 cm)

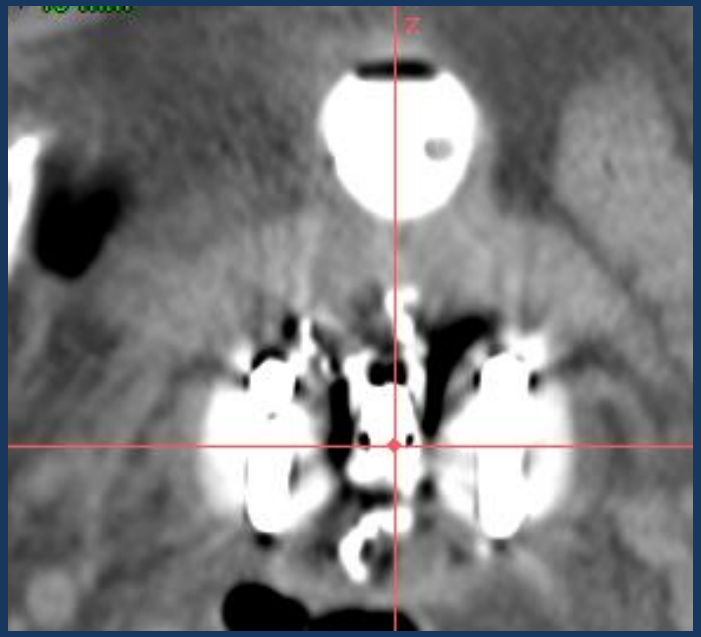
Reporting- Level 3 – Research oriented

- All that is reported in Level 1 and 2
- OAR volumes, points:
  - Additional bladder and rectum points
  - Sigmoid point
  - Anal-canal point (e.g., low-vagina point)
  - Vulva point (e.g., low-vagina point)
- Other points of interest
- OAR-dose reporting:
  - Length of treated vagina
- Isodose surface volumes:
  - 85 Gy EQD2 volume
  - 60 Gy EQDW volume

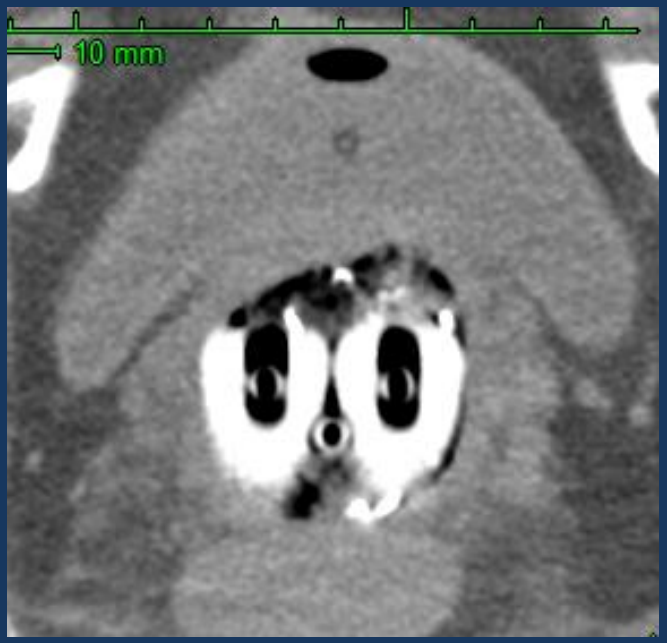
CT Imaging

- Metal (SS applicators), produces streak artifacts in CT images
- CT/MR compatible applicators made of plastic/titanium-zirconium alloy (non ferromagnetic materials) produce less artifacts

SS Applicator



CT/MR Applicator



Imaging protocol - CT

- 3-5 mm slice thickness
- HFS (if FFS, check for orientation)
- Optimize WL / WW (to minimize the artifacts in SS applicator to visualize OARs)
- Not necessarily full body contour as EXRT
- Bladder protocol - (empty/50cc – inst protocol)
- Markers required ? – institutional protocol
- Contrast

Summary

- Soft tissue structures cannot be visualized in radiographs , therefore, doses to surrogates are used to represent target and OARs.

- Standard loading pattern and Point A plan is a good start for complicated plans and hence recommended by ICRU 89

- Point A dose is NOT a surrogate for tumor dose. For small tumors, 2D planning delivers high dose to the tumor while exceeding the dose to the OARs, For large tumors, 2D Planning under-dose the tumor

- ICRU Rectal point over estimates and bladder point over estimates as compared to D2cc

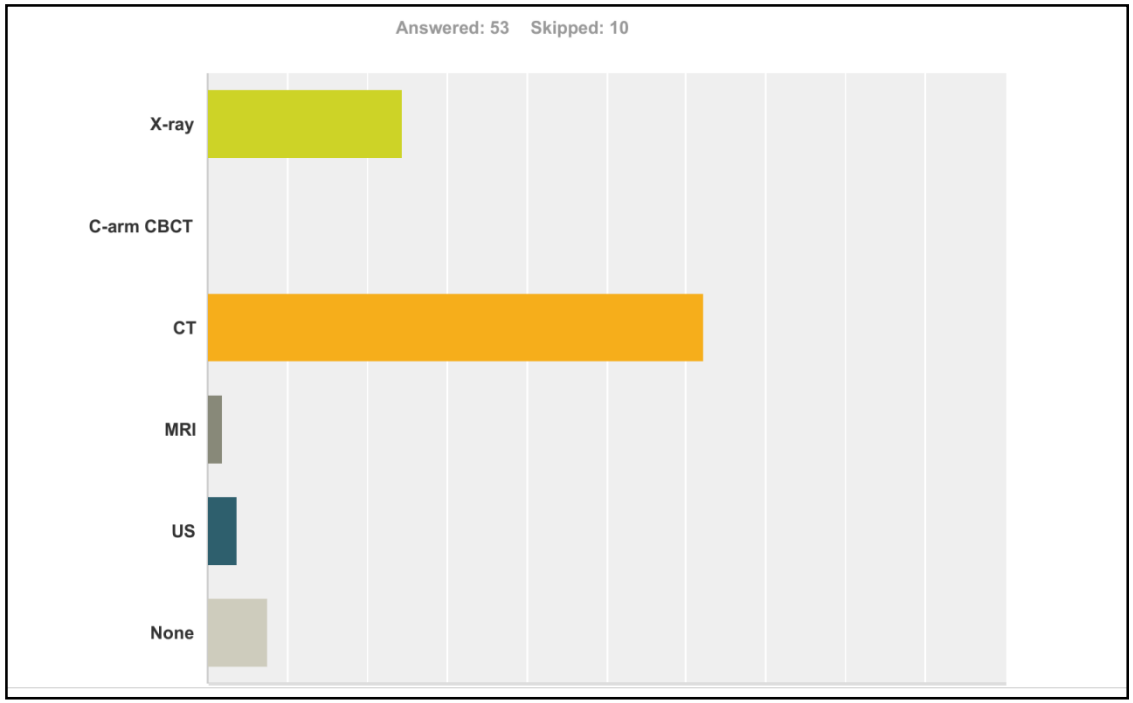
MR imaging – Physics point of view

- No electron density information
  - Image registration with CT can be done
  - With iridium sources, tissue density is of less influence on the dose calculation due to the predominant Compton effect
- Image distortion
- Image artifacts
- Poor applicator visualization

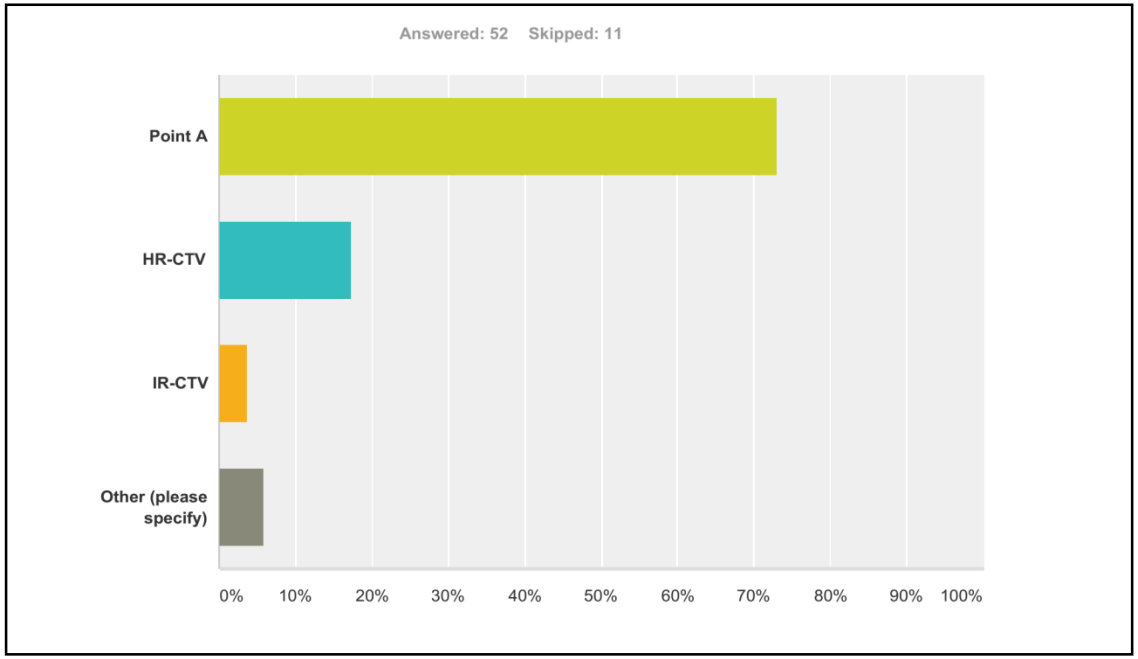
Tata Memorial Hospital

ROUTINE GYN BRACHYTHERAPY PRACTICE

- GYN BT Applications: 4 - 10 (Avg. 6)
- BT procedures under anesthesia per day : 4-8 (Avg: 6) includ,. IC+ IS
- Vault BT (Endometrium /Cervix post-op): 1 - 2
- Interstitial Templates : 1-2 Interstitial /wk
- Planning Details* : 3-4 orthogonal X-ray based ; 2-3 CT; 1 MR Based
- All patient undergo CT based planning mandatory for first fraction



CT Imaging Availability



Point A Based BT Planning

TRANSITION FROM 2D to 3D

INCORPORATION OF CT IMAGING FOR ROUTINE BT PLANNING

- CT Based Planning for external beam radiotherapy : Widely practiced
- CT Based Contouring in External Beam Radiotherapy : Vast Experience
- Incorporation of CT imaging for BT Planning: Logistics and practicality!
- CT Imaging for first application & Contouring of OAR's
- Subsequent fractions : CT / Orthogonal Radiography

TRANSITION FROM 2D to 3D

2 Major Tasks

1. INCORPORATION OF CT IMAGING FOR ROUTINE BT PLANNING

2. CT BASED TARGET CONCEPT

TRANSITION FROM 2D to 3D

2 Major Tasks

1. INCORPORATION OF CT IMAGING FOR ROUTINE BT PLANNING

2. CT BASED TARGET CONCEPT

TRANSITION FROM 2D to 3D

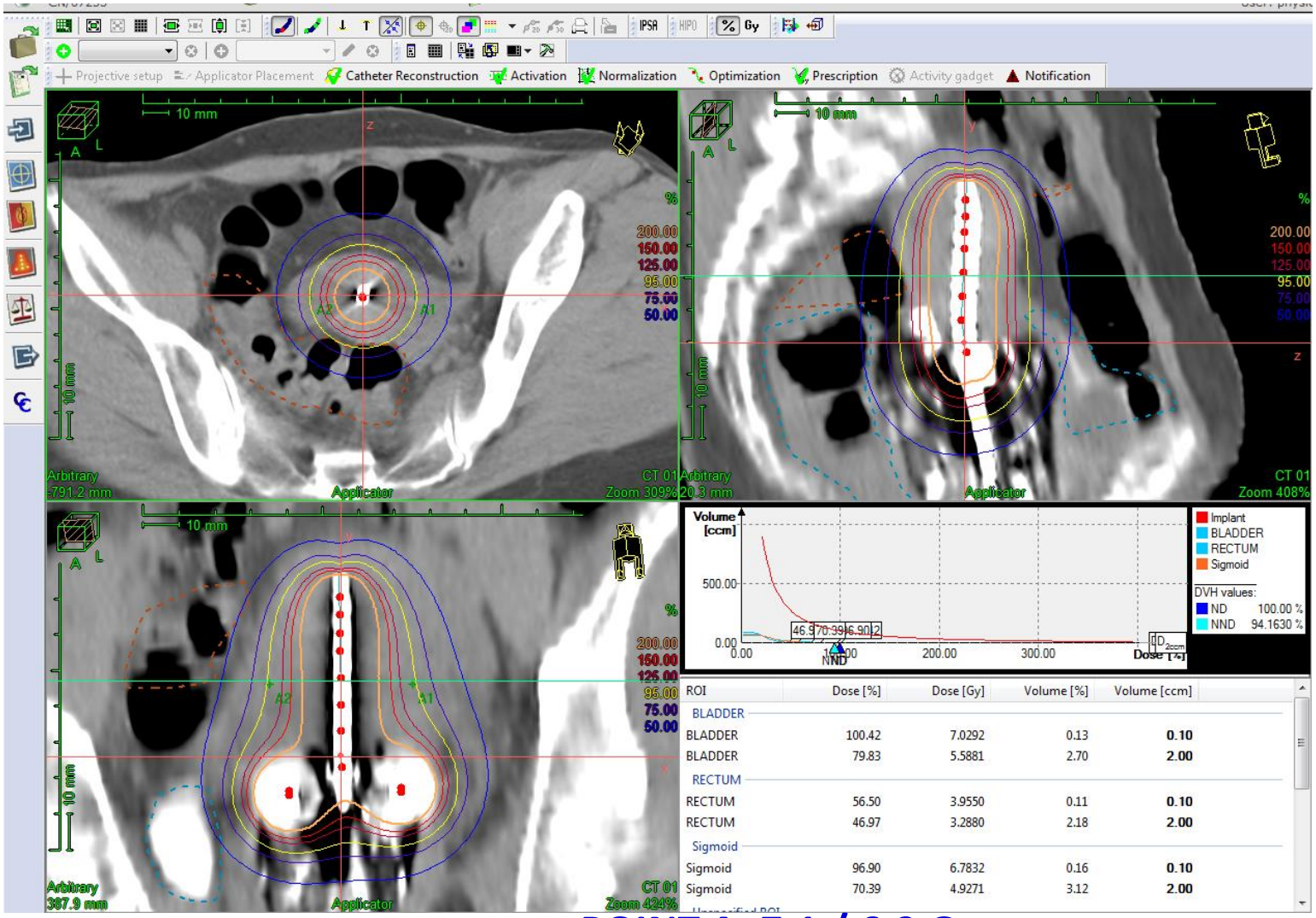
1. INCORPORATION OF CT IMAGING FOR ROUTINE BT PLANNING

- BT Application under Anesthesia
- Preferably using CT Compatible Applicator
- 1st fraction : CT Imaging Mandatory
- Subsequent fractions : Tailor the imaging (CT / Orthogonal Radiography

1st ICA

EXAMPLE NO. 1

PT ID: CN/07253



POINT A: 7.1 / 6.9 Gy

ICRUR: 3.7 Gy / 2 cm3 : 3.3 Gy

ICRUB: 2.6 Gy / 2 cm3 : 5.6 Gy

Sigmoid: 4. 0 Gy (2 cm3)

2nd ICA

EXAMPLE NO. 1

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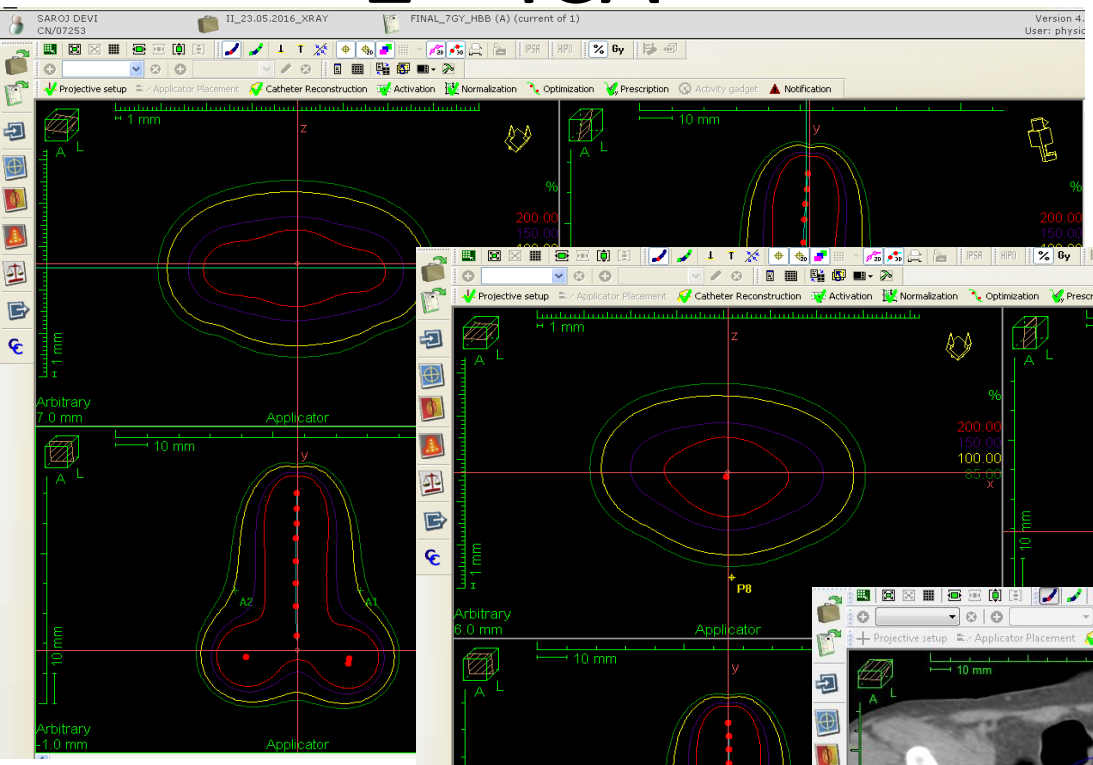
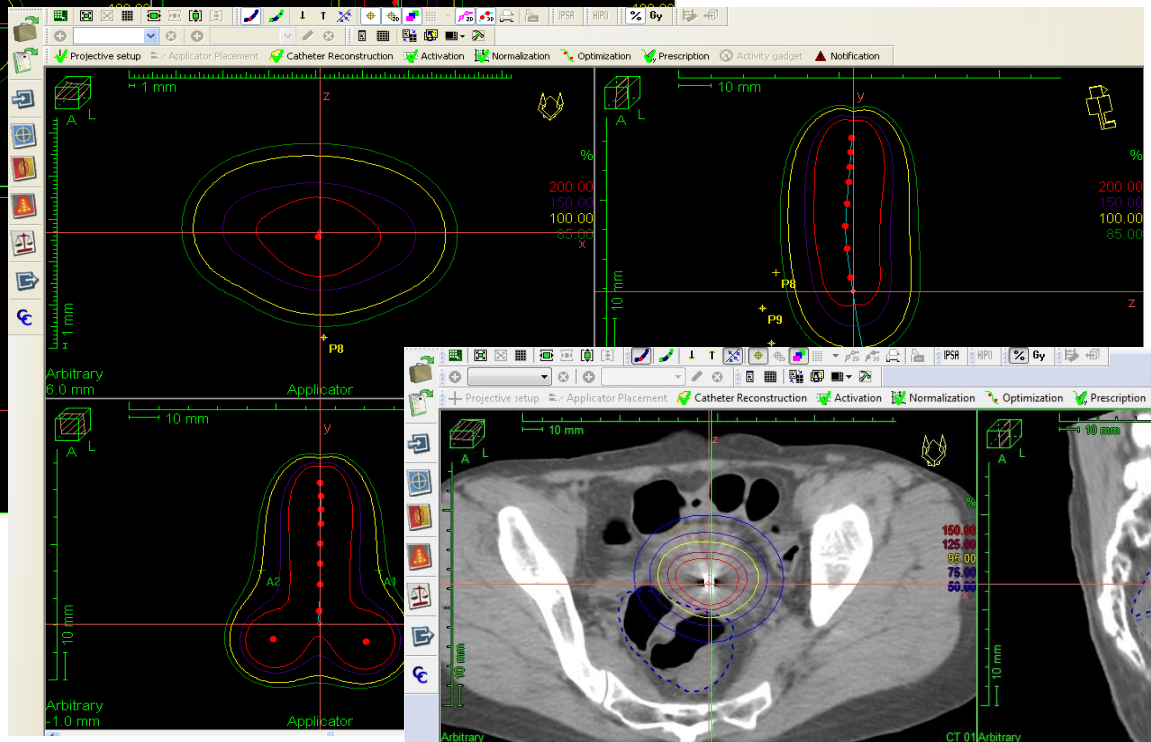
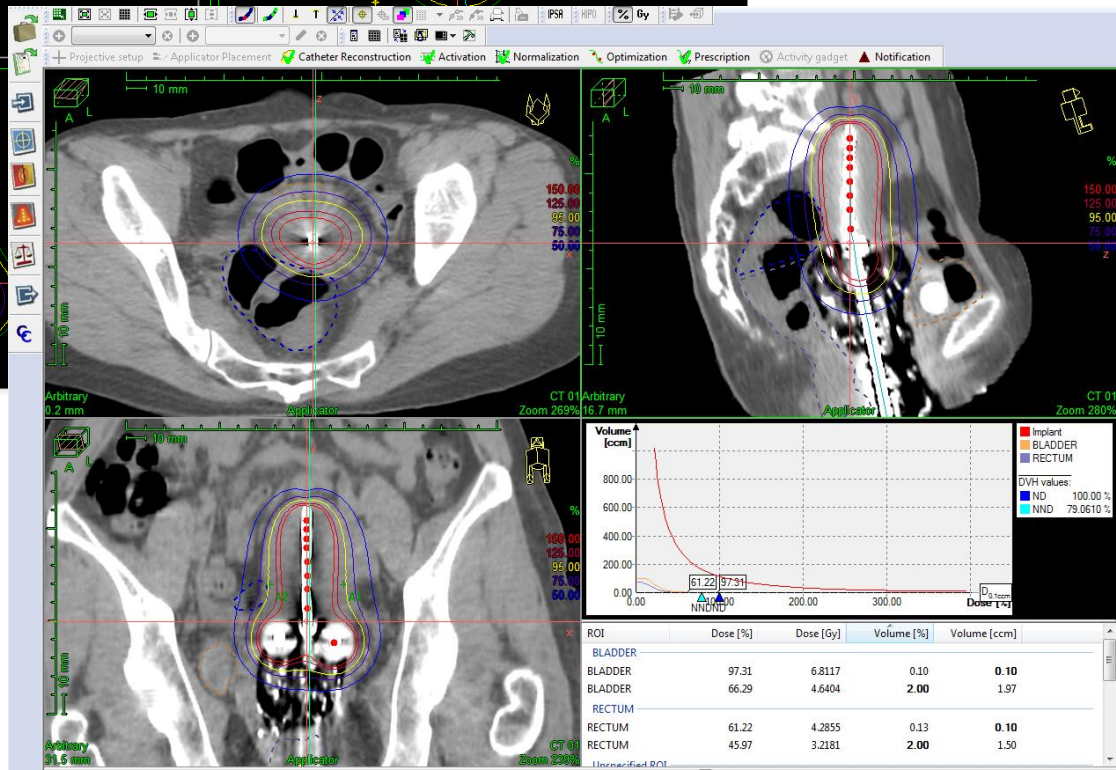


3rd ICA



4th ICA



PT ID: CN/07253

EXAMPLE NO. 1

Total doses in EQD2

EBRT (46 Gy / 23#) + 4 # BT (7 Gy to point A)

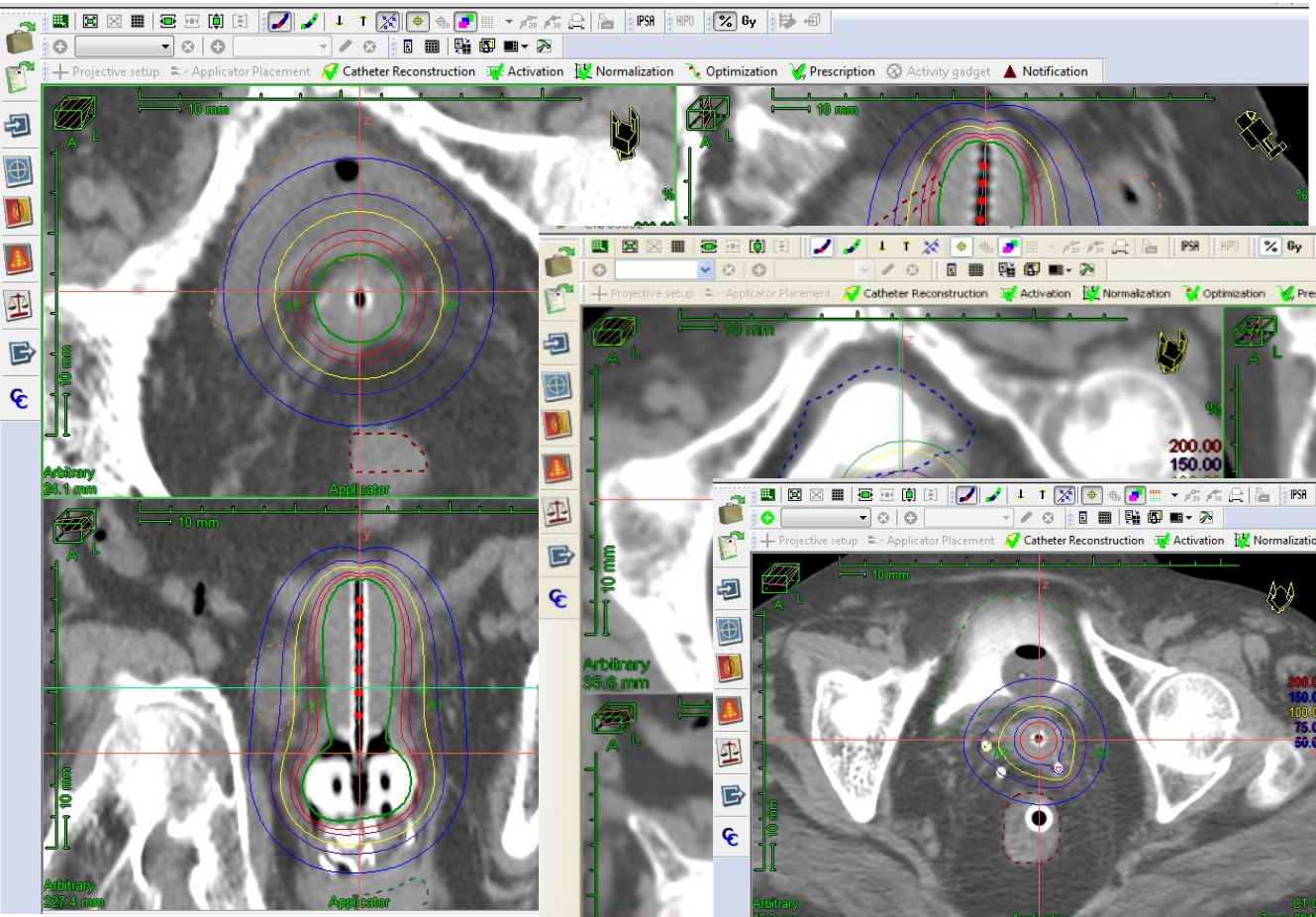
AT BT : RESIDUAL DISEASE AT CERVIX & MEDIAL THIRD PARA

BT#	PLANNING IMAGING	Point A (Left /Right)		ICRU Bladder	ICRU Rectum
I	CT	7.1	6.9	2.6 (2 cm3 : 5.6)	3.7 (2cm3 : 3.3)
II	X-RAY	6.8	7.2	2.1	2.7
III	X-RAY	7	7	1.8	5.2
IV	CT	7.1	6.9	2.7 (2 cm3 : 4.6)	5 (2cm3 : 3.1)
TOTAL	EQD2	85.6 Gy	85.8 Gy	66.6 Gy (2 cm3: 80 Gy)	65.4 Gy (2cm3: 64 Gy)

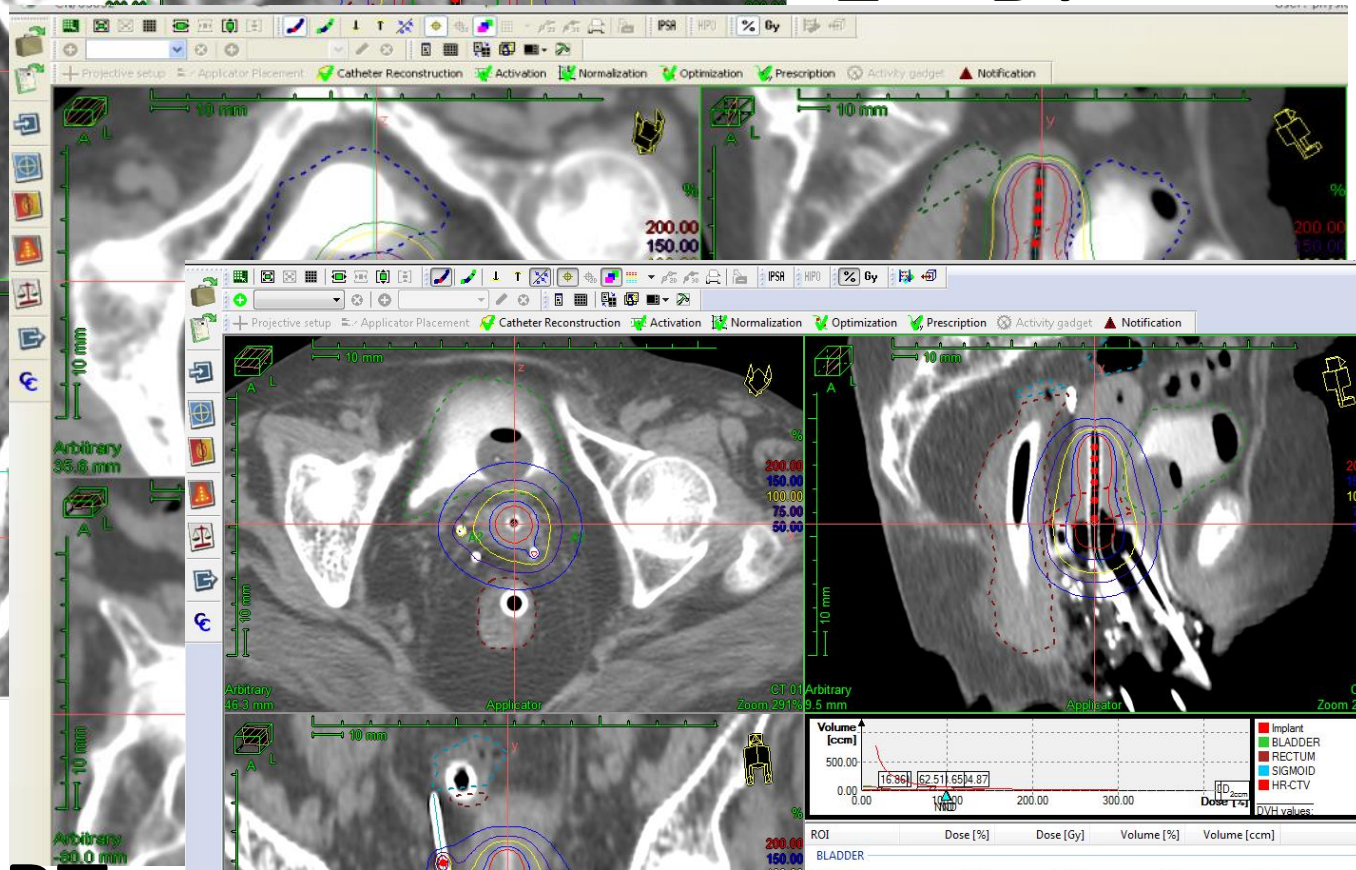
1st BT

EXAMPLE NO. 2

PT ID: CN/03032



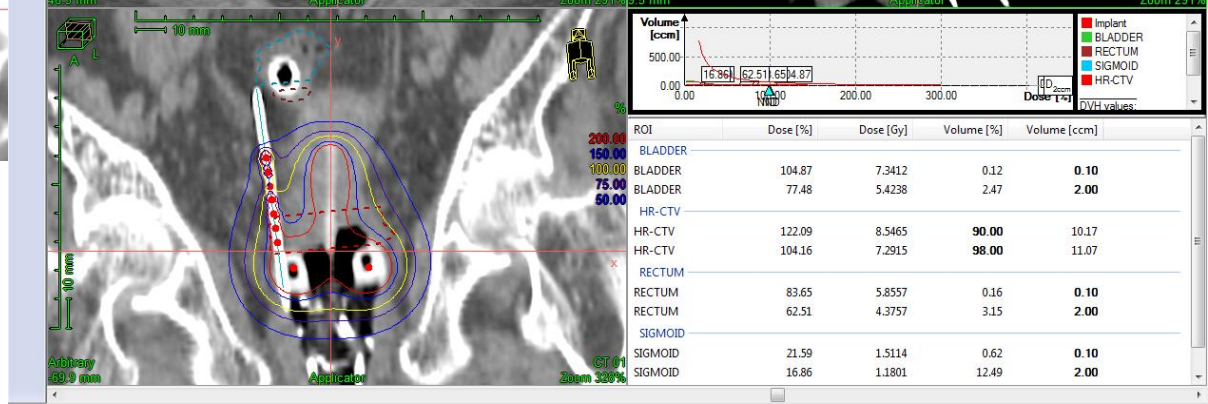
2nd BT



3rd & 4th BT

VIENNA APPLICATION

WITH NEEDLES IN RT PARA



PT ID: CN/03032

EXAMPLE NO. 2

Total doses in EQD2

EBRT (46 Gy/23#) + 4 # BT

AT BT : RESIDUAL DISEASE AT CERVIX (ATROPHIED) & RT PARA

CT PLANNING EVERY FRACTION

	Point A (Lt/Rt)		Bladder (2cc)	Rectum (2cc)	Sigmoid (2cc)
I	6.9	7.1	9.9	4.1	4.2
II	6.2	5.4	7	4.7	3
III*	5.9	6.9	5.4	4.4	1.2
IV*	5.9	6.9	5.4	4.4	1.2
EQD2	80 Gy	83 Gy	100.9 Gy	69.3 Gy	54.9 Gy

** VIENNA APPLICATION WITH NEEDLES IN RT PARA(1 Application 2# / 14 hours apart)*

TRANSITION FROM 2D to 3D

2 Major Tasks

1. INCORPORATION OF CT IMAGING FOR ROUTINE BT PLANNING

2. CT BASED TARGET CONCEPT

TRANSITION FROM 2D to 3D

2. CT BASED TARGET CONCEPT

- In Research Setting Only

- Only after understanding the target concepts on MR and atleast 20-25 patients initial MR Image Based BT Experience

Further Details & Disucssion during the Contouring Session in the afternoon

CLINICAL EXAMPLE

- Cervix carcinoma, FIGO stage II B

Clinical examination:

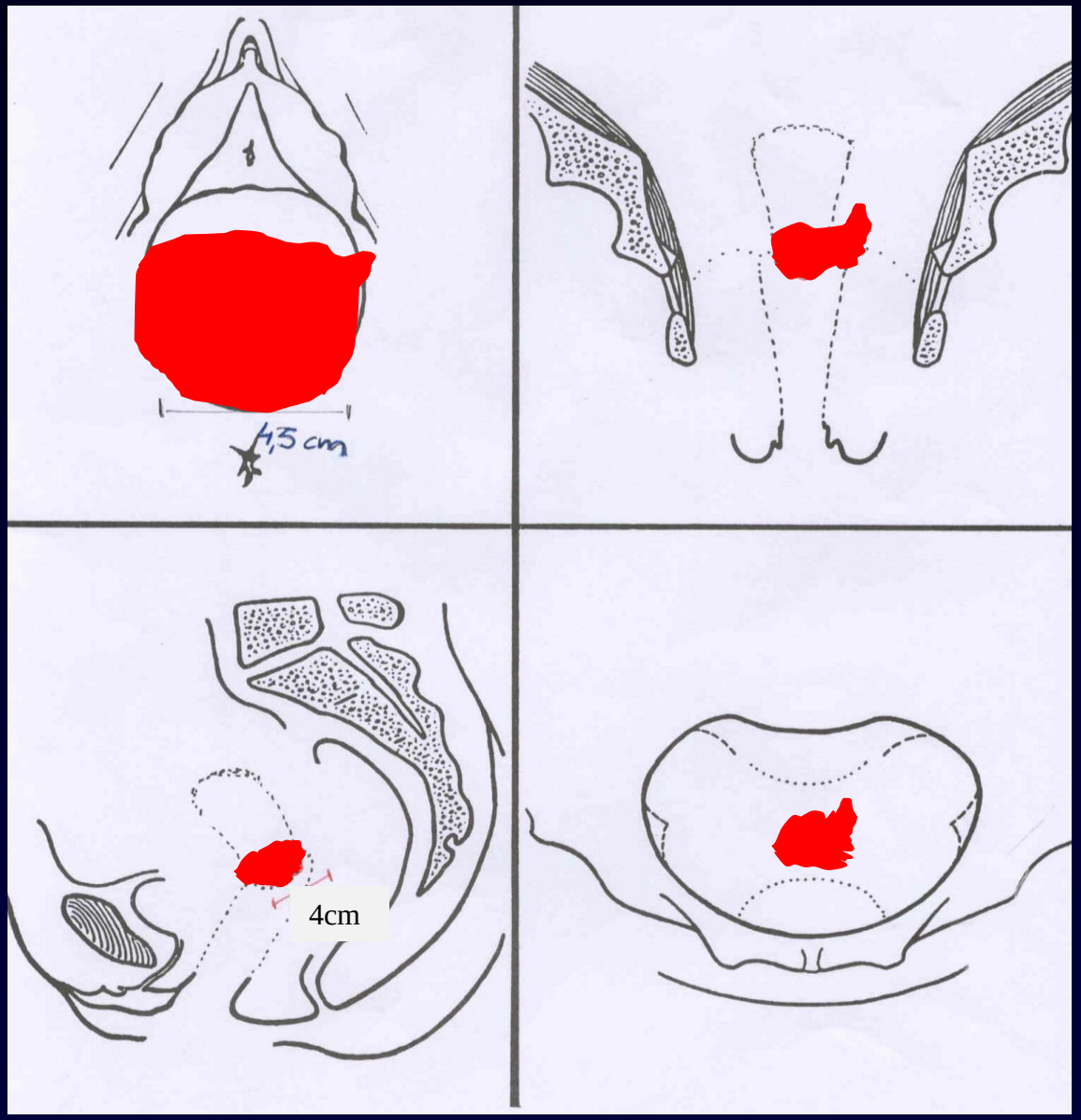
- TU lesion of 4.5 cm at the posterior lip and on the left lateral part of the cervix with extension to the left proximal parametrium

Initial MRI:

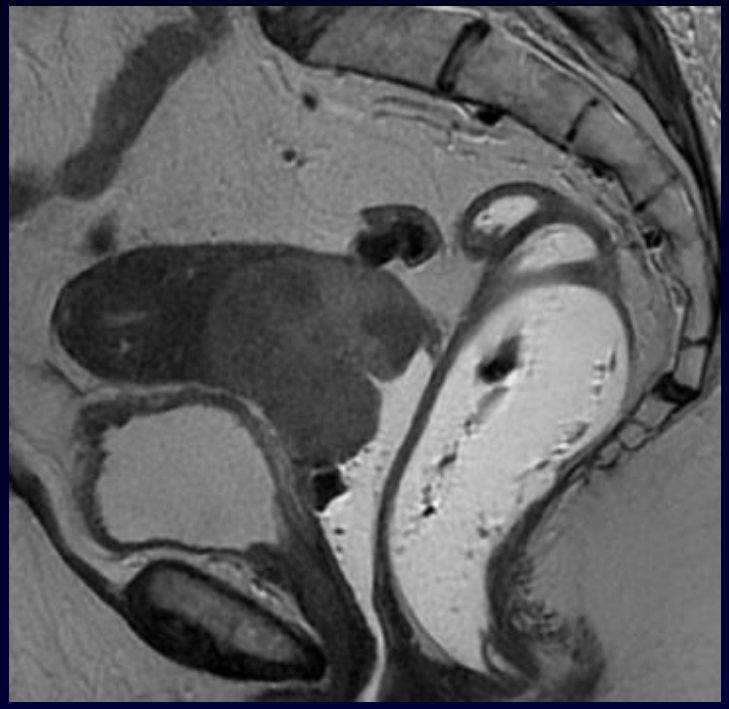
- lesion of 41 x 40 x 61 mm at the posterior part of the cervix, no LN metastases

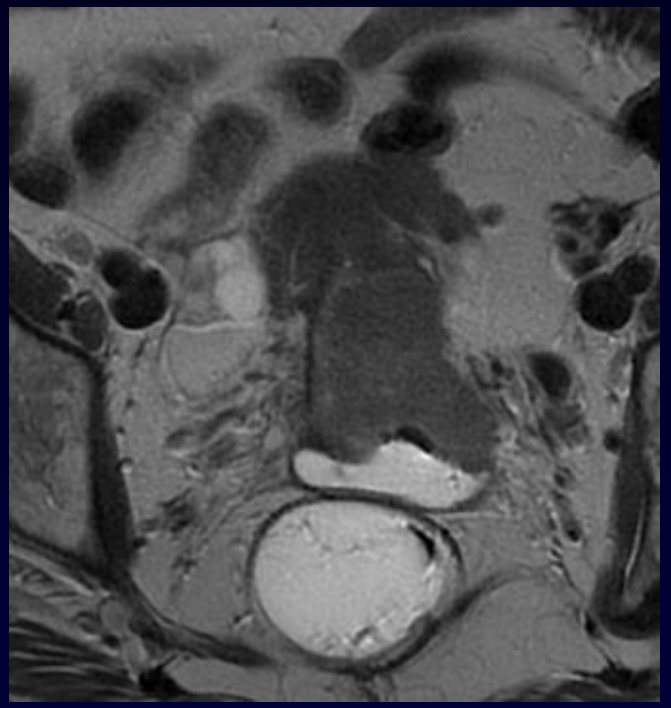
CLINICAL EXAMPLE

Initial tumor



CLINICAL EXAMPLE





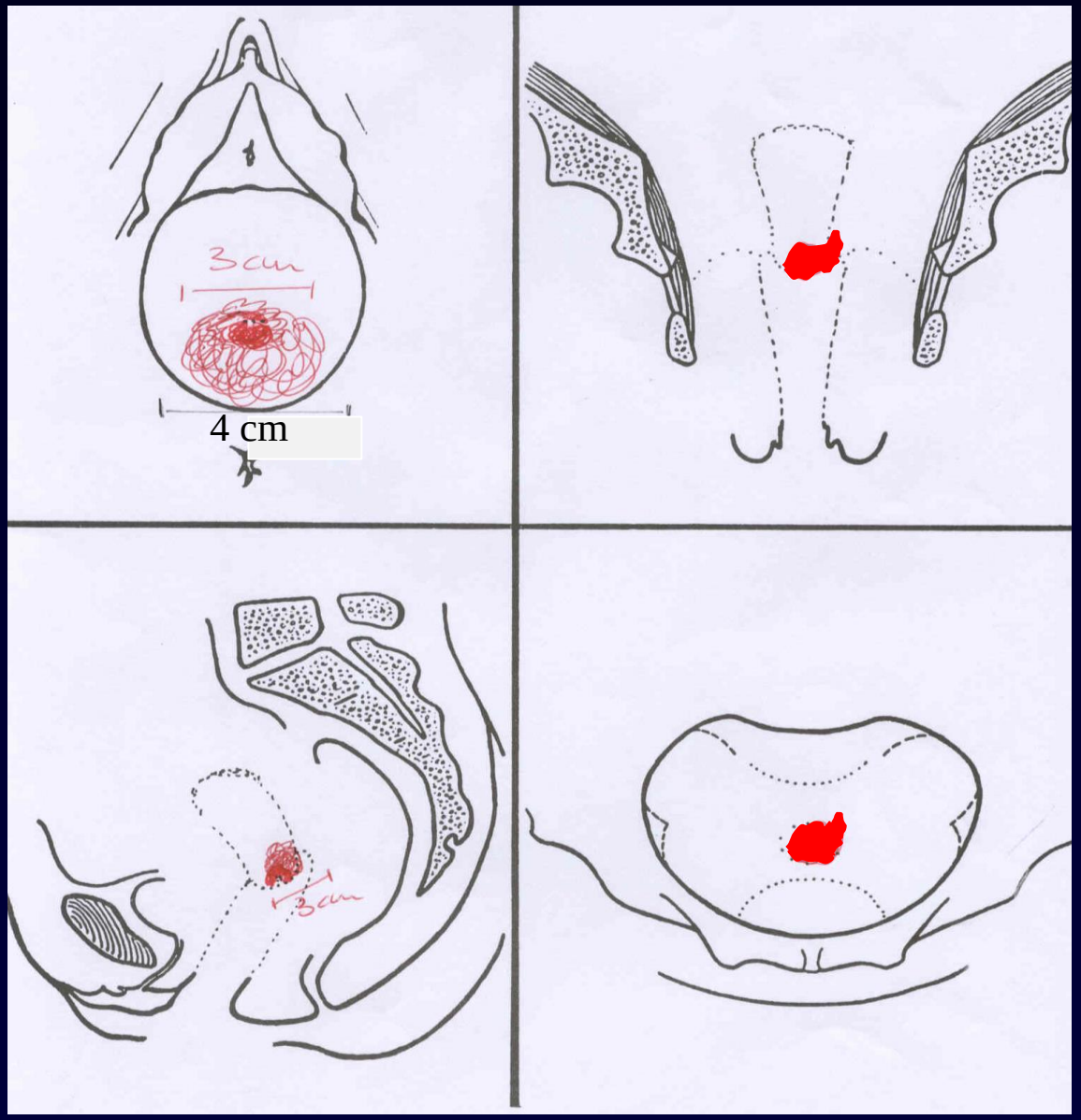
CLINICAL EXAMPLE

TREATMENT:

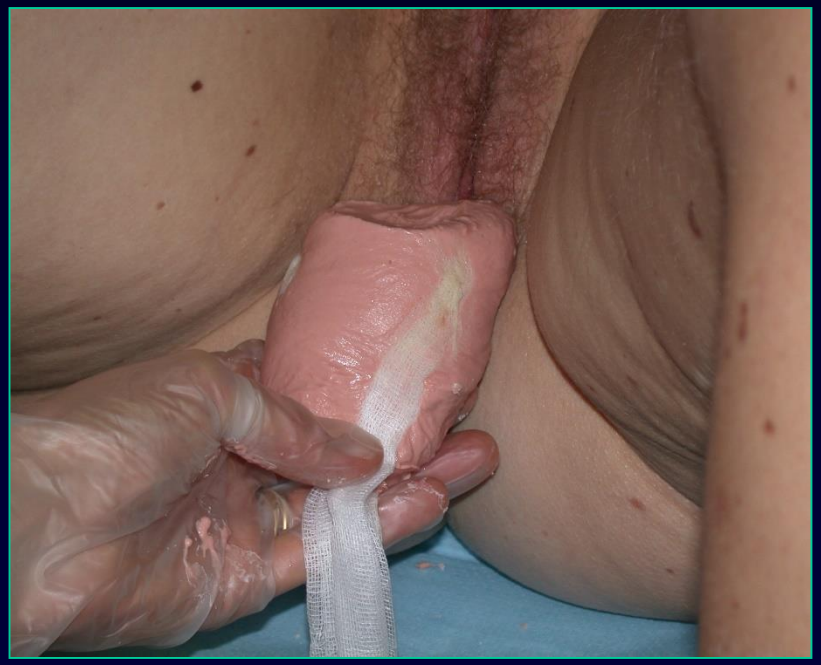
- EBT of the pelvis by 4 fields
- Total dose: 45 Gy
- Energy: 20 MV
- CISPLATIN 40 mg/m² weekly
- Intracavitary BT

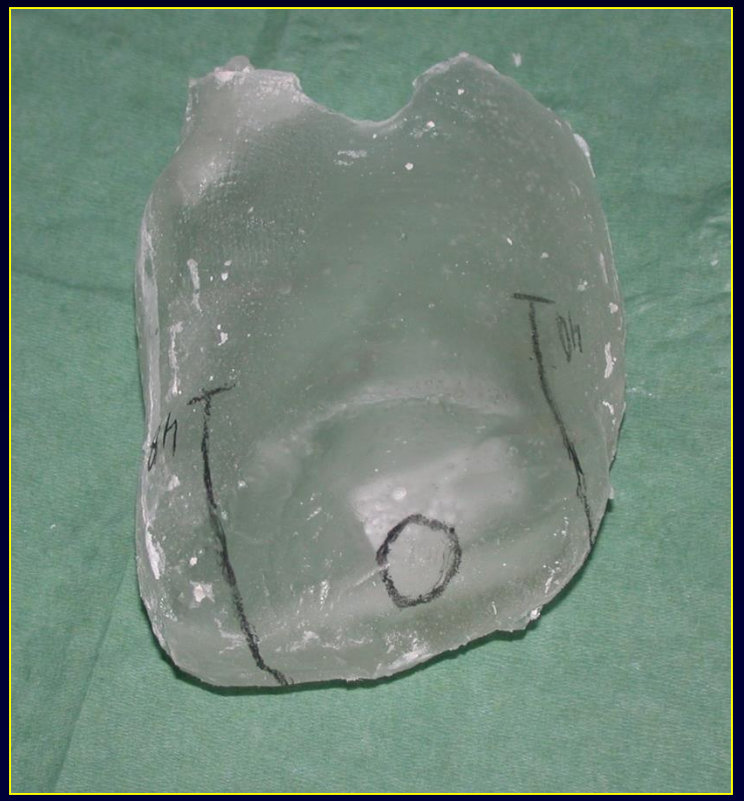
CLINICAL EXAMPLE

Residual TU volume
before BT
after ERT

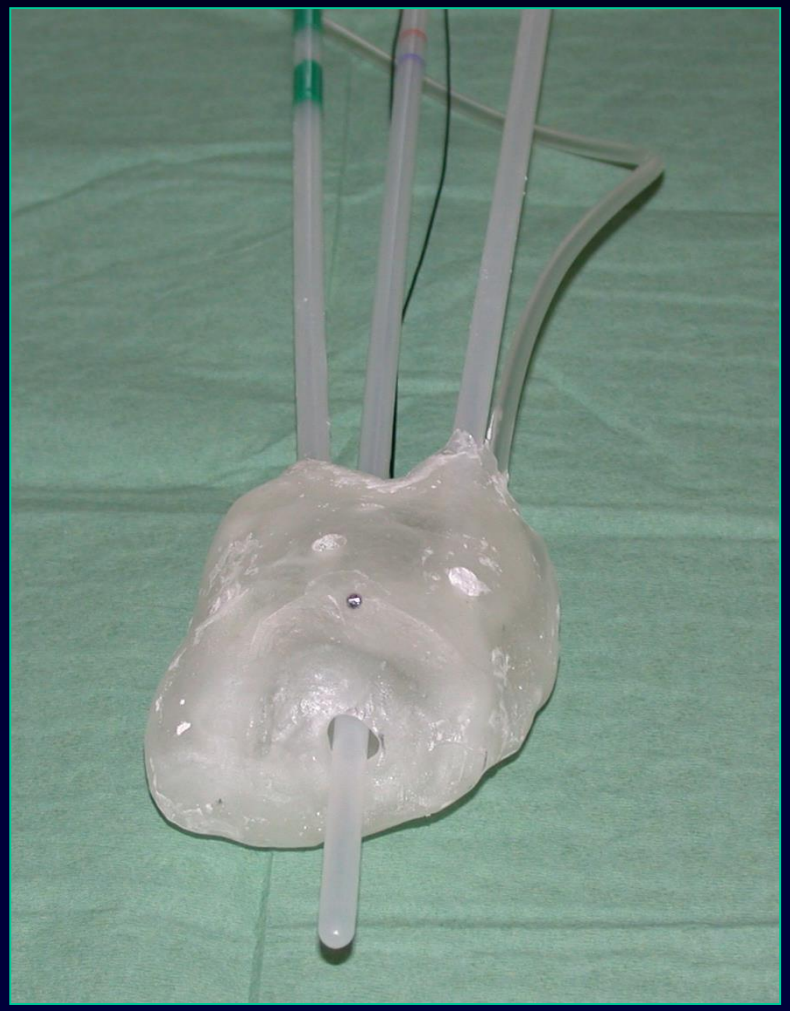


VAGINAL IMPRESSION

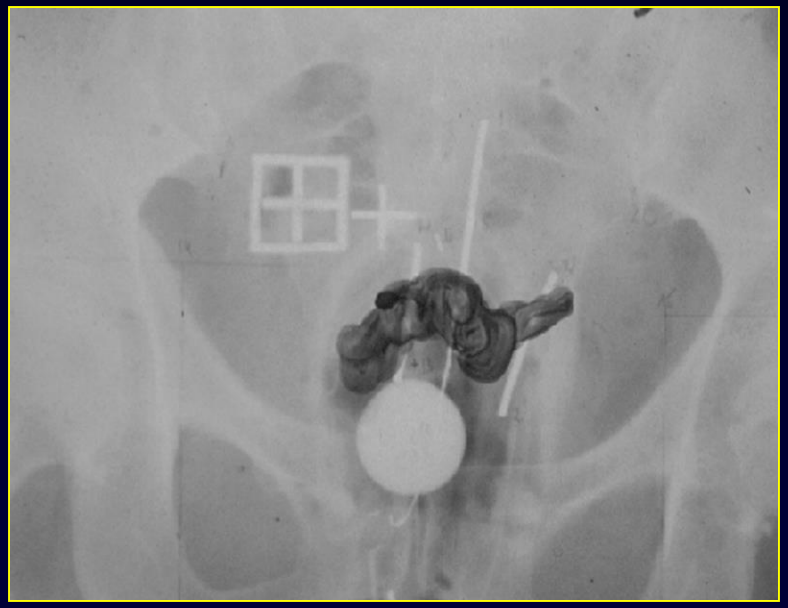


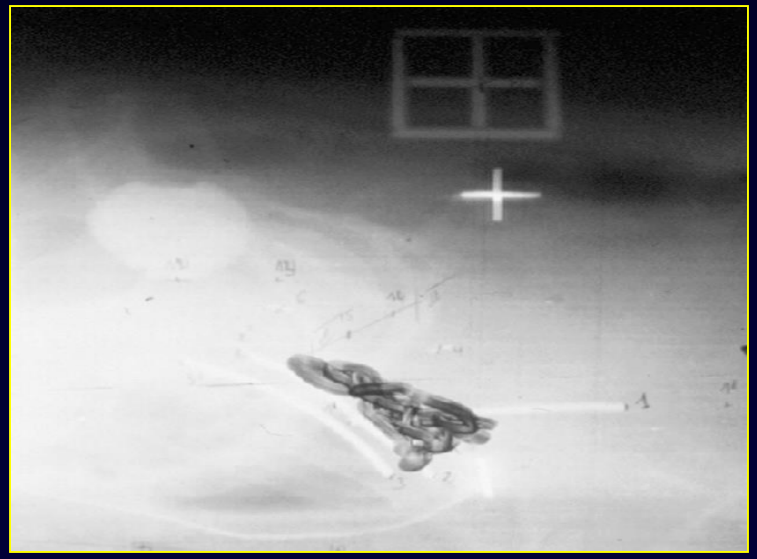


Mould applicator



Post application X Rays

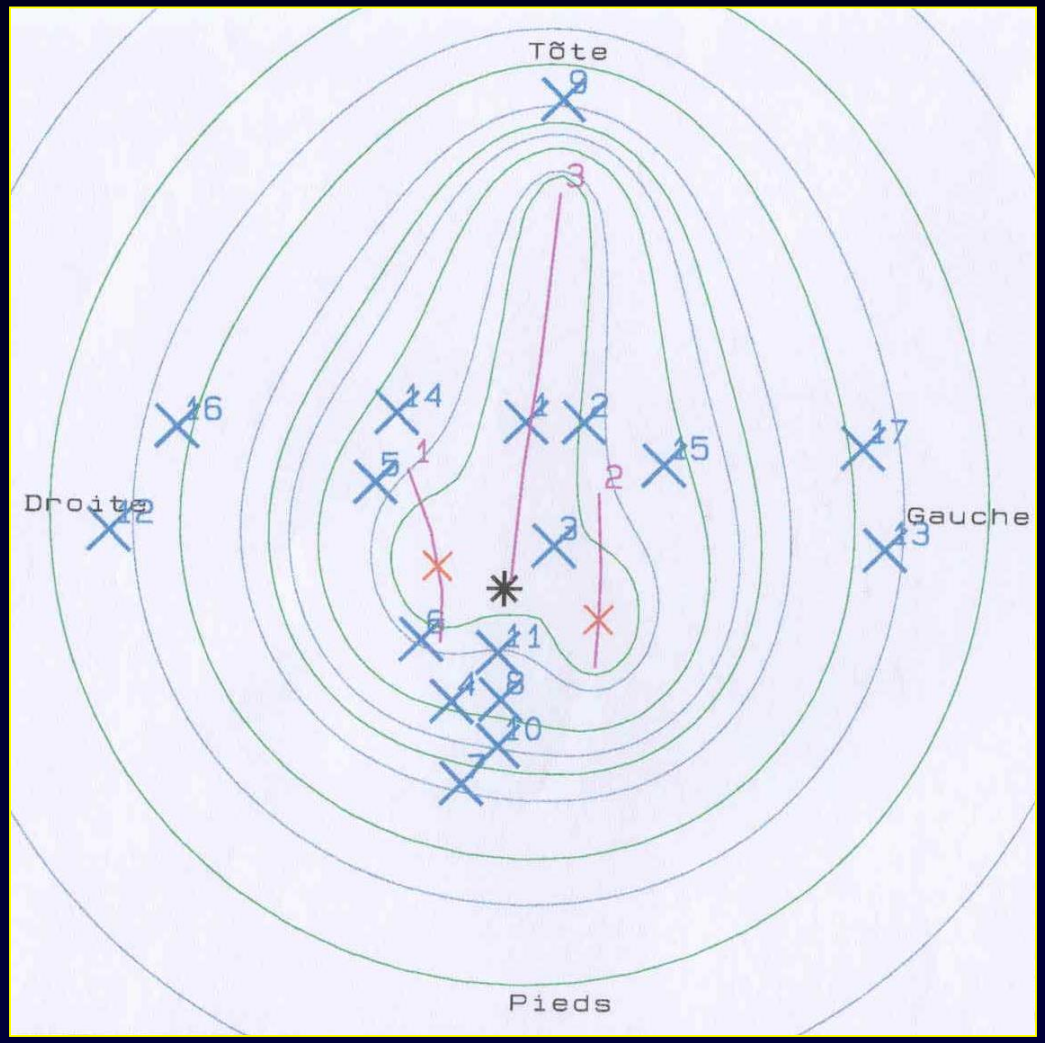




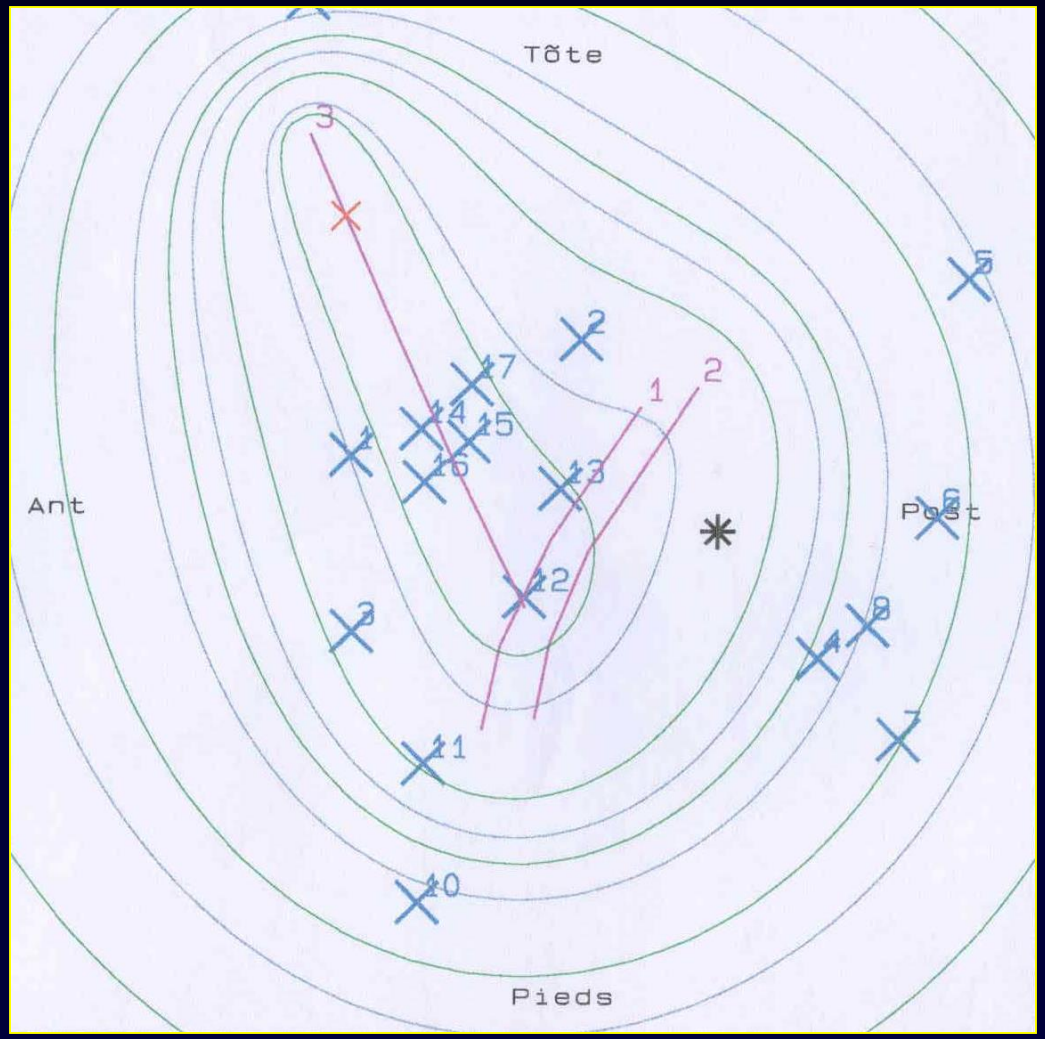
Dosimetry

- To give 15 Gy in a volume encompassing the initial CTV
- Compatible with the dose to critical organs

Dosimetry

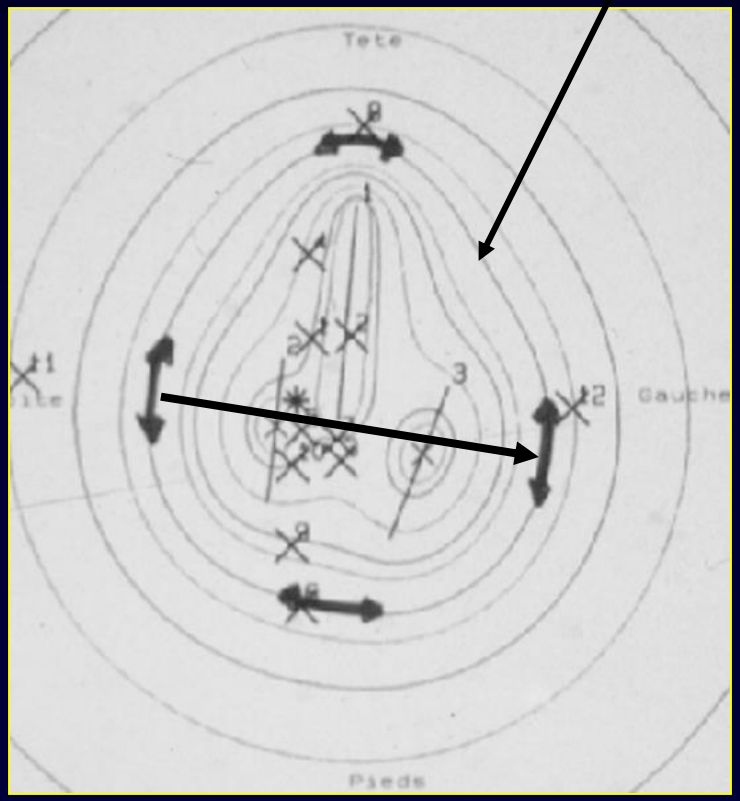


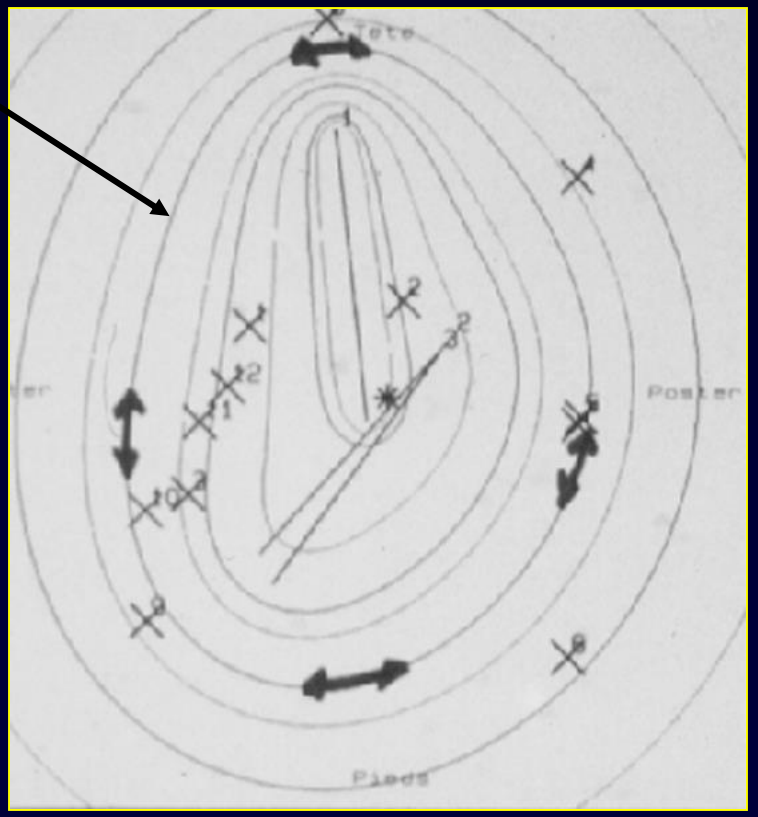
Dosimetry



15 Gy isodose

8Gy/day





CLINICAL EXAMPLE

DOSIGRAY le 12 2

Sources No.	Nat.	Longueur cm	Temps j	h	m	Activitõ uGyhm/cm
1	cs	3.9	2	0	0	27.07
2	cs	4.0	2	0	0	28.07
3	cs	5.6	2	0	0	28.46

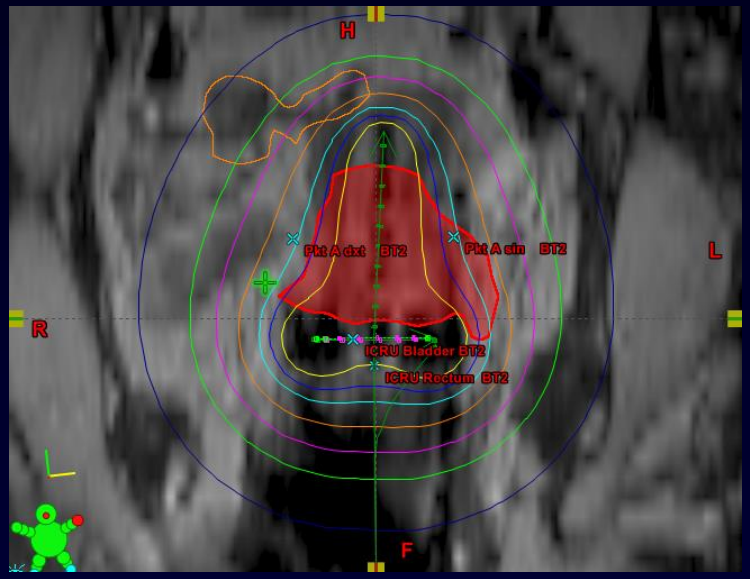
REPERES

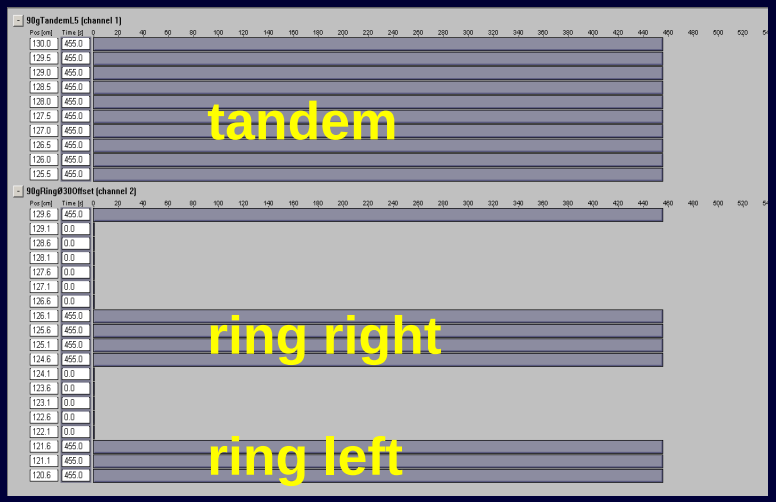
No.	Nom	Dose Gy
1	GRAIN ANT	63.272
2	GRAIN POST	35.026
3	GRAIN M ANT	40.783
4	GRAIN M POST	22.767
5	RECTUM	13.251
6	RECTUM	13.282
7	RECT MAX	19.107
8	SIGMOIDE	9.944
9	PT ALG	16.589
10	VESSIE	17.563
11	PPD	6.225
12	PPG	5.032

Dose to point A : 30 Gy

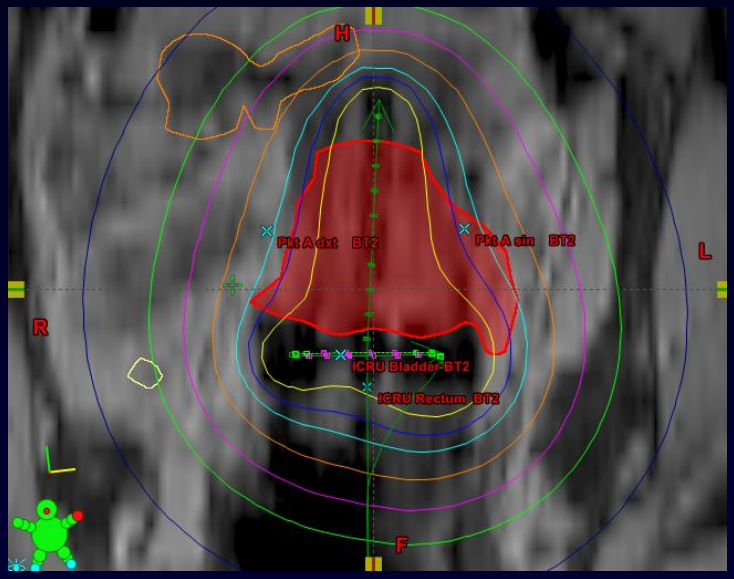
60 Gy volume : 180 cm3

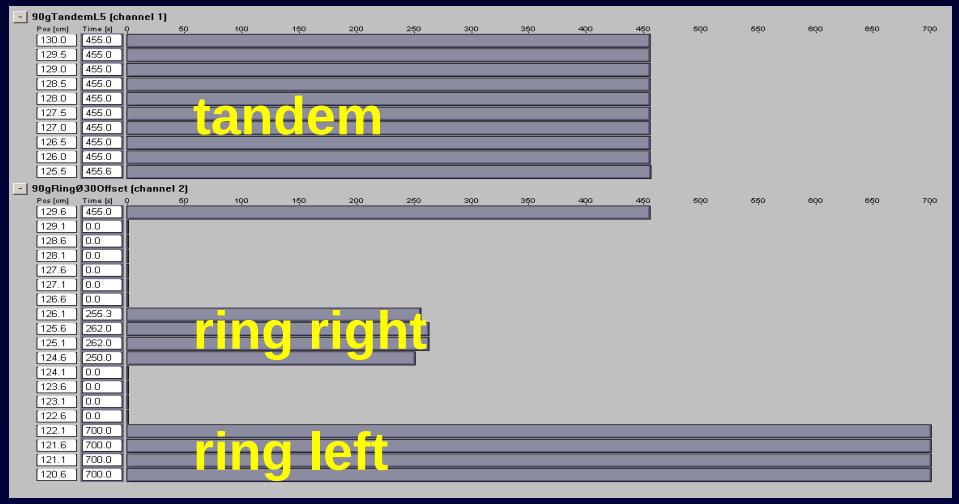
Standard





Optimised





ICRU89-GEC-ESTRO recommendations on dose volume reporting

Richard Pötter

Recommendations, DVH parameters

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]

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Journal of the

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Prescribing, Recording, an
Brachytherapy for Cancer

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ESTRO

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PRESCRIBING, RECORDING, AND REPORTING BRACHYTHERAPY FOR CANCER OF THE CERVIX

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ICRU/GEC ESTRO recommendations for gyneacological brachytherapy

- 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

Committee:
Chairmen: Richard Pötter, Christian Kirisits
B. Erickson, C. Haie-Meder, J. Lindegaard, E. van Limbergen, J. Rownd, K. Tanderup, B. Thomadsen

Learning Objectives (I)

- 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;

Learning Objectives (II)

- 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.

Three levels of reporting

- **Level 1 - *Minimum standard for reporting***
- **Level 2 - *Advanced standard for reporting***
- **Level 3 - *Research oriented reporting***

Level 1 - *Minimum standard for reporting*

Source and dose calculation:

- **Radionuclide and source model**
- **Source strength**
- **Dose calculation algorithm**

Level 1 – *minimum standard for reporting*

- **Comprehensive clinical gynecologic examination (diagnosis, BT)**
- **Volumetric imaging (MRI, CT, US, PET CT) at time of diagnosis and BT (as available)**
- **FIGO/TNM stage**
- **Baseline morbidity and QoL assessment**
- **Schematic 3D documentation on a clinical diagram indicating dimensions (width, thickness) and volumes for:**
  - **GTV_{init} (GTV at diagnosis)**
  - **GTV_{res} (GTV at brachytherapy)**
  - **CTV_{HR} (GTV_{res} (plus residual pathologic tissue plus whole cervix)**
  - **(CTV_{IR}: GTV_{init} and CTV_{HR} plus safefy margin if used for prescription)**

At Diagnosis [X]

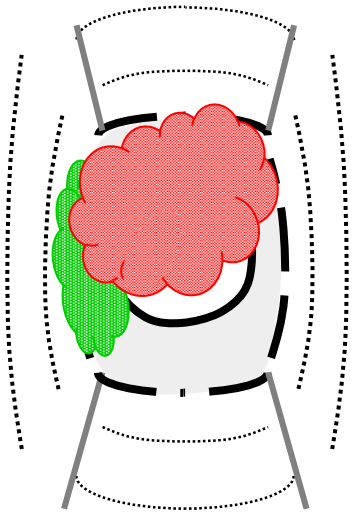
At Brachytherapy [ ]

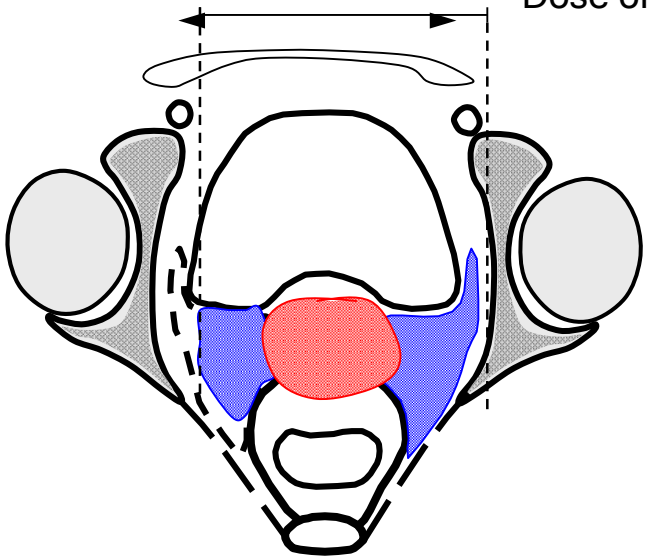
Dose of EBRT ___ Gy

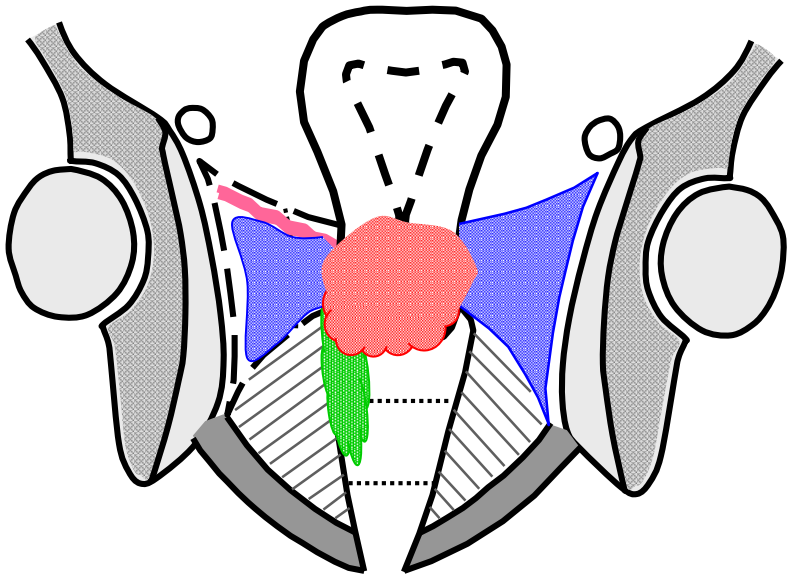
IIIB

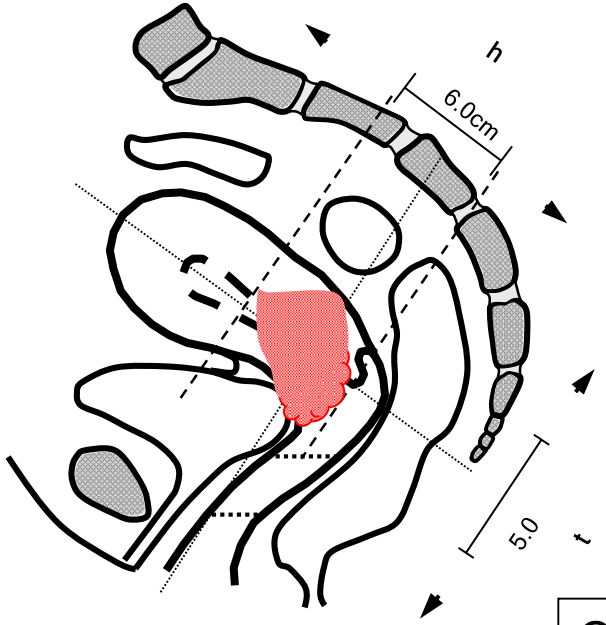
w = 9.0 cm
h = 6.0 cm
t = 5.0 cm

Vagina: 5 cm









dd/mm/yy
__/__/__

Signature

Note: vagina and parametria not included in h

Case IV

At Diagnosis ☐

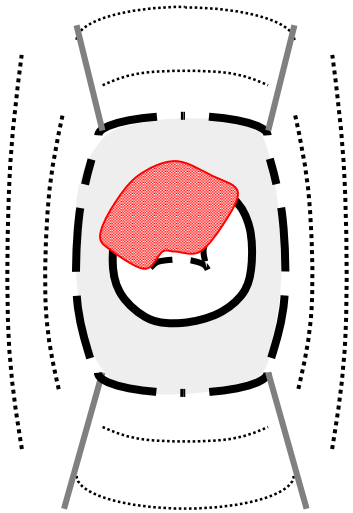
At Brachytherapy ☒

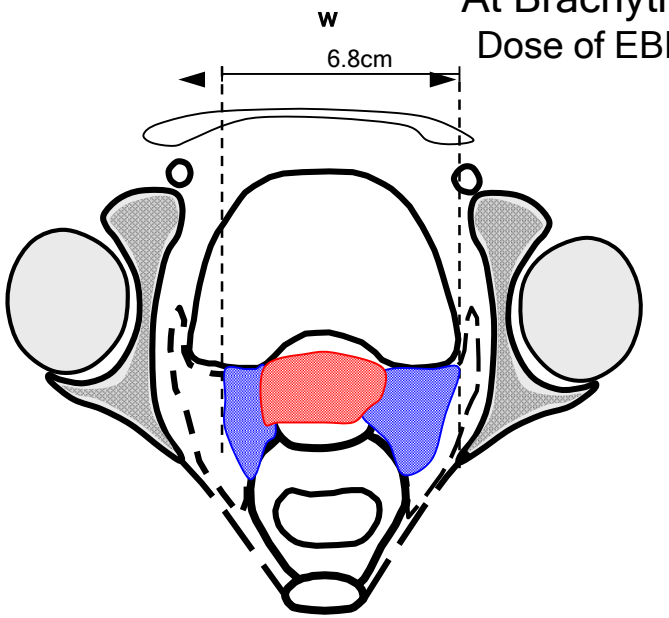
Dose of EBRT 50.4 Gy

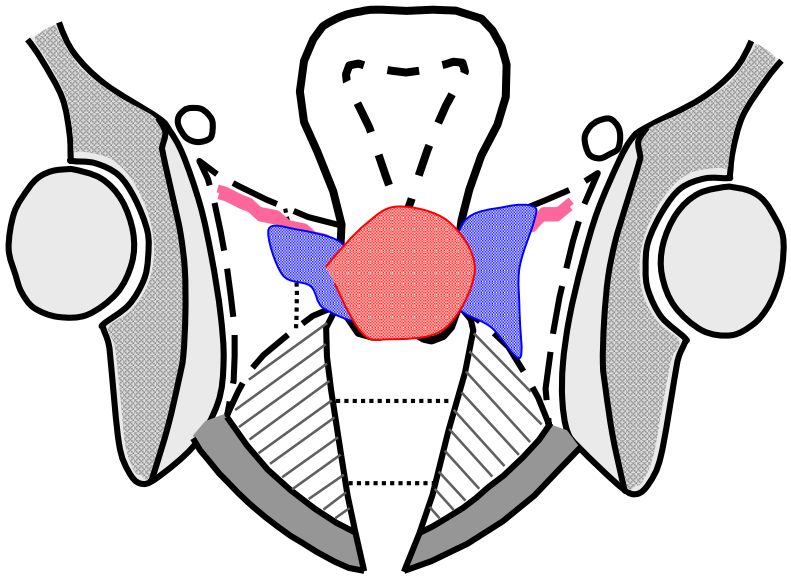
IIIB

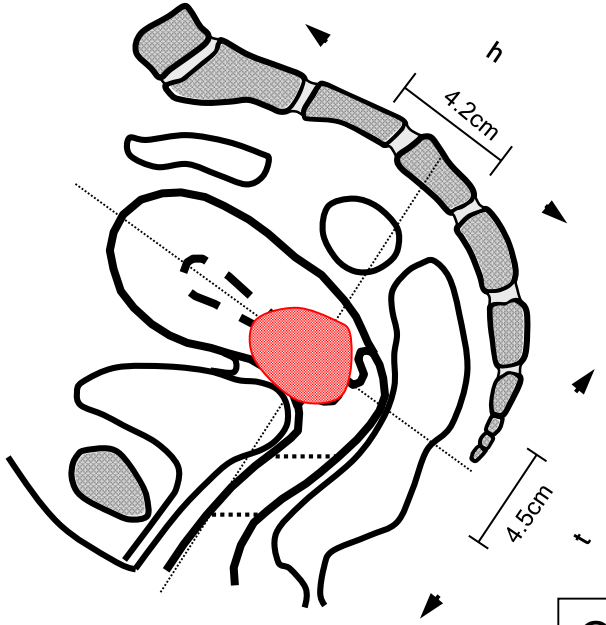
w = 6.8 cm
h = 4.2 cm
t = 4.5 cm

Vagina: 0 cm









dd/mm/yy
/ /

Signature

Note: parametria **not** included in **h**.

Case IV

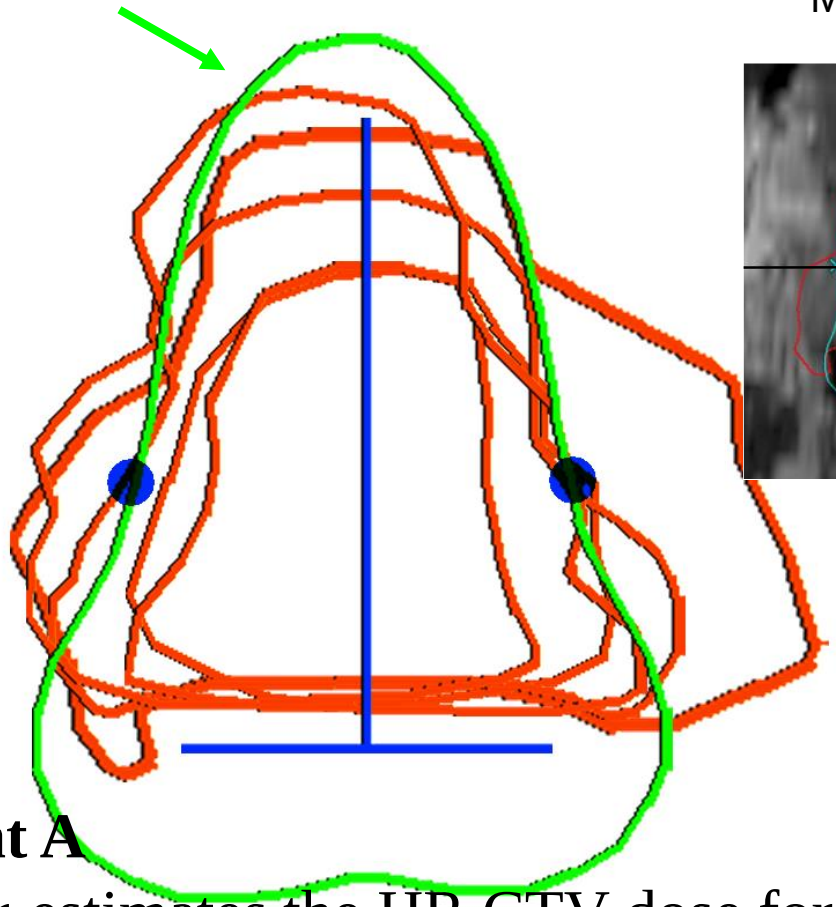
Level 1 – *minimum standard for reporting*

Dose reporting:

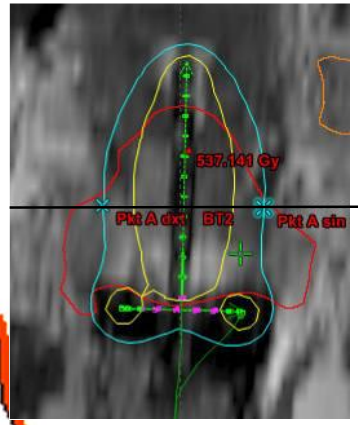
- **TRAK**
- **Point A dose**
- **Recto-vaginal reference point dose (prior: ICRU rectum point)**
- **Bladder reference point for radiographs (if 2D imaging)**
- **$D_{0.1cm^3}$, D_{2cm^3} for bladder, rectum (if 3D imaging)**
- **Overall treatment time**

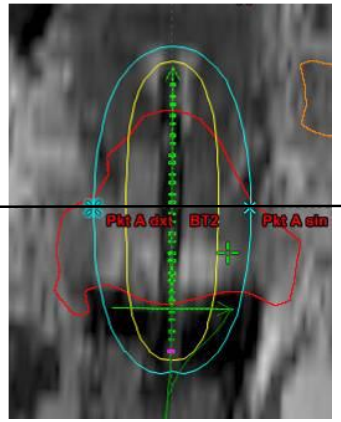
Point-A based brachytherapy and HR CTV volume and dose

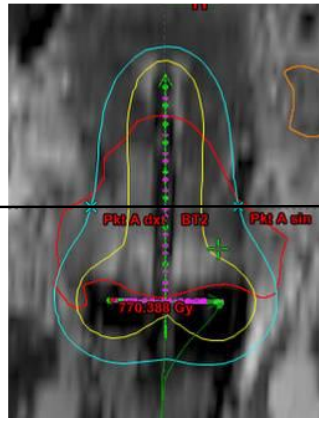
Point A isodose

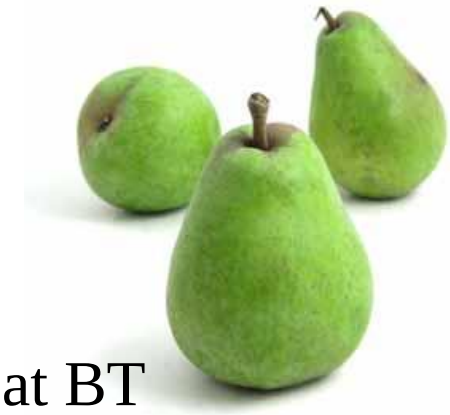


Milwaukee Toronto Vienna









Point A

Over-estimates the HR CTV dose for large tumors at BT

Under-estimates the HR CTV dose for small tumors at BT

Dose Delivery Pattern ICRU 89

Absorbed dose rate/dose per fraction

Number of fractions

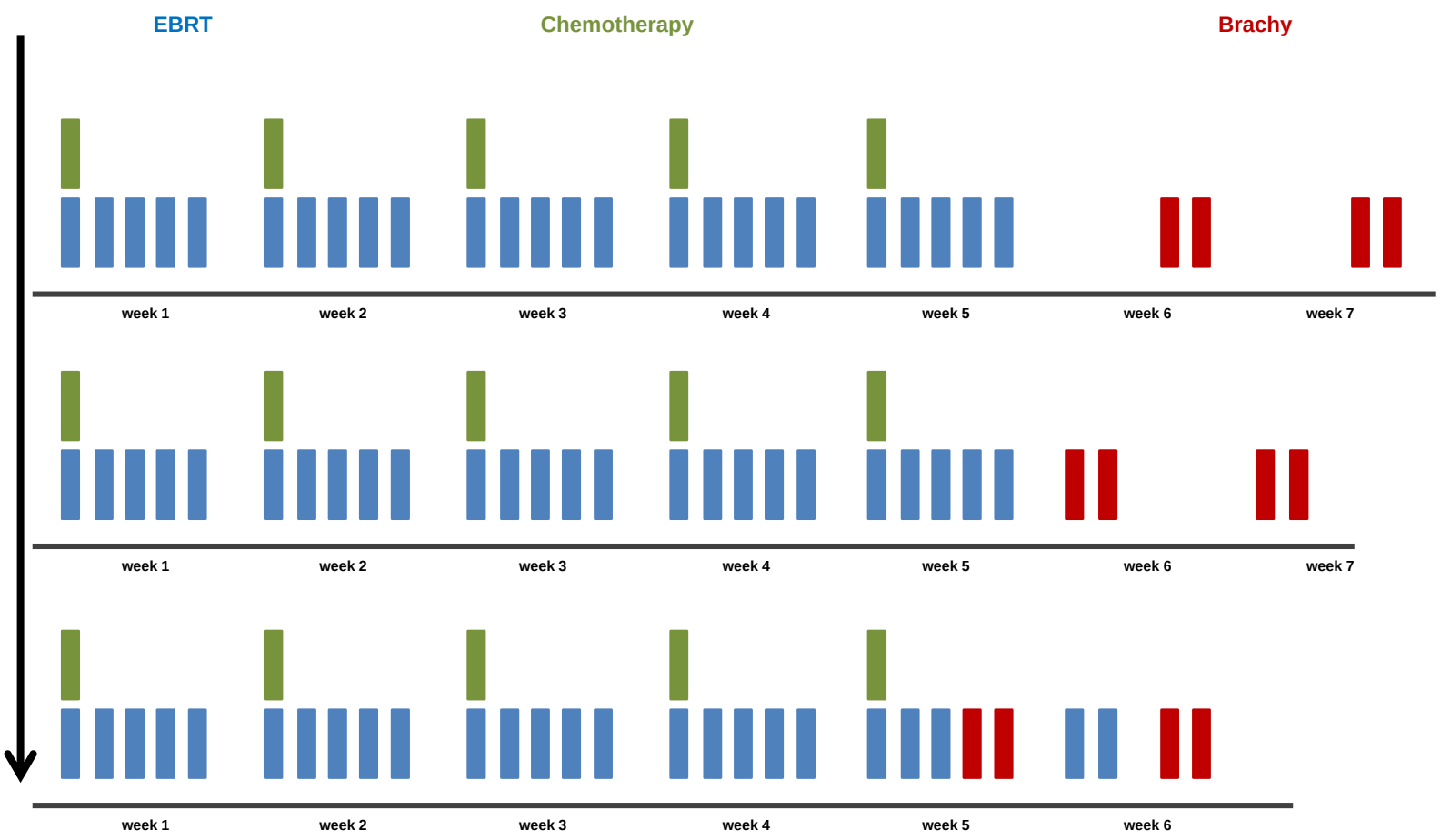
Time between fractions

(Pulse number, size, time, if PDR)

Overall treatment time

Total EQD2

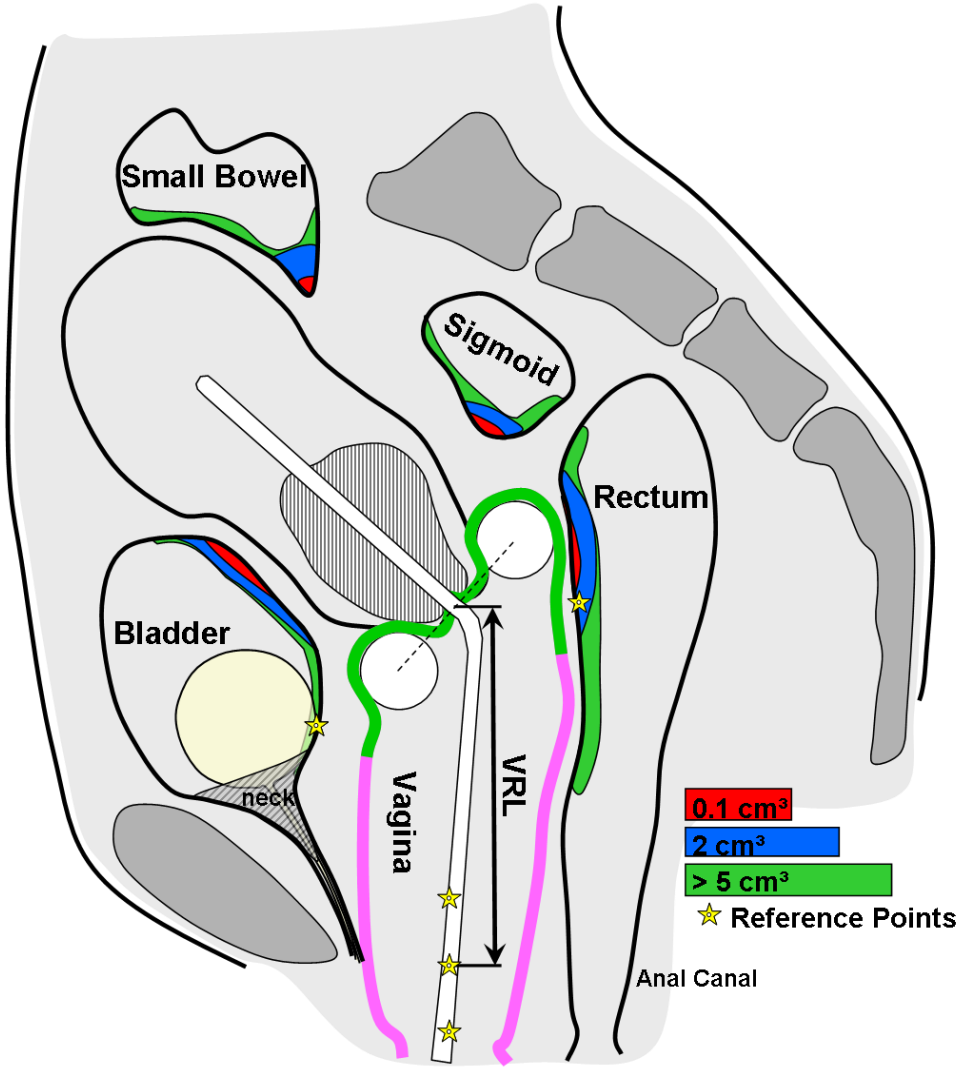
Overall Treatment Time (BT, EBRT, total)



When comparing total dose to point A and total dose to 90% of the HR CTV (D90)

A. Dose in point A is always lower than D90
B. Dose in point A is always higher than D90
C. Dose in point A is always similar/equal to D90
D. In small tumors point A dose is smaller than D90
E. In large tumors D90 is larger than point A dose

DVH Parameters and Reference Points,



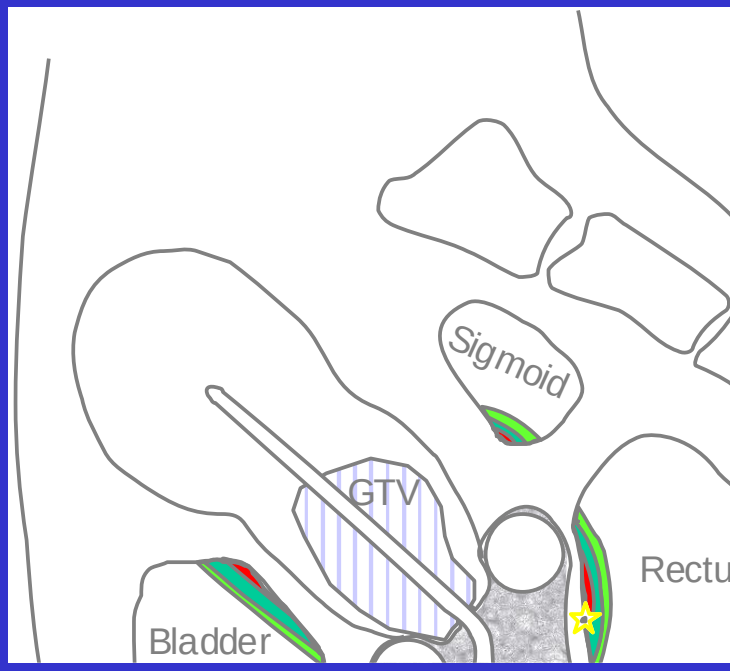
ICRU/GEC ESTRO
report 89, 2016

Fig. 6.4, Fig. 8.8

3D-based Dose Volume Parameters for OAR

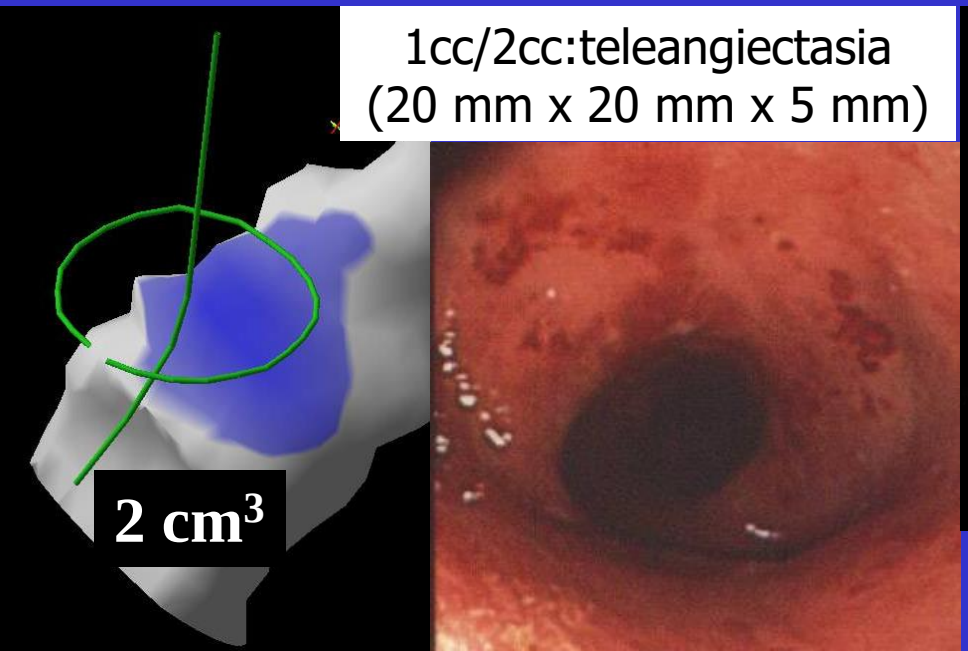
CLASSICAL MAX DOSE in 2D:
in 3D a voxel is no clinical relevant endpoint

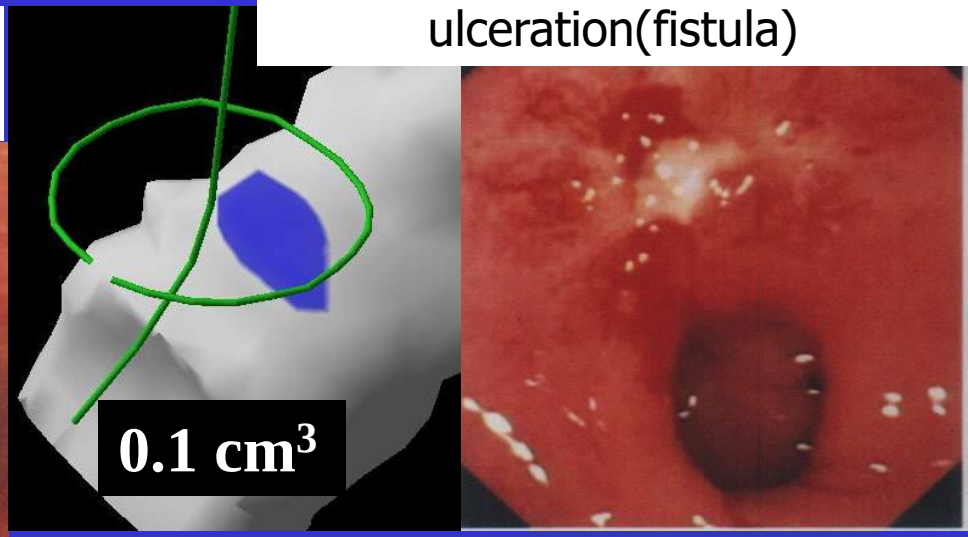
FIXED VOLUME: tolerance dose (total dose)-
"minimum dose to the most exposed tissue"*



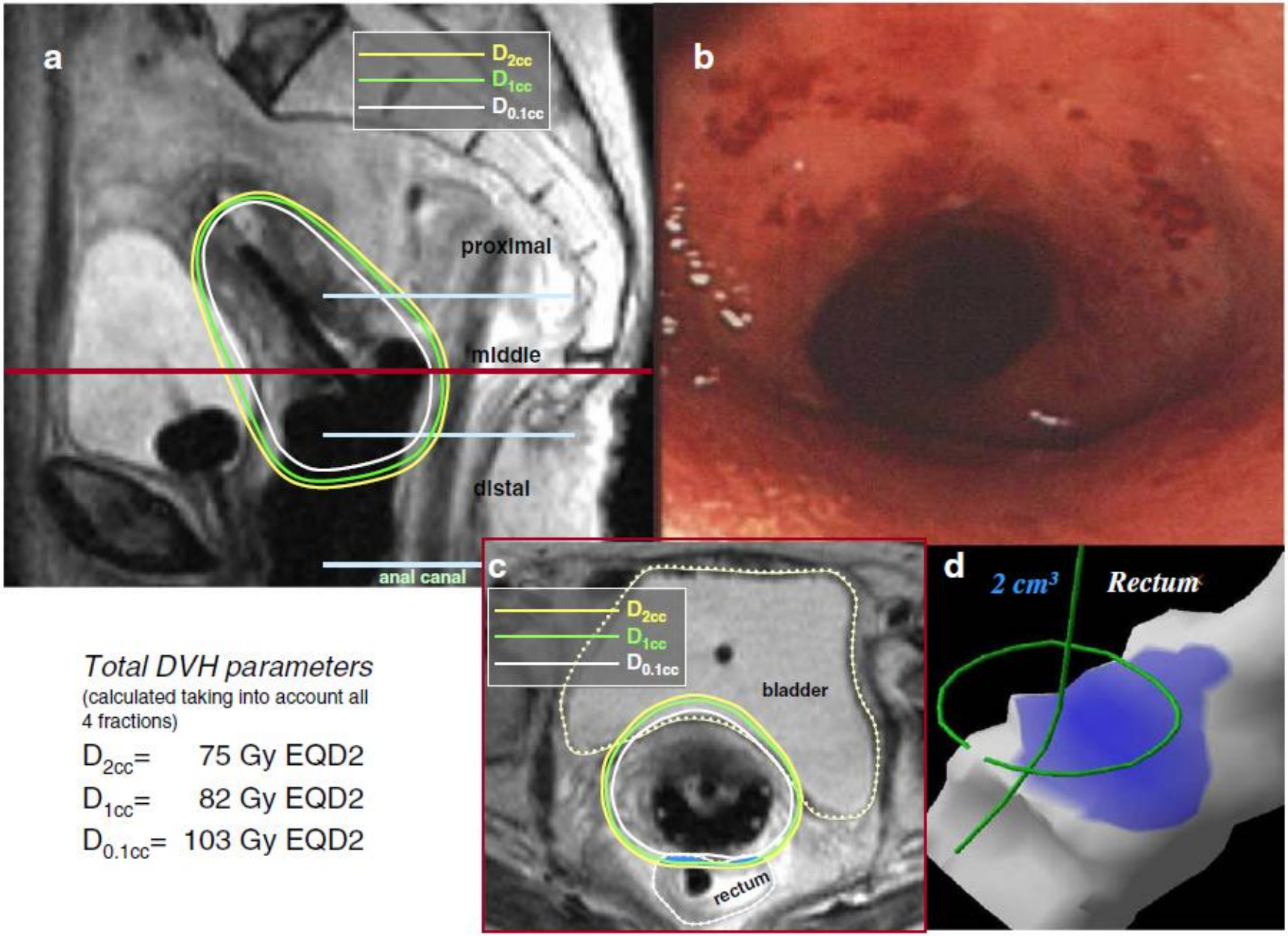
0.1 cc: 3D"maximum dose":
ulceration(fistula)

1cc/2cc:teleangiectasia
(20 mm x 20 mm x 5 mm)





*GYN GEC ESTRO Recommendations(II)
Radiother Oncol 2006



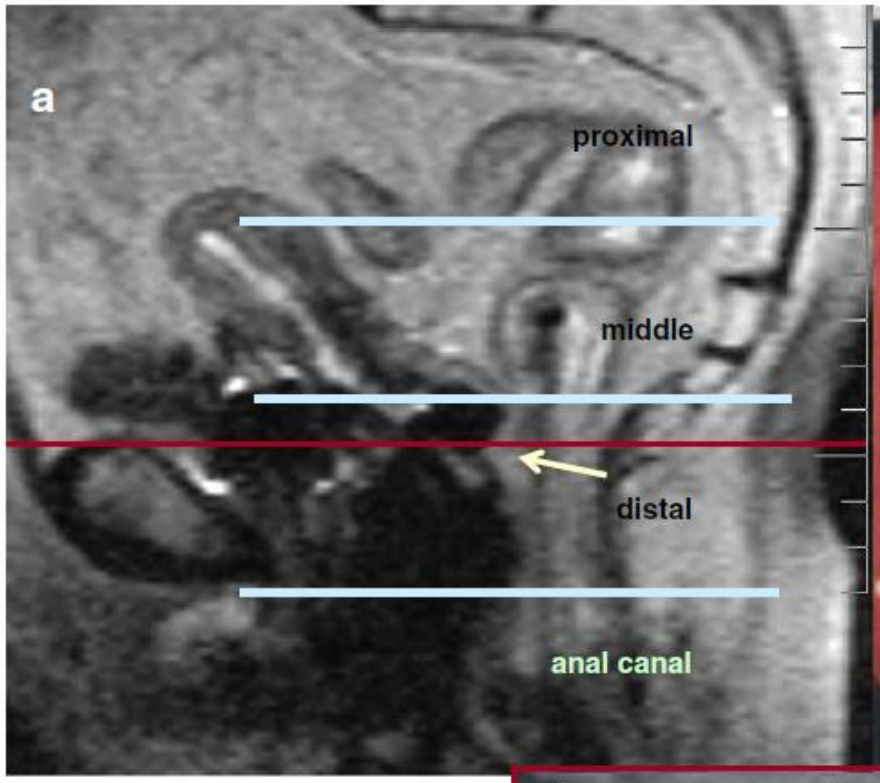
Total DVH parameters
(calculated taking into account all 4 fractions)

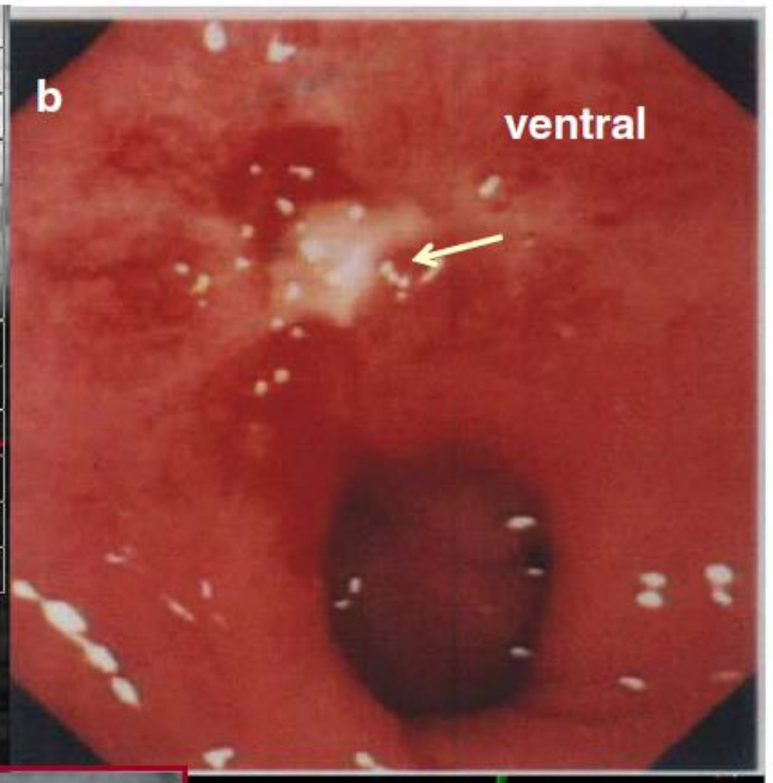
D_{2cc}= 75 Gy EQD2

D_{1cc}= 82 Gy EQD2

$D_{0.1cc}$= 103 Gy EQD2

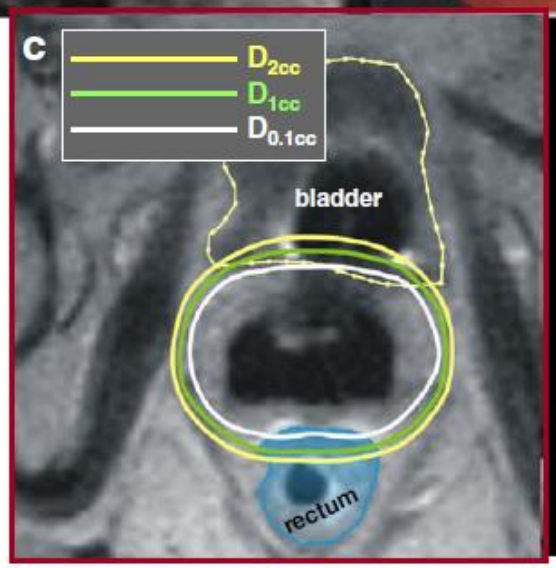
Georg P et al. Radiother and Oncol 2009

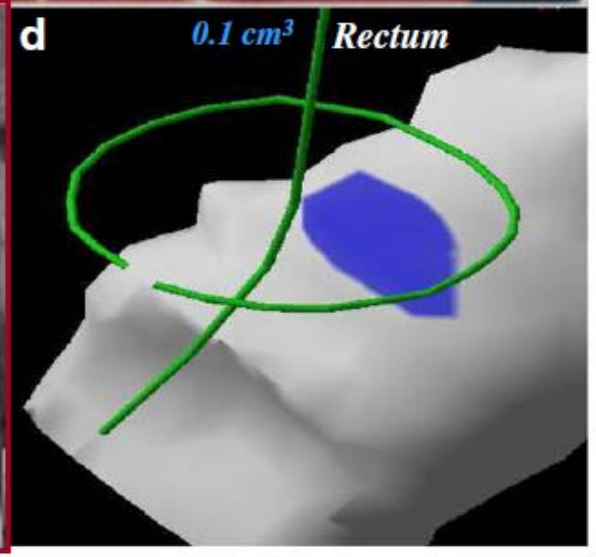




Total DVH parameters
(calculated taking into account all 4 fractions)

D_{2cc}= 81 Gy EQD2
D_{1cc}= 90 Gy EQD2
$D_{0.1cc}$= 108 Gy EQD2



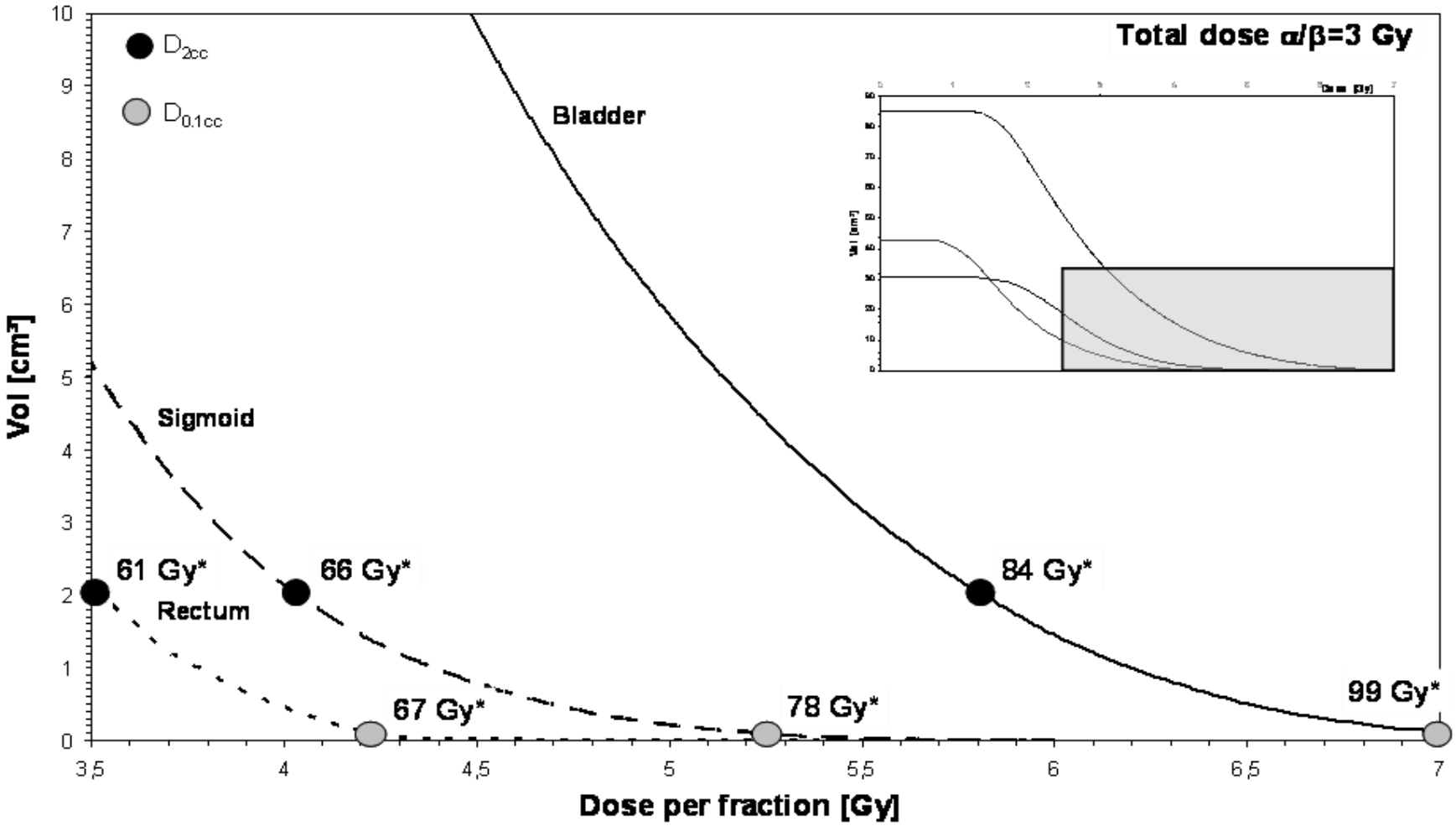


Georg P et al. Radiother and Oncol 2009

D_{2cm3} for rectum is endpoint for

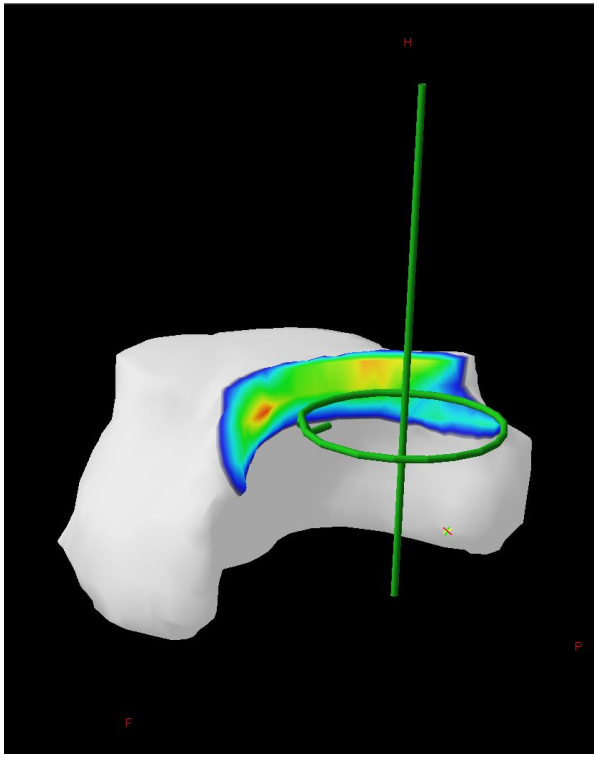
A. Rectum stenosis
B. Anal incontinence
C. Rectal bleeding, ulceration, fistula

DVH Parameters for organs at risk (ICRU 89)

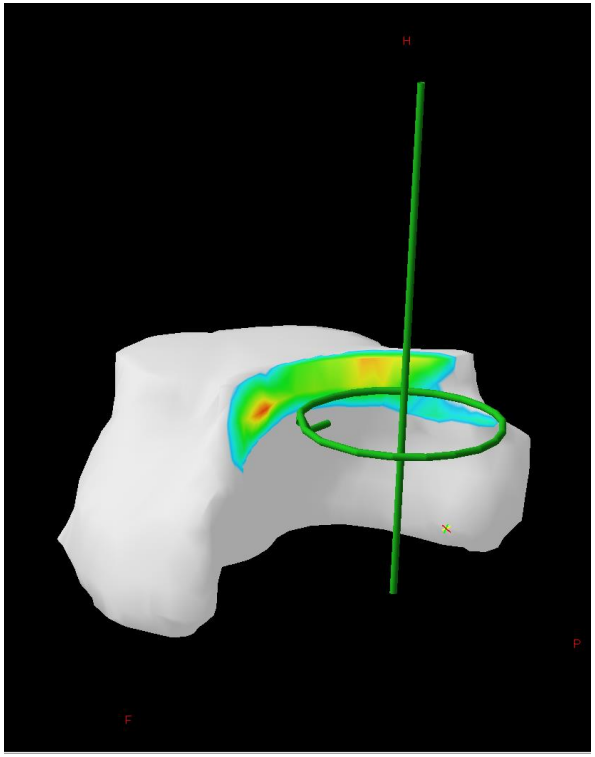


Bladder

D_{2cc}
w x h:
40mm x 20mm

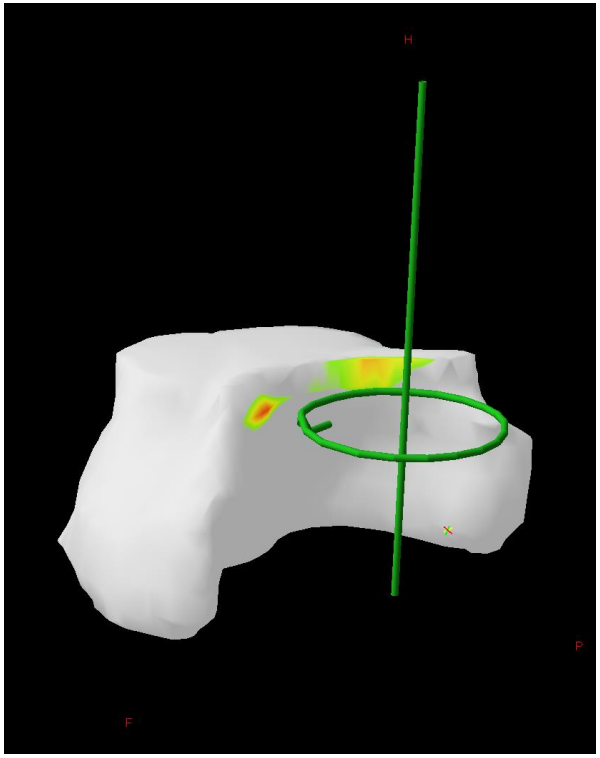


D_{1cc}



$D_{0.1cc}$

20mm x 10mm

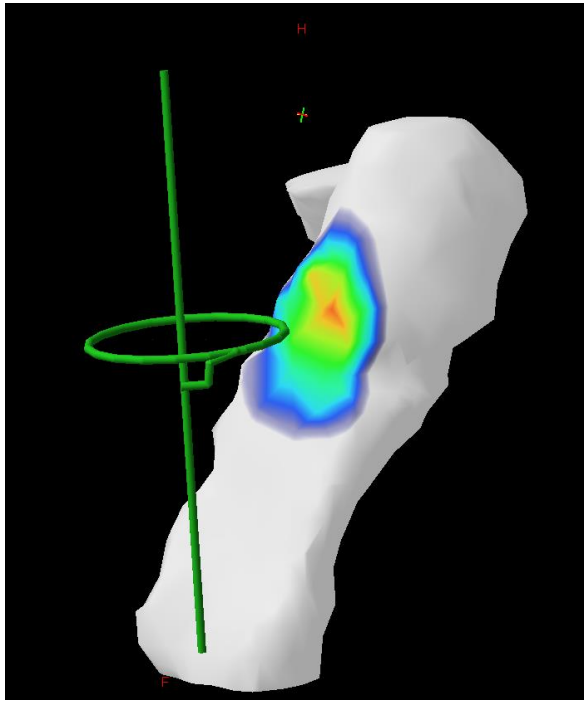


Rectum

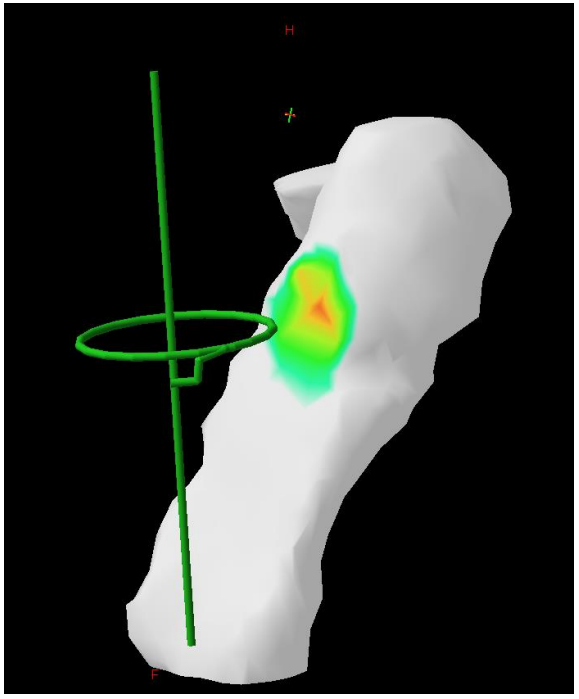
D_{2cc}

w x h:

30mm x 30mm

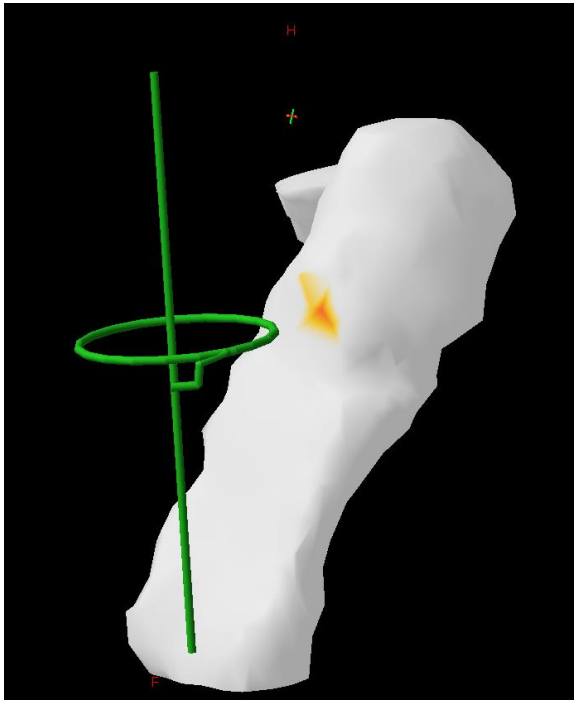


D_{1cc}



$D_{0.1cc}$

10mm x 10mm

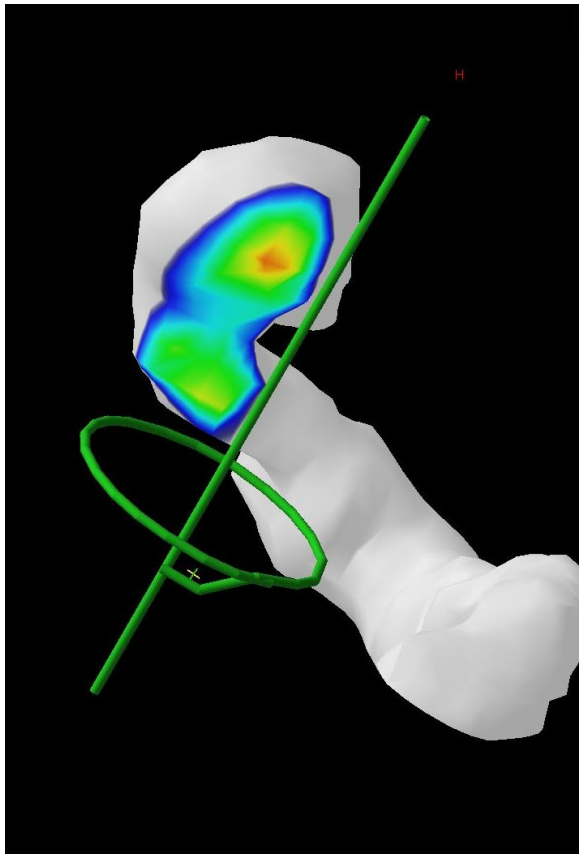


Sigmoid

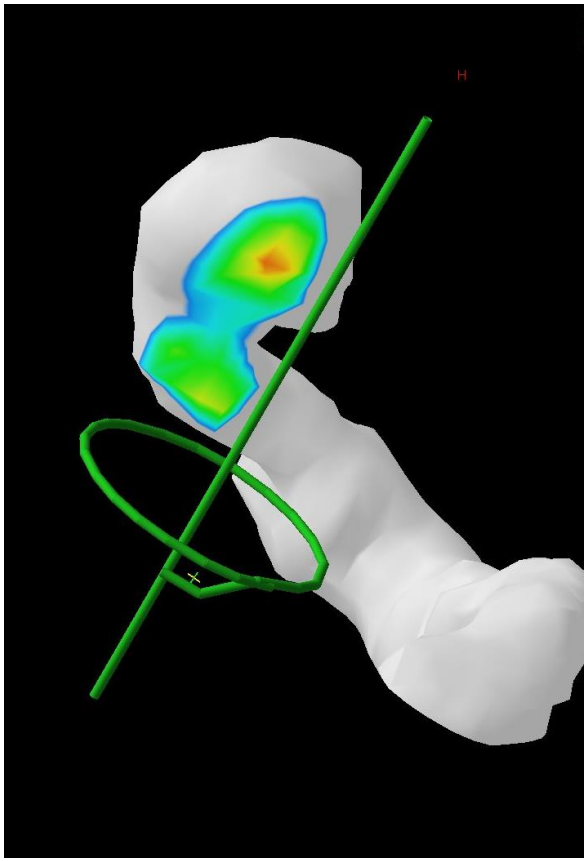
D_{2cc}

w x h:

25mm x 20mm

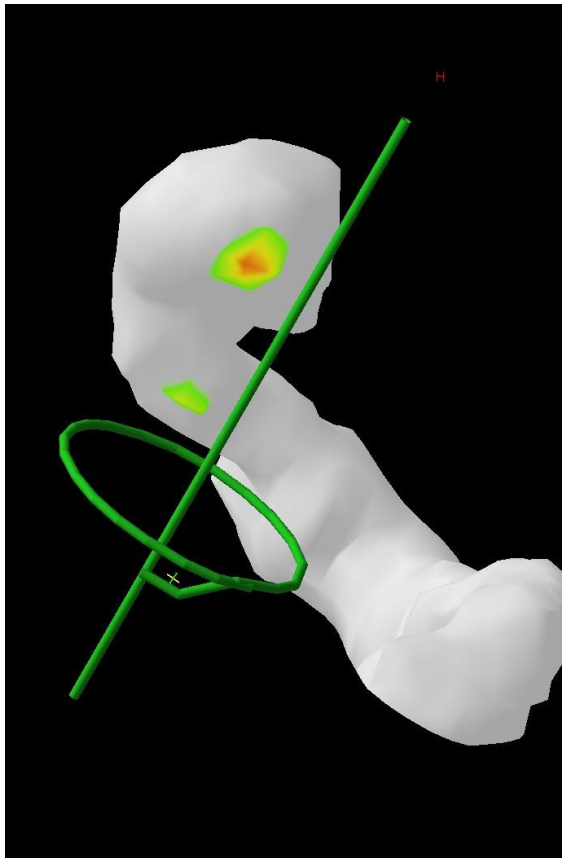


D_{1cc}

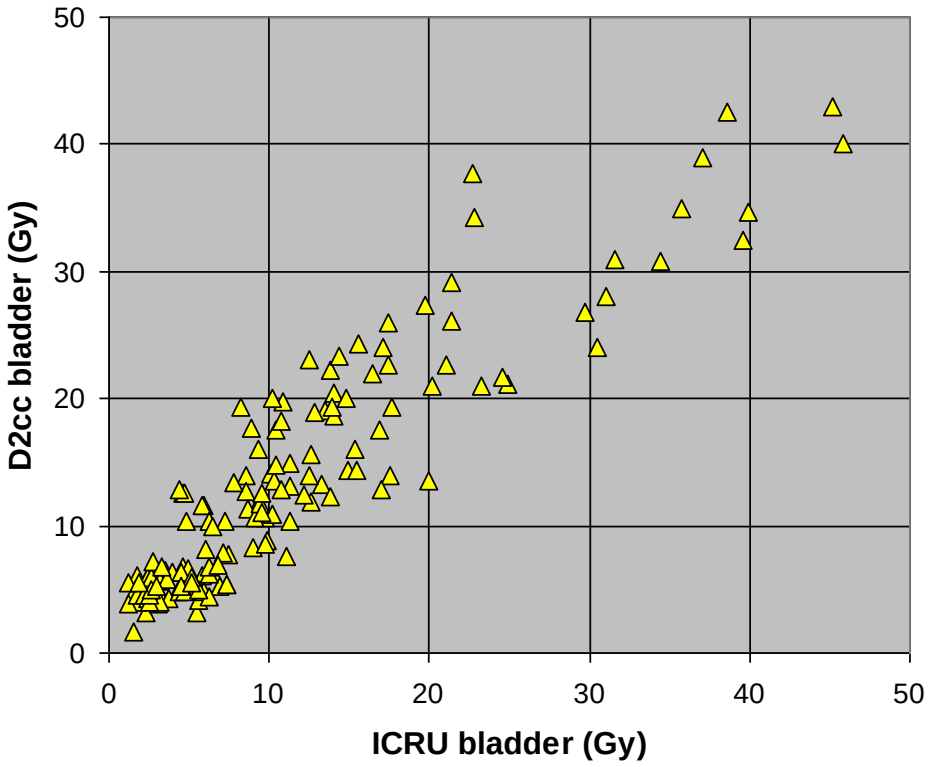


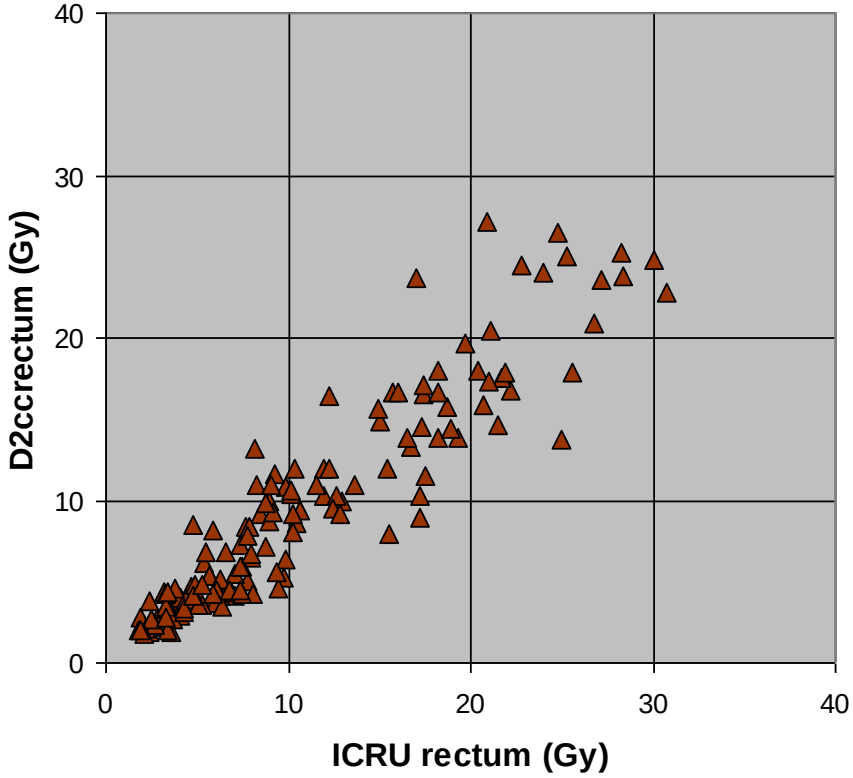
$D_{0.1cc}$

10mm x 10mm



ICRU point dose and D2cc doses

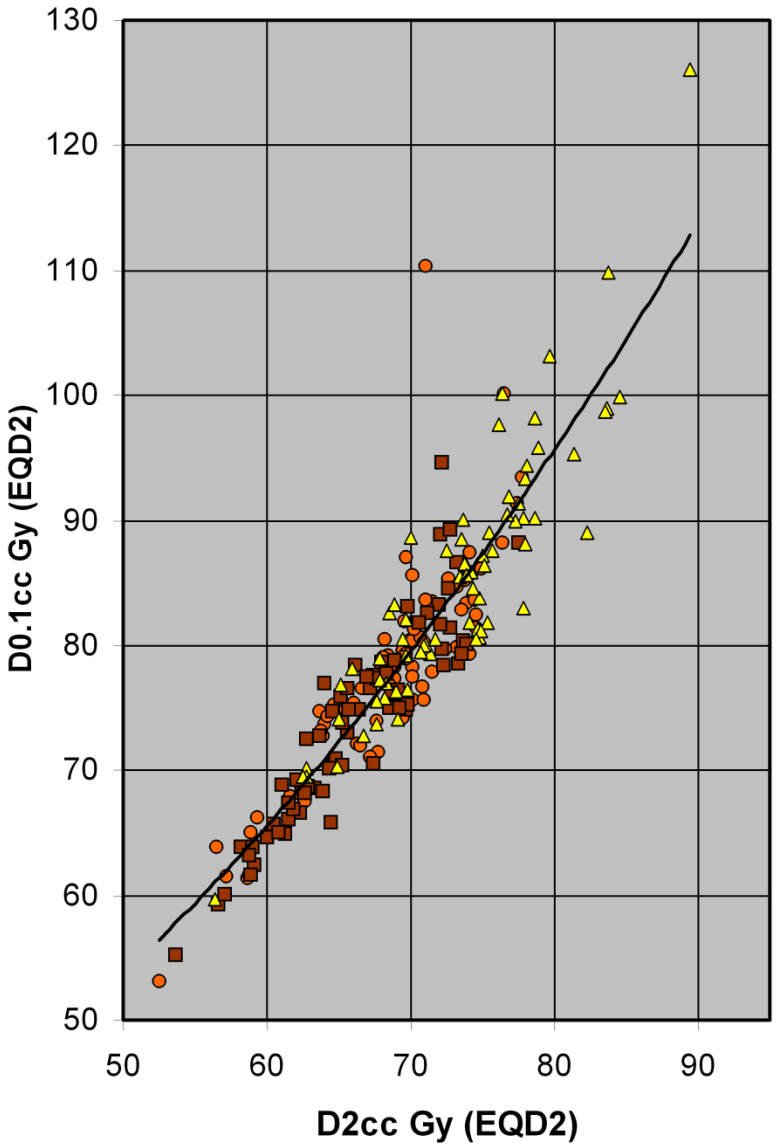




EMBRACE data, Tanderup et al.

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

D_{2cm3} and $D_{0.1cm3}$ for OAR

A. D_{2cm3} is identical to $D0.1_{cm3}$
B. D_{2cm3} is larger than $D0.1_{cm3}$
C. D_{2cm3} is smaller than $D0.1_{cm3}$

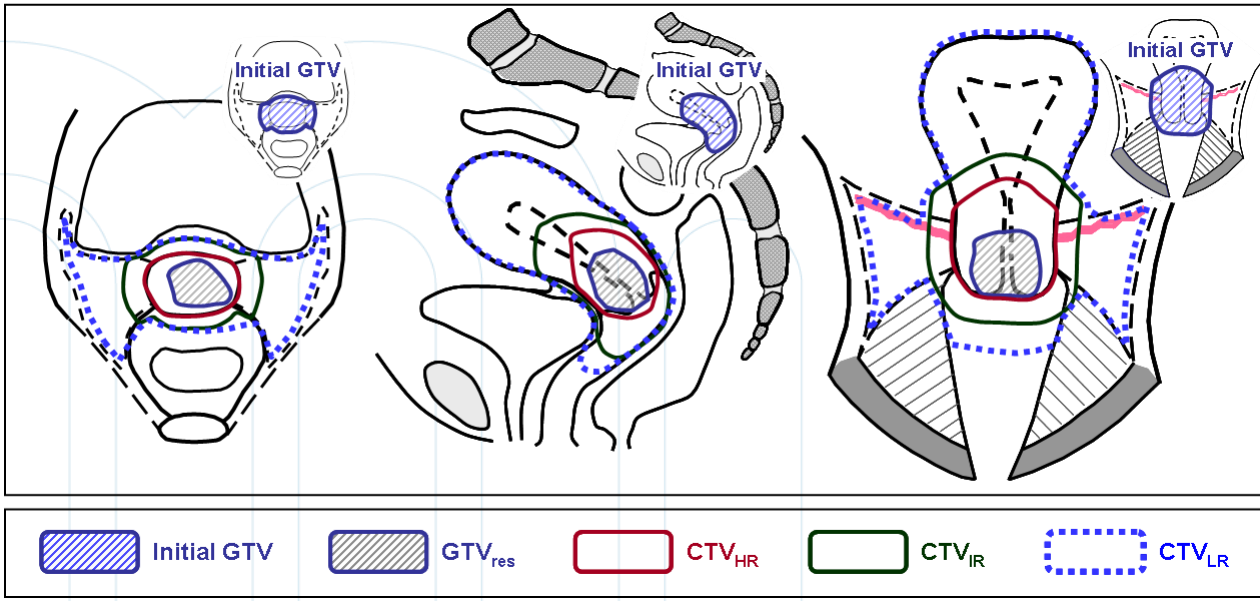
Level 2 - *Advanced standard for reporting* All that is reported in level 1 plus (ICRU 89):

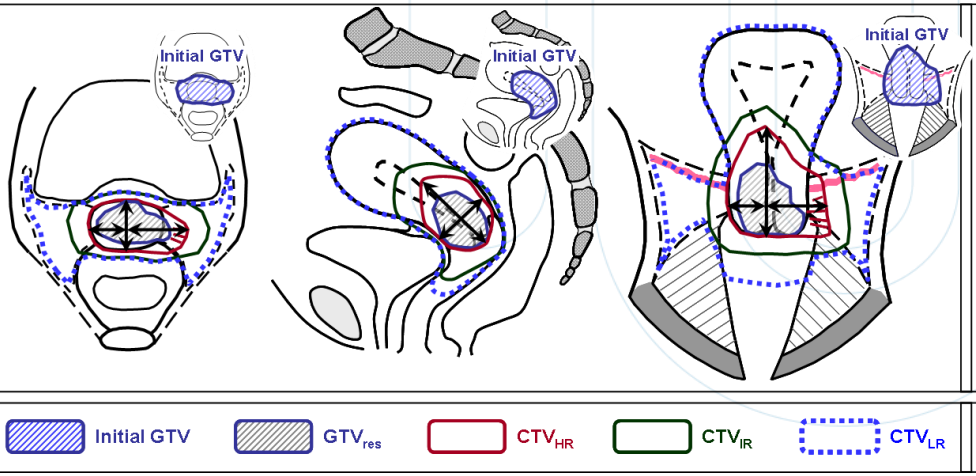
3D delineation of volumes (on volumetric images with applicator and on clinical diagrams):

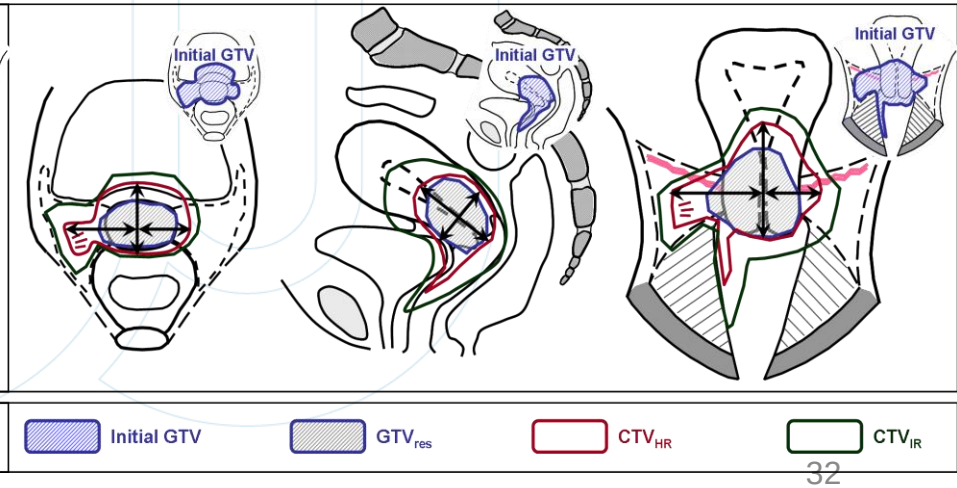
- **(GTV_{init})**
- **GTV_{res}**
- **CTV_{HR}**
- **(CTV_{IR} if used for prescription)**
- **With maximum width, height, thickness and with volume**

Overview of the adaptive target concept in cervix cancer stage IB, IIB, IIIB

- Initial and residual GTV
- Res. patholog. tissue
- High Risk CTV
- Intermediate Risk CTV
- (Low Risk CTV)





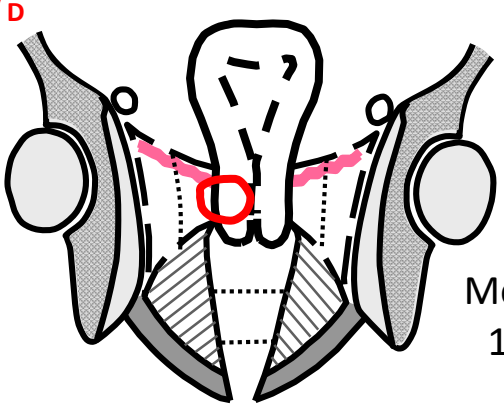


GEC ESTRO Rcommendations I, 2005; ICRU/GEC ESTRO report 89, 2016, Fig. 5.9-11

At diagnosis
GTV_D

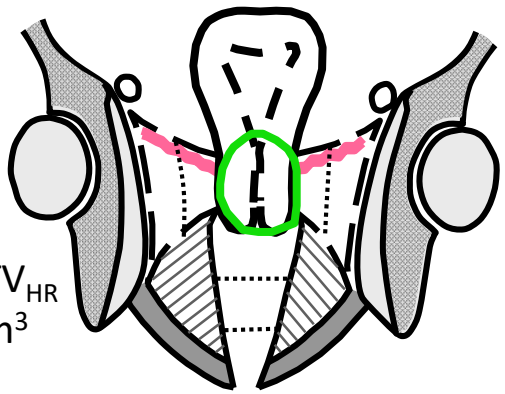
N=481 (IIB=342, IIIB=139)

At brachytherapy
HR-CTV

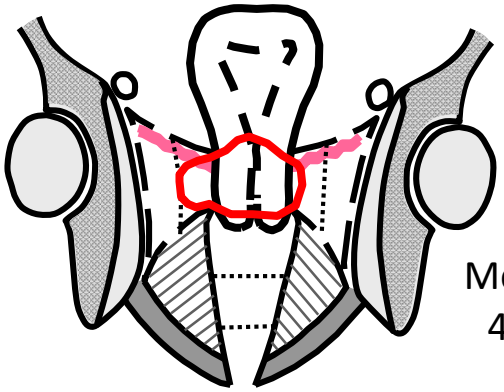


Group 1
"Stage IB_1-like"
N=55 (11%)

Mean GTV_D
12.6 cm^3

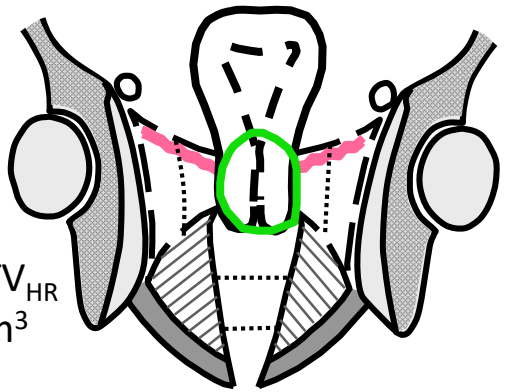


Mean CTV_{HR}
23.7 cm^3

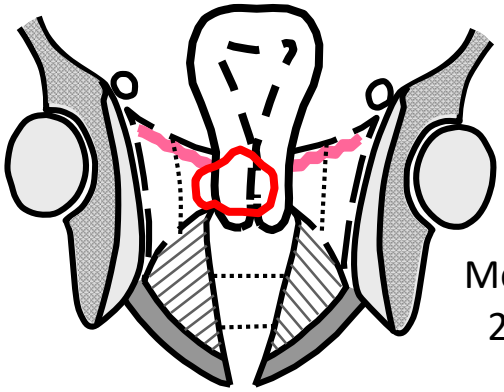


Group 2
Good response
N=78 (16%)

Mean GTV_D
47.5 cm^3

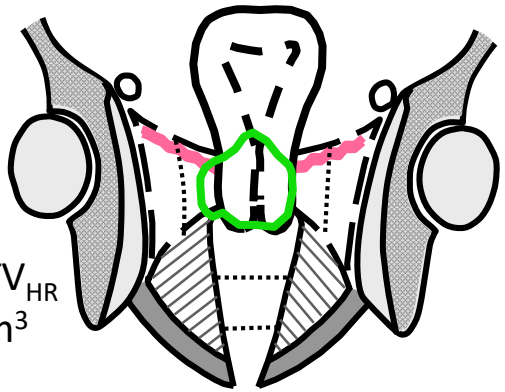


Mean CTV_{HR}
25.3 cm^3



Group 3
Small, moderate response
N=123 (26%)

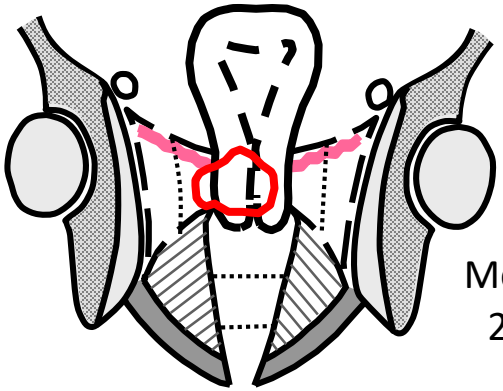
Mean GTV_D
23.9 cm^3



Mean CTV_{HR}
29.9 cm^3

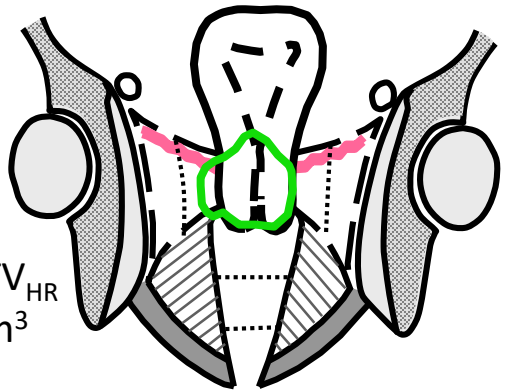
Jastaniyah N, Yoshida K *et al*; fellows at MUW/AKH Vienna, ASTRO 2014, IJROBP 2016

continued

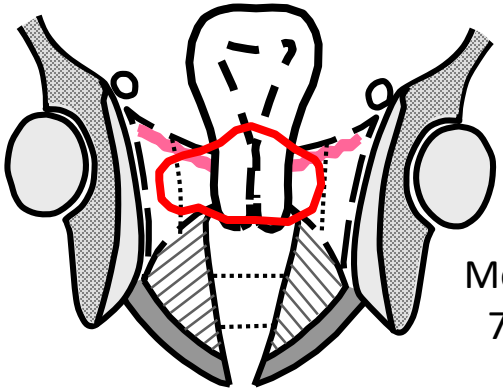


Group 3
Small, moderate response
N=123 (26%)

Mean GTV_D
23.9 cm^3

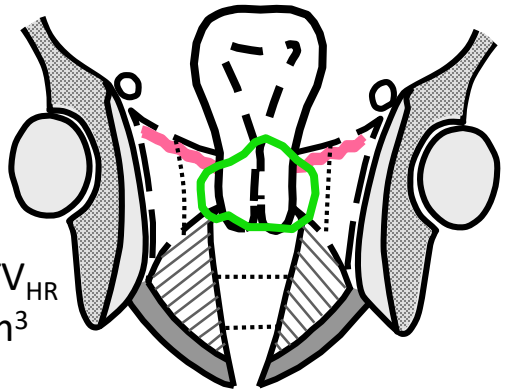


Mean CTV_{HR}
29.9 cm^3

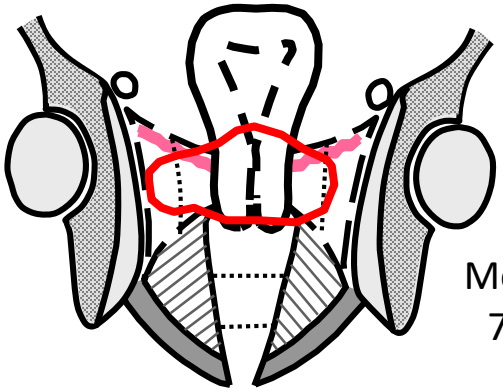


Group 4
Large, moderate response
N=147 (31%)

Mean GTV_D
73.4 cm^3

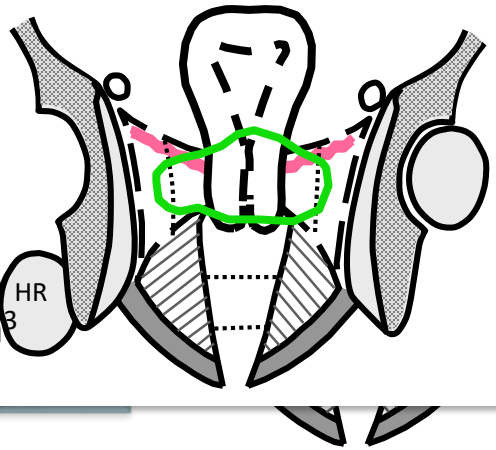


Mean CTV_{HR}
38.5 cm^3



Group 5
Poor response
N=75 (16%)

Mean GTV_D
79.4 cm^3



Mean CTV_{HR}
59.5 cm^3

GTV
HR CTV

Jastaniyah N, Yoshida K *et al*; fellows at MUW/AKH Vienna, ASTRO 2014, IJROBP 2016

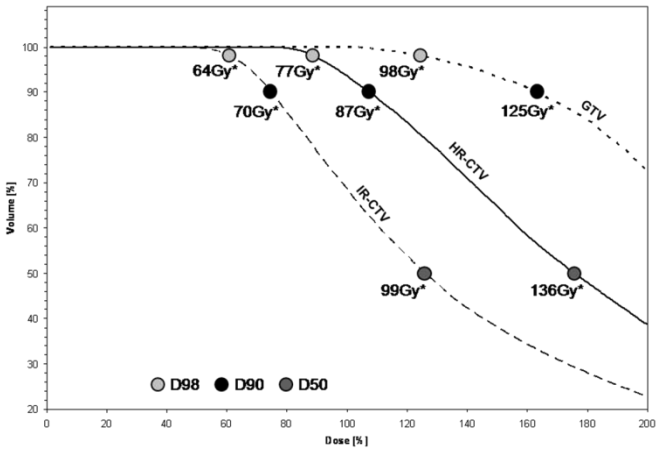
Level 2 - *Advanced standard for reporting* All that is reported in level 1 plus (ICRU 89):

Dose reporting for defined volumes based on volumetric imaging:

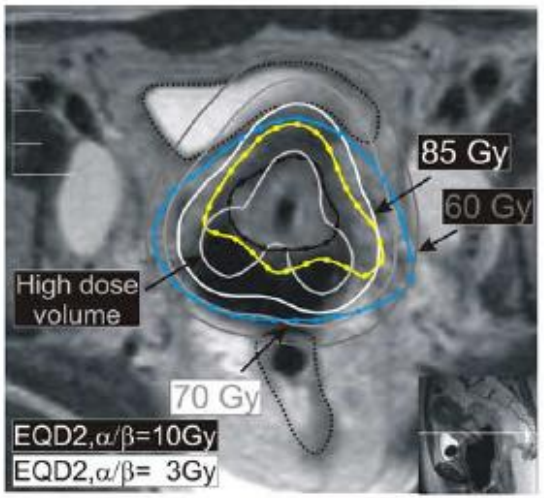
- **D_{98}, D_{90}, D_{50} for CTV_{HR}**
- **(D_{98}, D_{90}, D_{50} for CTV_{IR} if used for prescription)**
- **D_{98} for GTV_{res}**
- **D_{98} for pathological lymph nodes**

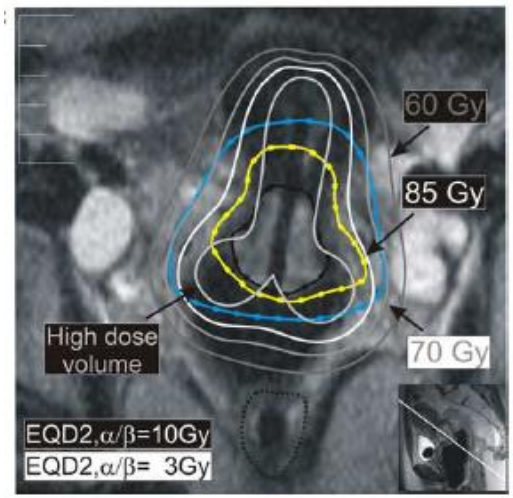
DVH-parameters CTV-T_{HR} (ICRU 89)

- **D90: Minimum dose within most exposed 90% of volume of interest**
  - **reliable and reproducible, but 10% „neglected“ (clin relevance)**
- **D 98: Minimum dose within most exposed 98% of volume of interest**
  - **reliable and reproducible, 2% not included**
- **[V100: Volume recieving prescribed physical dose (V150%/V200%)]**
  - **indicates target coverage;**
    only relevant within a specific dose (rate) and fractionation schedule
- **D50: Minimum dose within most exposed 50% of volume of interest**



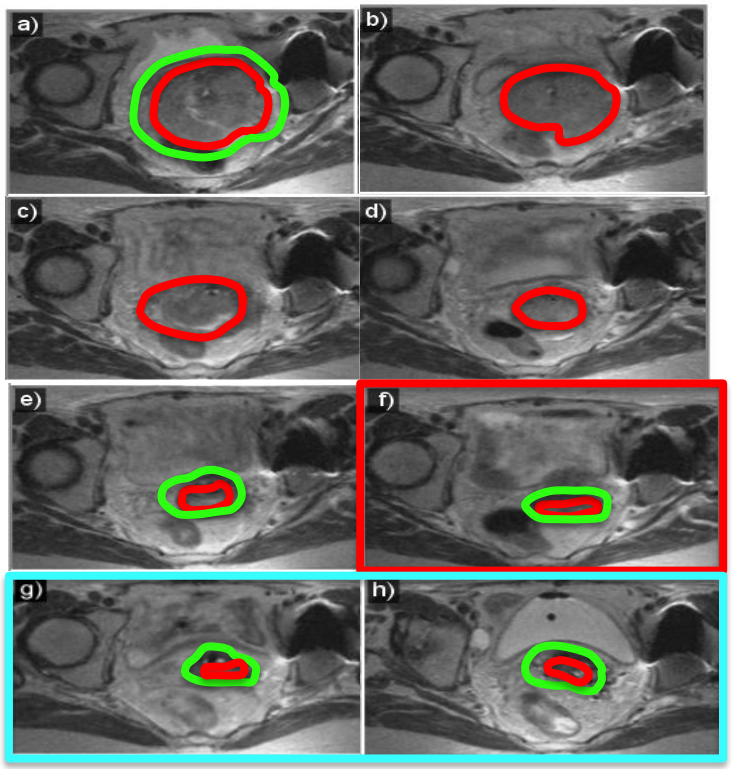
GEC ESTRO Rec II, 2006

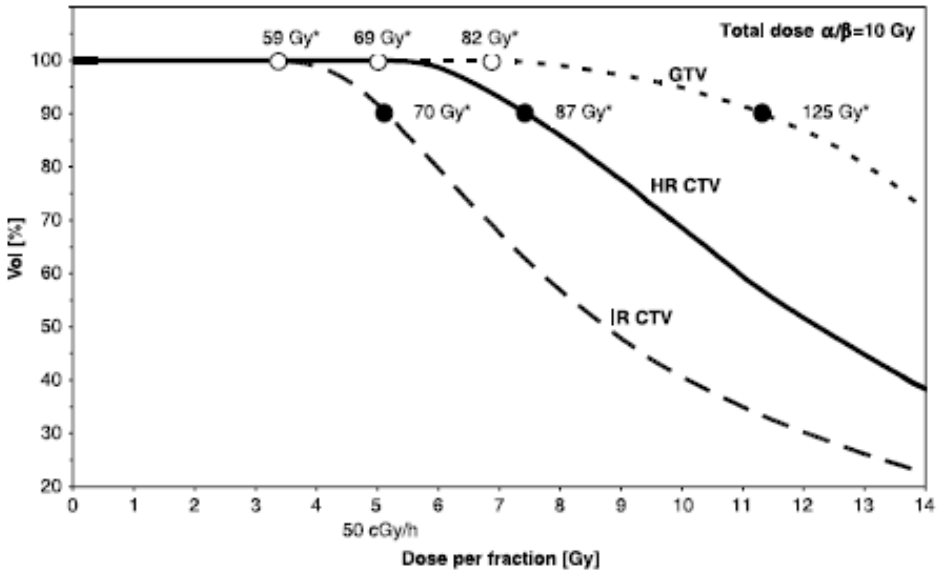




Dose and Volume Parameters (Vienna data 1998-2008)

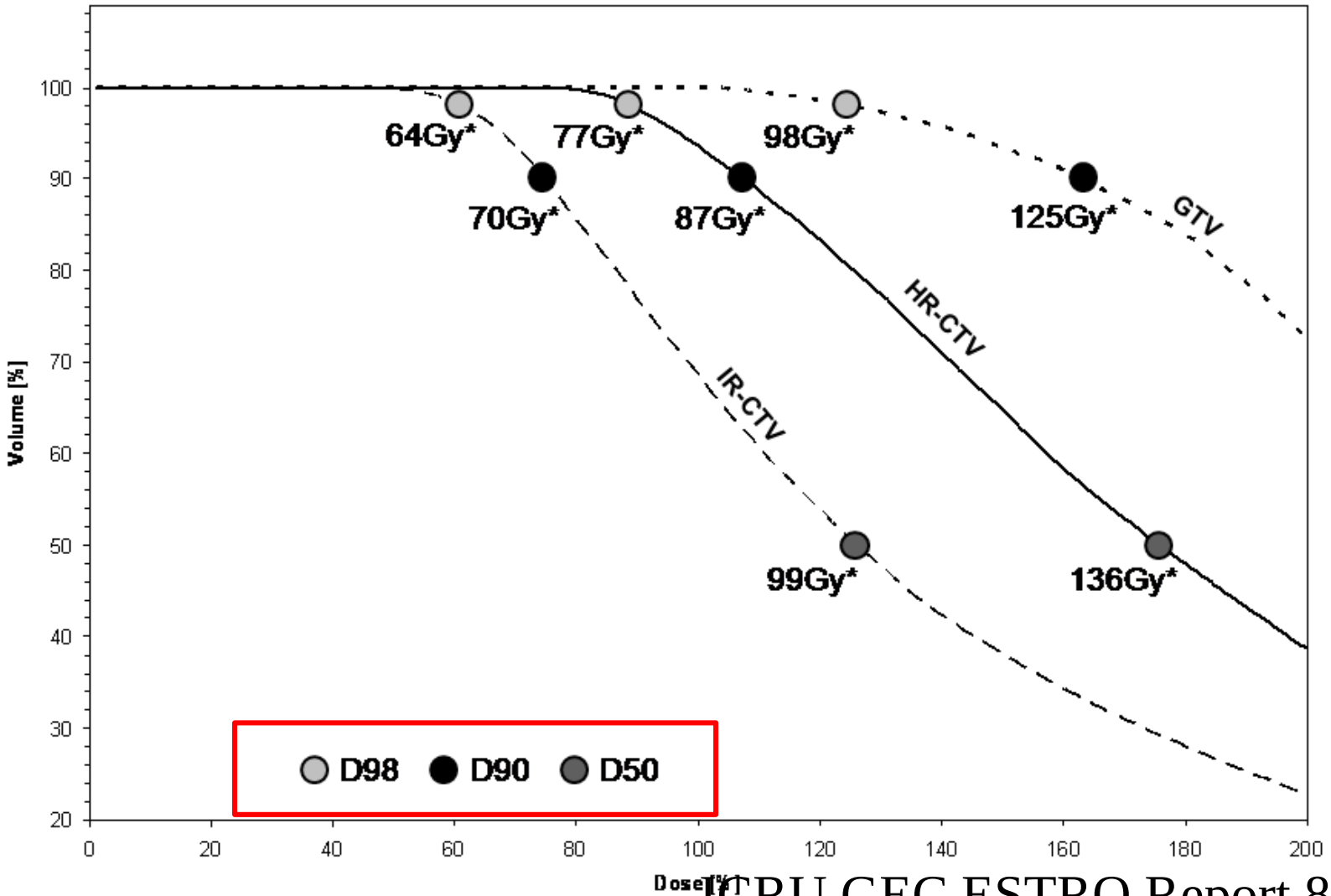
IR CTV-T	~ 100 cm^3	~ 66 Gy EQD2 (D90)
HR CTV-T	~ 39 cm^3	~ 89 Gy EQD2 (D90)
Res. GTV-T	~ 9 cm^3	~ 119 Gy EQD2 (D100)





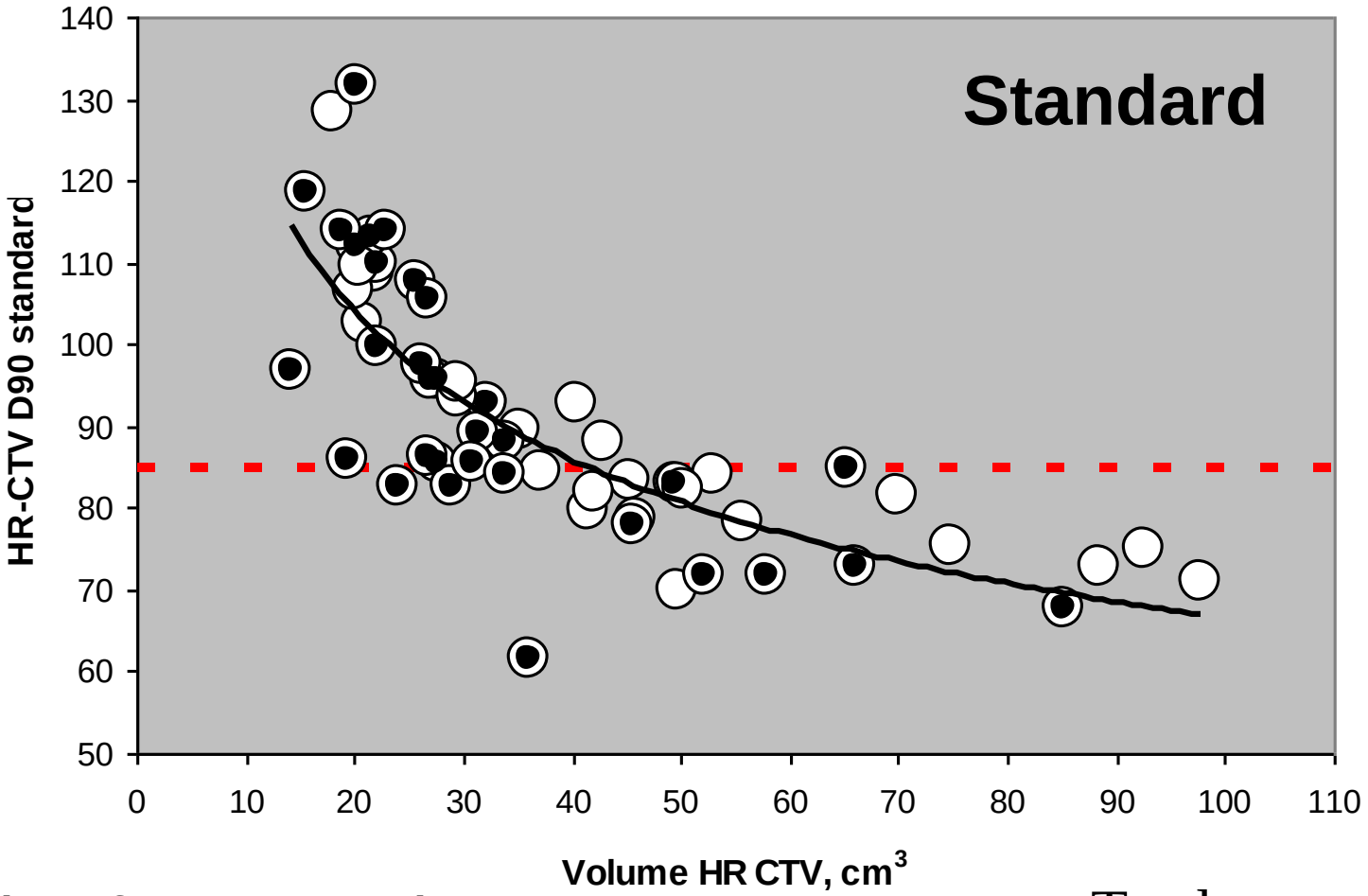
GEC ESTRO Rec II, 2006

DVH parameters targets: GTV, CTV-HR, CTV-IR



ICRU GEC ESTRO Report 89, 2016

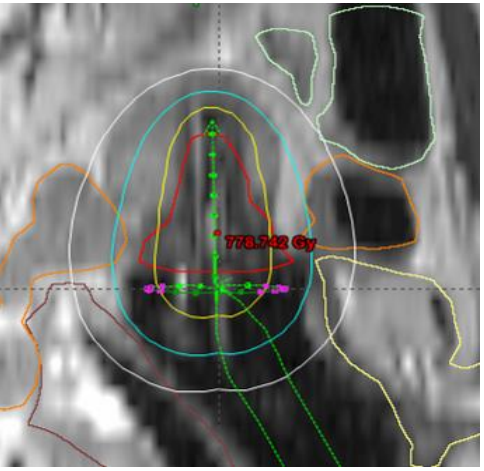
Dose in D90 and HR CTV for point A prescription
High Target Doses in small tumours
Low Target Doses in large tumours



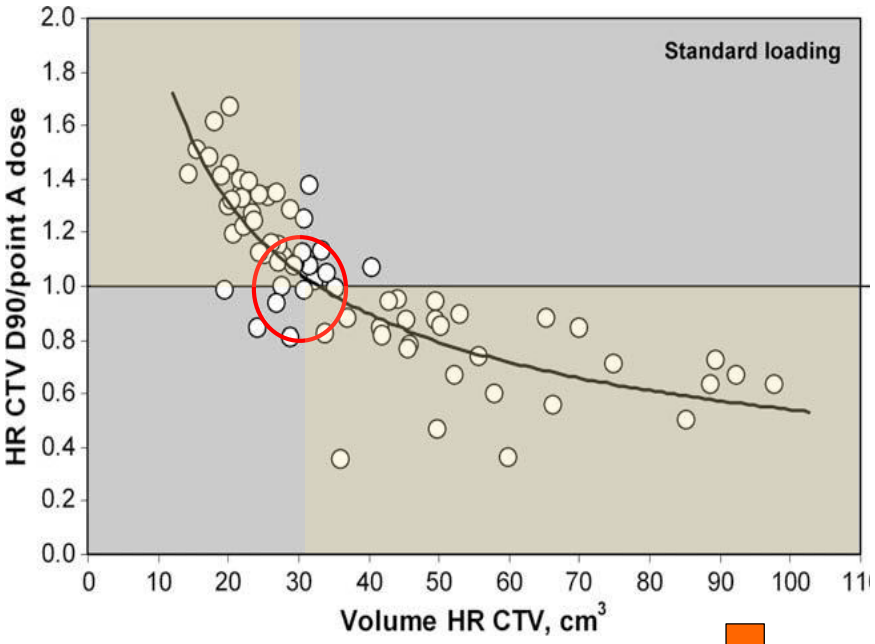
Violation of OAR constraint

Tanderup et al.

Consequences of prescribing to Point-A

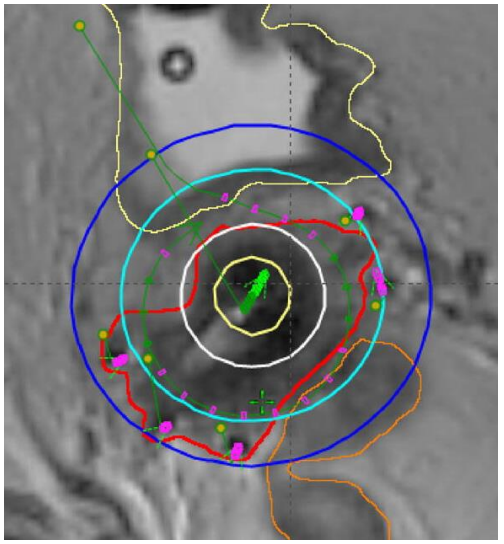


Overdosing organs at risk



Tanderup et al, Radiotherapy Oncol 2010

Underdosing the tumour



Level 2 - *Advanced standard for reporting* All that is reported in level 1 plus (ICRU 89):

.

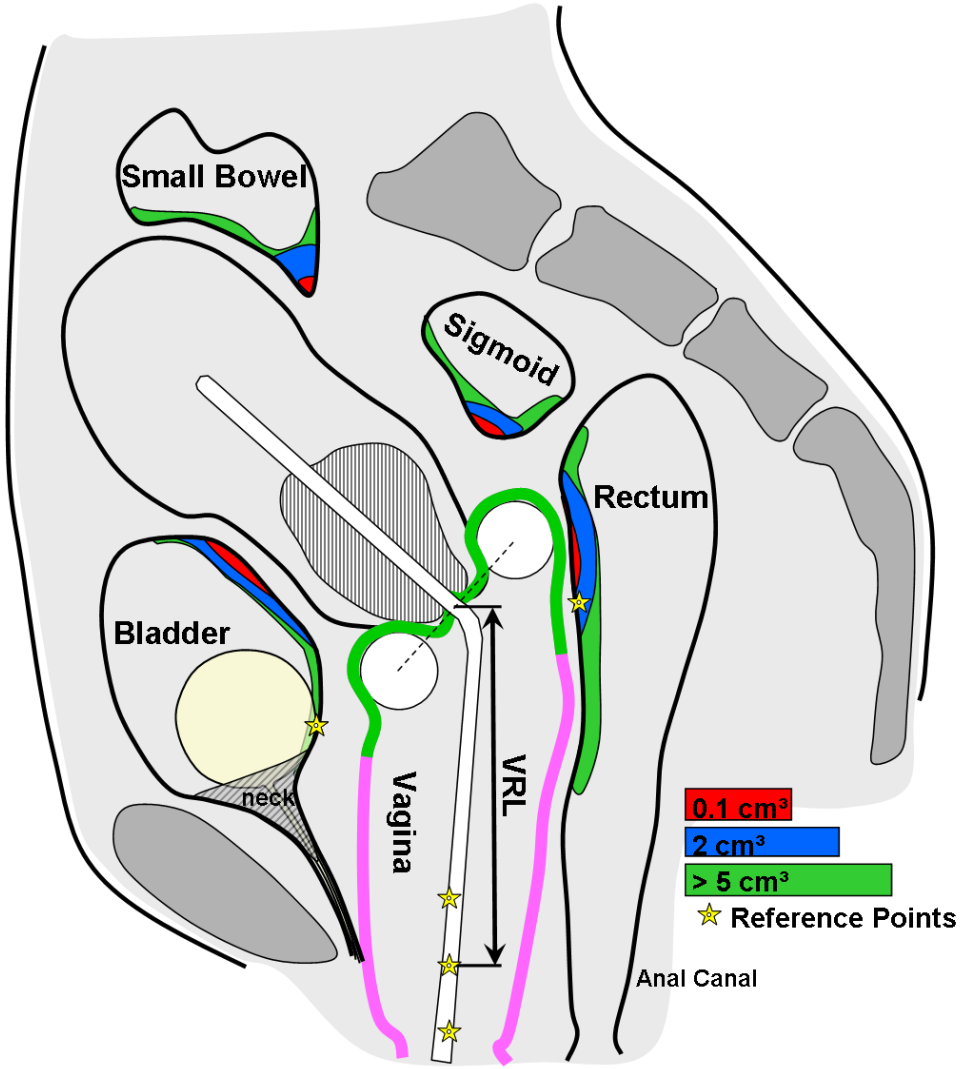
Dose reporting based on volumetric imaging for OARs:

- **Bladder reference point dose**
- **$D_{0.1cm^3}$,D_{2cm^3} for sigmoid**
- **D_{2cm^3} bowel**
- **Intermediate and low dose parameters in bladder, rectum, sigmoid, bowel (e.g. V_{15Gy}, V_{25Gy}, V_{35Gy}, V_{45Gy} or $D_{98\%}$, $D_{50\%}$, $D_{2\%}$)**
- **Vaginal point doses at level of sources (lateral at 5 mm)**
- **Lower and mid-vagina doses (PIBS, PIBS ±2cm)**

DVH Parameters and Reference Points,

ICRU/GEC ESTRO report 89, 2016

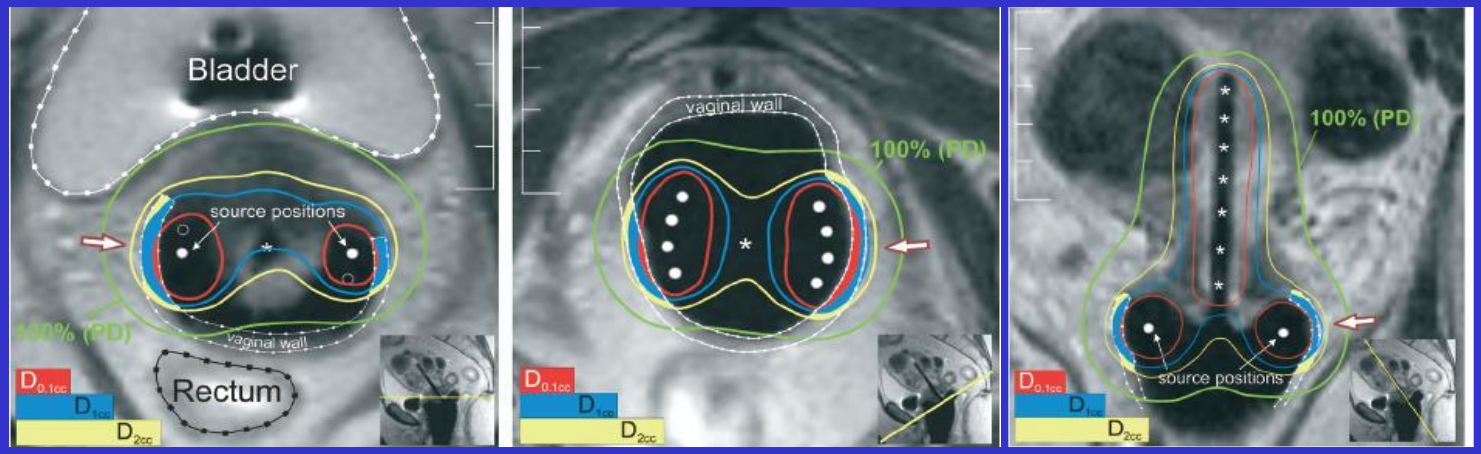
Fig. 6.4, Fig. 8.8



Vaginal dose assessment and reporting

UNCERTAINTIES IN ASSESMENT OF THE VAGINAL DOSE FOR INTRACAVITARY BRACHYTHERAPY OF CERVICAL CANCER USING A TANDEM-RING APPLICATOR

DANIEL BERGER, M.SC., JOHANNES DIMOPOULOS, M.D., PETRA GEORG, M.D., DIETMAR GEORG, PH.D., RICHARD PÖTTER, M.D., AND CHRISTIAN KIRISITS, SC.D.

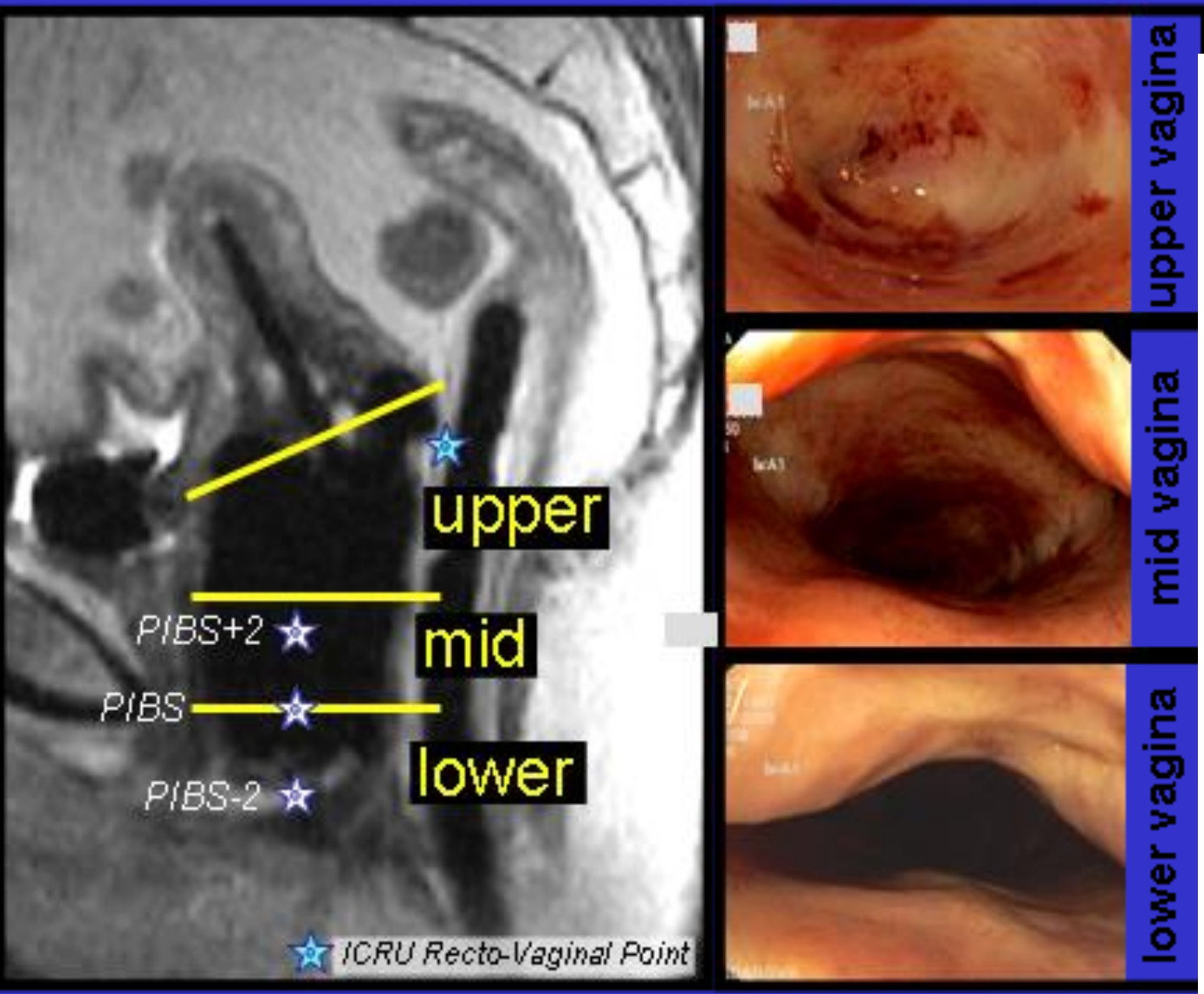


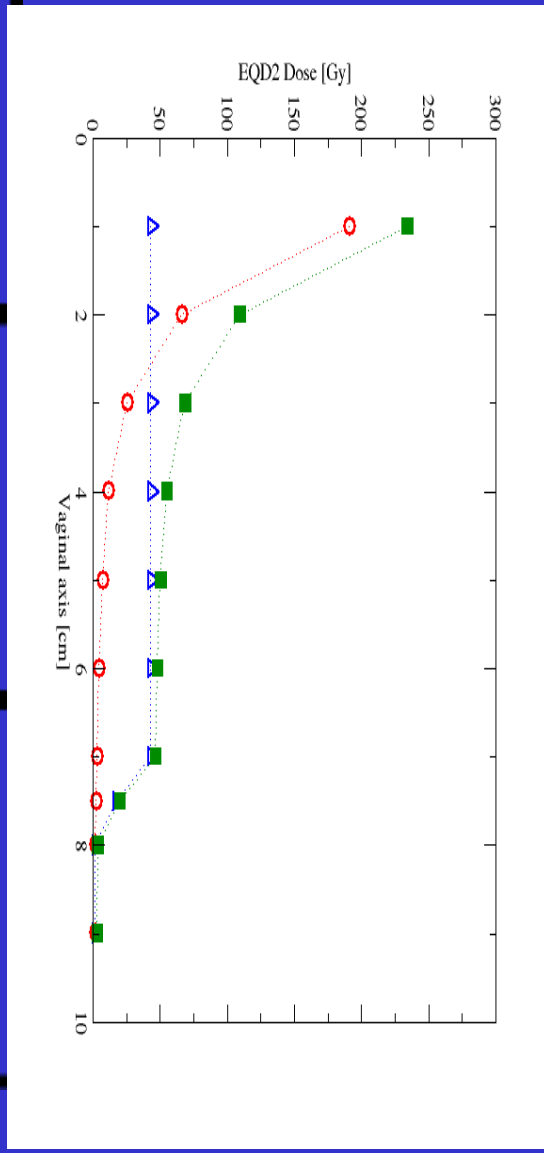
DVH parameters have HIGH uncertainty for representative vaginal dose estimation

They are influenced by the resolution of sectional imaging, contouring accuracy and applicator reconstruction

Berger et al, IJROBP 2007

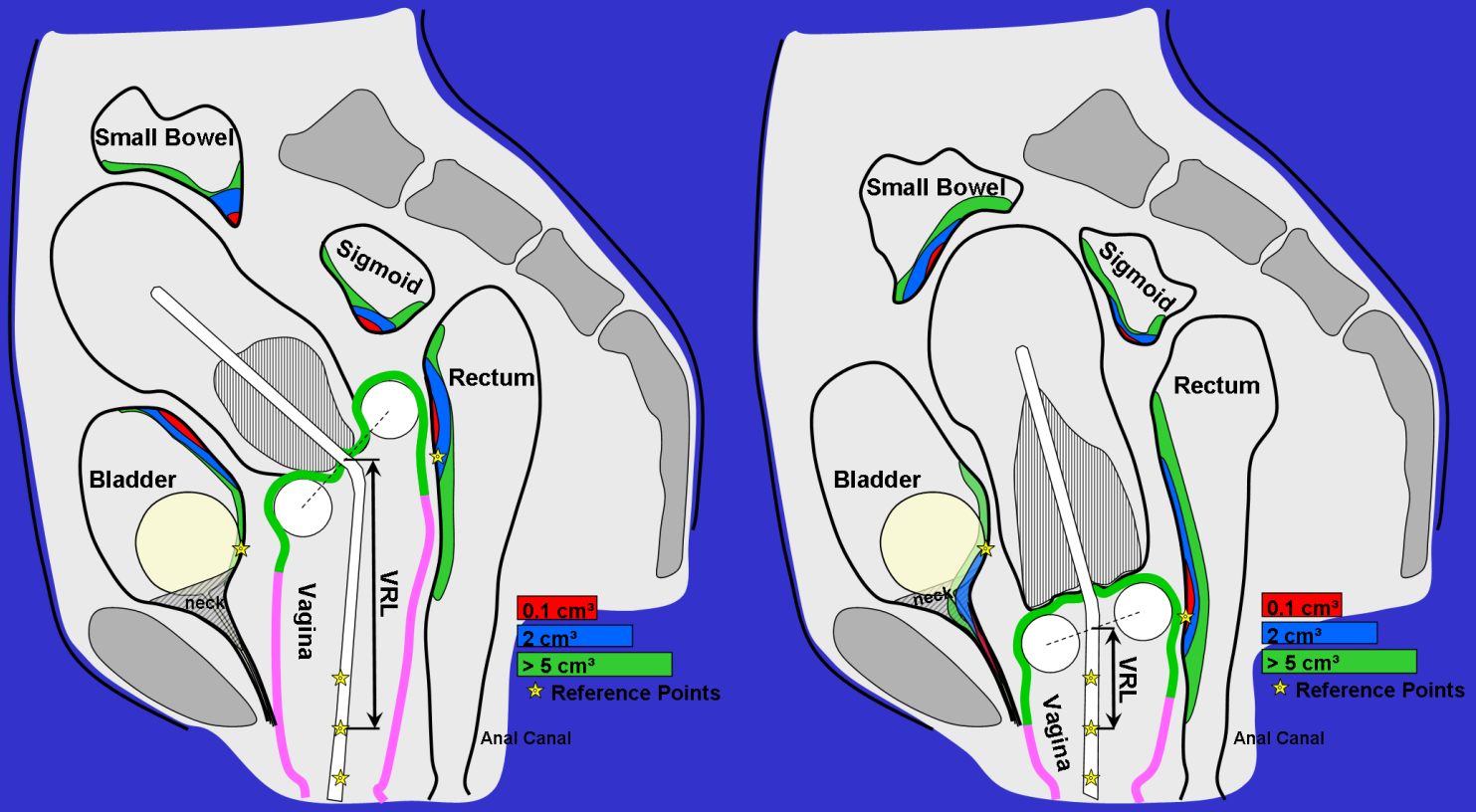
Vaginal morbidity and radiation doses





ICRU/GEC ESTRO Report 89 Fig. 6.1/Fig. 8.11

DVH Parameters and Reference Points, Vaginal point: *variations in application*



ICRU/GEC ESTRO
report 89, 2016
Fig. 6.4, Fig. 8.8

Vaginal Reference Length (VRL)

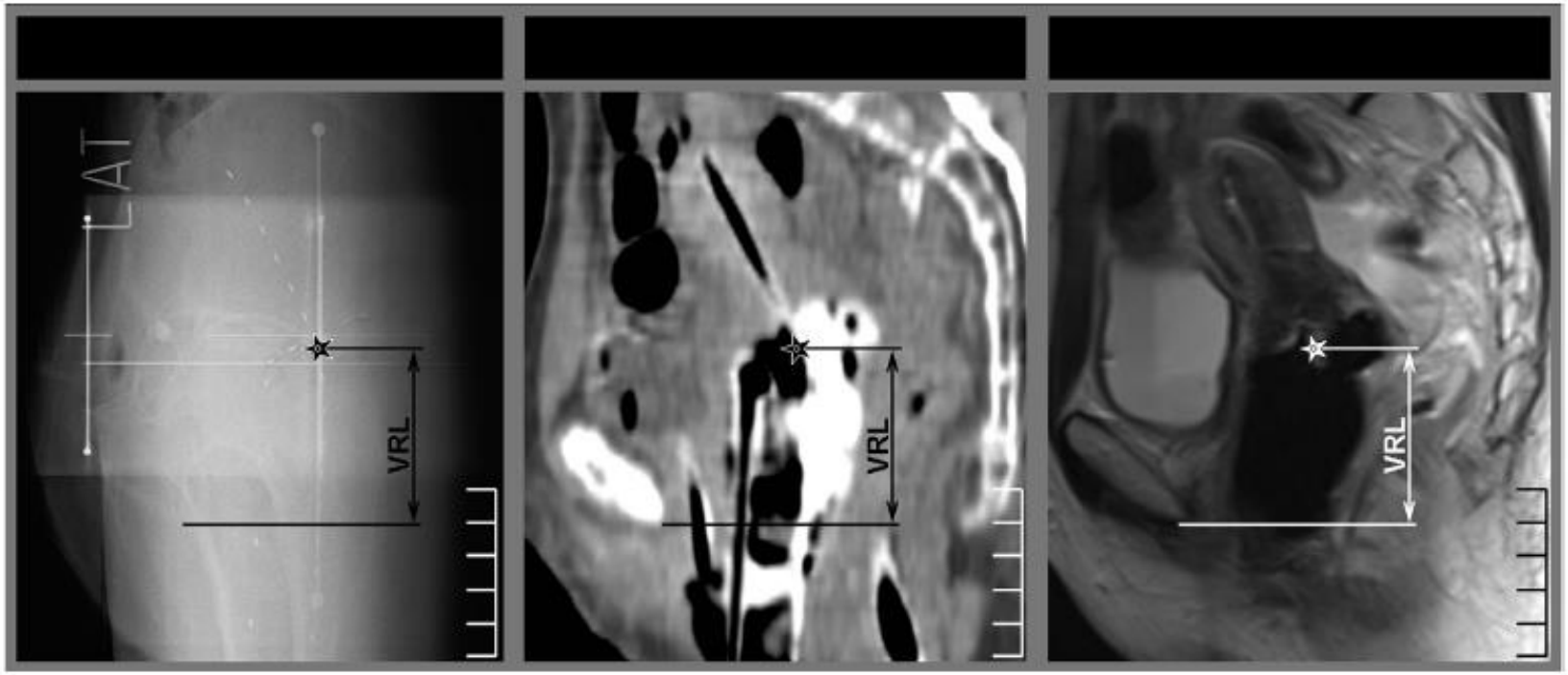
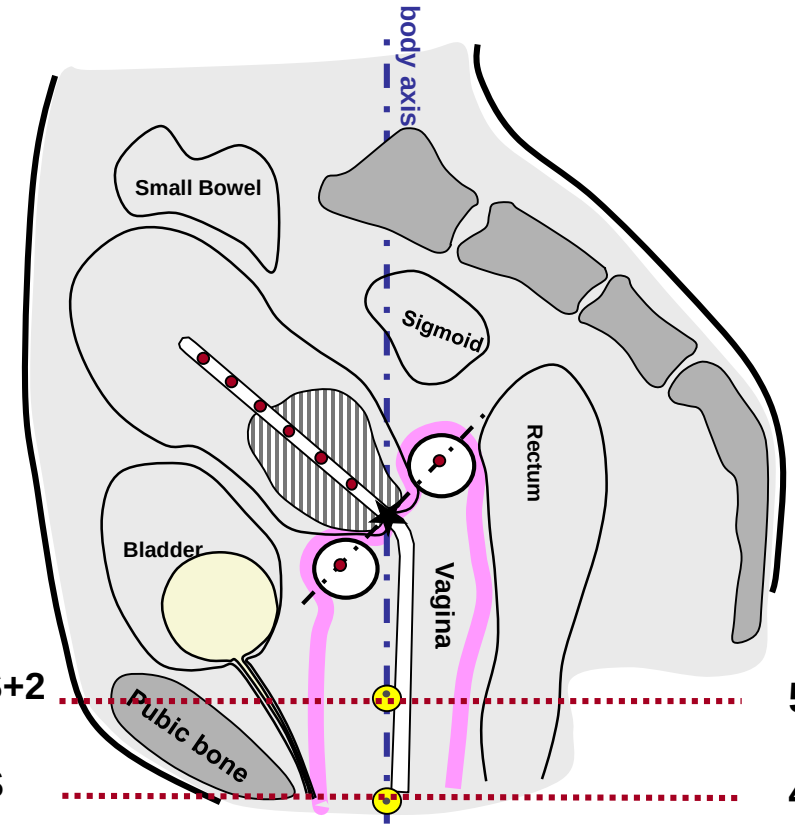


Fig. 1. Definition of vaginal dose points and vaginal reference length (VRL). (A) Vaginal dose points are defined in relation to a point at the level of the posterior–inferior border of the symphysis (PIBS) on sagittal (reconstructed) CT or MR images used for EBRT and BT treatment planning. The star at PIBS level represents the vaginal reference point. In the table on the right side mean (SD) and median (min–max) values are given for each level in EBRT and for total dose in EQD2. Additionally, total doses to the top are given for all four clockwise positions at the vaginal surface and 5 mm depth (e.g. median total dose at 3 o'clock is respectively 266 and 115 Gy for surface and 5 mm depth). (B) VRL at time of BT with a ring applicator in situ on a lateral radiograph, sagittal MPR CT image and sagittal MRI view. VRL is measured from centre of the ring (indicated by a star) to the PIBS level, indicated by the solid line orthogonal to the body axis.

Vaginal reference points



PIBS+2 — 53 (32-109) Gy (mid vagina)

PIBS — 41 (4-81) Gy

PIBS-2 — 5 (1-51) Gy (introitus)

Vienna Data (n=59)

Westerveld et al. Radioth and Oncology 2013

D_{2cm3} and $D0.1_{cm3}$ for OAR are recommended

A. for the vagina
B. for the bladder only
C. for rectum, sigmoid, bladder

General principles for reporting of physical and equieffective EBRT and BT dose (ICRU/GEC ESTRO report 88)

Physical dose and number of fractions is assessed for target, OARs, dose points:

- BT

- EBRT

Total equi-effective dose (EQD2) is calculated according to the linear quadratic model through the following steps:

- BT EQD2 for each fraction
- Total BT EQD2
- Total EBRT EQD2
- Accumulated total EBRT+BT EQD2*

**Based on current assumptions outlined in ICRU 88 chapter 9*

Reporting of radiobiological parameters:

α/β values for tumour and OARs*

In addition $T_{1/2}$ and recovery model for LDR and PDR treatments*

*At present: α/β=3 Gy for late effects in OAR and 10 Gy for tumour, and $T_{1/2}$=1.5h

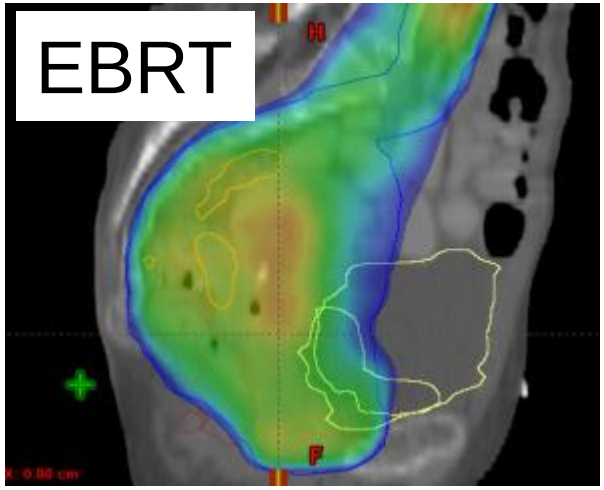
Pelvic EBRT (elective) + BT

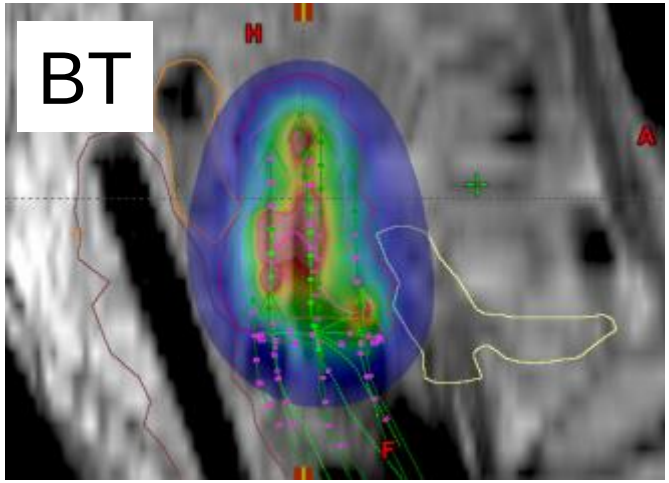
- **Elective target volume and CTV-T:**
  - **Normally homogeneous dose within 95%-107% of PD**

Recommended assessment of total EQD2 dose:

Target (HR CTV-T): $D90_{EQD2}$ **(total) =** PD_{EQD2}**(EBRT) +** $D90_{EQD2}$**(BT)**

OAR: $D_{2cm3,\ EQD2}$ **(total) =** PD_{EQD2}**(EBRT) +** $D_{2cm3,\ EQD2}$ **(BT)**





Calculation of EQD2 in spreadsheet

- **EBRT+BT**
- **EQD_2 calculations**
  - **Tumor: α/β = 10 Gy**
  - **OAR: α/β = 3 Gy**
  - **T½ = 1.5 h**

DVH analysis of MR-guided intracavitary PDR brachytherapy

Pt. ID								
Optimized plan	Variable	Unit	BT_1	BT_2	BT_3	Sum BT	EBRT+BT
	Date		29-12-06	05-01-06	12-01-06	*Mean*	*Stddev*
Applicator	Tandem length	mm	50	50	50		
	Ring diameter	mm	30	30	35		
Time/dose pattern	Number of pulses	no.	10	10	10		
	Puls duration	min	24	24	7		
	Puls interval	min	36	36	53		
	Source strength factor		266	284	94		
	Total treatment time	sek	5310	5128	4268	14706	
	TRAK (Gy at 1m)	cGy	0,60	0,58	0,48	1,66	
TUMOR	Prescribed Dose (PD)	Gy	10,0	10,0	10,0	30,0	80,0
α/β (Gy) = 10,0	**PD_{iso} (EQ2)**	Gy	11,2	11,2	11,2	33,6	83,6
T½ (h) = 1,5	Volume of PD	cm^3	89,3	86,2	66,3	*80,6*	*10,2*
EBRT dose 50,0	PD*2	Gy	20,0	20,0	20,0		
EBRT fx 25	**$PD*2_{iso}$ (EQ2)**	Gy	28,1	28,1	28,3	84,5	134,5
EBRT EQ2 50,0	Volume of PD*2	cm^3	32,7	30,4	22,9	*28,7*	*4,2*
	PD Point-A level left	mm	21,1	19,6	15,4	*18,7*	*2,4*
	PD Point-A level right	mm	19,4	19,2	16,5	*18,4*	*1,3*
Point-A	Dose point A_{left}	Gy	10,7	9,9	7,4		
	D_{iso} point A_{left} (EQ2)	Gy	12,1	11,0	7,7	30,9	80,9
	Dose point A_{right}	Gy	9,6	9,3	8,1		
	D_{iso} point A_{right} (EQ2)	Gy	10,6	10,2	8,6	29,4	79,4
	Dose point A_{mean}	Gy	10,1	9,6	7,7		
	D_{iso} point A_{mean} (EQ2)	Gy	11,4	10,6	8,2	30,1	80,1
Clinical tumor size	Width	mm	40	40	40		
	Height	mm	30	30	25		
	Thickness	mm	40	40	40		
	Clinical tumor volume	cm^3	25,1	25,1	20,9	*23,7*	*2,0*
GTV	Volume of GTV	cm^3	6,6	4,5	4,9	*5,3*	*0,9*
	D100 =MTD	Gy	11,5	15,1	13,9		
	$D100_{iso}$	Gy	13,4	19,2	17,1	49,8	99,8
	D90	Gy	18,5	20,7	18,3		
	$D90_{iso}$	Gy	25,3	29,6	25,0	79,9	129,9
	V100	%	100,0%	100,0%	100,0%	*100,0%*	*0,0%*
HR CTV	Volume of HR CTV	cm^3	29,5	29,1	24,5	*27,7*	*2,3*
	D100 =MTD	Gy	9,4	9,6	9,3		
	$D100_{iso}$	Gy	10,4	10,6	10,2	31,3	81,3
	D90	Gy	13,7	14,9	13,3		
	$D90_{iso}$	Gy	16,7	18,7	16,2	51,7	101,7
	V100	%	99,9%	100,0%	100,0%	*100,0%*	*0,1%*

When adding doses from EBRT and BT You assume for the HR CTV for BT that

A. 50% of the ICRU point dose of EBRT has been applied (or of median EBRT dose)
B. 90% of the dose of the ICRU point dose of EBRT has been applied (or of median EBRT dose)
C. 100% of the dose of the ICRU point dose of EBRT has been applied (or of median EBRT dose)

When adding doses from EBRT and BT You assume for the 2 cm3 for OAR that

A. 50% of the EBRT ICRU point dose has been applied (or of median EBRT dose)
B. 90% of the EBRT ICRU point dose has been applied (or of median EBRT dose)
C. 100% of the EBRT ICRU point dose EBRT has been applied (or of median EBRT dose)

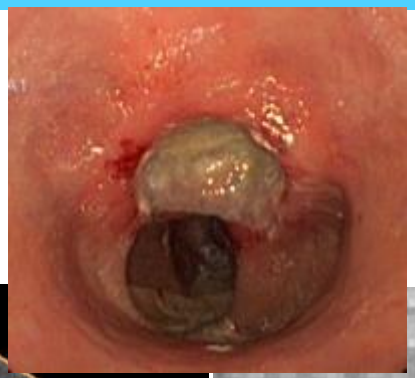
Limitations of adding doses according to „ICRU point-3D model“ both for CTV and OAR

- Non-homogenous dose distribution EBRT
  e.g. IMRT, VMAT…
- Parametrial boost
- Lymph node boost
- Limitations of the linear-quadratic model

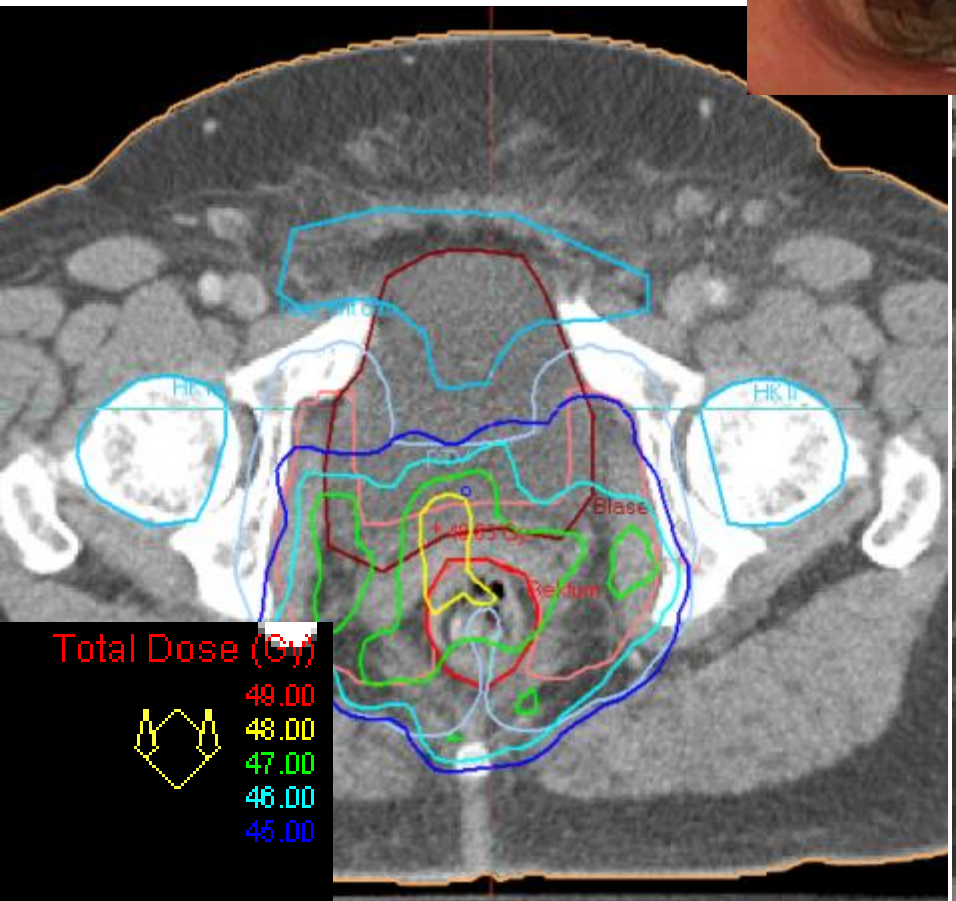
- Future solution for complex adding doses….

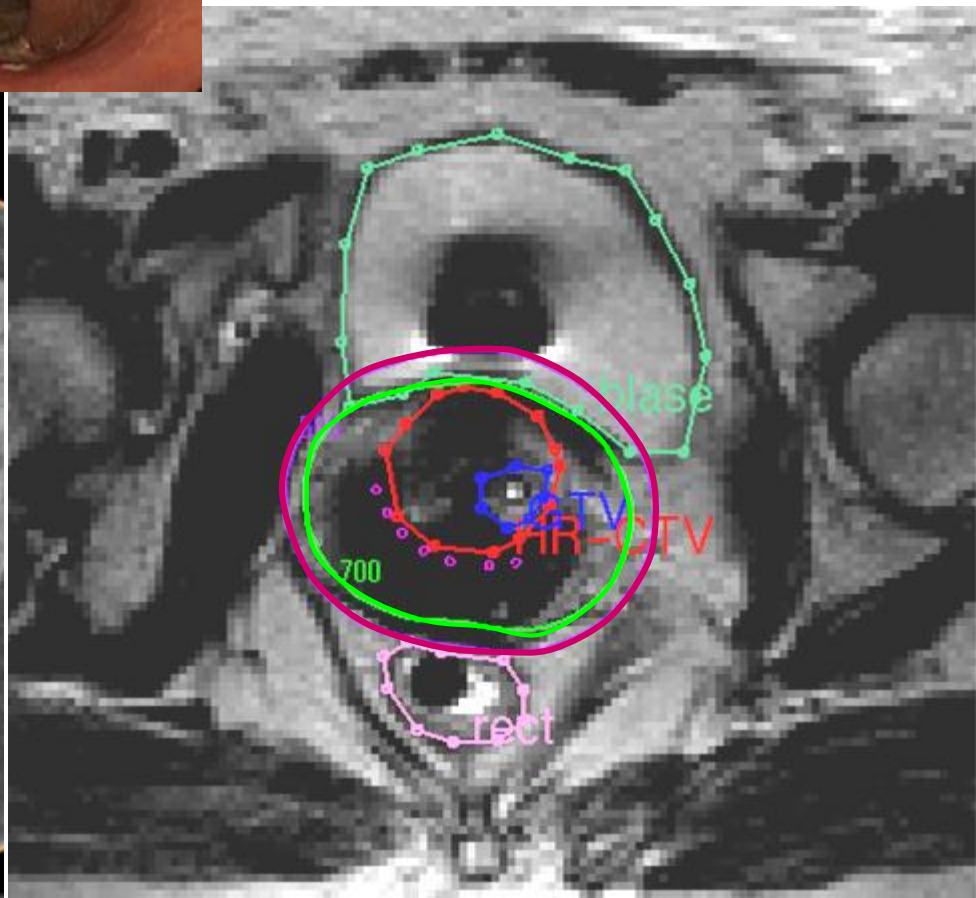
How could this happen?

D2cc = 65.7 Gy EQD2$_{(\alpha/\beta=3)}$

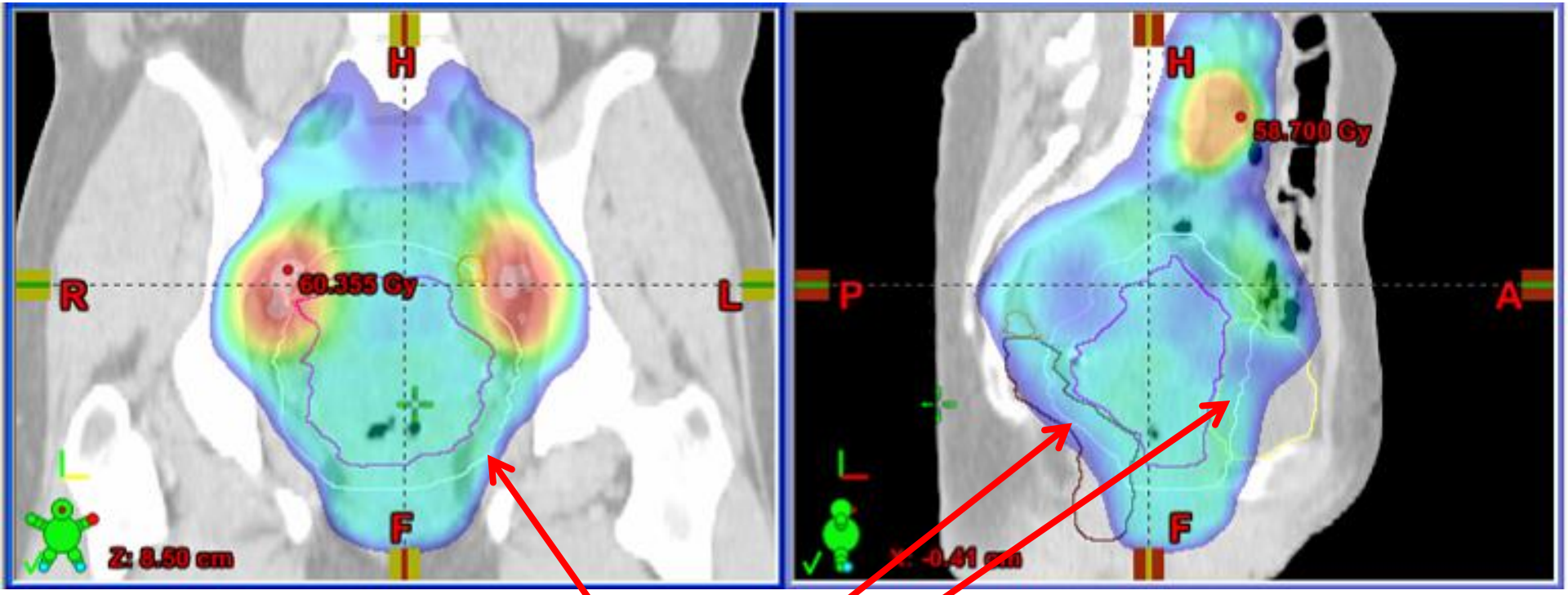


D2cc = 79.2 Gy EQD2$_{(\alpha/\beta=3)}$

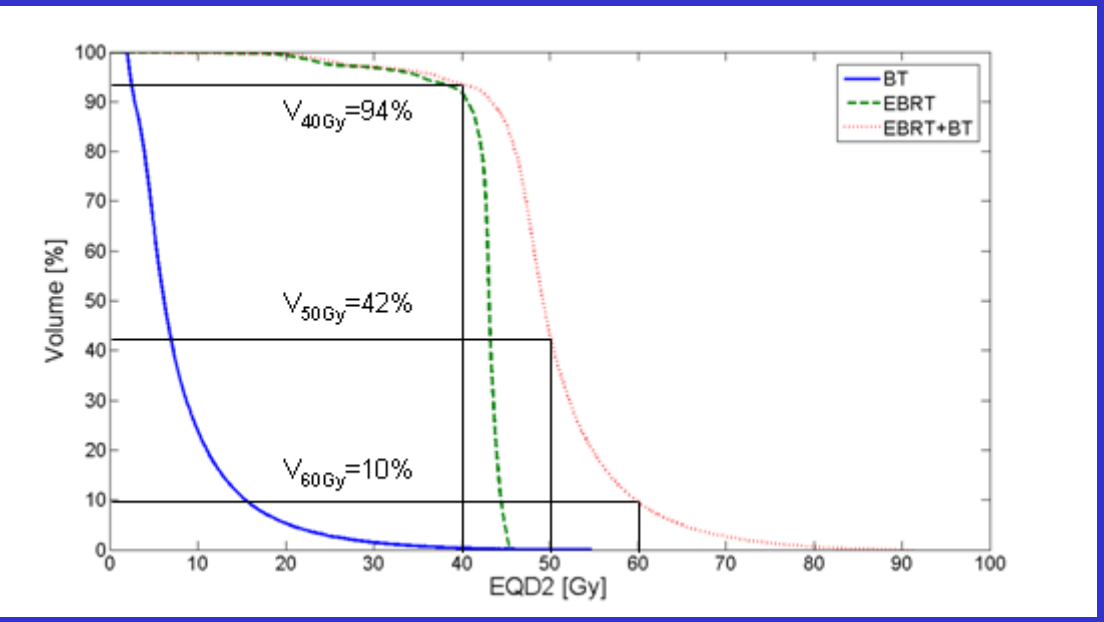


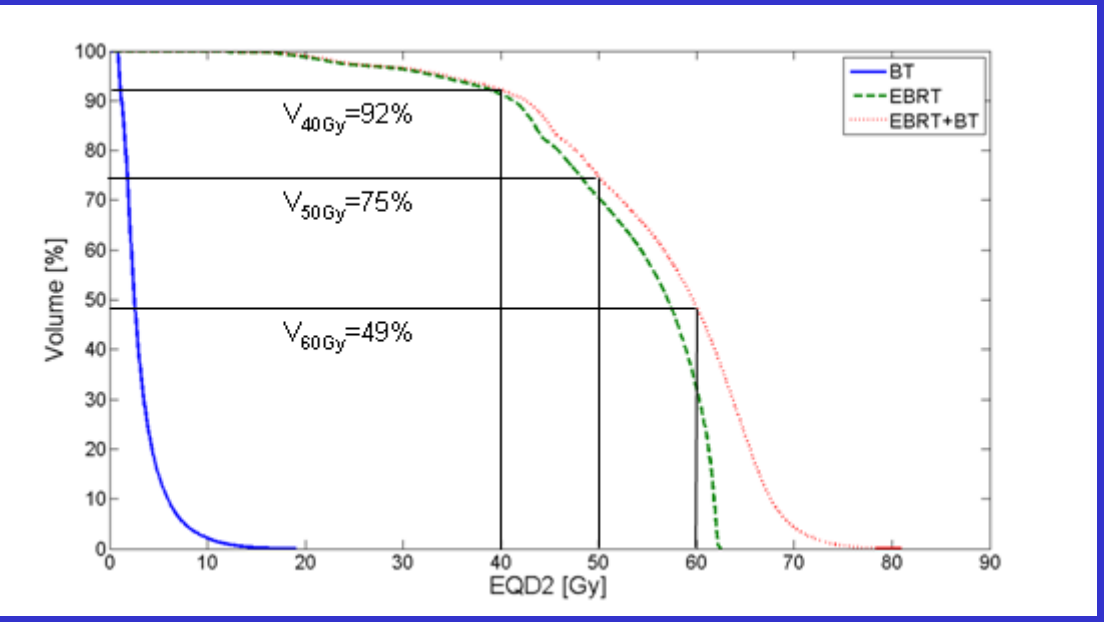


Be aware of IMRT hot spots in the BT region!



Homogenous volume for inverse dose planning





DVHs for different contributions of EBRT and BT *and* specific morbidity endpoints

ICRU/GEC ESTRO report 89 Fig. 8.8

FROM PLANNING AIMS TO PRESCRIPTION

Traditional concepts:

"when prescribing to a target, the prescription dose is the planned dose to cover this target as completely as possible."

or

prescription to a 100% isodose which is "to cover" the target volume"

Need for common terminology according to ICRU reports on proton treatment and IMRT

- **Planning aim dose**
  - **Set of dose and dose/volume constraints for a treatment**
- **Prescribed dose**
  - **Finally accepted treatment plan (which is assumed to be delivered to an individual patient)**
- **Delivered dose**
  - **Actually delivered dose to the individual patient**

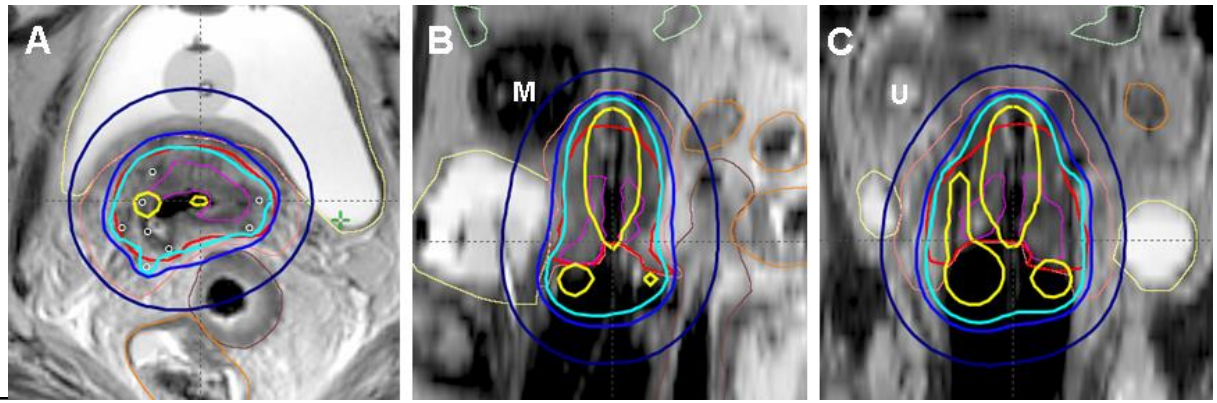
Planning aim and prescription dose

- **Planning aim: what you want to obtain**
- **Prescribed dose: what you decide to treat**

Case 6

Appendix,

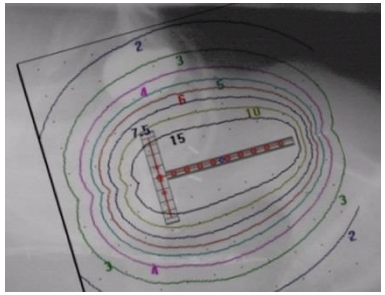
ICRU 89



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

Planning aim and prescription dose

- **Planning aim: what you want to obtain**
- **Prescribed dose: what you decide to treat**



Example 2

Structure	Dose parameter	Planning aim, Gy	Prescribed dose Gy
Target	Point A	7Gy	6.5Gy
Bladder	ICRU point	≤ 7Gy	6.8 Gy
Rectum	ICRU point	≤ 75% of 7Gy	5.3 Gy

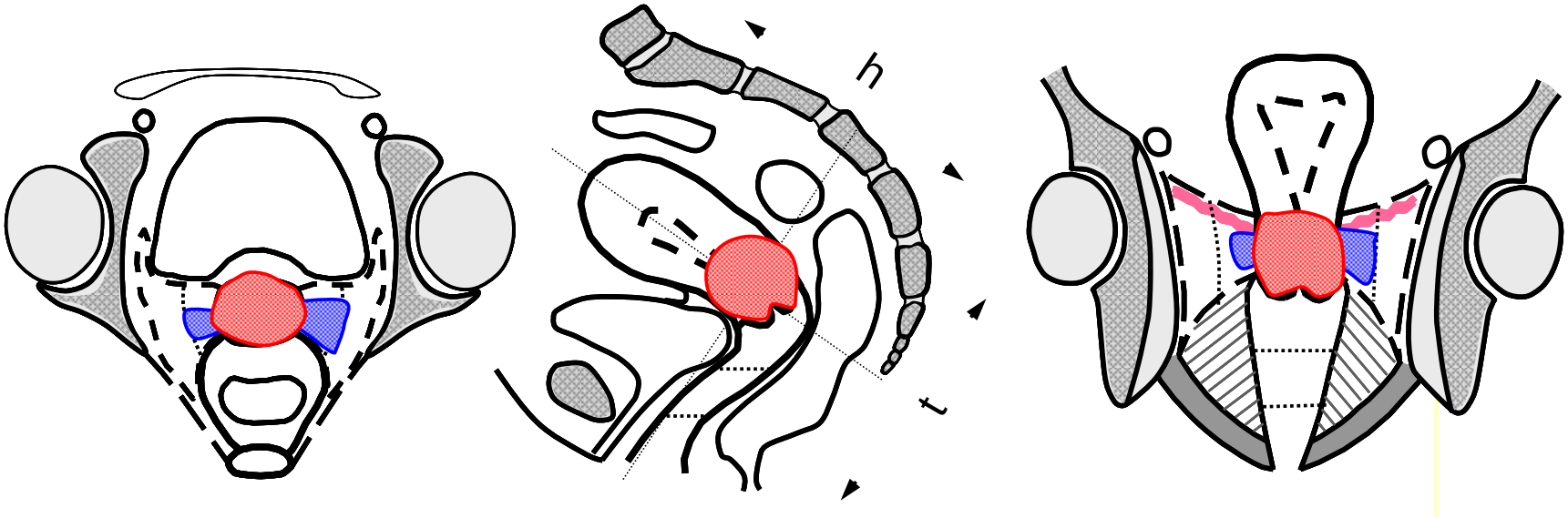
Example

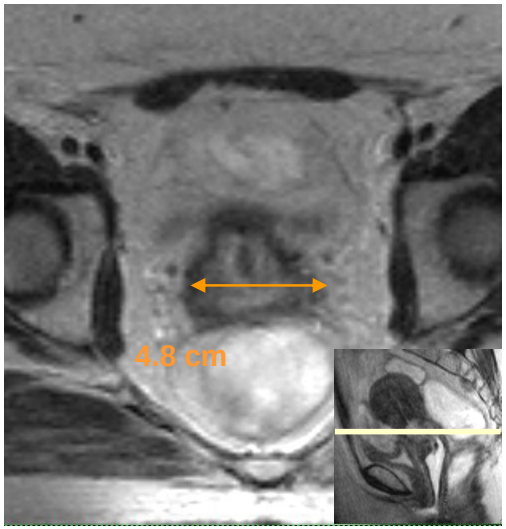
(Appendix case 5, ICRU 89)

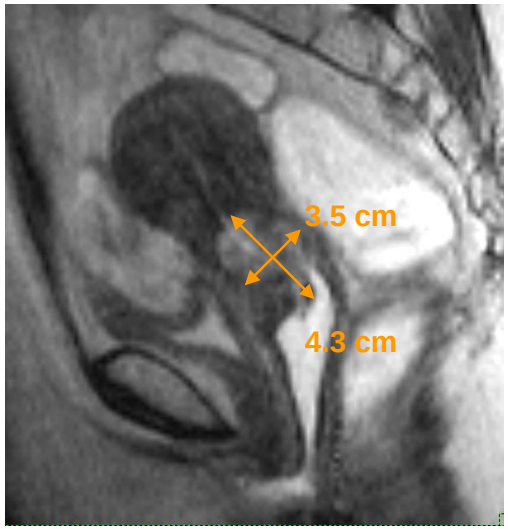
Table A.5.3. Treatment planning aim and prescribed doses.

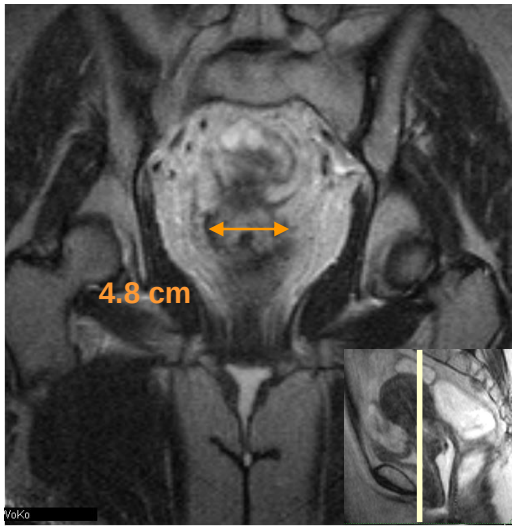
			Planning aim (Gy)	Prescribed dose (Gy)
CTV_{HR}	D_{90}	$EQD2_{10}$	≥85	92.3
Bladder	D_{2cm^3}	$EQD2_3$	≤90	80.6
Rectum	D_{2cm^3}	$EQD2_3$	≤70	64.3
Sigmoid	D_{2cm^3}	$EQD2_3$	≤75	51.7

Example – disease at BT (Appendix case 5, ICRU 89)









Example (Appendix case 5, ICRU 89)

Dimensions and volumes of GTVs and CTVs at diagnosis and at brachytherapy

		Diagnosis	BT1+2	BT3+4
Clinical dimensions GTV	w * t (mm)	60 *40	-	-
MRI dimensions GTV	w * t * h (mm)	55*40*45	35*35*43	35*35*43
MRI volume GTV	(cm^3)	52	33	33
Clinical dimensions CTV_{HR}	w * t (mm)	-	50*40	50*40
MRI dimensions CTV_{HR}	w * t * h (mm)	-	48*35*43	46*32*41
CTV_{HR}	(cm^3)	-	43	43
CTV_{IR}	(cm^3)	-	88	88
Left parametrium		proximal	proximal	proximal
Right parametrium		proximal	proximal	proximal
Vagina		upper third	not involved	not involved
Bladder		not involved	not involved	not involved
Rectum		not involved	not involved	not involved

Example (Appendix case 5, ICRU 89)

Applicators and $EQD2_{10}$ isodose surface volumes

	1st application	2nd application
Nominal tandem length	60 mm	60 mm
Nominal ring diameter	30 mm	30 mm
Number of active needles	3	3
TRAK	2 x 4.3 mGy	2 x 4.2 mGy
60 Gy volume	*262 cm^3*	*250 cm^3*
75 Gy volume	*181 cm^3*	*168 cm^3*
85 Gy volume	*85 cm^3*	*83 cm^3*

Example (dose points) (Appendix case 5, ICRU 89)

			1st application		2nd application		Total dose
			BT1	BT2	BT3	BT4	EBRT+BT
			(Gy)	(Gy)	(Gy)	(Gy)	(Gy in EQD2)
Point	A	right	x*	x*	x*	x*	x*
		left	7.0	7.0	7.8	7.8	87.2
Pelvic Wall	Point	right	1.1	1.1	1.0	1.0	48.2
		left	1.0	1.0	1.1	1.1	48.2
Bladder	ICRU	point	2.8	2.8	5.5	5.5	68.4
Recto-Vaginal	ICRU	point	2.4	2.4	3.5	3.5	57.5
Vagina	5 mm	right	7.5	7.5	7.6	7.6	106.9
		left	7.3	7.3	7.2	7.2	102.7
	PIBS**	+2 cm	5.9	5.9	6.3	6.3	88.8
		0 cm	2.6	2.6	2.4	2.4	53.4
		- 2 cm	0.6	0.6	0.7	0.7	7.3

Example (DVH parameters) (Appendix case 5, ICRU 89)

		1st application		2nd application		Total dose
		BT1	BT2	BT3	BT4	EBRT+BT
		(Gy)	(Gy)	(Gy)	(Gy)	(Gy in EQD2)
GTV_{res}	D_{98}	10.1	10.1	10.7	10.7	115.0
	D_{90}	11.9	11.9	12.4	12.4	134.0
CTV_{HR}	D_{98}	6.5	6.5	6.7	6.7	80.8
	D_{90}	7.9	7.9	8.1	8.1	92.3
	D_{50}	11.7	11.7	11.5	11.5	127.8
CTV_{IR}	D_{98}	3.7	3.7	4.1	4.1	62.3
	D_{90}	4.6	4.6	5.3	5.3	69.0
	D_{50}	8.5	8.5	8.7	8.7	97.6
Bladder	$D_{0.1cm^3}$	7.2	7.2	7.2	7.2	102.0
	D_{2cm^3}	5.6	5.6	5.4	5.4	80.6
Rectum	$D_{0.1cm^3}$	4.8	4.8	5.0	5.0	74.2
	D_{2cm^3}	3.8	3.8	3.9	3.9	64.3
Sigmoid	$D_{0.1cm^3}$	1.9	1.9	4.4	4.4	59.9
	D_{2cm^3}	1.5	1.5	2.6	2.6	51.7

Learning Objectives (I)

- 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;

Learning Objectives (II)

- 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.

Applicator Reconstruction, geometry and image fusion

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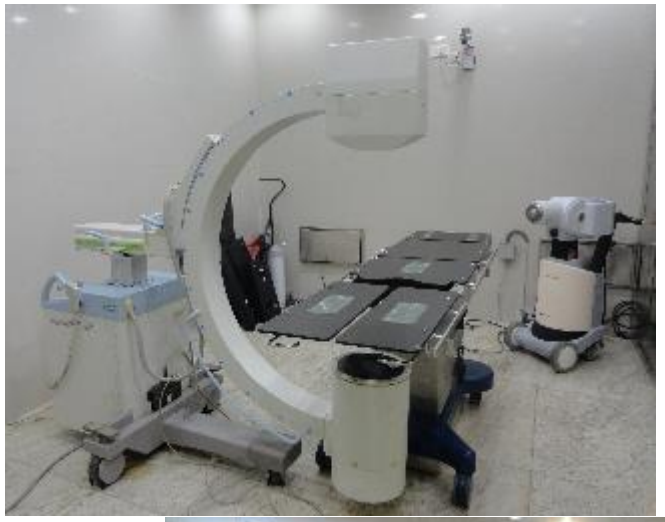
Localization techniques

Conventional simulator, C-arm

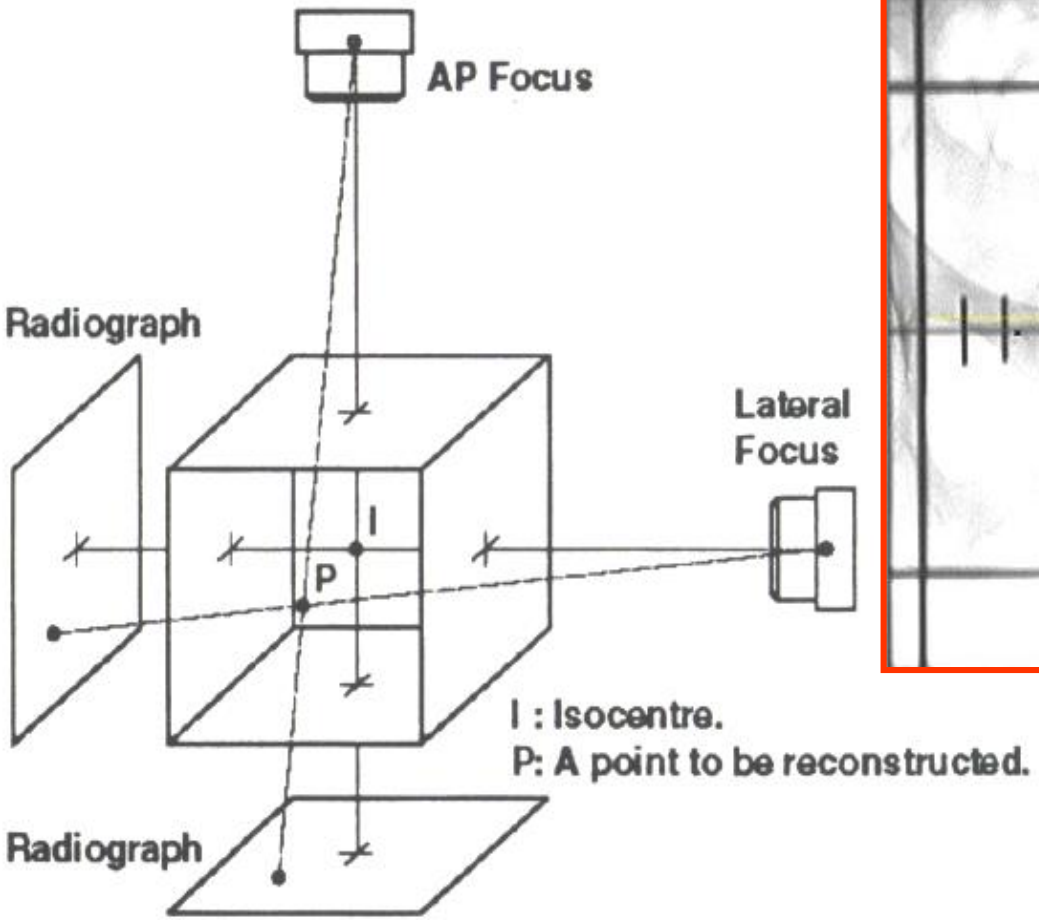
- Orthogonal images
- Semi-orthogonal
- Variable angle
- Stereo-shift

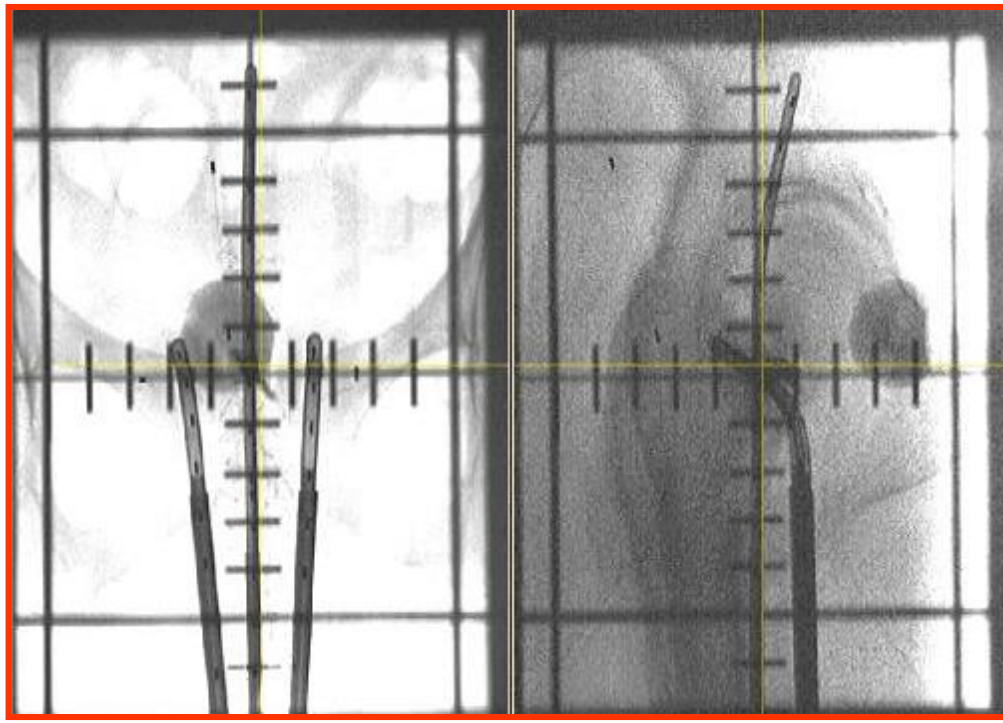


3D sectional images

- CT
- MR

Orthogonal images





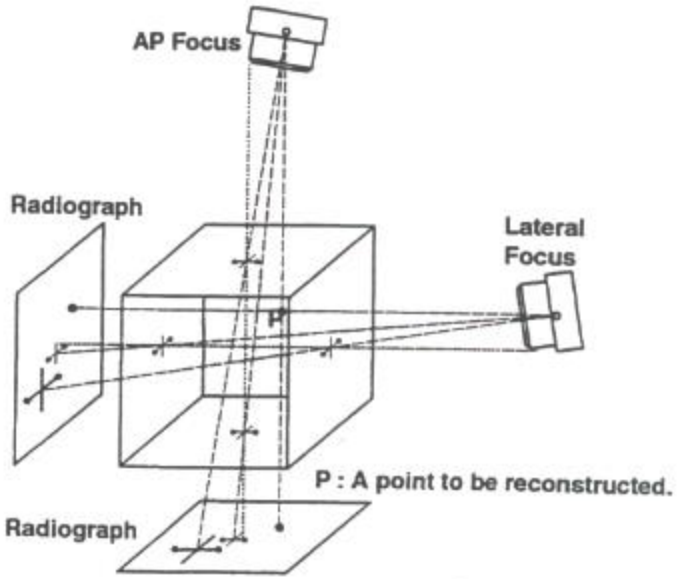
From: Plato user manual

- Magnification = FFD/FAD
- Markers locked
- may not be useful for Ring applicators

Semi-orthogonal

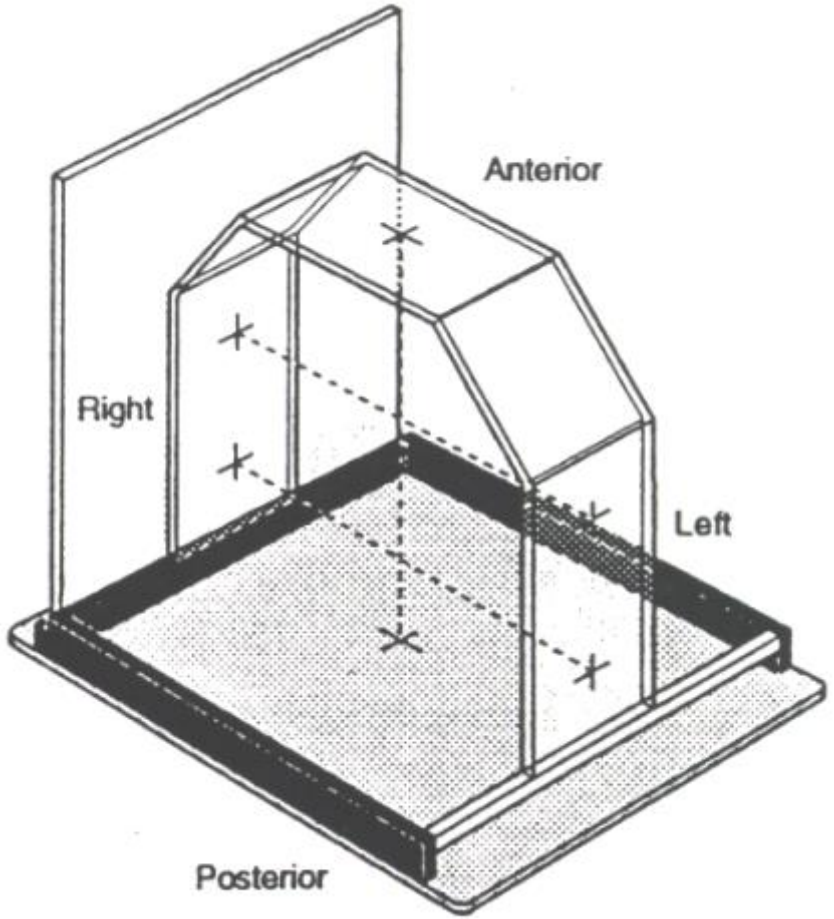
Note

If there is only a portable or mobile radiographic unit available, the semi-orthogonal reconstruction method is the only technique for treatment planning .



Reconstruction Box

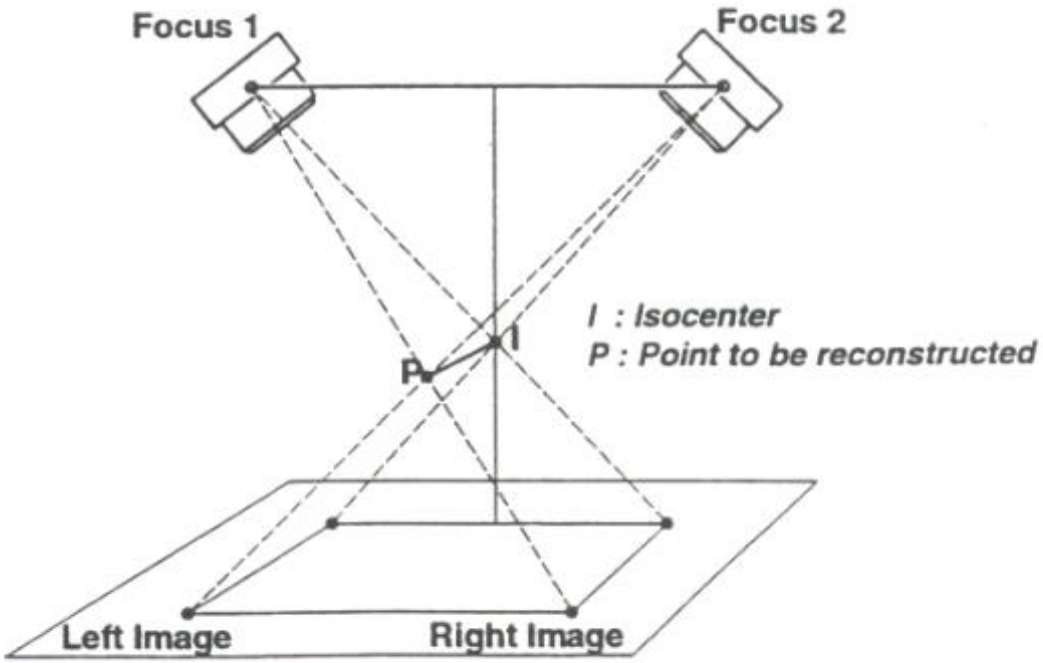
The reconstruction box is constructed with radiopaque initials AP and LAT within the appropriate sides of the box. These initials will appear on the radiograph as a large AP image which corresponds



From: Plato user manual

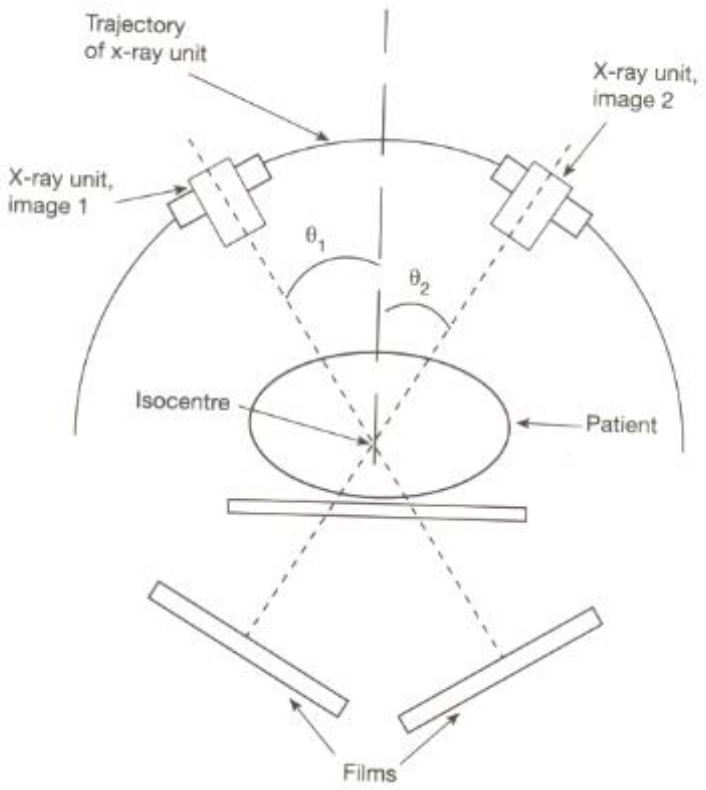
Stereo-shift

This method is particularly useful
when only an X-ray unit is available for localization

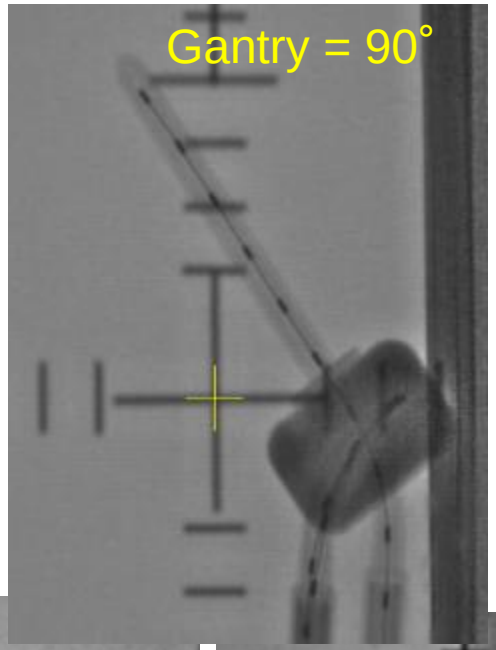


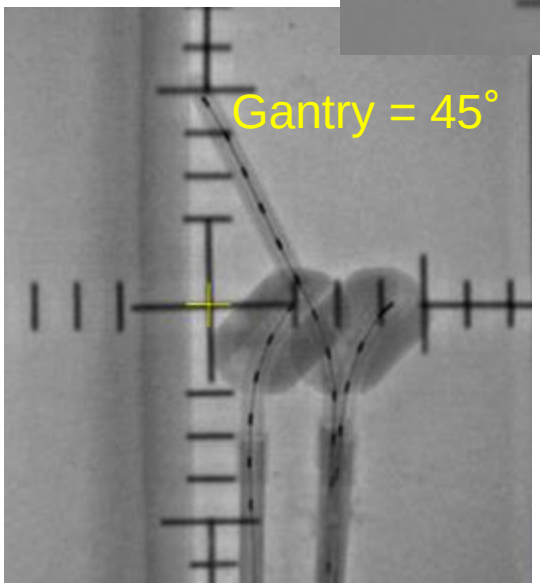
From: Plato user manual

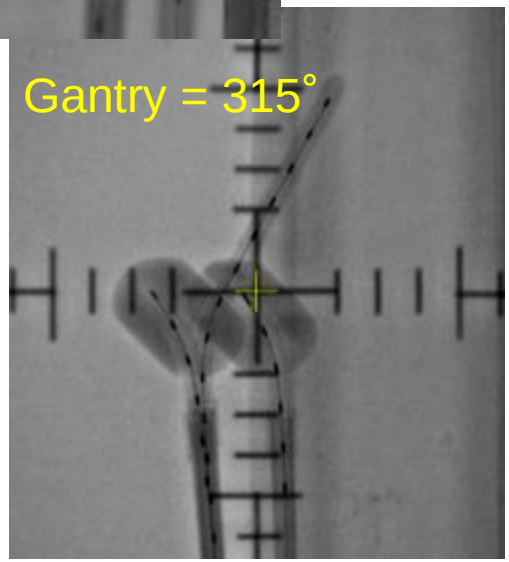
Variable angle



From: Thomadsen “Achieving quality in brachytherapy”, IoP 2000







Reconstruction

- Library plans
- Direct reconstruction
- New reconstruction method

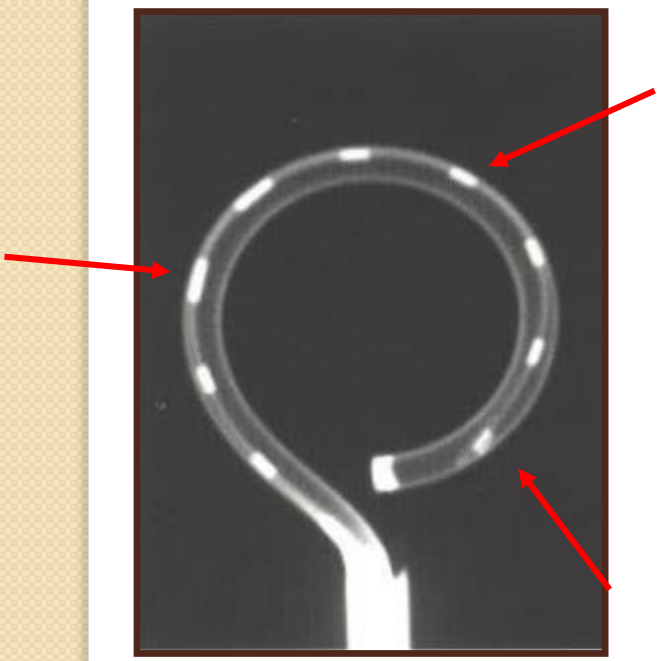
Library plans

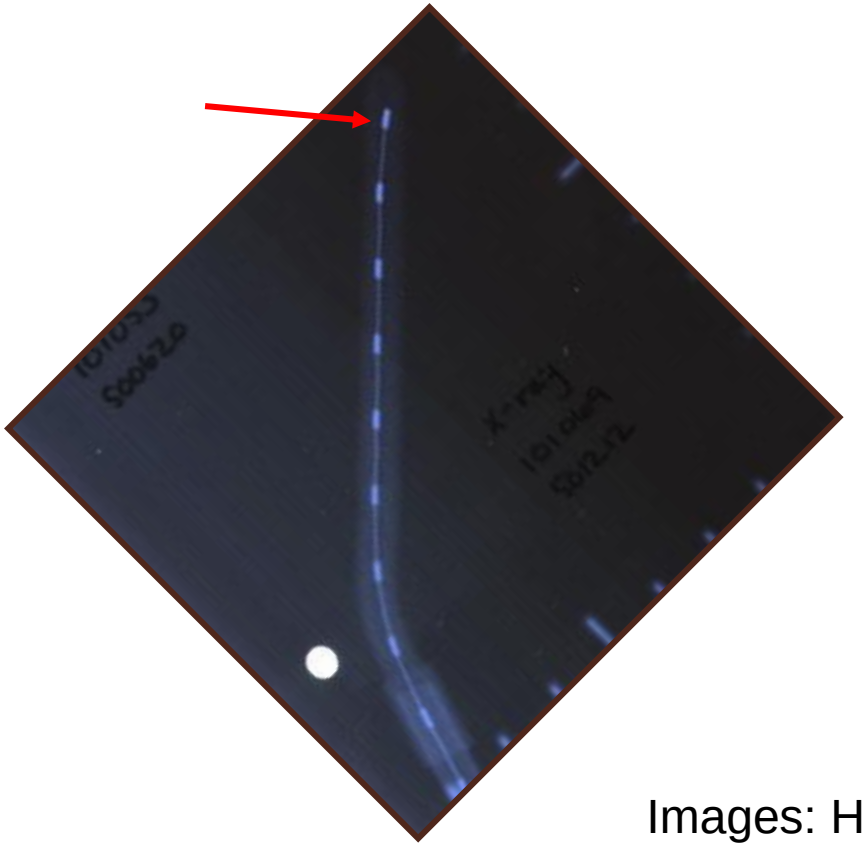
- Accurate compared to other methods
- Used only for rigid applicators (ring)
- A pre-defined library file with the source path geometry is used and imported into the clinical image set.
- Well defined points should be used to merge with the co ordinate system

Producing library plans – 2D radiographs

Needs minimum three well defined points that can be easily recognized in the clinical images.
Points on the x-ray catheters are often used

Example:

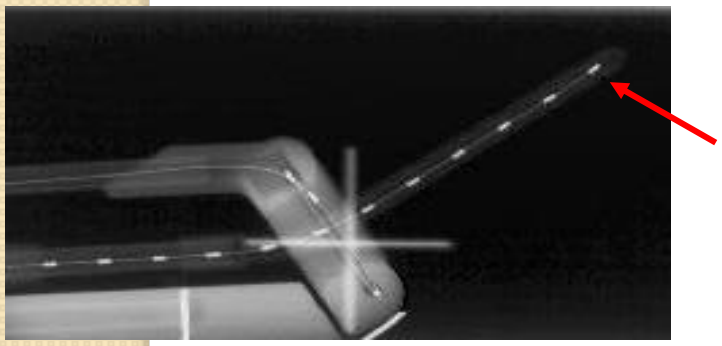


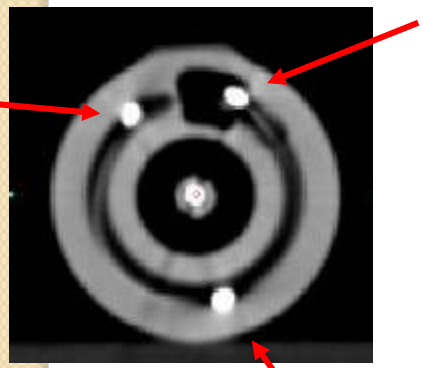


Images: Hellebust

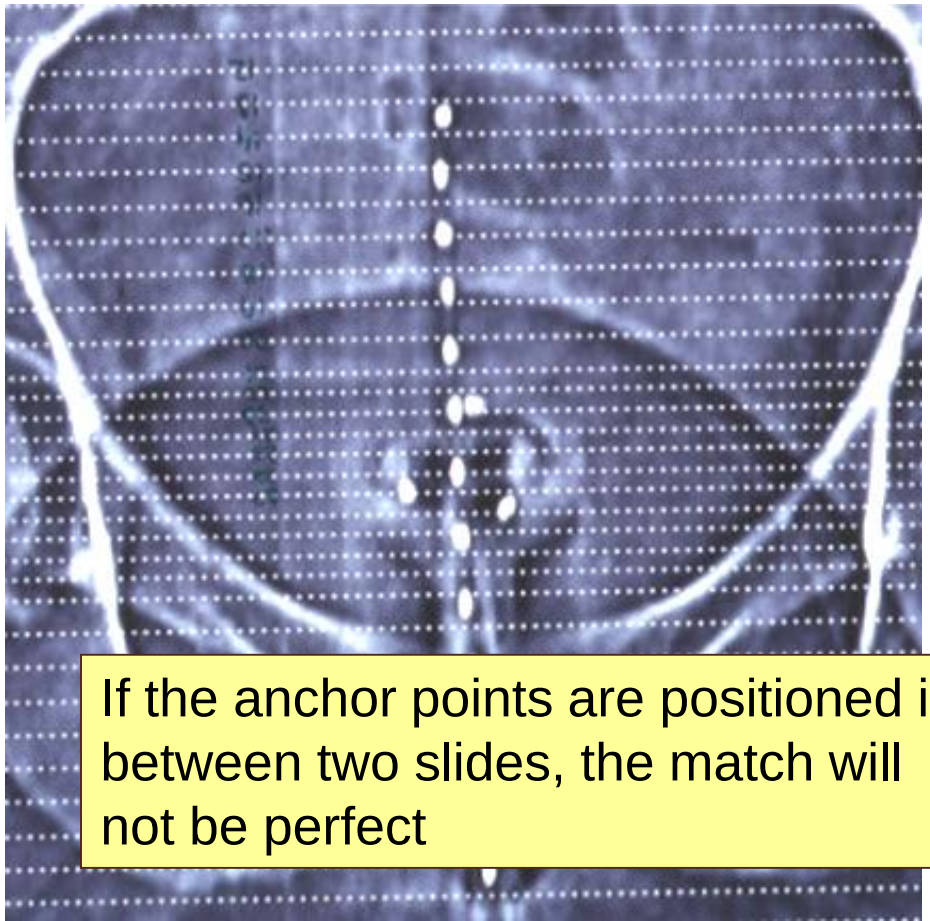
Library plans – 3D sectional images

Requires minimum three well defined points (anchor points) to position the applicator in the 3D study





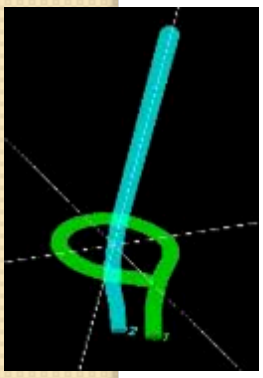
Ack: Hellebust TP

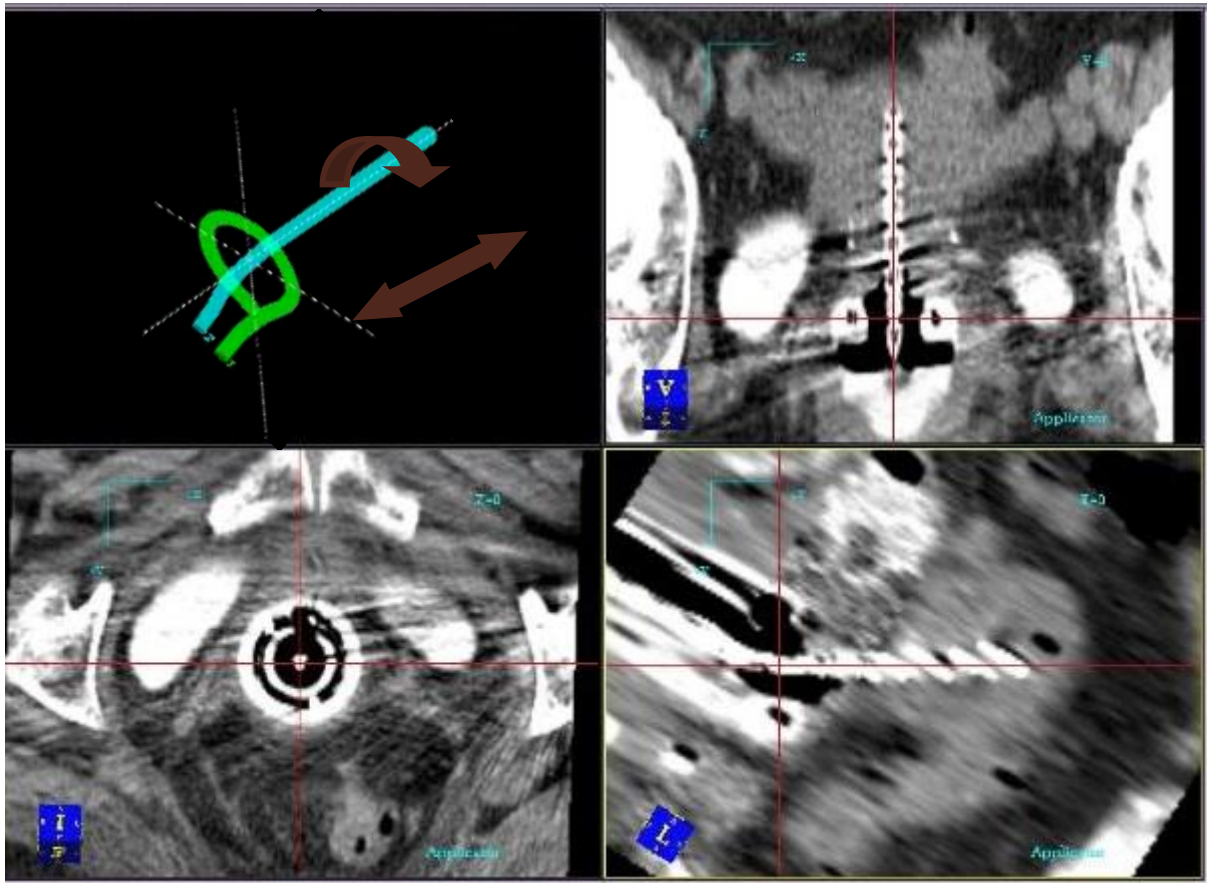


If the anchor points are positioned in between two slides, the match will not be perfect

Library plans – An advantage in image based planning

A facility to rotate and translate the applicator in the 3D study is more optimal

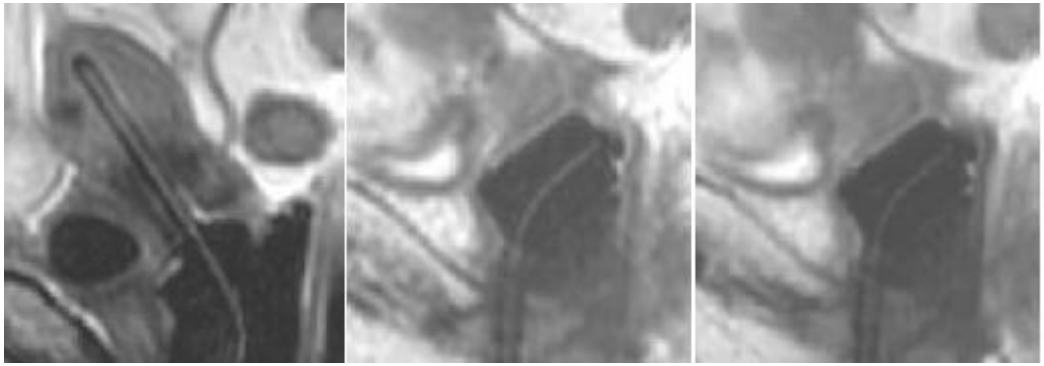




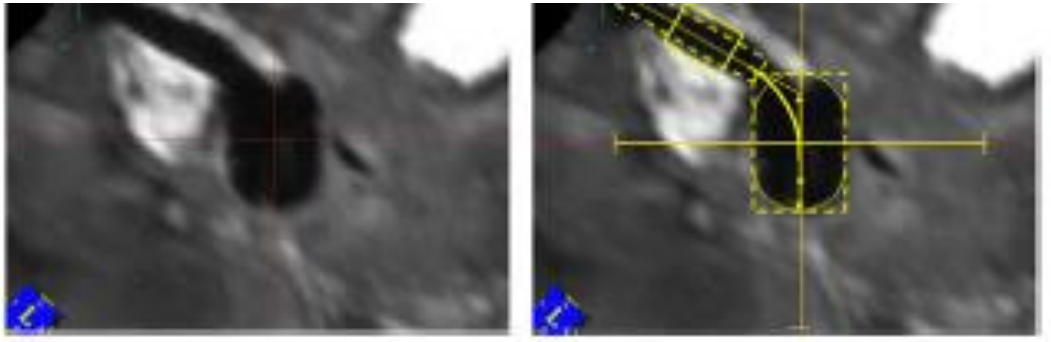
Ack: Hellebust TP

Applicator reconstruction – MPR

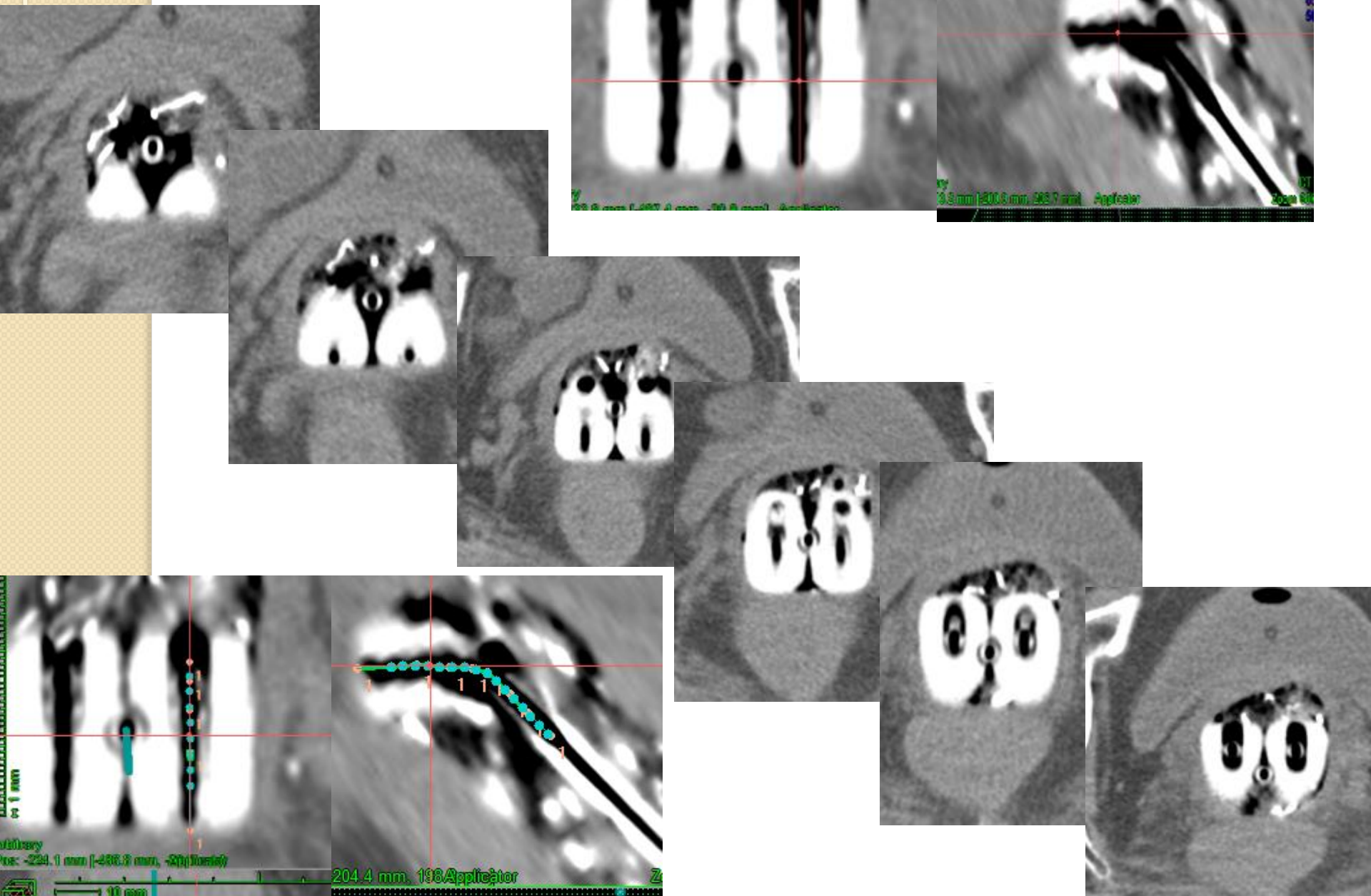
- Clear visualization of the source channels in a single plane.
- Check the geometry of the applicator verified during commissioning.
- Especially useful for curved applicators (ovoid/ring)



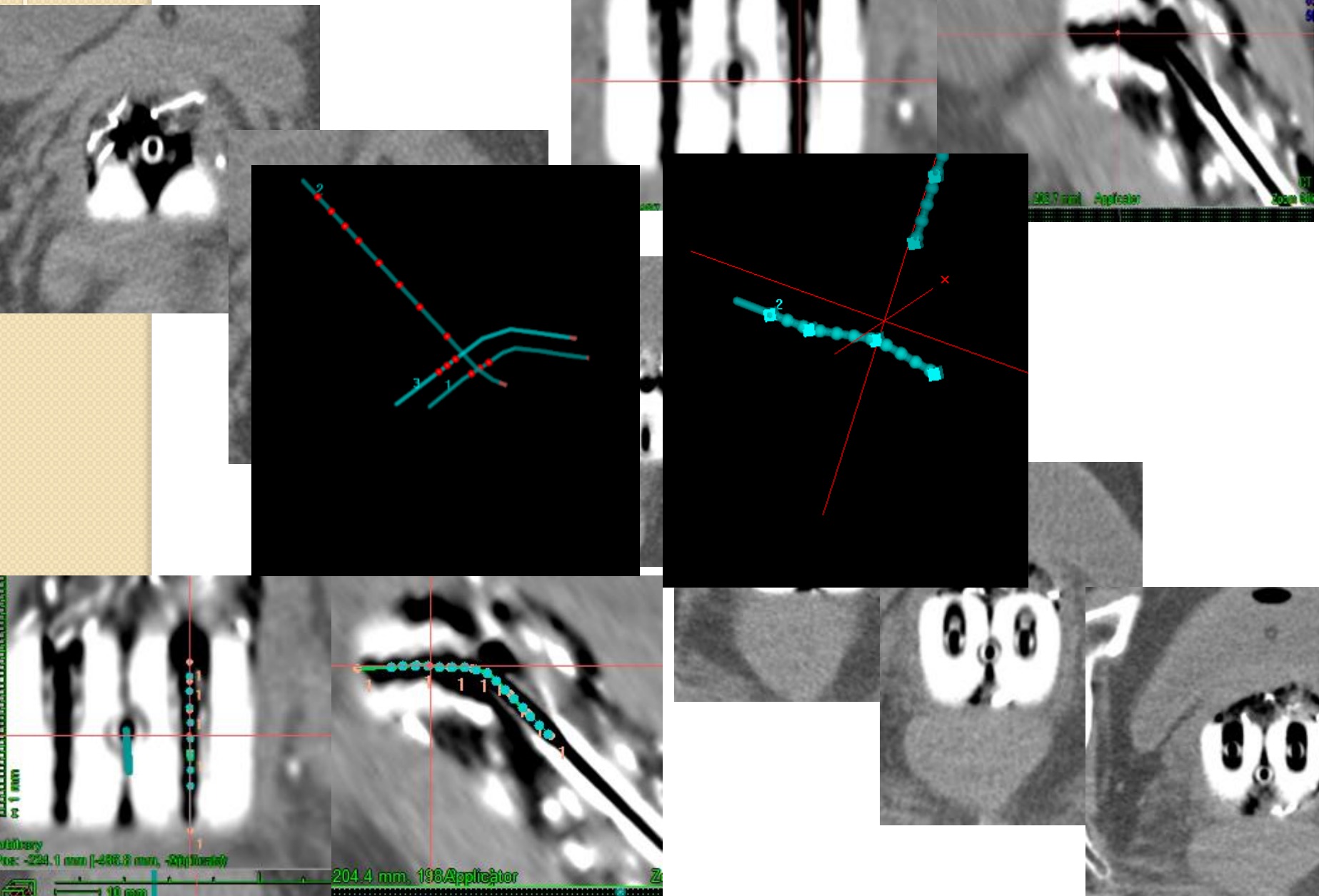
Leeuw et al, RO,2009



MPR- T/O

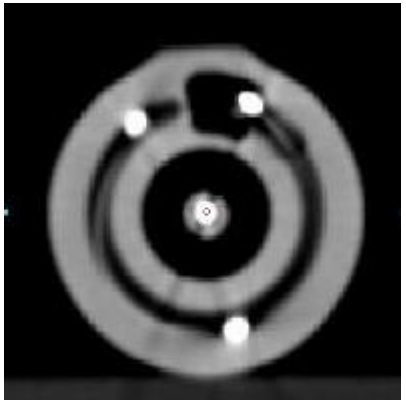


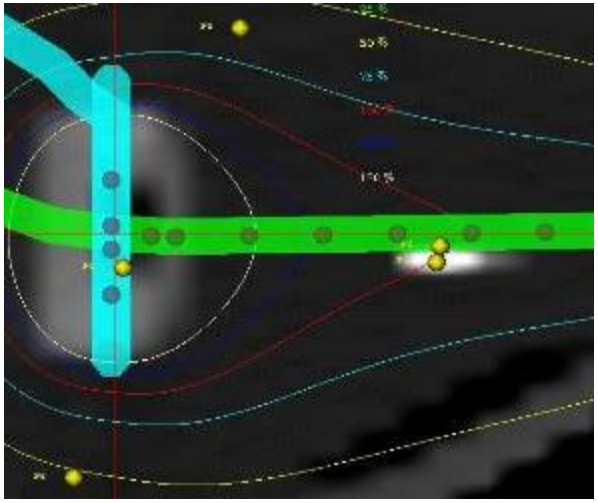
MPR – T/O



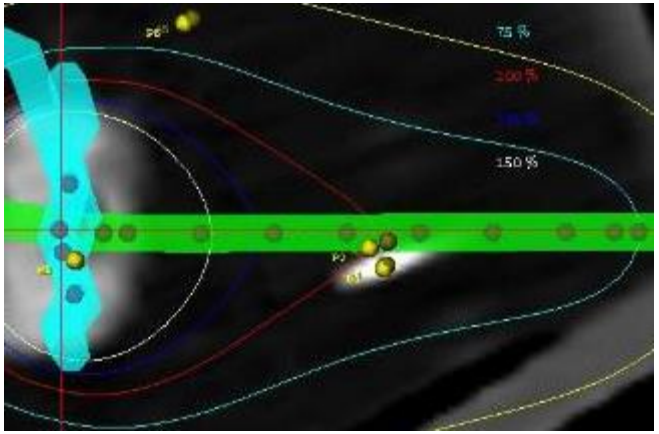
MPR- Ring

Ring in one slice





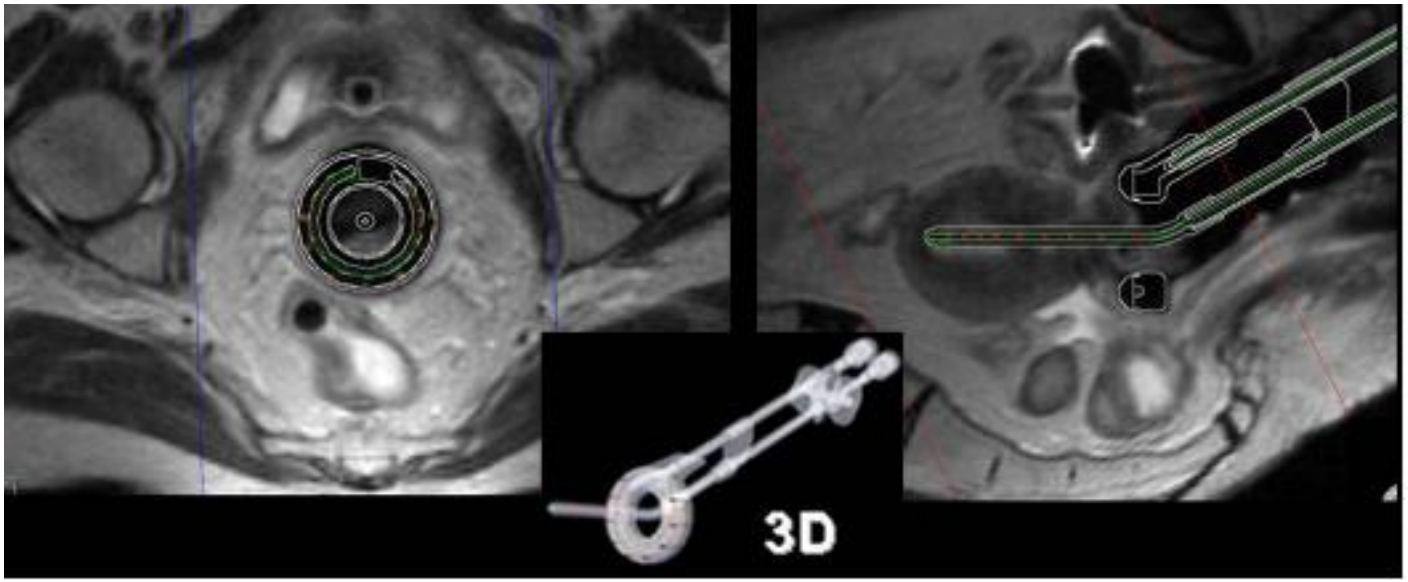
Ring in several slices



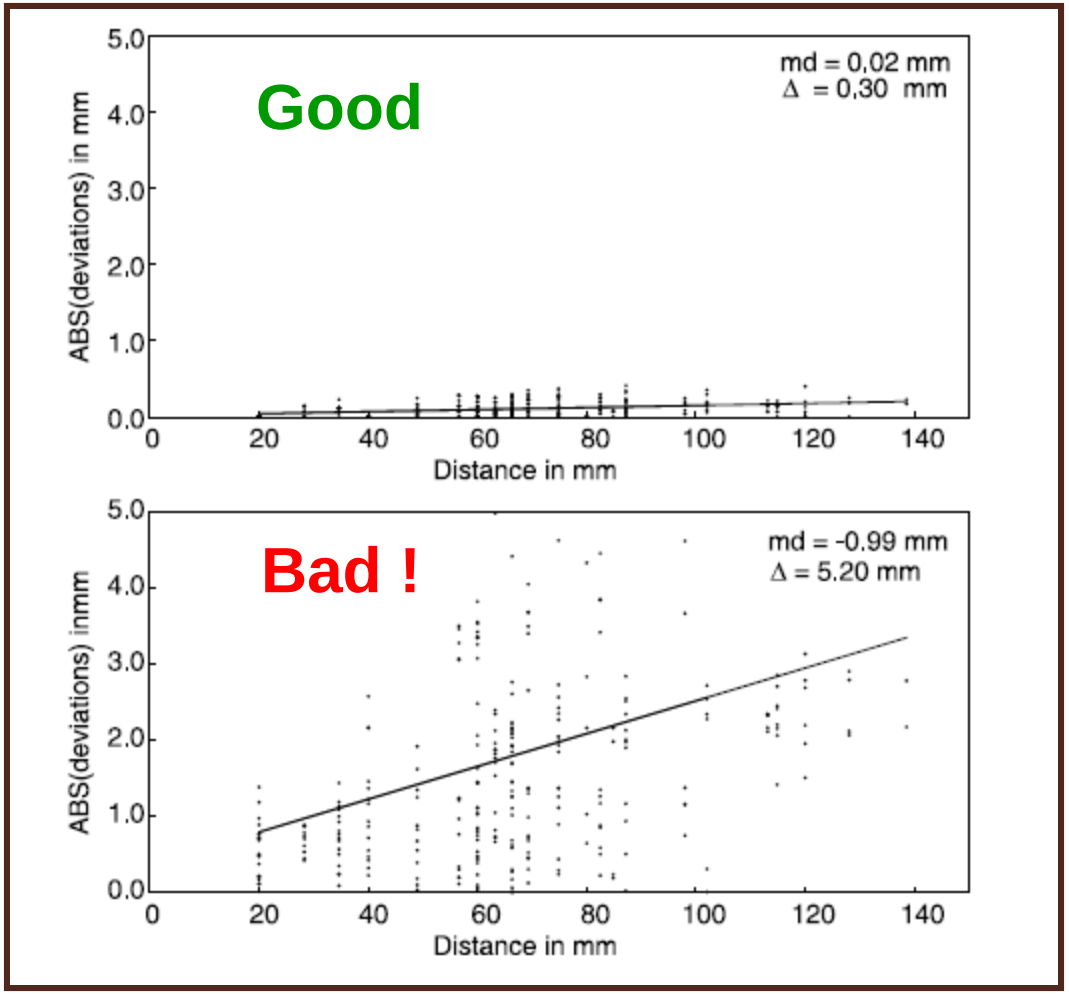
Ack: Hellebust

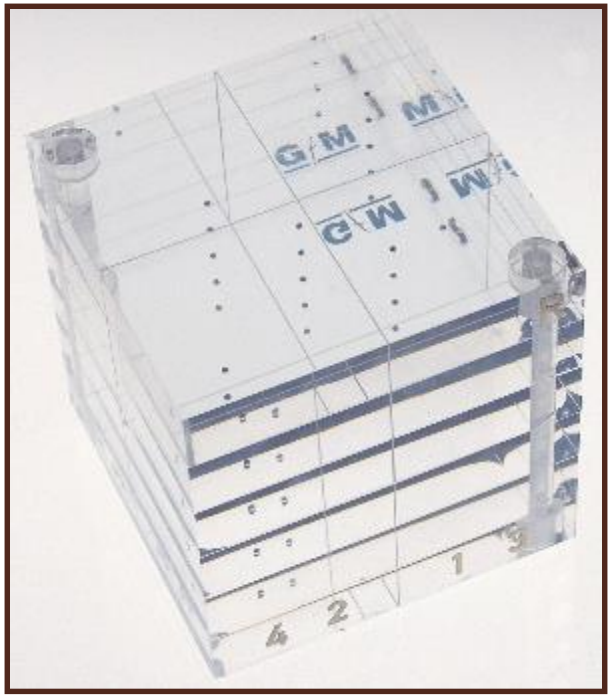
Applicator reconstruction – new method

- Some TPSs contain an applicator library which includes information about the physical outer applicator dimensions, an applicator file can be imported and rotated and translated until it matches the black area in the patient MR images
- Fast, simple, and less prone to reconstruction errors.



Localization – Quality Assurance



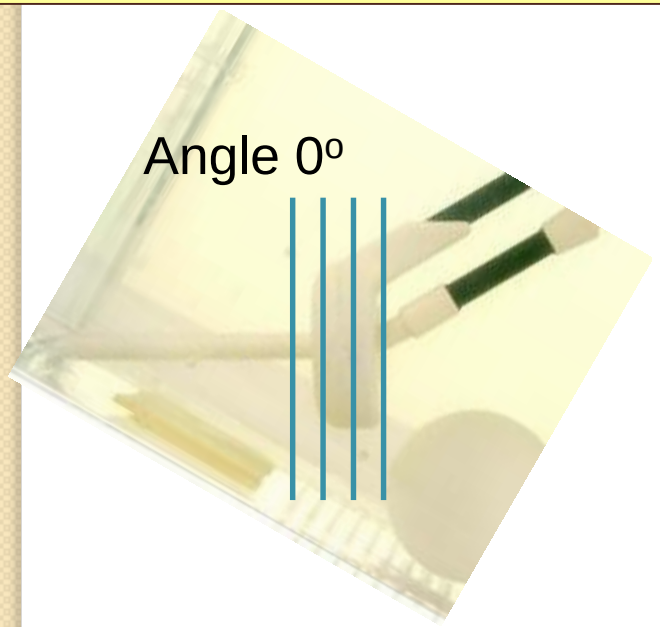


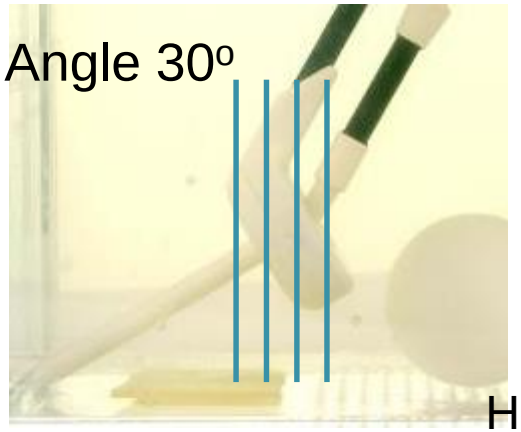
Roué A et al ESTRO-EQUAL audit on geometric reconstruction, R&O, 2006

Reconstruction accuracy, CT

Phantom filled with gel and a ring applicator set, six lead pellets and a table tennis ball

CT scan of the phantom with four different angles





Hellebust et al

Reconstruction accuracy

The ring applicator was reconstructed using three different methods:

- Library plan (LIB) (the markers on the x-ray catheter were used as matching points)
- Reconstructing directly from the CT images (DR)
- Digitising from Multi Planar Reconstruction images (MPR)

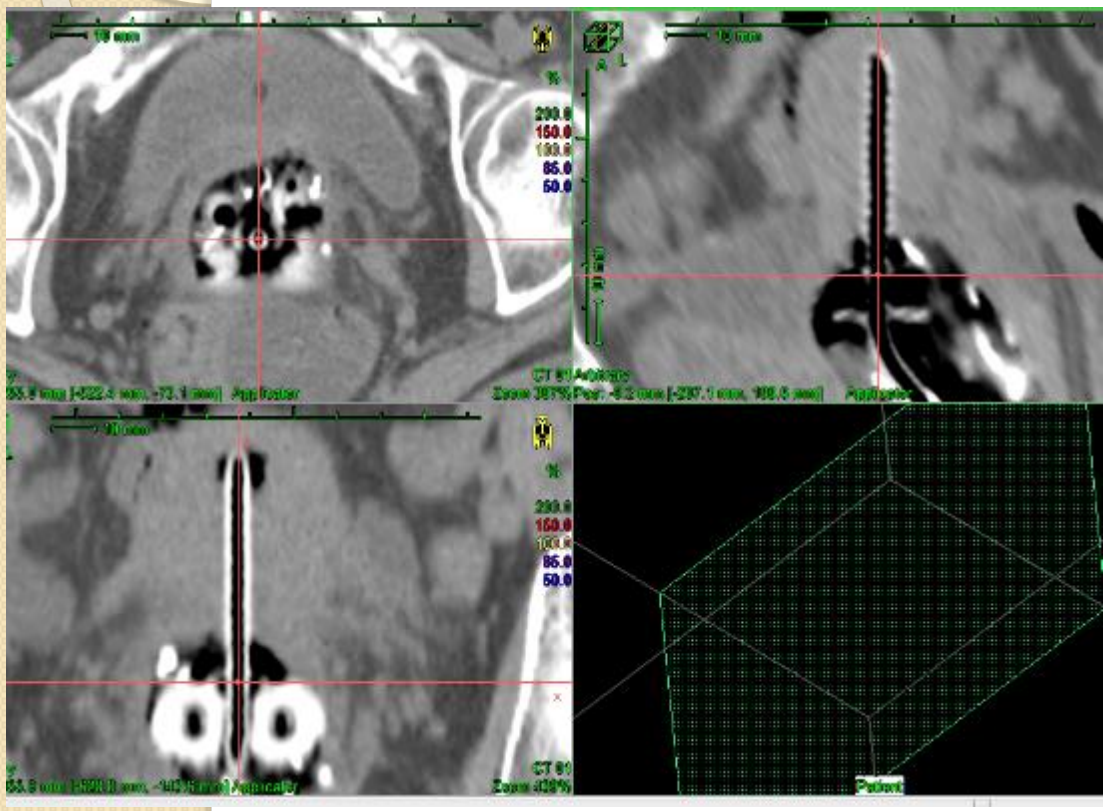
Accuracy, reconstruction method

Point	DR	MPR	LIB
P1	1.27	1.07	0.85
P2	1.63	1.49	1.43
P3	3.70	2.12	2.22
P4	2.82	2.06	1.65
P5	2.16	1.75	2.12
P6	2.78	1.90	1.47

Relative standard deviation

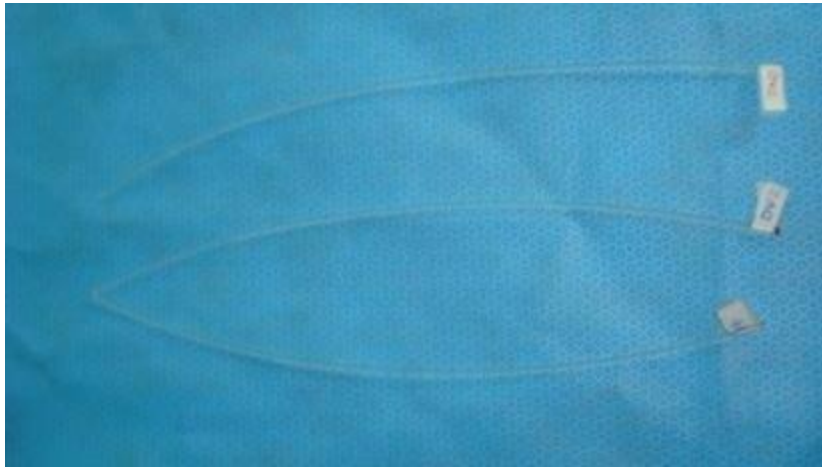
Hellebust et al, PMB 52 (2007)

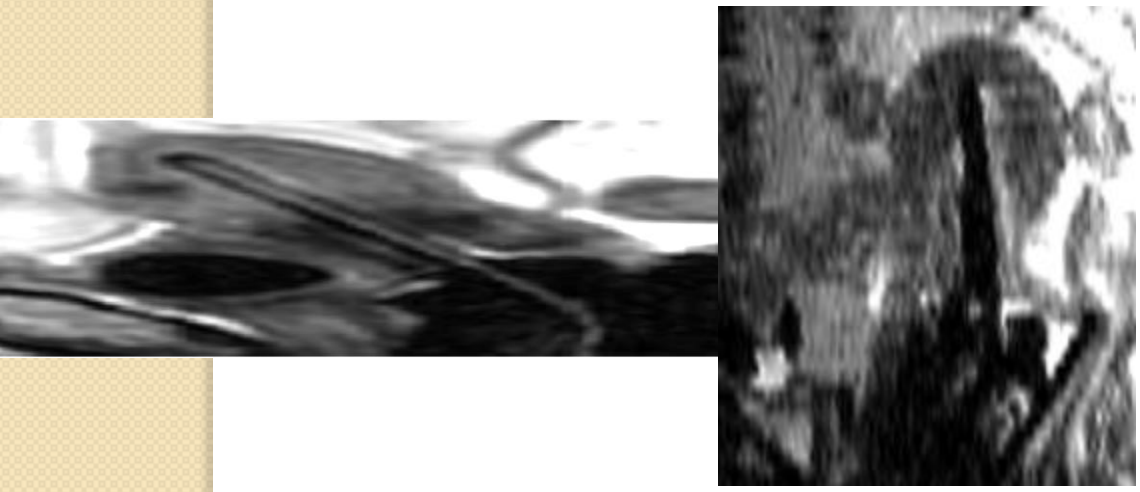
Applicator reconstruction using CT images

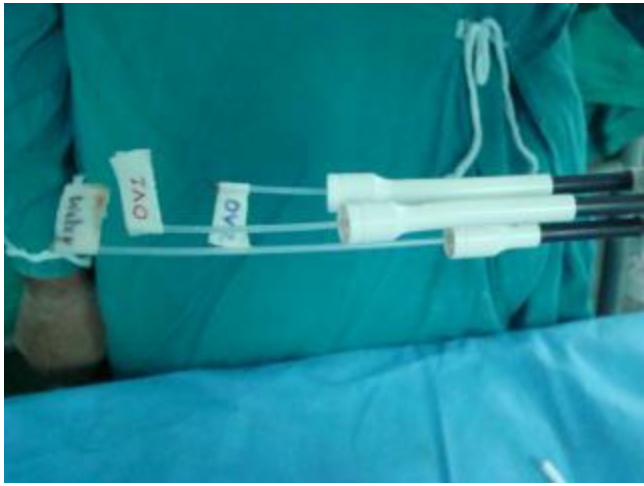


- Easy to visualize source channel
- Need not use the marker

Applicator reconstruction using MR images

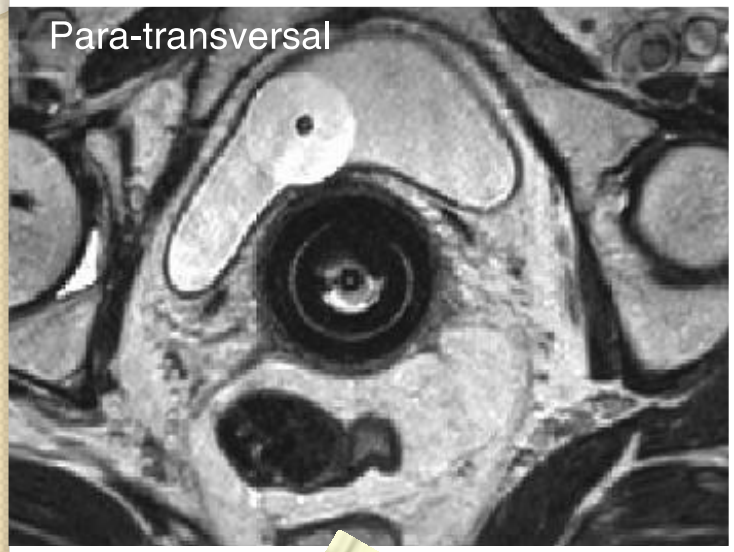


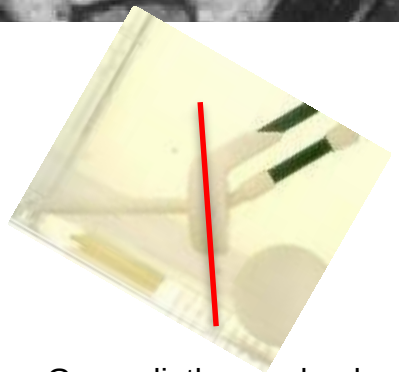




Applicator reconstruction using MR images

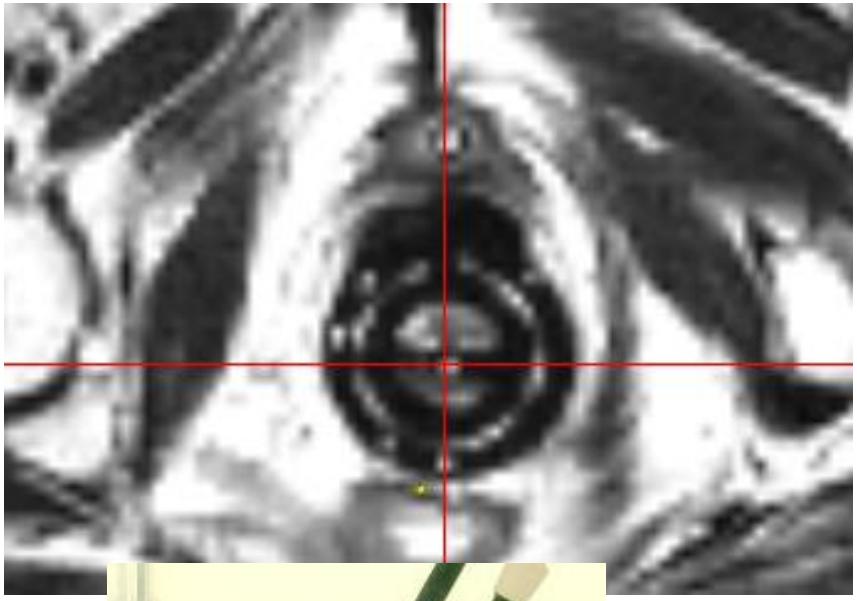
- Para transverse





From Gyn radiotherapy book,
Editor: A viswanathan,
Kirisits C, Erickson B, Potter P

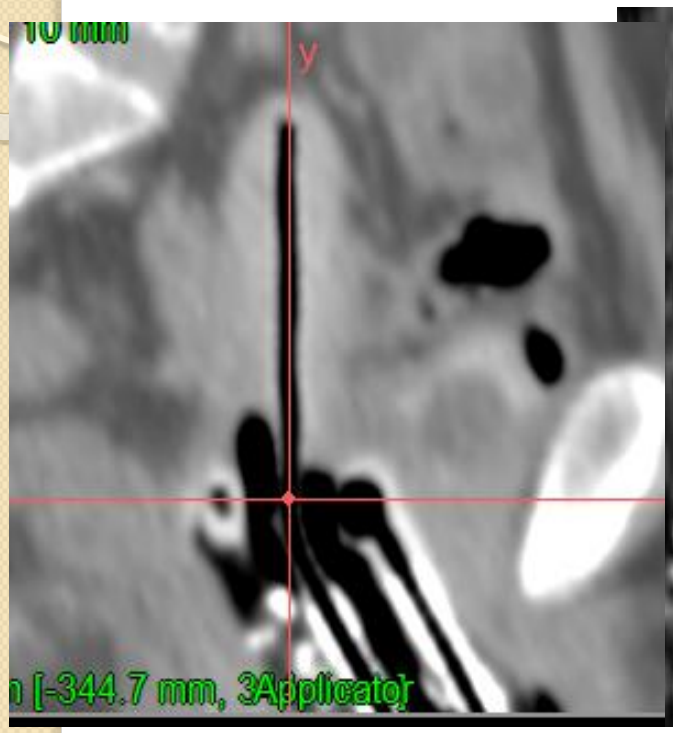
- Transverse (MP Reconstructed)

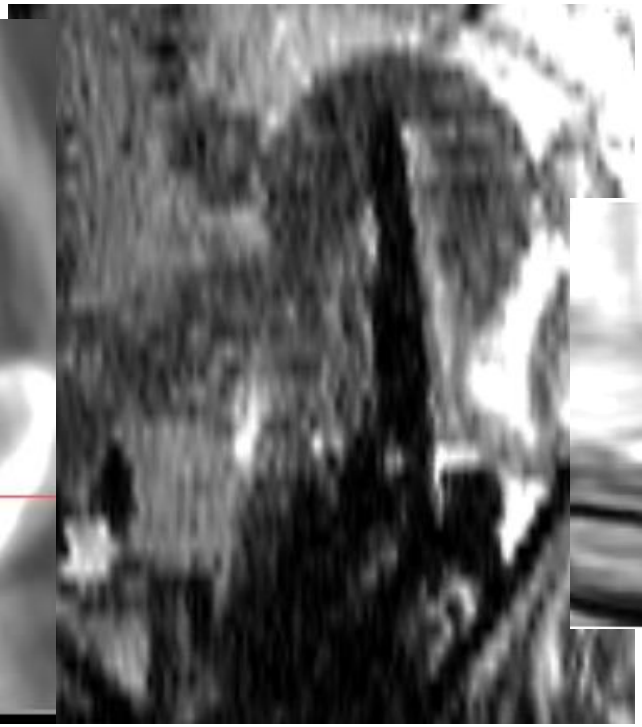


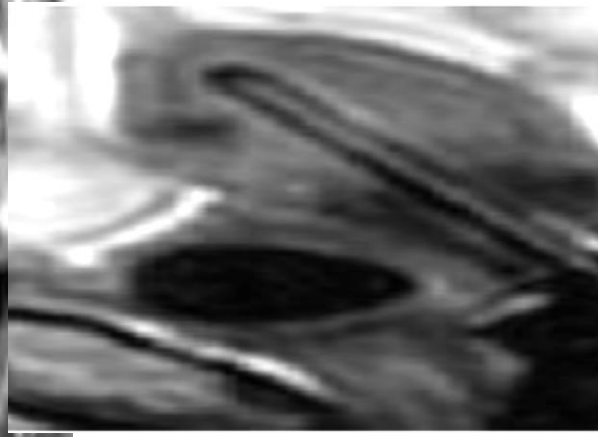
Application of registration in Brachytherapy

- Applicator reconstruction
- Target volume delineation- Transfer of volumes
  - MR to CT
  - MR(T2) to MR(T1)

Role of registration: applicator Reconstruction







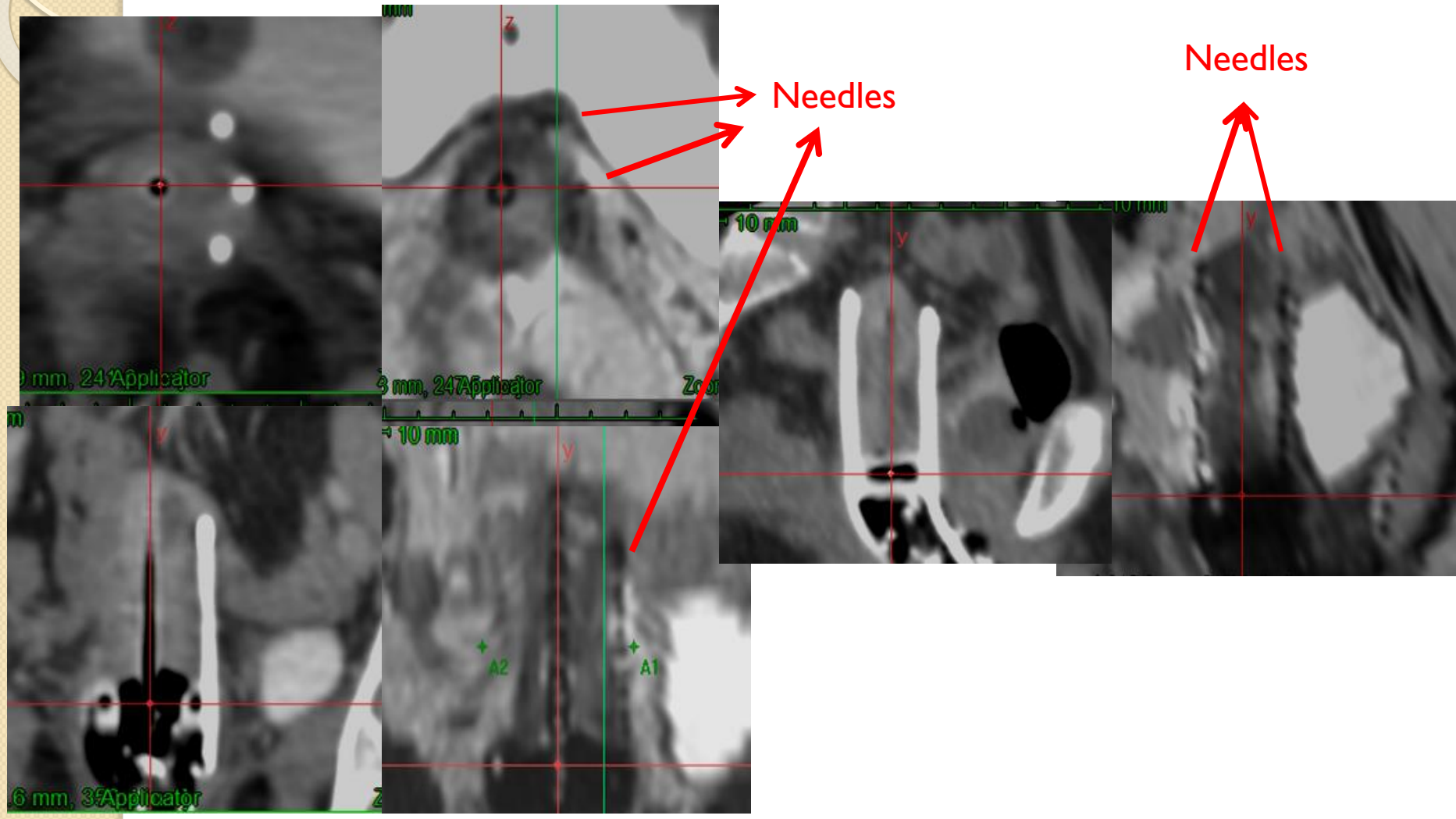
CT – No marker

MR – No marker

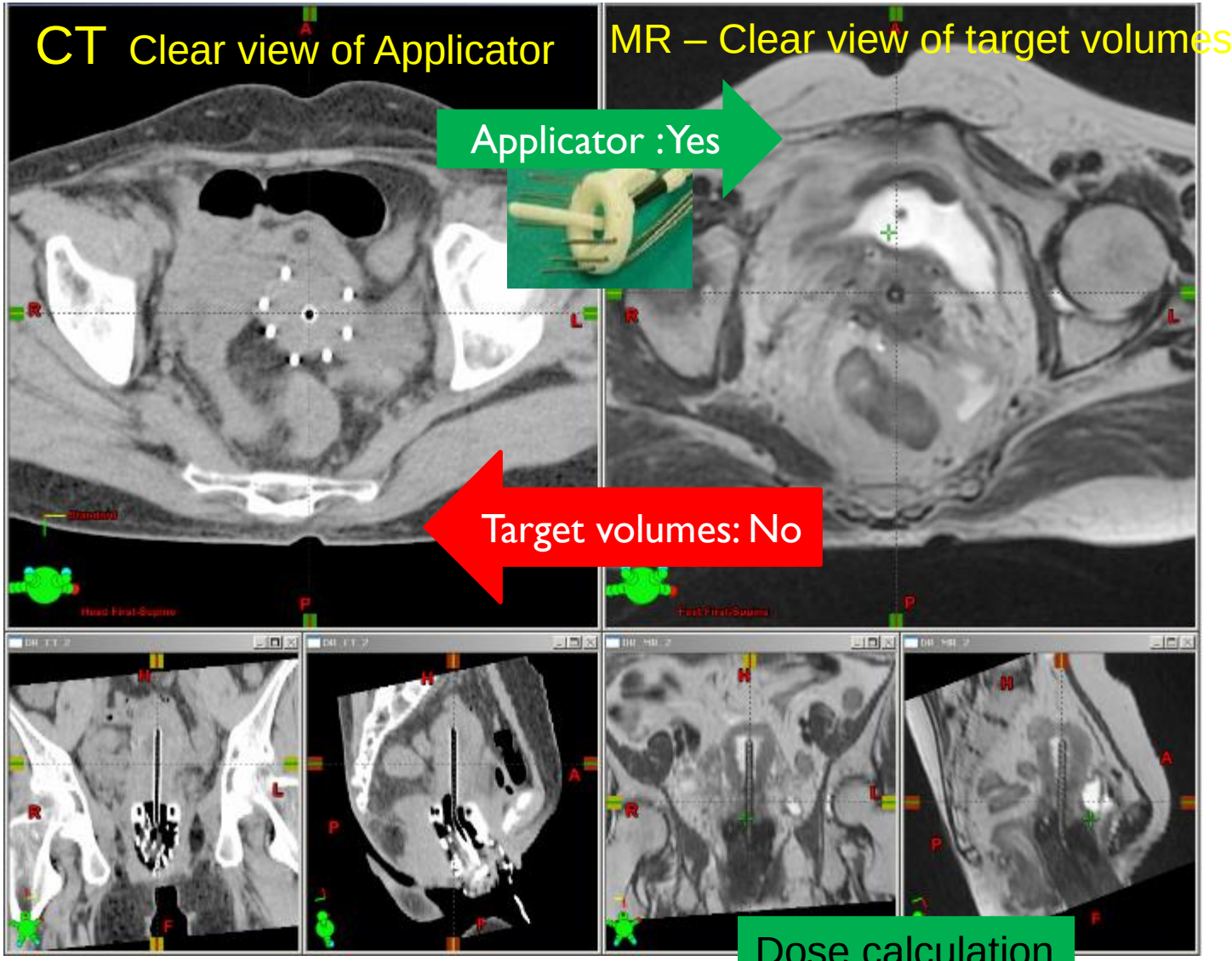
MR – Water marker

Role of registration: applicator

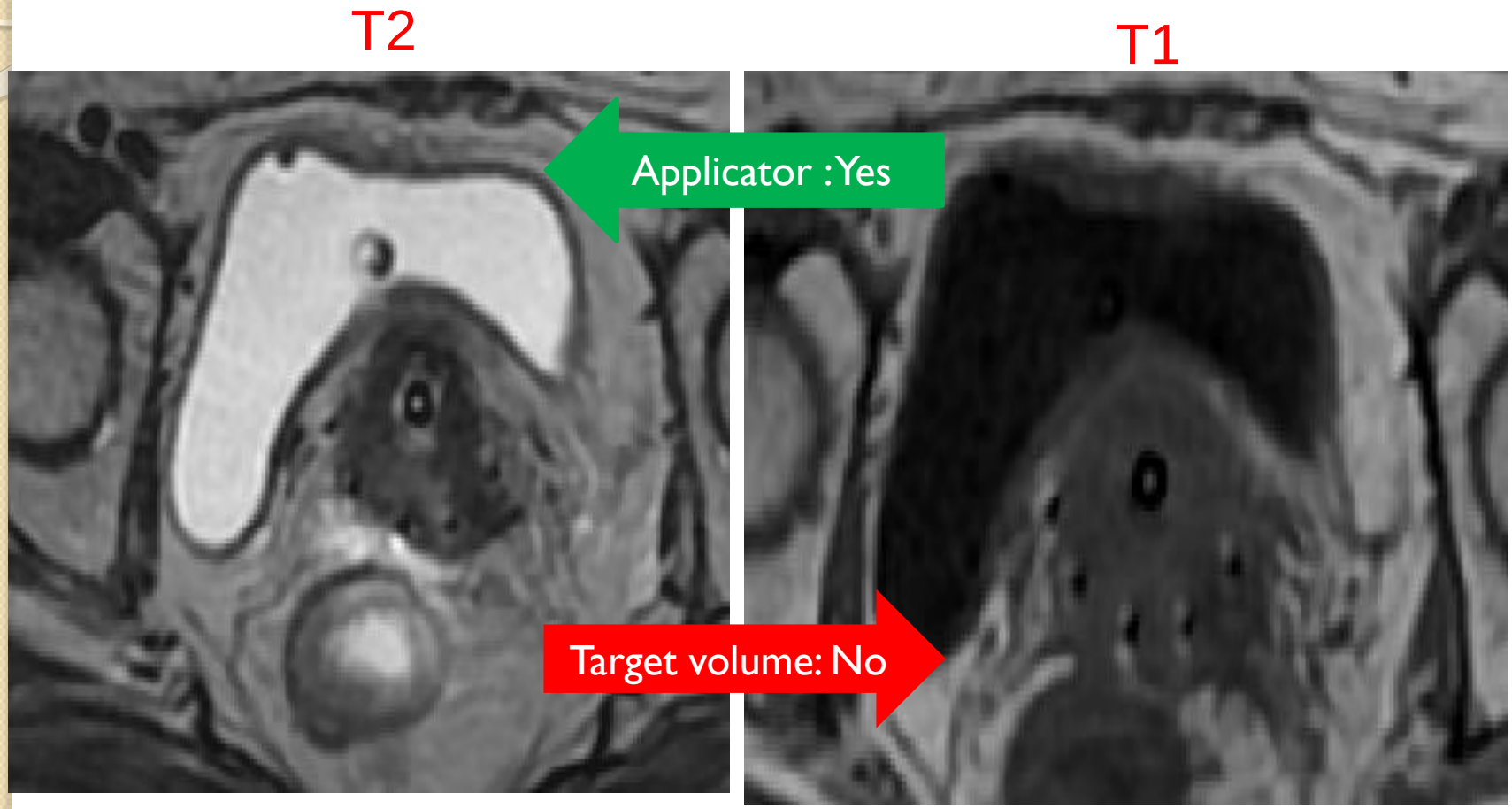
Reconstruction : needles



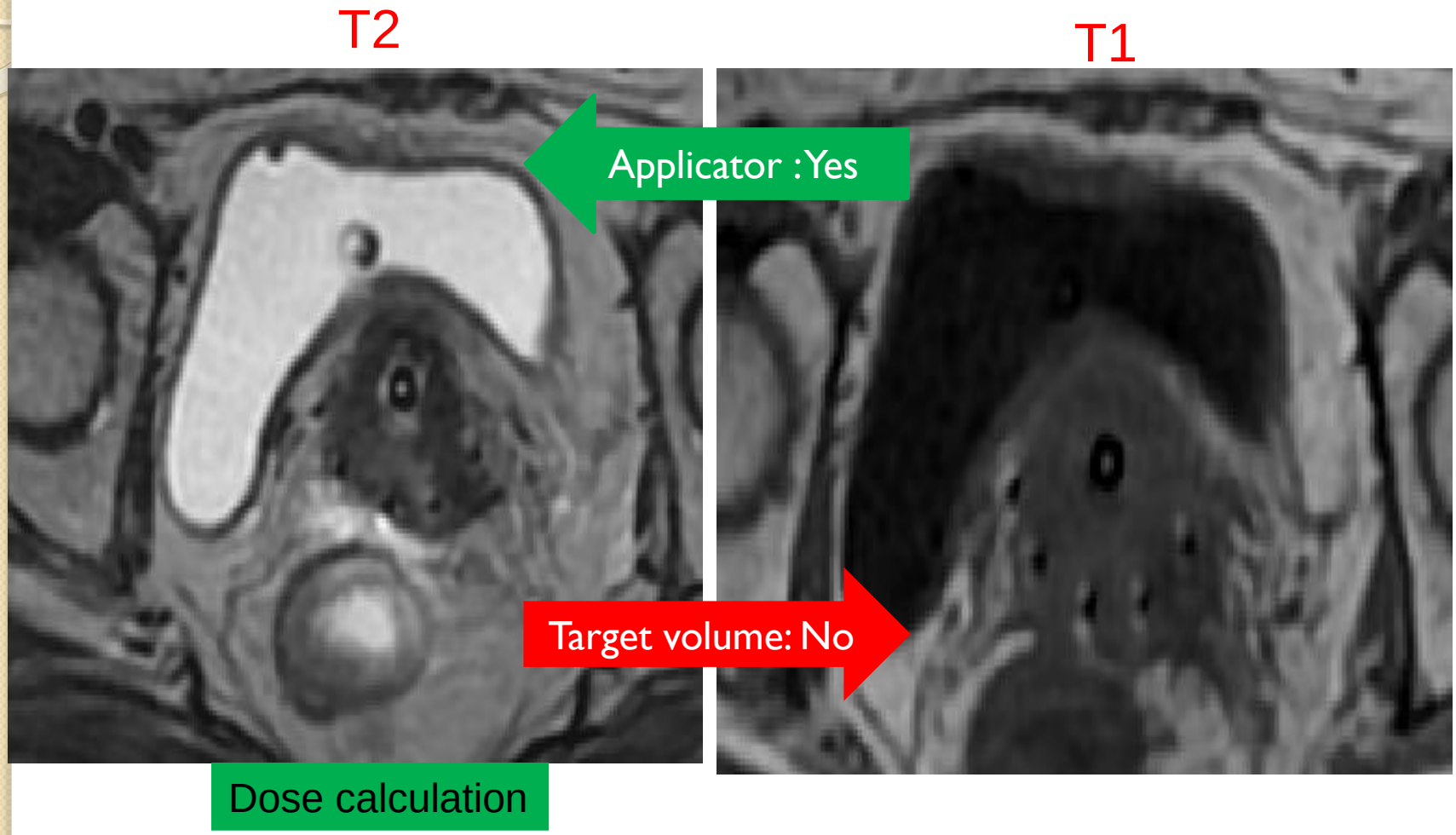
Registration of CT vs MR – Reconstruction



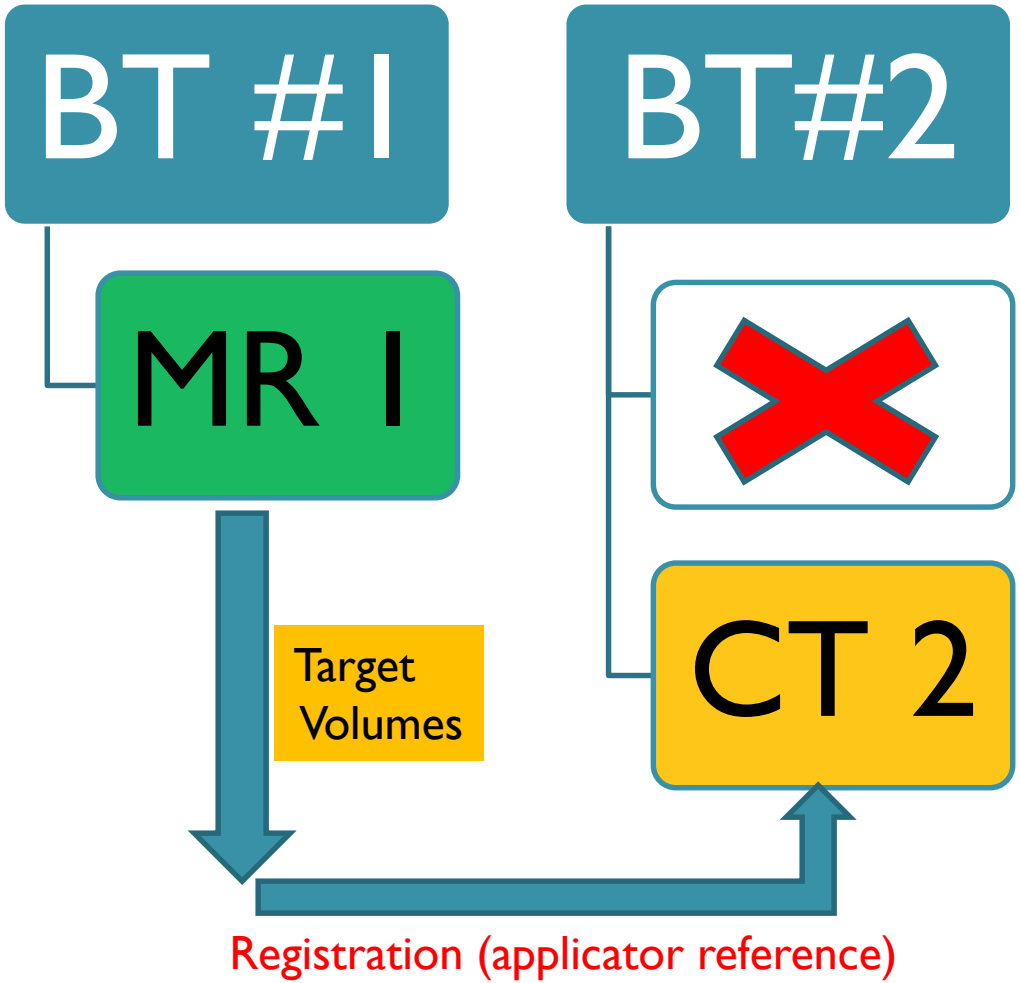
Registration of T1 vs T2 for Reconstruction



Registration of T1 vs T2 for Reconstruction



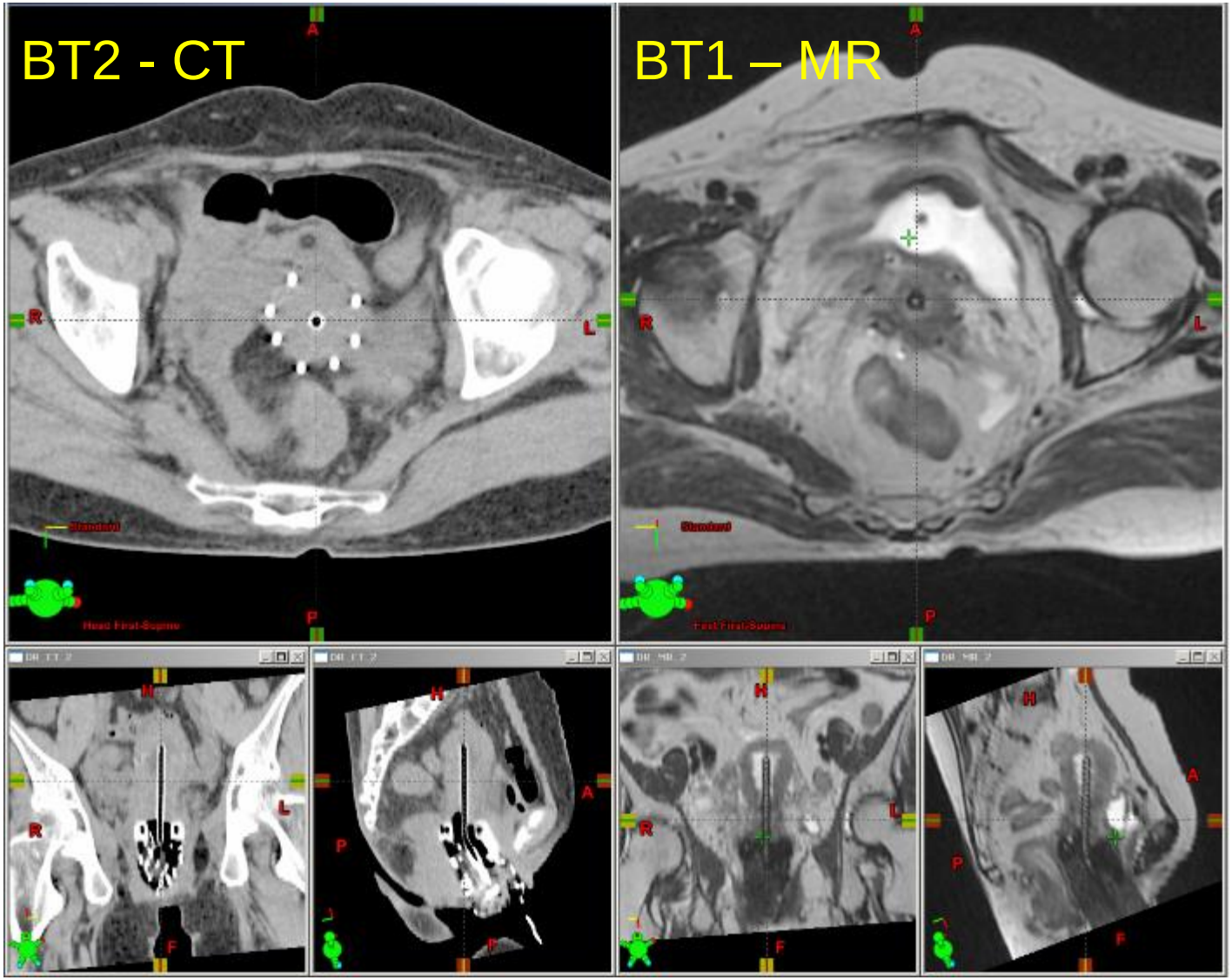
Role of registration in BT – Target



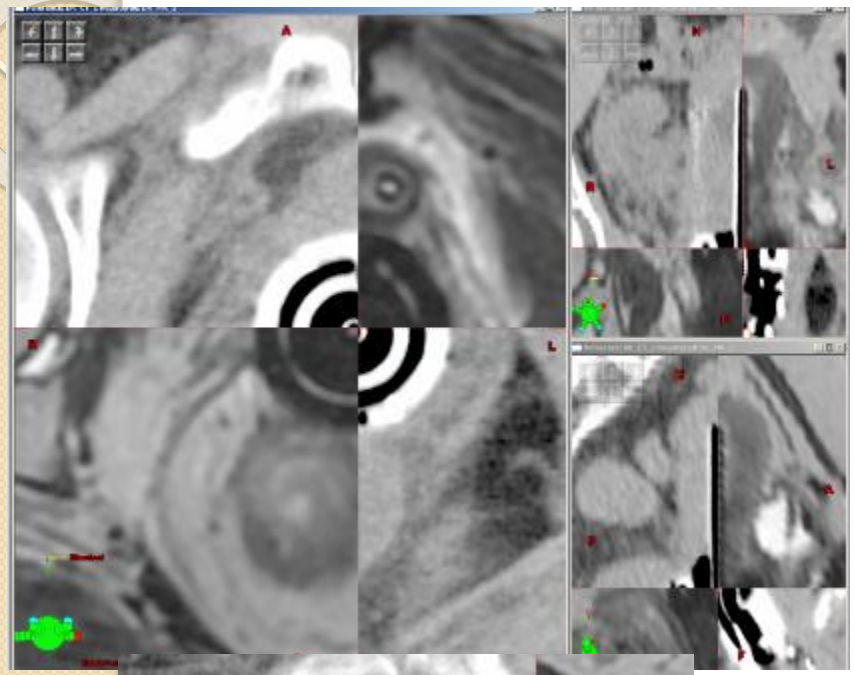
Affordable solution

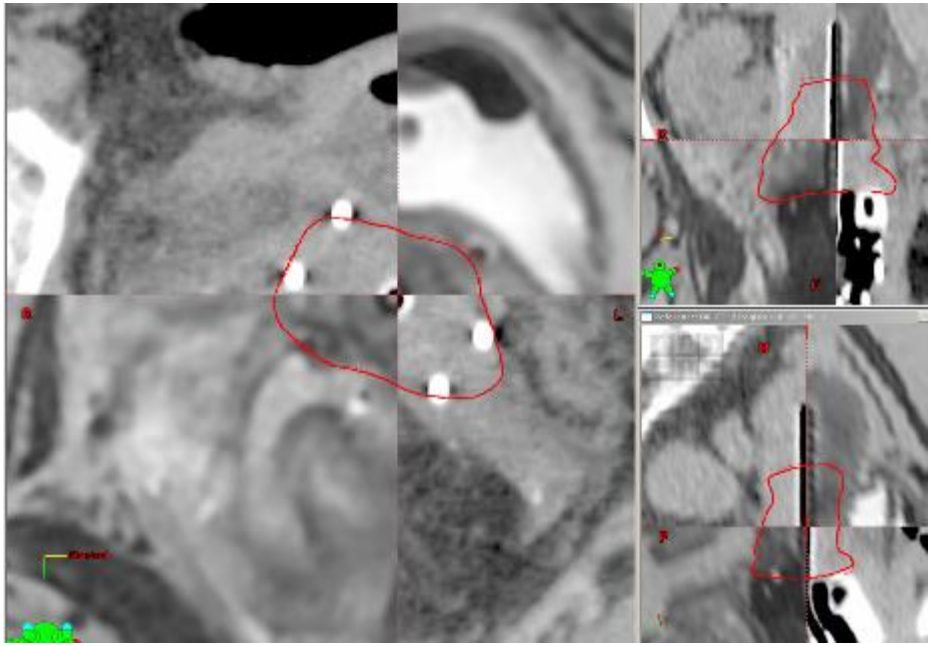
Nesvacil et al 2012

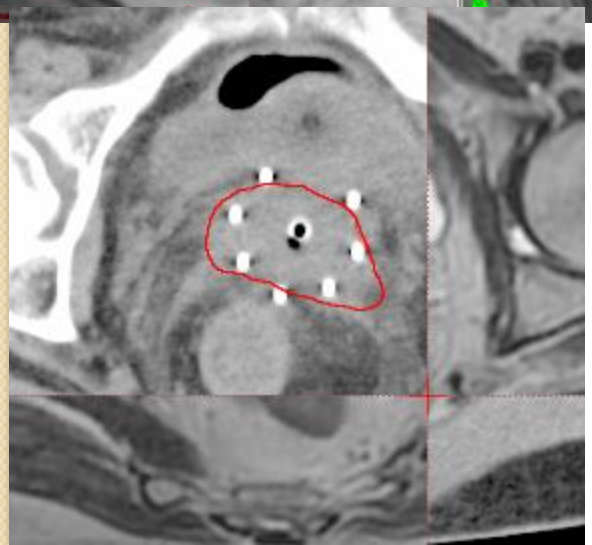
Registration of CT vs MR – Target volume Transfer

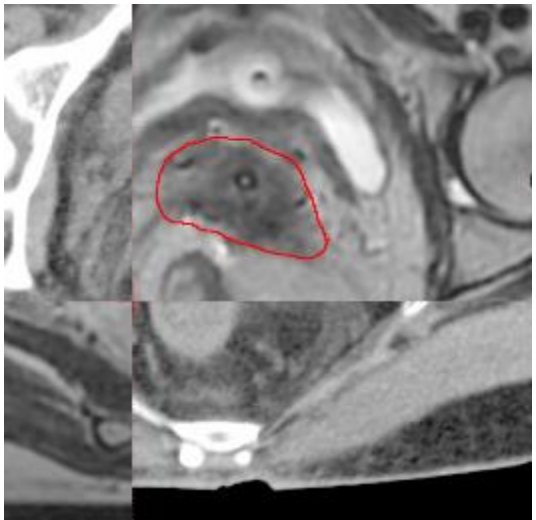


CT vs MR (Target volume transfer)

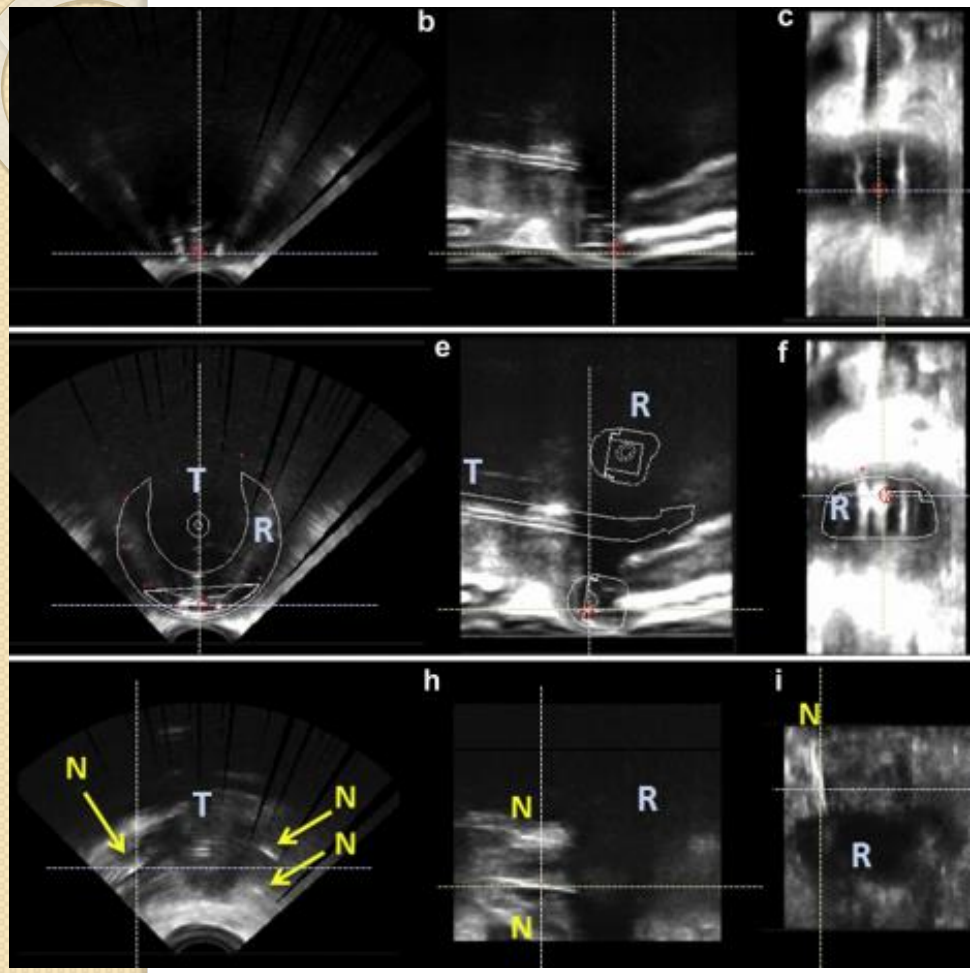


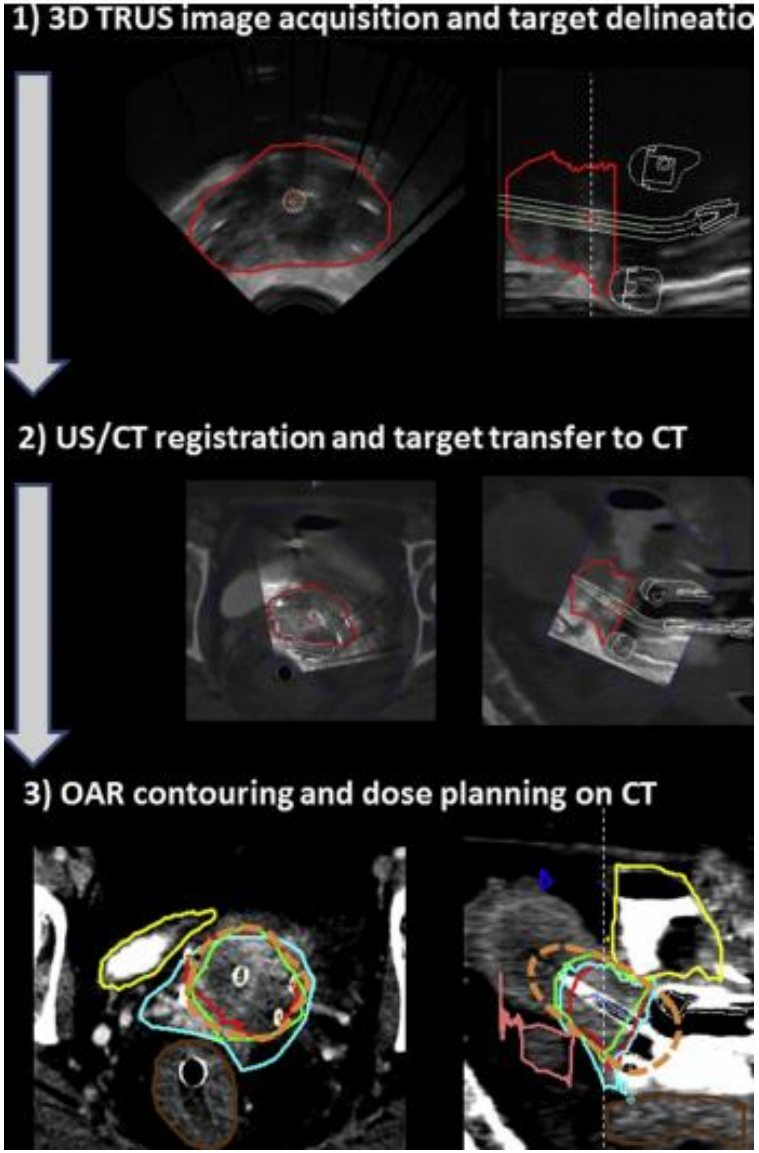






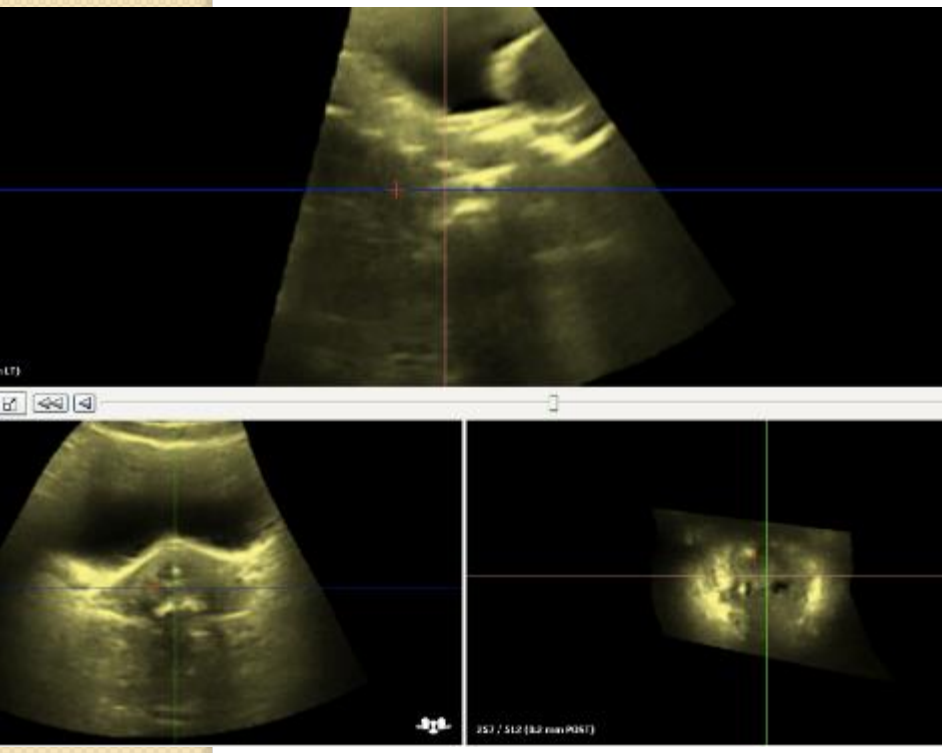
Rigid Registration – TRUS and CT

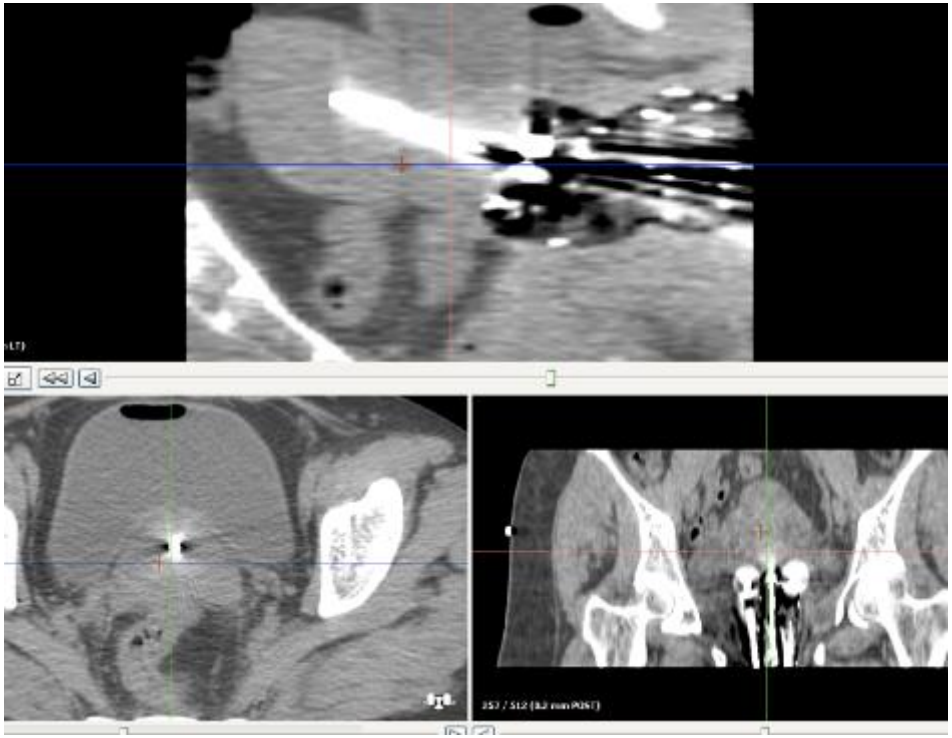




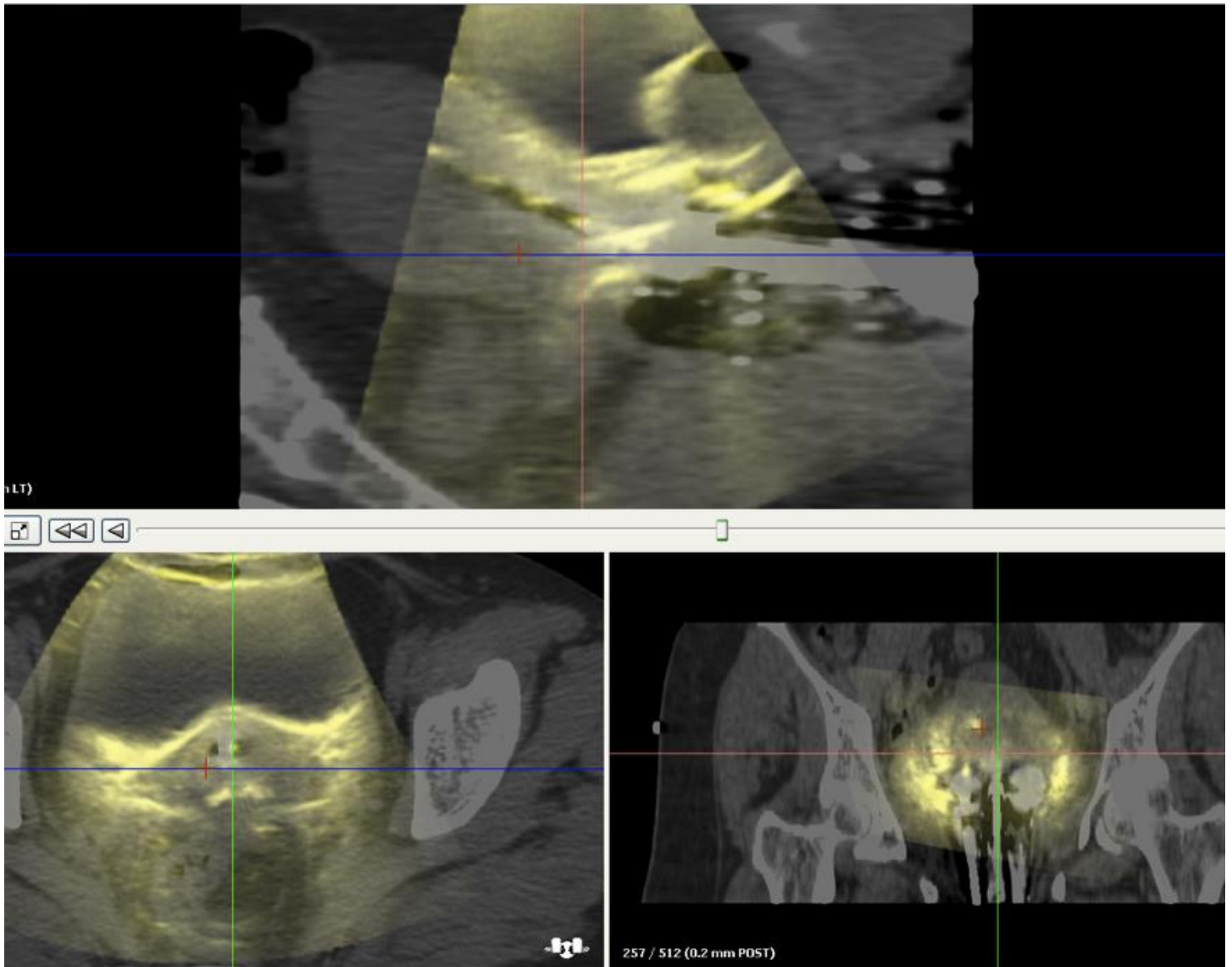
Nesvacil et al 2016

Registration of CT vs Trans abdominal US

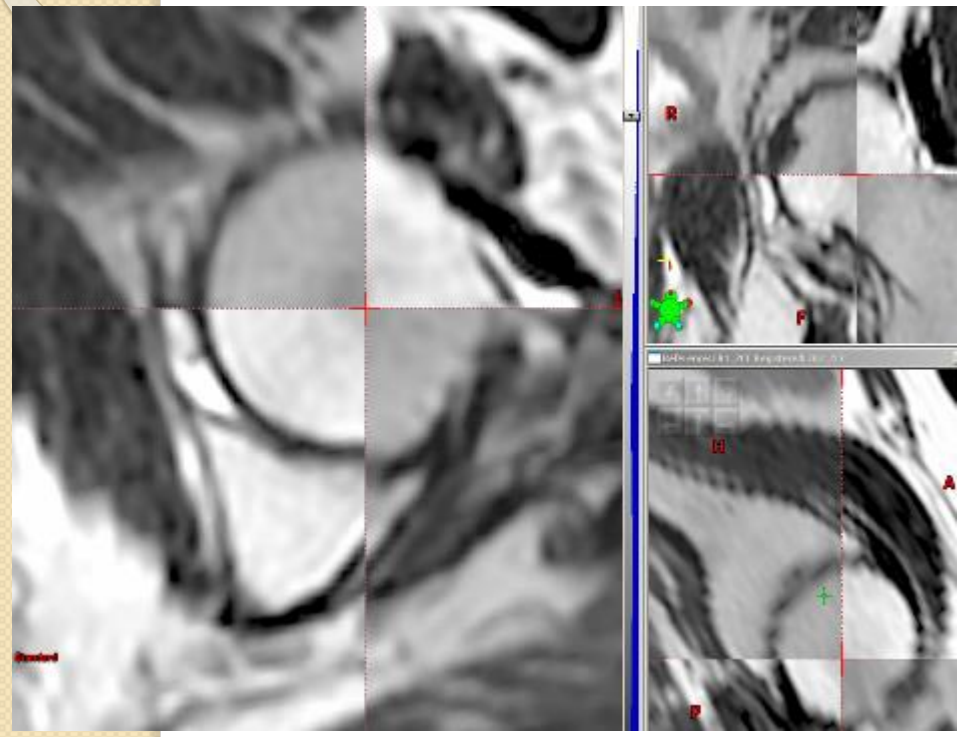




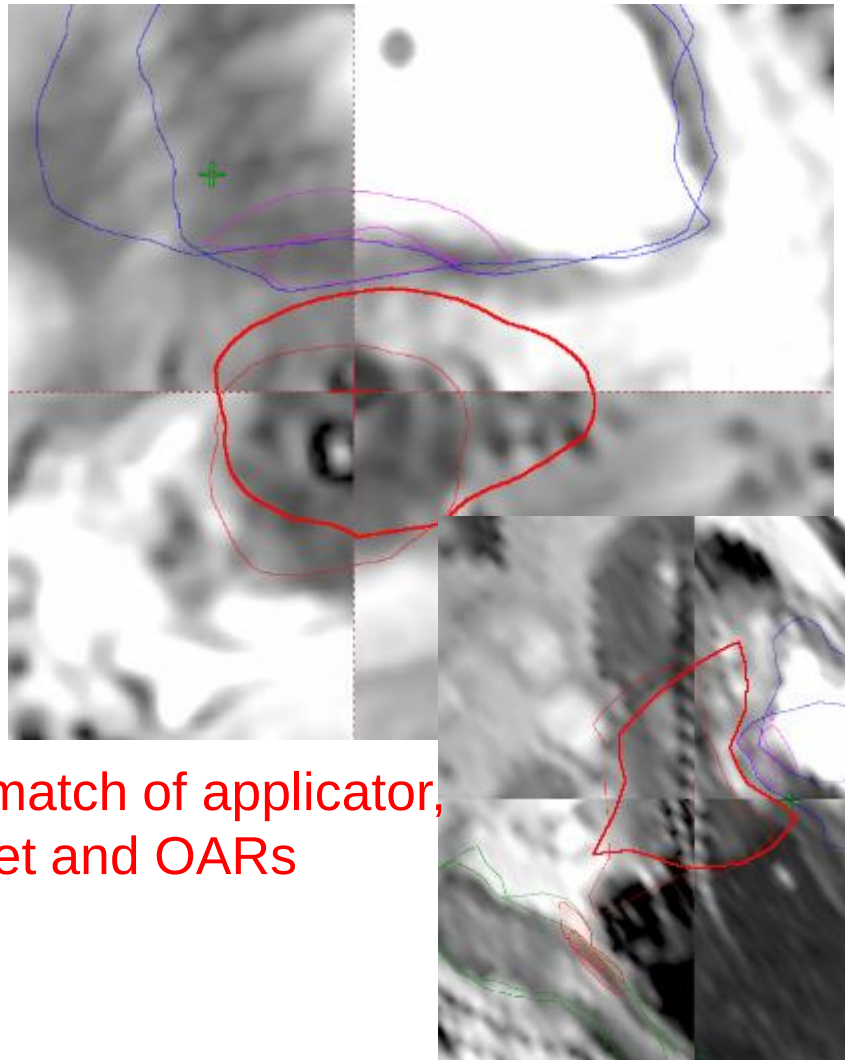
Registration of CT vs US



Registration in Brachytherapy – Bone as a reference ? No

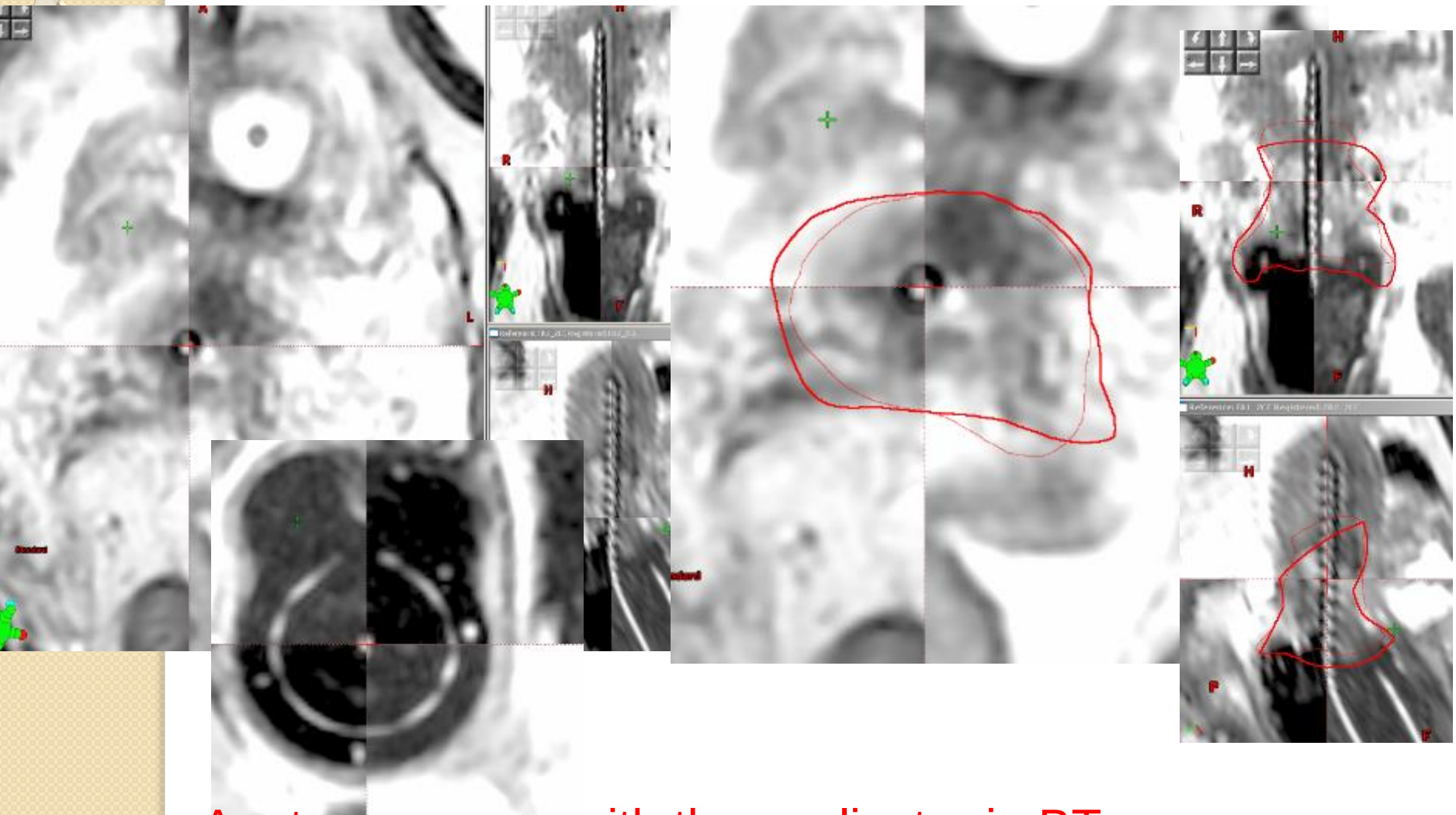


Good matching of bones



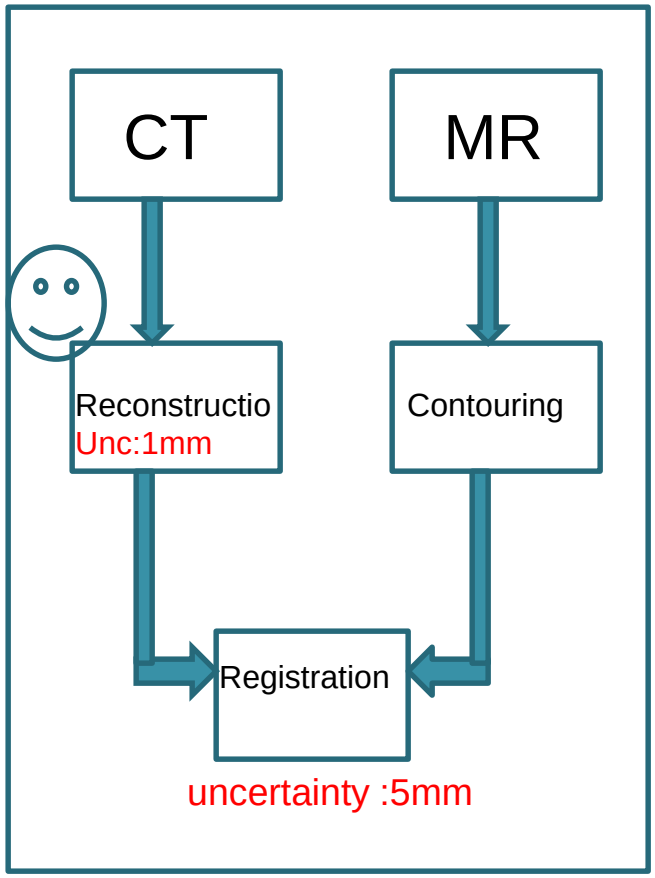
Mismatch of applicator, target and OARs

Registration in Brachytherapy – applicator as a reference? -Yes

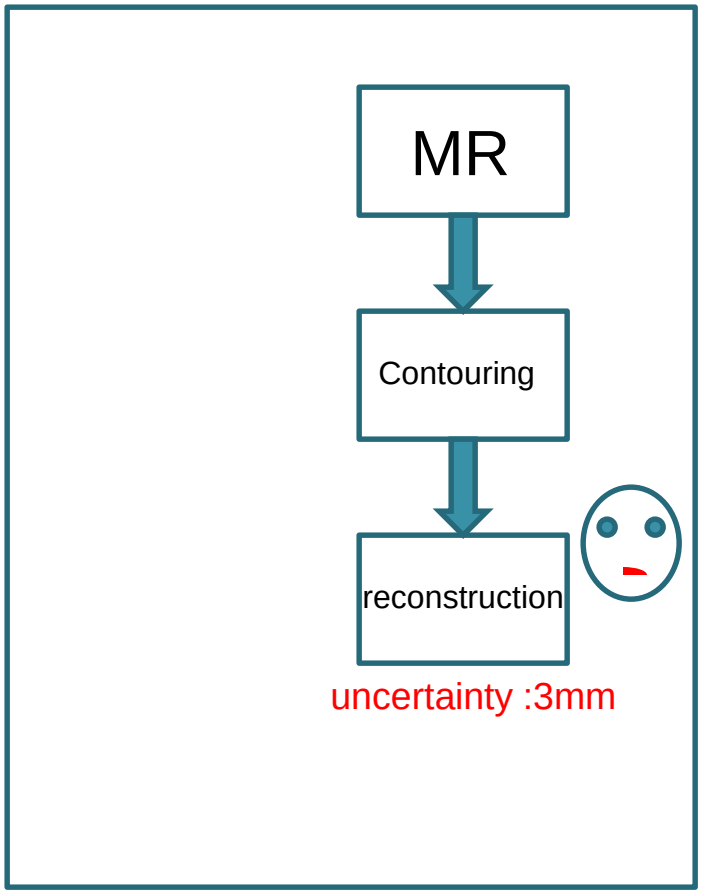


Anatomy moves with the applicator in BT

How to reduce uncertainties



Scenario 1

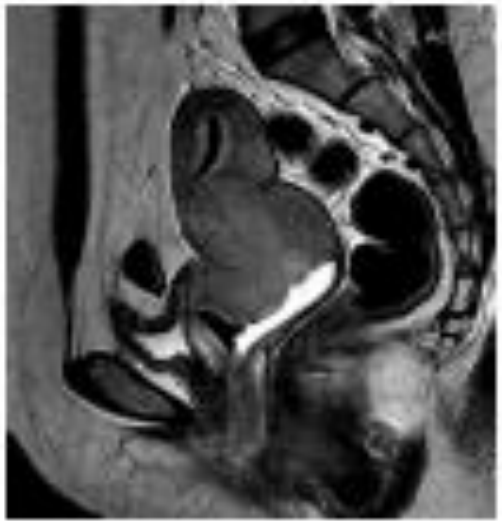


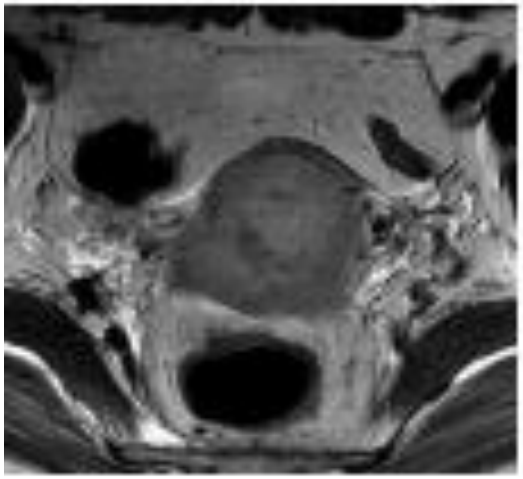
Scenario 2

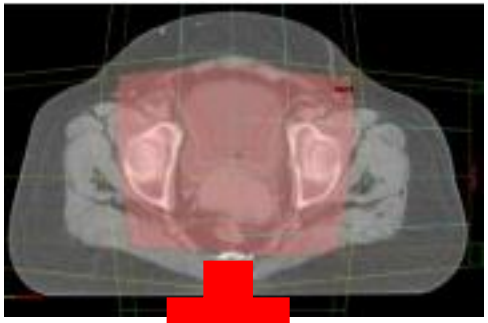
Which is preferred?

Registration of EBRT & BT images ?

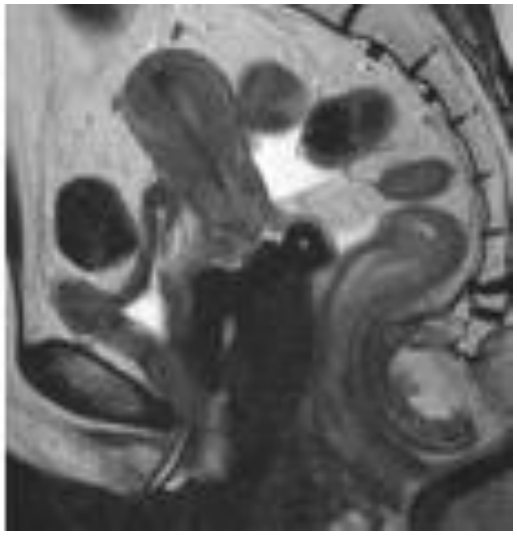
Pre RT

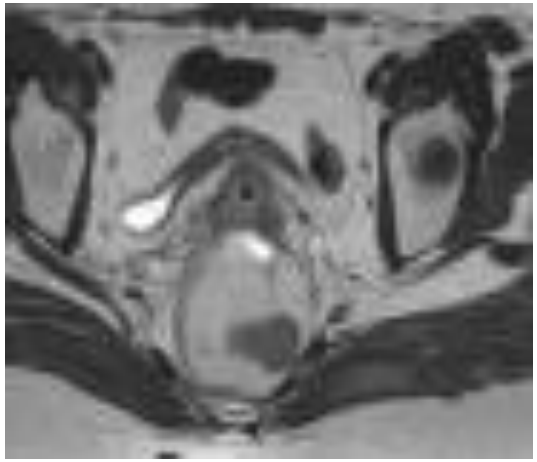






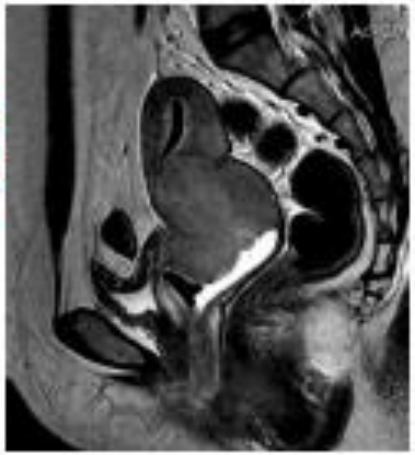
Brachytherapy

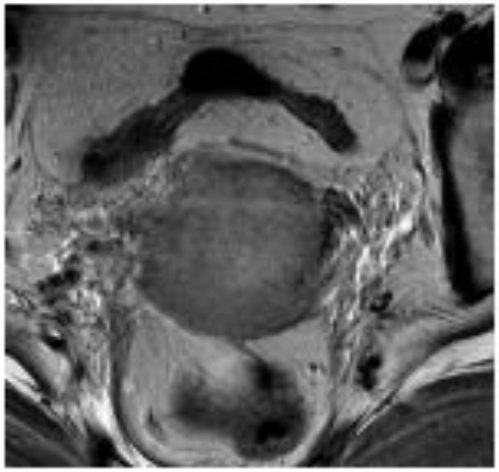


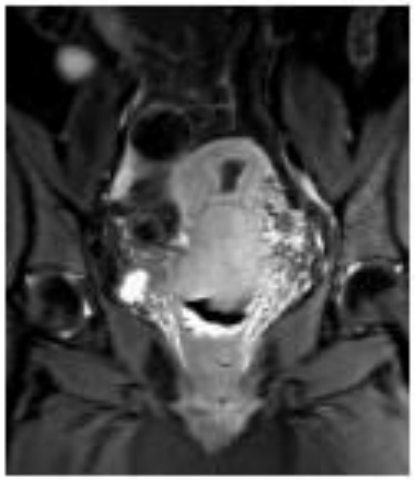


Can we register these two image sets? No

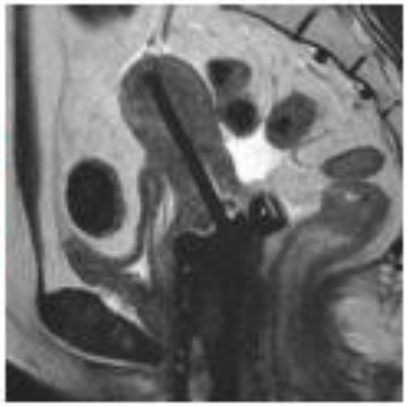
Pre Rx

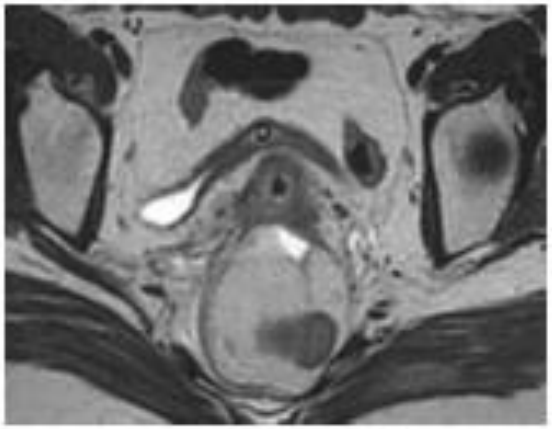


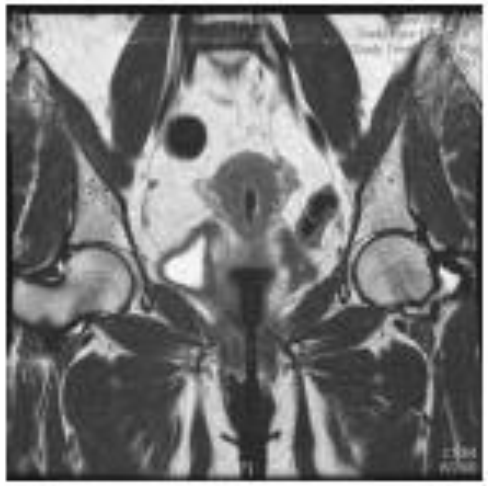




Post Rx

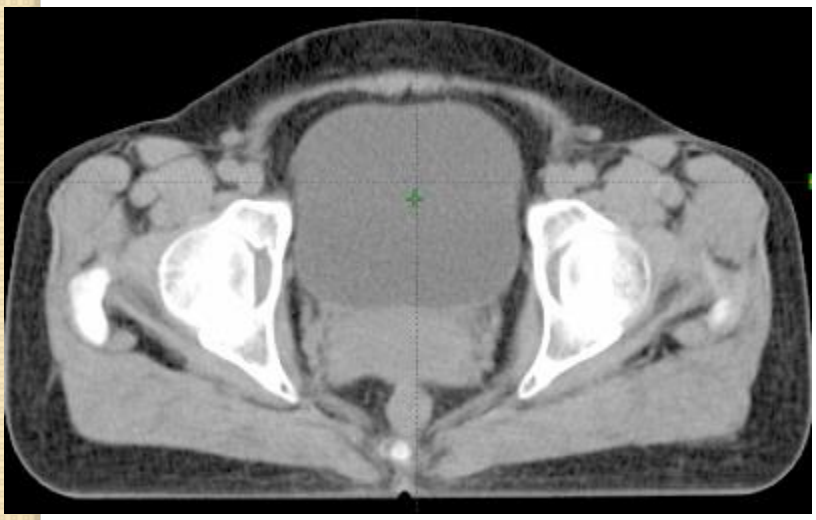




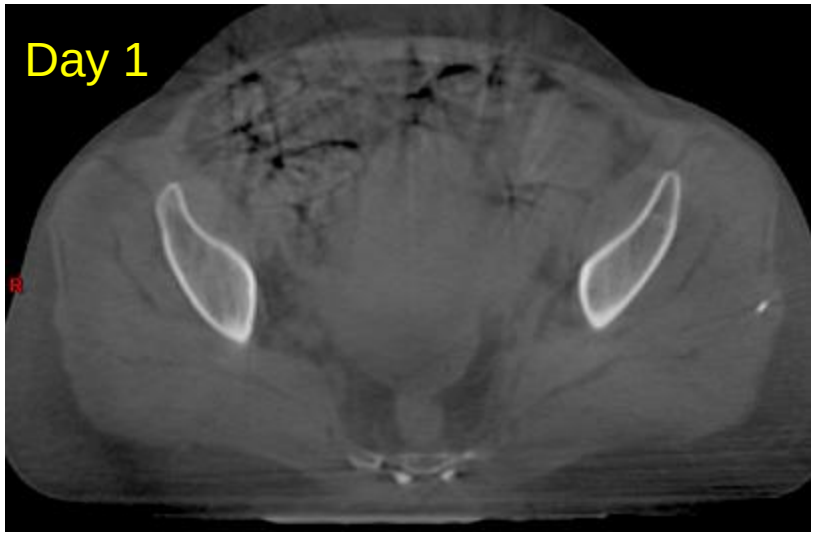


External beam Radiotherapy

- Planning CT images

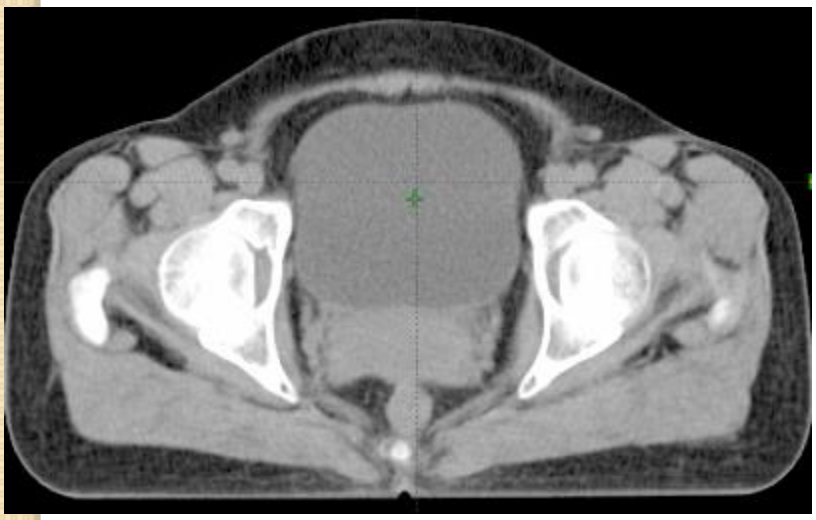


- CBCT images

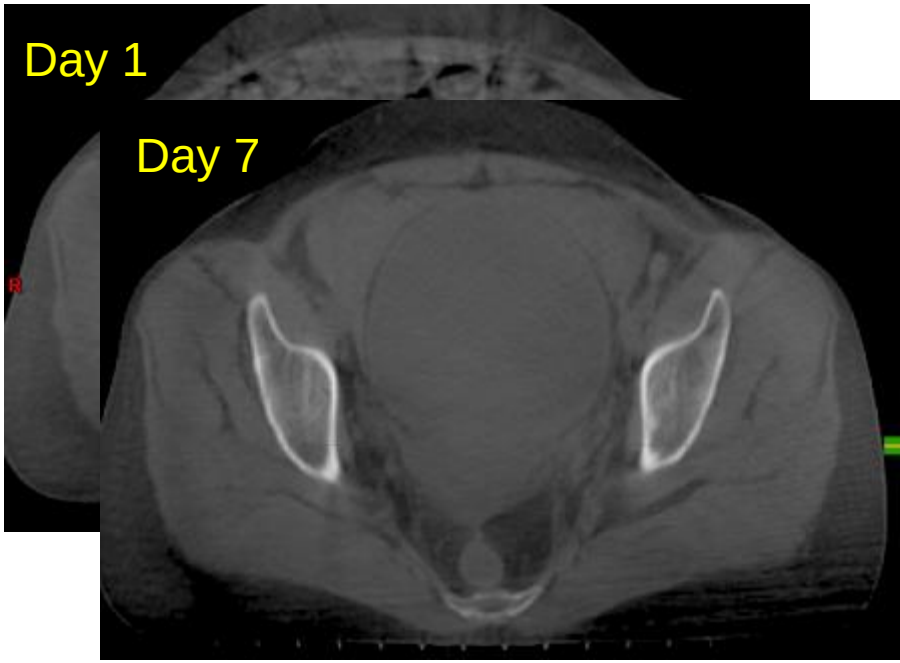


External beam Radiotherapy

- EXRT images

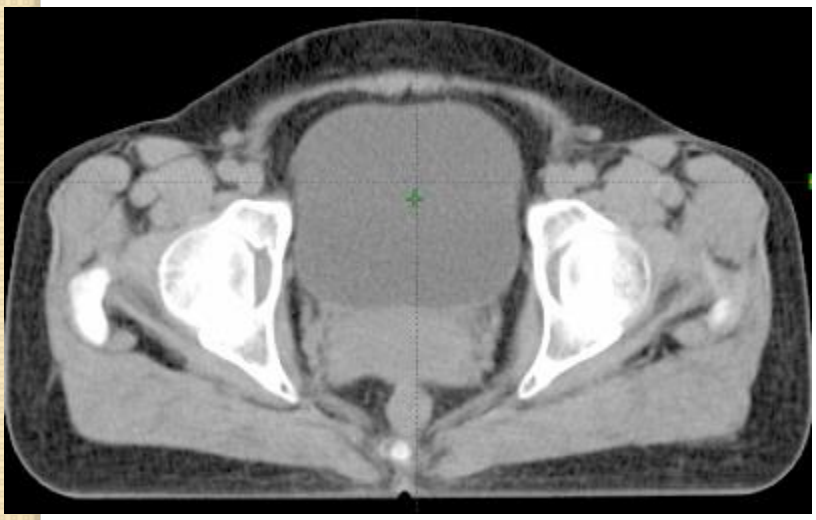


- CBCT images

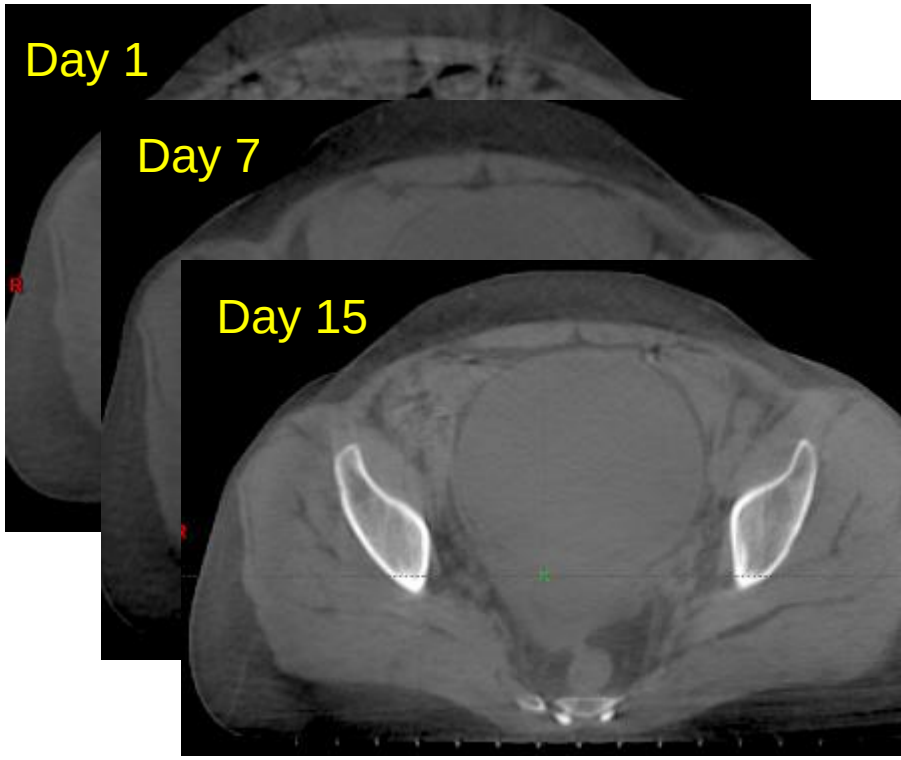


External beam Radiotherapy

- EXRT images

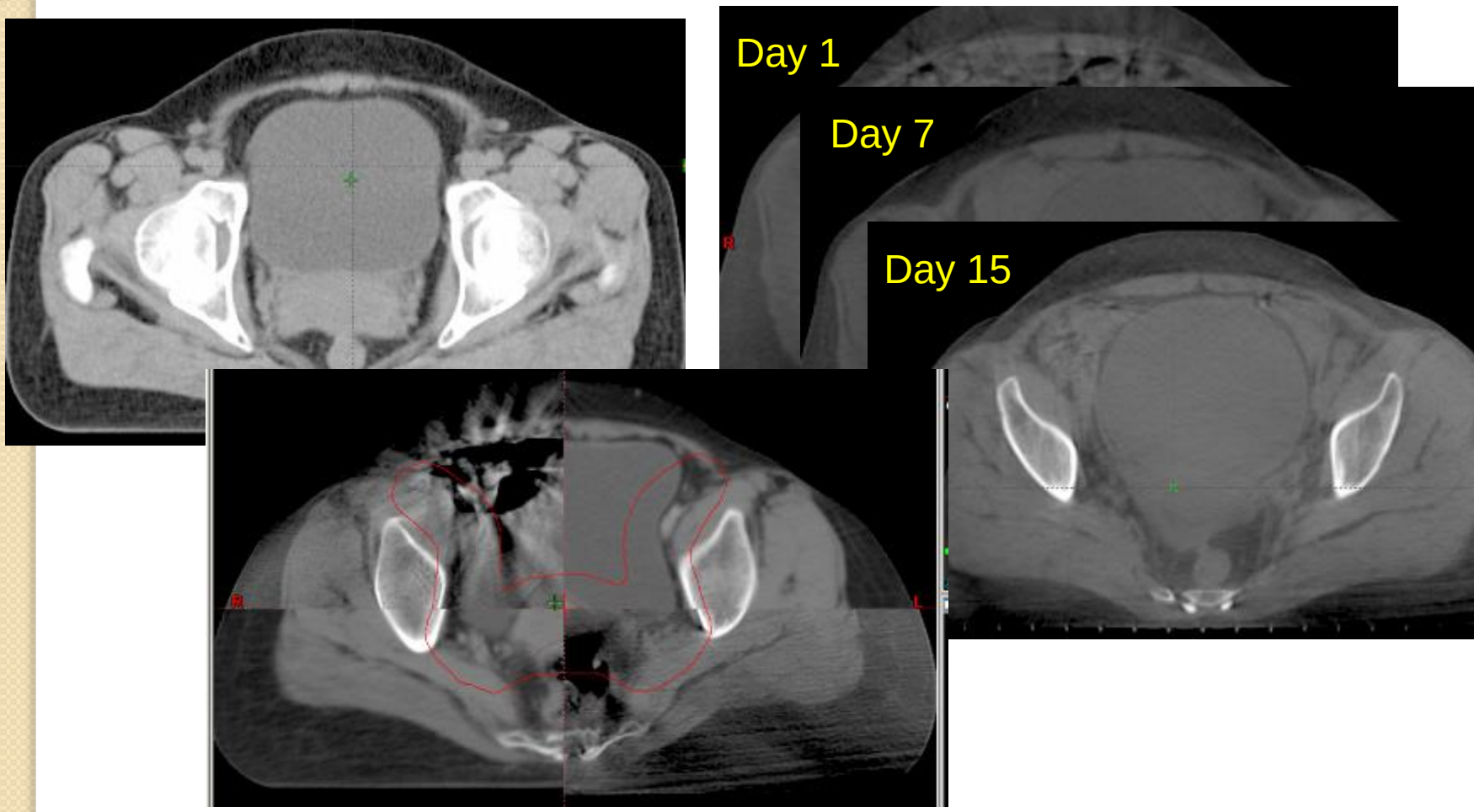


- CBCT images



External beam Radiotherapy: Rigid registration

- EXRT images
- CBCT images



Summary

- Localization techniques – Orthogonal, semi orthogonal
- Library plans
- Co-Registration
  - Applicator reconstruction
  - Target volume mapping
  - EXRT + BT ✘
  - Pre Treatment + BT ✘

Thank you

Applicator reconstruction using MR images

- Guides
  - Artifacts
  - Templates

Courtesy Daniel Berger

Radiotherapy and Oncology 104 (2012) 192–198

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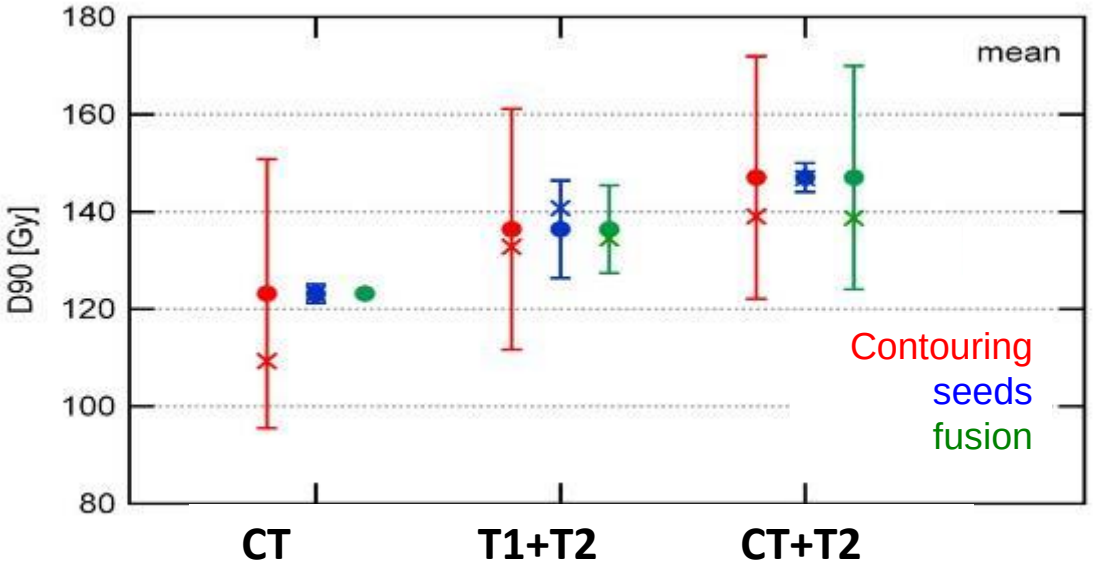
Prostate brachytherapy

Prostate post-implant dosimetry: Interobserver variability in seed localisation, contouring and fusion

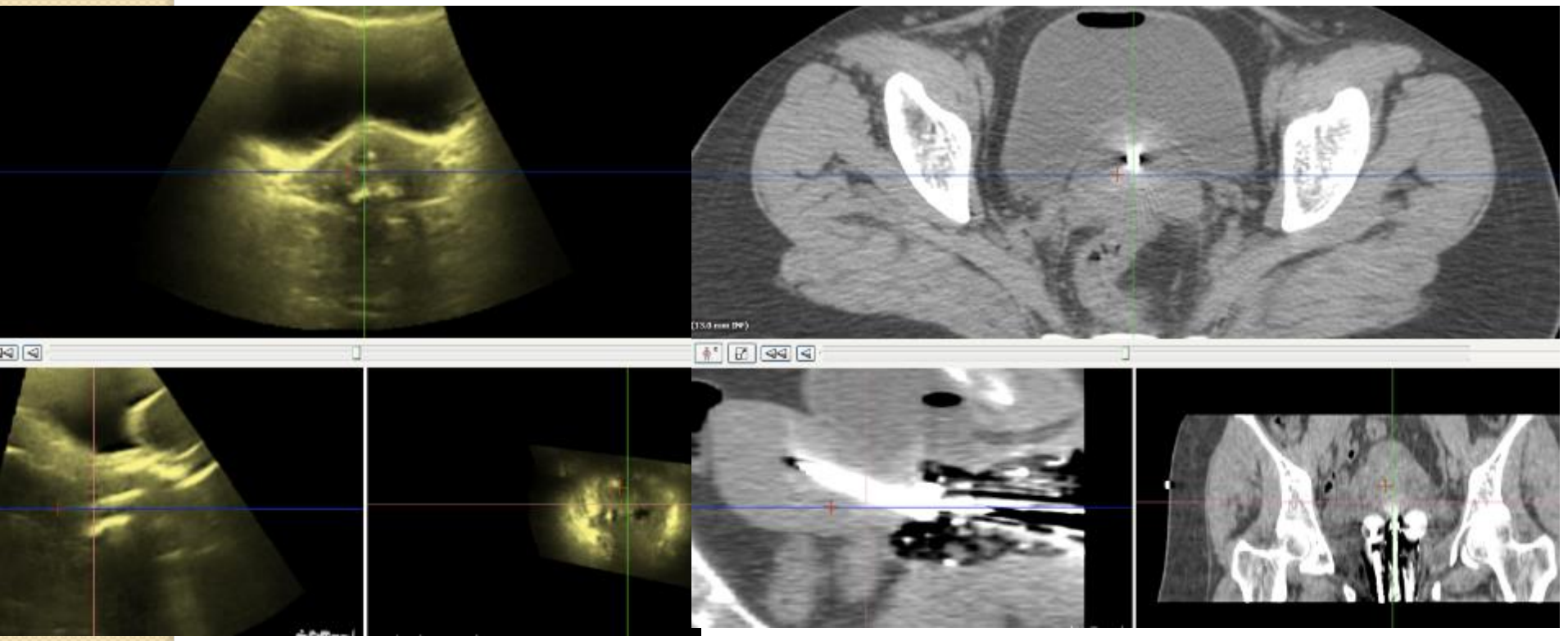
Marisol De Brabandere [a,*], Peter Hoskin [b], Karin Haustermans [a], Frank Van den Heuvel [a], Frank-André Siebert [c]

[a] University Hospital Gasthuisberg, Leuven, Belgium; [b] Mount Vernon Cancer Centre, Middlesex, UK; [c] University Hospital of Schleswig-Holstein, Kiel, Germany

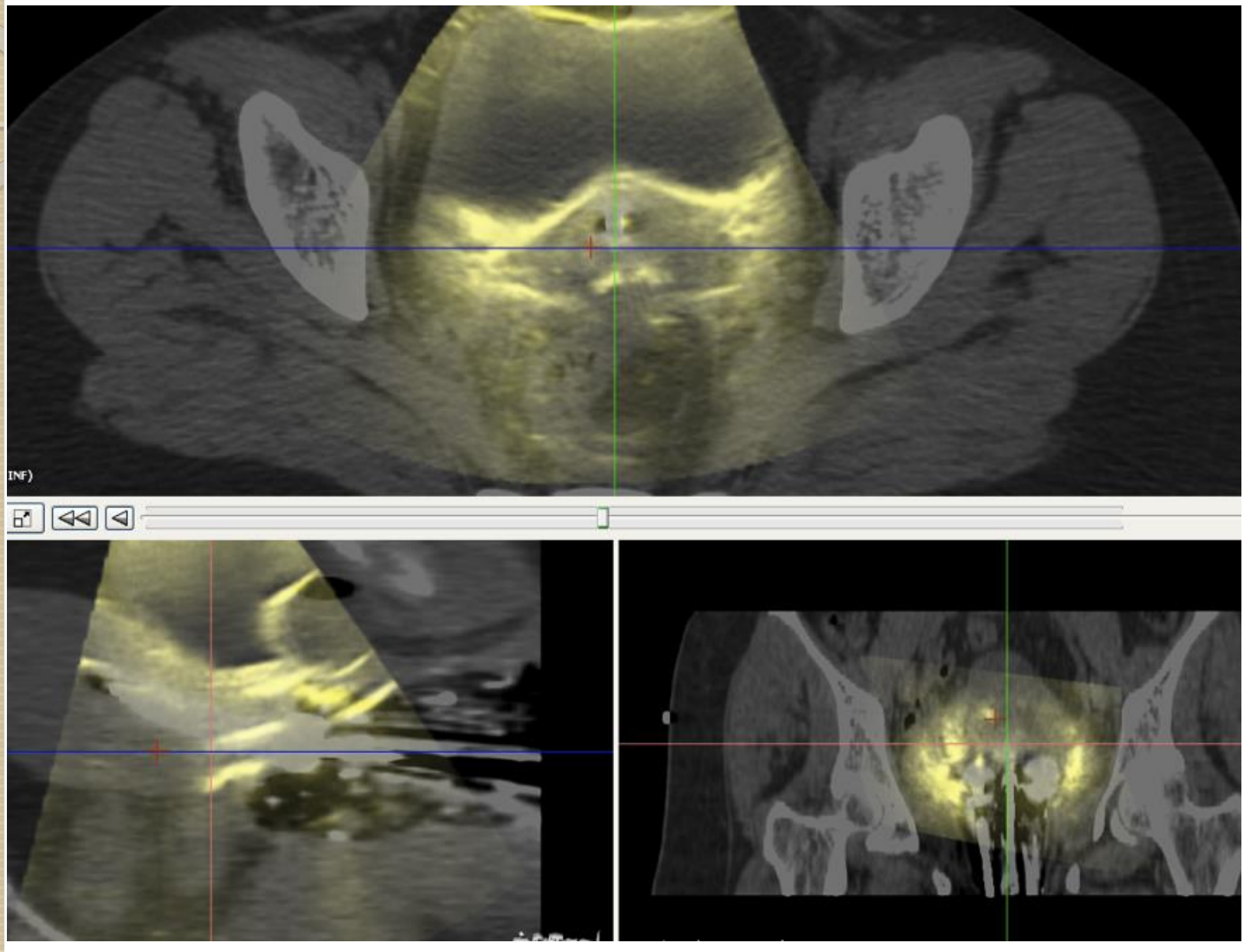
Mean 3 patients



Registration of CT vs US



Registration of CT vs US



Physics aspects of treatment planning intracavitary +/- interstitial techniques in cervix cancer

ESTRO-AROI Teaching Course
Transition from conventional 2D to 3D radiotherapy with a special emphasis on brachytherapy in cervical cancers

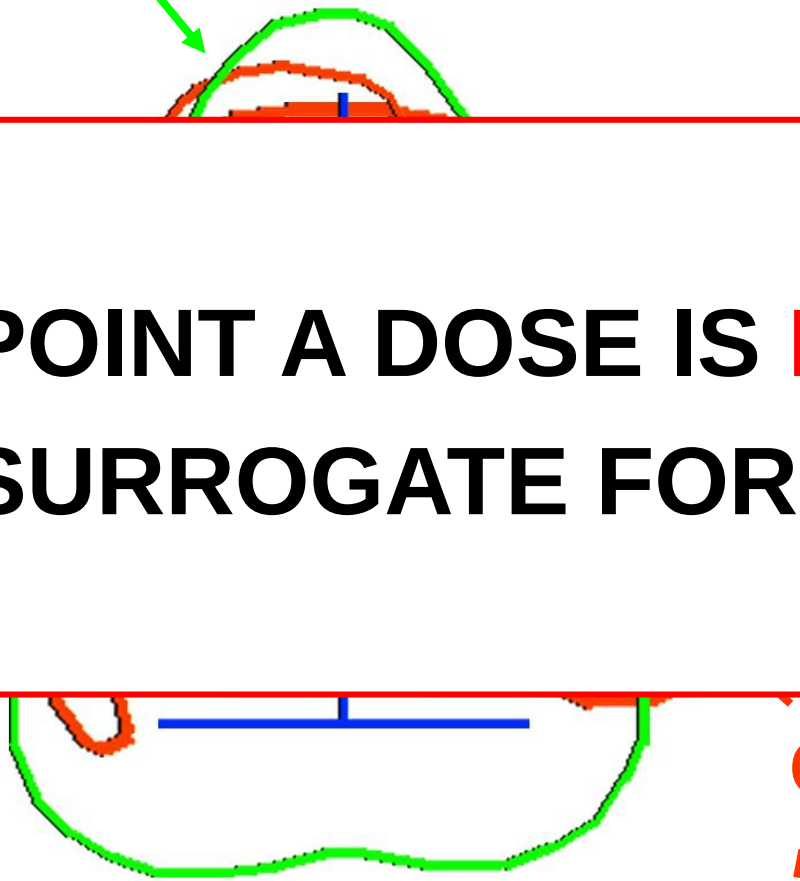
Bengaluru 2017

Prof Kari Tanderup, PhD

Aarhus University Hospital

Limitation of point A and standard loading pattern

Point A isodose



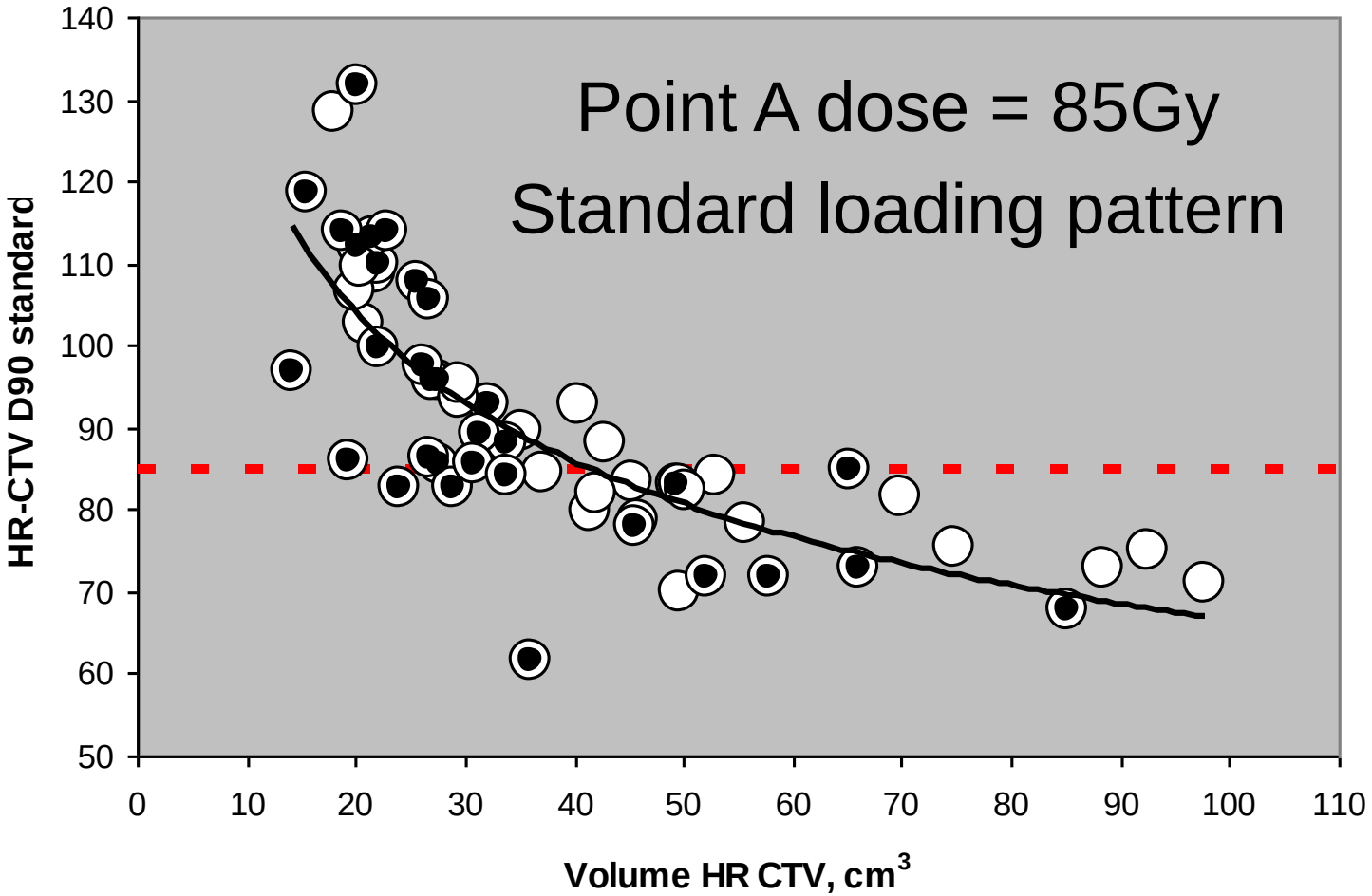
Minimum HR-CTV dose relative to point A:

POINT A DOSE IS NOT A GOOD SURROGATE FOR TARGET DOSE

CTV's assessed from MRI

5 pt's

Limitation of standard loading pattern with dose prescription to point A



◉ Violation of OAR constraint

K Tanderup et al, Radiother Oncol 2010

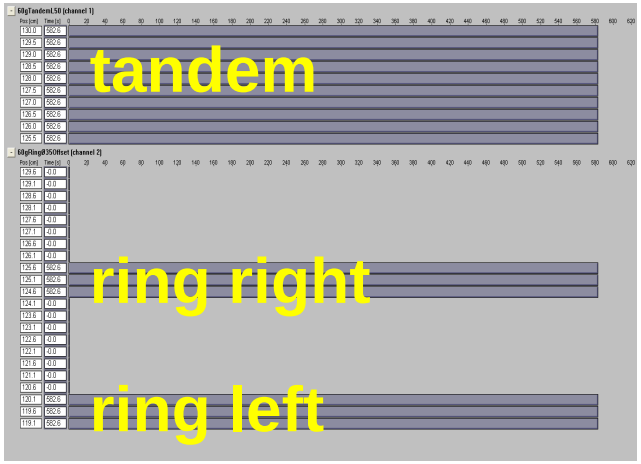
Tools for dose optimisation

- **Manual dose optimisation**
- **Graphical optimization / Dose shaper**
- **Inverse planning**

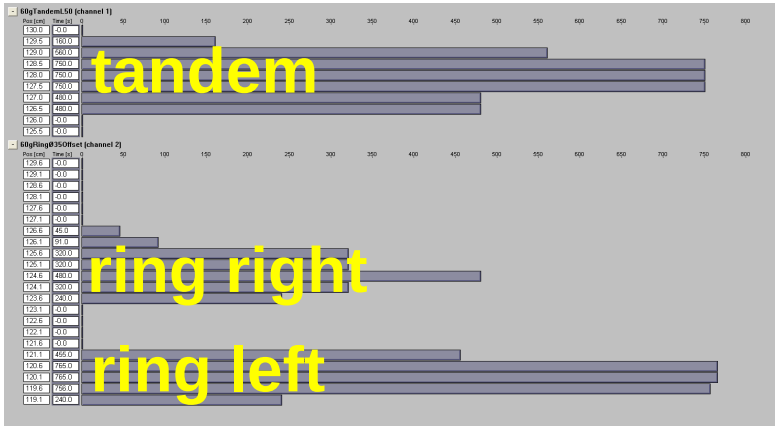
Manual optimisation

Dwell times

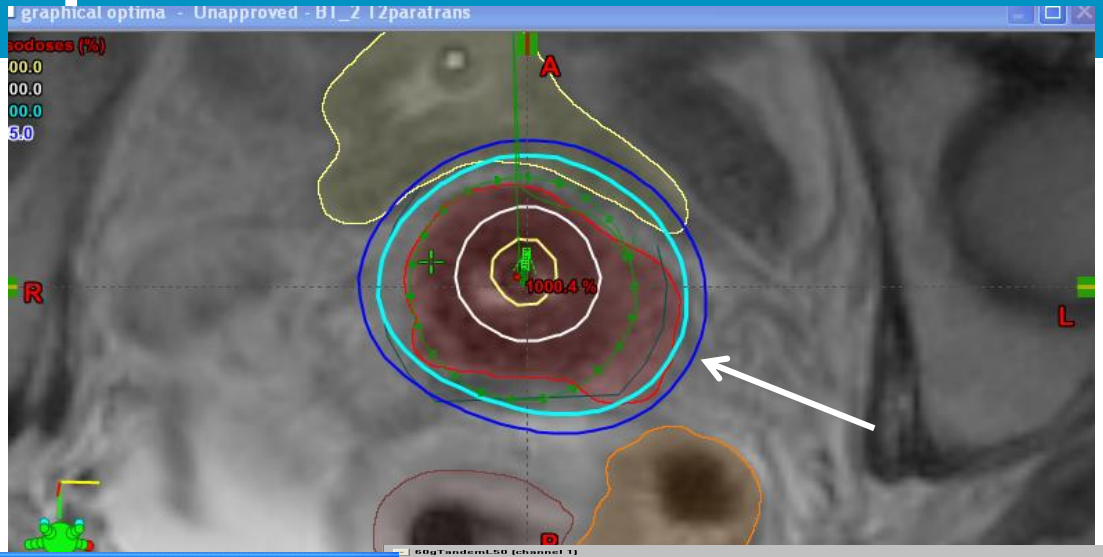
Standard

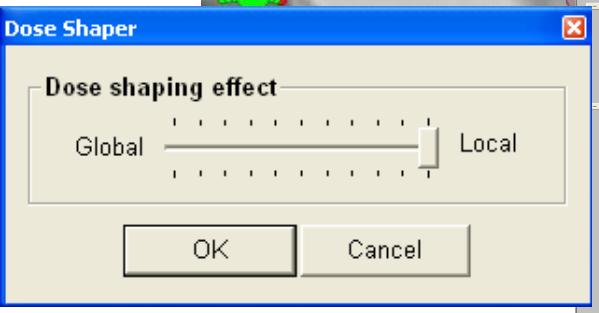


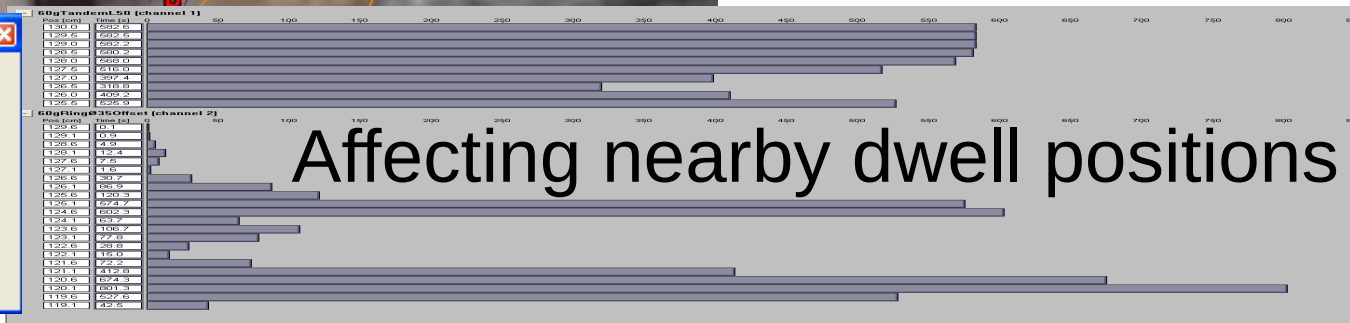
Manually optimised



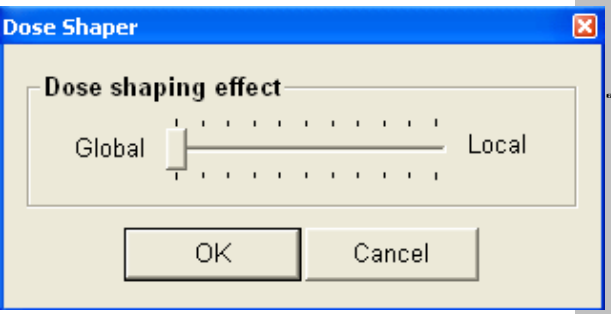
Graphical dose optimisation – “drag and drop”

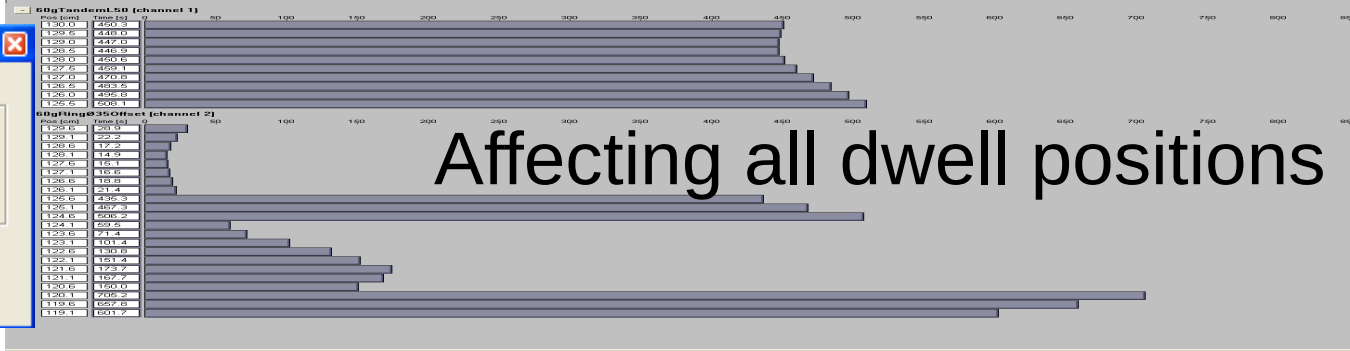






Affecting nearby dwell positions

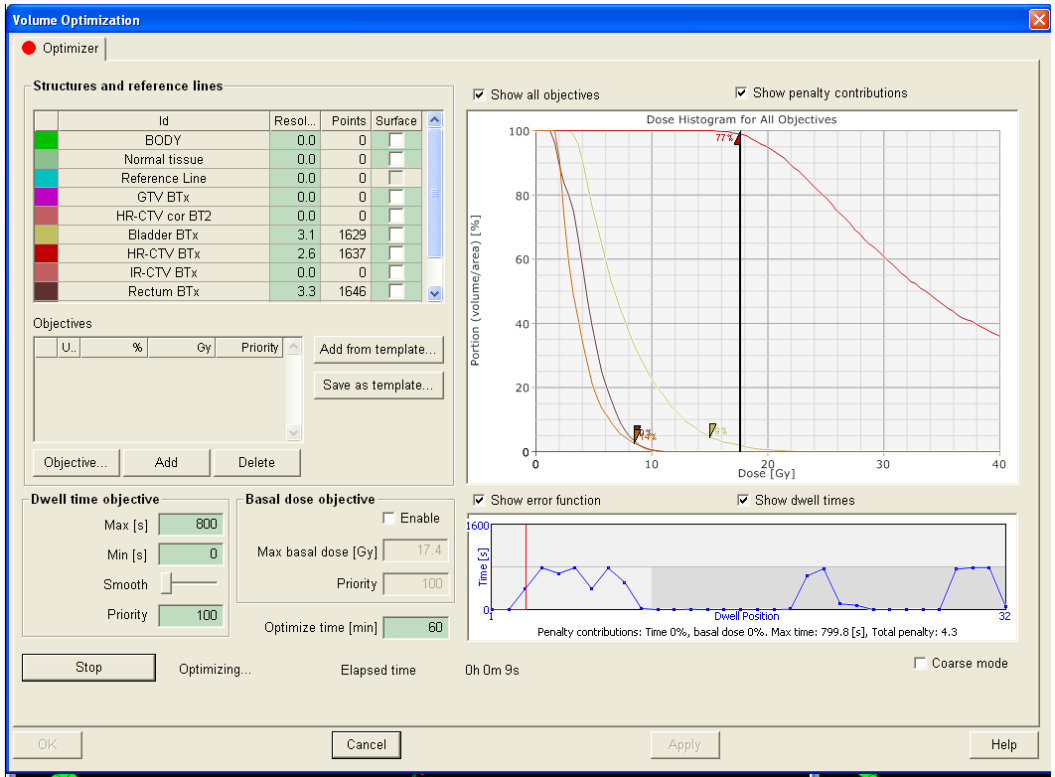


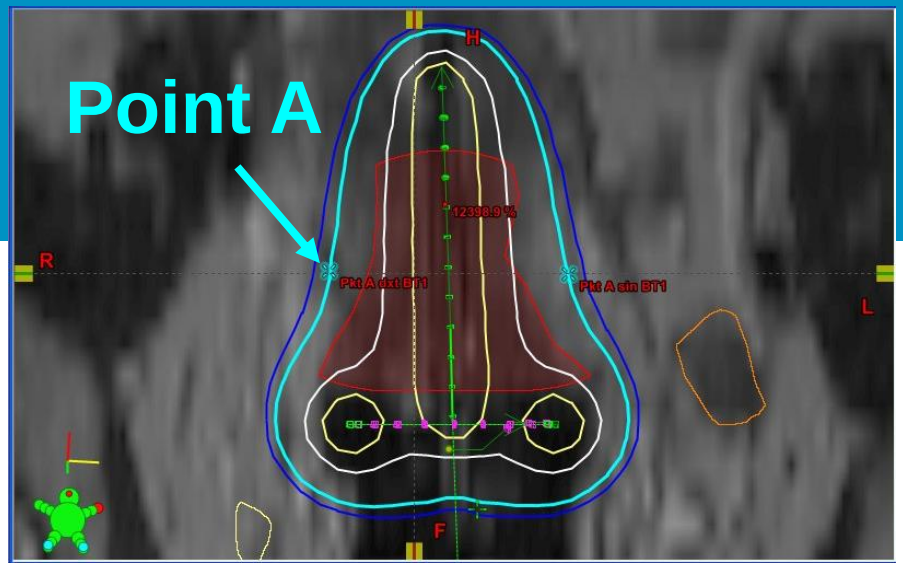


Affecting all dwell positions

Inverse dose optimisation

- **Controlled by DVH constraints**
- **Weighting factors for different structures**





Always start optimisation with Standard loading pattern Standard prescription

Calculation on MRI? It is OK!

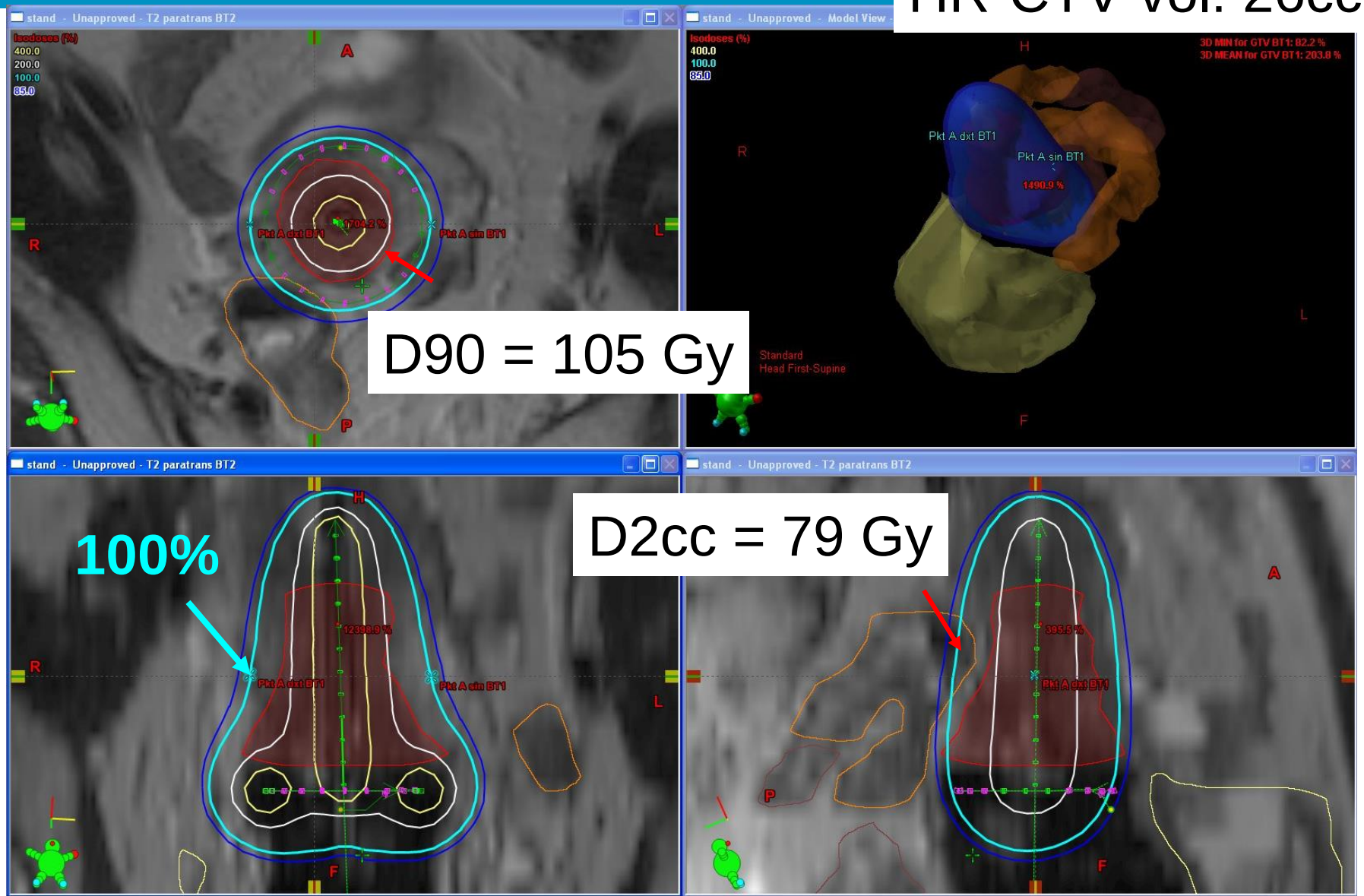
- **TG43 algorithm is based on water calculation and can be done on CT, MRI and US**
- **Model based algorithms take tissue into account (based on CT), but has limited impact for gyn brachy**

Implant	% Variation
Surface Mould (Nose)	9 ± 7
Head and Neck (Base of Tongue)	8 ± 8
Breast APBI –Multi Catheter	8 ± 2.0
Lip Implant	11 ± 14
Eye Lid	22 ± 37
Gynaecology – Vienna applicator (Polymer)	1 ± 0.2
Gynaecology – Ring applicator (SS)	4 ± 0.7

Courtesy Jamema Swamidas

Example 1: good response stage IB2 Standard plan

HR-CTV vol: 26cc



D90 = 105 Gy

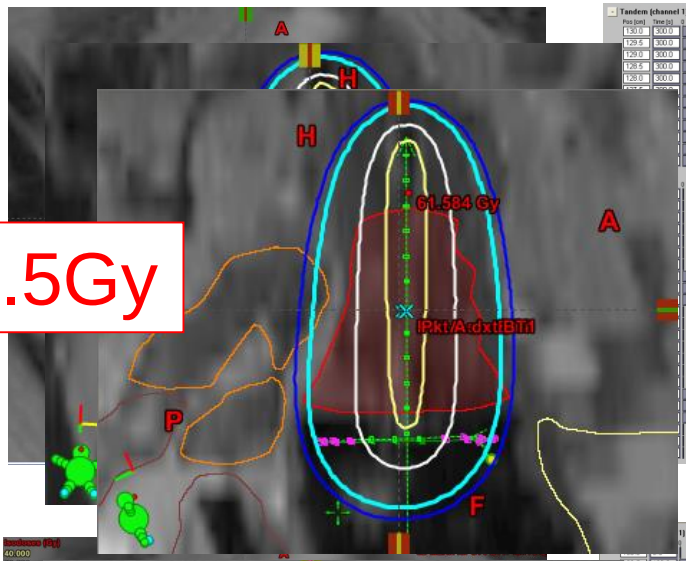
D2cc = 79 Gy

Example 1
Manual dose optimisation

Dose **Dwell times**

Standard

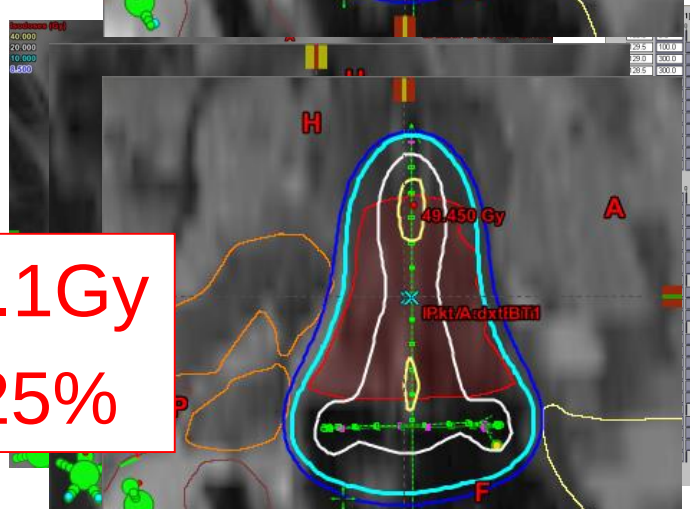
Point A = 17.5Gy

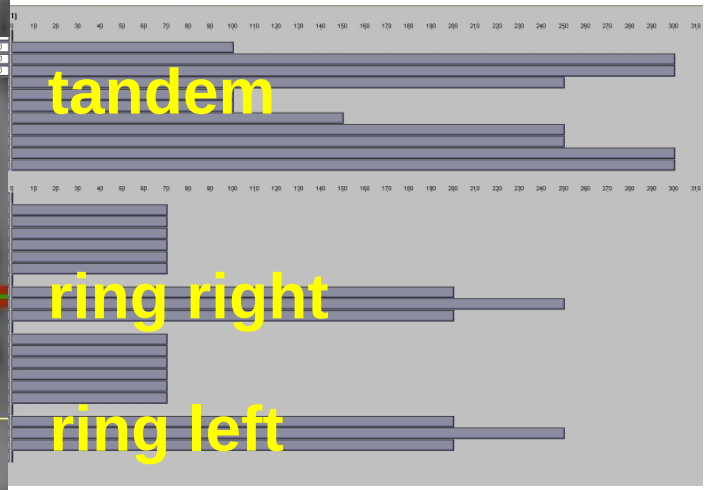


Manual optimisation

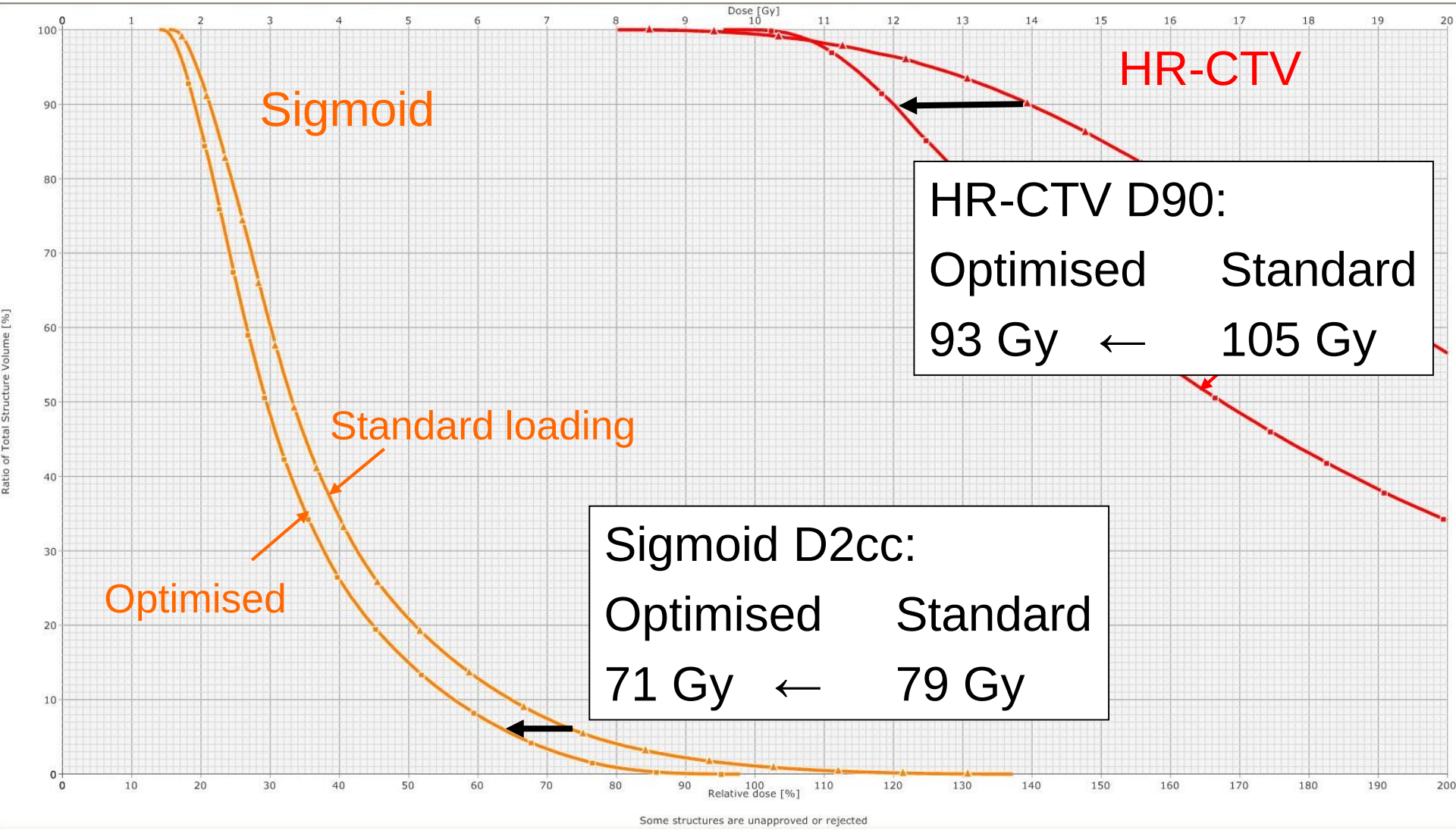
Point A = 13.1Gy

Reduction: 25%





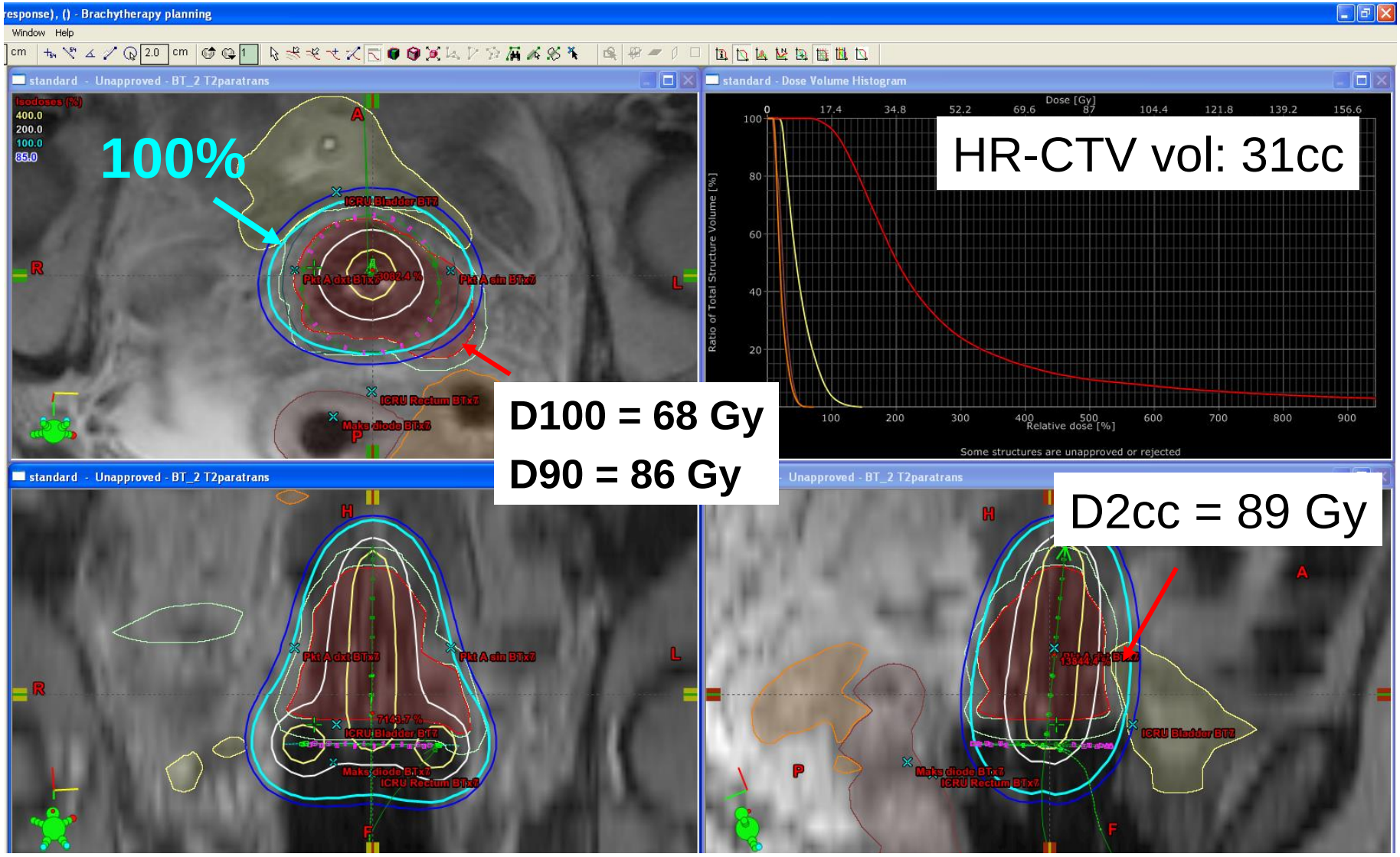
Example 1, DVH



Example 1, summary

- **Small tumour (HR-CTV vol 26cc)**
- **Decrease of pear (and point A dose)**
- **OAR dose decreased**
- **Planning aim: >85Gy**
- **Prescribed dose HR CTV D90: 93Gy**
- **100% isodose adjusted by ~5mm**

Example 2, Stage IIB Standard plan

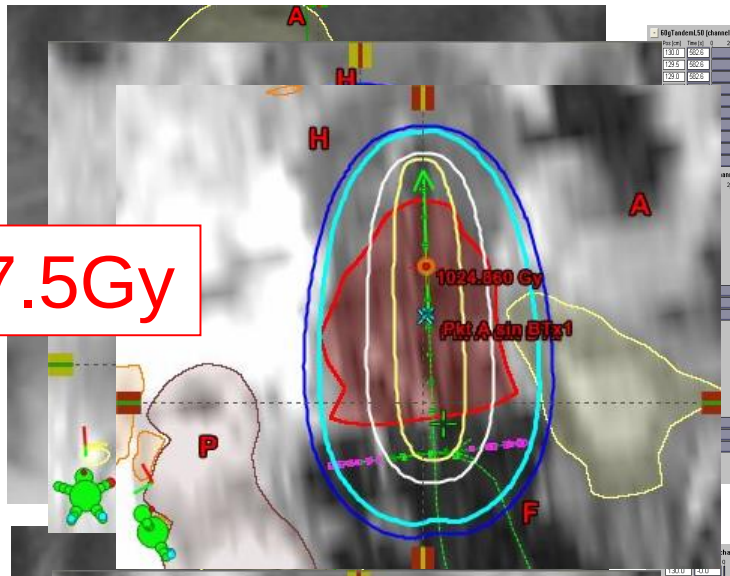


Example 2
Manual dose optimisation

Dose **Dwell times**

Standard

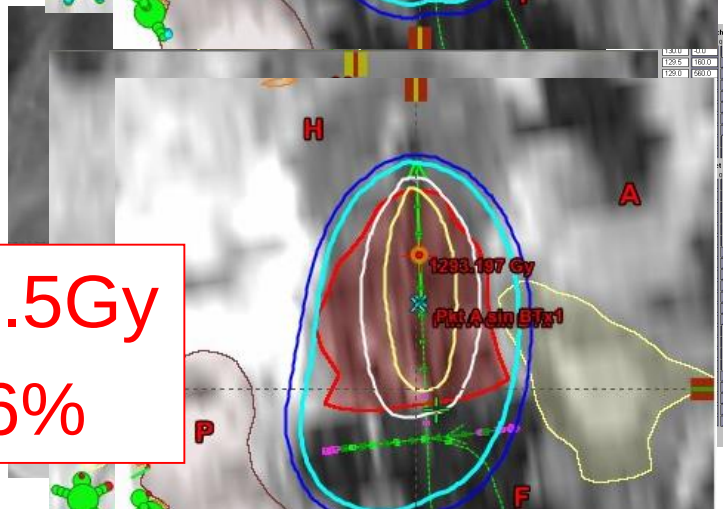
Point A = 17.5Gy

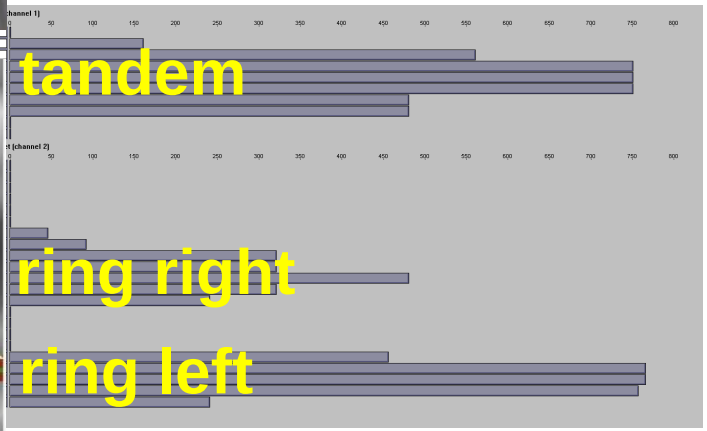


Manual optimisation

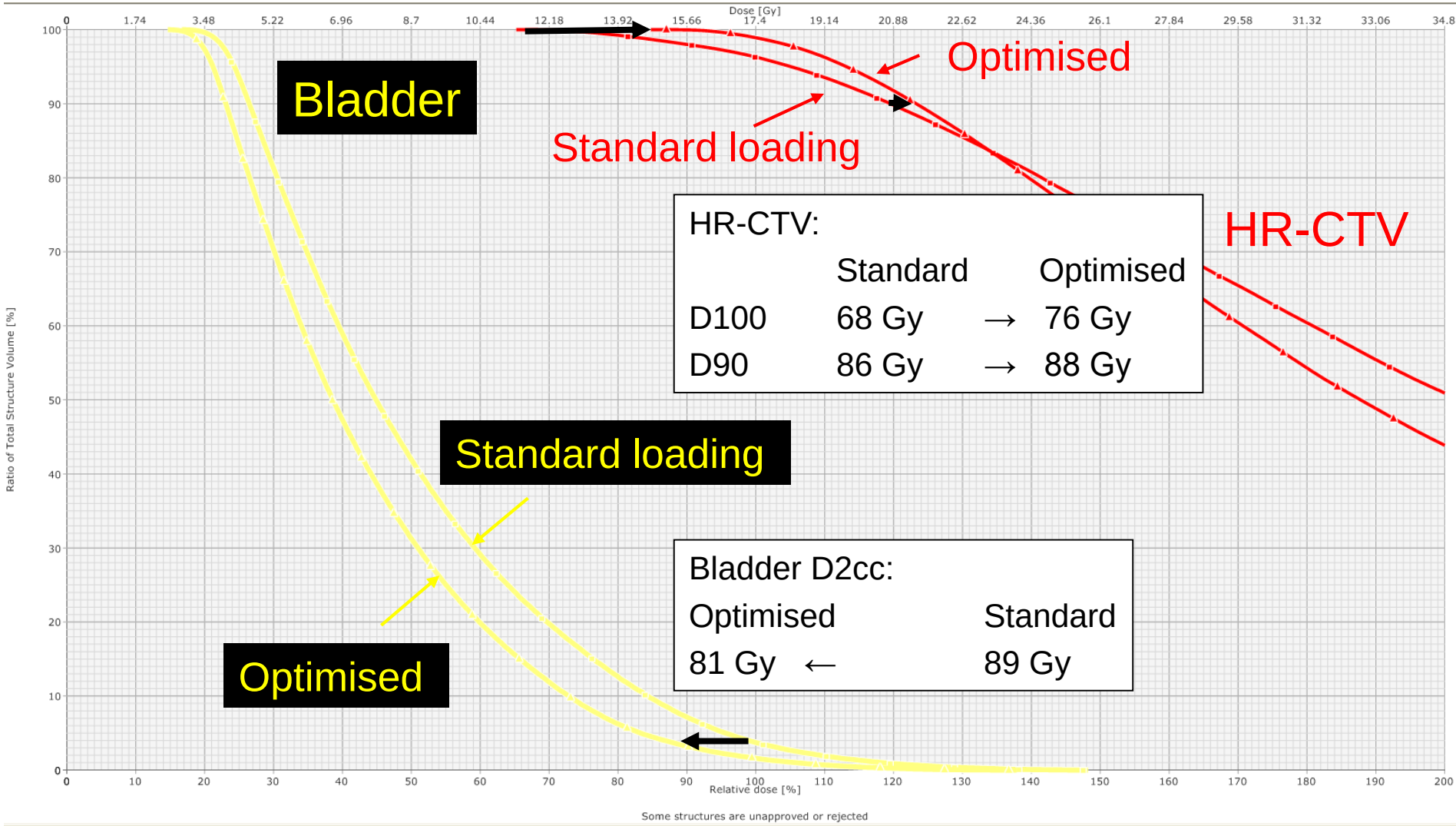
Point A = 16.5Gy

Reduction: 6%





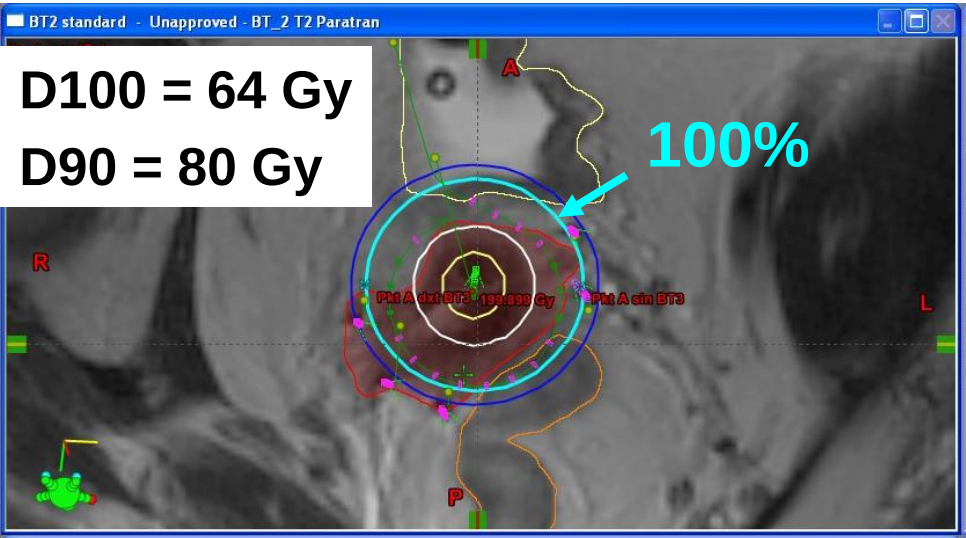
Example 2, DVH

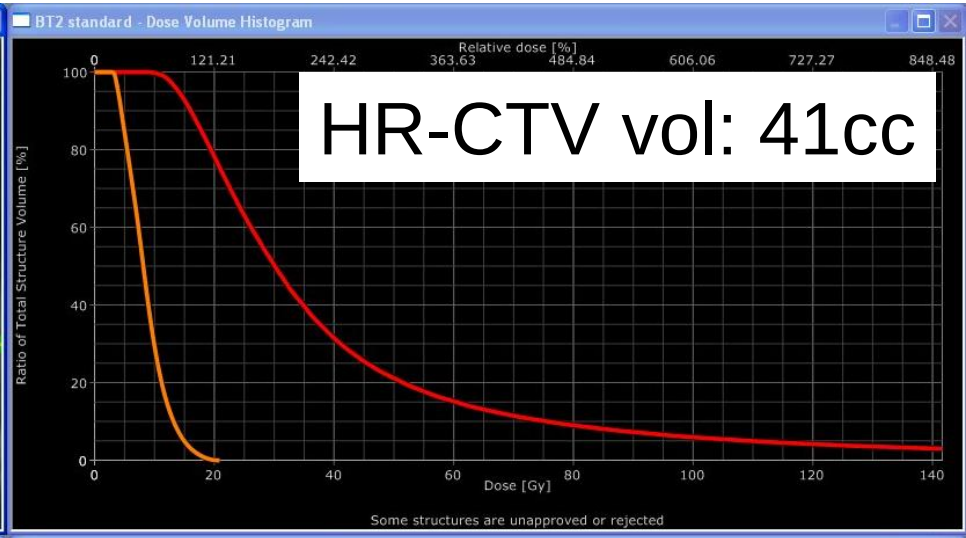


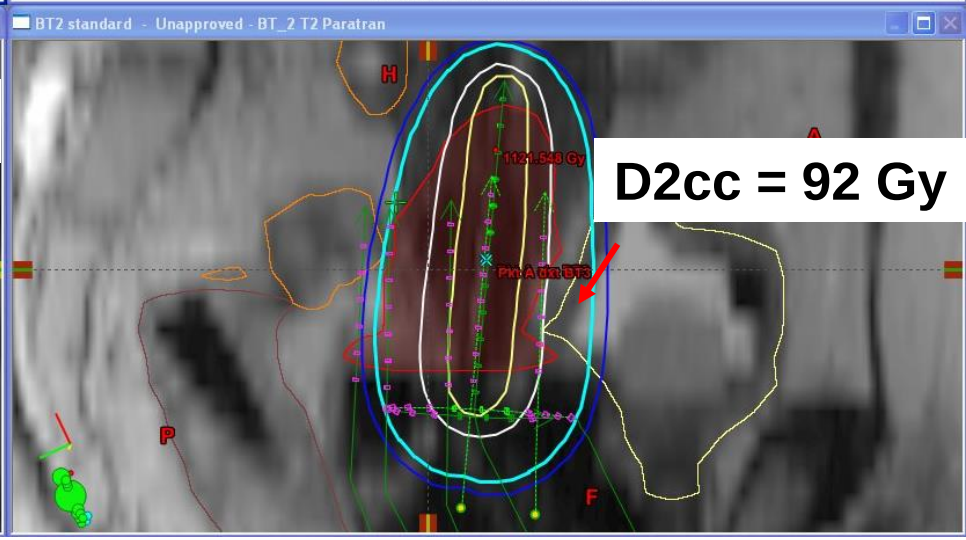
Example 2, summary

- **Small tumour (HR-CTV vol 31cc)**
- **Relatively small adaptations of the standard pear shaped isodose**
- **Target coverage increased – OAR dose decreased**
- **Planning aim: >85Gy**
- **Prescribed dose HR CTV D90: 88Gy**
- **100% isodose adjusted by ~5mm**

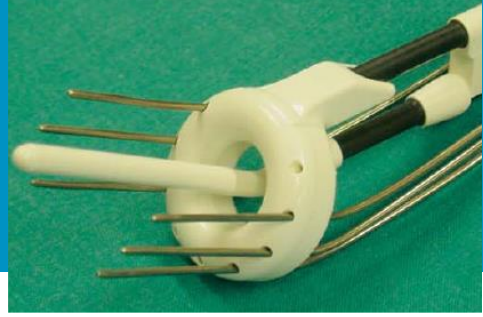
Example 3, Stage IIIB
Standard dose plan







Example 3
Manually optimised plan



Dose **Dwell times**

Standard

TRAK = 2.1 cGy

Manual optimisation

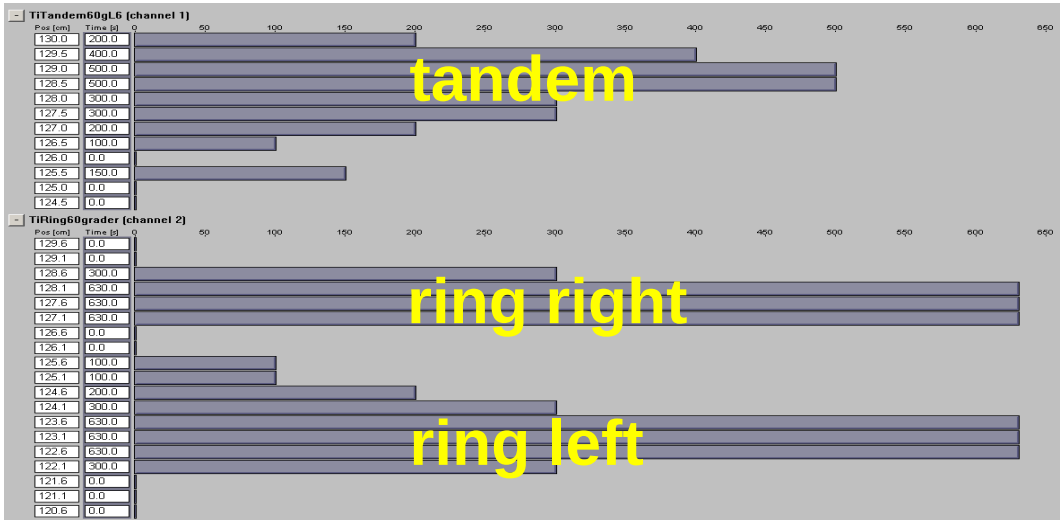
TRAK = 2.2 cGy

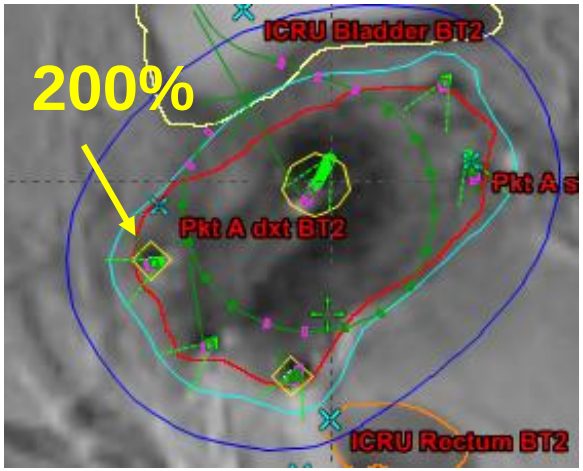
Increase: 7%

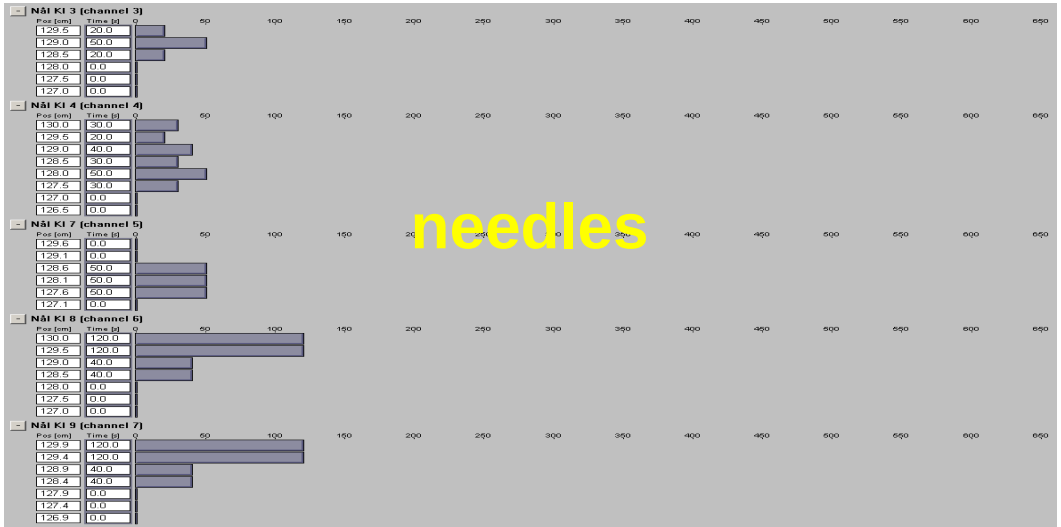
Loading of needles: dwell times and isodoses

Dwell times needles:

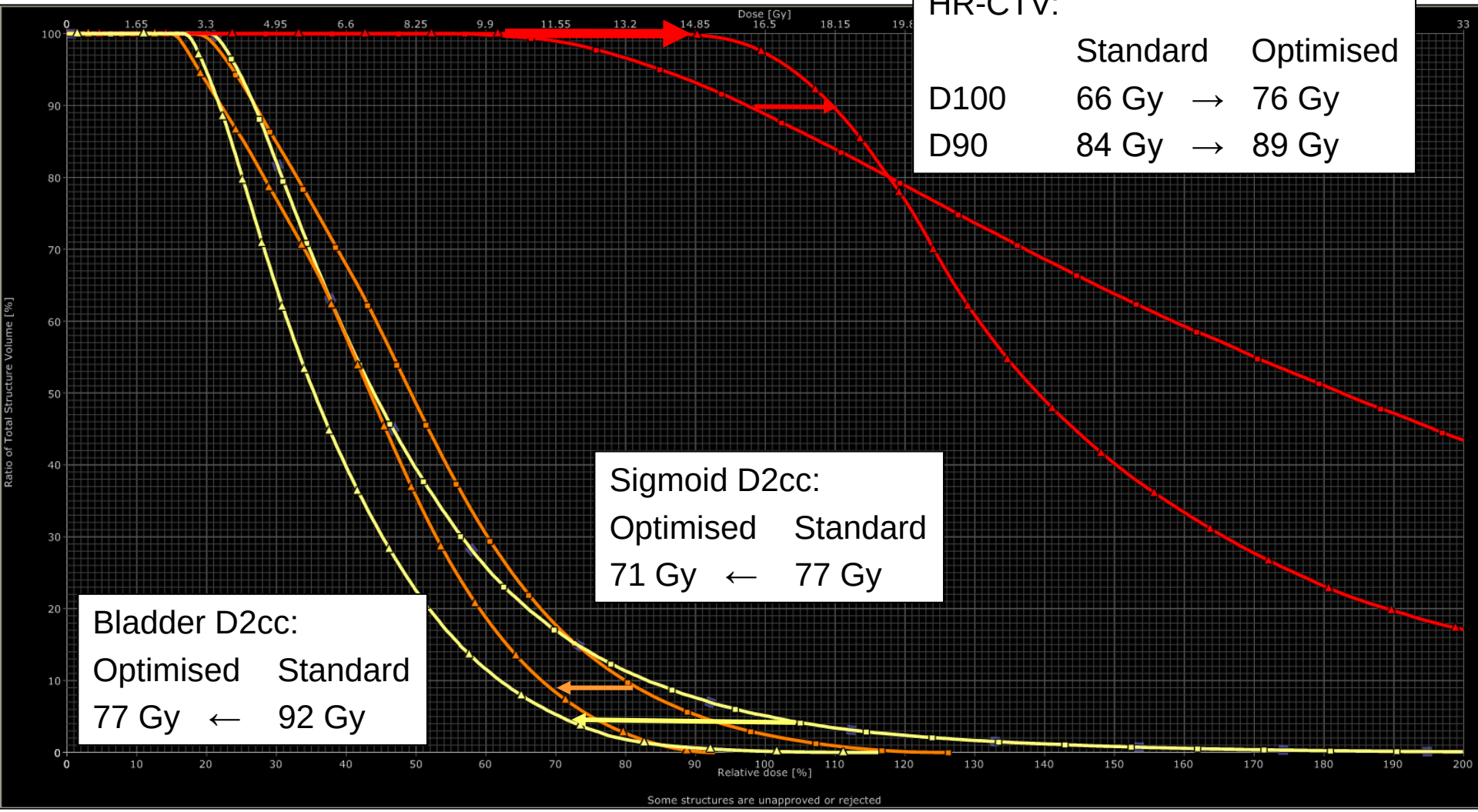
- **10-20% of dwell time in tandem/ring**
- **May be >10-20% if needle is placed directly in the GTV**







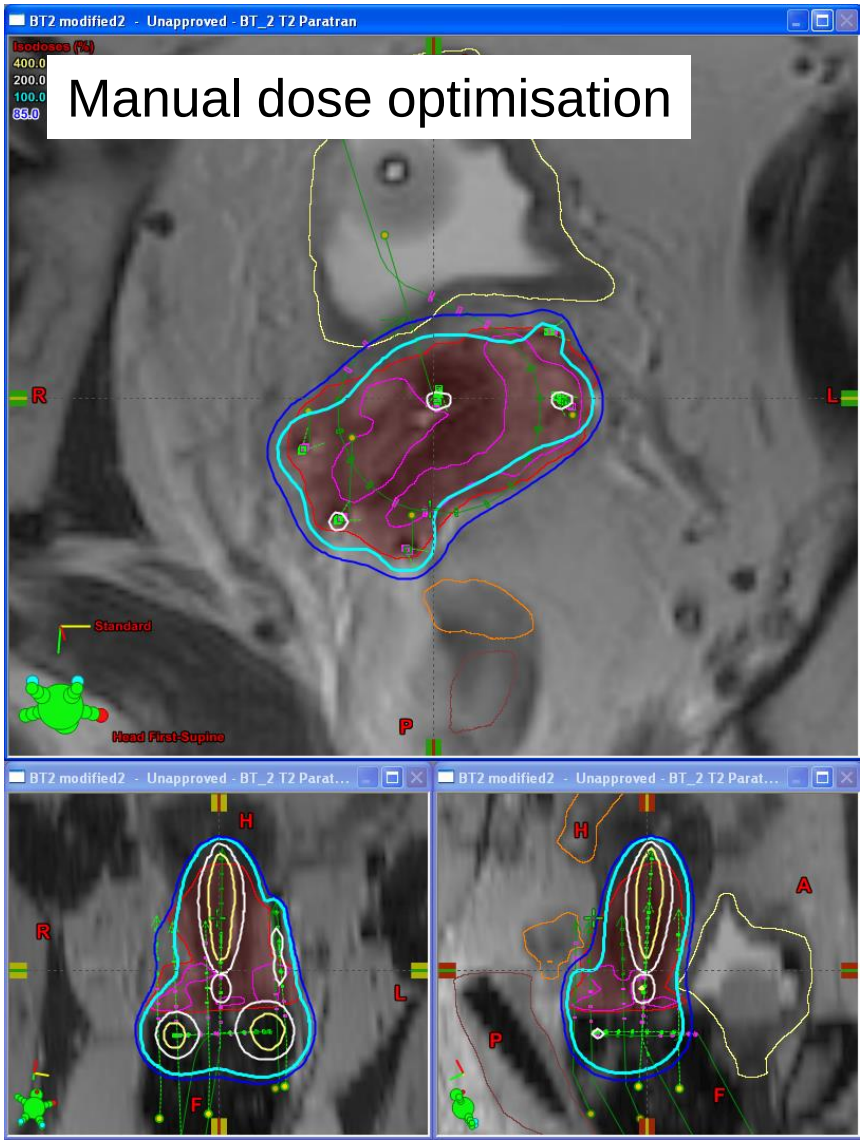
Example 3, DVH

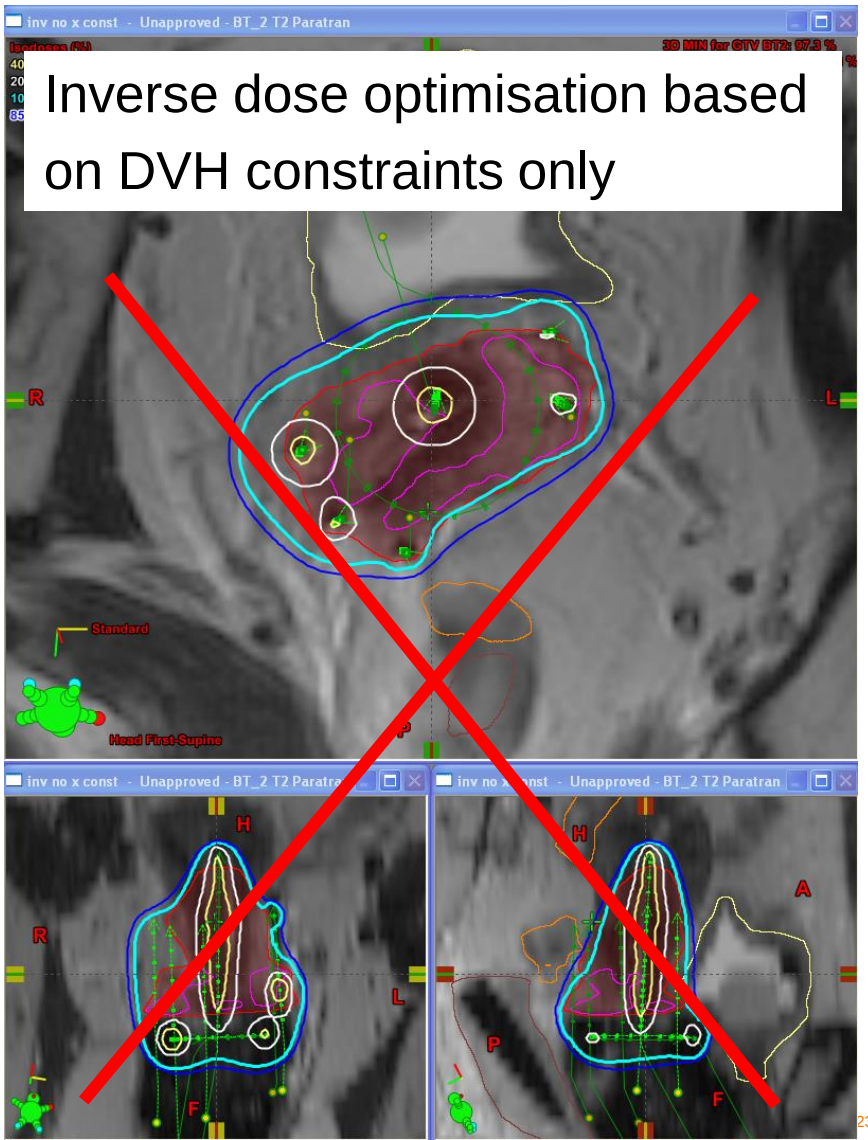


Example 3, summary

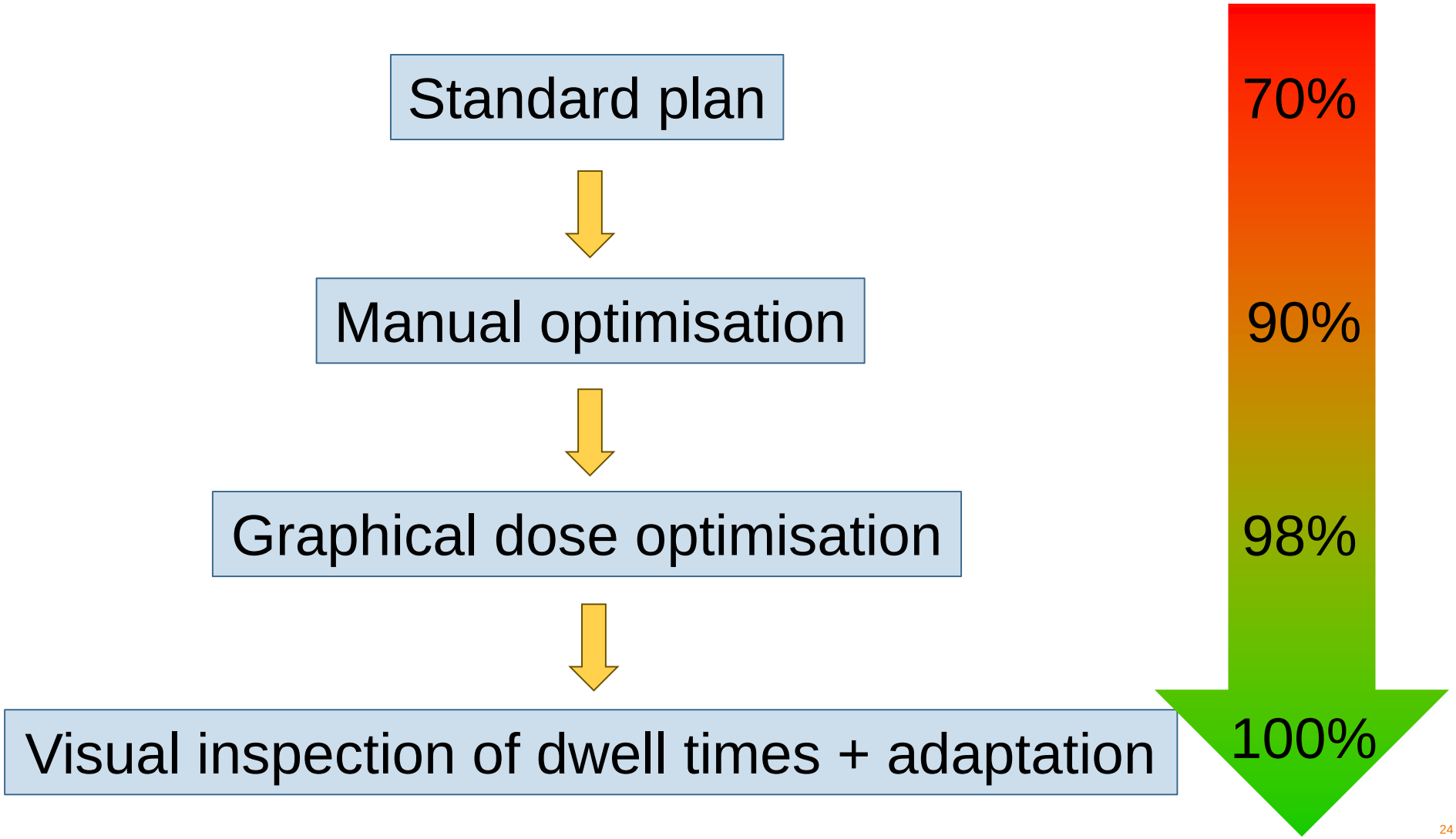
- **Bad response (HR-CTV vol 41cc)**
- **Need of modified applicator (ring+needles)**
- **Needle loading: <20%**
- **Target coverage significantly increased – OAR dose significantly decreased**
- **Planning aim: >85Gy**
- **Prescribed dose HR CTV D90: 89Gy**
- **100% isodose adjusted by ~ 10 mm**

Example 3, inverse planning

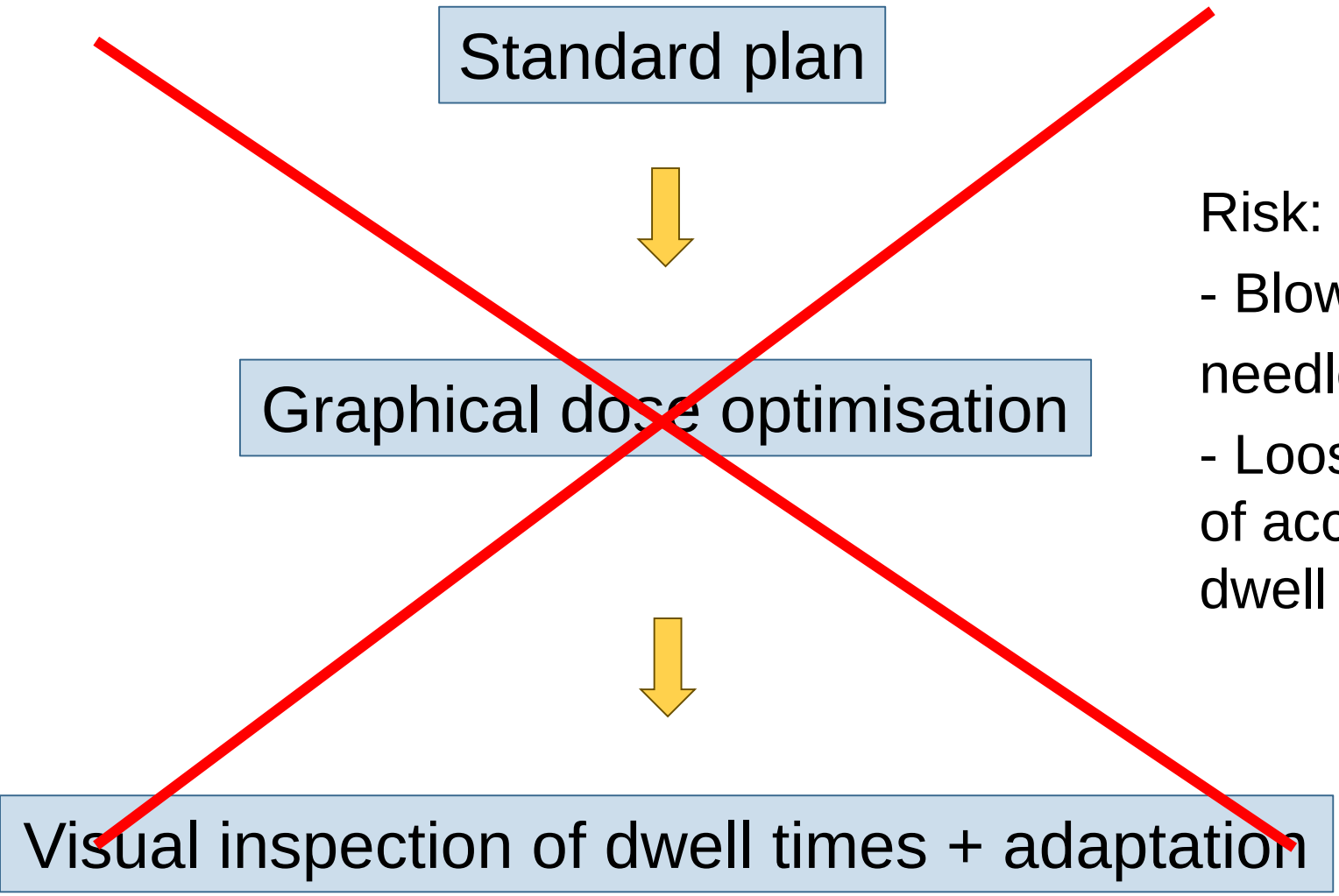




When to use graphical dose optimisation (dose shaper)?



When to use graphical dose optimisation (dose shaper)?

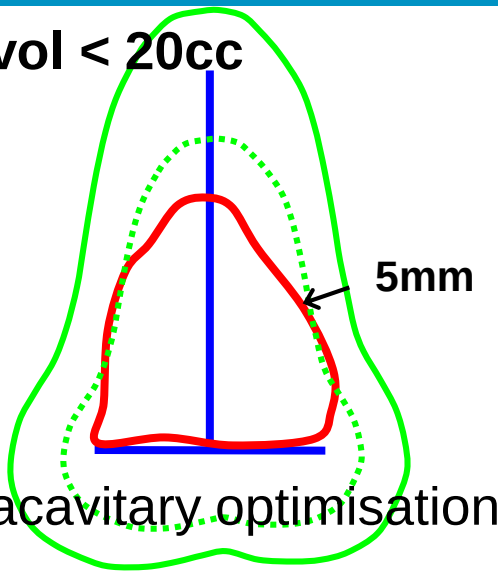


Risk:

- Blowing up needle loading
- Loosing intuition of acceptable dwell times

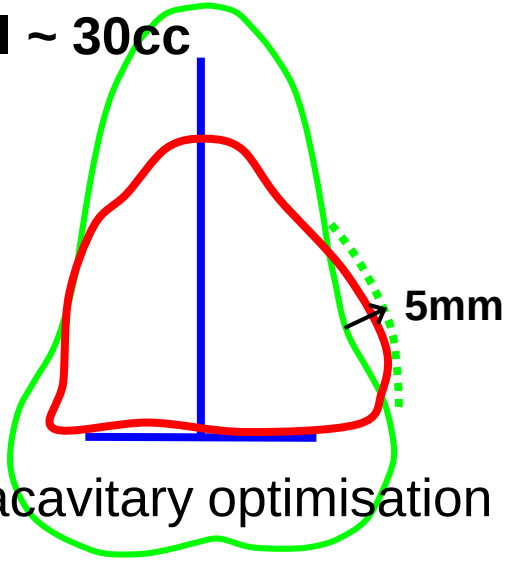
Typical scenarios of dose optimisation

HR-CTV vol < 20cc



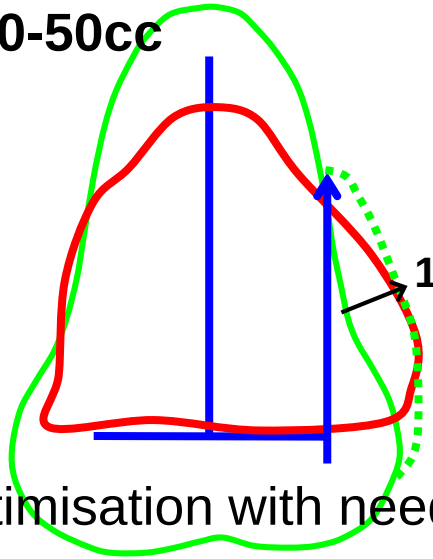
Intracavitary optimisation

HR-CTV vol ~ 30cc



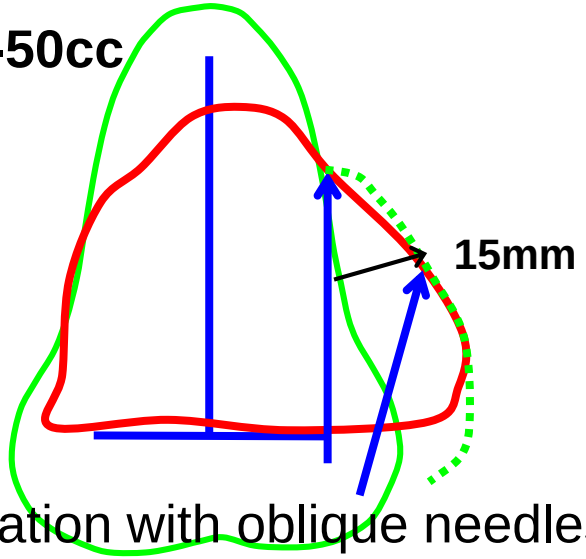
Intracavitary optimisation

HR-CTV vol > 40-50cc



Optimisation with needles

HR-CTV vol > 40-50cc



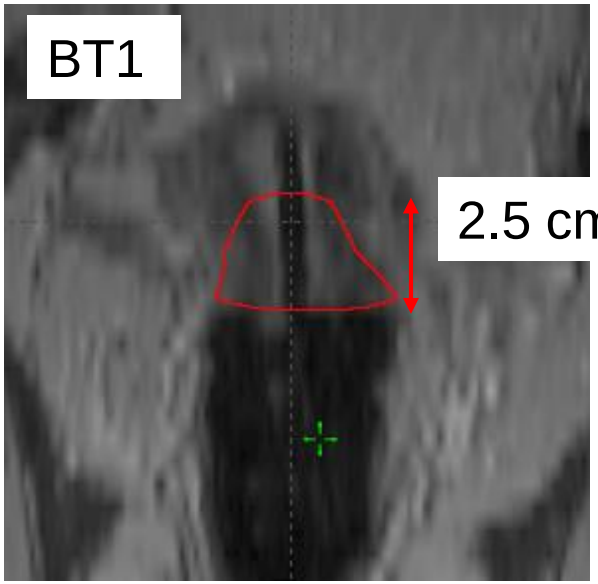
Optimisation with oblique needles

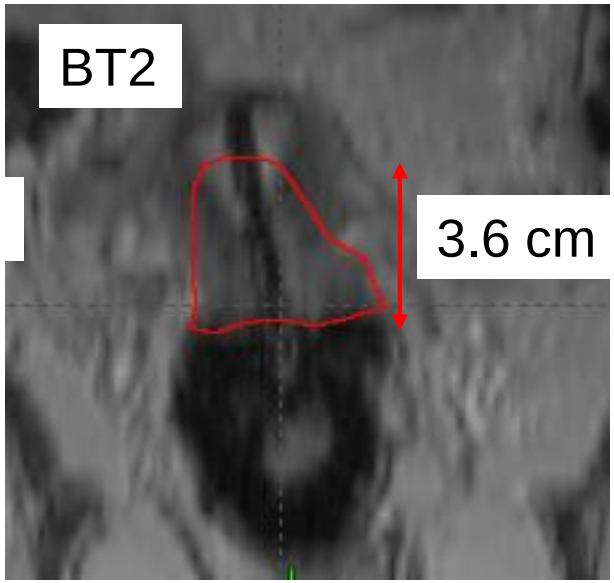
Conclusion – optimisation techniques

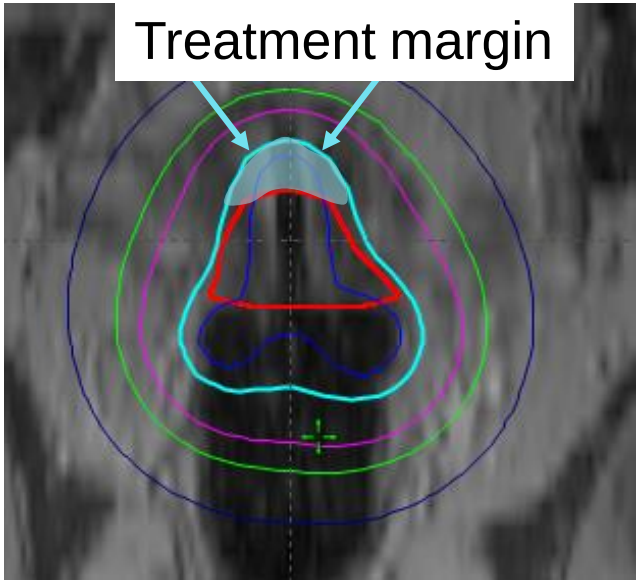
Manual	Conservative and “safe” Iterative procedure Dependent on experience of dose planner
Graphical	Fast for small adaptations and fine tuning after manual opt Beware of: -dwell times -deviations from standard loading
Inverse	Fast Requires extra contouring + manual adaptations Beware of: -dwell times -high dose regions -dose to non-contoured tissue -deviations from standard loading

Example contouring uncertainty

- **Variation in cranial border of HR-CTV**
- **Intra-observer variation!**
- **<u>Load the tandem above the CTV_{HR} when feasible</u>**

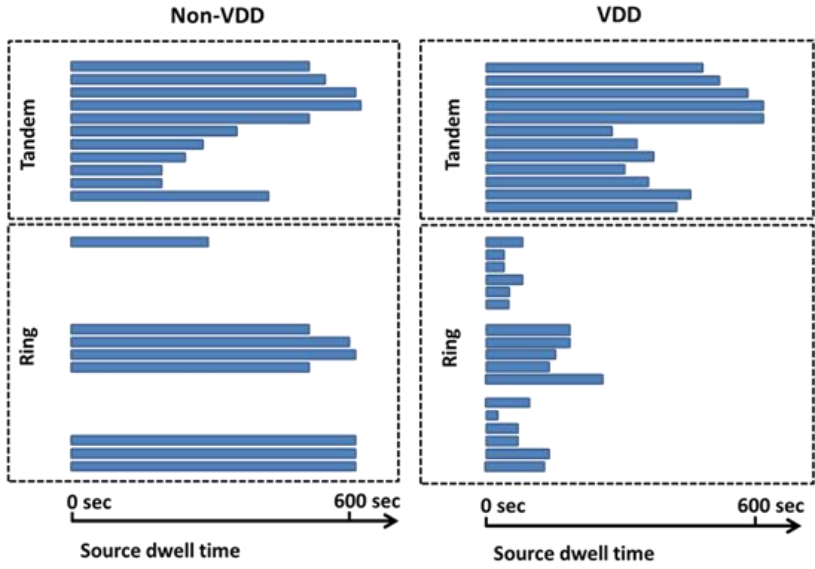


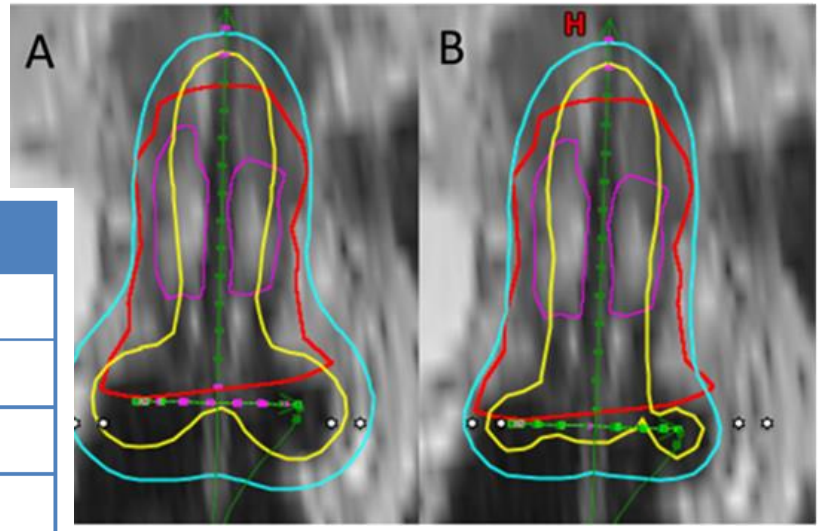




Vaginal dose de-escalation

- **Change of loading pattern:**
  - **Shift of dwell time from vaginal sources to tandm/needles**
  - **E.g. 140% isodose out of vaginal mucosa**
  - **Aim for <30-40% loading in ring/ovoids**

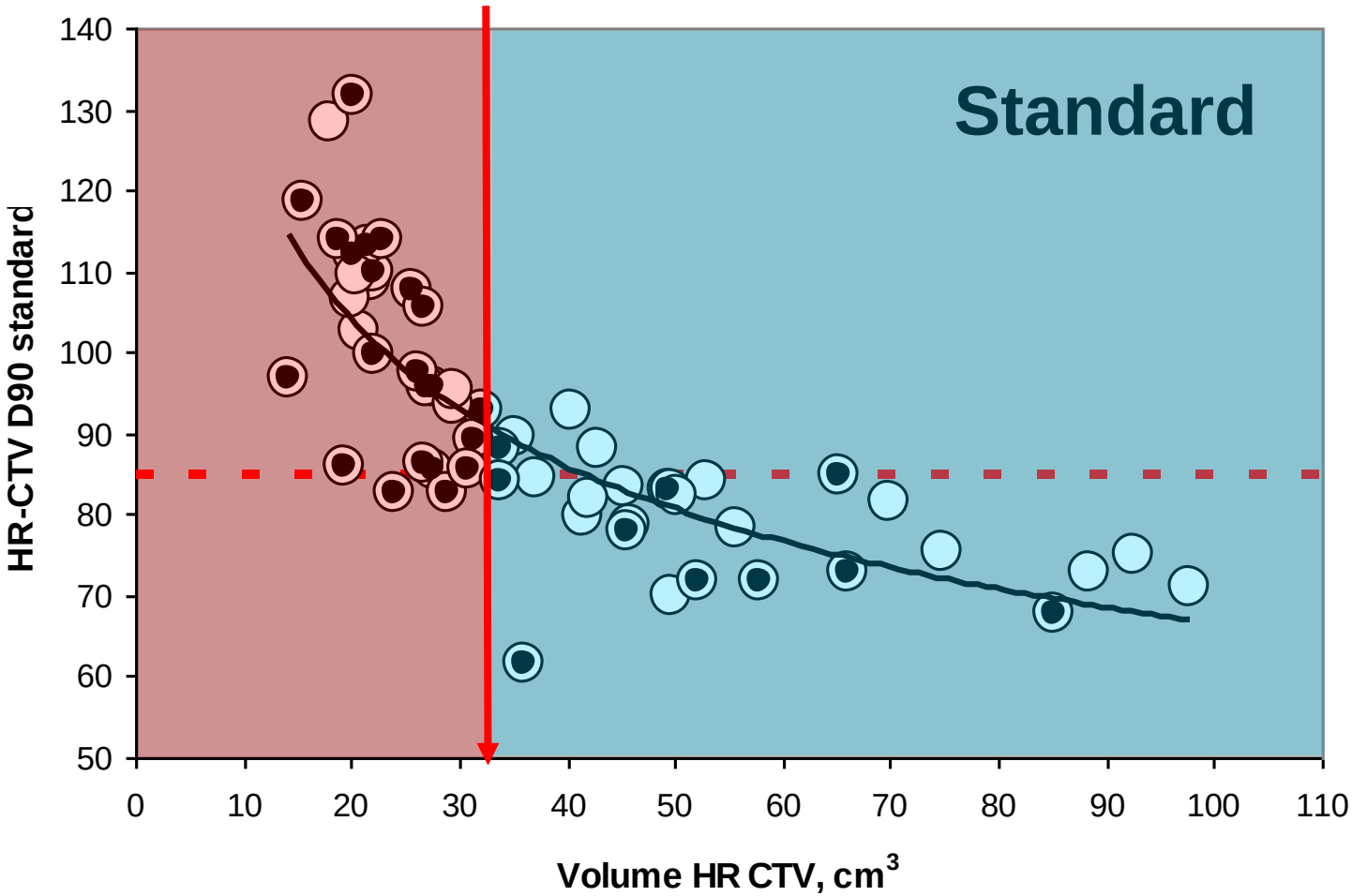




	Aim	Priority
ICRU recto-vaginal point dose	<65Gy EQD2 (EBRT+BT)	Primary
The ratio of vaginal TRAK and total TRAK	<30-40%	Secondary
Vaginal lateral dose points at 5mm	<85Gy EQD2 (EBRT+BT)	Secondary
Visual inspection of the 140% isodose	Intruding as little as possible into vaginal tissue, and preferentially located within the applicator	Secondary

Volume is important!

Median volume: 32cc

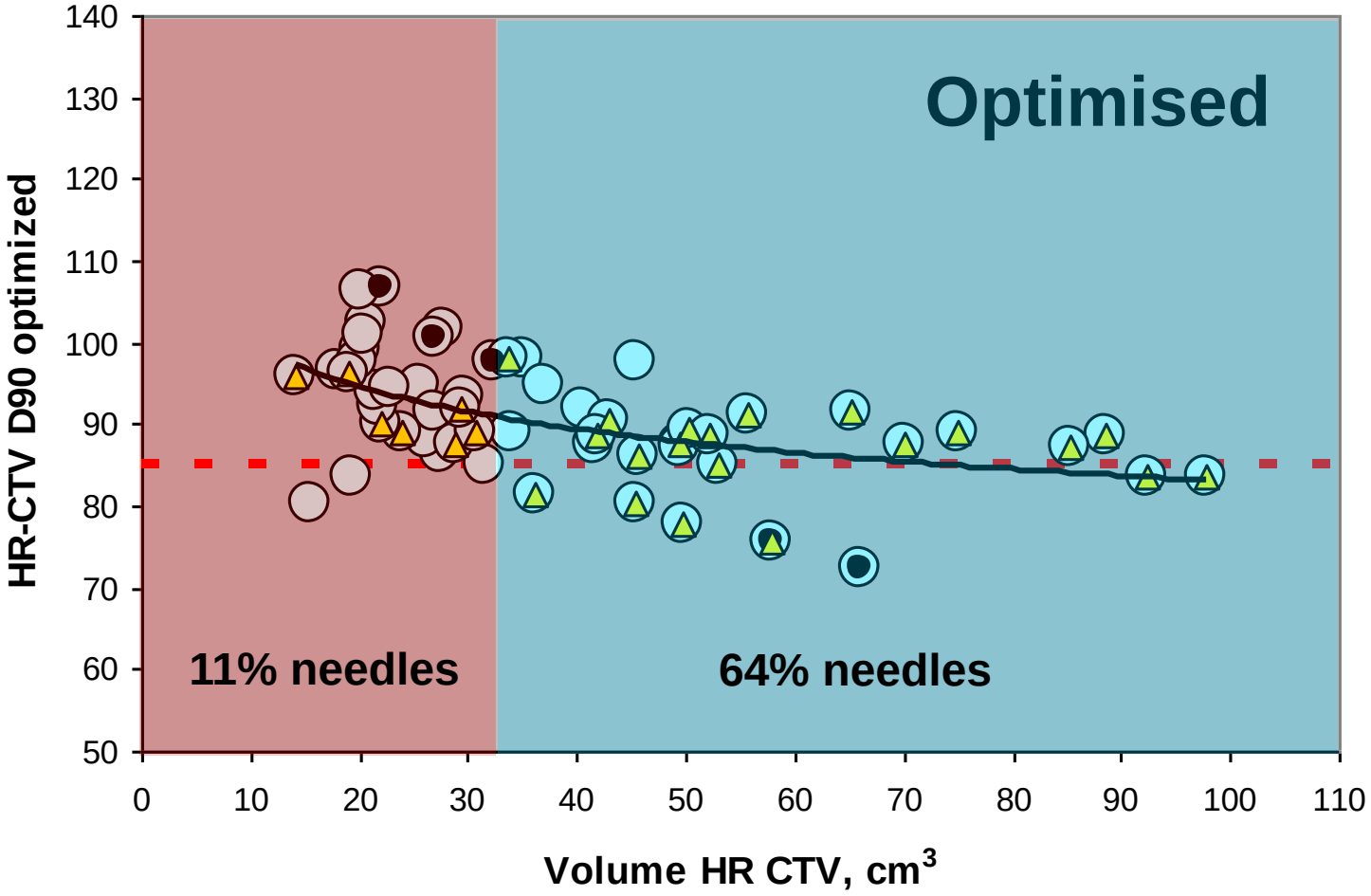


- Violation of OAR constraint

K Tanderup et al, Radiother Oncol 2010

Volume is important!

K Tanderup et al, Radiother Oncol 2010

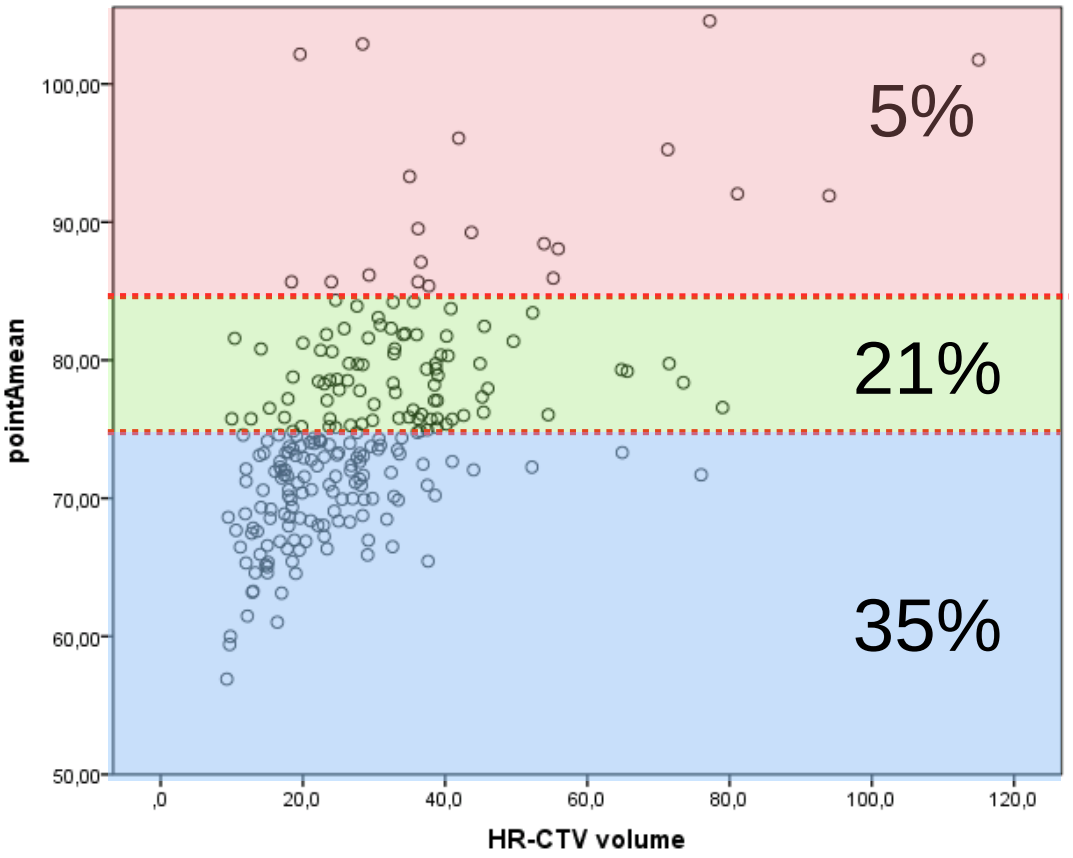


Violation of OAR constraint

Application of needles

Point A dose and HR CTV volume EMBRACE - Intracavitary applications

- **There is a significant variation of point A dose as compared to traditional levels like 75Gy and 85Gy**
  - **35% < 75Gy**
  - **44% either >85Gy or IC/IS**

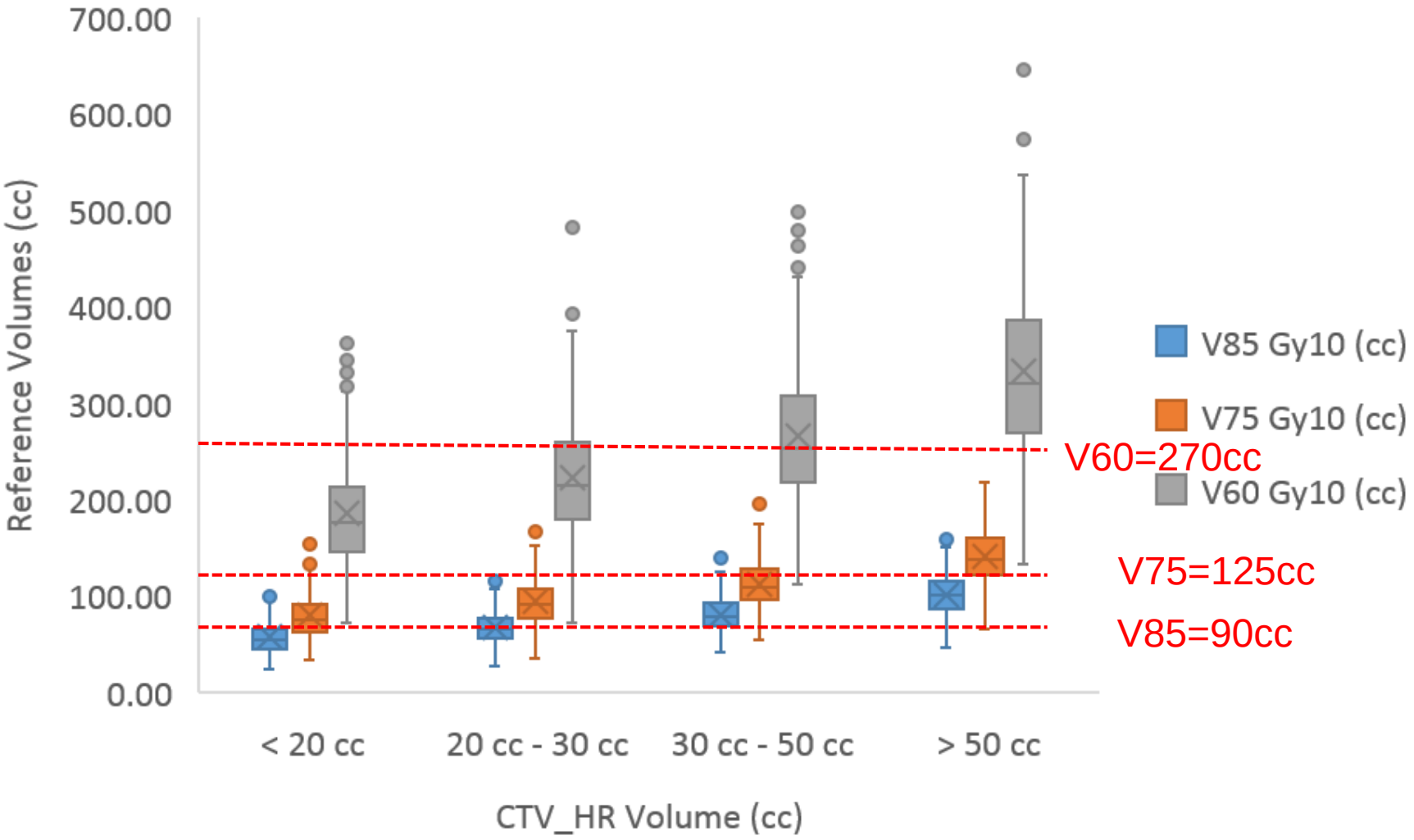


+ 39% IC/IS

Irradiated volumes of optimised plans

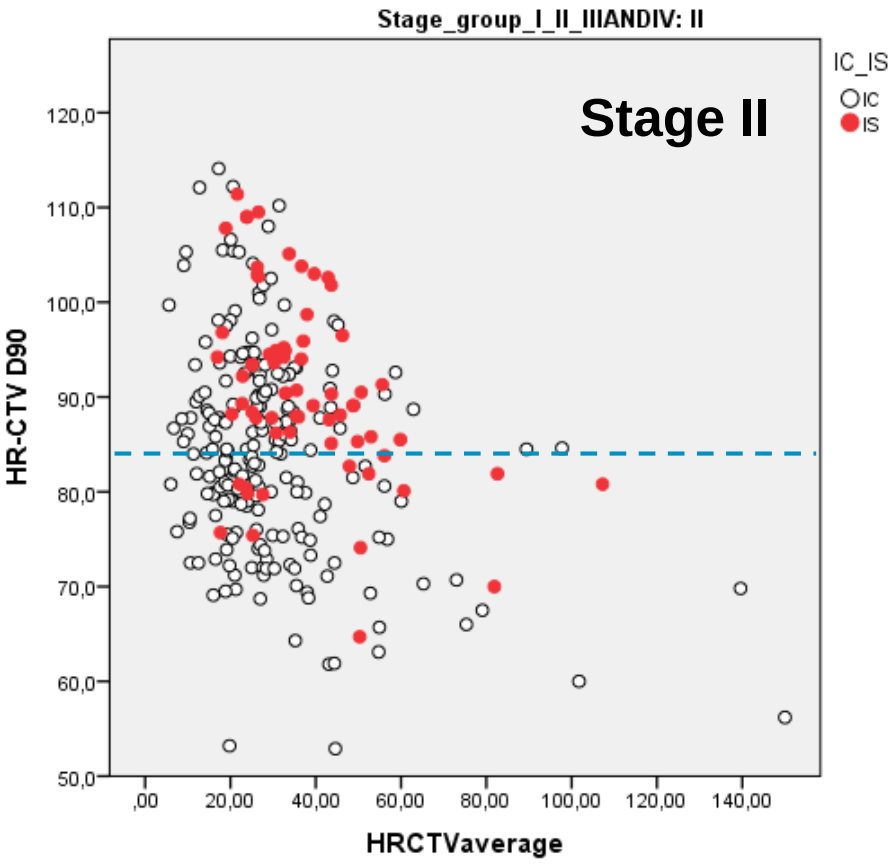
	No. patients	V85 Gy $EQD2_{10}$ (cm^3)	V75 Gy $EQD2_{10}$ (cm^3)	V60 Gy $EQD2_{10}$ (cm^3)
All patients	1204	71 (23 ÷ 184)	99 (34 ÷265)	230(72 ÷ 786)
CTV_{HR} < 30 cm^3	670	60 (23 ÷ 118)	83 (34 ÷ 166)	195 (72 ÷ 392)
$CTV_{HR} \geq 30$ cm^3	534	86 (41 ÷ 184)	119 (55 ÷265)	278 (112 ÷ 786)
Stage I & II	957	69 (23 ÷ 184)	96 (34 ÷265)	225 (71 ÷786)
Stage III & IV	230	80 (28 ÷ 171)	111 (37 ÷ 230)	258 (79 ÷ 645)
Standard plan (T&R, T&O)	-	89 (78, 100)	124 (109, 138)	270 (247, 293)

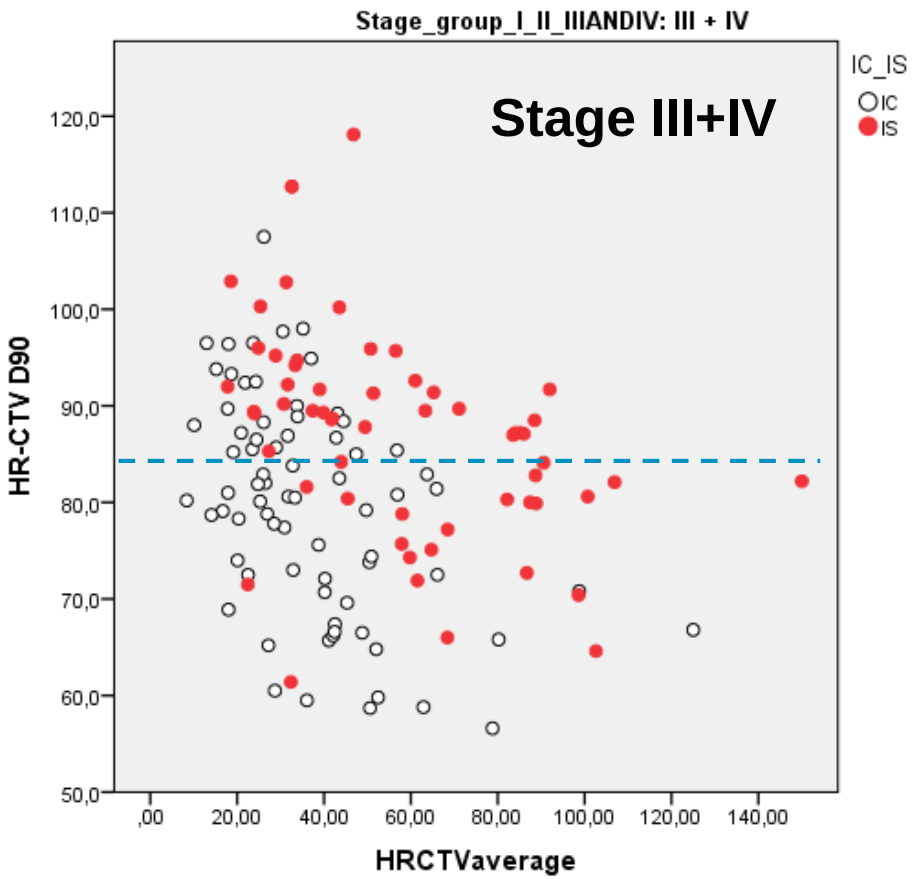
Irradiated volumes of optimised plans



Importance of needles

IC/IS increases therapeutic window by ~10Gy ***(Fokdal L et al. Radiother Oncol 2013 April;107(1):63-8)***





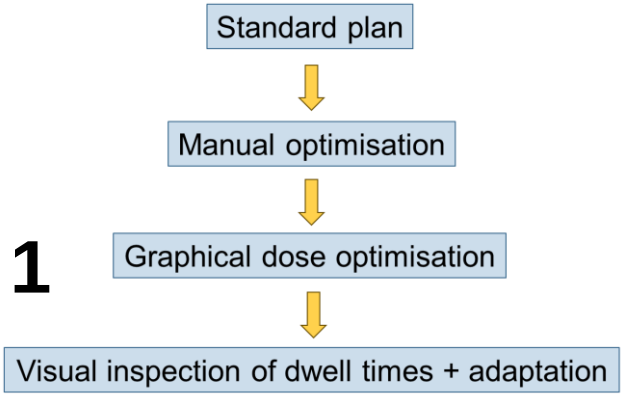
Take home message – dose optimisation

- **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%**

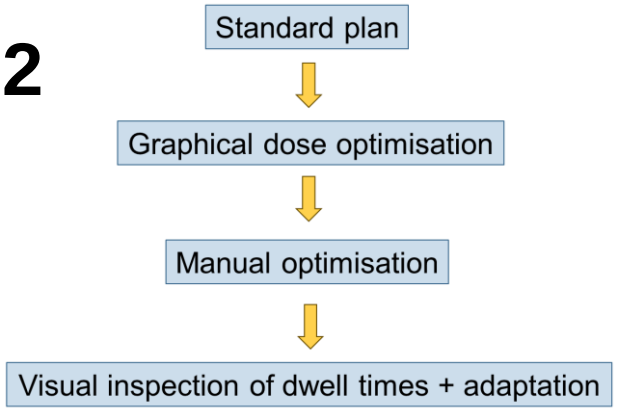
- **Application of combined intracavitary-interstitial applicator: increased therapeutic window by ~10Gy**

I prefer to do optimisation

A. Flow 1

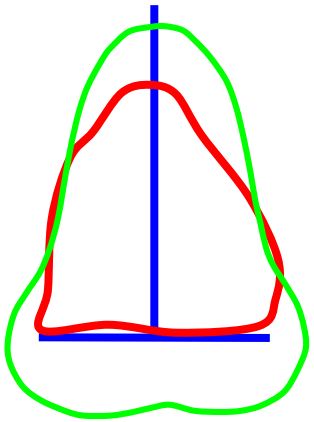


B. Flow 2

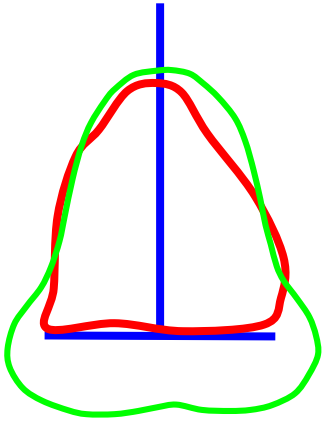


Which dose distribution do you prefer?

A. **Plan 1**



B. **Plan 2**



Radiobiological models to combine dose from external beam radiotherapy and brachytherapy (HDR, MDR, LDR, PDR)

Daniel Berger, Kari Tanderup

ESTRO-AROI Teaching Course
Transition from conventional 2D to 3D radiotherapy with a special emphasis on brachytherapy in cervical cancers

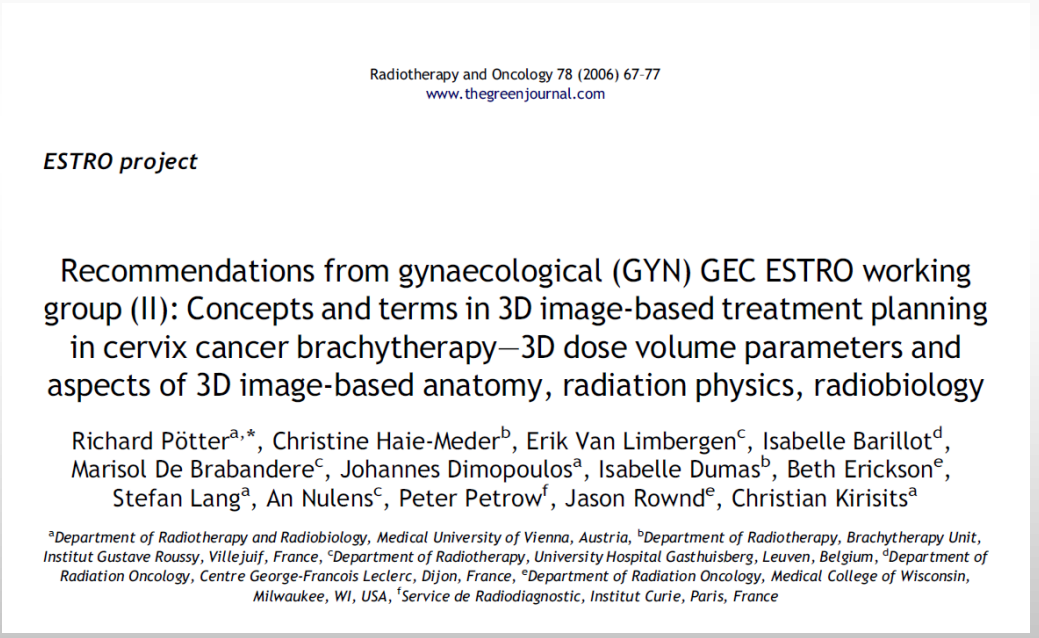
Bengaluru 2017

Challenge

- Brachytherapy is hypo-fractionated
- A variety of schedules exist:
  - 7Gy x 3
  - 9Gy x 2
  - 7Gy x 4
- How to communicate doses between institutions?
- We need biologically equieffective doses!

Prescribing, Recording and reporting: GEC ESTRO and ICRU

GEC ESTRO recommendations II



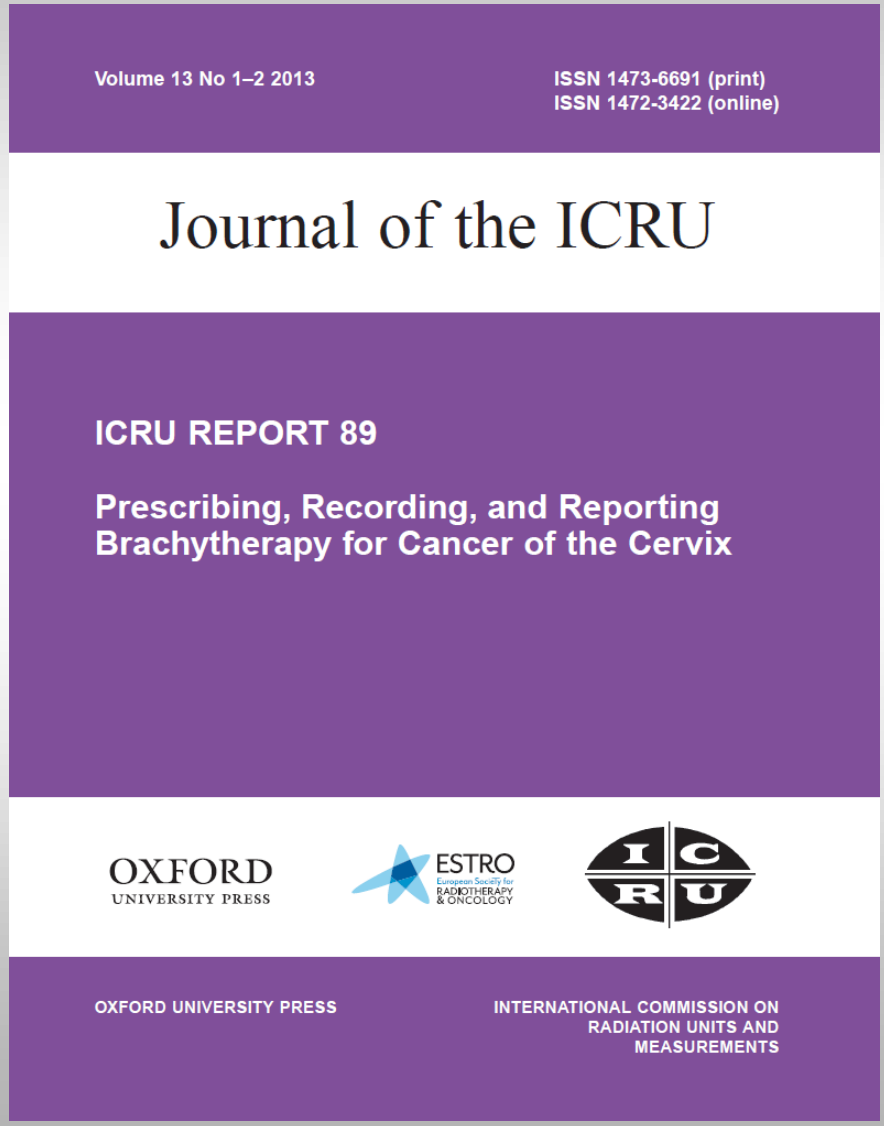
Radiotherapy and Oncology 78 (2006) 67–77
www.thegreenjournal.com

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]

[a]*Department of Radiotherapy and Radiobiology, Medical University of Vienna, Austria,* [b]*Department of Radiotherapy, Brachytherapy Unit, Institut Gustave Roussy, Villejuif, France,* [c]*Department of Radiotherapy, University Hospital Gasthuisberg, Leuven, Belgium,* [d]*Department of Radiation Oncology, Centre George-Francois Leclerc, Dijon, France,* [e]*Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, USA,* [f]*Service de Radiodiagnostic, Institut Curie, Paris, France*



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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

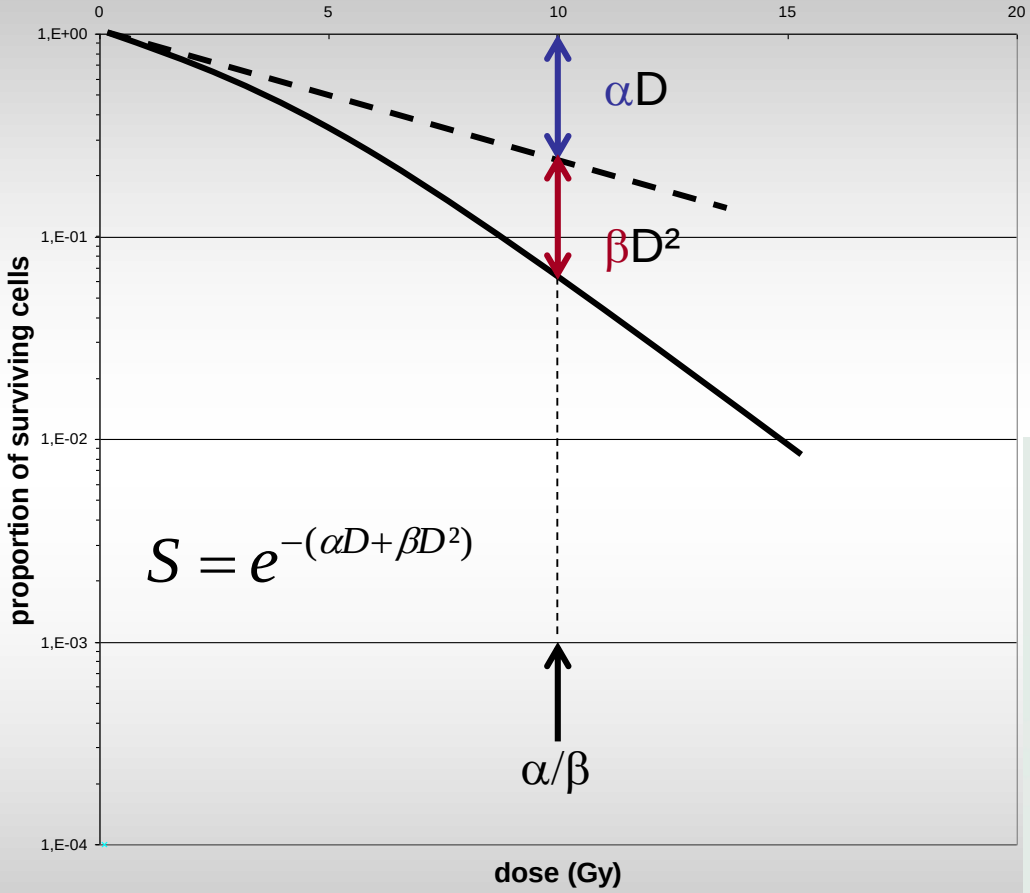
4 R's of radiobiology

- Repair
  - Repair of sub-lethal DNA damage
- Redistribution
  - Radiosensitivity depends on phase in the cell cycle → redistribution changes radiosensitivity
- Repopulation
  - Cell divide during a radiotherapy treatment
- Reoxygenation
  - Radiosensitivity changes due to change in oxygenation

Which of the following radiobiological effect(s) is(are) taken into account in the EQD2 calculation when using the LQ-model?

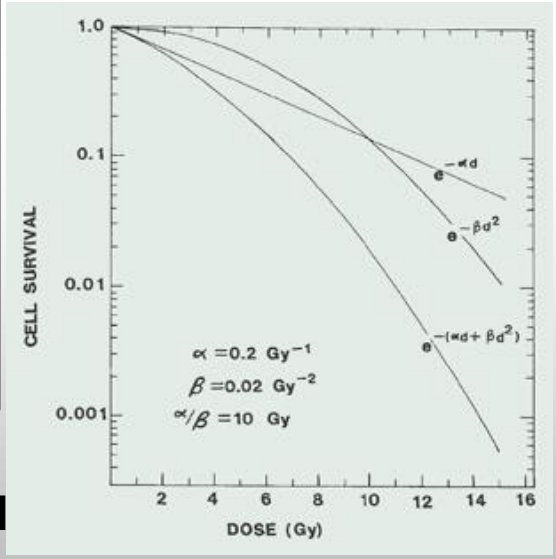
A. Repair
B. Redistribution
C. Repopulation
D. Reoxygenation
E. all

Linear-Quadratic Model



-> Lethal damage

-> Sublethal damage



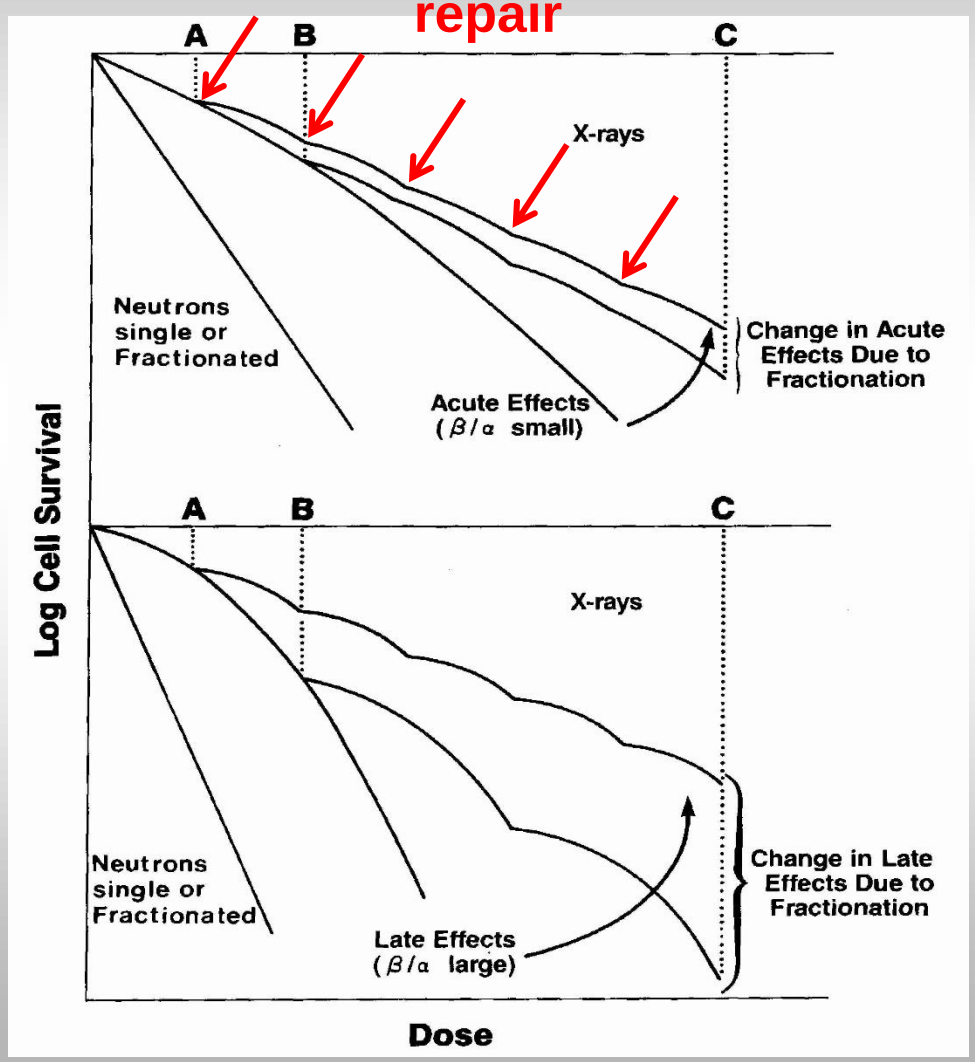
Survival curve according to the LQ-model

This can be used to fit a continuously bending curve to cell survival data

remember survival curve by Puck and Marcus

Fractionation & acute and late reacting tissue

Repair between fractions:
- The shape of curve starts over again!



LQ model

- **Recovery or Repair (half-time ~1.5hour)**
- ~~**Redistribution**~~
- ~~**Repopulation (< 1 day)**~~
- ~~**Reoxygenation**~~

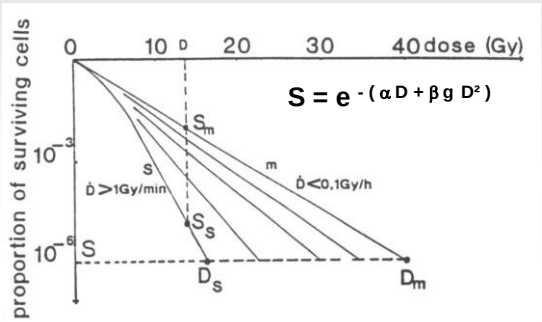
Considered in the mathematical description (“equation”)

Radiobiological Considerations HDR

Linear - Quadratic model for incomplete monoexponential sublethal (DNA) damage repair

- **Biologically Effective Dose:**

$$BED = nd\,[\,1 + d\,/\,(\alpha/\beta)\,]$$



The Role of Dose Rate in Brachytherapy (J. Dutreix) In: A Practical Manual of Brachytherapy (Pierquin / Marinello, Medical Physics Publishing)

- **BED ... <u>virtual dose value</u> that produces the same biological effect as the physical dose with an infinite low dose rate**

n ... number of equal fractions
d … dose per fraction

<u>tissue dependent parameters :</u>

α/β ...parameter describing lethal / sublethal lesions

Calculation of EQD2 for HDR

EQD2: Absorbed doses that, when delivered with 2Gy per fraction, would produce the same biologic effect

$$EQD_2 = n \cdot d \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

- n: number of fractions
- d: fractional dose
- Tumor $\alpha/\beta=10$
- Late morbidity $\alpha/\beta=3$

EXAMPLE: Calculation of EQD2 for HDR 1 fraction of 7Gy

- D: total dose
- d: fractional dose
- Tumor $\alpha/\beta=10$
- Late morbidity $\alpha/\beta=3$

$$EQD_2 = n \cdot d \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

Tumour

$$EQD_2 = 7 \cdot \frac{7+10}{2+3} Gy = 10Gy$$

Organ at risk

$$EQD_2 = 7 \cdot \frac{7+3}{2+3} Gy = 14Gy$$

EXAMPLE: Calculation of EQD2 for HDR 3 fractions of 7Gy

- D: total dose
- d: fractional dose
- Tumor $\alpha/\beta=10$
- Late morbidity $\alpha/\beta=3$

$$EQD_2 = n \cdot d \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

Tumour

$$EQD_2 = 7 \cdot 3 \cdot \frac{7+10}{2+3} Gy = 30Gy$$

Organ at risk

$$EQD_2 = 7 \cdot 3 \cdot \frac{7+3}{2+3} Gy = 42Gy$$

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.)**
- **Overall uncertainty of the biological dose calculation (values) in the range of ~10% -> Reasonable rounding of values**

EBRT + BT dose

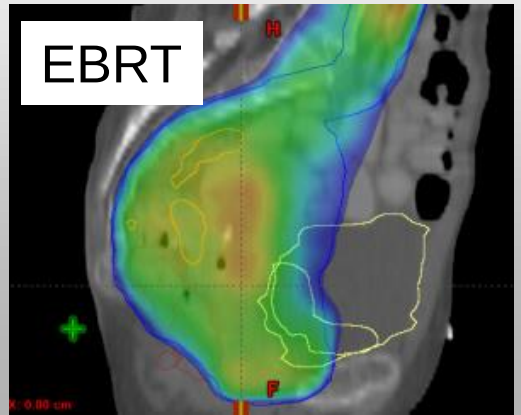
- Dose in elective target volume:
  - Assumption: homogeneous dose 95%-107% of prescribed dose (PD)

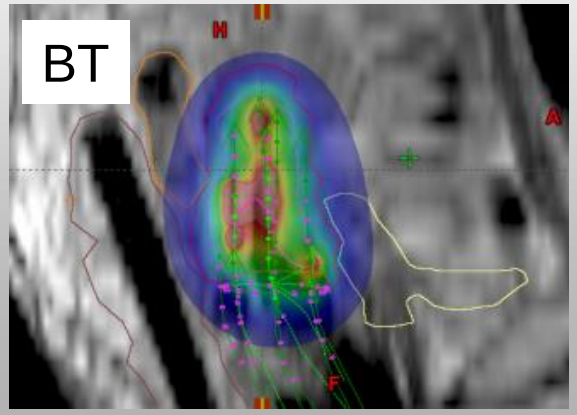
Good approximation:

Target: $D90\ (total) = PD_{(EBRT)} + D90(BT)$

OAR: $D_{2cm3}\ (total) = PD_{(EBRT)} + D_{2cm3}(BT)$

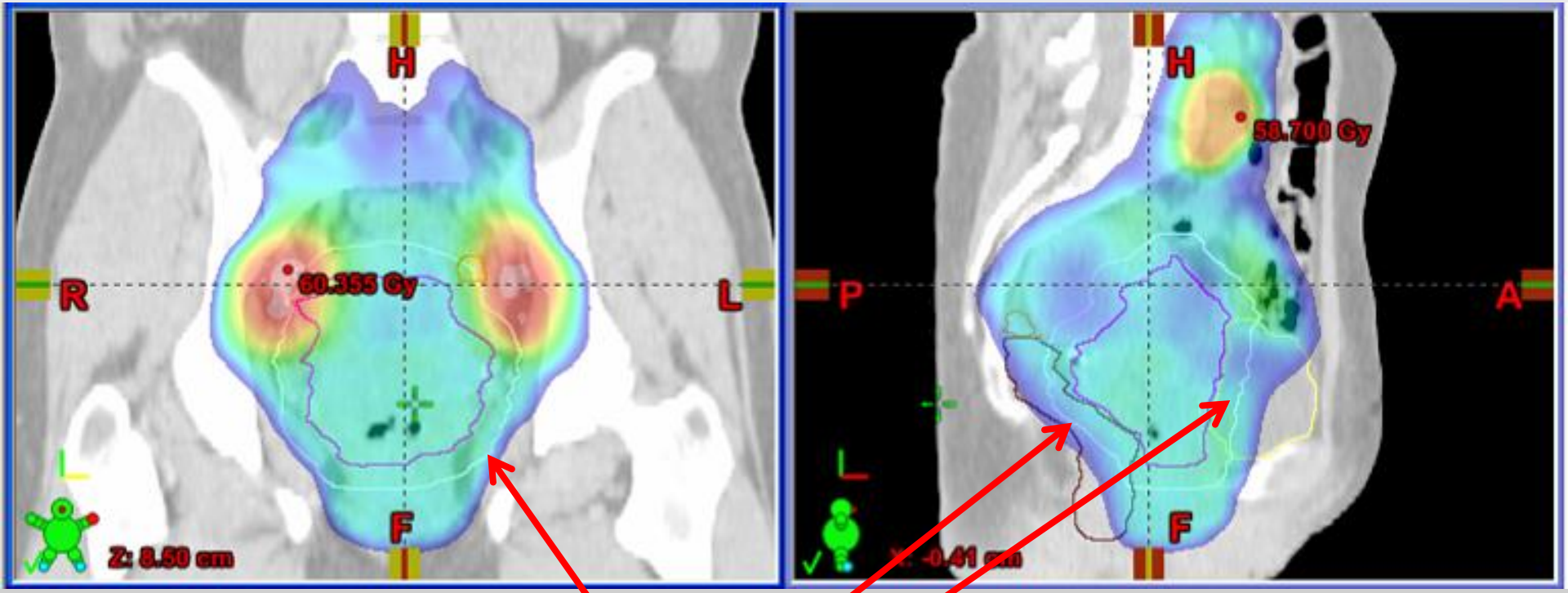
~~**NOT:** $D_{2cm3}\ (total) = D_{2cm3\ (EBRT)} + D_{2cm3}(BT)$~~





Be aware of IMRT hot spots in the BT region!

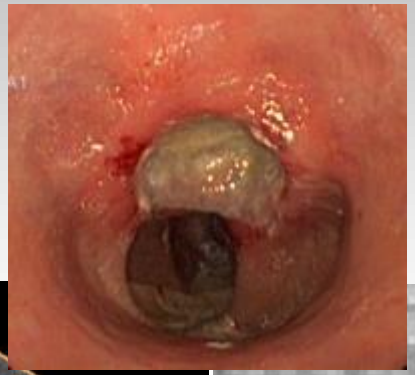
Lymph node boost: Create homogeneous dose during planning!



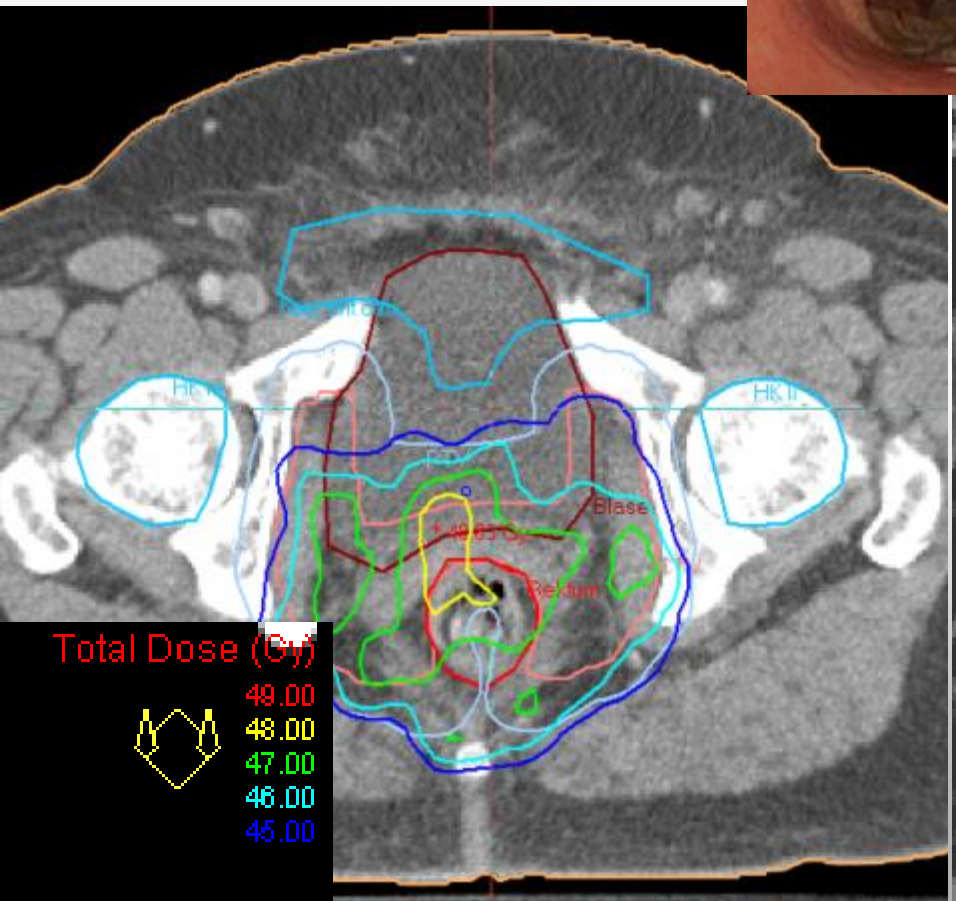
Homogenous volume for inverse dose planning

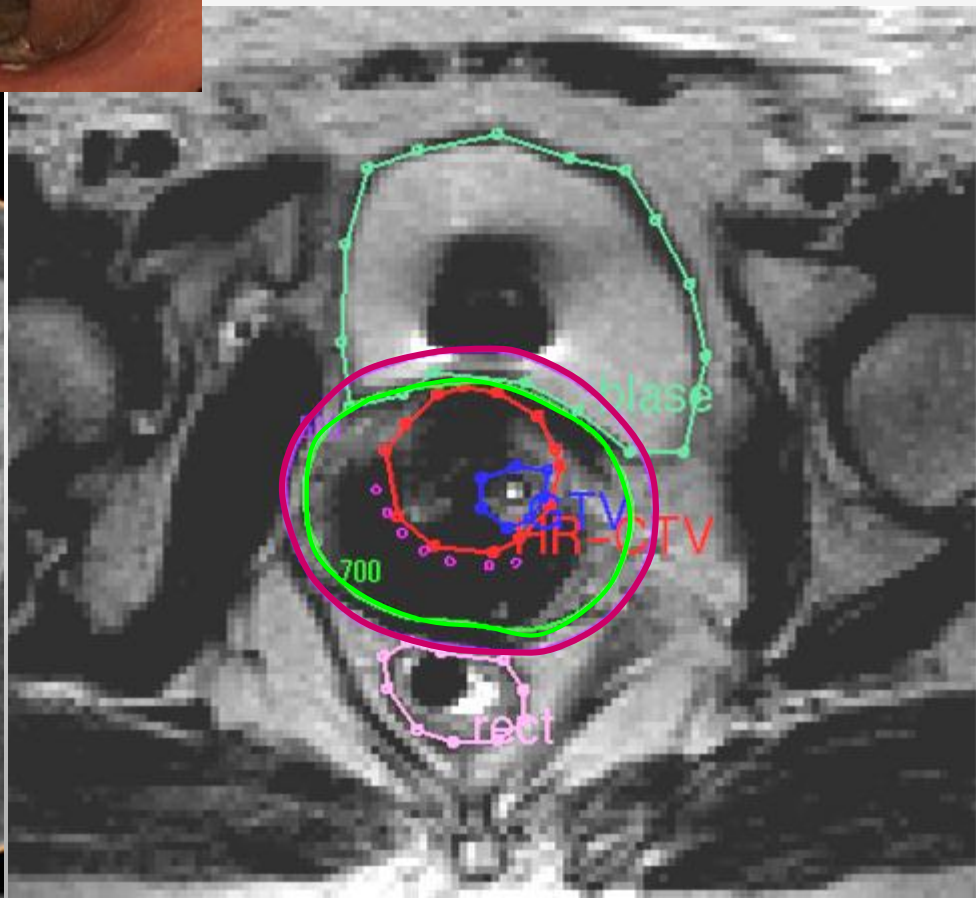
How could this happen?

D2cm3 = 65.7 Gy EQD2$_{(\alpha/\beta=3)}$



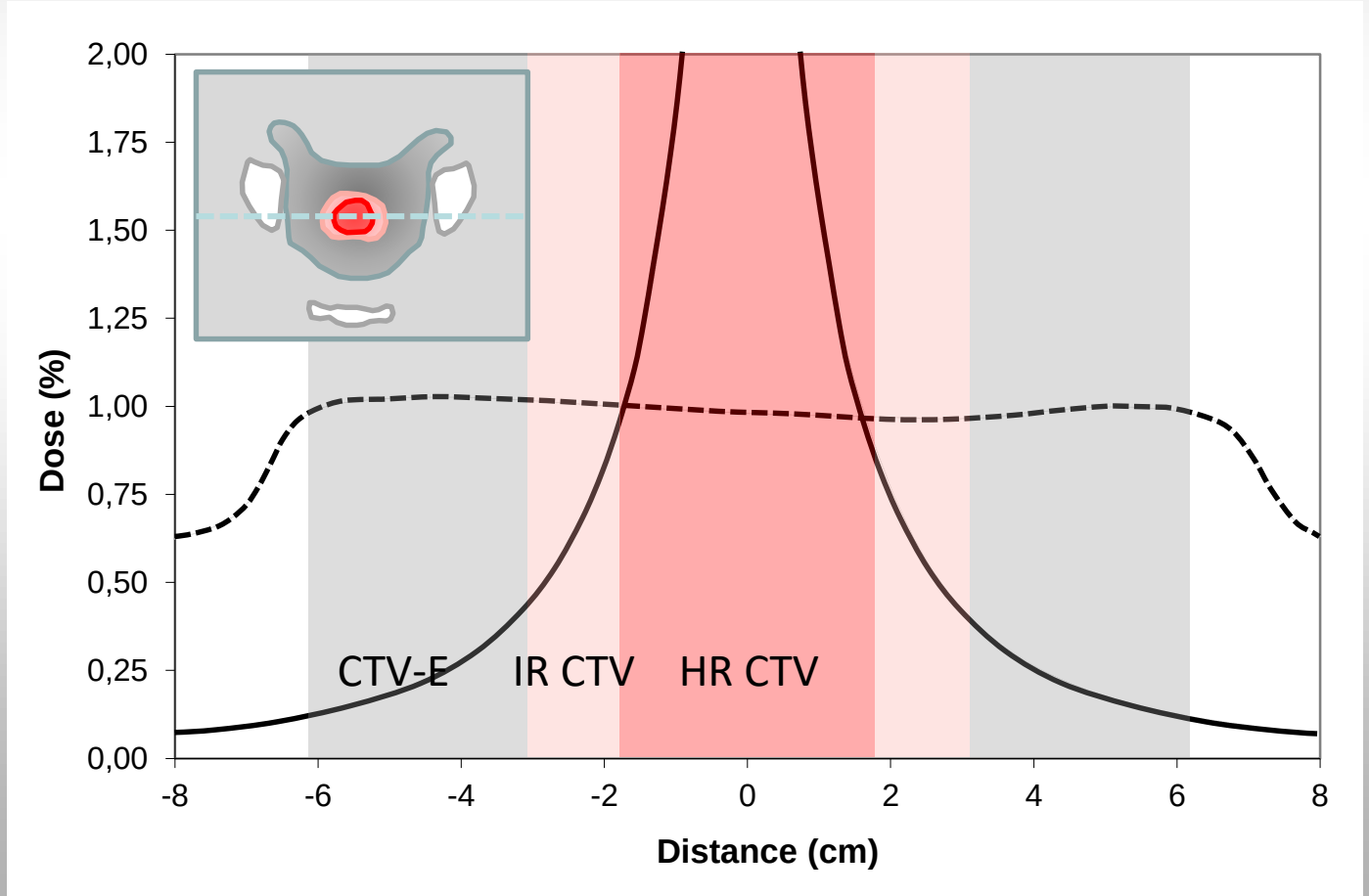
D2cm3 = 79.2 Gy EQD2$_{(\alpha/\beta=3)}$



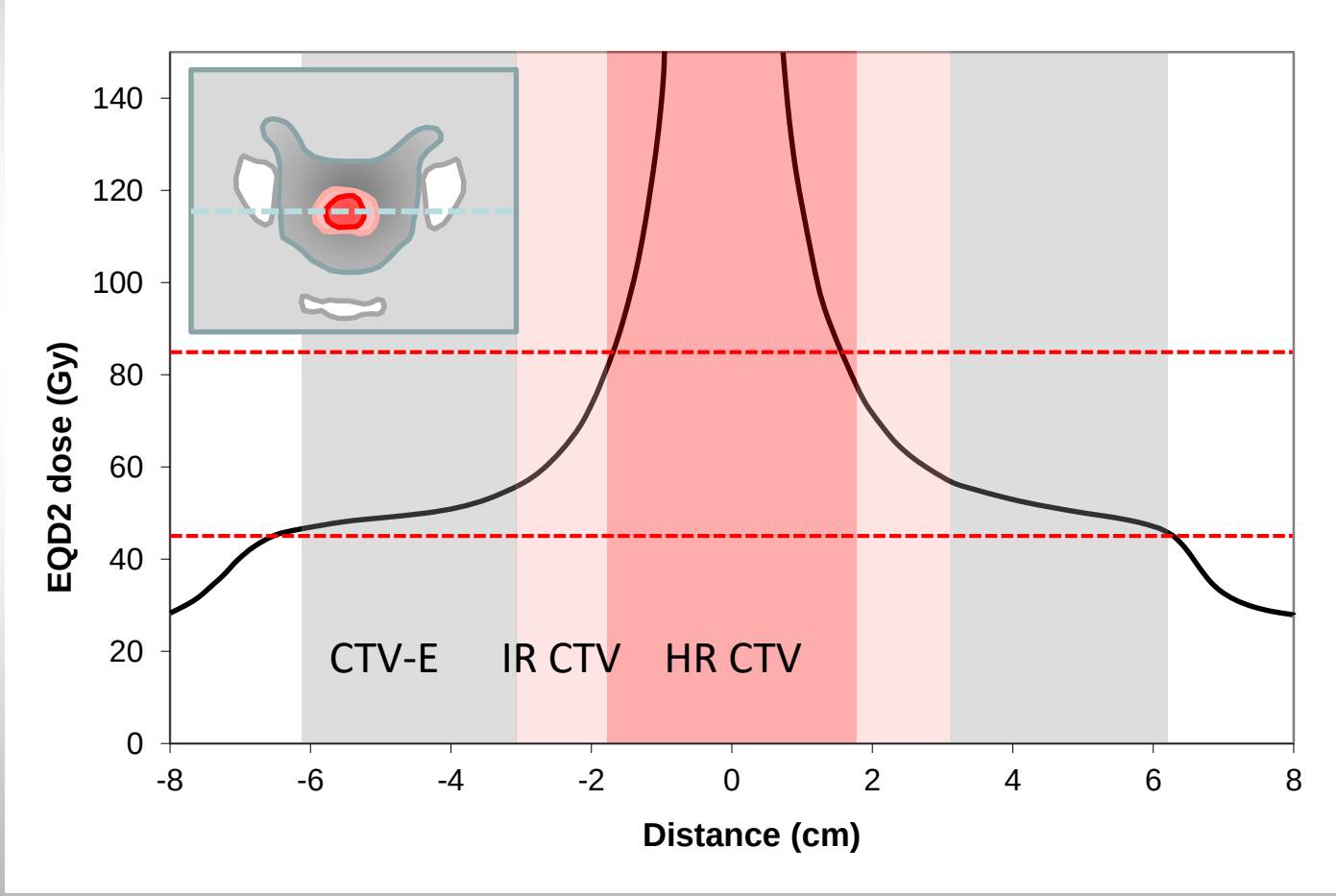


Depth dose: physical dose

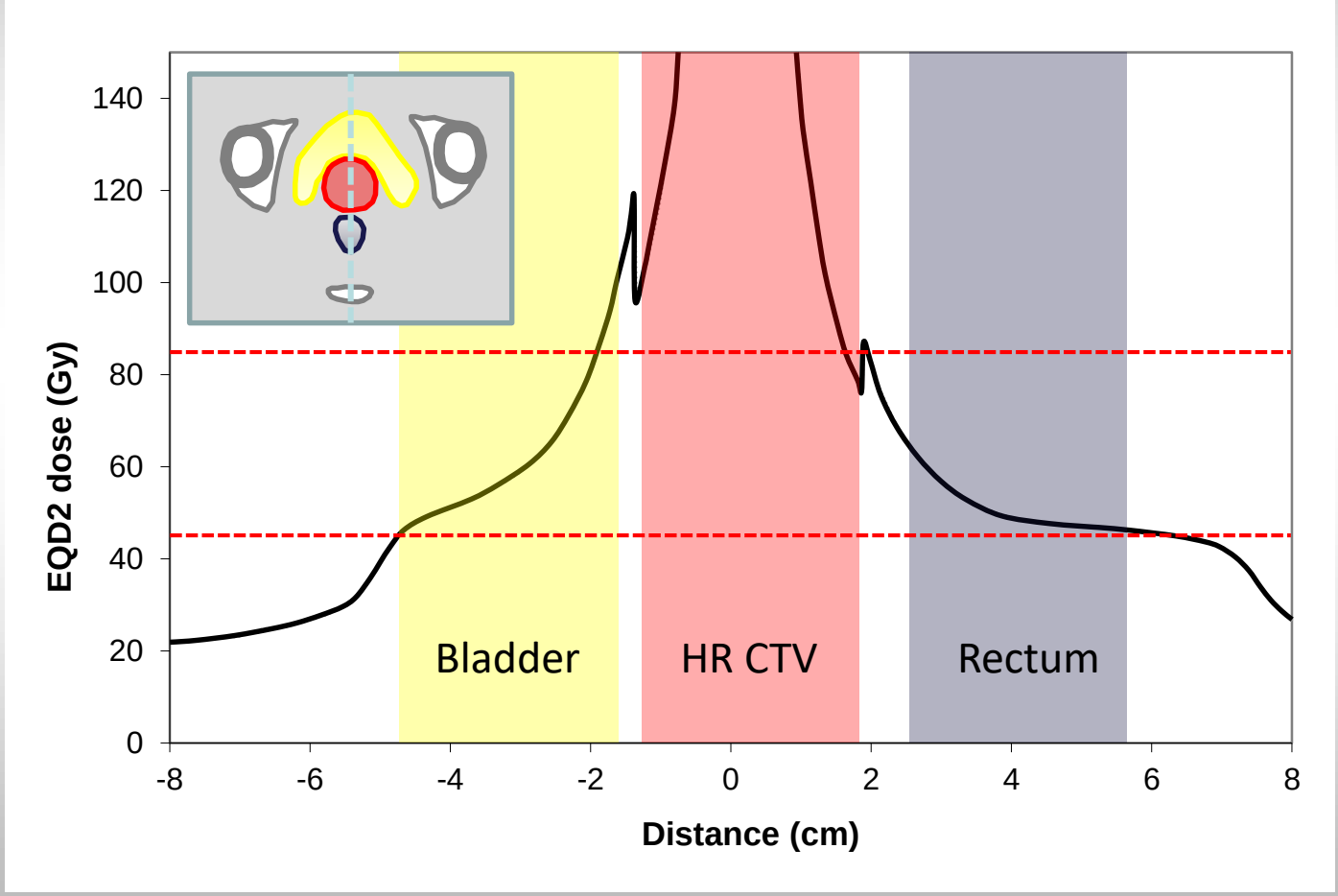
High, intermediate, low doses within mm
Dose gradient: 6% pr mm at point A



EBRT+BT: total EQD2 tumour



EBRT+BT: total EQD2 OARs



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

A single fraction HDR dose of 7Gy to the tumour corresponds to a EQD2 of

A. 5Gy
B. 7Gy
C. 10Gy

Limitation

4 Rs of Radiobiology

- **Recovery or Repair (half-time ~1hour)**
- ~~**Redistribution**~~
- **Repopulation (< 1 day)**
- ~~**Reoxygenation**~~

Repopulation
– changing the overall treatment time -

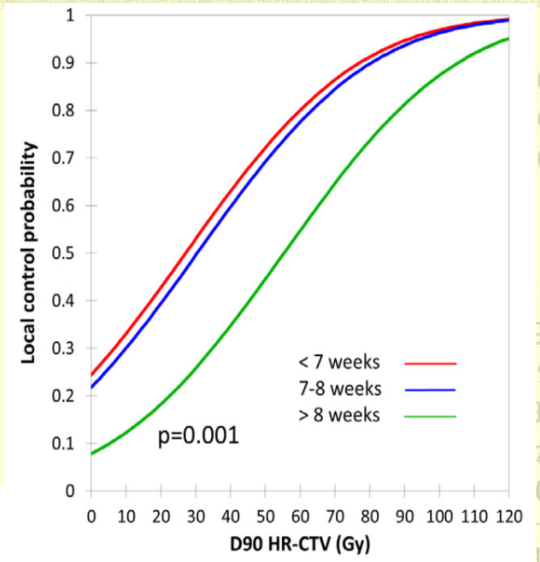
Influencing the local control rate

$$EQD_{2,T} = EQD_{2,t} - (T - t)D_{prolif}$$

- Increasing OTT by one week is equivalent to a loss of 5 Gy in CTV_{HR} D90

Tanderup, retroEMBRACE, 2016, submitted

- Timing of the BT boost?



Mazeron et al, Radiother Oncol 2015

EBRT ⟺ BT

„Per day delay in overall treatment time results in loss of ~ 0.3 – 0.8 Gy/day“

Treatment planning documentation of fractionated gynaecological BT (HDR)

PHYSICAL - BIOLOGICAL DOCUMENTATION OF GYNAECOLOGICAL HDR BT

PATIENT , ID-number

tumour entity cervix ca

FIGO, TNM IIB cT2b pN0

GTV at diag. 88 cm^3

chemoth. cisplatin

EXTERNAL BEAM THERAPY

		TUMOUR	OAR
dose per fraction	1,8	D_{iso} [α/β=10Gy]	D_{iso} [α/β=3Gy]
fractions without central shield	25	44,3	43,2
fractions with central shield		0,0	0,0
total dose	**45,0**	**44,3**	**43,2**

BRACHYTHERAPY

dose values in Gy

	F 1	F 2	F 3	F 4	F 5	F 6
date						
physicist						
MR / CT	MR	MR	MR	MR		
applicator(s): type	tandem-ring	tandem-ring	tandem-ring	tandem-ring		
applicator(s): dimensions	r34i60	r34i60	r34i60	r34i60		
eval plan, remarks	2	2	3	2		

TOTAL BT	TOTAL BT + EBT
mean	*stddev*

Treatment planning documentation of fractionated gynaecological BT (HDR)

	TRAK [cGy at 1m]	0,54	0,49	0,47	0,44			**1,94**	
	prescribed dose PD	7	7	7	7				
	PD $_{iso}$ [α/β=10Gy]	9,9	9,9	9,9	9,9	0,0	0,0	39,7	**83,9**
	volume of PD [cm^3]	121,1	106,9	97,7	89,5			***103,8***	*11,7*
	PDx2	14,0	14,0	14,0	14,0	0,0	0,0		
	PDx2 $_{iso}$ [α/β=10Gy]	28,0	28,0	28,0	28,0	0,0	0,0	112,0	156,3
	volume of PDx2 [cm^3]	41,6	33	30	26,1			*32,7*	*5,7*
	pres. point level (A / My / [mm])	A	A	A	A				
	pres. point [mm $_{left}$ / mm $_{right}$]	22 / -22	A	A	19 / -19				
	dose to + A left	7,6	7,1	6,7	6,5				
	A_{left} - D_{iso} [α/β=10Gy]	11,1	10,1	9,3	8,9	0,0	0,0	39,5	**83,8**
	dose to - A right	7,8	6,9	7,3	6,7				
	A_{right} - D_{iso} [α/β=10Gy]	11,6	9,7	10,5	9,3	0,0	0,0	41,1	**85,4**
	dose to A mean	7,7	7,0	7,0	6,6	0,0	0,0		
	A_{mean} - D_{iso} [α/β=10Gy]	11,4	9,9	9,9	9,1	0,0	0,0	40,3	**84,6**
GTV [cm^3]		8,8	7,8	5,5	6,1			*7,1*	*1,3*
	D 100 = MTD	9,3	8,9	6,9	6,2				
	D 100 $_{iso}$ [α/β=10Gy]	15,0	14,0	9,7	8,4	0,0	0,0	47,1	91,3
	D 90	13,3	12,0	11,7	10,6				
	D 90 $_{iso}$ [α/β=10Gy]	25,8	22,0	21,2	18,2	0,0	0,0	87,2	**131,4**
	V 100 = volume of PD [%]	100,0%	100,0%	99,9%	99,1%			***99,8%***	*0,4%*
CTV [cm^3]		53,5	51,5	40	40,4			*46,4*	*6,2*
	D 100 = MTD	5,0	5,0	3,5	3,8				
	D 100 $_{iso}$ [α/β=10Gy]	6,3	6,3	3,9	4,4	0,0	0,0	20,8	65,1
	D 90	8,1	7,0	6,9	6,4				
	D 90 $_{iso}$ [α/β=10Gy]	12,2	9,9	9,7	8,7	0,0	0,0	40,6	**84,8**
	V 100 = volume of PD [%]	95,9%	90,4%	89,3%	86,8%			***90,6%***	*3,3%*
	volume of mean A-dose [%]	92,7%	90,4%	89,3%	88,9%			*90,3%*	*1,5%*

Treatment planning documentation of fractionated gynaecological BT (HDR)

BLADDER [cm³]	98,5	76,1	86,9	101,4			*90,7*	*10,0*
ICRU - dose	7,2	8,1	5,5	6,3				
ICRU - D_{iso} [α/β=3Gy]	14,7	18,0	9,4	11,7	0,0	0,0	53,7	**96,9**
ICRUcr1,5cm - dose	8,3	10,6	5,4	7,0				
ICRUcr1,5cm - D_{iso} [α/β=3Gy]	18,8	28,8	9,1	14,0	0,0	0,0	70,7	113,9
ICRUcr2,0cm - dose	8,6	12,2	5,4	7,1				
ICRUcr2,0cm - D_{iso} [α/β=3Gy]	20,0	37,1	9,1	14,3	0,0	0,0	80,5	123,7
0,1cm³ - dose	8,0	8,0	9,5	7,5				
0,1cm³ - D_{iso} [α/β=3Gy]	17,6	17,6	23,8	15,8	0,0	0,0	74,7	117,9
1cm³ - dose	6,4	6,5	7,2	6,3				
1cm³ - D_{iso} [α/β=3Gy]	12,0	12,4	14,7	11,7	0,0	0,0	50,8	94,0
2cm³ - dose	6,0	6,0	6,4	5,9				
2cm³ - D_{iso} [α/β=3Gy]	10,8	10,8	12,0	10,5	0,0	0,0	44,1	**87,3**
RECTUM [cm³]	45,1	33,1	34,8	38,5			*37,9*	*4,6*
ICRU - dose	4,2	5,0	3,4	3,0				
ICRU - D_{iso} [α/β=3Gy]	6,0	8,0	4,4	3,6	0,0	0,0	22,0	**65,2**
ICRUprobe - dose	4,0	4,9	3,4	3,0				
ICRUprobe - D_{iso} [α/β=3Gy]	5,6	7,7	4,4	3,6	0,0	0,0	21,3	64,5
0,1cm³ - dose	5,9	4,9	4,6	4,3				
0,1cm³ - D_{iso} [α/β=3Gy]	10,5	7,7	7,0	6,3	0,0	0,0	31,5	74,7
1cm³ - dose	4,8	4,2	3,7	3,6				
1cm³ - D_{iso} [α/β=3Gy]	7,5	6,0	5,0	4,8	0,0	0,0	23,2	66,4
2cm³ - dose	4,3	3,9	3,4	3,3				
2cm³ - D_{iso} [α/β=3Gy]	6,3	5,4	4,4	4,2	0,0	0,0	20,2	**63,4**
SIGMOID [cm³]	17,4	21,1	24,6	26,3			*22,4*	*3,4*
0,1cm³ - dose	6,6	5,7	4,7	5,2				
0,1cm³ - D_{iso} [α/β=3Gy]	12,7	9,9	7,2	8,5	0,0	0,0	38,4	81,6
1cm³ - dose	5,4	4,7	3,8	4,2				
1cm³ - D_{iso} [α/β=3Gy]	9,1	7,2	5,2	6,0	0,0	0,0	27,5	70,7
2cm³ - dose	4,7	4,2	3,4	3,8				
2cm³ - D_{iso} [α/β=3Gy]	7,2	6,0	4,4	5,2	0,0	0,0	22,8	**66,0**

Which of the following radiobiological effect(s) is(are) taken into account in the EQD2 calculation when using the LQ-model?

A. Repair
B. Redistribution
C. Repopulation
D. Reoxygenation
E. all

Take home messages

- EQD2 calculation is simple
- EQD2 has shown useful in pooling of data across fractionation schedules (EMBRACE)
- LQ model does not tage OTT time into account – remember loss of 5Gy per week at OTT>50 days
- Implement a spreadsheet in your department

$$EQD_2 = n \cdot d \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

$$EQD_2 = 7 \cdot \frac{7+10}{2+3} Gy = 10Gy$$

BLADDER [cm³]	98,5	76,1	86,9	101,4			*90,7*	*10,0*
ICRU - dose	7,2	8,1	5,5	6,3				
ICRU - D_{2Gy} [α/β=3Gy]	14,7	18,0	9,4	11,7	0,0	0,0	53,7	**96,9**
ICRUcr1,5cm - dose	8,3	10,6	5,4	7,0				
ICRUcr1,5cm - D_{2Gy} [α/β=3Gy]	18,8	28,8	9,1	14,0	0,0	0,0	70,7	113,9
ICRUcr2,0cm - dose	8,6	12,2	5,4	7,1				
ICRUcr2,0cm - D_{2Gy} [α/β=3Gy]	20,0	37,1	9,1	14,3	0,0	0,0	80,5	123,7
0,1cm² - dose	8,0	8,0	9,5	7,5				
0,1cm² - D_{2Gy} [α/β=3Gy]	17,6	17,6	23,8	15,8	0,0	0,0	74,7	117,9
1cm² - dose	6,4	6,5	7,2	6,3				
1cm² - D_{2Gy} [α/β=3Gy]	12,0	12,4	14,7	11,7	0,0	0,0	50,8	94,0
2cm² - dose	6,0	6,0	6,4	5,9				
2cm² - D_{2Gy} [α/β=3Gy]	10,8	10,8	12,0	10,5	0,0	0,0	44,1	**87,3**

RECTUM [cm³]	45,1	33,1	34,8	38,5			*37,9*	*4,6*
ICRU - dose	4,2	5,0	3,4	3,0				
ICRU - D_{2Gy} [α/β=3Gy]	6,0	8,0	4,4	3,6	0,0	0,0	22,0	**65,2**
ICRUprobe - dose	4,0	4,9	3,4	3,0				
ICRUprobe - D_{2Gy} [α/β=3Gy]	5,6	7,7	4,4	3,6	0,0	0,0	21,3	64,5
0,1cm² - dose	5,9	4,9	4,6	4,3				
0,1cm² - D_{2Gy} [α/β=3Gy]	10,5	7,7	7,0	6,3	0,0	0,0	31,5	74,7
1cm² - dose	4,8	4,2	3,7	3,6				
1cm² - D_{2Gy} [α/β=3Gy]	7,5	6,0	5,0	4,8	0,0	0,0	23,2	66,4
2cm² - dose	4,3	3,9	3,4	3,3				
2cm² - D_{2Gy} [α/β=3Gy]	6,3	5,4	4,4	4,2	0,0	0,0	20,2	**63,4**

SIGMOID [cm³]	17,4	21,1	24,6	26,3			*22,4*	*3,4*
0,1cm² - dose	6,6	5,7	4,7	5,2				
0,1cm² - D_{2Gy} [α/β=3Gy]	12,7	9,9	7,2	8,5	0,0	0,0	38,4	81,6
1cm² - dose	5,4	4,7	3,8	4,2				
1cm² - D_{2Gy} [α/β=3Gy]	9,1	7,2	5,2	6,0	0,0	0,0	27,5	70,7
2cm² - dose	4,7	4,2	3,4	3,8				
2cm² - D_{2Gy} [α/β=3Gy]	7,2	6,0	4,4	5,2	0,0	0,0	22,8	**66,0**

Time dose fractionation for EBRT + HDR BT

ESTRO-AROI Teaching Course
Transition from conventional 2D to 3D radiotherapy with a special emphasis on brachytherapy in cervical cancers

Bengaluru 2017

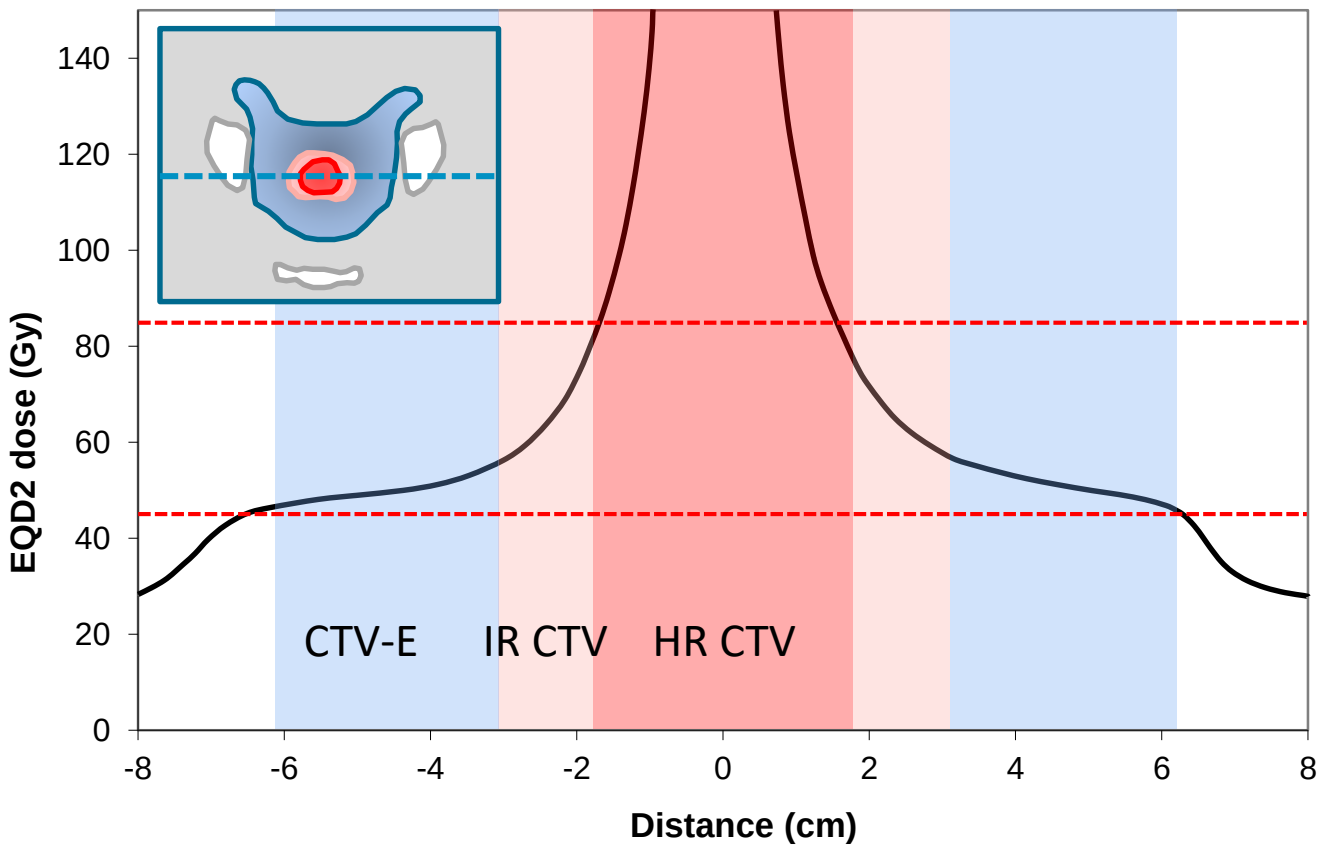
Prof Kari Tanderup, PhD
Prof Richard Pötter

Aarhus University Hospital

Combination of EBRT and BT

- EBRT dose and fractionation
- BT dose and fractionation
- Timing of BT boost
- Overall treatment time

EBRT+BT: total EQD2 tumour

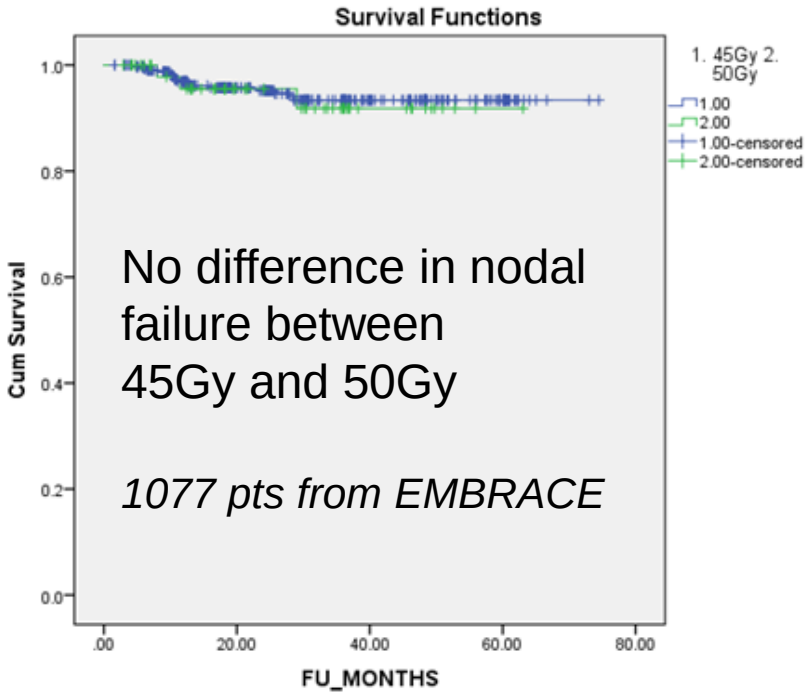


Which dose do you deliver to the elective lymph node target?

A. 45-46Gy whole pelvis
B. 50Gy whole pelvis
C. 50-55Gy with midline block after 40-45Gy
D. Other

What do we know about dose to the elective target volume?

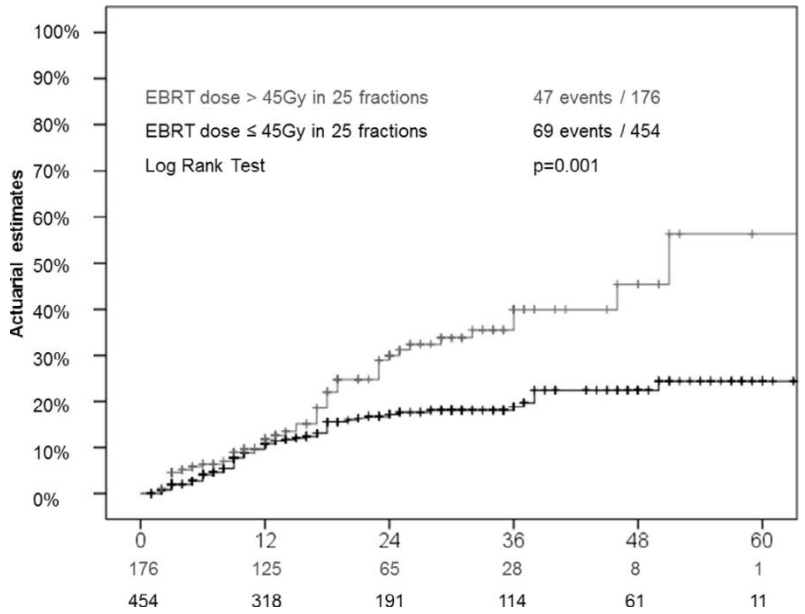
- **Do we need 45Gy or 50Gy for control of microscopic disease in lymph nodes with chemoradiation?**



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

Which total EBRT dose do you deliver to pathologic lymph nodes?

A. No boost

B. ~ 55Gy

C. ~ 60Gy

D. >60Gy

What do we know about dose to pathological nodes?

Nodal recurrence in pathological nodes after boost

Pittsburgh, IJROBP 2015:

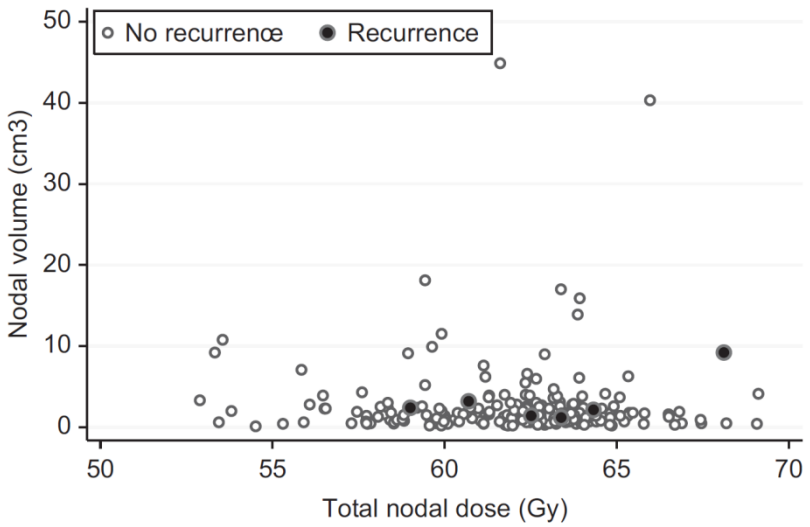
0% after boost dose of 55Gy

EMBRACE I:

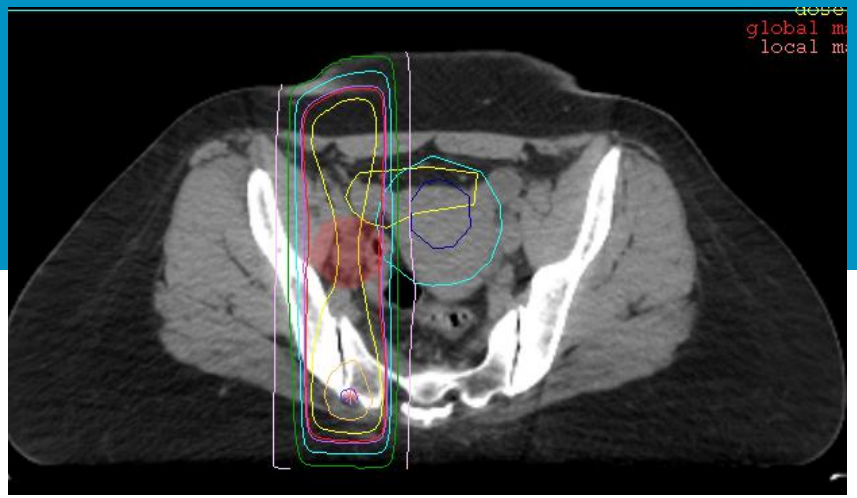
8% at median FUP of 2 years in patients boosted with a median dose of 59Gy

Ramlov et al, Acta Oncol, 2015:

limited dose effect for pathological nodes (~55-65Gy boosts)



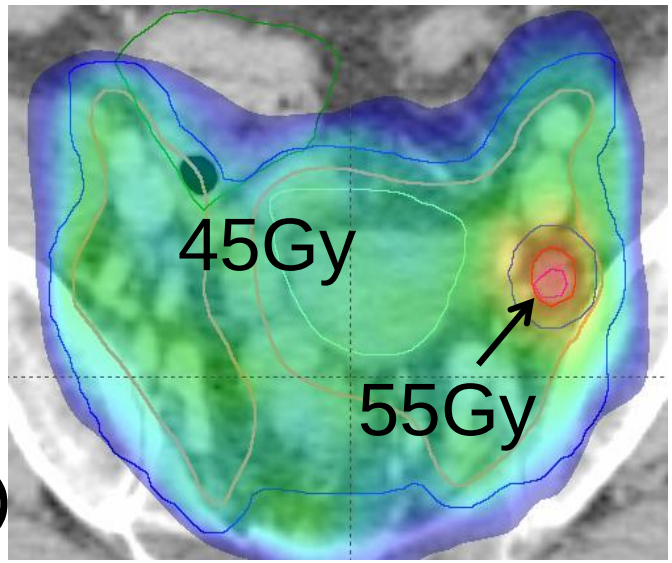
Post-boost with CRT



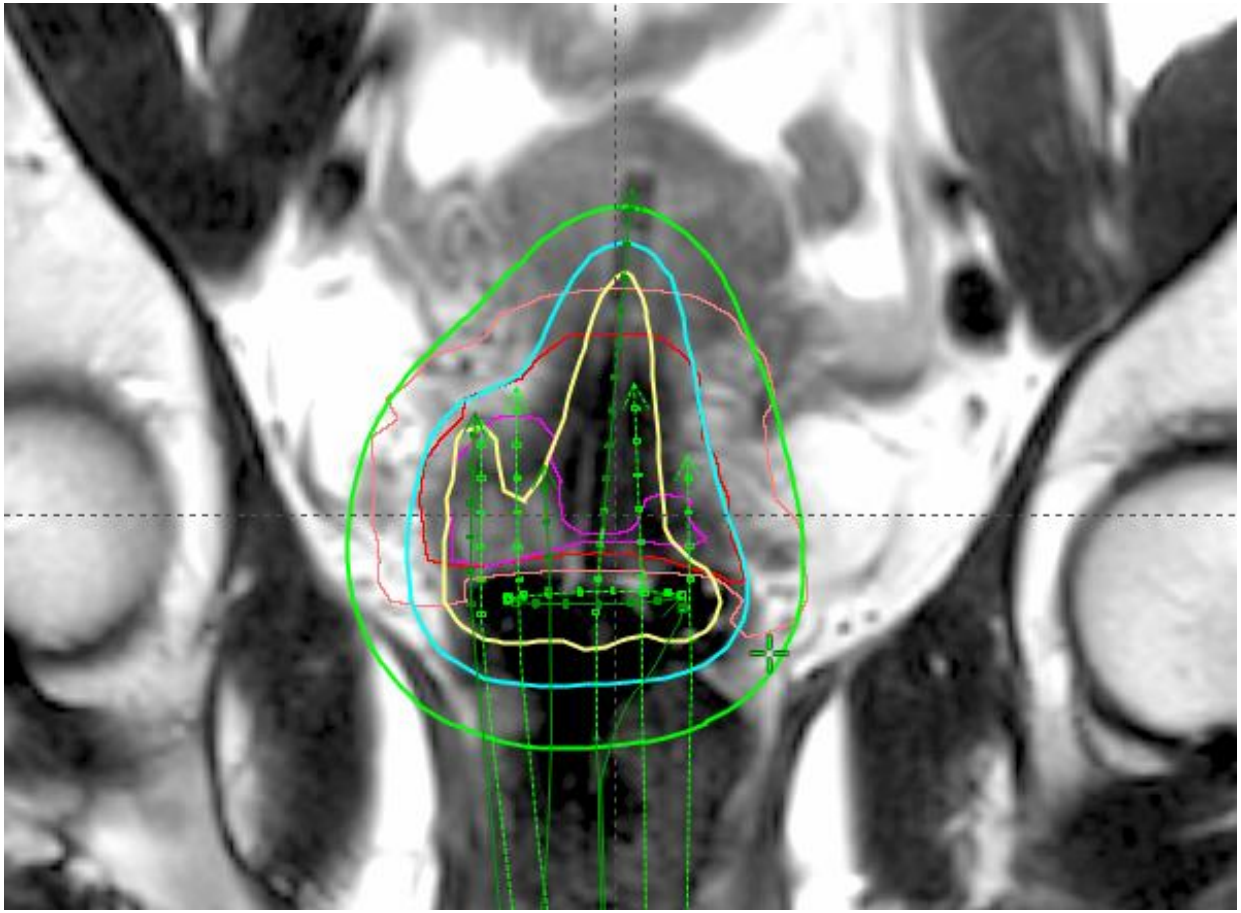
- AP-PA or 4 Field Box
- Avoid central pelvis irradiation
- Assessment of BT contribution (~0-6Gy)
- Examples of dose and fractionation:
  - Aim for total EBRT+BT dose of 55-60Gy
  - E.g. 50Gy whole pelvis + 5Gy
  - E.g. 45Gy whole pelvis + 10Gy

Recommendation of EMBRACE II: Simultaneously integrated lymph node boost (SIB)

- **Simultaneously integrated lymph node boost:**
  - **IMRT**
  - **Dose planning with two dose levels**
    - **Elective target**
    - **Pathological lymph node target**
  - **In case of very big nodes: to consider a replan after 20-25Gy**
- **Recommended lymph node dose in EMBRACE II**
  - **Total 60Gy EQD2**
  - **45Gy/25fx to elective CTV**
  - **55Gy/25fx (within pelvis: 3-4Gy BT)**
  - **57.5Gy/25fx (outside pelvis: 0Gy BT)**



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

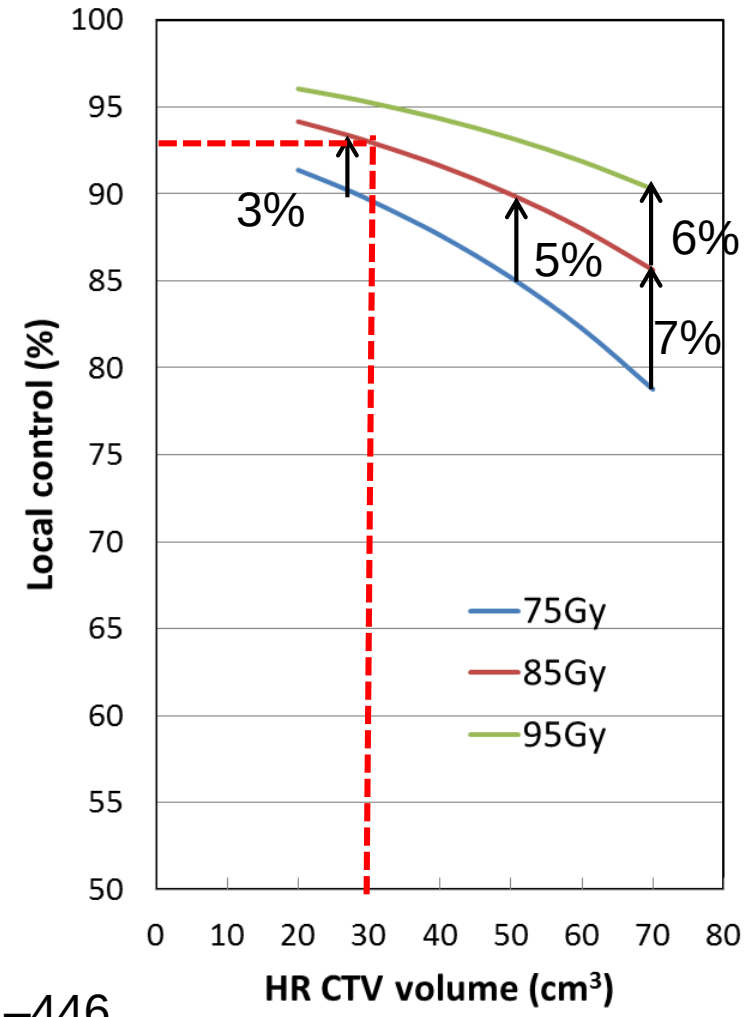
What do we know about dose and local control for CTV_{HR}?

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

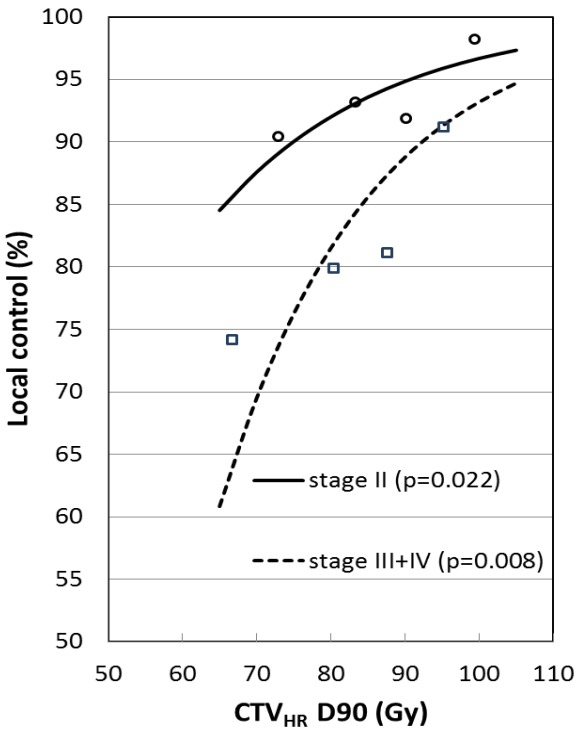
Local control at 3 years

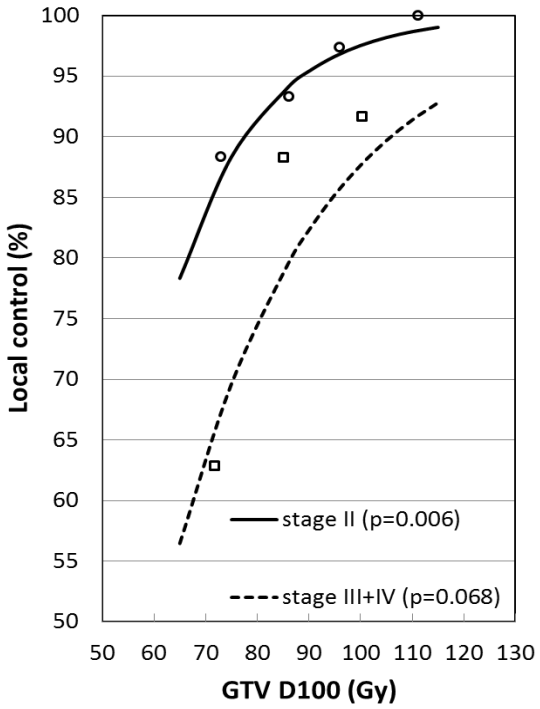


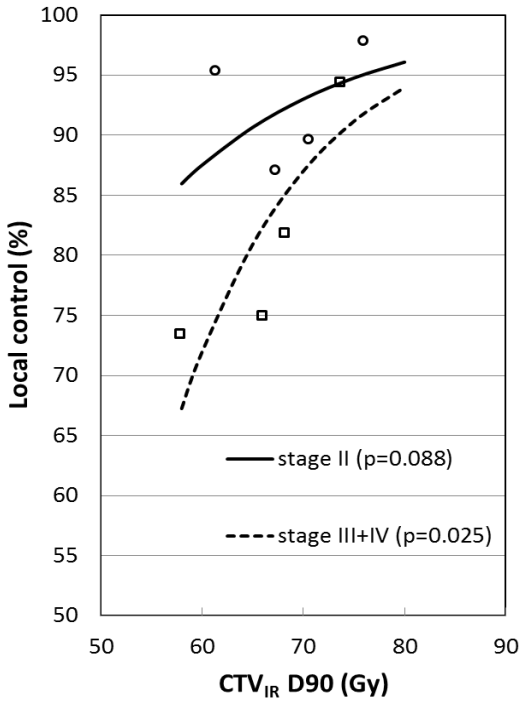
Tanderup et al, Radiother Oncol 120 (2016) 441–446

Dose effect GTV, CTV_{HR} and CTV_{IR}

Analysis according to stage







Tanderup et al, Radiother Oncol 120 (2016) 441–446

When do you preferentially start BT boost after initiation of EBRT for stage IIB?

A. **Week1**

B. **Week 2**

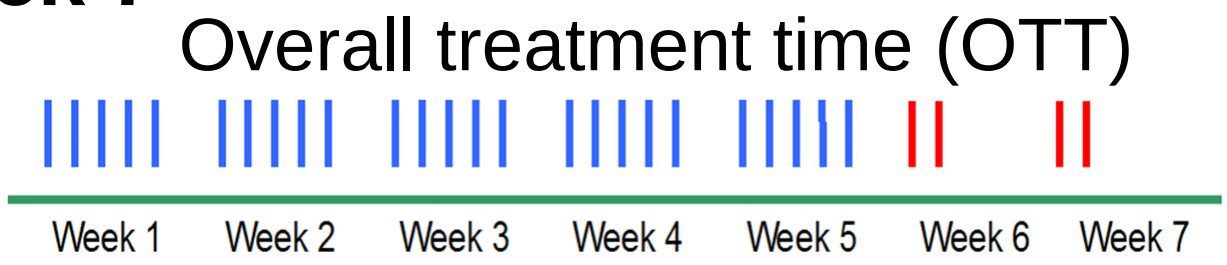
C. **Week 3**

D. **Week 4**

E. **Week 5**

F. **Week 6**

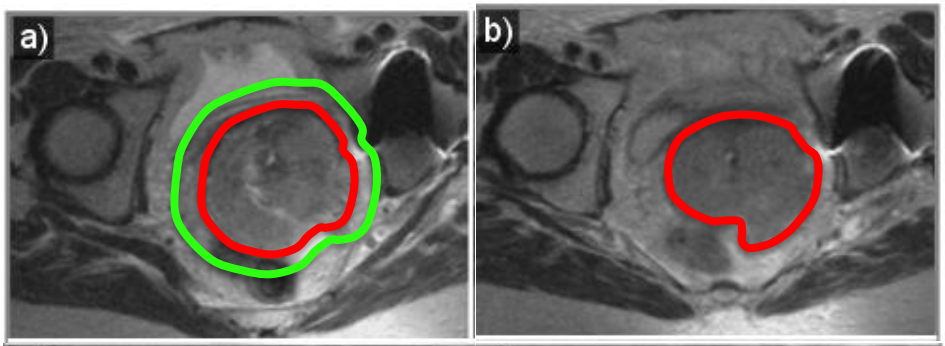
G. **Week 7**



Example: cervical cancer, FIGO IIIB: total dose 90 Gy EQD2

EBRT dose

0 Gy →



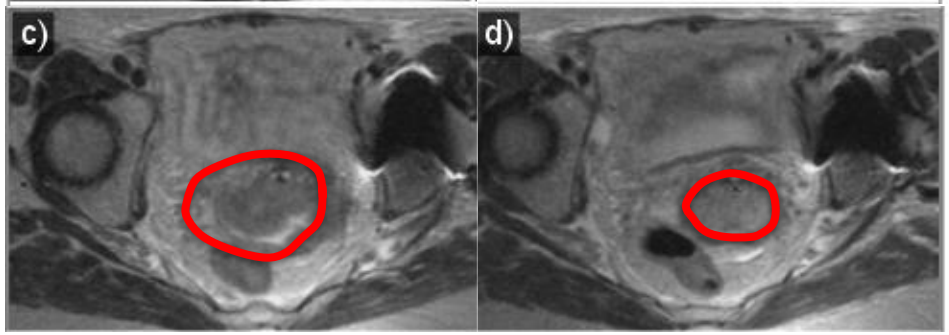
← 9 Gy

EBRT dose

Cisplatin (40 mg/m²) x1

18 Gy →

Cisplatin (40 mg/m²) x2

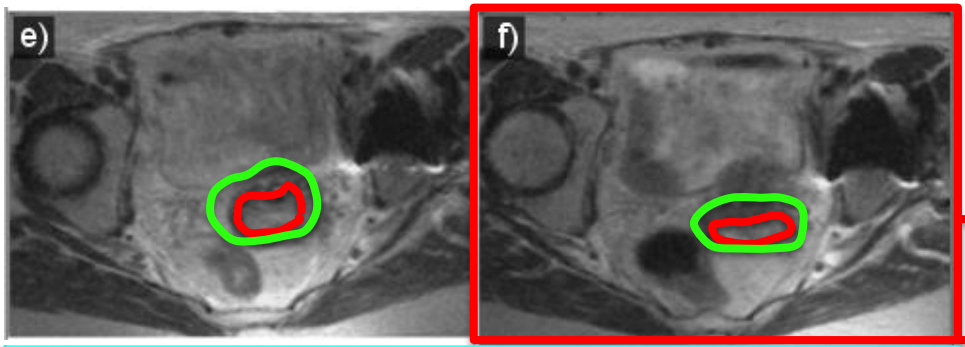


← 27 Gy

Cisplatin (40 mg/m²) x3

36 Gy →

Cisplatin (40 mg/m²) x4

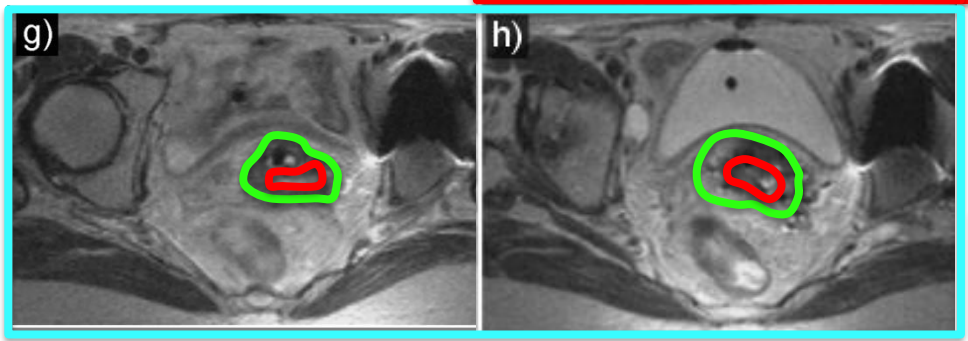


← 45 Gy

Pre-brachytherapy

EBRT45 Gy →

Cisplatin (40 mg/m²) x5



← IGABT 45 Gy

Brachytherapy

GTV
CTV

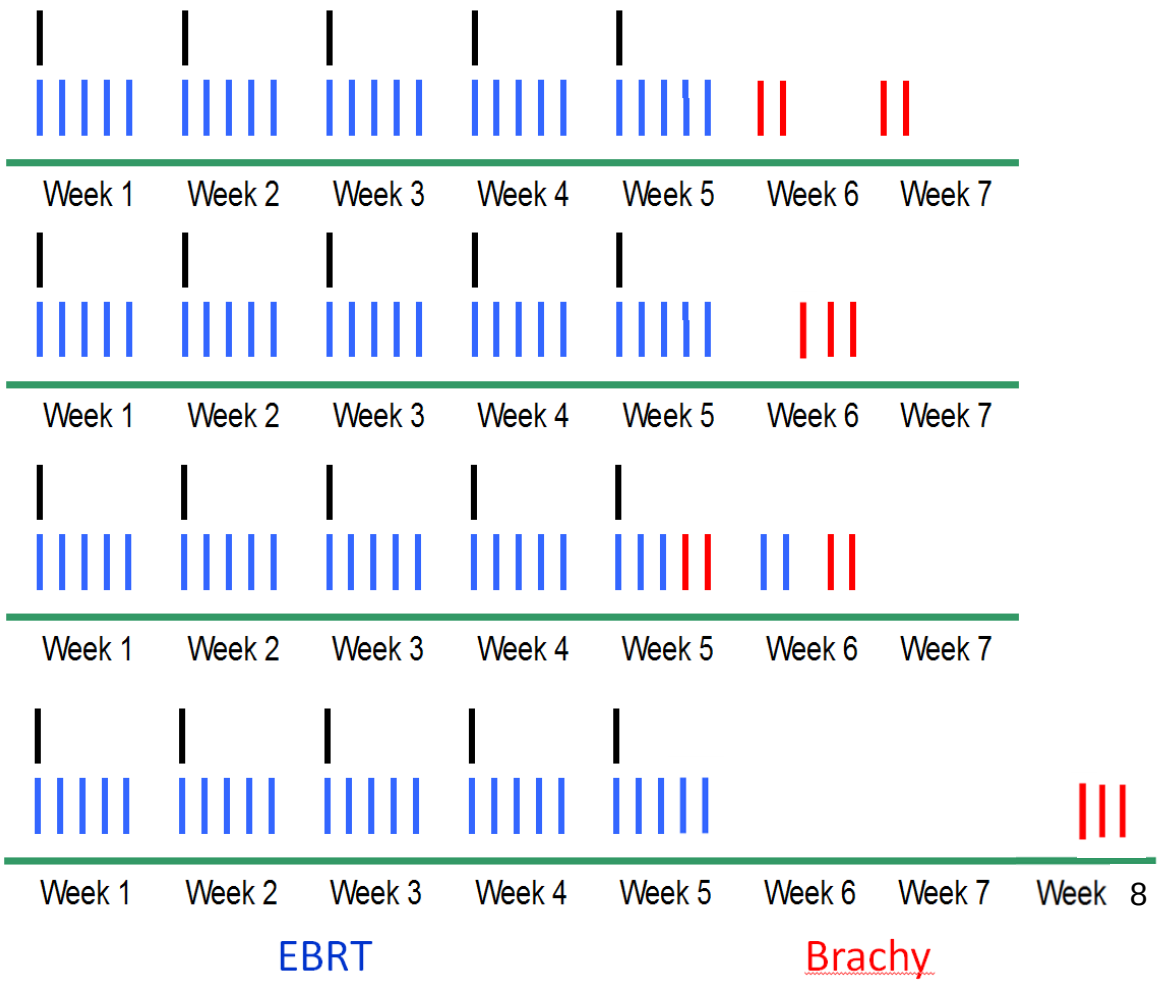
Impact of overall treatment time

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

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	30-40Gy	80-85Gy

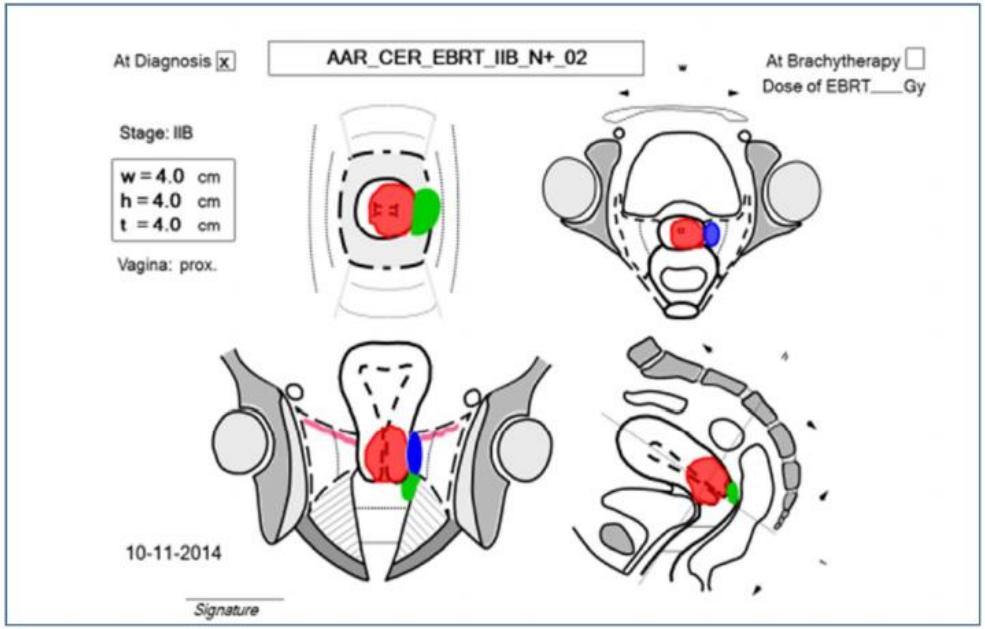
Take home messages

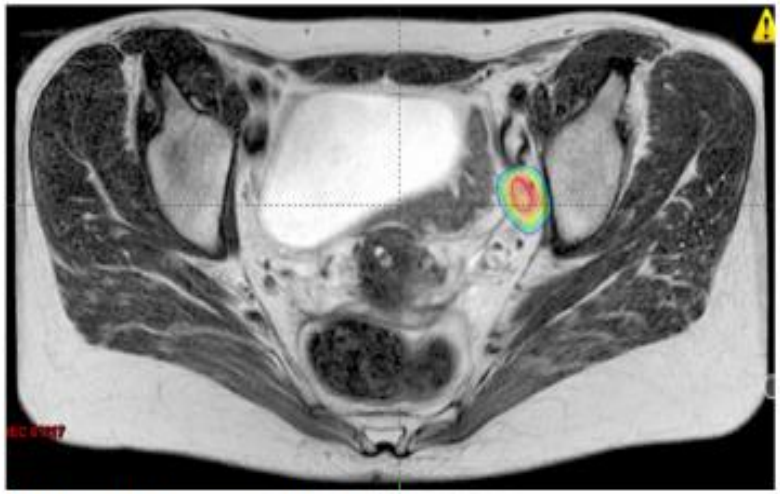
- **Elective lymph node target: 45-50Gy EBRT**
  - **Perspective of reducing morbidity with 45Gy**
- **Pathological lymph nodes: 55-60Gy EBRT**
  - **Balance between tumour control and morbidity**
- **Primary tumour (CTV_{HR}): >85-90Gy EBRT+BT**
  - **Balance between EBRT and BT**
  - **With more IC/IS BT it is possible to reduce EBRT dose to 45Gy**
- **Overall treatment time: <50 days**

Feedback and Discussion on Homework Cases

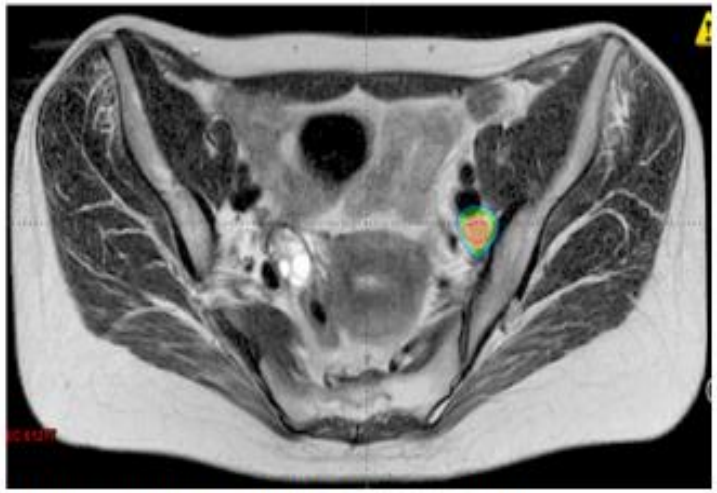
EBRT HOMEWORK CASE

Clinical drawing at diagnosis:



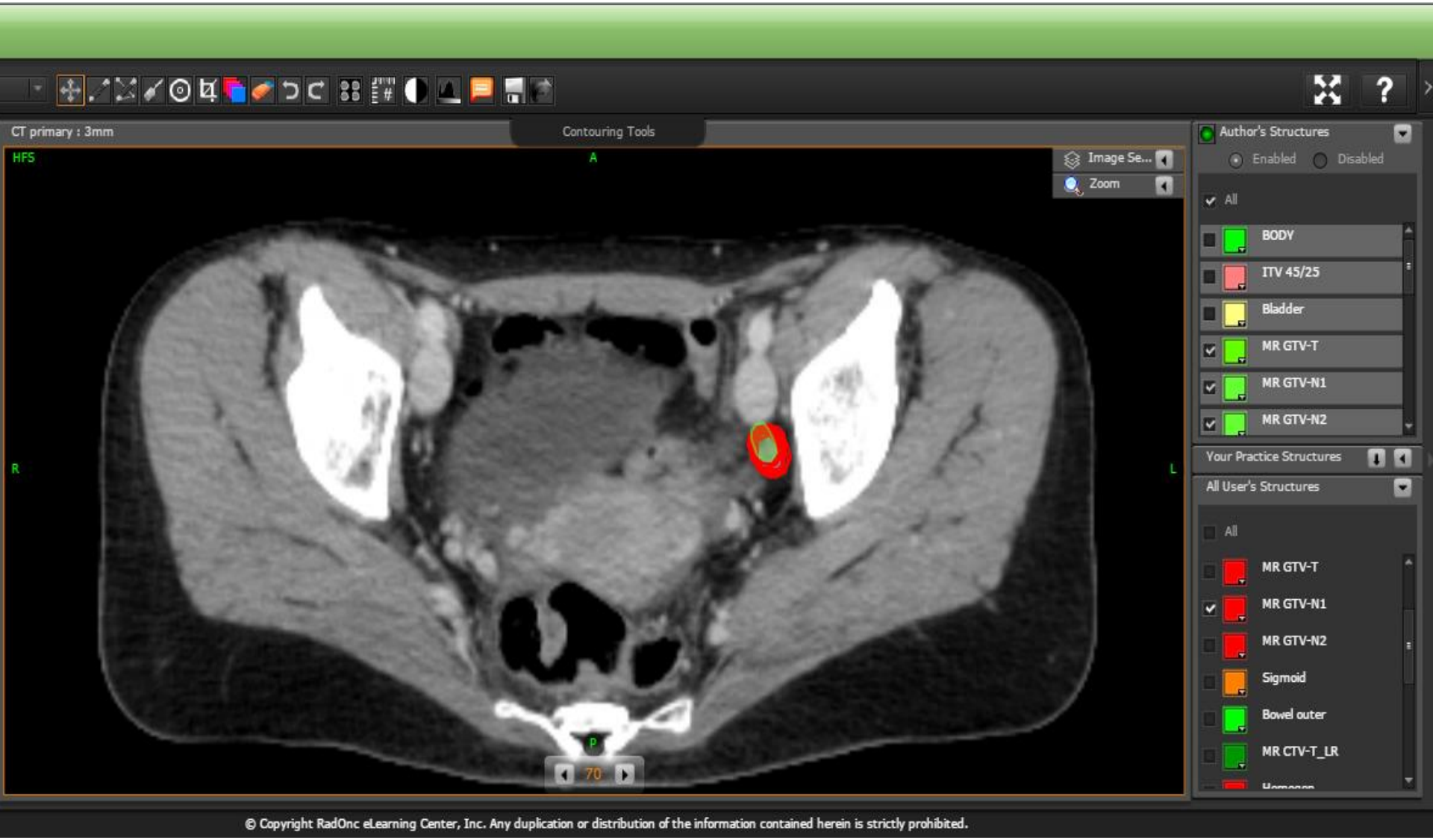


N1 in left fossa obturatoria.

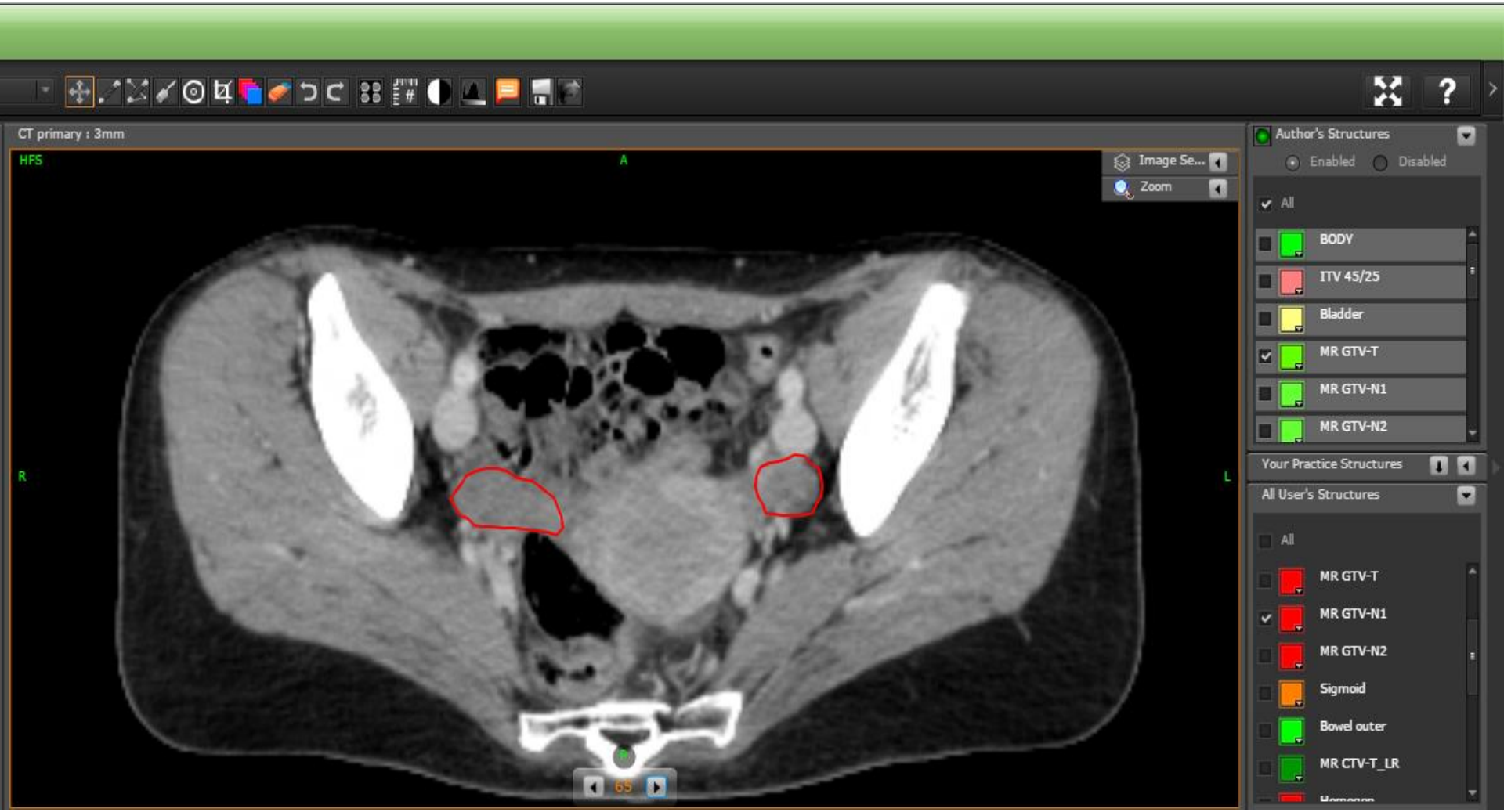


N2 in relation to the left external iliac.

MR GTV- N1



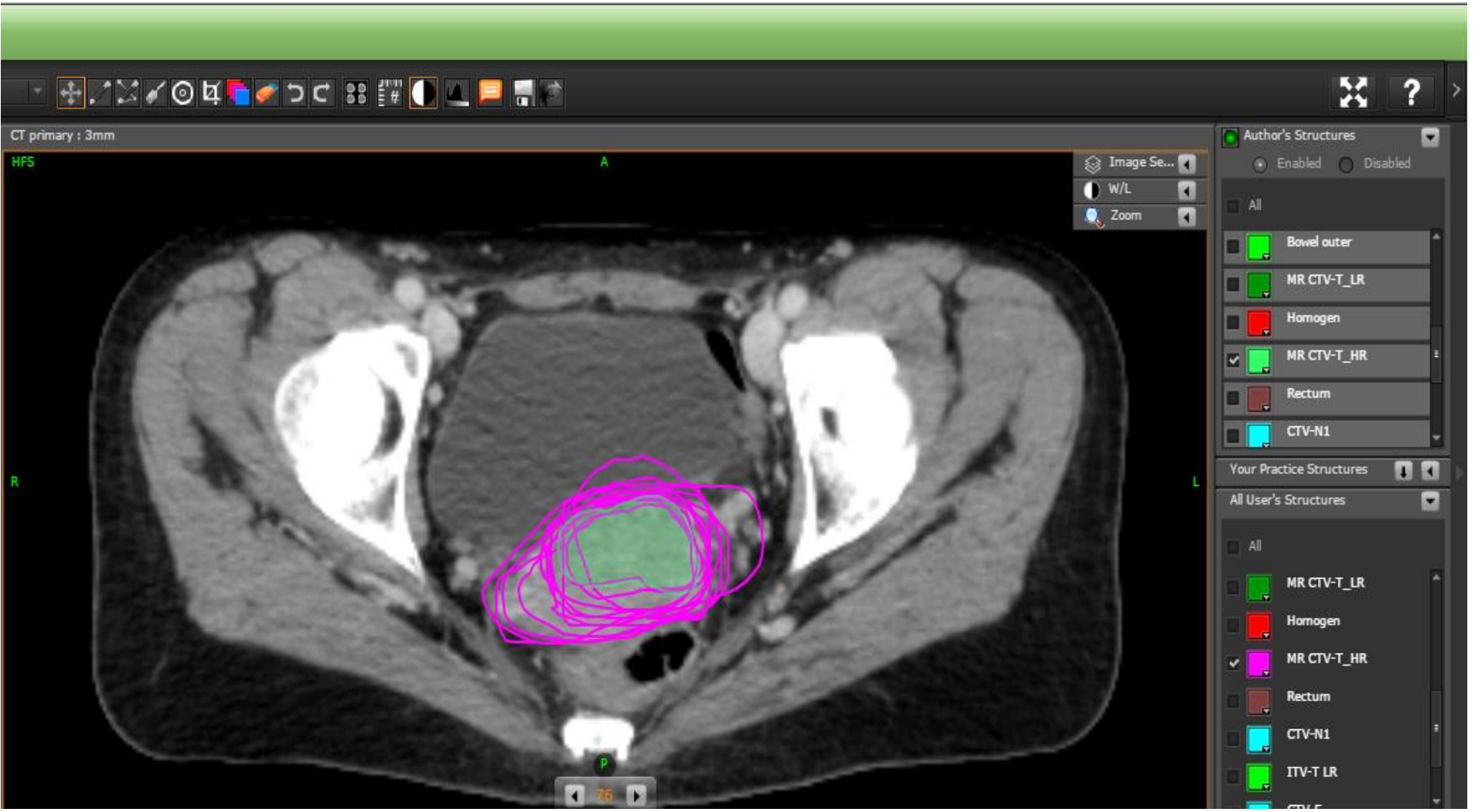
MR GTV- N1



Do not contour

Bilateral ovaries contoured at GTV-N

CTV- HR



Over-estimation

Bladder cannot be part of CTV in this case

CTV- HR

CTV-LR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Author's Structures
All
ITV 45/25
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MR CTV-T_LR
MR GTV-N1
MR GTV-N2
MR GTV-T
Your Practice Structures
All User's Structures
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Homogen
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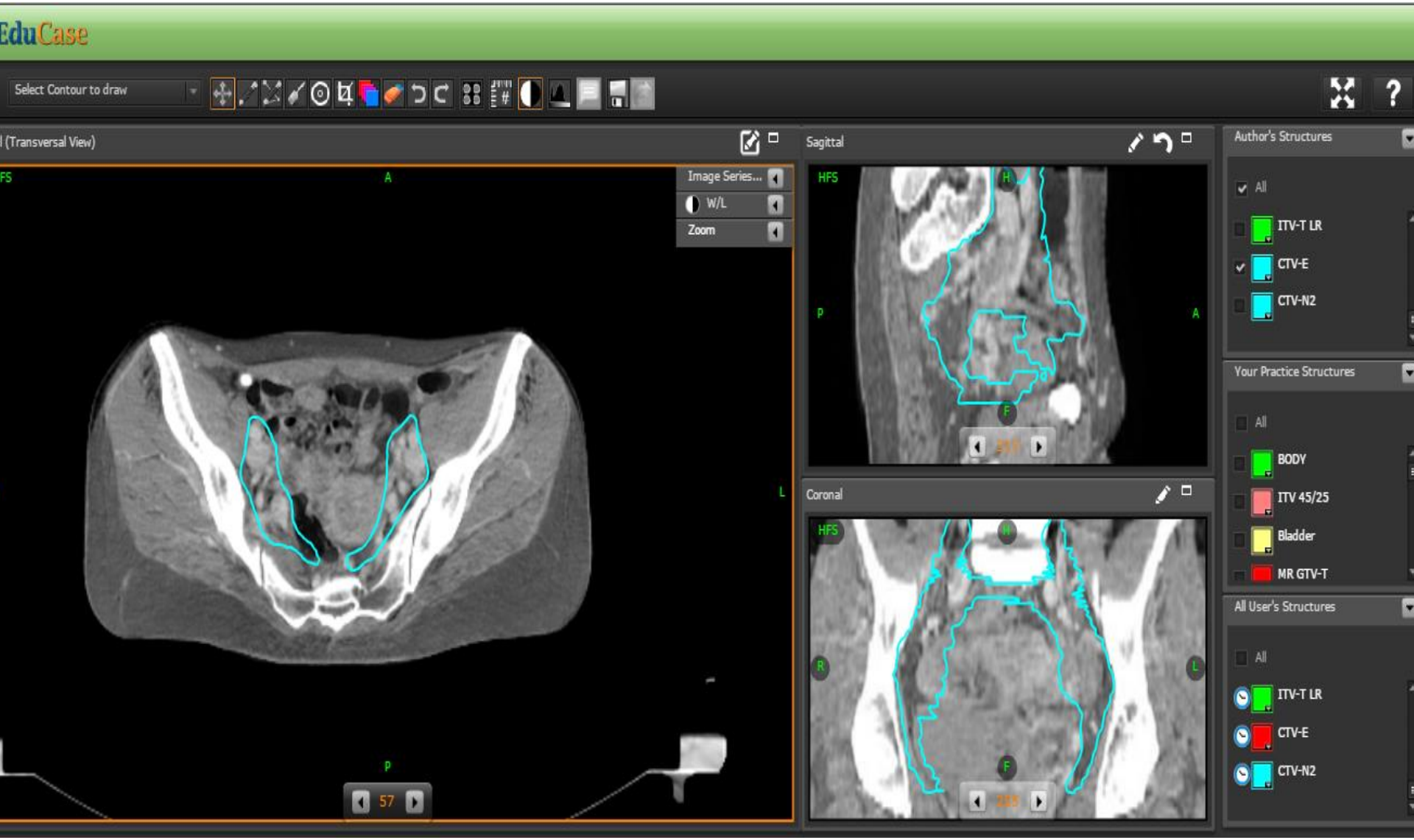
MR GTV-N1
MR GTV-N2

CTV- E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CTV-N2
Your Practice Structures
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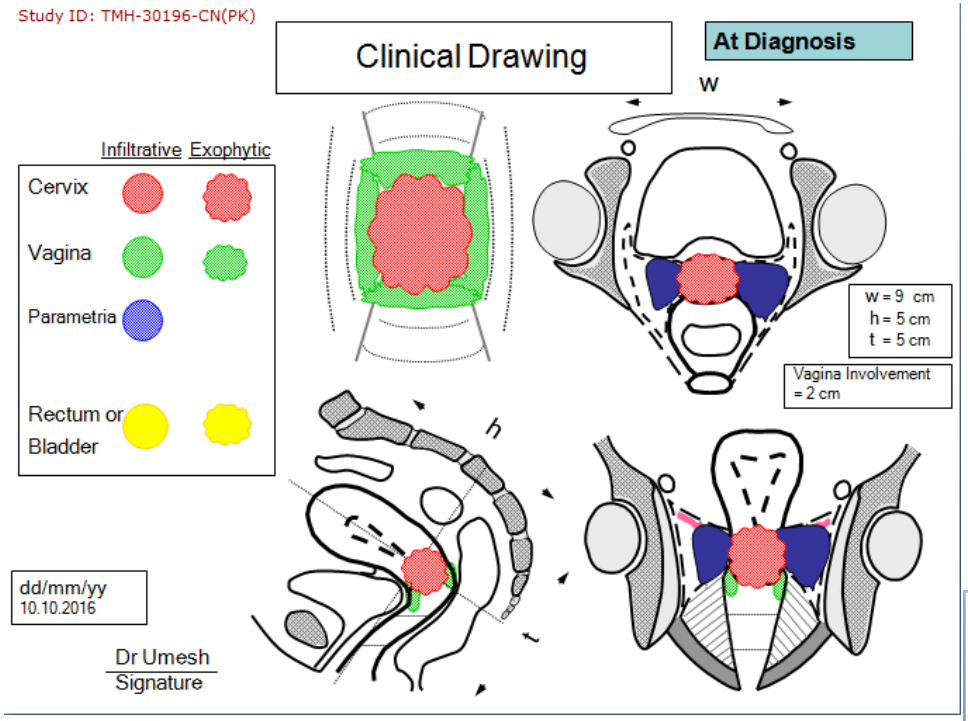
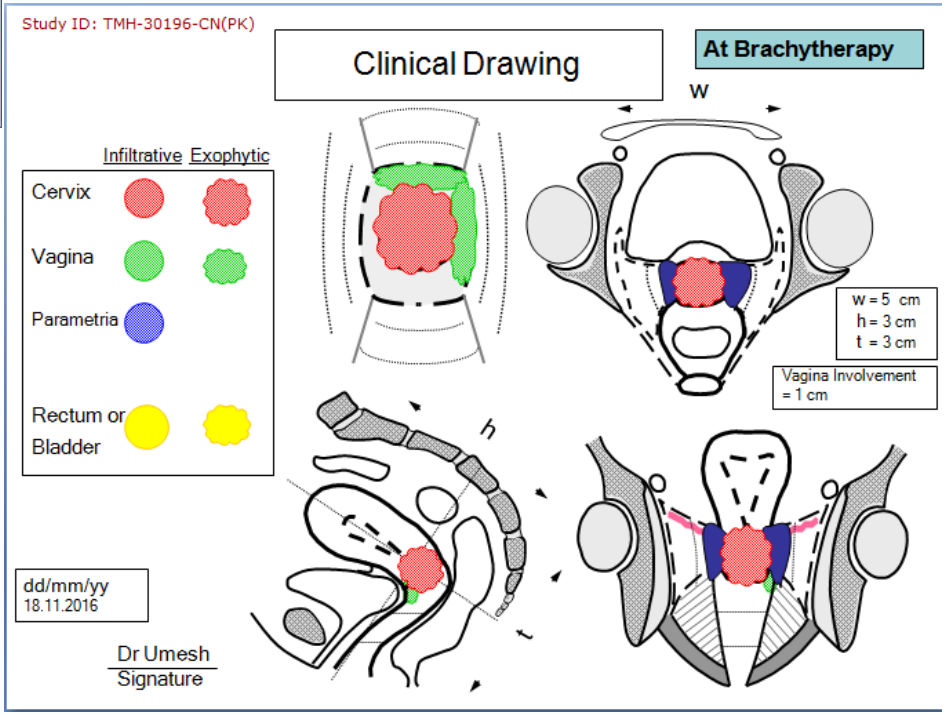
CTV-N2

TATA003- HOMEWORK & WORKSHOP CASE





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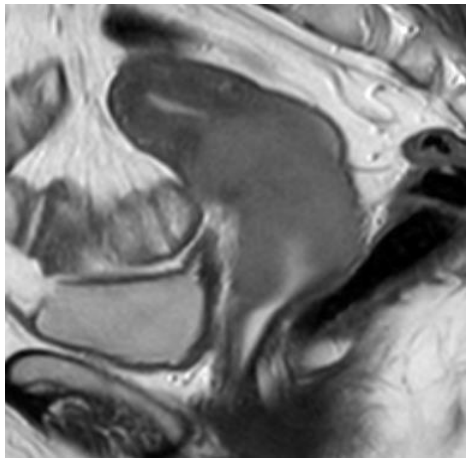
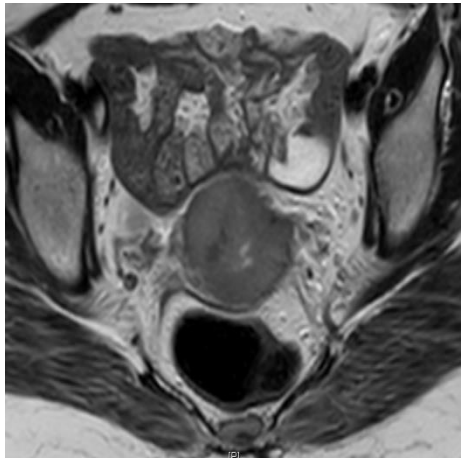
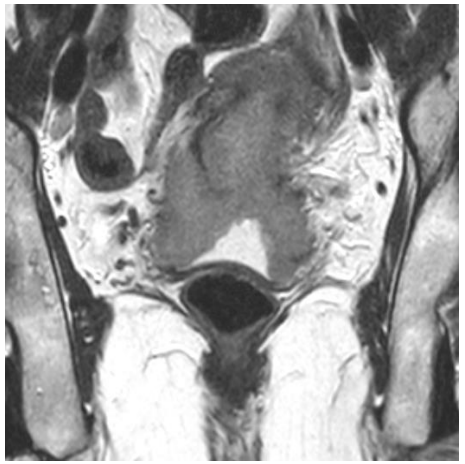
Diagnosis

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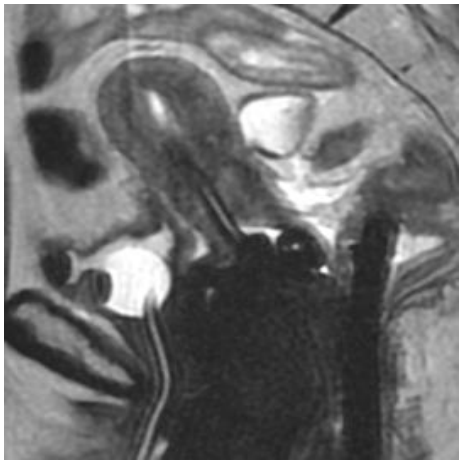
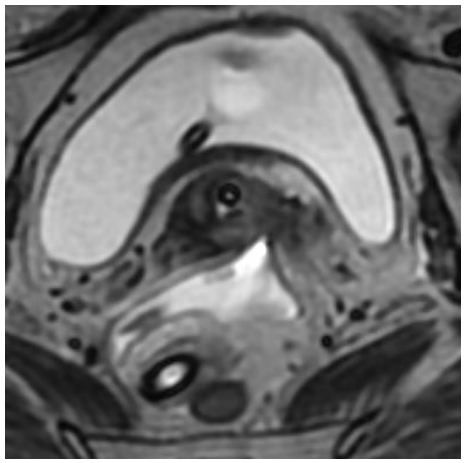
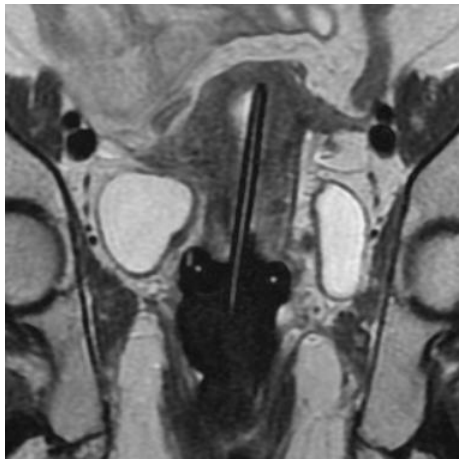
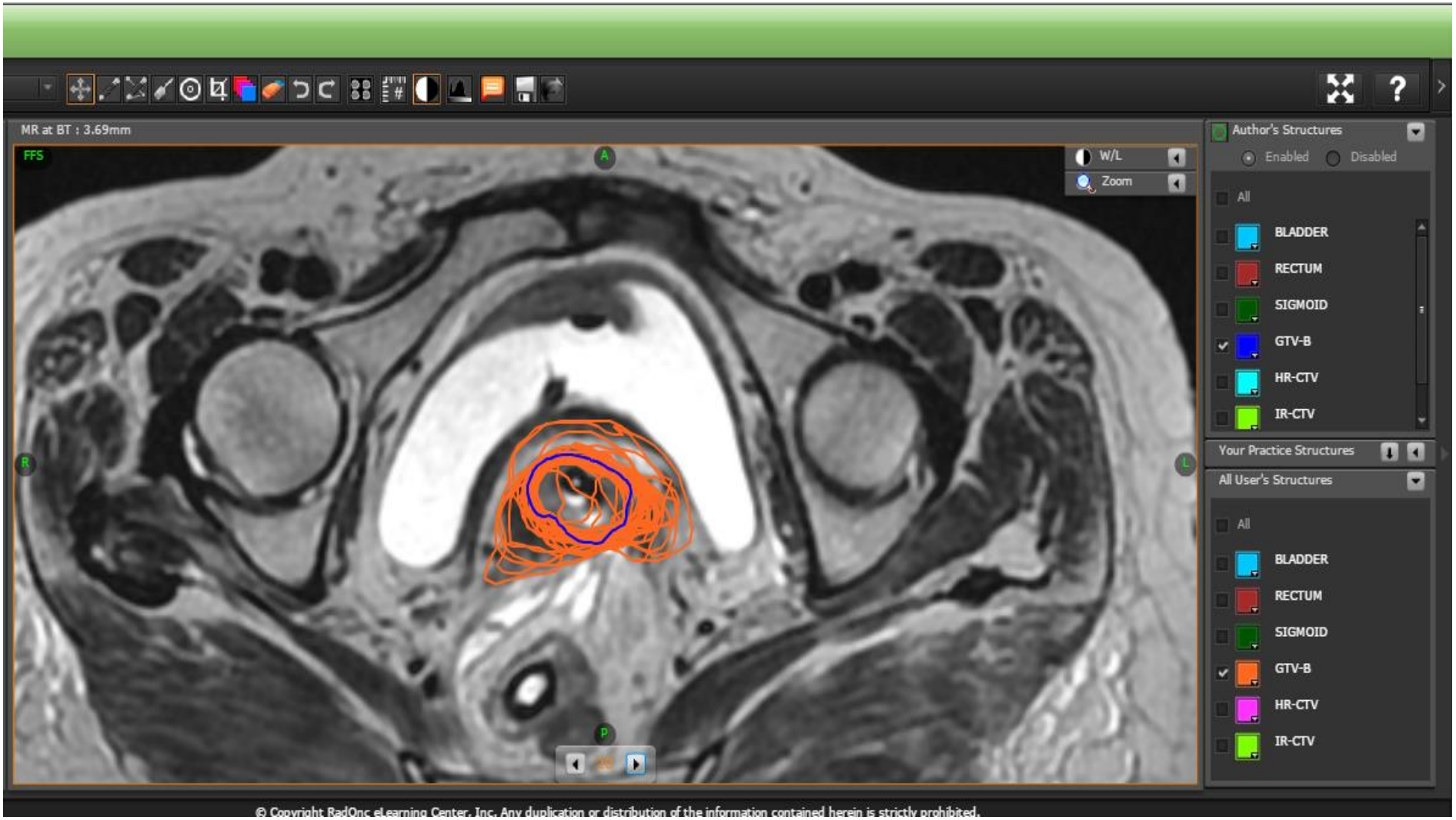
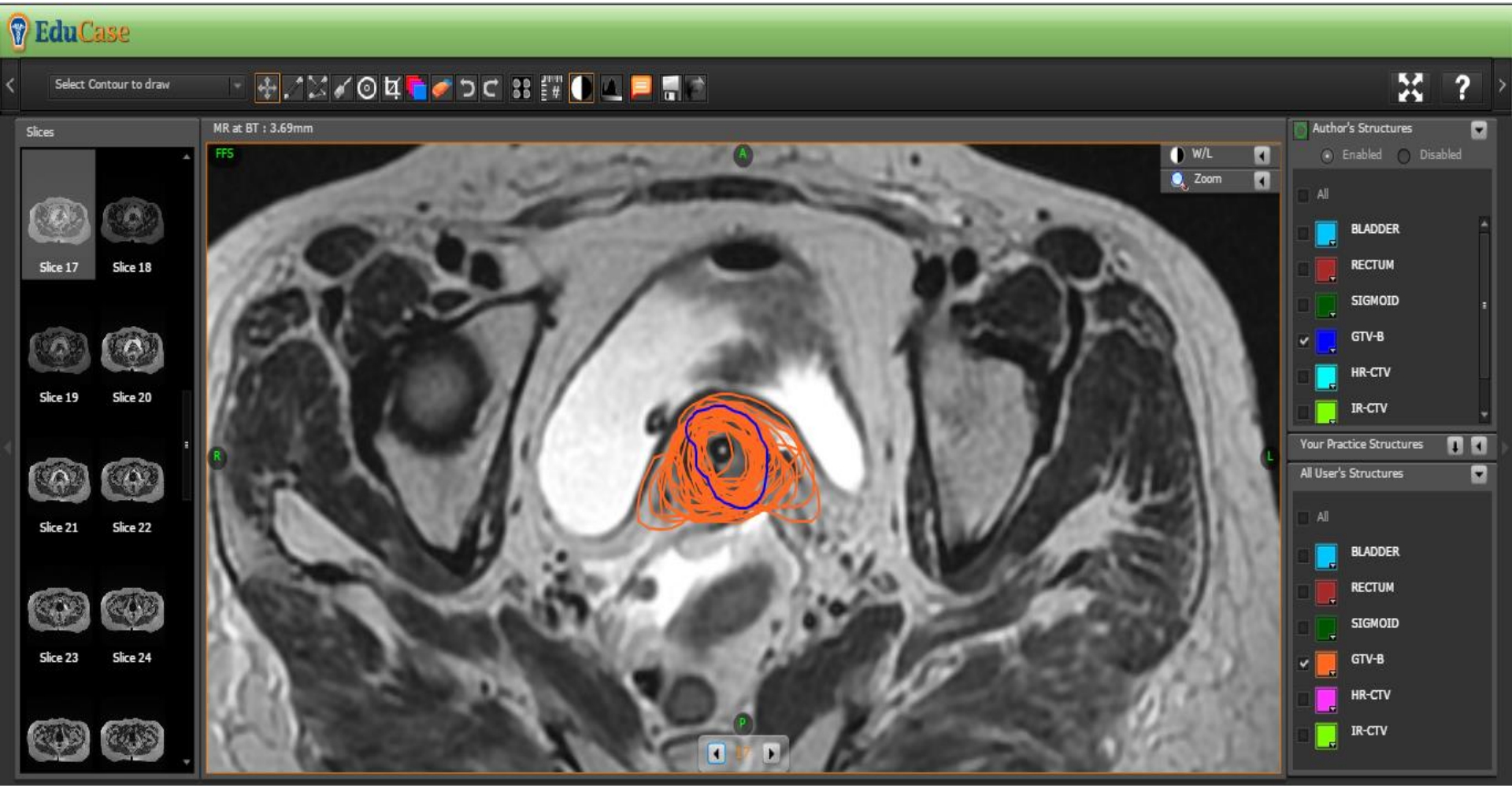




GTV-B



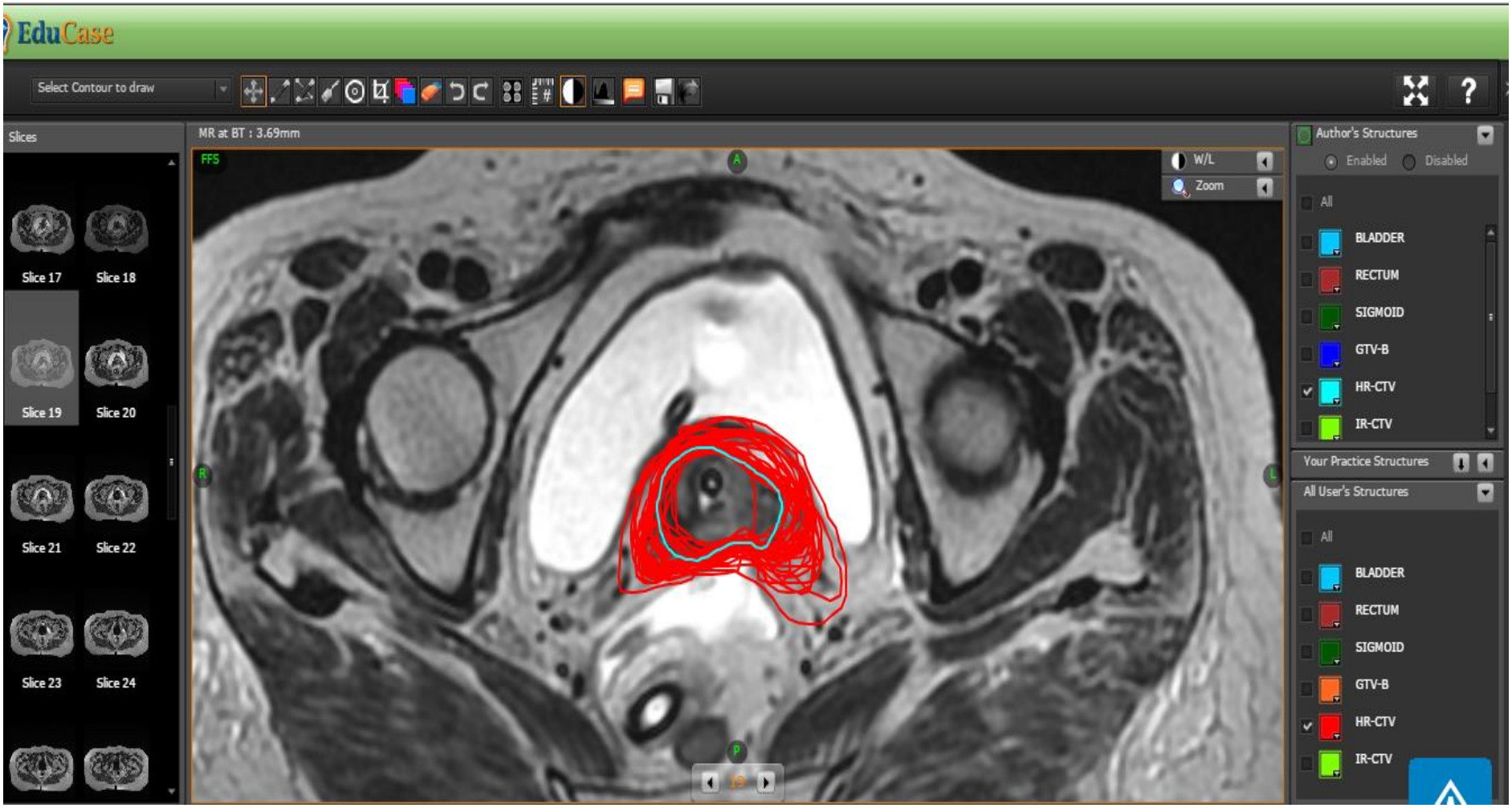
Large Variation

GTV-B



Overestimation

HR-CTV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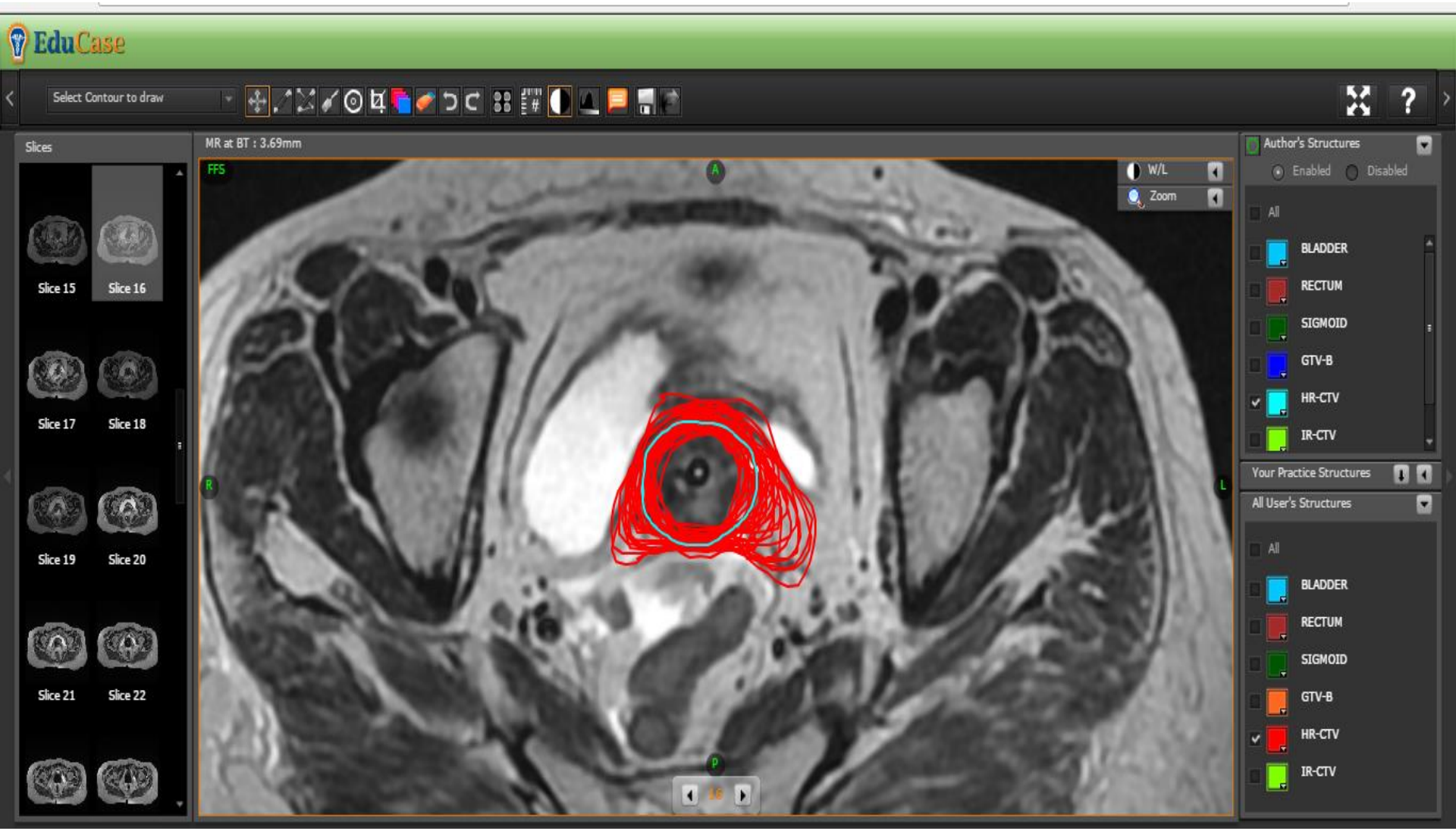
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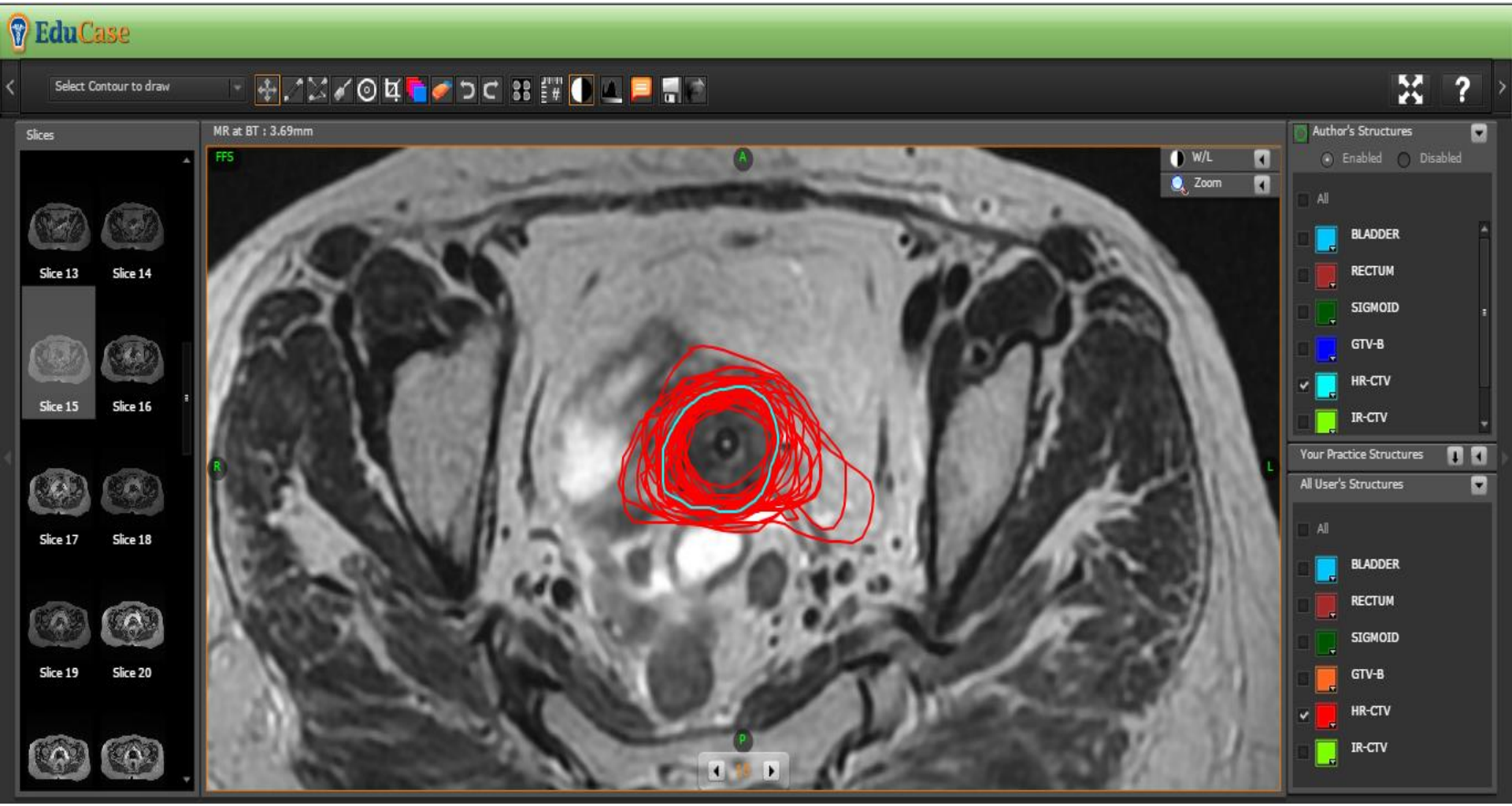
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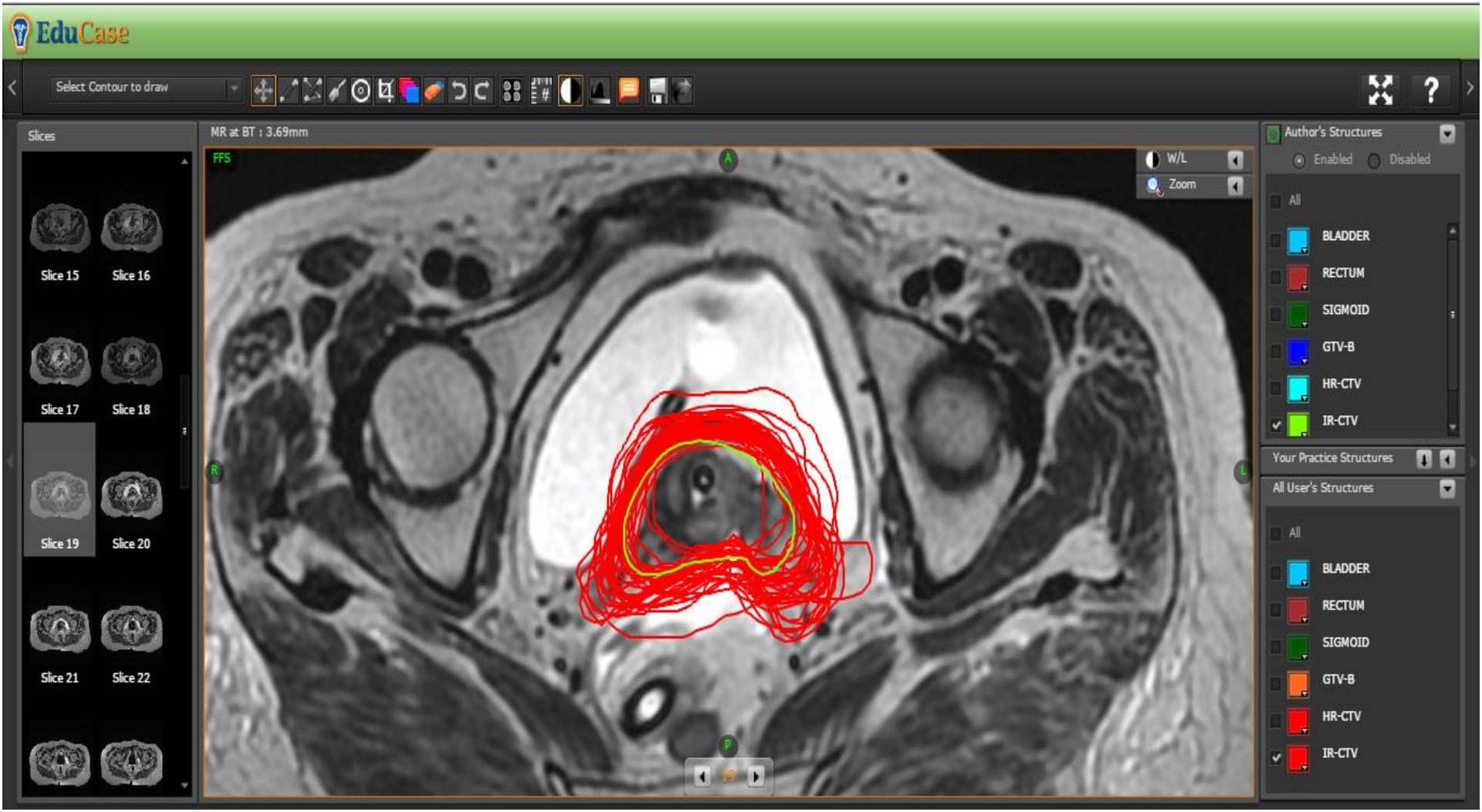
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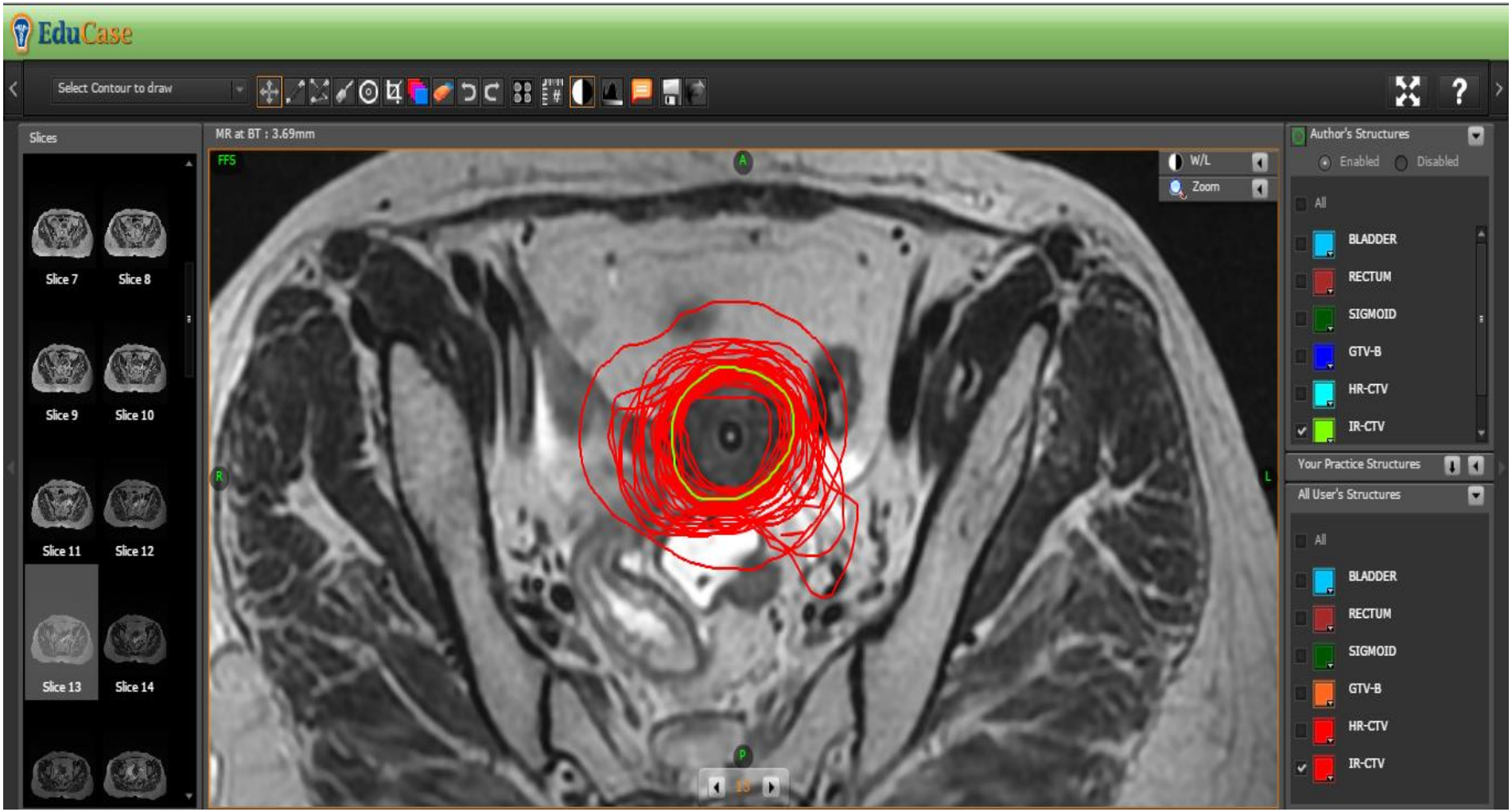
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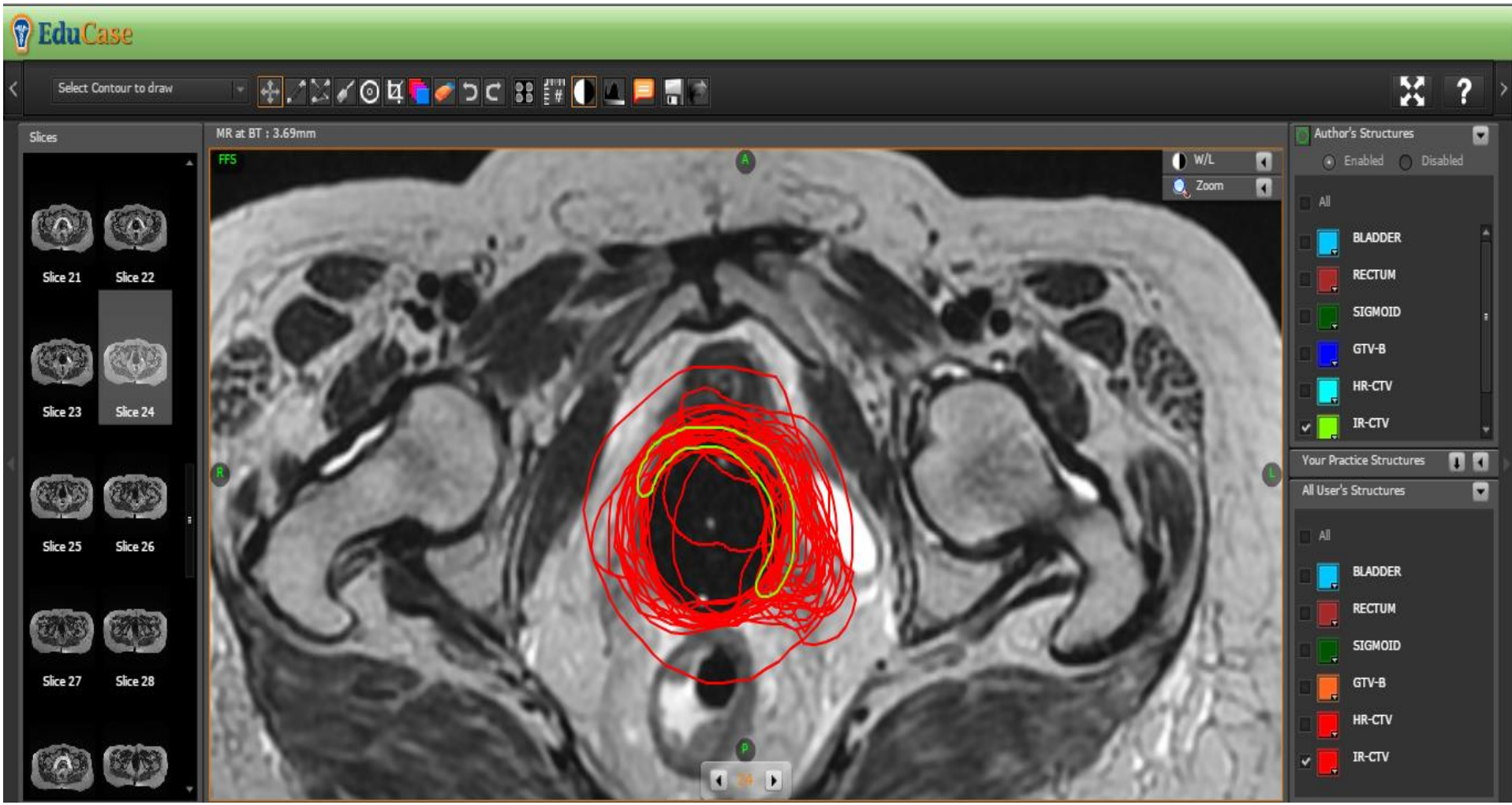
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Recap of BT planning principles: Radiography based/ CT information

- Clinical Drawings and Documentation
- Principles of Conventional Radiography Based BT planning
  - Point A definition
  - Standard Loading and Manual Optimization
  - ICRU 38 reporting (ICRU 89- Level 1)
- Understanding the STD Pear shaped distribution and its clinical implications

Motivate for 3D Imaging environment

Recap of BT planning principles: Radiography based/ CT information

Utilization of CT Imaging

- **Non – MRI Environment :**

  - CT imaging for BT application

  - Contouring of OAR's

  - Conventional Planning : Point A normalization & Prescription

  - Evaluation of OAR doses : ICRUB, ICRUR, 2 /0.1cm3 doses

  - Report: Point A , OAR doses in total EQD2 for each patient

Motivate for MR environment

Recap of BT planning principles: Radiography based/ CT information

Utilization of CT Imaging

- **MRI at Diagnosis Environment :**

  - CT imaging for BT application
  - Establish CT protocol: IV Contrast, bladder contrast
  - Contouring of OAR's mandatory
  - High Risk CTV Concept: Pre Rx (MR) & at BT Clinical drawing
  - Conventional Planning : Point A normalization & Prescription
  - Evaluation of doses to CT-HR CTV and OAR's
  - Report: Point A , CT-HR CTV, OAR doses in total EQD2 for each patient

Motivate & Mobilize few patients for MR environment at BT


Working for success
will make you a Master;
But
Working for satisfaction
will make you a Legend.
GOOD MORNING!

Medical aspects of treatment planning and dose constraints: focus on BT

Clinical evidence for dose-effects

ESTRO AROI Teaching Course
Transition from conventional 2D to 3D Radiotherapy with a special emphasis on brachytherapy in cervical cancer

Bengaluru March 2017

Richard Pötter

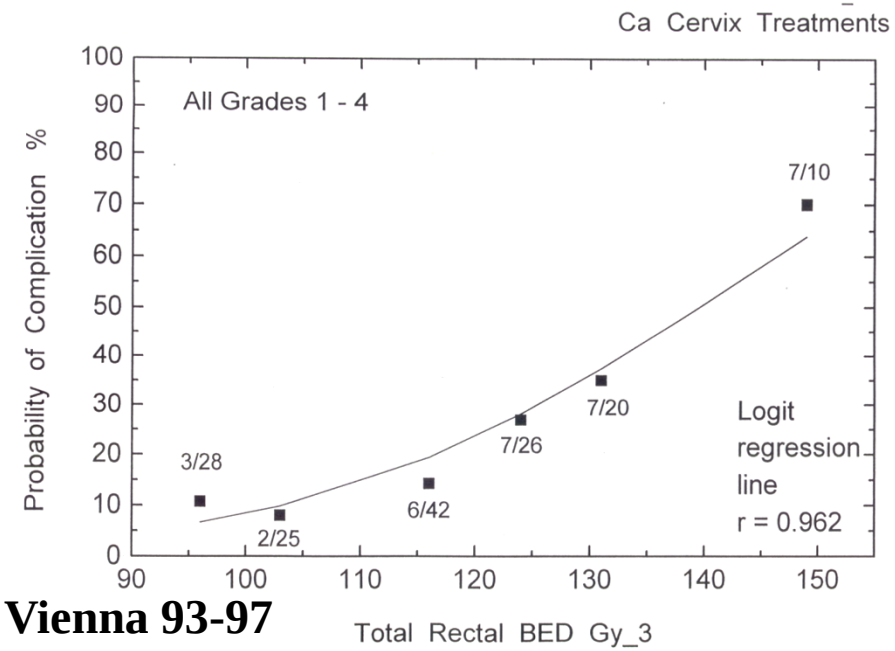
Kari Tanderup

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)

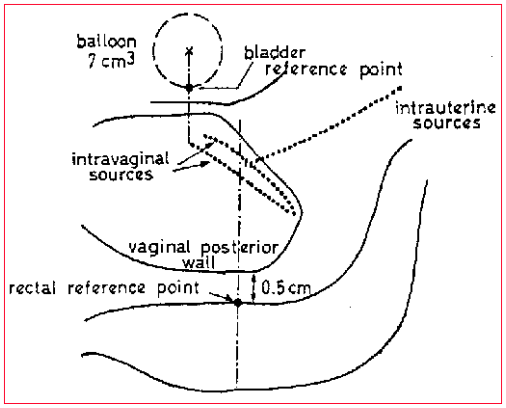


Vienna 93-97

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)

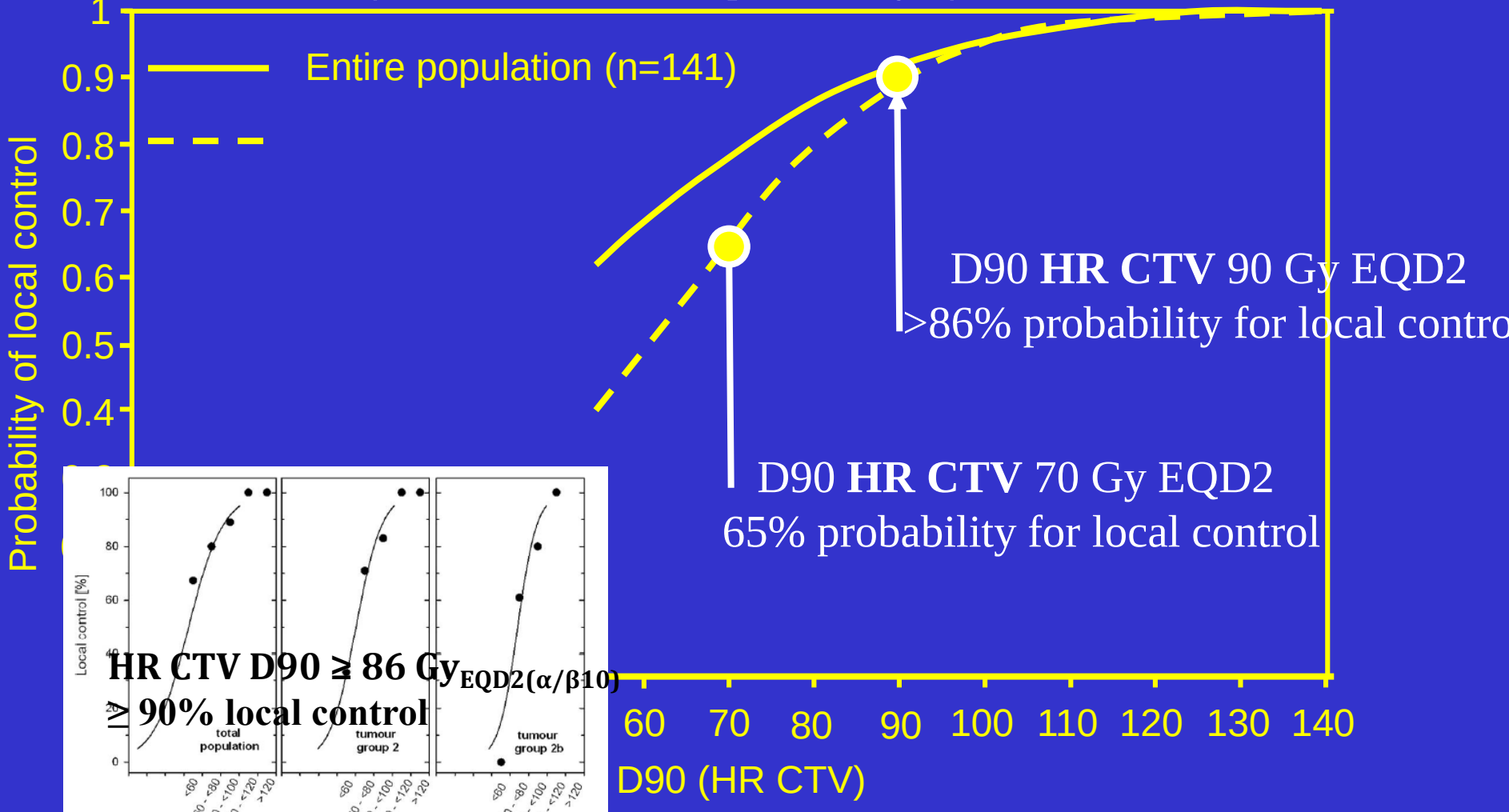
- **Vienna** (Dimopoulos 2008, 2010, Georg 2009,2011(Pötter 2007, 2011))
- **Seoul** (Kim et al. 2008)
- **Paris** (Mazeron 2014, 2015 (Castelnaud-Marchand 2015, Haie-Meder))
- **Aarhus** (Lindegaard, Tanderup 2014)
- **Leuven** (Ribeiro, Limbergen 2016)

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

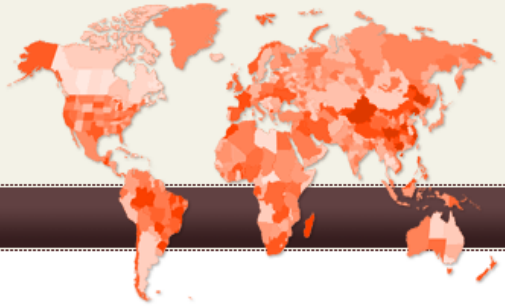


HR CTV D90 ≥ 86 Gy$_{EQD2(\alpha/\beta10)}$
≥ 90% local control

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**

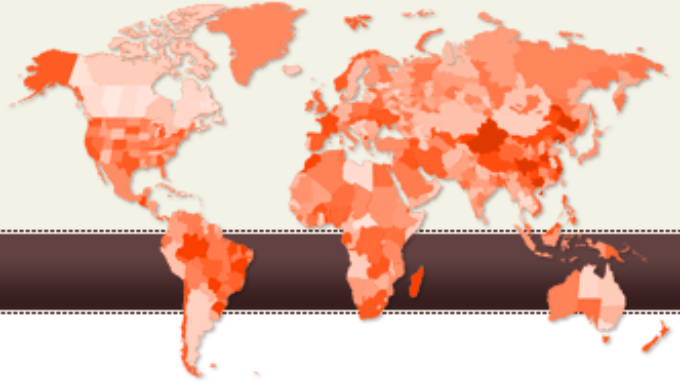
Overall outcome published by Sturdza et al. Radioth Oncol 2016

VARIAN medical systems | A partner for life

Nucletron Improving patient care

EMBRACE

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



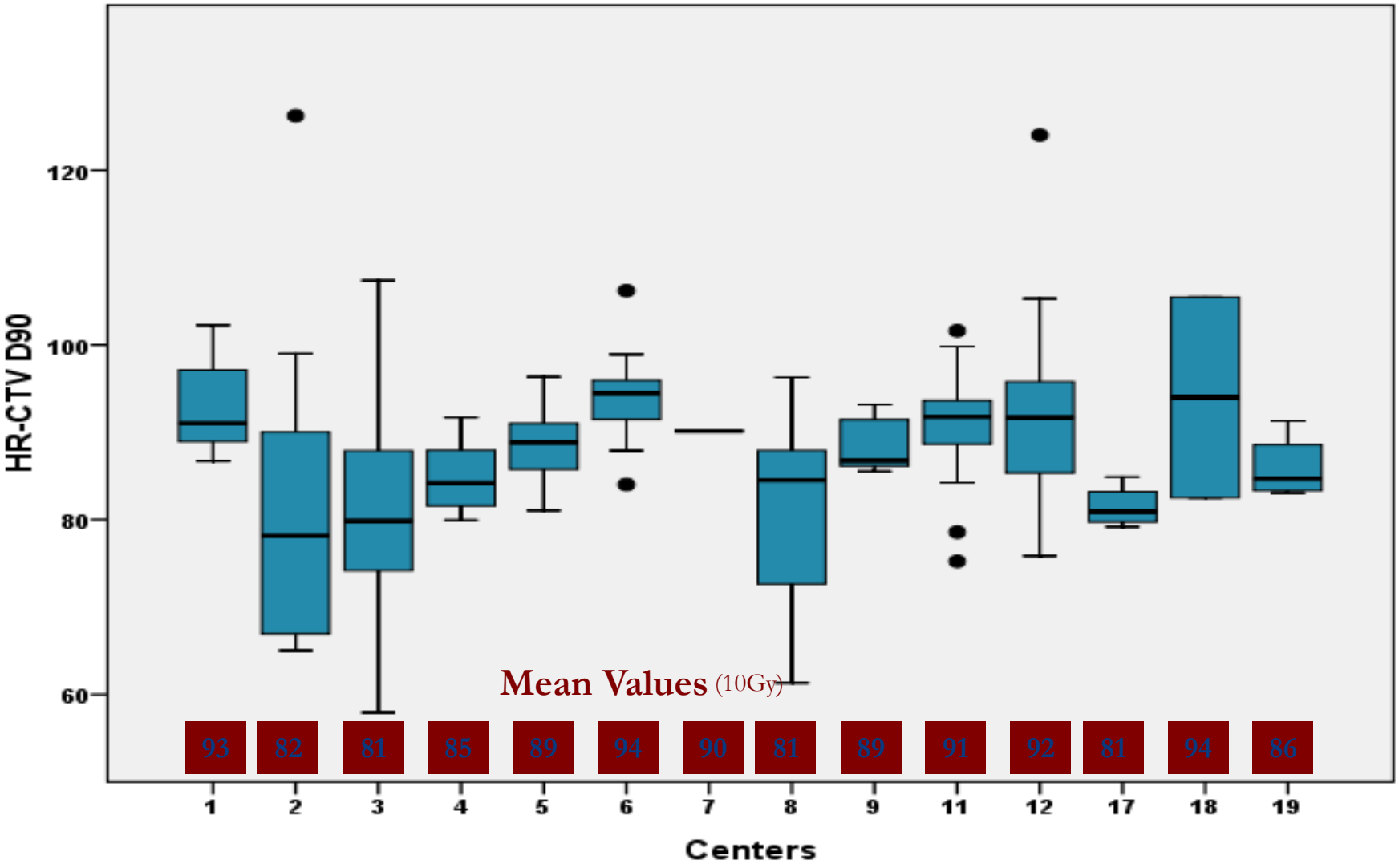
About Embrace | Contacts | Participation | Login

- **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**

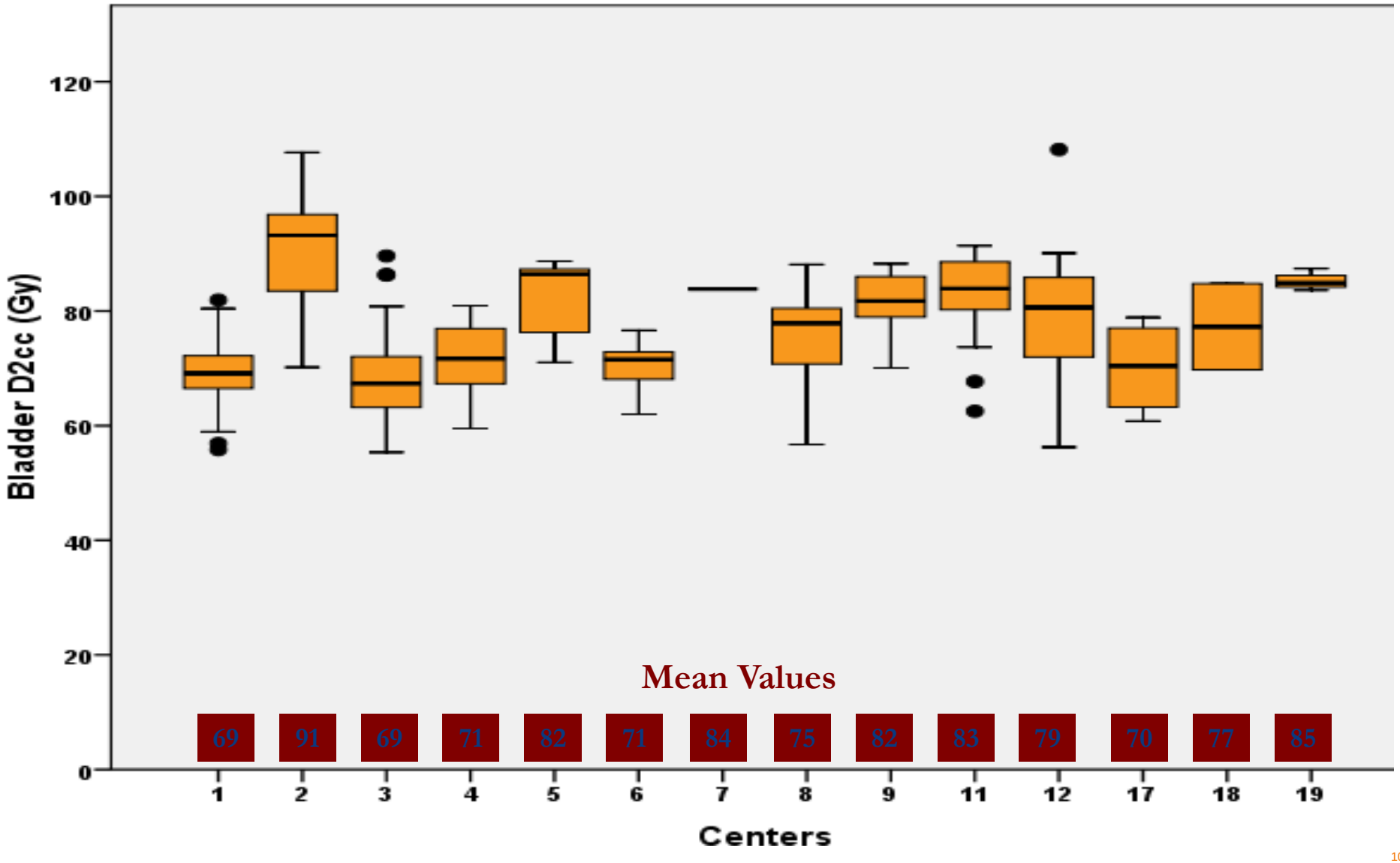
VARIAN medical systems | A partner for life

Nucletron Improving patient care

Heterogeneity of dose prescription: HRCTV D90

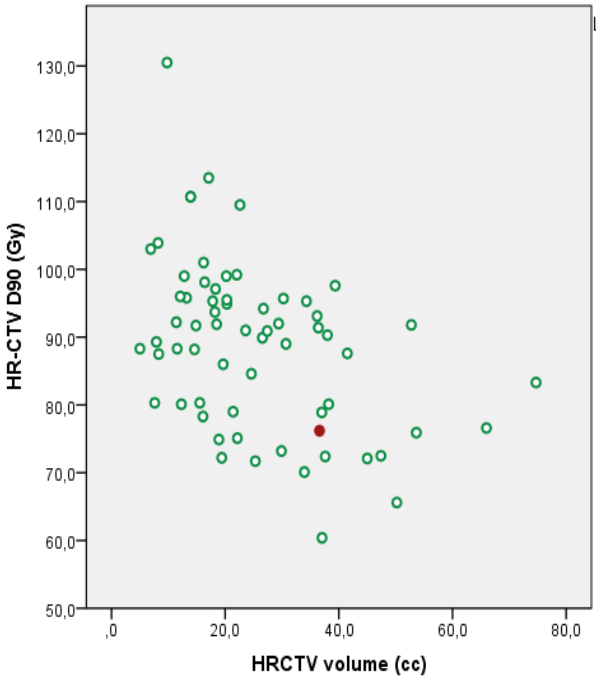


Heterogeneity of dose prescription: Bladder D2cc

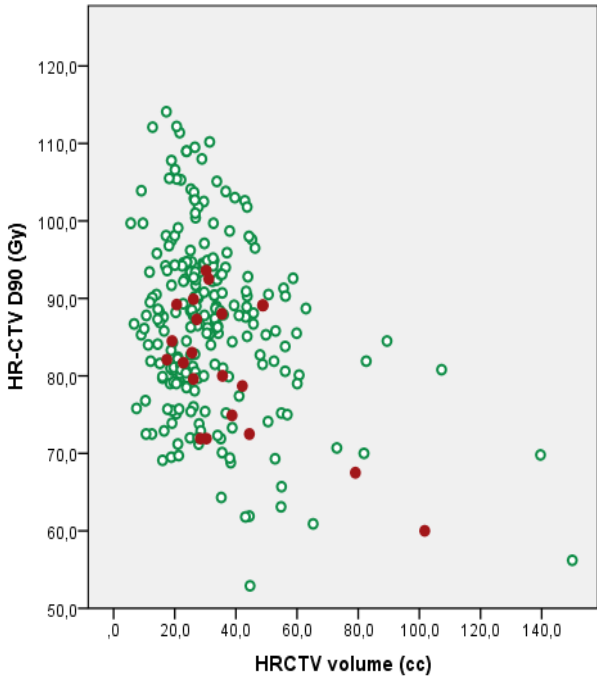


Recurrences according to dose and volume

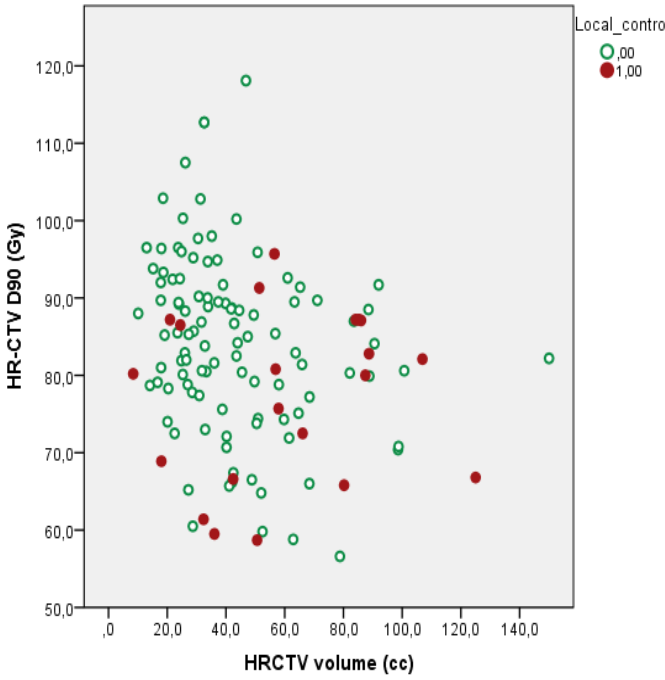
Stage I



Stage II

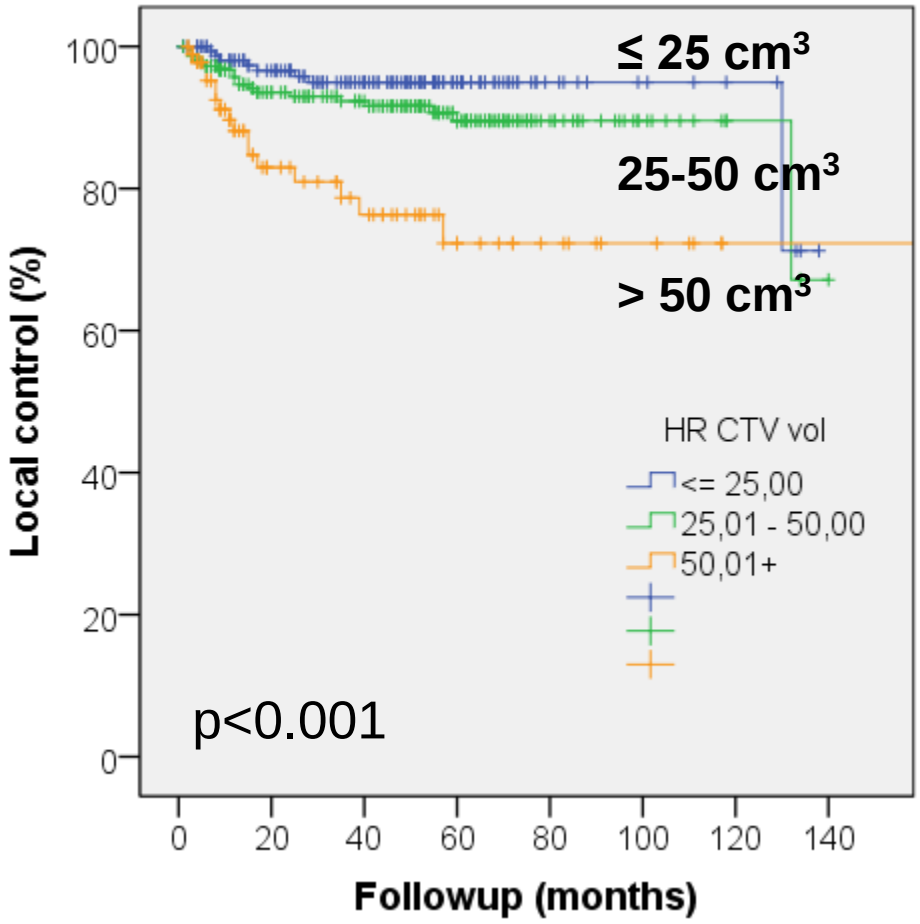


Stage III+IV

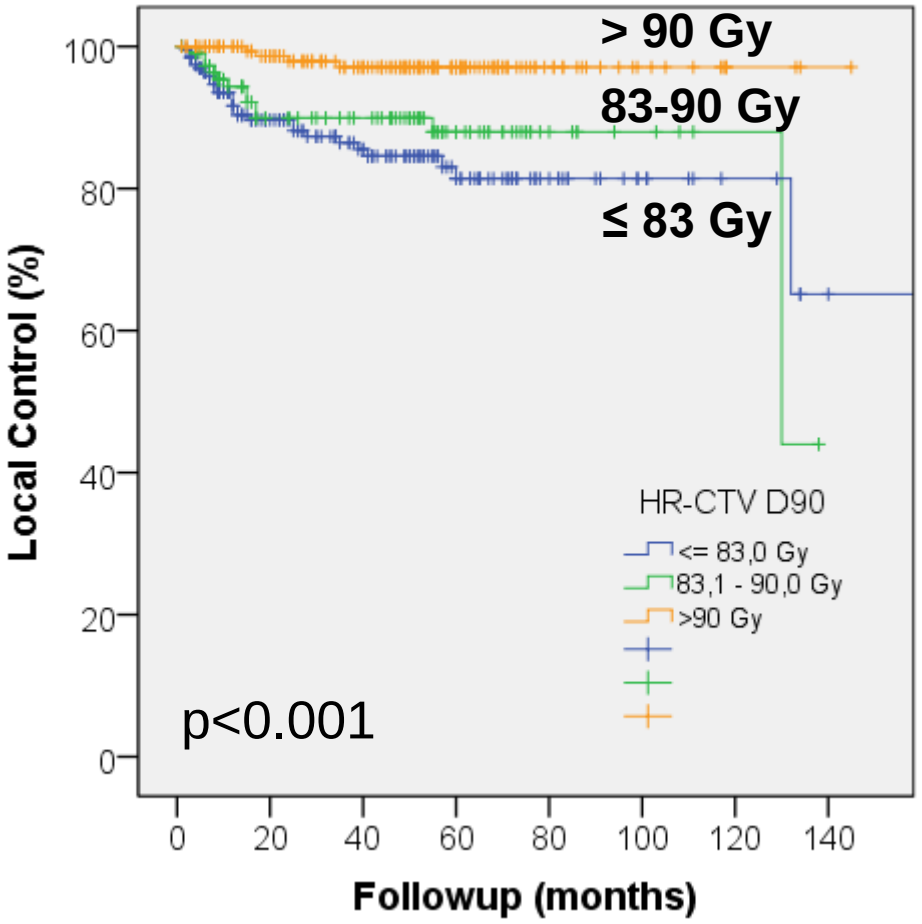


Actuarial local control: univariate analysis separate for HR CTV volume and dose

CTV_{HR} volume



CTV_{HR} dose



Tanderup et al 2015

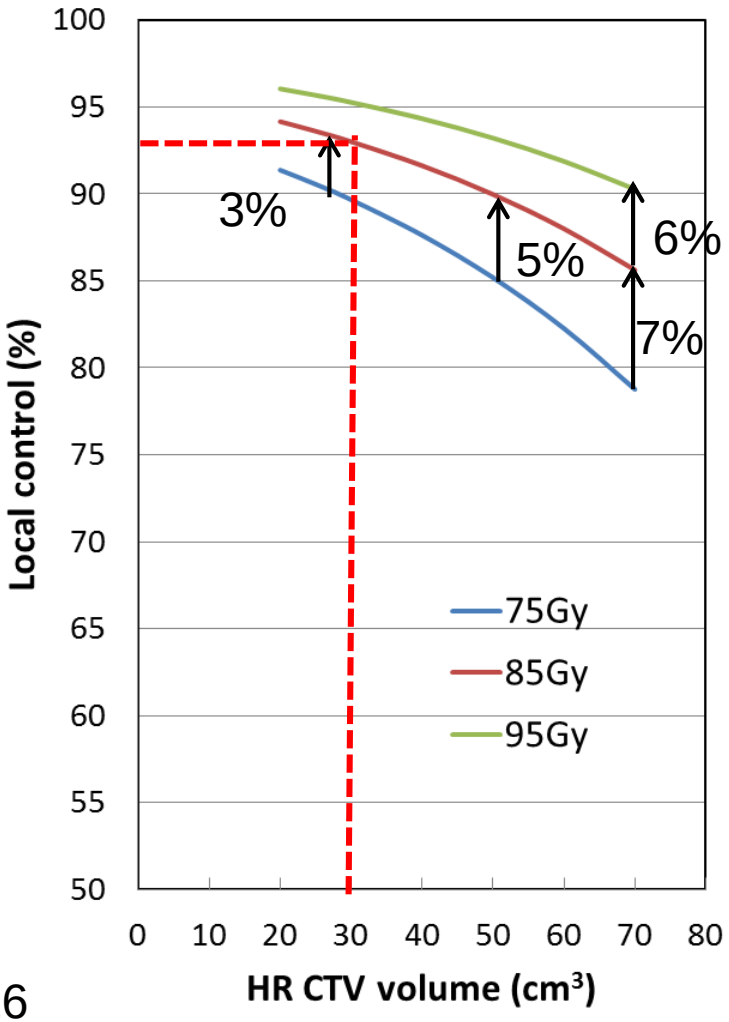
Dose, volume, and time effect

Effect of dose, volume and time:

Dose: 10Gy → 5% LC
Time: 7 days ~ 5Gy
Volume $10cm^3$ ~ 5Gy

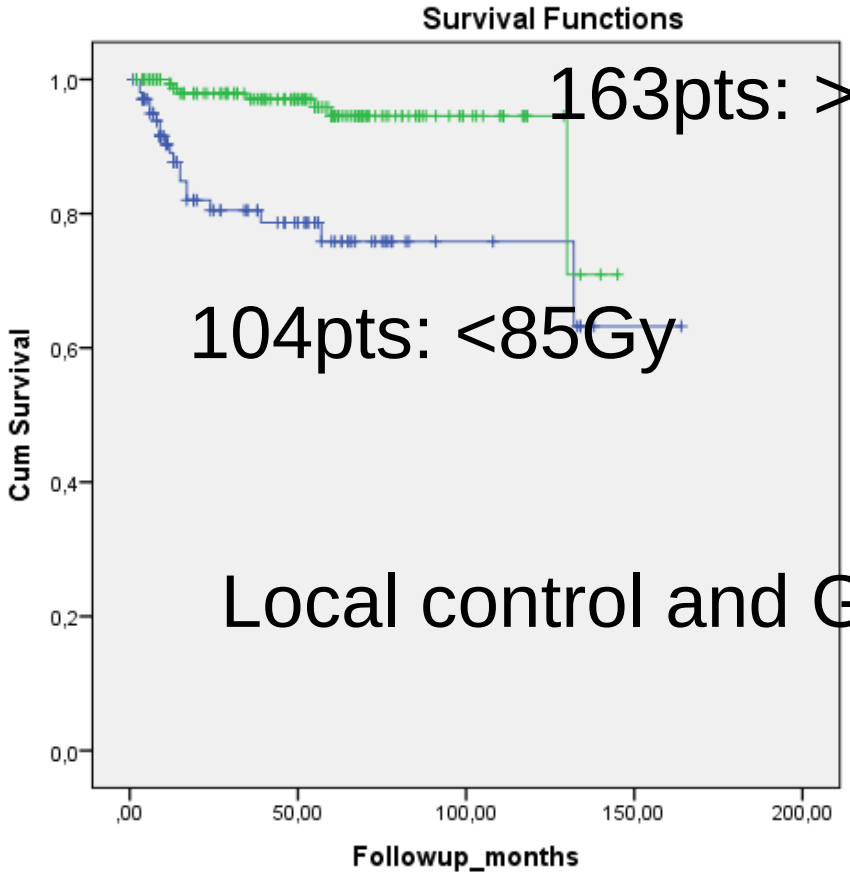
85Gy for $30cm^3$ CTV_{HR}: 93% LC

Local control at 3 years



Tanderup et al, Radiotherapy and Oncology 2016

Dose volume response for GTV



163pts: >85Gy

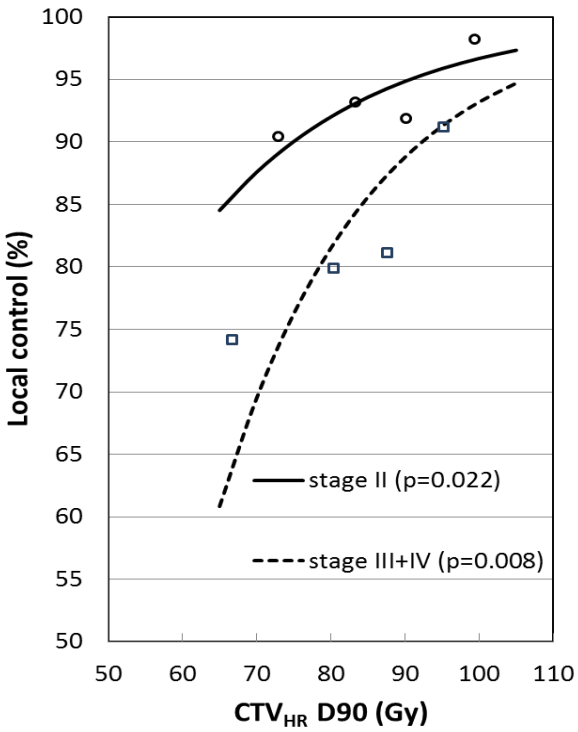
104pts: <85Gy

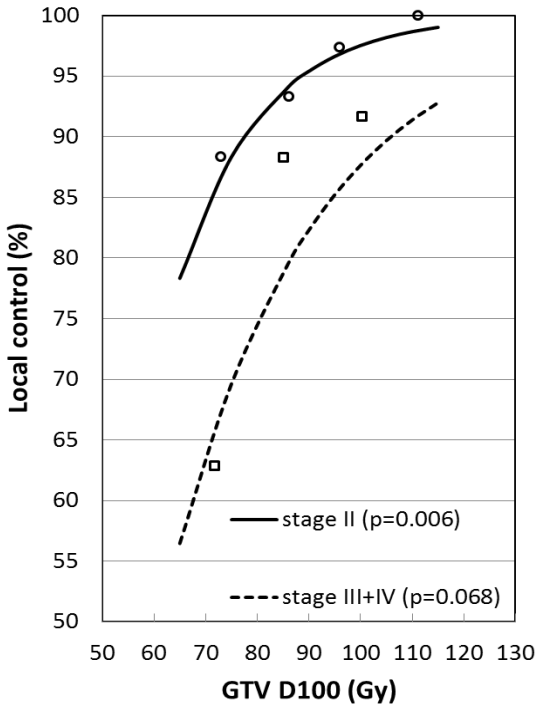
Local control and GTV dose

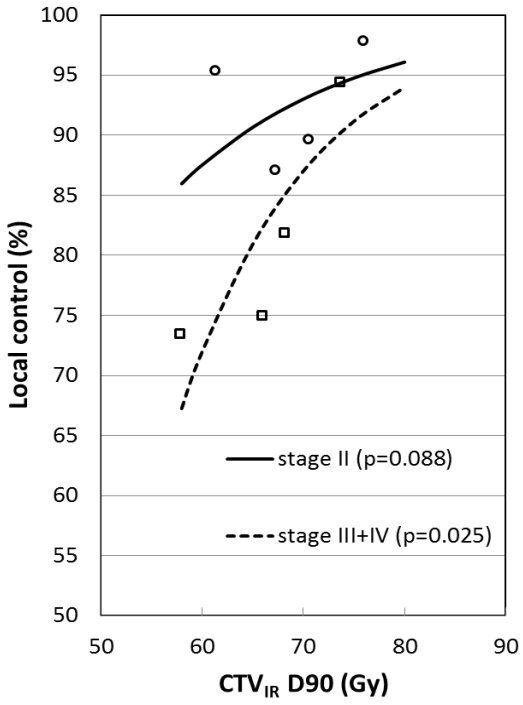
Tanderup 2015
Preparation for EMBRACE II

Dose effect GTV, CTV_{HR} and CTV_{IR}

Stage-related analysis

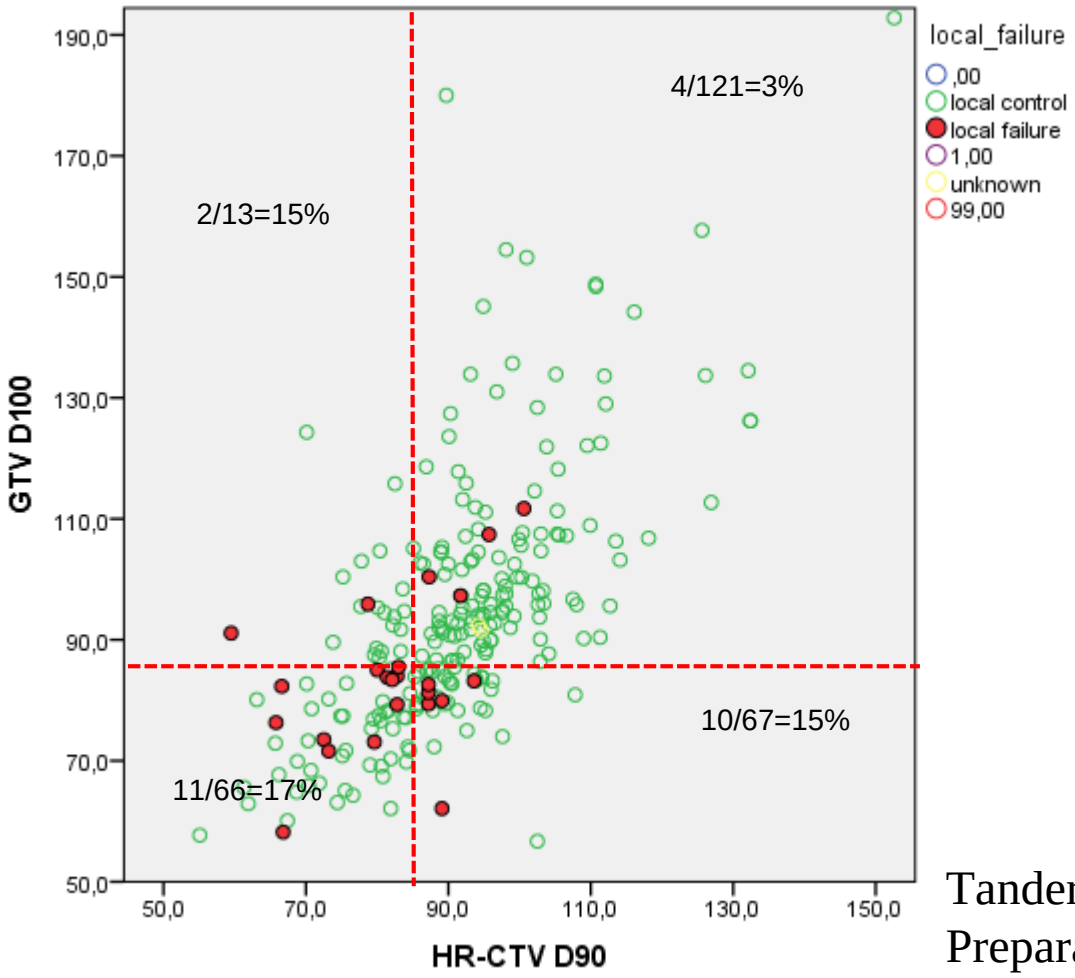






Tanderup et al. Radiotherapy and Oncology 2016

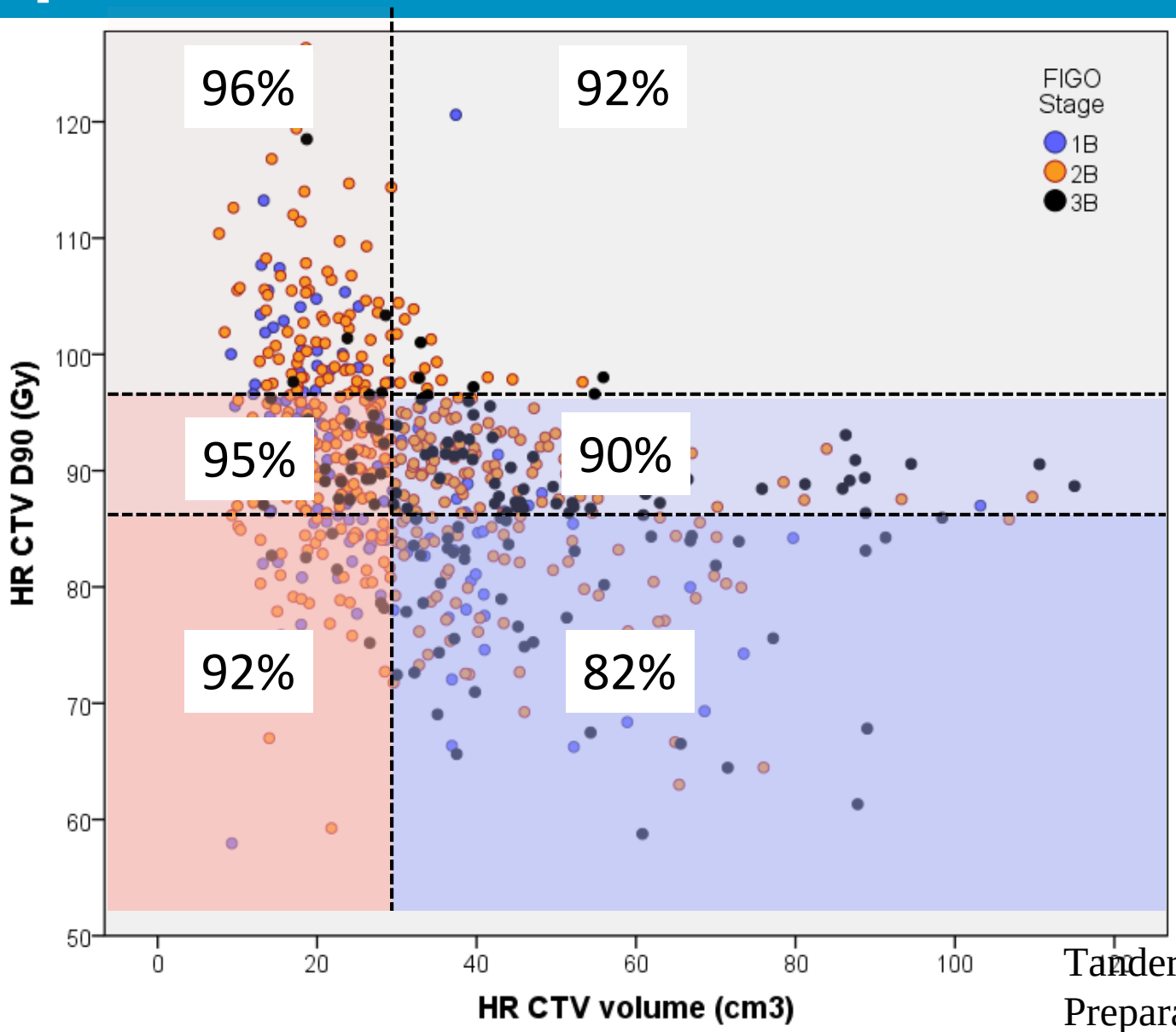
Combined constraints for GTV and CTV_{HR}



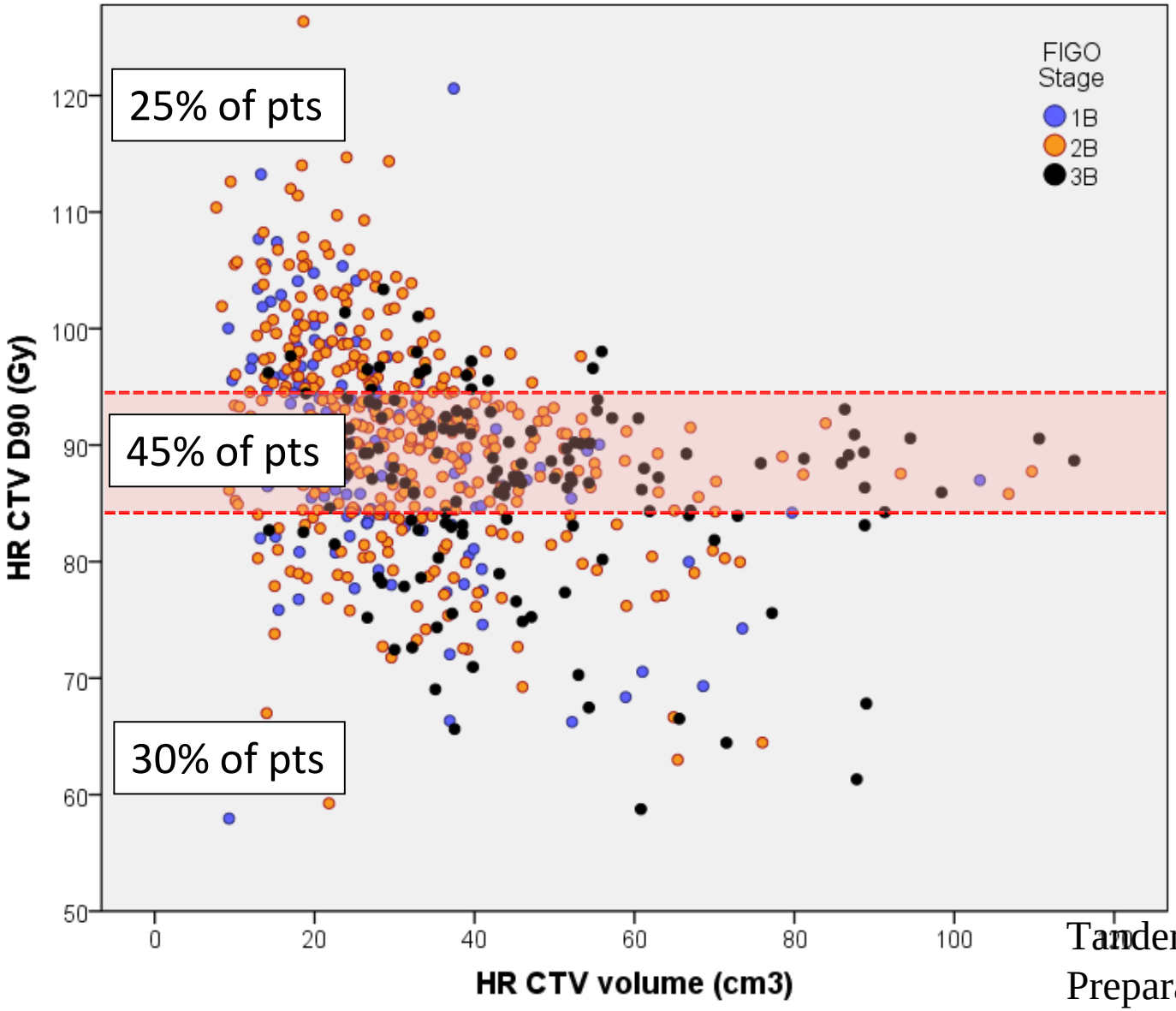
Tanderup 2015
Preparation for EMBRACE II

Practice in EMBRACE I and predicted local control from RetroEMBRACE

769 pts EMBRACE



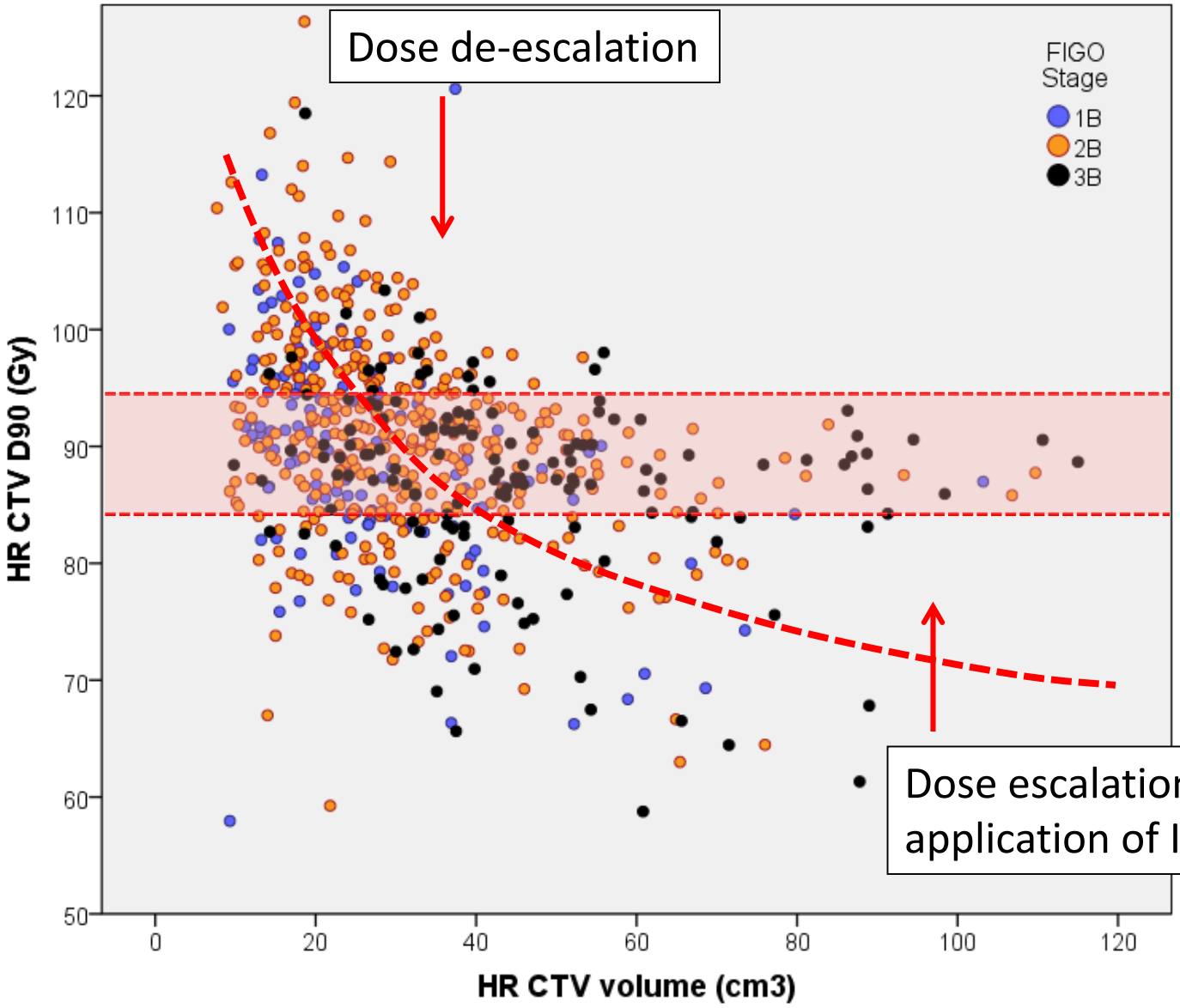
EMBRACE I practice



769 pts EMBRACE

HR CTV D90 85-95Gy

EMBRACE II dose prescription



769 pts EMBRACE

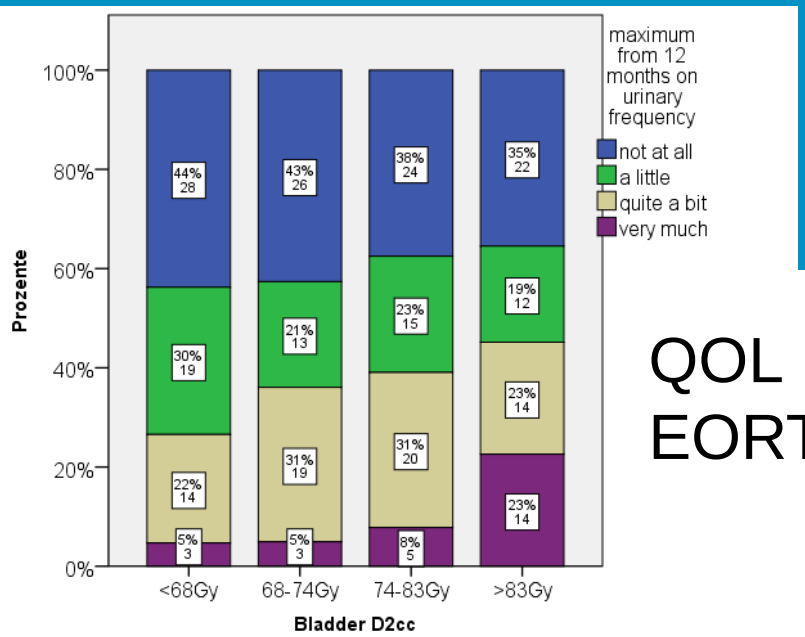
HR CTV D90 85-95Gy

Tanderup 2015

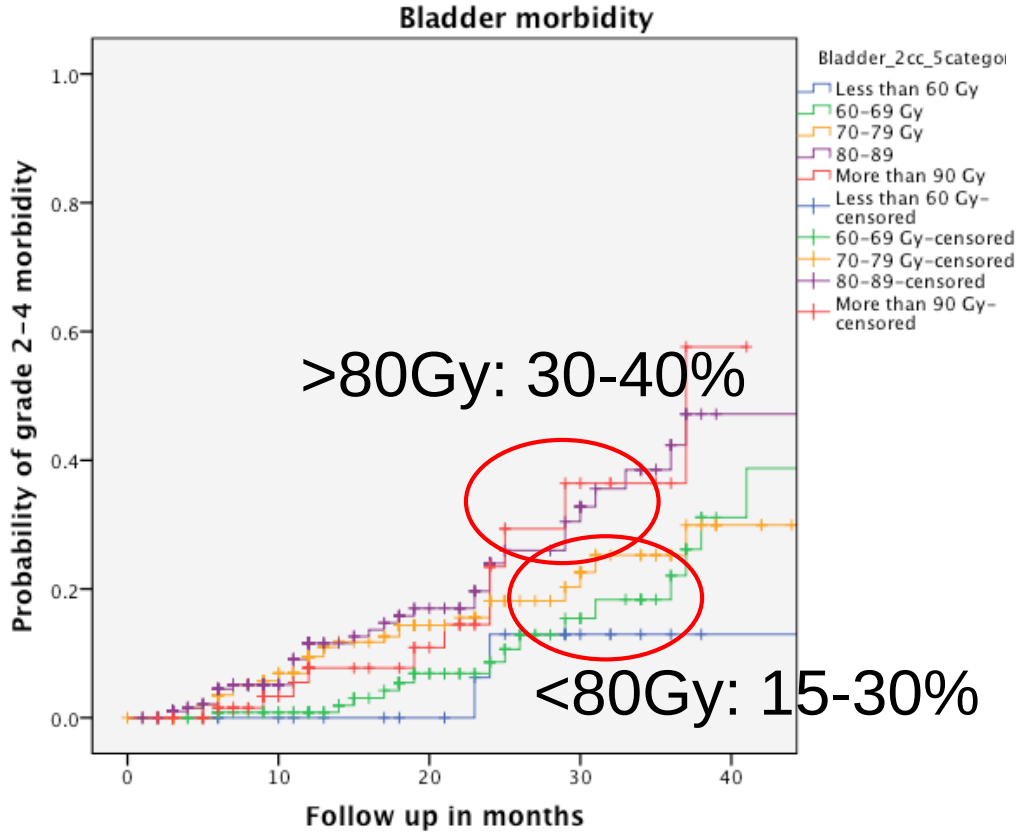
Beach boy approach – Barcelona 2013

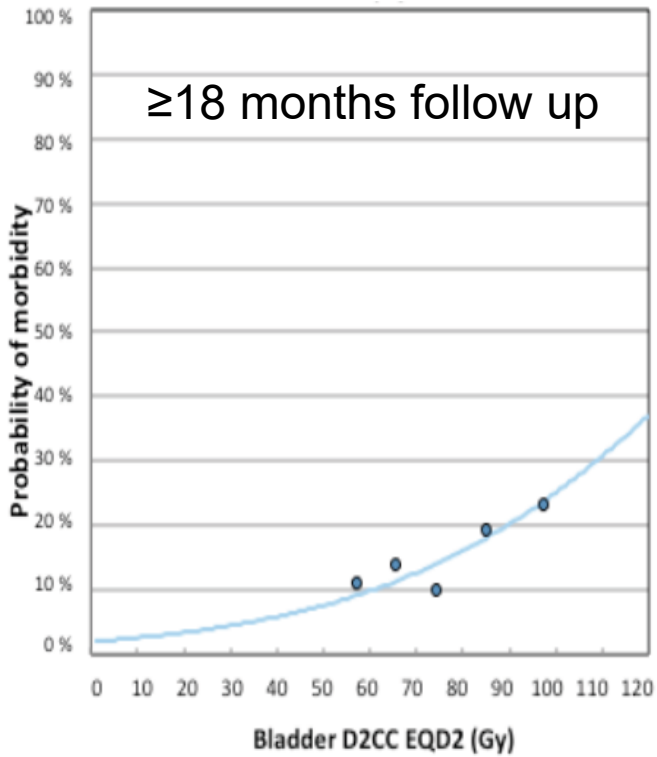
Bladder D_{2cm3}

- **EMBRACE CTCAE**
- **All endpoints except ureter stenosis G≥2**



QOL EORTC

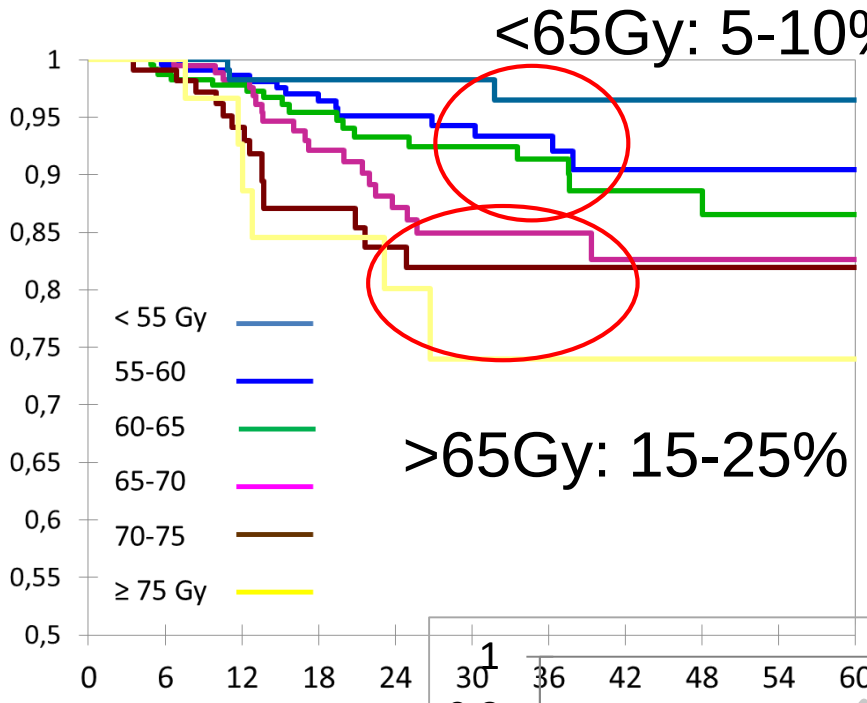




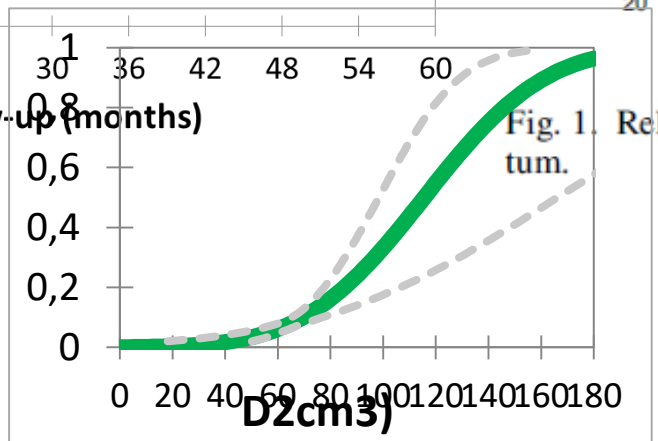
Fokdal et al 2015

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)

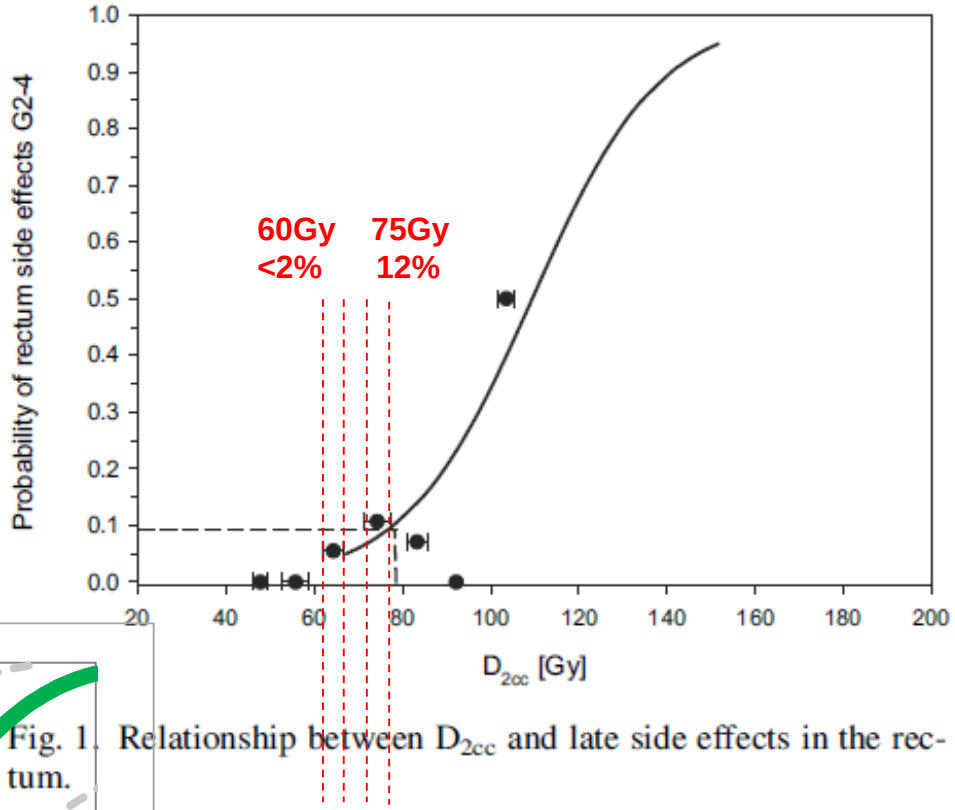
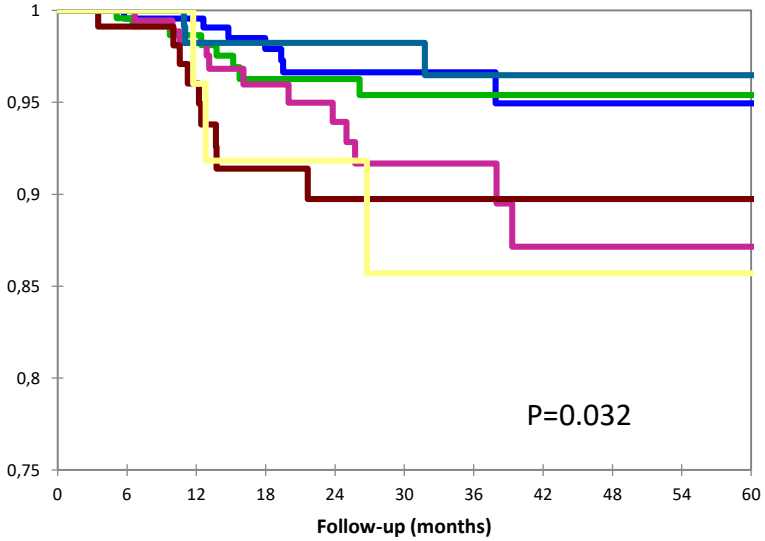


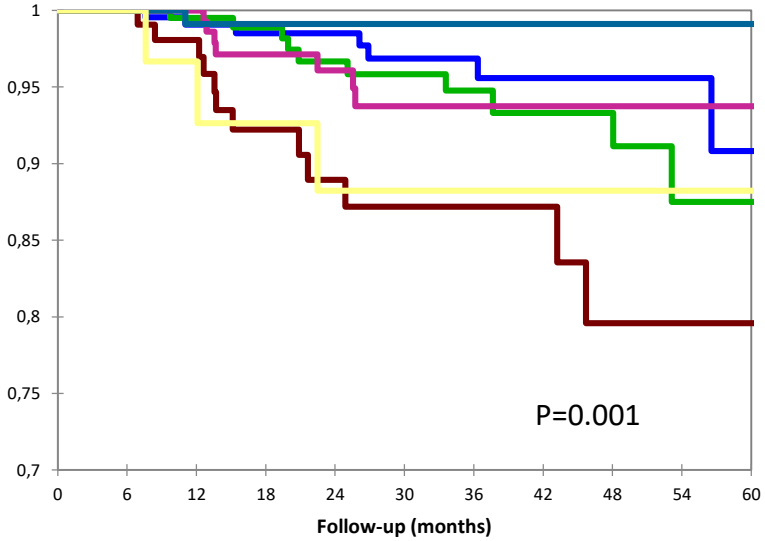
Fig. 1. Relationship between D_{2cc} and late side effects in the rectum.

P. Georg et al.,
IJROBP 2011

Proctitis



Bleeding



dose effects for different endpoints for rectal morbidity EMBRACE (n=960)

< 55 Gy

55-60

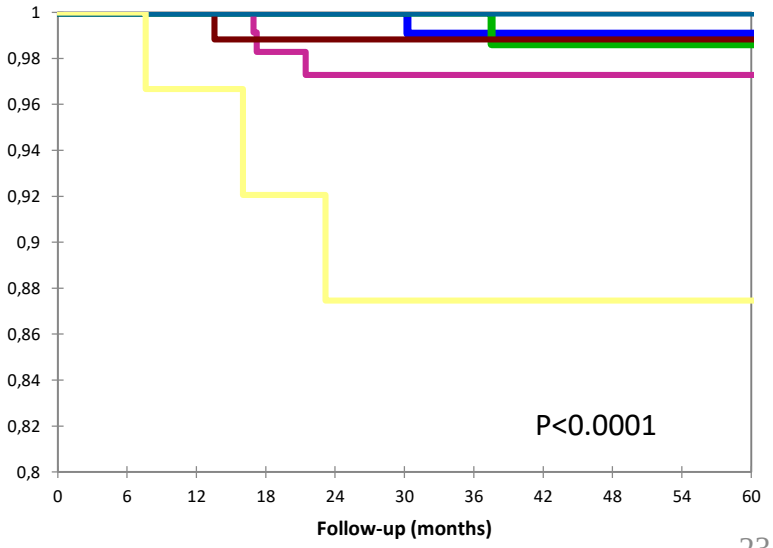
60-65

65-70

70-75

≥ 75 Gy

Fistula

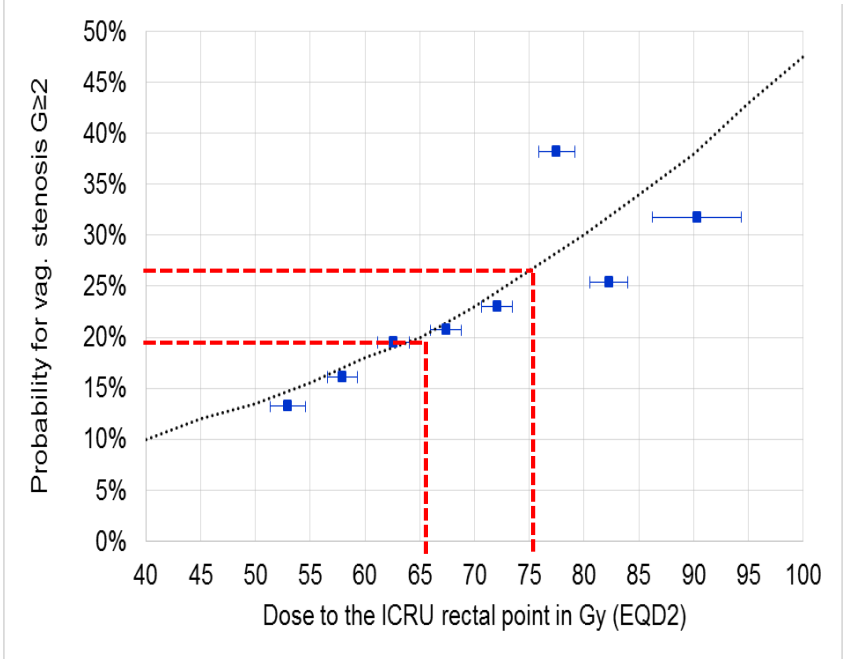


Mazeron et al, RadiothOncol 2016

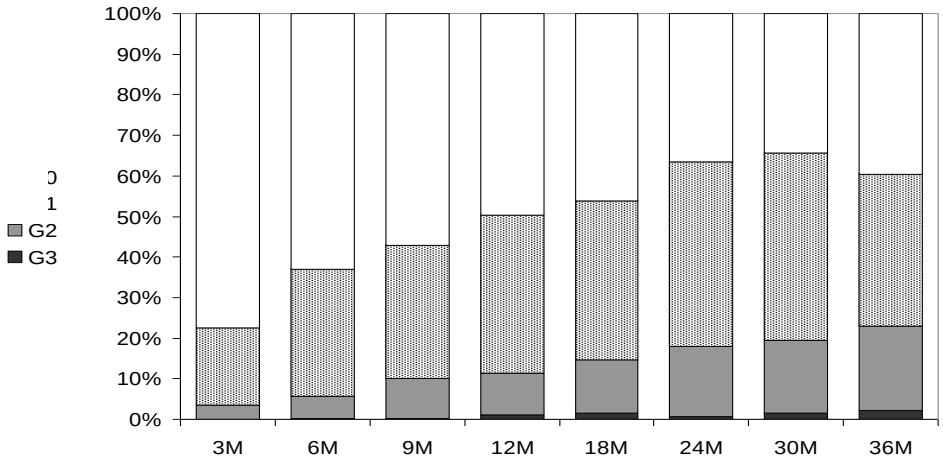
Vaginal stenosis and ICRU recto-vaginal point (630 pts)

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



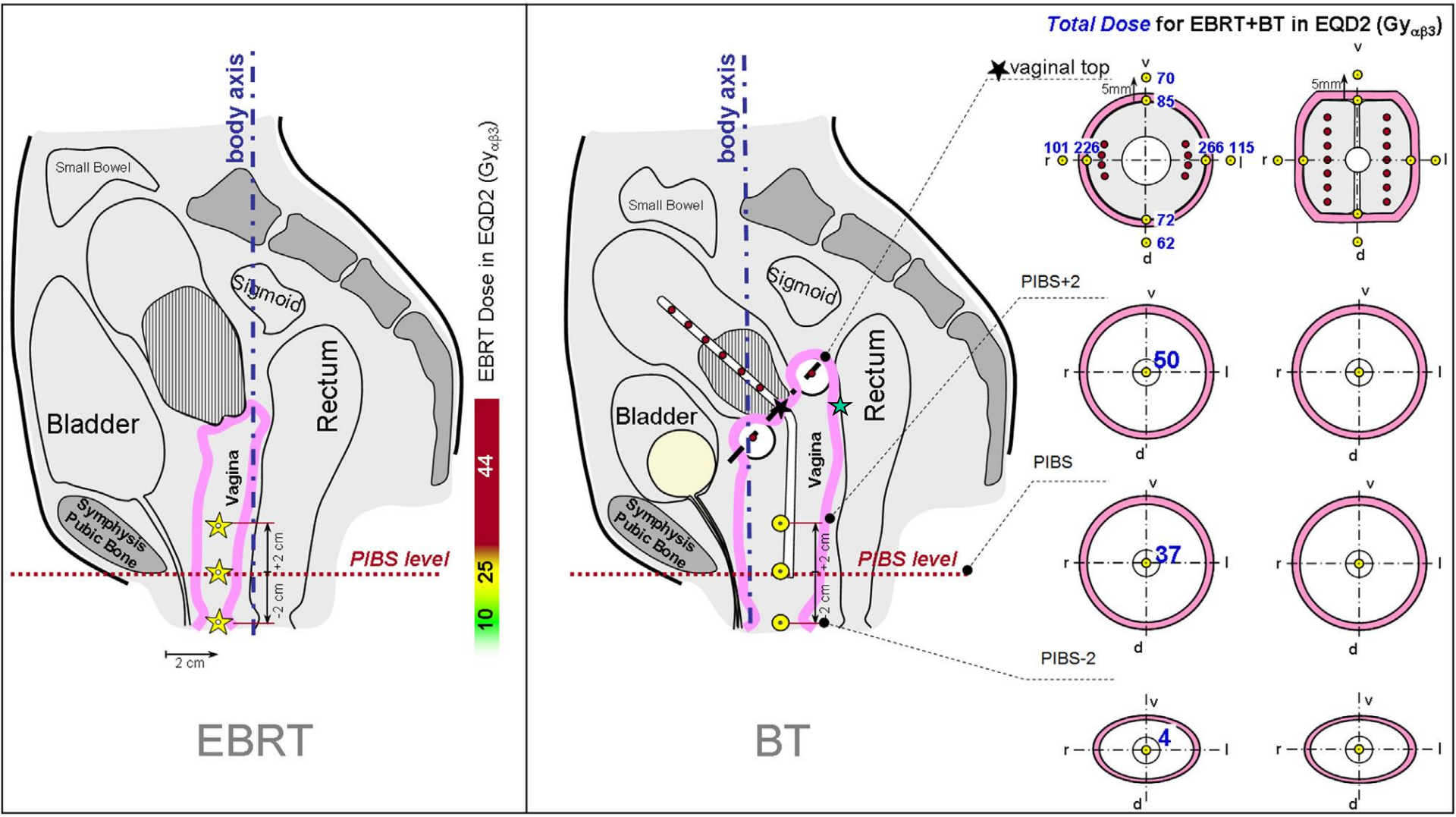
Prevalence vaginal stenosis



Kirchheiner K et al.Manifestation pattern of early-late vaginal morbidity. IJROBP 2014 May 1;89(1):88-95

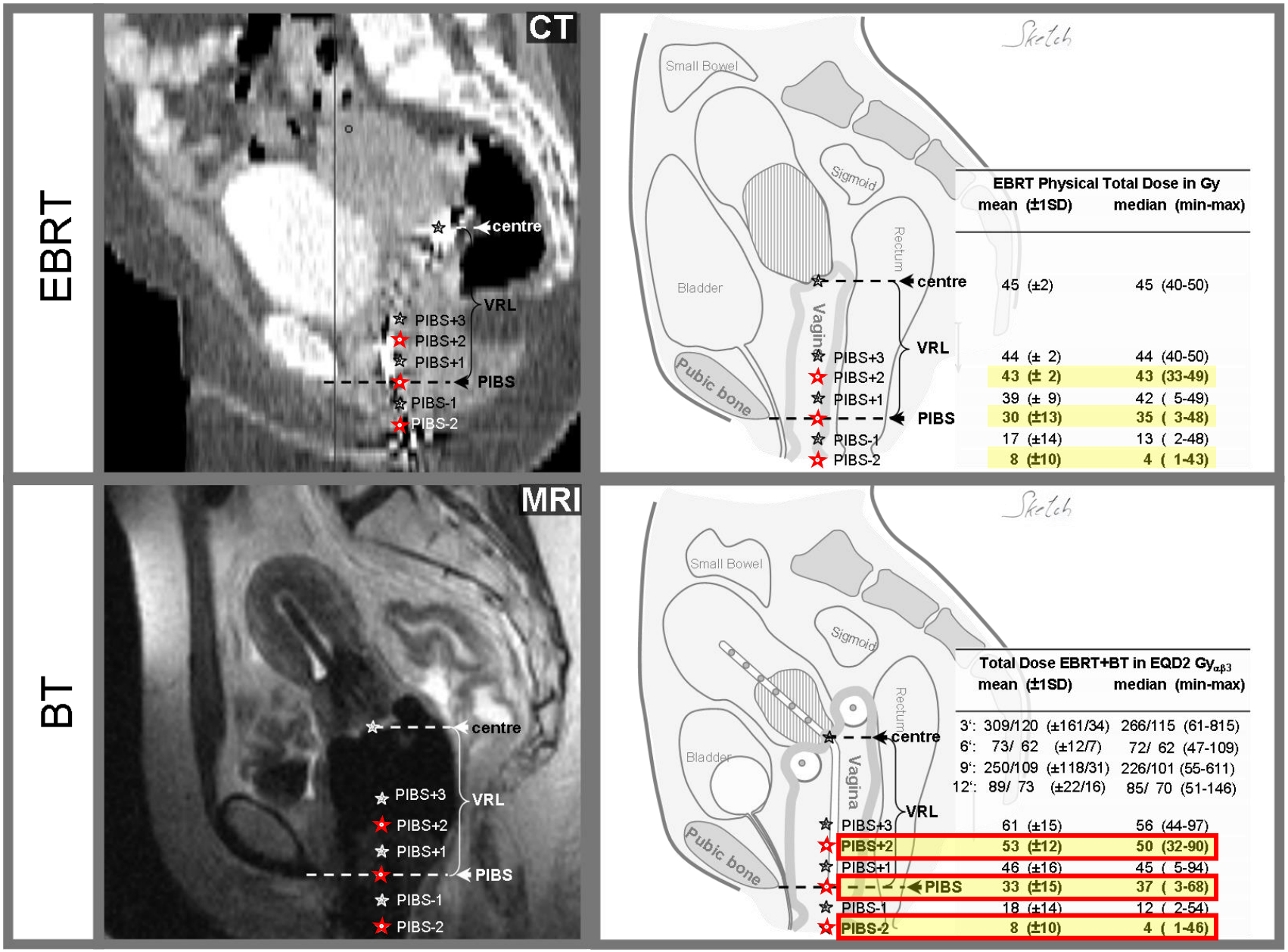
K Kirchheiner et al, EMBRACE data MUW/AUH, RadiothOncol 2016

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)

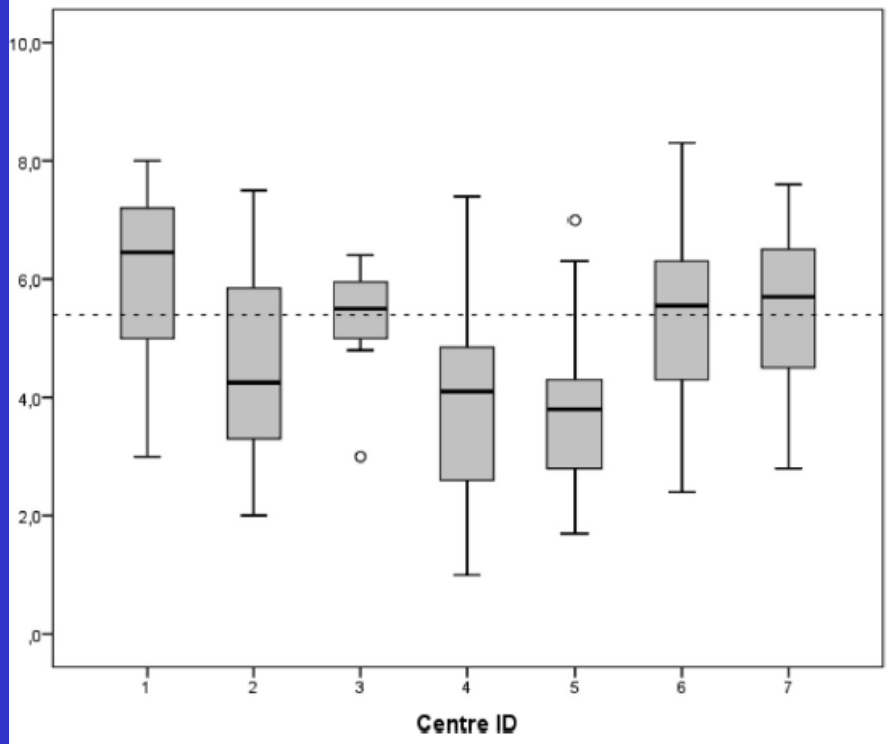


Westerveld et al. Radiotherapy and Oncology 2013

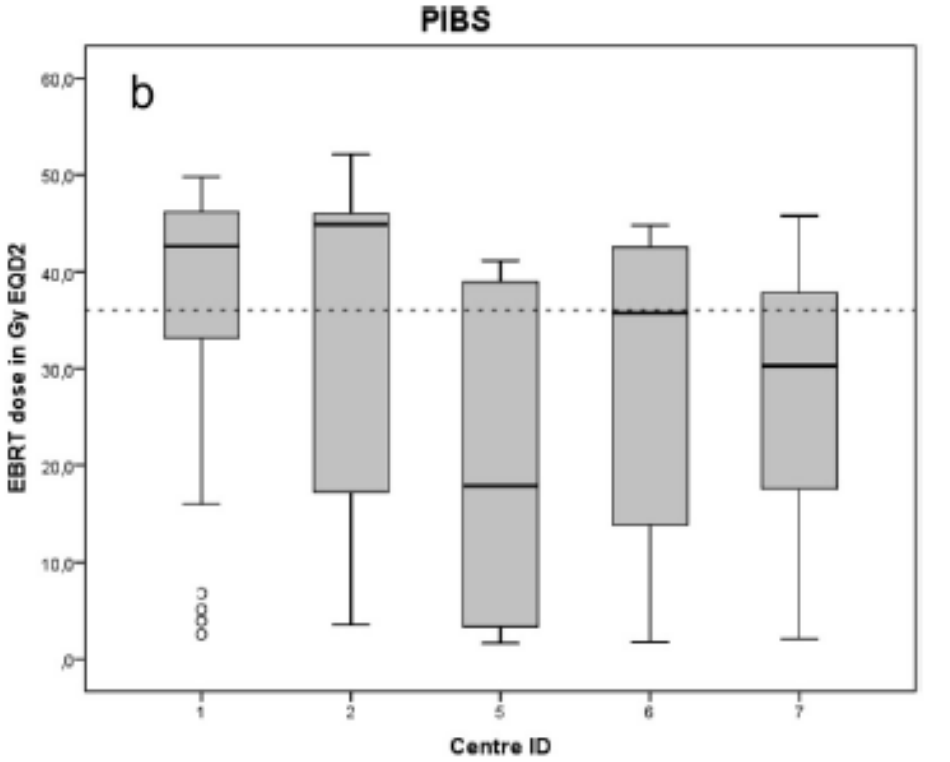
Multicentre evaluation of a novel vaginal dose reporting method in 153 cervical cancer patients

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

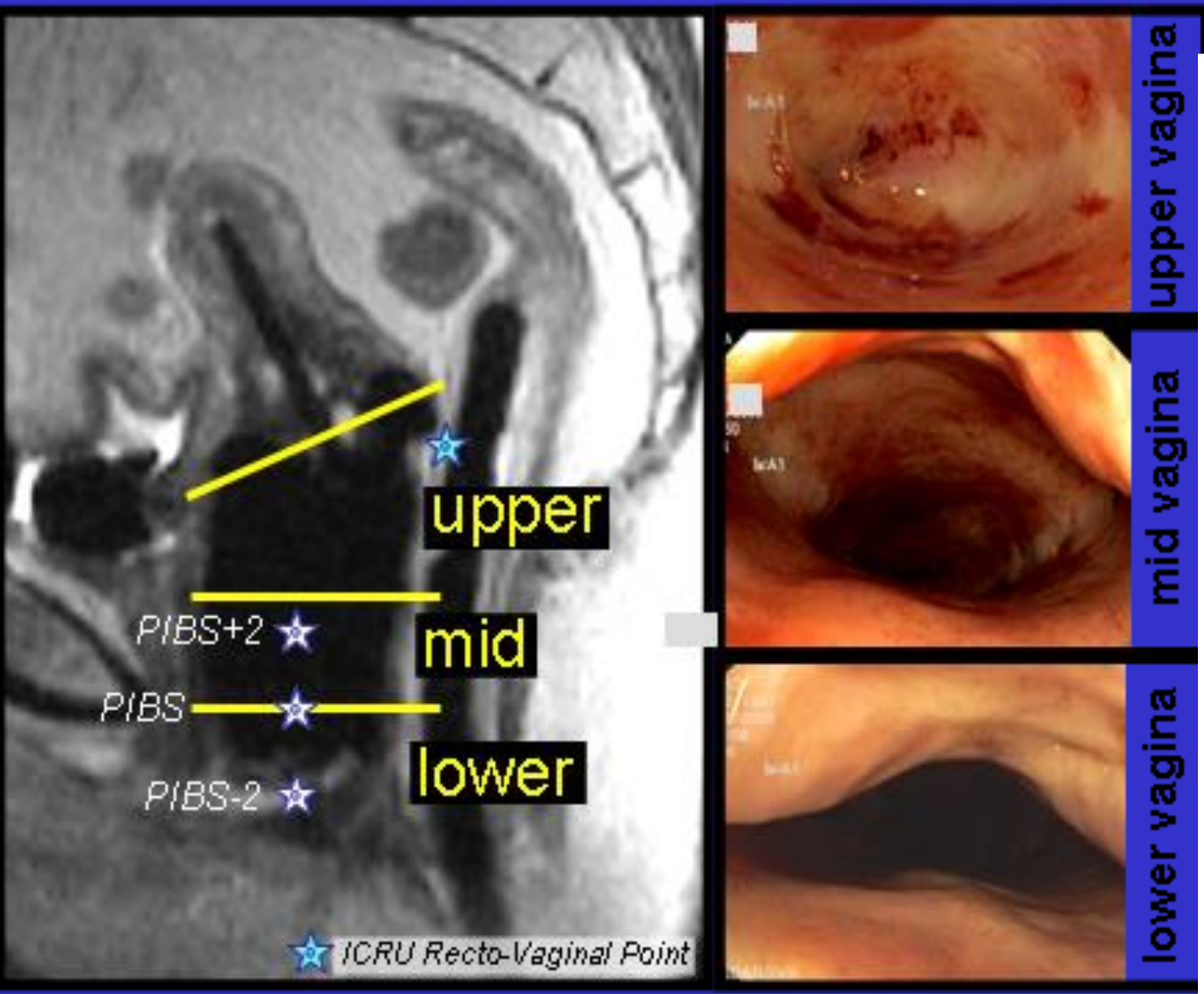
[a] *Department of Radiotherapy, Academic Medical Centre, University of Amsterdam, The Netherlands;* [b] *Department of Radiation Oncology, Comprehensive Cancer Centre, Medical University of Vienna, Austria;* [c] *Department of Radiation Oncology, University Medical Centre Utrecht, The Netherlands;* [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*

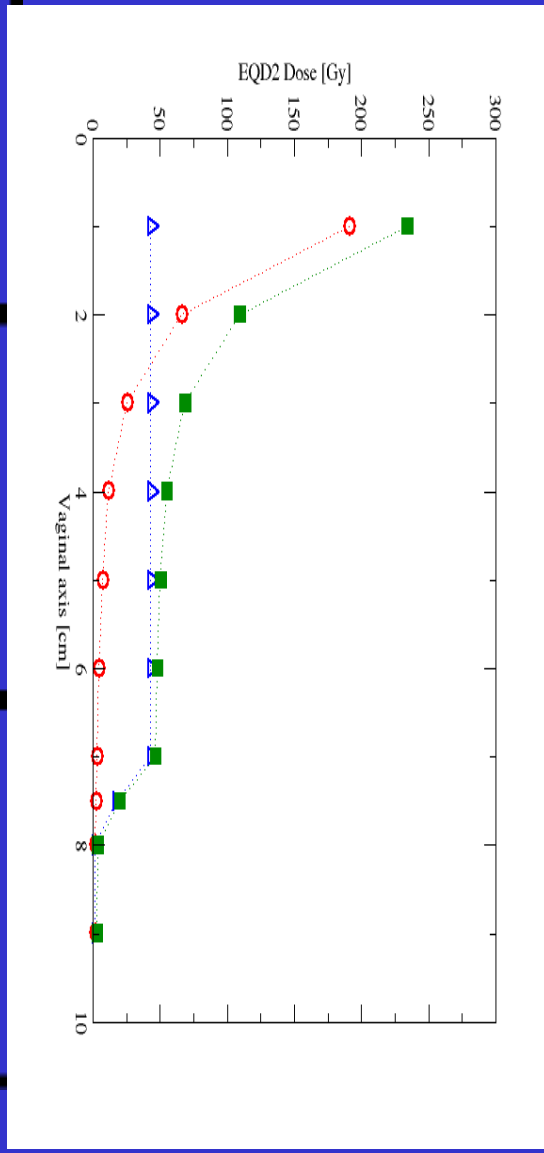


ginal reference length (VRL) in cm per centre. The dotted line represents the median length of the entire cohort.



Vaginal morbidity and radiation doses



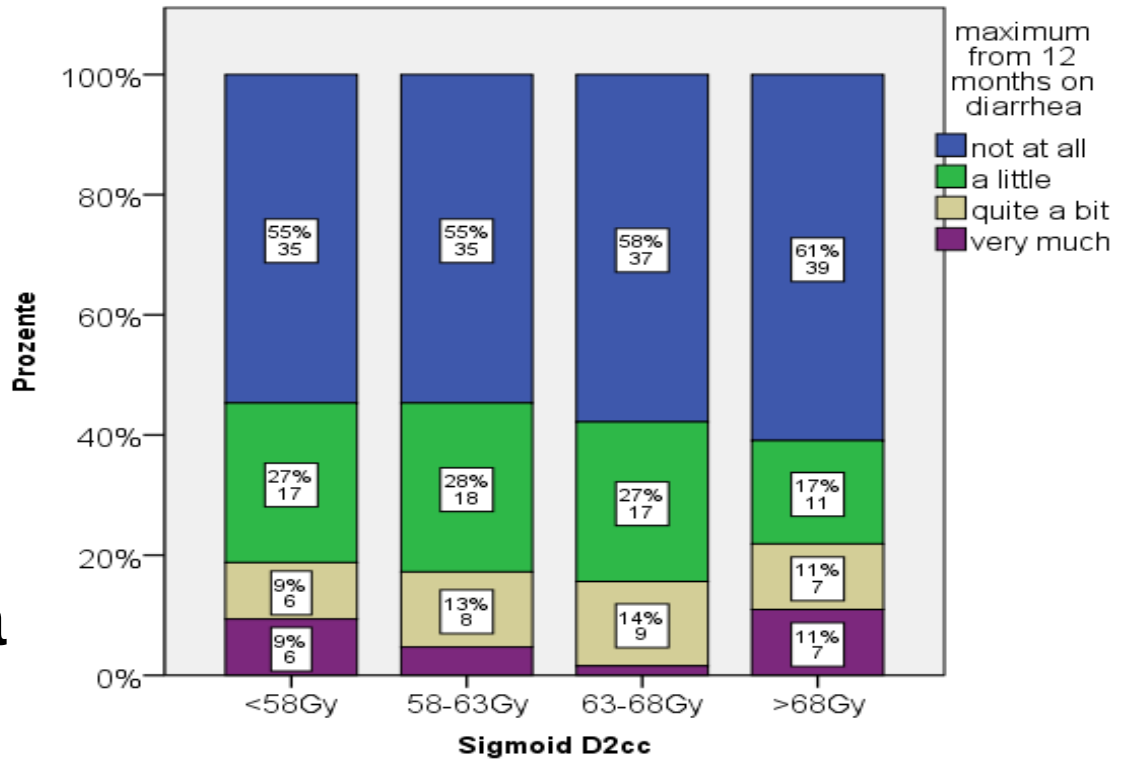


ICRU/GEC ESTRO Report 89 Fig. 6.1/Fig. 8.11

Sigmoid D_{2cm3}, preliminary data (2015)

- **No dose effect established – (so far)**

Diarrhea

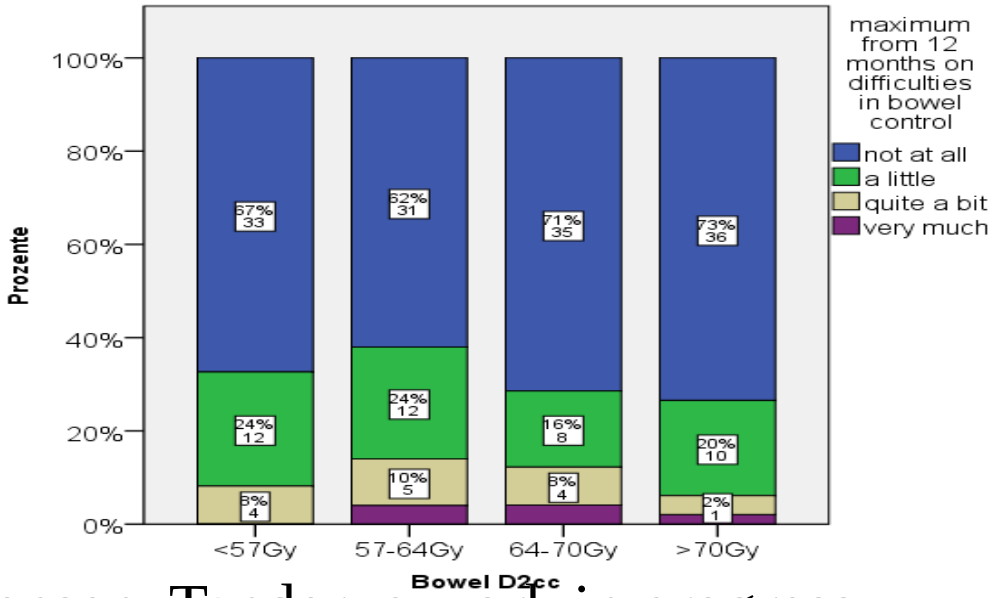


Bowel D_{2cm3}, and EBRT preliminary data

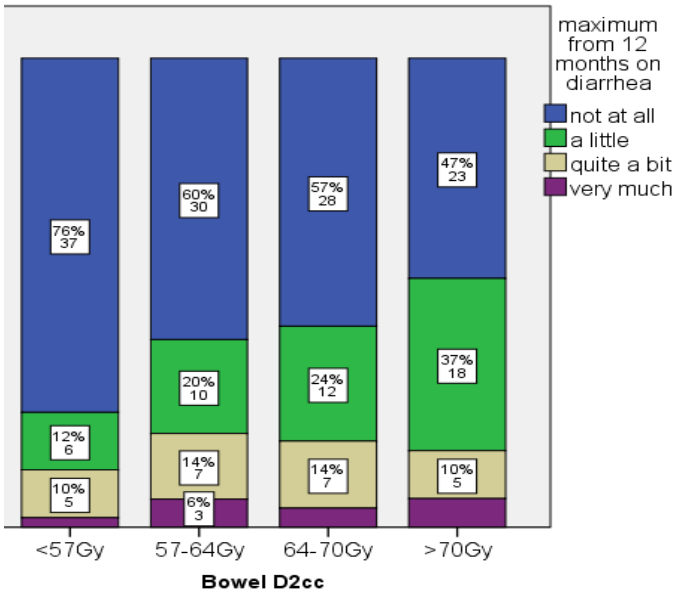
- **dose effect likely to become established for diarrhea**

2 cm^3 (BT) and EBRT: dose (45/50Gy), boost, PA RT

Bowel control



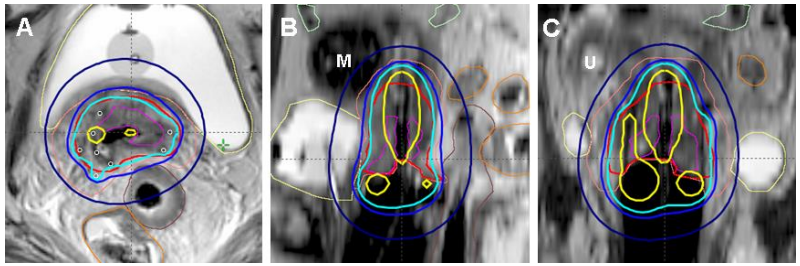
Diarrhea



Jensen, Tanderup work in progress

Planning aim and prescription dose

- **Planning aim: what you want to obtain**
- **Prescribed dose: what you decide to treat**



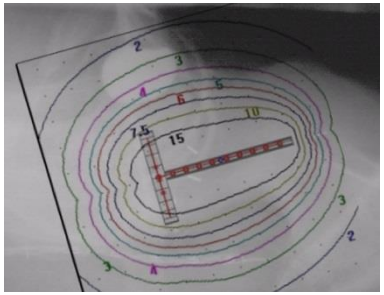
Example 1

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

Planning aim and prescription dose

- **Planning aim: what you want to obtain**
- **Prescribed dose: what you decide to treat**

Example 2



Structure	Dose parameter	Planning aim, Gy	Prescribed dose Gy
Target	Point A	7Gy	6.5Gy
Bladder	ICRU point	≤ 7Gy	6.8 Gy
Rectum	ICRU point	≤ 75% of 7Gy	5.3 Gy

Conclusion dose effect BT (I)

- **Dose effect demonstrated for:**
  - **Residual GTV D100, adaptive CTV_{HR} D90, and CTV_{IR} D90**
  - **Bladder D 2cm^3**
  - **Rectum D 2cm^3**
  - **Vagina (recto-vaginal point)**

- **Upcoming evidence:** **Bowel D 2cm^3 + EBRT dose/volume**
  Vagina PIBS: EBRT + BT

- **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: 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	-	-

What is the proposed planning aim for D90 CTV_{HR} – indicate all correct answers

A. **Planning aim: 90-95Gy**
B. **Hard constraint: >85Gy**
C. **Hard constraint: >90Gy**
D. **Hard constraint: <95Gy**

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*

Which treatment plan would you prefer?

A. **Sigmoid D2cm3=75Gy, Bladder D2cm3=85Gy**

B. **Sigmoid D2cm3=70Gy, Bladder D2cm3=90Gy**

Which treatment plan would you prefer?

A. **HR-CTV D90=95Gy, Bladder D2cm3=90Gy, Rectum D2cm3=75Gy**

B. **HR-CTV D90=90Gy, Bladder D2cm3=85Gy, Rectum D2cm3=70Gy**

C. **I cannot decide without more clinical information**

Parametrial and nodal boost including midline block: combination of EBRT and BT

ESTRO-AROI Teaching Course
Transition from conventional 2D to 3D radiotherapy with a special emphasis on brachytherapy in cervical cancers

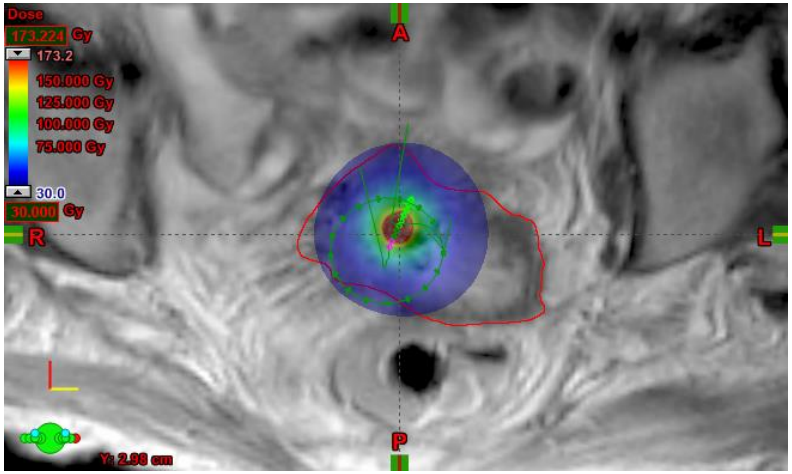
Bengaluru 2017

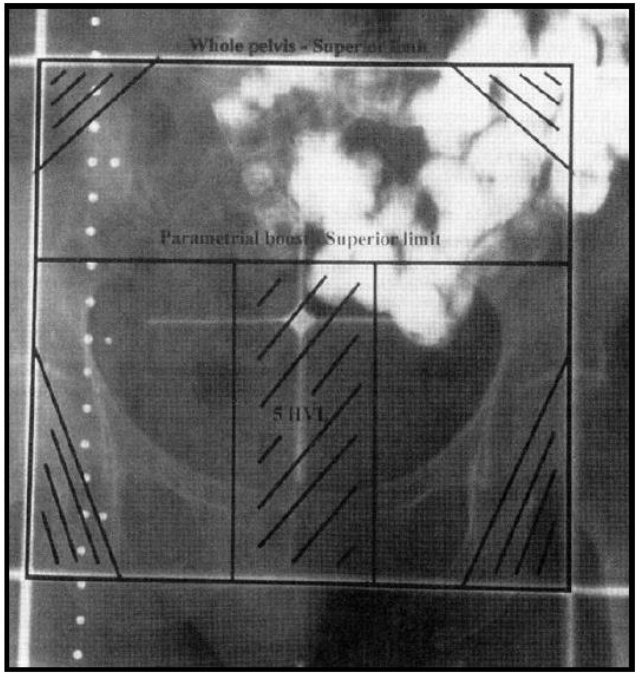
Kari Tanderup
Ina Jürgenliemk-Schulz

Aarhus University Hospital

Indication for parametrial boost

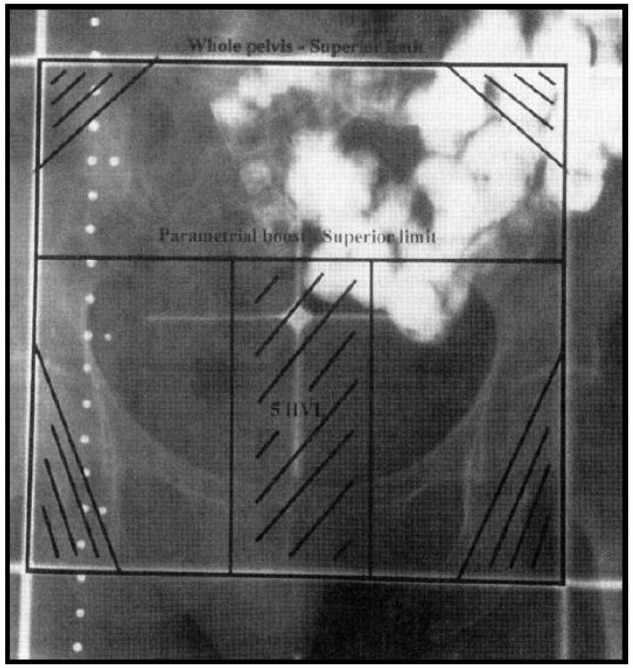
- **Bulky stage IIB and IIIB**
- **Insufficient coverage of BT dose**





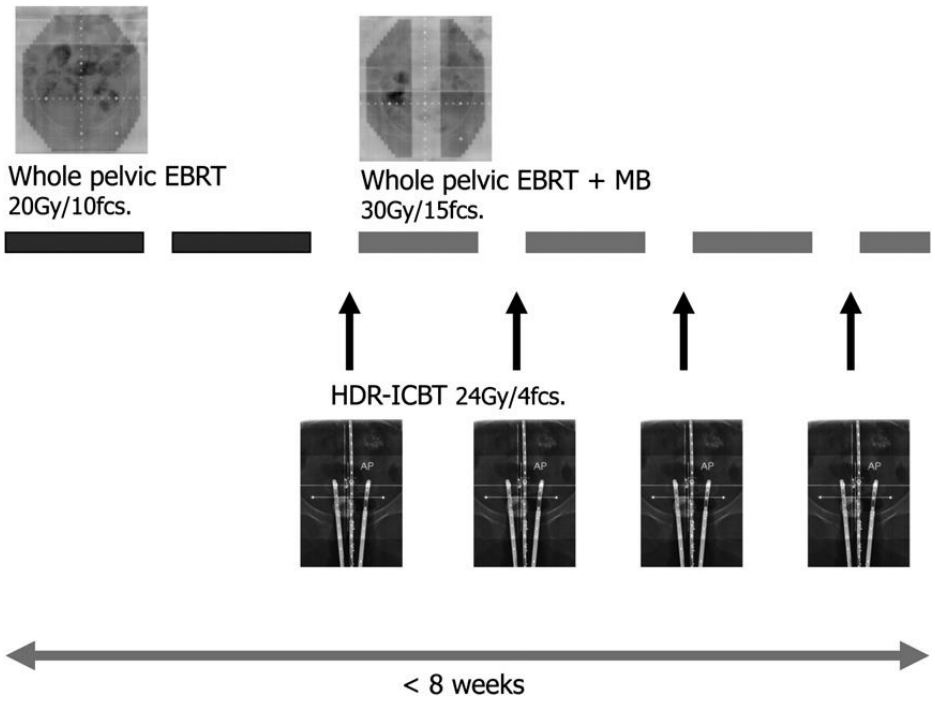
Standard technique

- Delivered after 45-50Gy EBRT
- Midline block of 4cm
- Upper border: bottom of sacroiliac joints
- 3-5 fractions of 1.8Gy
- GOG standard:
  - 5.4Gy in stage IIB
  - 9Gy in stage IIIB



Midline block

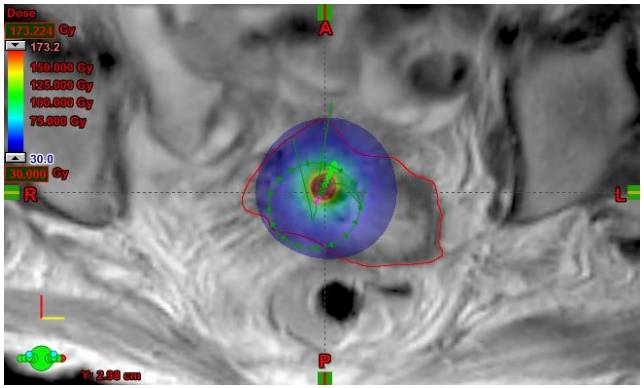
- EBRT whole pelvis to 20-30Gy
- Application of midline block
- Higher amount of BT applied
  - e.g. 6.5Gy in 6 fractions
- BT is started early during EBRT
  - e.g. week 1 or 2
- Widely used in Japan
  - 70% of patients in Japan, Patterns of care 1999-2001, Toita et al IJROBP 70(3) 2008



Toita et al, IJROBP, Vol. 82, No. 1, 49–56, 2012

Challenge: Midline block dose calculation

- **Which dose does midline block fields deliver to HR-CTV and IR-CTV (D90 and D100)?**
- **Does midline blocked fields deliver dose to bladder, rectum and sigmoid (D2cc)?**
- **Challenge for dose calculation:**
  - **BT and EBRT physical doses cannot be directly added and transformed to EQD2 dose**
  - **Anatomy changes between EBRT and BT**



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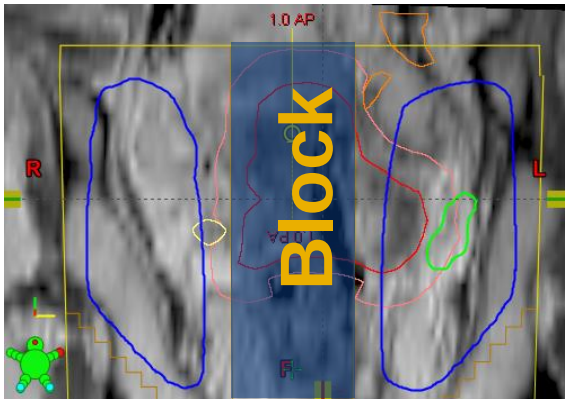
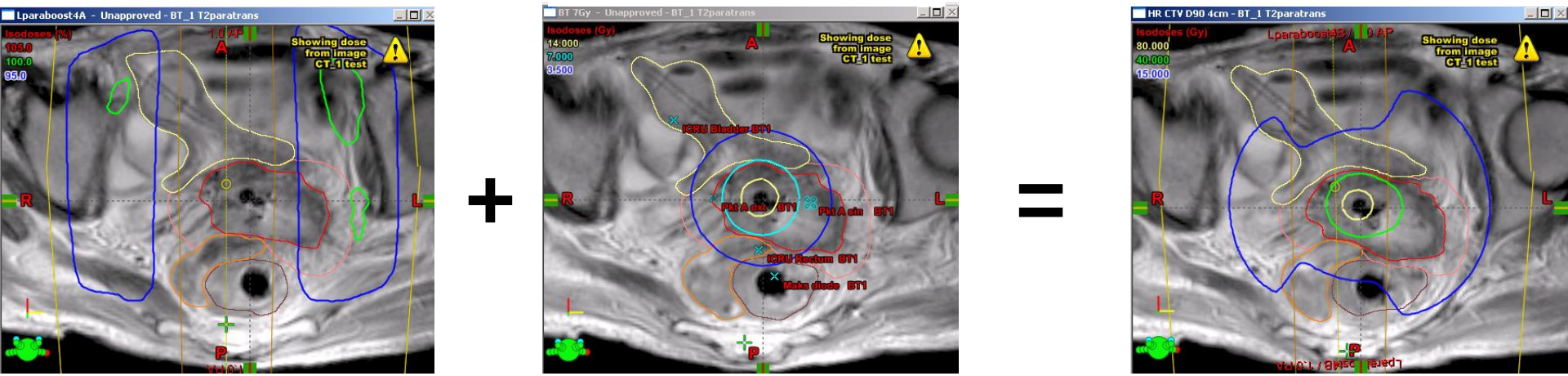


= ?

Accumulation of dose

- 6 patients with large tumours and/or unfavourable topography were analysed
- HR-CTV volumes of 31-100 ccm
- Radiotherapy schedule:
  - 45 Gy (25fx) whole pelvis EBRT
  - 9 Gy (5fx) midline block boost
  - 4x7 Gy HDR intracavitary BT

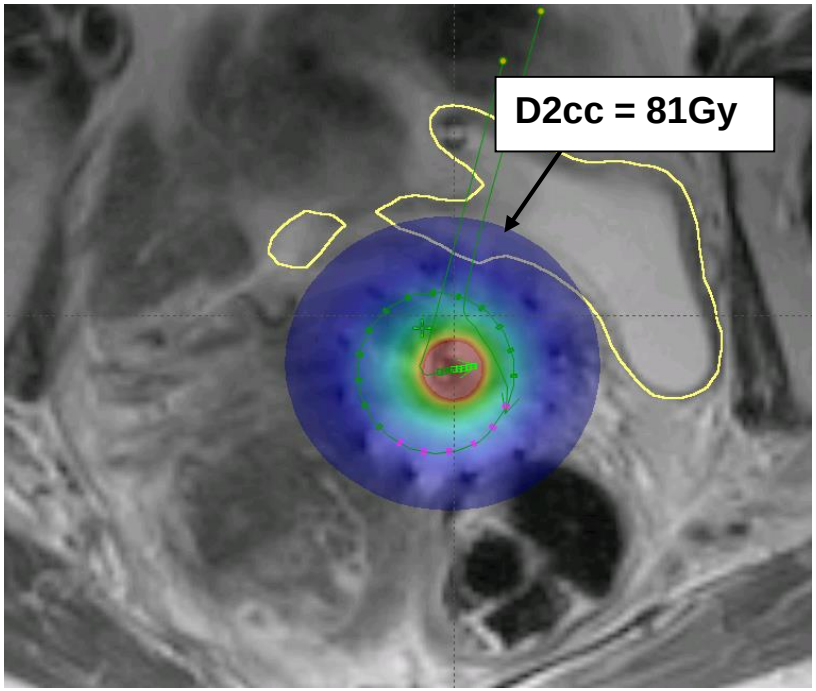
Midline block + *Intracavitary BT* = *Midline block + BT*



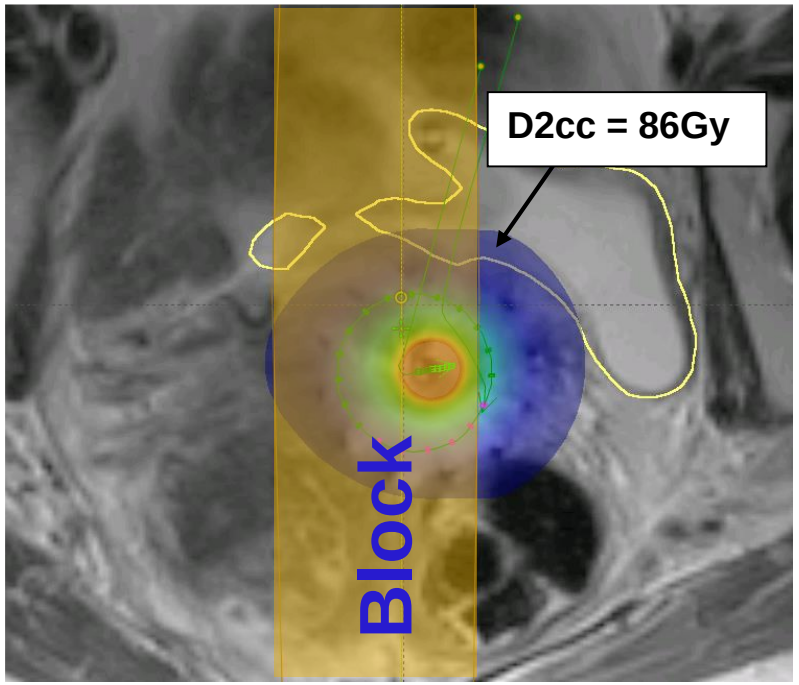
L. Fenkell et al, IJROBP 2011

Example, dose to OAR

BT



BT + midline boost



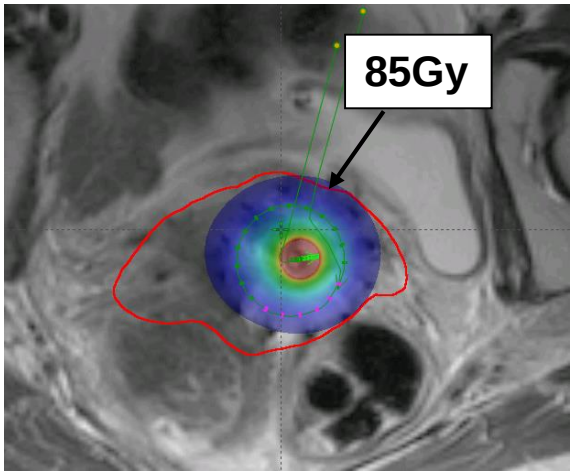
L. Fenkell et al, IJROBP 2011

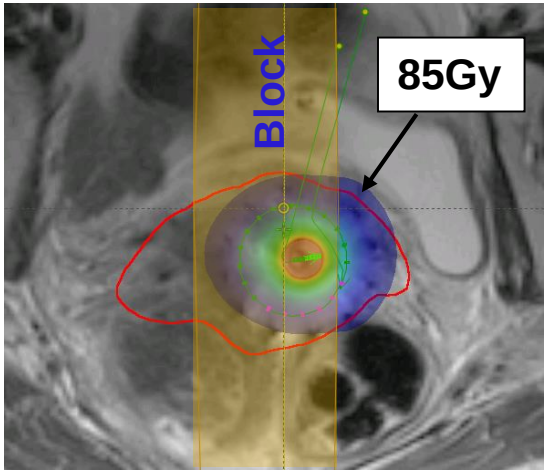
Example, dose to HR and IR CTV

BT

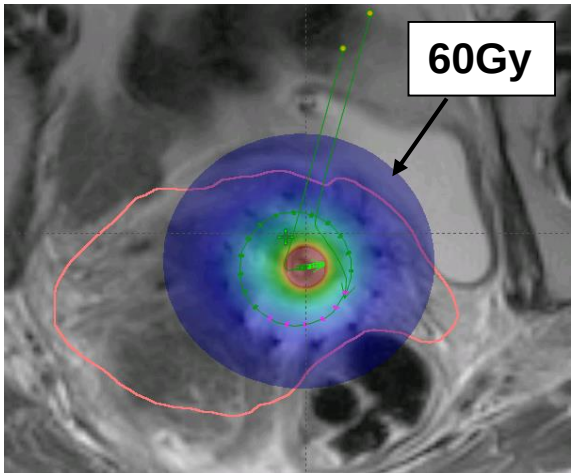
BT + midline boost

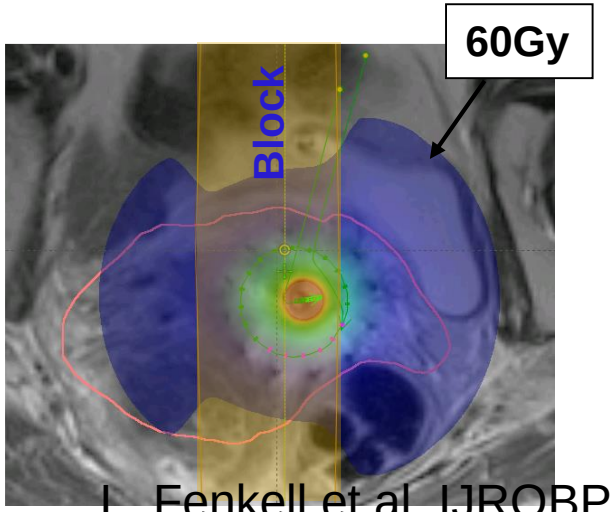
HR CTV





IR CTV



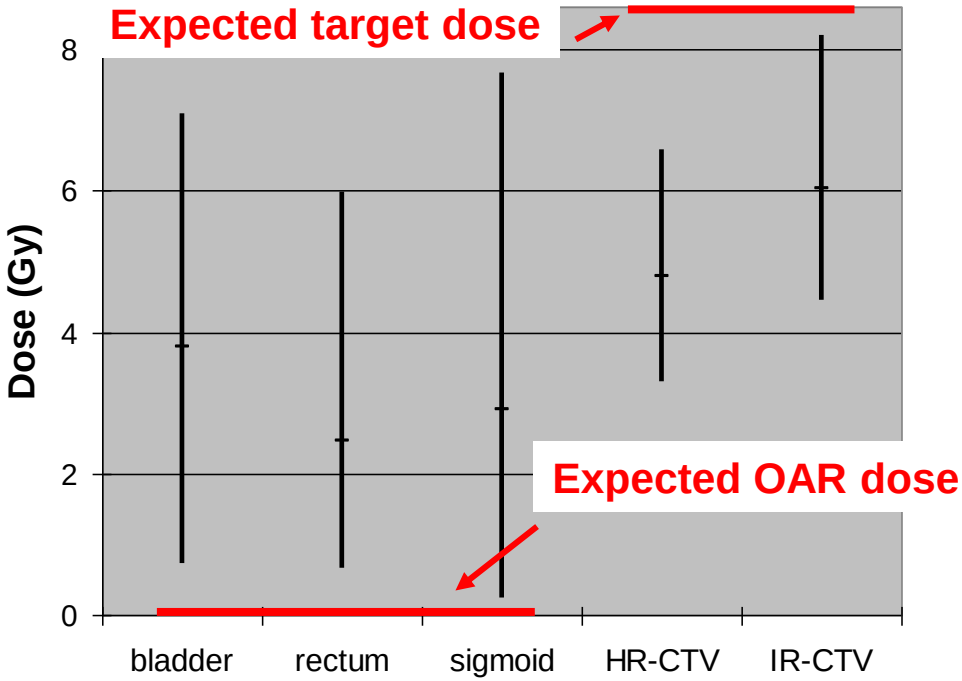


L. Fenkell et al, IJROBP 2011

Addition of BT dose and EBRT parametrial boost dose

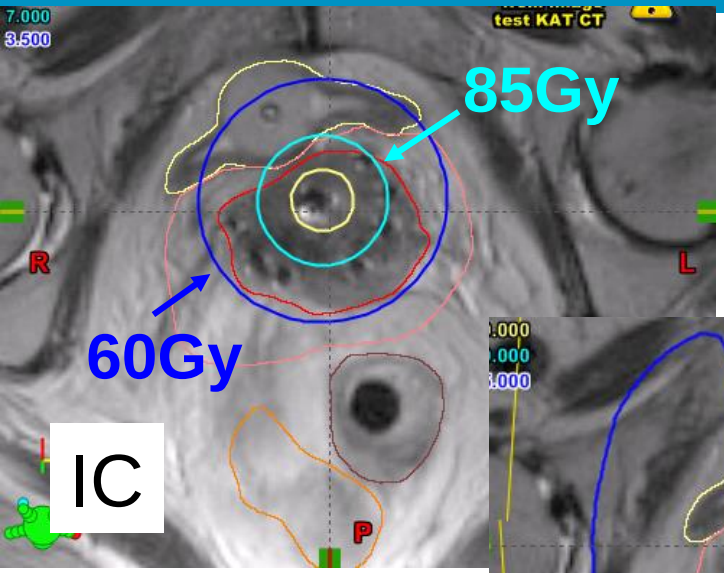
Significant uncertainties for addition of BT and parametrial boost!!

- 9 Gy parametrial boost
- Target dose << 9Gy
- Significant OAR dose

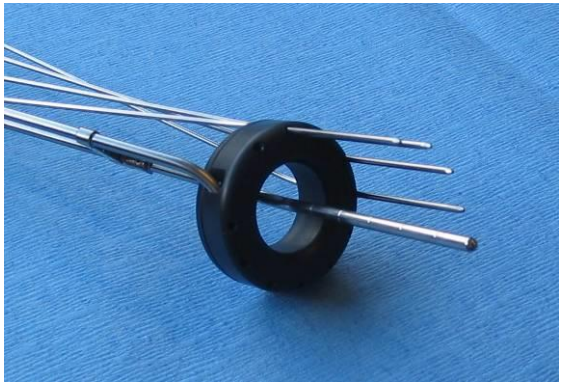


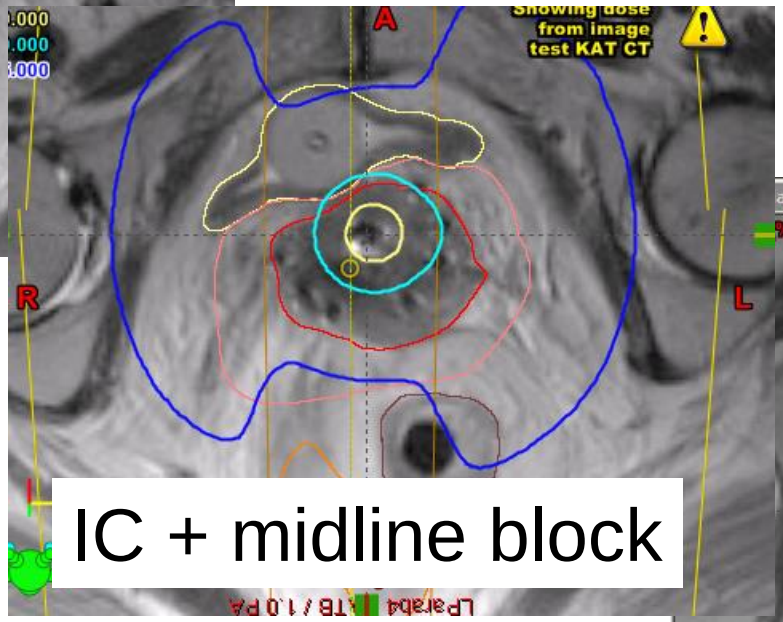
L. Fenkell et al, IJROBP 2011

Midline block boost compared to interstitial needles



IC





IC + midline block

IC + IS

Comparison between IC+BT and IC/IS

A number of 23 patients (stage II, III, IV)
with parametrial involvement at time of BT

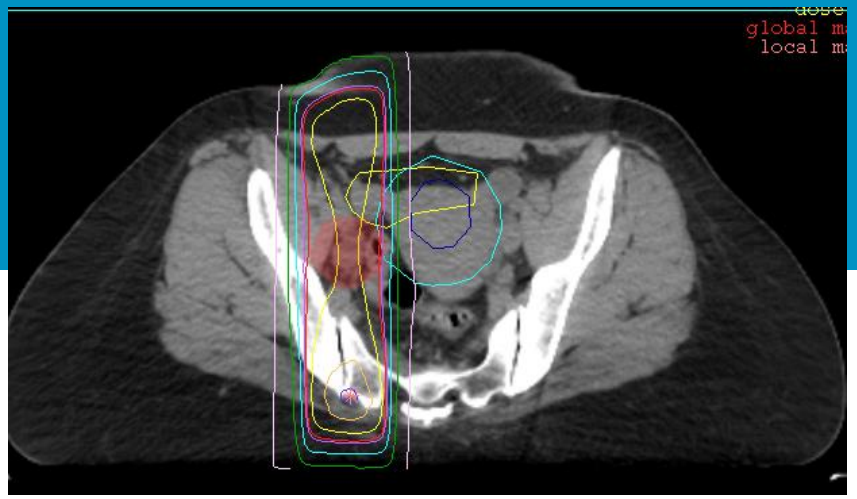
EQD2 (Gy)	IC+PB Mean (SD)	IC/IS Mean (SD)	Diff IC+PB - IC/IS	p value
GTV D90	110.7 (15.7)	106.5 (10.5)	4.0 (11.2)	0.10
HR CTV D90	88.7 (5.3)	89.0 (3.4)	-0.3 (4.8)	0.79
D_{2cm3} Bladder	77.2 (5.9)	71.8 (5.0)	5.4 (4.0)	<0.001
D_{2cm3} Rectum	68.1 (6.3)	64.1 (4.8)	4.4 (2.7)	<0.001
D_{2cm3} Sigmoid	67.5 (5.5)	62.6 (5.2)	5.0 (2.9)	<0.001
D_{2cm3} Bowel	68.3 (6.9)	62.1 (6.7)	6.2 (3.5)	<0.001

Mohamed et al, Brachytherapy 2014

Techniques for boosting of pathologic lymph nodes

- **Techniques:**
  - **Post boost with CRT**
  - **Simultaneous integrated boost with IMRT**

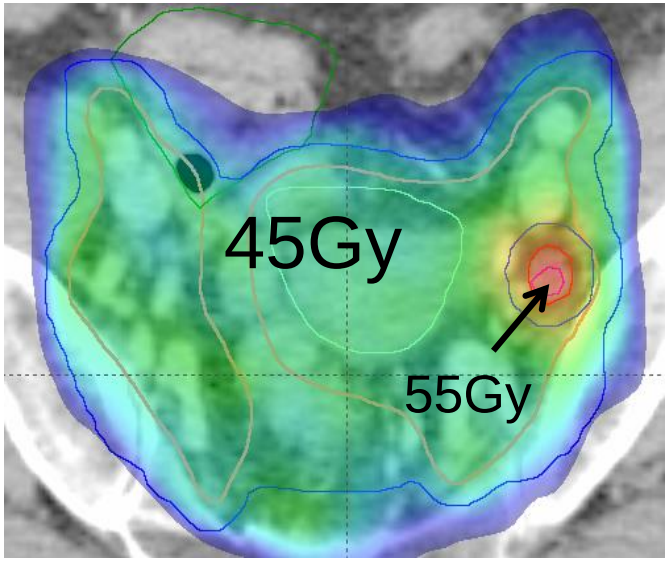
Post-boost with CRT



- AP-PA or 4 Field Box
- Avoid central pelvis irradiation
- Assessment of BT contribution (~0-6Gy)
- CTV according to residual GTV (taking shrinkage into account)
- Examples of dose and fractionation:
  - Aim for total EBRT+BT dose of 55-60Gy
  - E.g. 50Gy whole pelvis + 5Gy
  - E.g. 45Gy whole pelvis + 10Gy

Simultaneously integrated lymph node boost (SIB)

- **Simultaneously integrated lymph node boost:**
  - **IMRT**
  - **Dose planning with two dose levels**
    - **Elective target**
    - **Pathological lymph node target**
- **Recommended lymph node dose in EMBRACE II:**
  - **45Gy/25fx to elective CTV**
  - **55Gy/25fx (within pelvis)**
  - **57.5Gy/25fx (outside pelvis)**

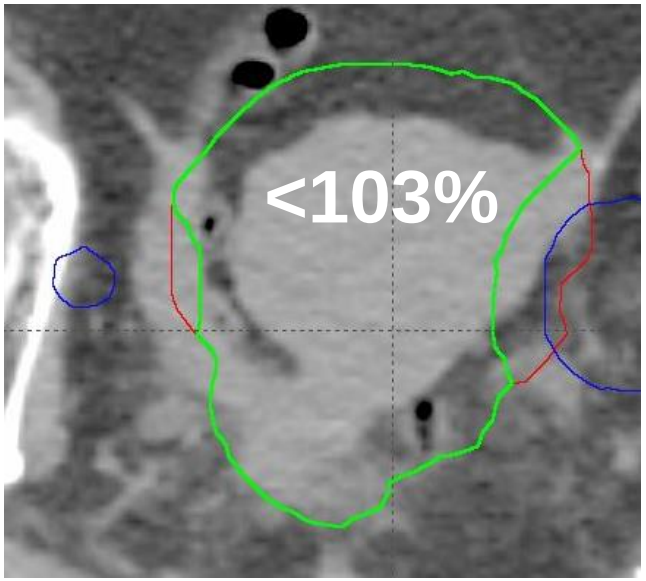


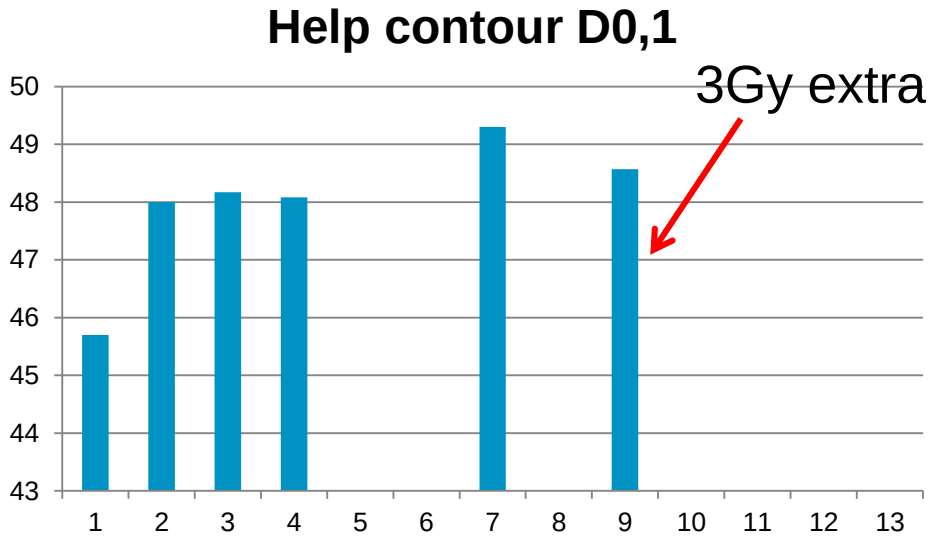
Advantages and disadvantages of SIB boost

- **Advantages:**
  - **Limits overall treatment time of nodal target (hypo-fractionation of small volumes)**
  - **Limits irradiation of normal tissue as compared to AP-PA post boost**
  - **Is robust to inter-fraction motion**
- **Disadvantages:**
  - **In case of large lymph nodes, the boost volume becomes higher – can be modified through replanning after e.g. 20-25Gy**

Help contour in the region of the primary tumour where BT is delivered

- **Homogeneity is particularly relevant when boosting lymph nodes**
- **Control of dose in the BT region**
- **Help contour:**
  - **Margin of 1cm to initial GTV or CTV_{HR}**
  - **Strict constraint on max dose: 103%**



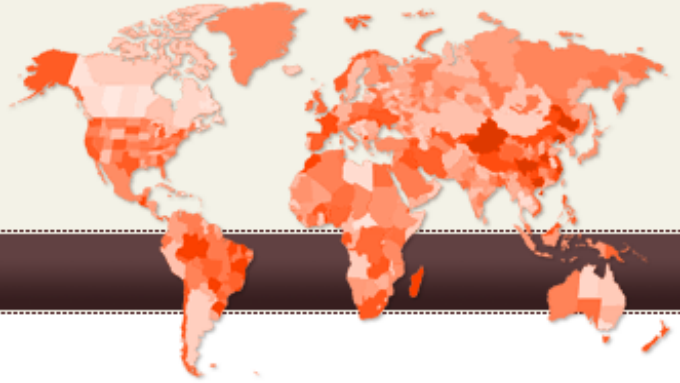


Conclusion

- **Combination of parametrial boost and BT:**
  - **High EBRT and BT gradients in the same region**
  - **Difficult to predict target dose**
  - **Difficult to predict OAR dose**
  - **Large normal tissue volume irradiated to a significant dose**
- **Combination of interstitial BT and intracavitary BT:**
  - **Higher target dose (compared with para-boost)**
  - **Reduced OAR dose (compared with para-boost)**
  - **Better conformality with HR-CTV and IR-CTV**
- **Simultaneous integrated boost**
  - **Limits overall treatment time**

EMBRACE

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



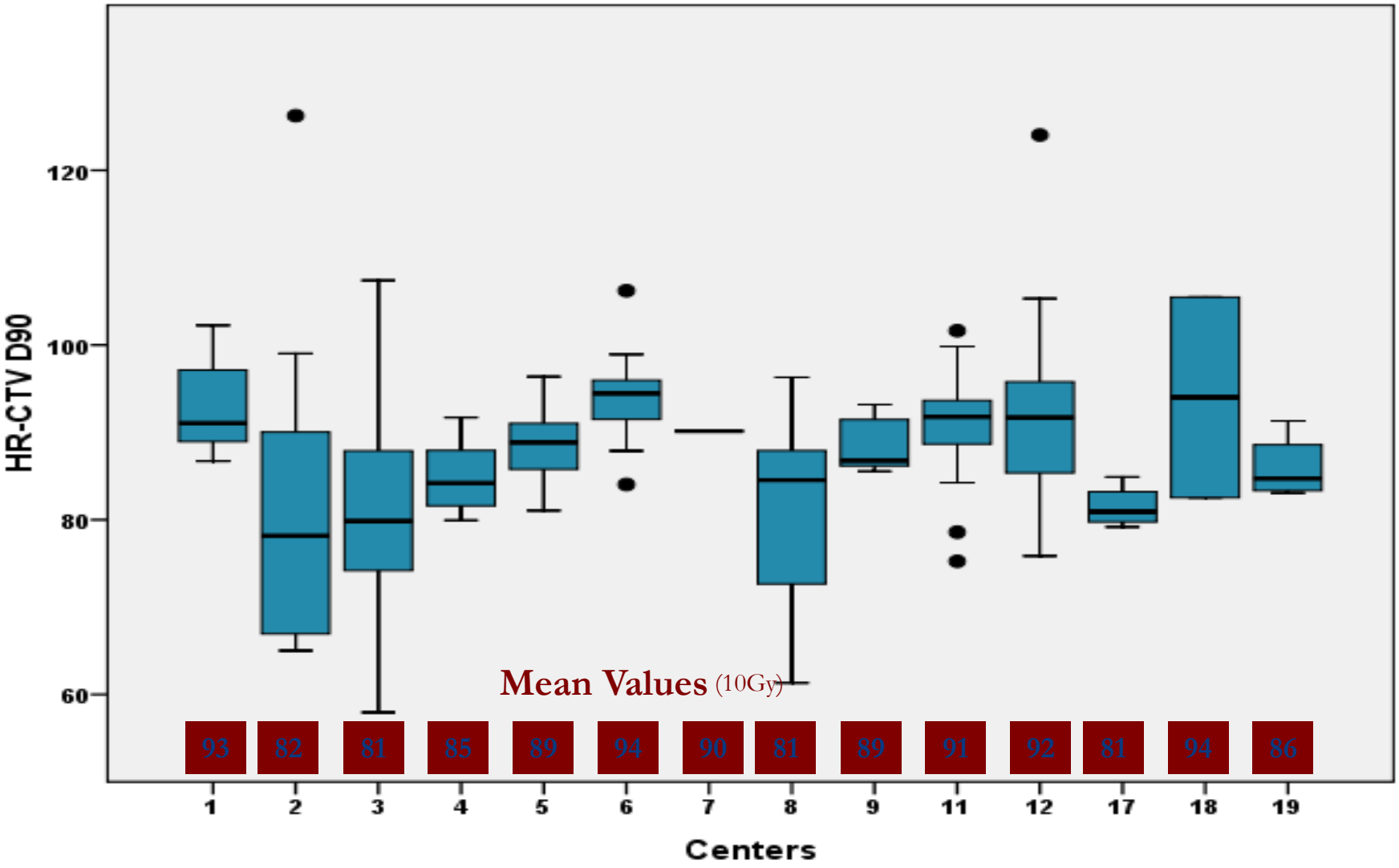
About Embrace | Contacts | Participation | Login

- **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

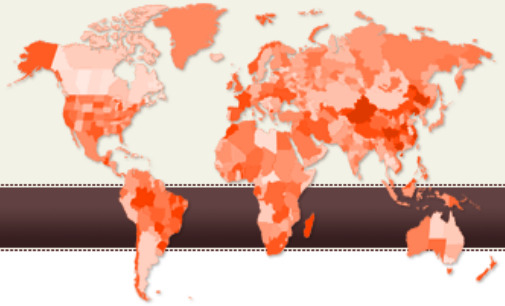
Nucletron Improving patient care

Heterogeneity of dose prescription: HRCTV D90



RETRO EMBRACE

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



About Retro-Embrace | Contacts | Login

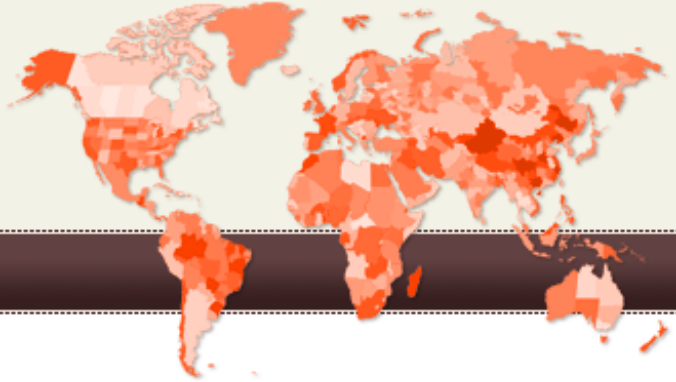
- **Web-based database with a retrospective multicentre collection of data on 3D RT plus IGABT in cervical cancer**
- **780 pts**
- **Eligibility criteria:**
  - **Diagnosis of cervical cancer and treatment with curative intent by IGABT**
  - **Reporting according to GEC ESTRO recommendations**

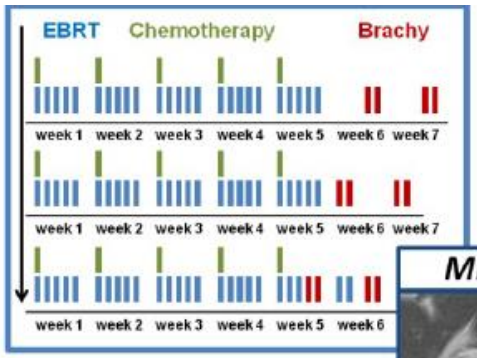
VARIAN medical systems | A partner for life

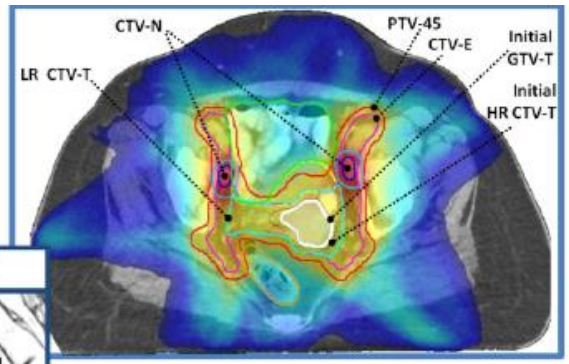
Nucletron Improving patient care

EMBRACE II

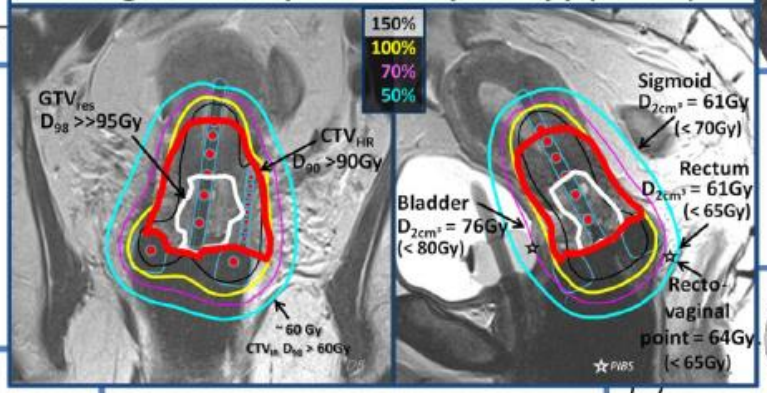
An intErnational study
on MRI-guided BRachytherapy
in locally Advanced CErvical cancer

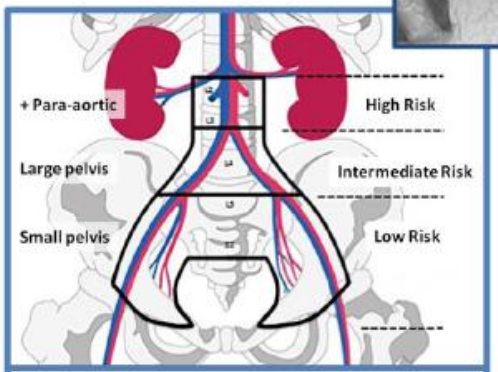




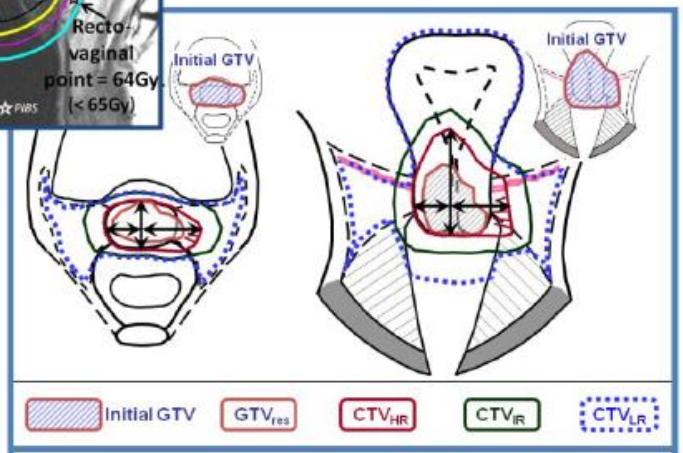


MRI guided adaptive brachytherapy (IGABT)





Nodal CTV-E based on Risk Group



Residual GTV-T, Adaptive HR CTV-T, IR CTV-T

EMBRACE II design

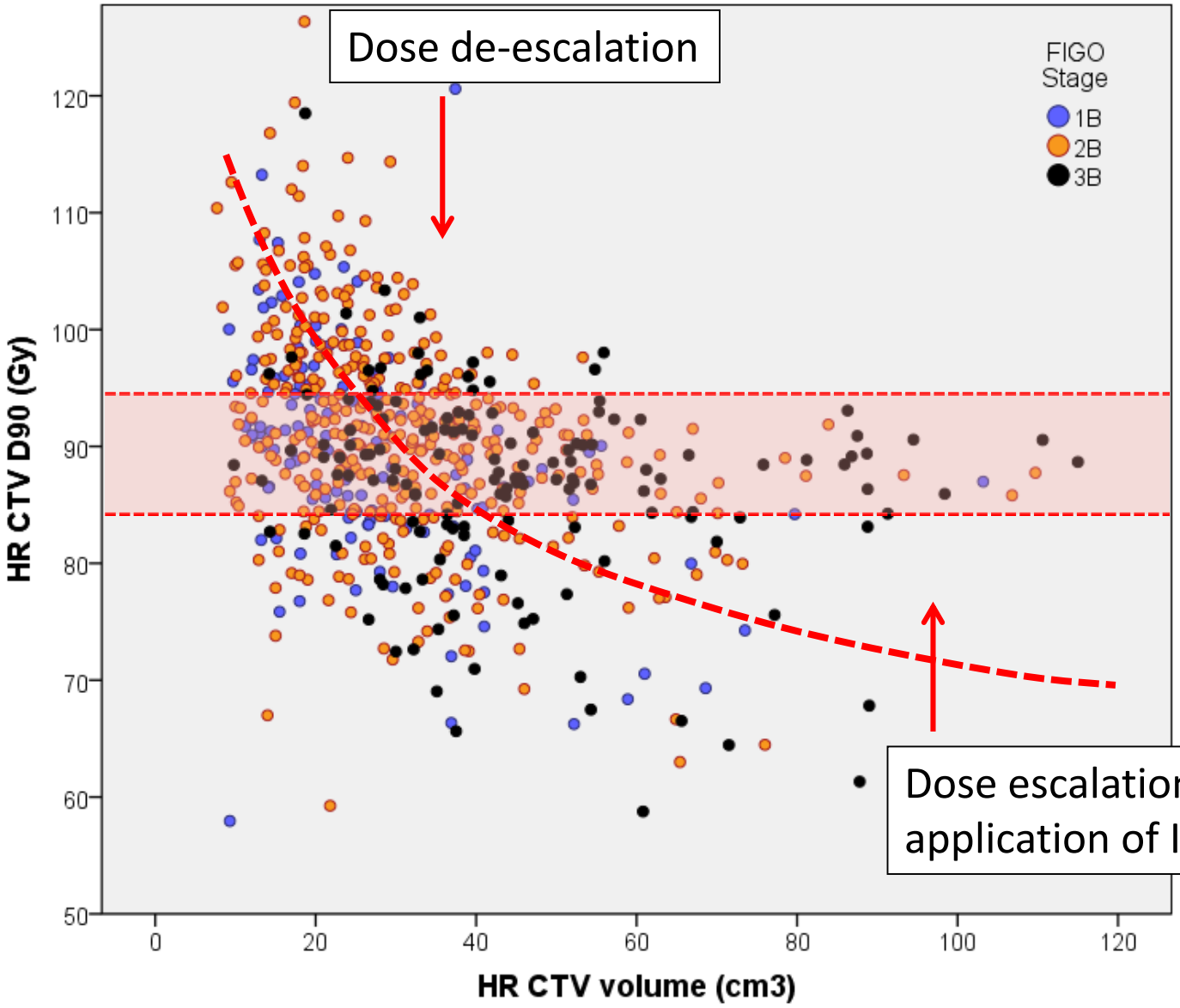
- **Prospective interventional and observational study**
- **Multiple endpoints**
- **Multicenter: >25 centers**
  - **25 current EMBRACE centers and >10 new centers**
- **1000 patients in 4 years and follow up for 5 years**

- **Substudies on**
  - **Adaptive EBRT**
  - **Vaginal morbidity**
  - **Functional imaging**
  - **Translational research**

EMBRACE II interventions

- **Increased use of IC/IS technique in BT:**
  - **HR CTV >30cm3: utilisation of IC/IS of >70% in 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 dose prescription



769 pts EMBRACE

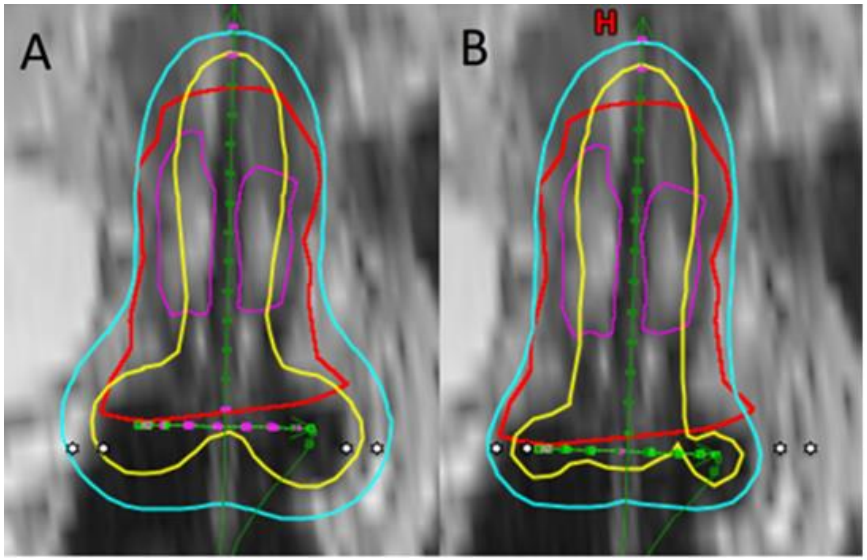
HR CTV D90 85-95Gy

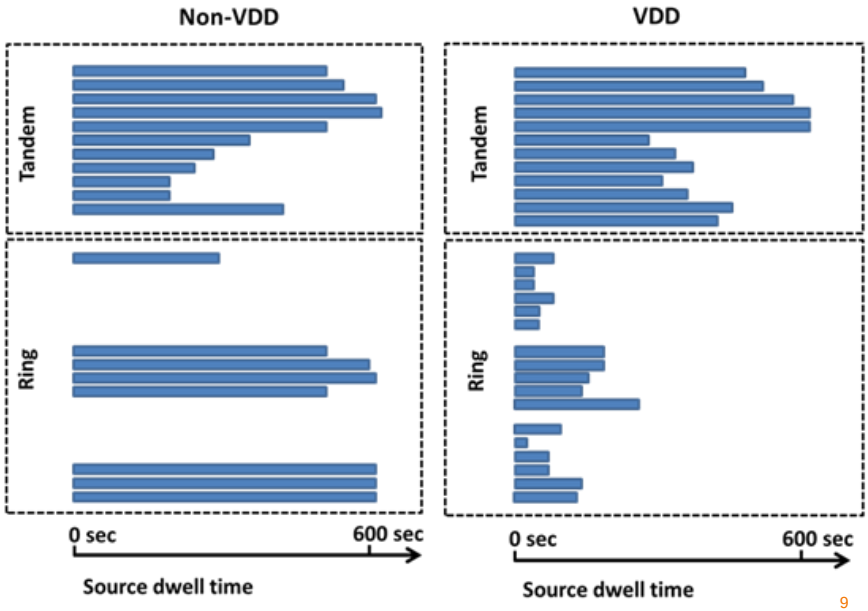
EMBRACE II interventions

- **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**

Vaginal dose de-escalation

	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



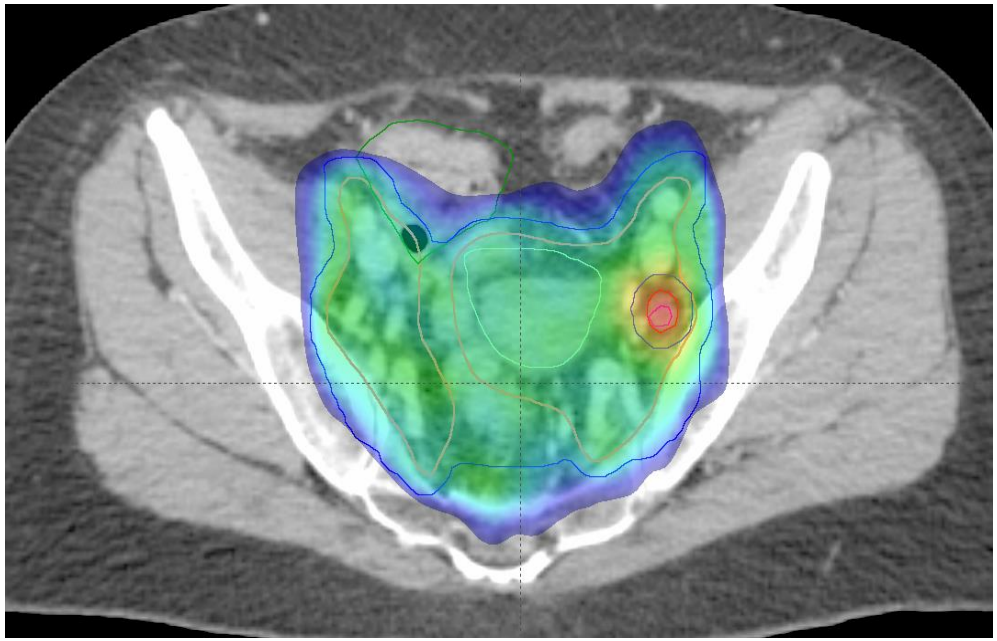


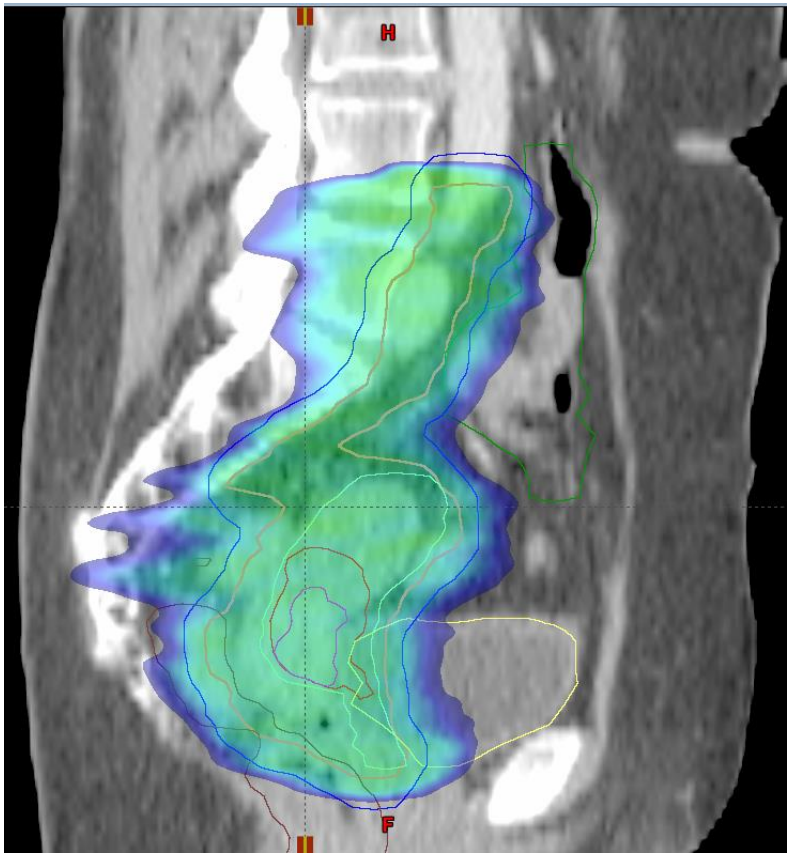
EMBRACE II interventions

- **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**

IMRT + daily IGRT

- 5mm PTV margin
- SIB LN boosting



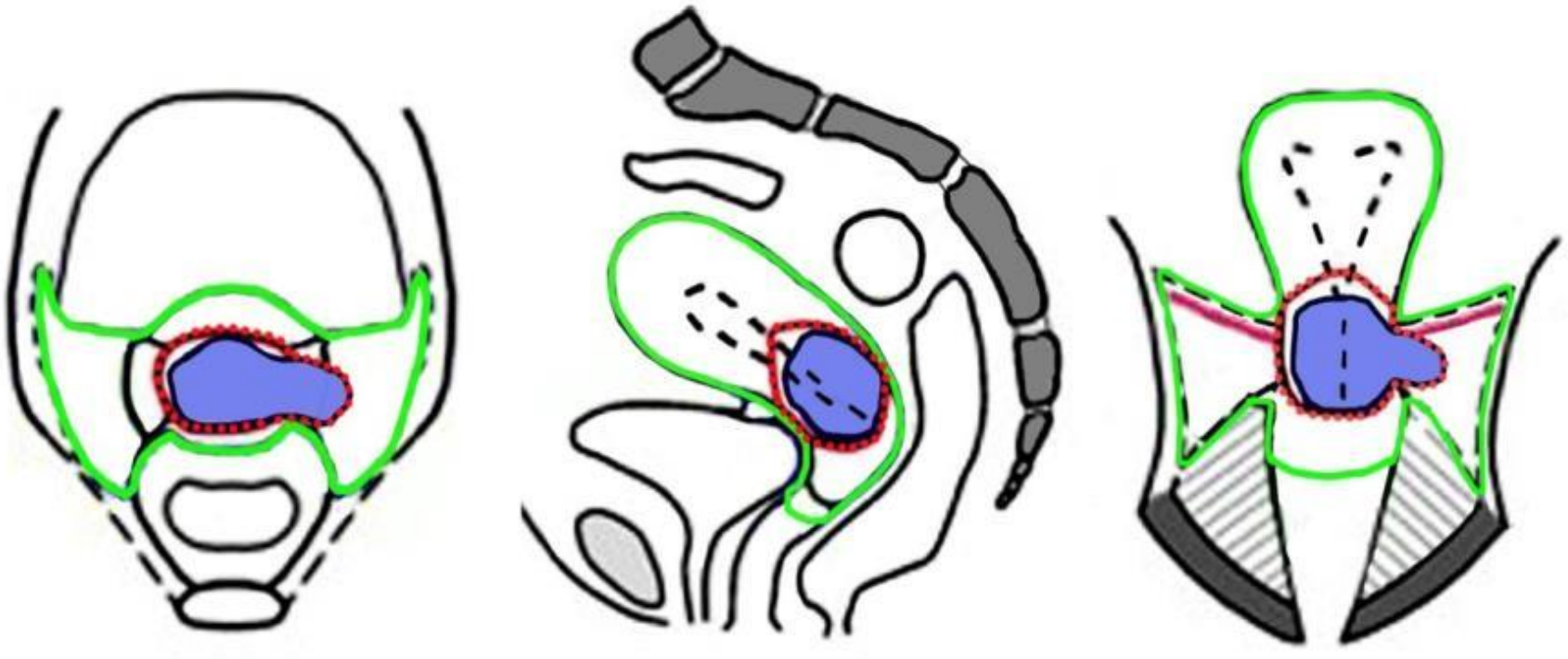


EMBRACE II interventions

- **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**

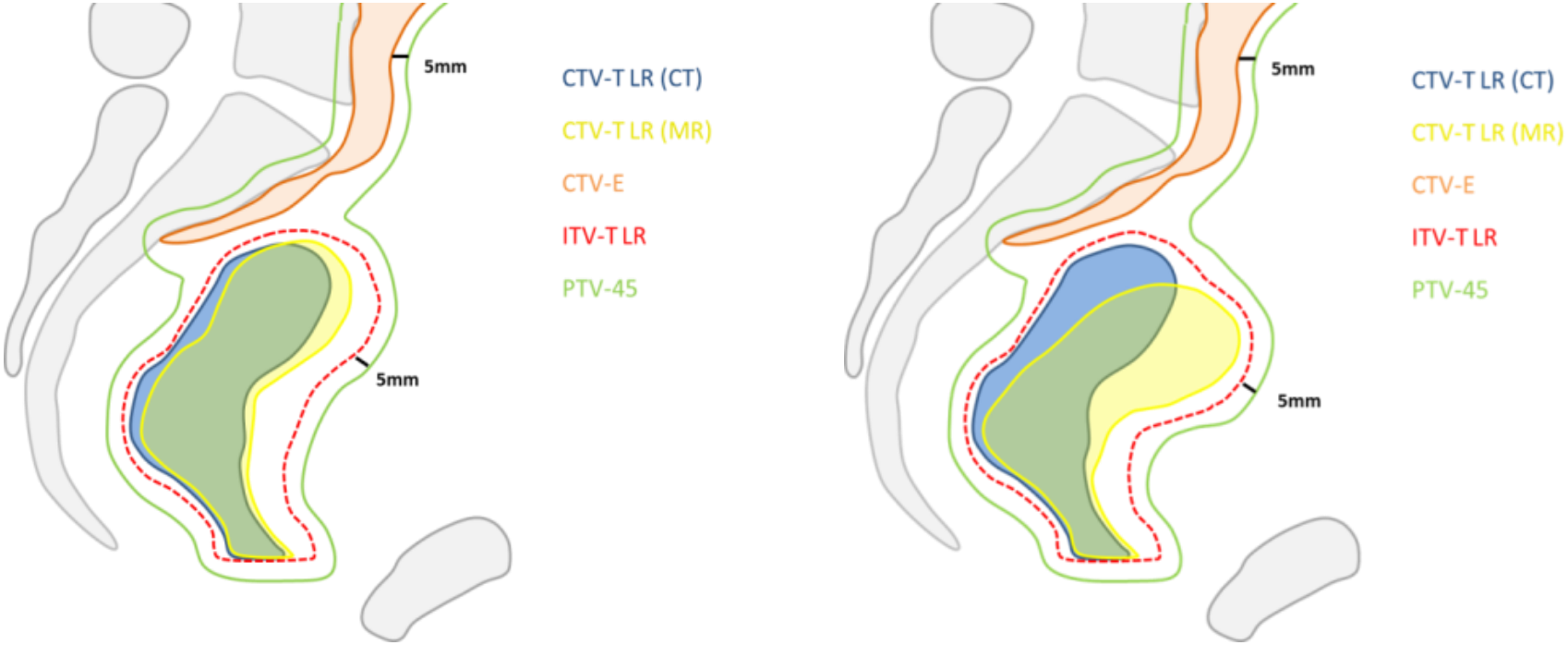
Target concept related to primary tumour

- **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

EBRT dose prescription

- **CTV-E:**
  - **45Gy/25fx**

- **CTV-N**
  - **Delivered as SIB**
  - **Suggested dose and fractionation**
    - **55Gy/25 fx inside pelvis (assuming 3-4Gy BT contribution)**
    - **57.5Gy/25fx outside pelvis**
    - **Equivalent to a total of 60Gy EQD2**

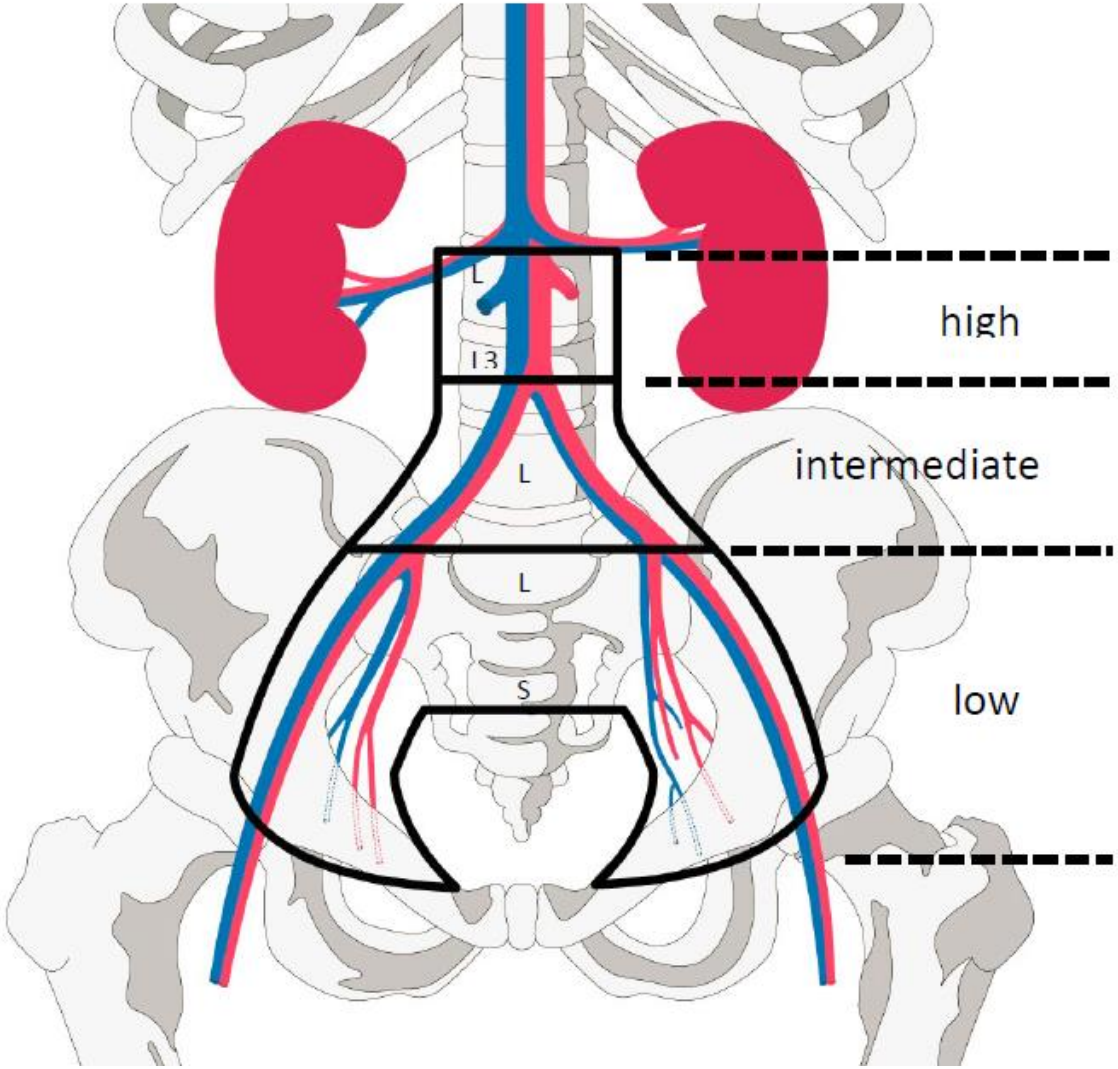
EMBRACE II interventions

- 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

Risk Group LN	Definition	EBRT lymph node regions
Low Risk (LR LN)	Tumour size ≤4cm AND stage IA/IB1/IIA1 AND N0 AND squamous cell carcinoma AND no uterine invasion	**"Small Pelvis"** internal iliac external iliac obturator presacral
Intermediate Risk (IR LN)	Not low risk No high risk features	**"Large Pelvis"** Nodes included in "Small Pelvis" and common iliac region (including the aortic bifurcation). In addition: • inguinal in case of distal vaginal involvement. • Mesorectal space in case of mesorectal nodes and advanced local disease
High Risk (HR LN)	Based on nodal pathology • ≥ 1 pathologic node at common iliac or above • OR ≥ 3 pathologic nodes	**"Large Pelvis + Para-aortic"** Nodes included in "Large Pelvis" and para-aortic region with the upper border of CTV minimum at the level of renal veins (usually incl. L2), and at least 3 cm cranial of the highest pathological node in case of para-aortic nodes].

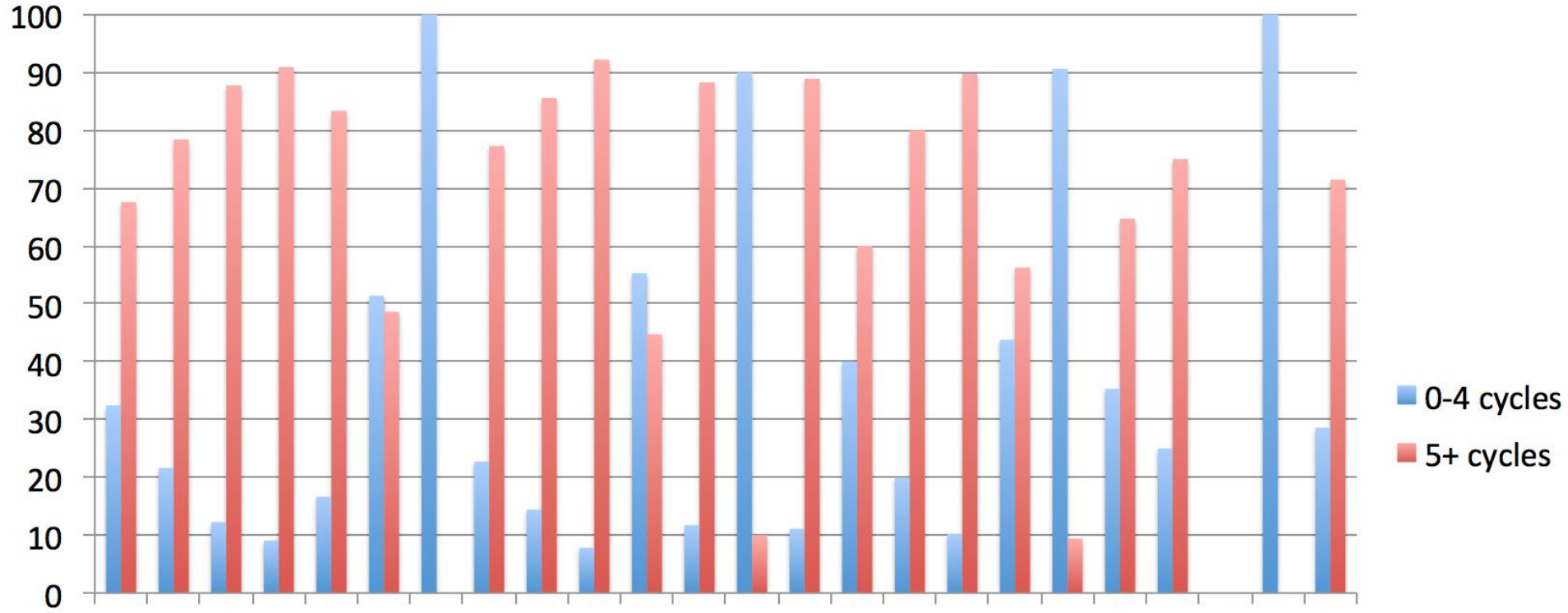
Target concept related to elective lymph nodes



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**

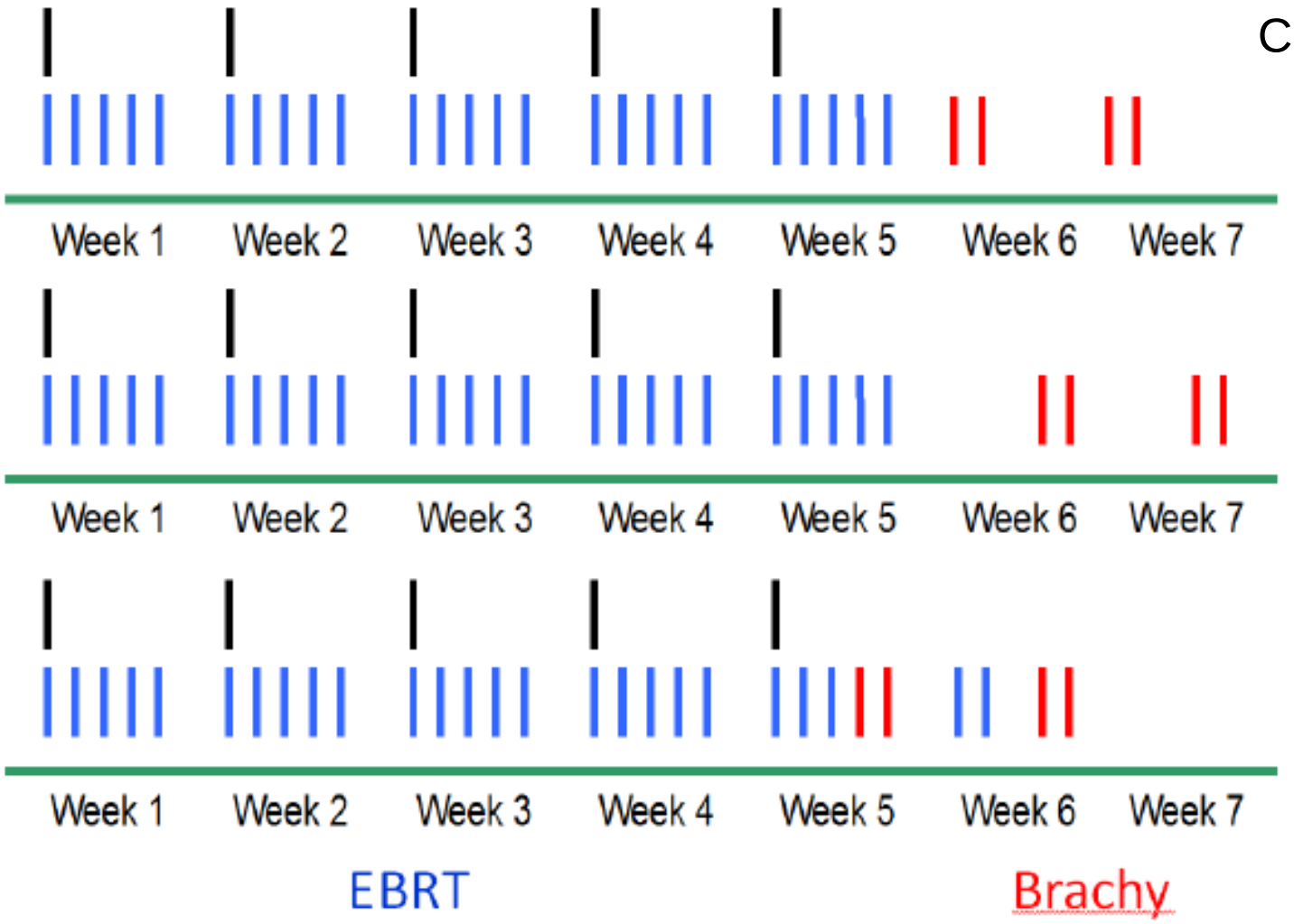
Administration of chemotherapy in EMBRACE I



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 (50% of patients in EMBRACE I)**

Control of OTT: 3 examples of schedules



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**

Roadmap EMBRACE II

- **Oct 2015:** **Protocol distributed to EMBRACE centers**
- **Nov 2015:** **Protocol distribution to interested centers**
- **Spring 2016:** **Dummy run EMBRACE centers**
- **April 2016:** **Start of accrual**
- **Autumn 2016 →** **Dummy run new centers**

Contact to EMBRACE office for interested centers:

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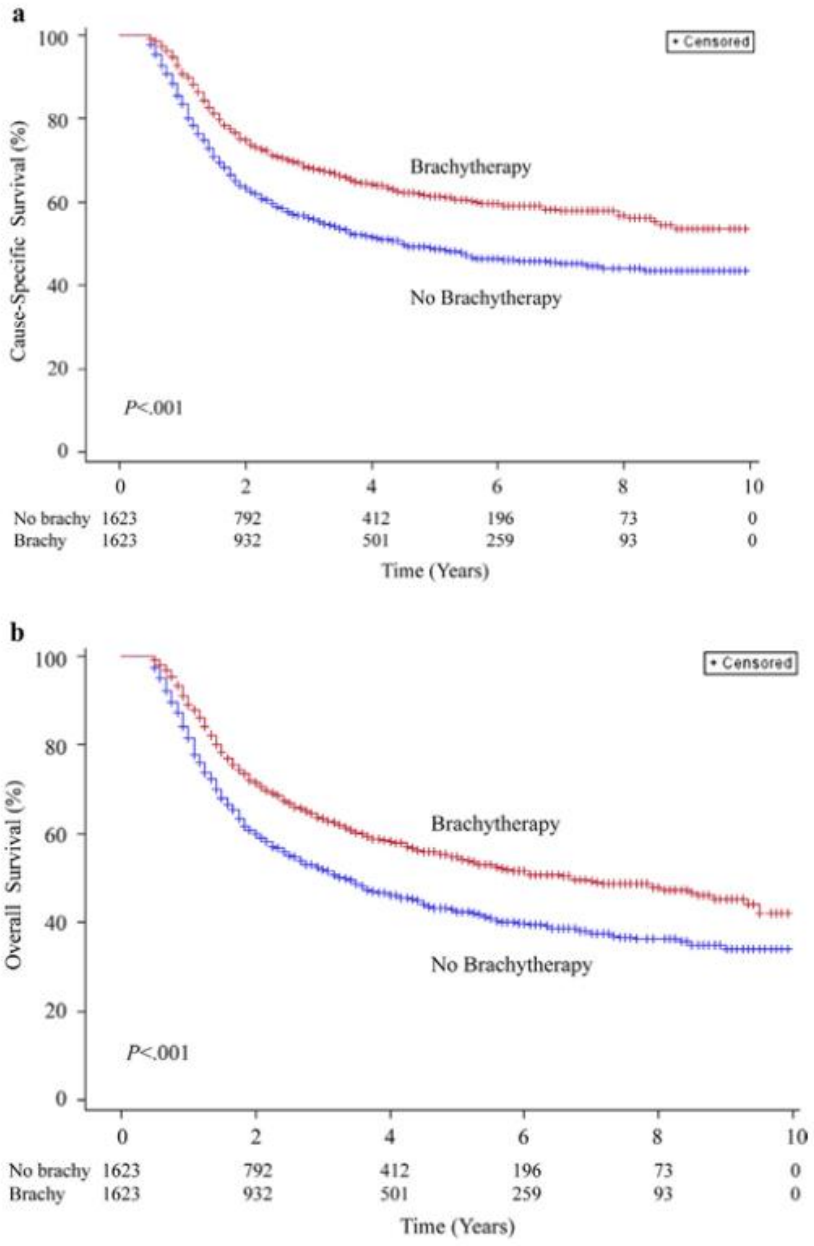
Karitand@rm.dk

Clinical Outcome : Disease and Toxicities

Christine Haie Meder

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Importance of brachytherapy +++



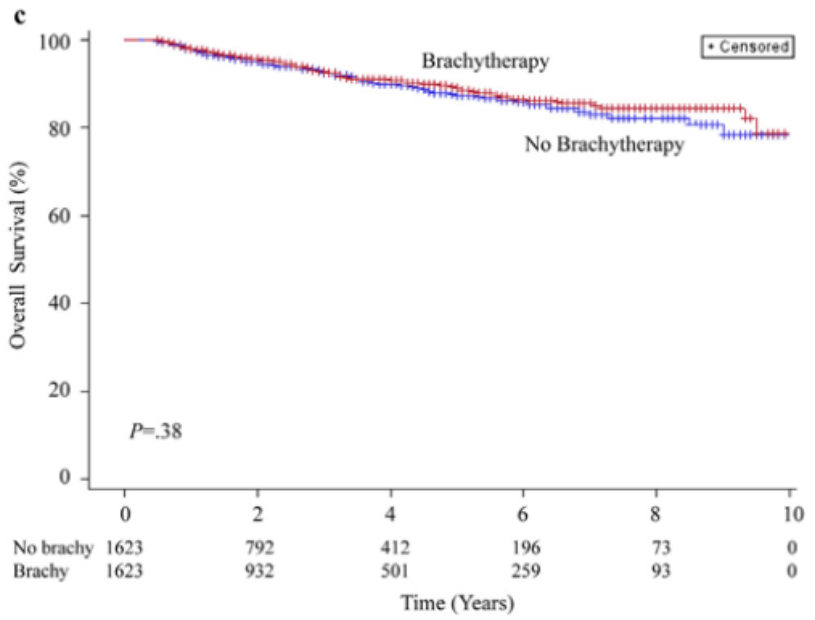


Fig. 2. Survival by brachytherapy use for matched cohort between 2000 and 2009. (a) Cause-specific survival; (b) overall survival, and (c) non-cancer-related survival.

Clinical Investigation: Gynecologic Cancer

Trends in the Utilization of Brachytherapy in Cervical Cancer in the United States

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EDITORIAL

Curative Radiation Therapy for Locally Advanced Cervical Cancer: Brachytherapy Is NOT Optional

Kari Tanderup, PhD,*,† Patricia J. Eifel, MD,‡ Catheryn M. Yashar, MD,§
Richard Pötter, MD,‖ and Perry W. Grigsby, MD*

Int J Radiation Oncol Biol Phys 88:537-9;2014

Results of radiotherapy in early-stage disease (before the era of concomitant chemo-radiotherapy and IGABT)

Authors	N° pts	Stage	5-yr survival (%)	Local control (%)
Manchester 80-88 LDR	294	I/IIA	90-94 (DFS)	
Hunter 1993	45	IB	71 (OS)	
1993 (62)	70	IIB	52 (OS)	
Perez (87) LDR	384	IB	85	90
	128	IIA	70	81
	353	IIB	72	77
Fletcher (35) LDR	494	IB IIA MDAH	84	93
	207	IIB MDAH	70	82
French cooperative group LDR	229	I MDAH	89 (89)	93 (95)
	315	IIA MDAH	81 (85)	83 (88)
Horiot (53)	314	IIB MDAH	76 (76)	80 (78)
Kim (66) LDR	169	IB	82	89
	83	IIA	78	91
Lowrey (74 LDR	130	IB	81	88
	64	IIA	74	84
Pernot (92) LDR	173	IIA-B prox.	74	79
Coia (18)	203	IB	80	90
Joslin (64, 65) HDR	95	I	94	97
	170	II	62	74
Petereit (93) HDR	59	IB	86	85
	64	II	65	80
Vienna HDR	42	IB/IIA	85 (DSS)	97
Pötter (96)	124	IIB	69 (DSS)	82

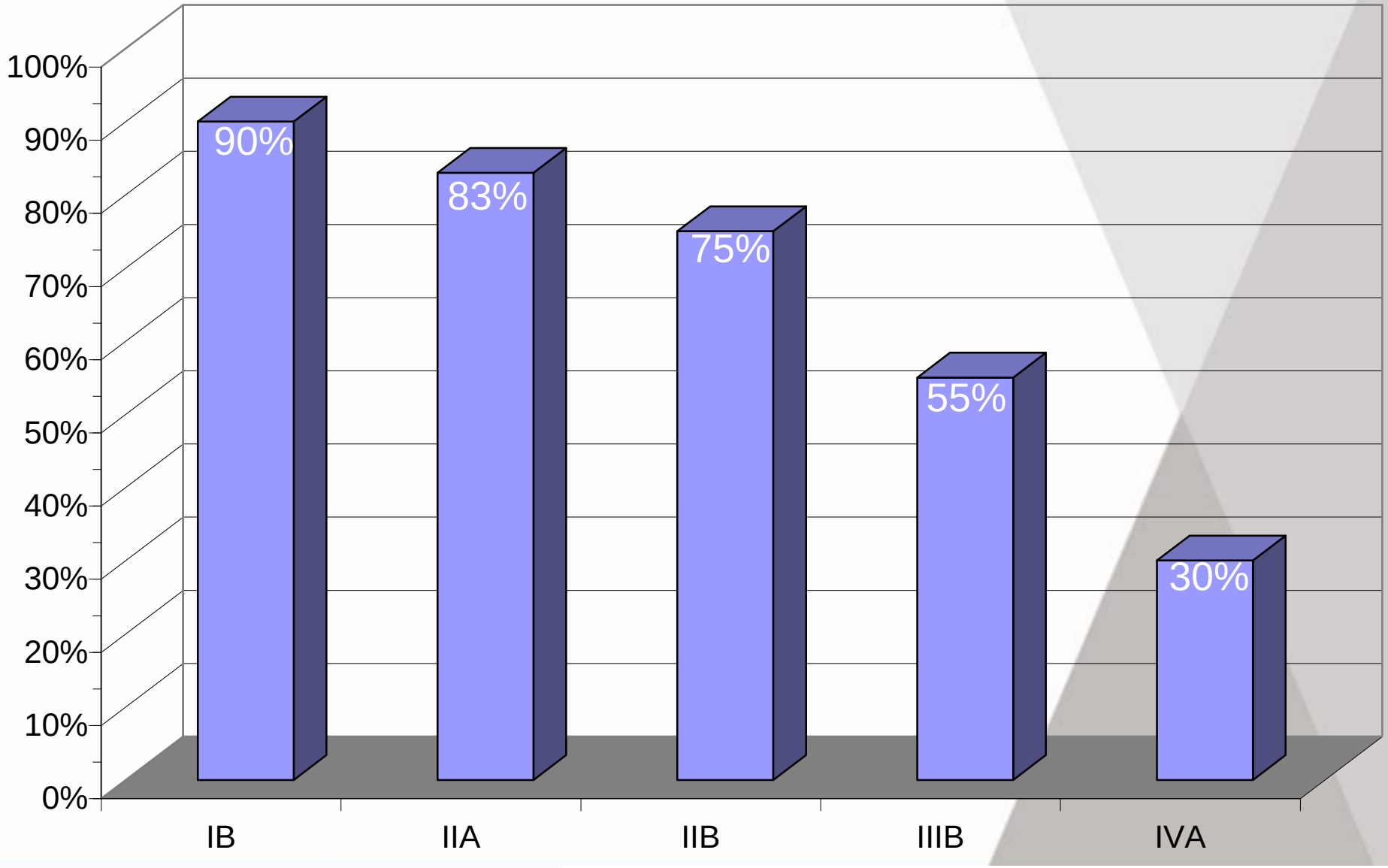
Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma. In: Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Van Limbergen E, eds. (2002) The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO

Results of radiotherapy in advanced disease (before the era of concomitant chemo-radiotherapy and IGABT)

Authors	N° pts	Stage	5-yr survival (%)	5-y Local control (%)
Manchester 1993 LDR Hunter 2001 (62)	50	III	34 OS	
Perez (86) LDR	293 20	III IV	52 DFS 0	59 25
Houston MDAH (26, 28) Fletcher LDR (73)	73 a* 25 b* 983	IB_2 IIB (bulk) IIIB (UICC)	44 OS 60 OS 36 DSS	67 84 78
French cooperative group LDR (53)	266 216 32	IIIA MDAH IIIB MDAH IV	61 OS (62) 39 OS (50) 20 OS	68 (63) 45 (57) 18
Paris IGR (42) LDR	58 416	Distal II IIIA-B, IV	65 OS 42 OS	78 66
Pernot (92) LDR	60 107	Distal IIB III	70 OS 42 OS	77 54
Joslin (64, 65) HDR	106	III	38 OS	56
Petereit (93) HDR	50	IIIB	33 OS	44
Vienna HDR Pötter (96)	78 12	IIIB IVA	48 DSS 19 DSS	65 48

Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma. In: Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Van Limbergen E, eds. (2002) The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO

Results of definitive radiotherapy 2D X-ray based point A prescription



Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma. In: Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Van Limbergen E, eds. (2002) The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO

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

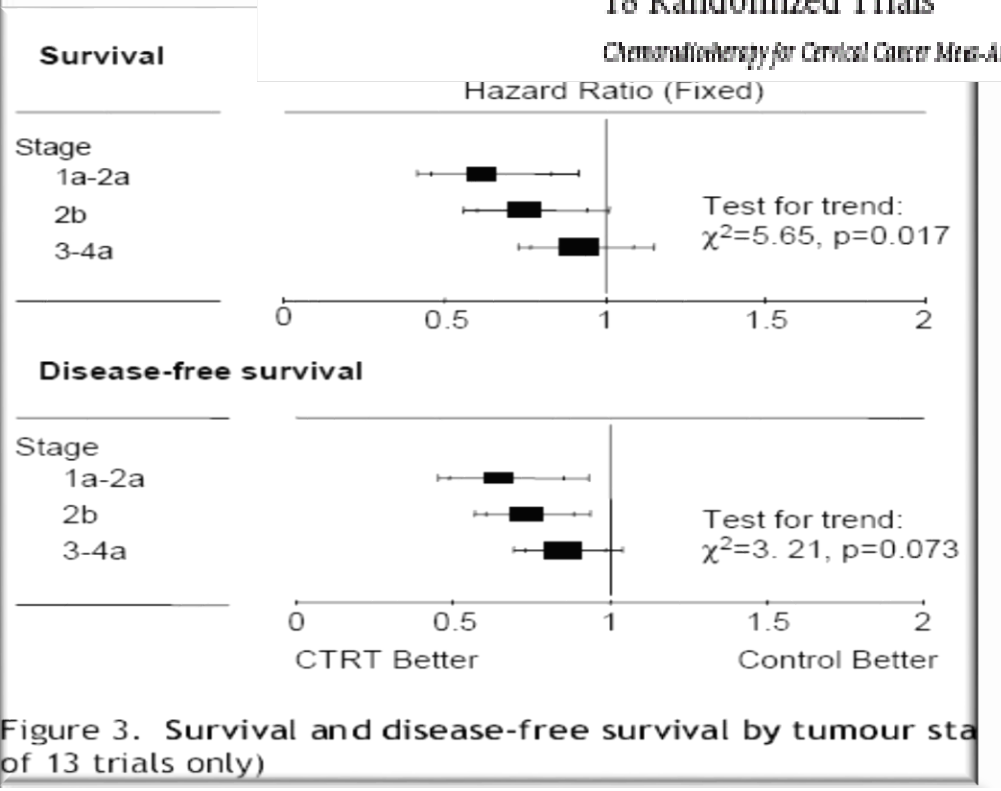
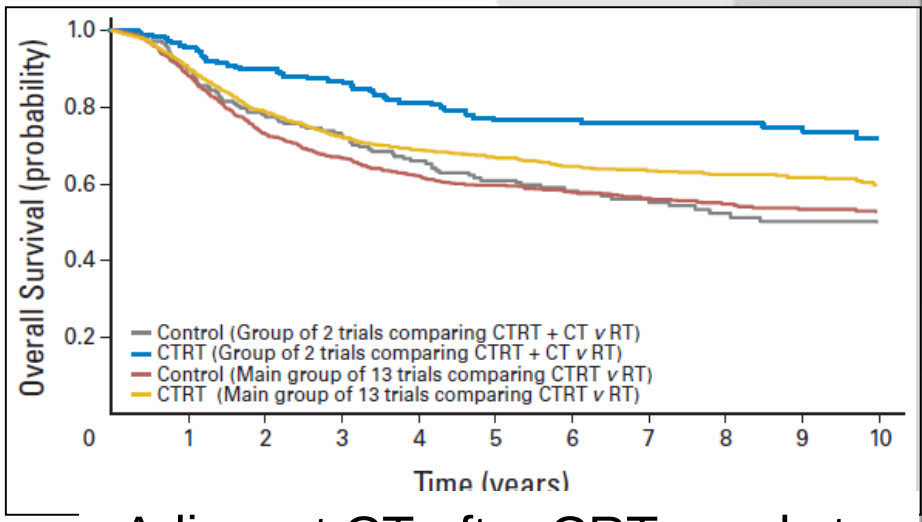


Figure 3. Survival and disease-free survival by tumour sta
of 13 trials only)



Adjuvant CT after CRT needs to be further explored

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% (stage Ib-IIa), 7% (stage IIb) and 3% (stage III-IVa) at 5-years**

JCO Dec 08

Results of definitive radiotherapy with IGABT

- **New paradigms**

  - 3D representation of GTV / CTV / OAR

  - DVH parameters based on
  individualised 3D treatment planning
  (D90 CTV: HR and IR CTV)

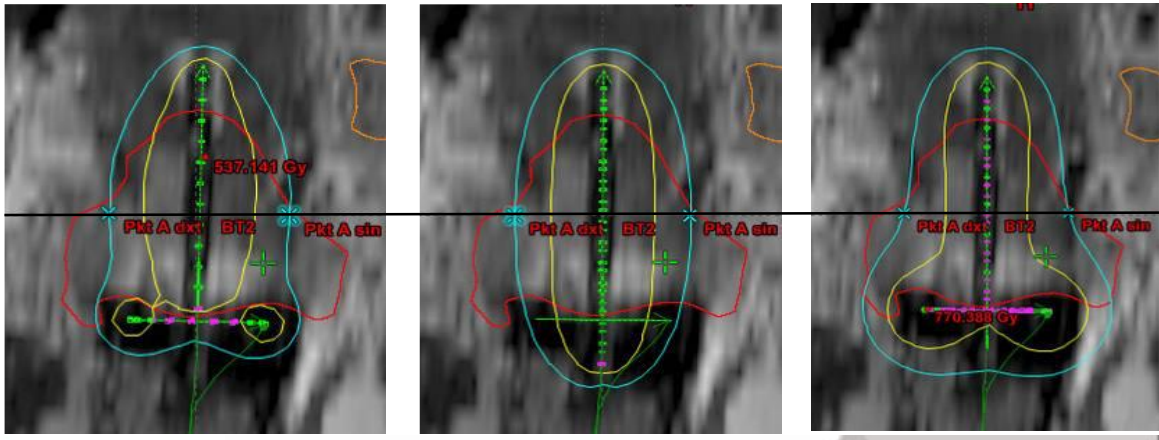
- **Did we improve the practice heterogeneity in prescription?**

- **Clinical results**

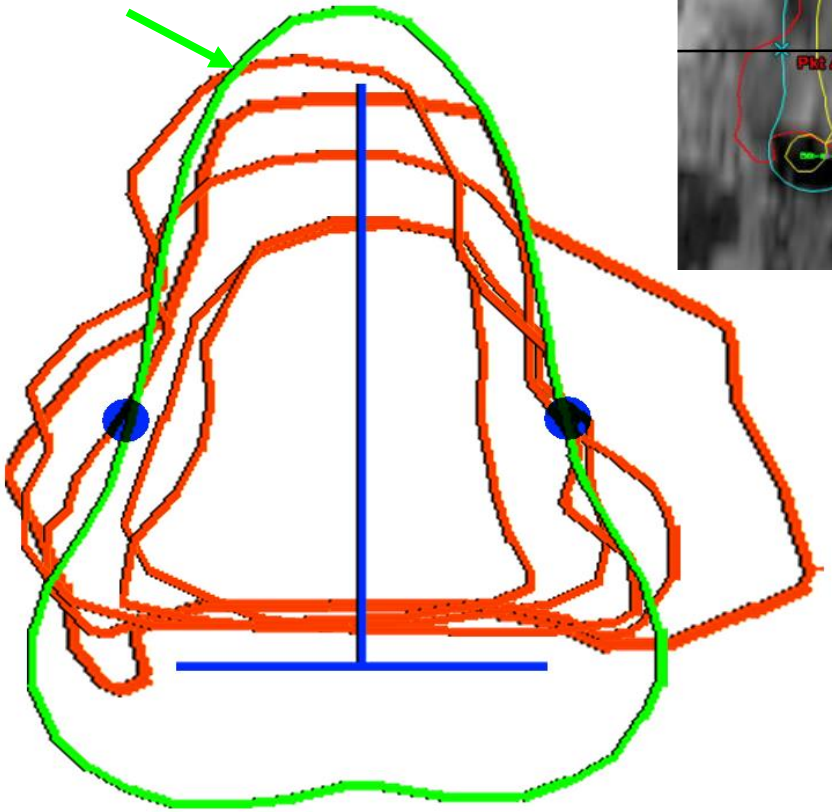
  - Local control related to 3D dose volume parameters

Prescription to point A

Milwaukee Toronto Vienna



Point A isodose



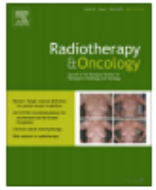
IGABT cervix cancer
Practice homogeneity

Radiotherapy and Oncology 94 (2010) 339–345

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Cervix cancer brachytheraphy

Variation of treatment planning parameters (D90 HR-CTV, D_{2cc} for OAR) for cervical cancer tandem ring brachytherapy in a multicentre setting: Comparison of standard planning and 3D image guided optimisation based on a joint protocol for dose–volume constraints

Ina M. Jürgenliemk-Schulz [a,1], Stefan Lang [b,*,1], Kari Tanderup [c], Astrid de Leeuw [a], Christian Kirisits [b], Jacob Lindegaard [c], Primoz Petric [d], Robert Hudej [d], Richard Pötter [b], On behalf of the Gyn GEC ESTRO network

Table 1
Treatment concepts of the different ring centres (R1–R6): EBRT dose, BT dose rate and fractionation schedule, additional interstitial sources.

Centre	R1	R2	R3	R4	R5	R6
EBRT						
Physical dose (Gy)	45	45	45	45	45	45
Fractionation	25 × 1.8	25 × 1.8	25 × 1.8	25 × 1.8	25 × 1.8	25 × 1.8
Brachytherapy						
Dose rate	PDR	PDR	HDR	HDR	HDR	HDR
Number of fractions	3	2	6	5	4	3
Prescribed physical dose/fraction (Gy)	12	20	4.7	5.5	7	7
Interstitial needles	Yes	Yes	No	No	Yes	No

IGABT cervix cancer
Practice homogeneity

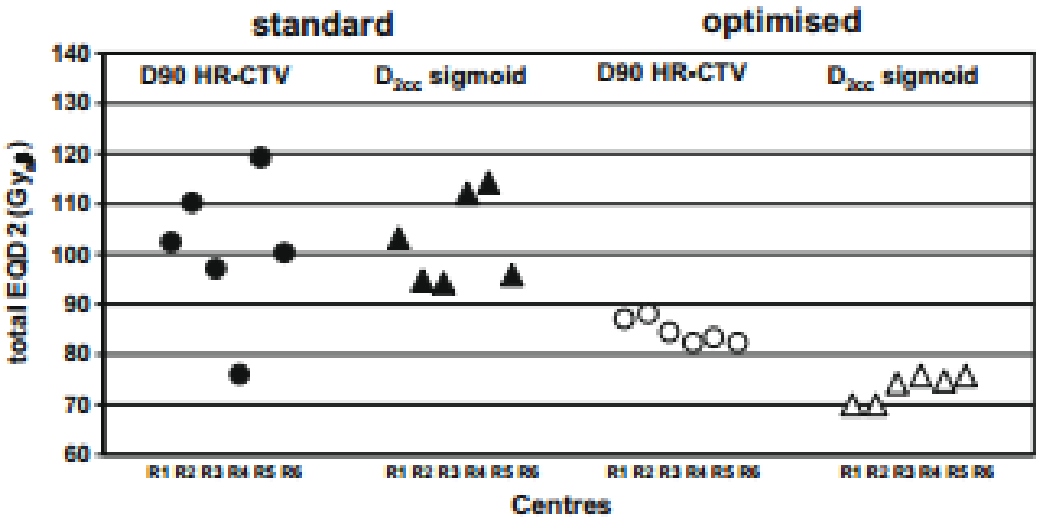


Fig. 2. Dose level variations (D90 HR-CTV and D_{2cc} sigmoid) in standard and optimised plans from the different centres for the limited volume case. The radiobiological effect of dose rate (PDR: R1/R2, HDR: R3/R4/R5/R6) and fractionation is indicated for the different treatment schedules (3rd and 4th column). Number of fractions is decreasing and dose per fraction is increasing for R3–R6 (compare Table 1).

Jürgenliemk-Schulz Radiother Oncol 2010;94:339-45

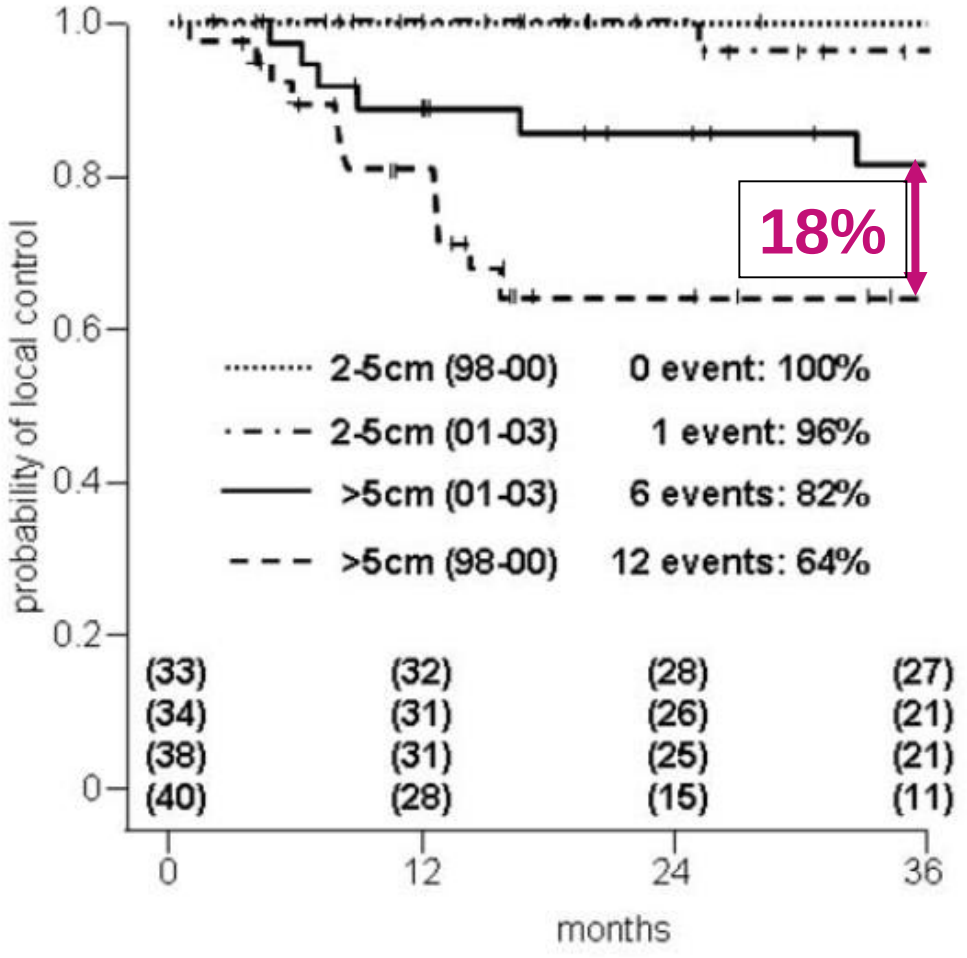
IGABT cervix cancer
Mono-institutional results

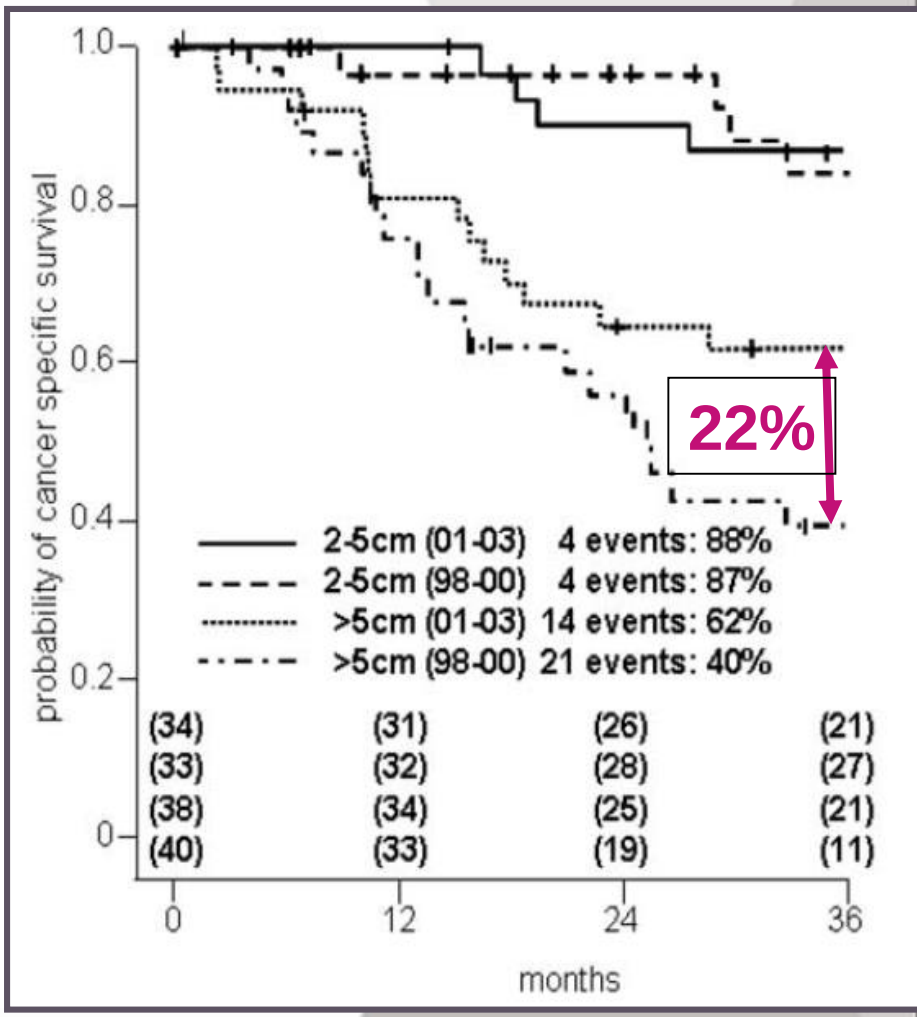
Author	Pt nb	image modal.	BT modal.	Total EQD2 D90 HR-CTV	Local control
Haie-Meder 2010	84	MRI	LDR	79	90%
Beriwal 2011	44	Hybrid	HDR	83	88%
Potter 2011	156	MRI	HDR	93	97%
Mahantshetty 2012	24	MRI	HDR	71	21/24
Lindegaard 2013	140	MRI	PDR	91	90%
Mazeron 2013	163	MRI	PDR	78	95%
Nomden 2013	46	MRI	PDR/HDR	84	93%
Refaat 2013	40	MRI/CT	PDR	±80	90%
Tharavichitkul 2013	47	MRI	HDR	93	98%
Rikjmans 2014	83	MRI	HDR	81	93%
Castelnau 2015	225	MRI	PDR	80	86%
Ribeiro 2016	170	MRI	PDR	85	96%

IGABT cervix

Local control and cancer specific survival (1998-2003)

Treatment period (-/+ IGABT) and tumor size





mean 81 Gy vs. 90 Gy in HR CTV

Pötter R. et al Radiother Oncol 2007

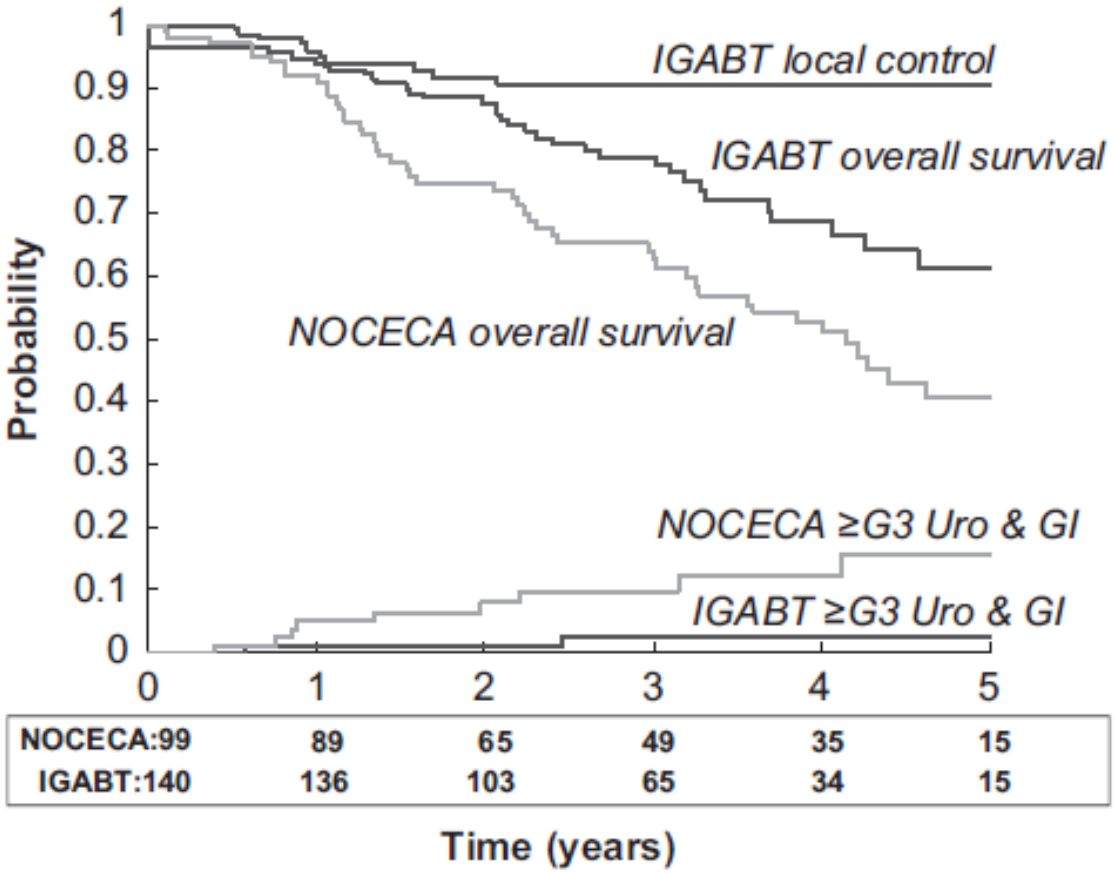


Figure 3. Actuarial local control, overall survival and ≥grade 3 combined urological-gastrointestinal morbidity in 140 patients treated with IGABT (black lines). For comparison the curves for overall survival and morbidity in 99 patients treated with 2D x-ray-based brachytherapy (NOCECA) are indicated (grey lines). Patient number at risk for overall survival is indicated below the x-axis.

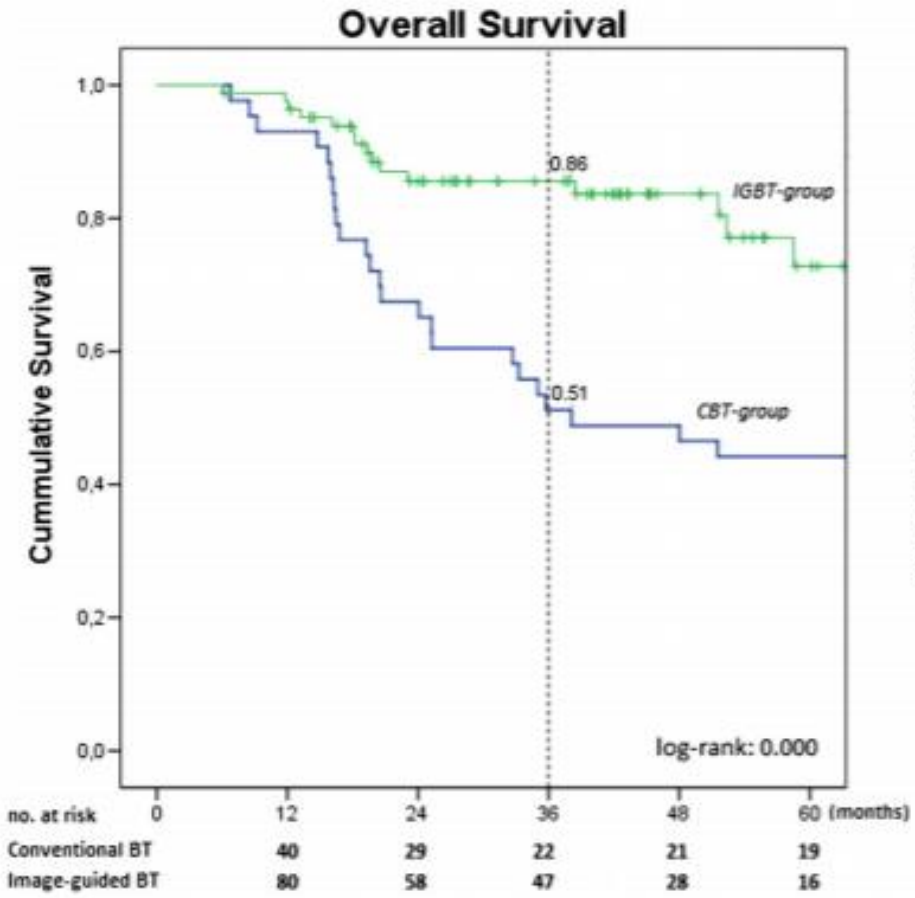
3 y-LC : 90%

3 y-OS :
IGABT/ChTh : 79%
NOCECA : 63%

3 y-morbidity ≥G3 :
10%
3%

Lindegaard et al. Acta Oncologica 2013

126 patients:
43 conventional BT
83 IGABT



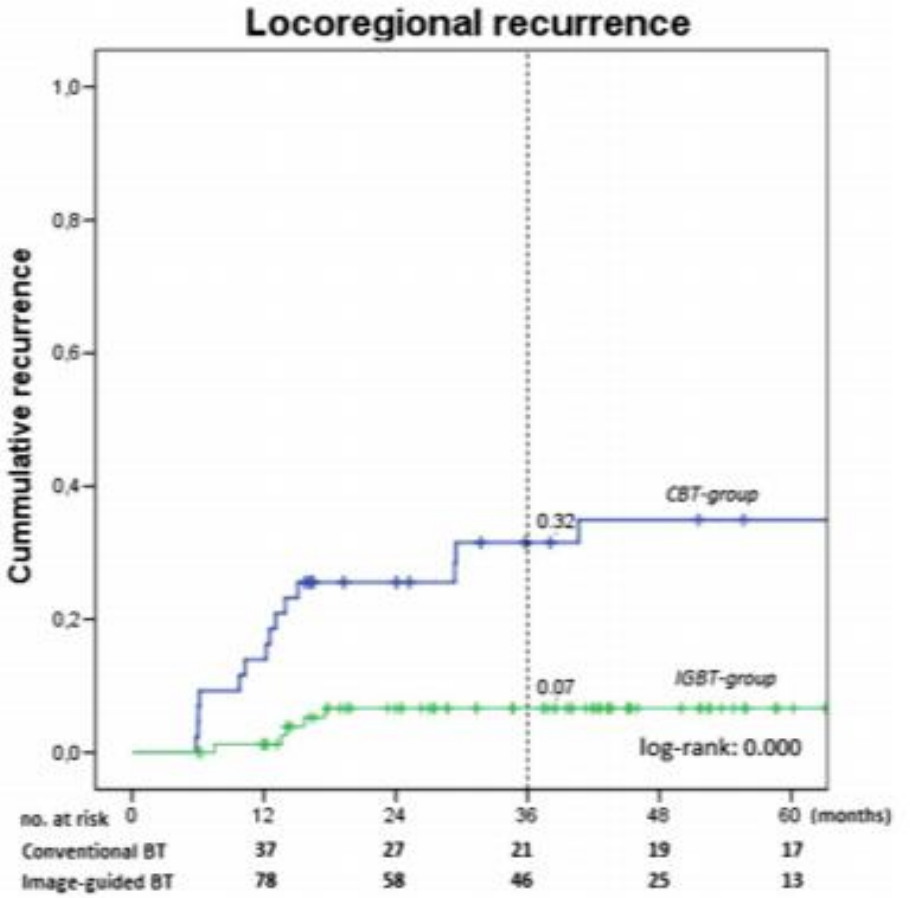


Fig. 1. Overall survival and pelvic recurrence rates by treatment group (CBT vs. IGBT).

Rikjmans et al. Gynecol Oncol 2014

Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy

Renaud Mazeron [a,b,*], Pauline Castelnau-Marchand [a], Isabelle Dumas [c], Eleonor Rivin del Campo [a], Léopold Kamsu Kom [a], Florent Martinetti [c], George Farha [a], Anne Tailleur [a], Philippe Morice [d], Cyrus Chargari [a], Dimitri Lefkopoulos [b,c], Christine Haie-Meder [a]

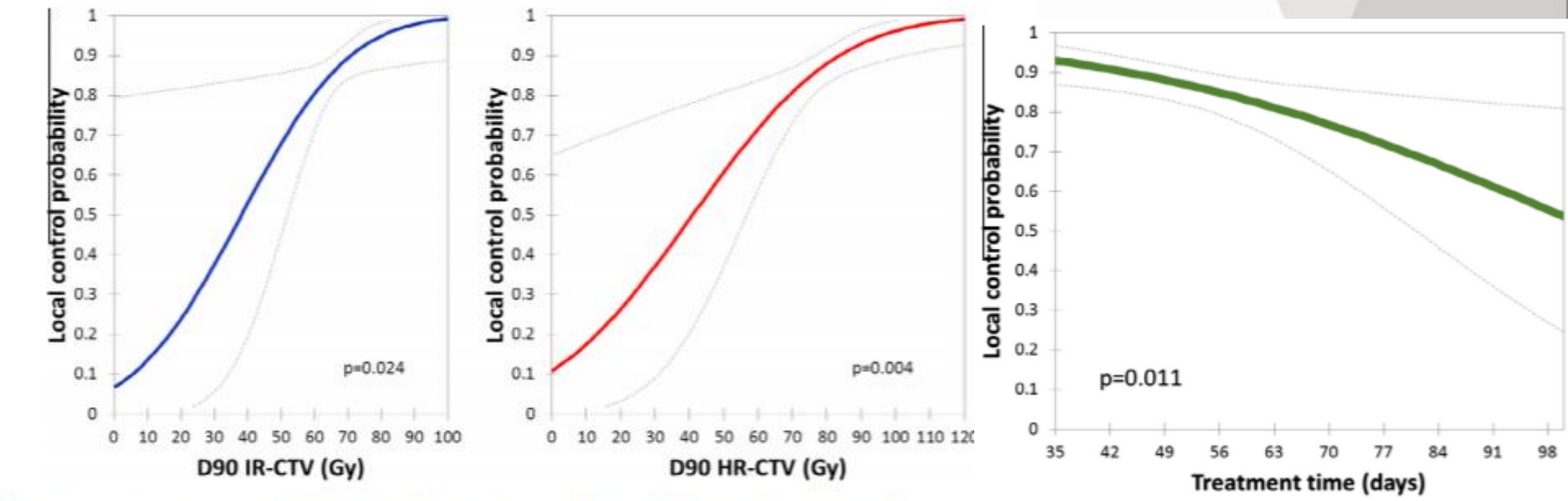


Fig. 2. Dose–response relationships for local control: D90% HR-CTV and D90% IR-CTV Greay dashes: 95% confidence interval.

Cervical cancer brachytherapy

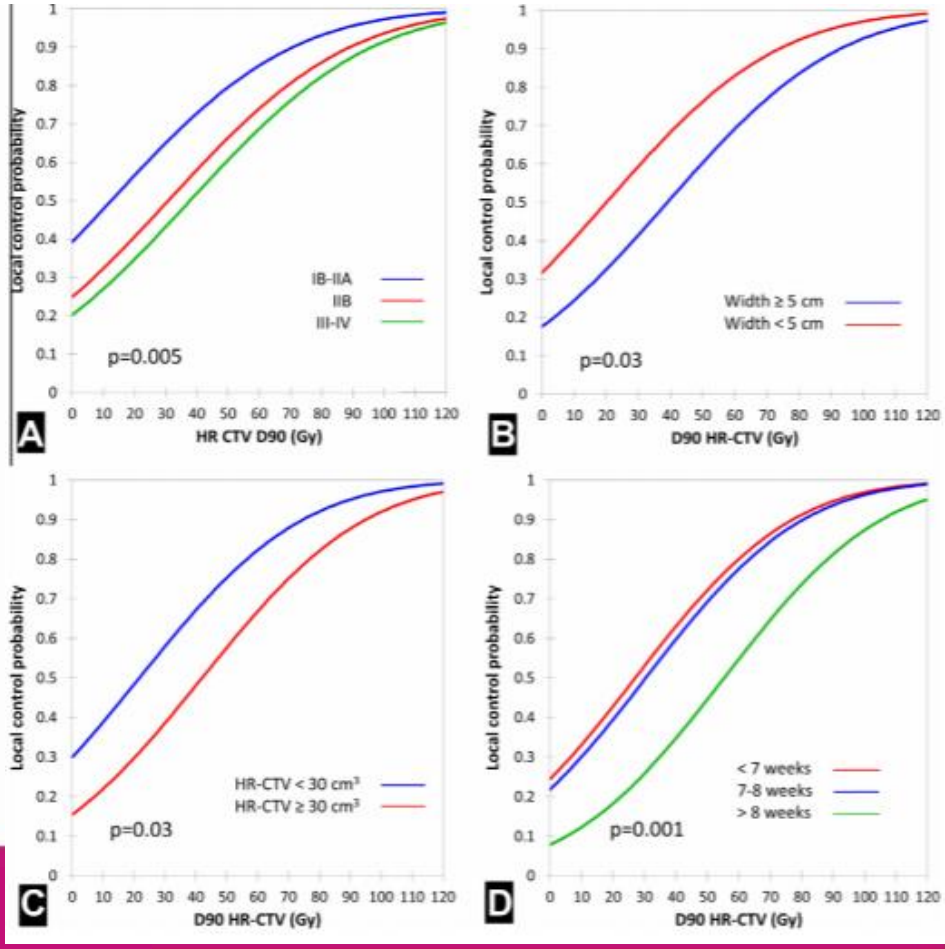
Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy

Renaud Mazeron [a,b,*], Pauline Castelnau-Marchand [a], Isabelle Dumas [c], Eleonor Rivin del Campo [a], Léopold Kamsu Kom [a], Florent Martinetti [c], George Farha [a], Anne Tailleur [a], Philippe Morice [d], Cyrus Chargari [a], Dimitri Lefkopoulos [b,c], Christine Haie-Meder [a]

To achieve a 90% LC probability D90 to HR-CTV should be :

- 71.5 Gy in tumor stage IB–IIA
- 89.7 Gy in IIB
- 97 Gy in III–IV

Based on the HR-CTV volume
92 Gy if volumes ≥ 30 cm3
73.9 Gy if volumes < 30 cm3



Radiother Oncol 2015;114:257–63

Multicenter studies with IGABT in cervix carcinoma

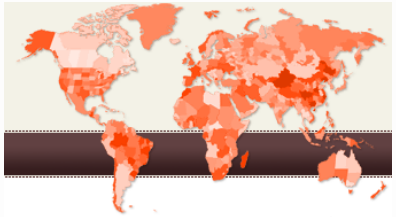
STIC

- Prospective
- 2D vs. 3D (CT)
  - Non random.
  - Availability
- Completed
- 2005-2008
- 20 centers
- 705 pts

- **Def. EBRT+BT**
- Preop BT
- Preop. EBRT+BT

Retro Embrace

- Retrospective
- Before Embrace



- Completed
- 1998-2012
- 12 centers
- 731 pts

- **Def. EBRT+BT**

Embrace

- Prospective
- Phase IV (MRI)

- Completed
- 2008-2012
- 24 centers
- 1419 pts

- **Def. EBRT+BT**

Radiotherapy and Oncology 103 (2012) 305–313

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Prospective trial in 3D PDR brachytherapy

Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: Results of the French STIC prospective study ☆

Claire Charra-Brunaud [a,*], Valentin Harter [a], Martine Delannes [g], Christine Haie-Meder [c], Philippe Quetin [d], Christine Kerr [e], Bernard Castelain [f], Laurence Thomas [b], Didier Peiffert [a]

Table 1
Comparison of main clinical factors between 2D and 3D arms.

	Group 1 BT followed by surgery		Group 2 EBRT BT surgery		Group 3 EBRT BT		p^*
	2D	3D	2D	3D	2D	3D	
Number of patients	76	89	142	163	118	117	
Mean age	47.6	46.6	49	47.6	56.1	53.4	0.07
Histology							0.08
Squamous cell	50 (66%)	60 (67%)	120 (84%)	123 (75%)	106 (90%)	99 (85%)	
Adenocarcinoma	22 (29%)	26 (29%)	21 (15%)	38 (23%)	12 (10%)	17 (14%)	
Other	4 (5%)	3 (4%)	1 (1%)	2 (2%)	0	1 (1%)	
FIGO stage							0.27
IB1	66 (87%)	83 (93%)	13 (9%)	16 (10%)	6 (5%)	11 (9%)	
IB2 IIA IIB	10 (13%)	6 (7%)	118 (83%)	127 (78%)	70 (59%)	77 (66%)	
IIIA IIIB	0 (0%)	0 (0%)	11 (8%)	20 (12%)	42 (36%)	29 (25%)	
Mean tumor maximal size (mm)	23 ± 9	28 ± 13	46 ± 16	46 ± 14	49 ± 16	48.5 ± 16	0.44
Pelvic node[1]	3 (4%)	2 (2%)	45 (32%)	63 (39%)	52 (44%)	54 (46%)	0.34
LomboAortic node[1]	0	0	16 (11%)	16 (10%)	22 (19%)	17 (15%)	0.33

[1] nodes diagnosed on imagery (CT/MRI/ or PET CT).
* 2D–3D brachytherapy comparison: Generalized Estimated Equations adapted for nested analysis.

Prospective trial in 3D PDR brachytherapy

Charra-Brunaud Radiother Oncol 2012;103:305-13

Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: Results of the French STIC prospective study ☆

Claire Charra-Brunaud [a,*], Valentin Harter [a], Martine Delannes [g], Christine Haie-Meder [c], Philippe Quetin [d], Christine Kerr [e], Bernard Castelain [f], Laurence Thomas [b], Didier Peiffert [a]

Clinical results at 2 years

At 24 months	Group 1 (%)		Group 2 (%)		Group 3 (%)		P^*
	2D	3D	2D	3D	2D	3D	
LFRS	91.9	100	84.7	93	73.9	78.5	0.003
RLRFS	87.9	96.1	77.2	88.6	61.2	69.6	0.001
DFS	86.5	89.7	73	77.1	55.2	60.3	0.086
OS	95	96	85	86	65	74	0.27
Grade 3–4 toxicity							
Urinary	5.8	1.3	7.6	5.5	9.2	1.2	0.02
Digestive	6.8	1.2	0.9	4.8	9	0	0.17
Urinary + digestive	9.9	2.5	7.8	9	13.8	1.2	0.027
Gynecologic	5.7	7.5	6.4	2.8	15.4	1.4	0.01
Global	14.6	8.9	12.5	8.8	22.7	2.6	0.002
Grade 2–4 toxicity							
Urinary	13.1	7.9	20.4	13.3	23.1	13.7	0.03
Digestive	8.3	7.4	8.3	8.8	18.7	15.2	0.45
Gynecologic	18.7	12.9	17.9	14.7	35.7	19.4	0.125
Global	37.5	23.2	40.6	29.4	53.4	42.4	0.028

LRFS: local free relapse survival; RLRFS: loco regional relapse free survival; DFS: disease free survival; OS: Overall Survival.

* 2D-3D brachytherapy comparison: Cox proportional hazard model adjusted for regimens.

Original article

Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study

Radiother Oncol 2016;120:428-33

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]

Image guided brachytherapy in cervical cancer

Radiother Oncol 2016;120:434–40

Image guided adaptive brachytherapy with combined intracavitary and interstitial technique improves the therapeutic ratio in locally advanced cervical cancer: Analysis from the retroEMBRACE study

Lars Fokdal [a,*], Alina Sturdza [b], Renaud Mazeron [c], Christine Haie-Meder [c], Li Tee Tan [d], Charles Gillham [e], Barbara Šegedin [f], Ina Jürgenliemk-Schultz [g], Christian Kirisits [b], Peter Hoskin [h], Richard Pötter [b], Jacob C. Lindegaard [a], Kari Tanderup [a]

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

Radiother Oncol 2016;120:441–46

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]

RetroEMBRACE outcome data

- **Primary Objective: Local control in IGABT within multi-institutional frame prior to EMBRACE study**

- **12 institutions participating January 1998 - August 2012**
  - 852 patients included, 49 excluded for unknown disease status and 72 excluded due to adjuvant therapy, 731 analyzed

- **2 IA (0.3%), 123 IB (16.8%), 42 IIA (5.7%), 368 IIB (50.3%), 23 IIIA (3.1%), 145 IIIB (19.8%), 23 stage IVA (3.1%), 5 IVB (0.7%)**

- **Median width at diagnosis: 50 mm clinical, 46 mm at MRI examination**

- **Nodal status : N+ 40%, N- 60%**

Sturdza Radiother Oncol 2016;120:428-33

RetroEMBRACE outcome data

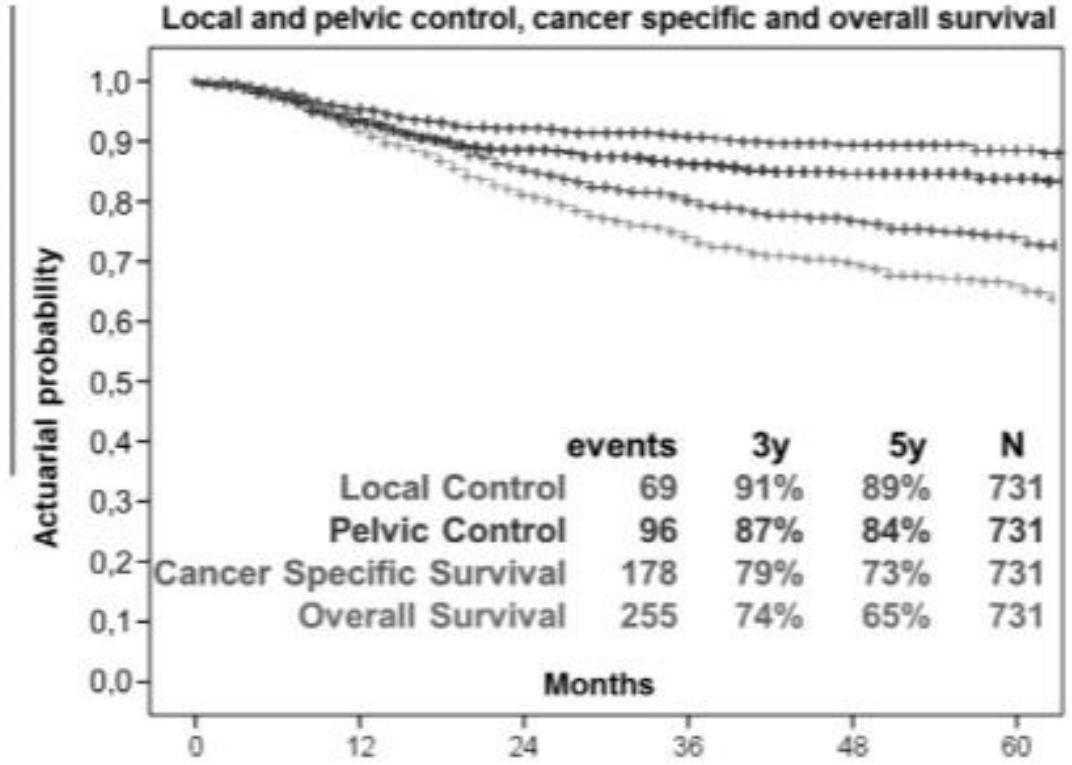


Fig. 1. Actuarial Kaplan–Meyer estimates for local control (LC), pelvic control (PC), cancer specific survival (CSS) and overall survival (OS) in 731 patients. Absolute number of events and actuarial estimates for outcome at 3 and 5 years are indicated.

Mean HR-CTV volume :
37 ± 24 cm3

Mean D90 (EQD210) :
HR-CTV 87 ± 15 Gy
IR-CTV 69 ± 8 Gy

Mean D90 HR-CTV
Stage I 93 ± 17 Gy
Stage IIB 88 ± 14 Gy
Stage IIIB 83 ± 13 Gy

Sturdza Radiother Oncol 2016;120:428-33

RetroEMBRACE outcome data

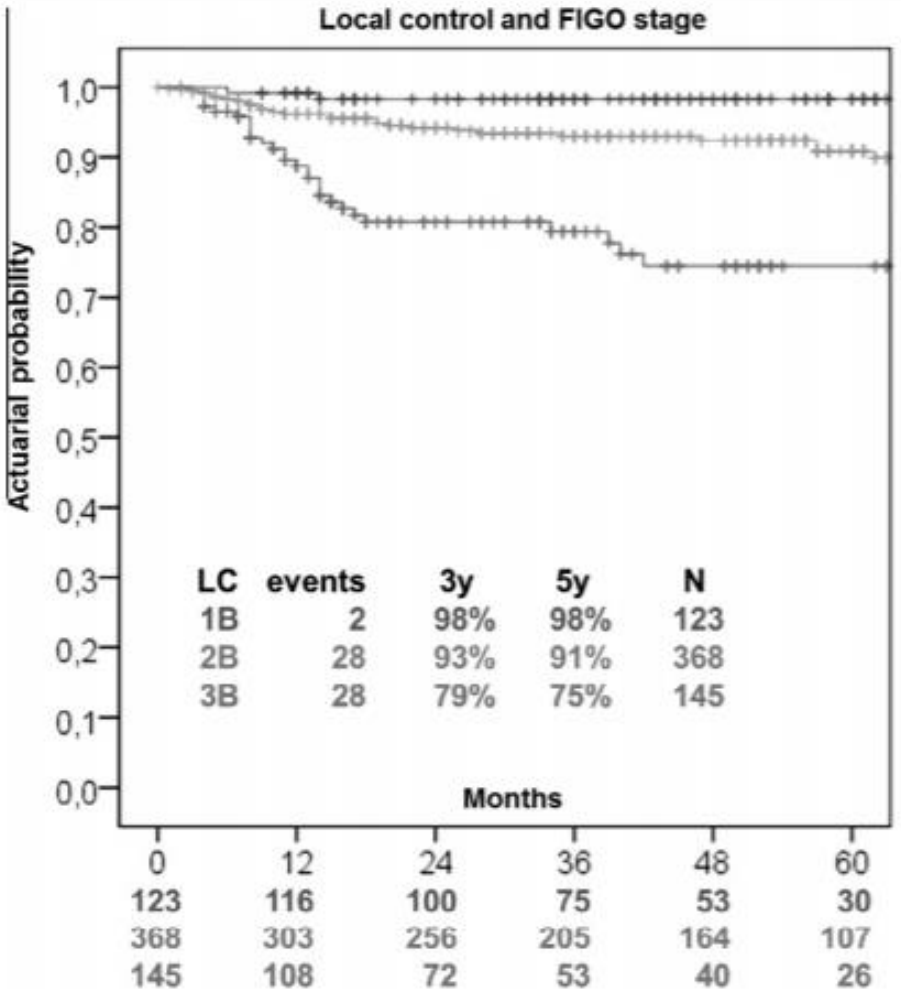


Fig. 2. Actuarial Kaplan–Meier estimates for stage related local control (LC) in patients with stage IB, IIB, IIIB disease ($n = 636$). Absolute number of events and actuarial estimates for outcome at 3 and 5 years are indicated.

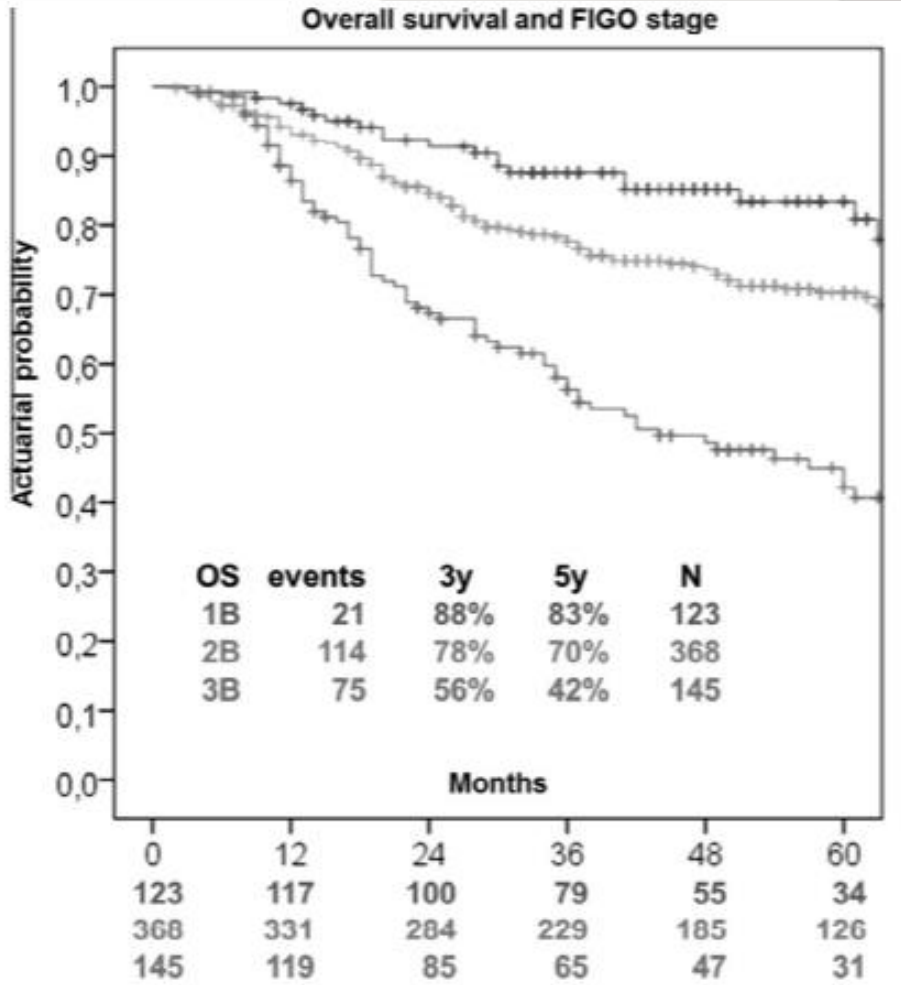
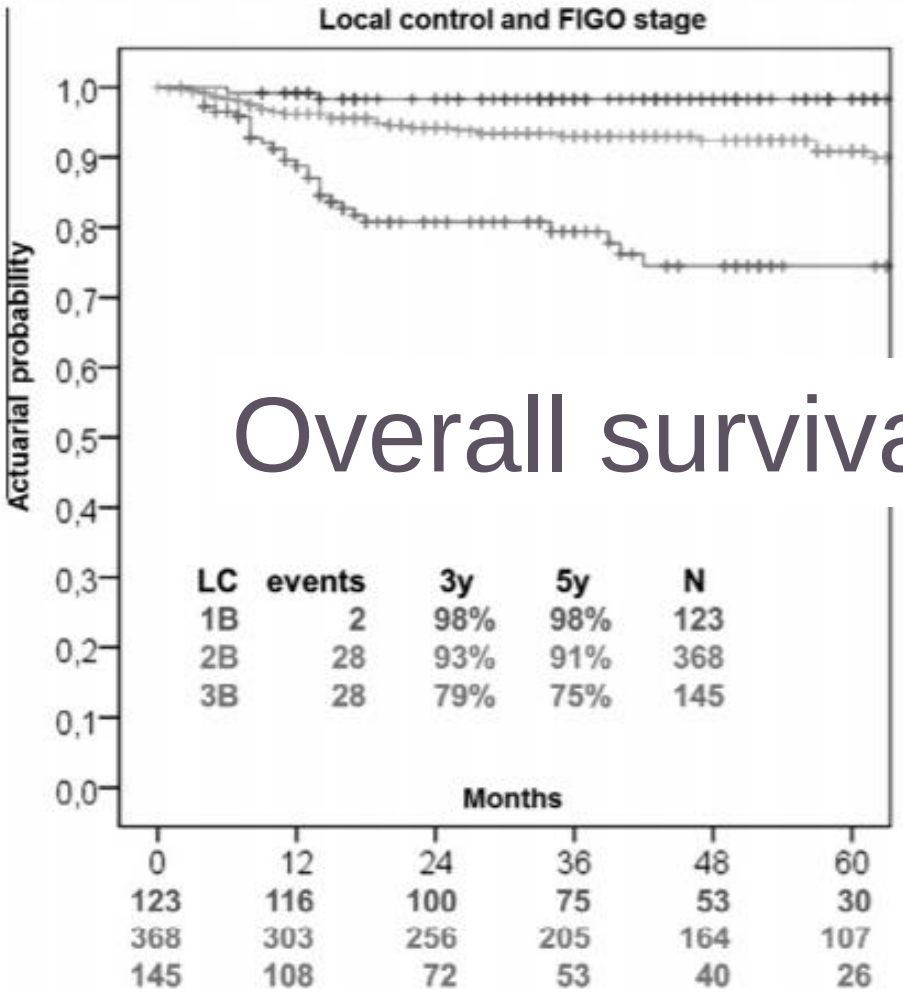


Fig. 4. Actuarial Kaplan–Meier estimates for stage related overall survival (OS) in patients with stage IB, IIB, IIIB disease ($n = 636$). Absolute number of events and actuarial estimates for outcome at 3 and 5 years are indicated.

Sturdza Radiother Oncol 2016;120:428-33

RetroEMBRACE outcome data



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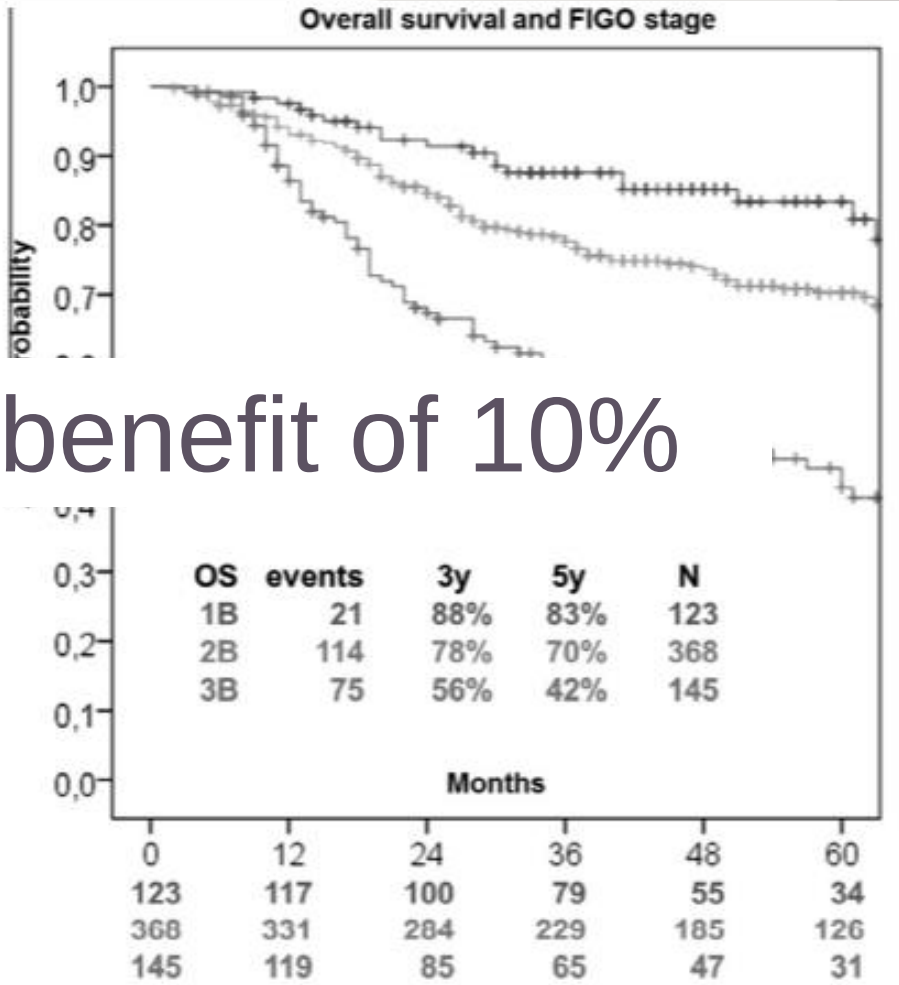


Fig. 4. Actuarial Kaplan–Meier estimates for stage related overall survival (OS) in patients with stage IB, IIB, IIIB disease ($n = 636$). Absolute number of events and actuarial estimates for outcome at 3 and 5 years are indicated.

Overall survival benefit of 10%

Sturdza Radiother Oncol 2016;120:428-33

RetroEMBRACE role of interstitial BT

610 patients with LACC retroEMBRACE study :

IC group N = 310

IC/IS group N = 300

Table 1
Patient characteristics.

Variable		IC/IS group (*N* = 300)	IC group (*N* = 310)	*P*-value
Median age (years)		56 (23–89)	53 (24–91)	0.01
FIGO stage	IB	18%	19%	0.40
	2A	6%	7%	
	2B	48%	49%	
	3A	3%	4%	
	3B	21%	17%	
	4A + 4B	4%	4%	
Tumour width	Clinical	51 (20–100)	49 (10–100)	0.11
Staging with laparoscopy		28%	24%	0.25
Lymph nodes	Pelvic	42%	42%	0.36
	PAN	4%	10%	0.02
	Groin	2%	3%	0.60
Histology	SQCC	86%	83%	0.39
	AC + other	14%	17%	
Follow up (Months)		40 (3–163)	41 (3–138)	0.80

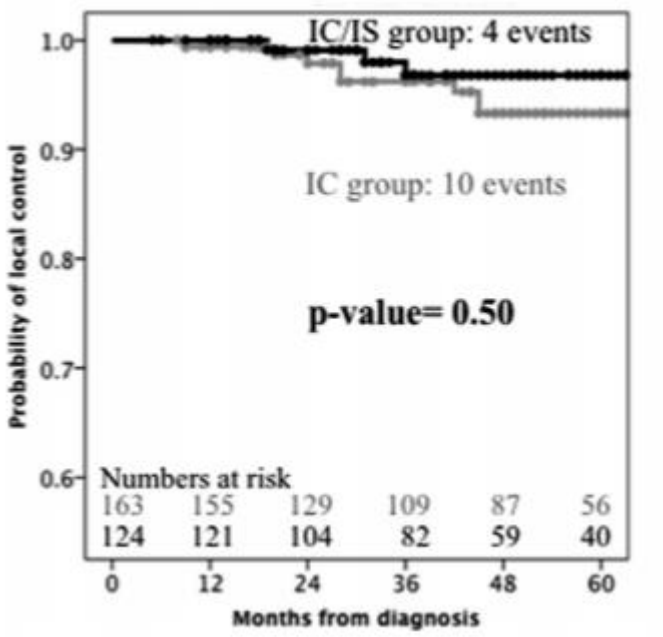
Fokdal Radiother Oncol 2016;120:434-40

RetroEMBRACE role of interstitial BT

Table 3
Dose volume parameters in all patients and in the intracavitary/interstitial group or intracavitary group.

Variable doses in Gy	All patients ($N = 610$)	IC/IS group ($N = 300$)	IC group ($N = 310$)	p-Value
Volume HR CTV	36 ± 24	39 ± 25	33 ± 24	<0.01
HR CTV D90	88 ± 14	92 ± 13	83 ± 14	<0.01
D2CC Bladder	81 ± 22	79 ± 12	83 ± 29	0.07
D2CC Rectum	64 ± 8	65 ± 7	64 ± 10	0.12
ICRU Rectum	69 ± 13	69 ± 9	69 ± 15	0.84
D2CC Sigmoid	65 ± 10	65 ± 7	66 ± 12	0.38

2C. Small target volume (CTV_{HR}<30 cm^3)



Fokdal Radiother Oncol 2016;120:434-40

2B. Large target volume (CTV_{HR}≥30 cm^3)

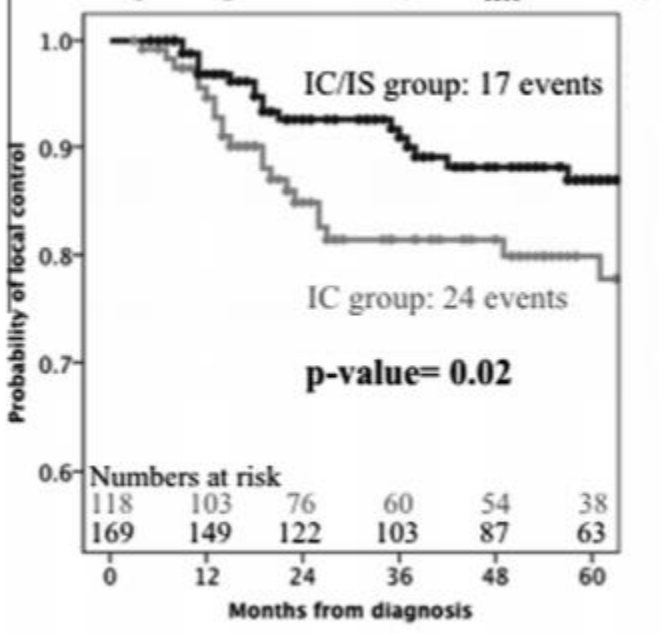


Table 2
Local failures (crude percentage) are listed according to stage, as well as CTV_{HR} volume and total $EQD2_{10}$ (EBRT + BT) doses for CTV_{HR}, GTV and CTV_{IR} (mean and standard deviation).

Stage	# local failures/# pts	% local failures	CTV_{HR} volume 488 pts	CTV_{HR} D90 488 pts	GTV D100 267 pts	CTV_{IR} D90 353 pts
All stages	43/488	8.8%	36 ± 22 cm^3	86 ± 12 Gy	92 ± 19 Gy	68 ± 7 Gy
IB	1/67	1.5%	25 ± 15 cm^3	89 ± 13 Gy	101 ± 27 Gy	71 ± 7 Gy
IIA + IIB	21/280	7.5%	33 ± 19 cm^3	87 ± 11 Gy	93 ± 18 Gy	69 ± 6 Gy
IIIA + IIIB + IV	21/141	14.9%	47 ± 27 cm^3	83 ± 12 Gy	88 ± 18 Gy	66 ± 7 Gy

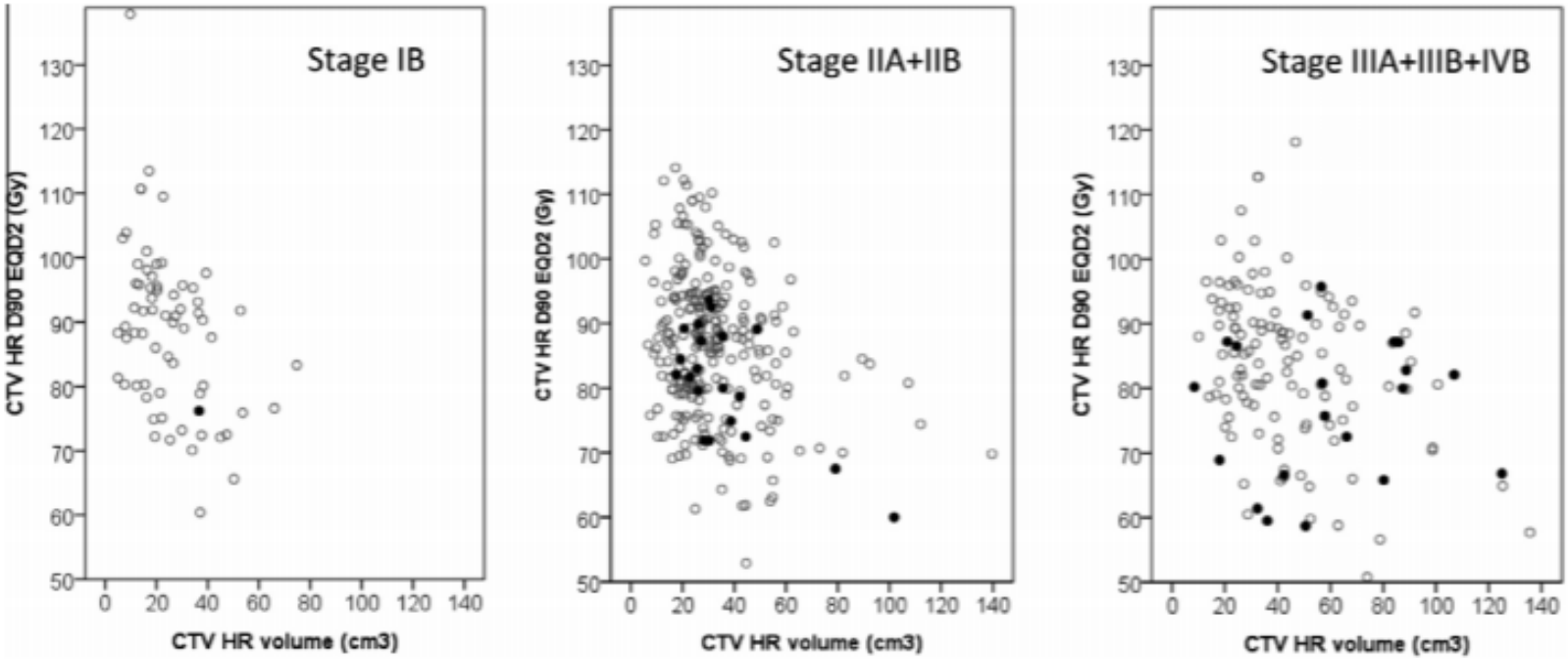


Fig. 1. Distribution of local failures according to stage as a function of CTV_{HR} volume and dose (D90). Patients with local control are indicated with open circles. Patients with local failure are indicated with filled circles.

Demonstration of clinical evidence for dose effect for CTVHR

3-year local control rates D90 CTVHR dose ≥85 Gy in 7 weeks:

- >94% in limited size CTVHR (20 cm3)
- >93% in intermediate size CTV HR (30 cm3)
- >86% in large size CTVHR (70 cm3)

Doses of 90–95 Gy add 1–4% to local control

An increase of OTT by one week is equivalent to de-escalating CTVHR dose by 5 Gy

An increased CTVHR volume by 10 cm3 requires an additional 5 Gy for equivalent local control.

Tanderup Radiother Oncol 2016;120:441–46

IGABT: main carcinologic event : metastasis

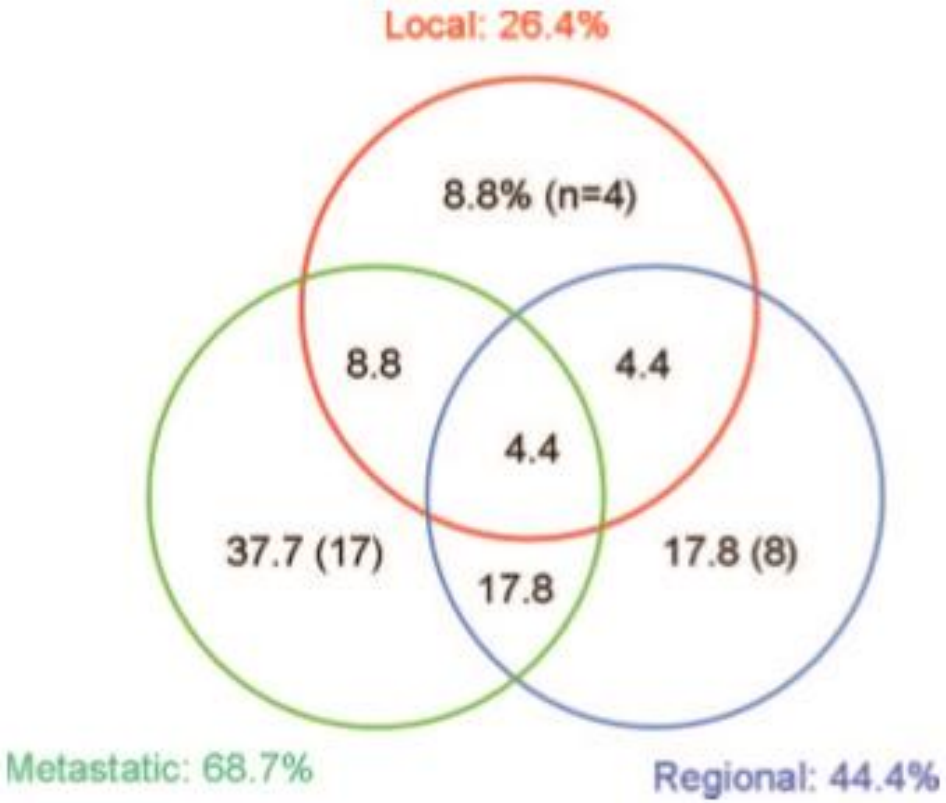


Figure 1. Pattern of relapses.

Mazeron et al. The Oncologist 2013

Clinical Outcome IGABT : Toxicities

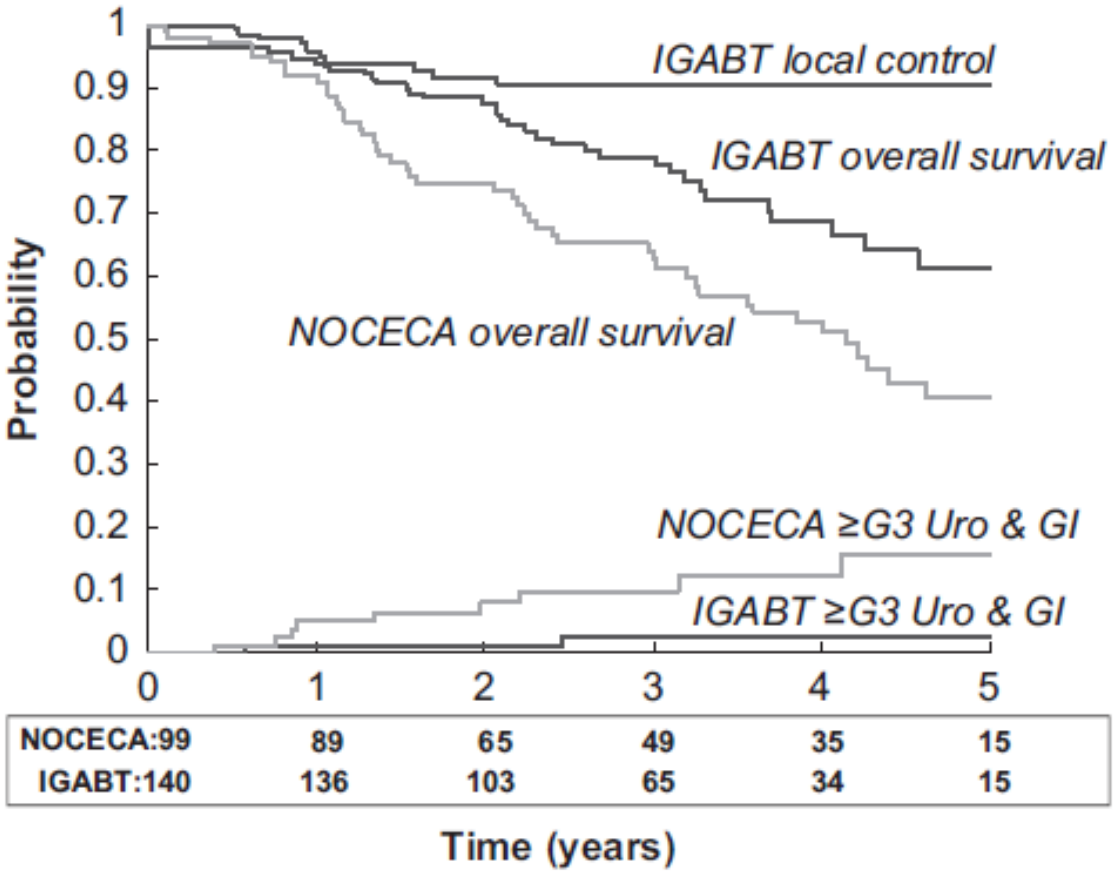


Figure 3. Actuarial local control, overall survival and ≥grade 3 combined urological-gastrointestinal morbidity in 140 patients treated with IGABT (black lines). For comparison the curves for overall survival and morbidity in 99 patients treated with 2D x-ray-based brachytherapy (NOCECA) are indicated (grey lines). Patient number at risk for overall survival is indicated below the x-axis.

3 y-LC : 90%

3 y-OS :
IGABT/ChTh : 79%
NOCECA : 63%

3 y-Morbidity ≥G3 :
10%
3%

Lindegaard et al. Acta Oncologica 2013

Pulsed-dose rate image-guided adaptive brachytherapy in cervical cancer: Dose–volume effect relationships for the rectum and bladder

Renaud Mazeron [a,b,*], Pierre Maroun [a], Pauline Castelnau-Marchand [a], Isabelle Dumas [c], Eleonor Rivin del Campo [a], Kim Cao [a], Andrea Slocker-Escarpa [a], Rodrigue M'Bagui [a], Florent Martinetti [c], Anne Tailleur [a], Alain Guemnie-Tafo [c], Philippe Morice [d], Cyrus Chargari [a,b], Dimitri Lefkopoulos [b,c], Christine Haie-Meder [a]

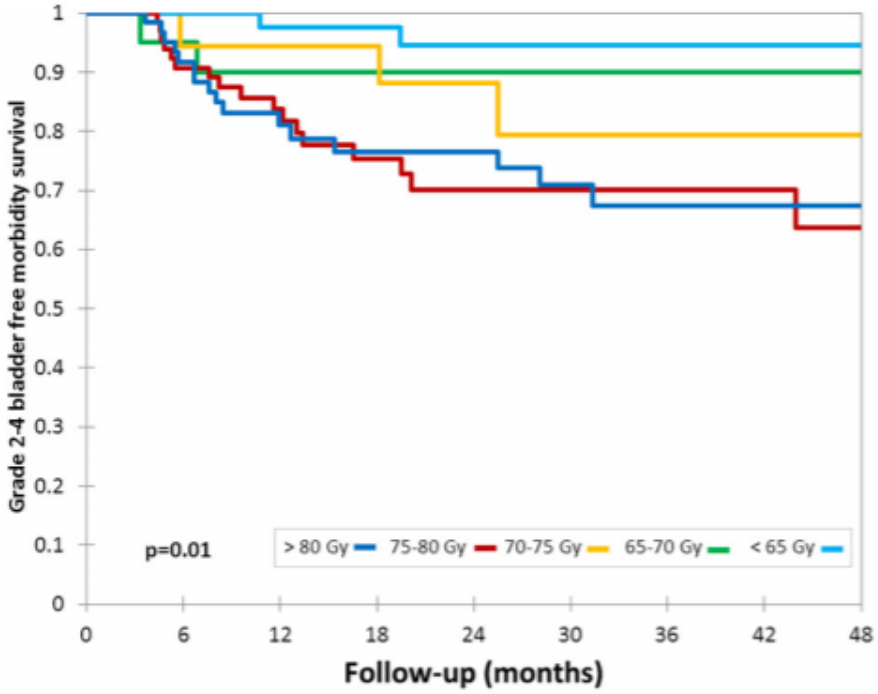
Table 2
Dosimetric parameters according to grade.

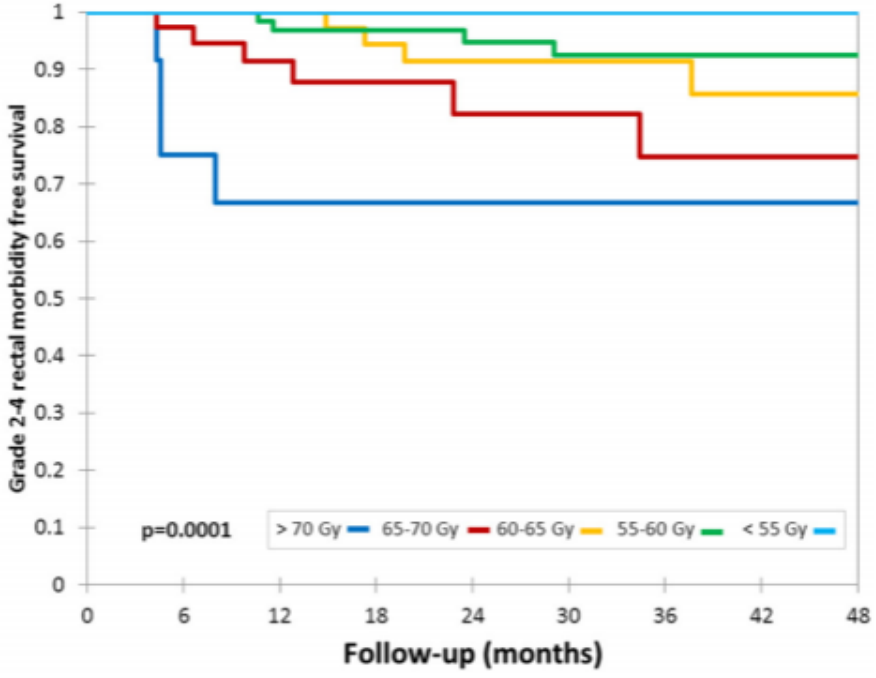
		N (%)	D0.1 cm^3 (Gy)		D2 cm^3 (Gy)	
			Mean ± SD	p^*	Mean ± SD	p^*
Bladder	Grade 0	119 (54.8)	83.9 ± 18.3	0.009	68.3 ± 8.7	0.006
	Grade 1	56 (25.8)	84.0 ± 17.1		67.3 ± 7.9	
	Grade 2	34 (15.7)	90.6 ± 18.7		71.1 ± 8.6	
	Grade 3	8 (3.7)	99.8 ± 23.3		76.3 ± 9.1	
Rectum	Grade 0	166 (76.5)	68.0 ± 11.0	0.360	59.3 ± 6.3	0.072
	Grade 1	36 (16.6)	69.5 ± 12.3		60.5 ± 6.9	
	Grade 2	13 (6.0)	74.2 ± 17.4		63.9 ± 7.4	
	Grade 3	2 (0.9)	84.8 ± 21.5		70.0 ± 10.9	

N: number of patients, SD: standard deviation.
* Kruskal–Wallis test.

225 patients treated with PDR IGABT

Consistent improvements of morbidity outcomes for D2 cm3 <75 Gy for the bladder and <65 Gy for the rectum





> 80 Gy	21	14	11	4	2
75-80 Gy	18	17	13	6	3
70-75 Gy	43	36	26	16	4
65-70 Gy	69	63	48	33	21
< 65 Gy	66	61	49	31	26

> 70 Gy	13	13	11	6	3
65-70 Gy	36	28	22	11	10
60-65 Gy	42	37	24	16	11
55-60 Gy	70	63	51	34	20
< 55 Gy	56	50	39	28	14

Fig. 3. Grade 2–4 morbidity free survivals according to D2 cm^3 levels.

Mazeron et al. Radiother Oncol 2015

Prospective trial in 3D PDR brachytherapy

Charra-Brunaud Radiother Oncol 2012;103:305-13

Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: Results of the French STIC prospective study ☆

Claire Charra-Brunaud [a,*], Valentin Harter [a], Martine Delannes [g], Christine Haie-Meder [c], Philippe Quetin [d], Christine Kerr [e], Bernard Castelain [f], Laurence Thomas [b], Didier Peiffert [a]

Clinical results at 2 years

50% reduction of grade 3-4 morbidity with IGABT

At 24 months	Group 1 (%)		Group 2 (%)		Group 3 (%)		P*
LFRS							0.003
RLRFS							0.001
DFS							0.086
OS							0.27
Grade 3–4 toxicity							
Urinary	5.8	1.3	7.6	5.5	9.2	1.2	0.02
Digestive	6.8	1.2	0.9	4.8	9	0	0.17
Urinary + digestive	9.9	2.5	7.8	9	13.8	1.2	0.027
Gynecologic	5.7	7.5	6.4	2.8	15.4	1.4	0.01
Global	14.6	8.9	12.5	8.8	22.7	2.6	0.002
Grade 2–4 toxicity							
Urinary	13.1	7.9	20.4	13.3	23.1	13.7	0.03
Digestive	8.3	7.4	8.3	8.8	18.7	15.2	0.45
Gynecologic	18.7	12.9	17.9	14.7	35.7	19.4	0.125
Global	37.5	23.2	40.6	29.4	53.4	42.4	0.028

LRFS: local free relapse survival; RLRFS: loco regional relapse free survival; DFS: disease free survival; OS: Overall Survival.

* 2D-3D brachytherapy comparison: Cox proportional hazard model adjusted for regimens.

No significant difference in late actuarial grade 2–5 or grade 3–5 bladder or GI
Trend of higher actuarial grade 3–5 vaginal morbidity in the IC/IS group (p = 0.08)

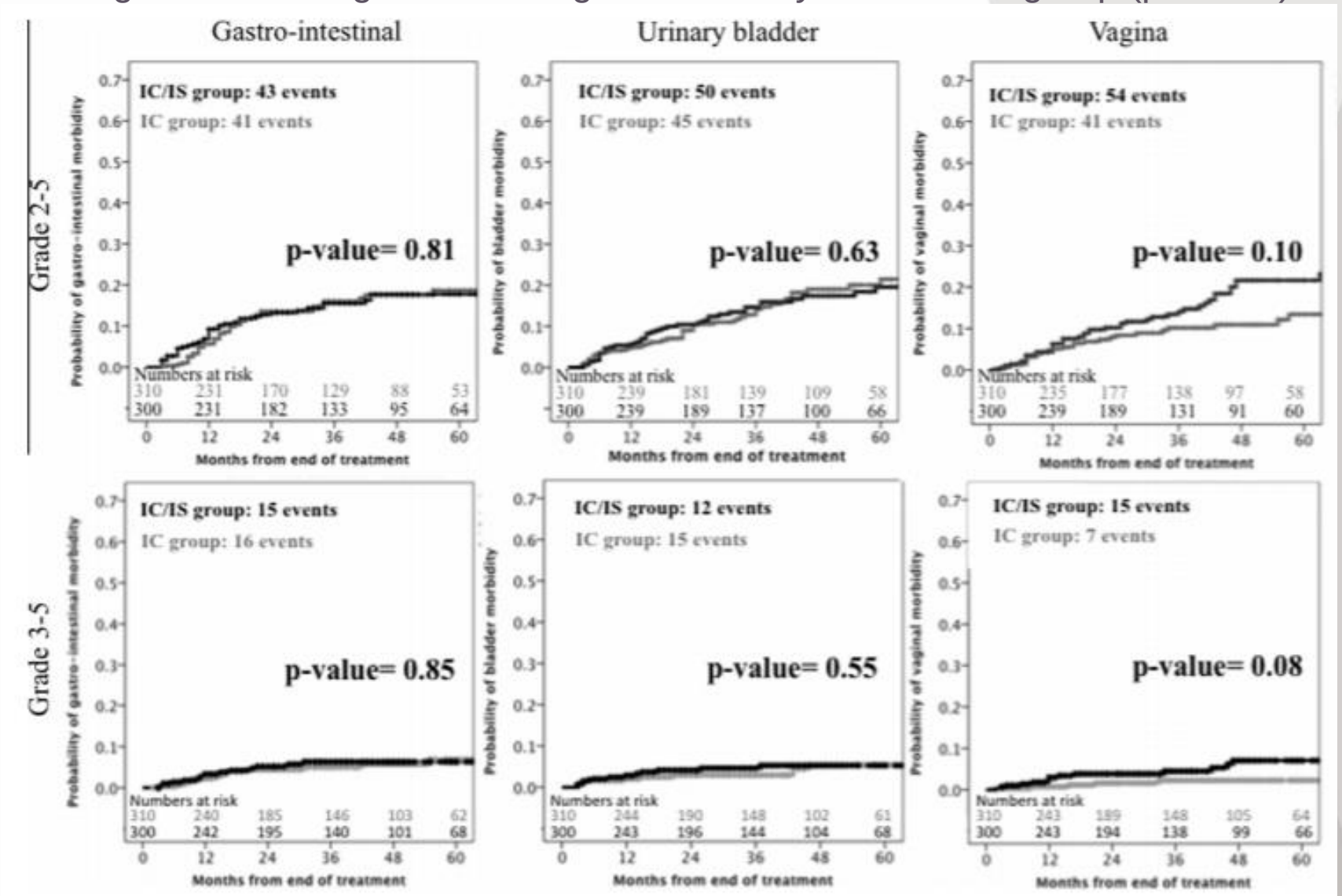


Fig. 3. Late morbidity in the intracavitary group in dark grey and combined intracavitary/interstitial group in black.

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]

960 patients Median FU : 25,4 months

Depiction of rectal morbidity.

	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
Grade2	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

N: number, %: percentage of the series.

Mazeron et al. Radiother Oncol 2016

Late rectal morbidity EMBRACE data

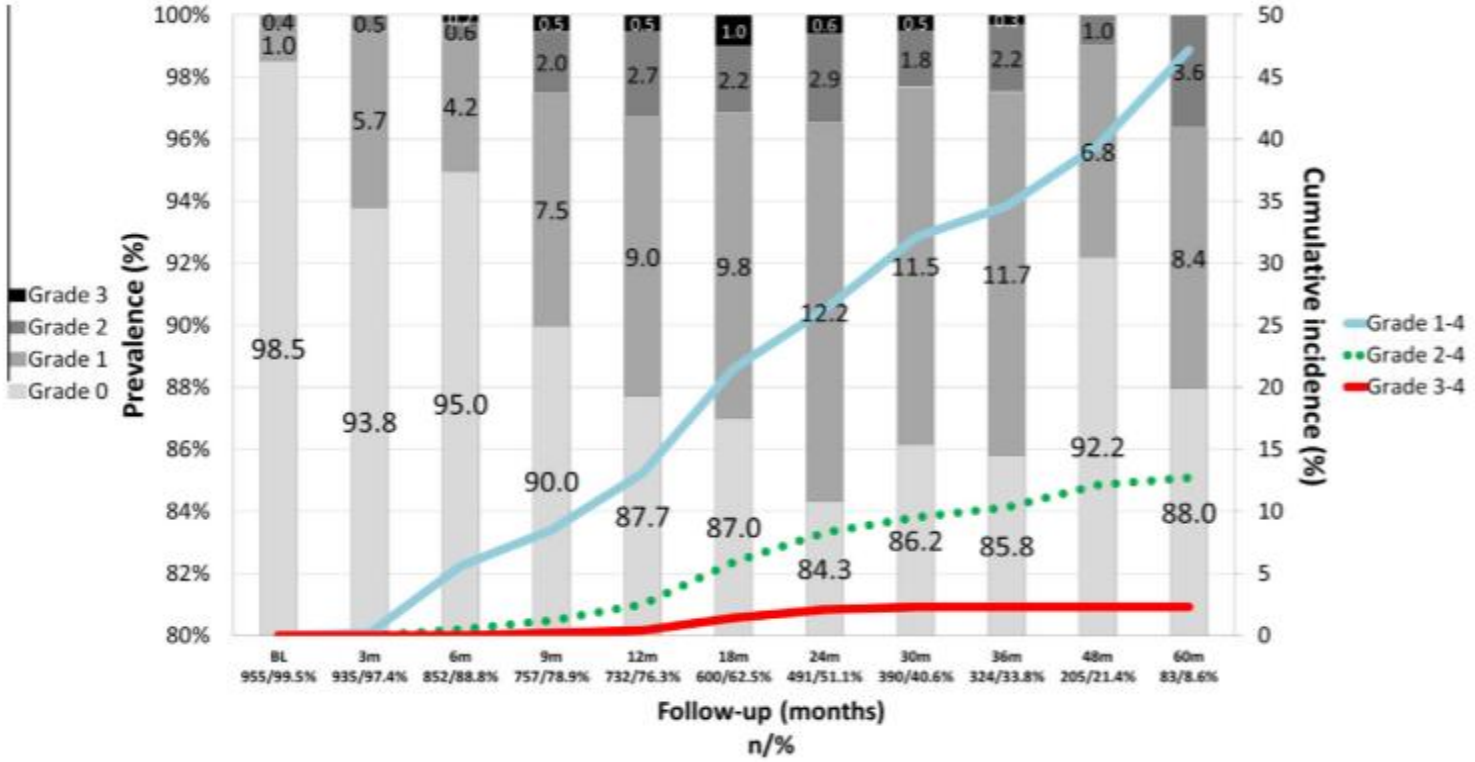
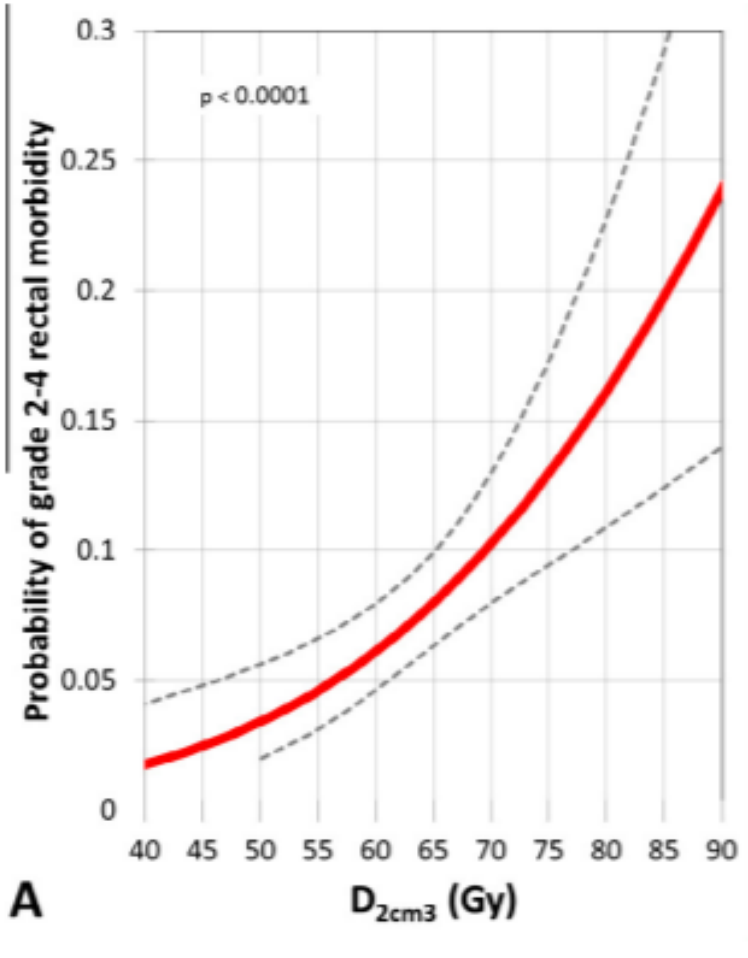


Fig. 1. Incidence and prevalence of rectal morbidity. BL: baseline. m: months. Prevalence is represented using histograms, with legends on the left, and incidence using curves, legends on the right. Prevalence rates according to grade and time are presented on the histograms.

Mazeron et al. Radiother Oncol 2016

Actuarial estimate evaluation of overall rectal morbidity at 3 years
D2cm3 ≥75Gy risk of 30% of grade 2–4
D2cm3 ≤65 Gy risk of <10% of grade 2-4



Mazeron et al. Radiother Oncol 2016

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]

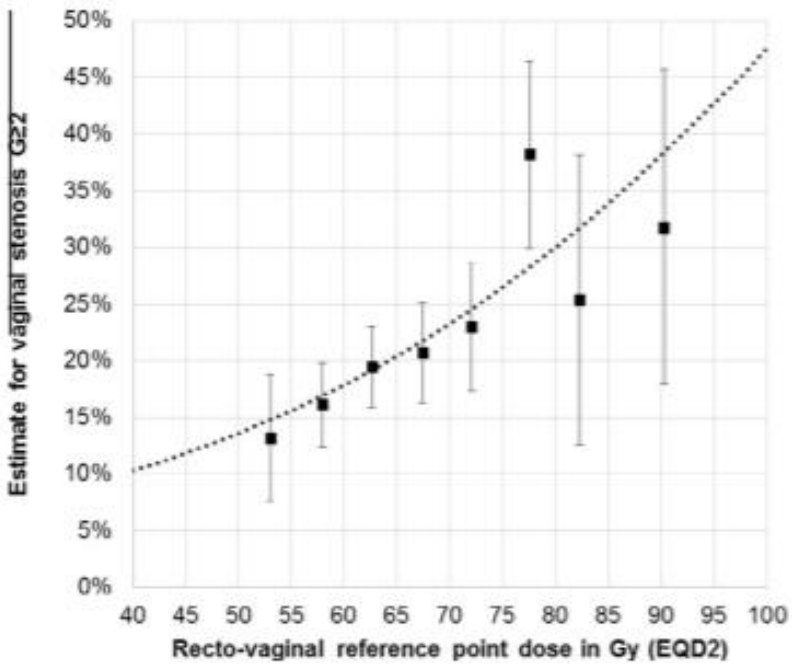


Fig. 4. Dose–effect relationship of the combined EBRT and brachytherapy dose to recto-vaginal reference point in EQD2 and vaginal stenosis $G \geqslant 2$ in $N = 630$ patients.

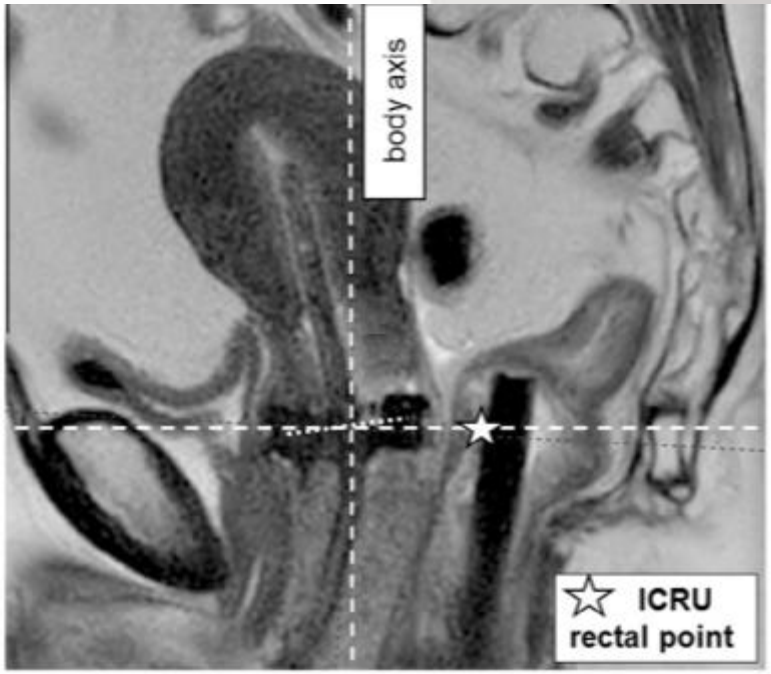


Fig. 1. ICRU rectal point depicted on sagittal T2 MRI, positioned at the intersection level between tandem and the source positions in the ring and 5 mm dorsal of the posterior vaginal wall on the axis perpendicular to the body axis.

Kircheiner et al. Radiother Oncol 2016

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]

Recommendations:

- ERT dose not exceeding 45Gy
- Planning aim ≤65 Gy EQD2 ICRU recto-vaginal point

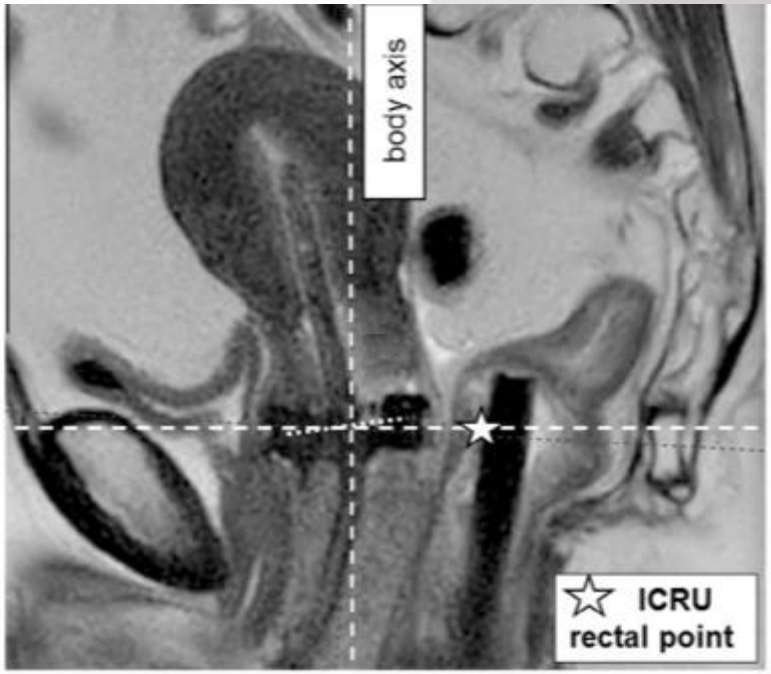


Fig. 1. ICRU rectal point depicted on sagittal T2 MRI, positioned at the intersection level between tandem and the source positions in the ring and 5 mm dorsal of the posterior vaginal wall on the axis perpendicular to the body axis.

Kircheiner et al. Radiother Oncol 2016

Summary

90% LC probability D90 (EQD2) to HR-CTV

92 Gy if volumes ≥ 30 cm3

OTT < 50 days

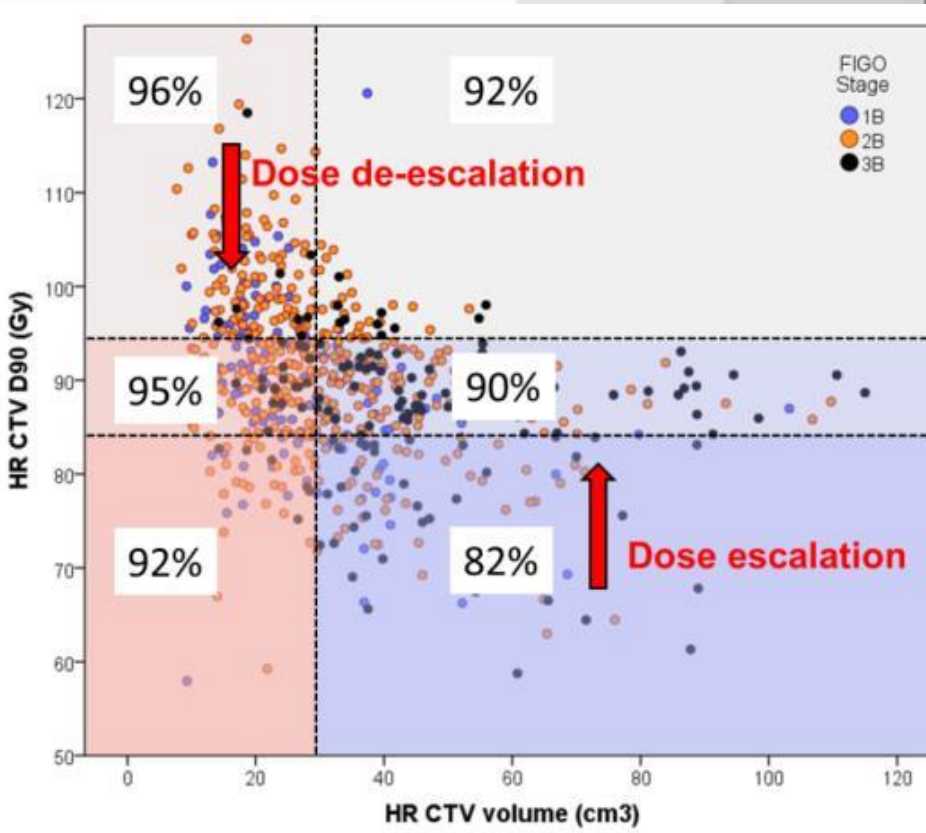
D2 cm3 (EQD2)
<80 Gy for the bladder
<65 Gy for the rectum

ICRU recto-vaginal point ≤65 Gy

ERT dose = 45 Gy

Future research

- Dose escalation for advanced disease in HR CTV
- Dose de-escalation for limited and favourable advanced disease (good response,…)
- Testing Dose/Volume constraints and morbidity/QoL
- Concomitant ERT-CT and adjuvant chemotherapy for subgroups with high risk of distant metastases
- Biomarker investigation (Hypoxia, HPV, EGFR, VEGF..)



1st AROI - ESTRO GYN Teaching Course

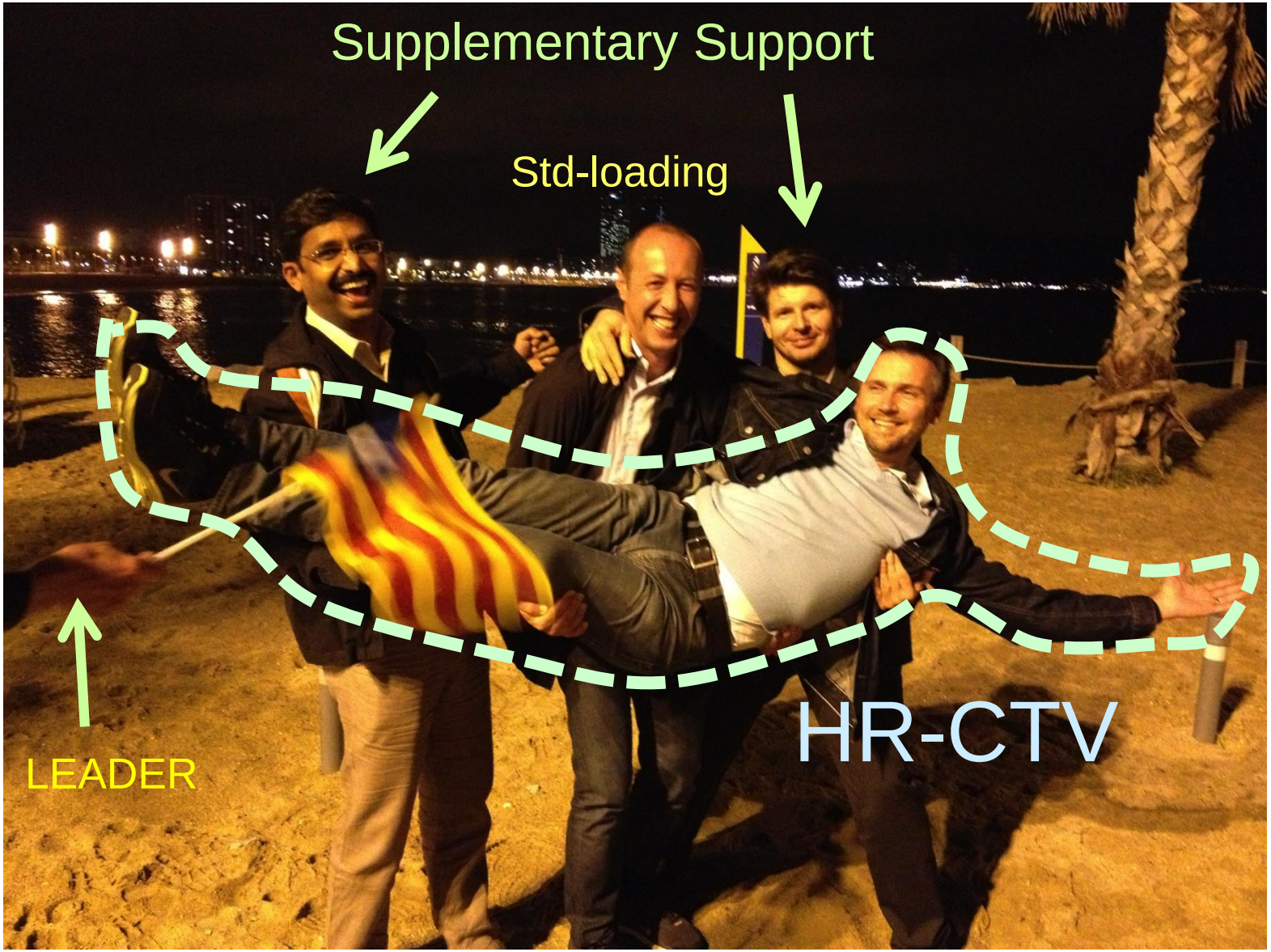
Transition from "Conventional 2D to 3D Radiotherapy" with a special emphasis on "Brachytherapy in Cervical Cancers"

ESTRO School

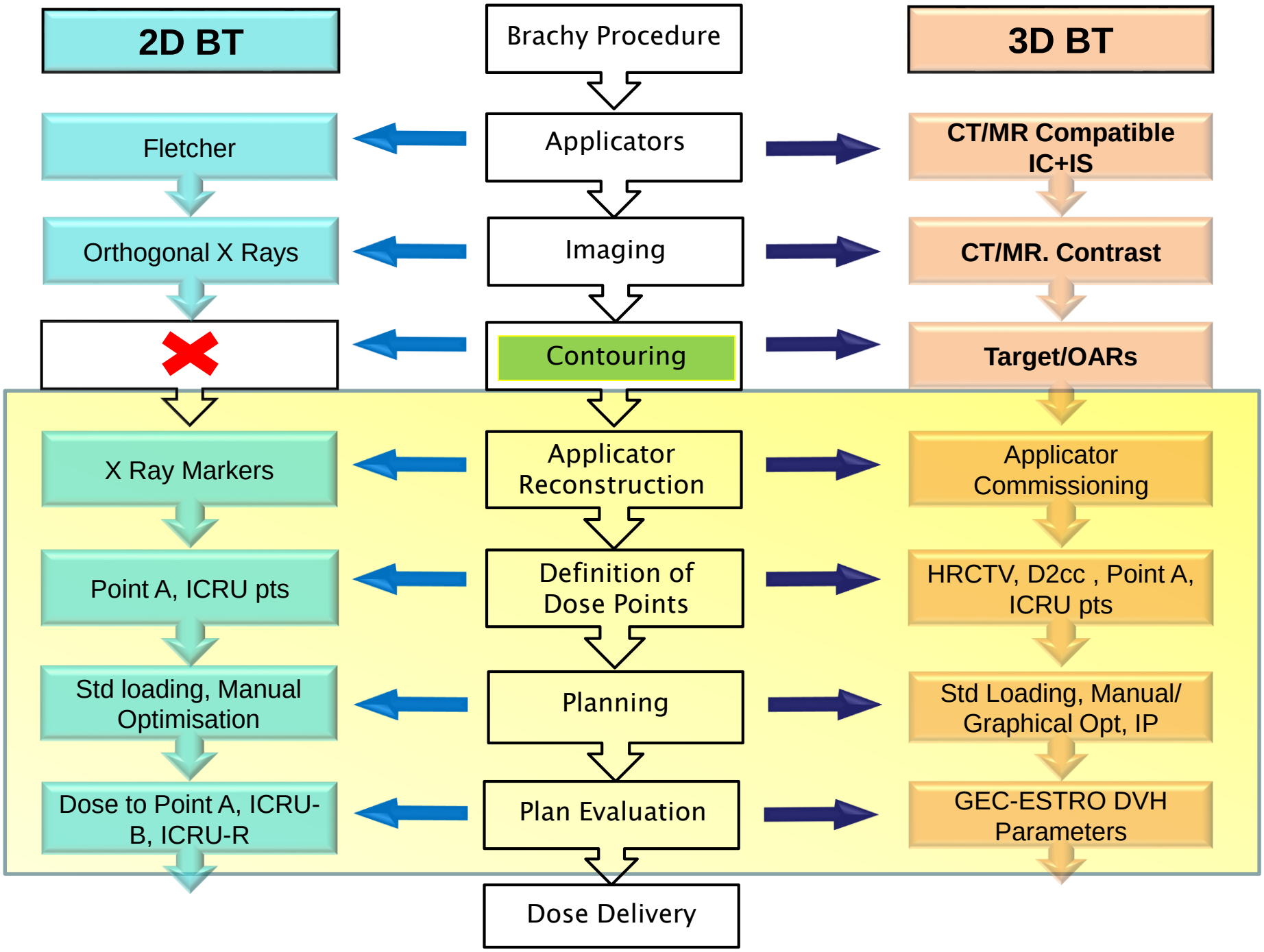
Tips and Tricks

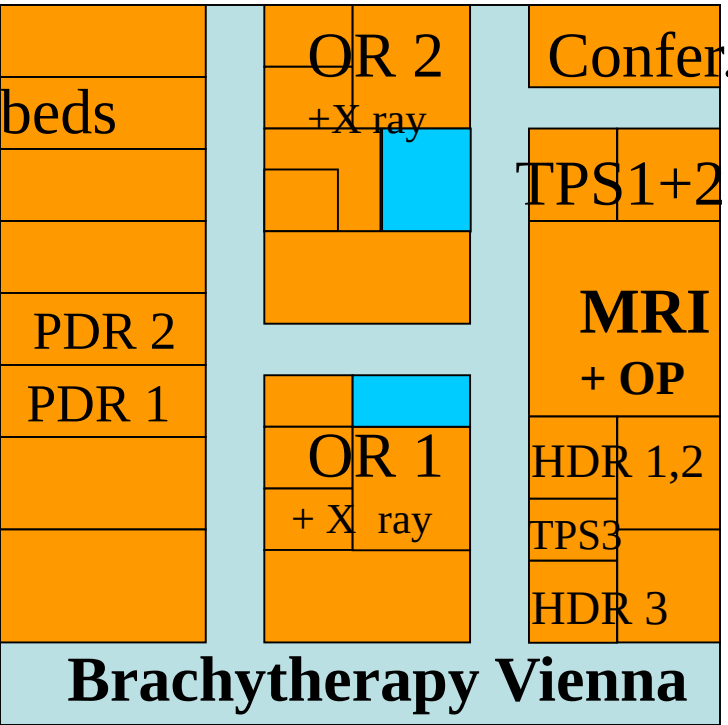
U. Mahantshetty, D Berger and R Pötter

Team work at TC Barcelona 2013



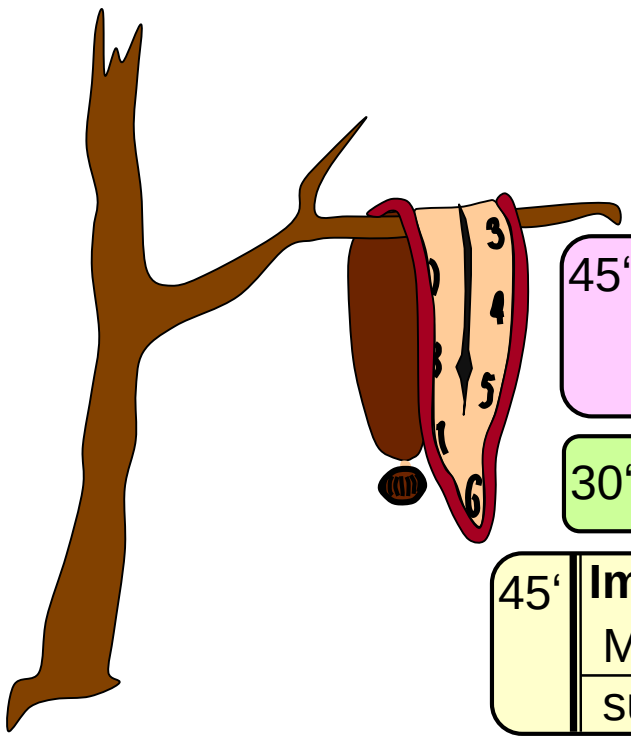
With permission


2D BT
Brachy Procedure
3D BT
Fletcher
Applicators
CT/MR Compatible IC+IS
Orthogonal X Rays
Imaging
CT/MR. Contrast
Contouring
Target/OARs
X Ray Markers
Applicator Reconstruction
Applicator Commissioning
Point A, ICRU pts
Definition of Dose Points
HRCTV, D2cc , Point A, ICRU pts
Std loading, Manual Optimisation
Planning
Std Loading, Manual/ Graphical Opt, IP
Dose to Point A, ICRU-B, ICRU-R
Plan Evaluation
GEC-ESTRO DVH Parameters
Dose Delivery



Costs for open MRI: ~500.000 €

Working Schedule Brachytherapy of Cervix Cancer

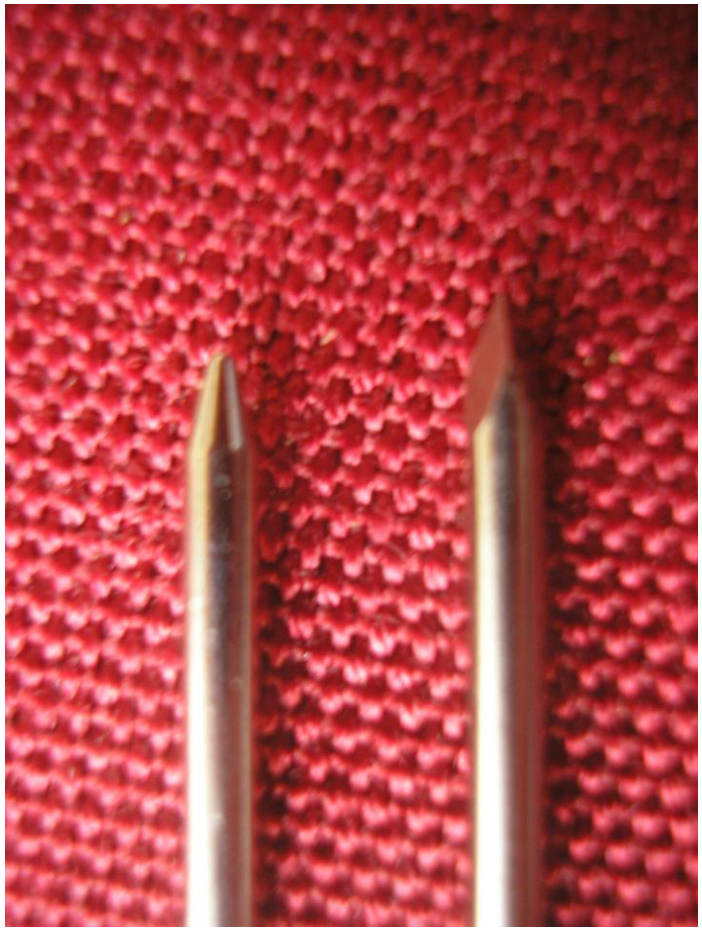


15‘	**Preparation** Patient med.tech. Documents DVH pre-planning	 Surgical-nurse /Physician Technician Physician and Physicist
45‘	**Anaesthesia** Spinal/Epidural or General	 Anaesthetist / Anaesthesia-nurse
30‘	**Application**	Physician / surgical-nurse
45‘	**Imaging** MR / CT supervision + discussion	 Technician Physician and Physicist
30‘	**Contouring** Organs at Risk Target Volume	 Technician / Physician Physician
45‘	**Treatment Planning** Reconstruction / Constraints Discussion and Validation	 Technician / Physicist Physicist and Physician
15‘	**Radiation Treatment**	Technician

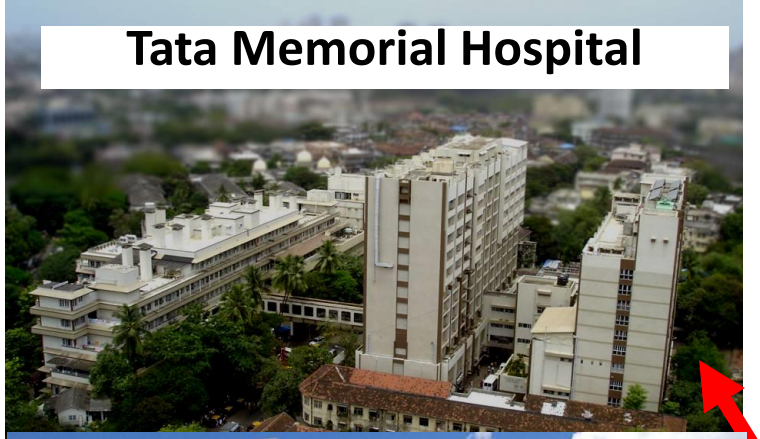
Total Time 3h 45min

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

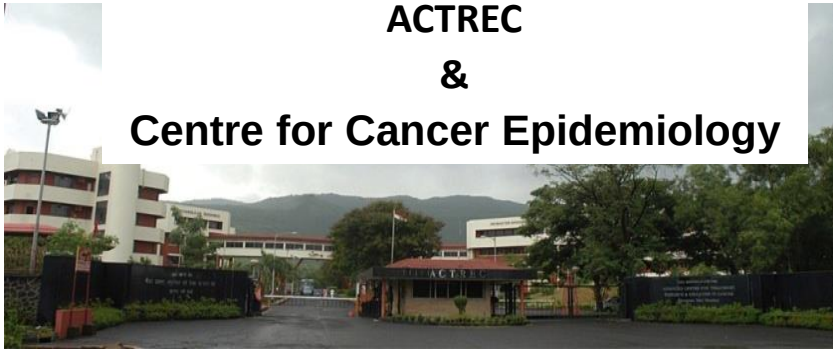


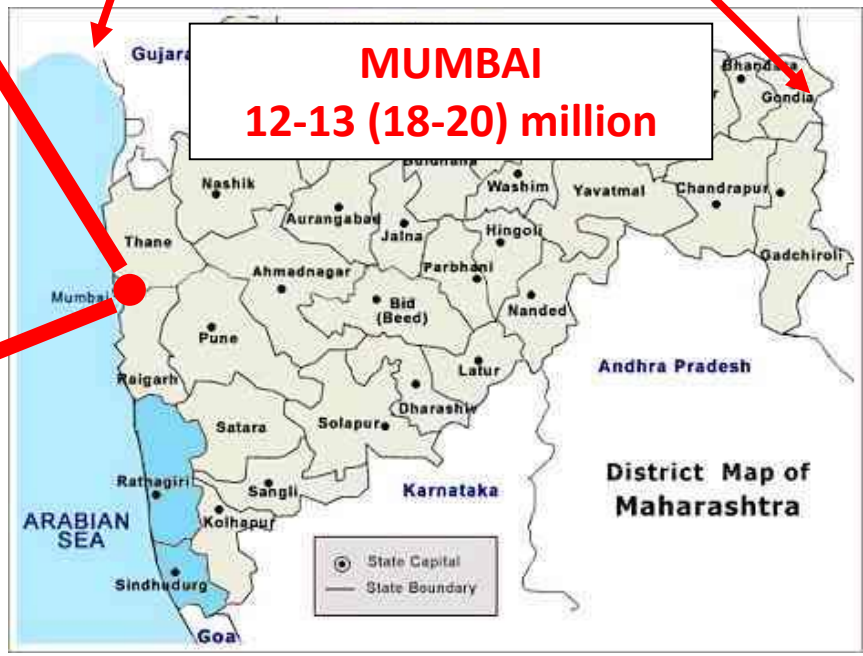
Tata Memorial Hospital



MISSION
Service
Research
Education

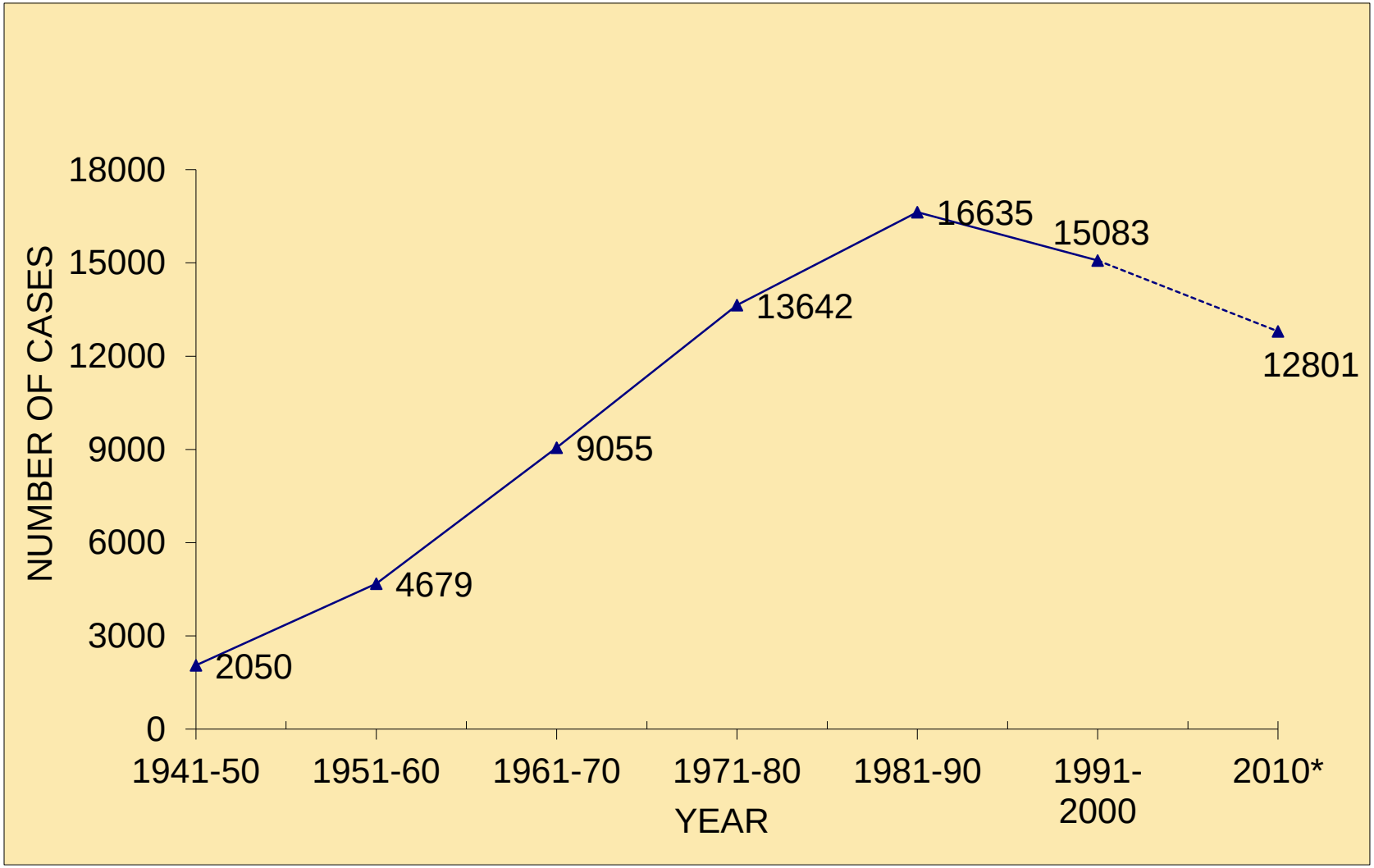
ACTREC
&
Centre for Cancer Epidemiology

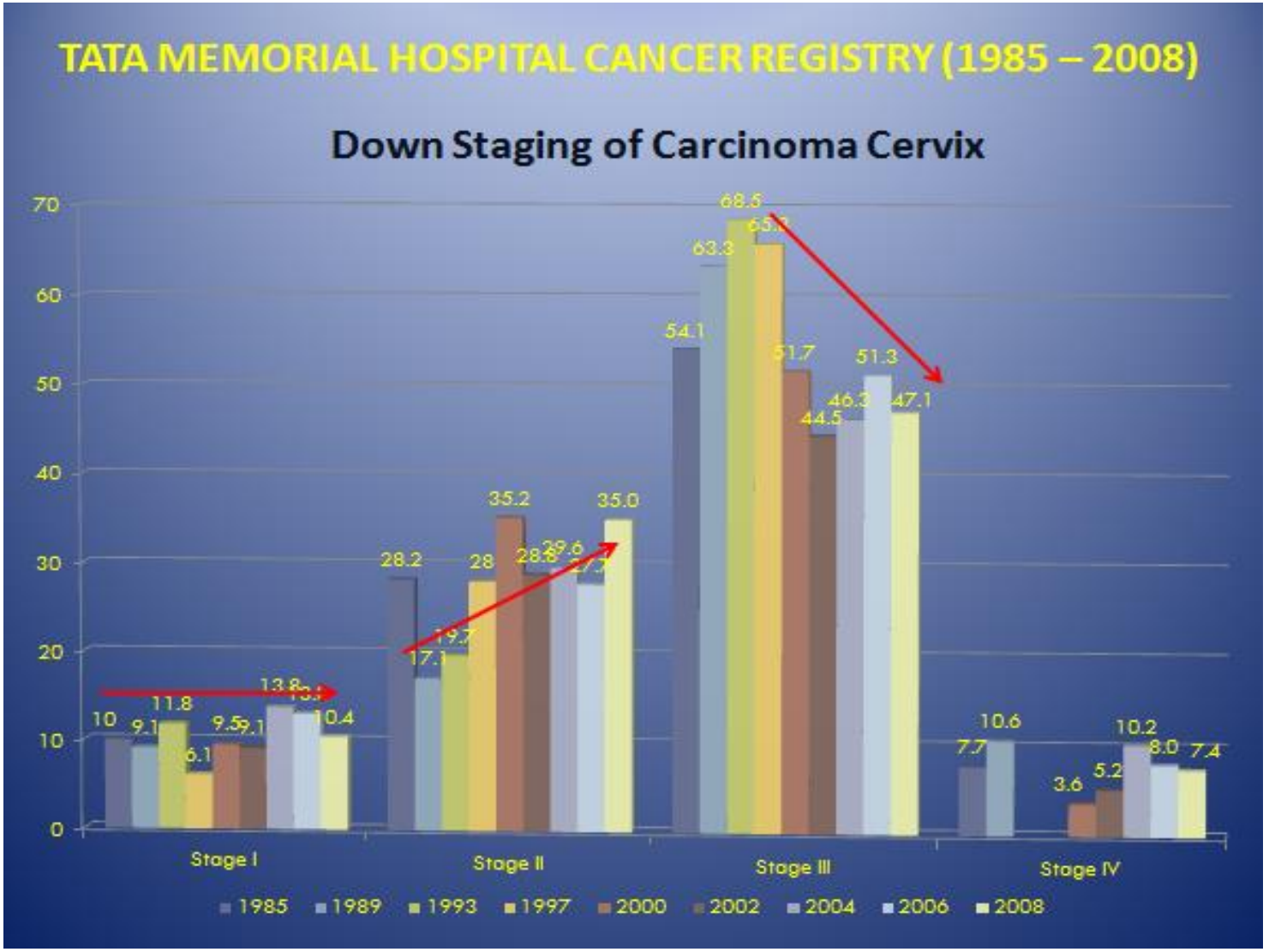




DOWN THE DECADES

CANCER CERVIX : TATA MEMORIAL HOSPITAL 1941-2010





- Routine Practice: Radical Rx : 550 – 600 patients annually
  - Average 6 (4 - 10) Cx brachy per day + 1-2 Interstitial /wk
  - 3-4 X-ray; 2-3 CT; 1 MR Based Planning
  - All procedures done under general anesthesia

Retrospective and feasibility study : Dec 2006 - May 2008 (N = 24)

Conventional Treatment Planning

Prescription to Point 'A'

MR Protocol Standardization and Understand the Volume Concepts

Retrospective contouring and evaluation of DVH parameters

International Journal of Gynecological Cancer:
August 2011 - Volume 21 - Issue 6 - pp 1110-1116
doi: 10.1097/IGC.0b013e31821caa55
Radiation Therapy

Reporting and Validation of Gynaecological Groupe Euopeen de Curietherapie European Society for Therapeutic Radiology and Oncology (ESTRO) Brachytherapy Recommendations for MR Image-Based Dose Volume Parameters and Clinical Outcome With High Dose-Rate Brachytherapy in Cervical Cancers: A Single-Institution Initial Experience

Mahantshetty, Umesh MD, DNBR, DMRT*; Swamidas, Jamema MSc, DRP*; Khanna, Nehal MD*; Engineer, Reena DNBR*; Merchant, Nikhil H. MD†; Deshpande, Deepak D. DRP, PhD*; Shrivastava, Shyamkishore MD, DNBR*

	Vienna IC IJROBP2005	Vienna IC/IS IJROBP2005	Brabandere RO 2008	Lindegaard IJROBP2008	Chargari IJROBP 2008	TMH study IJGC 2011
HRCTV						
Vol in cc	34 +/- 17	44 +/- 27	48+/-19	34+/- 12	36.3±35	**45.2 ± 15.8**
D100	66 +/- 7	70 +/- 6	64+/-6	76 +/- 7	61.66±7	**53.9 ± 6.5**
D90	87 +/-10	96 +/- 12	79+/-7	91 +/- 10	74.85±10	**70.3 ± 10.6**
Avg. Pt A	89 +/- 8	93 +/- 9	79+/-5	92 +/- 9	71.4±6	**73.4 ± 4.5**
Bladder						
Vol in cc	--	--		--		**80.3 (20.3-235)**
ICRU Bmax	75 +/-16	73 +/- 19	74+/-15	67 +/- 31	63.7±9	**80.4 ± 34.4**
D0.1cc						**136.0 ± 54.7**
D2cc						**91.4 ± 24.6**
Rectum						
Vol cc						**33.4 (11-64.6)**
ICRU Rmax						**63.5 ± 8.1**
D0.1cc						**67.2 ± 9.9**
D2cc						**57.9 ± 7.7**
Sigmoid						
Vol cc	--	--		--		**49.0 (14.5-97.5)**
D0.1cc	79 +/- 12	84 +/- 14	82+/-13	79 +/- 13	72.7±18	**101.9 ± 45.2**
D2cc	63 +/- 7	67 +/- 7	68+/-7	69 +/- 9	60.6±6	**74.4 ± 19.6**

LESSONS LEARNT

Retrospective Data: 24 patients

Tumor Volumes larger: Advanced Stages

Bladder and Sigmoid Doses Higher

Mahantshetty et al, IJGC Aug. 2011

CLINICAL OUTCOME

TMH Retrospective Data (Dec 2006 - May 2008) (N = 24)

Median Follow-up : 18 (12 - 40) months

	Stage			
	I B2 / IIA N=2	IIB N=10	IIIB N=12	Total N=24
Local	--	2*	1#	3
Pelvic Node	--	--	1	1
Dist. metastasis	--		1	1
Total	--	2	3	5

*** Point A: 79 Gy and HR-CTV D90 doses : 56.5, 67 Gy;**

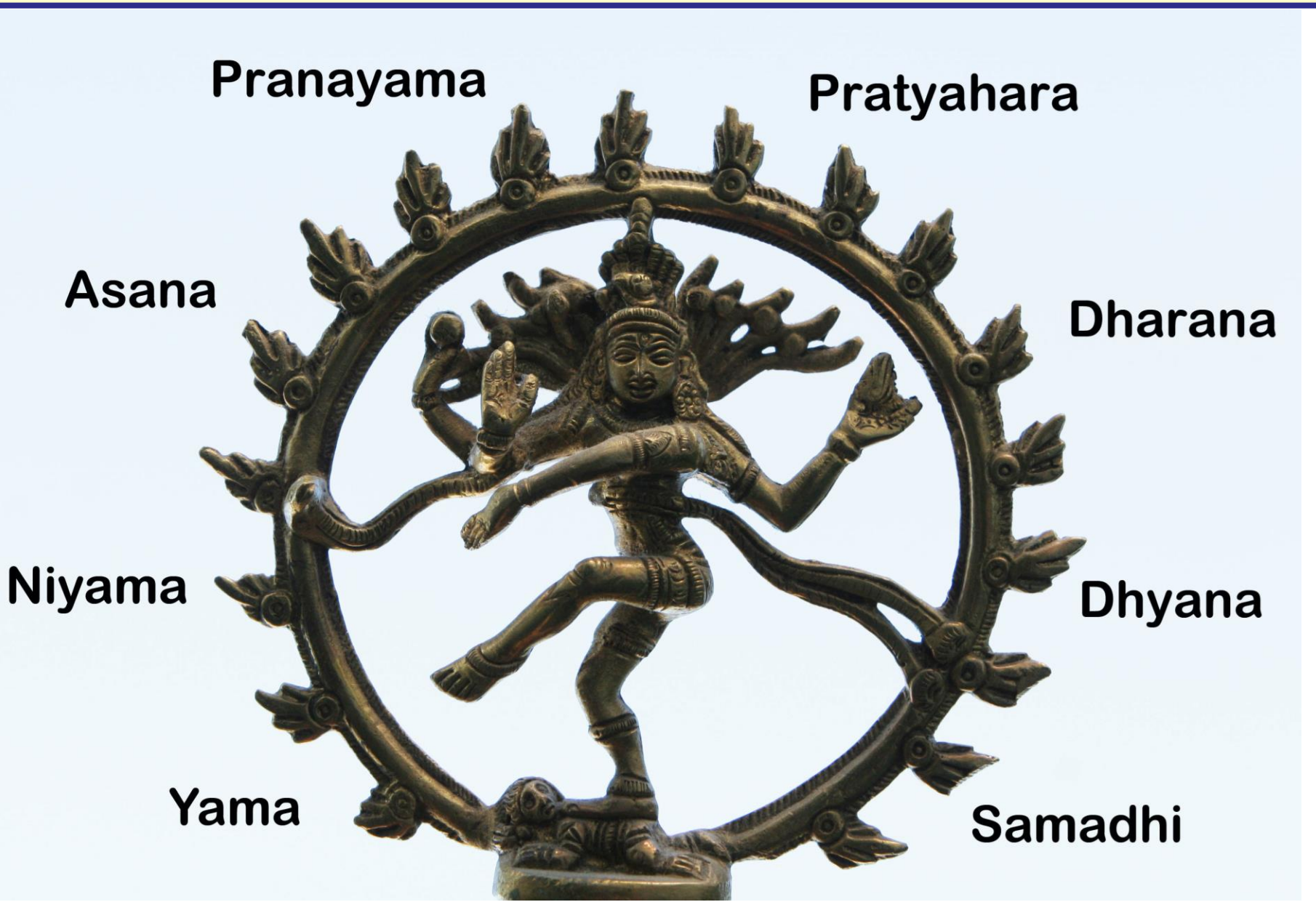
 # Point A: 70 Gy and HR-CTV D90 doses : 65Gy;

Late sequelae: 1 pt with protco-sigmoiditis

(0.1 and 2cc : R 46 & 64; S: 260 & 140 Gy)

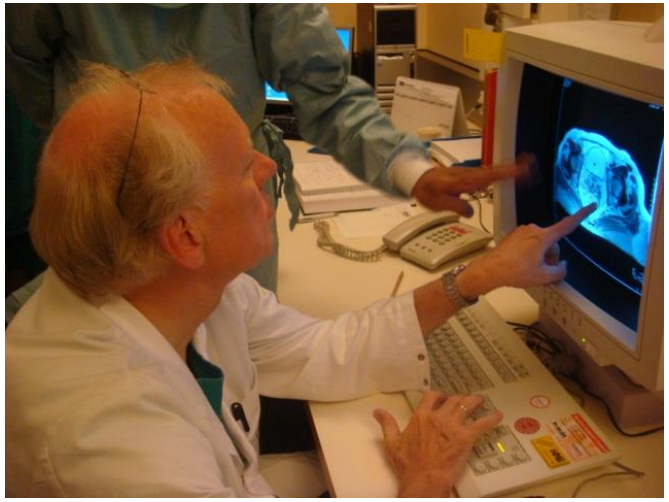
Mahantshetty et al, Clin. Oncol. 2011 ; IJGC Aug. 2011

TMH - AKH Collaboration: 2008-2009
Bilateral Exchange Program



TMH - AKH Vienna Collaboration: 2008 – 2009

Bilateral Exchange Program



Tata Memorial Hospital Participation in International Multicentric Studies

- Refine treatment standards

- GYN GEC-ESTRO Research Network

A European study on MRI-guided brachytherapy
in locally advanced cervical cancer

EMBRACE

(ENDORSED BY GEC ESTRO)

2009 ONWARDS

TATA HOSPITAL CONTRIBUTION TO EMBRACE

100 patients (IIB-IVA)

TMH EMBRACE Data
Prospective MR Based Brachytherapy
Dec 2009 – March 2014
N = 100 patients

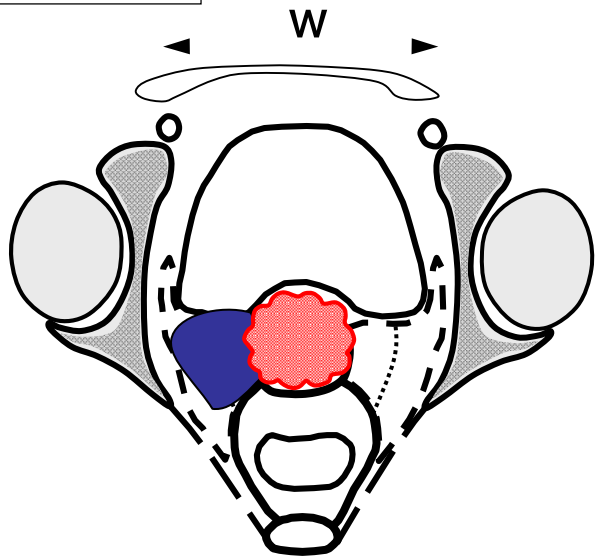
Total no of patients	**47/100 patients**
Median Age (range)	**51 ± 8 (28-65) years**
Histology	
Squamous Carcinoma	**40**
Adenocarcinoma	**05**
AdenoSquamous	**02**
FIGO Stage (n)	**47**
IIB	**18**
IIIB	**25**
IVA	**04**
Intracavitary Brachytherapy (HDR)	**4 fractions of 7 Gy to HRCTV**
Median follow-Up (Range)	**16 ± 8.3 (7-36) months**

w = 60 mm
h = 50 mm
t = 50 mm

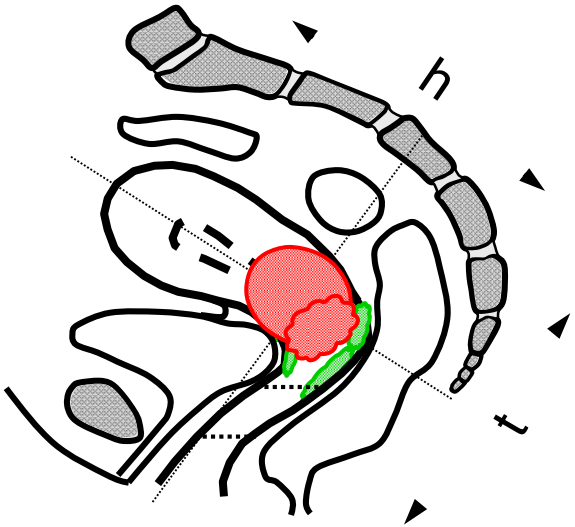
Vagina Involvement = 4 cm (Post)

A Clinical Example

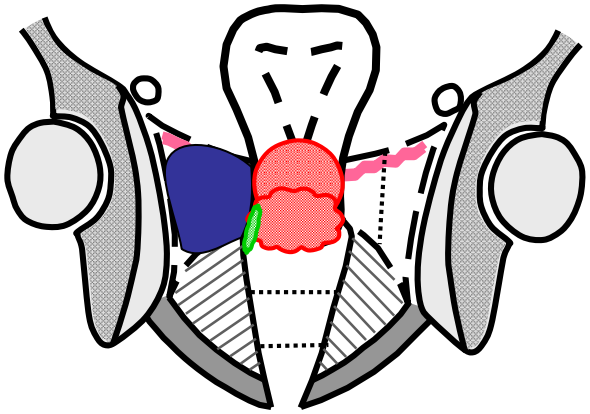
At Diagnosis



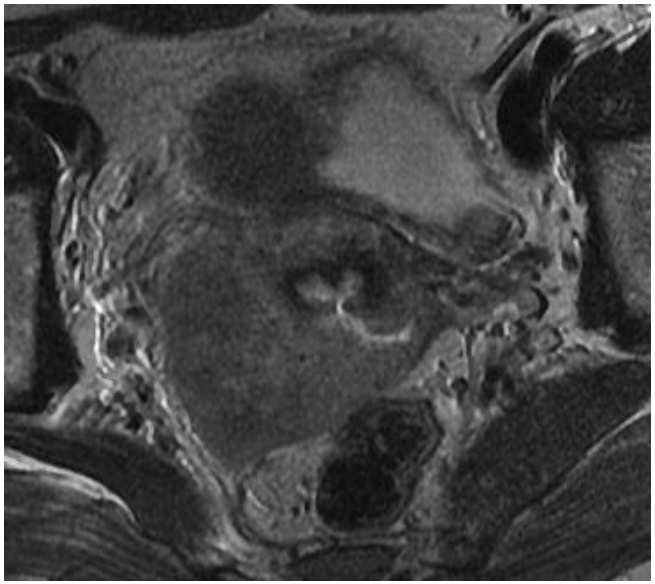
Axial

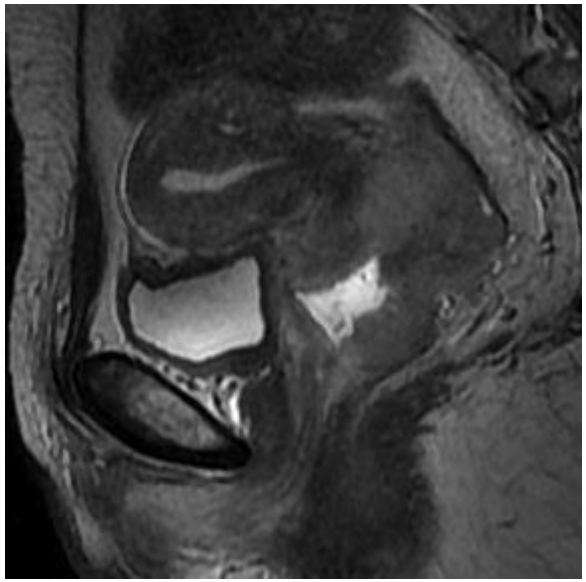


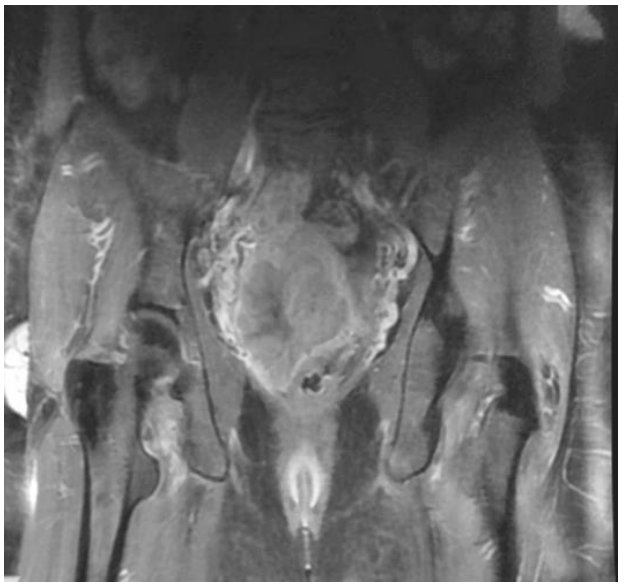
Sag



Coronal





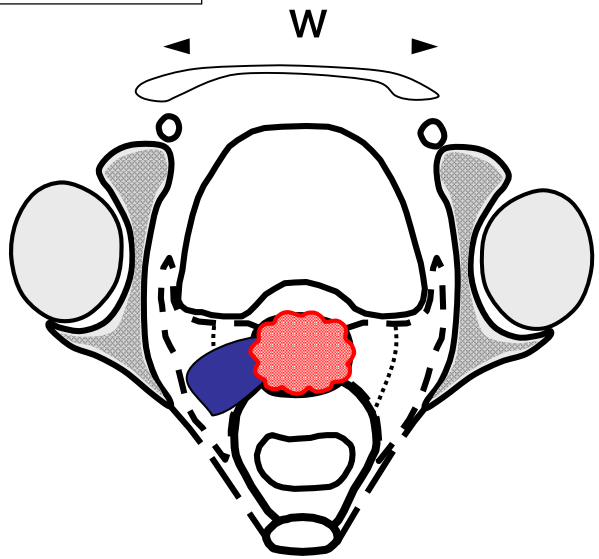


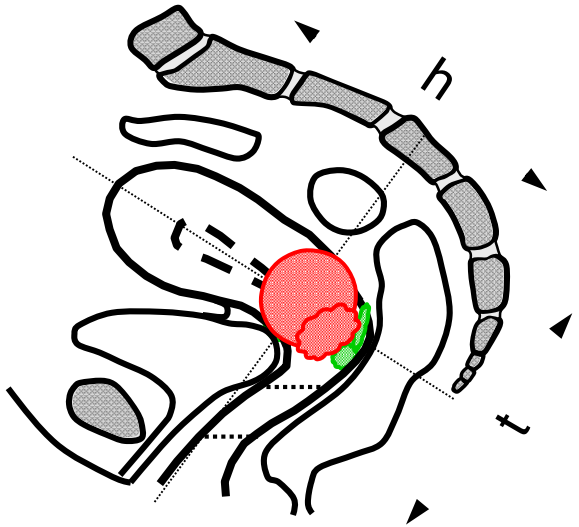
w = 60 mm
h = 40 mm
t = 30 mm

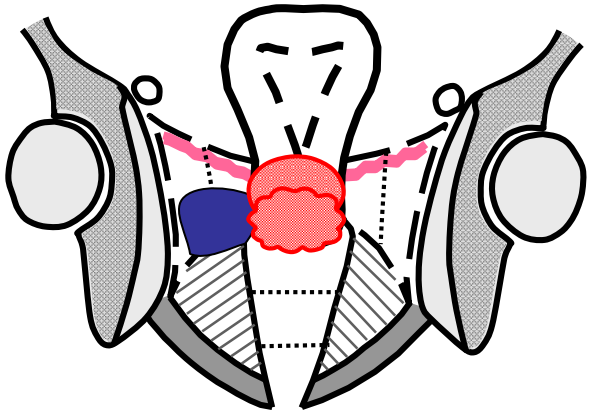
Vagina Involvement = 20mm (Post)

Clinical Drawing

At Brachytherapy



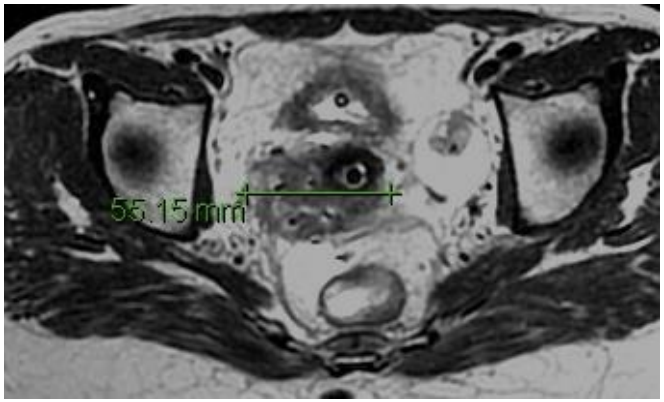


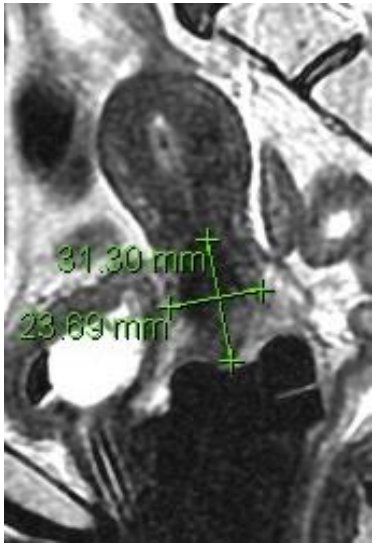


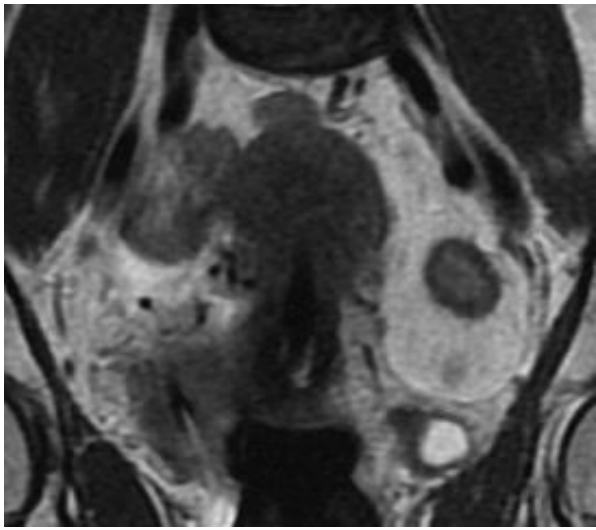
Axial

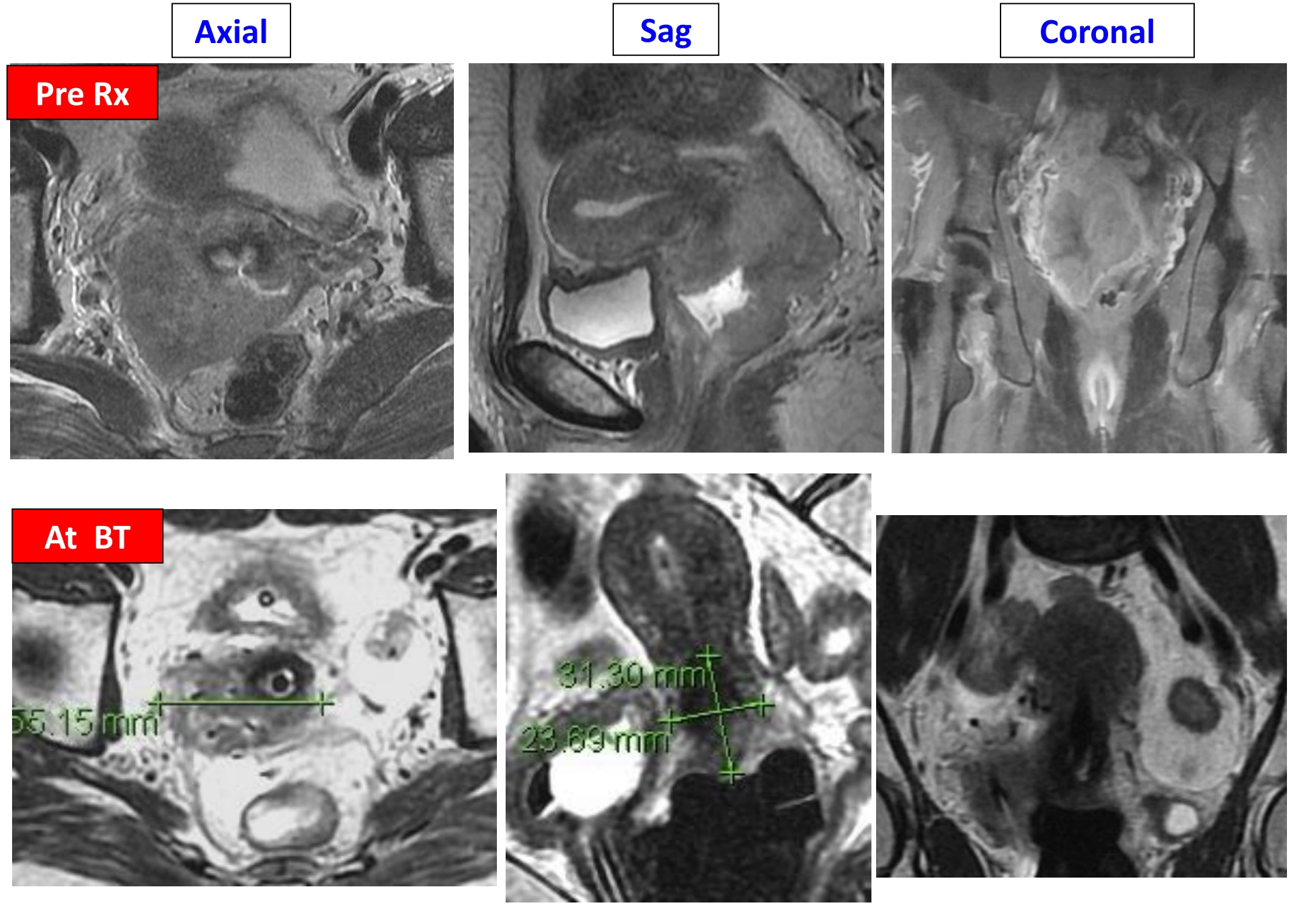
Sag

Coronal

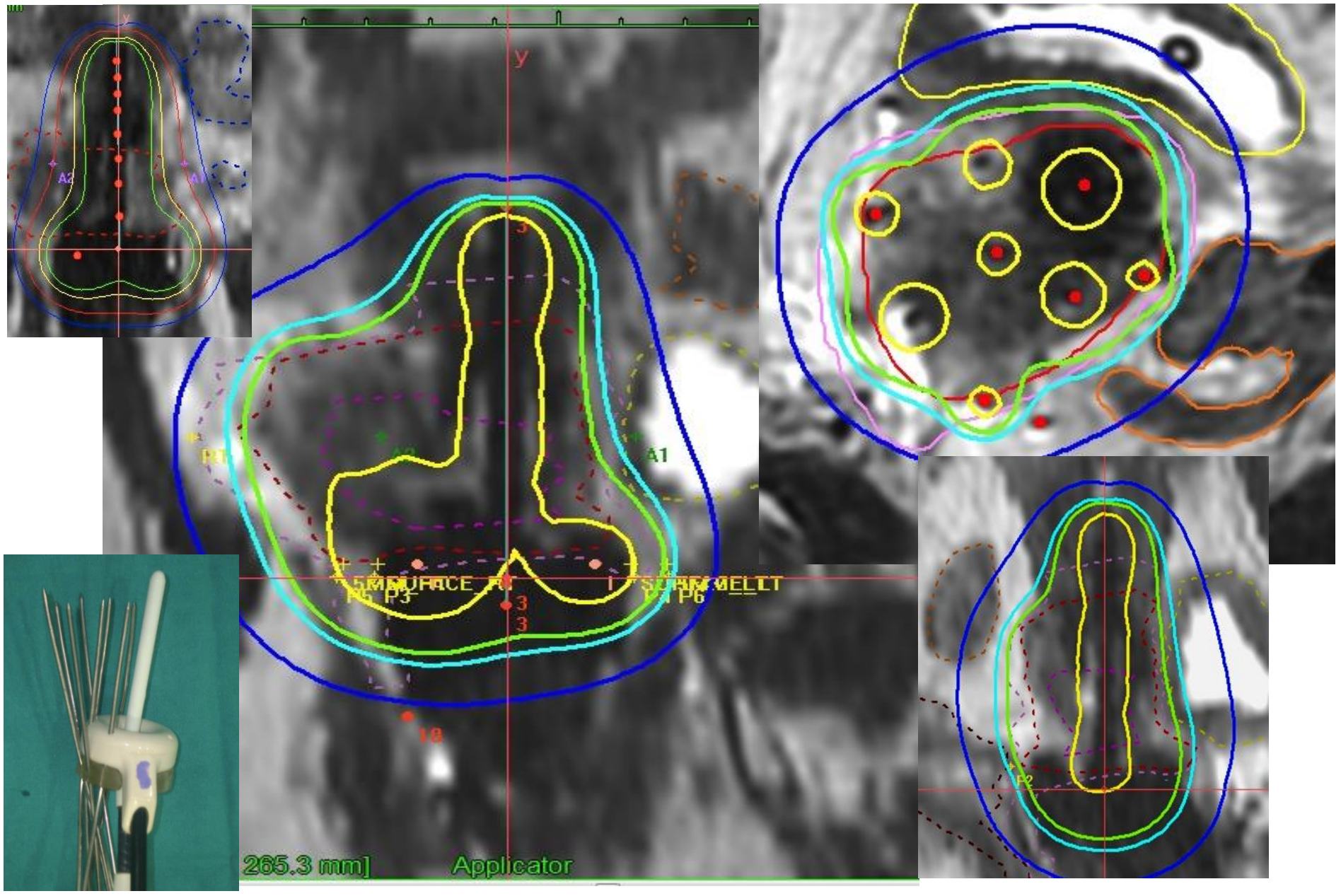







Axial
Sag
Coronal
Pre Rx
At BT
31.30 mm
23.69 mm

Treatment planning / optimization



Dosimetric Comparison (1# BT)

Parameters	Ring STD ICA Only	Vienna with one set of needles	Vienna (with additional needles)
HRCTV D90 (Gy)	4.38	6.2	8.3
HRCTV D98 (Gy)	3.45	4.5	7.0
SIGMOID 2CC	4.6	4.5	4.1
SIGMOID 0.1CC	6.1	5.8	5.2
BLADDER 2CC	7.9	6.5	5.5
BLADDER 0.1CC	10.2	8.5	6.5
RECTUM 2CC	3.9	3.8	4.2
RECTUM 0.1 CC	5.4	5.3	5.6

PLAN EVALUATION
External (45 Gy/ 25#) + HDR-BRT (7 Gy x 4#)

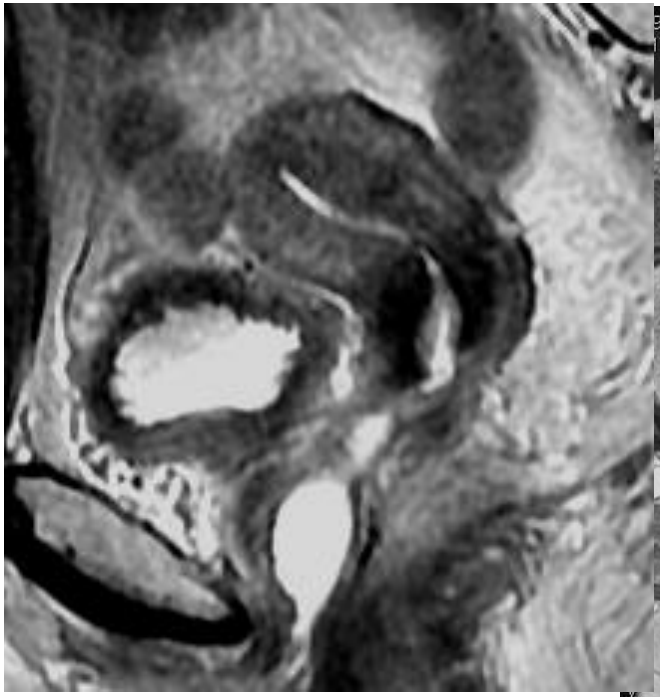
			Planning aim	**Prescribed dose**
CTV_{HR}	**D_{90}**	$EQD2_{10}$	≥ 85 Gy	96.2 Gy
Bladder	**D_{2cm^3}**	$EQD2_3$	≤ 90 Gy	82.9 Gy
Rectum	**D_{2cm^3}**	$EQD2_3$	≤ 70 Gy	68.3 Gy
Sigmoid	**D_{2cm^3}**	$EQD2_3$	≤ 70 Gy	67.4 Gy

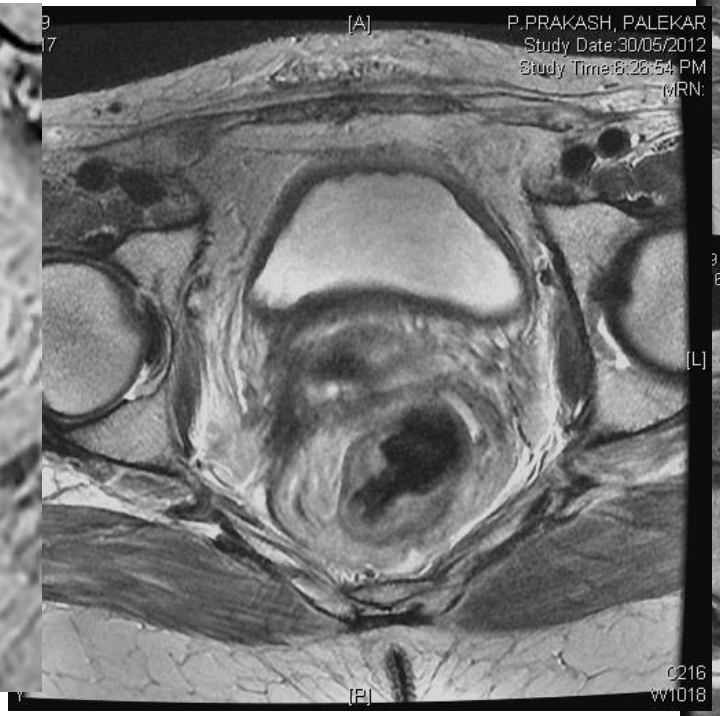
Patient ID: PP

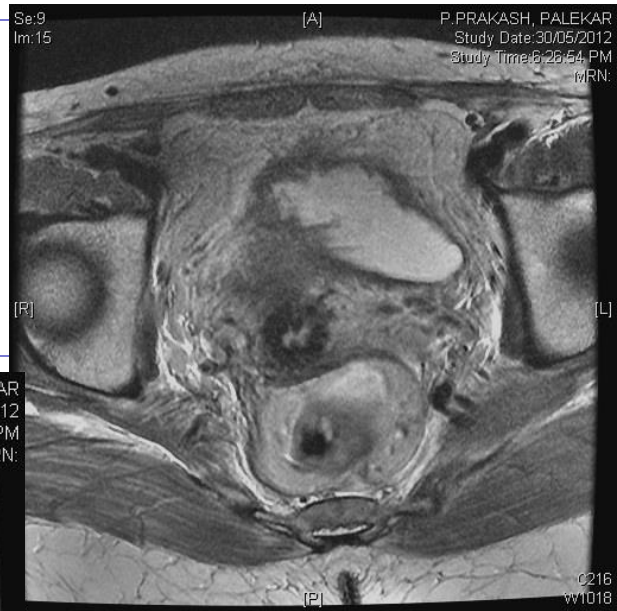
Post treatment 3months follow-up

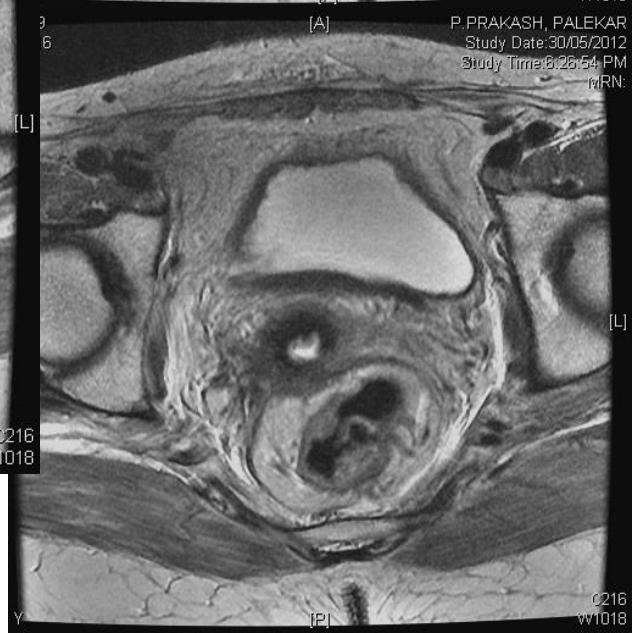
Clinical and MR findings

- **Portio:** Cervix flush with vagina;
- **Vagina:** Vaginal wall Normal
- **Parametria:** Right parametrium : fibrosed









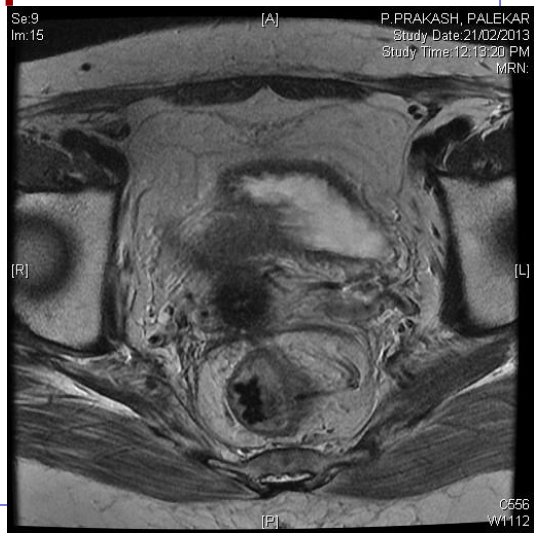
Clinico - Radiologically: Complete Response

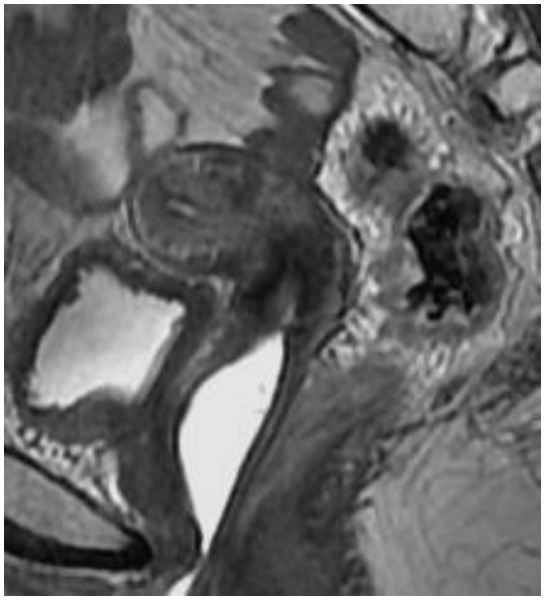
Patient ID: PP

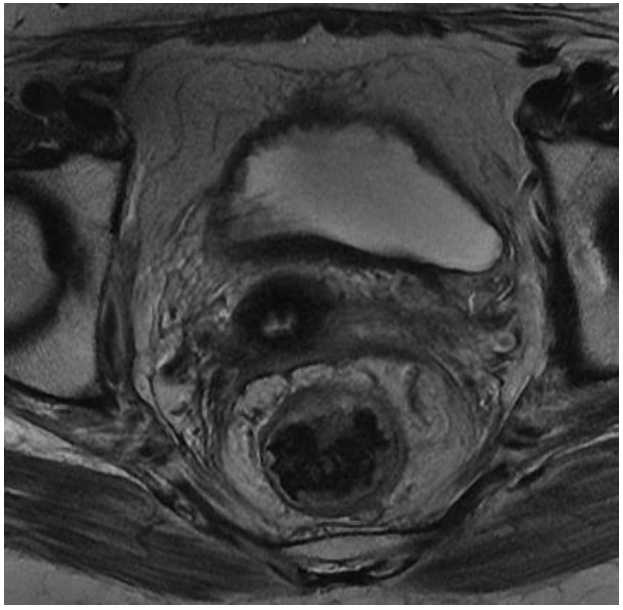
Post treatment 12 months follow-up

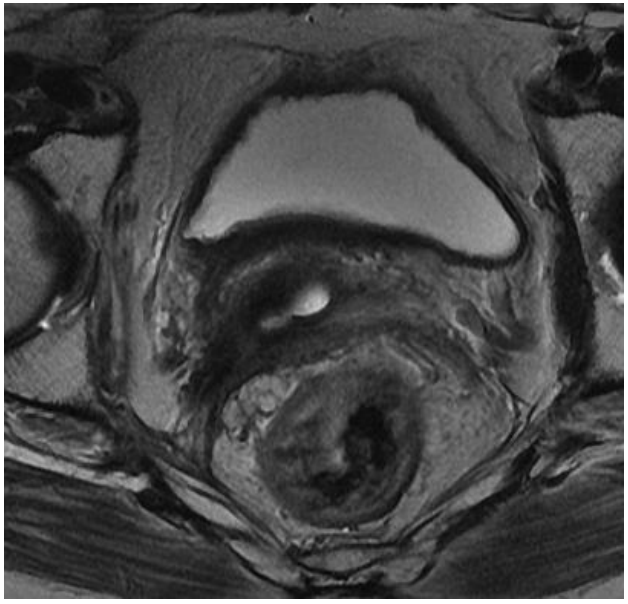
Clinical and MR findings

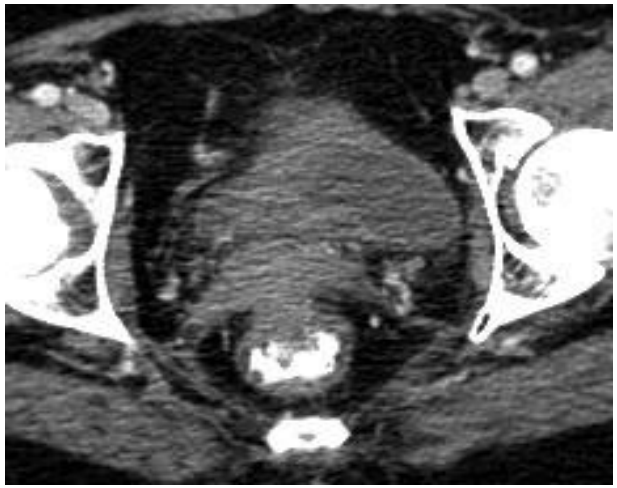
- **Portio:** Cervix flushed with vagina; No growth Palpable / seen
- **Vagina:** Normal
- **Parametria:** Rt para fibrosed ; Lt para supple
- **Sexual Activity :** Normal
- **CBC & renal function tests:** normal

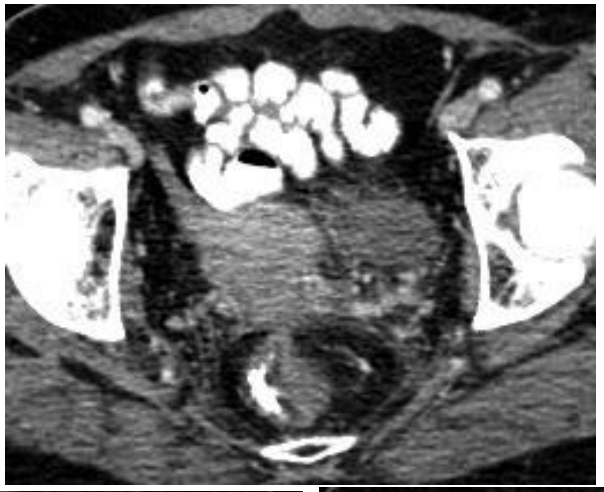






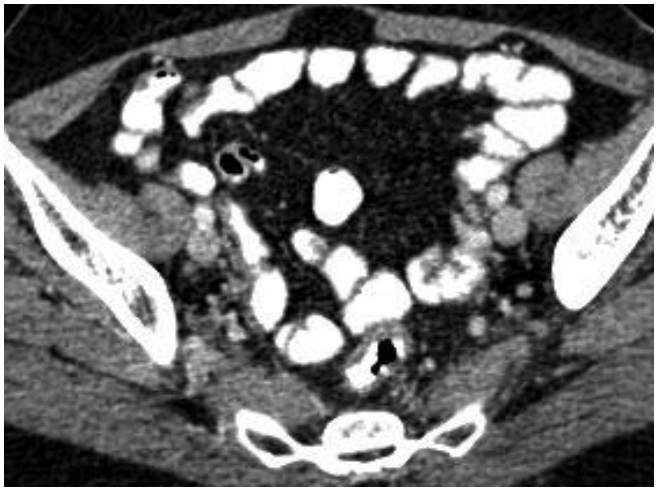


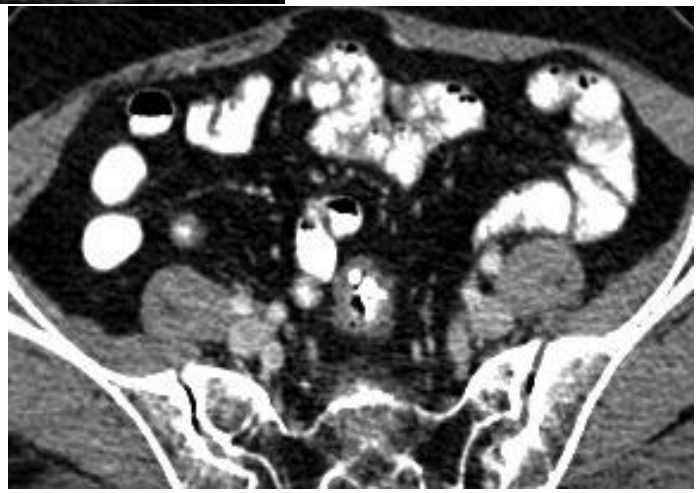


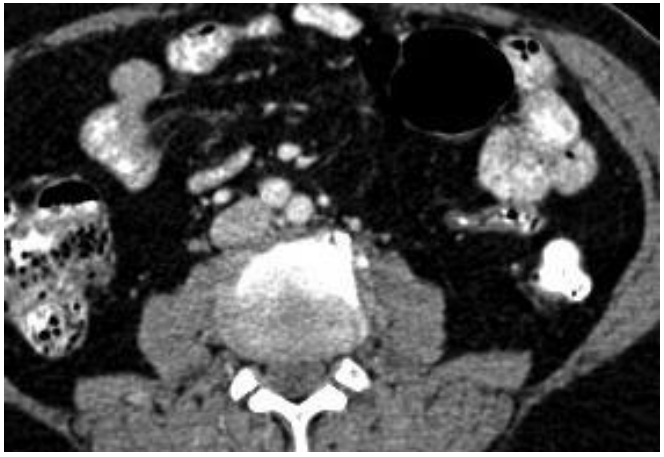


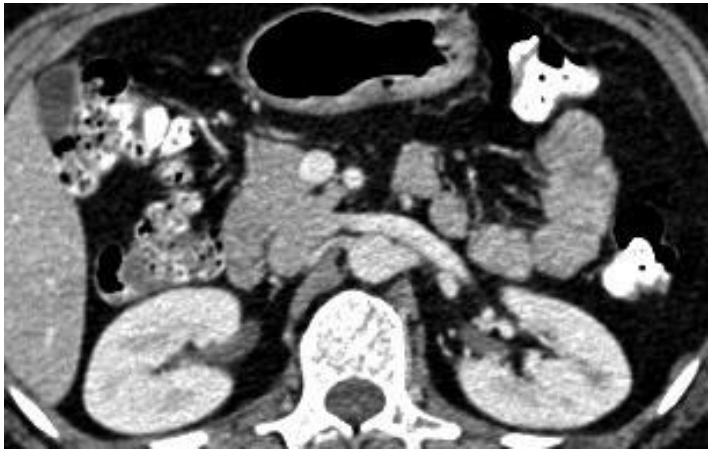
Post RT 36 months

follow-up CT Images

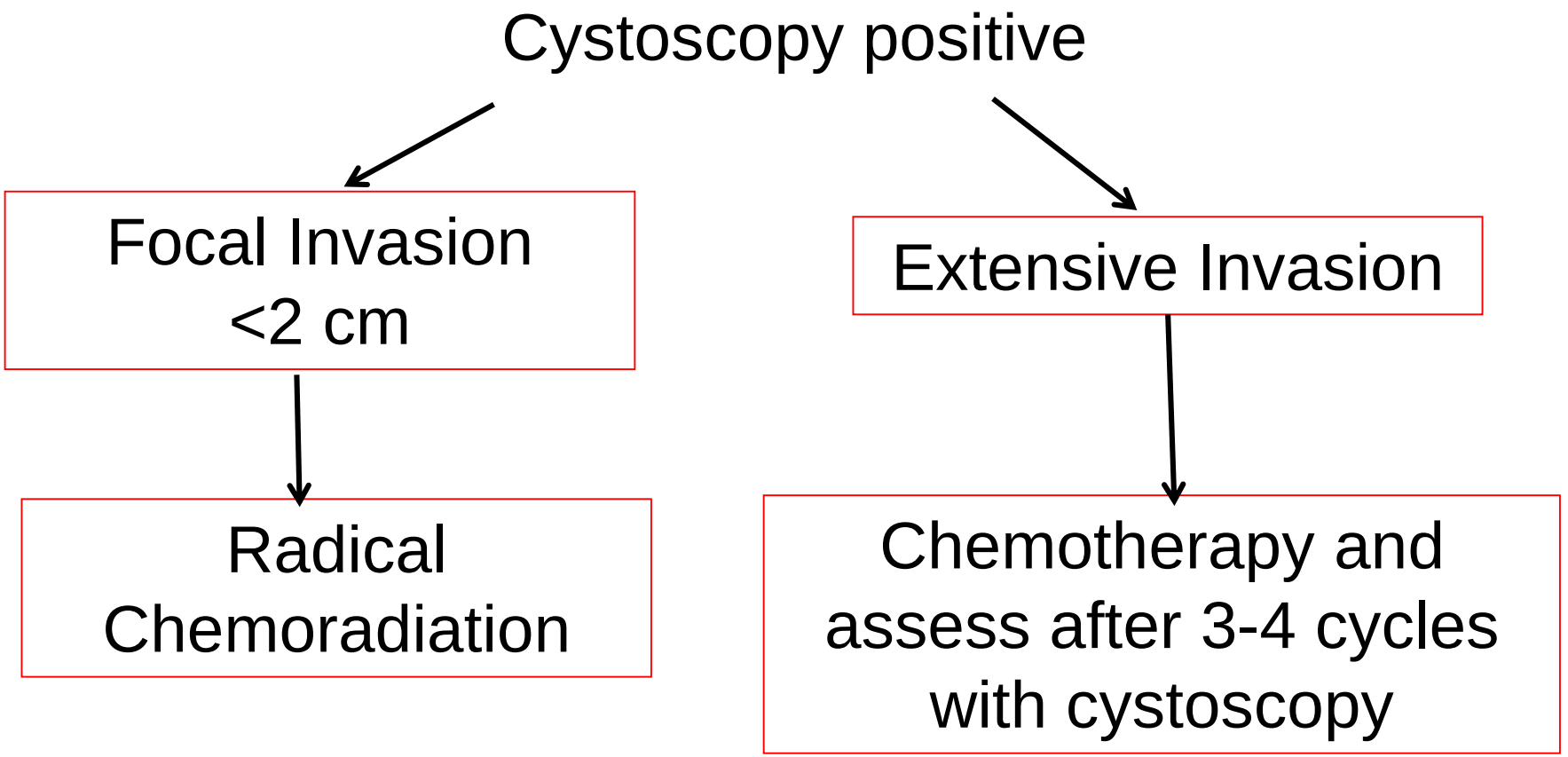








Cancer Cervix FIGO IV A (Bladder Mucosa Involved)
MRI and Cystoscopy shows bladder invasion at Diagnosis



Cancer Cervix FIGO IV A (Bladder Mucosa Involved)
MRI and Cystoscopy shows bladder invasion at Diagnosis

After 45- 50 Gy EBRT: A Repeat Cystoscopy is performed

Negative

Positive

MRI with BT Applicators

No Grey zones in bladder wall

Grey zones in bladder wall

High signal intensity in bladder wall

To include the involved wall in IR-CTV only but not in HR-CTV

To include the involved wall in HR-CTV

To include the involved wall and mucosa as GTV-B*

* If adjacent bladder wall shows grey zones then include it in HR-CTV

60 - 65 Gy EQD2

> 85 Gy EQD2**

90 -95 Gy EQD2 to GTV-B**
> 85 Gy EQD2 to HR-CTV

* * Risk of higher bladder toxicities to be anticipated

DOSIMETRIC COMPARISON: Retrospective Vs Prospective Data Vs Literature

	Vienna (IC)	VIE (IC/IS)	Brabandere	TMH: RD	TMH: PD
HRCTV					
Vol in cc	34 +/- 17	44 +/- 27	48+/-19	45.2 ± 15.8	46.9+24.6
D100	66 +/- 7	70 +/- 6	64+/-6	54.1 ± 6.5	65.7±4.6
D90	87 +/-10	96 +/- 12	79+/-7	70.9 ± 10.6	88.3+4.4
Avg. Pt A	82 +/- 9	--	79+/-5	73.4 ± 4.5	93.1 ±24.8
Bladder					
				80.4 ± 34.4	76.4 ±15.5
				139.1 ± 54.7	109.6 ±19.7
				93.4 ± 24.6	85.7+9.8
				63.5 ± 8.1	68 ±7.9
				66 ± 9.9	71.5 ±7.5
				57.8 ± 7.7	65.5+7.2
Rectum					
D0.1cc	79 +/- 12	85 +/- 14	82+/-13	109.4 ± 45.2	74 ±8.6
D2cc	63 +/- 7	67 +/- 7	68+/-7	74.6 ± 19.6	67+8.8

LESSONS LEARNT

Prospective Data: 94 patients

HR-CTV Volumes larger: Advanced Stages

Higher doses to HR-CTV

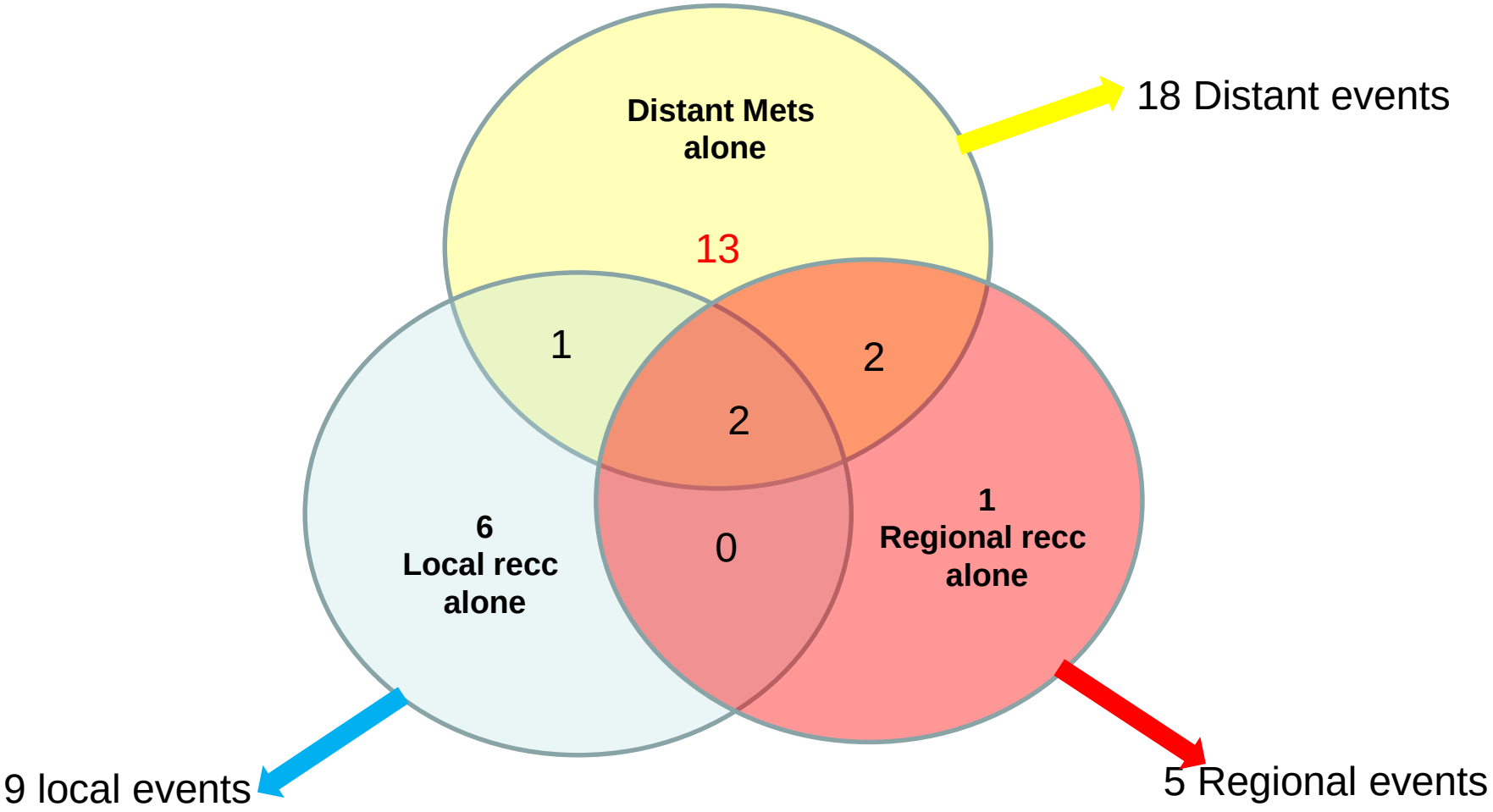
Bladder and Sigmoid Doses Better

TMH – Embrace Outcomes

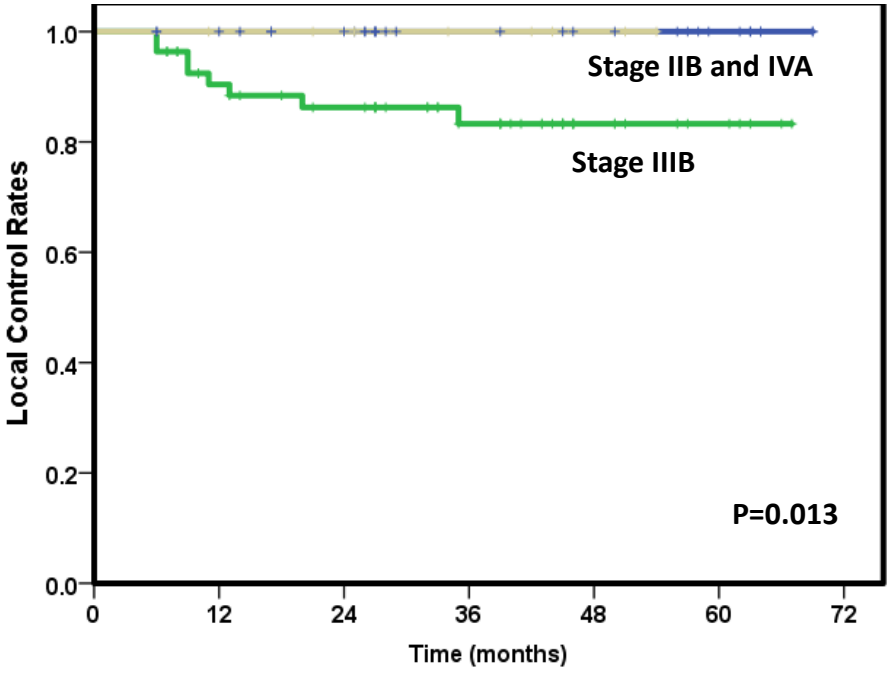
Total 94 patients : stage IIB-IV A

Median Follow up 39 months

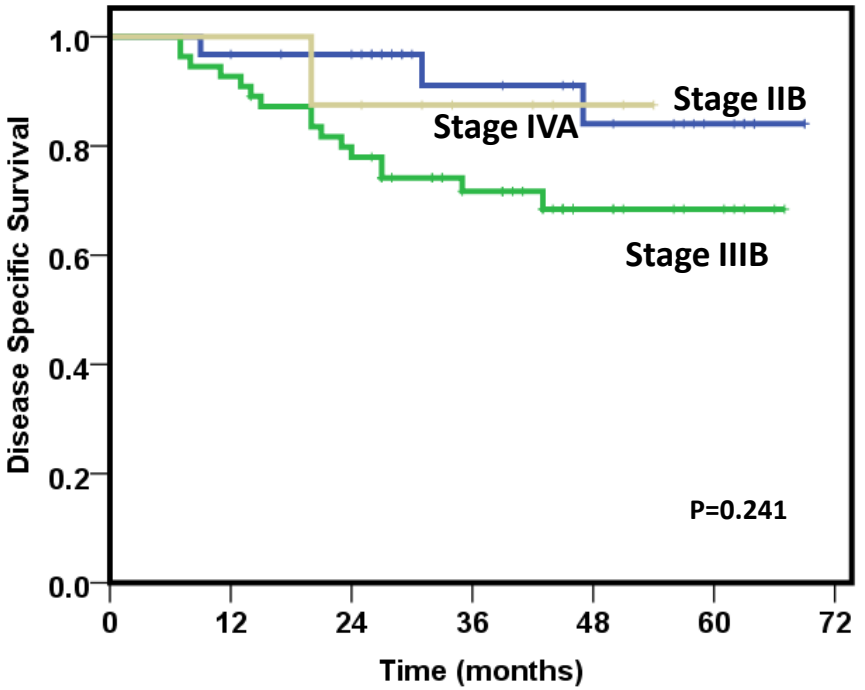
Overall Relapses : 25 pts (26.6%)



MR IMAGE BASED BRACHYTHERAPY
EMBRACE STUDY : 1400 PATIENTS
TMH ACCRUAL: 100 PATIENTS



IIB	31	28	24	15	12	07	01
IIIB	55	45	39	27	10	05	01
IVA	08	07	06	04	02	00	00

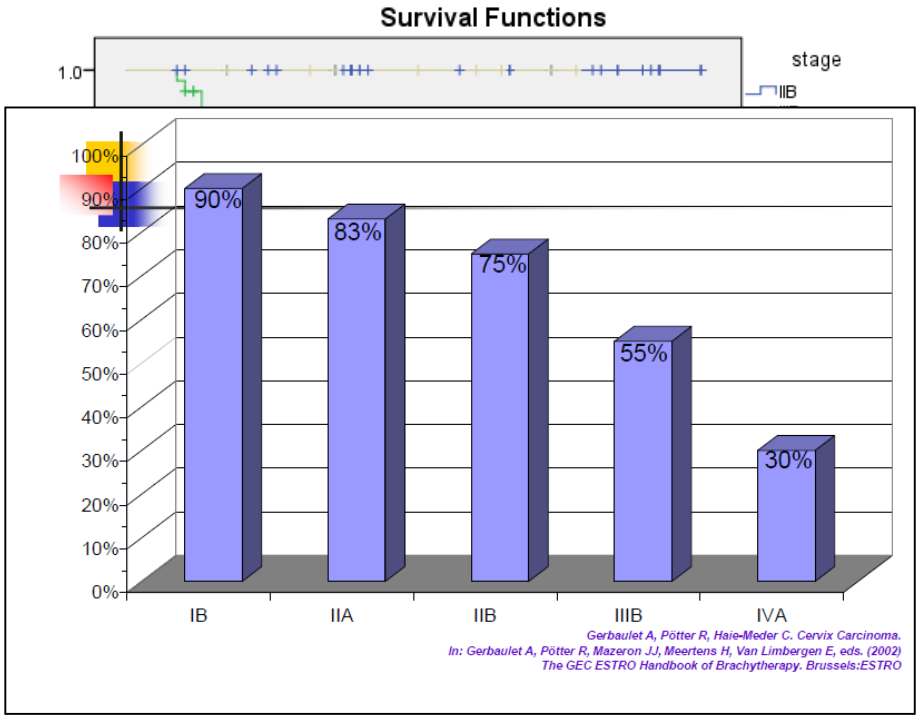


IIB	31	29	26	16	12	07	01
IIIB	55	51	43	28	10	05	01
IVA	08	08	07	04	02	00	00

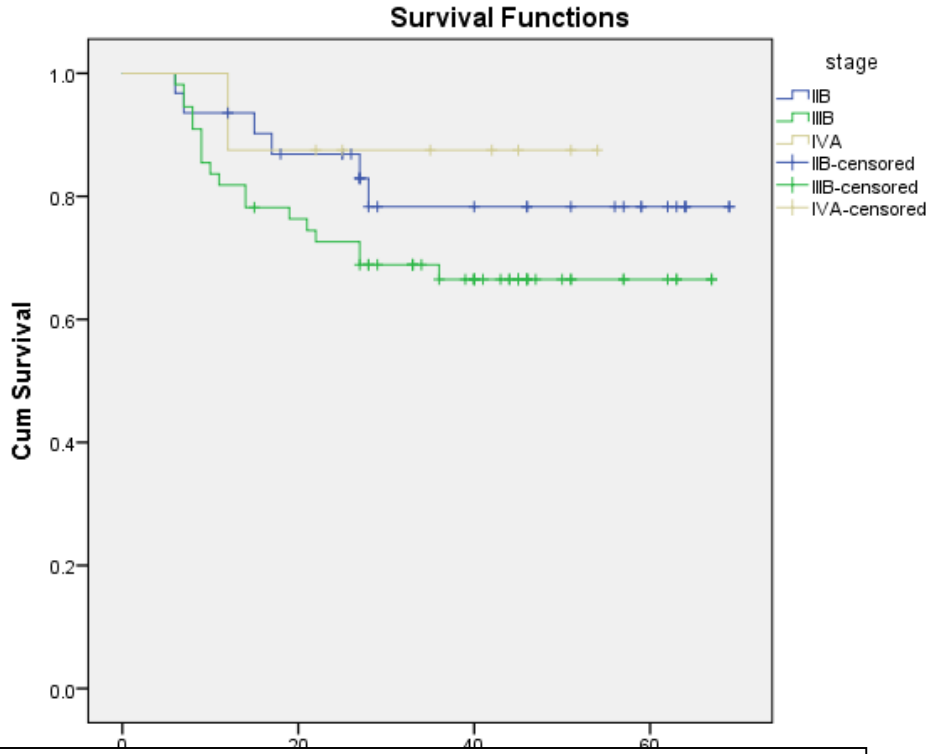
EXCELLANT LOCAL CONTROL RATES FOR ALL STAGES

COST BENEFIT ANALYSES : ONGOING

Actuarial local control



Progression free survival



	2D	2D + CT	3D + CT	
IIB	75%	85%	96-100%	~ 11%
IIIB	55%	65%	84-86%	~ 20%

IIIB	55	9	46	83.6%
IVA	8	0	8	100.0%
Overall	94	9	85	90.4%

IIIB	55	18	37	67.3%
IVA	8	1	7	87.5%
Overall	94	25	69	73.4%

HURDLES

TRANSITION FROM 2D TO 3D

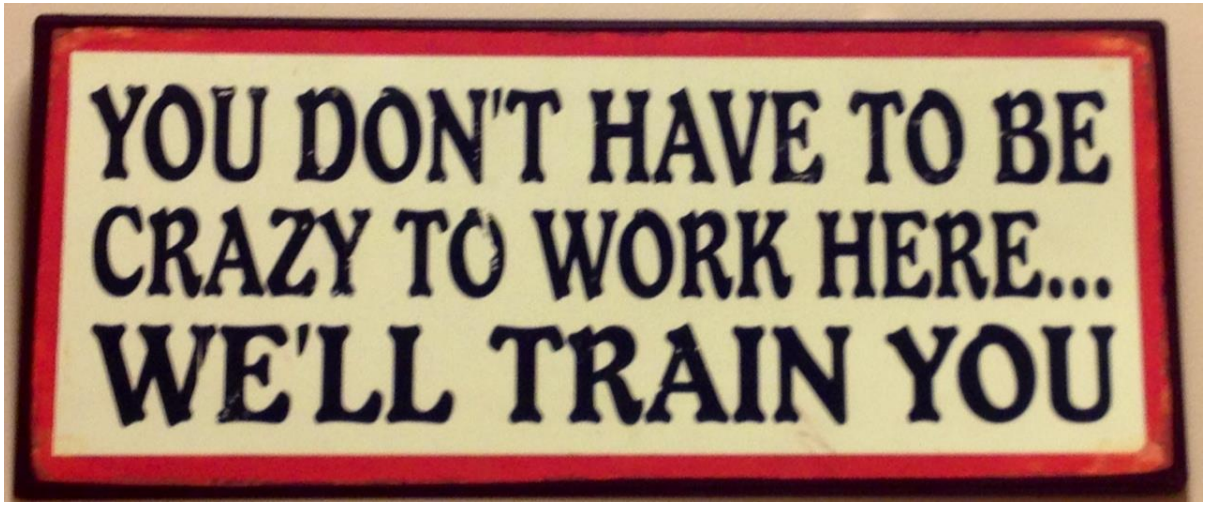
SECRET TO A SUCCESSFUL JOURNEY!

- Attended the GYN Teaching Course: Understand the Concepts
- Hands on Workshop including procedures : Atleast 1 – 2
- Learning Curve & Standardization of processes : 10 - 15 pts
- Retrospective Analyses and Introspection
- Transition to 3 D: MR / CT
- Prospective Collaborative Studies & Research
- Teaching / Hands on Workshops

Brachytherapy Skills

Work hard to Strengthen your skills

like laparoscopic and Robotic Surgeons!!



Teaching Courses!

Hands on

Workshops!

Cadeveric

workshops!

COMMITMENT!

BE OPTIMISTIC!

Communication, Co-ordination and Leadership

Co-ordination with Radiologist , Anesthetist, Physicist,Technologist and others

Discussion

Interaction

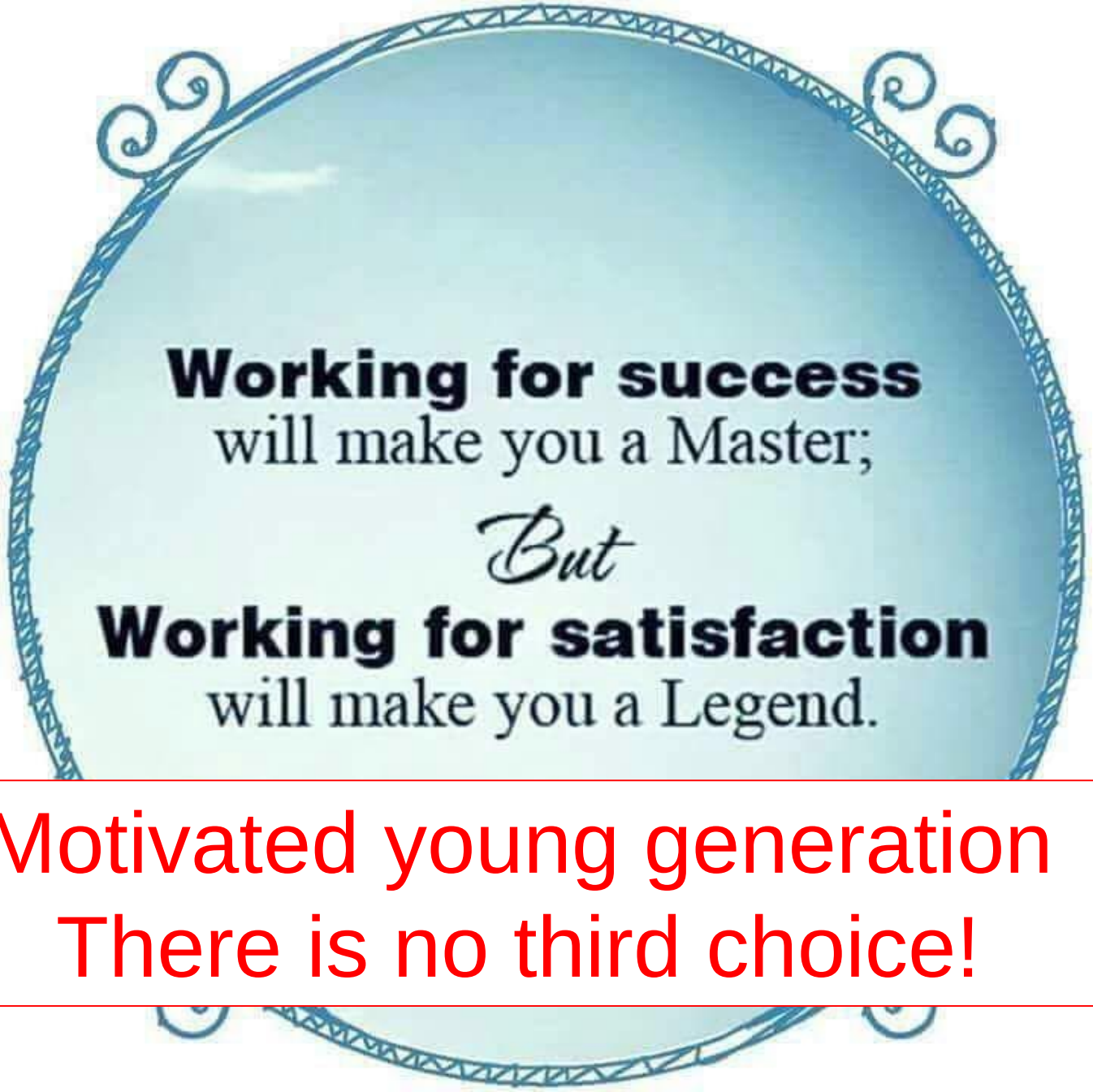
Teaching

PARTY!

Merci - Thank you

Committed hard working faculty!
Sleeping, tired and freeeeezing faculty

17th Edition of TC, Toronto 2016

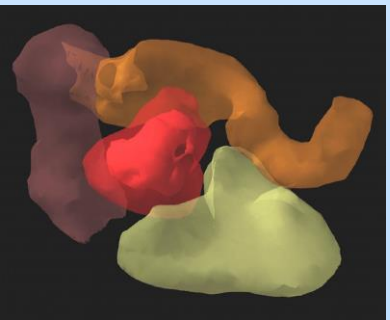


Motivated young generation
There is no third choice!

1st ESTRO AROI Teaching Course
Transition from 2-3D Gynaecologic Radiotherapy with focus on brachytherapy in cervix cancer

ONGOING ACTIVITIES IN 3-D BASED GYN BRACHYTHERAPY

EMBRACE



R. PÖTTER
K. TANDERUP

Gyn GEC ESTRO Net-work

MISSION & VALUES

GOVERNANCE / ORGANISATION

- General Assembly
- Board
- Policies
- Executive Council
- Professional & Membership Council
- Scientific Council
- Nominating Council
- Committees activities

HISTORY

AWARDS

EU PROJECTS

NATIONAL SOCIETIES

ESTRO CANCER FOUNDATION

STAFF

CONTACTS

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: Csaba Polgar
GEC-ESTRO Head and Neck - Chair: György Kovacs
GEC-ESTRO Urology - Chair: Peter Hoskin
GEC-ESTRO Gynaecology - Chair: Richard Pötter and 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.

Collaboration

Intraoperative Radiotherapy

Following a request from the European Group of the International Society of Intraoperative Radiotherapy (ISIORT), the GEC-ESTRO Annual Meeting will provide some visibility to that specialty. A separate pre-meeting workshop will take place at usual GEC-ESTRO meeting. The first event was held in Montpellier in May 2007 and a similar workshop has taken place in Porto in May 2009.

Brachytherapy Physics Data: TG43 - Radiation Protection Data

Direct link to TG43

Direct link to Radiation Protection Data

LINKS

GEC-ESTRO working groups activities:
GEC-ESTRO Breast
GEC-ESTRO Head & Neck
GEC-ESTRO Urology
GEC-ESTRO Gynaecology
GEC-ESTRO BRAPHYQS
GEC-ESTRO Anal

NEWS

MEMBERSHIP:
Why becoming an ESTRO member?

DOWNLOADS

ESTRO Vision for Radiation Oncology
ESTRO Laws
ESTRO 30th Anniversary Book

SEARCH
LOG IN
REGISTER

THE AIMS OF GYN GEC ESTRO NETWORK

The promotion of the field of 3D Gyn brachytherapy:

- Established 2005 based on the GEC ESTRO gyn working group
- Creating a platform for education
- Supporting research and development
- Spreading and testing the Gyn GEC ESTRO Recommendations for cervix cancer

Gyn GEC ESTRO NETWORK

chair Kari Tanderup, AUH, co-chair Richard Pötter, MUW

ESTRO NETWORK

Contouring of CTV, GTV, OAR	Applicator reconstruction	Treatment planning	Applicator development	MR imaging
WP1	WP2	WP3	WP4	WP5

WORK PACKAGES

EMBRACE Studies (EMBRACE 2008-2015) supported by Nucletron/Varian/Bebig

ACTIVITIES

- WORKSHOPS FOR CONTOURING Dublin, Washington, Milwaukee, Utrecht
- WORKSHOP FOR IMAGE GUIDED GYN BT UTRECHT 2006
- WORKSHOP FOR TREATMENT PLANNING Ljubljana 2007
- EMBRACE KICK OFF MEETING Brussels 2008
- WORKSHOP FOR APPLIATOR DEVELOPMENT Leuven 2009
- WORKSHOP FOR OUTCOME ASSESSMENT IN IGABT Paris 2010
- WORKSHOP ON UNCERTAINTIES IN IGABT AARHUS 2011
- WORKSHOP ON MORBIDITY AND DISEASE OUTCOME ATHENS 2012
- WORKSHOP on EMBRACE and retroEMBRACE research, anually since 2011
- ANNUAL EMBRACE MEETING VIENNA SINCE 2008…….3/2017……..

EMBRACE study and research group

PUBLICATIONS ON:

- CONTOURING
- DOSE REPORTING
- MR IMAGING
- INTER-OBSERVER VARIATIONS
- APPLICATOR RECONSTRUCTION
- TREATMENT PLANNING
- UNCERTAINTIES
- Clinical Outome (Retro)EMBRACE

Clinical Evidence in IGABT Cervix Cancer

Upcoming Evidence and networking

- Mono-institutional cohorts (ongoing, >10 publicat. since 2007)
- Multi-center cohorts with retrospective evaluation

  RetroEMBRACE (n=731, first publications in 2016)
- Prospective Trials

  STIC: comparative 2D vs. 3D (n=200; published 2012)

  EMBRACE I: observational, 08/2008 - 12/2015 (n=1412)

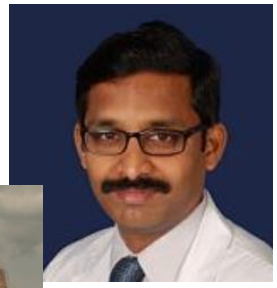
  EMBRACE II: interventional, start 04/2016

Current task groups (2017)

Task groups

Within the gyn network there are continuously a number of different active task groups / work packages.
Among current task group activities are:

Task group on CT contouring in cervix cancer (coordinator Umesh Mahantshetty)



Task group on treatment planning recommendations (coordinator Kari Tanderup)

Task group on vaginal brachytherapy (coordinator Remi Nout)

Task group on image registration (coordinators Jamema Swamidas, Christian Kirisits, Kari Tanderup

EMBRACE

www.embracestudy.dk

DIAGNOSIS

Inclusion criteria:

1. Biopsy proven cervical Ca
2. Treatment with curative intent
3. FIGO, TNM staged
4. MRI/CT pelvis and PAN at diagnosis
5. MR guided BT planned
6. Informed consent (copy to the study office)

Registration form

- Status at diagnosis form (MRI + CRF + cartoons)
- Baseline morbidity form
- Baseline QoL

TREATMENT

EBRT+/- Chemo → Status at BT form → MRI guided BT

- Treatment and DVH form (EBRT +/- Chemo + BT1-n)
- End of treatment QoL form

POSTREATMENT

Follow-up → **Every 3 months for 2 years; Every 6 months for 3 years**

Follow-up form

- Disease status
- Toxicity assessment

QoL form

Local recurrence or toxicity G>2 COMPREHENSIVE REPORT TO STUDY OFFICE!!!

Off study form

EMBRACE

(European Study on MRI Based 3D Brachytherapy in Locally Advanced Cervical Cancer): A PROSPECTIVE OBSERVATIONAL MULTI-CENTRE STUDY

AIMS:

- Implementation of 3D MRI based cervix cancer brachytherapy in a multi-centre setting in Europe and outside Europe
- Quality control of MRI based brachytherapy in a multi-centre setting applying Gyn GEC ESTRO Recommendations for reporting
- Prospective assessment of outcome for disease, morbidity and quality of life in patients receiving MRI based cervix cancer brachytherapy
- Correlation of local control and dose volume parameters for GTV, HR CTV and IR CTV with the establishment of hazard ratios and dose effect curves for the primary tumour
- Correlation of late morbidity and dose volume parameters for the OAR (rectum, sigmoid, bladder) with the establishment of hazard ratios and dose effect curves for OAR.
- Validation of the GYN GEC ESTRO recommendations in a multi-centre setting
- Publications upcoming: Kirchheiner, Mazeron, Mohammed, Sapru, Jastaniyah, Yoshida, Kirisits, Nomden, Fortin, Schmid …..

RETRO-EMBRACE

Retro-EMBRACE is a retrospective collection of data on 3D IGBT in locally advanced cervical cancer from all centres in which this modality is implemented.
780 patients included
Eligibility criteria to enter data on patients in this database are:
Diagnosis of cervical cancer and treatment with curative intend by way of IGBT (including MRI, CT, (US) or combination of these) before EMBRACE started accrual at your centre, irrespective of the follow up time.

The aim of this data collection is to gather information on the existing experience with IGBT in cervical cancer until EMBRACE data matures.
Publications upcoming: Sturdza, Tanderup, Fokdal……2016

Study Centers

Vienna
Aarhus
Utrecht
Leiden
Leuven
Ljubljana
London
Arnhem
Paris
Mumbai

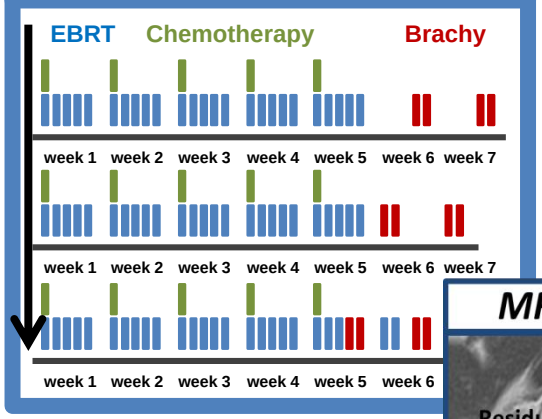
Pittsburgh
Milwaukee
Kaposvar
Maastricht
Trondheim
Leeds
Chandigarh
Edmonton
Oslo
Kuopio
Cambridge
Amsterdam

<u>22 Centres</u>
Europe-16
N.America-3
Asia-2

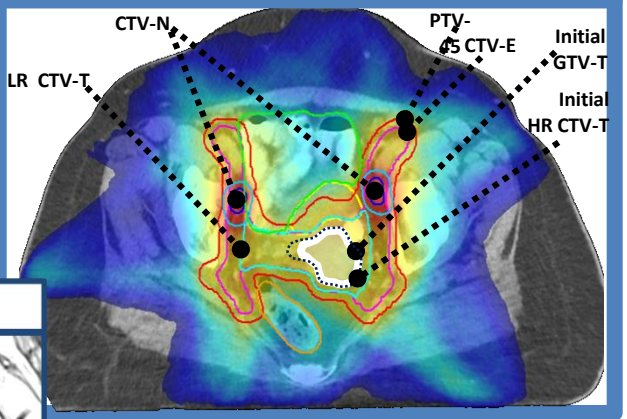
EMBRACE II

Start 4/2016

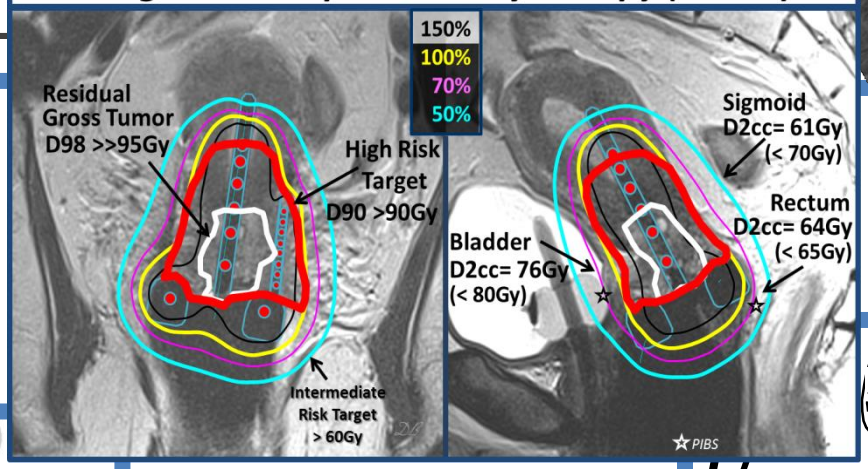
RChTh + BT in < 50 days

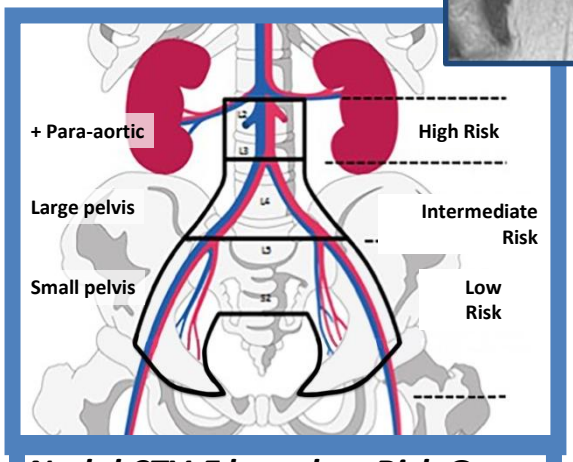


IMRT + IGRT

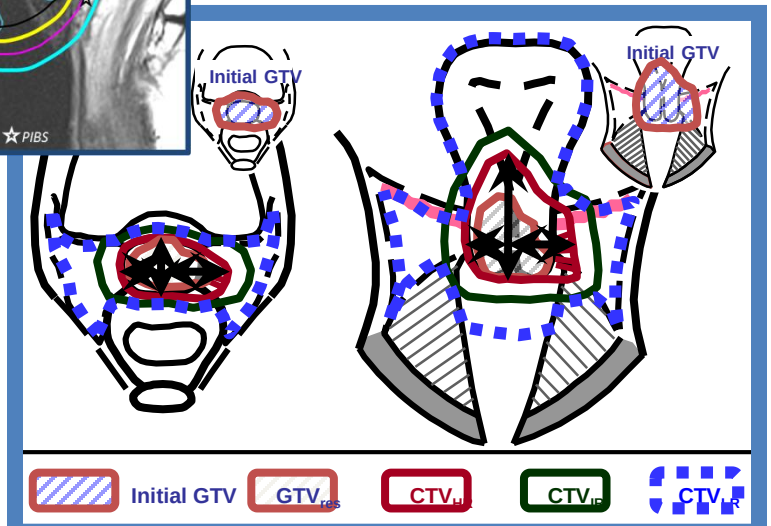


MRI guided adaptive brachytherapy (IGABT)





Nodal CTV-E based on Risk Group



Residual GTV-T, Adaptive HR CTV-T, IR CTV-T

Step 4: Defining MRI based (adaptive) Volumes and Doses

GYN GEC ESTRO recommendations I (Haie-Meder et al.) - contouring

GYN GEC ESTRO recommendations II (Pötter et al.) - dose vol. parameters

GYN GEC ESTRO recommendations III (Hellebust et al.) - reconstruction

GYN GEC ESTRO recommendations IV (Dimopoulos et al.) - imaging

ABS recommendations on GYN general (Viswanathan and Thomadsen, ABS Cervical Cancer Recommendations Committee) - general

ABS recommendations on GYN HDR (Viswanathan et al.)

ABS recommendations on GYN PDR (Lee et al.)

GEC ESTRO gyn network Step by step process
over the last 20 years...
EMBRACE study and research group
over the last 10 years

- Pioneering monoinstitutional experiences: from 1998
- GEC ESTRO Recom I: Target concepts (RO 2005)
- GEC ESTRO Recom II: Reporting (RO 2006)
- GEC ESTRO Recom III: Applicator reconstruction (RO 2010)
- GEC ESTRO Recom IV: Requirements for imaging (RO 2012)
- ICRU GEC ESTRO 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)

- 18 ESTRO teaching course since 2004 (~2000 participants)
- Annual hands-on workshops (education of >150 institutions)
- Web-based contouring teaching (ESTRO School, 2 editions)

More Ongoing Activities
Education & Training

I. Aalderwegen BT acad.

- Hands-on workshops (Vienna, Aarhus…>25)
- International hands-on workshops (~10)
- ESTRO School (international programmes):
  - ESTRO School technology transfer grants (since 2008)
  - web based contouring workshops (3 so far)
  - AROI ESTRO Teaching and Training Programme (2017-2019)
- Cambridge CCMO: web based e-learning program cervix cancer (EMBRACE II)

Umesh Mahant-shetty, AROI

C. Verfaillie ESTRO School

Jamema Swamidas, AROI

LT Tan, Cambridge

joint TRANSATLANTIC and EURO-ASIAN cooperation FOR 3D IMAGE-BASED GYNAECOLOGIC BRACHYTHERAPY

- Combines activities in Europe, North America, Asia with continuous exchange of information and joint meetings
- Multiple International workshops and ESTRO teaching courses in cooperation with

  ABS/ASTRO/AAPM/SEAROG/AROI/CSRO/CARO

  - WS: Washington 03/2006, Milwaukee 09/2006
  - WS: Tata 2013, Bangkok 2014, Gunma 2014, Seoul 2015, Hongkong 2015,
  - ESTRO TC: Manila 1/2009 (SEAROG), Chandigarh 3/2011 (AROI), Beijing 3/2012 (CSRO), Moscow 7/2013, Toronto 2016 (CARO), Bengaluru 2017 (AROI)

Gyn GEC ESTRO network
EMBRACE study and research group,
ICRU report committee

EMBRACE kick-off meeting Brussels 04/2008

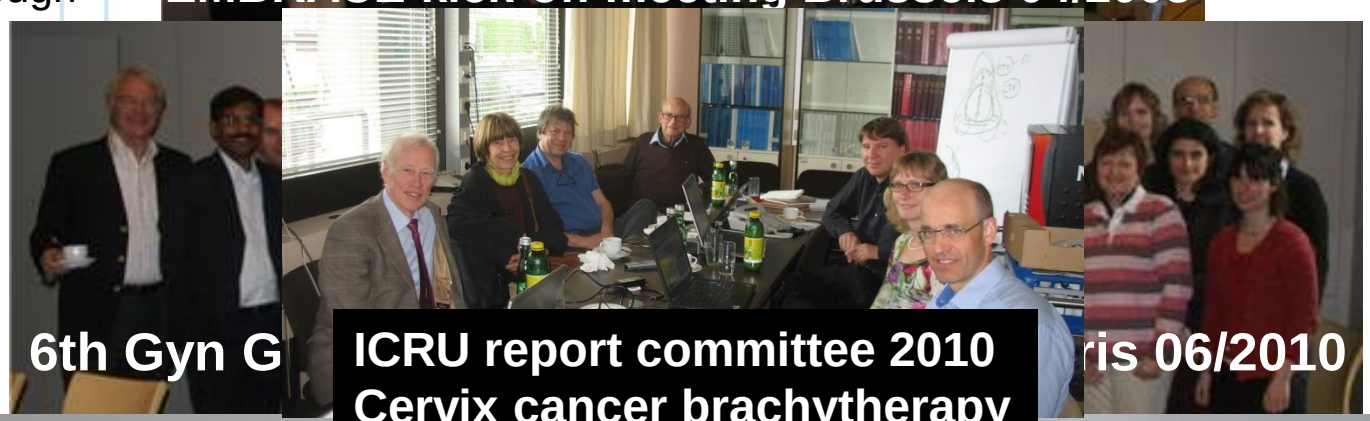
Support:

Nucletron
Improving patient care

VARIAN
medical systems

Facilitated through

ESTRO



6th Gyn G

ICRU report committee 2010
Cervix cancer brachytherapy

ris 06/2010

4th Annual EMBRACE meeting Vienna 12/2012

Information about EMBRACE study, retro-EMBRACE study and 3D Gyn GEC ESTRO network

- www.embracestudy.dk
- www.retroembrace.com
- www.estro.org *

**Also: GEC ESTRO Handbook of Brachytherapy*

1st edition 2002;

2nd edition developing since 12/2014

my and ….our Steps (n=12) R. Pötter

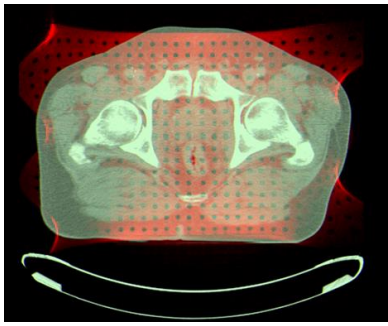
- Building up the vision for MRI
- Providing (some) infrastructure for image based RT (BT)
- Starting (CT) MRI based gynaecologic brachytherapy
- Defining MRI based (adaptive) volumes and doses
- Introducing dose volume constraints into clinical practice
- Developing combined intracavitary/interstitial techniques
- Providing clinical evidence (disease, morbidity, QoL)
- Analysing MRI based DVH parameters and outcome
- Assessing and minimizing uncertainties
- Educating, training and disseminating the „New“
- Designing and managing BT research & development
- Building local, national and international cooperation

Step 1: „building up the vision for MRI“

- Defining „MRI-assisted Simulation“ for EBRT:

  image distortion, fusion, MRI defined target, OAR

  Thesis (Habilitation) 1989, Radioth&Oncol 1991, 1995



- Applying „MRI simulation“ for various sites:

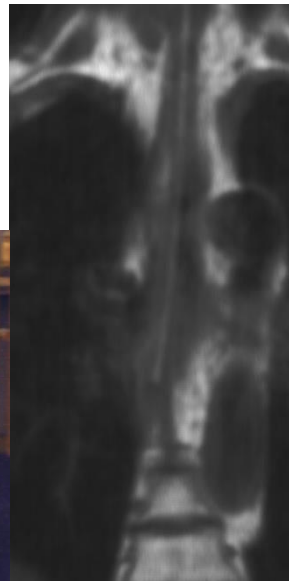
  brain, base of the skull, prostate, lymphoma

  Advances in Radiation Therapy 1993

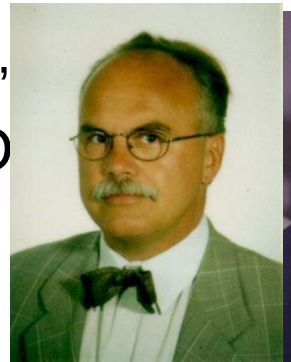
- Applying „MRI simulation“ for Brachytherapy

  Gynaecology, Oesophagus, GEC ESTRO 1990

  Activity 1992



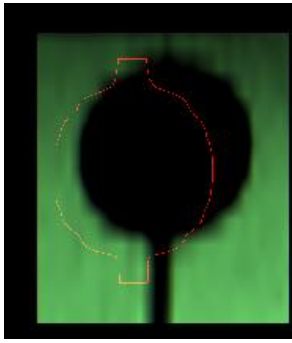
[in coop. with MRI team at Münster University, Germany, in particular U. Haverkamp,PhD G. Kovacs,++]



Step 2: „providing (some) infrastructure“

- Decision in Vienna in favour of an open MRI system for radiotherapy planning, within brachytherapy (1995)

  [instead of a digital fluoroscopy based planning system (500.000€)]



- *Installation, testing, tuning MRI for radiotherapy (97-9)*

  (Fransson et al. Strahlentherapie 2001)

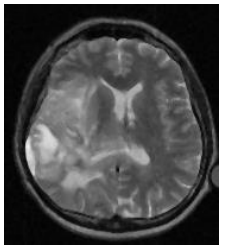
- *Developing specific sequences (prostate, gynae) (1998)*

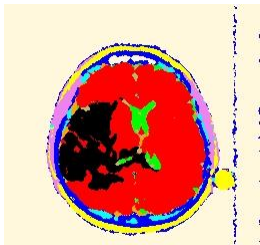
  (research grant MRI medical physics: A. Fransson, Karolinska, Stockholm)

- *Systematic Comparison MRI vs. CT based treatment planning: EBRT for brain and prostate tumours*

  (Fransson et al. Radioth&Oncol 2000,

  Petersch et al. Radioth&Oncol 2003)





Step 3: starting (CT) MRI based gynaecological BT (1994-98-2000+++)

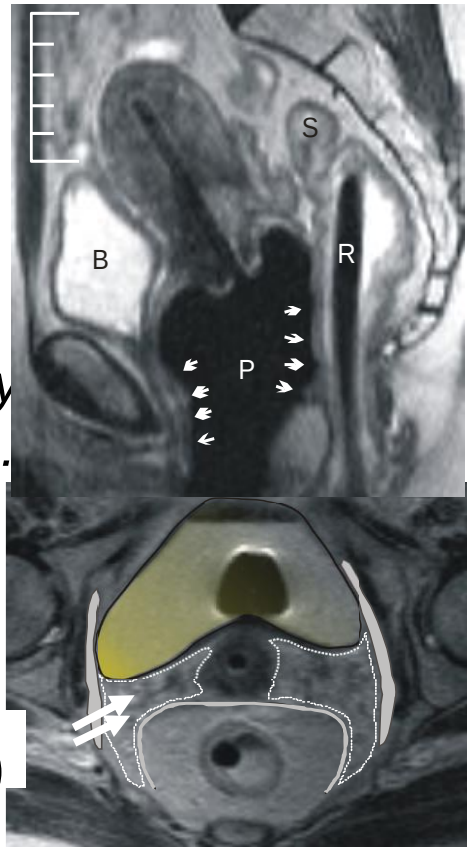
- „**Hardware“:** *MRI/CT compatible applicators, (1995)*
  MRI compatible anaesthesiological equipment

- **Specific demands for gyn BT application**:
  contrast for the tamponade, bladder balloon

- **Specific MRI protocol**: *at diagnosis, at brachytherapy*
  T2 (T1) images, slice orientation, bladder filling…

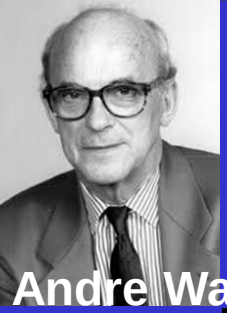
- **Defining the place of MRI**:
  (before) after clinical insertion of the applicator

- **Learning to read MRI after EBRT (with clin. Exam.)**
  with applicator in place:
  residual GTV, Cervix, grey zones…OAR…



[**cooperation with medical physics, diagnostic MRI expertise, industry]**

Vienna Radio-oncological gynaecological Brachytherapy Team 1993-2005 ++



Andre Wambersie
Visiting Professor Vienna 1995-2013

Natascha Gerstner

Tomas Knocke

Claudia Fellner/

Richard Pötter

Stephan Wachter

Waldhäusl

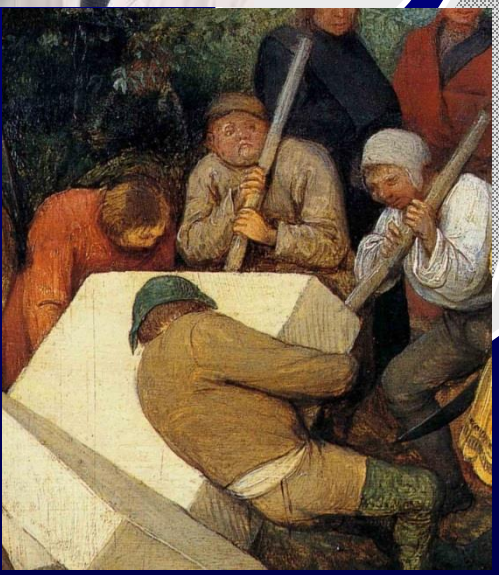
„Old“ Team

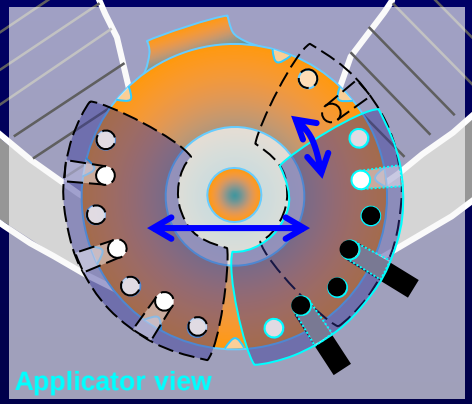
„Younger“ team

Stefan Lang
Hajo Weitmann
Petra Georg

Christian Kirisits
Johannes Dimopoulos
Daniel Berger

Applicator for up to distal parametrial residual GTV and residual pathologic tissue disease



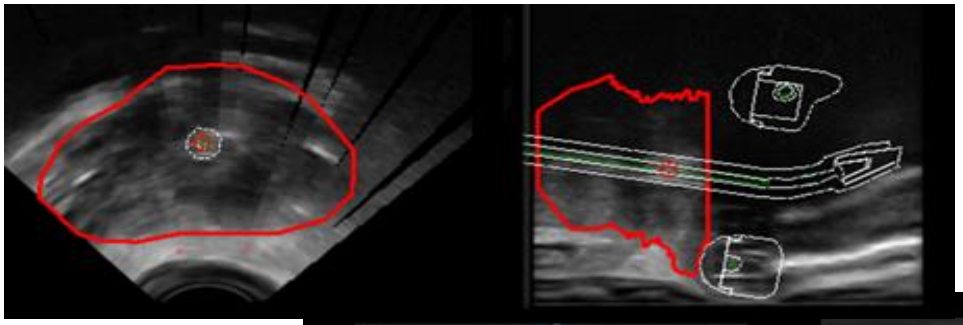


additional divergent template guided needles

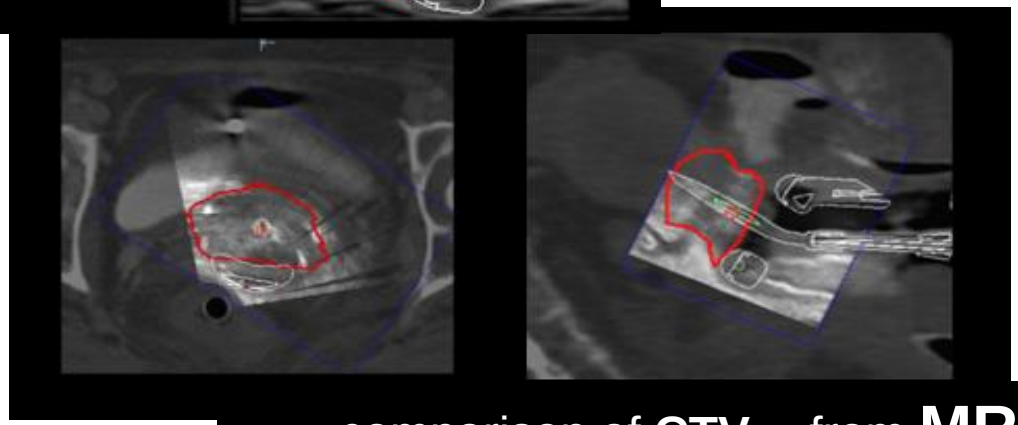
The Vienna II Applica

Kirisits, Berger et al. /Mahantshetty, Pötter et al. 2016

Imaging technology development integrating US, CT and MRI for CTV_{HR} contouring

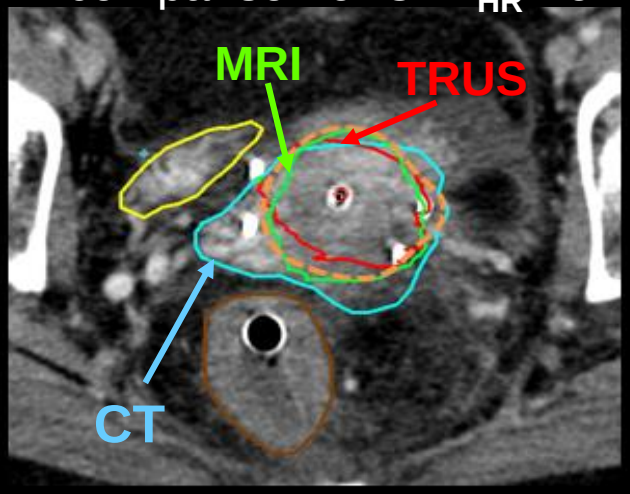


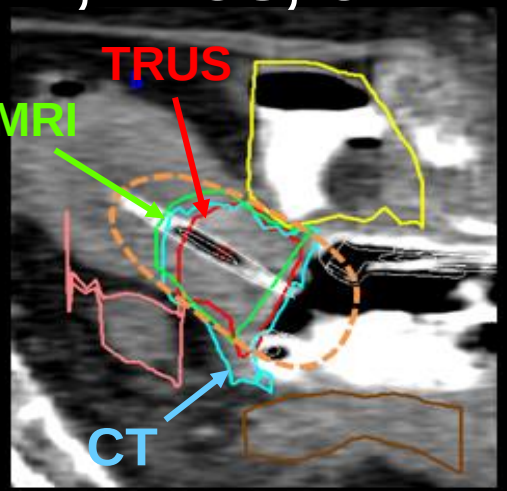
TRUS: **target delineation, applicator reconstsruction**



TRUS/CT
registration via applicator + target transfer to CT

comparison of **CTV_{HR}** from **MRI, TRUS, CT**





Vienna Group, work in progress:
N Nesvacil, M Schmid, C Kirisits

Team Vienna 2006-2016

Staff, PhD Students, Fellows

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(Staff, MD)

Nicole Nesvacil
(Staff, MSc, PhD)

Max Schmid
(Staff, MD)

Primoz Petric

Petra Trnkova

Elena Fidarova

Elena Magri

Karen Nkiwane

Christiane Lemaire

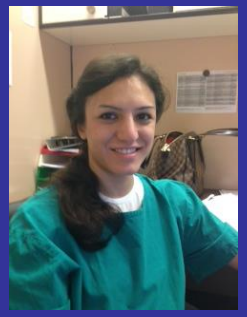
Kathrin Kirchheiner
(Staff, MA, PhD,
Psycho-oncologist)

Tijana Frank

Martine Franckena

Henrike Westerveld

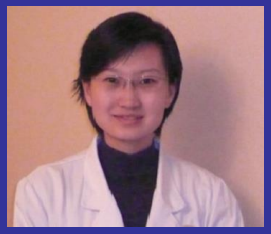
Mario Federico



Noha Jastaniyah

Kenji Yoshida

Israel Fortin



An Jusheng

Neamat Hegazy

Pittaya Dankulchai

1st AROI - ESTRO GYN Teaching Course

Transition from "Conventional 2D to 3D Radiotherapy" with a special emphasis on "Brachytherapy in Cervical Cancers"

ESTRO School

GOALS AND TIMELINES: EBRT

	PHYSICIAN	PHYSICIST
EMBRACE II Target Concept Implementation		
CTV to PTV margins Primary Nodes: Pathological and elective		
Bladder protocol		
IMRT/VMAT		
IGRT protocol Imaging / frequency		
Dose and fractionation modifications		

GOALS AND TIMELINES: BT

	PHYSICIAN	PHYSICIST
BT Application:		
Imaging:		
Planning Process :		
Dose and fractionation modifications:		
Research Interests: **For eg. EMBRACE like…**		

GOALS

SHORT TERM EBRT

- **Embrace II Target Concept:**

  - Possibility of Implementation in more than 50% Participants

  - Others : Institutional Discussion and decide

- **CTV-PTV margins:**

  - Majority have defined some values

- **Bladder filing Protocol:**

  - Some form of bladder filing will be adpated in almost all Institutions

  - However, heterrogenous range : 300 – 750 ml after 30-45 minutes

GOALS

SHORT TERM EBRT cont.

- **IGRT Protocol:**
  - **Bony match/ CBCT : majority**
  - **Frequency : Variation in the protocol**

- **Dose fractionation:**
  - **Majority to shift from 50 Gy to 45 Gy**
  - **A few : to implement SIB for nodal disease**

GOALS

SHORT TERM BT

- **BT Application:**

  - Shift from IC to IC + IS around 8-10 Institutions

  - Around 30% already doing IC + IS

- **Imaging :**

  - CT Environment : Majority to adapt CT Information

Recap of BT planning principles: Radiography based/ CT information

Utilization of CT Imaging

- **Non – MRI Environment :**

  - CT imaging for BT application

  - Contouring of OAR's

  - Conventional Planning : Point A normalization & Prescription

  - Evaluation of OAR doses : ICRUB, ICRUR, 2 /0.1cm3 doses

  - Report: Point A , OAR doses in total EQD2 for each patient

Motivate for MR environment

GOALS

SHORT TERM BT

- **BT Planning Process:**

  - CT based planning

  - MR in 1st fraction and CT based subsequently

  - Plan Optimization and planning

- **Dose and fractionation modifications :**

  - Significant centers would modify

GOALS

BT

EMBRACE like Research