WELCOME
ESTRO Teaching Course

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

Prague 22.-26. October 2017

Richard Pötter

Kari Tanderup

ESTRO
European SocieTy for
RADIOTHERAPY
& ONCOLOGY

Image-guided cervix radiotherapy – with a special focus on adaptive brachytherapy

In the ESTRO school for 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 Bangalore (6th intern.) : 80 participants AROI-ESTRO
- 19th edition Prague 10 2017: 101 participants

Discussion of Course Directors

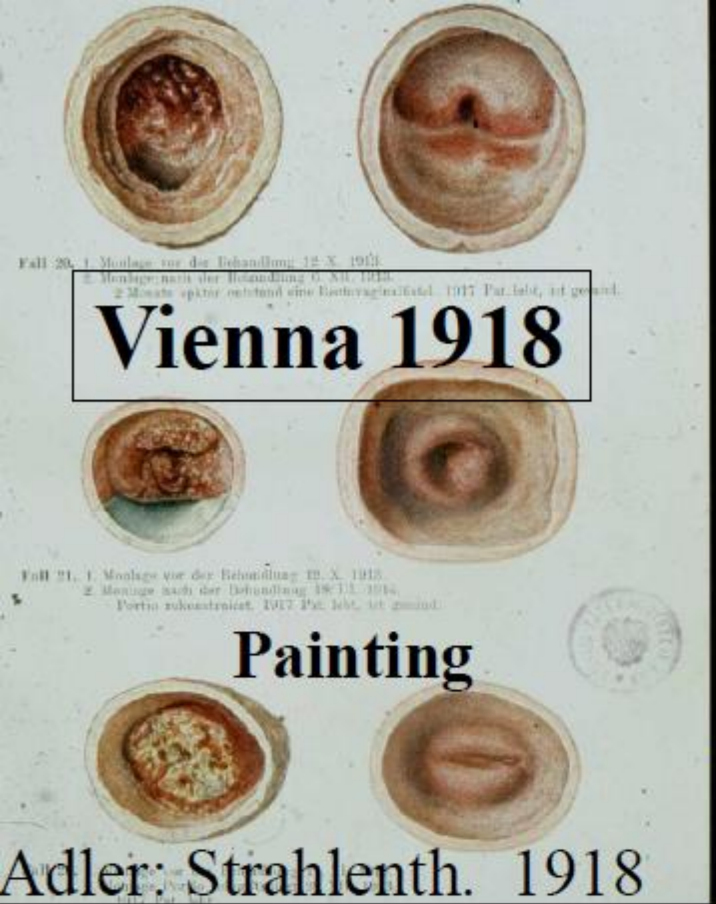
Discussion of Course Directors

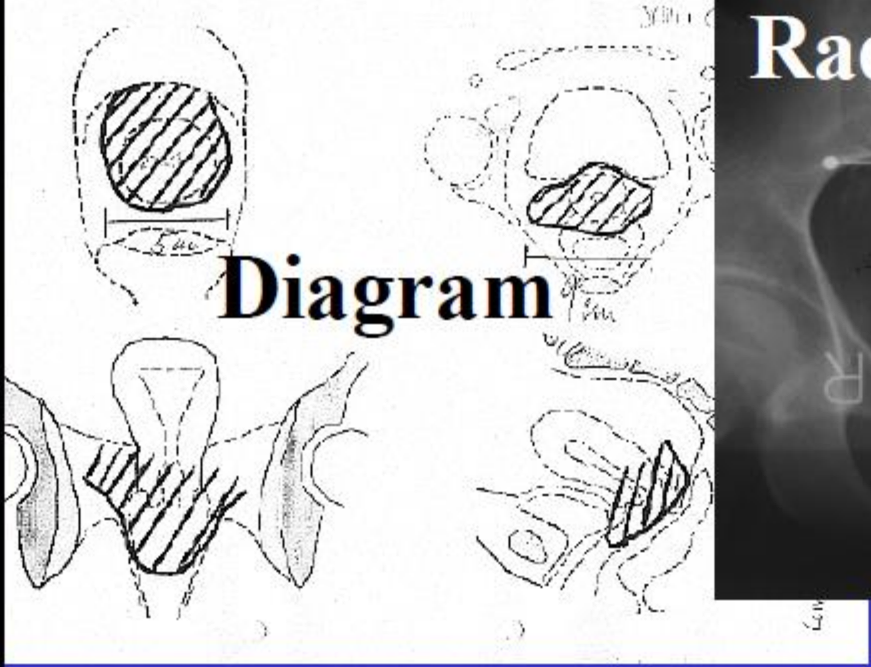
In total ~ 2000 participants

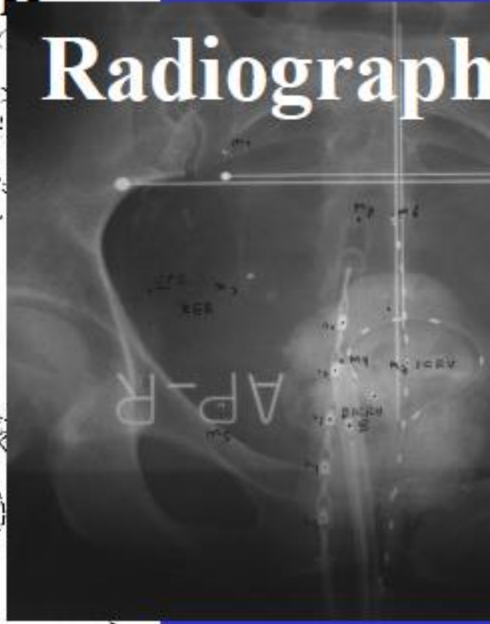
Faculty

- ***<u>Course directors</u>***
  - Richard Pötter, Rad Onc, Medical University of Vienna (AUT)
  - Kari Tanderup, Physicist, Aarhus University Hospital, Århus (DEN)
- ***<u>Faculty</u>:***
  - Christine Haie-Meder, Rad Onc, Institut Gustave Roussy, Villejuif (FRA)
  - Ina Jürgenliemk-Schulz, Rad Oncologist, Medical Center Utrecht (NL)
  - Taran Paulsen-Hellebust, Physicist, Norwegian Radium Hospital, Oslo (NOR)
  - Peter Petrow, Radiologist, Institut Curie, Paris (FRA)
  - Nicole Nesvacil, Physicist, Medical University of Vienna (AUT)
  - Remi Nout, Rad Onc, Leiden University Medical Center, Leiden (NL)
  - Jamema Swamidas, Physicist, Tata Memorial Hospital (IN)
- ***<u>ESTRO Faculty „at home“:</u>***
  - Johannes Dimopoulos, Rad Onc, Metropolitan Hospital, Athens (GRE)
  - Primoz Petric, Rad Onc, National Centre for Cancer, Doha, Qatar (QAT)
  - Umesh Mahantshetty, Rad Onc, Tata Memorial Hospital (IN)
  - Daniel Berger, Physicist, Medical University of Vienna (AUT)

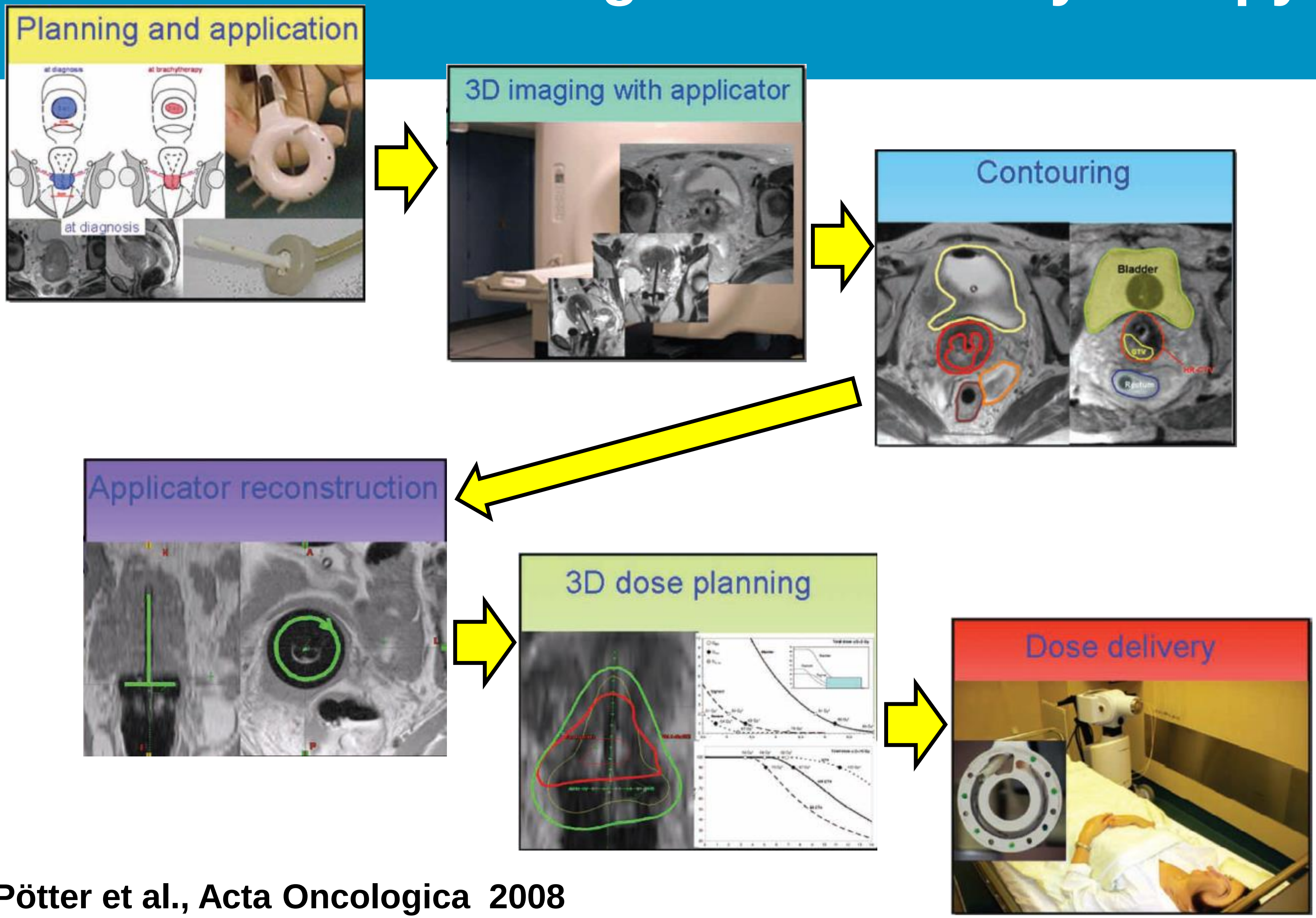
Clinical Evaluation







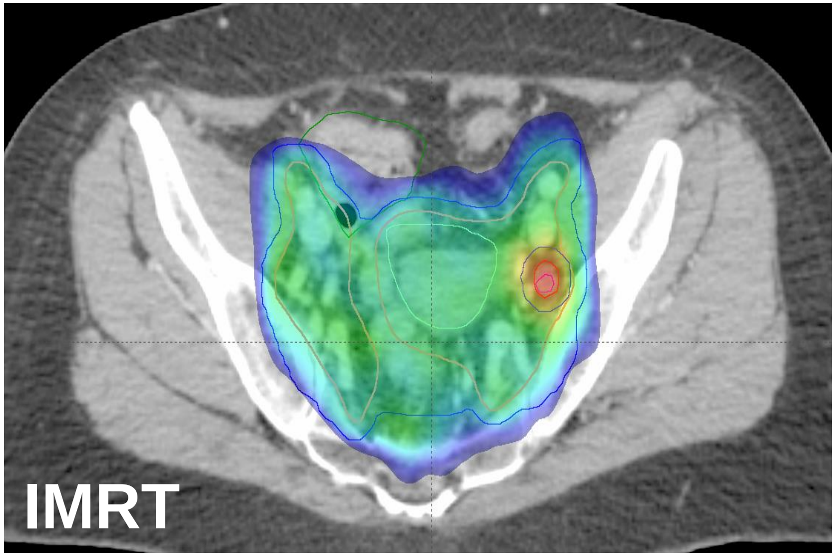
3D Image based brachytherapy

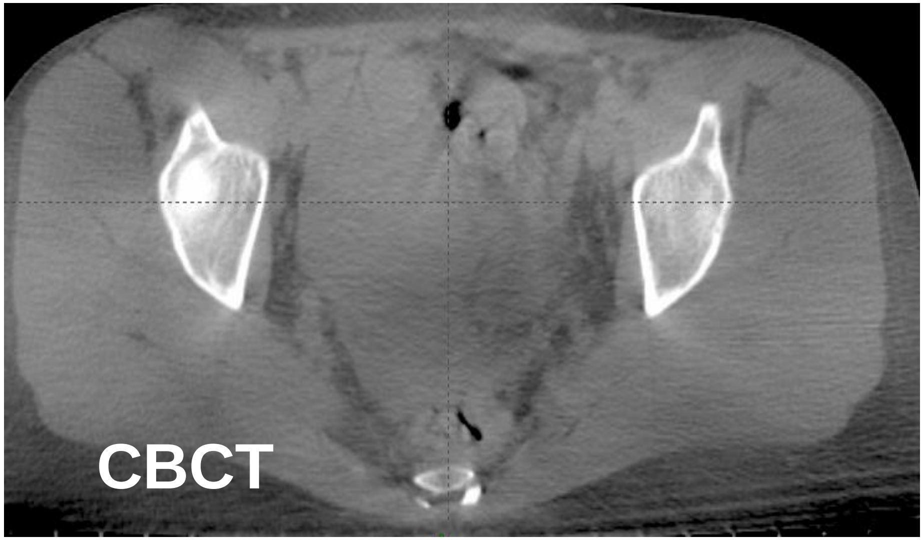


Pötter et al., Acta Oncologica 2008

Advanced image guided EBRT

- Target concepts
- Techniques:
  - IMRT
  - IGRT





Contents of the course

- Anatomy, staging, imaging
- Target concepts and treatment planning for EBRT and BT
- Techniques for brachytherapy
- Dose reporting including equi-effective dose concept
- Evidence for chemoradiotherapy
- Outcome: disease and morbidity
- Workshops
  - EBRT and brachytherapy contouring (physicians)
  - EBRT ad brachytherapy treatment planning (physicists)
  - Case discussion (physicians)
- Interactive sessions
  - Treatment planning demonstration
  - Dose reporting
  - Tips and tricks for implementation
  - What have you learned: MCQs

- Web-based database with a retrospective multicentre collection of data on 3D RT plus IGABT in cervical cancer

- 780 pts

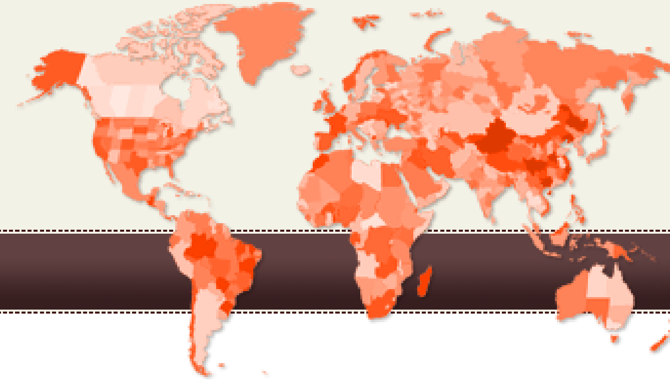
- Eligibility criteria:
  - Diagnosis of cervical cancer and treatment with curative intent by IGABT
  - Reporting according to GEC ESTRO recommendations

VARIAN medical systems

Elekta

EMBRACE

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



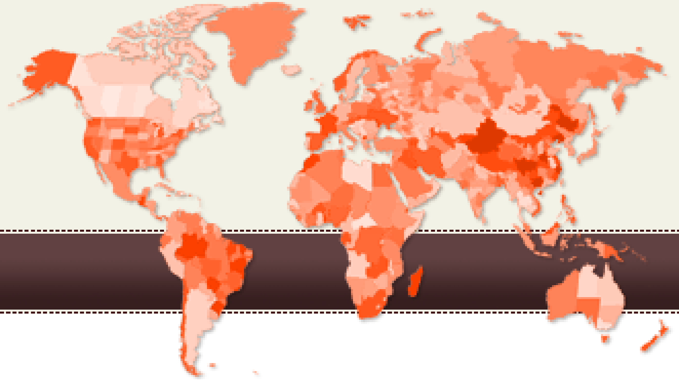
About Embrace | Contacts | Participation | Login

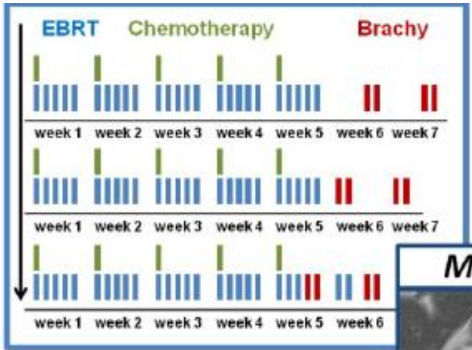
- **EMBRACE - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer**
- **A prospective observational multi-centre trial**
- **Enrollment of patients 2008-2015, 1416 pts accrued**

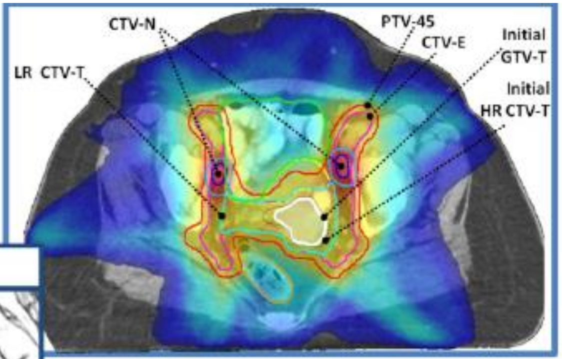
VARIAN medical systems

Elekta

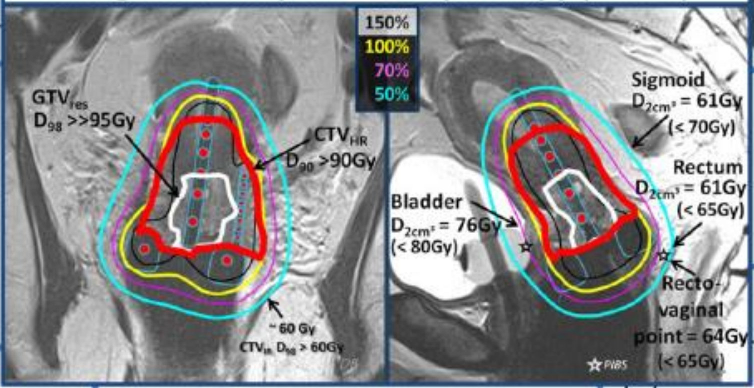
EMBRACE II { An intErnational study on MRI-guided BRachytherapy in locally Advanced CErvical cancer }

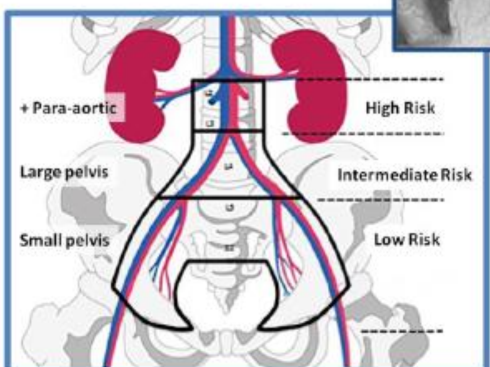




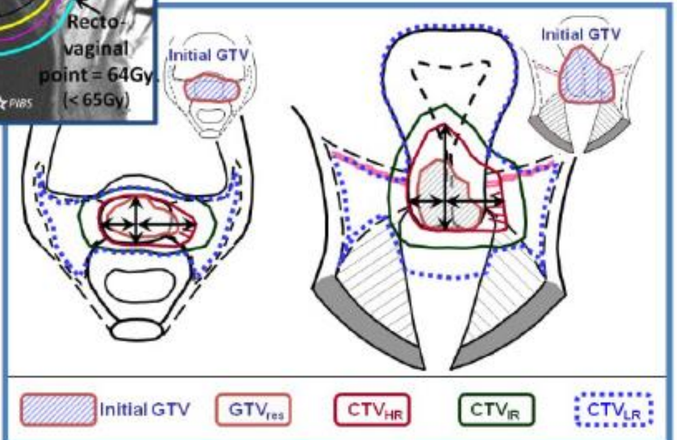


MRI guided adaptive brachytherapy (IGABT)





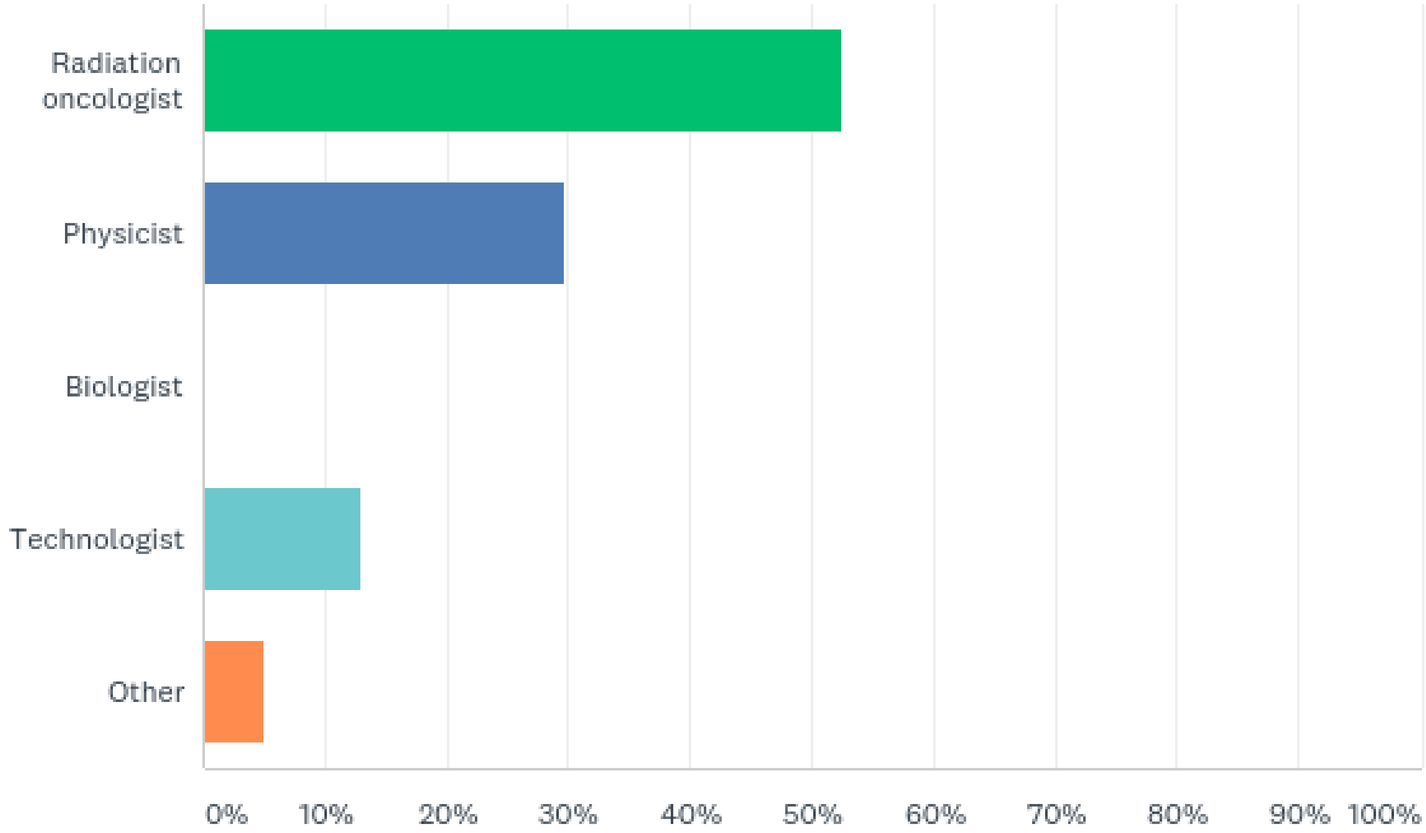
Nodal CTV-E based on Risk Group



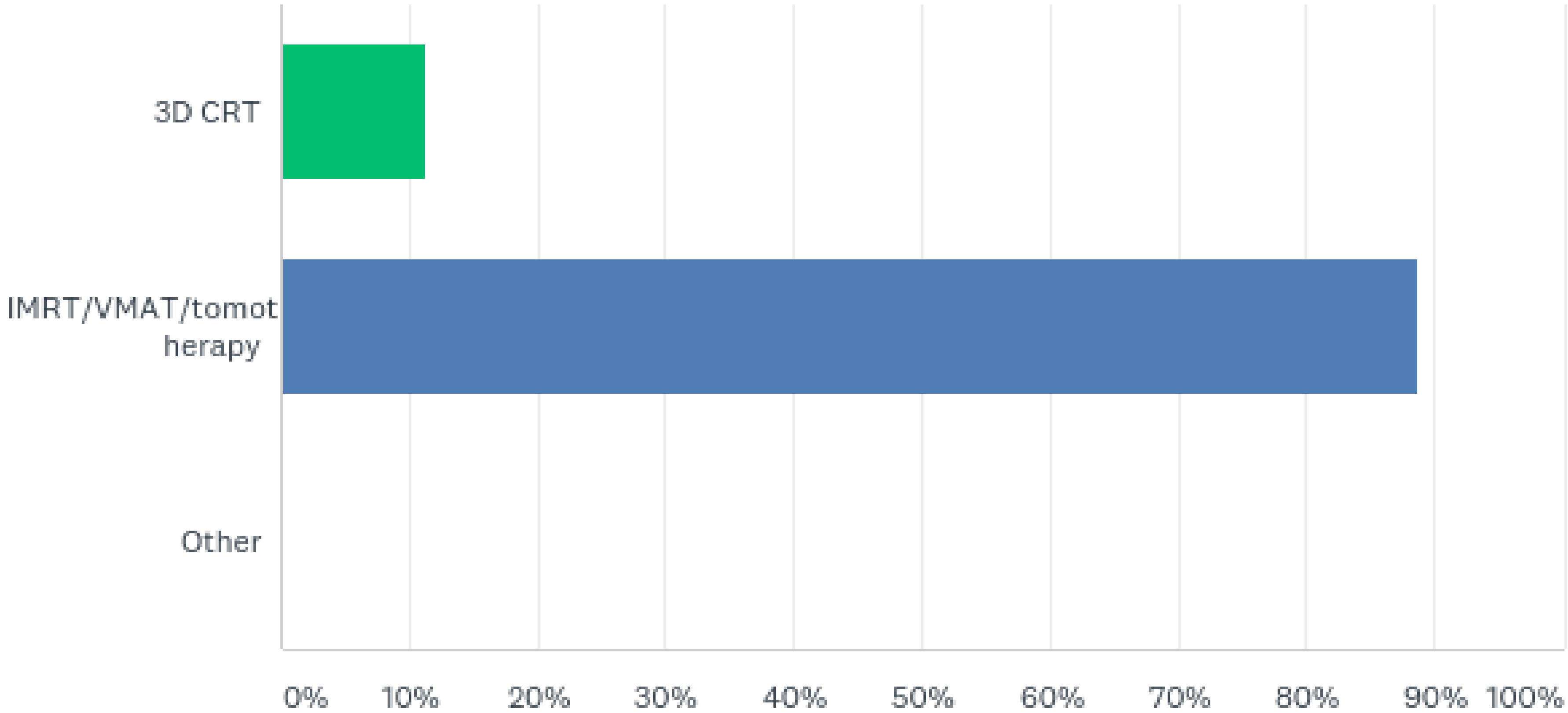
Residual GTV-T, Adaptive HR CTV-T, IR CTV-T

Who are you?

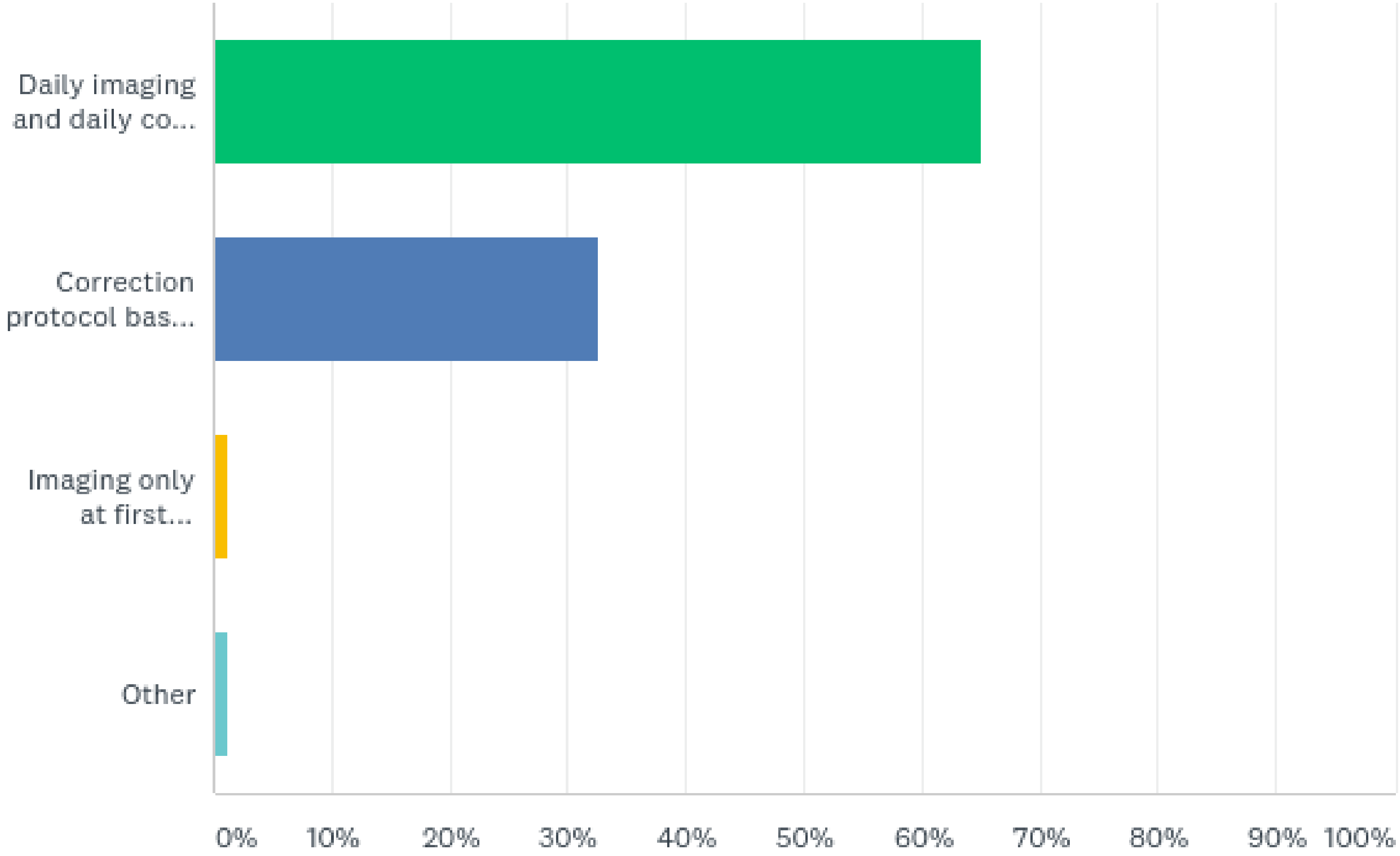
- **101 participants from 30 countries**



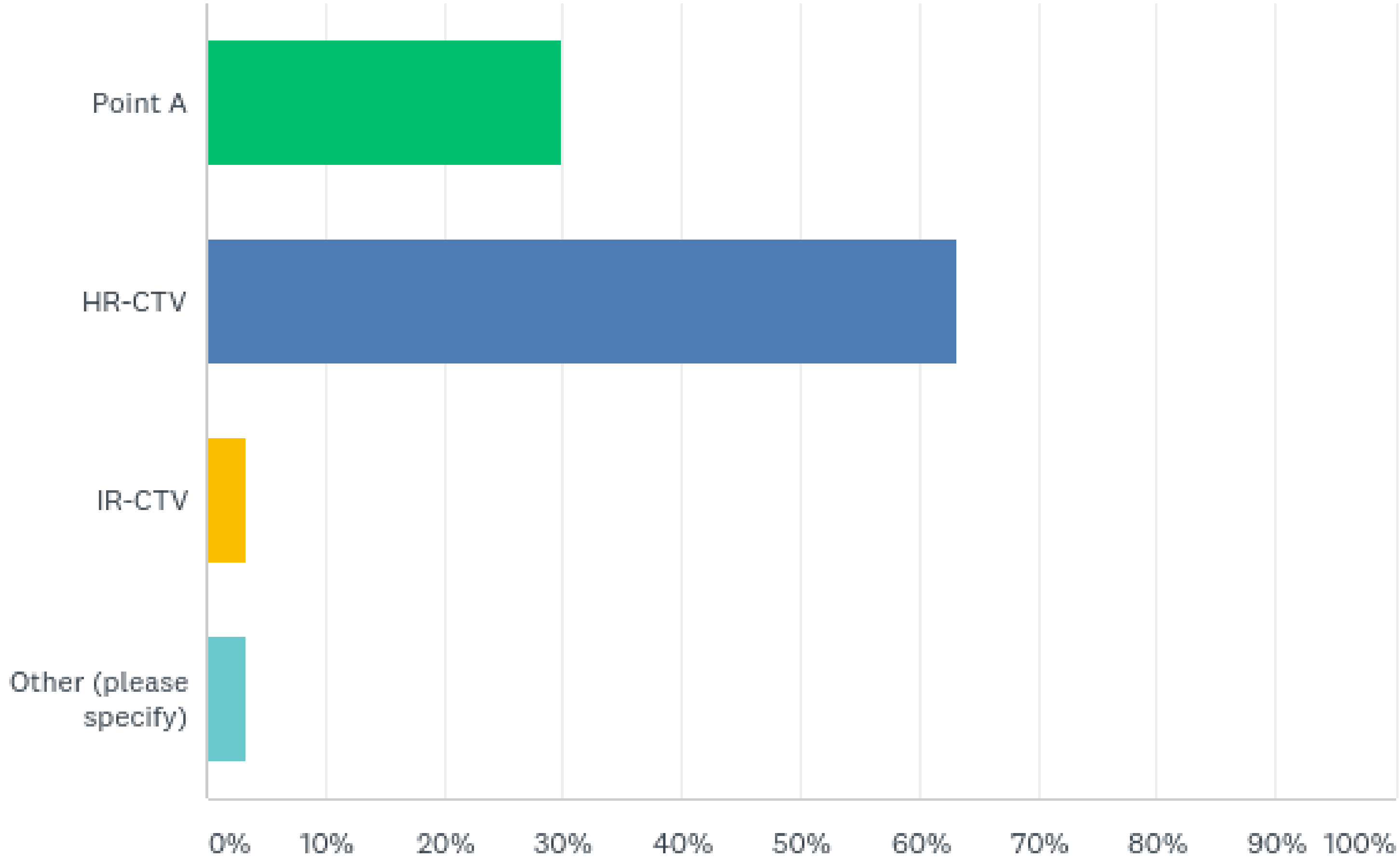
How is external beam pelvic radiotherapy typically delivered?



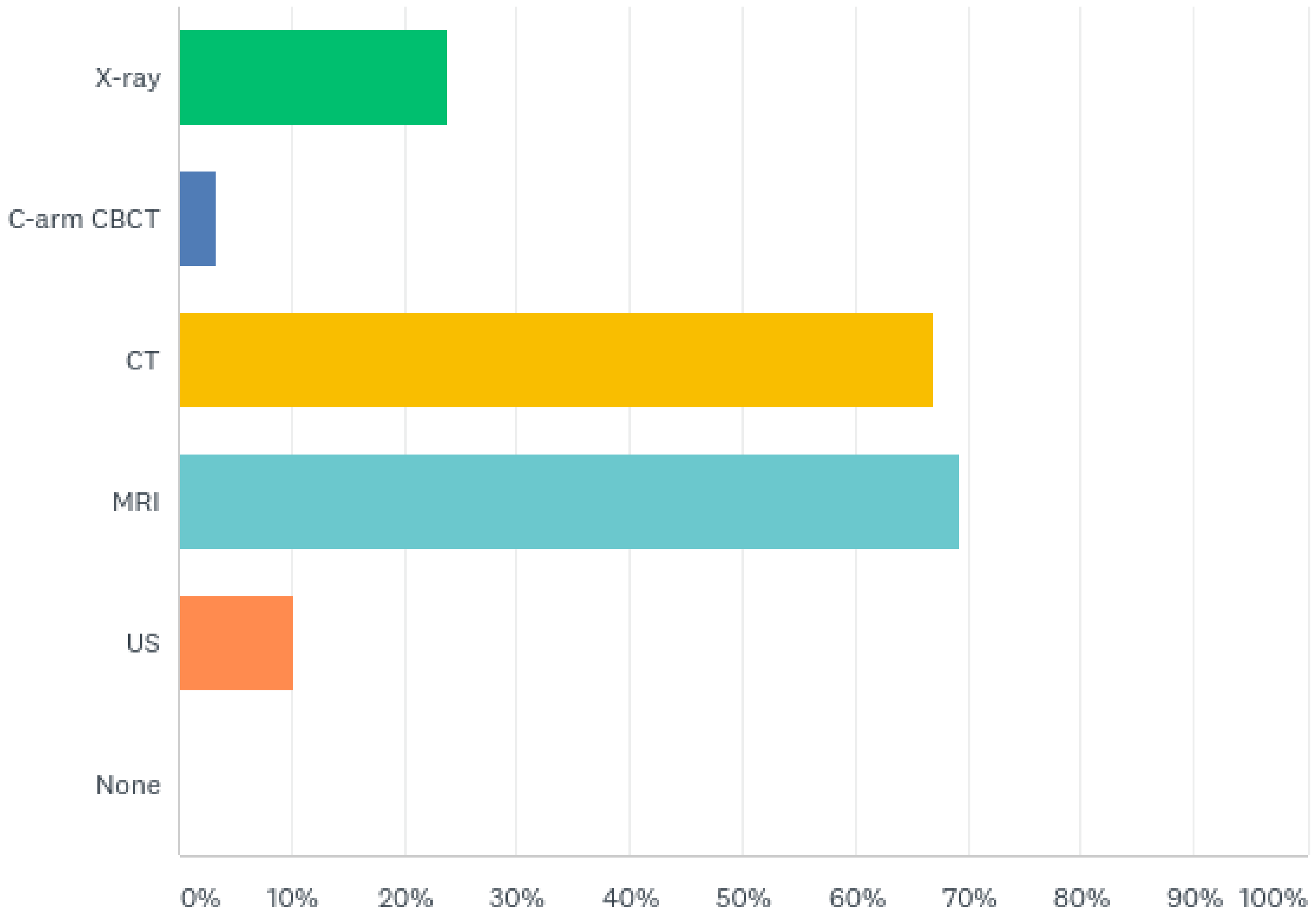
How do you perform image guidance for EBRT?



To which point/volume do you prescribe brachytherapy dose?

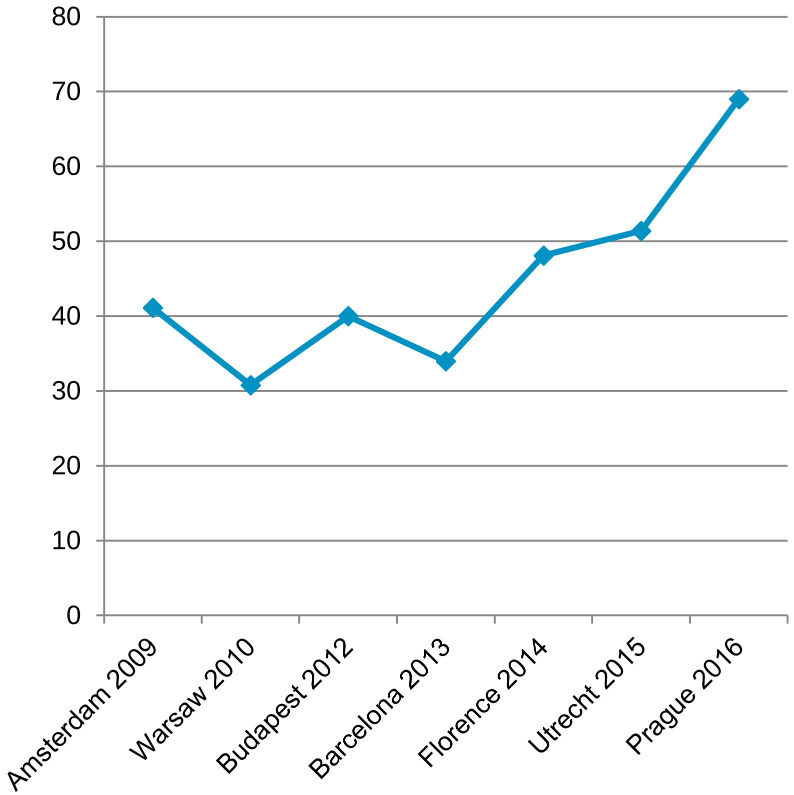


Which imaging do you perform with applicator in place?

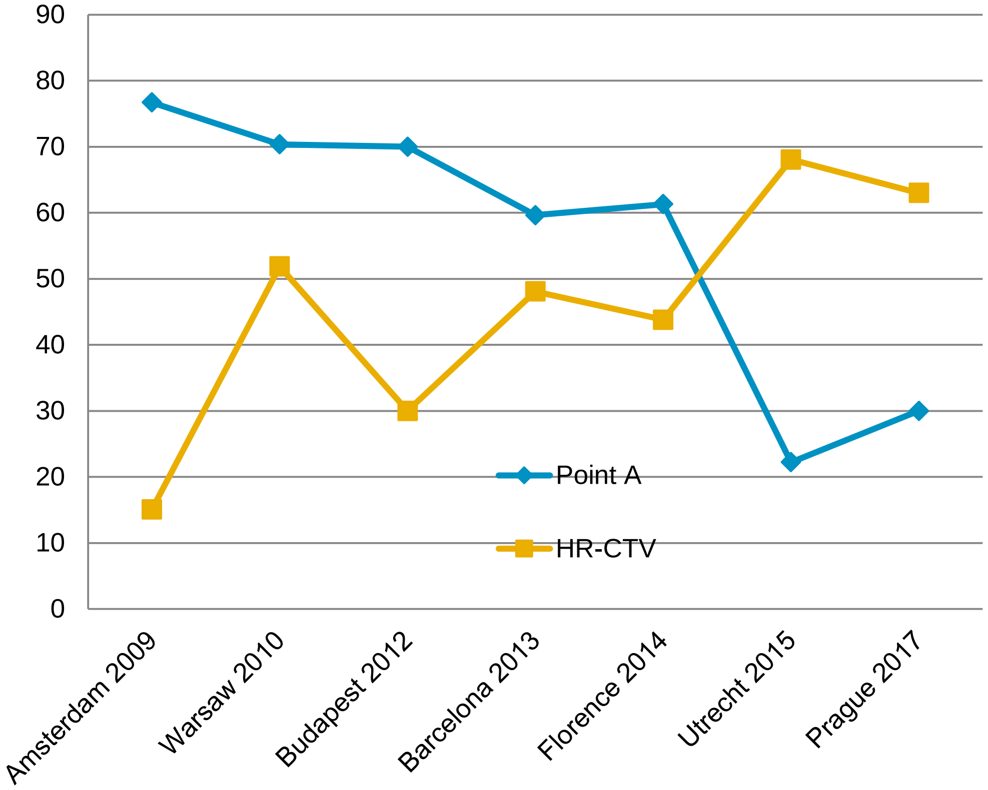


Evolution over time – ESTRO gyn course

MRI with applicator in place



Dose prescription



Support by industry

Elekta

VARIAN medical systems

Eckert & Ziegler
Contributing to saving lives

Organisation

- ***Local Organisor*:**
  - ***Hana Stankusova, Radiation Oncologist, University Hospital Motol (CZ)***
- ***ESTRO coordinator*:**
  - ***Melissa Vanderijst, Project Manager, ESTRO office, Brussels***
- ***Above all:***
  - ***The enthusiastic teaching staff***
  - ***The enthusiastic participants***

ESTRO School

Anatomical considerations
Role of clinical gynaecological examination
Staging

Christine Haie-Meder
Brachytherapy Unit

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

GUSTAVE ROUSSY
COMPREHENSIVE CANCER CENTER

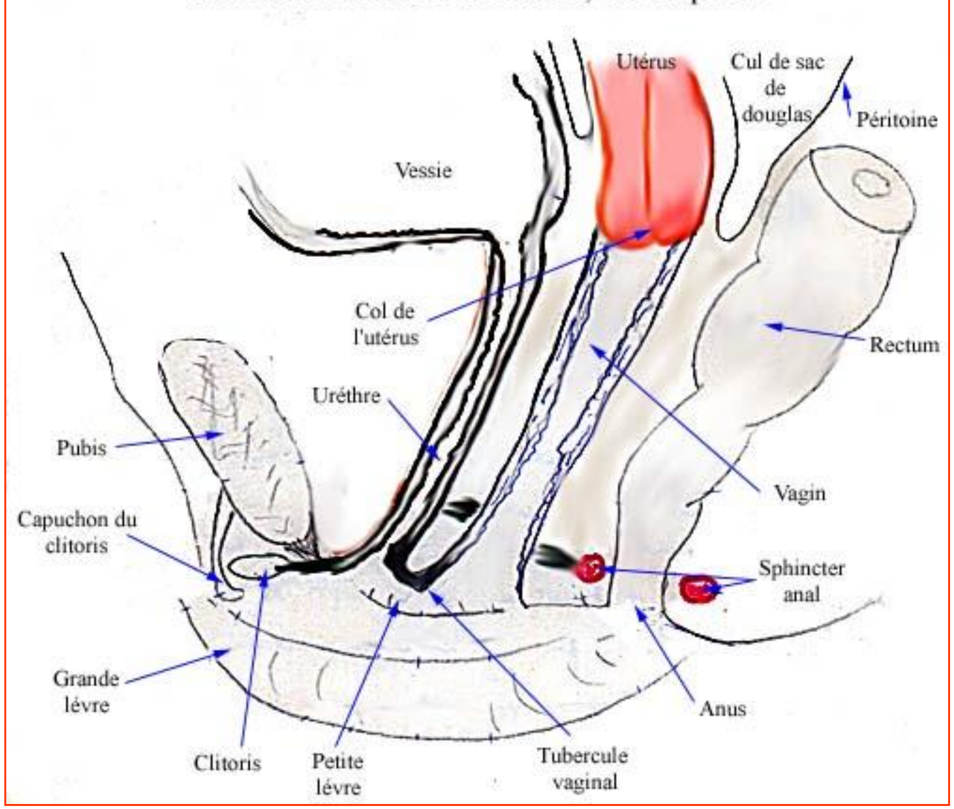
Cervix cancer : generalities

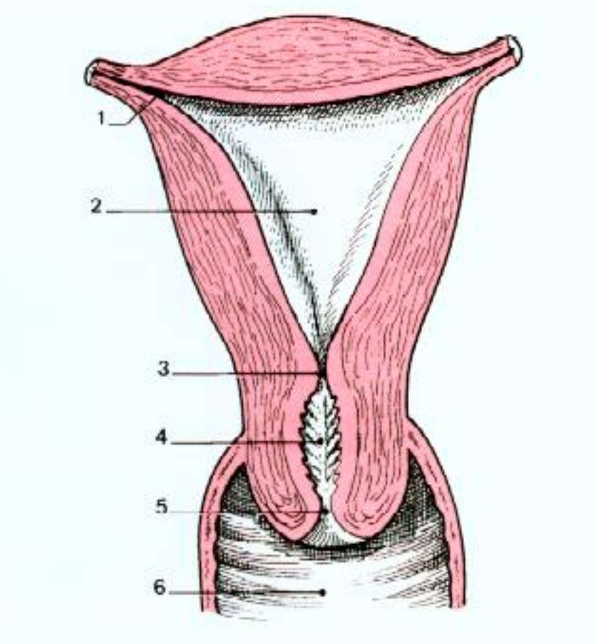
- **Curable disease**

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

Anatomical considerations

Uterus





Configuration interne de l'utérus (coupe frontale)

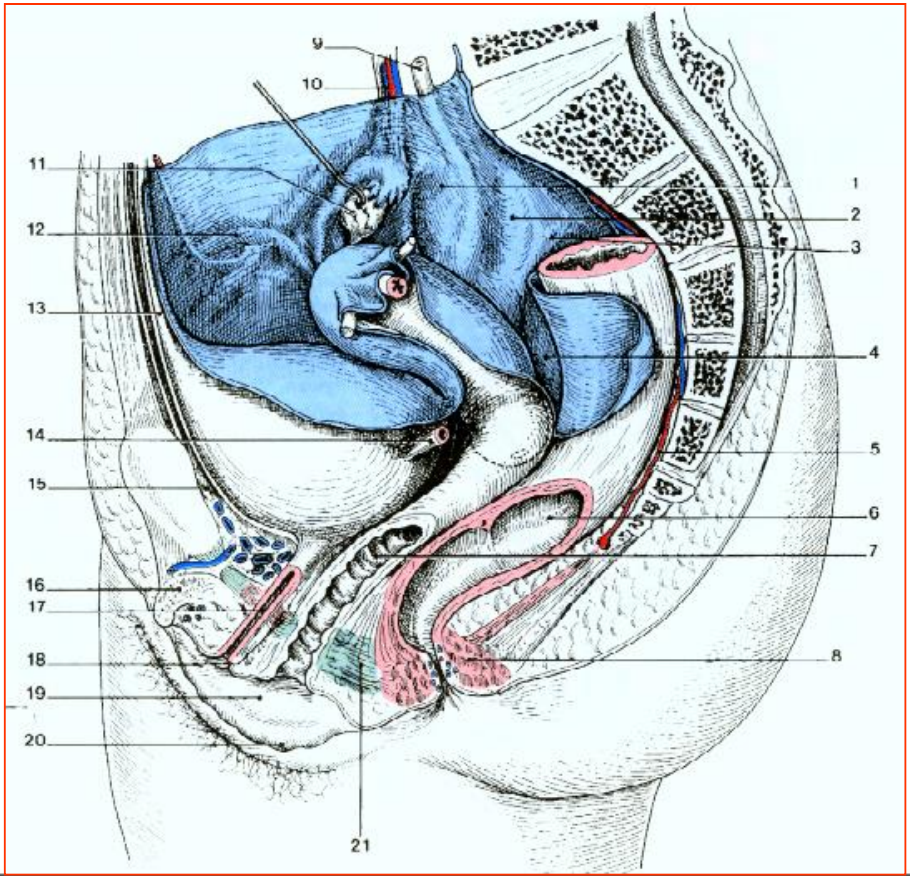
Hollow muscle

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

Anatomical considerations

Uterus

Supravaginal part
Bladder and rectum faces covered with peritoneum

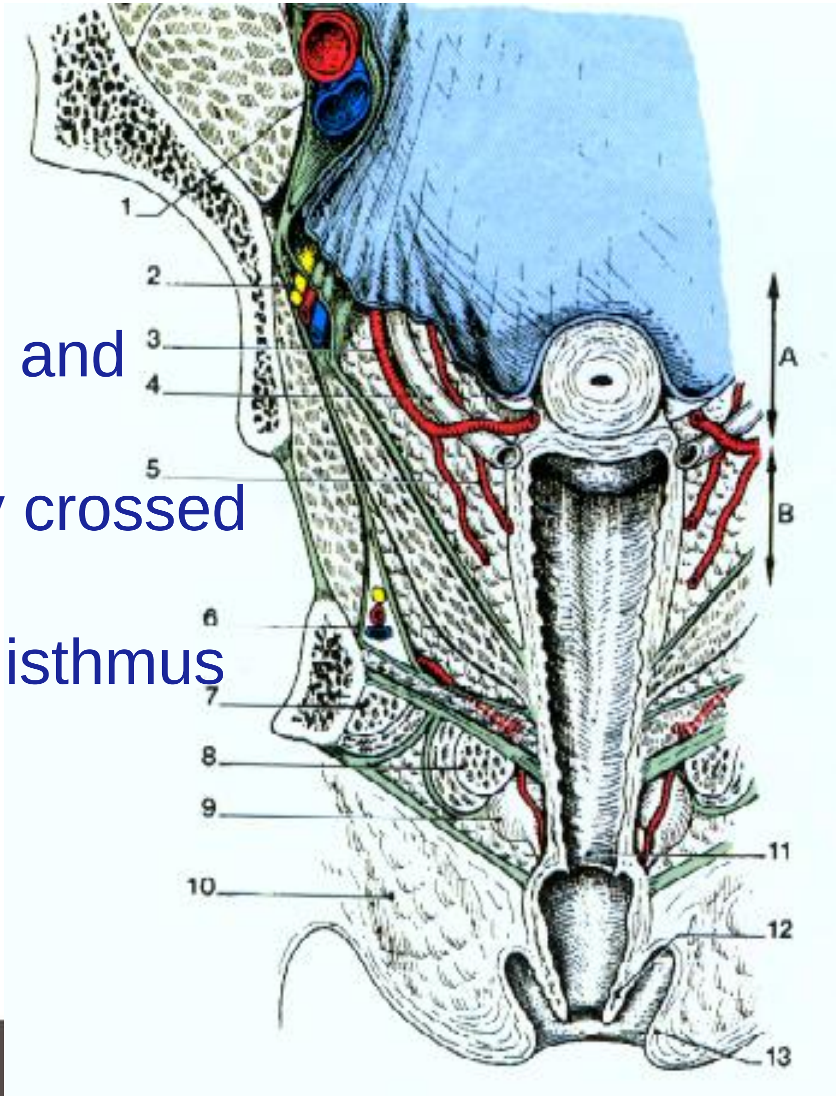


Vaginal part
Separated from the vagina
by vaginal fornices

Anatomical considerations

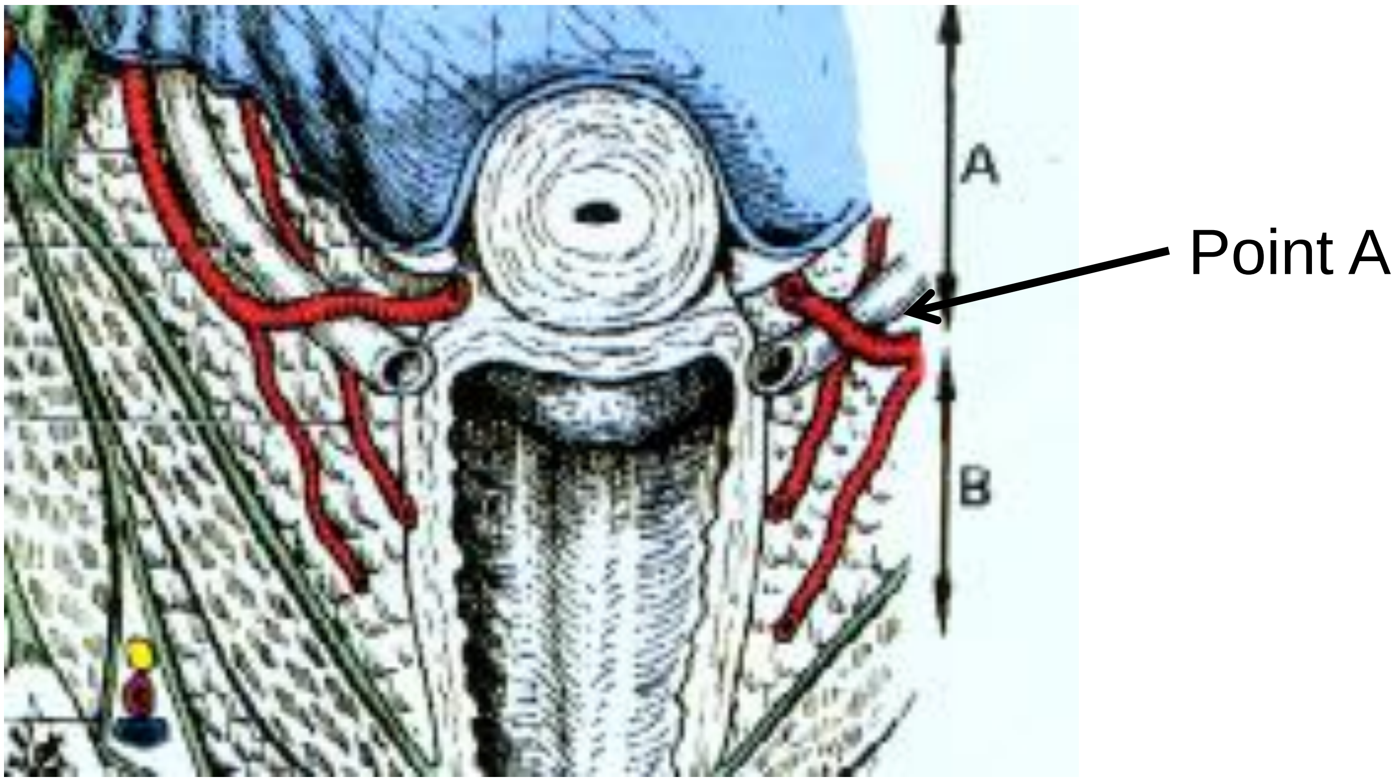
Uterus

- **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



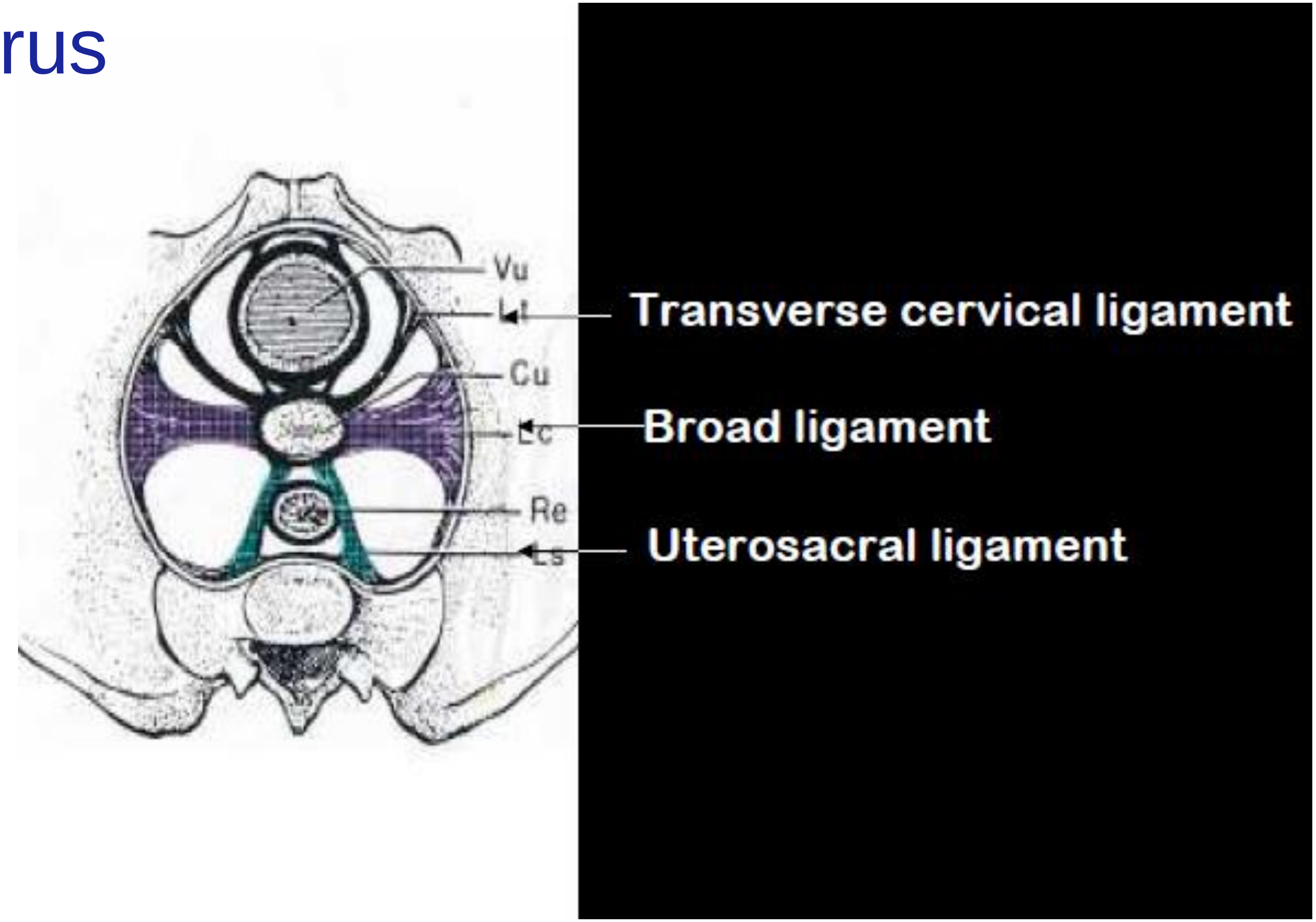
Anatomical considerations

Uterus



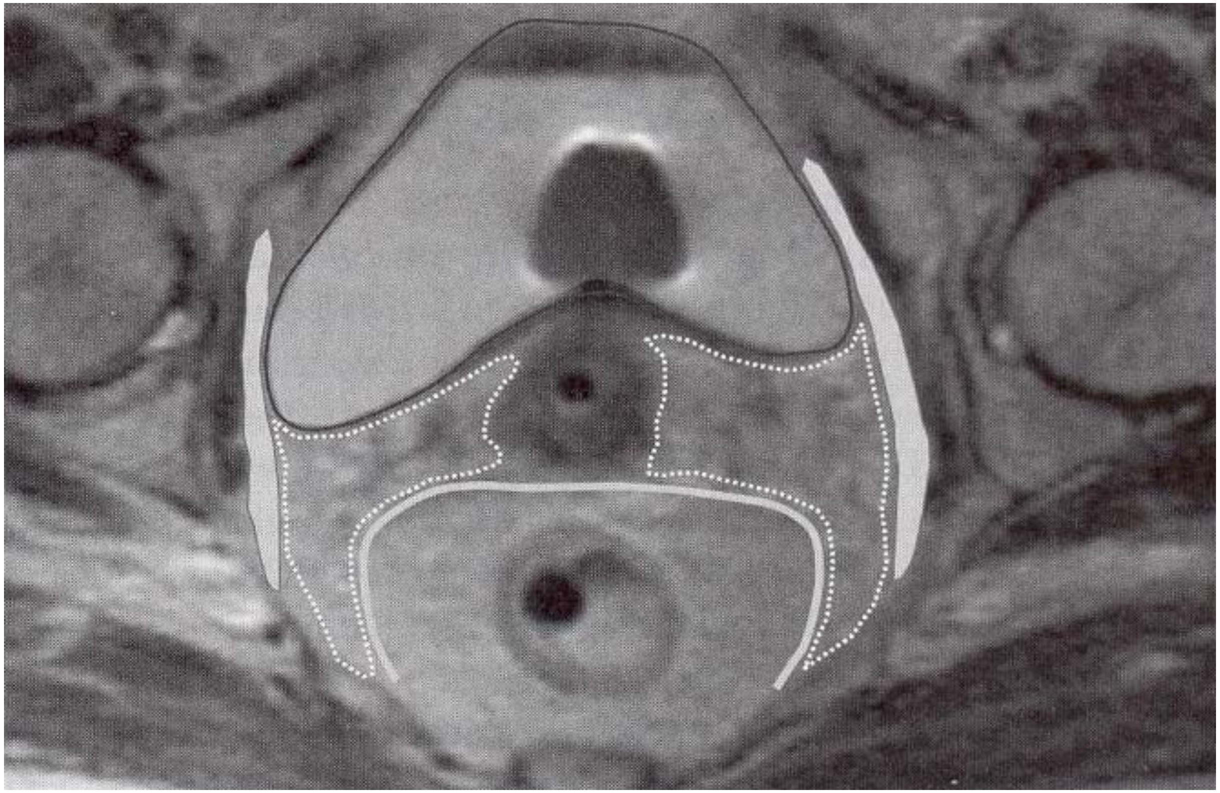
Anatomical considerations

Uterus



Anatomical considerations

Uterus Parametrial limits



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

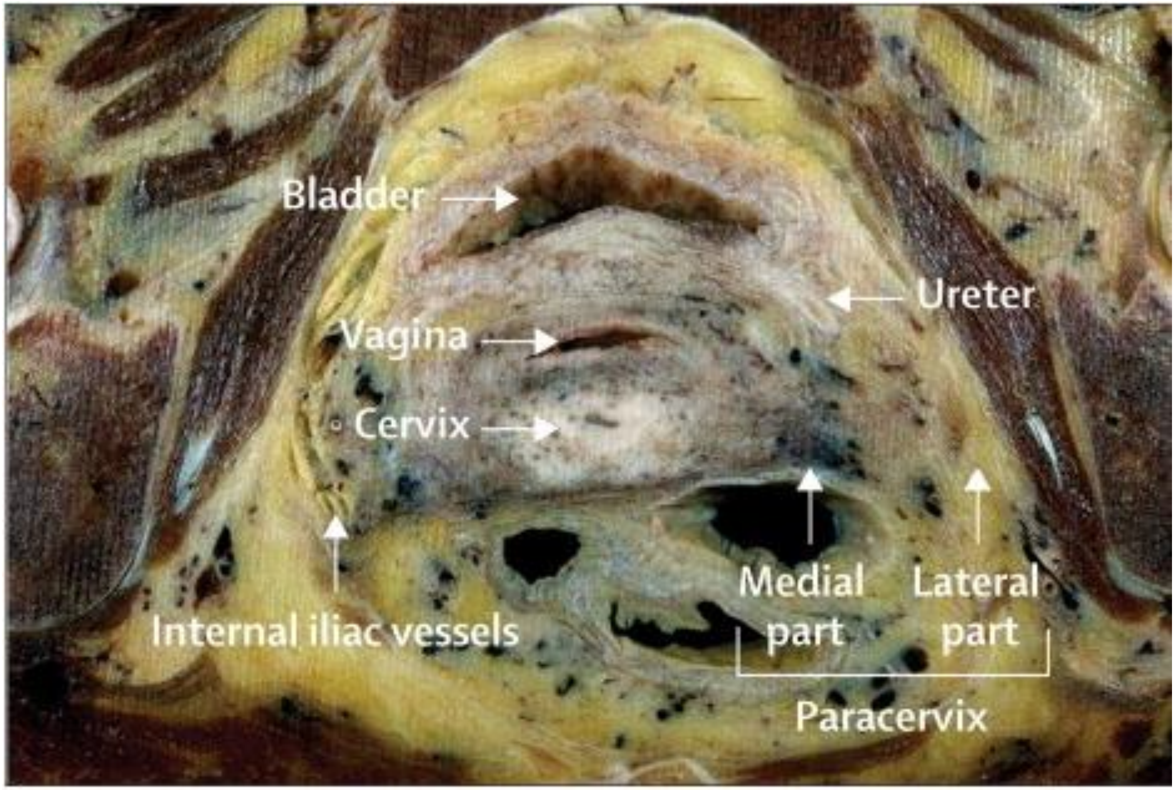


Figure 1

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.

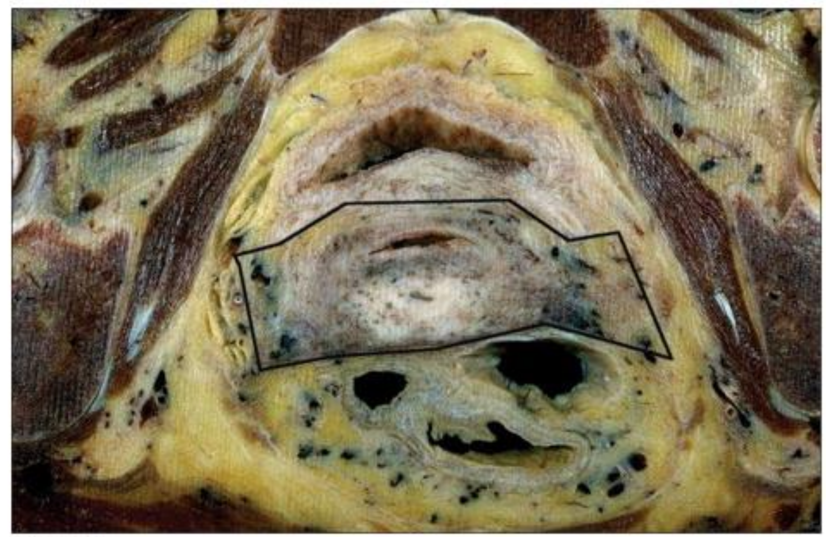


Figure 6

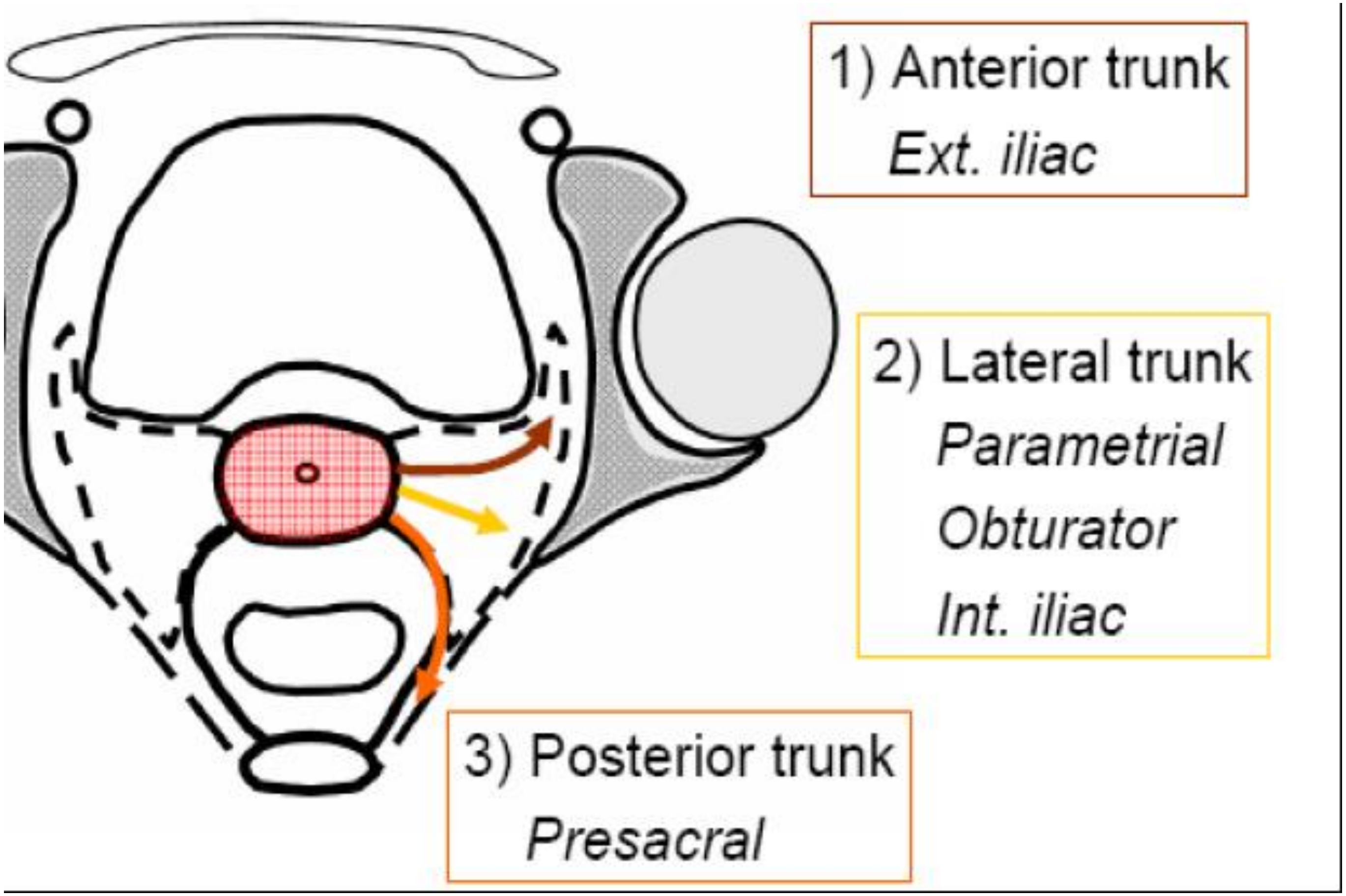
Type C2 radical hysterectomy

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

Anatomical considerations

Lymphatic drainage

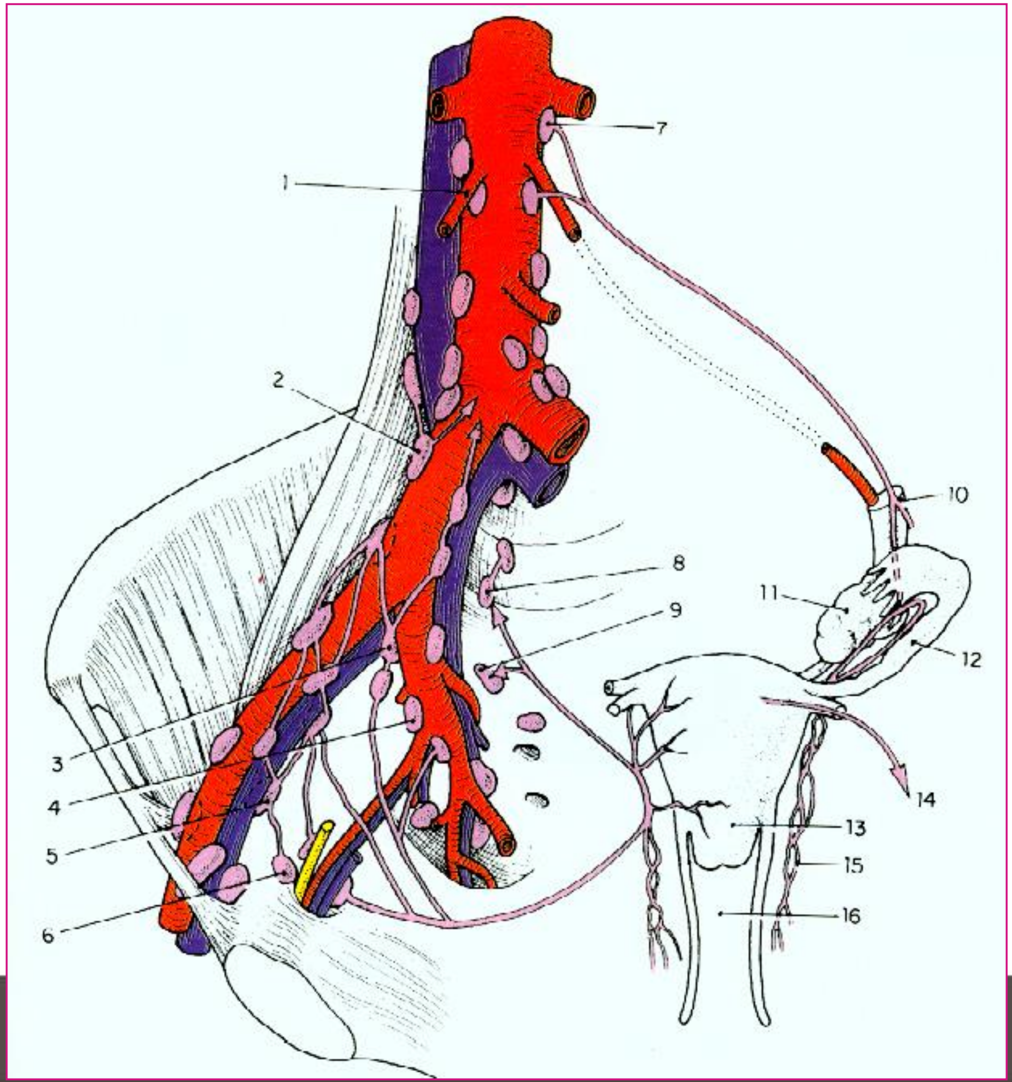
Uterus



Anatomical considerations

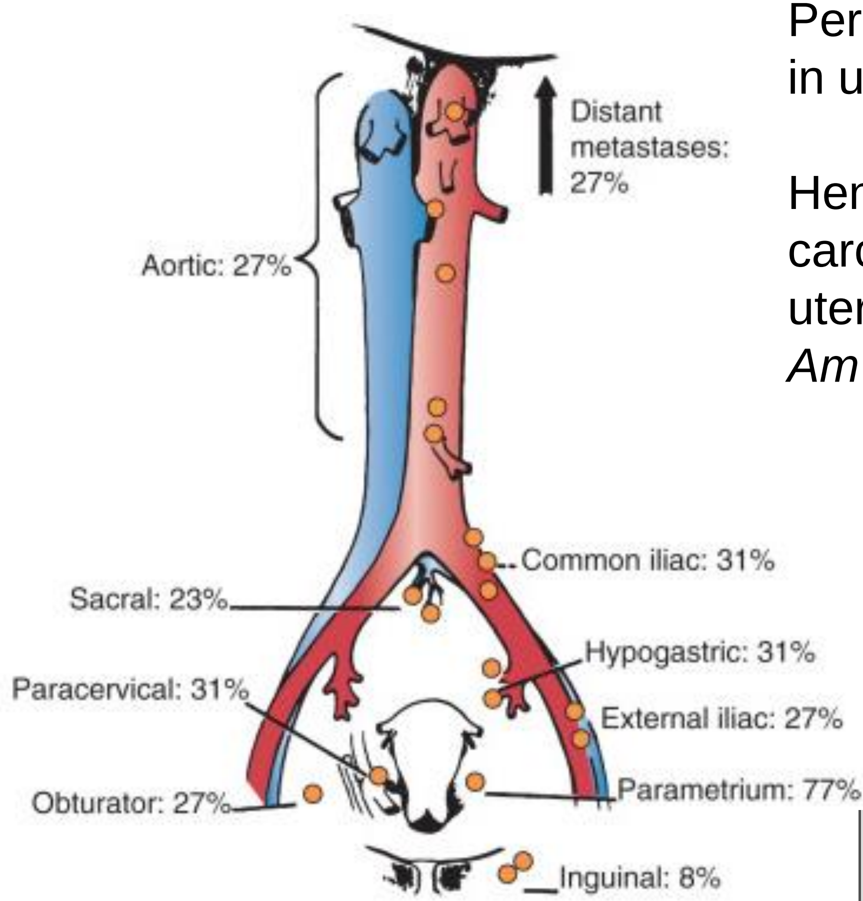
Lymphatic drainage

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

Lymph node involvement



Percentage involvement of draining lymph nodes in untreated patients with cervical cancer

Henriksen E. The lymphatic spread of carcinoma of the cervix and of the body of the uterus; a study of 420 necropsies
Am J Obstet Gynecol 1949;58:924-942

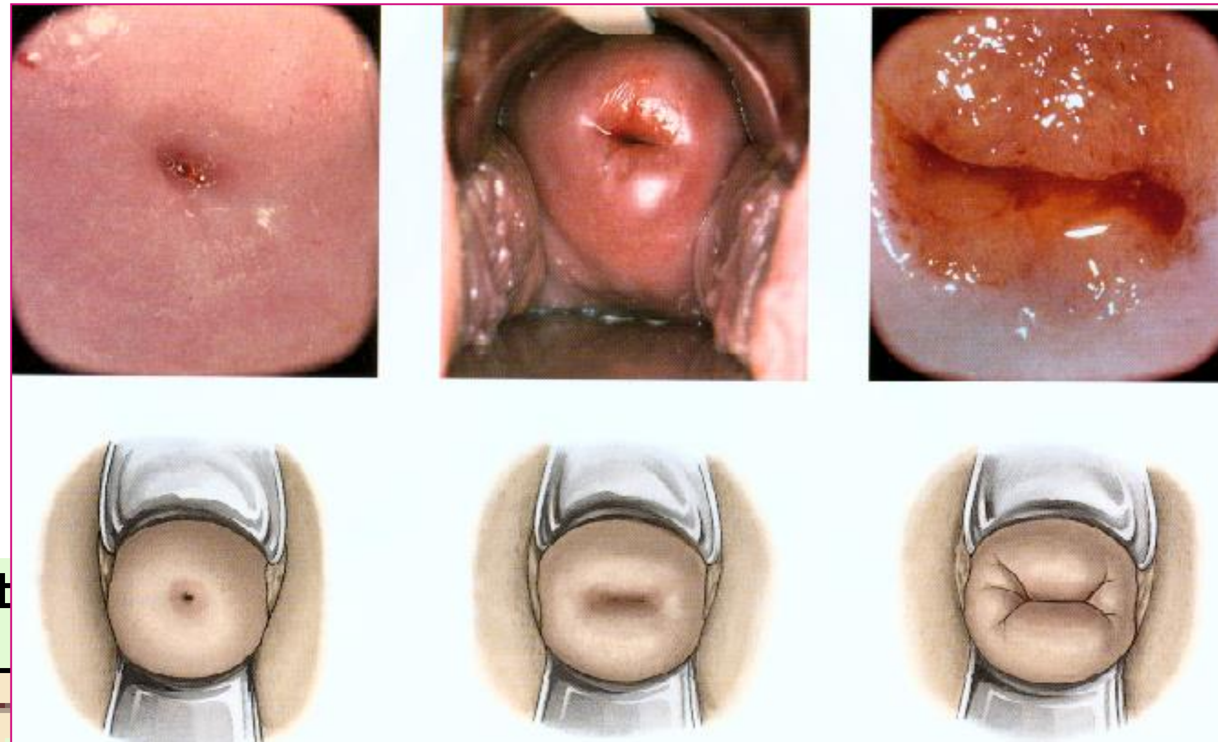
Percentage increase of pelvic and paraaortic node metastasis by clinical stage

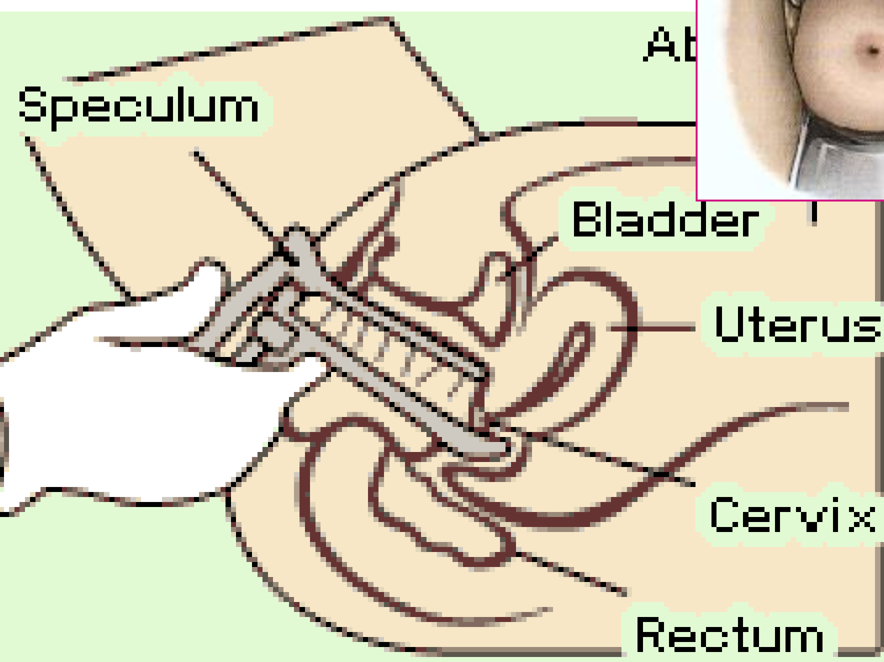
Clinical Stage	Positive Pelvic Nodes	Positive Periaortic Nodes
I	15.4	6.3
II	28.6	16.5
III	47.0	8.6

Role of clinical examination

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

Clinical examination





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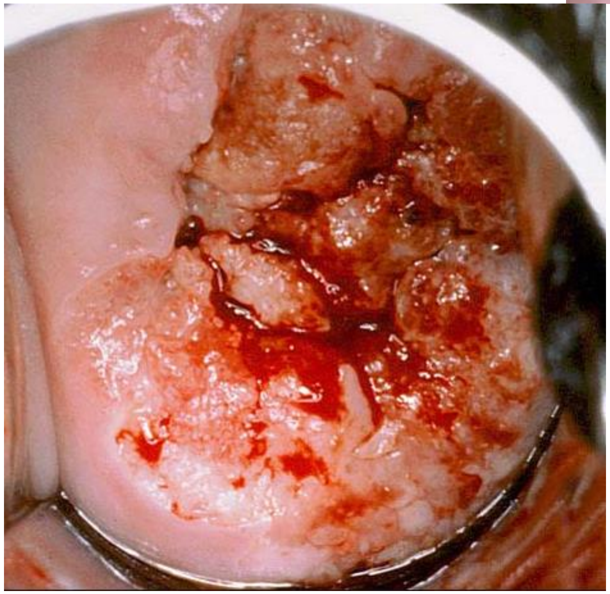
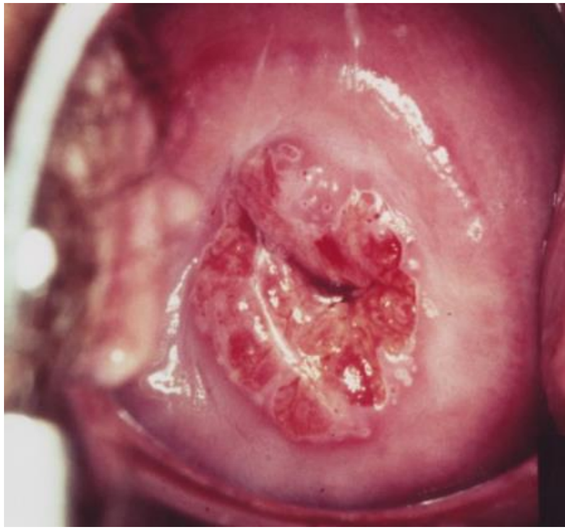
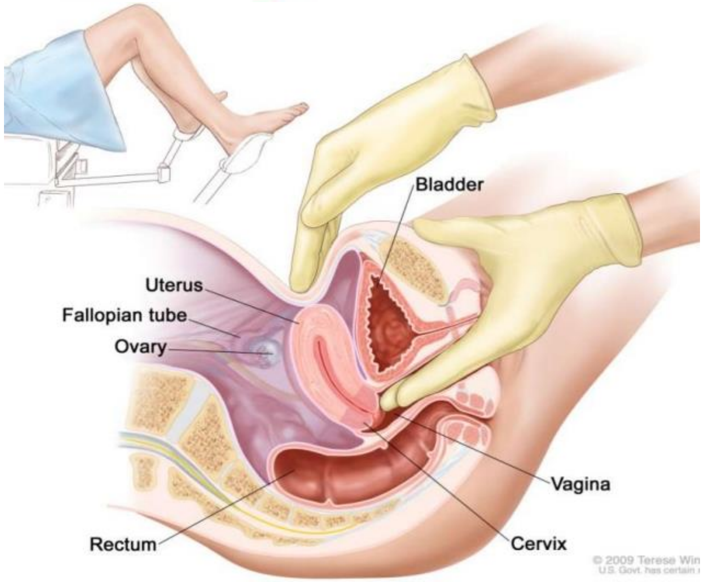




Clinical examination

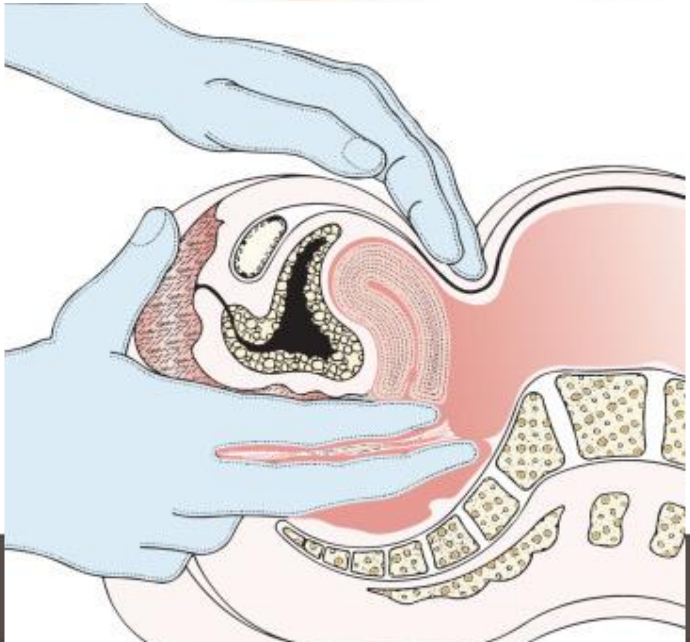


Tumor measurement

Tumor extension:

vagina (vaginal impression)

parametrium (rectal examination)



Staging

2 main classifications

- International Federation of Gynecology and Obstetrics : FIGO (last revision 2009)

- International Union against Cancer (UICC) : TNM

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

Seminars in Diagnostic Pathology

Issues and inconsistencies in the revised gynecologic staging systems

Lisa Cole, MD, Mark H. Stoler, MD

From the Robert E. Fechner Laboratory of Surgical Pathology, Department of Pathology, University of Virginia Health System, Charlottesville, Virginia.

Vulva = the only gynecologic site detailing pattern of nodal involvement, leading to very complex, heterogeneous pN/FIGO III staging categories

Table 1 Staging for vulvar carcinoma

TNM category	FIGO stage	Primary tumor (T)
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1a	IA	Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm†
T1b	IB	Lesions >2 cm in size or any size with stromal invasion >1.0 mm, confined to the vulva or perineum
T2‡	II	Tumor of any size with extension to adjacent perineal structures (lower/distal one-third of the urethra, lower/distal one-third of the vagina, anal involvement)
T3§	IVA	Tumor of any size with extension to any of the following: upper/proximal two-thirds of the urethra, upper/proximal two-thirds of the vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone
TNM category	FIGO stage	Regional lymph nodes (N)
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		One or 2 regional lymph node with the following features:
N1a	IIIA	• One or 2 lymph node metastasis each 5 mm or less
N1b	IIIA	• One lymph node metastasis 5 mm or greater
N2	IIIB	Regional lymph node metastasis with the following features:
N2a	IIIB	• Three or more lymph node metastases each less than 5 mm
N2b	IIIB	• Two or more lymph node metastases 5 mm or greater
N2c	IIIC	• Lymph node metastases with extracapsular spread
N3	IVA	Fixed or ulcerated regional lymph node metastases

*FIGO staging no longer includes stage 0 (Tis).

†The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

‡FIGO uses the classification T2/T3. This is defined as T2 in TNM.

§FIGO uses the classification T4. This is defined as T3 in TNM.

Cervix cancer

Table 3 Staging for cervix carcinoma

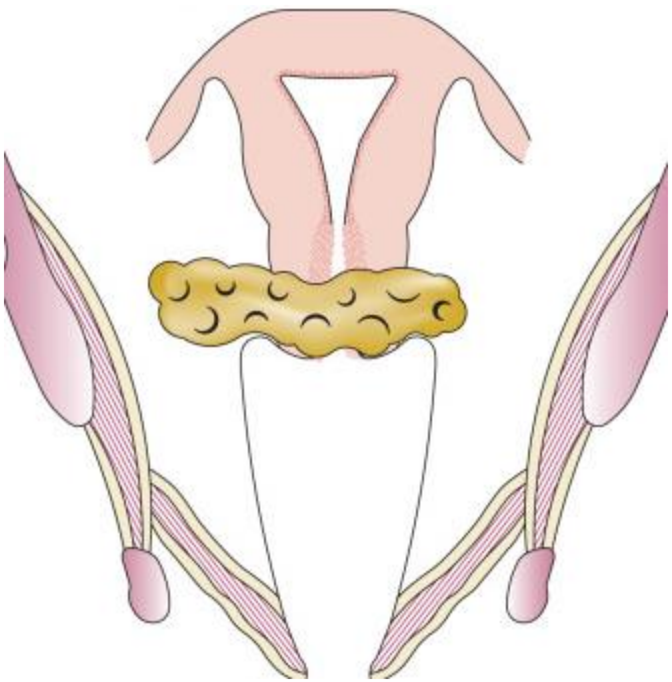
TNM category	FIGO stage	Primary tumor (T)
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a†	IA	• Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	• Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	• Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
T1b	IB	• Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	• Tumor without parametrial invasion
T2a1	IIA1	• Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	• Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	• Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIA	• Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	• Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)

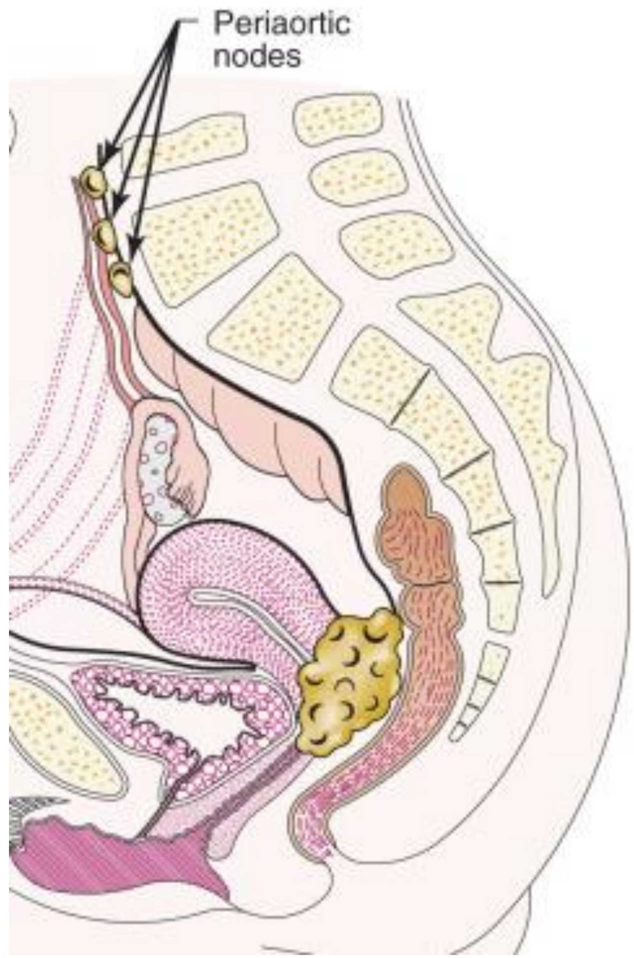
*FIGO staging no longer includes stage (Tis).
†All macroscopically visible lesions—even with superficial invasion—are T1b/IB.

Staging

- The most commonly used is FIGO classification
- Based on clinical examination
- Integration of MRI data

How would you stage the tumor with FIGO classification?

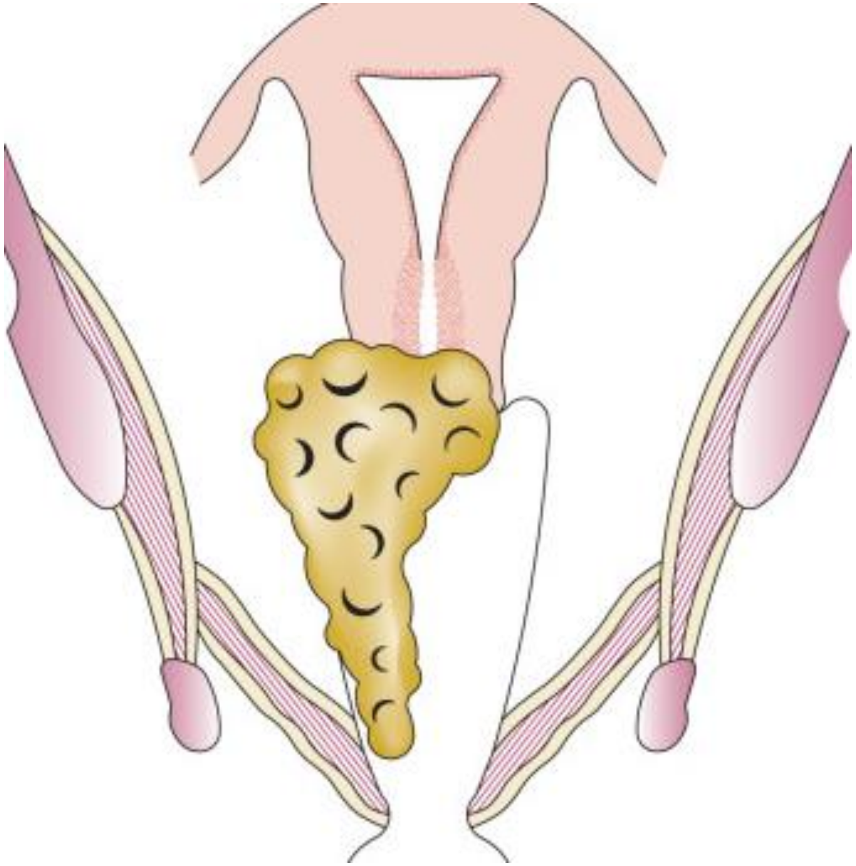




A. IB2
B. IIB
C. IIA2
D. IVA
E. IVB

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

How would you stage the tumor with FIGO classification?



A. IB2
B. IIB
C. IIA2
D. IIIA
E. IIIB

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)

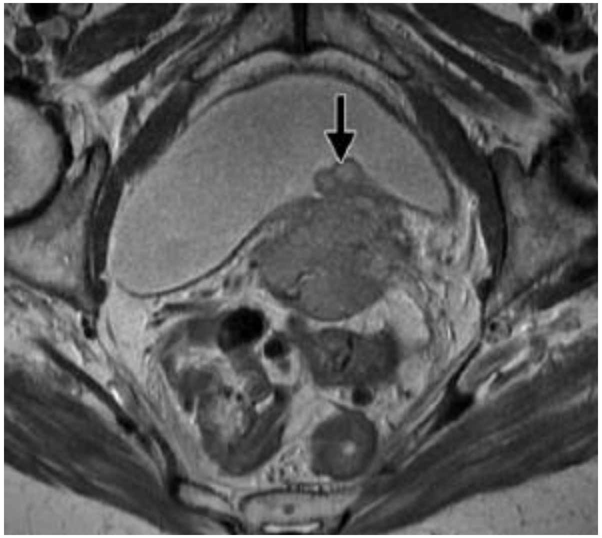
ANATOMIC STAGE/PROGNOSTIC GROUPS (FIGO 2008)			
Stage 0*	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIA1	T2a1	N0	M0
Stage IIA2	T2a2	N0	M0
Stage IIB	T2b	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

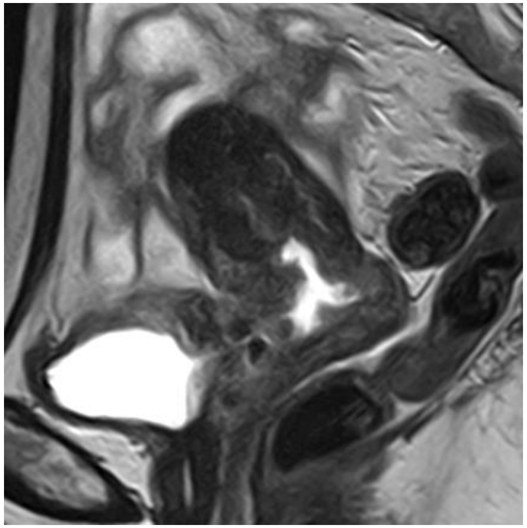
GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

ESTRO School

TABLE 2. MRI Staging

Stage	MRI Staging
Stage 0	Not visible
Stage I	
IAI	No tumor visible
IB2	Small enhancing tumor may be seen
IB	Tumor visible, intact stromal ring surrounding tumor
Stage II	
IIA	Disruption of low-signal-intensity vaginal wall (upper two thirds)
IIB	Complete disruption of stromal ring with tumor extending into the parametrium
Stage III	
IIIA	Invasion of lower one third of vagina
IIIB	Extension to pelvic muscles or dilated ureter
Stage IV	
IVA	Loss of low signal intensity in bladder or rectal wall
IIVB	Loss of low signal intensity in bladder or rectal wall





GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Clinical examination versus magnetic resonance imaging in the pretreatment staging of cervical carcinoma: systematic review and meta-analysis

Maarten G. Thomeer · Cees Gerestein · Sandra Spronk · Helena C. van Doorn · Els van der Ham · Myriam G. Hunink

- 3,254 patients included
- Pooled sensitivity for the evaluation of parametrial invasion:
  - 40 % (95 % CI 25–58) with clinical examination
  - 84 % (95 % CI 76–90) with MRI
- Pooled sensitivity for the evaluation of advanced disease:
  - 53 % (95 % CI 41–66) with clinical examination
  - 79 % (95 % CI 64–89) with MRI
- Pooled specificities were comparable between clinical examination and MRI
- Different technical aspects of MRI influenced the summary results

Clinical examination versus magnetic resonance imaging in the pretreatment staging of cervical carcinoma: systematic review and meta-analysis

Maarten G. Thomeer • Cees Gerestein • Sandra Spronk •
Helena C. van Doorn • Els van der Ham • Myriam G. Hunink

Key Points :

• MRI has a higher sensitivity than clinical examination for staging cervical carcinoma
• Clinical examination and MRI have comparably high specificity for staging cervical carcinoma
• Quality of clinical examination studies was lower than that of MRI studies
• The use of newer MRI techniques positively influences the summary results
• Anaesthesia during clinical examination positively influences the summary results

Eur Radiol 23:2005-18;2013

Conclusion

- Importance of clinical examination
- Lymphatic drainage
- Staging system knowledge
- Cervix cancer : TNM classification

ESTRO TEACHING COURSE BRACHYTHERAPY IN GYNAECOLOGIC MALIGNANCIES

3D image-based Normal Anatomy: UTERUS, PARAMETRIA, ORGANS AT RISK AND NODES (US, CT and MRI)

Dr Petrow – Department of Diagnostic Radiology

Institut Curie – Paris / France

institutCurie

Course's planning:

US, CT and MRI Radioanatomy:

- **Uterus (corpus uteri and cervix)**
- **Ovary**
- **Vagina**
- **Rectum, bladder**
- **MR radioanatomy of the parametrium**
- **MR radioanatomy in brachytherapy**

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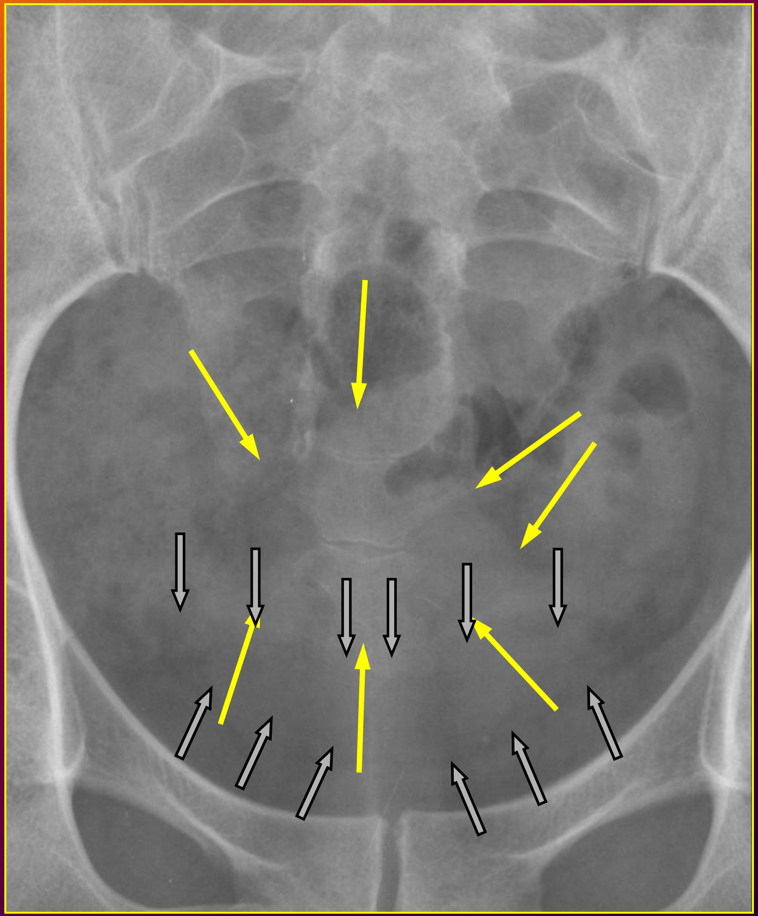
3D image-based anatomy: CR



CONVENTIONAL RADIOGRAPHY (CR):
UTERUS,VAGINA AND OVARY
HYSTEROGRAPHY

UTERUS

BLADDER

OVARIES ?

CERVIX UTERI ???

3D image-based anatomy: CR

CONVENTIONAL RADIOGRAPHY (CR):

UTERUS,VAGINA AND OVARY

HYSTEROGRAPHY:

- **Intracervical injection of CM**
- **Progressive injection of CM under pressure to obtain opacification of both tubae and the adjacent peritoneum**

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3D image-based anatomy: CR

3D image-based anatomy: CR

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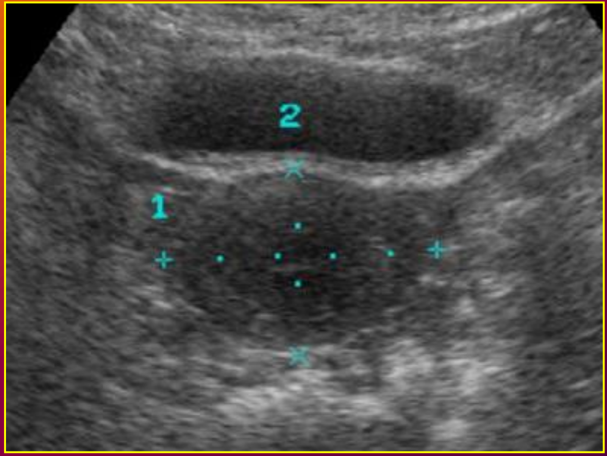
3D image-based anatomy: CT, US and MRI



Uterus - US:

Endometrium

- **3 phases:**
  - 1st phase :
    - thin
    - hyperechoic
    - <= 5 mm thickness
  - Periovulatory phase
  - 2nd phase :
    - thick
    - <= 10 mm

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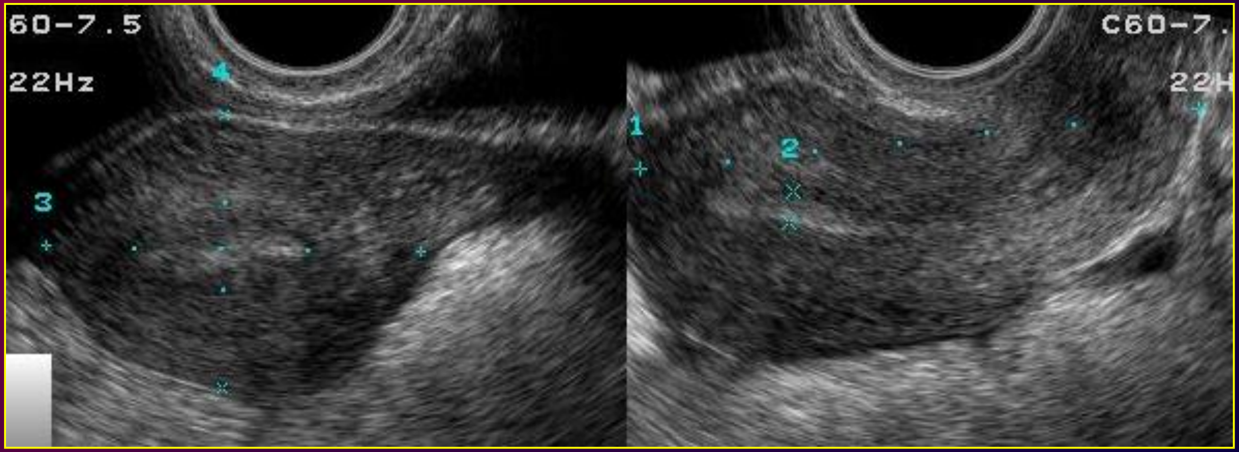
3D image-based anatomy: CT, US and MRI

Uterus – endovaginal ultrasound:

Endometrium



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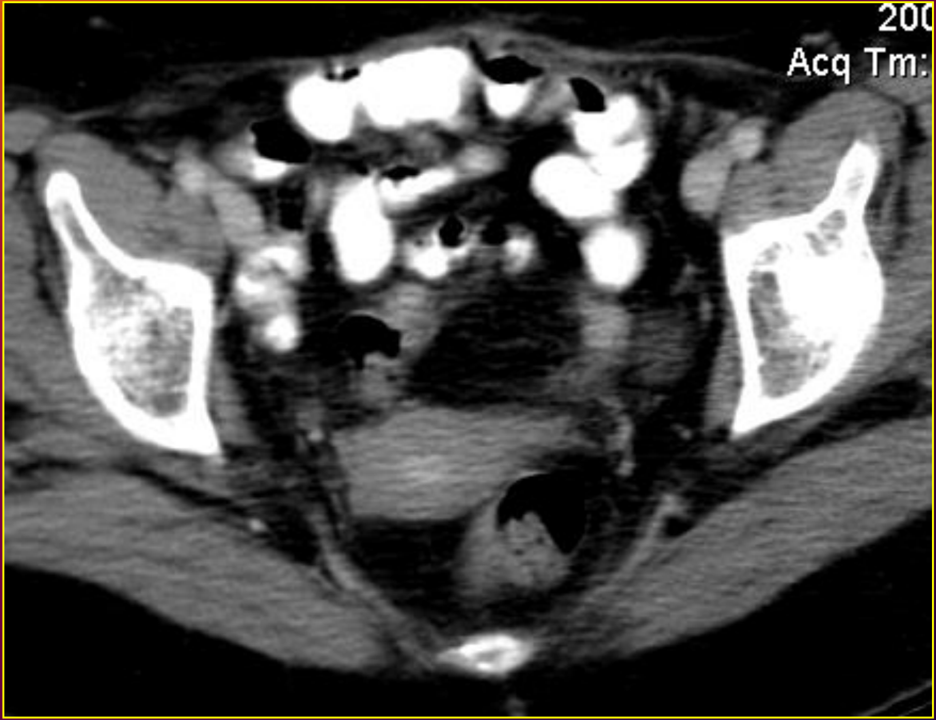
3D image-based anatomy: CT, US and MRI

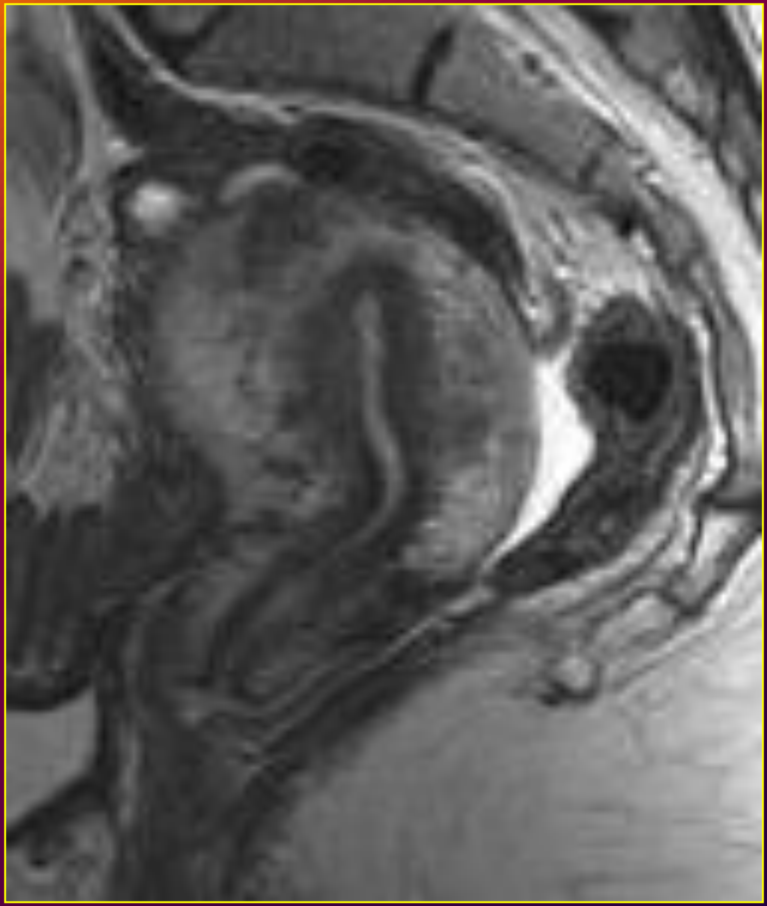


Uterus - CT:

Endometrium

- **hypointense**
- **Indistinguishable from myometrium on unenhanced CT scan**

3D image-based anatomy: CT, US and MRI

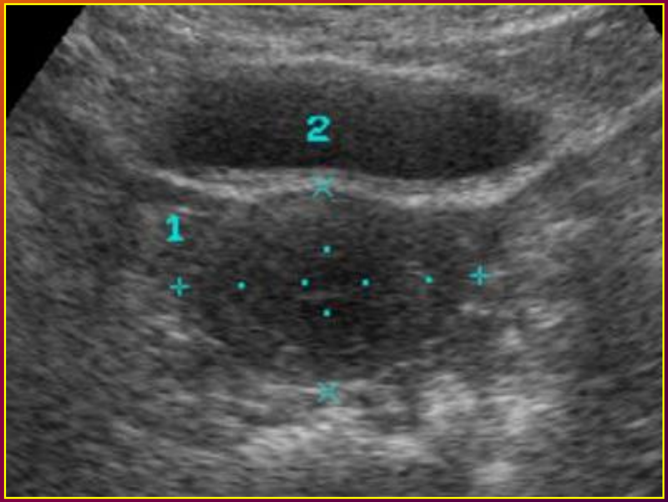


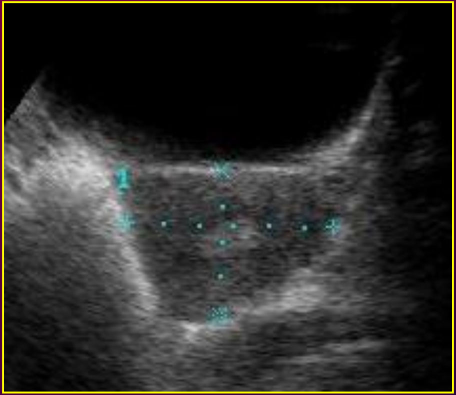
Uterus - MR:

Endometrium

- **High-signal intensity on T 2-weighted MR scans**
- **Indistinguishable from liquid in uterine cavity**
- **Enhancement variable**

3D image-based anatomy: CT, US and MRI





Uterus - US:

Myometrium

- **hypoechoic**
- **Can be the localisation of fibroids and adenomyosis**

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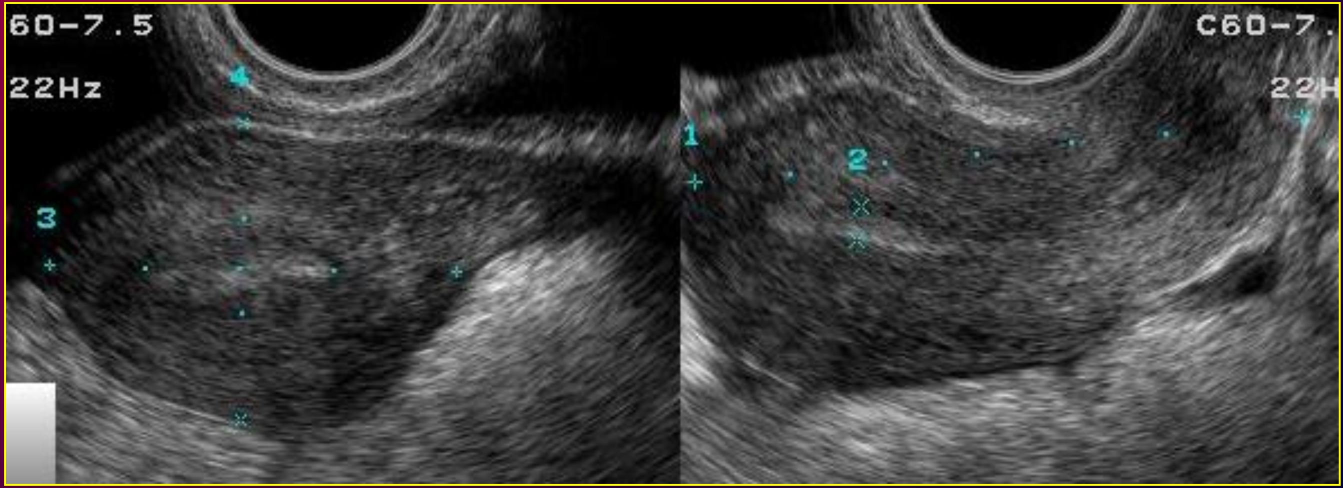
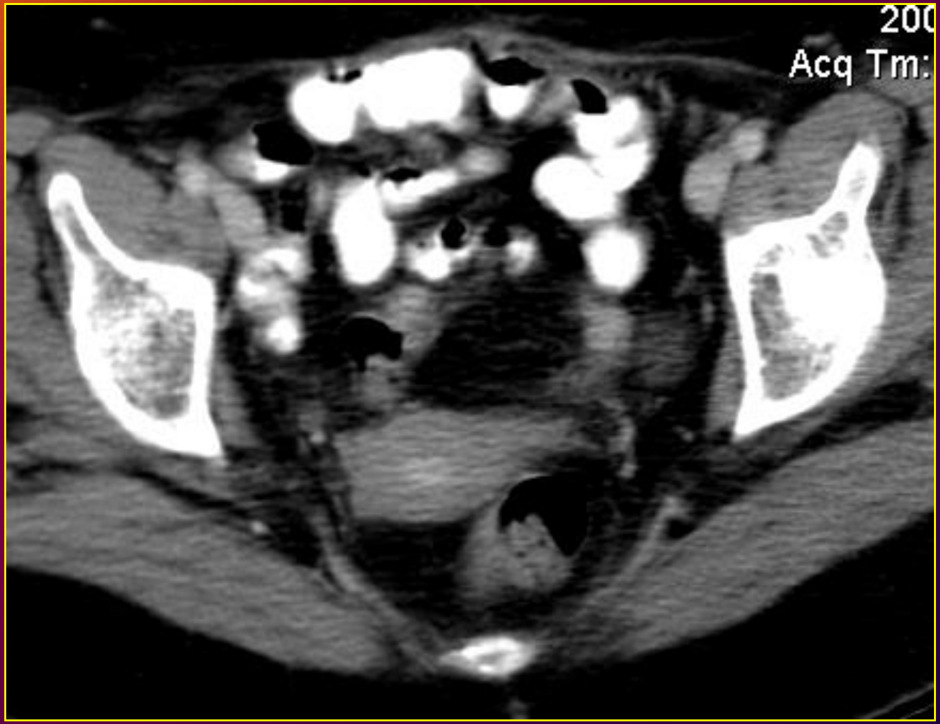
3D image-based anatomy: CT, US and MRI

Uterus – endovaginal ultrasound:

Myometrium



3D image-based anatomy: CT, US and MRI



Uterus - CT:

Myometrium

- **hypointense**
- **Indistinguishable from endometrium on unenhanced CT scan**
- **Enhances after CM injection,**
- **Homogenous on delayed CT scans**

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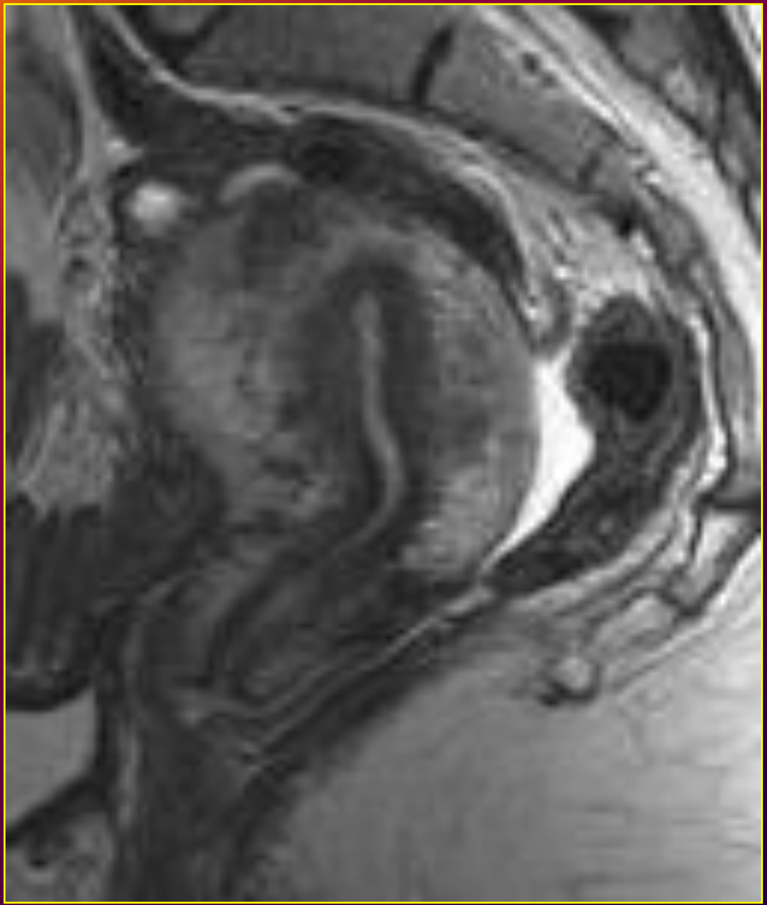
3D image-based anatomy: CT, US and MRI



Uterus - MR:

Myometrium

- **Inner myometrium = junctional zone = low signal intensity**
- **Outer myometrium = high-signal intensity**
- **Signal intensiy decreases with age**

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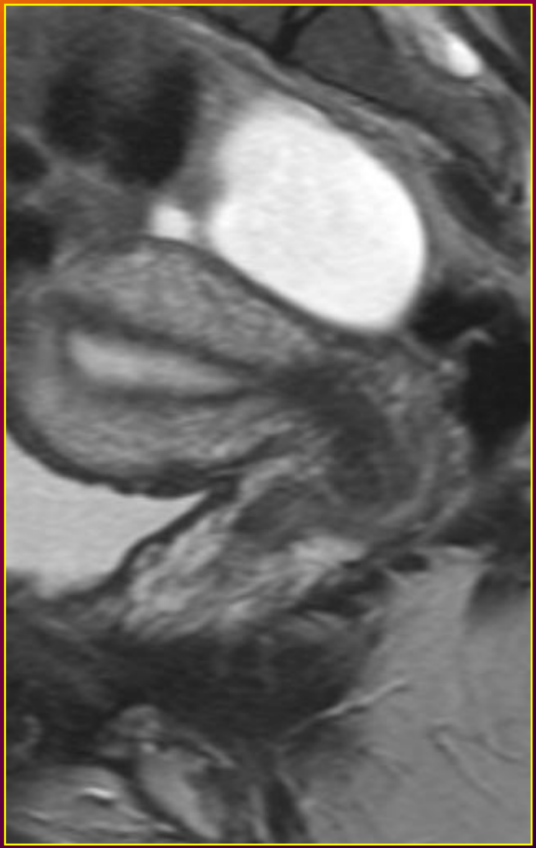
3D image-based anatomy: CT, US and MRI



Uterus - MR:

Myometrium

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- **Outer myometrium = high-signal intensity**
- **Signal intensiy decreases with age**

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3D image-based anatomy: CT, US and MRI

Uterus - MR:

Myometrium - Endometrium

- **Vascularisation**

3D image-based anatomy: CT, US and MRI

Uterus - MR:

Myometrium - Endometrium

- **Vascularisation**

3D image-based anatomy: CT, US and MRI

Uterus - MR:

Myometrium - Endometrium

- **Vascularisation**

3D image-based anatomy: CT, US and MRI

Uterus - MR:

Myometrium - Endometrium

- **Vascularisation**

3D image-based anatomy: CT, US and MRI

Uterus - MR:

Myometrium - Endometrium

- **Vascularisation**

3D image-based anatomy: CT, US and MRI

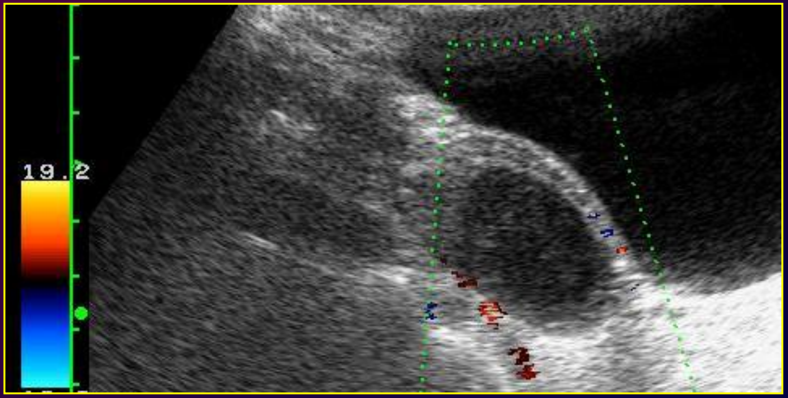
Ovary -Ultrasound:

Contains follicles

- **Peripherically located**
- **Number decreases with age**

Intraperioneal organ (mobility)

- **Ovarian stroma**
    - Central



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3D image-based anatomy: CT, US and MRI

Ovary - CT:

Hypointense

Peripheral enhancement

Limitation:

Decrease of number of follicles

Decrease of size

Fibrous bands

Contrast media

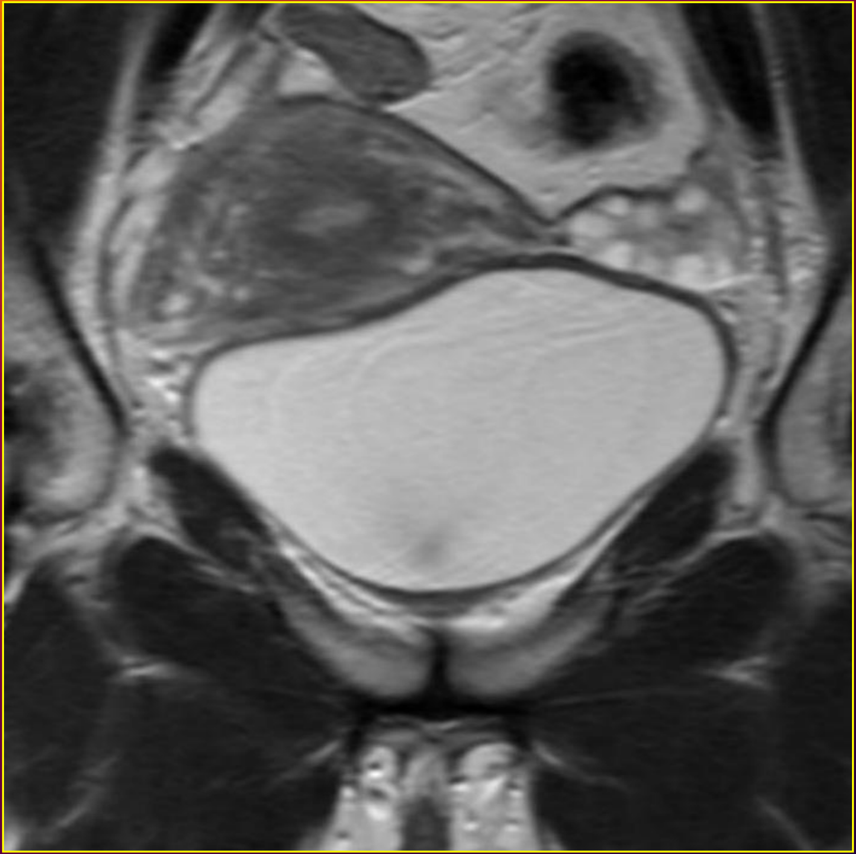
oral CM

intravenous CM

3D image-based anatomy: CT, US and MRI

3D image-based anatomy: CT, US and MRI

3D image-based anatomy: CT, US and MRI



Ovary - MR:

- **Follicle : High-signal intensity on T 2-weighted MR scans**
- **Ovarian capsule : low-signal intensity band**
- **Ovarian stroma : intermediate signal intensity**

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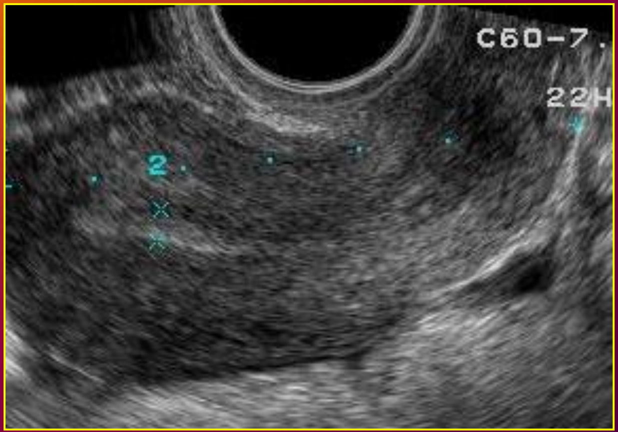
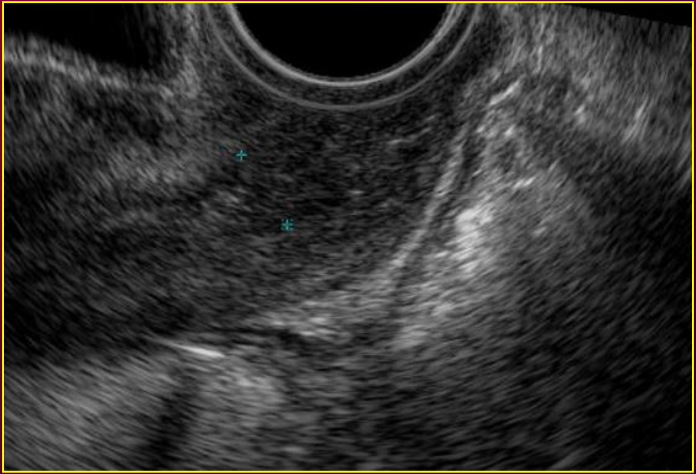
3D image-based anatomy: CT, US and MRI





Cervix - US:

Transabdominal : difficult examination

Endovaginal ultrasound:

- **Hyperechoic stripe**
- **Anechoic central stripe in 2nd part of cycle (cervical secretions)**

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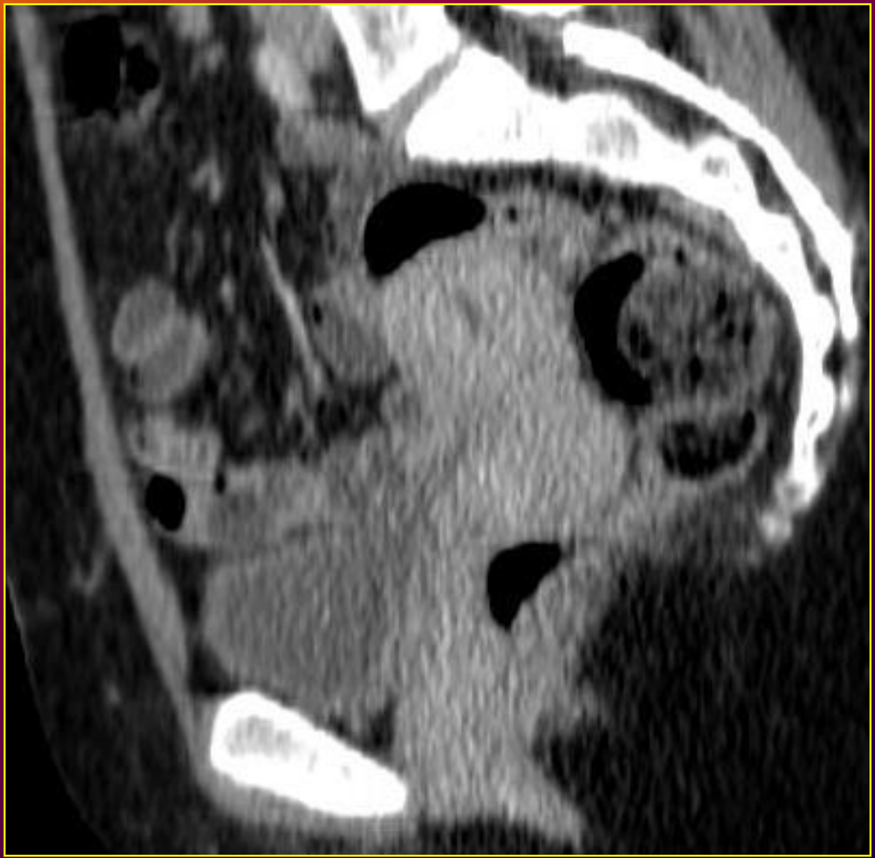
3D image-based anatomy: CT, US and MRI



Cervix - CT:

Difficult examination

(axial CT)

- **Confounding with vaginal fornices, bladder and rectum**
- **No distinguished border with corpus uteri**
- **Isointense to uterine body**
- **Less enhancing than corpus after CM injection**

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3D image-based anatomy: CT, US and MRI

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3D image-based anatomy: CT, US and MRI

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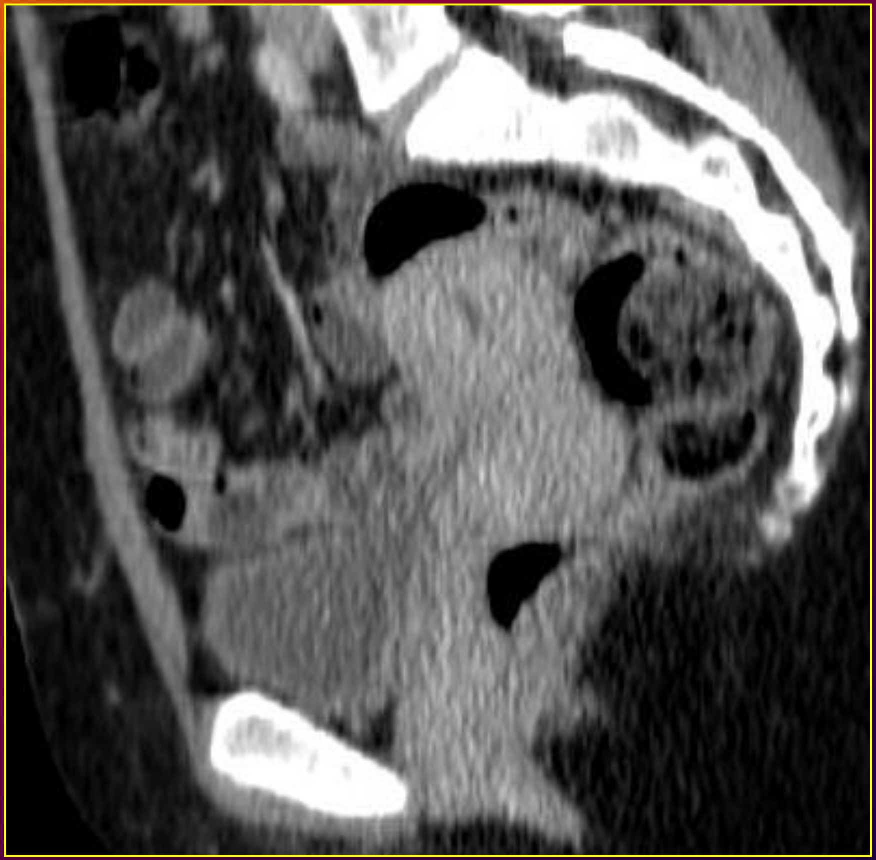
3D image-based anatomy: CT, US and MRI



Cervix - CT:

Difficult examination

(axial CT)

- **Confounding with vaginal fornices, bladder and rectum**
- **No distinguished border with corpus uteri**

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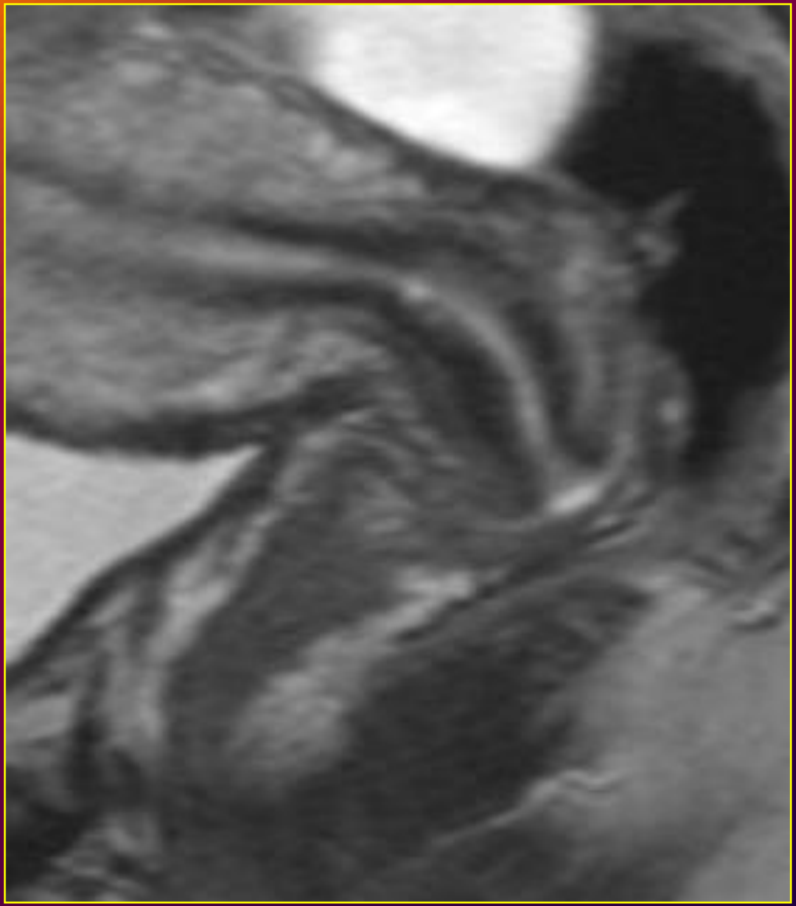
3D image-based anatomy: CT, US and MRI



Cervix - MR:

Zonal Anatomy (young)

- **Hyperintense endocervical canal (mucosal secretions and endocervical glands)**
- **Inner cervical stroma**

= low signal intensity

- **Outer cervical stroma**

= high signal intensity

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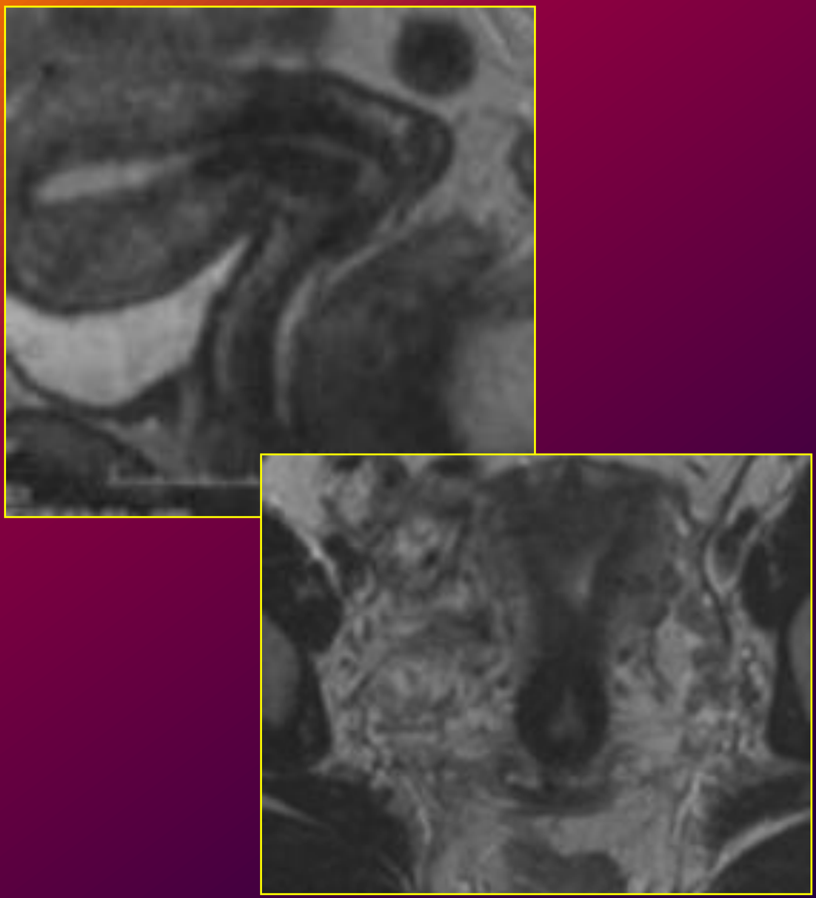
3D image-based anatomy: CT, US and MRI



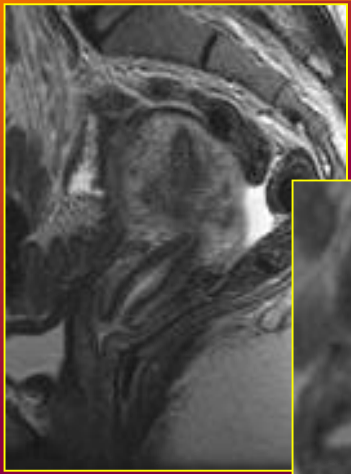
Cervix - MR:

Zonal Anatomy (young)

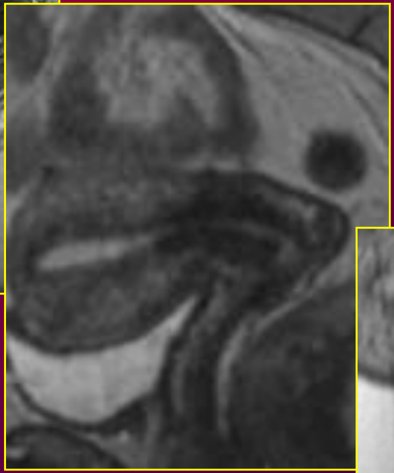
Limits :

- **Sagittal : corpus**
- **Axial : entry of the uterine artery 5 mm upwards**

3D image-based anatomy: CT, US and MRI



♀, 20 y



♀, 30 y

♀, 40 y

Cervix - MR:

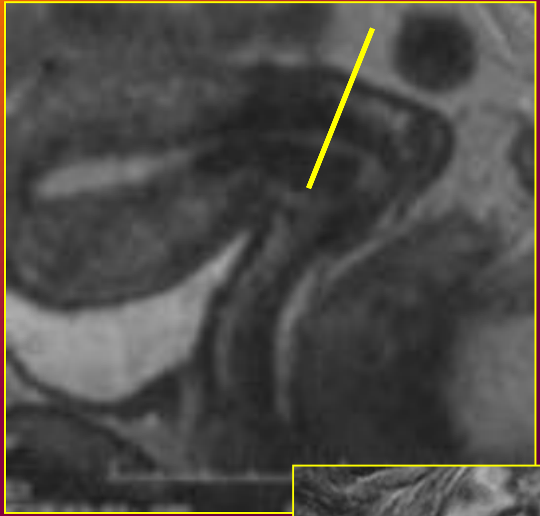
Zonal Anatomy (young)

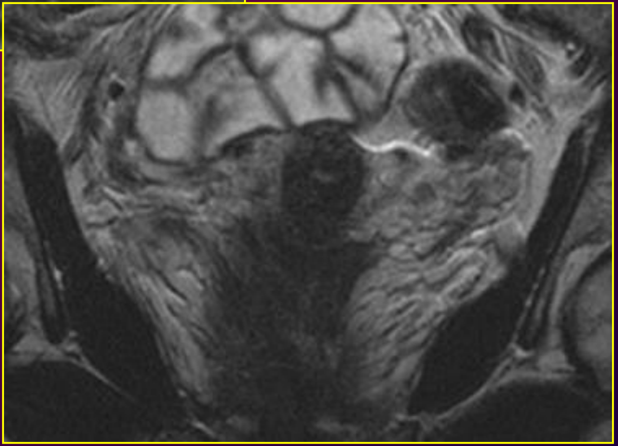
Limits :

- **Sagittal : corpus**
- **Axial : entry of the uterine artery 5 mm upwards**

Age-related modifications

3D image-based anatomy: CT, US and MRI





Coronal view

Cervix - MR:

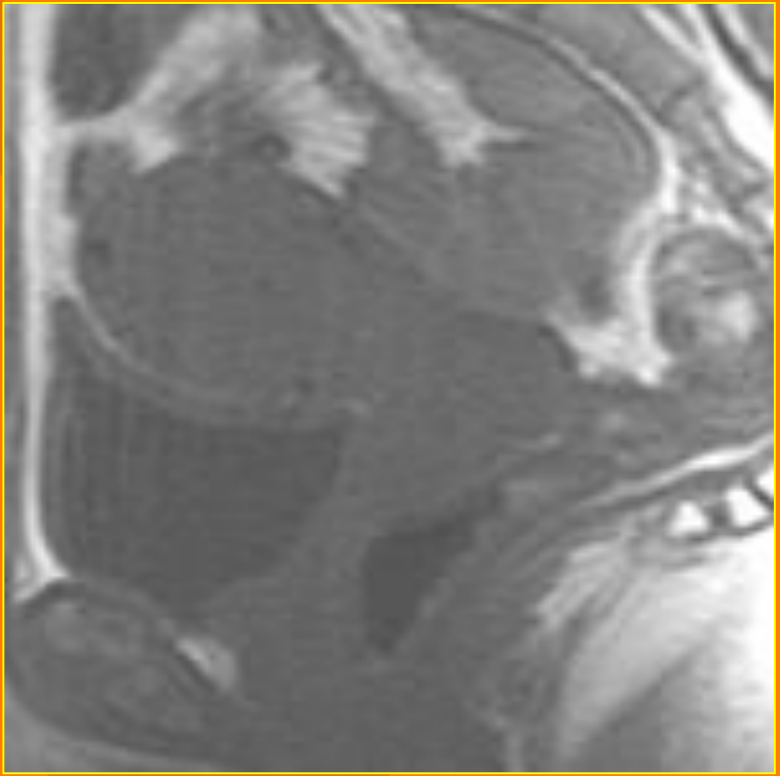
Zonal Anatomy (young)

Limits :

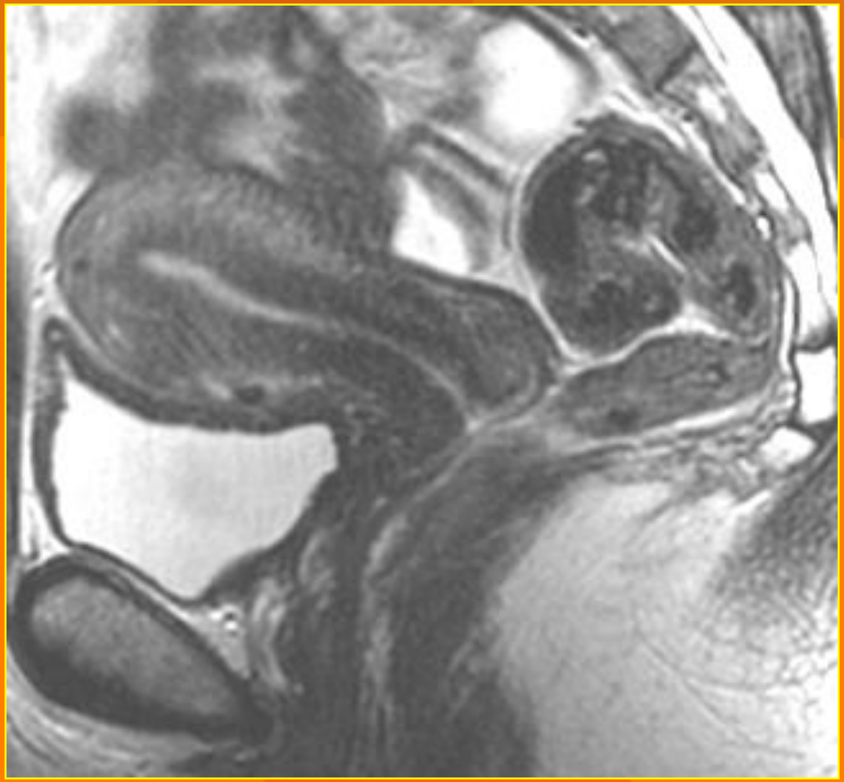
- **Sagittal : corpus**
- **Axial : entry of the uterine artery 5 mm upwards**

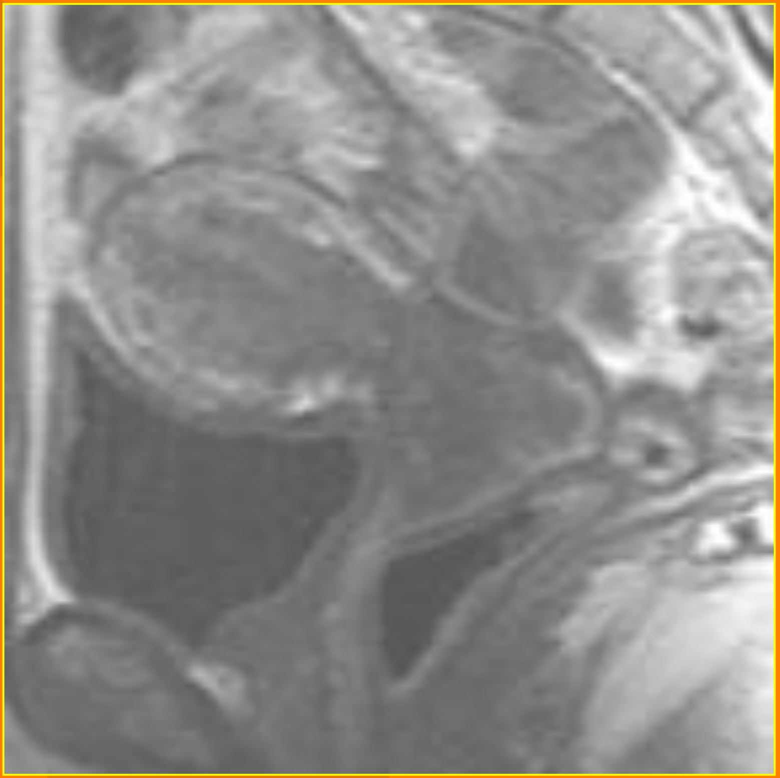
Coronal : hypointense « cervical stroma ring »

Fast SE T2-weighted MR image



SE T1-weighted MR image before IV CM injection





Fast SE T2-weighted MR image

SE T1-weighted MR Image 40 seconds after CM injection

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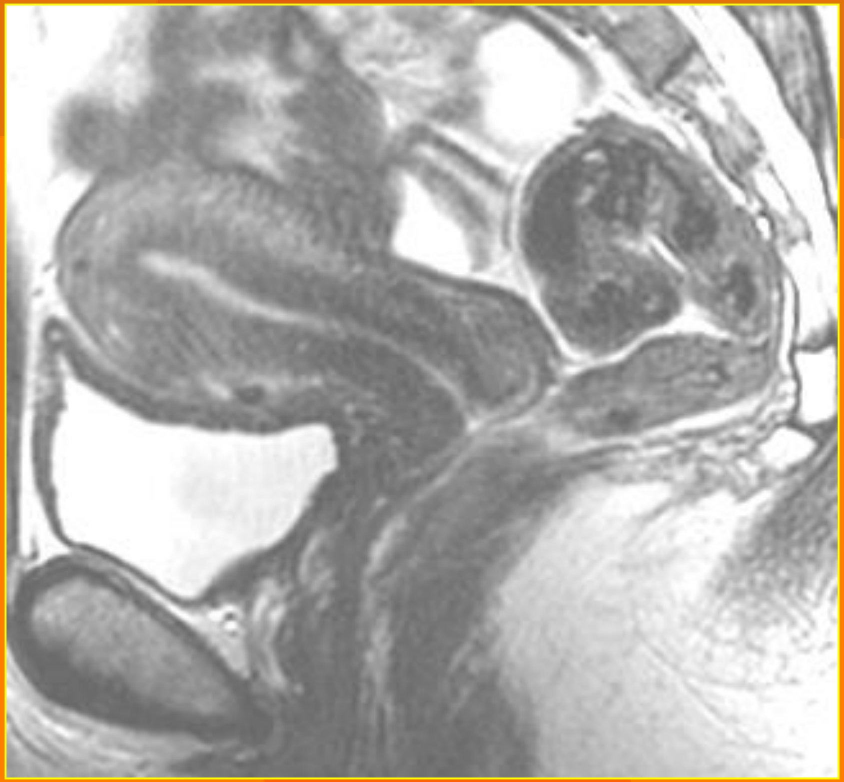
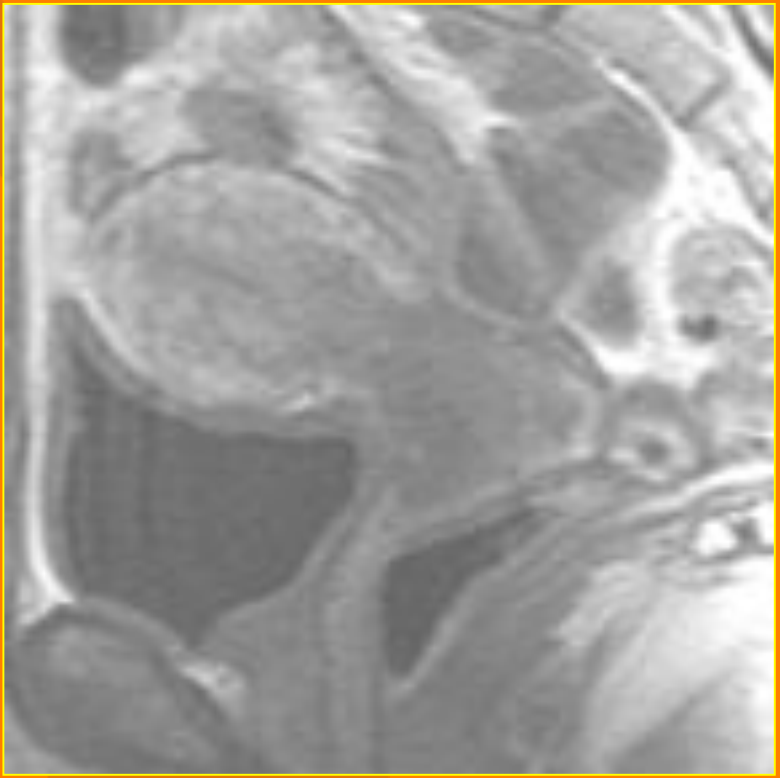
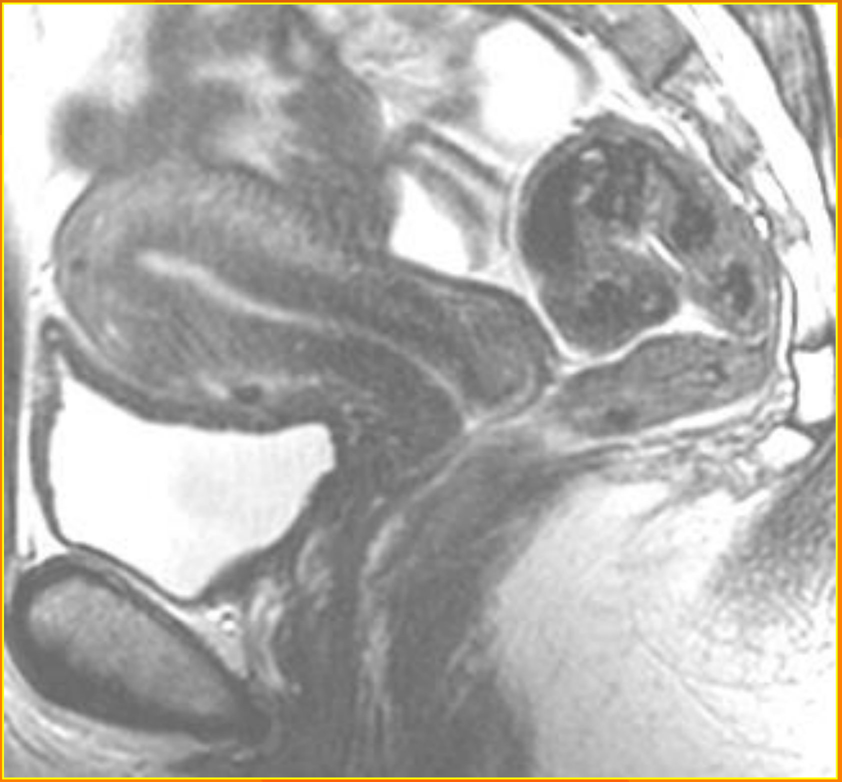


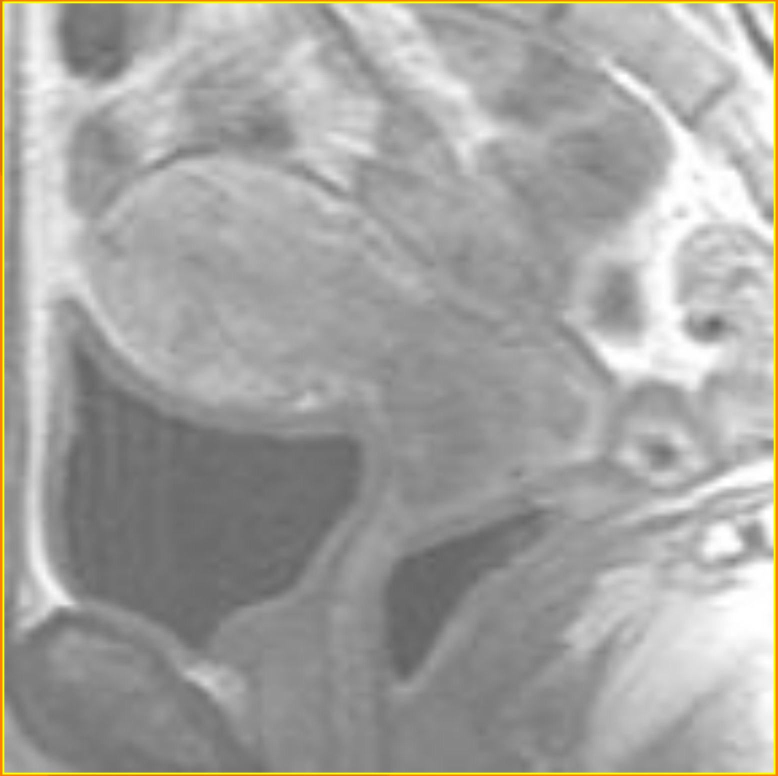
Fast SE T2-weighted MR image



SE T1-weighted MR Image 80 seconds after CM injection



Fast SE T2-weighted MR image



SE T1-weighted MR Image 120 seconds after CM injection

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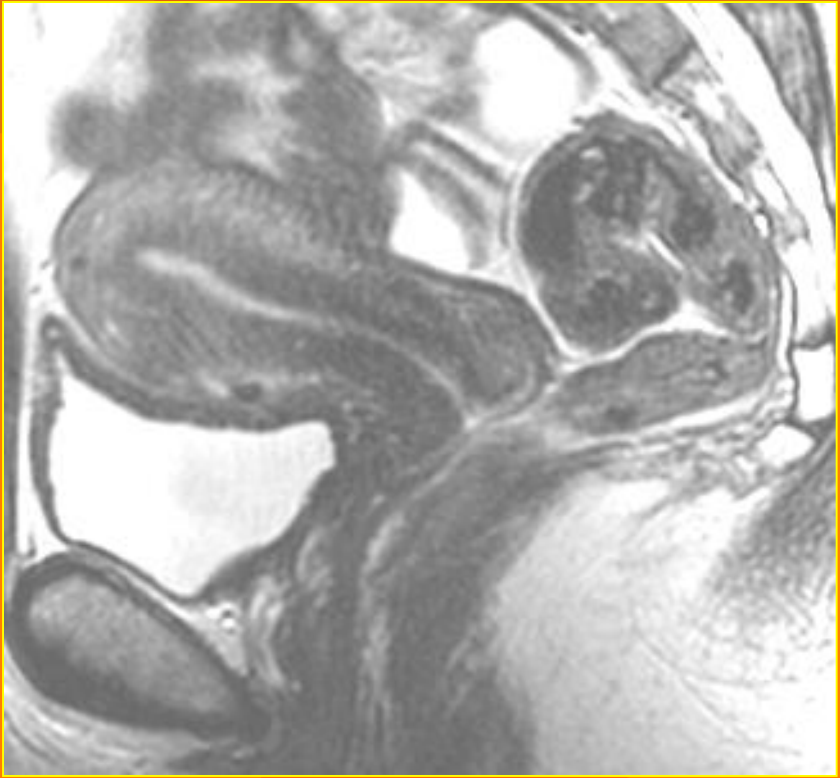
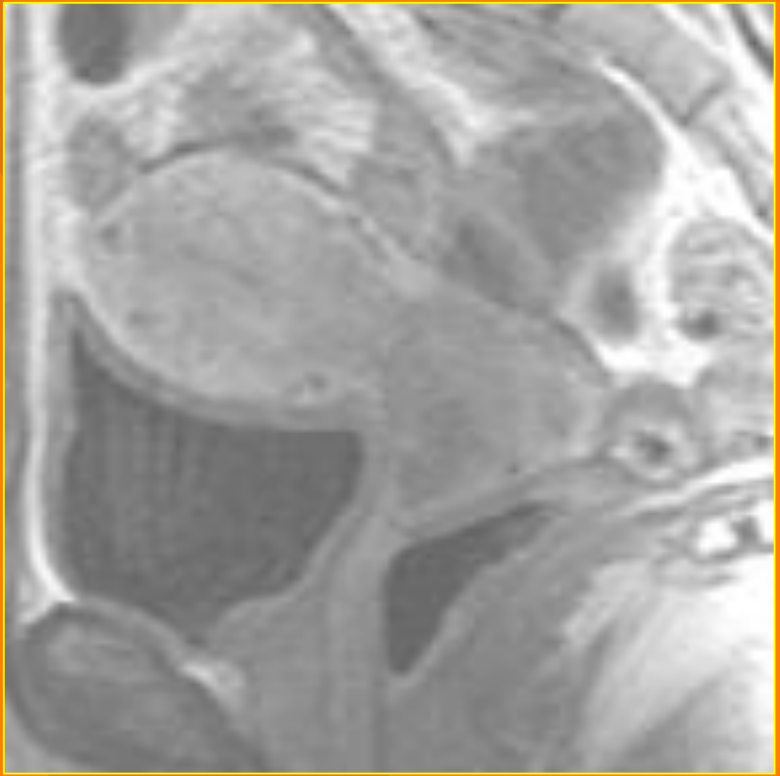


Fast SE T2-weighted MR image



SE T1-weighted MR Image 160 seconds after CM injection

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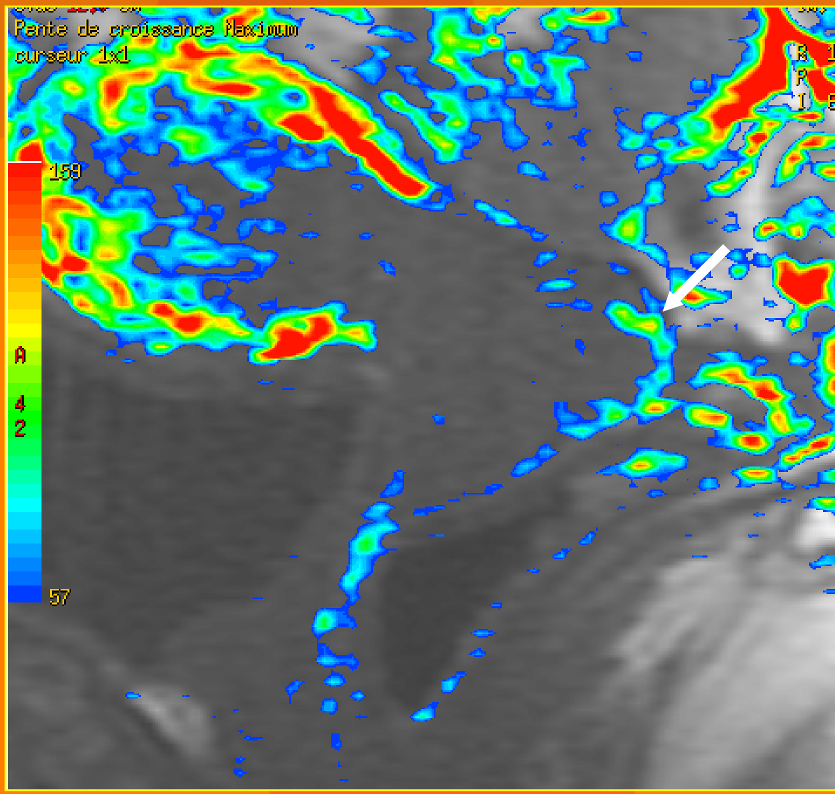

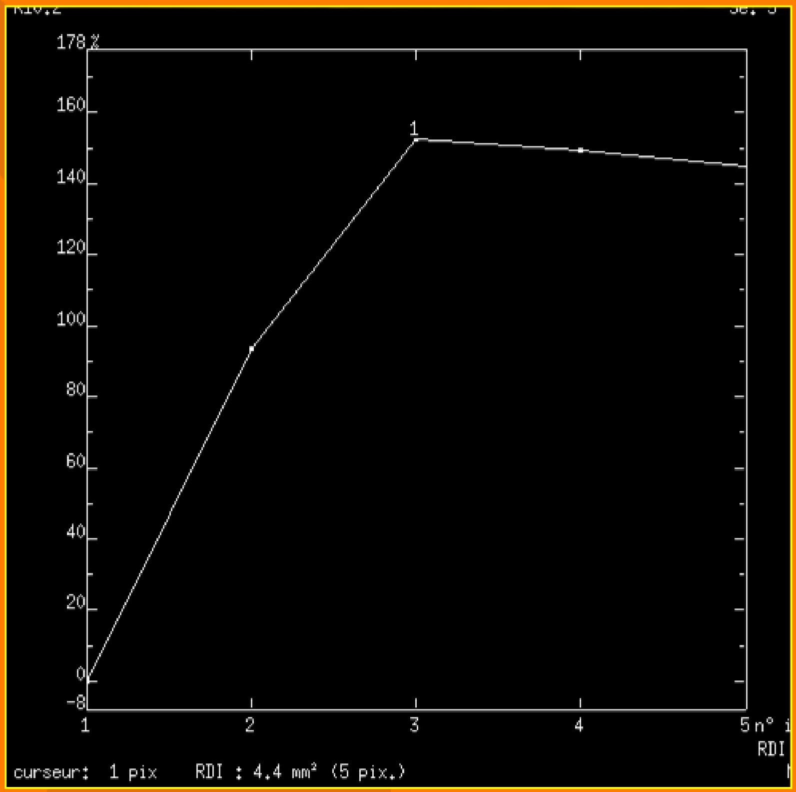

Color-encoded contrast-enhanced image

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3D image-based anatomy: CT, US and MRI

Vagina - US:

Transabdominal : difficult examination

- **Hyperechoic central stripe (interface between vaginal cavity and vaginal mucosa)**
- **Vagina : hypoechoic stripe**

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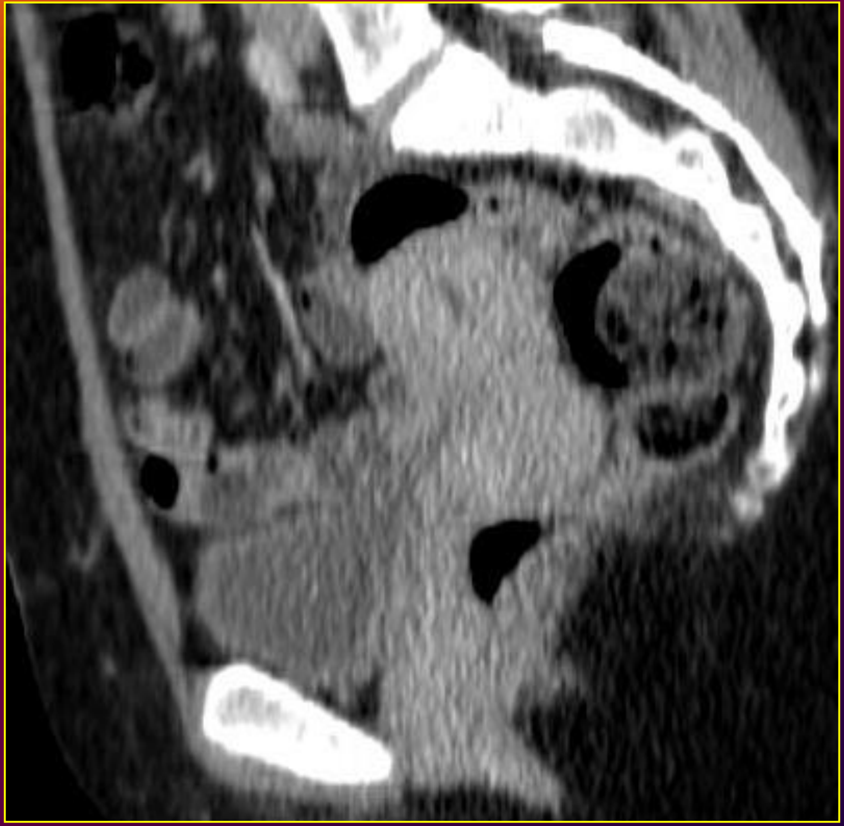
3D image-based anatomy: CT, US and MRI



Vagina - CT:

Visualization

- **Hypointense**
- **Confounding with cervix bladder and rectum**
- **Intravaginal contrast necessary**

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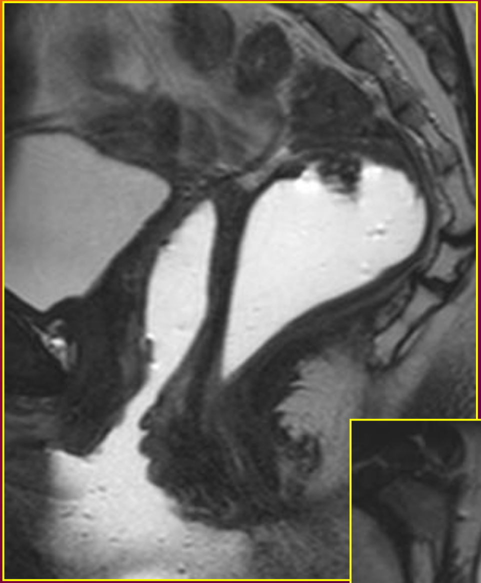
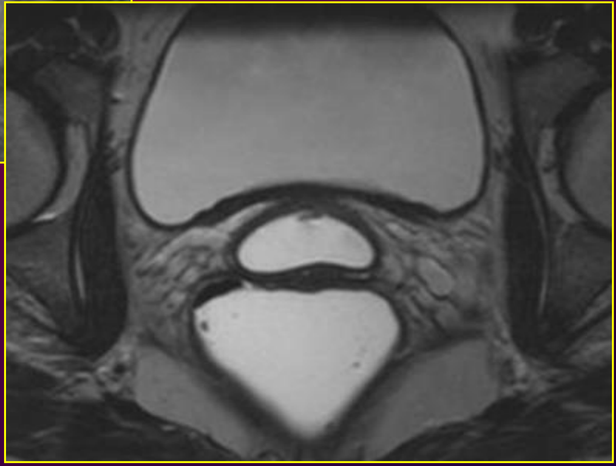
3D image-based anatomy: CT, US and MRI





Vagina - MR:

Excellent Soft tissue contrast

- Vaginal wall : low-signal intensity
- Clear delineation of vagina and paravagina
- Intravaginal contrast useful to delineate vagina from cervix

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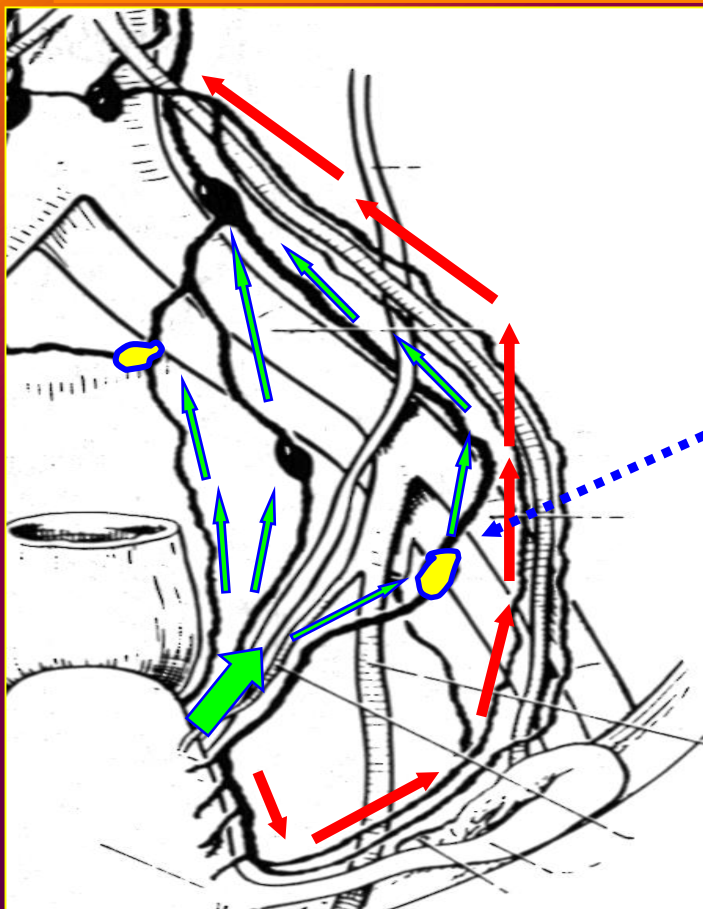
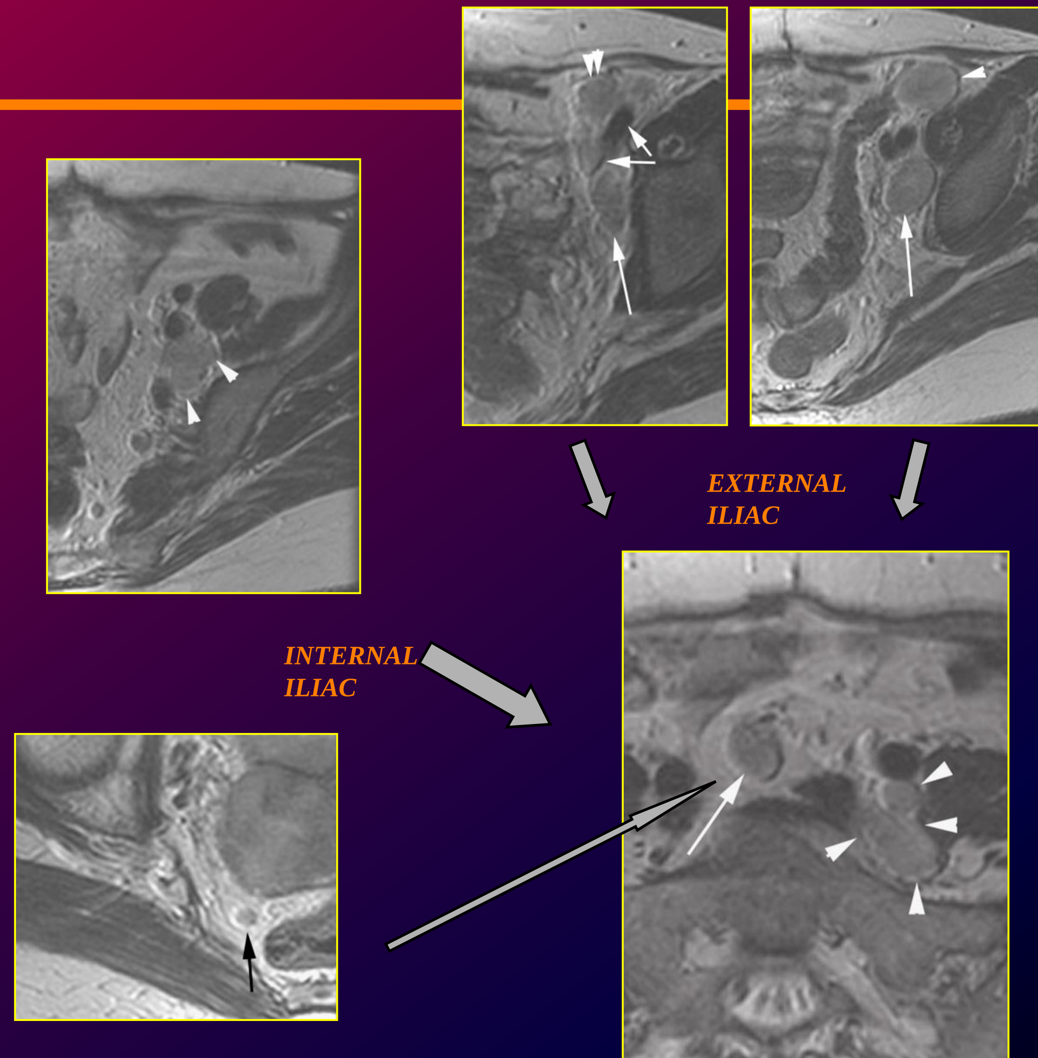
GYN CANCER – LYMPH NODE DRAINAGE

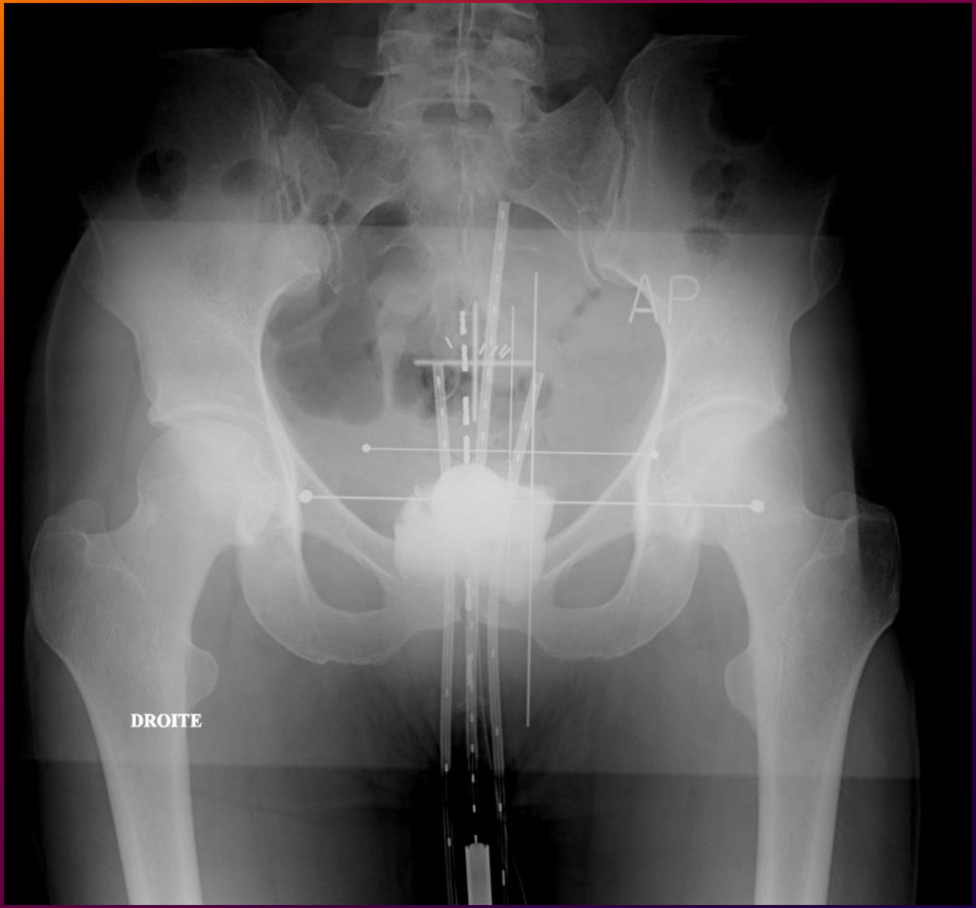




PARARECTAL

COMMON ILIAC

3D image-based anatomy: drawings and CR



CONVENTIONAL RADIOGRAPHY (CR): AT TIME OF BRACHYTHERAPY:

- **intravaginal applicator in place**
- **intrauterine and intravaginal probes**
- **dummy sources**
- **bladder and rectal probes**

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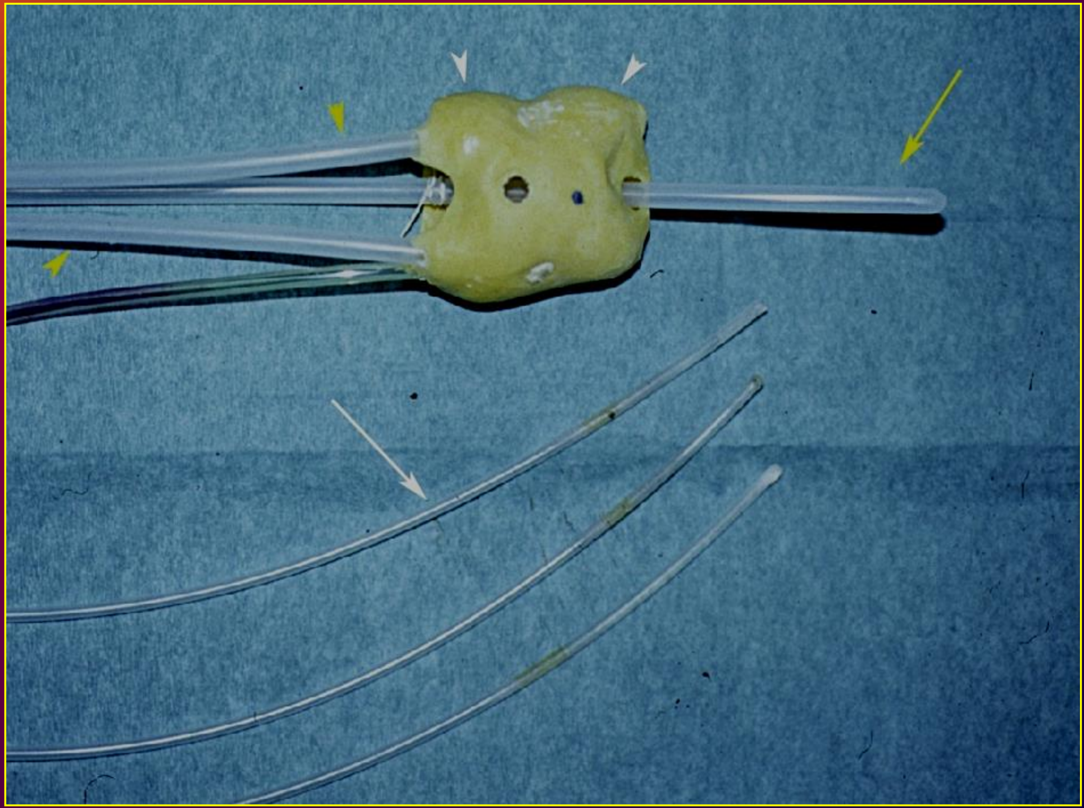
3D image-based anatomy: CT, US and MRI

MR - Radioanatomy in brachytherapy



- MR compatible Intravaginal applicator
- Resine-made moule

Vaginal plastic tubes (arrowheads)

- Endouterine plastic tube (yellow arrow)
- Dummy plastic sources

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3D image-based anatomy: CT, US and MRI

MR - Radioanatomy in brachytherapy

Uterine source

Bladder catheter

Intravaginal applicator

Vaginal tube

3D image-based anatomy: CT, US and MRI

MR - Radioanatomy in brachytherapy

Vaginal tube with high signal intensity intensity dummy source

3D image-based anatomy: CT, US and MRI

MR - Radioanatomy in brachytherapy

Air-fluid levels in bladder and hollow intravaginal applicator

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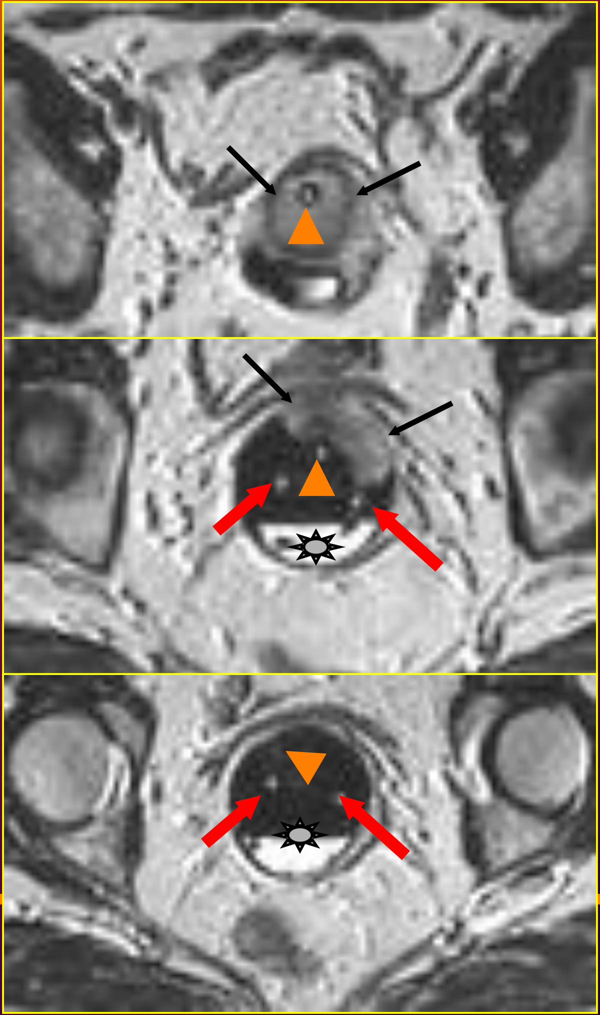
3D image-based anatomy: CT, US and MRI



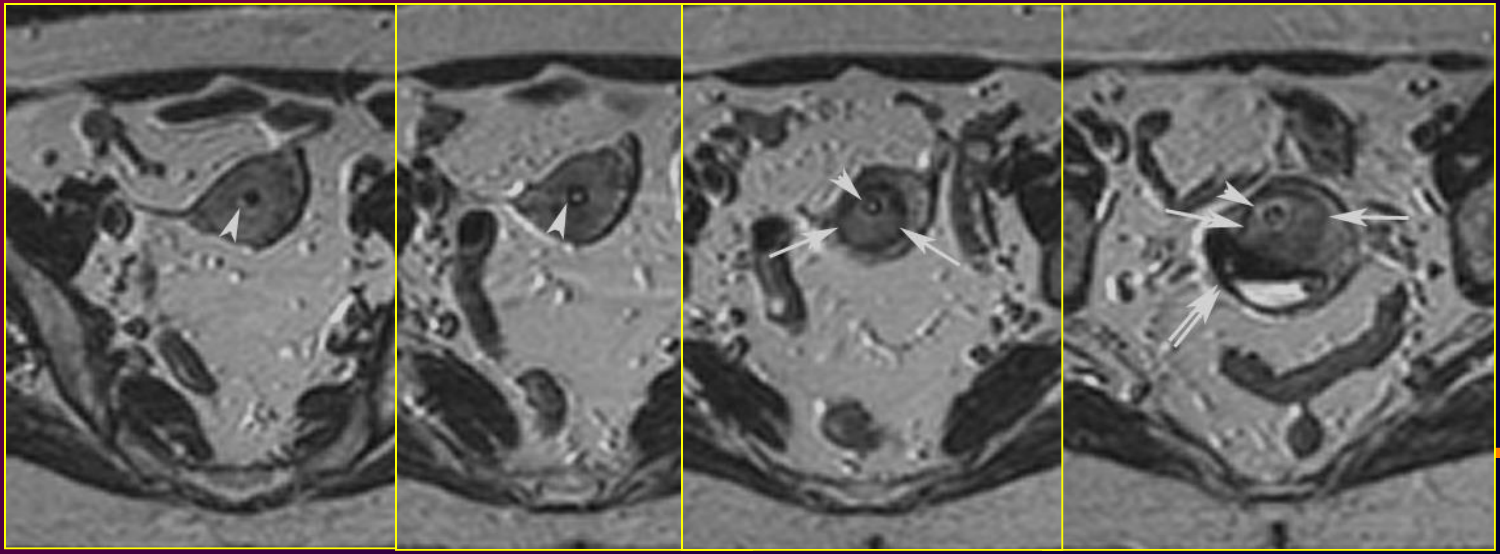
Uterine tube

Vaginal tubes

Air fluid level

tumour

MR - Radioanatomy in brachytherapy



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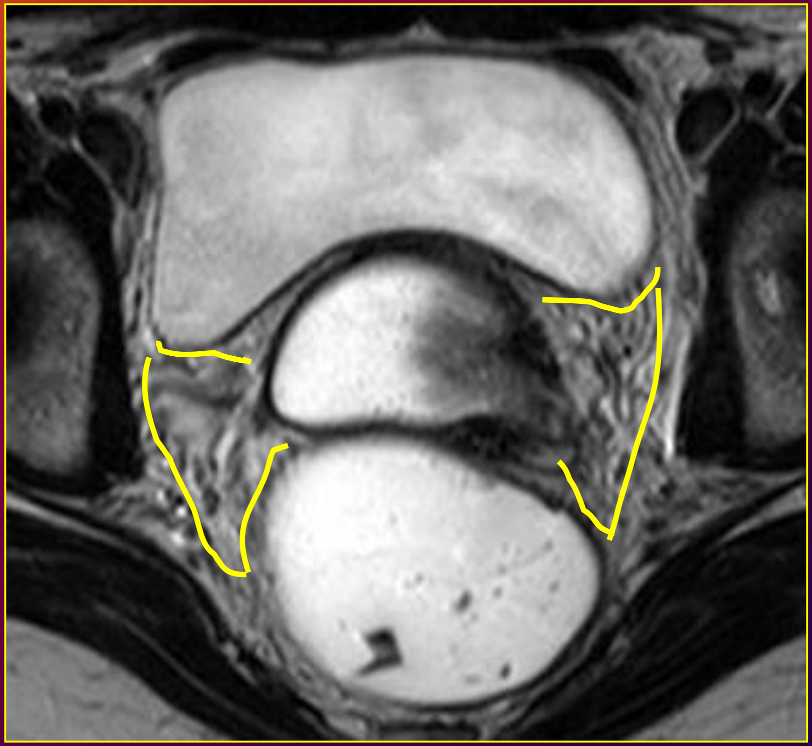
3D image-based anatomy: CT, US and MRI

MR - Radioanatomy of the parametrium



Limits : peripheral

anterior : bladder (anterior pillar)

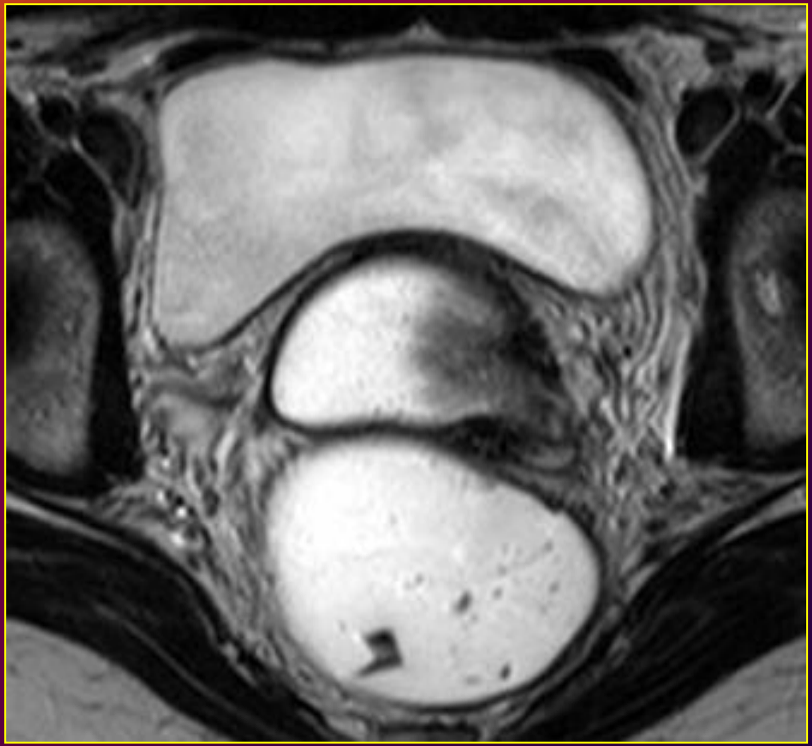
lateral : subperitoneal space adjacent to pelvic wall (internal obturator muscle)

posterior : utero-sacral ligament

superior : peritoneum

3D image-based anatomy: CT, US and MRI

MR - Radioanatomy of the parametrium



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superior : peritoneum

3D image-based anatomy: CT, US and MRI

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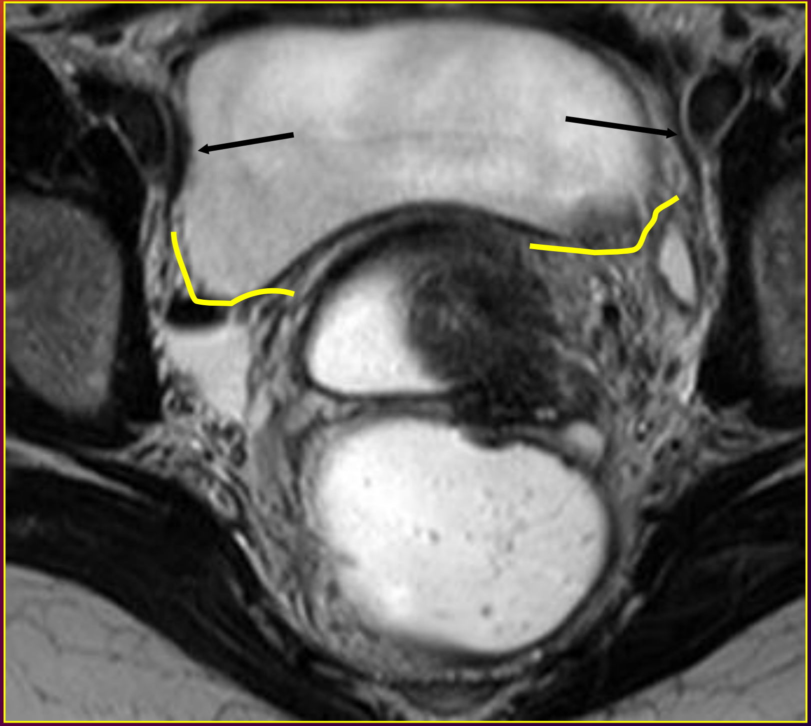

Limits :

anterior : bladder (anterior pillar)

- variable to bladder filling

- ends in the vicinity of the external iliac vessels (arrow)

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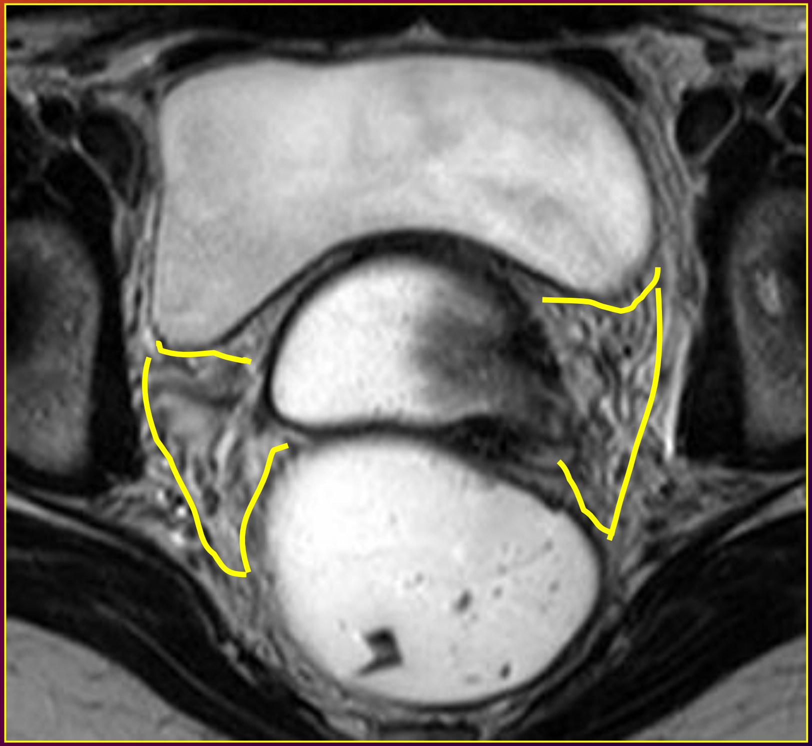
MR - Radioanatomy of the parametrium



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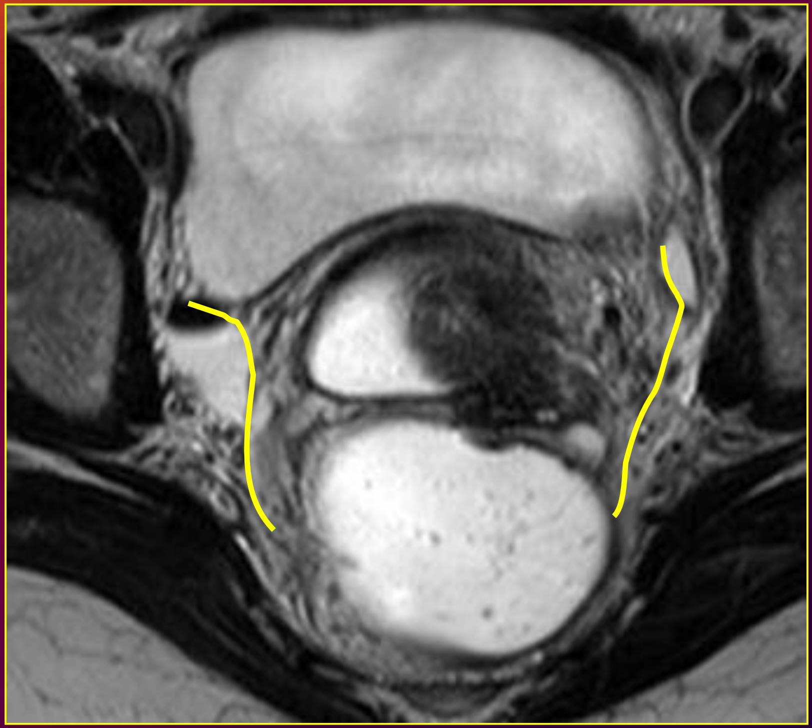
3D image-based anatomy: CT, US and MRI

MR - Radioanatomy of the parametrium



Limits : peripheral

lateral : subperitoneal space adjacent to pelvic wall (internal obturator muscle)

- variable to bladder filling, rectal filling and intraperitoneal fluid

- variable cranio-caudally

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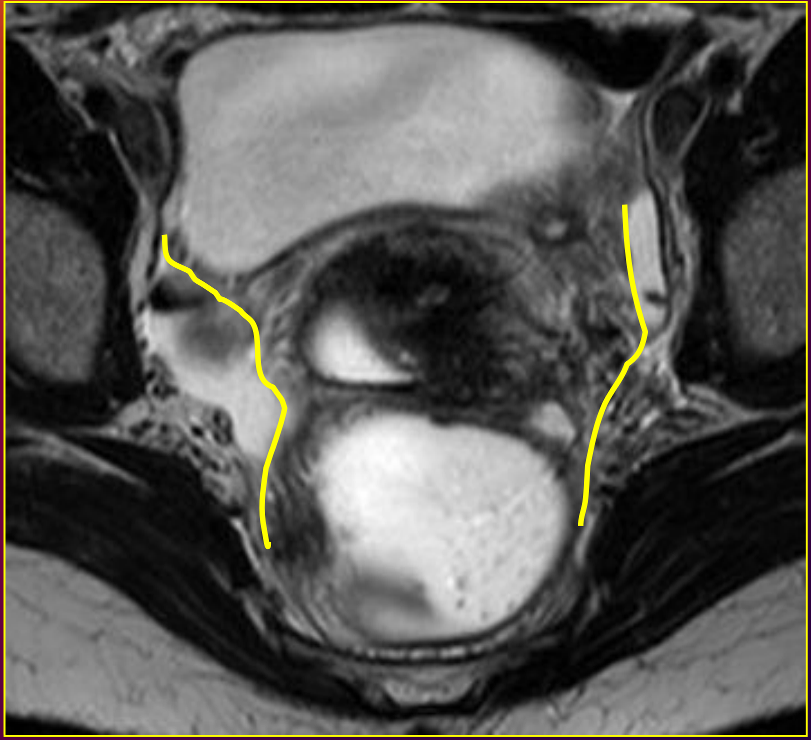
3D image-based anatomy: CT, US and MRI

MR - Radioanatomy of the parametrium



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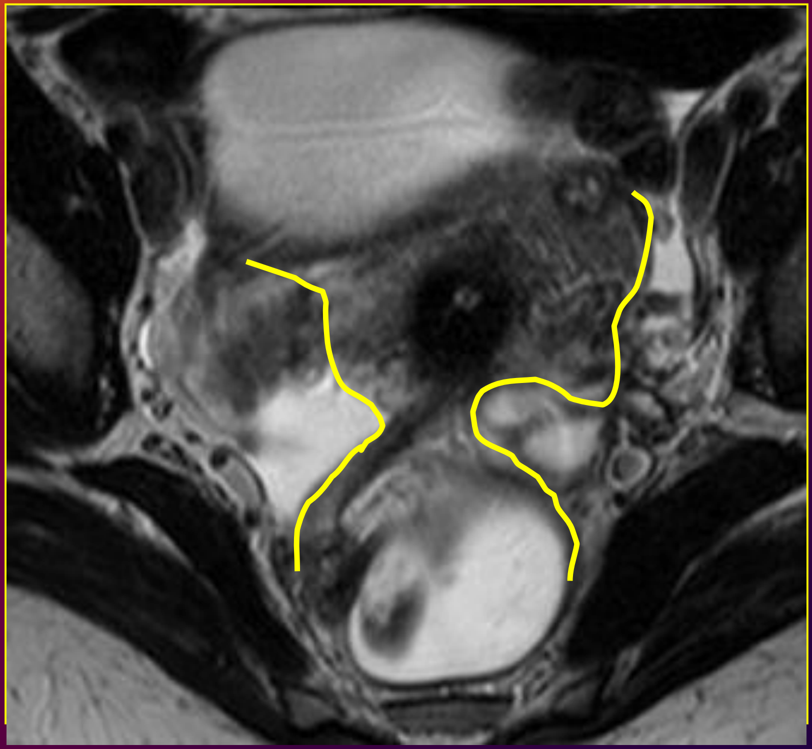

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3D image-based anatomy: CT, US and MRI

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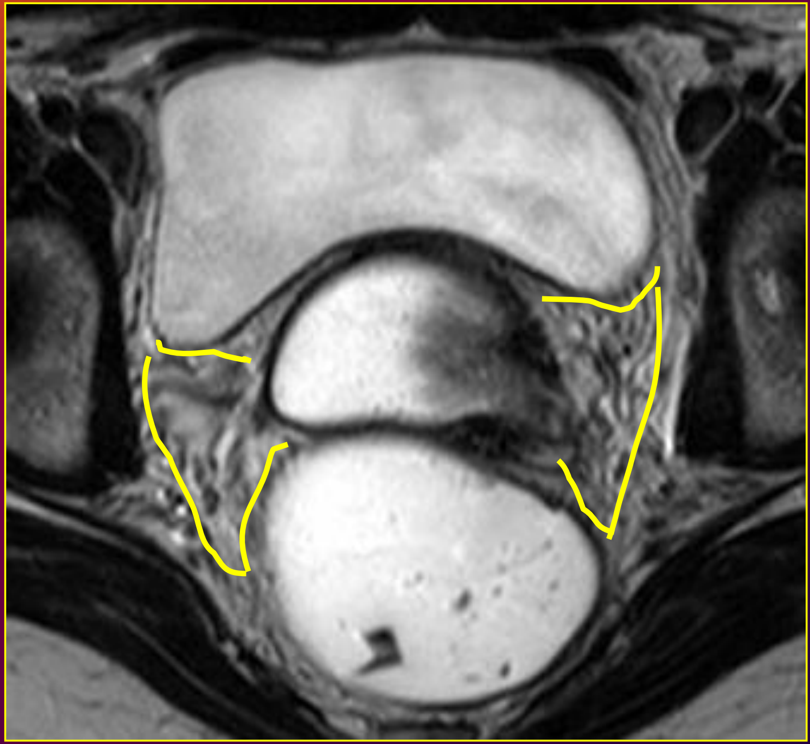

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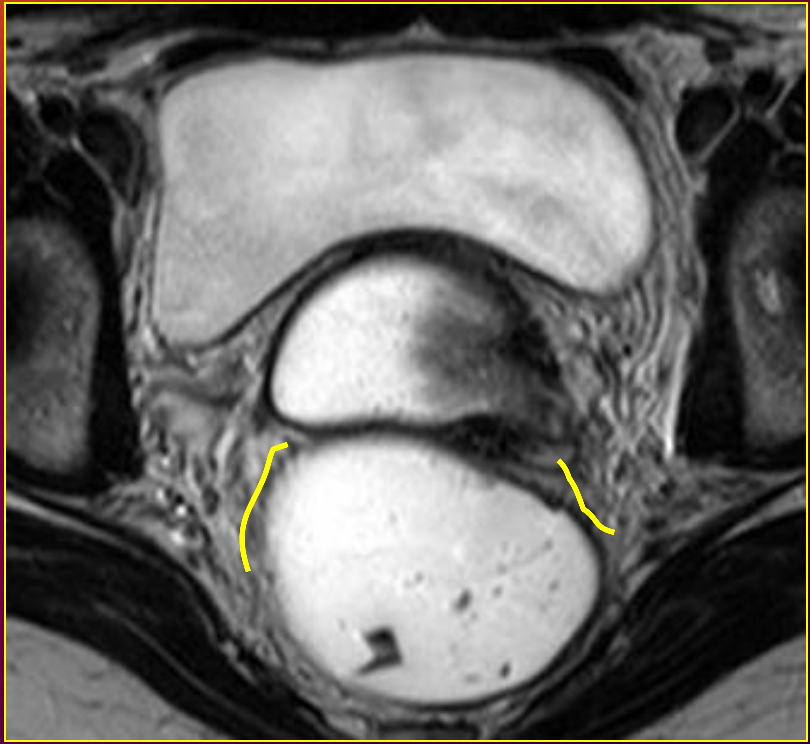
MR - Radioanatomy of the parametrium



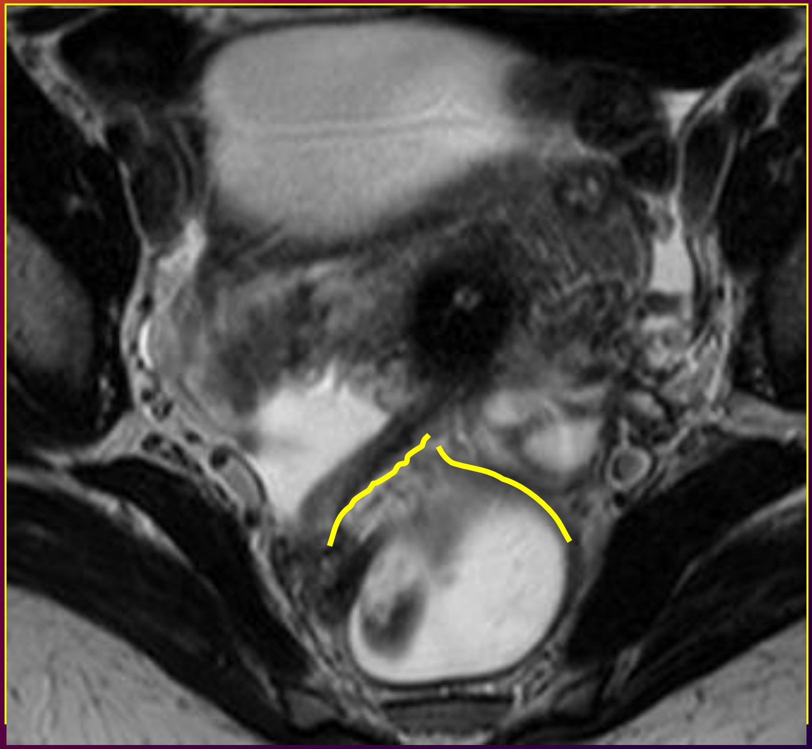
Limits : peripheral

posterior : utero-sacral ligament

- outlined by disease (endometriosis)

3D image-based anatomy: CT, US and MRI

MR - Radioanatomy of the parametrium



Limits : peripheral

posterior : utero-sacral ligament

- outlined by disease (endometriosis) and intraperitoneal fluid

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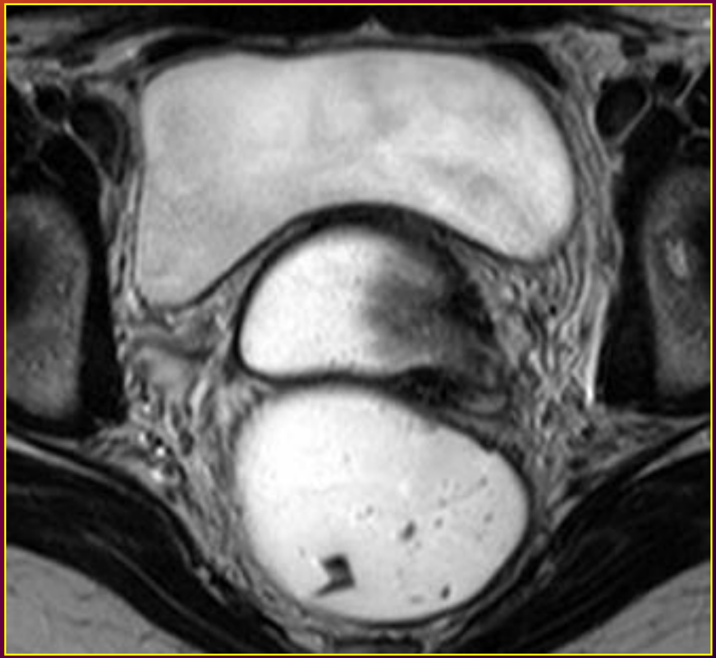
3D image-based anatomy: CT, US and MRI

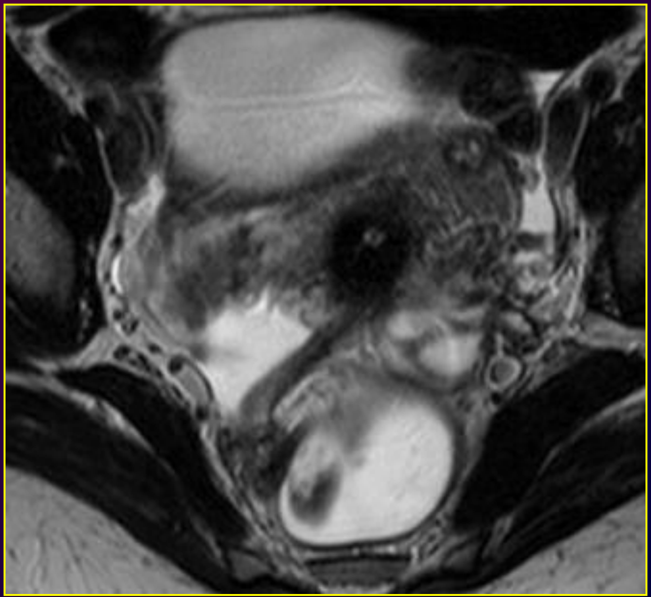
MR - Radioanatomy of the parametrium



Limits : central

inferior : vaginal wall

superior : cervix



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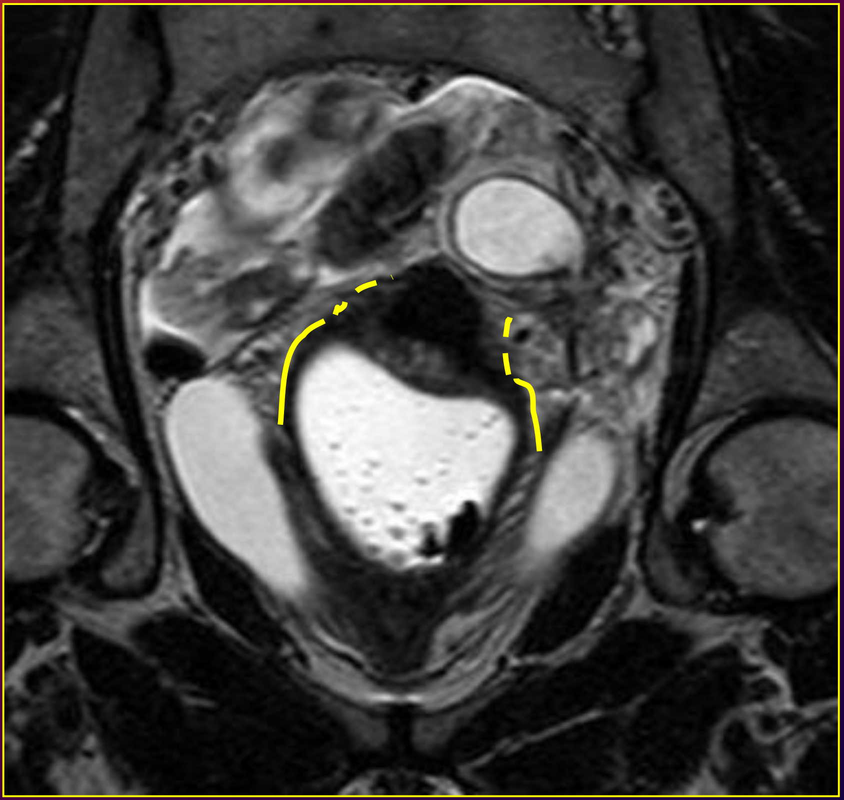
3D image-based anatomy: CT, US and MRI

MR - Radioanatomy of the parametrium



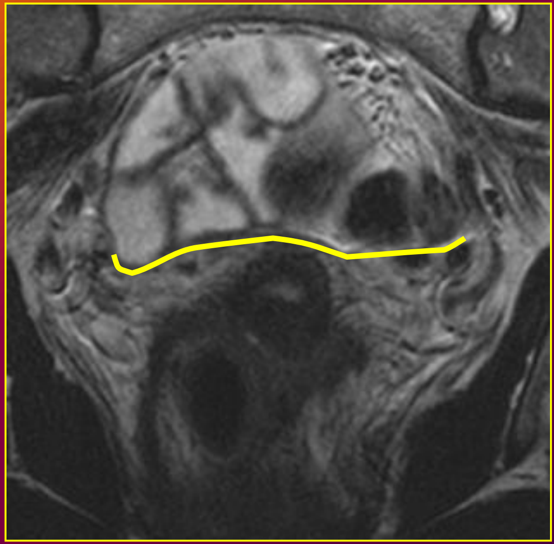
Limits : central

inferior : vaginal wall

superior : cervix

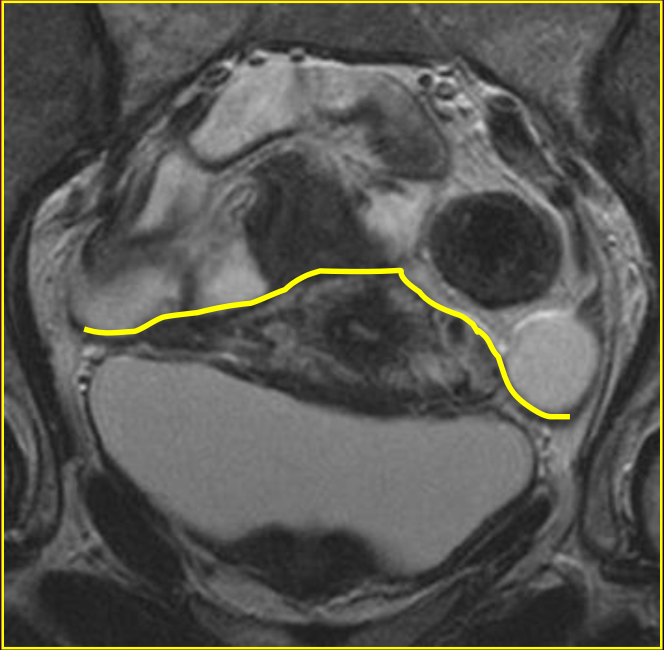
3D image-based anatomy: CT, US and MRI

MR - Radioanatomy of the parametrium



Limits : periphery

superior : peritoneum (small bowel, ovary, sigmoid colon)



3D image-based anatomy: CT, US and MRI

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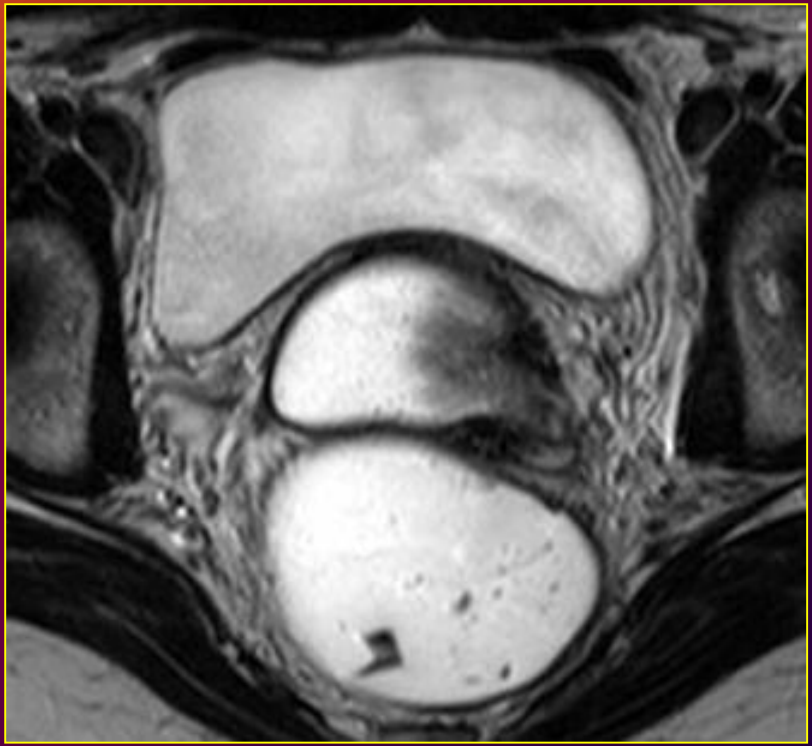

Content :

vessels :

- **artery (uterine and vaginal)**
- **veines + + + (uterine and vaginal)**

ureter

connective tissue

(adipocytes + +)

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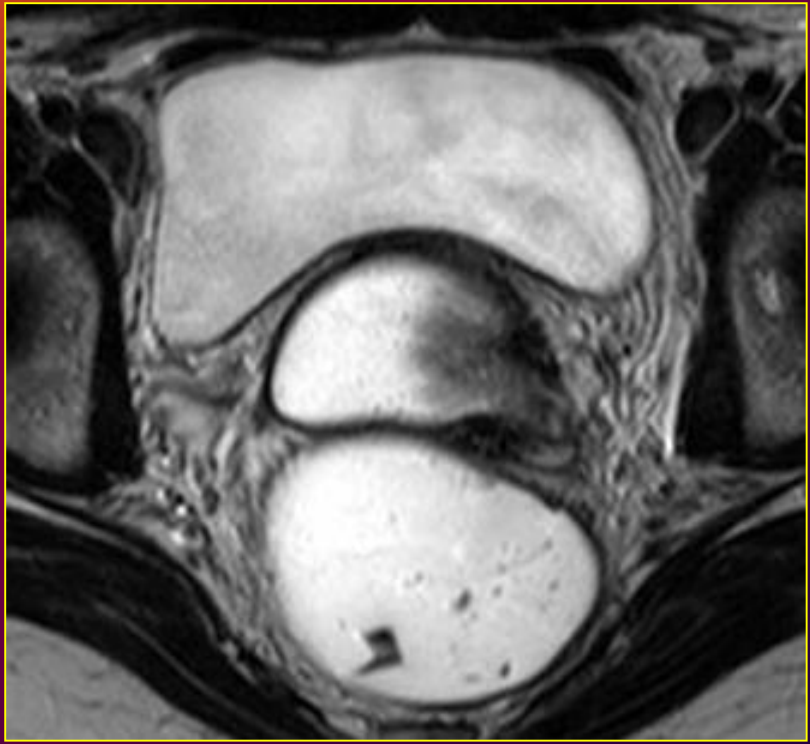
3D image-based anatomy: CT, US and MRI

MR - Radioanatomy of the parametrium



Content :

vessels :

- **artery (uterine and vaginal)**
- **veines + + + (uterine and vaginal)**

ureter

connective tissue

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3D image-based anatomy: CT, US and MRI

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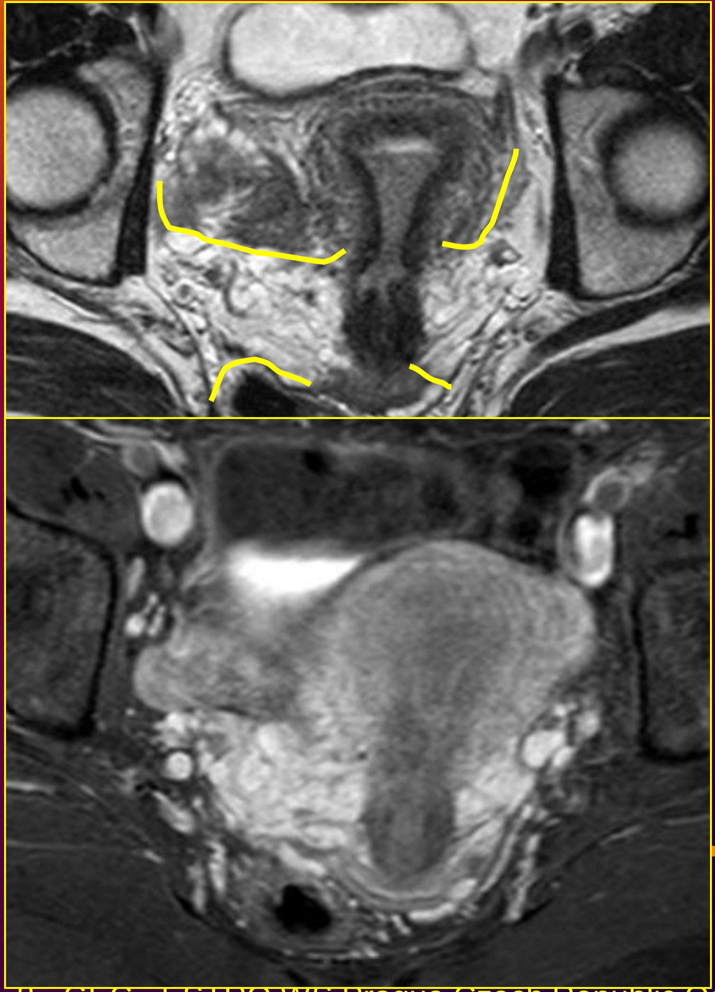

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- **artery (uterine and vaginal)**
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3D image-based anatomy: CT, US and MRI

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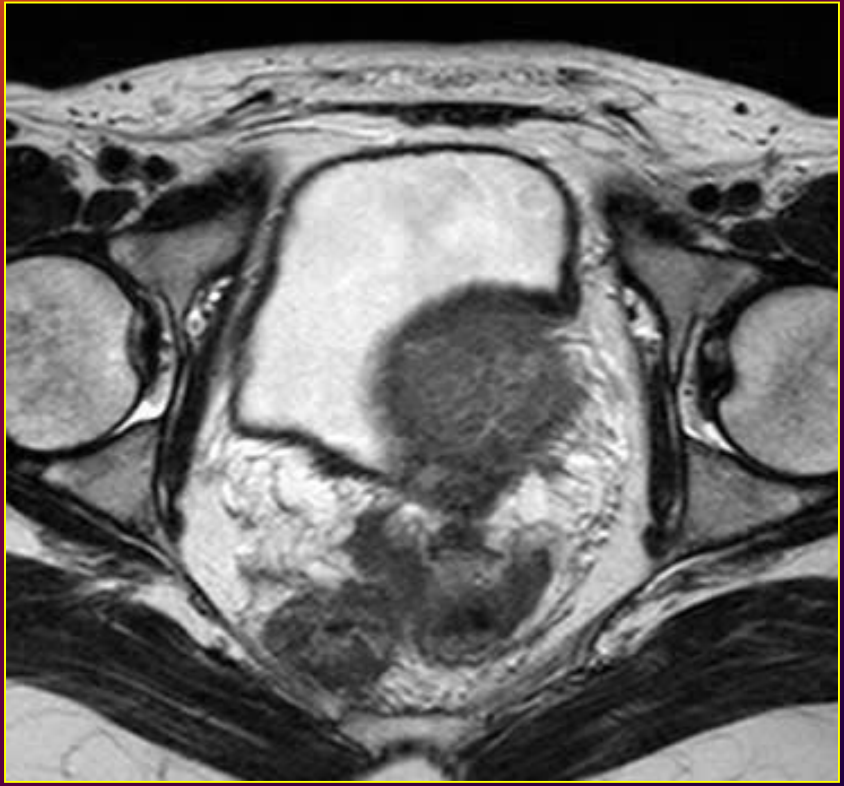

Content :

vessels :

- **artery (uterine and vaginal)**
- **veines + + + (uterine and vaginal)**

ureter

connective tissue

(adipocytes + +)

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3D image-based anatomy: CR, CT, US and MRI

CONCLUSION:

CT, US and MRI Radioanatomy:

- **MR > CT and US > CR**

  uterus cervix

  Parametrium

- **MR = CT > US > CR**

  Lymph node evaluation

- **MR > CT in Brachytherapy for evaluation of CTV, GTV (MSCT ?)**

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RADIOLOGIC PATHOLOGY OF GYNECOLOGIC TUMORS (including nodes)

- **Dr P Petrow – Departement of Diagnostic Radiology**

Institut Curie – Paris / France

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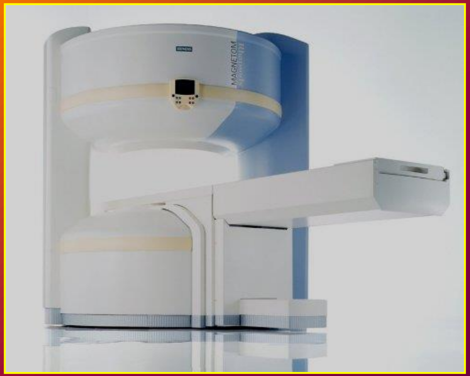
CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

Technical Requirements

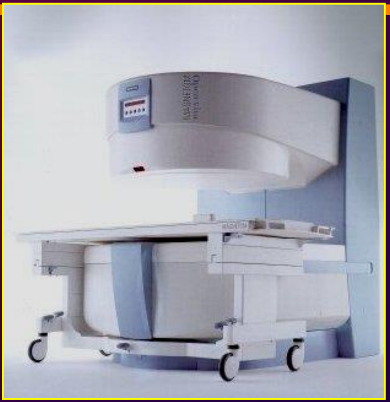
- **Field strength**
- **MR - Magnet Configuration**
- **Coils**
- **Patient preparation (bowel-motion reducing medication, intravaginal contrast)**
- **Image sequence algorythm (parameters, coverage, slice positionning)**
- **Tumor visualisation / extension**

CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS



1Tesla : Magnetom Rhapsody

Classic open configuration



0.3 Tesla : Magnetom Concerto

3 Tesla

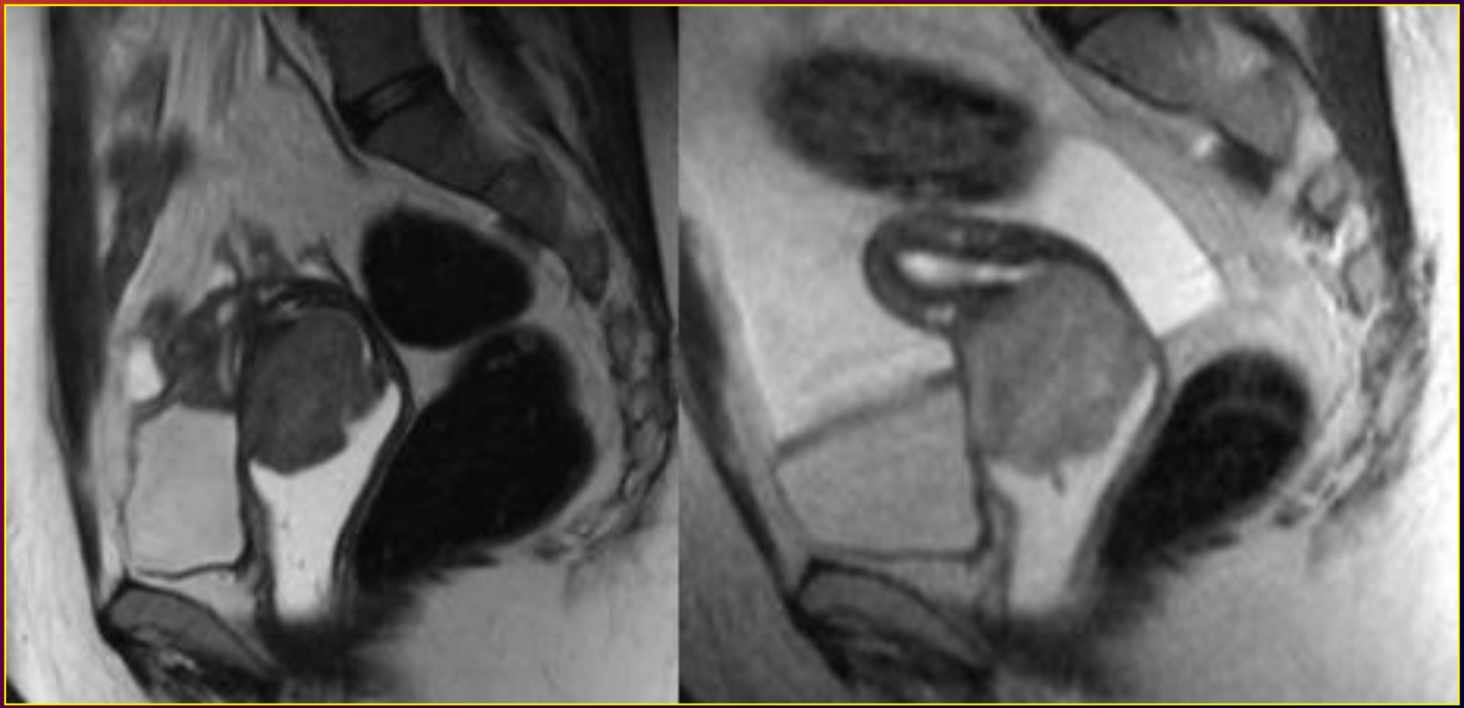
Classic closed configuration

1.5 Tesla

=> 7 Tesla

CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

FIELD STRENGTH



1.5 T　　　　0.23 T

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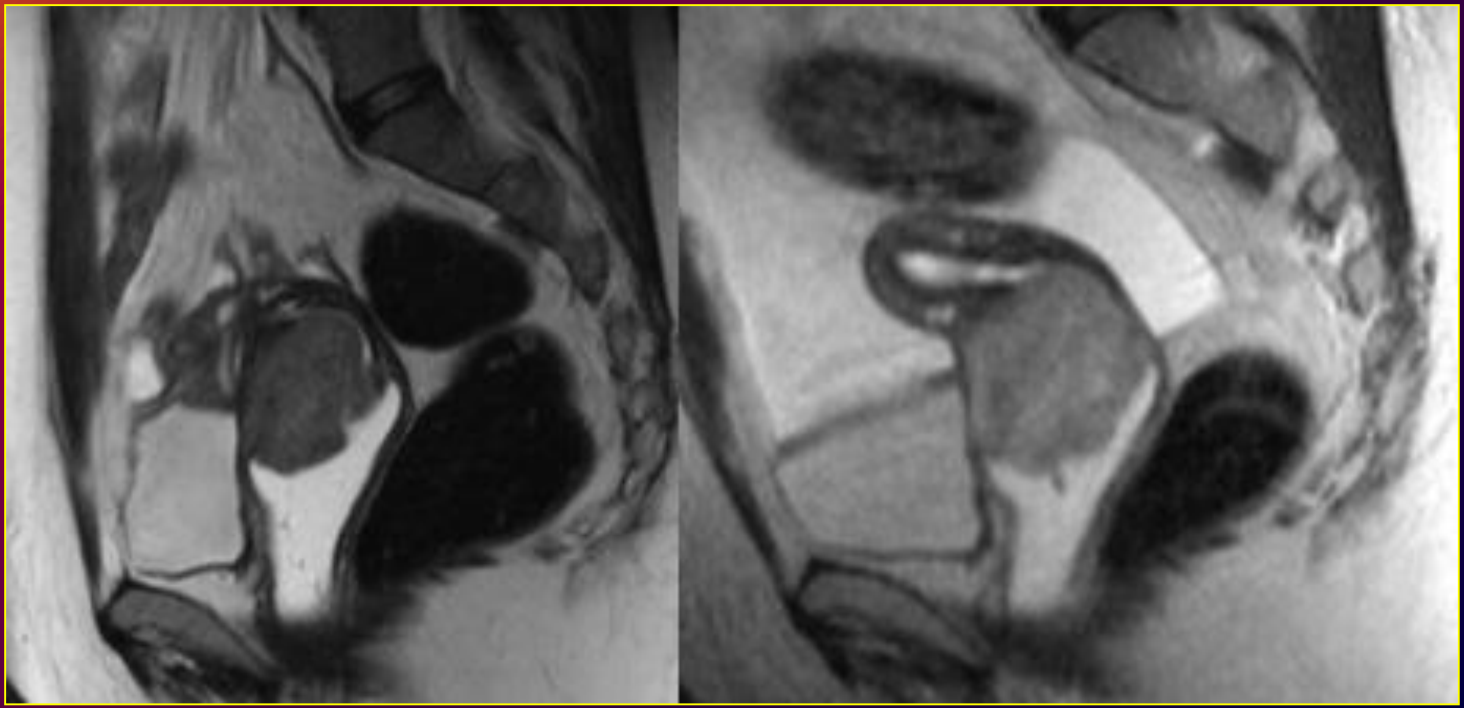
CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

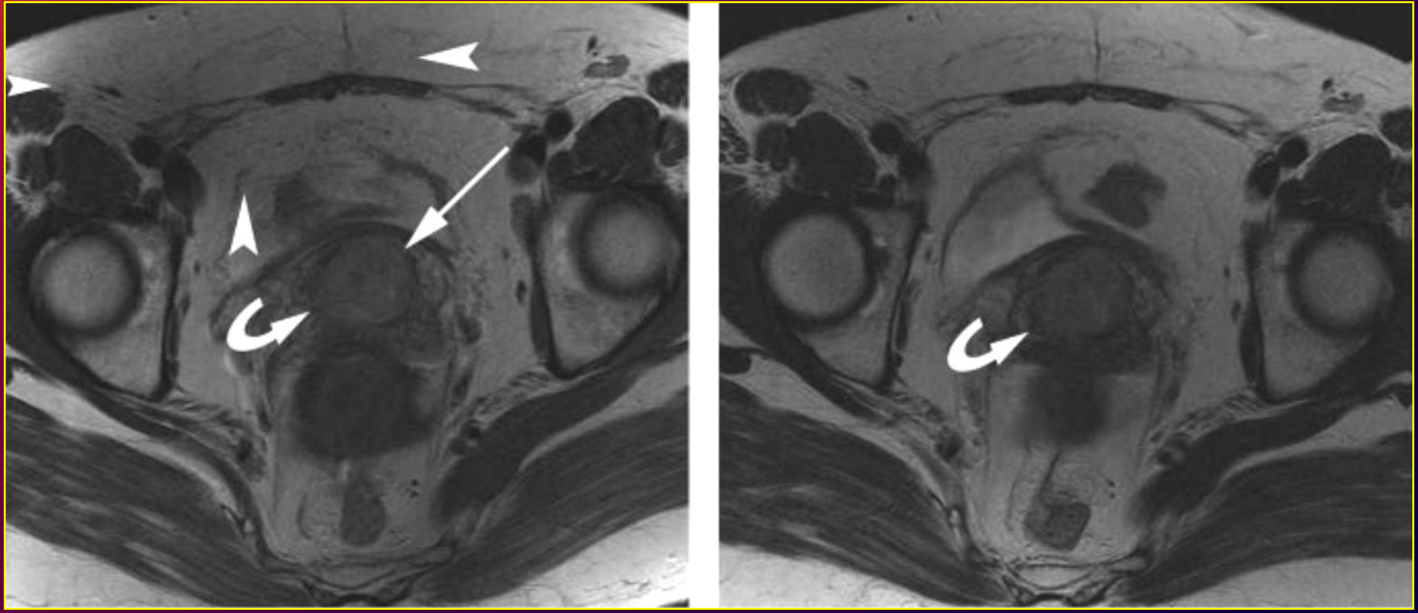
FIELD STRENGTH



1.5 T   0.23 T

CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

FIELD STRENGTH



3 T

1.5 T

Masatoshi et al.
Radiology 2009

CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

COILS

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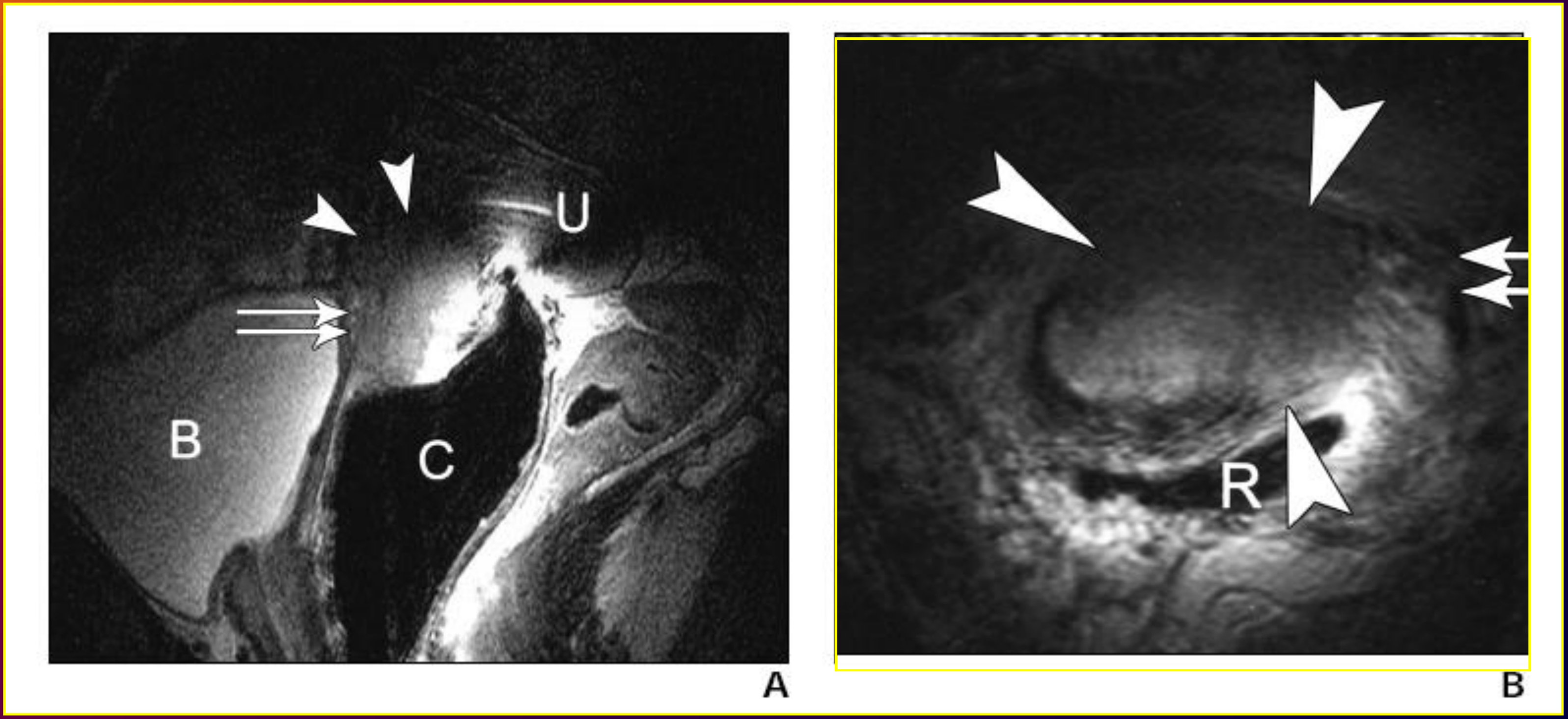
CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS



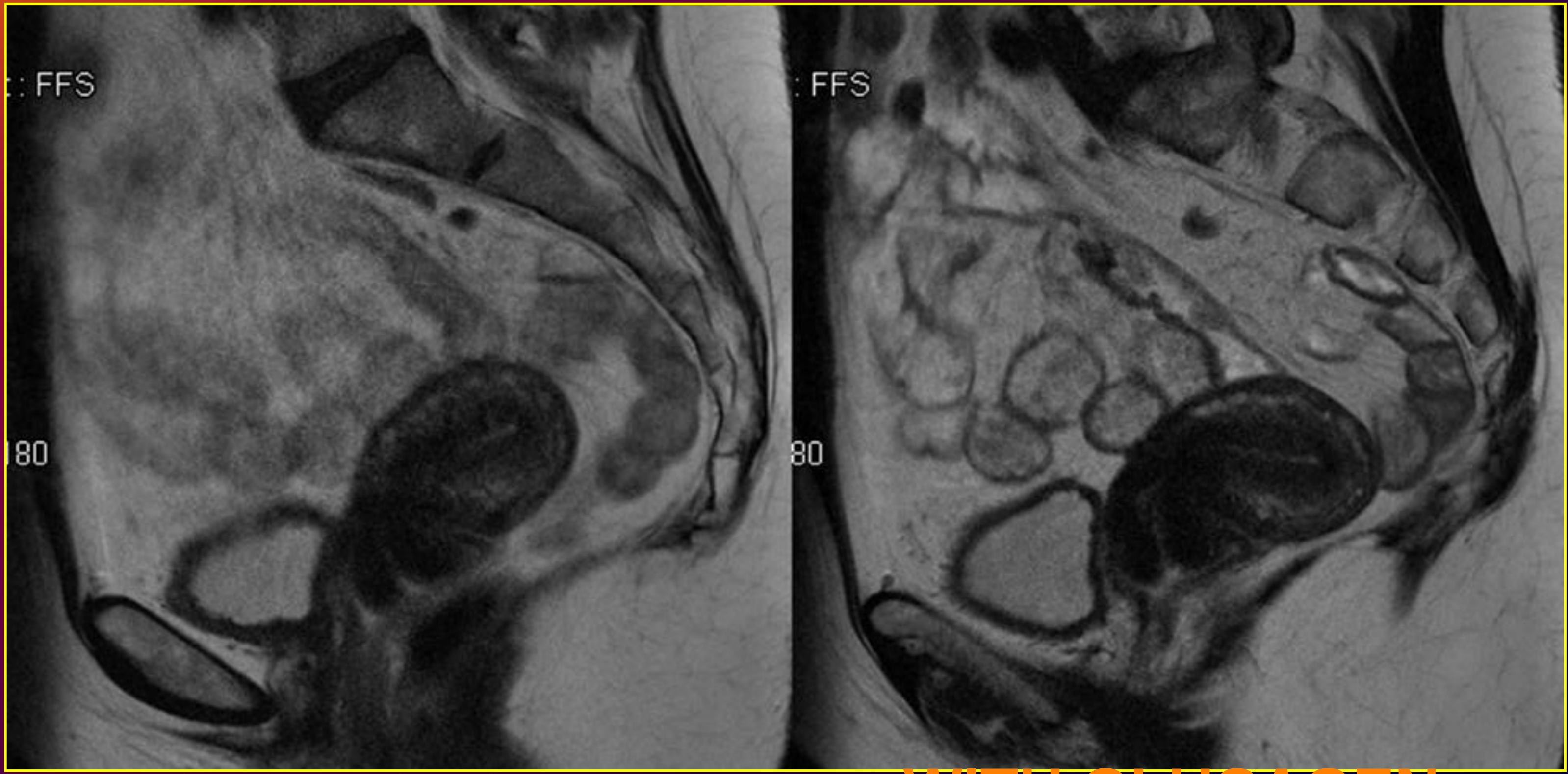
Yang AJR 2004

Desouza Gynecol Oncol. 2006

COILS

CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

MRI – technical parameters – bowel motion reduction



NO GLUCAGEN

WITH GLUCAGEN

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CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

MRI – technical parameters:

Vaginal filling

Material :

50 cc syrinyx

50 cc of ultrasound gel

rectal canula

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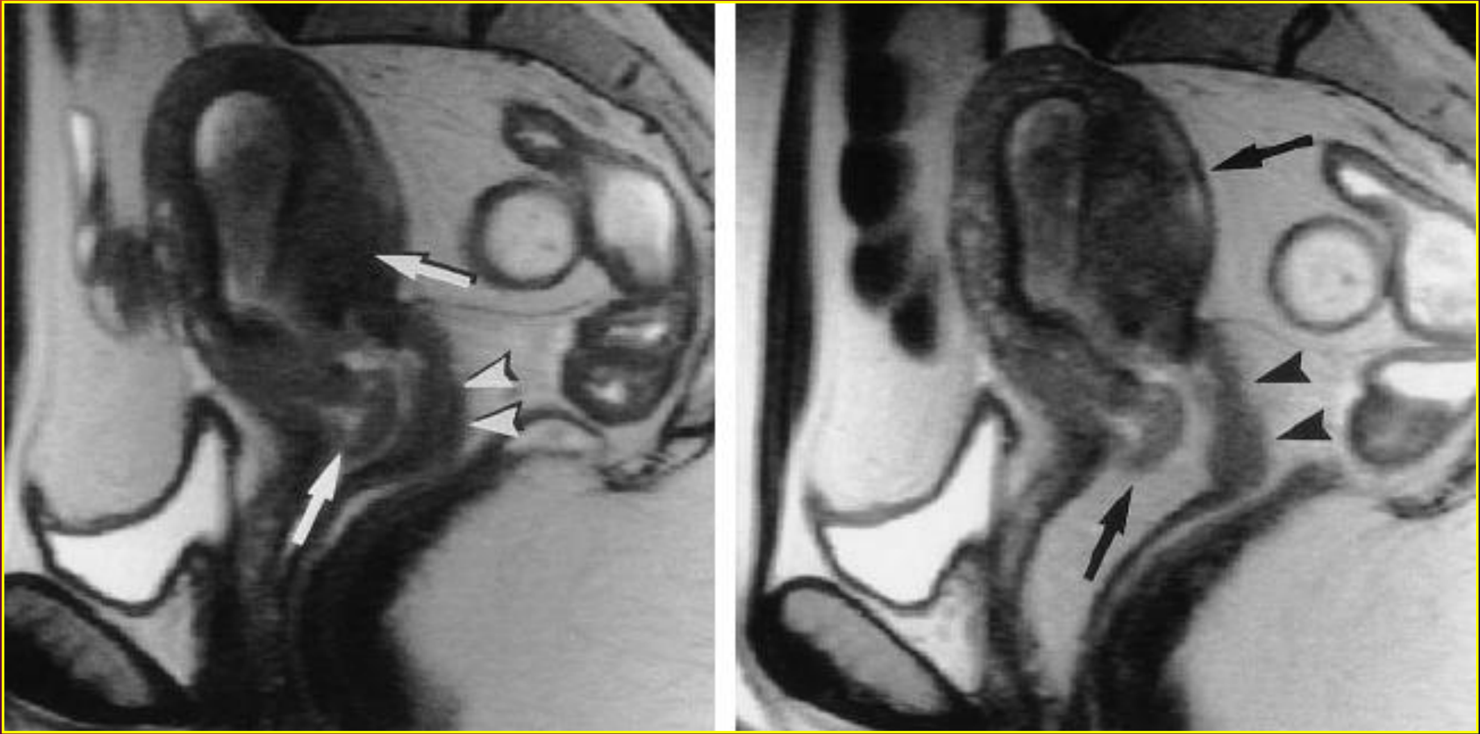
CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

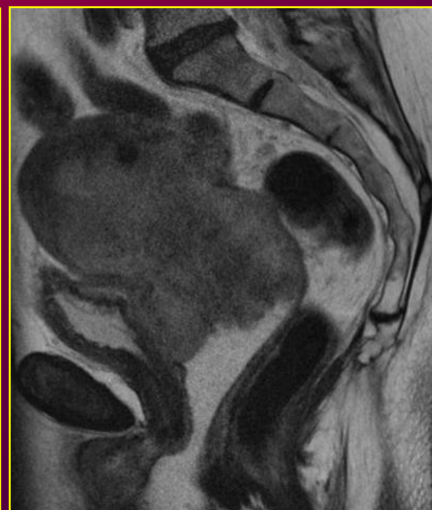
MRI – technical parameters: Vaginal filling

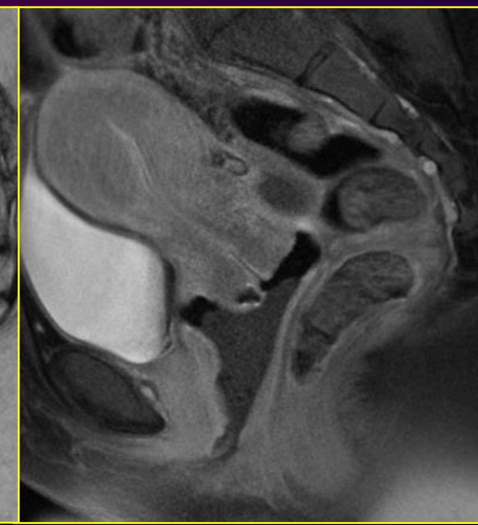


Van Hoe Radiology 1999

CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

MRI – technical parameters: Vaginal filling



- Intrarectal injection …

- Air Bubbles …

CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

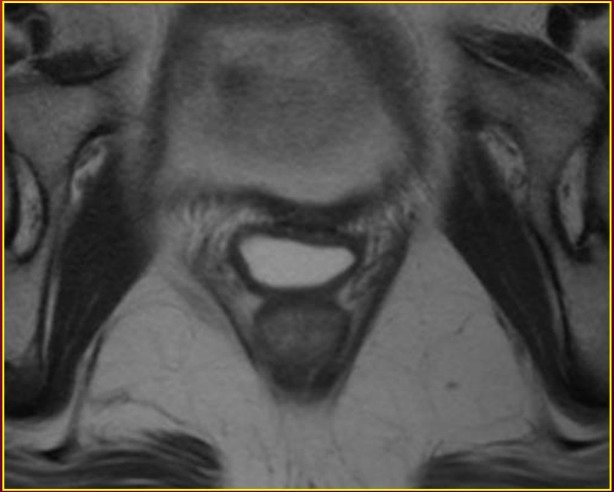
MRI – technical parameters: Vaginal filling

- Incomplete vaginal distention

- Synechia

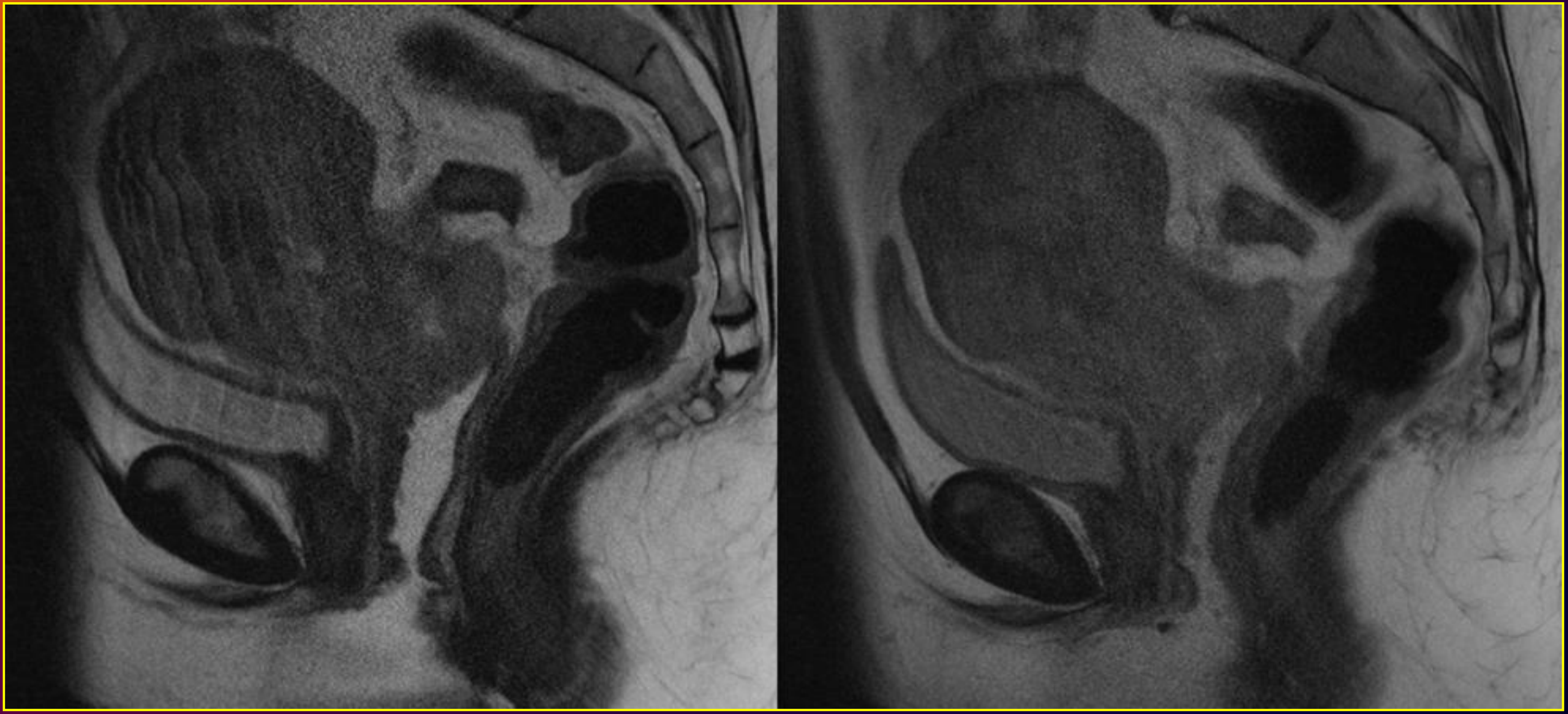
CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

MRI – technical parameters: Vaginal filling



CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS

MRI – technical parameters – presaturation band



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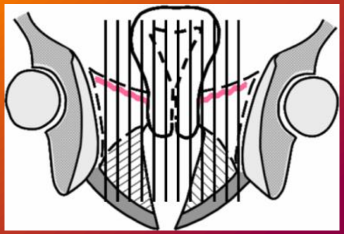
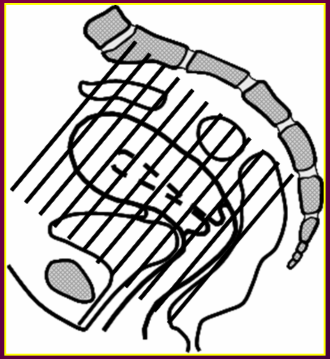
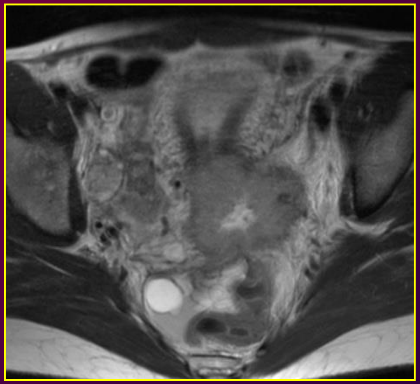
CT AND MR IMAGING : GYN GEC ESTRO RECOMMANDATIONS







Sagittal FSE T2:

-TR = 2000-6000 ms

-TE = 90 – 120 ms

- ETL = 4 - 32

- FOV = 35 – 48 cm2

- SW = 5-7 mm (3-4 mm for oblique view)

- ISG = 1 mm

- coverage : PS to PS

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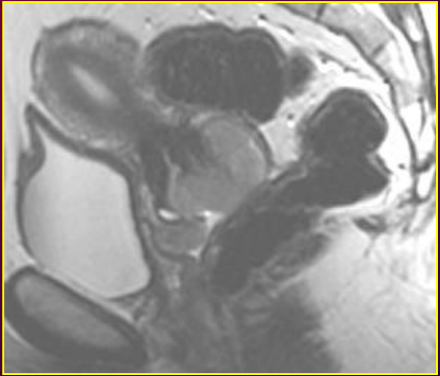
Cervical Cancer : Initial Staging and Follow-up



INITIAL
STAGING

FOLLOW-UP

Cervical Cancer : Initial Staging and Follow-up

MRI >> CT > US

Staging +++

RT treatment +++

follow-up +/-

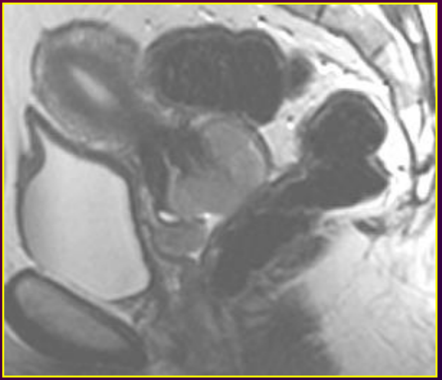
recurrence ++

Boss EA Eur Radiol 2000

Kim JCAT 1993

institutCurie

Cervical Cancer : Initial Staging and Follow-up



INITIAL
STAGING

FOLLOW-UP

Cervical Cancer : Initial Staging

RADIOANATOMY

T2

- cervix : fibrous stroma

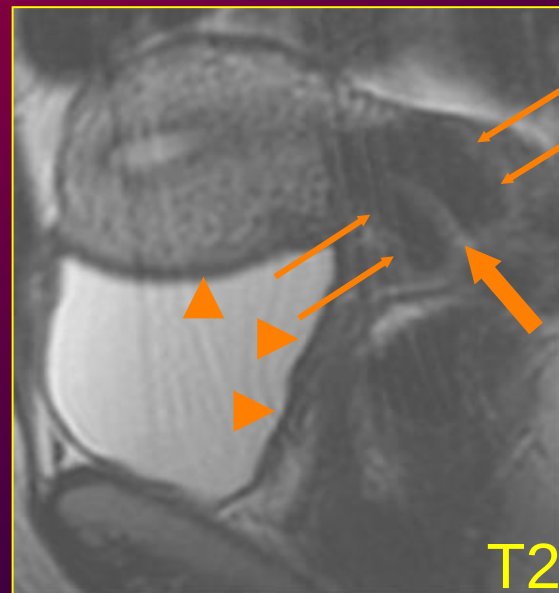
⇓ **T2**

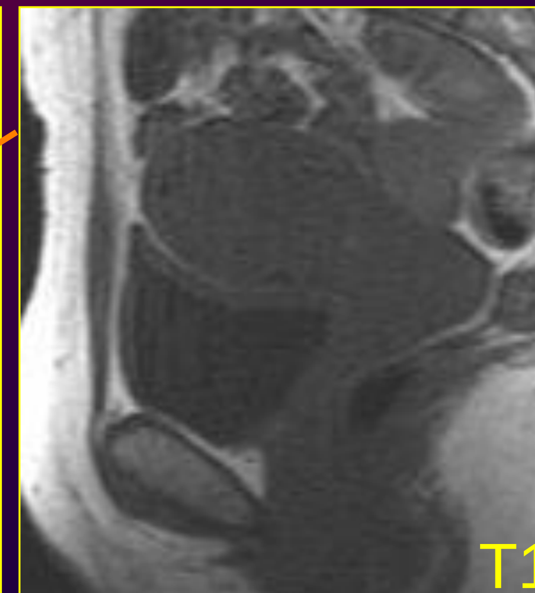
- vagina / rectum / bladder

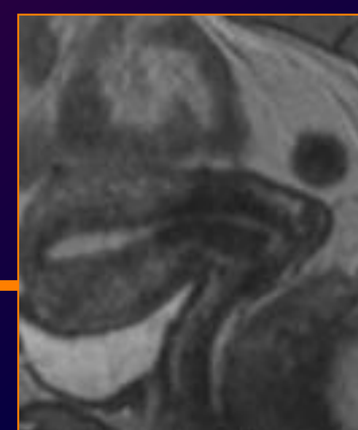
⇓ **T2**

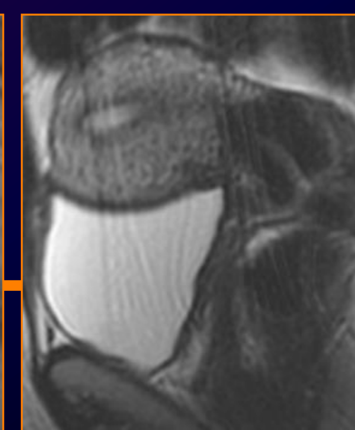
- low SI T2 stroma

⇑ age









Cervical Cancer : Initial Staging

- CM Injection : Indications

- Small / non visible tumors on T2
- Vaginal mucosa visualization
- Complications (abcess / fistulas)

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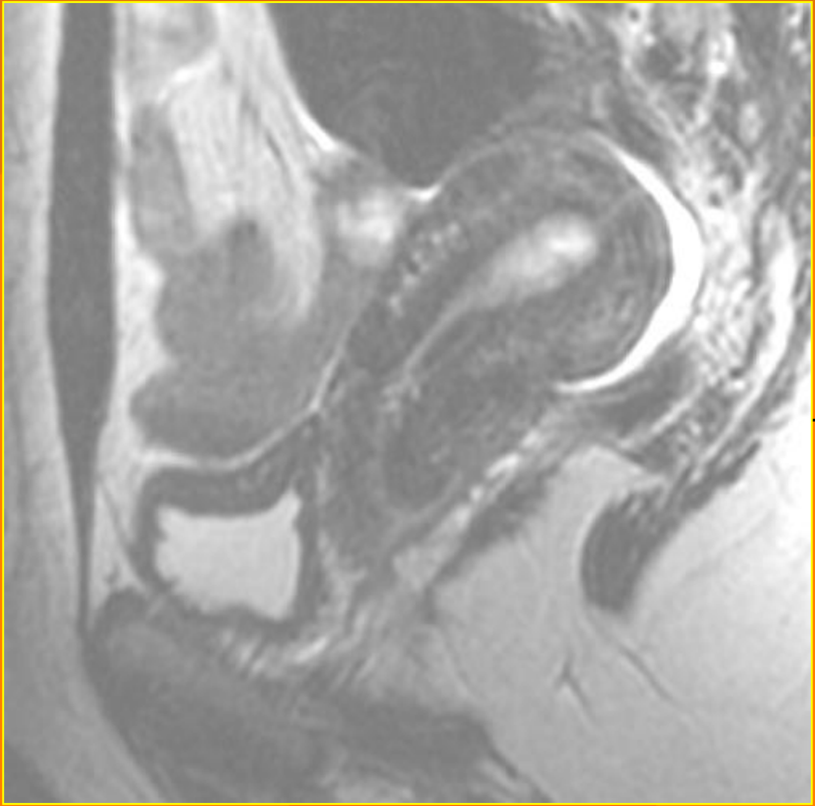
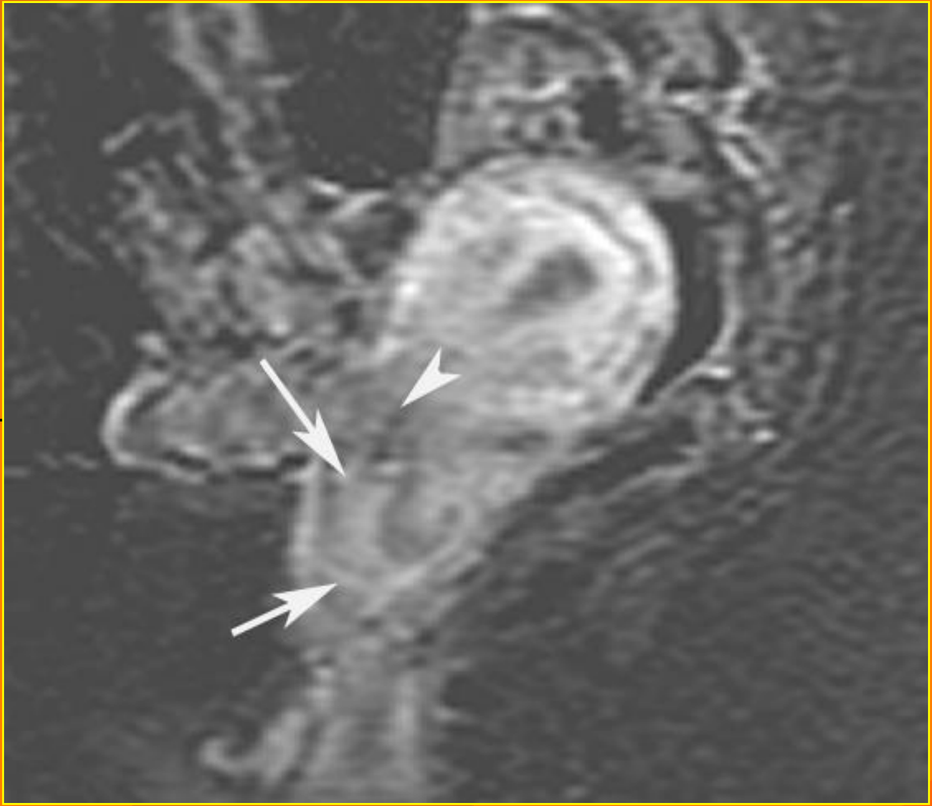
33 y, endocervical tumor (biopsy), adenocarcinoma, FIGO IB1

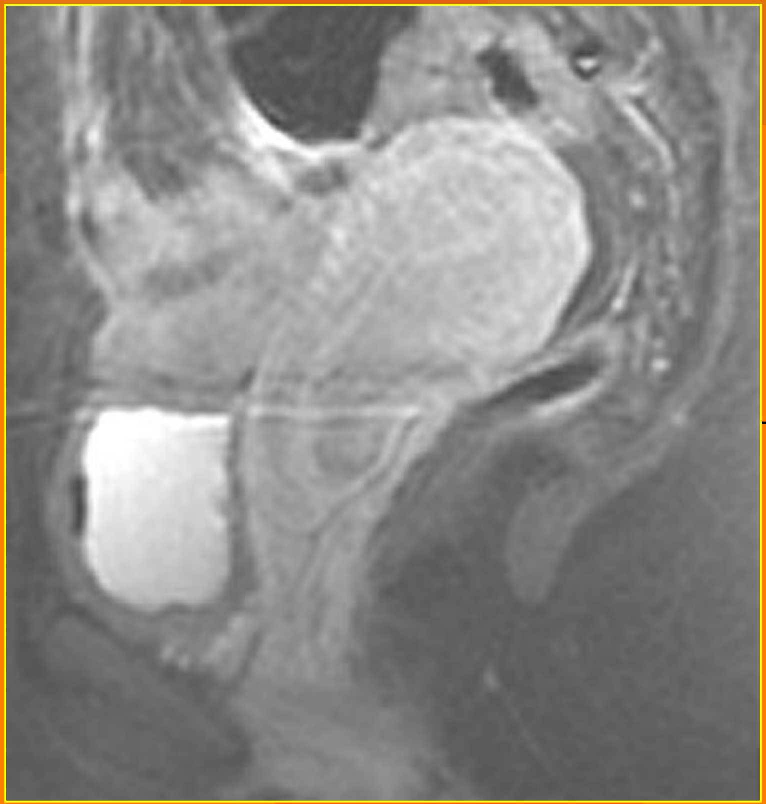


Fast SE T2

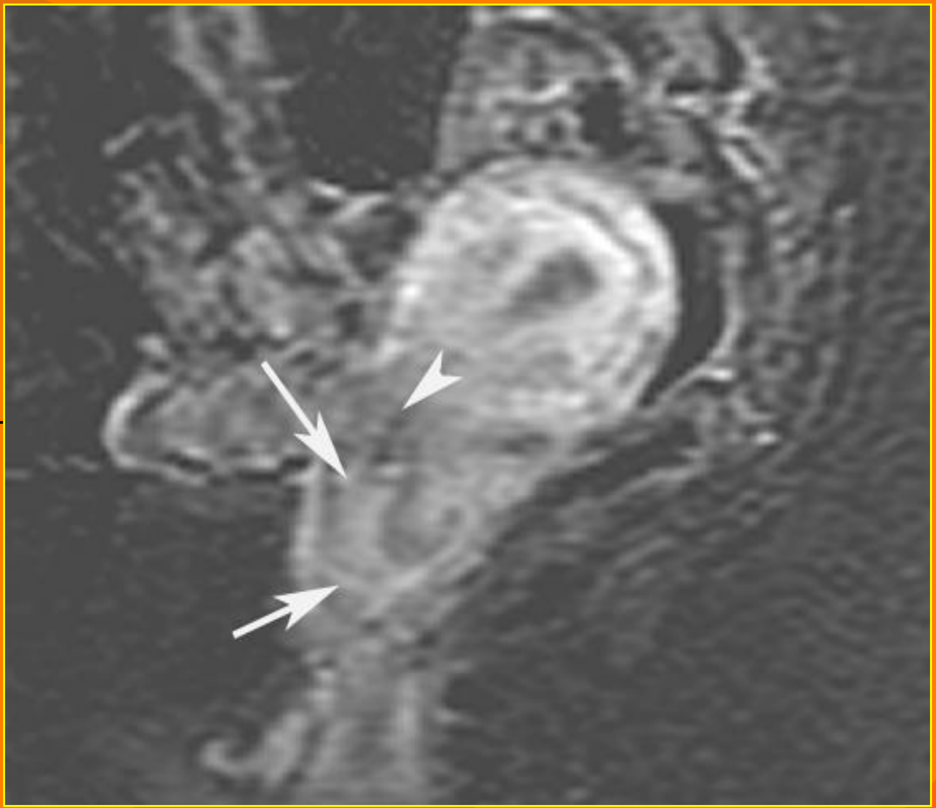


Dynamic-acquisition subtracted contrast-enhanced SE T1-weighted image (1 image every 40 seconds)

33 y, endocervical tumor (biopsy), adenocarcinoma, FIGO IB1

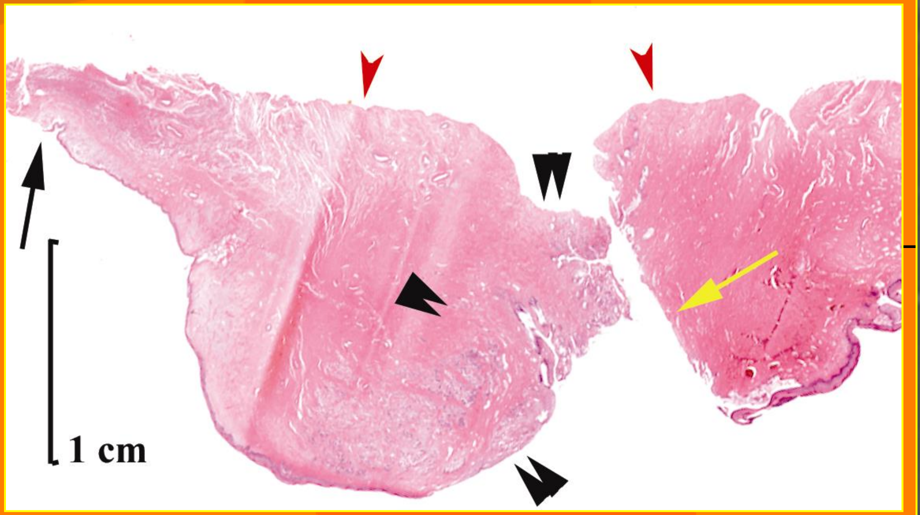


Post-contrast fat-suppressed SE T1 –weighted image

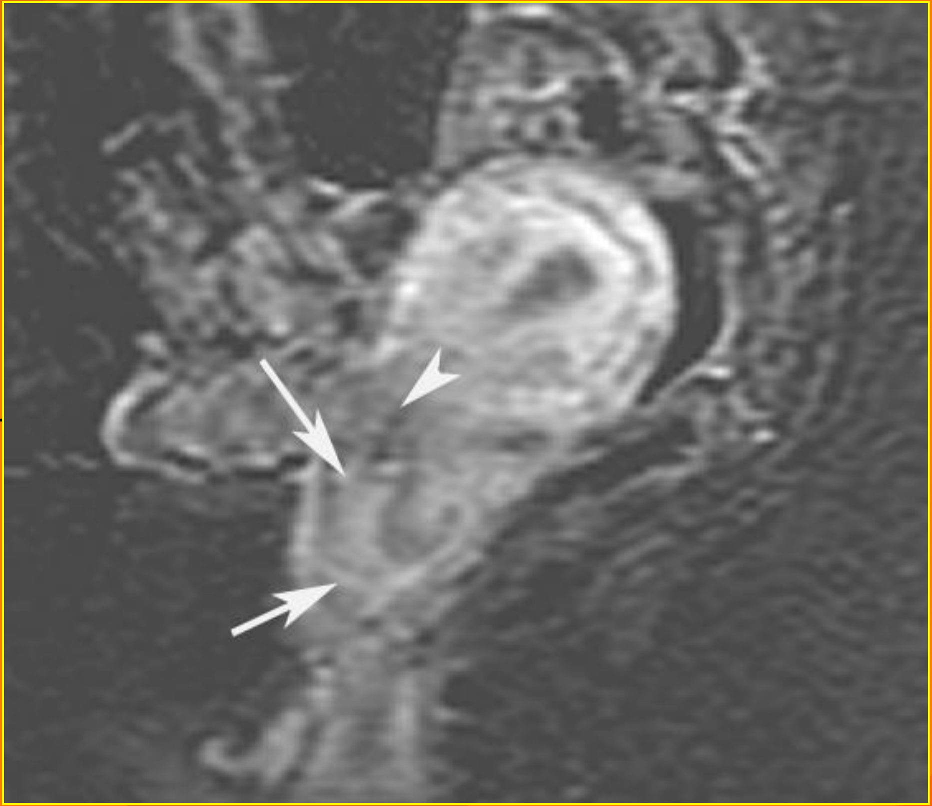


Dynamic-acquisition subtracted contrast-enhanced SE T1-weighted image (1 image every 40 seconds)

33 y, endocervical tumor (biopsy), adenocarcinoma, FIGO IB1



Histological specimen (H&E) after radial trachelectomy



Dynamic-acquisition subtracted contrast-enhanced SE T1-weighted image (1 image every 40 seconds)

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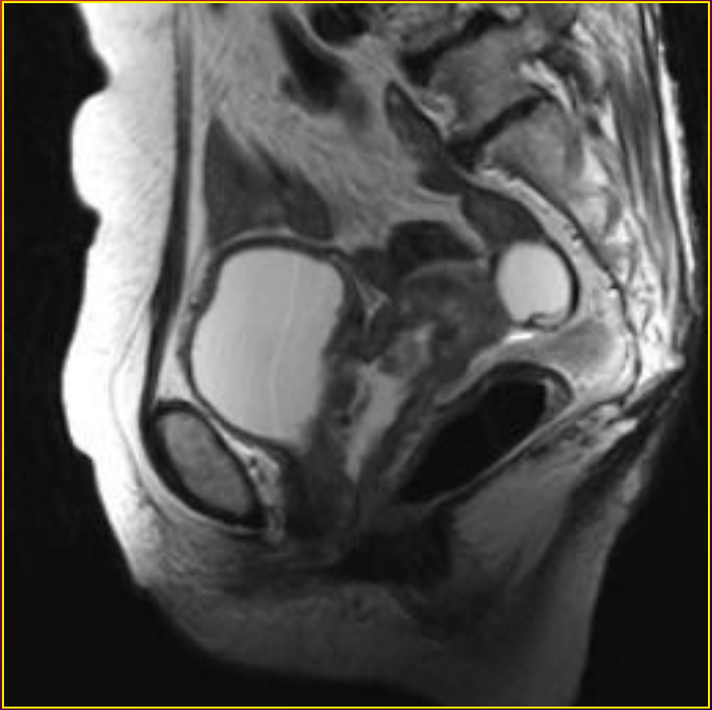
Cervical Cancer : Initial Staging

- CM Injection : Indications



Cervical Cancer : Initial Staging

T = TUMOUR

M = METASTASIS

N = NODE INVOLVEMENT

Cervical Cancer : Initial Staging

T = TUMOUR

M = METASTASIS

N = NODE INVOLVEMENT

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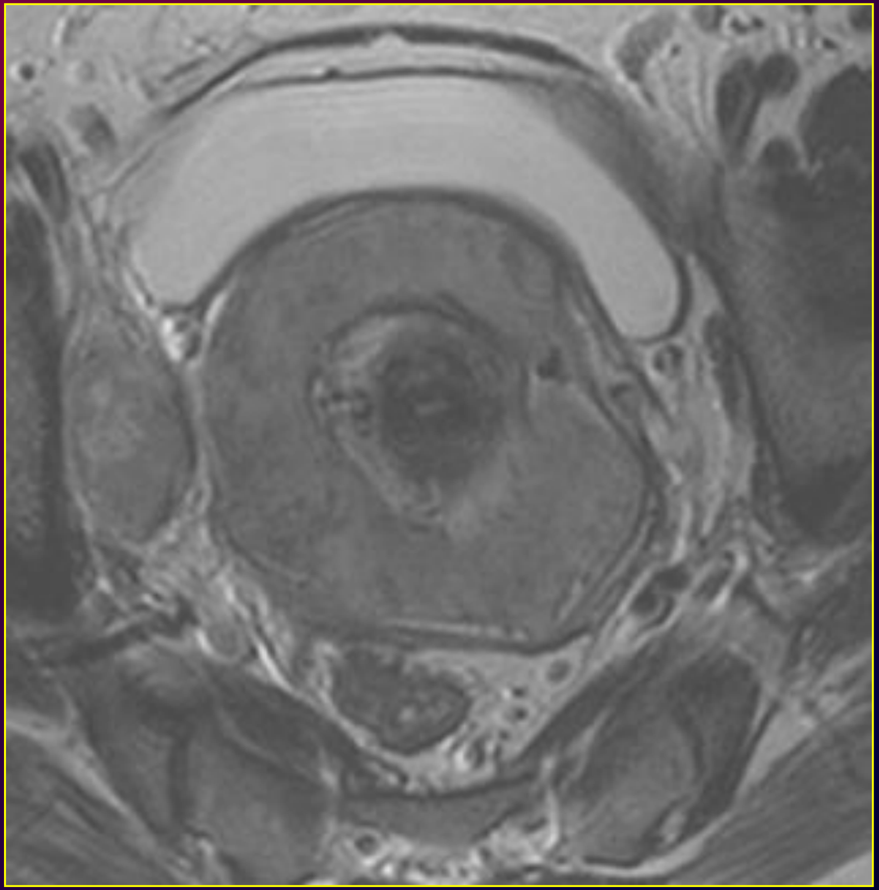
Cervical Cancer : Initial Staging

TUMOUR - SHAPE

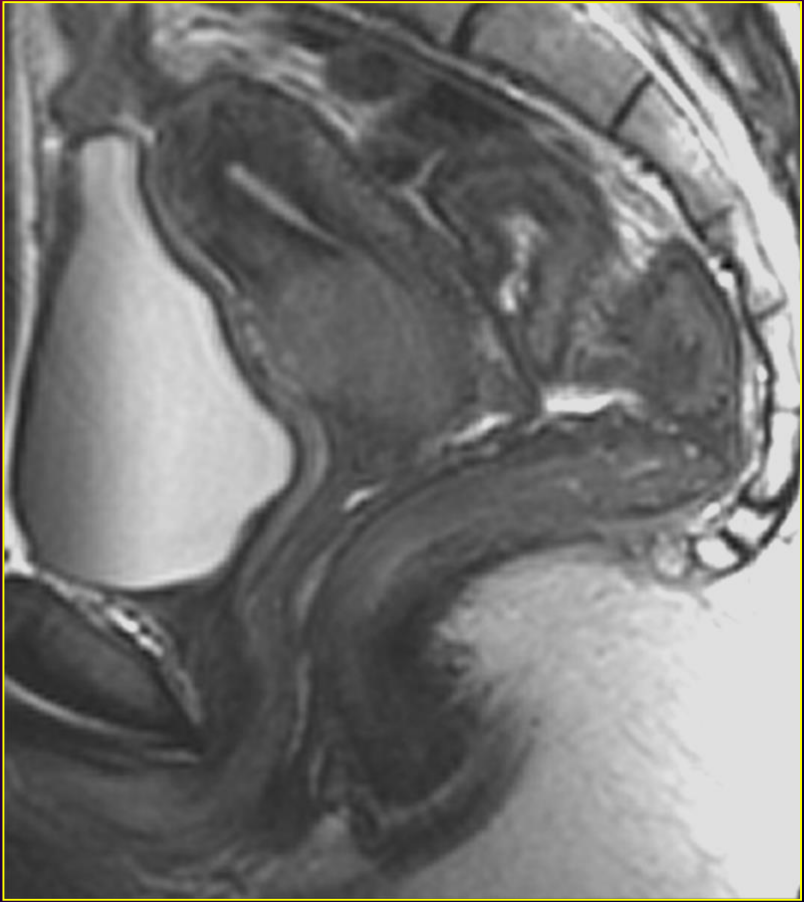
- exophytic



Cervical Cancer : Initial Staging

TUMOUR - SHAPE

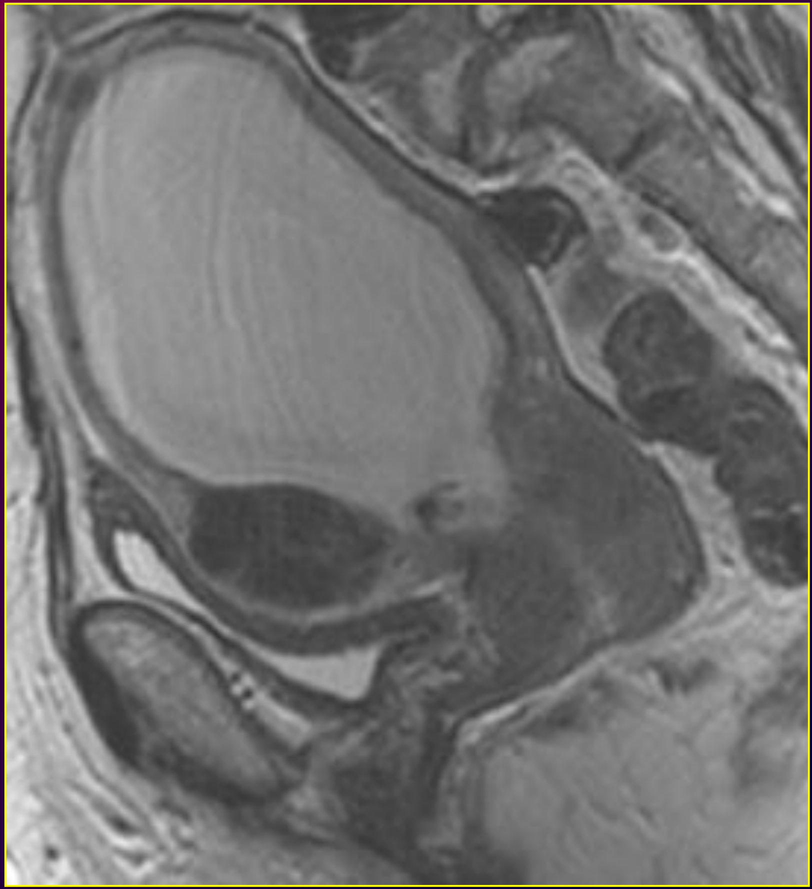
- exophytic
- endocervical



Cervical Cancer : Initial Staging

TUMOUR - SHAPE

- exophytic
- endocervical
- infiltrating



Cervical Cancer : Initial Staging

TUMOUR - SIZE

DIAMETER

< 4 cm IB1

> 4 cm IB2

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Cervical Cancer : Initial Staging

TUMOUR - EXTENSION		FIGO
• parametrium	INTACT	*IB*
	INVASION	*IIB*
	INVASION => PSW	*IIIB*
• ureter		
• bladder / rectum		*IVA*

Cervical Cancer : Initial Staging

TUMOUR – EXTENSION – PARAMETRIUM (1)

INTACT

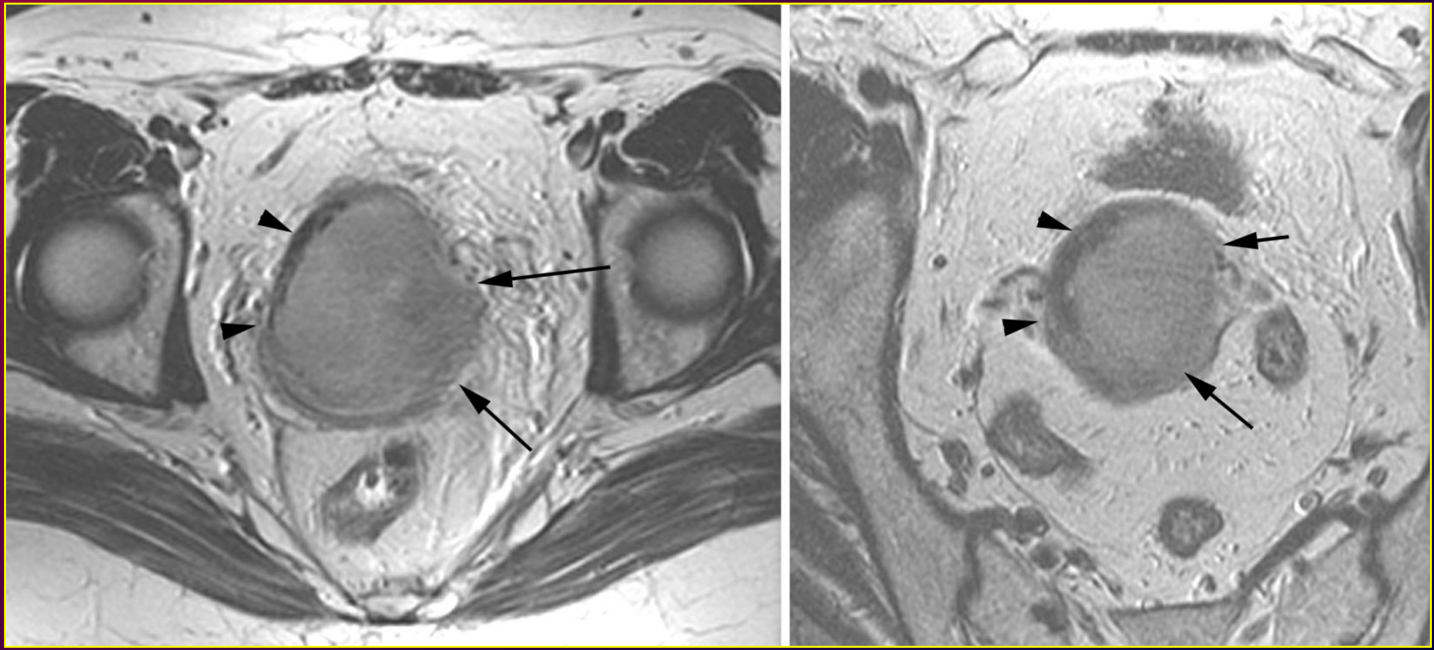
FIGO

IB

Cervical Cancer : Initial Staging

TUMOUR – EXTENSION – PARAMETRIUM (2)

INVASION

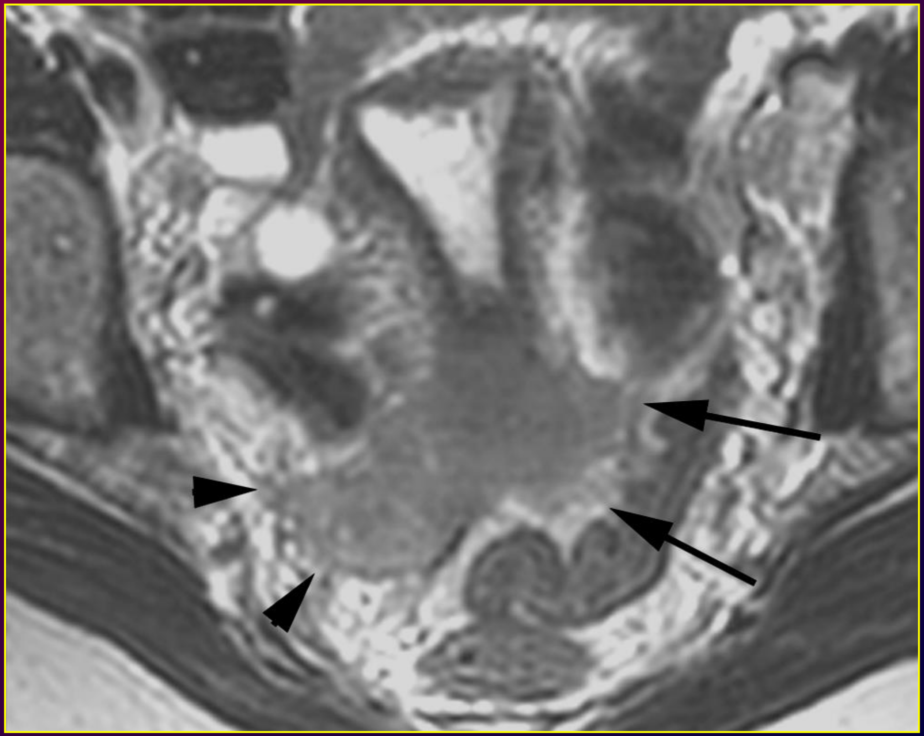


FIGO ***IIB***

Cervical Cancer : Initial Staging

TUMOUR – EXTENSION – PARAMETRIUM (3)

INVASION =>
PELVIC SIDE
WALL



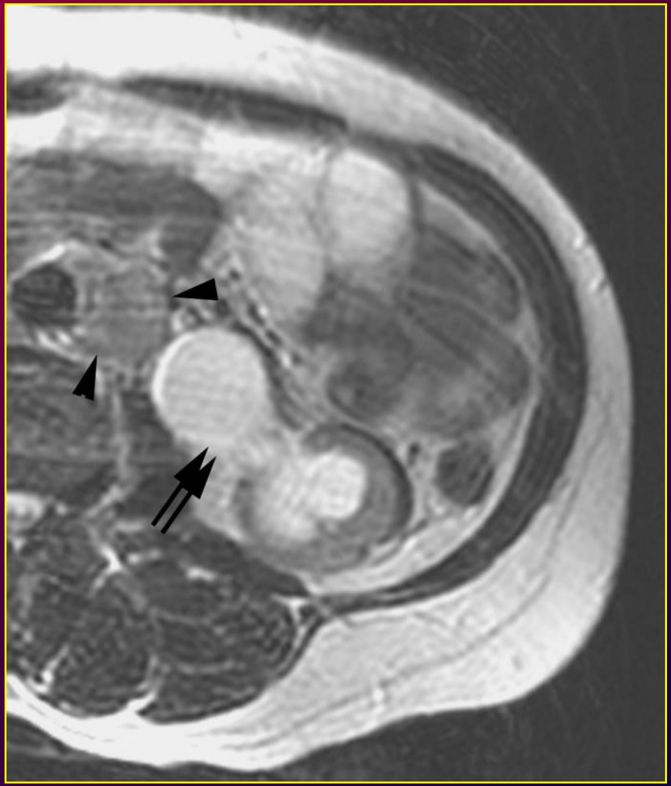
FIGO

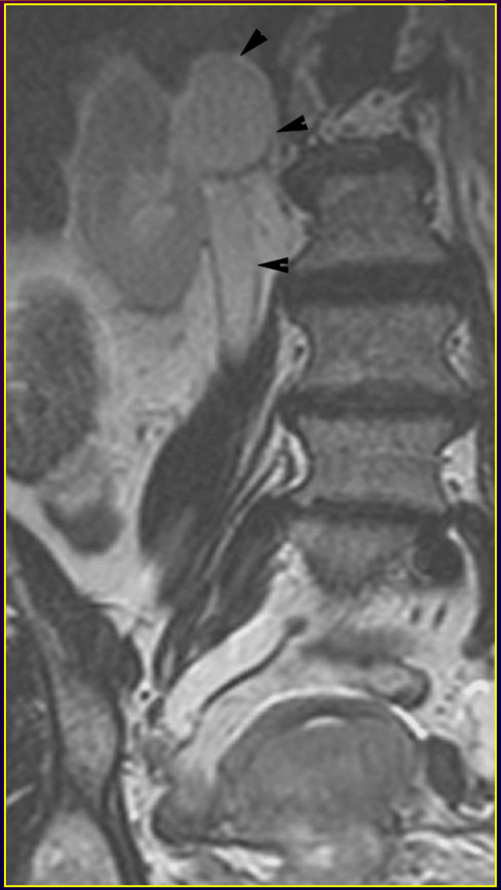
IIIB

Cervical Cancer : Initial Staging

TUMOUR – EXTENSION : URETER

FIGO IIIB



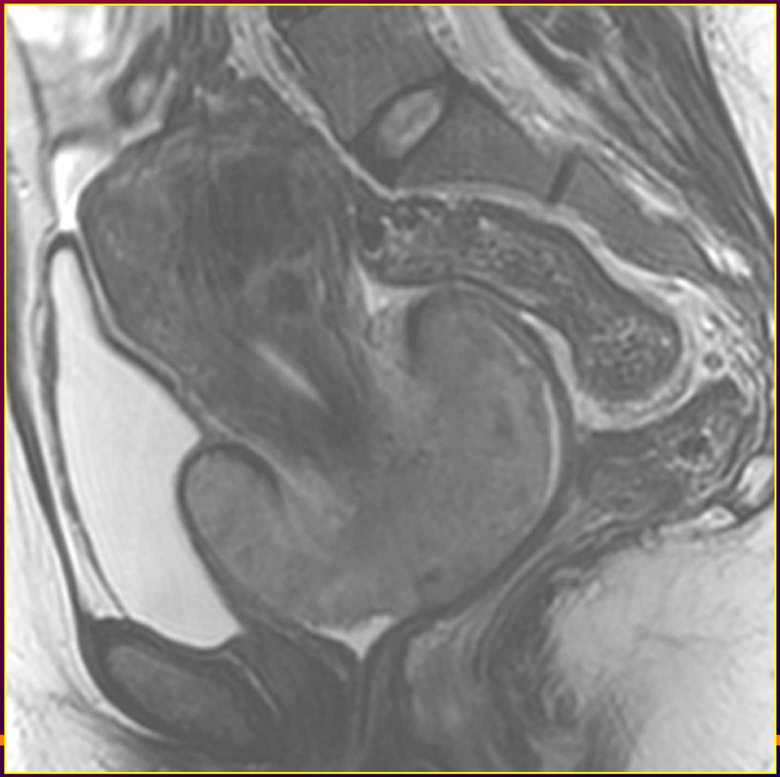


Cervical Cancer : Initial Staging

TUMEUR – EXTENSION : VAGINA

1/3 inf - => IIA

1/3 inf+ => IIIA



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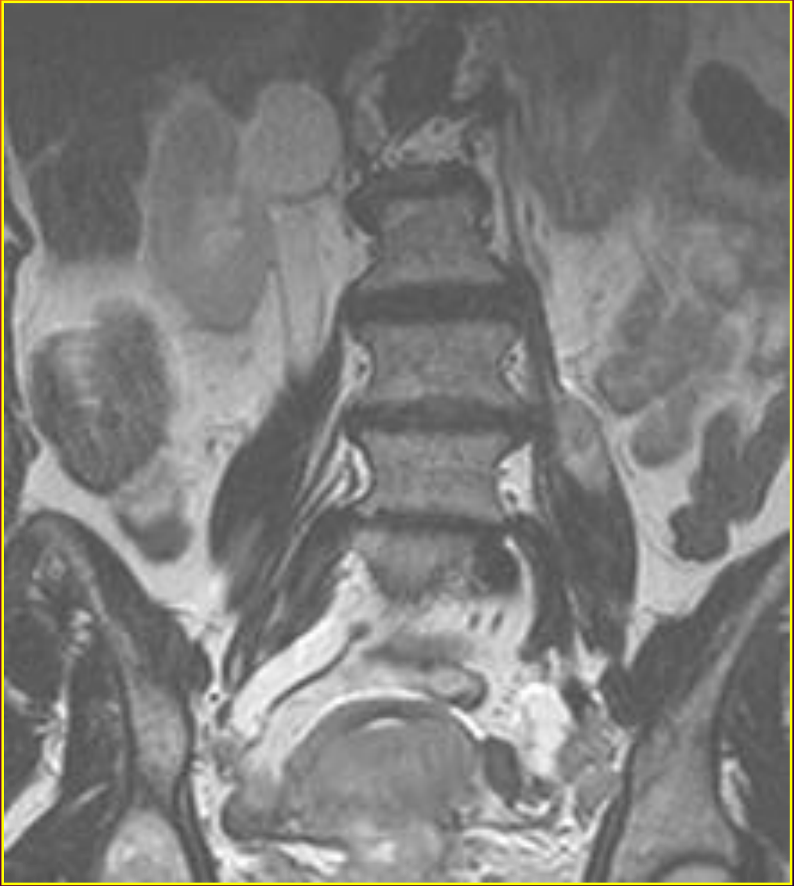
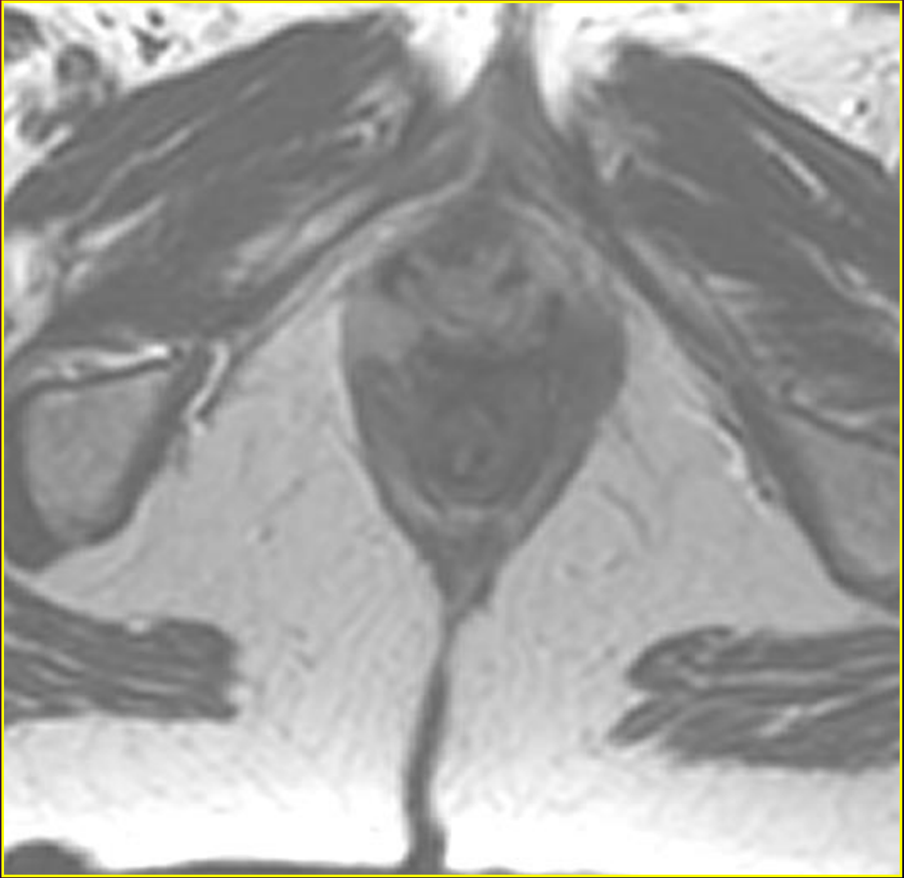
Cervical Cancer : Initial Staging





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OTHER GYNECOLOGICAL TUMROS

OTHER GYNECOLOGICAL TUMORS

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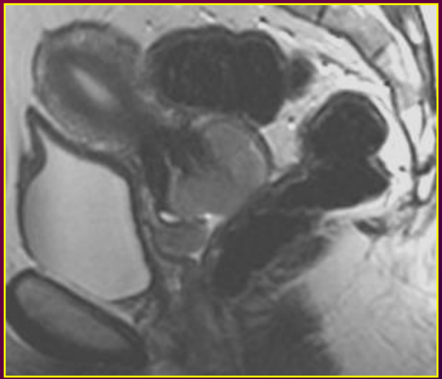
Cervical Cancer : Initial Staging and Follow-up



INITIAL
STAGING

FOLLOW-UP

- **Chemotherapy**
- **Surgery**
- **(Chemo)Radiation Therapy**
- **Recurrence**

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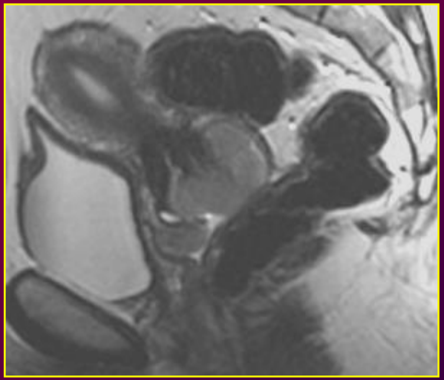
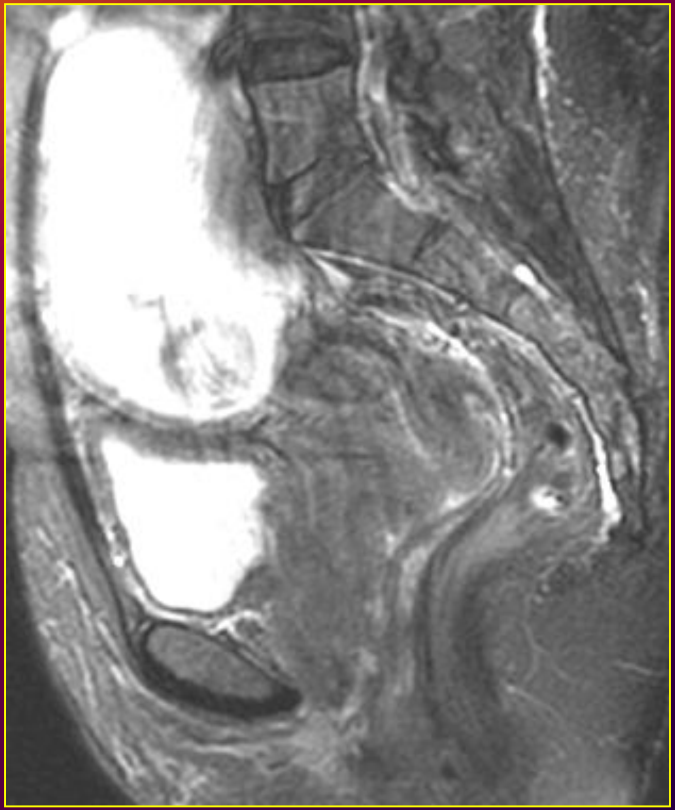
Cervical Cancer : Initial Staging and Follow-up



INITIAL
STAGING

FOLLOW-UP

Cervical Cancer : Follow-up



MRI before treatment

MRI after chemoradiation (2 m)

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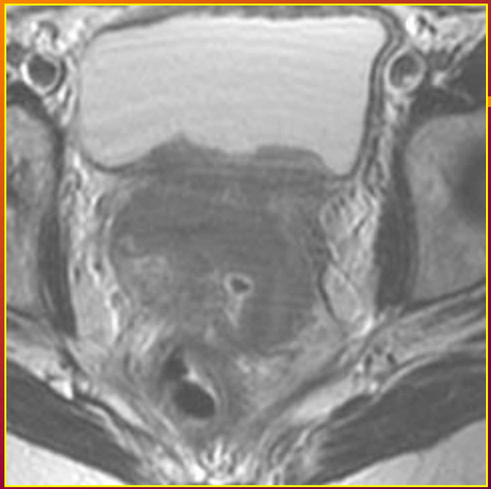
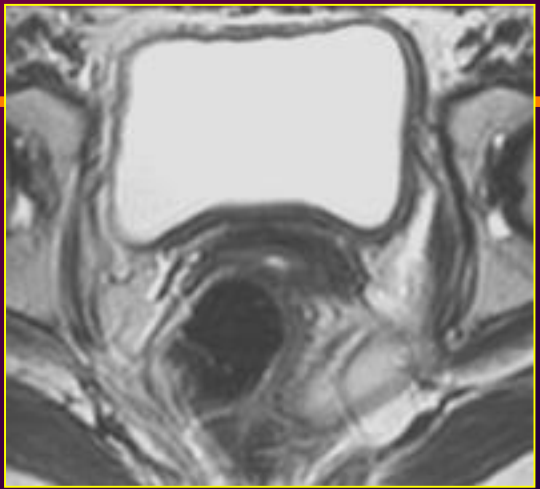


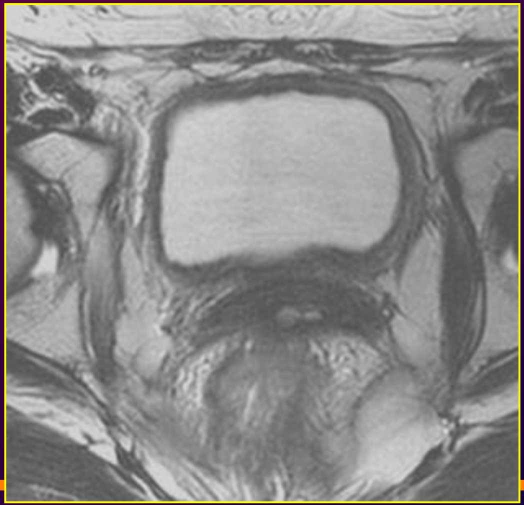
Initial MRI

3 mo. End of RT



5 mo. (2 mo. after BT)

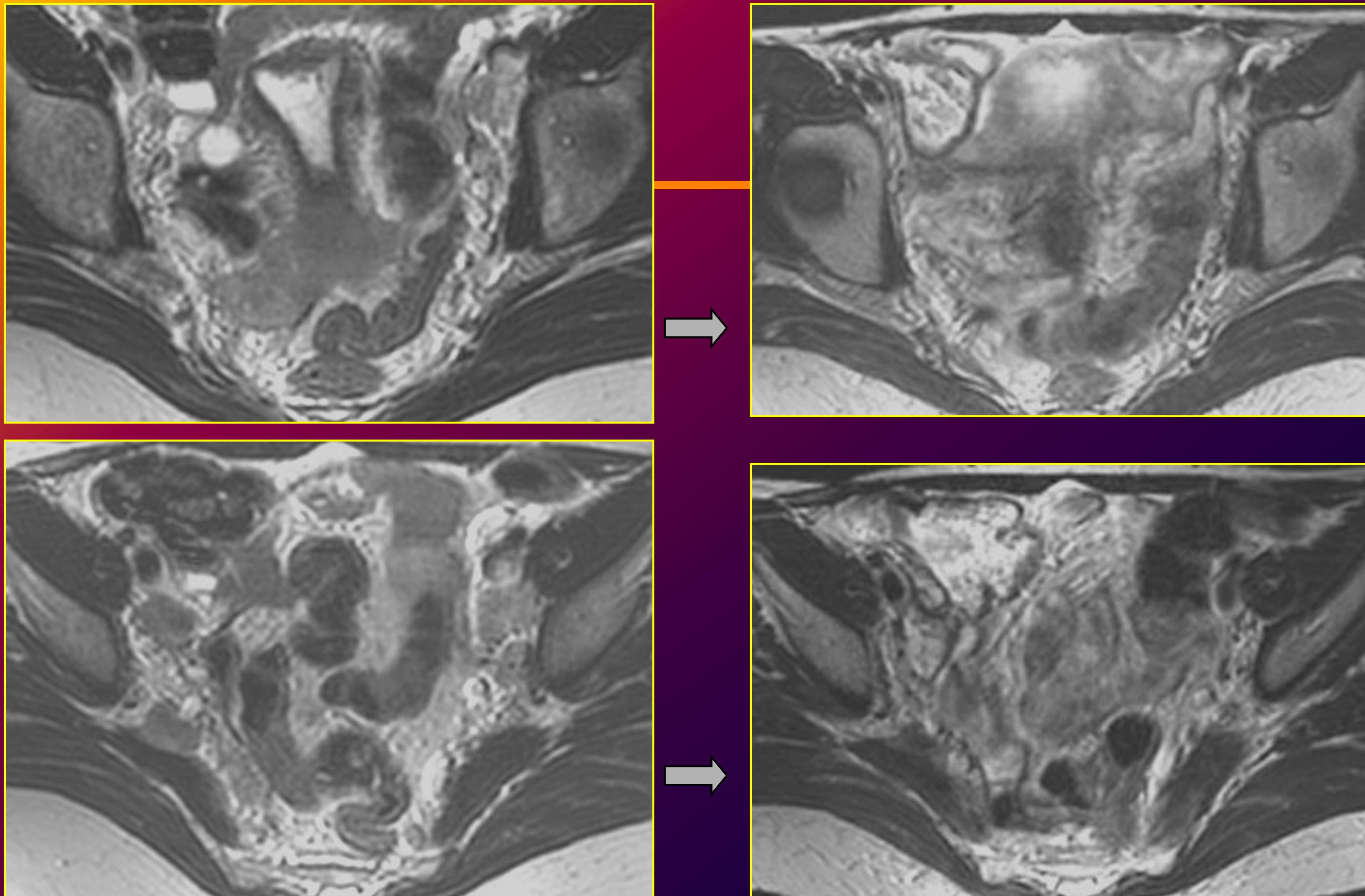
11 mo.



20 mo.

Arrivé Radiology 1989

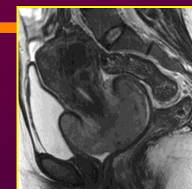
Blomlie Radiology 1996, 1997



RADIATION ONCOLOGIST

RADIOLOGIST

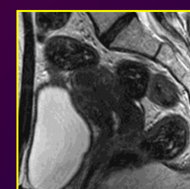
Clinical examination



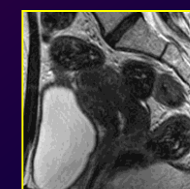
MRI PELV STAGING

EXTERNAL BEAM THERAPY (EBT)

BRACHYTHERAPY

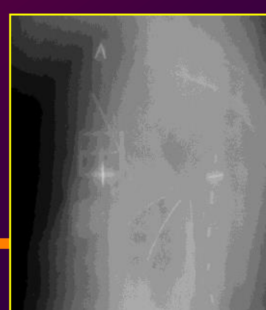


MRI PELV post EBT (45Gy)

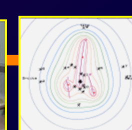


MRI PELV post EBT (45Gy + Brachy)

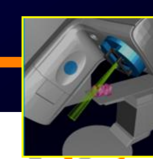
PLAIN FILM



SIMULATION – DOSIMETRY – CONTOURING (OAR)



TREATMENT



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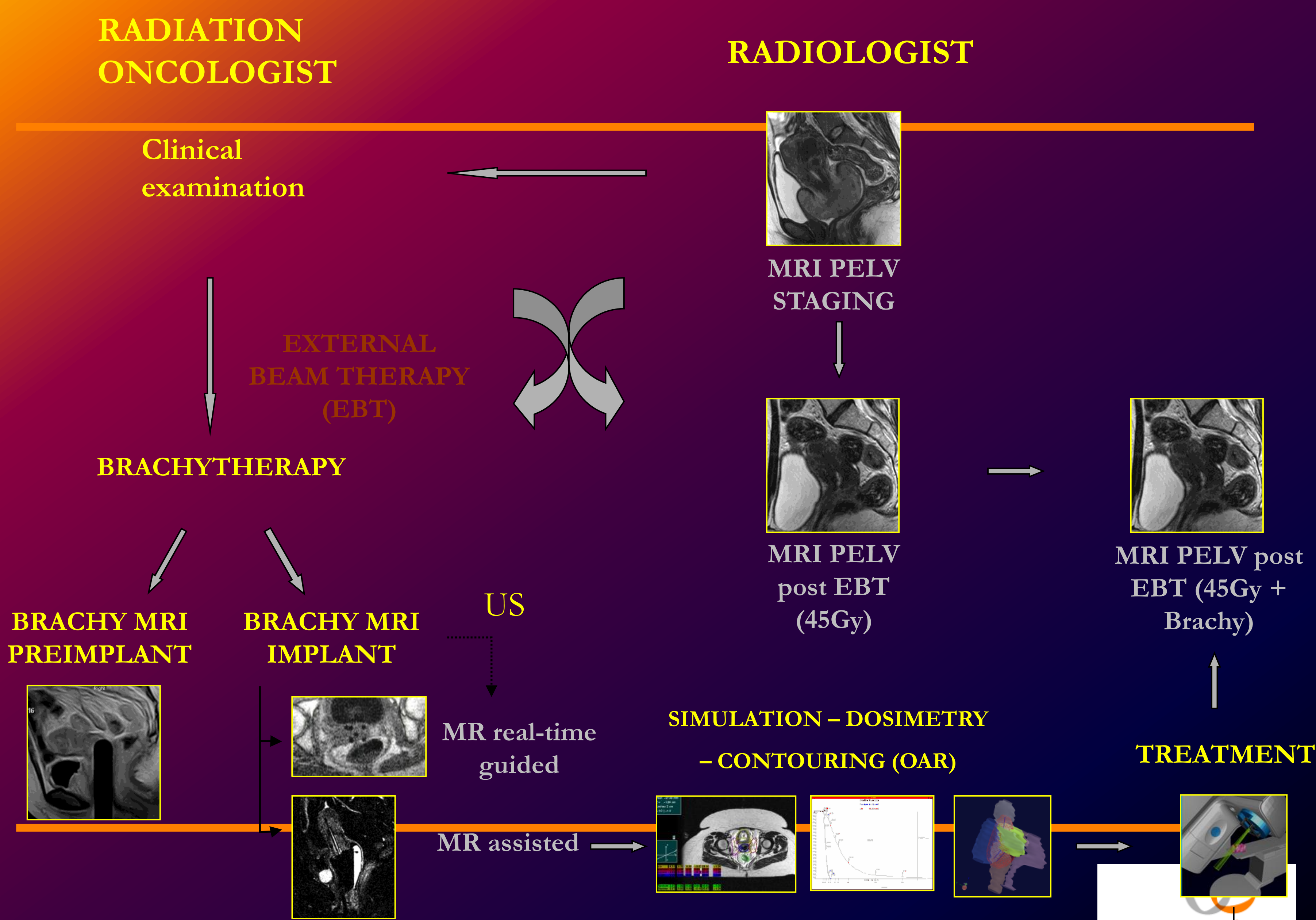

GEC ESTRO WS Prague Czech Republic October 2017

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ASSESSMENT OF NODAL PATHOLOGY

- **BASIC NODAL EVALUATION (US/CT/MR/PET-CT)**
- **SPECIFIC CONTRAST MEDIA (USPIO-MRI)**
- **MR DIFFUSION IMAGING**
- **CONCLUSION**

ASSESSMENT OF NODAL PATHOLOGY

- **NODAL STATUS : TNM CLASSIFICATION OF THE AJCC**
- **LN STATUS : IND. PROGNOSTIC FACTOR / SURVIVAL**
- **LN STATUS : INFLUENCES TREATMENT**
  - LN STAGING SURGERY
  - NODAL IRRADIATION

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ASSESSMENT OF NODAL PATHOLOGY

PERIOD PRIOR OF CROSS-SECTIONAL IMAGING:

- bipedal LYMPHOGRAPHY
  - CE imaging
  - study of internal architecture
  - functional and physiologic study of the lymphatic system

LIMITATIONS

- limited exploration
- invasive
- time-consuming

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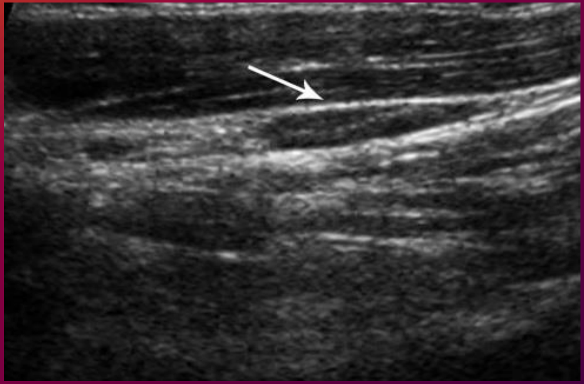
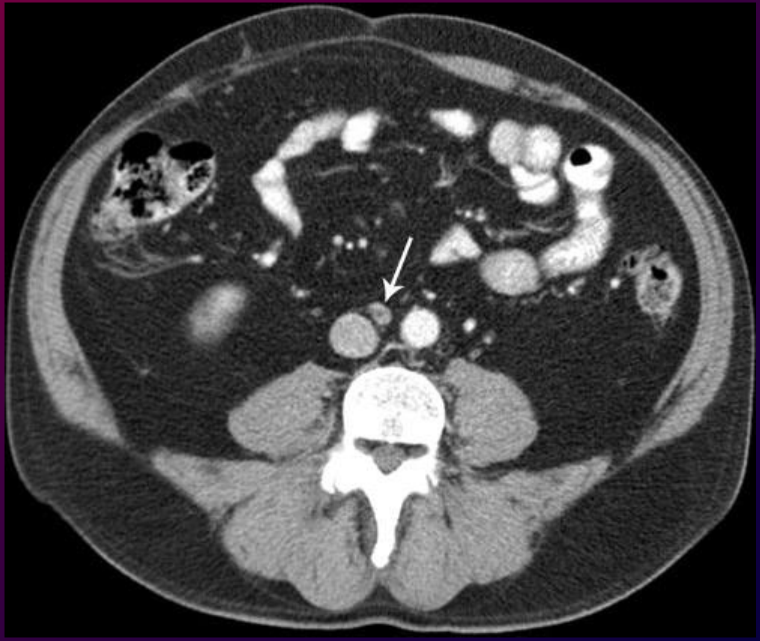
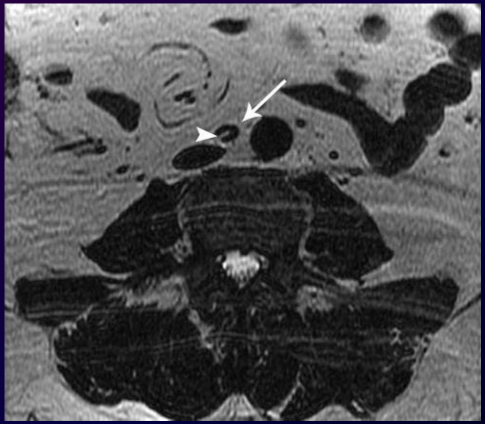
ASSESSMENT OF NODAL PATHOLOGY

PERIOD OF CROSS-SECTIONAL IMAGING: US / CT/ MRI -

- ANATOMIC / MORPHOLOGIC imaging & evaluation





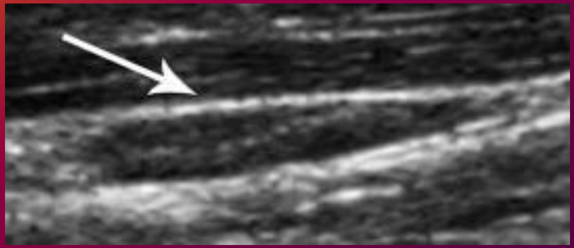


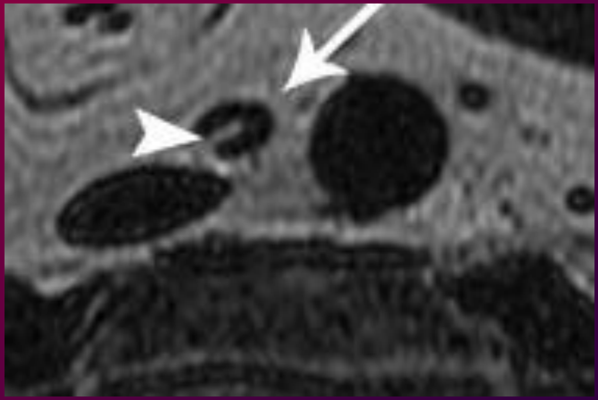
Torabi M, J Nucl Med 2004 ; 45 : 1509-18

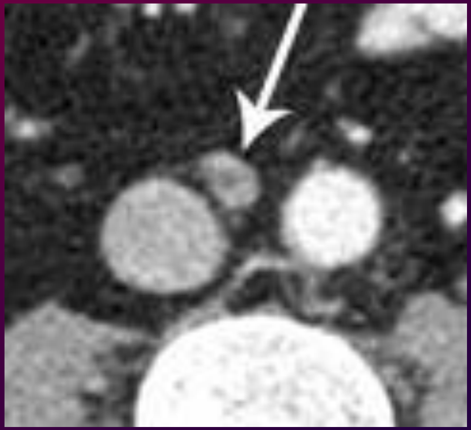
ASSESSMENT OF NODAL PATHOLOGY

PERIOD OF CROSS-SECTIONAL IMAGING: US / CT/ MRI -

- ANATOMIC / MORPHOLOGIC imaging & evaluation







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

Size criterion : < 10 mm

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

ASSESSMENT OF NODAL PATHOLOGY

PERIOD OF CROSS-SECTIONAL IMAGING: US / CT/ MRI -

- ANATOMIC / MORPHOLOGIC imaging & evaluation

Summary of Literature Indicating Upper Size Limit for Benign Lymph Nodes According to Anatomic Site on Cross-Sectional Imaging

Anatomic site	Reference: Author	Reference: No.	Reference: Year	Lymph node: Maximum short-axis diameter (mm)	Lymph node: Maximum long-axis diameter (mm)
Axillary	Yoshimura et al.	*(16)*	1999	NA	10
Internal mammary	Kinoshita et al.	*(17)*	1999	NA	5
Pelvic	Vinnicombe et al.	*(18)*	1995	10	NA
Mediastinum	Ingram et al.	*(19)*	1989	10	NA
Jugulodigastric region	Van den Brekel et al.	*(20)*	1990	11	NA
Nonretropharyngeal nodes	Van den Brekel et al.	*(20)*	1990	10	NA
Lateral retropharyngeal	Van den Brekel et al.	*(20)*	1990	5	NA
Inguinal	Hawnaur et al.	*(21)*	2002	10	NA

NA = not applicable.

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

ASSESSMENT OF NODAL PATHOLOGY

PERIOD OF CROSS-SECTIONAL IMAGING: US / CT/ MRI -

- ANATOMIC / MORPHOLOGIC imaging & evaluation

Summary of Published Clinical Trials with CT/MRI

Reference			No. of patients	Region	CT/MRI		
Author	No.	Year			Sensitivity (%)	Specificity (%)	Accuracy (%)
Kau et al.	(22)	1999	70	Head and neck	65/88	47/41	NA
Dwamena et al.	(23)	1999	2,226	Lung	60/—*	77/—*	75/—*
Pieterman et al.	(24)	2000	102	Lung	75/—*	66/—*	69/—*
Gagliardi et al.	(25)	2002	28	Pelvic	—*/67	—*/71	—*/69
Bipat et al.	(26)	2003	NA	Uterine cervical	43/60	Both >90	NA
Anzai et al.	(27)	2003	147	All body regions	54	82	68
Antoch et al.	(28)	2003	27	Lung	70/—*	59/—*	63/—*

*This modality was not evaluated.
NA = not applicable.

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

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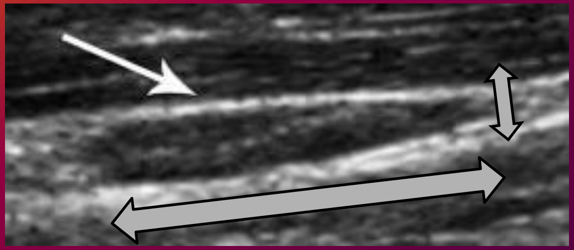
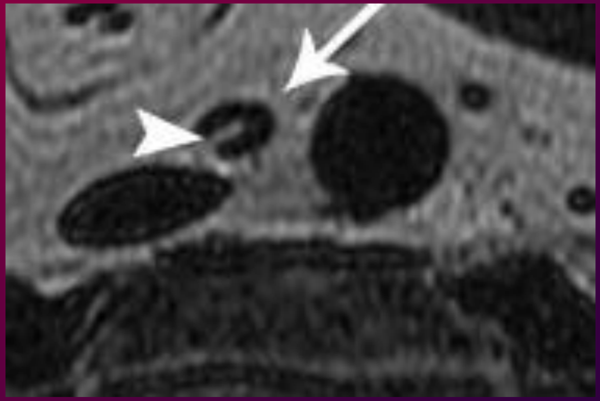
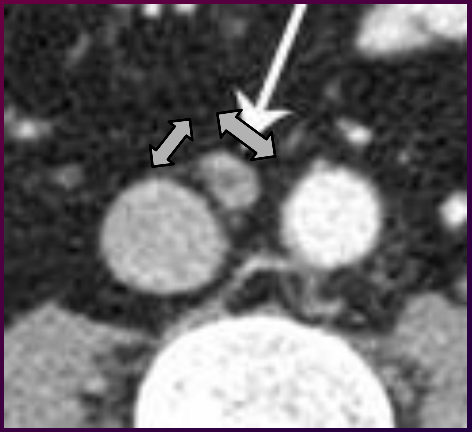
ASSESSMENT OF NODAL PATHOLOGY

PERIOD OF CROSS-SECTIONAL IMAGING: US / CT/ MRI -

- ANATOMIC / MORPHOLOGIC imaging & evaluation (2)







- Ratio Short axis / long axis : 0.8

ratio criterion : 0.8 < S : benign

ratio criterion : S >= 0.8 : malignant

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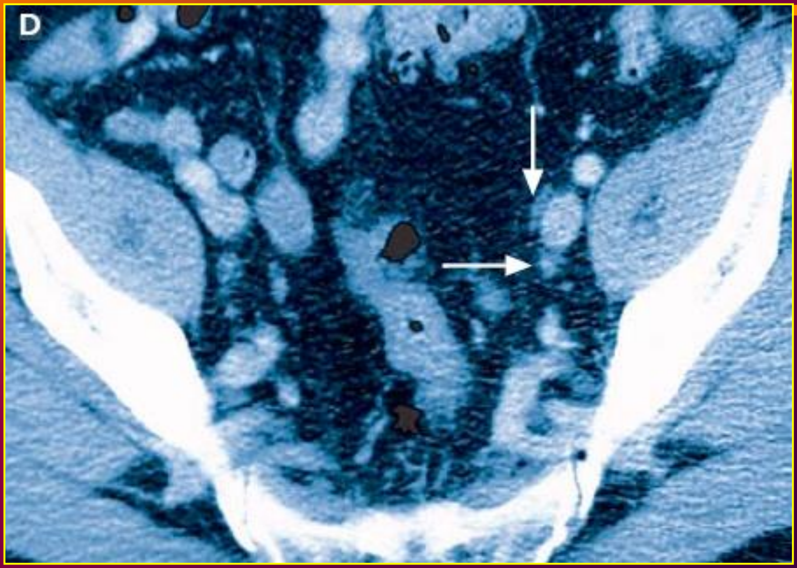
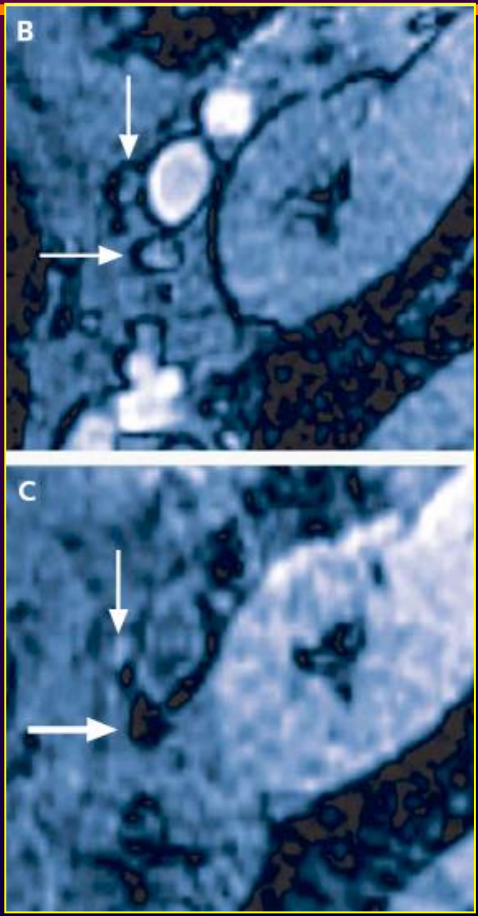
IMAGING THE LYMPH NODE – ACTUAL STATUS



USPIO - MRI

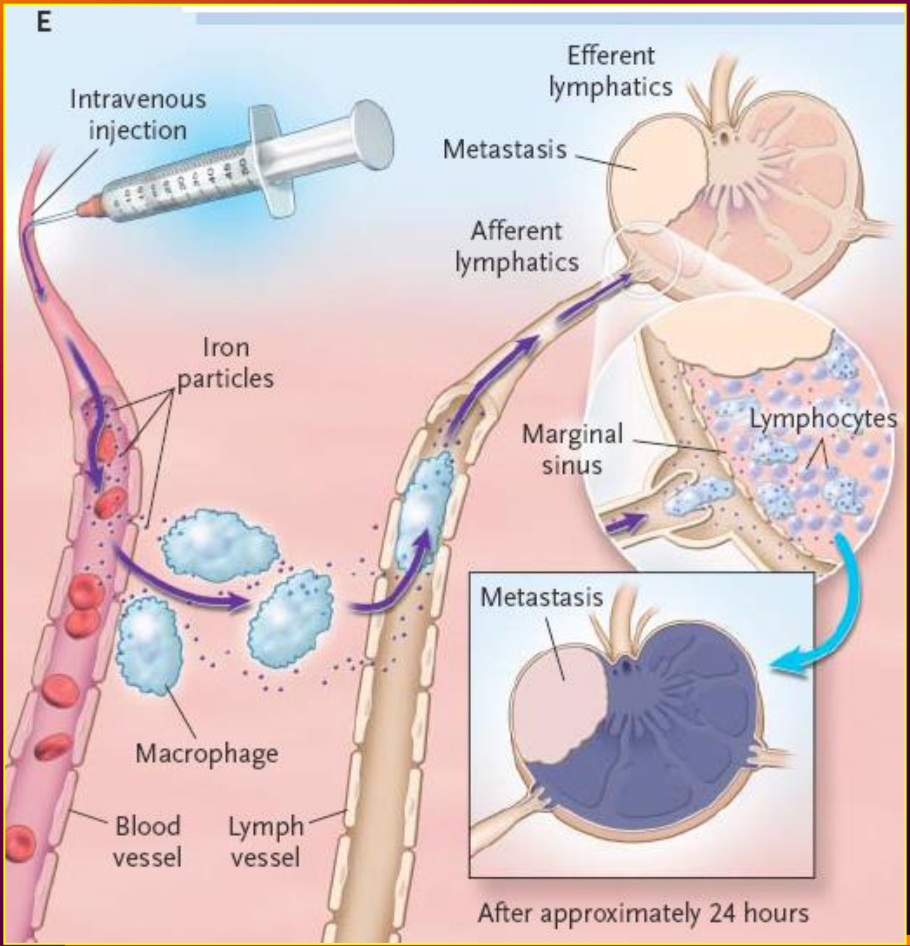


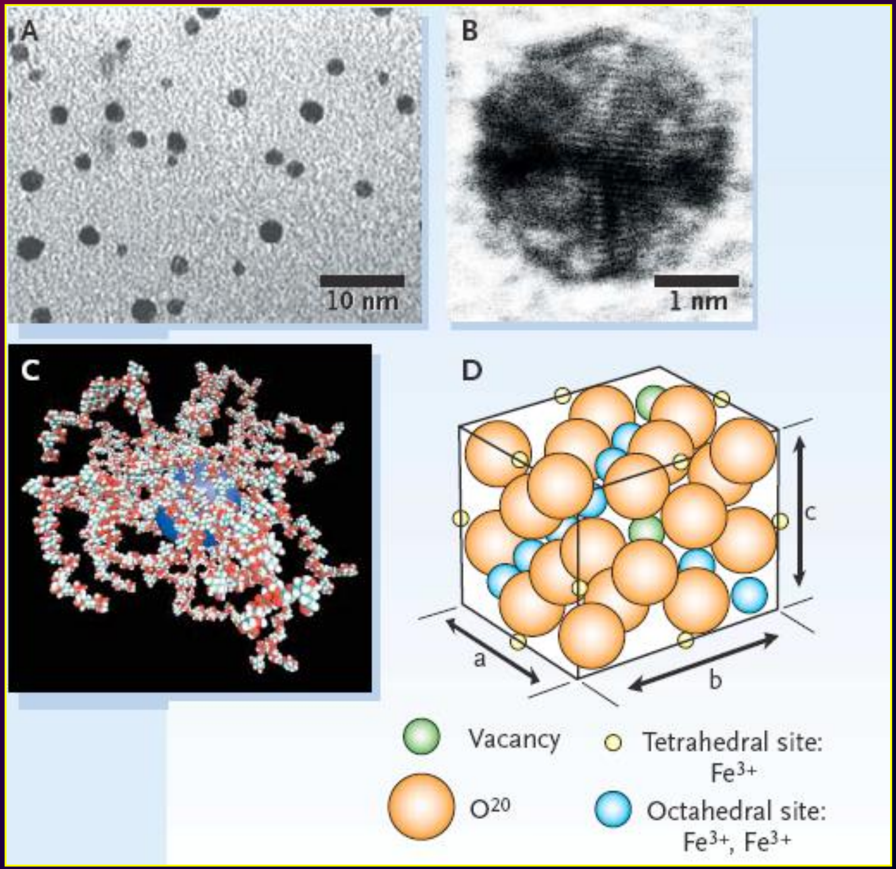
Only admitted criterion in CT and MRI:

- Small diameter < 10 mm

Rockall, A. G. et al. J Clin Oncol; 23:2813-2821 2005

MECANISM OF USPIO (ultrasmall particle of iron-oxide)





NEJM Harisingani 2003

MECANISM OF USPIO (ultrasmall particle of iron-oxide)

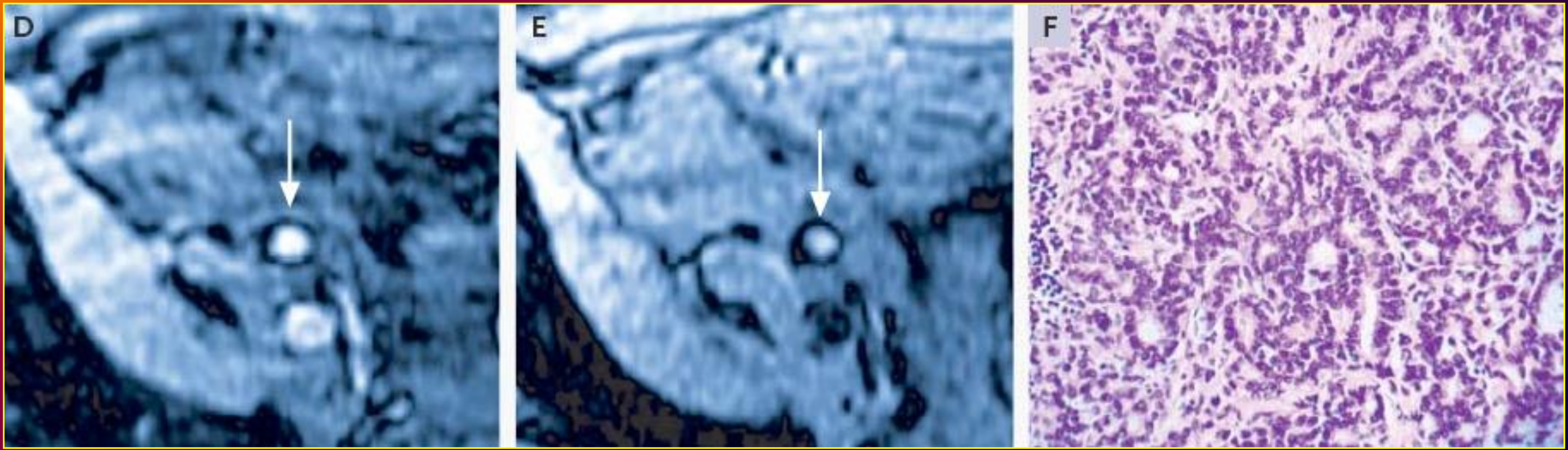
MRI T_0:
T2*

MRI T_{h24}:
T2*

Local perturbation of the magnetic field => local signal loss

→ Physiological evaluation of the lymph node function

MECANISM OF USPIO (ultrasmall particle of iron-oxide)

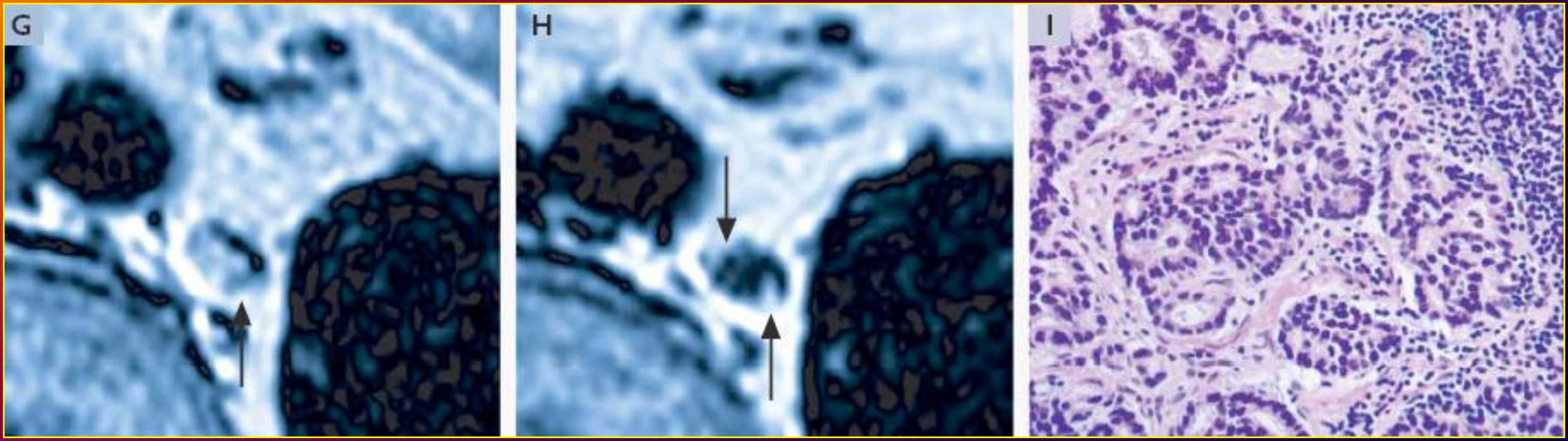


MRI T_0:
T2*-weighted sequence

MRI T_{h24}:
T2*-weighted sequence

10 mm
metastatic LN

MECANISM OF USPIO (ultrasmall particle of iron-oxide)

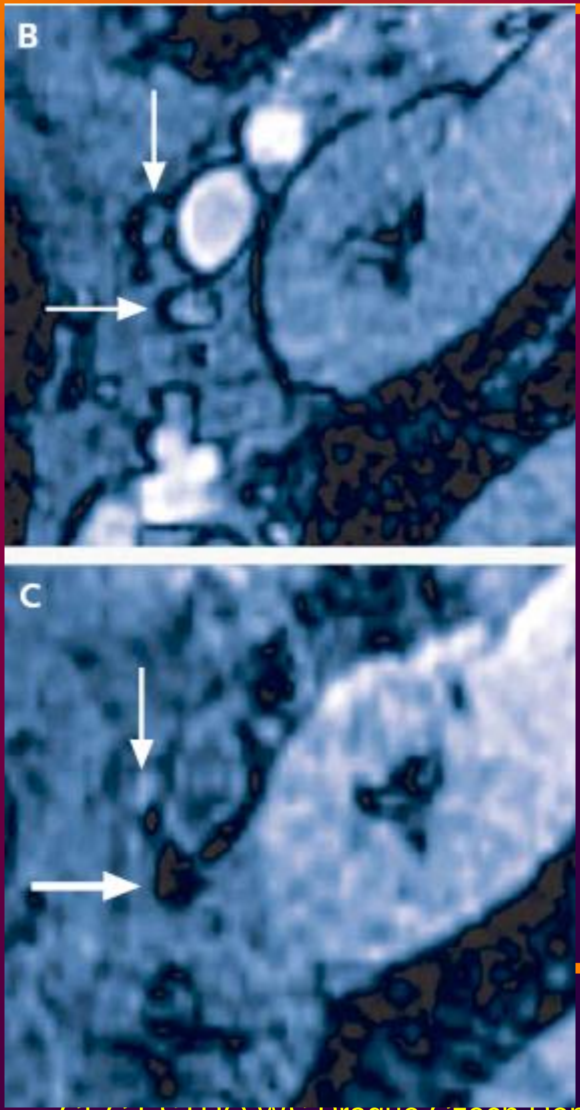


MRI T_0:
T2*-weighted sequence

MRI T_{h24}:
T2*-weighted sequence

3mm micrometastasis in a otherwise normal LN

MECANISM OF USPIO (ultrasmall particle of iron-oxide)



MRIT_0:
T2*-weighted sequence

Small 5 mm metastasis in a LN

MRI T_{h24}:
T2*-weighted sequence

MECANISM OF USPIO (ultrasmall particle of iron-oxide)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 19, 2003 VOL. 348 NO. 25

Noninvasive Detection of Clinically Occult Lymph-Node Metastases in Prostate Cancer

Mukesh G. Harisinghani, M.D., Jelle Barentsz, M.D., Ph.D., Peter F. Hahn, M.D., Ph.D., Willem M. Deserno, M.D., Shahin Tabatabaei, M.D., Christine Hulsbergen van de Kaa, M.D., Ph.D., Jean de la Rosette, M.D., Ph.D., and Ralph Weissleder, M.D., Ph.D.

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Table 2. **Sensitivity, Specificity, Accuracy, and Positive and Negative Predictive Values of MRI Alone and MRI with Lymphotropic Superparamagnetic Nanoparticles.**

Variable	MRI Alone	MRI with Lymphotropic Superparamagnetic Nanoparticles	P Value
Results per patient (n=80)			
Sensitivity (%)	45.4	100	<0.001
Specificity (%)	78.7	95.7	
Accuracy (%)	65.0	97.5	
Positive predictive value (%)	60.0	94.2	
Negative predictive value (%)	67.2	100	
Results per individual lymph nodes of all sizes (n=334)			
Sensitivity (%)	35.4	90.5	<0.001
Specificity (%)	90.4	97.8	
Accuracy (%)	76.3	97.3	
Positive predictive value (%)	55.9	95.0	
Negative predictive value (%)	80.3	97.8	
Area under the curve	0.756	0.975	<0.001
Results for nodes with a short-axis diameter of 5–10 mm (n=45)			
Sensitivity (%)	28.5	96.4	<0.001
Specificity (%)	87.2	99.3	
Accuracy (%)	78.3	98.9	
Positive predictive value (%)	28.5	96.4	
Negative predictive value (%)	87.2	99.3	
Results for nodes with a short-axis diameter of <5 mm (n=17)			
Sensitivity (%)	0	41.1	
Specificity (%)	100	98.1	
Accuracy (%)	86.4	90.4	
Positive predictive value (%)	NA*	77.7	
Negative predictive value (%)	86.4	91.3	

* NA denotes not applicable.

ASSESSMENT OF NODAL PATHOLOGY

… and CT - PET

evaluation of pelvic and paraaortic lymph node extension + + +
« One-shot whole body » evaluation of disease extent

CT = MRI for pelvic and paraortic LN staging

… and CT versus MRI

Yang AJR 2000 ; Scheidler JAMA 1997

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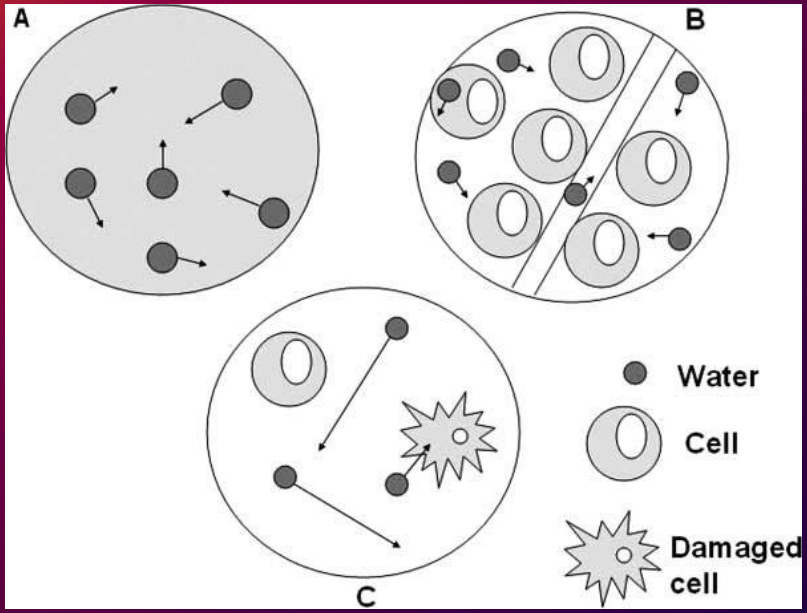
ASSESSMENT OF NODAL PATHOLOGY

MR DIFFUSION-WEIGHTED IMAGING



MR DIFFUSION-WEIGHTED IMAGING

Imaging of H2O movement
(Brownian motion of H20)

A. Water cavities (bladder, ascites)

B. Cells:
- **intravasculaire, intercellular, intracellular**

B. Damaged cells:
- **Disruption of membranes (CT / RT)**

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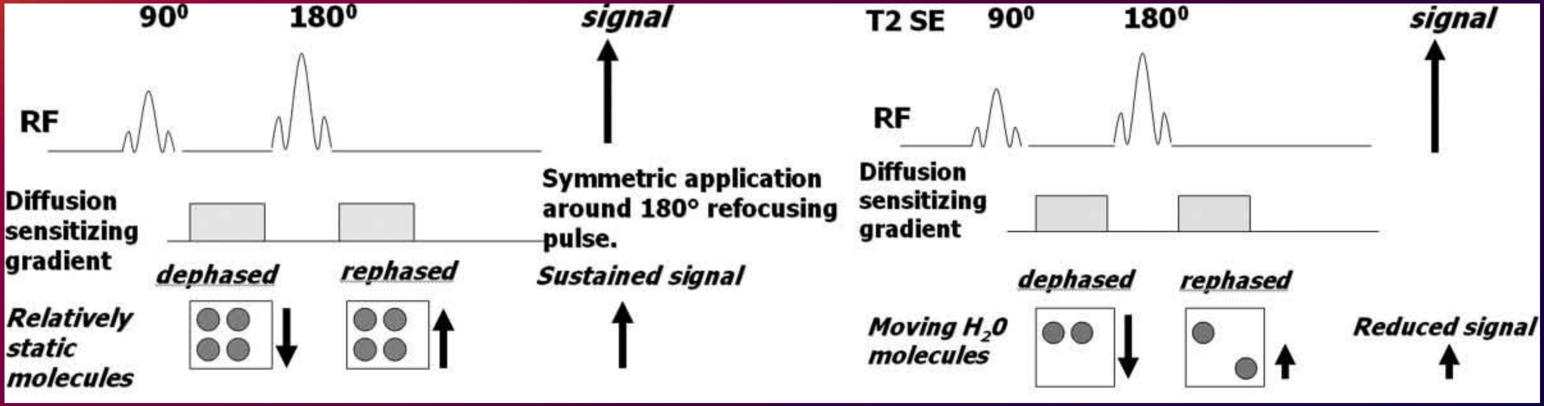
ASSESSMENT OF NODAL PATHOLOGY

MR DIFFUSION-WEIGHTED IMAGING



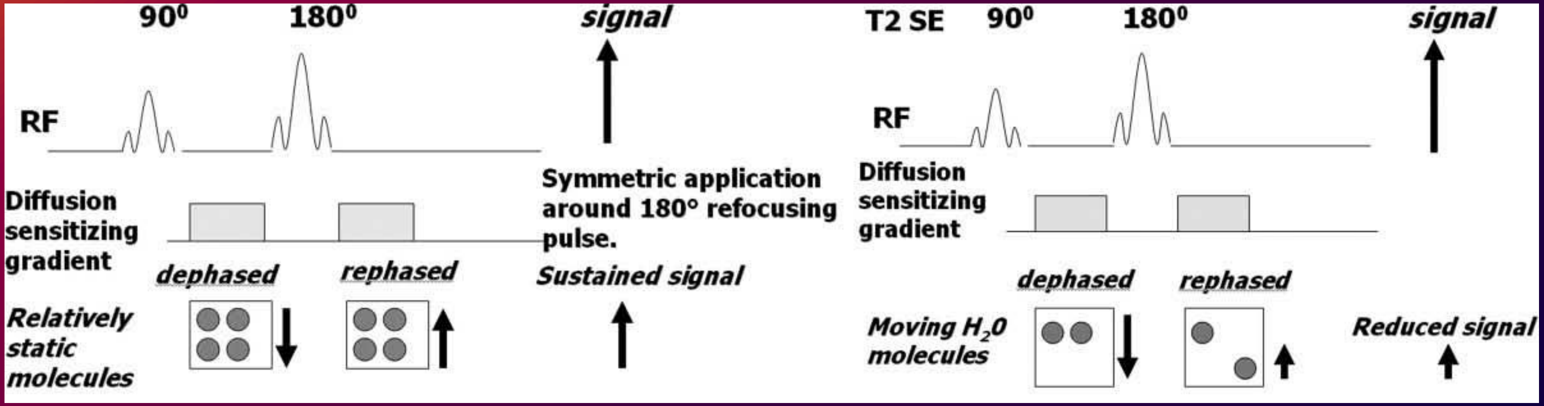
MR DIFFUSION-WEIGHTED IMAGING : T2 Sequence

T2 Sequence : modified by a sensitizer gradient (b value : sec / mm2)

- b=0 : no modification (T2)
- b=500/600 or 1000 : 1200 : Diffusion weighted

ASSESSMENT OF NODAL PATHOLOGY

MR DIFFUSION-WEIGHTED IMAGING



MR DIFFUSION-WEIGHTED IMAGING : T2 Sequence

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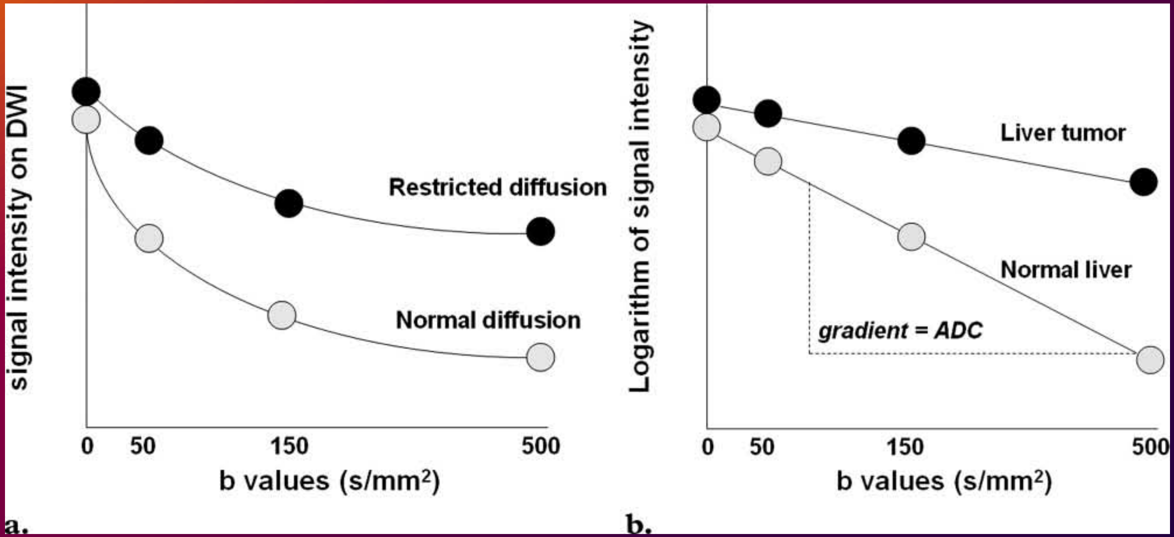
ASSESSMENT OF NODAL PATHOLOGY

MR DIFFUSION-WEIGHTED IMAGING



restricted diffusion (high cellular density):

- **tumor**
- **neuronal tissue (brain, spinal cord)**

pitfalls:

- **normal lymph node**
- **slow blood flow**
- **T2 shine-through**

ASSESSMENT OF NODAL PATHOLOGY

MR DIFFUSION-WEIGHTED IMAGING

Inconviences :

- low S/N Ratio(high cellular density):
  - 3T > 1,5 T (but susceptibility artifacts)
- not possible at low-field (0,2T)
- coarse matrix (128 * 128 on 1,5 T) => contouring ???
- ADC differs from scanner to scanner
- comparaison not yet easy
- temperature

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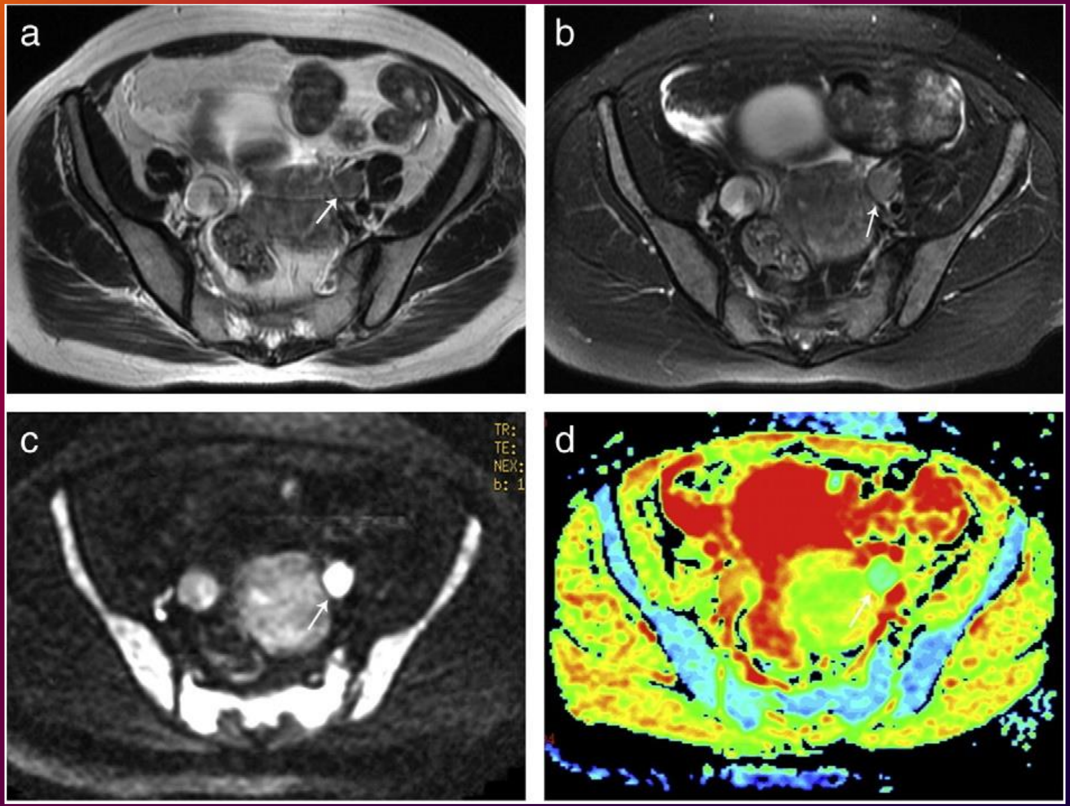
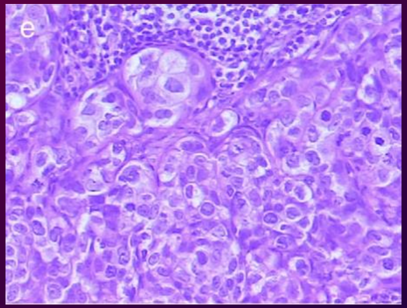
ASSESSMENT OF NODAL PATHOLOGY

T2 T2 +FATSAT



DW-T2 ADC- DW

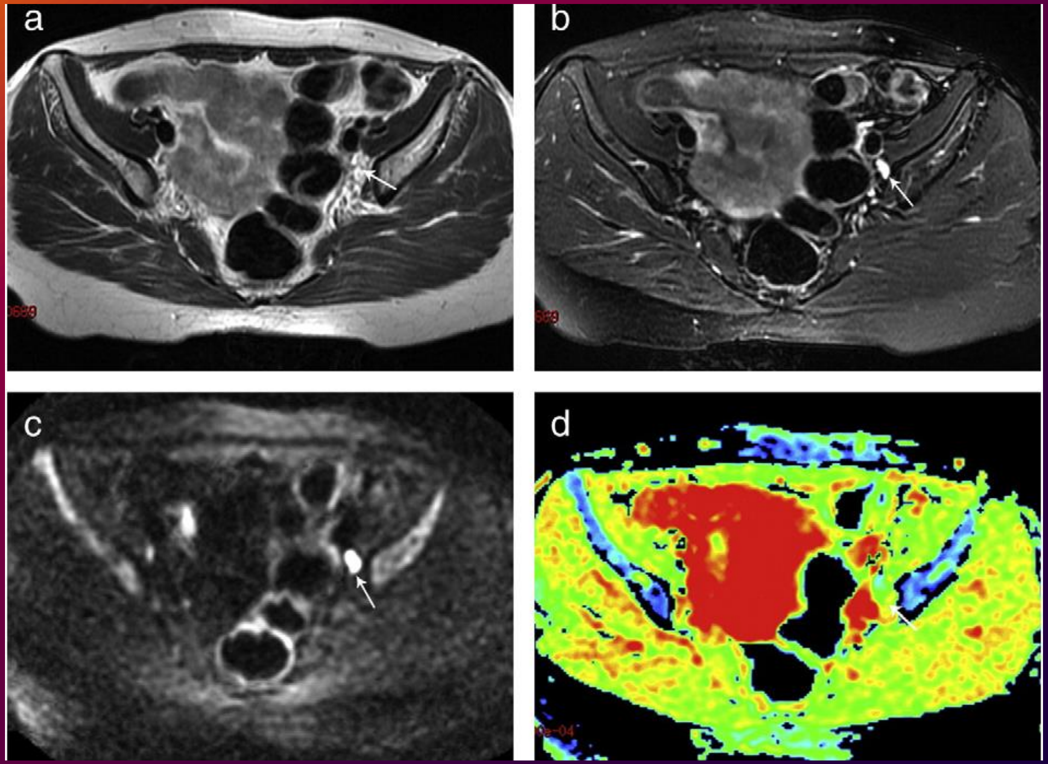


metastatic LN

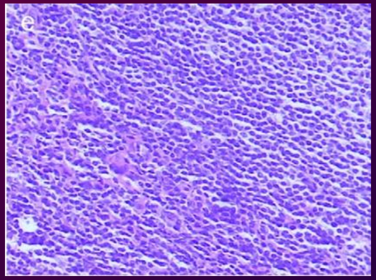
Liu Y. et al.,Gynecologic Oncology 122 (2011) 19–24

ASSESSMENT OF NODAL PATHOLOGY

T2 T2 +FATSAT



DW-T2 ADC- DW



Normal LN

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

ASSESSMENT OF NODAL PATHOLOGY

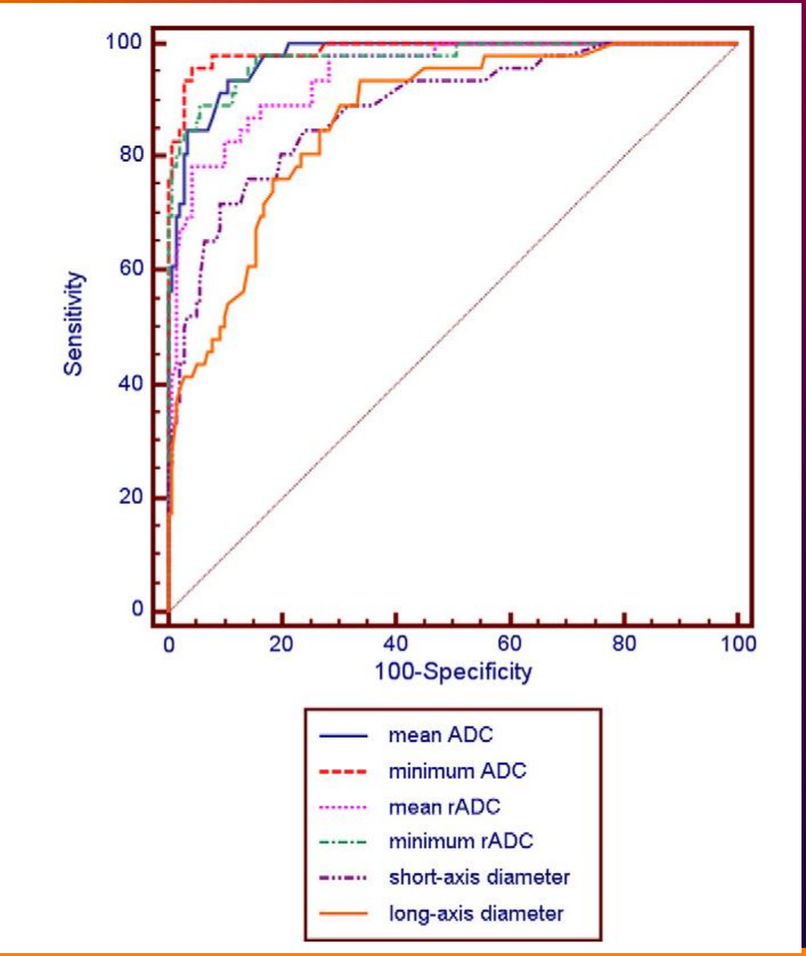
Table 3
Comparision of the diagnostic performance of the size-based criteria and ADC-based criteria.

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

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

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

ASSESSMENT OF NODAL PATHOLOGY



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

CONCLUSION – NODAL ASSESSMENT

- CT/MR/US : Can depict large, evident LN Involvement
- PET-CT : Whole body depiction of LN Metastasis

- DW imaging for minimal ADC mapping
- (discordance PET-CT/MRI)

- Surgical LN Sampling

- Image-guided (CT) LN Sampling

Conclusion

QUESTIONS ?

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Radiologic Pathology of gynaecologic tumors incl. nodes
At time of Brachytherapy

Primoz Petric, MD, Msc
Senior Consultant

Department of Radiation Oncology
NCCCR, HMC
Doha, Qatar

Adapted and Presented by

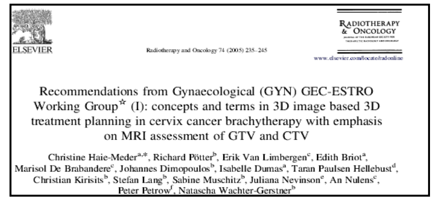
Peter PETROW, Institut Curie

Prague, Czech Republic October 2017

Gold standard I : T2W MRI

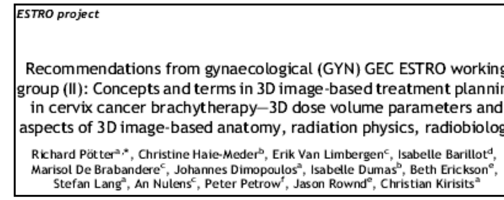
Magnetic Resonance Imaging

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


Radiotherapy and Oncology 74 (2005) 235–245

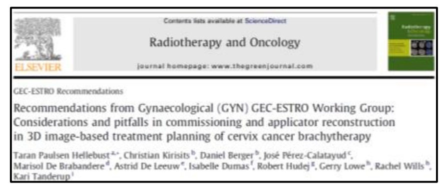
Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group☆ (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV

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


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, Christine Haie-Meder, Erik Van Limbergen, Isabelle Barillot, Marisol De Brabandere, Johannes Dimopoulos, Isabelle Dumas, Beth Erickson, Stefan Lang, An Nulens, Peter Petrow, Jason Rownd, Christian Kirisits


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

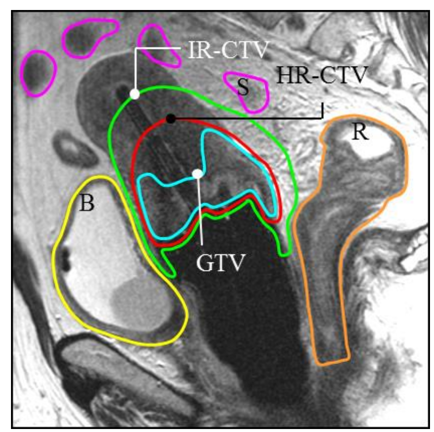
Taran Paulsen Hellebust, Christian Kirisits, Daniel Berger, José Pérez-Calatayud, Marisol De Brabandere, Astrid De Leeuw, Isabelle Dumas, Robert Hudej, Gerry Lowe, Rachel Wills, Kari Tanderup

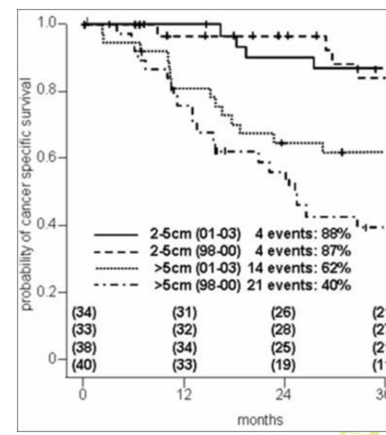

Radiotherapy and Oncology

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

Johannes C.A. Dimopoulos, Peter Petrow, Kari Tanderup, Primoz Petric, Daniel Berger, Christian Kirisits, Erik M. Pedersen, Erik van Limbergen, Christine Haie-Meder, Richard Pötter





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

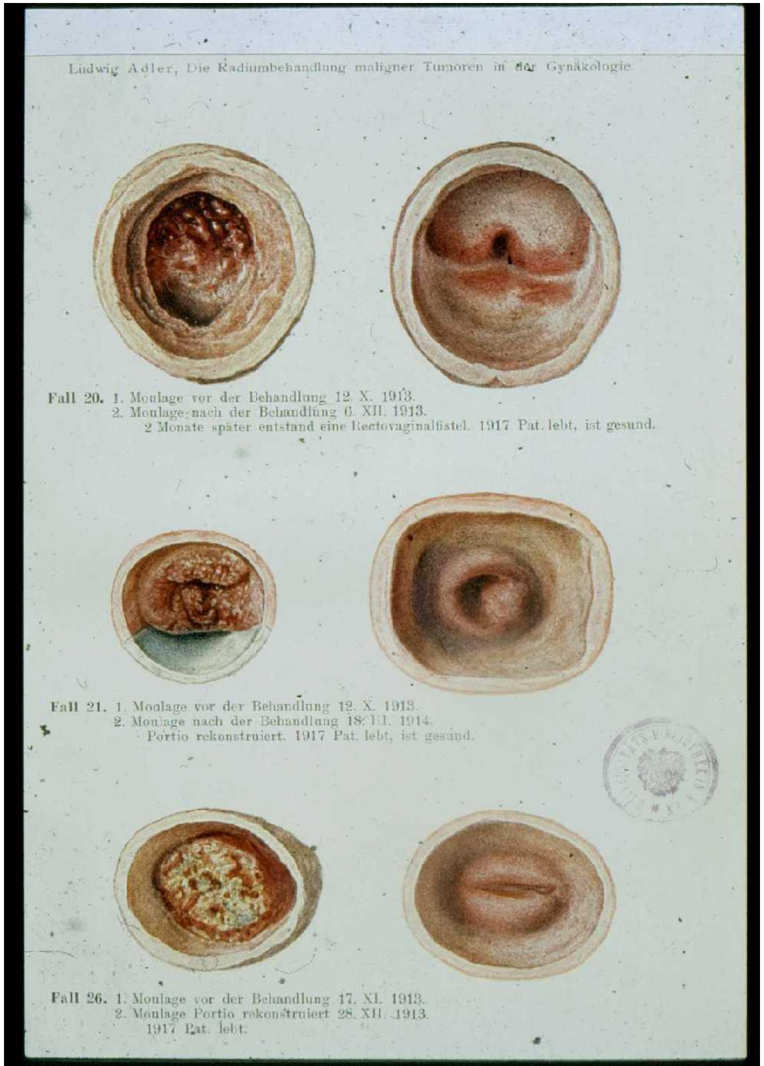
Pötter. Radiother Oncol 2011
Pötter. Radiother Oncol 2007
Lindegaard J. Radiother Oncol 2008
De Brabandere M. Radiother Oncol 2008
Jurgenliemk Shulz IM. Radiother Oncol 2009
Cahrgari N. IJROBP 2009

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

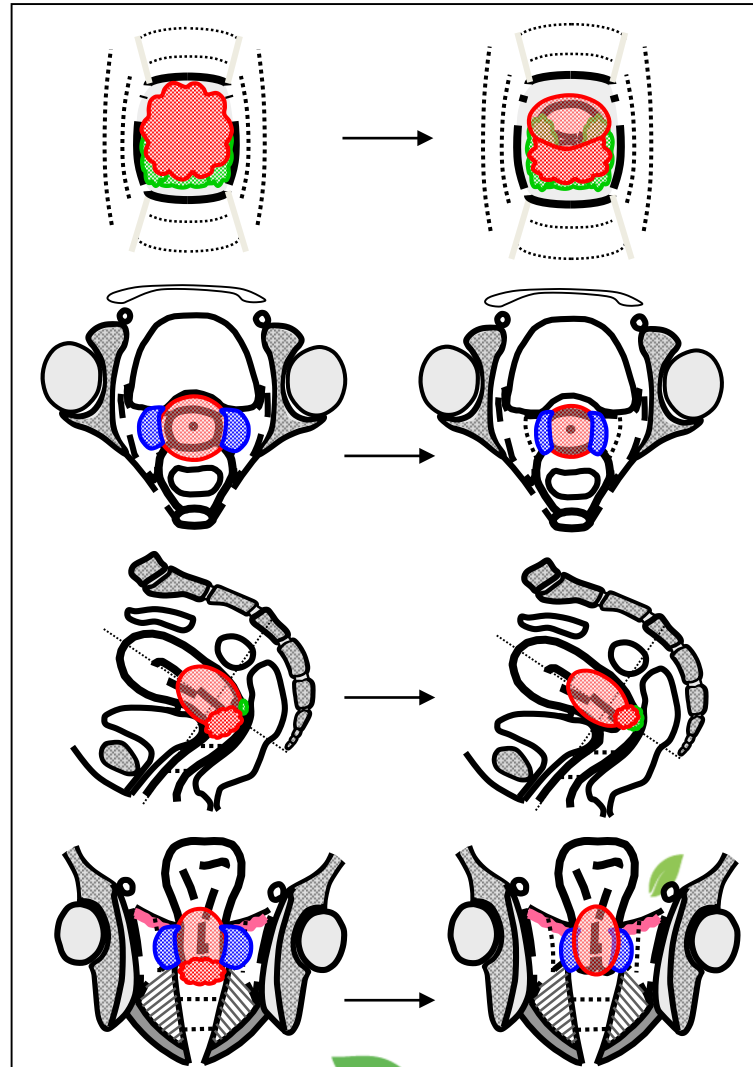
Mitchell. J Clin Oncol 2006
Oszarlak O. Radiol 2003
Hricak H. Radiology 2007
Yu KK. Radiology 1997
Sala E. Radiology 2006
Yu KK. Radiology 1999

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

Adler: Strahlentherapie, 1918

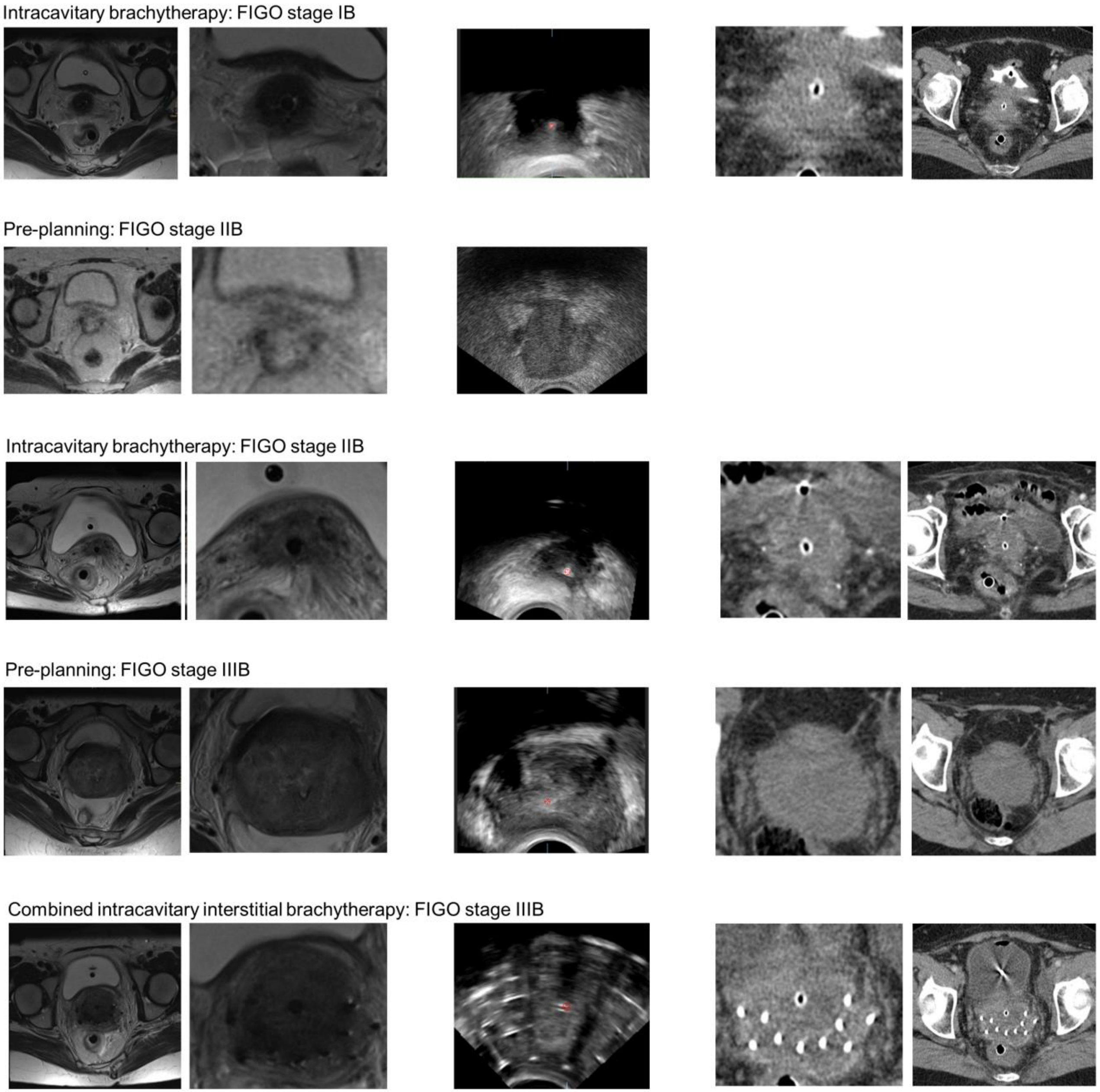


EMBRACE study protocol, 2011



Courtesy: R. Pötter, MUW

Imaging at BT



M. Schmid, Vienna, ongoing clinical study

MRI (gold)

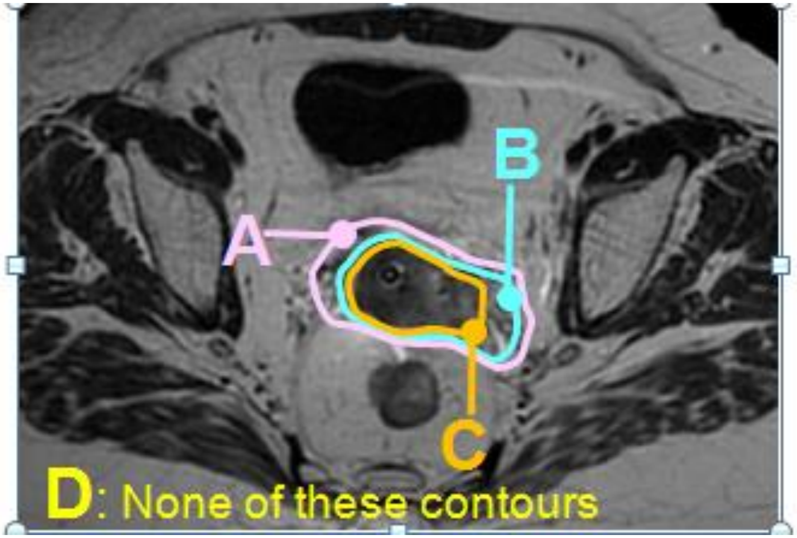
US (silver+)

CT (bronze)

Clinical drawing (gold)

Interpretation of imaging findings at BT

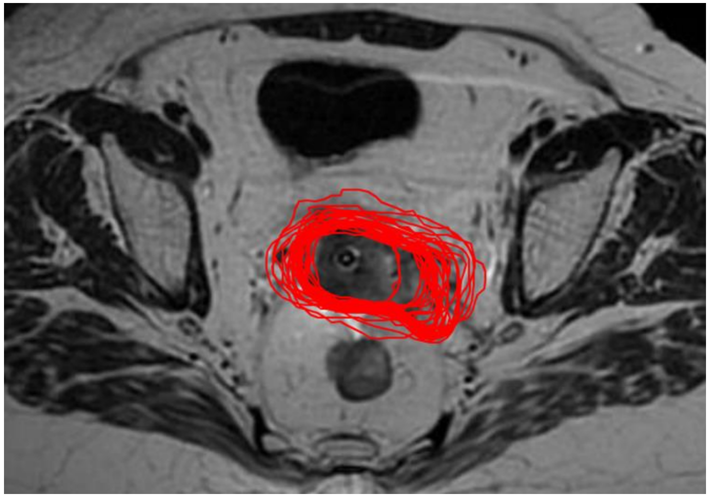
What is the High Risk CTV on this slice? (your best guess)



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

Interpretation of imaging findings at BT

Contouring uncertainties: weakest link in Image guided BT?



Harmonization of practice!

Contouring guidelines

Contouring training

High quality imaging

Systematic assessment

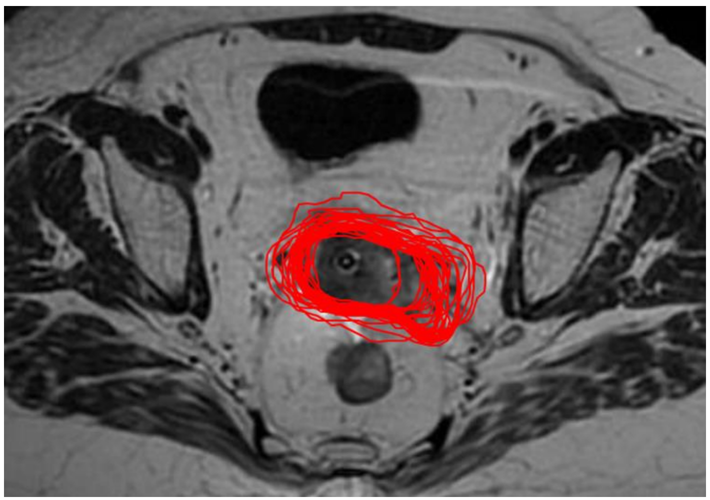
Selection & delineation

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?



Harmonization of practice!

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Njeh CF, et al. Med Phys 2008
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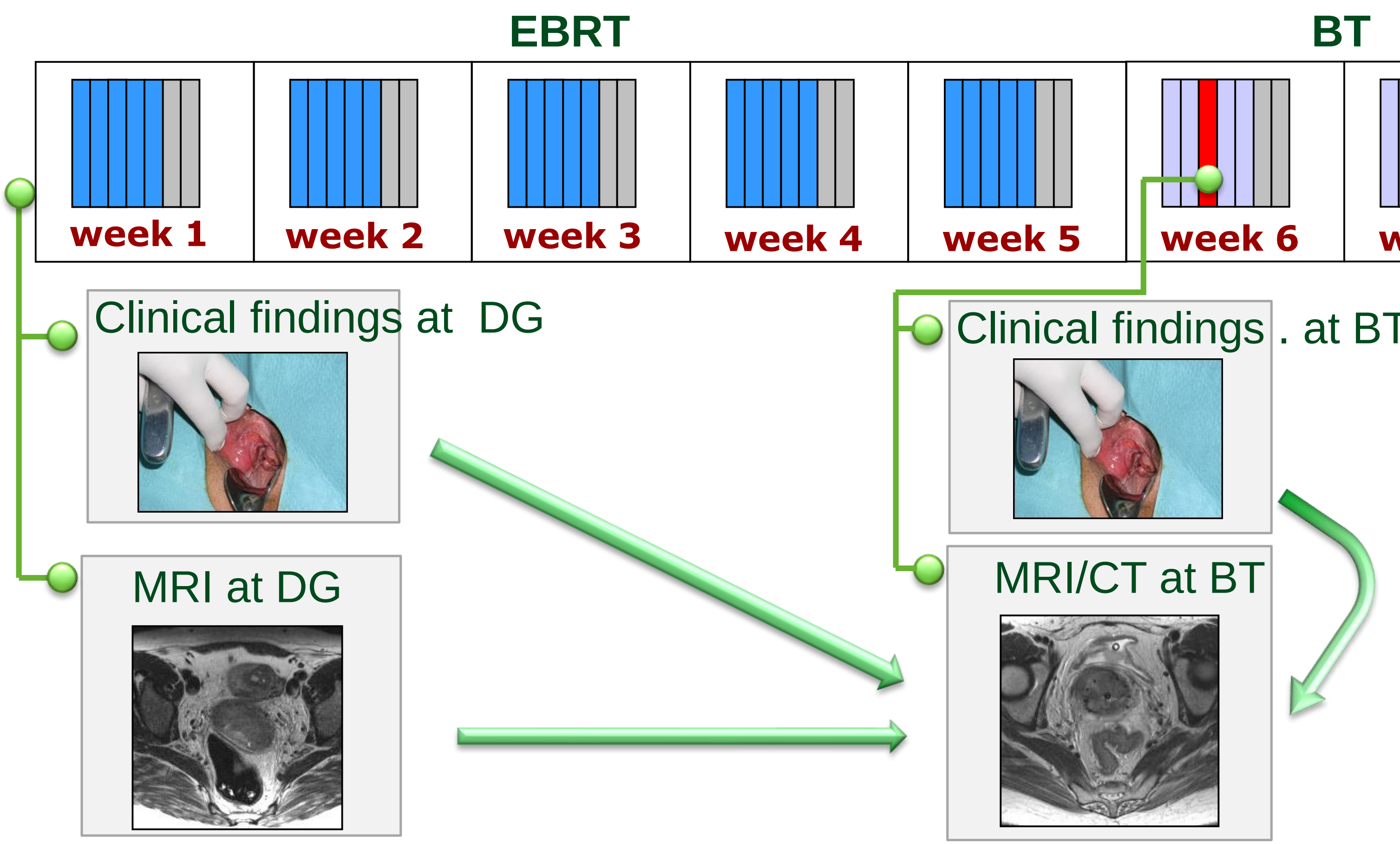
Assessment of sectional imaging at time of BT

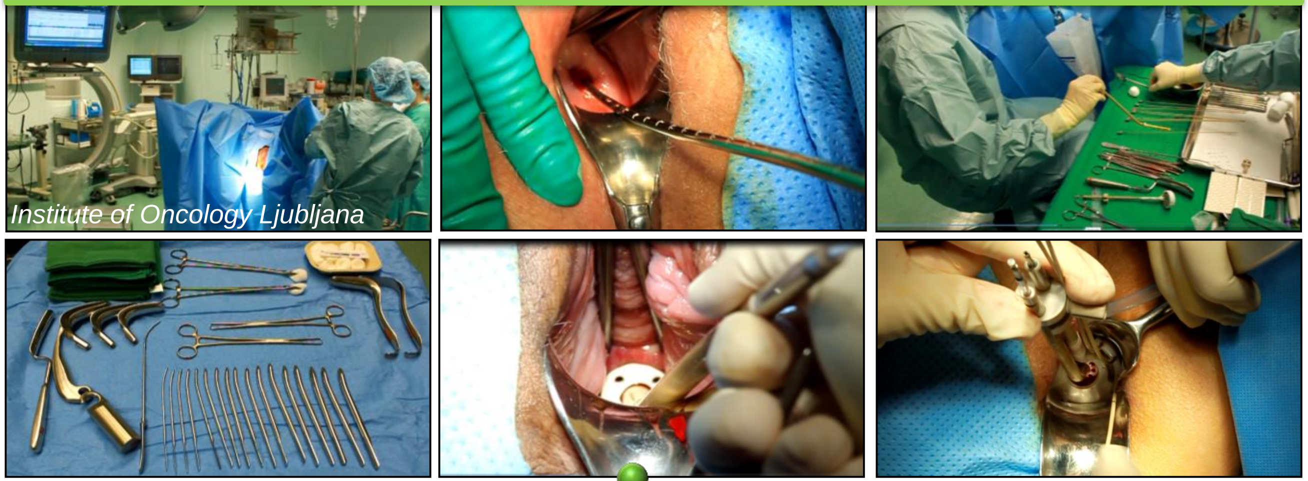
General principles



MRI and/or CT/US with clinical drawings

STEPS of Assessment of MRI/CT at BT

THEATRE



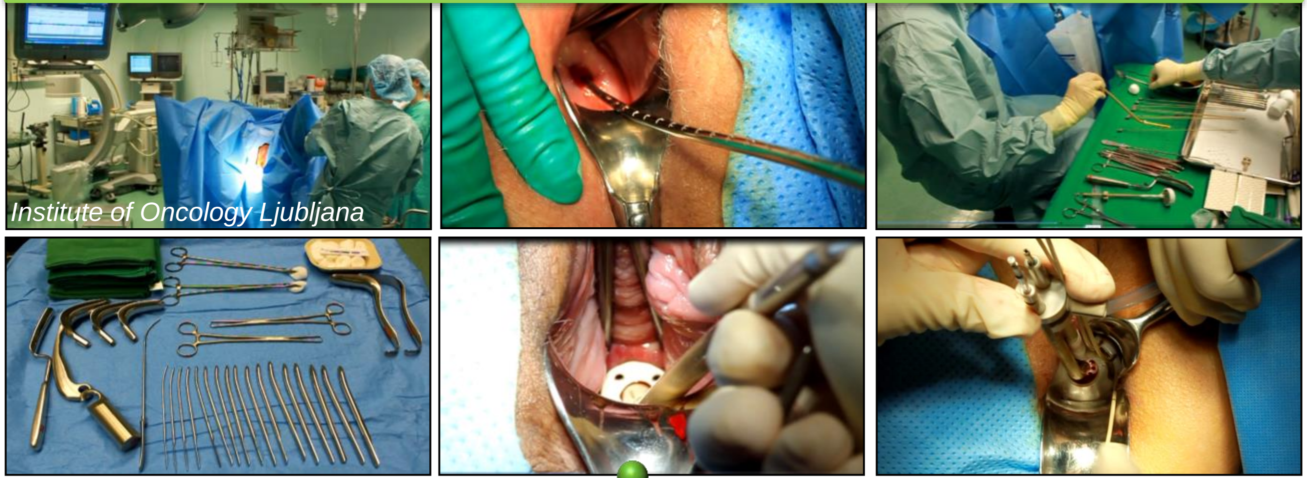
MRI and/or CT/US with clinical drawings

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

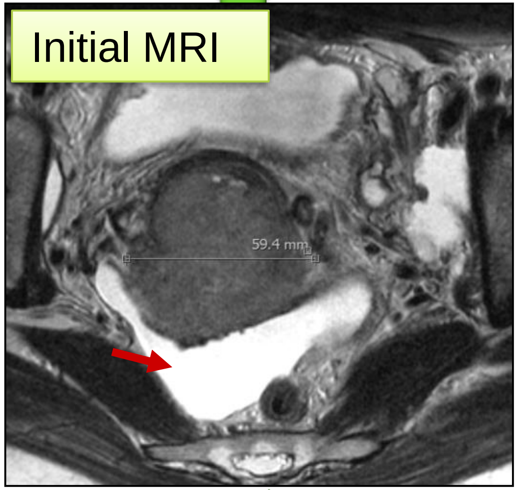
1. Rule out ***FLOP***

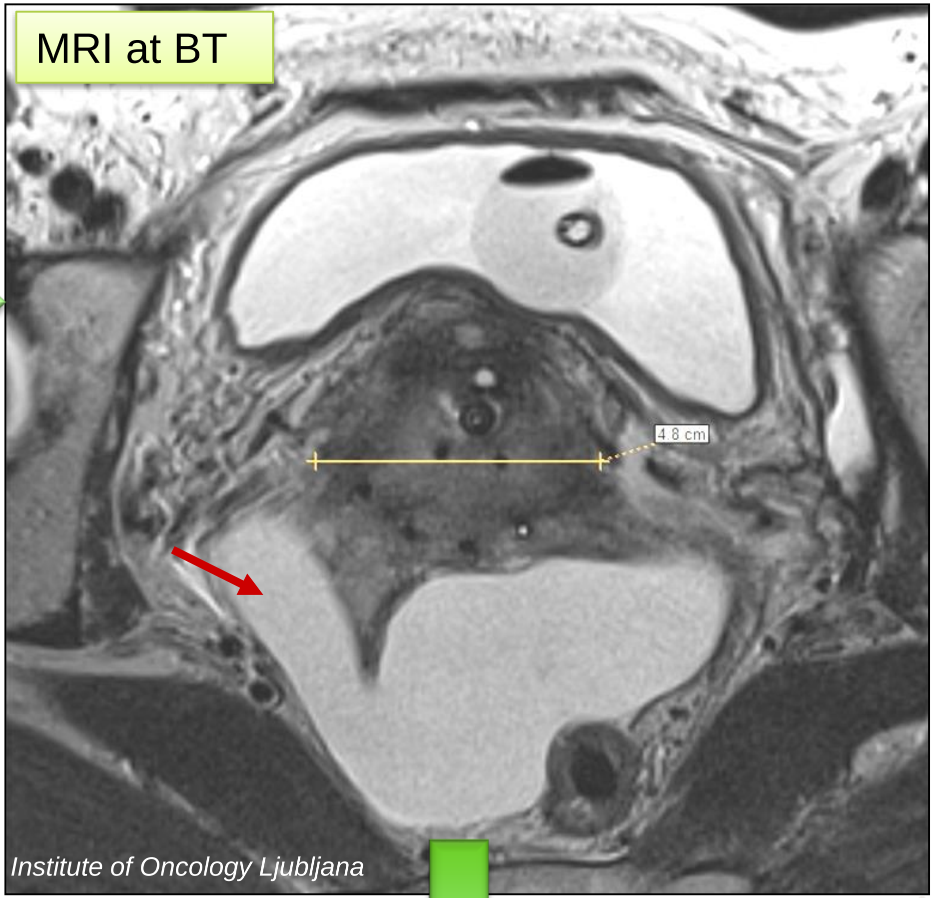
2. Set the ***STAGE*** for contouring

1. Rule out **FLOP**

FL **FL**uid in abdomen?

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



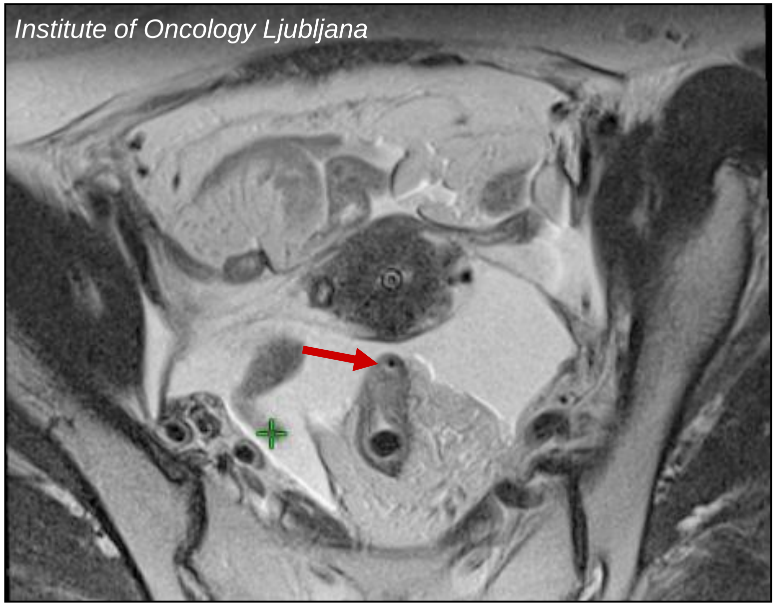


Compare with initial findings!

1. Rule out **FLOP**

FL **FL**uid in abdomen?

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



Action? ⇨ Have institutional policies and protocols ready!

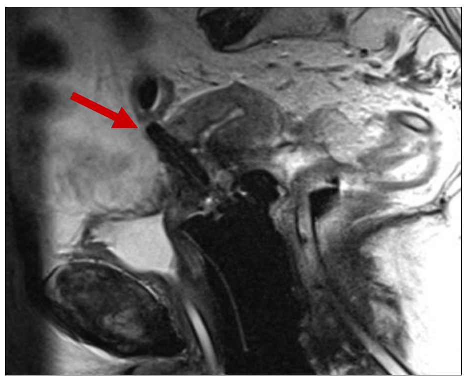
1. Rule out **FLOP**

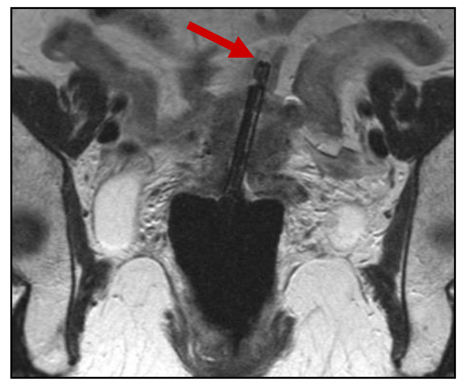
FL **FL**uid in abdomen?

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

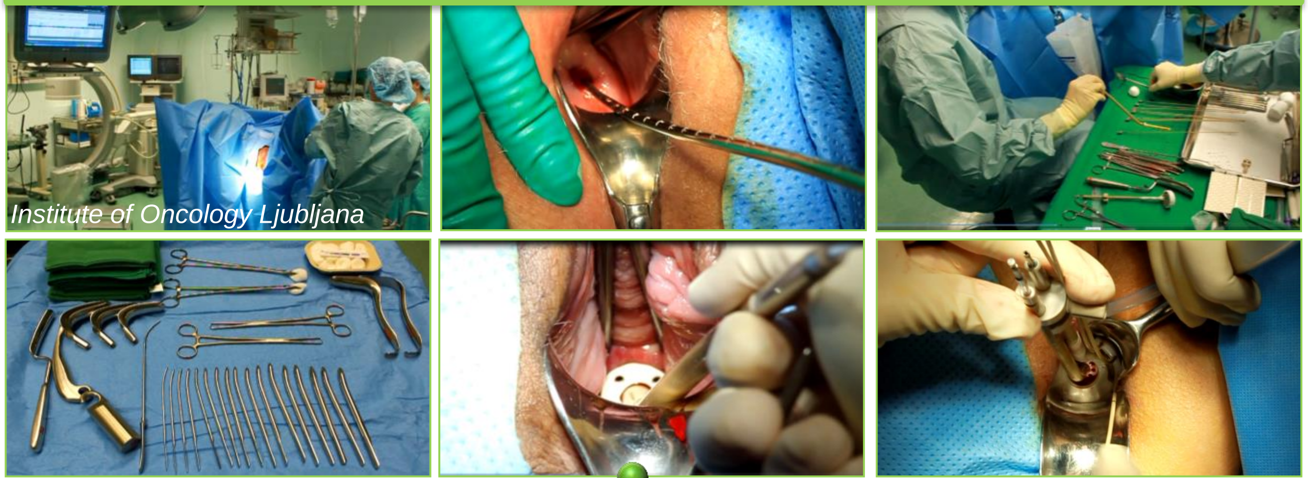
Jhingran A, Eifel PJ. IJROBP 2000
Barnes EA, et al. Int J Gynecol Cancer 2007
Lanciano R, et al. IJROBP 1994

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?
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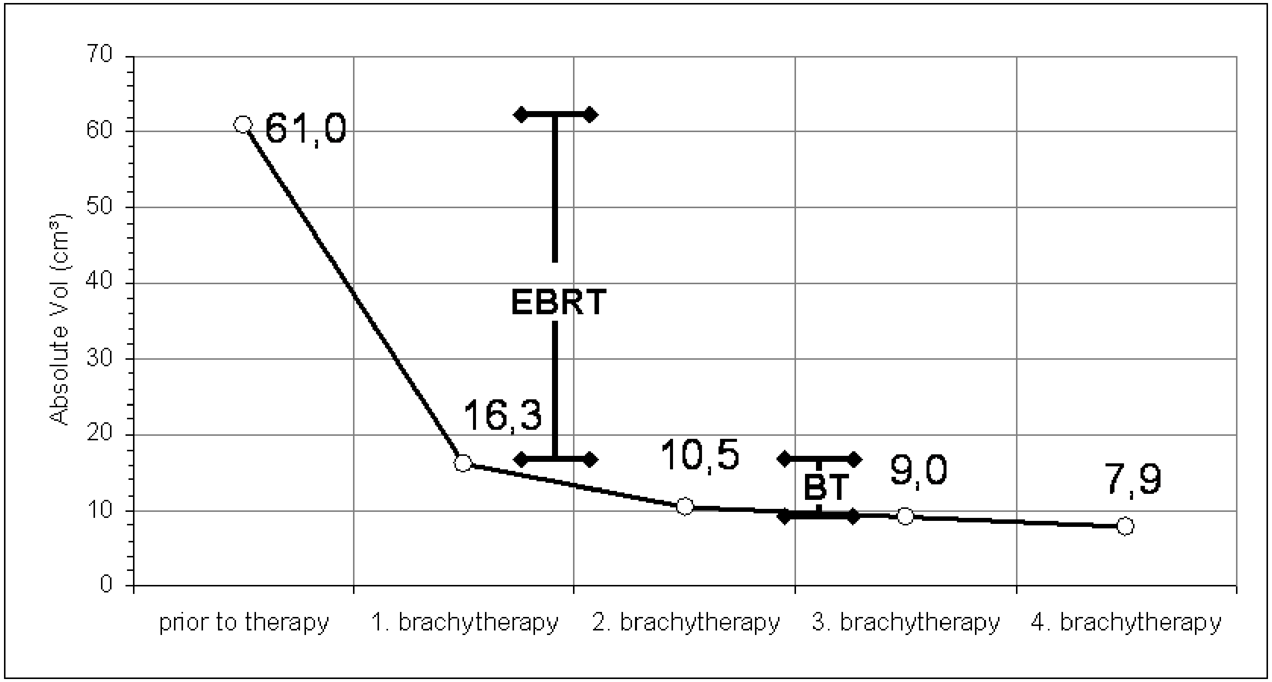
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

Size of the tumor at Brachytherapy

Volume change during treatment



Dimopoulos J, et al.Strahlenther Onkol 2009

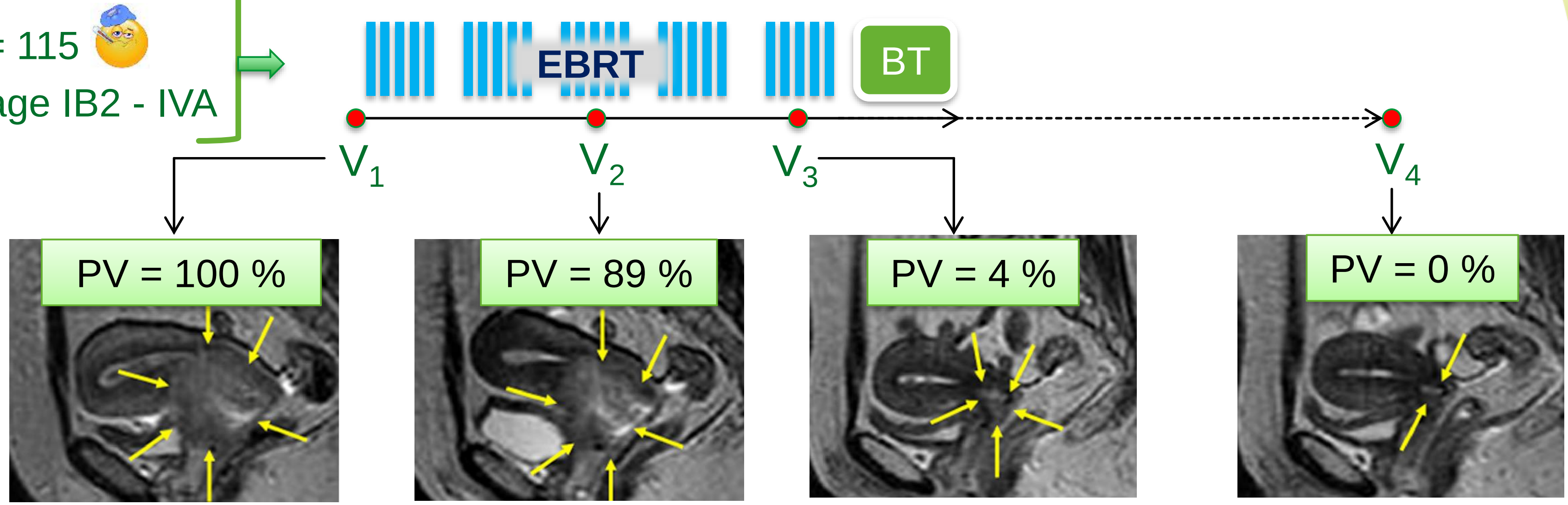
EBRT: tumor regression ≈ 75%
Brachytherapy: tumor regression ≈ 10%

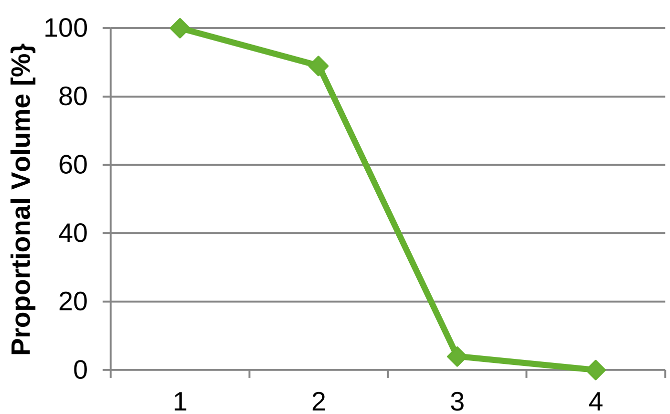
Size of the tumor at Brachytherapy

Volume change during treatment

N= 115

stage IB2 - IVA





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

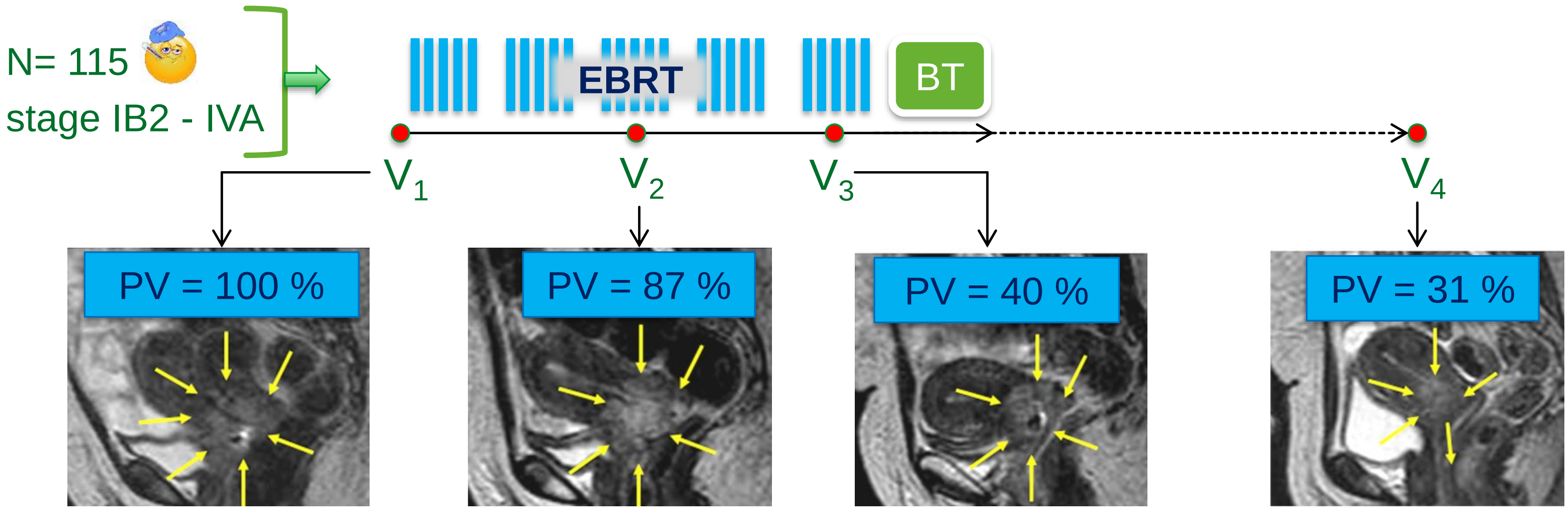
Alive & well at 7 y

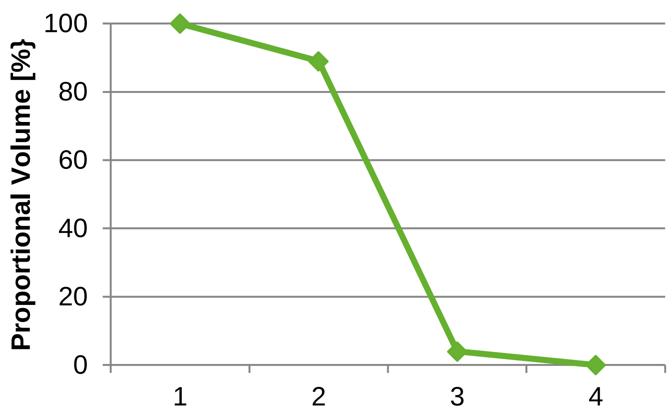
Mayr NA, et al. Int J Radiat Oncol Biol Phys 2010
Wang JZ, et al. Cancer 2010

Size of the tumor at Brachytherapy

Volume change during treatment

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





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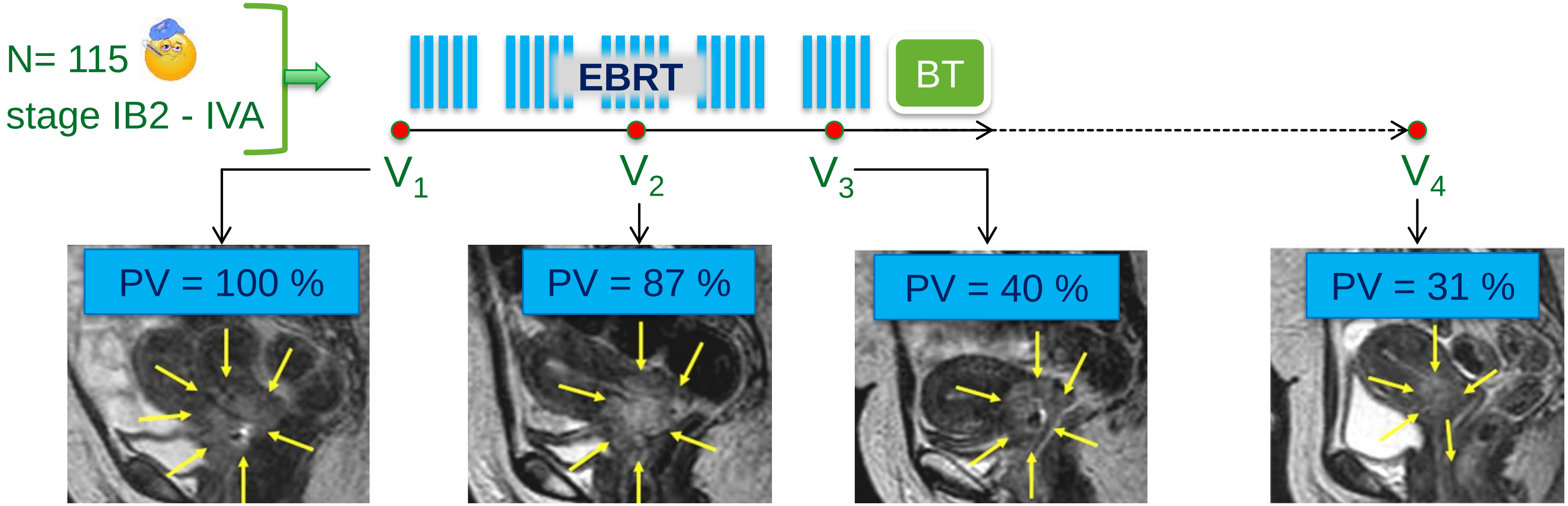
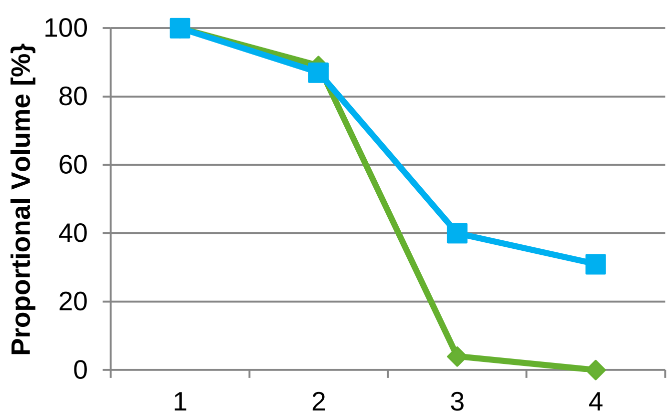
Regression to **P**roportional **V**olume: **PV = V_x / V_1 [%]**





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

Alive & well at 7 y

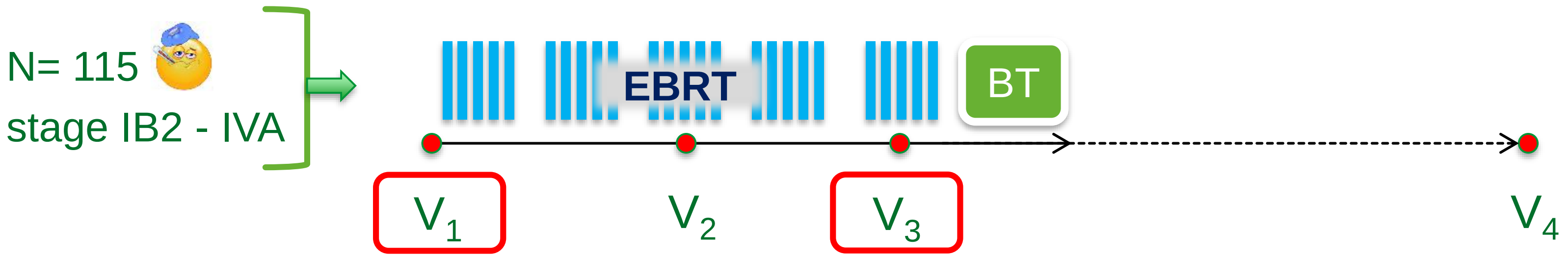
- Slow response: 0.8% / Gy
- Low slope
- High AUC (50 %)

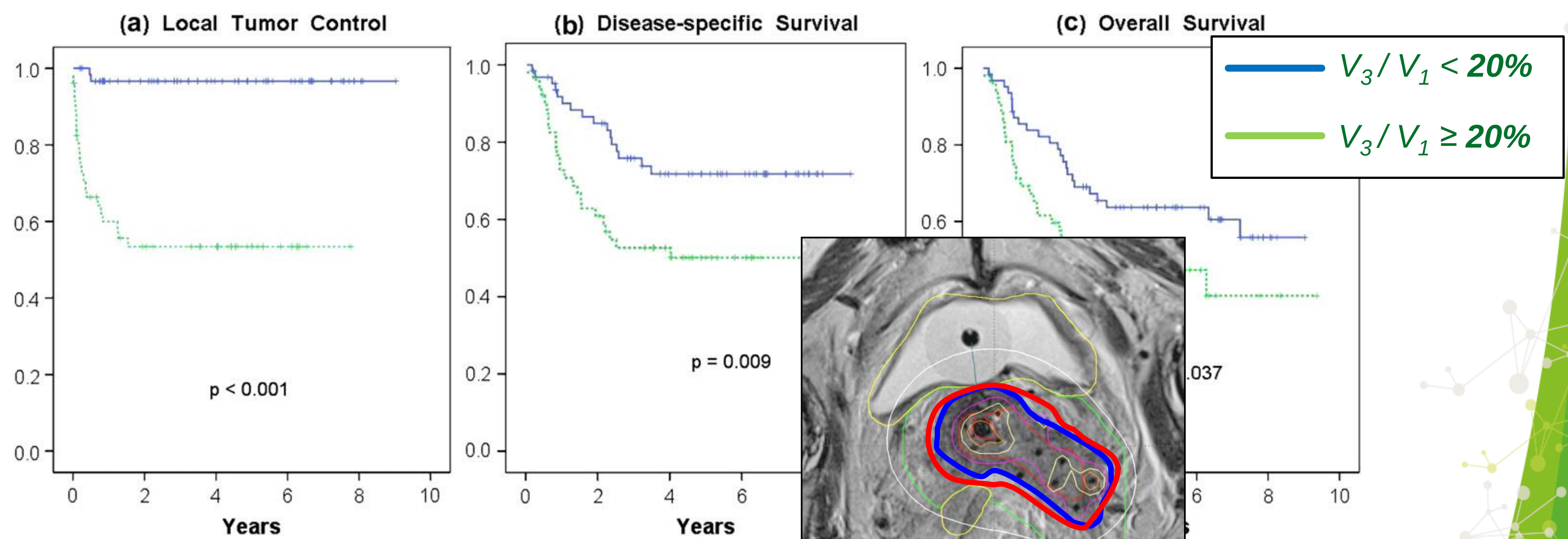
LR at 1 y
Death at 2 y

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





Mayr NA, et al. Int J Radiat Oncol Biol Pl

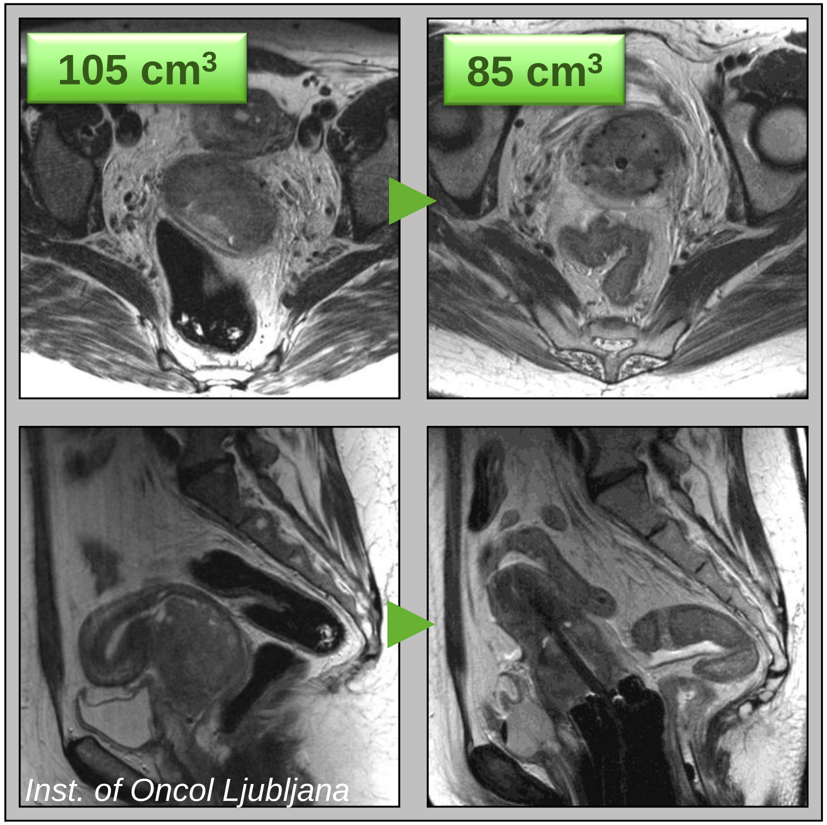
Wang JZ, et al. Cancer 2010

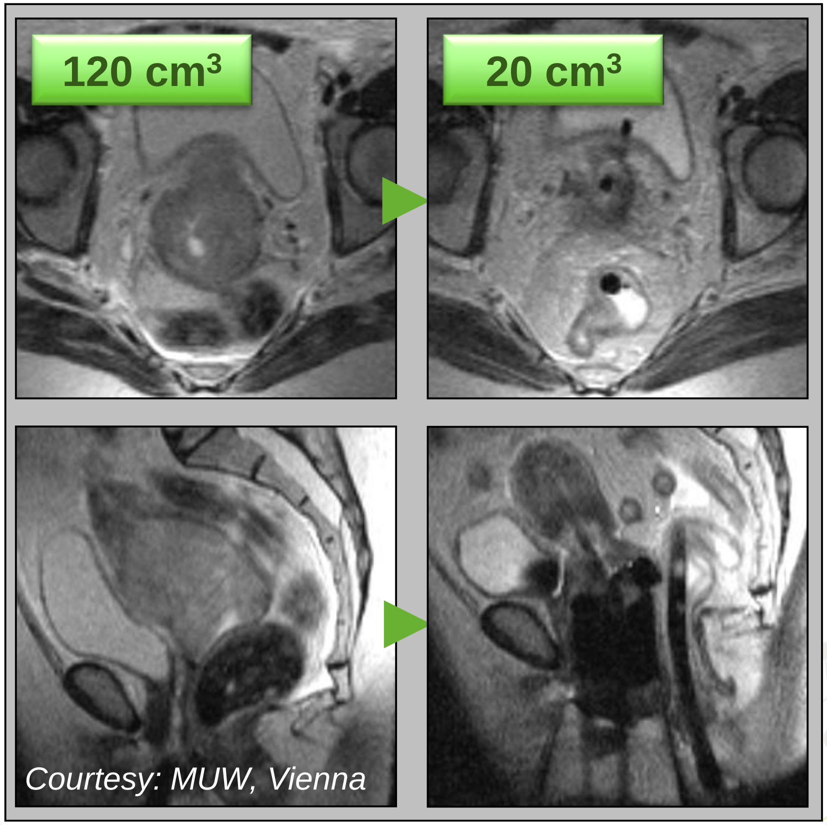
Rad. Onc. Perspective in context of image guided BT!

Size of the tumor at Brachytherapy

Qualitative vs. quantitative

Bad response	Good response





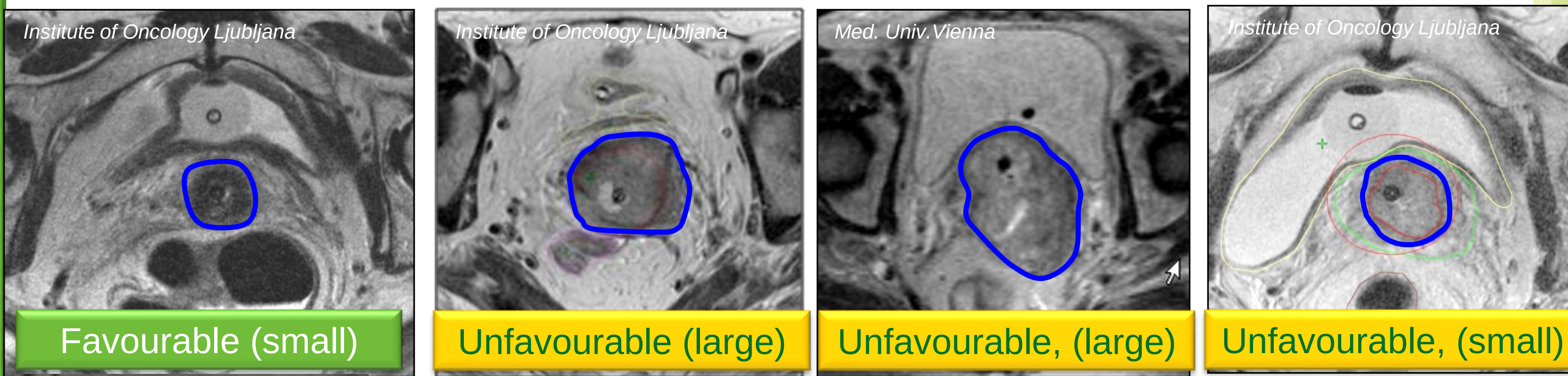
81 %	17 %

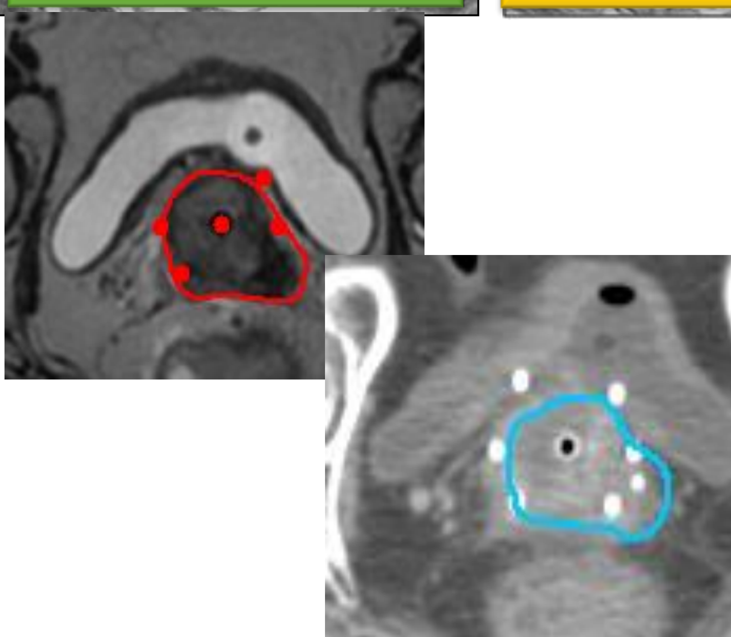
Set the **STAGE** before contouring

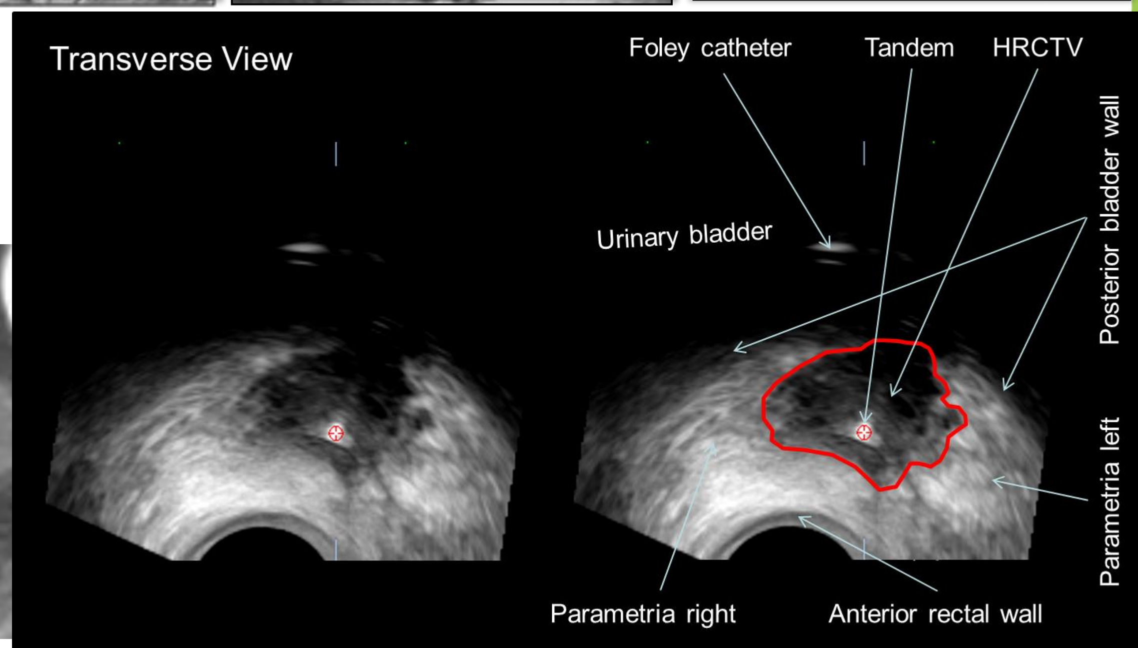
- **S**ize of the residual tumor?
- **T**opography of the target V?
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

Topography of the tumour

Tumour and Target shape and extent







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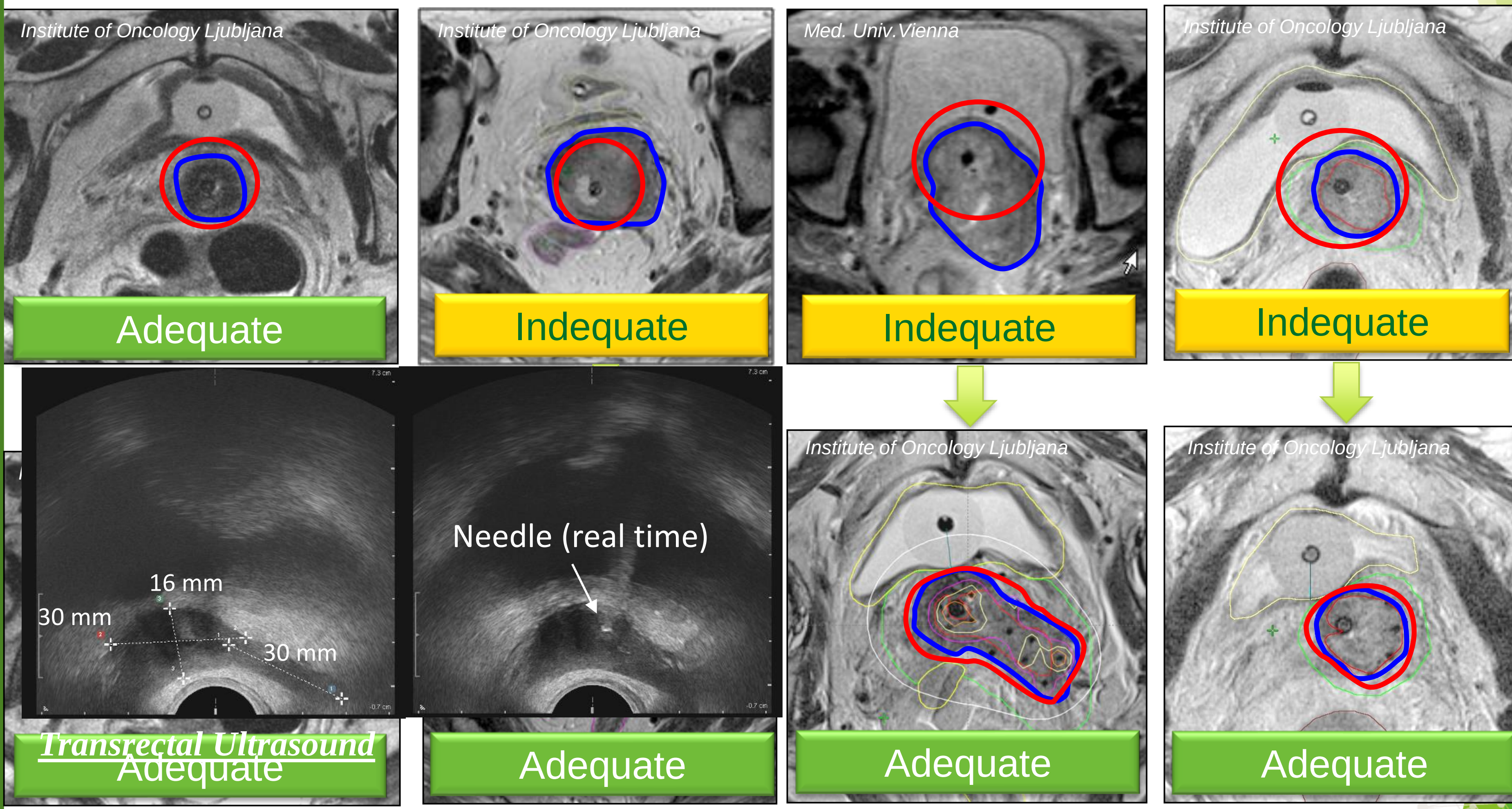
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

Adequacy of the implant

Relation: Applicator(s) - Target V - Organs



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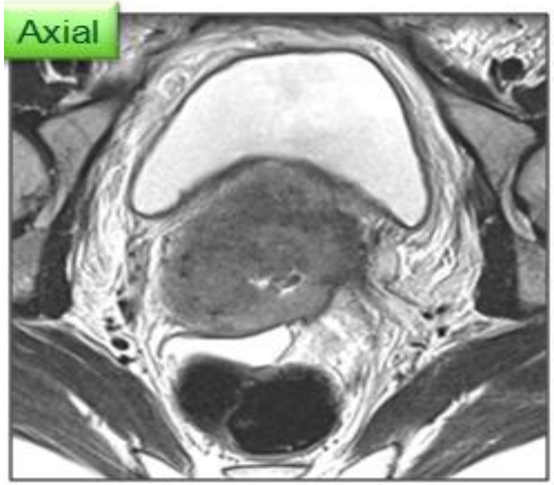
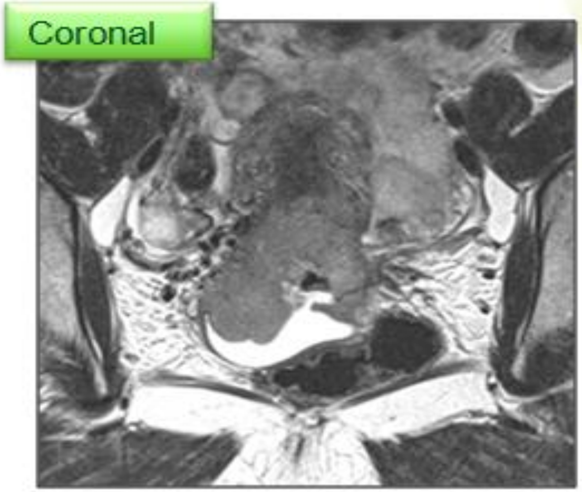
Grey zones

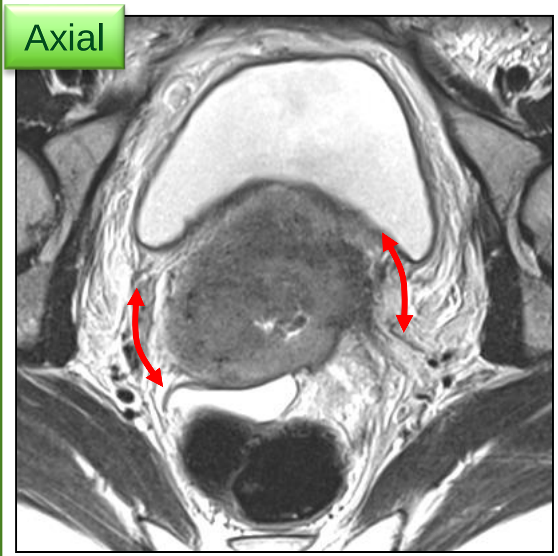
Grey zones at BT correlate with *Initial spread*

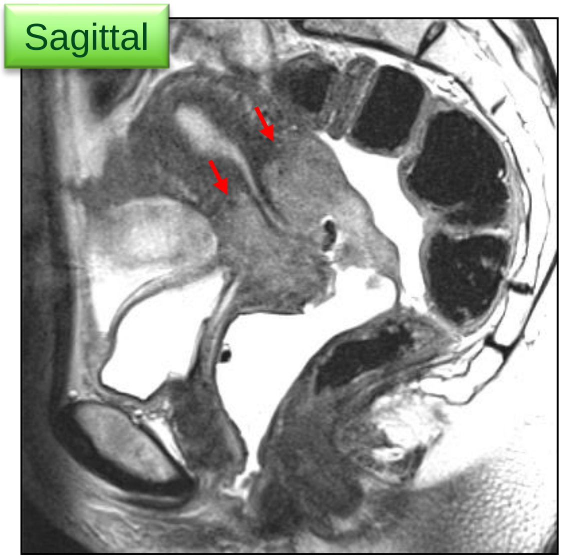


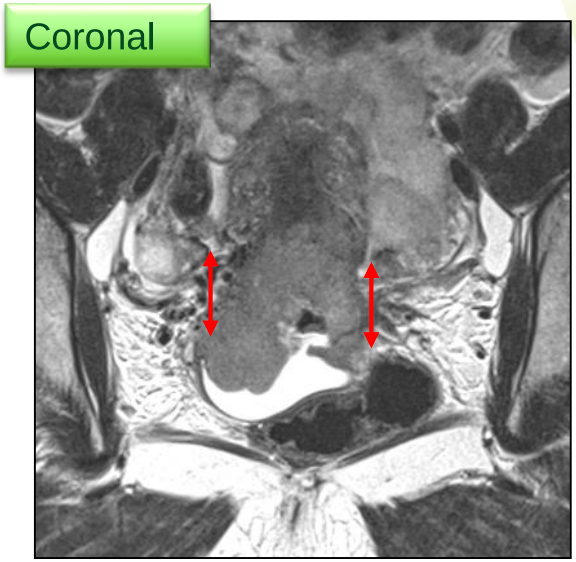


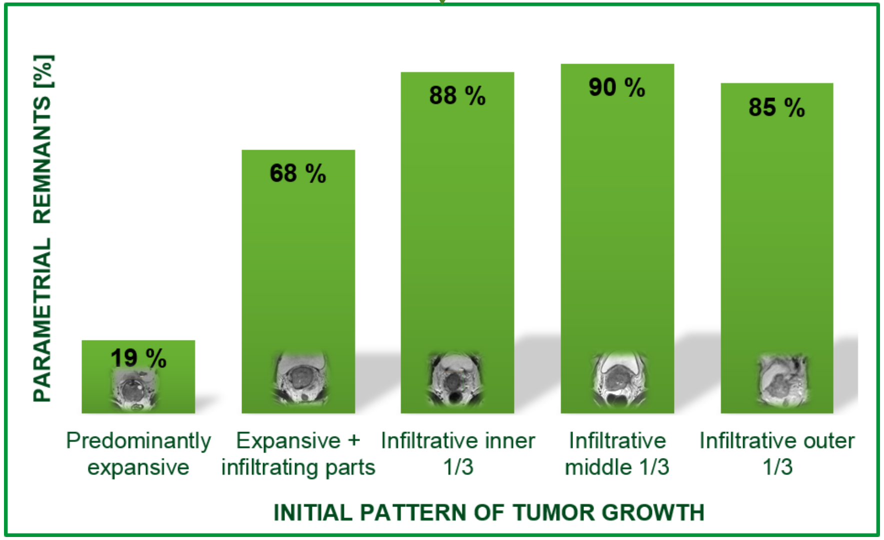
Grey zones

Grey zones at BT correlate with *Initial spread*





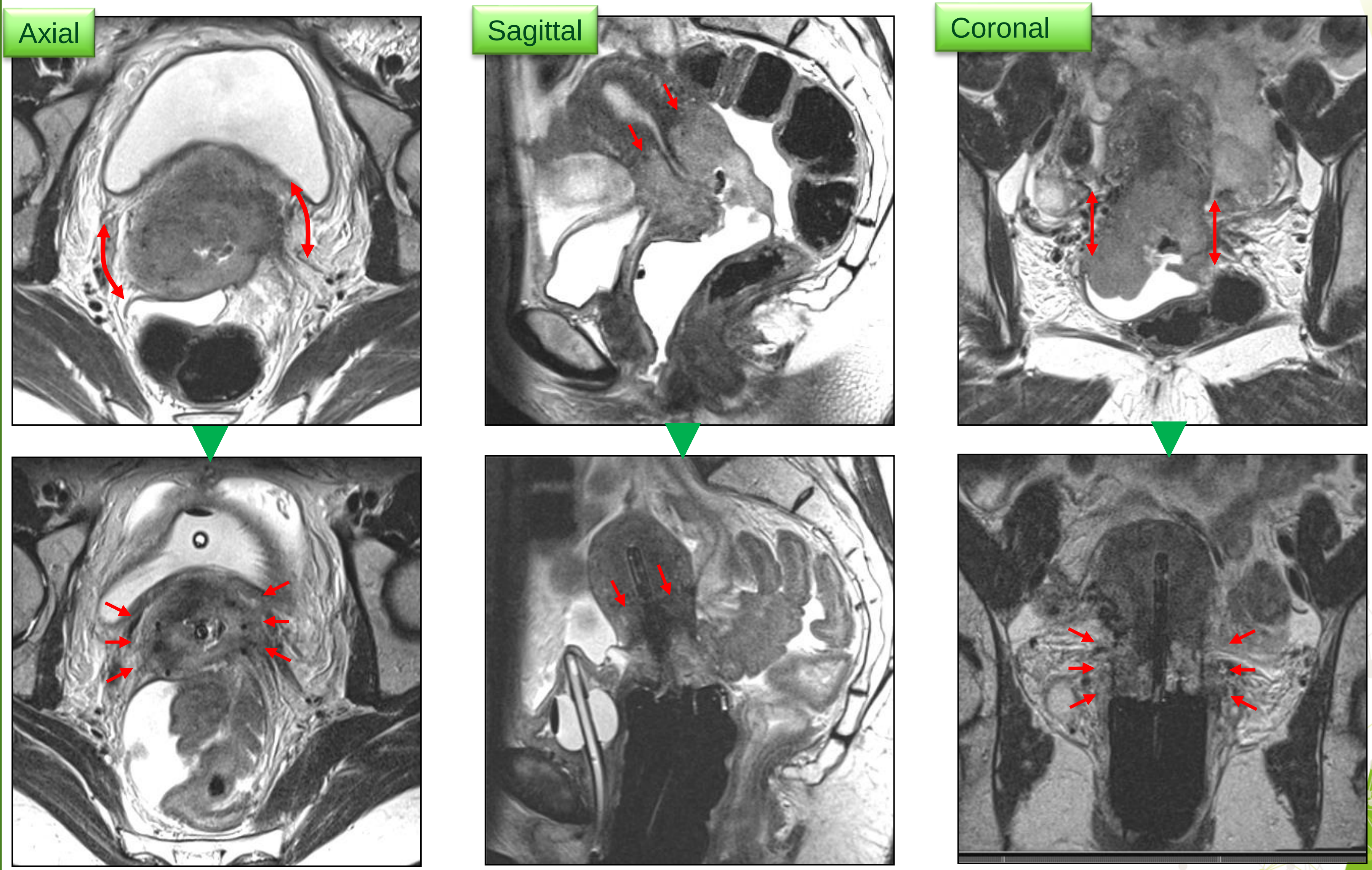




Schmid MP, et al. Acta Oncol 2013
Yoshida K, et al. IJROBP 2016

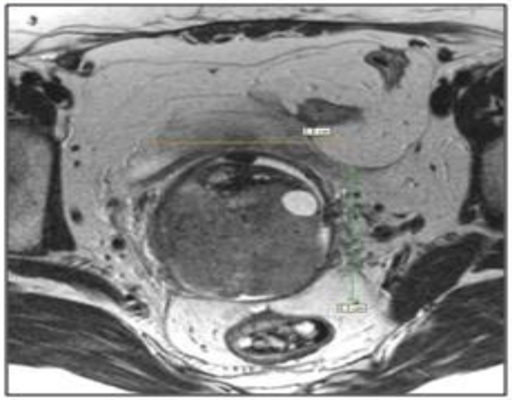
Grey zones

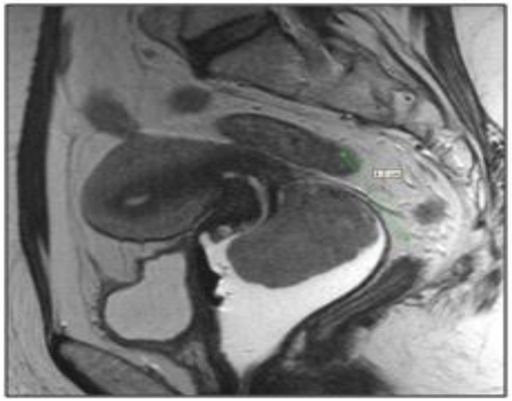
Grey zones at BT correlate with *Initial spread*

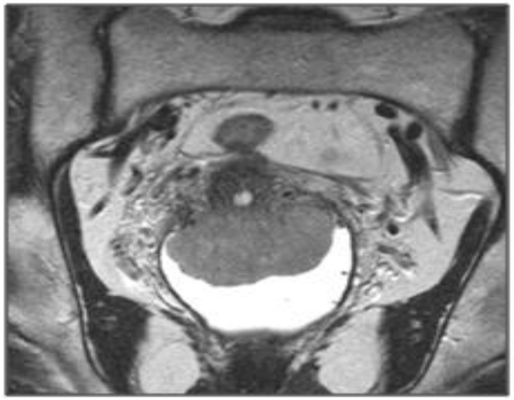


Grey zones

Grey zones at BT correlate with *Initial spread*



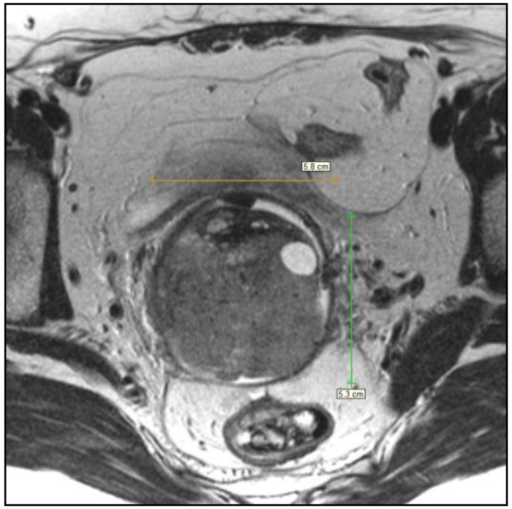


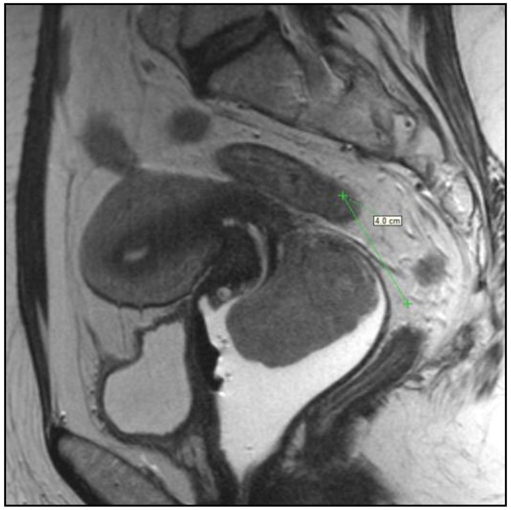


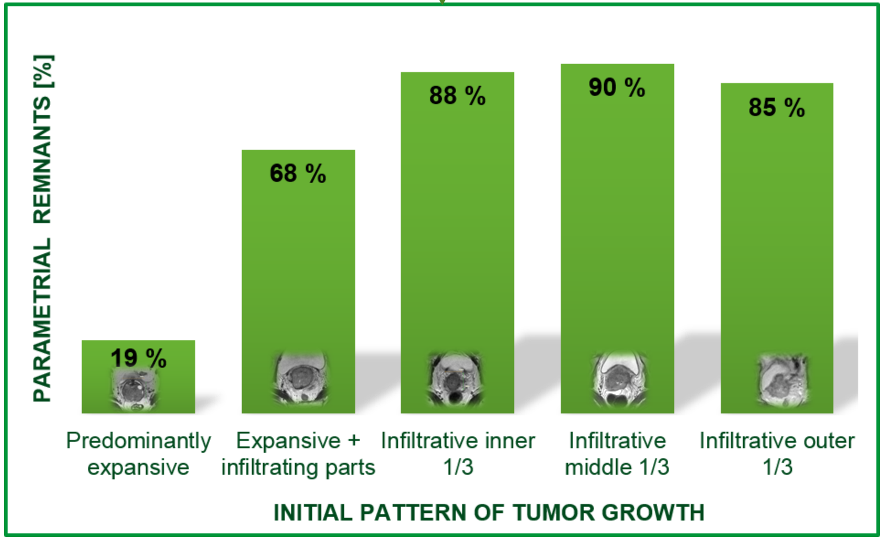
Estimate probability for residual pathological tissues in parametria after EBRT for this patient:

Grey zones

Grey zones at BT correlate with *Initial spread*



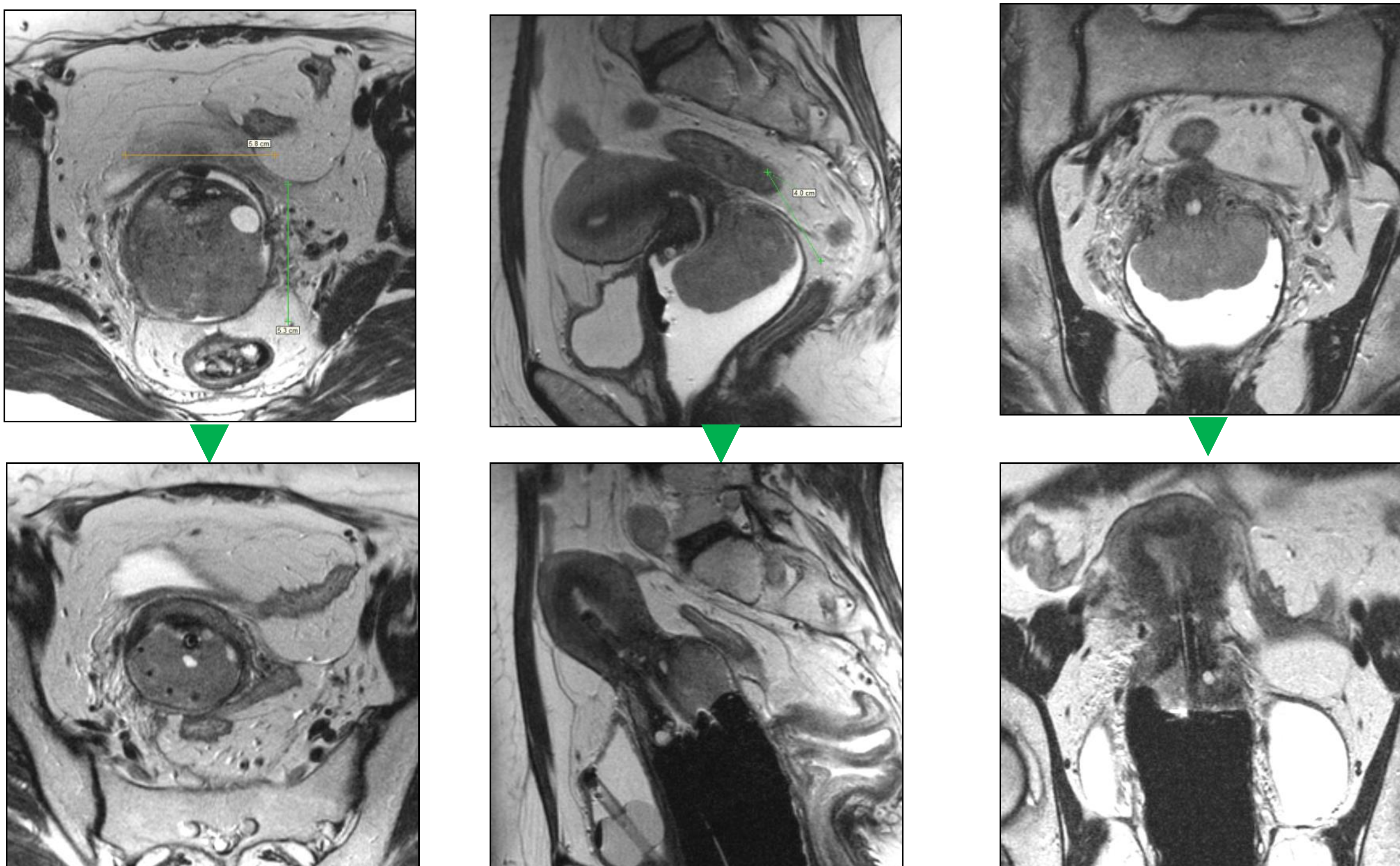




Schmid MP, et al. Acta Oncol 2013
Yoshida K, et al. IJROBP 2016

Grey zones

Grey zones at BT correlate with *Initial spread*



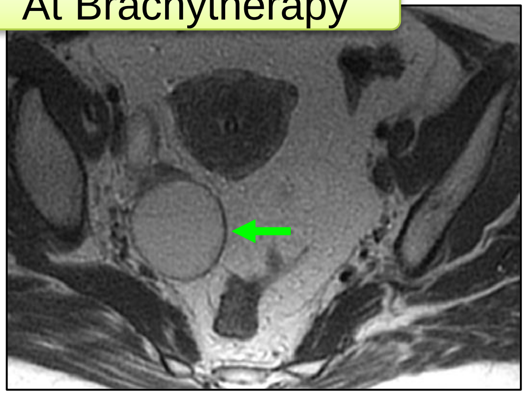
Set the **STAGE** before contouring

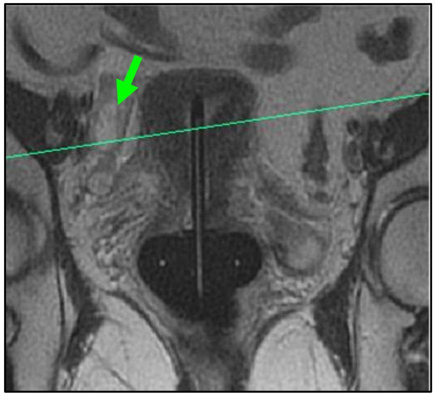
- **S** ize of the residual tumor?
- **T** opography of the target V?
- **A** dequacy of the implant?
- **G** rey zones in relation to GTV_{DG}?
- **E** xtra findings?

“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)

MRI and/or CT/US with clinical drawings

Rule out **FLOP**

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

Set the **STAGE** for contourig

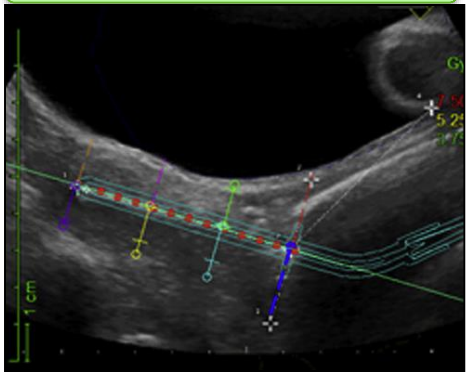
1. **S**ize of the tumor:
   - 8 cm^3 (ellipsoid formula)
   - Regression to Proportional V: PV = 20 % initial V
2. **T**opography: unfavourable due to right parametrial extension.
3. **A**dequate insertion geometry.
4. **G**rey zones correspond to initial infiltrative tumor: proximal third of right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

Petric P Journal of Contemporary Brachytherapy 2014

Choice of imaging modality for IGABT

ULTRASOUND

Transabdominal

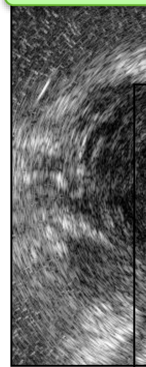


Van Dyk et al. Brachytherapy 2015

Transrectal

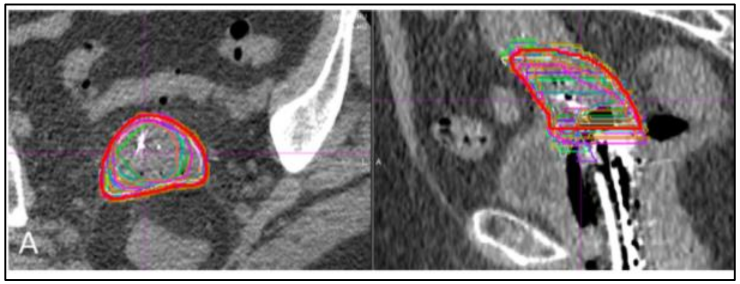
Schmid MP, et al. Radiother Oncol 2016

Rotatir

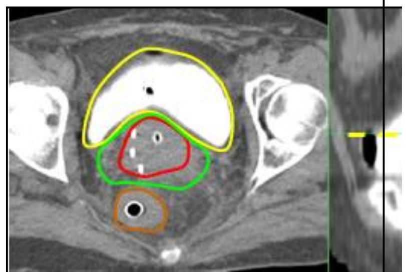


Petric P, Kir

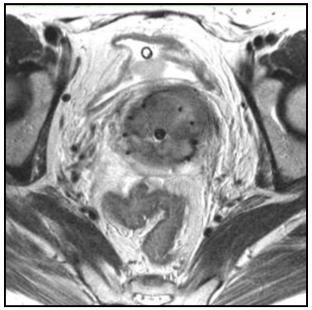
CT

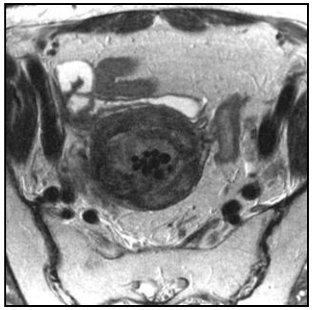


Viswanathan AN, et al Int J Radiat Oncol Biol Phys 2014

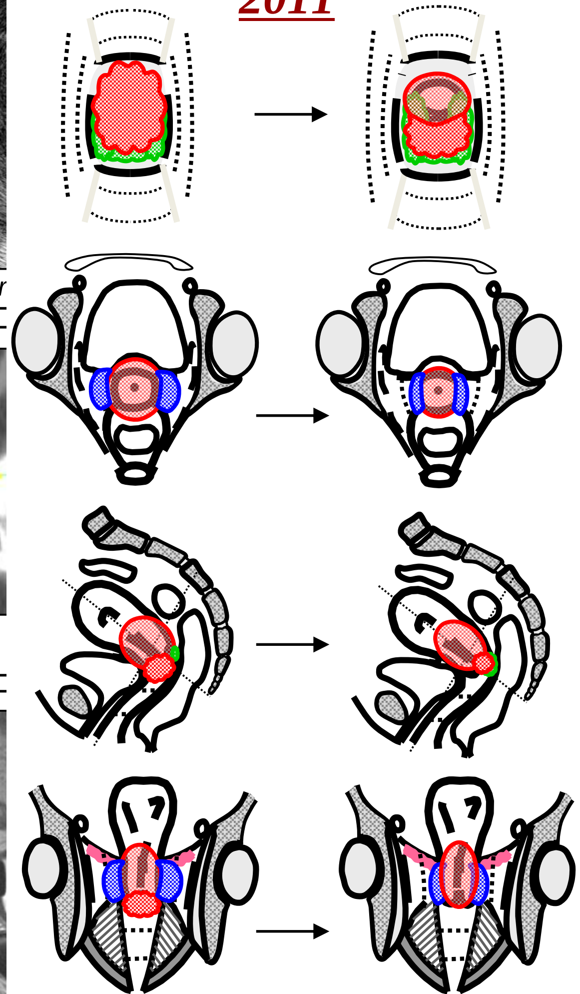


MRI





EMBRACE study protocol, 2011



ESTRO TEACHING COURSE ON IMAGE-GUIDED RADIOTHERAPY & CHEMOTHERAPY IN GYNAECOLOGICAL CANCER – WITH A SPECIAL FOCUS ON ADAPTIVE BRACHYTHERAPY
PRAGUE, CZECH REPUBLIC - OCTOBER 22-26, 2017

Imaging Protocols MRI and CT:
Patient preparation for EBRT and IGABT

Johannes C. Athanasios Dimopoulos

METROPOLITAN HOSPITAL

presented by Peter Petrow,
Institut Curie et ACRIM Compiègne

institutCurie

ACRIM

Imaging protocols MRI and CT
Modality of choice, EBRT and IGABT

Imaging modalities for EBRT and BT:

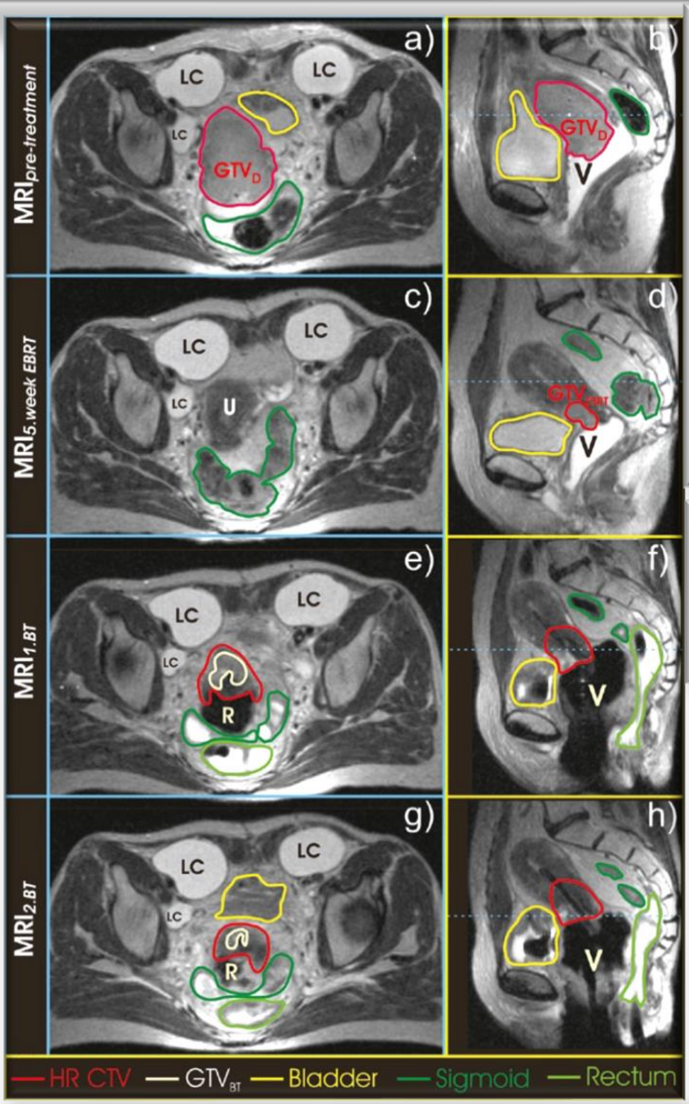
CT = gold standard for EBRT

In EBRT MRI may assist delineation due to image fusion with CT

MRI = gold standard for IGABT

CT = alternate option (if MRI not available)

Imaging protocols MRI and CT
Changes during EBRT and IGABT

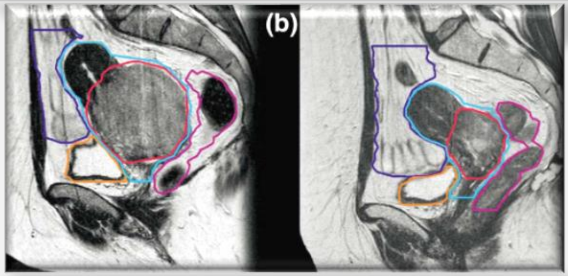


What changes do we expect during radiochemotherapy?

- Tumor regression **75 %**
- Organ and Target movement

… CTV, ITV definition – central issue for modern RT techniques e.g. IMRT … shrinking target and IGABT

After 30 Gy EBRT mean GTV volume reduction 46%
Authors recommend re-planning if IMRT is applied



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

Van de Bunt et al. IJROBP 2008

Imaging protocols MRI and CT
Changes during EBRT (Organ – Target Movement)

Considerable extent of internal-organ motion with uterine displacements ranging from 8 mm up to 48 mm

Chan P et al. Int J Radiat Oncol Biol Phys 2008;70:1507–15.
Lee JE et al. Gynecol Oncol 2007;104:145–51.
Taylor A, Powell MEB. Radiother Oncol 2008;88:250–7.
Kerkhof EM et al. Radiother Oncol 2009;93:115–21.

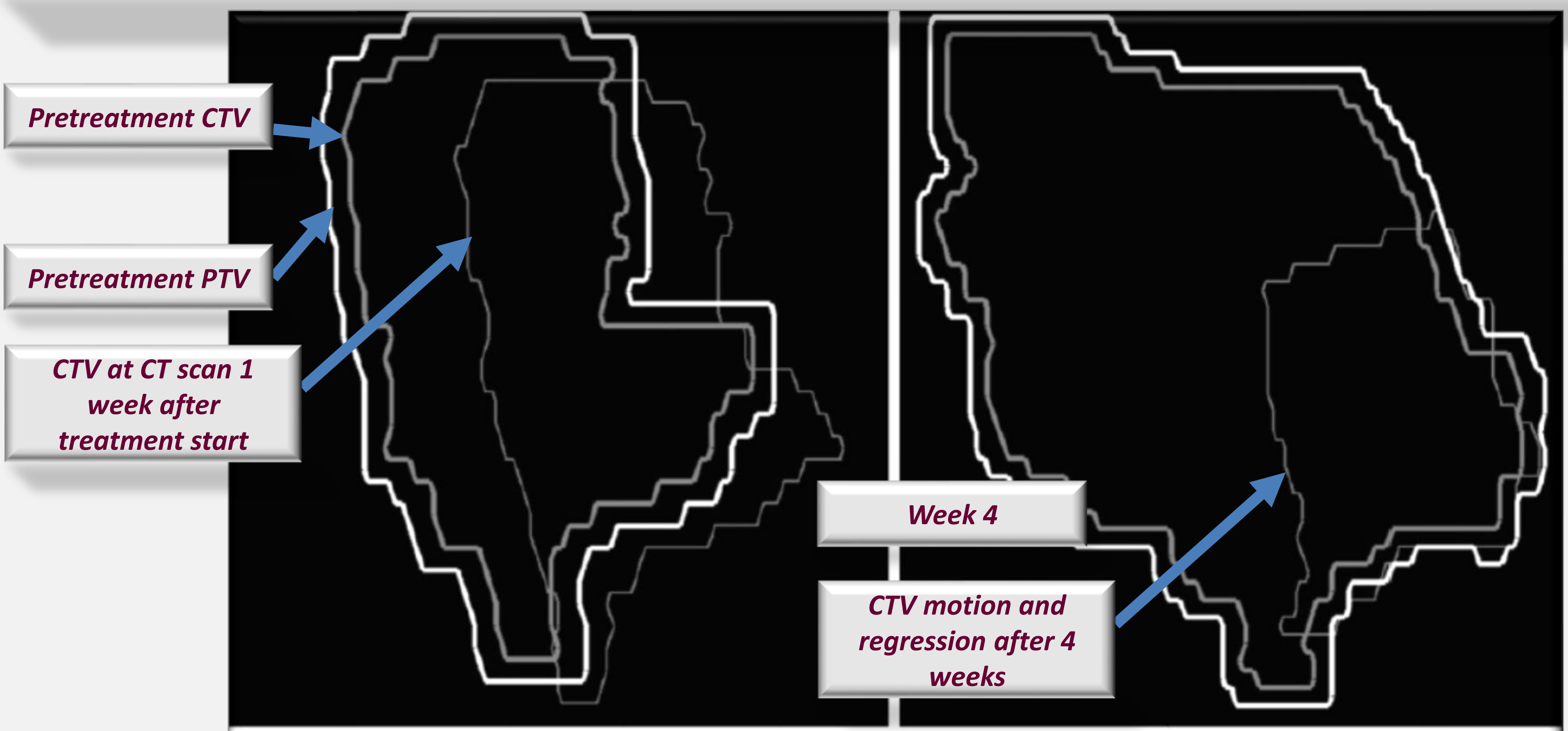
Most studies support that the greater impact on cervix-uterus motion is caused by variations in bladder filling

Buchali A et al. Radiother Oncol 1999;52:29–34.
Taylor A, Powell MEB. Radiother Oncol 2008;88:250–7.
Han Y et al. Int J Radiat Oncol Biol Phys 2006;65:617–23.

One study found that the change in the rectum correlated significantly but weakly with the motion of the cervix and uterus in the AP direction

van de Bunt L et al. Radiother Oncol 2008;88:233–40.

Imaging protocols MRI and CT
Changes during EBRT and IGABT (Interaction)



Repetitive Imaging and Repetitive Planning:

Target regression during treatment in the presence of organ motion and deformation can mitigate the need for a replan or … everything may happen if a small PTV margin is applied

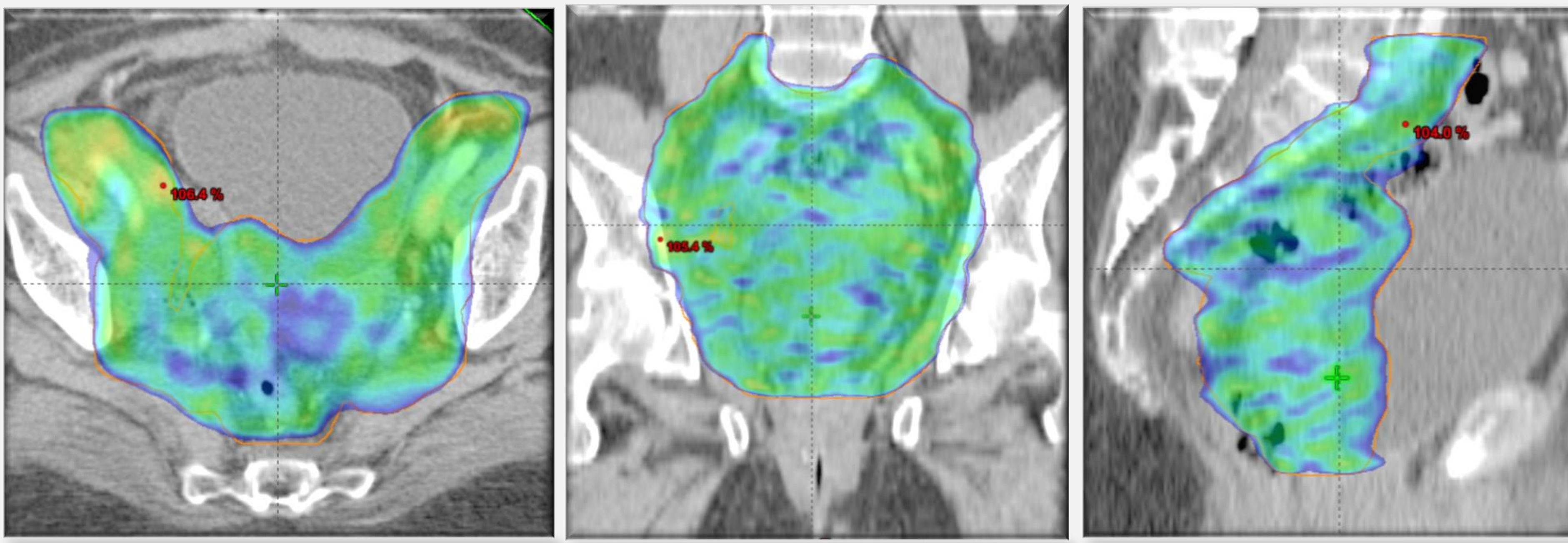
Stewart et al. IJROBP 2010

Repetitive imaging: Frequency of Imaging during EBRT

To give recommendation is outside the scope of this presentation

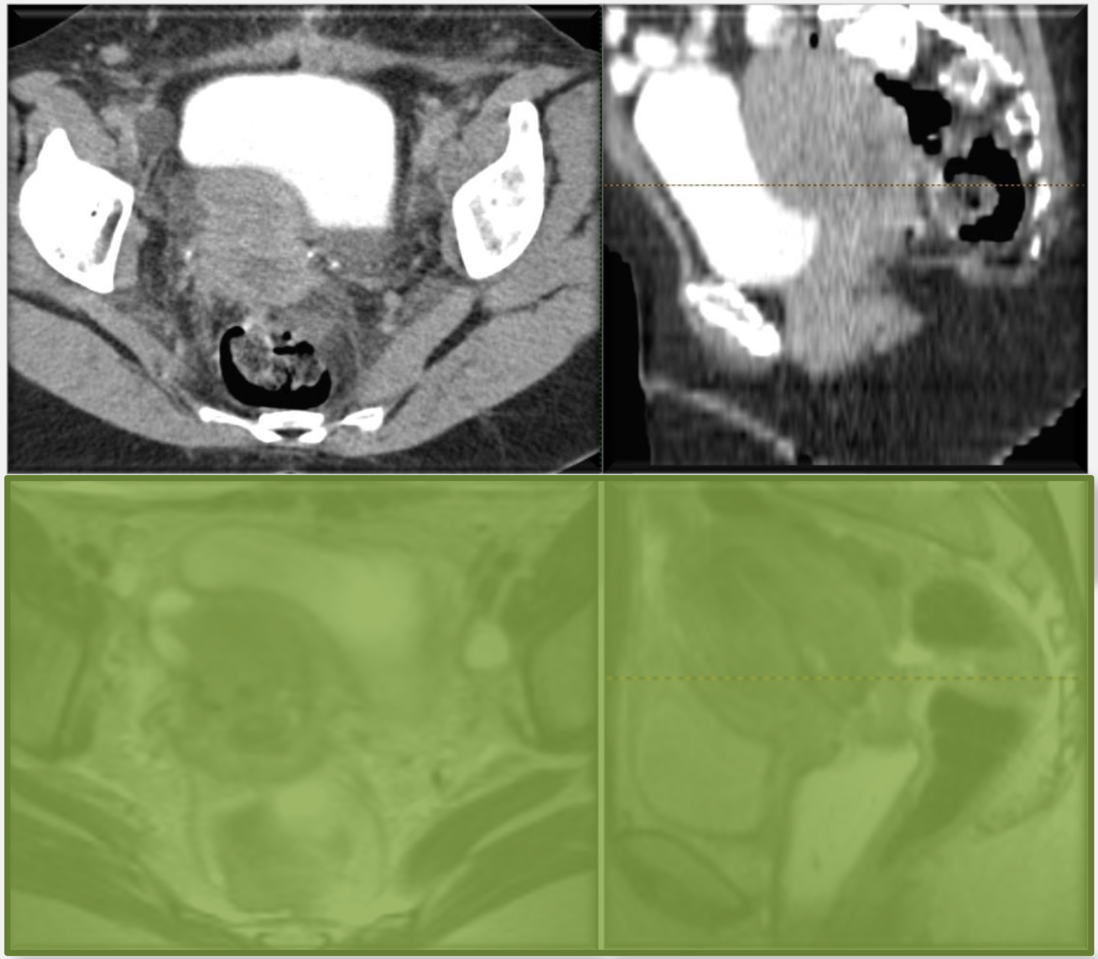
- ***Required for highly conformal EBRT !!!!***
- ***Not able to predict changes !!!!***
- ***Logistics !!!!***

CT IMAGING FOR EBRT



Imaging protocols MRI and CT

Key issues when using CT for EBRT- Image acquisition



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

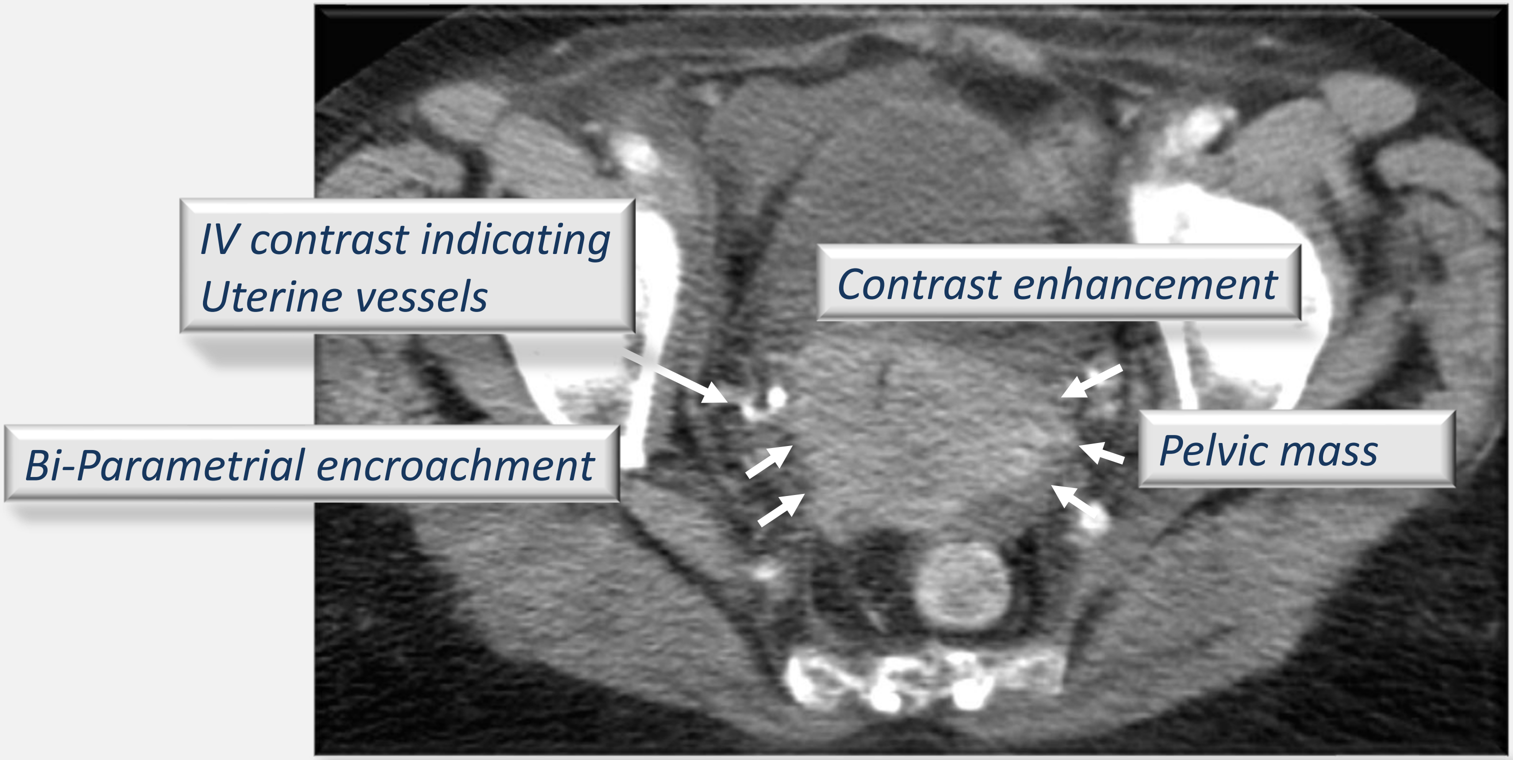
administration of iv contrast

delayed image acquisition for bladder visualisation

administration of oral iodine or barium based contrast

patient positioning

Imaging protocols MRI and CT
Key issues: IV contrast for EBRT imaging

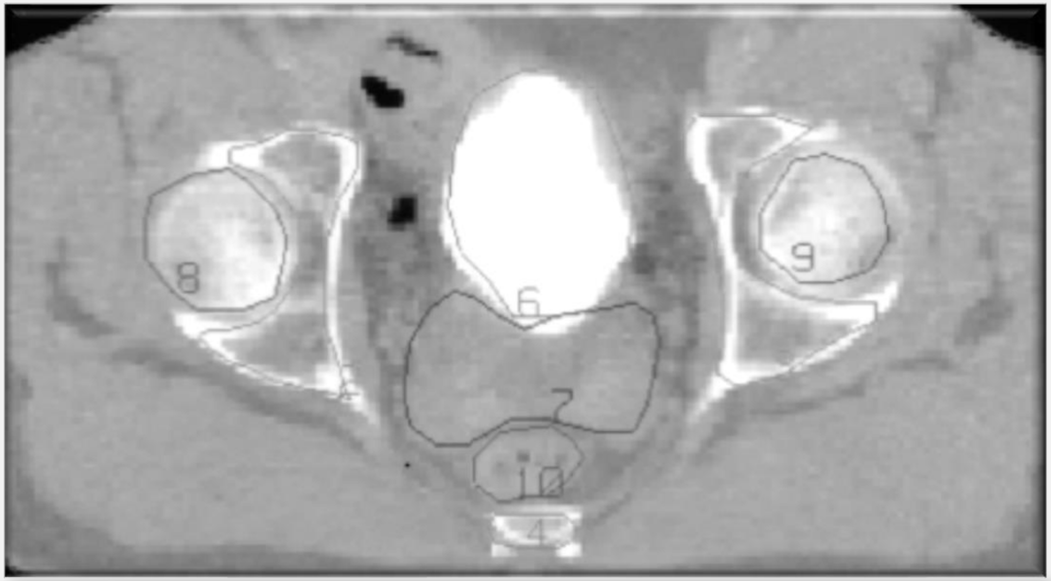


Imaging protocols MRI and CT
Key issues: IV contrast delayed image acquisition and oral contrast

Iv contrast – delayed image acquisition for bladder

Imaging protocols MRI and CT
Key issues: IV contrast for EBRT imaging

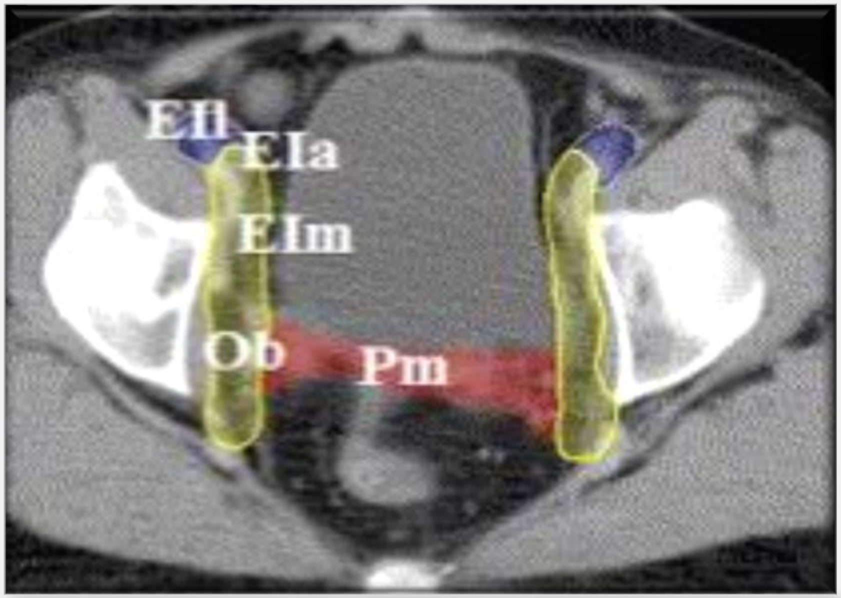
IV contrast – delayed image acquisition for bladder
Impact on dosimetry



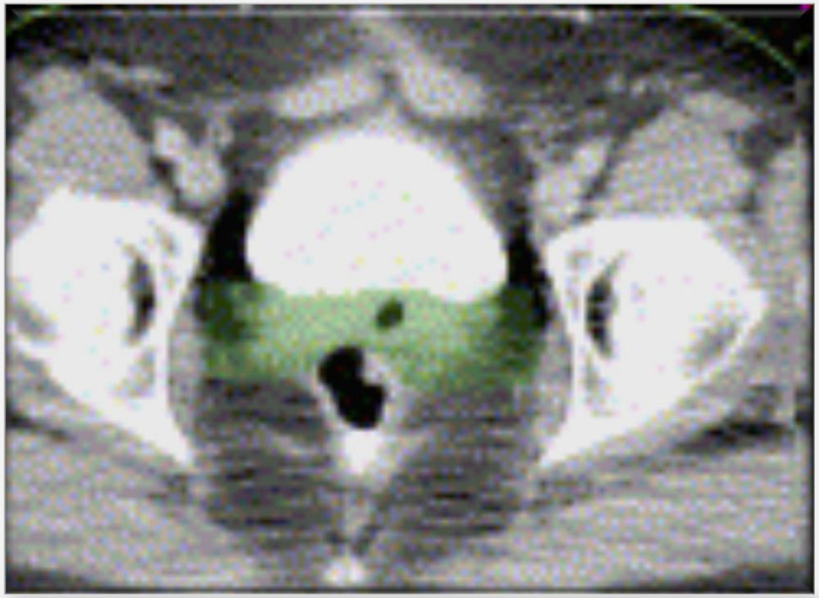
Weber et al. Radiother Oncol 2001 -
Bladder opacification does not influence dose distribution in conformal radiotherapy of prostate cancer

Ghosh et al. Gynecol Oncol 2001 –
However, modern TPSs allow contouring
on series with contrast and dose calculation on series without (see fusion)

Imaging protocols MRI and CT
Key issues: IV contrast for EBRT imaging and contouring guidelines



Taylor A et al. IJROBP 2005

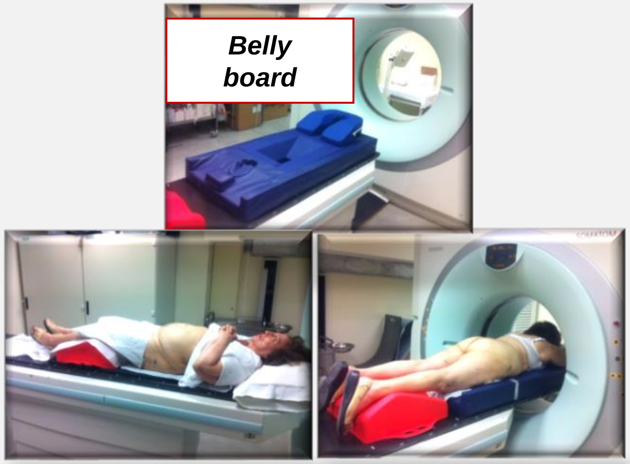


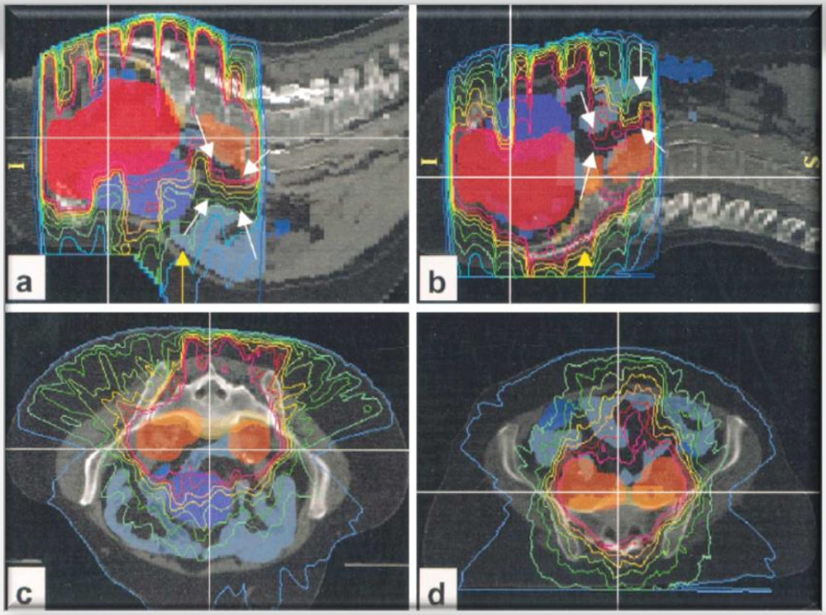
Small W et al. IJROBP2008

It seems that there is no gold standard …

Imaging protocols MRI and CT
Key issues: Patient positioning prone versus supine

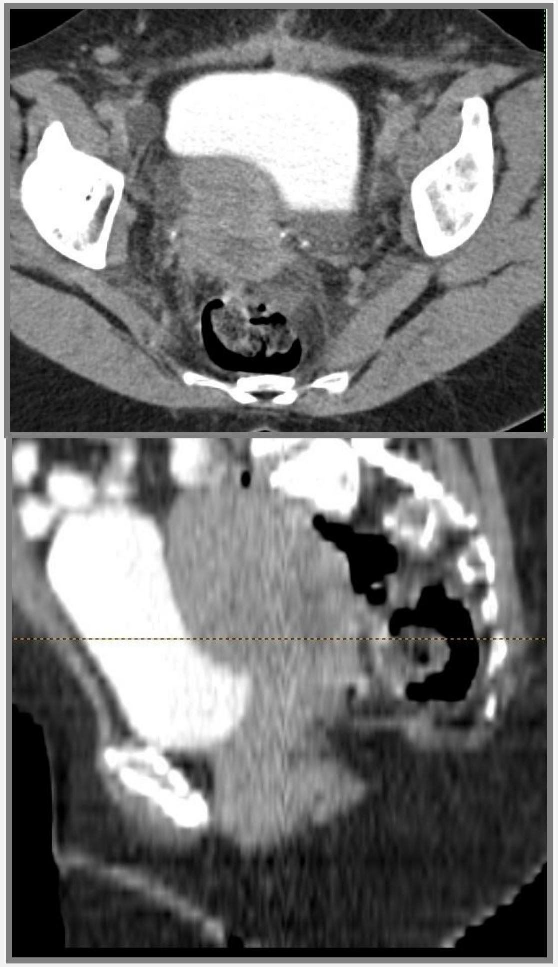
Prone versus supine – prone is superior in some patients, but …





Weber et al. Radiother Oncol 2001 – Prone positioning has to be used with specific imobilization devices e.g. belly board
Adli et al. IJROBP 2003 – Dosimetric results

Imaging protocols MRI and CT
Key issues: CT for EBRT- Patient preparation

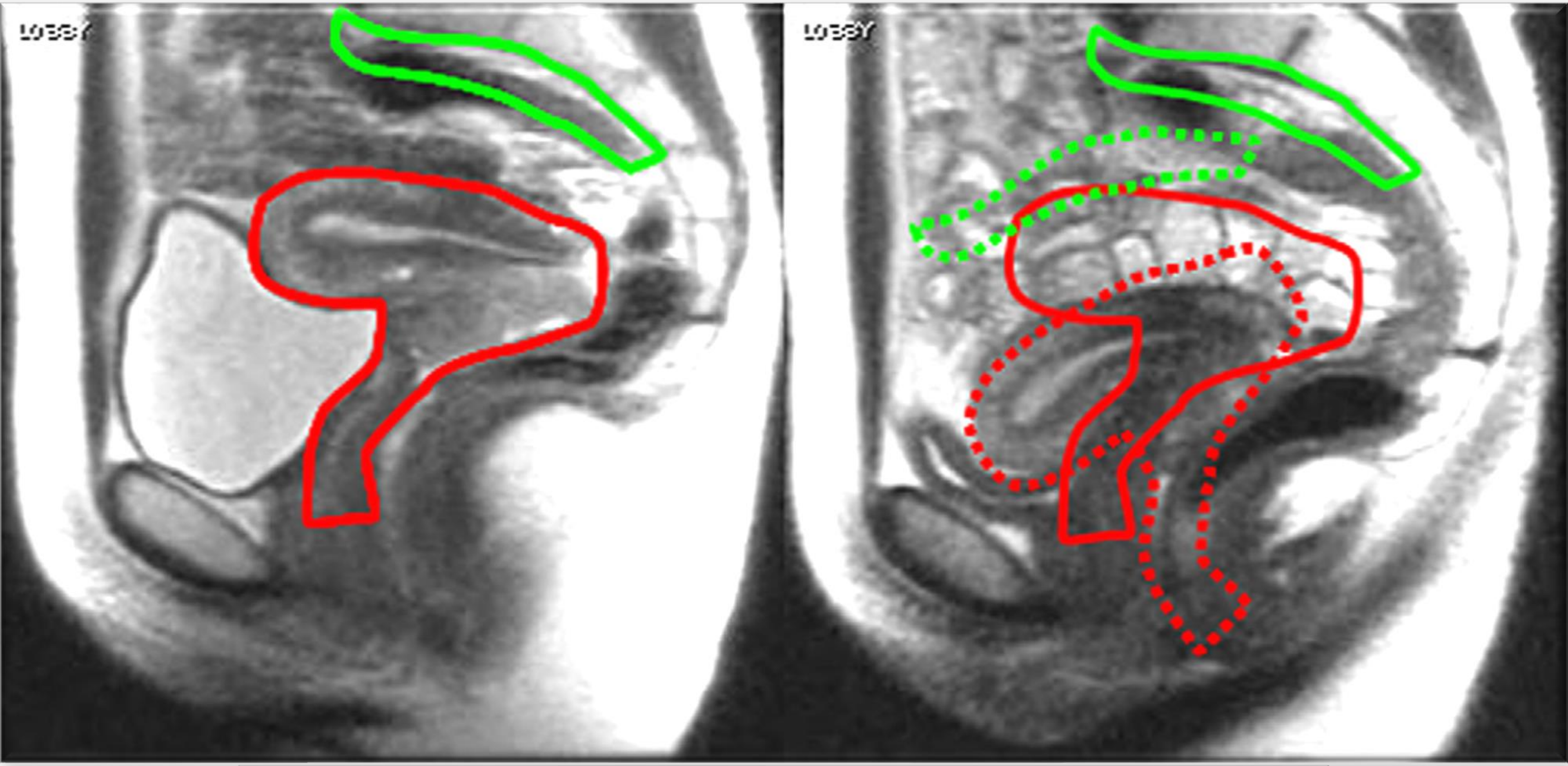


What are the key issues for patient preparation?

- ***bladder filling***
- ***dietary protocol?***
- ***rectum filling***

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

Imaging protocols MRI and CT
Key issues: Preparation for EBRT - Bladder filling

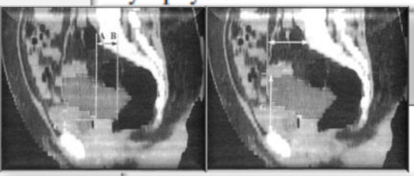


Lim et al. IJROBP 2011- Consensus guidelines for CTV delineation…

Imaging protocols MRI and CT
Key issues: patient preparation for EBRT imaging
Impact of bladder filling on:

Impact on uterine position

	Empty organ		Full organ		Differences (full versus empty organ)		P-value
	Median	$CI_{95\%}$	Median	$CI_{95\%}$	Median	$CI_{95\%}$	
C: cervix: lower margin – symphysis	10	5 to 17	14	7 to 21	4	− 1 to 6	< 0.05
F: corpus: anterior margin – promontorium	34	2 to 59	35	21 to 55	5	0 to − 9	< 0.05
0: corpus: upper margin – syinphysis	92	70 to 100	108	76 to 112	7	3 to 15	< 0.05



Impact on dose to bladder

Buchali et al. Radiother Oncol 1999

		Empty organ		Full organ		P-value
		Median	$CI_{95\%}$	Median	$CI_{95\%}$	
1/2 of bladder volume	All patients	93.5	82.0–92.5	86.5	73.4–86.4	< 0.05
	Definitive rt	81.0	75.0–93.9	80.0	67.8–89.5	< 0.05
	Post-operative rt	93.0	84.2–95.0	88.0	73.0–89.0	n.s.
2/3 of bladder volume	All patients	77.5	68.8–83.5	60.5	56.7–72.1	< 0.005
	Definitive rt	67.0	63.0–87.4	56.0	52.1–76.3	< 0.05
	Post-operative rt	79.0	67.7–86.0	65.0	54.4–74.7	< 0.05
3/3 of bladder volume	All patients	42.0	40.3–51.5	38.5	36.1–39.1	< 0.005
	Definitive rt	42.0	38.9–60.0	39.0	35.0–40.0	< 0.005
	Post-operative rt	41.0	38.2–46.7	38.0	35.8–39.7	< 0.005

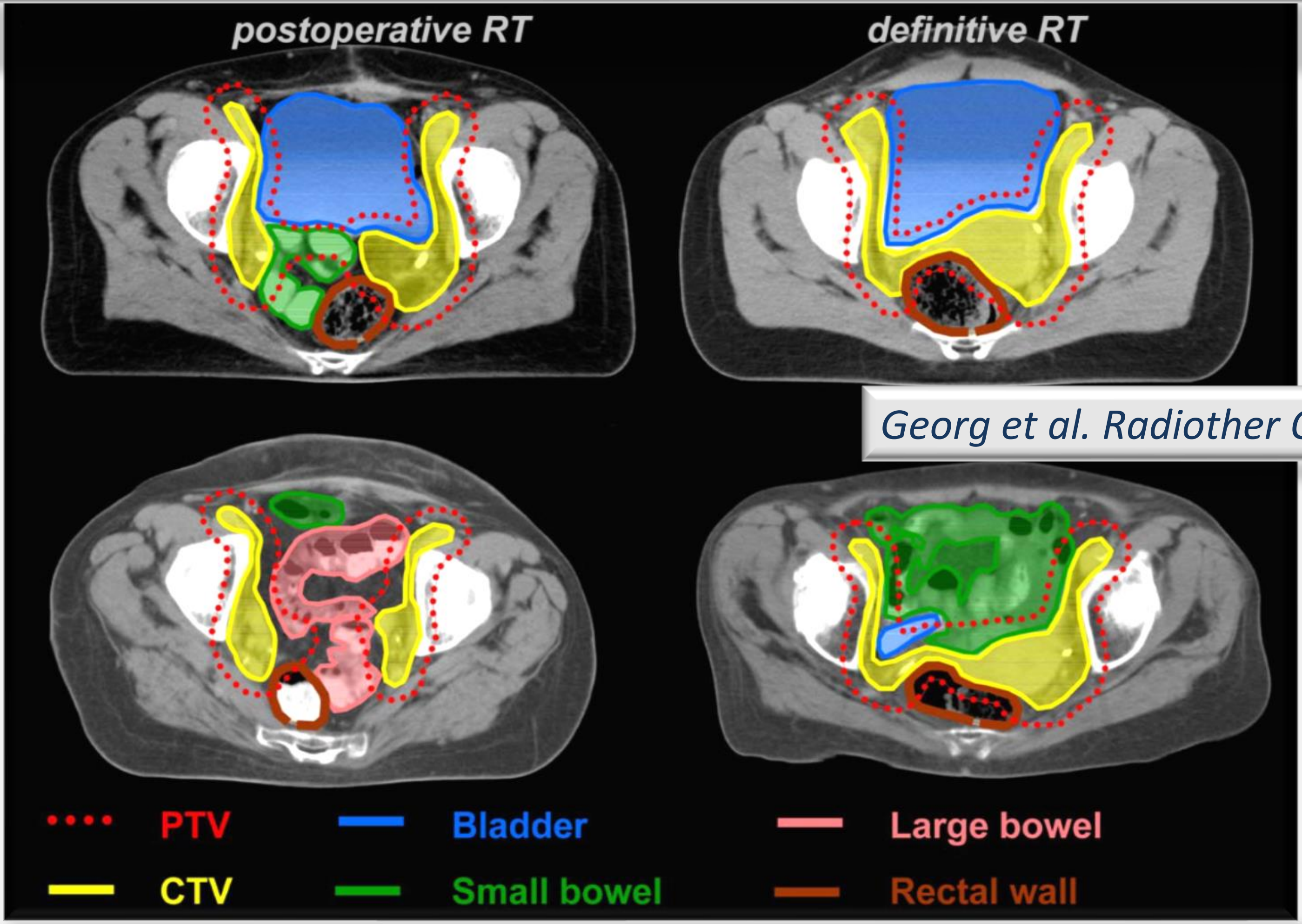
Imaging protocols MRI and CT
Key issues: patient preparation for EBRT imaging
Impact of bladder filling on:

Impact on dose to rectum

		Empty organ		Full organ		*P*-value
		Median	$CI_{95\%}$	Median	$CI_{95\%}$	
1/2 of rectum volume	All patients	95.0	83.4–94.3	98.0	84.8–96.4	n.s.
	Definitive rt	94.0	78.2–96.2	98.0	78.4–99.2	n.s.
	Post-operative rt	95.0	83.7–97.1	98.0	86.0–98.5	n.s.
3/3 of rectum volume	All patients	18.0	16.4–29.3	13.5	17.7–31.6	n.s.
	Definitive rt	18.0	12.7–31.6	12.0	14.9–36.2	n.s.
	Post-operative rt	18.0	14.4–32.7	15.0	14.5–33.4	n.s.

Buchali et al. Radiother Oncol 1999

Imaging protocols MRI and CT
Key issues: patient preparation for EBRT imaging
Impact of bladder filling on small bowel dose



Georg et al. Radiother Oncol 2006

Imaging protocols MRI and CT
Key issues: patient preparation for EBRT imaging
Impact of dietary advice on dosimetry during EBRT

Impact of dietary advice

- ***977 prostate patients treated with IMRT (739 without and 105 with diet)***

  Antiflatulent dietary advice does not decrease intrafraction motion

  Lips et al. IJROBP 2011

- ***49 prostate patients (23 without and 26 with diet)***

  Feces, gas and moving gas decreased significantly in the diet group

  Smitsmans et al. IJROBP 2008

- ***No studies for GYN patients with dosimetric results***

MR IMAGING FOR pre-RT examination

Imaging protocols MRI and CT

Key issues when using MRI for pre-RT examination

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

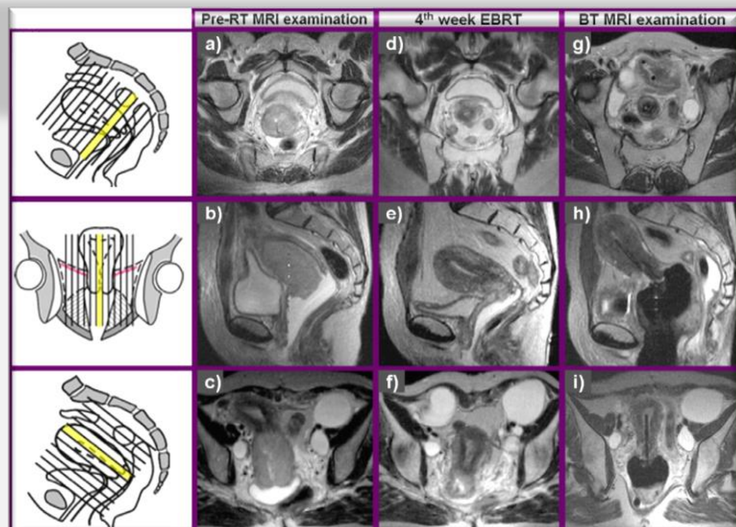
journal homepage: www.thegreenjournal.com

Original article

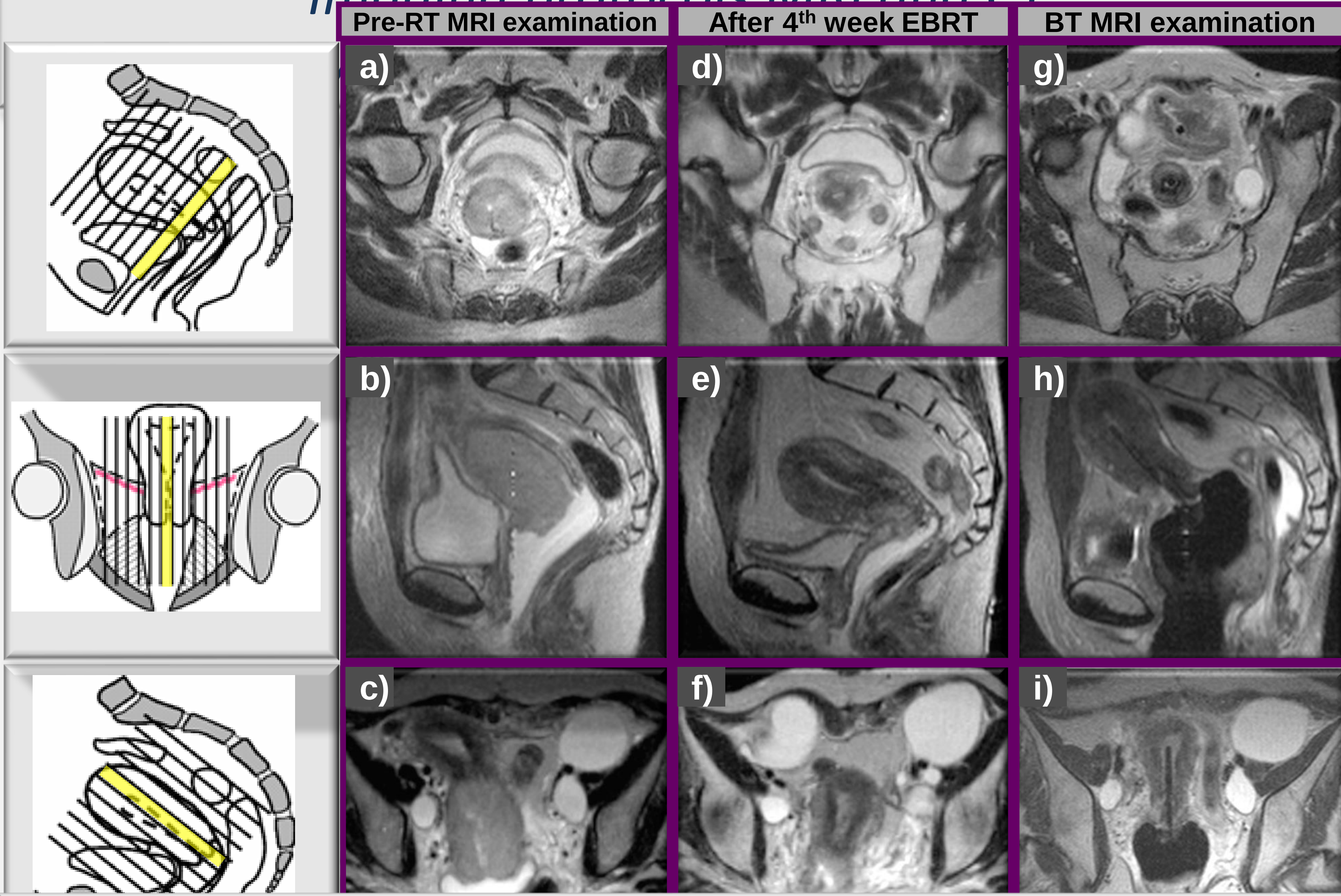
Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy

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



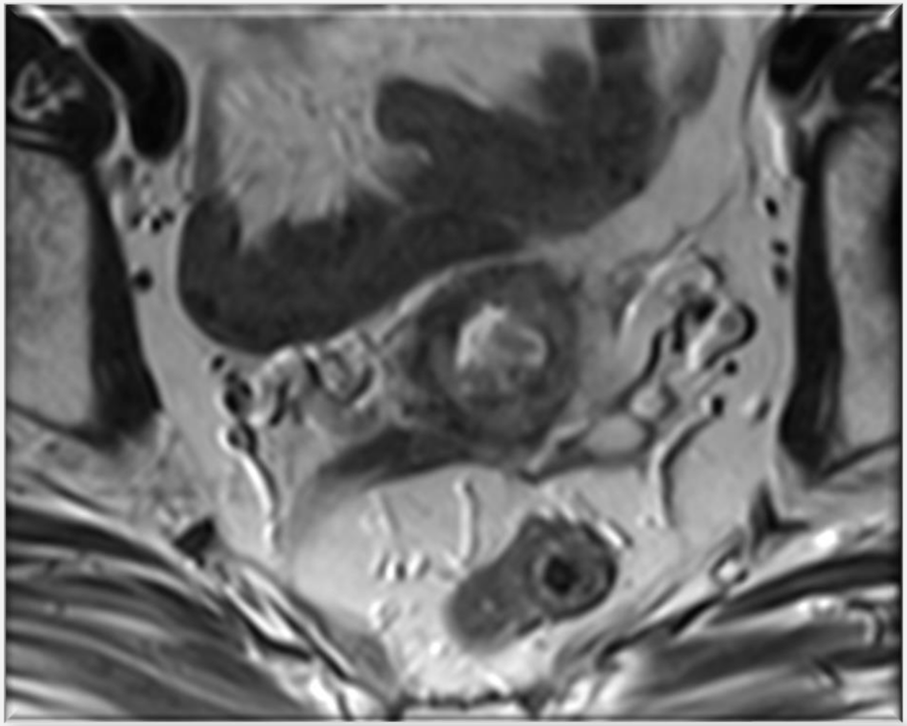
Imaging protocols MRI and CT

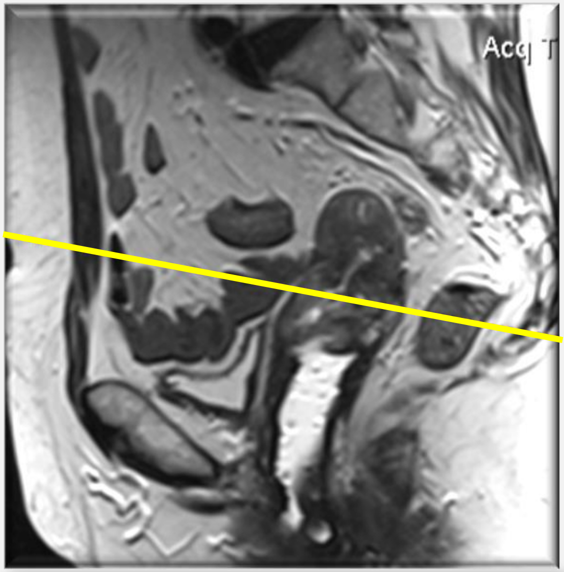


GYN GEC ESTRO recommendations Radiother Oncol 2012

Imaging protocols MRI and CT
Key issues for image-guided radiotherapy

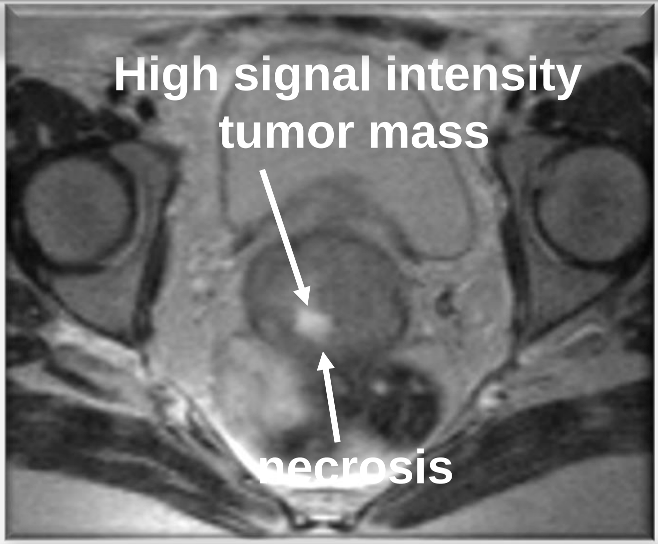
Plane orientation – orthogonal and parallel to uterine axis



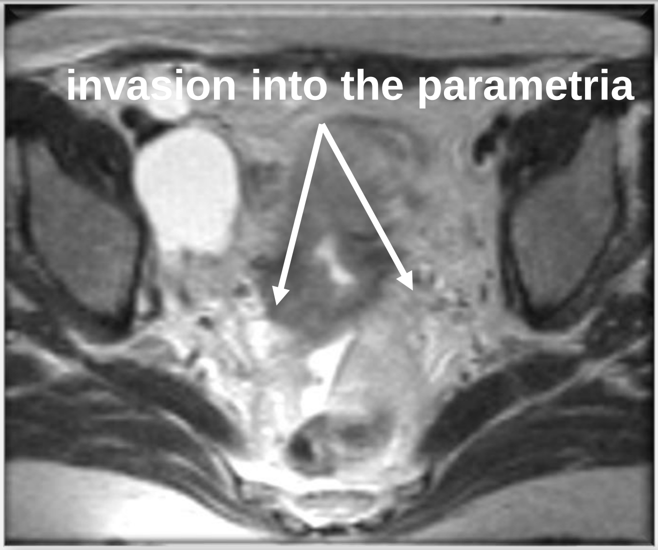


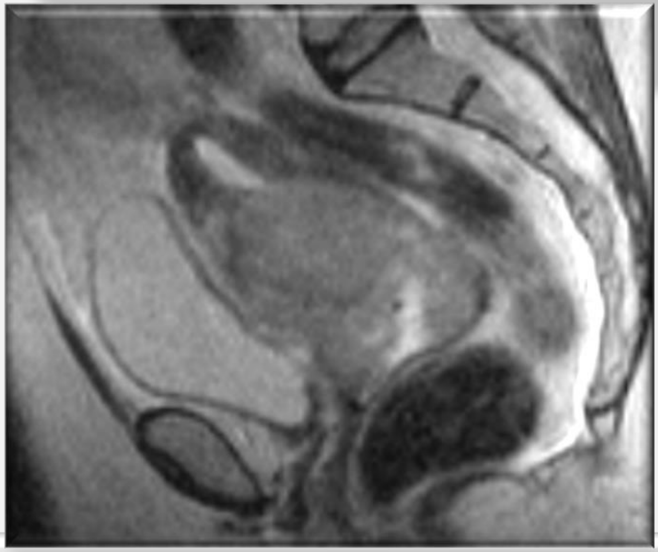
Imaging protocols MRI and CT

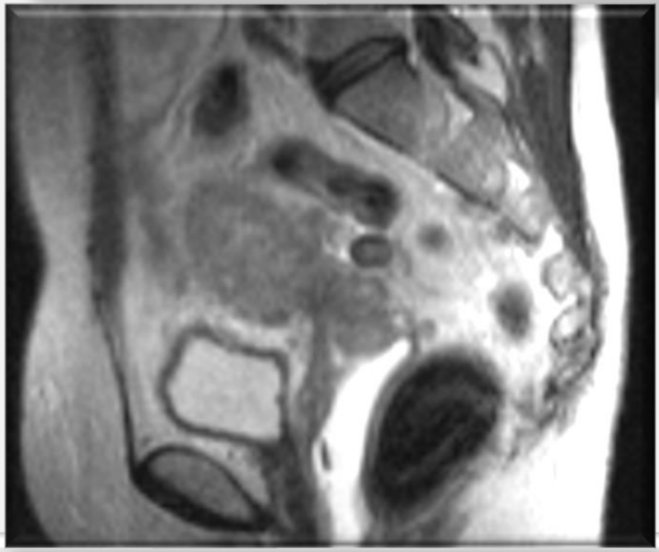
Key issues for image-guided radiotherapy



GTVD

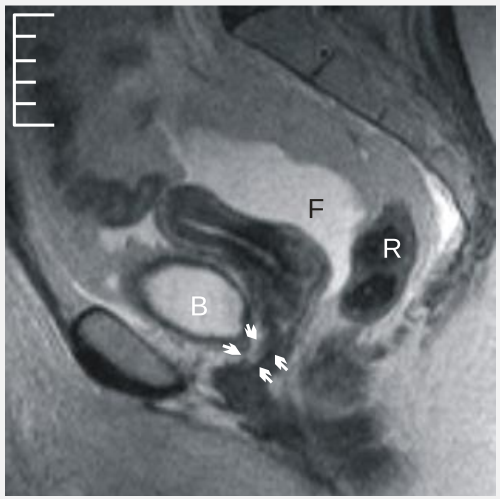




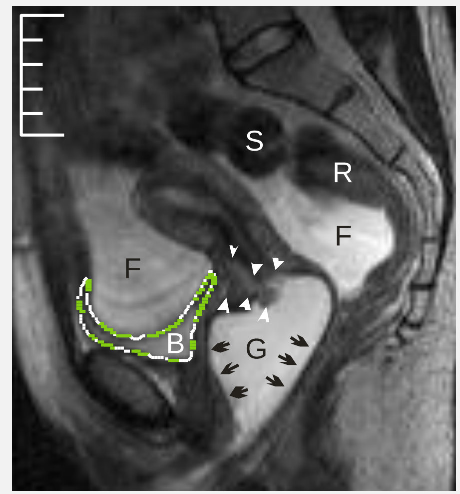


Imaging protocols MRI and CT
Key issues: pre-RT MRI examination
Impact of vaginal marking

Impact of vaginal marking



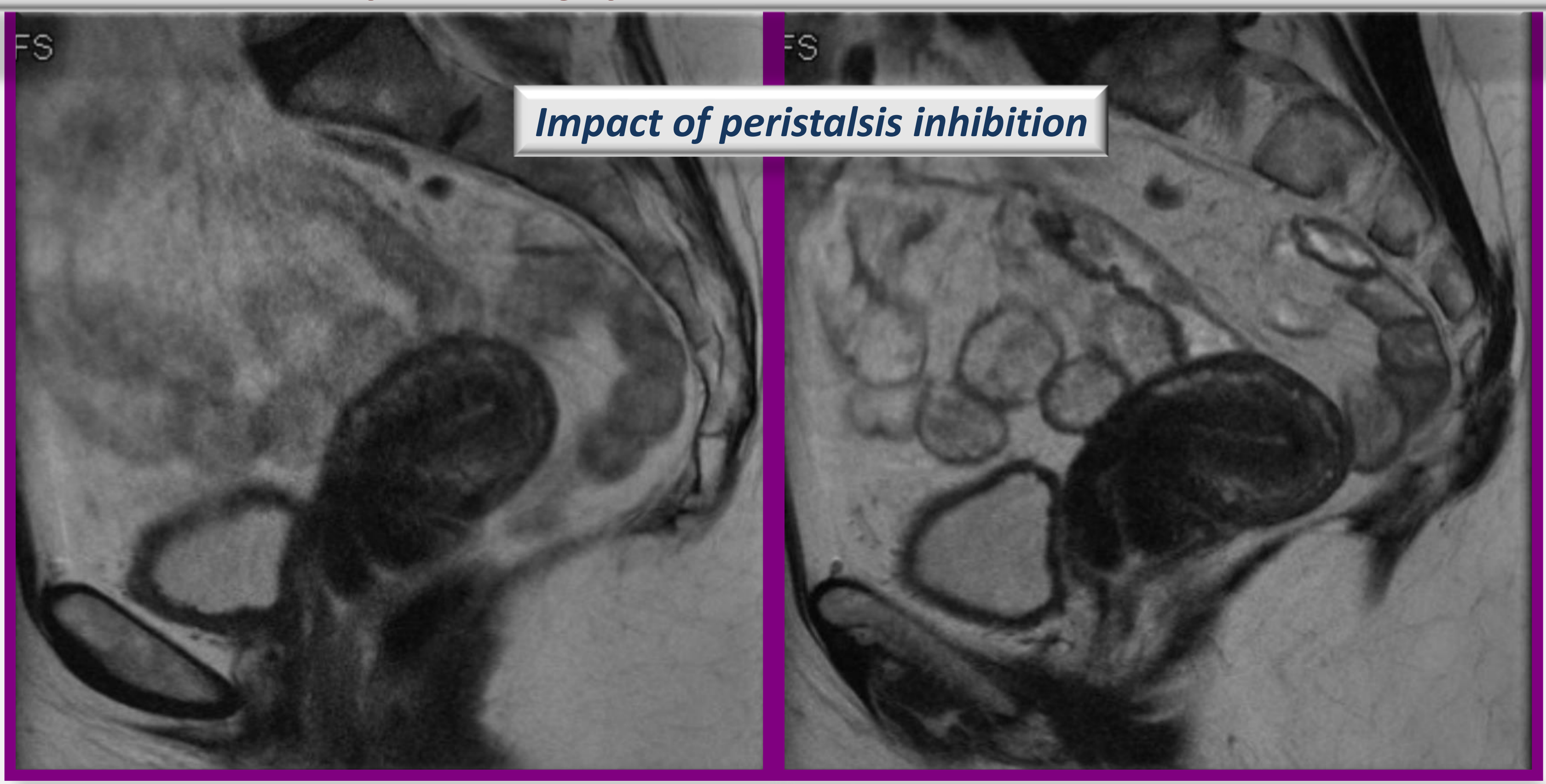
at diagnosis without vaginal marking



at diagnosis with vaginal marking

Dimopoulos et al. IJROBP 2006

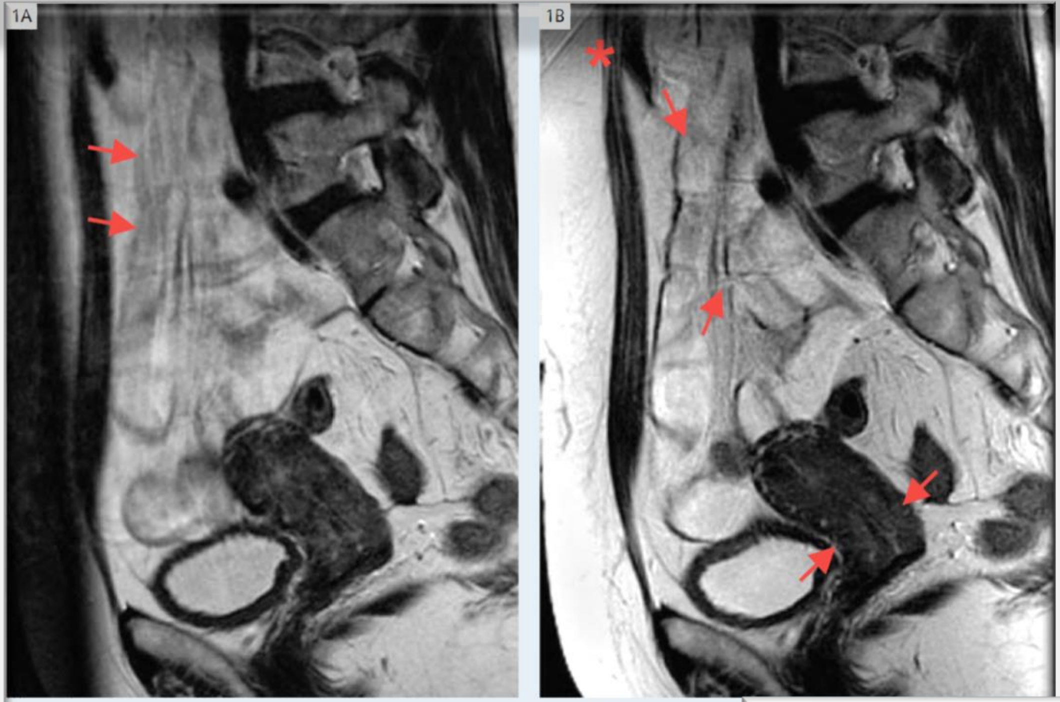
Imaging protocols MRI and CT
Key issues: pre-RT MRI examination
Impact of peristalsis inhibition



without inhibition

with inhibition

Imaging protocols MRI and CT
Key issues: pre-RT MRI examination
Impact of peristalsis inhibition



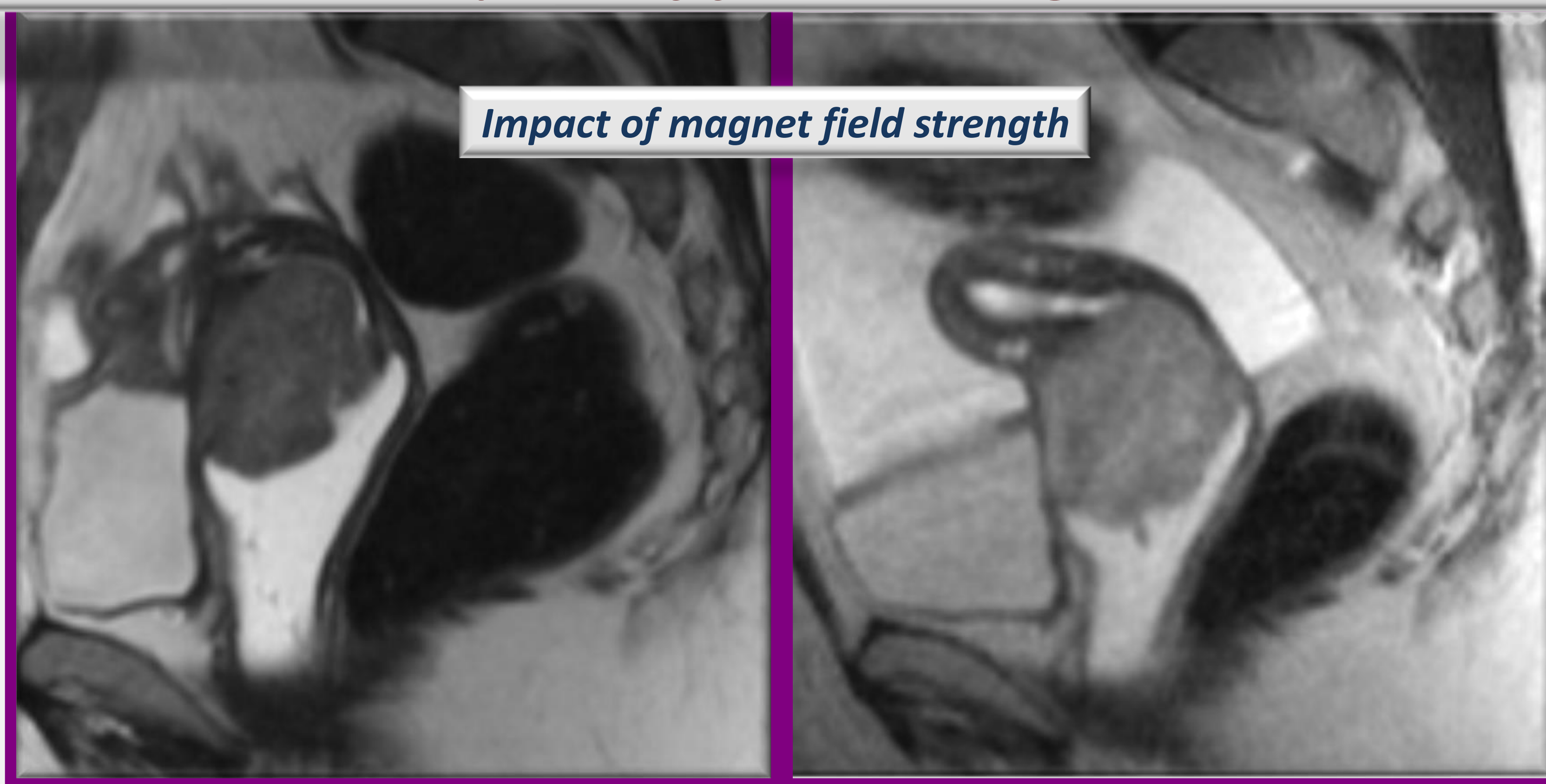
Conventional TSE *syngo* BLADE

http://usa.healthcare.siemens.com

Propeller acquisition technique
Syngo BLADE non-Cartesian data acquisition technique for motion correction

Imaging protocols MRI and CT
Key issues: pre-RT MRI examination
Impact of field strength

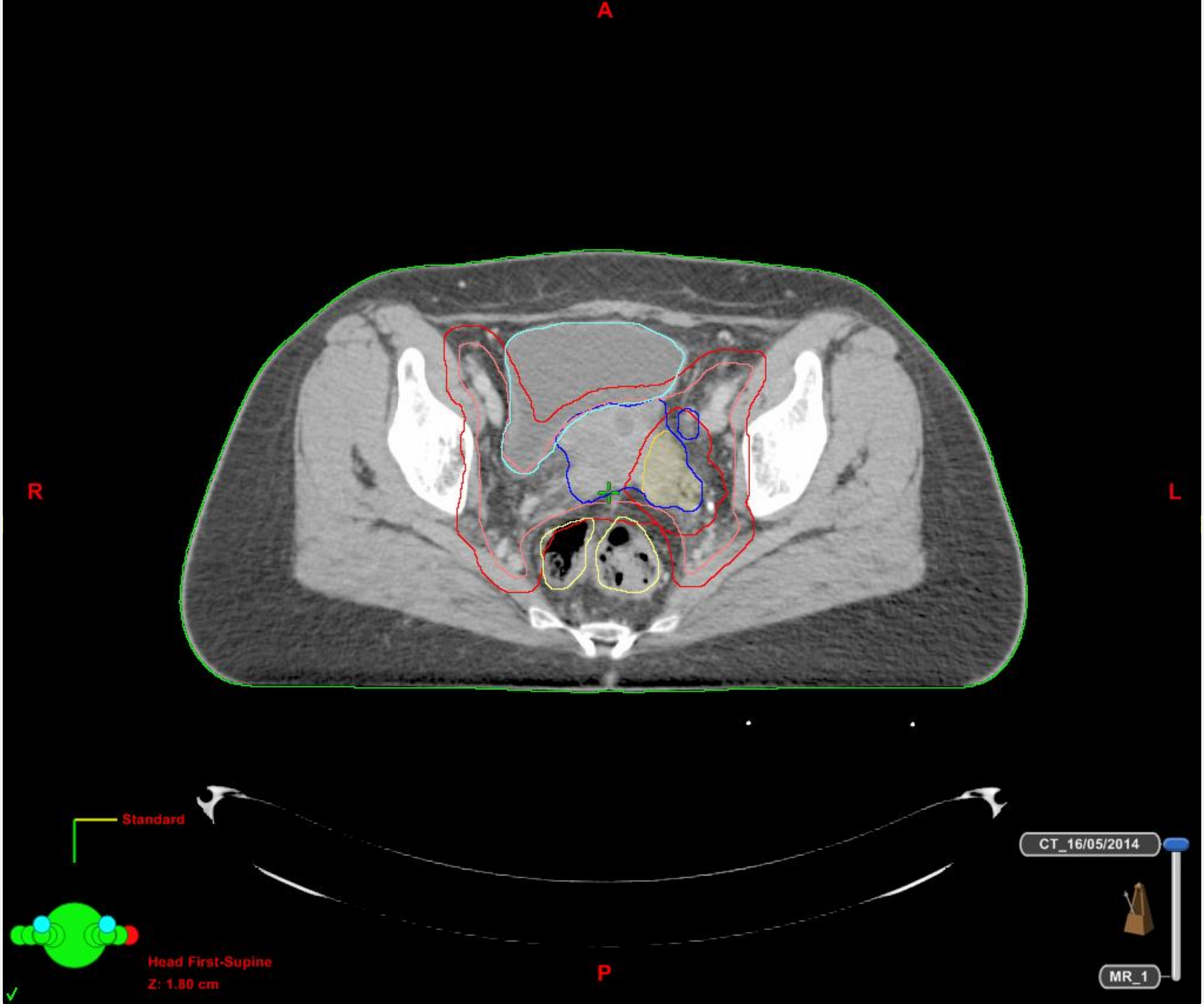
Impact of magnet field strength



1.5 Tesla | **0.2 Tesla**

GYN GEC ESTRO recommendations Radiother Oncol 2012

CT – MRI IMAGE FUSION FOR EBRT CONTOURING

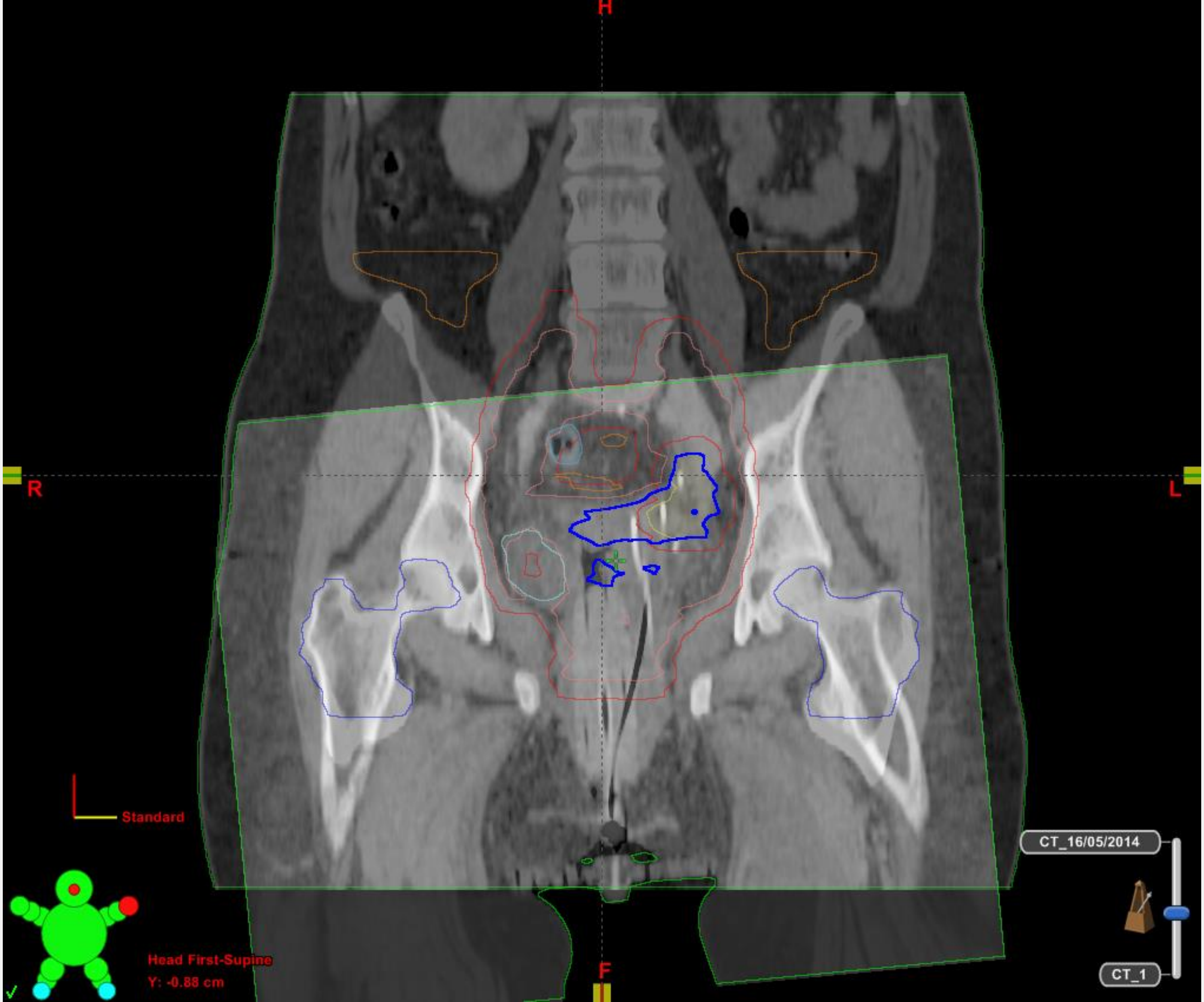


A
R
L
P
Standard
Head First-Supine
Z: 1.80 cm
CT_16/05/2014
MR_1

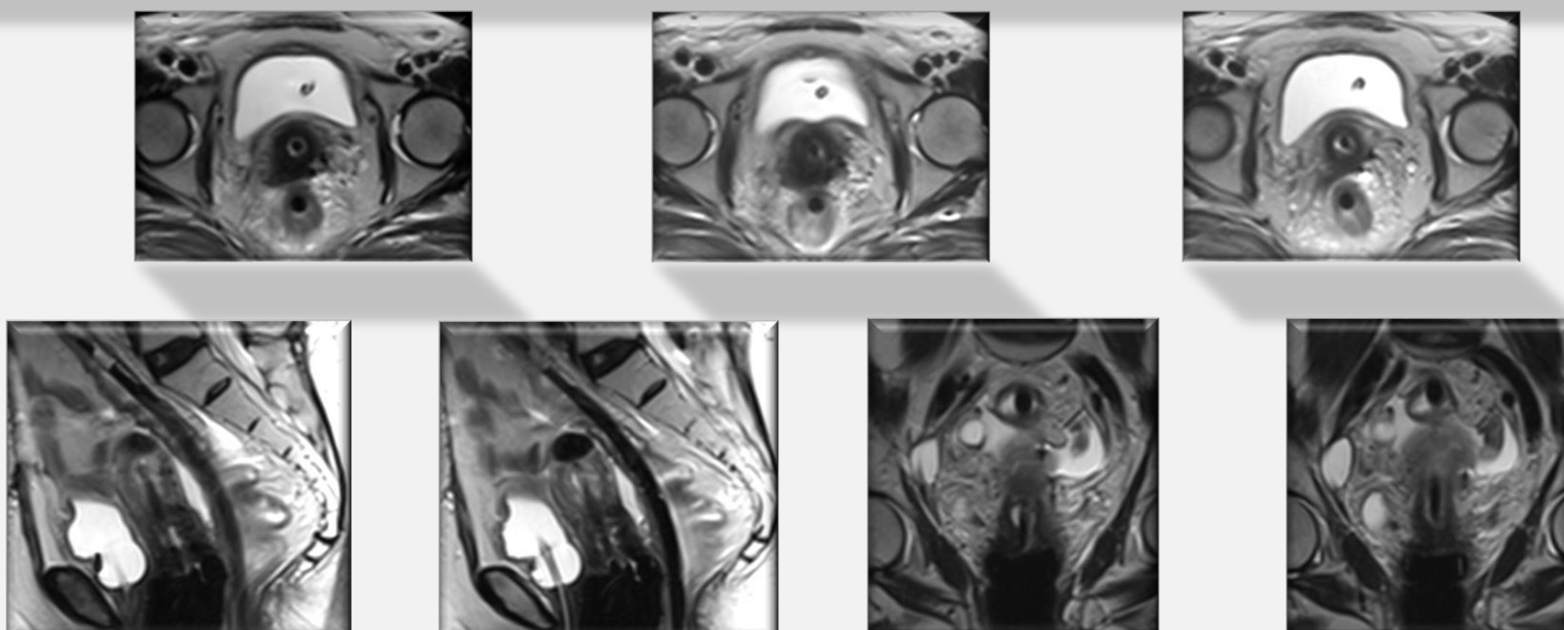

A
R
L
P
Standard
Head First-Supine
Z: 1.80 cm
CT_16/05/2014
MR_1


H
R
L
Standard
CT_16/05/2014
MR_1
Head First-Supine
Y: -2.25 cm
F

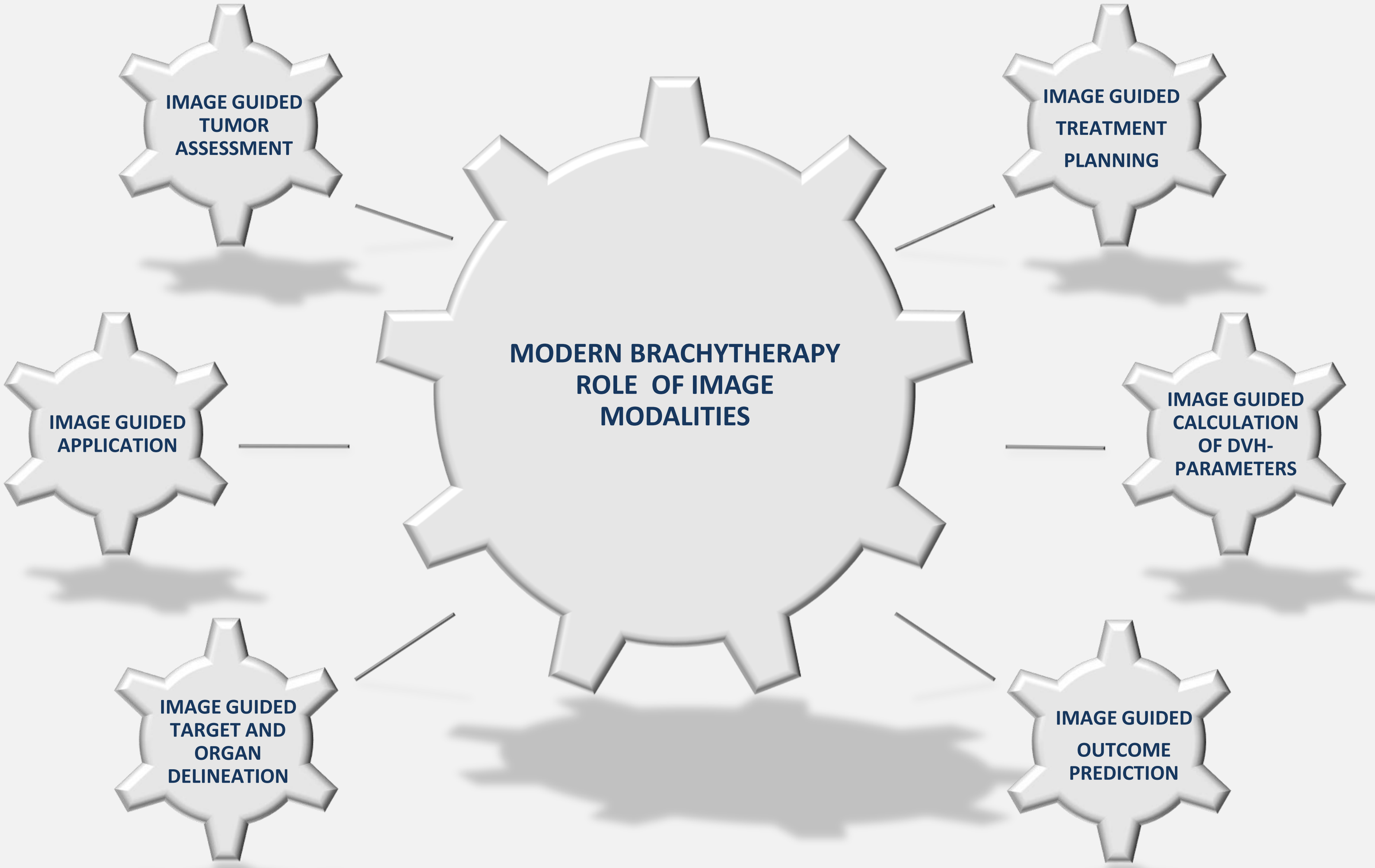
58.028 Gy
58.0
57.000 Gy
56.000 Gy
55.000 Gy
54.000 Gy
53.000 Gy
52.000 Gy
51.000 Gy
50.000 Gy
49.000 Gy
48.000 Gy
47.000 Gy
46.000 Gy
45.000 Gy
44.000 Gy
42.5
42.500 Gy
H
3D MAX for PTV: 58.028 Gy
3D MIN for PTV: 40.371 Gy
3D MEAN for PTV: 49.417 Gy
R
L
57.246 Gy
Standard
Head First-Supine
Y: -1.80 cm
F


H
R
L
Standard
Head First-Supine
Y: -0.88 cm
F
CT_16/05/2014
CT_1

CT and MR Imaging for IGABT

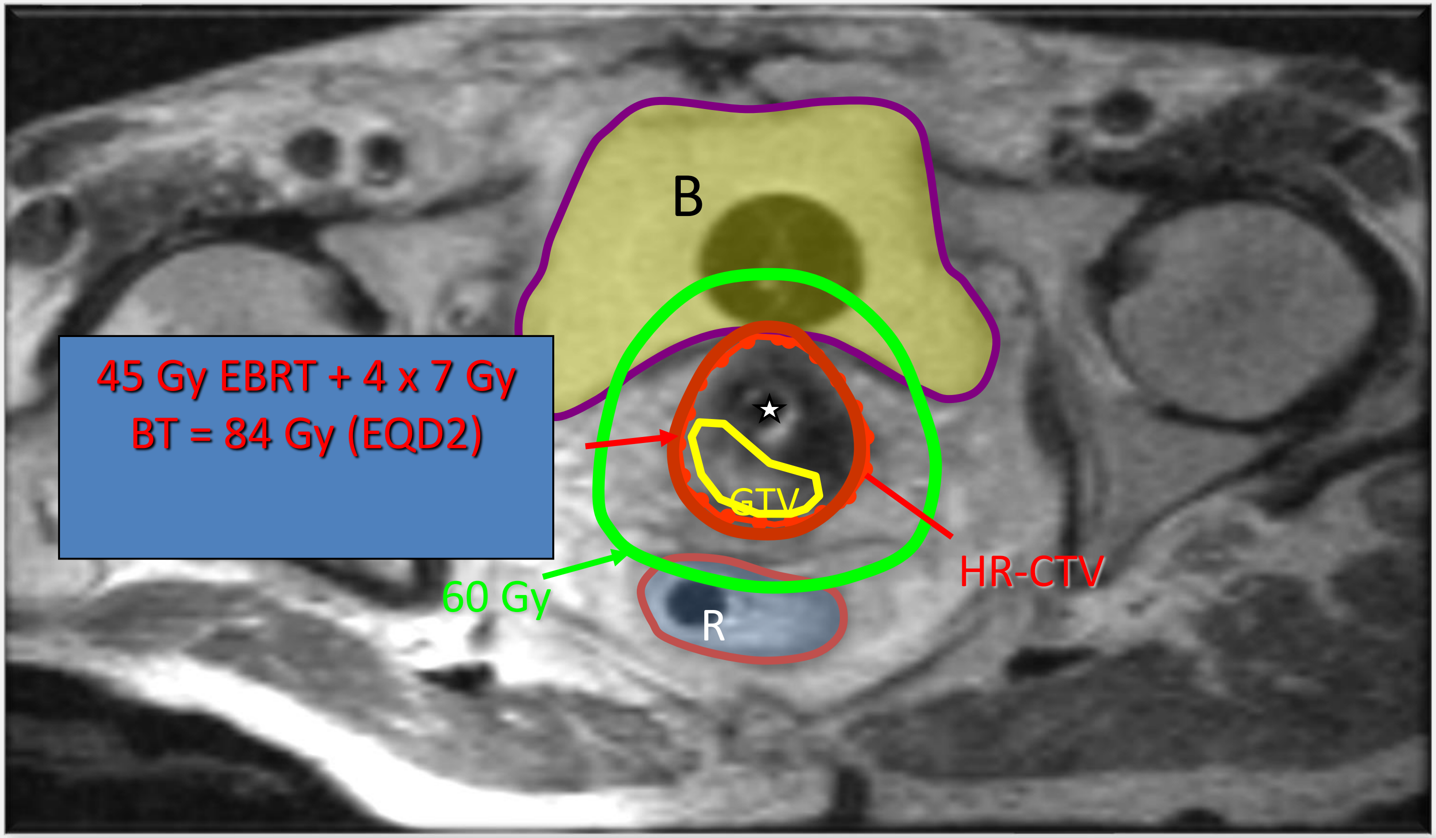


IMAGING IN GYNAECOLOGICAL BRACHYTHERAPY PROCEDURE „STEP BY STEP“



ROLE OF IMAGING MODALITIES
GYNAECOLOGICAL BRACHYTHERAPY – MRI

Gold Standard for Image-Guidance of cervical cancer brachytherapy



ROLE OF IMAGING MODALITIES - MRI

GEC ESTRO RECOMMENDATIONS!

ELSEVIER

Radiotherapy and Oncology 74 (2005) 235–245

RADIOTHERAPY & ONCOLOGY

www.elsevier.com/locate/radonline

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

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

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

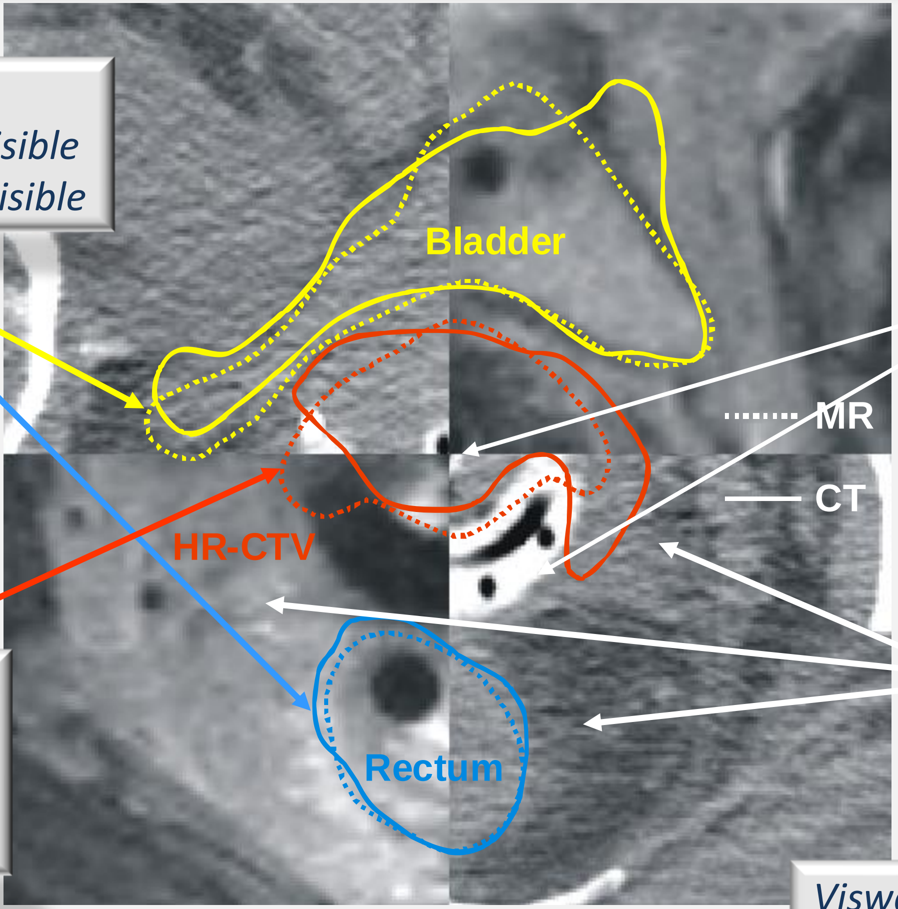
Richard Pötter[a,*], Christine Haie-Meder[b], Erik Van Limbergen[c], Isabelle Barillot[d], Marisol De Brabandere[c], Johannes Dimopoulos[a], Isabelle Dumas[b], Beth Erickson[e], Stefan Lang[a], An Nulens[c], Peter Petrow[f], Jason Rownd[e], Christian Kirisits[a]

Imaging protocols MRI and CT

Key issues when using CT or MRI for IGABT

Target, OARs, Applicator, Patho-anatomical structures

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



Applicator
MRI↑
CT↑

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

patho-anatomical
Structures
MRI↑
CT ↓

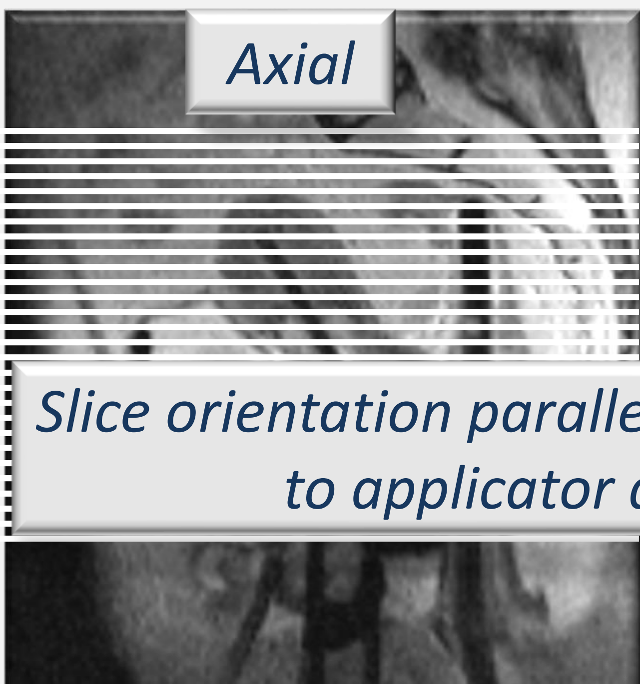
Viswanathan et al. IJROBP 2007

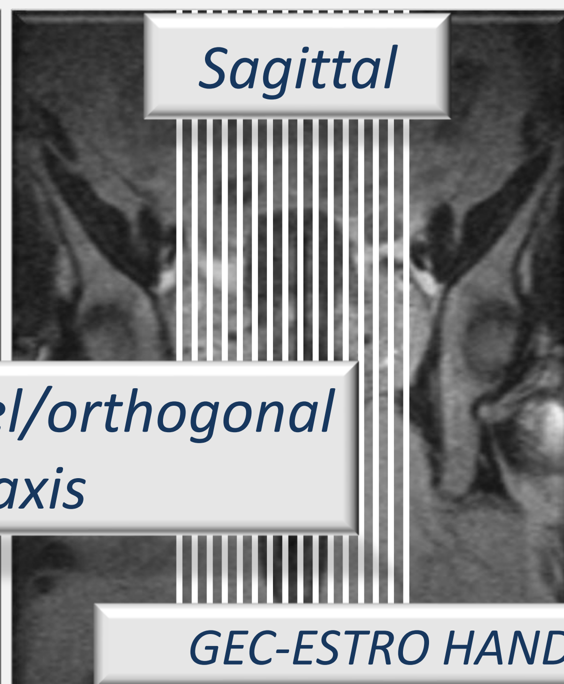
Imaging protocols MRI a

Key issues when using MRI f

Improvement with specific

PLANE	COVERAGE-BOR	
T2 axial	discus L5	infer
T2 sagittal	pelvic wall (obturator muscle)	pelvi
T2 frontal or frontal oblique	entire uterus - cervix - vagina - tumor	

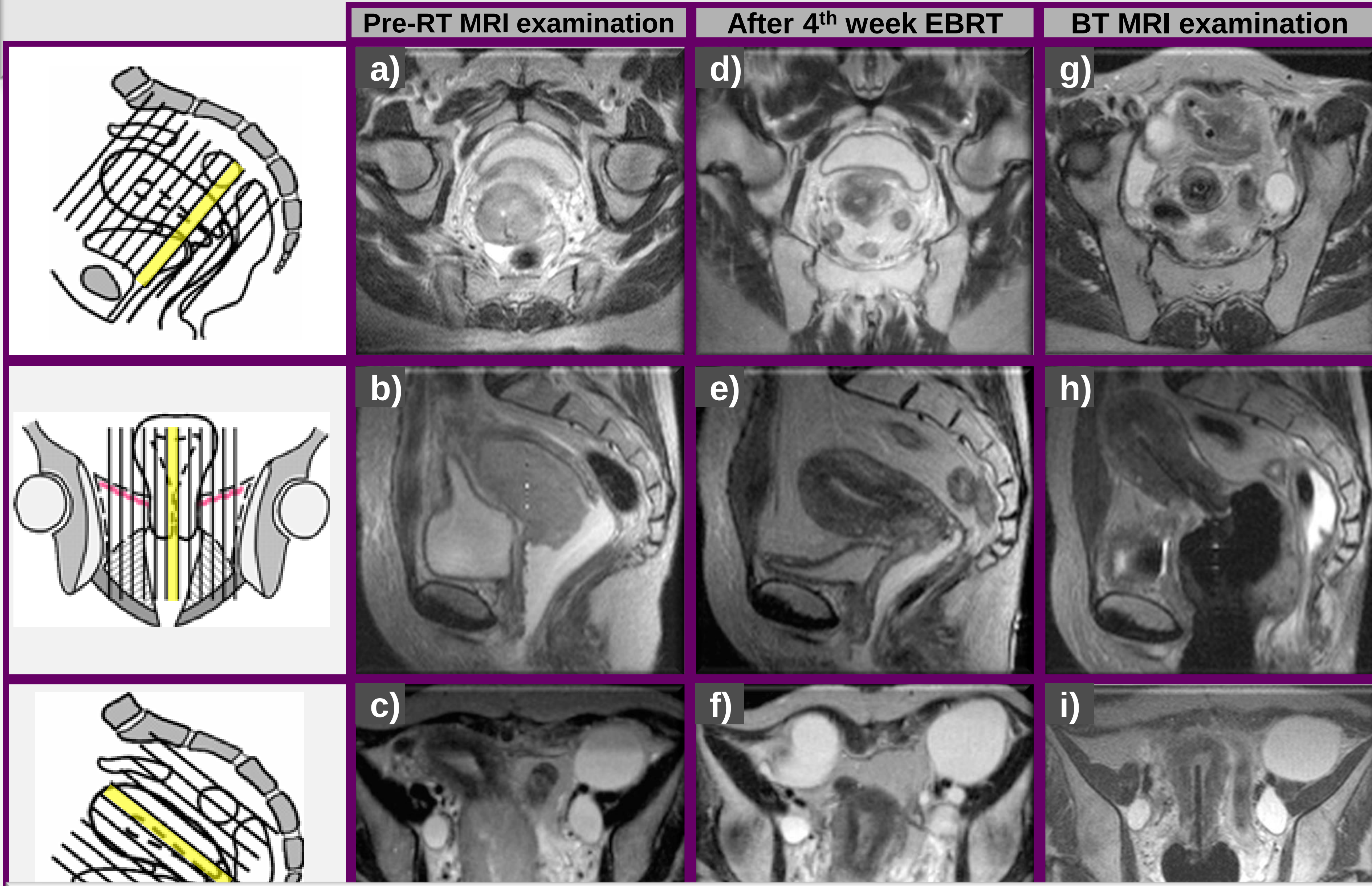




Slice orientation parallel/orthogonal to applicator axis

GEC-ESTRO HANDBOOK OF BRACHYTHERAPY

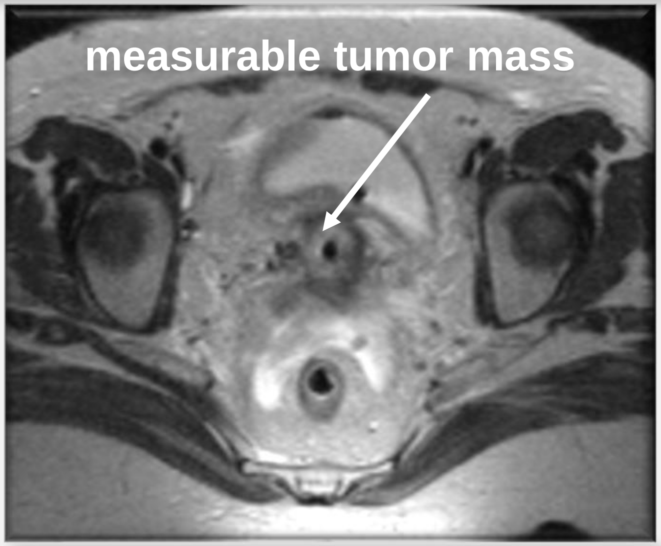
Imaging protocols MRI and CT

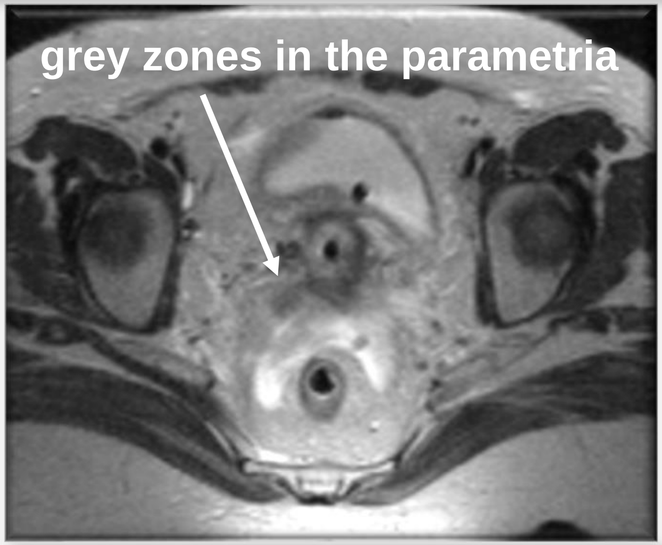


GYN GEC ESTRO recommendations Radiother Oncol 2012

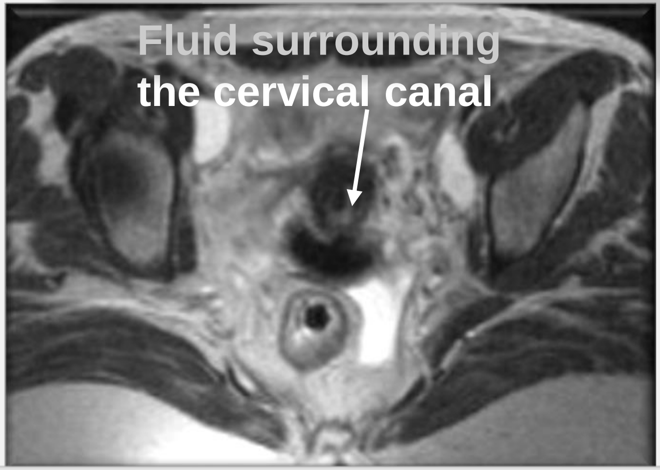
Imaging protocols MRI and CT

Key issues for image-guided radiotherapy



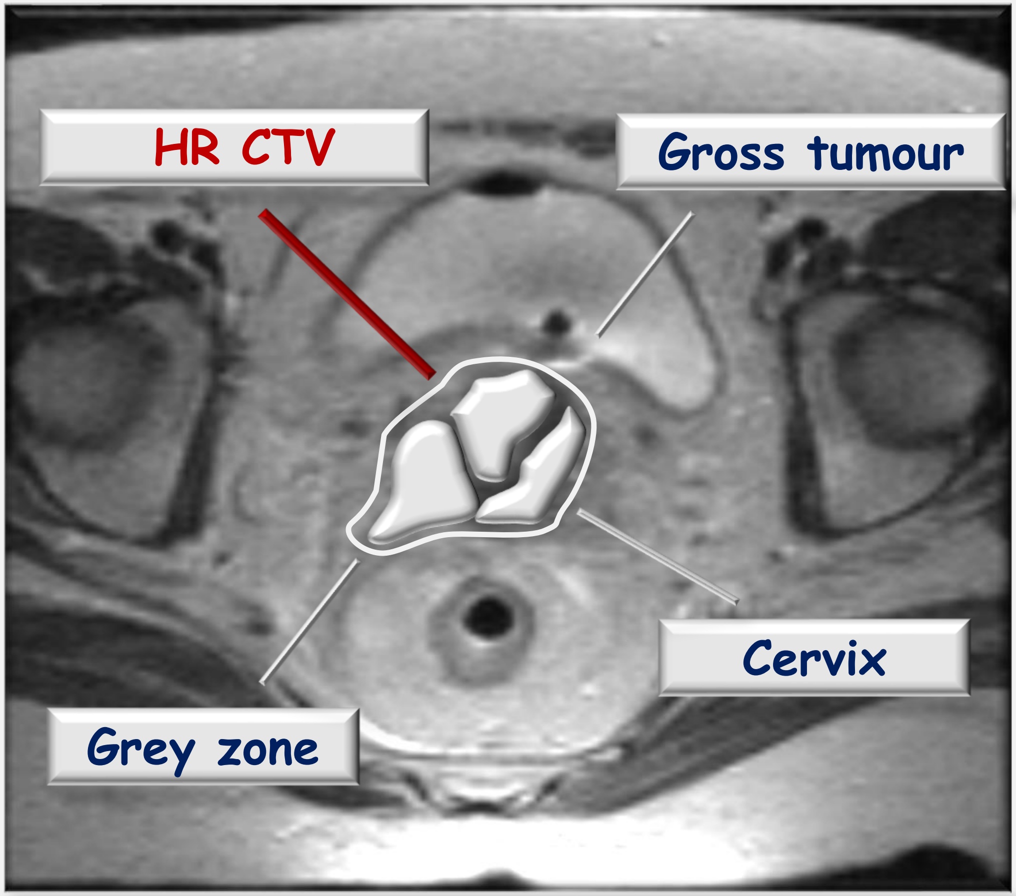


HR-CTV



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

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



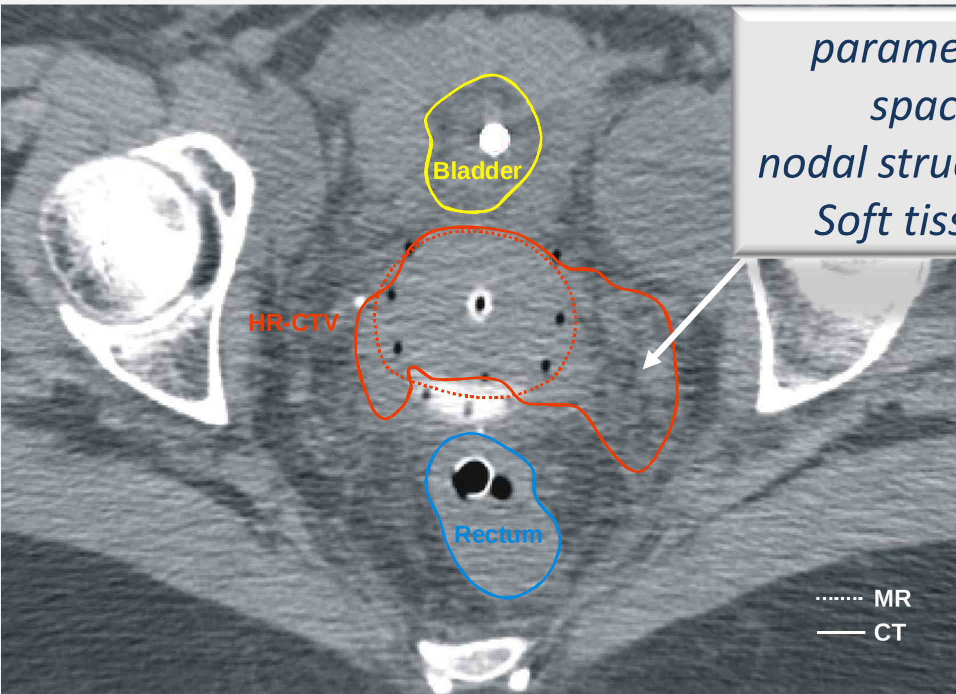
Imaging protocols MRI and CT
Key issues when using CT for IGABT

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

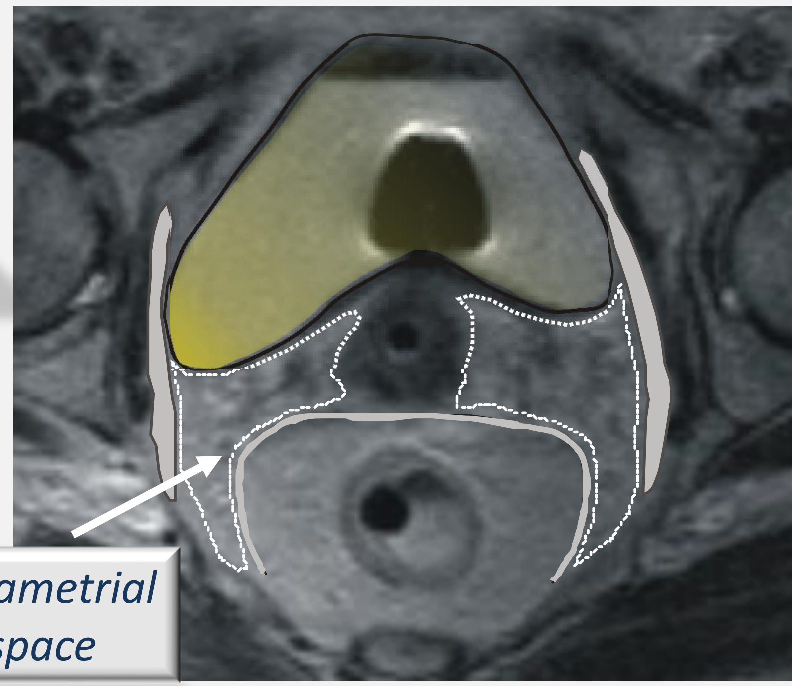
GTV-contouring as it is done on MRI is not possible on CT!

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

Patho-anatomical structures CT/MRI



parametrial space
nodal structures?
Soft tissue?



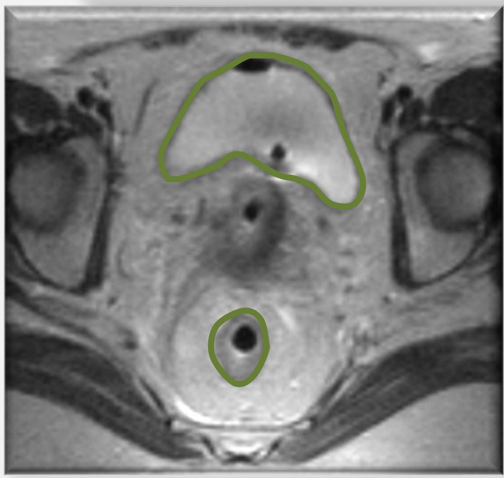
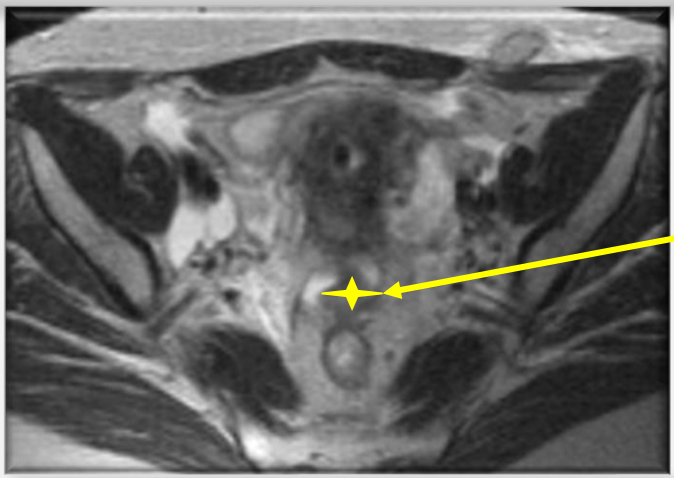
parametrial space

Viswanathan et al. IJROBP 2007

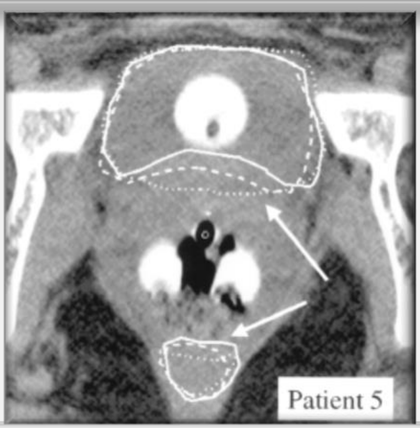
Dimopoulos et al. IJROBP 2006

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

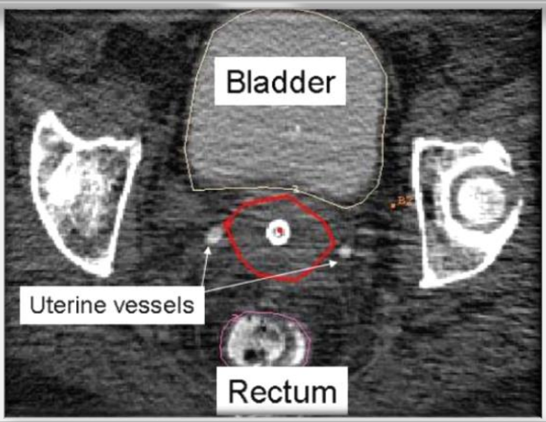
Organs at Risk - MRI


Organs at Risk - CT



Saarnak et al. / R&O 2000

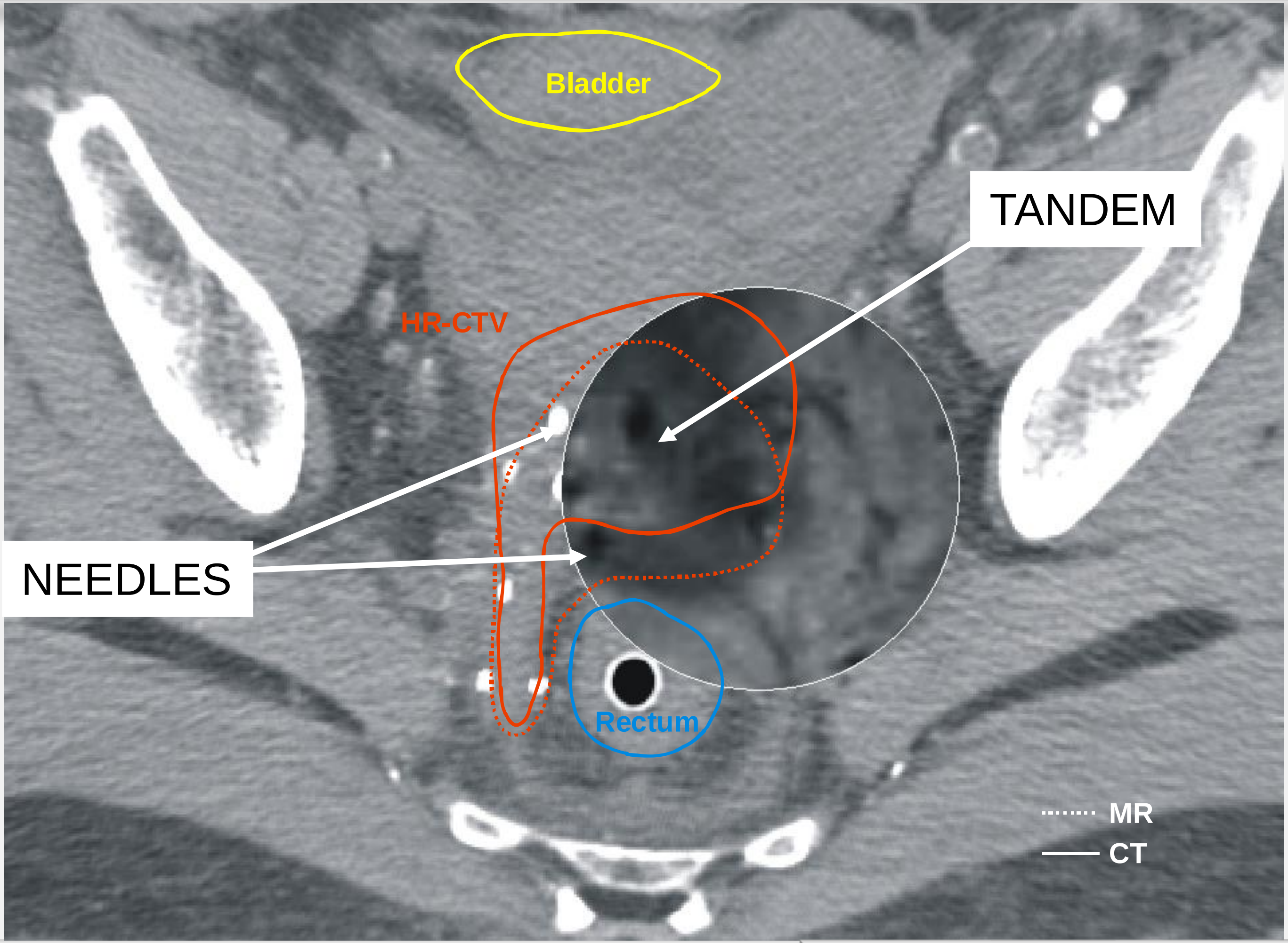


Viswanathan et al. IJROBP 2007

Imaging protocols MRI and CT

Key issues when using MRI or CT for IGABT

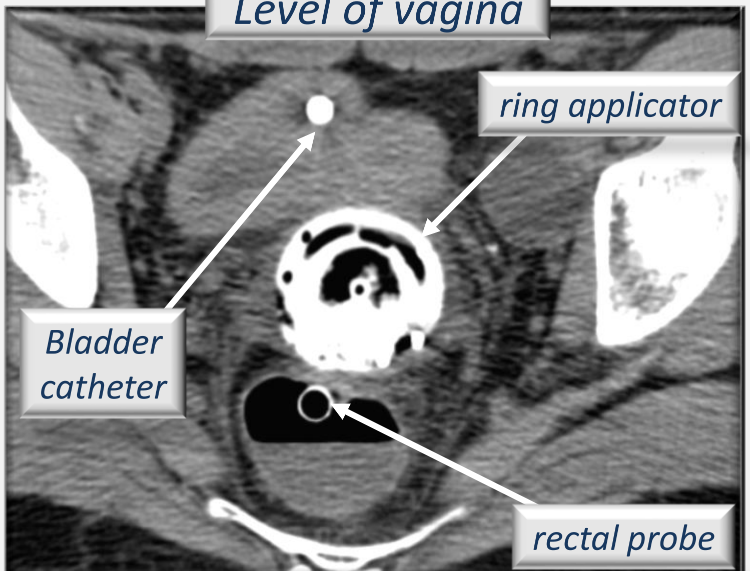
Applicator MRI /CT

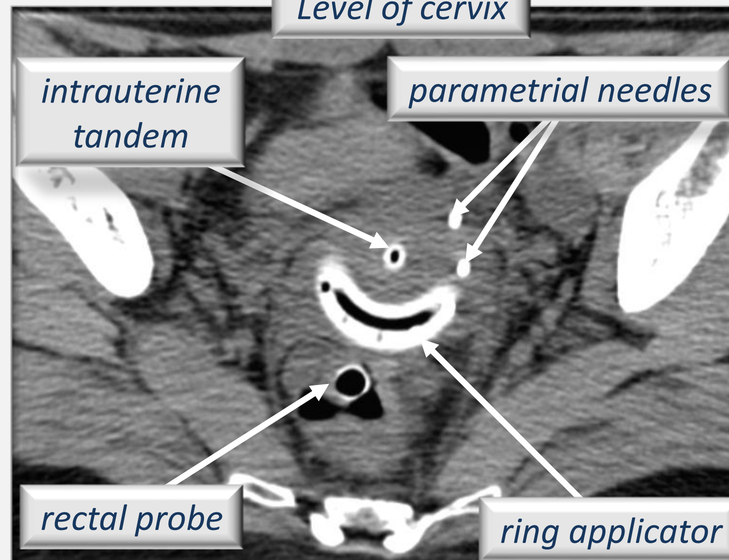


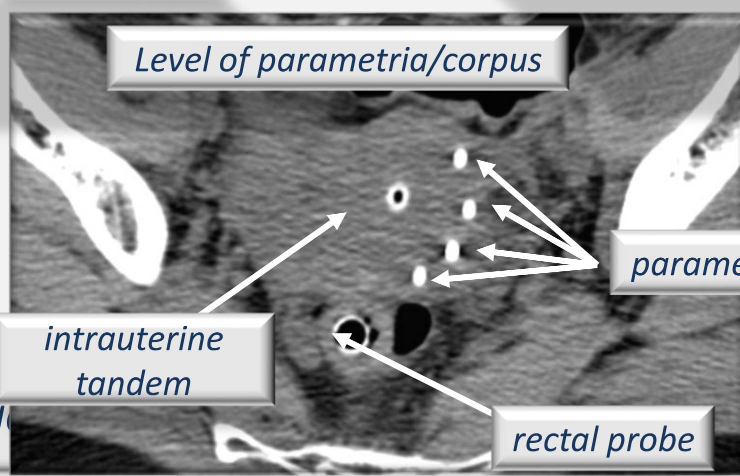
Viswanathan et al. IJROBP 2007

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

Applicator CT

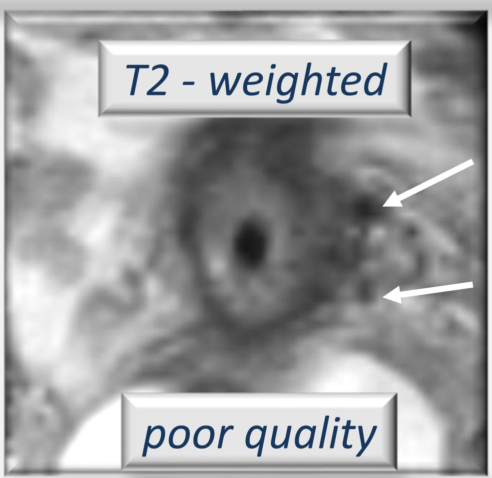


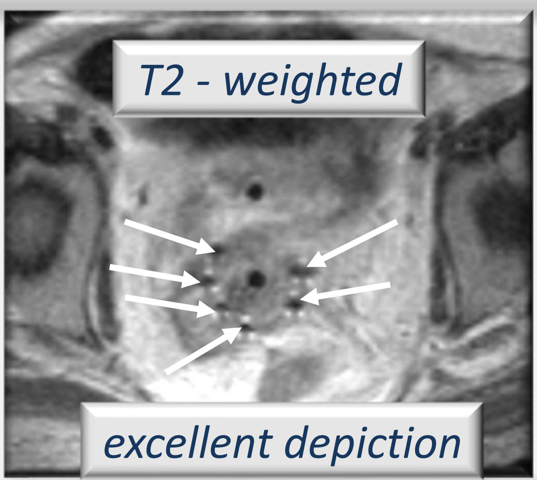


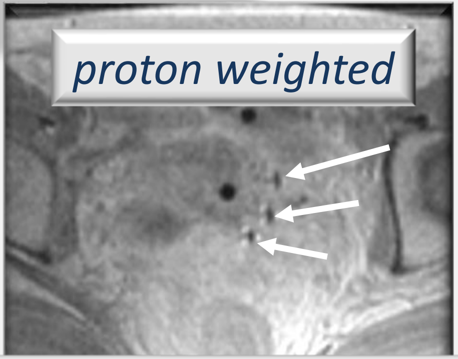


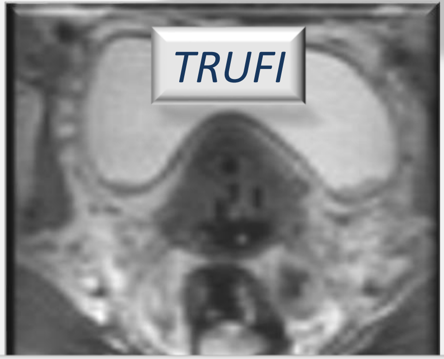
Imaging protocols MRI and CT
Key issues when using MRI for IGABT

Applicator MRI







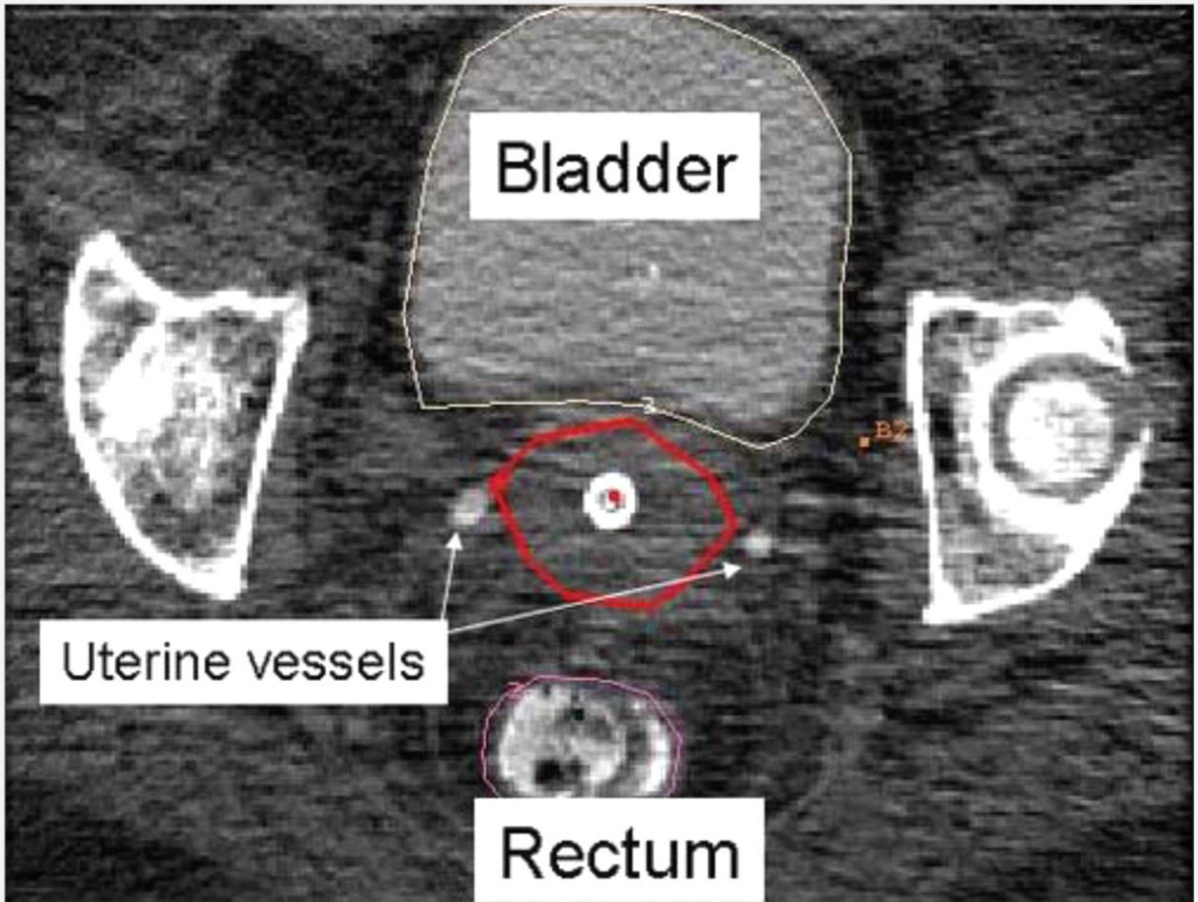


improvement for needles / loss of soft tissue depiction quality

Imaging protocols MRI and CT

Key issues when using CT for IGABT

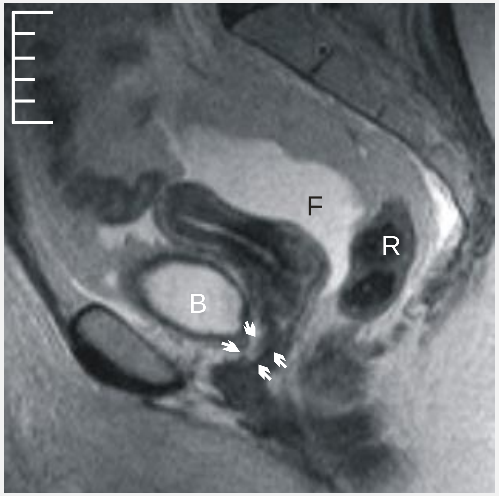
Improvement with specific protocol



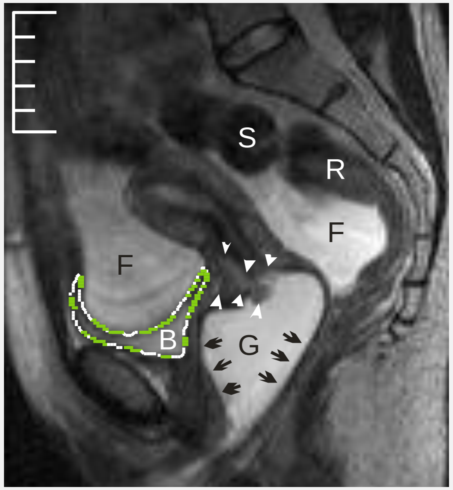
Viswanathan et al. IJROBP 2007

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

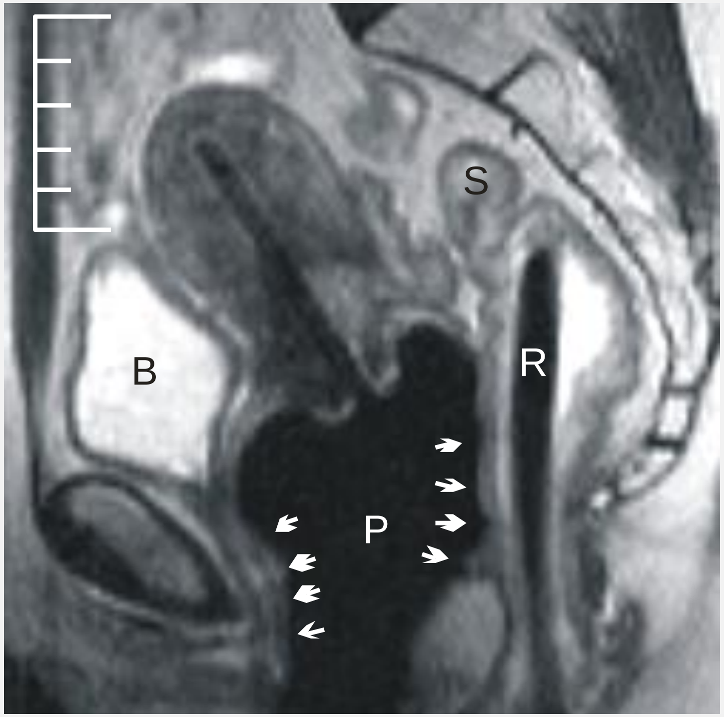
Improvement with specific protocol



at diagnosis without vaginal marking



at diagnosis with vaginal marking



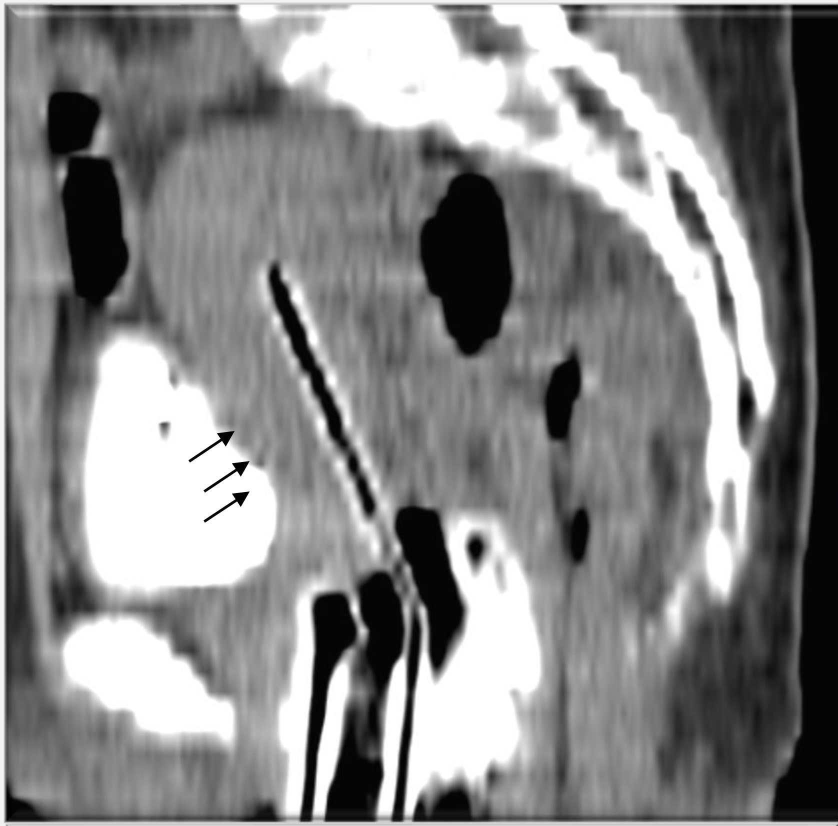
at brachytherapy with specific protocol

Dimopoulos et al. IJROBP 2006

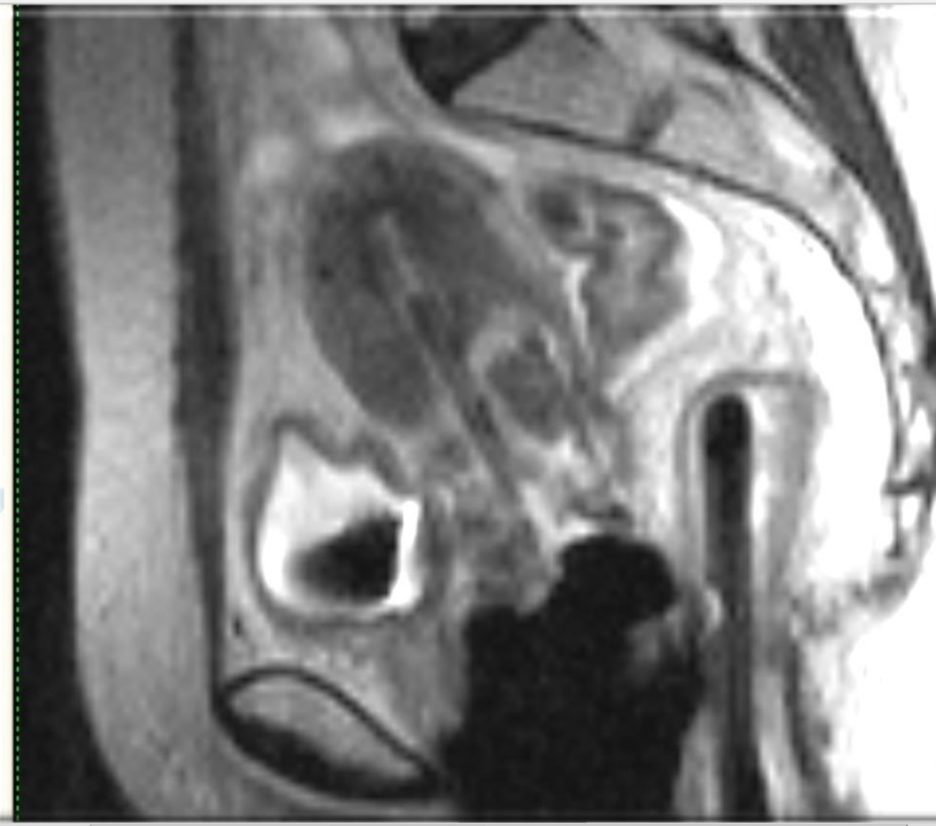
Imaging protocols MRI and CT

Key issues when using MRI or CT for IGABT

Multiplanar Imaging CT / only with reconstruction
(improvement with specific protocols and modern scanners)



uterine border/pre-vesical space invisible

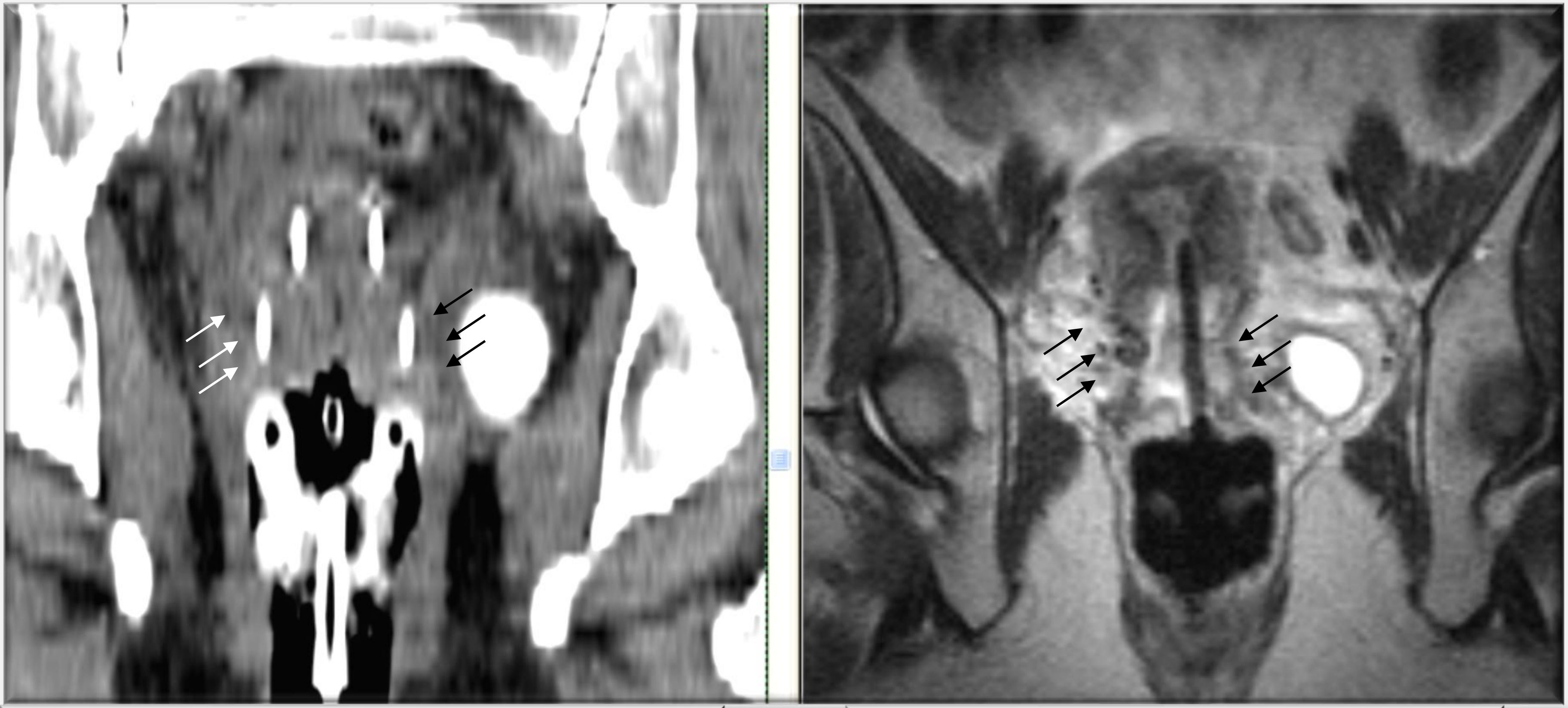


uterine border/pre-vesical space visible

Imaging protocols MRI and CT

Key issues when using MRI or CT for IGABT

Multiplanar Imaging CT / only with reconstruction
(improvement with specific protocols and modern scanners)



Lateral uterine/tumour border not visible

Lateral uterine/tumour border visible

Imaging protocols MRI and CT

Image acquisition protocol and patient preparation
For pre-RT MRI scan and BT MRI scan

PROTOCOL	INTRACAVITARY FILLING / DEVICES	SEQUENCE			CM[2]	PLANE		COVERAGE	
		priority	n°	type		orientation	inclination	upper / lateral / anterior	lower / lateral / posterior
		M	1	T2 FSE	no	para-axial	yes, perpendicular to long axis of cervix uteri	entire uterus - cervix - vagina - tumor	entire uterus - cervix - vagina - tumor
		M	2	T2 FSE	no	sagittal	none	pelvic wall (obturator muscle)	pelvic wall (obturator muscle)
pre-RT MRI scan	intravaginal contrast	M	3	T2 FSE	no	para-coronal	yes, parallel to the long axis of cervix uteri	entire uterus - cervix - vagina - tumor	
		M	4	T2 FSE	no	axial	none	discus L4-L5	inferior border of symphysis pubis, vagina if involved distally, inguinal regions if distal vaginal involvement
		O	5	T1 FSE or 3D GRE	no	axial	none	discus L4-L5	inferior border of symphysis pubis, inguinal regions if distal vaginal involvement
		O	6	T1 FSE or 3D GRE	yes	sagittal	none	entire uterus - cervix - vagina - tumor	entire uterus - cervix - vagina - tumor
		O	7	T1 FSE or 3D GRE	yes	axial	none	entire uterus - cervix - vagina - tumor	entire uterus - cervix - vagina - tumor
BT MRI scan	no intravaginal contrast	M	1	T2 FSE	no	para-axial	yes, perpendicular to intrauterine device	above uterine corpus	>2-3cm below lower surface of vaginal applicator and vagina if involved distally
	intravaginal applicator	M	2	T2 FSE	no	para-sagittal	yes, parallel to intrauterine device	pelvic wall (obturator muscle)	pelvic wall (obturator muscle)
		M	3	T2 FSE	no	para-coronal	yes, parallel to intrauterine device	entire uterus - cervix - vagina - tumor	
		O	4	T2 FSE	no	axial	none	above uterine corpus	>2-3cm below lower surface of vaginal applicator and vagina if involved distally
		O	5	3D T2 FSE isotropic	no	coronal or axial with reconstructions	none	large coverage inherent in this sequence	large coverage inherent in this sequence
		O	6	T1 FSE, FLASH (e.g. true fisp), T1 GRE 3D	no			at least whole applicator	at least whole applicator

GYN GEC ESTRO recommendations Radiother Oncol 2012

Imaging protocols MRI and CT

Image acquisition protocol and patient preparation
For pre-RT MRI scan and BT MRI scan

PROTOCOL	Sequence parameters											INTEREST
	Fatsat	TR (ms)	TE (ms)	ETL	FOV (cm²)	M(f)	M(p)	Nex	BW	SW	NPW	
pre-RT MRI scan	no	2000-5000	90-120	4-20	35 x 20	512	256	2	16	3-4	yes	tumor evaluation, pelvic lymph nodes, parametrium
	no	2000-5000	90-120	4-20	35 x 40	512	256	2	16	5	yes	tumor evaluation, pelvic lymph nodes
	no	2000-5000	90-120	4-20	35 x 20	512	256	2	16	3-4	yes	tumor evaluation, pelvic lymph nodes, parametrium
	no	2000-5000	90-120	4-20	35 x 40	512	256	2	16	5	yes	tumor evaluation, pelvic and inguinal (if distal vaginal involvement) lymph nodes, parametrium
	no/yes	500-700	10-20	NA	35 x 20	512	256	2	16	5-7	yes	pelvic and inguinal (if distal vaginal involvement) lymph node evaluation[12]
	no/yes	500-700	10-20	NA	35 x 20	256	256	2		3-5	yes	complication, tumour visualisation if not well seen on T2[12]
	no/yes	500-700	10-20	NA	35 x 20	256	256	2		3-5	yes	complication, tumour visualisation if not well seen on T2[12]
BT MRI scan	no	2000-5000	90-120	4-20	35 x 20	512	256	2	16	3-5	yes	target volume (GTV, HR CTV, IR CTV) and organ at risk evaluation/contouring, pelvic lymph nodes
	no	2000-5000	90-120	4-20	35 x 40	512	256	2	16	3-5	yes	target volume (GTV, HR CTV, IR CTV) and organ at risk evaluation/contouring, pelvic lymph nodes
	no	2000-5000	90-120	4-20	35 x 20	512	256	2	16	3-5	yes	target volume (GTV, HR CTV, IR CTV) and organ at risk evaluation/contouring, pelvic lymph nodes
	no	2000-5000	90-120	4-20	35 x 40	512	256	2	16	3-5	yes	for contouring in treatment planning systems which do not accept import of para-axial planes
	no	see references [22, 48-56] for sequence parameters										fusion with para-axial for applicator reconstruction and contouring fusion with para-axial for applicator reconstruction purpose

GYN GEC ESTRO recommendations Radiother Oncol 2012

ADVANCED MR IMAGING
FOR
EBRT AND IGABT

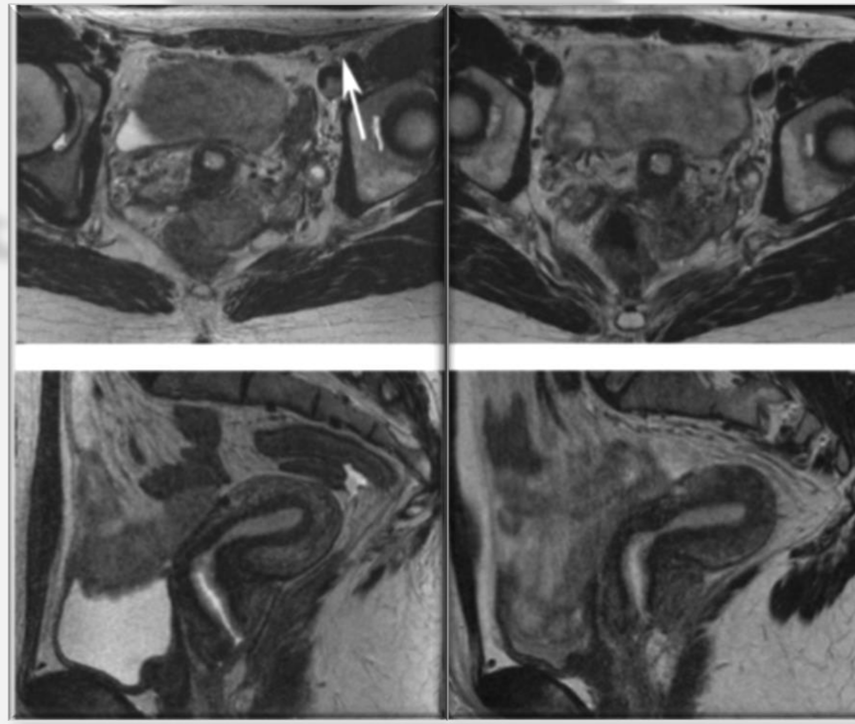
Imaging protocols MRI and CT

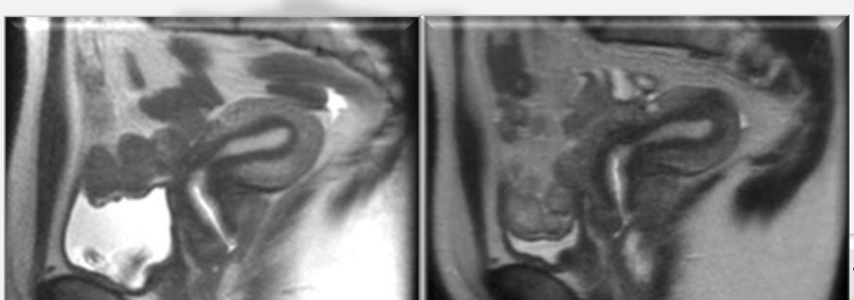
ADVANCED MRI

MRI

GYN BRACHY IMAGING MODALITIES

Cervical Cancer





3.0T versus 1.5T MRI- *image quality and contrast of zonal anatomy and cervical structure superior on 3.0T*

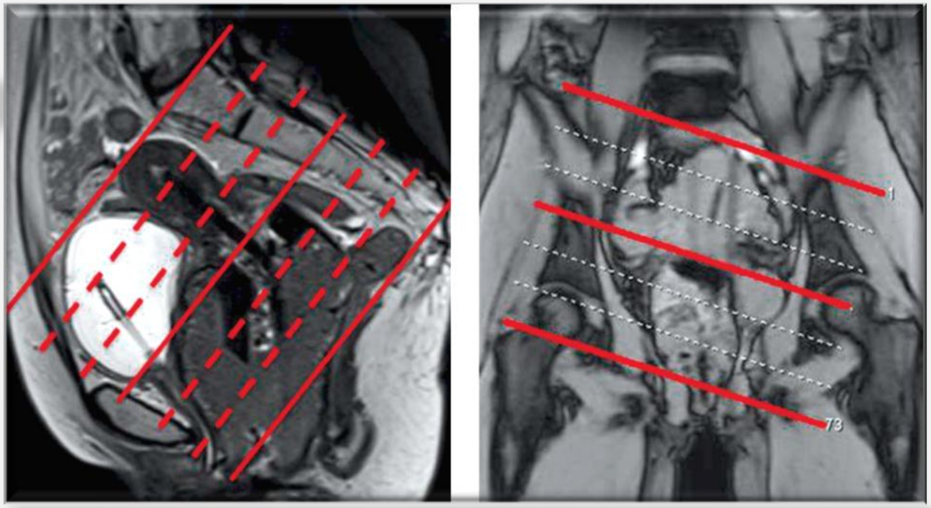
taoka et al. J MAGN RES IMAG 2007; 25: 527–534.

Imaging protocols MRI and CT
ADVANCED MRI

MRI

GYN BRACHY IMAGING MODALITIES

Cervical Cancer



3.0T MRI interobserver Study

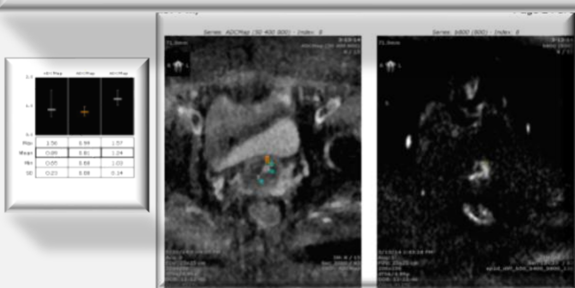
2D versus 3D T2 weighted Imaging

2D double oblique sequence superior due to less motion artefacts Less scanning time

Dempsey et al. J Contemp Brachyterapy 2014; 6(1): 3-9

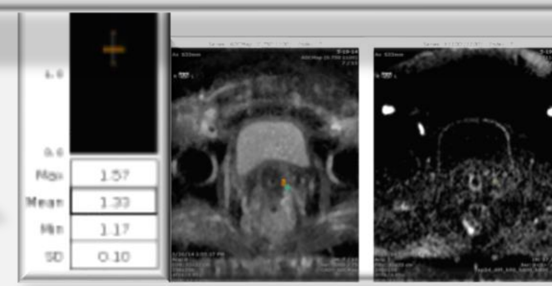
Imaging protocols MRI and CT

ADVANCED MRI

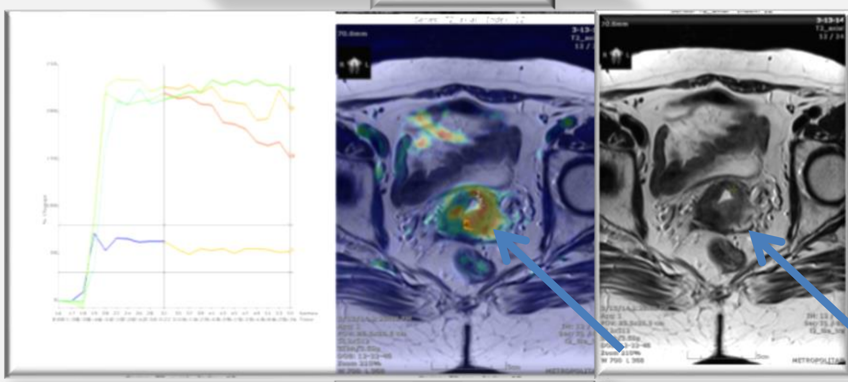


Diffusion

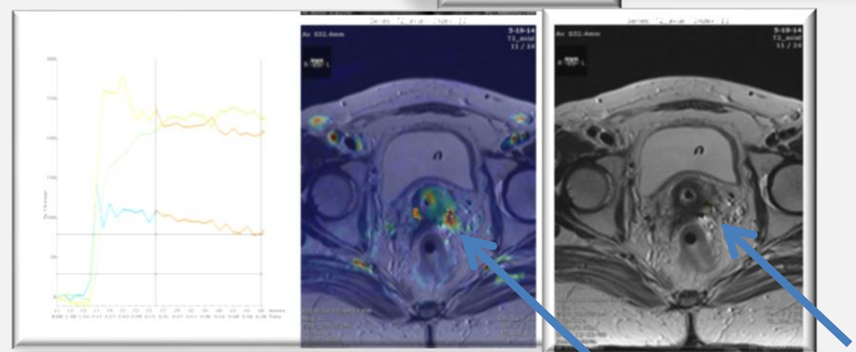
Current investigation: Dimopoulos JCA, Varaki K et al.



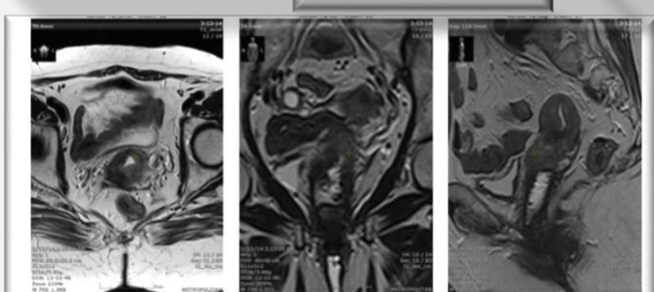
Diffusion



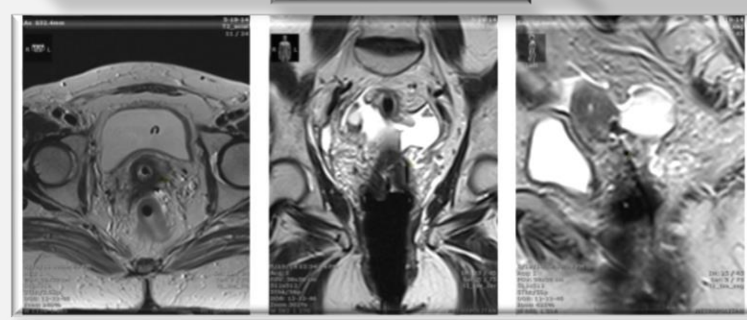
Perfusion DCE



Perfusion DCE



T2 weighted images



T2 weighted images

Imaging protocols MRI and CT
Conclusions

Imaging modalities for EBRT :

-**CT = gold standard for EBRT**

Key issuses for image acquisition and patient preparation:

IV and oral contrast
Delayed acquisition for bladder
Filled bladder
Patient positioning: e.g. belly board
Dietary advices
Most authors recommend repetitive-imaging, especially for IMRT

-MRI may assist delineation for EBRT due to fusion with CT, but it is required for IGABT

specific protocol is required (see GYN GEC ESTRO recommendations)

Imaging modalities for BT:

-**MRI = gold standard for BT**

Key issues for image acquisition:

see GYN GEC ESTRO recommendations ***(ADVANCED MRI !!!)***

-**CT = alternate option (if MRI not available)**

Key issues for image acquisition

retrograde contrast to bladder
IV contrast
multiplanar imaging

GTV, CTV and OAR 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

Definitions (upcoming definitions in the frame of adaptive thinking)

GTV = Gross Tumor Volume

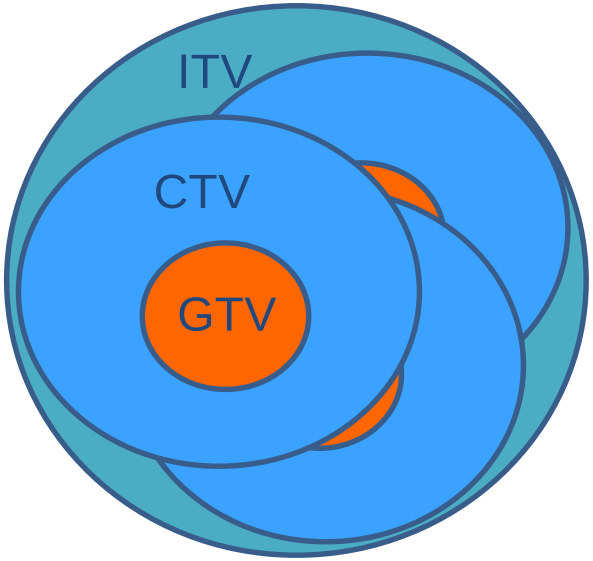
Macroscopic tumor, visible clinically and with imaging

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



ICRU reports

The CTV of the primary tumor always includes ?

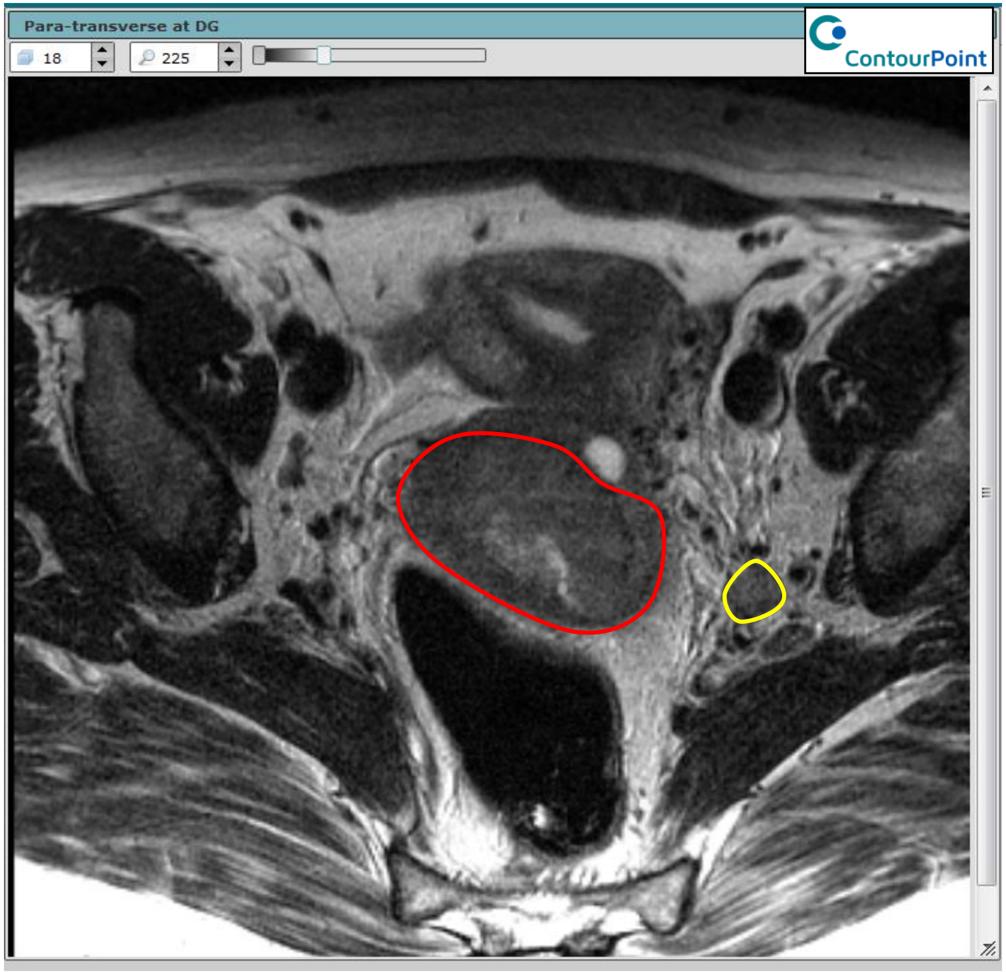
A. GTV
B. Remaining unaffected cervix
C. Parametria
D. Uterus
E. Upper Vagina
F. Involved organs (FIGO IVA)
G. Ovaries

GTV (GTV initial)

High signal intensity on T2 weighted MRI

GTV is composed of

- Primary tumor
- Macroscopic lymph node metastases

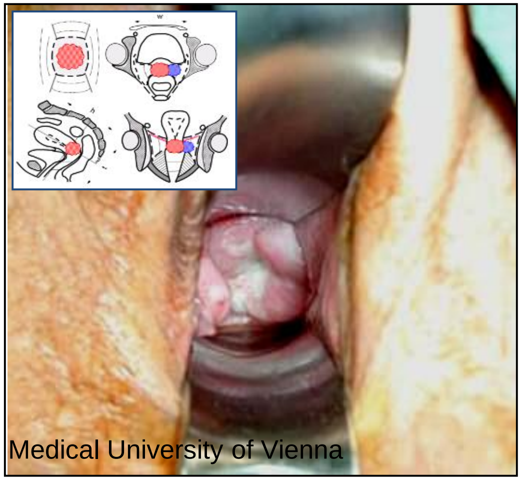


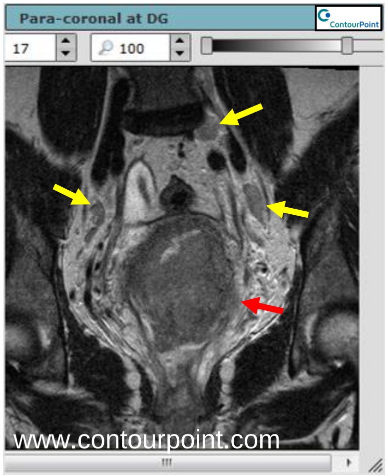
GTV

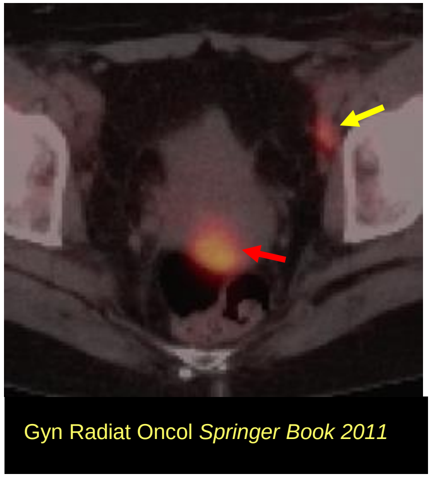
Consists of <u>Primary Tumor</u> and <u>nodal</u> GTV (GTV-T*initial* and GTV-N*initial*)

Different imaging modalities are currently used in clinical routine !

Clinical Examination | Imaging (MRI, PET CT, US) | Invasive







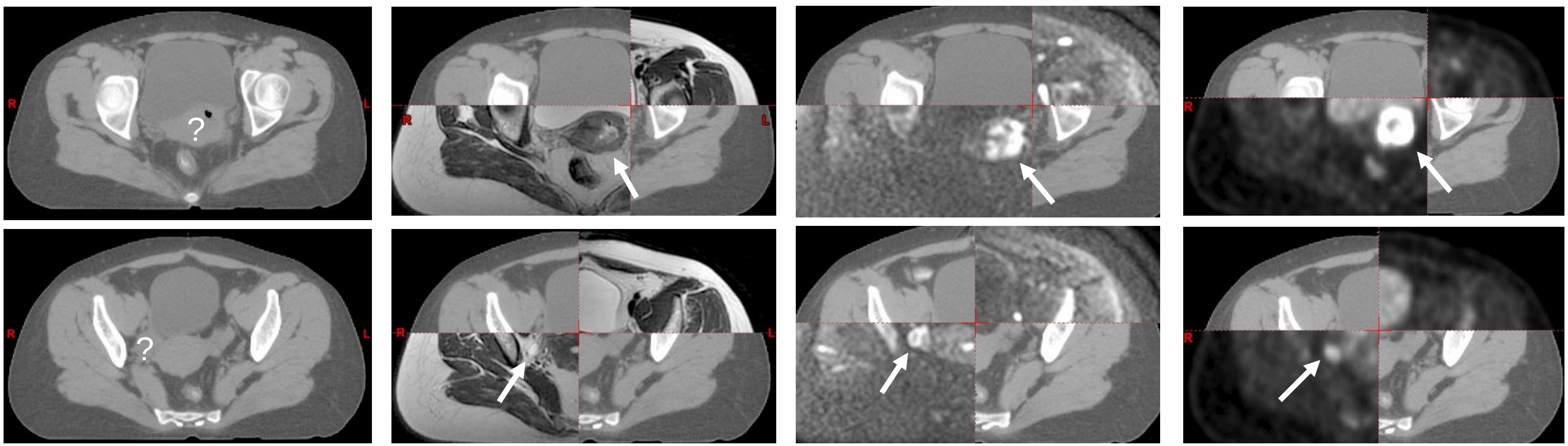
For GTV contouring combine information from different modalities !

Initial GTV contouring (“composite GTV“)

Co-registration of different imaging modalities?

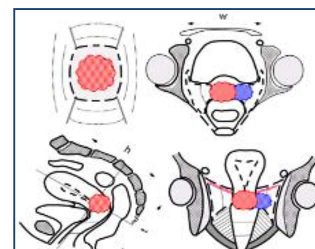
Imaging in <u>same (treatment) position:</u> CT, MRI, PET-CT simulator

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



Example; NCCCR, Doha, Qatar

- Combined imaging answers many questions, but opens some new ones...
- Don’t forget clinical judgment !



Initial CTV components

CTV has components of *Primary tumor* + *Nodal* CTV

Primary tumor related CTV components :

- GTV
- Remaining unaffected cervix
- Parametria
- Uterus
- Vagina
- Involved organs (FIGO IVA)

$\left.\begin{array}{l}\text{GTV}\\\text{Remaining unaffected cervix}\end{array}\right\}$ ***HR-CTV-T** initial*

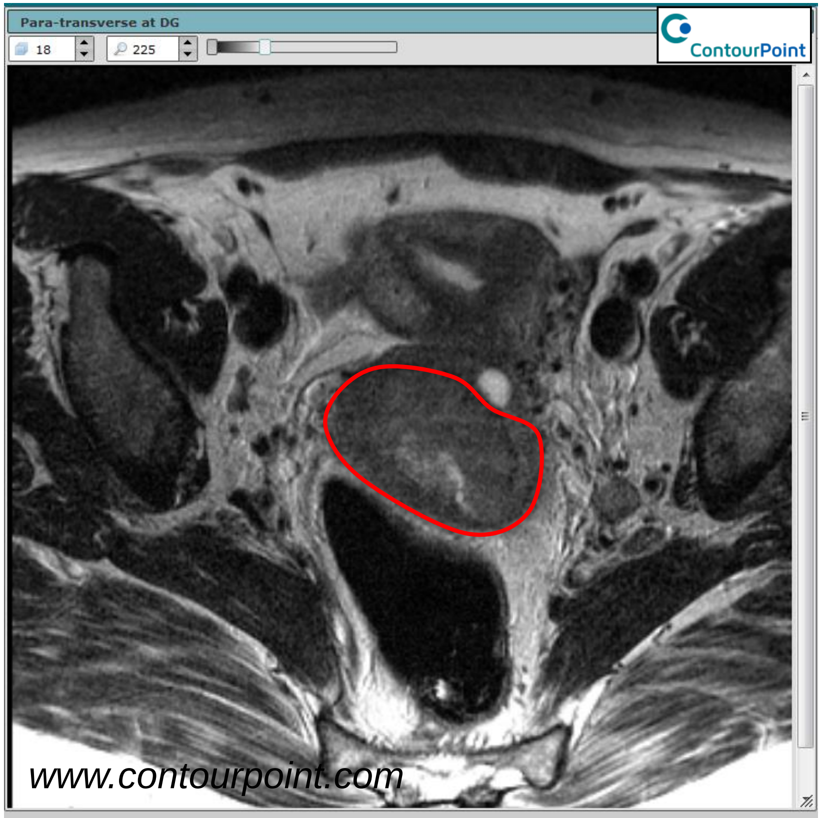
$\left.\begin{array}{l}\text{GTV}\\\text{Remaining unaffected cervix}\\\text{Parametria}\\\text{Uterus}\\\text{Vagina}\\\text{Involved organs (FIGO IVA)}\end{array}\right\}$ ***LR-CTV-T** initial*

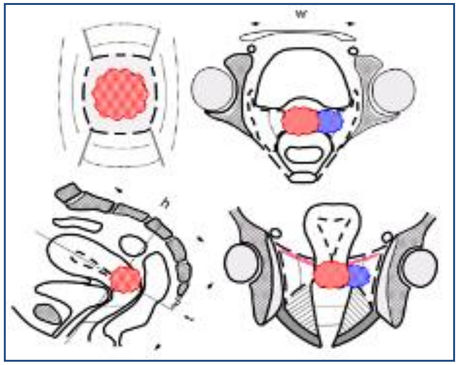
Nodal CTV related components:

- Elective draining lymphatic regions (vessel orientated) ***CTV-E***
- CTV's for affected lymph-nodes ***CTV-N***

Initial CTV components: ***GTV-T****initial*

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



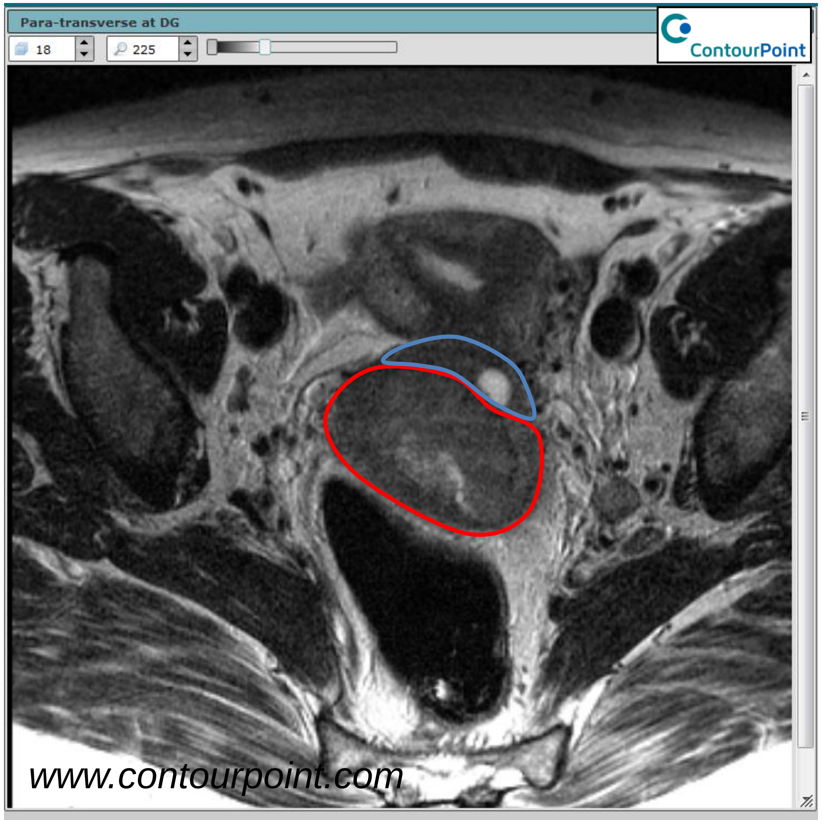


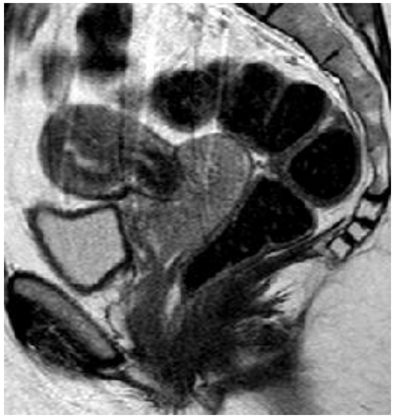
Initial CTV components: *HR-CTV-T*initial

- GTV
- Cervix

} *HR-CTV-T initial*

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

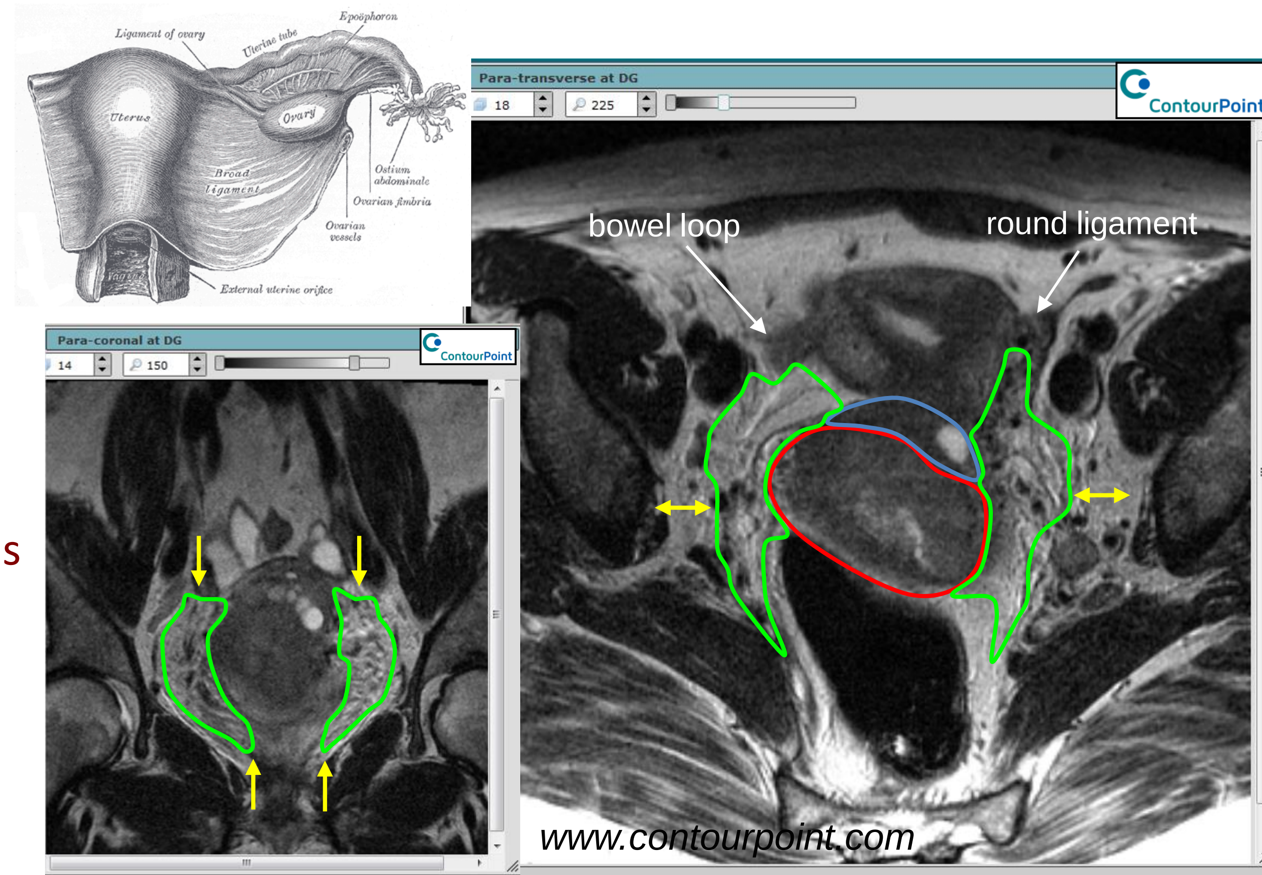




Initial CTV components: *LR-CTV-T*$_{initial}$

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

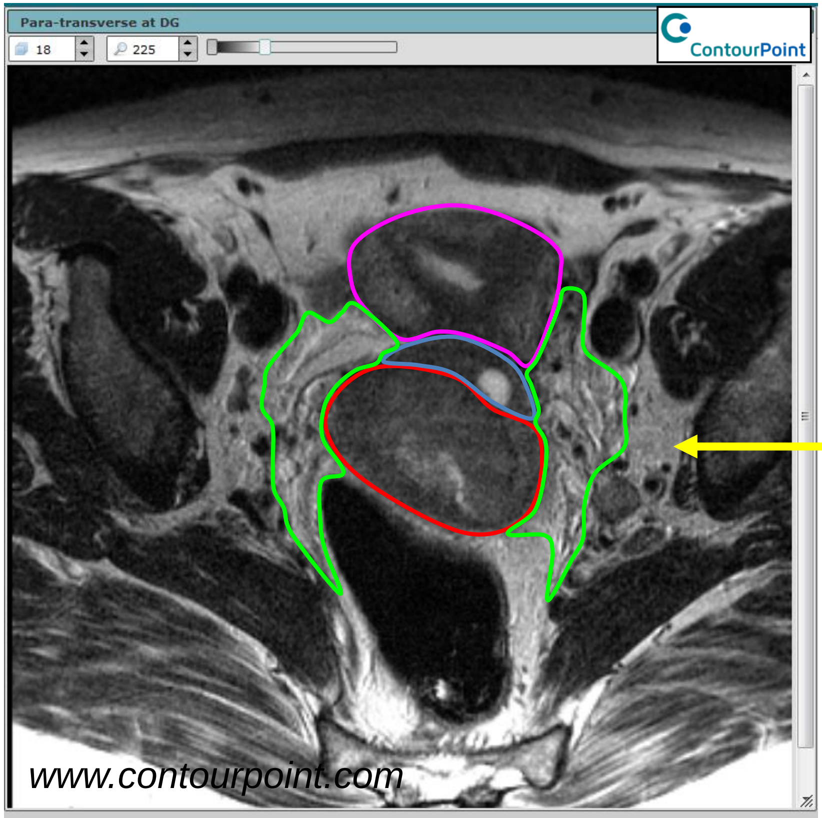
- GTV
- Cervix
- Parametria
- Uterus
- Upper Vagina
- Involved organs

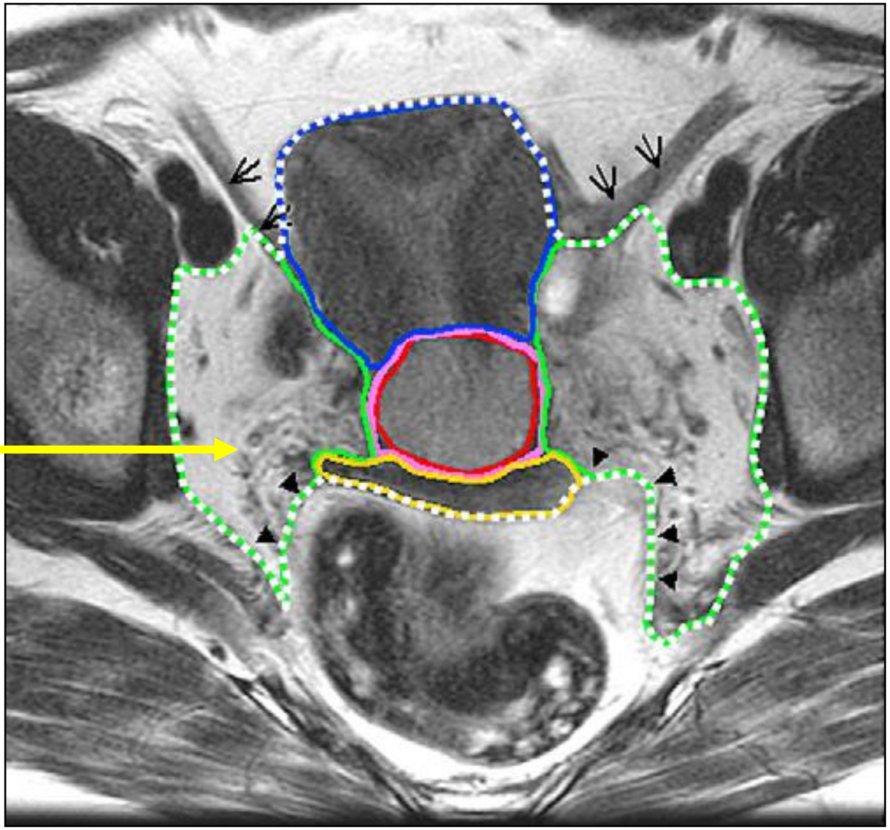


Anatomical boundaries

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 components: ***LR-CTV-T***$_{initial}$

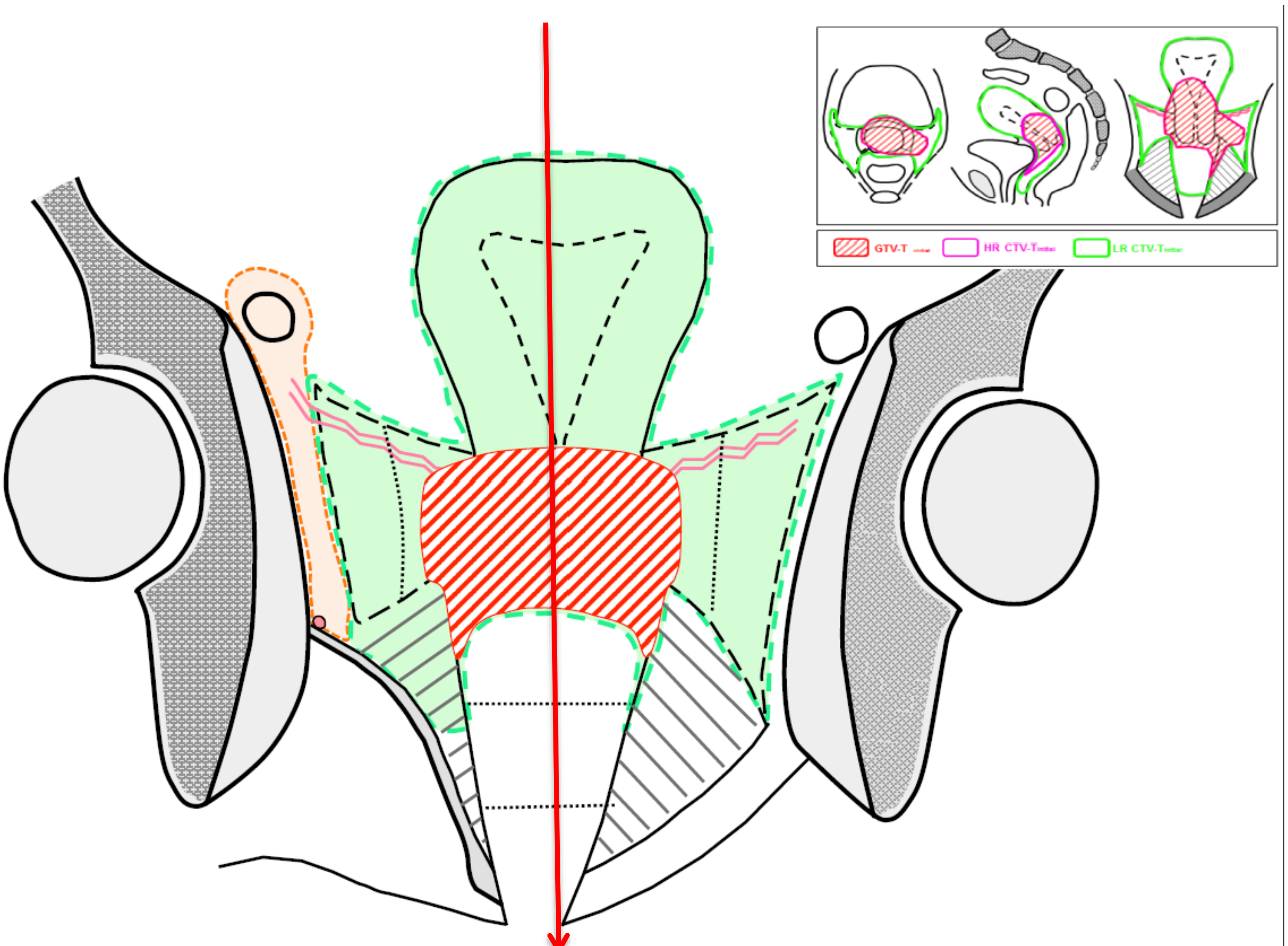




From original publication: Lim K, et al. IJROBP 2010:

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

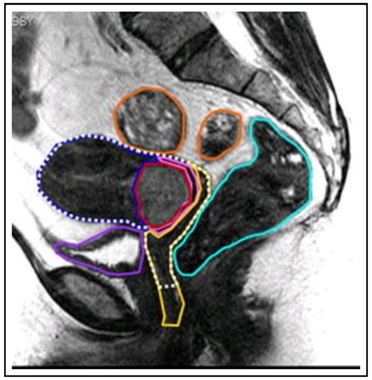
LR-CTV-$T_{initial}$ and CTV-E

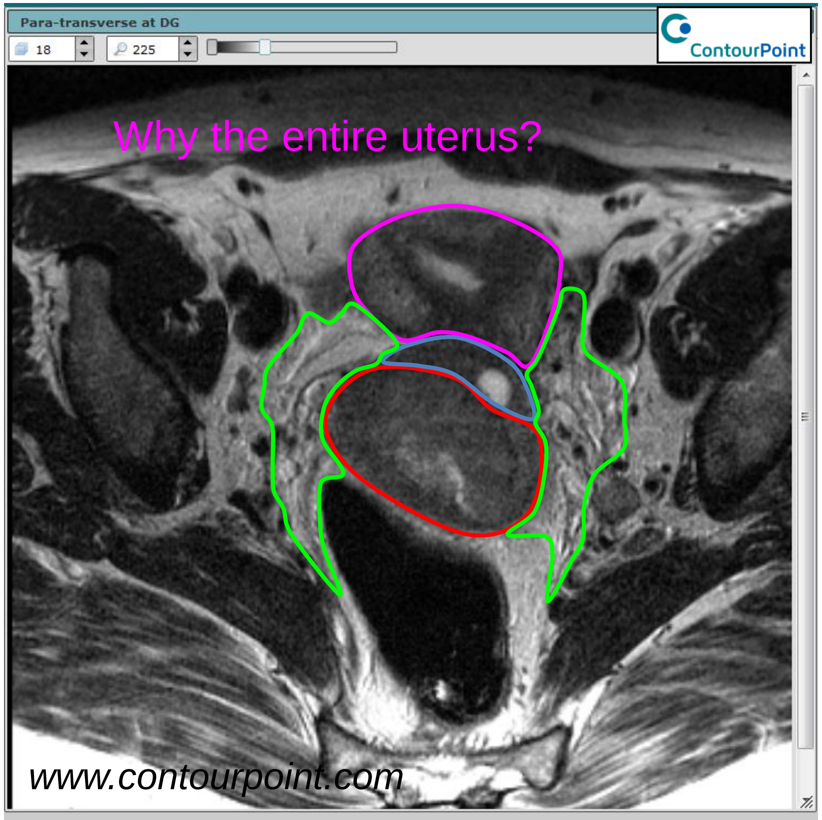


Courtesy Remi Nout

Initial CTV components: *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

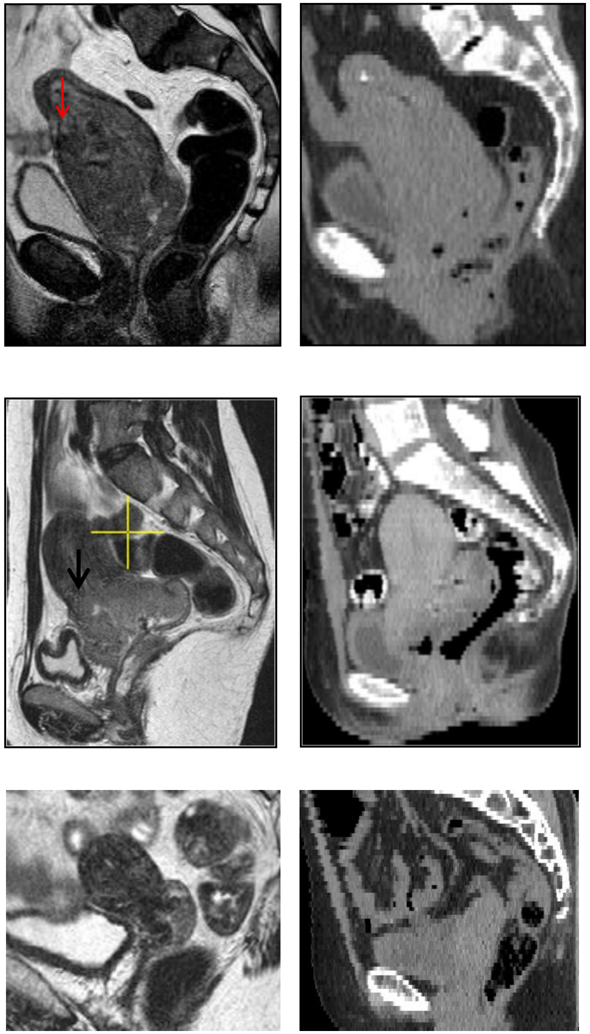
Trachelectomy, early stage disease[a]:

- 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

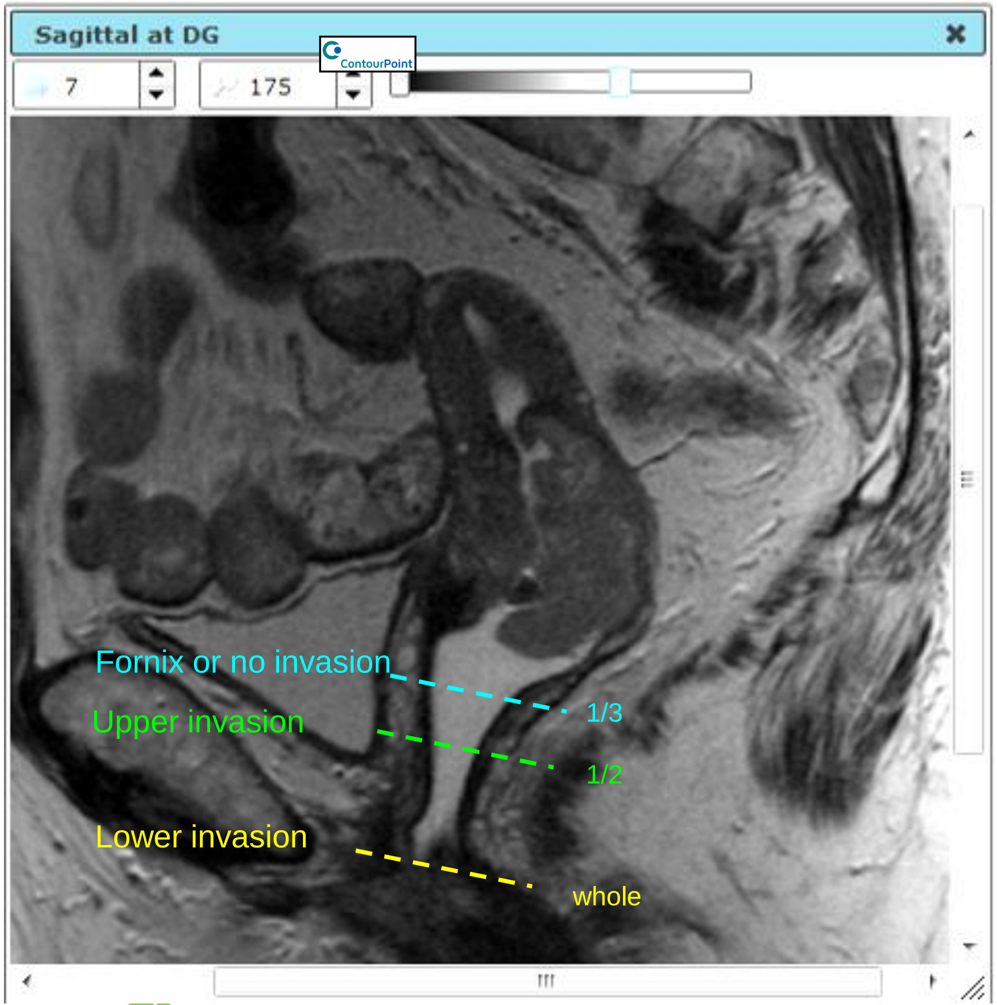


Lim K, et al. IJROBP 2010
[a]Plante M. Gynecol Oncol 2008
[b]Bali A, et al. Gynecol Oncol 2008
[c]Diaz JP, et al. Gynecol Oncol 2008
[d]Hertel H, et al. Gynecol Oncol 2006
[e]Nishio H, et al. Gynecol Oncol 2009

Initial CTV components: *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

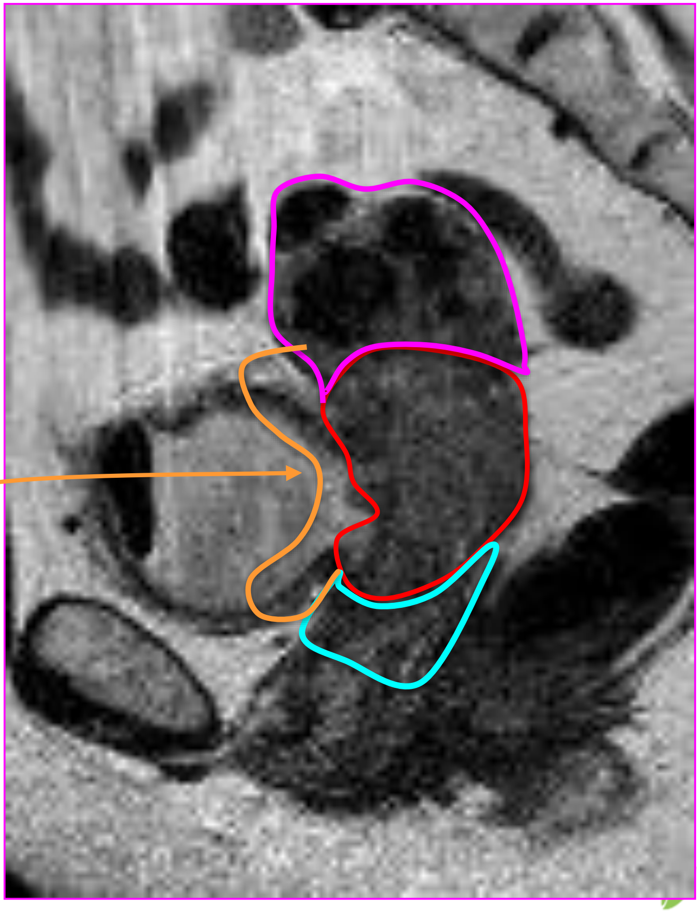
- GTV
- Cervix
- Parametria
- Uterus
- Vagina with varying length
- Involved organs (FIGO IVA)



Initial CTV components: *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)

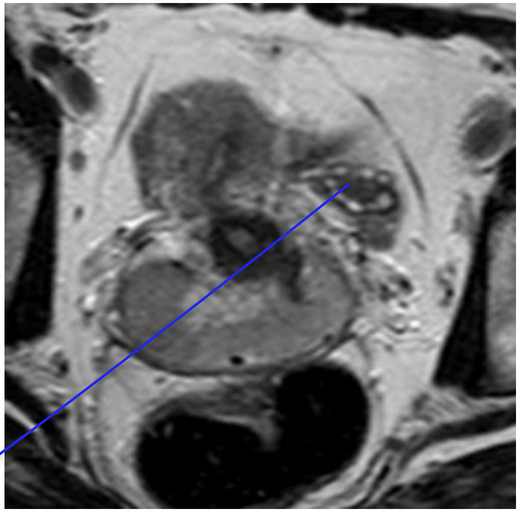


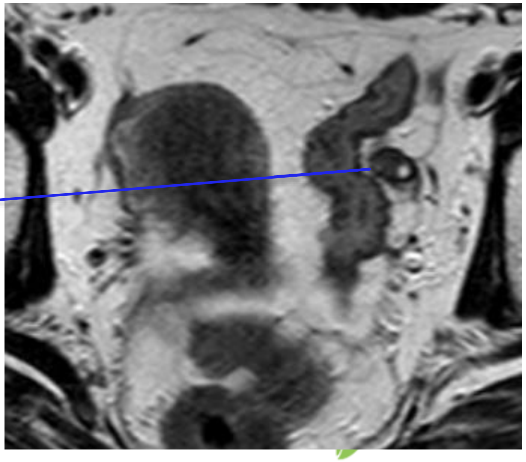
Initial CTV components: *LR-CTV-T*$_{initial}$

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

LR-CTV-T initial

- Ovaries ?





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 !

The CTV of the primary tumor always includes ?

A. GTV

B. Remaining unaffected cervix

C. Parametria

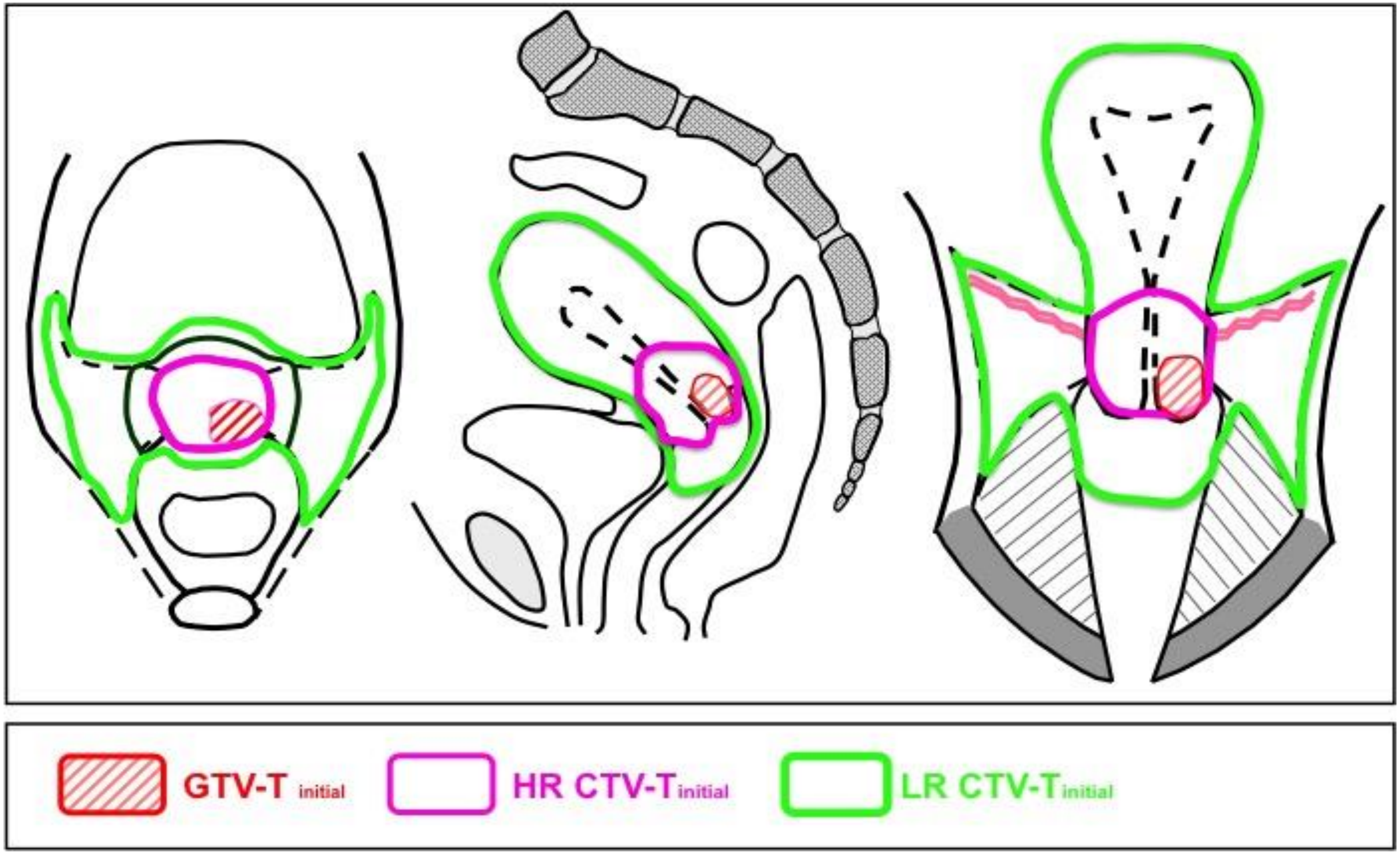
D. Uterus

E. Upper Vagina

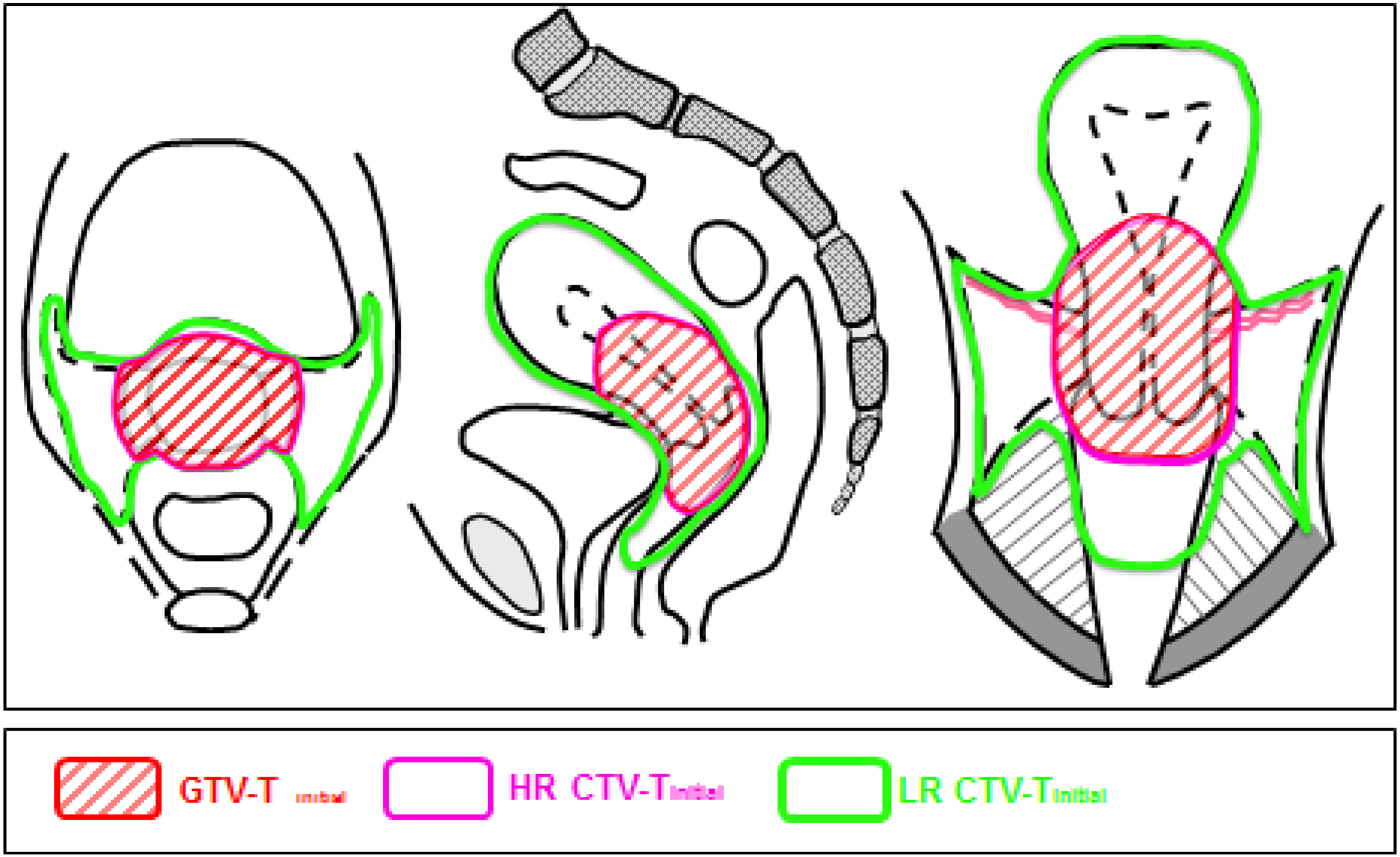
F. Involved organs (FIGO IVA)

G. Ovaries

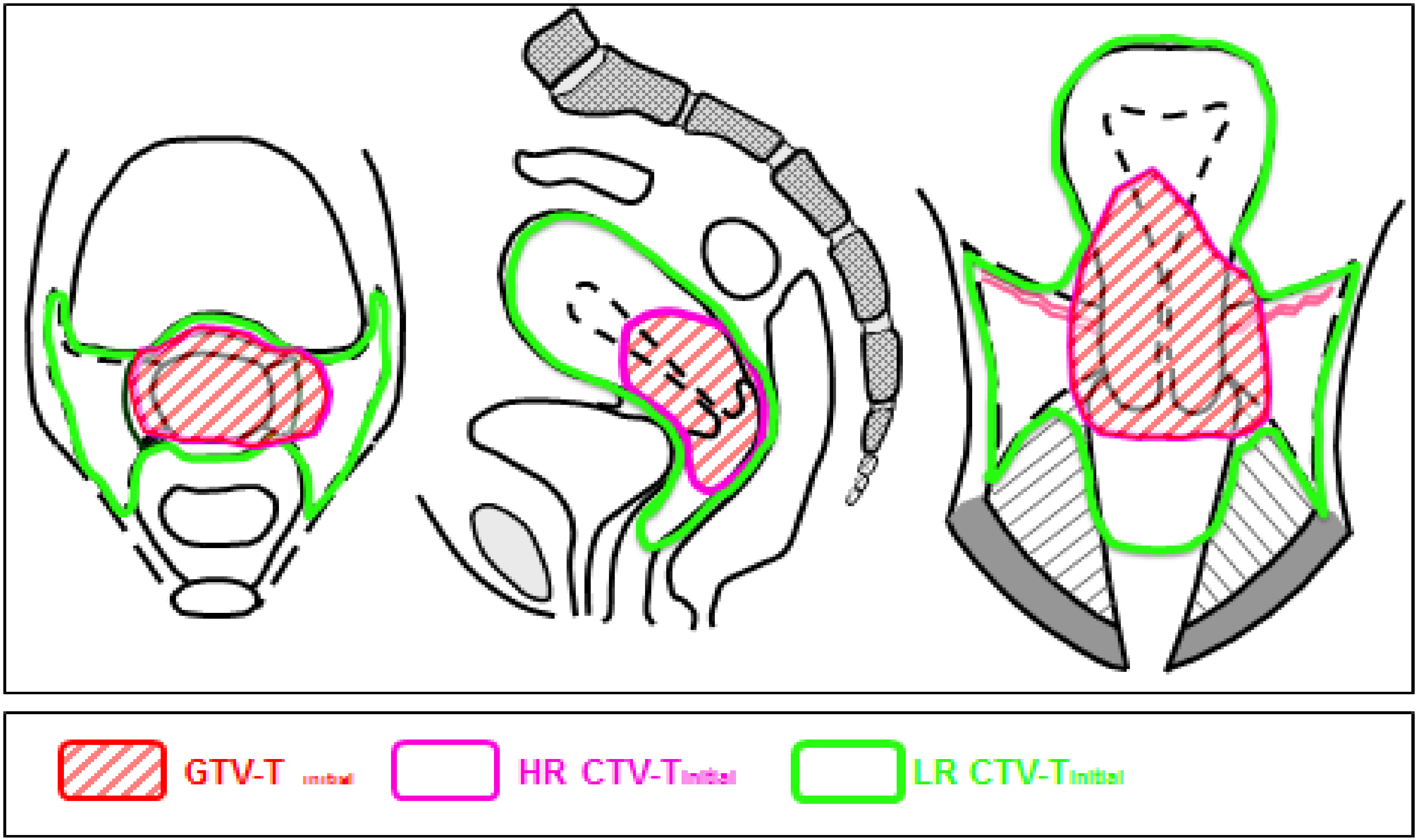
EMBRACE II
CTV-T: initial GTV, HR-CTV-T, LR-CTV-T for Stage IB1



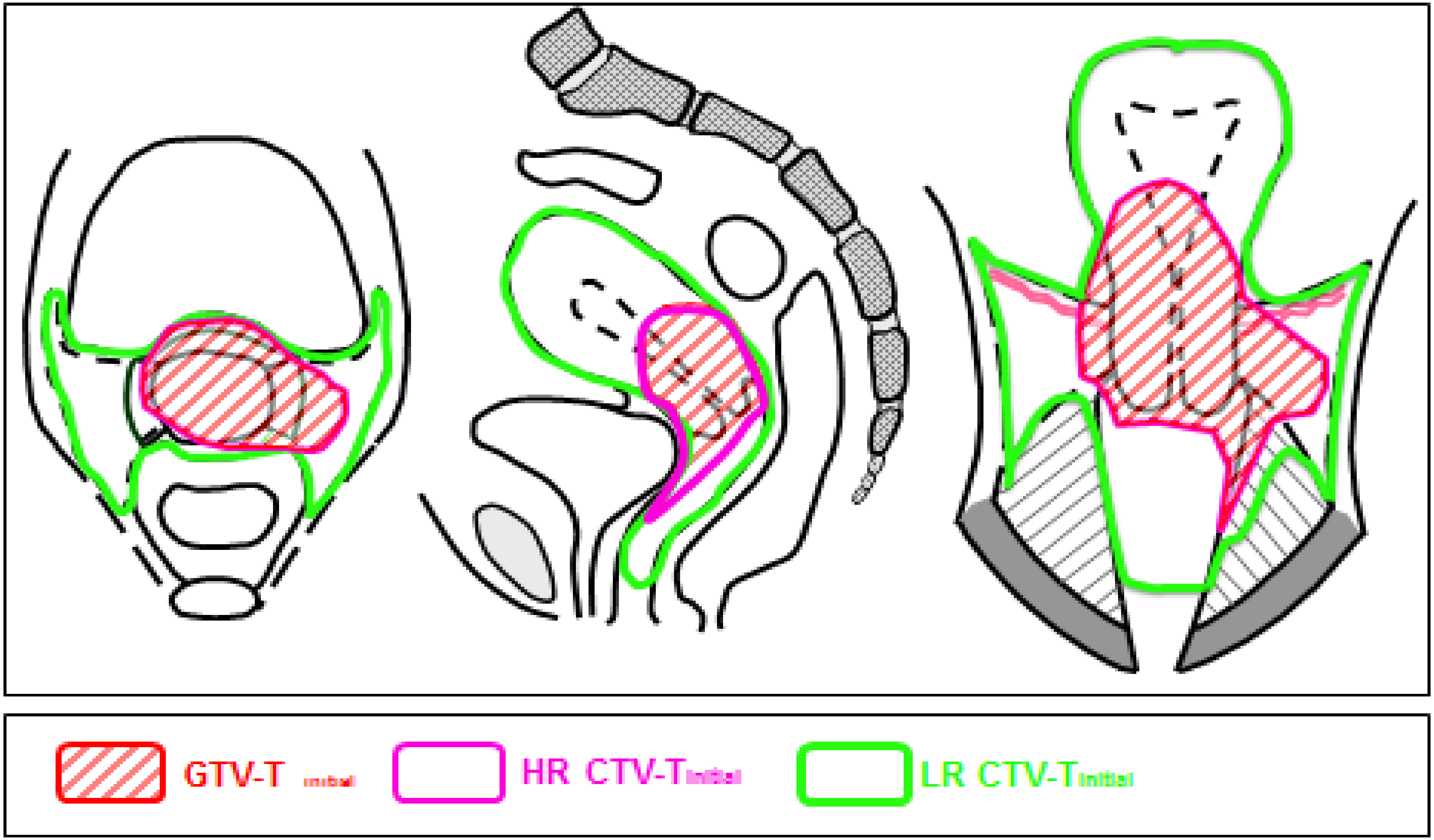
EMBRACE II
CTV-T: initial GTV, HR-CTV-T, LR-CTV-T for Stage IB2



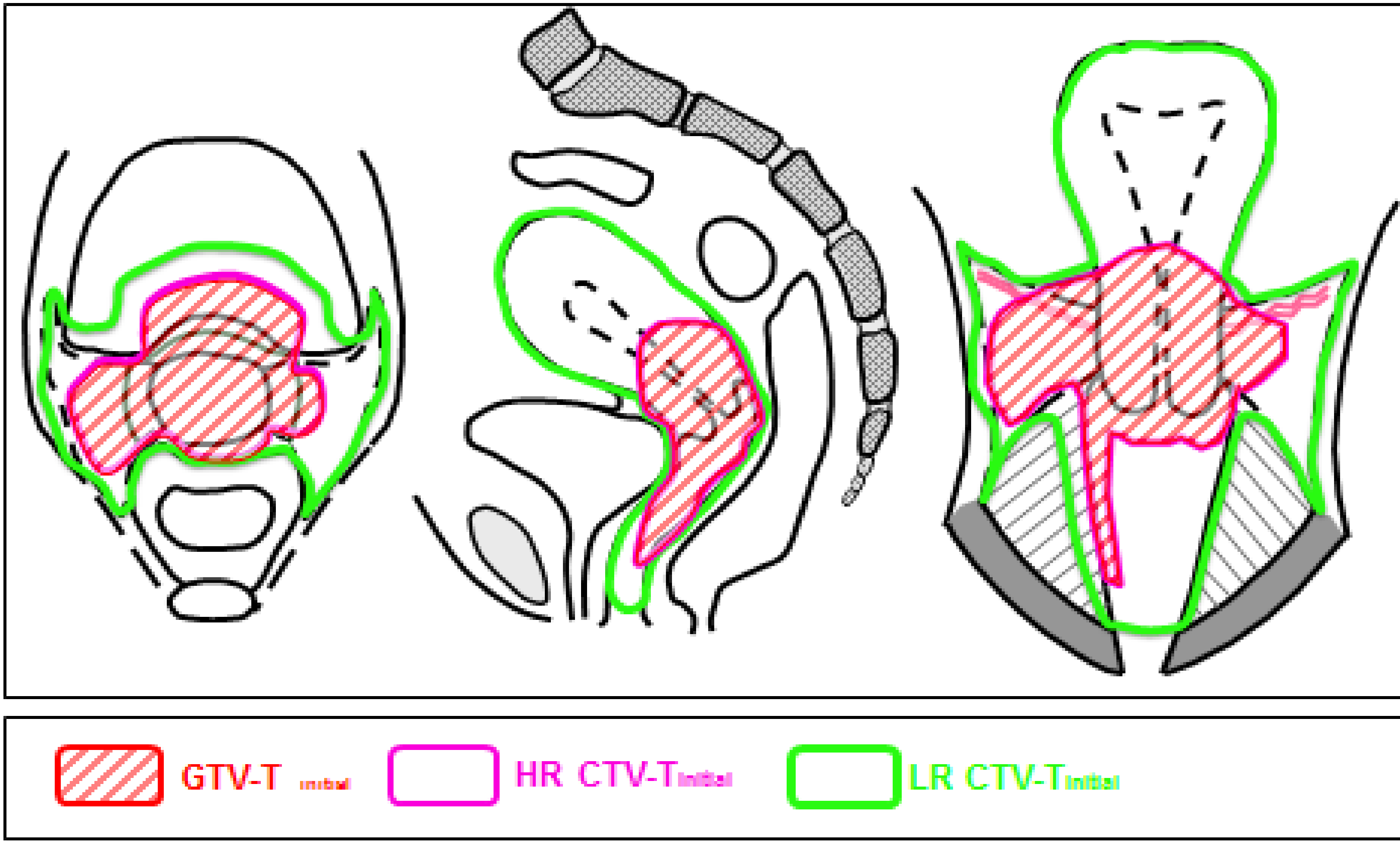
EMBRACE II
CTV-T: initial GTV, HR-CTV-T, LR-CTV-T for Stage IIB



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



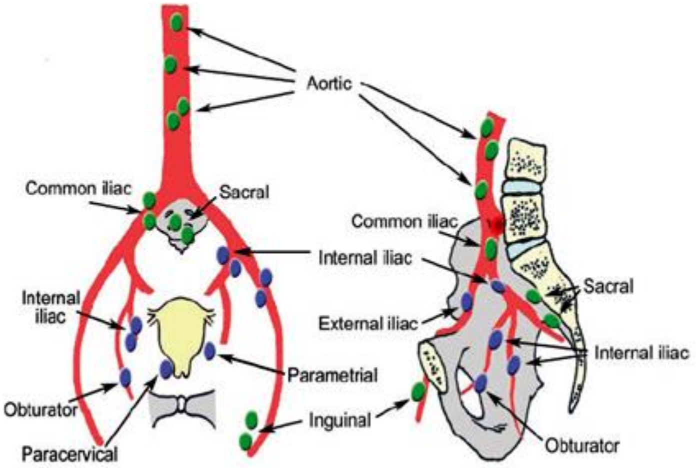
EMBRACE II
CTV-T: initial GTV, HR-CTV-T, LR-CTV-T for Stage IVA



Nodal CTV *(CTV-E)*

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?

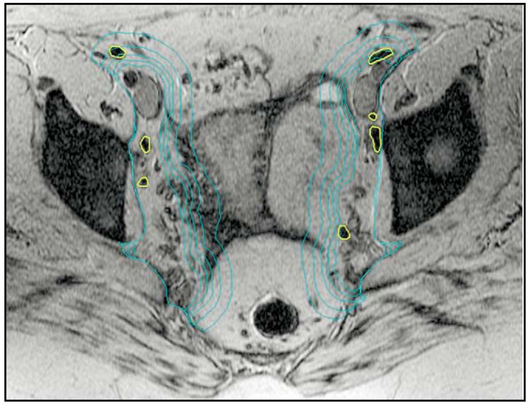
A. 5 mm
B. 7 mm
C. 10 mm
D. 5 mm with small adaptations
E. 7 mm with small adaptations
F. 10 mm with small adaptations

Nodal CTV *(CTV-E)*

Taylor A et al., IJROBP 2005

Ultrasmall Particles of Iron Oxide (USPIO) data

- 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 cm³**	190 cm³	266 cm³

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

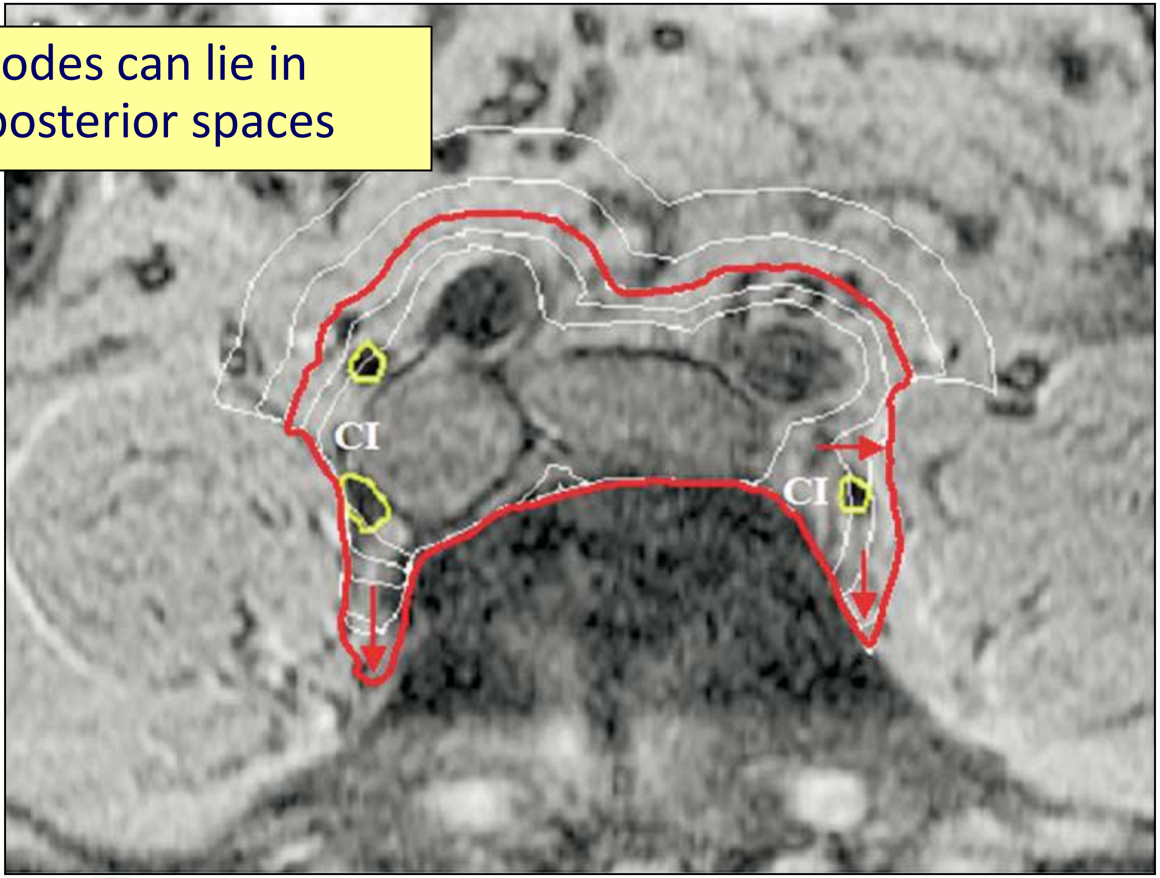
Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol 63.no.5, 1604-1612, 2005.

Nodal CTV *(CTV-E)*

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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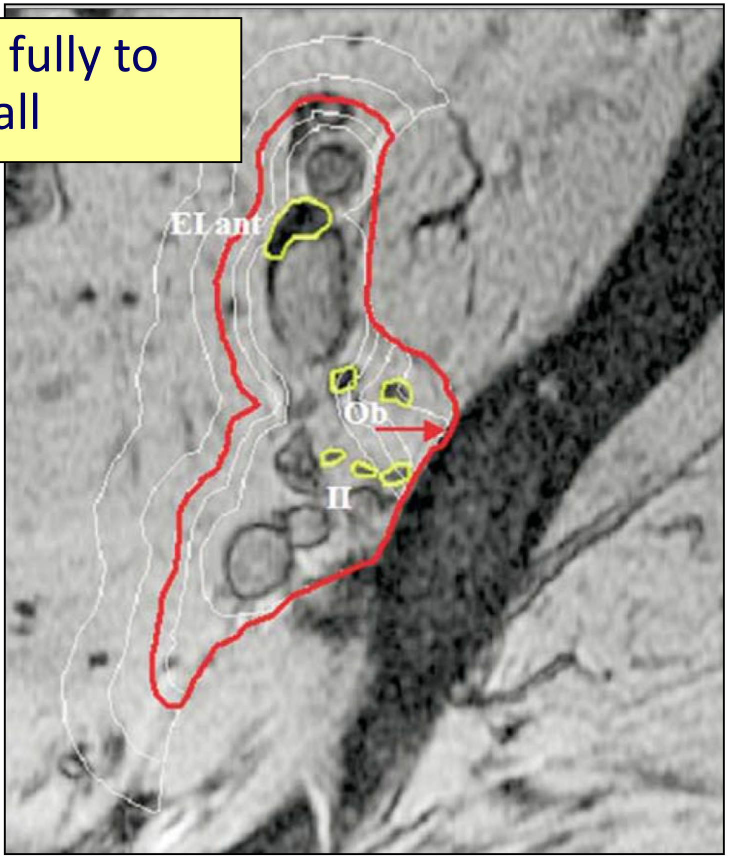
Nodal CTV *(CTV-E)*

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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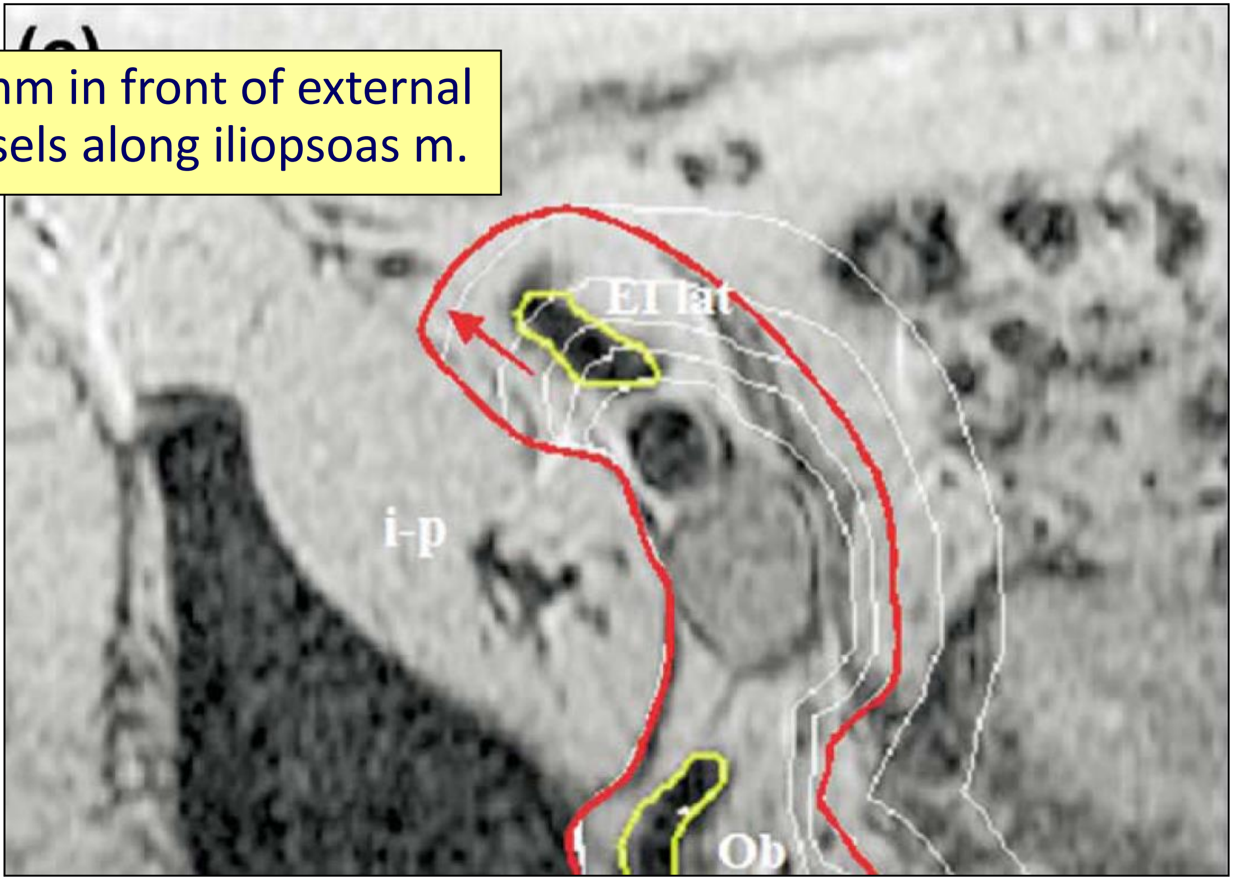
Nodal CTV *(CTV-E)*

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 *(CTV-E)*

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 *(CTV-E)*

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.

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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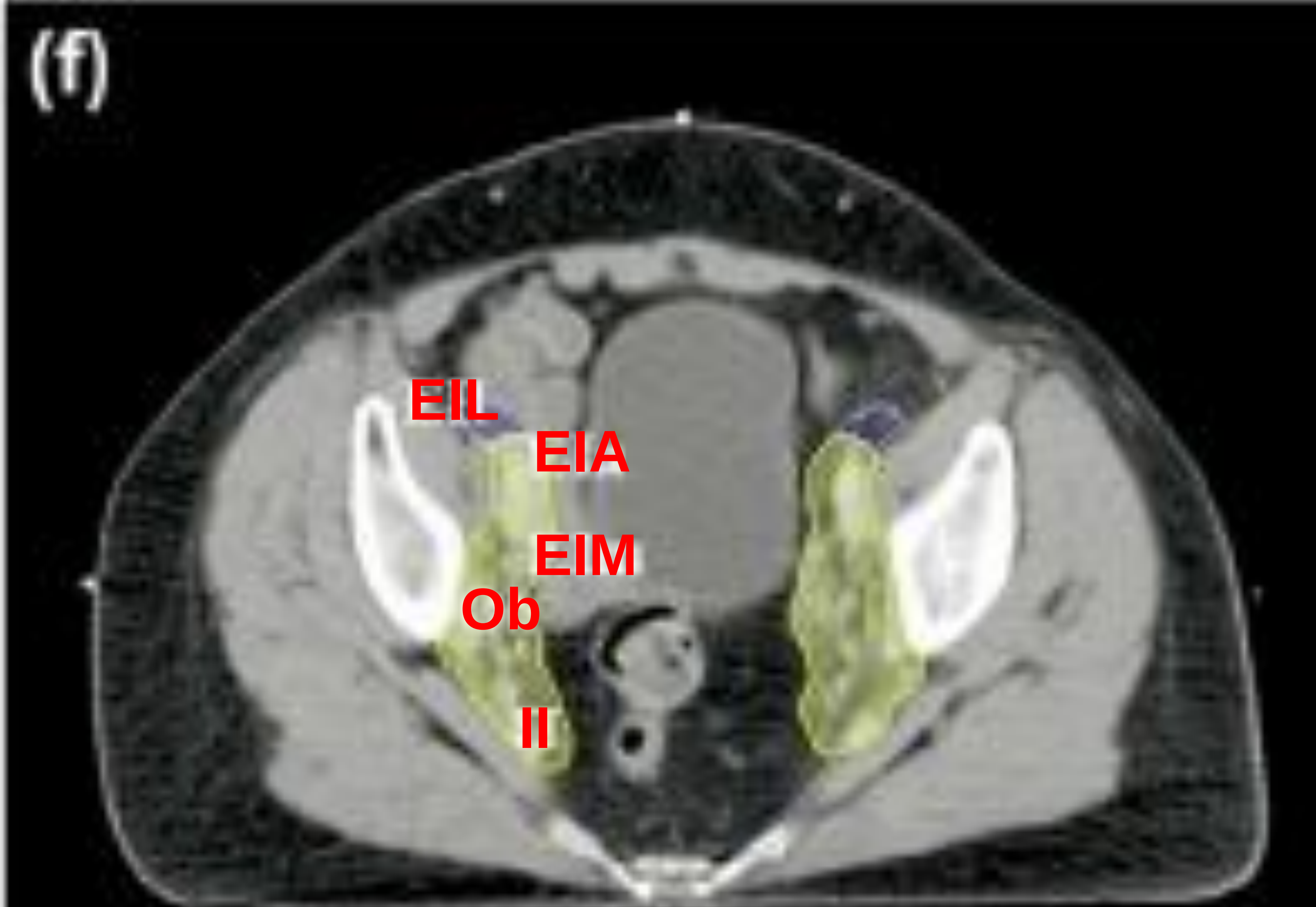
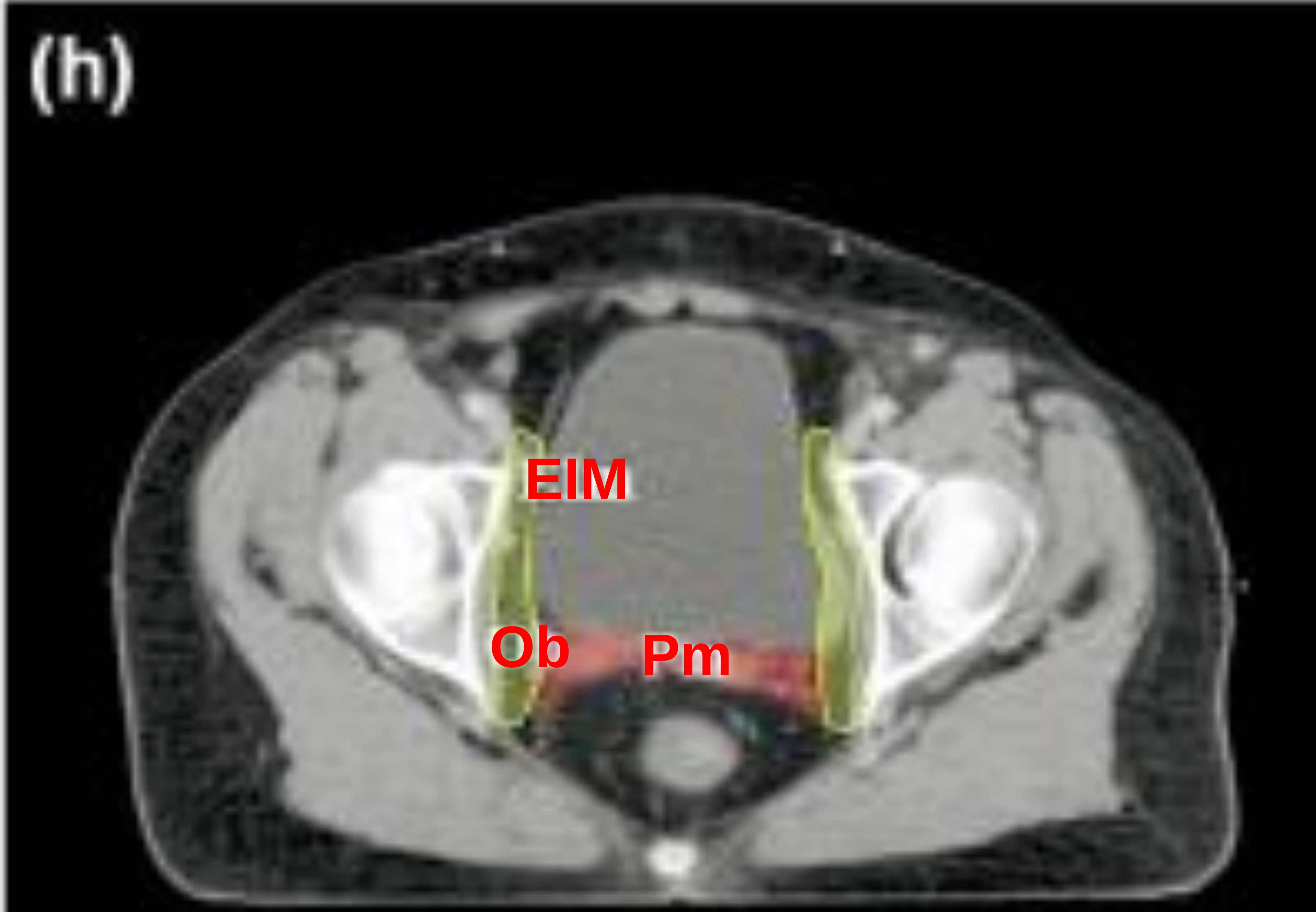


Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol 63.no.5, 1604-1612, 2005.



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 *(CTV-E)*

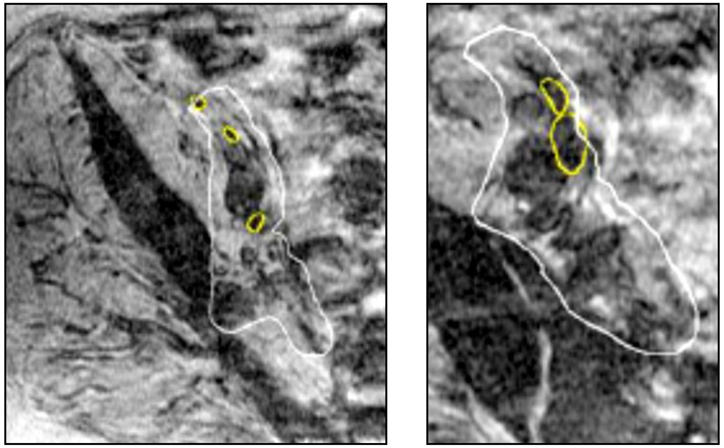
Ultrasmall Particles of Iron Oxide (USPIO) data

Vilarino-Varela MJ, et al. Radiother Oncol 2008

A verification study

- 10 patients
- Inexperienced radiation oncologist trainee
  - Contouring on pre-contrast MRI
  - Respecting Taylor recommendations
- Post-contrast (USPIO) nodal outlines were then revealed

99 % of nodes were covered by the trainee



Vilarino-Varela MJ, Taylor A, rockall A et al. Radiotherapy and Oncology 89 (2008), 192-196

RTOG, GOG, NCIC, ESTRO, ACRIN Consensus

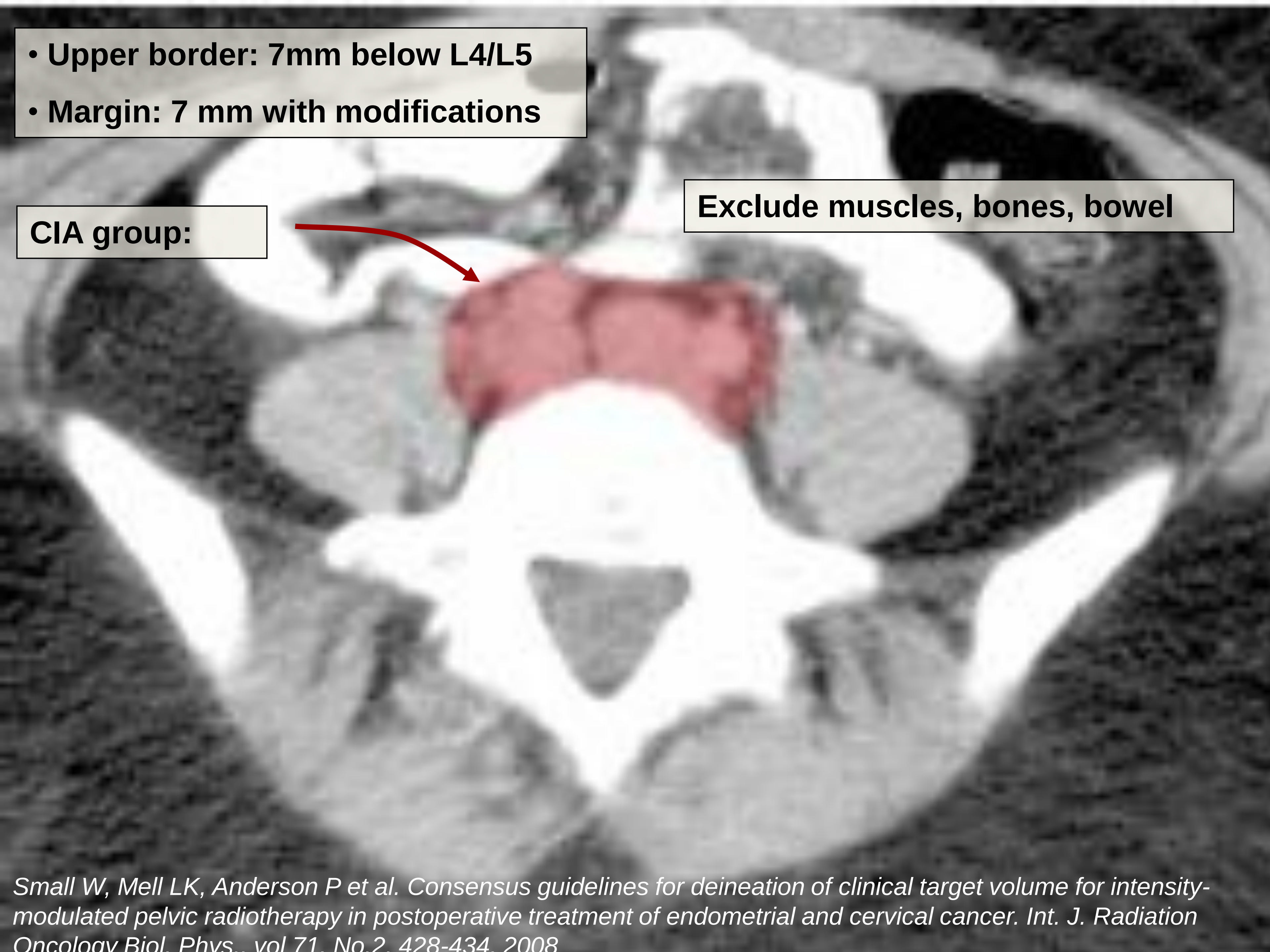
Small W, et al. IJROBP, 2008

(postoperative setting)

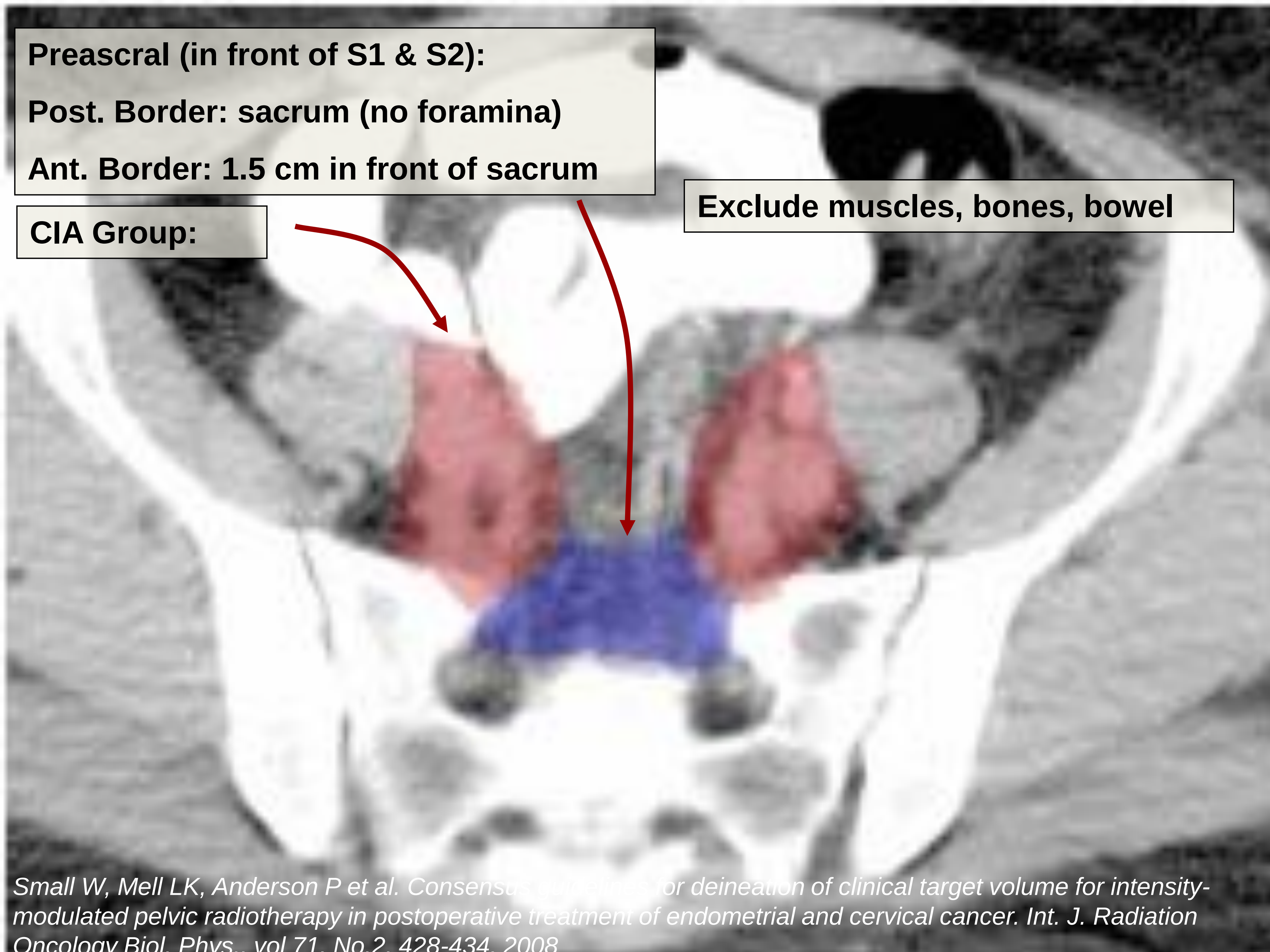
Pelvic nodal groups for cervix and endometrial cancer contouring

- Common iliac
- External iliac
- Internal iliac
- Presacral (cervix cancer and endometrial cancer with cervix invasion)

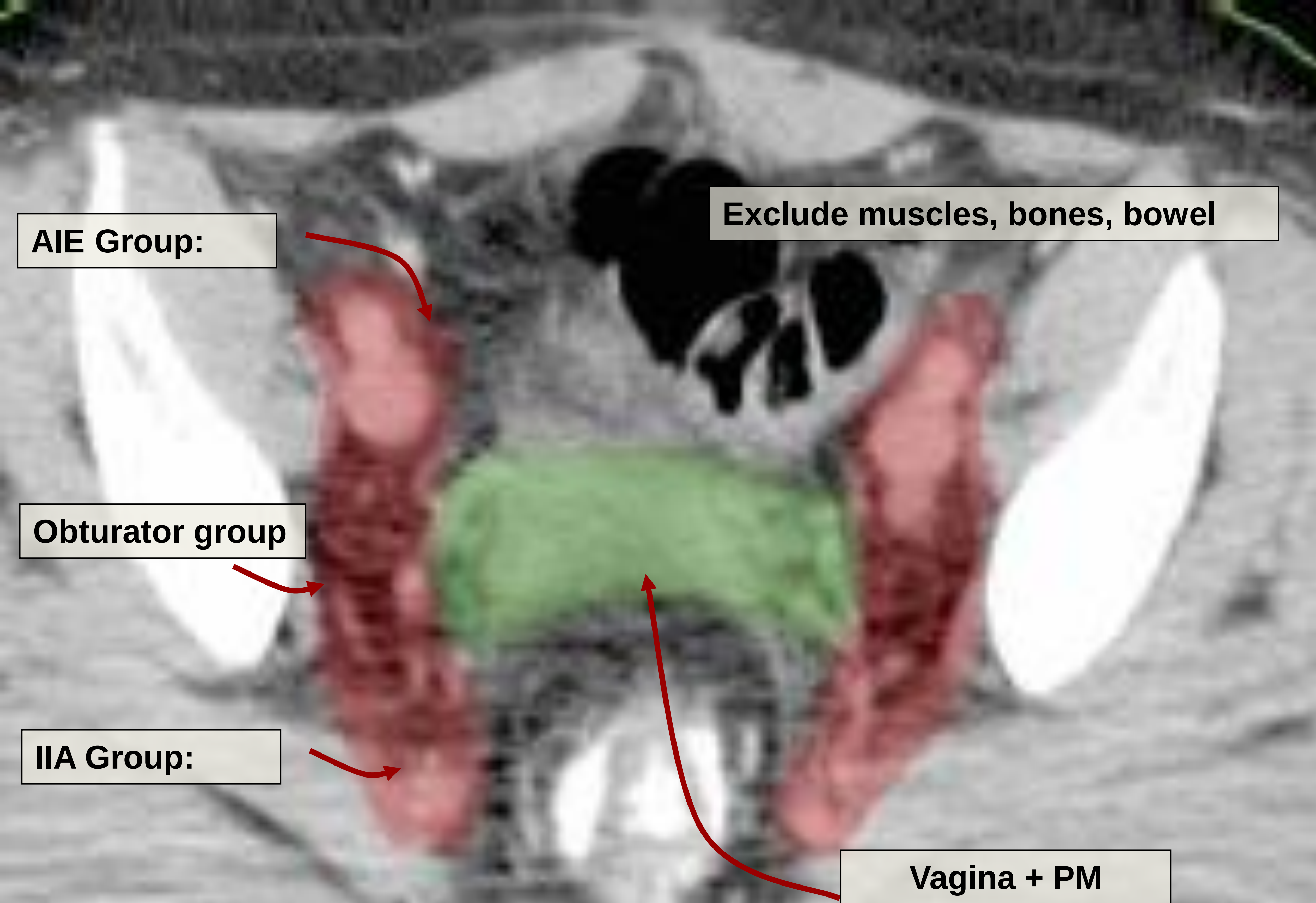
Small W, Mell LK, Anderson P et al. Consensus guidelines for deineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int. J. Radiation Oncology Biol. Phys., vol 71, No.2, 428-434, 2008



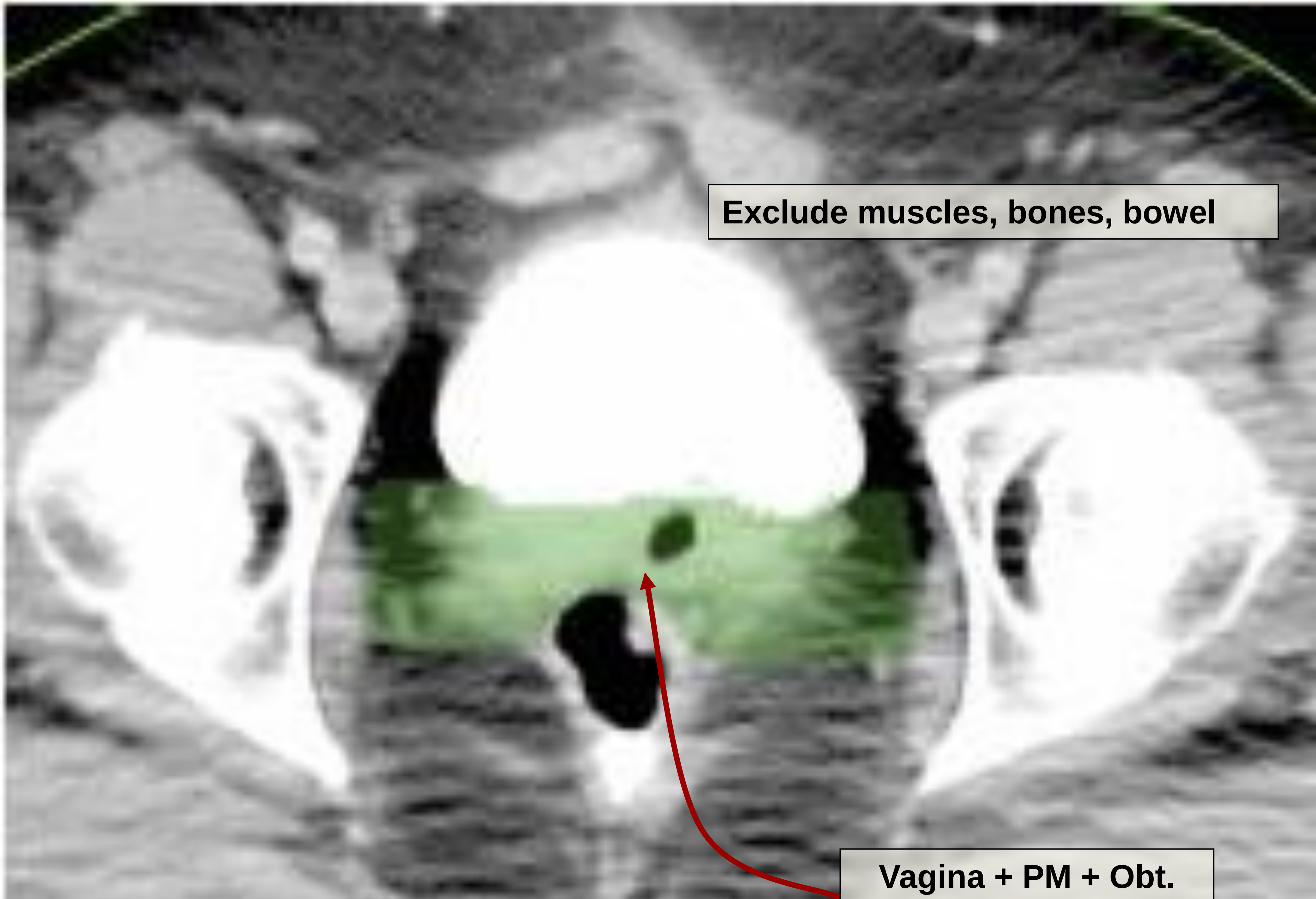
Small W, Mell LK, Anderson P et al. Consensus guidelines for deineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int. J. Radiation Oncology Biol. Phys., vol 71, No.2, 428-434, 2008



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



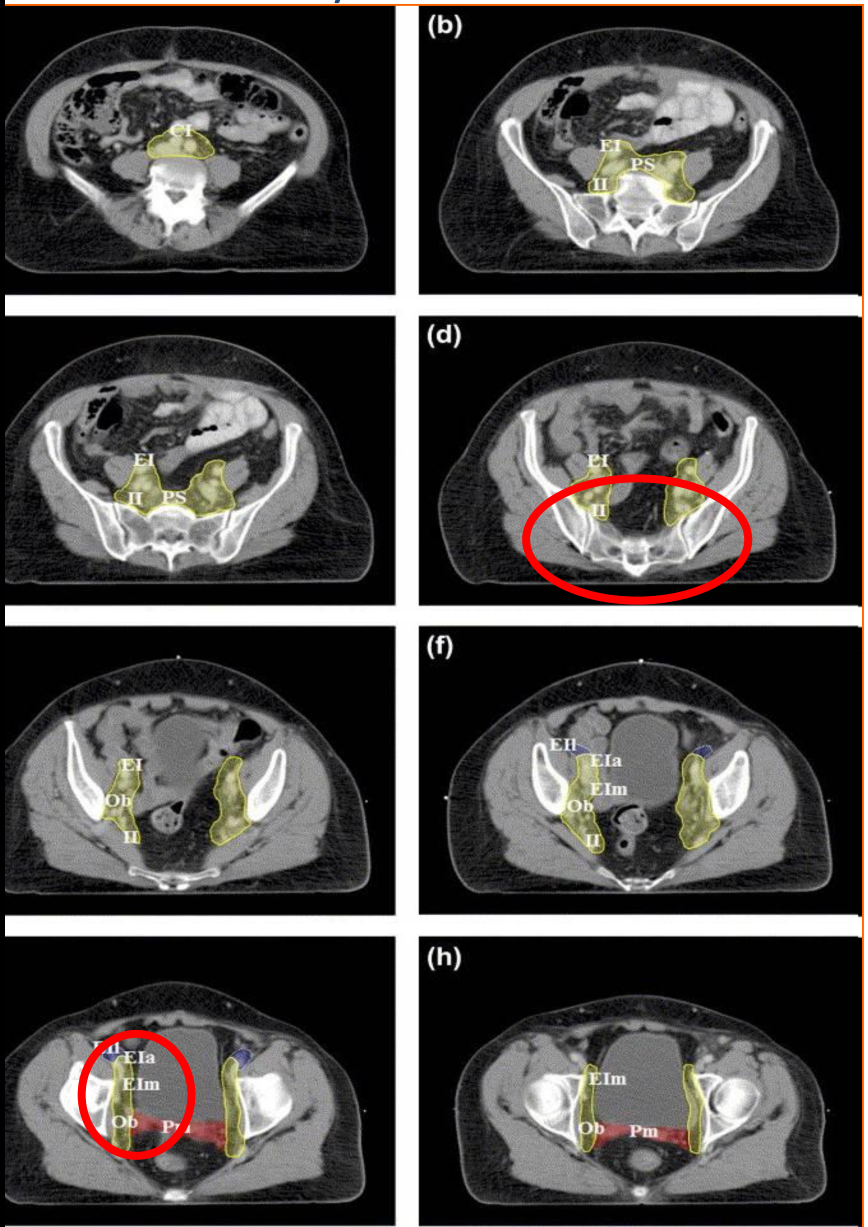
Small W, Mell LK, Anderson P et al. Consensus guidelines for deineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int. J. Radiation Oncology Biol. Phys., vol 71, No.2, 428-434, 2008



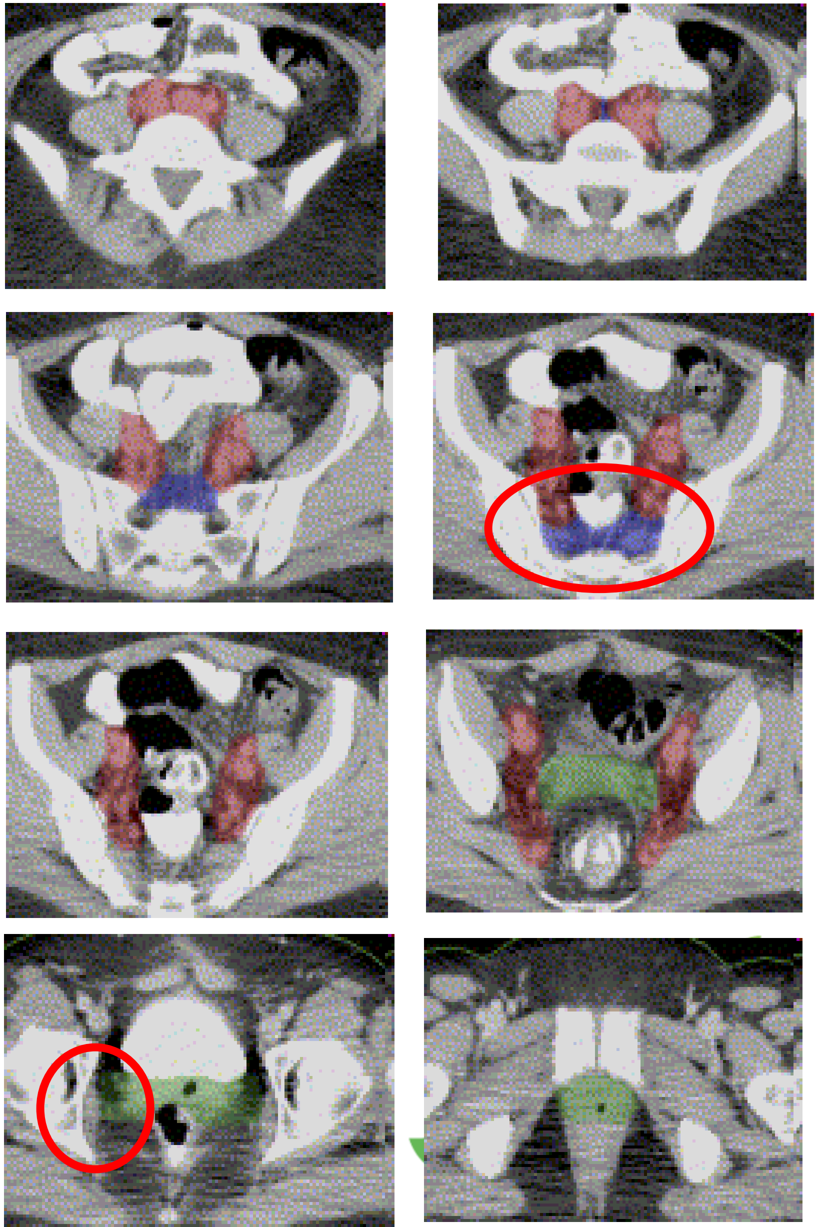
Small W, Mell LK, Anderson P et al. Consensus guidelines for deineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int. J. Radiation Oncology Biol. Phys., vol 71, No 2, 428-434, 2008.

Taylor vs. Small

Taylor 2007

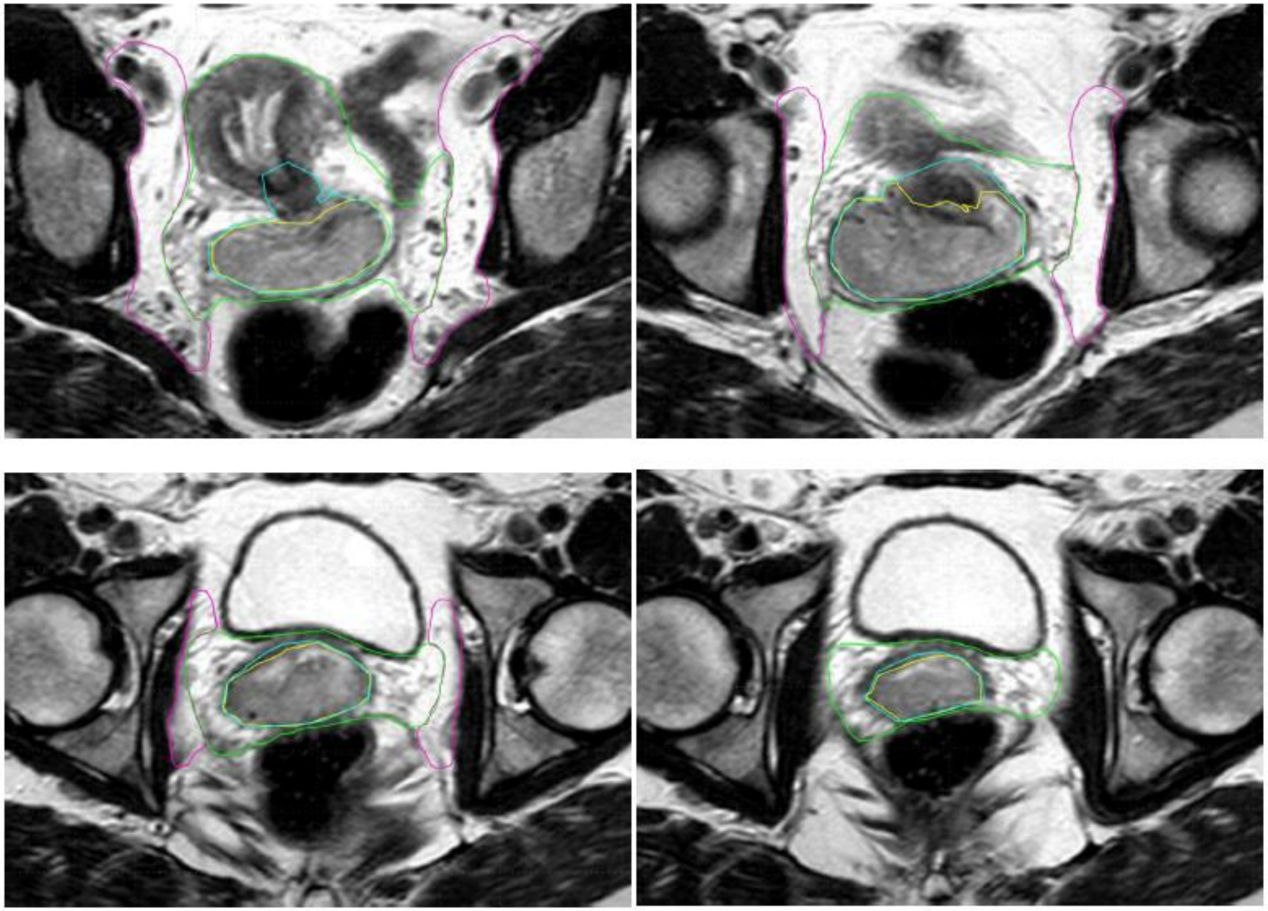


Small 2008



Elective nodal CTV: Caudal extension

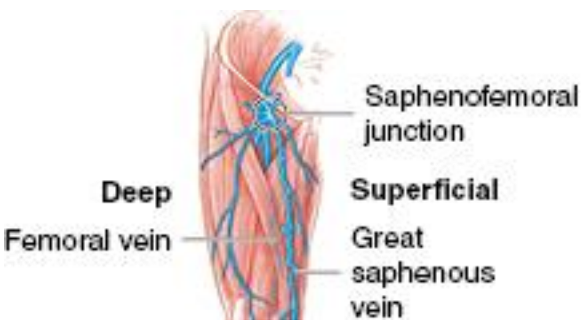
Transition zone goes down to the pelvic floor (usually at the upper part of the obturator foramen, below femoral head, were internal iliac vessels enter or leave the true pelvis)

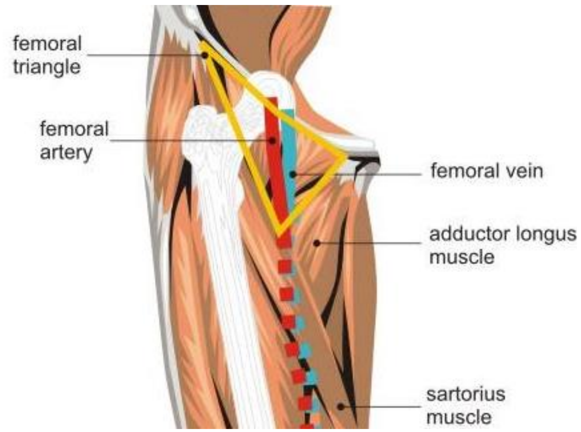


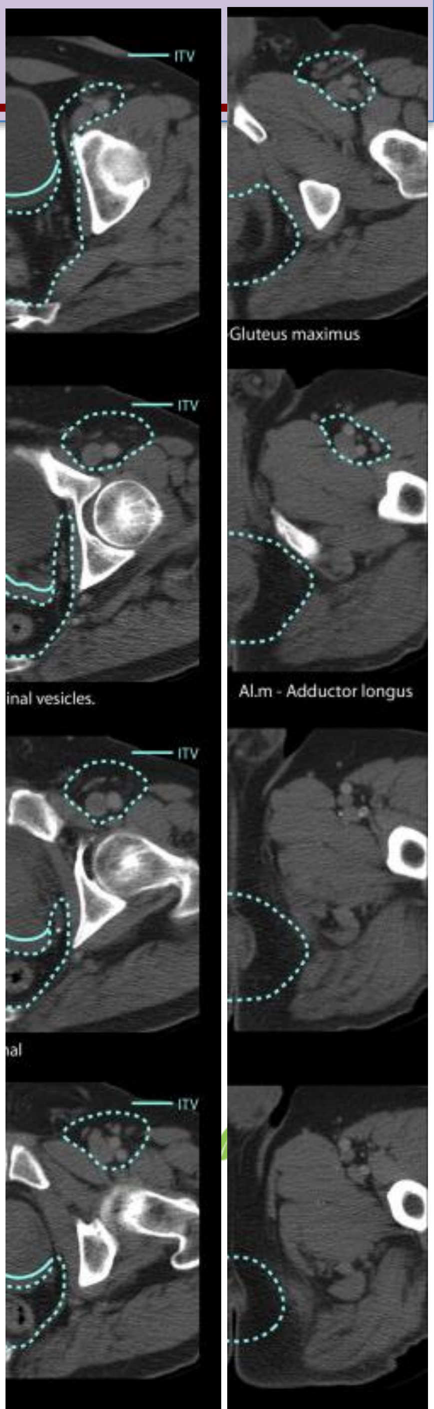
From EMBRACE II protocol

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





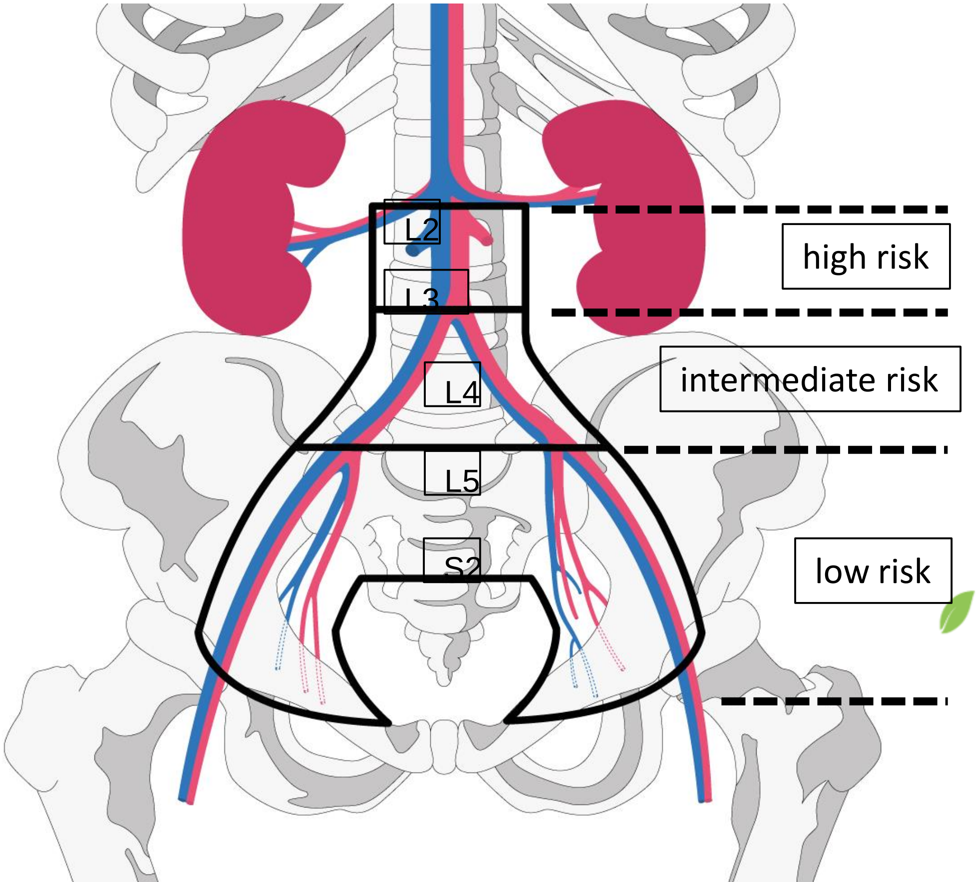


Ng et al., Australasian Gastrointestinal Trials Group (AGITG) Contouring Atlas and Planning Guidelines for Intensity-Modulated Radiotherapy in Anal Cancer, Int. J. Radiation Oncology Biol. Phys., Vol 83, 1455-1462, 2005.

Elective nodal CTV according to risk on nodal spread

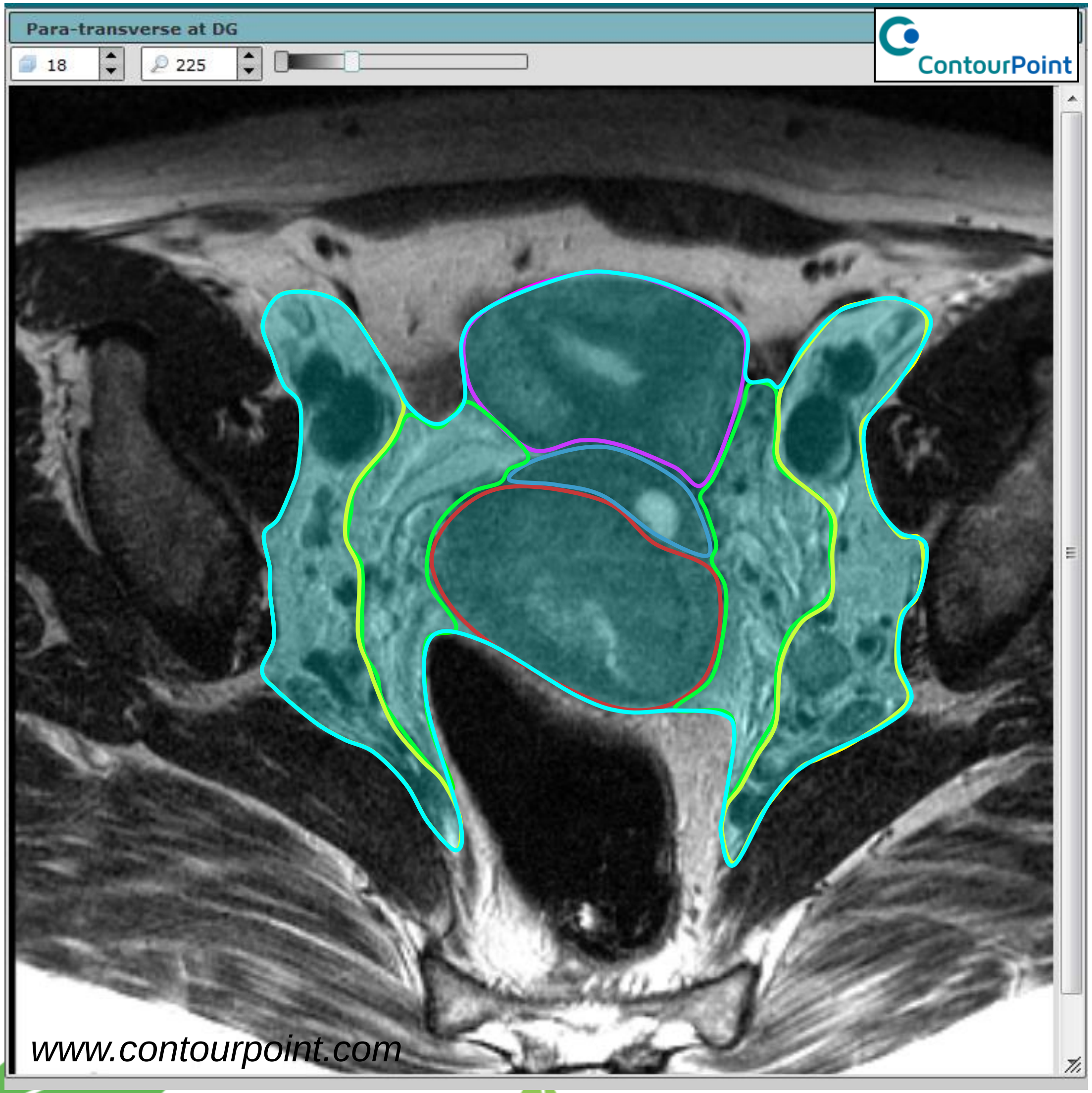
Risk profile according to EMBRACE II study protocol

- **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



Total CTV for definitive cervix cancer EBRT

Initial CTV-T + CTV-E



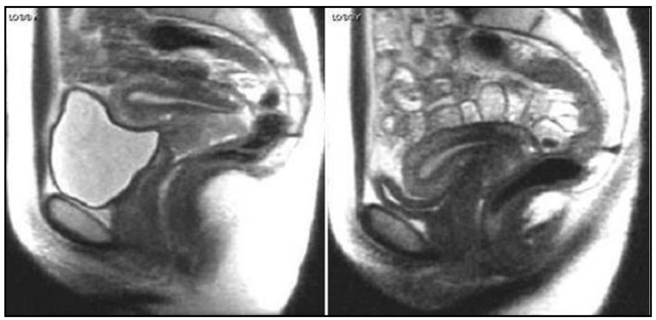
The margin needed to include 99% of detectable lymph nodes is?

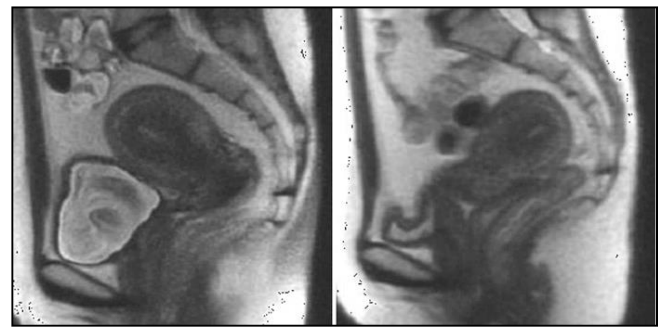
A. 5 mm
B. 7 mm
C. 10 mm
D. 5 mm with small adaptations
E. 7 mm with small adaptations
F. 10 mm with small adaptations

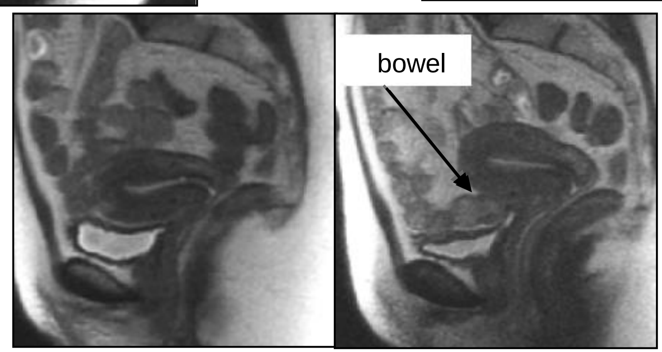
ITV-T – Internal Target Volume

ITV = CTV + margin for internal motion & deformation

- Several studies deal with tumor motion
- MRI studies provide best insight
- Large inter- fraction motion is found in majority of studies







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

ITV-T – Internal Target Volume

ITV = CTV + margin for internal motion & deformation

Author (year)	Van de Bunt (2008)		Chan (2008)		
Number of patients [median age (range)]	n = 20 (not stated)		n = 20 [47 years (33–70)]		
Methods	Cervix cancer MRI baseline & weekly Target motion not directly measured. Margins required to encompass GTV & CTV from week to week used as a surrogate for target shifts		Cervix cancer MRI & cine MRI – done baseline & weekly during standard EBRT Point of interest study – uterine fundus, uterine canal & cervical os		
	Inf = 8	Inf = 8			
Ant/post (mm)	Ant = 12 Post = 14	Ant = 24 Post = 17	AP = 14.5	AP = 13.1	AP = 11.2
Left/right (mm)	Rt = 12 Lt = 11	Rt = 12 Lt = 6	–	–	–
Comments	Bladder & bowel prep. not specified CTV-PTV margins recommendation: Ant = 24 mm; Post = 17 mm; Rt = 12 mm; Lt = 16 mm; Sup = 11 mm; Inf = 8 mm		Bladder & bowel prep. specified Suggested inter-fraction margins – fundus (10–40 mm); canal (10–25 mm), os (10–15 mm) Intra-fraction motion measured from 11,564 cine MRI frames Suggested intra-fraction margins- fundus (10 mm), canal (50 mm), os (5 cm)		

Margin recommendations for ITV range from 10 – 24 mm

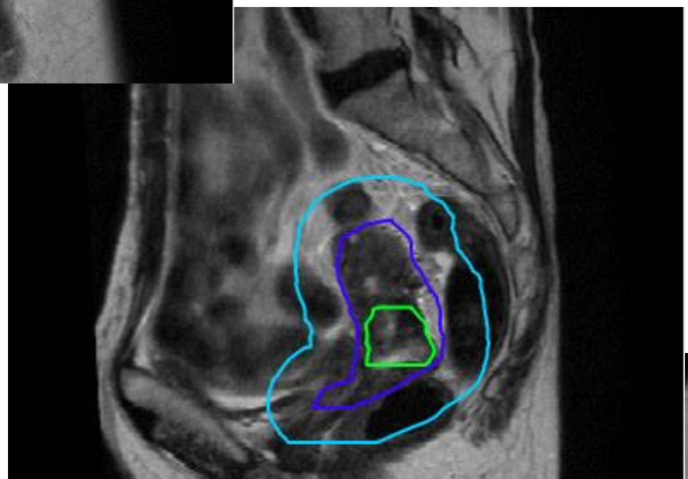
Lim K, et al. Image guidance...In: Viswanathan et al., eds. Gyn Radiat Oncol. Springer 2011

Chan P, et al. IJROBP 2008; van de Bunt L, et al. Radiother Oncol 2008

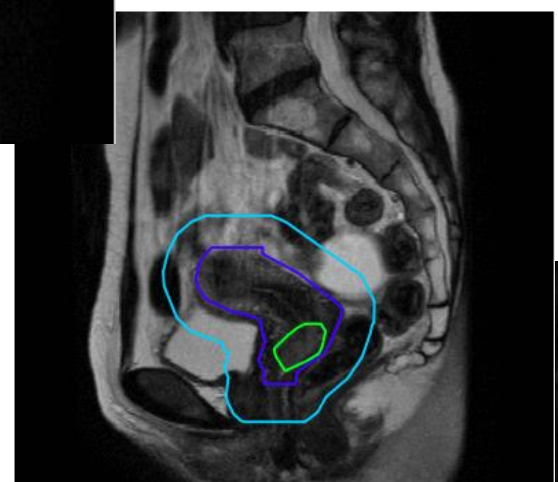
Target (CTV-T) motion during EBRT

- 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



High impact of bladder and bowel

High impact of bladder

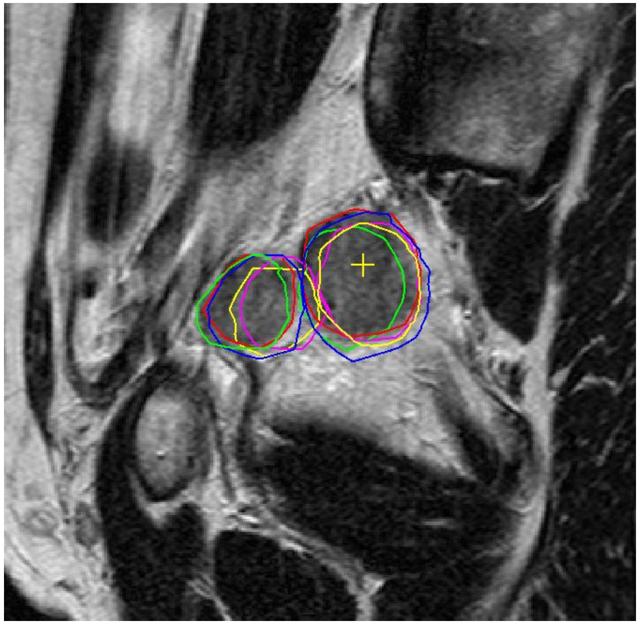
GTV
CTV
PTV

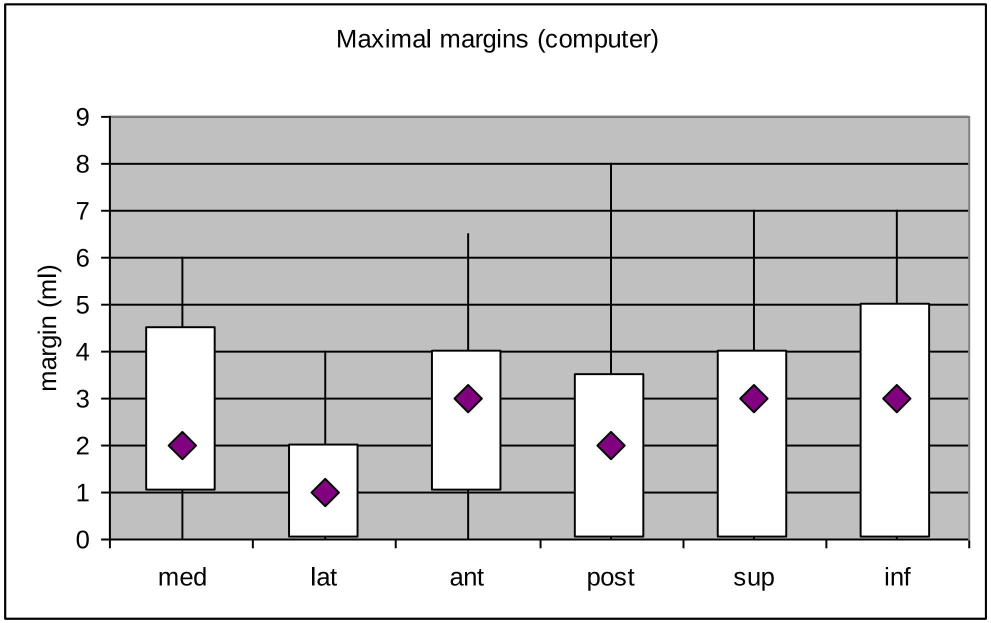
Van de Bunt et al 2008

ITV-T – Internal Target Volume

Nodes also move! (a little)

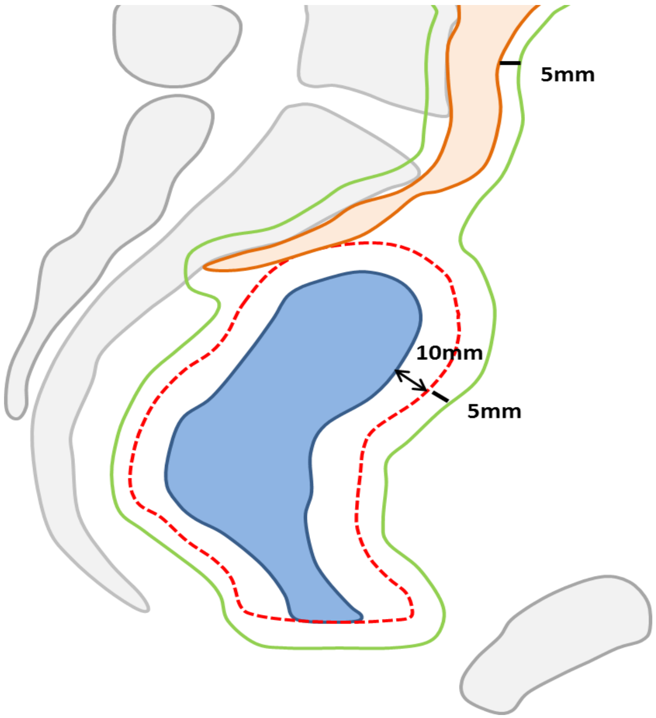
- 48 nodes, 15 patients, repeat MRI during EBRT
- Position shift in 6 directions assessed
- Affected nodes also change their position
- Order of magnitude lower than for primary GTV (< 10 mm)



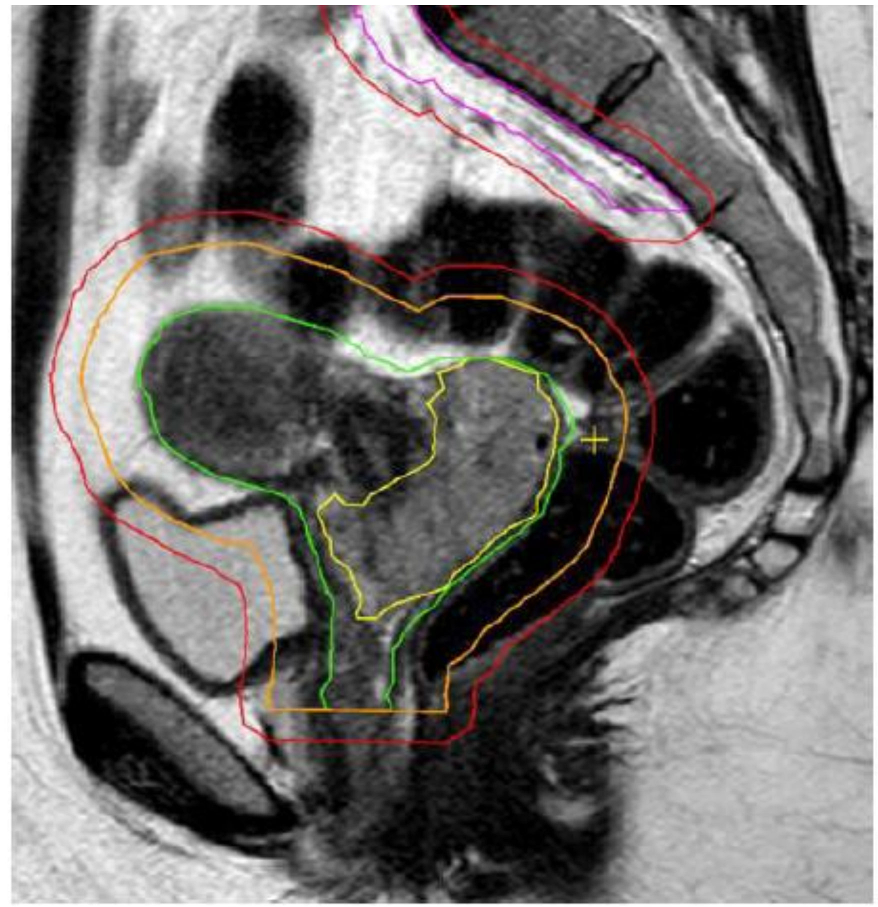


Schippers M, et al. 2011

ITV-T based on standard margin approach

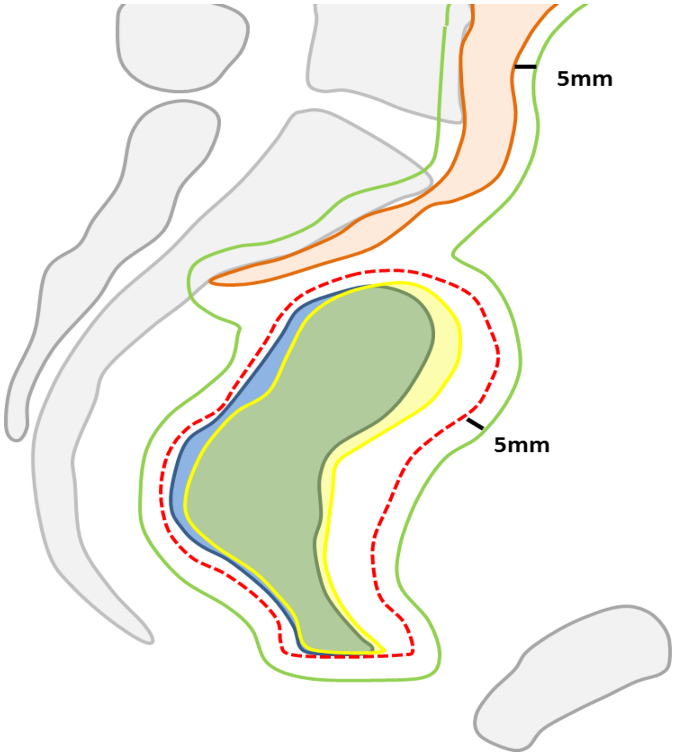


CTV-T LR (CT)
CTV-E
ITV-T LR
PTV-45



From EMBRACE II protocol

ITV-T based on individualized margin approach



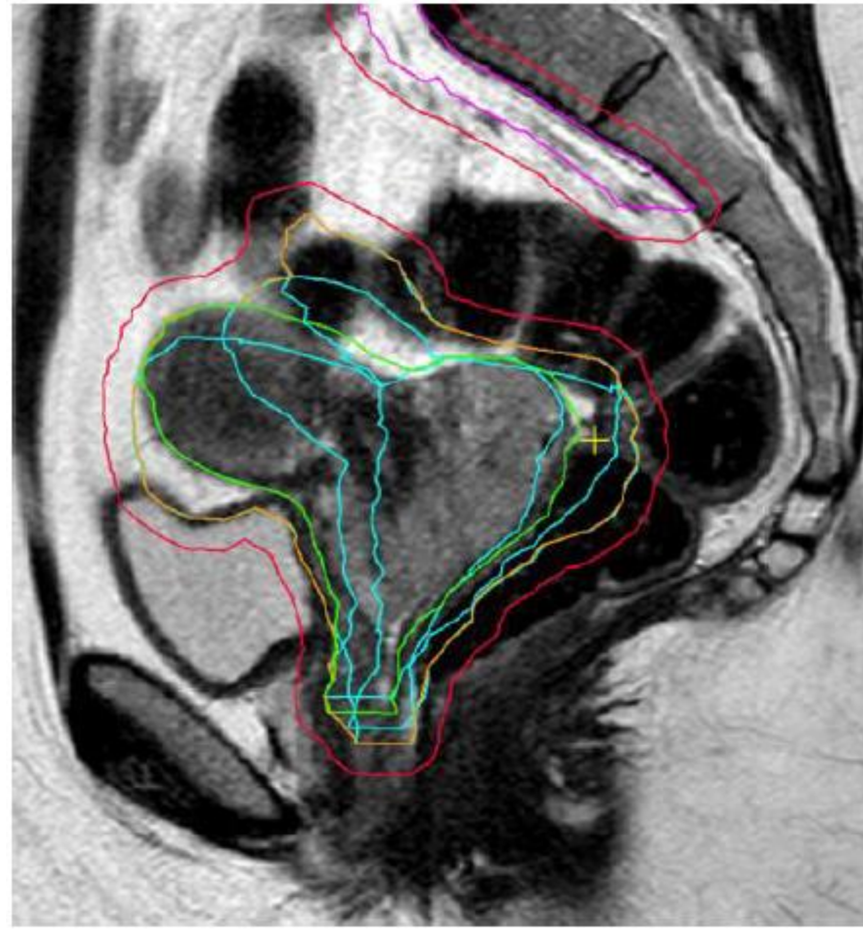
CTV-T LR (CT)

CTV-T LR (MR)

CTV-E

ITV-T LR

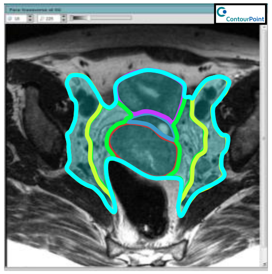
PTV-45

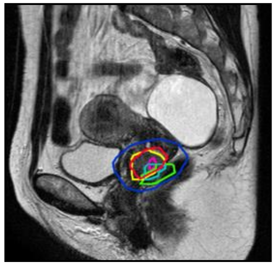
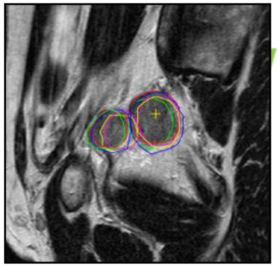


From EMBRACE II protocol

Conclusions for target contouring

- GTV, CTV, ITV concept is complex
- CTV consists of primary tumor and nodal components
- International consensus exists for contouring guidelines with small matters of debate
- ITV concept is developed to account for target and OAR motion and deformation
- ITV-T can be individualized
- Nodes move a little, too!
- Position verification issues will be addressed later!!



Delineation of Organs At Risk for EBRT planning

From EMBRACE II protocol

9.4 CONTOURING OF ORGANS AT RISK, REFERENCE POINTS

The outer contour of the following organs should be delineated separately:

Bladder	Whole organ including the bladder neck
Rectum	From the ano-rectal sphincter to the recto-sigmoid junction
Sigmoid	From the recto-sigmoid junction to the left iliac fossa
Bowel	Outer contour of bowel loops including the mesenterium
Femoral heads	Both femoral head and neck to the level of the trochanter minor

Reference points:

Vagina	Lower and mid-vagina doses (PIBS, PIBS ± 2 cm)

For para-aortic irradiation in addition:

Kidneys	Outer contour excluding renal pelvis
Spinal cord	Outer contour

Optional (if para-aortic RT above L1 is applied):

Duodenum	Whole organ

In case of ovarian transposition

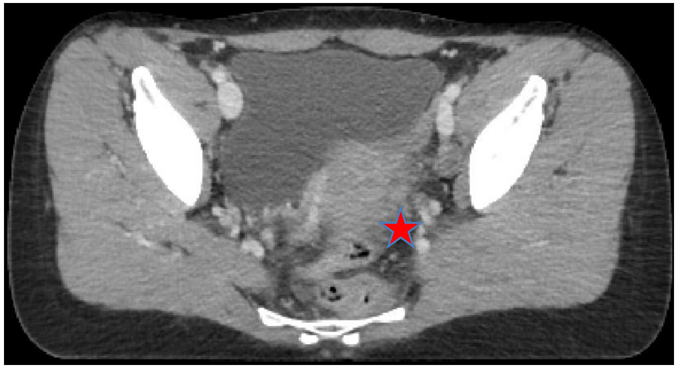
Ovary	Outer contour

MRI- vs. CT-based contouring of OAR

COMPUTED TOMOGRAPHY VERSUS MAGNETIC RESONANCE IMAGING-BASED CONTOURING IN CERVICAL CANCER BRACHYTHERAPY: RESULTS OF A PROSPECTIVE TRIAL AND PRELIMINARY GUIDELINES FOR STANDARDIZED CONTOURS

Akila N. Viswanathan, M.D., M.P.H.,[*] Johannes Dimopoulos, M.D.,[†] Christian Kirisits, Sc.D.,[†] Daniel Berger, M.Sc.,[†] and Richard Pötter, M.D.,[†]

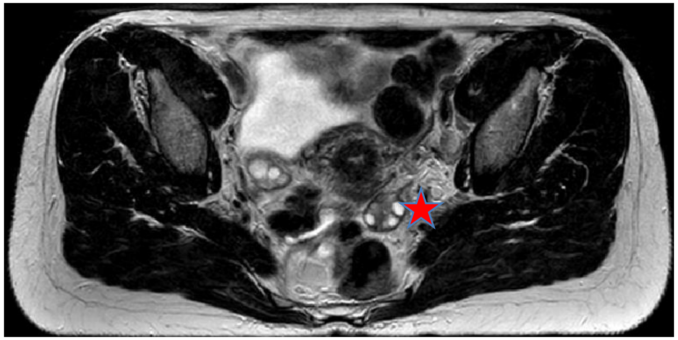
Conclusion: Computed tomography-based or MRI-based scans at brachytherapy are adequate for OAR DVH analysis. However, CT tumor contours can significantly overestimate the tumor width, resulting in significant differences in the D_{90}, D_{100}, and volume treated to the prescription dose or greater for the HR-CTV compared with that using MRI. MRI remains the standard for CTV definition. © 2007 Elsevier Inc.



Common opinion

CT is OK for OAR, but suboptimal for HR CTV and IR CTV

...oversimplification for the OAR?



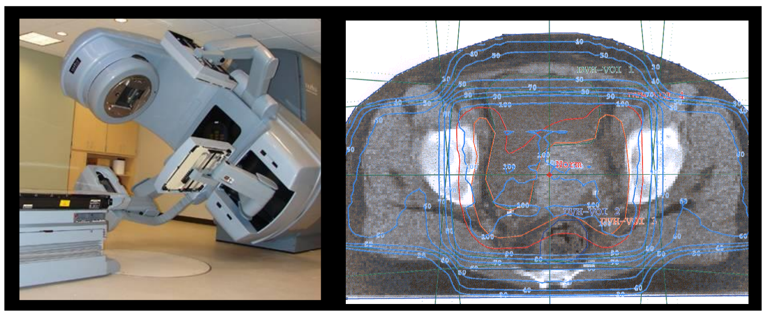
Viswanathan AN, et al. Radiother Oncol 2007

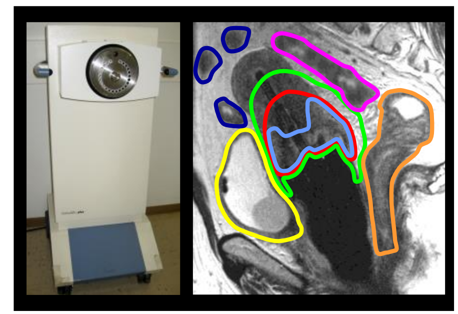
Background

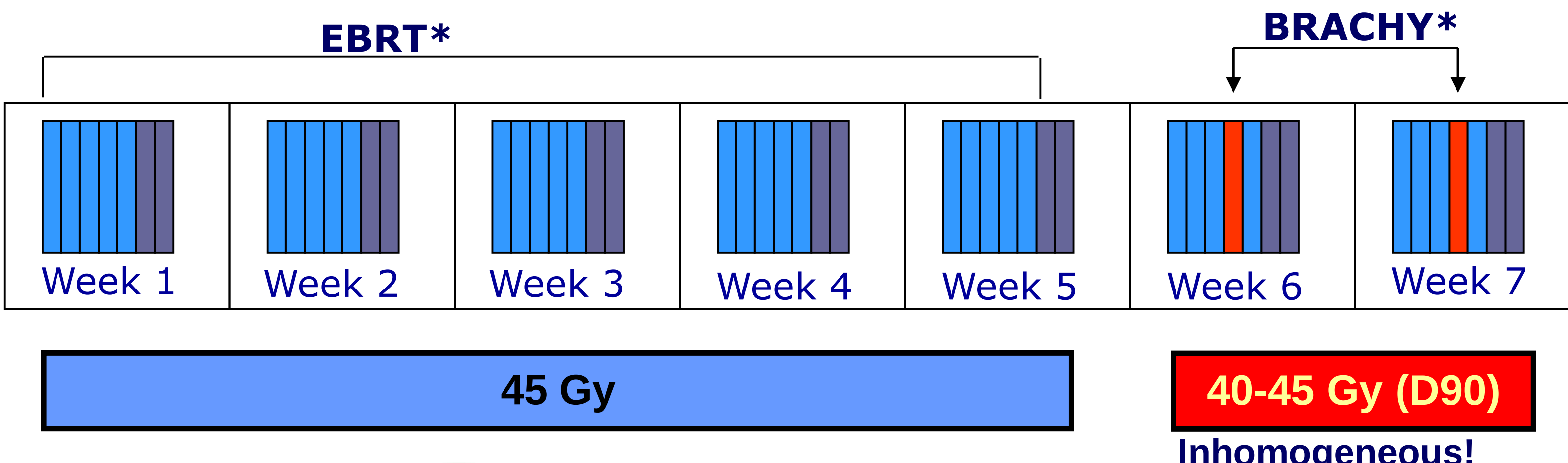
Tolerance of normal pelvic structures

↓ **Limiting factor**

Applying the dose to the target volume



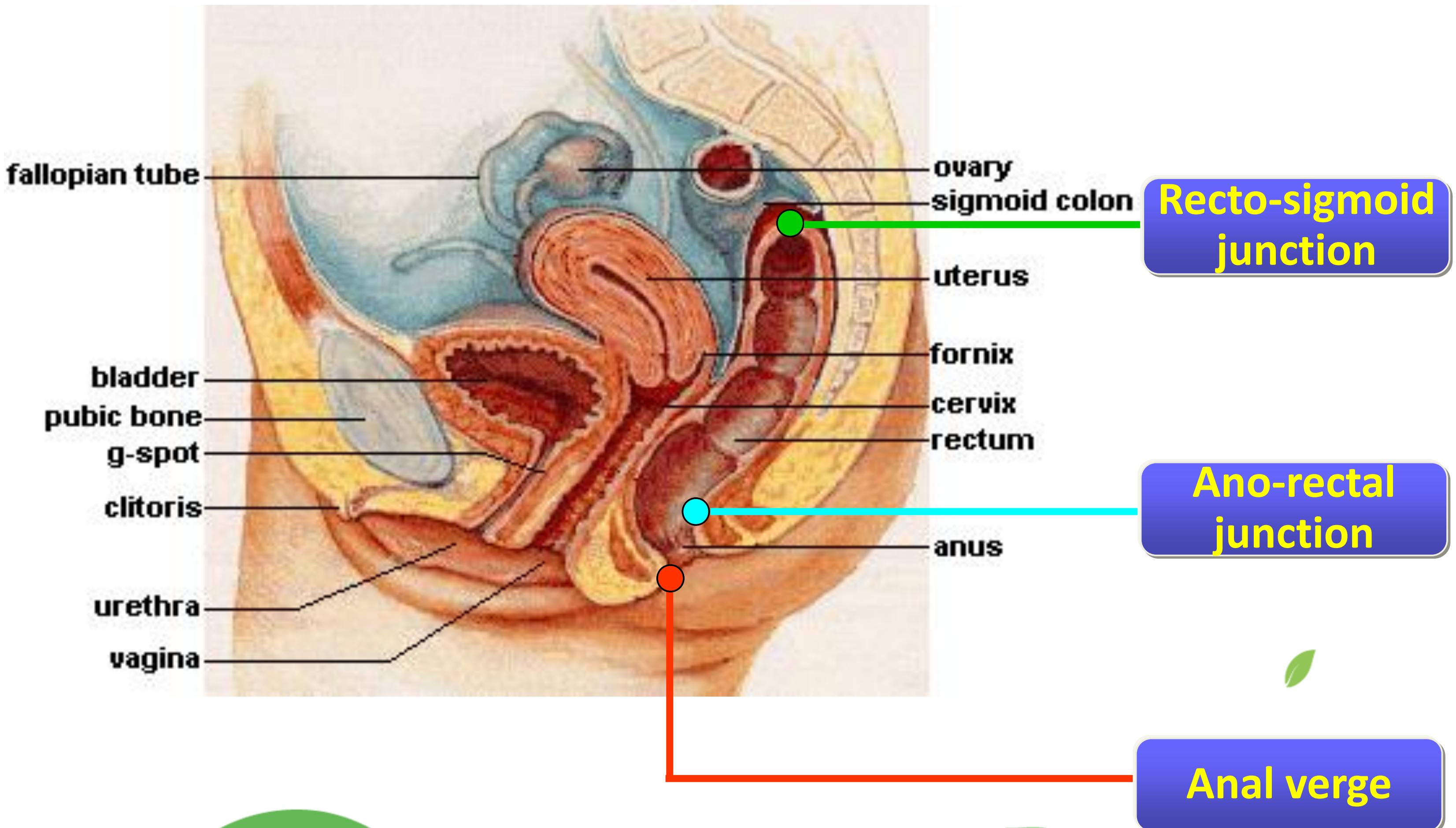




**Example: Treatment schedule outline; cervix cancer. Inst of Oncol Ljubljana (biologically equivalent doses!, LQ model)*

Anorectum

Anatomy



Anorectum

Varying definitions of rectum in RT studies and practice

Superior:

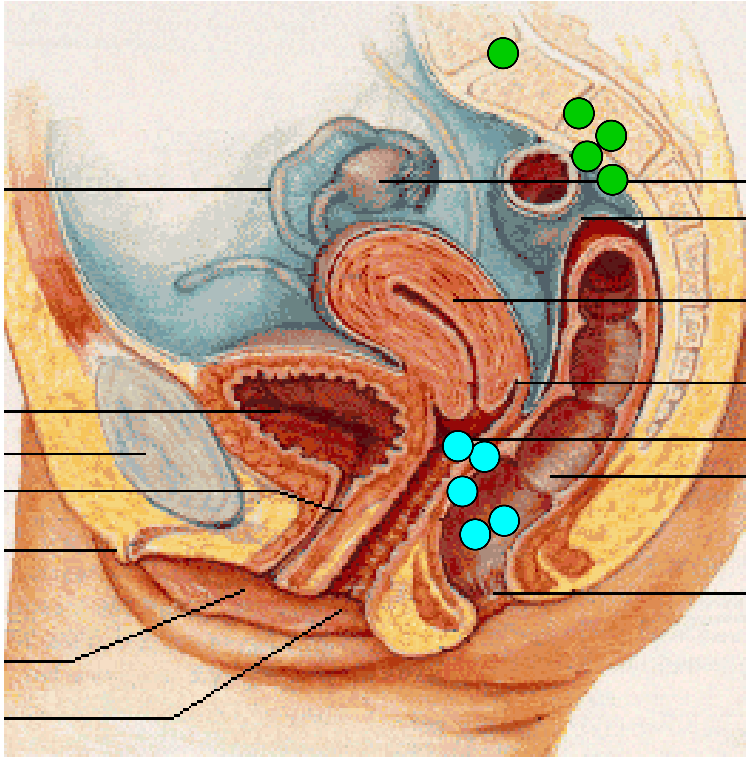
- Rectosigmoid junction
- 12 cm from the anus
- Top of acetabula
- At the level of ≈ S3
- Inferior level of sacroiliac joints
- 1 cm above the PTV

Inferior:

- Anal verge
- Ano-rectal junction
- 1cm below PTV
- Ischial tuberosities
- Ischial tuberosities + 2 cm

Circumferential:

- Rectum + contents
- Rectal wall

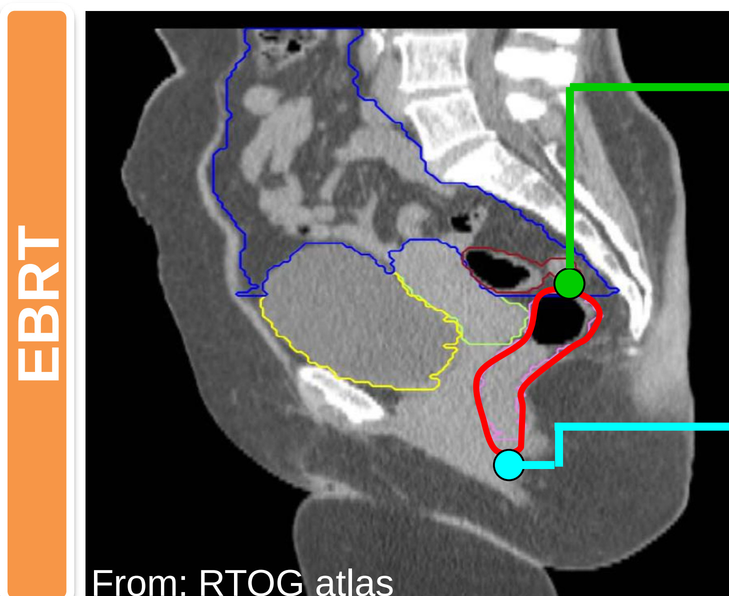


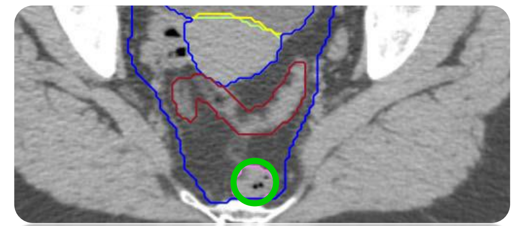
Anorectum

Empty the rectum at EBRT simulatio

Avoid systematic error in PTV coverage

Delineate Rectum + contents





Recto-sigmoid junction

Where rectum looses round shape in axial plane & loops anteriorly to connect with sigmoid colon Commonly: close to inferior level of SI joints.

Ano-rectal sphincter

Use metallic marker at anal verge. Commonly: bottom of ischial tuberosities

Separate delineation of anus not specified…

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

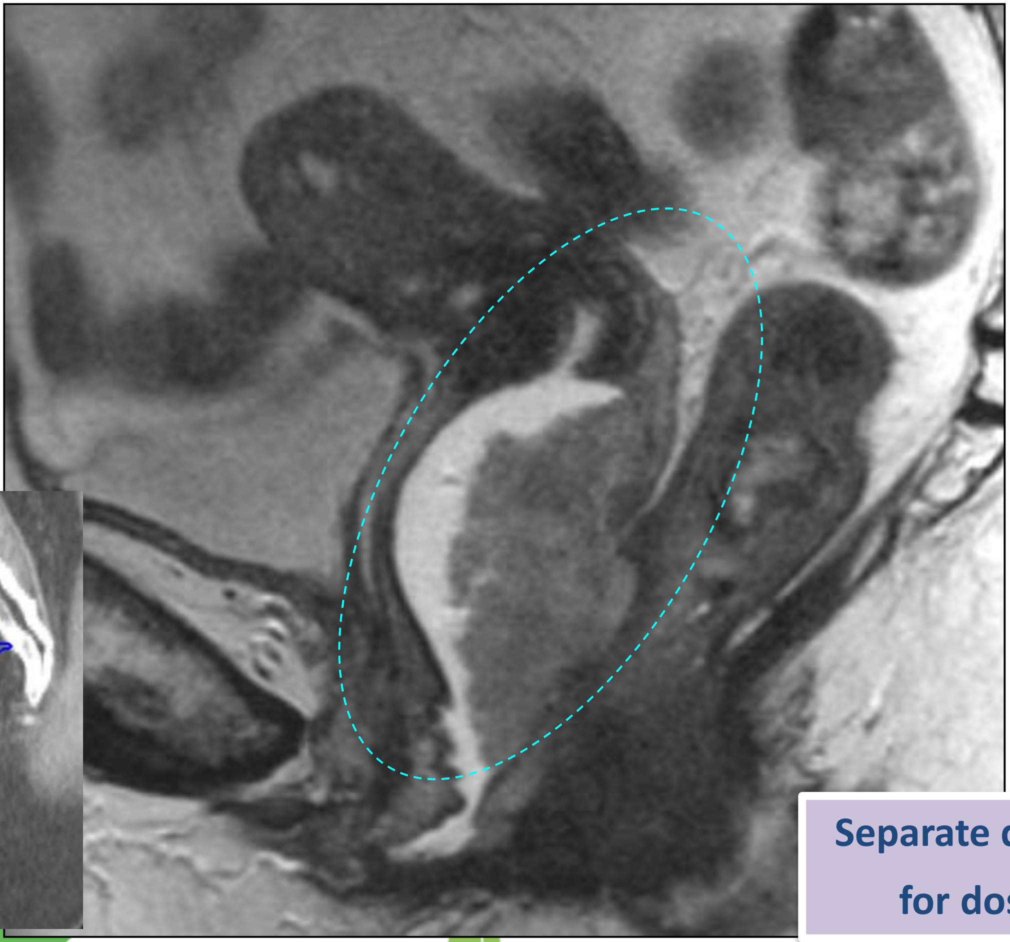
http://www.rtog.org/CoreLab/ContouringAtlases/Anorectal.aspx

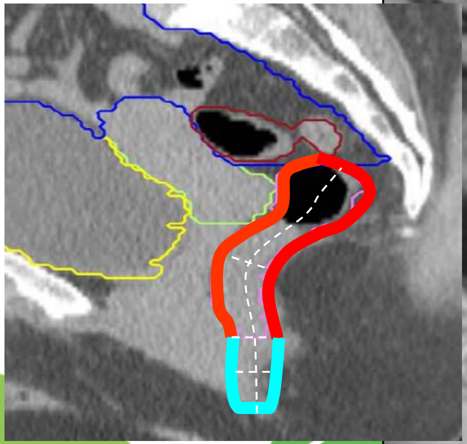
Michalski 2010 IJROBP

Anorectum: separate delineation of anus?

Ongoing discussion

Special BT situations: high anal dose





Separate delineation of anus for dose assessment!

Bladder

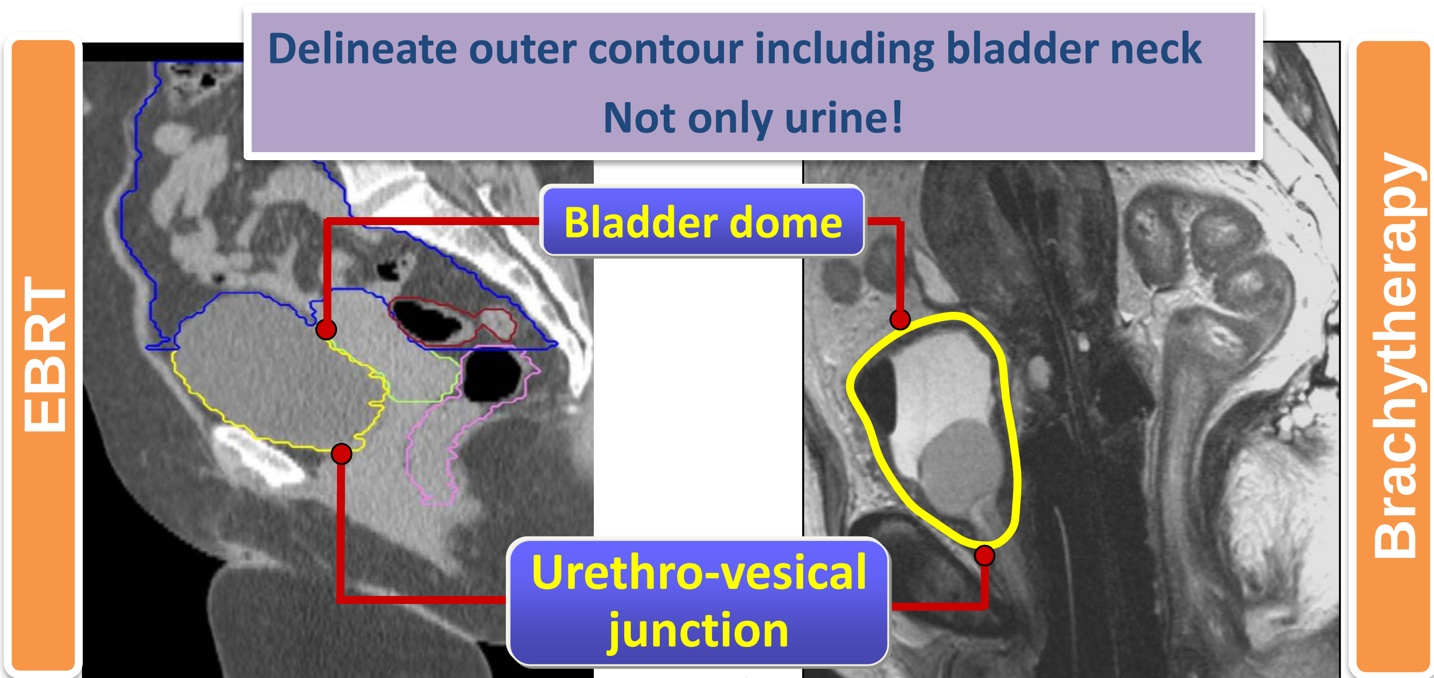
International Journal of Radiation Oncology biology • physics

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

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

Table RTOG male and female pelvis normal tissue consensus definitions

Organ	Standardized TPS name	Tumor category	Consensus definition
Bladder	Bladder	GU, GYN, GI	Inferiorly from its base and superiorly to the dome.



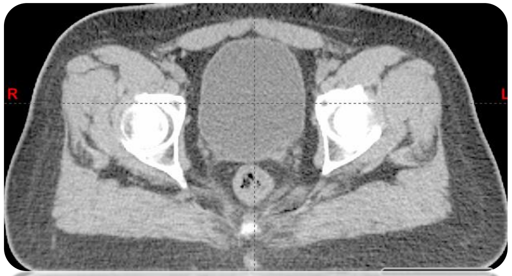
Gay H, et al. Int J Radiat Oncol Biol Phys 2012;83(3):353-362.

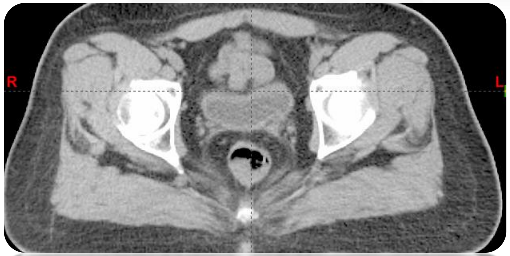
Bladder

Challenges

- Highly distensible, V depends on filling
- Moving (positioning, respiration, bowell filling)
- SimDVH unlikely the same as TxDVH...
- Aim at constant bladder filling (difficult to maintain)
- Different regions – Different endpoints

Full and empty bladder scans (for ITV generation)





Hellebust TP, Radiother Oncol 2001
Muren LP, Radiother Oncol 2003
Turner SL, IJROBP 1997
Viswanathan AN, et al. IJROBP 2010

Sigmoid colon

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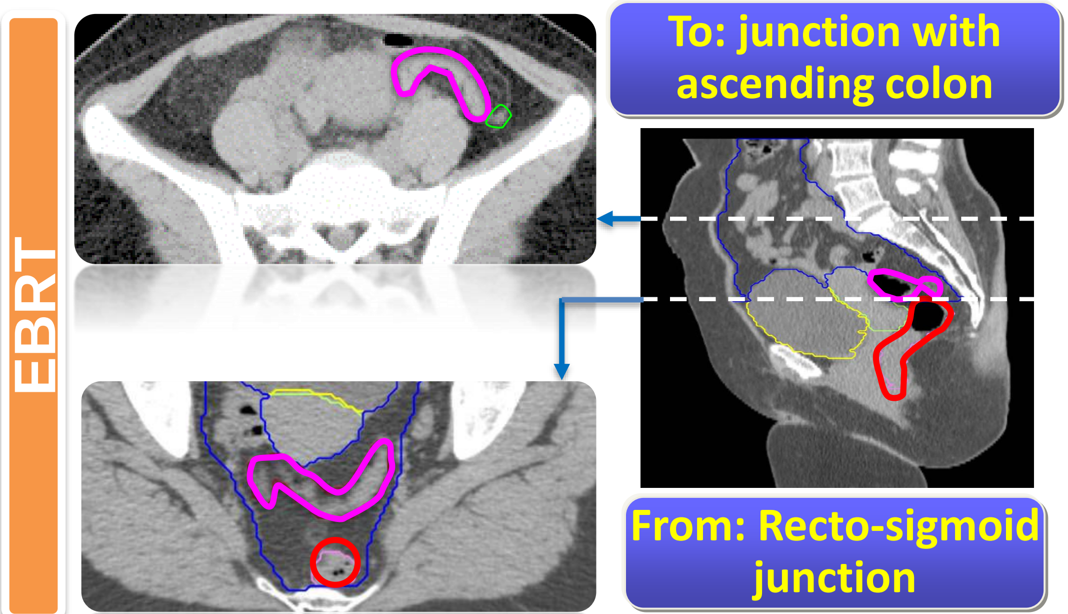
Organ	Standardized TPS name	Tumor category	Consensus definition
Sigmoid	Sigmoid	GYN	Bowel continuing where the AnoRectum contour ended. Stops before connecting to the ascending colon laterally. Contoured when a brachytherapy applicator rests in the uterus. Any sigmoid adjacent or above the uterus, as well as the brachytherapy applicator, should be contoured.



Gay H, et al. Int J Radiat Oncol Biol Phys 2012;83(3):353-362.
GEC ESTRO Recommendations I & II

Bowel

General Remarks (uncertainties)

- Missing Clear Links between DVH parameters and Toxicity
- Bowel = Small + Large Bowel in most studies
- Highly mobile organ:

  Only ≈ 20% occupies same position during the course of treatment

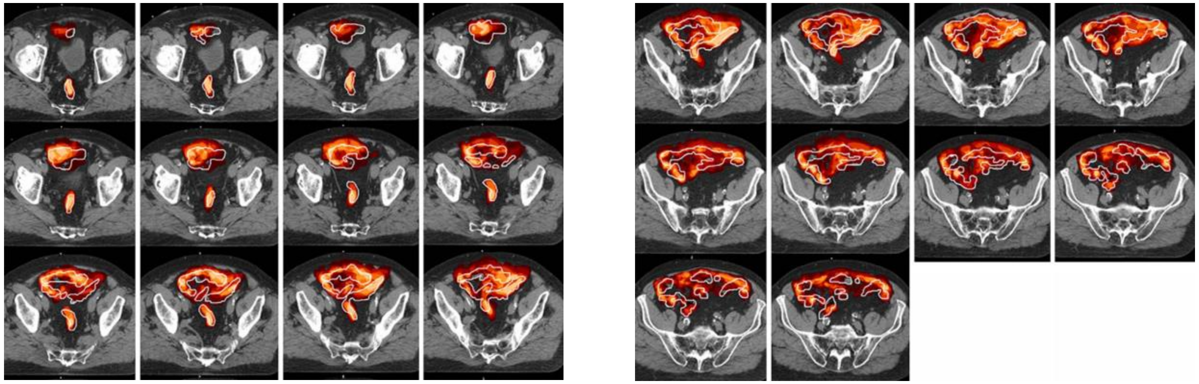
  → Blurring the evidence on DVH - Toxicity relations

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

Bowel: What to contour?

High mobility → A need for a margin (PRV)?

Hysing 2006: Bowel location probability mapping



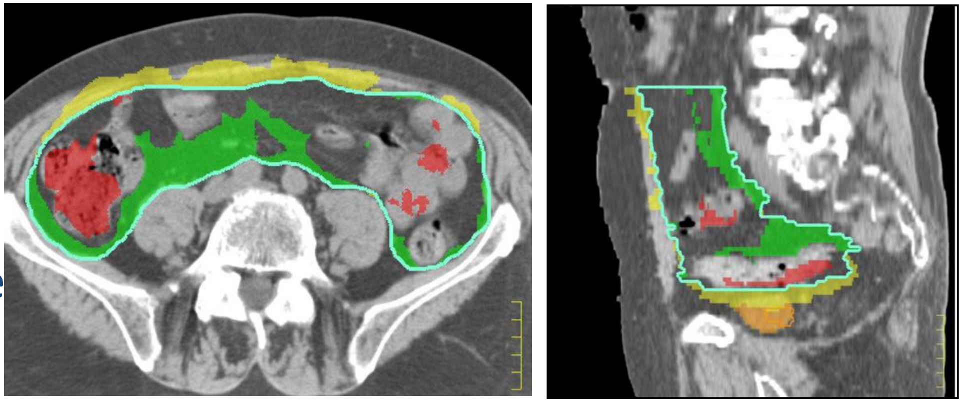
≈10 mm margin around visible bowel loops proposed

Hysing LB. Radiother Oncol 2006

Bowel: What to contour?

Three Strategies to contour bowel

- Bowel Segments
- Bowel Segments + 1 cm
- Intestinal cavity ("bowel bag")



Contouring of bowel bag proposed as a robust method to take organ motion into account

Outer contour of bowel loops including the mesenterium

Sanguineti LB. Radiother Oncol 2008 *Fiorino C. IJROBP 2009 (modified definition)* *Kavanagh BD, et al. IJROBP 2010*

Gyn Recommendation: Contour Bowel Bag

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Table RTOG male and female pelvis normal tissue consensus definitions

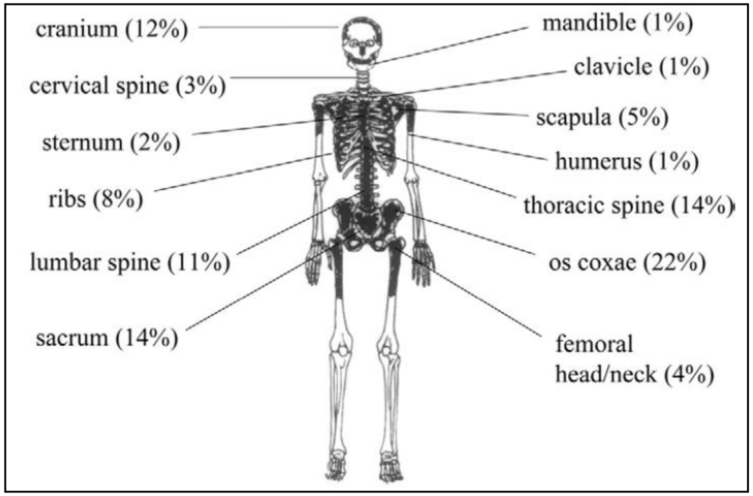
~~Organ~~	Standardized TPS name	Tumor ~~category~~	Consensus definition
Bowel bag	BowelBag	GU, GYN	Inferiorly from the most inferior small or large bowel loop or above the Rectum (GU) or AnoRectum (GYN), whichever is most inferior.* If, when following the bowel loop rule, the Rectum or AnoRectum is present in that axial slice, it should be included as part of the bag; otherwise, it should be excluded. Tips: Contour the abdominal contents excluding muscle and bones. Contour every other slice when the contour is not changing rapidly, and interpolate and edit as necessary. Finally, subtract any overlapping non-GI normal structures. If the TPS does not allow subtraction, leave as is.
Small bowel	SmallBowel	GI	To distinguish from large bowel, the use of oral contrast is encouraged.* After administration of contrast (*e.g.*, 3 oz of Gastrografin (Bracco Diagnostics Inc., Princeton, NJ) and 3 oz of water–barium mixture) 30 minutes before scanning, the small bowel can be outlined as loops containing contrast.

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

Bone Marrow

Around 50% of adult BM located in lower L spine and pelvic bones

- Red BM is active compartment
- High sensitivity for radiation
- Repopulation capability



Pelvic RT

- ↓ **White blood cell count**
- ↓ **Hemoglobin**
- ↓ **Platelet count**

Concomitant ChT increases BM toxicity

Mell LK. IJROBP 2006
Sacks EL. Cancer 1978
Rubin P. Cancer 1973
Brixey CJ. IJROBP 2002
Lujan AE. IJROBP 2003
Fiorino C. Radiother Oncol 2009
Ahmed RS IJROBP 2004
Roeske JC Radiother Oncol 2005

Bone Marrow

Concomitant ChT - RT increases BM toxicity

Meta-analysis Group results

VOLUME 26 · NUMBER 35 · DECEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

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

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration

"Serious hematologic toxicity increased by approximately 2- to 10-fold in individual trials."

Vale C, Journal of Clinical Oncology, 2008

Red bone Marrow

Radiotherapy and Oncology 123 (2017) 164–168

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Red bone marrow segmentation

The feasibility of semi-automatically generated red bone marrow segmentations based on MR-only for patients with gynecologic cancer

Anna Andreychenko [a,*], Petra S. Kroon [a], Matteo Maspero [a], Ina Jürgenliemk-Schulz [a], Astrid A.C. De Leeuw [a], Marnix G.E.H. Lam [b], Jan J.W. Lagendijk [a], Cornelis A.T. van den Berg [a]

[a] Department of Radiotherapy; and [b] Department of Nuclear Medicine, Center for Image Sciences, University Medical Center Utrecht, The Netherlands

Conclusion: This study shows that delineations of the RBM for the radiotherapy with RBM sparing can be generated semi-automatically using MR scans only.

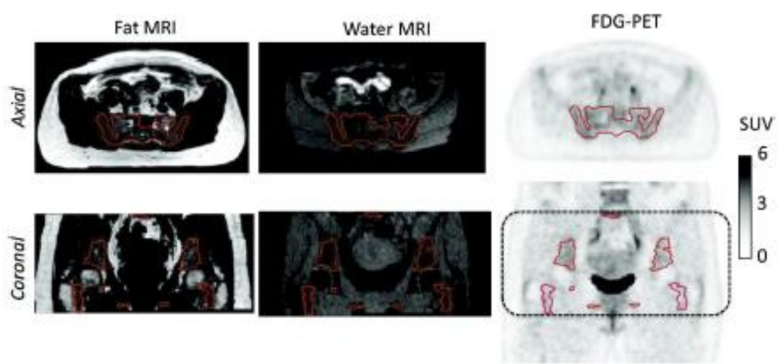


Fig. 2. The segmented RBM regions (red contours) superimposed on fat/water MR and FDG-PET images are shown on axial and coronal planes. The dashed rectangle in PET image outlines the field of view of the MR images.

Conclusion

Delineation of red bone marrow can be generated semi-automatically

Proximal Femurs

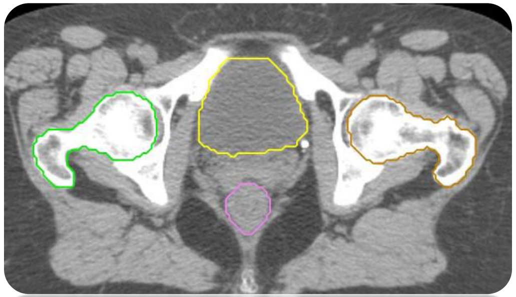
International Journal of Radiation Oncology biology • physics

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

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

Table RTOG male and female pelvis normal tissue consensus definitions

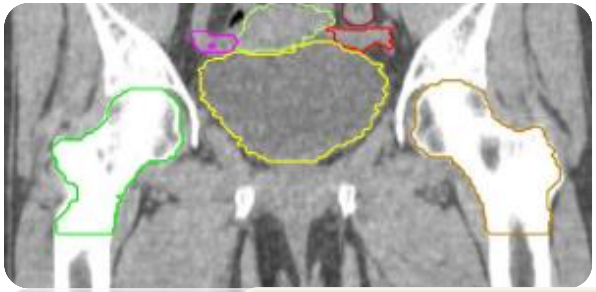
Organ	Standardized TPS name	Tumor category	Consensus definition
Proximal femurs	Femur_R Femur_L	GU, GYN, GI	The proximal femur inferiorly from the lowest level of the ischial tuberosities (right or left) and superiorly to the top of the ball of the femur, including the trochanters. Tips: Auto-contouring threshold parameters with bone can facilitate this process but requires editing any auto-contouring artifacts.



Each femur separately

Superior: top of the head of femur

Inferior: Lowest level of ischial tuberosities



Include trochanters

Auto contouring + editing helpful

Interpolation + editing helpful

Both femoral heads to the level of trochanter minor

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

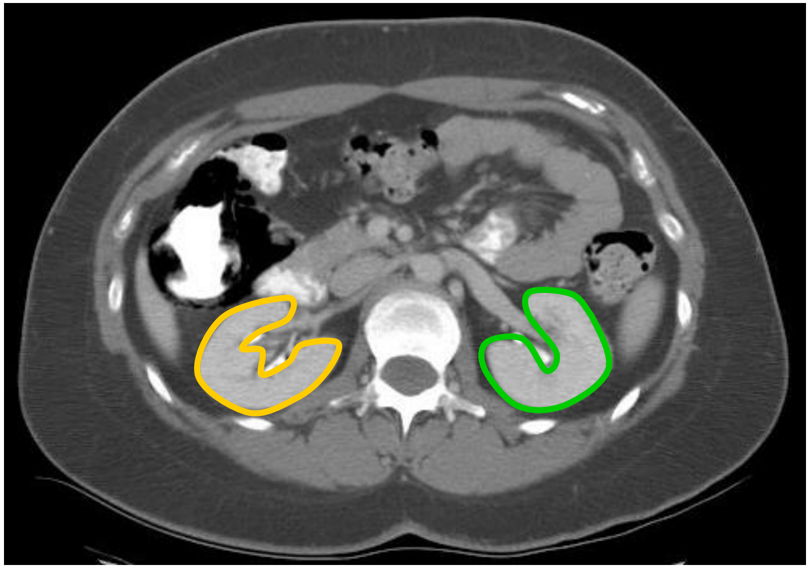
Kidneys

Delineate each kidney separately

Ideally, parenchyma: functional compartment

Include collecting system? error introduced; magnitude unclear

Evaluate dose to each kidney and both togethter

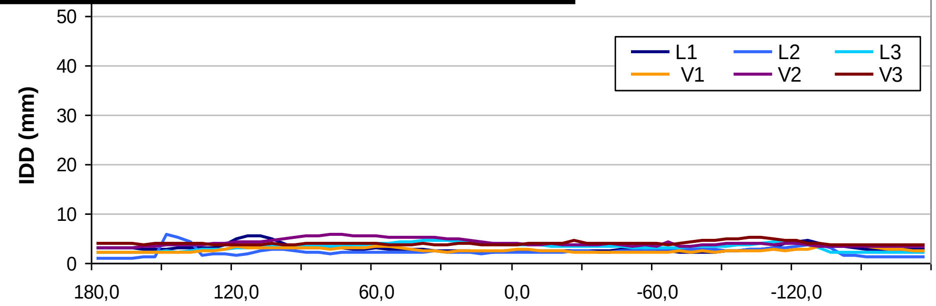


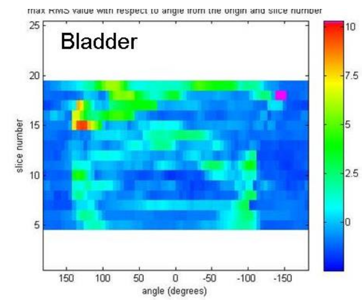
Dawson LA. IJROBP 2010

Accurate contouring

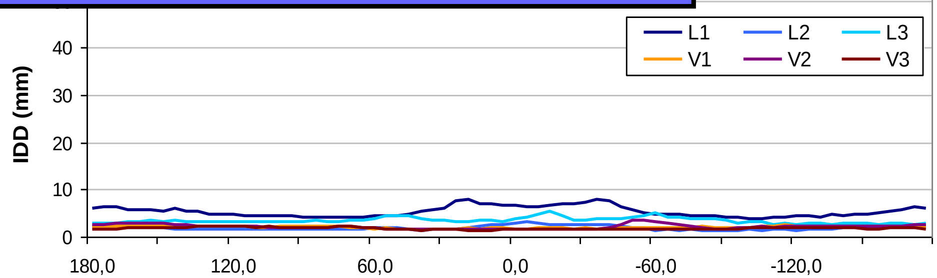
Pre-requisite for success of highly conformal RT but not that easy !

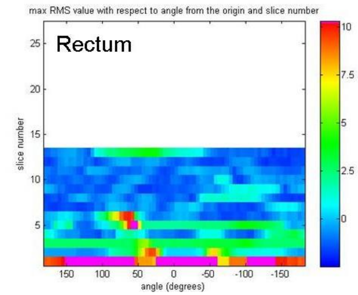
Uncertainty bladder: ≅ 3 mm

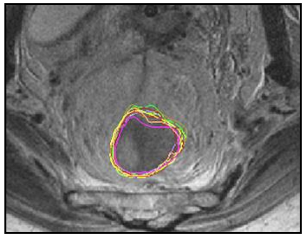




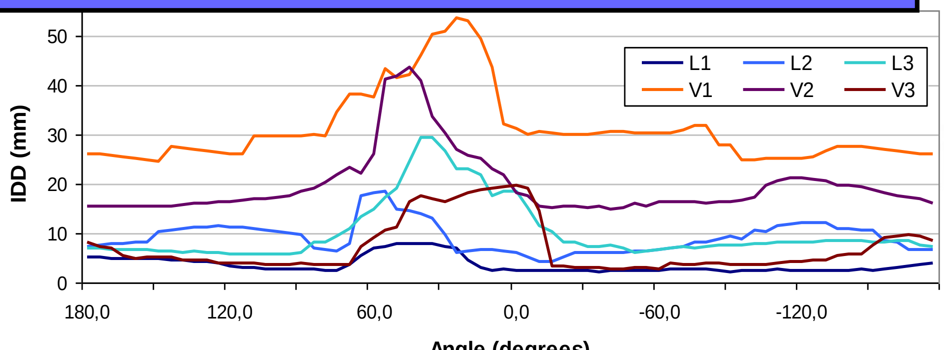
Uncertainty Rectum: up to ≅ 5 mm

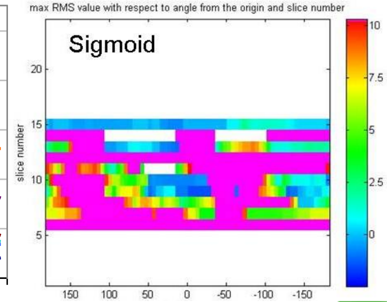


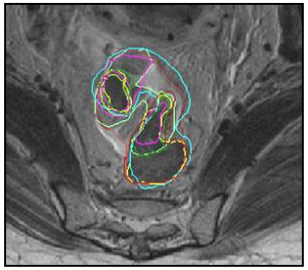




Uncertainty sigmoid colon: up to several cm!







Petric P, et al. Eur J of cancer 2013;49(2):S726 (Abstract; ECCO/ESMO/ESTRO, Amsterdam 2013)

Image guidance, organ motion and ITV/PTV

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

Prague 2017

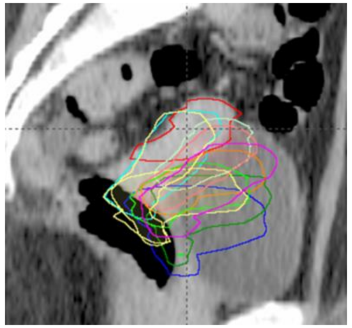
Kari Tanderup

Richard Pötter

Aarhus University Hospital

ITV and PTV

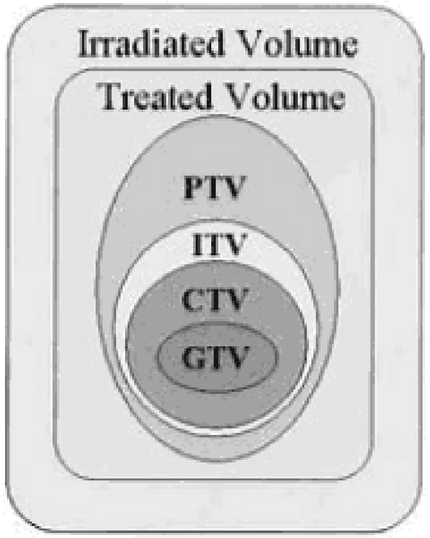
- **ITV: Internal variations**
  - **Position, size and shape of CTV**
    - **Tumour shrinkage**
    - **Organ movement**
    - **Organ deformation**

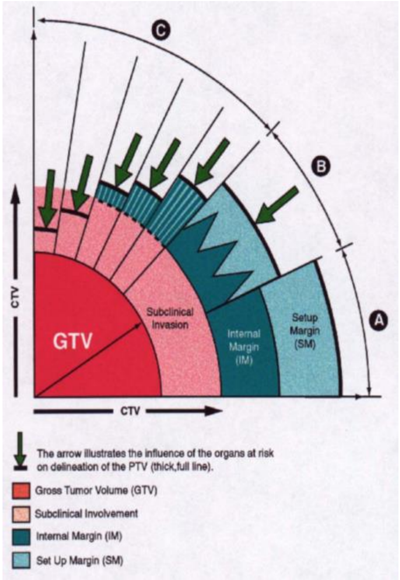


- **PTV: External variations**
  - **Beam positioning**
  - **Patient set-up (e.g. uncertainties when setting up according to skin marks)**

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

- **ITV and PTV margins are not directly "additive"**





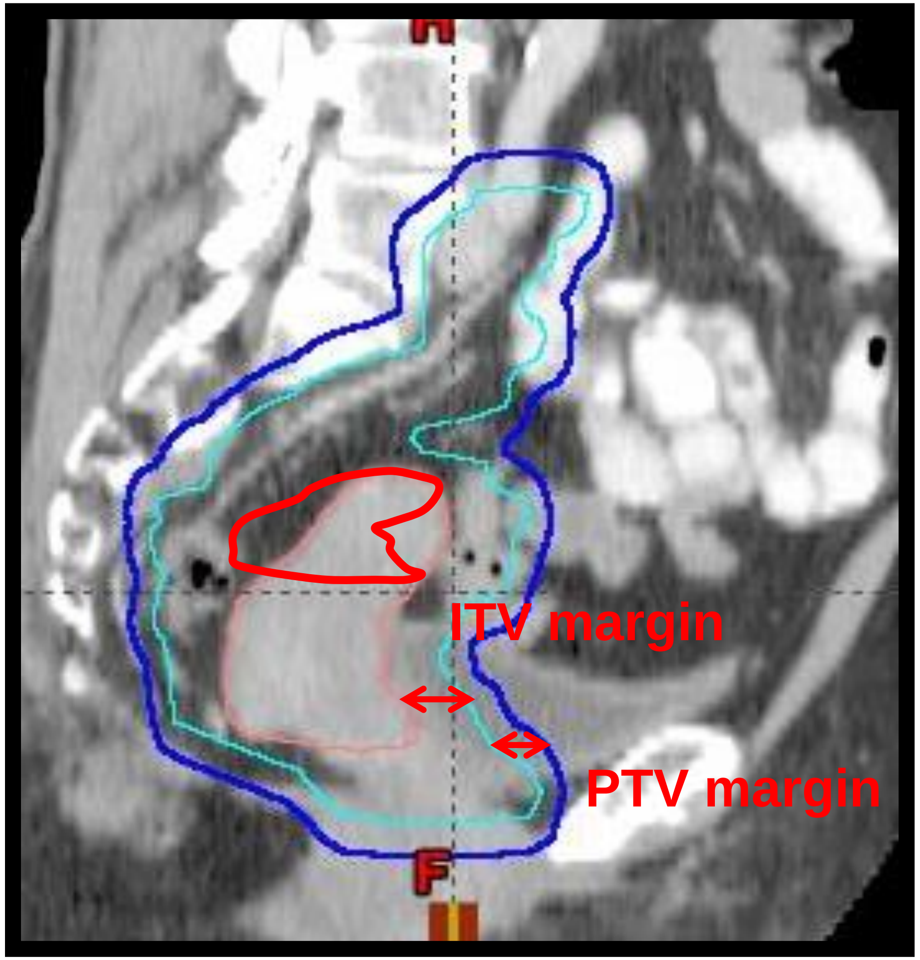
On which target volumes should we add ITV margin?

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

Margins in cervix cancer

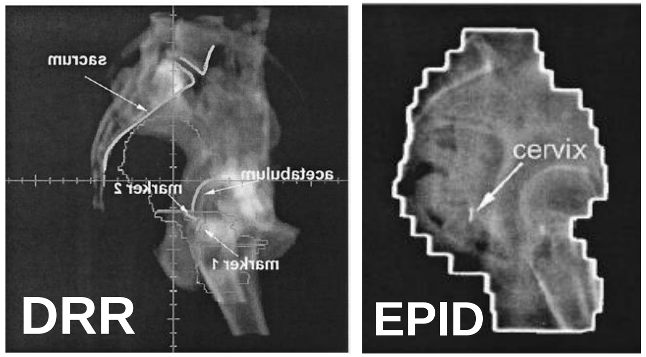
- Primary CTV
  - ITV margin
  - PTV margin
- Pathologic nodes
  - PTV margin
- Elective CTV
  - PTV margin

- Role of on-board imaging?

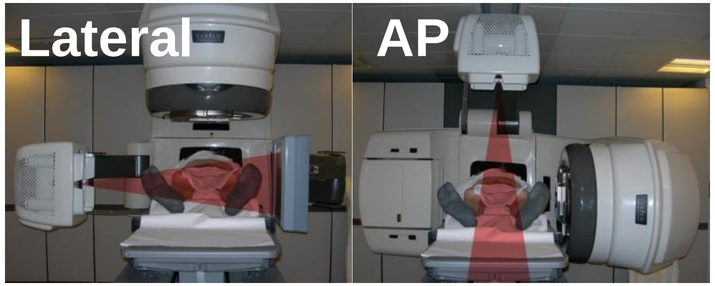


IGRT methods

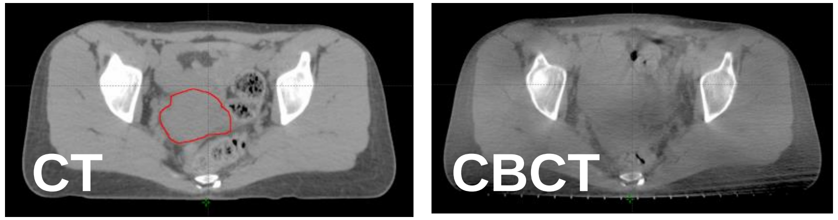
- **EPID (Electronic Portal Imaging Device)**
  - **MV**
  - **2D**



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



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

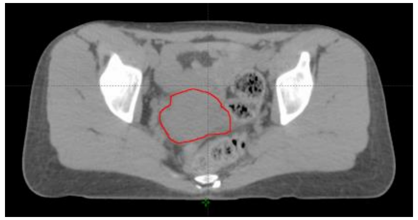


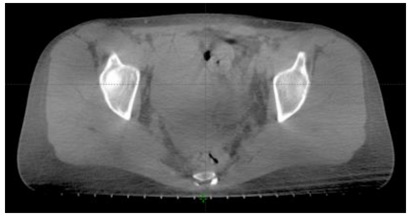
How to fuse CT planning scan to on-board imaging (CBCT, kV, EPID)?

A. Bony fusion

B. Fusion on cervix

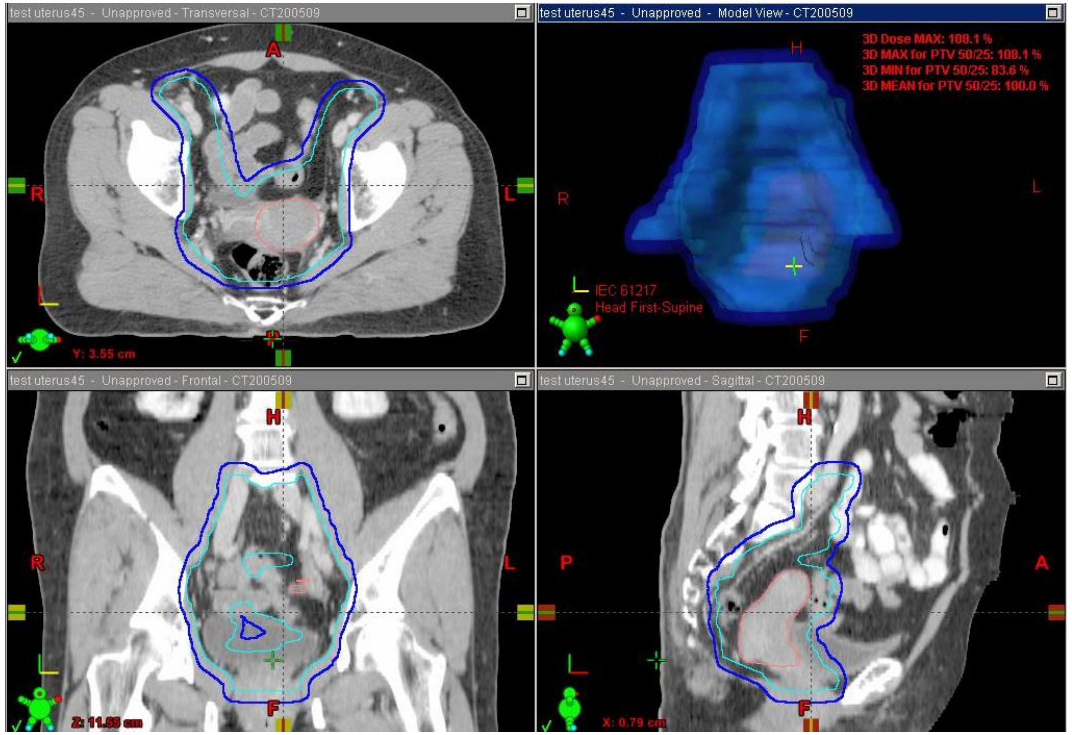
C. Fusion on markers in cervix





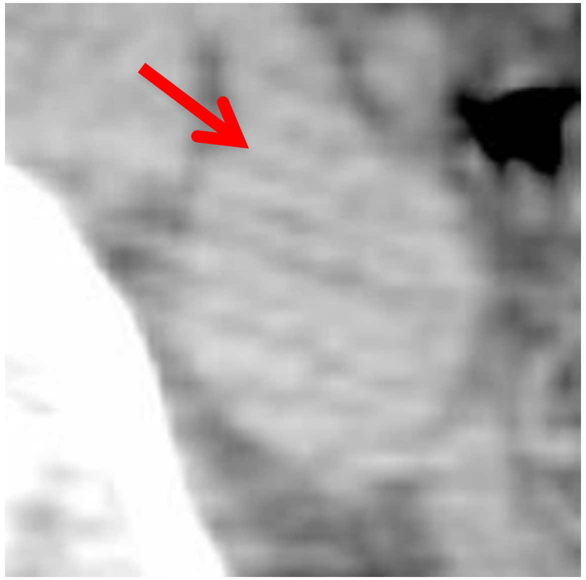
PTV elective target volume

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

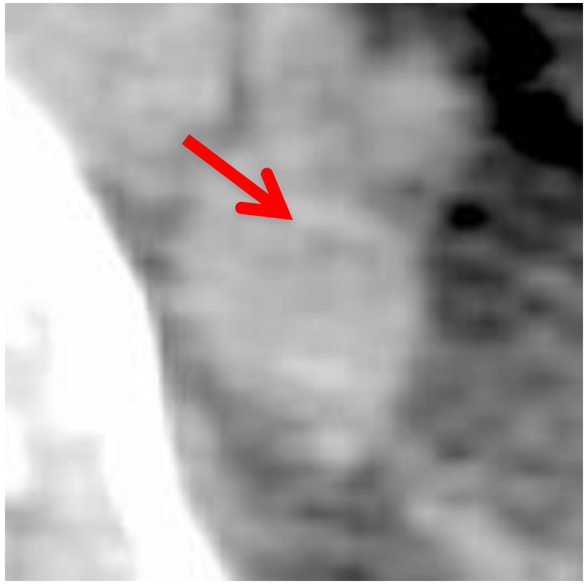


PTV pathological lymph nodes

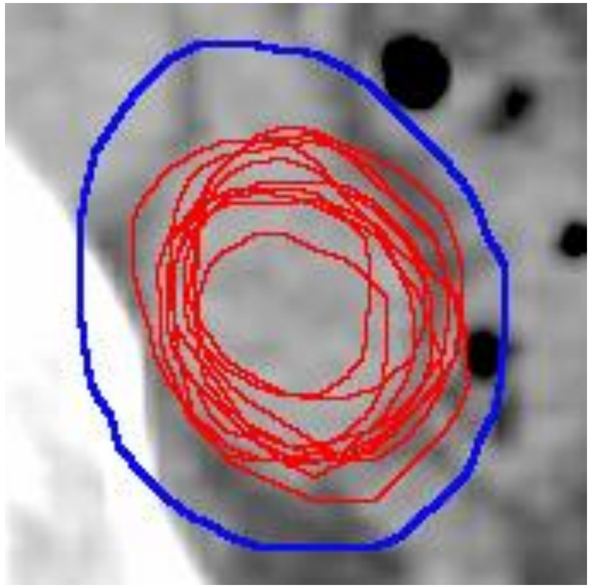
- **Assumption:**
  - **Lymph nodes are in a relatively fixed relation to bony anatomy**
  - **Bony registration aligns pathological lymph node target**
- **Most often pathological lymph nodes shrink during RT**



CBCT 1st treatment



CBCT 24th treatment

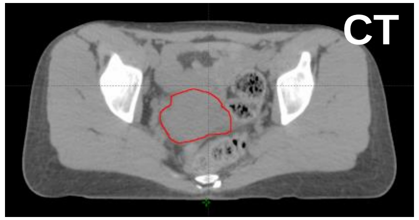


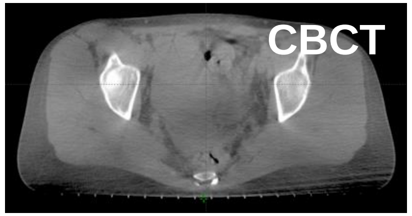
PTV (blue)
GTV on 10 CBCT (red)

Anne Ramlov, Radiother Oncol, in press

Skin marks versus daily bony registration

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





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

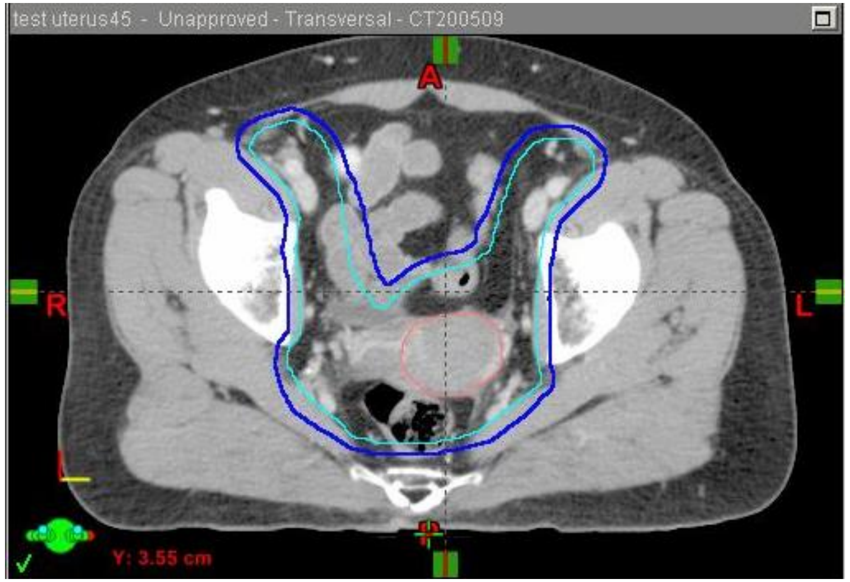
Variable	Vertical [mm]	Lateral [mm]	Longitudinal [mm]
Mean (M)	0,4	2,7	0,4
Σ	3,6	2,9	2,6
σ	3,6	3,2	2,4
Margin*	11,6	9,6	8,2

*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?

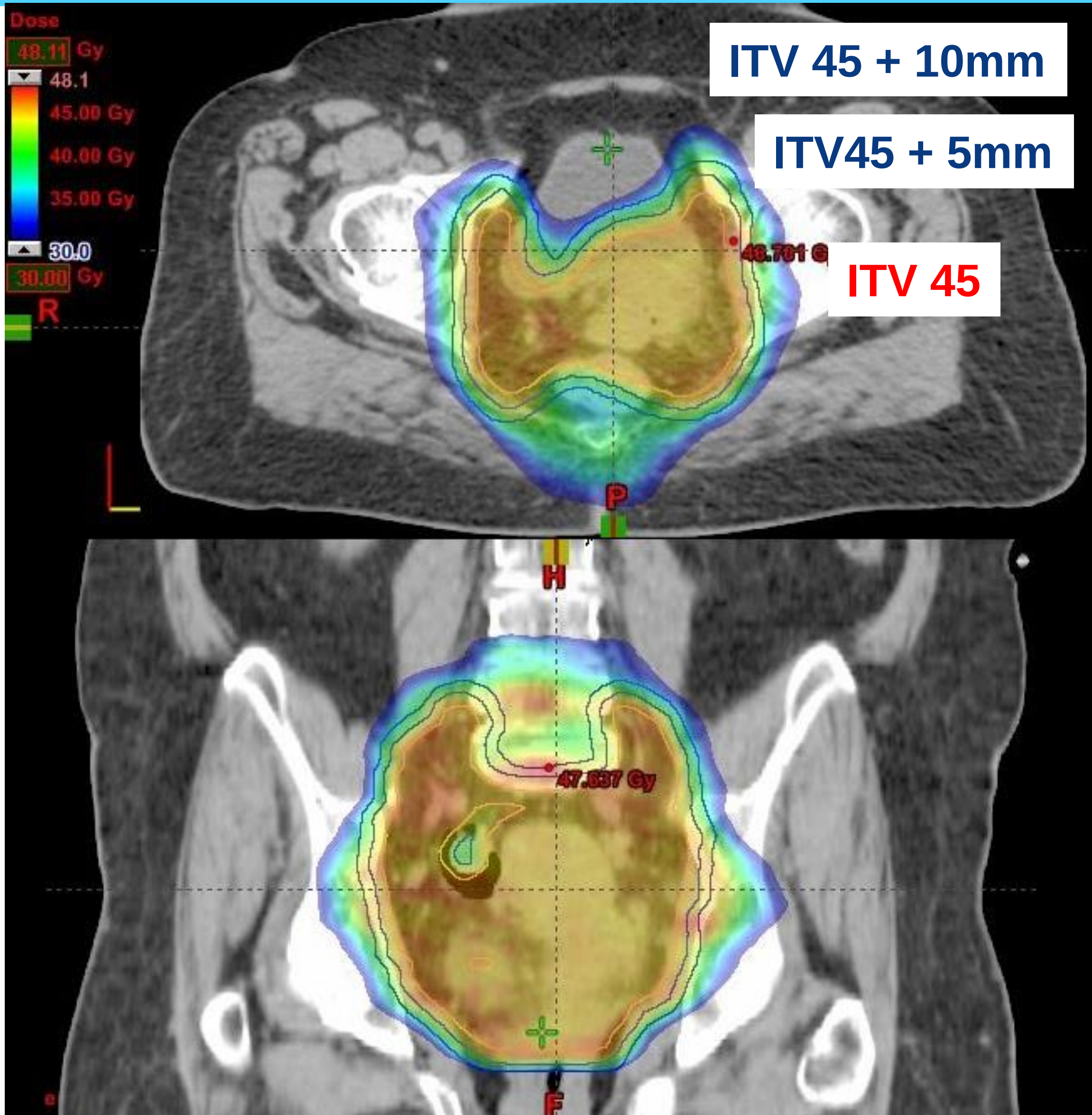
A. It is too many ressources to implement daily IGRT
B. It will not have impact on morbidity
C. 5mm PTV margin is not safe for target coverage
D. PTV margin reduction to 5mm is worthwhile

Why does the margin matter?

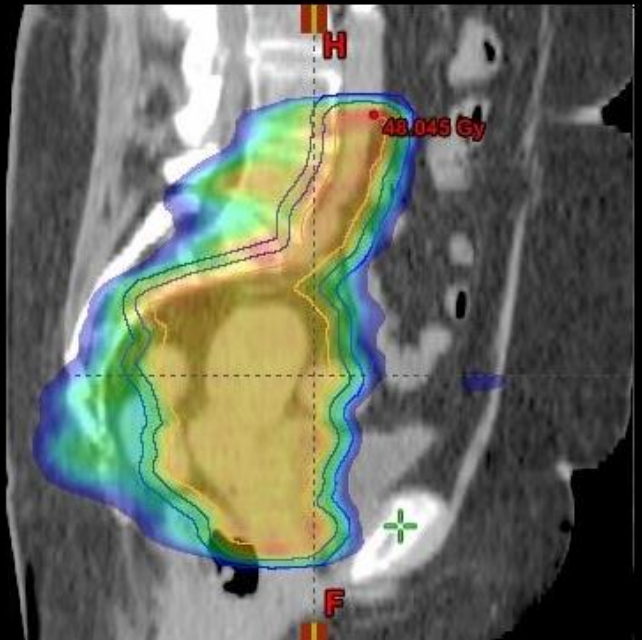
D. Verellen *et al.*, Nature Reviews Cancer 2007

$$r$$
$$\downarrow$$
$$\pi r^2$$
$$\downarrow$$
$$4/3\pi r^3$$

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

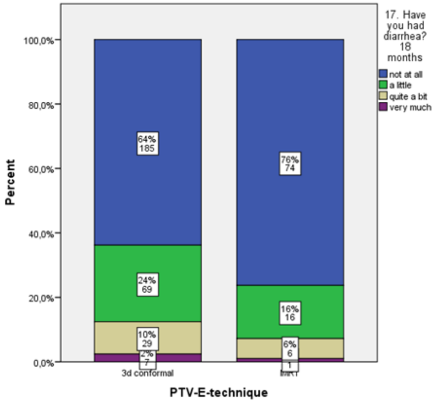


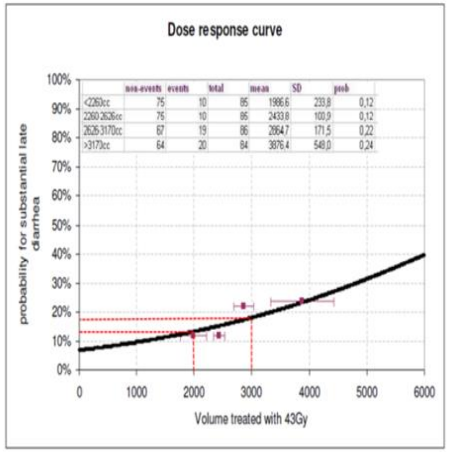
ITV 45	ITV 45 + 5mm	ITV 45 + 10mm
1000 cc	1500 cc	2000 cc



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**





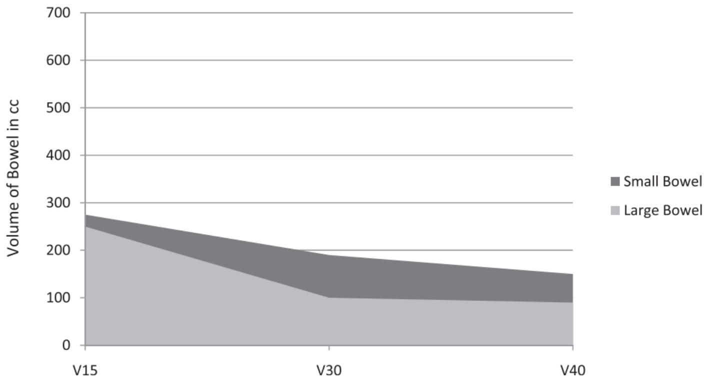
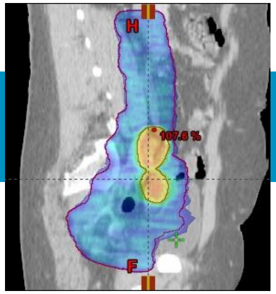


Fig. 1. Recommended dose–volume histogram. Restricting small bowel and large bowel volume doses within the recommended area under curve can restrict late bowel toxicity to within 5%.

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

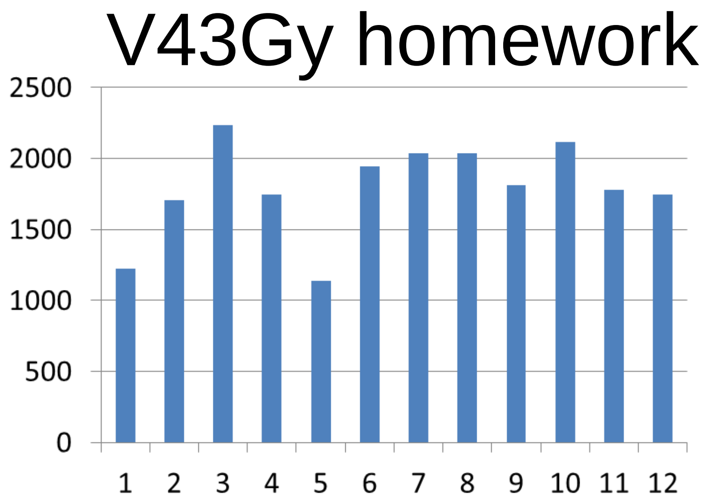
Nodal boost	Pelvic
V57 (cc) EMBRACE I	160 cm^3
CTV-N vol (cc)	10cc per node
PTV-N vol (cc) 5mm margin	30cc per node
V50Gy (cc) EMBRACE II	120 cm^3

Change of practice: EMBRACE I → EMBRACE II

CRT → IMRT : ↘ 500cm^3 (V43)

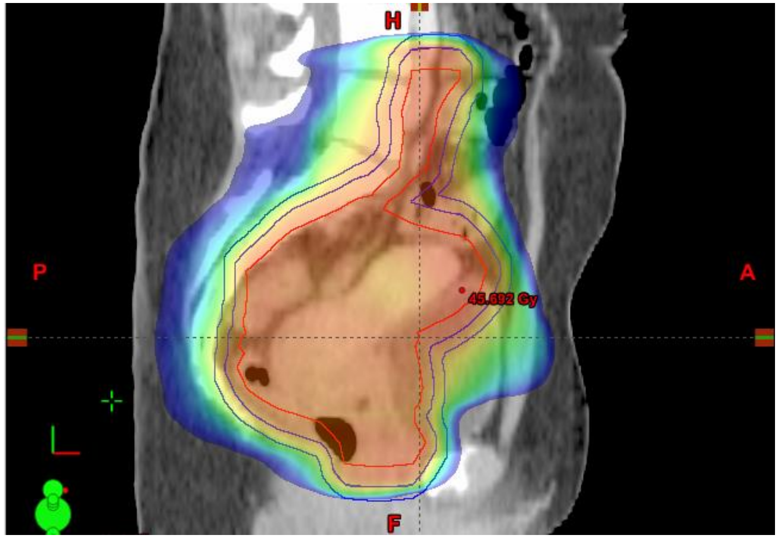
50Gy → 45Gy : ↘ 400cm^3 (V43)

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

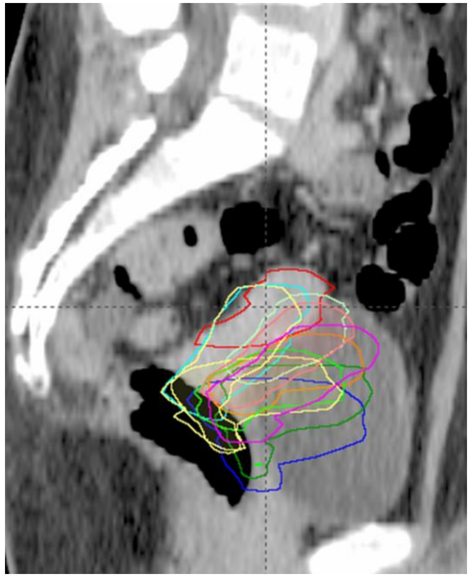
- Jadon et al. A systematic review of organ motion and image-guided strategies in external beam radiotherapy for cervical cancer. Clin Oncol (R Coll Radiol). 2014 Apr;26(4):185-96
  - 39 relevant studies
  - Patient specific motion: 5-40mm
  - Population based margins would be large (up to 40mm)

- 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}

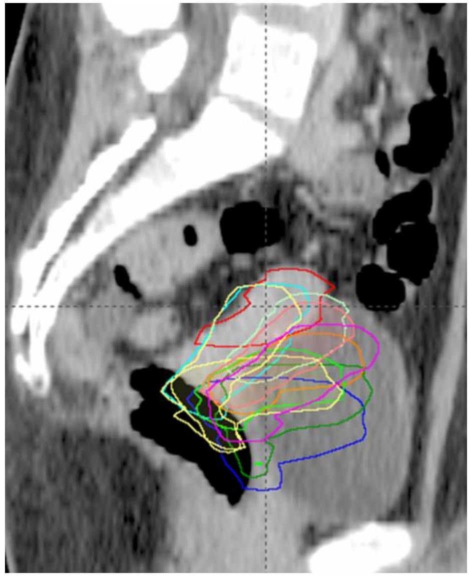


A. 20Gy
B. 30Gy
C. 35Gy
D. >40Gy

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**

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

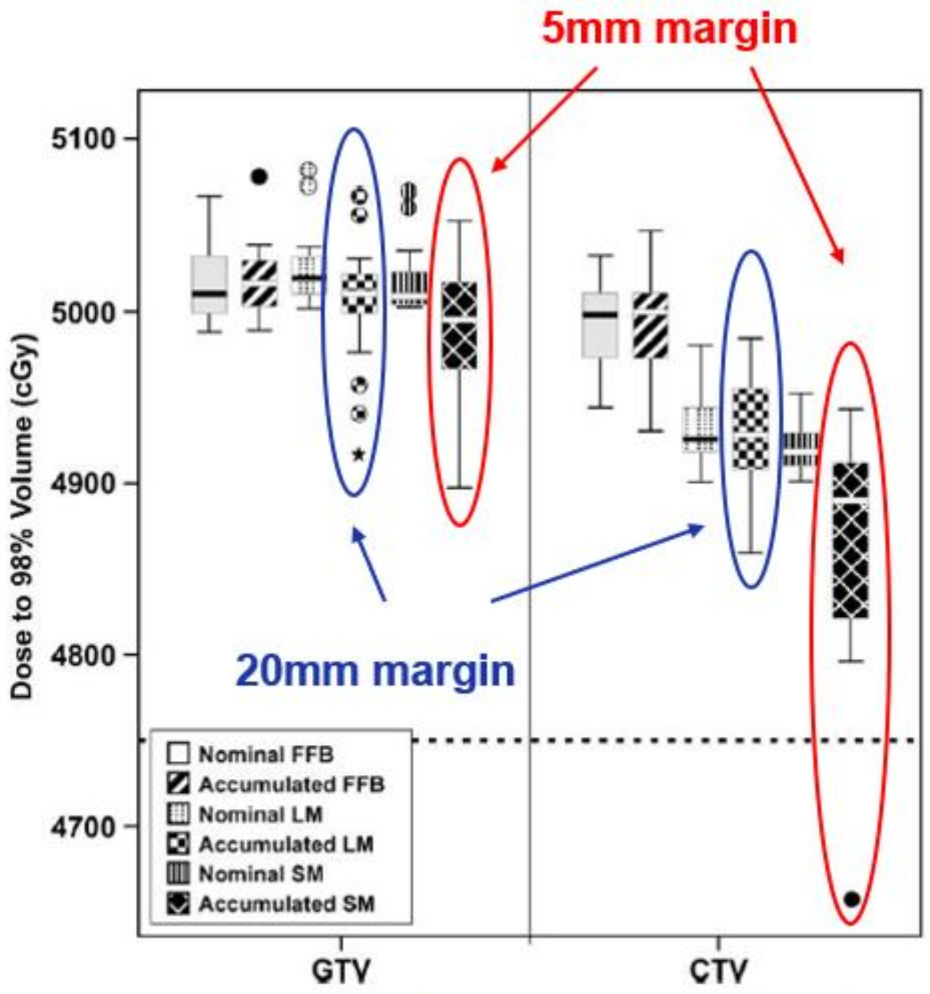
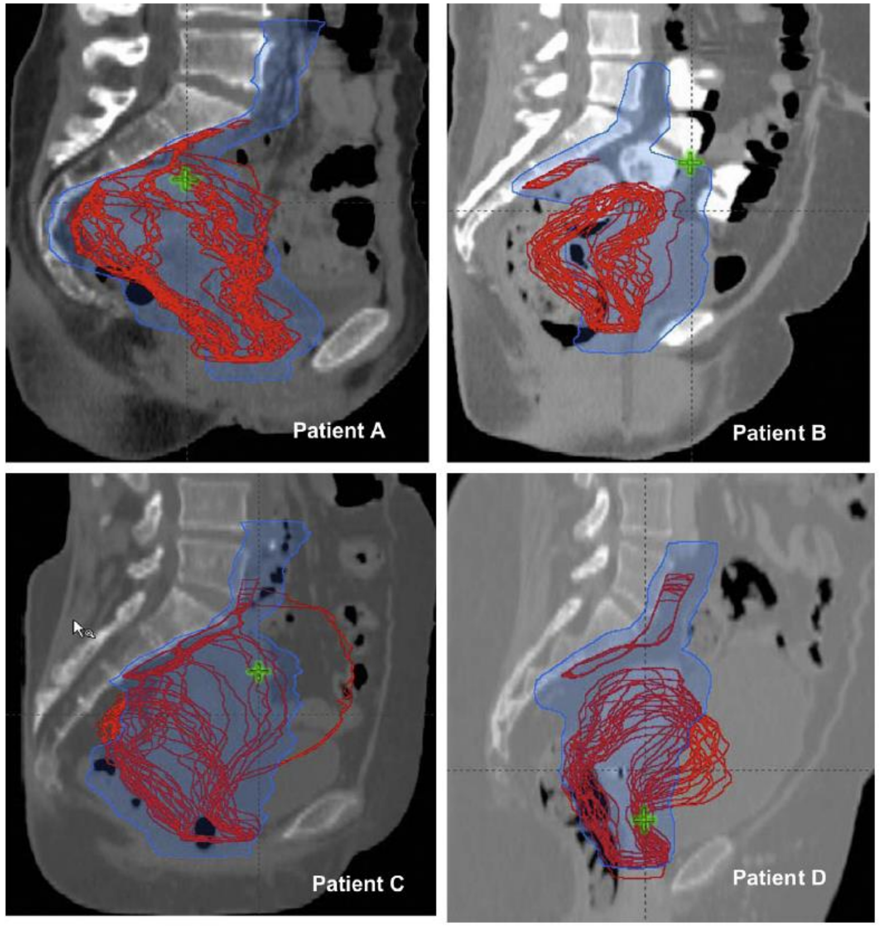


Fig. 4. Box plots of nominal and accumulated dose to 98% of gross tumor volume and primary tumor clinical target volume for four-field box (FFB), large-margin (LM), and small-margin (SM) plans.

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



A. A

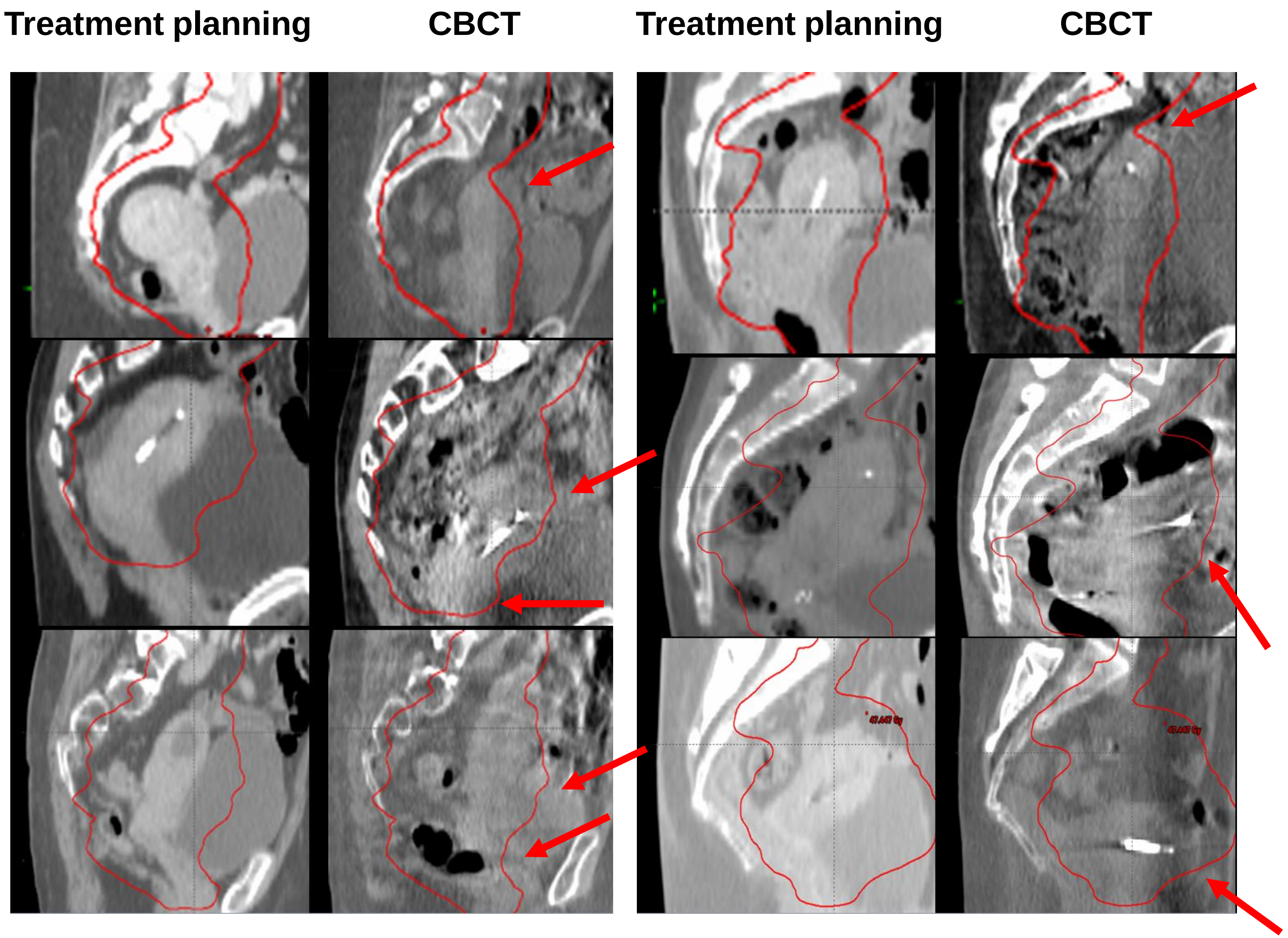
B. B

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

CBCT monitoring



Daily CBCT monitoring by RTTs

91% of CBCTs evaluable

7/23 pts replanned

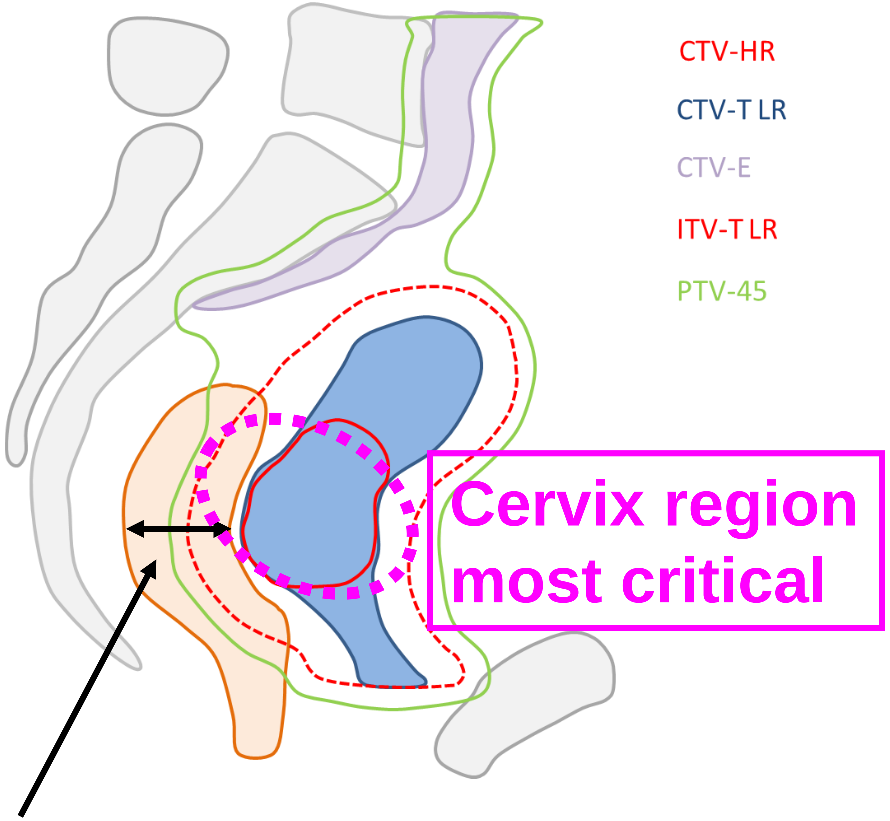
3/23 had benefit

- **2 cervix**
- **1 uterus**

ITV-T LR and PTV-T LR

- **"Standard" approach:**
  - **10-15mm ITV margin**
  - **5mm PTV margin**
  - **Total 15-20mm margin**

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



Maximum rectal filling at treatment planning scan: 40mm

Bladder filling strategy in your department?

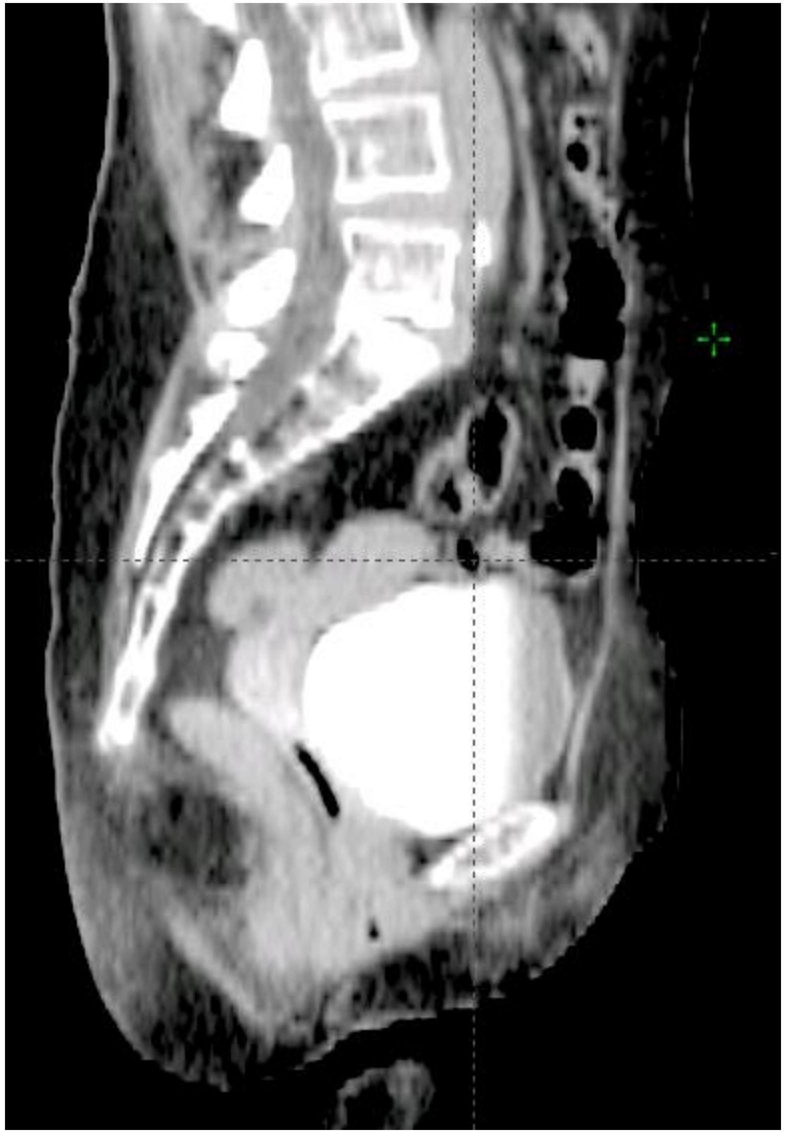
A. No bladder filling protocol
B. Patient to void before each fraction for reproducible bladder filling
C. Instruct patients to keep full bladder at treatment
D. Specific drinking protocol

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!**

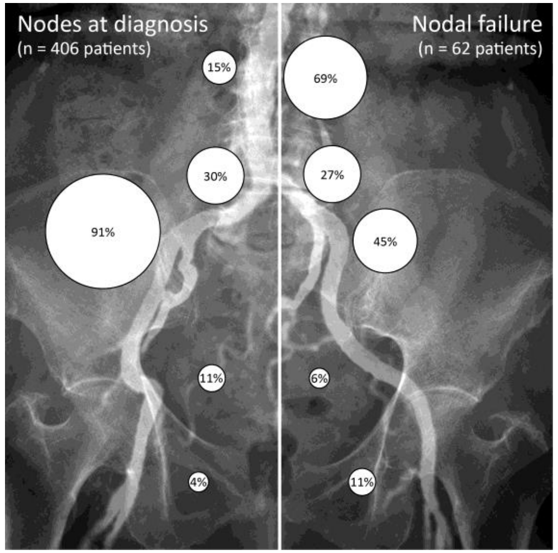


What has most impact on bowel dose?

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

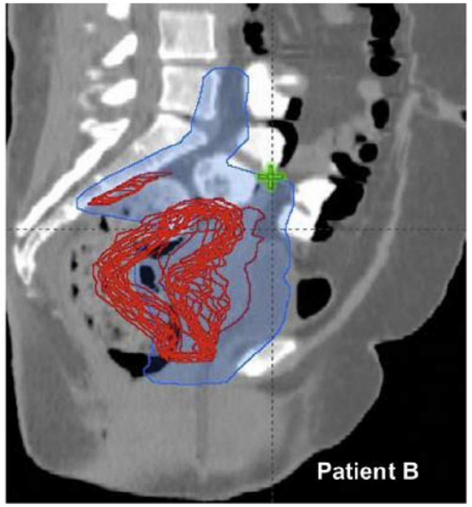
Take home message: nodal CTV

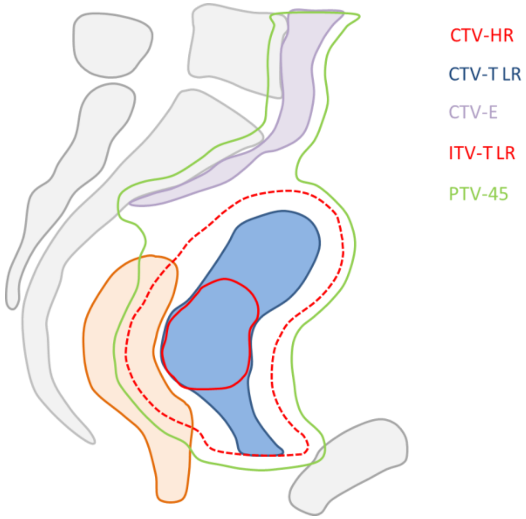
- **Margins add to considerable irradiation of normal tissue**
- **PTV margin for elective target volume:**
  - **7-10mm margin without daily image guidance**
  - **5mm margin with daily image guidance and bony fusion**
- **Potential in pelvic elective radiotherapy to reduce irradiated volume by 40%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





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Medical aspects of dose constraints including DVH parameters for EBRT planning

Ina Jürgenliemk-Schulz
Universtity Medical Centre Utrecht

Umesh Mahantshetty
Tata Memorial Centre, Mumbay

ESTRO
European Society for Therapeutic Radiology and Oncology

ESTRO GYN TEACHING COURSE
Prague 2017

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Which statement is wrong?

A. IMRT helps to reduce organ dose

B. IMRT is able to reduce treatment related morbidity

C. For IMRT planning pre-defined dose volume constraints are not important

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Contents

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

- Brachy part not included!

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EBRT for gyn cancer treatment

- Elective dose including draining lymphatic system
- Boost to regional pathologic nodes
- Boost to primary tumor if brachytherapy is not feasible
- Dose needed for tumor control to high for surrounding OAR
- Reduction according to ALARA, as low as reasonably achievable
- Dose constraints and DVH parameters help to balance between tumor dose and OAR dose

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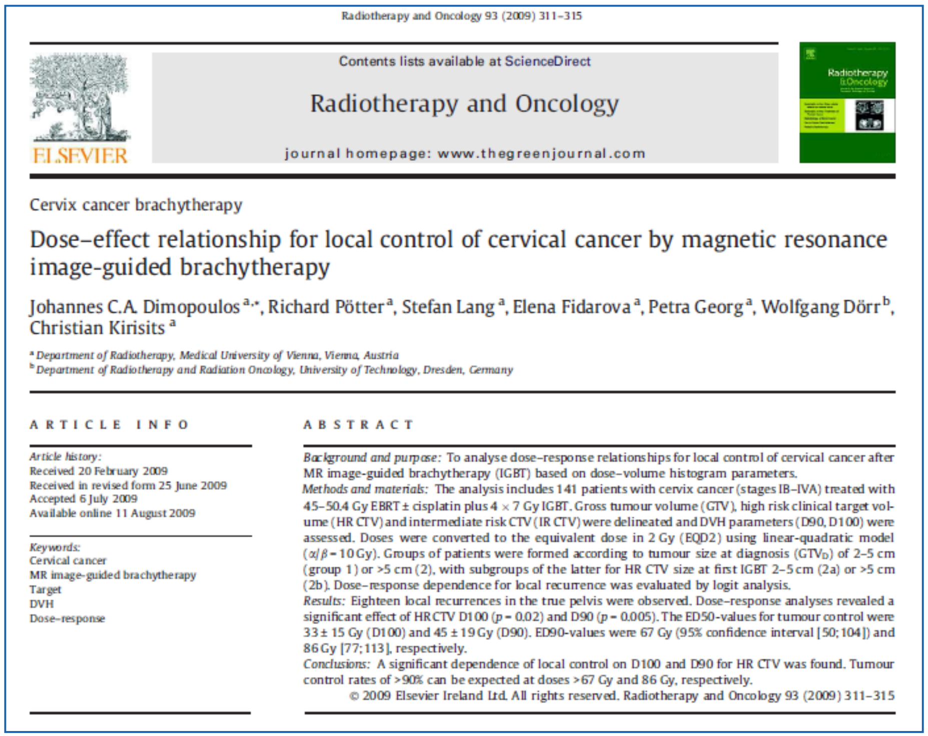
Evidence for dose needed to control primary tumor

Primary gyn tumors need dose (EBRT + BT)

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

Dimopoulos 2009


Radiotherapy and Oncology 93 (2009) 311–315

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Cervix cancer brachytherapy

Dose–effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy

Johannes C.A. Dimopoulos [a,*], Richard Pötter [a], Stefan Lang [a], Elena Fidarova [a], Petra Georg [a], Wolfgang Dörr [b], Christian Kirisits [a]

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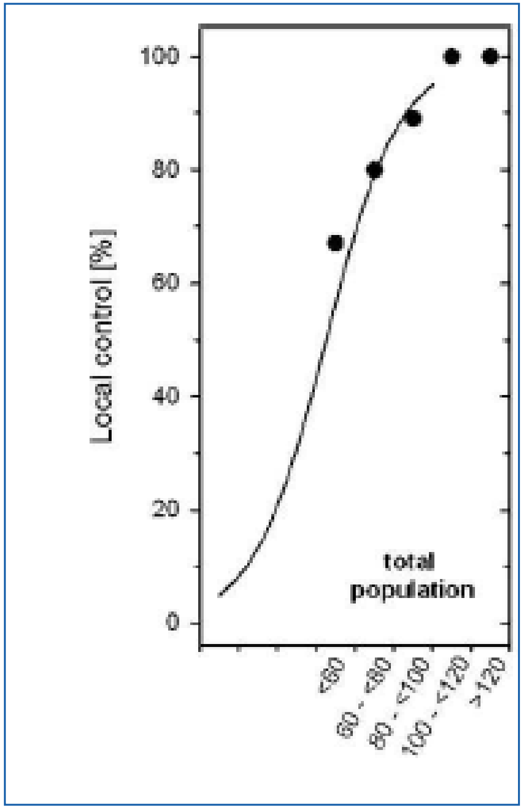
Target
DVH
Dose–response

ABSTRACT

Background and purpose: To analyse dose–response relationships for local control of cervical cancer after MR image-guided brachytherapy (IGBT) based on dose–volume histogram parameters.
Methods and materials: The analysis includes 141 patients with cervix cancer (stages IB–IVA) treated with 45–50.4 Gy EBRT ± cisplatin plus 4 × 7 Gy IGBT. Gross tumour volume (GTV), high risk clinical target volume (HR CTV) and intermediate risk CTV (IR CTV) were delineated and DVH parameters (D90, D100) were assessed. Doses were converted to the equivalent dose in 2 Gy (EQD2) using linear-quadratic model (α/β = 10 Gy). Groups of patients were formed according to tumour size at diagnosis (GTV_D) of 2–5 cm (group 1) or >5 cm (2), with subgroups of the latter for HR CTV size at first IGBT 2–5 cm (2a) or >5 cm (2b). Dose–response dependence for local recurrence was evaluated by logit analysis.
Results: Eighteen local recurrences in the true pelvis were observed. Dose–response analyses revealed a significant effect of HR CTV D100 (p = 0.02) and D90 (p = 0.005). The ED50-values for tumour control were 33 ± 15 Gy (D100) and 45 ± 19 Gy (D90). ED90-values were 67 Gy (95% confidence interval [50; 104]) and 86 Gy [77; 113], respectively.
Conclusions: A significant dependence of local control on D100 and D90 for HR CTV was found. Tumour control rates of >90% can be expected at doses >67 Gy and 86 Gy, respectively.
 Radiotherapy and Oncology 93 (2009) 311–315



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Evidence for dose needed to control primary tumor

Bigger tumors need more dose

- Local control depends on applied dose in a certain volume

Tanderup 2016

Radiotherapy and Oncology 120 (2016) 441–446

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Image guided brachytherapy in cervical cancer

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

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

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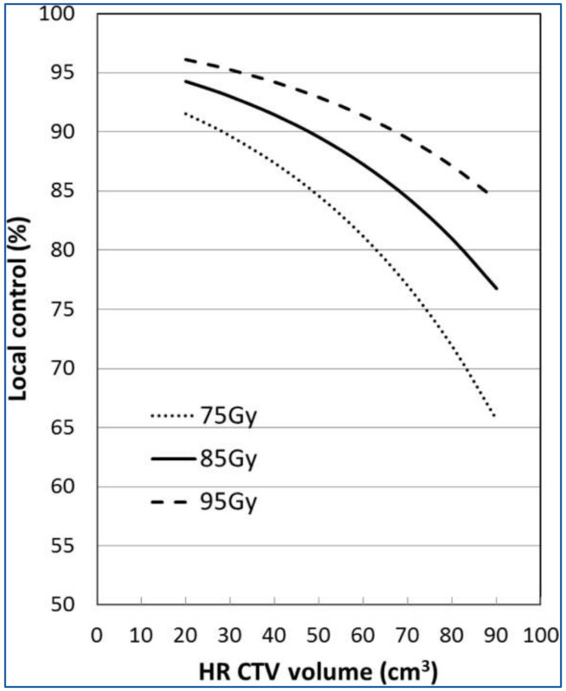

UMC Utrecht

Evidence for dose needed to control primary tumor

Preliminary results with SBRT, no brachy

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

Mendez 2016

Clinical Oncology 29 (2017) 378–384

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

ELSEVIER

Original Article

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

CrossMark

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

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

Abstract

Aims: To summarise and evaluate the current literature in gynaecological tumours treated with stereotactic ablative body radiotherapy (SABR) through a systematic review using the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) guideline.
Materials and methods: A literature search through Medline, EMBASE and Cochrane databases resulted in 22 pertinent manuscripts. Selected studies evaluated the locoregional role of SABR in gynaecological tumours, regardless of SABR clinical indication. Data on local control, toxicity and SABR dose and technique were extracted by at least two investigators.
Results: In total, 330 patients received locoregional SABR for gynaecological tumour and had measurable clinical outcomes. Six different clinical scenarios were identified: (i) boost to external beam radiotherapy (EBRT) for cervical cancer as radical treatment; (ii) boost to EBRT for non-operable endometrial cancer; (iii) treatment for pelvic and/or para-aortic node metastases; (iv) adjuvant treatment after surgery in uterine/cervix cancers; (v) salvage of non-nodal pelvic recurrences and (vi) vulvar or vaginal malignancies. Except for SABR as a boost for non-operable endometrial cancer, local control over 80% was found in a range of median follow-up of 4–132 months. Local control in non-operable endometrial tumours receiving SABR was 53%. In salvage treatments for non-nodal pelvic relapses, SABR was associated with about a 20% grade 3–4 gastrointestinal toxicity.
Conclusion: There is no clear consensus or evidence on the defined role of SABR in gynaecological tumours. Local control and toxicity associated with SABR seems reasonable for most clinical indications found by this review with a short median follow-up. When used for salvage of non-nodal pelvic recurrences, SABR may be associated with high rates of grade 3–4 late gastrointestinal toxicity.

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

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Evidence for dose needed to control primary tumor

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

Mendez 2016

Table 1
Summary of studies, dose and local control of stereotactic ablative body radiotherapy (SABR) in different clinical scenarios (the five patients with vaginal or vulvar cancers are not reported)

Reference	Design	Number of patients	Total number of patients	EBRT	Number of patients with respective BED (α/β=10)	Median SABR BED	PTV (cm^3)	Follow-up (months)	Local control % (no. patients)	Combined local control
(A) SABR as a cervical boost										
[11]	Retrospective	11	34	Yes	11 48 Gy	39.1 Gy	31–68	6	100 (11)	91%
[12]	Retrospective	9		Yes	1 19.2 Gy, 1 19.5 Gy, 2 28 Gy, 1 33.6 Gy, 3 39.1 Gy, 1 51.3 Gy		NR	NR	77.8 (7)	
[13]	Retrospective	6		Yes	5 28 Gy, 1 32.1 Gy		NR	14	100 (6)	
[14]	Retrospective	4		Yes	1 7.5 Gy, 1 22.5 Gy, 1 35.5 Gy, 1 37.5 Gy		11–174[‖]	4	100 (4)	
[15]	Retrospective	2		Yes	2 28 Gy		NR	12	100 (2)	
[16]	Case report	1		Yes	1 33.6 Gy		NR	22	100 (1)	
[17]	Retrospective	1		Yes	1 22.5 Gy		258	13	0 (0)	
(B) SABR as an endometrial boost										
[18]	Retrospective	11	13	Yes	9 45 Gy, 1 38,4 Gy, 1 30 Gy	45 Gy	NR	18	55 (6)	53%
[14]	Retrospective	1		Yes	1 31.2 Gy		45.8[‖]	4	100 (1)	
[17]	Retrospective	1		Yes	1 22.5 Gy		180	15	0% (0)	
(C) SABR for pelvic or para-aortic lymph node metastases										
[19]	Retrospective	83[#]	83[*]	43 patients[§]	44 89.7 Gy; 19 100–137 Gy; 33 51–79 Gy	89.7 Gy	NR	20.4	80 (67)	83%
[20]	Retrospective	52		12 patients	Not possible to define		NPD	31	92 (48)	
[21]	Retrospective	30		4 patients	5 69.3 Gy; 1 29.9 Gy; 2 60 Gy; 5 79 Gy; 3 84.3 Gy; 11 89 Gy; 2 100 Gy; 1 112 Gy		1.3–57.3	19	67 (20)	
[22]	Retrospective	13		NR	Not possible to define		NR	4.6	100 (13)	
[23]	Phase I	6		NPD	Not possible to define		NPD	15.5	NPD	
[24]	Retrospective	5		4 patients	1 28 Gy, 4 45 Gy		NPD	16	80 (4)	
(D) Adjuvant SABR										
[25]	Retrospective	26	38[†]	Yes	26 23.8 Gy	23.8 Gy	NR	47	92 (24)	92%
[26]	Retrospective	23		NR	23 28.8 Gy		NR	132	NPD	
[15]	Retrospective	12		Yes	12 23.8 Gy		NR	12.6	92(11)	
(E) Salvage SABR to pelvic recurrences (non-nodal)										
[27]	Retrospective	19	57[‡]	Yes	12 22.5 Gy; 2 60 Gy; 2 15 Gy; 1 47.6 Gy;1 30 Gy; 1 12 Gy	22.5 Gy	37–619	22	81 (16)	86%
[28]	Retrospective	16		Yes, 15/16	Not possible to define. 15–40 Gy in 3–5		25–310[¶]	12	93.7 (15)	
[17]	Retrospective	9		Yes	9 22.5 Gy		55–619	20	77 (7)	
[29]	Retrospective	8		Yes	Not possible to define		Not possible to define			
[30]	Retrospective	5		Yes	5 57.6 Gy		NR	10.6	NPD	
[31]	Retrospective	5		Yes	1 32 Gy, 1 36 Gy, 1 46 Gy, 1 57.6 Gy and 1 61.7 Gy		20–217	9	80 (4)	
[14]	Retrospective	4		Yes	3 37.5 Gy, 1 42.6 Gy		98–348[‖]	4	75 (3)	

(continued on next page)

L.C. Mendez et al. / Clinical Oncology 29 (2017) 378–384

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Evidence for dose to control elective region

Elective regions need dose

- Effective elective dose in endometrial and vulvar cancer is 46-50 Gy

Creutzberg 2000

Lancet 2000; **355:** 1404–11

ARTICLES

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

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

Perez 1998

ELSEVIER

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

● *Clinical Investigation*

IRRADIATION IN CARCINOMA OF THE VULVA: FACTORS AFFECTING OUTCOME

Carlos A. Perez, M.D.,* Perry W. Grigsby, M.D.,* K. S. Clifford Chao, M.D.,* Andrew Galakatos, M.D.,† Melahat Garipagaoglu, M.D.,‡ David Mutch, M.D.† and Mary Ann Lockett, M.B.A.*

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

Purpose: This report reviews the increasing role of radiation therapy in the management of patients with

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Evidence for dose to elective region and lymph node metastases

Lymph node metastases need dose

- Elective fields (including PAO) for cervix cancer are controlled with 45 Gy
- Node control is excellent after 55-60 Gy including sib

Vargo 2014

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

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

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

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

Summary

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

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Dose needed for lymph node metastases control

In literature still some uncertainty !

- Escalation typically recommended up to 55-60Gy

Grigsby PW, et al Int J Radiat Oncol Biol Phys 2001, 49(3):733–738.
Beadle BM, et al Int J Radiat Oncol Biol Phys 2010, 76(5):1396–1403.

- SIB IMRT – 55Gy/25# with option of sequential boost -10Gy/5#

Gynecologic Oncology 135 (2014) 239–243

- FDG avid nodal disease -62Gy/31# SIB

Cihoric *et al. Radiation Oncology* 2014, **9**:83

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Evidence that OAR do not like dose

Surrounding organs do not like dose; example bowel

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

Andreyev 2007

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

Overview

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

H. J. N. Andreyev

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

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

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

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

Tumors need dose

As high as intended and reasonably achievable

OAR do not like dose

A As
L Low
A As
R Reasonably
A Achievable

Validated dose constraints and DVH parameters help to make choices for treatment planning !

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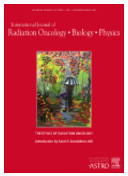
OAR DVH parameters in literature

Emami 1991,2013



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

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

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

Table 2: Normal Tissue Tolerance for Standard Fractionation

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

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

Not to forget!

Emami 2013

- Morbidity is not only a matter of dose
- Age, comorbidity, smoking…..

Table 1: Variables That Can Impact Normal Tissue Tolerance

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

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

Fiorino
IJROBP, 2009

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

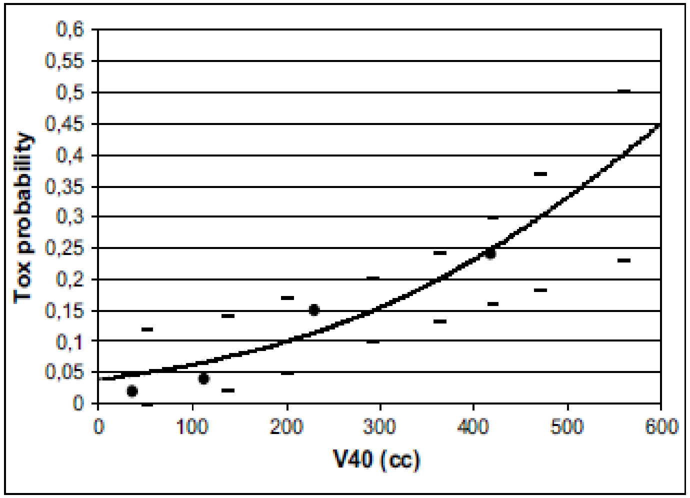


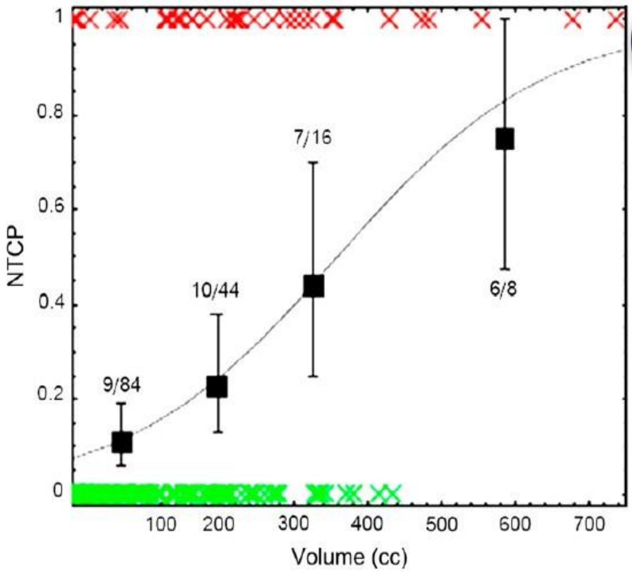
Fig. 1. The relationship between the V40 of the intestinal cavity (outside the planning target volume) and the risk of Grade 2–3 acute bowel toxicity is plotted, together with 95% confidence intervals (lo-

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

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

153 rectal cancer patients
3-field EBRT with concomitant chemotherapy
21 % acute G3 diarrhea

Robertson
IJROBP, 2010



Impact of V15 on diarrhea seemed strongest

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

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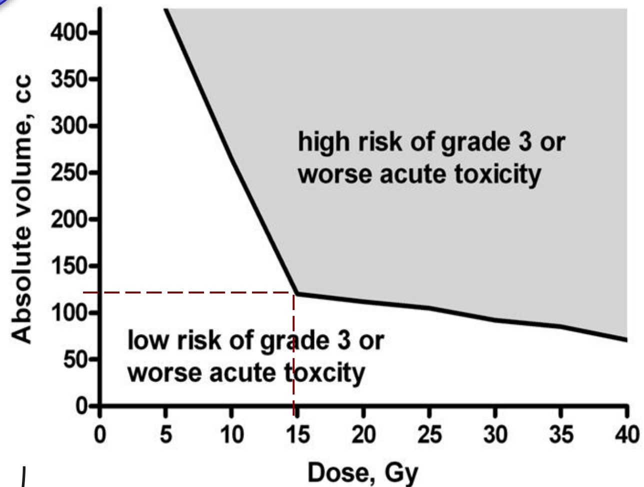
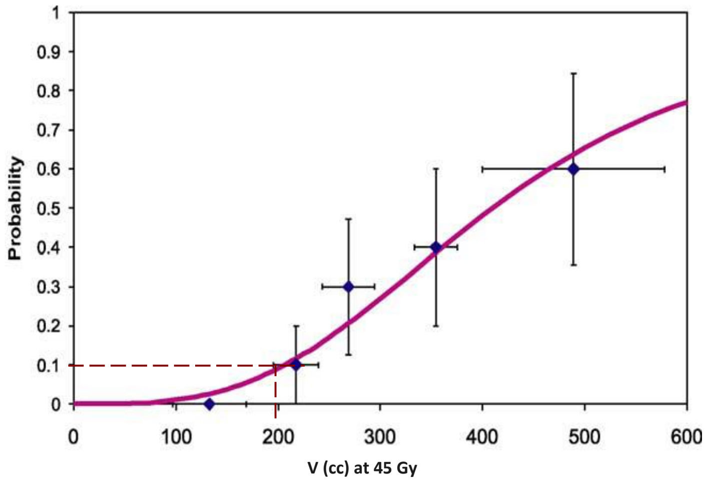
Dose constraints depend on contouring approach

Treshold – based risk models

Baglan
IJROBP, 2002

Roeske
Radiother Oncol
2003





Based on delineation of Bowel Loops

Based on delineation of Bowel bag

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

Review: Kavanagh DB, IJROBP 2010 (QUANTEC)

Marks: IJROBP 2010 (QUANTEC)

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DVH and patient reported outcome

Sini 2017

- Multicenter Italian study, prostate cancer, EBRT 50-55.4 Gy
- 206 patients with complete DVH parameters for bowel
- PRO using IBDQ-B (inflammatory bowel disease questionnaire)


Radiotherapy and Oncology 124 (2017) 296–301

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Bowel dose-volume toxicity

Patient-reported intestinal toxicity from whole pelvis intensity-modulated radiotherapy: First quantification of bowel dose–volume effects

Carla Sini [a], Barbara Noris Chiorda [b], Pietro Gabriele [c], Giuseppe Sanguineti [d], Sara Morlino [e], Fabio Badenchini [f], Domenico Cante [g], Viviana Carillo [h], Marcella Gaetano [h], Tommaso Giandini [i], Valeria Landoni [j], Angelo Maggio [k], Lucia Perna [a], Edoardo Petrucci [l], Vincenzo Sacco [b], Riccardo Valdagni [e,f,m], Tiziana Rancati [f], Claudio Fiorino [a,*], Cesare Cozzarini [b]

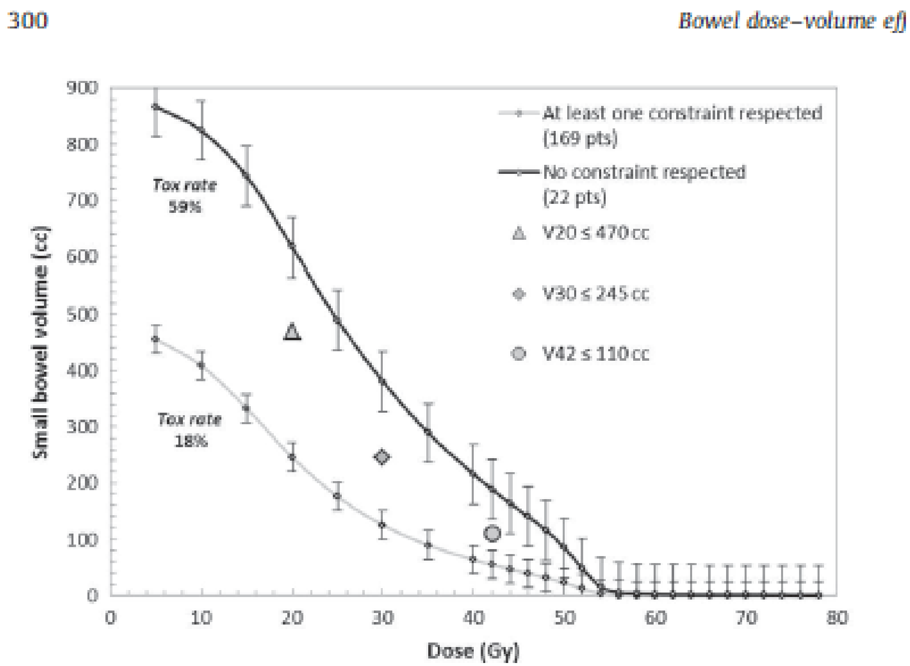

Fig. 4. Absolute average DVHs for patient with/without liquid evacuation (endpoint ΔIBDQ5 < −2) for high risk (V20 > 470 cm^3, V30 > 245 cm^3, V42 > 110 cm^3, n = 22) and low risk (the others, n = 169) patients. Error bars denote standard error.

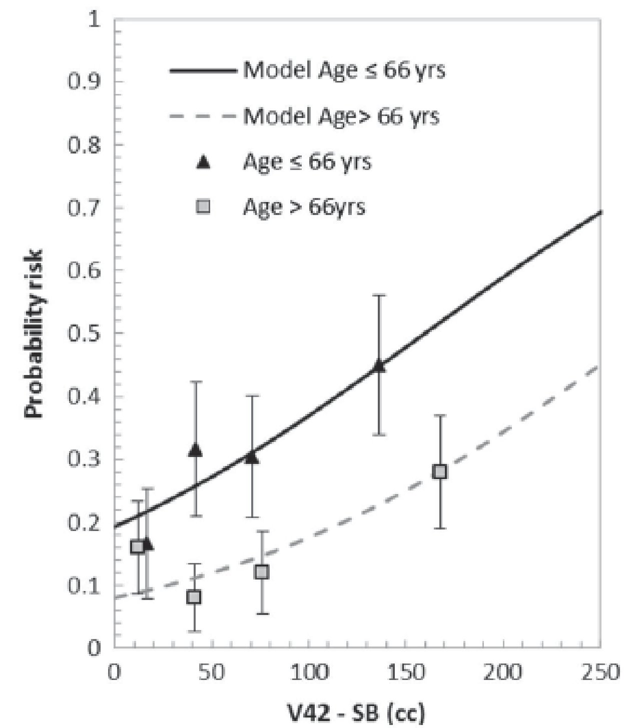

Fig. 3. Risk of acute liquid evacuation vs bowel V42 for patients older and younger than 66 years.

Not to forget!

Emami 2013

- Morbidity is not only a matter of dose
- Age, comorbidity, smoking…..

Table 1: Variables That Can Impact Normal Tissue Tolerance

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

Bowel including duodenum

Verma
IJROBP, 2014

- For duodenum IMRT limiting V55 to less than 15% - statistically significant differences in 3-year rate of actuarial duodenal toxicity

Poorvu
IJROBP, 2013

- IMRT allows sufficient sparing of the small bowel to allow dose escalation to 65Gy

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Literature data dose constraints rectum and bladder

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

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Vagina

Also vagina does not like EBRT dose

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

Kirchheiner 2016

Radiotherapy and Oncology 118 (2016) 160–166

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Brachytherapy

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

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

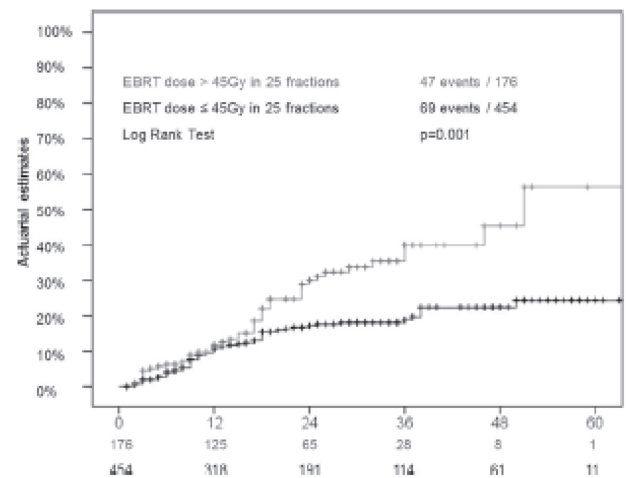

Fig. 3. Actuarial estimates for vaginal stenosis G ≥ 2 in patients according to the EBRT dose.

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Do we need dose constraints and DVH parameters?

Yes !

- Dose needed to control macroscopic tumors is high
- Dose levels different for primary tumors and node metastases
- Dose levels for elective targets 45-50Gy
- Evidence for importance of DVH parameters is constantly increasing
- Dose to OAR should be as low as possible “ALARA”

How to achieve the required dose gradients ?

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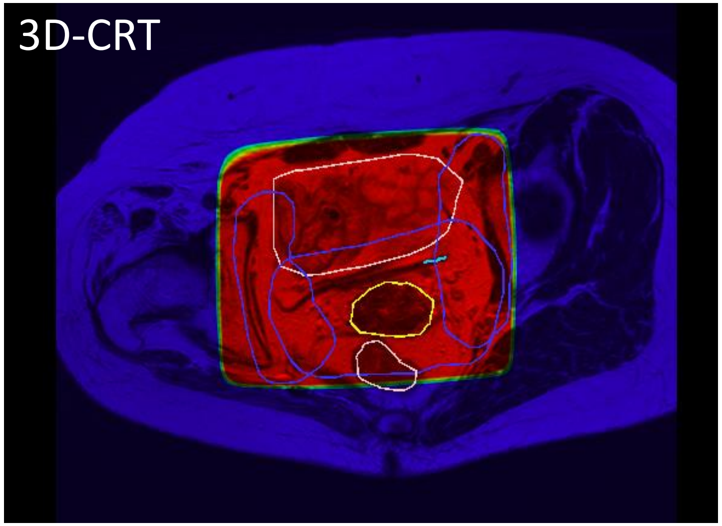
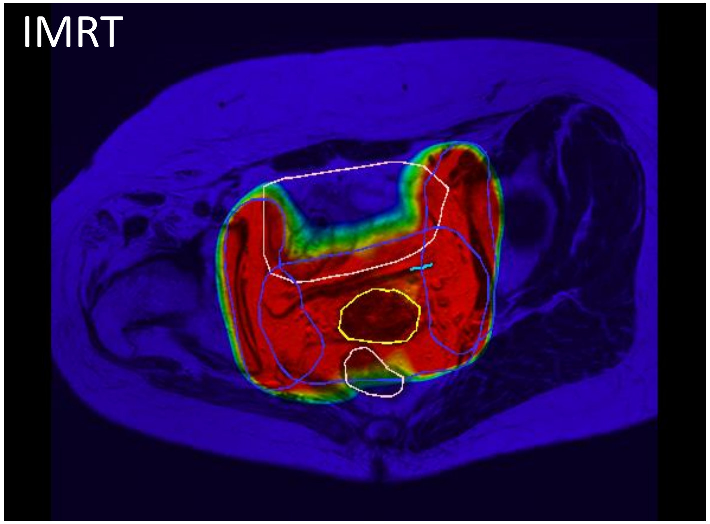
Modern EBRT planning; IMRT

3D conformal



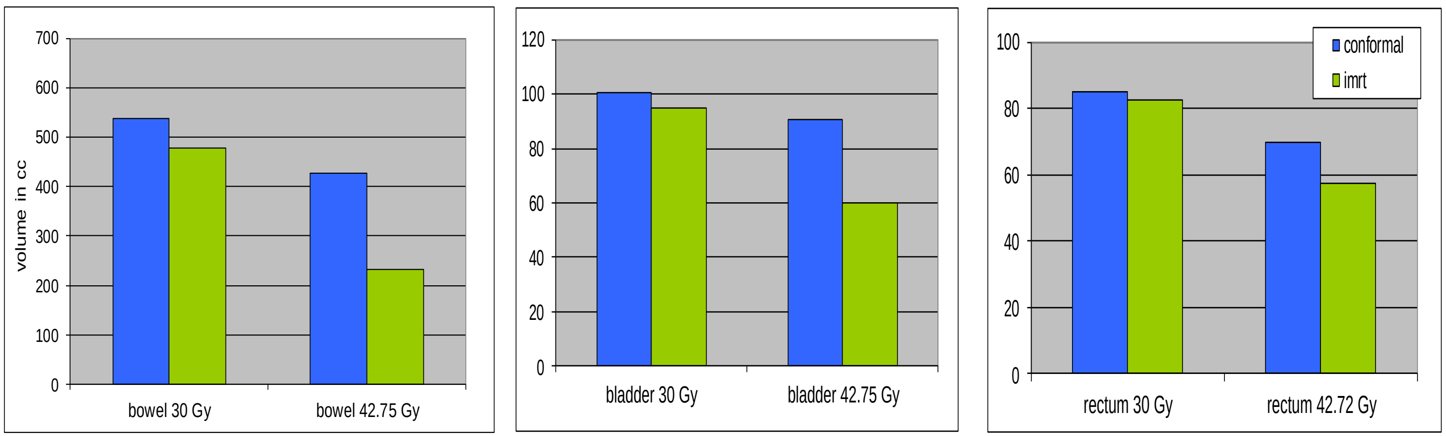
7 beam IMRT



IMRT versus 3D-CRT

Single institution experience

- Advantage IMRT over 3D Conformal for organ sparing
- Volume of OAR receiving high dose significantly smaller with IMRT



CLINICAL INVESTIGATION — Cervix

CONVENTIONAL, CONFORMAL, AND INTENSITY-MODULATED RADIATION THERAPY TREATMENT PLANNING OF EXTERNAL BEAM RADIOTHERAPY FOR CERVICAL CANCER: THE IMPACT OF TUMOR REGRESSION

Linda van de Bunt, M.D.,* Uulke A. van der Heide, Ph.D.,* Martijn Ketelaars, Ph.D.,* Gerard A. P. de Kort, M.D.,† and Ina M. Jürgenliemk-Schulz, M.D., Ph.D.*

Departments of *Radiation Oncology and †Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

Van de Bunt 2006

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IMRT versus 3D-CRT

Single institution experience IMRT versus 3D CRT

- Comparable PTV dose, less dose to OAR

Mundt 2002

Int. J. Radiation Oncology Biol. Phys., Vol. 52, No. 5, pp. 1330–1337, 2002

0360-3016/02/$–see front matter

ELSEVIER

PII S0360-3016(01)02785-7

CLINICAL INVESTIGATION — Cervix

INTENSITY-MODULATED WHOLE PELVIC RADIOTHERAPY IN WOMEN WITH GYNECOLOGIC MALIGNANCIES

Arno J. Mundt, M.D.,* Anthony E. Lujan, Ph.D.,* Jacob Rotmensch, M.D.,*† Steven E. Waggoner, M.D.,† S. Diane Yamada, M.D.,† Gini Fleming, M.D.,‡ and John C. Roeske, Ph.D.*

Departments of *Radiation and Cellular Oncology, †Obstetrics and Gynecology, Section of Gynecologic Oncology, and ‡Internal Medicine, Section of Hematology/Oncology, University of Chicago Pritzker School of Medicine, Chicago, IL

Purpose: To describe our initial clinical experience with intensity-modulated whole pelvic radiotherapy (IM-WPRT) in women with gynecologic malignancies.
Methods and Materials: Between February 2000 and August 2001, 40 gynecology patients underwent IM-WPRT. After fabrication of customized immobilization, all patients underwent contrast-enhanced CT, and a clinical target volume was contoured consisting of the upper vagina, parametria, uterus (if present), and presacral and pelvic lymph node regions. The clinical target volume was expanded by 1 cm to create a planning target volume (PTV). Using commercially available software, 7- or 9-field, 6-MV, coplanar IM-WPRT plans were generated for all patients. The worst acute gastrointestinal and genitourinary toxicity during treatment was scored on a 4-point scale: 0, none; 1, mild, no medications required; 2, moderate, medications required; and 3, severe, treatment breaks or cessation, hospitalization. As a comparison, acute toxicities in 35 previously treated conventional WPRT patients were analyzed. No significant differences were noted in the clinicopathologic and treatment factors between the two groups.
Results: IM-WPRT plans provided excellent PTV coverage, with considerable sparing of the surrounding normal tissues. On average, 98.1% of the PTV received the prescription dose. The average percentage of the PTV receiving 110% and 115% of the prescription dose was 9.8% and 0.2%, respectively. IM-WPRT was well tolerated, with no patient developing Grade 3 toxicity. Grade 2 acute gastrointestinal toxicity was less common in the IM-WPRT group (60 vs. 91%, $p = 0.002$) than in the conventional WPRT group. Moreover, the percentage of IM-WPRT and WPRT patients requiring no or only infrequent antidiarrheal medications was 75% and 34%, respectively ($p = 0.001$). Although less Grade 2 genitourinary toxicity was seen in the IM-WPRT group (10% vs. 20%), this difference was not statistically significant ($p = 0.22$).
Conclusion: IM-WPRT is a promising approach in gynecology patients. IMRT planning resulted in excellent PTV coverage, with considerable sparing of normal tissues. Treatment was well tolerated and associated with less acute gastrointestinal sequelae than conventional WPRT. Longer follow-up and more patients are needed, however, to evaluate the full merits of this novel approach. © 2002 Elsevier Science Inc.

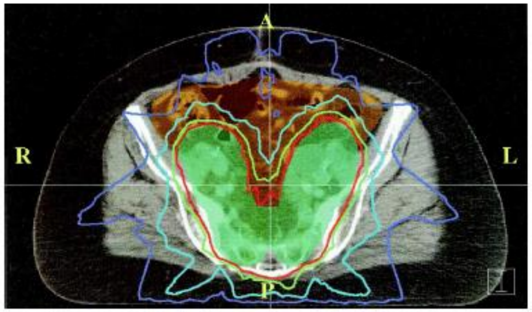

Fig. 2. Isodose curves from an IM-WPRT plan superimposed on an axial CT slice through the upper pelvis. The small bowel and PTV are shaded in orange and green, respectively. Highlighted are the 100% (red), 90% (green), 70% (light blue), and 50% (dark blue) isodose curves.

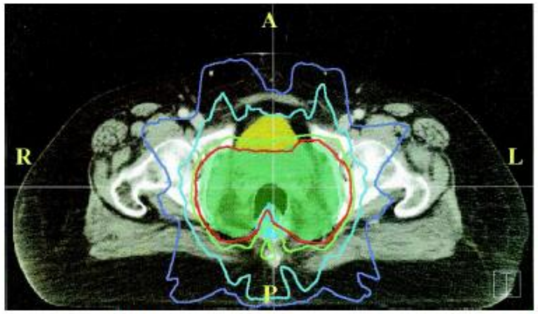

Fig. 3. Isodose curves from an IM-WPRT plan superimposed on an axial CT slice through the lower pelvis. The bladder, rectum, and PTV are shaded in yellow, light blue, and green, respectively. Highlighted are the 100% (red), 90% (green), 70% (light blue), and 50% (dark blue) isodose curves.

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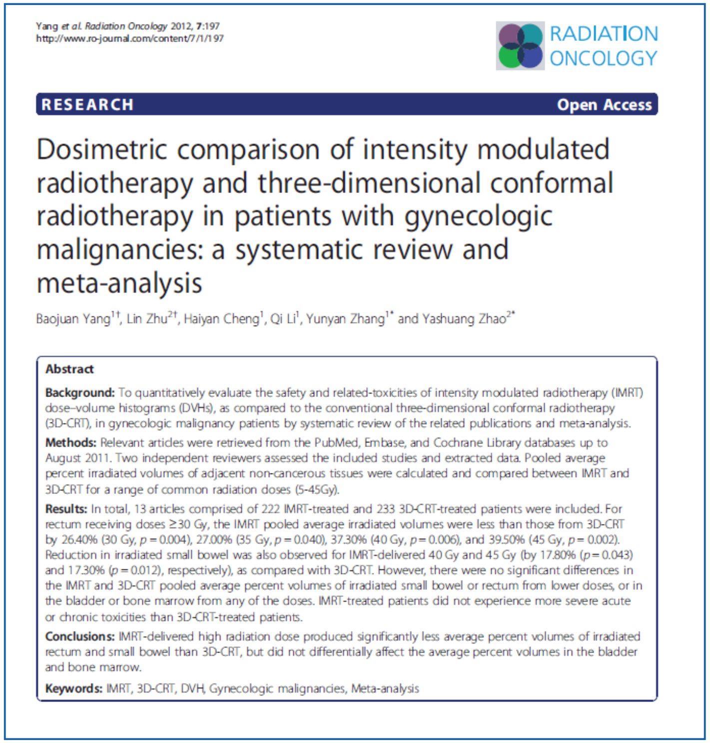
IMRT versus 3D-CRT

Meta-analysis

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

Yang 2012



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

RADIATION ONCOLOGY

RESEARCH Open Access

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

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

Abstract

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

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

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

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

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

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13 papers

Yang 2012

Table 1 Basic characteristics of papers analyzed

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.

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Summary dosimetric gain meta-analysis

Pooled averages of volume reduction for different dose levels

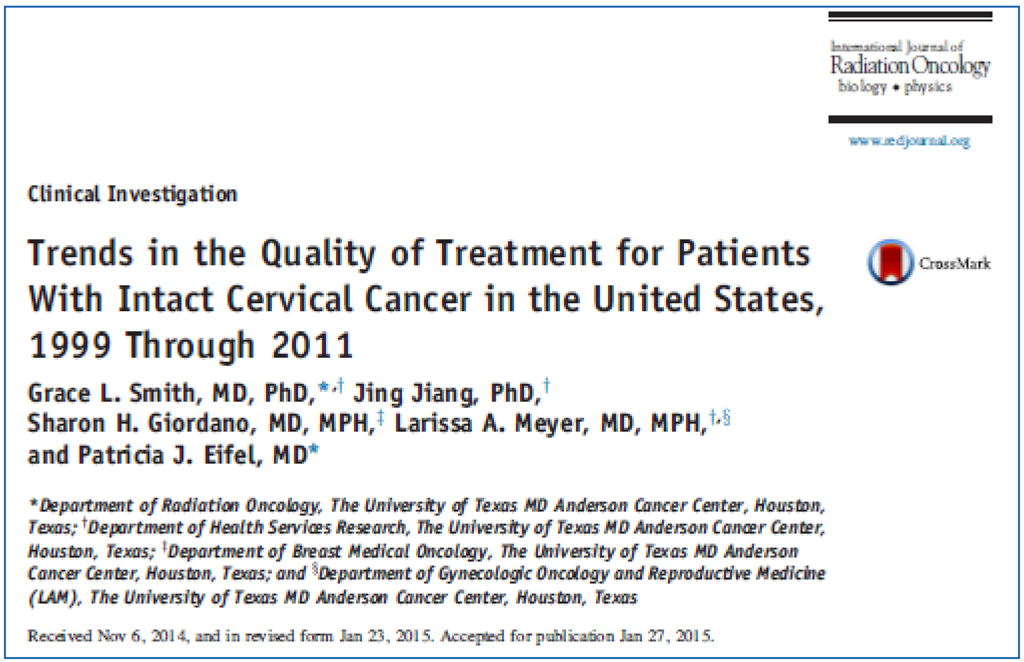
Yang 2012

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

Increasing utilization of IMRT

Trends for patients with gyn cancers; intact cervix 1999-2011

Smith 2015



International Journal of
Radiation Oncology
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Clinical Investigation

Trends in the Quality of Treatment for Patients With Intact Cervical Cancer in the United States, 1999 Through 2011

CrossMark

Grace L. Smith, MD, PhD,[*,†] Jing Jiang, PhD,[†]
Sharon H. Giordano, MD, MPH,[‡] Larissa A. Meyer, MD, MPH,[†,§]
and Patricia J. Eifel, MD[*]

[Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; †Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, Texas; ‡Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; and §Department of Gynecologic Oncology and Reproductive Medicine (LAM), The University of Texas MD Anderson Cancer Center, Houston, Texas]

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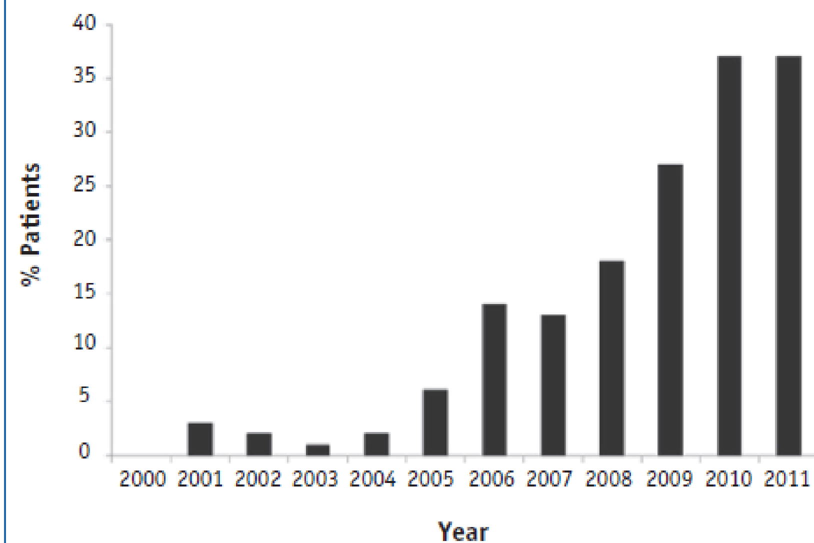

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Developments in IMRT technique

Planning study IMRT versus VMAT; fixed beam versus volumetric arc

- 5 coplanar equally spaced fields, 6MV
- 360°arc rotation,10 beam angles, 6 MV

Cozzi 2008

Radiotherapy and Oncology 89 (2008) 180–191
www.thegreenjournal.com

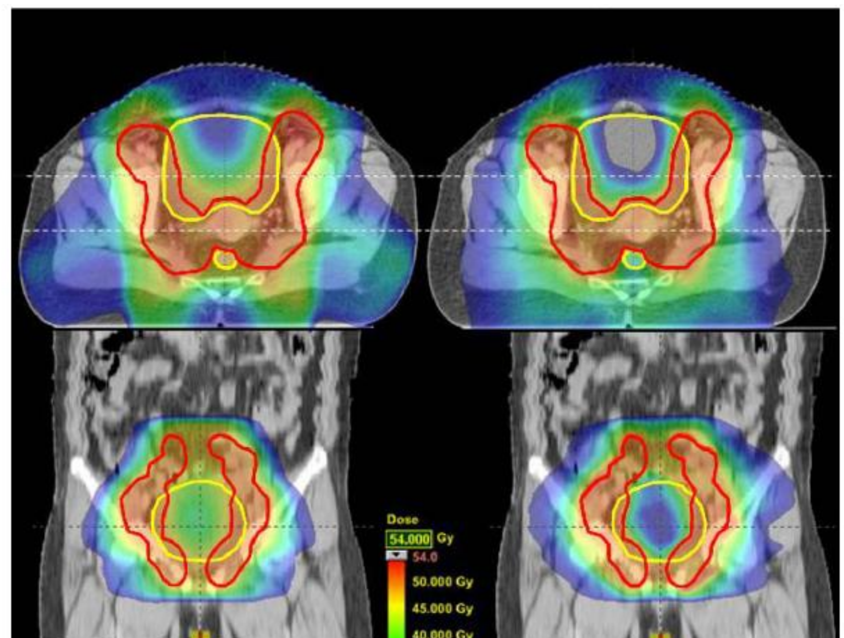
Cervix cancer radiotherapy

A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy

Luca Cozzi[a,b,*], Ketayun Ardeshir Dinshaw[c], Shyam Kishore Shrivastava[c], Umesh Mahantshetty[c], Reena Engineer[c], Deepak Dattatray Deshpande[c], S.V. Jamema[c], Eugenio Vanetti[a], Alessandro Clivio[a], Giorgia Nicolini[a], Antonella Fogliata[a]

[a]Oncology Institute of Southern Switzerland, Medical Physics Unit, Bellinzona, Switzerland, [b]University of Lausanne, Faculty of Medicine, Lausanne, Switzerland, [c]Department of Radiation Oncology & Medical Physics, Tata Memorial Hospital, Mumbai, India

IMRT **VMAT**



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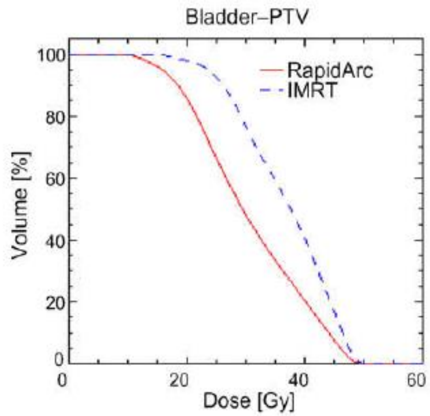
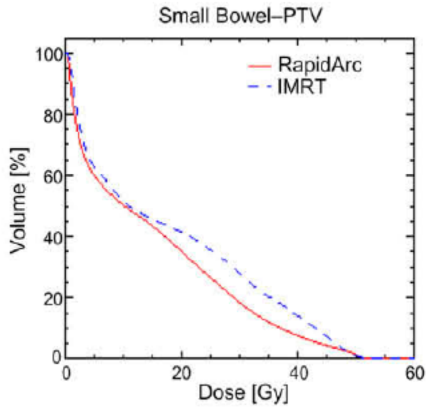
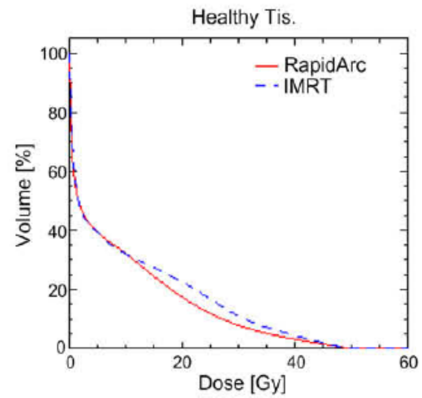
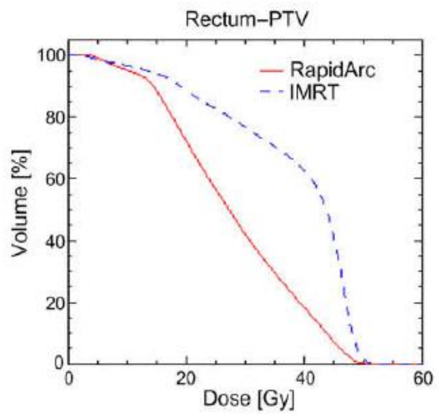
IMRT versus VMAT







Cozzi 2008



Organ	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

Shorter delivery time, at least by a factor 2!

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Developments in proton therapy for gyn cancers

Proton IMRT versus photon IMRT/VMAT/Tomotherapy

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

Cozzi
2008

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

RADIATION ONCOLOGY

RESEARCH Open Access

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

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

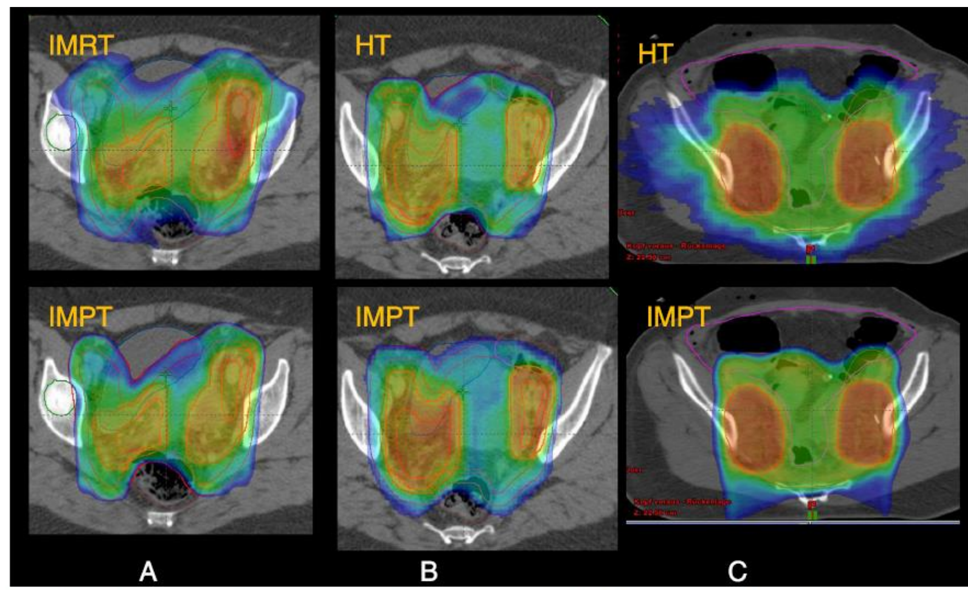

Figure 3 Examples of rectum and bowel sparing potential between techniques. **A** and **B**: rectum, colorwash is at 45 Gy; **B**: SB, colowash is at 30 Gy.

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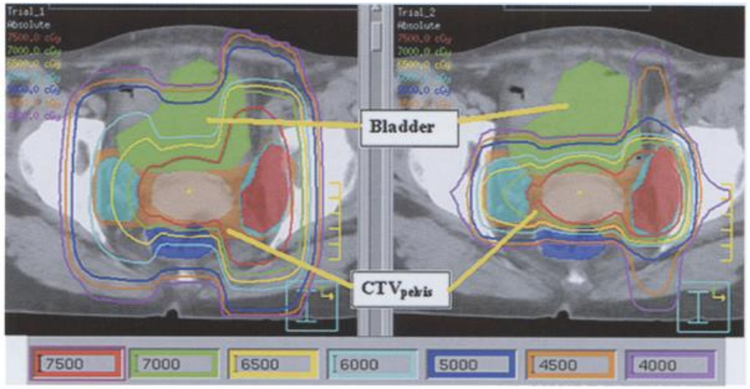
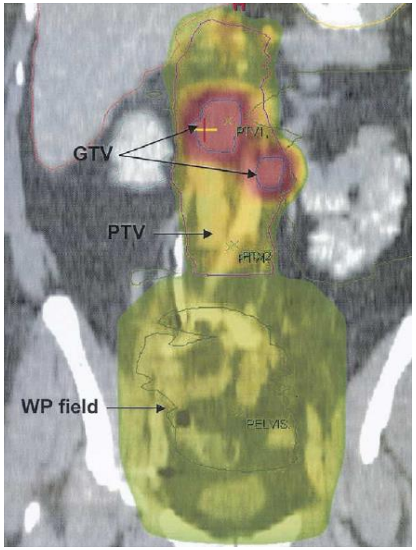
Summary IMRT dosimetric gain

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





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Clinical outcome IMRT versus 3D-CRT for gyn tumors

Mundt 2002

Postoperative cervix and endometrial cancer

- 40 patients IMRT, 35 3D CRT
- Less dose to OAR by IMRT
- Reduced GU and GI acute toxicity

Table 3. Acute GI and GU toxicities in IM-WPRT patients

Grade	GI (%)	GU (%)
0	5 (12)	28 (70)
1	11 (28)	8 (20)
2	24 (60)	4 (10)
3	0 (0)	0 (0)

Abbreviations: GI = gastrointestinal; GU = genitourinary; IM-WPRT = intensity-modulated whole pelvic radiotherapy.

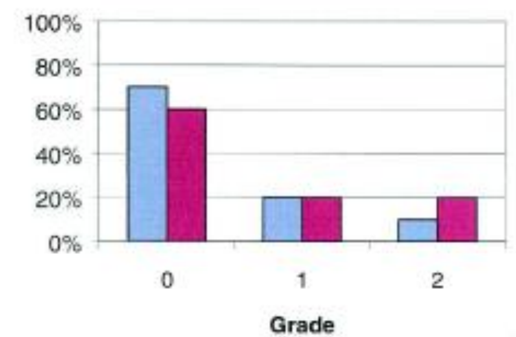

Fig. 5. Incidence of acute GU toxicity in the IM-WPRT (blue bars) and WPRT (red bars) groups.

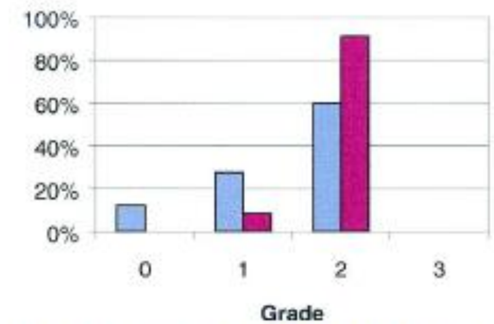

Fig. 4. Incidence of acute GI toxicity in the IM-WPRT (blue bars) and WPRT (red bars) groups.

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Studies on toxicity after IMRT for cervix and endometrial cancer

Gynecol Oncol 130, 2013

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

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Clinical outcome including toxicity

Ghandi 2013

IMRT versus conventional pelvic radiotherapy

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

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

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

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

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

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

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

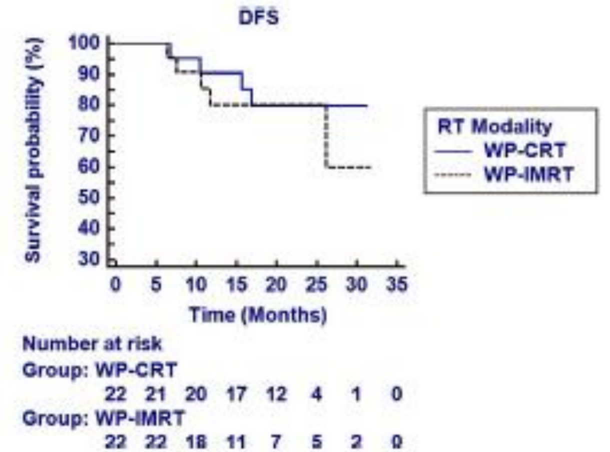

Fig. 2. Disease-free survival of WP-CRT and WP-IMRT arm. *Abbreviations:* DFS = disease-free survival; RT = radiation therapy; WP-CRT = whole pelvic conventional radiation therapy; WP-IMRT = whole pelvic intensity modulated radiation therapy.

Clinical outcome including toxicity

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

Ghandi 2013

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

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

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

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

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

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Randomised trial IMRT versus 3D CRT, TMH

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

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

- IMRT reduces acute and late RT toxicity's by 15-25%
- Accrual period 5 years, finished
- However, 10 Gy more in IMRT arm

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Interim analysis, comparable toxicities

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

Shrivastava
ICARO& ASTRO
2013

- Interim analysis
- Higher rate of acute toxicity with IMRT
- Final analysis expected

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PARCER trial (TMH), focus on bowel doses and morbidity

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

Chopra
ASTRO, 2015

- Interim analysis
- Significant less volume irradiated with IMRT after surgery

Bowel Dose	IMRT	3DCRT	P value
V15 Small Bowel ≥ 275 cc	8 (13.1%)	25 (44.6%)	<0.0001
V40 Small 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

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PARCER, primary endpoint late bowel morbidity

Chopra
ASTRO, 2015

- Median Follow Up = 20 months
- 14% absolute difference in late Grade ≥ 3toxicity
- Statistically insignificant at interim analysis

	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**

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New OAR of interest

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

- International multicenter Phase II/III Trial of IMRT (45-50.4 Gy) with Cisplatin CT
- Stage I-IVA cervix cancer, primary treatment or post-op, inclusion 425 patients intended
- Primary Endpoint: Acute G3 Hematologic + G2 GI Toxicity
- Intended: Phase III randomized trial of BM sparing IMRT vs. IMRT/ 3D CRT
- Central IMRT QA (MDA and Wash U.)

UC San Diego
RADIATION ONCOLOGY

CART UCSD
CENTER FOR ADVANCED RADIOTHERAPY TECHNOLOGIES

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Conclusion

- IMRT (including VMAT) offers better possibilities to balance between tumor dose needed and OAR dose to be avoided than conventional treatment planning algorithms
- We have medical evidence that IMRT reduces toxicity
- However, IMRT treatment planning offers more degrees of freedom
- Predefined dose parameters are essential for clinically acceptable treatment plans
- Therefore we must use current knowledge on dose volume relations
- However, we still need to learn !

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Ongoing evidence for improving treatment planning

EMBRACE II study protocol v.1.0

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

EMBRACE-II

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

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Dose constraint and DVH table for EBRT planning in EMBRACE II

Initial version based on ICRU and literature data

		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	

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Dose constraint and DVH table for EBRT planning in EMBRACE II

Current version adapted due to growing experience

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

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

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

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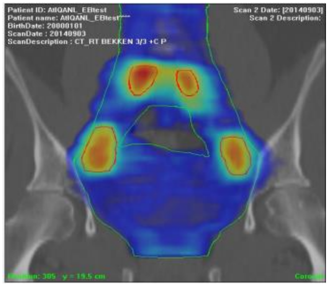
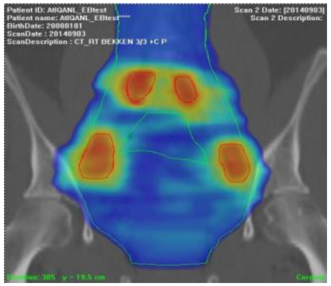
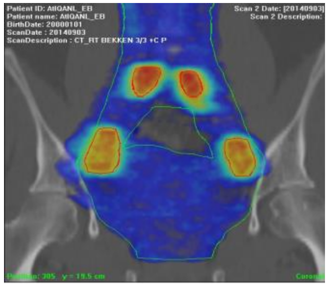
Why such a difference?

- DVH parameters for EMBRACE II were initially based on ICRU guidelines and literature evidence
- Hard and soft constraints were based on current evidence for dosimetric gain and clinical outcome improvement
- First planning experience using these parameters revealed that
  - DVH constraints not sufficient for conformal dose planning
  - For spatial dose distributions still room for improvement
  - More parameters to be defined, especially for patients with lymph node metastases
- Commercially available treatment planning systems need quite specific information when conformal dose distributions are intended
- Example: 45 Gy elective, nodal boost up 55 Gy obturator region, 55.7 Gy common iliac region







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- Based on broader treatment planning experience DVH constraints could be adapted for patients with and without nodes

- Current table is provided based on data from 52 patients and 3 centers

- Aim is that values for soft constraints should be reached in 70-80%, allowing for outliers in case of exceptional anatomy or other planning problems

- DVH parameters are tight but feasible for different treatment planning systems

Results OAR	Soft constraint	EMBRACEII protocol planning guidelines	Percentage of patients complying to original	70-80th percentile	Updated planning guidelines
Bowel No para-aortic irradiation	V40Gy (cm^3)	< 100	20%	221 - 276	**< 250**
	V30Gy (cm^3)	< 275	28%	491 - 500	**< 500**
Bowel Para-aortic irradiation	V40Gy (cm^3)	< 220	36%	319 - 355	**< 300**
	V30Gy (cm^3)	< 450	29%	678	**< 650**
Bladder	V40Gy (%)	< 55	60%	60 - 69	**< 60**
	V30Gy (%)	< 80	60%	85 - 92	< 80
Rectum	V40Gy (%)	< 75	69%	77 - 82	< 75
	V30Gy (%)	< 90	54%	94 - 97	**< 95**
Body Conformality	(V43/Volume of PTV)	1.15	88%	1.10 - 1.11	**1.10**
			Data September 2017		

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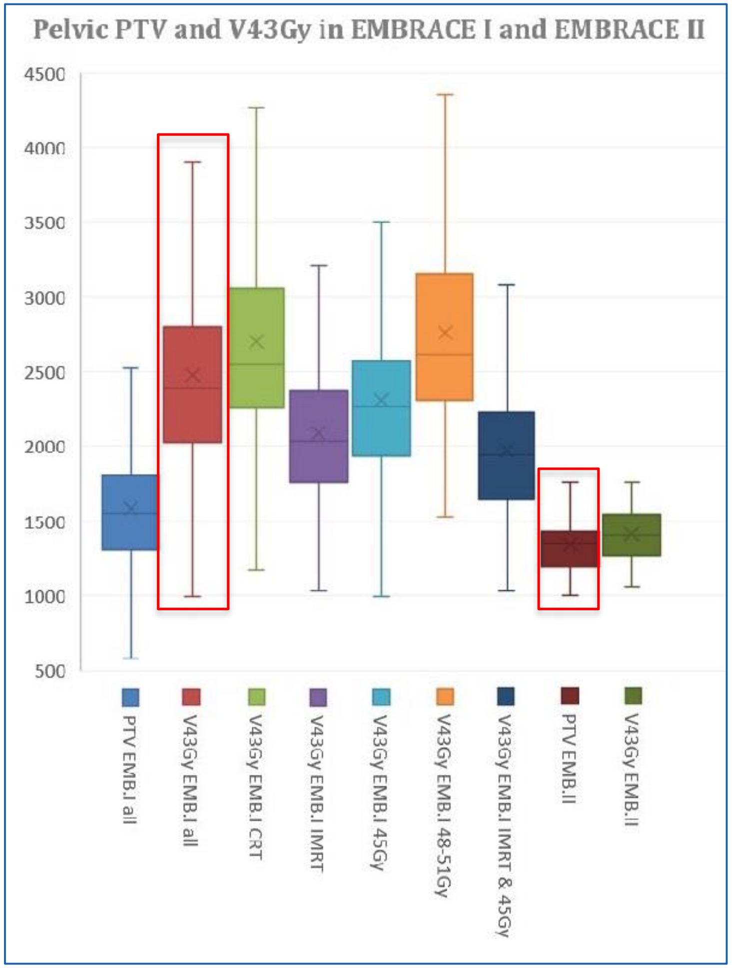
- Try to find the best balance between tumor and OAR dose!

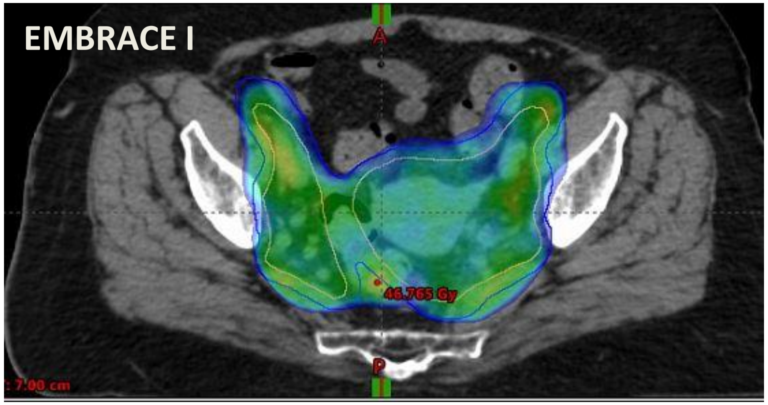
Impact on dose distribution

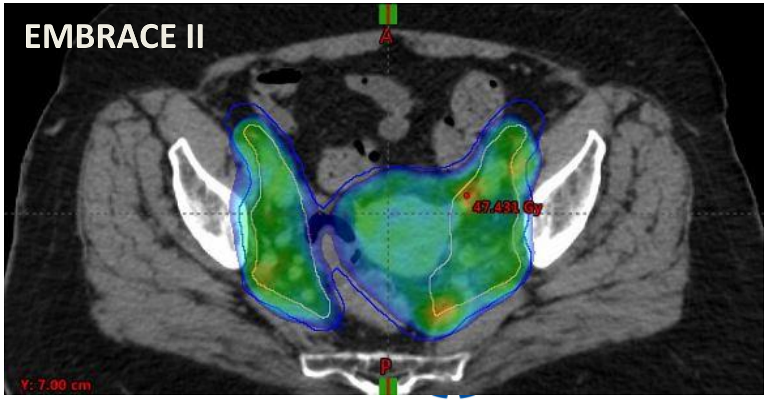
Comparison EBRT volumes treated in EMBRACE I and EMBRACE II

- V 43Gy reduced with about 1000 cc



Courtesy Thomas Berger

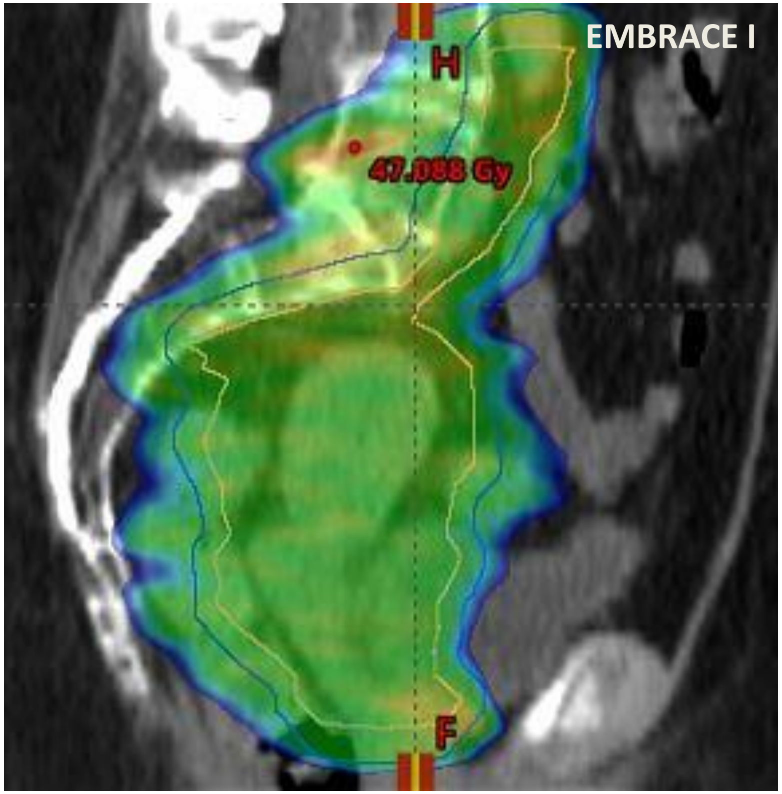


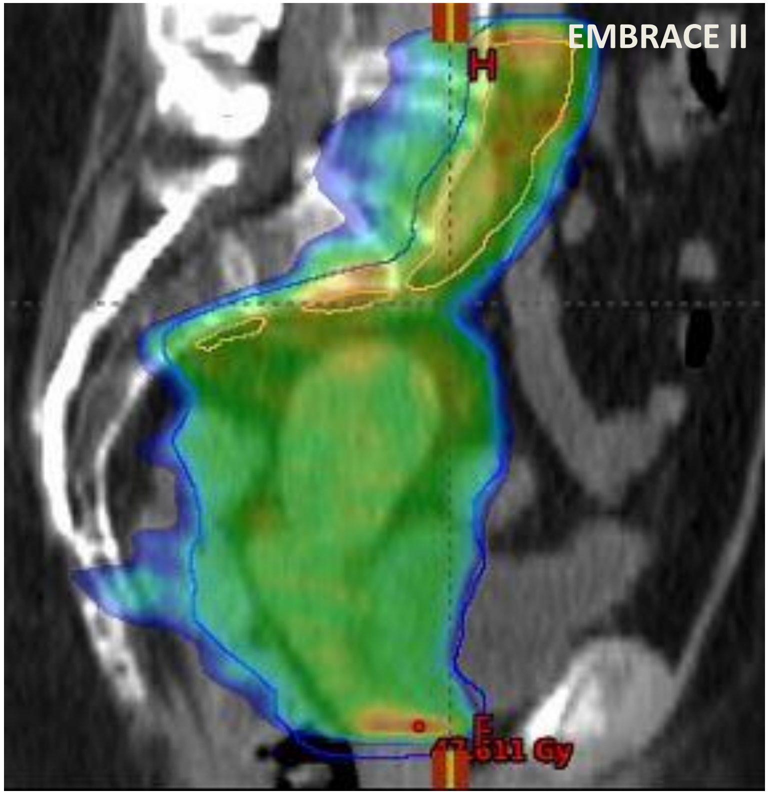


Impact on dose distribution

Comparison EBRT volumes treated in EMBRACE I and EMBRACE II

- V 40 Gy





Courtesy Thomas Berger

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To consider beyond dose constraints and DVH parameters

- Treatment plan evaluation is based on DVH parameters and assessment of spatial dose distribution
- Cooperation of radiation oncologist, clinical physicist and RTT essential
- Important to realize that treatment planning reflects anatomical situation at one moment in time
- Current CTV-ITV-PTV margins take into account anatomical changes of targets but not OAR
- Daily CBCT position verification allows to detect anatomical changes for targets and OAR
- Plan adaption during the course of EBRT can be necessary in case of major anatomical chances
- Adaptive IGRT accounts for these changes in a structured way and will help to improve balance between tumor and OAR dose
- Our knowledge on dose constraints and DVH parameters is constantly improving

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External Beam Treatment Techniques and Optimization – Physics aspects

Jamema Swamidas PhD, Mumbai

Prof. Taran Hellebust PhD, Oslo

Prof. Kari Tanderup PhD, Aarhus

ESTRO School

ESTRO teaching course
Prague 22-26 Oct 2017

What kind of techniques do we have?

- AP-PA / Four Field Box – Radiograph based
- 3DCRT
- IMRT
- VMAT
- Helical Tomotherapy
- Proton Therapy

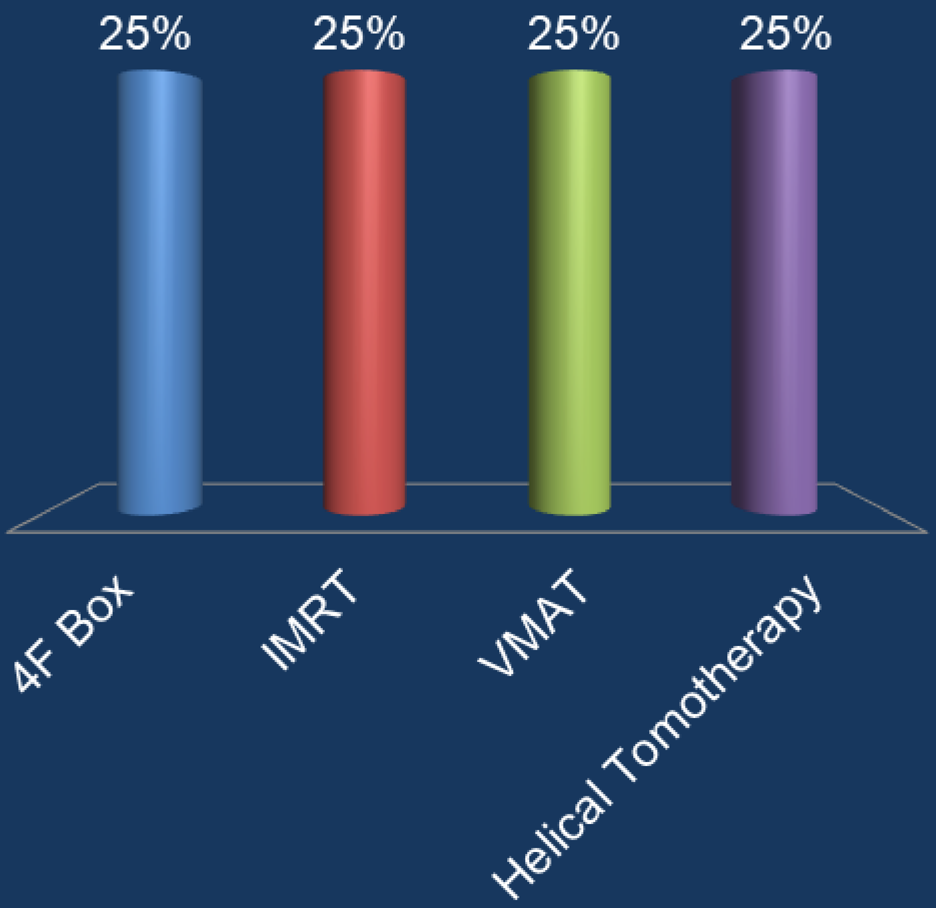
Which Technique do you use in your clinic

A. 4F Box

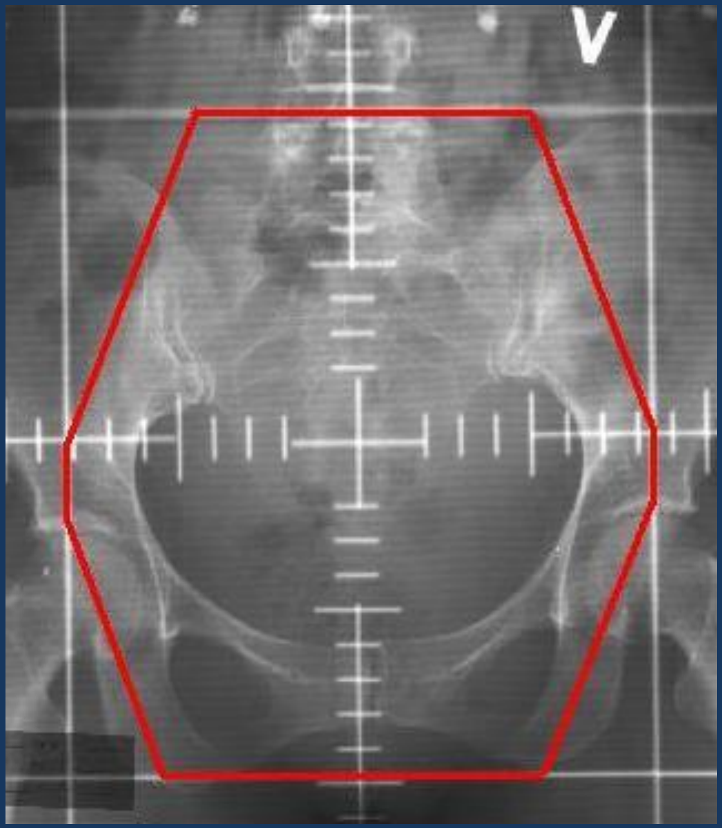
B. IMRT

C. VMAT

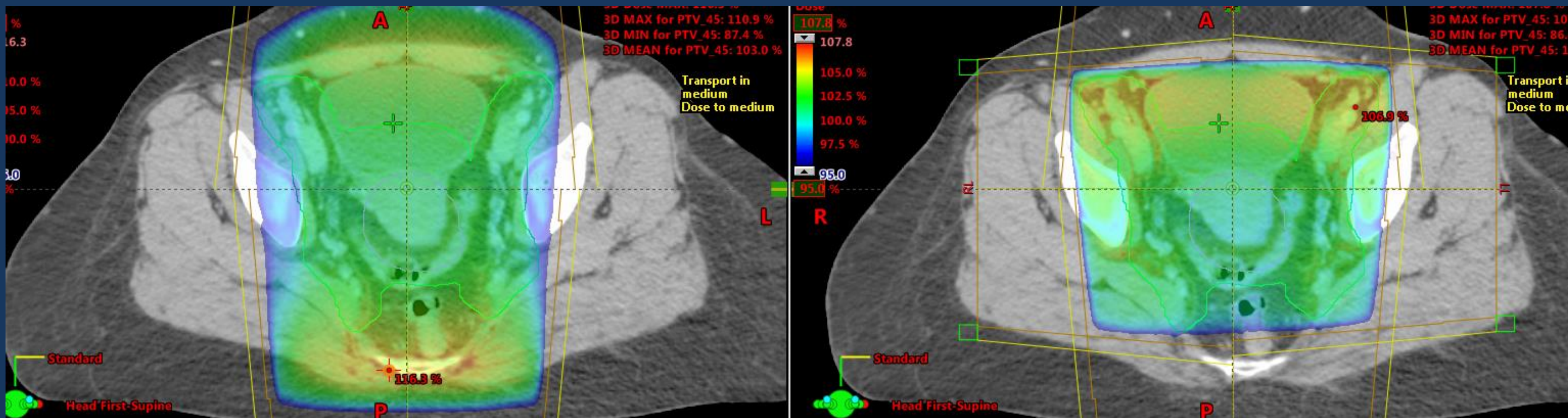
D. Helical Tomotherapy

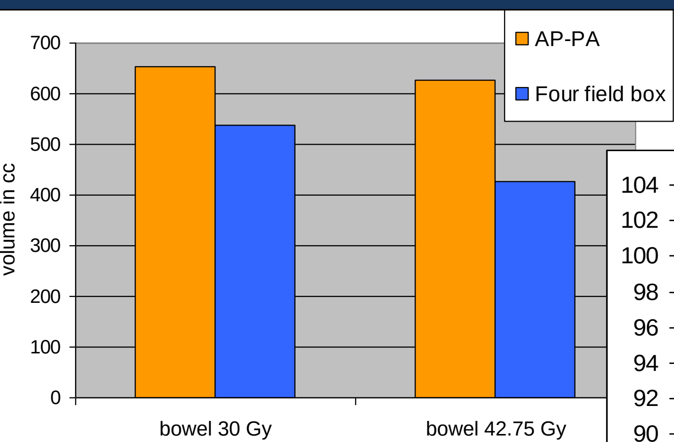


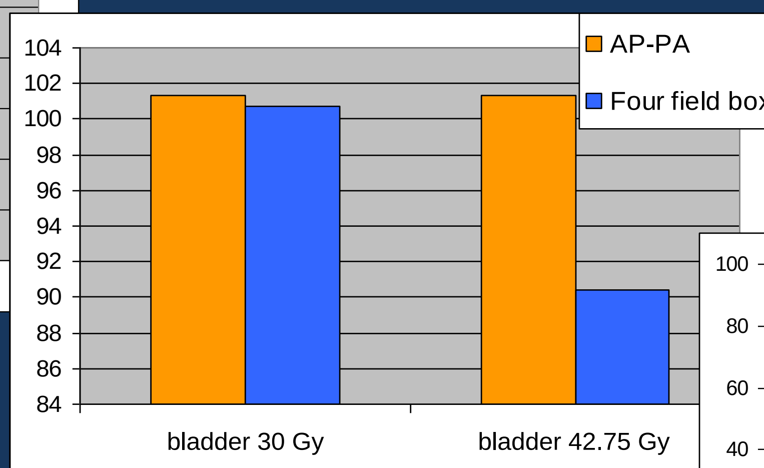
AP/PA or 4F box – Radiograph based

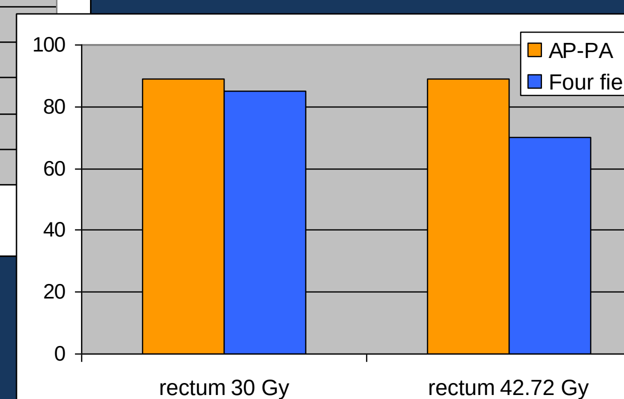


AP/PA vs 4F Box





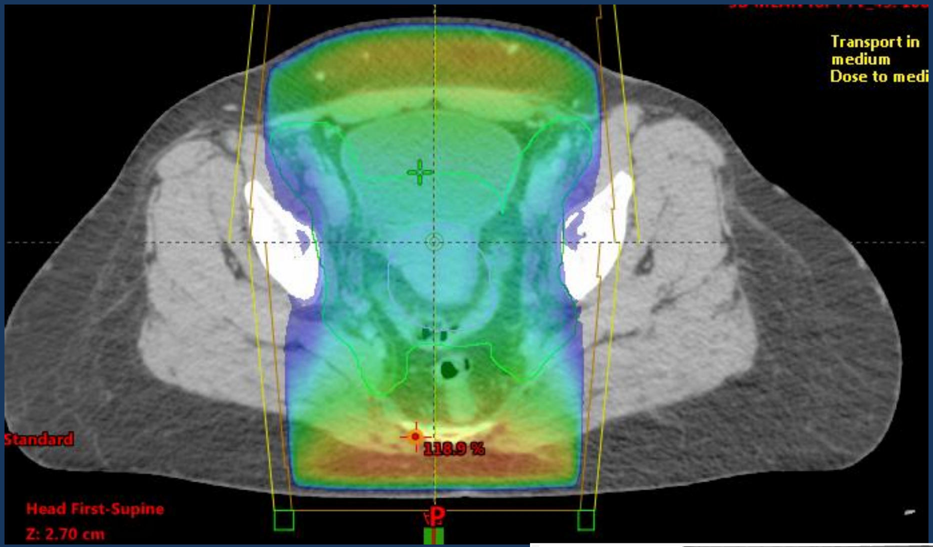




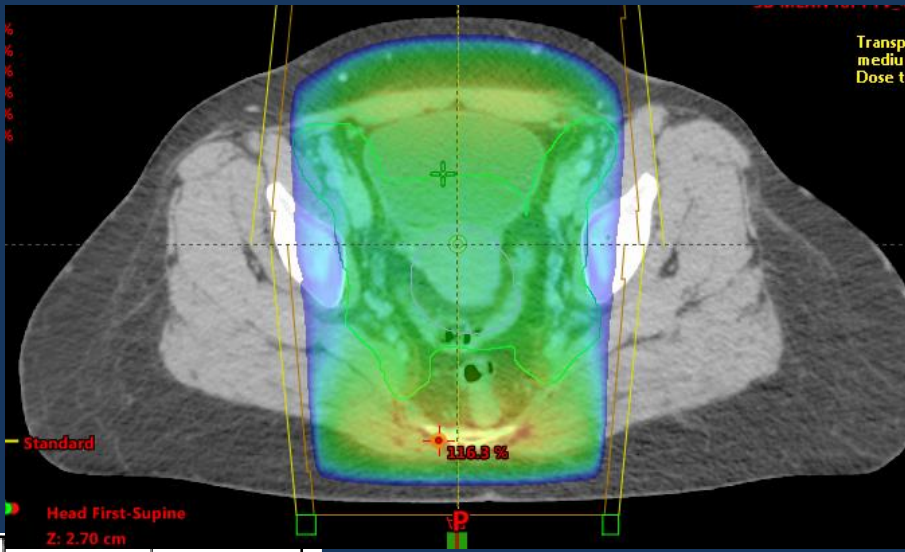
Van de Bunt et al 2006

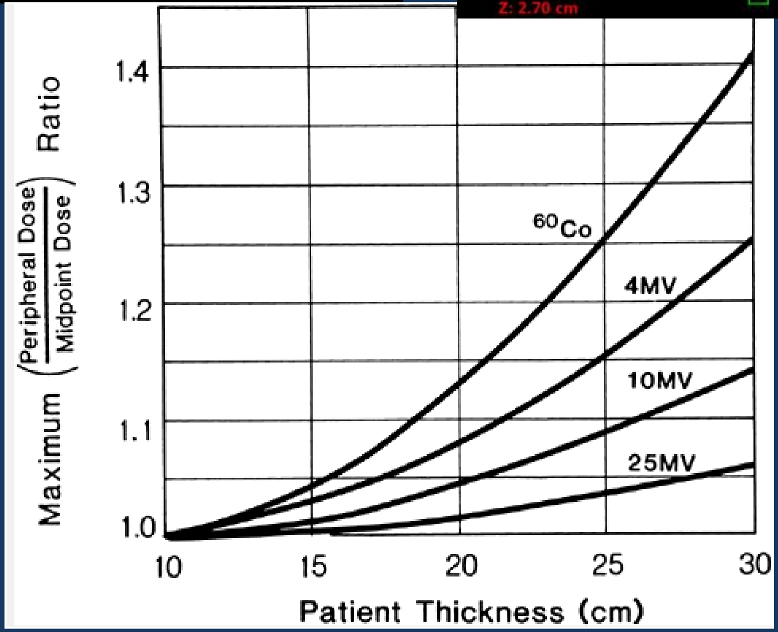
Choice of energy

6MV



15 MV

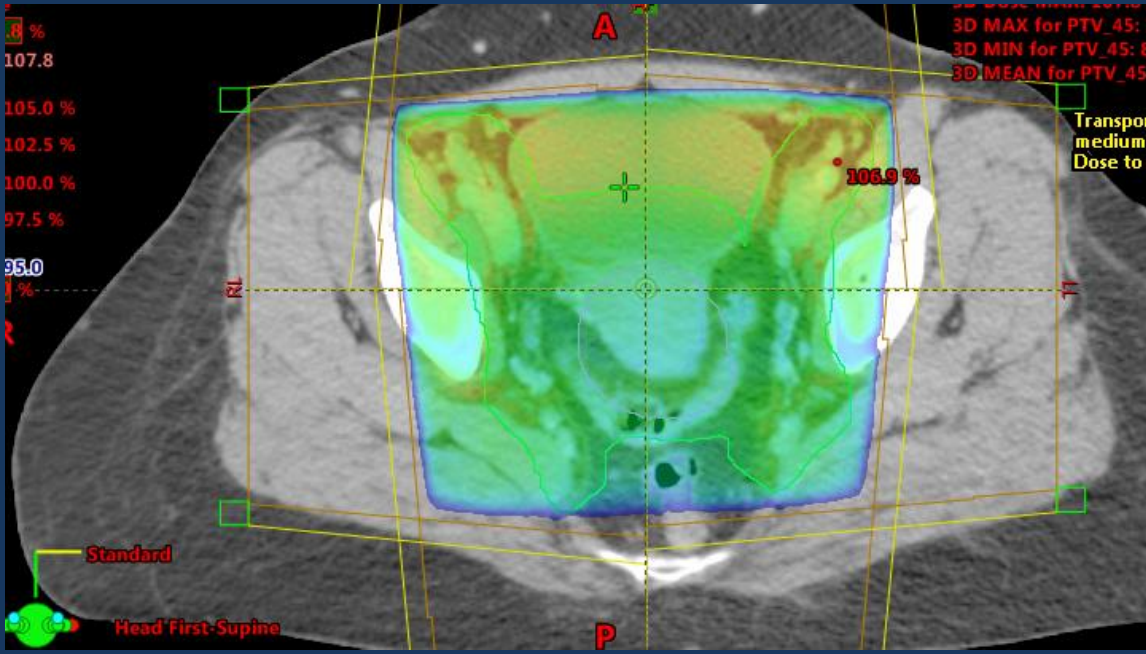




Khan 1994

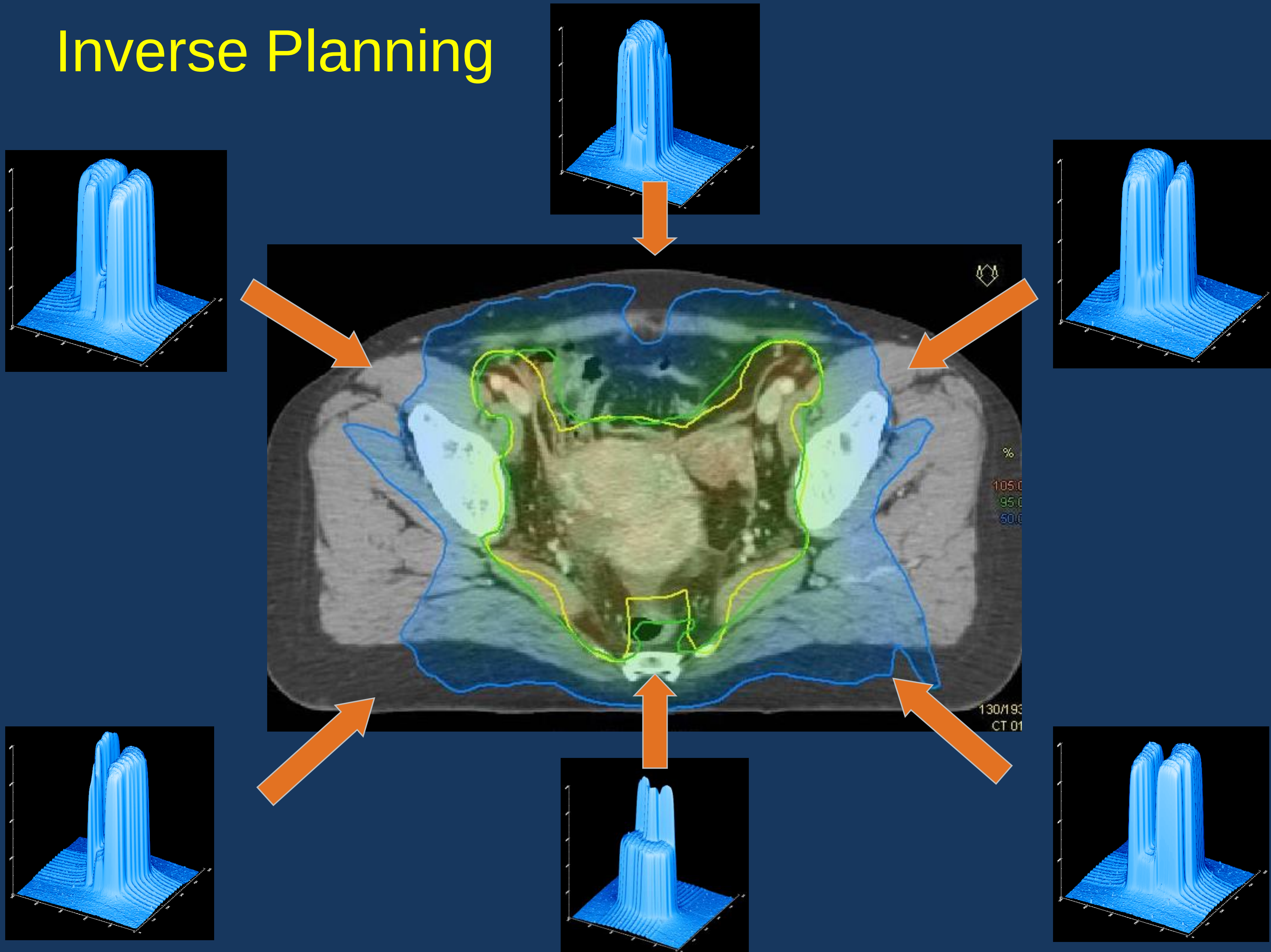
Forward planning

- Energy
- Number of fields
- MLC shape
- Field Weights
- Wedges



- Iteratively change

Inverse Planning



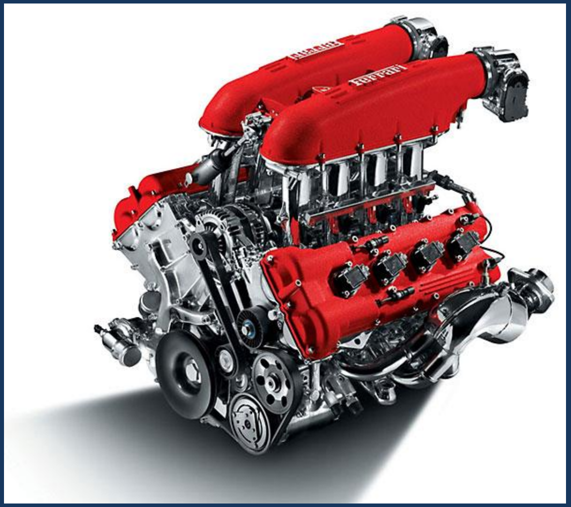
Inverse Planning – what is available

- IMRT
- VMAT
- Helical Tomotherapy

- IMPT

Inverse Planning - Issues

- Beam Modelling



- Treatment Planning

Inverse Planning - Beam Modeling

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

  ✓ Beam Penumbra – MLC.

  ✓ transmission and scattering properties of MLC

  ✓ Output factor for small field size.

  ✓ Accuracy of dose calculation algorithm.

  ✓ Approximations of leaf sequence generation algorithm.

  ✓ Leaf positioning accuracy.

Inverse Planning – Treatment Planning

- Planning objectives (with priorities)
  - Dose to target (Hard Constraint)
  - Dose to OAR (Soft Constraint)
  - Low dose spillage
- Optimization Volumes

Planning Objectives for target e.g – EMBRACE II

- PTV 45: **V95% > 95%**
- ITV 45 **Dmin > 95%** (42,75Gy)

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

Planning Objectives for OAR e.g – EMBRACE II

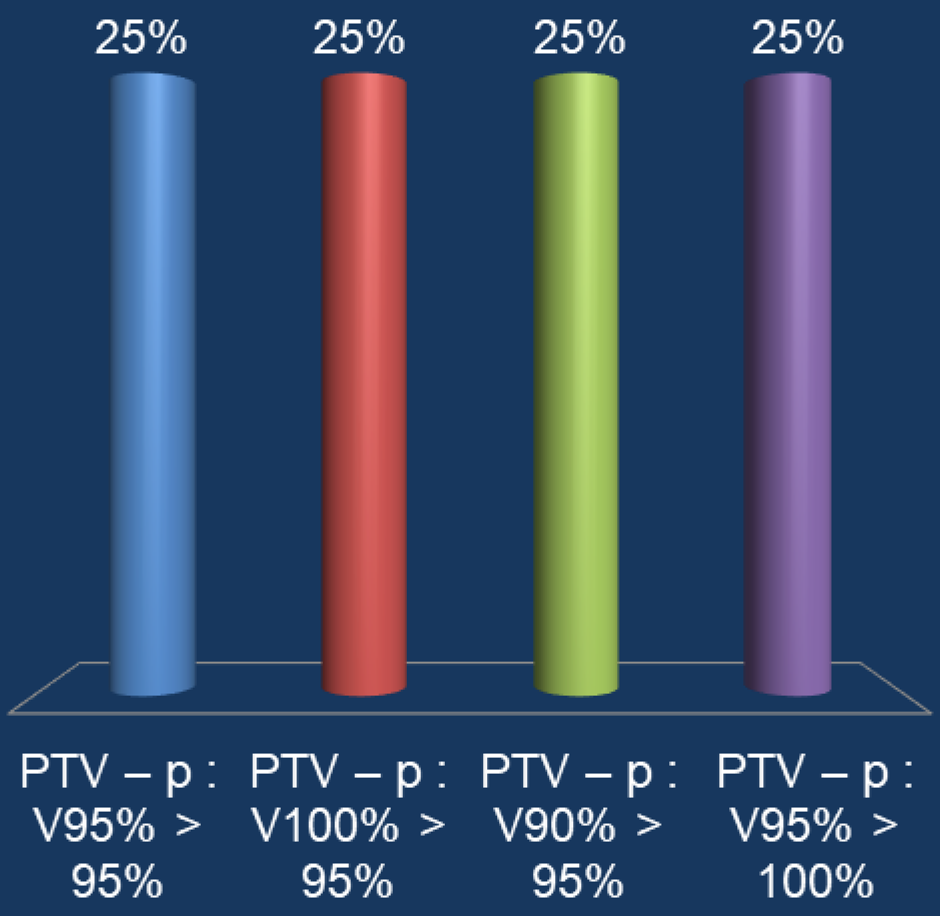
Bowel	Dmax < 105%	V40Gy < 250cm³* V30Gy < 500cm³*	Dmax < 105% in regions outside 10-15mm from PTV-N	When no para-aortic irradiation: V40Gy < 250cm³* V30Gy < 500cm³* For para-aortic irradiation: V40Gy < 300cm³* V30Gy < 650cm³*
Sigmoid	Dmax < 105%		Dmax < 105% in regions outside 10-15mm from PTV-N	
Bladder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

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

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

What is the hard constraint to PTV - primary in your department?

A. PTV – p : **V95% > 95%**
B. PTV – p : **V100% > 95%**
C. PTV – p : **V90% > 95%**
D. PTV – p : **V95% > 100%**

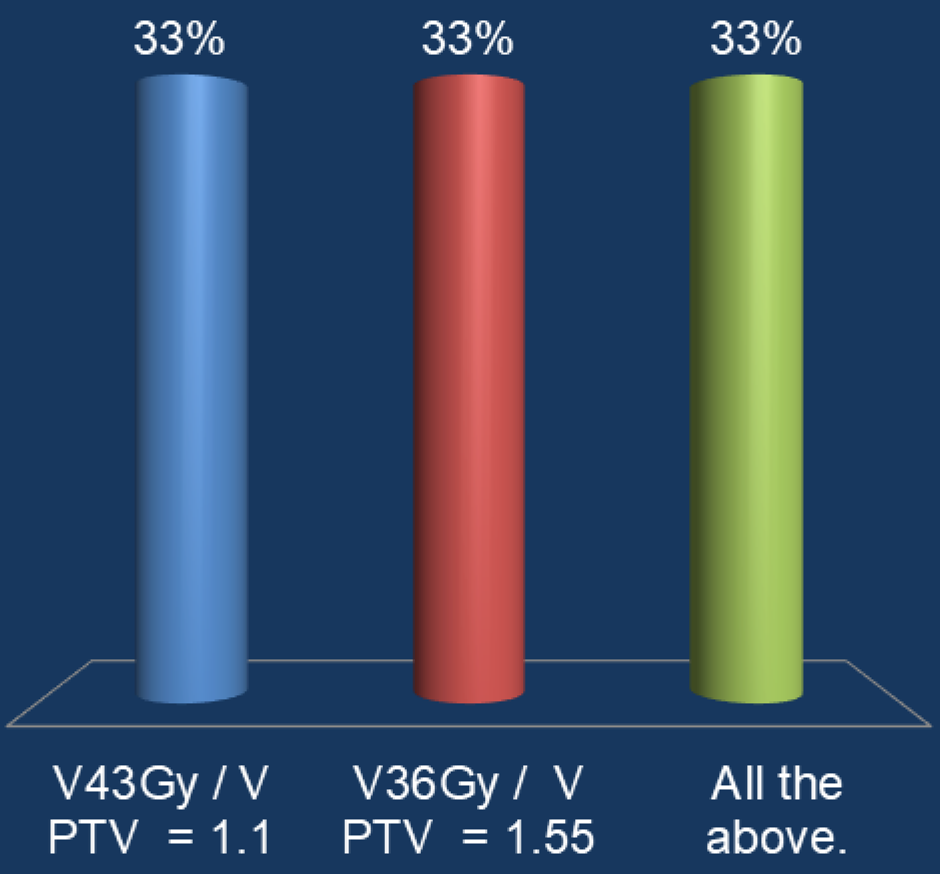


Conformality in IMRT can be quantified as

A. V43Gy / V PTV = 1.1

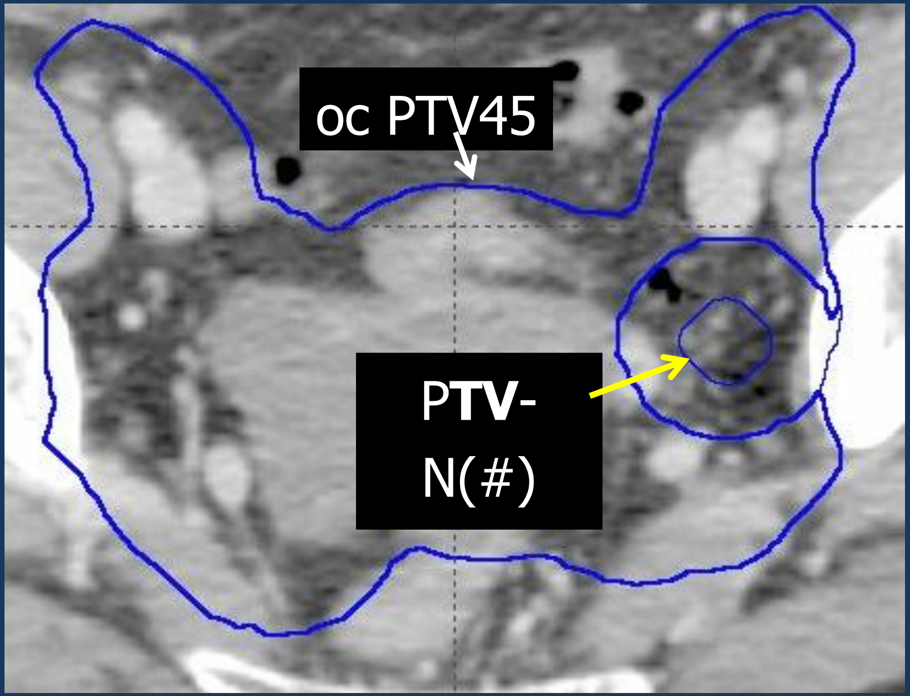
B. V36Gy / V PTV = 1.55

C. All the above.



Optimization volumes e.g : **oc PTV45**

oc PTV45 = PTV45 cropped with 1cm to PTV-N(#)



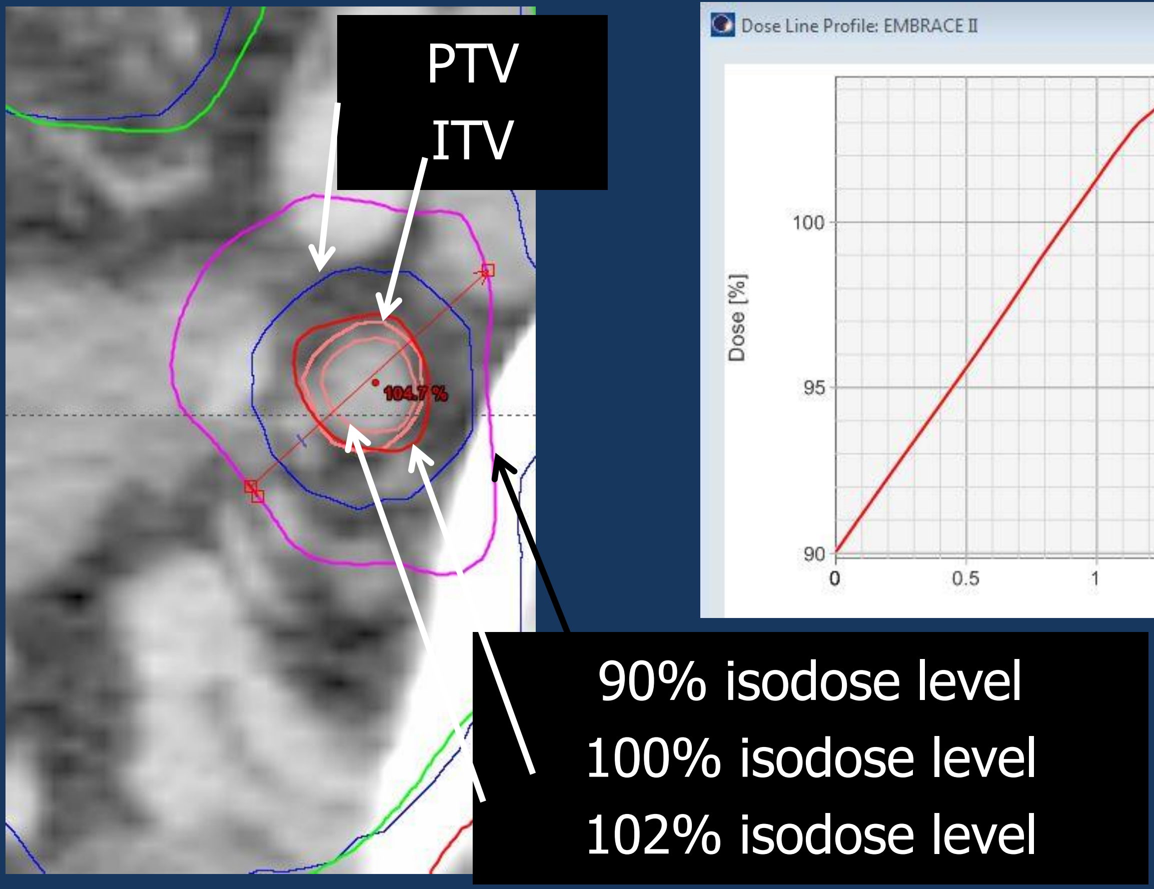
Purpose:

To reduce Dmax in
areas away from boost.
Dmax < 107% of 45Gy

oc PTV45 mean: 45.1Gy to 45.5Gy

Courtesy :Marianne S Assenholt

Coverage Probability - CoP



Courtesy :Marianne S Assenholt

Optimization volume: **o PTV-(N#)**

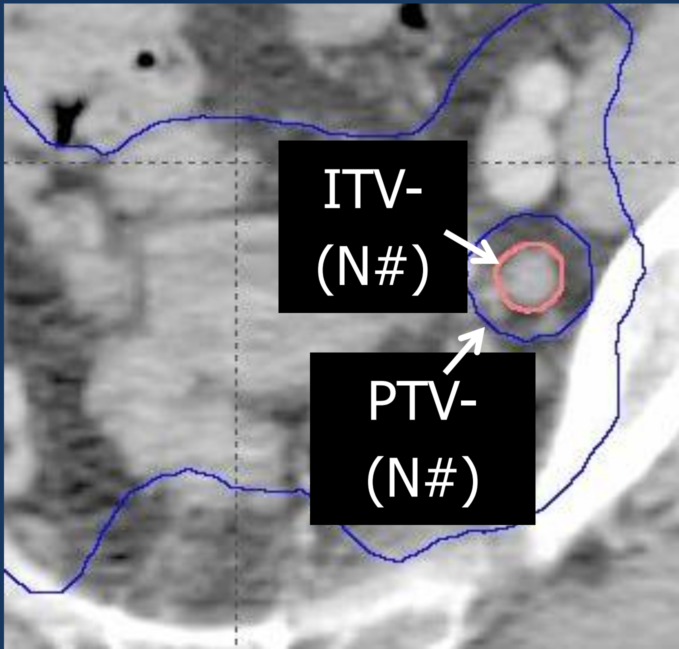
o PTV-(N#) = PTV-(N#) subtract ITV-(N#)

Purpose:

press down the dose around ITV-(N#)

Dmax ≈ 100% of prescribed dose

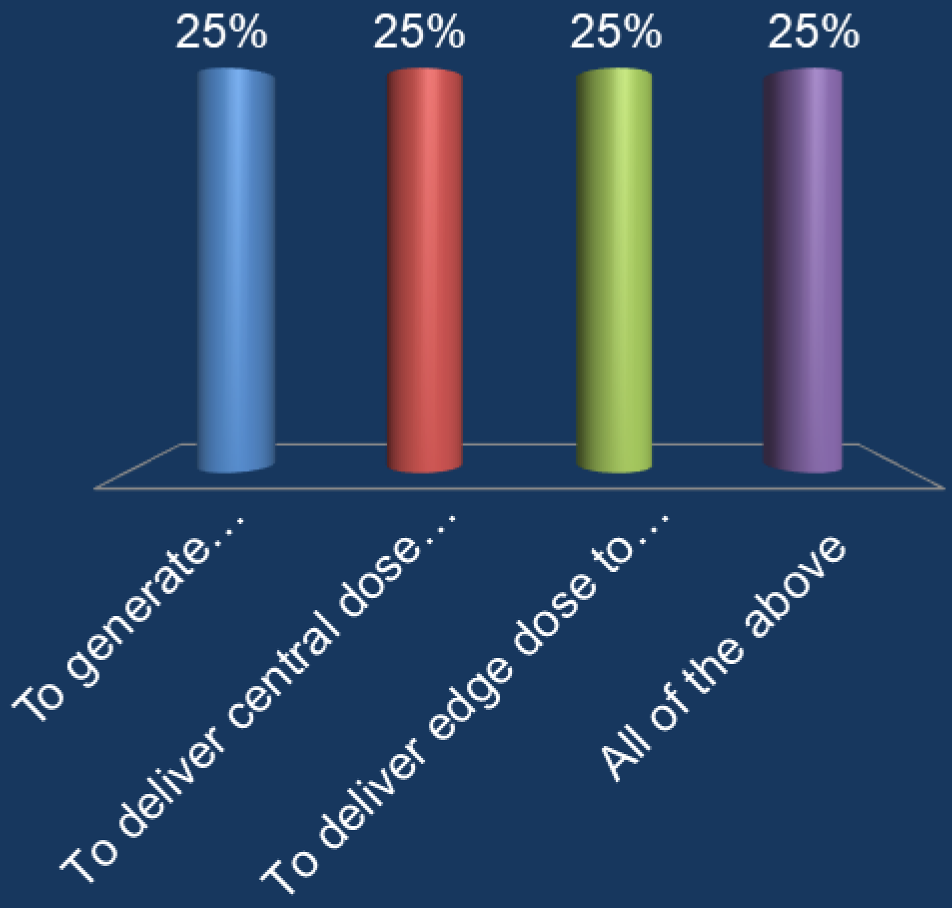
Dmin ≈ 90% of prescribed dose.



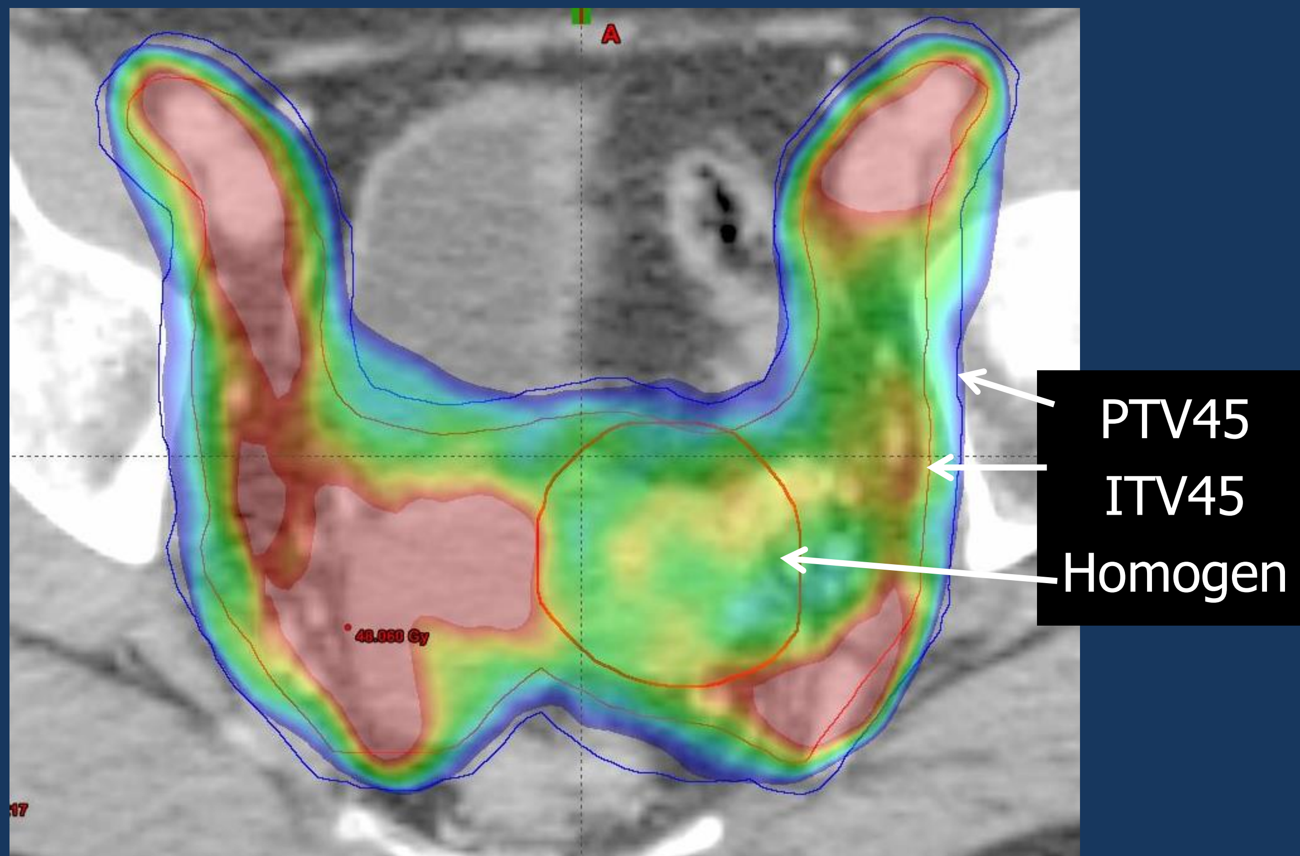
Courtesy :Marianne S Assenholt

Coverage Probability Principle aims

A. To generate heterogeneous dose across PTV –N
B. To deliver central dose >100%
C. To deliver edge dose to cool down to 90%.
D. All of the above



Aware of BT region during IMRT – Avoid hot spots



Red area: Dose > 103% of 45Gy
Colored area: Dose > 95% of 45Gy

Courtesy :Marianne S Assenholt

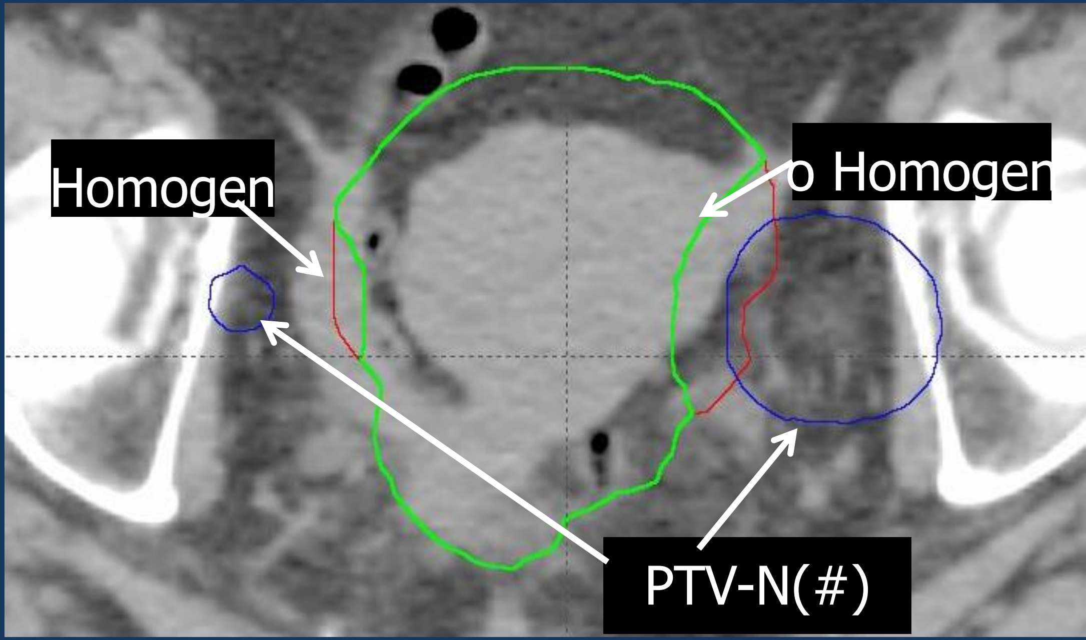
Optimization volume: **o Homogen**

o Homogen = Homogen cropped with 1 cm to PTV-N(#).

Purpose:

To avoid dose higher than 103% of 45Gy.

Especially around bladder, rectum and sigmoid hot area should be avoided, because in the homogen area brachy dose is added to the external beam dose.



Courtesy :Marianne S Assenholt

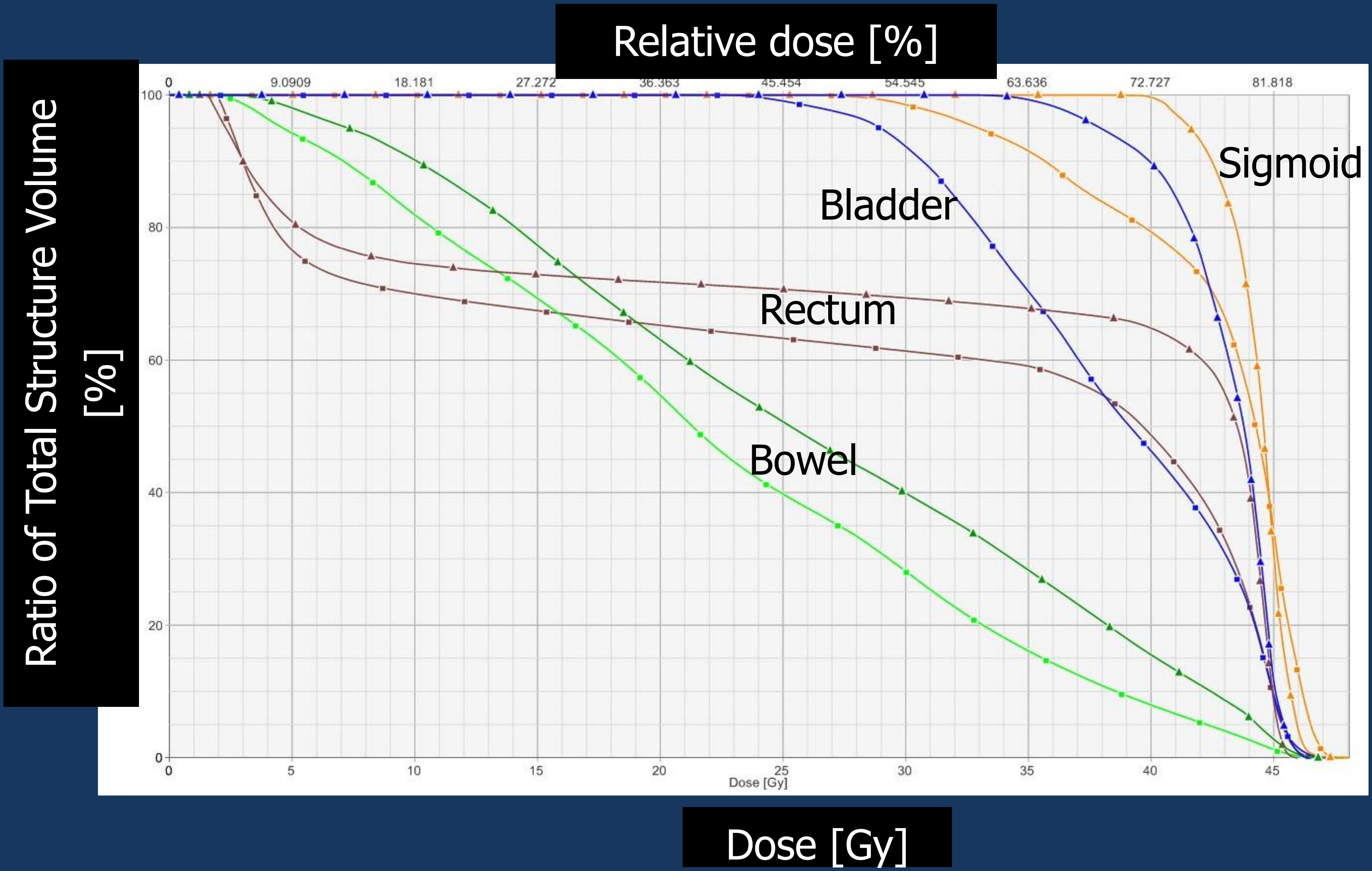
Organs at risk – ALARA

- Bowel
- Bladder
- Rectum
- Sigmoid

Often partly inside target
Only soft constrains

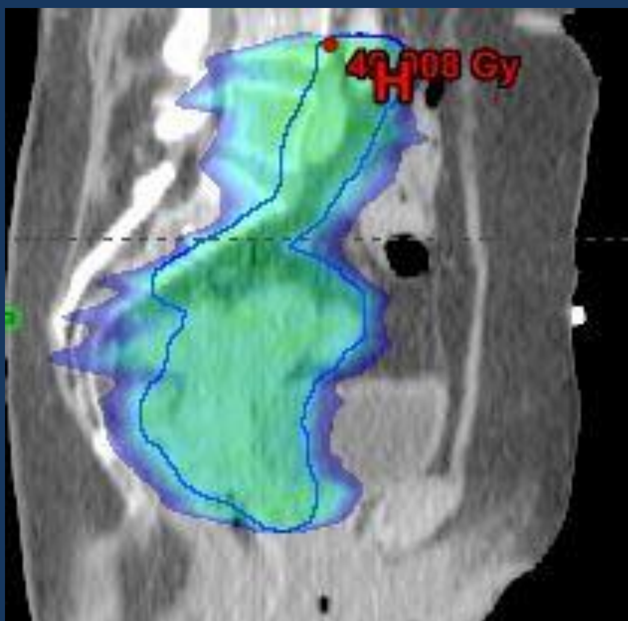
- Femoral heads — Dmax < 50Gy
- Spinal cord — Dmax < 48Gy
- Kidney — Dmean < 15Gy

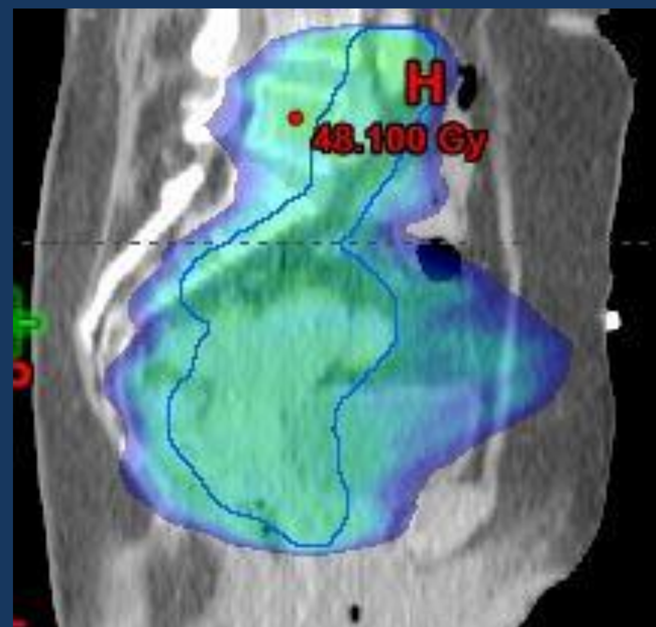
Competing plans - DVH for OAR

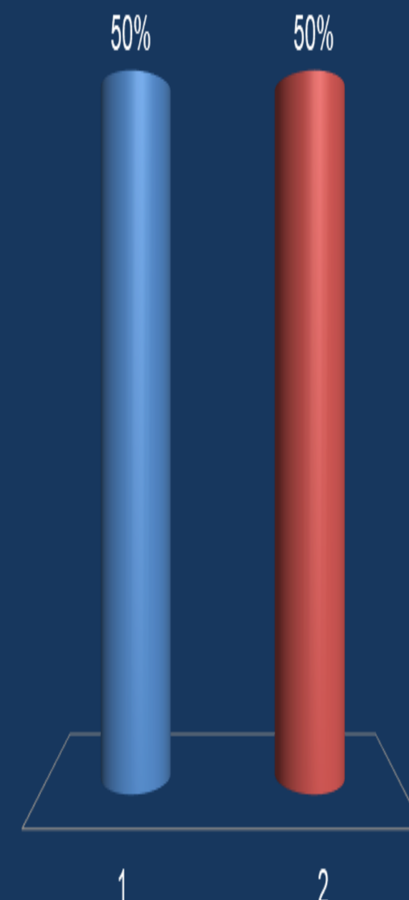


Courtesy :Marianne S Assenholt

Which is the good plan in terms of low dose spillage?





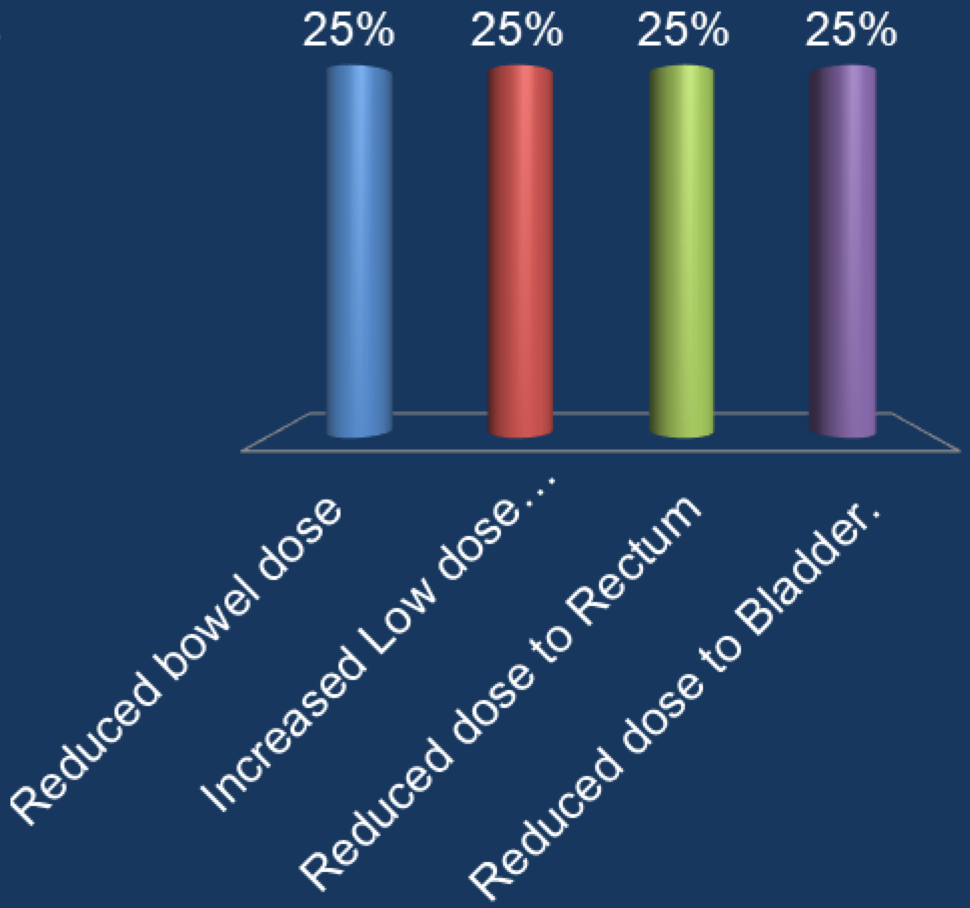


A. 1

B. 2

What is one major advantage of IMRT over 4F Box

A. Reduced bowel dose
B. Increased Low dose volume
C. Reduced dose to Rectum
D. Reduced dose to Bladder.



CRT vs IMRT, meta-analysis

Table 1 Basic characteristics of papers analyzed

First author, [Reference]	Country	Prescribed dose, Gy	Sample size IMRT*	Sample size 3D-CRT+	Organs at risk	Level of the dose, Gy
Heron DE [26]	USA					10, 20, 30, 40, 45
Chen MF [36]	Taiwan					5, 10, 15, 20, 25, 30, 35, 40, 45
Mell LK [30]	USA					5, 10, 20, 30, 40, 45
Igdem S [31]	Turkey					5, 10, 15, 20, 25, 30, 40, 45
Roeske JC [37]	USA					5, 10, 15, 20, 25, 30, 35, 40, 45
Portelance L [17]	USA					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					10, 20, 30, 40
Mundt AJ [38]	USA					5, 10, 15, 20, 25, 30, 35, 40, 45
Salama JK [40]	USA					5, 10, 15, 20, 25, 30, 35, 40, 45
Georg D [41]	Austria					5, 10, 15, 20, 25, 30, 35, 40, 45

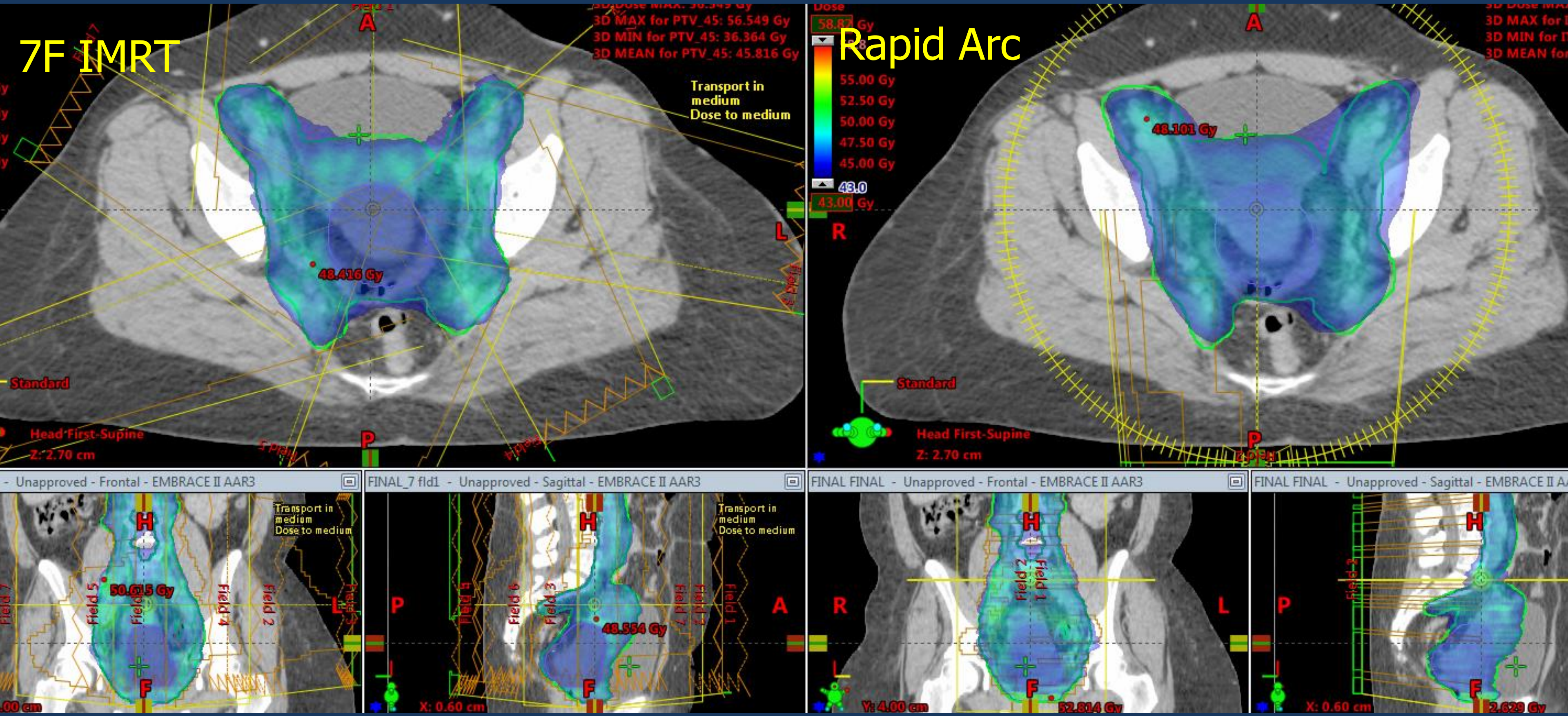
* intensity modulated radiotherapy; +

IMRT significantly reduced the average percent of the **rectum** volume that was irradiated to dose > 30 Gy and for the **small bowel** volume > 45 Gy

In the bladder and bone marrow, the advantages of IMRT over CRT were not significant

Yang et al Radiat Oncol 2012

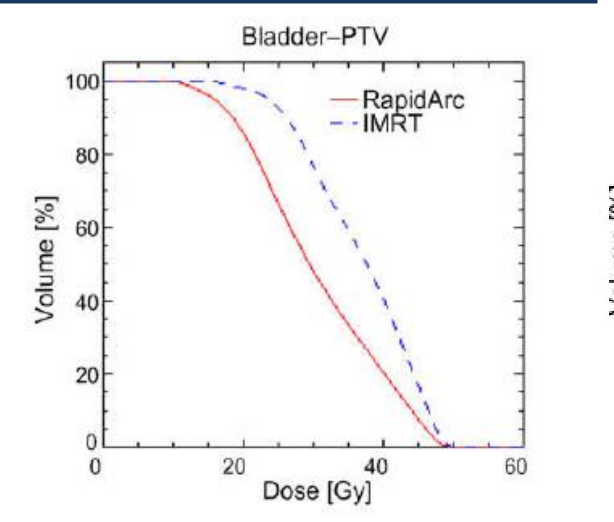
IMRT vs VMAT

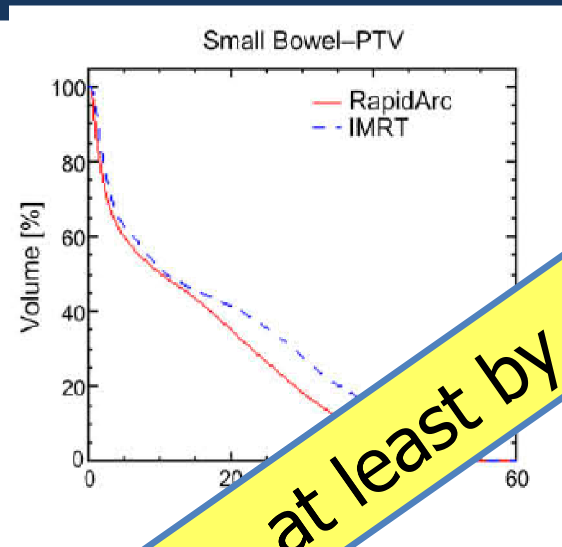


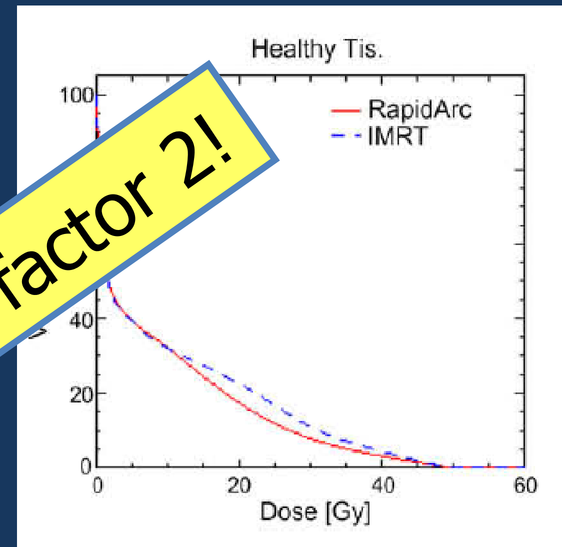
7F IMRT
Rapid Arc
3D MAX for PTV_45: 56.549 Gy
3D MIN for PTV_45: 36.364 Gy
3D MEAN for PTV_45: 45.816 Gy
Transport in medium
Dose to medium
48.416 Gy
48.101 Gy
55.00 Gy
52.50 Gy
50.00 Gy
47.50 Gy
45.00 Gy
43.00 Gy
Standard
Head First-Supine
Z: 2.70 cm
Unapproved - Frontal - EMBRACE II AAR3
FINAL_7 fld1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

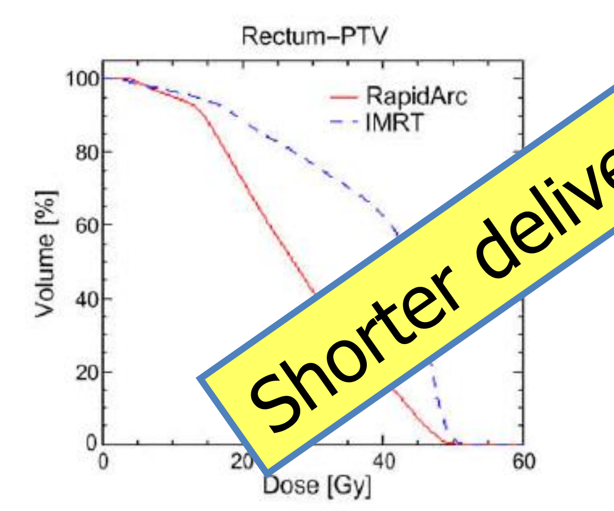
IMRT vs VMAT (RapidArc)

8 patients with ca. cervix







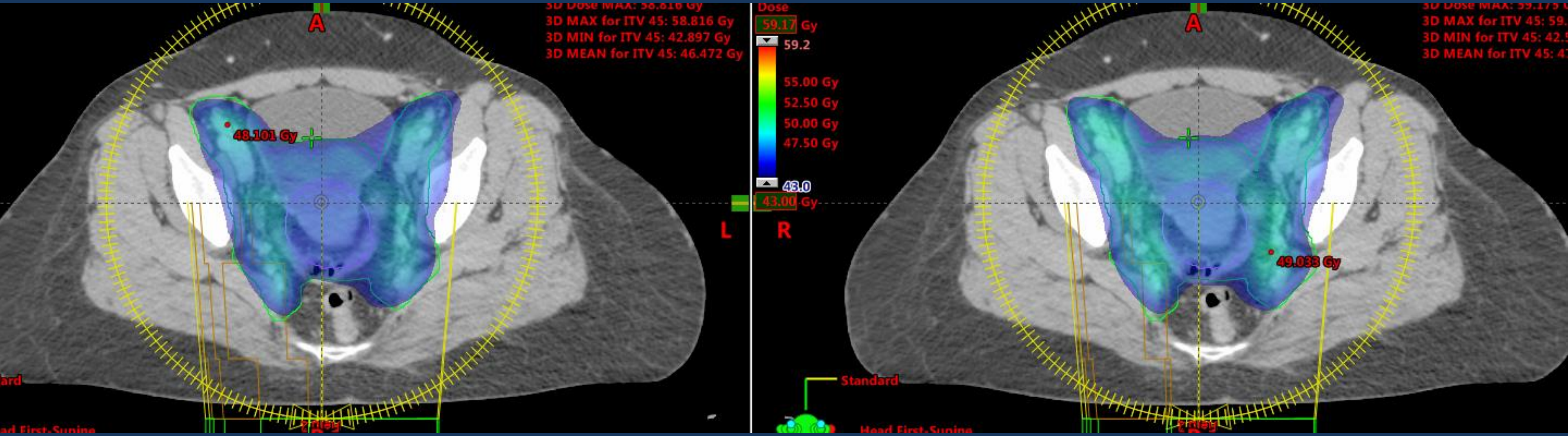


Shorter delivery time, at least by a factor 2!

	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

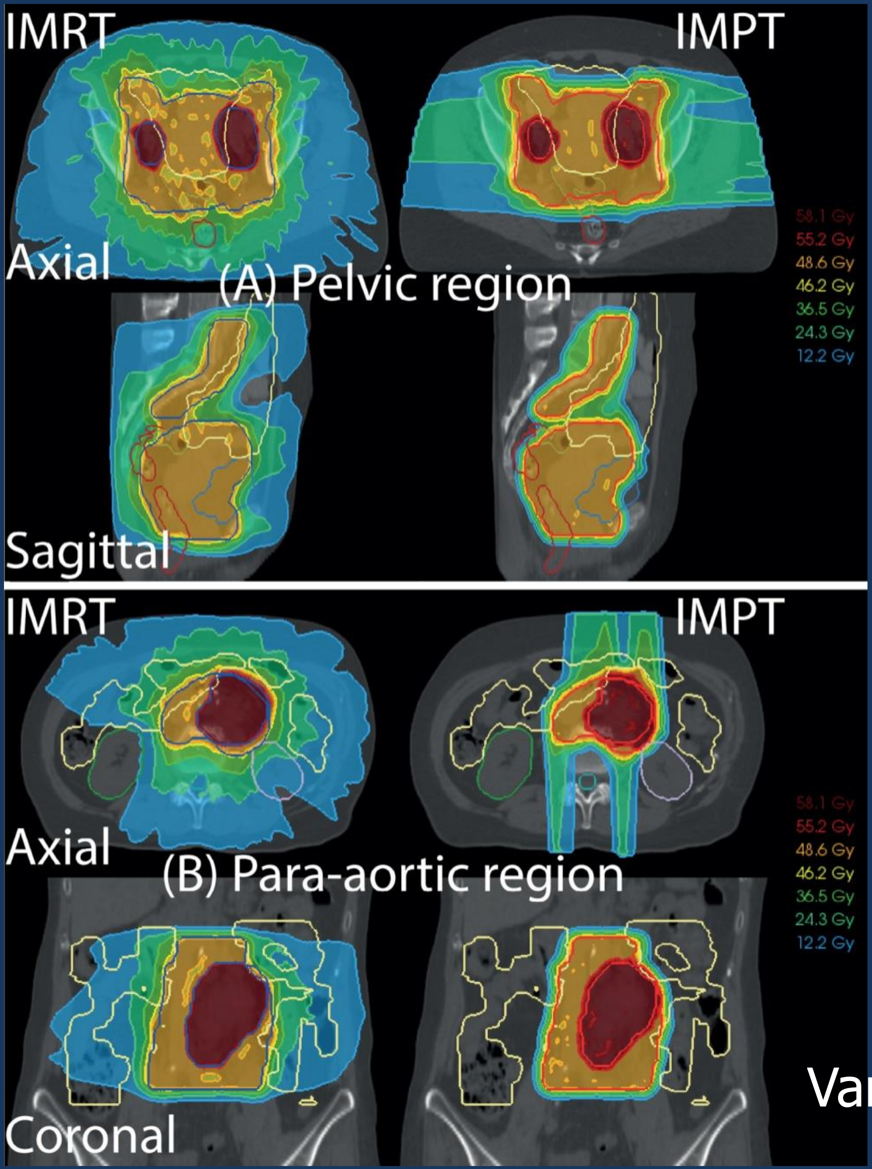


- No differences in dose distribution between for OARs and target.
- Reduction of beam-on time

  11% less for 6FFF-VMAT and 16% less for 10FFF -VMAT

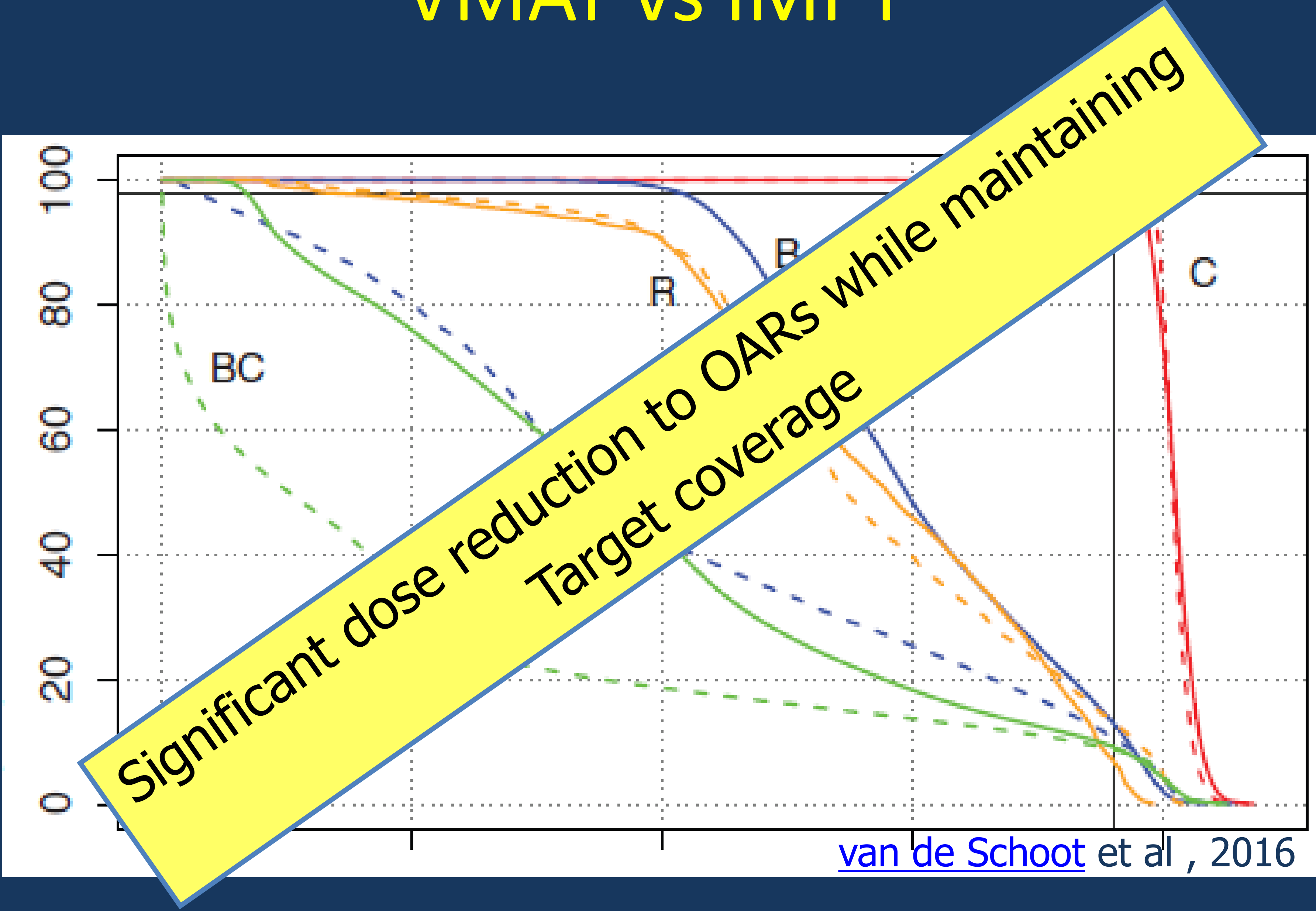
Fuli Zhang et al. Oncology and Translational Medicine August 2016, Qiao et al

IMRT vs IMPT



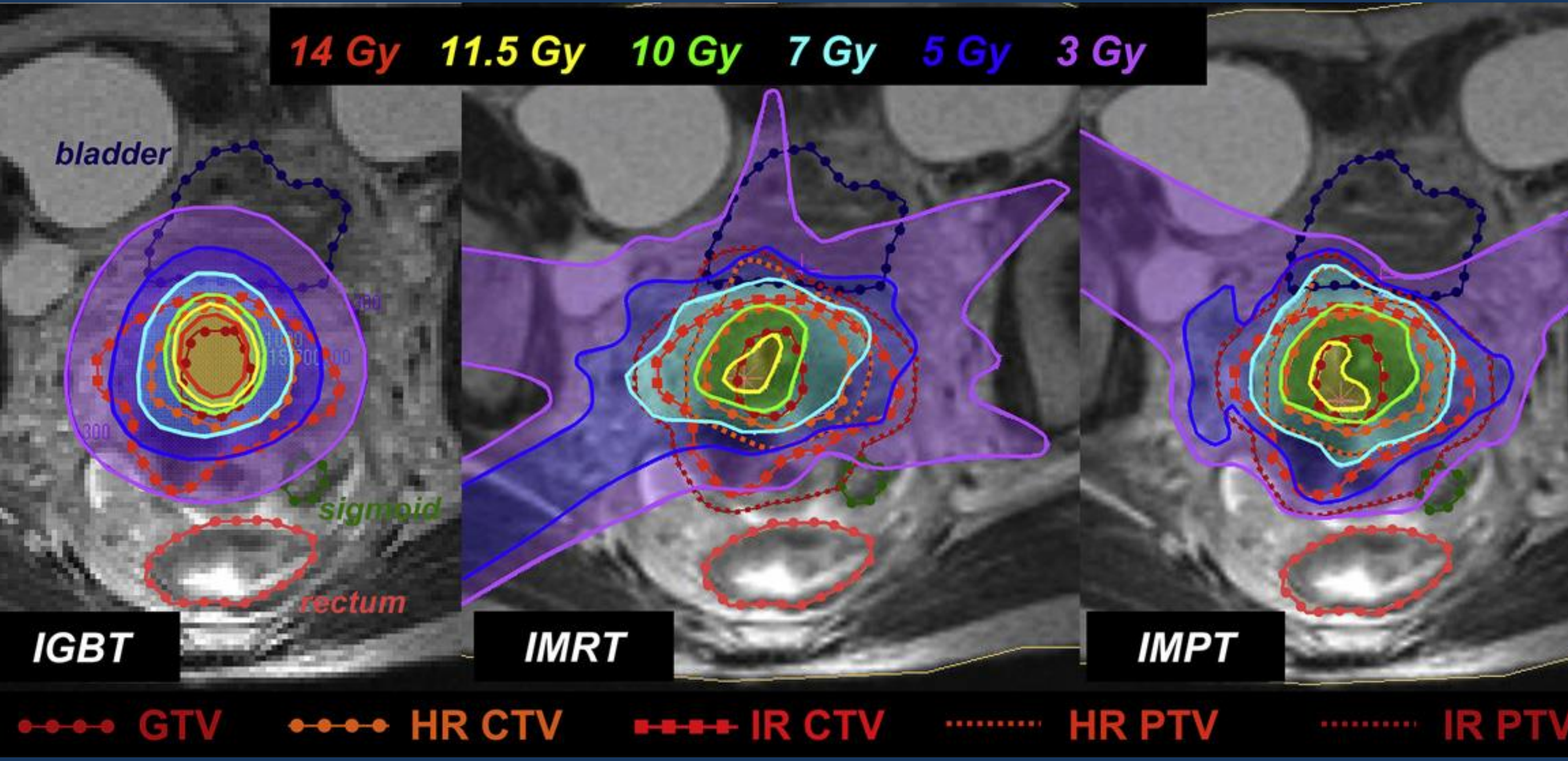
Vande san de et al, 2016

VMAT vs IMPT



van de Schoot et al , 2016

IMRT vs IGBT 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

Conclusion

- 3DCRT vs IMRT – Significant organ sparing
  - Bowel and rectum dose
- Inverse Planning
  - Constraints
  - Optimization volumes
- IMRT vs VMAT – Significant reduction of MU
- VMAT vs IMPT – Significant reduction of dose to OARs

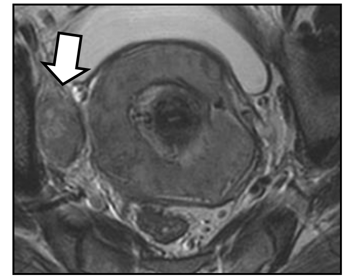
Advanced BT is superior to IM(R/P)T

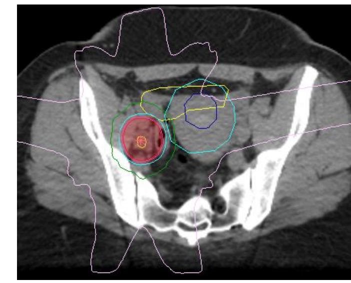
Acknowledgements

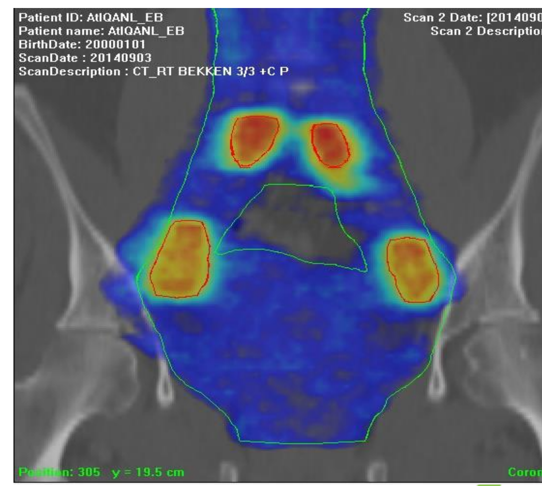
- Prof. Taran Paulsen Hellebust PhD, Oslo.
- Prof. Kari Tanderup PhD, Aarhus

Nodal boost

Background, Techniques
Dose Contribution of Brachytherapy





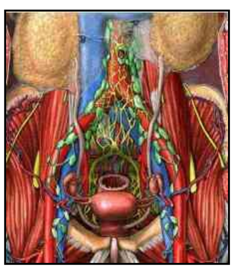


Ina Jürgenliemk-Schulz
University Medical Centre Utrecht, The Netherlands

Risk of nodal spread

Surgical series

Risk of nodal disease related to stage, invasion depth and LVSI



Depth of invasion	Risk of Pelvic N+
< 3 mm	< 1%
3-5 mm	1 – 8 %
6 – 10 mm	15 %
11 – 15 mm	22 %
LVSI	**Risk of Pelvic N+**
Absent	8%
Present	25%

Inoue et al. Cancer 1984
Delgado G, et al. (GOG study). Gynecol Oncol 1989
Coia L, et al. Cancer 1990
Leibel & Philips Textbook

Risk of nodal spread

Journal of Clinical Oncology | Original Report

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

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

PET-CT helps to detect nodal metastases if no surgical staging is performed

Table 2. Comparison of Pelvic and Para-Aortic Lymph Node Metastasis by Stage From Combined Historical Data[3,16-19] and Data From This Study With FDG-PET Lymph Node Staging

	Pelvic Nodal Metastasis (%)		Para-Aortic Metastasis (%)	
FIGO Stage	Historical Data	Current Study	Historical Data	Current Study
I	12-38	9-51	0-5	0-9
IIA	10-45	50	0-12	21
IIB	26-62	54	10-21	17
IIIA	39-59	50	21-33	25
IIIB/IV	39-88	55-85	13-38	27-60

Abbreviations: FDG-PET, positron emission tomography with $[^{18}F]$fluorodeoxyglucose; FIGO, International Federation of Gynecology and Obstetrics.

Inoue et al. Cancer 1984
Delgado G, et al. (GOG study). Gynecol Oncol 1989
Coia L, et al. Cancer 1990
Stehman f, et al. Cancer 1991
Berman ML, et al. Gynaecol Oncol 1984
Christiensen A, et al. Acta Obstet Gynecol Scand 1964
Wharton J, et al. Obstet Gynecol 1977
Hackett TE, et al. Gynecol Oncol 1995

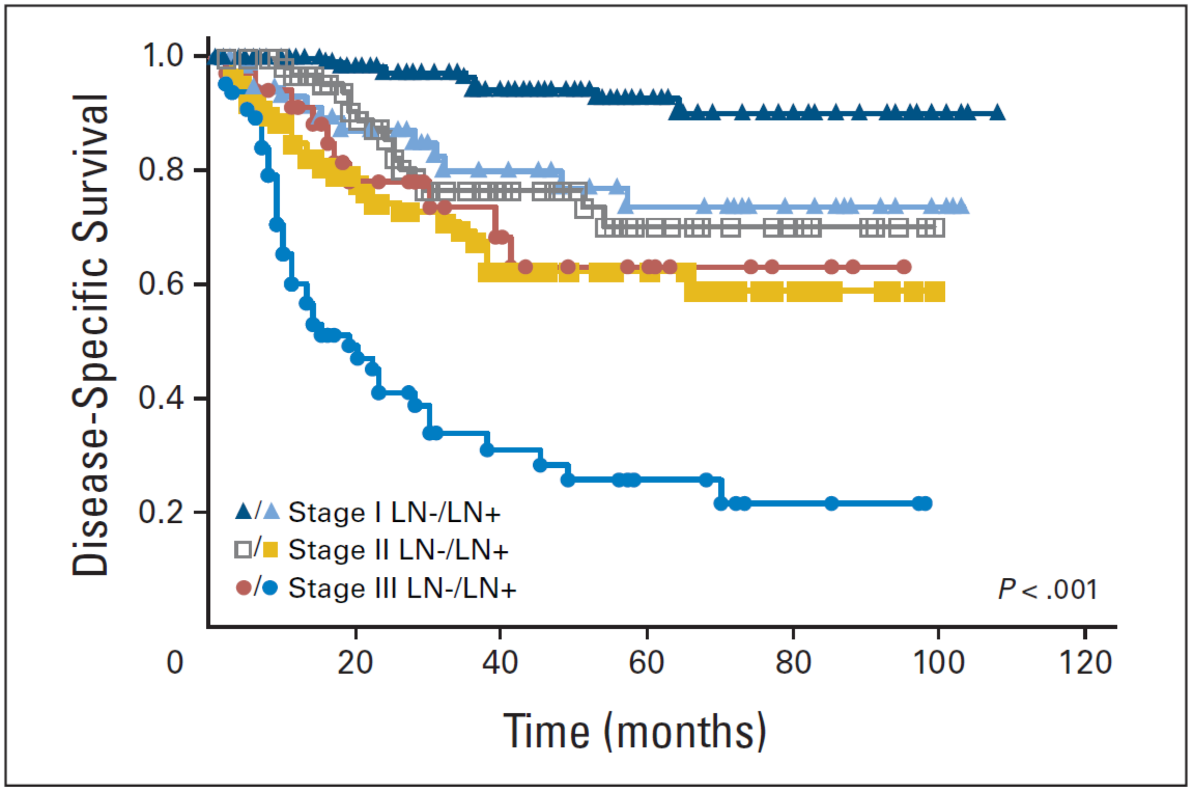
Prognostic impact of nodal status

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

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

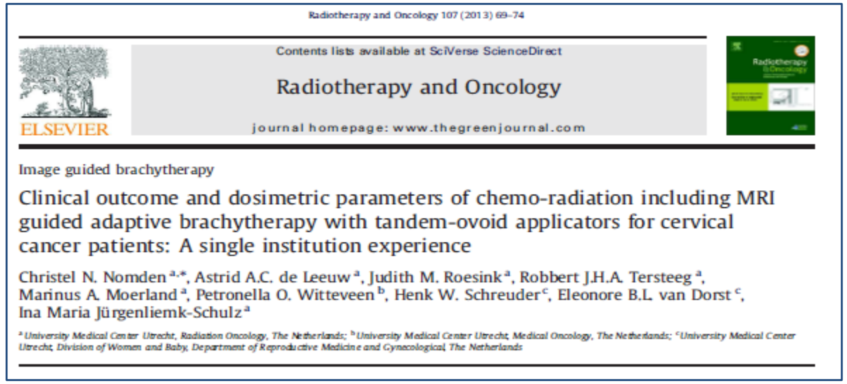
Elizabeth A. Kidd, Barry A. Siegel, Farrokh Dehdashti, Janet S. Rader, David G. Mutch, Matthew A. Powell, and Perry W. Grigsby

Nodal disease is a negative prognostic factor



Kidd EA, et al. JCO 2010

Prognostic impact of nodal status


Radiotherapy and Oncology 107 (2013) 69–74

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

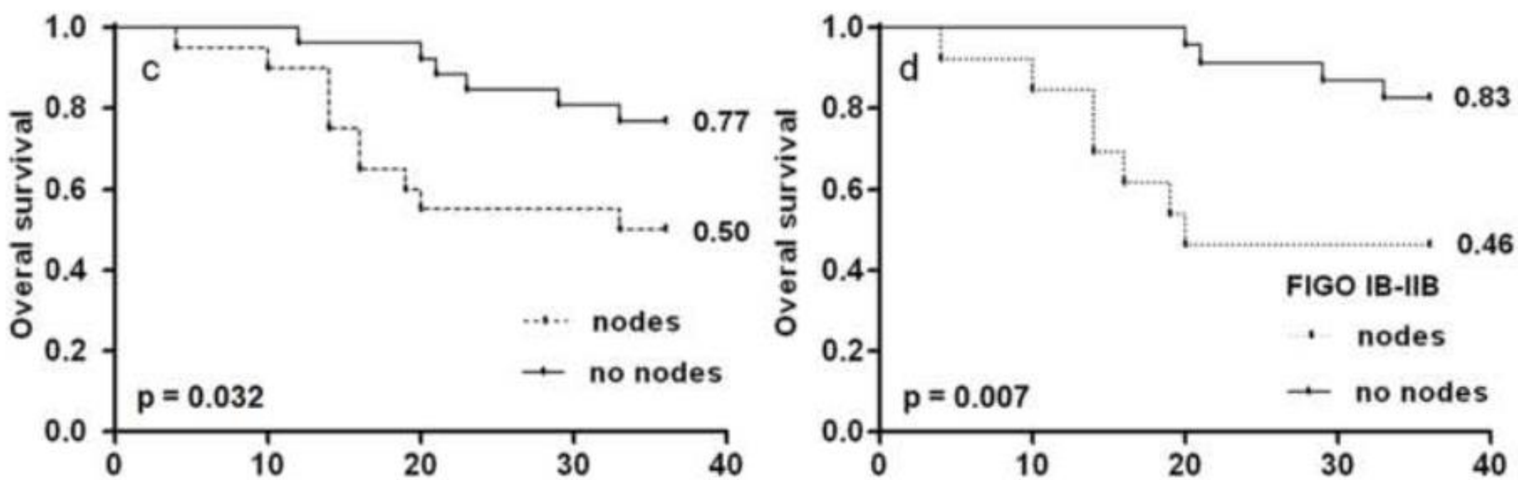
Image guided brachytherapy

Clinical outcome and dosimetric parameters of chemo-radiation including MRI guided adaptive brachytherapy with tandem-ovoid applicators for cervical cancer patients: A single institution experience

Christel N. Nomden [a,*], Astrid A.C. de Leeuw [a], Judith M. Roesink [a], Robbert J.H.A. Tersteeg [a], Marinus A. Moerland [a], Petronella O. Witteveen [b], Henk W. Schreuder [c], Eleonore B.L. van Dorst [c], Ina Maria Jürgenliemk-Schulz [a]

[a] University Medical Center Utrecht, Radiation Oncology, The Netherlands; [b] University Medical Center Utrecht, Medical Oncology, The Netherlands; [c] University Medical Center Utrecht, Division of Women and Baby, Department of Reproductive Medicine and Gynecological, The Netherlands

Nodal disease is a negative prognostic factor



Pettersson F, et al. Int J Gynaecol Obstet 1992

Inoue T, et al. Cancer 1990

Patterns of regional recurrence after RT

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 5, pp. 1396–1403, 2010

0360-3016/10/$–see front matter

ELSEVIER

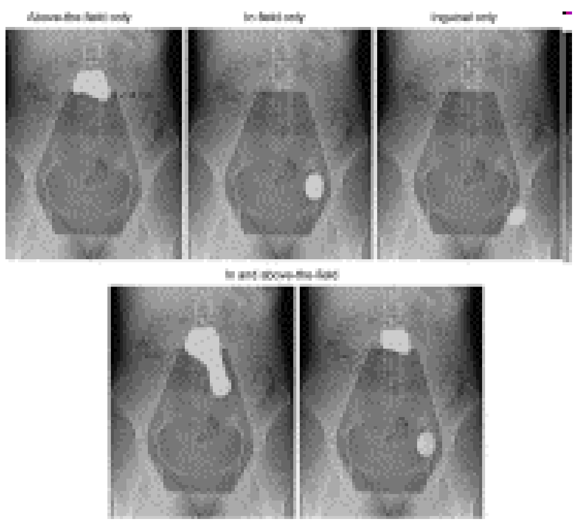
doi:10.1016/j.ijrobp.2009.04.009

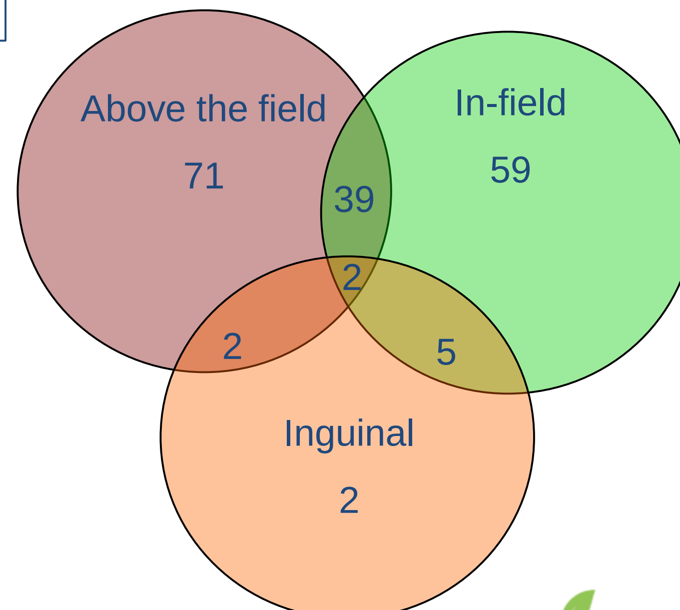
CLINICAL INVESTIGATION **Cervix**

PATTERNS OF REGIONAL RECURRENCE AFTER DEFINITIVE RADIOTHERAPY FOR CERVICAL CANCER

Beth M. Beadle, M.D., Ph.D.,* Anuja Jhingran, M.D.,* Sue S. Yom, M.D., Ph.D.,* Pedro T. Ramirez, M.D.,† and Patricia J. Eifel, M.D.*

Departments of *Radiation Oncology and †Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX





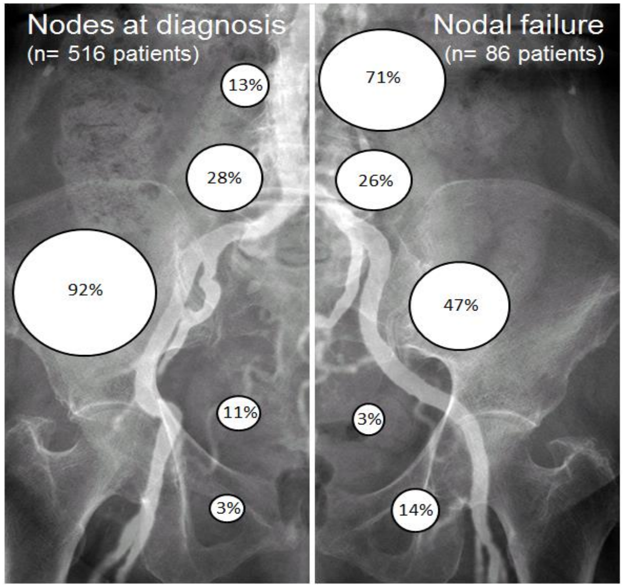
Inside the field = problem with dose and detection
Outside and marginal = geographical miss

Beadle BM, et al. IJROBP 2010

Patterns of regional recurrence after RT

Sub-study on nodal recurrence within EMBRACE (work in progress)

- 1077 patients, all stages cervix cancer, M0
- Overall node control 93 % (at 2 years)
  - 12 % recurrences in N1 patients
  - 5 % in N0
- At time of diagnosis majority of pathologic nodes in the pelvis
- At time of first relapse majority at upper field border/PAO



Percentage of patients with pathologic lymph nodes at time of diagnosis (left) and the percentage of patients with nodal failure (right) per nodal region

Inside the field = problem with dose and detection
Outside and marginal = geographical miss

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

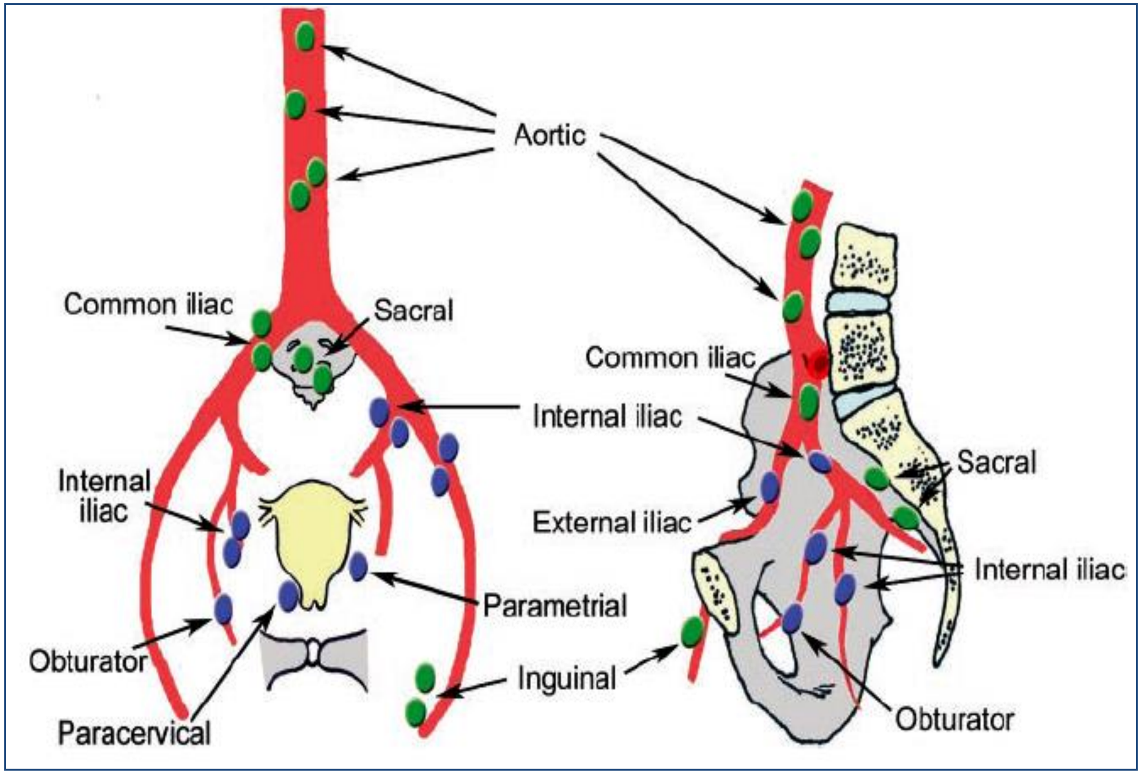
Nomden et al

Reduction of geographical miss

Better detection of affected nodes and boost target

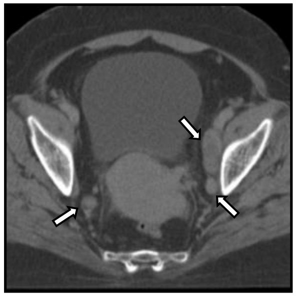
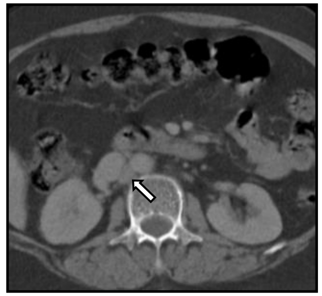
Imaging

- CT
- MRI
- PET CT

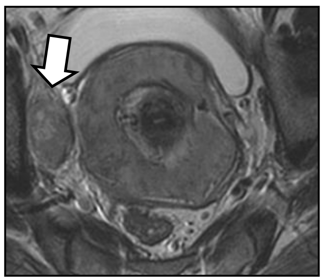
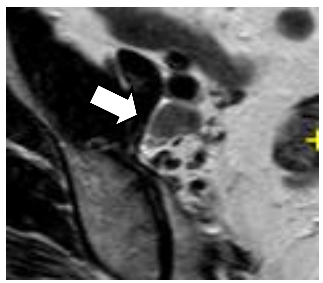
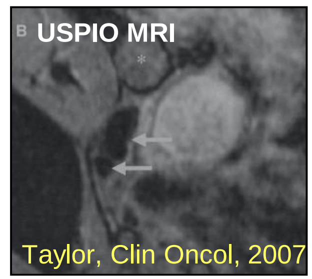


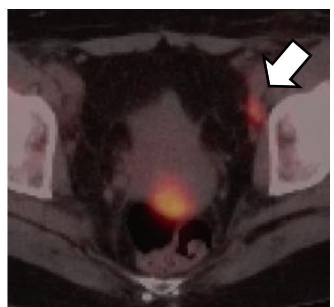
GTV for nodal RT boost

Imaging: indirect proof (morphological & functional characteristics)

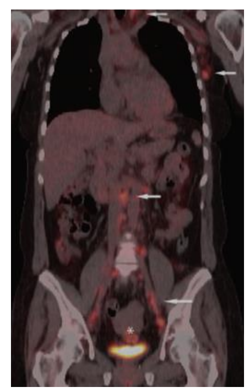




Sensitivity	Specificity	
21-73 %	82-93 %	
53 - 87 %	92 - 98 %	
68 - 94 %	95 %	Pelvis
33 - 100 %	95 - 99 %	PAO

Gyn Radiat Oncol
Springer Book 2011



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. Perez-Medina et al. Int J.Gyn Cancer 2013, Oncoline.nl/cervixcarcinoom

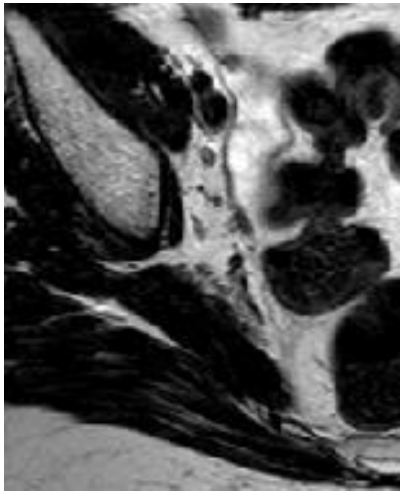
GTV for nodal RT boost

Example

Node 8 mm, PET negative, no boost

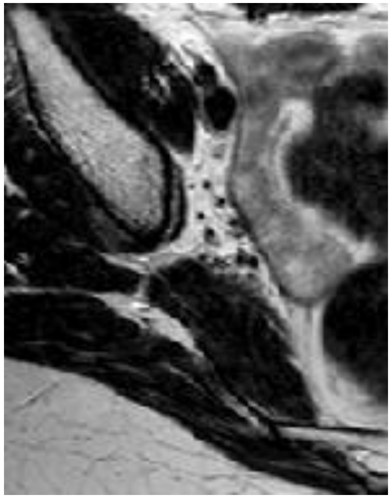
At diagnosis

Irregular appearance and irregular border



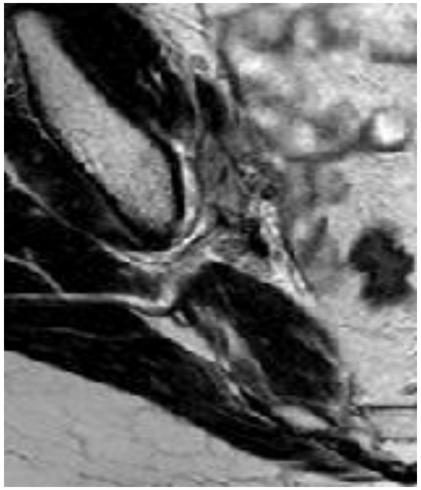
4th week of EBRT

Nearly gone in week 4



6 weeks post-CRT

Nearly no rest 6 weeks after treatment



12 months post-CRT

Nodal failure

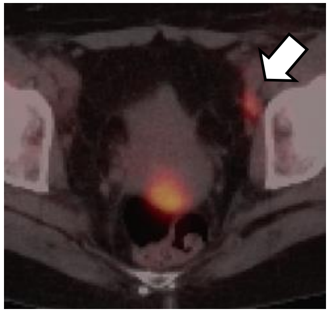
GTV for nodal RT boost

Imaging: indirect proof (morphological & functional characteristics)

Consider nodal involvement if

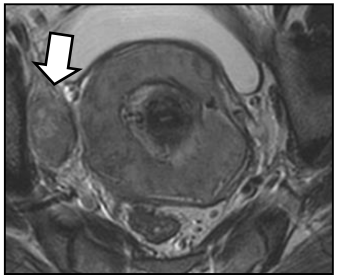
1. Nodes are PET positive

- Also PET negative nodes can contain metastases!
  - Small ones if cell load low
  - Big ones if large necrotic center



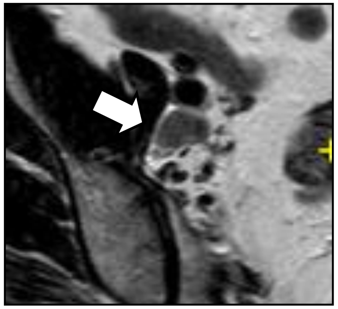
2. Nodes > 10 mm short axis diameter on CT or MRI

- Can be reactive!



3. Nodes between 5 and 10 mm on MRI if

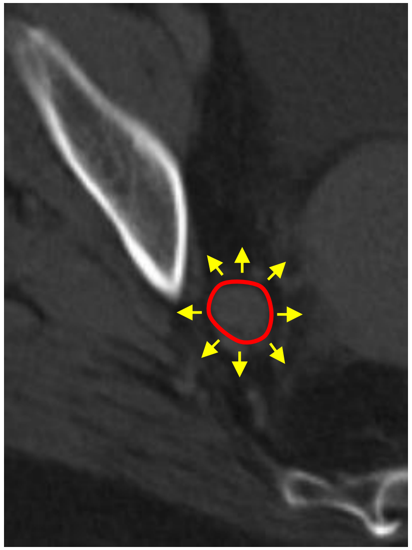
- PET positive
- Irregular shape
- Lost nodal architecture
- Inhomogeneous appearance (“necrotic center”)
- Irregular border



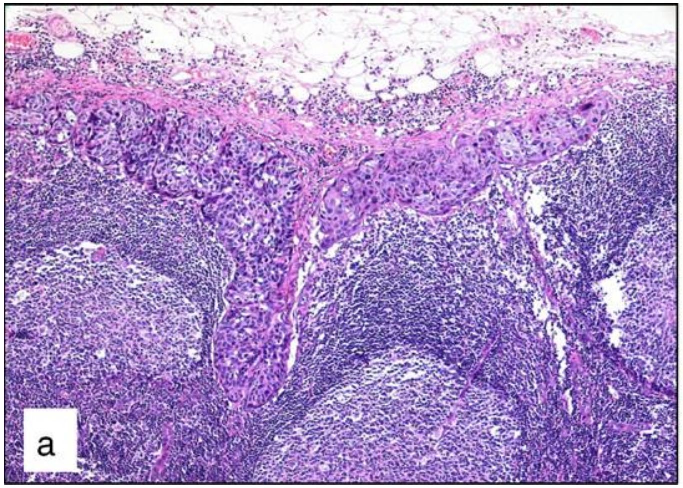
From GTV to CTV

Should we add margin around the nodal GTV?

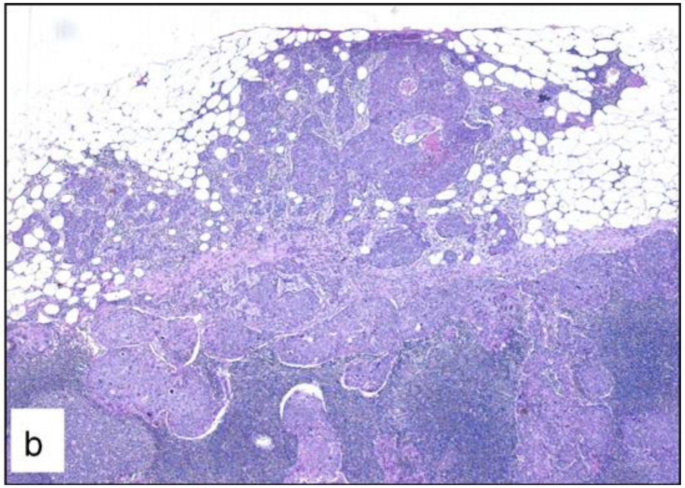
Risk of extracapsular extension (ECE)!



Node without ECE

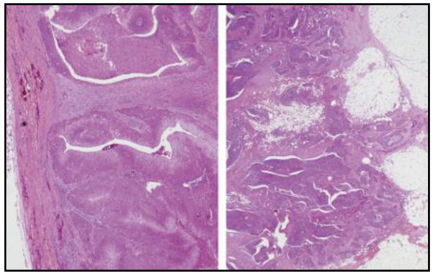


Node with ECE



From GTV to CTV

Should we add margin around the nodal GTV?



The risk of ECE in operable cervix cancer

- 95 patients (stage I, II)
- **52 %** of N+ cases had ECE

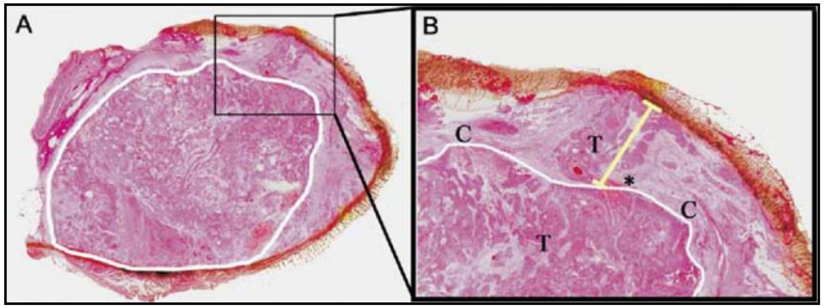
Metindir J, et al. Eur J Gynaecol Oncol 2008

What about locally advanced inoperable cases?

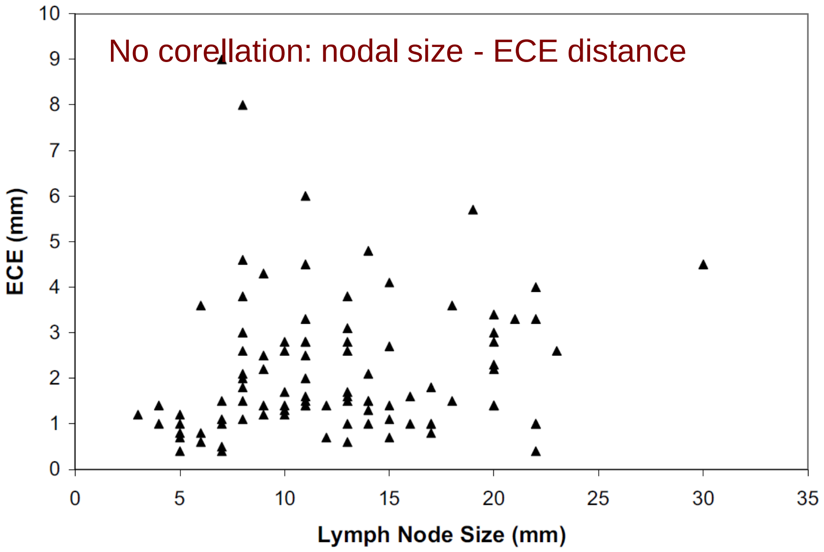
From GTV to CTV

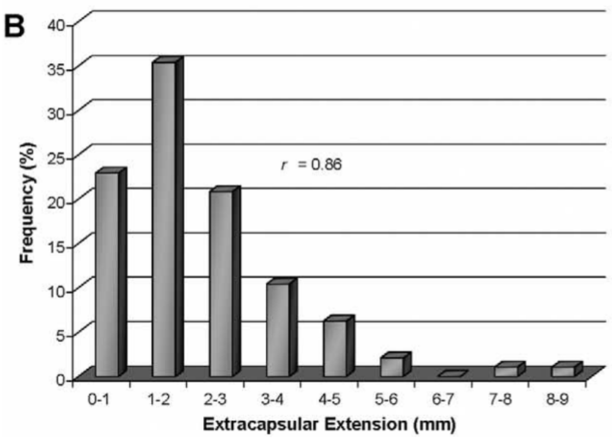
What should be the margin around the nodal GTV?

MDAH Study, 96 nodes with ECE, head and neck cancer



- Median ECE: 1.6 mm
- Range: 0.4 – 9 mm
- **96 % nodes: < 5mm**





Apisarnthanarax S, et al. IJROBP 2005

From GTV to CTV

What should be the margin around the nodal GTV?

The risk of extracapsular extension (ECE) has to be taken into account!

- Consider 3-5 mm around nodal GTV for ECE (and internal position shifts)
- Take into account anatomical barriers (muscle, bone, surrounding organs)
- Node CTV should be included in the elective CTV (45 -50 Gy)

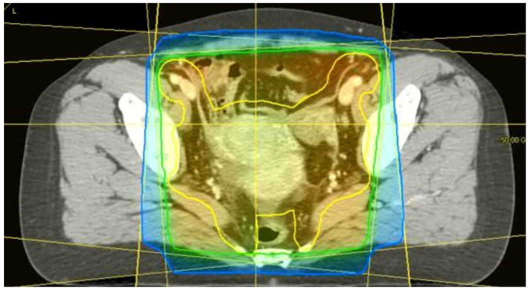
EBRT techniques for nodal boost

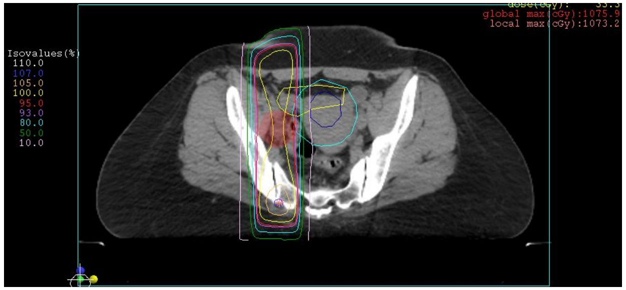
"Standard" approach

Week 1-5

Week 6-7

Sequential boost





RT technique

- AP/PA or 3D Conformal RT
- Avoid central pelvis irradiation

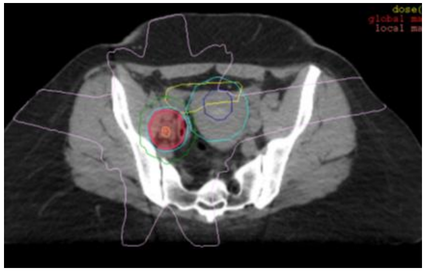
Can we improve?

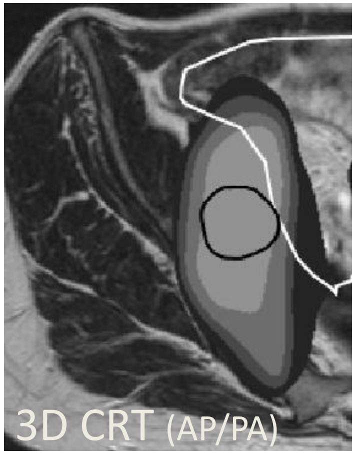
EBRT techniques for nodal boost

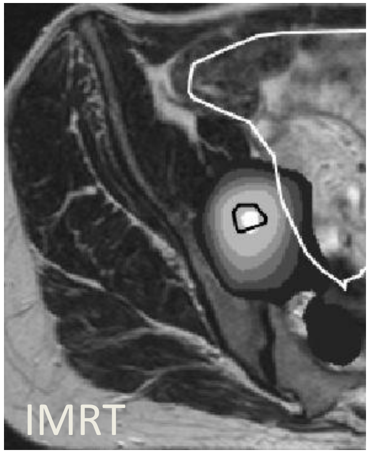
Can we improve the technique?

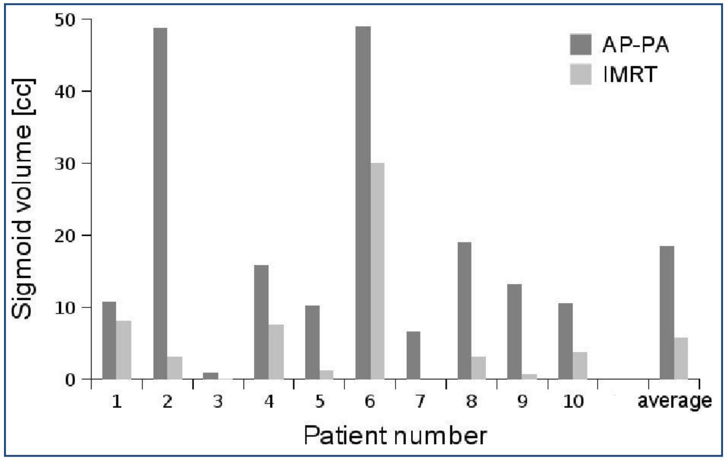
IMRT– *GAINS:*

- Smaller and highly conformal treated volumes
  - Dose escalation → ↑ disease control?
  - ↓ Dose to organs at risk → ↓ complication rates?









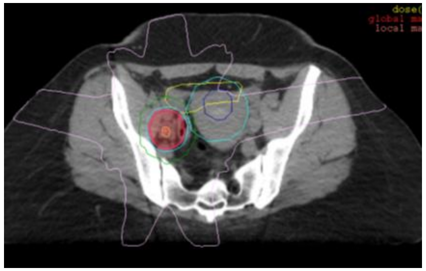
L. Dijkstra, E.Kerkhof

EBRT techniques for nodal boost

Improving the technique !

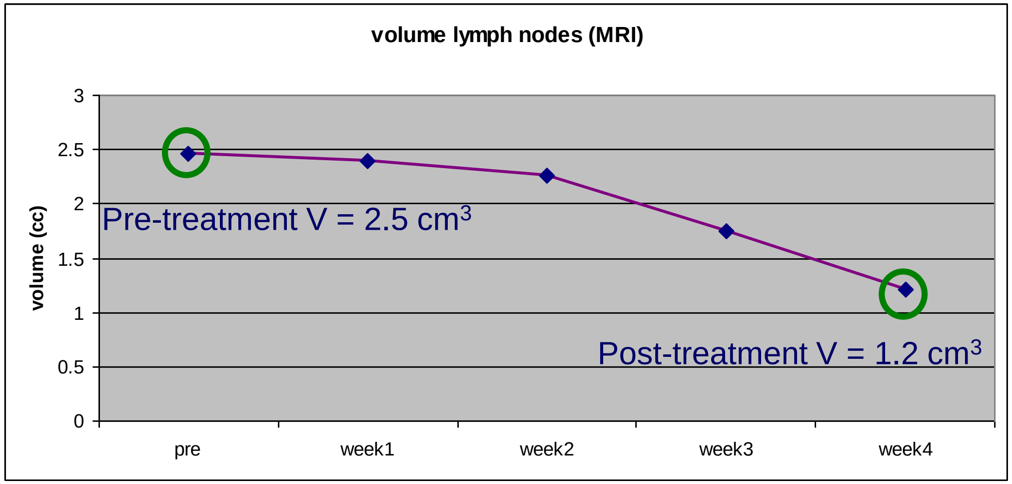
IMRT– *PITFALL:*

Uncertainties in hitting the target volume



Nodes shrink to about 50 % of initial volume

Schippers M, et al.: 48 nodes contoured on MRI in 15 pts

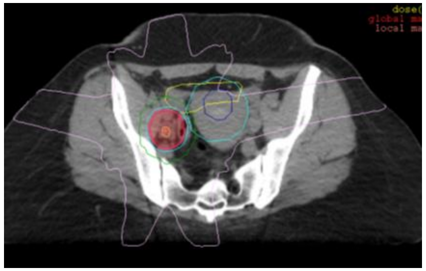


EBRT techniques for nodal boost

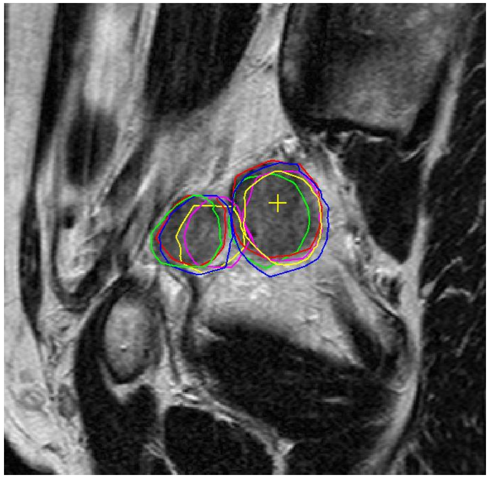
Improving the technique !

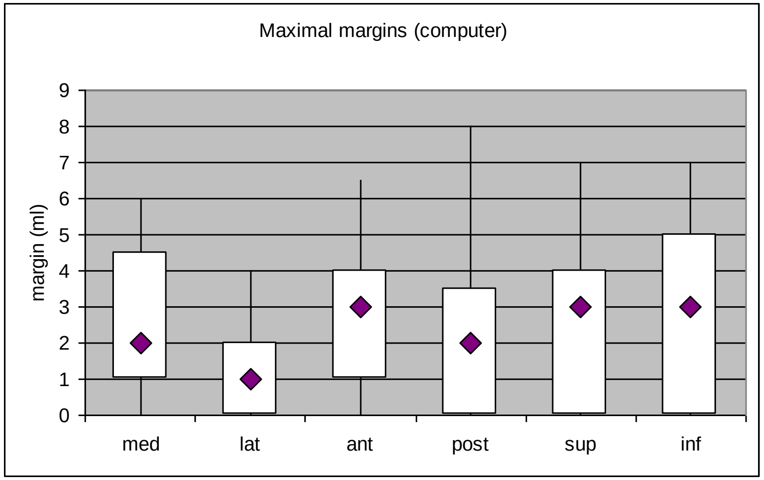
IMRT– *PITFALLS:*

Uncertainties in hitting the target volume



Nodes move: up to 8 mm, majority < 4 mm





Less movement than primary tumor, but should be taken into account!

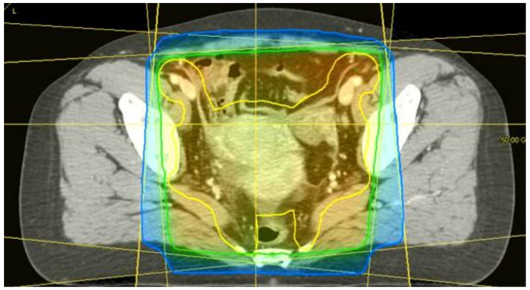
EBRT techniques for nodal boost

Improving the timing ?

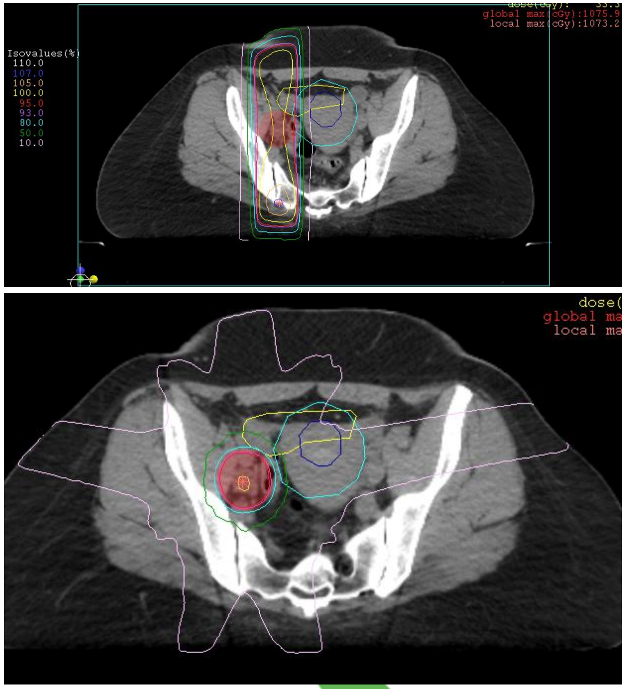
Sequential boost – pro

Regression and brachy dose can be taken into account

Week 1-5



Week 6-7



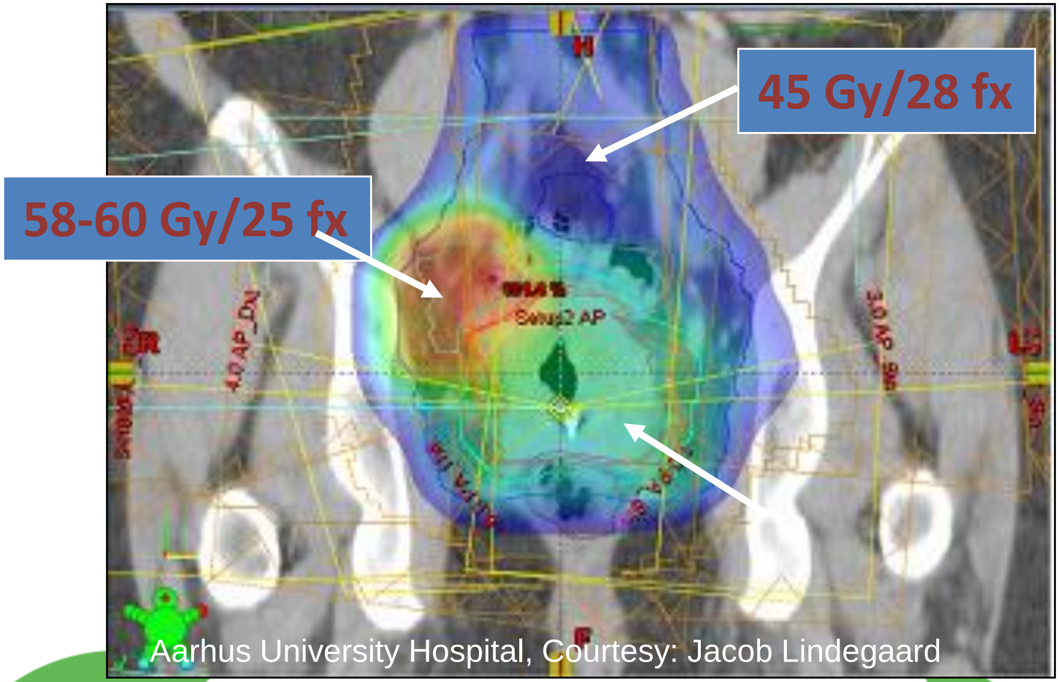
EBRT techniques for nodal boost

Can we improve the timing?

Concomitant boost - pros :

Reduction of totally administered dose

Reduction of overall treatment time !



What dose is needed for the positive nodes?

Classical radiation dose-control data

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

From: Kupets R, et al. Gynecol Oncol 2002

Dose to macroscopic nodal disease

Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 3, pp. 706–712, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2003.12.038

CLINICAL INVESTIGATION **Cervical**

LYMPH NODE CONTROL IN CERVICAL CANCER

Perry W. Grigsby, M.D.,*†§ Anurag K. Singh, M.D.,*§ Barry A. Siegel, M.D.,†§ Farrokh Dehdashti, M.D.,†§ Janet Rader, M.D.,‡§ and Imran Zoberi, M.D.*§

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

Purpose: The aim was to evaluate pretreatment lymph node size, irradiation dose, and failure patterns.
Methods: Pretreatment PET and CT were performed in 208 patients. Lymph nodes were scored as either positive or negative by PET and lymph node size was measured by CT. Lymph node irradiation dose and sites of failure were recorded.
Results: The mean pelvic lymph node doses were: PET negative nodes, ≤1 cm, 66.8 Gy, and 0/76 failures; PET positive nodes, ≤1 cm, 66.8 Gy, and 3/89 failures; 1.1–≤2 cm, 66.9 Gy, and 0/21 failures; 2.1–≤3 cm, 69.4 Gy, and 2/15 failures; and 3.1 to ≤4 cm, 74.1 Gy, and 0/5 failures. The mean paraaortic lymph node dose was 43.3 Gy and there were no paraaortic failures for 24 patients with PET positive ≤1 cm nodes, 0/5 failures for 1.1 to ≤2 cm, and 0/4 failures for 2.1 to ≤3 cm. The most common site of failure was distant metastases.
Conclusions: The irradiation doses given in this study were adequate to control most lymph node metastases. Positive lymph nodes of any size at diagnosis were the most significant predictor for developing distant metastases.

Dose to macroscopic nodal disease

- 208 patients, all stages cervix cancer
- Lymph node status defined by CT and PET
  - all enlarged nodes and some small ones were PET positive and were boosted
- Pelvis
  - Doses level depending on node size
  - Overall rather high doses 67 – 74 Gy
- PAO
  - Lower dose, mean 45, max 60 Gy
- Excellent node control

Above 60 Gy to much ?

Table 1. Pelvic lymph nodes

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

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

Dose to macroscopic nodal disease

Acta Oncologica, 2015; Early Online: 1–7

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

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

Impact of radiation dose and standardized uptake value of (18)FDG PET on nodal control in locally advanced cervical cancer

ANNE RAMLOV[1], PETRA S. KROON[2], INA M. JÜRGENLIEMK-SCHULZ[2], ASTRID A. C. DE LEEUW[2], LARS CHRISTIAN GORMSEN[3], LARS ULRIK FOKDAL[1], KARI TANDERUP[1] & JACOB CHRISTIAN LINDEGAARD[1]

[1]*Department of Oncology, Aarhus University Hospital, Denmark,* [2]*Department of Radiation Oncology, University Medical Center Utrecht, The Netherlands and* [3]*Department of Nuclear Medicine and PET Center, Aarhus University Hospital, Denmark*

ABSTRACT

Background. Despite local control now exceeding 90% with image-guided adaptive brachytherapy (IGABT), regional and distant metastases continue to curb survival in locally advanced cervical cancer. As regional lymph nodes often represent first site of metastatic spread, improved nodal control could improve survival. The aim of this study was to examine optimal volume and dose of external beam radiotherapy (EBRT) to maximize regional control including dose contribution from IGABT.

Material and methods. In total 139 patients from the EMBRACE study were analyzed. Individual nodal dose was determined by dose-maps from EBRT and IGABT. All PET/CT scans were re-evaluated and nodal maximal standard uptake value (SUV_{max}) was determined. Nodal failures were registered to planning scans and related to boosted nodes and treated volume. Relation between SUV_{max} and nodal control as well as the pattern of regional nodal failure were analyzed.

Results. Eighty-four patients were node positive. Nine patients had all metastatic nodes surgically removed. Seventy-five patients had 209 nodes boosted with EBRT. Median nodal boost dose was 62 Gy EQD2 (53–69 Gy EQD2). Median SUV_{max} was 6 (2–22). No patients had persistent nodal disease, but six patients recurred in a boosted node. SUV_{max} was significantly higher in nodes that recurred ($p = 0.02$). However, there was no correlation to nodal dose or volume. Twenty-one patients had a nodal failure including para-aortic nodal (PAN) metastases above the irradiated volume. Nine patients had a PAN-only failure. Patients receiving ≤ 4 cycles of weekly cisplatin had higher risk of nodal failure ($p < 0.01$).

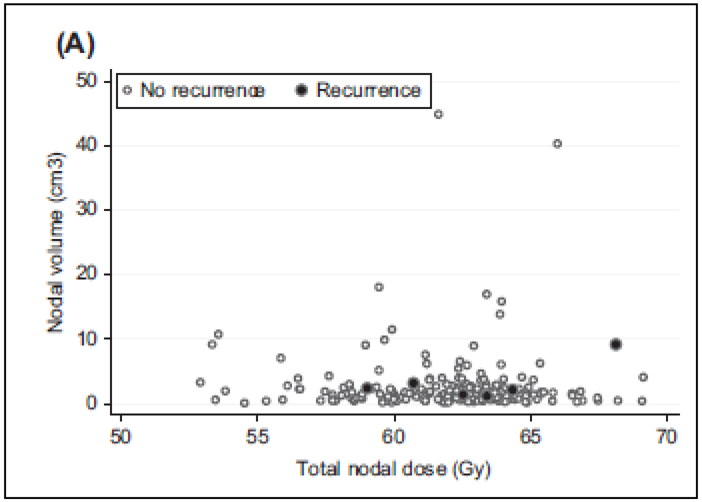
Conclusion. Current RT practice provides a high level of control in both boosted nodes and the elective irradiated regional target. However, a high nodal SUV_{max} is a negative prognostic predictor for nodal control. Attention should be raised to administration of a complete schedule of concurrent chemotherapy as well as treatment of para-aortic nodes.

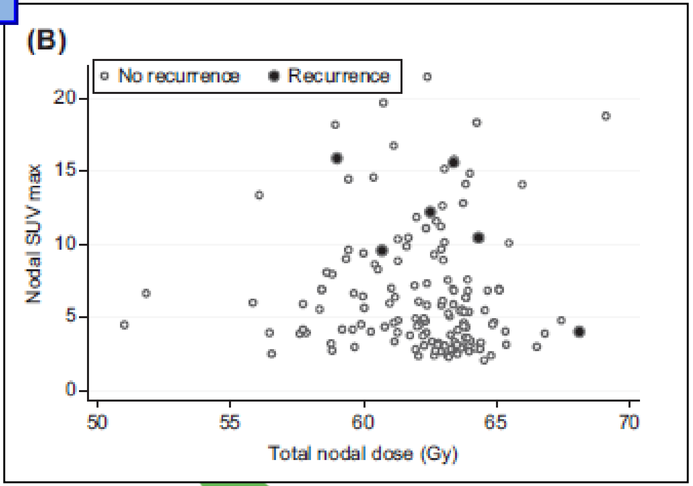
Dose to macroscopic nodal disease

- 139 patients, all EMBRACE
- All stages cervix cancer, 84 N1
- 209 nodes identified
  - D98 mean 62 Gy EQD2 (53 to 69)
  - Including BT contribution
- Excellent control in boosted nodes

No relation initial node volume - dose - failure

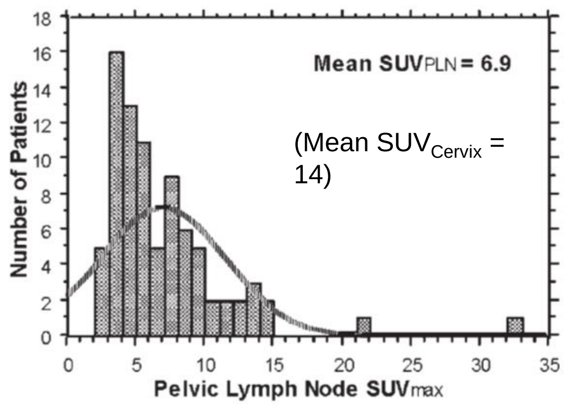
- Initial SUVmax higher in nodes that relapsed
- More failures when chemo < 5 cycles

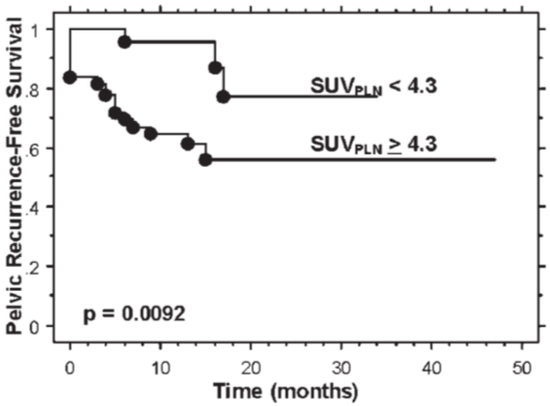


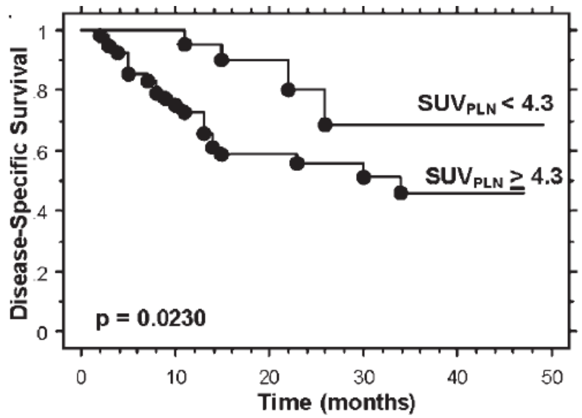


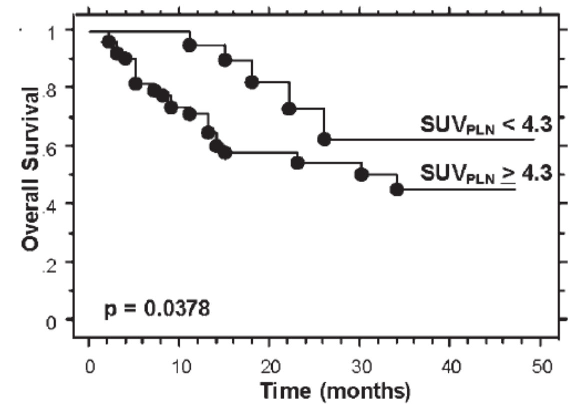
GTV for nodal RT boost

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









FDG-PET is a prognostic biomarker predicting treatment response !

Elizabeth A. Kidd, MD[1]; Barry A. Siegel, MD[2,3]; Farrokh Dehdashti, MD[2,3]; and Perry W. Grigsby, MD[1,2,3,4] *Cancer, 2010*

What dose is needed for the positive nodes?

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

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

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(Received 14 December 2012; revised 9 July 2013; accepted 10 July 2013)

Radiation therapy (RT) for metastatic pelvic lymph nodes (PLNs) is not well established in cervical cancer. In this study the correlation between size of lymph nodes and control doses of RT was analyzed. Between January 2002 and December 2007, 245 patients with squamous cell carcinoma of the cervix treated with a combination of external beam irradiation with or without boost irradiation and high-dose rate brachytherapy were investigated. Size of lymph node was measured by computed tomography before RT and just after 50 Gy RT. Of the 245 patients, 78 had PLN metastases, and a total of 129 had enlarged PLNs diagnosed as metastases; 22 patients had PLN failure. The PLN control rate at 5 years was 79.5% for positive cases and 95.8% for negative cases. In cases with positive PLNs, 12 of 129 nodes (9.3%) developed recurrences. There was significant correlation between PLN control rate and size of PLN after 50 Gy (<10 mm: 96.7%, ≥ 10 mm: 75.7 % (P<0.001)). In addition, the recurrence in these poor-response nodes was significantly correlated with dose of RT. Nine of 16 nodes receiving ≤ 58 Gy had recurrence, but none of 21 nodes receiving > 58 Gy had recurrence (P = 0.0003). These results suggested that the response of lymph nodes after RT was a more significant predictive factor for recurrence than size of lymph node before RT, and poor-response lymph nodes might require boost irradiation at a total dose of > 58 Gy.

Dose to macroscopic nodal disease

Lymph node status by CT and MRI at diagnoses and after 50 Gy

- Total node dose mean 55 Gy (43-60)
- Good response group with node size < 10 mm after 50 Gy
- Bad response group

Excellent node control

- 3 recurrences in good response group, no relation with dose
- 9/37 recurrences in bad response group, but none after > 58 Gy

58 to 60 Gy EBRT gives high control rates

Radiation for PLN in cervical cancer 143

Table 4. The correlations between lymph node recurrence and dose of external radiation were analyzed in the good response and poor response groups

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

Rec = recurrence.

Dose to macroscopic nodal disease

International Journal of
Radiation Oncology
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Clinical Investigation

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

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Received Apr 22, 2014, and in revised form Jun 25, 2014. Accepted for publication Aug 11, 2014.

Purpose: Positron emission tomography/computed tomography (PET/CT) is commonly used for nodal staging in locally advanced cervical cancer; however the false negative rate for para-aortic disease are 20% to 25% in PET-positive pelvic nodal disease. Unless surgically staged, pelvis-only treatment may undertreat para-aortic disease. We have treated patients with PET-positive nodes with extended field intensity modulated radiation therapy (IMRT) to address the para-aortic region prophylactically with concomitant boost to involved nodes. The purpose of this study was to assess regional control rates and recurrence patterns.

Methods and Materials: Sixty-one patients with cervical cancer (stage IBI-IVA) diagnosed from 2003 to 2012 with PET-avid pelvic nodes treated with extended field IMRT (45 Gy in 25 fractions with concomitant boost to involved nodes to a median of 55 Gy in 25 fractions) with concurrent cisplatin and brachytherapy were retrospectively analyzed. The nodal location was pelvis-only in 41 patients (67%) and pelvis + para-aortic in 20 patients (33%). There were a total of 179 nodes, with a median number of positive nodes of 2 (range, 1-16 nodes) per patient and a median nodal size of 1.8 cm (range, 0.7-4.5 cm). Response was assessed by PET/CT at 12 to 16 weeks.

Results: Complete clinical and imaging response at the first follow-up visit was seen in 77% of patients. At a mean follow-up time of 29 months (range, 3-116 months), 8 patients experienced recurrence. The sites of persistent/recurrent disease were as follows: cervix 10 (16.3%), regional nodes 3 (4.9%), and distant 14 (23%). The rate of para-aortic failure in patients with pelvic-only nodes was 2.5%. There were no significant differences in recurrence patterns by the number/location of nodes, largest node size, or maximum node standardized uptake value. The rate of late grade 3+ adverse events was 4%.

Conclusions: Extended field IMRT was well tolerated and resulted in low regional recurrence in node-positive cervical cancer. The dose of 55 Gy in 25 fractions was effective in eradicating disease in involved nodes, with acceptable late adverse events. Distant metastasis is the predominant mode of failure, and the OUTBACK trial may challenge the presented paradigms.

Dose to macroscopic nodal disease

- CRT, pelvis + PAO (upper border renal vessels), IMRT, image guided BT
  - 40 patients positive pelvic nodes, elective PAO RT, elective dose 45 Gy
  - 21 patients positive pelvic and PAO nodes, PAO sib boosts up to 55 Gy (54-59.4)

- Nodal control excellent !
- Low morbidity rates

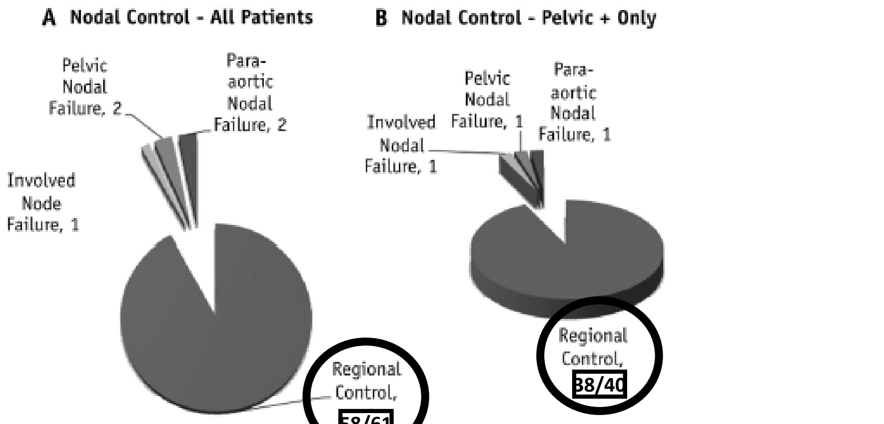


Fig. 1. Summary of regional recurrence patterns for all patients (A, n=61) and for patients with pelvic node−positive yet para-aortic node−negative (B, n=40) by positron emission tomography/computed tomography. Notice that some patients had more than 1 site of nodal relapse.

55 to 60 Gy EBRT gives high control rates

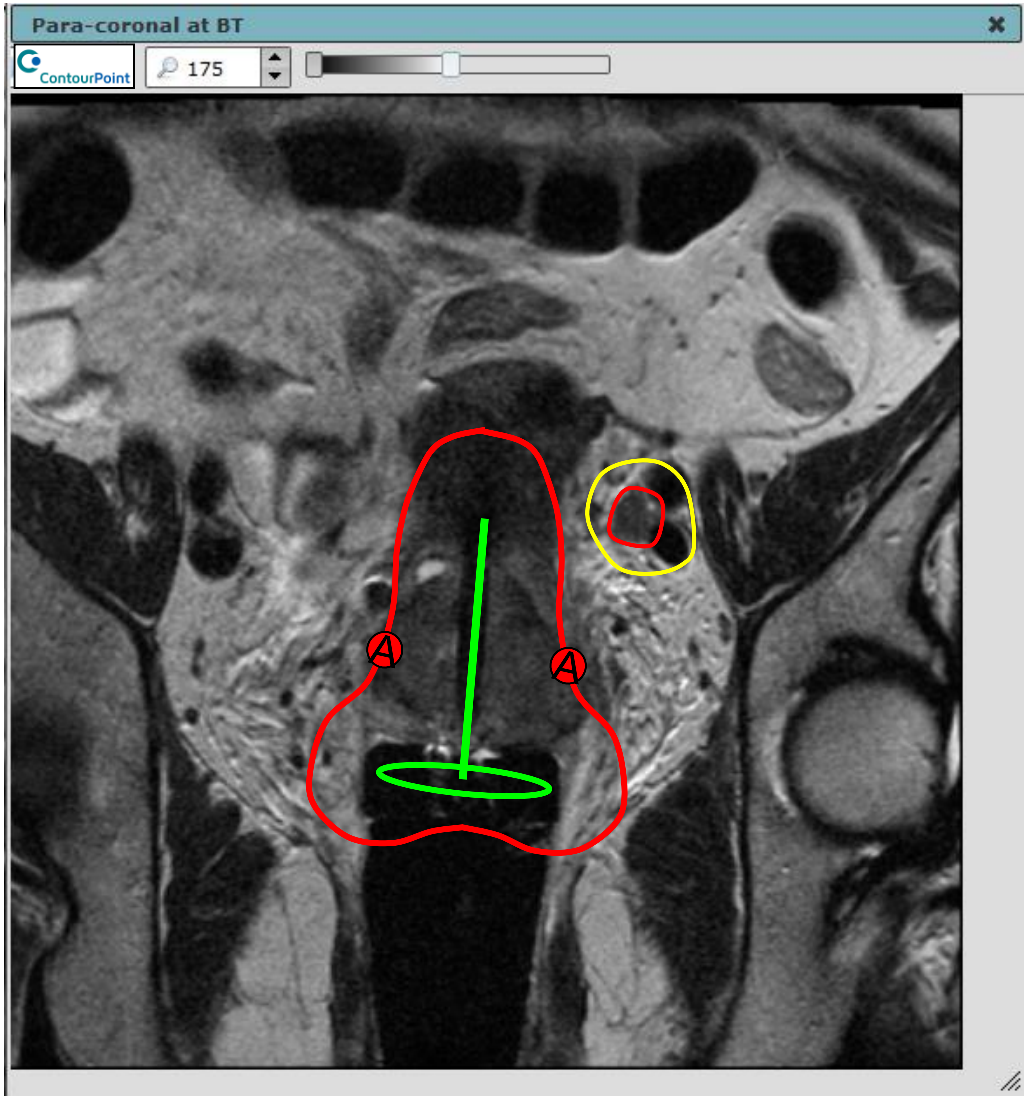
What dose is needed for the positive nodes?

- Evidence suggests: 55 - 60 Gy
- “Elective” dose: 45 – 50 Gy + boost 10 to 20 Gy
- Don’t forget BT dose contribution
- Don’t forget normal tissue constraints!!

- It’s not only a matter of dose !
    - Initial SUV and SUV regression during EBRT
    - Volume or diameter regression during EBRT

From: Kupets R, et al. Gynecol Oncol 2002

Contribution of Brachytherapy



Contribution of Brachytherapy

First experience in Utrecht

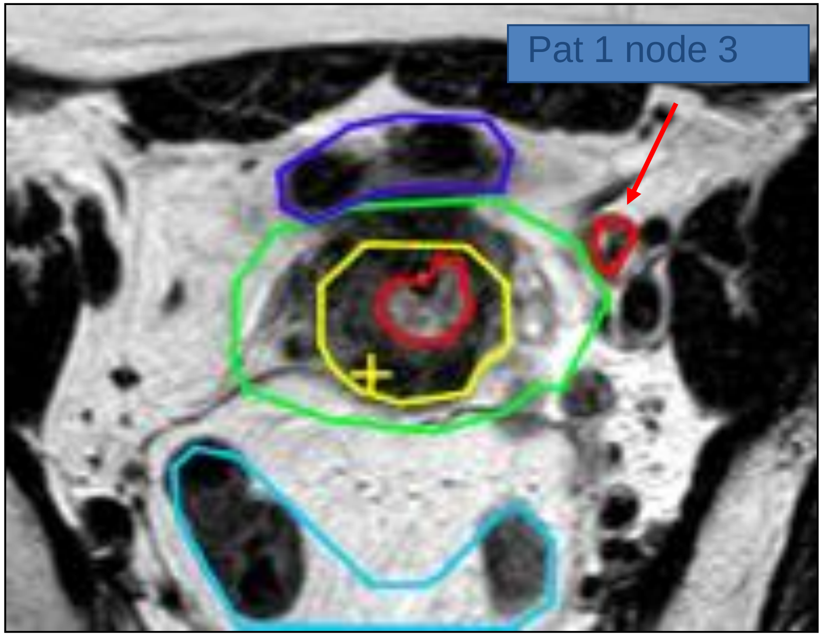
5 patients, 16 nodes delineated

2 PDR fractions

Planning aim: D90 (HR-CTV) = 40 Gy

Contribution to the nodal dose

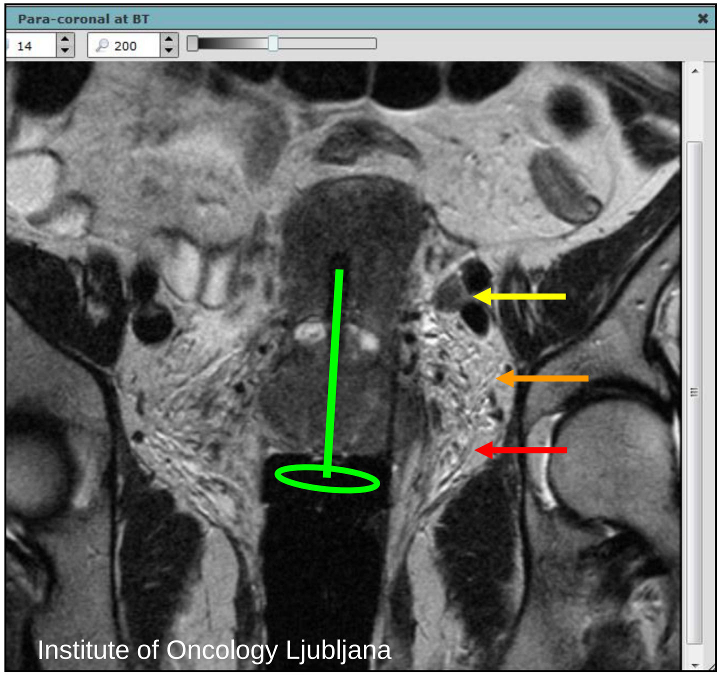
D90: **6 Gy** (3.1 – 12 Gy)
D50: **6.6 Gy** (3.2 – 13.6 Gy



Contribution of Brachytherapy

patient	HR-CTV cm3		EQD2 D90 (Gy); α/β =10				
			node1	node2	node3	node4	node5
#71	32,7	F1 and F2	5,6	5,8	6,0	5,8	
#79	15,9	F1 and F2	5,4	5,9			
#80	**91,3**	**F1 and F2**	**5,1**	**8,7**	**12,0**	**9,0**	**5,1**
#81	29,3	F1 and F2	5,4	5,2	3,1		
#82	19,5	F1 and F2	3,5	3,7			

Contribution decreases with distance from the applicator



Influence of interstitial component, when present..

Contribution of Brachytherapy

J Contemp Brachytherapy 2014; 6, 1: 21–27

Clinical Investigations

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

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

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

ELSEVIER

Brachytherapy 12 (2013) 555–559

BRACHYTHERAPY

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

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

[1]Department of Radiation Oncology, University of Kansas School of Medicine, Kansas City, KS

[2]Department of Radiation Oncology, University of California Davis Medical Center, Sacramento, CA

ELSEVIER

CrossMark

Brachytherapy 14 (2015) 56–61

BRACHYTHERAPY

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

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

[1]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

[2]Department of Radiation Oncology, NCI, Cairo University, Cairo, Egypt

[3]Department of Medical Physics, Aarhus University Hospital, Aarhus, Denmark

[4]Department of Radiology, Aarhus University Hospital, Aarhus, Denmark

[5]Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark

- Quite some range for individual nodes
- Individual dose calculation is time consuming, eventually helpful in case of parametrial nodes or exceptional tumor extension
- For clinical routine estimate of 3-4 Gy is considered a good estimate

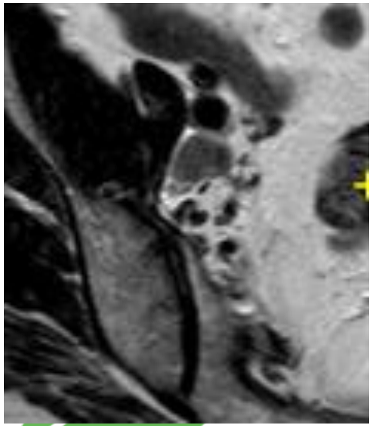
Treatment of nodal metastases

Promising developments

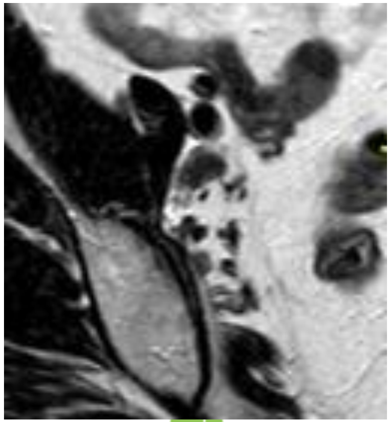
- Diagnostic tools
- Surgical approaches
- RT strategies
- Dose volume relations …….
  - Currently investigated in one of the EMBRACE sub studies

Work in progress!

Pre-treatment



Week 4 of EBRT



Post-treatment

Cervical Cancer
FIGO IIB

PRACTICAL EXAMPLE

AAR 003

Clinical history –status at diagnosis:

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

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

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

Radiology reports:

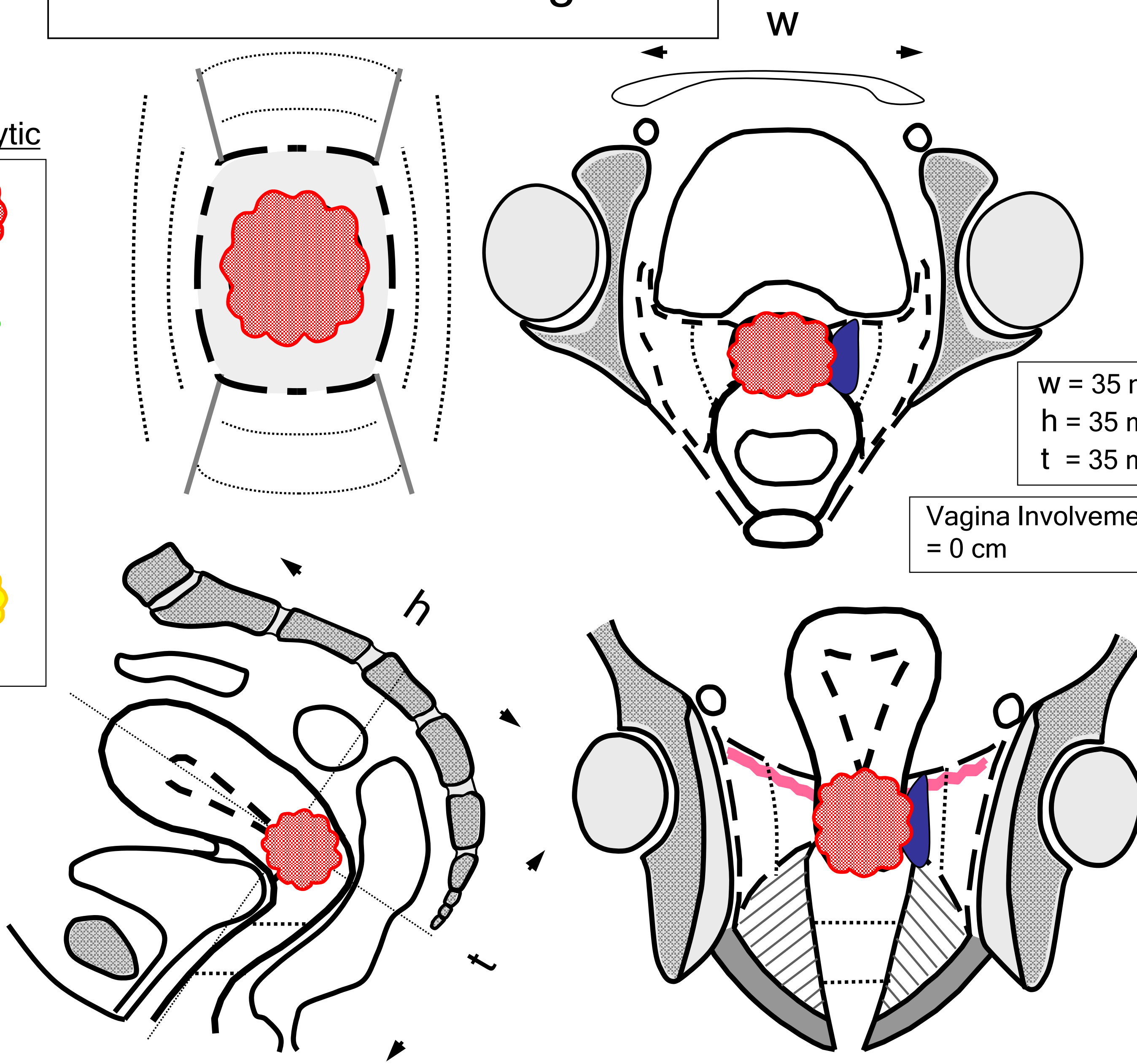
o **PET-CT:** FDG-activity in cervix uteri + FDG-activity in a lymph node laterally to the right common iliac artery + FDG-activity in a lymph node posterior to the right external iliac artery

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

Clinical Drawing

At Diagnosis

	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		



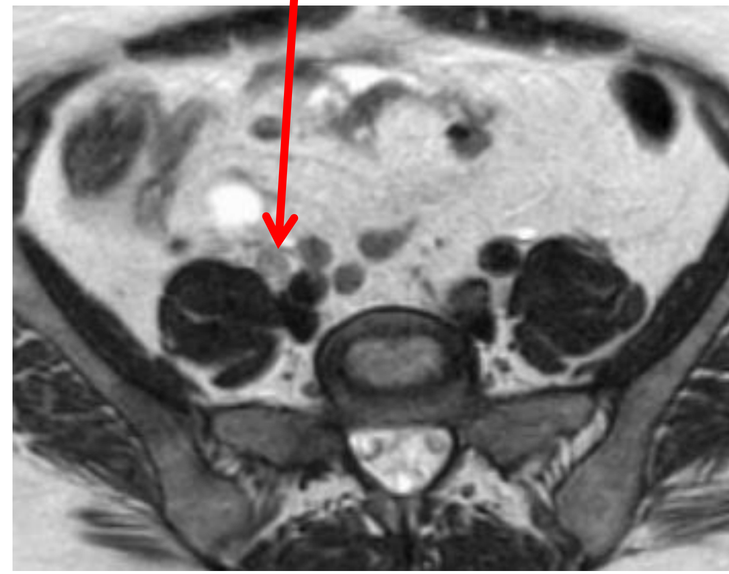
w = 35 mm
h = 35 mm
t = 35 mm

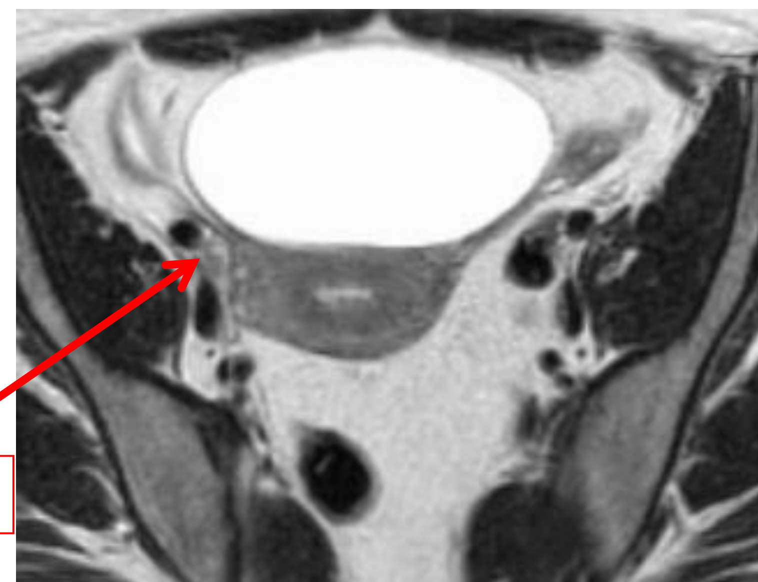
Vagina Involvement
= 0 cm

dd/mm/yy

Signature

Initial





RT Common Iliac node

RT para invasion

RT Ext Iliac node

Planned for Conformal EBRT, and Chemotherapy

EBRT CONTOURING EXERCISE

EMBRACE II DEFINITIONS

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

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

Clinical example : cervix cancer

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

UNIVERSITÉ PARIS SUD

ÉCOLE DES SCIENCES DU CANCER GUSTAVE ROUSSY

Example : cervix cancer

57 year-old patient

WHO = 0

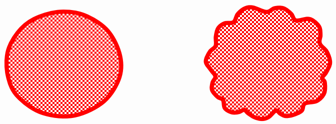
Vaginal bleeding

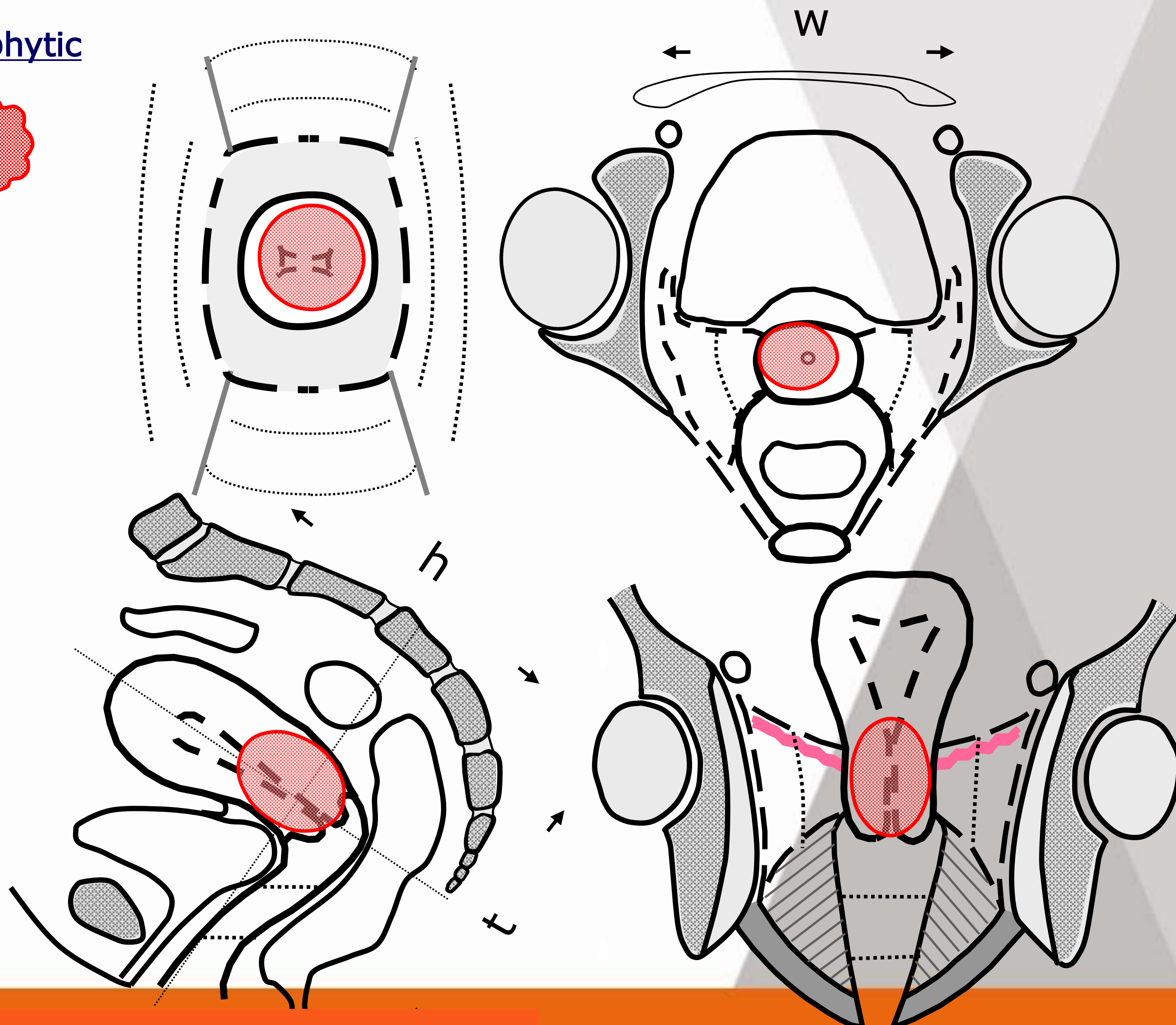
Biopsy: poorly differentiated
squamous cell carcinoma

Initial clinical drawings

Infiltrative Exophytic

Cervix





Dimensions (cm):

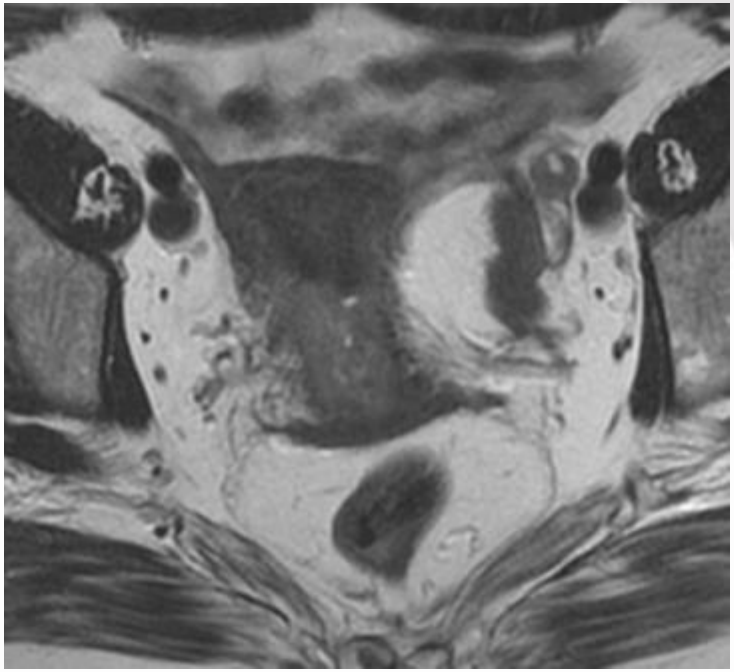
Width: 2.5 cm

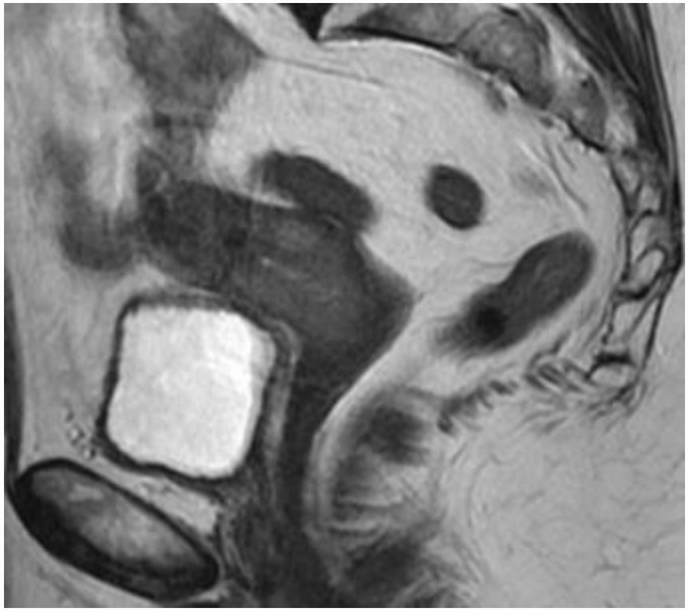
Thickness: 2.5 cm

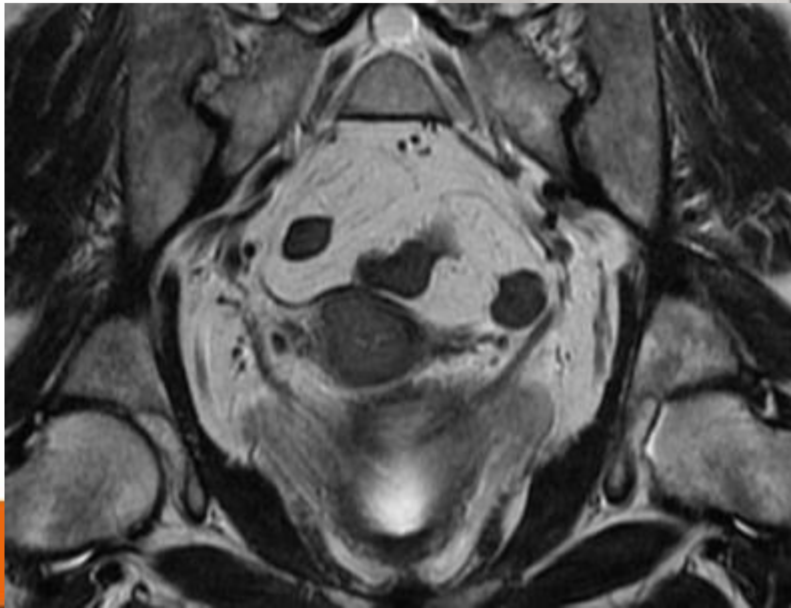
Height: 3 cm

MRI findings at diagnosis

Tumoral assessment

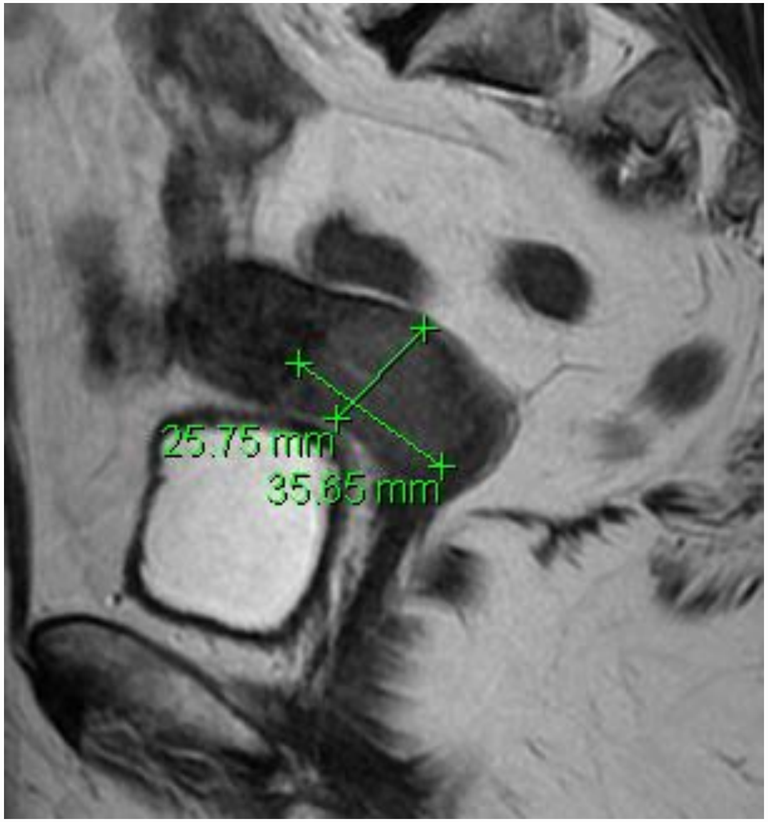


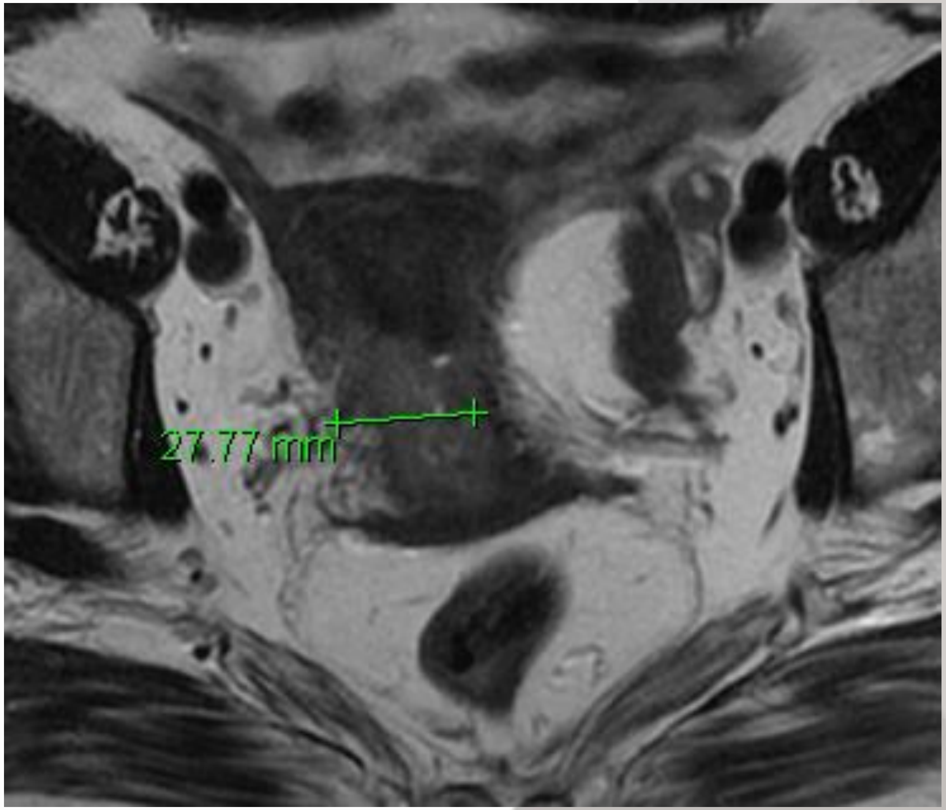




MRI findings at diagnosis

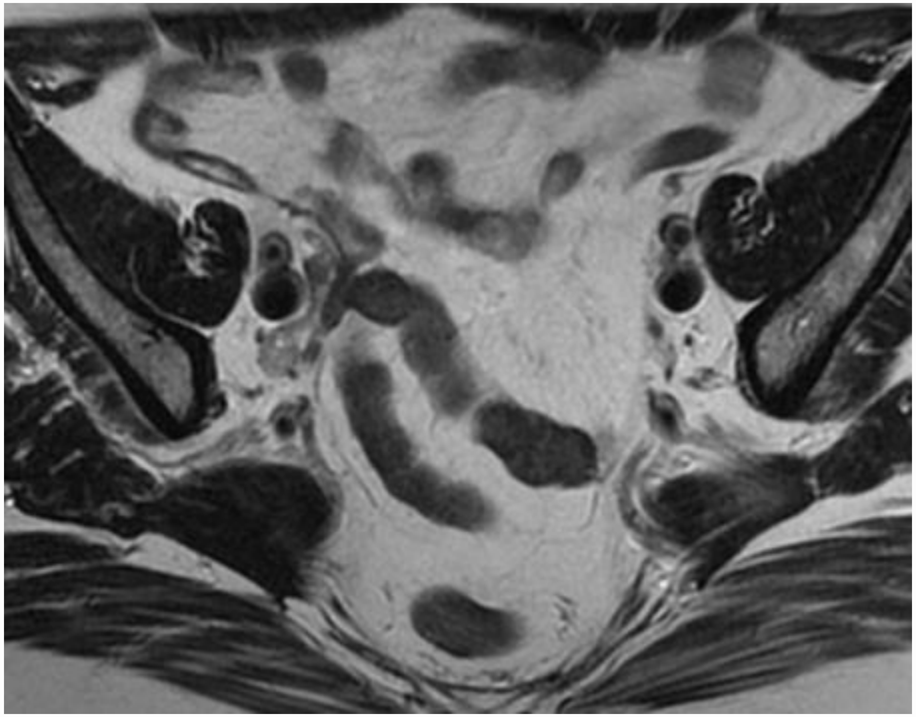
Tumoral assessment

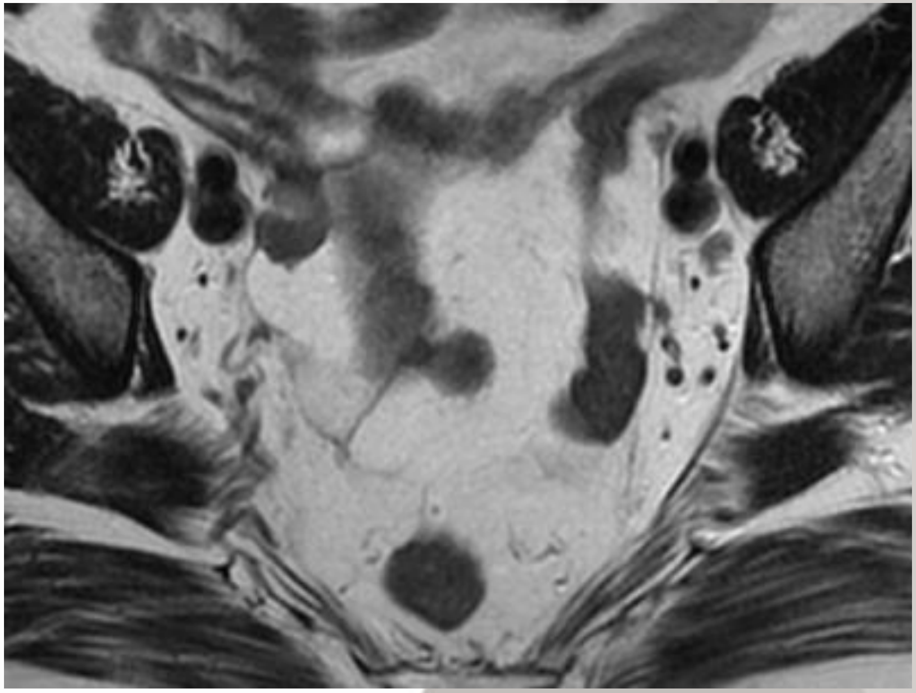




MRI findings at diagnosis

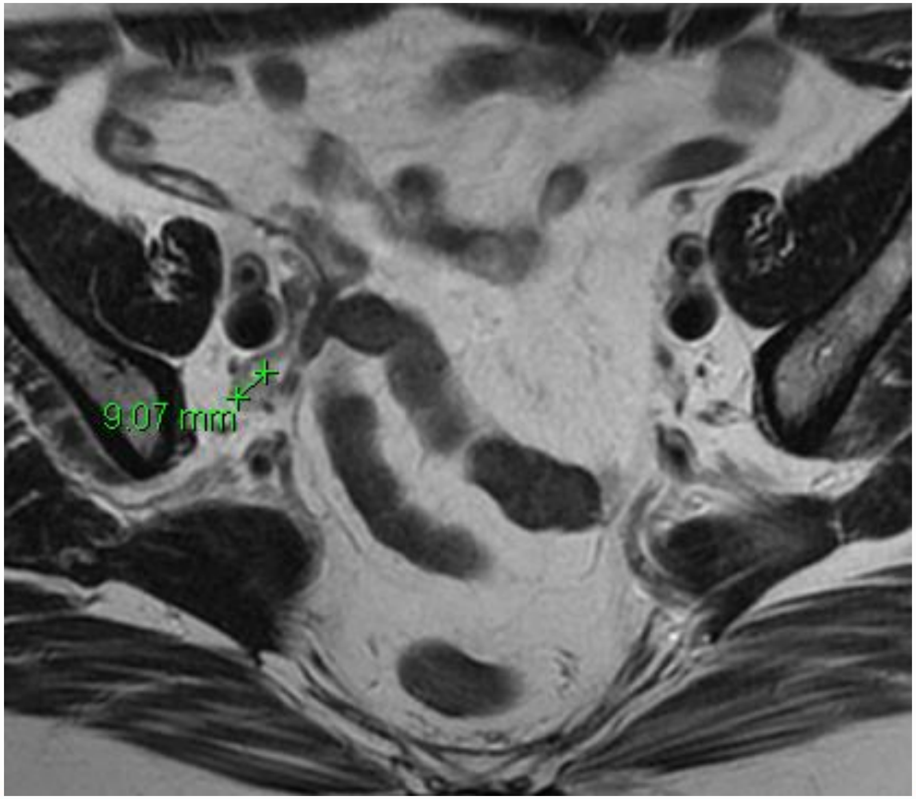
Nodal assessment

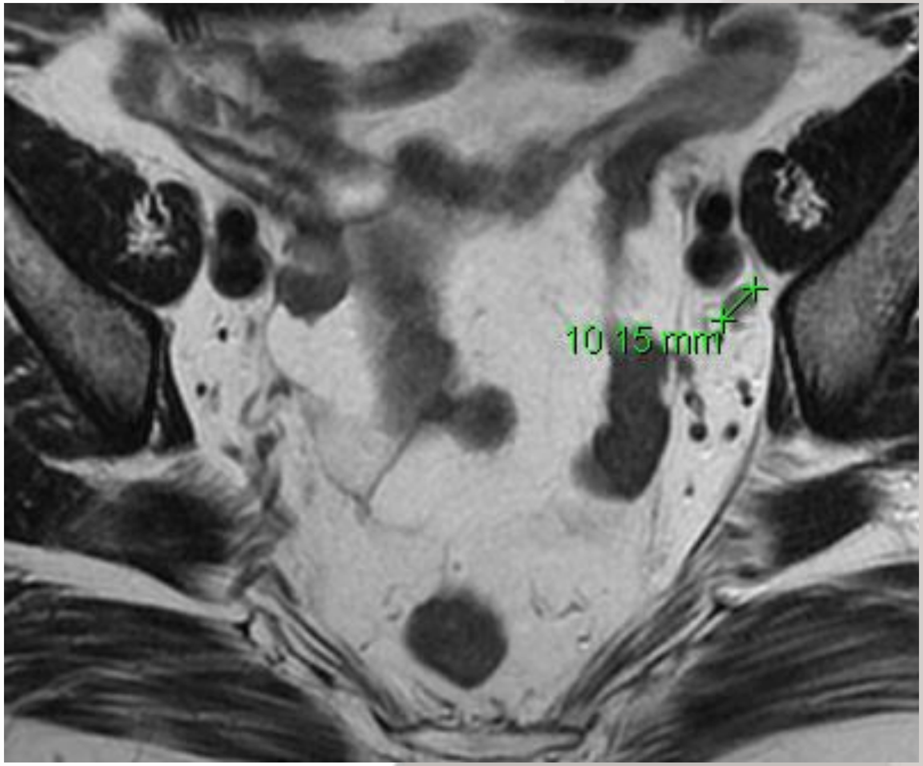




MRI findings at diagnosis

Nodal assessment





FIGO staging?

Complementary exams?

Can nodal status be better assessed?

Treatment?

Clinical example : endometrial cancer

Case description

65 years old patient

WHO = 0; BMI = 33

Post-menopausal bleeding

Clinical investigation:

No pathological findings

Vaginal ultrasound:

≈50% myometrium invaded no cervical infiltration

Curettage:

G1 **endometrial adenocarcinoma**

no signs of cervical infiltration

Chest x-ray:

No pathological findings

Primary treatment: surgery

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

Histopathological findings:

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

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

Postoperative management

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

ESTRO School

Results of chemo-radiation trials in cervical cancers

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CANCER CAMPUS
GRAND PARIS

Chemotherapy Schemes

- Neo - adjuvant chemotherapy followed by RT or surgery
- Concomitant chemoradiotherapy (postop or exclusive)
- Concomitant chemoradiotherapy followed by adjuvant

chemotherapy

PERGAMON

European Journal of Cancer 39 (2003) 2470–2486

European Journal of Cancer

www.ejconline.com

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

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

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

Tierney J, et al.

Comparison 1
NACT followed by RT vs RT

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

Comparison 1

NACT followed by RT vs RT

Table 3
All endpoints in comparison 1

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

- **Significant heterogeneity among the trials**
- **May be inappropriate to combine the trials**
- **Trials divided in two ways:**
  - Cycle interval (> 14 d vs ≤ 14 d)
  - Cisplatin dose intensity (< 25 vs ≥ 25 mg/m^2/wk)

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

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

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

Comparison 2

NACT followed by surgery vs RT

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

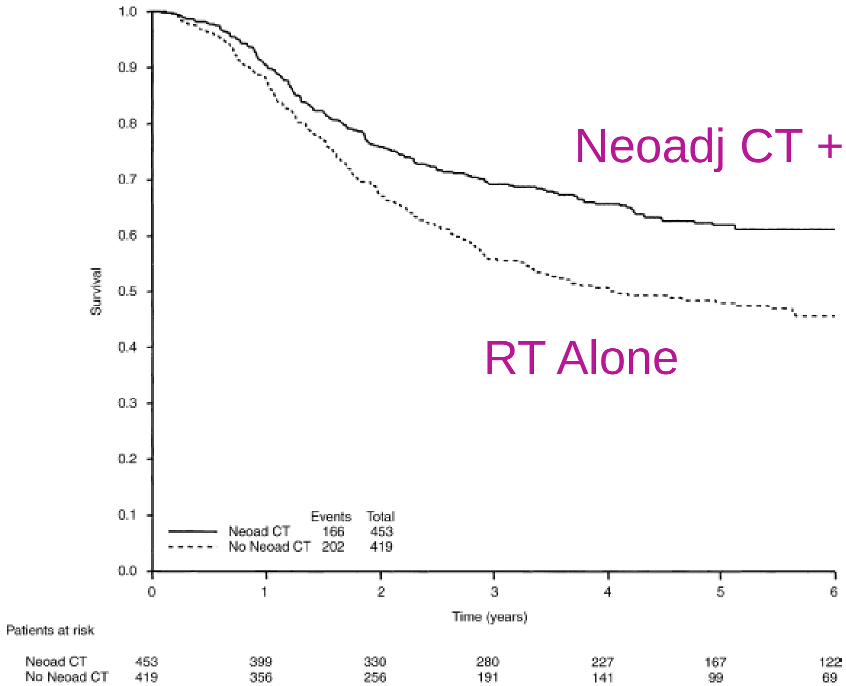


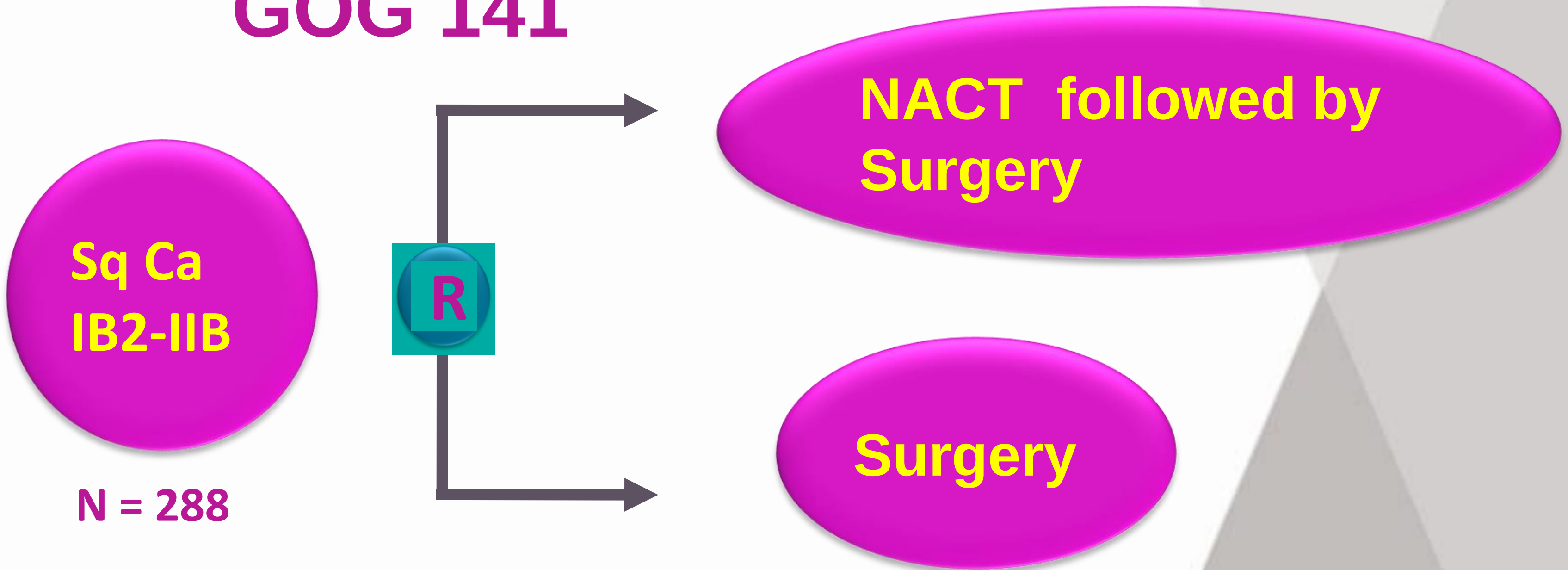
Fig. 5. Kaplan–Meier curves of overall survival in comparison 2. Neoad CT, neoadjuvant chemotherapy.

Caveats

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

NeoAdj CT + surgery vs surgery alone

GOG 141



Surgery – Radical hysterectomy + LN dissection

Chemo - cisplatin 50 mg/m2 + VCR 1 mg/m2 every 10 days x 3

Treatment of ("bulky") stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: A phase III trial of the gynecologic oncology group

Gary L. Eddy [a,*], Brian N. Bundy [b,1], William T. Creasman [c], Nick M. Spirtos [d], Robert S. Mannel [e], Edward Hannigan [f], Dennis O'Connor [g]

- GOG 141
- Started 1996, closed early because of poor accrual
- N = 288
- IB2
- Squamous – 77%

[Intervention Review]

Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

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

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

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

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

Cochrane – NACT + surgery vs surgery

- Use of post-op RT was balanced in the two arms
- 3 trials used high cisplatin dose intensity (>25mg/m^2) and 3 used lower intensity
- Chemotherapy drugs
  - Cisplatin
  - Bleomycin
  - Vincristine
  - 5-FU
  - Mitomycin

Cochrane Library

Cochrane Database of Systematic Reviews

2012

Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer (Review)

Rydzewska L, Tierney J, Vale CL, Symonds PR

Cochrane – NACT + surgery vs surgery

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

Furthermore, two ongoing randomised phase III trials (EORTC 55994, NCT00193739) are currently comparing neoadjuvant chemotherapy followed by surgery with concomitant chemoradiation and the results of these trials may also be important in determining whether neoadjuvant chemotherapy prior to surgery is a valid alternative to chemoradiation.

Rationale for concomitant chemoradiation

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

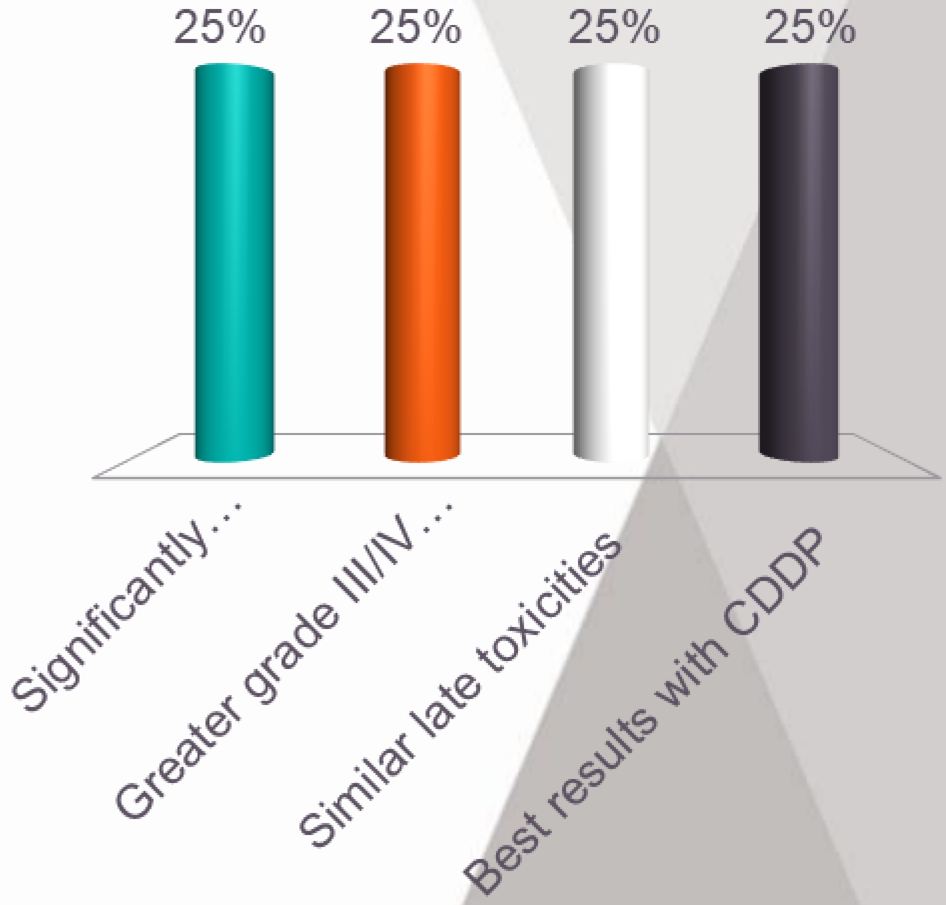
- Synergistic action with RT

  - potentiates the sub-lethal damage

  - inhibits the DNA damage repair induced by RT

To your knowledge, which of the following statement on concomitant chemoradiation is wrong?

A. Significantly improvement in OS
B. Greater grade III/IV acute toxicities
C. Similar late toxicities
D. Best results with CDDP



Radiosensitizing chemotherapeutic agents

- HYDROXYUREA
- 5 FLUROURACIL
- CISPLATIN
- CARBOPLATIN

- VINCRISTINE
- ETOPOSIDE
- BLEOMYCIN
- PACLITAXEL
- MITOMYCIN

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

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

Phase III trials with concurrent chemo-radiotherapy in stage IB2-IVA cervix cancer: Dose of Cisplatin/m^2

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

Chemoradiation

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

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

VOLUME 26 · NUMBER 35 · DECEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

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

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration

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

MEDICAL RESEARCH COUNCIL CLINICAL TRIALS UNIT- UK

JCO December 2008

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

OVERALL SURVIVAL AND DISEASE FREE SURVIVAL

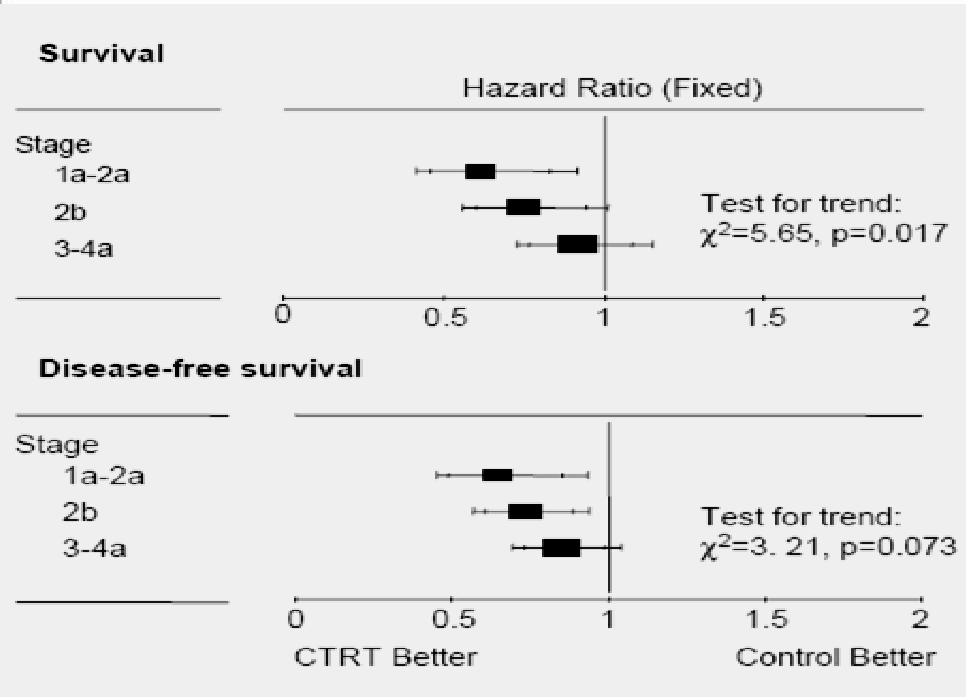
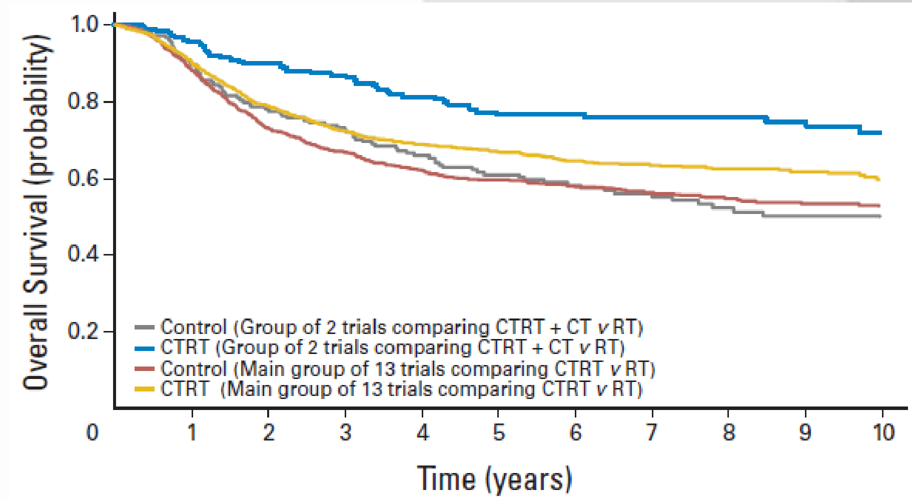


Figure 3. Survival and disease-free survival by tumour sta
of 13 trials only)



Adjuvant CT after CRT needs to be explored further

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

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

JCO Dec 08

Gynecologic Oncology 145 (2017) 374–385

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

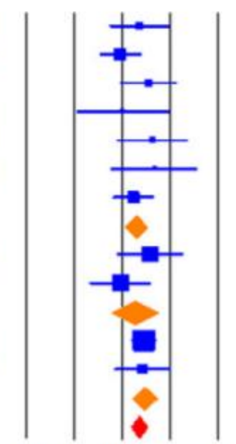
Concurrent chemoradiotherapy *vs.* radiotherapy alone in locally advanced cervix cancer: A systematic review and meta-analysis

Niloy Ranjan Datta [a,*], Emanuel Stutz [a], Michael Liu [a], Susanne Rogers [a], Dirk Klingbiel [b], Alexander Siebenhüner [c], Shalini Singh [d], Stephan Bodis [a,e]

(b) Risk difference: Long-term locoregional control (CTRT vs. RT)

Group by CTRT Group	Study name	Statistics for each study: Risk difference	Lower limit	Upper limit	Z-Value	p-Value	LRC / Total: CTRT	RT	Relative weight
CDDP (Alone)	Zuliani AC, 2014	0.090	-0.071	0.251	1.099	0.272	42 / 72	37 / 75	12.79
CDDP (Alone)	Srivastava K, 2013	-0.011	-0.123	0.100	-0.200	0.842	84 / 155	83 / 150	26.40
CDDP (Alone)	Mitra D, 2006	0.138	-0.015	0.290	1.767	0.077	41 / 80	30 / 80	14.17
CDDP (Alone)	Garipagaoglu M, 2004	0.000	-0.248	0.248	0.000	1.000	17 / 22	17 / 22	5.37
CDDP (Alone)	Singh T, 2003	0.157	-0.035	0.348	1.606	0.108	34 / 43	26 / 41	9.02
CDDP (Alone)	Sehgal CM, 2002	0.167	-0.065	0.398	1.410	0.158	23 / 30	18 / 30	6.14
CDDP (Alone)	Pearcey R, 2002	0.058	-0.055	0.170	1.006	0.314	93 / 127	85 / 126	26.11
CDDP (Alone)		0.067	0.010	0.125	2.301	0.021	334 / 529	296 / 524	
CDDP (Combination)	Negi RR, 2011	0.145	-0.033	0.322	1.597	0.110	38 / 50	32 / 52	46.18
CDDP (Combination)	Tseng C, 1997	-0.010	-0.175	0.154	-0.122	0.903	41 / 60	43 / 62	53.82
CDDP (Combination)		0.061	-0.059	0.182	0.996	0.319	79 / 110	75 / 114	
Mitomycin C	Lorvidhaya V, 2003	0.113	0.040	0.186	3.022	0.003	186 / 217	172 / 231	81.02
Mitomycin C	Roberts KB, 2000	0.105	-0.046	0.256	1.365	0.172	51 / 78	45 / 82	18.98
Mitomycin C		0.111	0.045	0.177	3.315	0.001	237 / 295	217 / 313	
Overall		0.084	0.041	0.126	3.874	0.000	650 / 934	588 / 951	

Risk difference and 95% CI



Test for heterogeneity, $I^2 = 0.000$, p:ns
Subgroup analysis: Q = 1.112, df = 2, p: ns

Gynecologic Oncology 145 (2017) 374–385

Contents lists available at ScienceDirect

Gynecologic Oncology

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Review Article

Concurrent chemoradiotherapy *vs.* radiotherapy alone in locally advanced cervix cancer: A systematic review and meta-analysis

Niloy Ranjan Datta [a,*], Emanuel Stutz [a], Michael Liu [a], Susanne Rogers [a], Dirk Klingbiel [b], Alexander Siebenhüner [c], Shalini Singh [d], Stephan Bodis [a,e]

- The results confirm that CTRT significantly improves outcomes in LACC : 10.2% for CR ($p = 0.027$), 8.4% for LRC ($p< 0.001$) and 7.5% for OS ($p< 0.001$)
- Greater (10.3%) grade III/IV acute toxicities
- Similar late toxicities
- None of the 3 CT regimens were found to have any significant impact on these endpoints

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database Syst Rev. 2016;11:CD005342

Adjuvant platinum-based chemotherapy for early stage cervical cancer (Review)

Falcetta FS, Medeiros LRF, Edelweiss MI, Pohlmann PR, Stein AT, Rosa DD

Implications for practice

Women with operable early stage cervical cancer (IA2 to IIA) may benefit from the addition of cisplatin-based chemotherapy to adjuvant radiotherapy. However, since subgroup analyses according to stage and size were not possible, it is not clear that the survival benefits apply equally to all early stage lesions. Severe acute toxicities are more likely to occur with chemoradiation than with radiotherapy alone. There is insufficient evidence on late toxicity.

Implications for research

There are very few trials in this area due to difficulties in accrual. We identified three ongoing trials: one trial comparing primary radiotherapy with primary chemoradiation in stage IB to IIB cervical cancer with no high-risk factors (Hong 2013) and two multicentre trials comparing adjuvant chemoradiation with adjuvant radiotherapy in stages I to IIA with intermediate- and high-risk factors (GOG 0263; NCT 00806117). In addition to these ongoing trials, RCTs comparing adjuvant platinum-based chemotherapy with adjuvant radiotherapy and/or chemoradiation for early invasive cervical cancer would be helpful to our understanding of the treatment options for this condition. Such trials should be stratified by FIGO stage and should include evaluation of QoL and toxicity. Since cervical cancer is much more prevalent in developing countries, researchers should collaborate with centres in these regions.

Ongoing studies

RTOG-0724 Lead Group: RTOG	SWOG NSABP NCIC NCCTG GOG ECOG CALGB ACOSOG	**POST-OP HIGH RISK CERVICAL CANCERS:** Phase III Randomized Study of Concurrent Chemotherapy and Pelvic RT With or Without Adjuvant (Pacli + Carbo every 21 days x 4 cycles) Chemotherapy in High-Risk Patients with Early-Stage Cervical Carcinoma Following Radical Hysterectomy	**To Date:** 163 **Target:** 400 (09/15/14)
GOG-0263 Lead Group: GOG	SWOG RTOG NSABP NCIC NCCTG ECOG CALGB ACOSOG	**POST-OP INTERMEDIATE RISK CERVICAL CANCERS:** Randomized Phase III Clinical Trial of Adjuvant Radiation Versus Chemo-radiation in Intermediate Risk, Stage I/IIA Cervical Cancer Treated with Initial Radical Hysterectomy and Pelvic LND dissection	**Target:** 534

Ongoing studies

Depth of stromal invasion and LVSI to be pathologically confirmed:

- Positive capillary-lymphovascular space involvement **and** one of the following:
- Deep third penetration
- Middle third penetration, clinical tumor ≥ 2 cm
- Superficial third penetration, clinical tumor ≥ 5 cm
- Middle or deep third penetration, clinical tumor ≥ 4 cm

GOG-0263 Lead Group: GOG	SWOG RTOG NSABP NCIC NCCTG ECOG CALGB ACOSOG	**POST-OP INTERMEDIATE RISK CERVICAL CANCERS:** Randomized Phase III Clinical Trial of Adjuvant Radiation Versus Chemo-radiation in Intermediate Risk, Stage I/IIA Cervical Cancer Treated with Initial Radical Hysterectomy and Pelvic LND dissection	**Target:** 534

Ongoing studies

RTOG-0724 Lead Group: RTOG	SWOG NSABP NCIC NCCTG GOG ECOG CALGB ACOSOG	**POST-OP HIGH RISK CERVICAL CANCERS:** Phase III Randomized Study of Concurrent Chemotherapy and Pelvic RT With or Without Adjuvant (Pacli + Carbo every 21 days x 4 cycles) Chemotherapy in High-Risk Patients with Early-Stage Cervical Carcinoma Following Radical Hysterectomy	**To Date:** 163 **Target:** 400 (09/15/14)

Patients with clinical stage IA2, IB or IIA squamous, adenosquamous, or adenocarcinoma of the cervix who have any/all of the following high-risk features after surgery:

- Positive pelvic nodes
- Positive parametrium
- Positive para-aortic nodes- completely resected, PET/CT negative (PET only required if positive para-aortic nodes during surgery)

Rationale for adjuvant chemotherapy after concomitant chemo-radiation

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

after concomitant chemoradiation and brachytherapy

- Adjuvant CT was part of few trials of chemo-radiation
- No proper large study evaluating adjuvant CT

VOLUME 29 · NUMBER 13 · MAY 1 2011

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

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

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

Arm A (n= 259 pts)

CCRT + Brachytherapy + Adj. CT

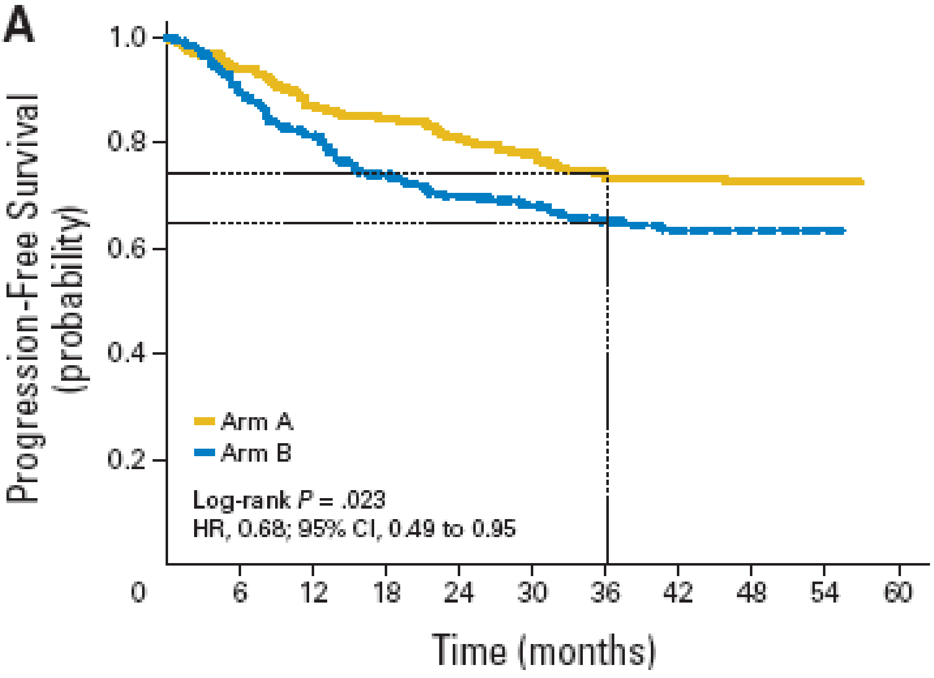
Concurrent Chemo - Weekly Cis 40 mg/m2
+ Gemcitabine 125mg/m2
Adjuvant chemo -2 weeks after brachy
Cisplatin and Gemcitabine 2 cycles

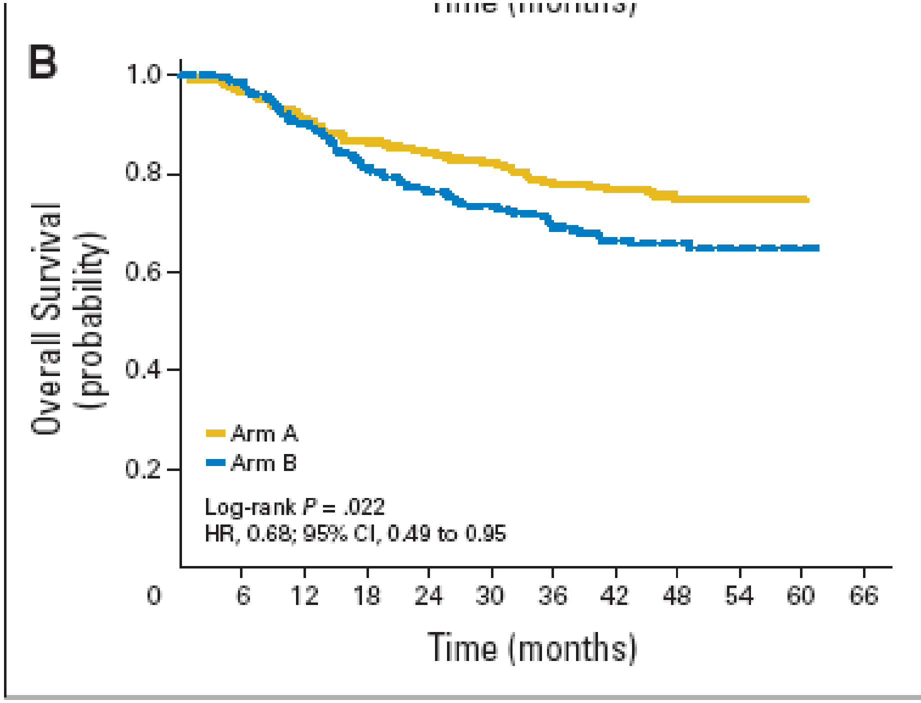
ARM B (n= 256 pts)

CCRT+ BRT
with
Weekly Cis 40mg/m2

Adverse effects

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





Results

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

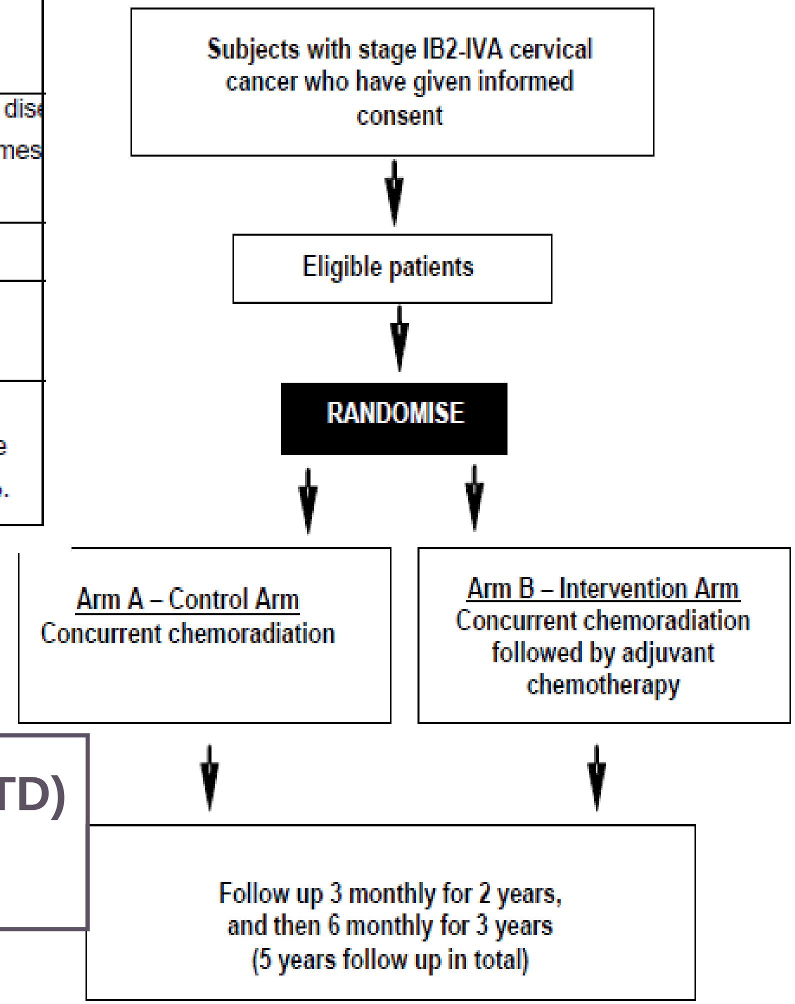
Conclusion: Gemcitabine + cisplatin CRT followed by brachy & adjuvant gem/cis CT improved survival outcomes with increased but clinically manageable toxicity compared to standard Rx

Concurrent CTRT + Adjuvant CT

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

Outback trial multicentric phase III study

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



Cisplatin based concurrent chemo-radiation (STD) vs CCRT followed by Pacli + Carbo x 3 cycles

Induction chemotherapy followed by concomitant chemoradiation in advanced stage cervix carcinoma : A phase III randomized trial (INTERLACE Study - NCT01566240)

Carcinoma Cervix Stage FIGO Ib2-IVA

385 patients	385 patients
Concomitant chemo radiotherapy weekly Cisplatin (40 mg/m2 x 4 - 5 #)	Induction chemotherapy with weekly x 6weeks Paclitaxel (80 mg/m2) + Carboplatin (AUC2) Concomitant chemoradiotherapy weekly Cisplatin (40 mg/m2 x 4 - 5 #) &

Outcomes:

Primary: Overall Survival

Secondary: Progression free Survival

Acute toxicities

Late Toxicities

Initiated in 2012

Accrual period: 4 years

Completion: 2021

BIOLOGIC AGENTS - BEVACIZUMAB

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

REGISTER

Pelvic RT:

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

↓

LDR x 2 or HDR x 5

↓

Parametrial boost (if indicated)

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

Cisplatin: Weekly infusion x 6 weeks

- 60 patients from 25 institutions were enrolled between 2006 and 2009
- 49 patients evaluable
- Median follow-up time 3.8 years (Mostly IIB 63%, squamous-80%)
- There were 15 (31%) protocol specified treatment-related AEs, most common were hematologic (12/15 =80
- 3-year OS 81%, DFS 67%, LRF 23%

Int J Radiat Oncol Biol Phys 88:101-5; 2014

GOG 240 Schema

Eligibility:

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

2. Measureable disease

3. GOG PS 0-1

R A N D O M I Z E

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

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

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

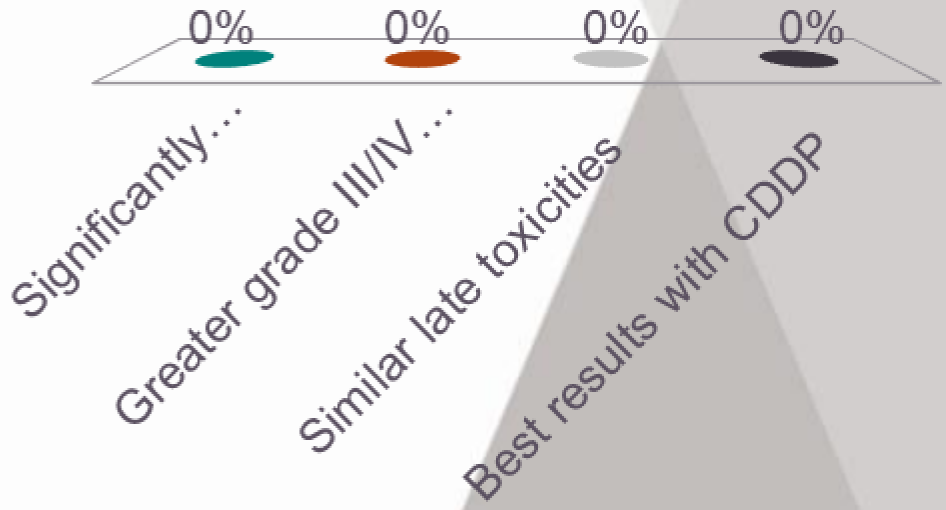
Regimen IV
Paclitaxel 175 mg/m^2 IV d1 (3h)
Topotecan 0.75 mg/m^2 d1-3 (30m)
Bevacizumab 15 mg/kg IV d1
Q21d to progression/toxicity

GOG 240: Conclusions

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

To your knowledge, which of the following statement on concomitant chemoradiation is wrong?

A. Significantly improvement in OS
B. Greater grade III/IV acute toxicities
C. Similar late toxicities
D. Best results with CDDP



Summary and conclusions

- Radical radiation therapy : established treatment modality
- Neo-adjuvant CT approaches: investigational
- CRT with Cisplatin extensively tested for cervical cancer
- Concomitant Chemo-radiation with wkly cisplatin (40 mg/m2) : STD of care
  - CRT with weekly cisplatin recommended for FIGO Stage I B2 - IIB
  - Post Wertheim's high risk Patients : CRT
  - CRT for FIGO Stage III-IVA: to be established further
- Role of concomitant chemo-brachytherapy is not clearly established
- Alternatives to Cisplatin: No much progress including biological agents
- Adjuvant CT after CRT & Induction CT: Phase III studies ongoing
- Targeted therapy / biological agents: Bevacizumab

Leiden University
Medical Center

Endometrial Cancer

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

Remi Nout

Dept of Radiation - Oncology

Leiden University Medical Centre, The Netherlands

Disclosures

I have no disclosures

Learning objectives

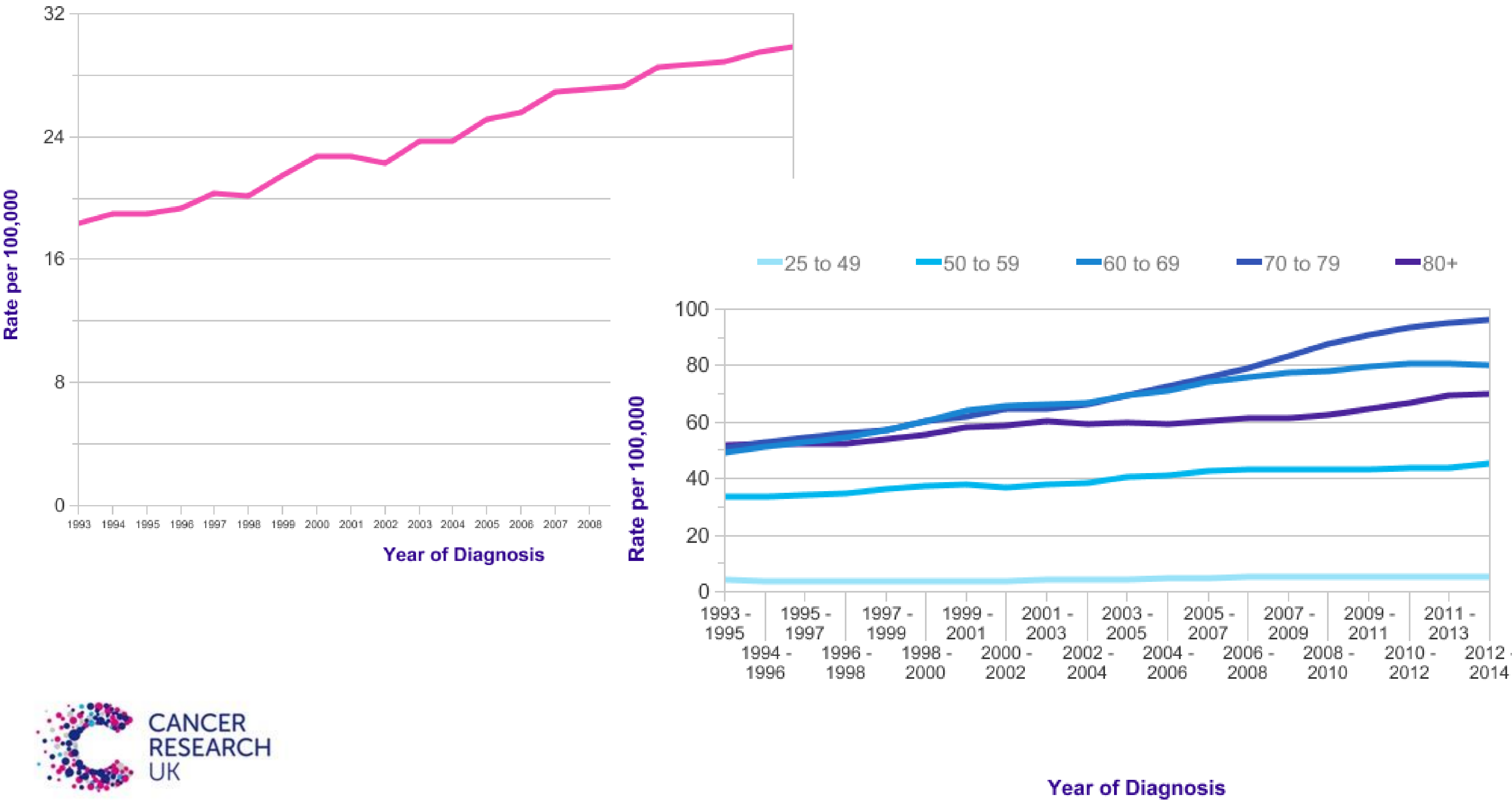
- Prognostic factors & risk stratification for adjuvant treatment
- Clinical trials which form the basis for current treatment
- How different radiotherapy techniques impact on morbidity and quality of life
- Upcoming (molecular) prognostic factors and ongoing trials

Which statement is correct?

A. Endometrial cancer incidence is stable over the last decades
B. Age is a prognostic factor for recurrence
C. FIGO staging is based on clinical examination
D. Incidence of second cancers is increased after pelvic external beam treatment but not after brachytherapy

Uterine Cancer (C54-C55): 1993-2014

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

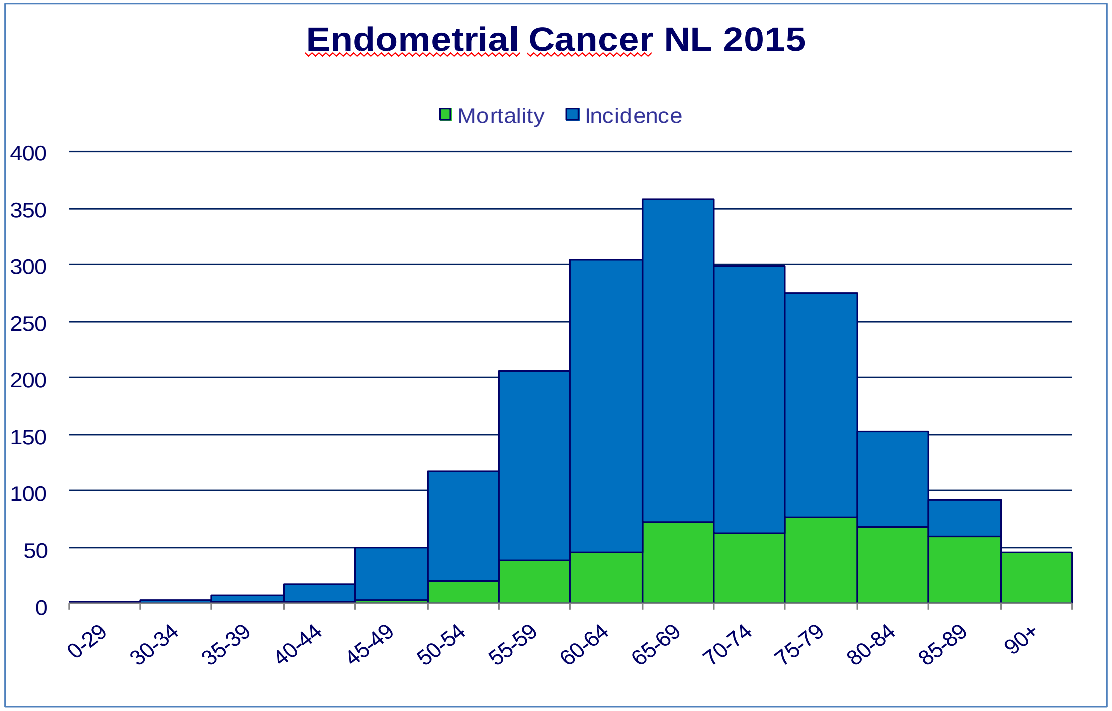


CANCER RESEARCH UK

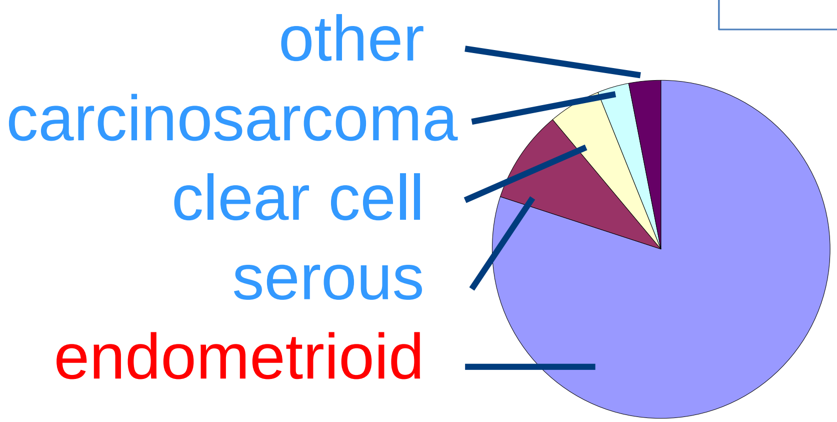
Endometrial Carcinoma

Incidence
22 / 100.000

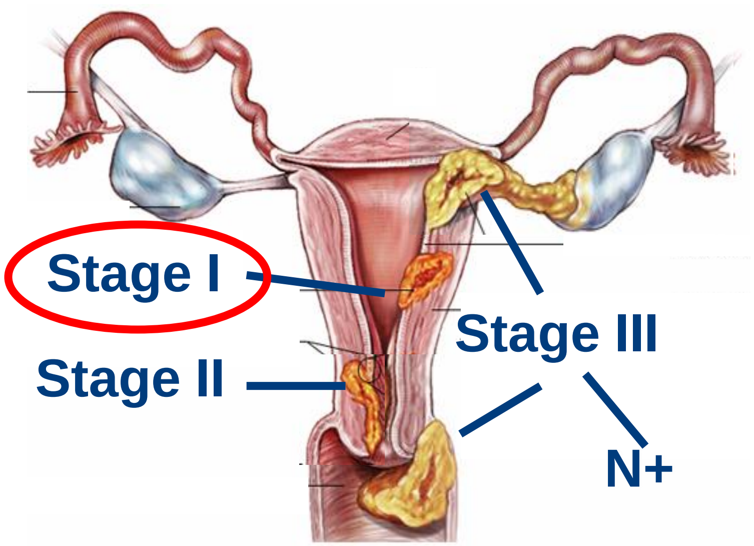
Mortality
5.5 / 100.000

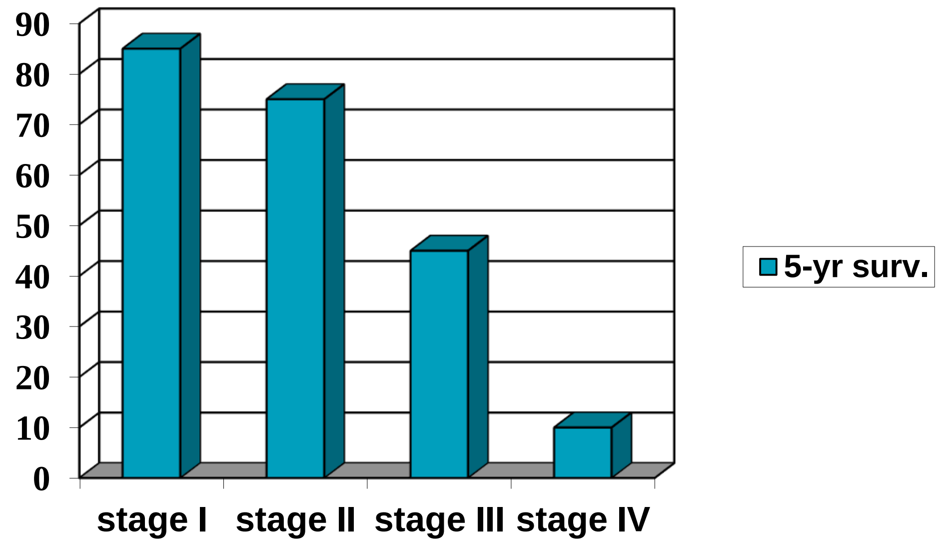


Histology



Stage and histologic subtype





<u>Histological type (5 yr OS)</u>

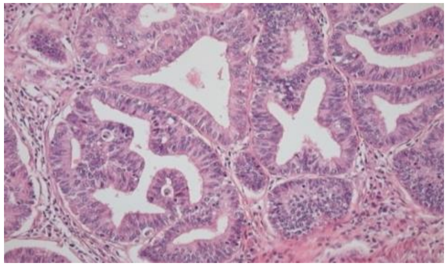
endometrioid carcinoma: 80-85%

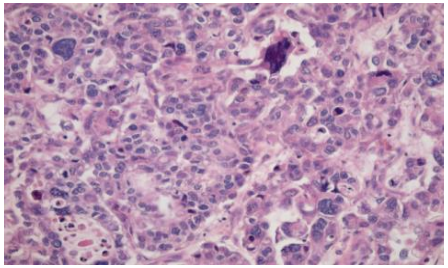
serous carcinoma: 50-55%

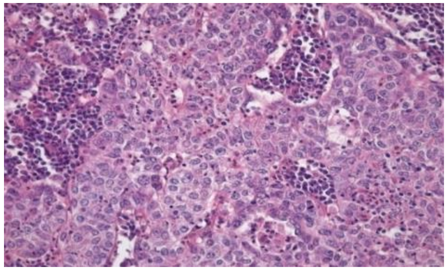
clear cell carcinoma: 60-65%

Major prognostic factors

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







Lymph node metastasis (GOG)

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

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

Creasman et al., Cancer 1987

Historic Risk Groups

- *Low risk:*

  stage I grade 1-3 no invasion

  stage I grade 1 <50% invasion
- *Intermediate risk:*

  stage I grade 2-3 <50% invasion

  stage I grade 1-2 ≥50% invasion
- *High risk:*

  stage I grade 3 ≥50% invasion; stage II / III / IV

  NEEC: serous, clear-cell carcinoma, carcinosarcoma

Low risk endometrial cancer

Surgery alone

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

➢ *No vaginal brachytherapy*:

Randomized trial, vaginal recurrence rate:

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

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

Intermediate Risk – Randomised trials

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

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

PORTEC-1 trial (1990-1997)

Stage I intermediate risk (n=714):

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

pelvic radiotherapy

46 Gy / 23# / 5 wks

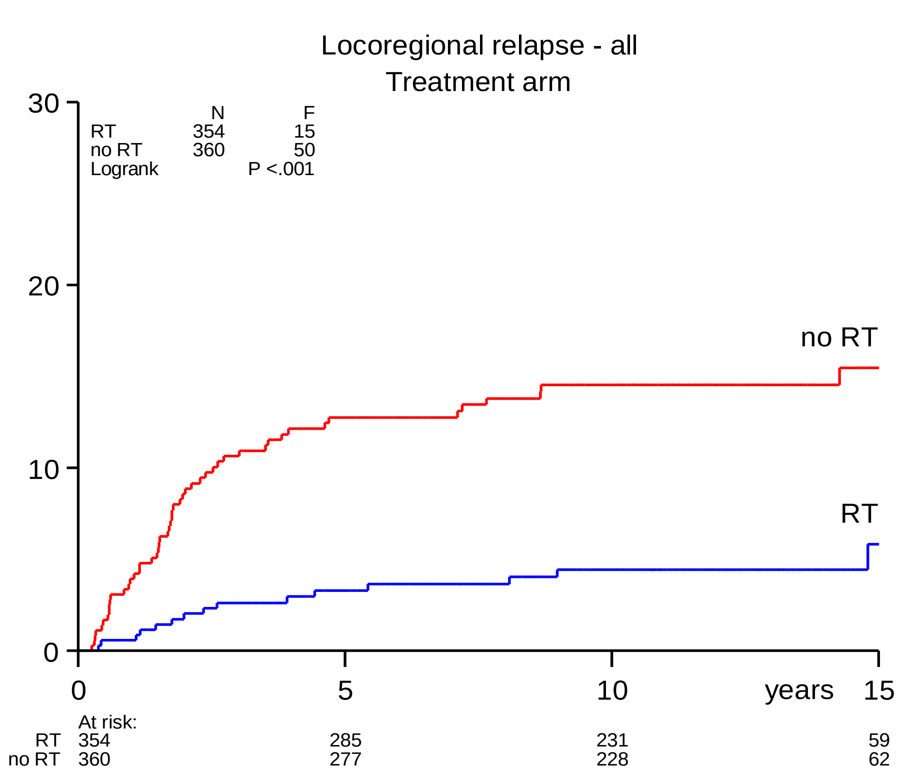
R

no further treatment

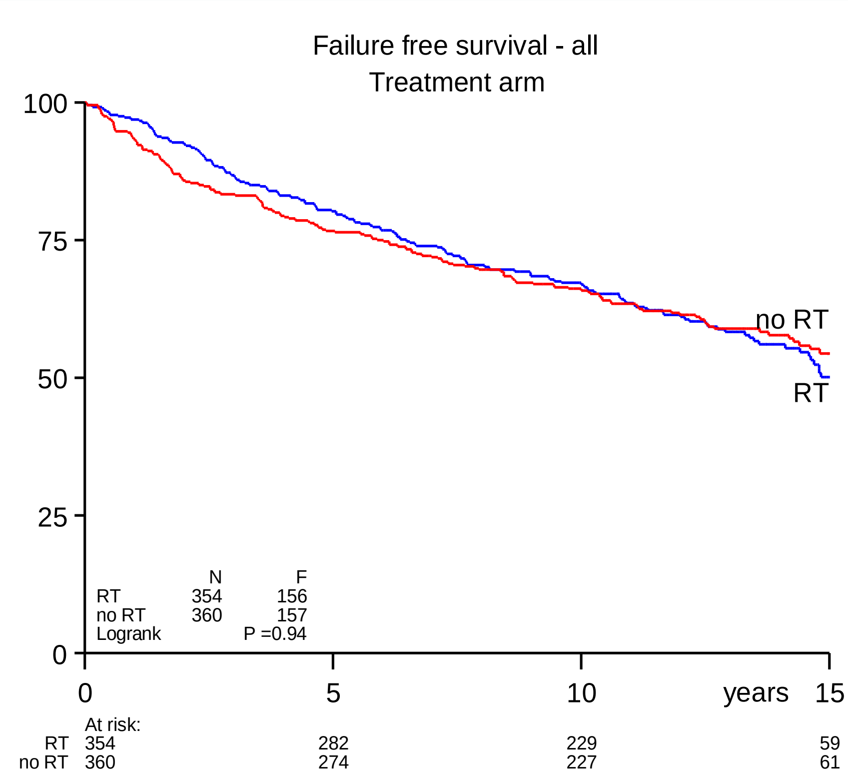
Creutzberg et al, Lancet 2000

15-year outcomes PORTEC-1

Locoregional Recurrence

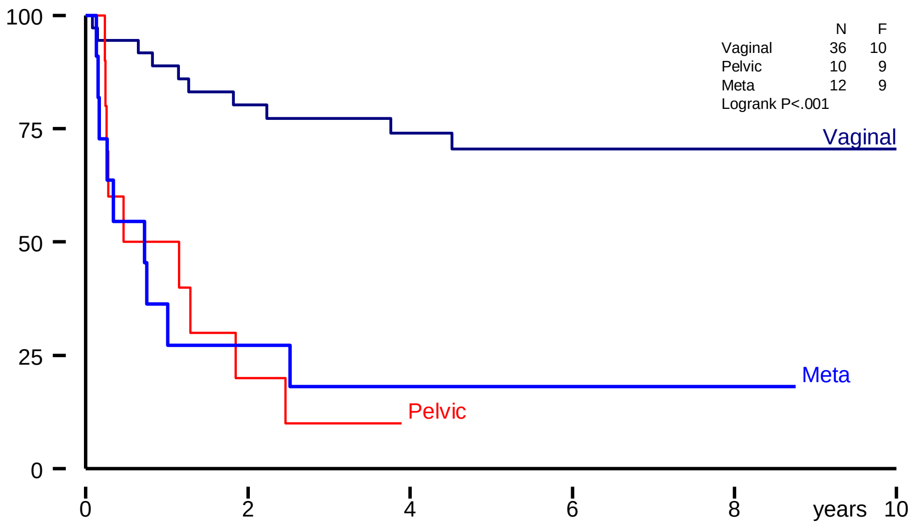


Failure Free Survival

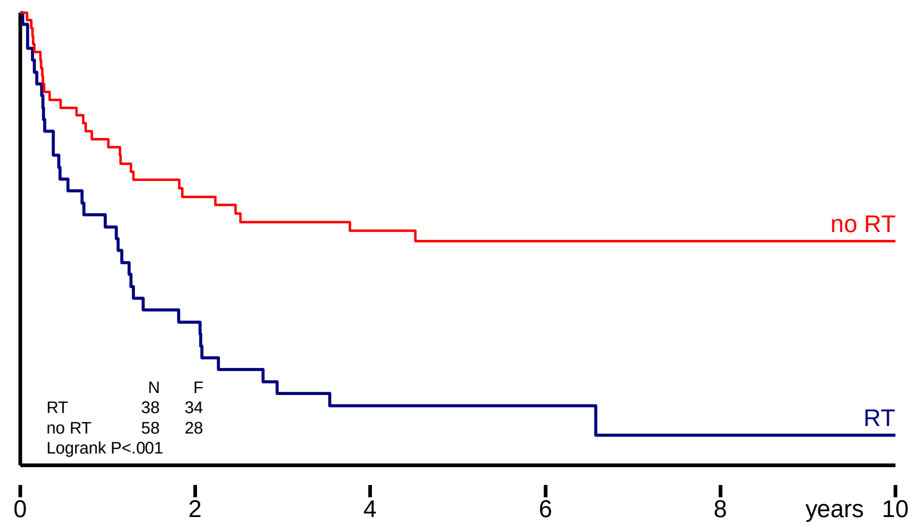


Survival after relapse in PORTEC-1

By site of relapse



By treatment arm

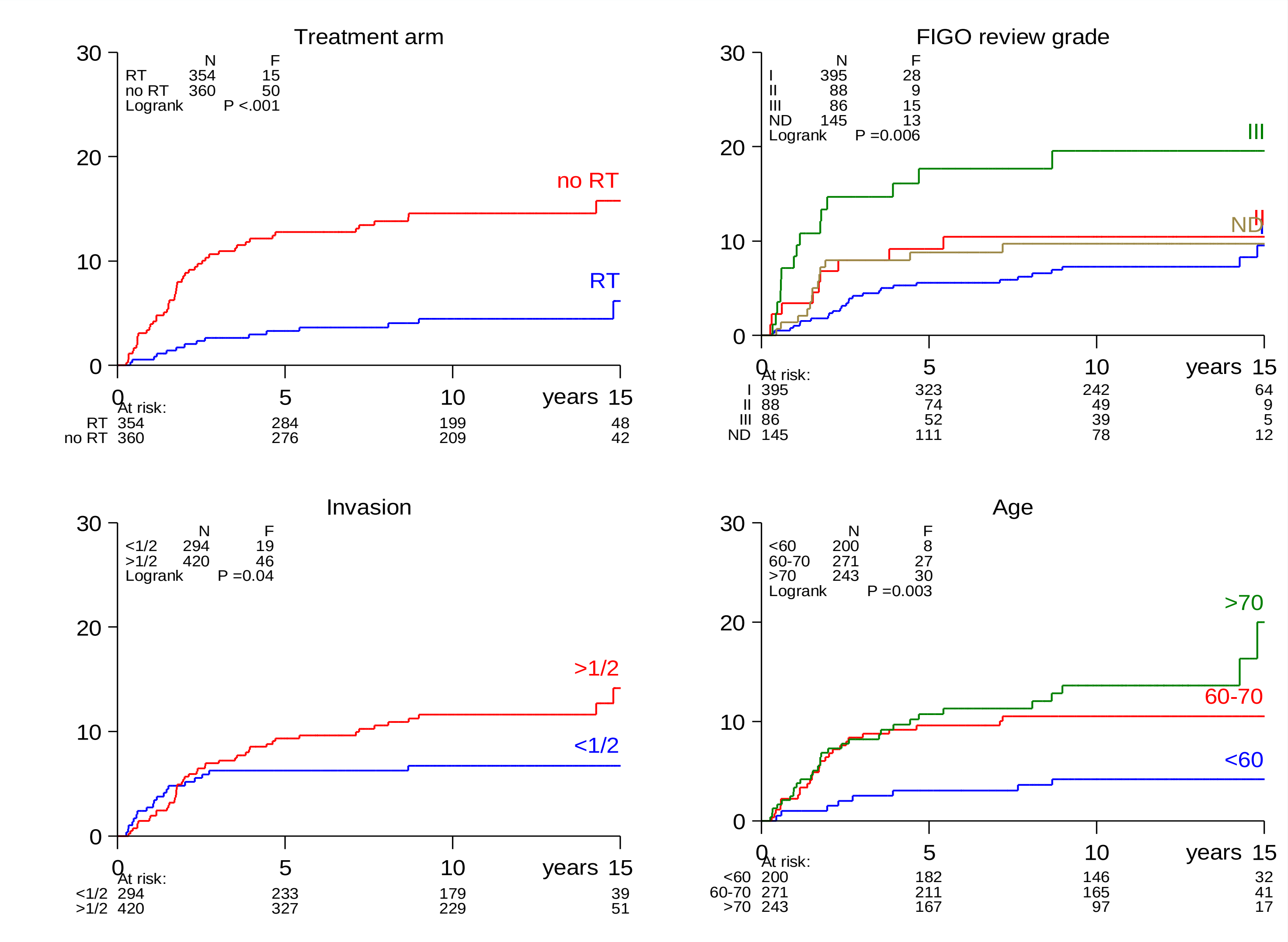


➢ Vaginal brachytherapy?

Creutzberg et al, Gynecol Oncol 2003

PORTEC-1: risk factors for locoregional relapse

PORTEC Locoregional relapse



Creutzberg et al, ASTRO 2009, IJROBP 2011

PORTEC-1: high-intermediate risk

3 major risk factors:

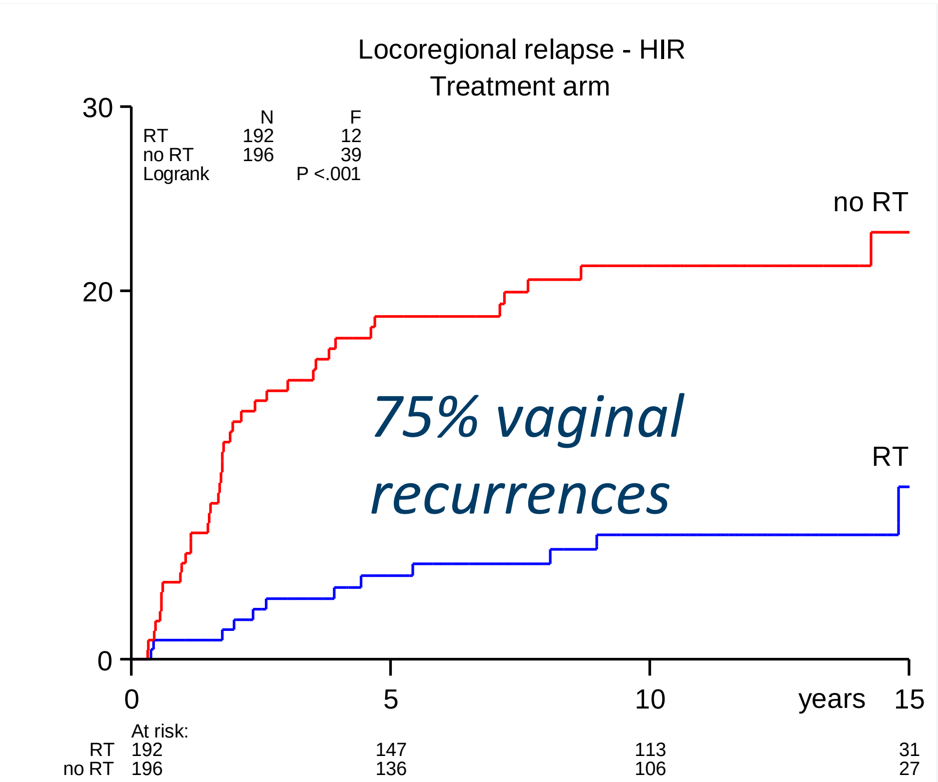
- grade 3
- outer 50% invasion
- age ≥ 60 years

RT indication only if 2 or more risk factors

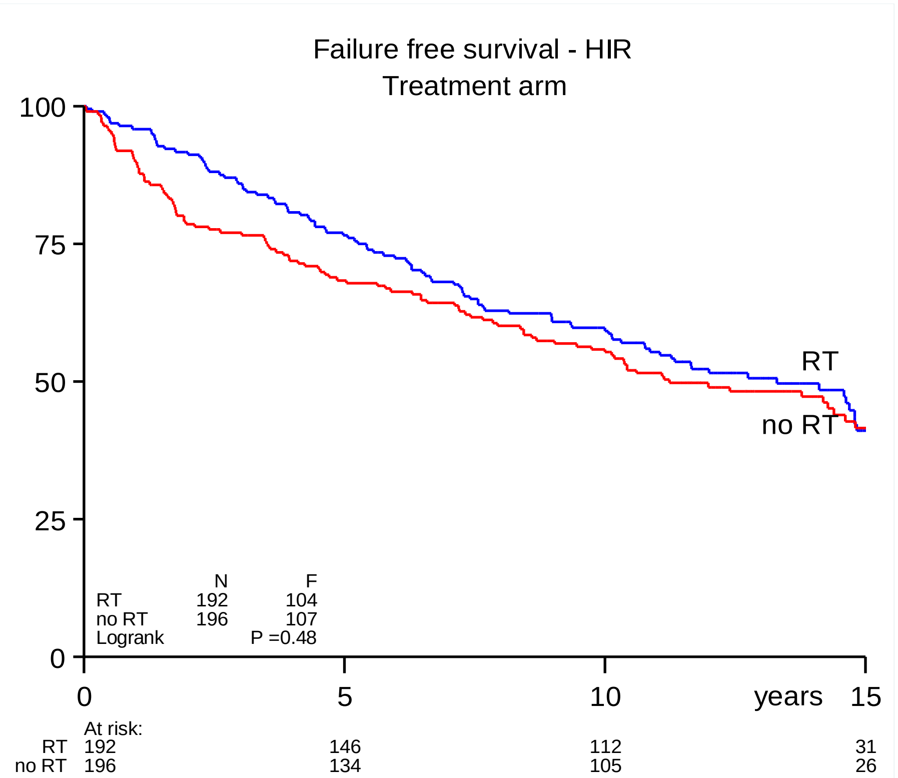
➢ *Reduction of RT-indication by 50%*

PORTEC-1: 15-year outcomes for HIR patients

Locoregional Recurrence



Failure Free Survival

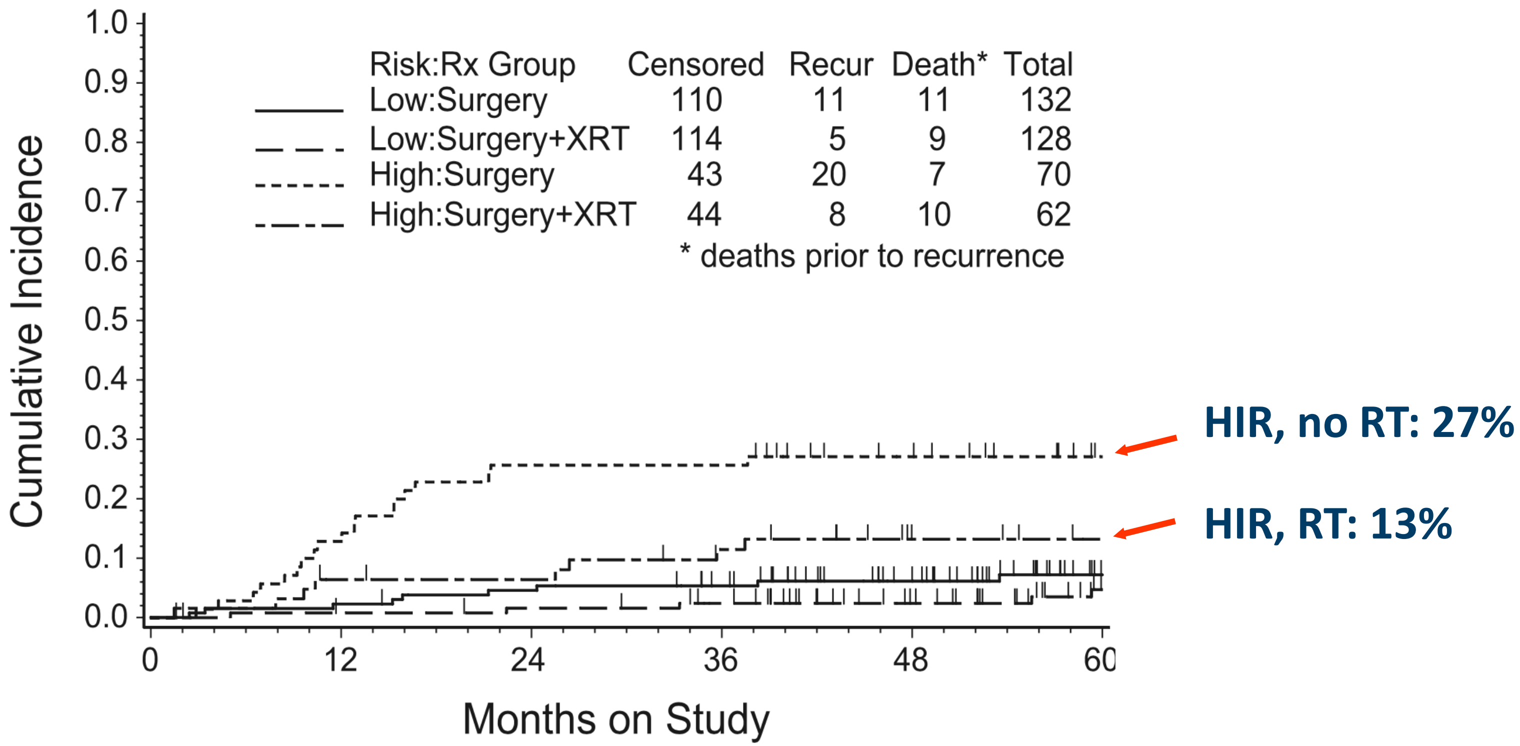


High intermediate risk

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

Creutzberg et al. 2000; Keys et al 2004

GOG#99 - recurrence



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

- *in patients who had lymphadenectomy and were pN0*

High intermediate risk

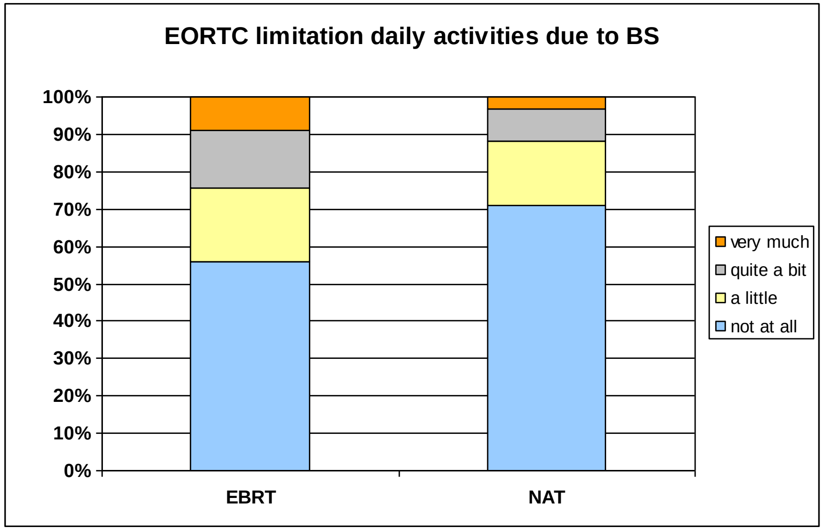
	PORTEC-1	GOG #99
	NAT vs. RT	NAT vs. RT
PORTEC risk groups		
- 10 yr LR relapse	23% vs. 5% (RR 0.22)	
GOG risk groups		
- 10 yr LR relapse	22% vs. 8% (RR 0.36)	
- 4 yr any relapse		27% vs. 13% (RR 0.48)
- 4 yr local relapse		13% vs. 5% (RR 0.38)

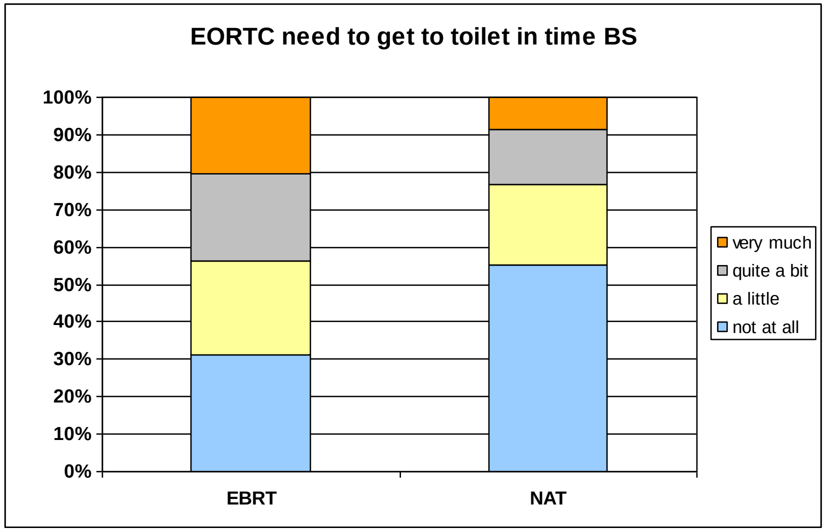
PORTEC-1: morbidity

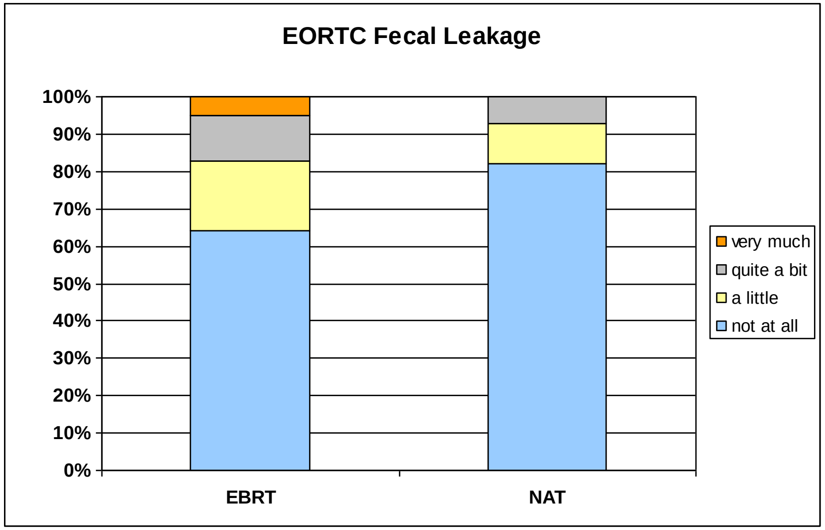
- 5-year actuarial grade 1-4:
  - Overall EBRT 26% versus NAT 4%
  - Grade 1: EBRT 17% versus NAT 4%
  - Majority gastrointestinal tract
- Grade 3-4 after EBRT 3%
- 4-field box technique less late complications
  - 30% treated with parallel opposing fields
- GOG#99 extended surgery + EBRT 13% grade 3-4

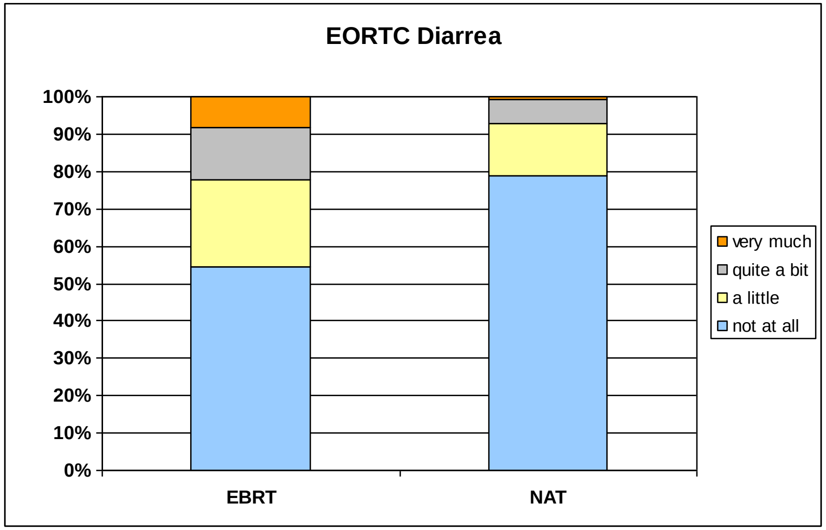
Creutzberg et al, IJROBP2001; Keys et al 2004

Bowel symptoms



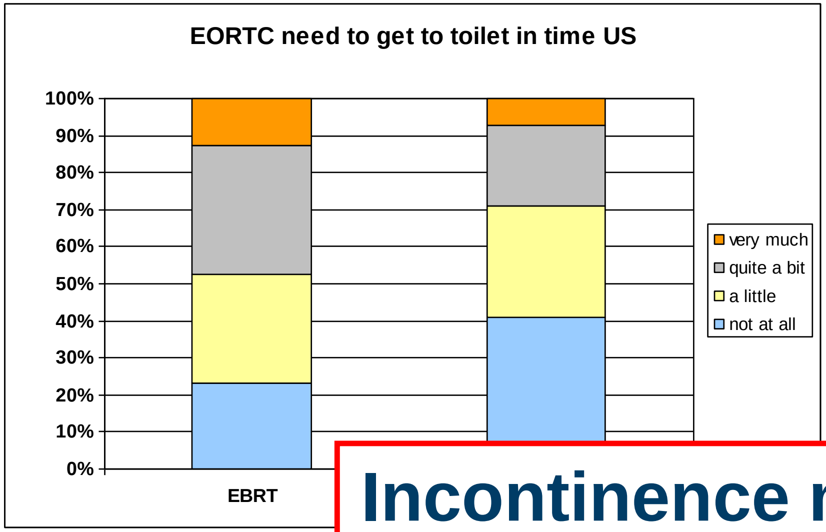


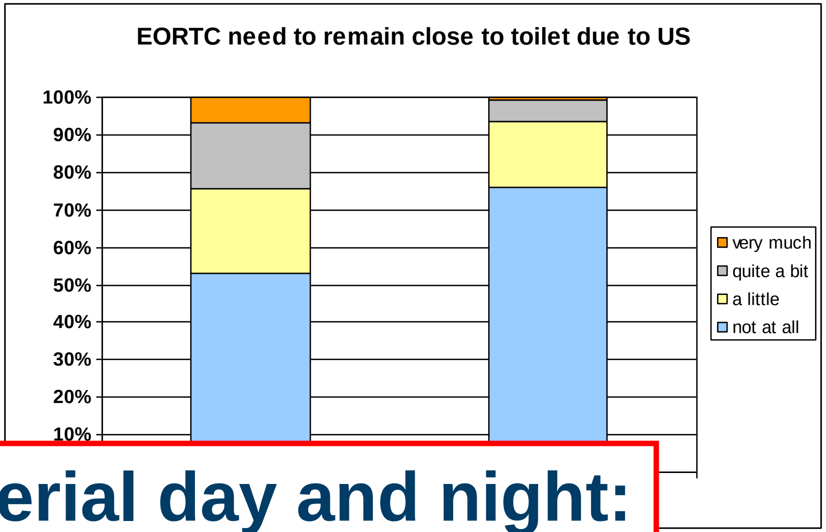




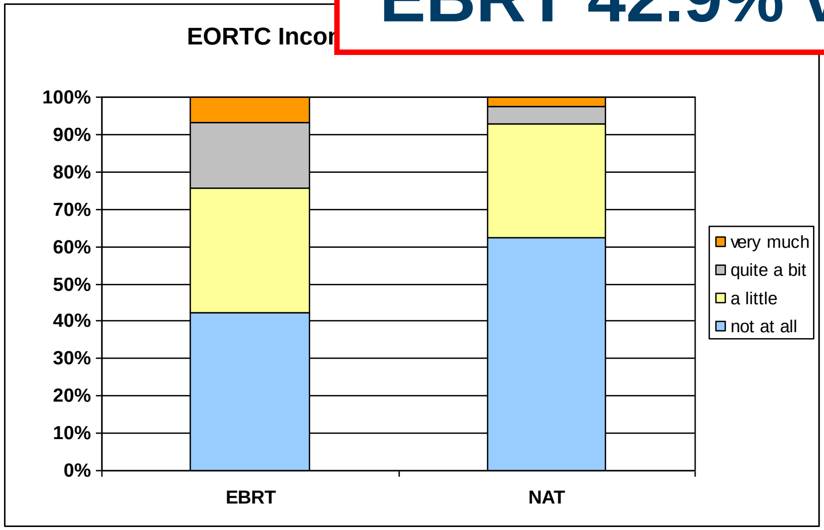
Nout et al, JCO 2011

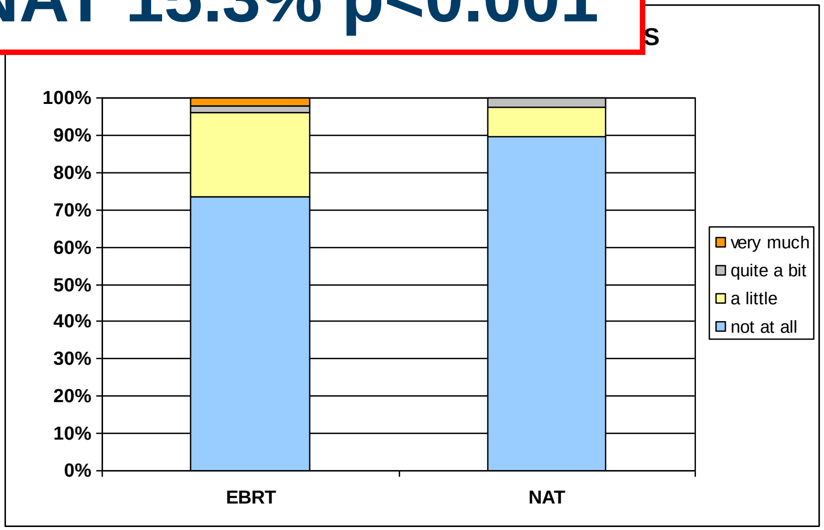
Urinary symptoms





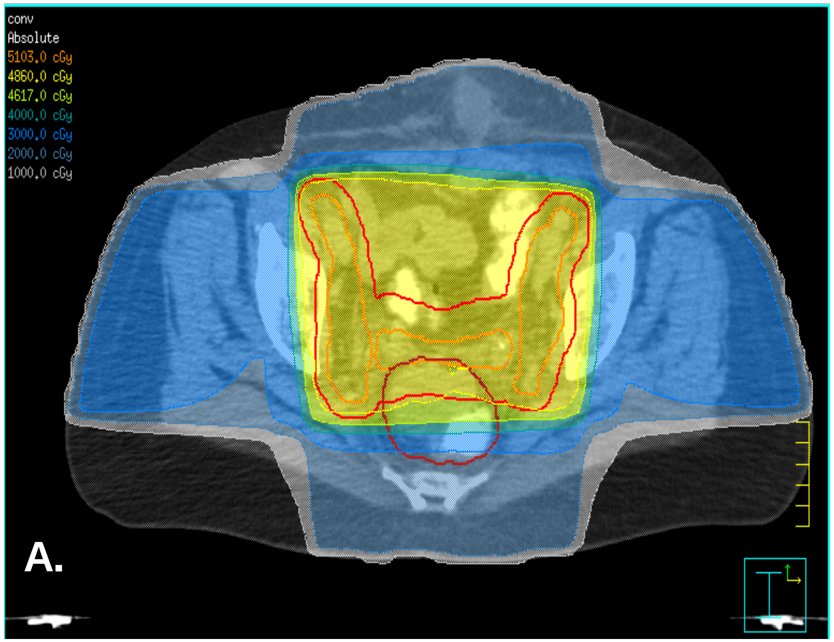
Incontinence material day and night:
EBRT 42.9% vs. NAT 15.3% p<0.001



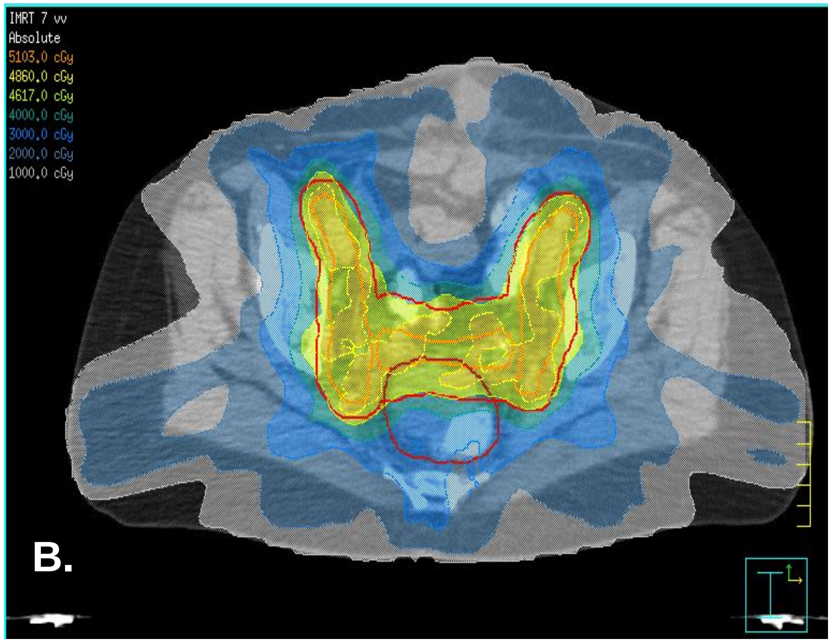


Improvement of EBRT techniques

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



IMRT

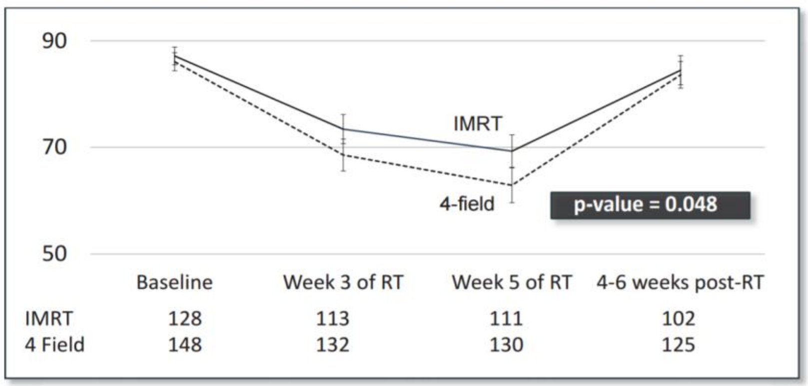


Creutzberg IJROBP 2001; Nout et al, JCO 2011

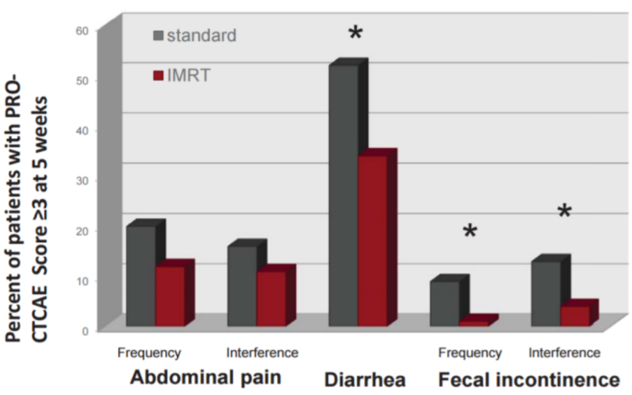
Pelvic IMRT: reduced toxicity

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

EPIC Bowel Score



Pro-CTCAE Results



Summary – intermediate risk

15 year PORTEC-1 results

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

EBRT has long-term impact on quality of life

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

EBRT to be avoided in intermediate risk cases

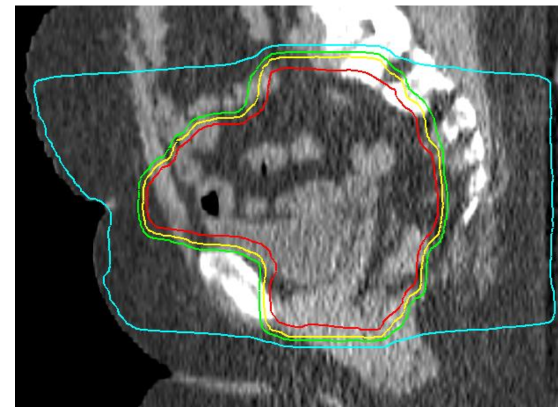
- HIR criteria for treatment selection
- vaginal brachytherapy

Creutzberg et al IJROBP 2011, Nout et al JCO 2011

PORTEC-2 trial (2002-2006)

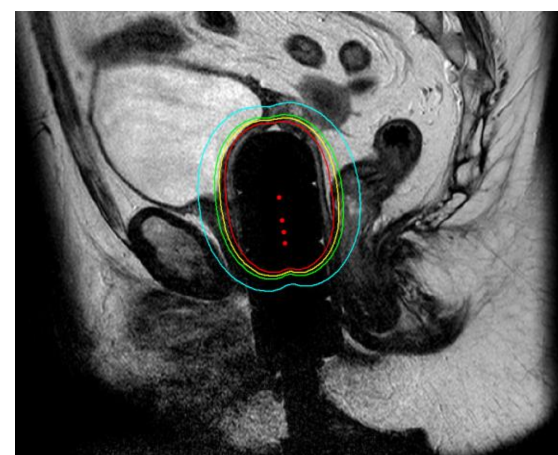
Stage I high-intermediate risk (n = 427)

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



R

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

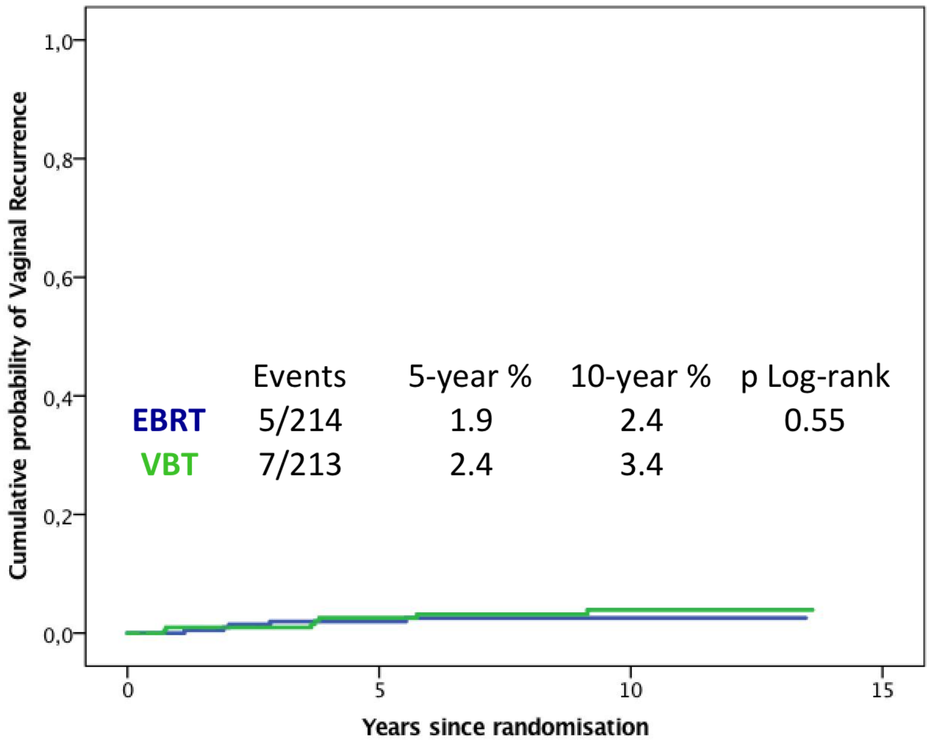


Nout et al, Lancet 2010

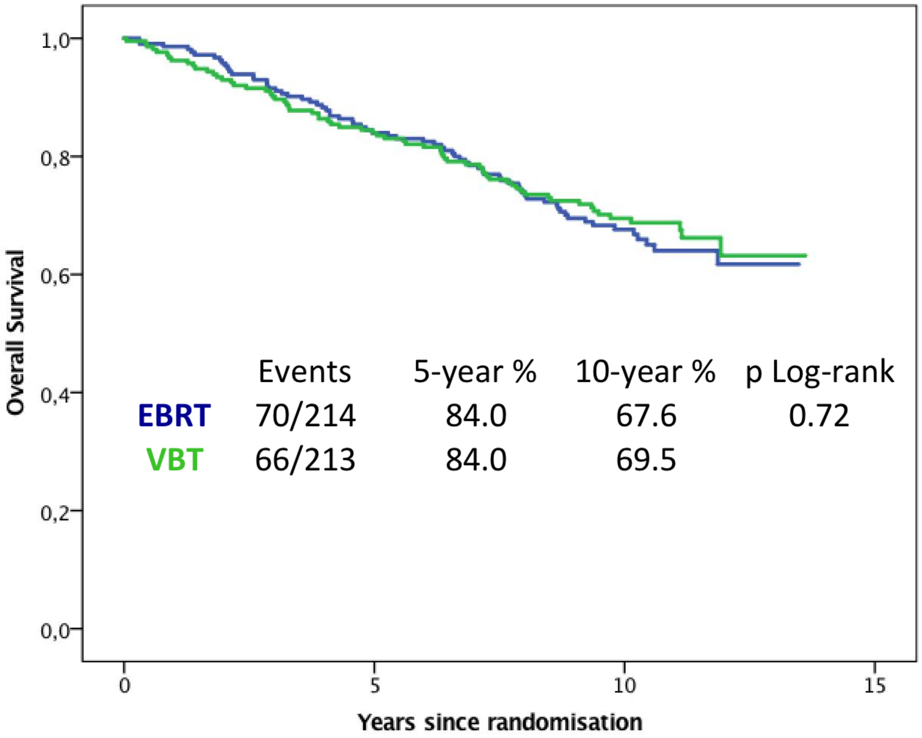
Vaginal Recurrence & Overall Survival

- Median follow-up 10.5 years

Vaginal Recurrence



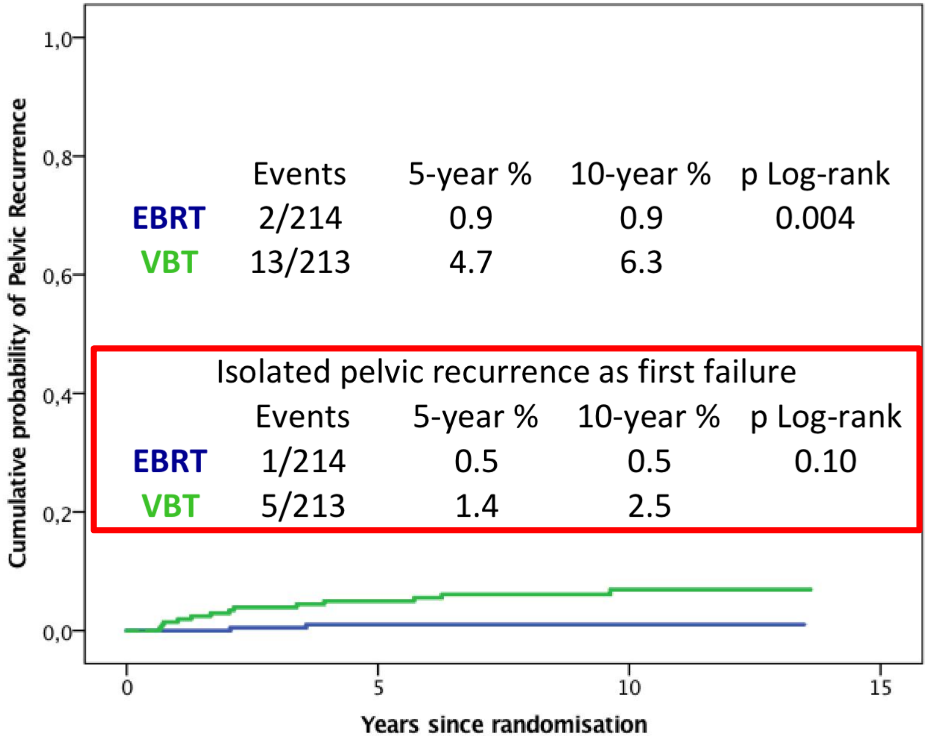
Overall Survival



Vaginal Recurrence & Overall Survival

- Median follow-up 10.5 years

Pelvic Recurrence

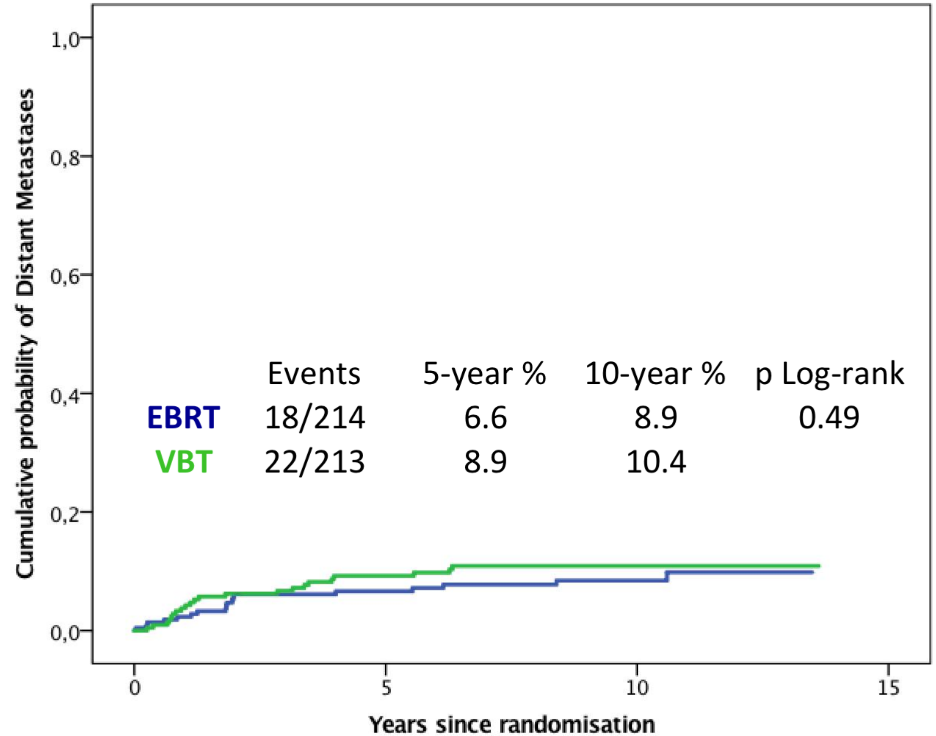


	Events	5-year %	10-year %	p Log-rank
EBRT	2/214	0.9	0.9	0.004
VBT	13/213	4.7	6.3	

Isolated pelvic recurrence as first failure

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

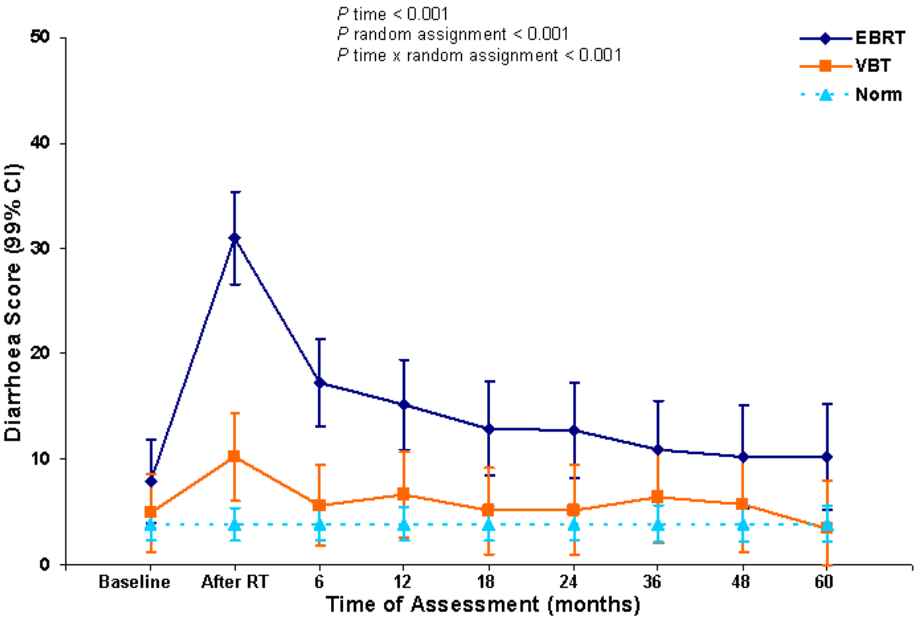
Distant Metastases



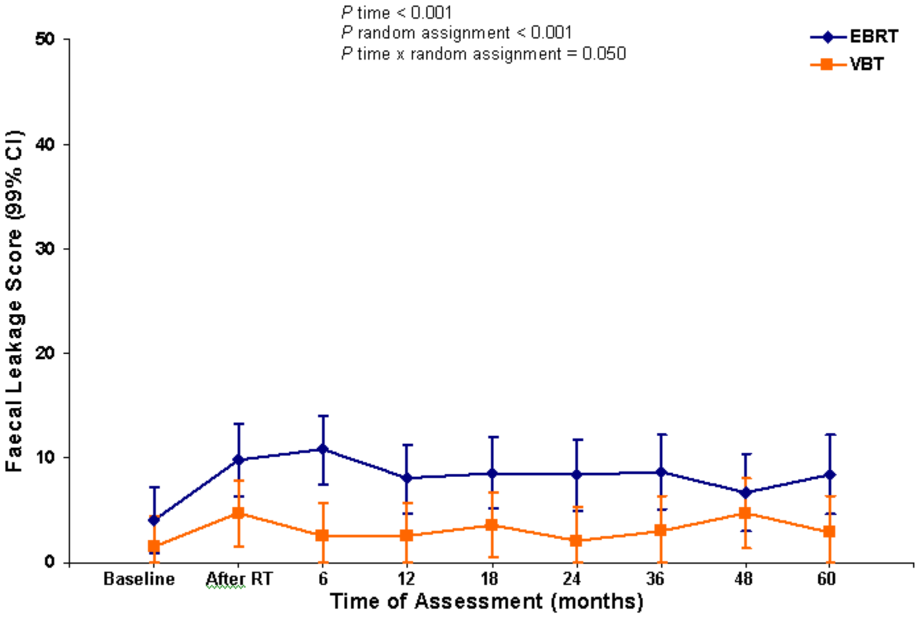
	Events	5-year %	10-year %	p Log-rank
EBRT	18/214	6.6	8.9	0.49
VBT	22/213	8.9	10.4	

Quality of Life – bowel symptoms

Diarrhoea



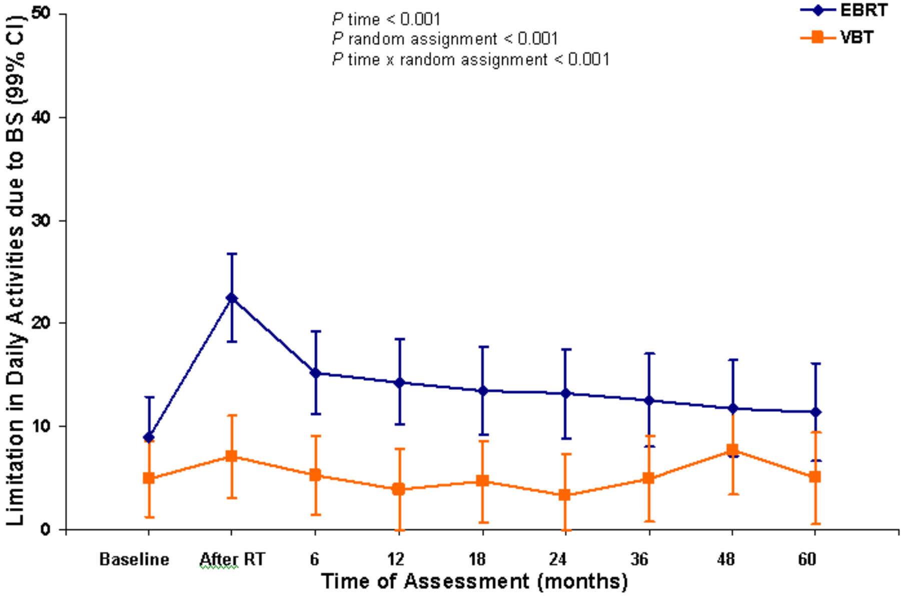
Feacal Leakage



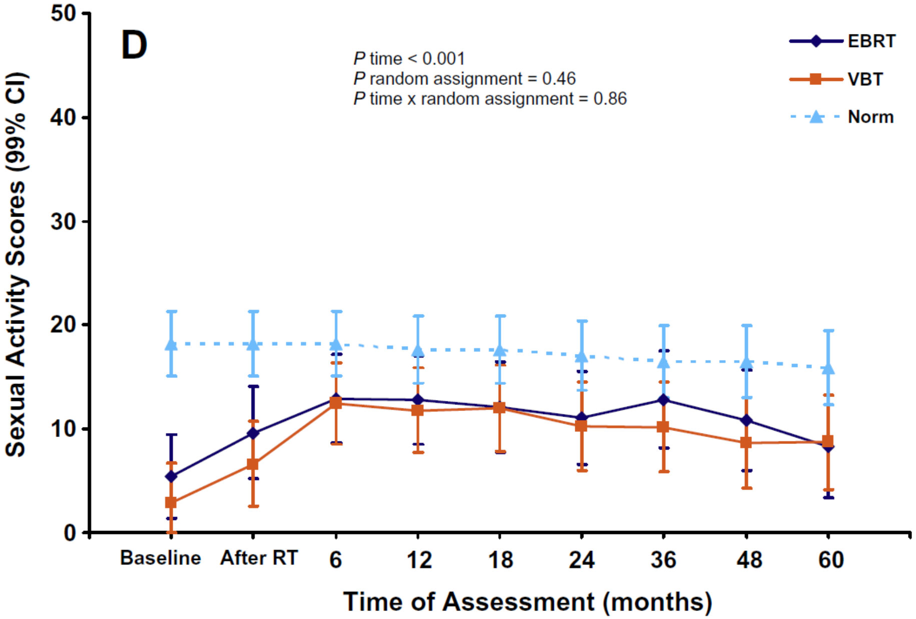
Nout et al, JCO 2009, EJC 2011, de Boer 2014

Quality of Life – bowel symptoms

Daily activities limited by bowel problems?



Sexual activity



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

Swedish randomised trial (1997-2008)

Stage I ‘medium risk ‘ (n=527)

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

- Similar QoL results favoring VBT alone

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

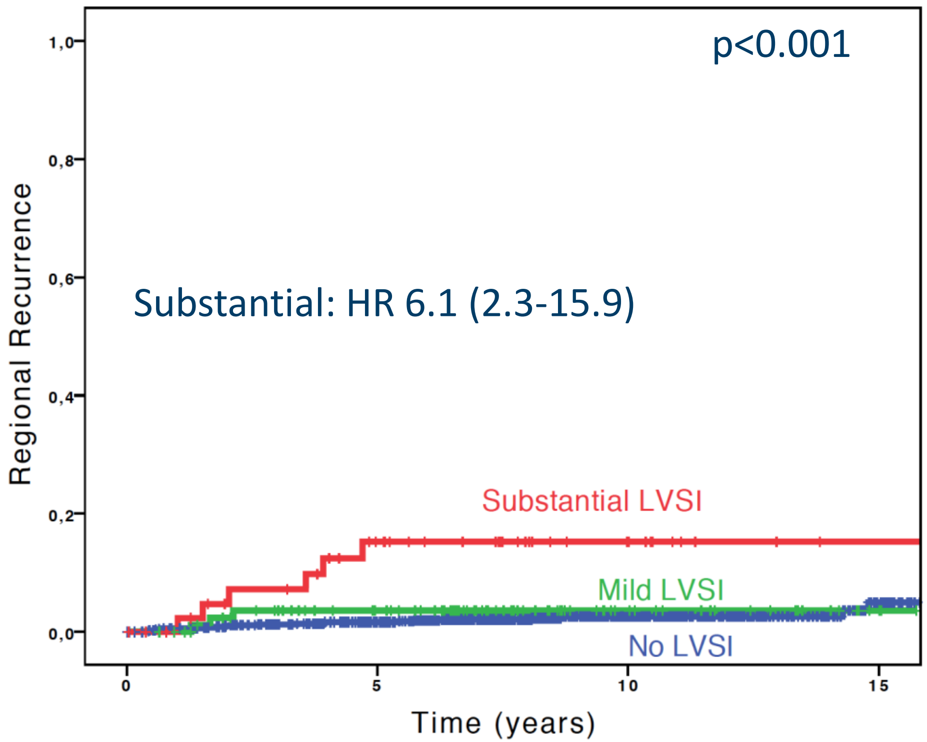
Quatification of LVSI in PORTEC-1 and 2

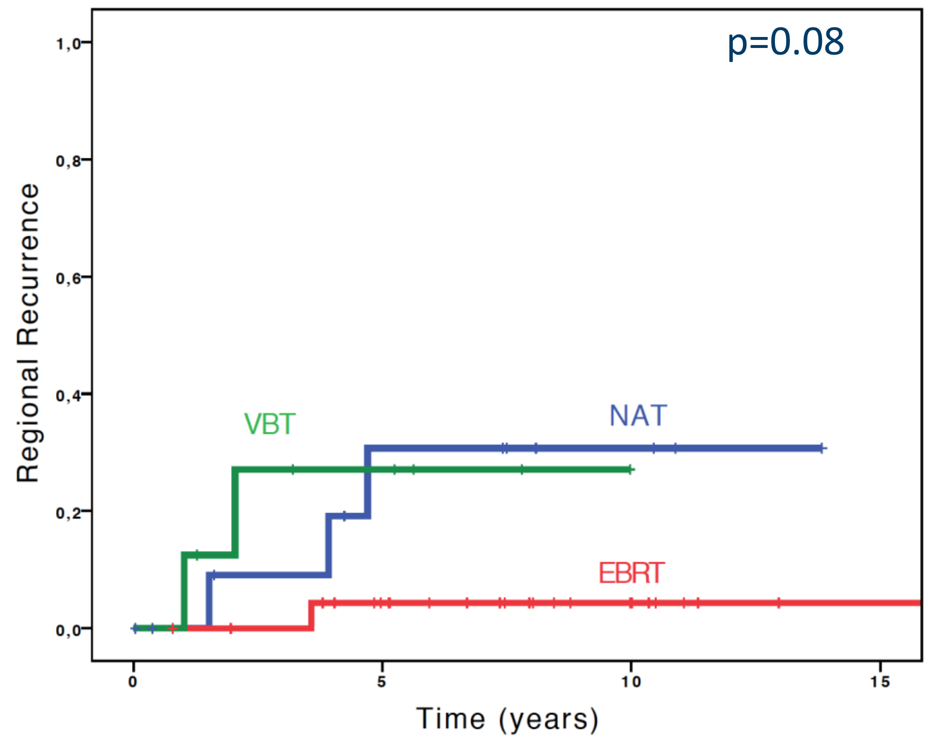
- Pelvic nodal recurrence

5%

All 954 patients

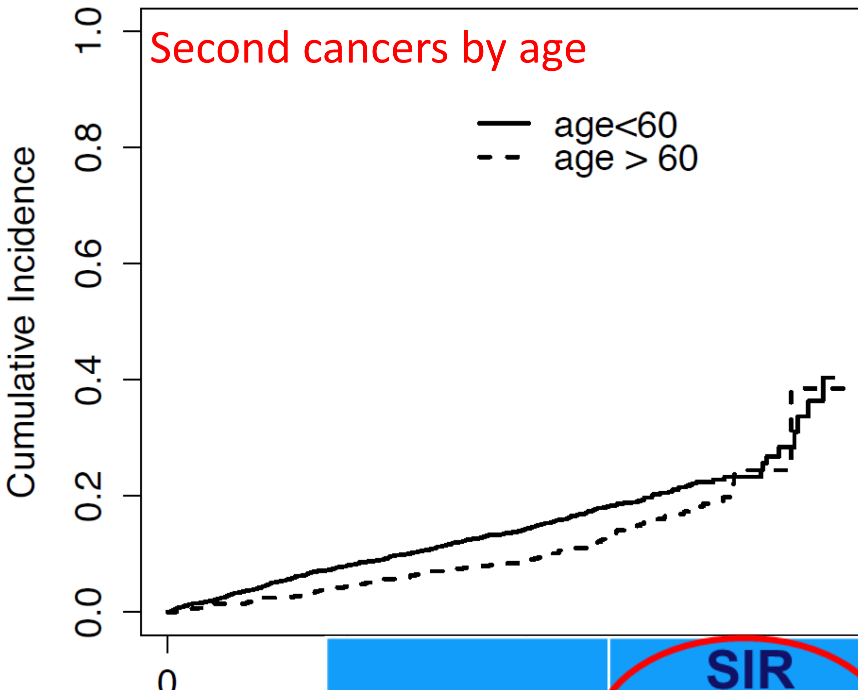
Substantial LVSI: 46 patients

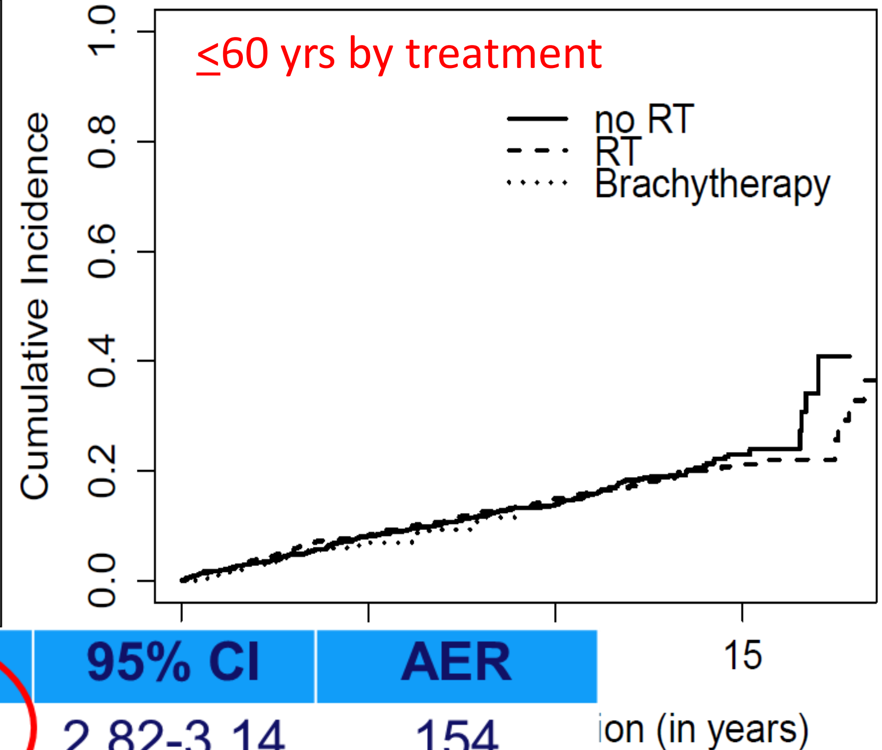




Bosse, T. et al *EJC* 2015, Nout, R. *ASTRO* 2014

Risk of second cancers





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

Wiltink et al, J Clin Oncol 2015

Summary high-intermediate risk

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

Q1: Current best definition of risk groups?

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

No RT

VBT

Pelvic IMRT

Endometrial Cancer Consensus: Adjuvant Treatment

ESMO ESGO ESTRO European Society for RADIOTHERAPY & ONCOLOGY

Leiden University Medical Center

Endometrial Cancer

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

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

ESMO-ESGO-ESTRO consensus: risk groups

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

No RT

VBT

Pelvic IMRT

- Radiotherapy?
- Chemotherapy?
- Both?

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

In my clinic women with stage IB <u>endometrioid type</u> grade 3 receive:

A. Vaginal brachytherapy
B. External beam radiotherapy
C. Chemotherapy
D. Combined chemotherapy and radiotherapy

In my clinic women with serous type endometrial cancer receive:

A. Vaginal brachytherapy
B. External beam radiotherapy
C. Chemotherapy
D. Combined chemotherapy and radiotherapy

GOG-122

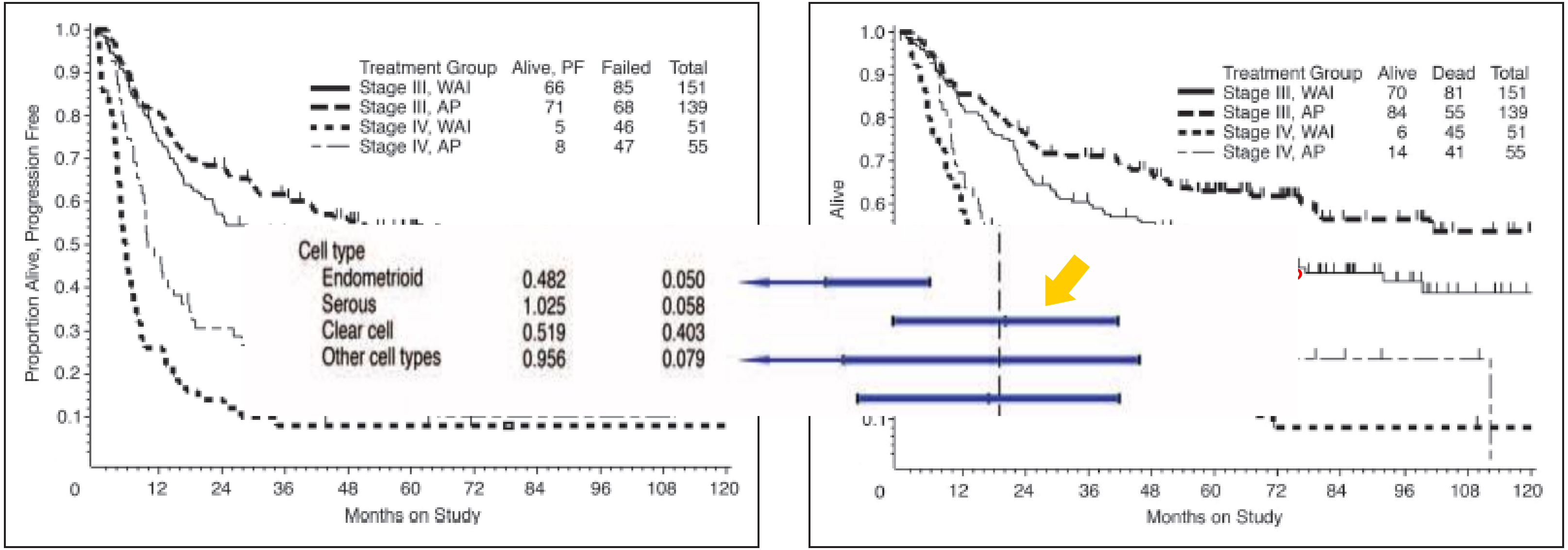


Fig 3. Progression-free survival by treatment and stage. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation; PF, progression free.

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

Progression-free Survival

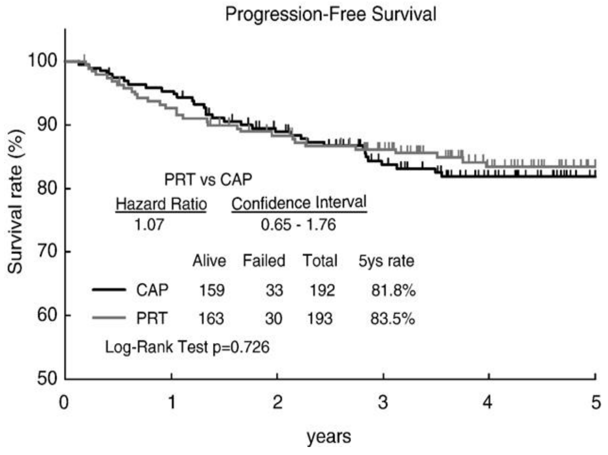
Overall Survival

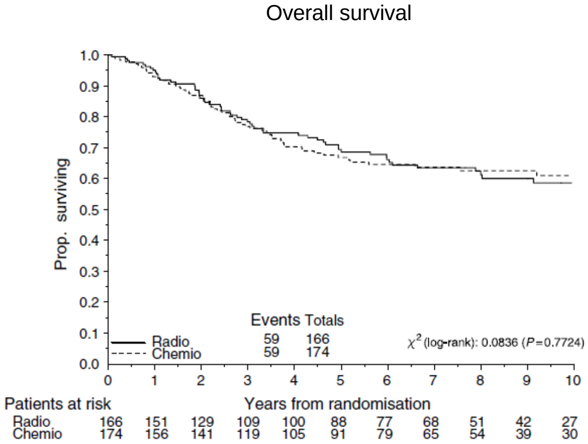
Randall et al, JCO 2006

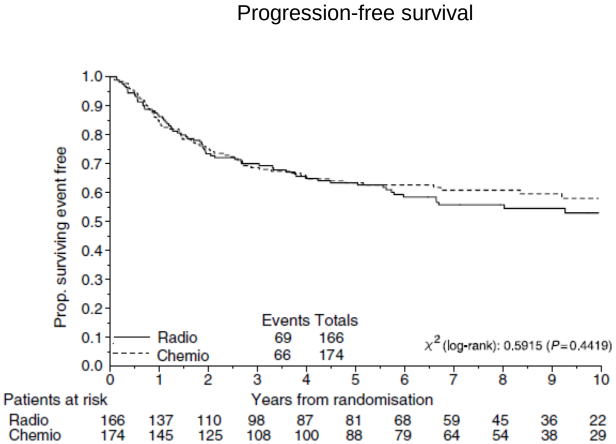
Radiotherapy vs Chemotherapy

JGOG - 385 pts
RT vs chemo* x3

Italian trial - 345 pts
RT vs chemo* x5







* cyclophosphamide – doxorubicin - cisplatin

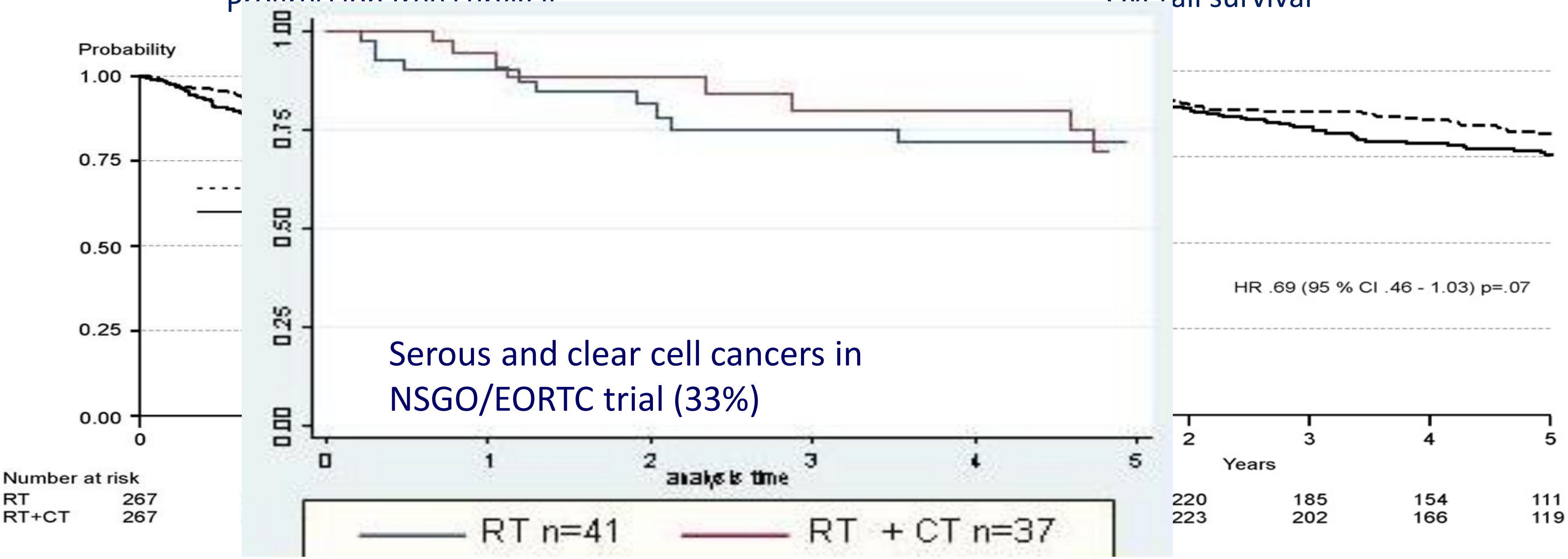
- **Radiotherapy delays local recurrence, chemotherapy delays distant metastasis**

Susumu , Gynecol Oncol 2008; Maggi, Br J Cancer 2006

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

Progression free survival

Overall survival



Serous and clear cell cancers in NSGO/EORTC trial (33%)

PFS 69 vs 78%, p=0.009

OS 75 vs 82%, p=0.07

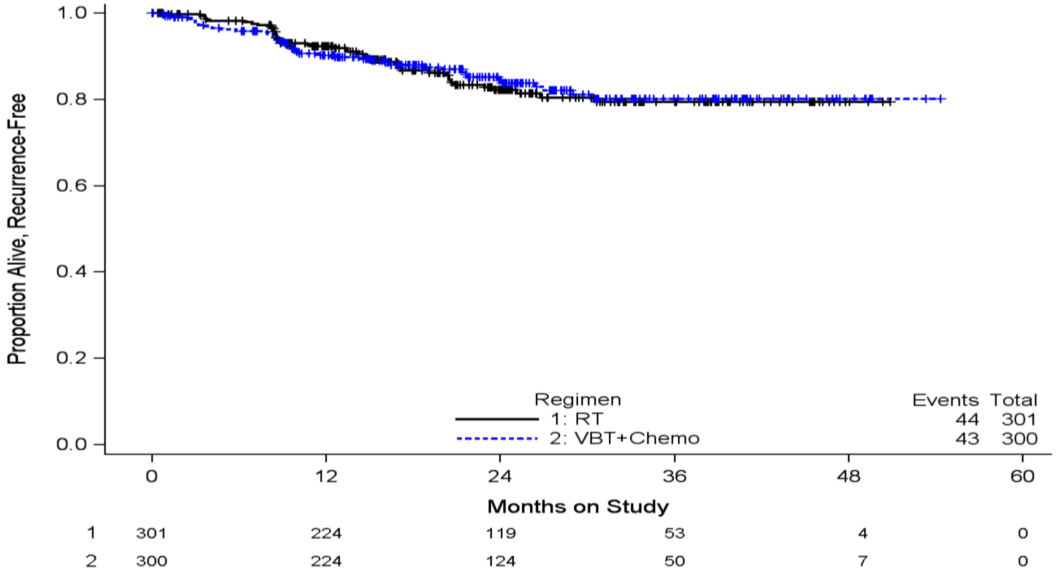
First GOG#249 results

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

R

Pelvic RT

3x carboplatin
+ paclitaxel + VBT



Completed accrual 2012

N=601, primary endpoint PFS

89% underwent lymphadenectomy

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

Update, median FU 53 months

No difference RFS and Overall Survival

First GOG#249 results

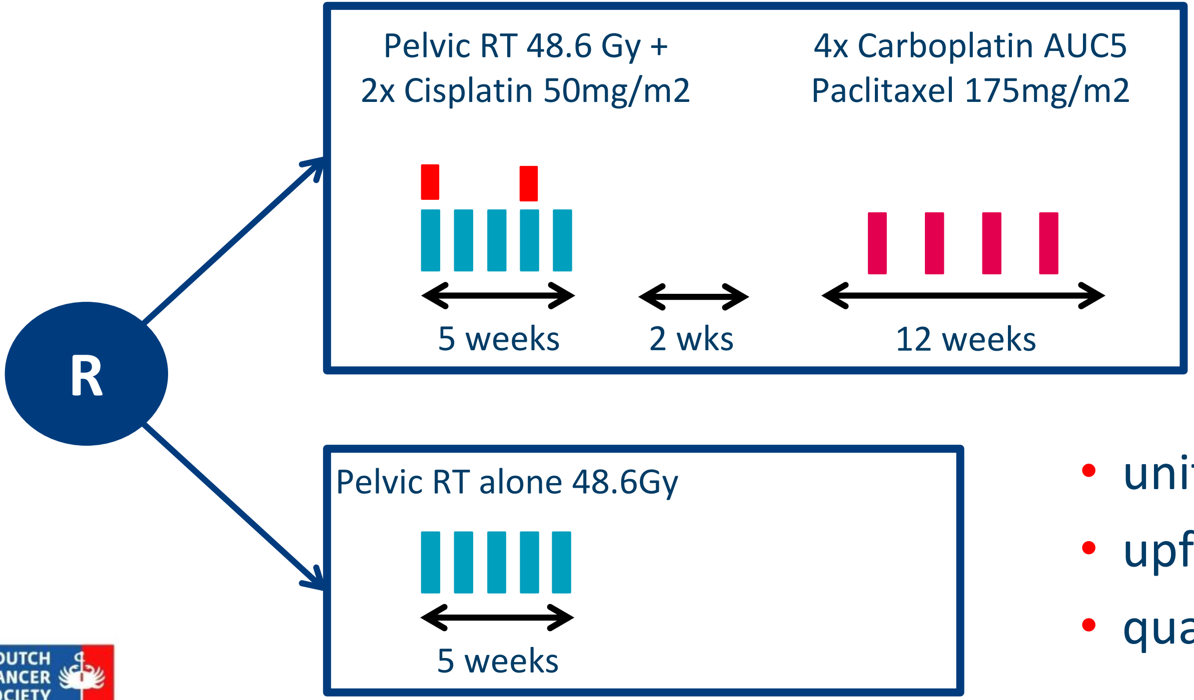
Site of Recurrence	Pelvic RT (N=301)	VBT/Chemo (N=300)
Vaginal	5 (1.6%)	3 (1%)
Pelvic	2 (0.6%)	19 (6.3%)
Para-aortic	2 (0.6%)	3 (1%)
Distant	32 (10.6%)	24 (8%)

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

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

PORTEC-3 trial design

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



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

CONSORT diagram

PORTEC-3
686 patients randomised (2006-2013)

Excluded: N=26
- Immediate IC withdrawal: 13
- Not eligible: 13

Intention to treat population
N = 660

CTRT (N = 330)
- Received allocated treatment: 325
- Received RT alone: 5

RT (N = 330)
- Received allocated treatment: 328
- Received CTRT: 2

Median FUP 60.2 months

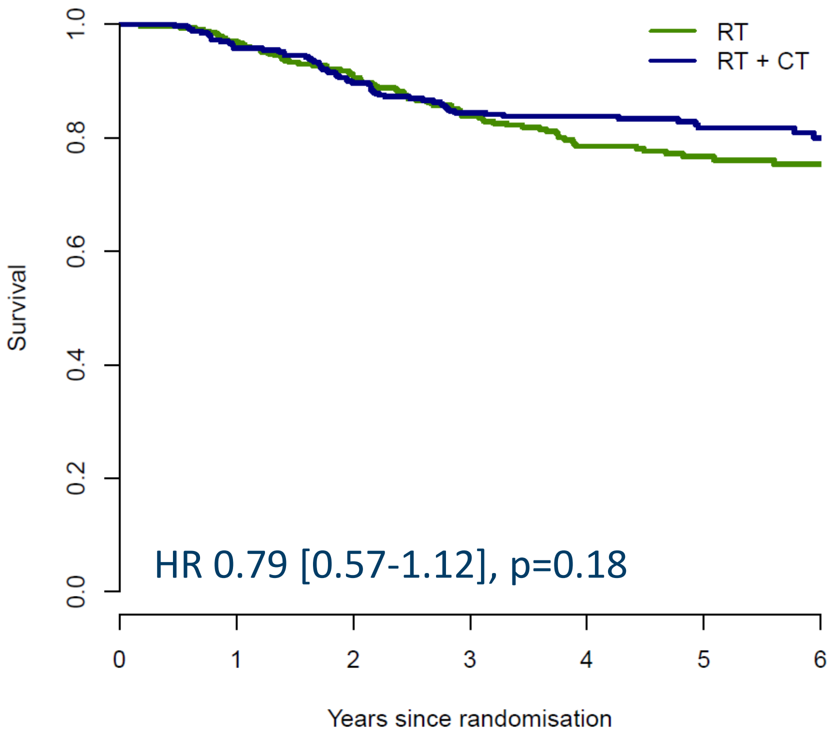
Tumour characteristics

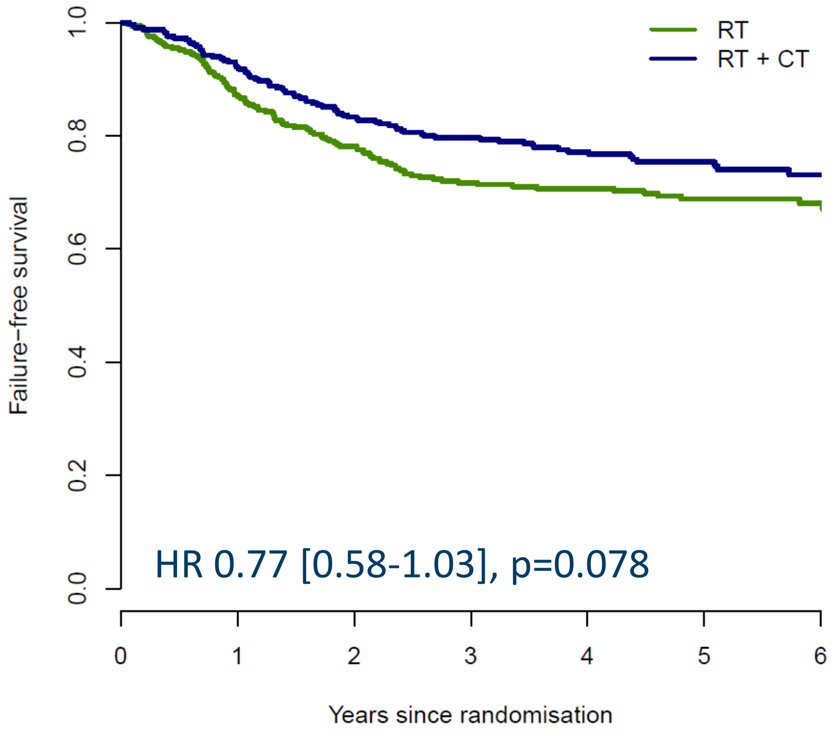
Tumour characteristics	RT alone	CTRT
Histology		
Endometrioid grade 1-2	39.7%	38.5%
Endometrioid grade 3	32.1%	32.4%
Serous/ clear cell/ other	28.2%	29.1%
LVSI		
Yes	58.2%	59.7%
No	41.8%	40.3%
Stage (%)		
I	29.4%	29.7%
II	27.3%	24.2%
III	43.3%	46.1%

Treatment characteristics

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

Survival, median follow-up 60.2 months





5 yr OS: 82% (CTRT) versus 77% (RT)

5 yr FFS: 76% (CTRT) versus 69% (RT)

First sites of recurrence

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

Survival results per stage

Patients with stage III EC:

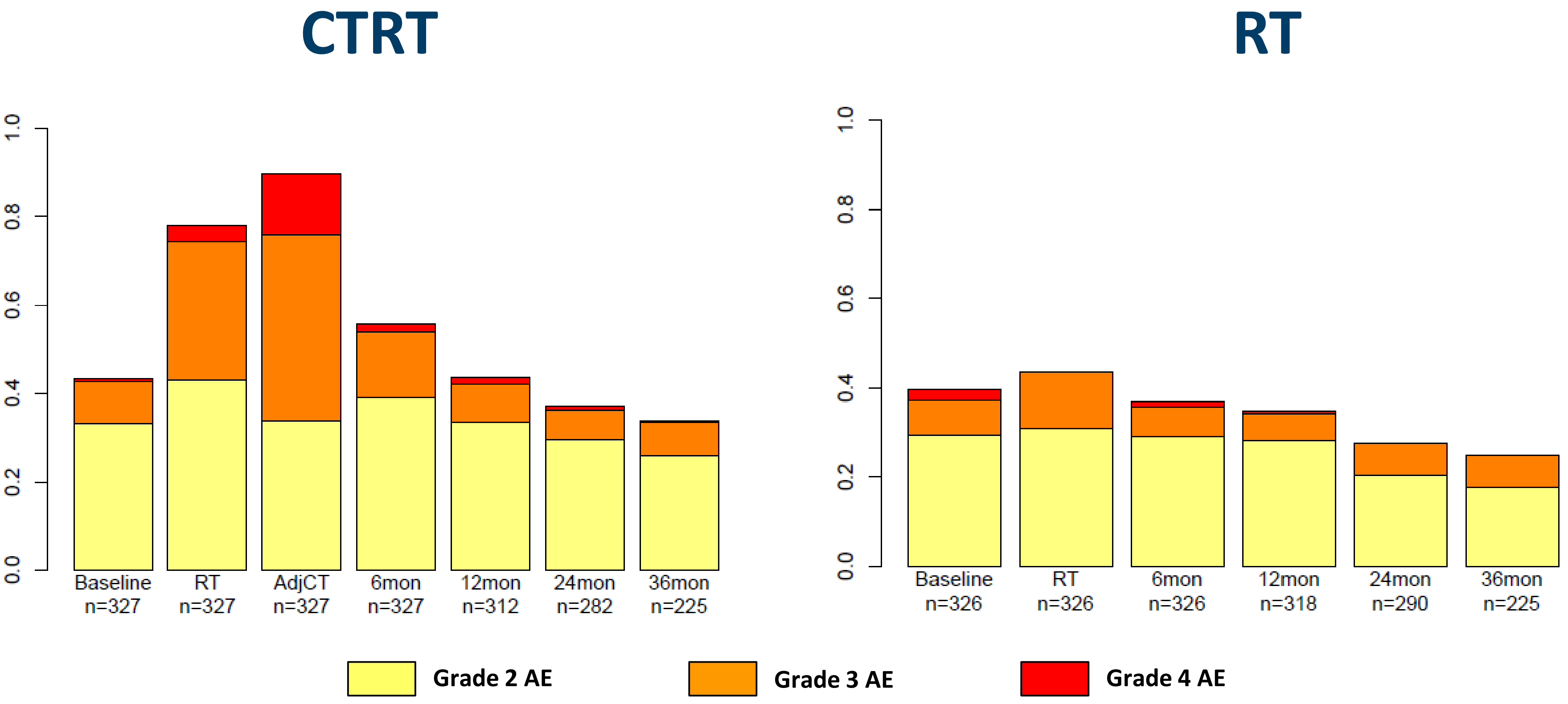
- Lower 5-year FFS and OS:
  - FFS: 64% stage III versus 79% for stage I-II (p<0.001)
  - OS: 74% vs 83% (p=0.003)

- Greatest benefit of CTRT
  - 5-year FFS 69% for CTRT vs 58% for RT

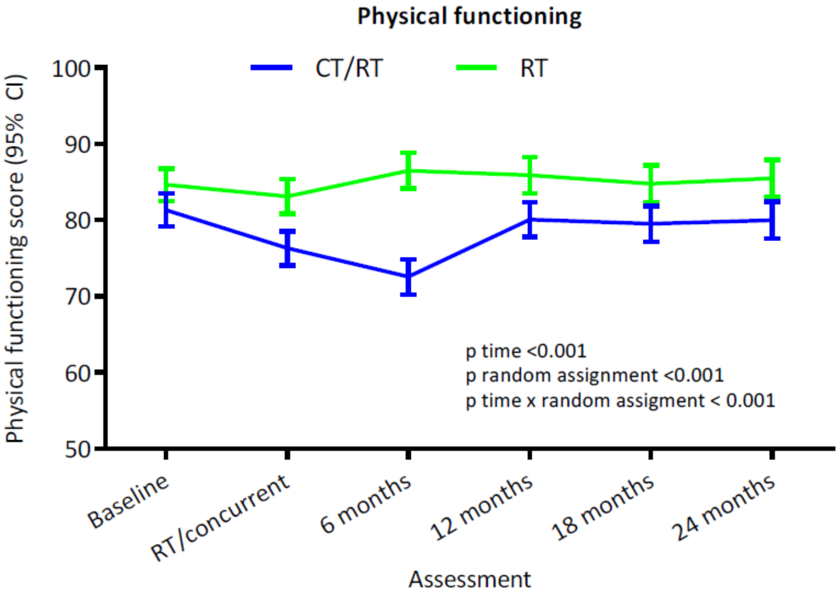
    [HR 0.66, 95% CI 0.45-0.97, **p=0.032**]
  - 5-year OS 79% vs 70%

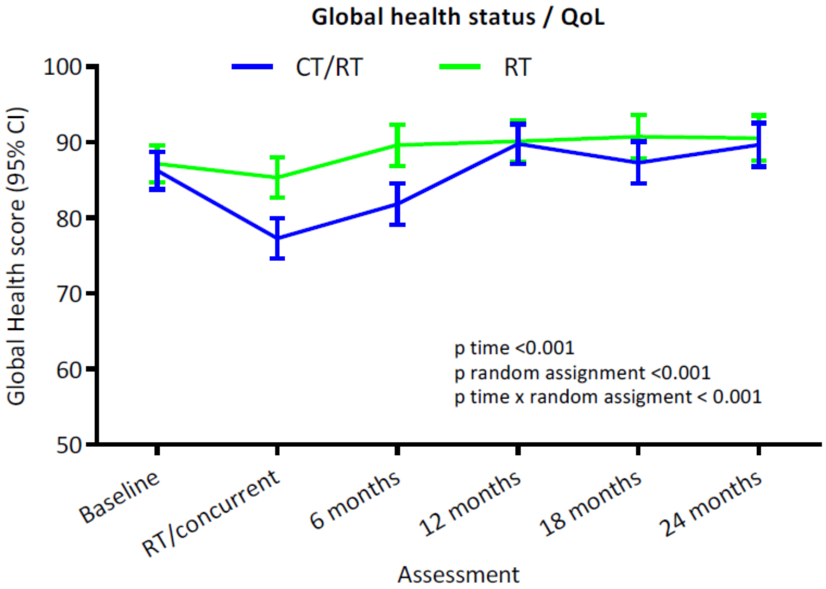
    [HR 0.69, 0.44-1.09, p=0.114]

Adverse events (CTCAE v3.0)



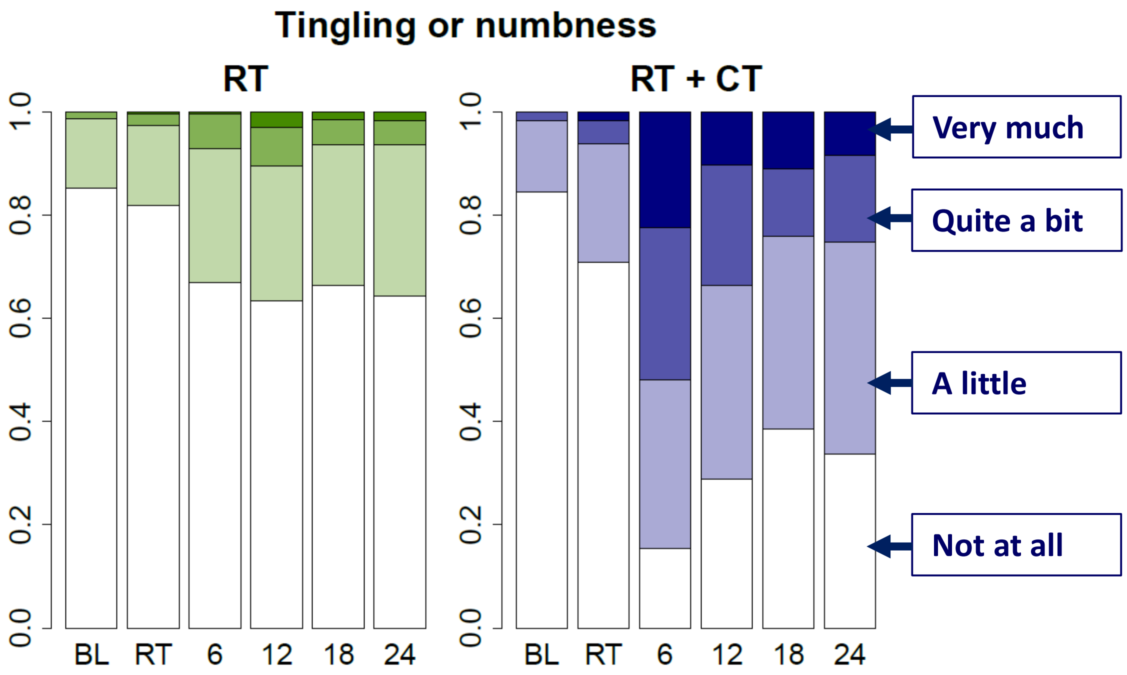
Quality of life





De Boer et al, Lancet Oncology 2016

Quality of life



Sensory neuropathy ("quite a bit" or "very much"): 25% vs 6%

GOG-258 design

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

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

Randomization 1:1

Regimen 1: C-RT (n=407)

Cisplatin 50 mg/m^2 IV Days 1 and 29 plus **Volume-directed radiation therapy (45Gy+/- brachytherapy)**
followed by
Carboplatin AUC 5* plus Paclitaxel 175 mg/m^2 q 21 days for 4 cycles with G-CSF support

Regimen 2: CT (N=406)

Carboplatin AUC 6 plus Paclitaxel 175 mg/m^2
q 21 days for 6 cycles

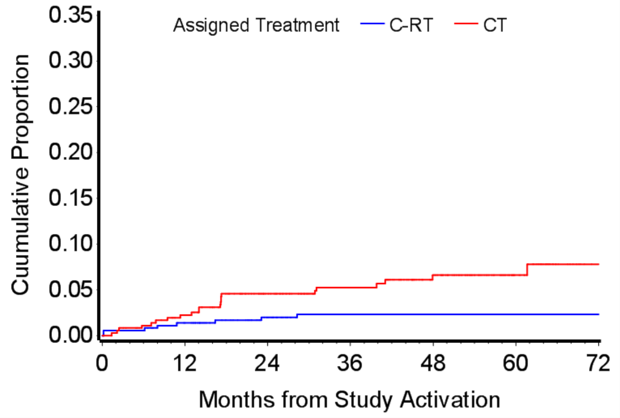
<u>Eligibility:</u>
Surgical Stage III or IVA EC (FIGO 2009)
Stage I or II clear cell or serous EC + cytology
GOG Performance Status of 0-2
Adequate organ function

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

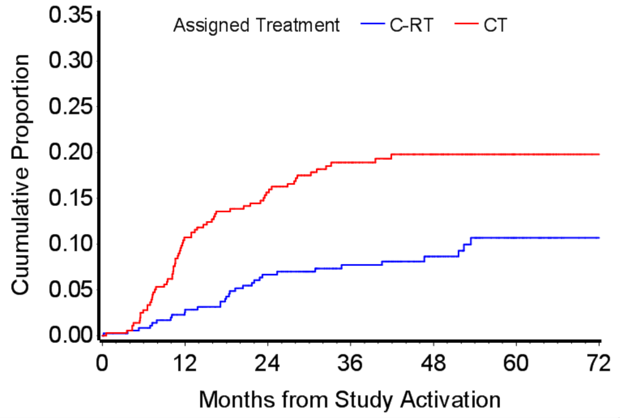
<u>Stratification:</u>
Age >/< 65
Gross residual disease

First GOG-258 results

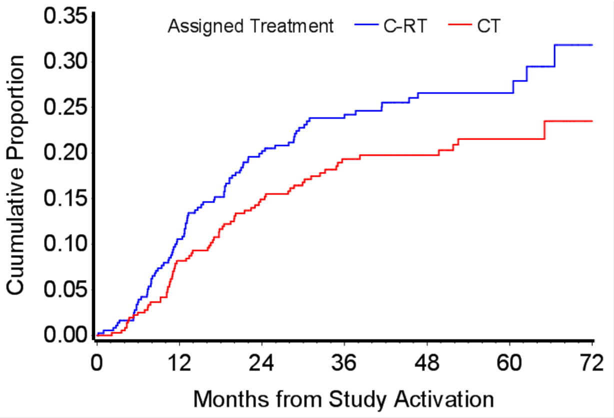
Vaginal Recurrence



Pelvic and PA Recurrence



Distant Recurrence

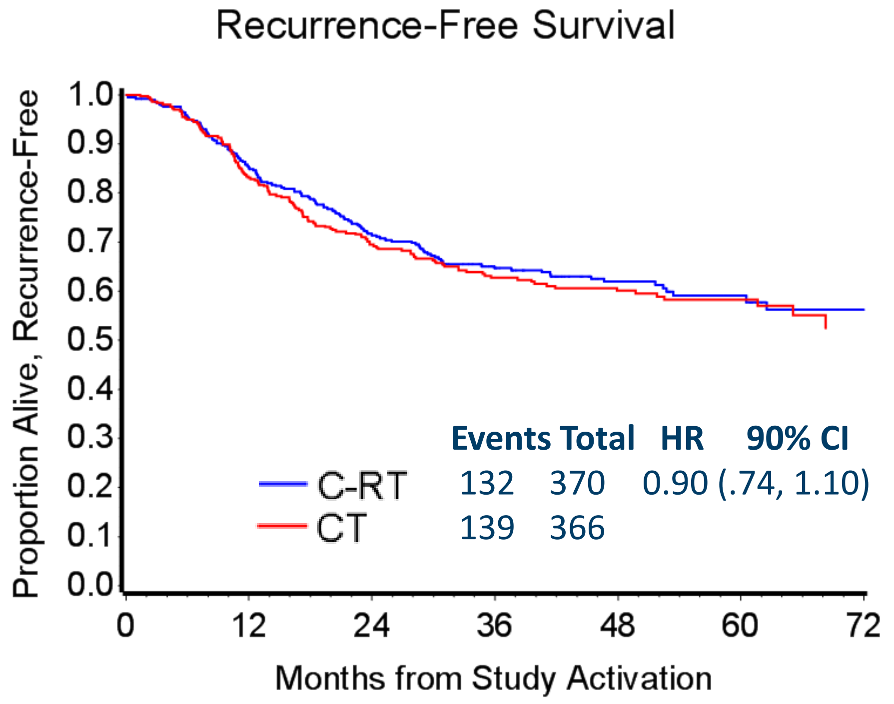


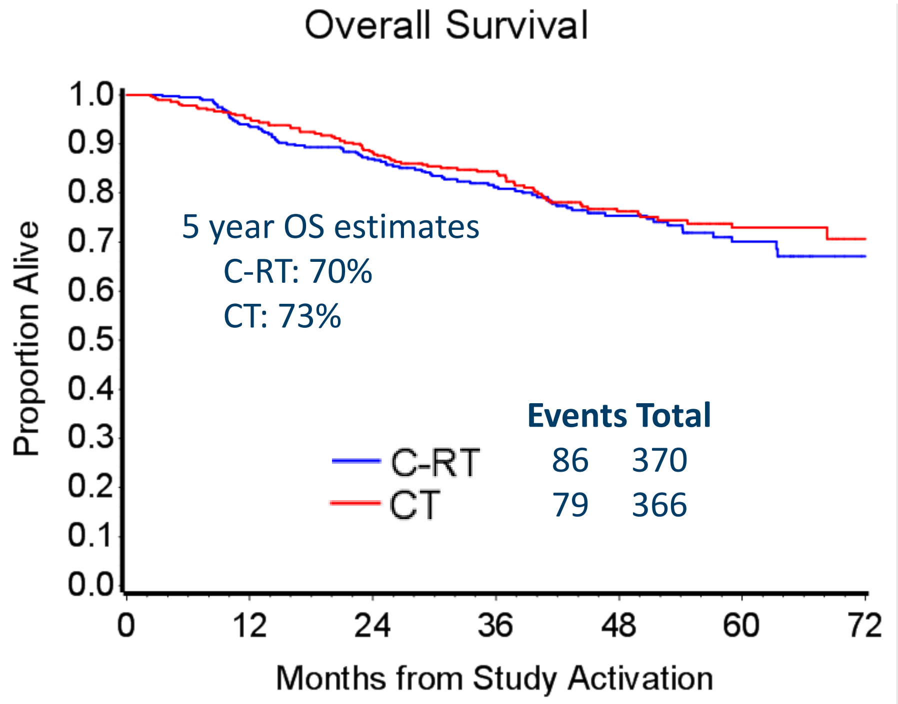
C-RT vs. CT : HR=0.36 (CI: 0.16-0.82)

HR=0.43 (CI: 0.28-0.66)

HR=1.36 (CI: 1.00-1.86)

First GOG-258 results





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

Conclusion High Risk: CT+RT vs RT

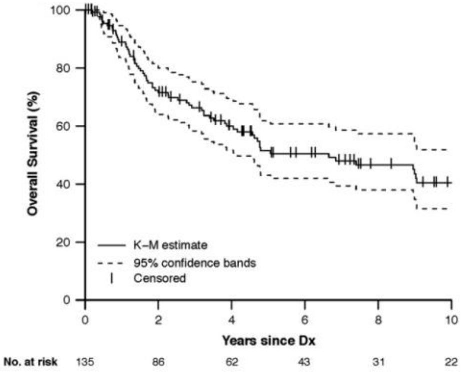
- NSGO-EORTC/Iliade: significant PFS benefit (9%); trend for OS (7%)
- PORTEC-3: trend for improved FFS (7%) with CT+RT
- Does benefit outweigh the added toxicity, without OS benefit?
- Good pelvic control with RT alone (PORTEC-3 and GOG-249)

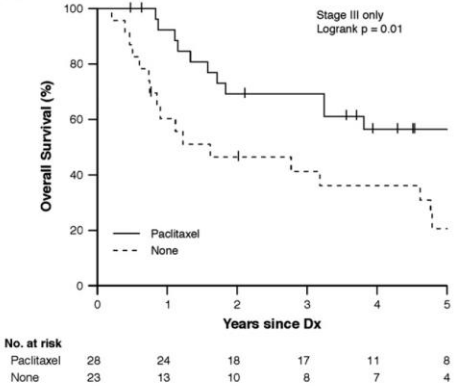
➢ CT+RT schedule cannot be recommended as standard for stage I-II
  - Translational studies will hopefully identify those who benefit

➢ Stage III disease largest FFS improvement with both CT+RT and CT
  - PORTEC-3 significant 11% FFS benefit for stage III with CT+RT
  - GOG-258 better local control with CT+RT

Serous and clear cell

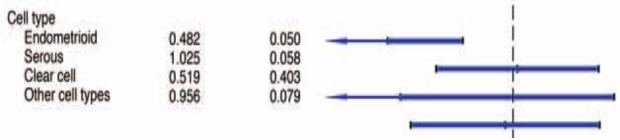
- Largest retrospective analysis suggest benefit of chemotherapy



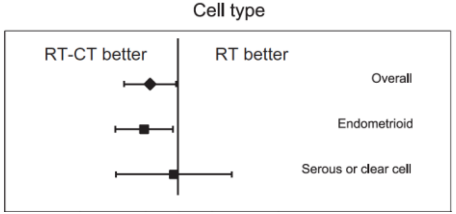


- Subgroups in randomized trials, no clear benefit:

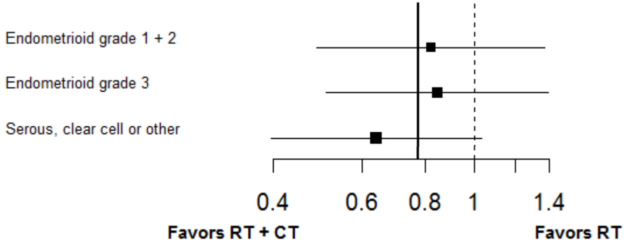
GOG-122



NSGO-EORTC/Iliade



PORTEC-3



Serous and clear cell

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

- Vaginal brachytherapy alone sufficient in stage IA

Barney BM. IJROBP 2013

Stage II

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

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

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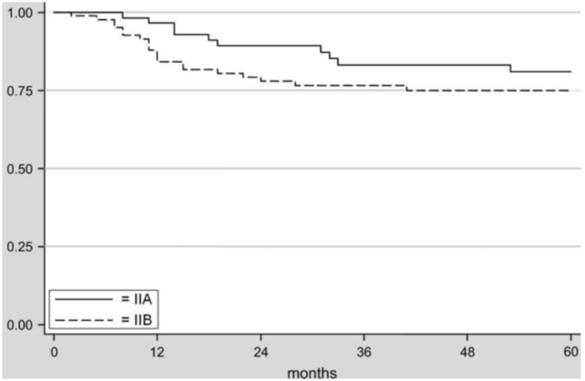
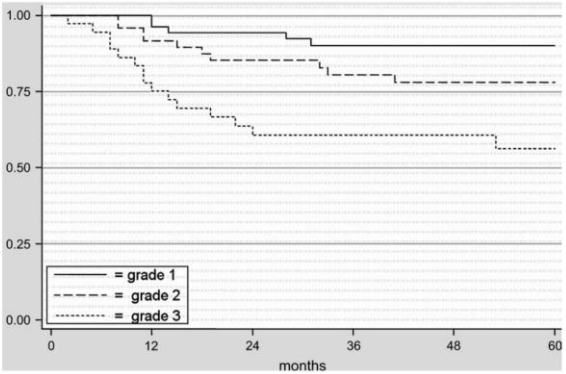
		IIA	IIB
vaginal recurrence		5.1% (3/59)	10.8% (9/83)
VBT	yes	1	4
	no	2	5
Grade	1		
	2	3	2
	3		7

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

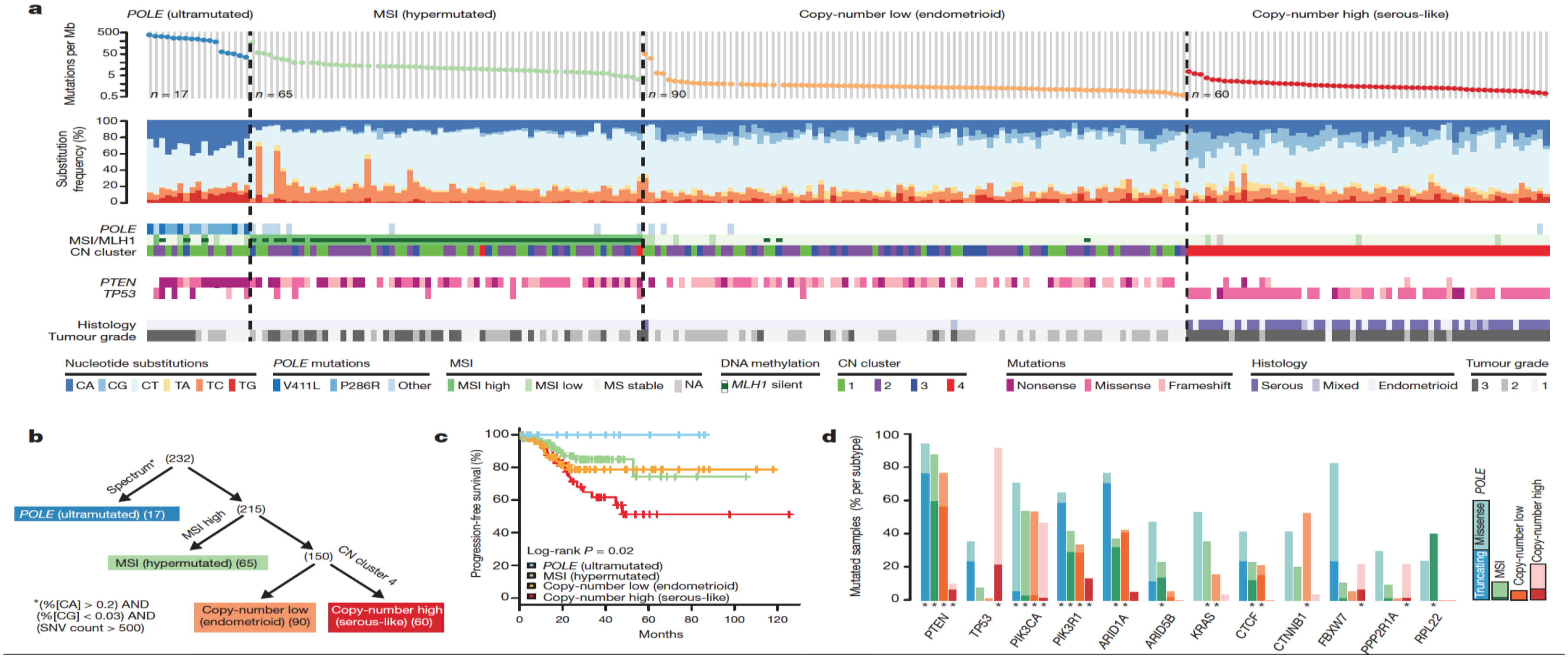
Characteristics	Stage IIA 59 (%)	Stage IIB 83 (%)	P
Age (years)			
<60	12 (20.3)	18 (21.7)	NS
≥60	47 (79.7)	65 (78.3)	
Grade			
1	26 (44.1)	28 (33.8)	
2	22 (37.3)	27 (32.5)	NS
3	10 (16.9)	27 (32.5)	
Unknown	1 (1.7)	1 (1.2)	
MI			
>0.5	29 (49.2)	67 (80.7)	<0.001
<0.5	29 (49.2)	16 (19.3)	
Unknown	1 (1.6)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





Upcoming molecular prognostic factors and ongoing trials

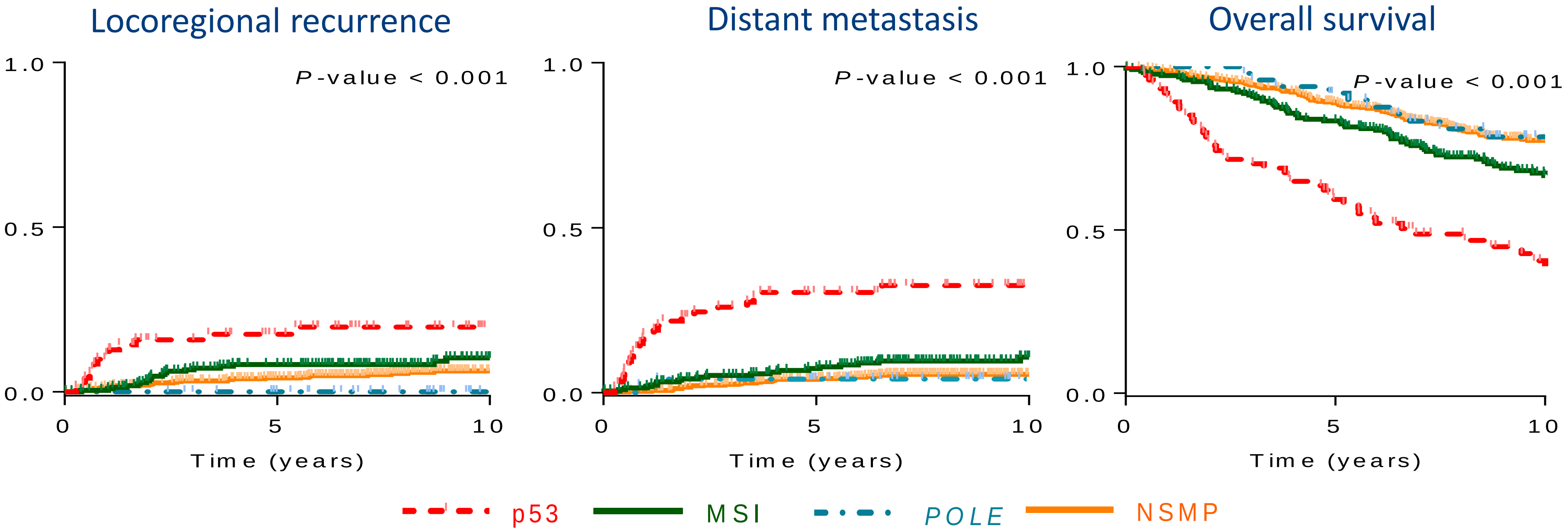
Molecular characteristics of endometrial cancer



TGCA, Kandoth et al, Nature 2013

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

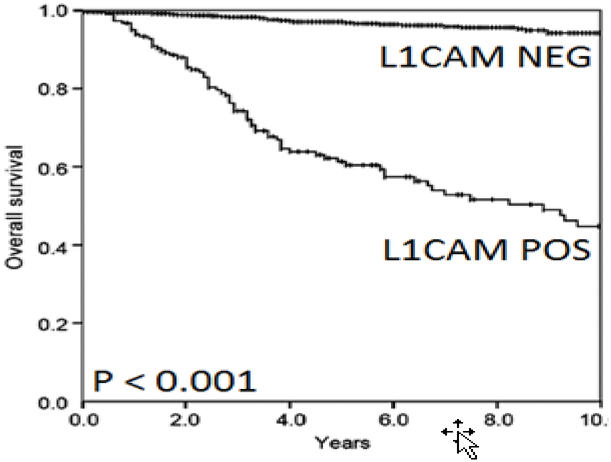
The 4 TCGA subgroups by surrogate markers



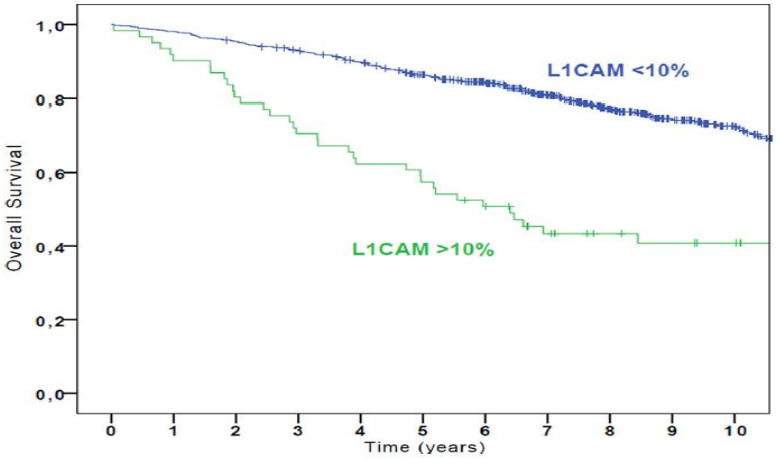
Stelloo et al, Clinical Cancer Research 2016

L1-CAM

Zeimet et al 2013



Bosse et al 2014

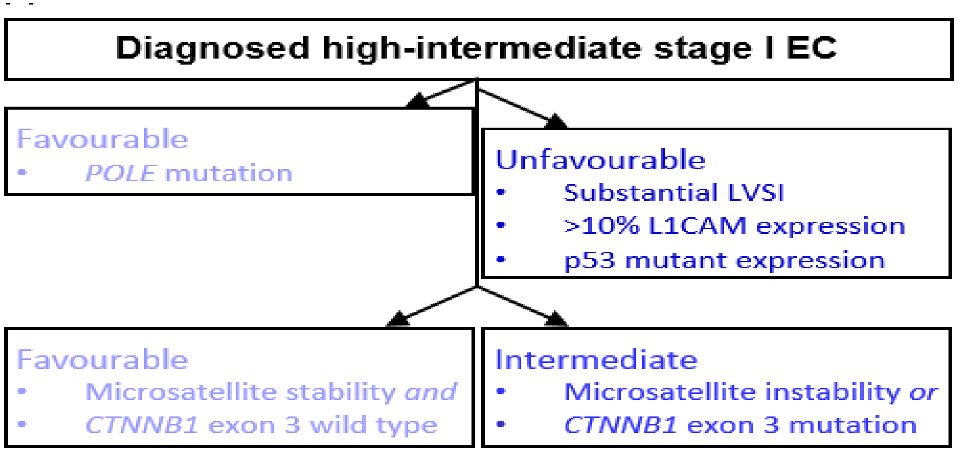


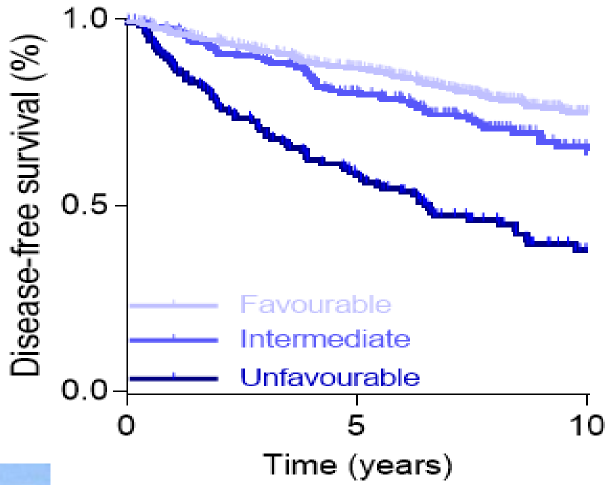
L1-CAM strong negative prognostic factor

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

ENITEC
ESGO European Network for Individualised Treatment of Endometrial Cancer

Molecular integrated risk profile PORTEC-1 and 2 cohort





- **55%** of high-intermediate r d to **favourable**
- **15%** of high-intermediate r d to **unfavourable**

PORTEC-4a trial design

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

Randomisation

2 ⇔ **1**

Individual treatment recommendation based on molecular pathology analysis

Favourable

Intermediate

Unfavourable

Observation (~55%)

Vaginal brachytherapy (~40%)

External beam radiation therapy (~5%)

Standard treatment recommendation based on clinicopathological factors

Vaginal brachytherapy

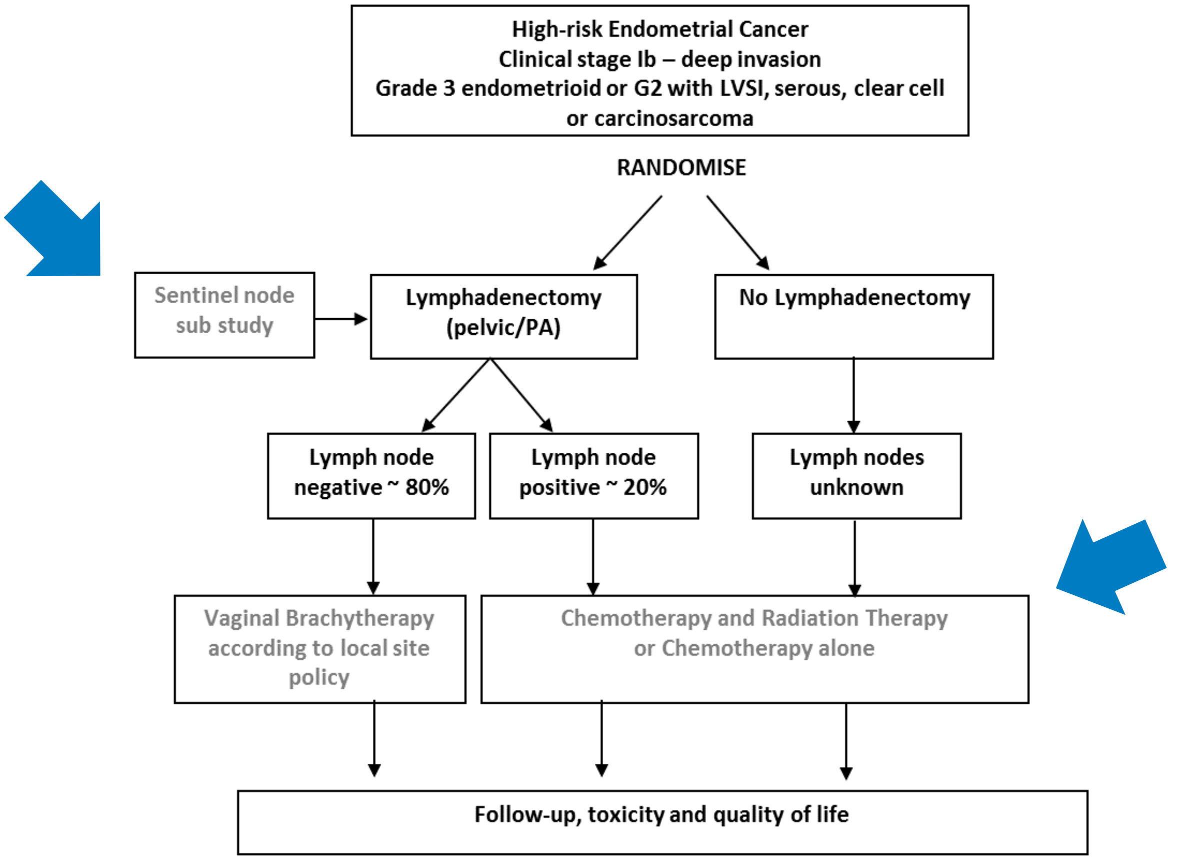
Follow-up and Quality of Life

DUTCH GOG
Dutch Gynaecological Oncology Group

DUTCH CANCER SOCIETY

PORTEC 4a

STATEC trial in high risk endometrial cancer



GYNECOLOGIC CANCER INTERGROUP

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

Thank You!

ICRU89-GEC-ESTRO recommendations for cervix cancer :

- GTV, CTVs at diagnosis and at time of brachytherapy
- OAR delineation

GUSTAVE ROUSSY

CANCER CAMPUS GRAND PARIS

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Journal of the ICRU

ICRU REPORT 89

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

OXFORD UNIVERSITY PRESS

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

OXFORD UNIVERSITY PRESS

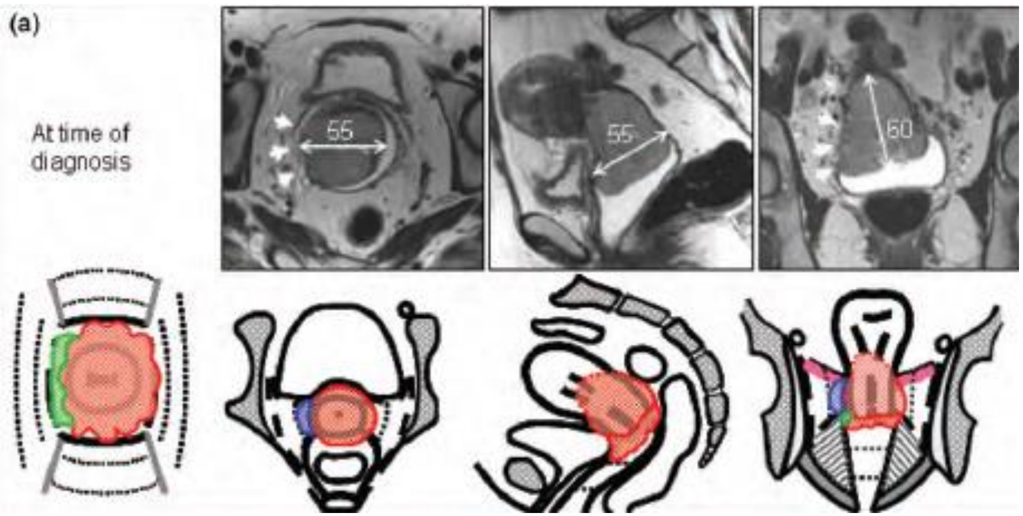
INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS

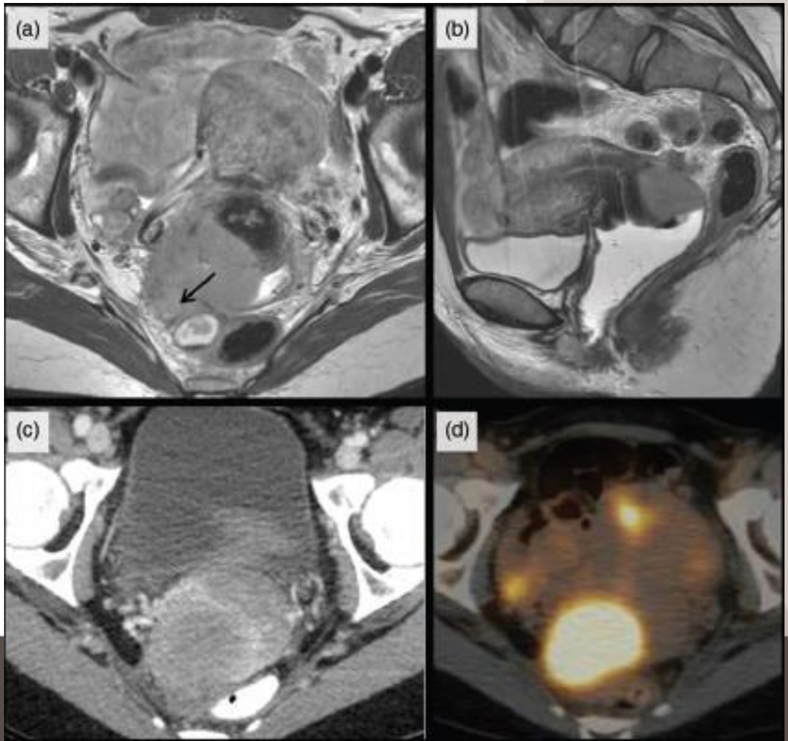
Tumor and target volume definitions for the primary tumor

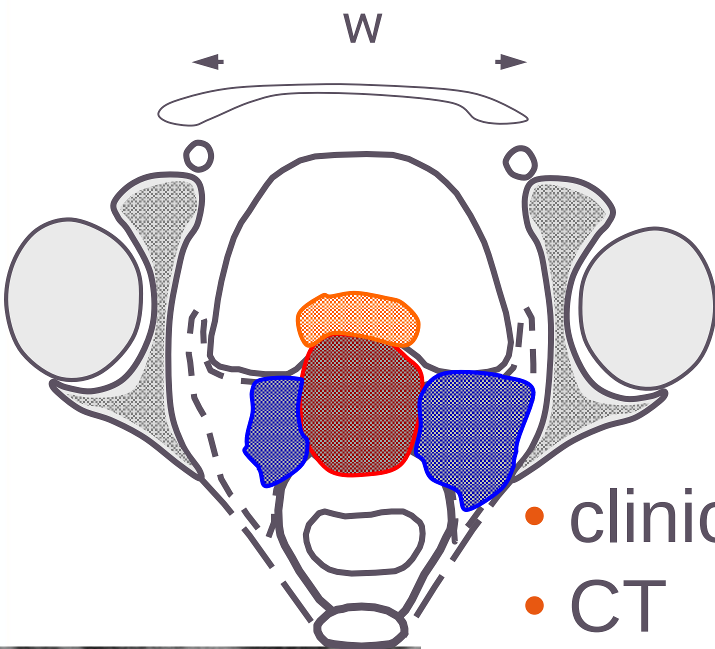
- GTV for the primary tumor (GTV-T)
- CTV for the primary tumor (CTV-T)
- Residual GTV-T ($GTV\text{-}T_{res}$)
- Adaptive CTV-T ($CTV\text{-}T_{adapt}$)
- High-Risk CTV-T ($CTV\text{-}T_{HR}$)
- Intermediate-Risk CTV-T ($CTV\text{-}T_{IR}$)
- Low-Risk CTV-T ($CTV\text{-}T_{LR}$)
- Planning Target Volume (PTV-T)

GTV for the primary tumor (GTV-T)

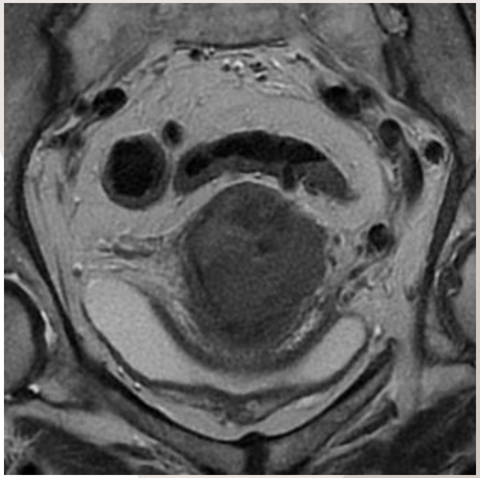
- basis for treatment prescription and planning
- clinical, imaging, and/or pathology investigations assessment
- represents macroscopic demonstrable disease for the primary tumor according to the UICC TNM classification
- composite GTV-T
- context of adaptive radiotherapy : GTV-T_{init} to distinguish this from the GTV-T_{res}





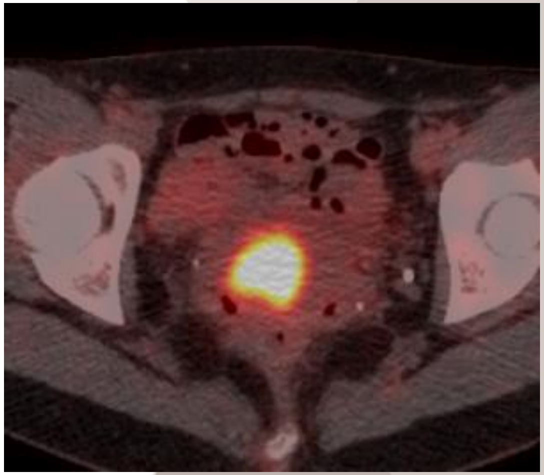


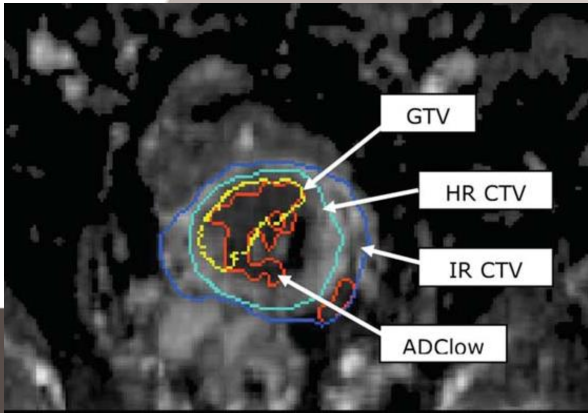
GTV_{init}



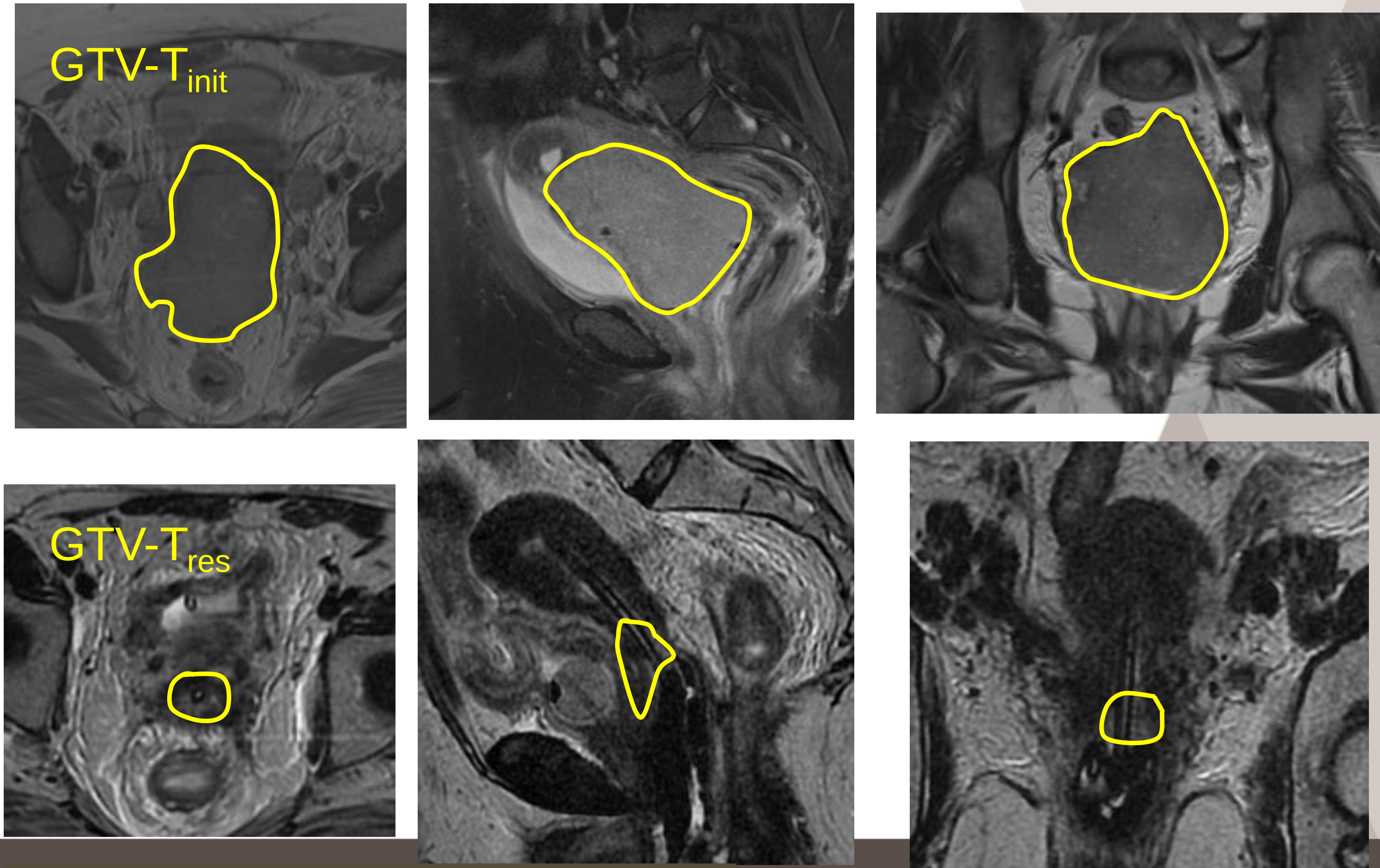
- clinical examination
- CT
- MRI
- PET-CT
- diffusion weighted MRI
- US

Composite GTV





GTV for the primary tumor
Example stage IIIB : GTV-T_{init} / GTV-T_{res}



CTV for the primary tumor (CTV-T)

- GTV and assumed sub-clinical malignant disease
- CTV-T encompasses the microscopic tumor spread at the boundary of the primary tumor GTV

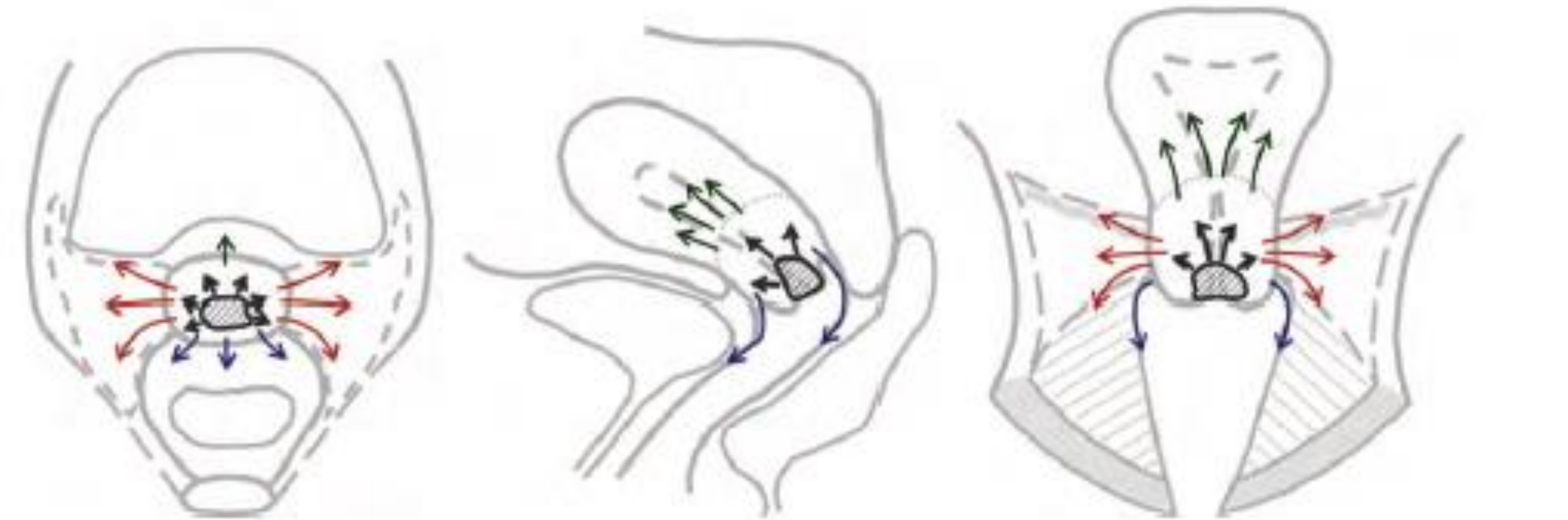


Figure 5.5. Schematic axial (left) mid-sagittal (middle) and mid-coronal (right) views of typical cervix cancer growth in—and outside—th cervix with extra-cervical infiltration into adjacent structures such as parametria, uterine corpus, vagina [see also electronic appendi Gyn GEC ESTRO Rec II (Lim *et al.*, 2011; Pötter *et al.*, 2006)].

CTV for the primary tumor (CTV-T)

Three different CTV-Ts have been defined in the GEC-ESTRO recommendations: “High Risk CTV,” “Intermediate Risk CTV,” and “Low risk CTV”

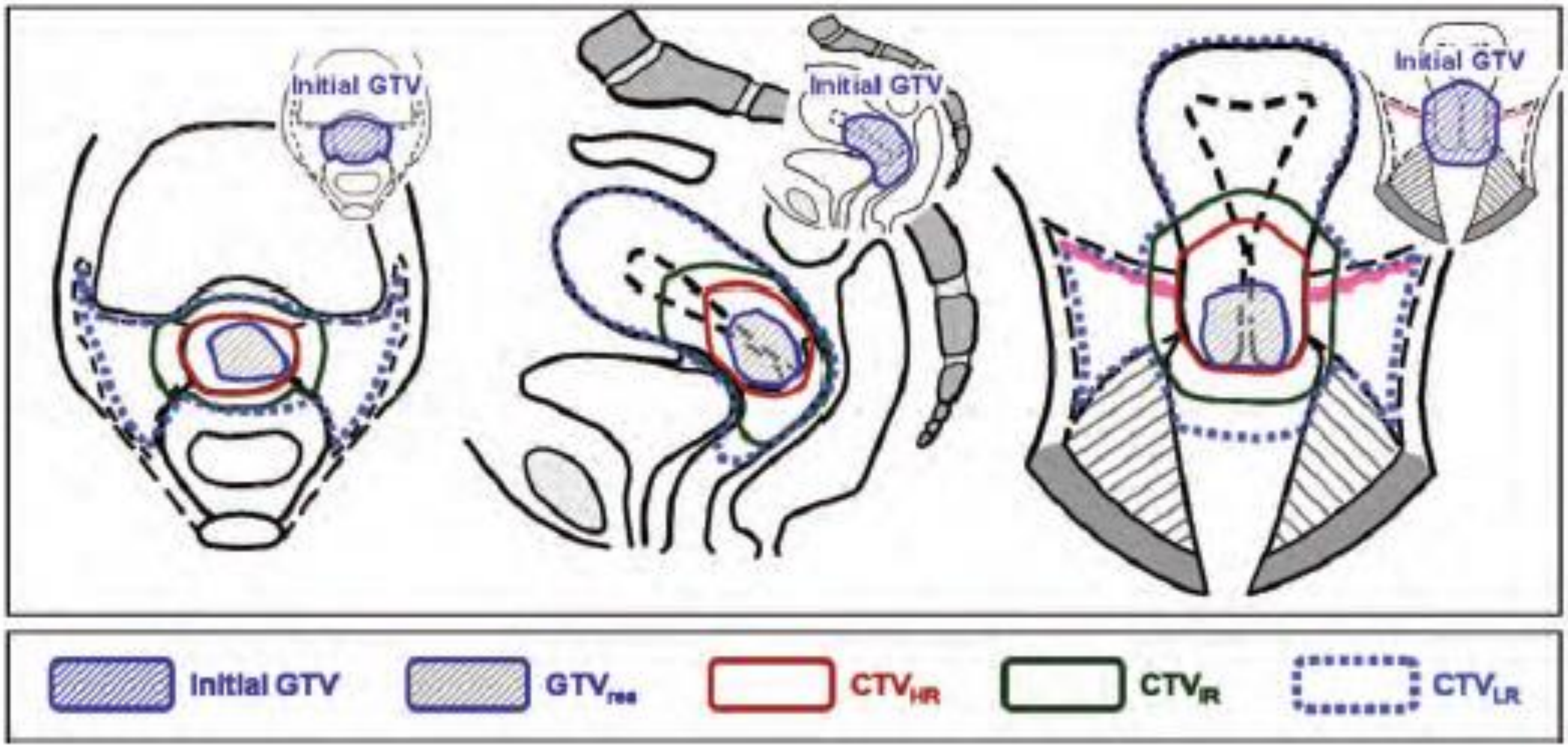
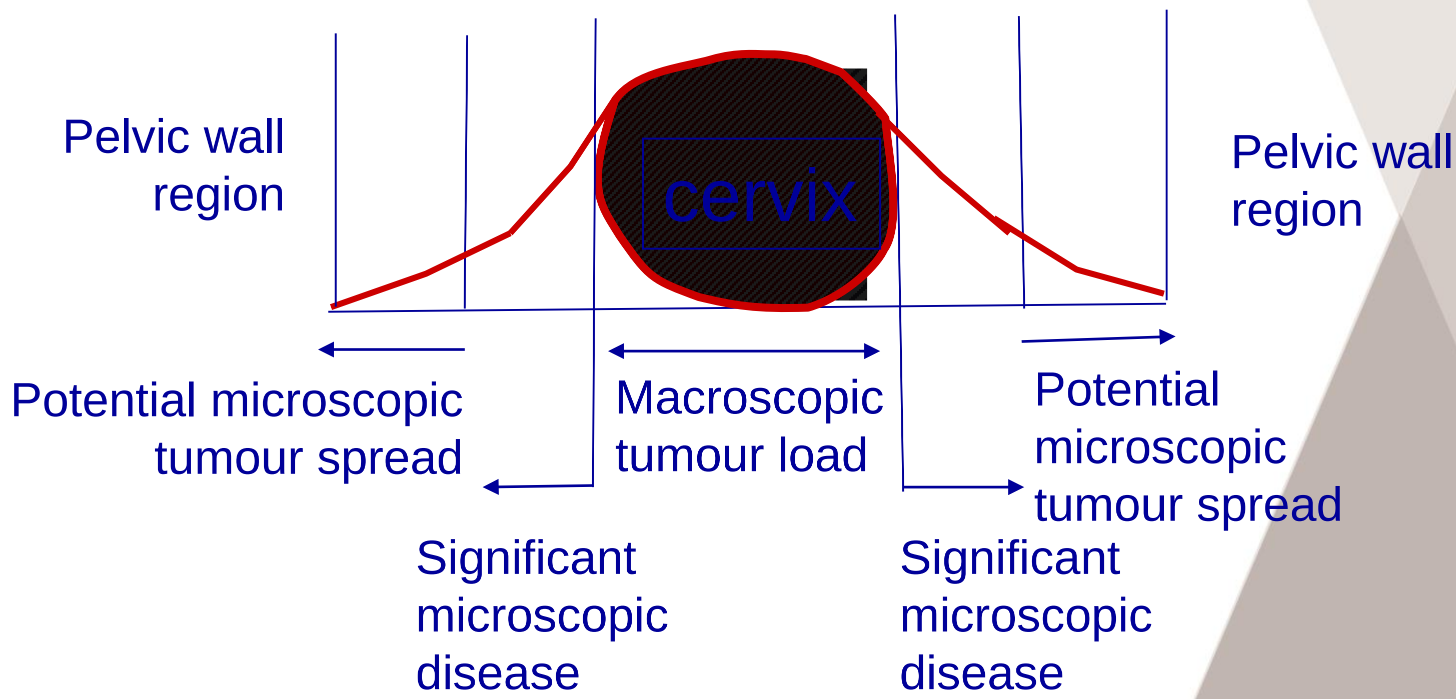


Figure 5.9. Schematic diagram for cervical cancer, Stage IB_2 (bulky disease), good response after chemo-radiotherapy: residual GTV-T ($GTV\text{-}T_{res}$), adaptive CTV-T ($CTV\text{-}T_{HR}$), initial GTV-T ($GTV\text{-}T_{init}$), intermediate risk CTV-T ($CTV\text{-}T_{IR}$) ($GTV\text{-}T_{init}$ plus margins around the $CTV\text{-}T_{HR}$), and $CTV\text{-}T_{LR}$ for adaptive brachytherapy: coronal, transversal, and sagittal view (see also Appendix Example 2 and 9).

CTVs concepts

Cancer cell density
in 3 different target volumes



CTV for the primary tumor (CTV-T)

CTV-T_{LR} for cervix cancer (for external irradiation) :

- whole uterus
- whole parametria
- upper vaginal third (if the vagina is not involved)

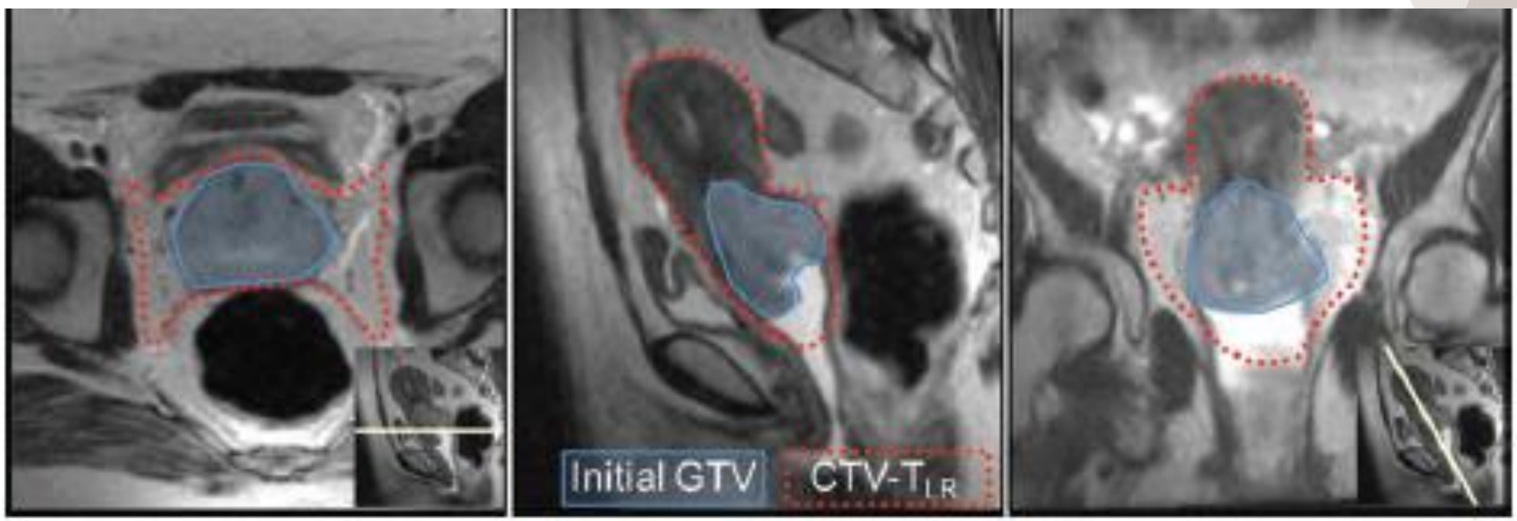
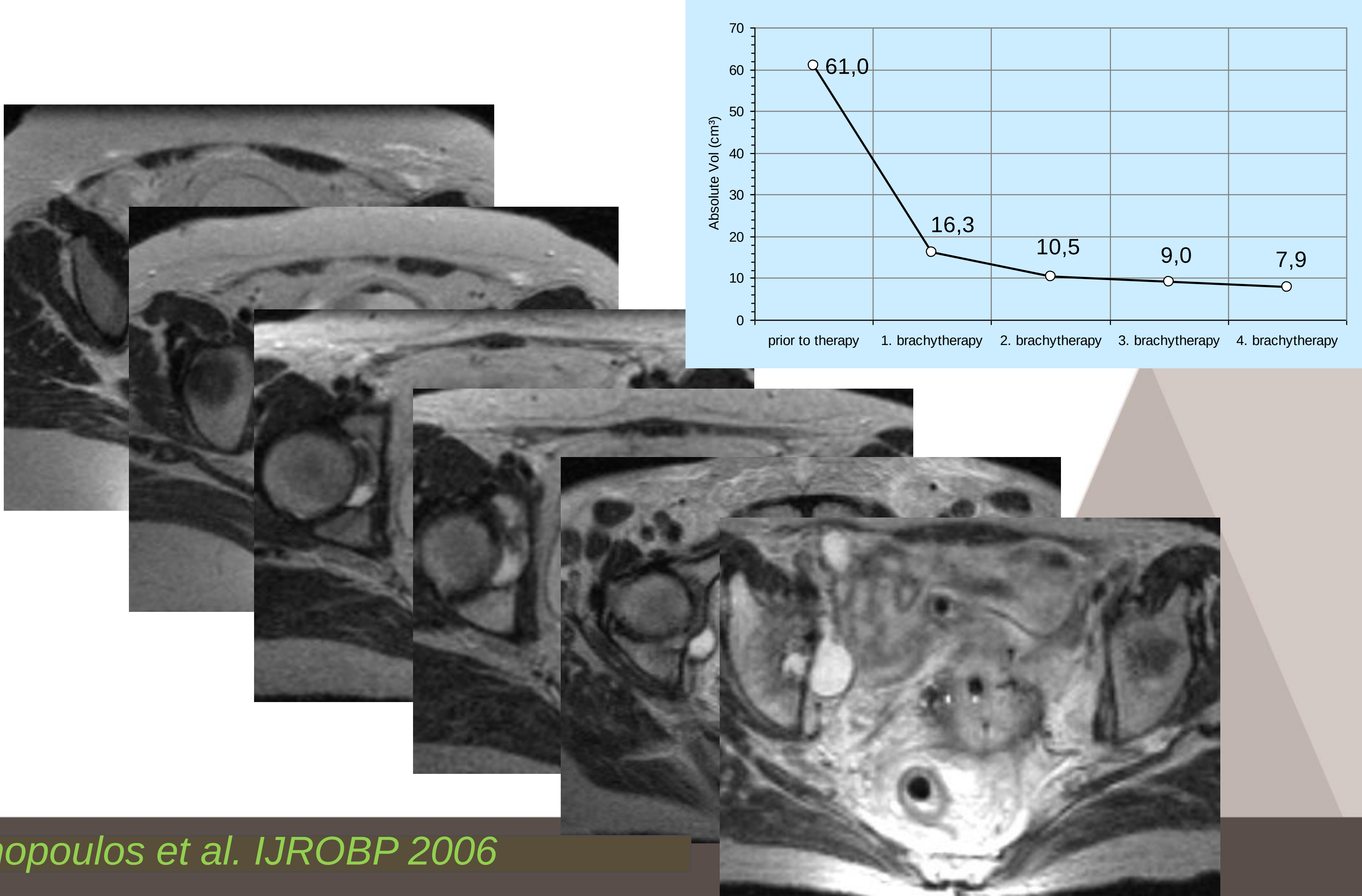


Figure 5.7. Magnetic resonance imaging at diagnosis of Stage IIB cervical cancer infiltrating both parametria with GTV-T_{init} and CTV-T_{LR} (CTV-T_3) including both parametria, uterine corpus, and upper vagina, contoured for treatment planning of EBRT.

Adaptive MRI based planning concept



Dimopoulos et al. IJROBP 2006

CTV for the primary tumor (CTV-T) : adaptive CTV-T concept

The CTV-T determination for the brachytherapy boost at the end of external therapy takes changes into account by applying the adaptive CTV-T concept with :

- $CTV\text{-}T_{HR}$
- $CTV\text{-}T_{IR}$

CTV for the primary tumor (CTV-T)

HR CTV :

- GTV **at the time of BT**
- CTV if complete response : limited to cervix
- CTV if uncomplete response : cervix plus adjacent structures with presumed residual disease - assessed by both clinical examination and imaging (~30-60 cc) including grey zones
- No safety margins
- Intent : 85 to 90 + Gy total dose to CTV in definitive radiotherapy in advanced disease
- Dose comparable with dose to point A

CTV for the primary tumor (CTV-T)

IR CTV :

- Integrates GTV **at the time of diagnosis**
- Always includes HR-CTV
- In case of major response :
  includes safety margins with regard to initial size GTV
- Intent : 60 + Gy total dose to CTV in definitive radiotherapy in advanced disease
- Dose comparable with dose to the 60Gy isodose (ICRU recommendations)

CTV for the primary tumor (CTV-T)

Intermediate Risk CTV :

GTV at time of diagnosis

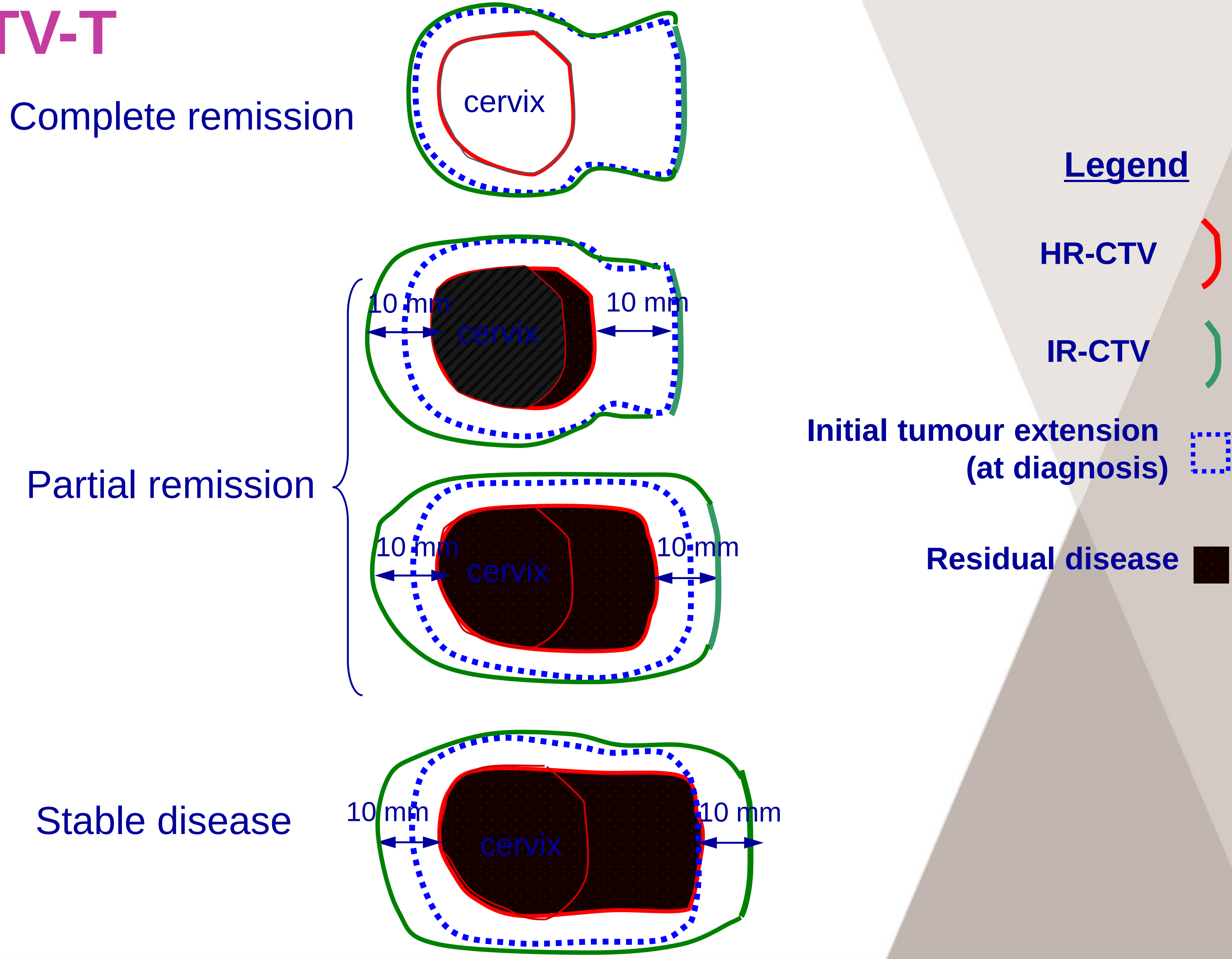
In all cases includes:

- HR-CTV
- integrates initial CTV

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

AIM : TO STERILIZE MICROSCOPIC TUMOUR

CTV-T


Complete remission
cervix
Partial remission
10 mm
10 mm
cervix
10 mm
10 mm
cervix
Stable disease
10 mm
10 mm
cervix
Legend
HR-CTV
IR-CTV
Initial tumour extension
(at diagnosis)
Residual disease

Patient n° 1

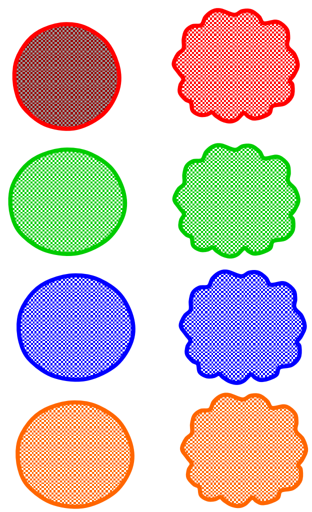
Mrs Odette TAM…
56 year-old
WHO=0, 70 kg, 1m69

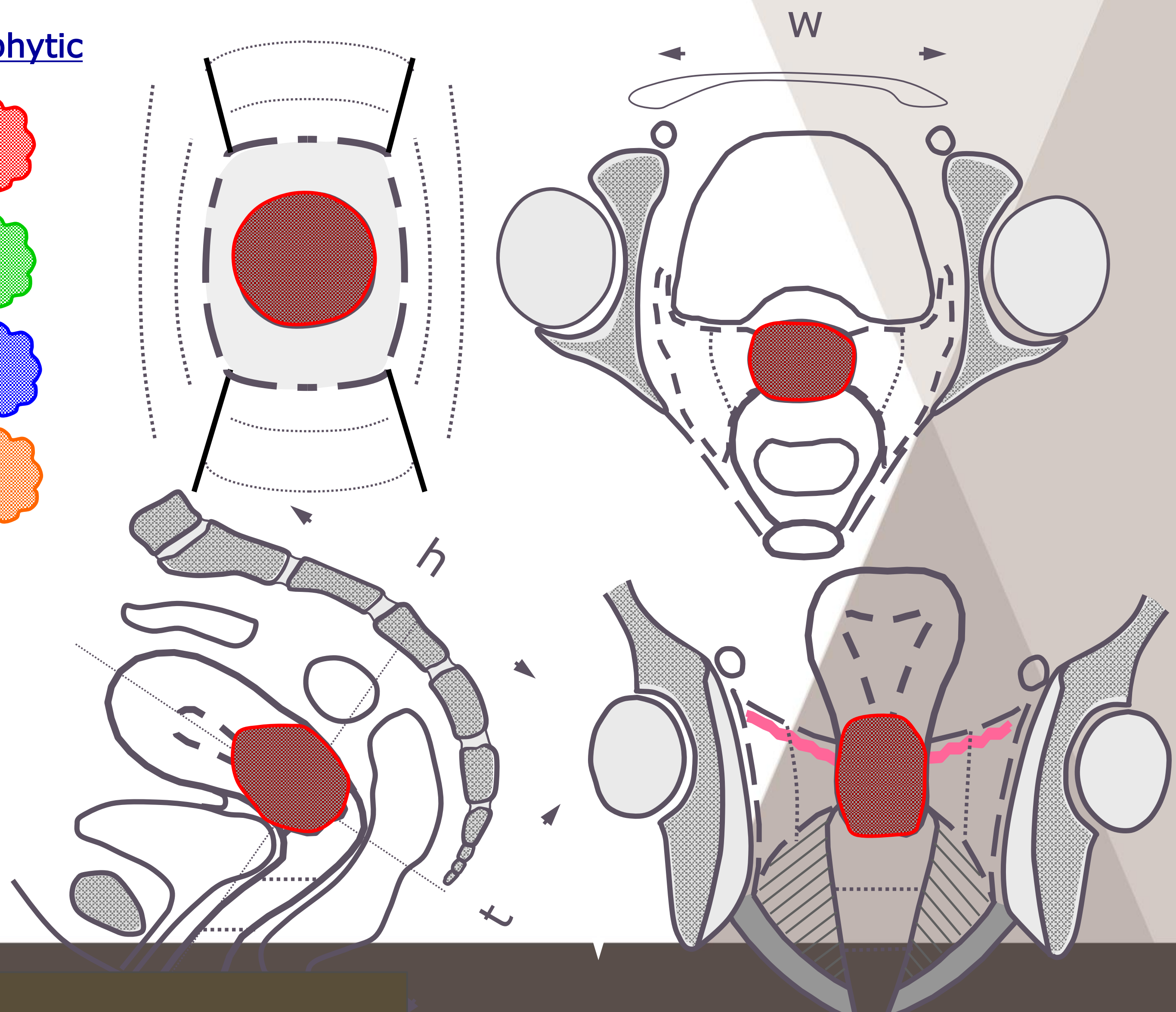
Vaginal bleeding

Biopsy: moderately differentiated squamous cell carcinoma

Stage IB1 : initial clinical examination

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		





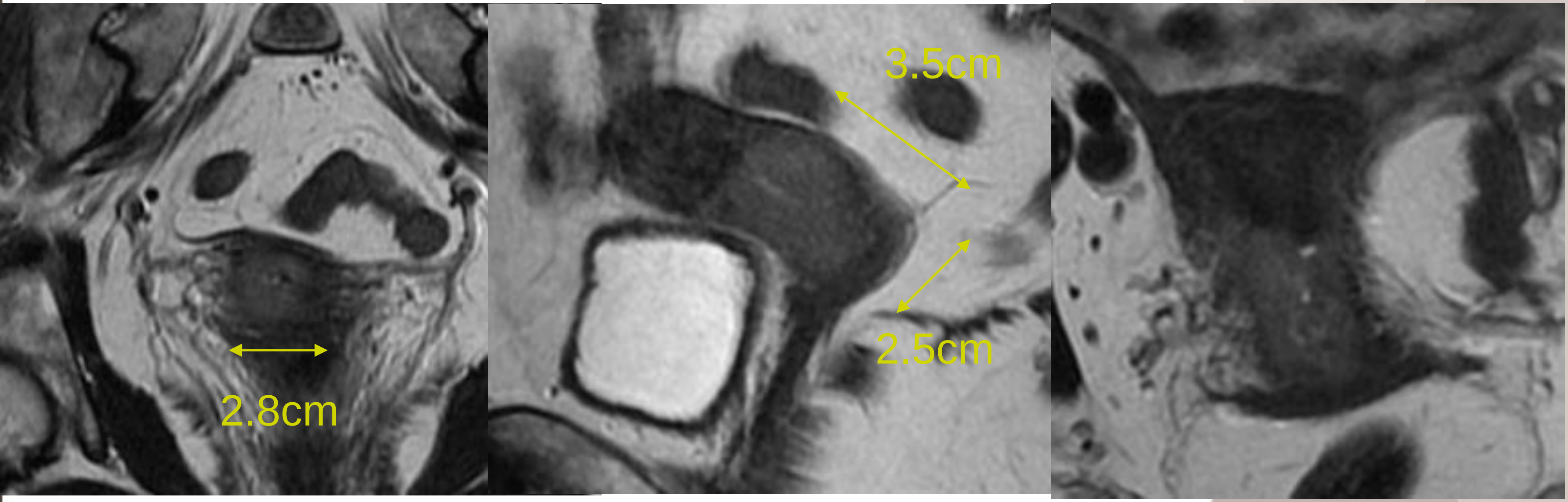
Dimensions (cm):

Width : 3

Thickness : 2.5

Height : 3

Stage IB1



Stage IB1 : at the time of brachytherapy

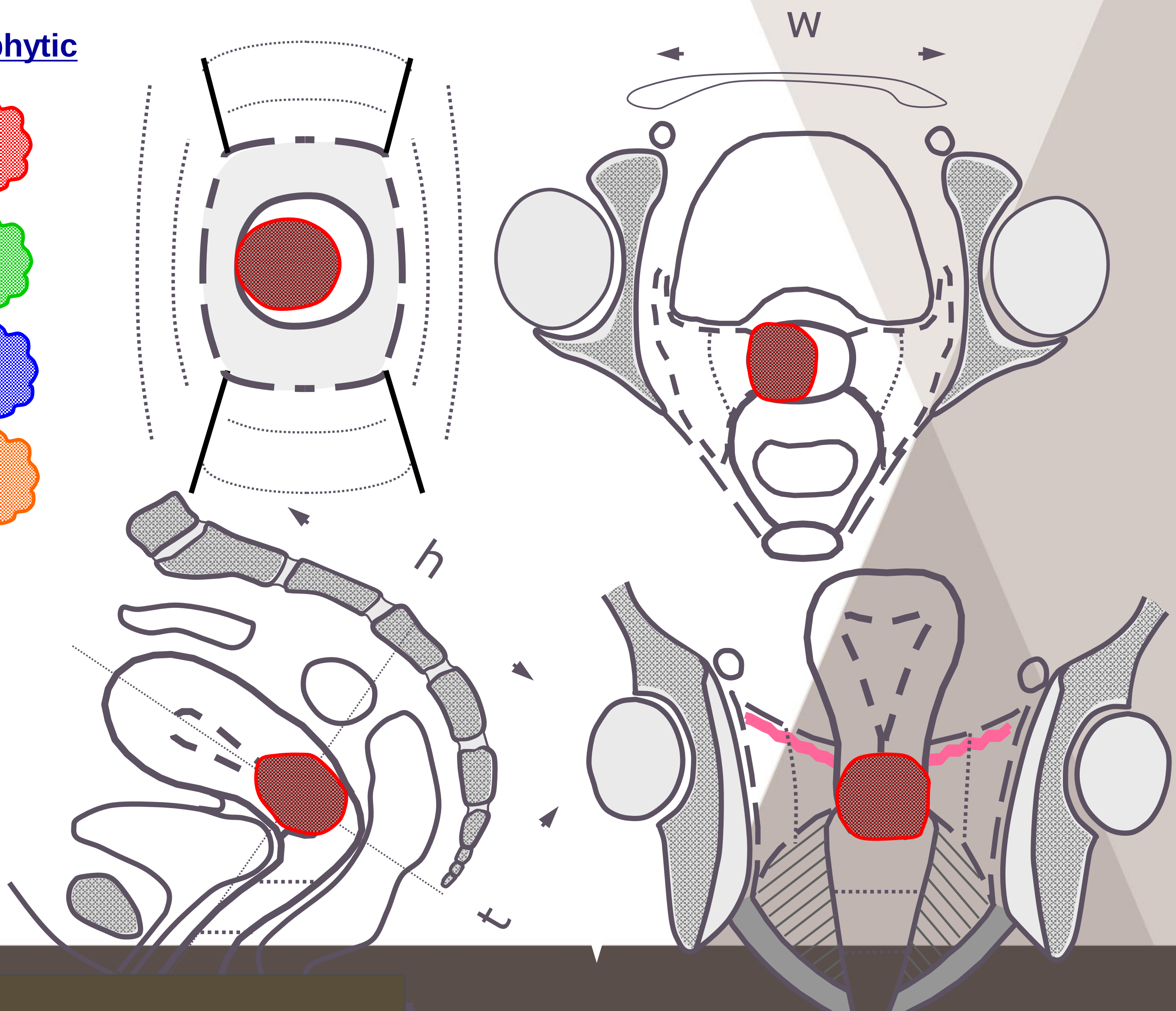
	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

Dimensions (cm):

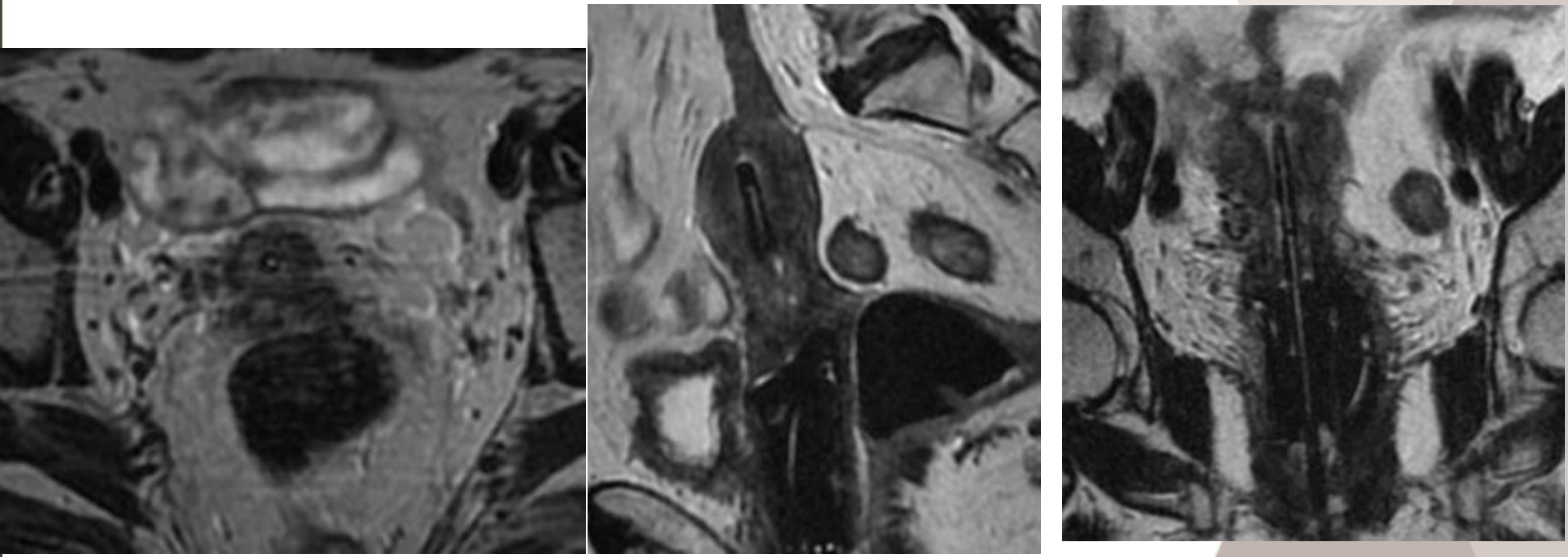
Width : 1.5

Thickness : 2

Height : 1.5



Stage IB1



Target volume concepts

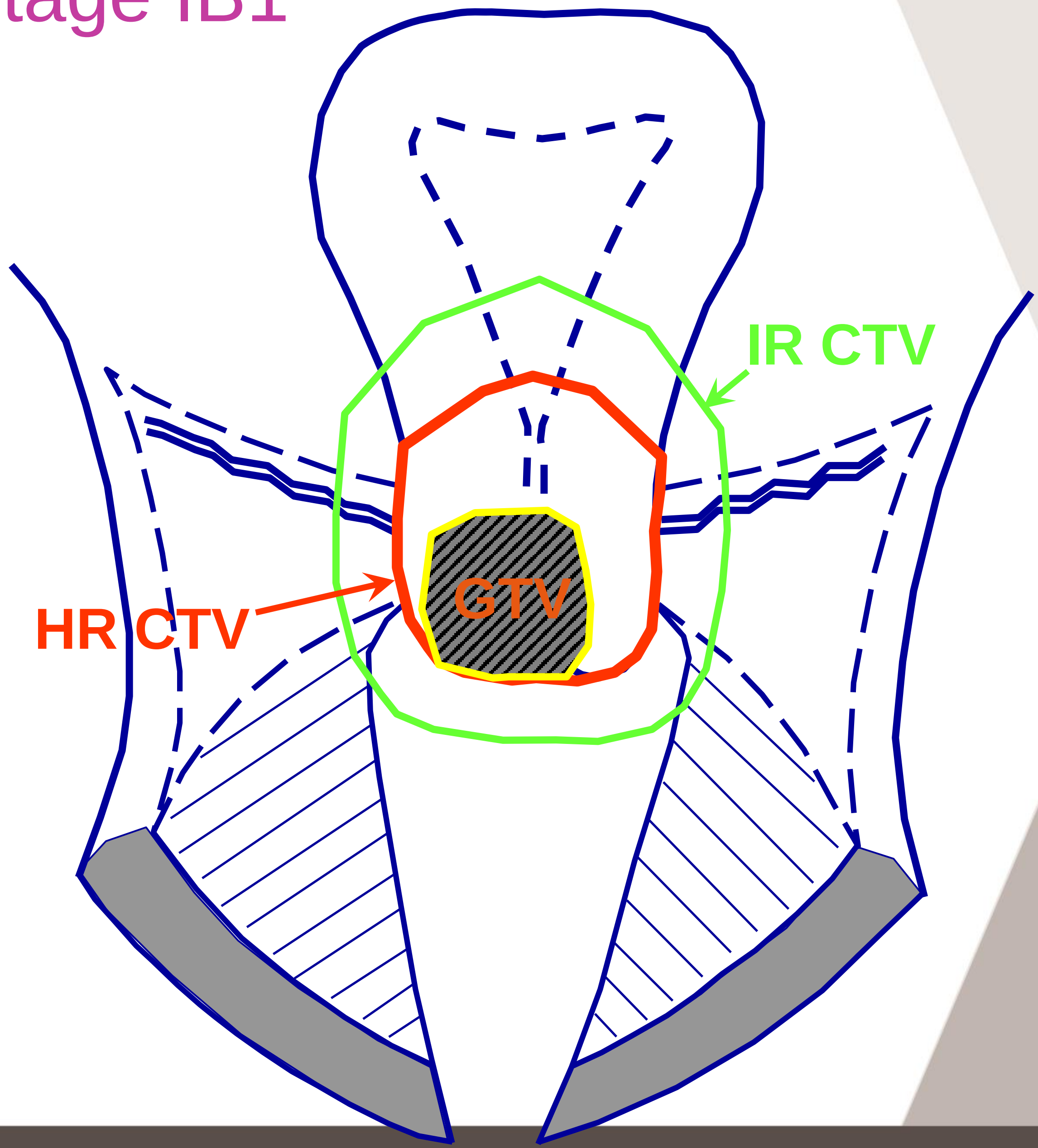
High Risk CTV :
GTV at time of brachytherapy
In all cases includes:
- Whole cervix
- [Presumed tumour extension (=0)]
- Clinical assessment
- [Residual grey zones on MRI]

NO SAFETY MARGINS

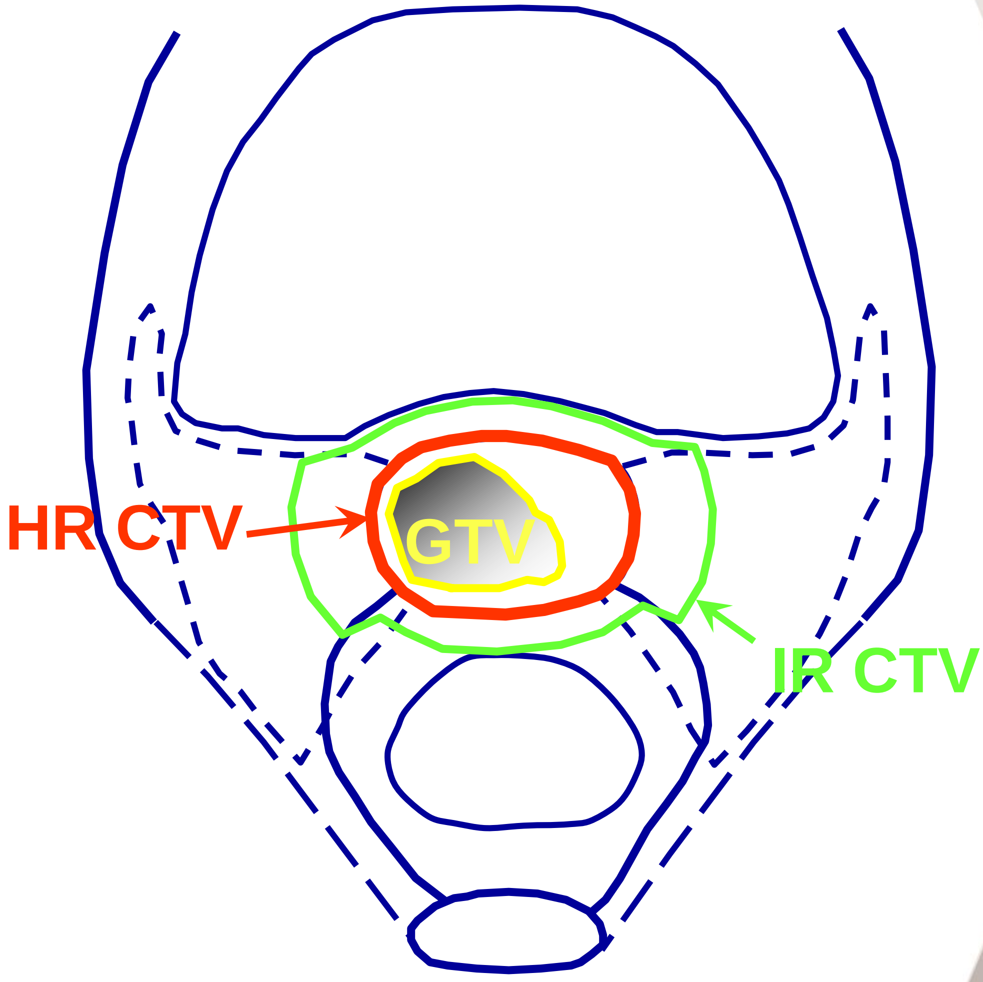
Intermediate Risk CTV :
GTV at time of diagnosis
In all cases includes:
- HR-CTV
- integrates initial CTV

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

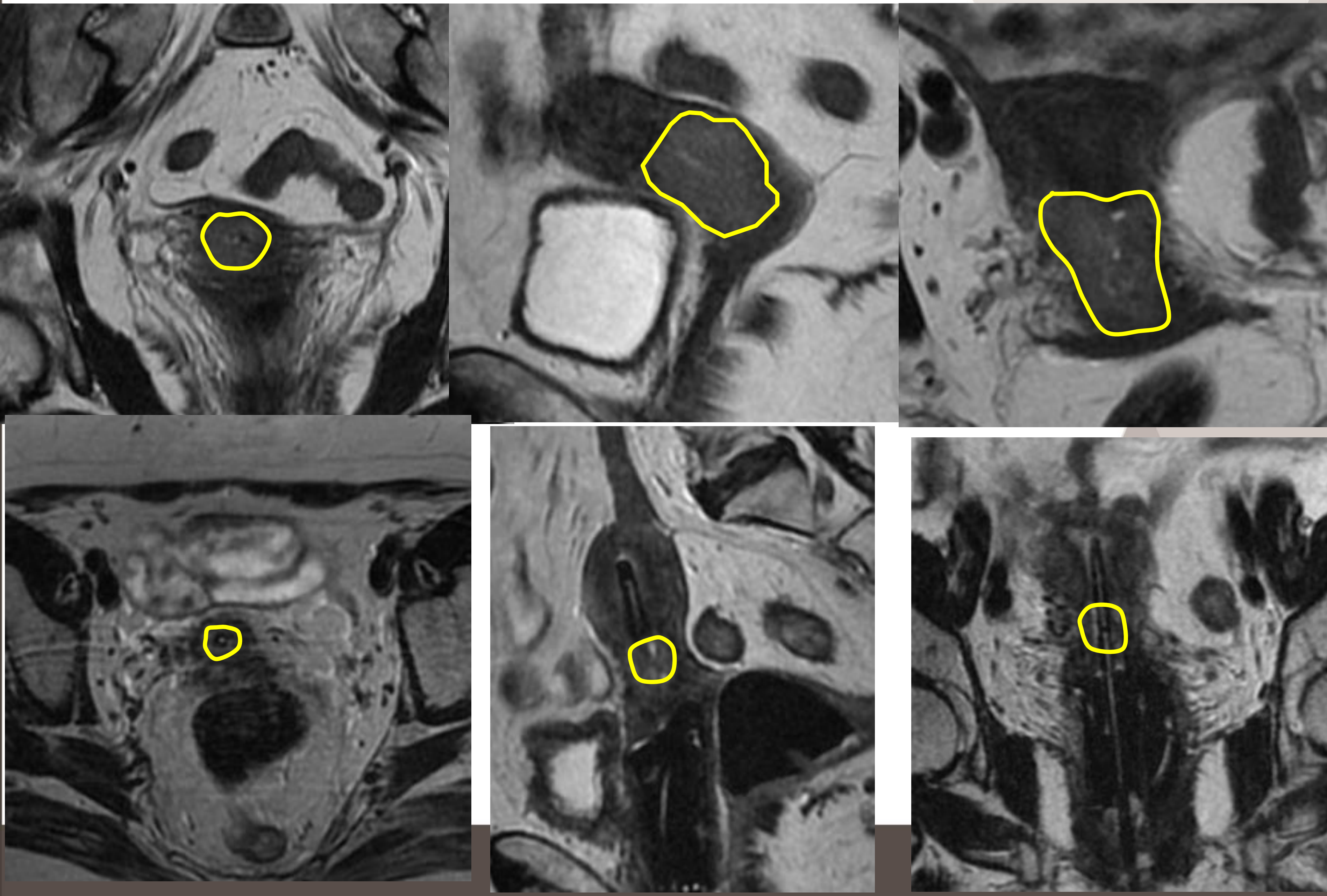
Stage IB1



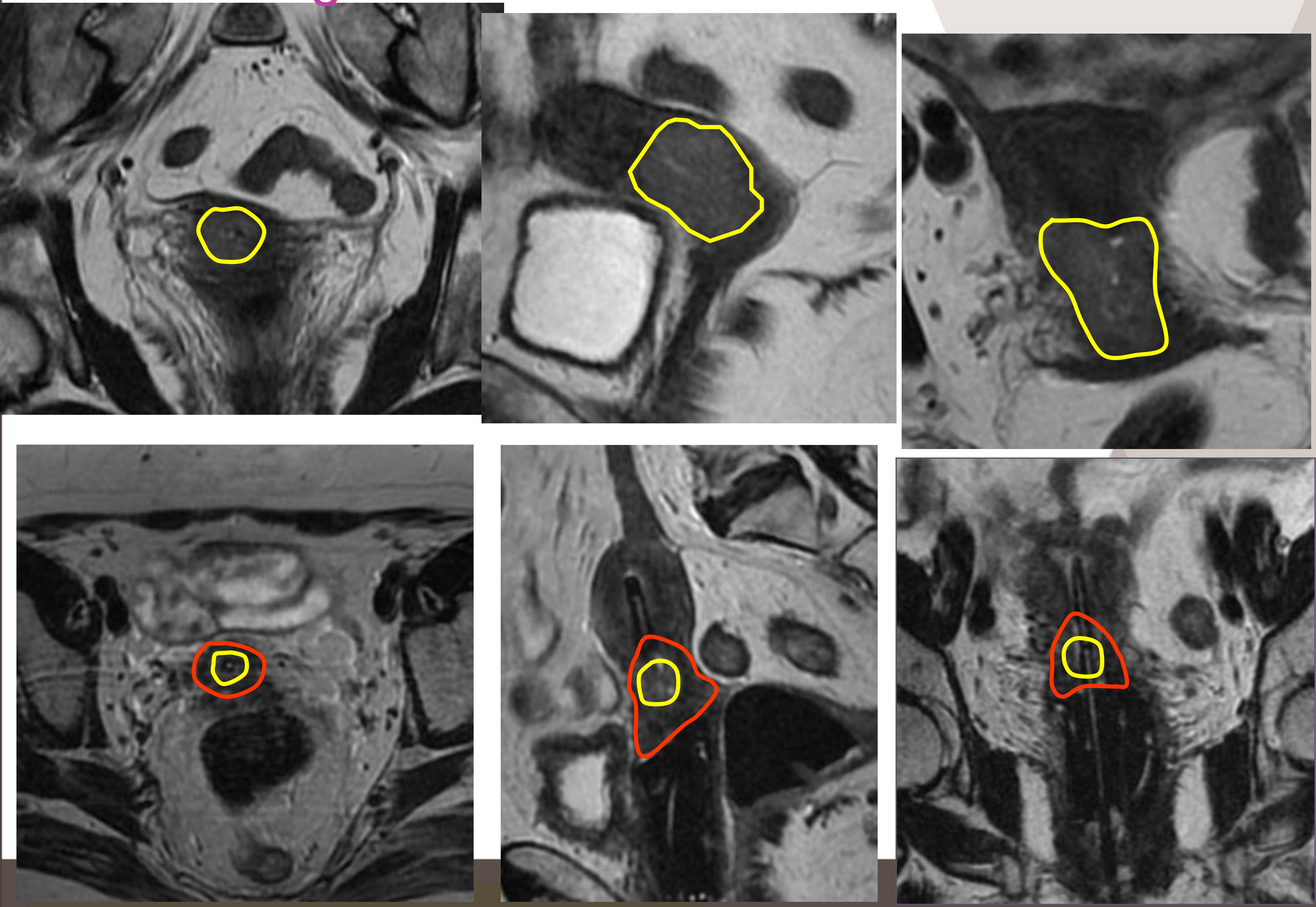
Stage IB1



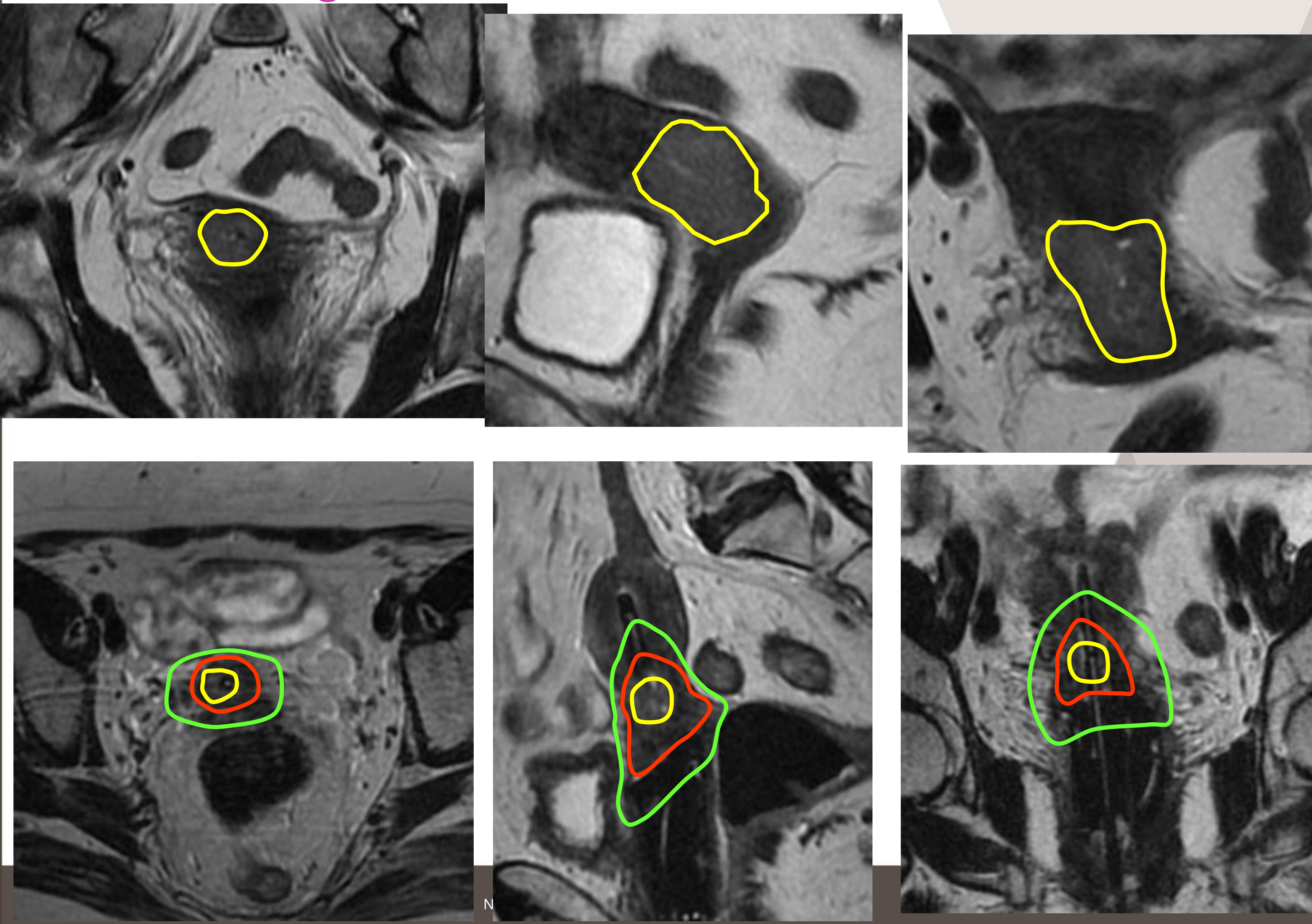
Stage IB1



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

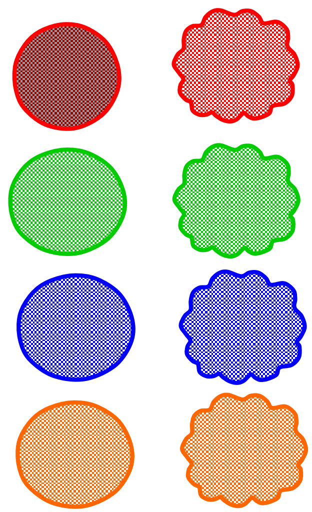
Infiltrating Exophytic

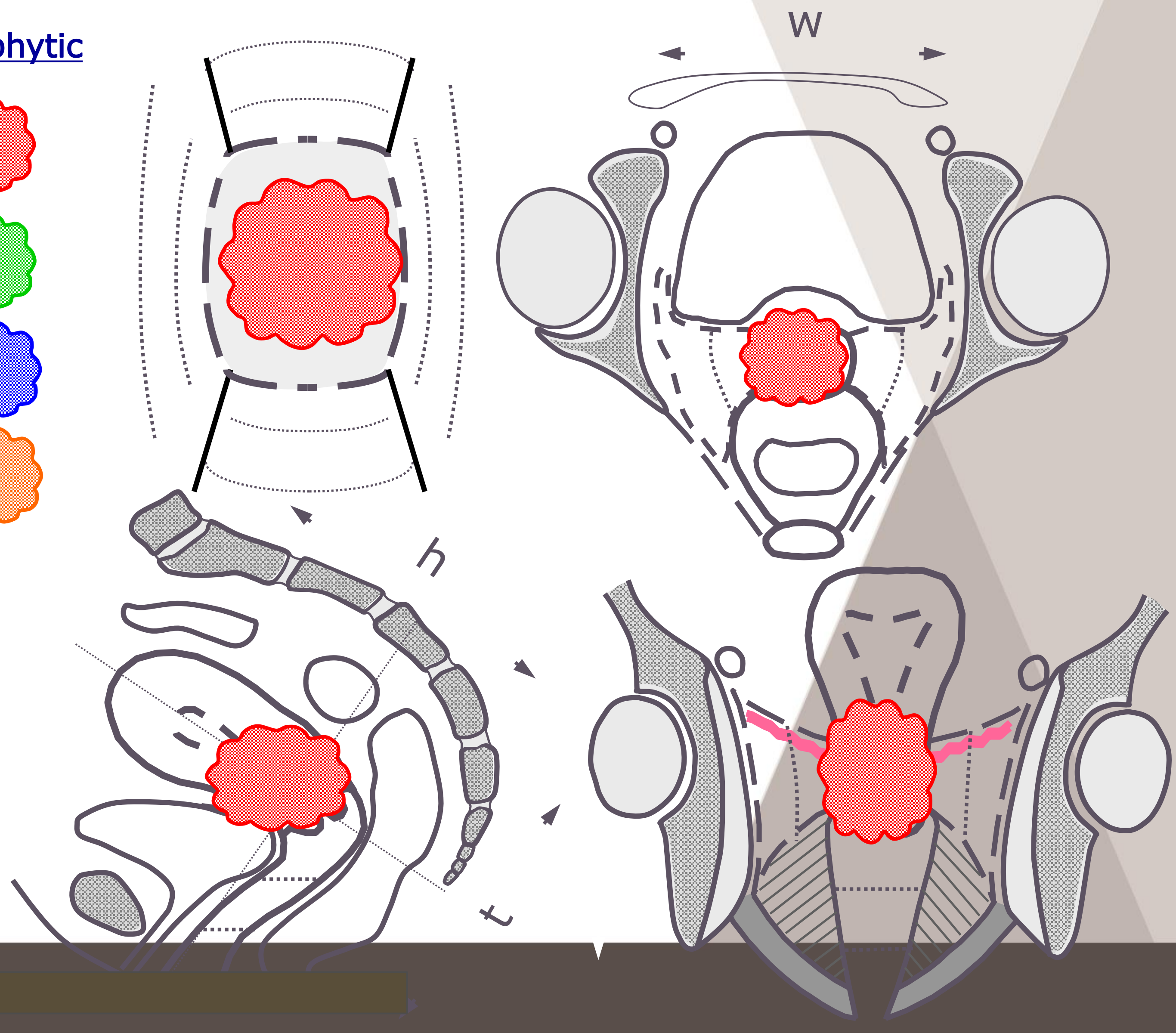
Cervix

Vagina

Parametrium

Rectum or Bladder





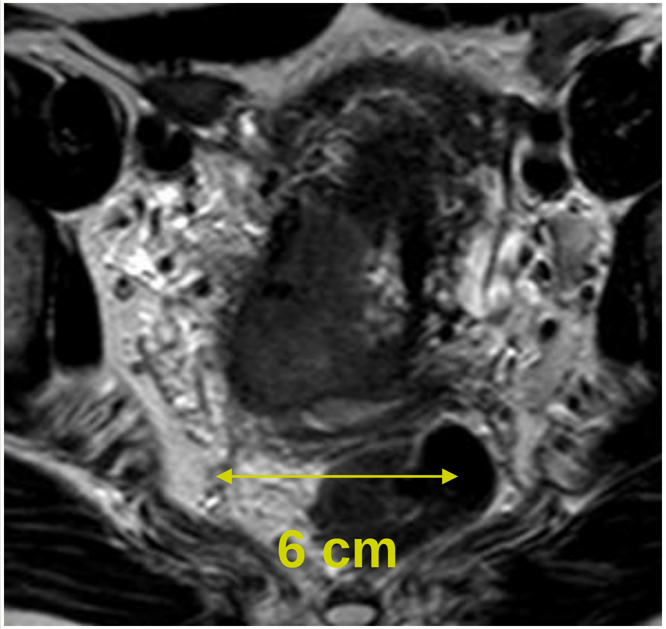
Dimensions (cm):

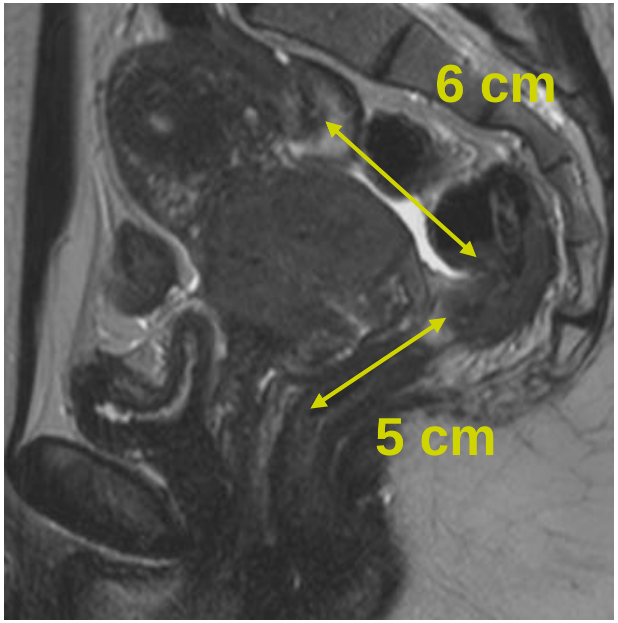
Width : 6

Thickness : 5

Height : 5

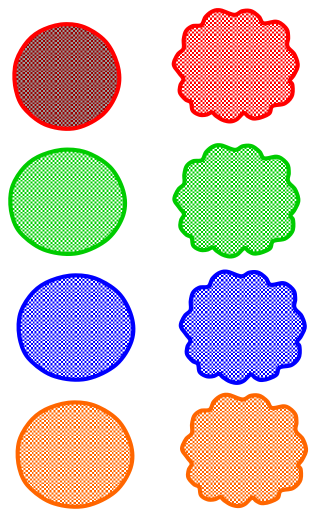
Stage IB2 : initial MRI





Stage IB2 : at the time of brachytherapy

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

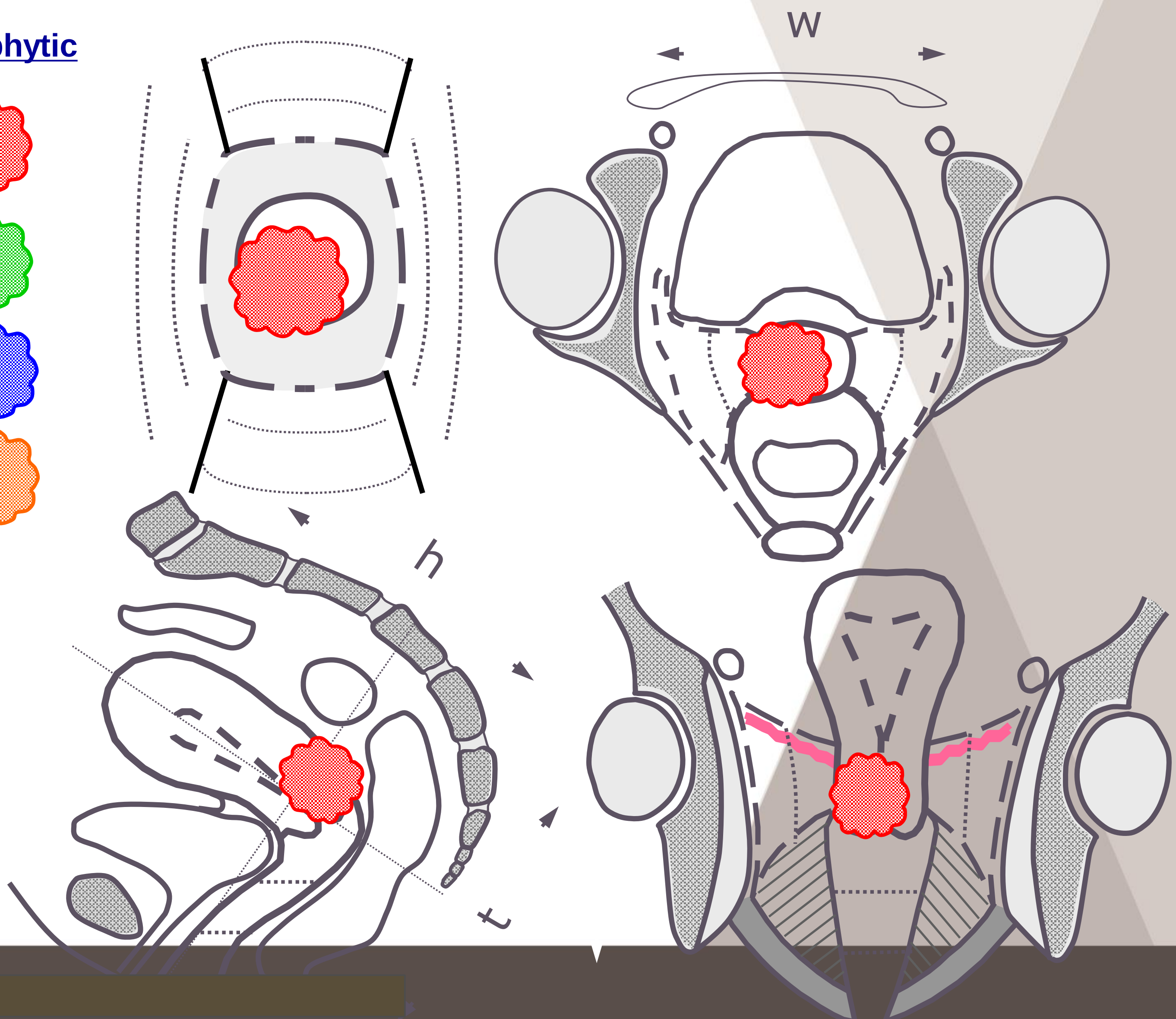


Dimensions (cm):

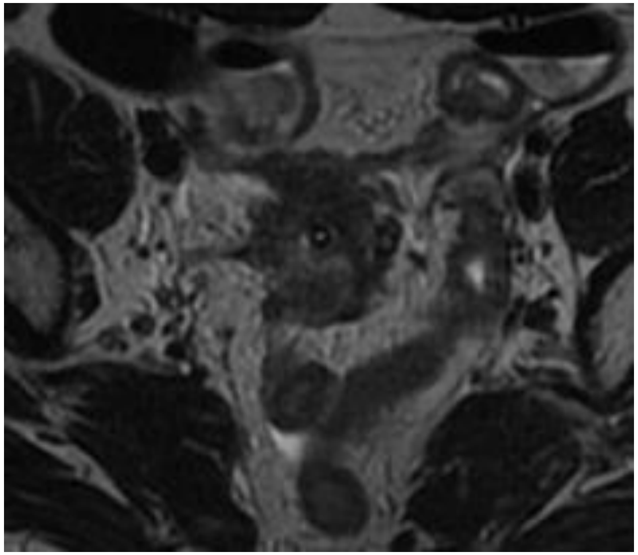
Width : 2.5

Thickness : 2

Height : 2.5



Stage IB2 : at the time of brachytherapy



In this patient HR-CTV includes:

A. the initial tumor extension
B. the whole cervix+ safety margins
C. the whole cervix only
D. the whole uterus

in this patient IR-CTV includes:

A. the whole cervix + initial tumor extension
B. the whole cervix + safety margins
C. the whole cervix only
D. the whole uterus

Target volume concepts

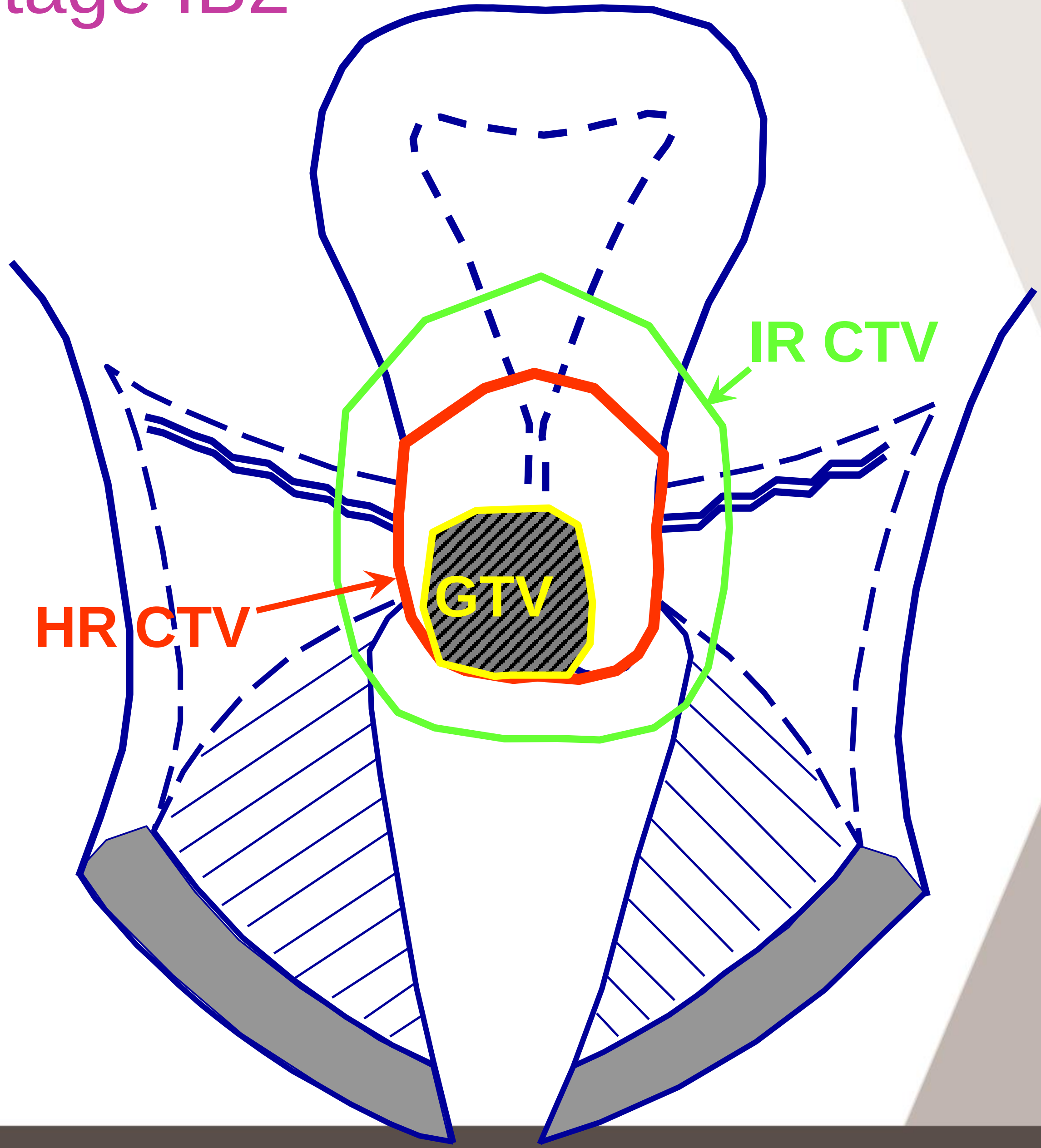
High Risk CTV :
GTV at time of brachytherapy
In all cases includes:
- Whole cervix
- Presumed tumour extension (=0)
- Clinical assessment
- (Residual grey zones on MRI)

NO SAFETY MARGINS

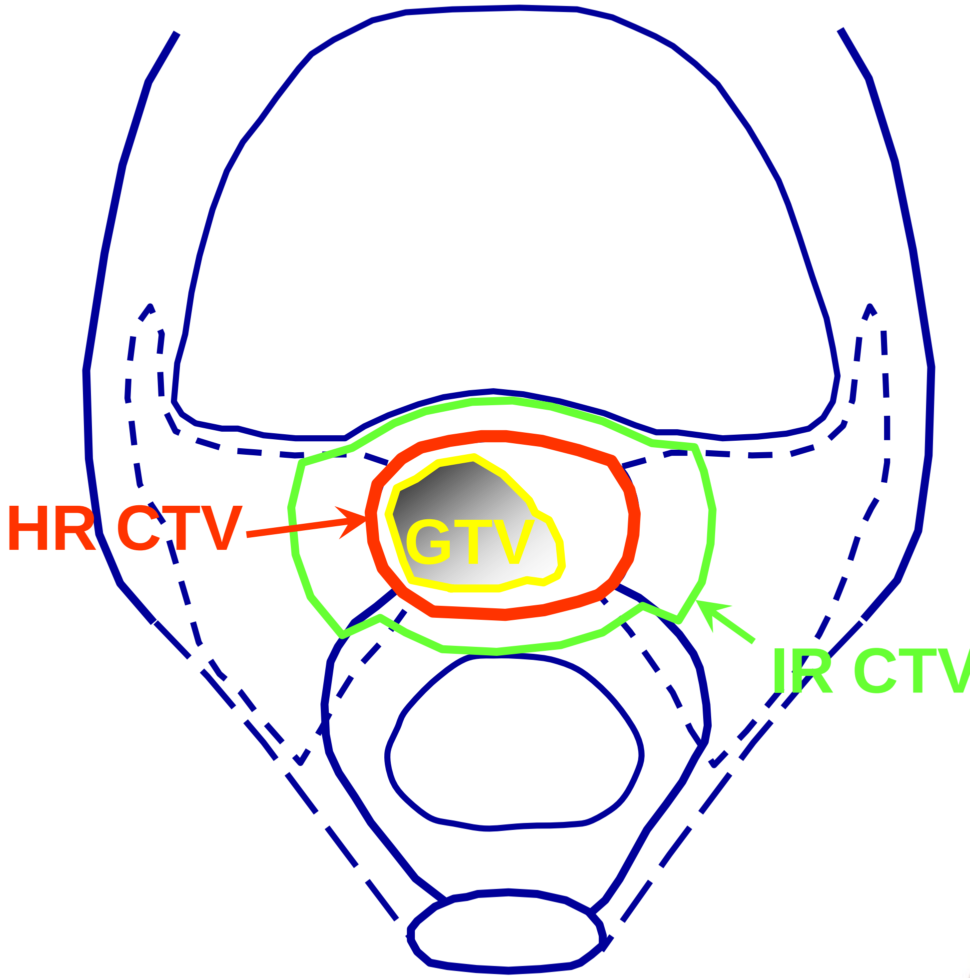
Intermediate Risk CTV :
GTV at time of diagnosis
In all cases includes:
- HR-CTV
- integrates initial CTV

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

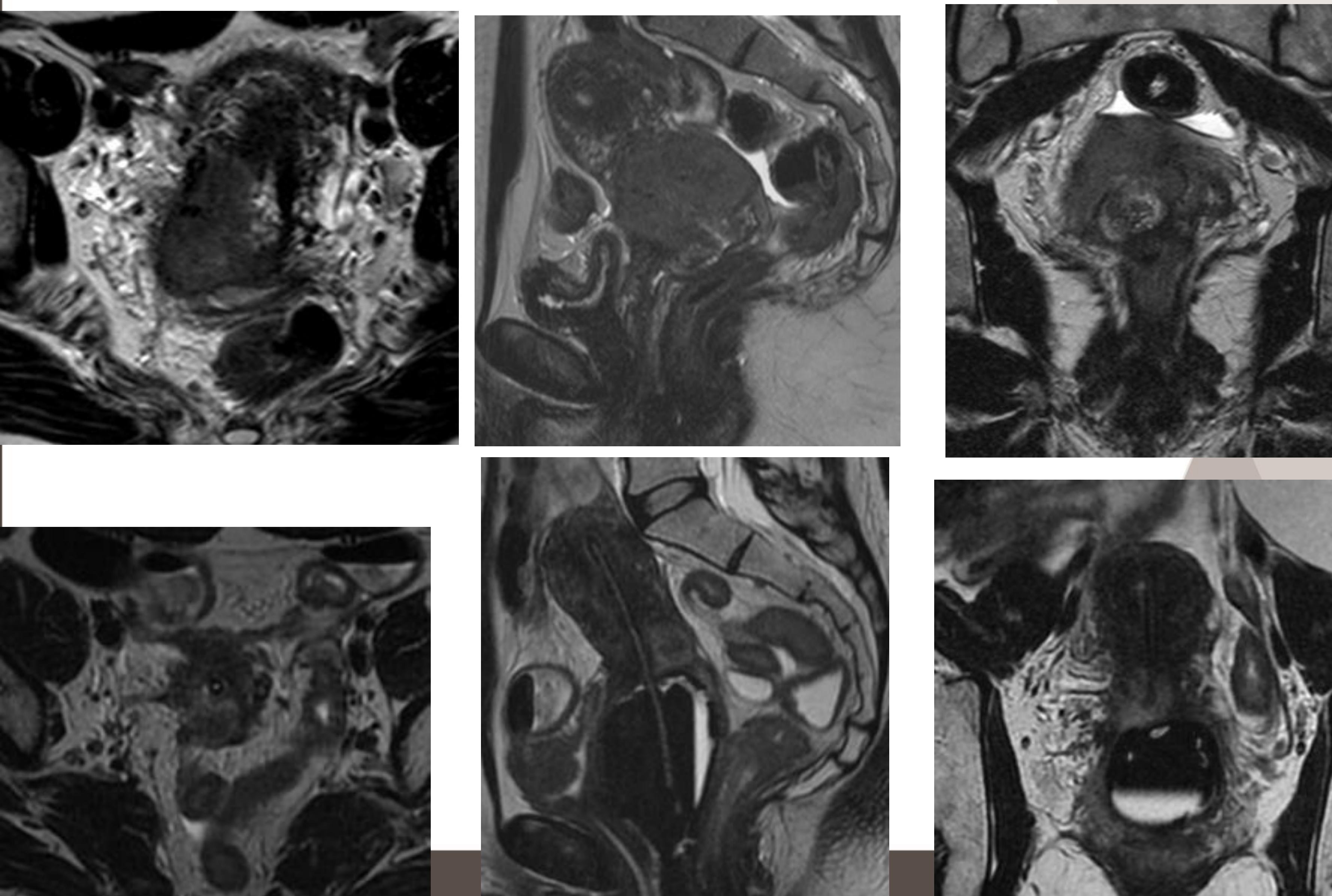
Stage IB2



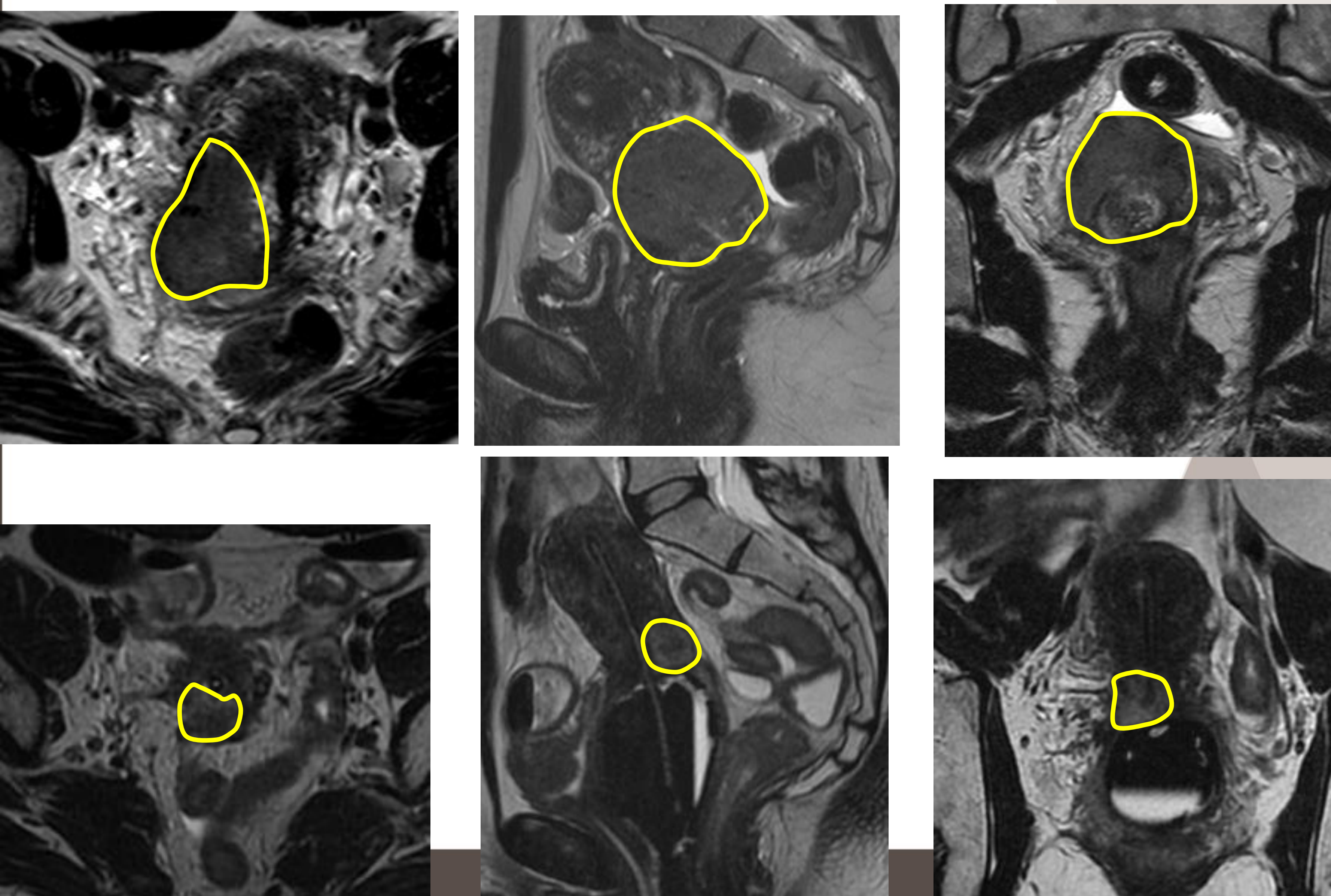
Stage IB2



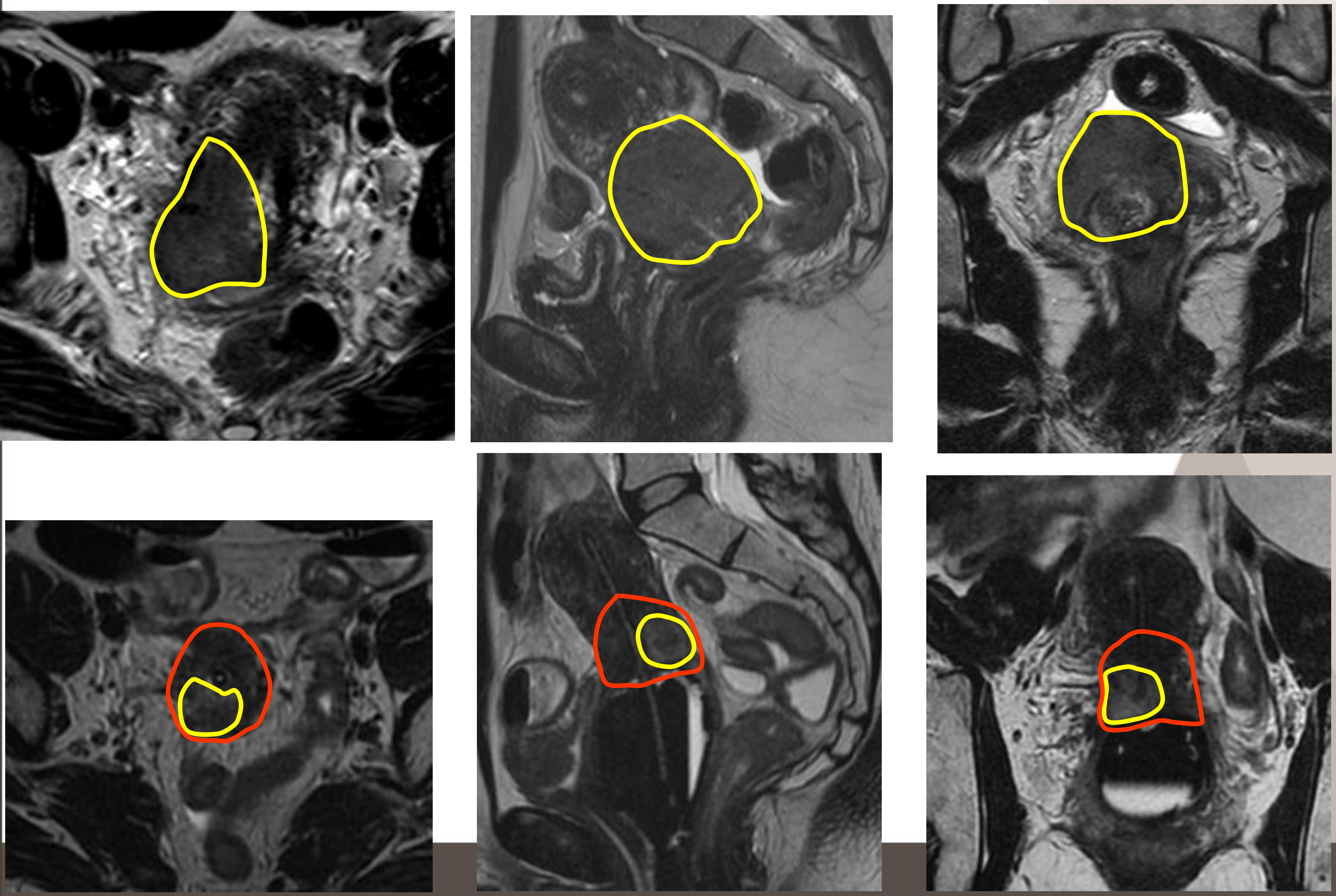
Stage IB2



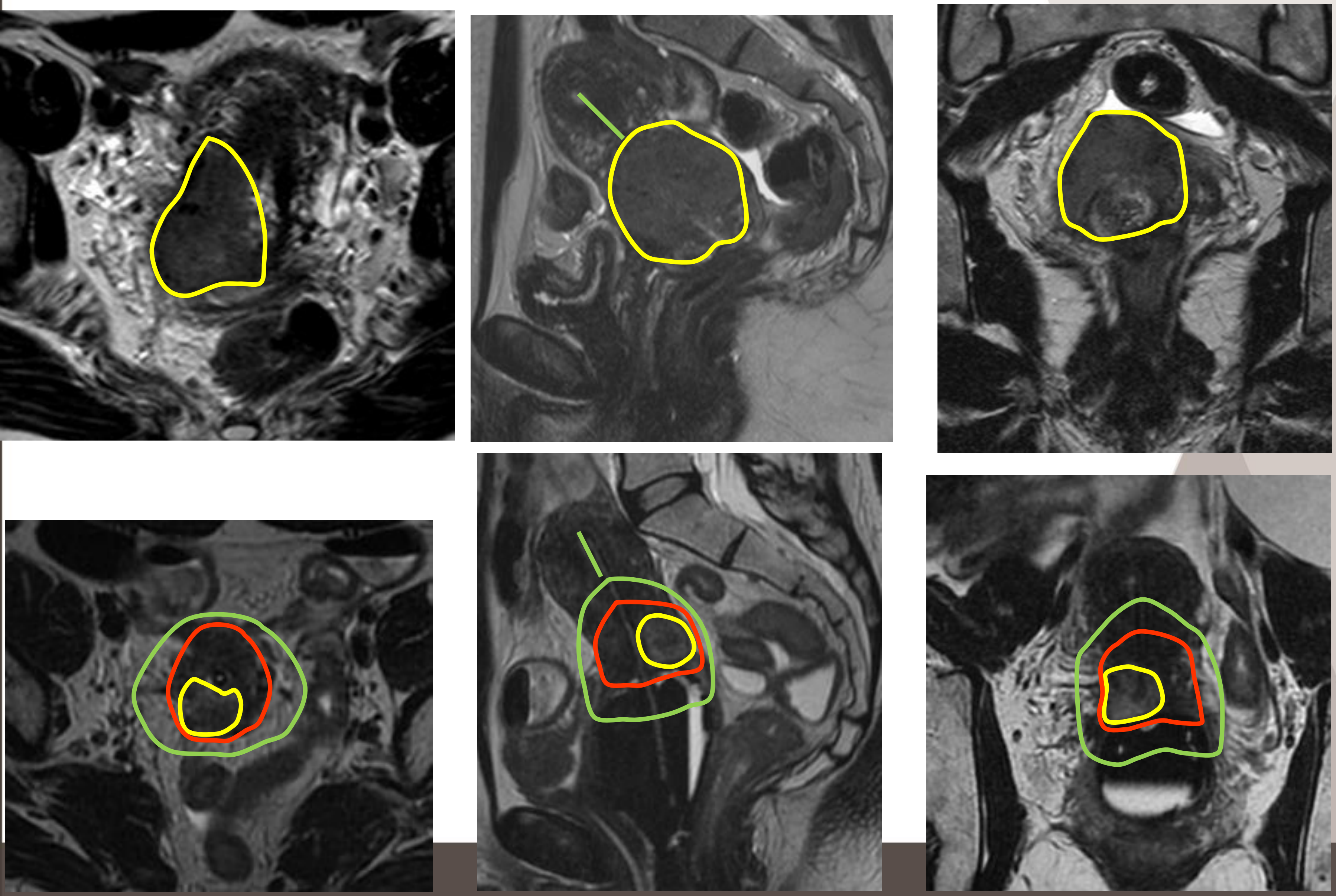
Stage IB2



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

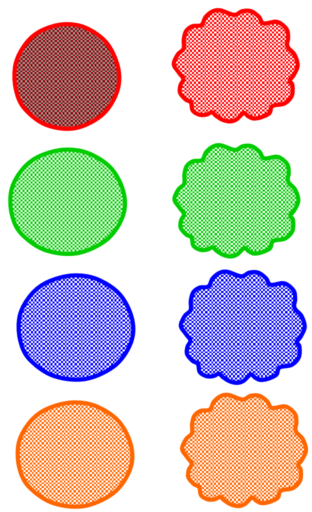
Infiltrating **Exophytic**

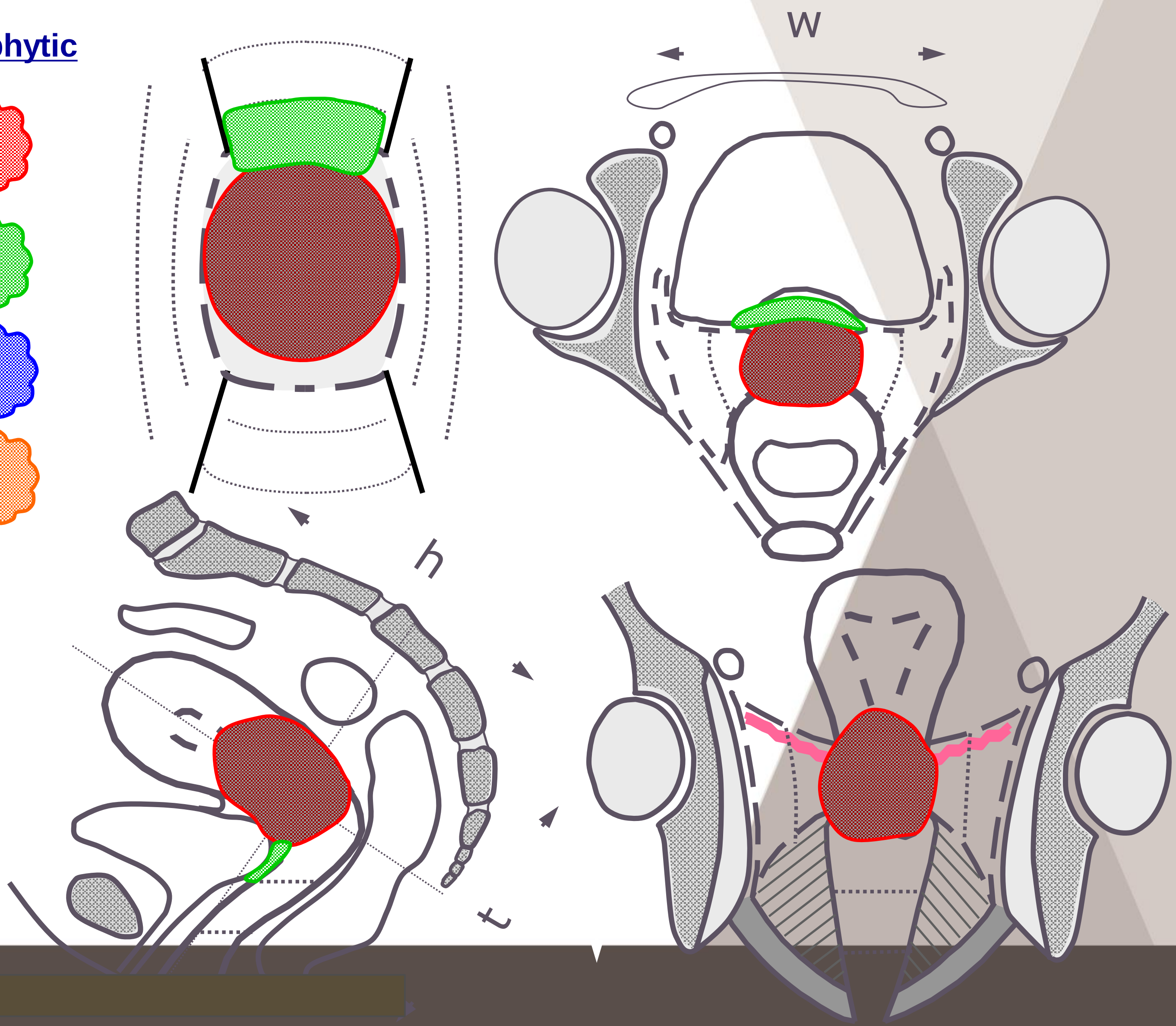
Cervix

Vagina

Parametrium

Rectum or Bladder





Dimensions (cm):

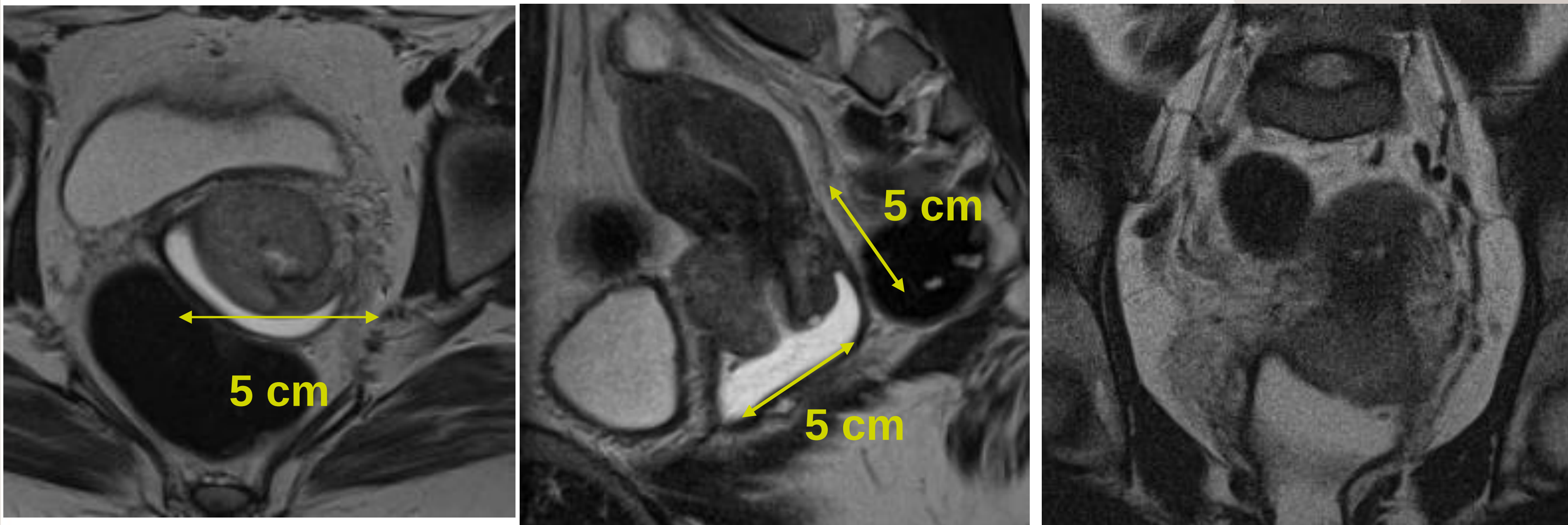
Width : 5

Thickness:4.5

Height : 5

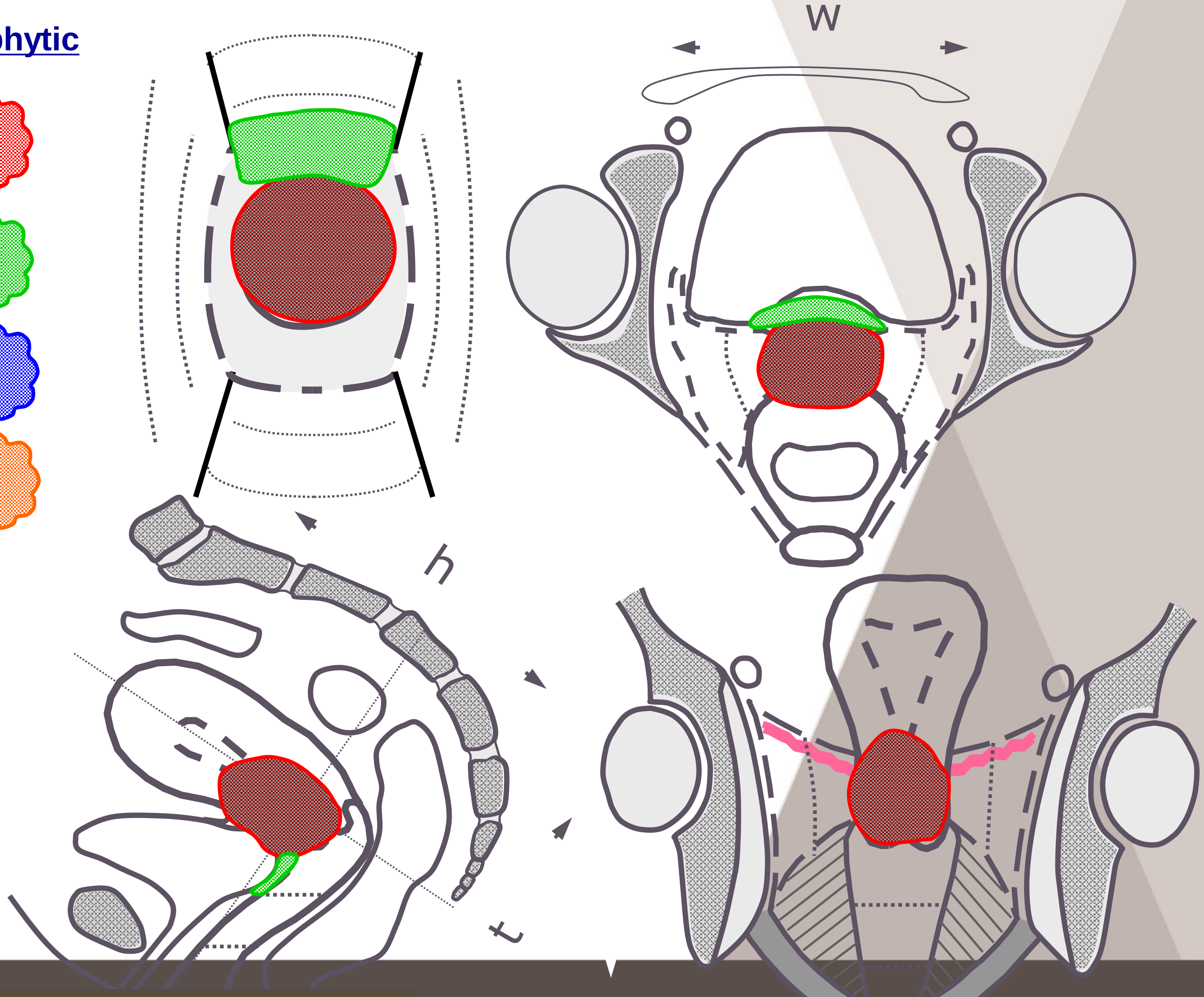
Vaginal involv 1.5

Stage IIA : initial MRI



Stage IIA : at time of brachytherapy

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		



Dimensions (cm):

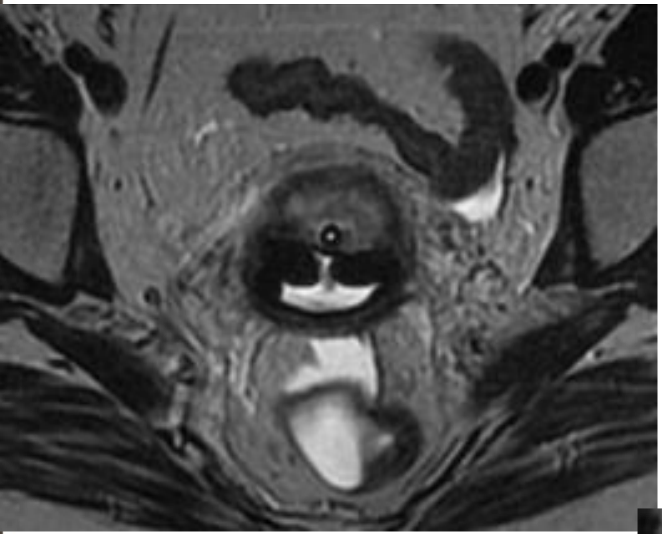
Width : 3.5

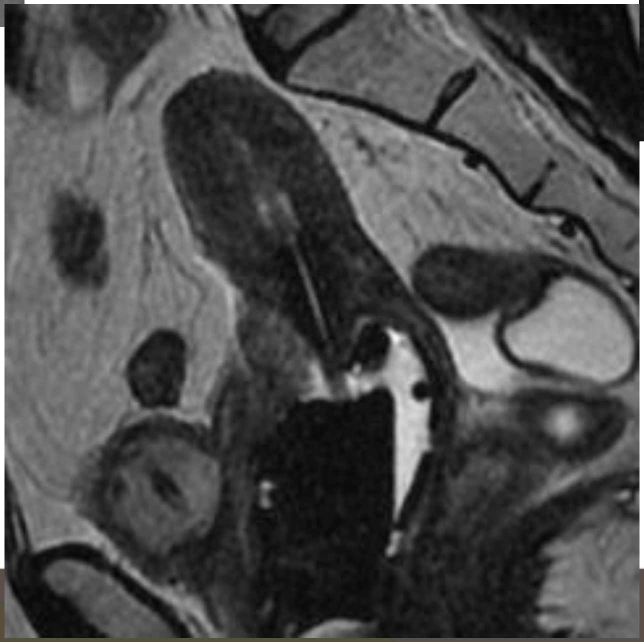
Thickness:3.5

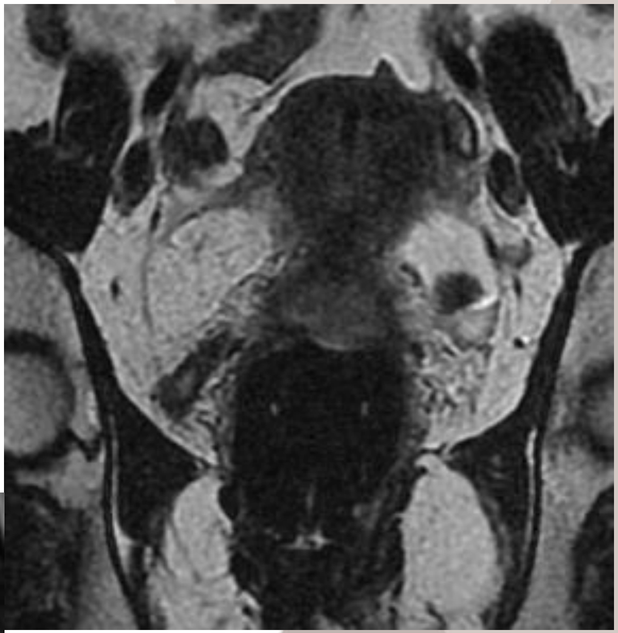
Height : 3

Vaginal involv :1

Stage IIA : MRI at time of brachytherapy







HR-CTV includes:

A. the initial tumor extension
B. the GTV + whole cervix + safety margins
C. the whole cervix only
D. the GTV + whole cervix

IR-CTV includes:

A. the initial tumor extension
B. the GTV + whole cervix + safety margins
C. the whole cervix only
D. the GTV + whole cervix

Target volume concepts

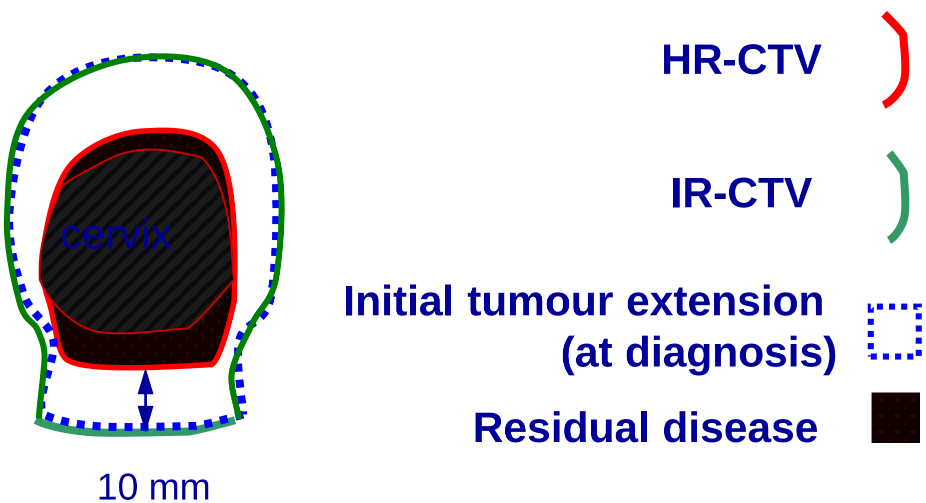
High Risk CTV :

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

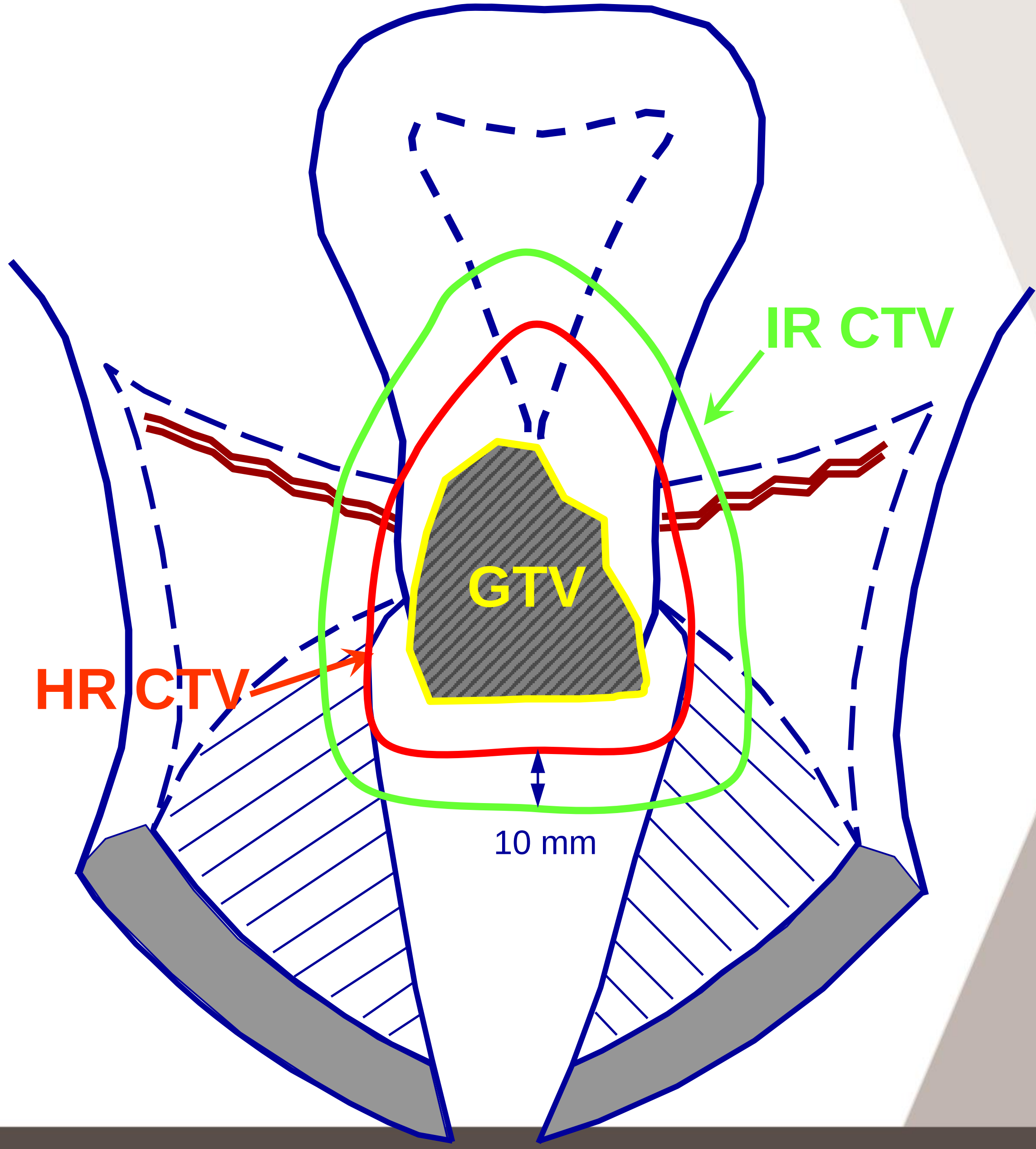
SAFETY MARGINS :

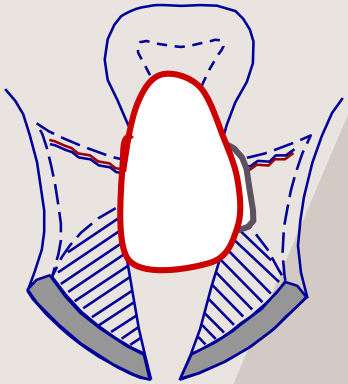
1-1.5 cm cranially

0.5cm antero-posteriorly

1cm laterally

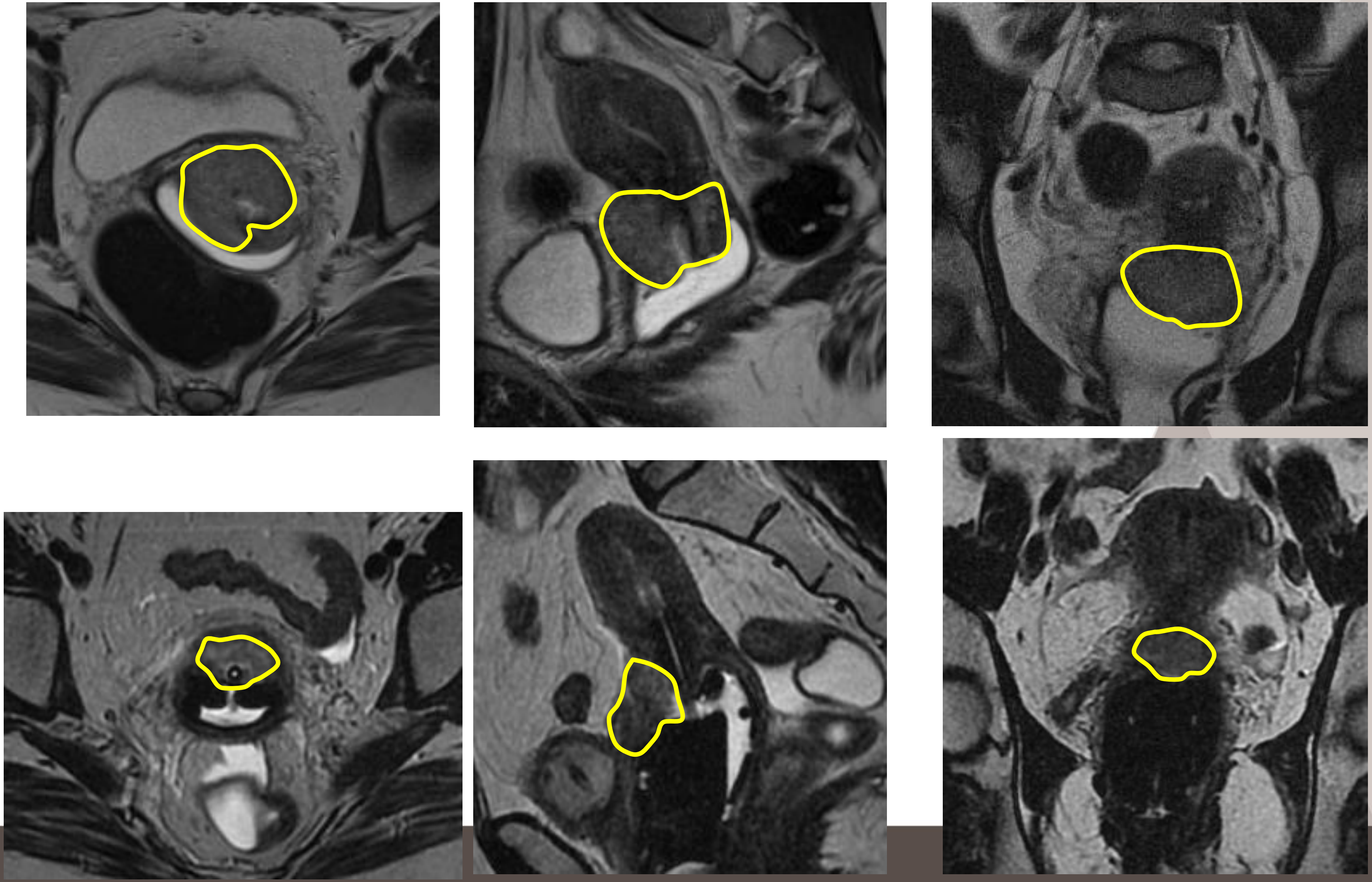
Stage IIA



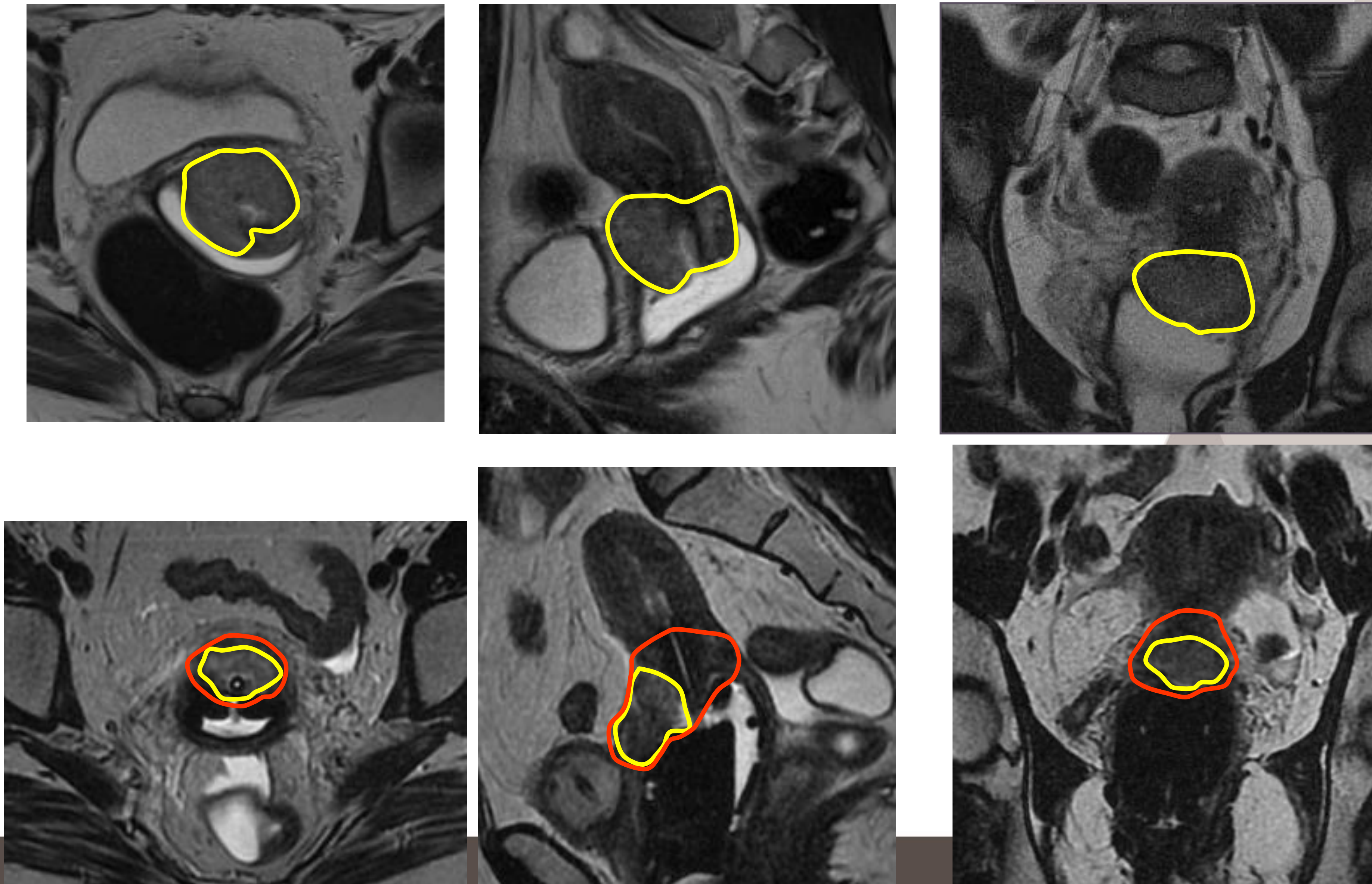


Tumor at time of diagnosis

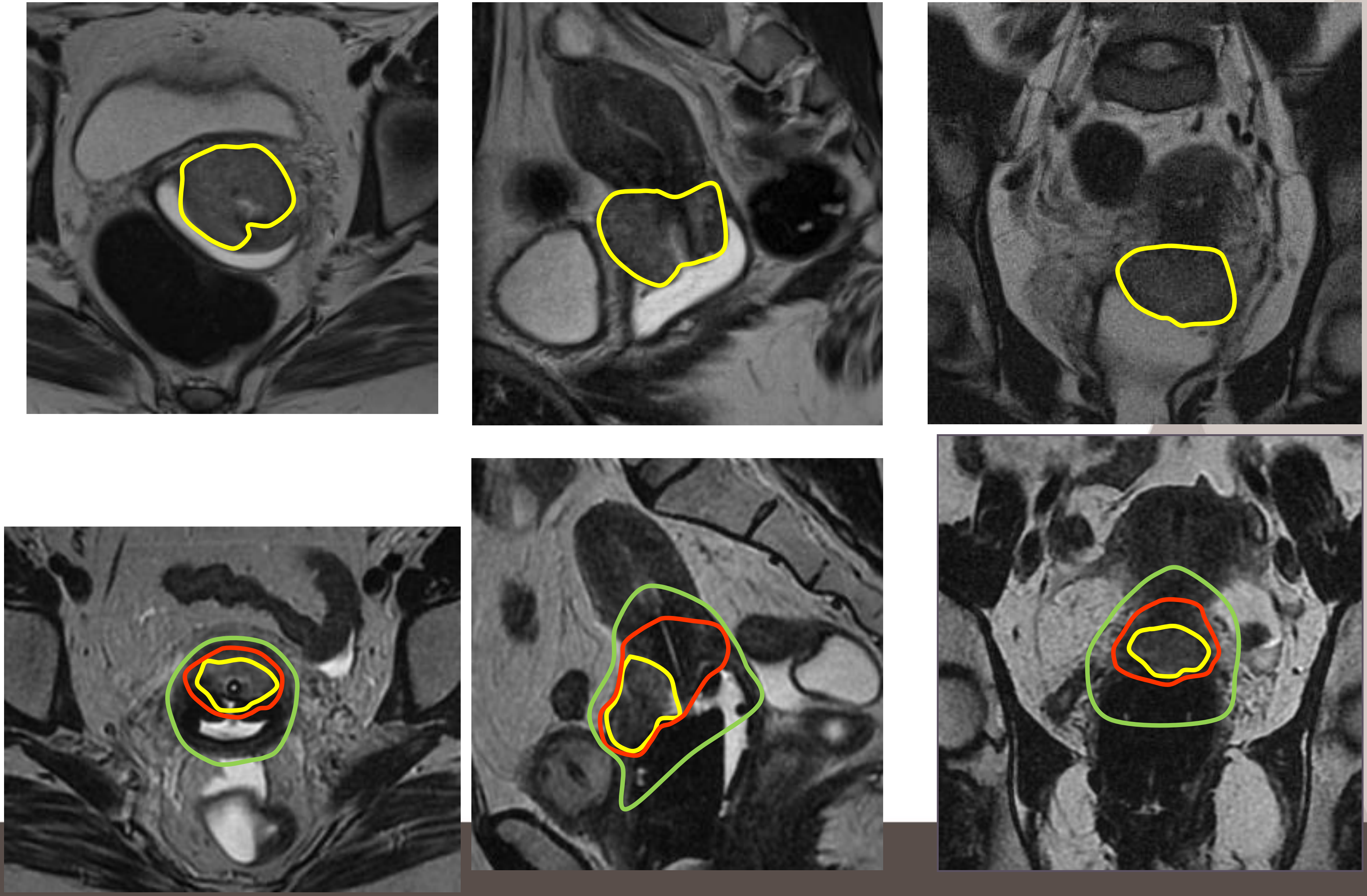
Stage IIA



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

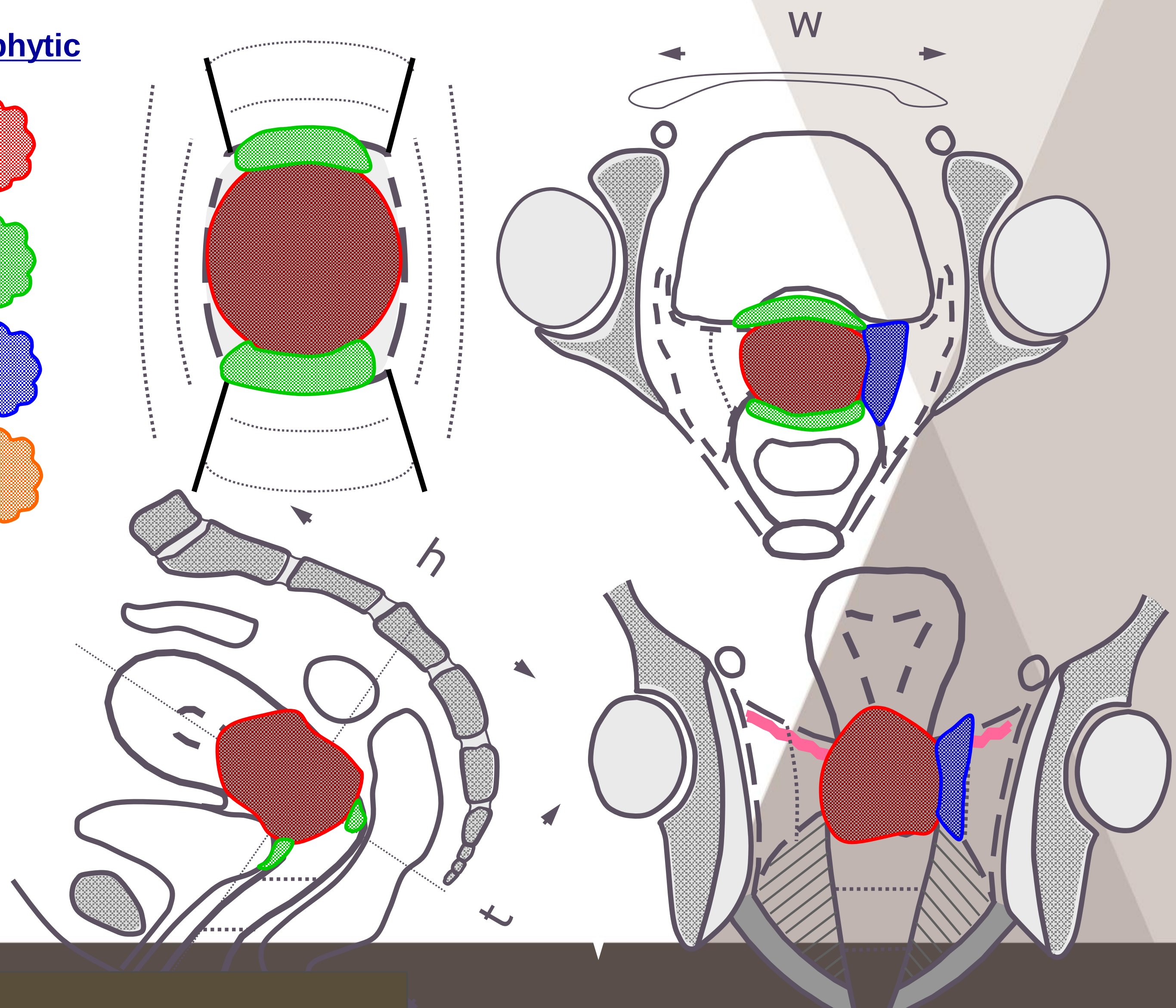
Infiltrating **Exophytic**

Cervix

Vagina

Parametrium

Rectum or Bladder



Dimensions (cm):

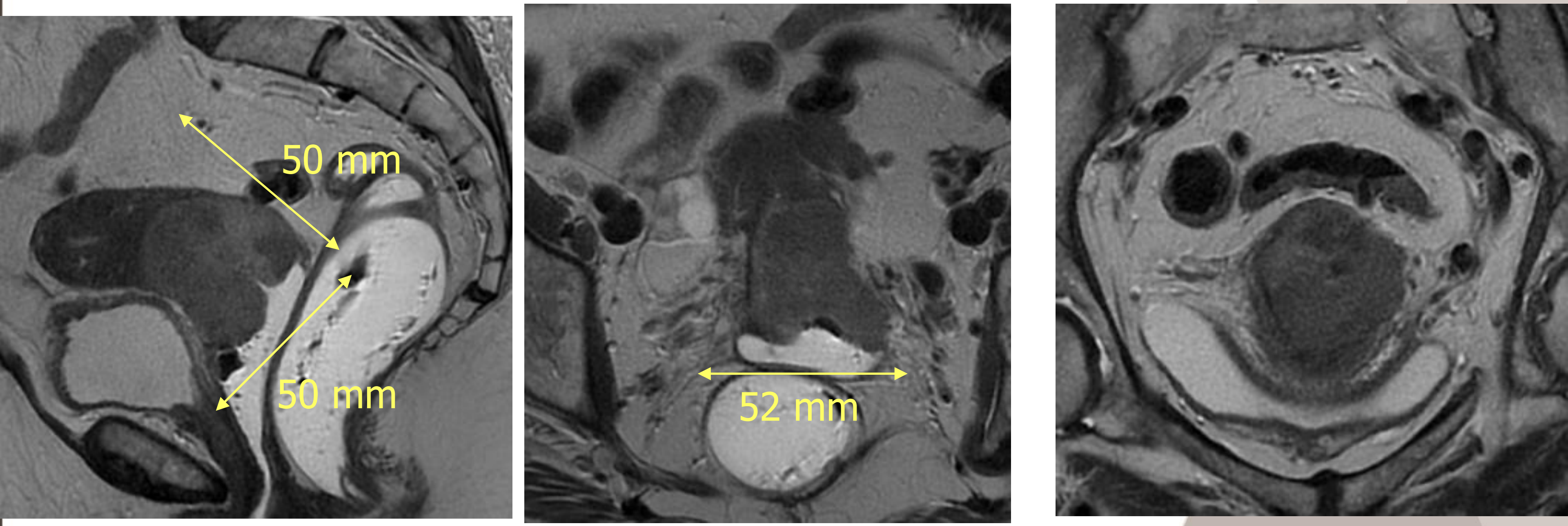
Width : 5

Thickness:5

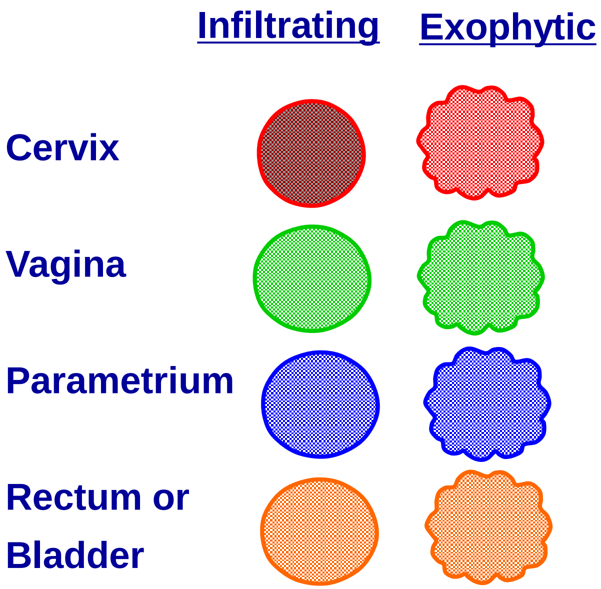
Height : 5

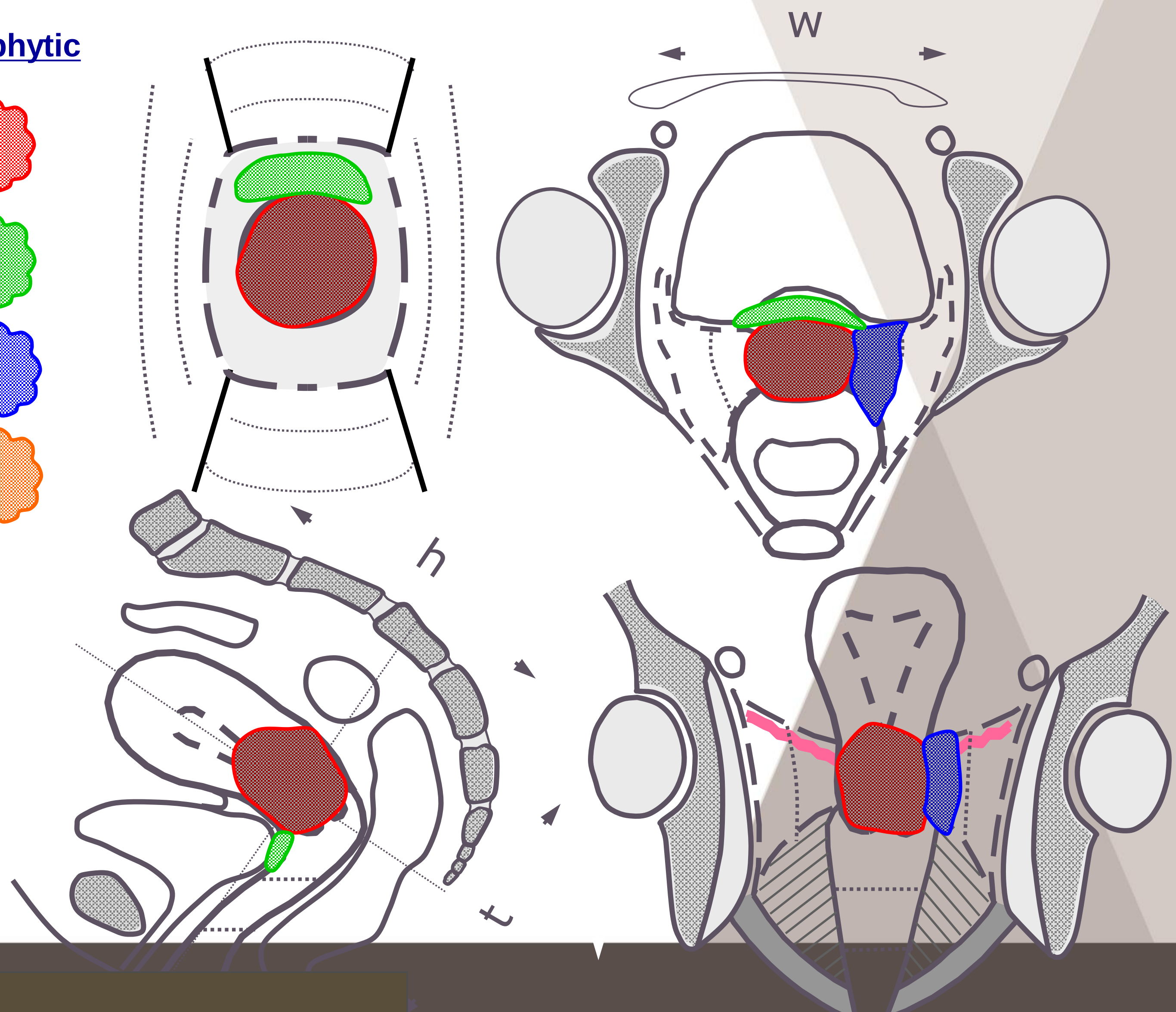
Fornix involv 1

Stage IIB : initial MRI



Stage IIB : at the time of brachytherapy





Dimensions (cm):

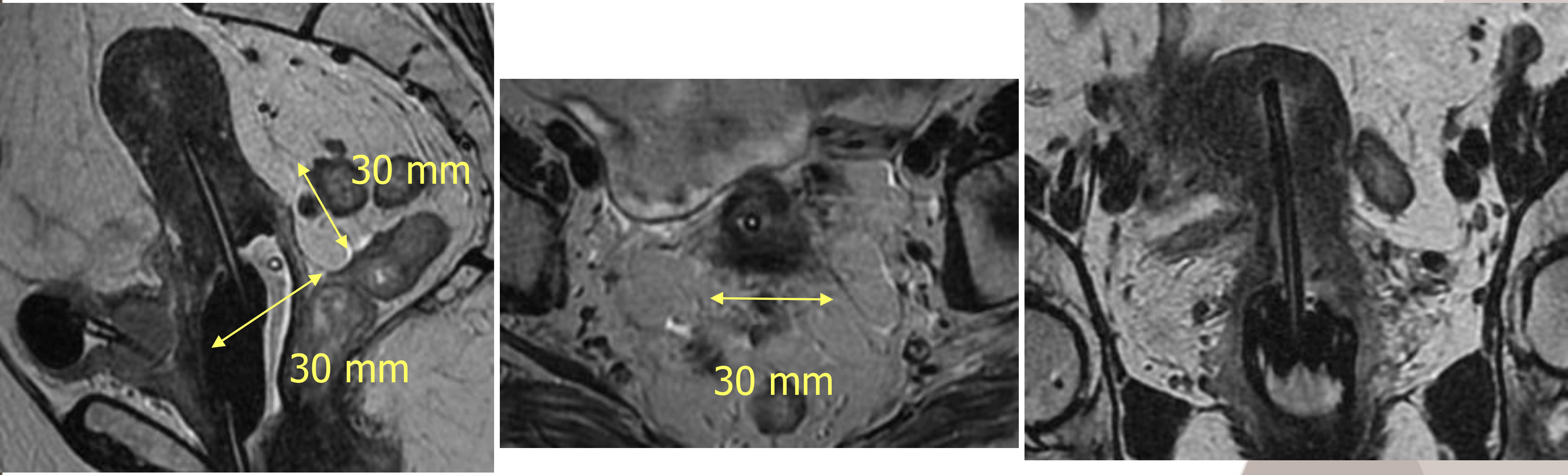
Largeur : 3

Epaisseur : 3

Hauteur : 3

Env. vaginal : 1

Stage IIB : MRI at the time of brachytherapy



Target volume concepts

High Risk CTV :

GTV at time of brachytherapy

In all cases includes:

- GTV + whole cervix
- Presumed tumour extension in adjacent tissues
  - **Clinical assessment**
  - **Residual grey zones on MRI**

NO SAFETY MARGINS

Intermediate Risk CTV :

GTV at time of diagnosis

In all cases includes:

- HR-CTV
- integrates initial CTV

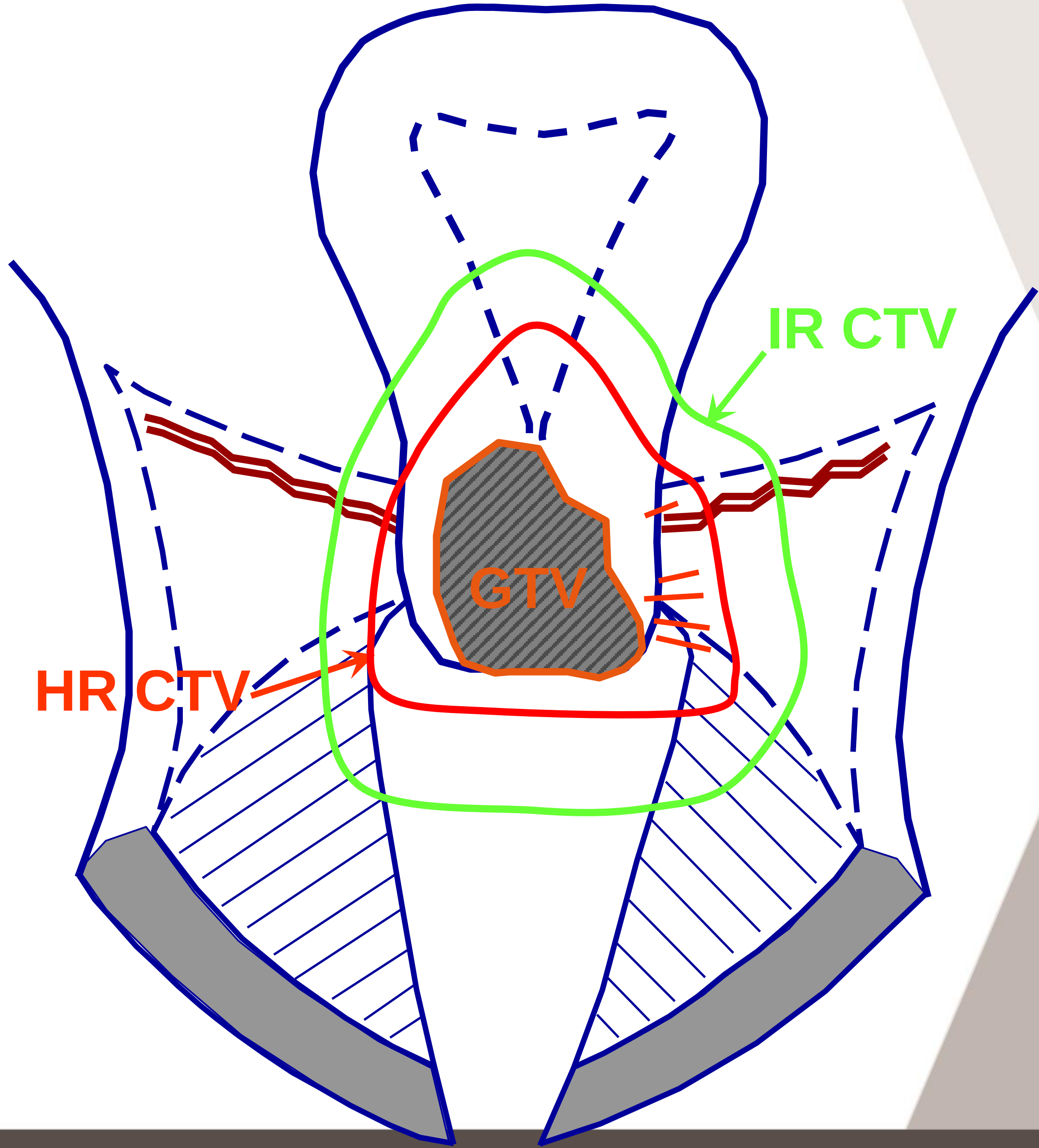
SAFETY MARGINS :

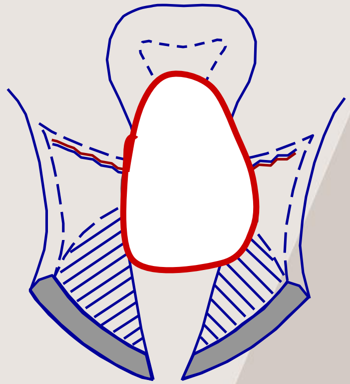
1-1.5 cm cranially

0.5cm antero-posteriorly

1cm laterally

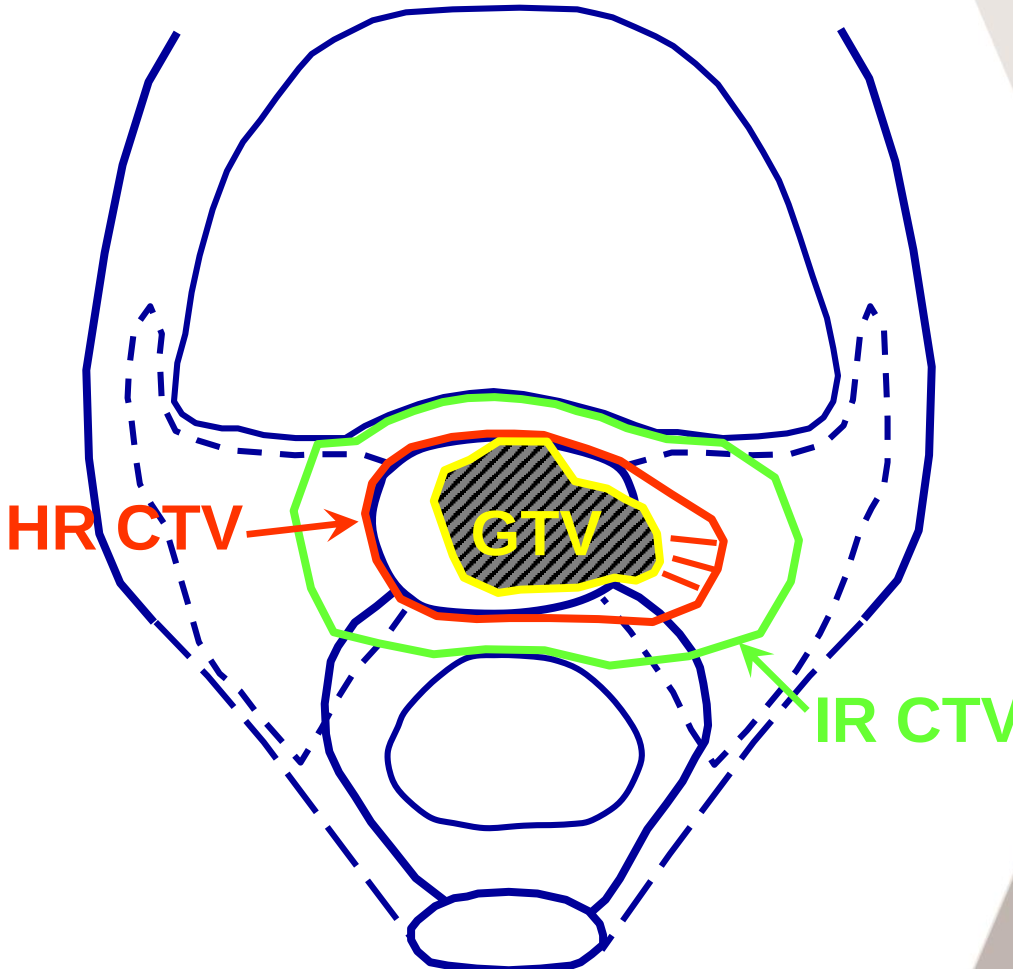
Stage IIB

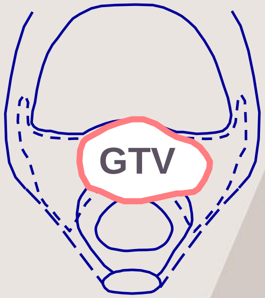




Tumor at time of diagnosis

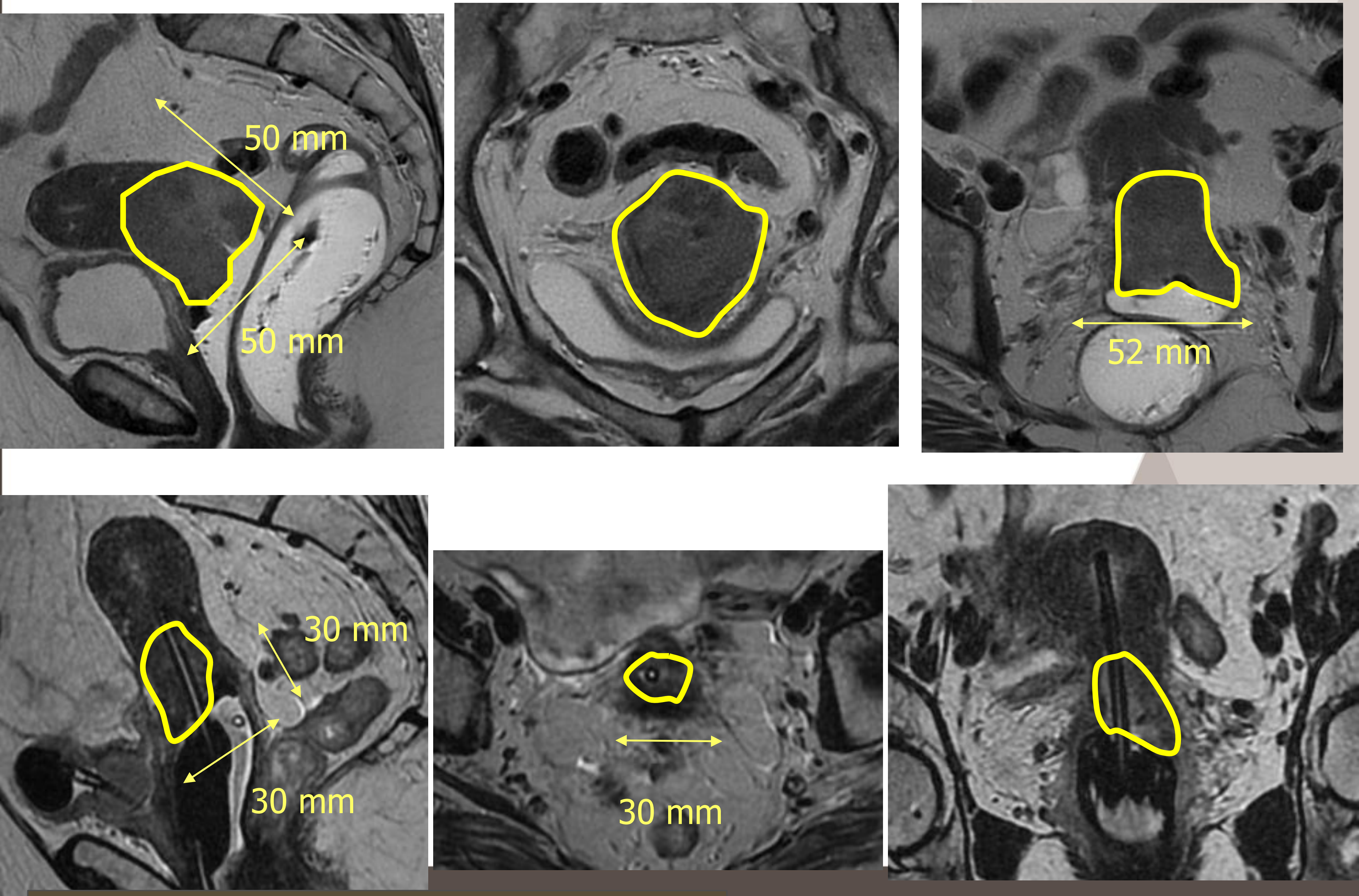
Stage IIB



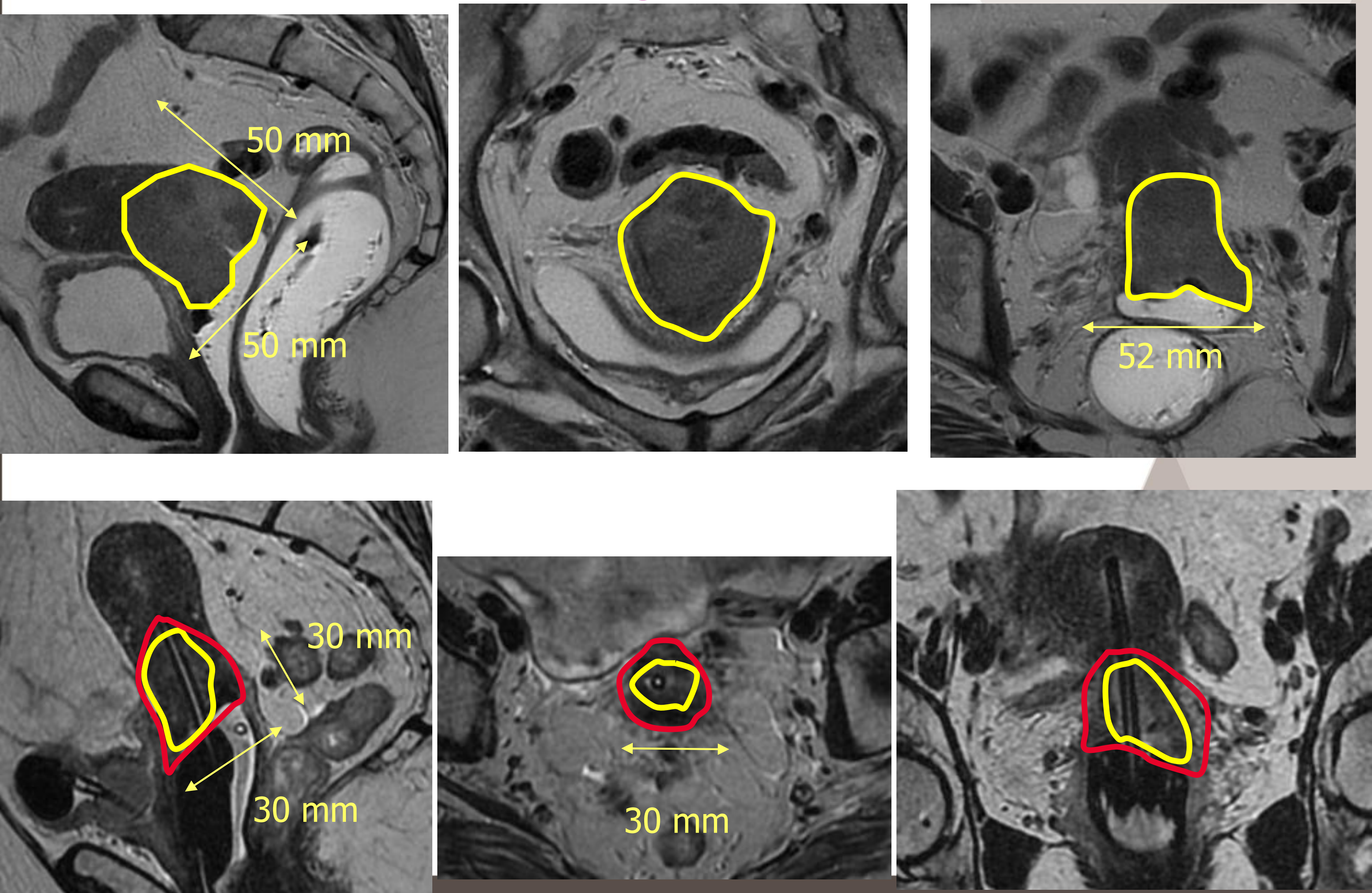


Tumor at time of diagnosis.

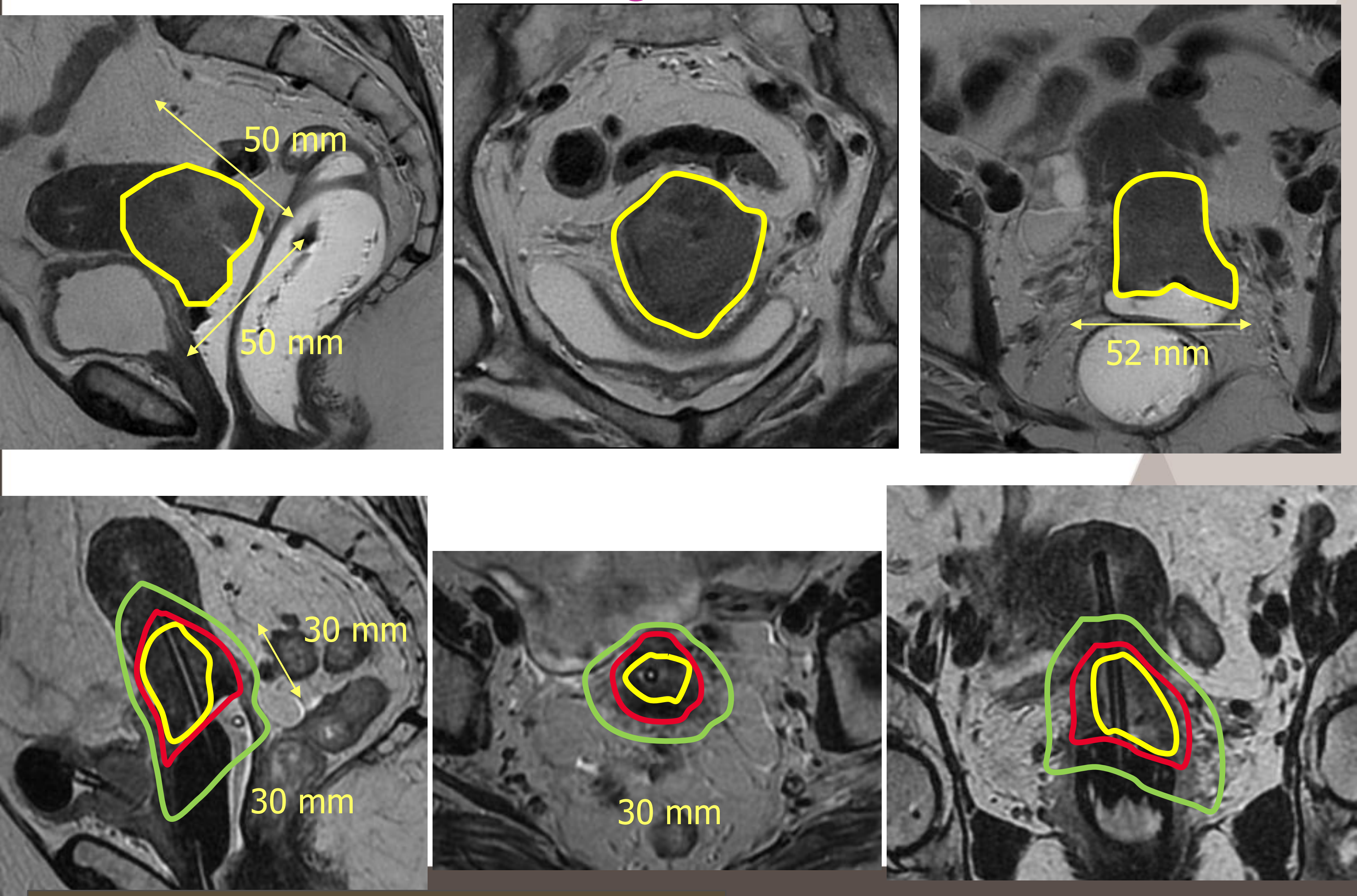
Stage IIB



Stage IIB



Stage IIB



Patient n° 7

Mrs Claudine BAR…
62 year-old

Vaginal bleeding for > 1 year, urinary retention

Biopsy: well differentiated squamous cell carcinoma

At clinical examination : cervical tumor + infiltration of the whole anterior and right vaginal wall + infiltration of the right parametrium to the pelvic wall + infiltration of the left distal parametrium

Cystoscopy : involvement of the trigonal area, + biopsy

Stage IVA : initial clinical examination

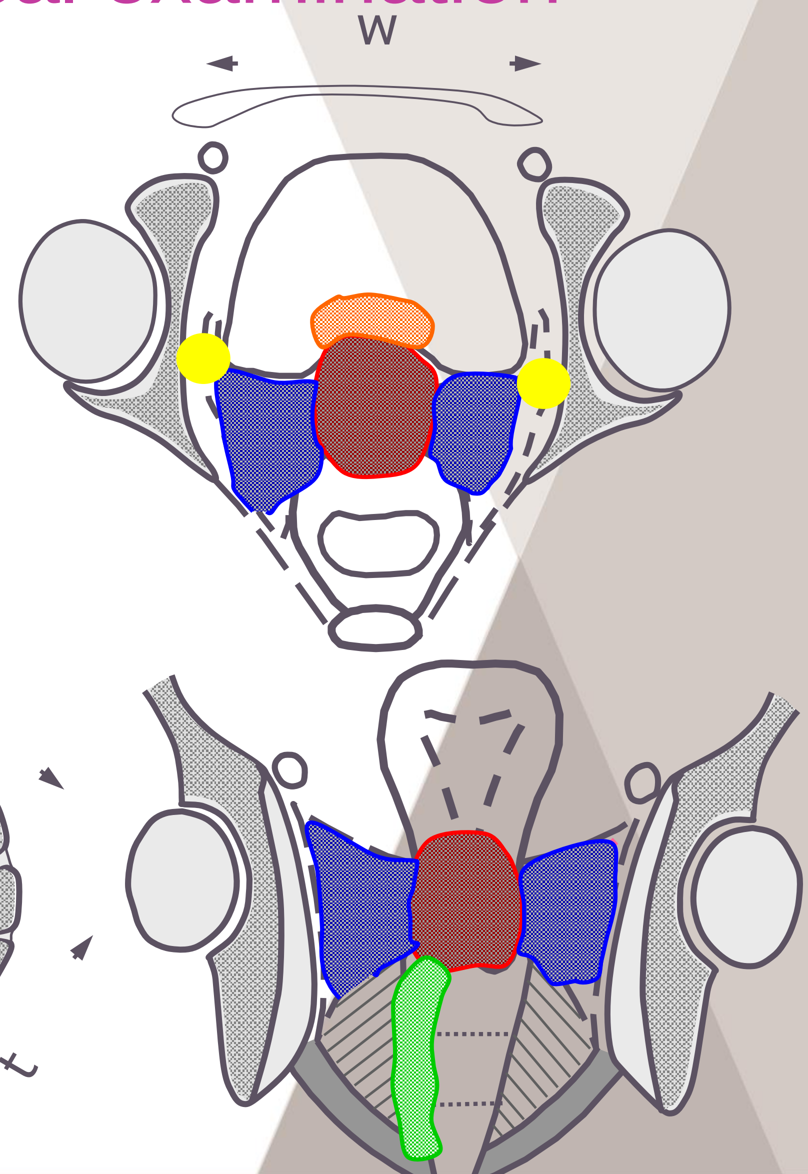
	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

Dimensions (cm):

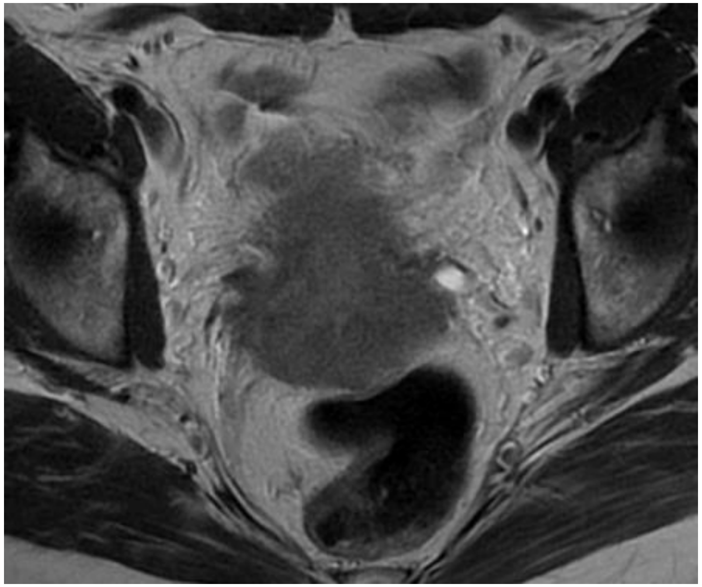
Width : 8

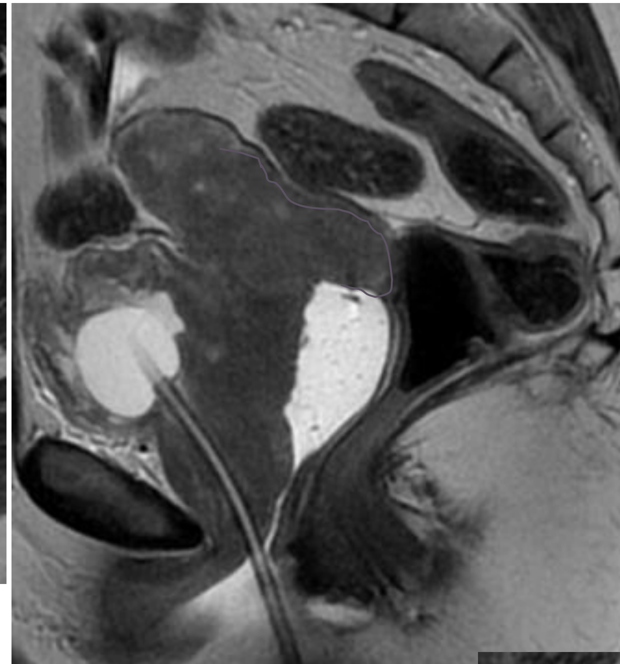
Thickness :6

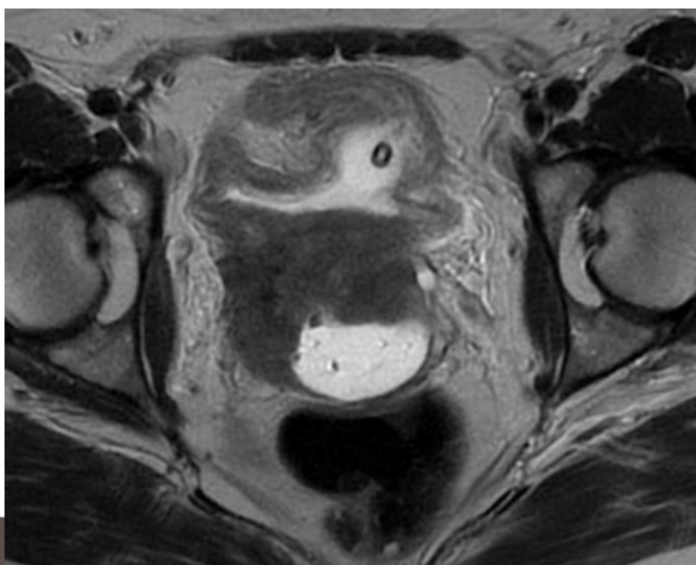
Height : 7

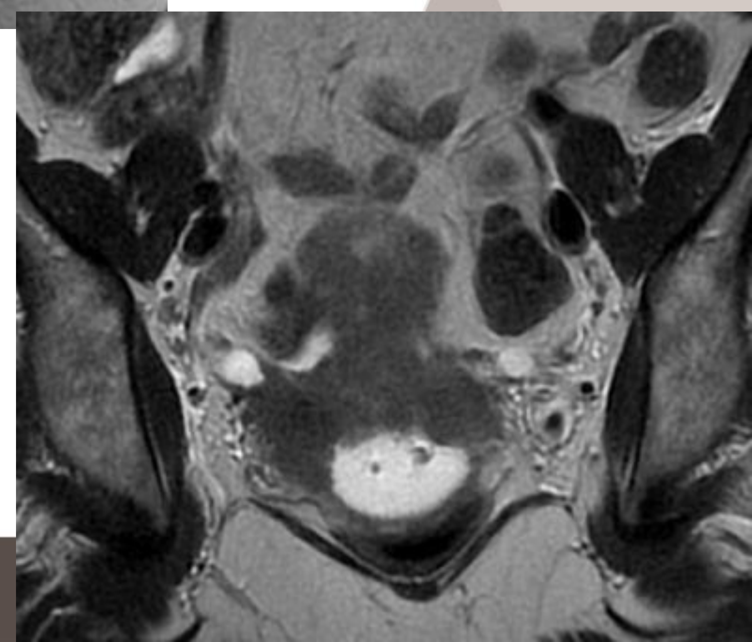


Stage IVA : initial MRI

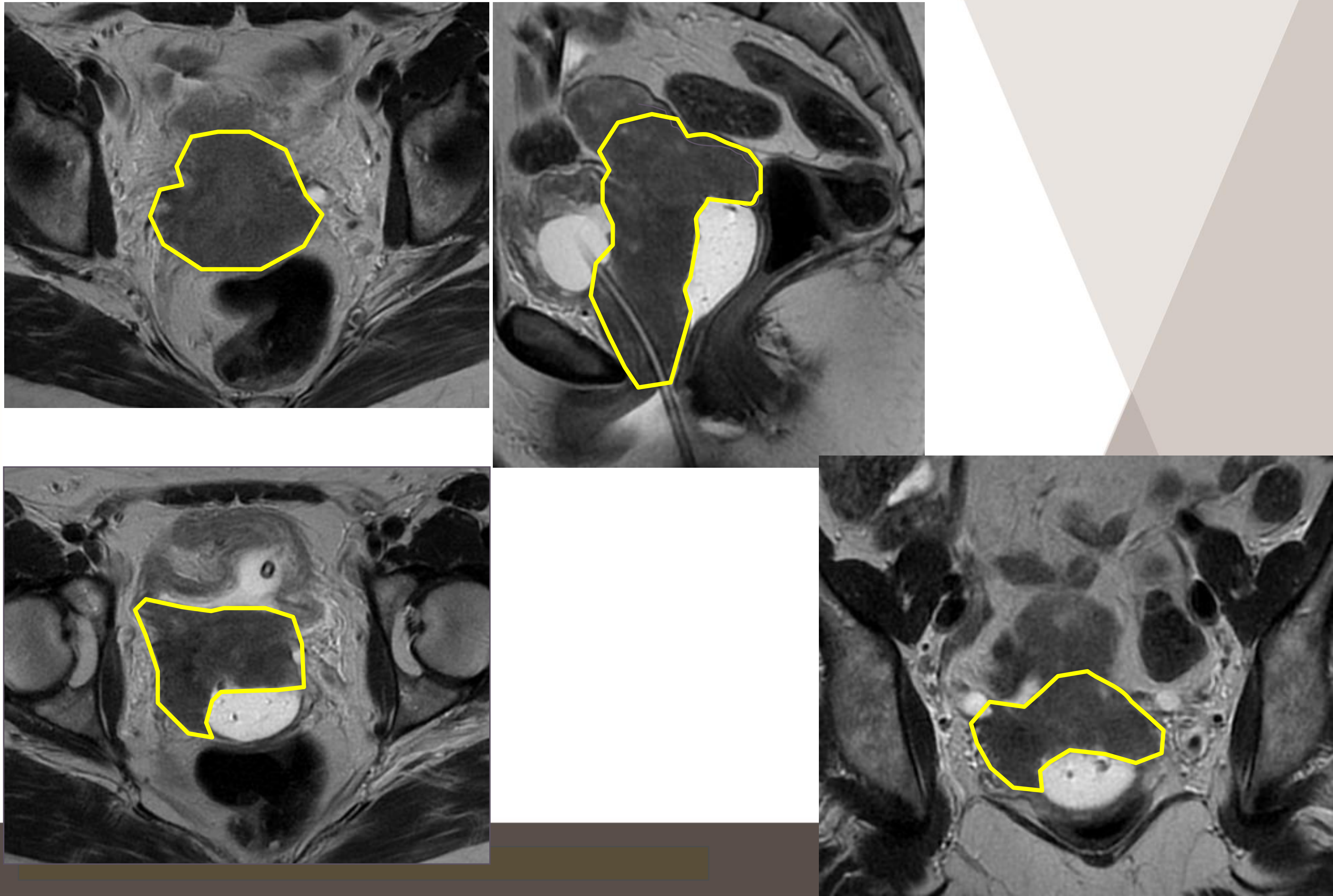






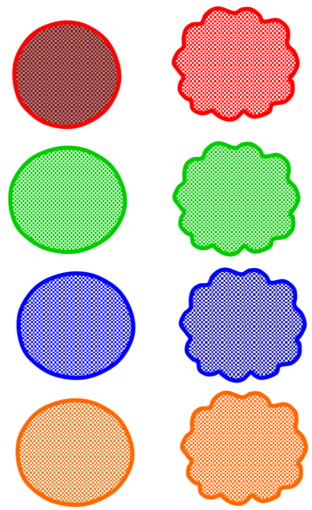


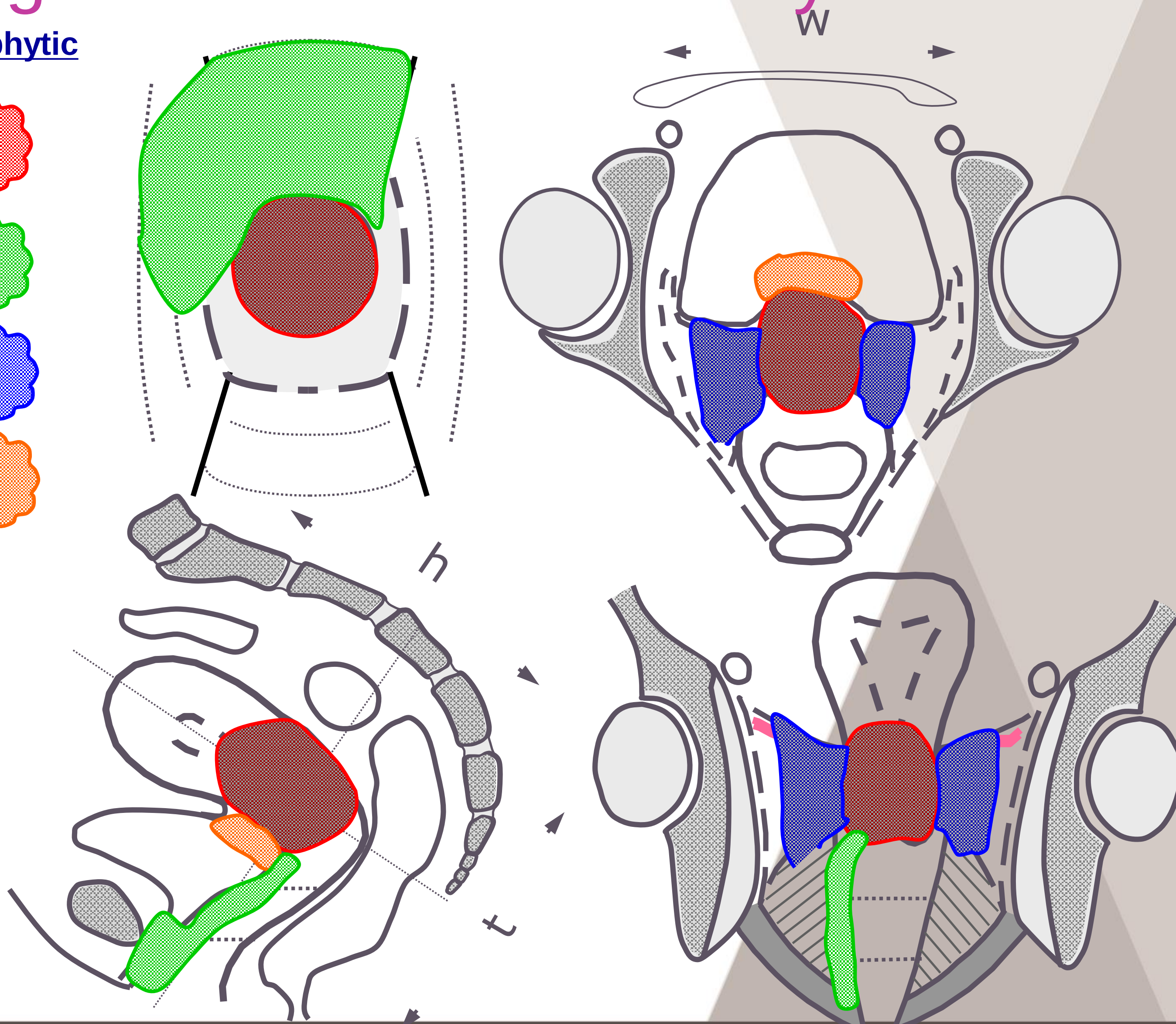
Stage IVA : initial MRI



Stage IVA : at time of brachy

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		





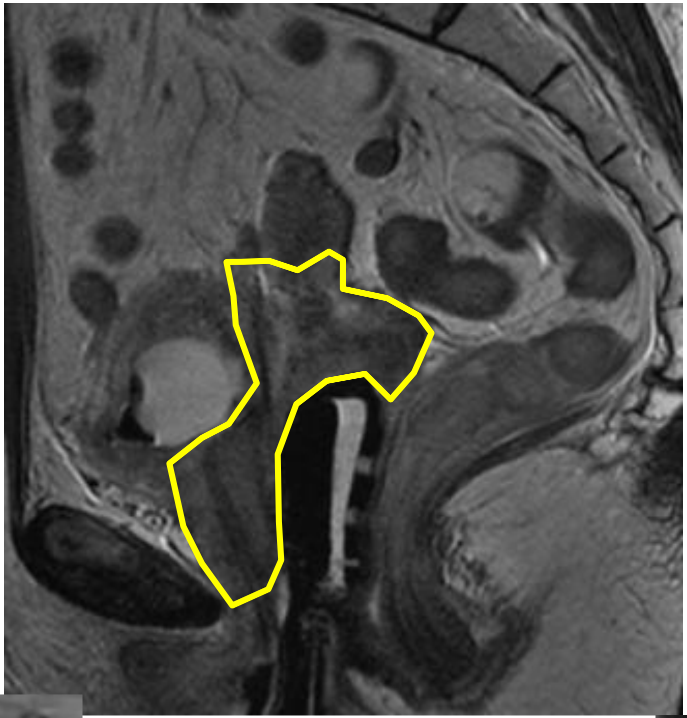
Dimensions (cm):

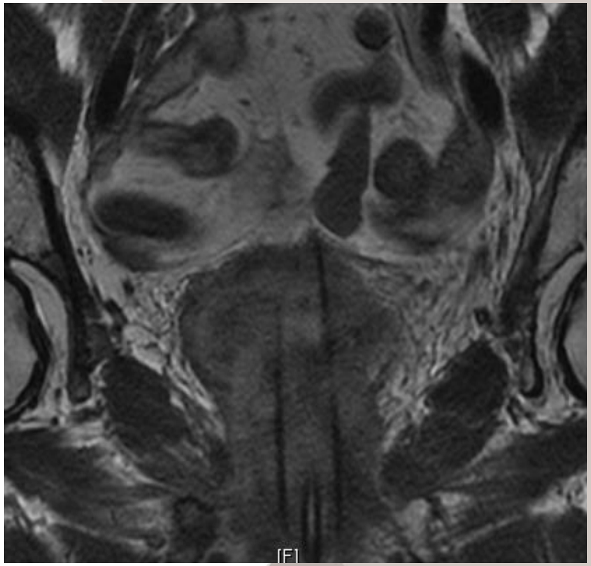
Width : 8

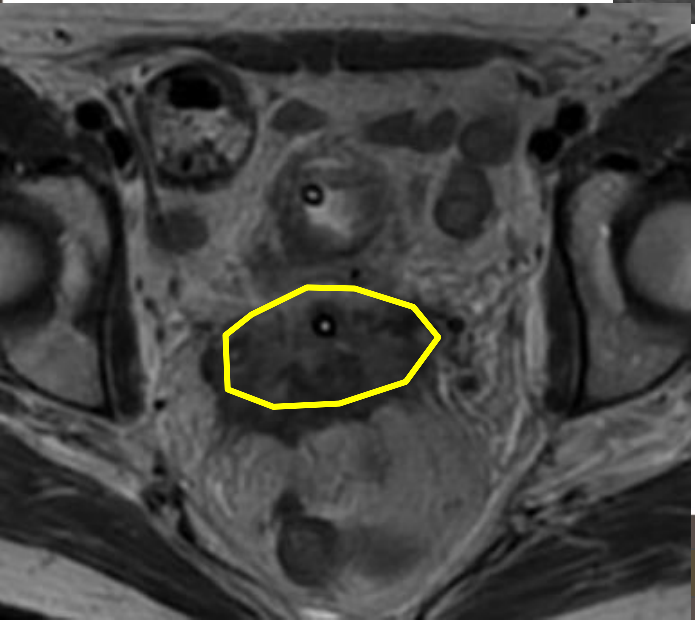
Thickness :6

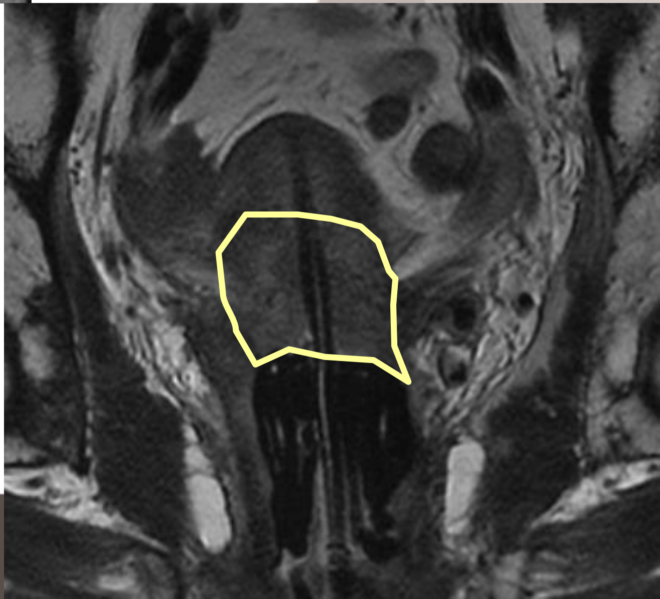
Height : 7

Stage IVA : at time of brachytherapy

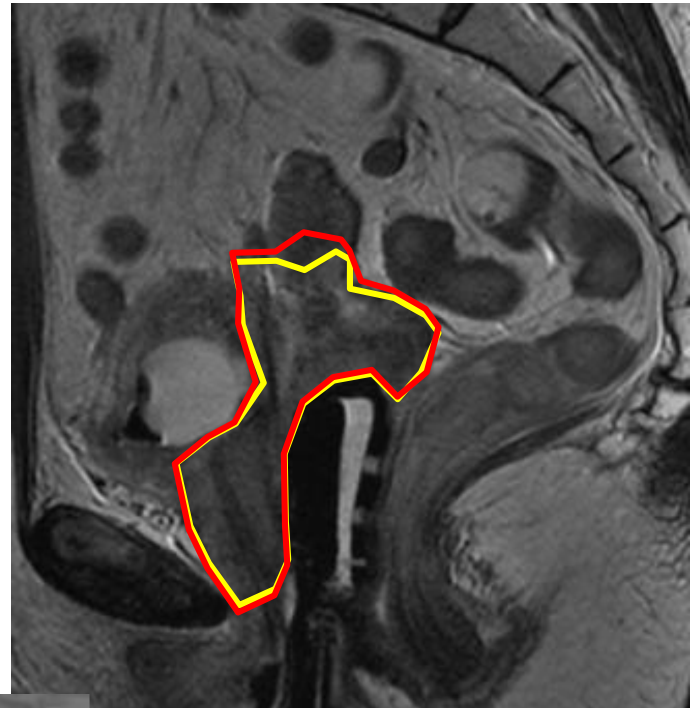


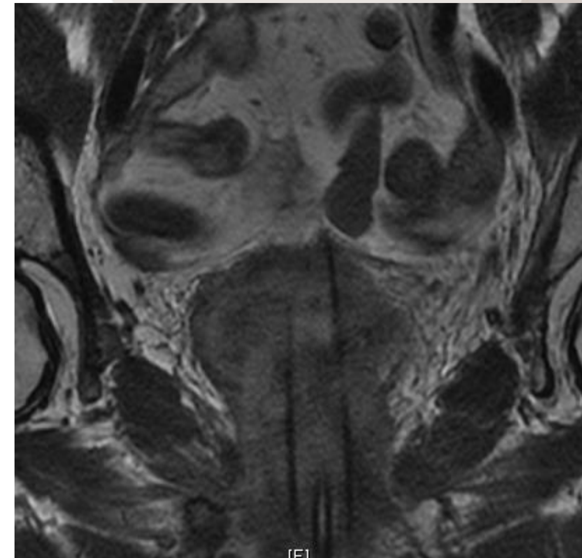


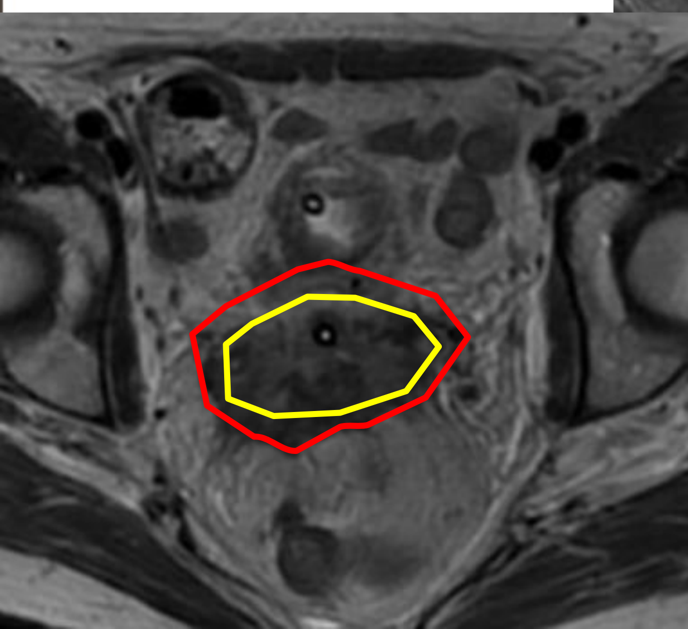


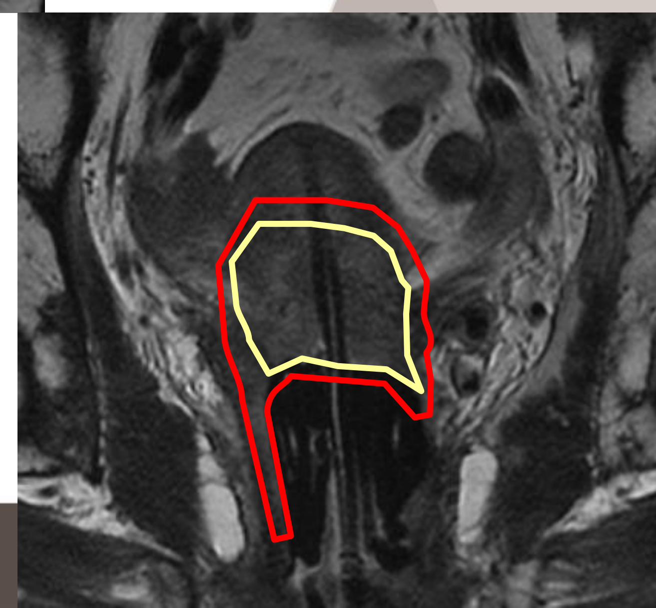


Stage IVA : at time of brachytherapy

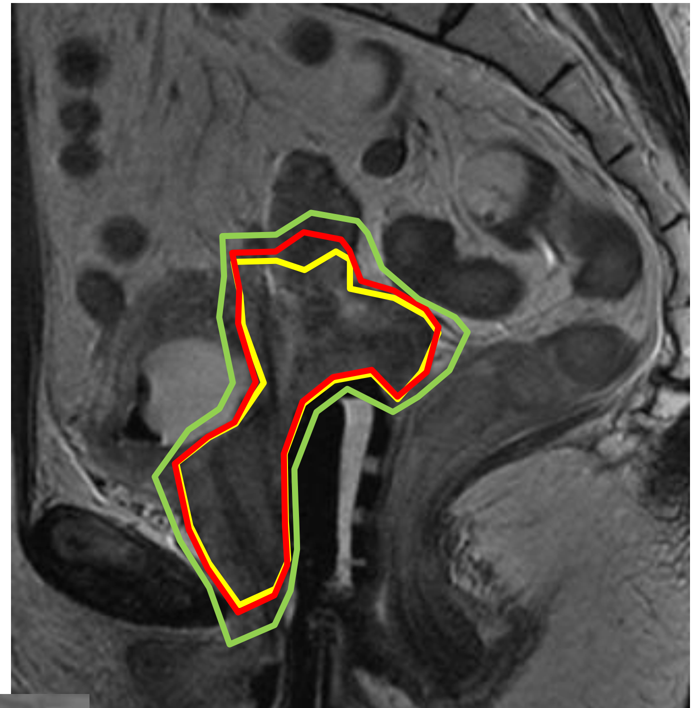


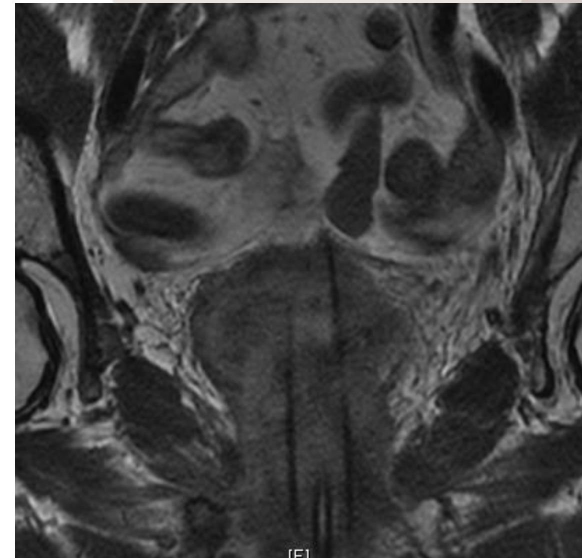


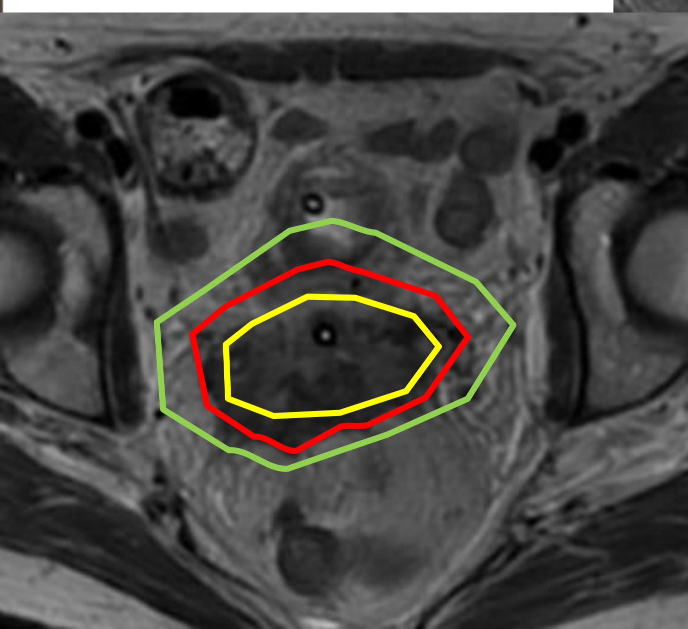


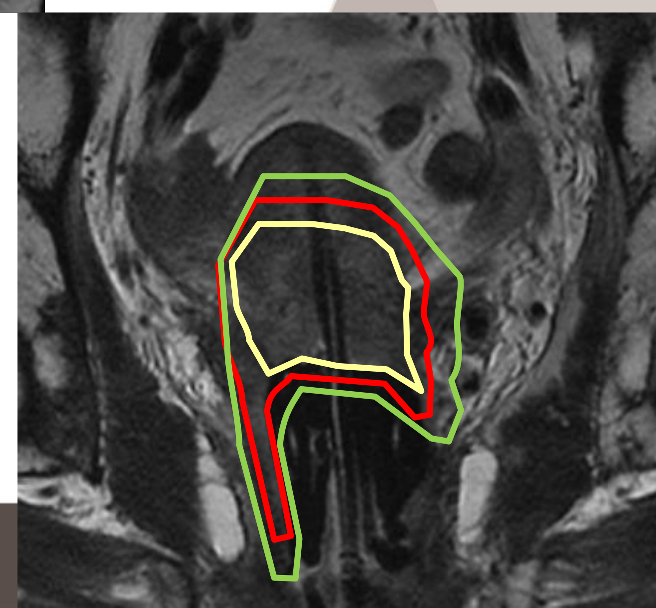


Stage IVA : at time of brachytherapy





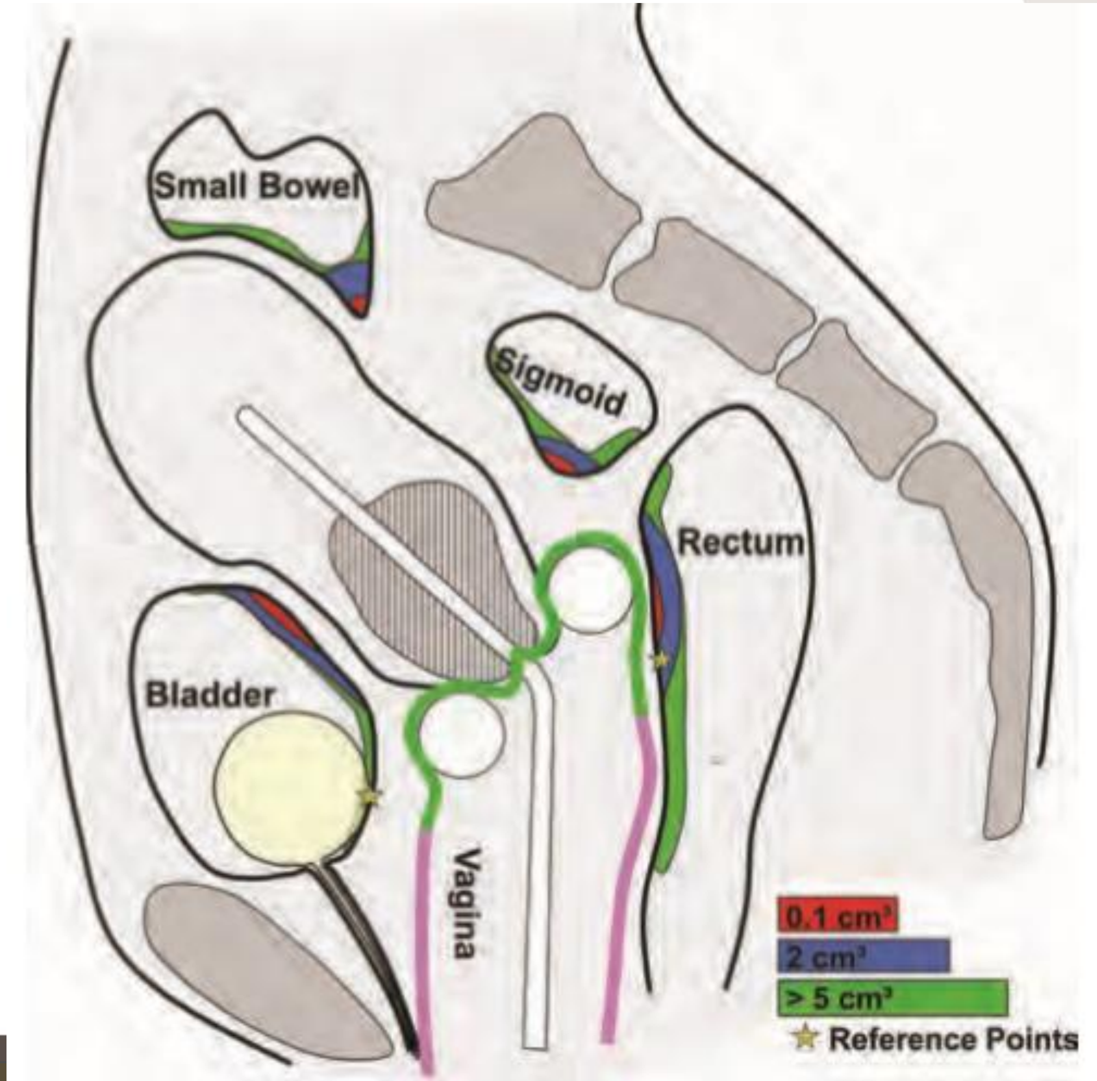




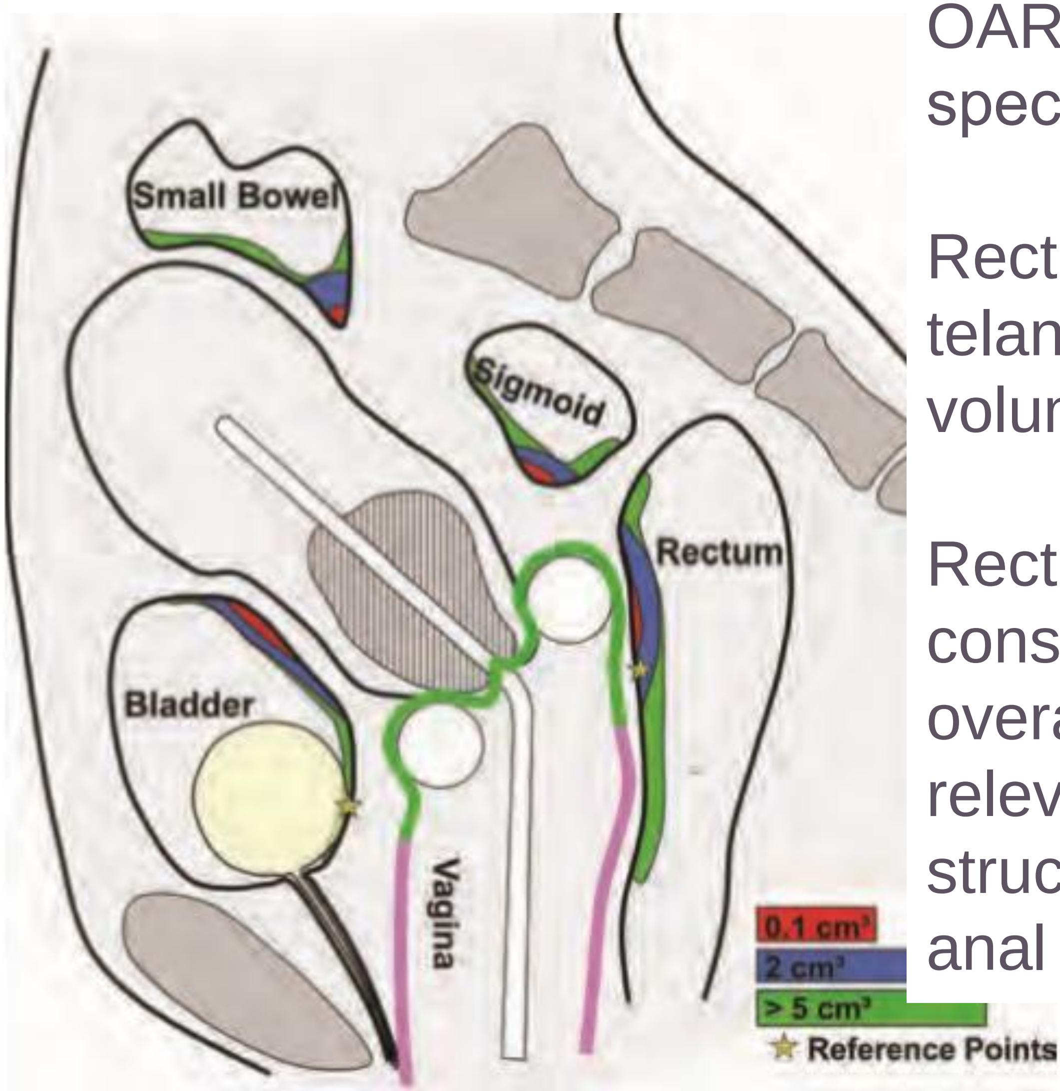
Organs at risk

Organs at risk

Small organ-wall volumes up to 2 cm^3–3cm^3 represent typical targets for brachytherapy-related morbidity



Organs at risk



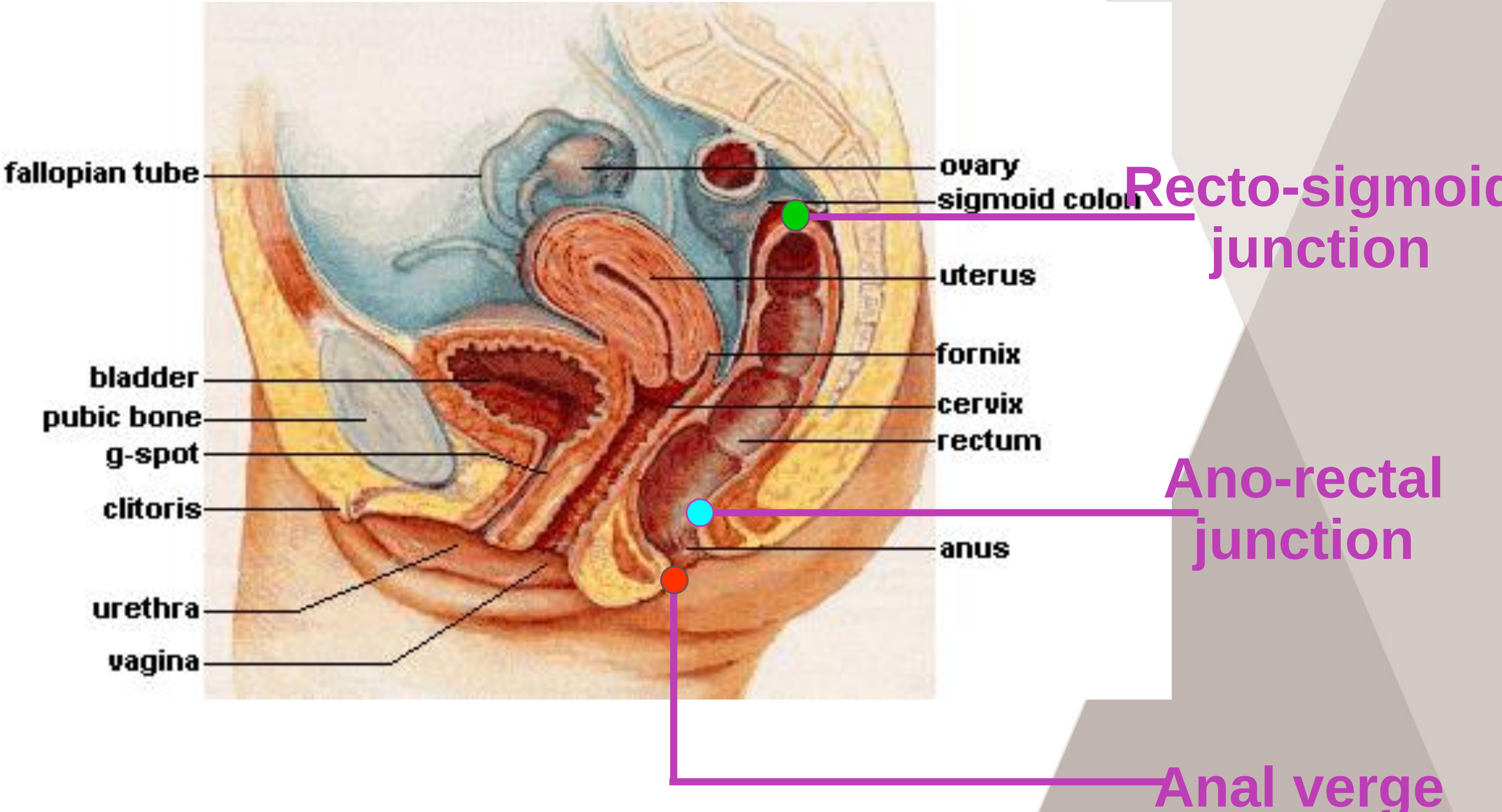
OAR-specific or OAR-sub-volume specific types of morbidity

Rectal and sigmoidal bleeding = telangiectasia even in small volumes

Rectal urgency/ continence = consequence of damage to the overall recto-anal wall, with the relevant muscle and nerve plexus structures regulating the recto-anal discharge

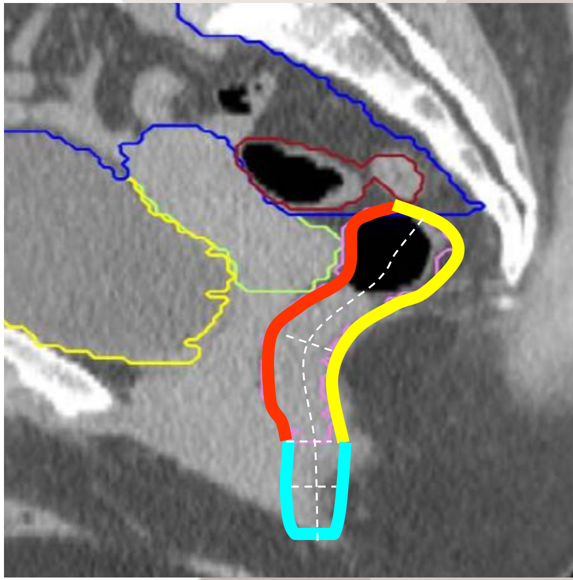
Anorectum

Anatomy



Anorectum

Perspectives



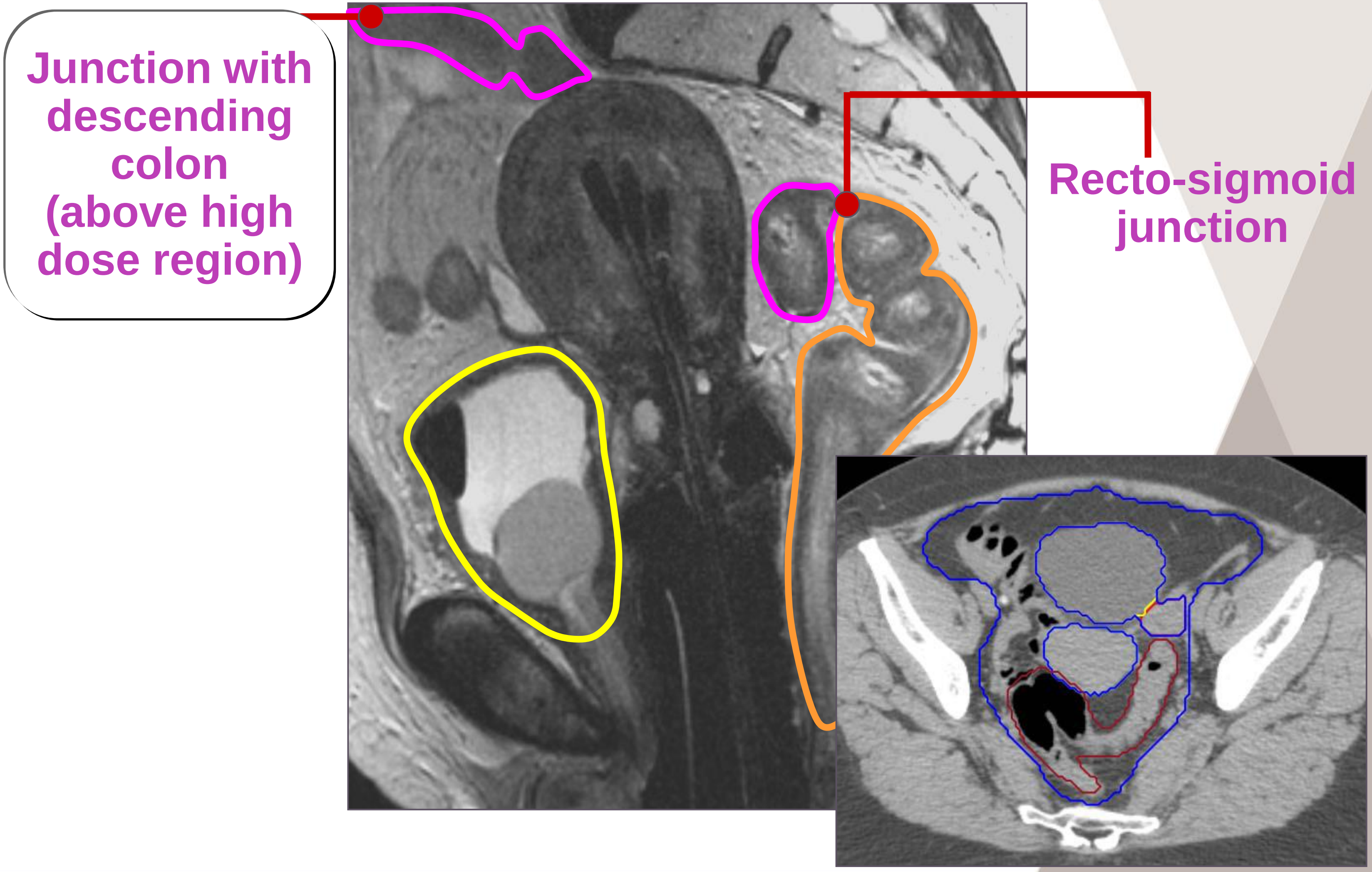
Separate delineation of ano-rectal regions

Separate assessment of DVH to different regions

Separate scoring & modelling of different endpoints

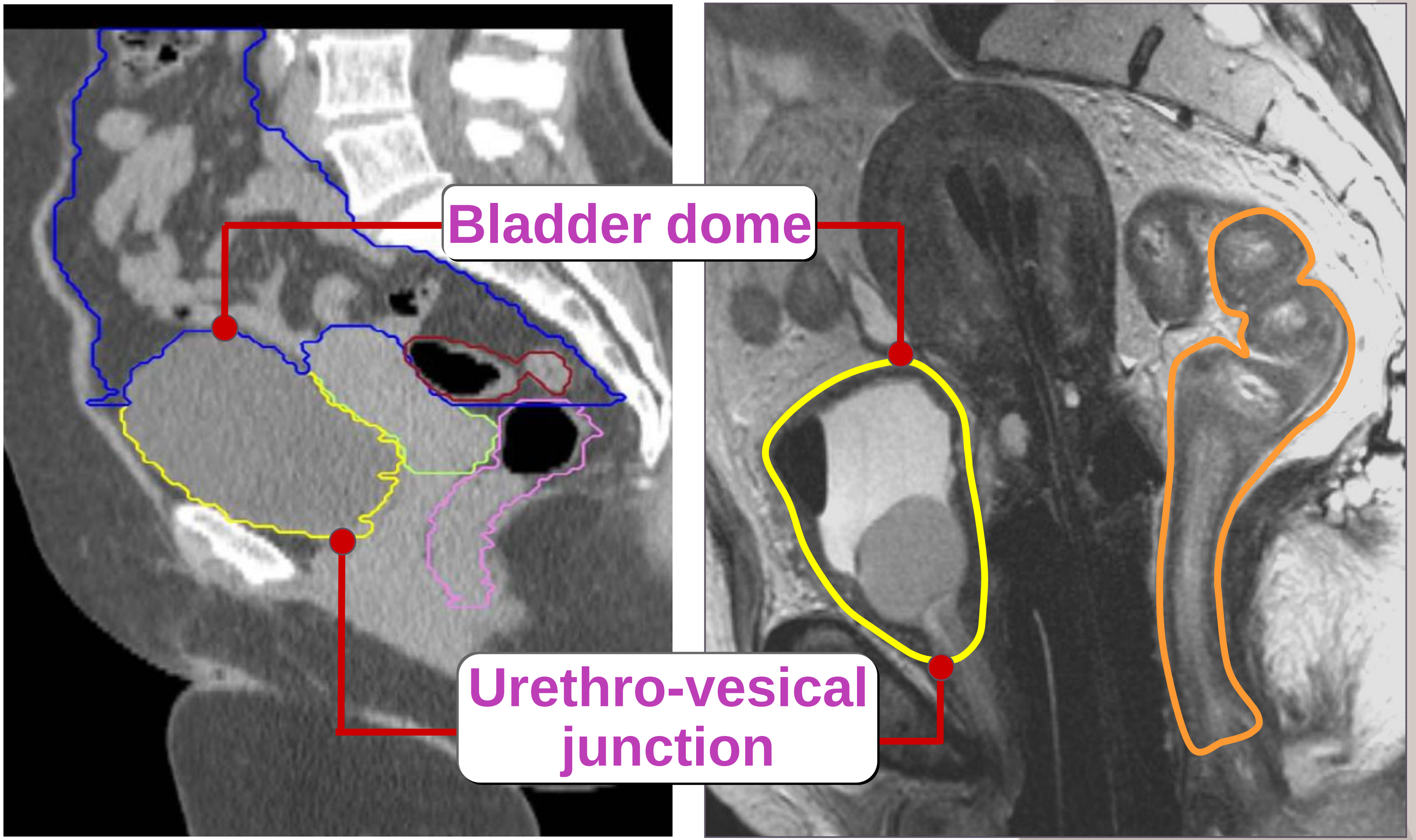
Determination of relevant structures for different endpoints

Sigmoid colon



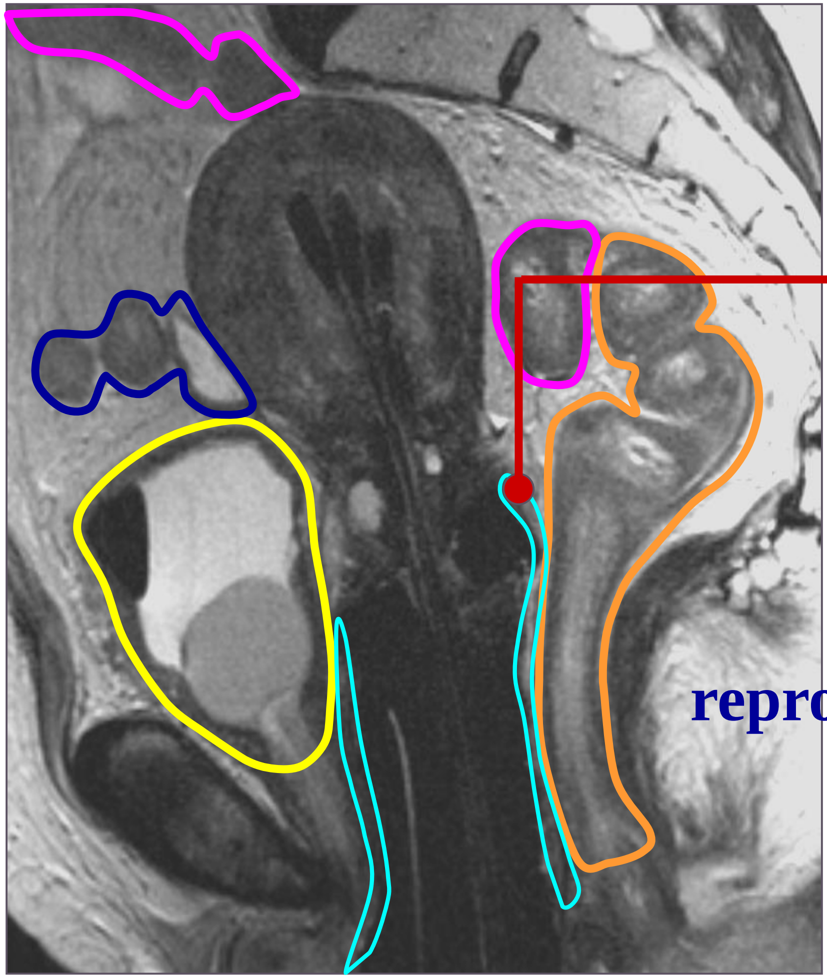
Bladder

What to delineate?



Viswanathan AN, et al. IJROBP 2010

Vagina



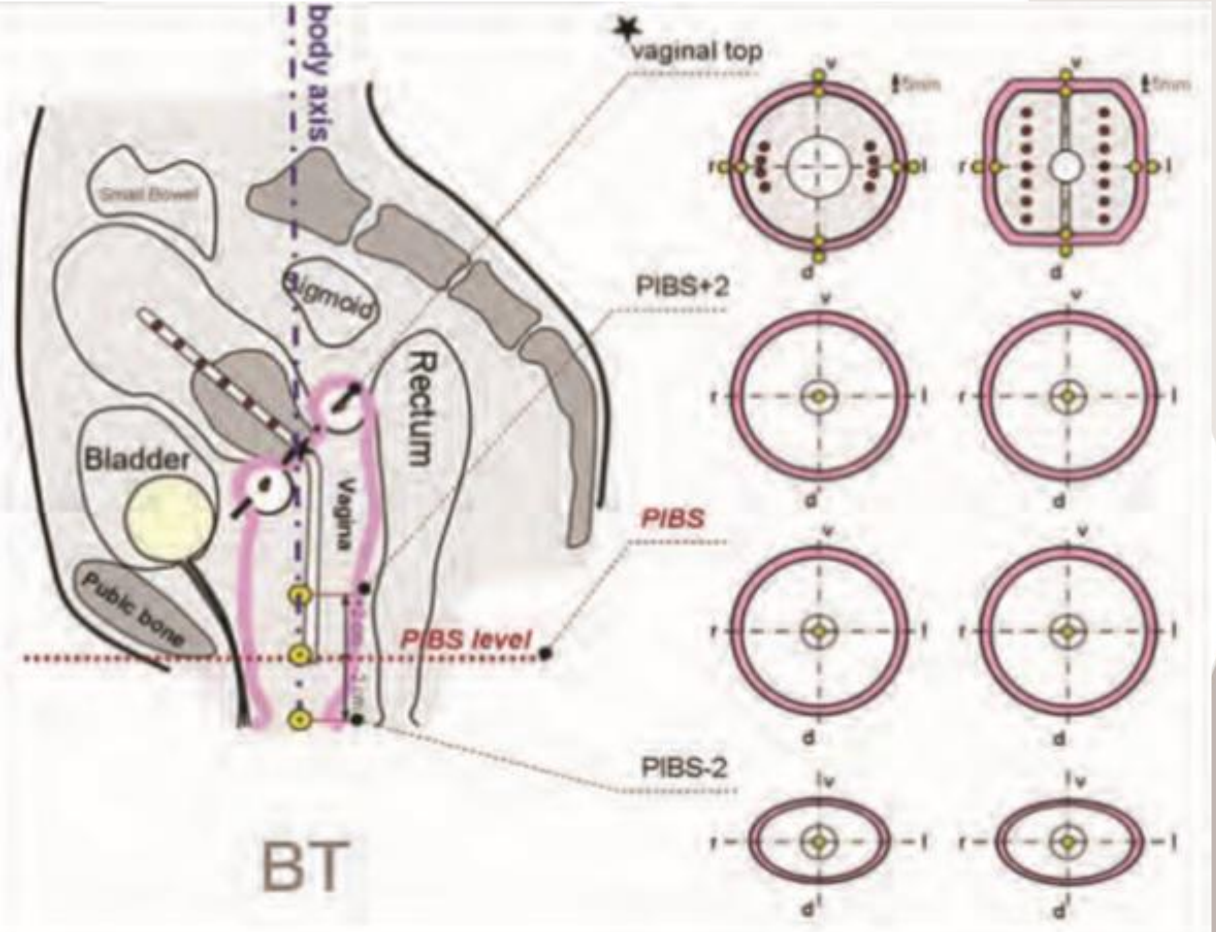
Vaginal wall

Delineation, DVH, Reporting:

- **↑ uncertainties**
- **↓ reproducibility**

Berger D, et al. IJROBP 2007

Vagina

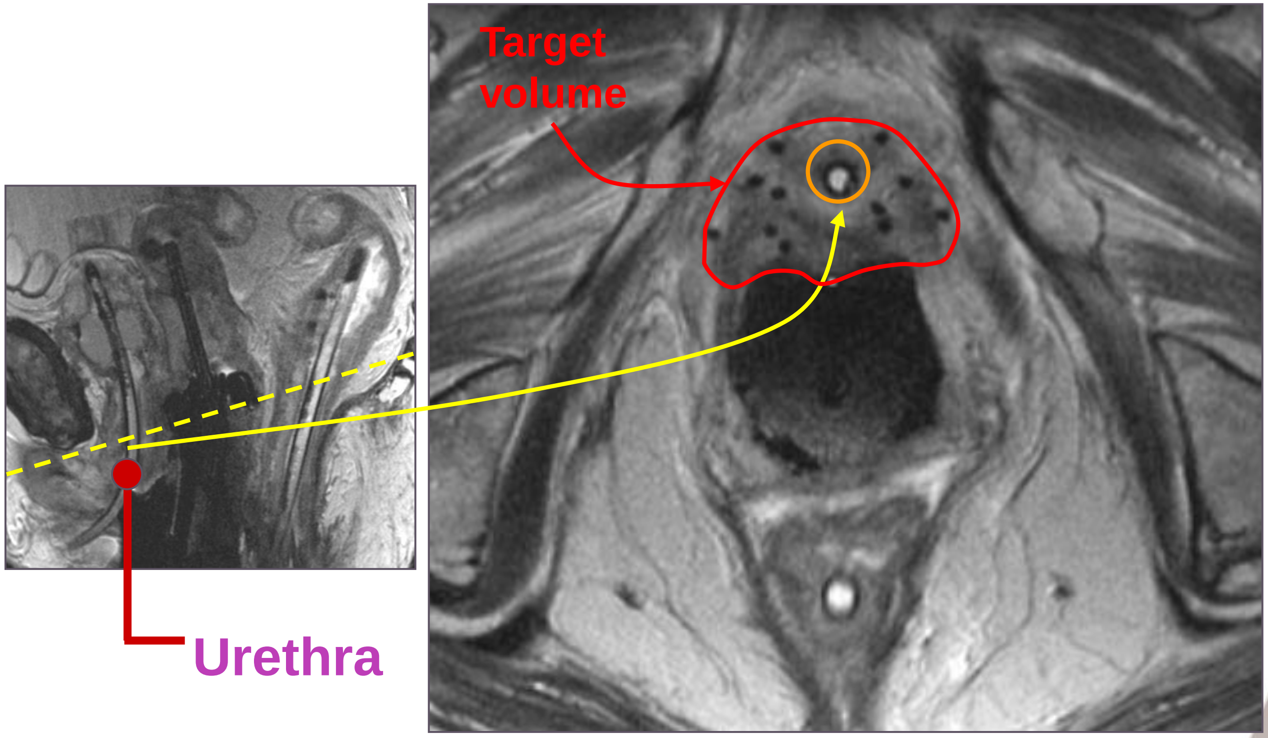


PIBS vaginal-dose point definition : 2 cm posterior from the posterior-inferior border of the pubic symphysis at the point of this line where it crosses the applicator tandem

2 additional points : 2 cm up and down along the vaginal axis PIBS+2 = the mid of the vagina and PIBS-2 = the introitus level

Other organs?

Urethra

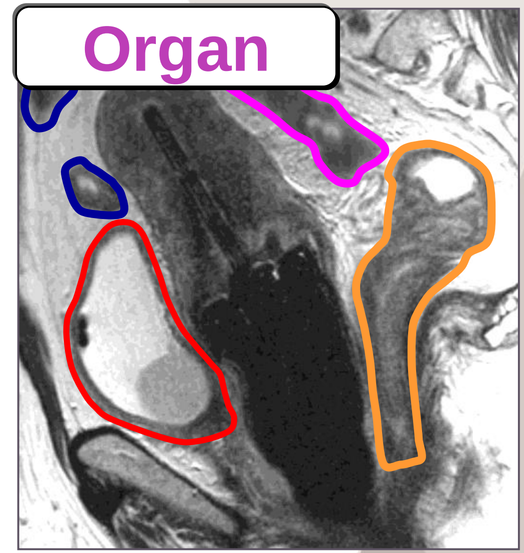


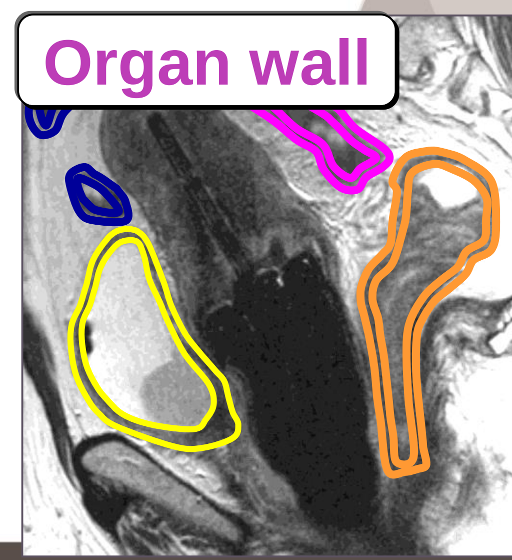
Delineate Organ or Organ wall?

Situation in Brachytherapy

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

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

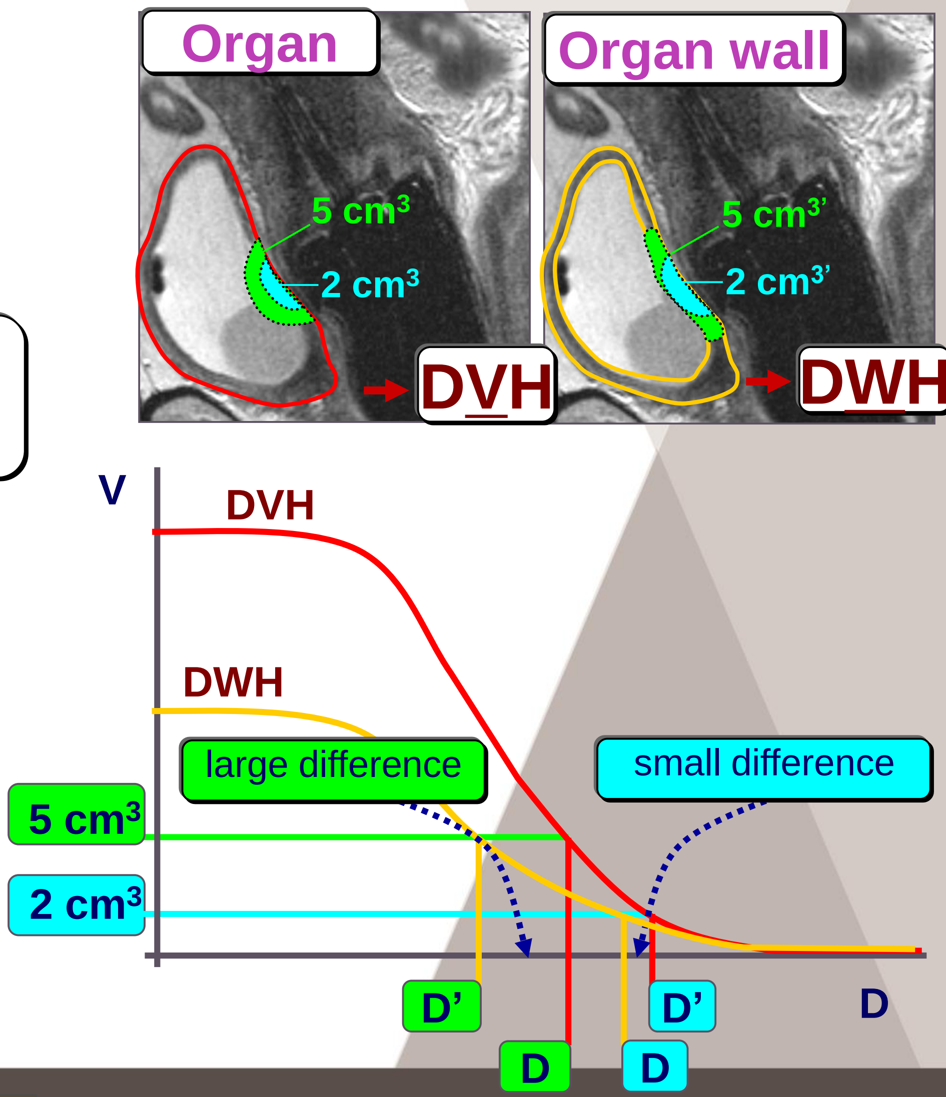




Delineate Organ or Organ wall?

Situation in Brachytherapy

Can we contour organs instead of organ walls?



Yes, if doses up to 2 cm^3 are evaluated

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

Conclusion

- Importance of GTV and CTV for the primary tumor
- Residual GTV-T (GTV-T_{res})
- Adaptive CTV-T (CTV-T_{adapt})
- High-Risk CTV-T (CTV-THR)
- Intermediate-Risk CTV-T (CTV-TIR)
- OAR delineation


Cafe de Flore
CAFE DE FLORE
CAFE DE FLORE
HOTEL

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

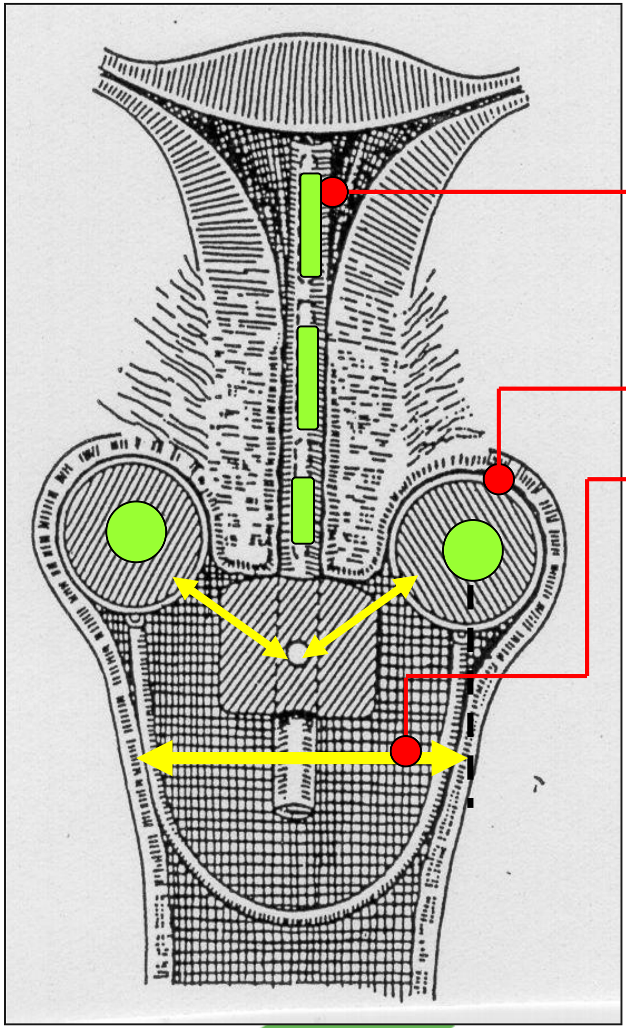
Bengaluru, 2017

30’

Historical Systems & Techniques

Historical Paris Technique

1910-1920: Curie Institute, Paris, France



GEC ESTRO *Handbook of Brachytherapy*

Applicator:

- Rubber tandem
- Cork colpostats (paraffin coated)

Rubber tandem and cork colpostats: 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

Historical
Paris
Stockholm
Manchester
Fletcher

Modern
Stockholm
Manchester & Fletcher
Mould

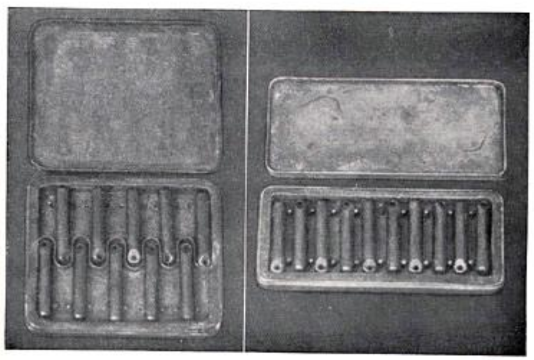
Limitations of IC Applicators

Emerging Technologies

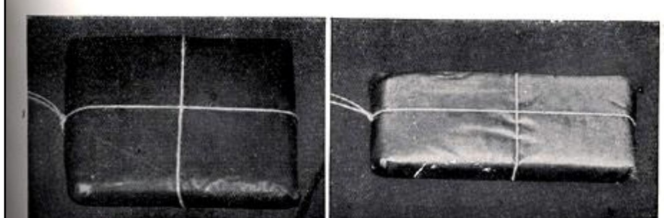
Classical Stockholm method

1913-1914: Radiumhemmet, Stockholm, Sweden

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

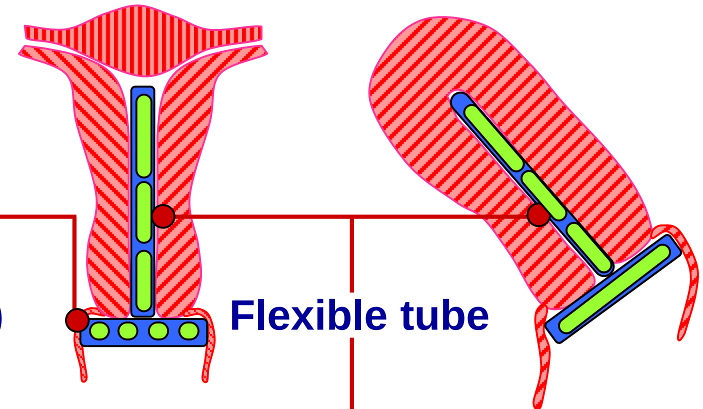


Figs. 9 and 10. The same applicators with their tubes.



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

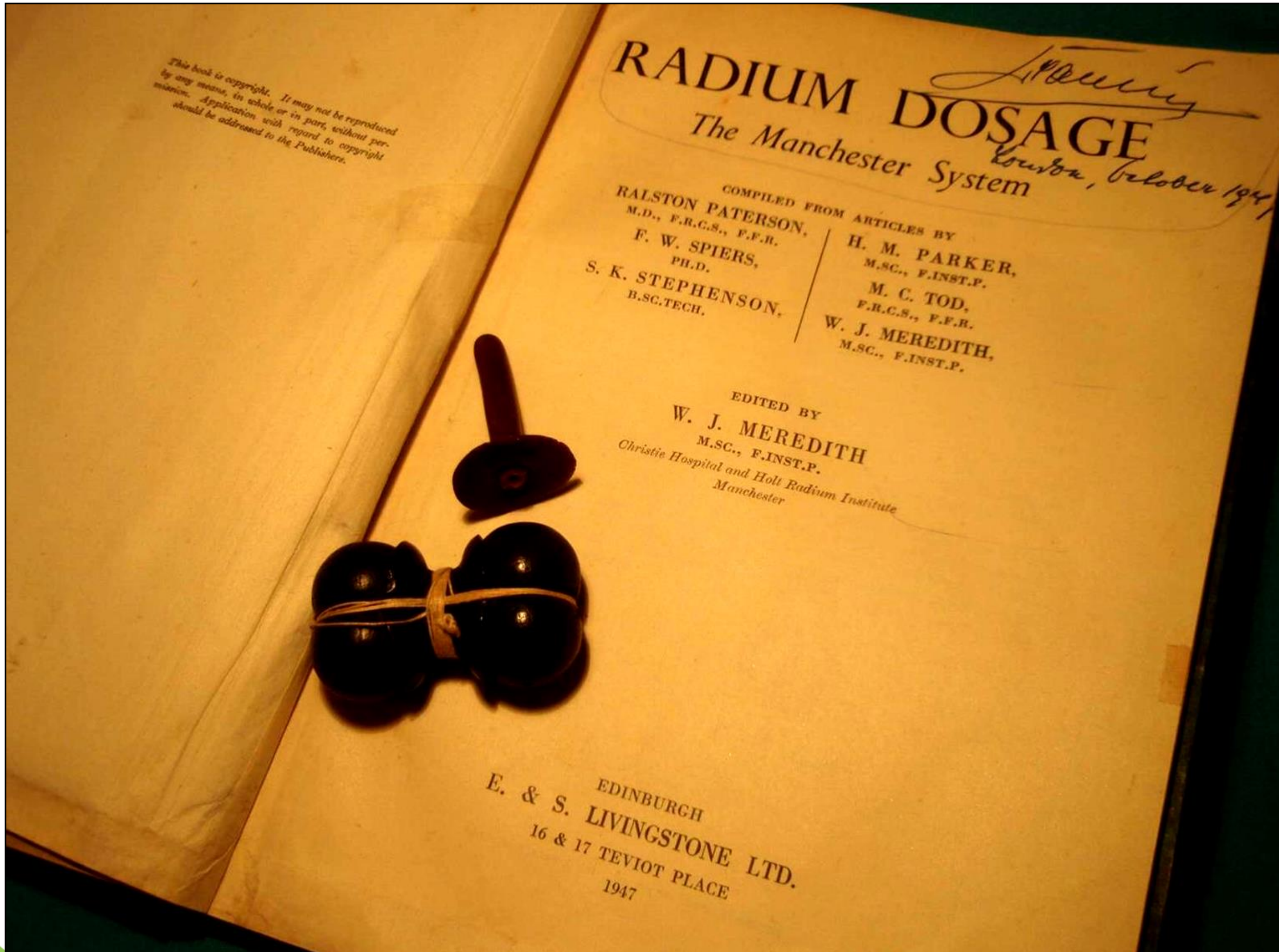
- X mg of ^{226}Ra for Y hours

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

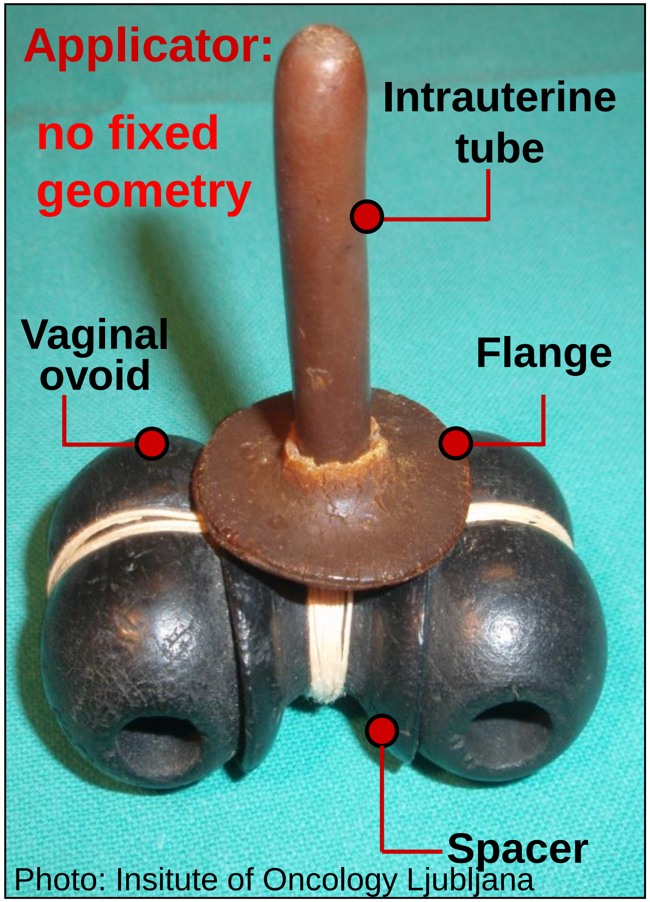
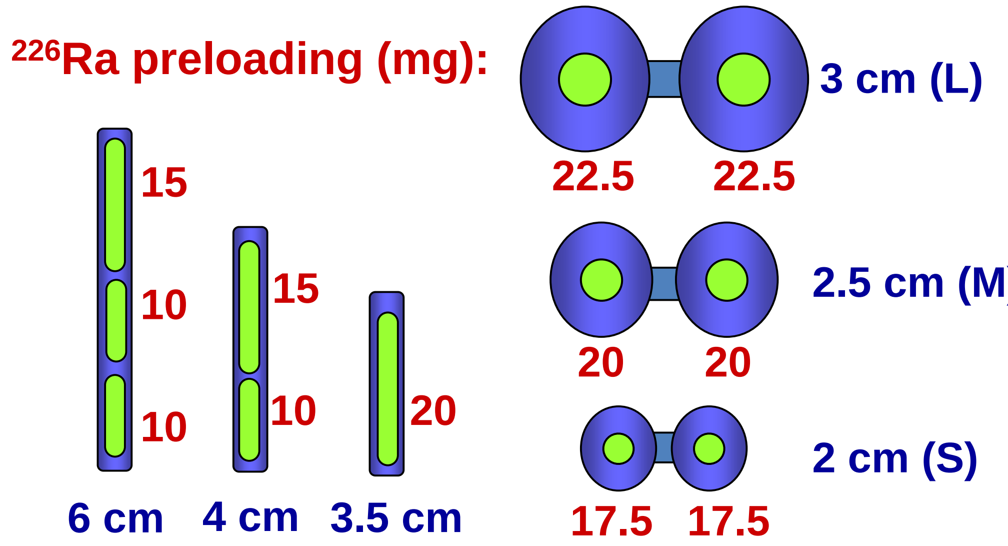
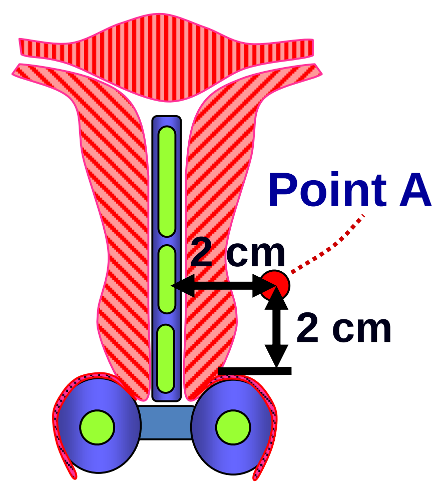


Photo: Insitute of Oncology Ljubljana



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



Given tumour volume

↓

A set of rules

- Geometry
- mg of ^{226}Ra
- Duration

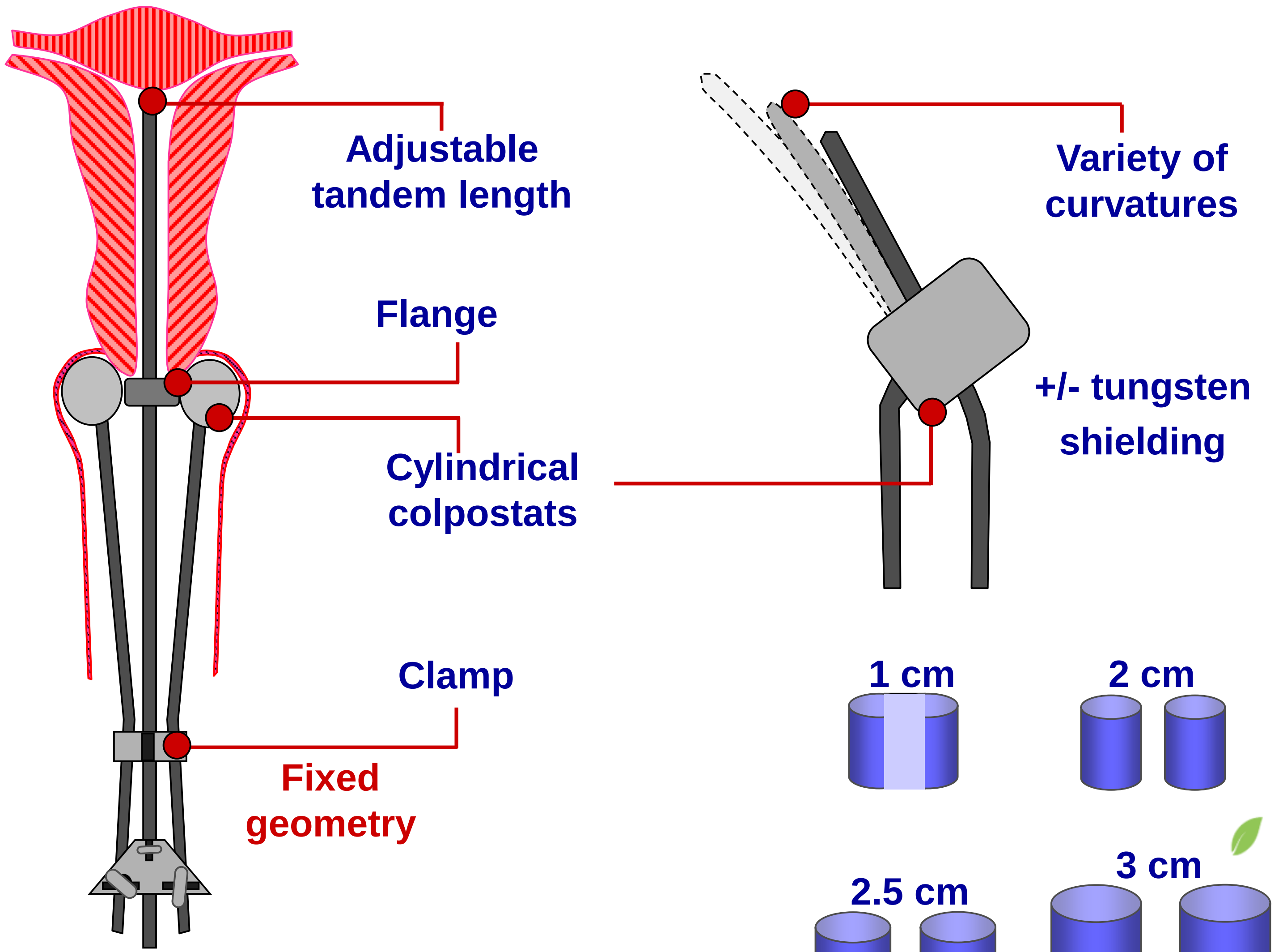
↓

Certain point A dose

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

Fletcher–Suit–Delclos–Horiot Technique

1950's: Fletcher

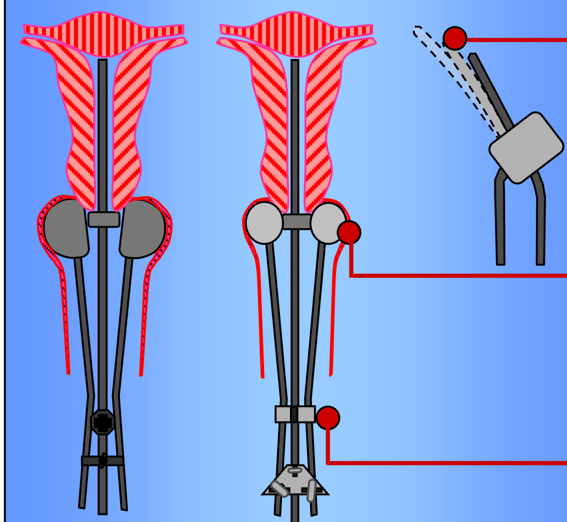


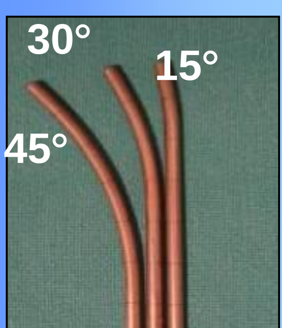
Modern Intracavitary Techniques

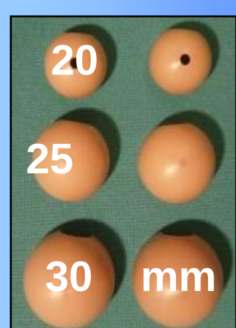
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher tyle







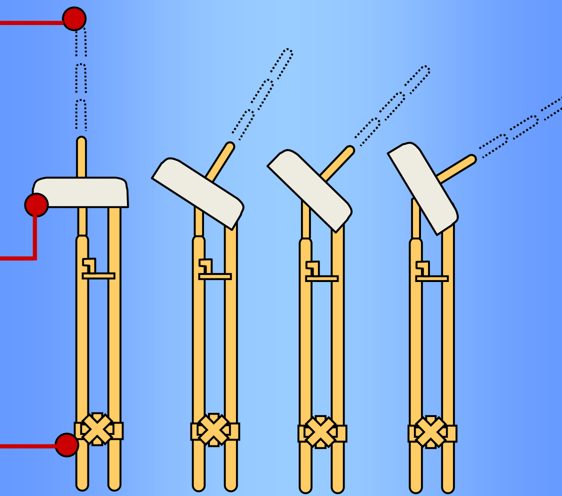
Common features:

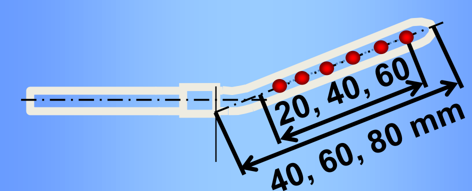
Uterine Tandem:
various lengths, angles or curvatures

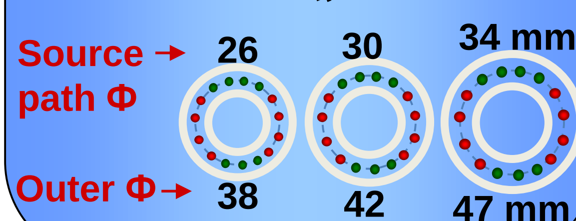
Ovoids, cylinders, rings
various outer & source path diameters

Clamp

Stockholm style



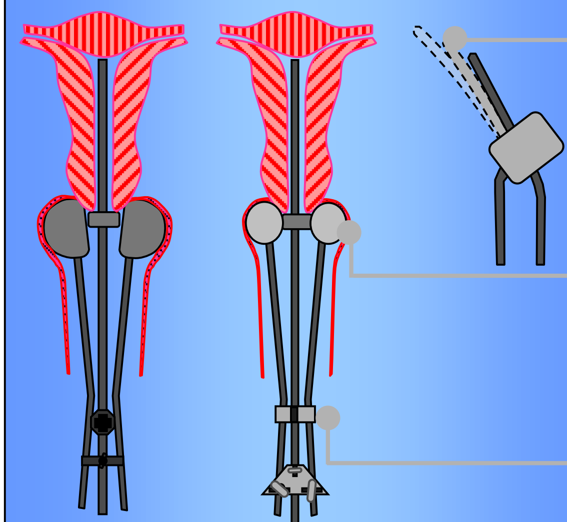




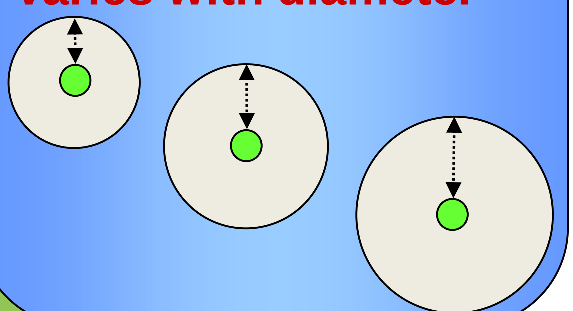
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Varies with diameter



Common features:

Uterine Tandem: various lengths, angles or curvatures

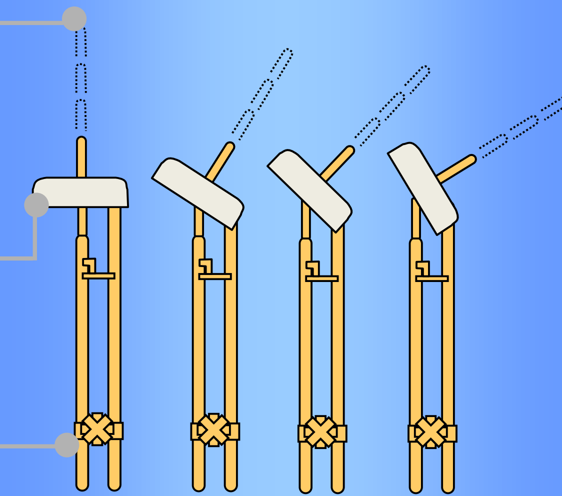
Ovoids, cylinders, rings various outer & source path diameters

Clamp

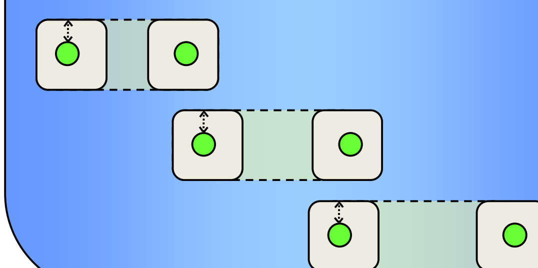
Differences:

Thickness of ovoids and rings

Stockholm style



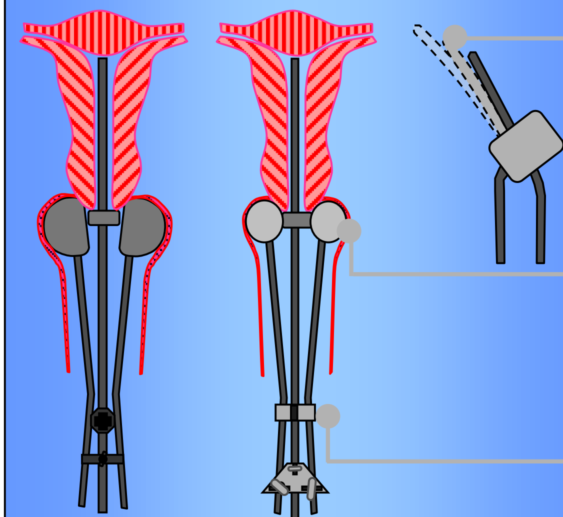
Constant



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



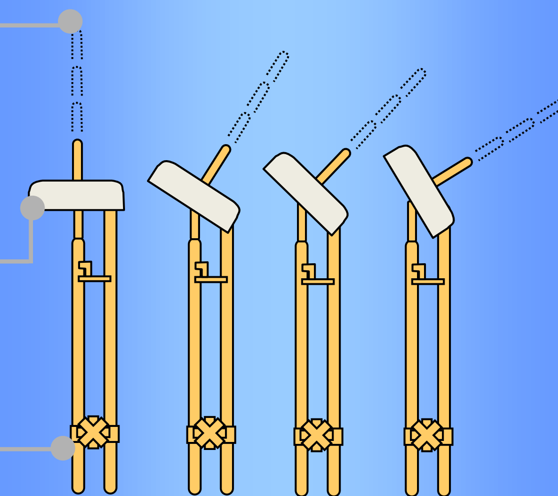
Common features:

Uterine Tandem: various lengths, angles or curvatures

Ovoids, cylinders, rings various outer & source path diameters

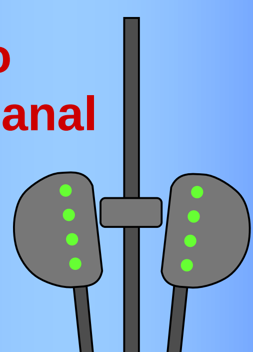
Clamp

Stockholm style



Differences:

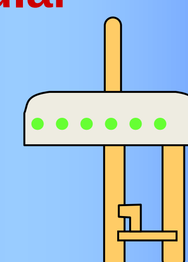
Parallel to cervical canal



Manchester style

Source path orientation

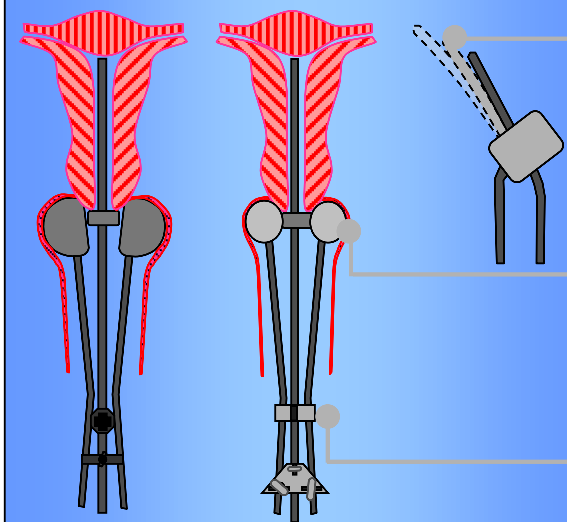
Perpendicular to cervical canal



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

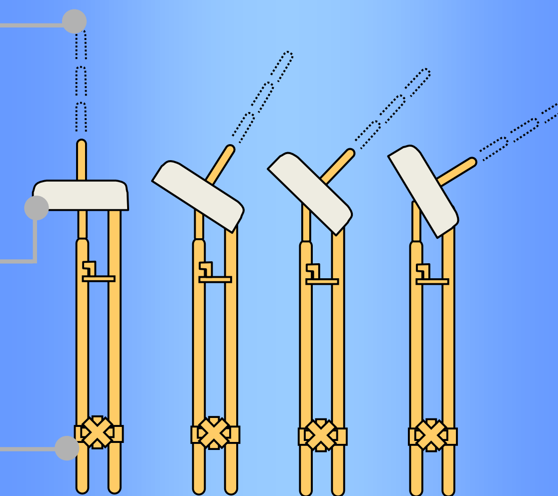
Manchester / Fletcher style



Common features:

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

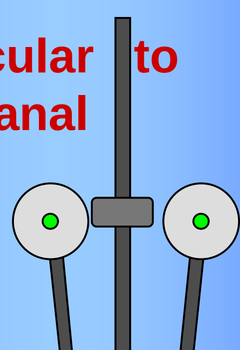
Stockholm style



Differences:

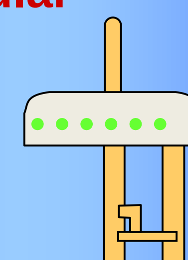
Source path orientation

Perpendicular to cervical canal



Fletcher style

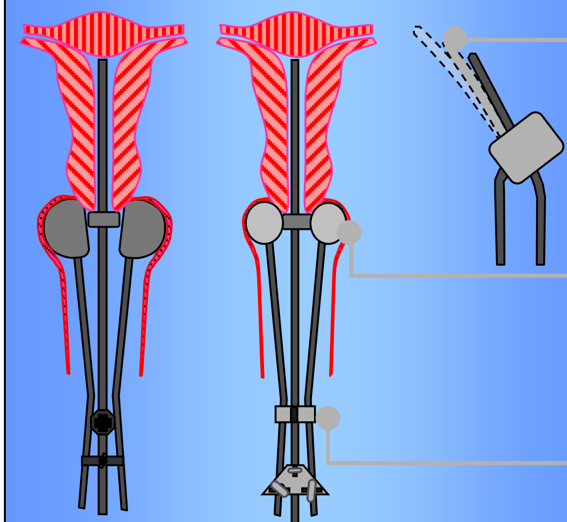
Perpendicular to cervical canal



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

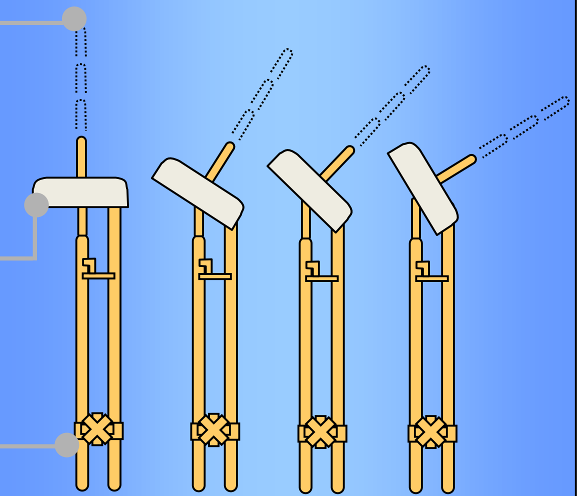
Manchester / Fletcher style



Common features:

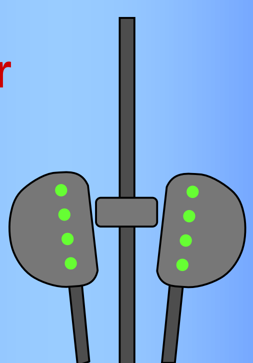
- Uterine Tandem: various lengths, angles or curvatures
- Ovoids, cylinders, rings various outer & source path diameters
- Clamp

Stockholm style



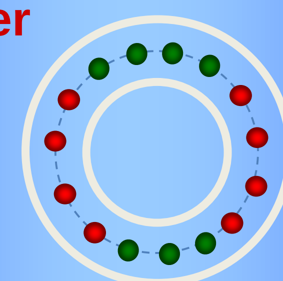
Differences:

Lower



Loading flexibility

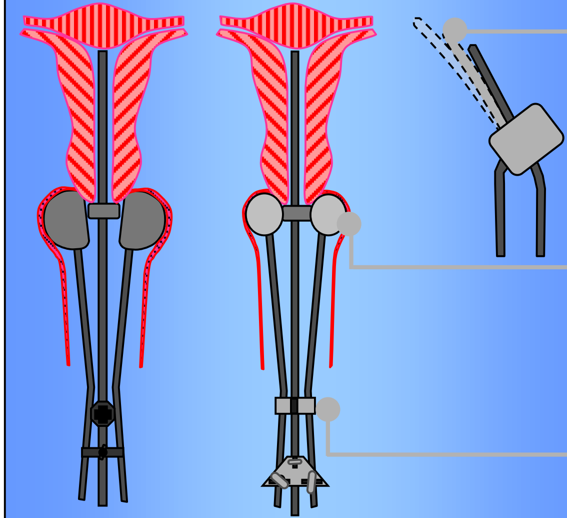
Higher



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



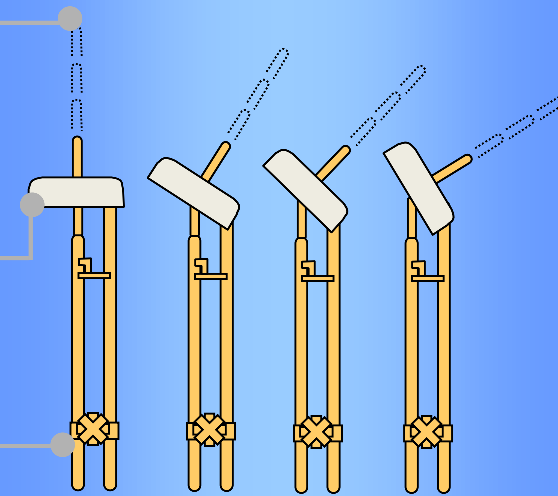
Common features:

Uterine Tandem: various lengths, angles or curvatures

Ovoids, cylinders, rings various outer & source path diameters

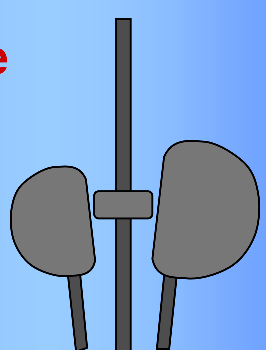
Clamp

Stockholm style



Differences:

Possible



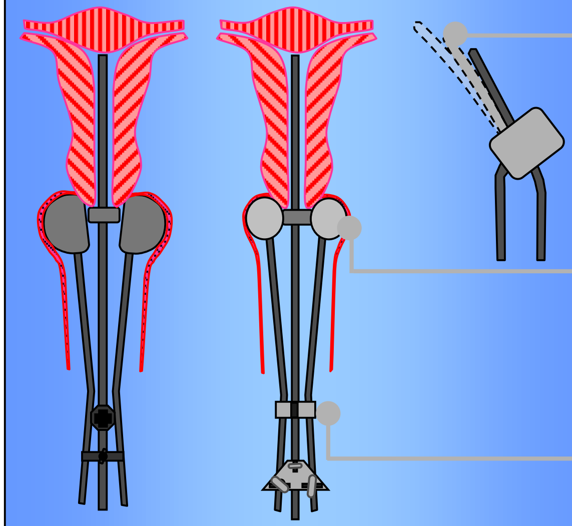
Asymetric insertion

Not applicable

Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



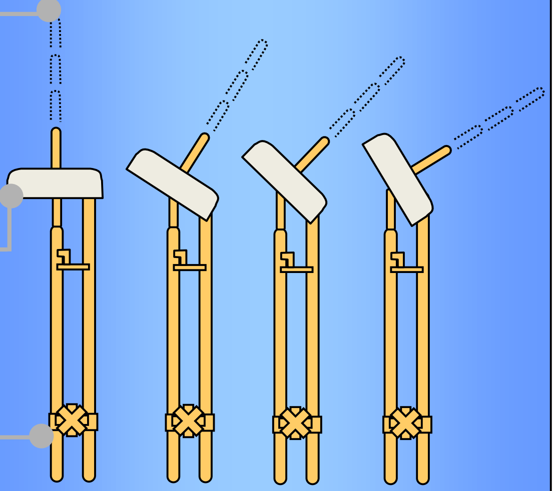
Common features:

Uterine Tandem: various lengths, angles or curvatures

Ovoids, cylinders, rings various outer & source path diameters

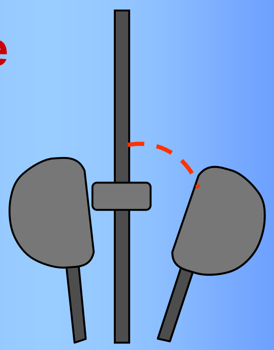
Clamp

Stockholm style



Differences:

Possible

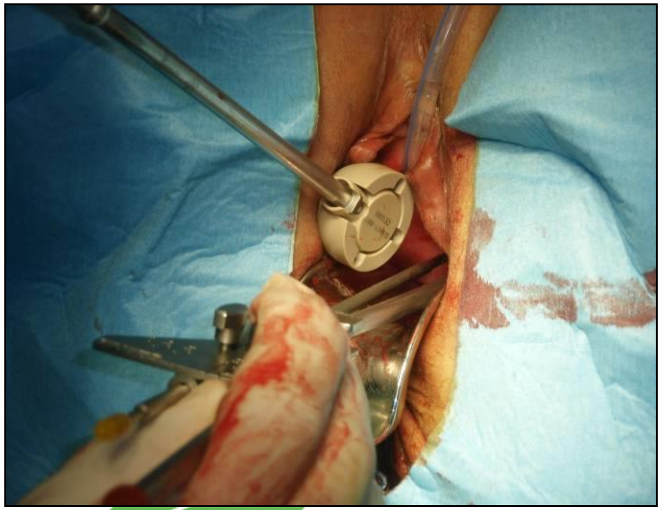


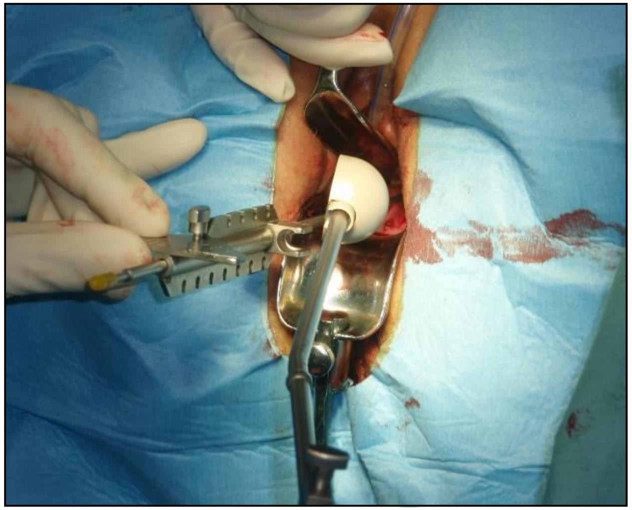
Adjustable spacing

Not applicable

Modern Intracavitary Techniques

Applicator insertion





Modern Intracavitary Techniques


Concept: same as 100 years ago…

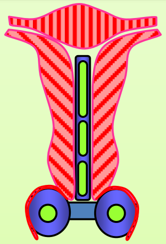
Modern IC techniques

Materials: Imaging…

Channel diameters: Smaller

Loading patterns: Mimicking historical

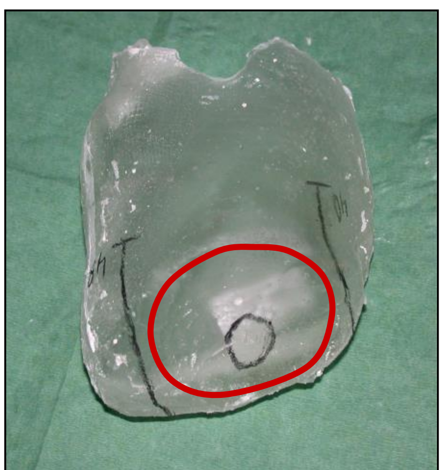


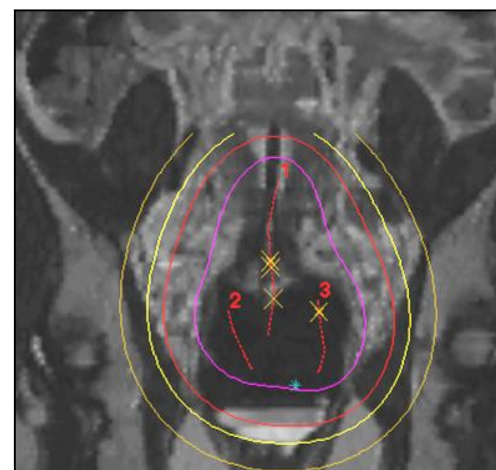


Mould Technique

Personalized applicators

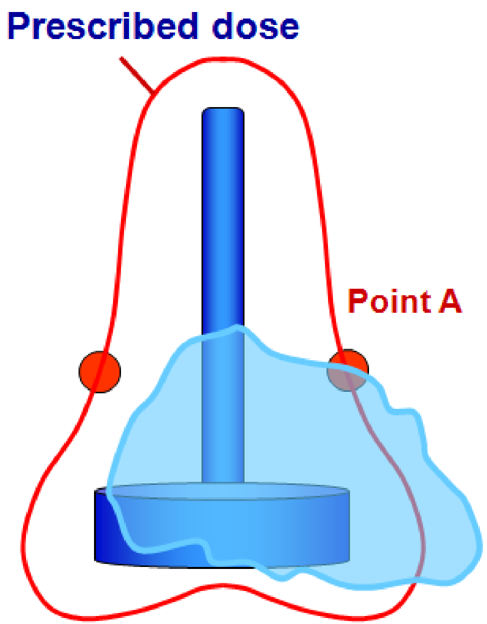
- Individually adapted to anatomy & tumour
- Good patient tolerance
- No need for vaginal packing
- MRI compatibility
- Prolonged bed rest avoided





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

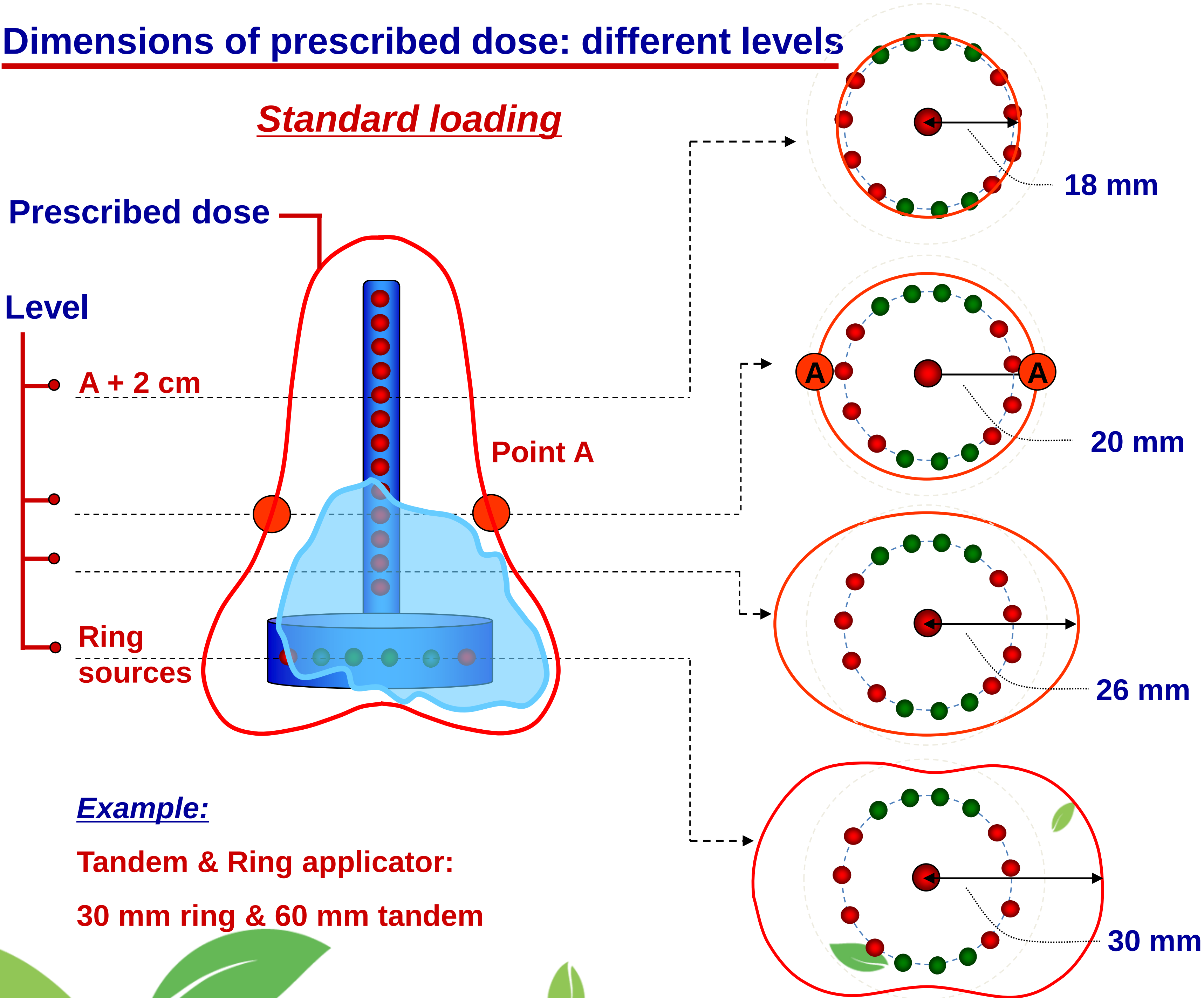
B. Up to ~ 5 mm

C. Up to ~ 10 mm

D. Up to ~ 20 mm

Dimensions of prescribed dose: different levels

Standard loading

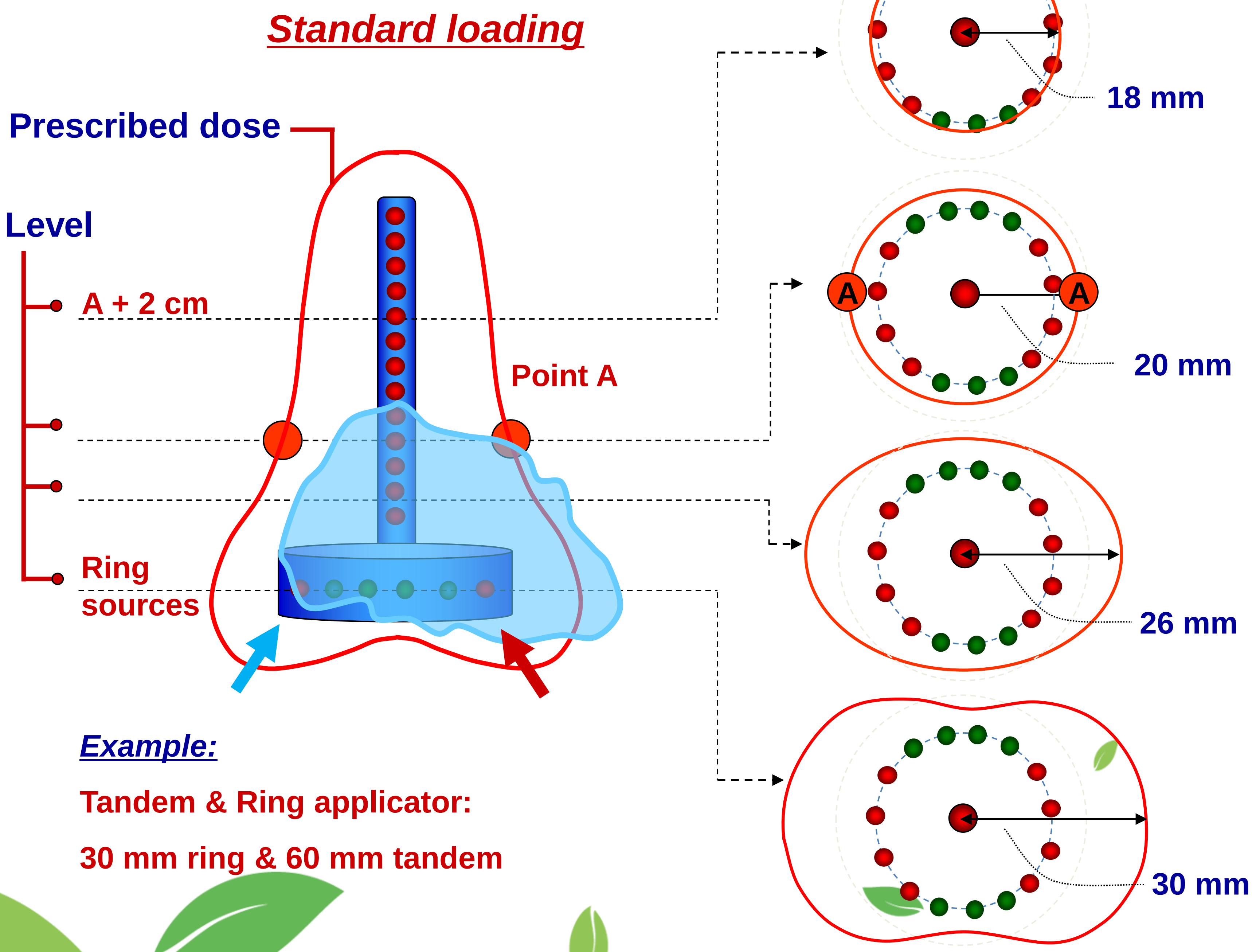


Example:

Tandem & Ring applicator:

30 mm ring & 60 mm tandem

Dimensions of prescribed dose: different levels

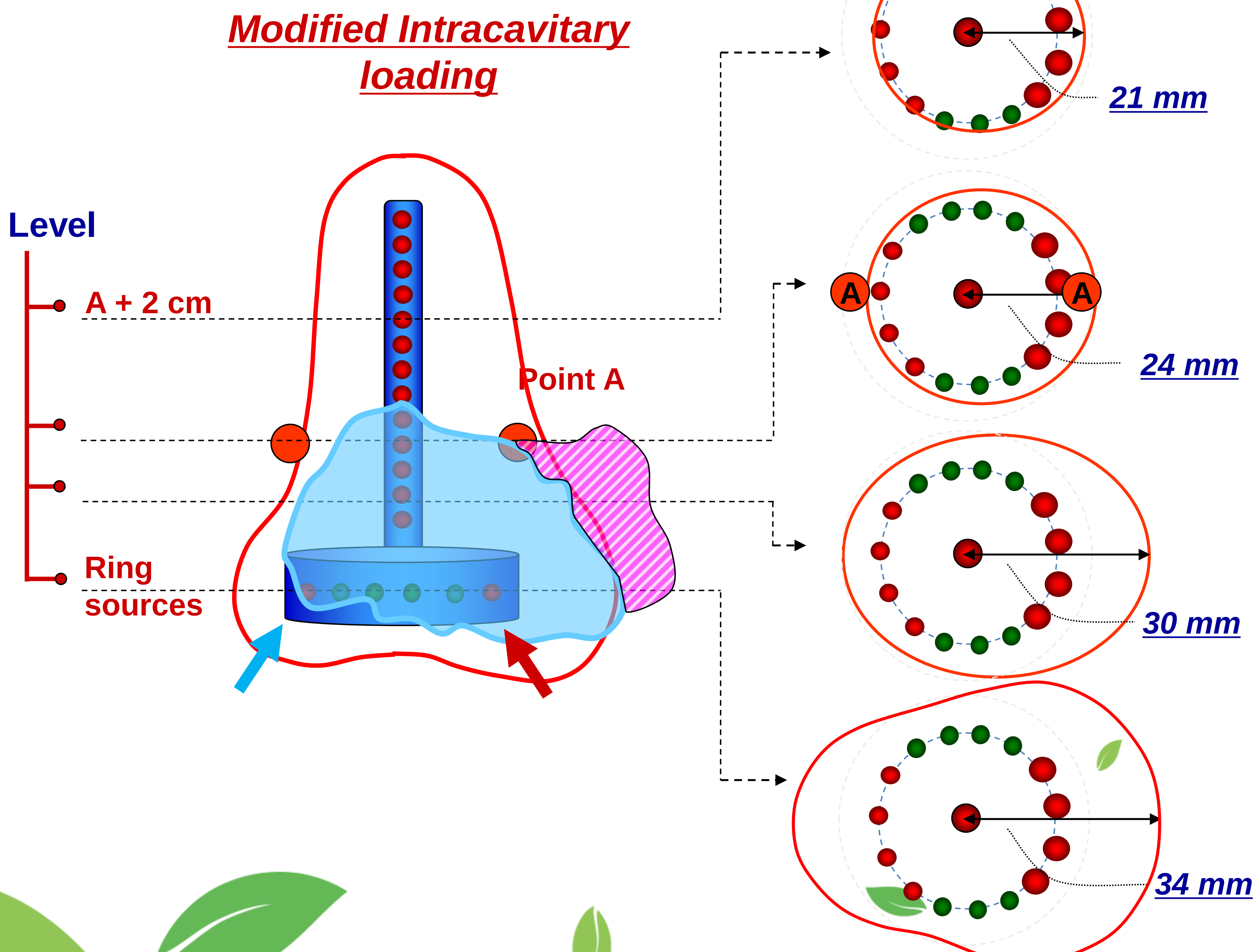


Example:

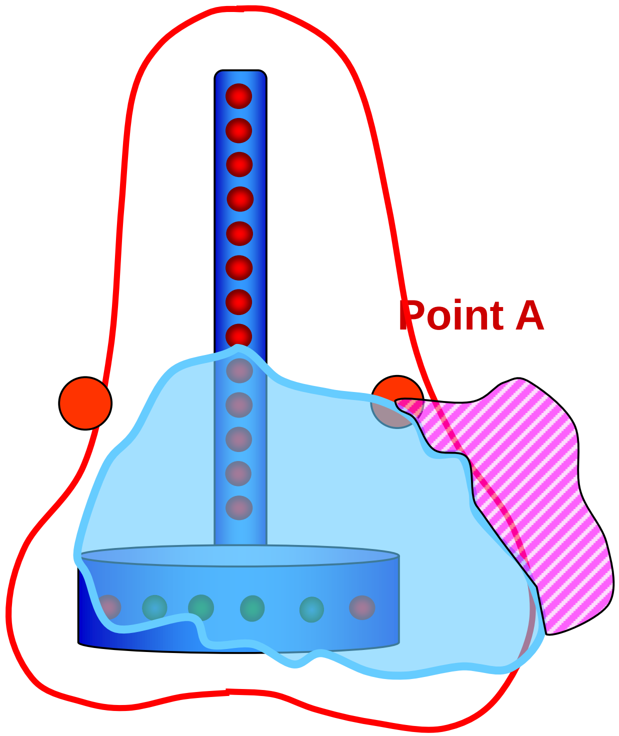
Tandem & Ring applicator:

30 mm ring & 60 mm tandem

Dimensions of prescribed dose: different levels

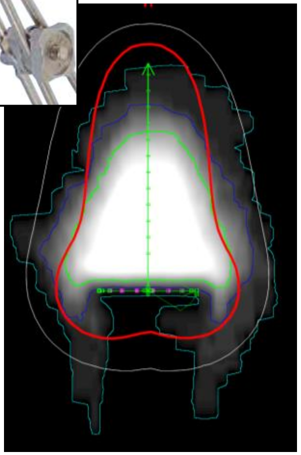


Overcoming limitations of IC applicators



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 3 D adaptation
- Emerging technologies:
  - Intracavitary/interstitial techniques
  - Comprehensive applicator IC/IS (Vienna II type)
  - 3D printing



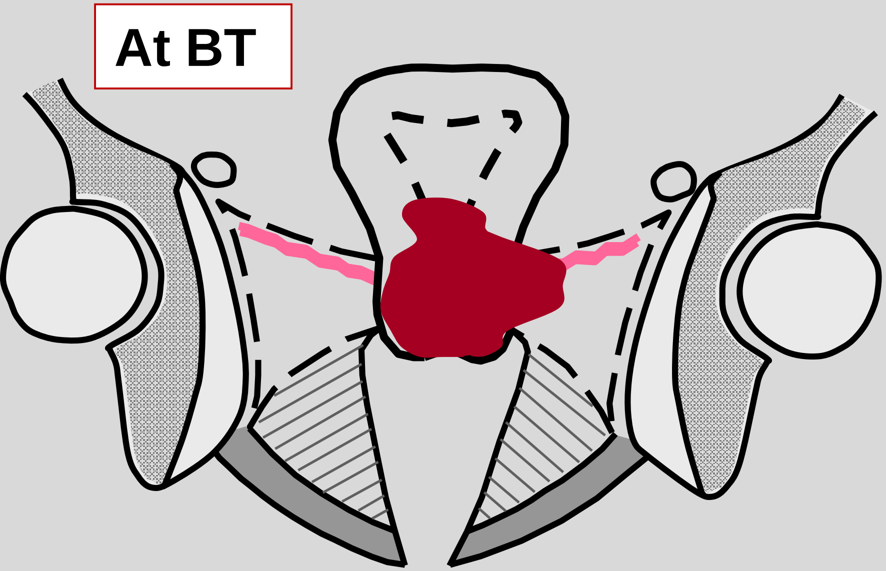
Combined intracavitary-interstitial technique for cervix cancer

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

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

Adapted and presented
Richard Pötter, Medical University of Vienna

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



A. Standard Intracavitary

B. Intracavitary + interstitial

C. EBRT boost

D. EBRT boost + Intracavitary

KBD

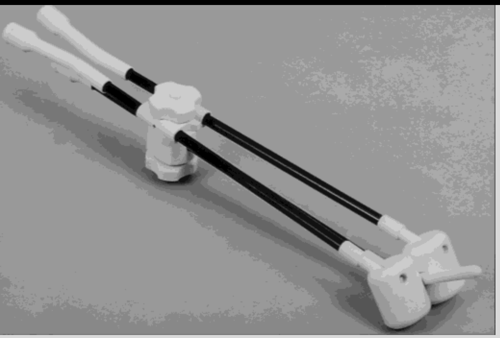
OUTLINE

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

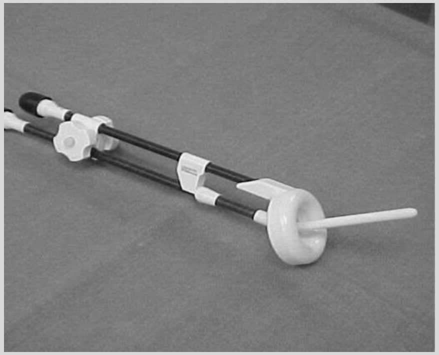
Limitations of pure intracavitary techniques

- *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



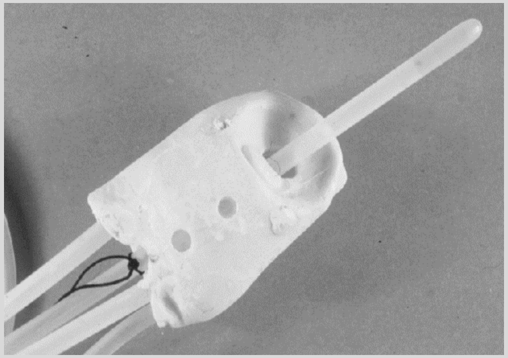
Modern Manchester Applicator

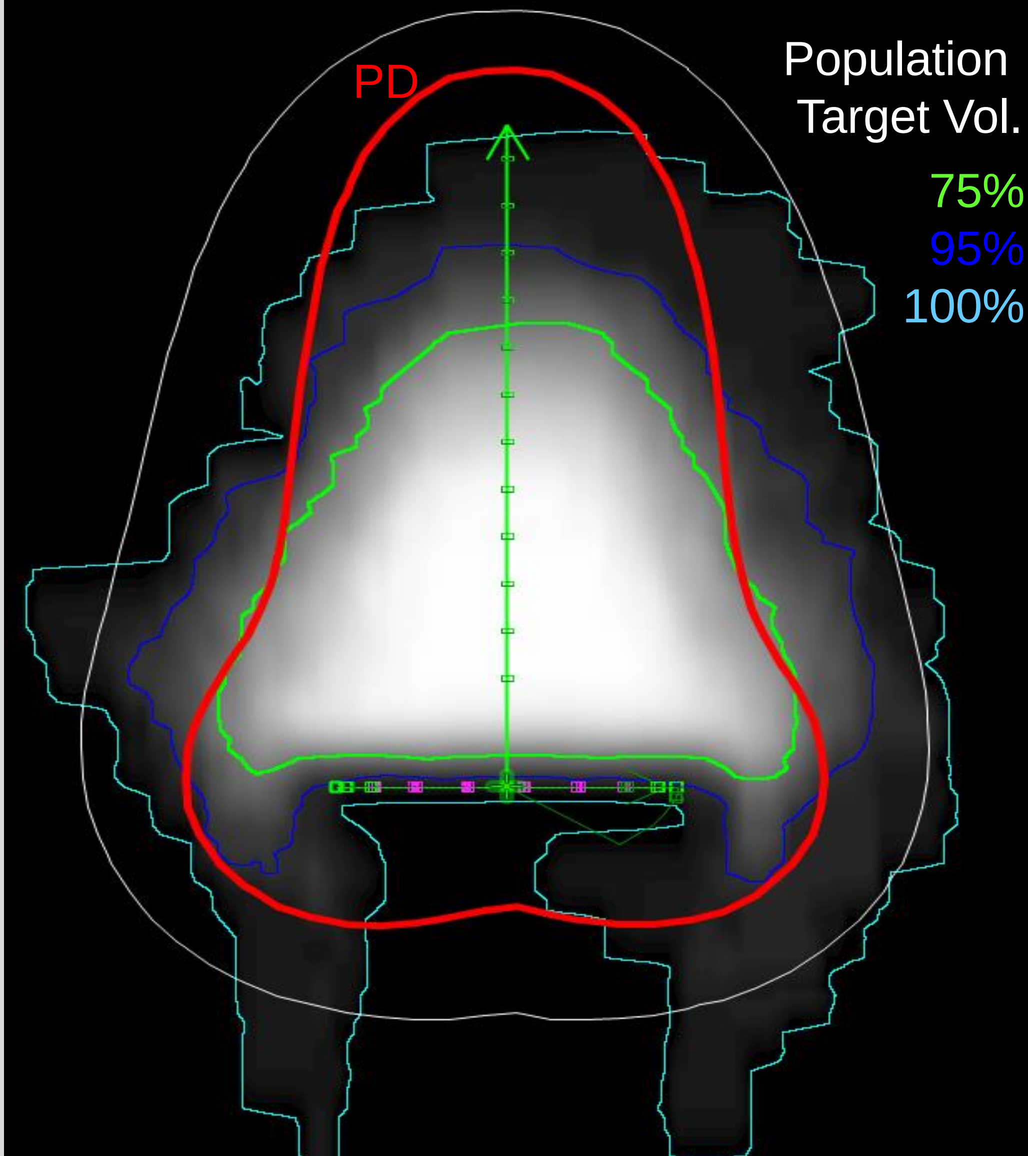


Modern Stockholm Applicator

Ring applicator

Mould Applicator





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

Courtesy: P. Petric,D. Berger

Indications for combined intracavitary/interstitial

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

INTERSTITIAL TECHNIQUES AIMS IN LOCALLY ADVANCED DISEASE

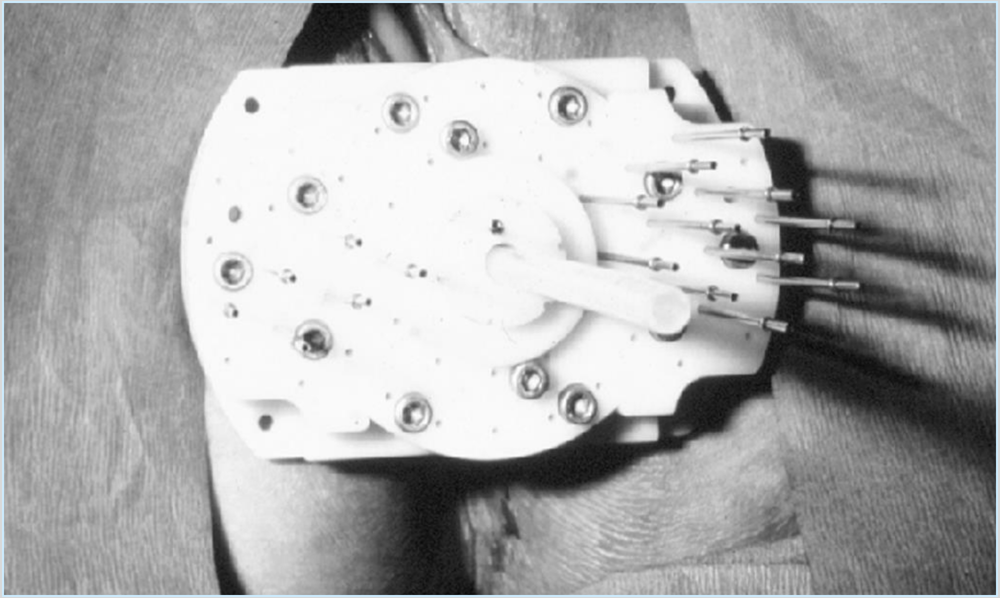
- *accurate and reproducible placement of needles*
- *tailor positions of needles to the target*
- *tailor dose distribution to target and OAR*
  - *adequate target coverage*
  - *Optimal sparing of OAR*

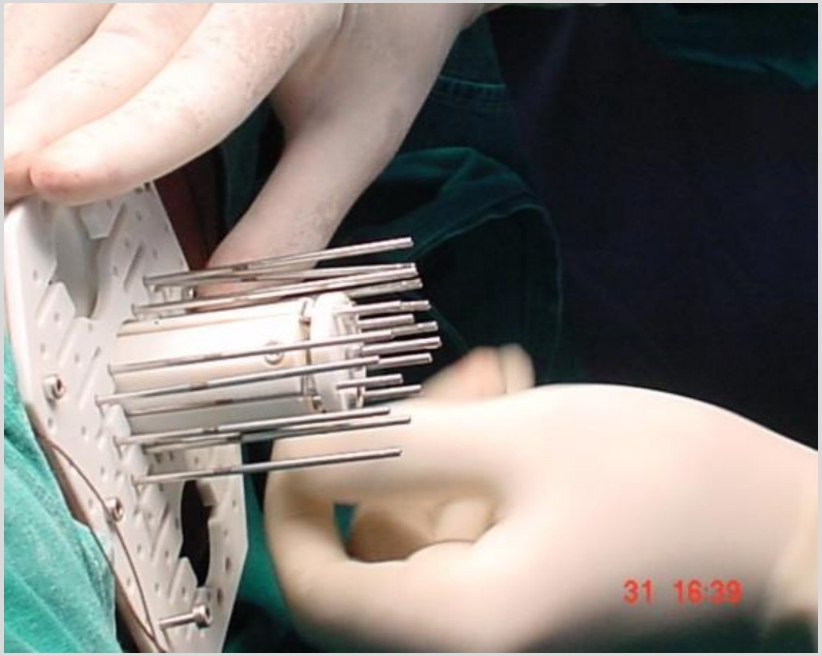
CLASSICAL INTERSTITIAL TECHNIQUES
FREEHAND PLACEMENT

CLASSICAL INTERSTITIAL TECHNIQUES
PERINEAL TEMPLATES

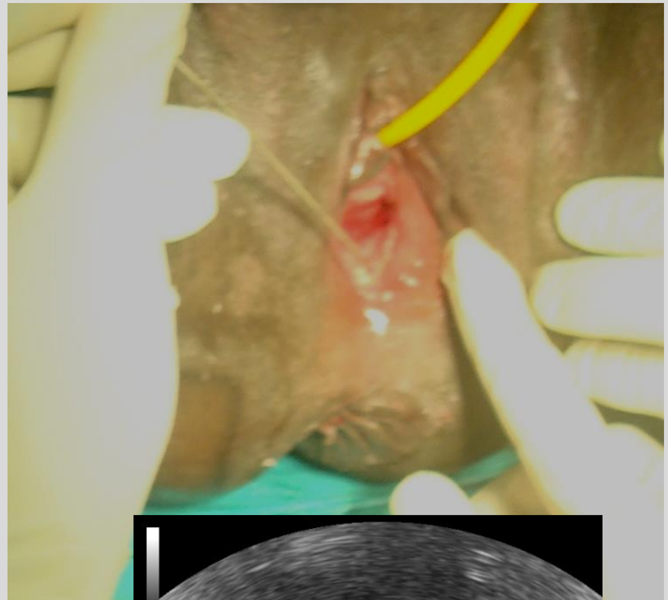
SYED

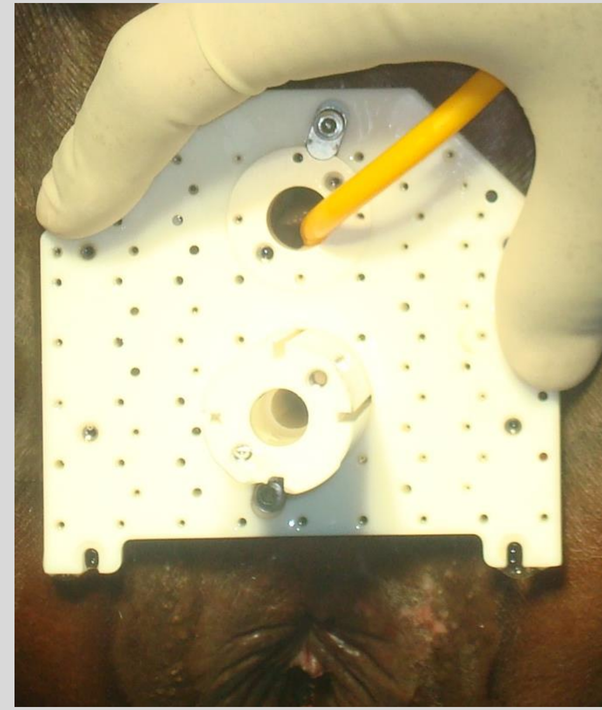
MUPIT

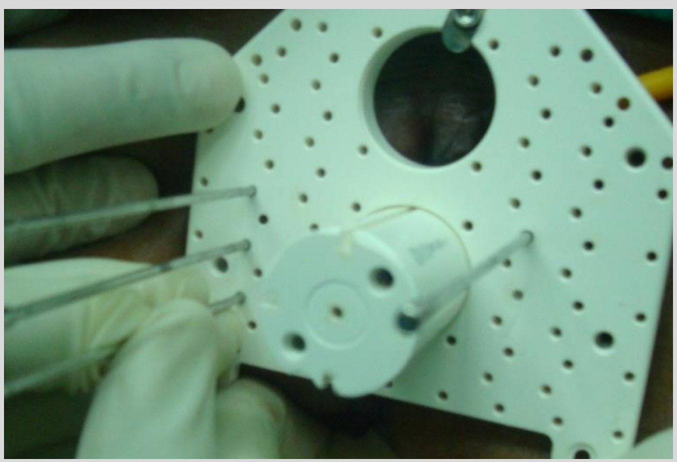


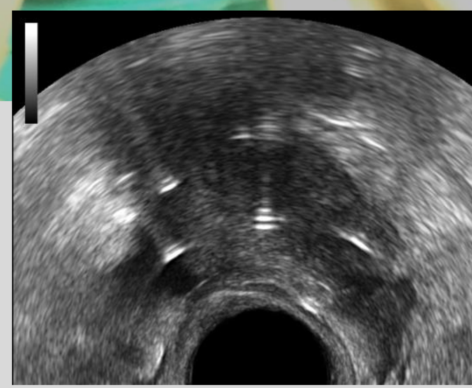


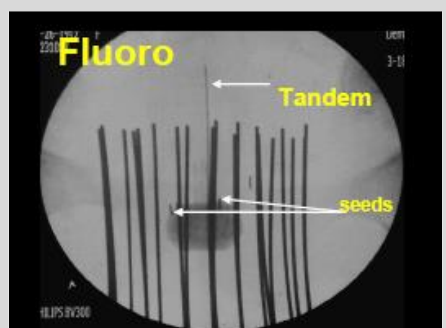
PRINICPLES OF MUPIT PROCEDURE

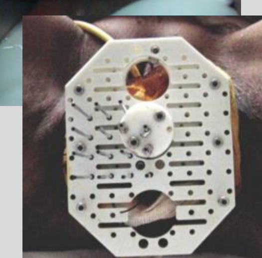






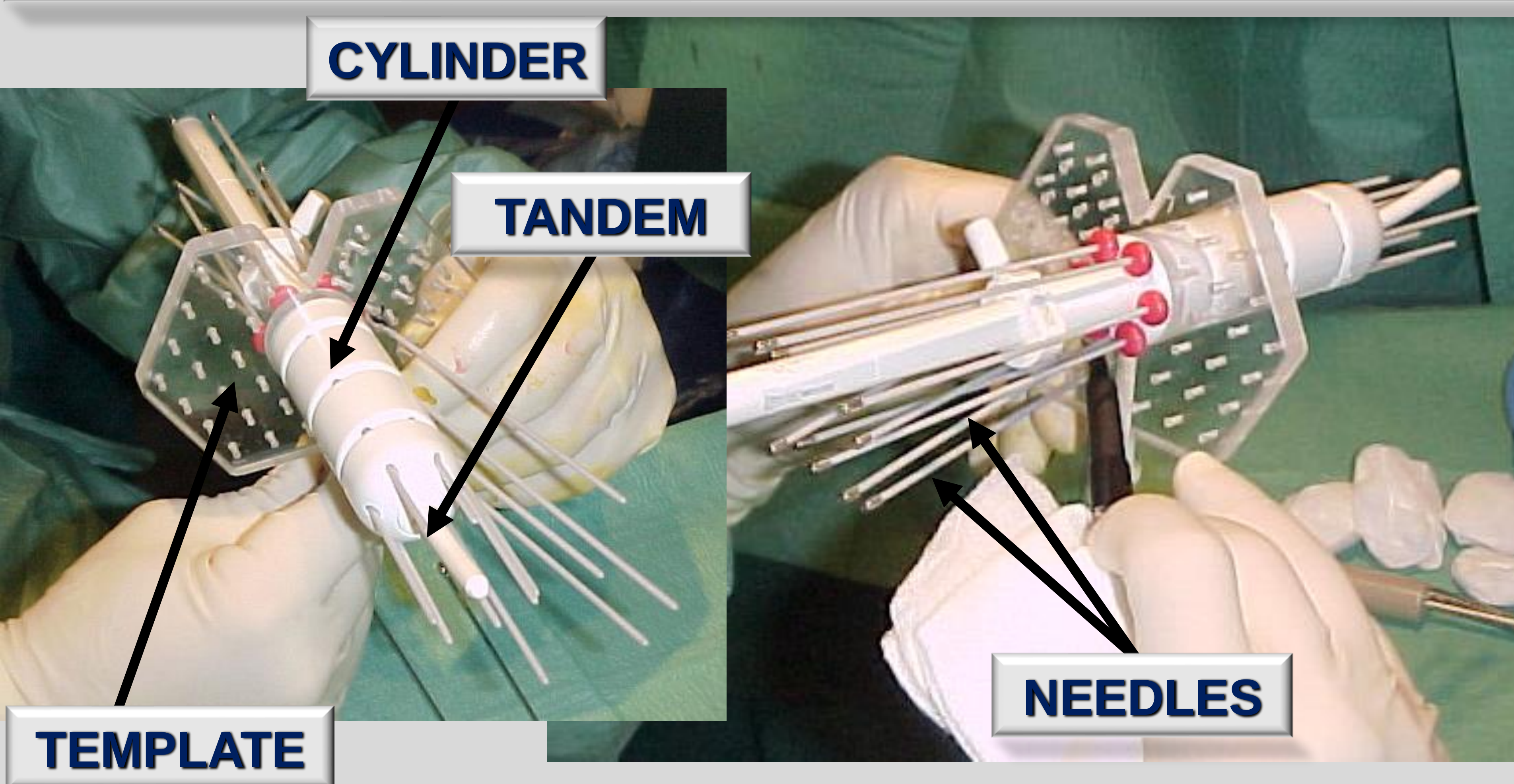






MODIFIED CLASSICAL INTERSTITIAL TECHNIQUES

MRI-compatible cylinder + tandem + template



CLASSICAL & MODIFIED INTERSTITIAL TECHNIQUES

DRAWBACKS

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

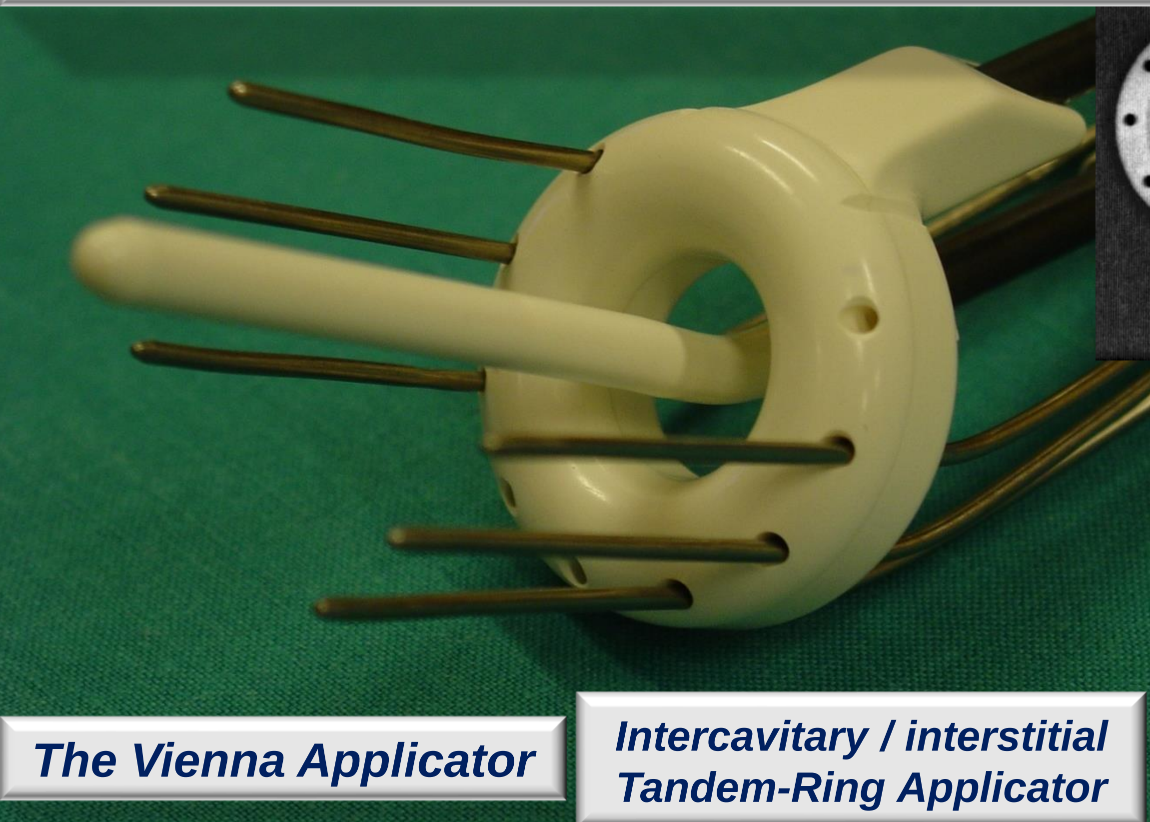
- *Perineal templates (Syed, MUPIT, others)*
  - *high number of needles used*
  - *long distances between template and target (loss of parallelism, inaccurate positioning)*
  - *impediment for general acceptance: considerable risk of serious acute/late complications*

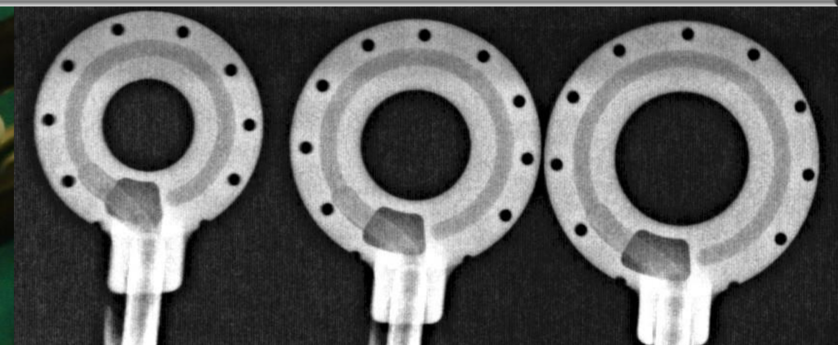
INTRACAVITARY + INTERSTITIAL TECHNIQUES

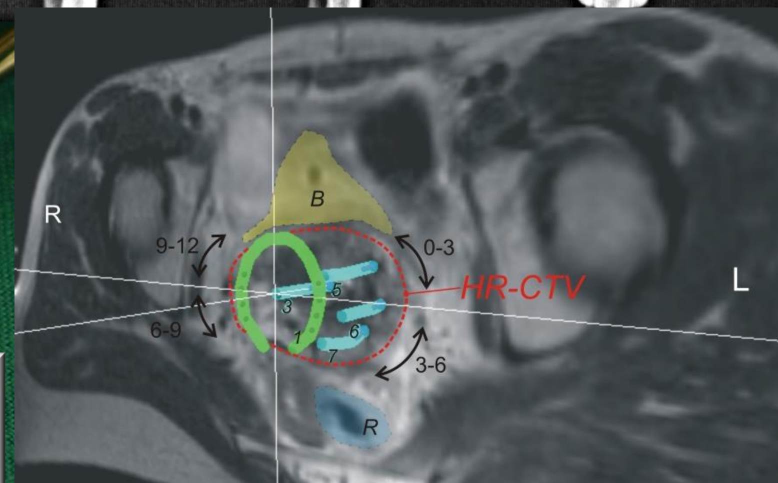
TASKS

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

MODERN INTERSTITIAL TECHNIQUES







The Vienna Applicator

Intercavitary / interstitial Tandem-Ring Applicator

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

Kirisits et al. IJROBP 2006 (technical note)
Dimopoulos et al. IJROBP 2006 (clinical results)

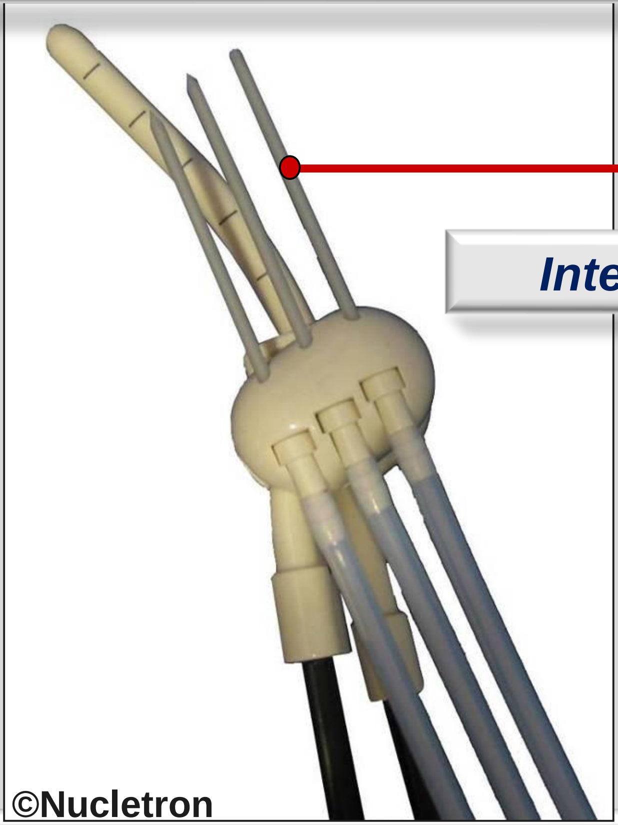
MODERN INTERSTITIAL TECHNIQUES

Applicators – special situations

Cervical cancer with moderate lateral expansion: modified principles of treatment

The Utrecht Applicator

Intracavitary / interstitial Fletcher Applicator



Schulz I, et al. Radiother Oncol., with permission

COMBINED INTRACAVITARY & INTERSTITIAL TECHNIQUES

SELECTION OF APPLICATION TECHNIQUE

Based on clinical examination and sectional imaging:

At the time of diagnosis

- Initial tumor extension

During EBRT

-Quantitative and qualitative tumor regression

At the time of brachytherapy

-Topography of residual tumor in relation to the applicator

Selection of Brachytherapy Technique

In General: depending on residual disease at brachytherapy

- Disease confined to cervix and medial third parametrium and

  favourable topography: IC alone

  unfavouable topography: combined IC + IS

- Extensions beyond medial third parametrium: IC + IS combination

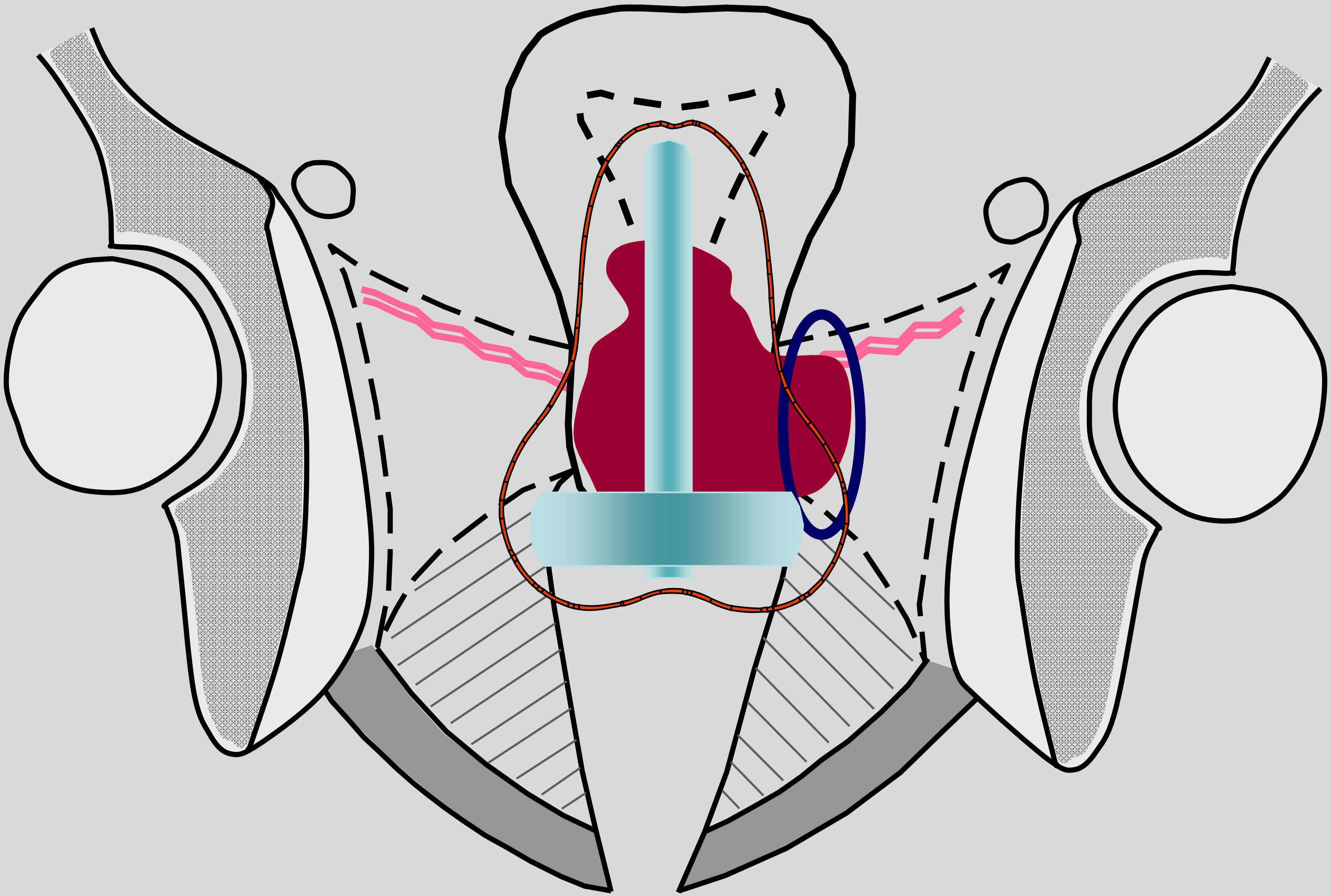
- Extensive vaginal disease at BT: vaginal cylinders + IC + IS

- Extensions beyond medial third parametrium: IC + IS combination

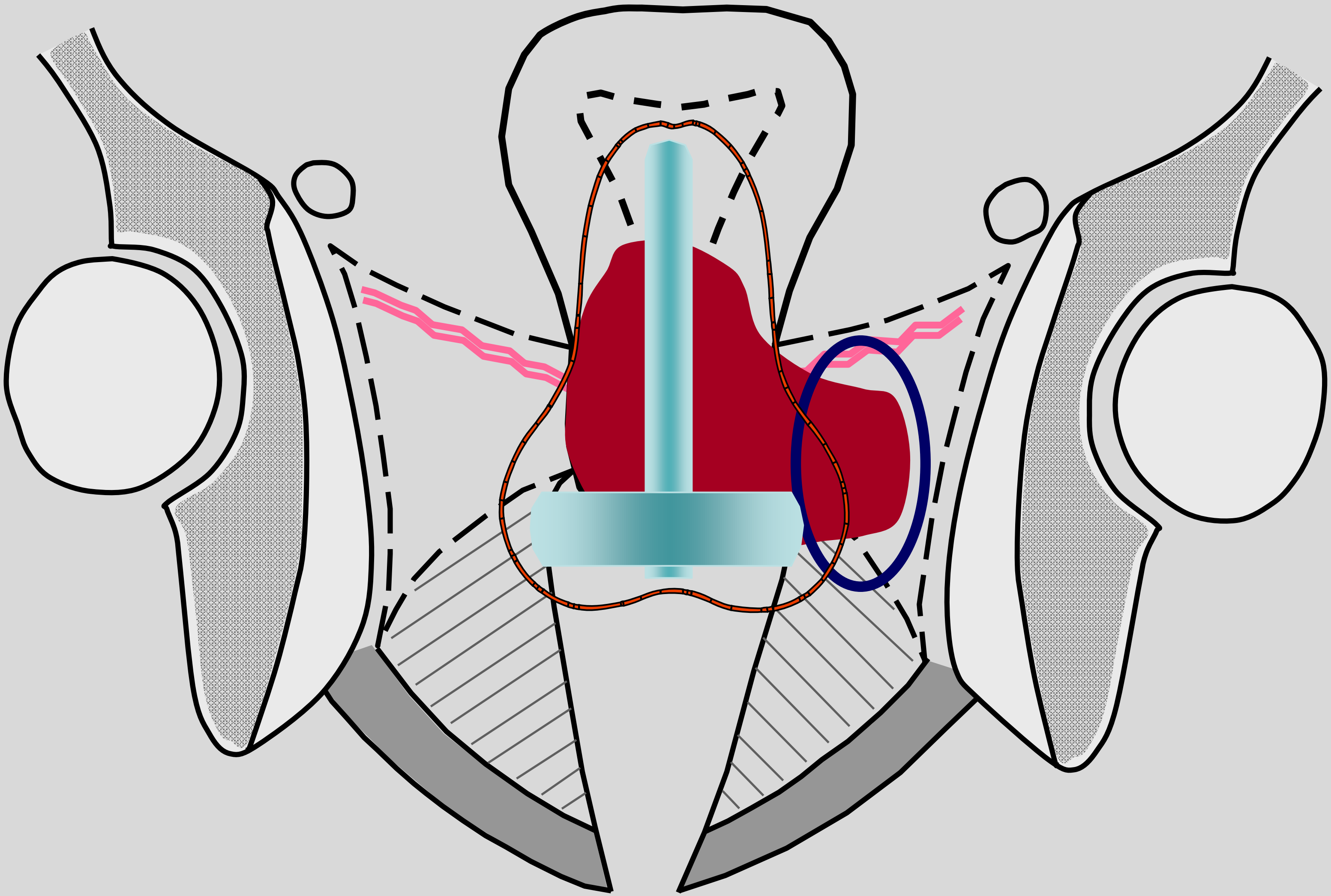
- Extensive disease not amenable to standard situations: IC + IS +…

• Applications my be modified in subsequent fractions (esp. HDR)

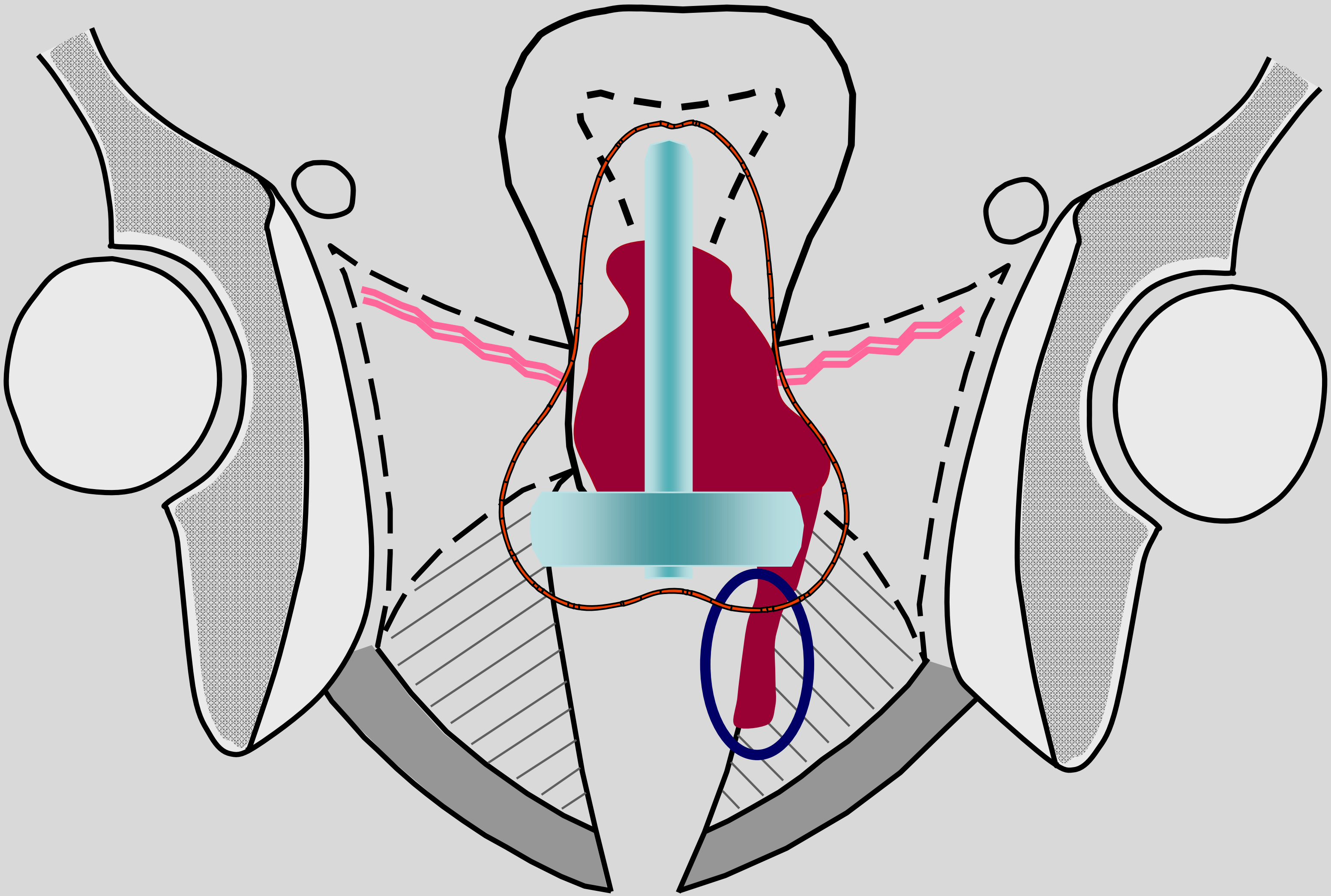
DETECTION OF INAPPROPRIATE COVERAGE: 1



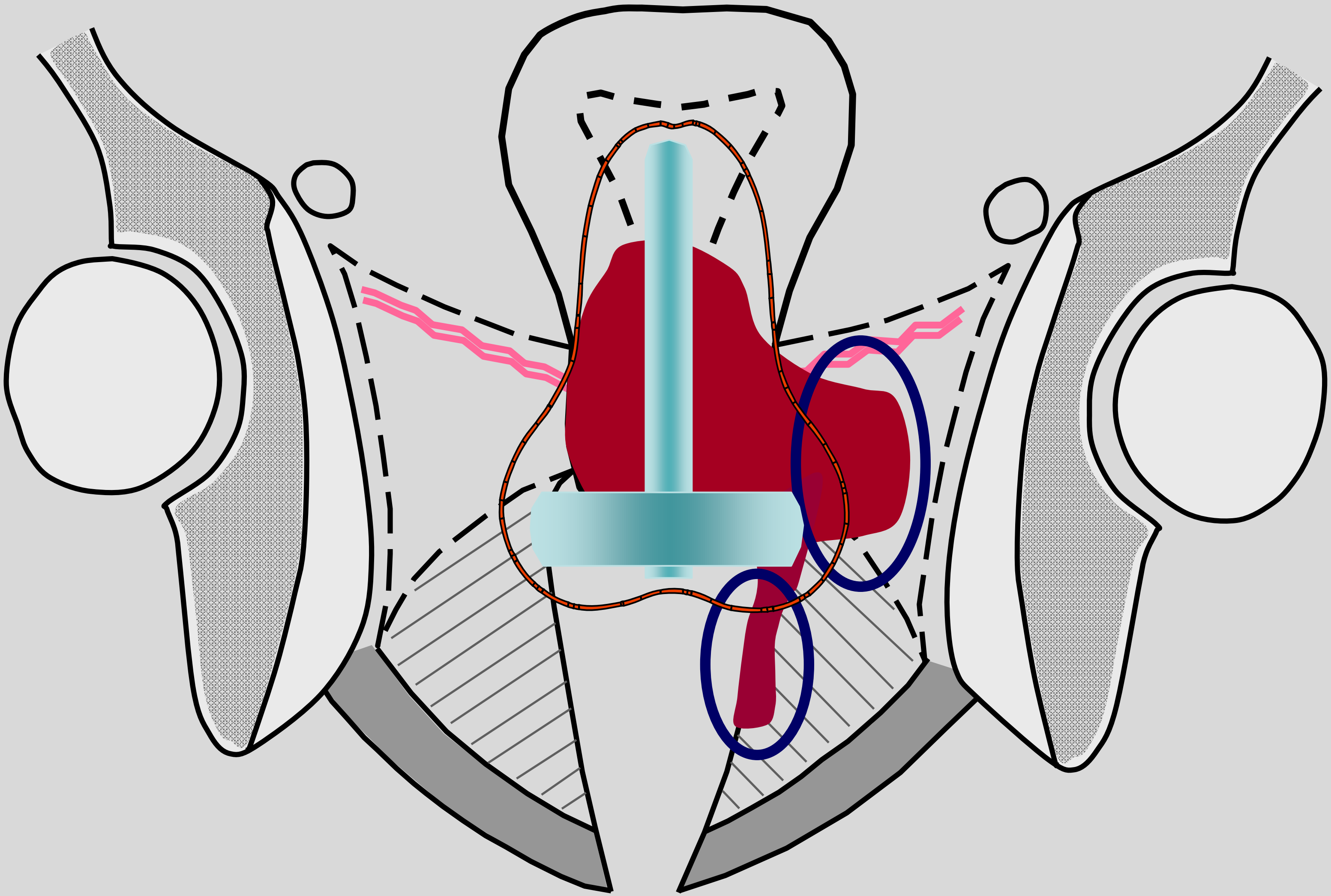
DETECTION OF INAPPROPRIATE COVERAGE: 1A



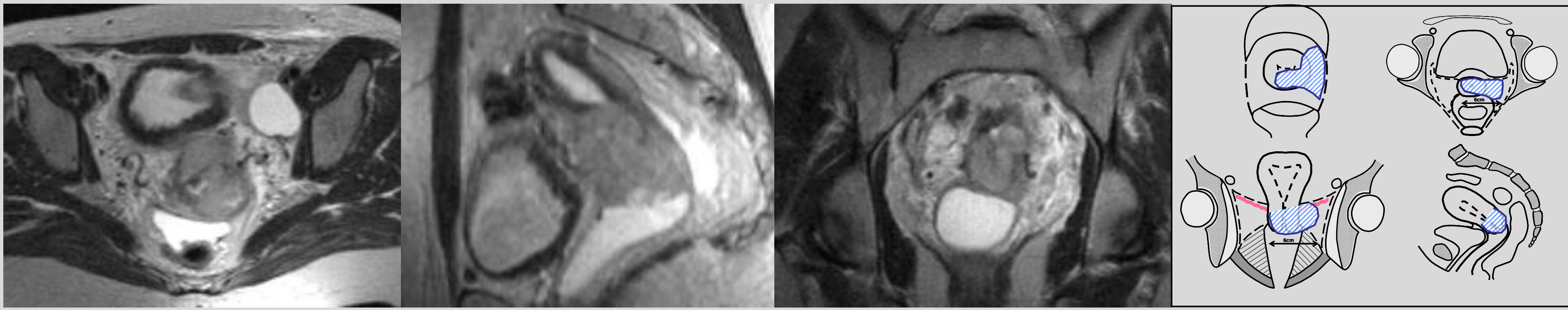
DETECTION OF INAPPROPRIATE COVERAGE: 2

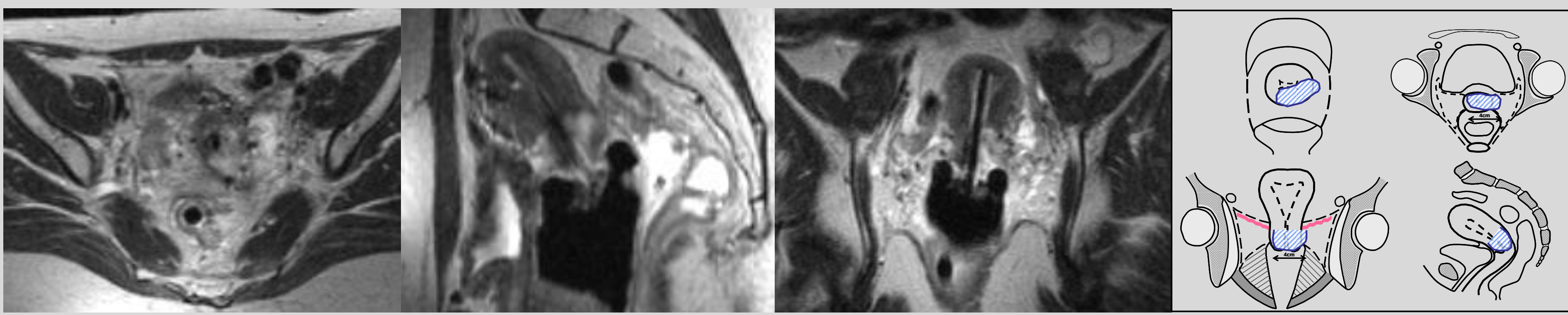


DETECTION OF INAPPROPRIATE COVERAGE: 2A



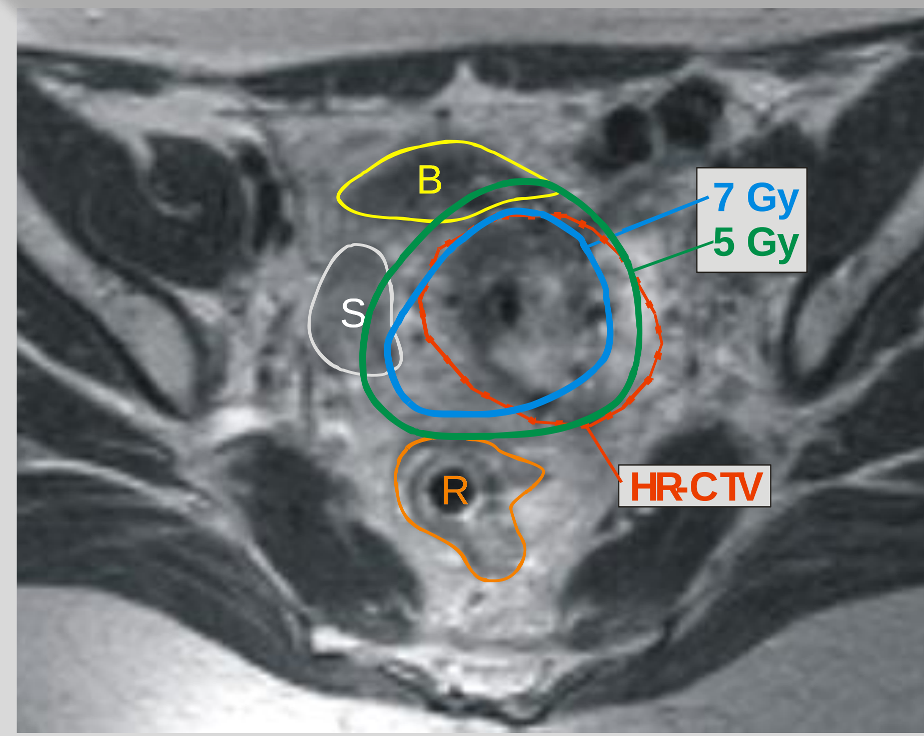
Clinical example
Stage IIB / distal / insufficient response

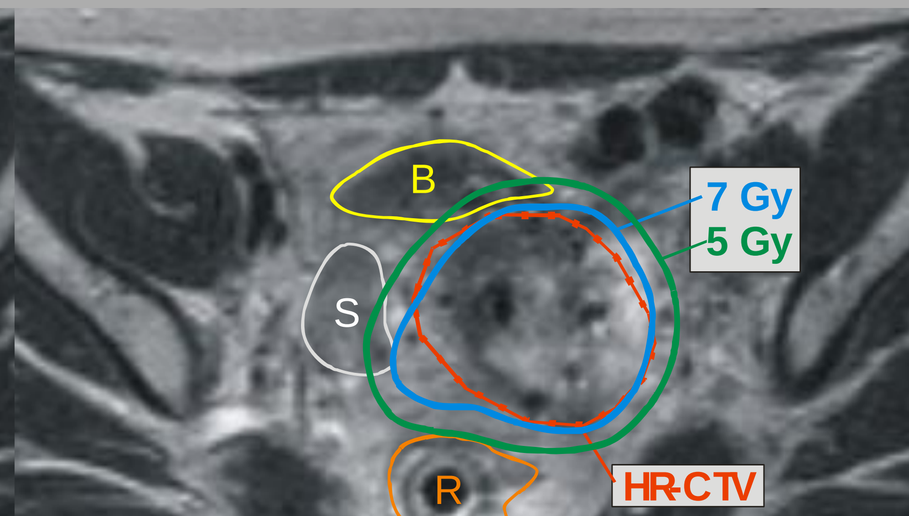




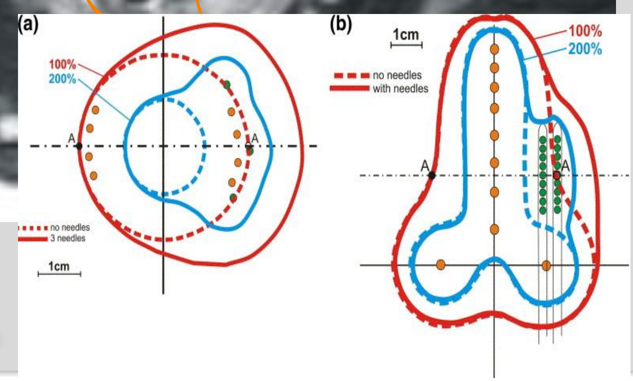
Clinical example - Interstitial Treatment MRI Based Treatment Planning plus Novel Application Technique

standard treatment plan | **optimized interstitial**



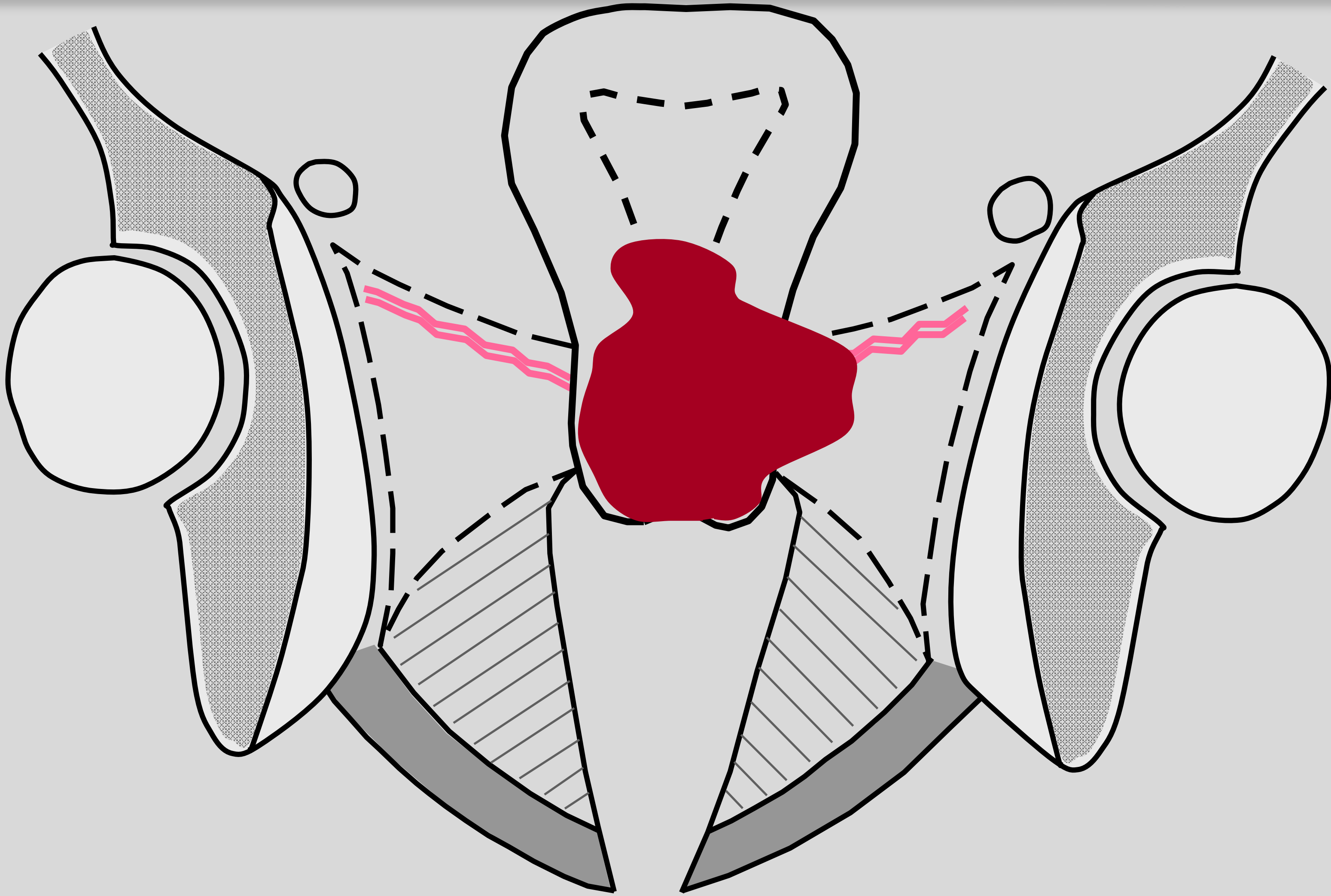


INTRACAVITARY PLUS NEEDLES LEFT PARAMETRIUM



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

Pattern of tumor regression: 1



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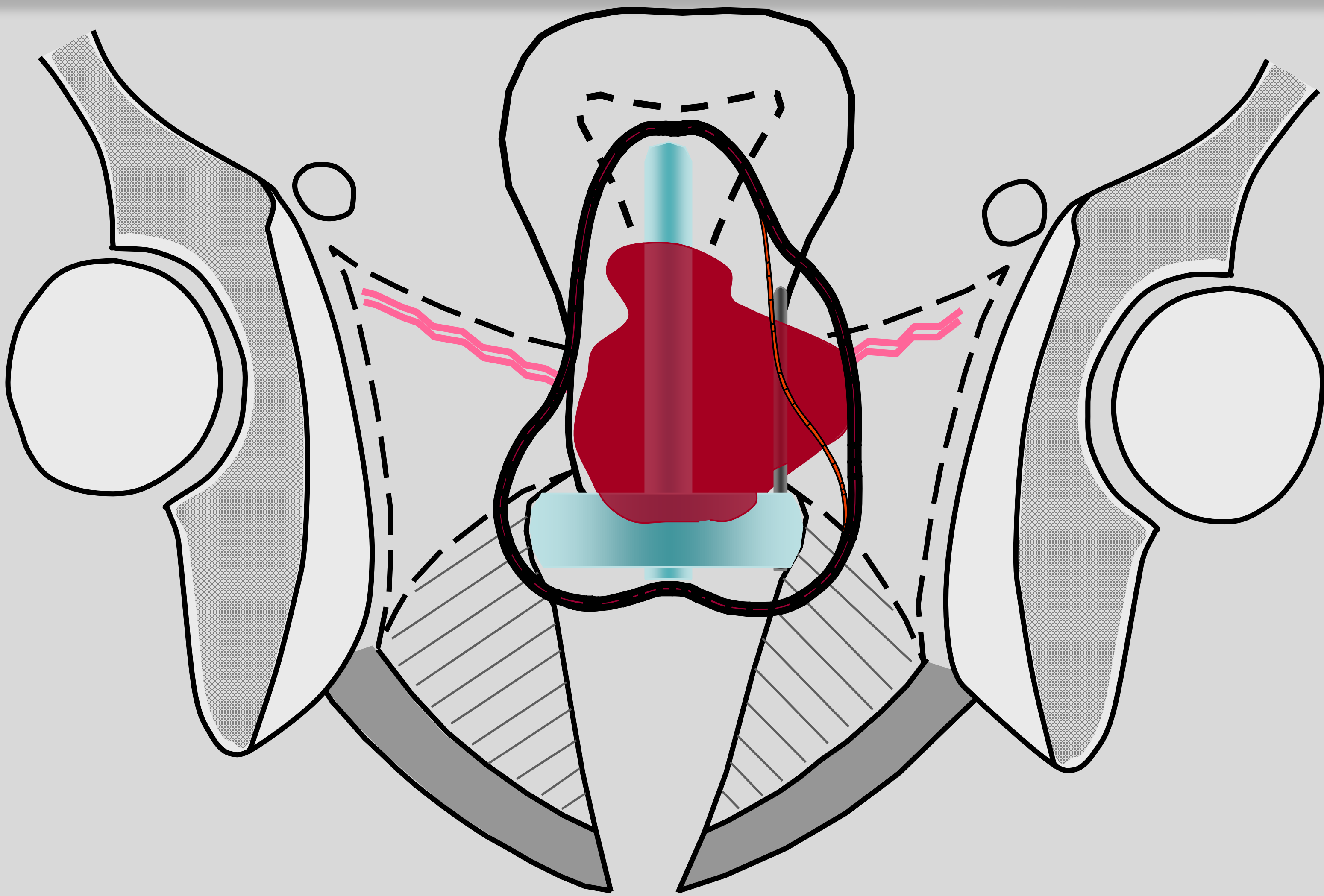
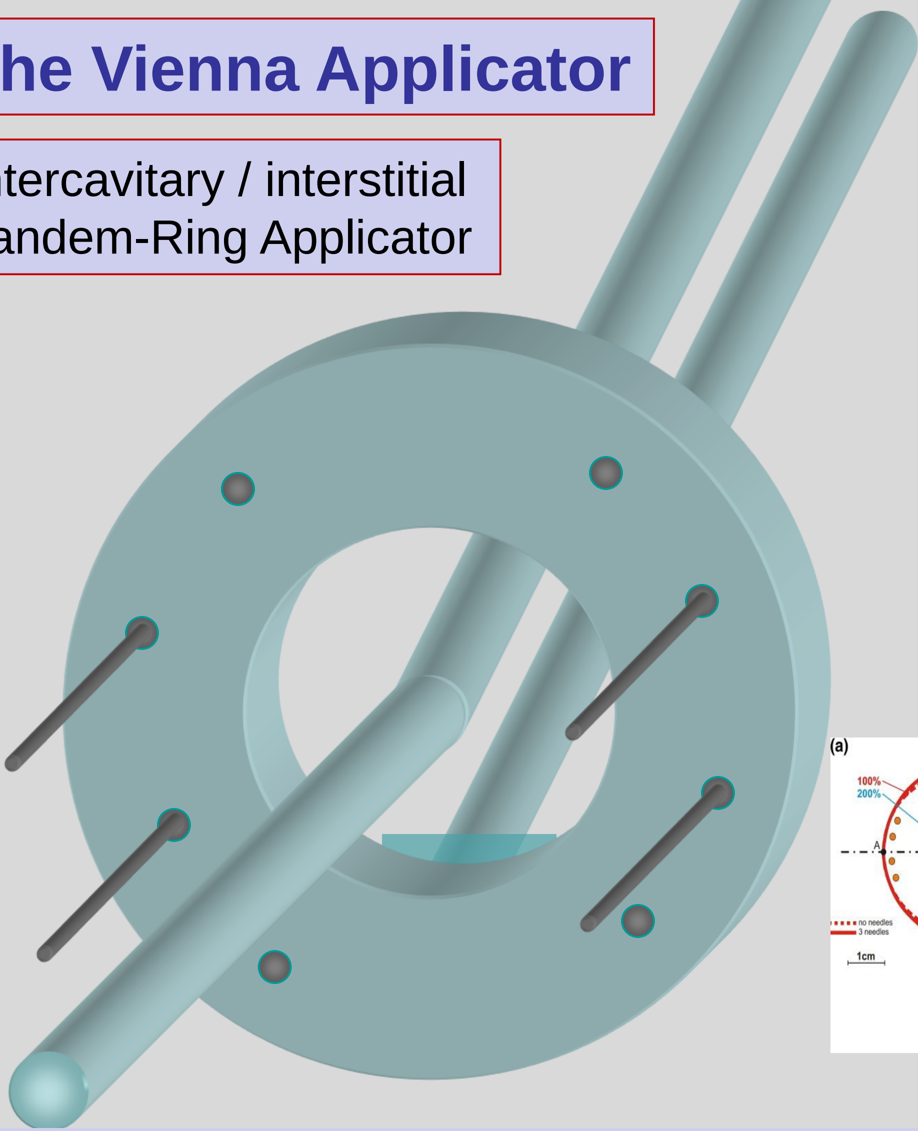
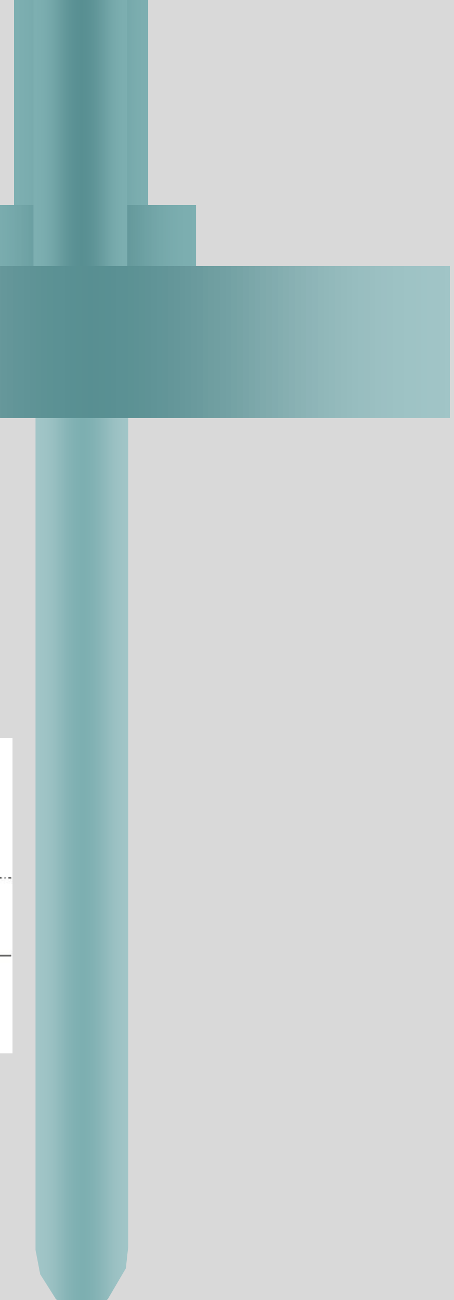
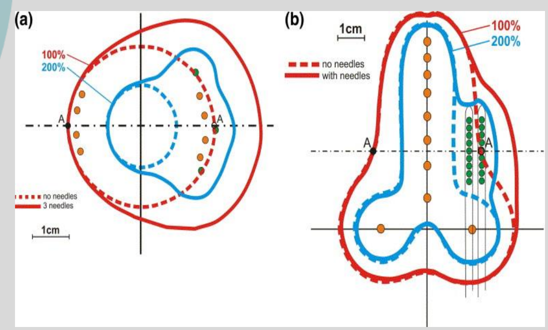


The Vienna Applicator

Intercavitary / interstitial
Tandem-Ring Applicator







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Kirisits et al. IJROBP 2006 (technical note)

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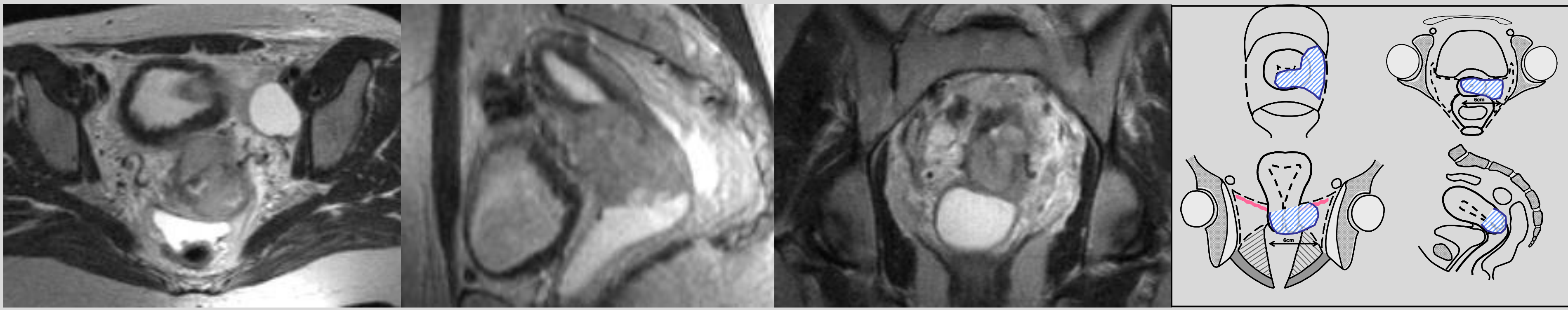
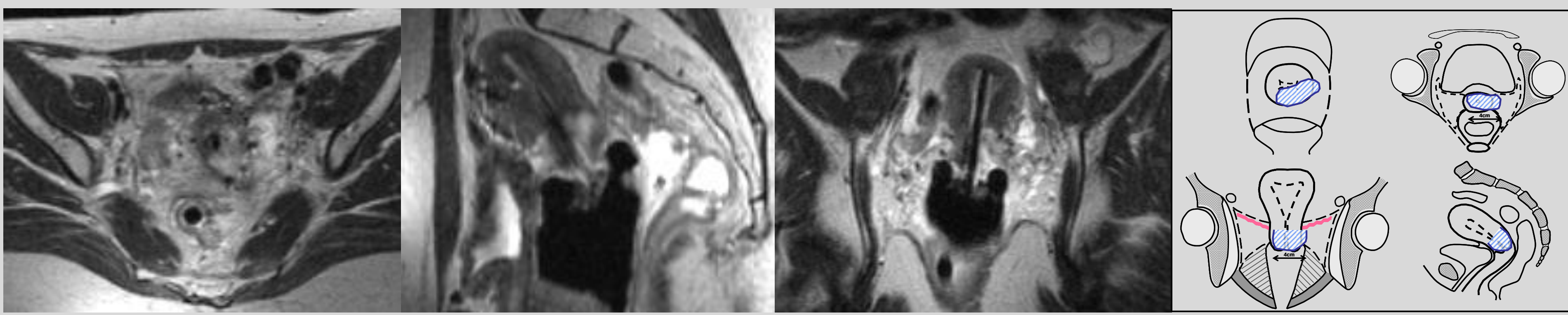
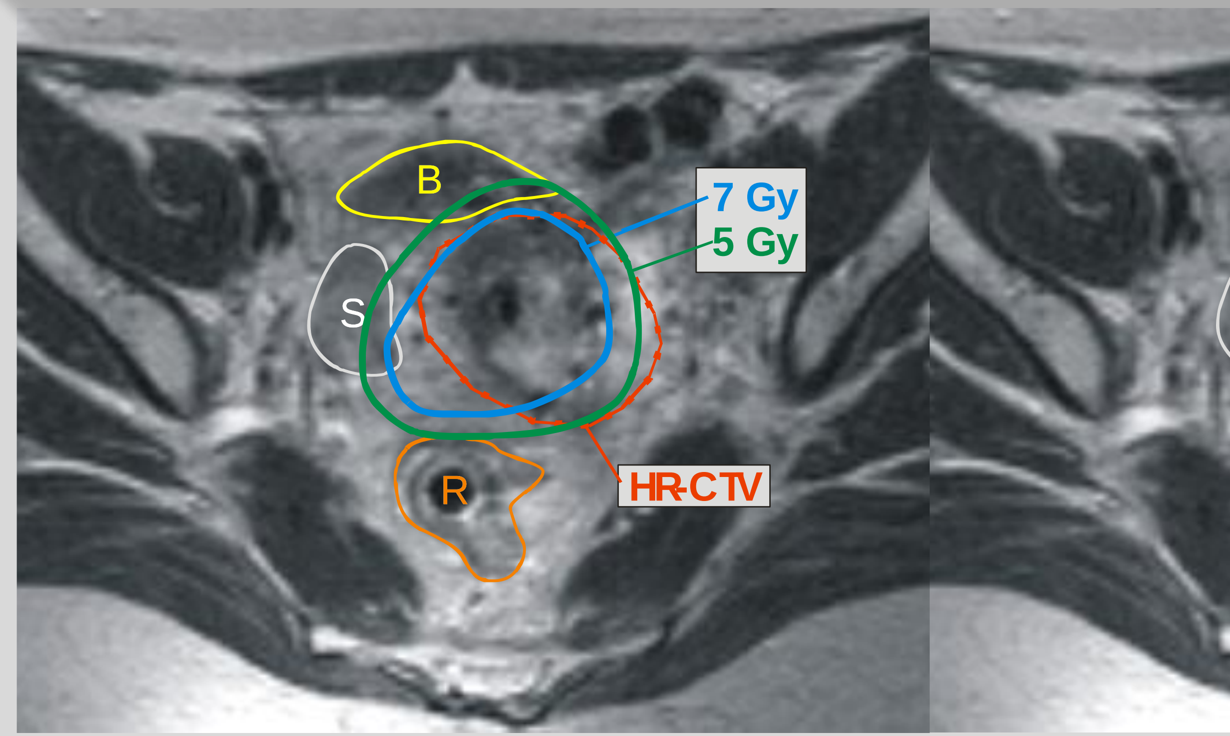
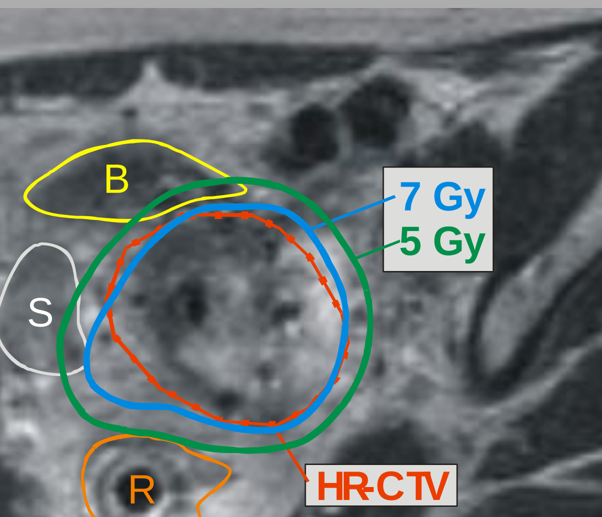


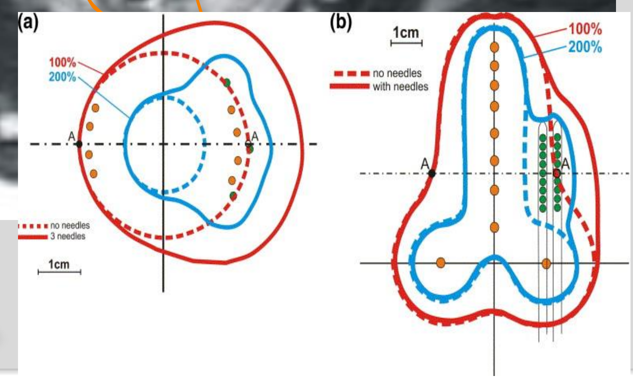


Clinical example - Interstitial Treatment
MRI Based Treatment Planning plus
Novel Application Technique

standard treatment plan | **optimized interstitial**







INTRACAVITARY PLUS NEEDLES LEFT PARAMETRIUM

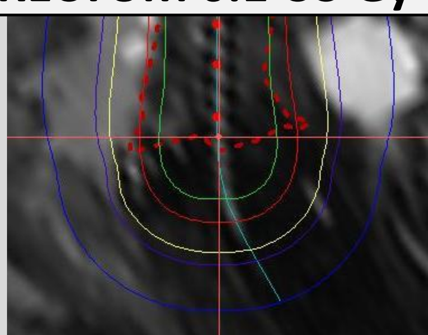
Improved placement control - Low number of needles – Combined with MRI based treatment planning

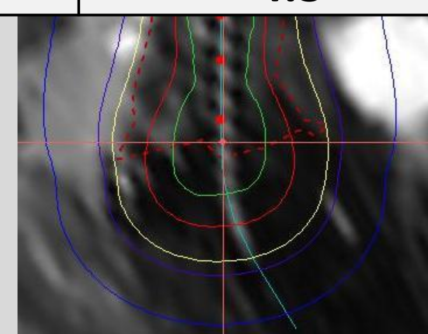
UNFAVORABLE TOPOGRAPHY FOR OAR'S: 1- 2A

STD INTRA-CAVITARY BT

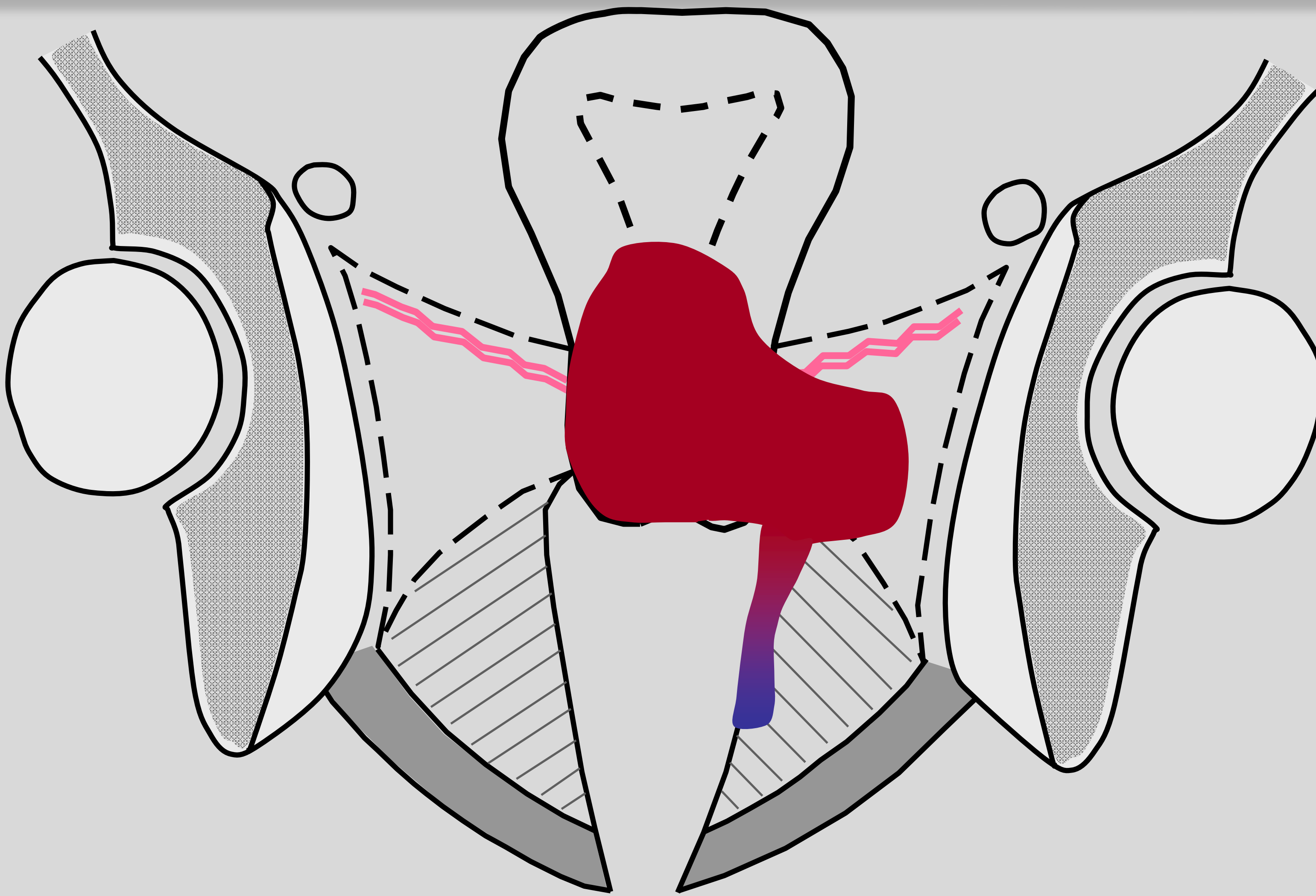
Vienna

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

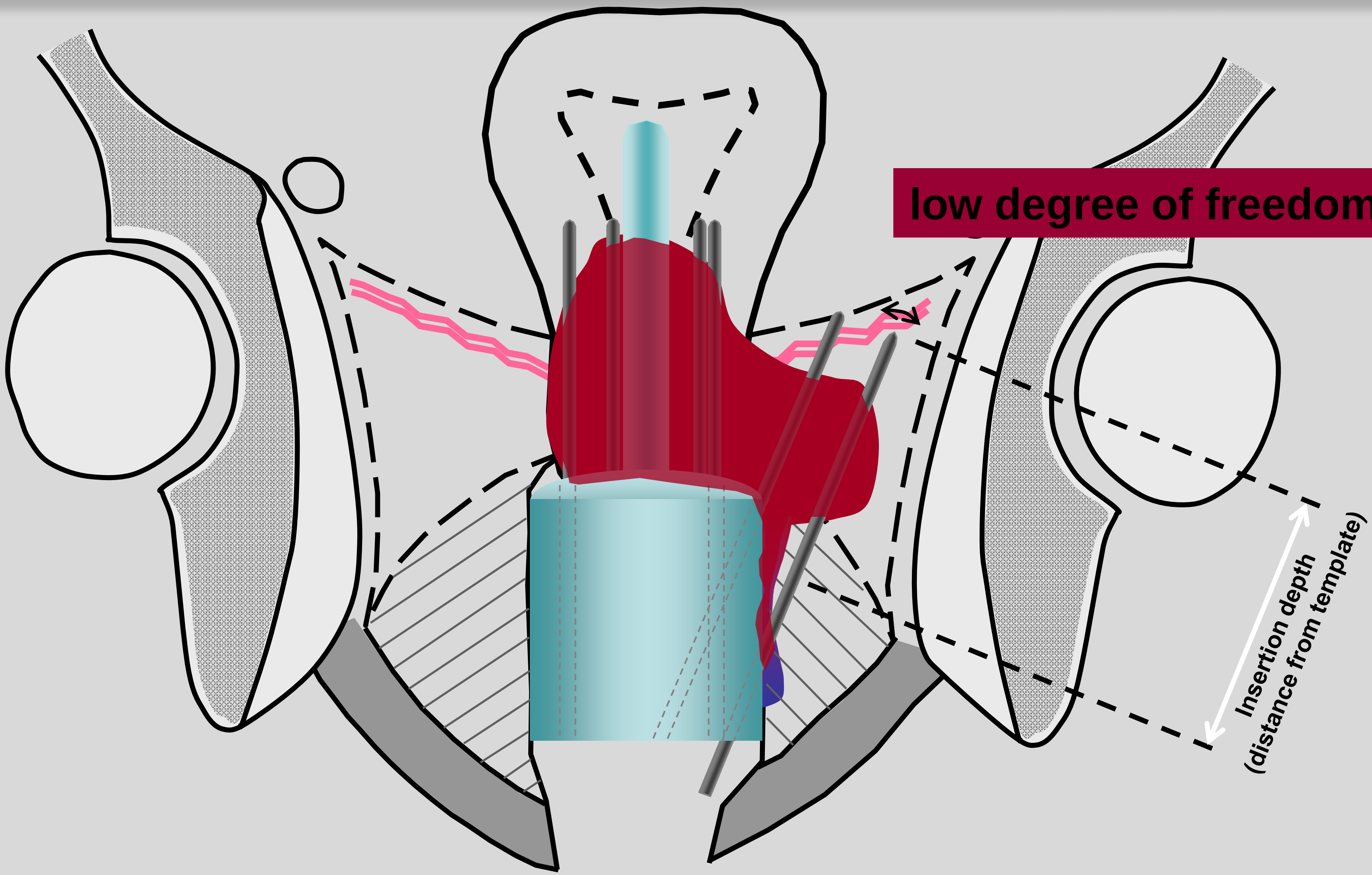




Pattern of tumor regression: 2-2A

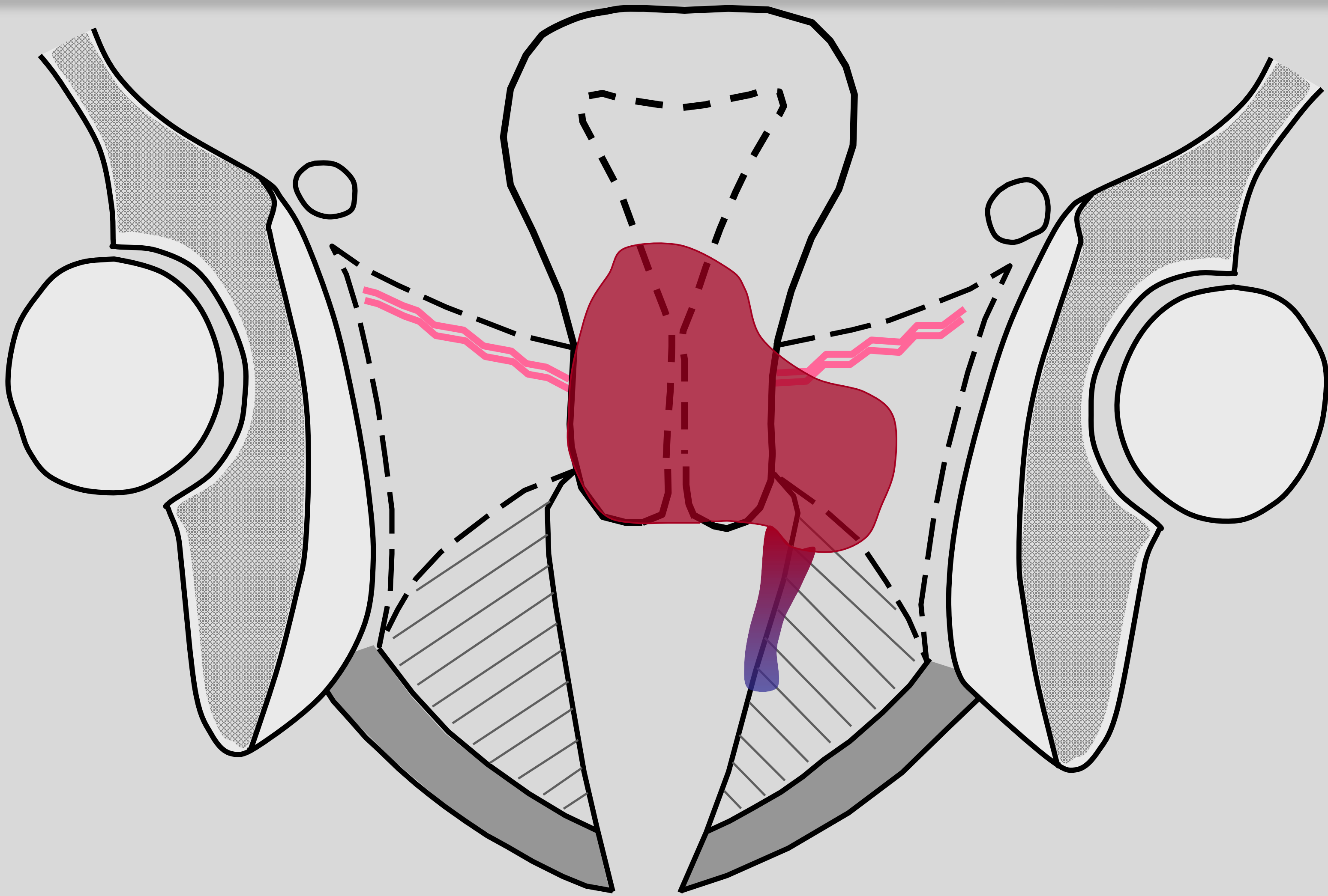


Pattern of tumor regression



Tandem + Cylinder + Needles

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



The Vienna II Applicator

Berger et al. ABS 2010

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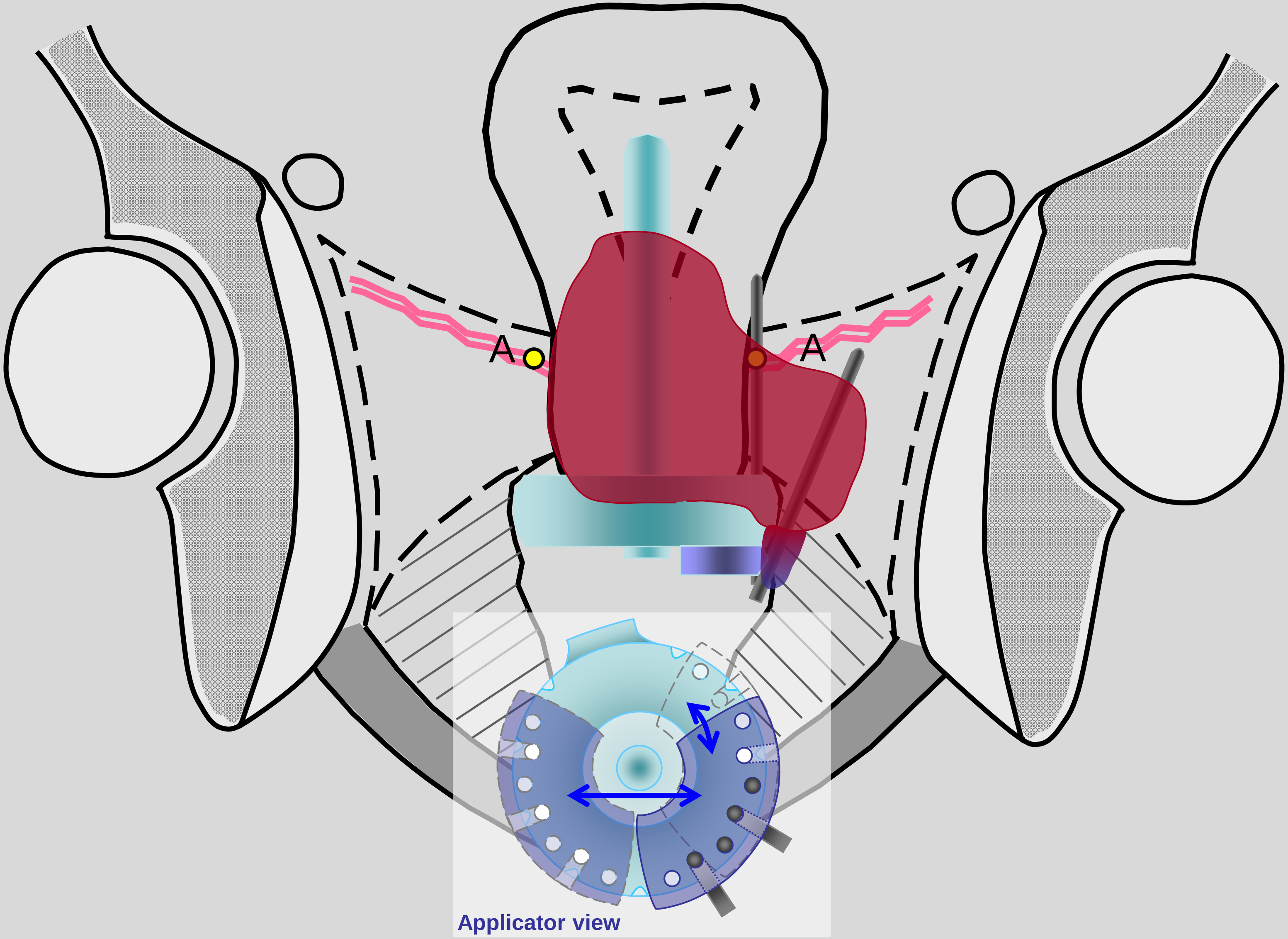


The Vienna II Applicator

Berger et al. ABS 2010

INTRACVITARY +INTERSTITIAL TECHNIQUES

VIDEO PRESENTATIONS

VIENNA I Ring APPLICATION AT AKH VIENNA (Alina)

VIENNA I Ring APPLICATION AT TATA (Umesh)

Intracavitary/interstitial Application at Ljubljana (Primoz)

INTERSTITIAL TECHNIQUES and image guidance
ATTEMPT TO IMPROVE PLACEMENT

NEEDLE PLACEMENT ACCURACY

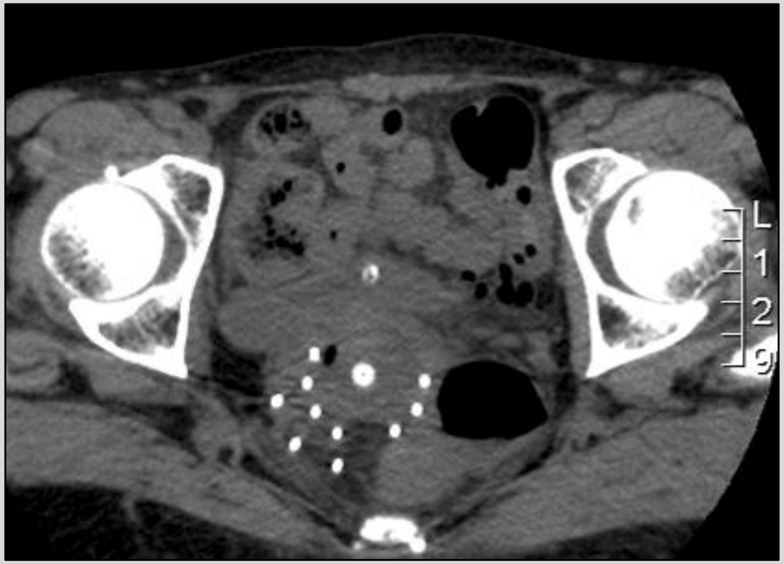
- *(Fluoroscopy)*
- *(Laparotomy guided implants)*
- *Computed tomography*
- *Ultrasound*
- *MRI and open MRI*

Computed Tomography

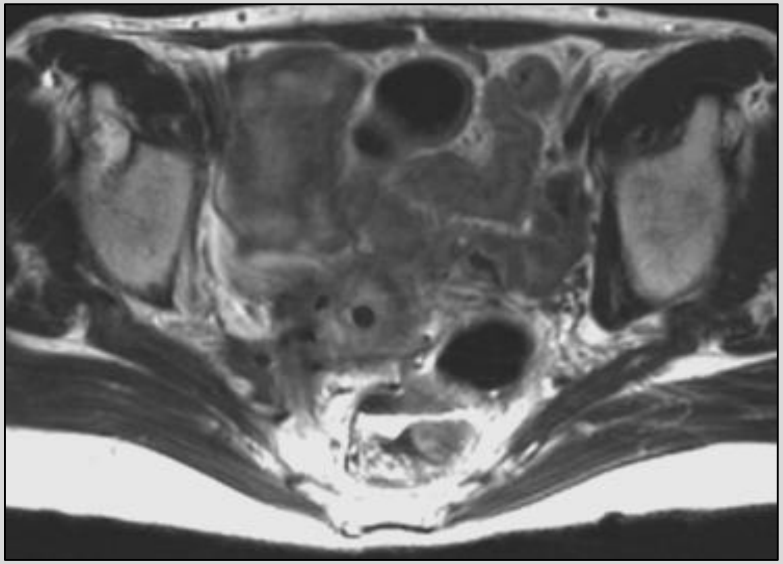
Findings at Brachytherapy

Example: cervix cancer

Assess Tumour size & Topography



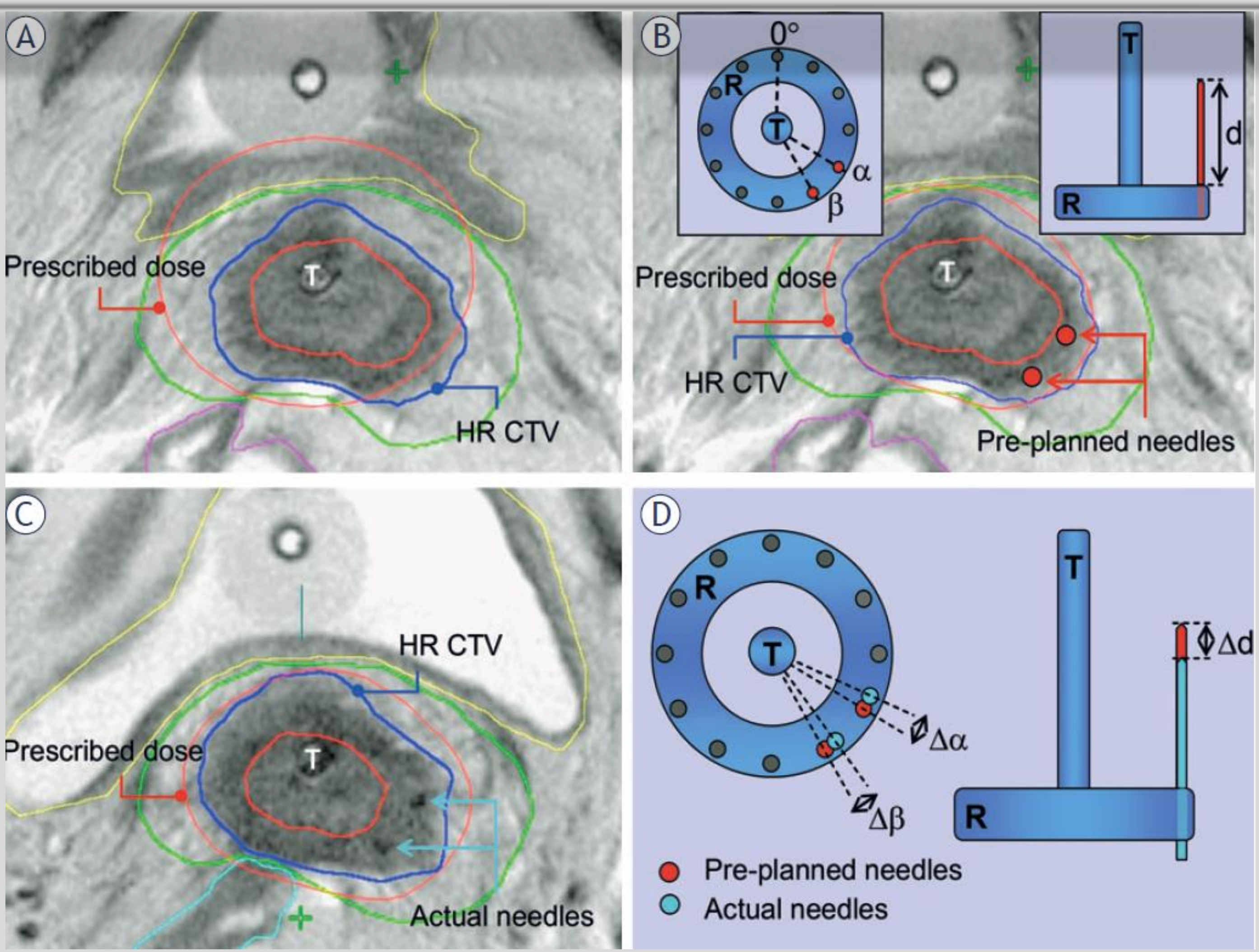
Native CT (no contrast)



T2W FSE MRI (same patient)

Courtesy; Jacob C Lindegaard, Aarhus University Hospital

INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

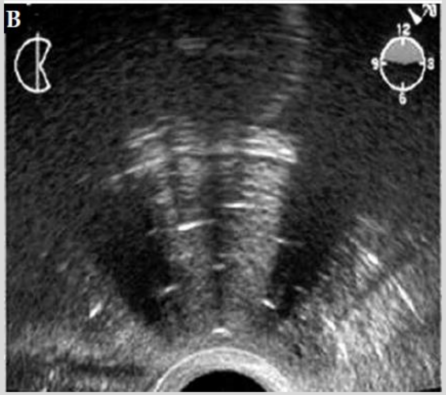


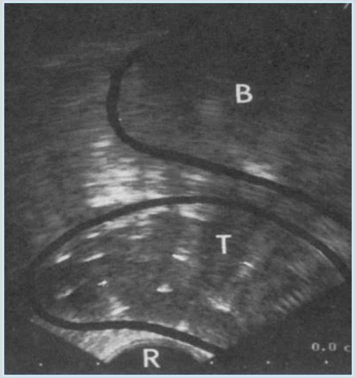
Petric et al. Radiol Oncol 2014; 48(3): 293-300.

INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

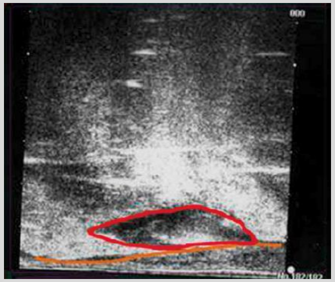
	Ultrasound	MRI
Accessibility in the operating room	High	Low
Real-time image guidance	High	Low
Catheter visualization	High	High
Target visualization	High	High
Volume based evaluation	Low	High
Treatment planning	Low	High
Experience with technique	Low	High
Clinical evidence	Low	High

Kamrava M. J Contemp Brachytherapy 2014





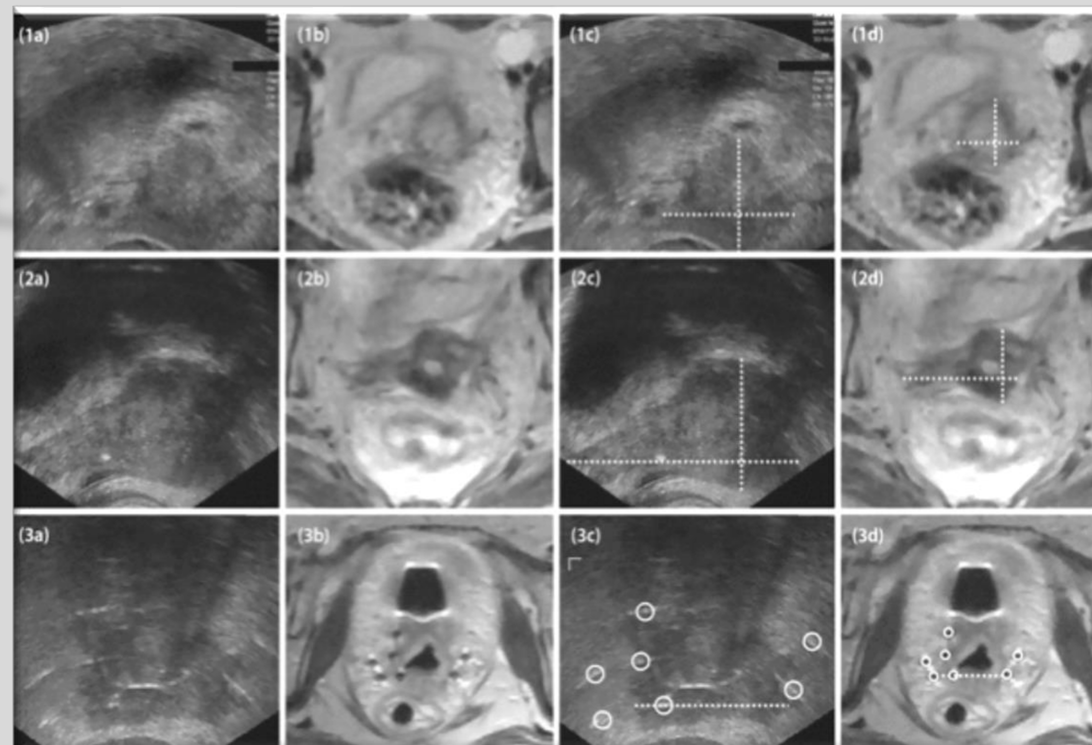
Weitmann HD et al. Strahlenther Onkol 2006; 182: 86-95.
Wenzel W. J Clin Ultrasound 1975; 3: 311-312.
Braschо DJ et al. Radiology 1978; 129: 163-167.
Stock RG et al. IJROBP 1997; 37: 819-825.
Sharma DN et al. J Gynecol Oncol 2010; 21: 12-17.



INTERSTITIAL TECHNIQUES
POTENTIAL OF MODERN US TECHNIQUES

US

GYN BRACHY IMAGING MODALITIES



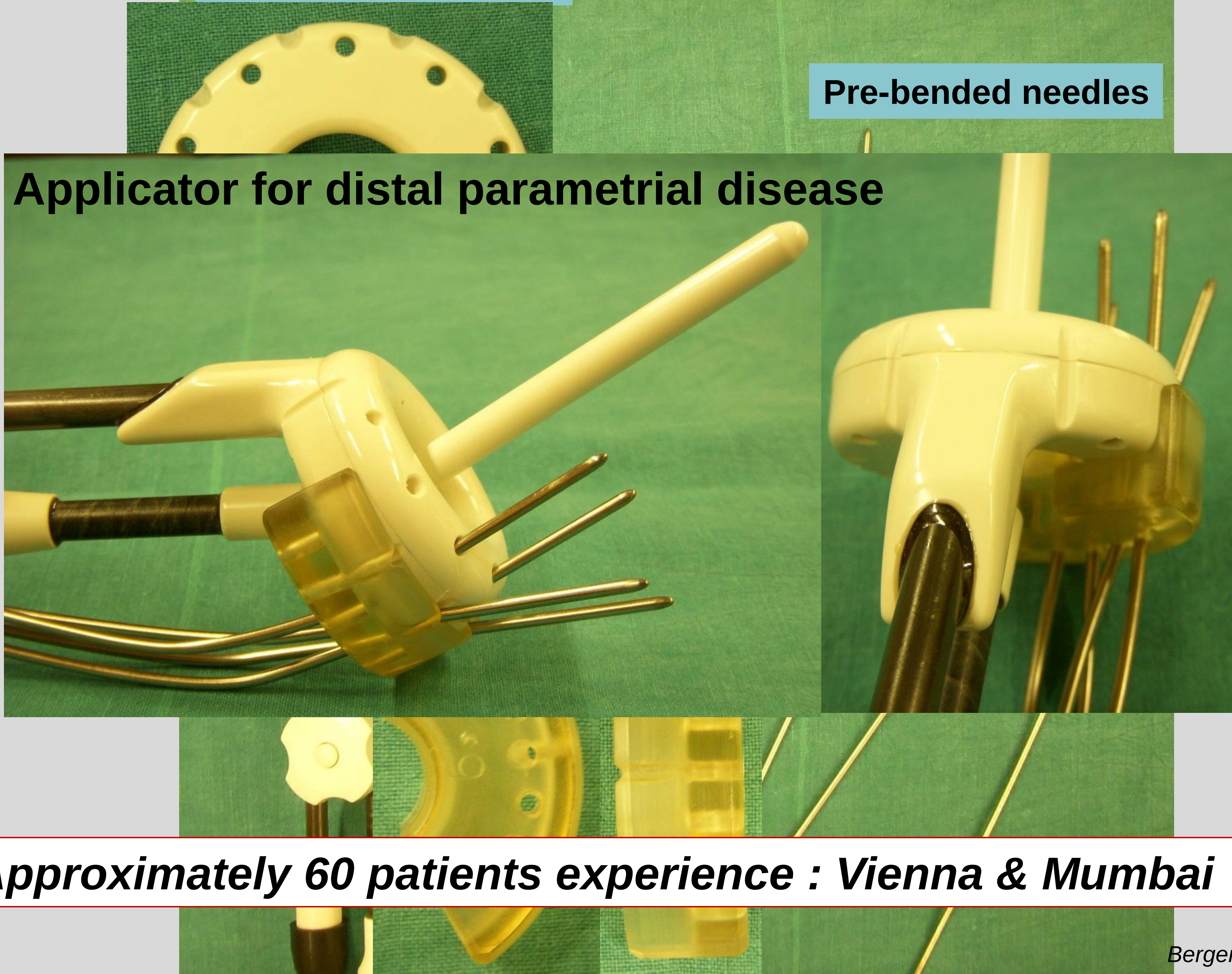
Schmid et al. Strahlenther Onkol 2013

Good correlation between US and MRI

Applicator for distal parametrial disease

Modified Vienna Ring

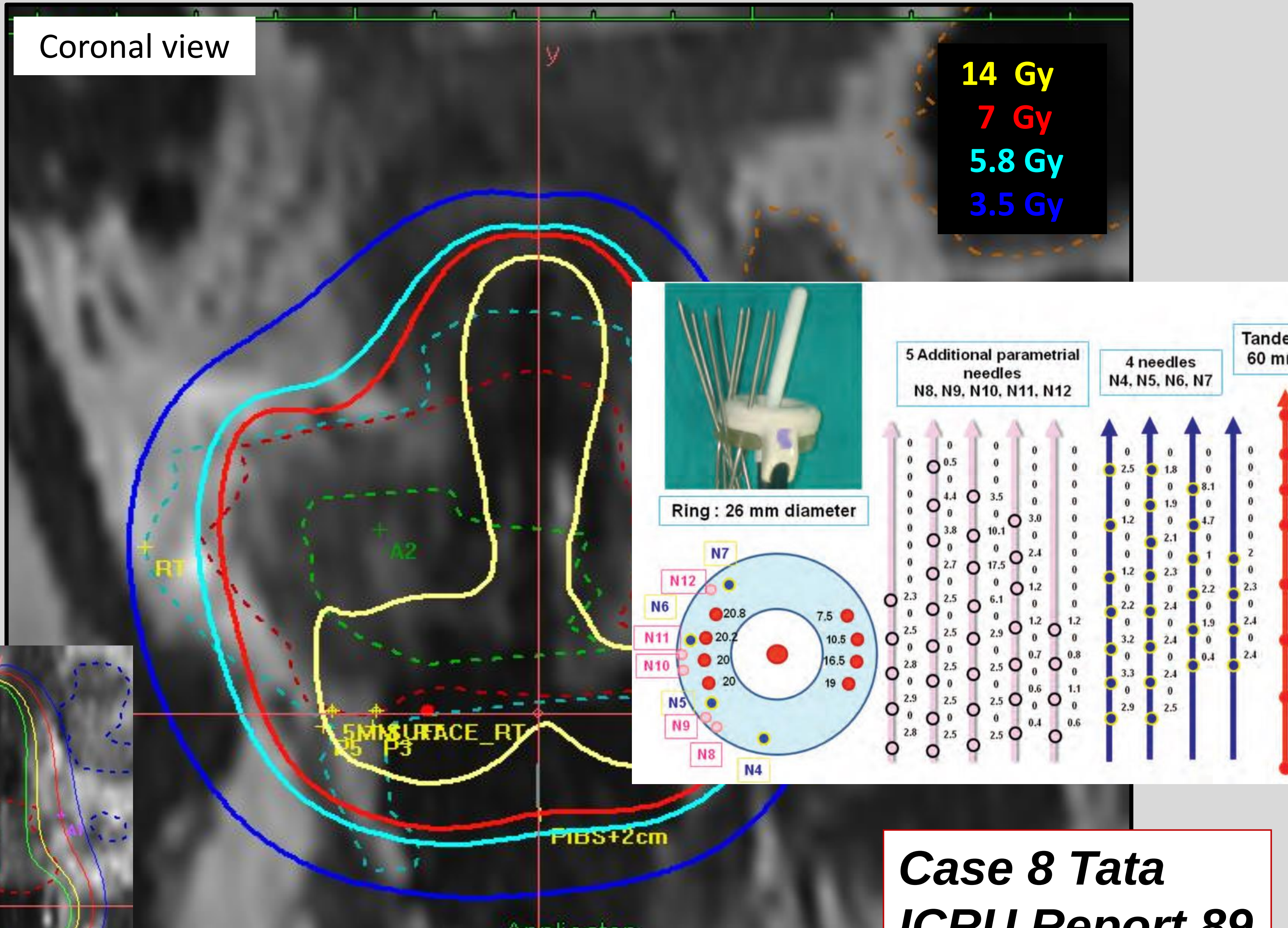
Pre-bended needles

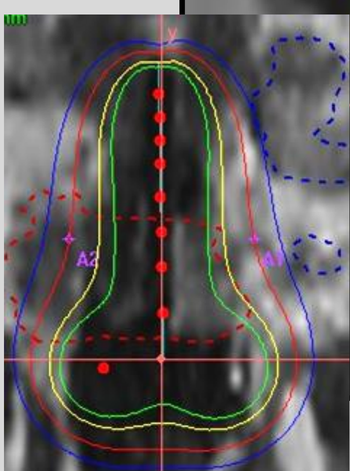


Approximately 60 patients experience : Vienna & Mumbai

Berger et al.

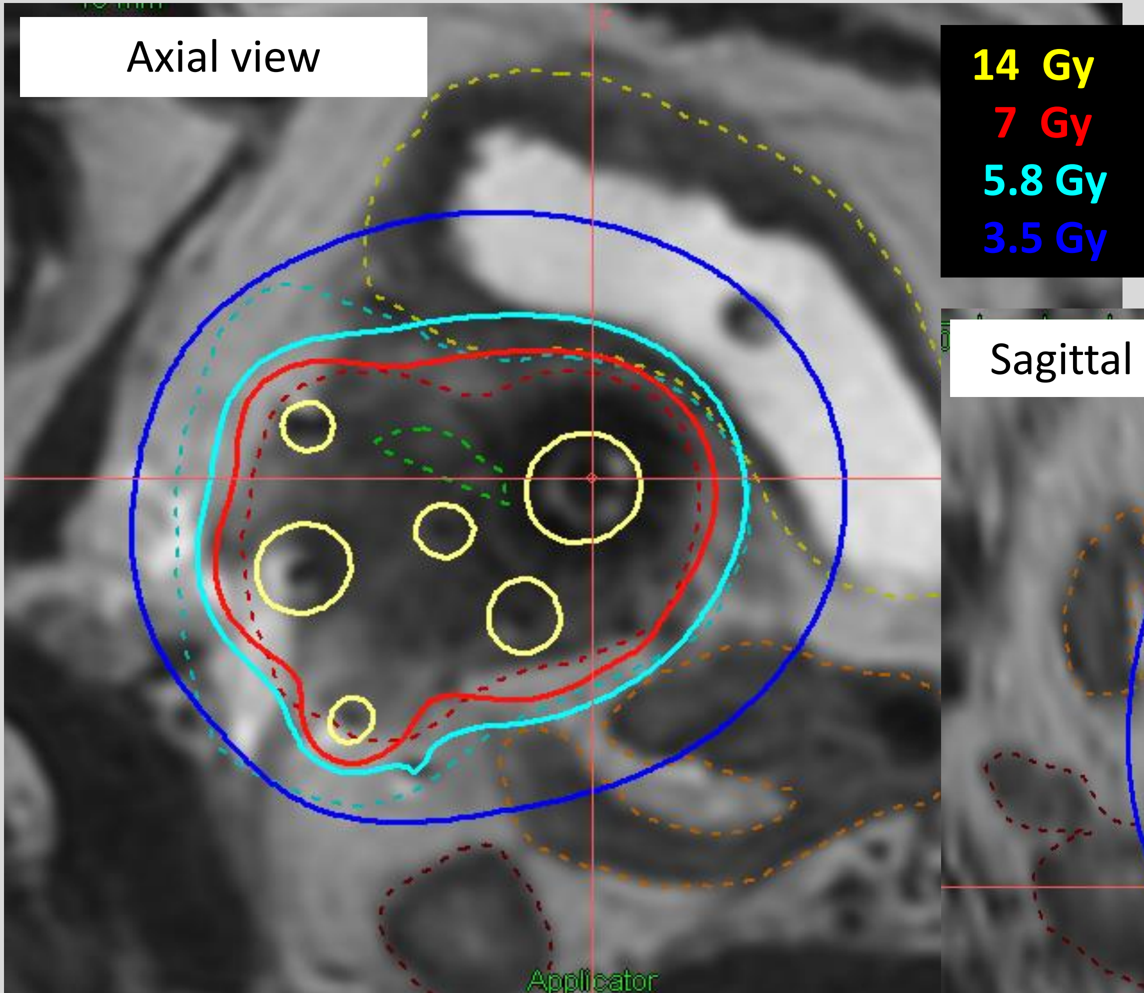
PLAN EVALUATION



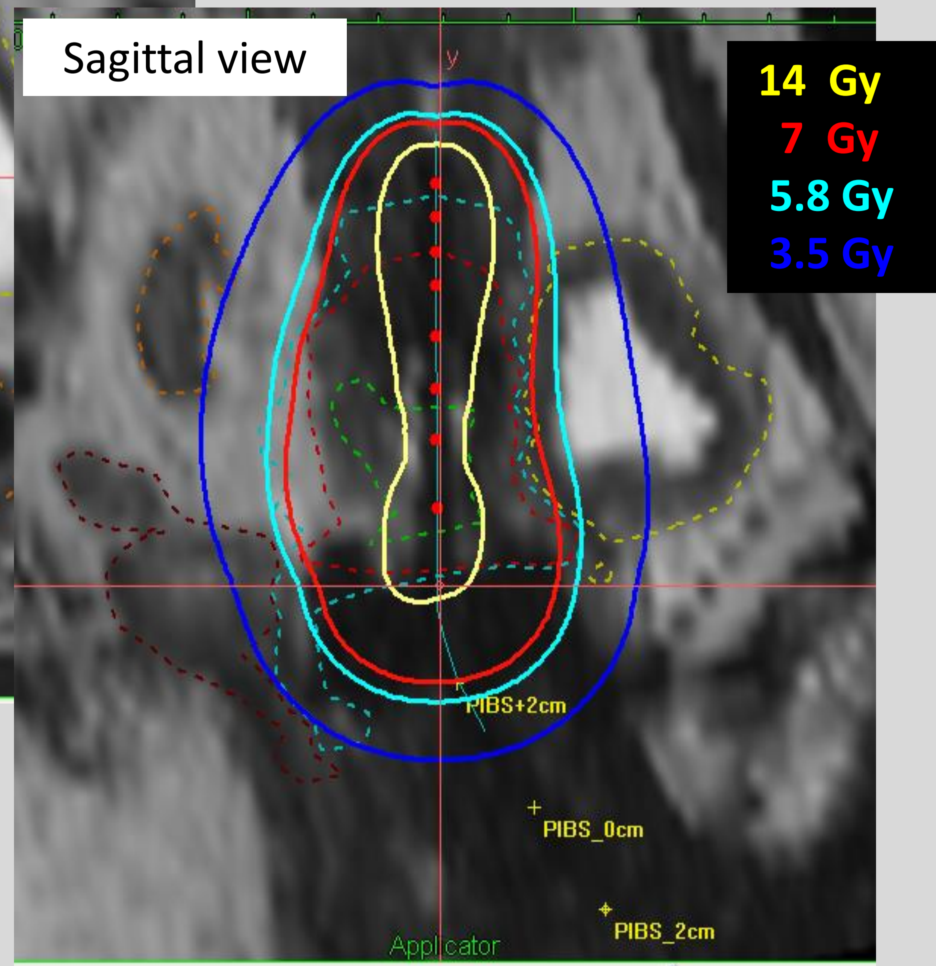


Case 8 Tata
ICRU Report 89
Page 217-224

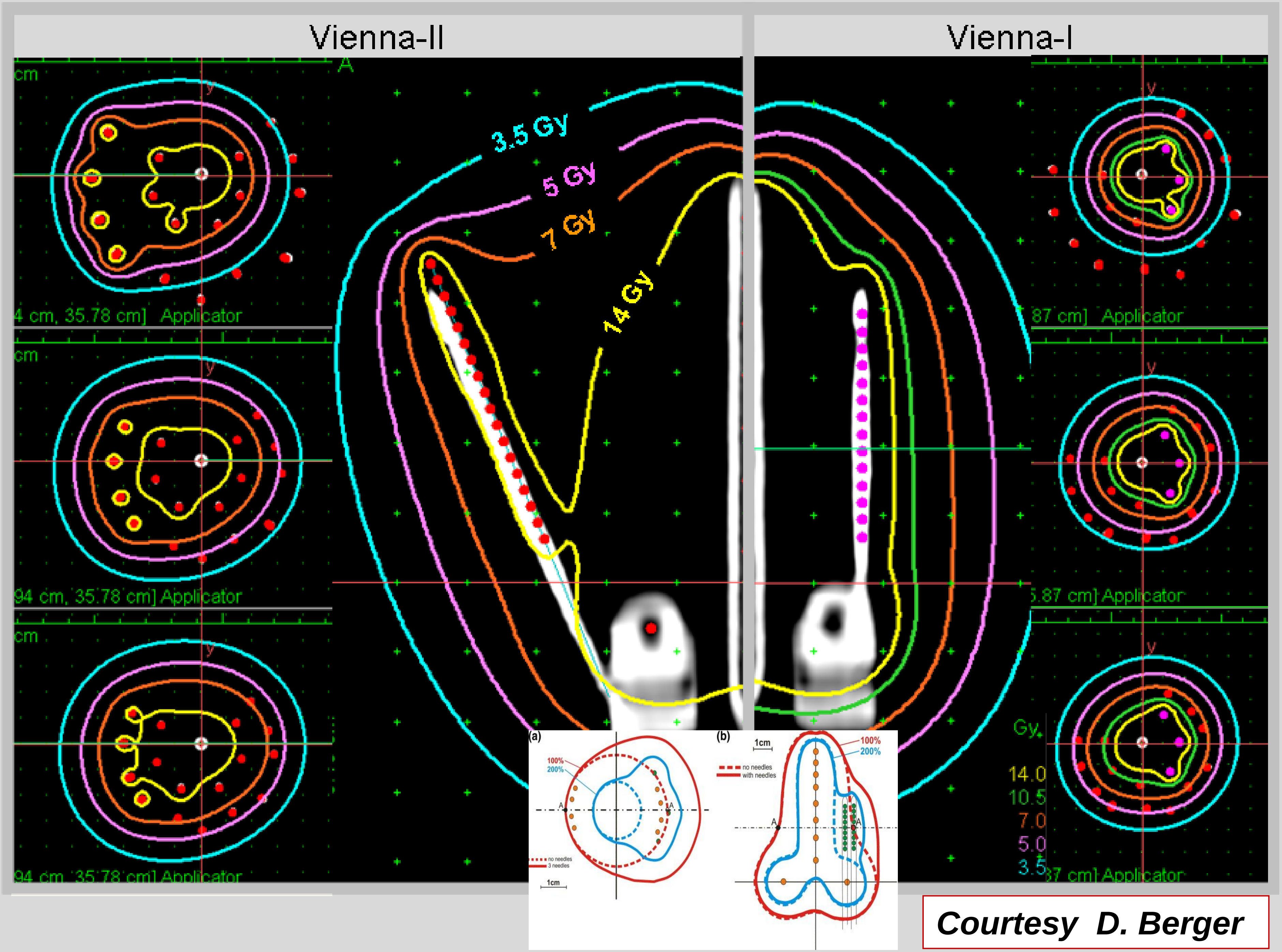
PLAN EVALUATION



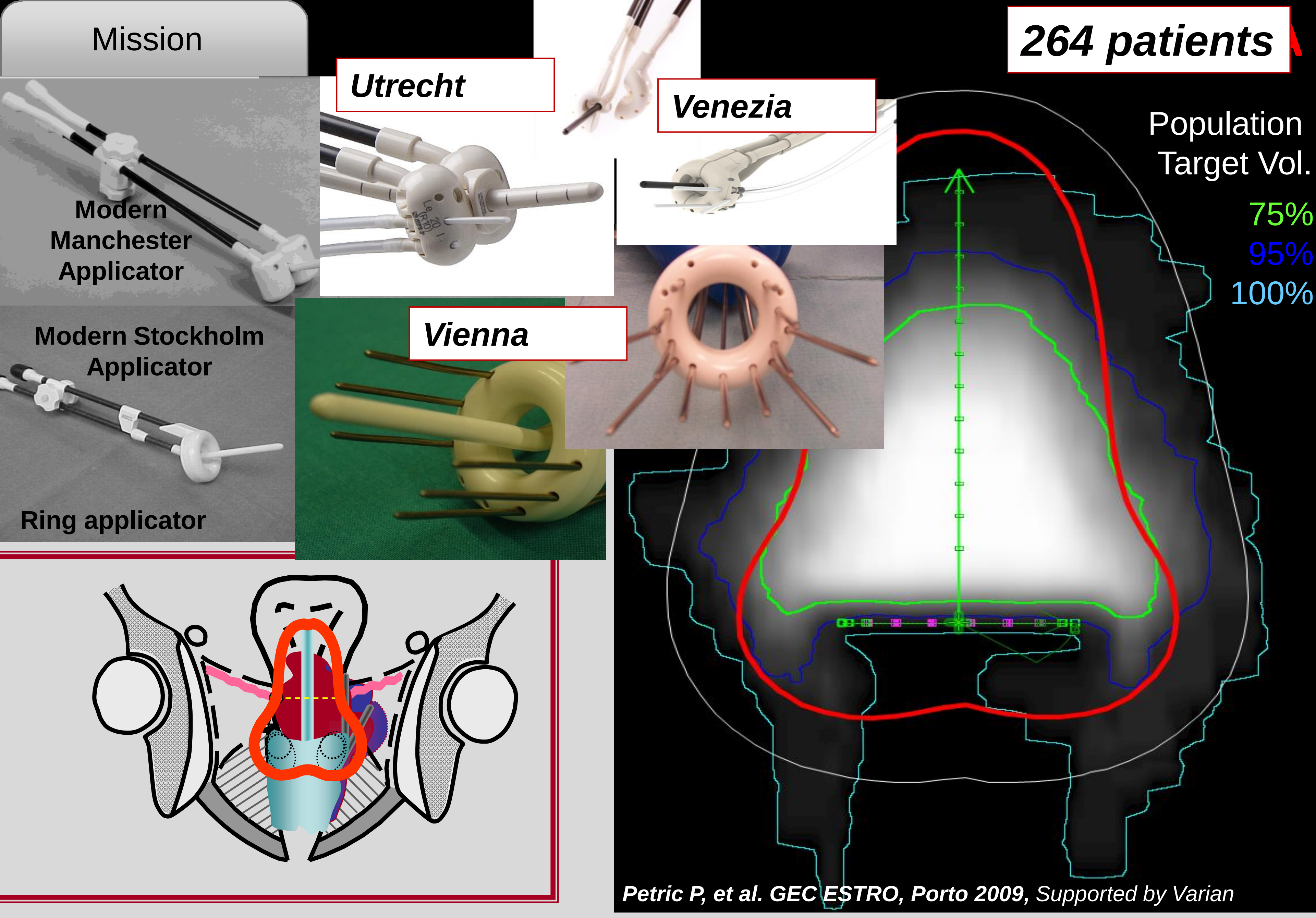
Case 8 Tata
ICRU Report 89
Page 217-224



PIBS:Postero-inferior border of pubic symphysis

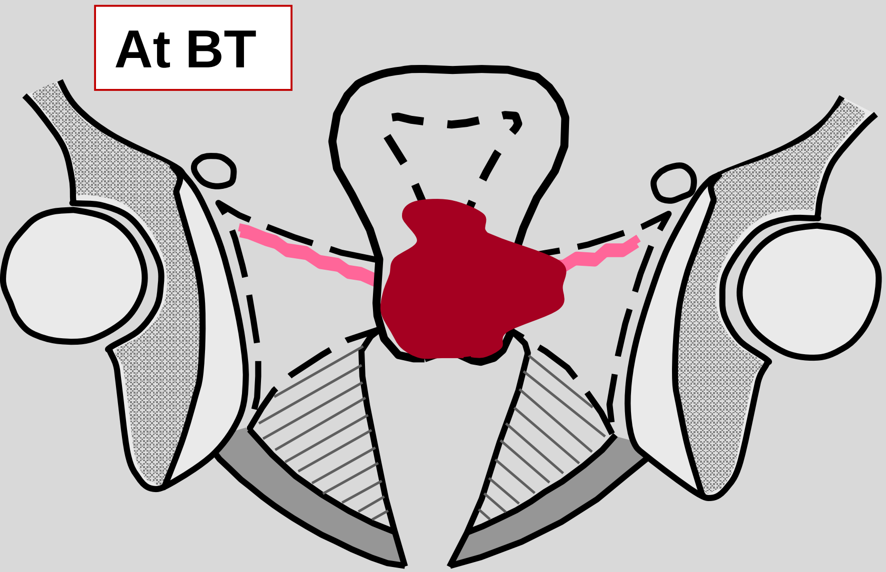


Courtesy D. Berger



Courtesy: P. Petric,D. Berger

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



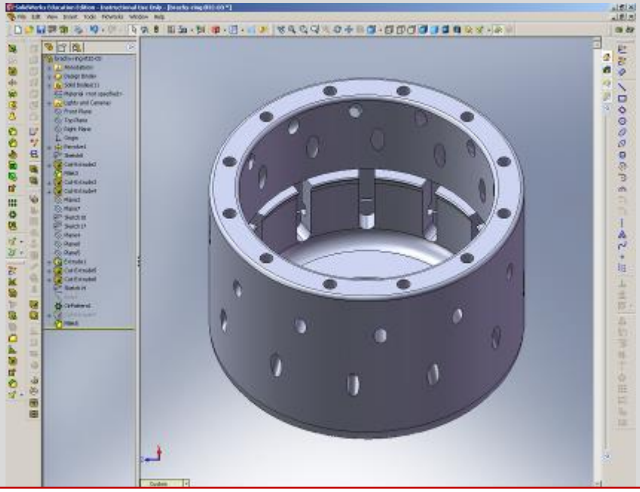
A. Standard Intracavitary
B. Intracavitary + interstitial
C. EBRT boost
D. EBRT boost + Intracavitary

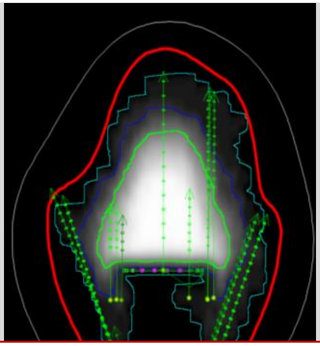
KBD

Adaptive BT applicators

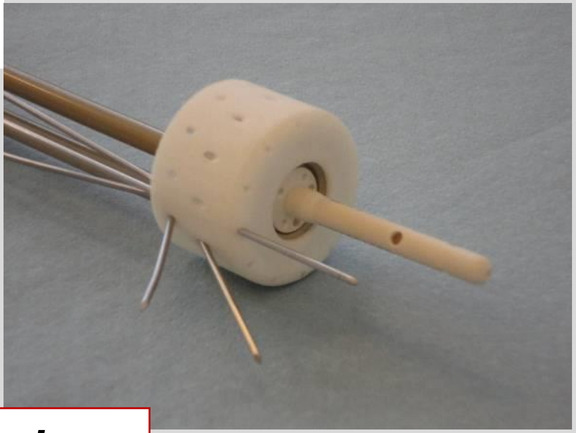
3D Printing

Virtual applicator





New applicator



264 patients with tumour mapping Ljubljana, Vienna, Aarhus

Provided by Primoz Petric and Jacob Lindegaard Ljubljana/Aarhus

SUMMARY & CONCLUSIONS

- *Combined Intracavitary & Interstitial techniques*

  in case of inappropriate coverage (topographic and dosimetric) with pure intracavitary techniques
- *Several approaches (applicators, image guidance) available*
- *Application technique: Various tumor topographies at BT*
- *Straightforward techniques availble*
- *Combined Intracavitary & Interstitial techniques:*

  associated with a learning curve for accurate placement

Clinical Diagrams

Ina Jürgenliemk-Schulz
Universtity Medical Centre Utrecht

Umesh Mahantshetty
Tata Memorial Centre, Mumbai

ESTRO GYN TEACHING COURSE
Prague 2017

Clinical drawings aid in

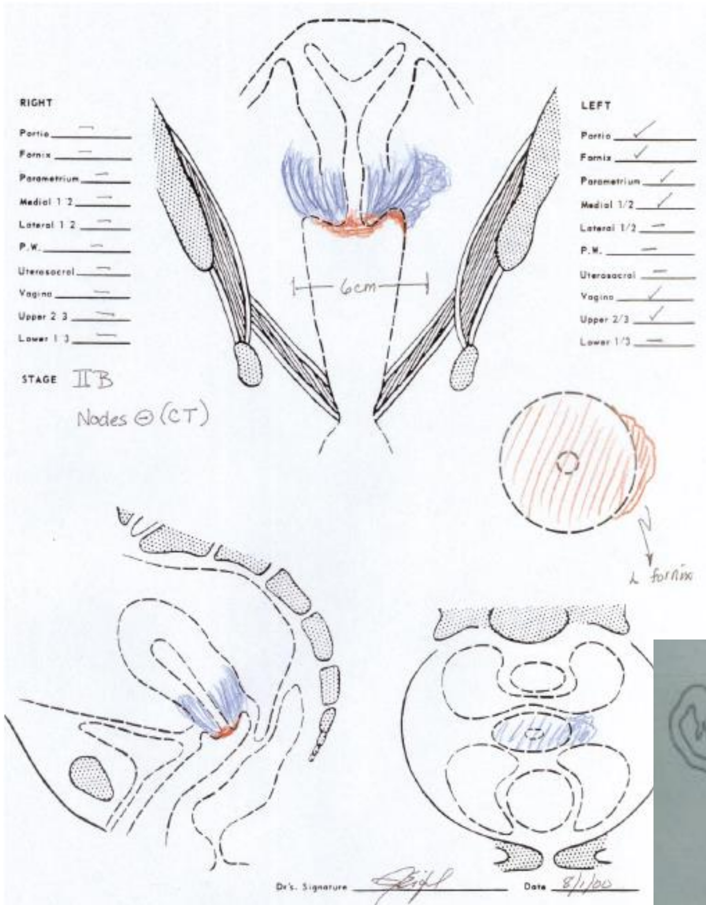
A. 3D Documentation
B. Evaluation of Disease remission
C. Selection of BT technique
D. All of the above

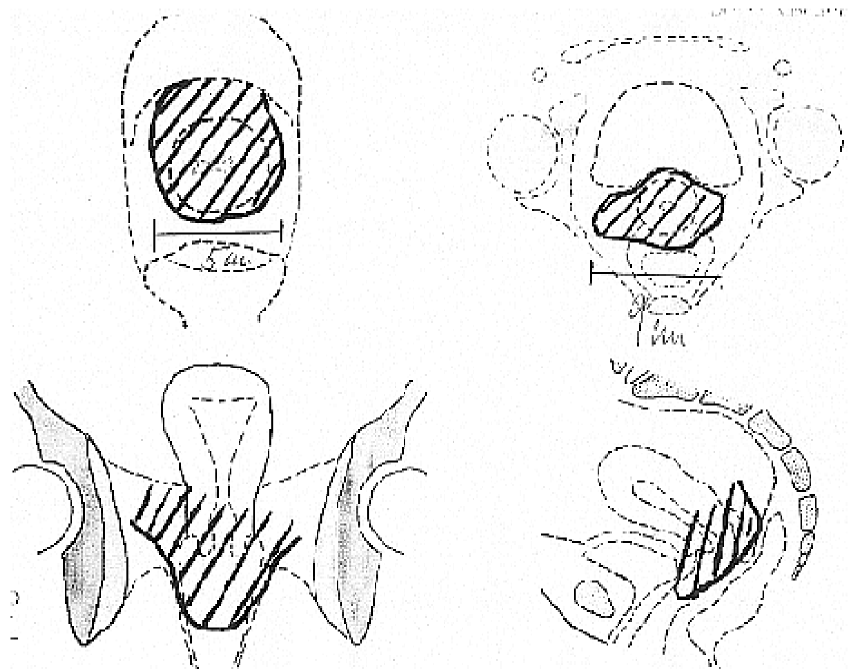
Eifel-Levenback (ed)

Atlas of clinical oncology 2001

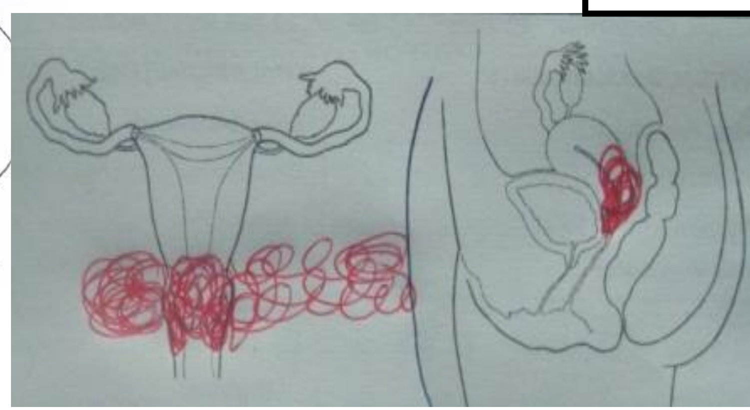
Clinical Diagrams

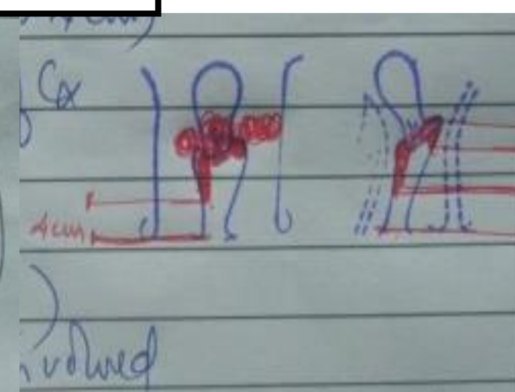
Vienna





TMH, Mumbai

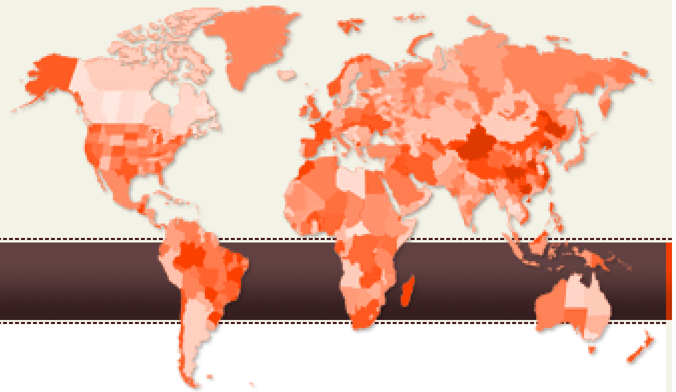




Clinical Mapping of disease extent: Critical for Image based brachytherapy practice !

EMBRACE

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



About Embrace | Contacts | Participation | Login

Appendix

- Extended CRF 60-120 Month Follow-ups
- Clinical Drawings (PowerPoint)
- Updated CRF July 2013
- CTCAE v3.0(PDF)
- Instructions for dummy-run (PDF)
- GYN GEC-ESTRO Guidelines I (PDF)
- GYN GEC-ESTRO Guidelines II (PDF)
- Applicator reconstruction catalogue (PDF)

ABOUT EMBRACE

- Synopsis
- Protocol PDF download
- Amendments
- Appendix
- Quality of Life sub-study
- Embrace study commitee
- Participants
- FAQ
- Sponsors

www.embracestudy.dk/AboutAppendix.aspx

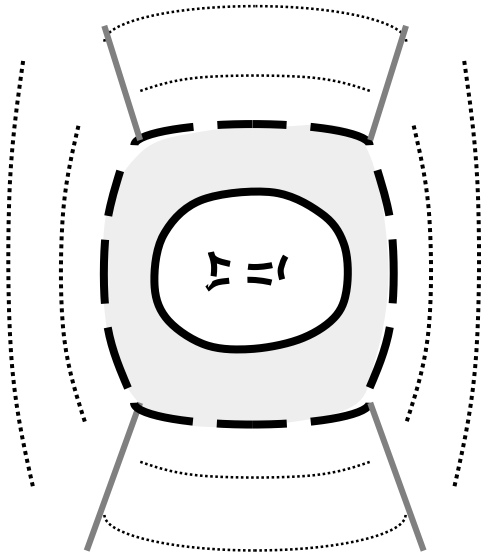
Patient : ABC

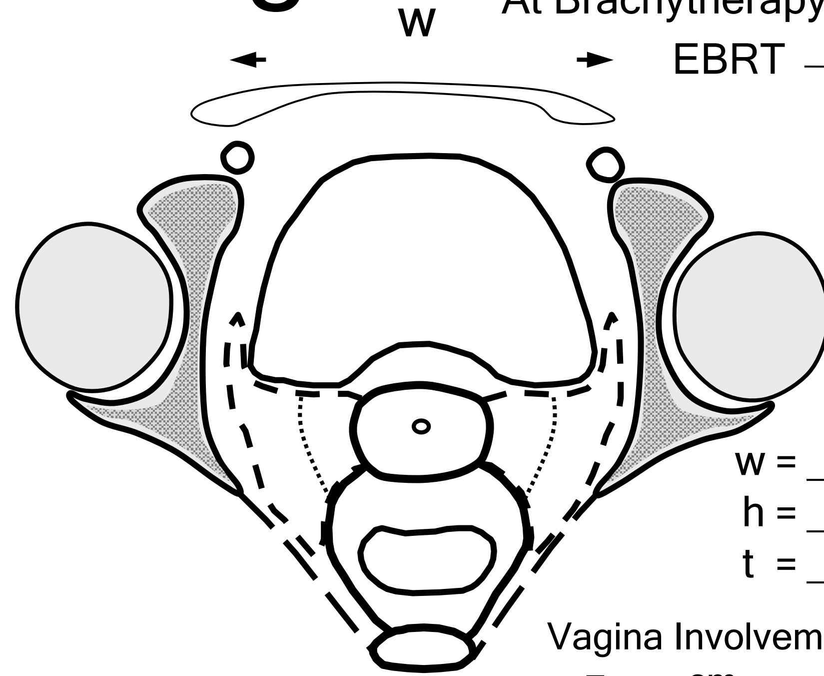
Clinical Drawing

At Diagnosis ☐

At Brachytherapy ☐

EBRT ___ Gy



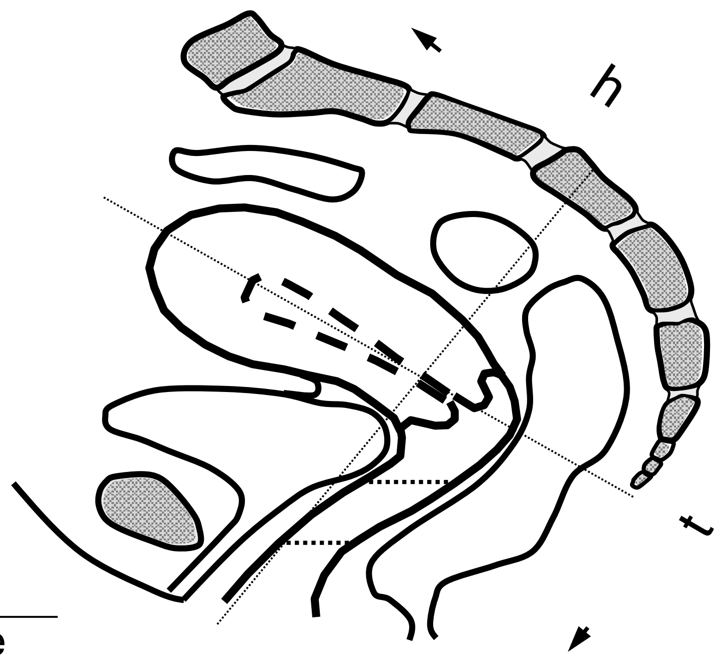


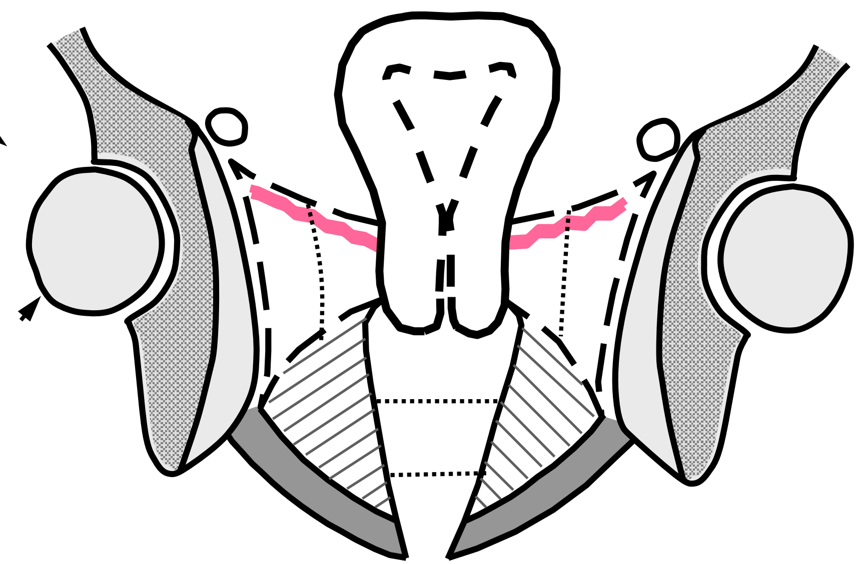
w = ____ cm

h = ____ cm

t = ____ cm

Vagina Involvement
= ____ cm





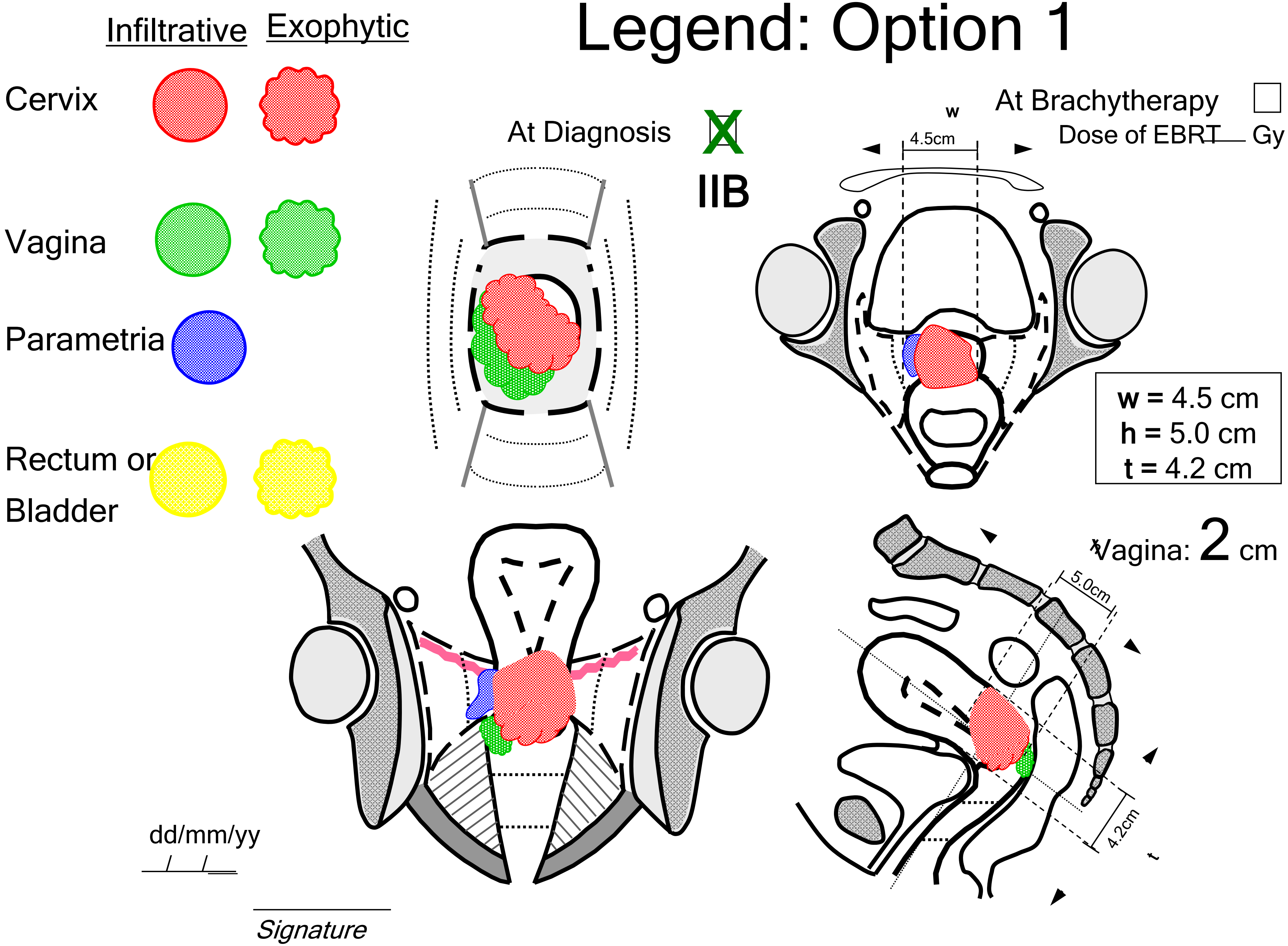
dd/mm/yy

___/___/_____

____

Signature

Legend: Option 1



Legend: Option 2

At Diagnosis ☒

At Brachytherapy ☐

Dose of EBT ____ Gy

IIIA

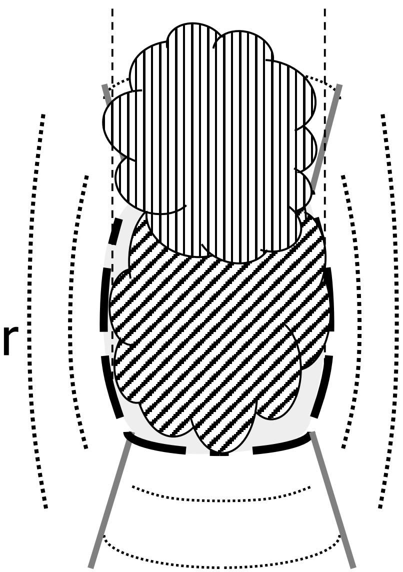
or Cervix

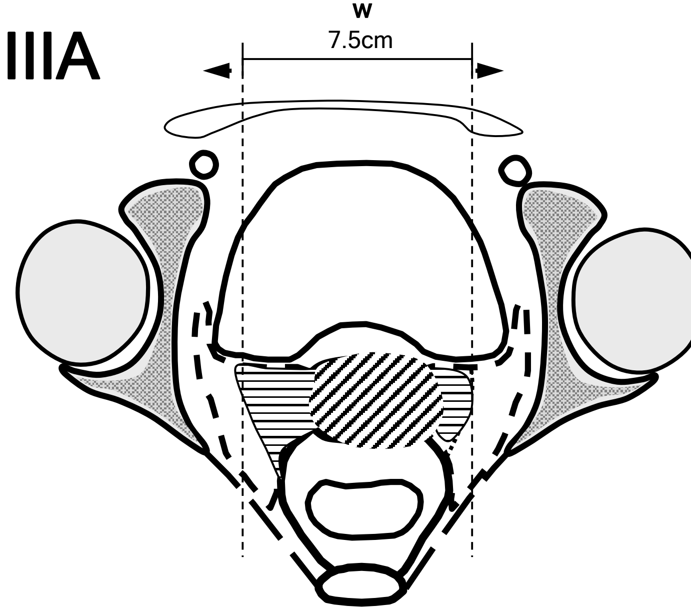
Vagina

Parametria

Rectum or Bladder Infiltration

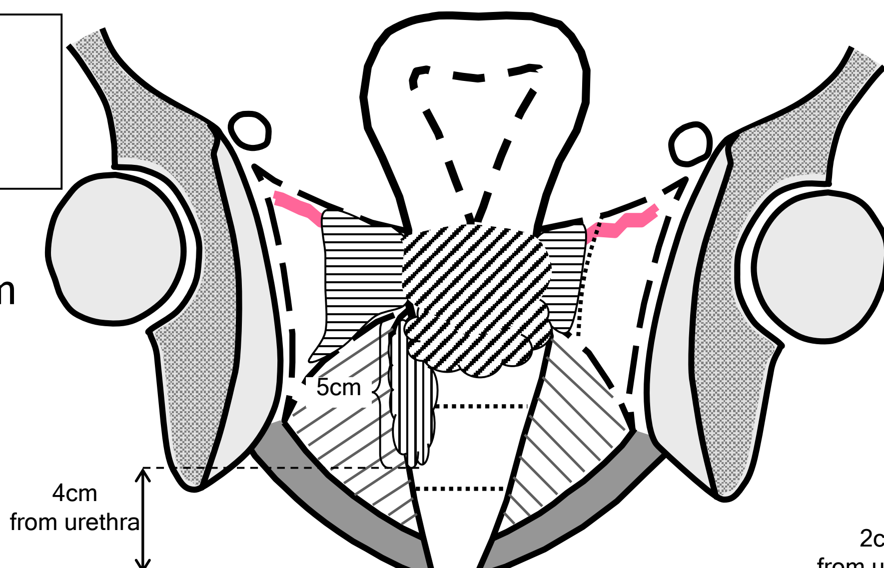
Exophytic

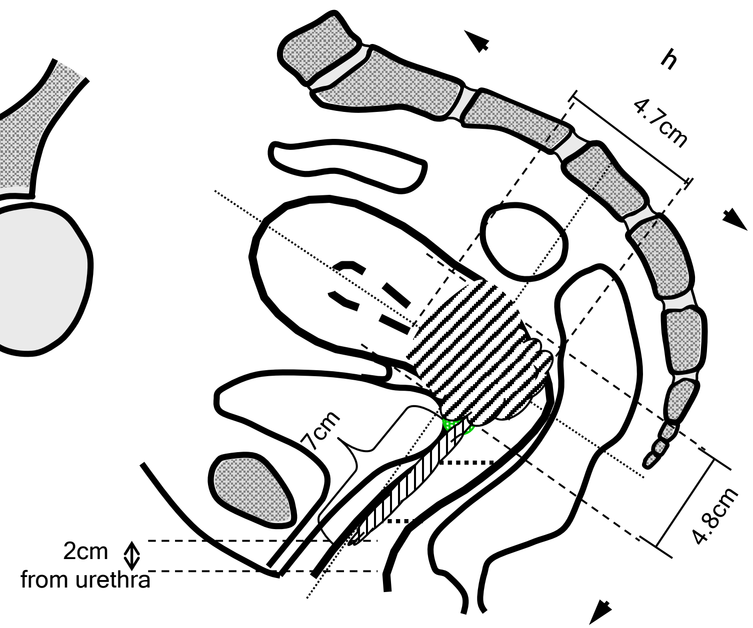




w = 7.5 cm
h = 4.7 cm
t = 4.8 cm

Vagina: 7 cm





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___/___/___

____
Signature

Option 3: Copy and Paste

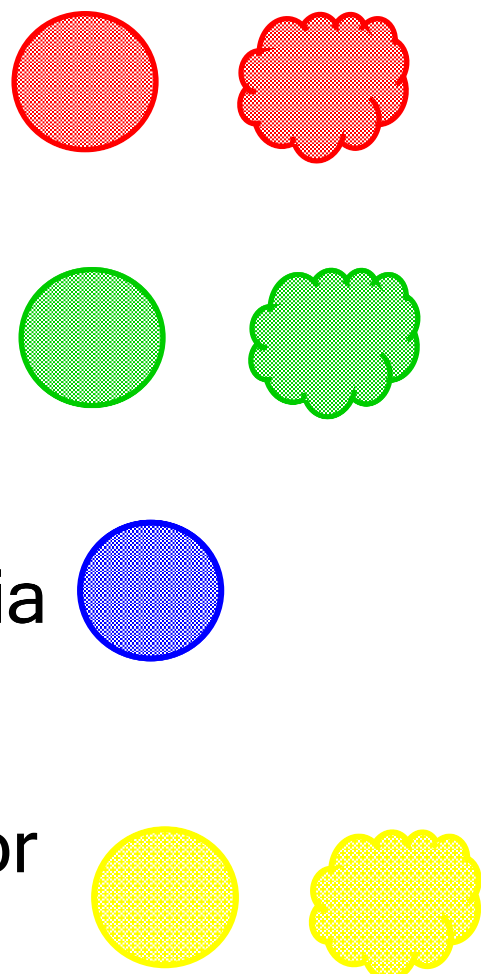
Cervix

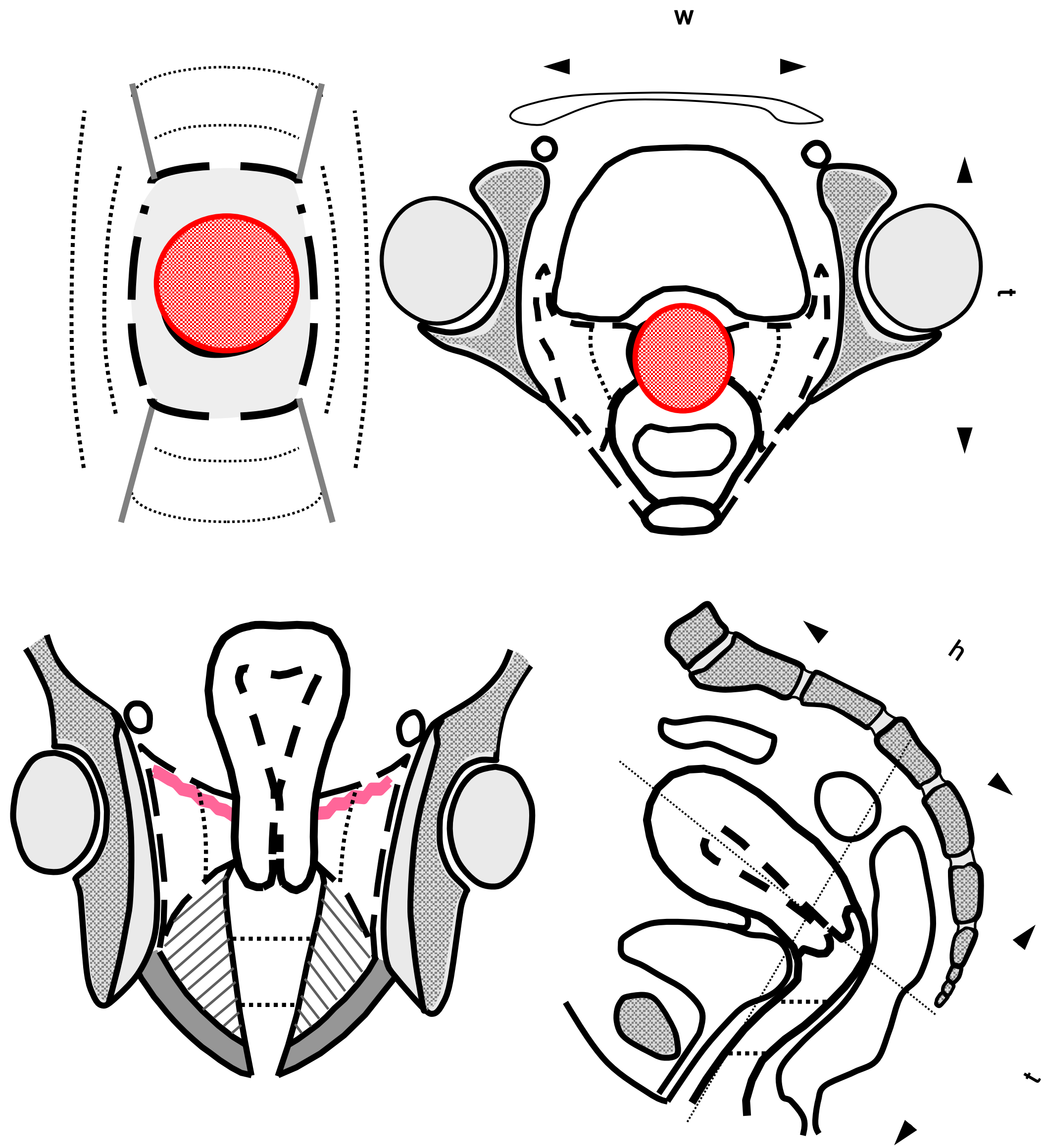
Vagina

Parametria

Rectum or

Bladder





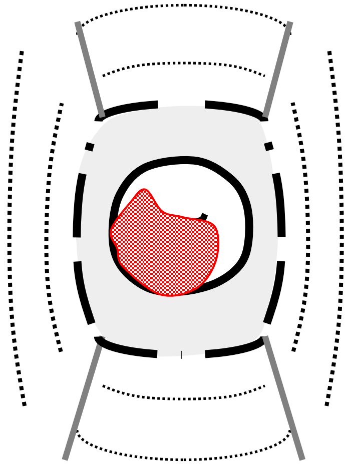
At Diagnosis X

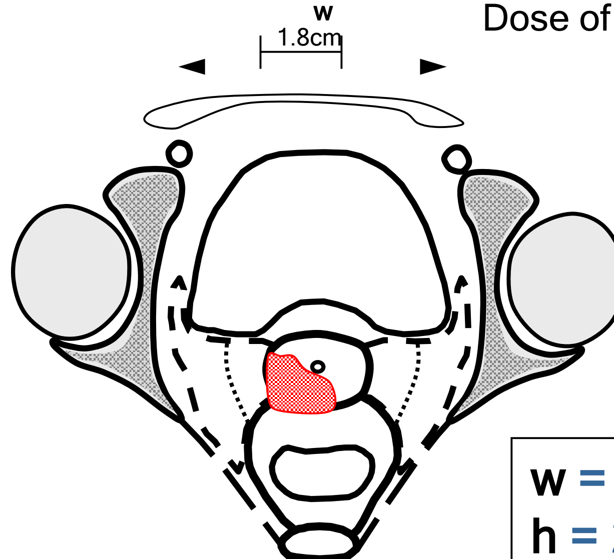
IB1

At Brachytherapy ☐

Dose of EBRT Gy

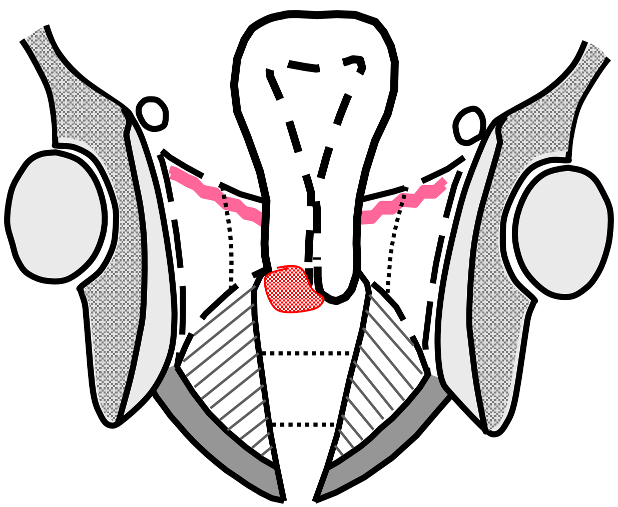
- Cervix: tumour at the posterior and right lip, from 5 to 10h
- Vagina: not involved
- Parametria: not involved

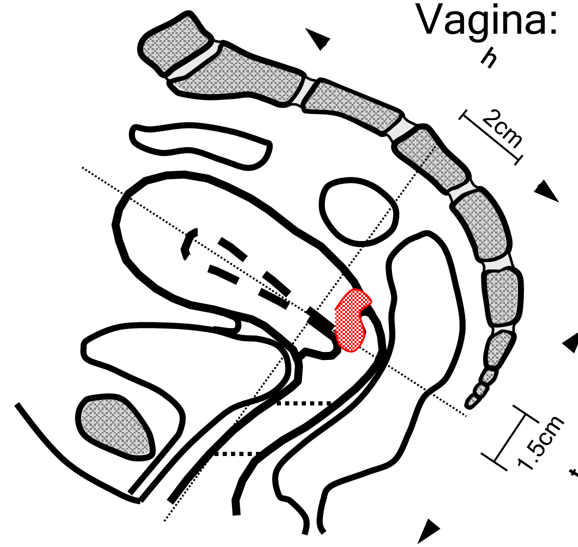




w = 1.8 cm
h = 2.0 cm
t = 1.5 cm

Vagina: 0 cm





dd/mm/yy
___/___/___

____
Signature

At Diagnosis ☐

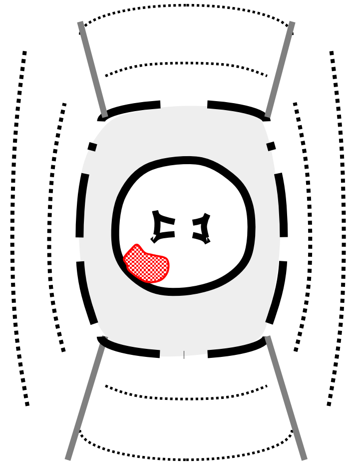
IB1

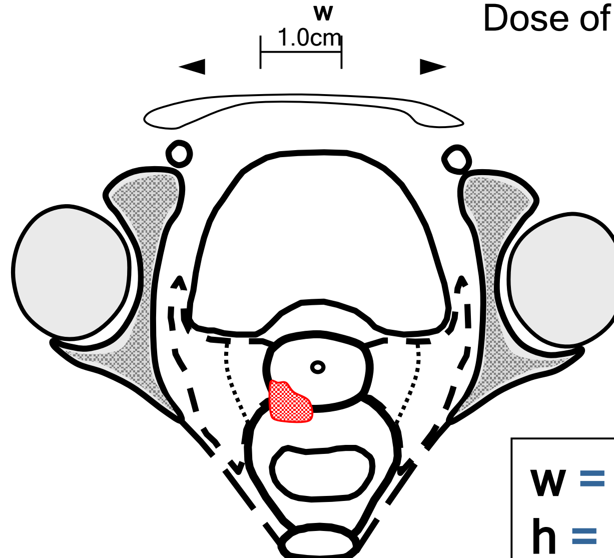
At Brachytherapy ☒

Dose of EBRT Gy

Good response

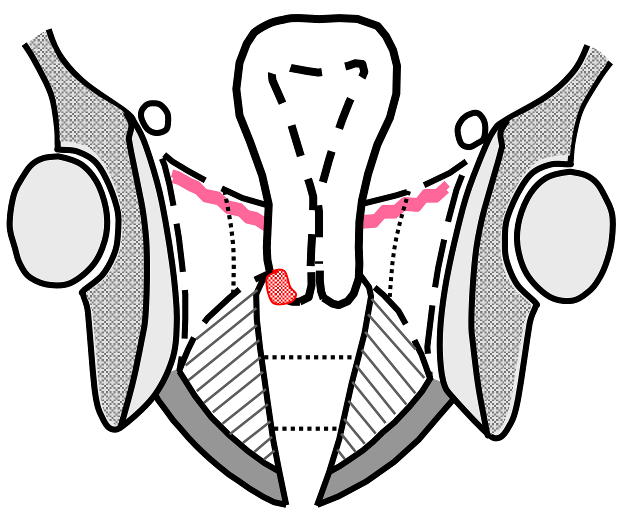
- Cervix: residual tumour from 7 to 9h
- Vagina: not involved
- Parametria: not involved

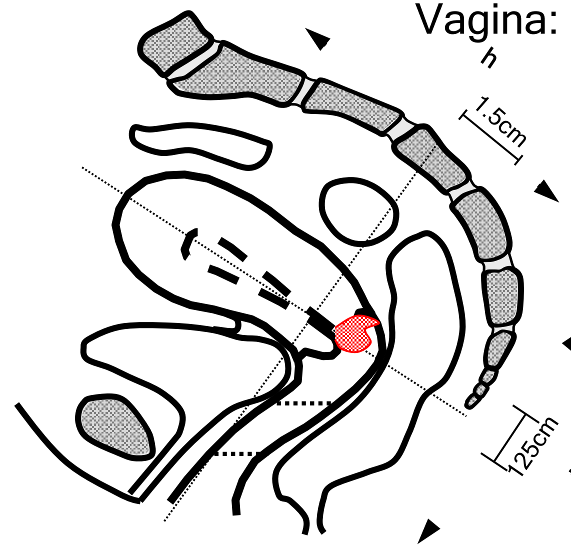




w = 1.0 cm
h = 1.5 cm
t = 1.2 cm

Vagina: 0 cm





dd/mm/yy

___/___/___

Signature

At Diagnosis ☒

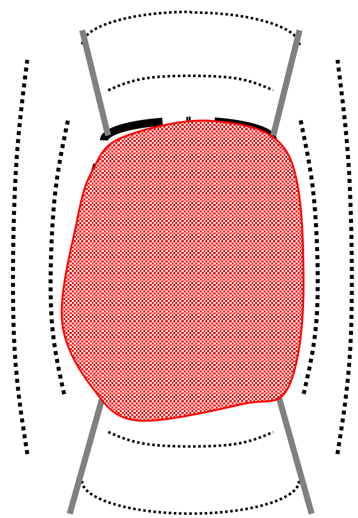
Special Case IB2 Bulky

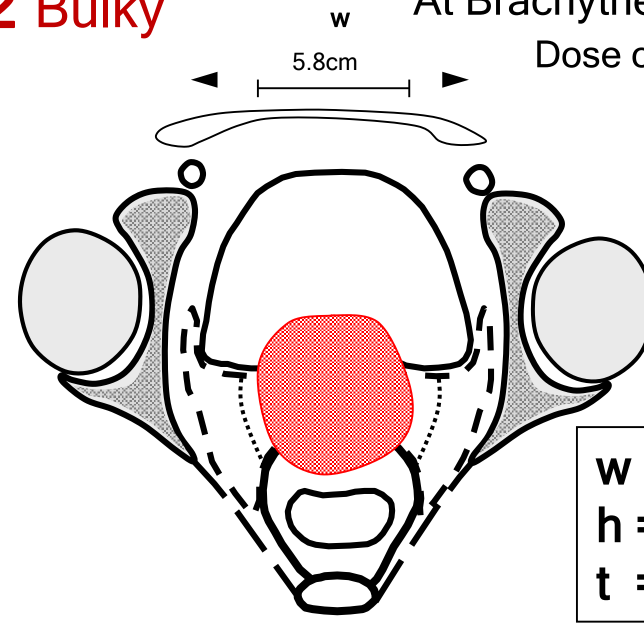
At Brachytherapy ☐

Dose of EBRT ____ Gy

bulky cervical tumour

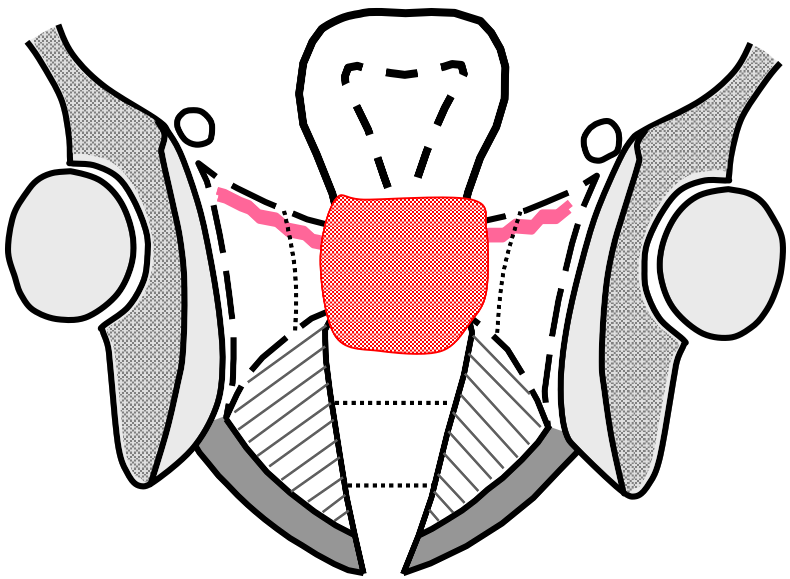
where the tumour bulges towards the vaginal, bladder and rectal walls, but these structures are not involved.

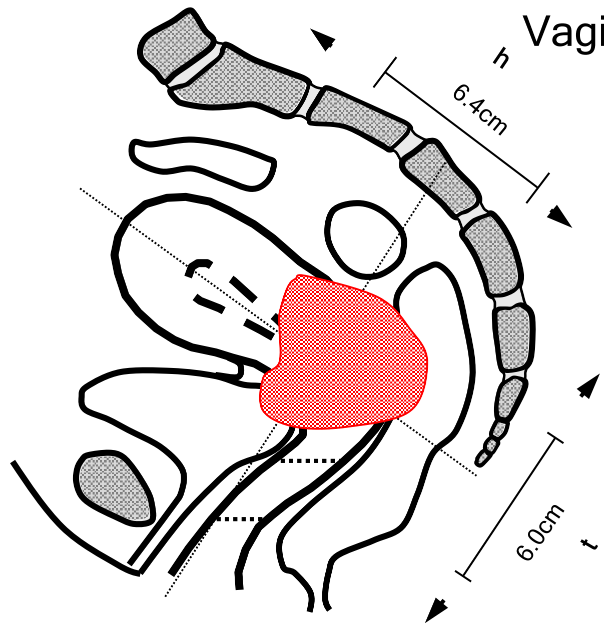




w = 5.8 cm
h = 6.4 cm
t = 6.0 cm

Vagina: 0 cm





dd/mm/yy

___/___/___

____

Signature

At Diagnosis X

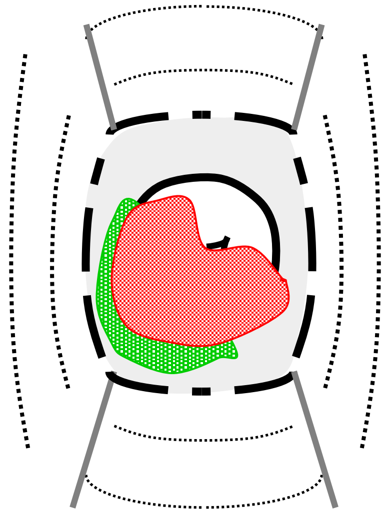
IIA

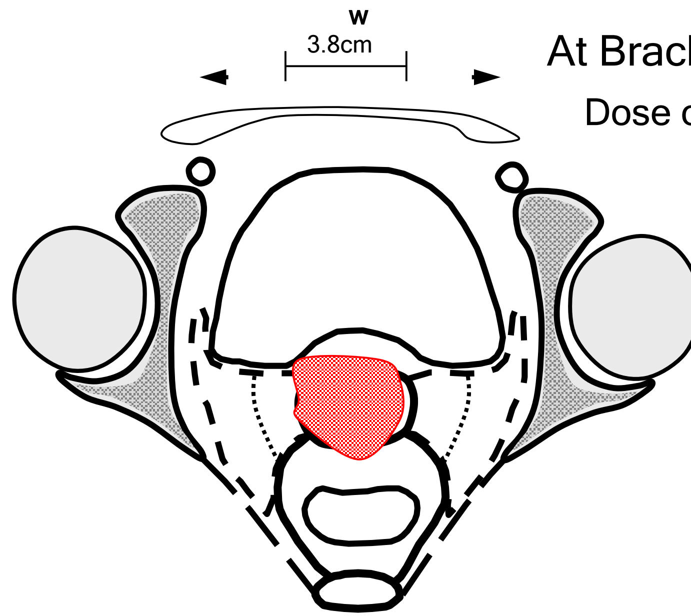
At Brachytherapy ☐

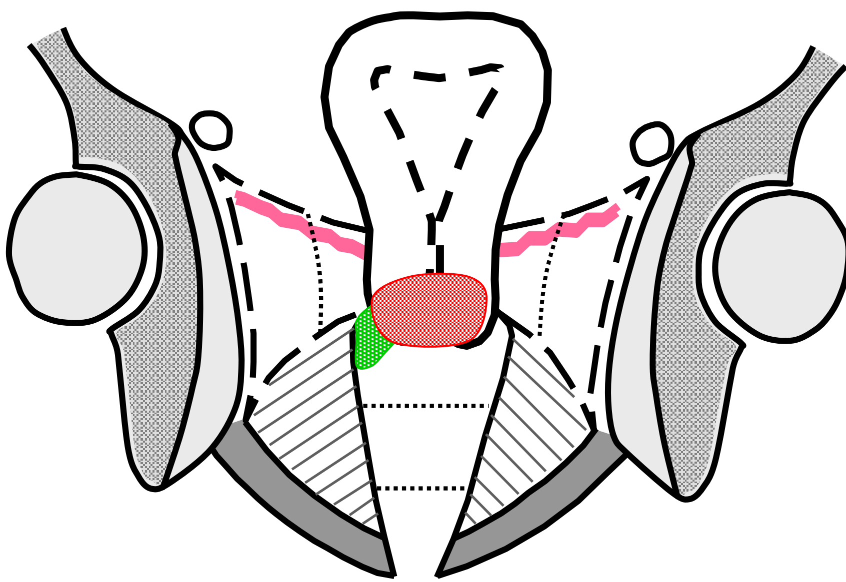
Dose of EBRT____ Gy

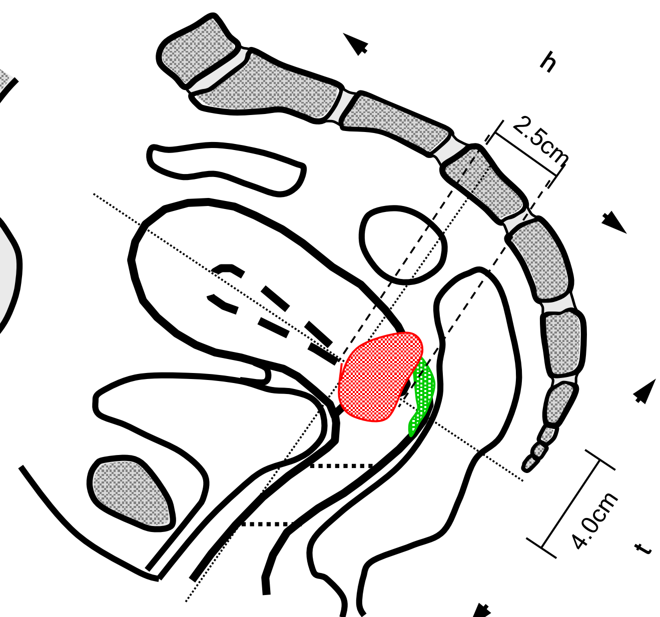
w = 3.8 cm
h = 2.5 cm
t = 4.0 cm

Vagina: 1.5 cm









dd/mm/yy
___/___/___

____
Signature

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

IIA

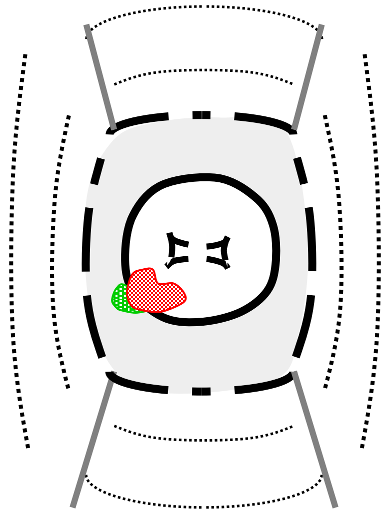
At Diagnosis ☐

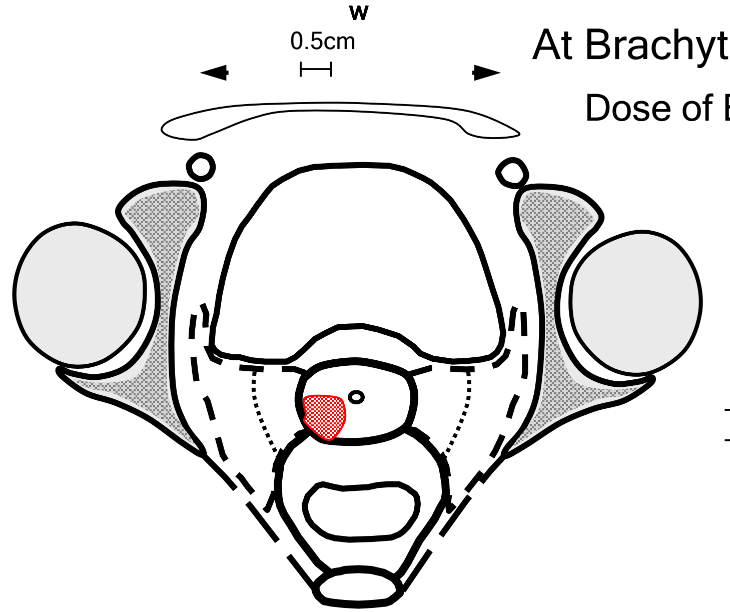
At Brachytherapy ☒

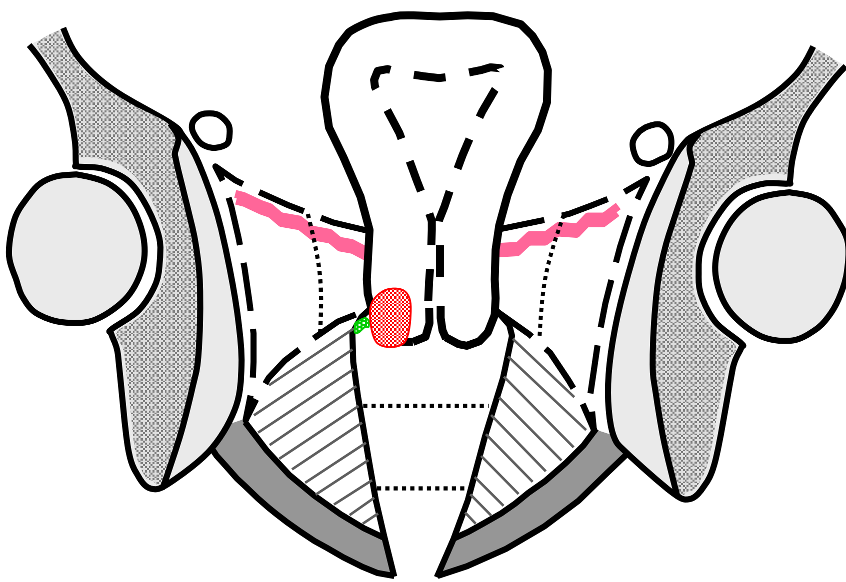
Dose of EBRT 45 Gy

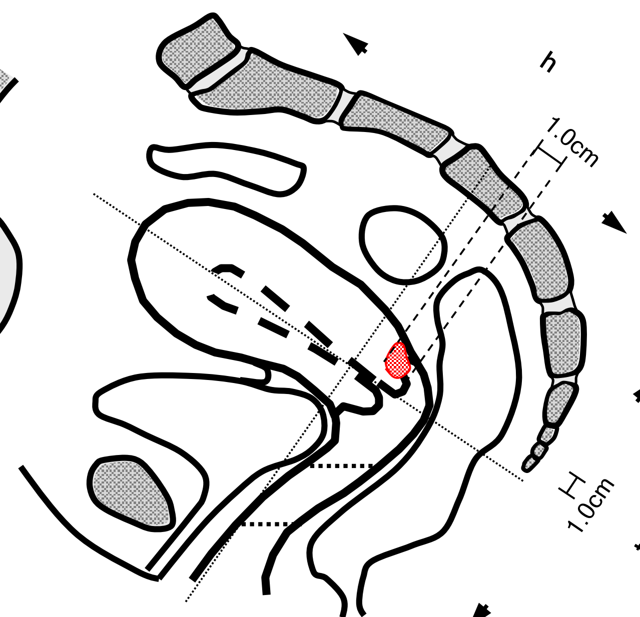
w = 1.0 cm
h = 1.0 cm
t = 1.0 cm

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 ☒

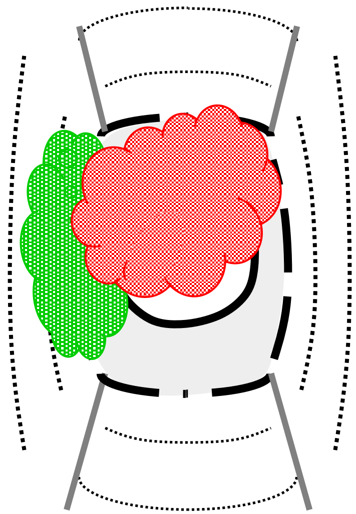
IIIB

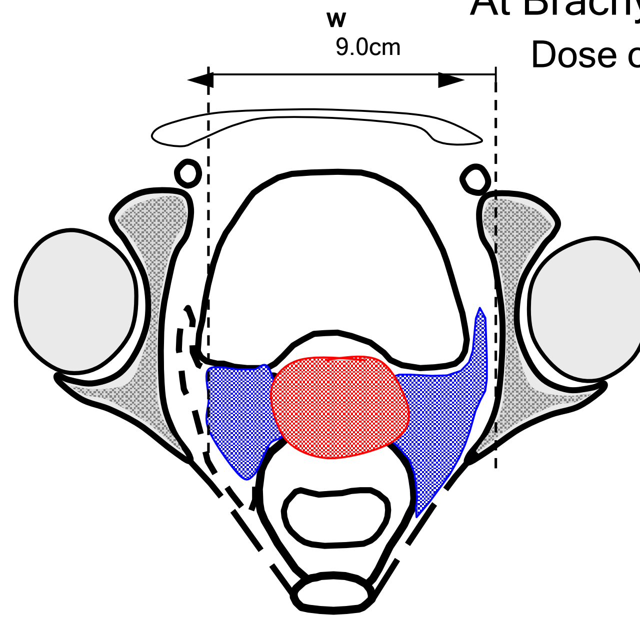
At Brachytherapy ☐

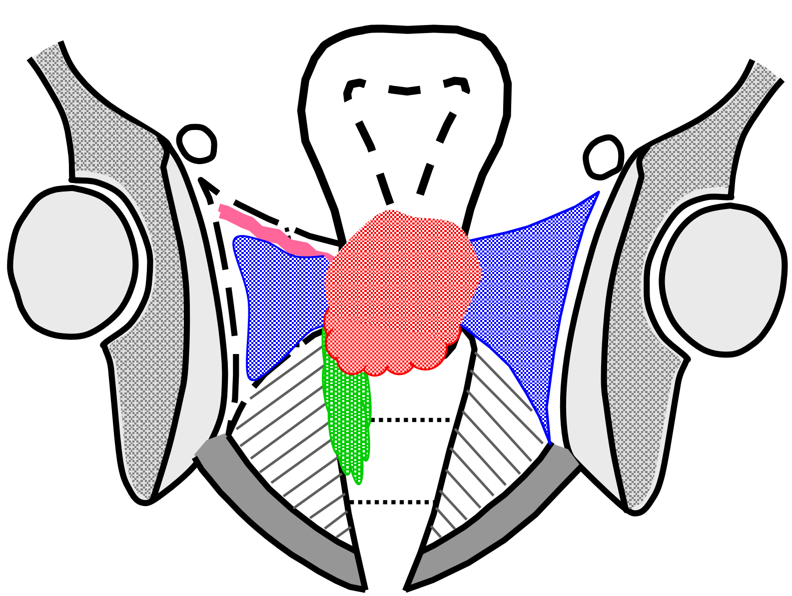
Dose of EBRT ____ Gy

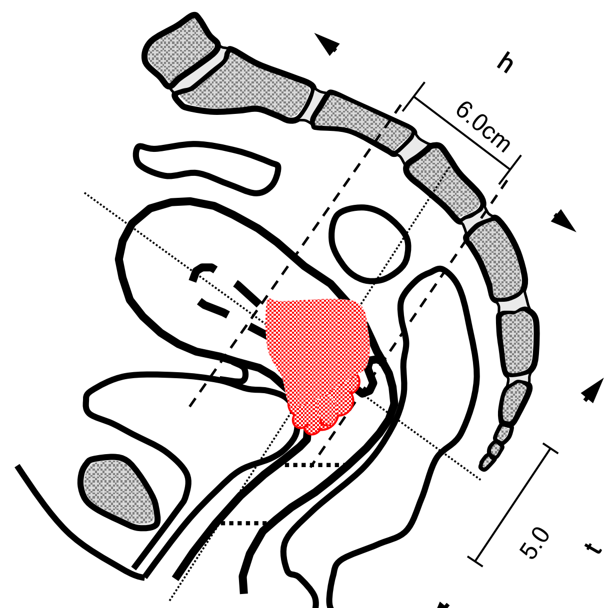
w = 9.0 cm
h = 6.0 cm
t = 5.0 cm

Vagina: 5 cm









dd/mm/yy
___/___/___

Signature

Note: vagina and parametria not included in **h**

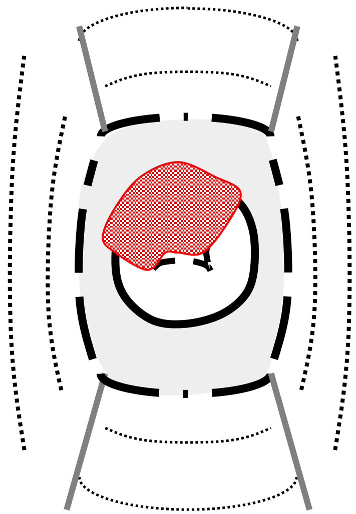
At Diagnosis ☐

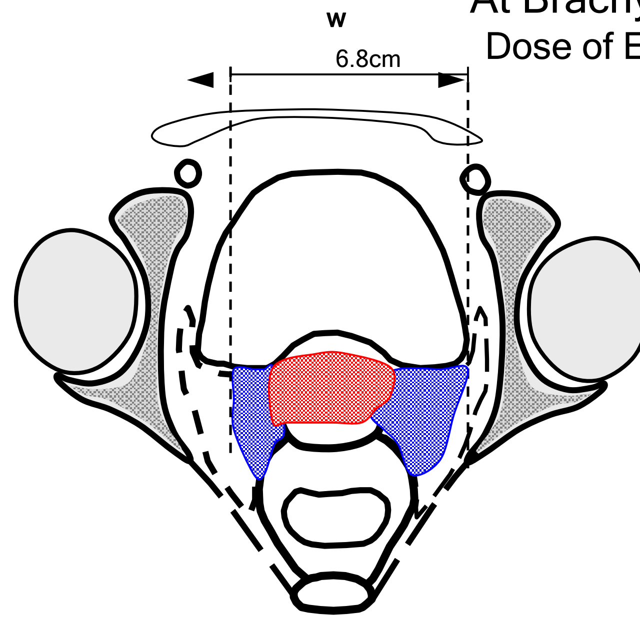
IIIB

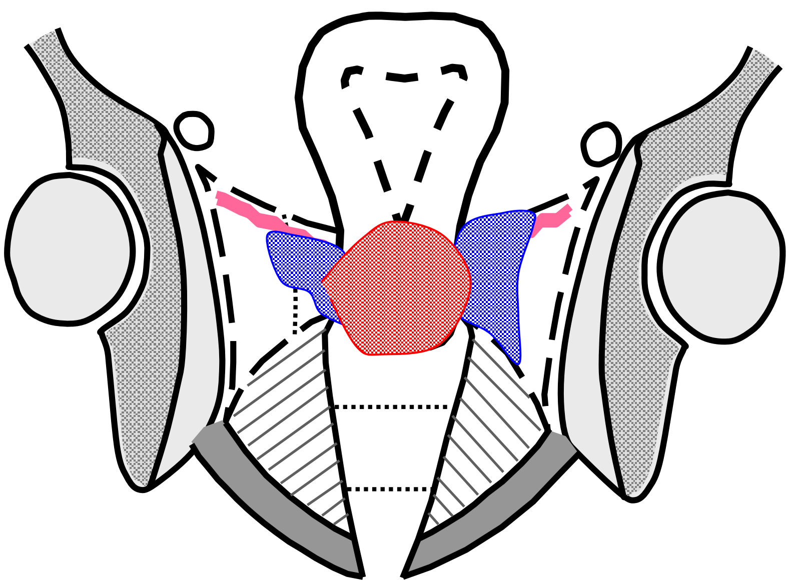
At Brachytherapy ☒
Dose of EBRT 50.4 Gy

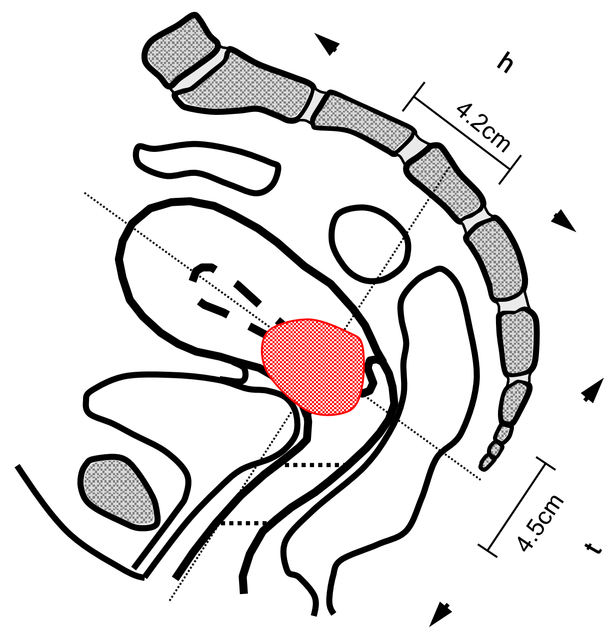
w = 6.8 cm
h = 4.2 cm
t = 4.5 cm

Vagina: 0 cm









dd/mm/yy
__/__/__

____
Signature

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

At Diagnosis ☒

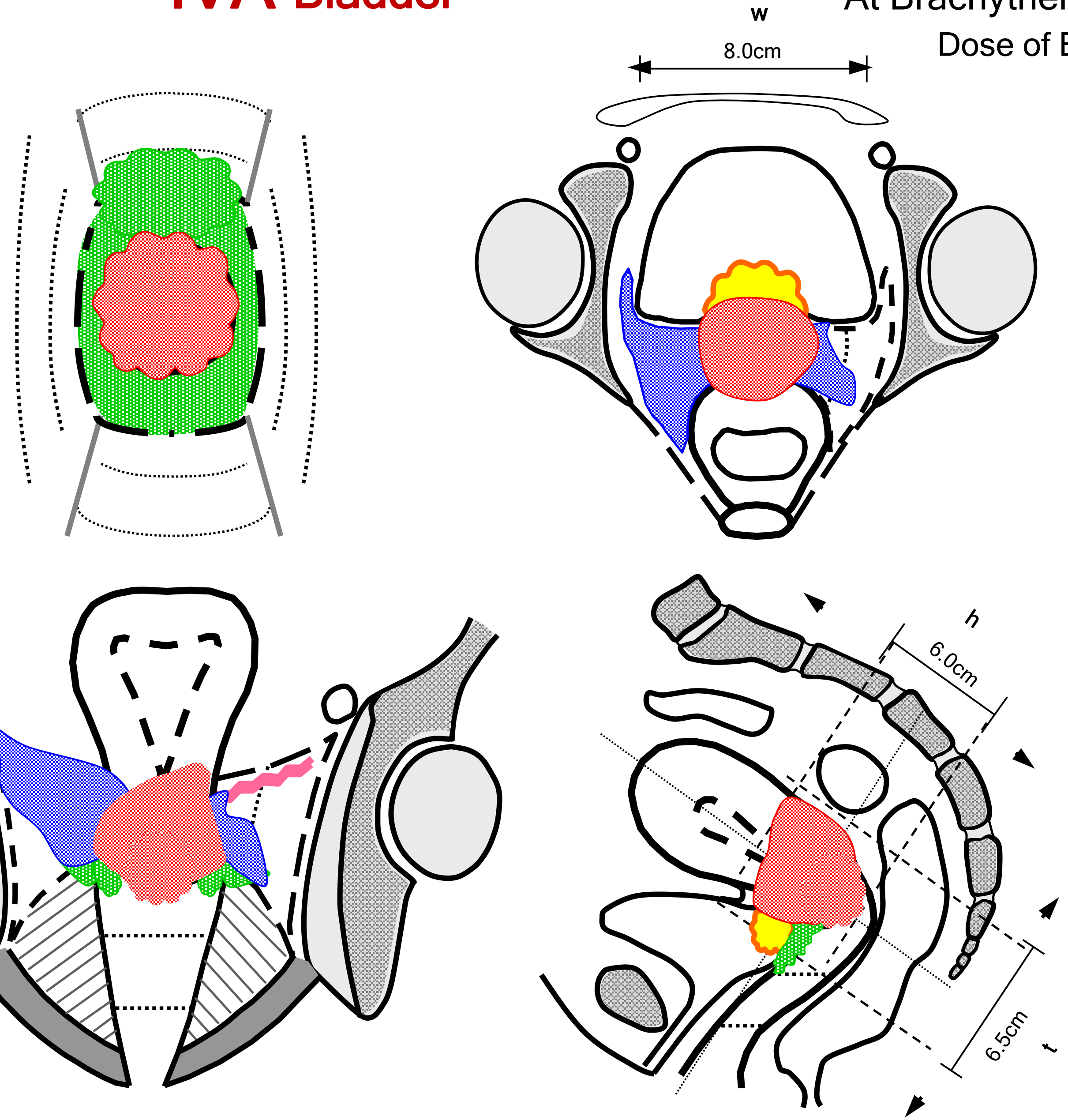
IVA Bladder

At Brachytherapy ☐

Dose of EBT____ Gy

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

Vagina: 5 cm



dd/mm/yy
___/___/___

____
Signature

At Diagnosis ☐

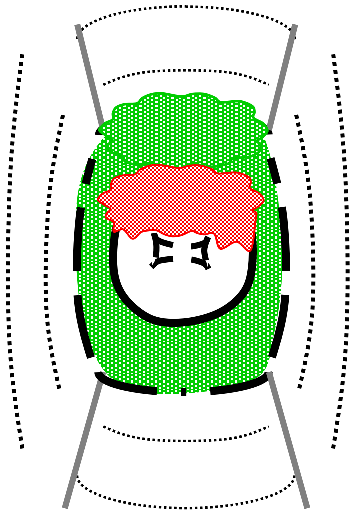
IVA Bladder

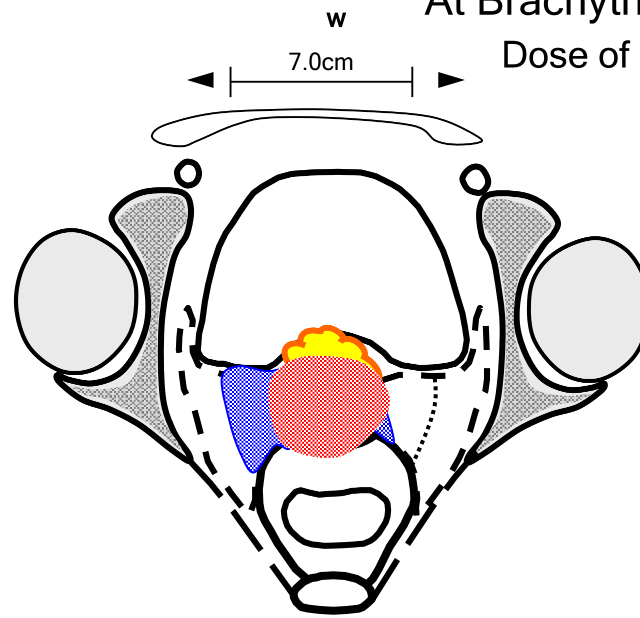
At Brachytherapy ☒

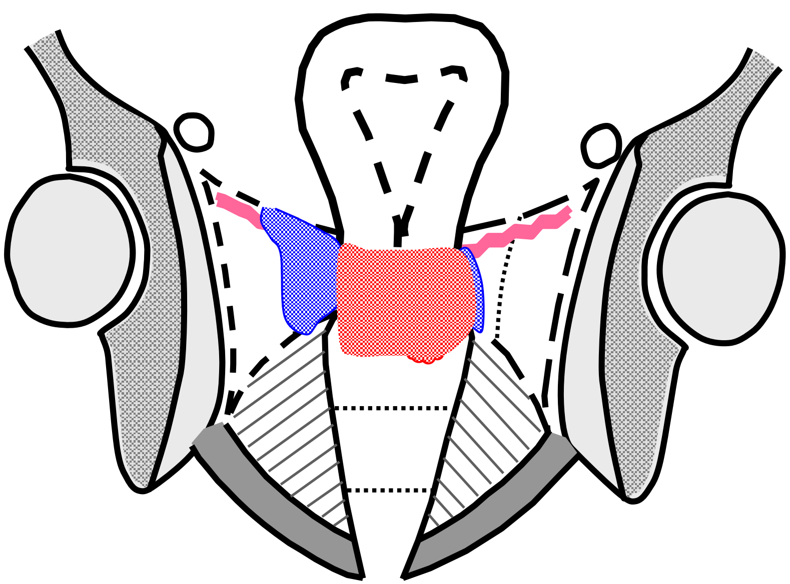
Dose of EBRT 45 Gy

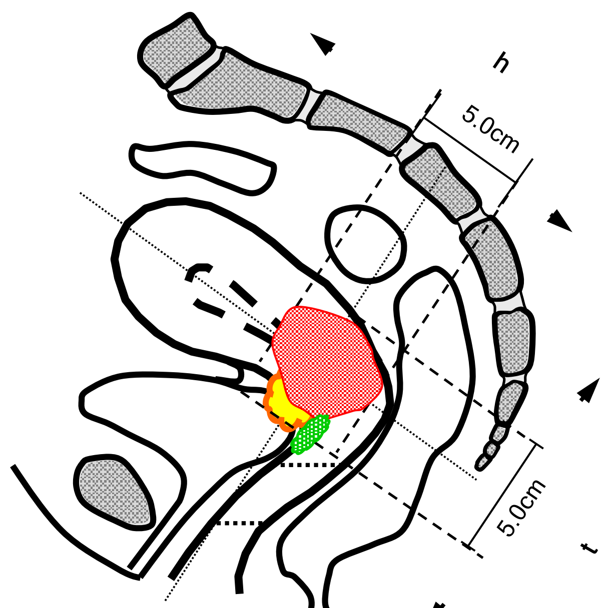
w = 7.0 cm
h = 5.0 cm
t = 5.0 cm

Vagina: 2.5 cm









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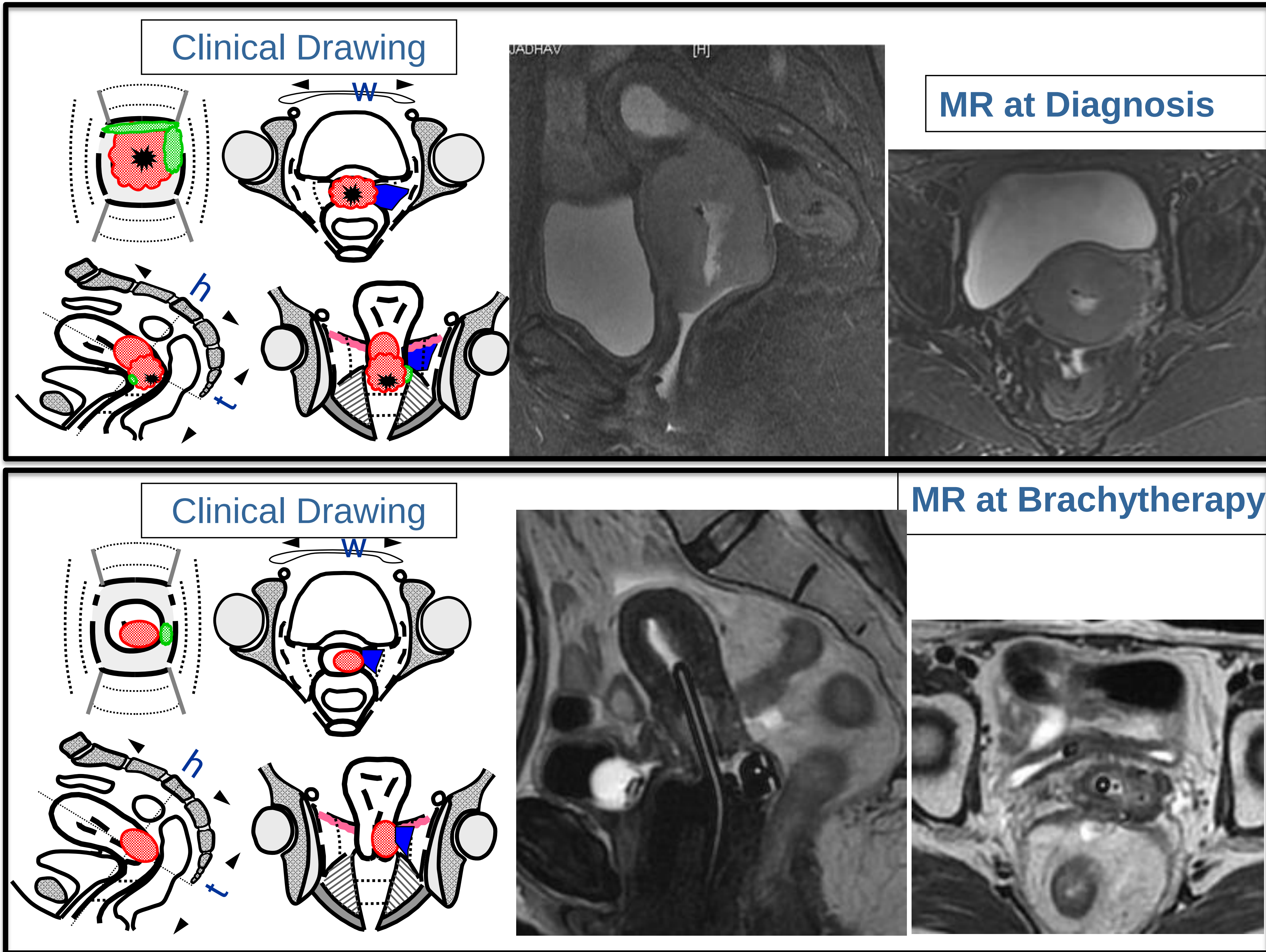
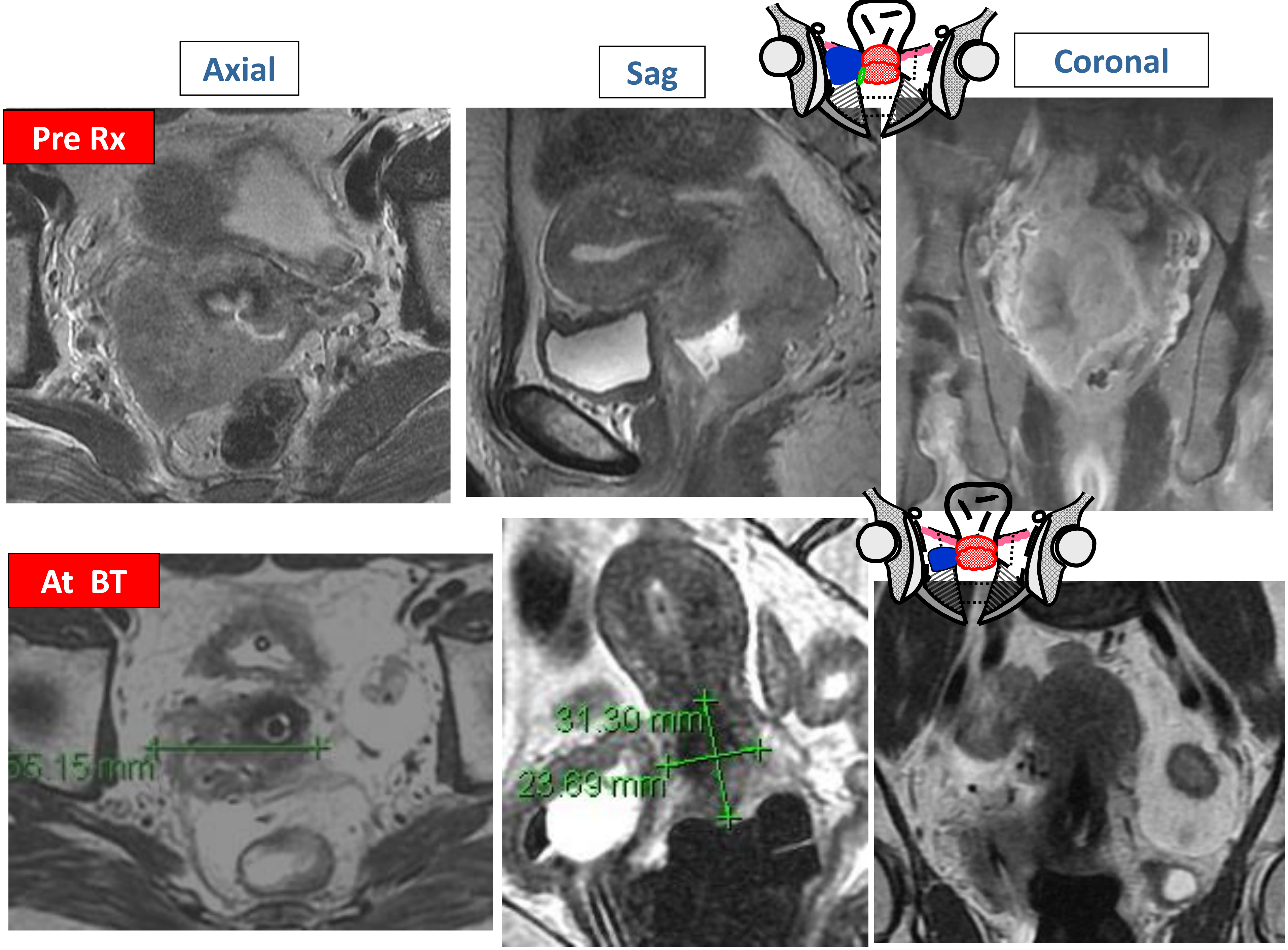
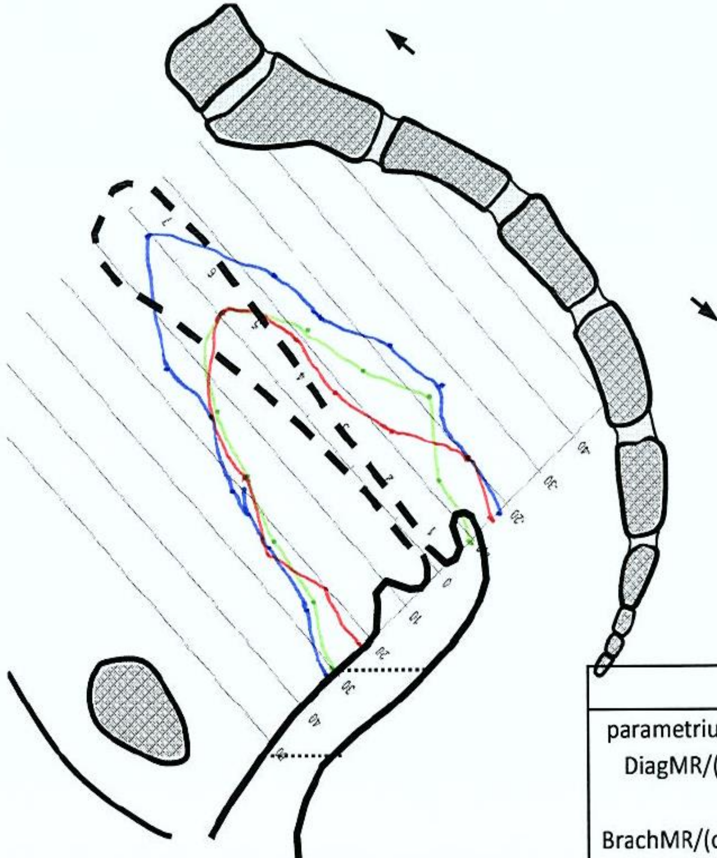
Signature

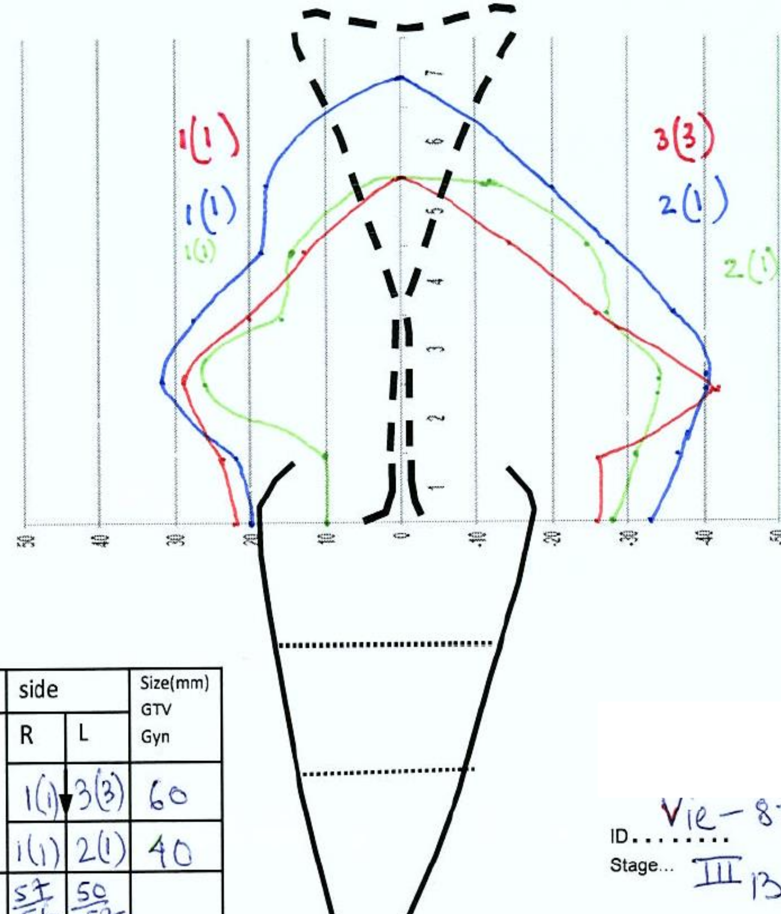

Clinical Drawing
w
h
t
JADHAV
[H]
MR at Diagnosis
Clinical Drawing
w
h
t
MR at Brachytherapy


Axial
Sag
Coronal
Pre Rx
At BT
31.30 mm
23.69 mm

10

MR
HR CTV
IR CTV





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

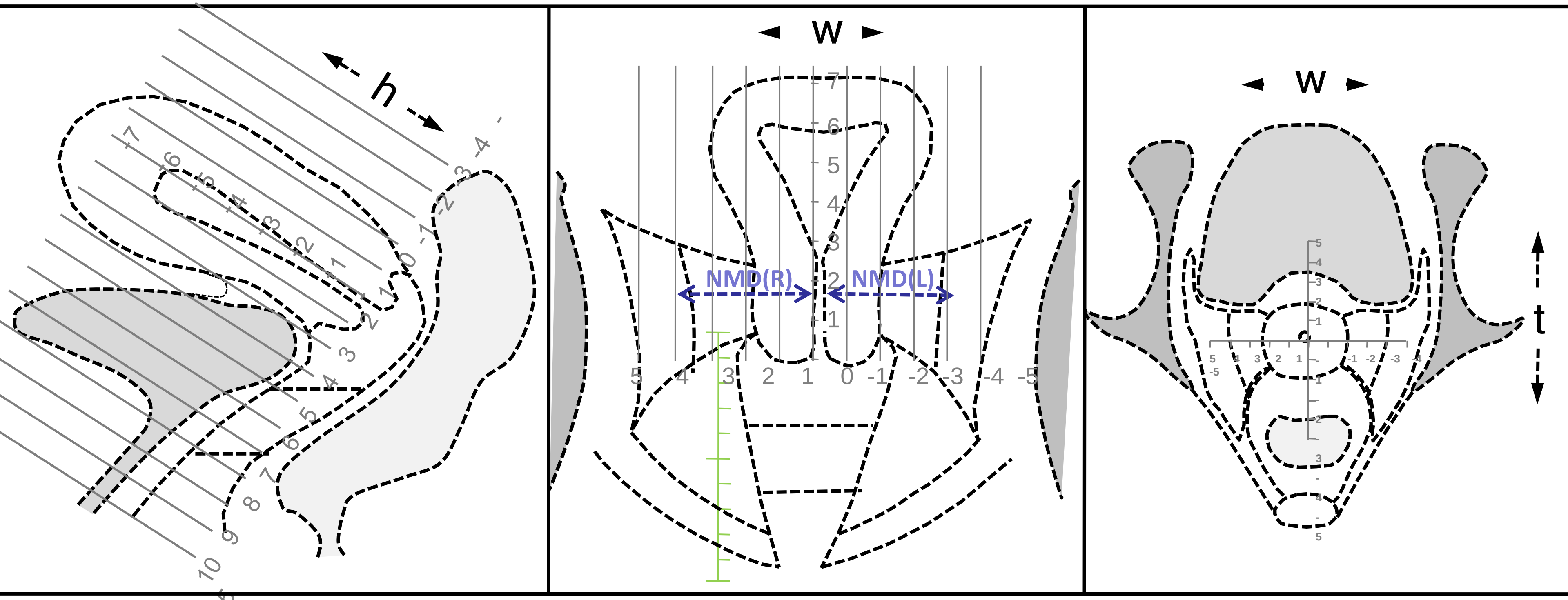
ID........ Vie-87
Stage... III B.

	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	16	20	26	10	22	29	26	32	26	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~~	14		

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. __]

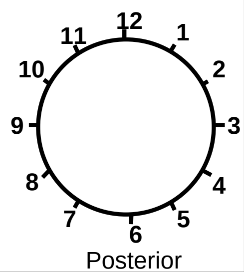


h = ____ cm **t = ____ cm** **w = ____ cm** **NMD (R) =____cm** **NMD (L) =____cm**

[NMD-Near Minimum Distance]

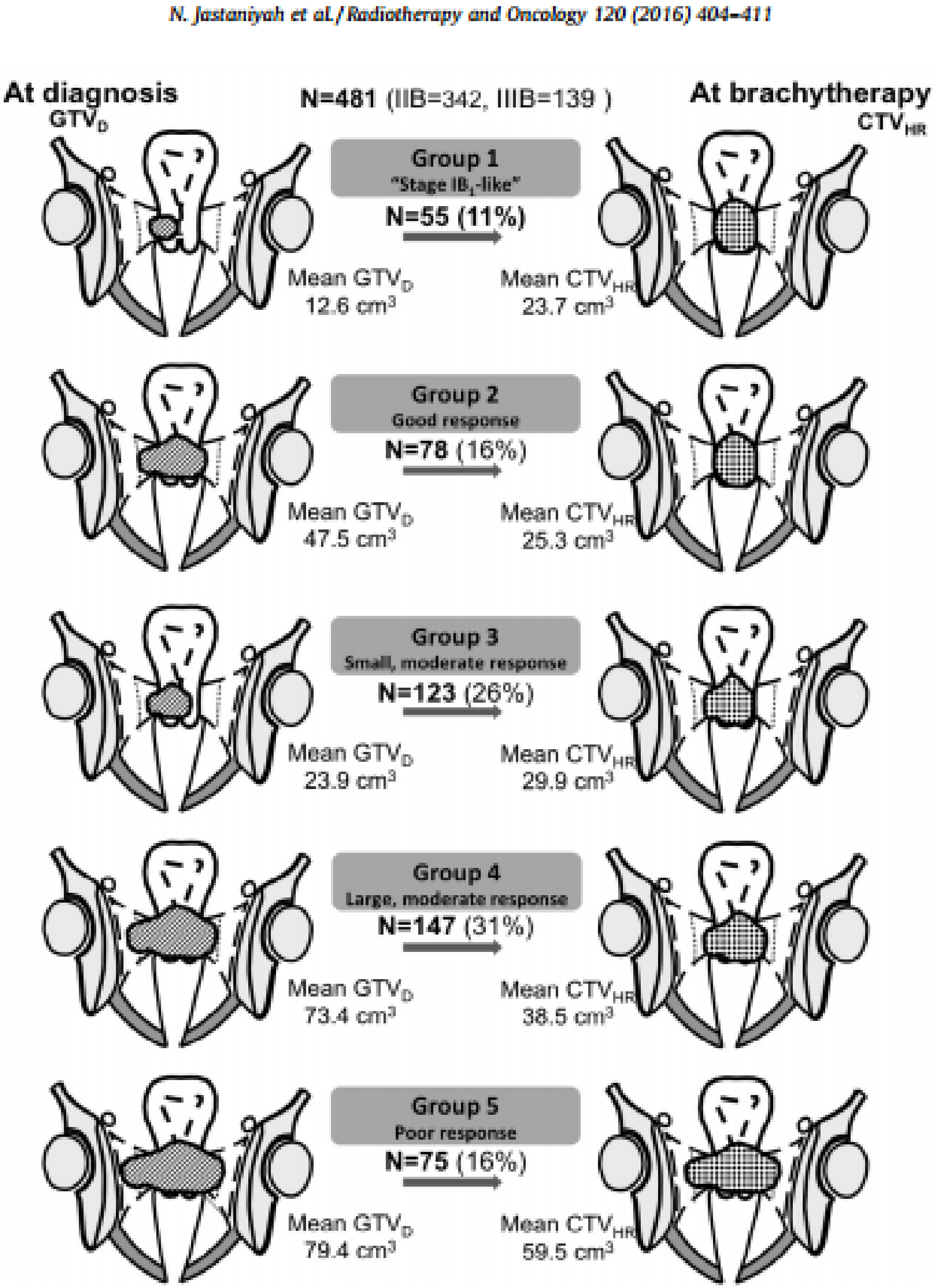
Vaginal Disease

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

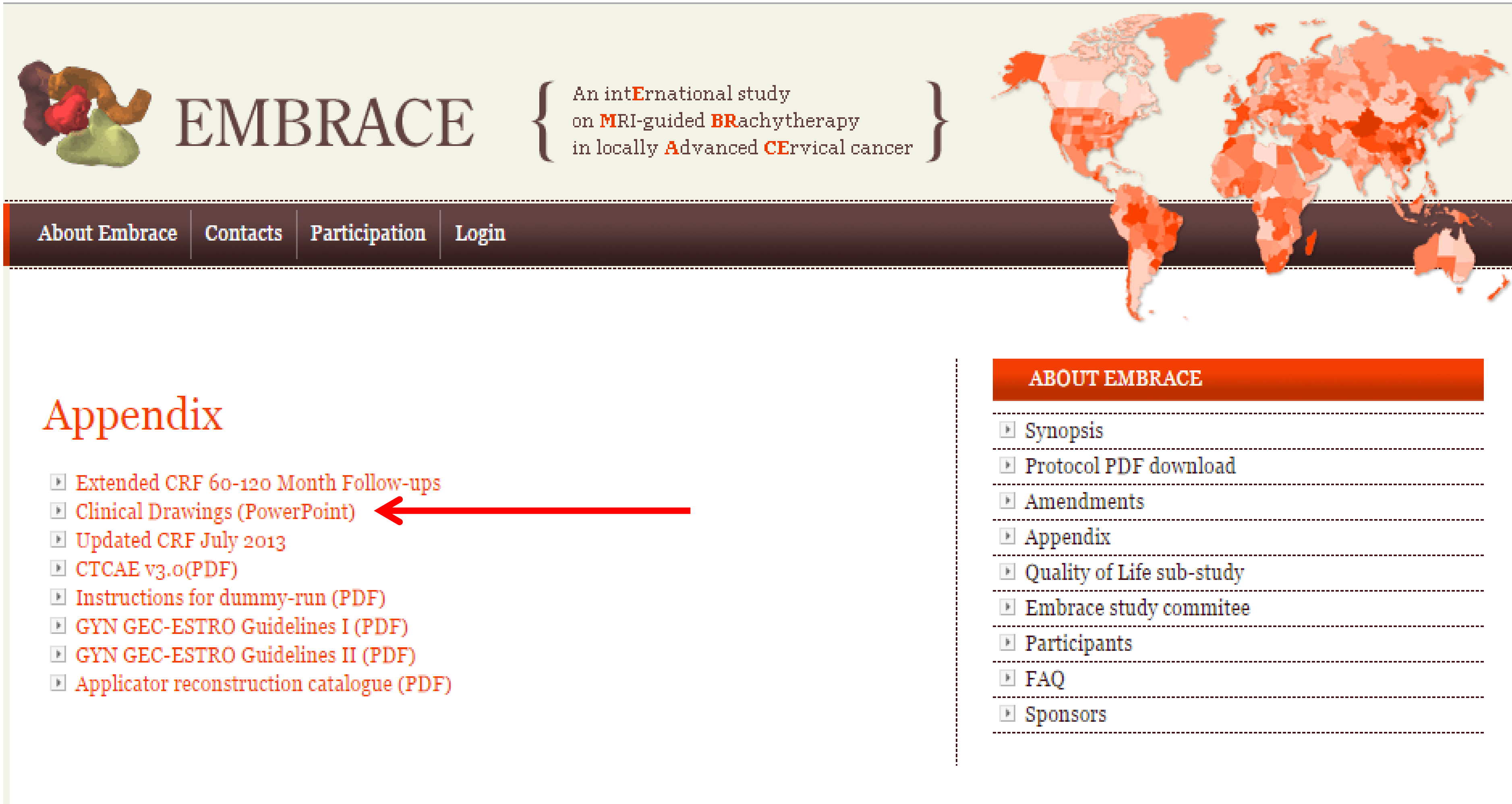
SUMMARY

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 !



www.embracestudy.dk/AboutAppendix.aspx

Workshop AAR03

Cervical Cancer
FIGO IIB

PRACTICAL EXAMPLE

AAR 003

Clinical history –status at diagnosis:

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

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

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

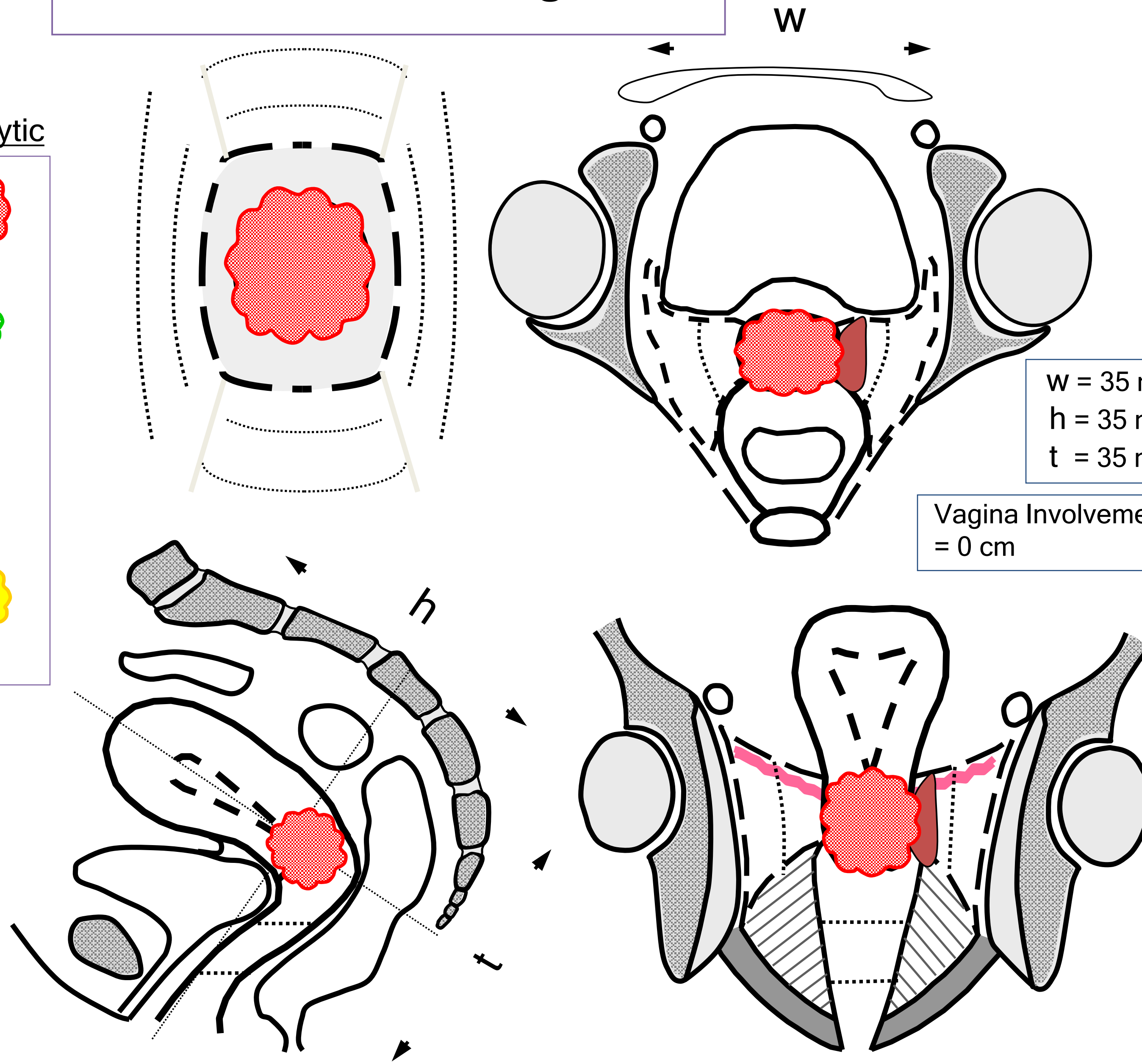
Radiology reports:

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

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

Clinical Drawing

At Diagnosis



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

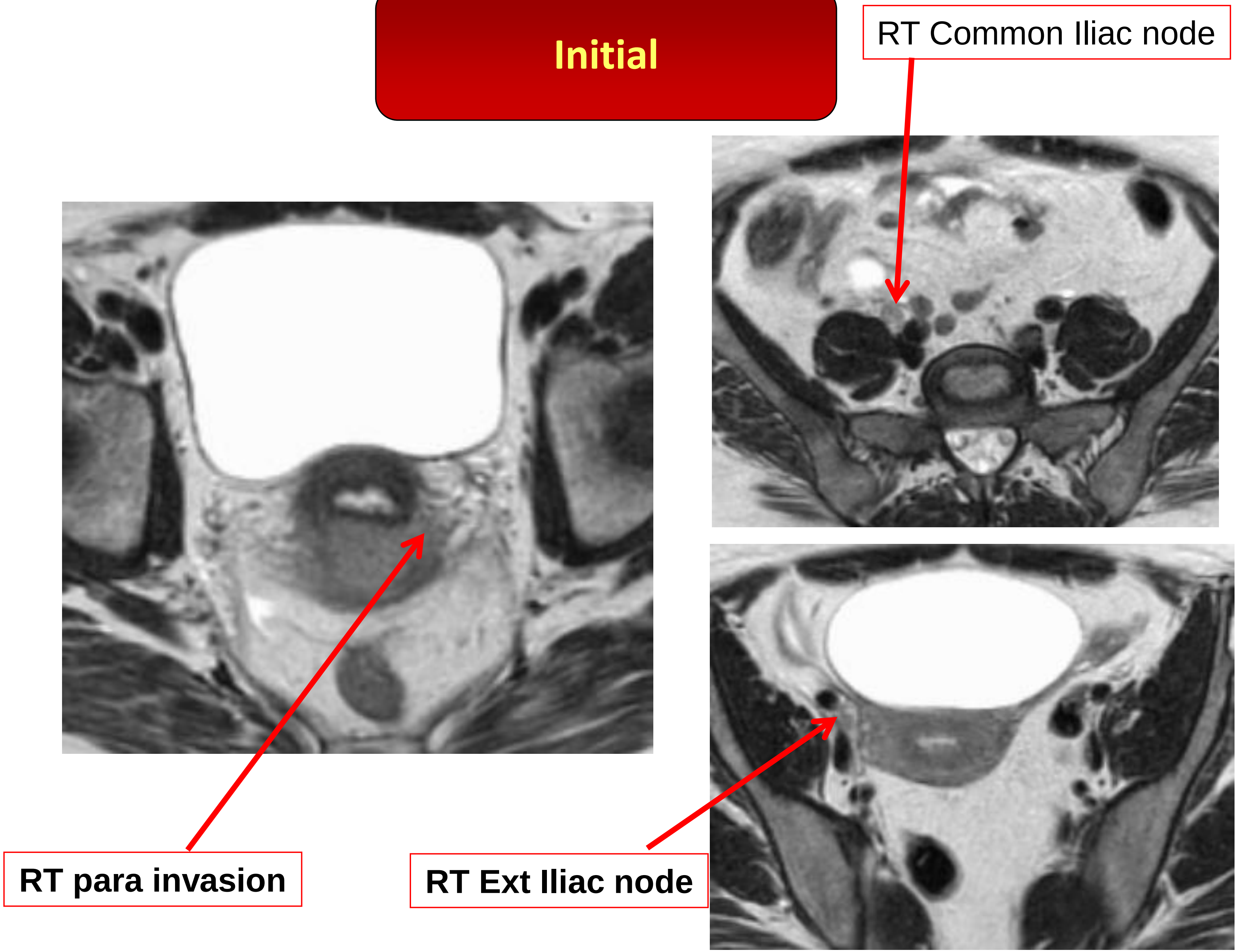
Vagina Involvement = 0 cm

	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

dd/mm/yy

Signature

Initial



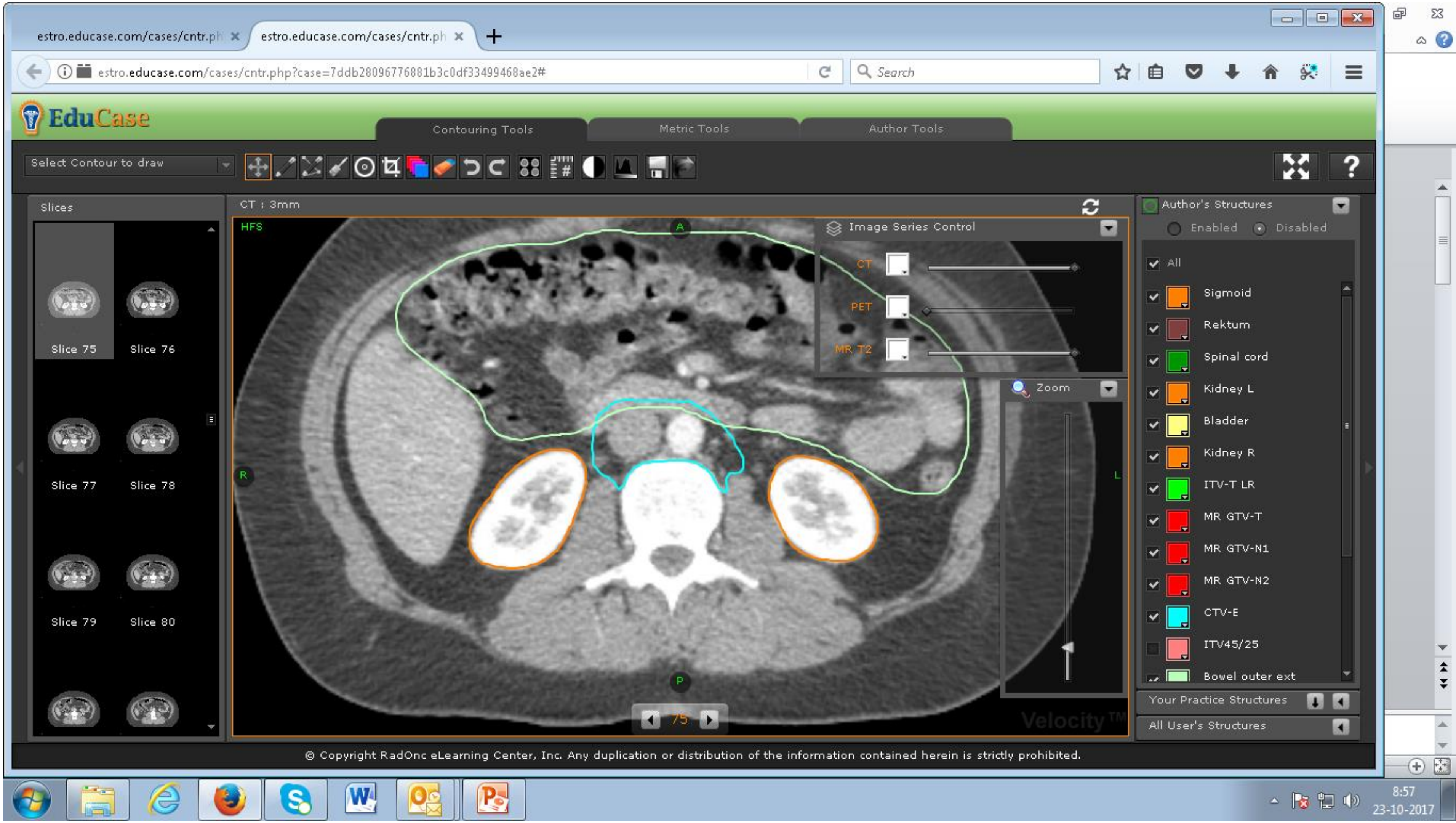
EBRT CONTOURING EXERCISE

EMBRACE II DEFINITIONS

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

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

PAO



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Kidney L
Bladder
Kidney R
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MR GTV-N1
MR GTV-N2
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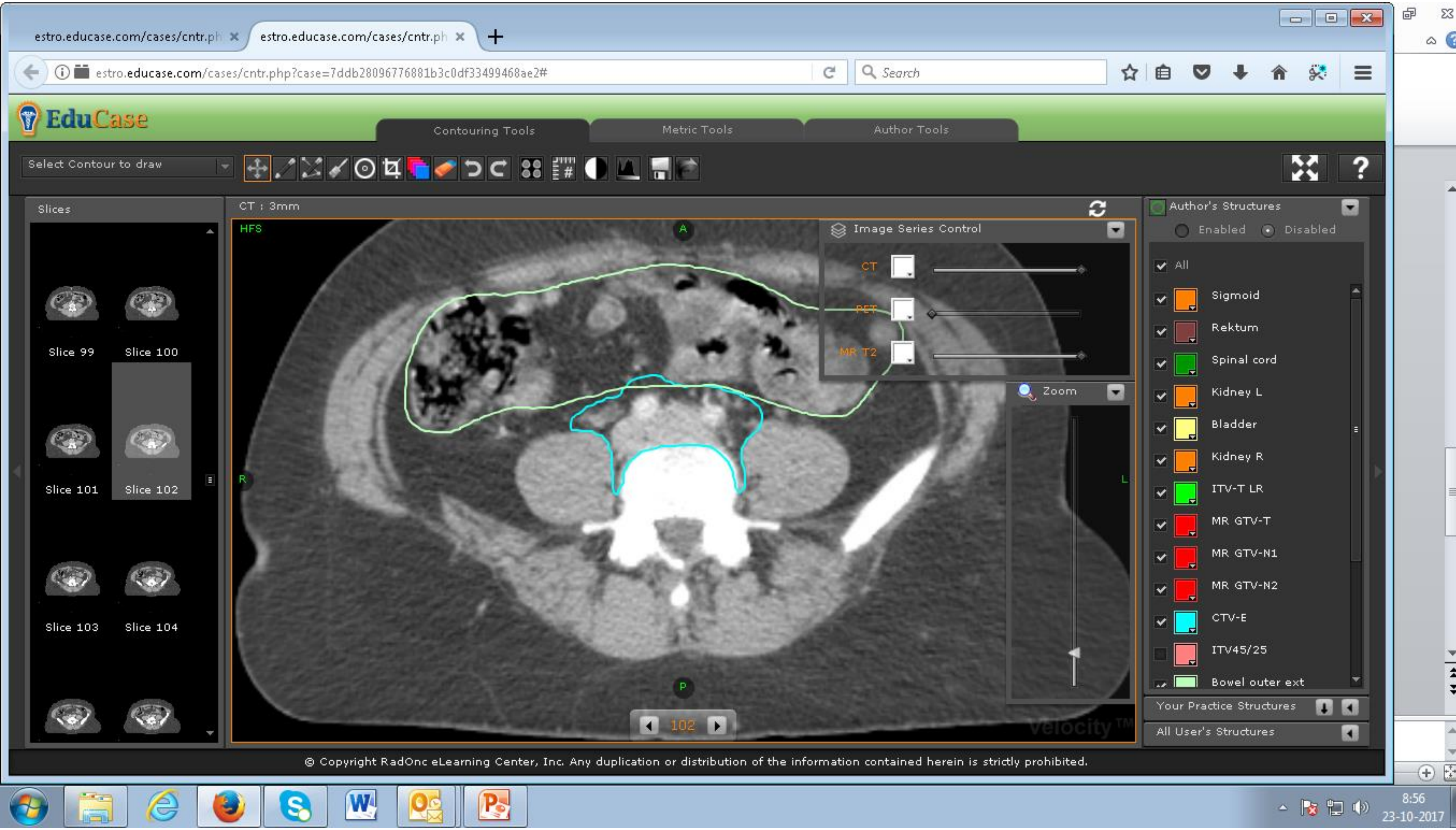
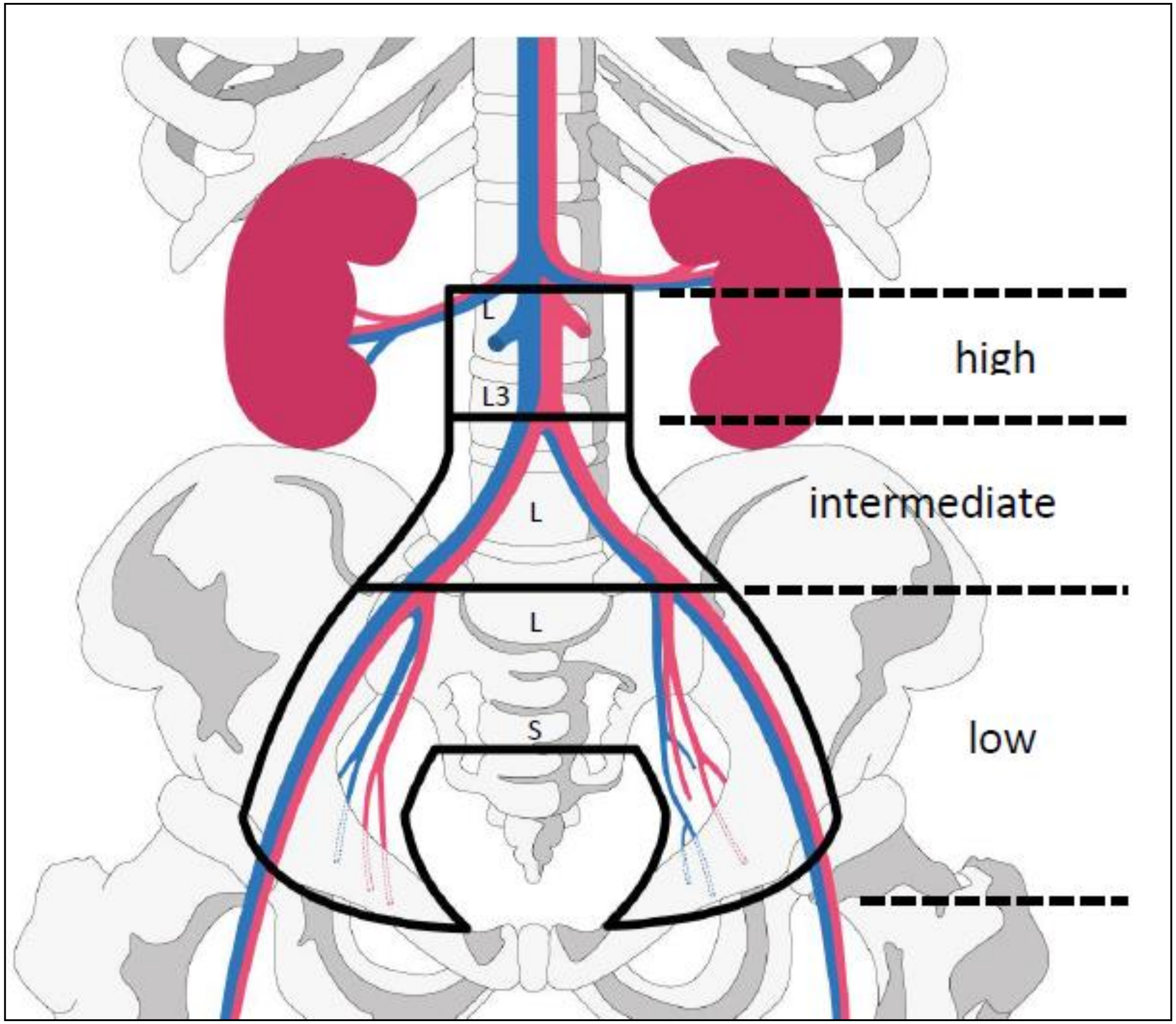
Common iliac



Common iliac bifurcation

Table 9.1: Risk groups for defining the elective clinical target volumes for lymph nodes and corresponding nodal targets defining the radiation field extensions.

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].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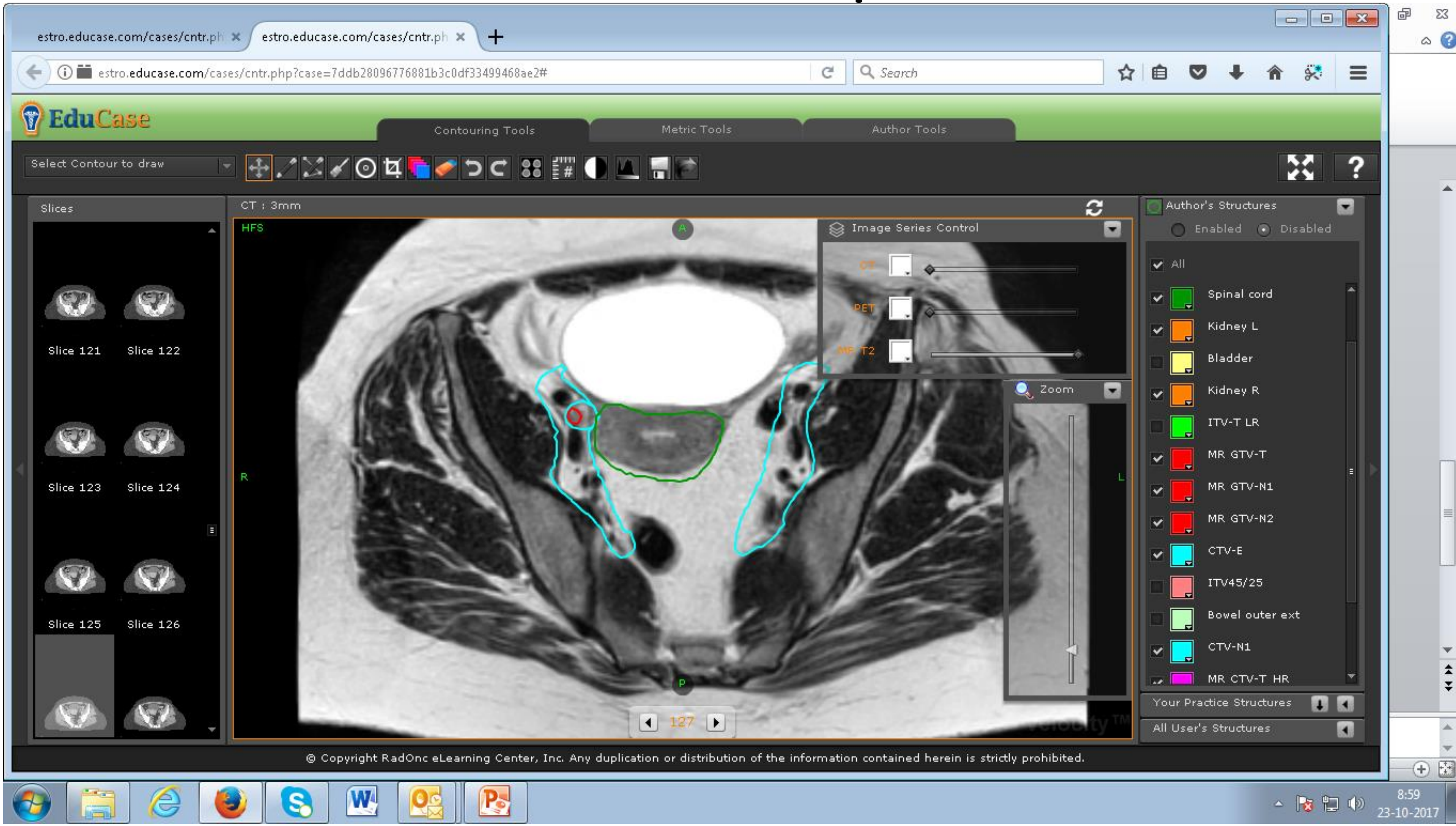
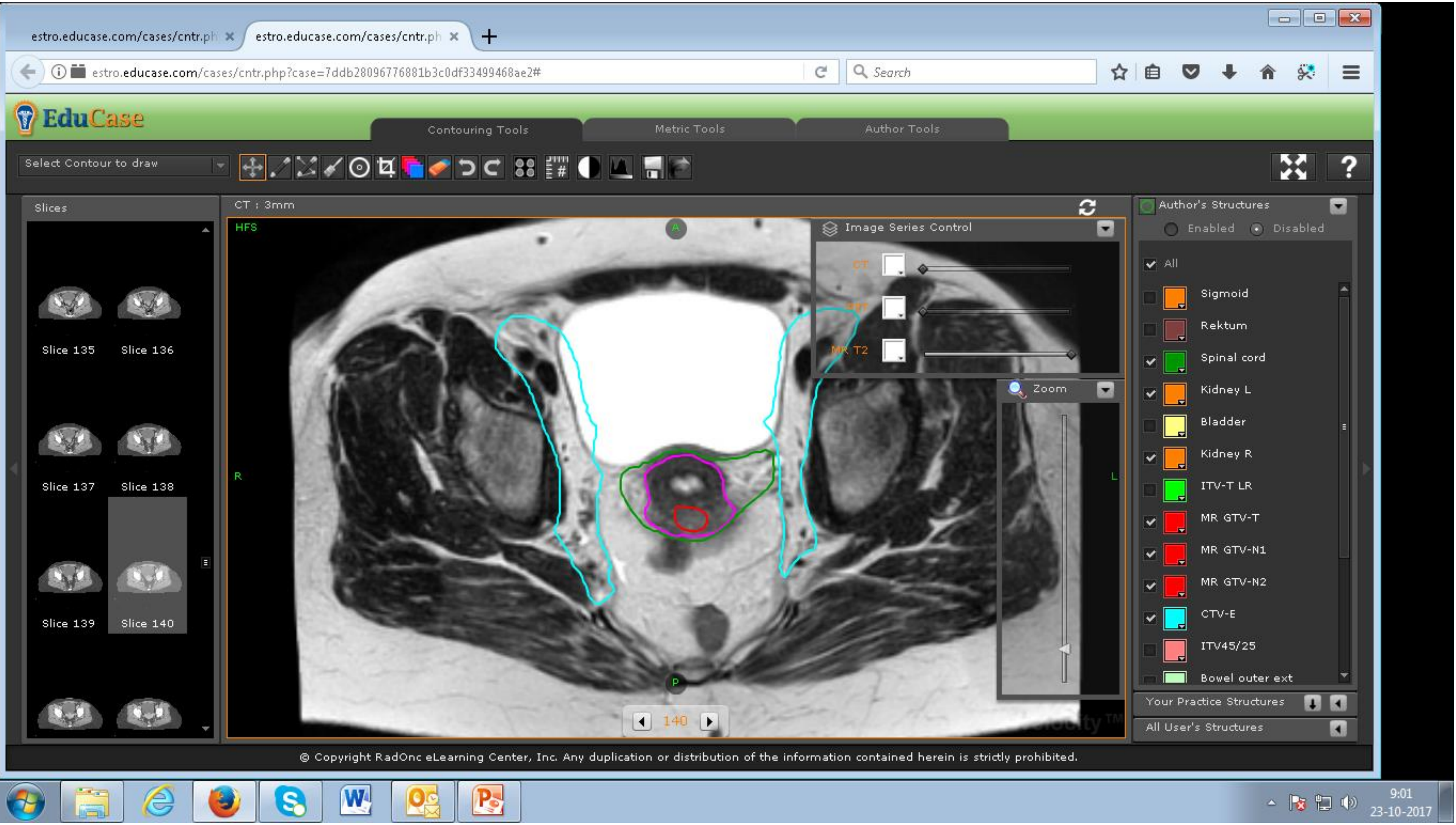
Common iliac bifurcation

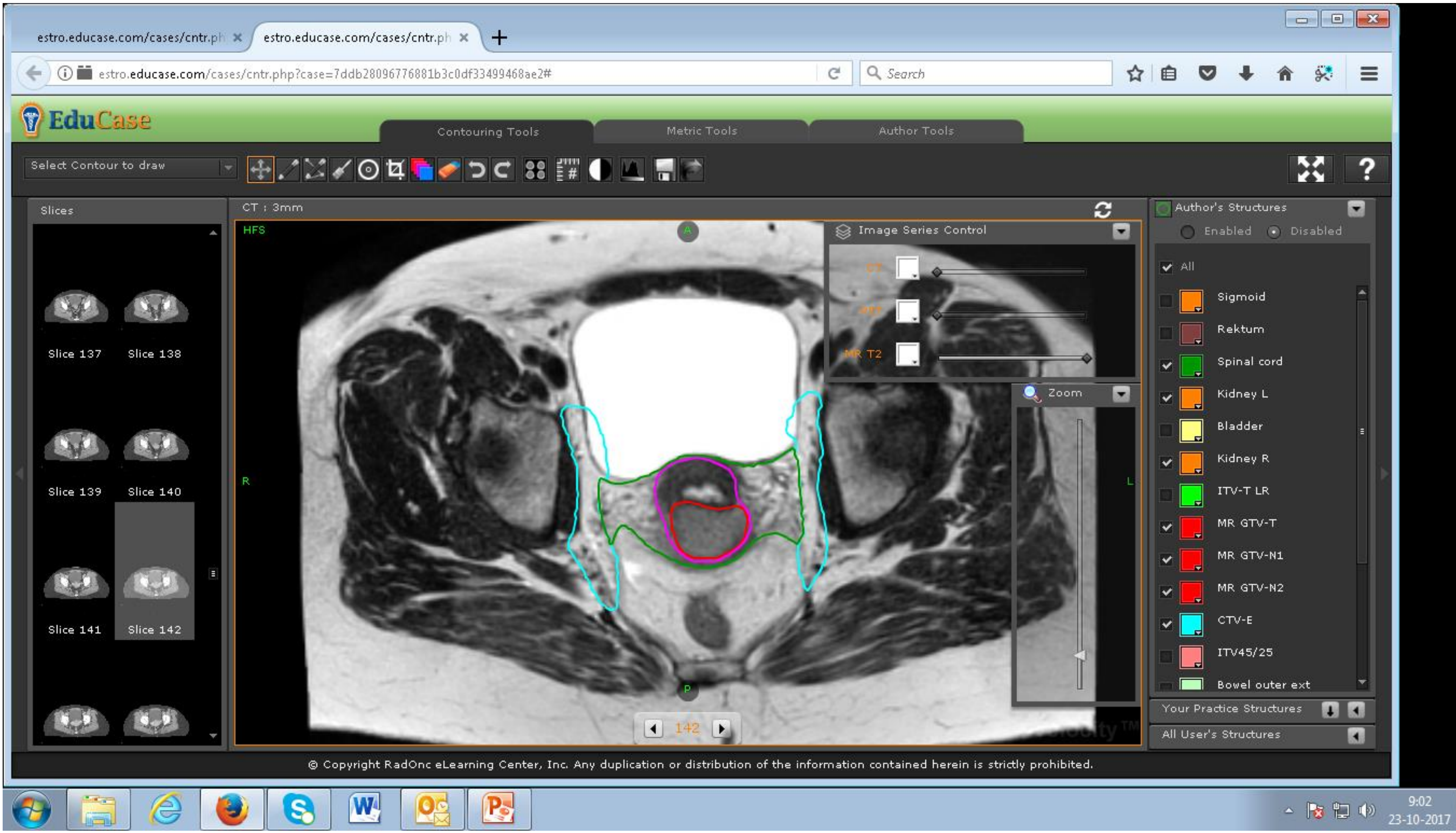
Internal, external iliac, obturator, uterine corpus



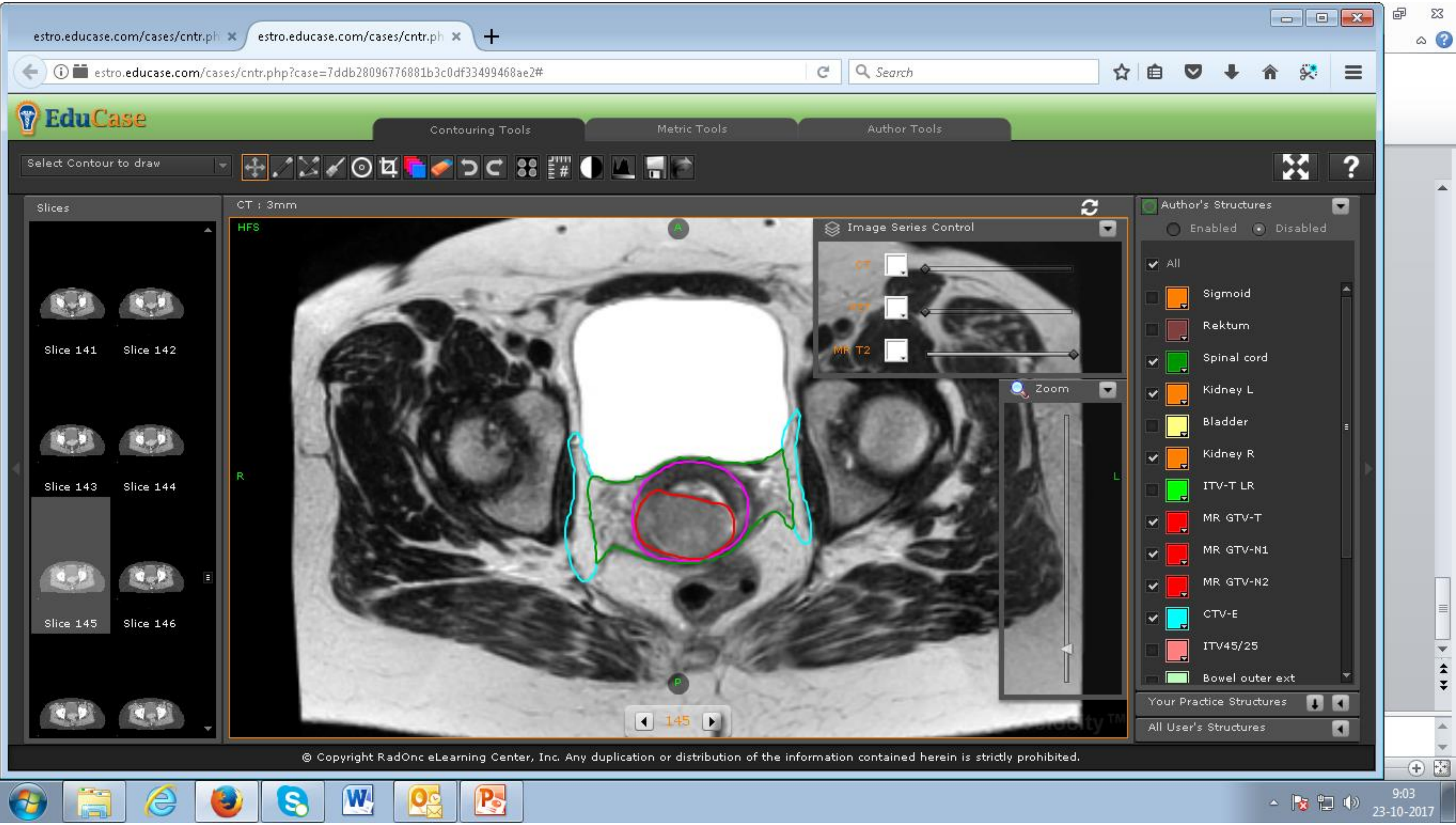
Internal, external iliac, cervix, GTV-T, parametrium



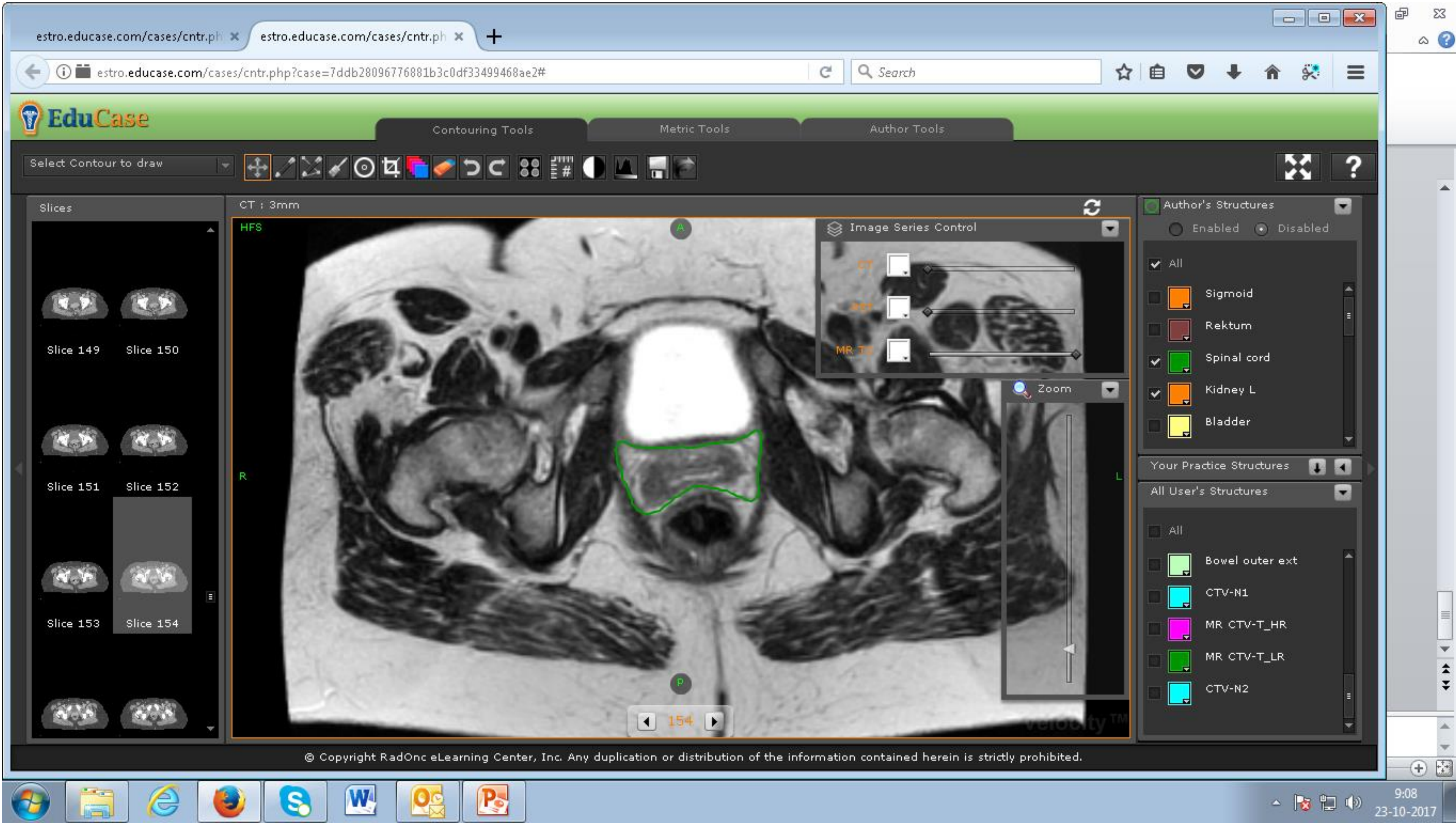
Internal, external iliac, cervix, GTV-T, parametrium



cervix, GTV-T, parametrium



vagina



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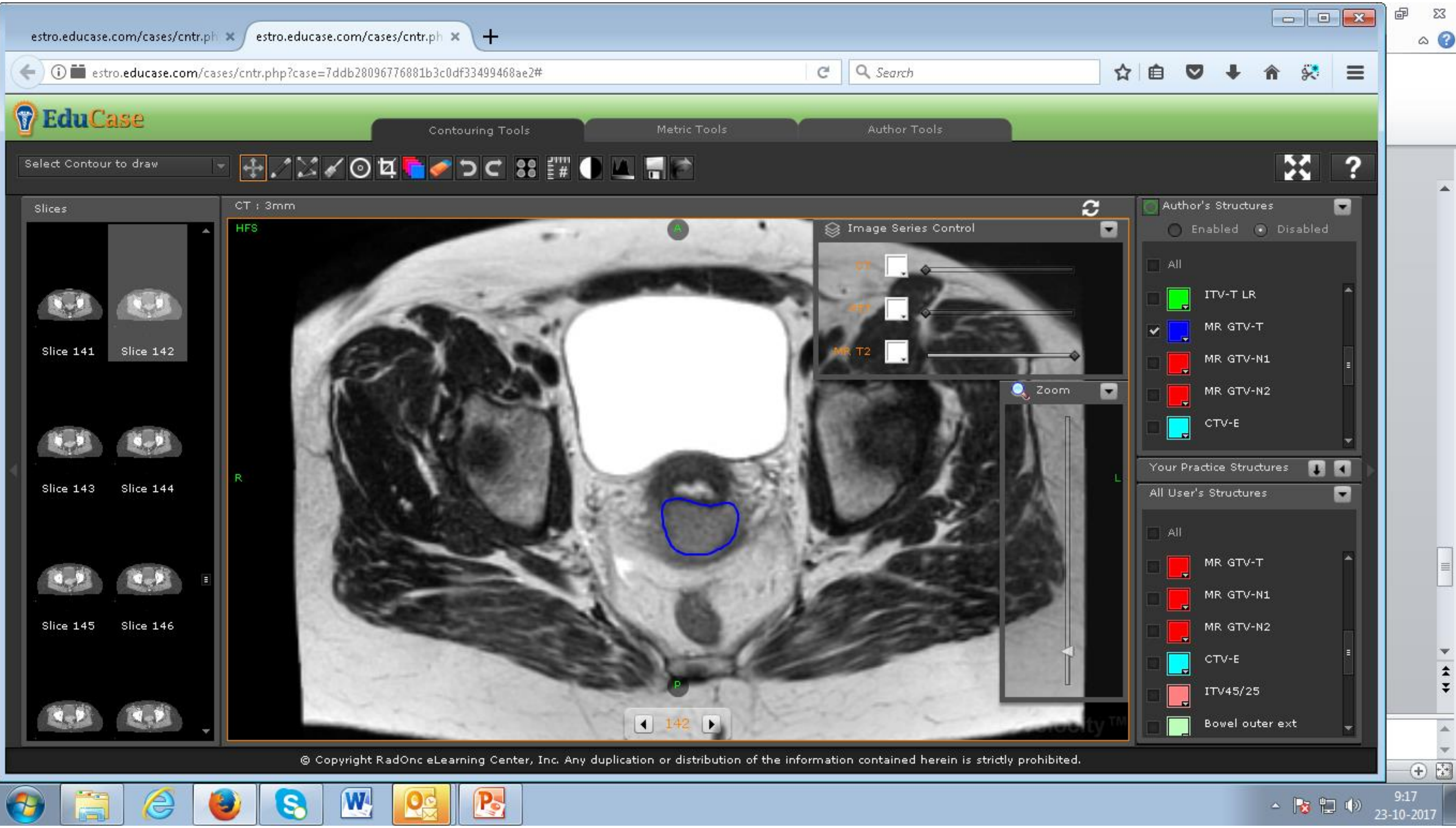
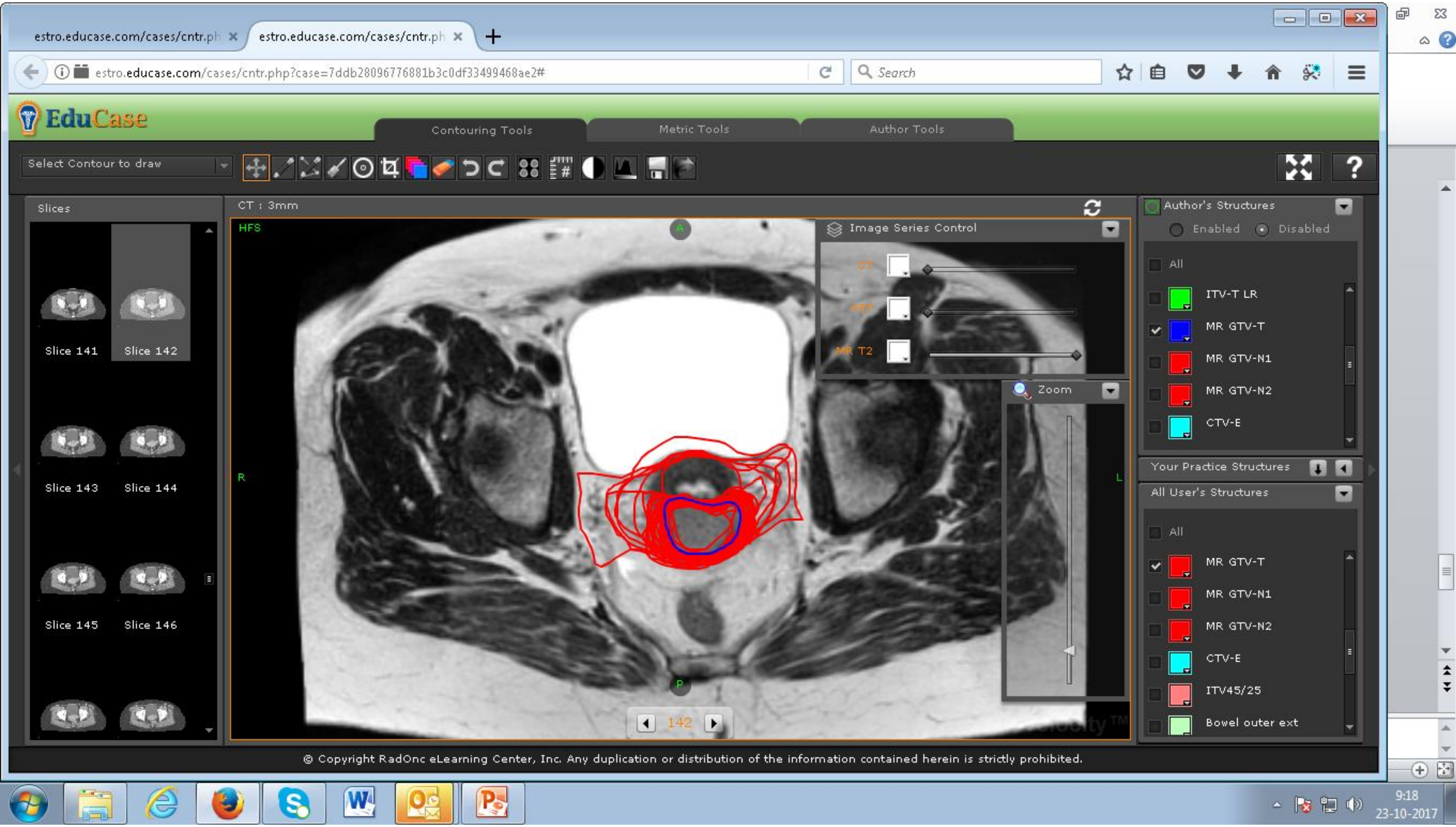
GTV-T_init

Extension (defined by T2 weighted MRI, supported by clinical investigation, FDG PET-CT information of the primary cervix tumour (inside and outside the cervix)



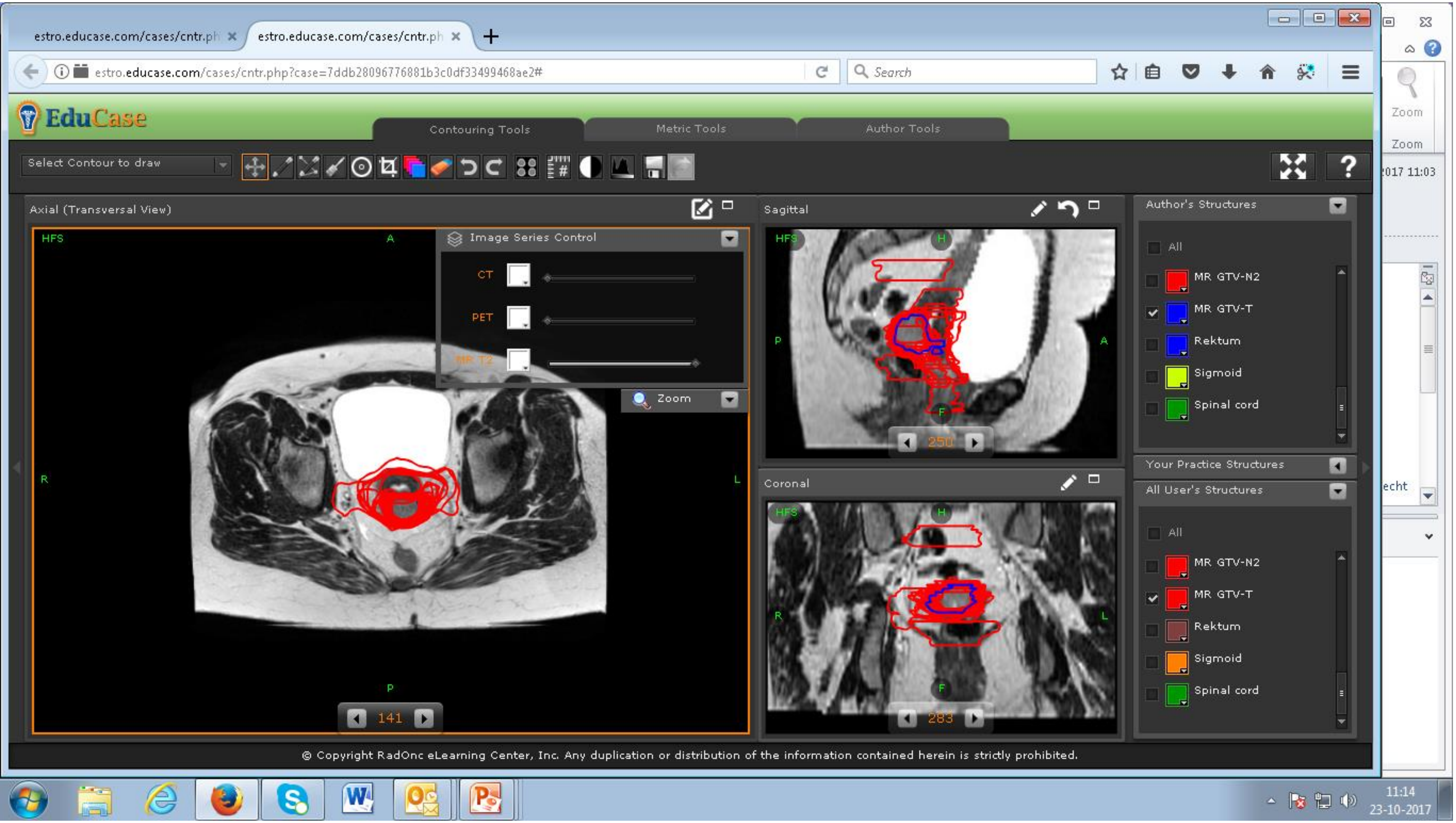
GTV-T_init

Extension (defined by T2 weighted MRI, supported by clinical investigation, FDG PET-CT information of the primary cervix tumour (inside and outside the cervix)



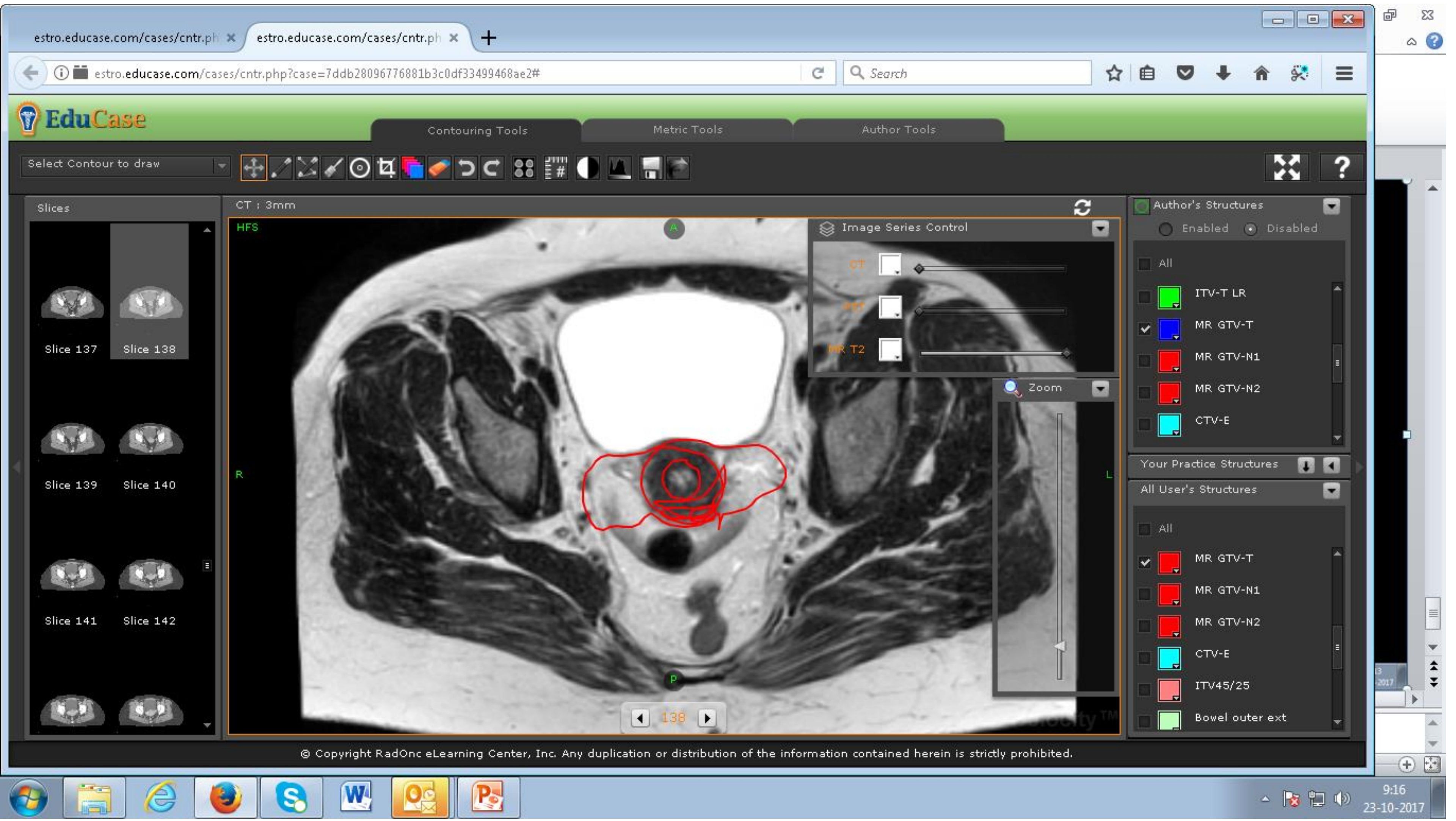
GTV-T_init

Extension (defined by T2 weighted MRI, supported by clinical investigation, FDG PET-CT information of the primary cervix tumour (inside and outside the cervix)

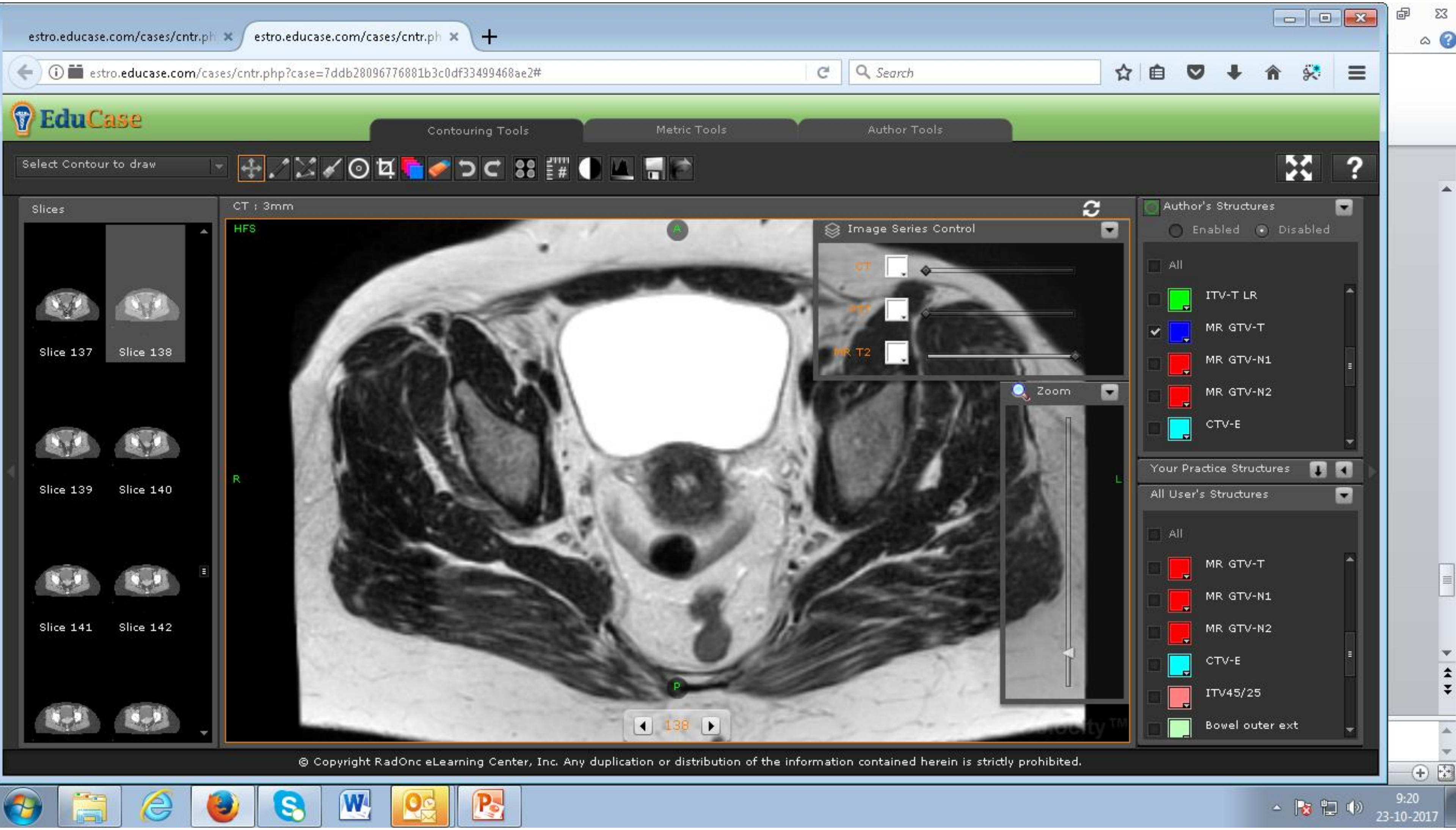


GTV-T_init

Extension (defined by T2 weighted MRI, supported by clinical investigation, FDG PET-CT information of the primary cervix tumour (inside and outside the cervix)



Cervix



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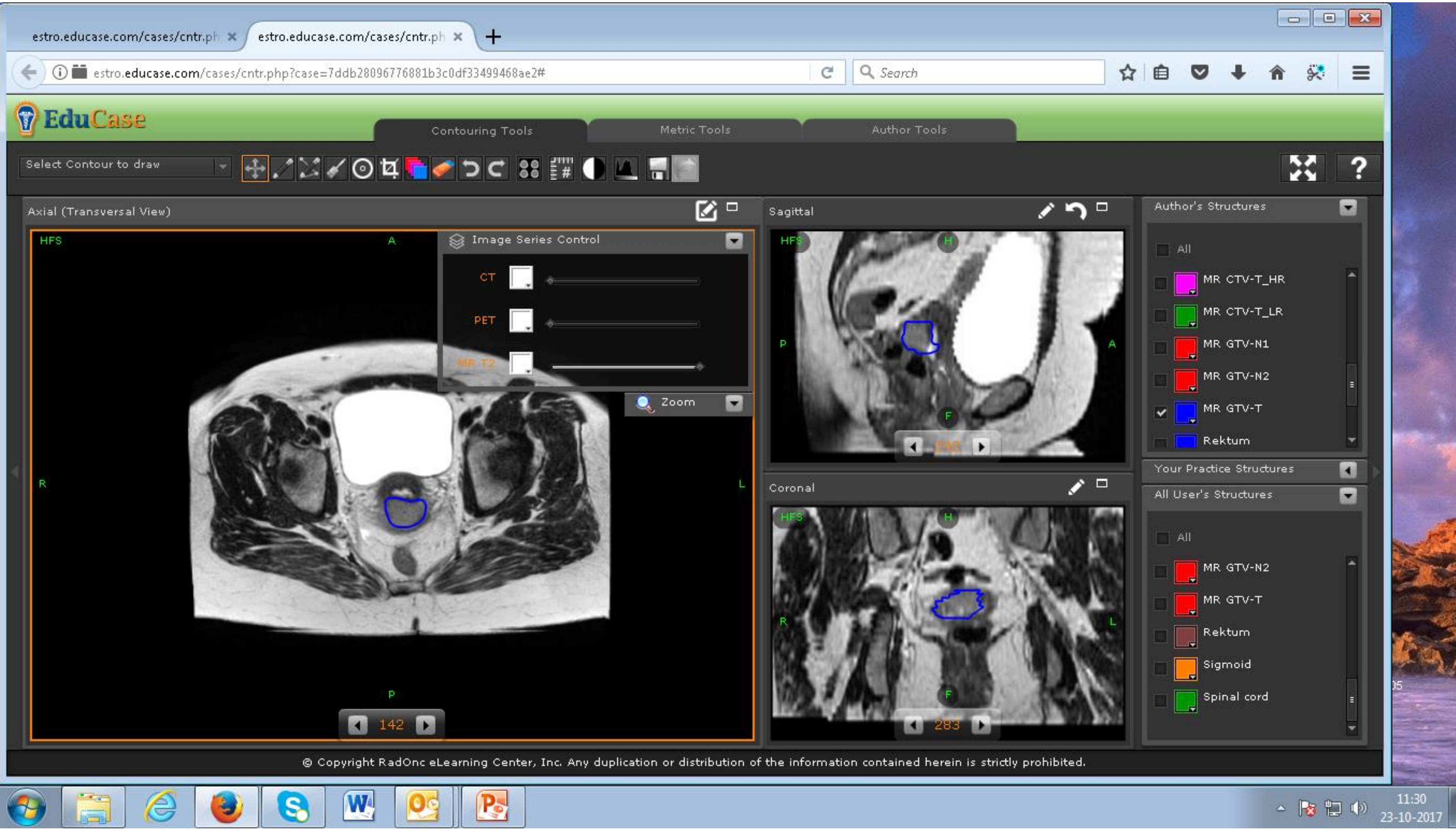
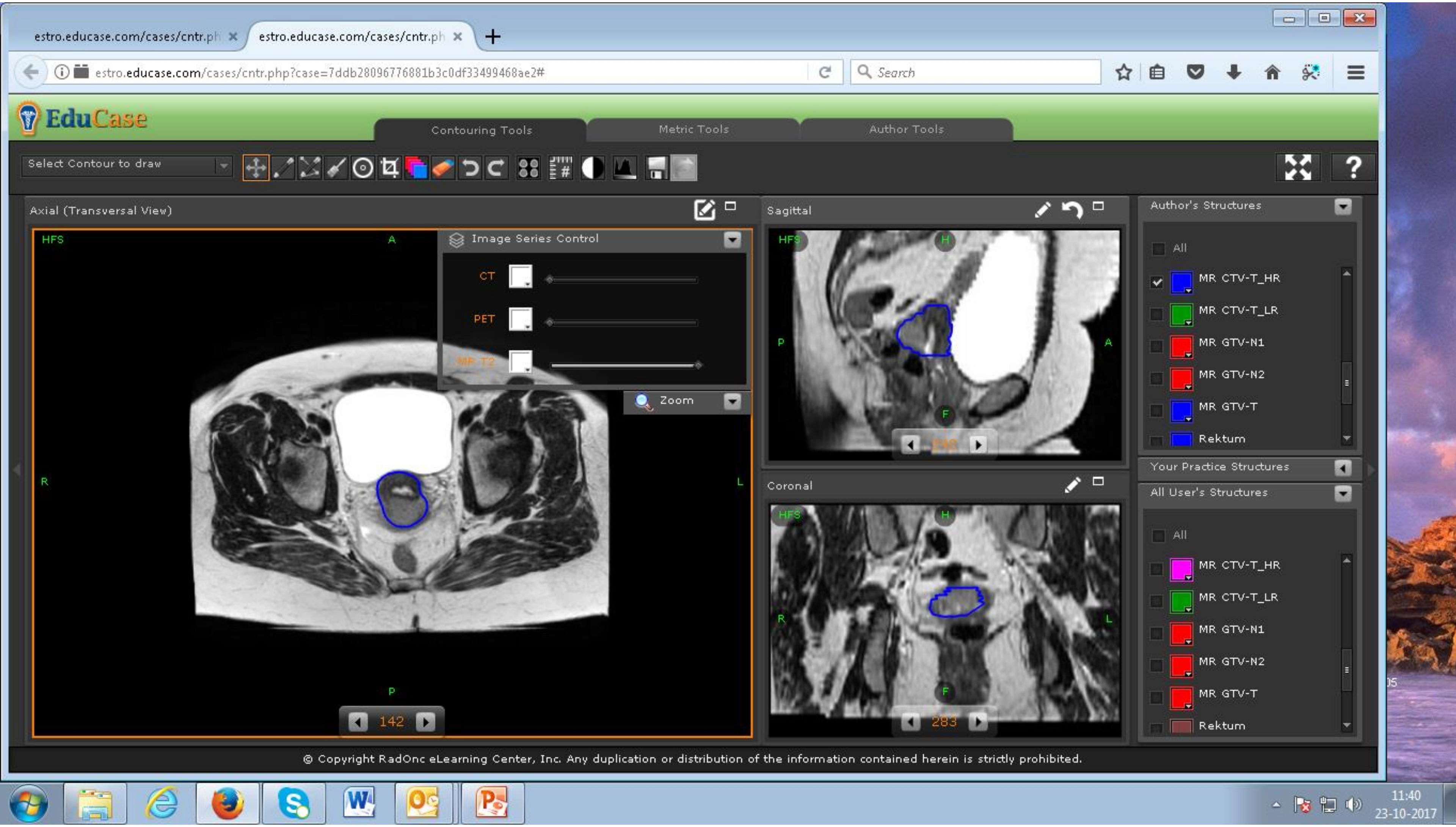
GTV-T_init

Extension (defined by T2 weighted MRI, supported by clinical investigation, FDG PET-CT informationn of the primary cervix tumour (inside and outside the cervix)



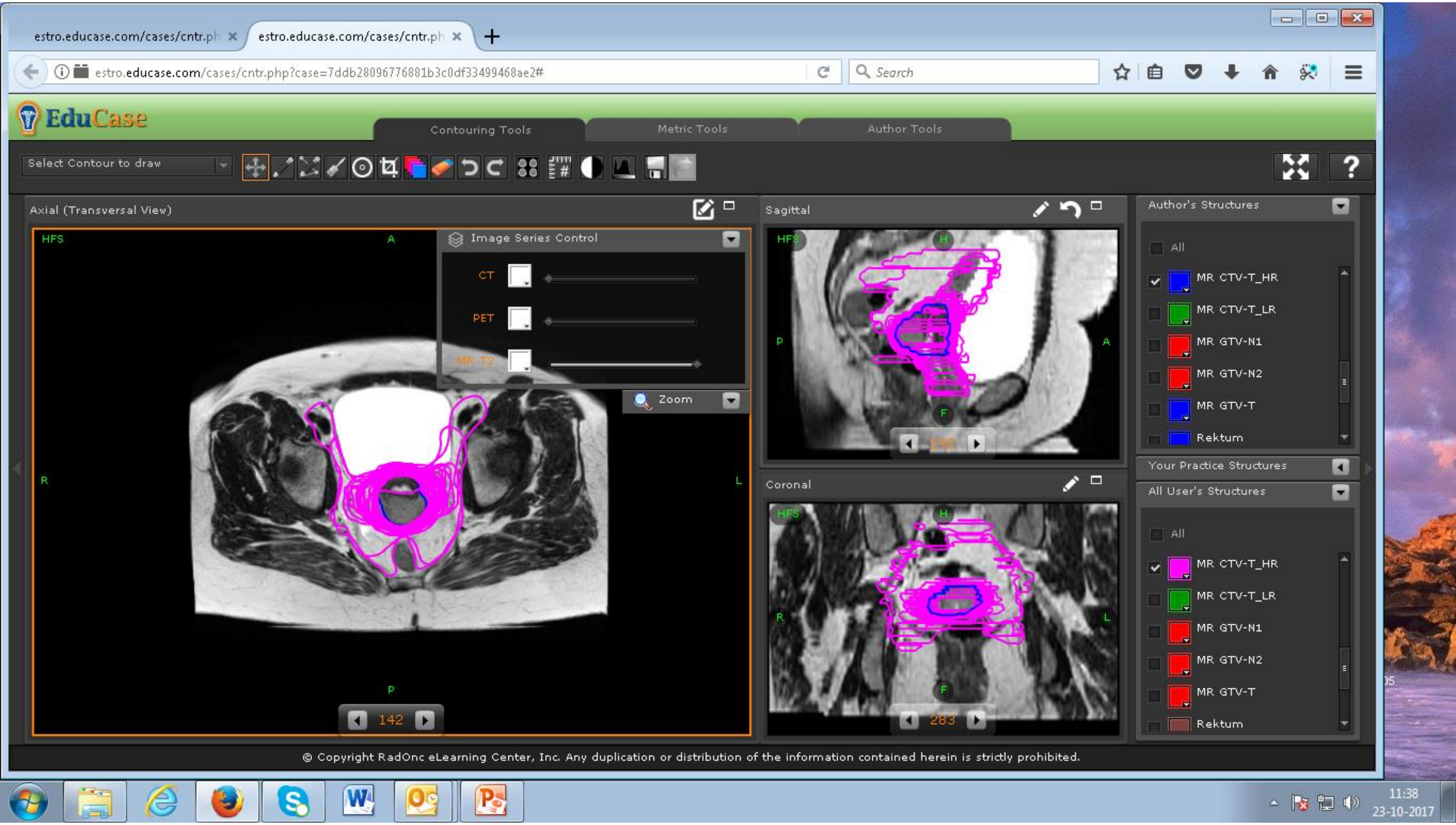
CTV-T HR_init

GTV-T and any remaining cervix not infiltrated by tumour.

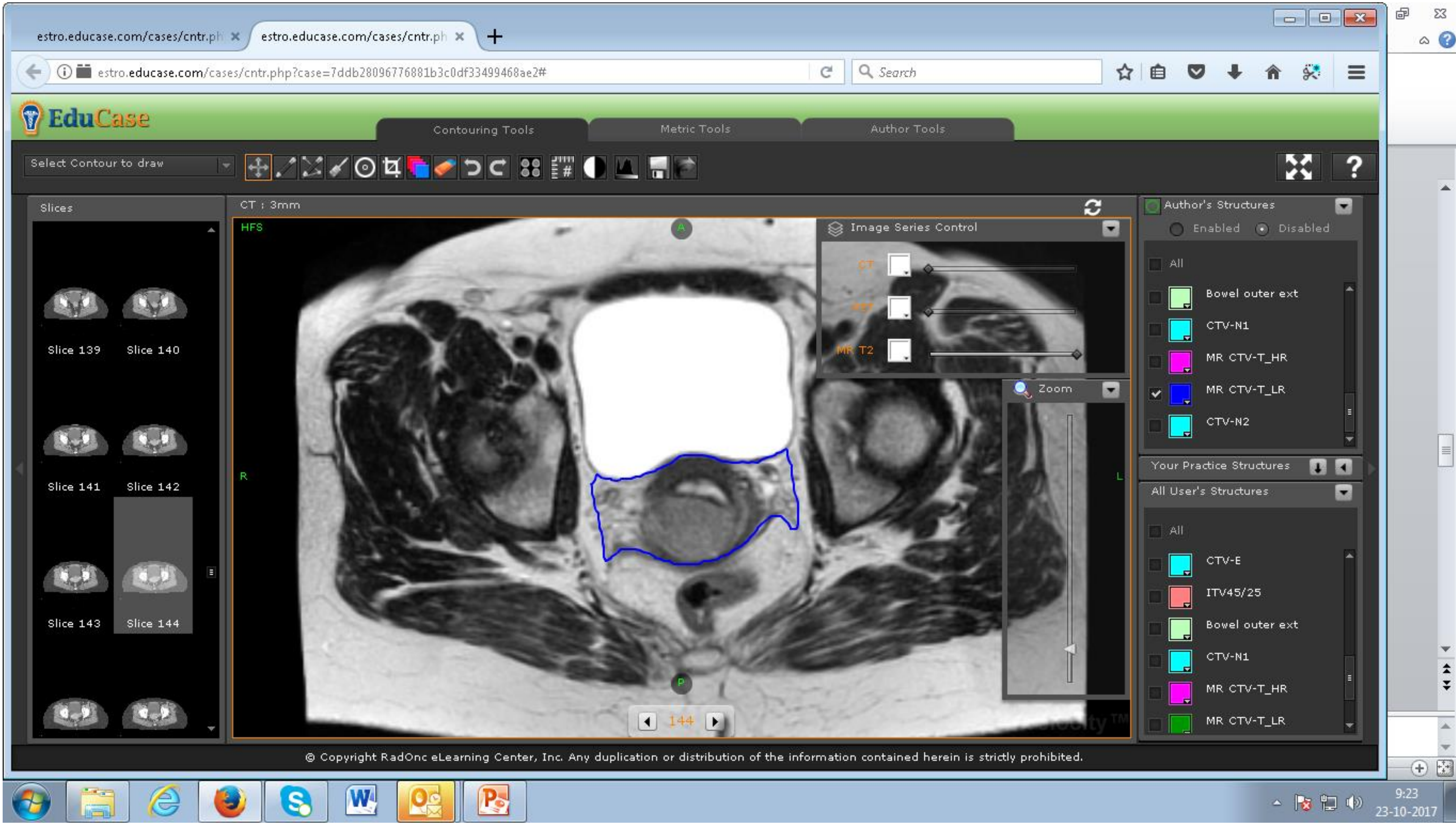


CTV-T HR_init

GTV-T and any remaining cervix not infiltrated by tumour.



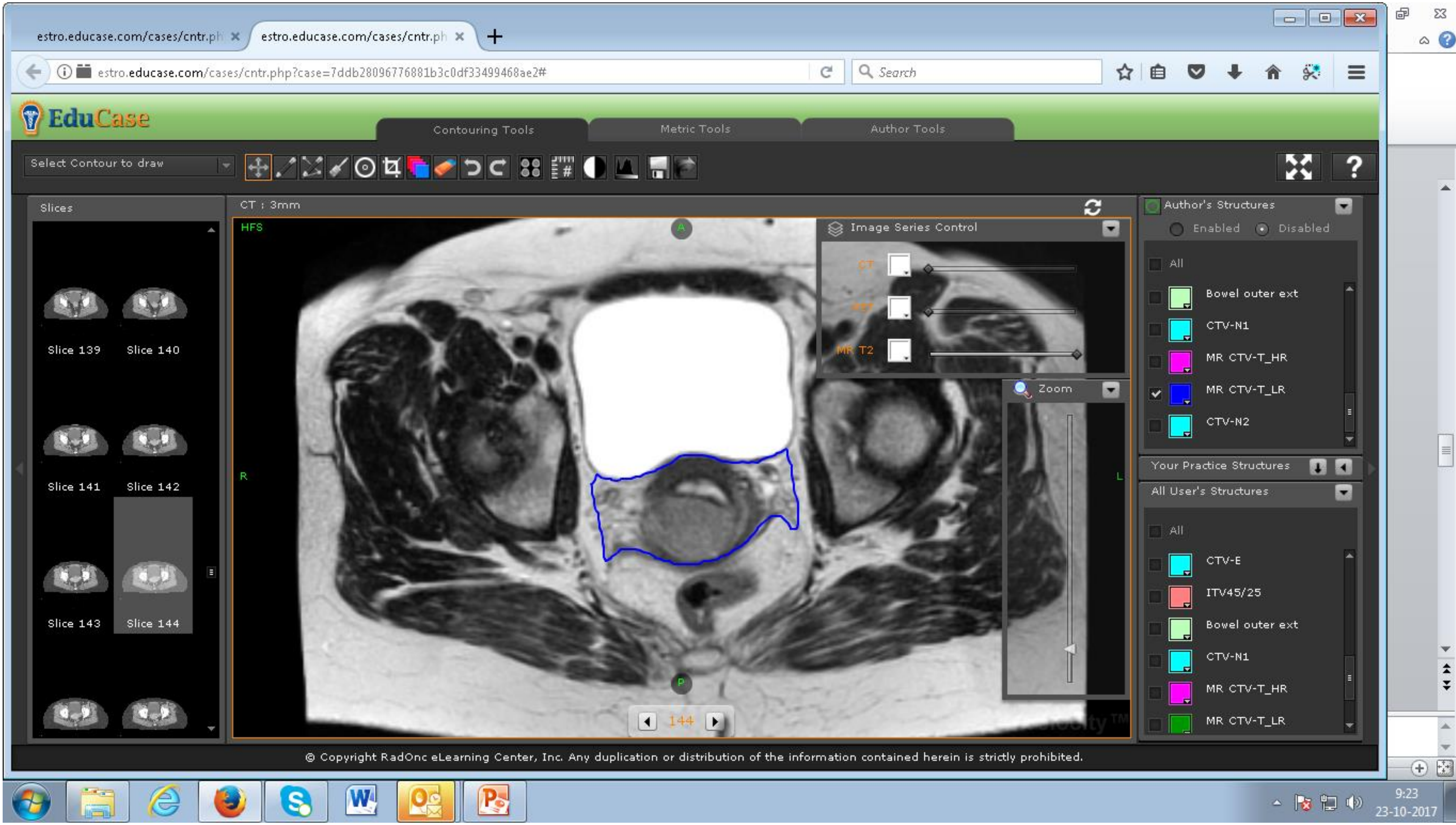
CTV-T LR initial



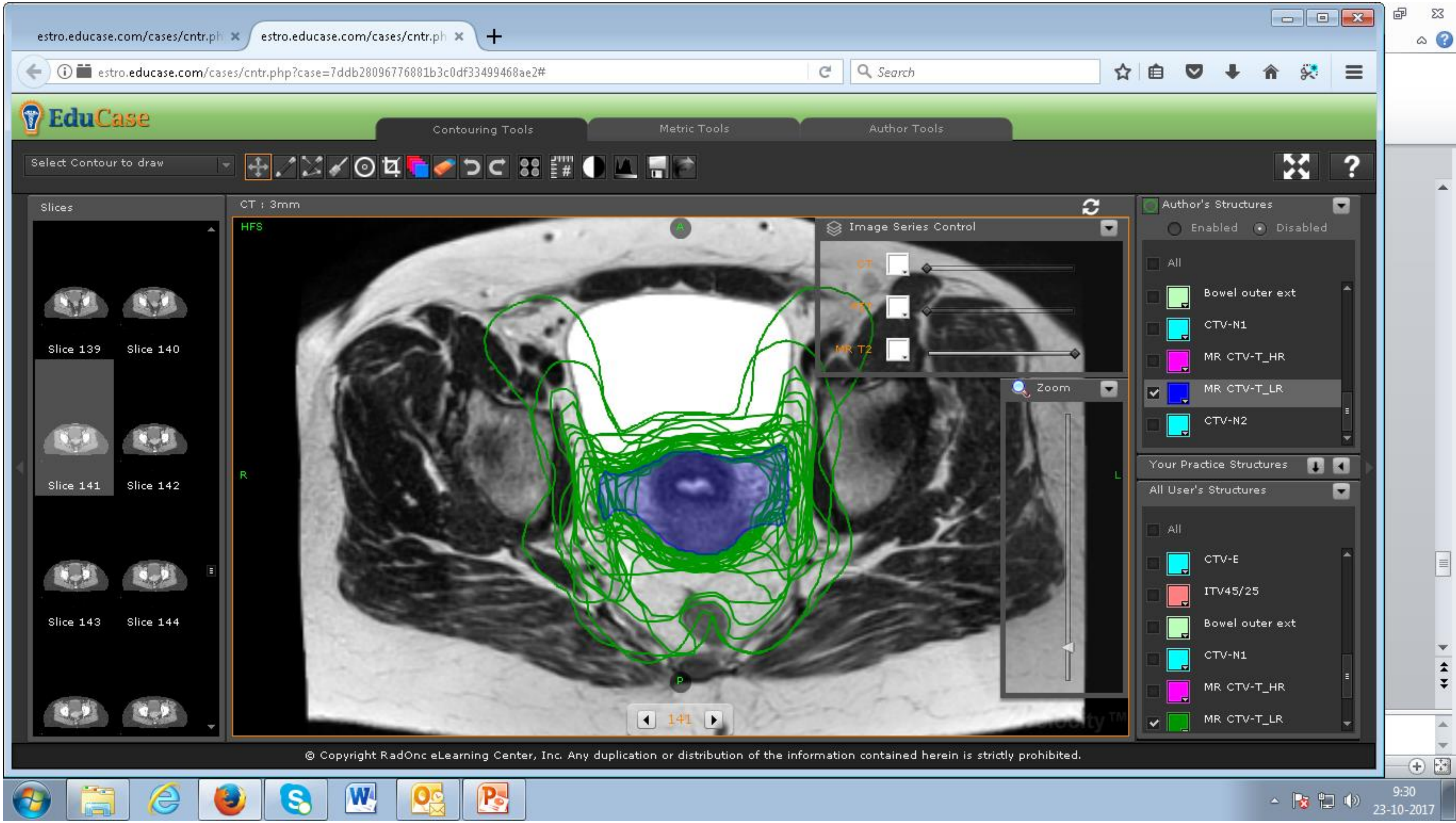
CTV-T LR initial

- a. Initial CTV-T HR
- b. The complete parametria bilaterally
- c. The entire uterus
- d. Uninvolved vagina with a 20 mm margin measured from the most inferior position of the initial HR CTV-T, along the vaginal axis (not starting in the fornix)
- e. CTV-T HR plus a margin of about 5 mm anterior and posterior towards bladder and rectum (excluding the non involved walls)
- f. In case of involvement of the pelvic wall, sacro-uterine ligaments, meso-rectum or other involved structures a 20 mm margin around the initial HR CTV-T will be extended into these structures.
- g. Any pathological lymph nodes in the parametrium may be included

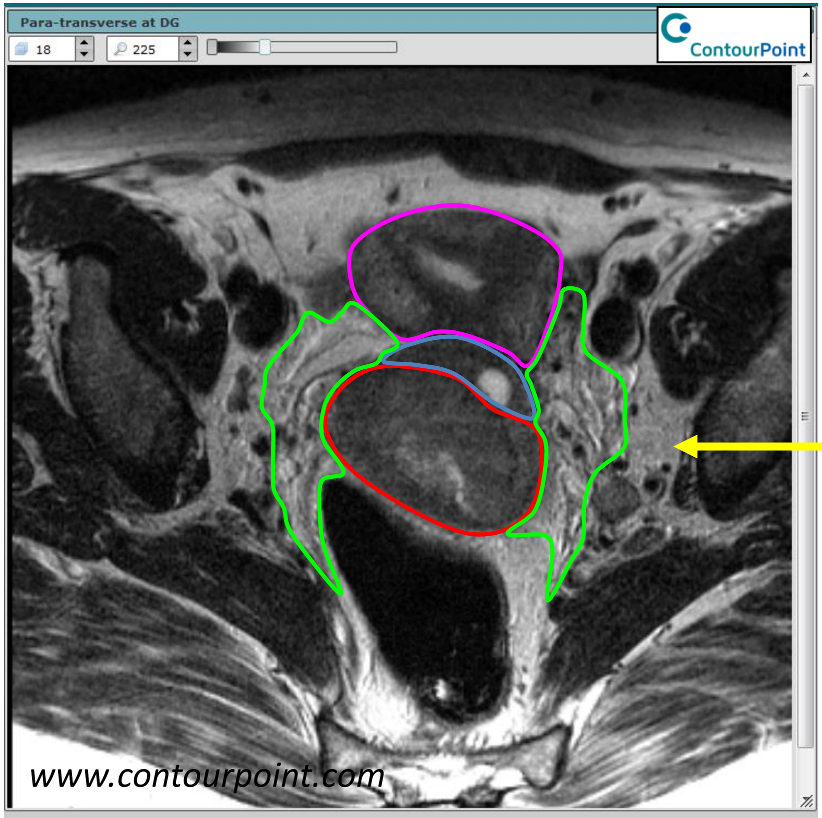
CTV-T-LR initial

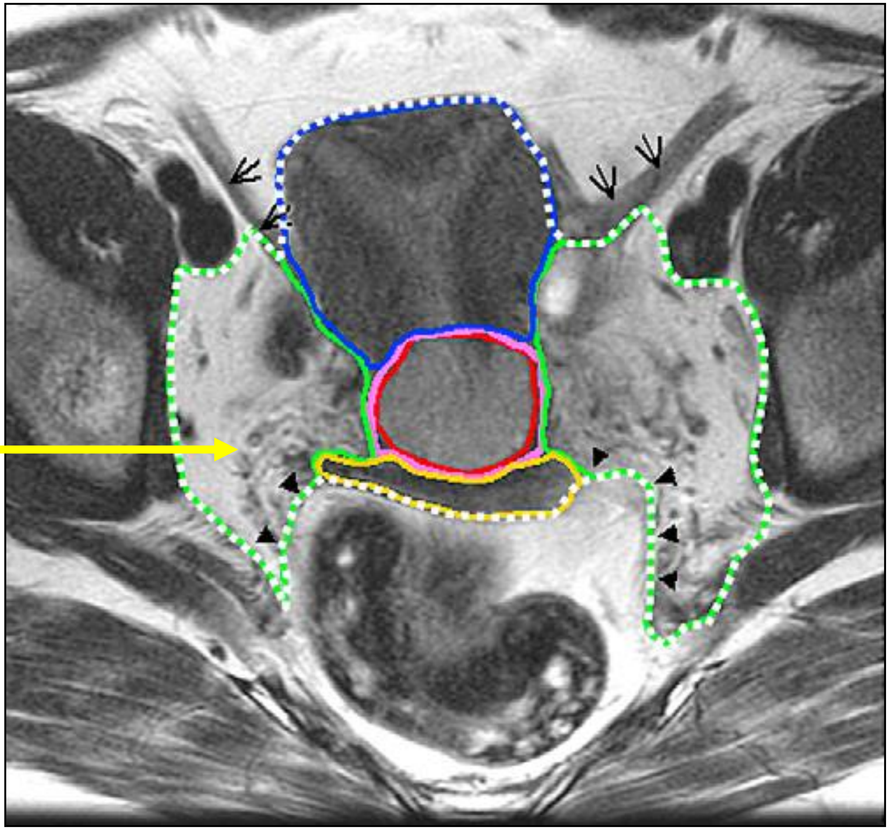


CTV-T-LR initial



Initial CTV components: CTV-T-LR 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

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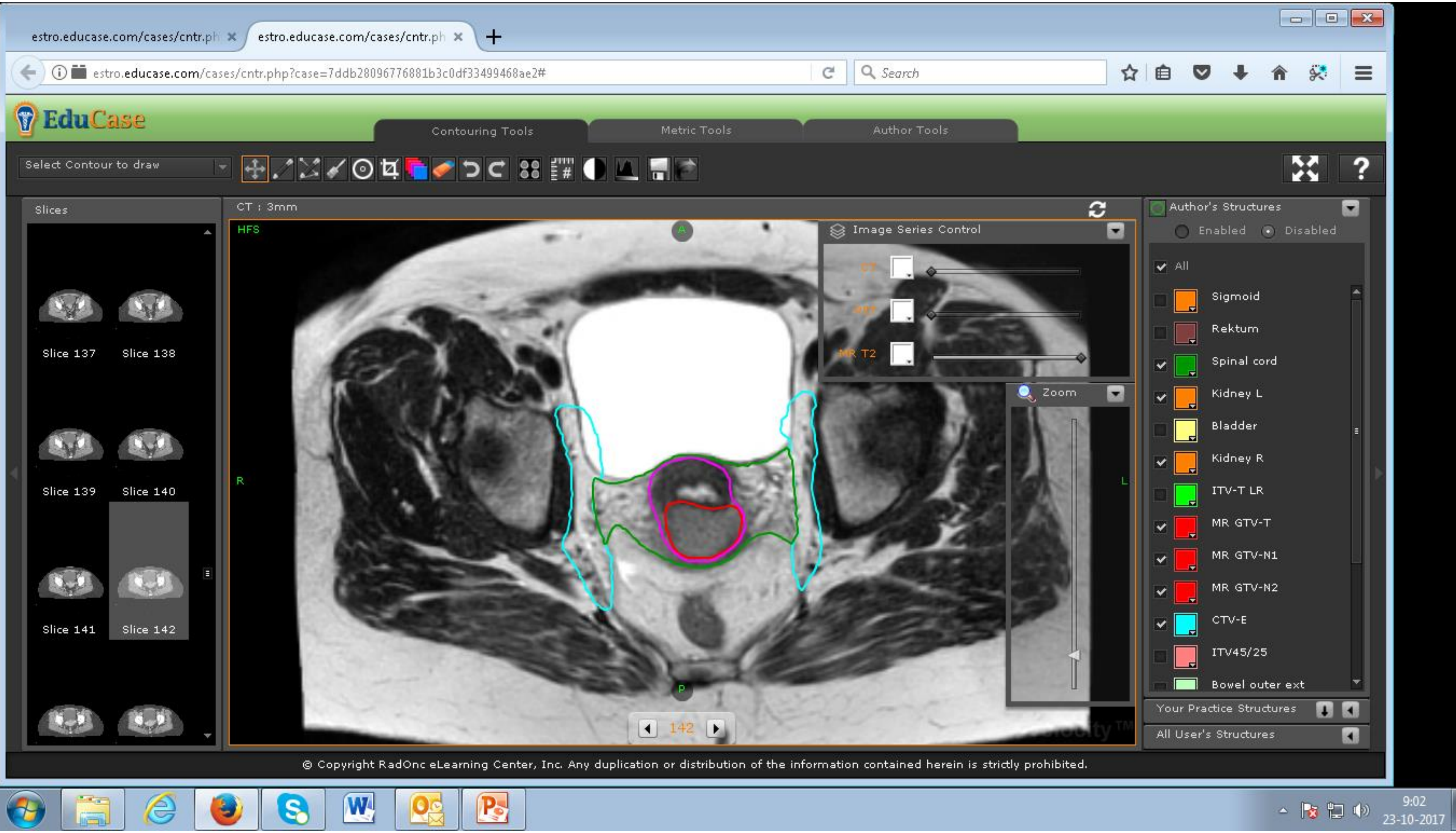

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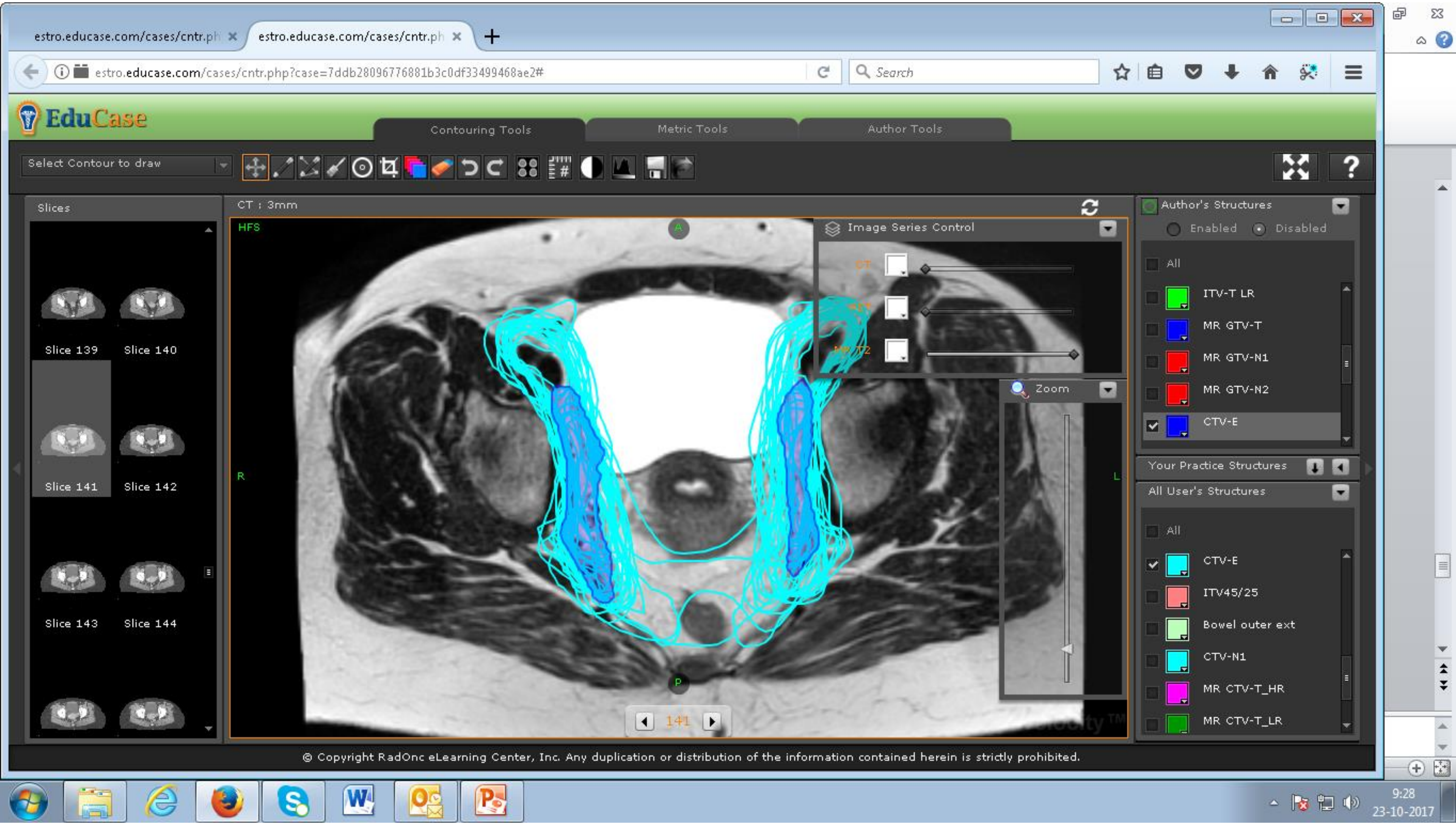

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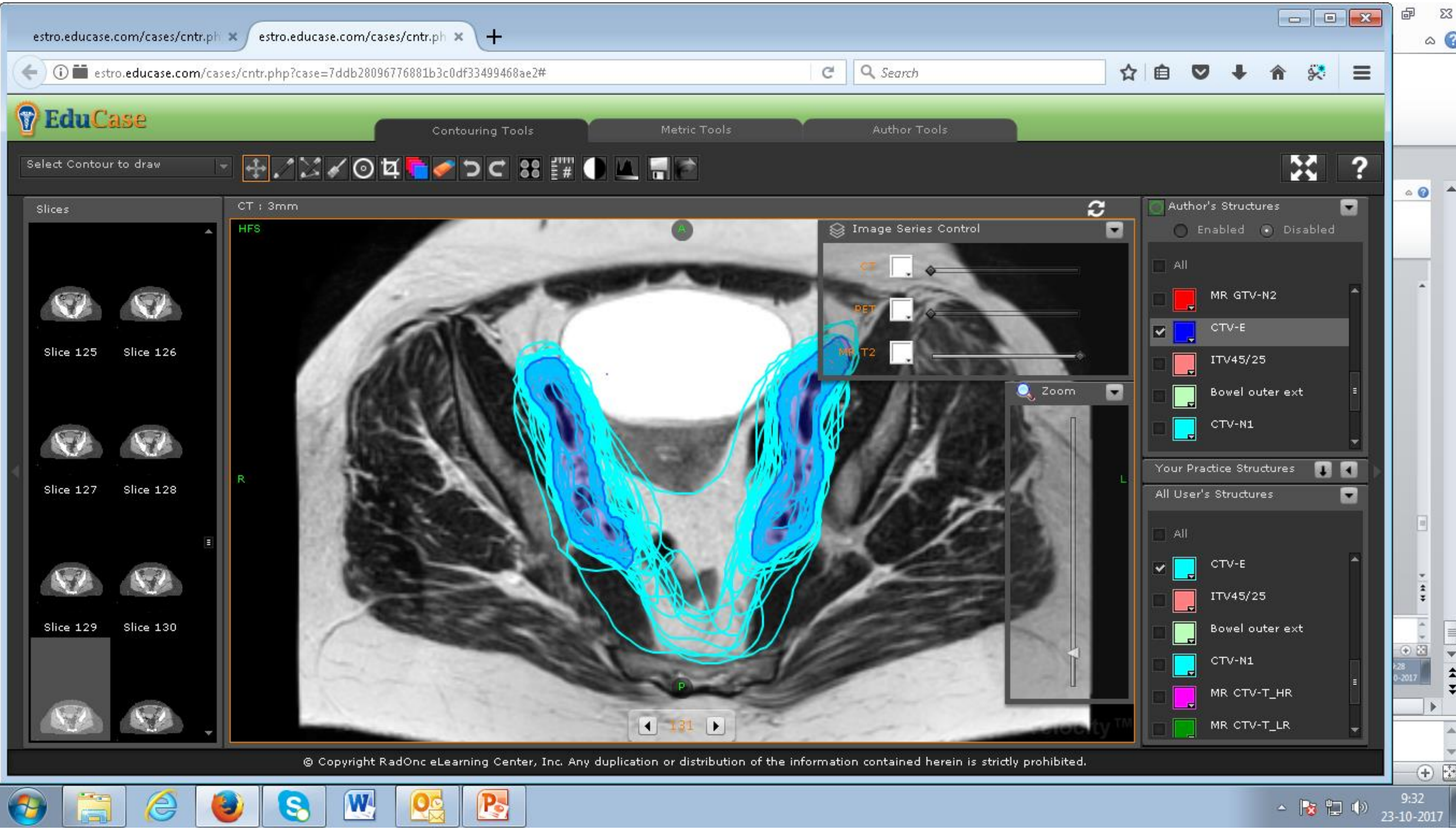

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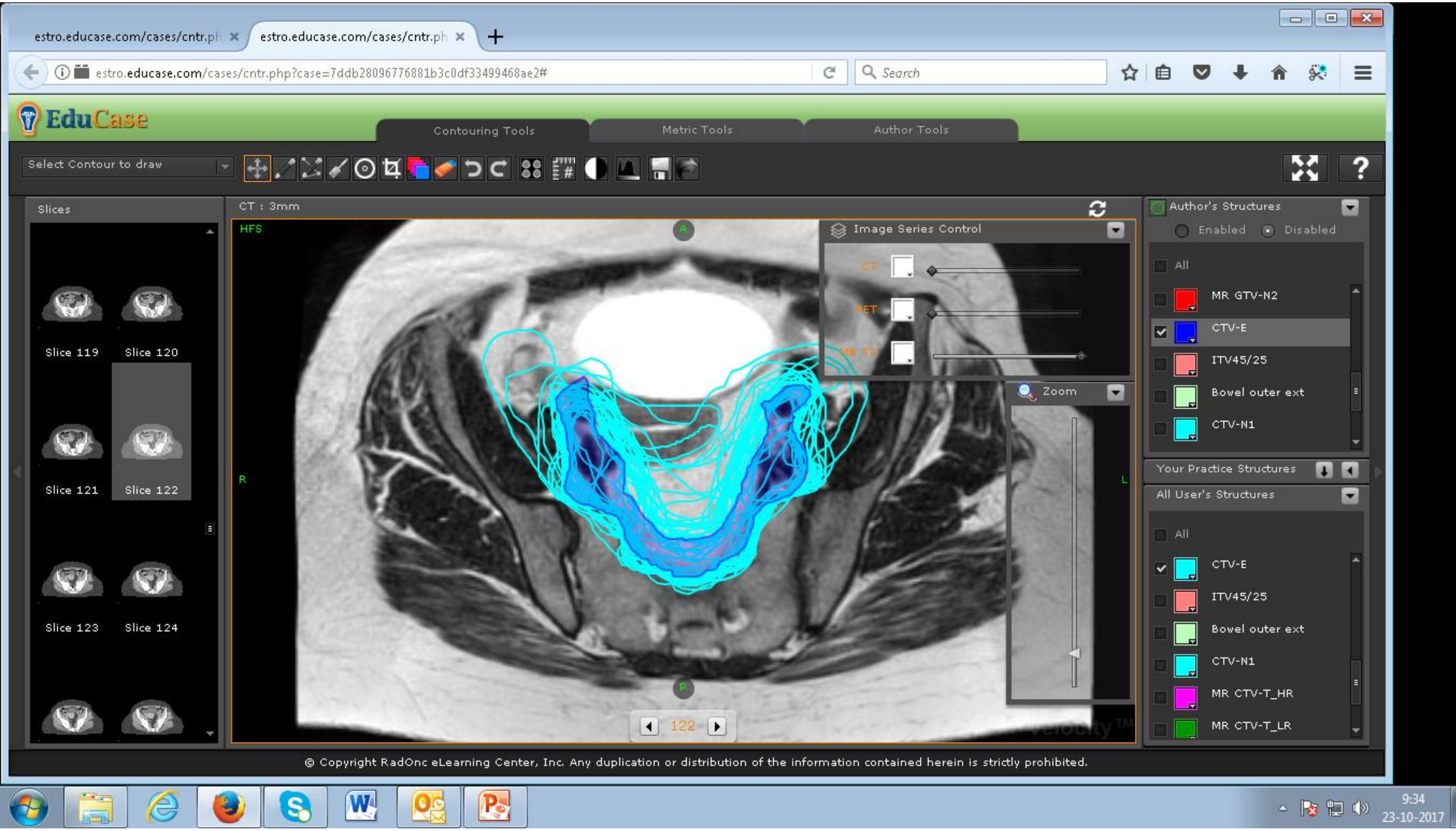

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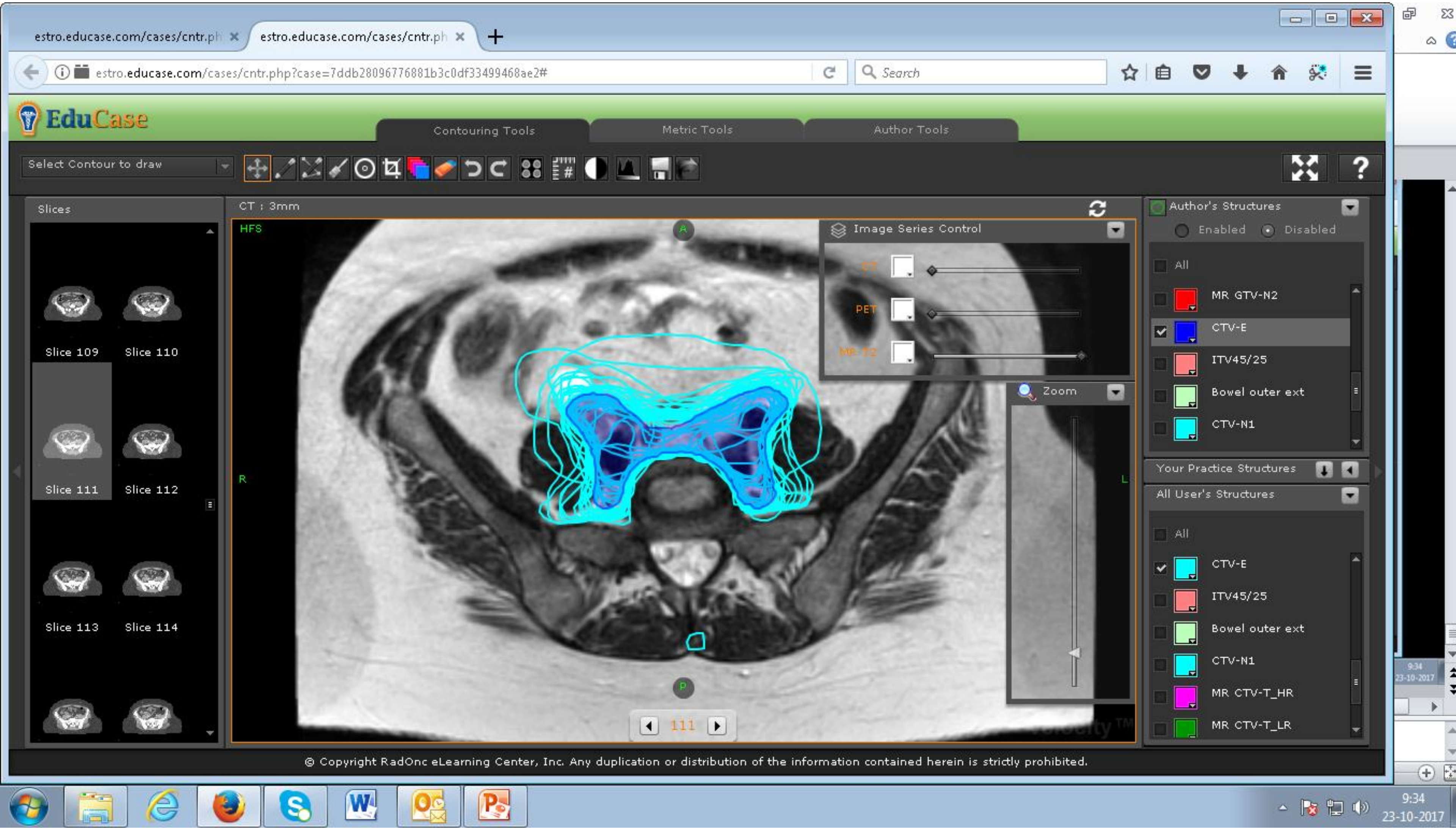

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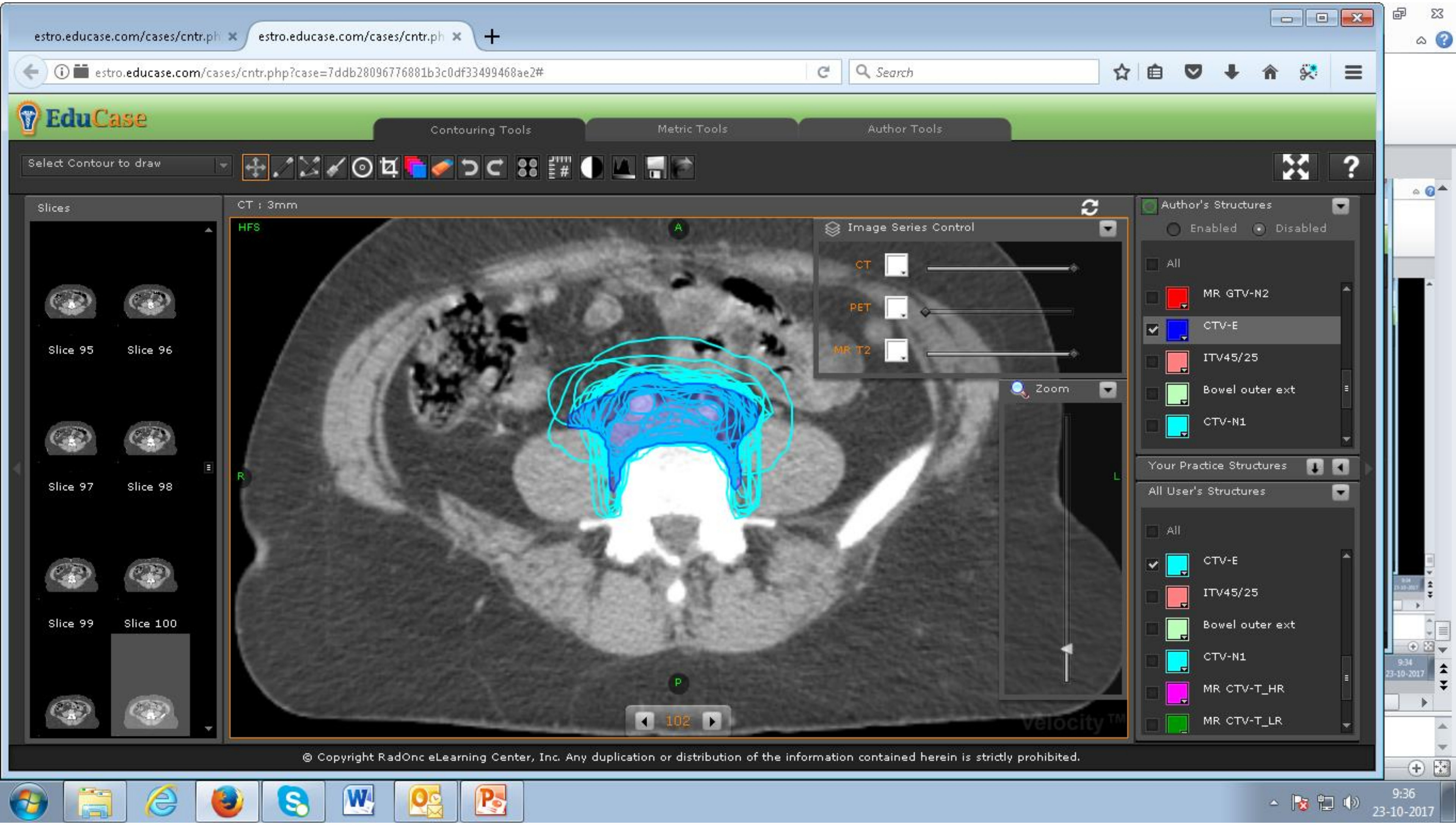

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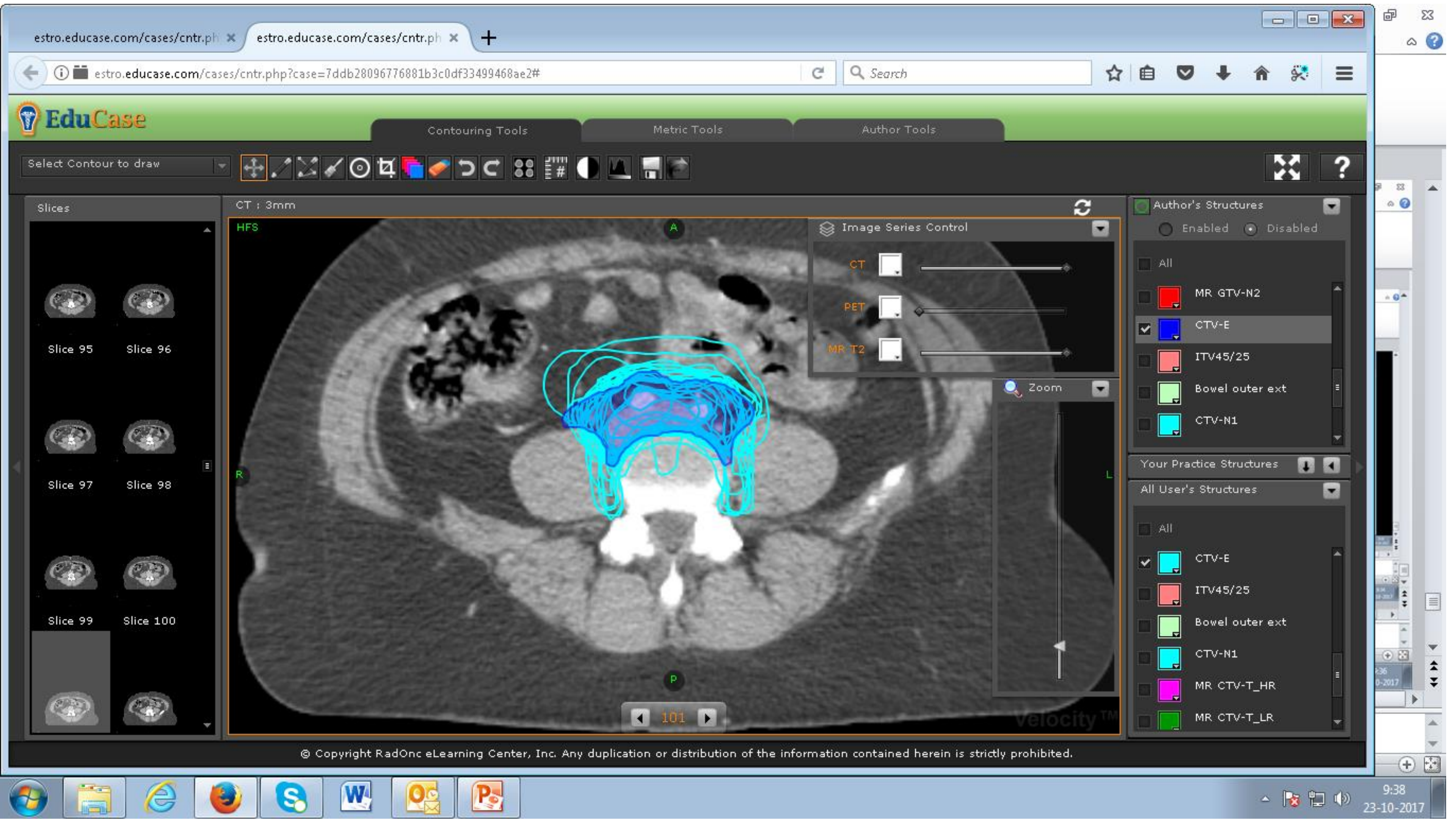

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MR CTV-T_LR
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CTV-E

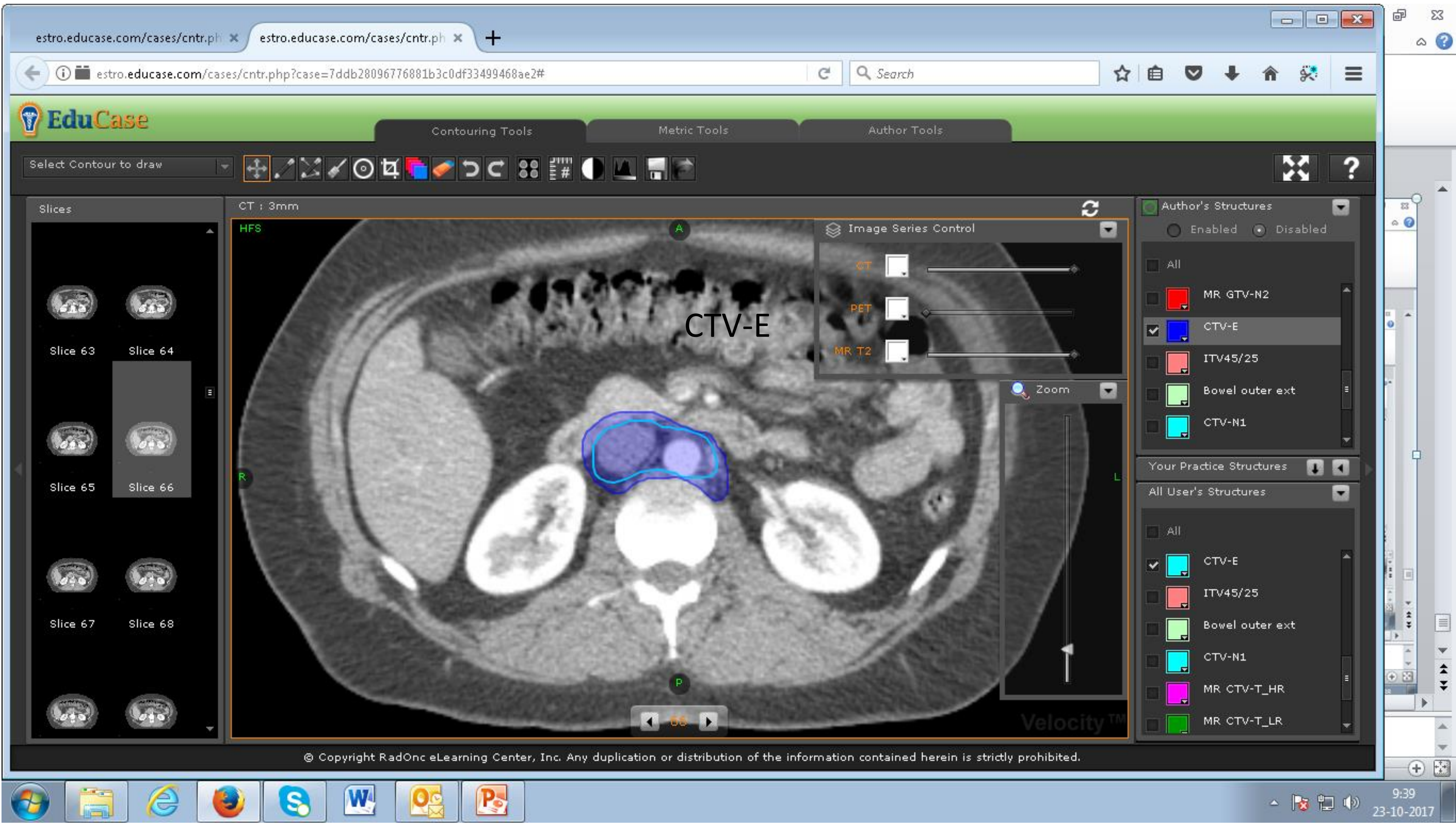

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Table 9.1: Risk groups for defining the elective clinical target volumes for lymph nodes and corresponding nodal targets defining the radiation field extensions.

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].

ITV-T-LR

9.3.6 STRATEGIES TO DERIVE THE ITV-T LR

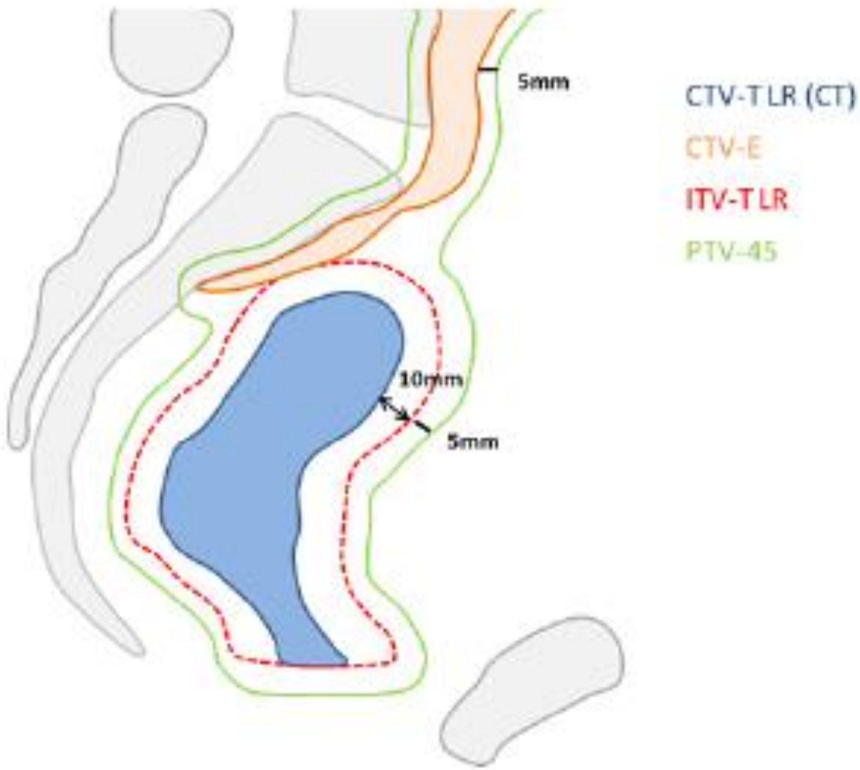
a) Basic IGRT, standard margin approach (Fig. 9.9.A)

The ITV-T LR includes (see also App. EBRT for Treatment Planning Figure 7):

- CTV-T LR with the following margins:
    - 10 mm anterior-posterior
    - 10 mm superior-inferior
    - 5 mm lateral
- At the distal vagina no additional margin along the vaginal axis in the inferior direction is applied
- The ITV-T LR should not go into the muscle and bony boundaries of the pelvis (in particular, manual adaptation is needed in the lateral parametria)
- In case of tumour involvement of the upper and most mobile uterus an extra 5 mm margin should be applied in all directions from the uterus body

Consider 15-20 in ap/pa directions

A

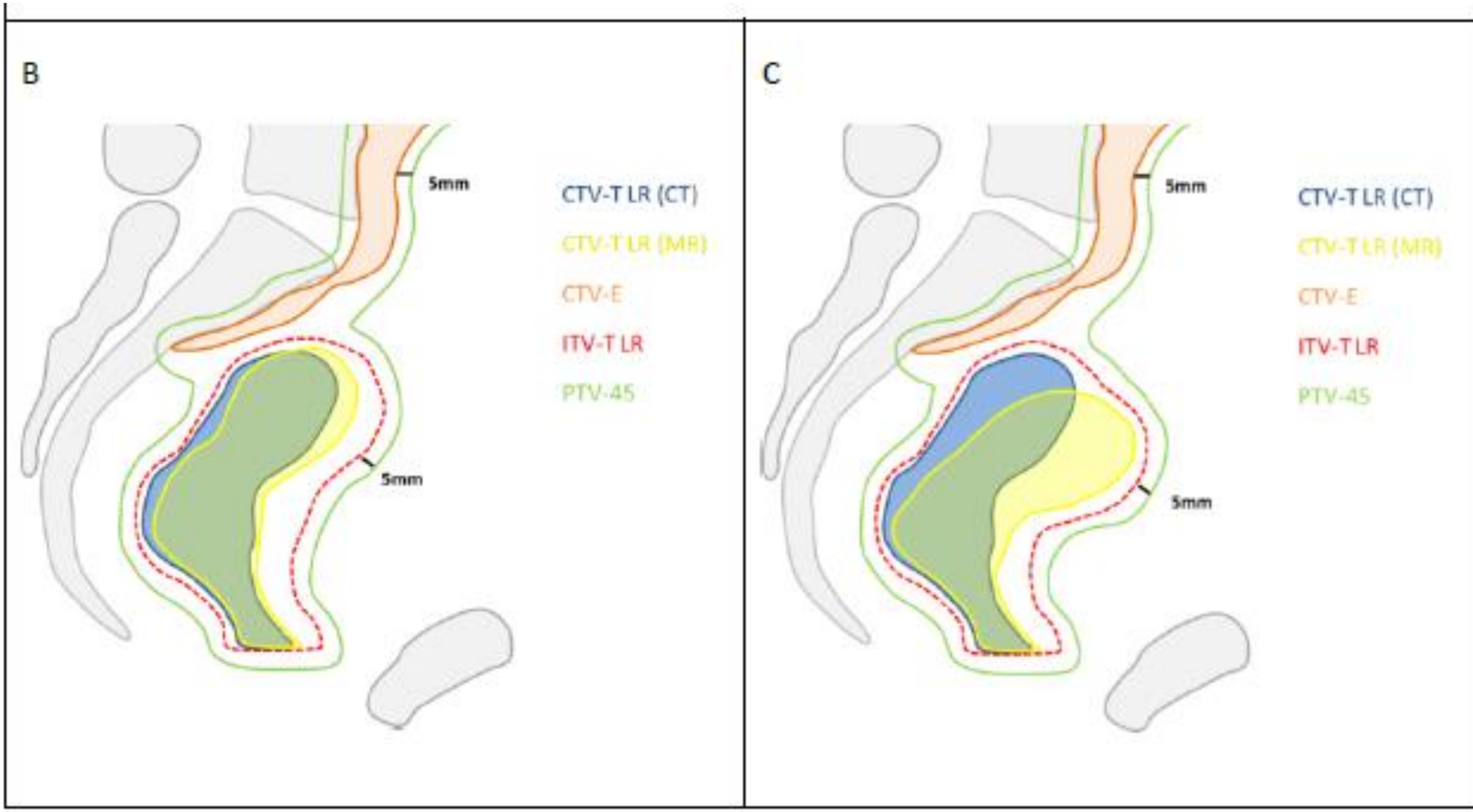


b) Intermediate IGRT, individualized ITV-T approach (Figure 9.9.B):

The key difference for an individualized ITV-T compared to the standard margin approach is that pre-treatment imaging, both diagnostic and for treatment planning, is used to assess the range of motion in an individual patient. A pre-requisite is that these imaging series have different filling status of bladder and rectum. For this purpose a full and empty bladder treatment planning CT can be useful. For patients with a smaller range of motion, a smaller ITV margin can be applied, whereas, in patients with a large range of motion, a margin comparable or larger than that derived from standard motion range may be required.

To generate the ITV-T LR, the different diagnostic and treatment planning image series should be fused to the treatment planning CT with comfortably filled bladder. The ITV-T LR margin is adapted based on the assessed range of motion within the individual patients, keeping in mind the proposed standard motion ranges (figure 9.9).

The margins used under "standard margin approach" should be the starting point and individualisation can be adapted from there. ITV-T LR should not go into the muscle and bony boundaries of the pelvis. Importantly, the ITV-T does not need to include the whole uterus as seen on an image series with an empty bladder, since with the drinking protocol this situation is not expected during the course of fractionated EBRT. It should be kept in mind though that some studies indicate that the average bladder volume decreases during the course of treatment. If daily soft tissue verification (CBCT) is used to monitor the daily uterus position, it is possible to shrink the individualised margins further according to the thresholds defined for re-planning.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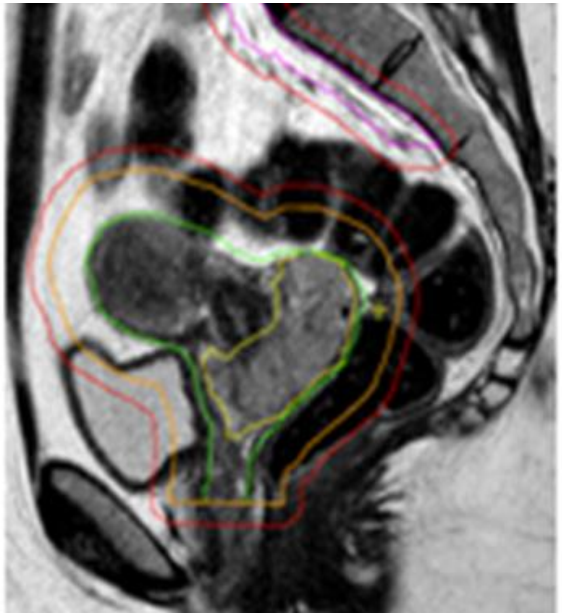
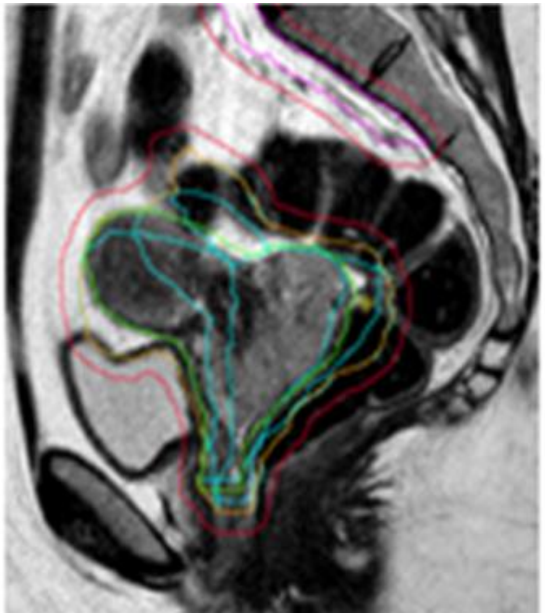
CTV-T LR (MR)
CTV-E
ITV-T LR
PTV-45
5mm
C
5mm
CTV-T LR (CT)
CTV-T LR (MR)
CTV-E
ITV-T LR
PTV-45
5mm

ITV-T standard, individualized, UTR2

PTV45 volume
1257 cc



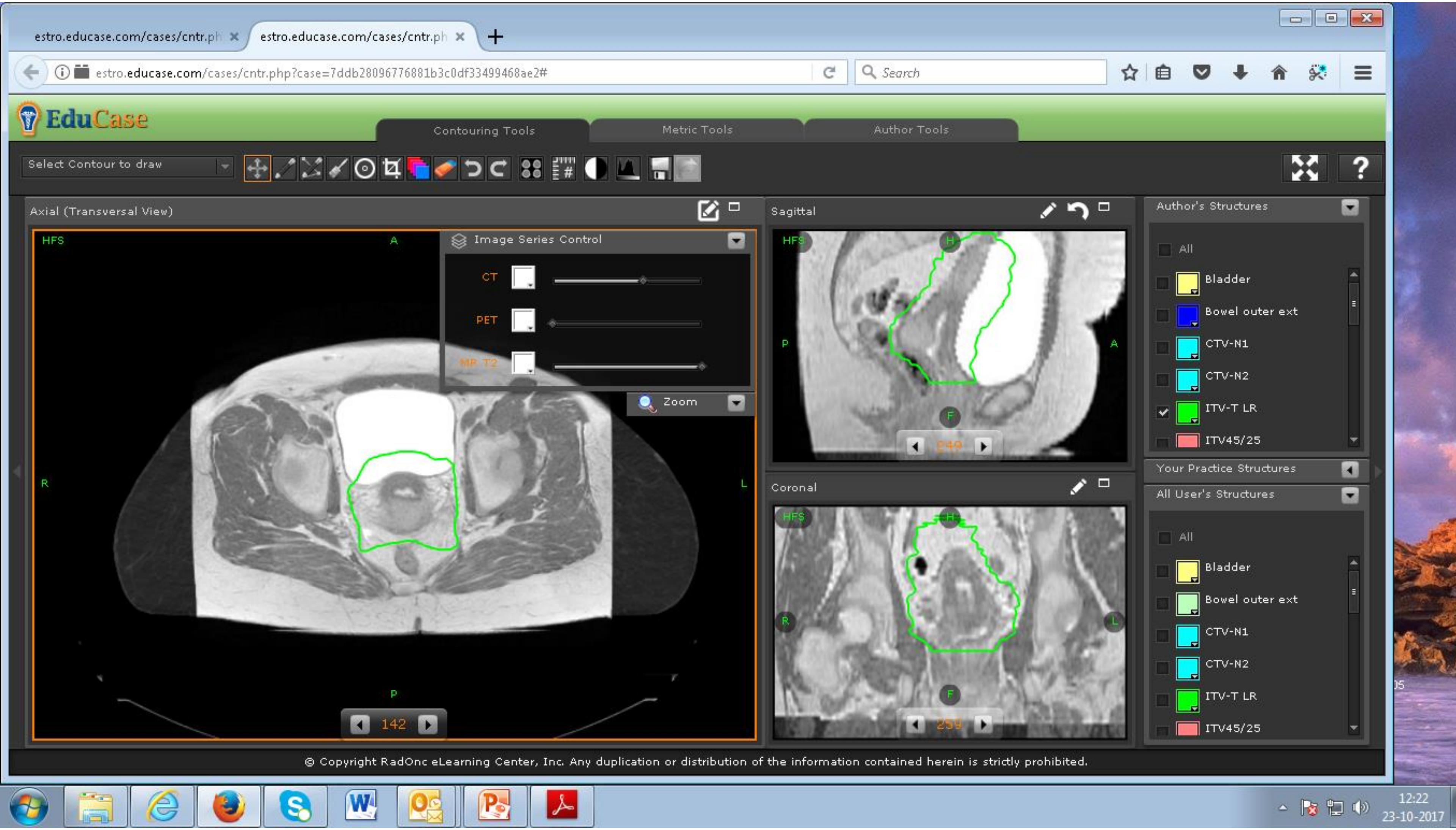
standard



individualized

PTV45 volume
1218 cc

ITV-LR AAR03



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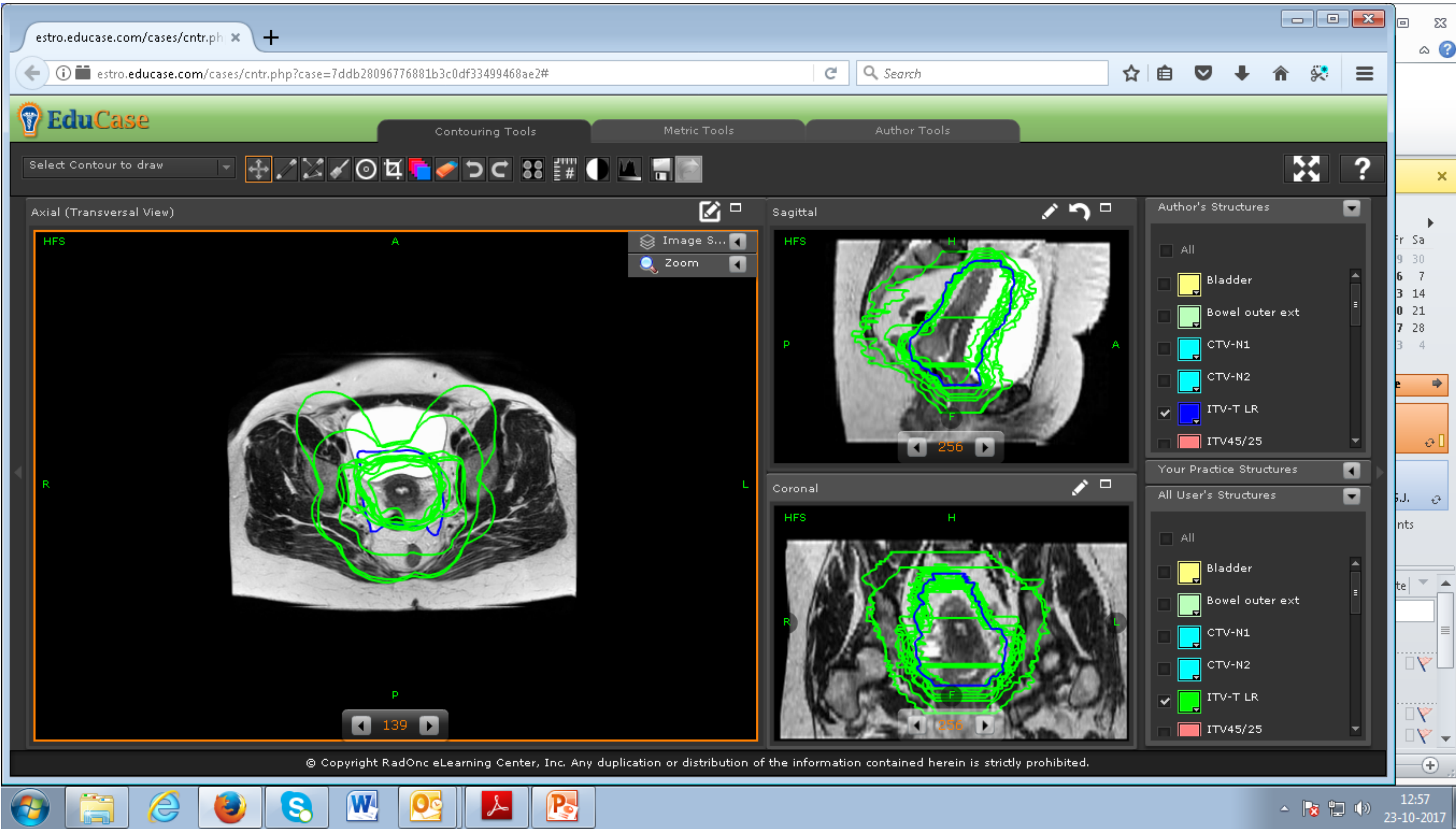
ITV-LR AAR03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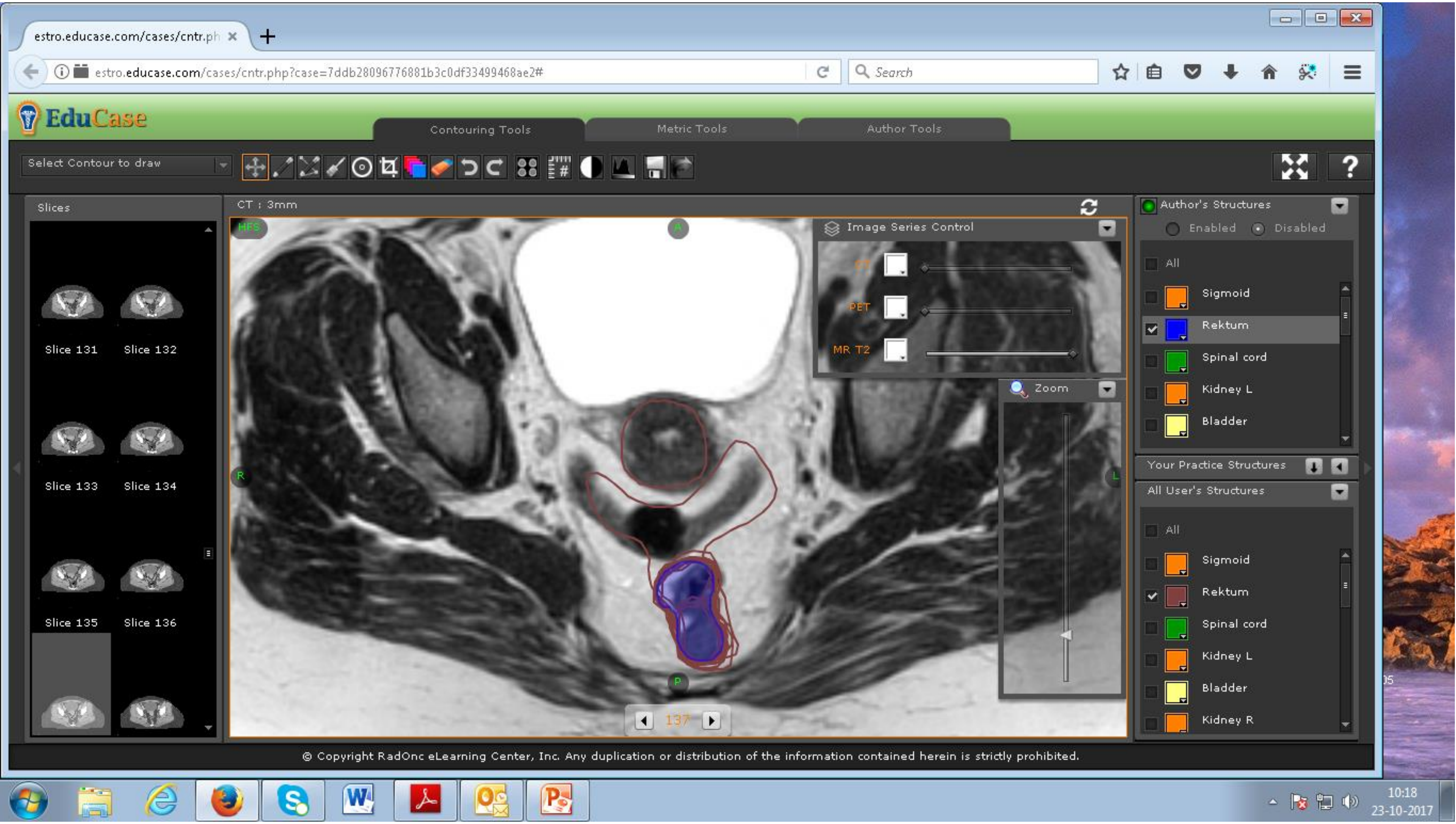
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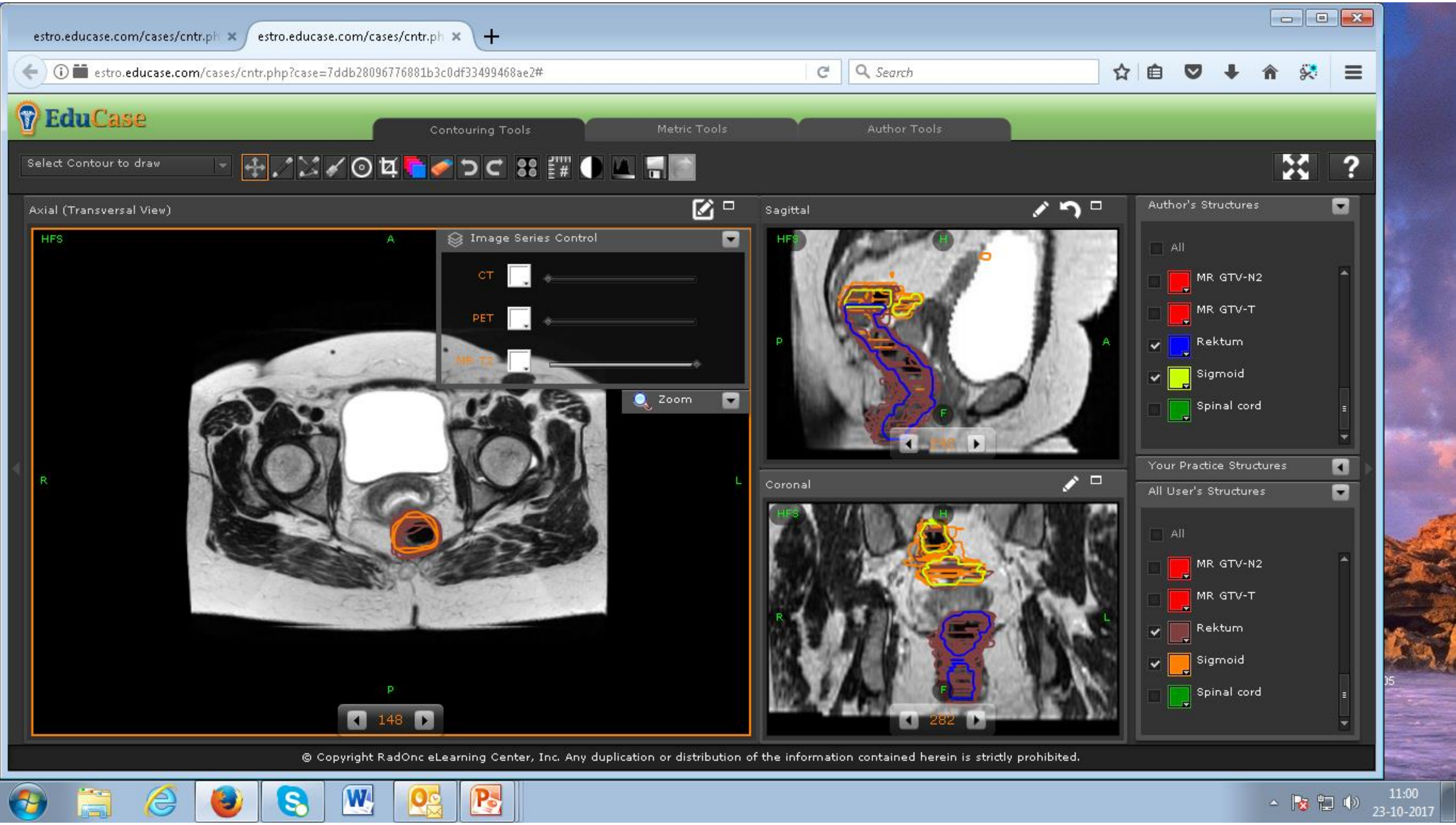

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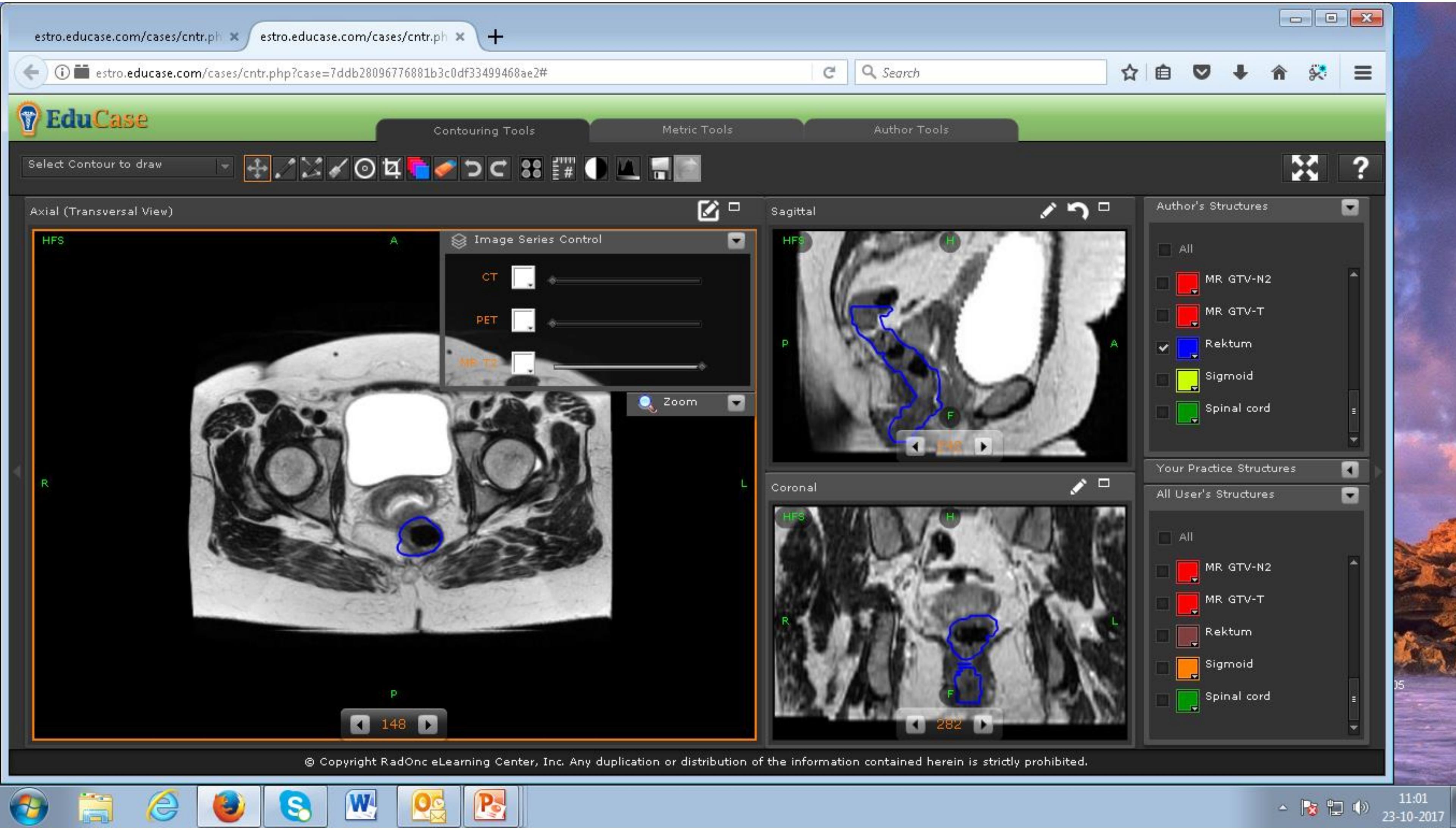
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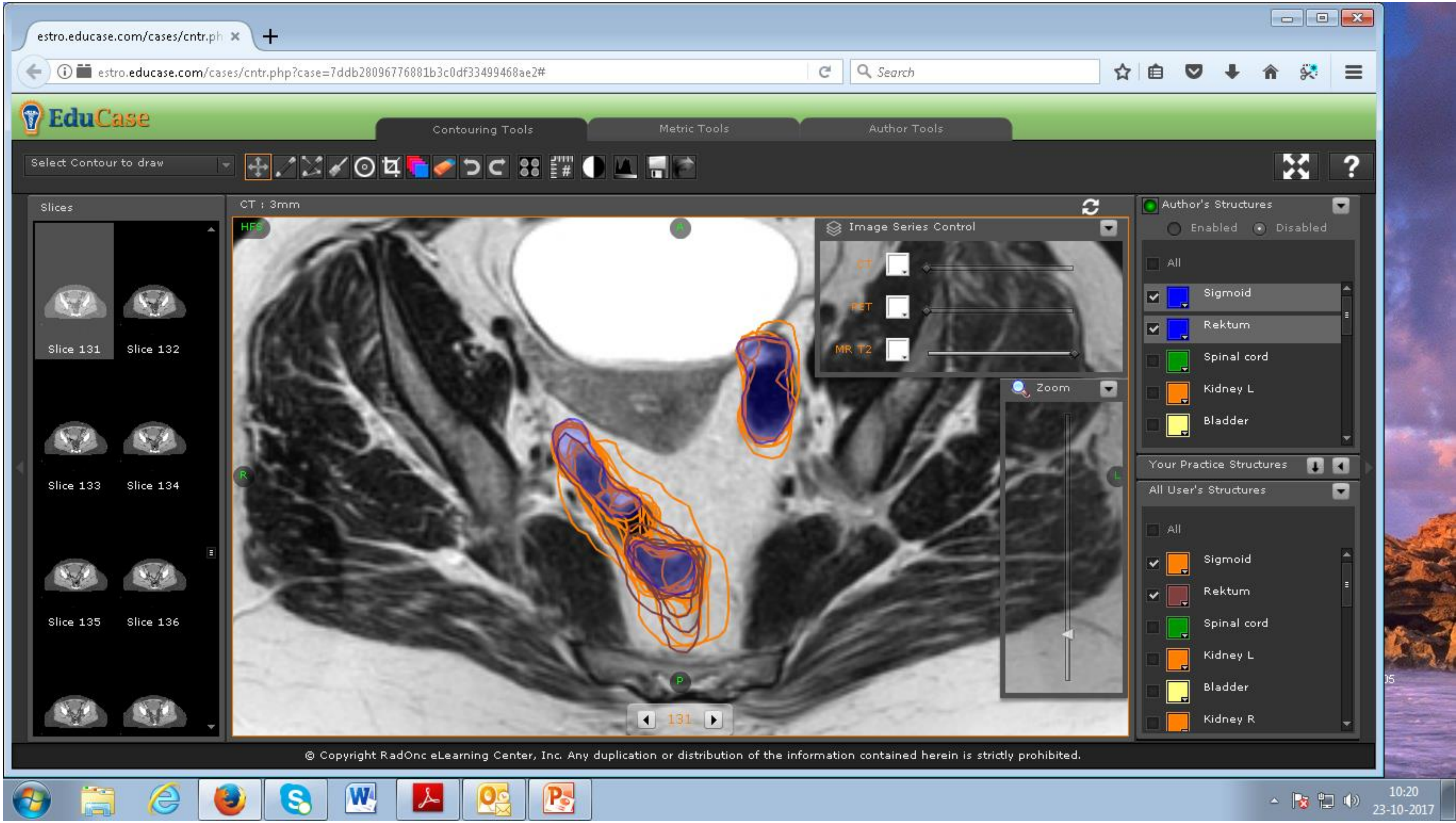

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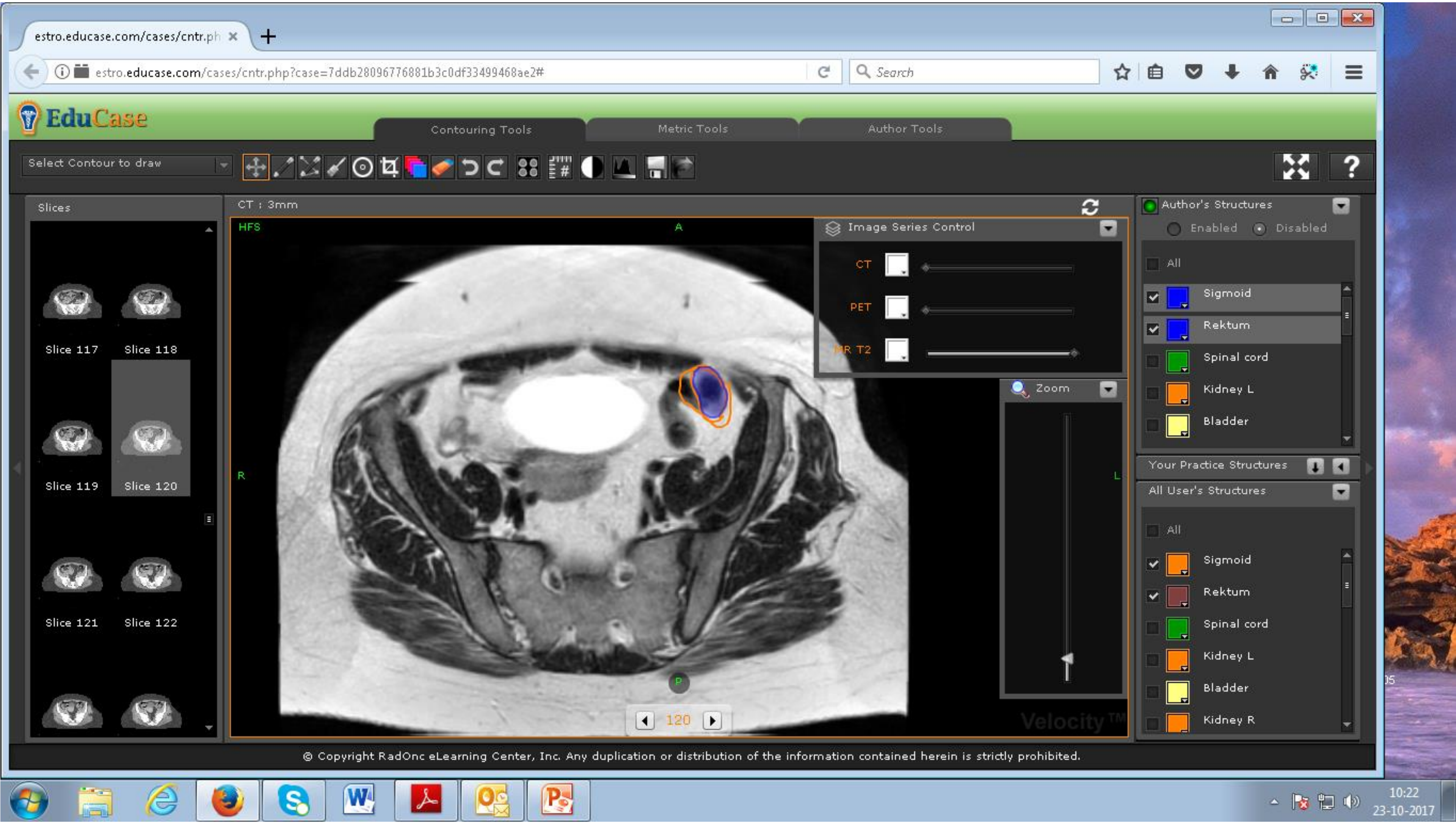
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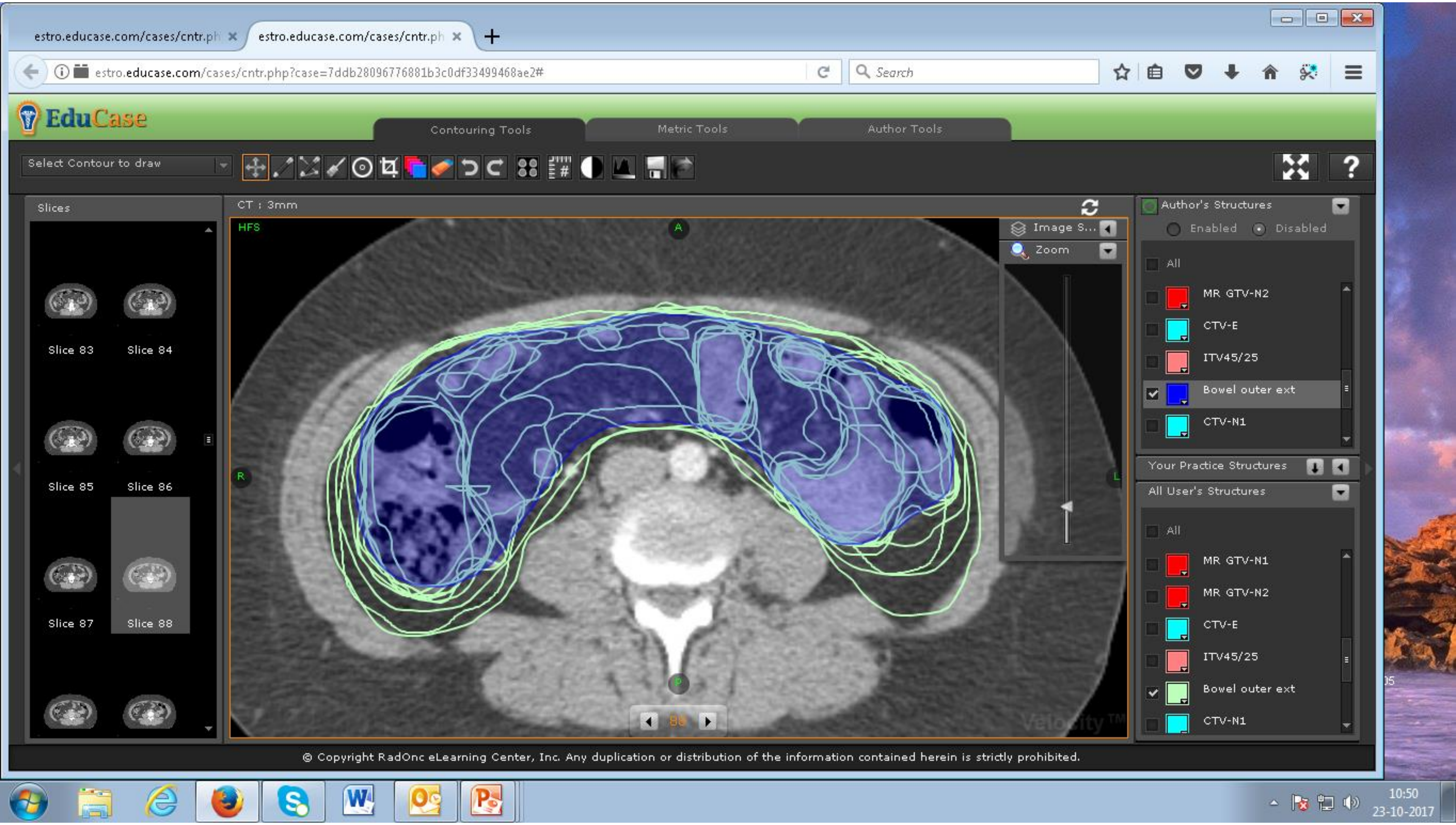

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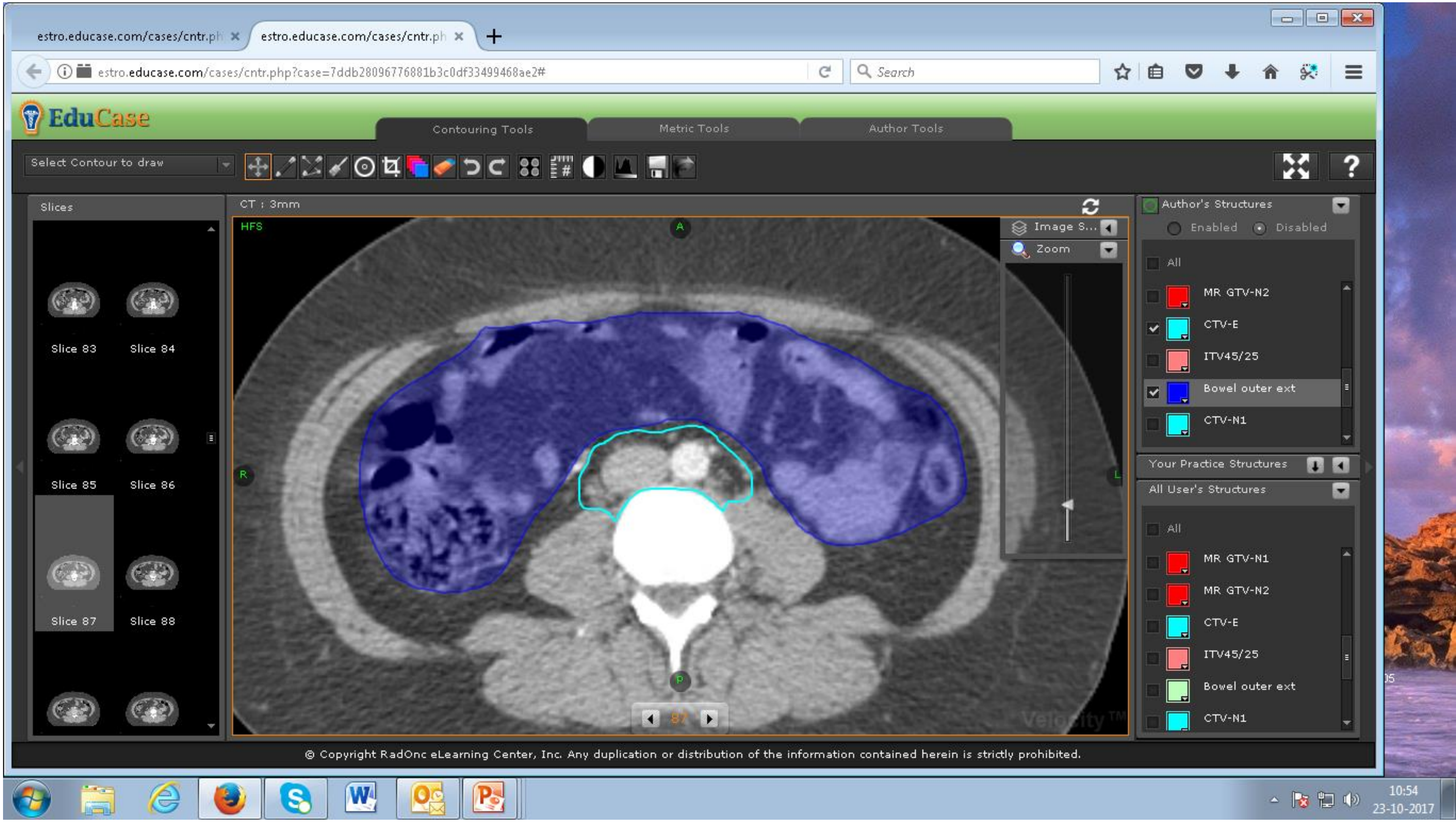

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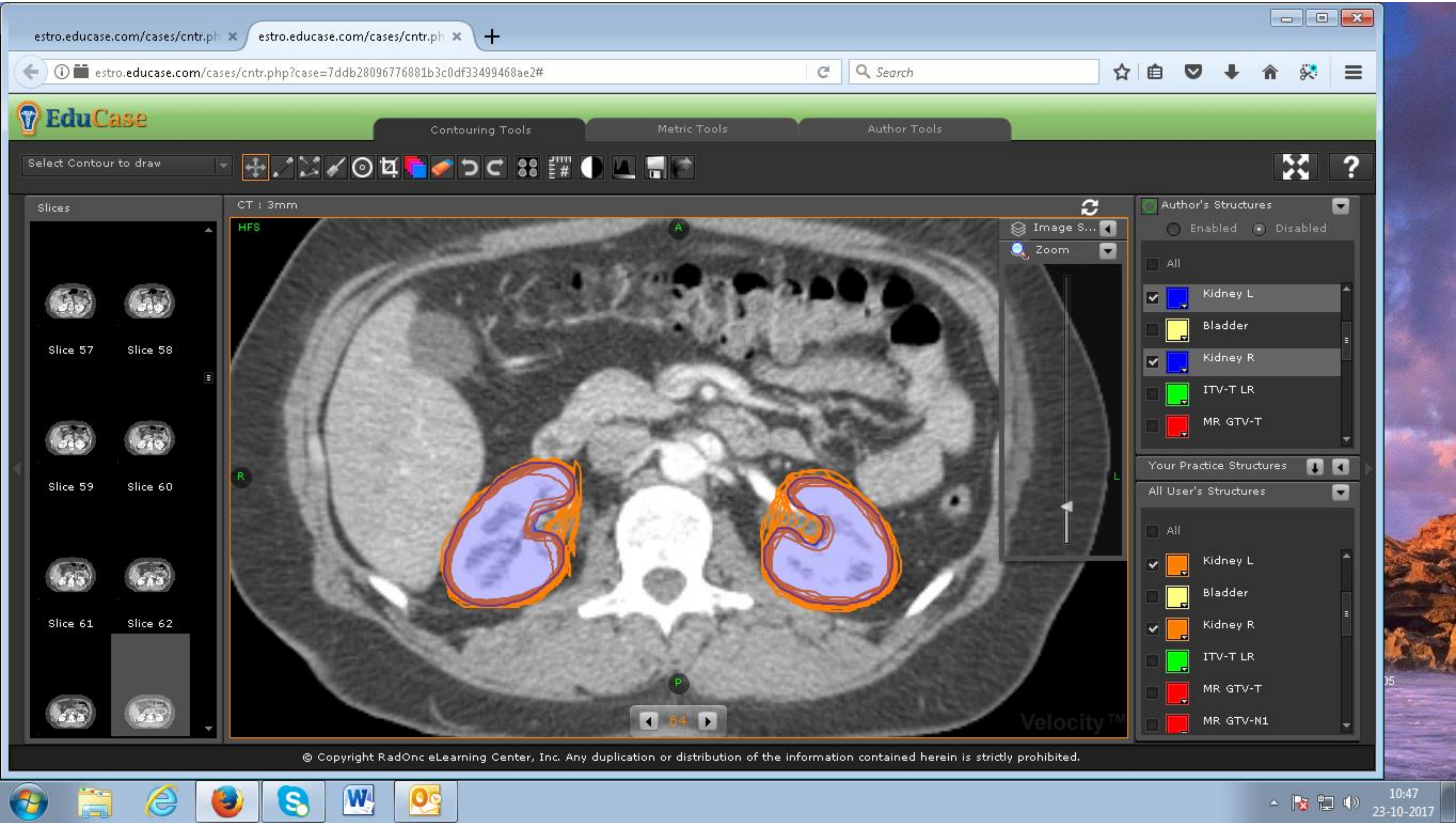
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Homework UTR2

patient ID:

Patient &Tumour

Patient:

41 years old

Tumour:

Histological type: SCC, G3

FIGO stage: Ib2

Initial clinical findings:

Portio:

exophytic tumour

Vagina:

not involved

Parametria:

Right: not involved

Left: not involved

Cystoscopy:

no involvement of bladder mucosa

Patient &Tumour

Patient:

41 years old

umour:

Histological type: SCC, G3

FIGO stage: Ib2

MRI:

Cervical tumor mass
no infiltration into vagina or parametria
2 nodes right pelvis, 9 and 8 mm short axis diameter
1 node left pelvis, 6 mm short axis
2 nodes common iliac, 6 and 6 mm

PET-CT:

Activity high in primary tumor,
low in 2/3 pelvic nodes
No activity in 3rd pelvic an bothe common iliac nodes

Patient:UTR2

Clinical Drawing

At Diagnosis [x]

At Brachytherapy [ ]

EBRT___Gy

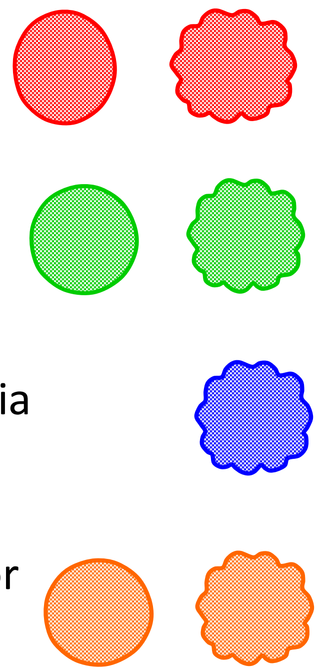
<u>Infiltrative</u> <u>Exophytic</u>

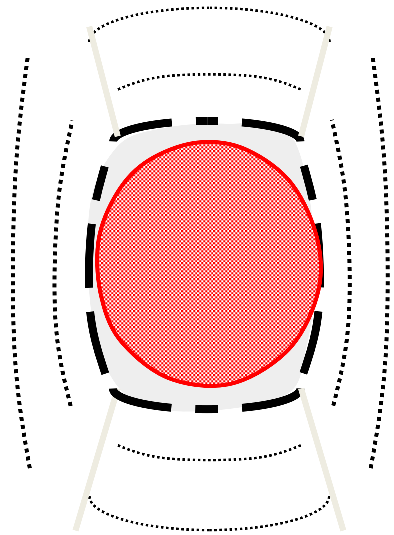
Cervix

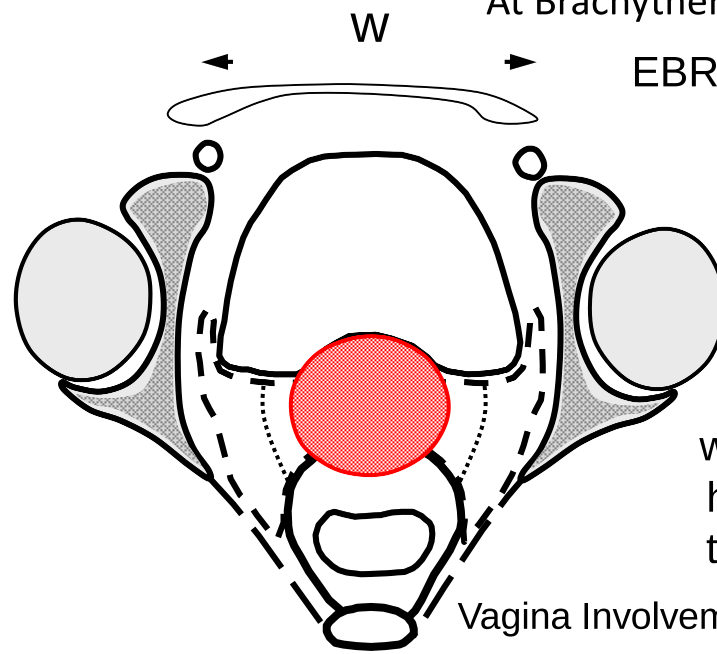
Vagina

Parametria

Rectum or Bladder

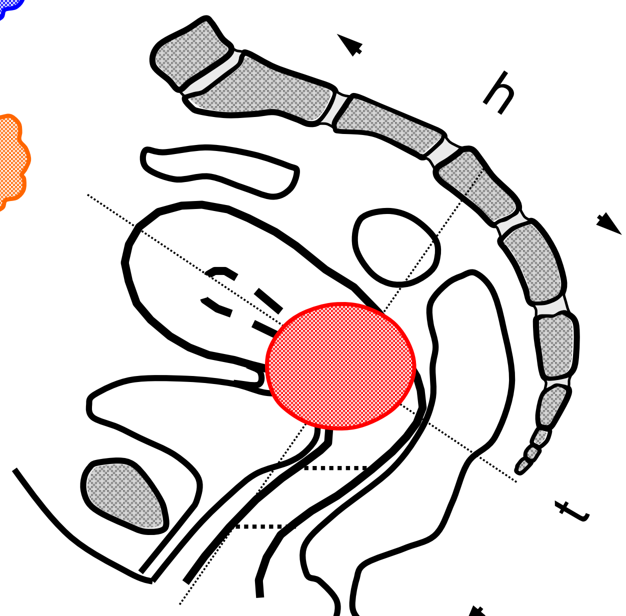


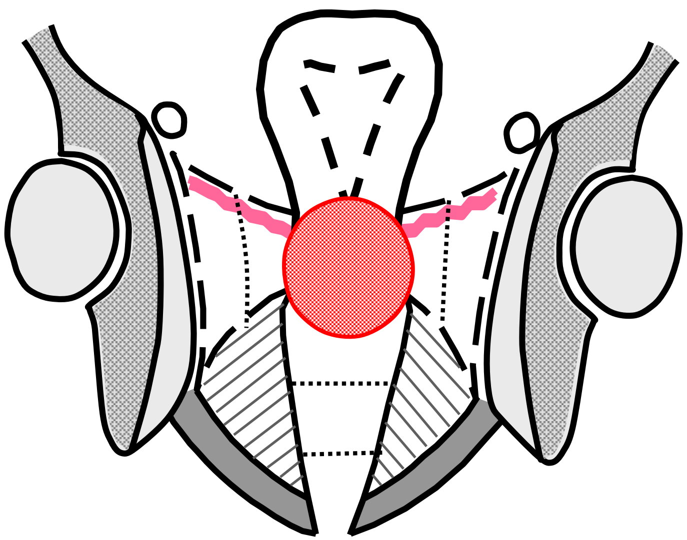




w = 6 cm
h = 5 cm
t = 6 cm

Vagina Involvement: no





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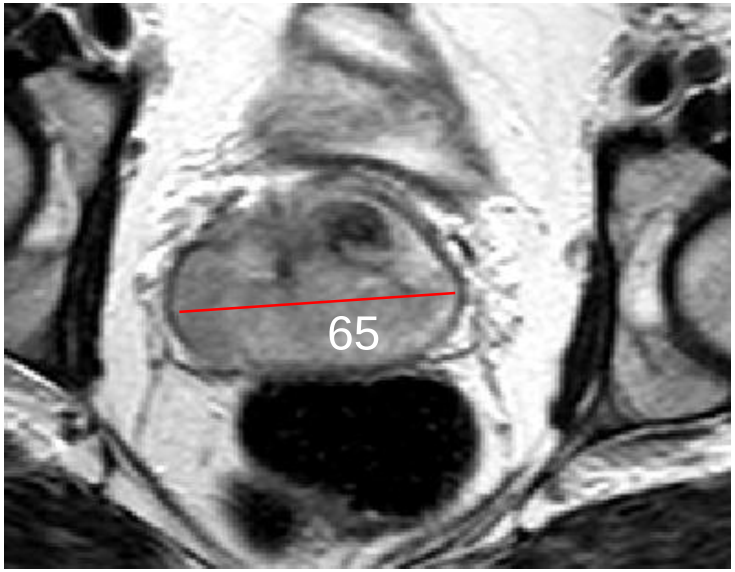
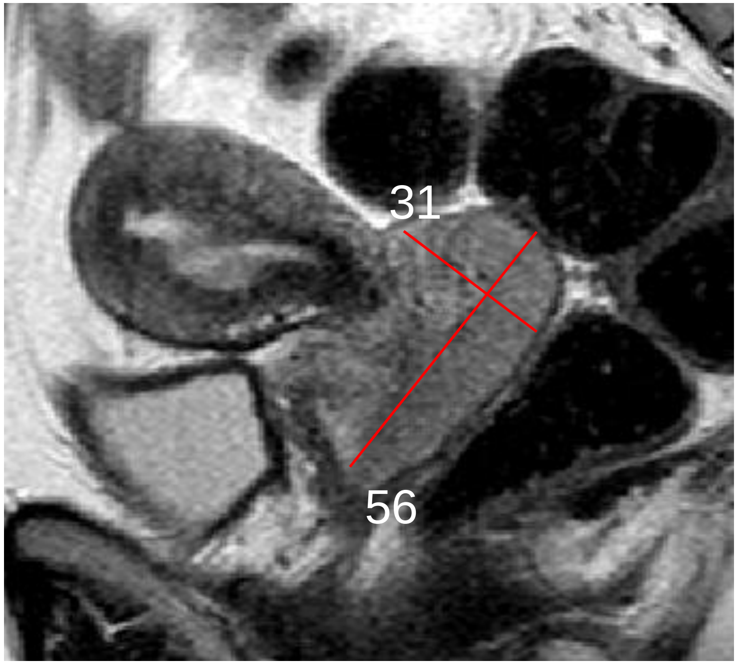
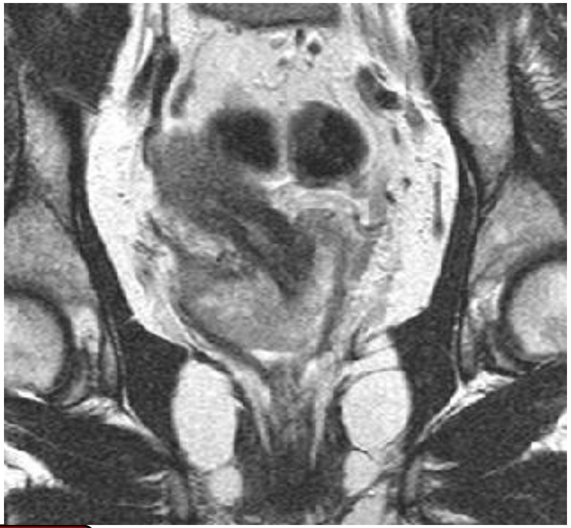


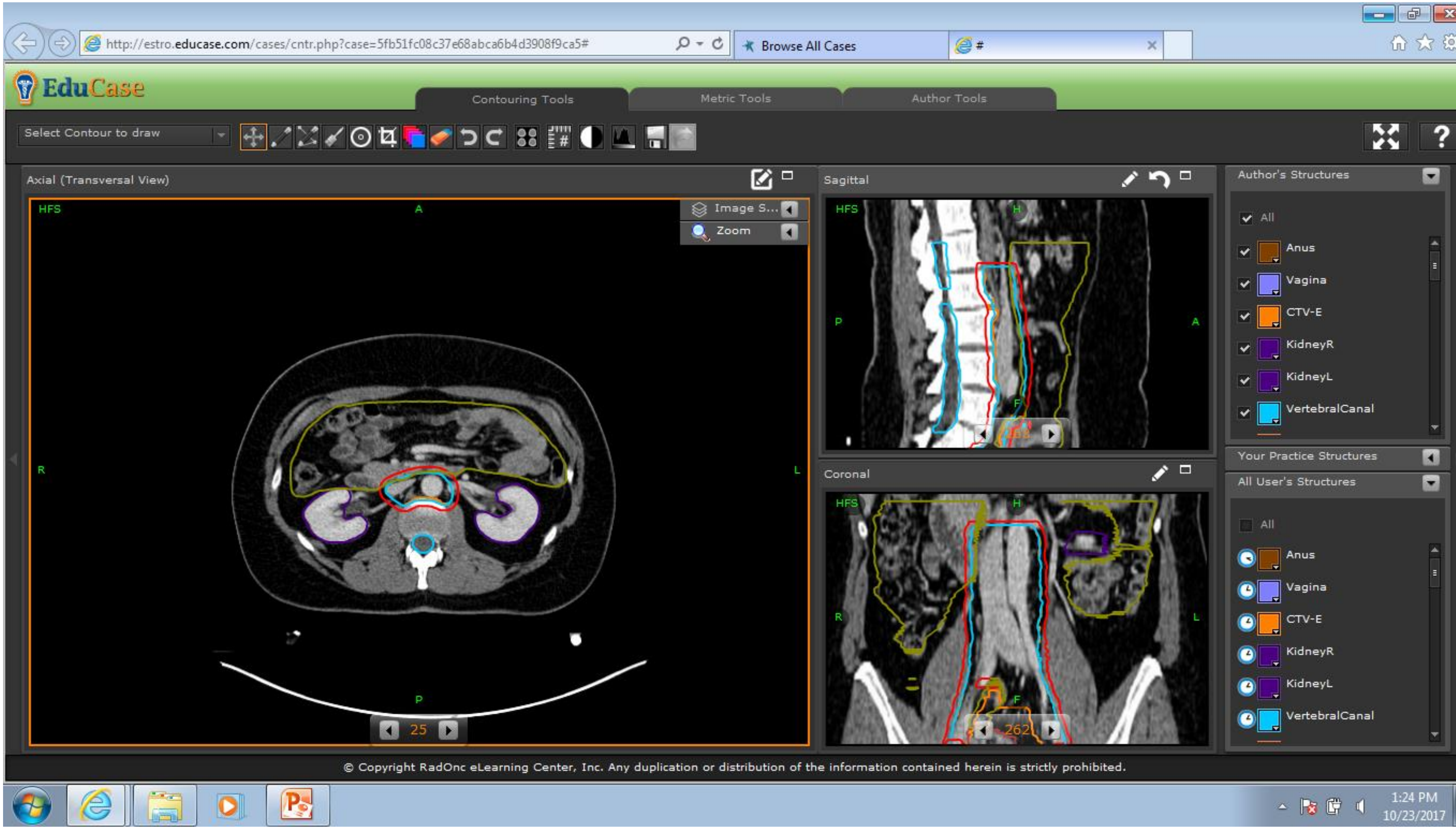




V= 62 cm^3

Only representative slices are shown

CTV-E Upper field border



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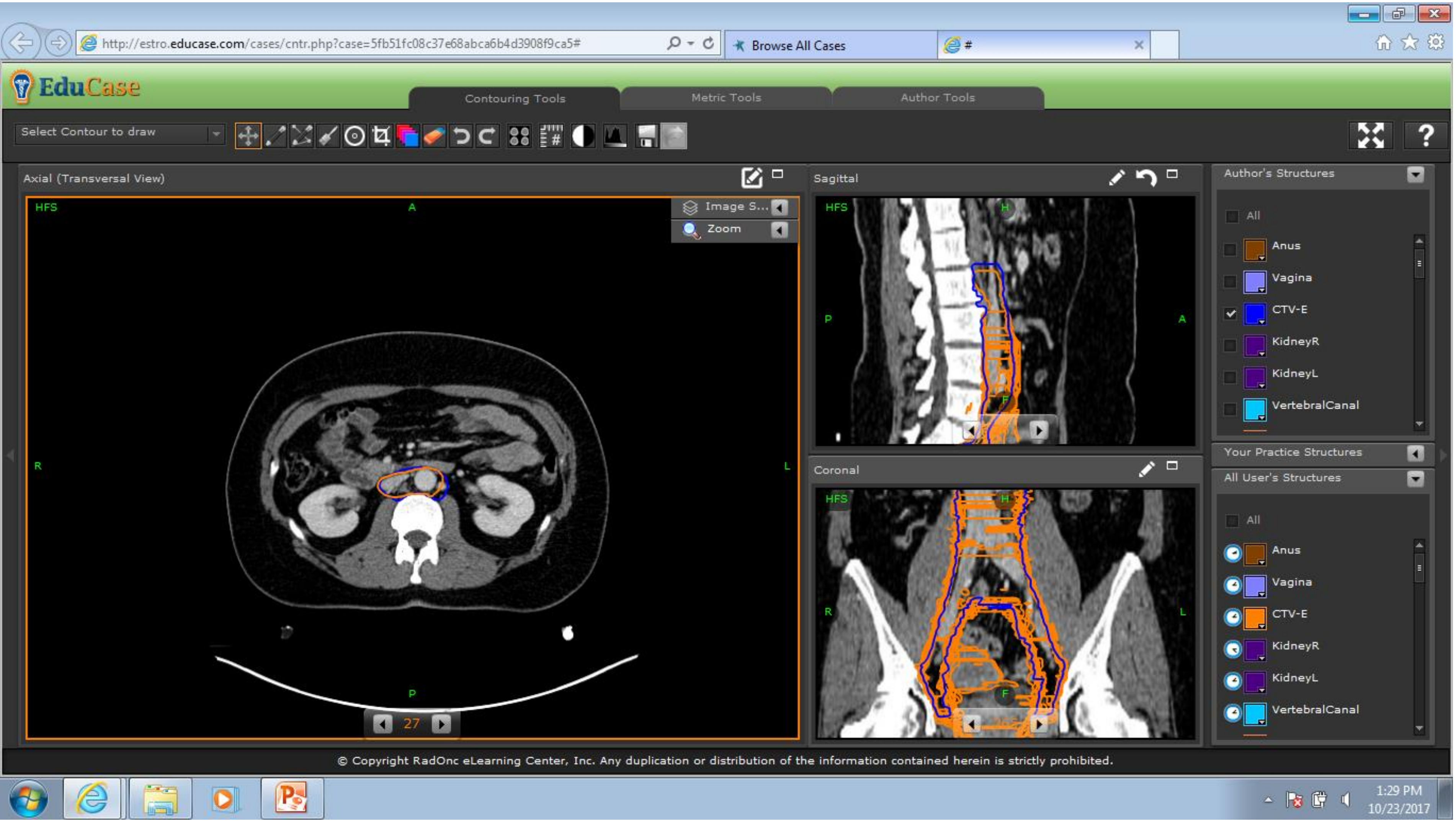

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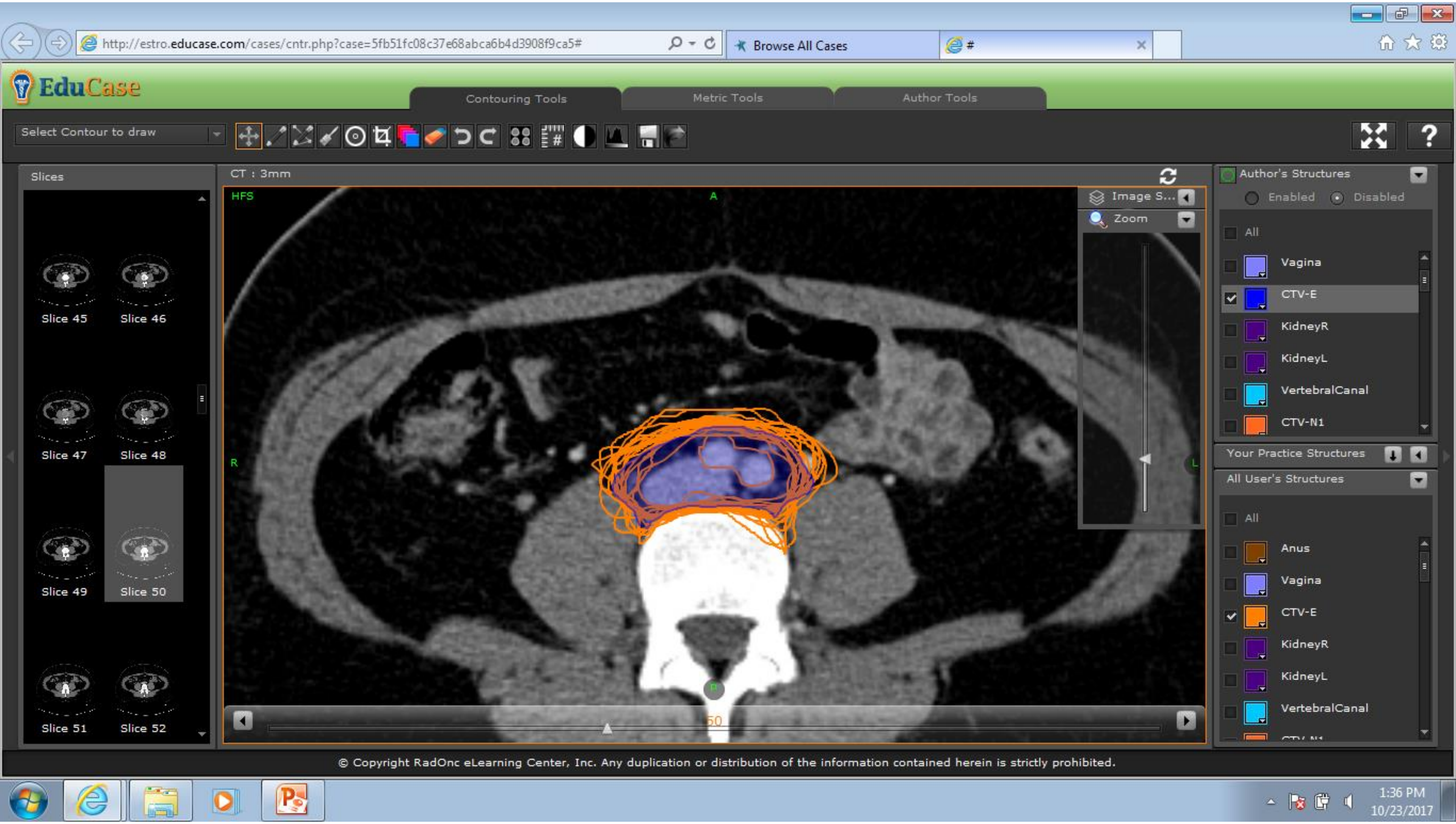
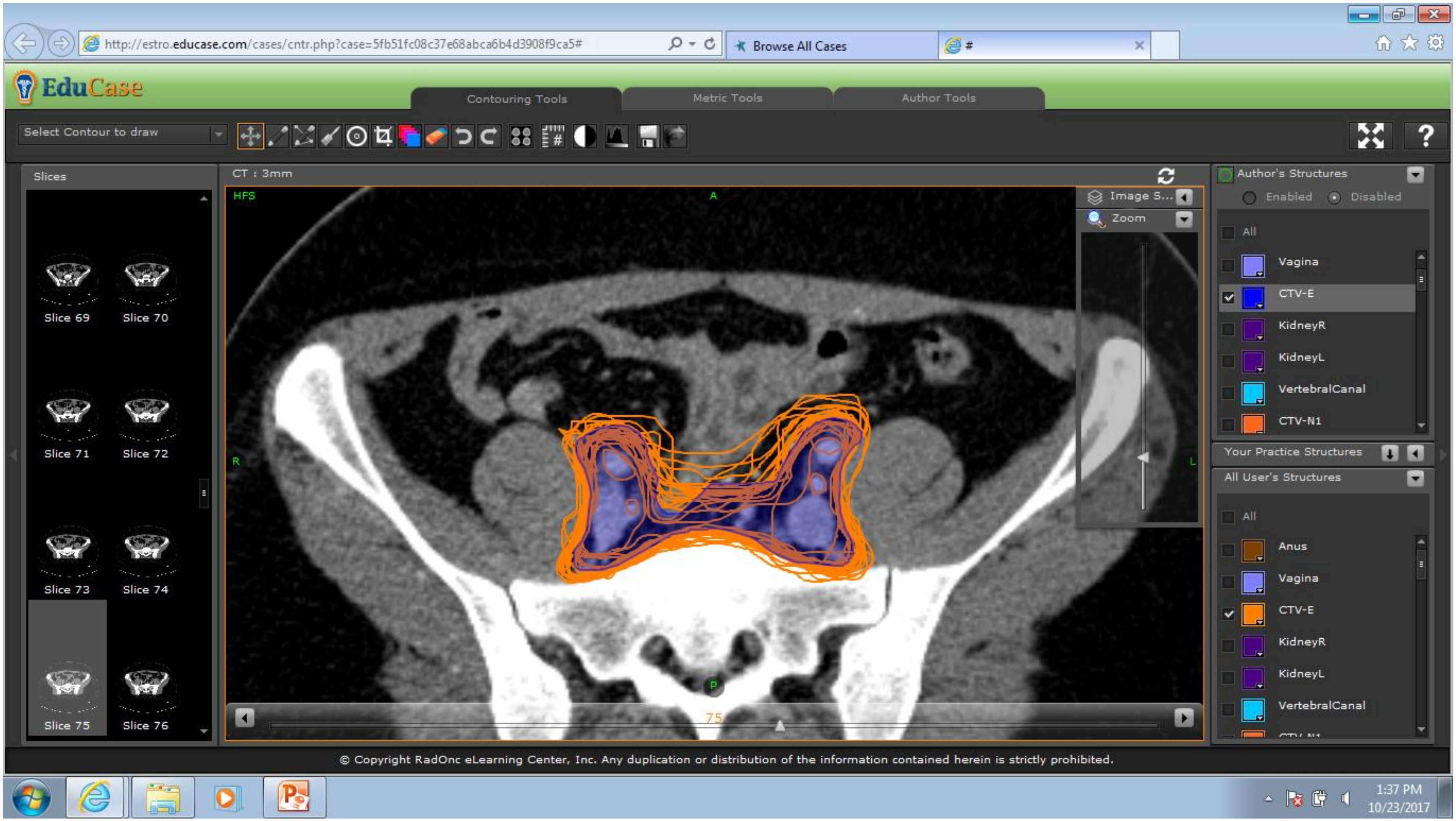
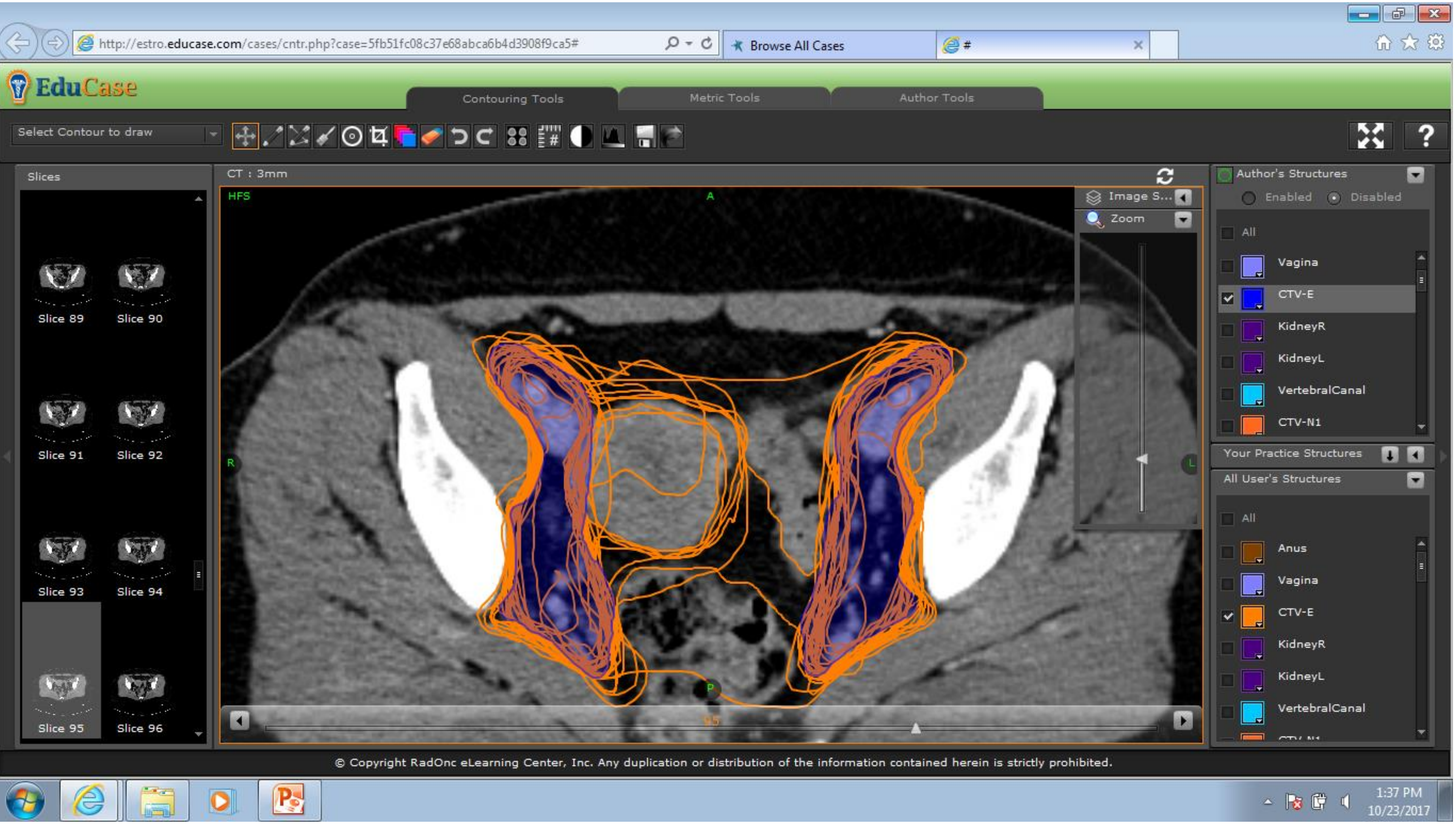
CTV-E Common iliac



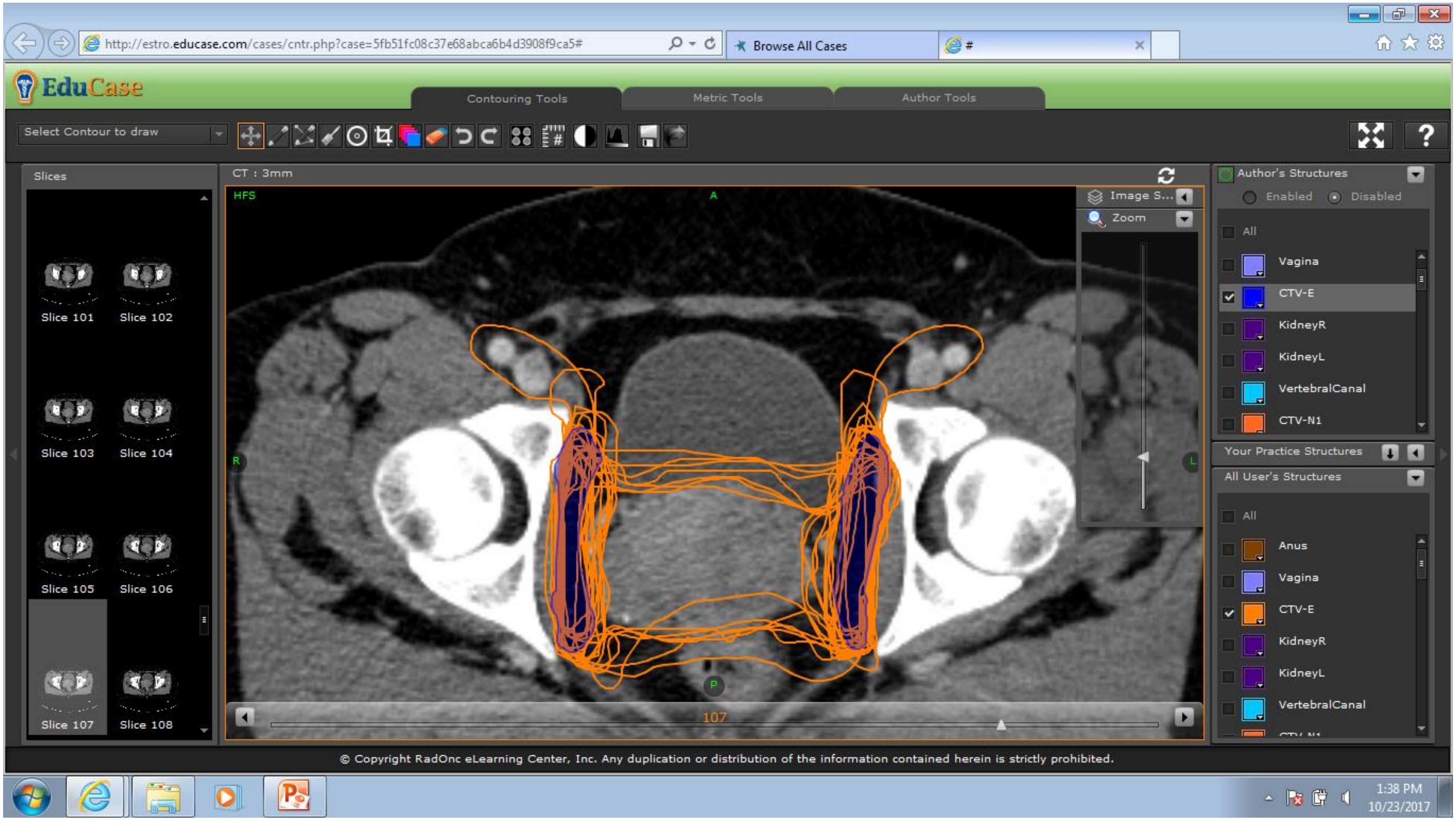
CTV-E Common iliac



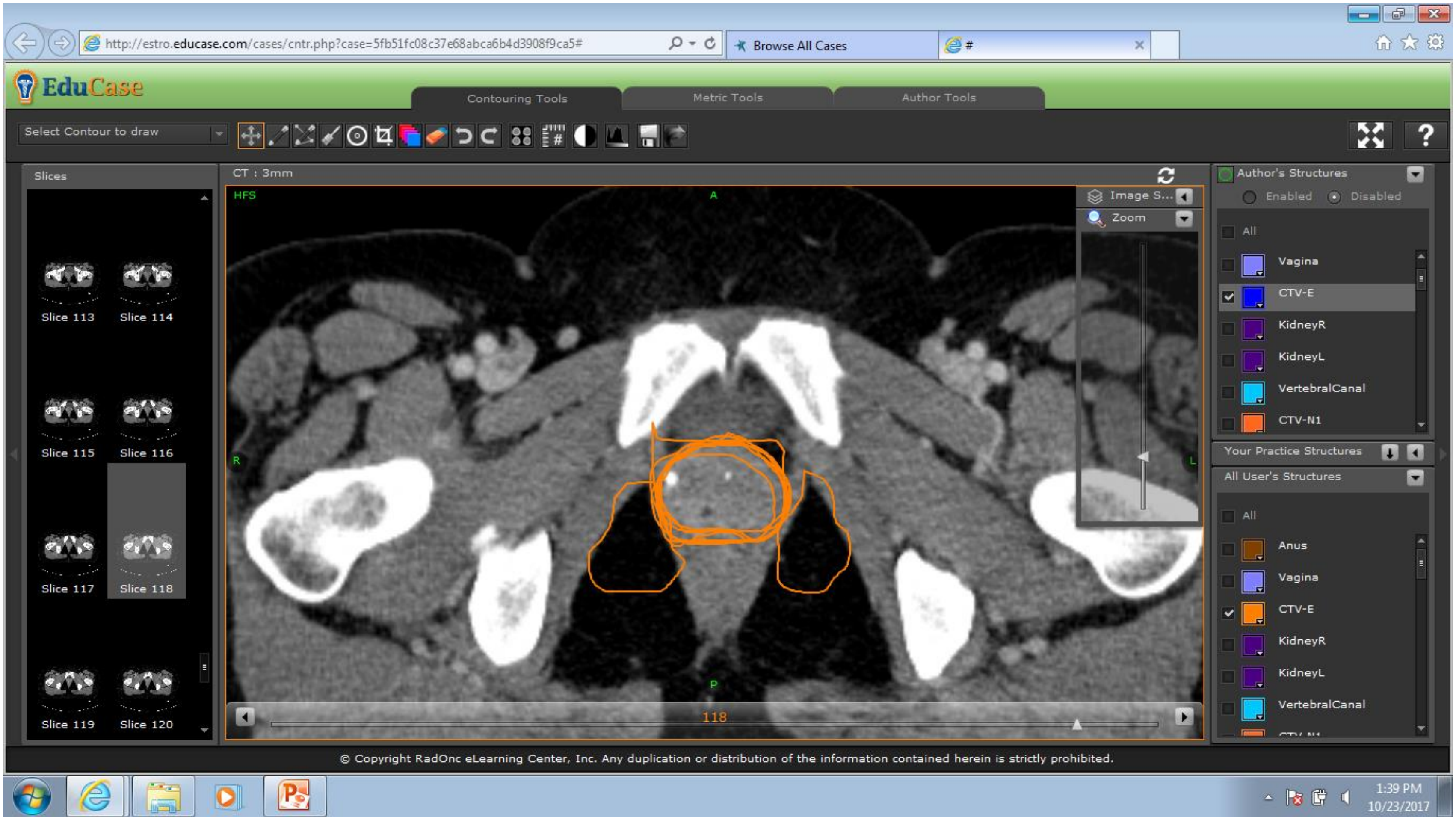
CTV-E Intern and external iliac, obturator



CTV-E Transition zone, tumor region



CTV-E vagina



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Browse All Cases
EduCase
Contouring Tools
Metric Tools
Author Tools
Select Contour to draw
Slices
Slice 113
Slice 114
Slice 115
Slice 116
Slice 117
Slice 118
Slice 119
Slice 120
CT : 3mm
HFS
A
R
L
P
118
Image S...
Zoom
Author's Structures
Enabled
Disabled
All
Vagina
CTV-E
KidneyR
KidneyL
VertebralCanal
CTV-N1
Your Practice Structures
All User's Structures
All
Anus
Vagina
CTV-E
KidneyR
KidneyL
VertebralCanal
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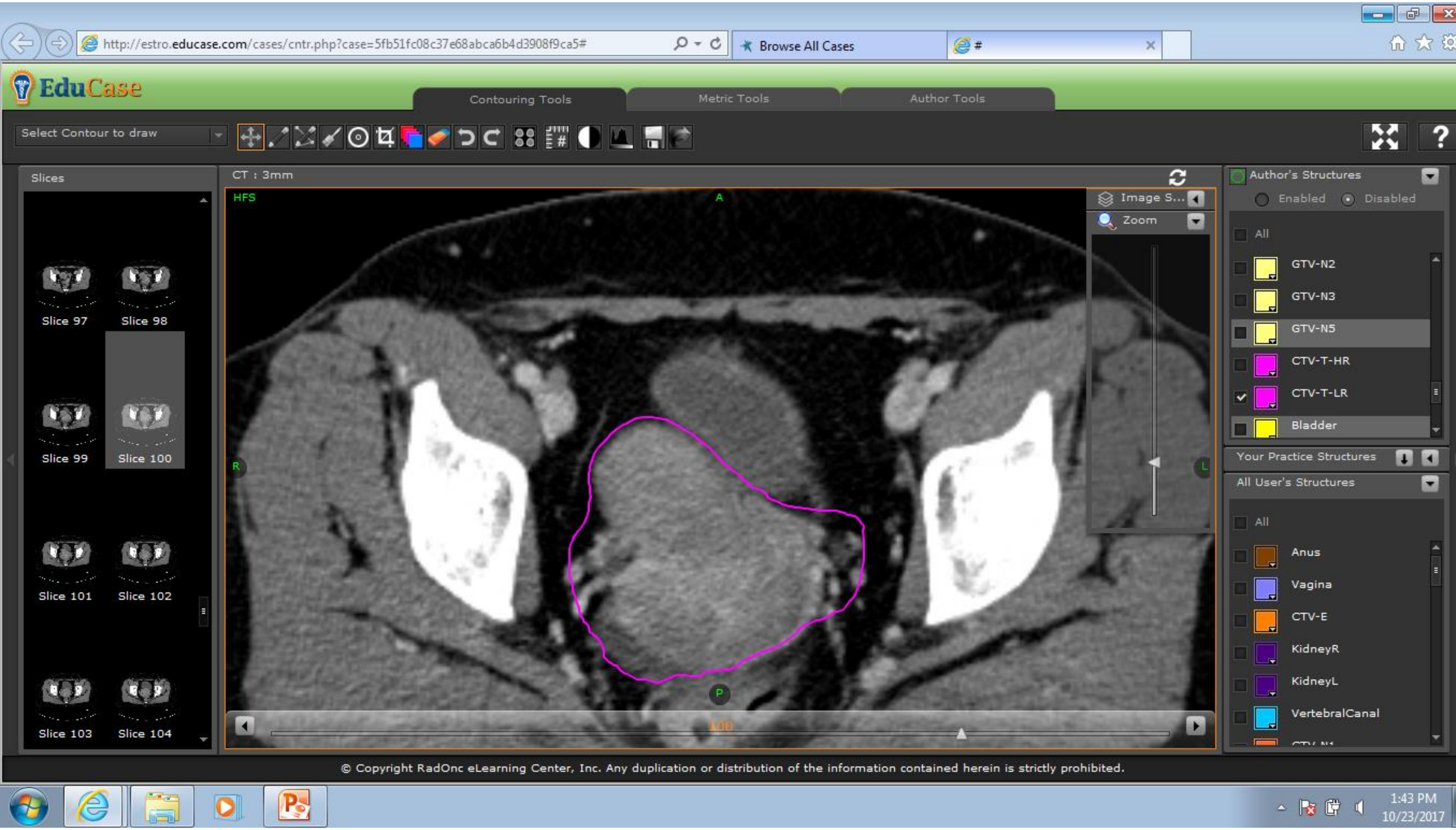
1:39 PM
10/23/2017

CTV-T-LR



http://estro.educase.com/cases/cntr.php?case=5fb51fc08c37e68abca6b4d3908f9ca5#
Browse All Cases
EduCase
Contouring Tools
Metric Tools
Author Tools
Select Contour to draw
Slices
CT : 3mm
HFS
Slice 97
Slice 98
Slice 99
Slice 100
Slice 101
Slice 102
Slice 103
Slice 104
Image S...
Zoom
Author's Structures
Enabled
Disabled
All
GTV-N2
GTV-N3
GTV-N5
CTV-T-HR
CTV-T-LR
Bladder
Your Practice Structures
All User's Structures
All
Anus
Vagina
CTV-E
KidneyR
KidneyL
VertebralCanal
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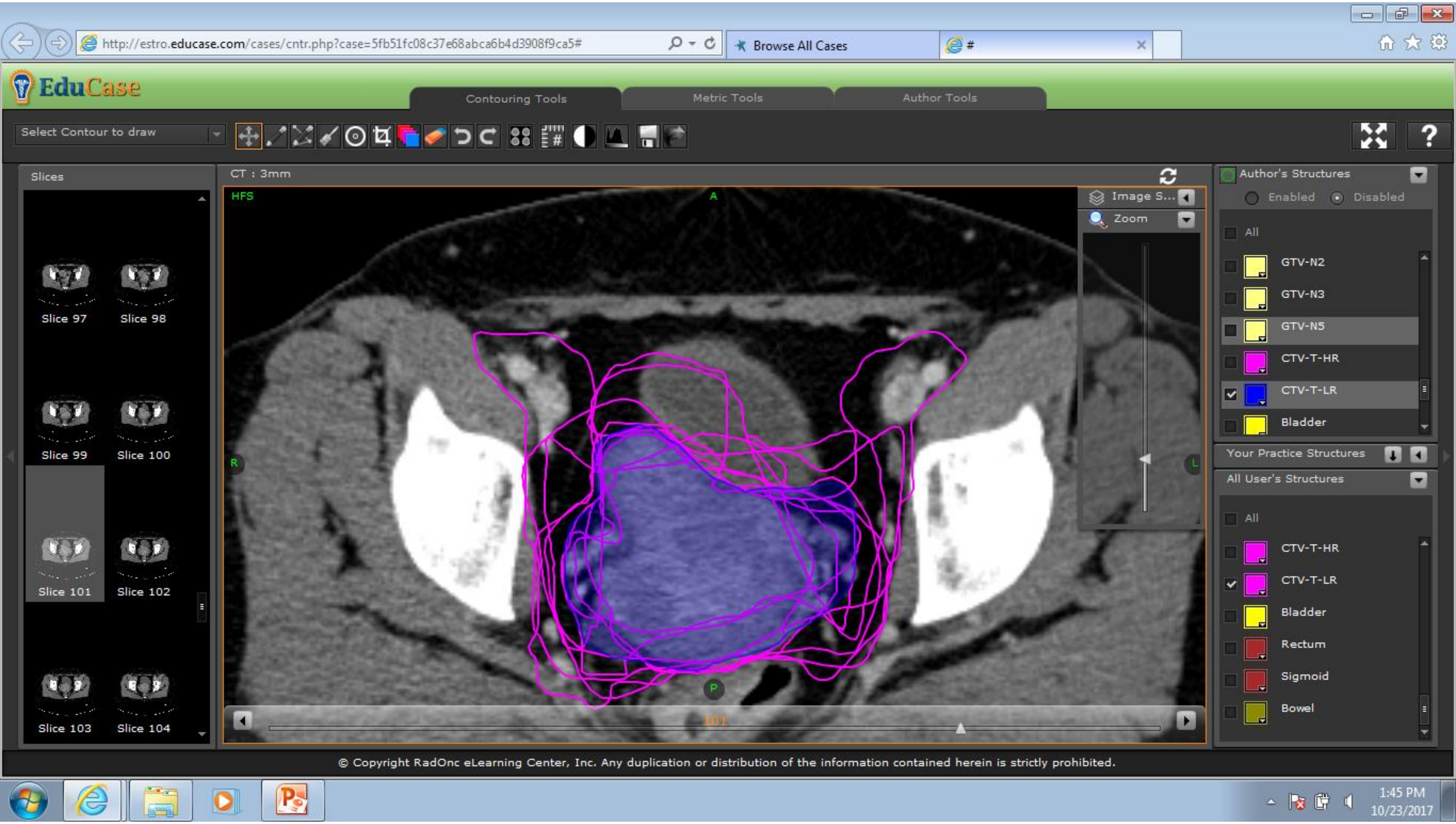
10/23/2017

CTV-T-LR



http://estro.educase.com/cases/cntr.php?case=5fb51fc08c37e68abca6b4d3908f9ca5#
Browse All Cases
EduCase
Contouring Tools
Metric Tools
Author Tools
Select Contour to draw
Slices
CT : 3mm
HFS
A
R
L
P
Image S...
Zoom
Slice 97
Slice 98
Slice 99
Slice 100
Slice 101
Slice 102
Slice 103
Slice 104
Author's Structures
Enabled
Disabled
All
GTV-N2
GTV-N3
GTV-N5
CTV-T-HR
CTV-T-LR
Bladder
Your Practice Structures
All User's Structures
All
CTV-T-HR
CTV-T-LR
Bladder
Rectum
Sigmoid
Bowel
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1:45 PM
10/23/2017

Homework EBRT planning

ESTRO GYN BT course

Prague 2017

Find your institution number

Aarhus reference plan	1
Regional Institute of Oncology, IASI	2
University Hospital, Prague	3
University of Halle, Germany	4
Hong Kong Sanatorium Hospital	5
University Hospital Hradec Králové	6
Faculty Hospital Kralovske Vinohrady, Prague	7
Queen Elizabeth Hospital	8
AZ Sint-Lucas Gent	9
Saint Lukes	10
Oslo University Hospital	11
klinikum-karlsruhe	12

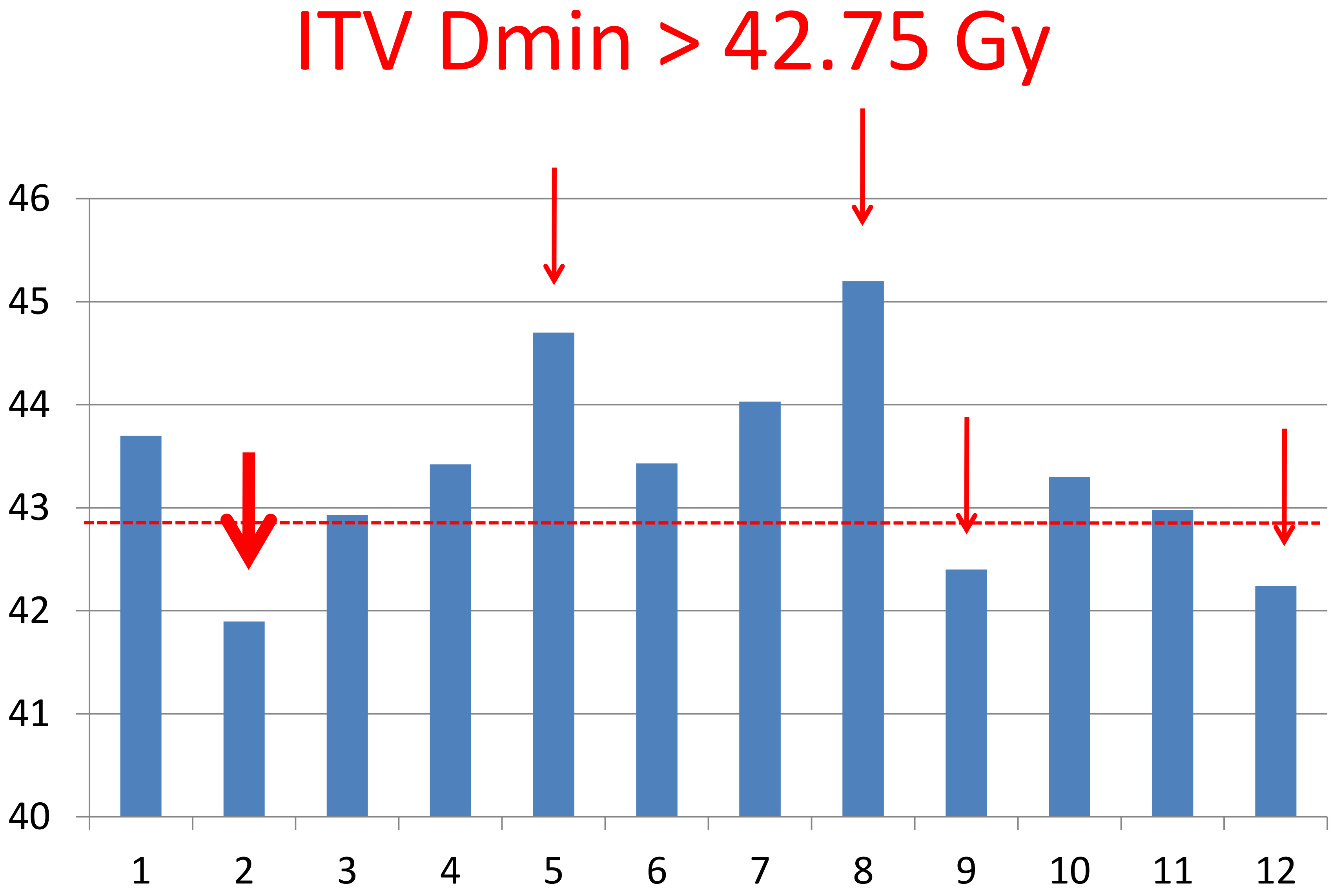
Evaluation

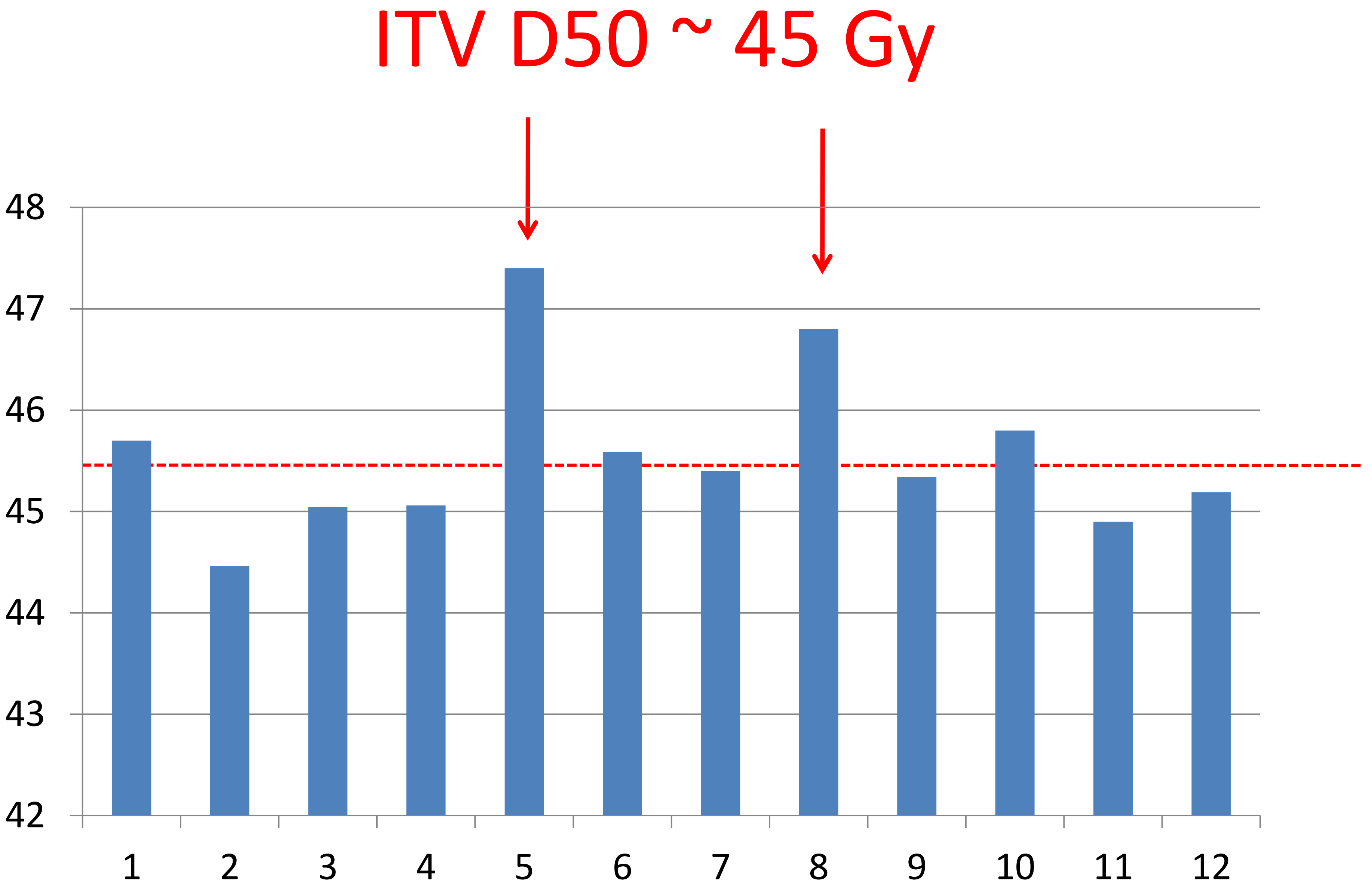
- Dose to the target
  - ITV, PTV – Elective target
  - ITV, PTV – Lymph node
- Dose to the OARs
  - Bladder, Rectum, sigmoid, bowel
- Dose to Normal tissues
  - Conformality, V50, V43,

Targets - Evaluation criteria

- Hard dose plan criteria must be fulfilled

		Hard 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


ITV Dmin > 42.75 Gy
46
45
44
43
42
41
40
1
2
3
4
5
6
7
8
9
10
11
12


ITV D50 ~ 45 Gy
48
47
46
45
44
43
42
1
2
3
4
5
6
7
8
9
10
11
12

ITV45

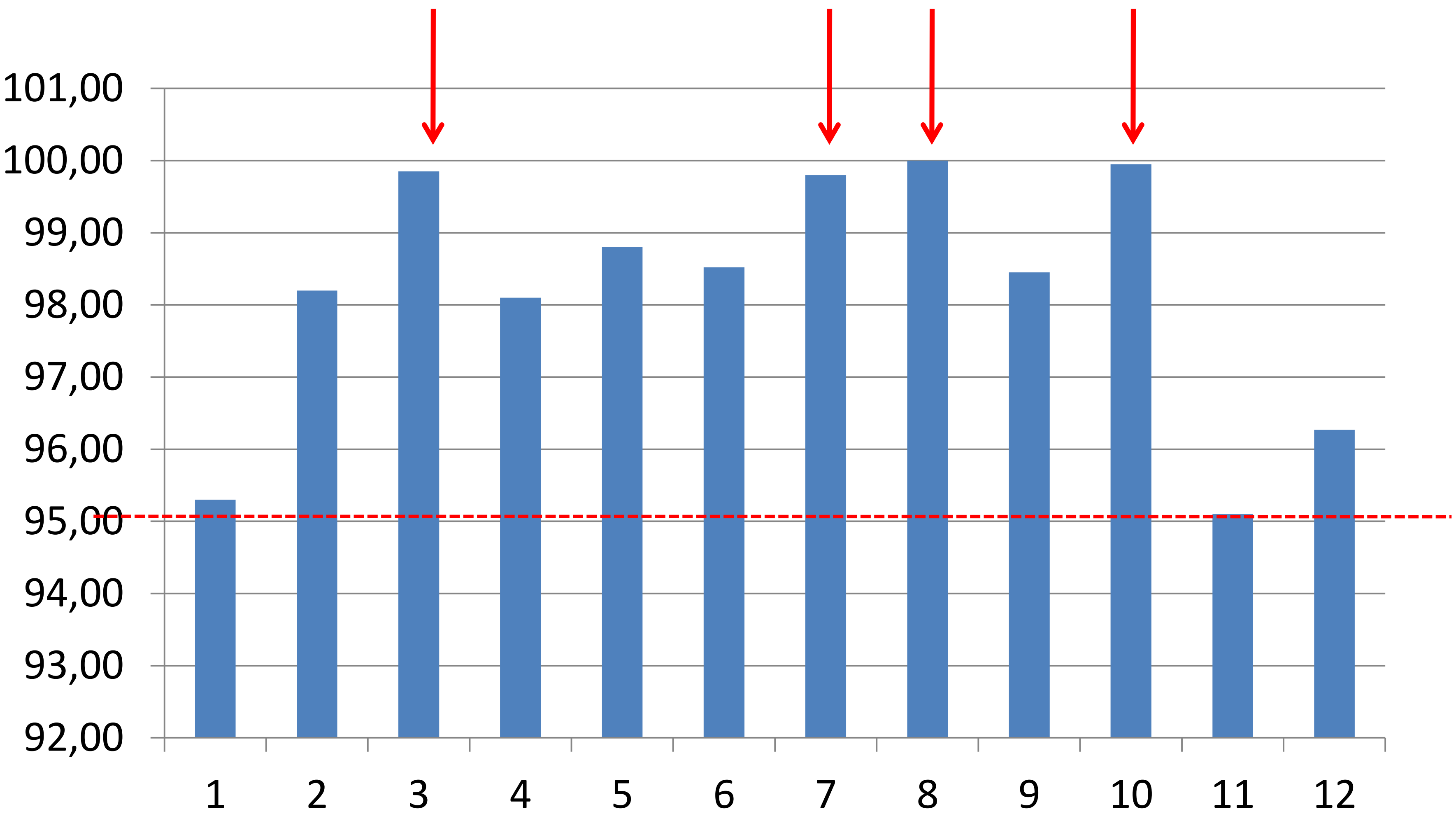
- ITV45 coverage
  - 3 institutions did not fulfill Dmin ≥ 95%

- ITV45 D50 too high
  - 2 institutions had D50>46.0Gy

PTV45

- Coverage criteria for PTV45: V95% ≥ 95%
  - The aim is to spare normal tissue as much as possible
  - A better coverage than the constraints is NOT a better dose plan ☺

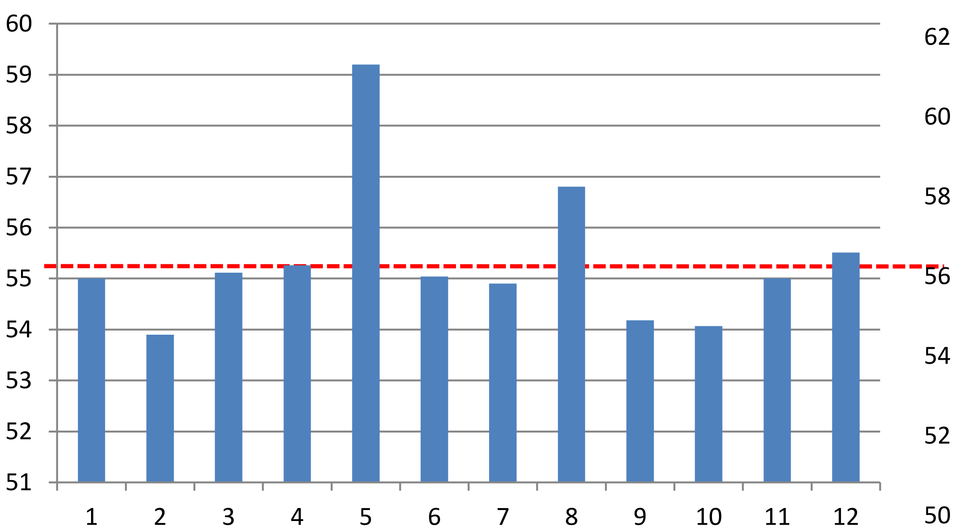
PTV45: V42.75Gy ≥ 95%



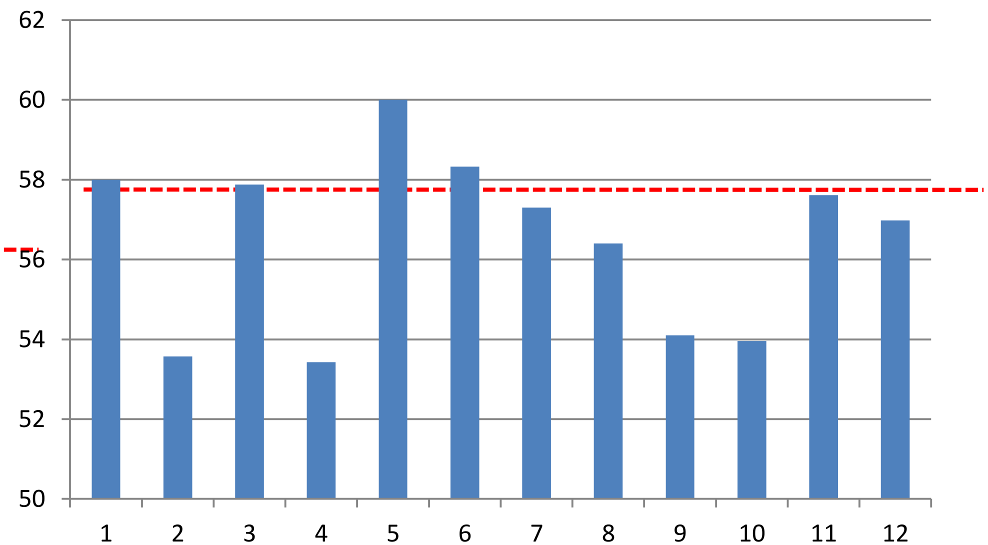
Nodal boosting

- CTV-N D98>100% of prescribed dose is a hard constraint since the coverage on the edge of PTV-N can be as low as 90% and the margins are small.
- Hard target coverage constraints overrules soft constraints e.g. Bowel

CTV N1 D98 D98>55Gy



CTV N2 D98 D98>57.5Gy



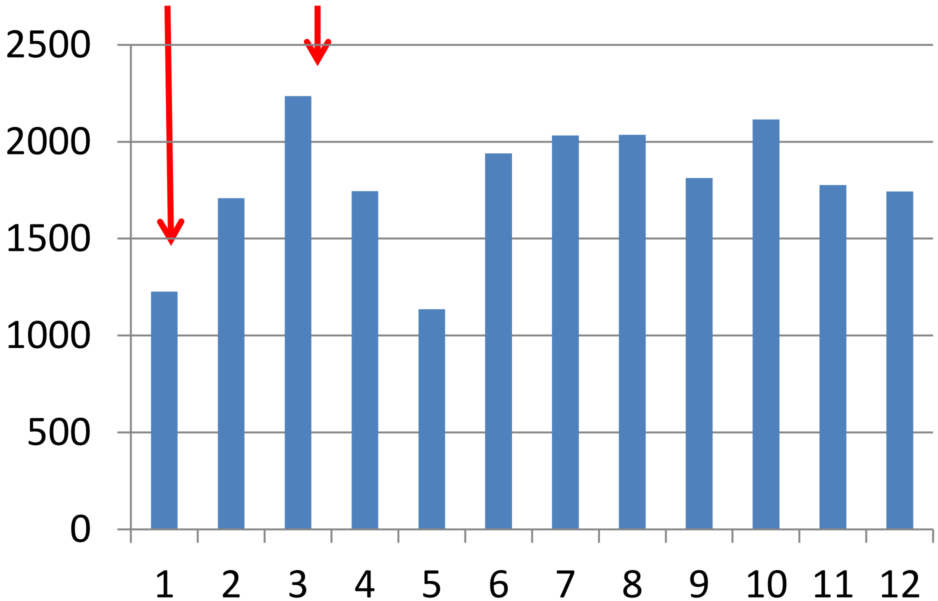
Irradiation of normal tissue

- Difference in irradiated body volume of 1000cm3 in Inst-3!
- Question of PTV margin
  - 5mm margin expands irradiated volume by 500cm3
  - 10mm margin expands irradiated volume by 1000cm3

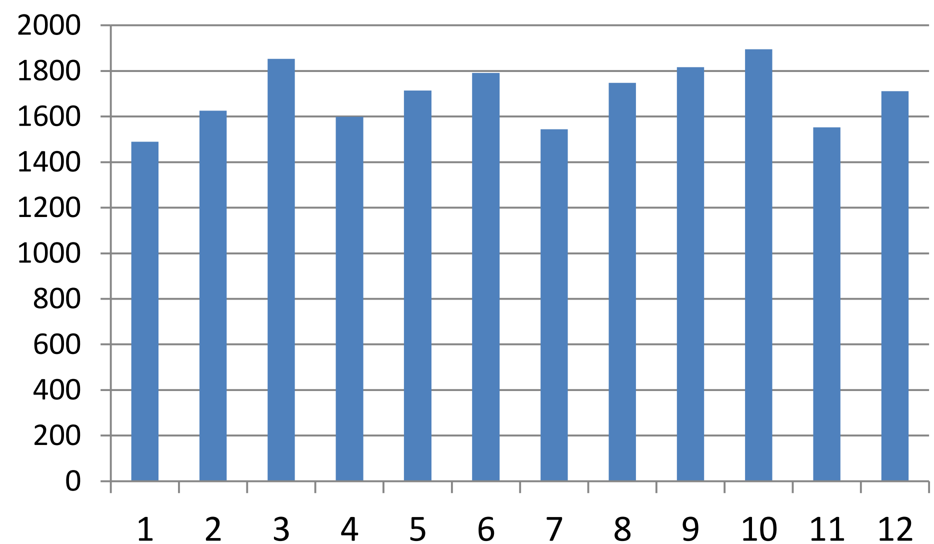
PTV margin 5mm

PTV margin 10mm?

Body V43



Bowel V15

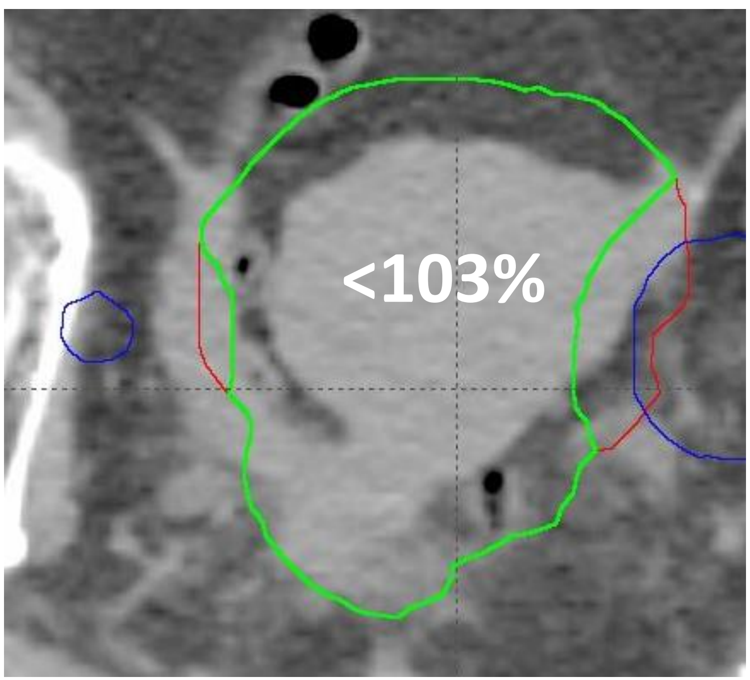


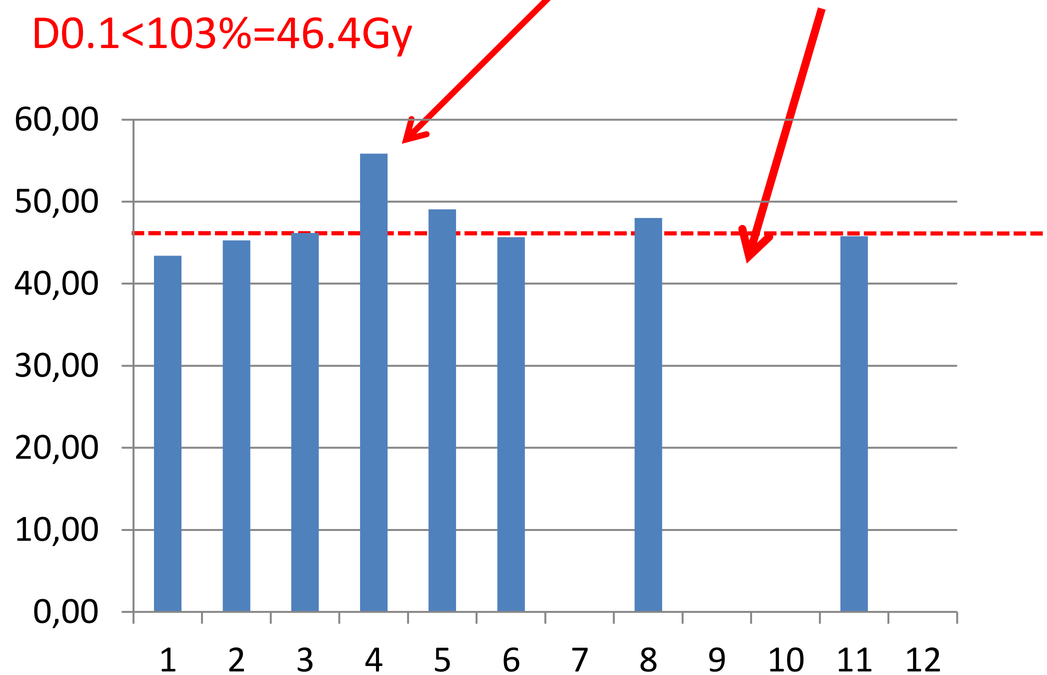
Help contour for homogenity

- Control of dose in the region where BT is delivered
- In particular relevant, when boosting lymph nodes with simultaneous integrated boost

10 Gy extra
Too much!

Did not report!





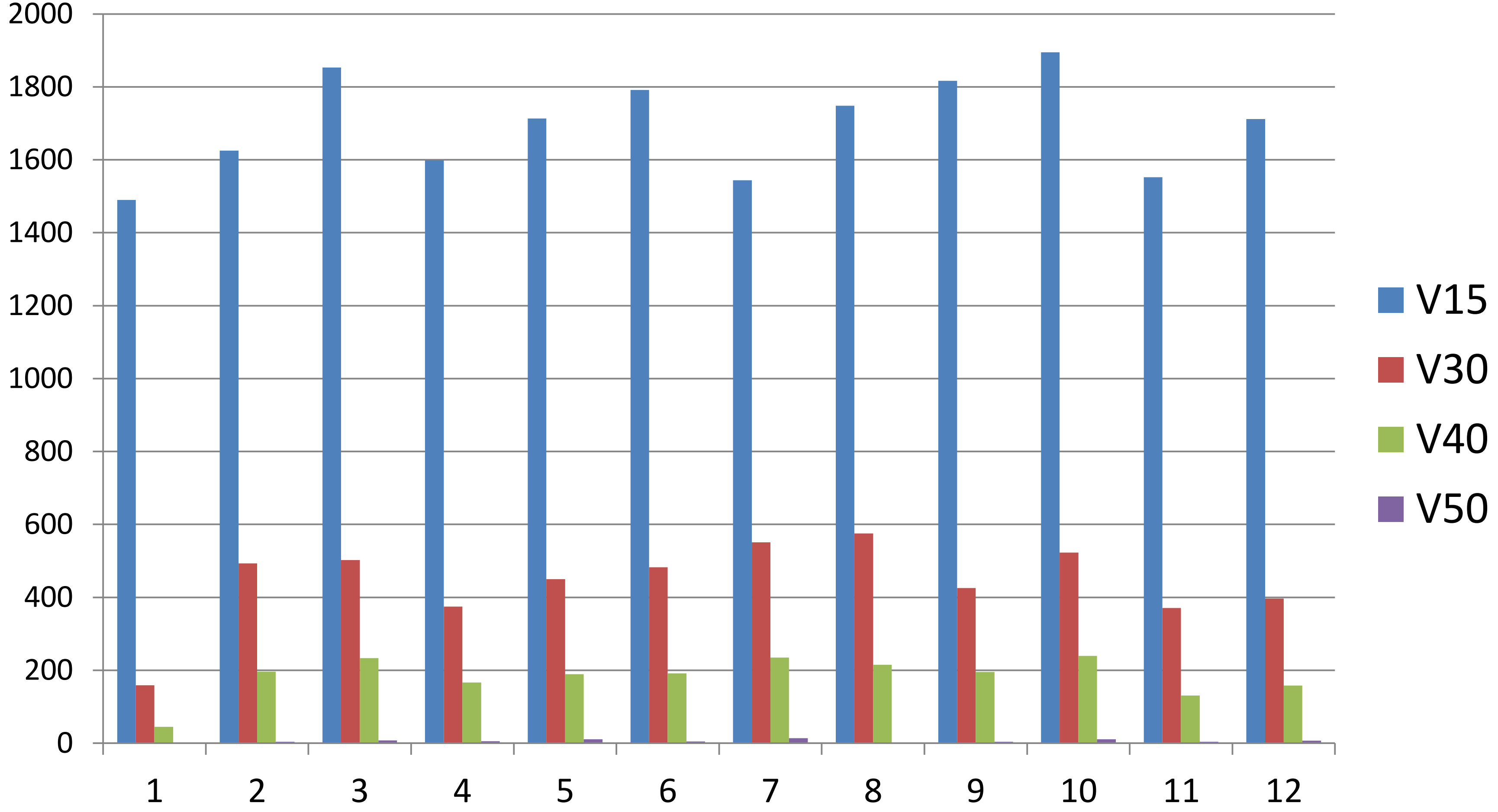
Planning Objectives for OAR e.g – EMBRACE II

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

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

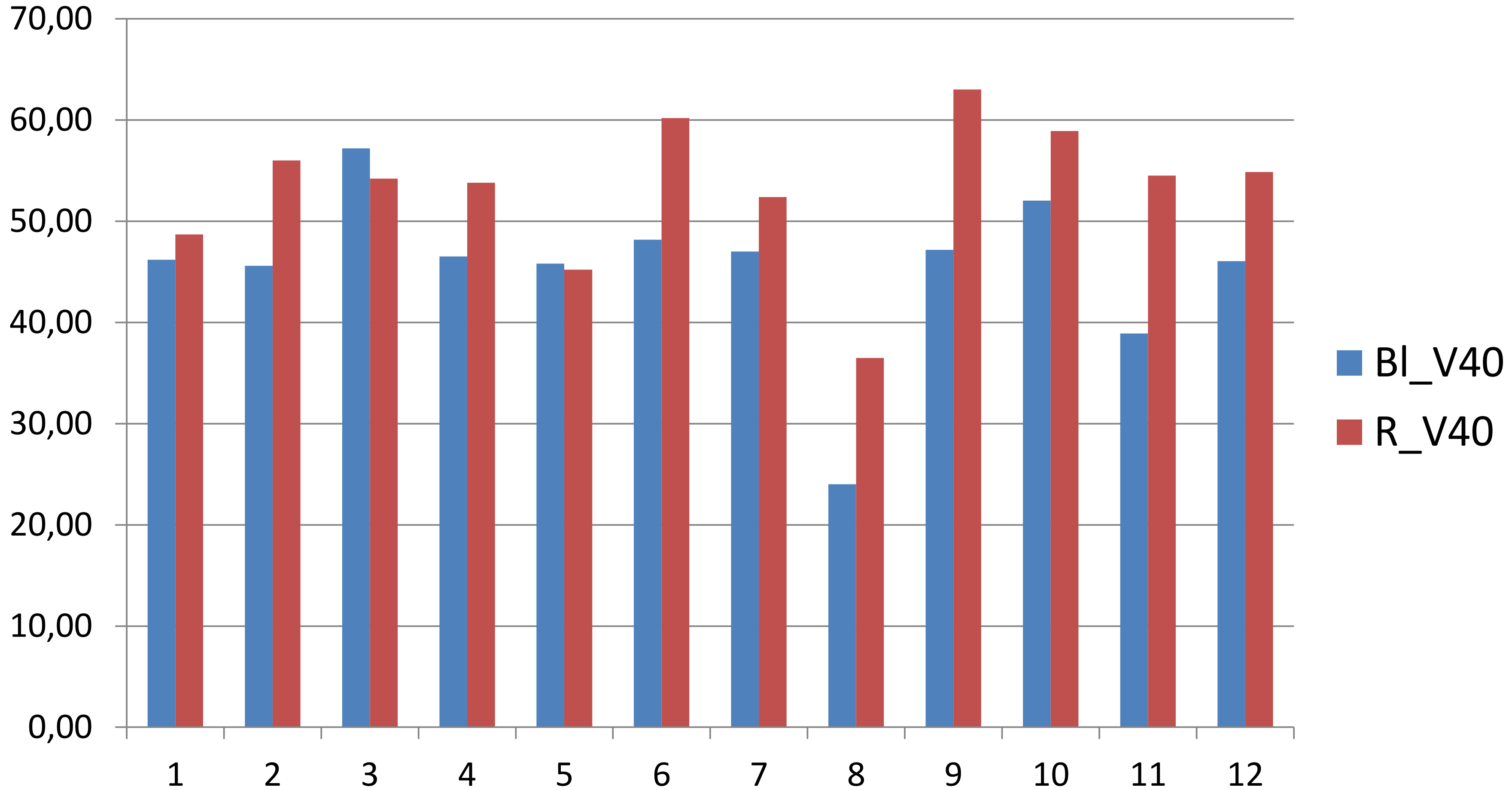
* Soft constraints which can be used as optimisation constraints as they are not based on clinical evidence.
The constraints are not supposed to be fulfilled by all patients, but rather by ~70-80% of the patients.

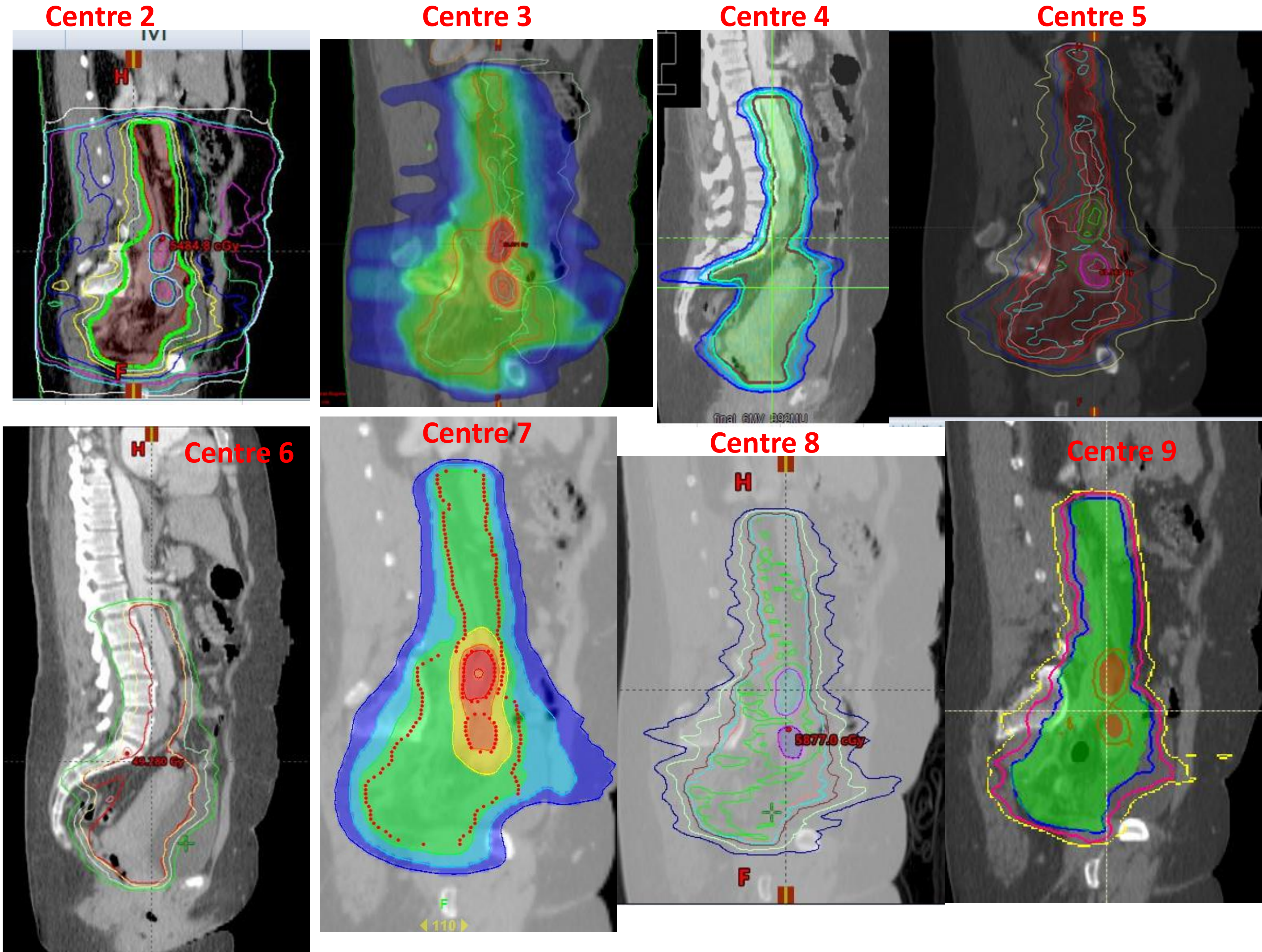
Bowel



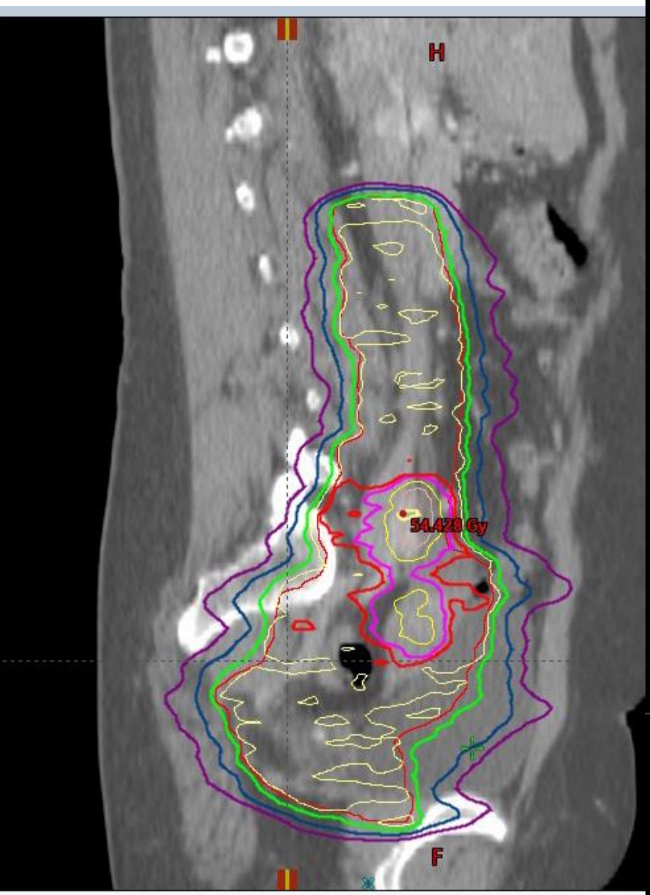
2000
1800
1600
1400
1200
1000
800
600
400
200
0
1
2
3
4
5
6
7
8
9
10
11
12
V15
V30
V40
V50

Bladder and Rectum – V40 Gy

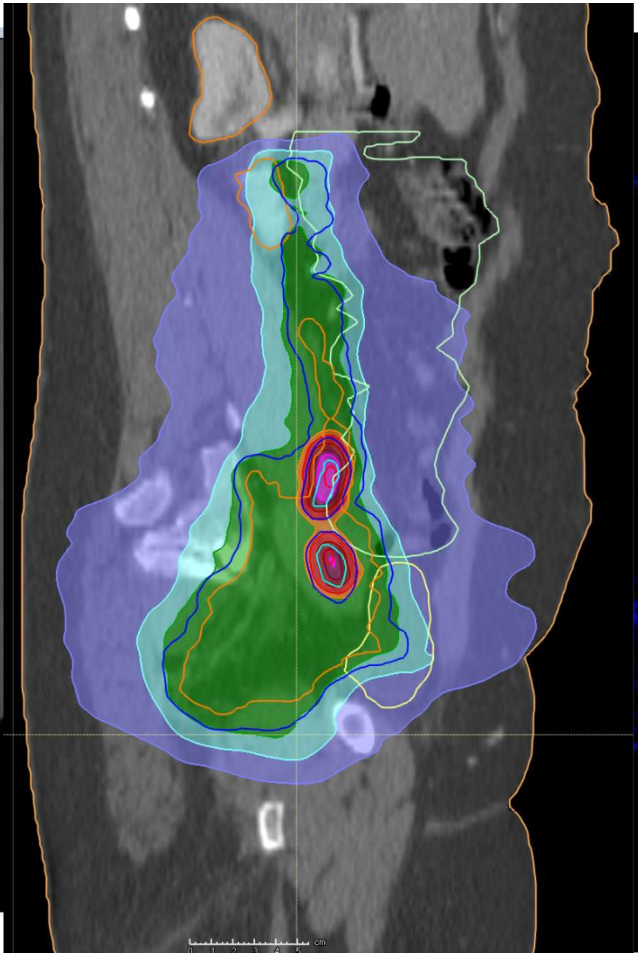



Centre 2
5484.8 cGy
Centre 3
Centre 4
Centre 5
Centre 6
Centre 7
Centre 8
5877.8 cGy
Centre 9

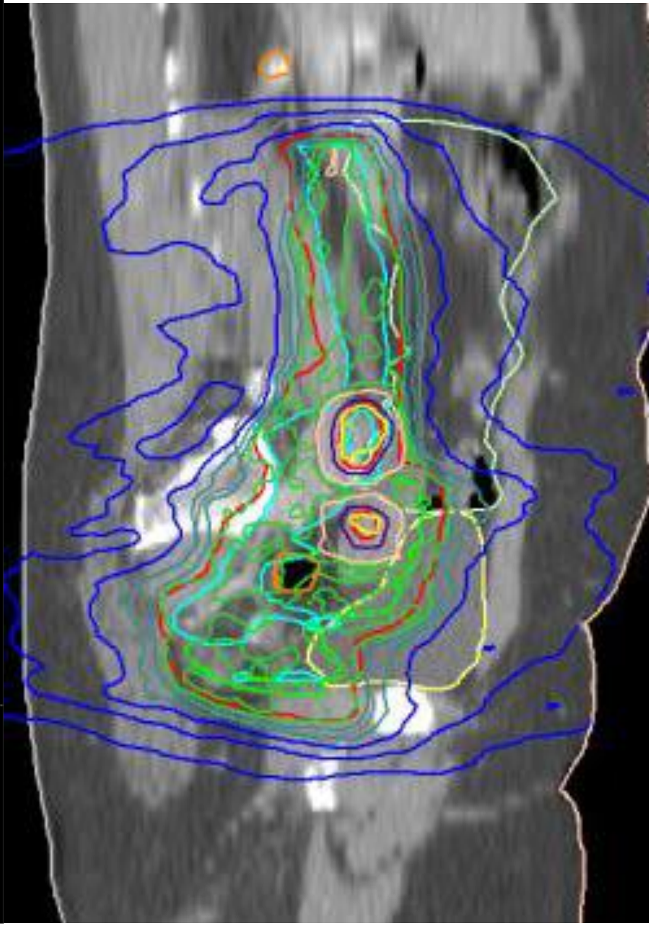
Centre 10



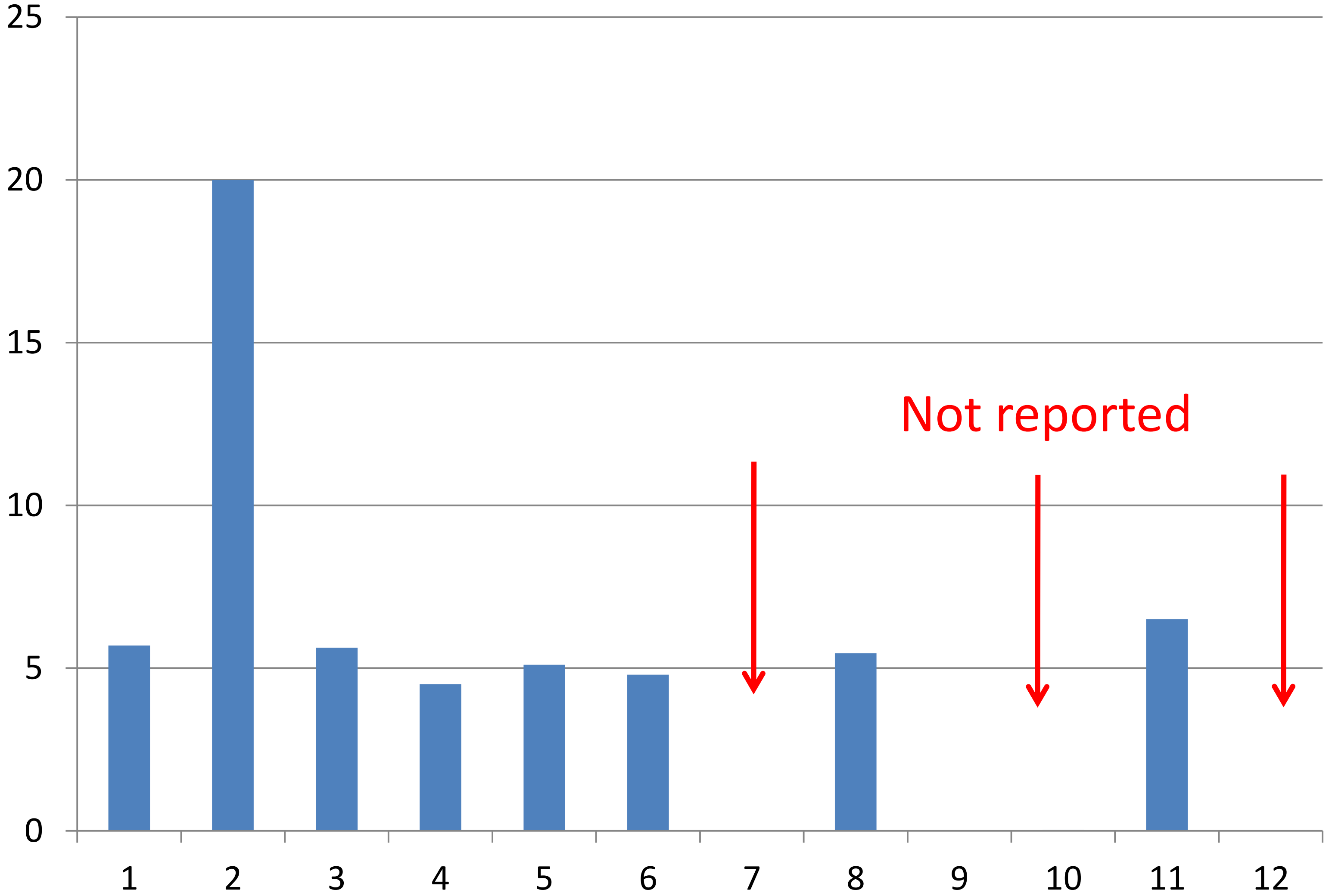
Centre 11



Centre 12

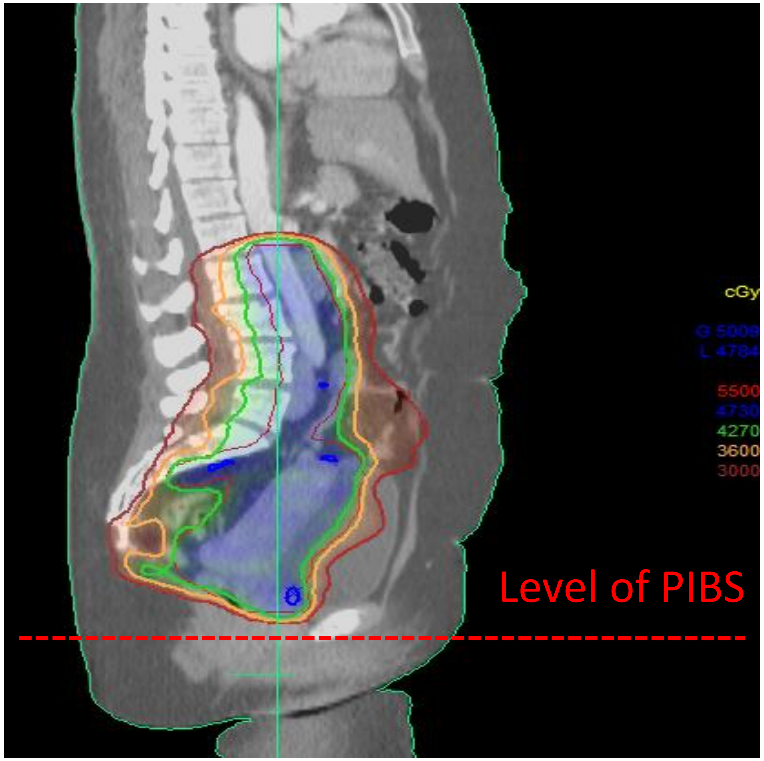


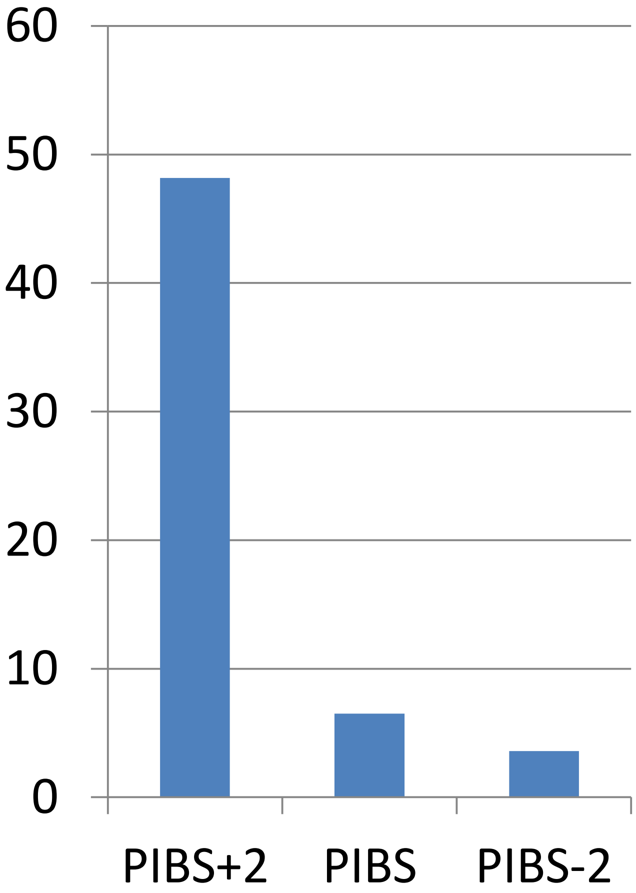
PIBS



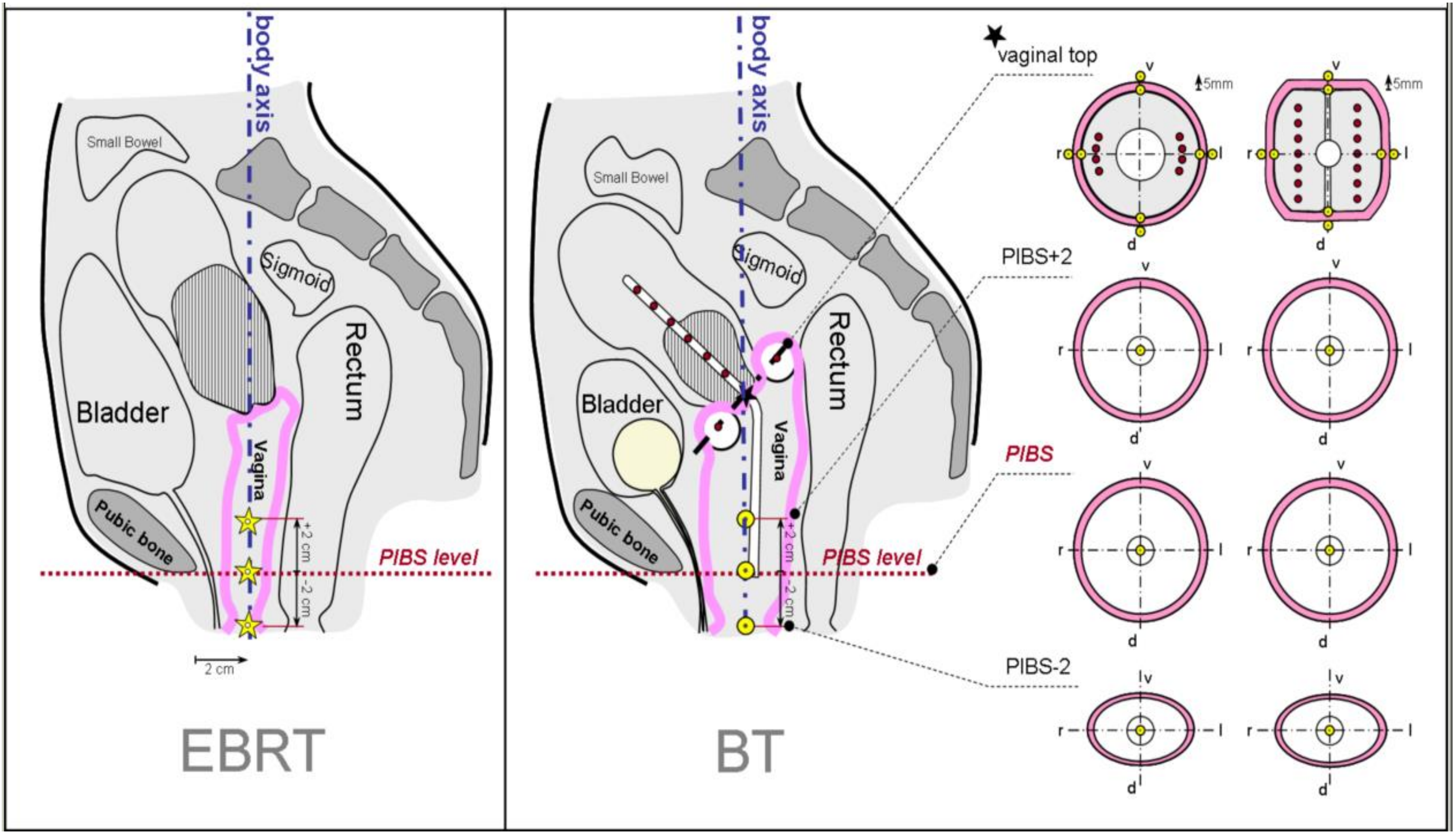
PIBS points

- Indicative of lower field border



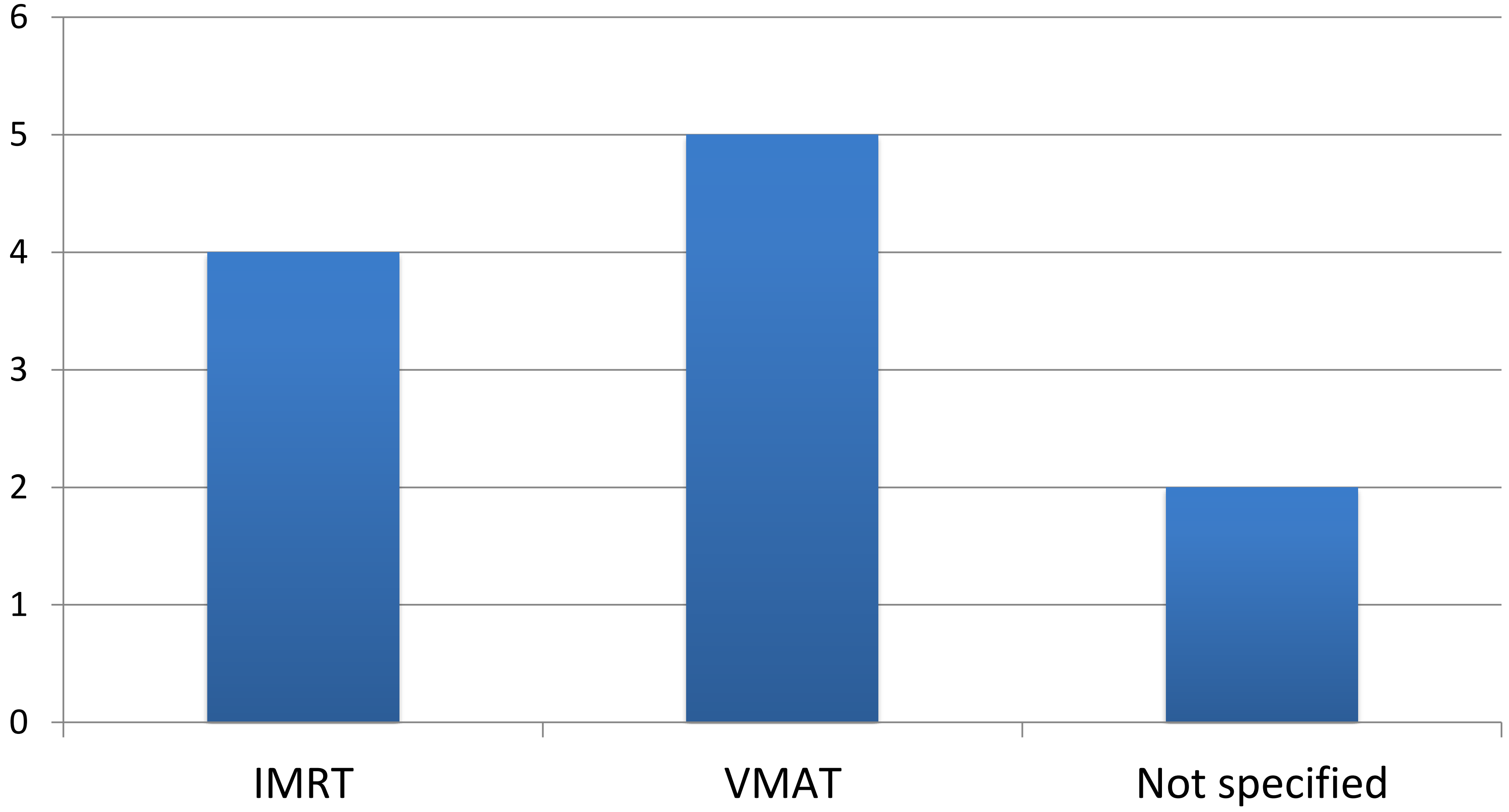


Vaginal Reference Points

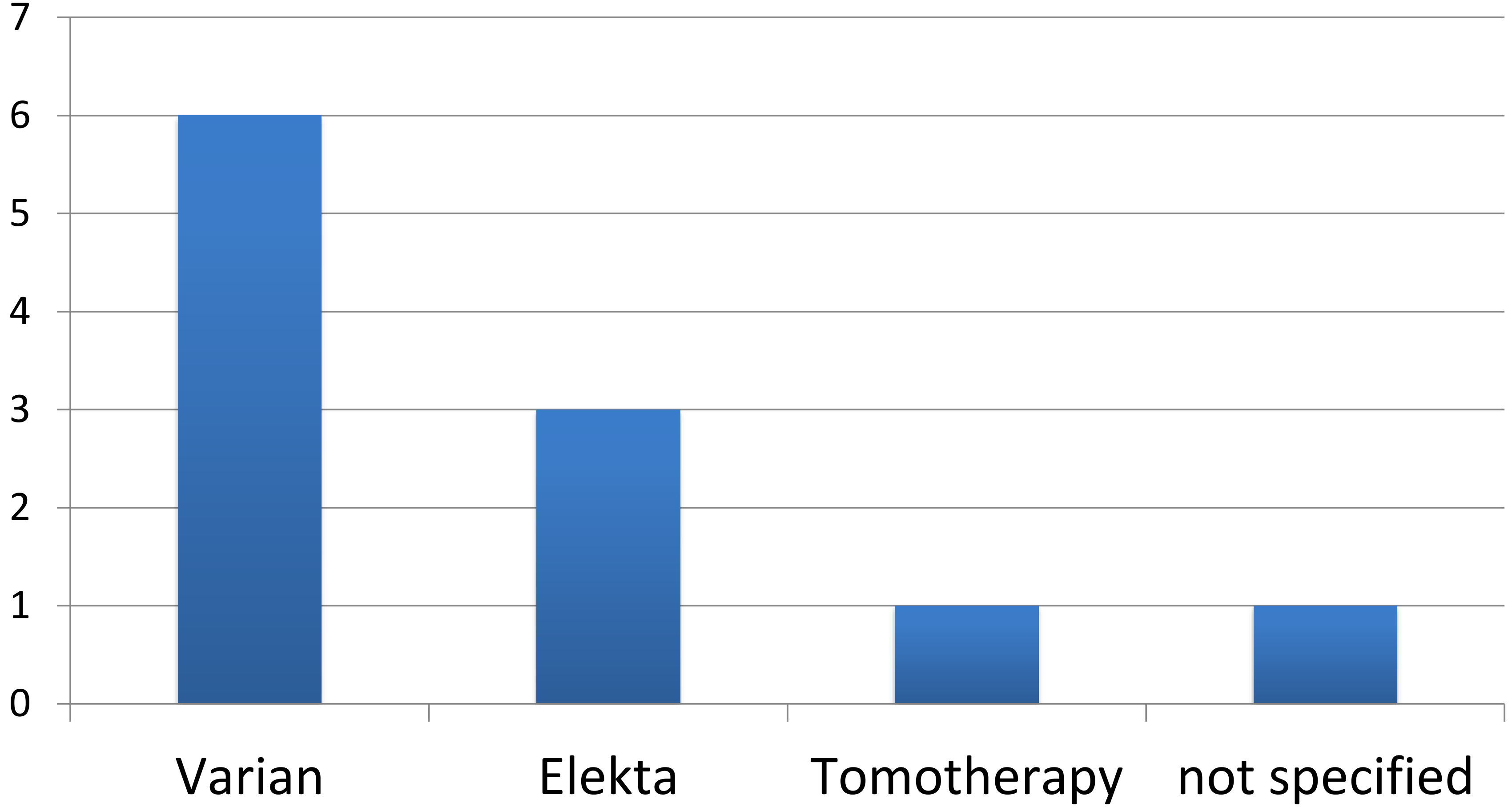


PIBS: Posterior-Inferior Border of Symphysis

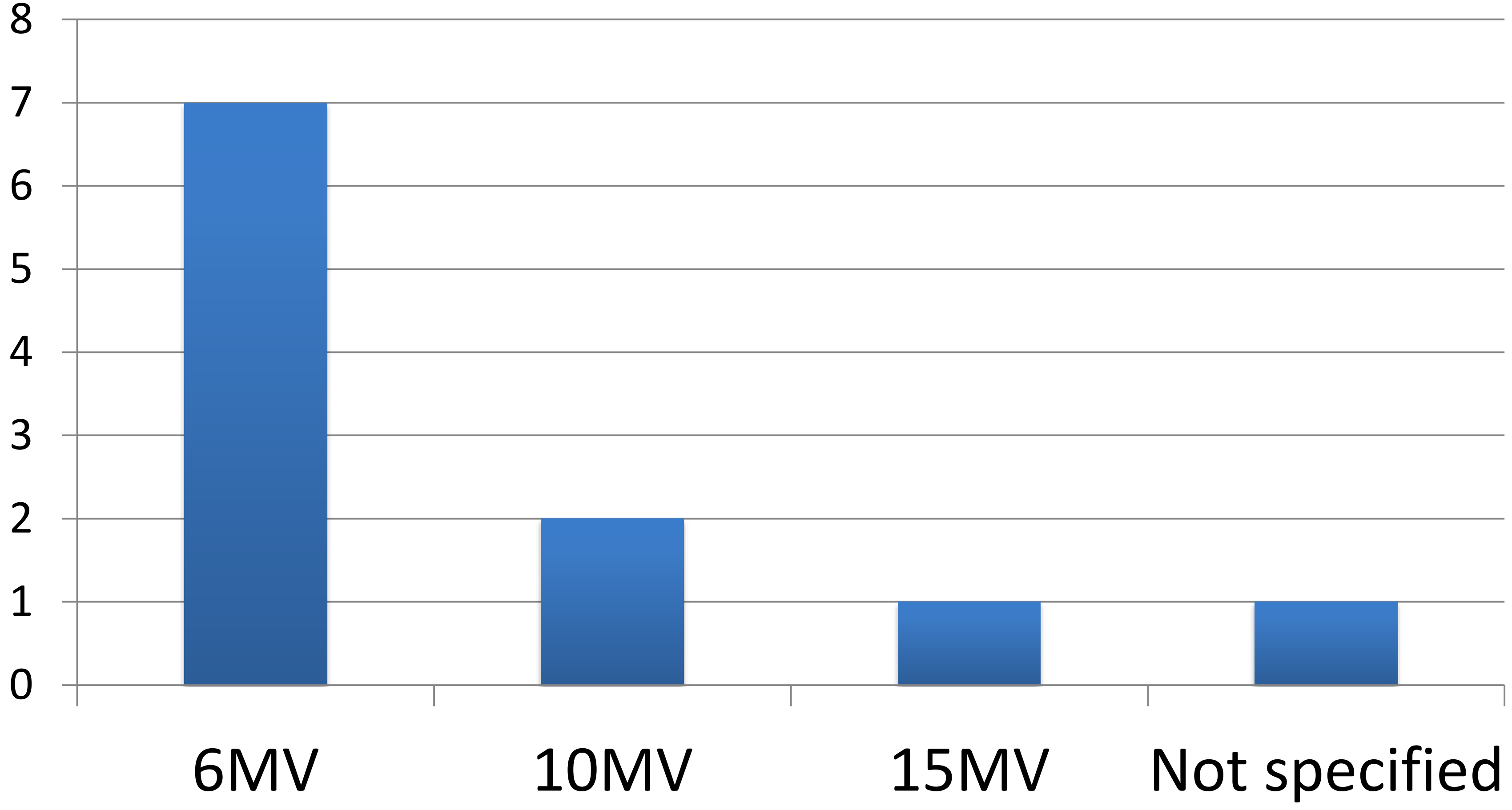
IMRT / VMAT



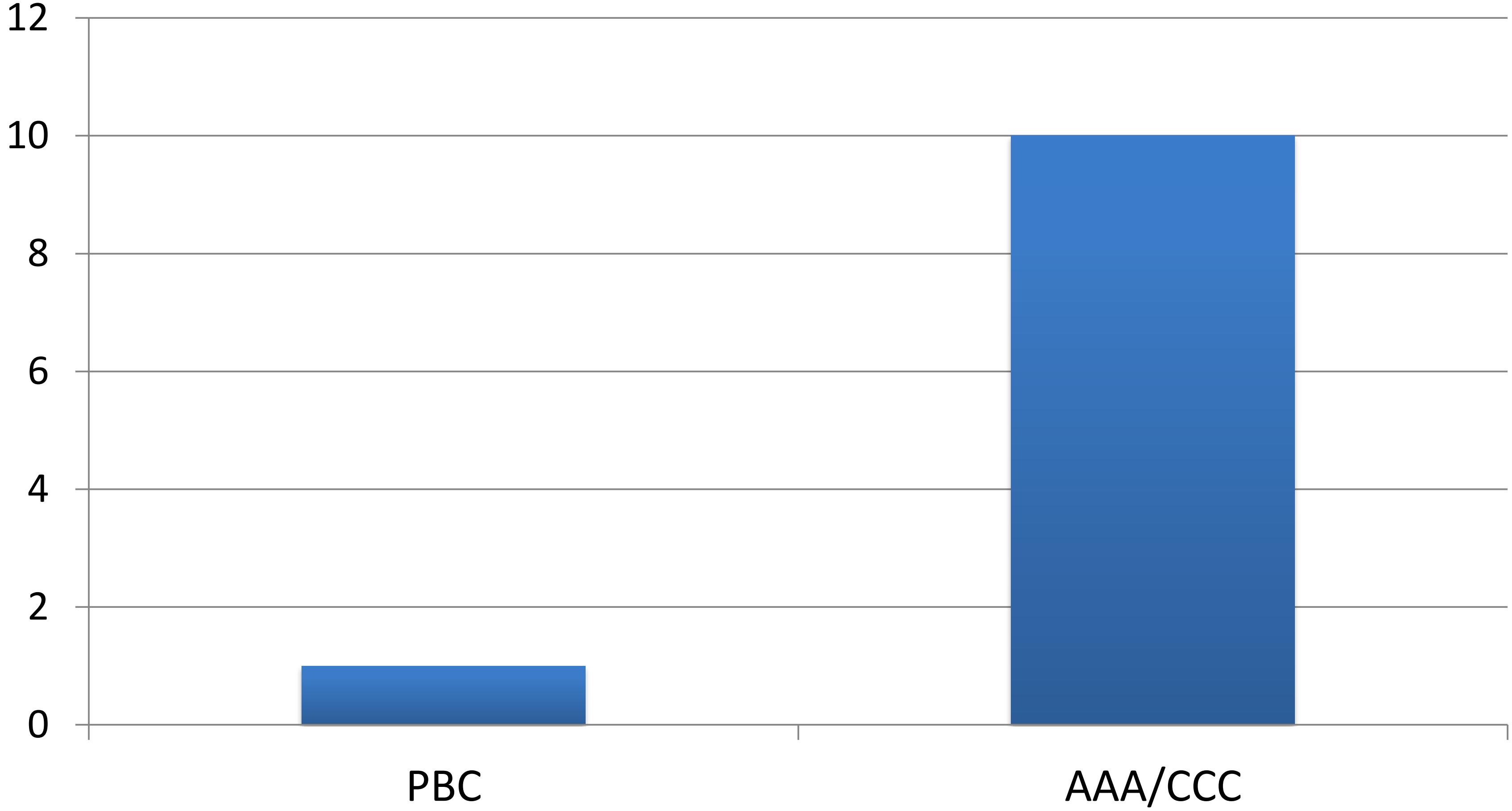
Treatment delivery machine



Energy



Dose calculation algorithm



Summary

- Target Coverage no major issues – mean dose was high
- Organ sparing - High low dose volumes
- V43Gy is 1844(306) cc.
- Inst -5 high PTV dose less V43 !!!
- PIBS and BT help contour - not reported by many.
- To avoid High enery(15 MV) and PBC for IMRT

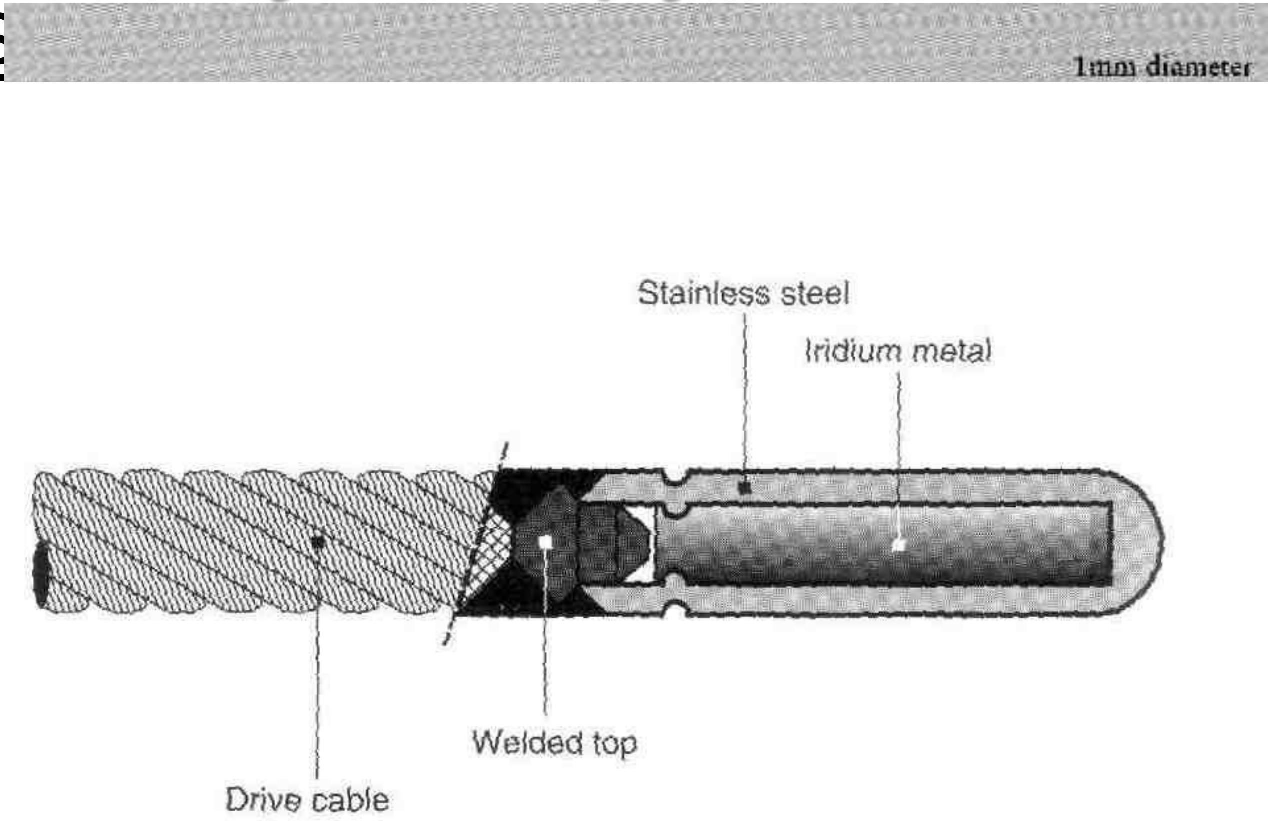
Basic brachytherapy physics and treatment planning principles

Taran Paulsen Hellebust
Medical physicist/Associate professor
Oslo University Hospital/The Norwegian Radium Hospital
Oslo, Norway

Sources in gynaecological brachytherapy

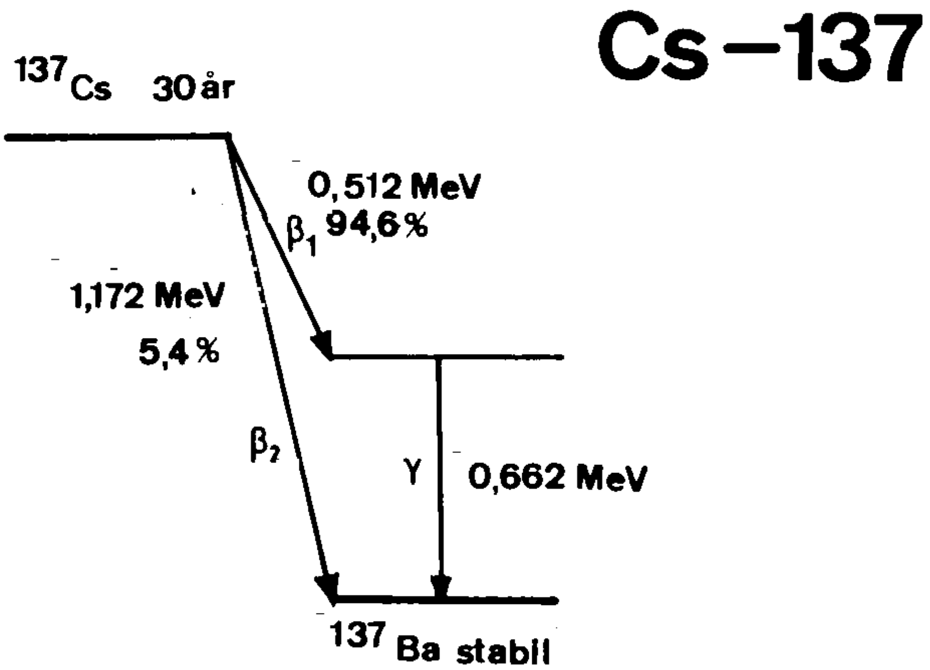
Source types

- sealed sourc
- different phy
  - HDR, L
  - tubes, p
  - small lir
  - steppin



Spectrum

- The source can emit alfa-, beta and/or gamma radiation
- What type and the energy of the radiation is unique for each nuclide



Physical properties of some nuclides

Radio Nuclide	Half time $T_{1/2}$	λ (s^{-1})	Average Photon Energy (keV)	Mass for 100 MBq (μg)
^{226}Ra	1600 y	$1.37\ 10^{-11}$	830	45
^{137}Cs	30 y	$7.27\ 10^{-10}$	662	31
^{60}Co	5.26 y	$4.18\ 10^{-9}$	1253	2.4
^{192}Ir	74.2 d	$1.08\ 10^{-7}$	380	0.29
^{125}I	60.2 d	$1.34\ 10^{-7}$	28	0.16
^{103}Pd	17 d	$4.72\ 10^{-7}$	21	0.04

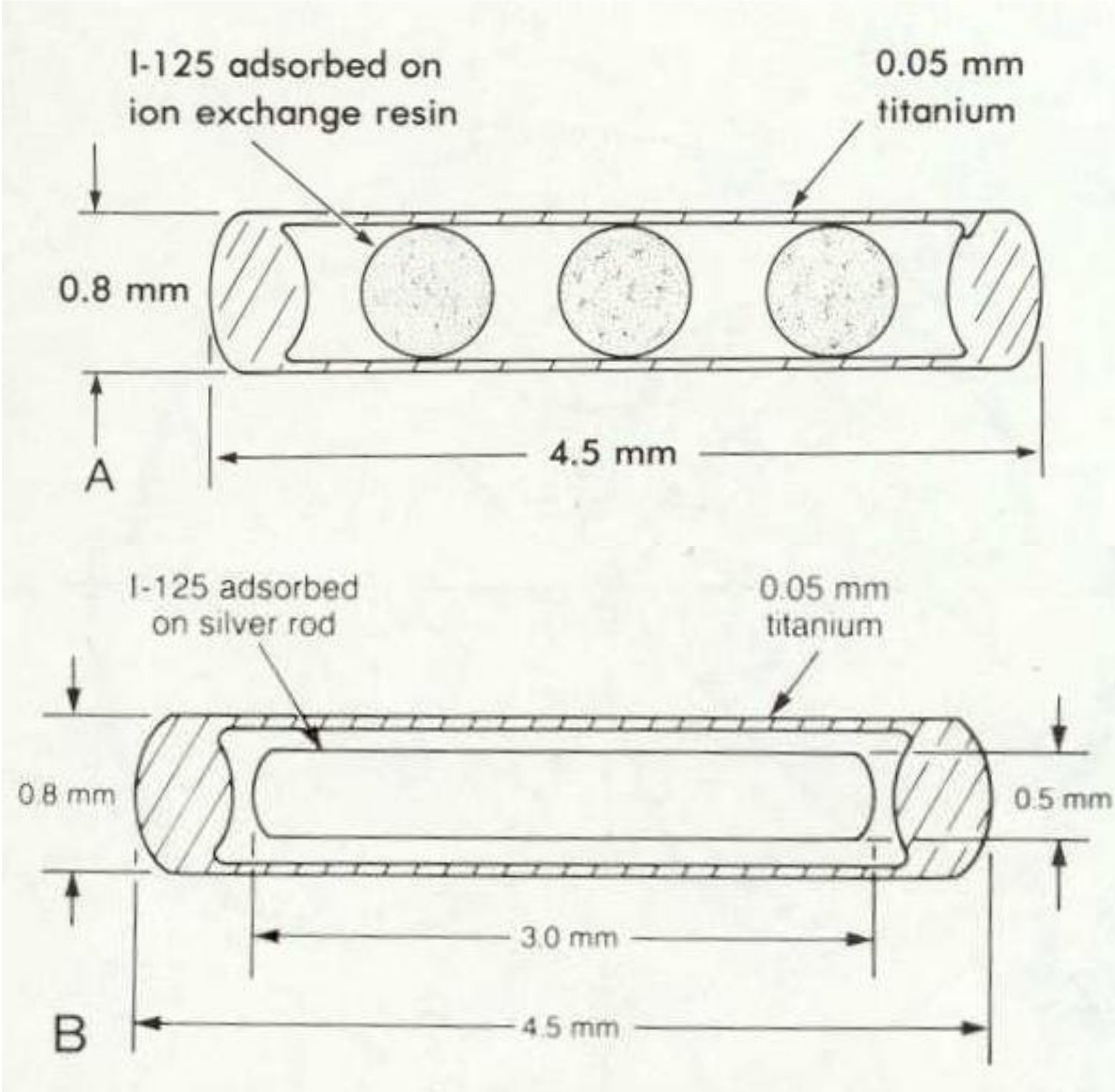
D Baltas, The physics of modern brachytherapy 2007

Source specification

Previously, source strength specification was based on "contents" , # of desintegrations per time unit

- 1 Ci (3.7 x 10^{10} s^{-1}) activity of 1g Ra-226
- in SI-units: 1 desintegration per sec = 1 Bq

  example: 1 mCi = 37 MBq


I-125 adsorbed on
ion exchange resin
0.05 mm
titanium
0.8 mm
4.5 mm
A
I-125 adsorbed
on silver rod
0.05 mm
titanium
0.8 mm
0.5 mm
3.0 mm
4.5 mm
B

Source specification

Previously, source strength specification was based on "contents" , # of desintegrations per time unit

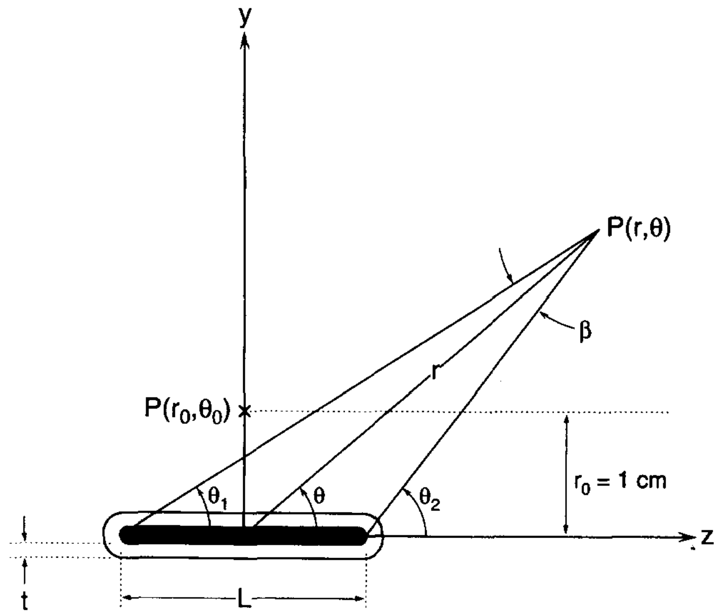
- 1 Ci ($3.7 \times 10^{10}\ s^{-1}$) activity of 1g Ra-226
- in SI-units: 1 desintegration per sec = 1 Bq

  example: 1 mCi = 37 MBq

Now, specification of sources is performed in terms of energy deposition, per unit of time at a given distance:

- in air kerma rate: $\mu Gy \cdot h^{-1}$ @ 1 m

Dose calculation



TG43 formalisme:

$$\dot{D}(r,\theta) = S_k \,\Lambda\, \frac{G(r,\theta)}{G(r_0,\theta_0)}\, g(r)\, F(r,\theta)$$

air kerma strength

dose rate constant

geometry function

radial dose function

anisotropy function

Dose calculation

y

TG43 dataset is given for a source type NOT for the nuclide

$$\dot{D}(r,\theta) = S_k \, \Lambda \, \frac{G(r,\theta)}{G(r_0,\theta_0)} \, g(r) \, F(r,\theta)$$

air kerma strength

dose rate constant

geometry function

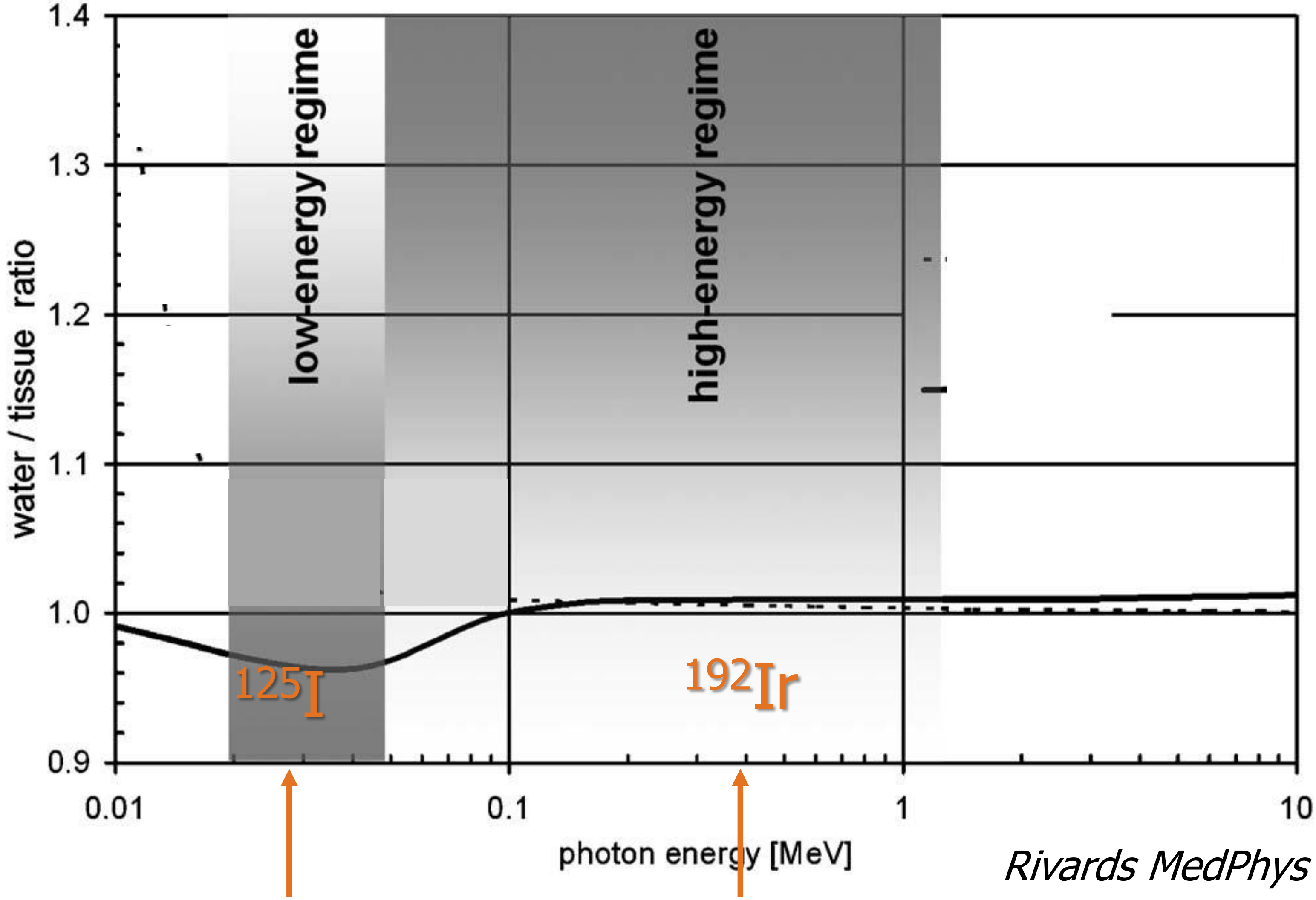
radial dose function

anisotropy function

Limitations of TG43 formalism

- Datasets used in the TG-43 are obtained
  - in a water phantom
  - with a fixed volume (sphere with 30 cm in diameter)
- This means that the TG43 formalism does NOT account for
  - different density of in the irradiated tissue
  - the lack of scatter material if the implant is located close to the skin surface

Ratio of absorbed dose in water and tissue @ 1 cm



Rivards MedPhys 2009

Is density correction important?

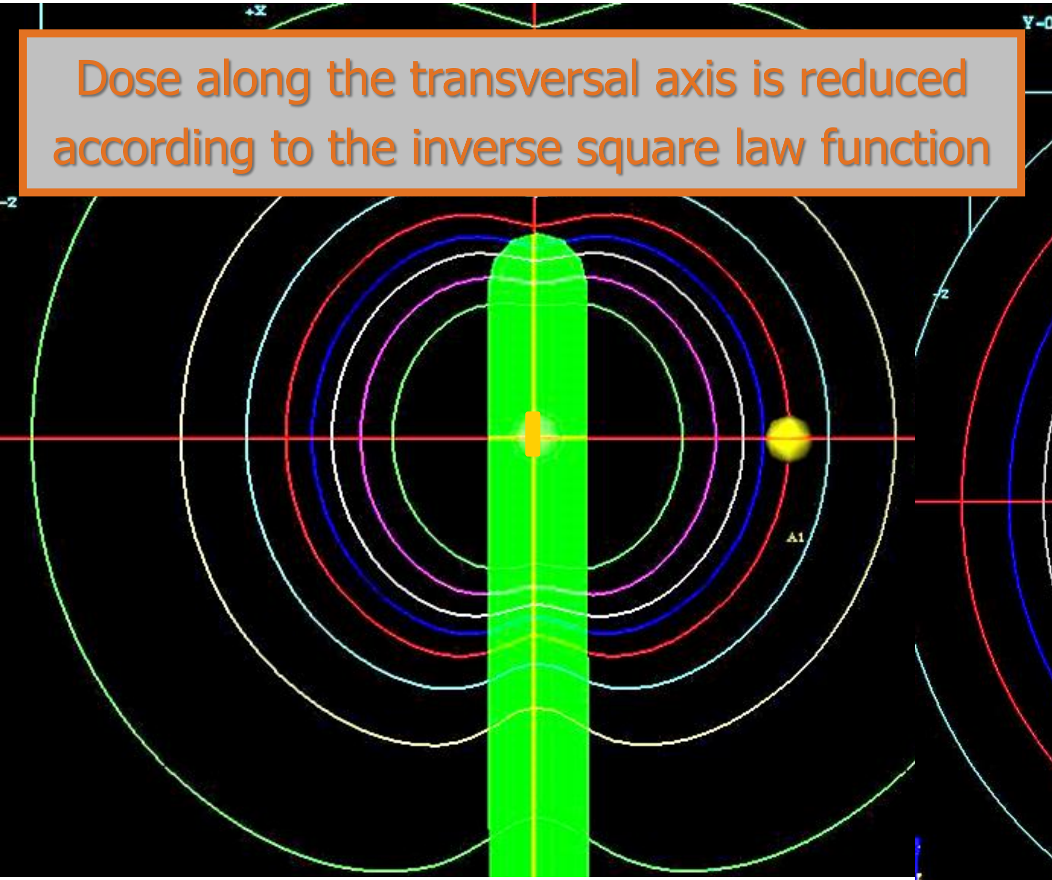
Anatomic site	Source energy	
GYN	High (e.g. ^{192}Ir, ^{137}Cs)	No*
Prostate	High (e.g. ^{192}Ir)	No
	Low (e.g. ^{125}I)	Yes

* If shielded applicators are used, density correction is important!

MR-based treatment planning will work well for GYN with ^{192}Ir or ^{137}Cs sources, since density correction is not important

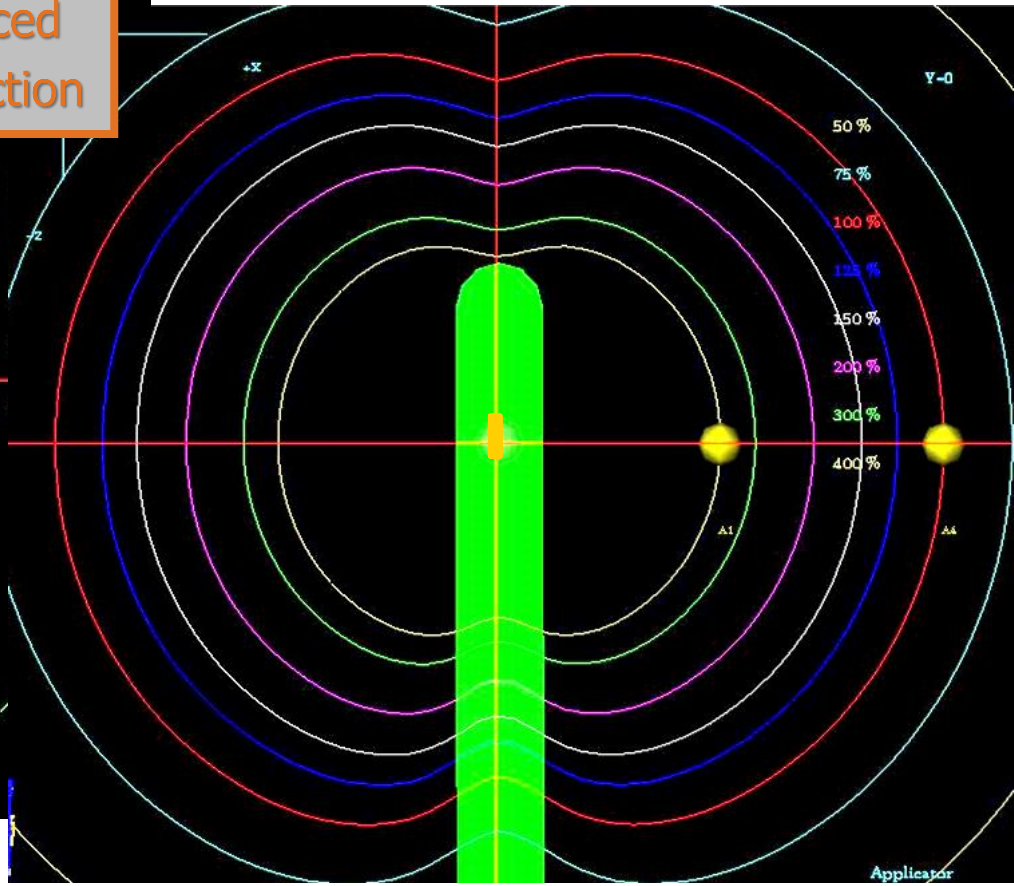
Distribution around one single Ir-source

Dose along the transversal axis is reduced according to the inverse square law function



1 Gy at 1 cm distance for a source strength 4.21 cGy/hcm2

15.6 sec

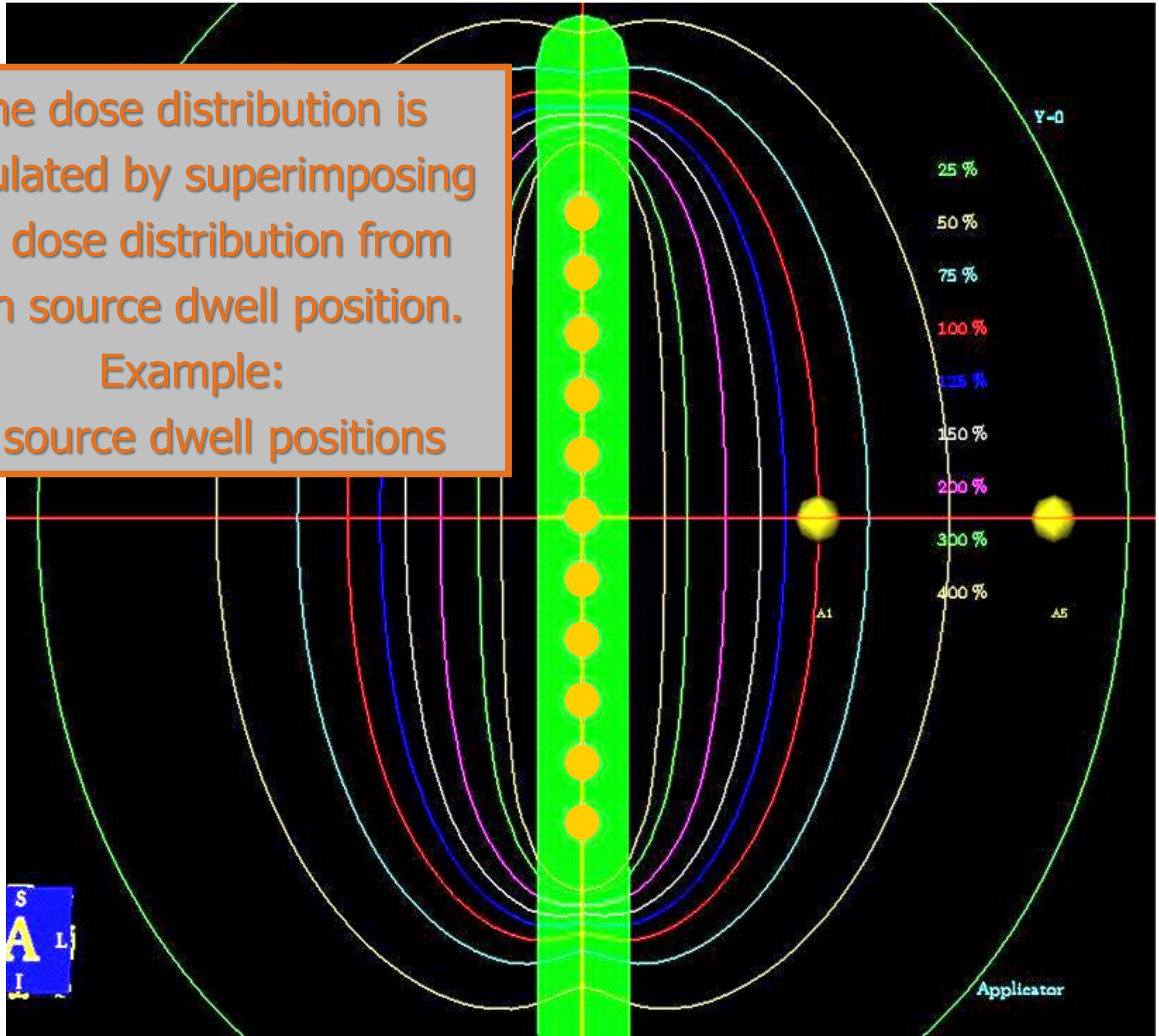


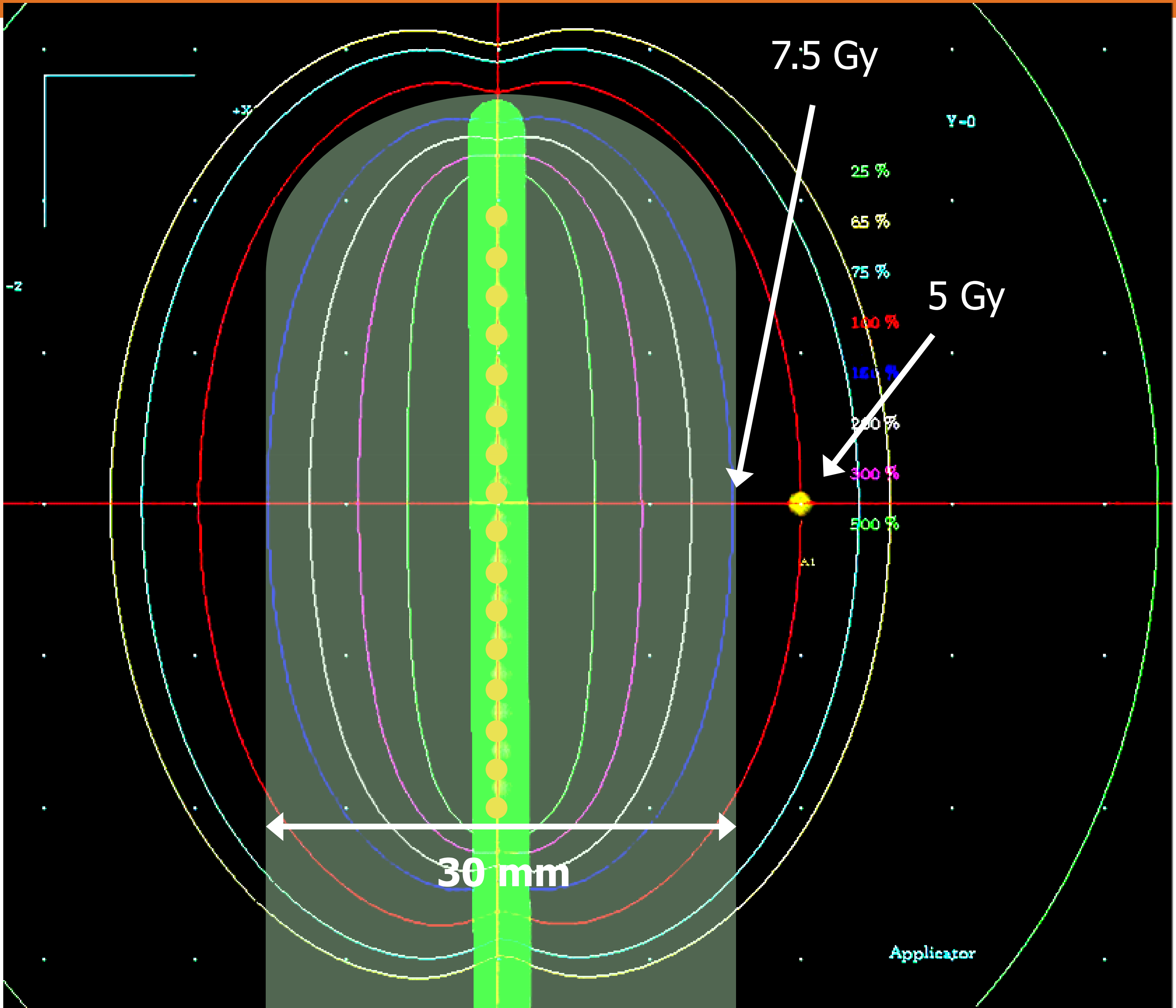
1 Gy at 2 cm distance for a source strength 4.21 cGy/hcm2

62.4 sec

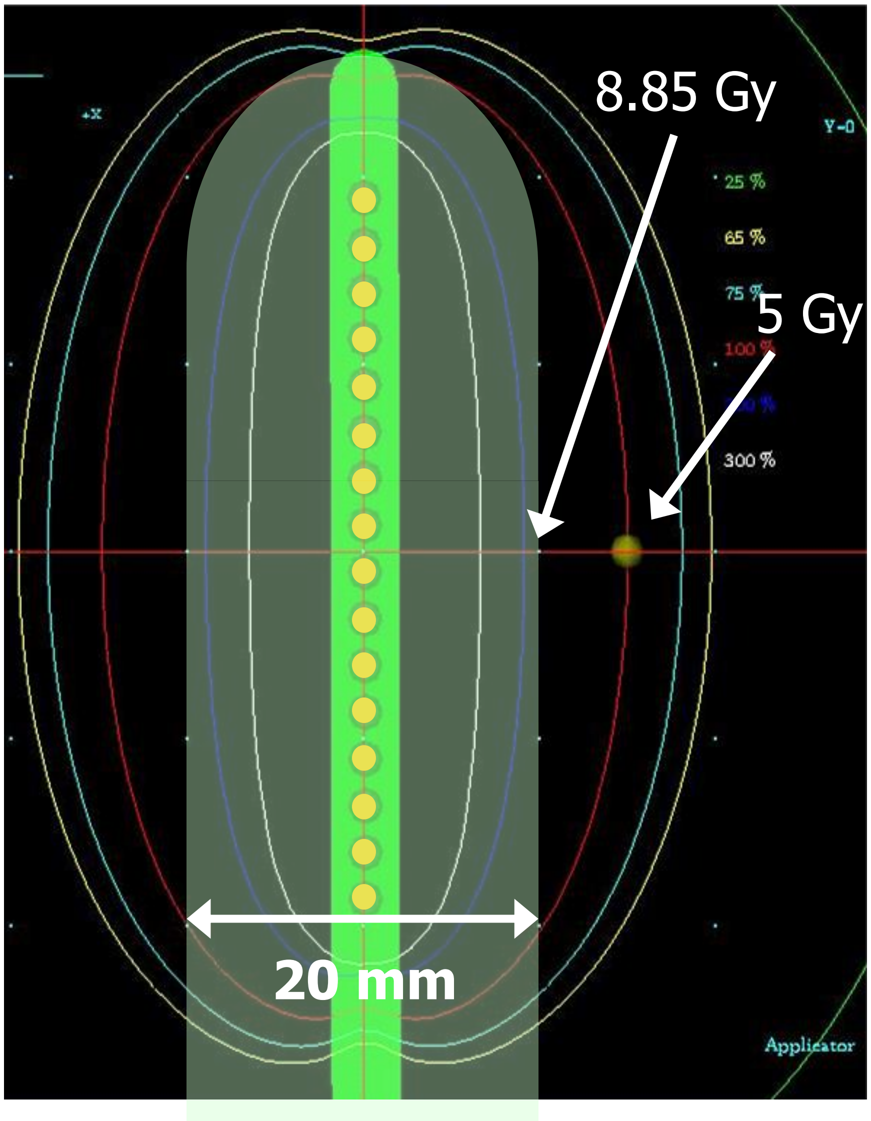
Distribution around a stepping source

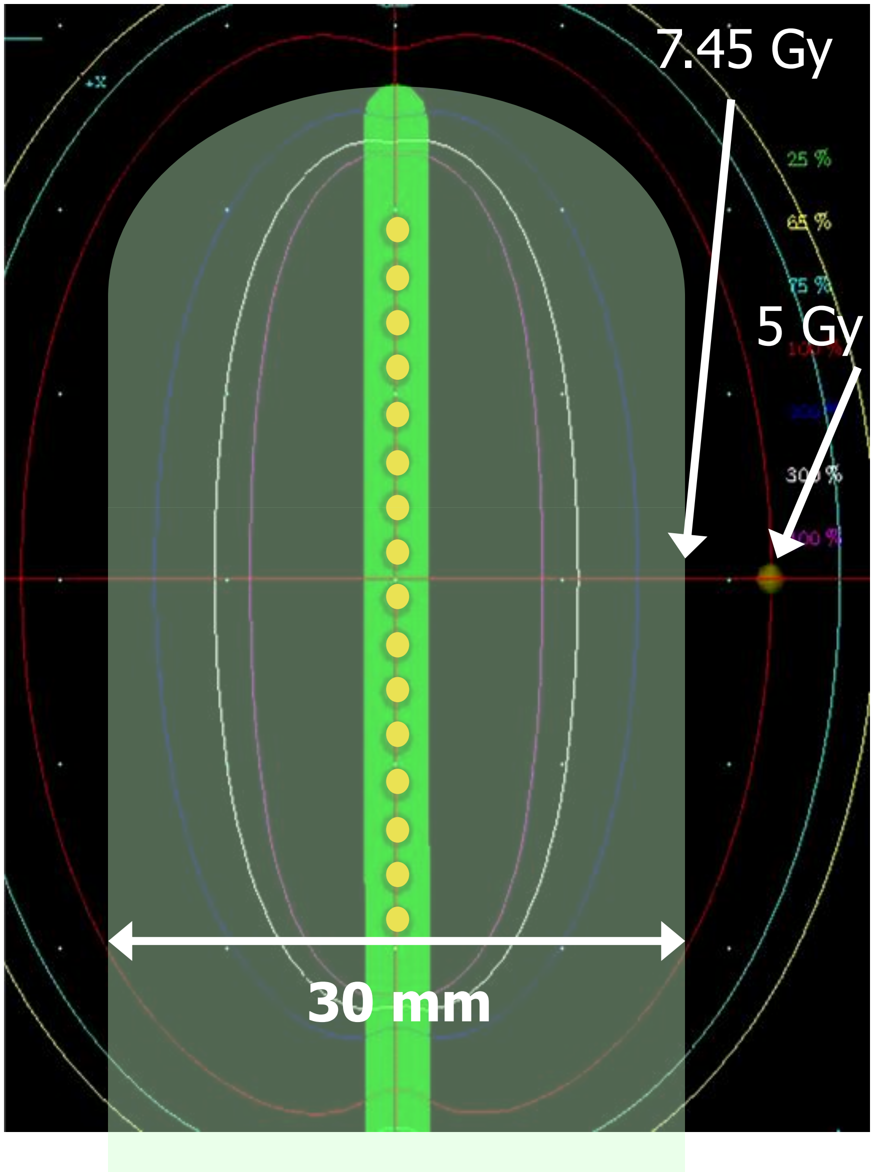
The dose distribution is calculated by superimposing the dose distribution from each source dwell position.
Example:
11 source dwell positions

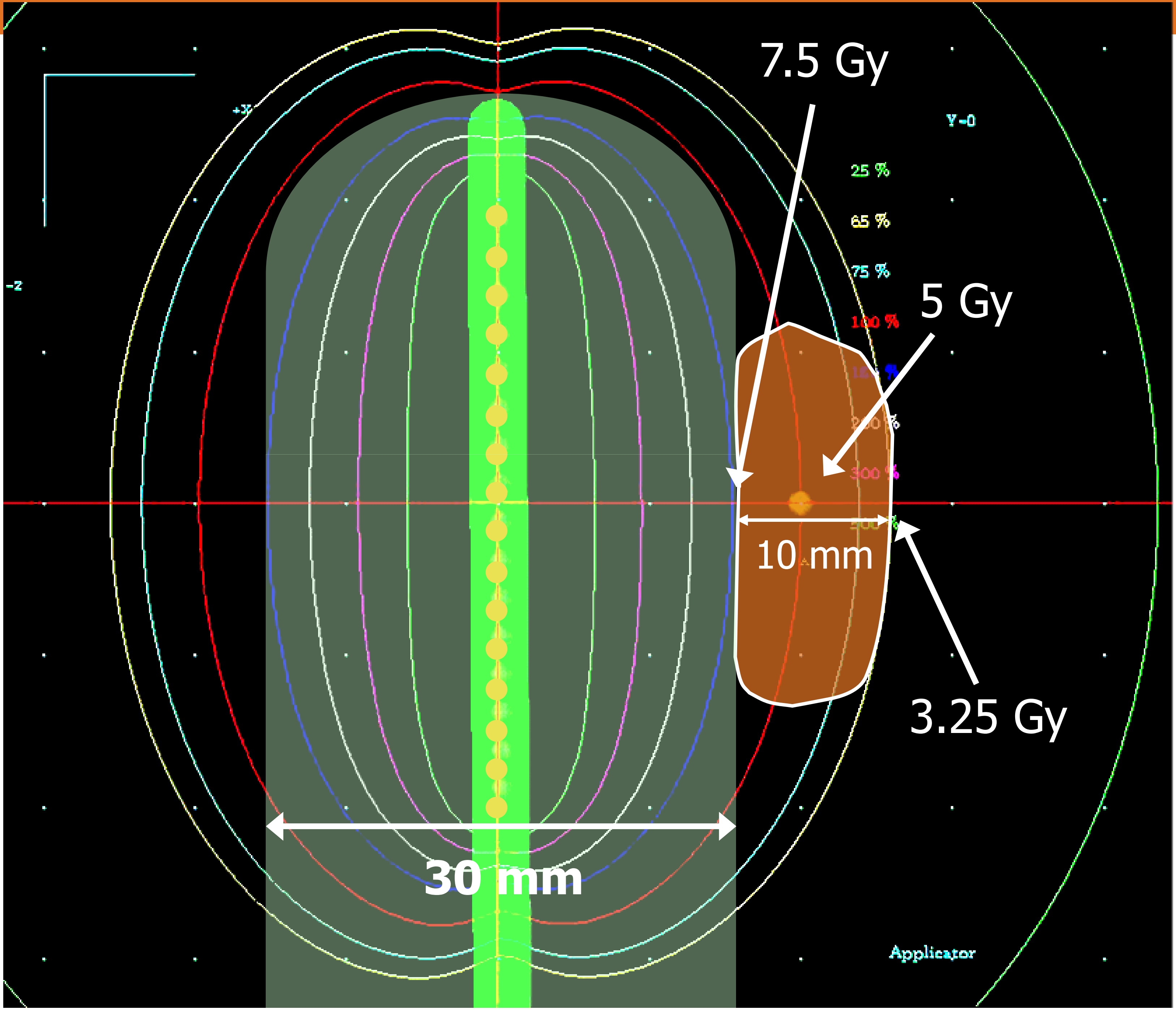



7.5 Gy
Y=0
25 %
65 %
75 %
5 Gy
100 %
200 %
300 %
500 %
+X
-Z
A1
30 mm
Applicator

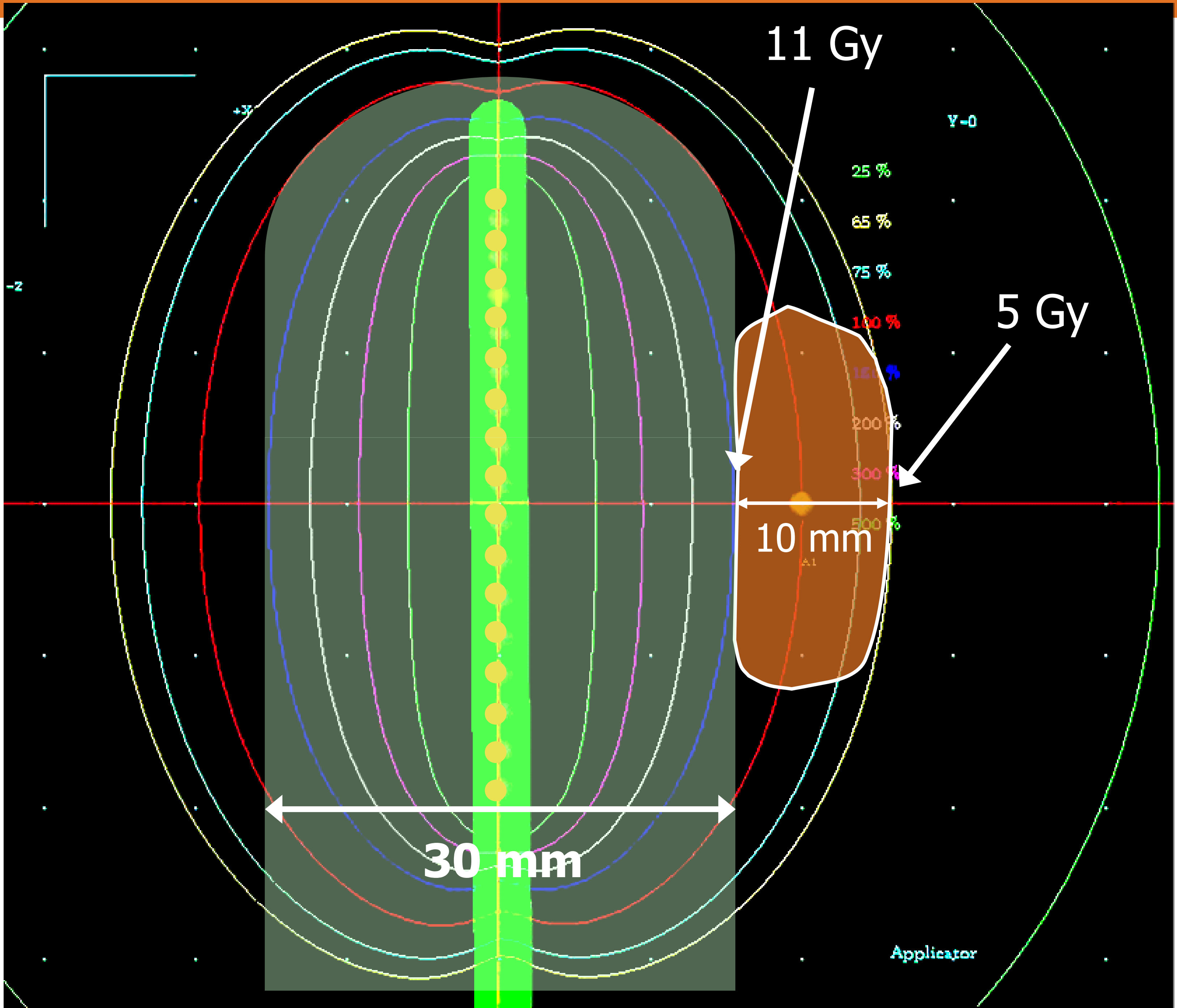
The surface dose is depending on applicator diameter

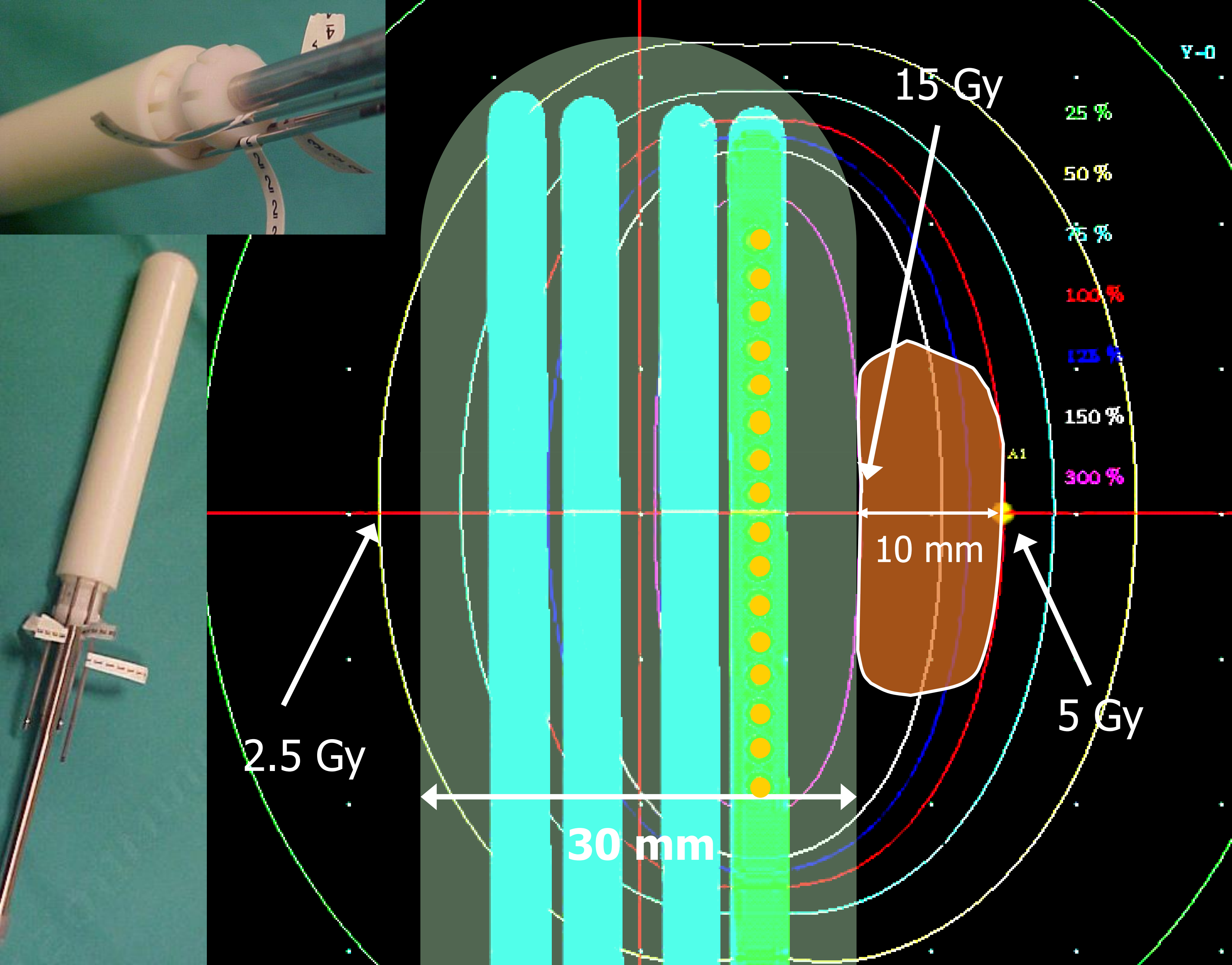






7.5 Gy
5 Gy
3.25 Gy
10 mm
30 mm
25 %
65 %
75 %
100 %
Applicator

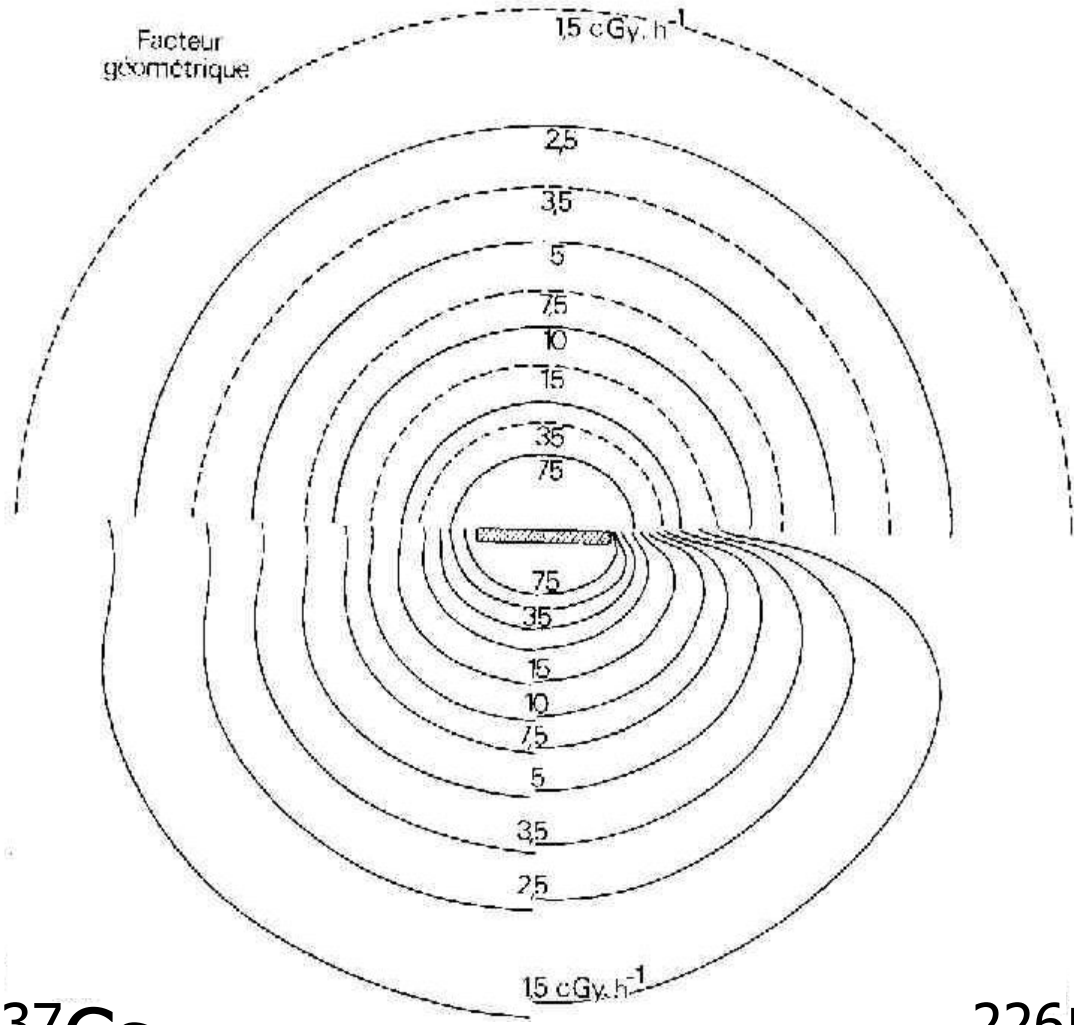

11 Gy
5 Gy
10 mm
30 mm
Y-0
25 %
65 %
75 %
100 %
200 %
300 %
500 %
Applicator


Y-0
15 Gy
25 %
50 %
75 %
100 %
125 %
150 %
300 %
10 mm
5 Gy
2.5 Gy
30 mm

Anisotropy

Without anisotropy correction

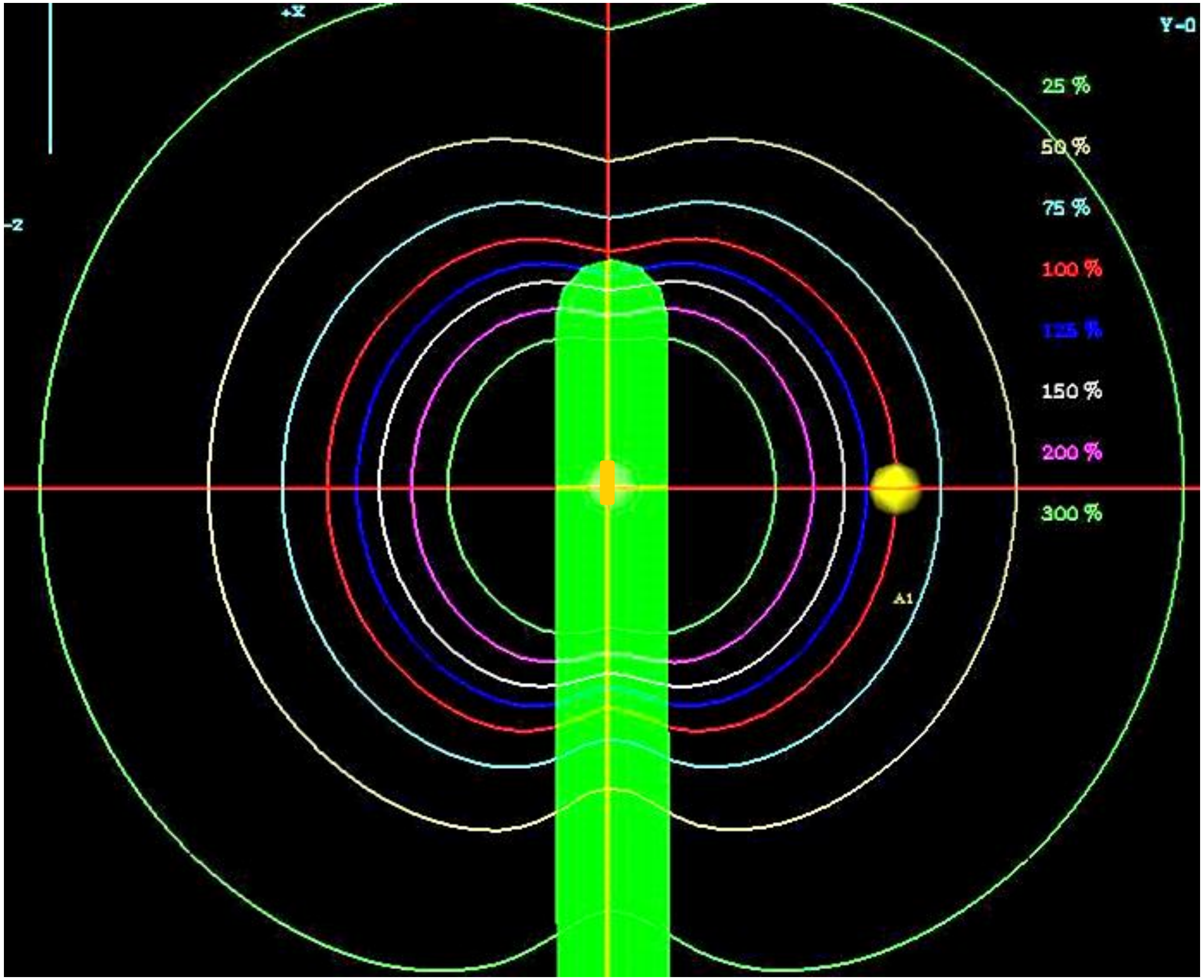
With anisotropy correction



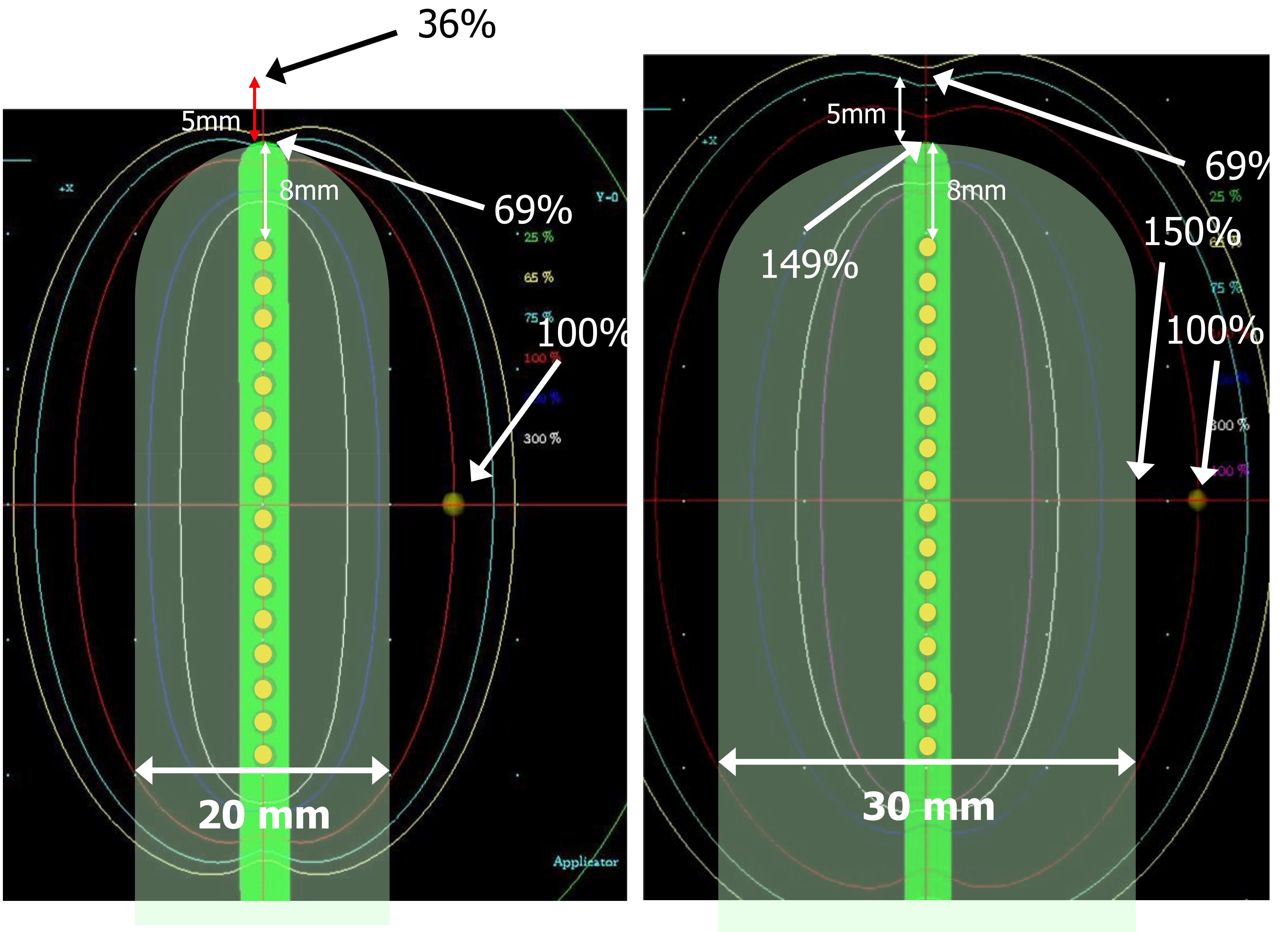
^{137}Cs

^{226}Ra

Anisotropy



^{192}Ir



36%
5mm
8mm
69%
25 %
65 %
75 %
100%
100 %
300 %
20 mm
Applicator
5mm
69%
8mm
149%
150%
25 %
75 %
100%
300 %
30 mm

Applicator commissioning, reconstruction, geometry and fusion

Jamema Swamidas PhD,

Assistant Professor

Department of Medical Physics

Tata Memorial Hospital,

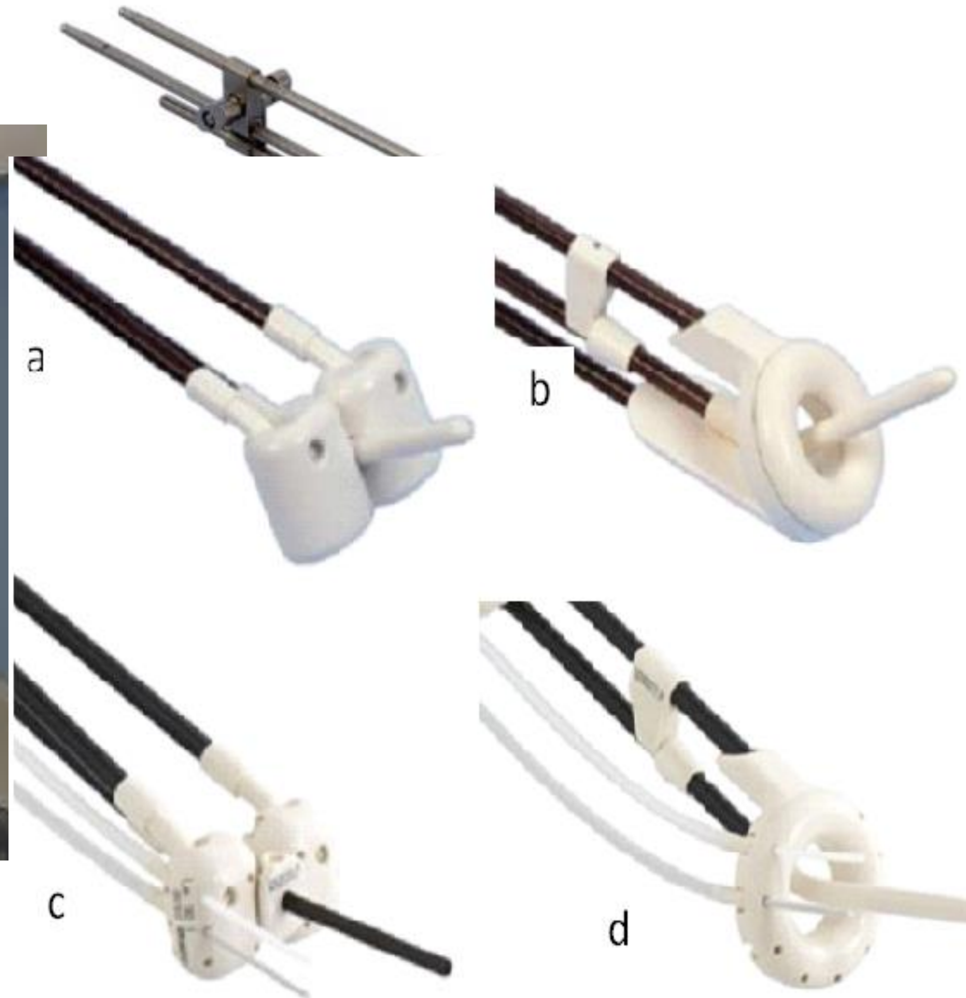
Mumbai,

India

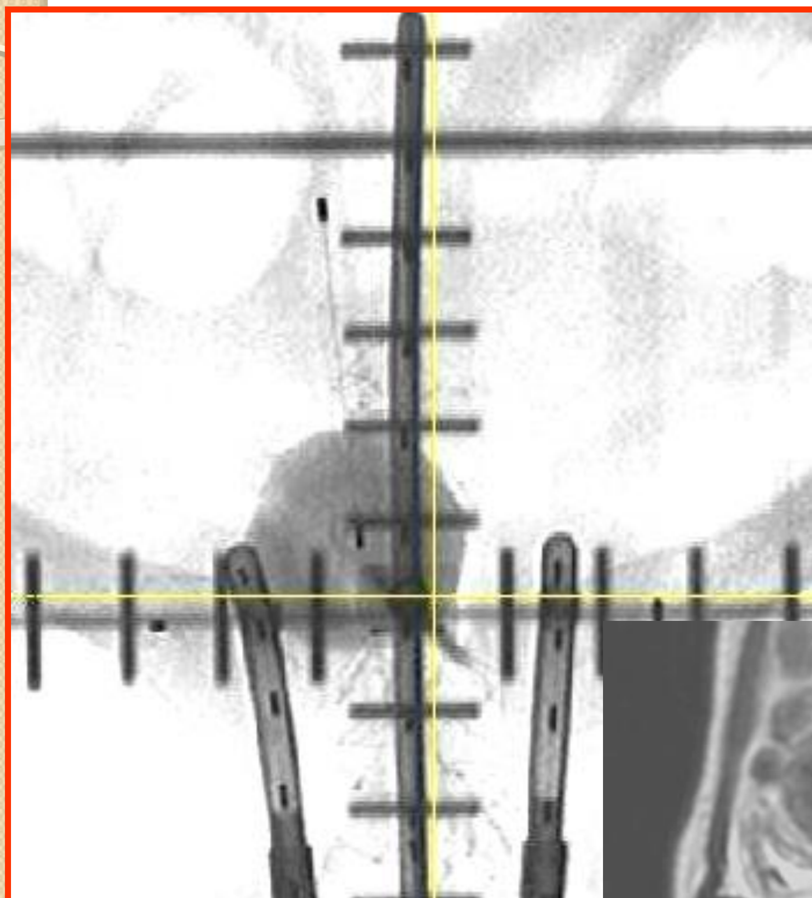
ESTRO

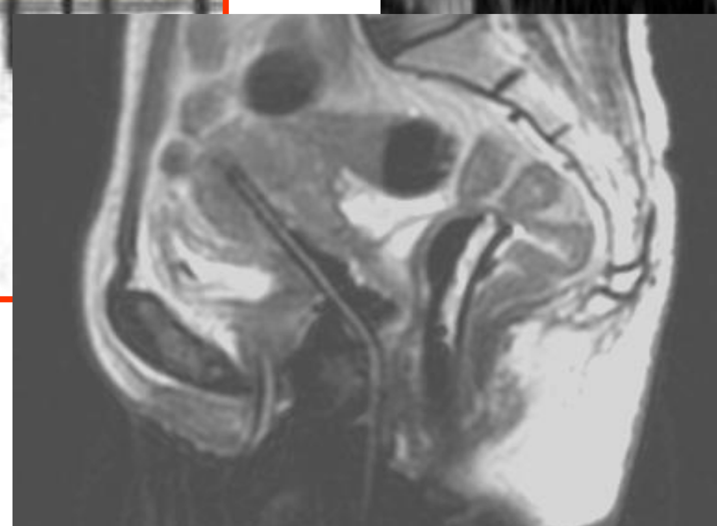
European Society for Therapeutic Radiology and Oncology

Commissioning



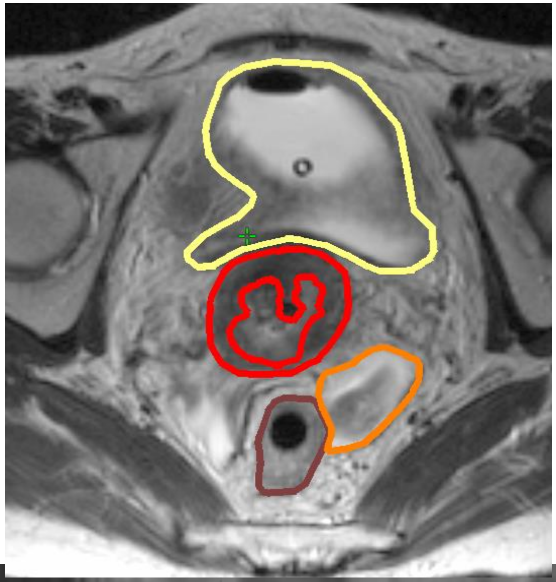
Why so much fuss about Applicator commissioning /reconstruction in 3D BT?

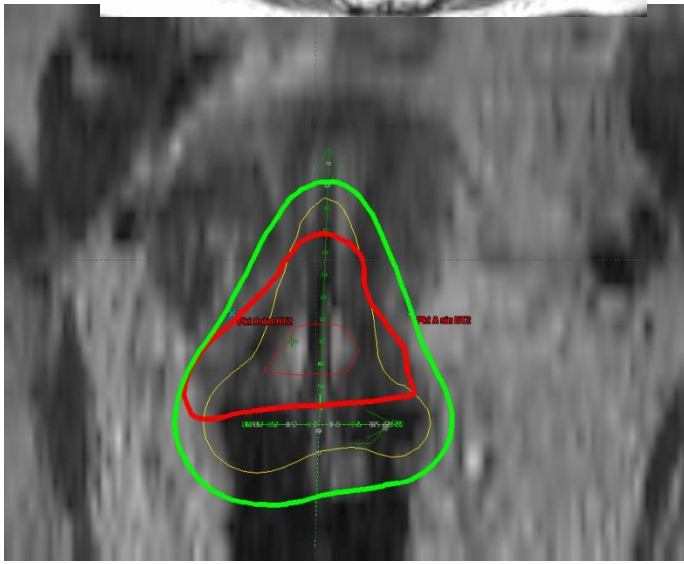




Clinical consequences

- 10 intracavitary cervical cancer patients
- MR scan with ring applicator in situ
- Contouring on transversal T2 images:
  - HR-CTV
  - Bladder
  - Rectum
  - Sigmoid
- Manual 3D dose optimisation
- DVH parameters:
  - D100, D90 for HR-CTV
  - D_{2cc} for bladder, rectum, sigmoid



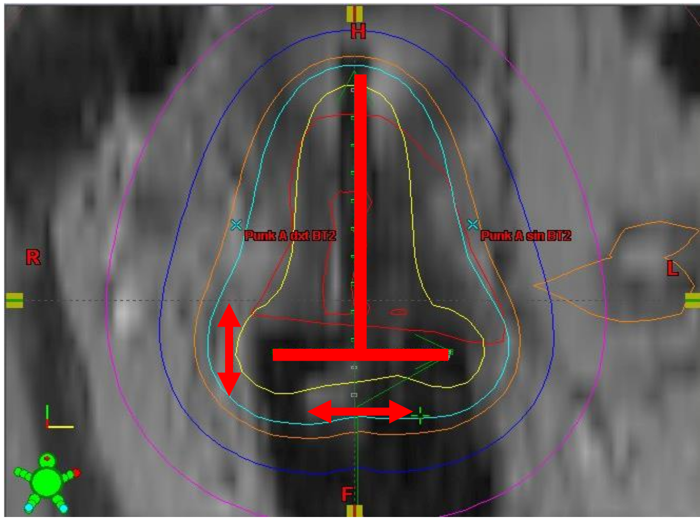


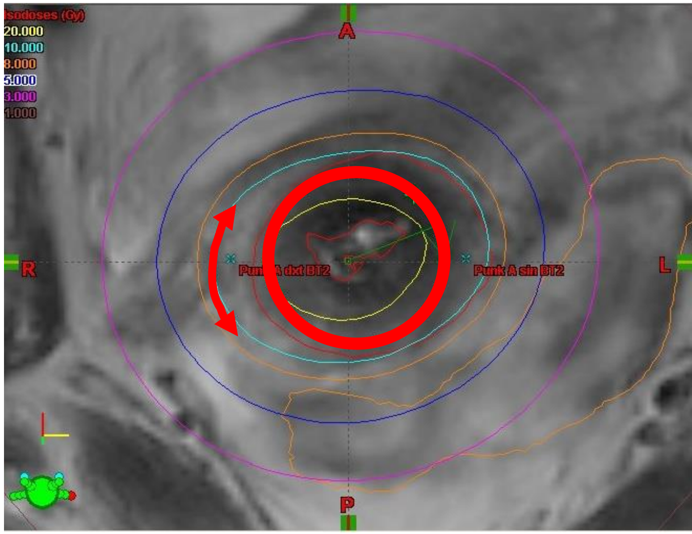
Tanderup et al, R&O 2008

Simulation of un-certainty

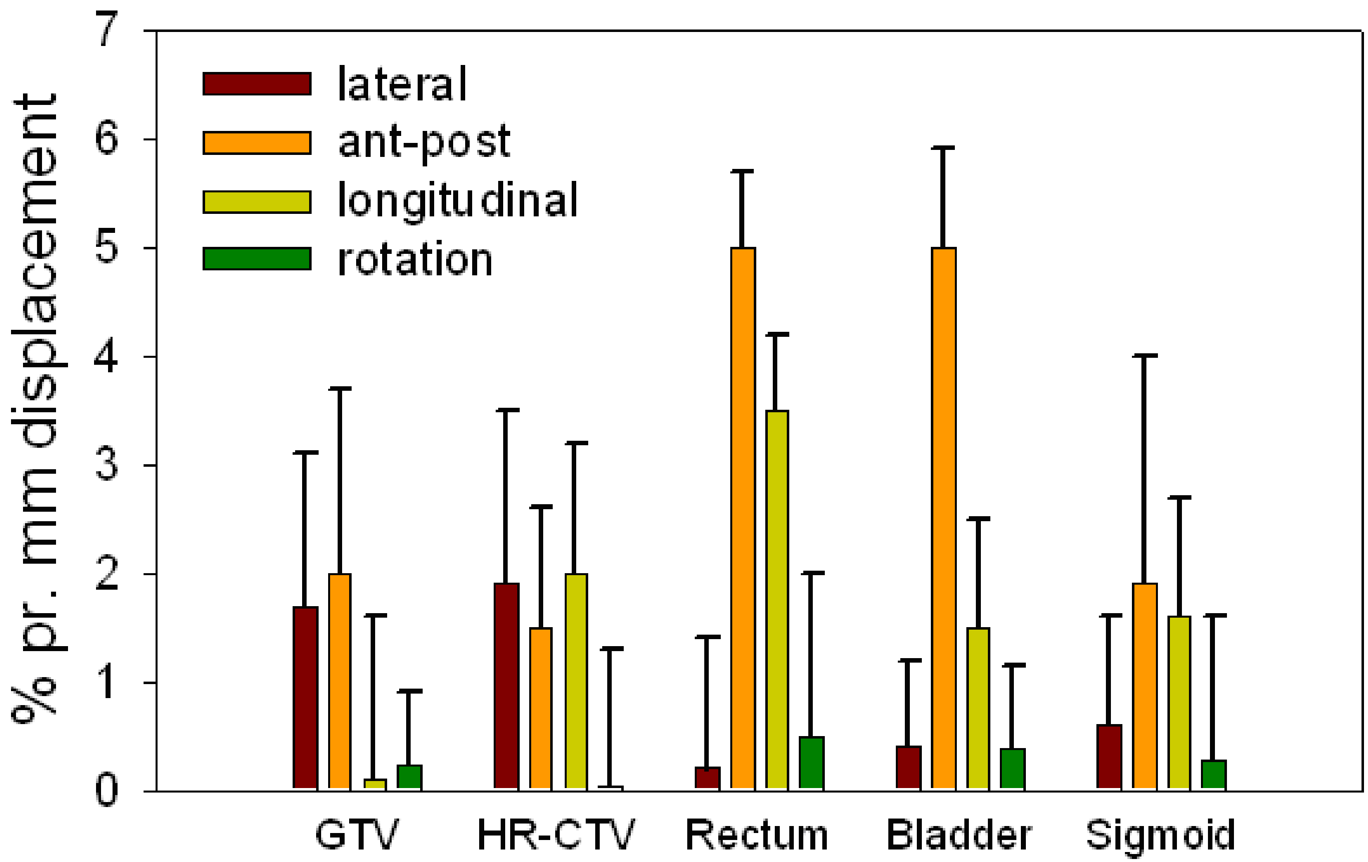
- Displacement in directions:
  - Longitudinal (along tandem):
    - ± 3 mm, ± 5 mm
  - Lateral:
    - ± 3 mm
  - Ant-post
    - ± 3 mm
- Rotation of ring:
  - ± 15 dgr (4 mm)

Tanderup et al, R&O 2008





Mean DVH shifts (%) pr mm



Tanderup et al, R&O 2008

Reading material

ELSEVIER

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

GEC-ESTRO Recommendations

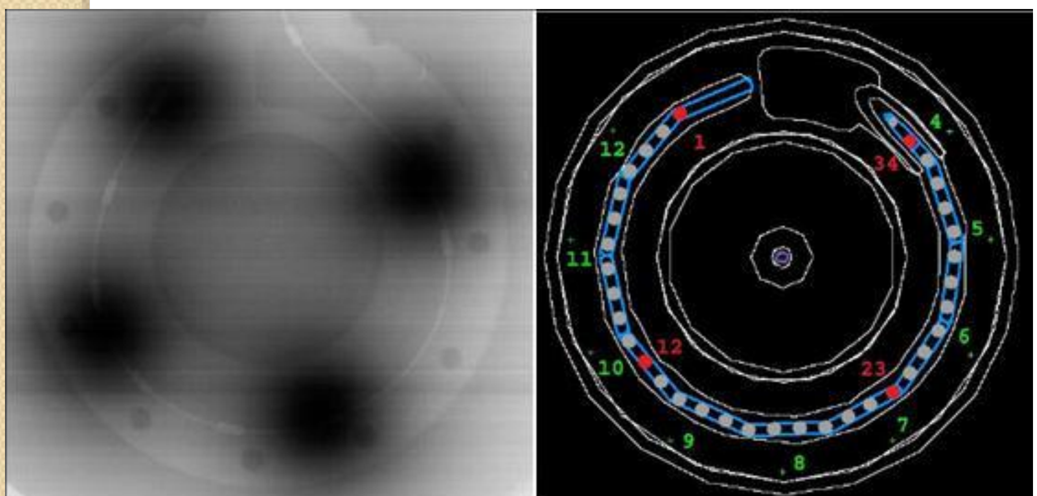
Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group: Considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer brachytherapy

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.

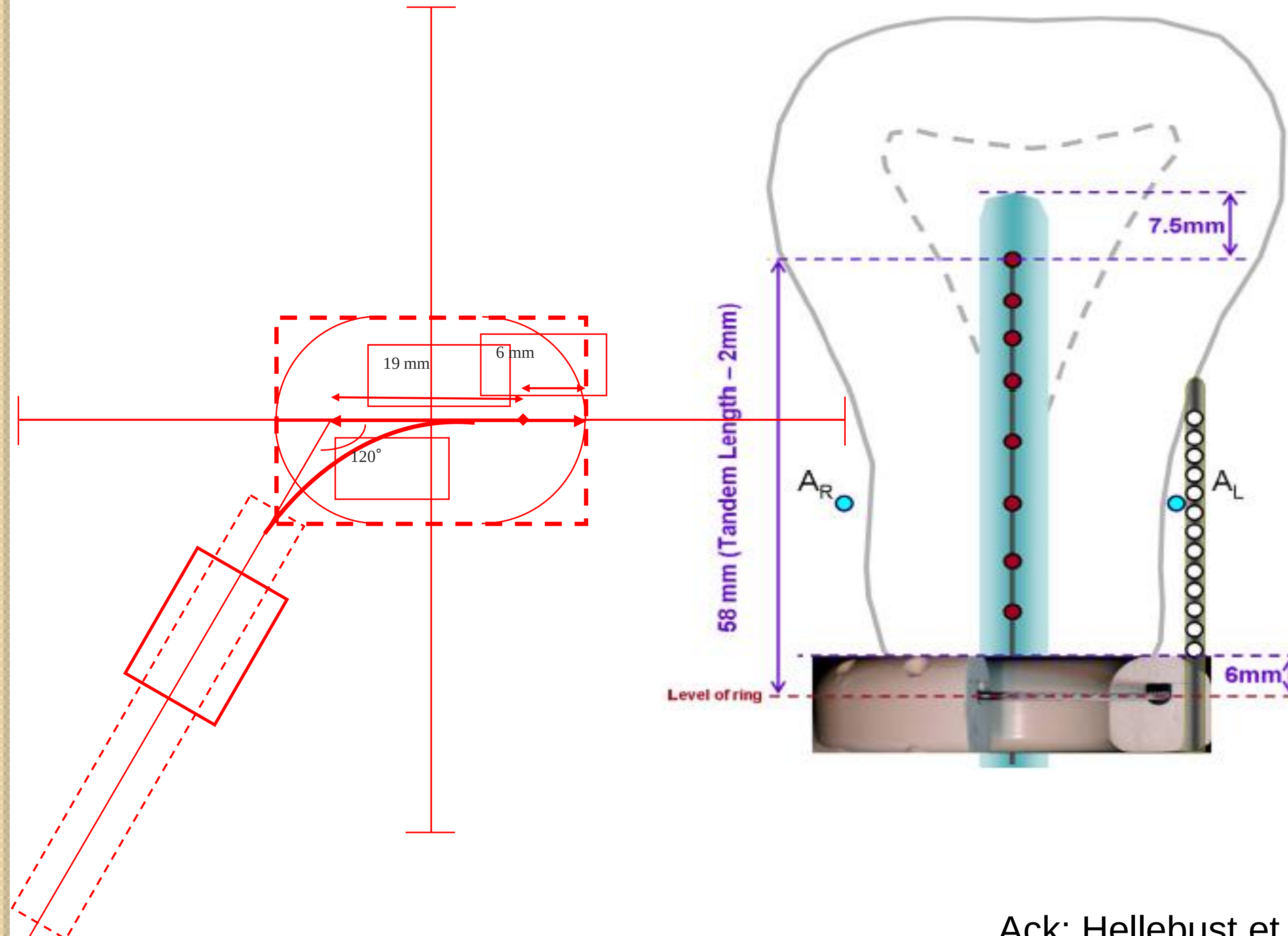
Commissioning of applicator



Ack: Hellebust TP

- The location of dwell positions is found in relation to one another or in relation to reference points in the applicator,
  - e.g., the distance from the tip of the tandem applicator to the first dwell position.

Step 1/5: Understand the geometry

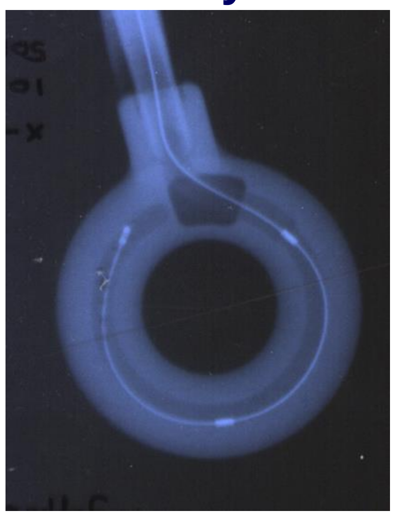


Ack: Hellebust et al

Step 1/5: Understand the geometry

The ring applicator from Bebig vs Elekta

X-ray



X-ray

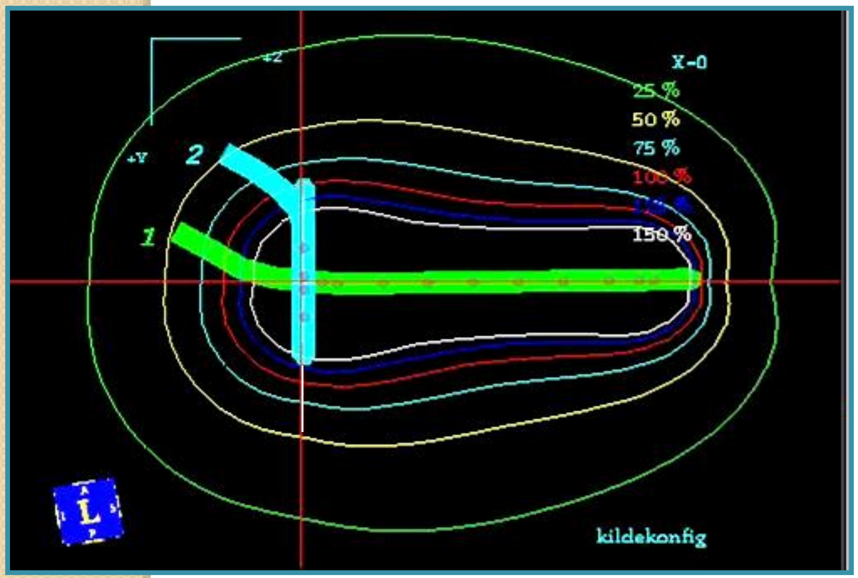
Elekta

Bebig

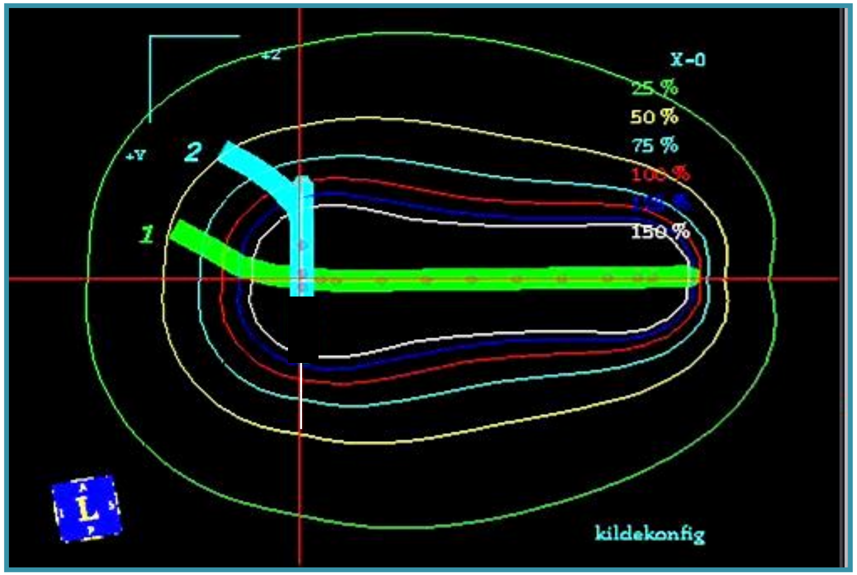
Slide courtesy :TP Hellebust

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

Elekta



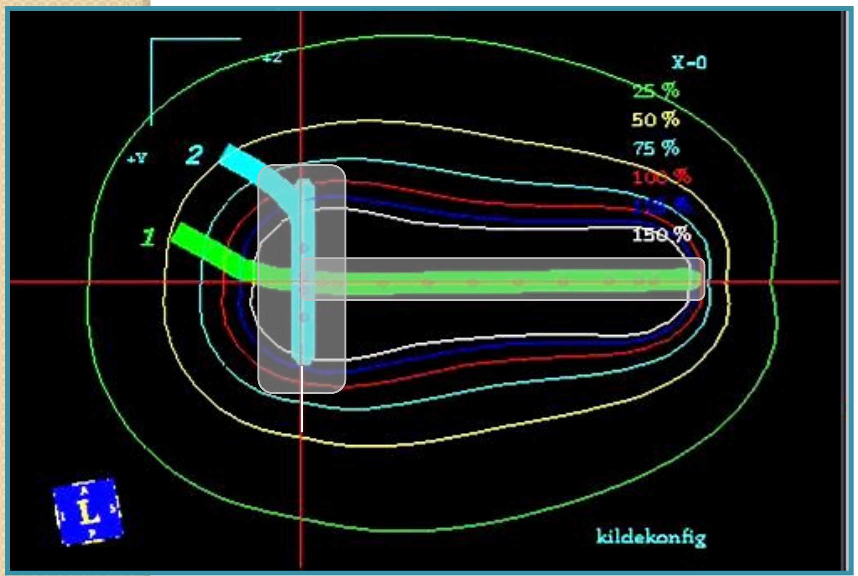
Bebig



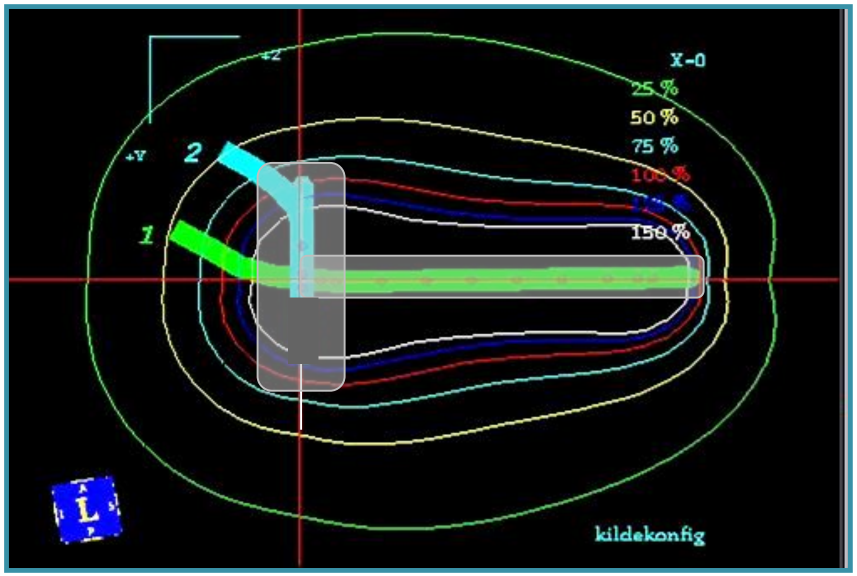
Slide courtesy :TP Hellebust

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

Elekta

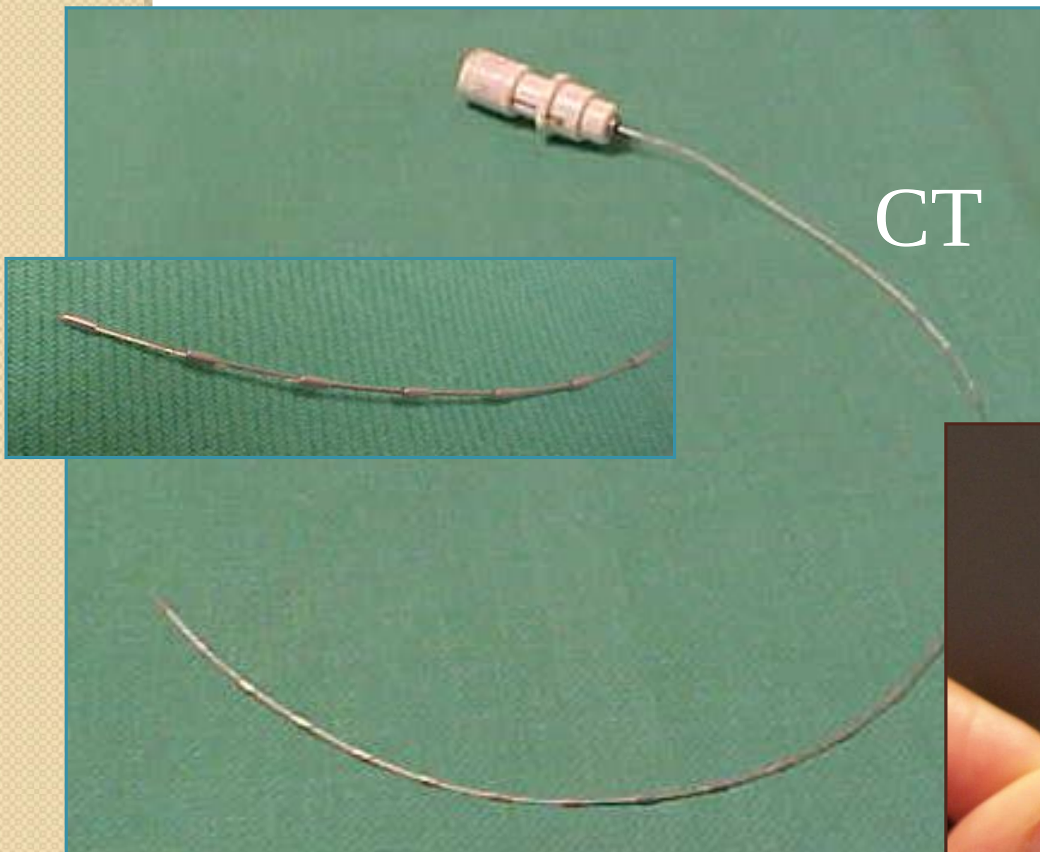


Bebig

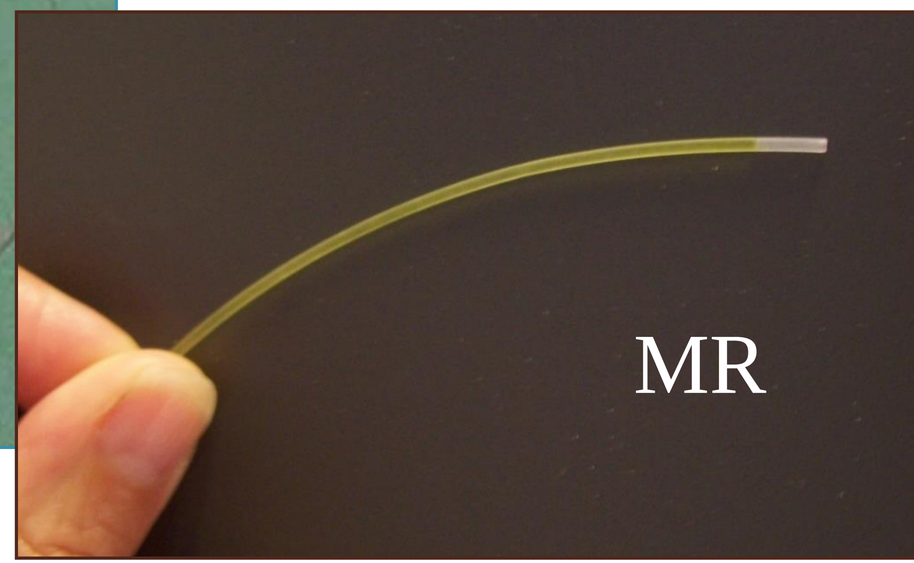


Slide courtesy : Hellebust

Step 2/5: Choose the Markers

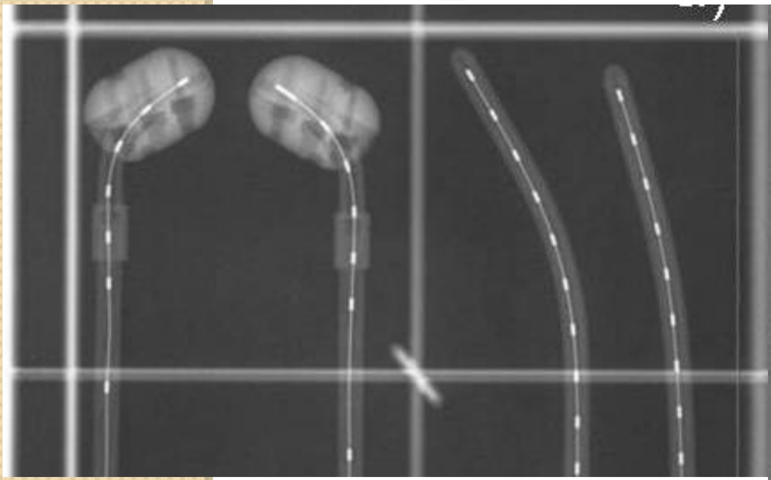


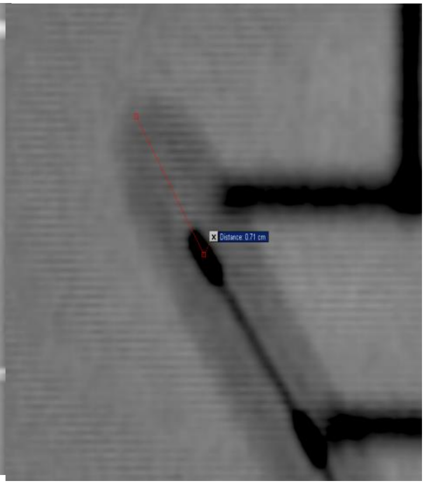
important: Dedicated for each type of applicator, check for locking!!

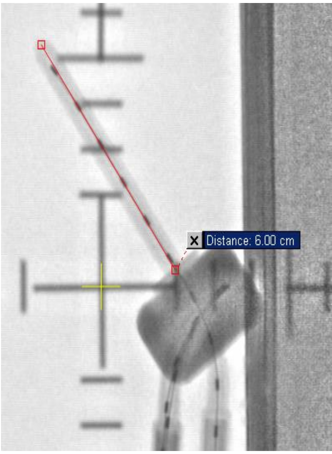


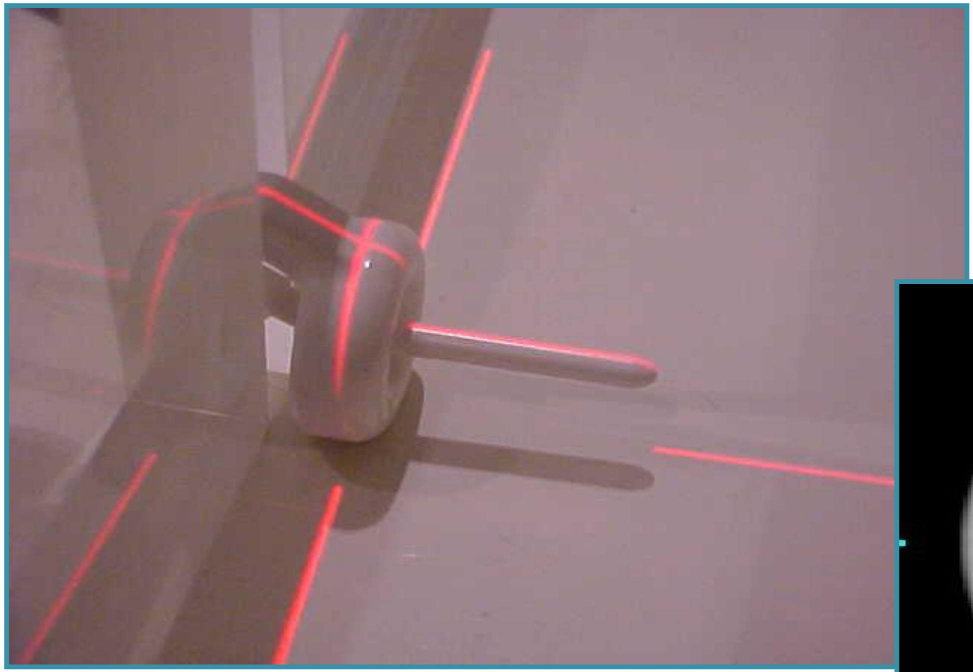
Ack: Hellebust

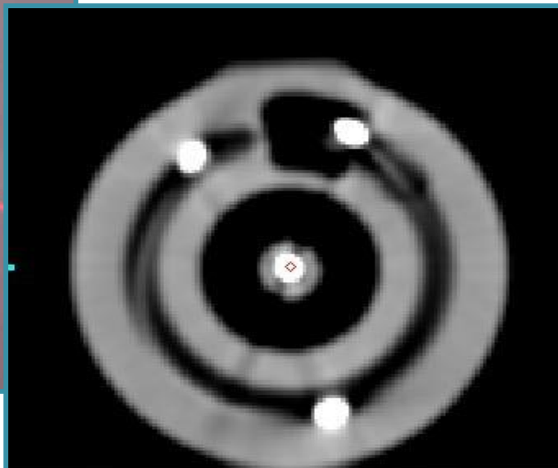
Step 3/5: Radiograph / CT / MR





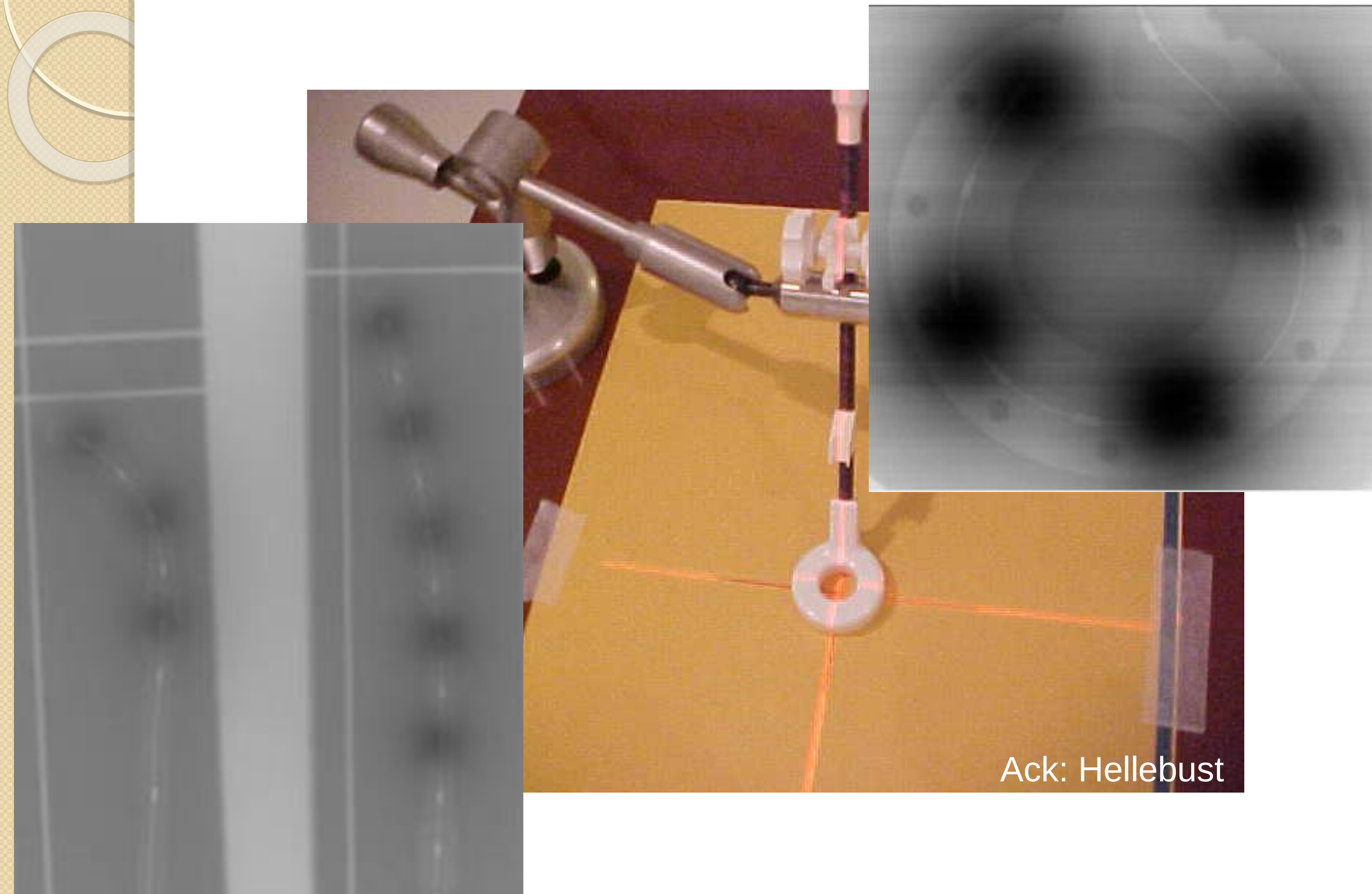






Ack: Hellebust TP

Step 4 /5 : Auto radiograph



Step 5/5 : Analysis

- Compare the auto radiograph with the manufacturer specifications
- Comparing step 1 with 3&4

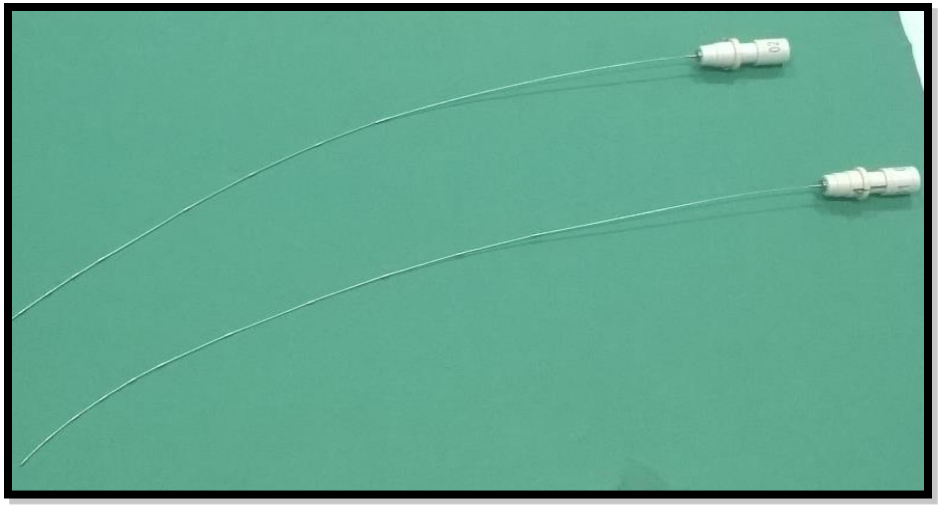
Phantom

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

Vienna Applicator

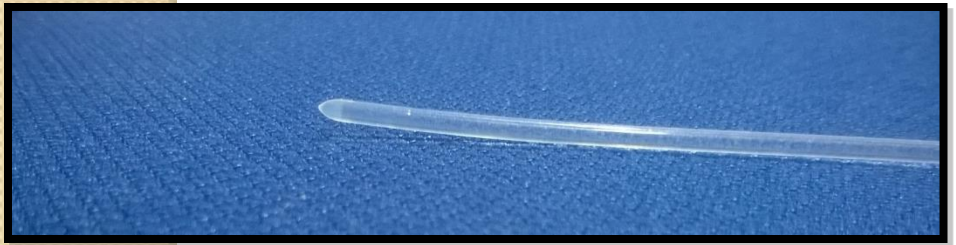
Medium:

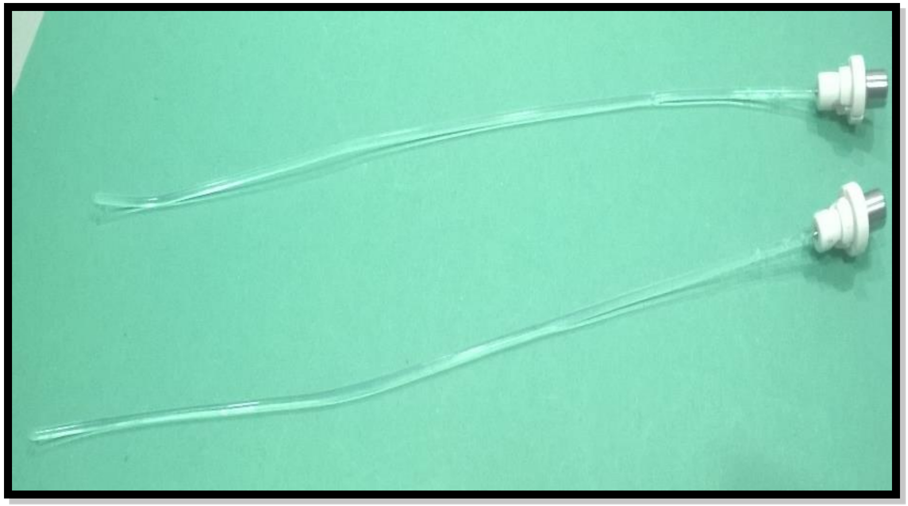
- Preferable if it resembles human tissue imaging qualities.
- Ideal for CT/ MR applicator is Agarose gel (3%) with CuSO4 (1 g/L)



X-ray markers for CT/MR applicator.

DO NOT USE X-RAY MARKER DURING MRI.

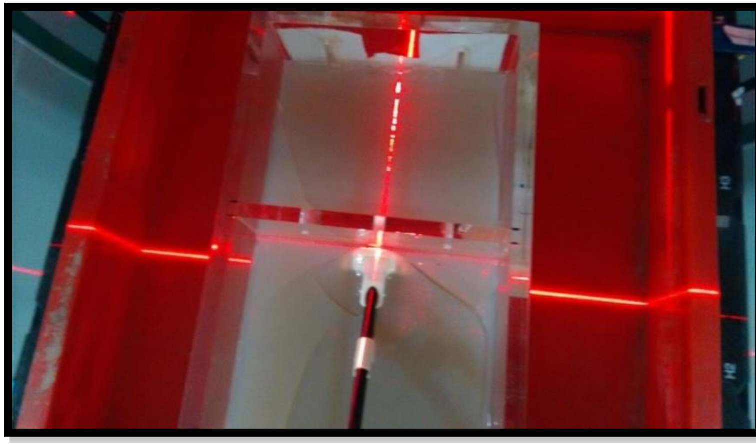




MR markers for CT/MR applicator.
They are filled with water.
$CuSO_4$ can also be used.

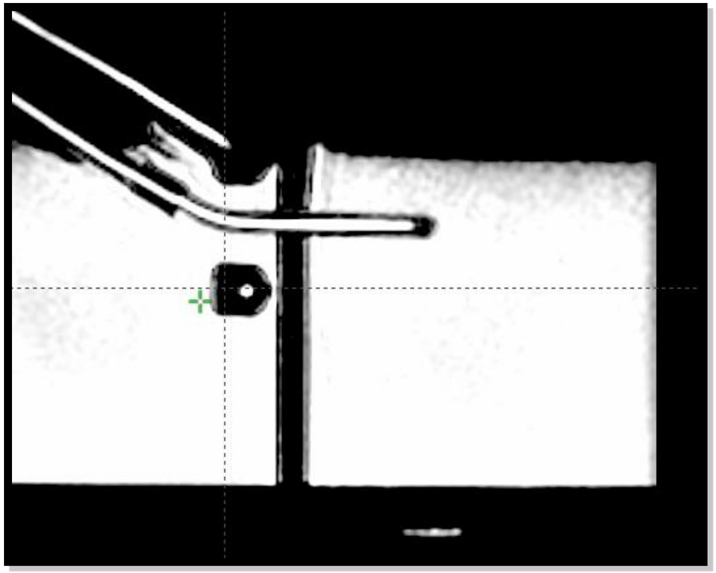
Imaging

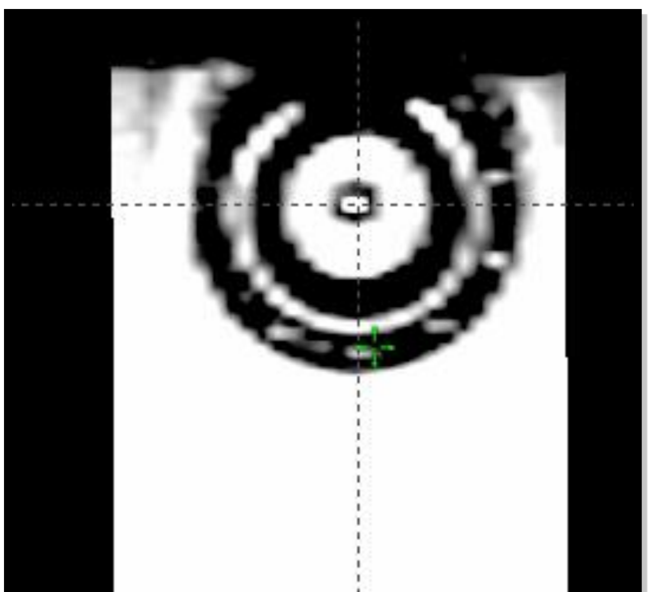
- Setup according to the external markers.
- Align the axis of the applicator along the saggital Laser.



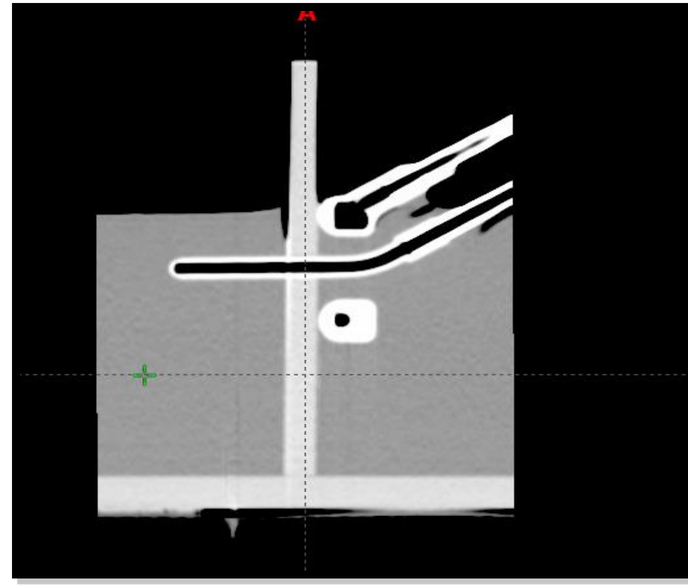
- Imaging Series
  - CT – <1 mm slice thickness
  - MRI – T1, T2 para-axial, para-saggital and para- coronal. 2- 3 mm slice thickness. Zero overlap

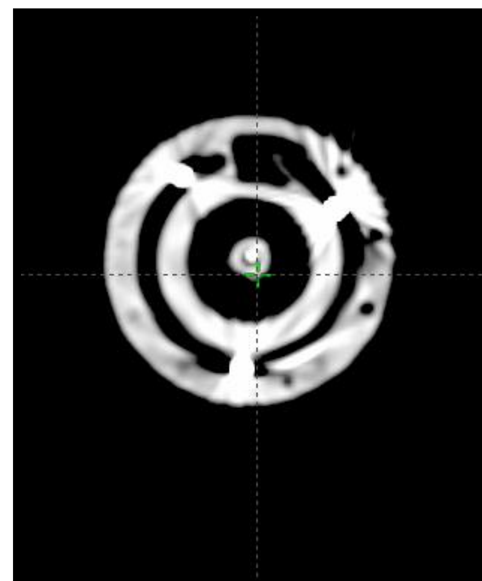
MRI



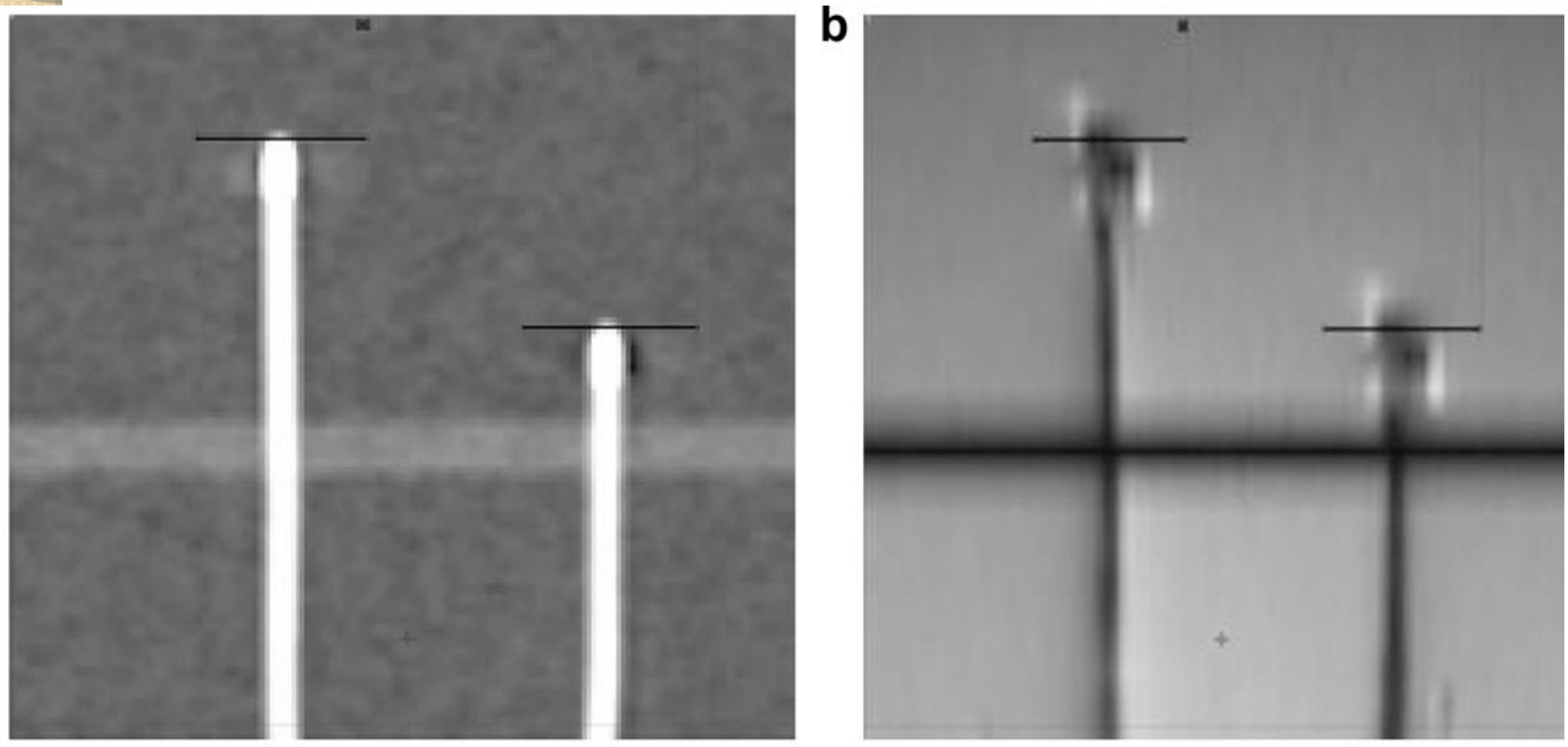


CT



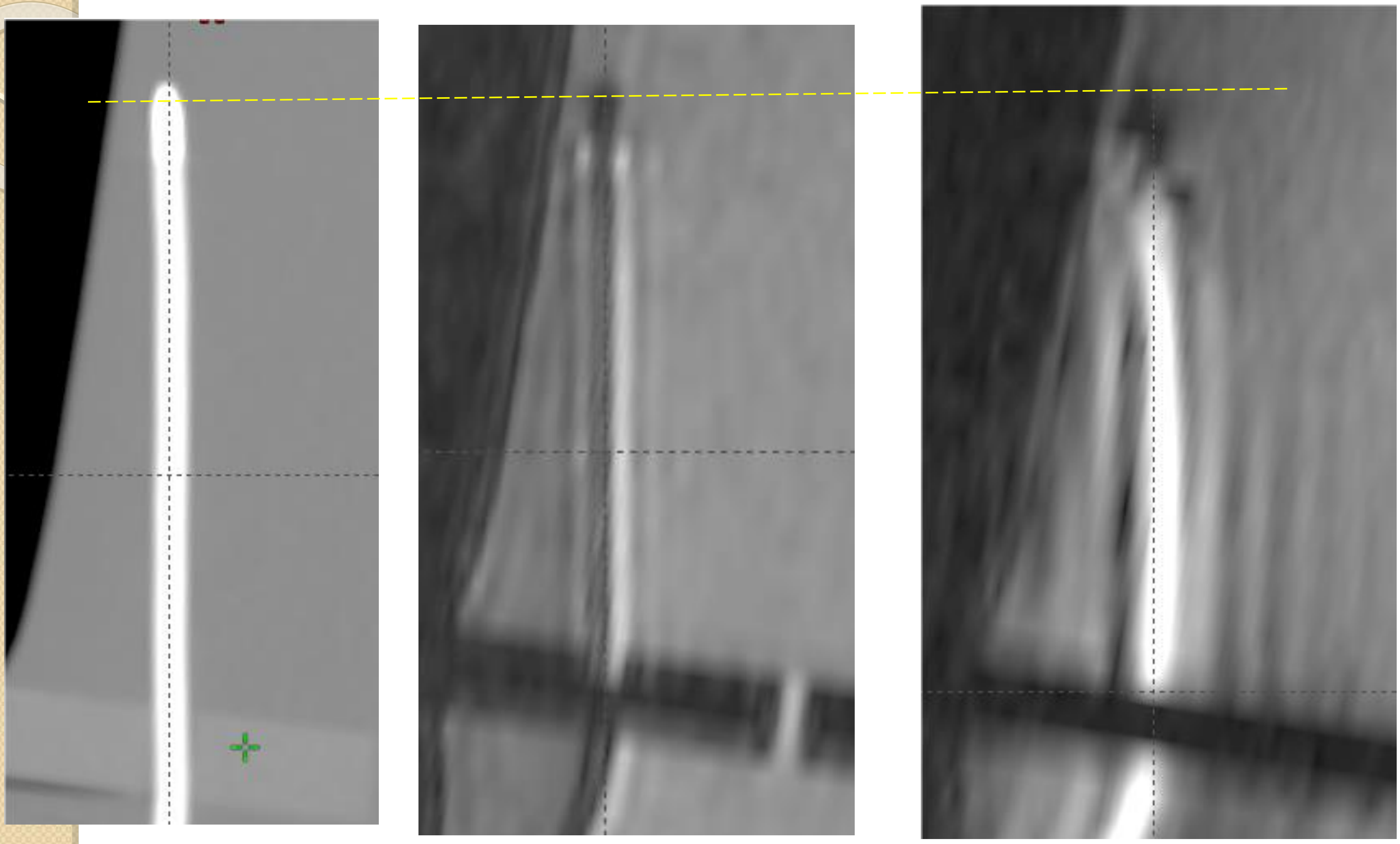


Titanium Needles

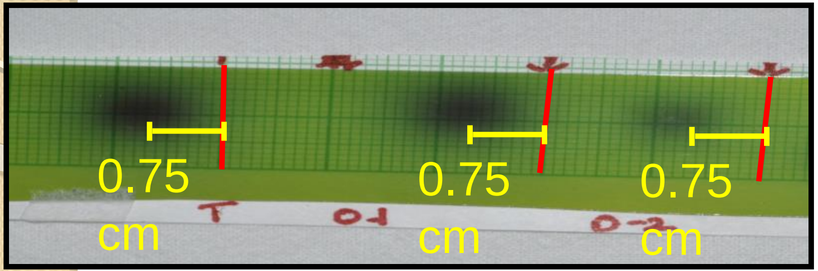


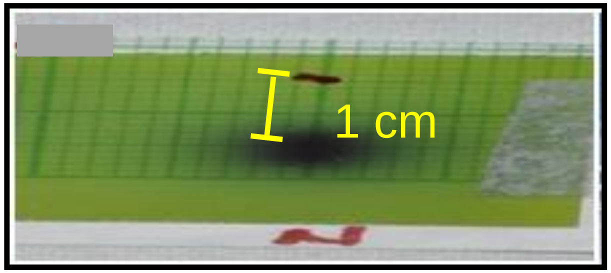
Haack et al, RO 2006

CT 1.5 T 3.0 T

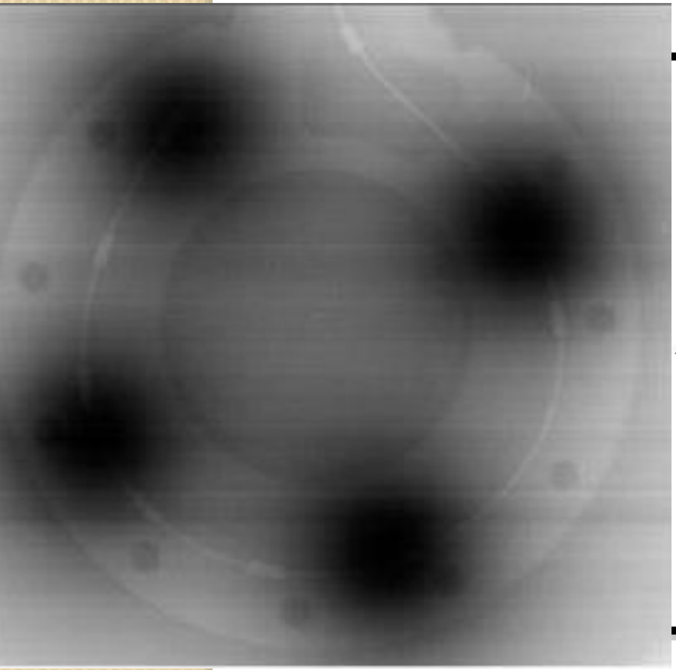


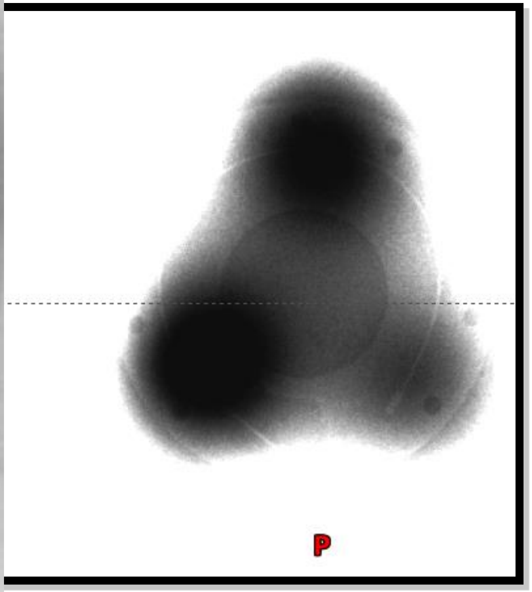
Auto Radiograph

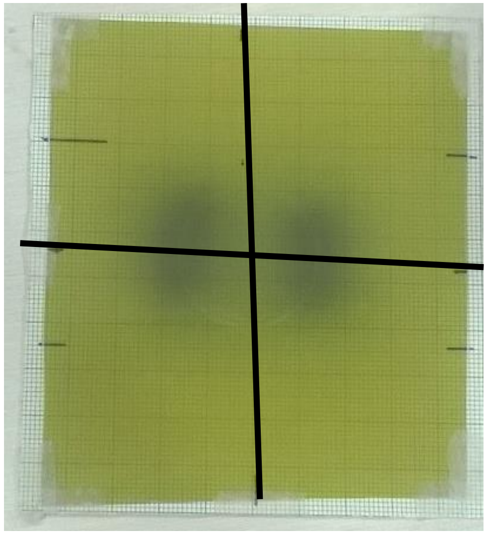




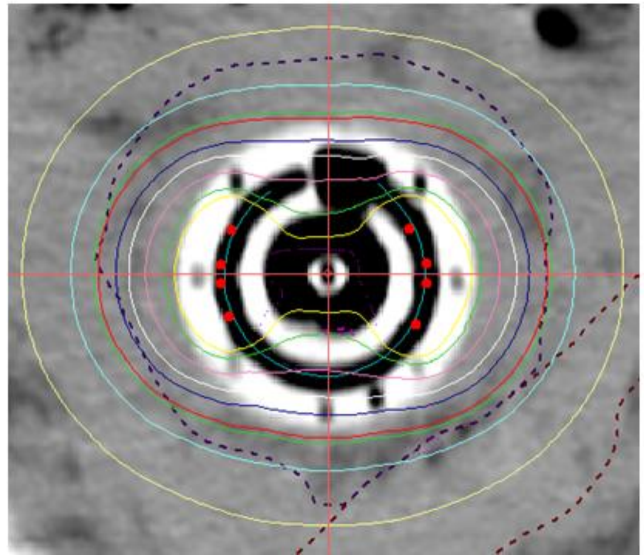
Red line indicates the physical tip

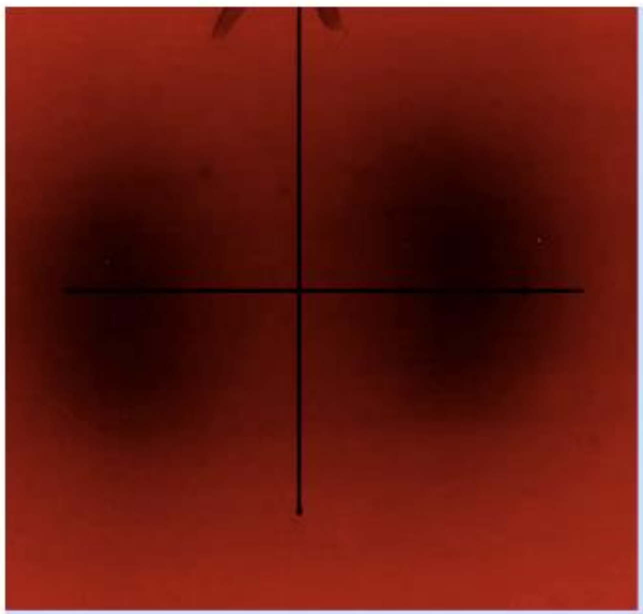


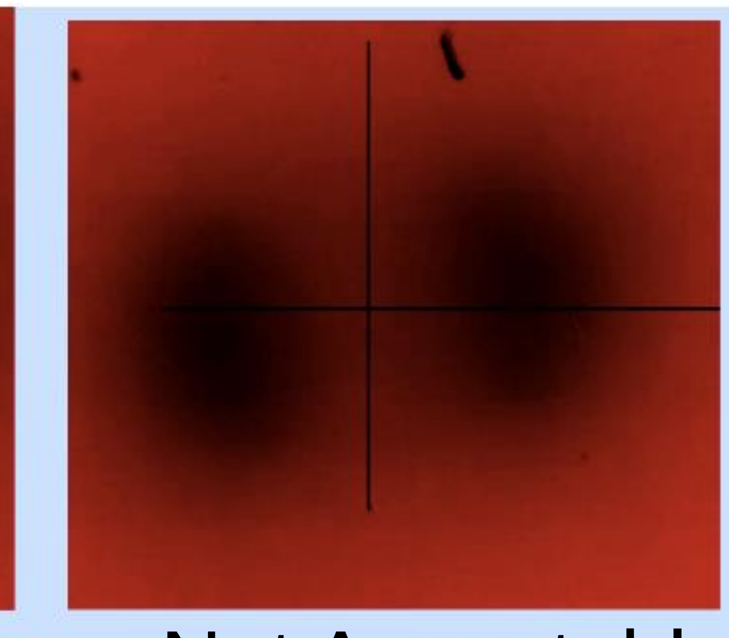




Ring Applicator





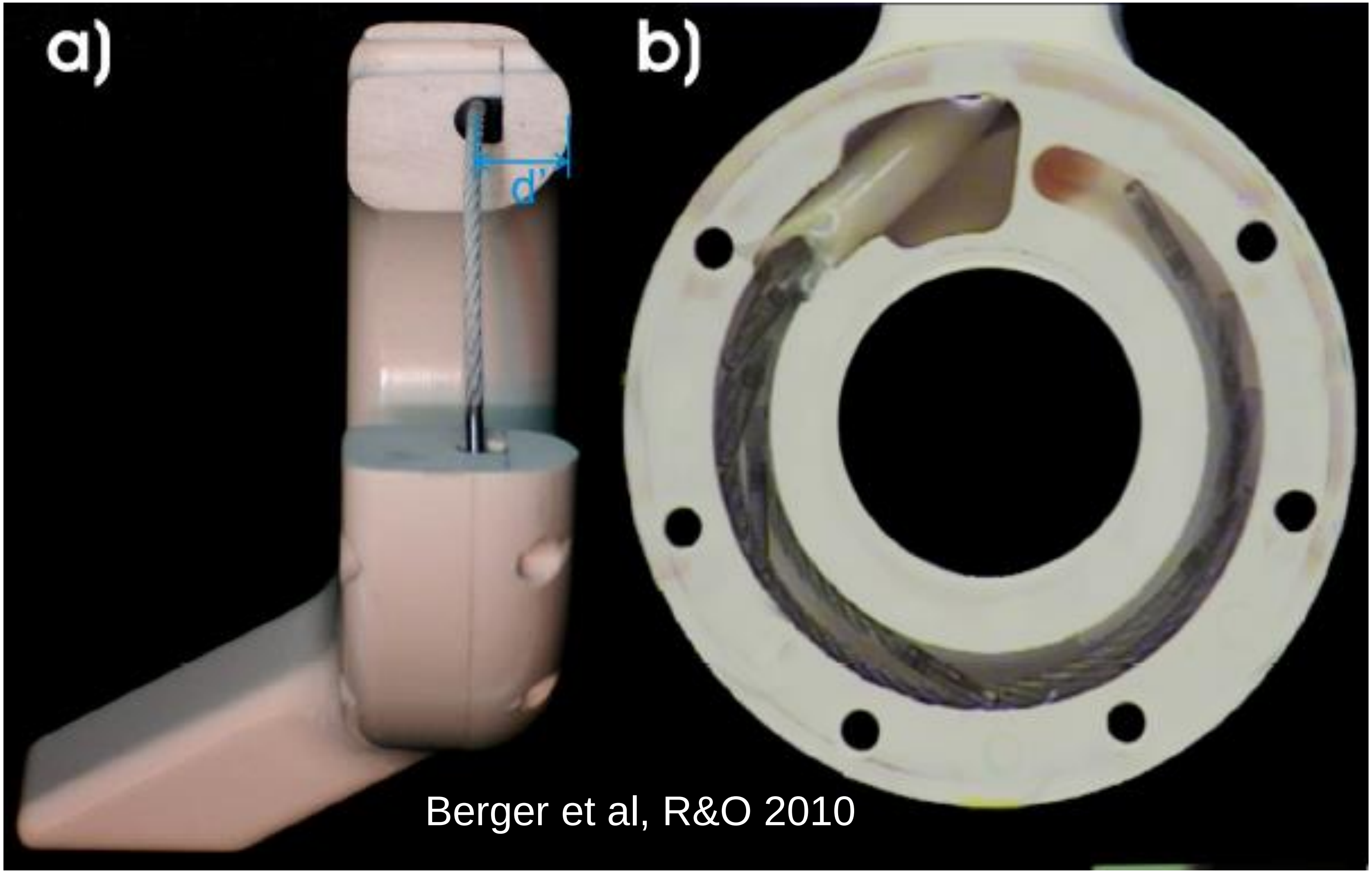


Acceptable

Not Acceptable

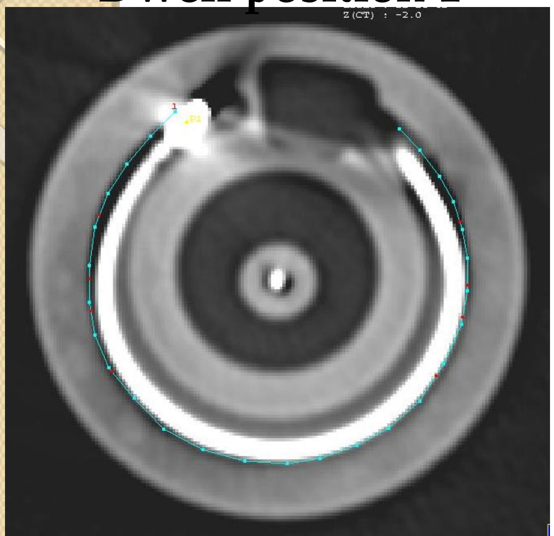
Images : Hellebust

Photo of the ring with the source

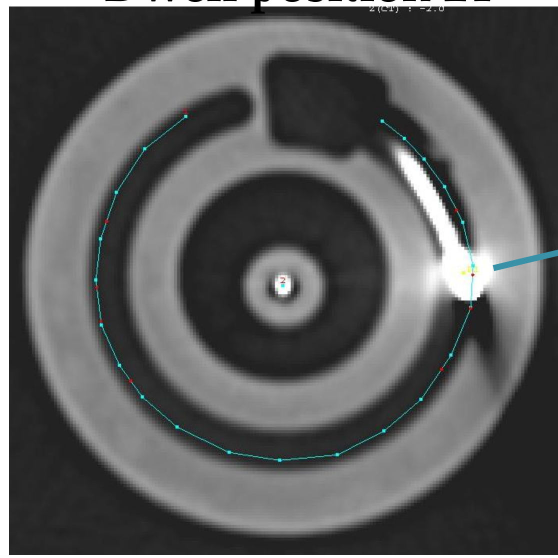


CT images of the ring with the source

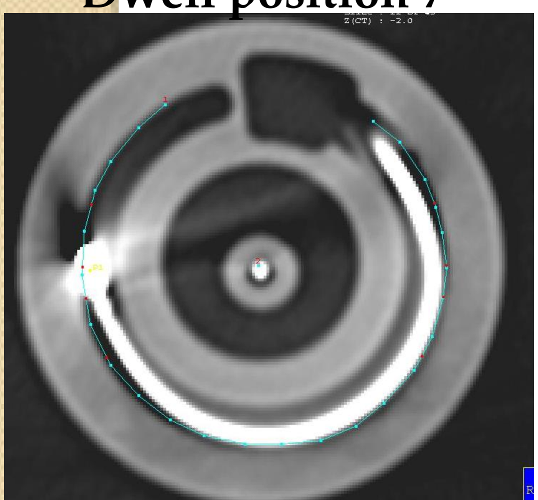
Dwell position 1

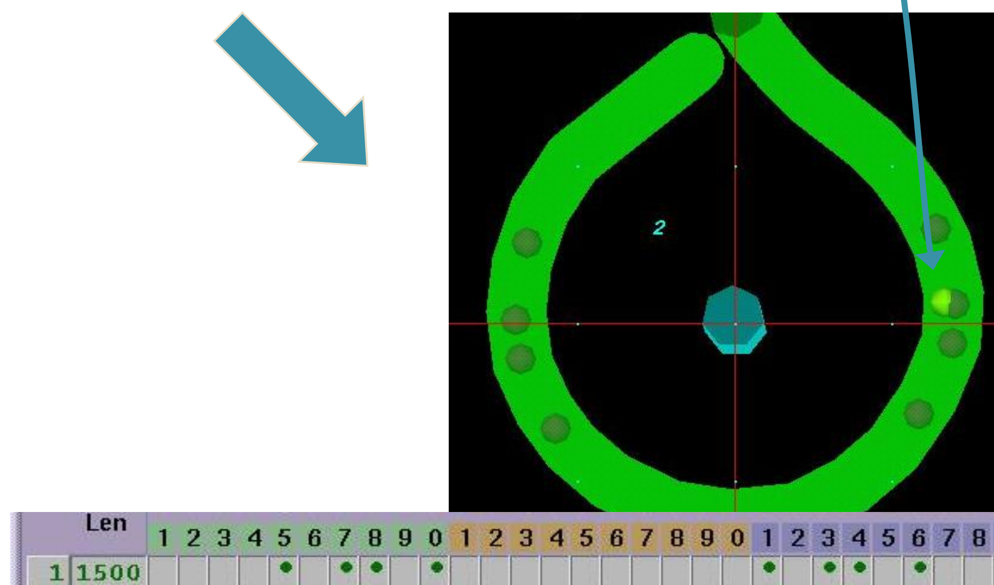


Dwell position 24



Dwell position 7





Hellebust et al, PMB 52 (2007)

Applicator Reconstruction

Localization techniques

Conventional simulator, C-arm

- Orthogonal images
- Semi-orthogonal
- Variable angle
- Stereo-shift

3D sectional images

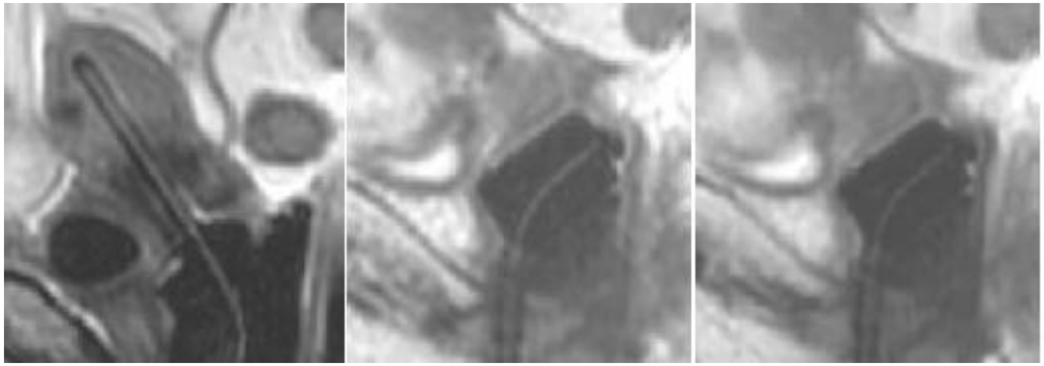
- CT
- MR

Reconstruction

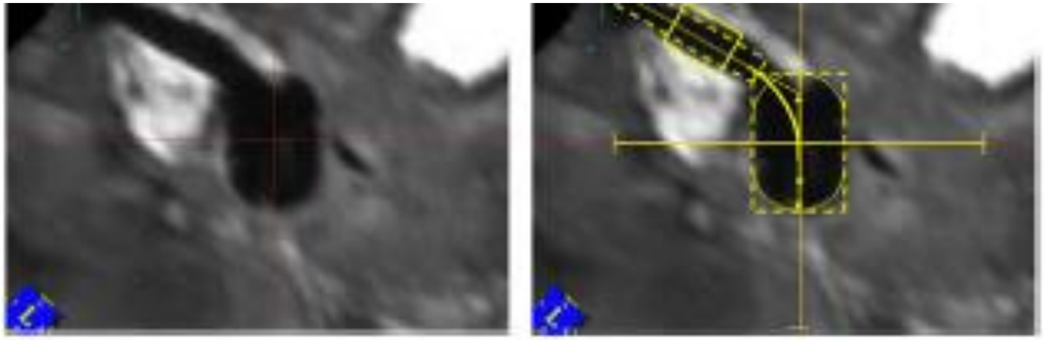
- Direct reconstruction
- Library of applicators

Direct Reconstruction

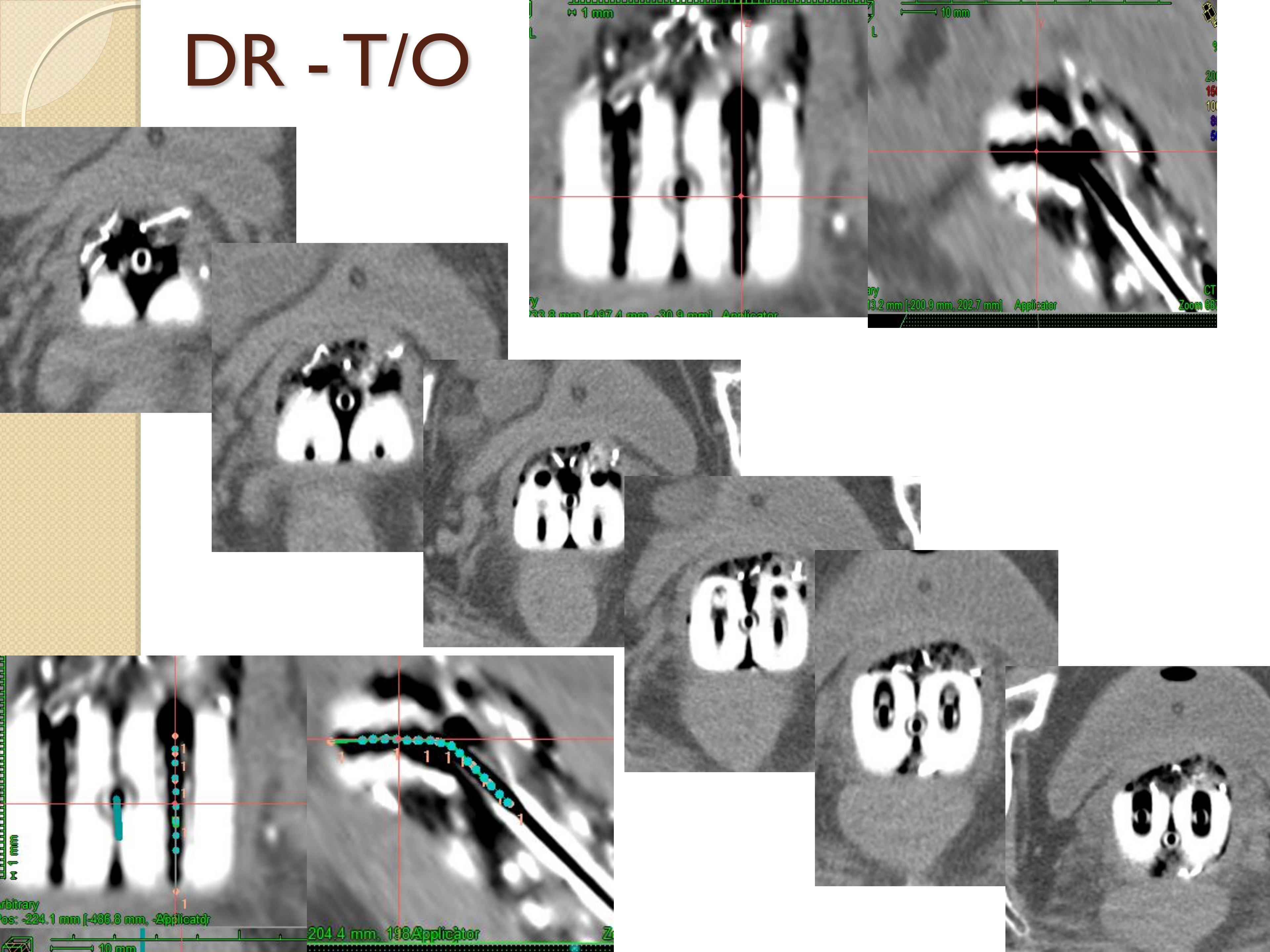
- Clear visualization of the source channels in a single plane.
- Check the geometry of the applicator verified during commissioning.
- Especially useful for curved applicators (ovoid/ring)



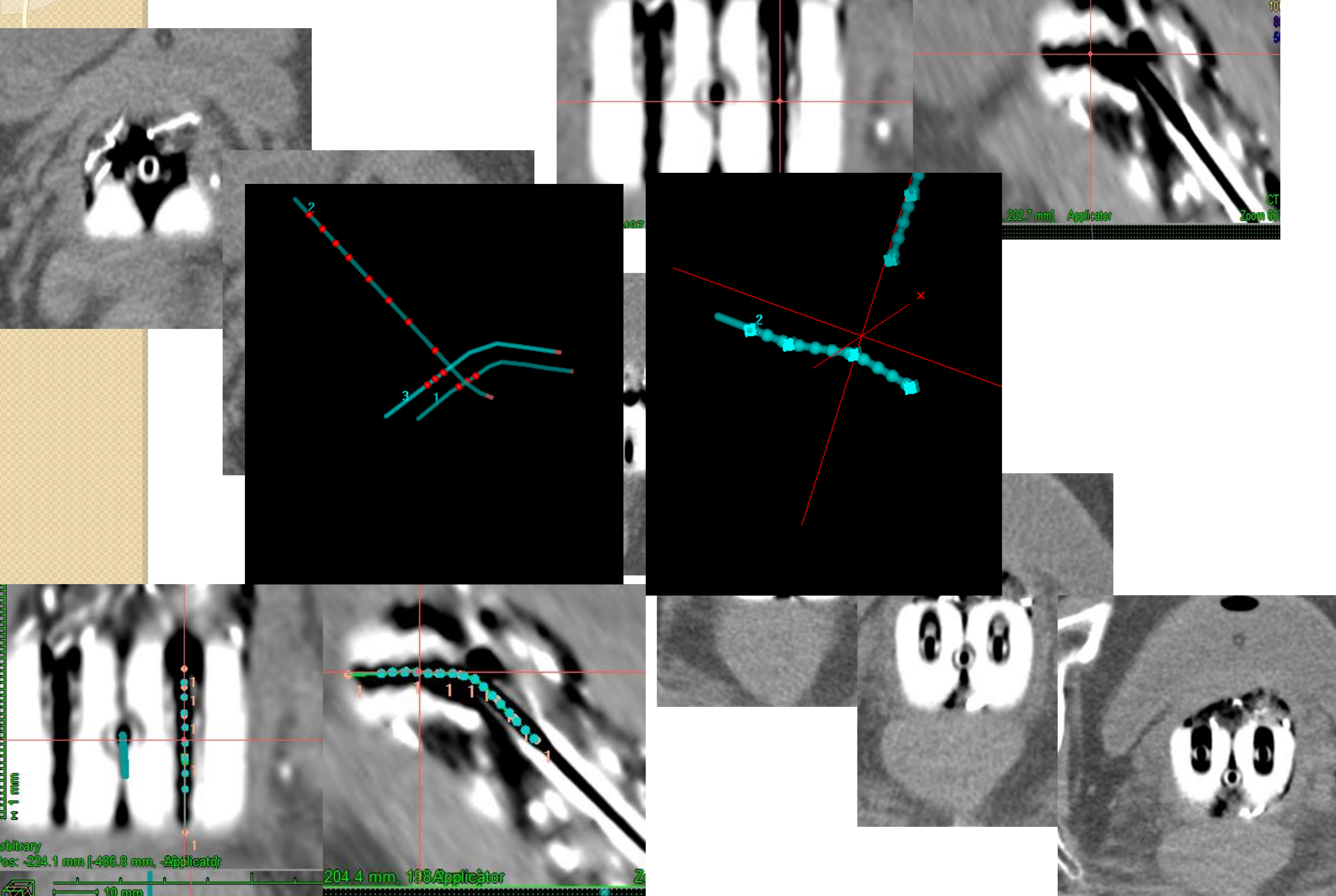
Leeuw et al, RO,2009



DR - T/O

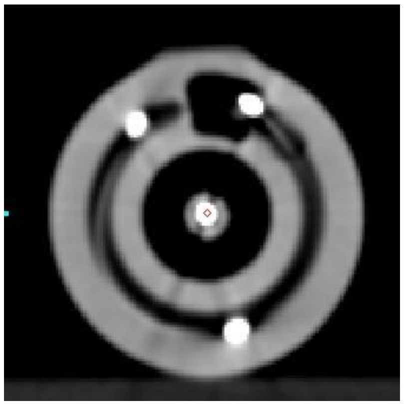


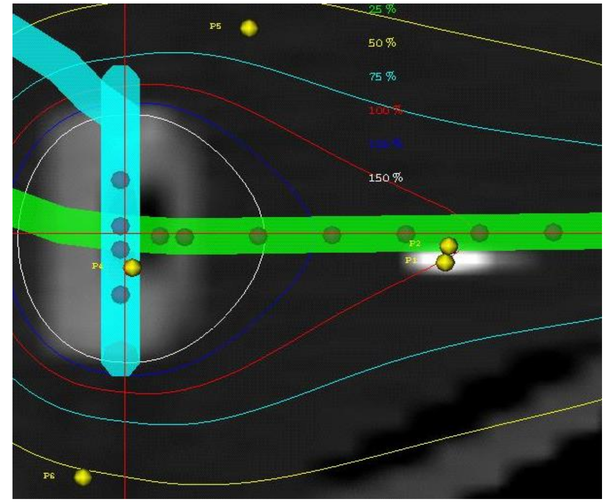
DR – T/O



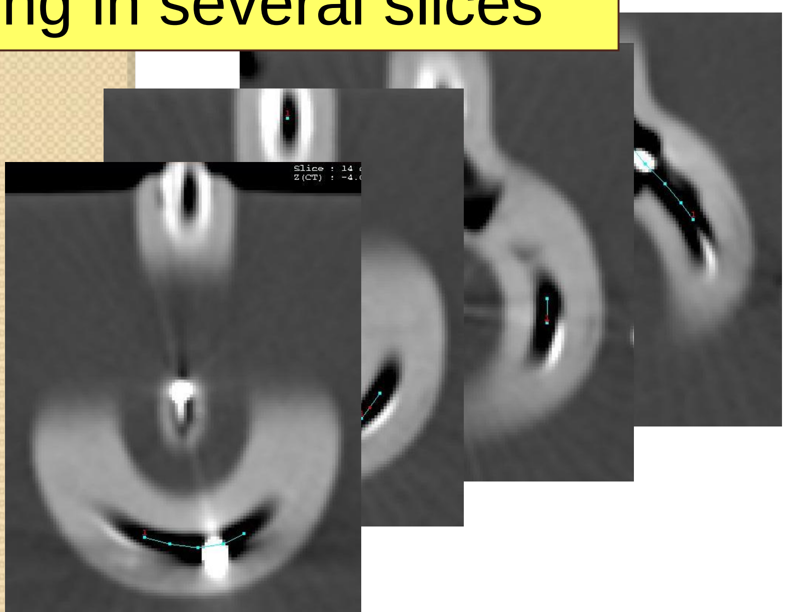
DR - Ring

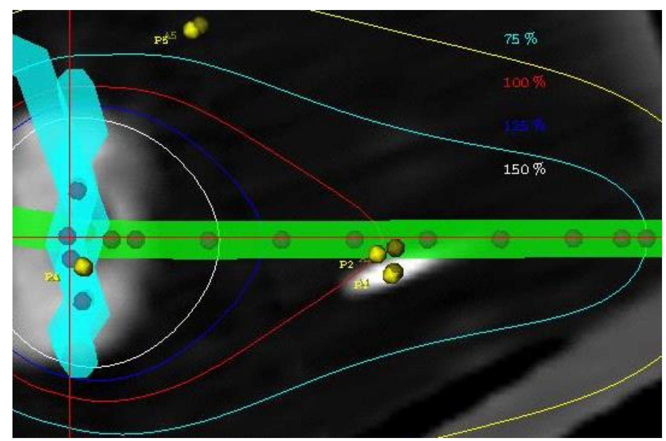
Ring in one slice





Ring in several slices

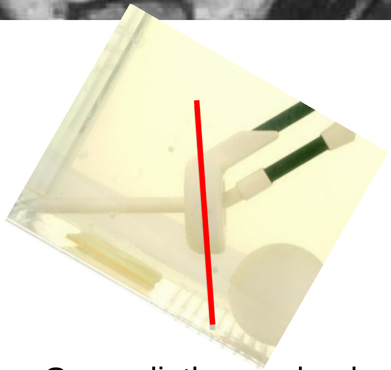




Ack: Hellebust

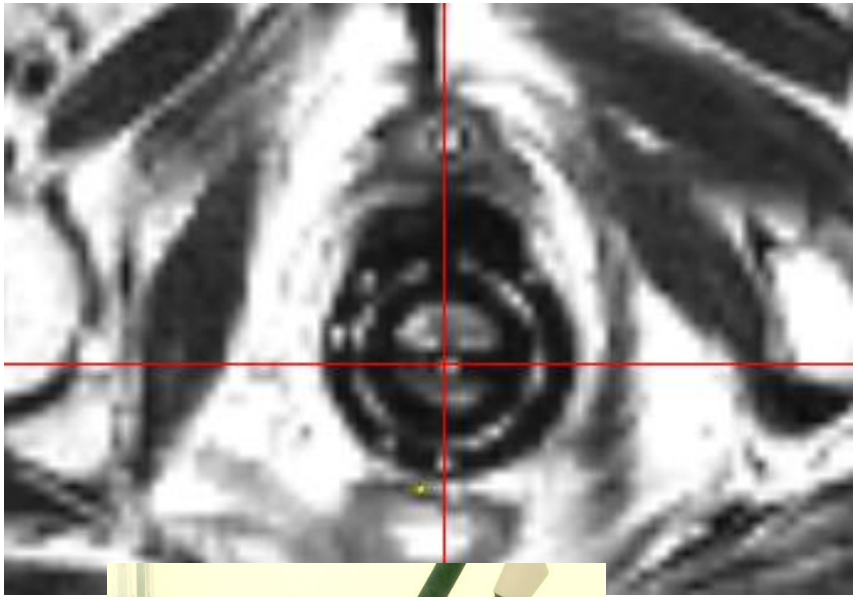
Orientation of the imaging sequence

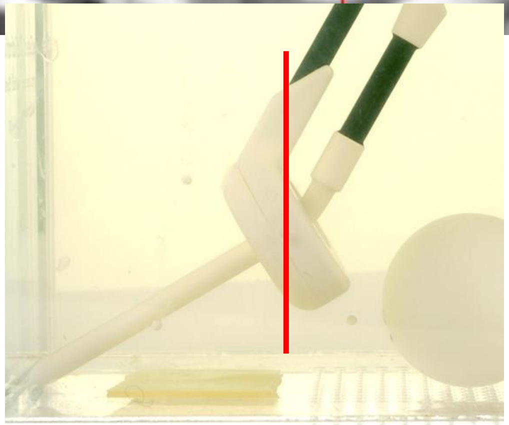
- Para transverse



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

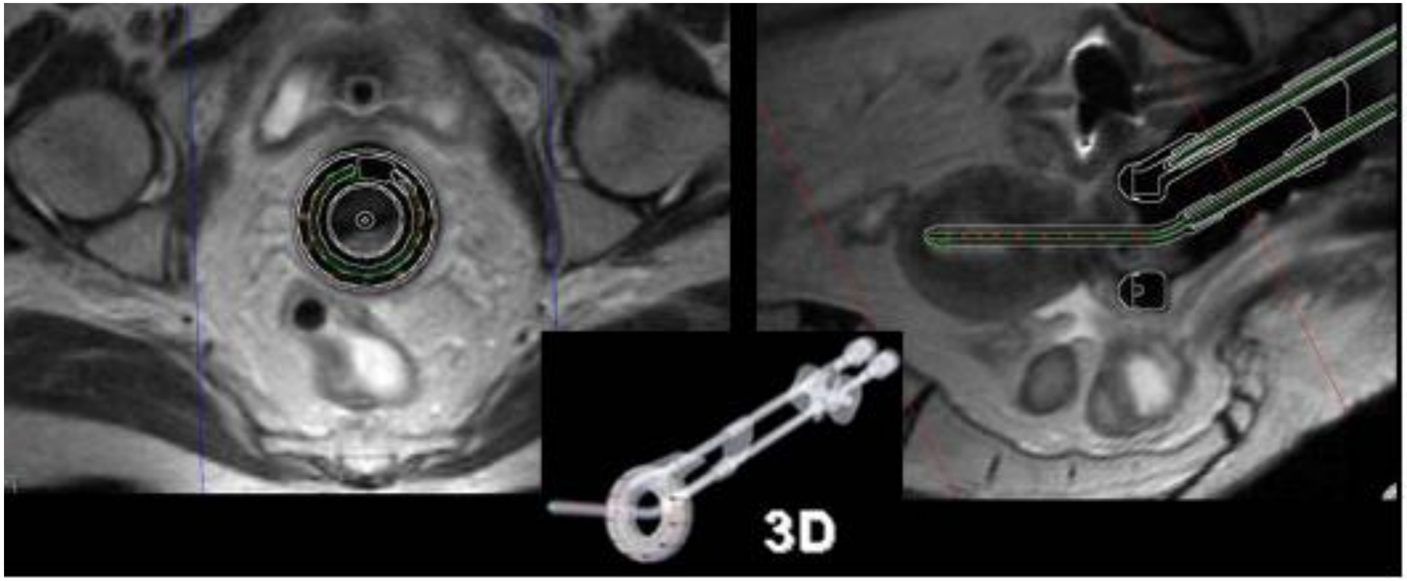
- Transverse (MP Reconstructed)



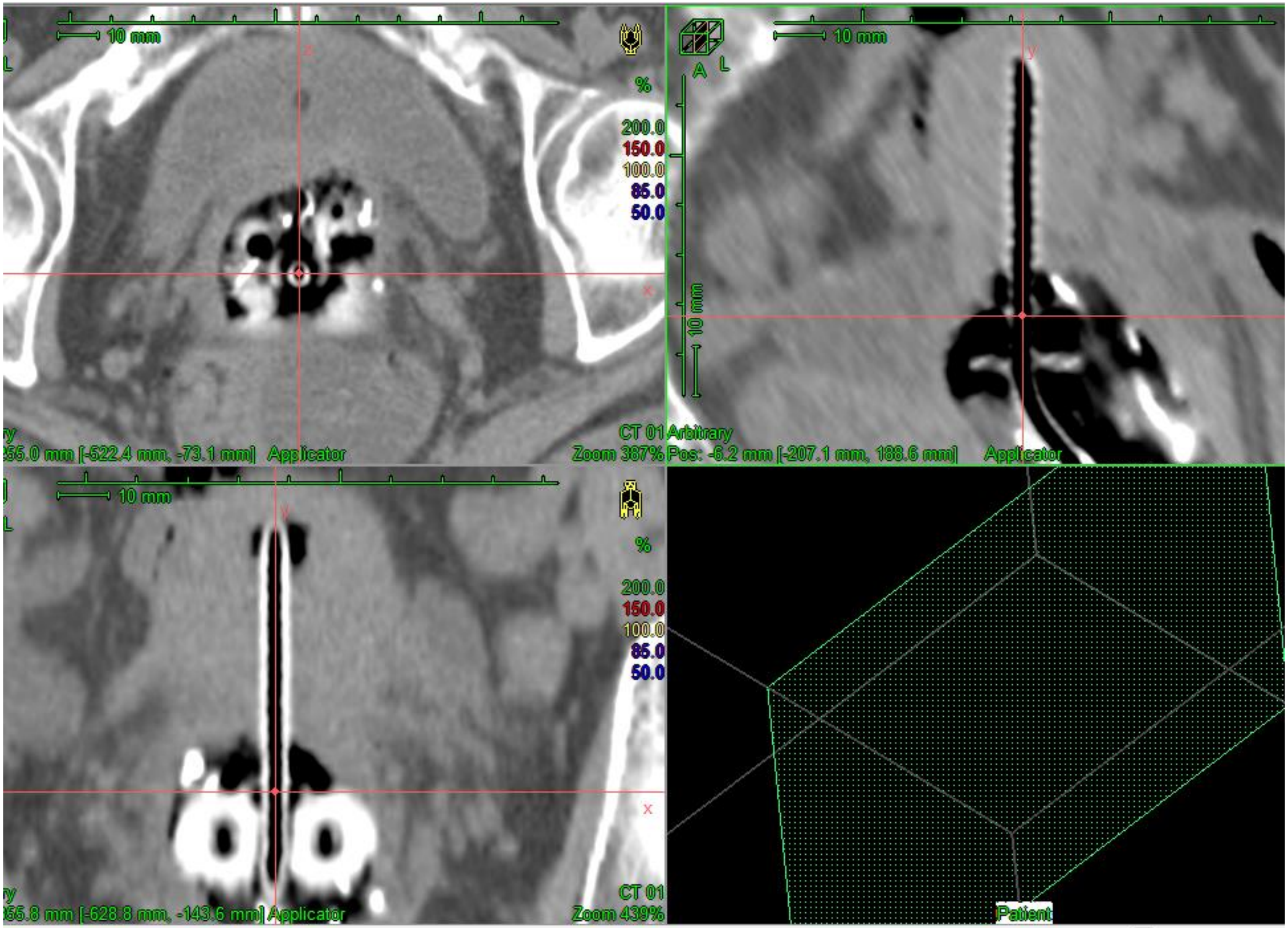


Library of applicators

- 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.



Applicator reconstruction using CT images

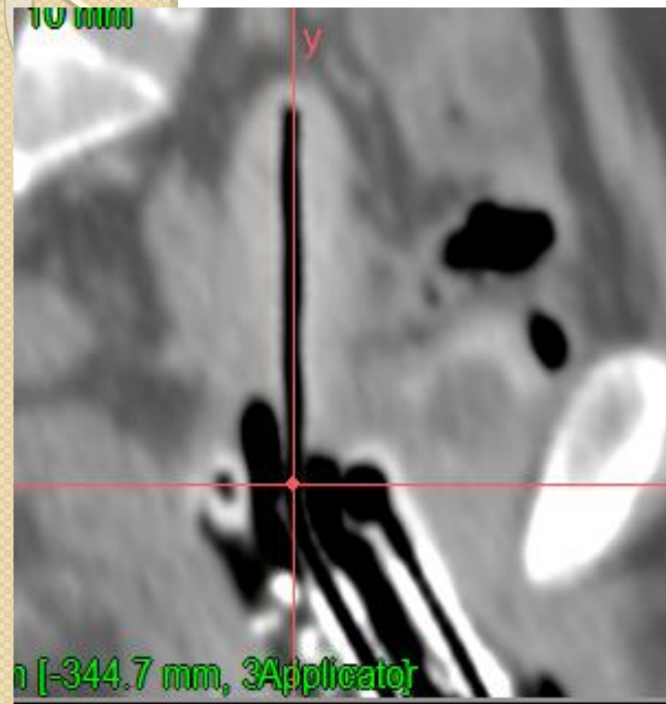


Applicator reconstruction using MR images

Markers: water filled 6F catheters

Role of Registration in applicator reconstruction

Role of registration: applicator Reconstruction

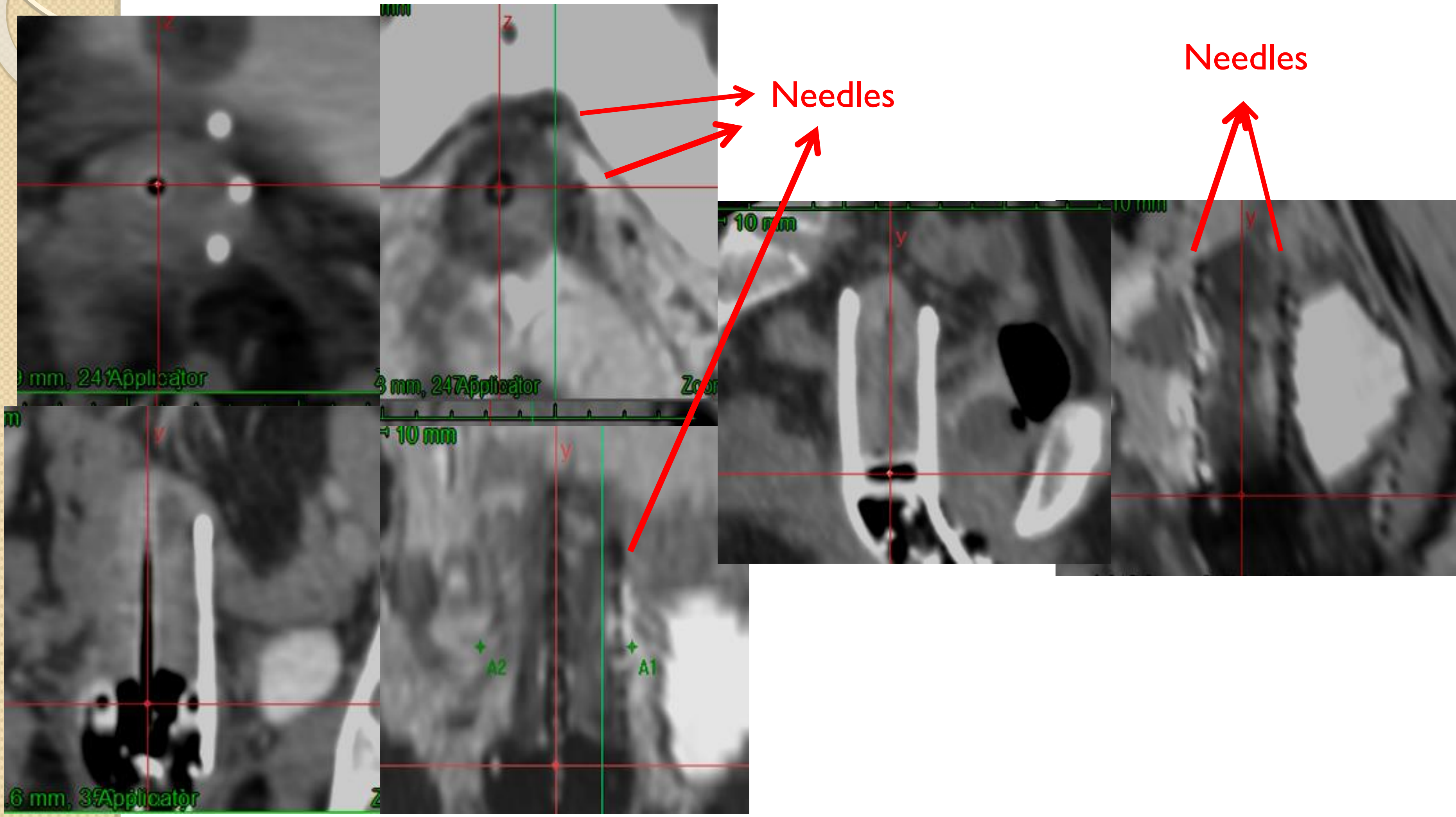


CT – No marker

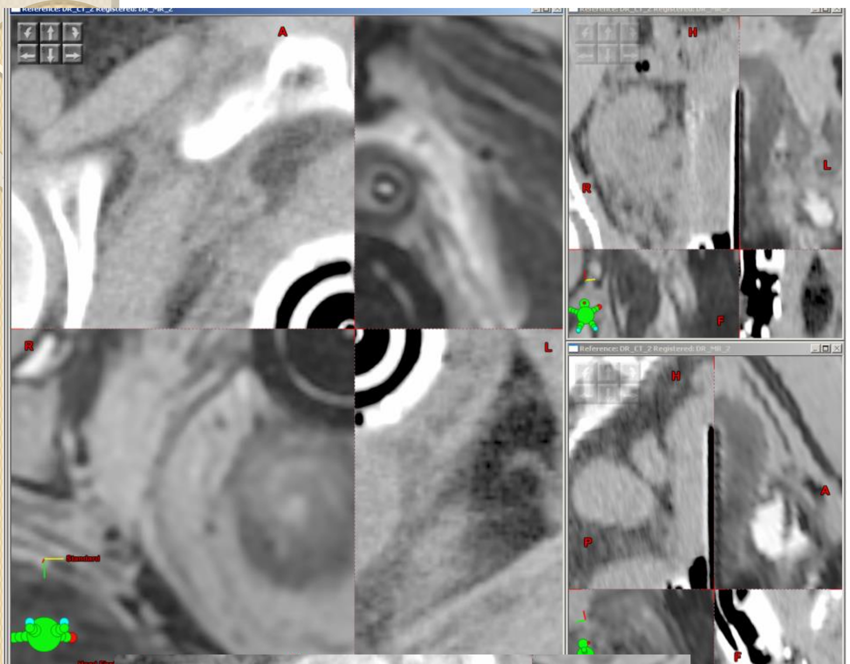
MR – No marker

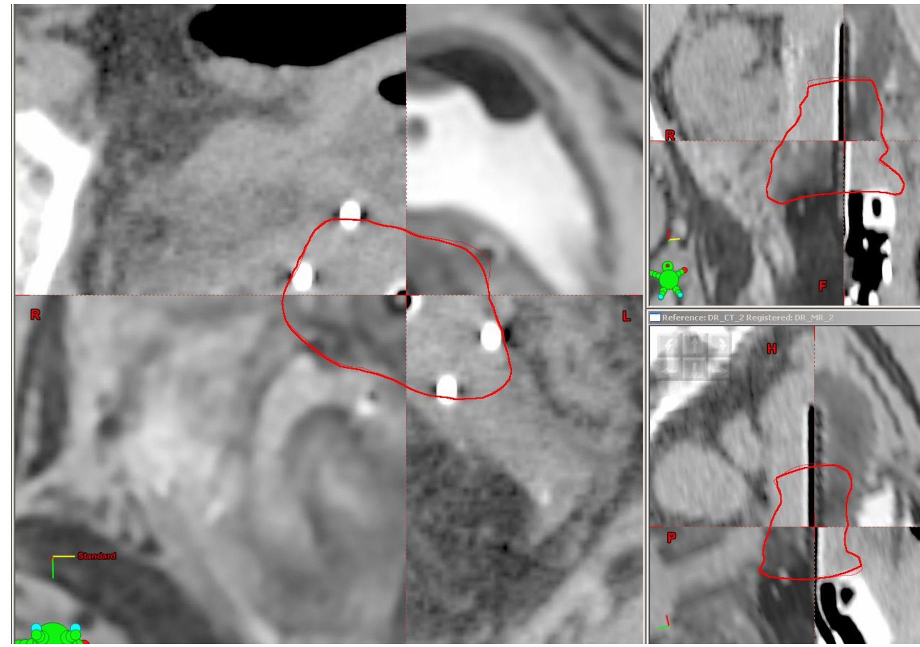
MR – Water marker

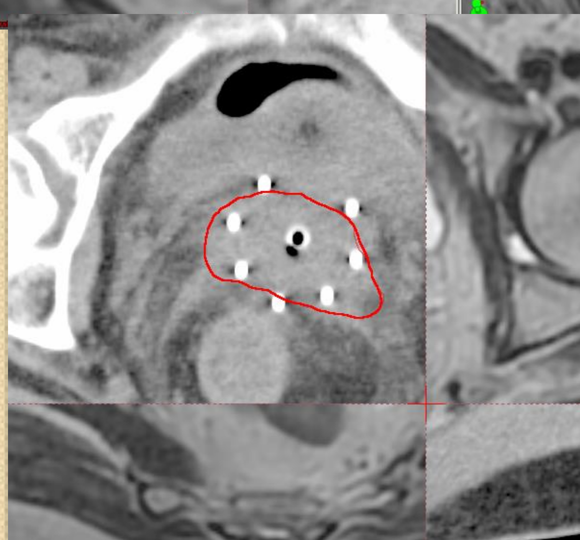
Role of registration: applicator Reconstruction : needles

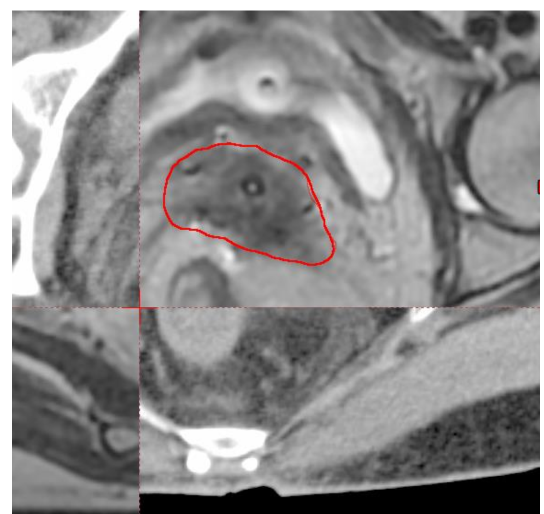


CT vs MR

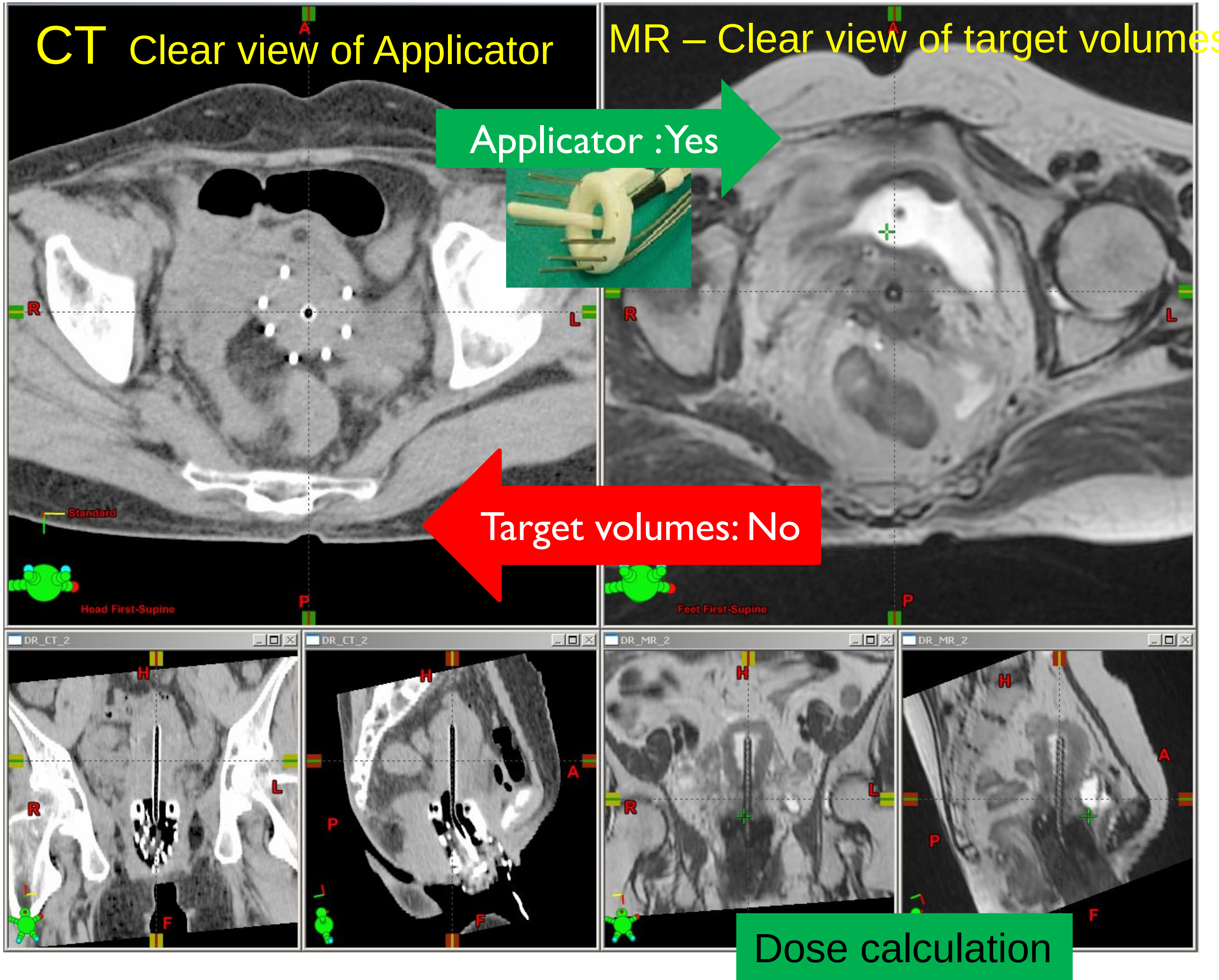

A
R
L
H
P
F
Standard


R
L
H
P
F
Standard
Reference: DR_CT_2 Registered: DR_MR_2

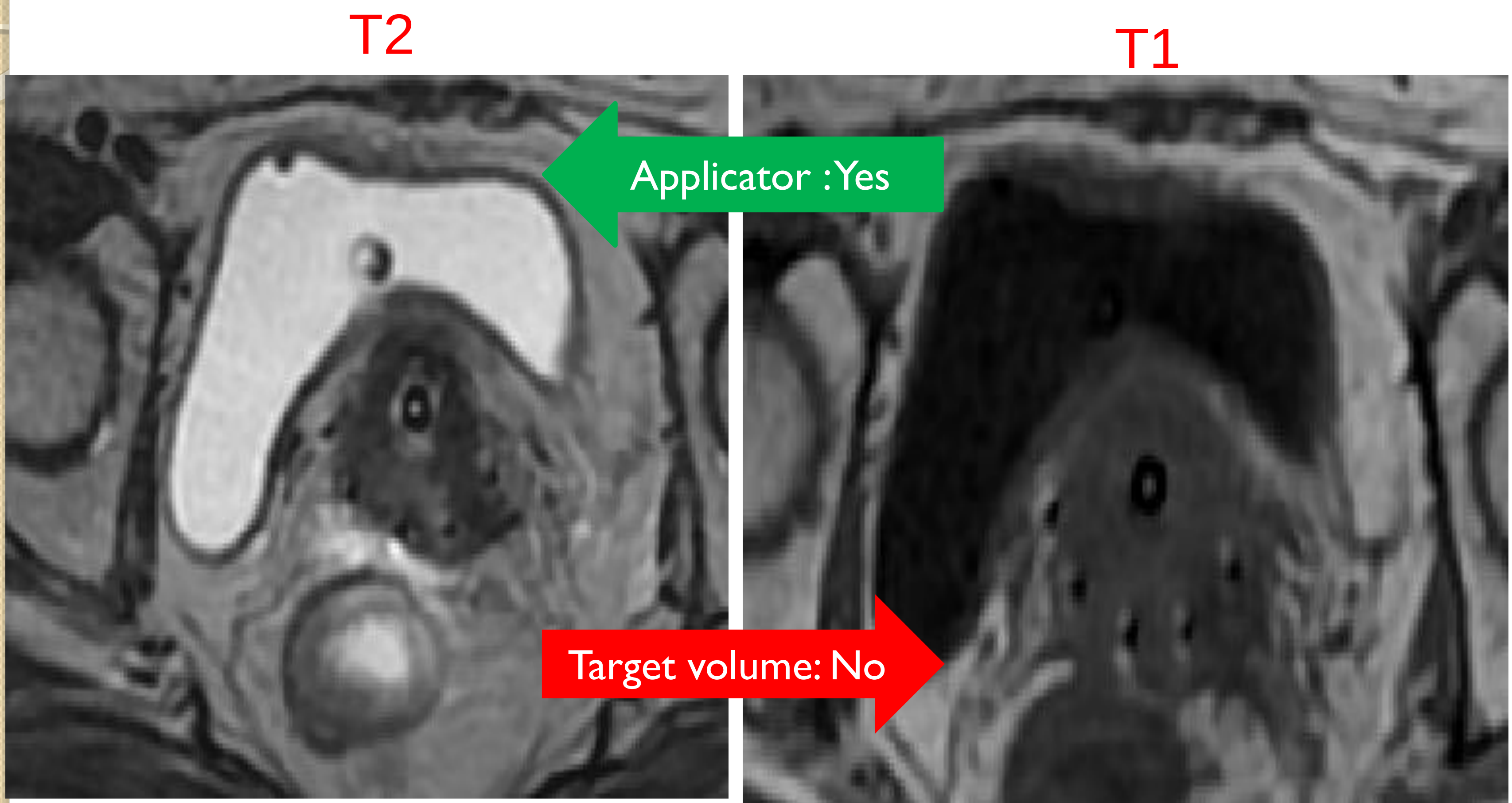




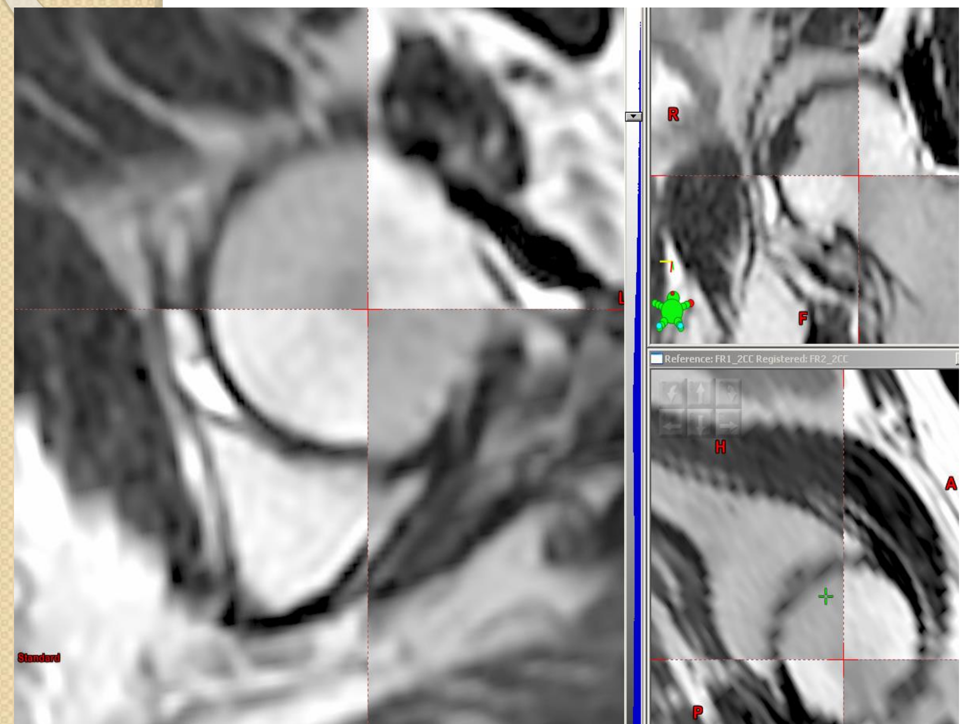
Registration of CT vs MR – Reconstruction



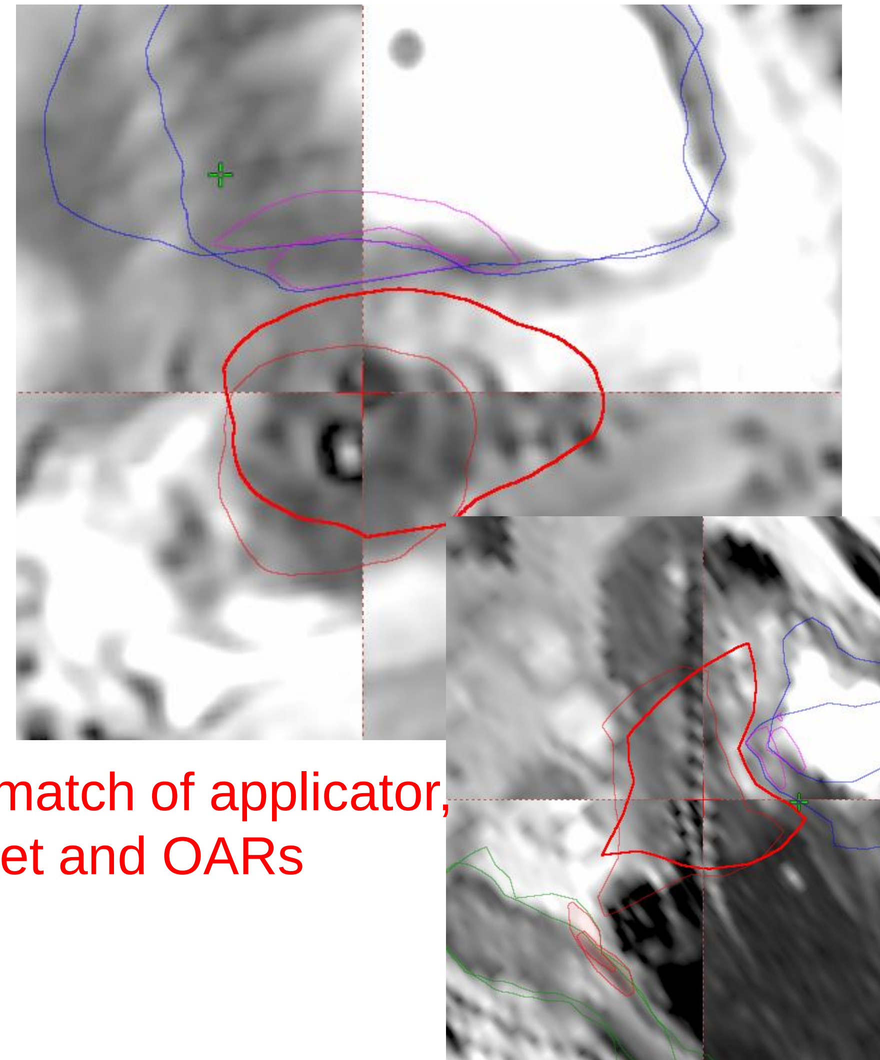
Registration of T1 vs T2 for Reconstruction



Registration in Brachytherapy – Bone as a reference ? No

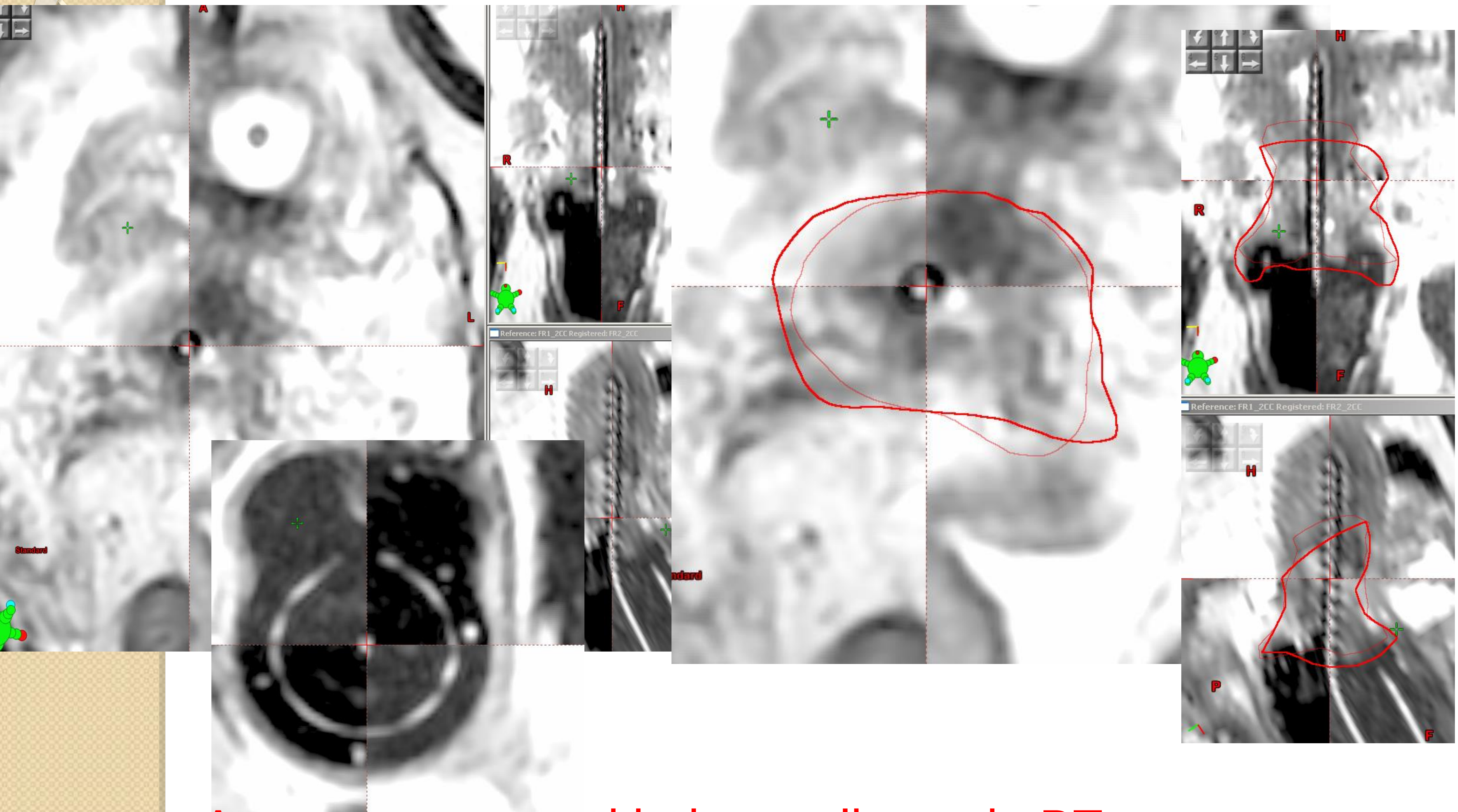


Good matching of bones



Mismatch of applicator, target and OARs

Registration in Brachytherapy – applicator as a reference? -Yes



Anatomy moves with the applicator in BT

Summary - commissioning

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

Summary

- Applicator reconstruction
  - Direct reconstruction
  - Library of applicators

- Registration
  - Applicator reconstruction based on applicator not on bone

Thank you

Leiden University Medical Center

Endometrial Cancer

Target volumes and brachytherapy techniques for definitive and post-operative treatment

ESTRO GYN teaching course,
Prague 2017

Remi Nout

With the help of: Primoz Petric, Ina Jürgenliemk-Schulz, Richard Pötter

Overview

Target concepts & brachytherapy techniques

- Postoperative brachytherapy:
  - Risk stratified approach
- Definitive treatment for intact uterus:
  - Medical inoperable (obesity)

Site of recurrence after surgery

- PORTEC-1: EBRT target volume proximal half of vagina

Outcome	Radiotherapy (n=354)			Control (n=360)		
	Number	5-year %	SE	Number	5-year %	SE
Locoregional relapse	11	4·2	1·3	40	13·7	2·1
Vaginal vault	5	1·6	0·7	19	6·4	1·4
Vagina	2	0·7	0·5	11	3·8	1·2
Pelvic	4	2·0	1·0	10	3·4	1·1

- Approximately 2/3 at vault
- Sub/peri-urethral region ~10%

➢ PORTEC-2: EBRT and VBT target volume proximal half

Institutional series >100 patients ”radiographic-era”

Author (ref) acrual period	No. patients, eligibili	Treatment	Vaginal recurrence	Locoregiona recurrence	Survival	Severe complications
Institutional series including at least 100 patients						
Sorbe et al.[35] publ 1990	404; Stage I		0,7%	3,0%	92% OS at 5-years	6.9% significant
MacLeod et al.[31] 1985-1993	141; Stage I-IIIA	4 x 8.5 Gy at surface	1,4%	2,0%	91% OS at 5-years	no grade 3/4
Weiss et al.[36] 1987-1993	122; Stage I-II	3 x 7 Gy at surface	1,6%	4,1%	94% NED at 5-years	no grade 3/4
Eltabbakh et al.[2 1958-1994	332; Stage IA grd 1-2	1 x 30 Gy LDR at surface	0,0%	0,6%	99% DFS at 5-years	2.1% grade 3/4
Petereit et al.[32] 1989-1997	191; Stage IA grd 1-2	2 x 16.2 Gy at surface ovoids	0,0%	0,5%	95% OS at 5-years	0.5% grade 4
Anderson et al.[2 1990-1996	102; Stage I	3 x 5 Gy at 0.5 cm	1,0%	1,9%	84% OS at 5-years	no grade 3/4
Horowitz et al.[29] 1989-1999	164; Stage I-II	3 x 7Gy at 0.5 cm	1,2%	0,6%	87% OS at 5-years	no grade 3/4
Alektiar et al.[25] 1987-2002	382; Stage I-II	3 x 7Gy at 0.5 cm	0,8%	0,0%	93% OS at 5-years	0.5% grd 3/0.3% grd 4
Solhjem et al.[33] 1998-2004	100; Stage I grd 2-3 a IB grd 1-2 if >2cm	3 x 7Gy at 0.5 cm	0,0%	0,0%	98% OS at 3-years	no grade 3/4
Ataham et al.[27] 1994-2005	128; Stage I	5 x 5.5 Gy at 0.5 cm	0,0%	1,6%	96% OS at 5-years	no grade 3/4

- Different: dose/fractionation & prescription
- Different applicators: most cylinder, but also ovoid, ring, mould

Studies comparing different dose levels

Author (ref) acrual period	No. patients, eligibili	Treatment	Vaginal recurrence	Locoregiona recurrence	Survival	Severe complications
Studies with different brachytherapy dose levels						
Kloetzer et al.[30] 1981-1990	108; Stage I-II	4 x 10 Gy at 0.5 cm 4 x 10 Gy at 1 cm 4 x 10 Gy at 1 cm + vag	0,0% 3,1% 0,0%	2,2% 3,1% 0,0%	98% OS at 3-years 97% OS at 3-years 97% OS at 3-years	2.2% / 0.0% grade 3/4 6.2% / 3.1% grade 3/4 6.8% / 12.6% grade 3/4
Osrund et al.[37] 1988-1996	217; Stage I-II	4 x 5.5 Gy at 0.5 cm 4 x 5.5 Gy individualized at 0.3-0.4-0.5 cm	1,0% 2,5%			26% / 8% grade 1/2 17% / 1% grade 1/2 no grade 3/4
Sorbe et al.[34] 1989-2003	290; Stage IA grd 1-2	6 x 2.5 Gy at 0.5 cm vs. 6 x 5.0 Gy at 0.5 cm	0,7%	1,4%	95% OS at 5-years	vaginal shortening 0.3 cm vs. 2.1 cm

- Higher dose + including whole length increased severe morbidity and shortening of the vagina
- Osrund: individualized prescription 0.3 – 0.4 – 0.5 cm less grade 1-2 vaginal morbidity

Randomized trials "radiographic-era"

Author (ref) acrual period	No. patients, eligibili	Treatment	Vaginal recurrence	Locoregiona recurrence	Survival	Severe complications
Randomized trial VBT versus NAT in low risk endometrial cancer						
Sorbe et al.[47] 1995-2004	645; Stage 1A grade 1	3 to 6 x 3 to 8 Gy at 0.5 cm vs. NAT	1,2% 3,1%	2,6%	96% OS at 5-years	no grade 3/4
Randomized trials VBT versus EBRT +/- VBT in (high) intermediate risk endometrial cancer						
Norwegian[1] 1968–1974	540; Stage I	1 x 60 Gy LDR at surf vs. EBRT + same VBT		6,9% 1,9%	91% OS at 5-years 89% OS at 5-years	1% grade 4 1.1% grade 4/5
PORTEC-2 2002–2006	427, age >60 IA grade IB grade 1–2 (HIR)	3 x 7Gy at 0.5 cm vs. EBRT	1,8% 1,6%	5,1% 2,1%	85% OS at 5-years 80% OS at 5-years	GI: VBT 0.5% vs 1.9% Vagina: 1.9% vs 0.5%
Swedish[7] 1997-2008	527; Stage I and (grade 3 or deep invasi or DNA aneuploidy) an nuclear grade 1-2	6 x 3 Gy at 0.5 cm 3 x 5.9 Gy at 0.5 cm 1 x 20 Gy LDR at 0.5 cm vs. EBRT + same VBT	2.7%* 1.9%*	5,0% 1,5%	90% OS at 5-years 89% OS at 5-years	grd 3 VBT vs EBRT + VBT GI: 0% vs 2% Vagina: 0.8% vs 0%

- Different dose/fractionation & prescription
- Treated lengths range proximal 1/3 – 1/2 (3-5cm)
- All seem effective

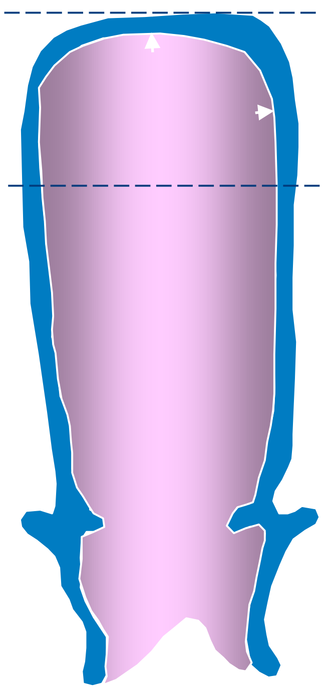
Summary literature "radiograph-era"

- Approximately 2/3 of recurrences at vault
- Effectiveness of ovoid, ring
- Higher dose and treating more length increases morbidity

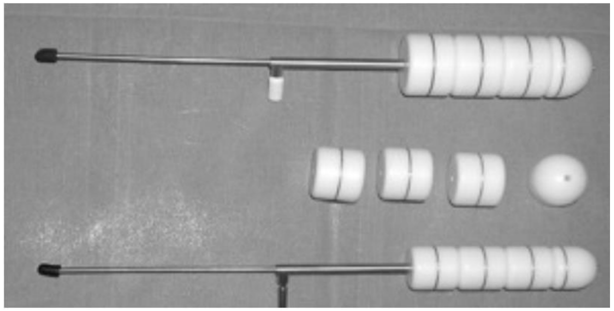
➢ Suggests that proximal 1/3 is long enough (3-4cm)

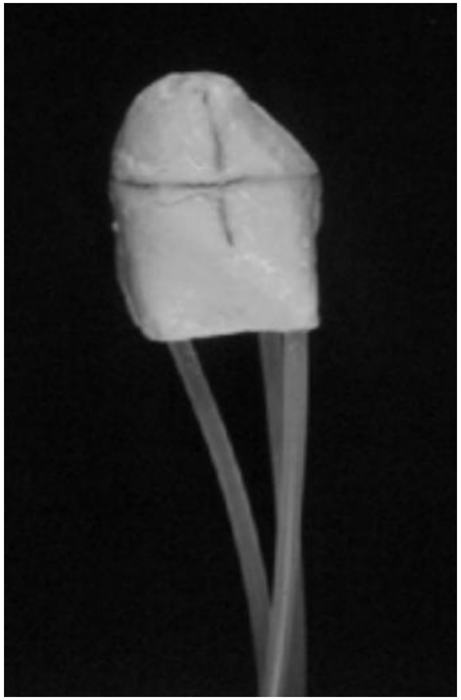
➢ PORTEC-2 & Swedish trial:

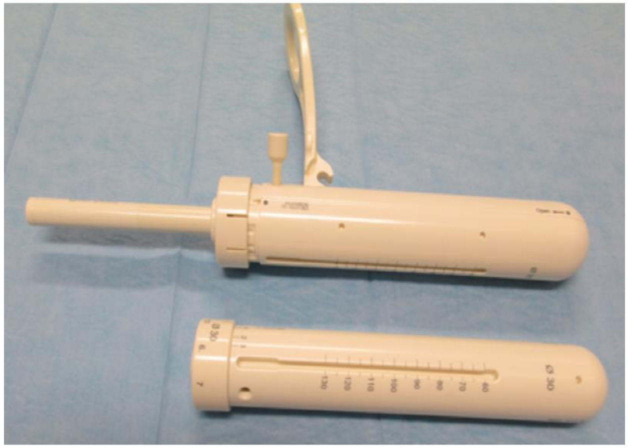
  - Vaginal recurrence 2-3%
  - Low rates of morbidity



Applicators



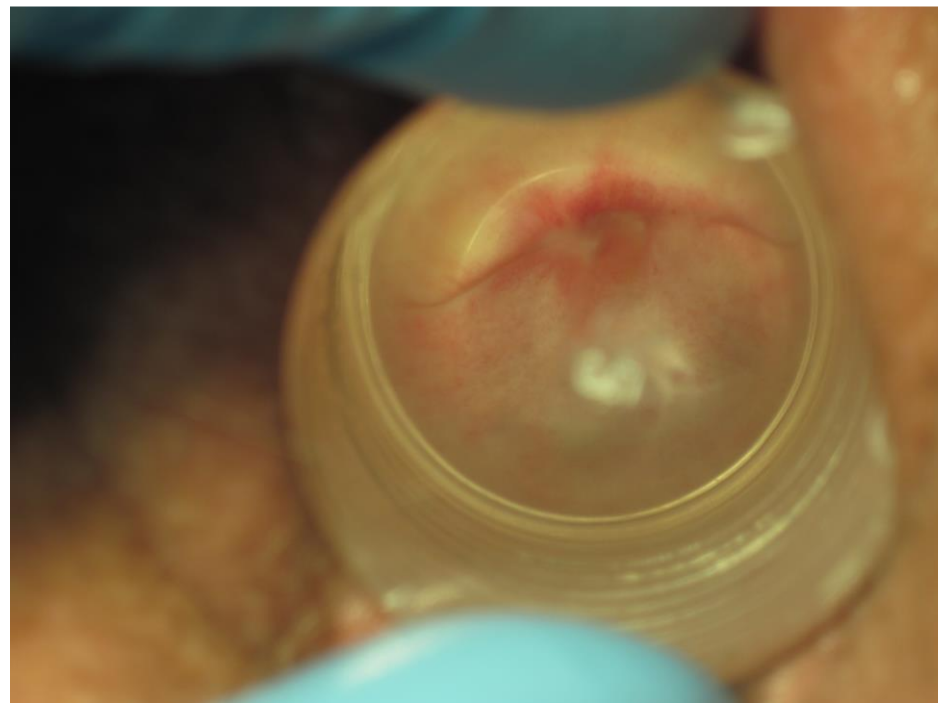




Practical points

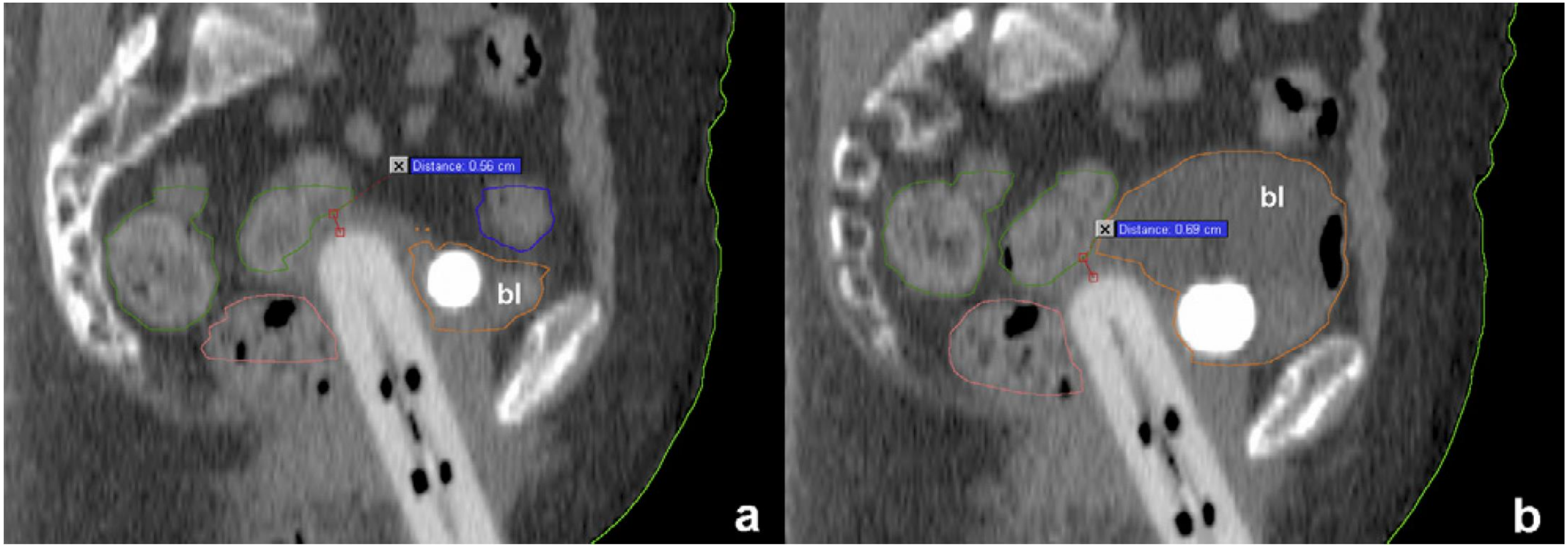
- Lubricant
- Pay attention to angle of vagina
- Make sure patient and pelvic floor muscles relax
- Measurement cylinders (plexi-glass) in different diameters
- Scale (cm) on the surface with magnifying effect





CT-based findings

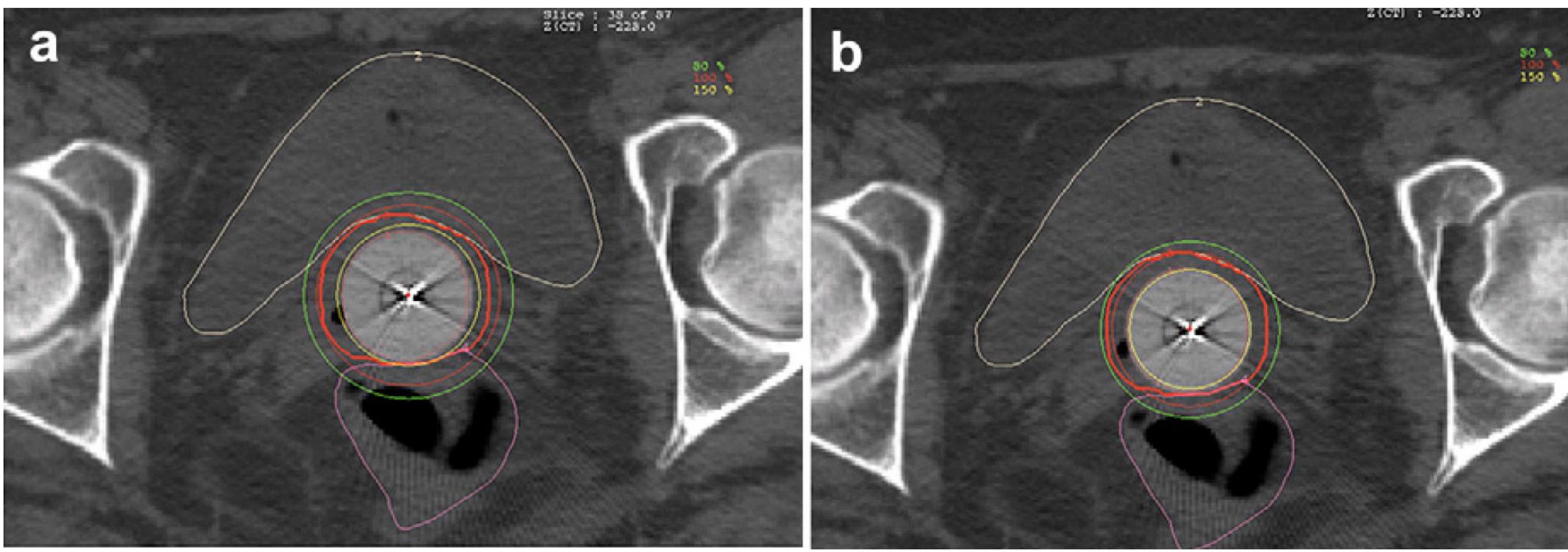
- Only first fraction CT is necessary: small within patient variaton
- Bladder filling: increased dose to bladder, decreased dose to small bowel
- Applictor angle: horizontal reduces bowel dose
- Airpockets: most distal, reduced by repositioning



Hoskin *Br J Rad* 2000; Stewart *IJROBP* 2008; Hung IJROBP 2010; Holloway *IJROBP* 2011

CT: target volume

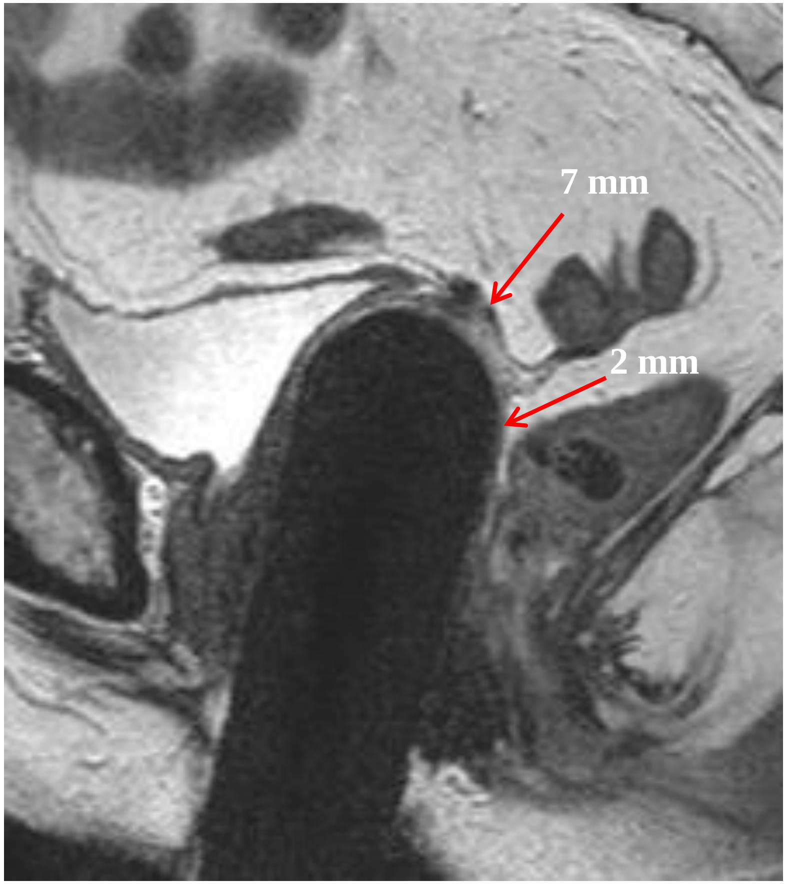
- CTV (Kim et al.):
- 0.5cm expansion of proximal 2.5cm of cylinder
- Editing to exclude bladder and rectum
- Superiorly edit based on ‘soft tissue seen’



Kim *Brachytherapy* 2012

MRI

- Superior soft tissue resolution:
- Visualization of the vaginal wall, thickness
- Surgical scar - ligaments
- Organs at risk

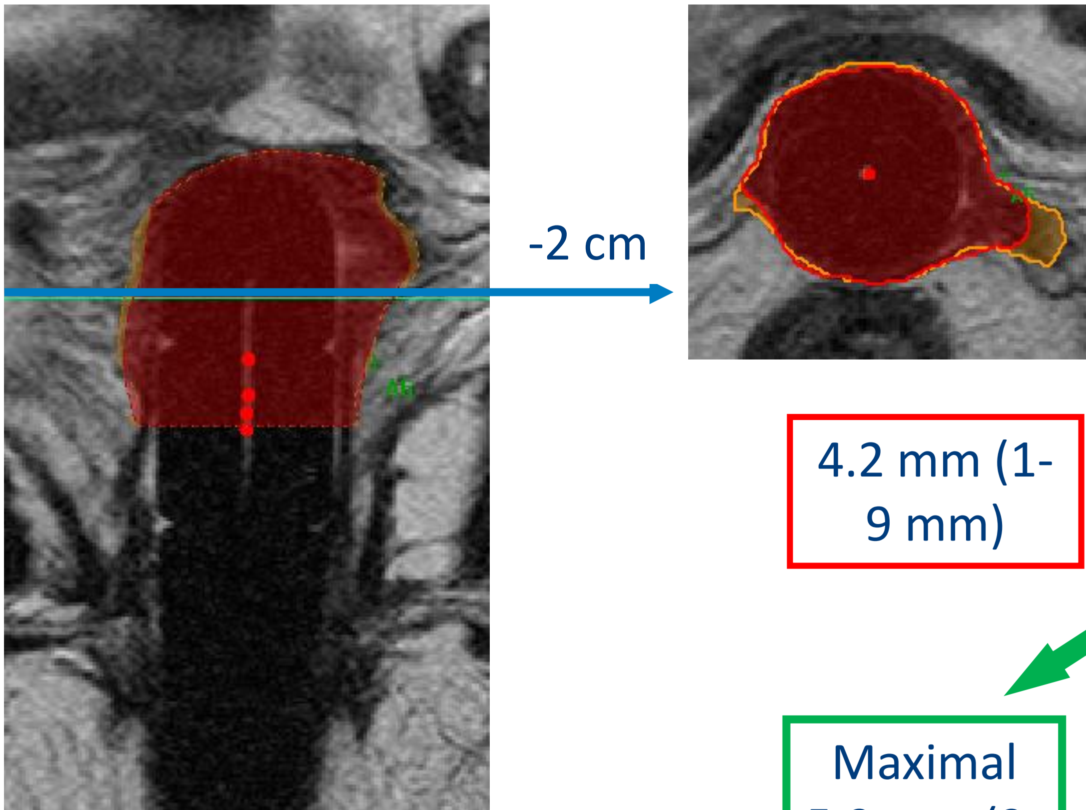


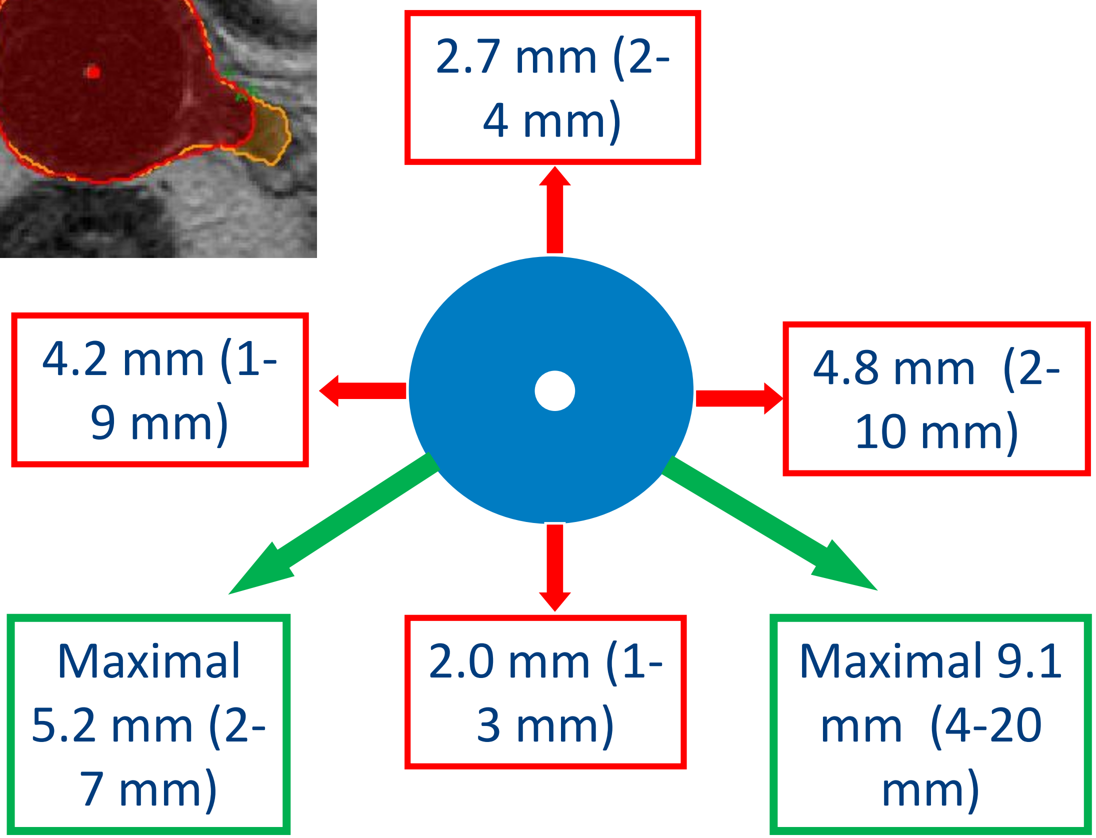
MRI: cylinder

Coronal

Axial

Mean distance to CTV (range)





MRI: cylinder

- Largest variation cranial and lateral in ‘folds’ and ligament structures

- Pathology study shows that 95% of lymph vessels are located in superficial 3 mm of vaginal tissue.

Consensus for study:

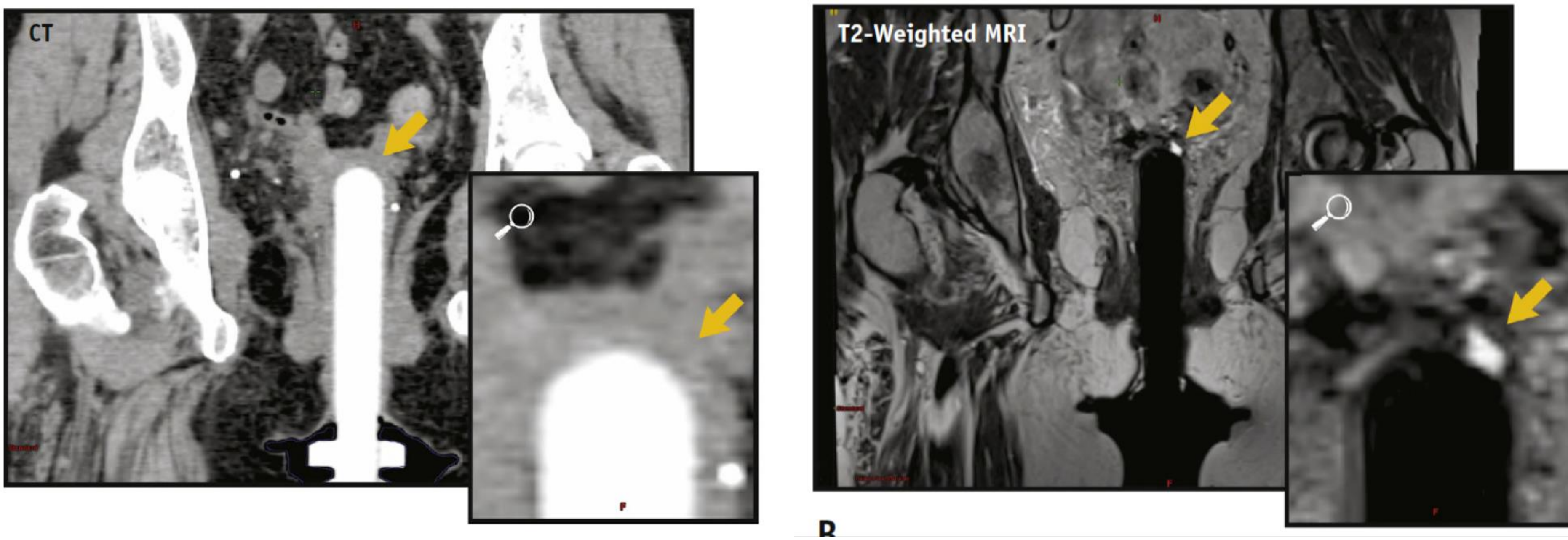
- Cylinder 3 mm ‘ring’ expansion, where necessary further expansion
- Include ‘vaginal folds’ to document dose in folds
- Exclude: ligament structures cranially; air, fluid

Nout, et al. GEC-*ESTRO* 2011; Choo et al. Brachytherapy 2005

MRI: cylinder

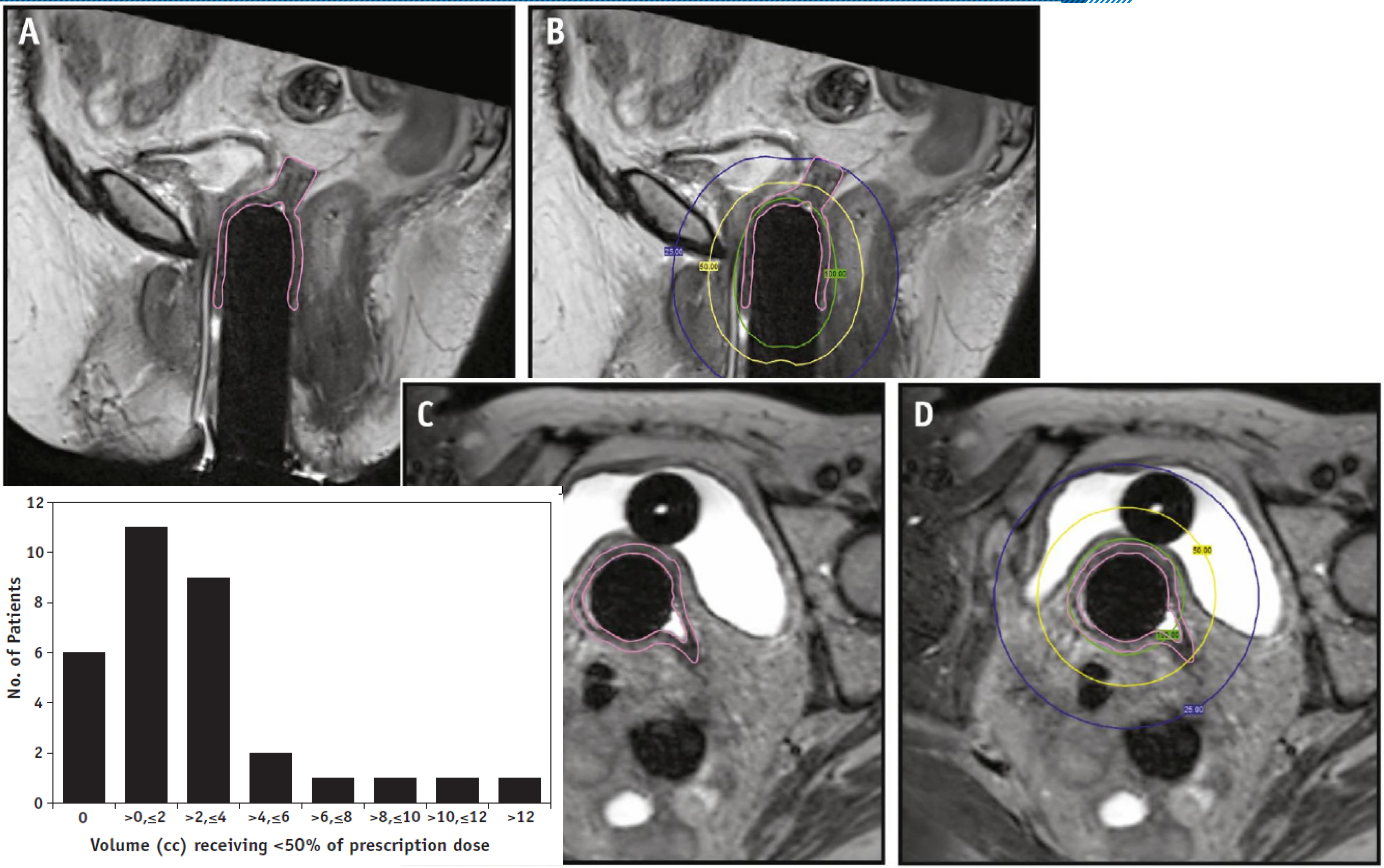
MRI-Based Evaluation of the Vaginal Cuff in Brachytherapy Planning: Are We Missing the Target?

Christina Hunter Chapman, MD,[*] Joann I. Prisciandaro, PhD,[*] Katherine E. Maturen, MD,[†] Yue Cao, PhD,[*,†,‡] James M. Balter, PhD,[*,‡] Karen McLean, MD, PhD,[§] and Shruti Jolly, MD[*]



Hunter Chapman et al. *IJROBP* 2015

MRI: cylinder



Hunter Chapman et al. *IJROBP* 2015

Summary CT-MRI

- More information on dose to OAR:
- Moderate bladder filling; horizontal angle

- MRI, visualization of vaginal wall:
- 0.3cm thick wall / ring, expand and include folds
- “Dog ears” potential under dosage
- Clinical relevance? (good clinical results)

- Aim: ensure optimal contact between applicator surface and vaginal wall, consider:
- Applicator: size cylinder, ovoid, ring, mould
- Position verification: X-ray, CT (MRI), marker

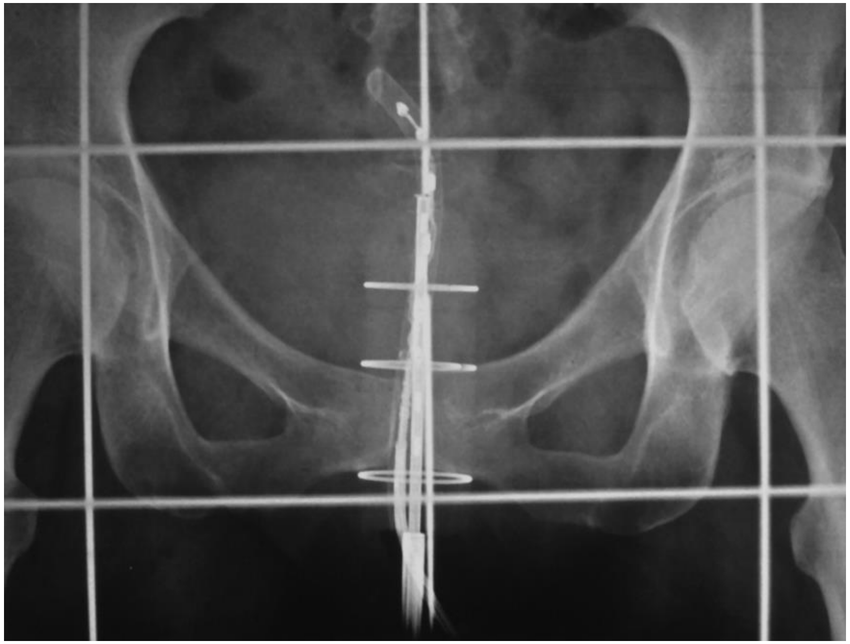
Treatment planning (other presentation)

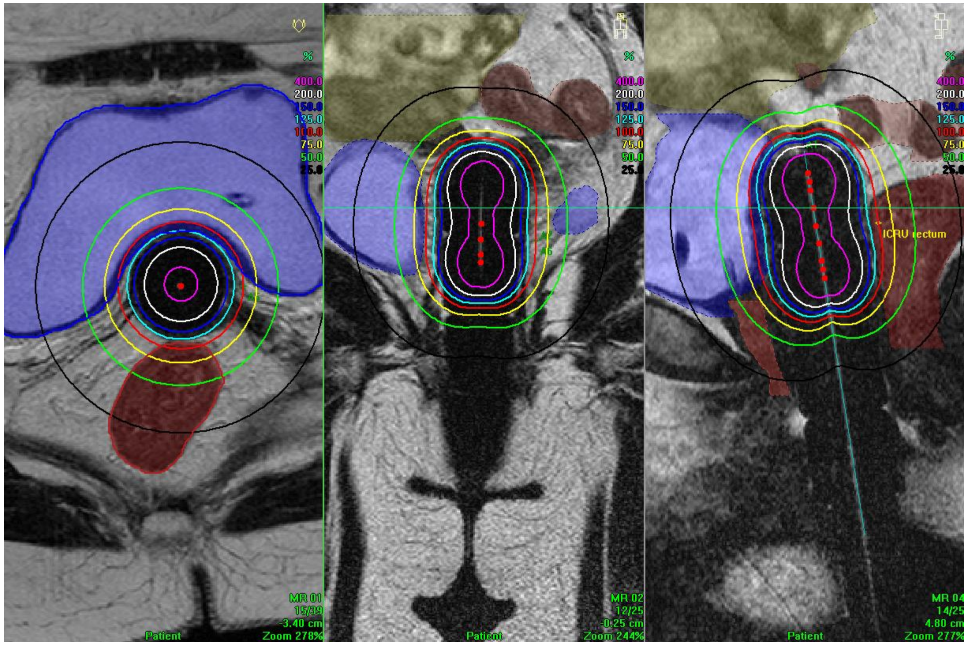
- Traditional standard treatment planning

- Orthogonal radiographs
- based on applicator dimensions, prescription depth and length

- 3D image guided treatment planning

- Based on target volumes and organs at risk

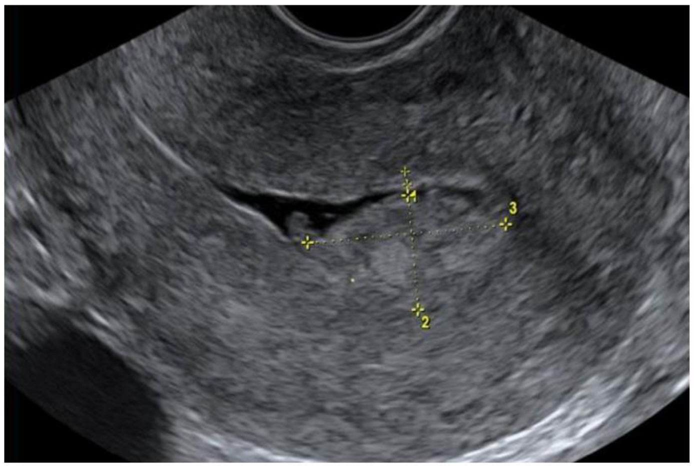




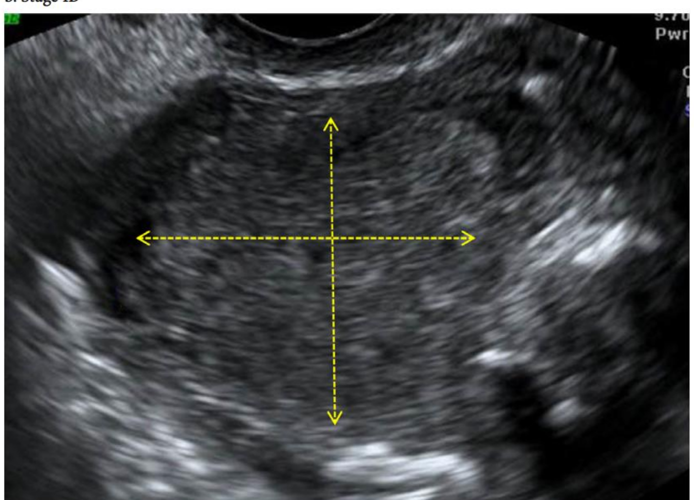
Endometrial cancer: imaging

- Ultrasound

a. Stage IA

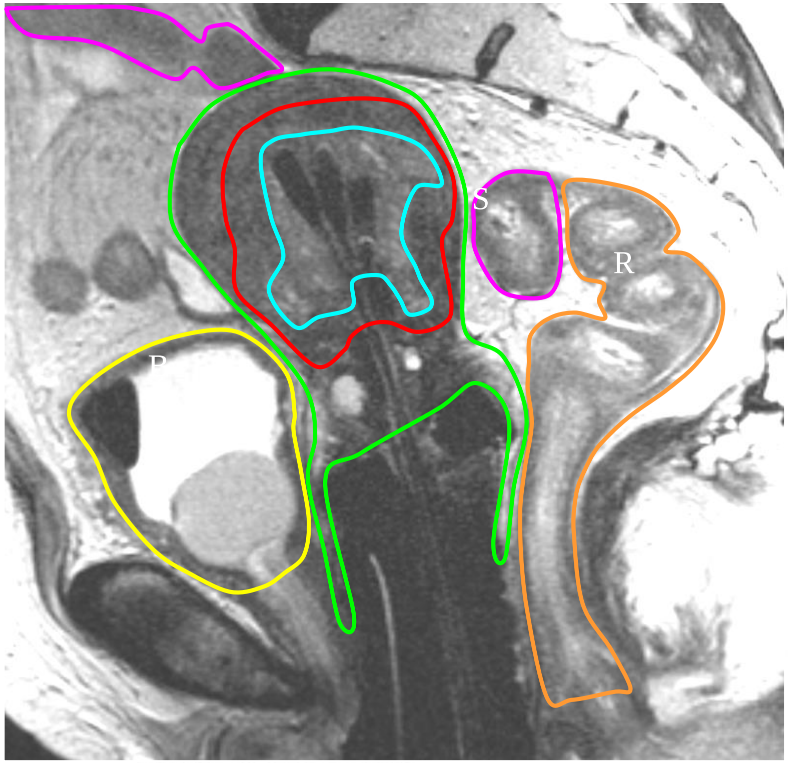


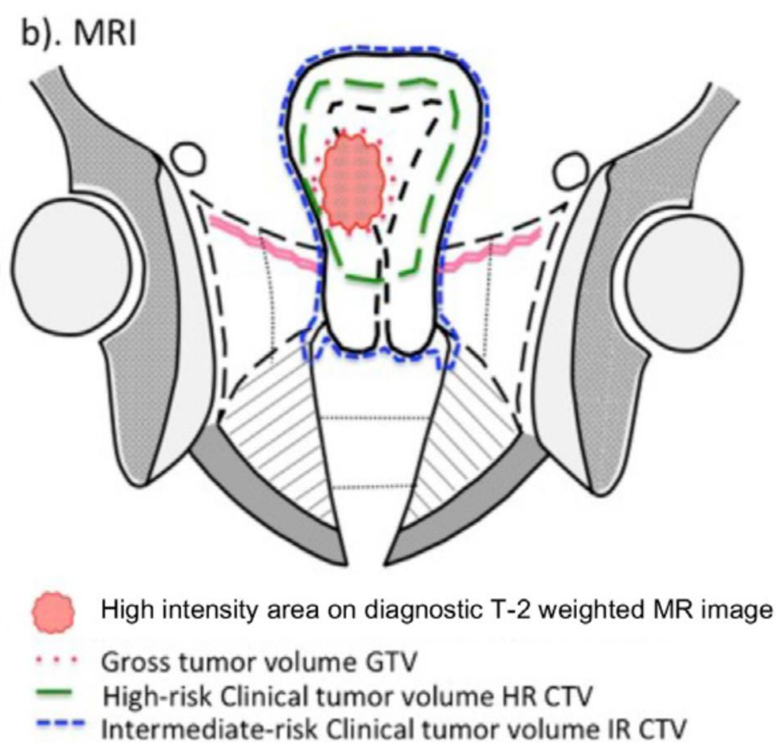
b. Stage IB



- MRI: gold standard
  - Superior to US/CT
  - Staging accuracy 85-93%

Target concept endometrium

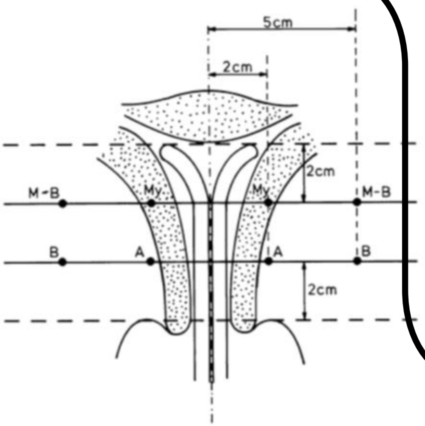




- CTV: whole uterus, cervix and upper 1/3 of vagina
  - Take all information into account (colposcopy, imaging) to delineate GTV
  - Depending of pattern of spread parametrial and paravaginal tissue may be included

Inoperable endometrial cancer: Review

Radiograph-era HDR:
955 patients
Local control
70%-90%



Author	Patient No.	Applicators	Dose prescription	Total dose in EQD2 ($\alpha/\beta = 10$)	Local control rates	Severe late complication rates (Grade 3–4) (%)
2D HDR						
Taghian et al[44]	104	NA	NA	NA	87.6% at 5 years; 85.1% at 10 years	17
Rouanet et al[45]	250	NA	NA	NA	75.9% at 5 years	3
Nguyen et al[46]	27	Tandem alone or one tandem and ovoid applicators	HDR alone: 20 Gy/2–3 Fr or EBRT WP 42 Gy + HDR 20 Gy/2–3 Fr	HDR alone: 27.4 Gy, or EBRT + HDR: 69.4 Gy	85.2% at 4 years	11
Knocke et al 1995 and 1997[47,48]	280	One channel intracavitary and intravaginal applicators	4–5 Fr × 8.5 Gy	52.4–65.5 Gy	75.4% at 5 years; 70% at 10 years	5.2
Kucera et al[49]	228	One-channel intracavitary and intravaginal applicators	4–5 Fr × 8.5 Gy	52.4–65.5 Gy	76.6% at 5 years; 73.9% at 10 years	4.6
Nguyen and Petereit[51]	36	One tandem and ovoid or cylinder applicators	5 Fr × 9 Gy	71.3 Gy	88% at 3 years	21
Fusco et al[50]	41	NA	EBRT WP 45–50 Gy + HDR 2–3 × 6–8 Gy	68.3–86 Gy	NA	10 (GI: Grade 2–3)
Inciura et al[52]	29	Three-channel intrauterine applicators	EBRT WP 16 Gy + HDR 5 Fr × 10 Gy	99.3 Gy	82.8% at 5 years	0 (Grade 1–2: 13.8%)
Ohkubo et al[33]	10	Rotte "Y" applicator	EBRT WP 30–30.6 Gy + HDR 4 Fr × 6 Gy (retrospective dose analysis in 3D)	62 Gy	100% at 5 years	0
3D HDR						
Weitmann et al[32]	13	Norman–Simon applicators with Heyman packing	6 Fr × 7 Gy to CTV (whole uterus, cervix and upper vagina)	59.5 Gy	100% at 4 years	0
Coon et al[34]	18	Rotte "Y" applicators	EBRT WP 45–50 Gy + HDR 5 Fr × 4 Gy, or HDR 5 Fr × 7 Gy b.i.d alone to CTV (whole uterus, cervix and upper vagina)	EBRT + HDR: 69.3–74.6 Gy, HDR only: 49.6 Gy	93.9% at 3 years	0 (13% was reported in 2D cases of this study)

CTV D90 ~ 60Gy

3D-HDR:
31 patients
Local control
90%-100%

Dankulchai & Hoskin BJR 2014

Applicators

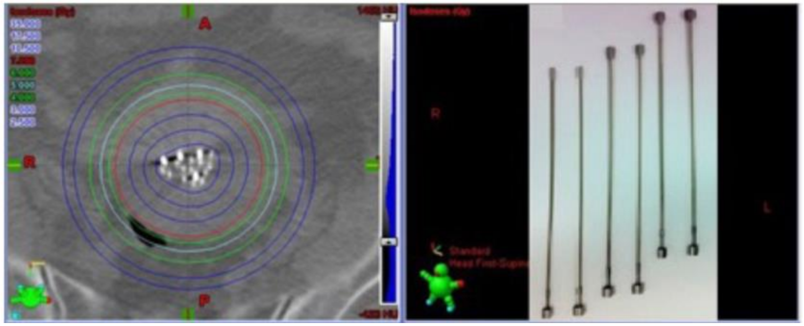
Intracavitary techniques

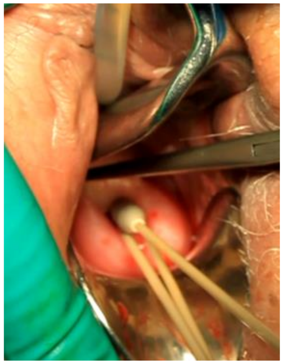
Individualised packing methods:

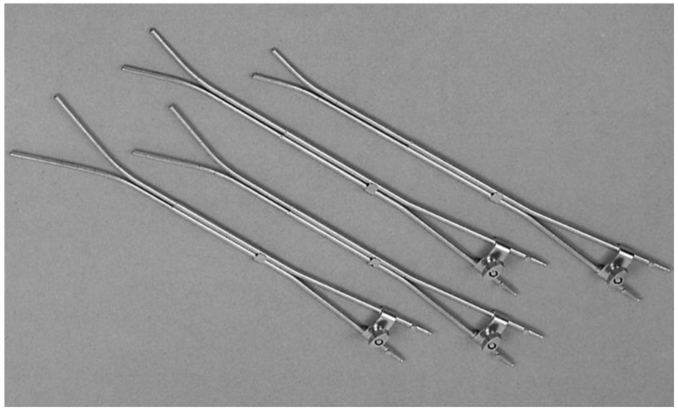
- Modified Heymann Packing
- Umbrella Technique

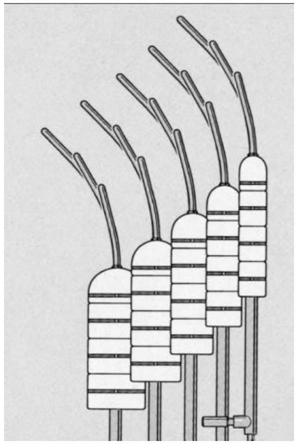
Standard applicators:

- Two or three channel applicator
- One channel applicator



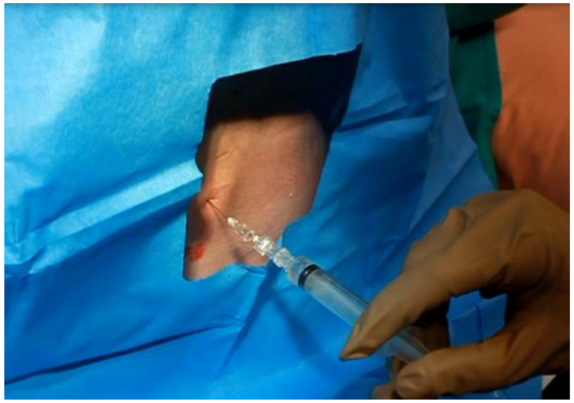


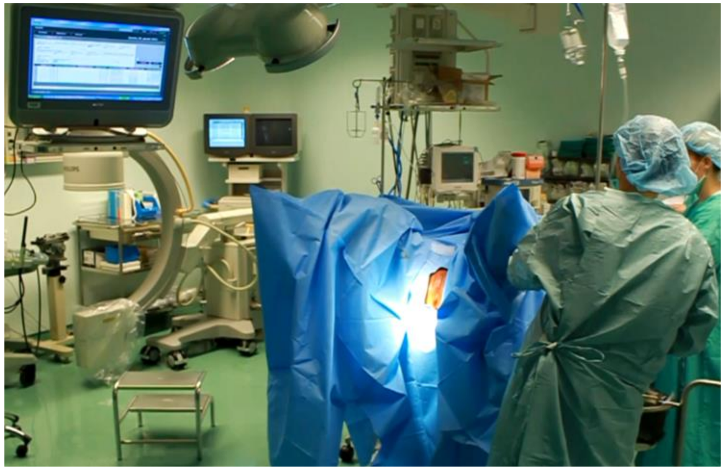


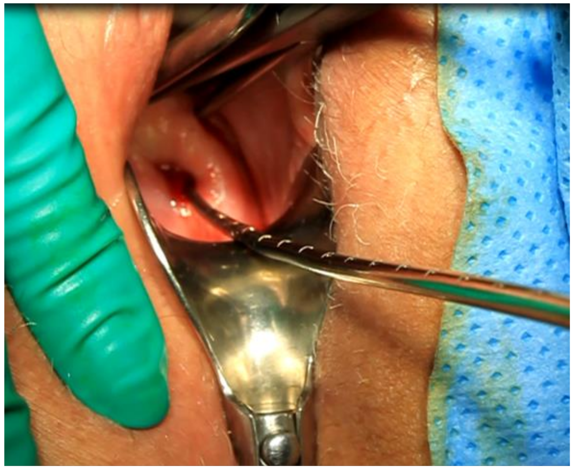


Practical points

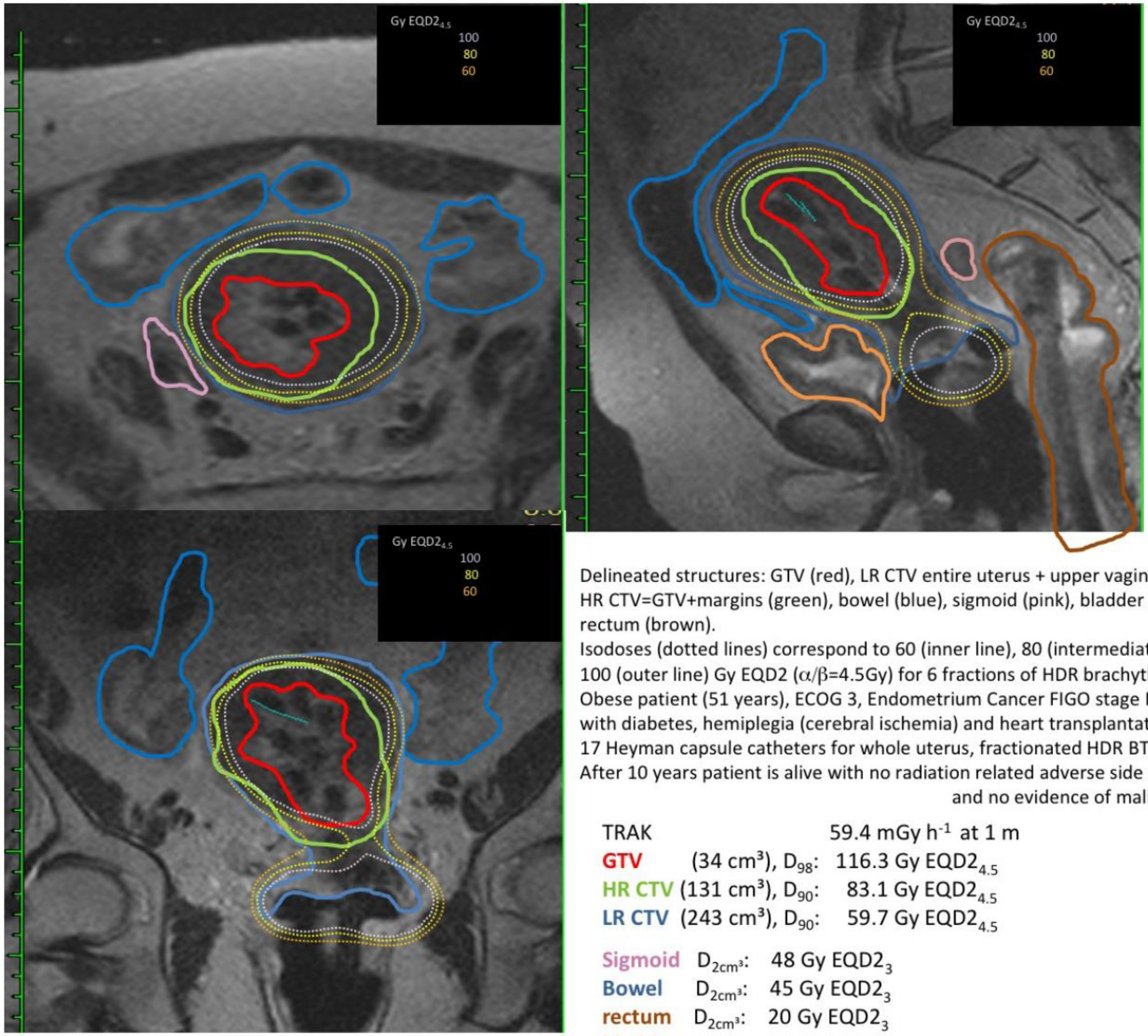
- Collaboration anaesthesiologist; consider local anaesthesia
- Co-morbidity & feasibility







Treatment planning (other presentation)



Delineated structures: GTV (red), LR CTV entire uterus + upper vagina (blue), HR CTV=GTV+margins (green), bowel (blue), sigmoid (pink), bladder (yellow), rectum (brown).
Isodoses (dotted lines) correspond to 60 (inner line), 80 (intermediate line) and 100 (outer line) Gy EQD2 (α/β=4.5Gy) for 6 fractions of HDR brachytherapy alone.
Obese patient (51 years), ECOG 3, Endometrium Cancer FIGO stage II, with diabetes, hemiplegia (cerebral ischemia) and heart transplantation, 17 Heyman capsule catheters for whole uterus, fractionated HDR BT, 2005;
After 10 years patient is alive with no radiation related adverse side effects and no evidence of malignant disease..

TRAK		59.4 mGy h^{-1} at 1 m
GTV	($34\ cm^3$), D_{98}:	116.3 Gy EQD$2_{4.5}$
HR CTV	($131\ cm^3$), D_{90}:	83.1 Gy EQD$2_{4.5}$
LR CTV	($243\ cm^3$), D_{90}:	59.7 Gy EQD$2_{4.5}$

Sigmoid	D_{2cm^3}:	48 Gy EQD2_3
Bowel	D_{2cm^3}:	45 Gy EQD2_3
rectum	D_{2cm^3}:	20 Gy EQD2_3
bladder	D_{2cm^3}:	53 Gy EQD2_3

Vaginal recurrence (other presentation)

Toward four-dimensional image-guided adaptive brachytherapy in locally recurrent endometrial cancer

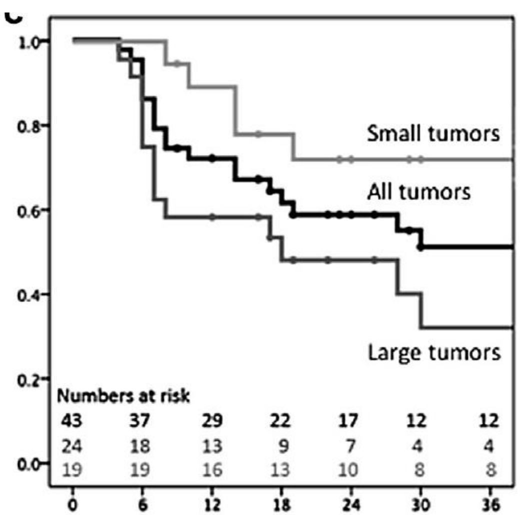
Lars Fokdal[1,*], Gitte Ørtoft[2], Estrid S. Hansen[3], Lisbeth Røhl[4], Erik Morre Pedersen[4], Kari Tanderup[1,5], Jacob Christian Lindegaard[1]

Brachytherapy 2013

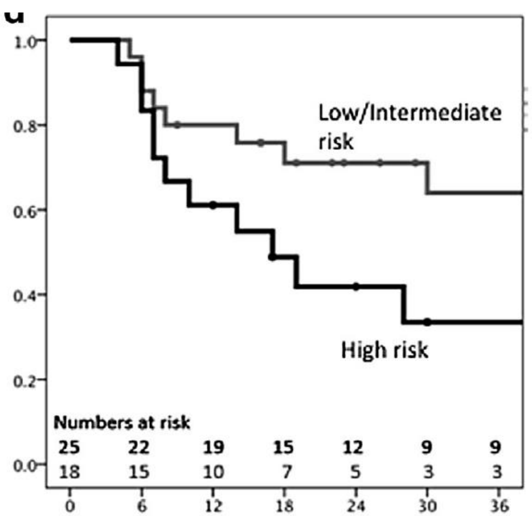
Aarhus 2006-2013 N=43; PDR; median follow-up 30 months

24 interstitial – 19 intracavitary

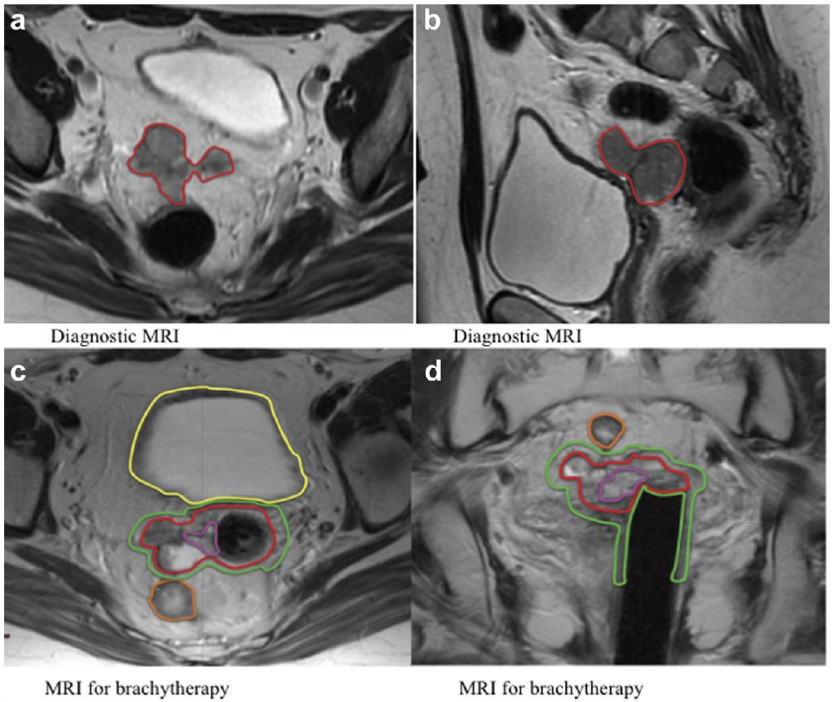
Late grade 3 morbidity 12%



Disease free survival by tumor size



Disease free survival by risk group



Conclusions

- Postoperative brachytherapy:
- Upper 1/3, ensure optimal contact with applicator
- 3D imaging: position verification
- 3D individualised optimization: for boost or recurrent disease

- Definitive treatment:
- Medical inoperable, rare (obesity)
- MRI gold standard
- Move towards 3D image guided approaches

ICRU-GEC-ESTRO recommendations on dose volume reporting

Richard Pötter

OUTLINE: Dose volume reporting in cervix cancer brachytherapy

- The major publications: 3D Cervix BT dose volume reporting

  GEC ESTRO Recommendations II (2005), ICRU Report 89 (2016)
- Learning Objectives (6-7)
- The level approach: minimum, advanced, research standards
- Minimum standards for reporing (9-33)
- Advanced standards for reporting (34-51)
- Equi-effective Doses and total dose reporting (52-55)
- Limitations (56-59)
- From Planning Aims to Prescription (60-63)
- Example 5 ICRU report 89: IIB, HDR BT ring/needles, (64-69)

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]

[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*

PRESCRIBING, RECORDING, AND REPORTING BRACHYTHERAPY FOR CANCER OF THE CERVIX (ICRU GEC ESTRO REPORT 88)

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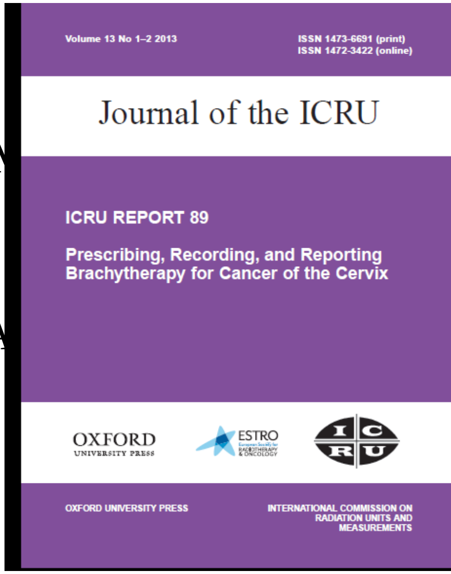
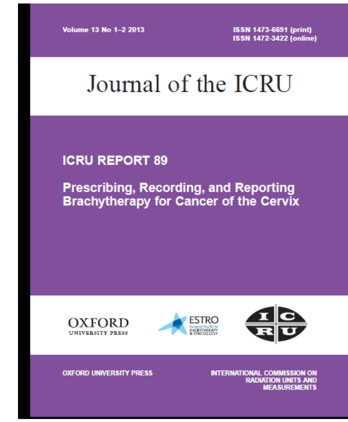


ICRU/GEC ESTRO recommendations for prescribing and reporting brachytherapy for cancer of the cervix



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 (ICRU 89)

- **Level 1 -** ***Minimum standard for reporting***

  Level 1 describes the minimum requirements that should be followed at all centers, for all patients, and represents the minimum standard of treatment;

- **Level 2 -** ***Advanced standard for reporting***

  Level 2 indicates advanced standards of dose planning and treatment that allows a more comprehensive and standardized exchange of information between centers and is based on a more complete set of parameters;

- **Level 3 -** ***Research oriented reporting***

  Level 3 describes new forms of planning and treatment largely related to research and development for which reporting criteria are yet to be established.

ICRU 89, 2016, Summary level 1, p. 161

Level 1: *Minimum standard for reporting*

Volumetric-imaging approximation based on:

- Comprehensive clinical gynecologic examination
- Volumetric imaging (MR, CT, US, PET–CT) at the time of diagnosis and brachytherapy

FIGO/TNM stage

Baseline morbidity and QoL assessment

Schematic 3D documentation on a clinical diagram indicating dimensions (width, thickness, height) and volumes for:

- GTV_{init} (the GTV at diagnosis)
- GTV_{res} (the GTV at brachytherapy)
- CTV_{HR} [the GTV_{res} (if present) plus residual pathologic tissue (if present) plus whole cervix]
- (CTV_{IR}: area of GTV_{init} and/or CTV_{HR} plus safety margin if used for prescription)

Dose reporting:

- TRAK
- Point A dose
- Recto-vaginal reference-point dose
- $D_{0.1cm^3}$ and D_{2cm^3} for the bladder and rectum

Dose delivery pattern:

- Absorbed-dose rate/dose per fraction
- Number of fractions
- Time between fractions
- (Pulse number, size, time, if PDR)
- Overall treatment time
- Total EQD2 dose

Source and dose calculation:

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

Radiographic approximation based on:

- Comprehensive clinical gynecologic examination
- Radiographic imaging (plus additional volumetric 3D imaging if available)

FIGO/TNM stage

Baseline morbidity and QoL assessment

Schematic 3D documentation on a clinical diagram indicating dimensions [width, thickness, (height)] and volumes for:

- GTV_{init} (the GTV at diagnosis)
- GTV_{res} (the GTV at brachytherapy)
- CTV_{HR} [the GTV_{res} (if present) plus residual pathologic tissue (if present) plus whole cervix]
- (CTV_{IR}: area of GTV_{init} and/or CTV_{HR} plus safety margin if used for prescription)

Dose reporting:

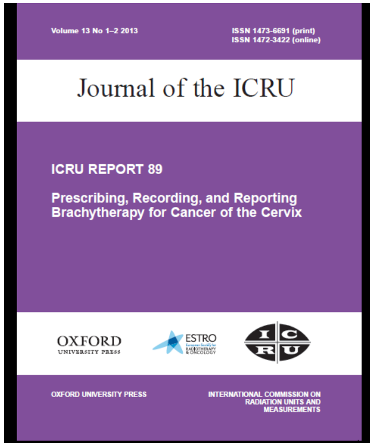
- TRAK
- Point A dose
- Recto-vaginal reference-point dose
- Bladder reference-point dose

Dose delivery pattern:

- Absorbed-dose rate/dose per fraction
- Number of fractions
- Time between fractions
- (Pulse number, size, time, if PDR)
- Overall treatment time
- Total EQD2 dose

Source and dose calculation:

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



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*

Clinical and volume reporting

- **Comprehensive clinical gynecologic examination (diagnosis, BT)**
- **Volumetric imaging (MRI, CT, US, PET CT) at time of diagnosis and BT (as available)**
- **TNM (FIGO) stage**
- **Baseline morbidity and QoL assessment**
- **Schematic 3D documentation on a clinical diagram indicating dimensions 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

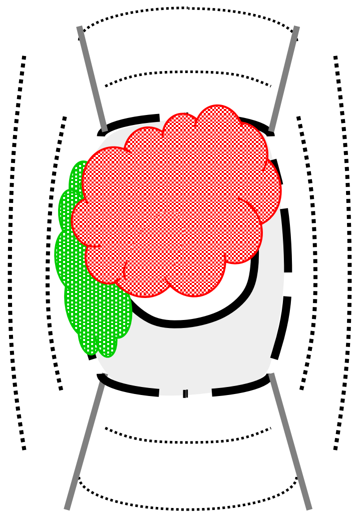
At Brachytherapy ☐

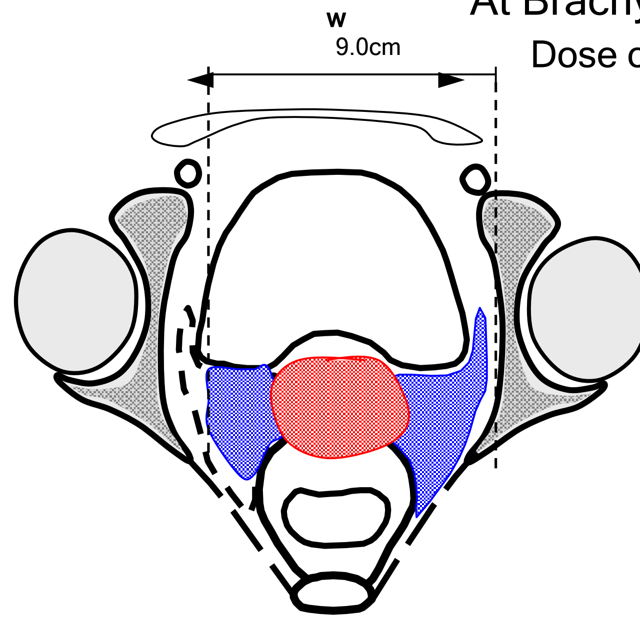
Dose of EBRT ____ Gy

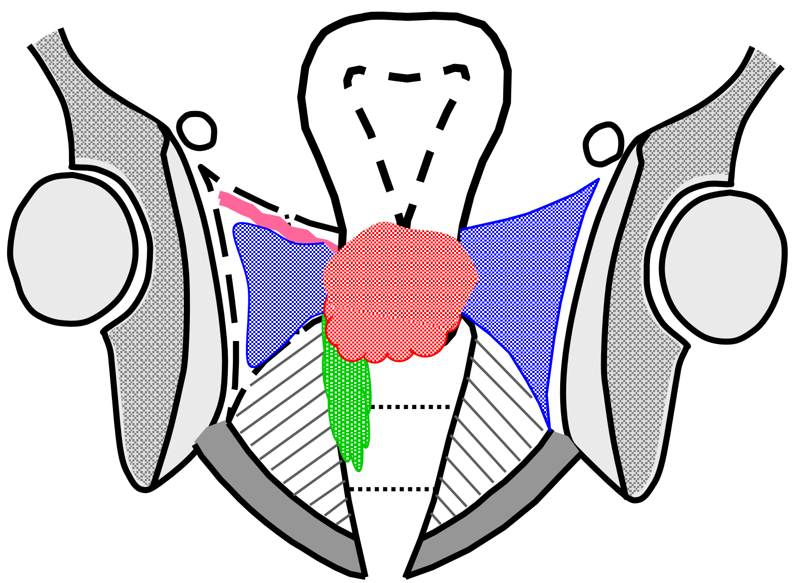
IIIB

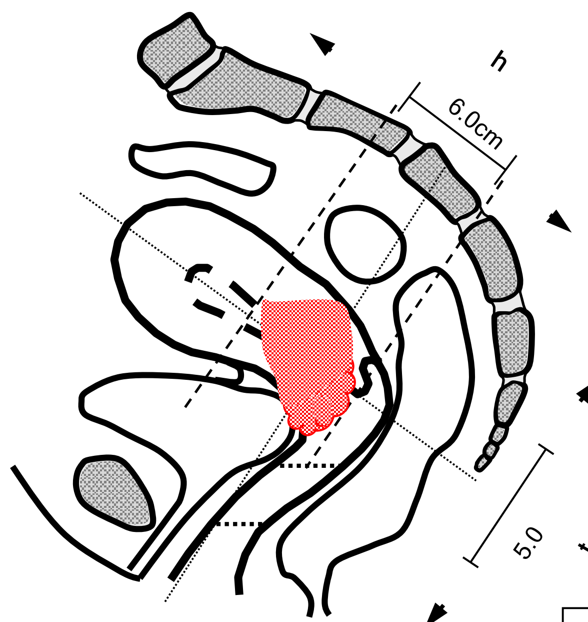
w = 9.0 cm
h = 6.0 cm
t = 5.0 cm

Vagina: 5 cm









dd/mm/yy
___/___/___

____
Signature

Note: vagina and parametria not included in h

Case IV

At Diagnosis ☐

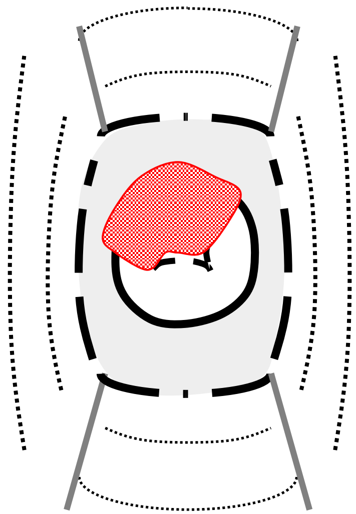
At Brachytherapy ☒

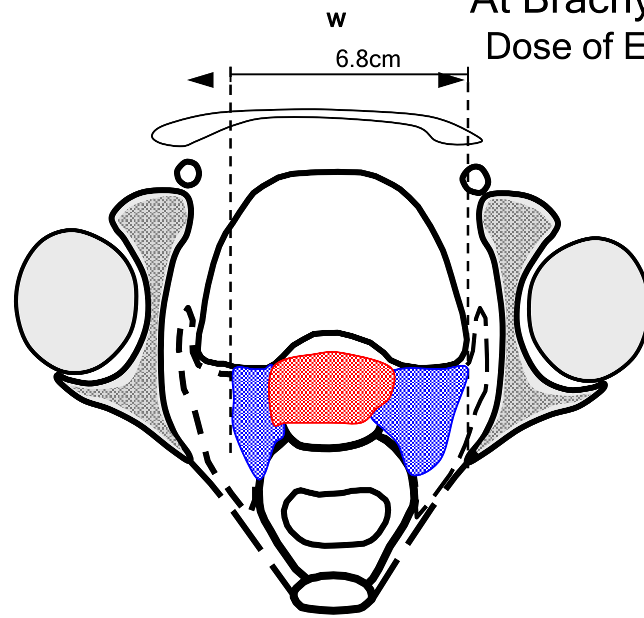
Dose of EBRT 50.4 Gy

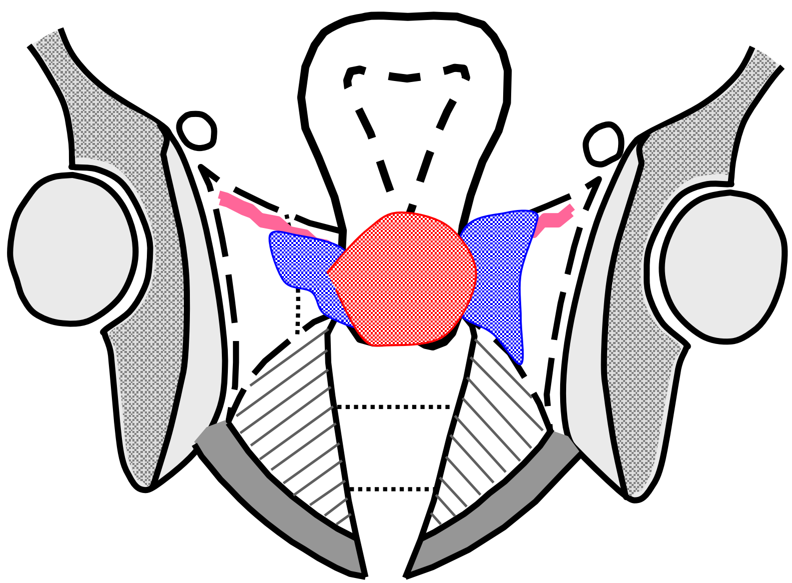
IIIB

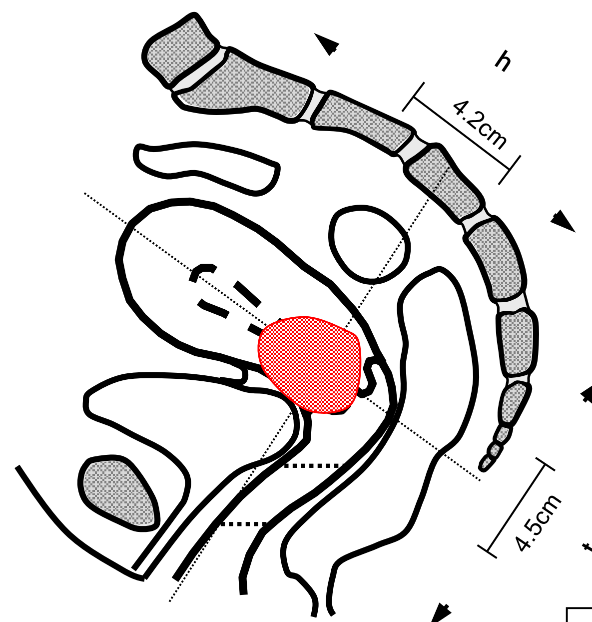
w = 6.8 cm
h = 4.2 cm
t = 4.5 cm

Vagina: 0 cm









dd/mm/yy
___/___/___

____
Signature

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

Case IV

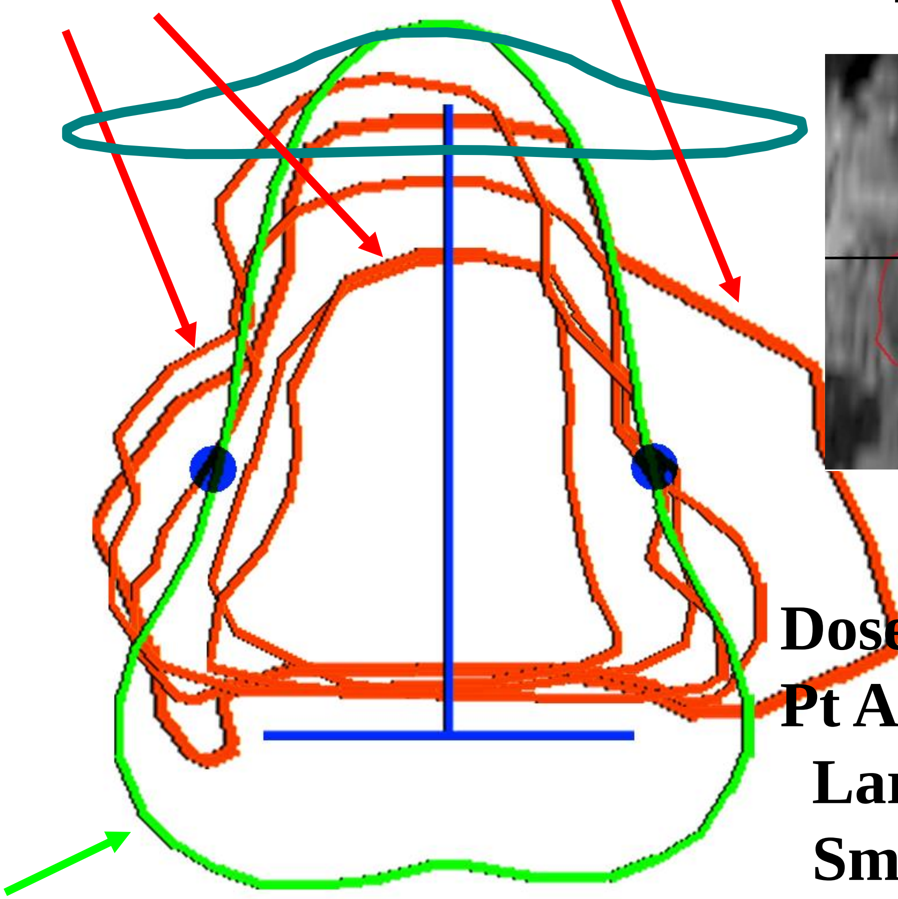
Level 1 – *minimum standard for reporting*

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

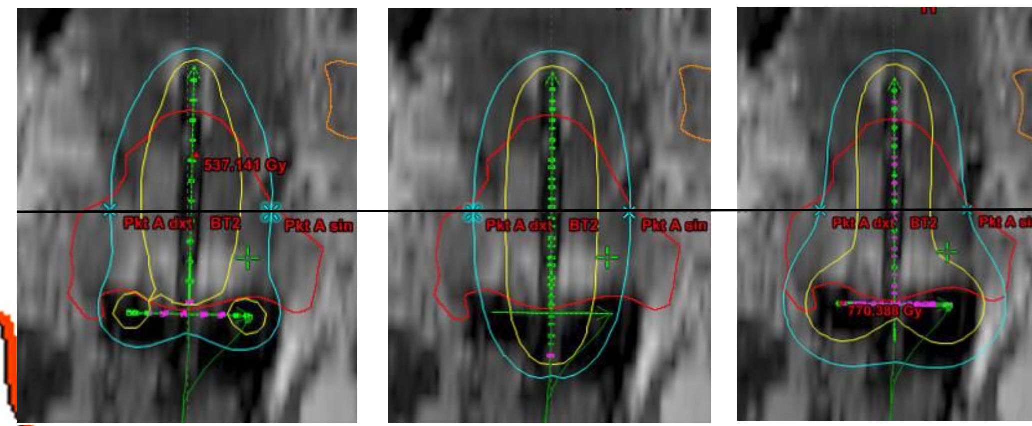
Point-A based brachytherapy: the dilemma facing a target volume

Small to large HR CTVs



Point A standard isodose

Milwaukee Toronto Vienna

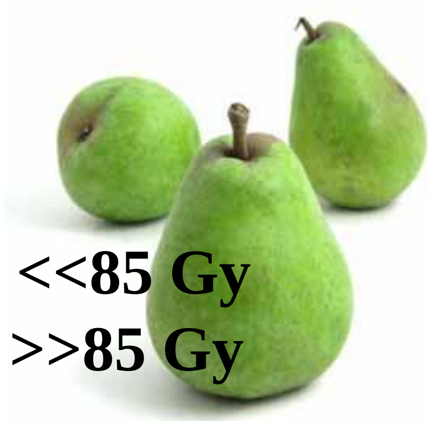


Doses:

Pt A: 85 Gy

Large HR CTVs: <<85 Gy

Small HR CTVs: >>85 Gy



Reporting Dose Delivery Pattern - Level 1

ICRU 89

Minimum standard for reporting

Absorbed dose rate/dose per fraction

Number of fractions

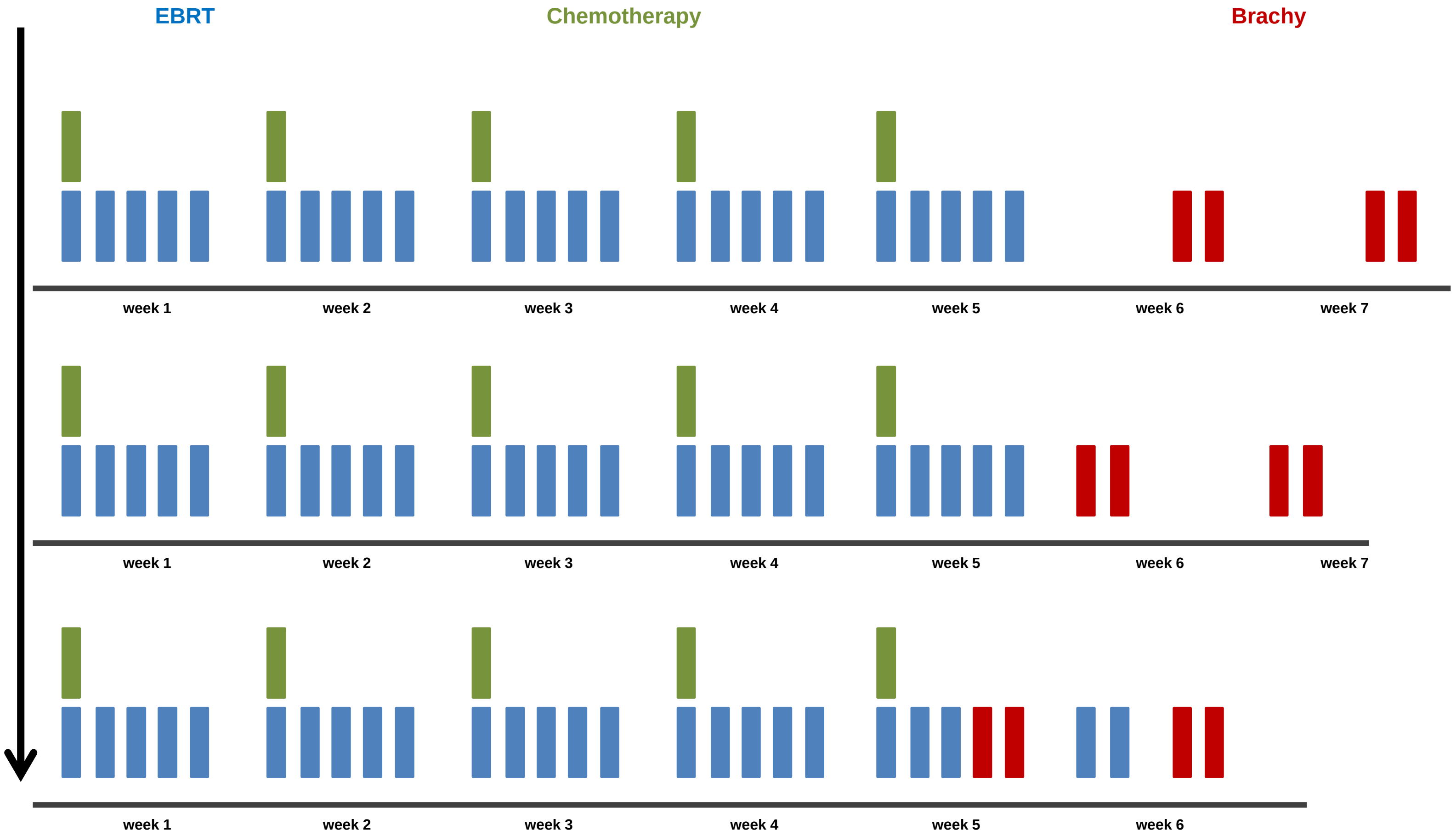
Time between fractions

(Pulse number, size, time, if PDR)

Overall treatment time

Total EQD2

Overall Treatment Time (BT, EBRT, total)

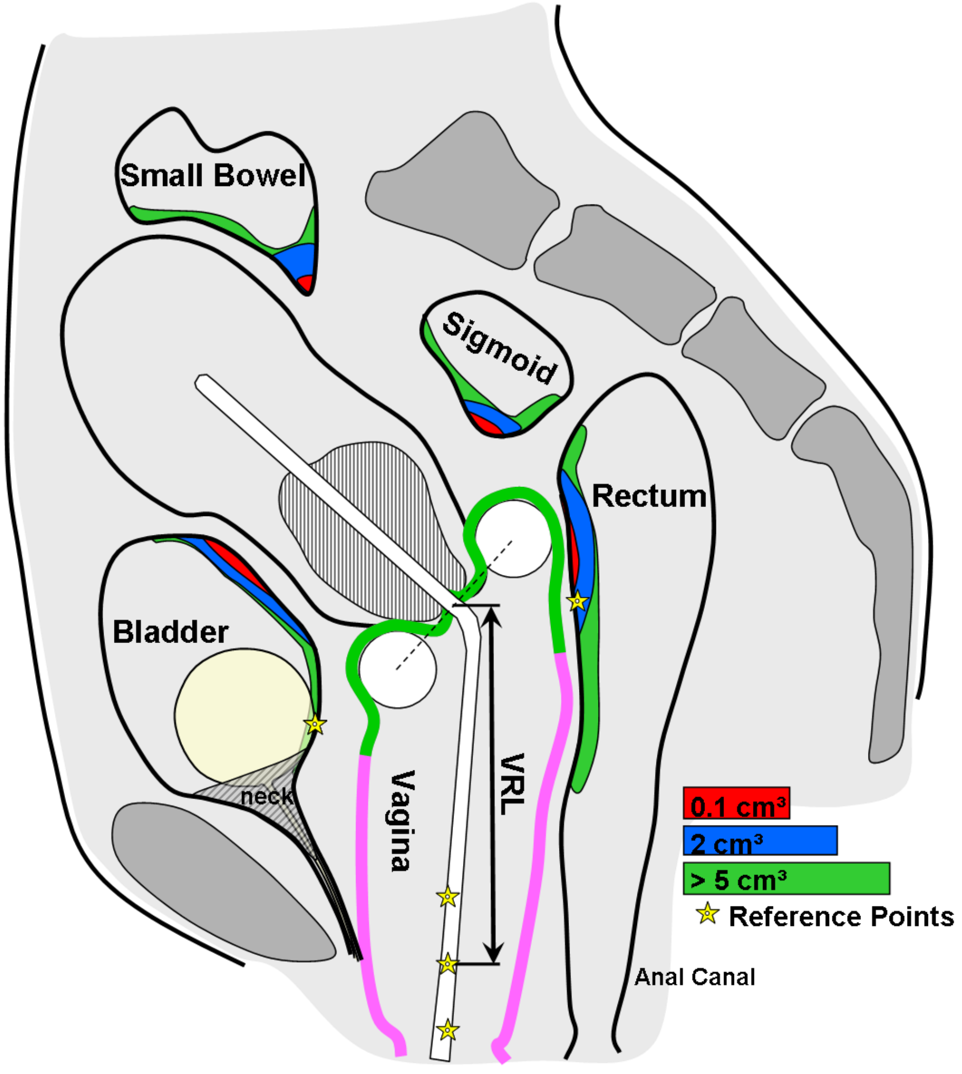


Minimum standard Level 1 reporting

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, minimum standard for reporting: level 1

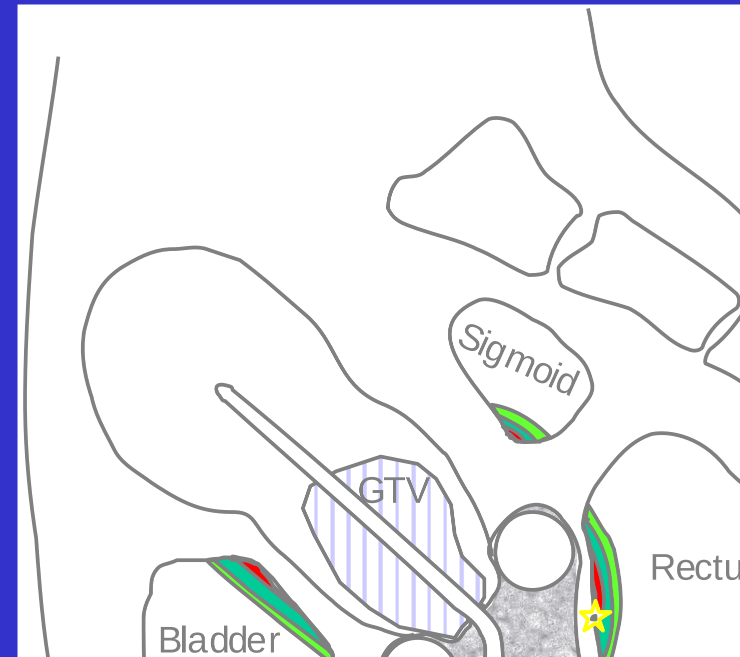


ICRU/GEC ESTRO report 89, 2016
Fig. 6.4, Fig. 8.8

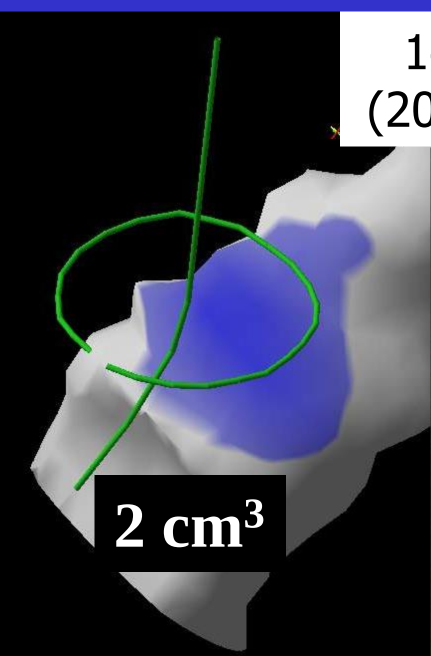
3D-based Dose Volume Parameters for OAR

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

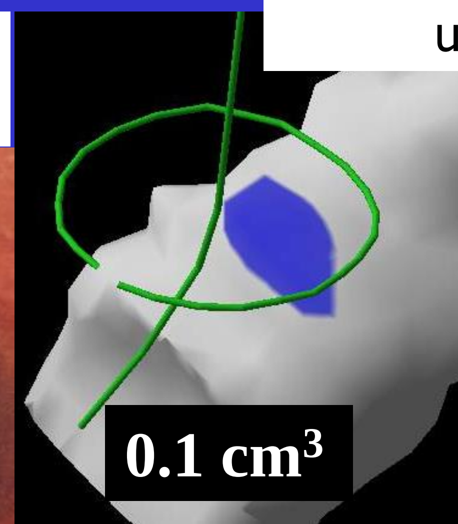
FIXED VOLUME: tolerance dose (total dose)-
"minimum dose to the most exposed tissue"*



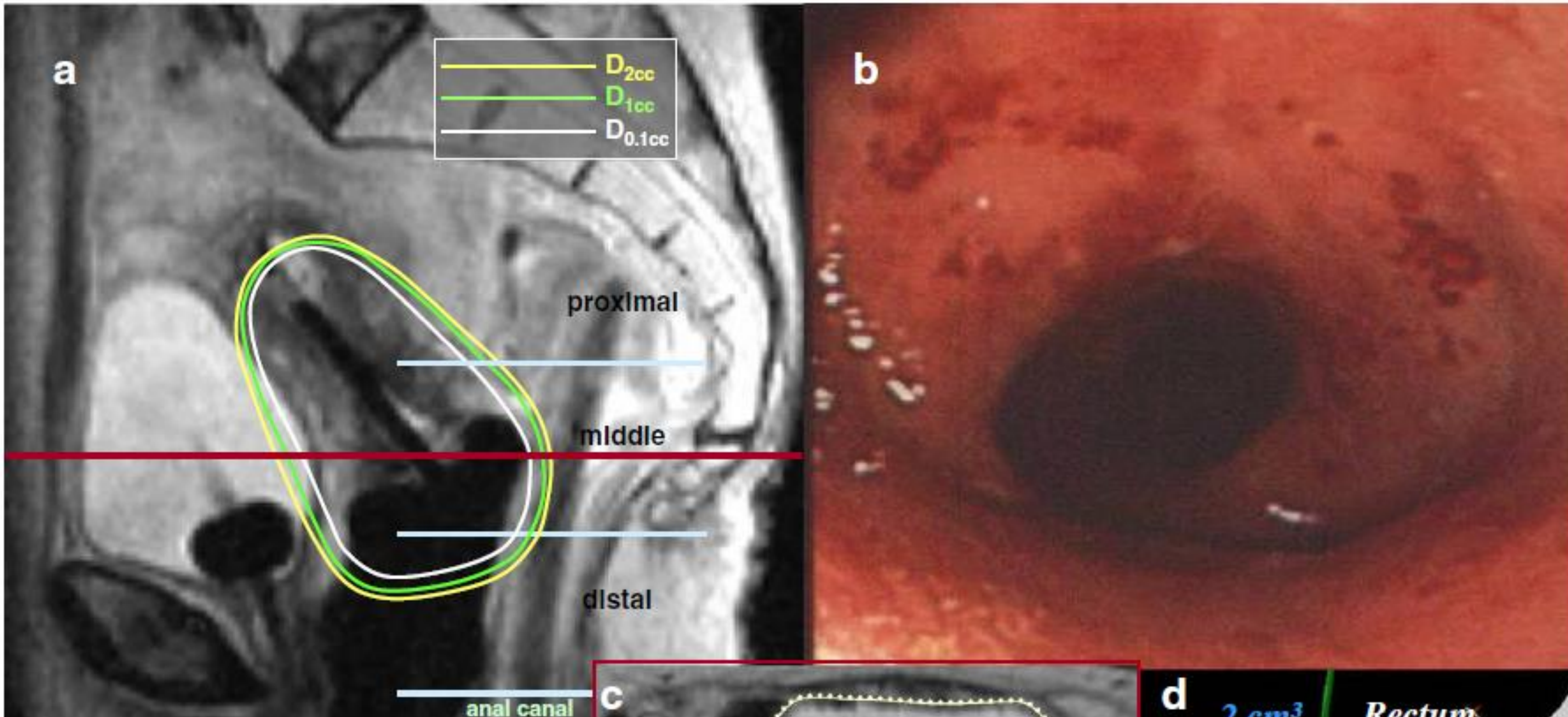
0.1 cc: 3D"maximum dose":
ulceration(fistula)

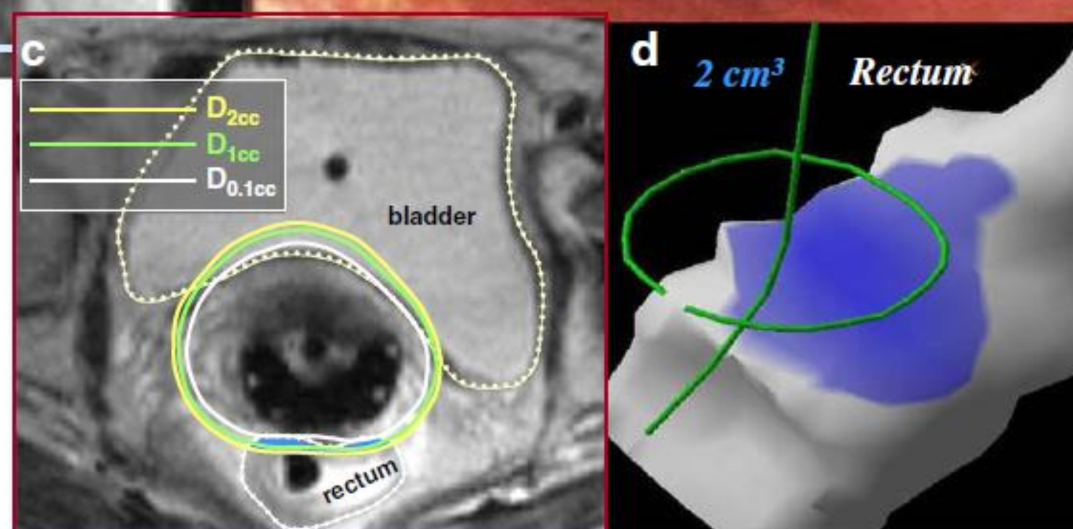


1cc/2cc:teleangiectasia
(20 mm x 20 mm x 5 mm)



**GYN GEC ESTRO Recommendations(II)*
Radiother Oncol 2006





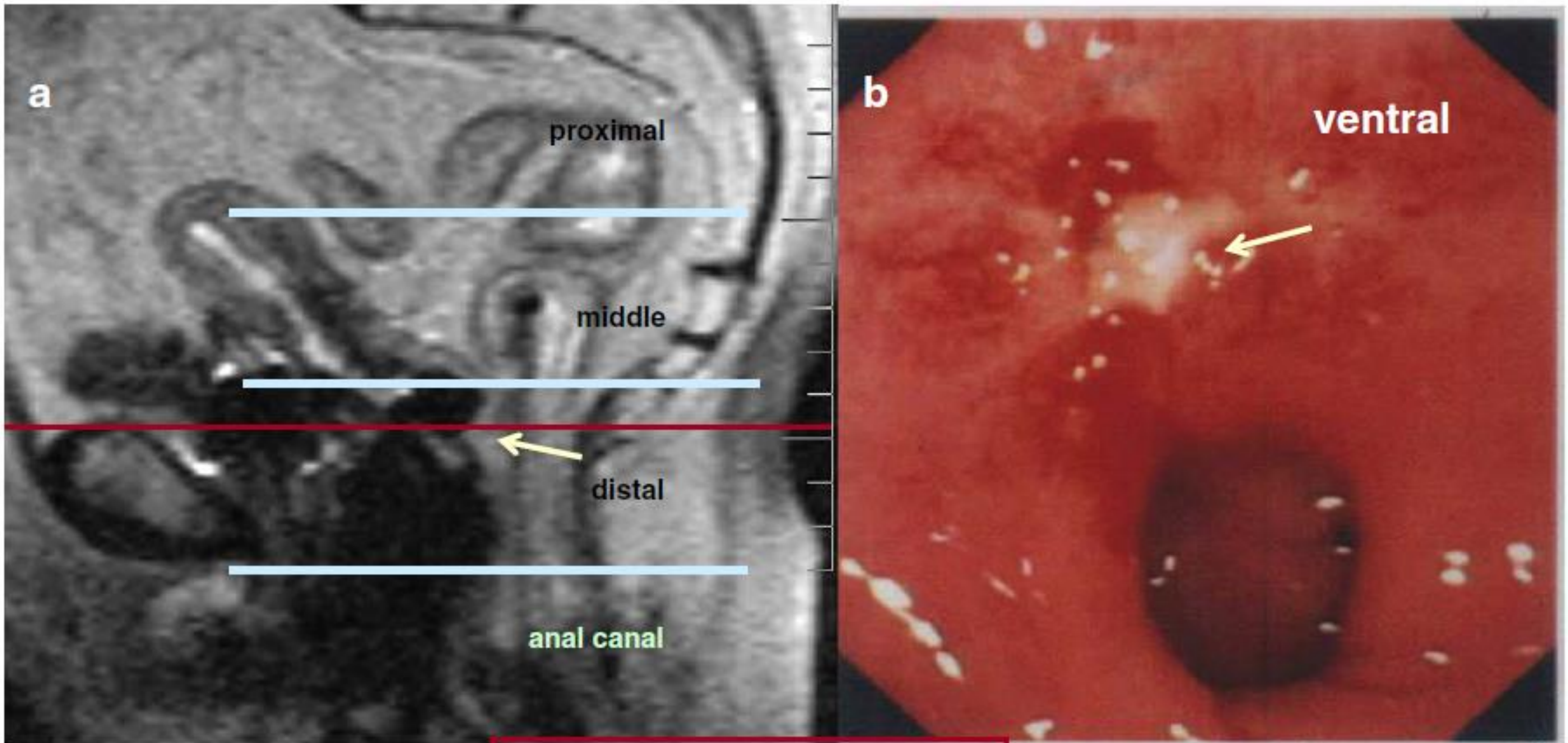
Total DVH parameters
(calculated taking into account all 4 fractions)

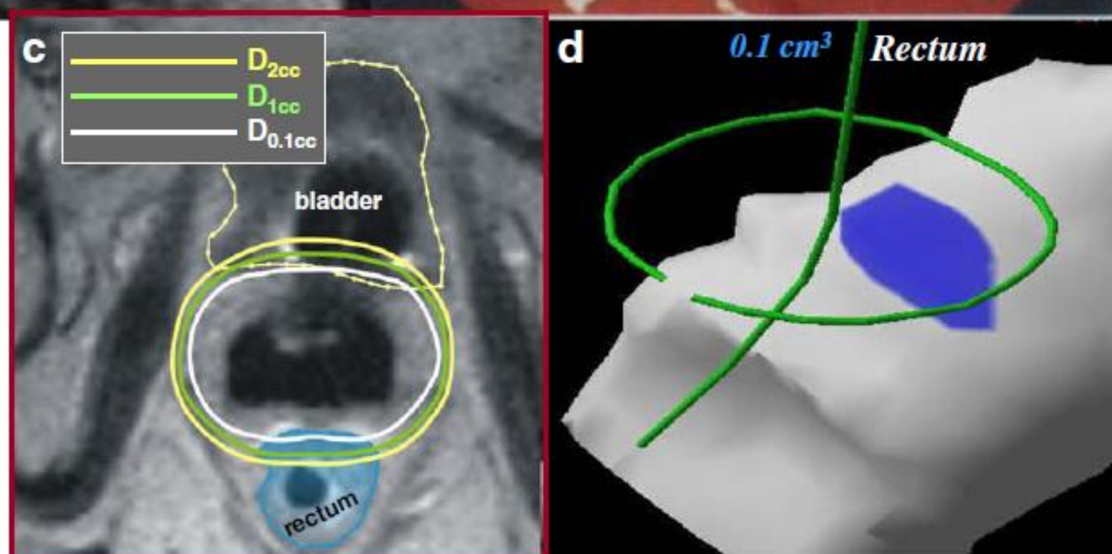
D_{2cc}= 75 Gy EQD2

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

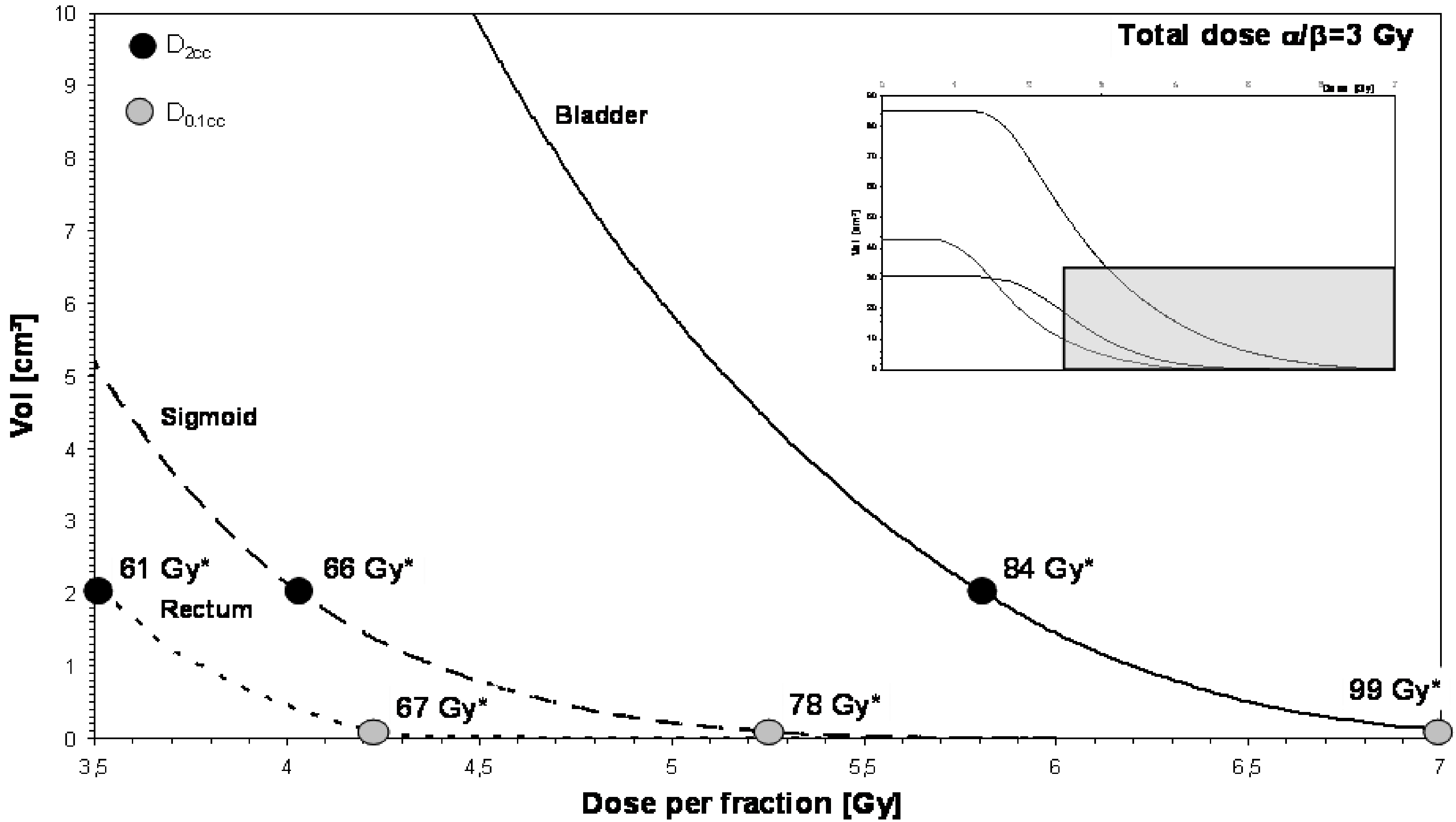
$D_{0.1cc}$= 108 Gy EQD2

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)

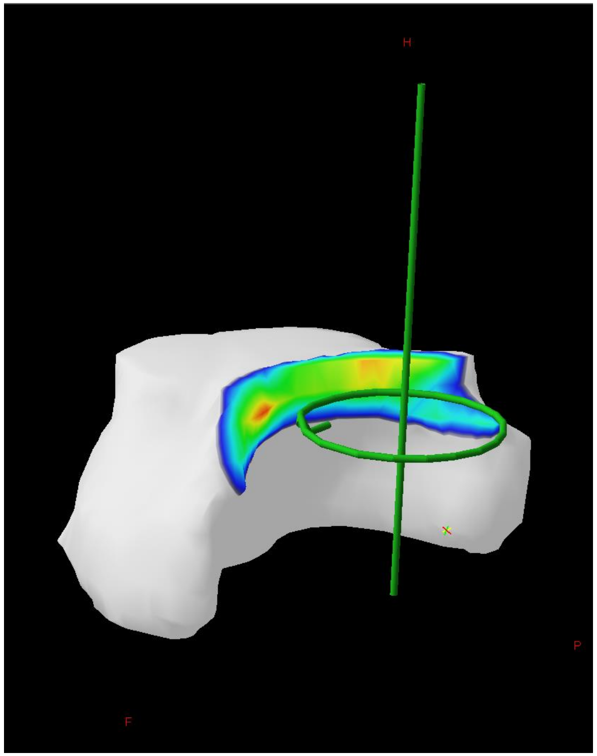


Bladder

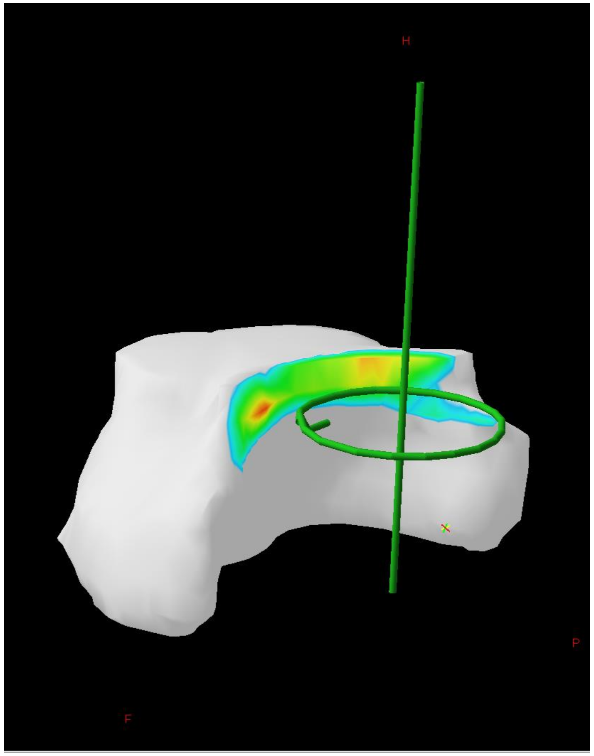
D_{2cc}

w x h:

40mm x 20mm

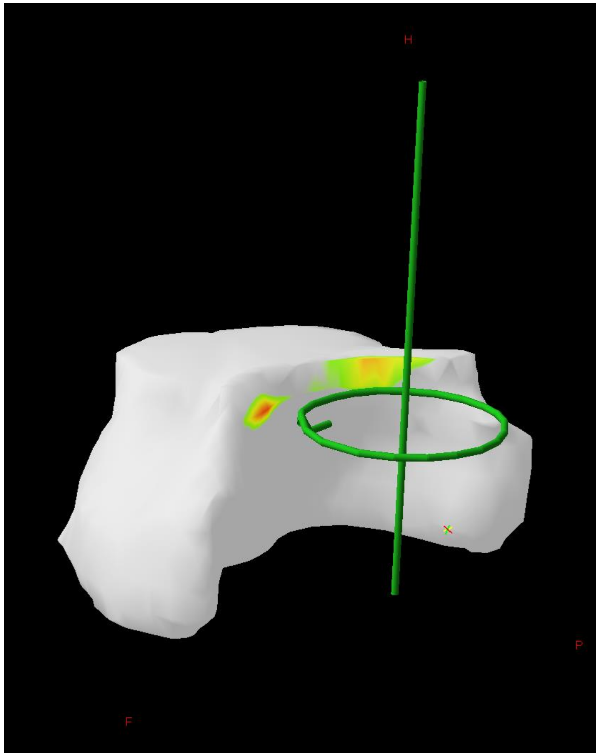


D_{1cc}



$D_{0.1cc}$

20mm x 10mm

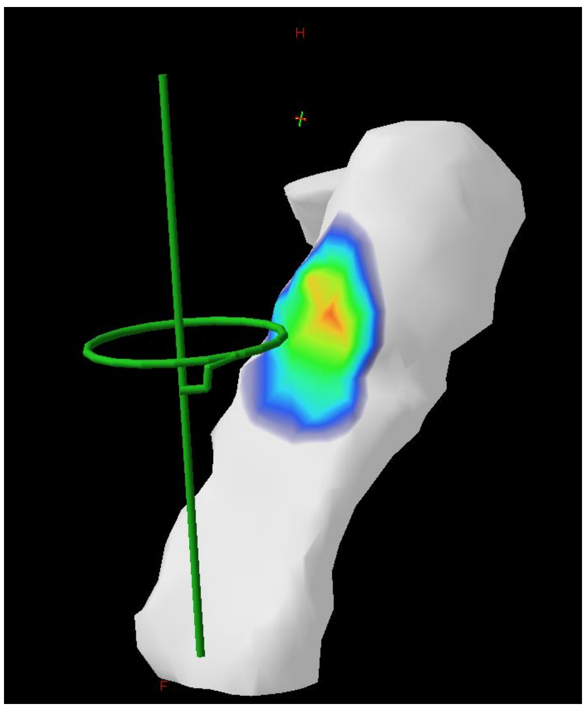


Rectum

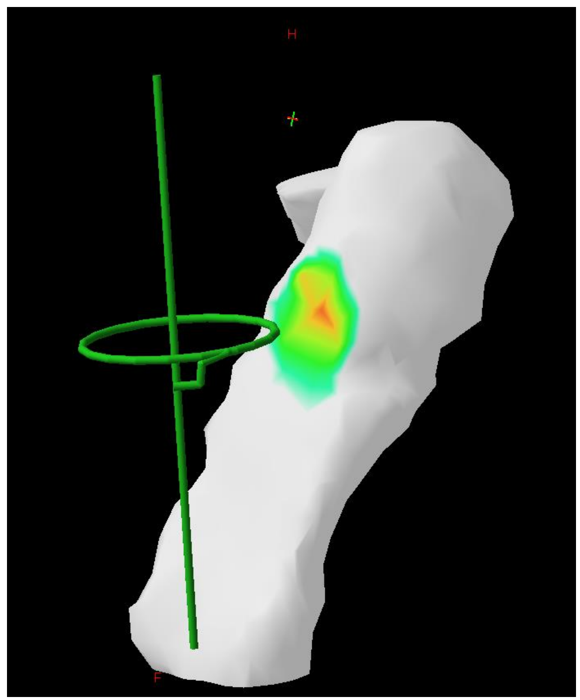
D_{2cc}

w x h:

30mm x 30mm

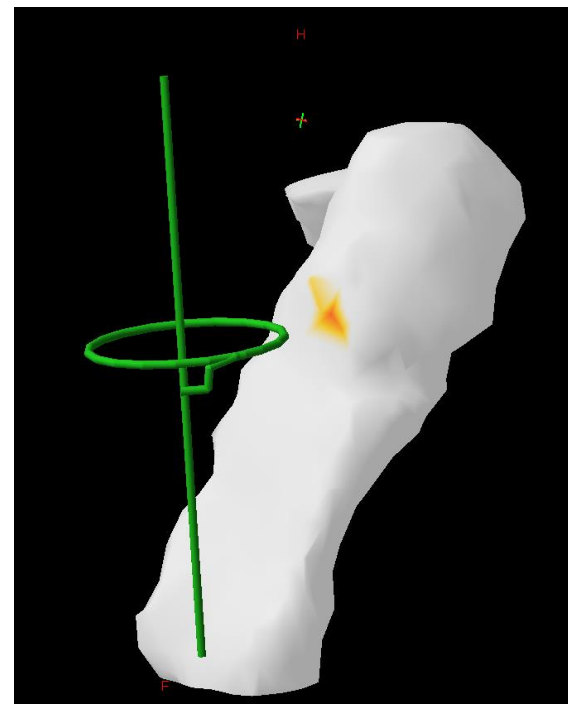


D_{1cc}



$D_{0.1cc}$

10mm x 10mm



Sigmoid

D_{2cc}

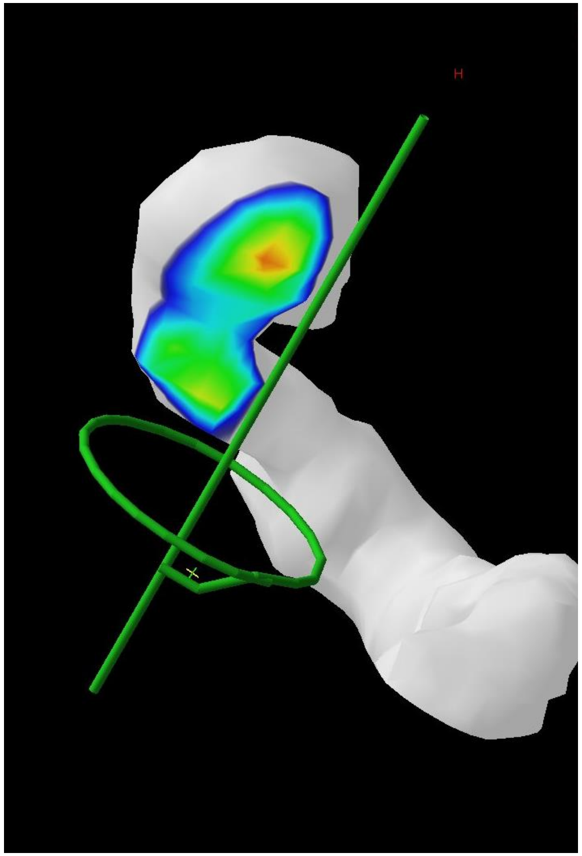
w x h:

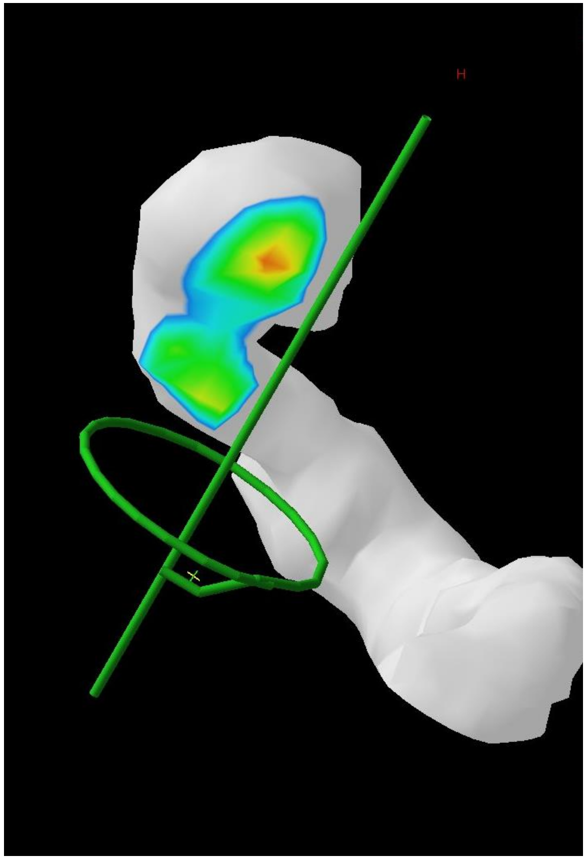
25mm x 20mm

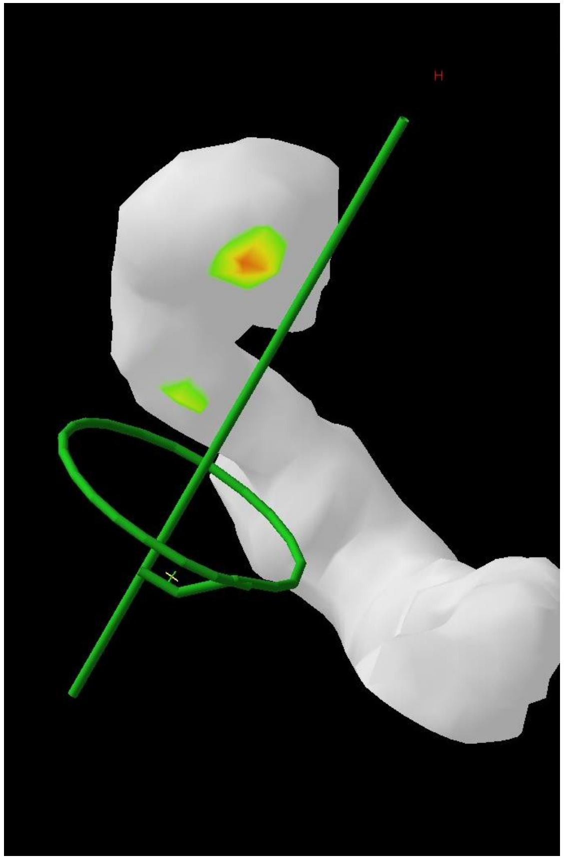
D_{1cc}

$D_{0.1cc}$

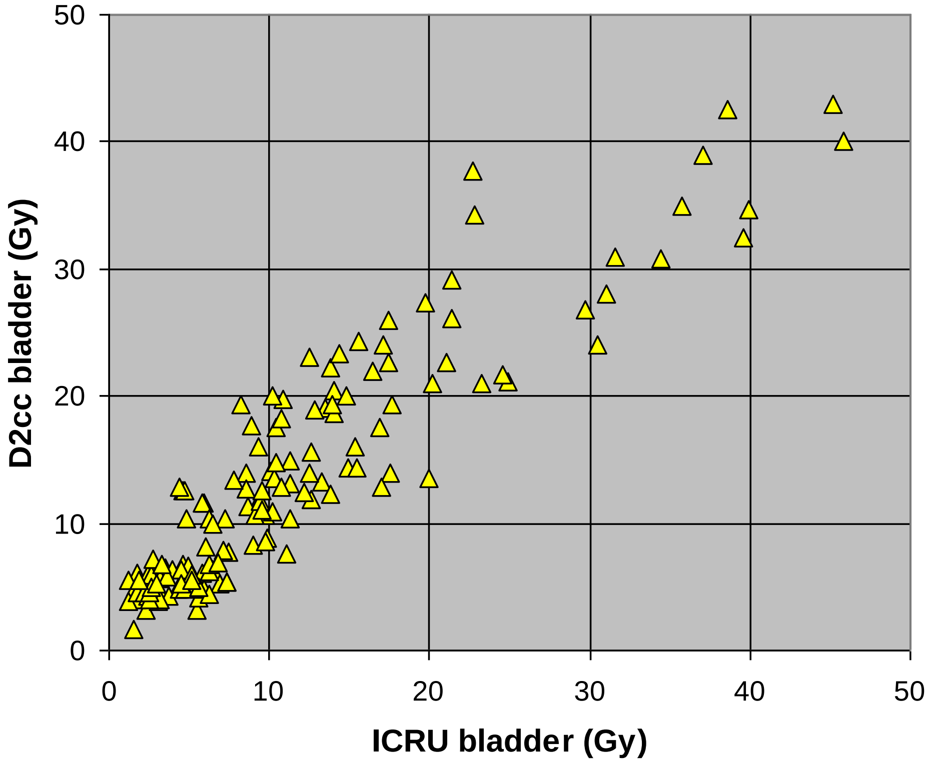
10mm x 10mm

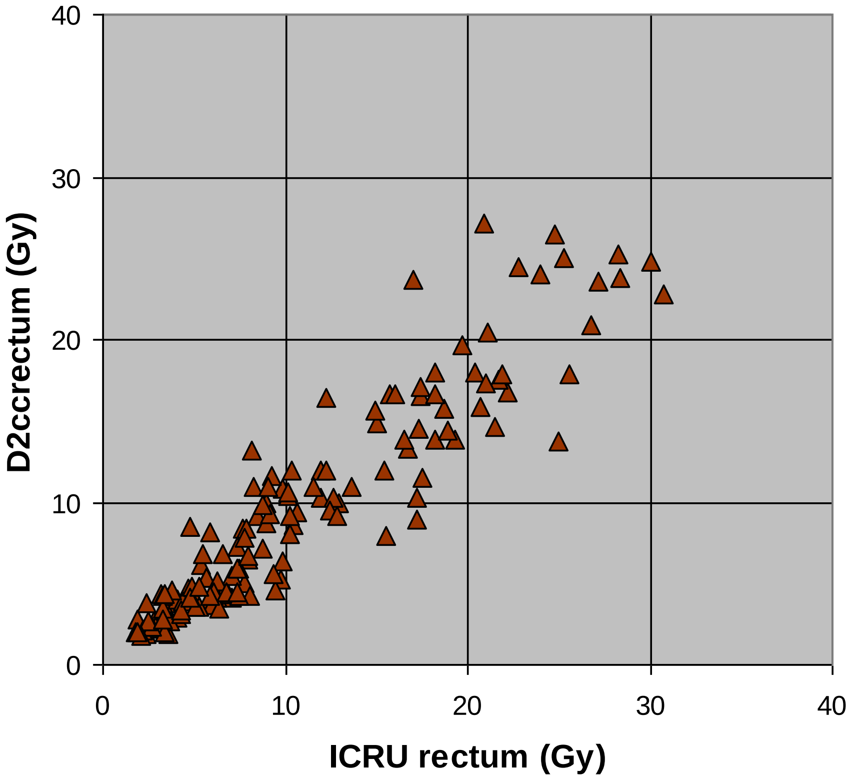






ICRU point dose and D2cc doses

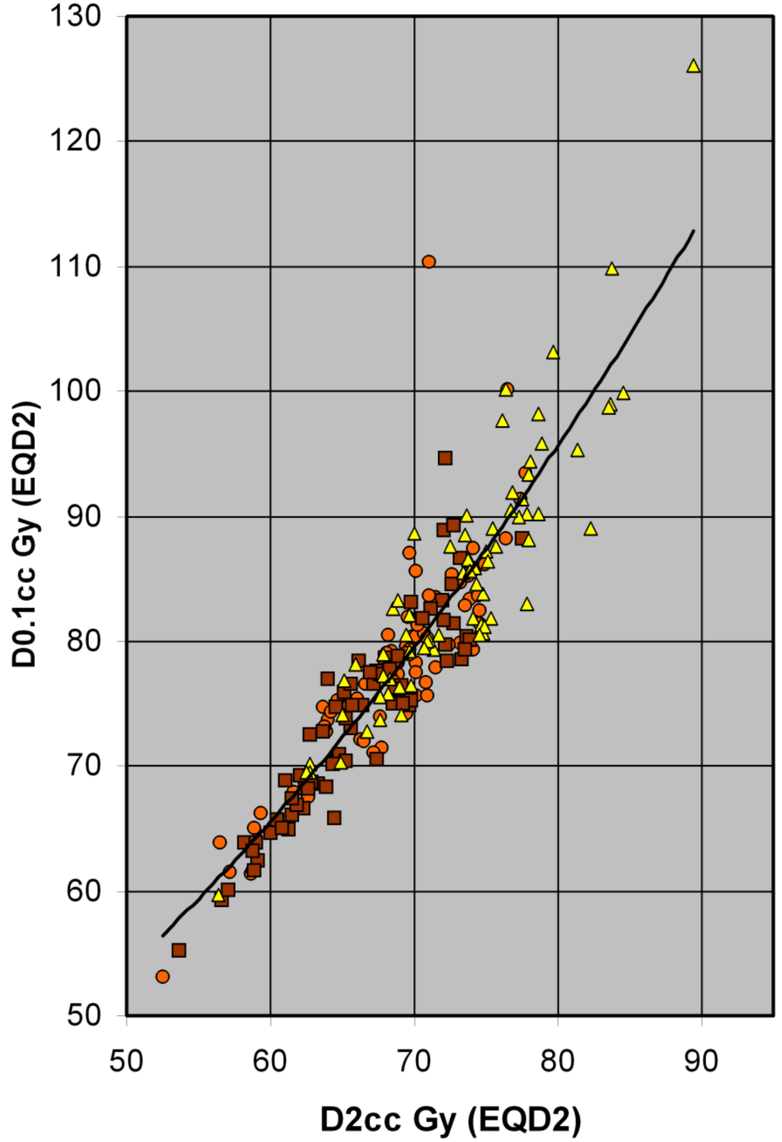




EMBRACE data, Tanderup et al.

D2cc and D0.1cc

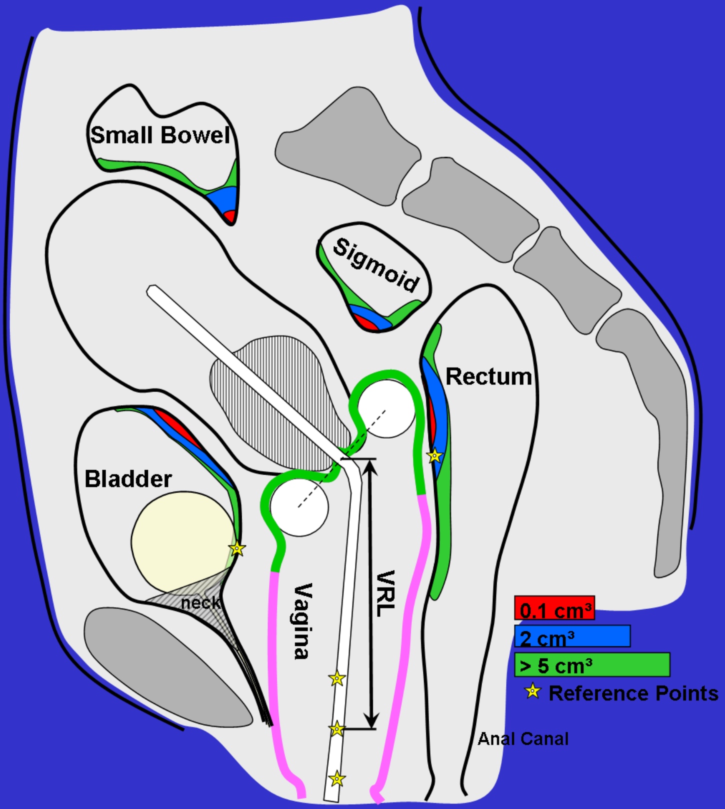
	D2cc Gy EQD2	D0.1cc Gy EQD2
Bladder	71 ± 7	81 ± 13
Rectum	65 ± 6	72 ± 8
Sigmoid	67 ± 6	74 ± 12



$D_{0.1cc} / D_{2cc}$: 134% ± 9%
(Physical doses)

Aarhus University Hospital: PDR BT

DVH Parameters and Reference Points:
variations in application and doses to OARs



ICRU/GEC ESTRO report 89
Fig. 6.4, Fig. 8.8

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 $D0.1_{cm3}$

ICRU 89, 2016, Summary level 2, p. 162

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

Level 2: *Advanced standard for reporting*
All that is reported in Level 1 plus:

Volumetric-imaging approximation based on:

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

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

Dose reporting for defined volumes:

- $D_{98\,\%}$, $D_{90\,\%}$, $D_{50\,\%}$ for the CTV_{HR}
- ($D_{98\,\%}$, $D_{90\,\%}$ for the CTV_{IR} if used for prescription)
- $D_{98\,\%}$ for GTV_{res}
- $D_{98\,\%}$ for pathological lymph nodes

Dose reporting OARs:

- Bladder reference point dose
- $D_{0.1\,cm^3}$, $D_{2\,cm^3}$ for sigmoid[a]
- $D_{2\,cm^3}$ bowel
- Intermediate- and low-dose parameters in bladder, rectum, sigmoid, bowel
  (*e.g.*, $V_{15\,Gy}$, $V_{25\,Gy}$, $V_{35\,Gy}$, $V_{45\,Gy}$ or $D_{98\,\%}$, $D_{50\,\%}$, $D_{2\,\%}$)
- Vaginal point doses at level of sources (lateral at 5 mm)[a]
- Lower- and mid-vagina doses (PIBS, PIBS $\pm$ 2 cm)[a]

Radiographic approximation based on:

Topography for volumes (on isodose plan with applicator/on radiographs with applicator)

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

Dose reporting for defined volumes:

- Estimated dose to CTV_{HR}
- (according to estimated maximum width and thickness)
- Pelvic wall point (optional)
- Lymphatic trapezoid (optional)

Dose reporting OARs:

- Vaginal point doses at level of sources (lateral at 5 mm)
- Lower- and mid-vagina doses (PIBS, PIBS $\pm$ 2 cm)

[a]Surrogate points for volumetric vaginal dose assessment.

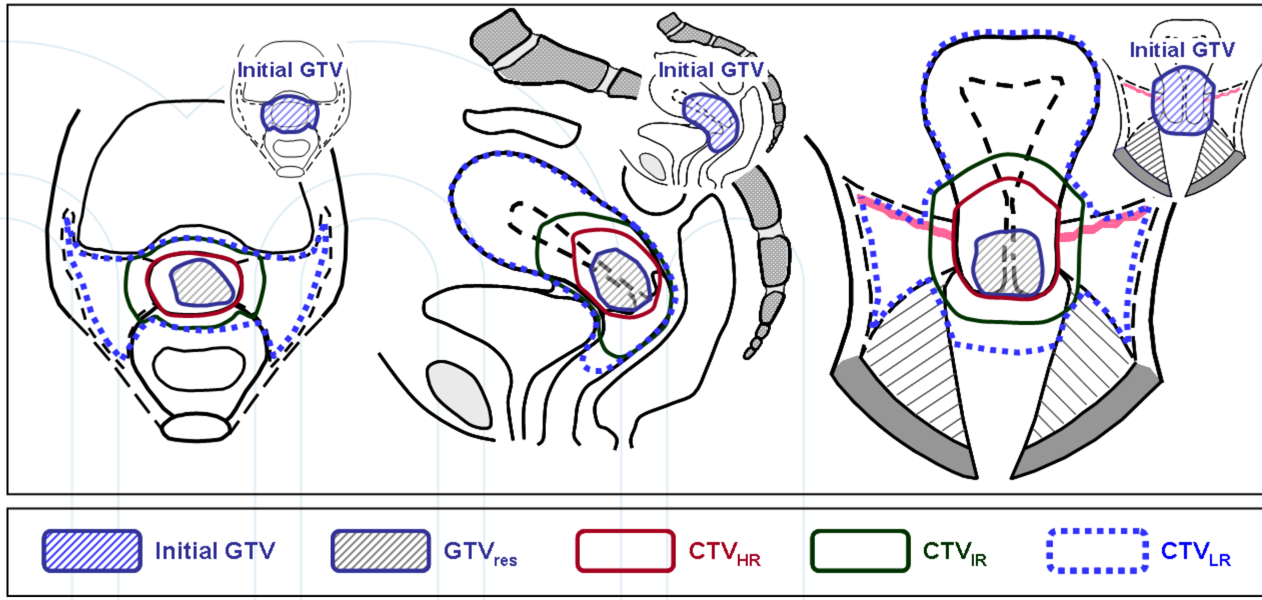
Level 2 - *Advanced standard for reporting* All that is reported in level 1 plus (ICRU 89):

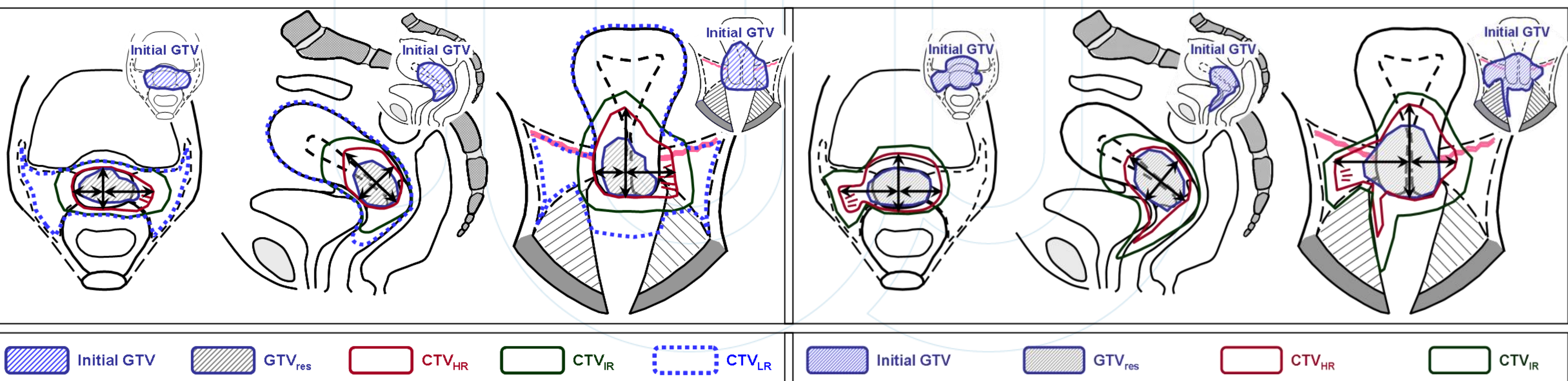
3D delineation of volumes (on volumetric images with applicator and on clinical diagrams):

- (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)



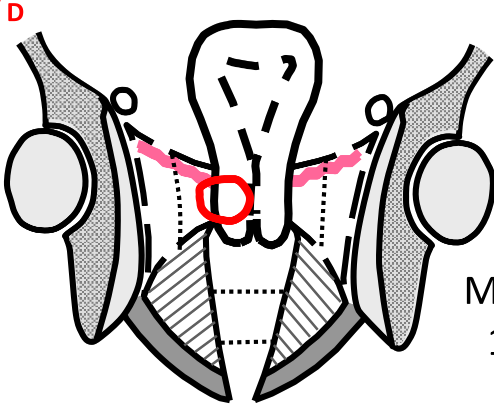


GEC ESTRO Rcommendations I, 2005; Upcoming ICRU/GEC ESTRO report 88, Fig. 5.9-11

At diagnosis
GTV_D

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

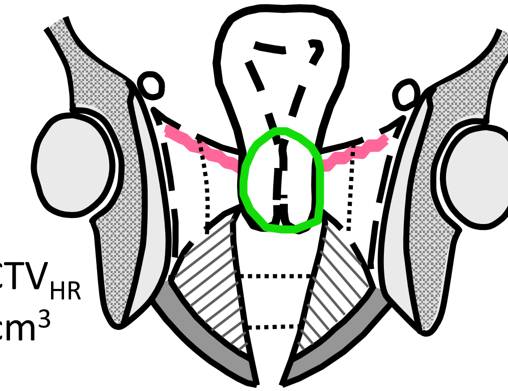
At brachytherapy
HR-CTV

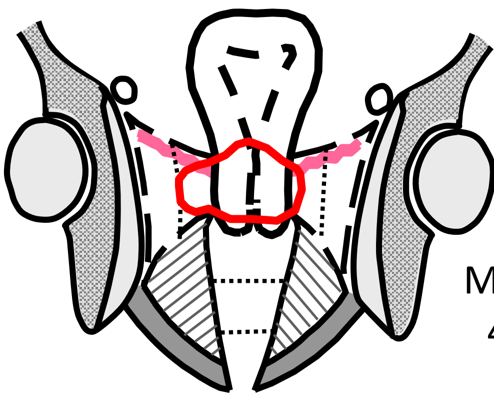


Group 1
"Stage IB_1-like"
N=55 (11%)

Mean GTV_D
12.6 cm^3

Mean CTV_{HR}
23.7 cm^3

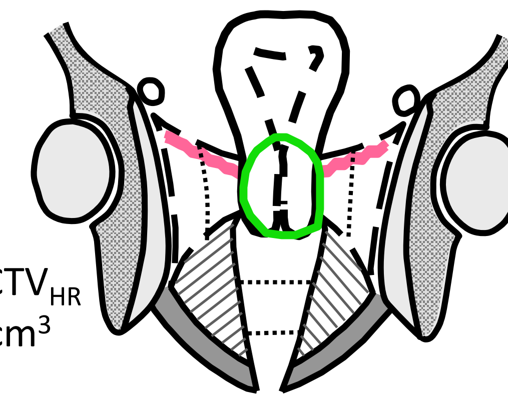


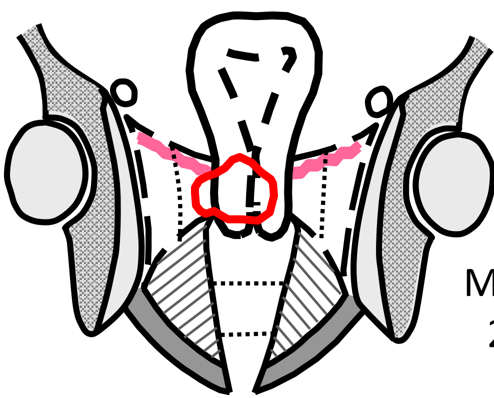


Group 2
Good response
N=78 (16%)

Mean GTV_D
47.5 cm^3

Mean CTV_{HR}
25.3 cm^3

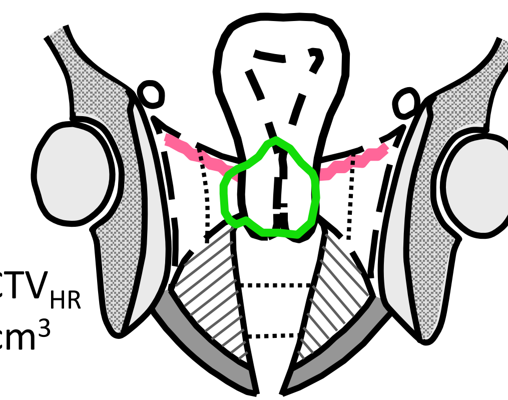




Group 3
Small, moderate response
N=123 (26%)

Mean GTV_D
23.9 cm^3

Mean CTV_{HR}
29.9 cm^3

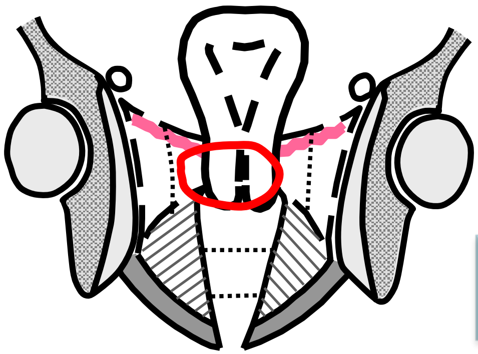


Jastaniyah N, Yoshida K *et al*; fellows at MUW/AKH Vienna, ASTRO 2014, IJROBP 2016

Volumetric tumour regression: FIGO stage IIB/IIIB cervical cancer, large tumor at diagnosis subgroup from EMBRACE data base, N=183/345

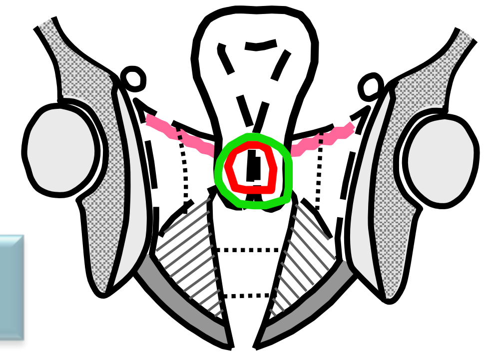
At diagnosis

At brachytherapy



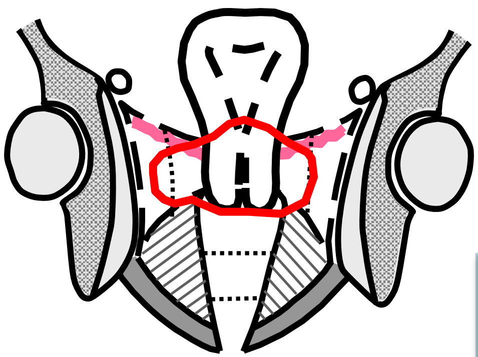
Good response

N=68



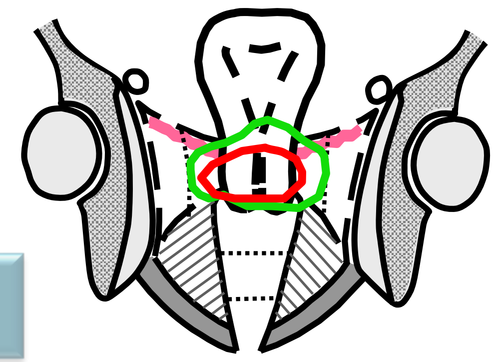
Mean GTV
45.2 cm^3

Mean HR CTV
24.6 cm^3



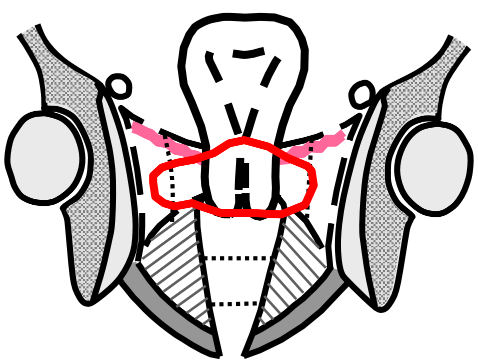
Moderate response

N=98



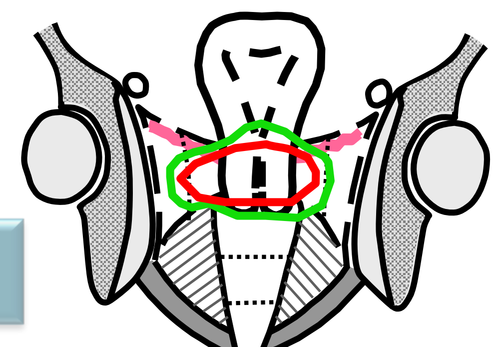
Mean GTV
76.7 cm^3

Mean HR CTV
40.1 cm^3



Poor response

N=17



Mean GTV
62.1 cm^3

Mean HR CTV
57.8 cm^3

Jastaniyah N, Yoshida K *et al*; fellows at MUW/AKH Vienna, ASTRO 2014, IJROBP 2016, full publication in radiotherapy and oncology 2016

GTV
HR CTV

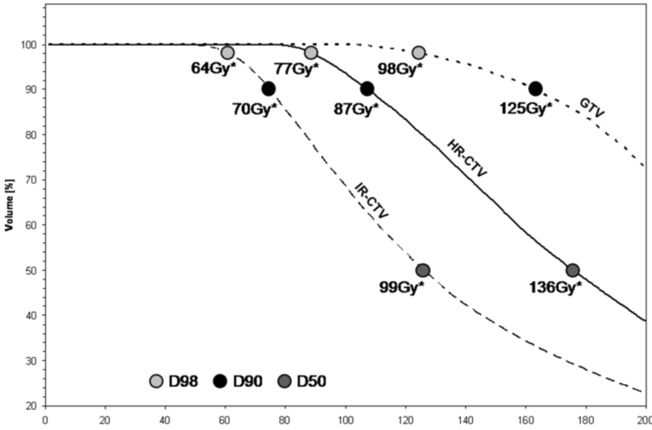
Level 2 - *Advanced standard for reporting* All that is reported in level 1 plus (ICRU 89):

Dose reporting for defined volumes based on volumetric imaging:

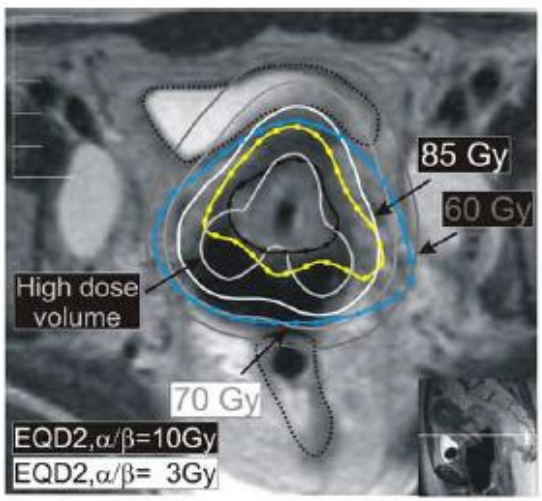
- **D_{98}, D_{90}, D_{50} for CTV_{HR}**
- **(D_{98}, D_{90}, D_{50} for CTV_{IR} if used for prescription)**
- **D_{98} for GTV_{res}**
- **D_{98} for pathological lymph nodes**

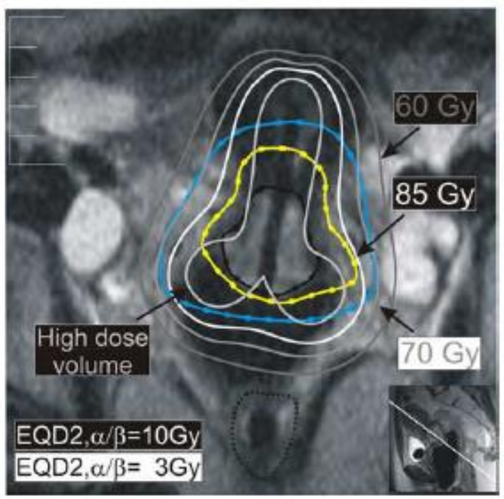
DVH-parameters CTV-T_{HR} (ICRU 89)

- **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**



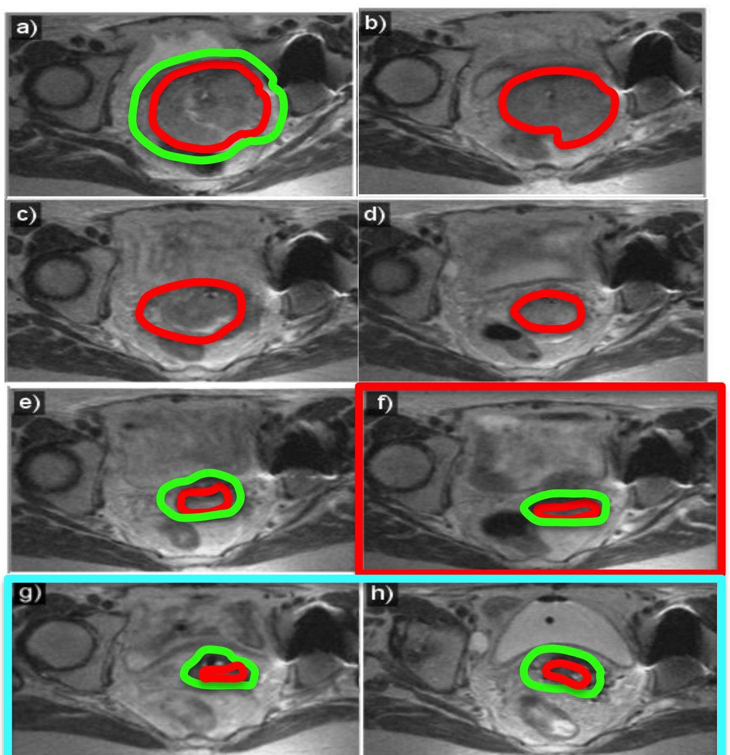
GEC ESTRO Rec II, 2006

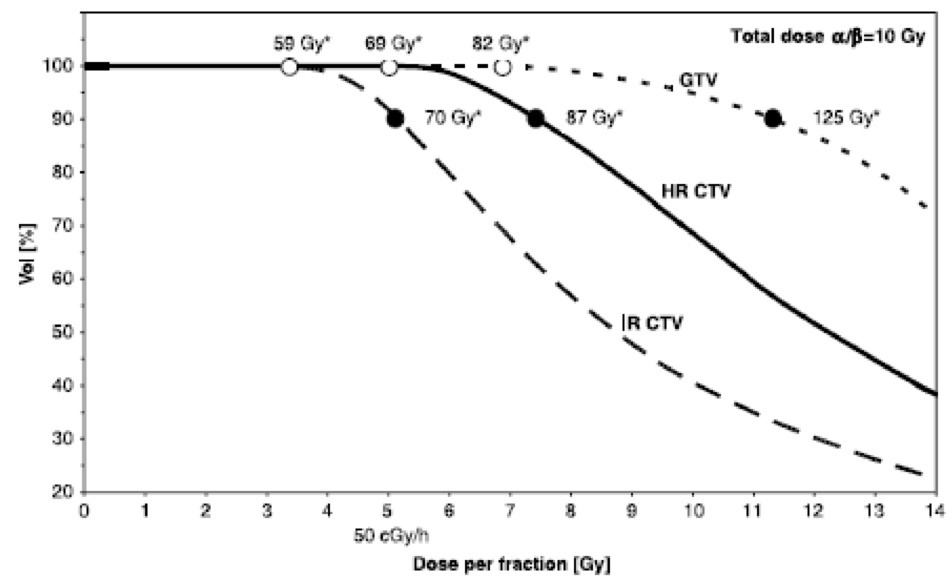




Dose and Volume Parameters (Vienna data 1998-2008)

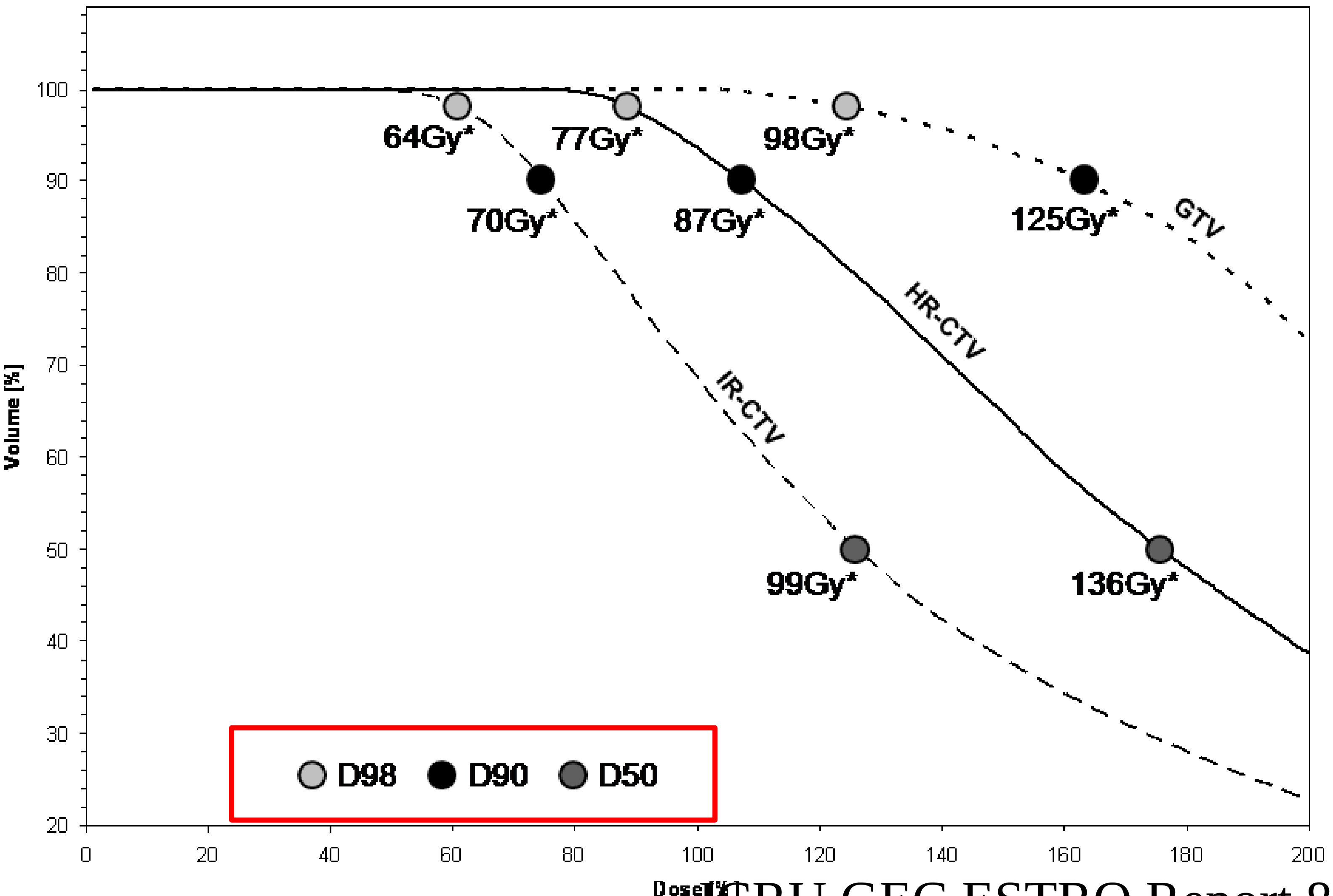
IR CTV-T	~ 100 cm^3	~ 66 Gy EQD2 (D90)
HR CTV-T	~ 39 cm^3	~ 89 Gy EQD2 (D90)
Res. GTV-T	~ 9 cm^3	~ 119 Gy EQD2 (D100)





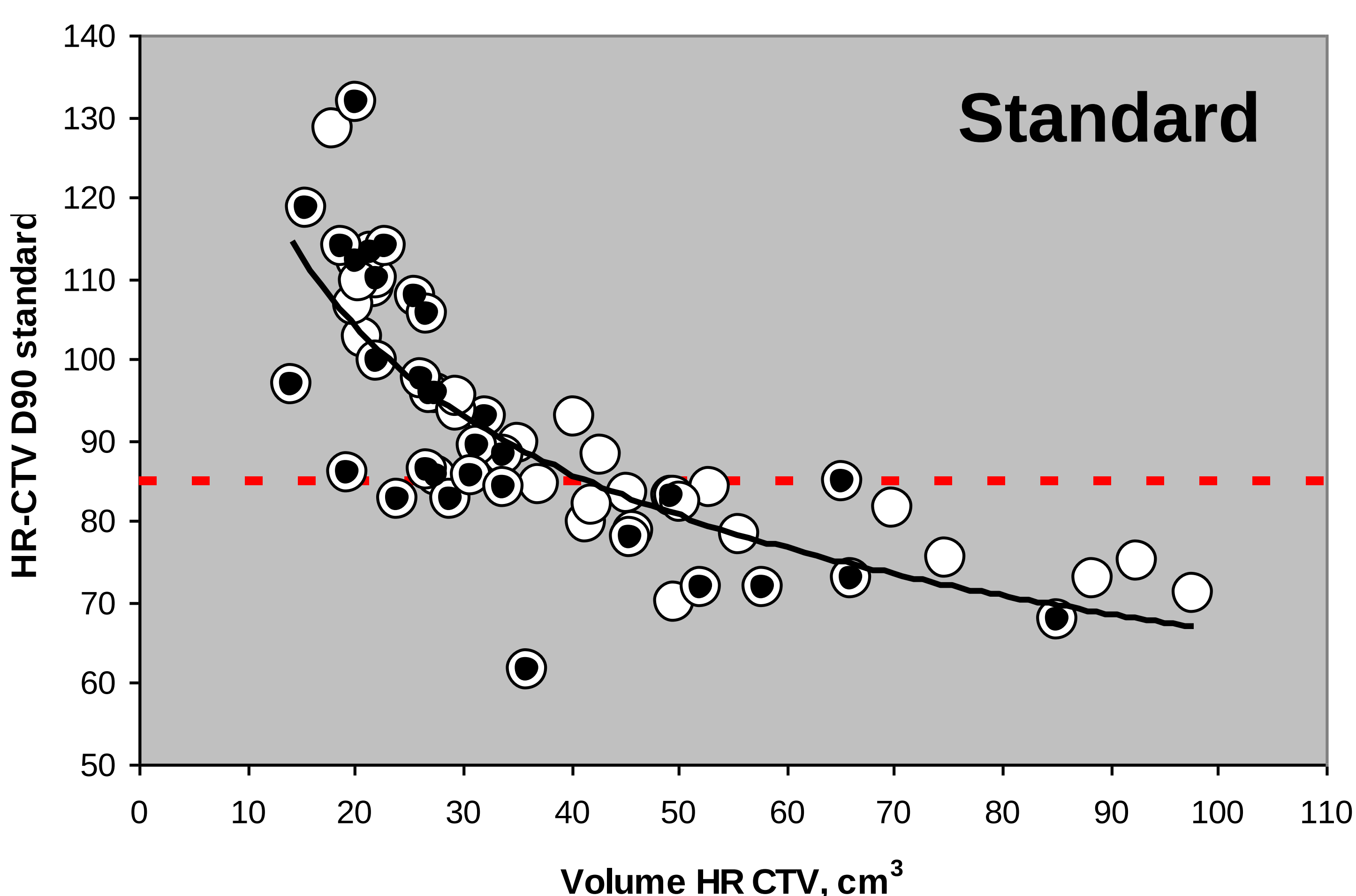
GEC ESTRO Rec II, 2006

DVH parameters targets (level 2 reporting) GTV, CTV-HR, CTV-IR



ICRU GEC ESTRO Report 89, 2016

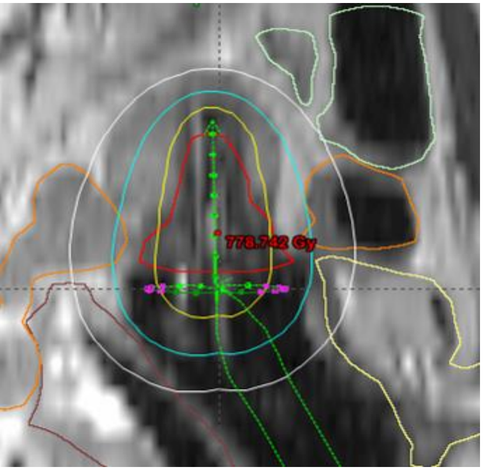
Dose in D90 and HR CTV for point A prescription
High Target Doses in small tumours
Low Target Doses in large tumours



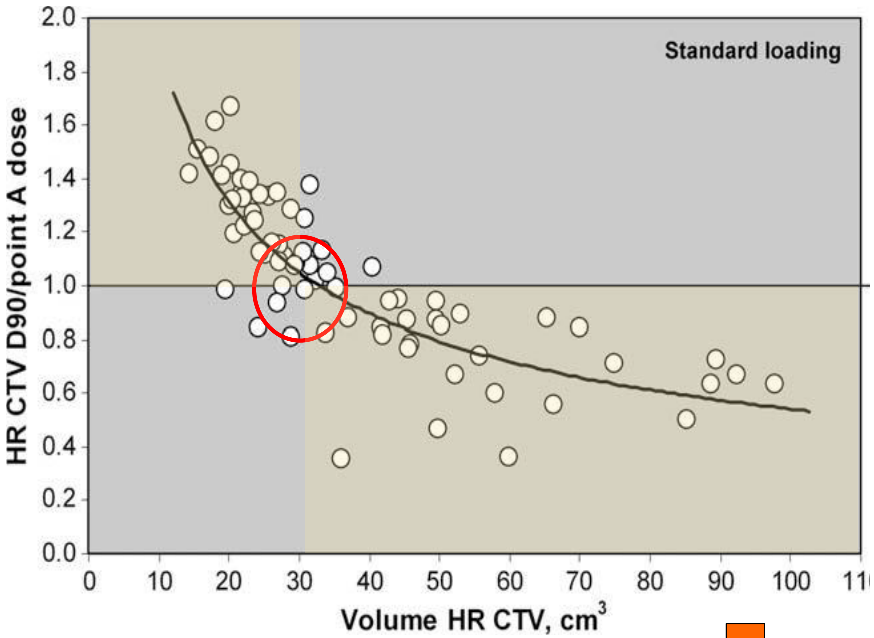
Violation of OAR constraint

Tanderup et al.

Consequences of prescribing to Point-A

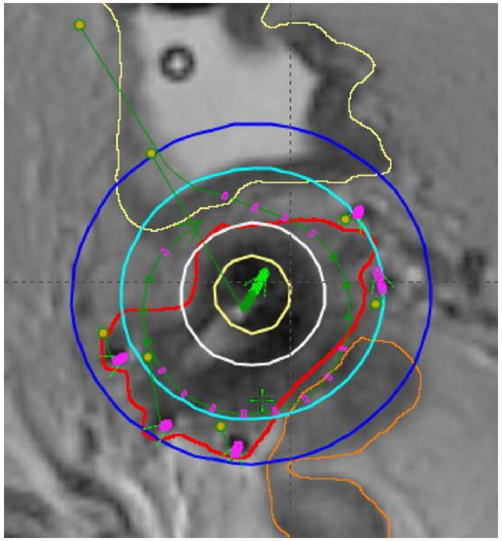


Overdosing organs at risk



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):

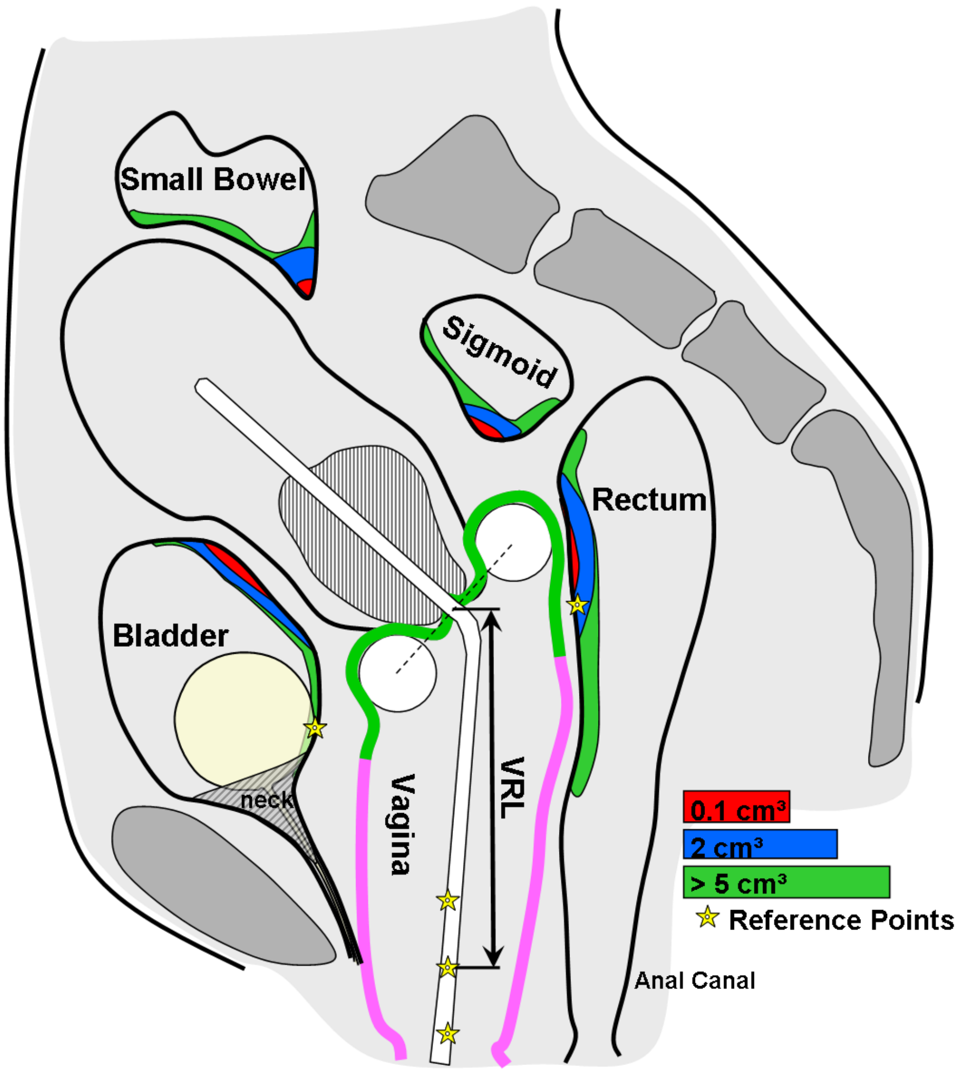
.

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: Vagina

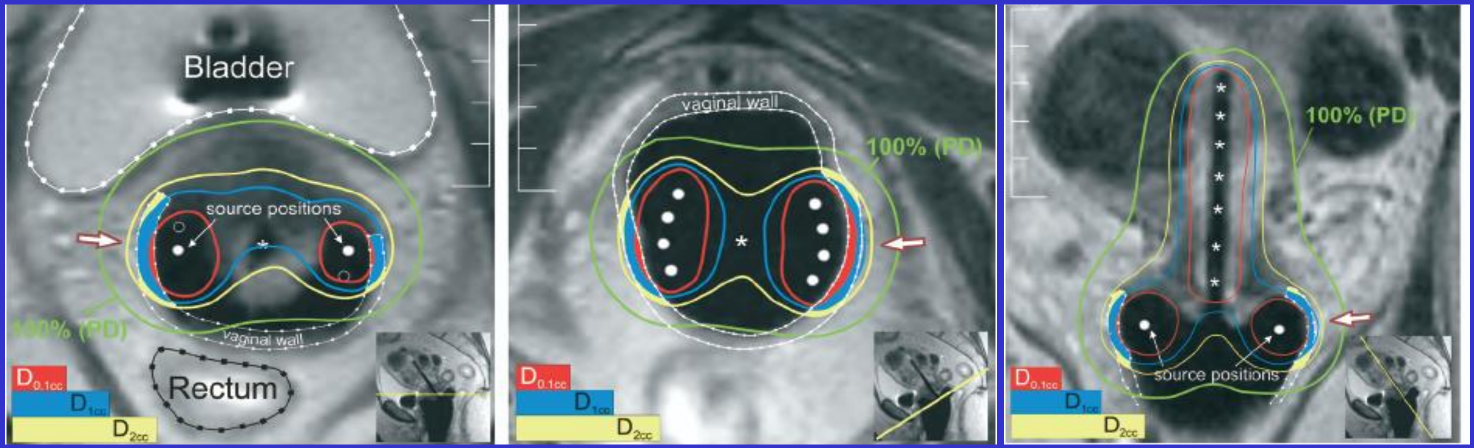
ICRU/GEC ESTRO report 89, 2016
Fig. 6.4, Fig. 8.8



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.

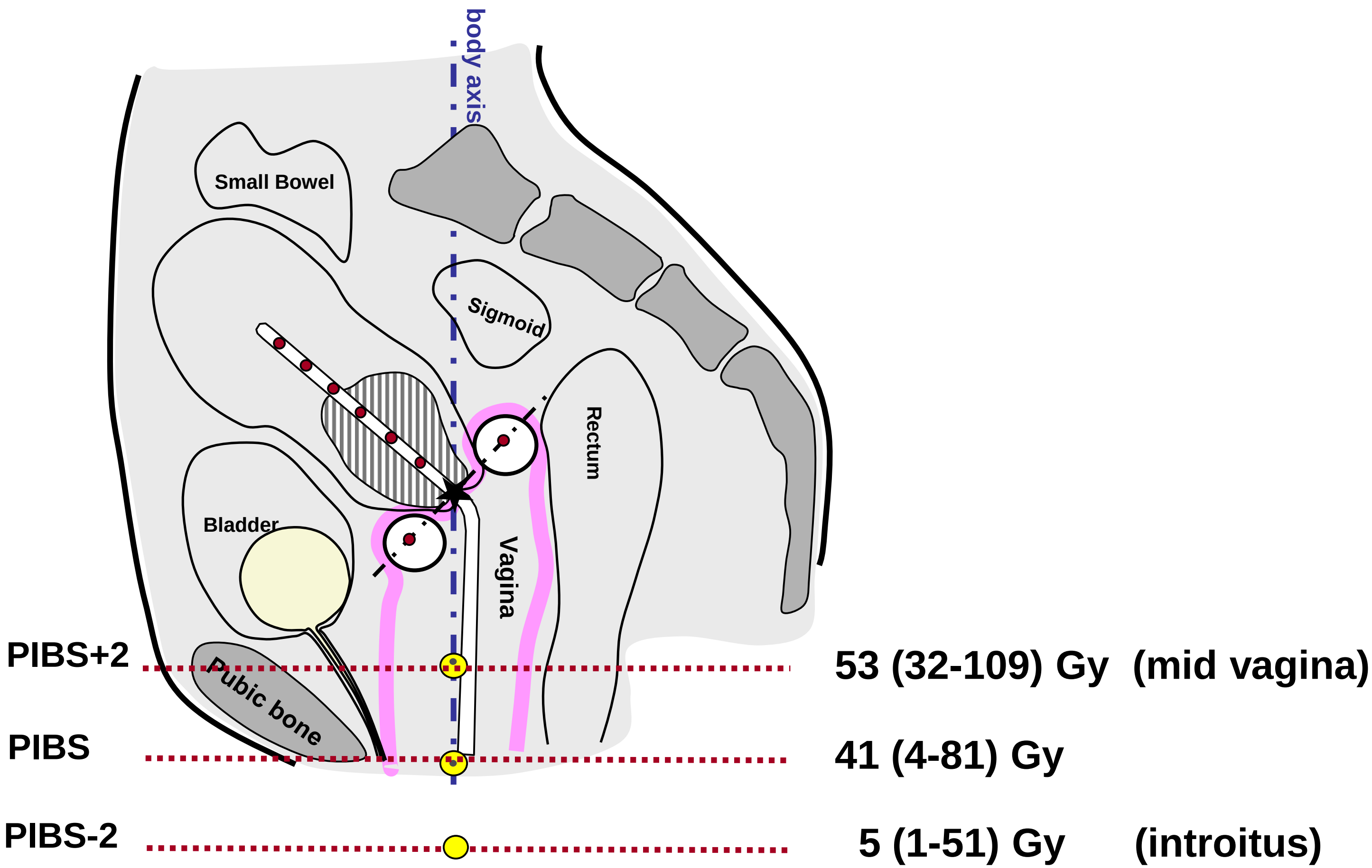


<u>DVH parameters have HIGH uncertainty for representative vaginal dose estimation</u>

They are influenced by the resolution of sectional imaging, contouring accuracy and applicator reconstruction

Berger et al, IJROBP 2007

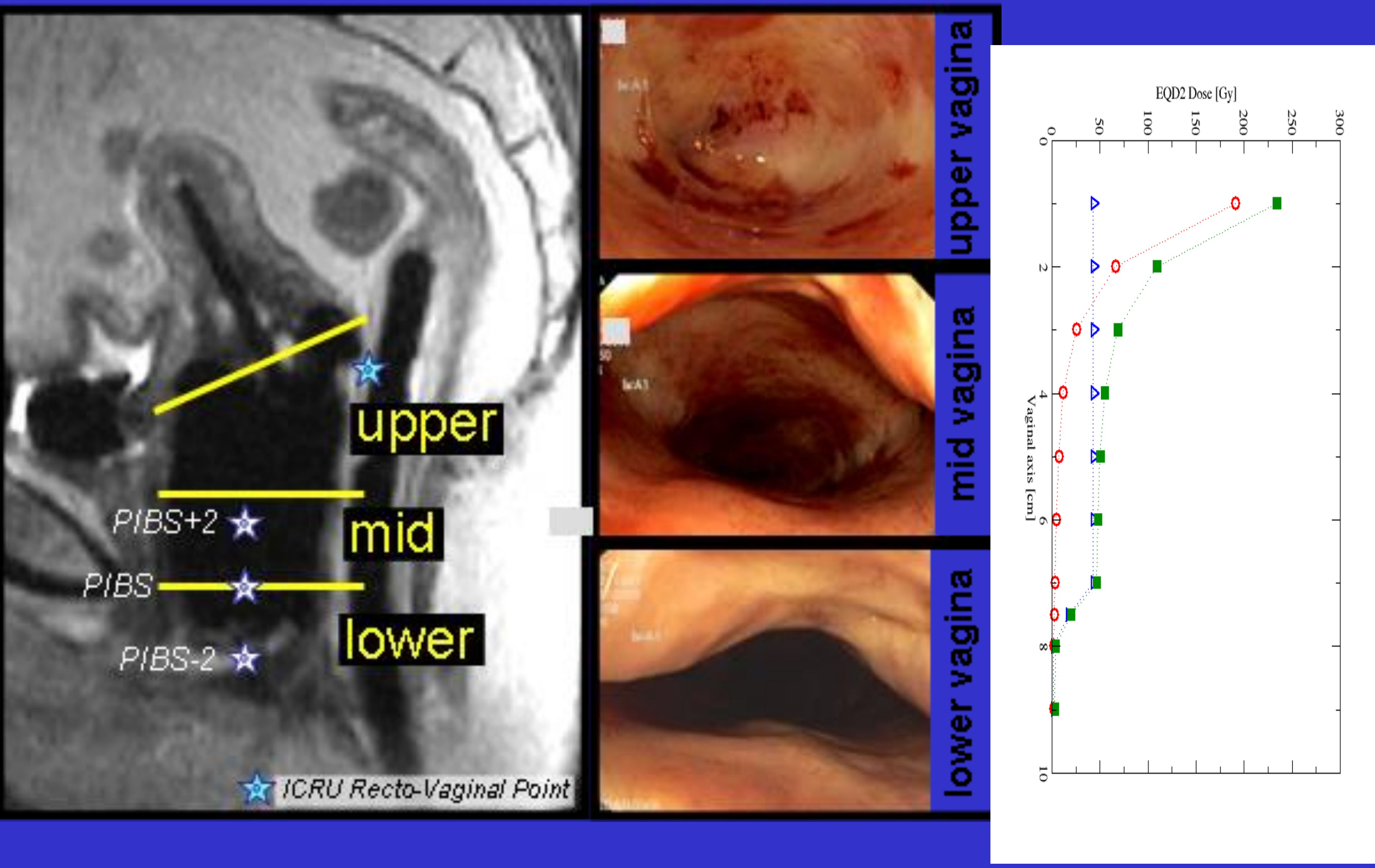
Vaginal reference points



Vienna Data

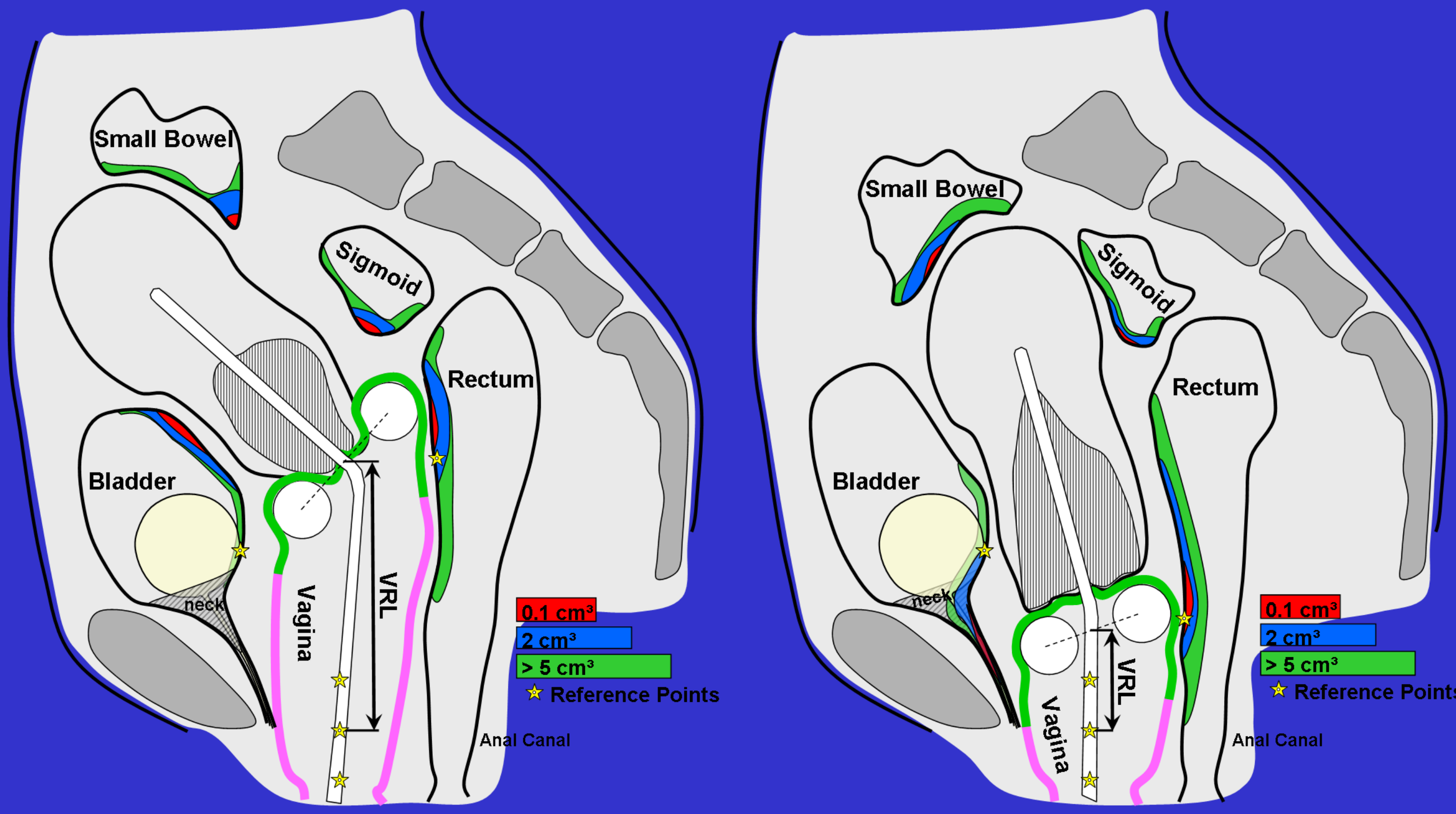
Westerveld et al. Radioth and Oncology 2014

Vaginal morbidity and radiation doses



ICRU/GEC ESTRO Report 89 2016 Fig. 6.1/Fig. 8.11

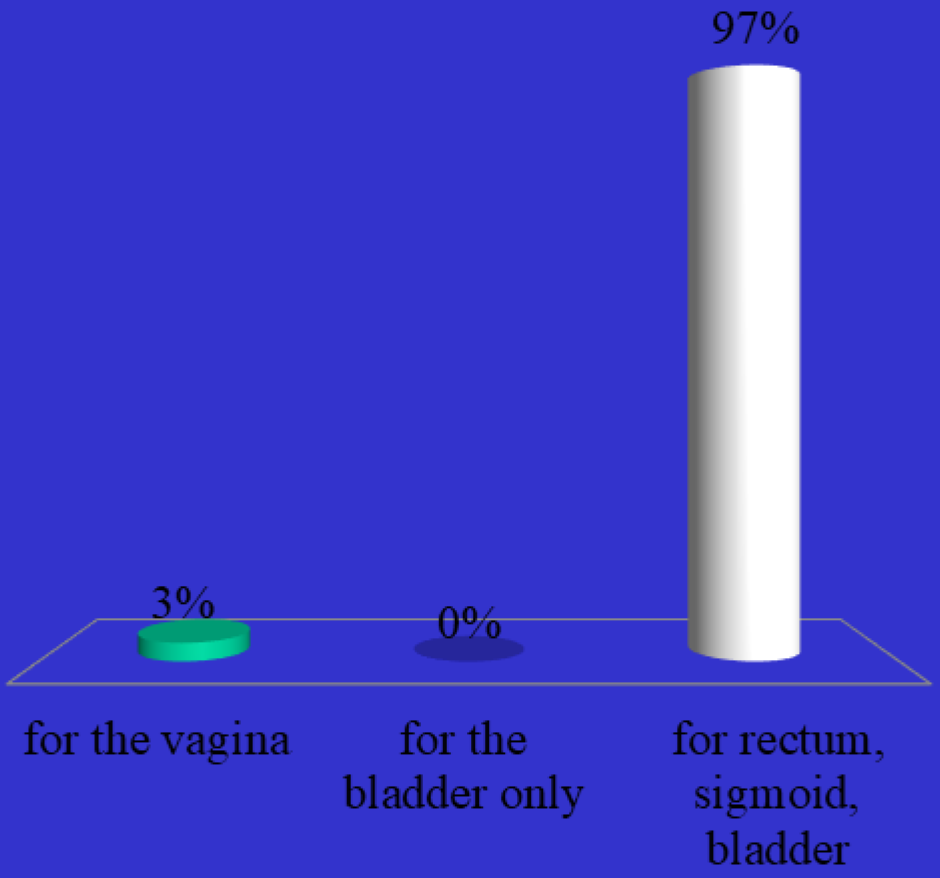
DVH Parameters and Reference Points, Vaginal point: *variations in application*



ICRU/GEC ESTRO report 89
Fig. 6.4, Fig. 8.8

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

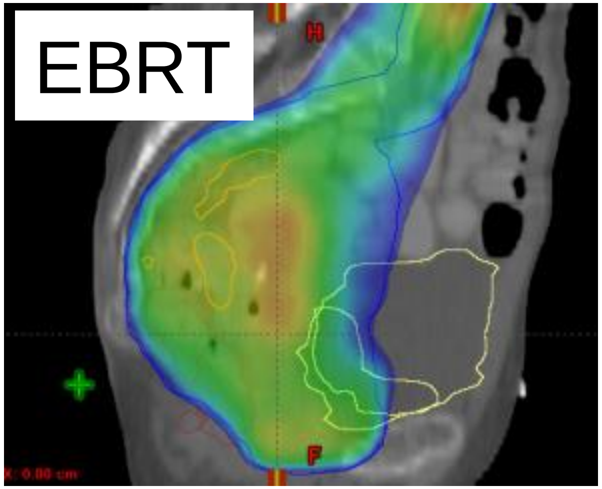
Pelvic EBRT (elective) + BT

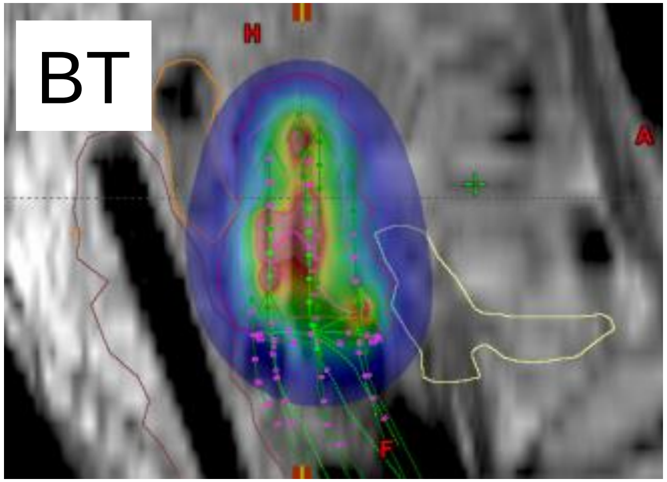
- **Elective target volume and CTV-T:**
  - **Normally homogeneous dose within 95%-107% of PD**

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 prescribed dose of EBRT has been applied
B. 90% of the dose of the prescribed dose of EBRT has been applied
C. 100% of the prescribed dose of EBRT has been applied

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

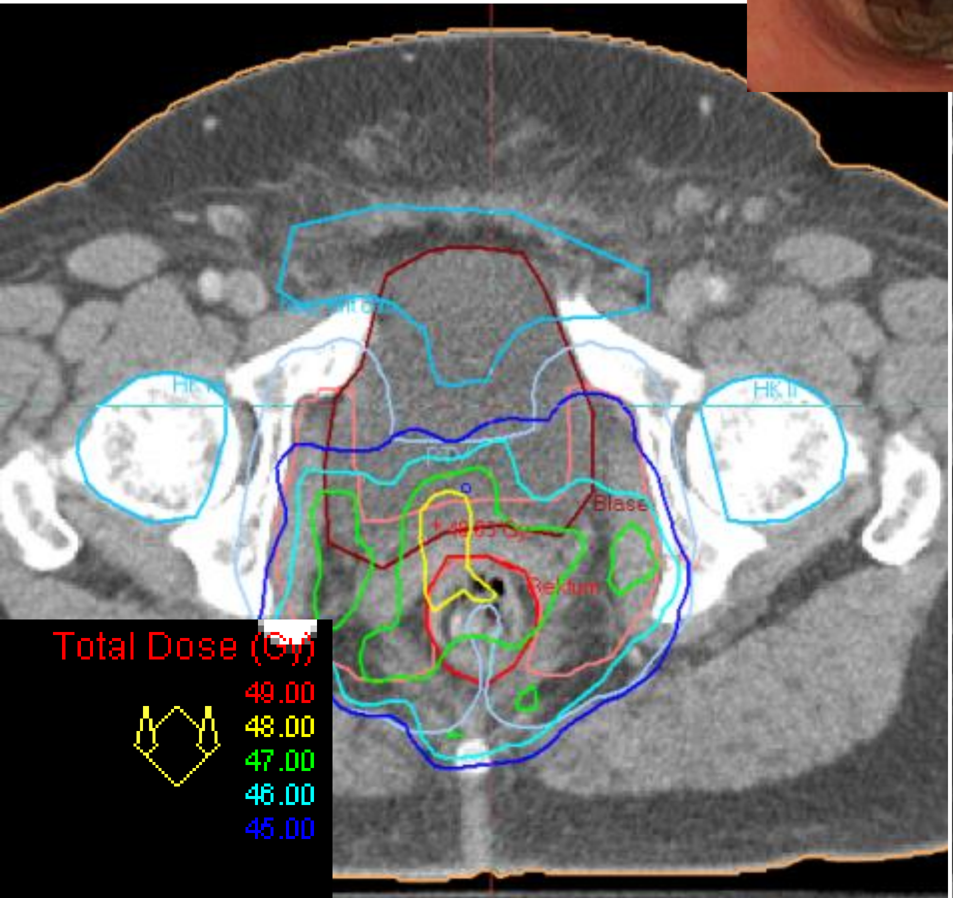
- **Non-homogenous dose distribution EBRT**
  e.g. IMRT, VMAT…
- **Parametrial boost**
- **Lymph node boost**
- **Limitations of the linear-quadratic model**

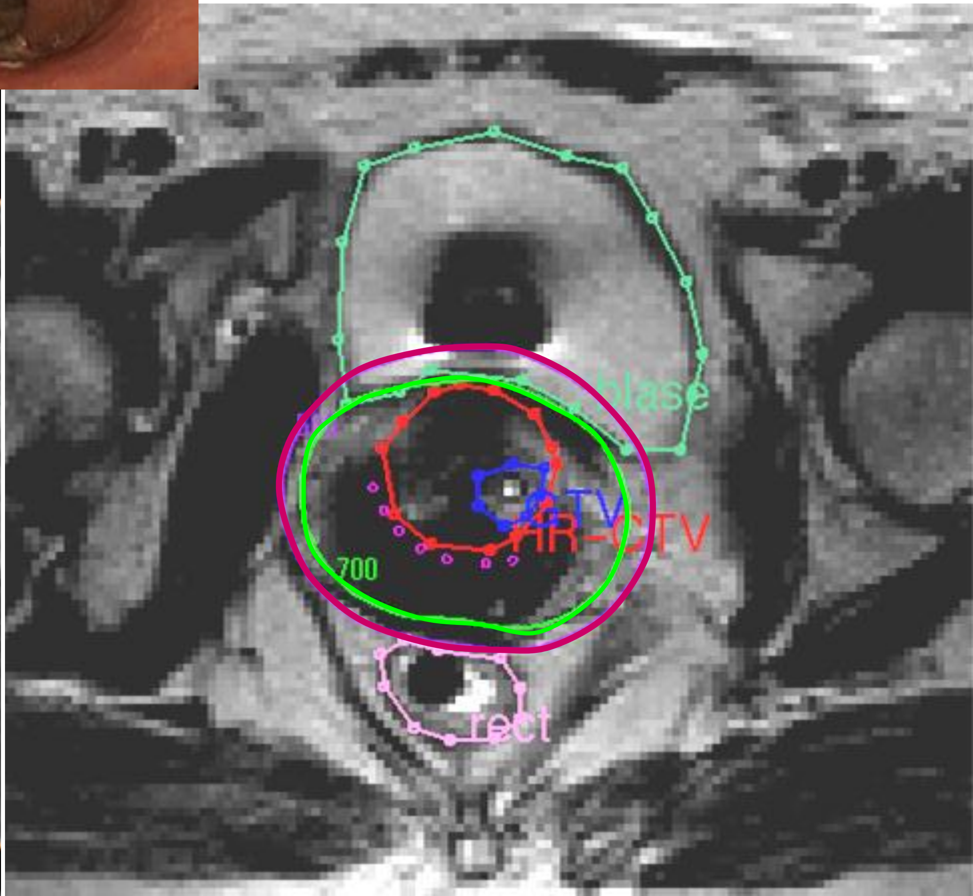
- **Future solution for complex adding doses….**

How could this happen?

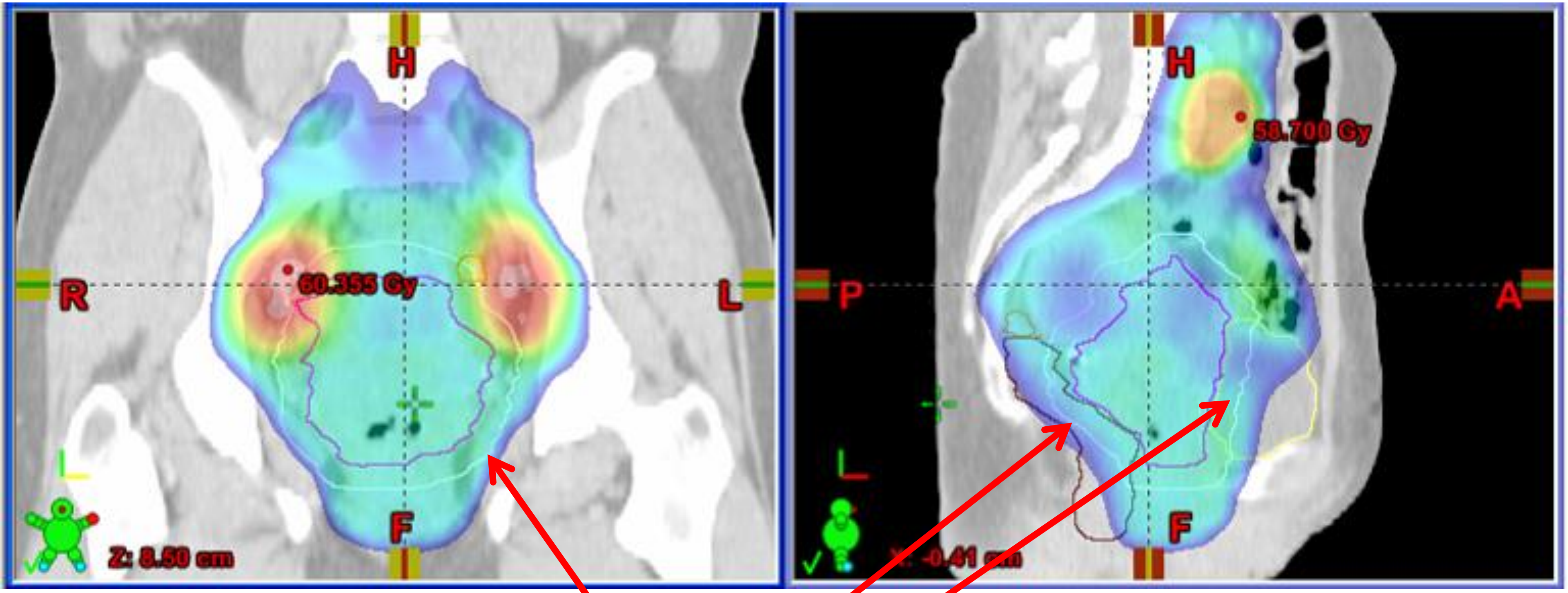
D2cc = 65.7 Gy $EQD2_{(\alpha/\beta=3)}$

D2cc = 79.2 Gy $EQD2_{(\alpha/\beta=3)}$



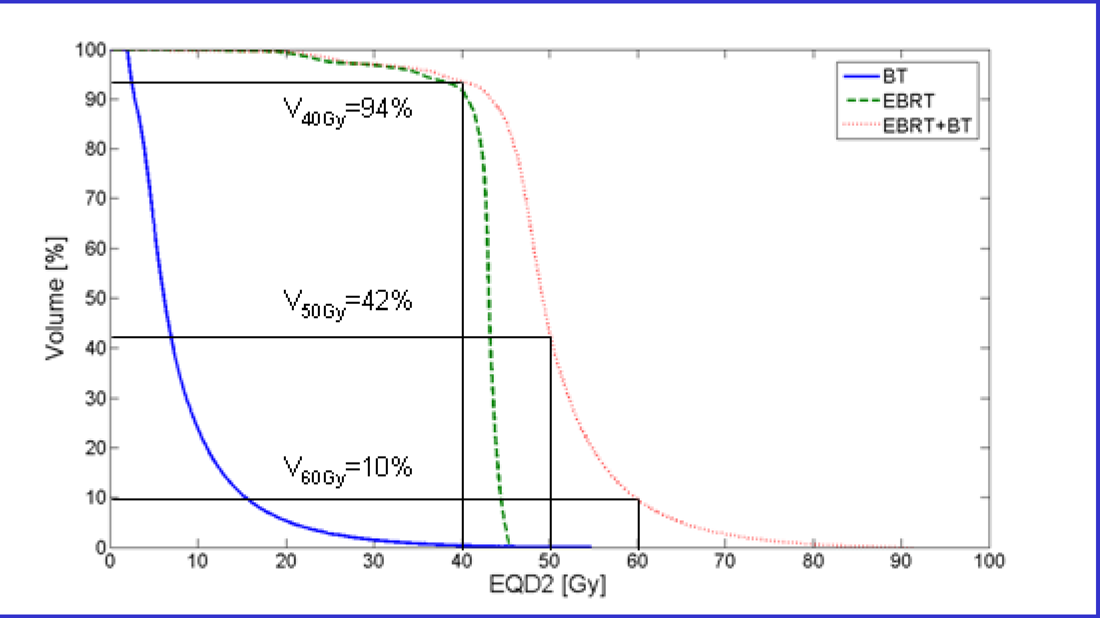


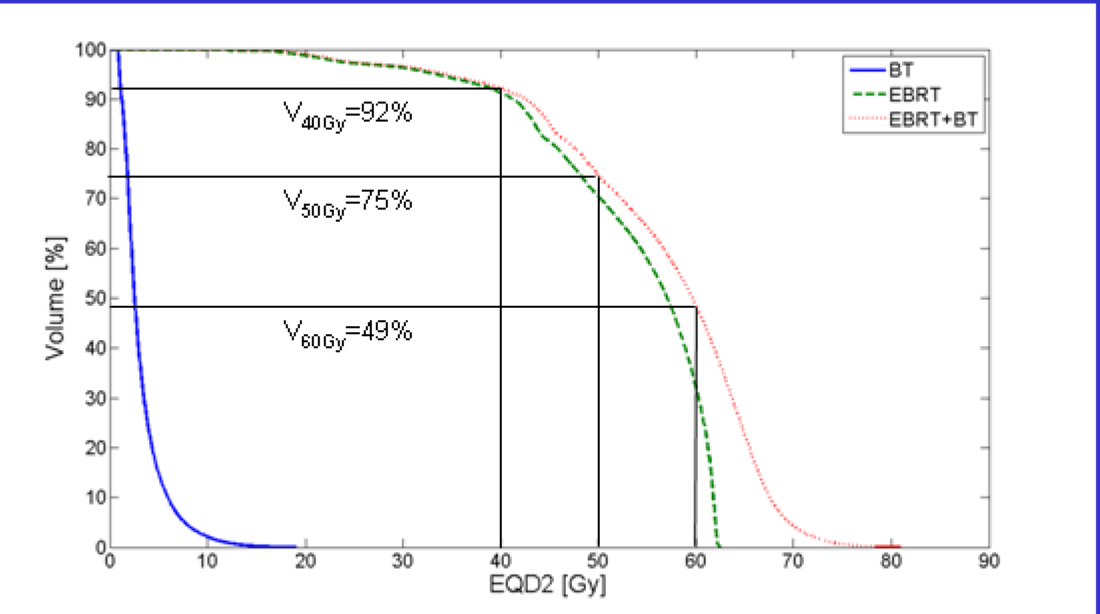
Avoid IMRT hot spots in the BT region!



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”

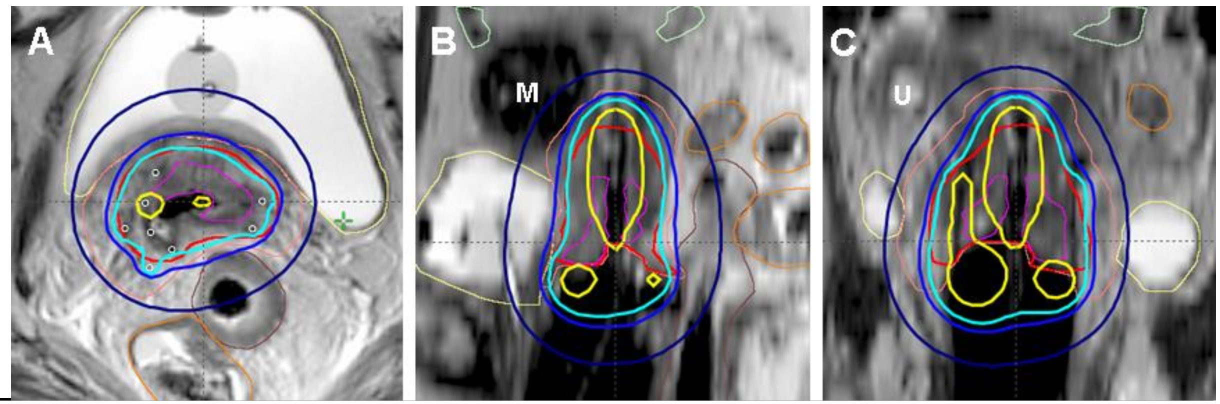
Need for common terminology according to ICRU reports on proton treatment and IMRT

- **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**

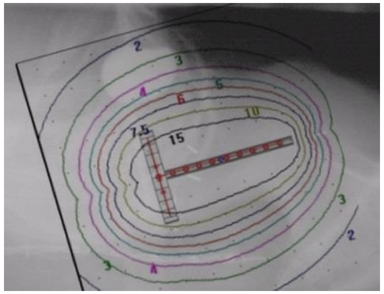
Case 6
Appendix,
ICRU 89



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	$\leq$ 7Gy	6.8 Gy
Rectum	ICRU point	$\leq$ 75% of 7Gy	5.3 Gy

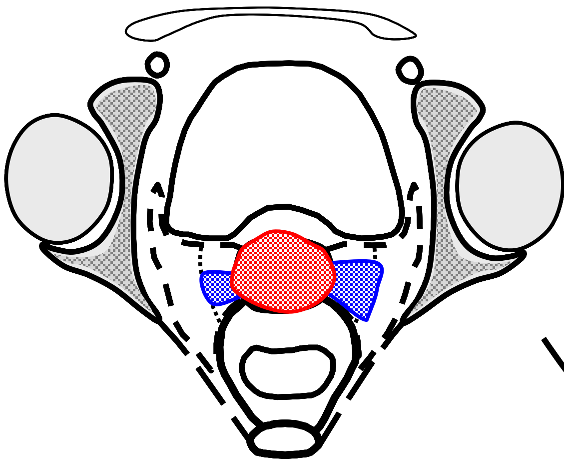
Example: Cervical Cancer Stage IIB (6 cm), N0, CCRT (3D CRT), MRI, Ring and Needles, HDR BT

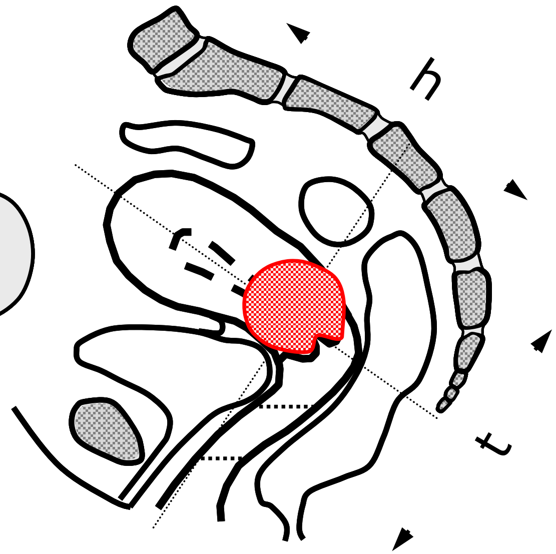
(case 5, ICRU 89, page 193-199)

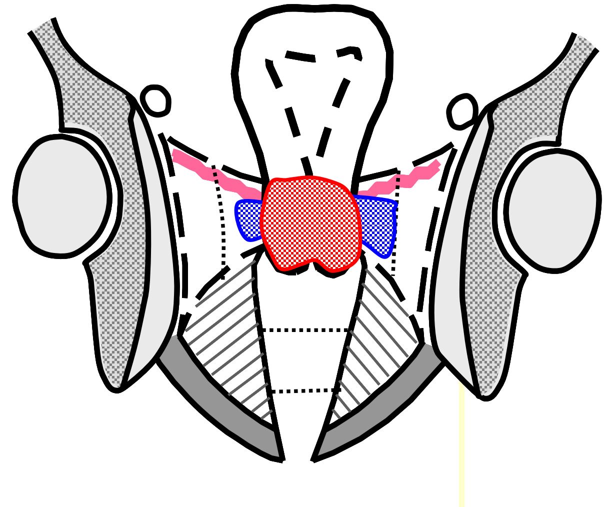
Table A.5.3. Treatment planning aim and prescribed doses.

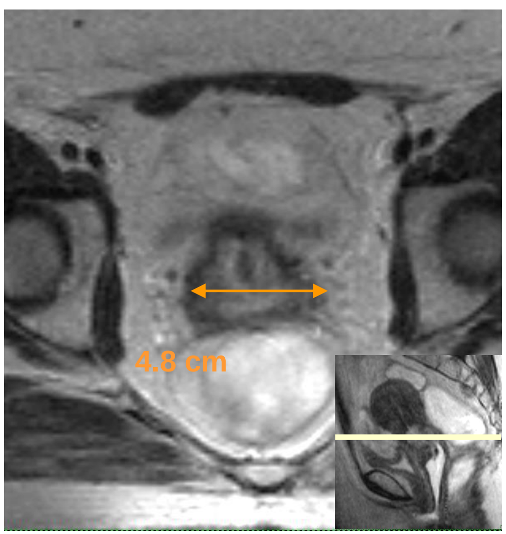
			Planning aim (Gy)	Prescribed dose (Gy)
CTV_{HR}	D_{90}	$EQD2_{10}$	≥ 85	92.3
Bladder	D_{2cm^3}	$EQD2_3$	≤ 90	80.6
Rectum	D_{2cm^3}	$EQD2_3$	≤ 70	64.3
Sigmoid	D_{2cm^3}	$EQD2_3$	≤ 75	51.7

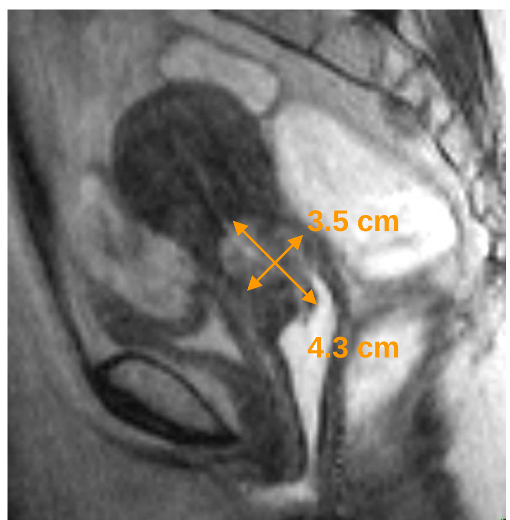
Example – disease at BT (Appendix case 5, ICRU 89)

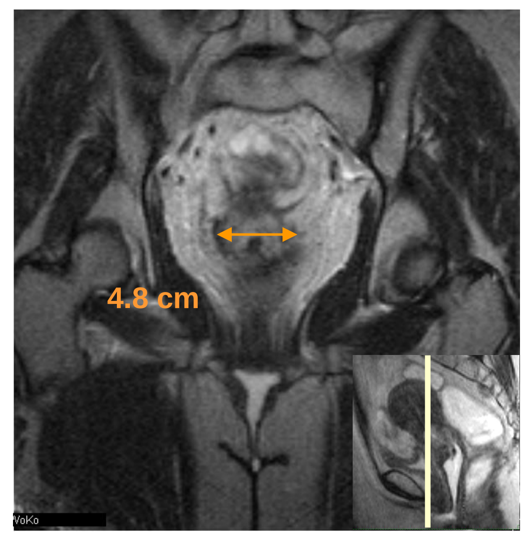












Example (Appendix case 5, ICRU 89)

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

	1^{st} application	2^{nd} 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

ESTRO School

General and image guided adaptive treatment strategies and BT techniques for vaginal and vulvar disease

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Vaginal and vulvar cancer: frequency

Estimated new cancer cases and deaths, United States, 2008

	Estimated new cases	Estimated deaths
Genital system (female)	**78490**	**28490**
Uterine cervix	11070	3870
Uterine corpus	40100	7470
Ovary	21650	15520
Vulva	**3460**	**870**

Rare gynaecological tumours

Vagina : 1% - 2% female reproductive tract cancers

Vaginal cancer

Primary vaginal cancer :

- Cervix and the vulva without history of cervix or vulvar cancer within 5 years
- 80% postmenopausal women
- Mean age : 60-65 years
- Exception : clear cell adenocarcinoma, young patients (mothers diethylstilbestrol (DES) during their pregnancies)

Vaginal cancer: natural history and pattern of spread

- 50% of vaginal cancers : upper third of the vagina even distribution on anterior/posterior/lateral walls

- 40-50% are multifocal

- Lower third of the vagina lymphatics communicate with those of the vulva

- Drainage:
  - either to the pelvic nodes or
  - to the inguinofemoral lymph nodes.

Vaginal cancer: initial work-up

- Clinical examination +++
  - Topography
  - Macroscopic characteristics
  - Drawings +++ / vaginal impression

- Transvaginal and/or transrectal sonography :
  - tumour thickness → BT technique

- MRI : tumour dimension, site, extension (bladder, rectum)
  enlarged pelvic and paraaortic nodes

- FDG-PET nodal disease twice as often as CT

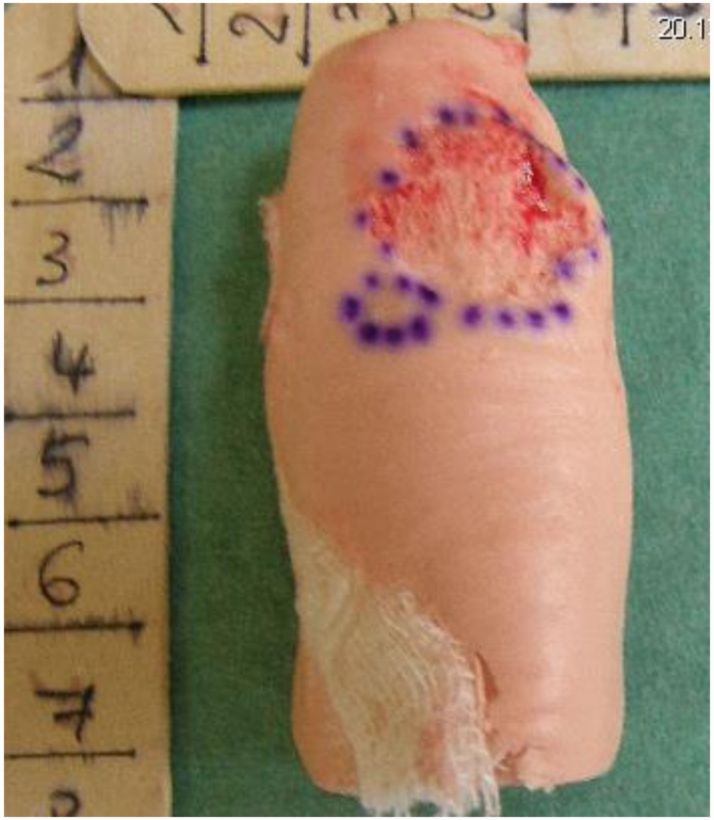
- Depending on tumoral extension : anuscopy/rectoscopy / urethrocystoscopy

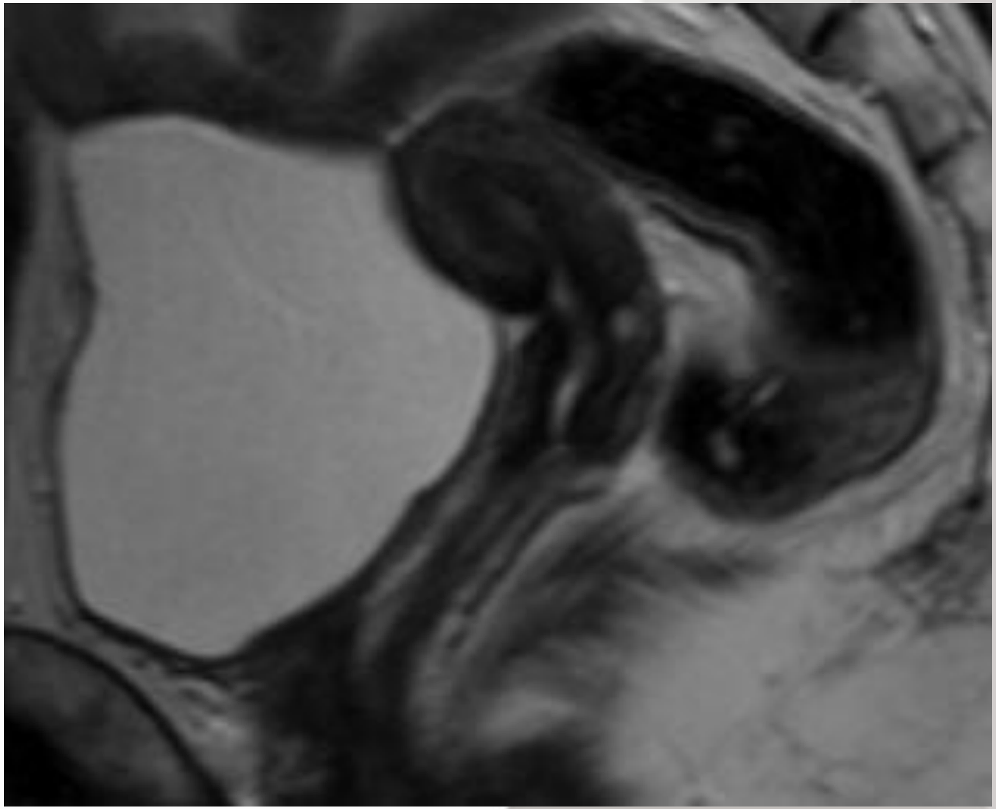
Vaginal cancer: initial work-up

- Vaginal impression

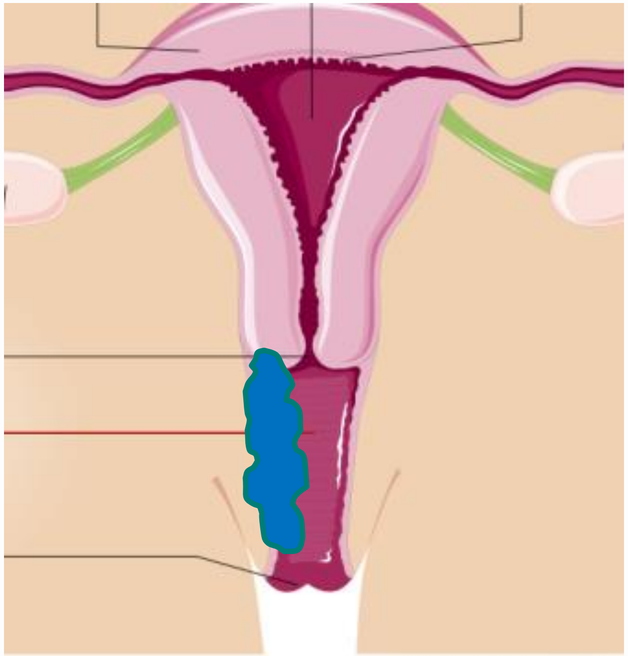
Vaginal cancer: initial work-up

- Vaginal impression





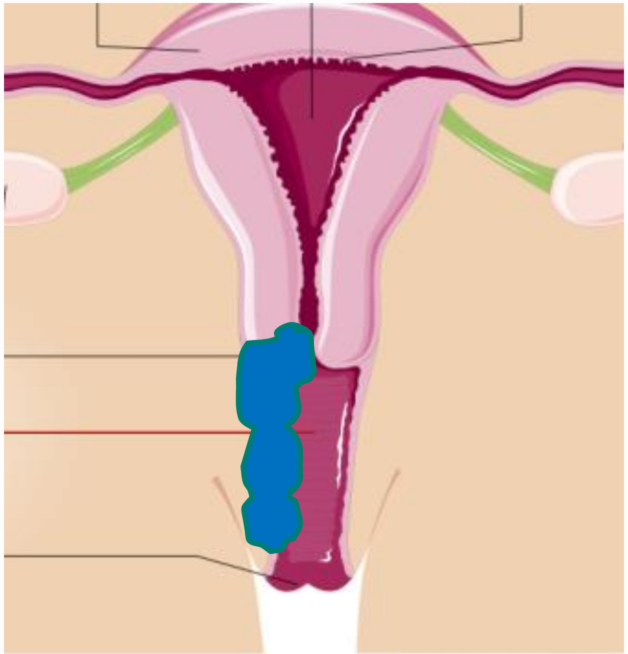
How would you classify this tumor using FIGO staging rules:



A. Primary vaginal cancer with cervical extension

B. Primary cervical cancer with vaginal extension

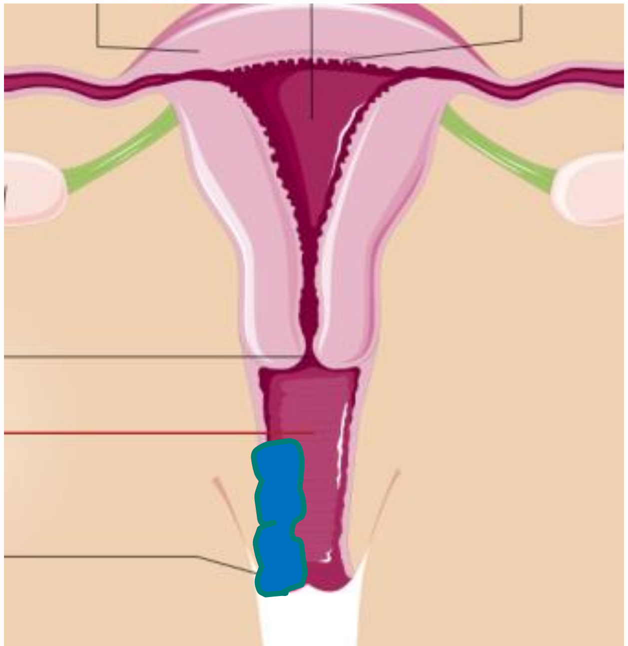
How would you classify this tumor using FIGO staging rules:



A. Primary vaginal cancer with cervical extension

B. Primary cervical cancer with vaginal extension

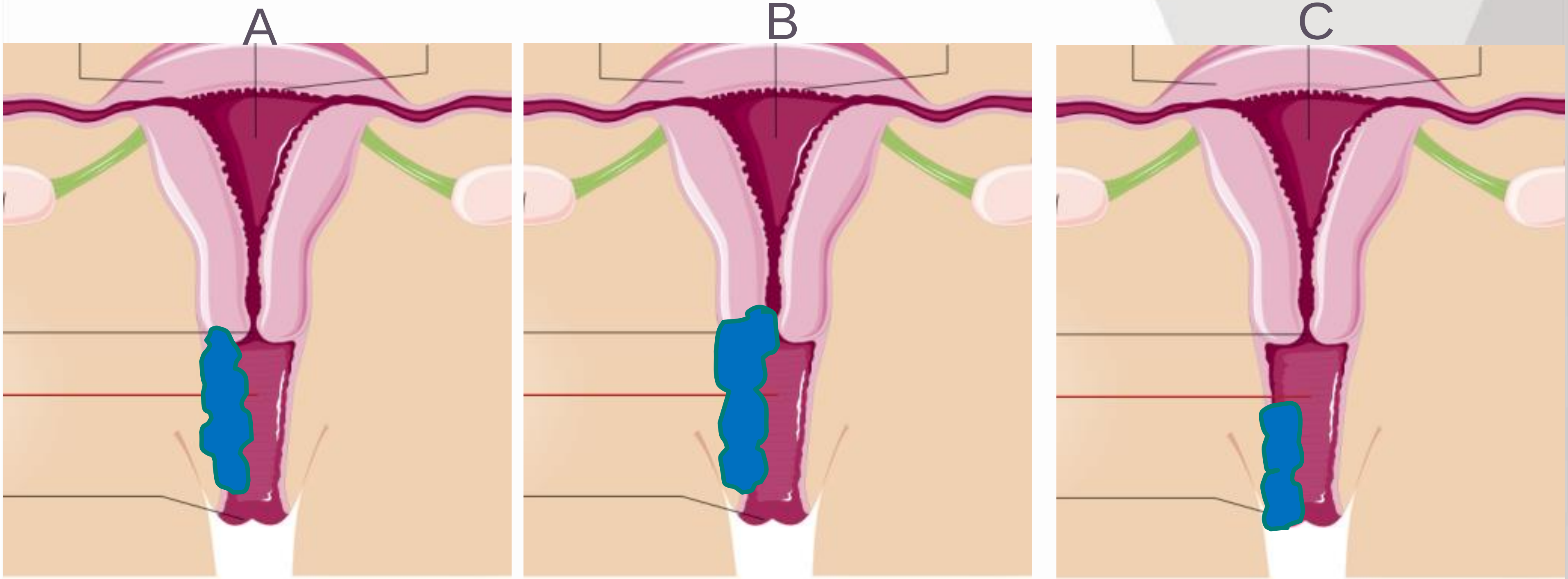
How would you classify this tumor using FIGO staging rules:



A. Primary vaginal cancer with vulvar extension

B. Primary vulvar cancer with vaginal extension

FIGO classification



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

- ‘cervical’ if the cervical os is involved (even if most of the tumor is in the vagina)
- ‘vulvar’ if any portion of the vulva is involved

Vaginal cancer : FIGO classification

0	Carcinoma in situ, intraepithelial carcinoma
I	Carcinoma limited to the vaginal wall
II	Paravaginal tissue extension, without reaching pelvic wall
III	Pelvic wall extension
IV	Extension beyond the true pelvis or bladder/rectum mucosa
IVA	Adjacent organs and/or direct extension beyond the true pelvis
IVB	Distant organs spread

Vaginal cancer: treatment

- Rarity of primary carcinoma of the vagina
- No randomized trial to assess :
  - the respective role of surgery and irradiation
  - to explore the value of concomitant chemoradiation
- Role +++ of brachytherapy

Vaginal cancer: treatment of VAIN

- Surgery alone (80%) young patients,
  ovarian function preservation
- Irradiation (5%-10) : exclusive BT
- Chemotherapy (4%-5%)

Results : brachytherapy VAIN

Patients characteristics		n=21
Age at diagnosis	Median (range)	53 (29-78)
Age at brachytherapy	Median (range)	66 (38-80)
History of	Cervical carcinoma	2
	endometrial carcinoma	1
	CIN	20
Multifocal	Yes	2
	No	19
Microinvasive carcinoma	Yes	2
	No	14
	NA	5

Median Follow-up: 79 months

Blanchard, Oncologist 2011;16:182-8

Results: Brachytherapy VAIN

BT characteristics	
Volume 60 Gy isodose (cm^3)	82 (18-121)
Vaginal volume treated	
upper half	14
upper two-third	4
whole vagina	3
ICRU Bladder Dose (Gy)	47 (8-74)
ICRU Rectum Dose (Gy)	69 (32-109)
Application duration (days)	4.5 (3-6)
Intraoperative Lugol staining (%)	18 (82)
Intraoperative fiducial placement (%)	6 (27)

Blanchard, Oncologist 2011;16:182-8

Brachytherapy: outcome

- Follow-up: 79 months
- 1 vulvar relapse (out of field)
- 1 « in field » relapse in a heavily pretreated patient
  - **previous surgery, radiotherapy, chemotherapy and brachytherapy for cervical carcinoma**
  - **unsuccessful interferon and laser therapy for VAIN**
- 19 cured patients

Blanchard, Oncologist 2011;16:182-8

Vaginal cancer: treatment of invasive tumours

- External beam radiotherapy (ERT) and brachytherapy (BT)
- Limited stage I : exclusive BT
- 45 Gy to the pelvis/prophylactic inguinal ERT if lower third tumoral extension
- Concomitant chemoradiation

Vaginal cancer: image-guided adaptive brachytherapy (IGABT)

- No recommendations for CTVs
- CTV_{HR} and CTV_{IR} concepts for cervix
- Transfer and adaptation to vaginal cancer

Target delineation recommendations of the GYN GEC-ESTRO Group for image-guided adaptive brachytherapy in primary vaginal cancer

Vaginal cancer: image-guided adaptive brachytherapy (IGABT)

GTV_{init}: macroscopic tumor at the time of diagnosis

GTV_{res}: macroscopic residual tumor at the time of brachytherapy

Clinical examination: This is the remaining visible and palpable residual macroscopic tumor at gynae examination

Imaging: T2-weighted MRI remaining mass with hyperintense to isointense signal intensity, within the initial tumor extension at diagnosis, GTV_{init}

Vaginal cancer: image-guided adaptive brachytherapy (IGABT)

CTV_{HR}: includes the *GTV_{res}* and areas at high risk for significant residual disease

Clinical: *GTV_{res}* and any abnormal thickened or irregular vaginal wall within the initial tumor extension (*GTV_{init}*)

Imaging: includes the *GTV_{res}* and any abnormal thickened or deformed vaginal wall within the initial tumor extension (*GTV_{init}*)

In case of tumors infiltrating the paravaginal or parametrial space at diagnosis, so called „grey zones"are included in the *CTV_{HR}*

Vaginal cancer: image-guided adaptive brachytherapy (IGABT)

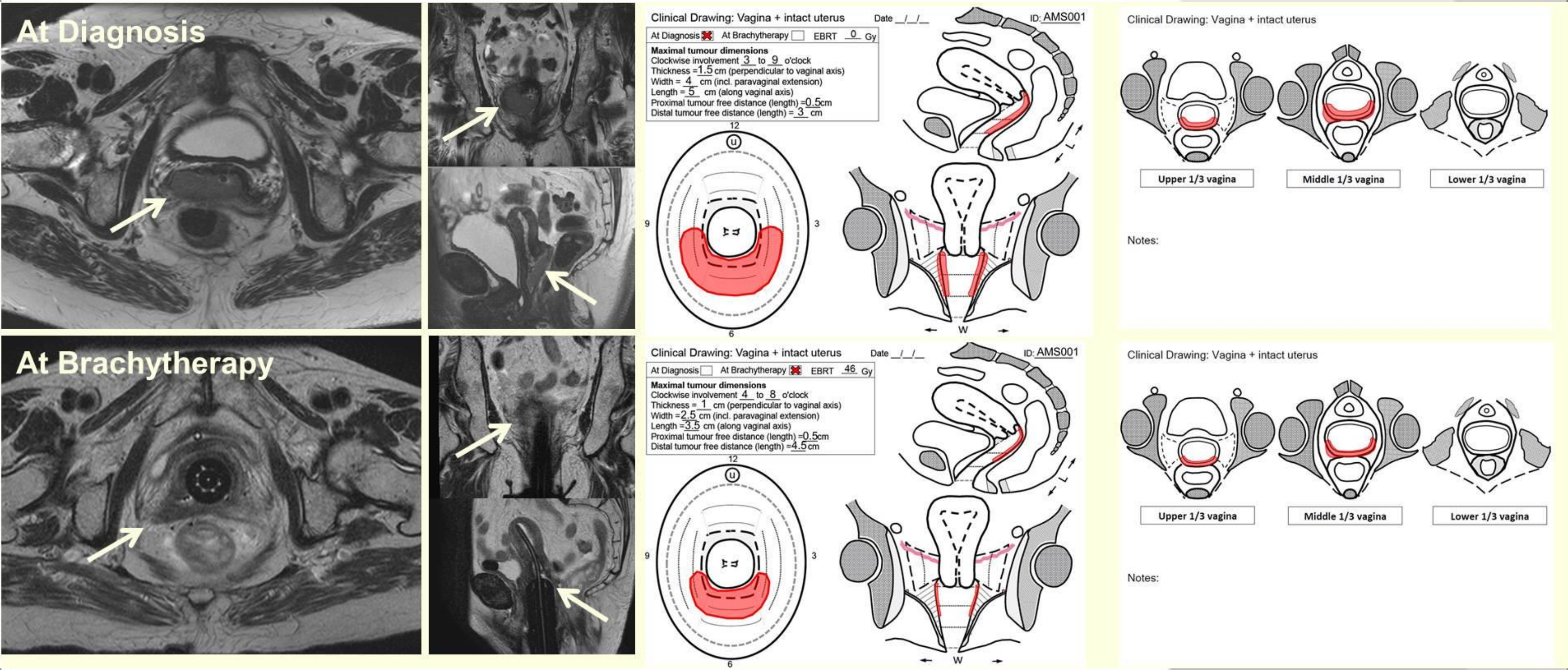
CTV_{IR}: safety margin for presumed adjacent significant microscopic disease

Integrates initial tumor extension at diagnosis (GTV_{init})

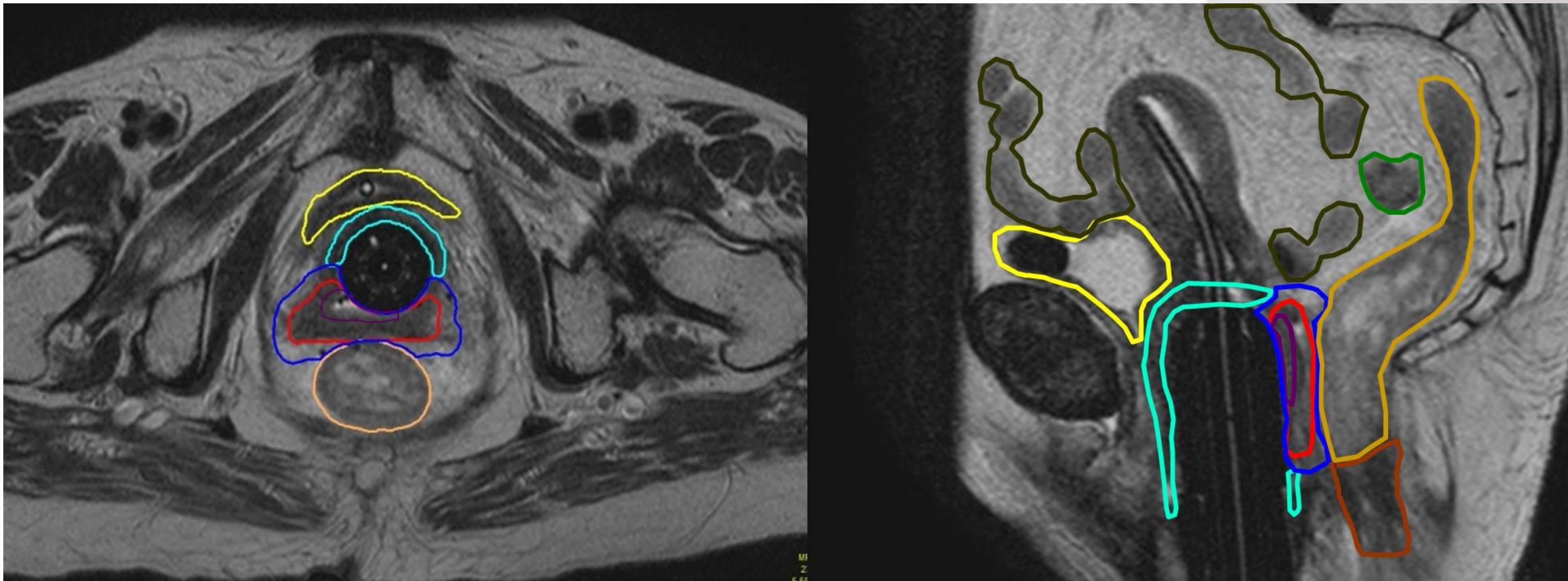
Includes the CTV_{HR} plus an isotropic margin of **minimal 5 mm** limited by previously unaffected anatomical borders/compartments: pubic bone, pelvic wall, pelvic floor musculature, bladder, urethra, mesorectal fascia, rectum, anal sphincter

In case of infitration of hollow organs (rectum, urinary bladder) before radiochemotherapy only the organ wall without the lumen should be included

Vaginal cancer: image-guided adaptive brachytherapy (IGABT)



Vaginal cancer: image-guided adaptive brachytherapy (IGABT)



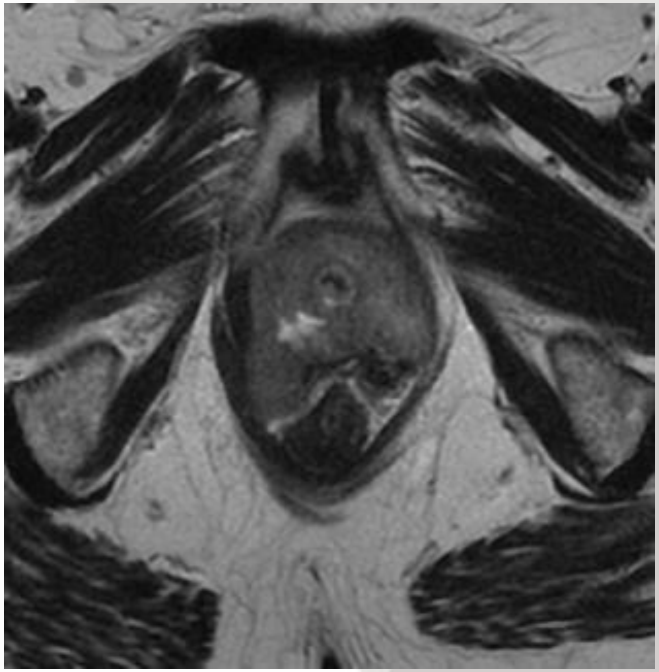
Vaginal cancer: brachytherapy

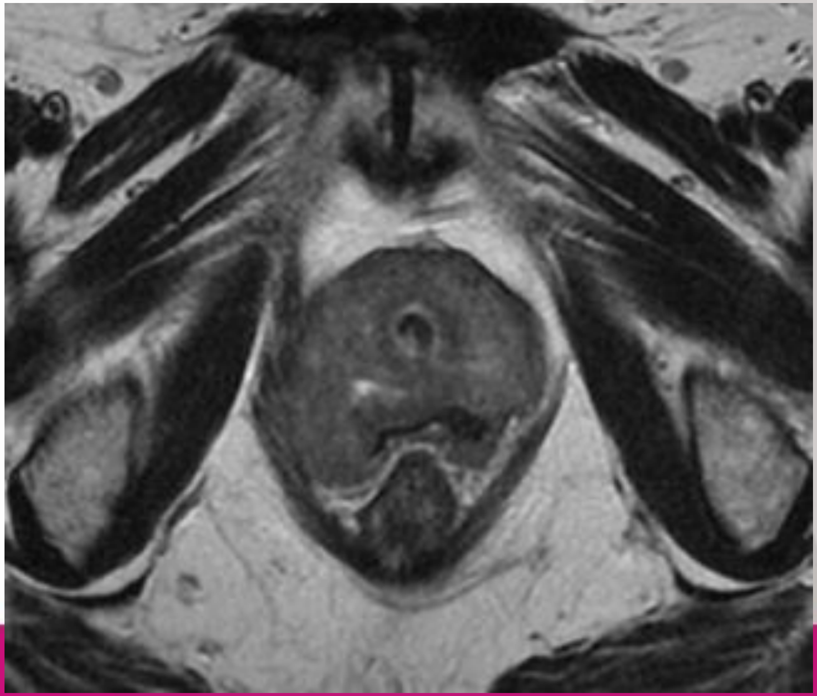
- Endocavitary
- Interstitial
- Endocavitary and interstitial combination
- Total dose : 80Gy to the GTV

Vaginal cancer: brachytherapy

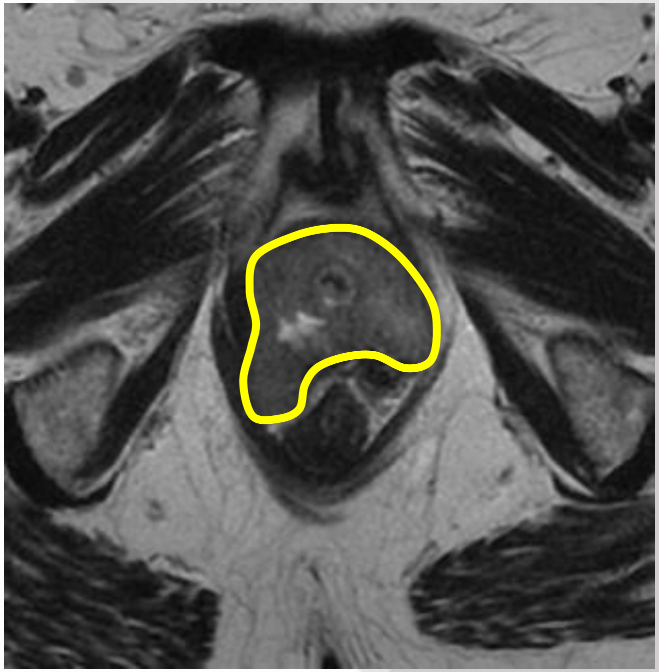
- Relative place of endocavitary and interstitial BT :
  - Tumour site
    - Recto-vaginal septum infiltration = relative contra-indication to interstitial BT
  - Tumour thickness
    - Interstitial BT if tumour thickness > 7-10mm
    - Para-vaginal infiltration = good indication to combine intracavitary and interstitial BT

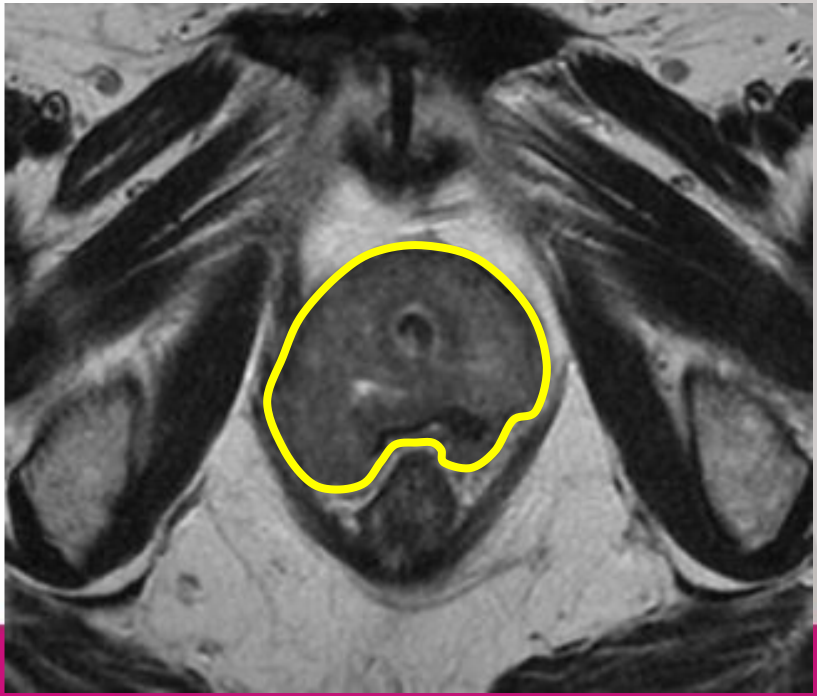
At diagnosis





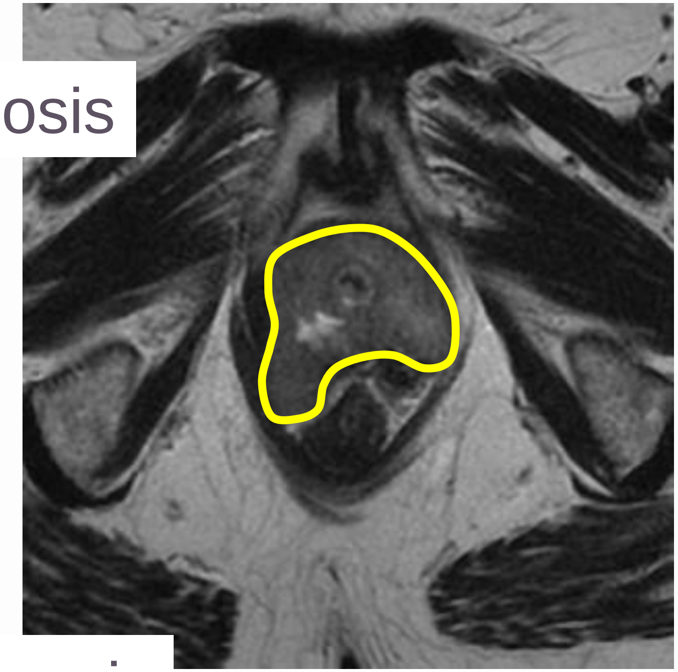
At diagnosis



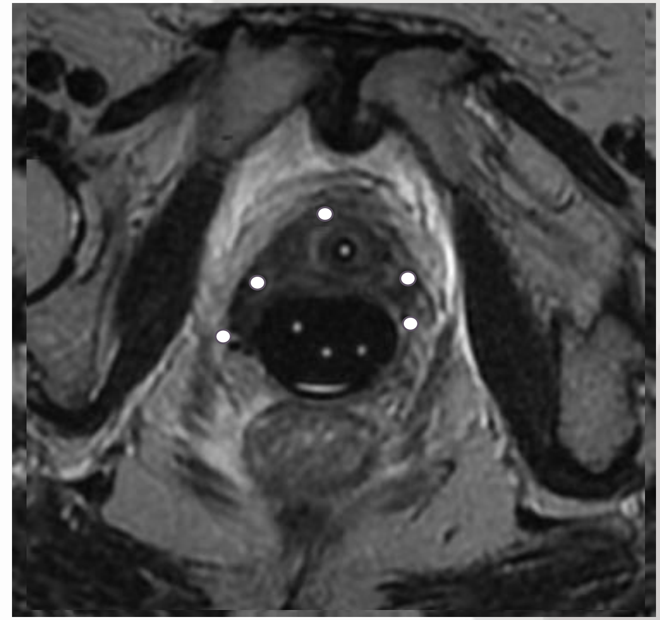


GTV_{init}

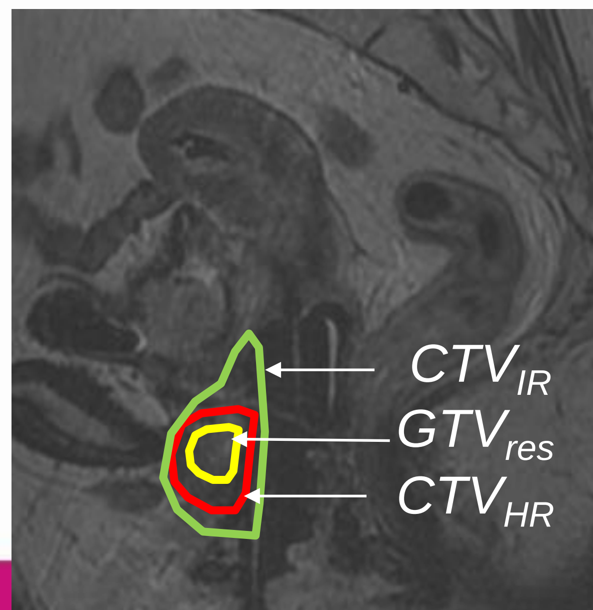
At diagnosis



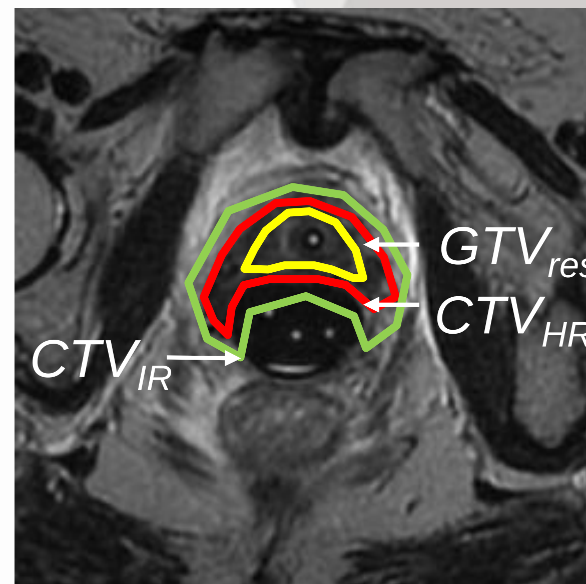
GTV_{init}



At diagnosis

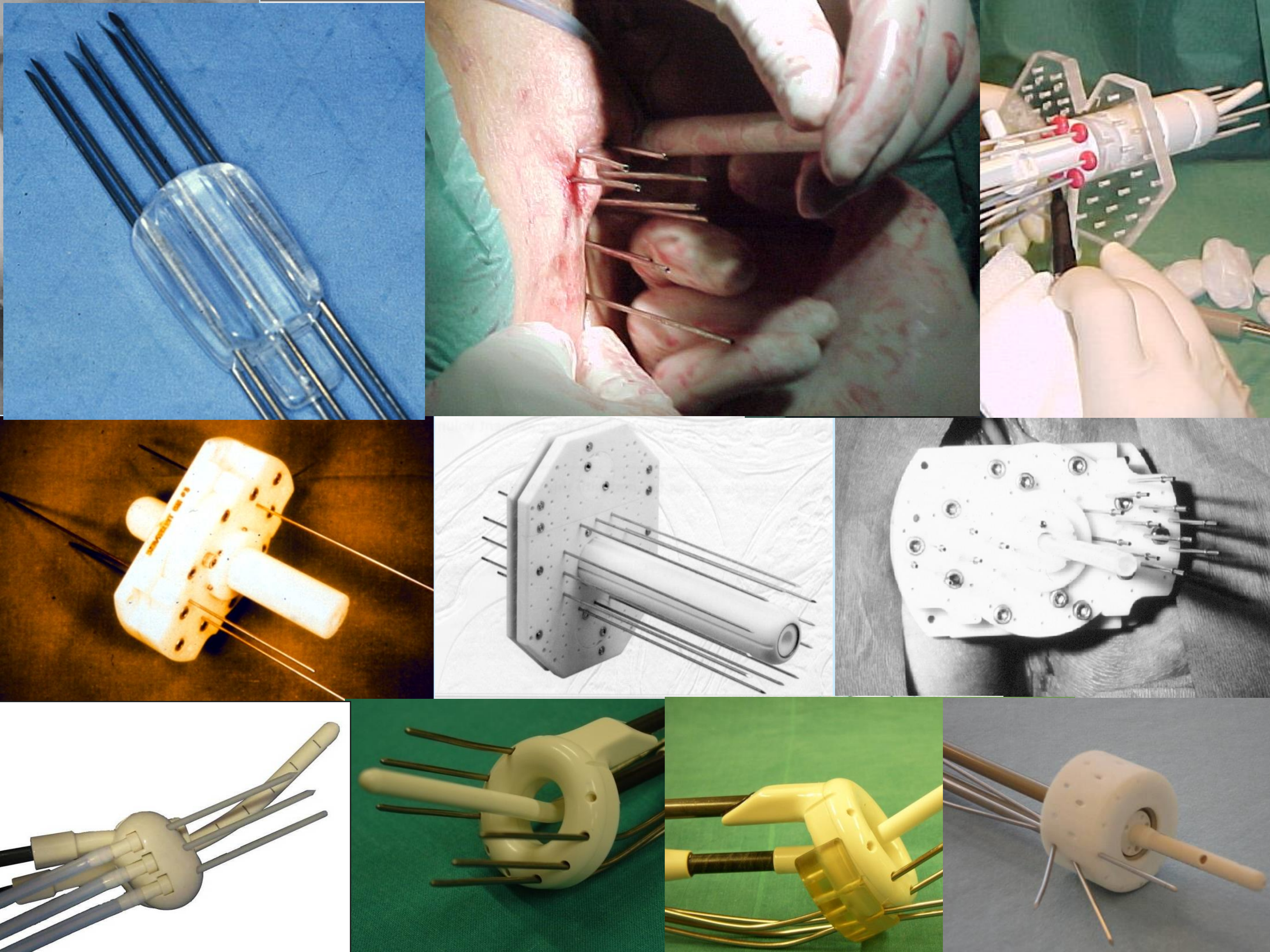


At brachy



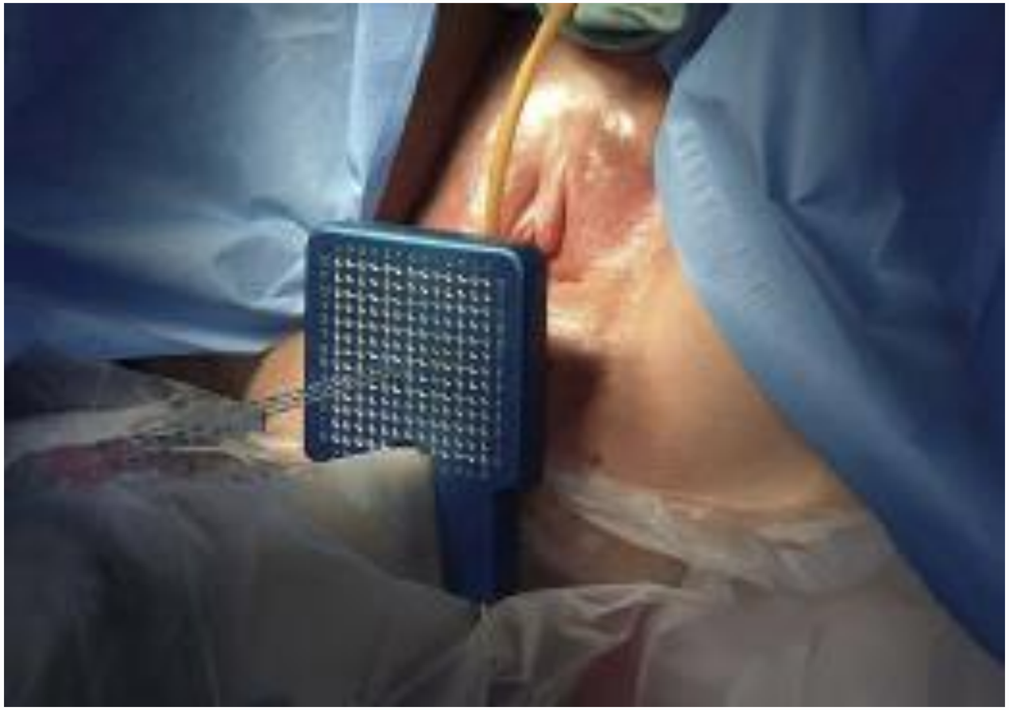
Vaginal cancer:

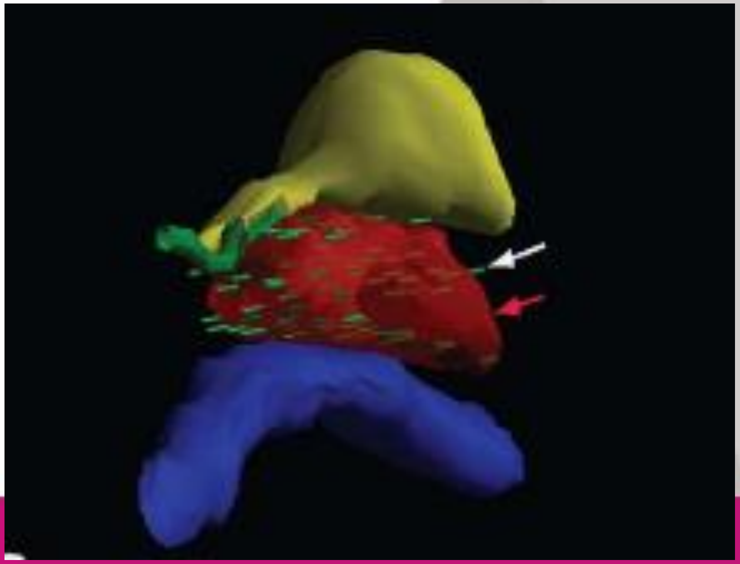
Interstitial techniques



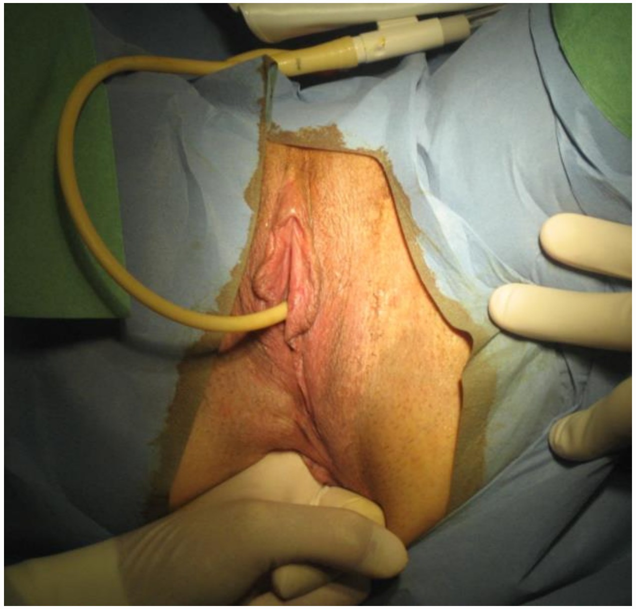
Interstitial techniques for vaginal cancers

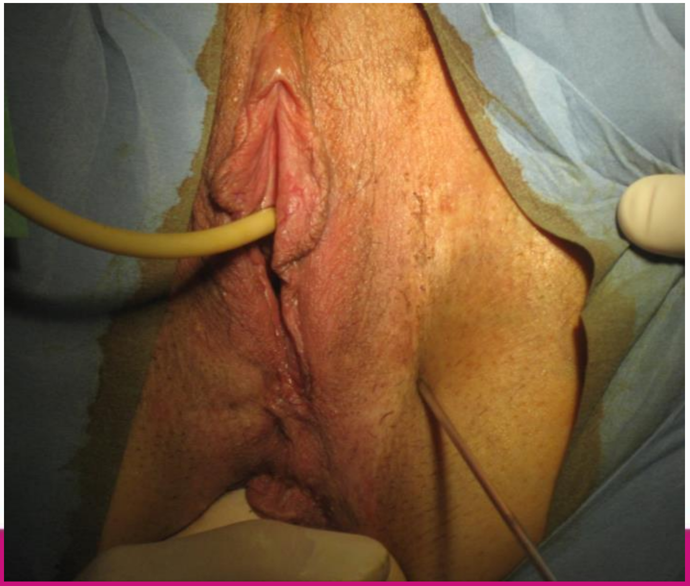
Transperineal template





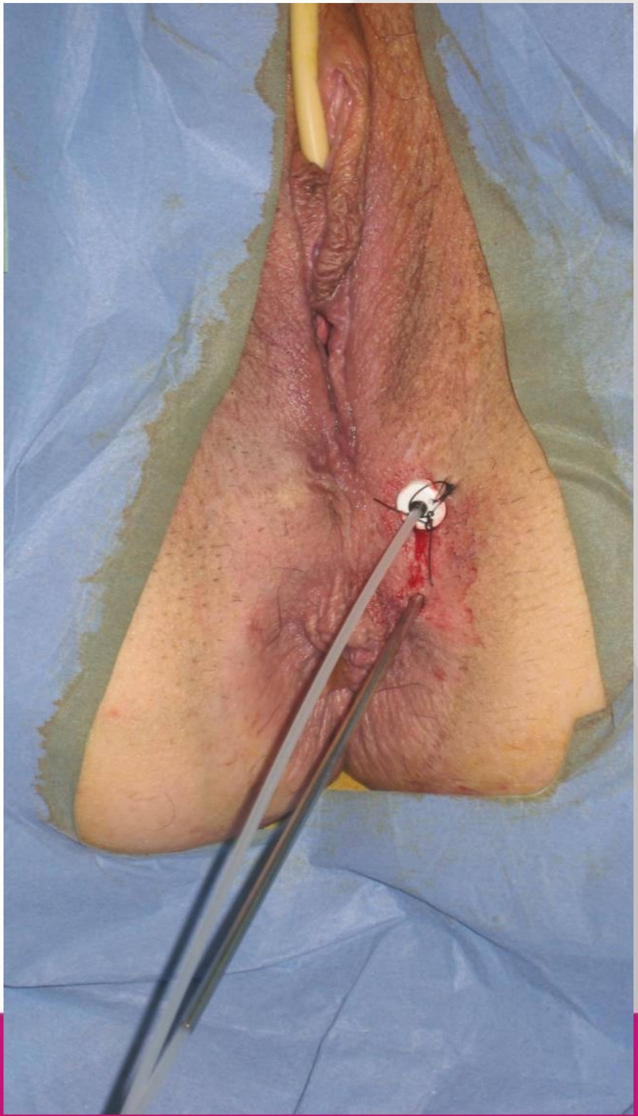
Interstitial techniques for vaginal cancers



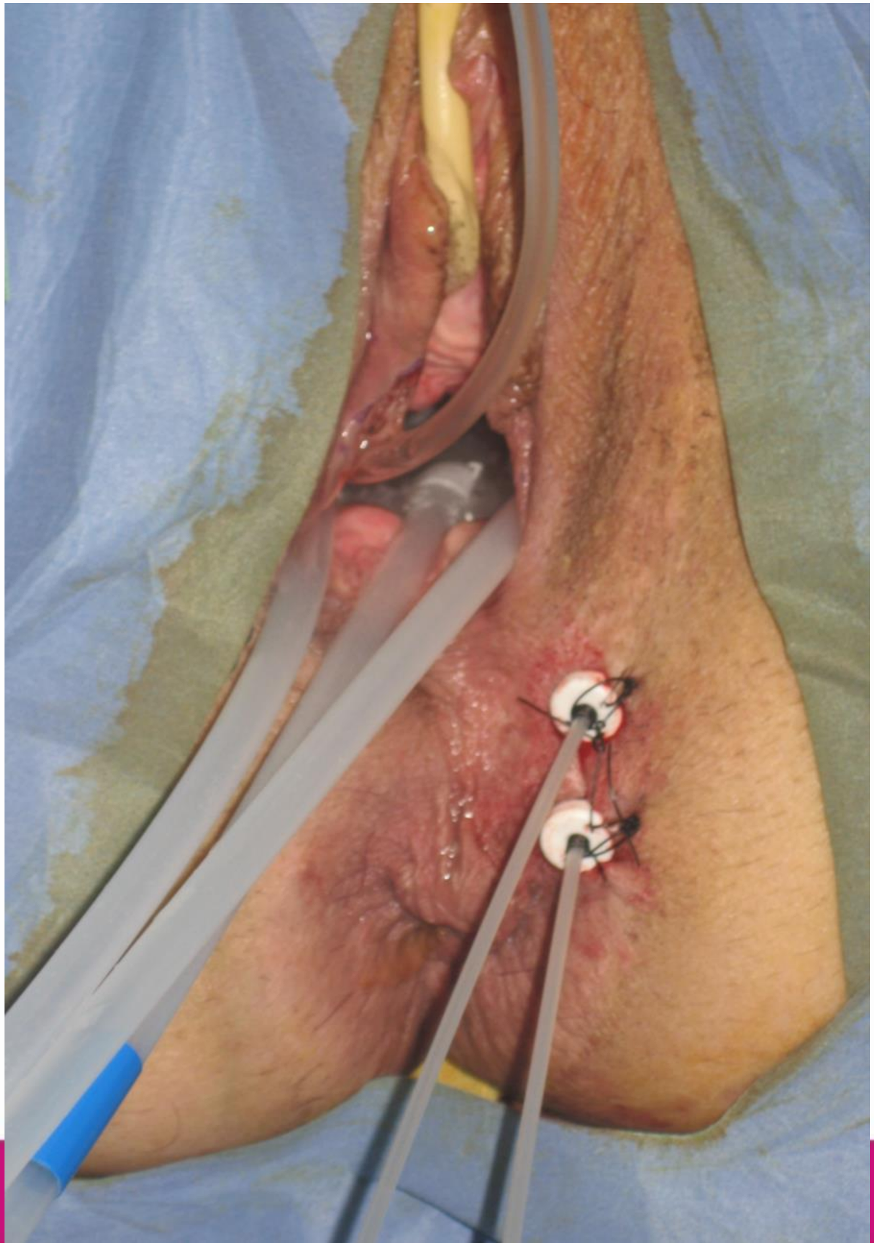


Free–hand placement

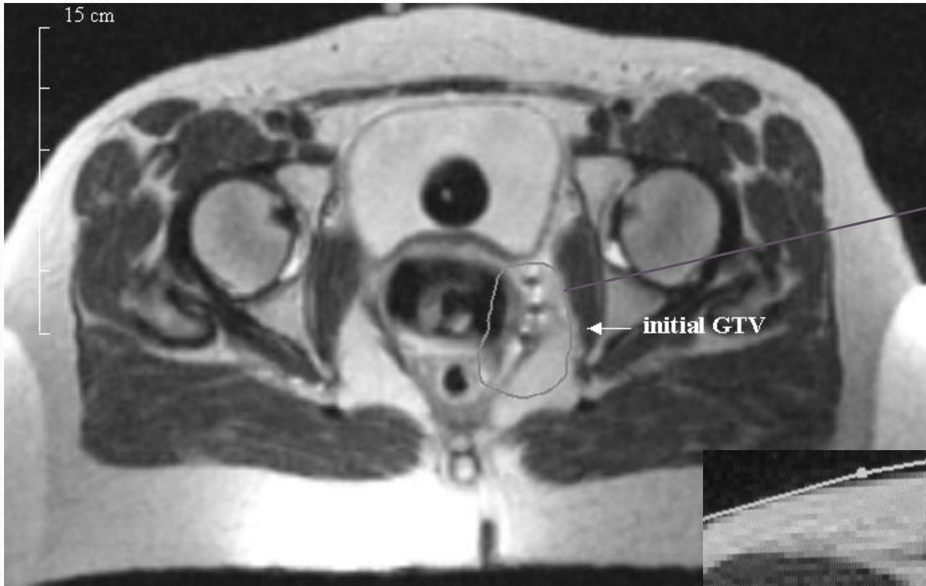
Interstitial techniques for vaginal cancers



Interstitial techniques for vaginal cancers

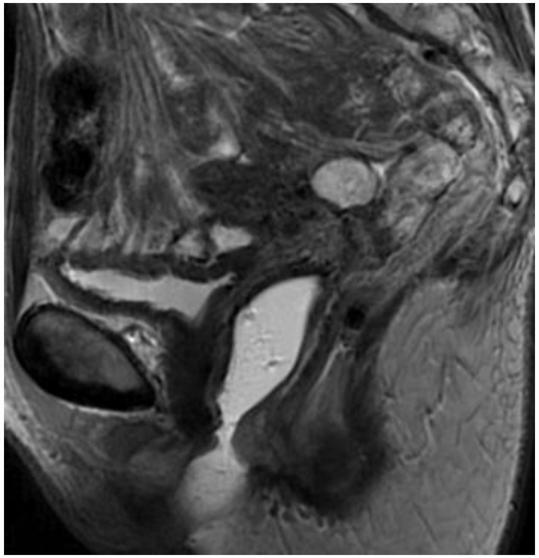
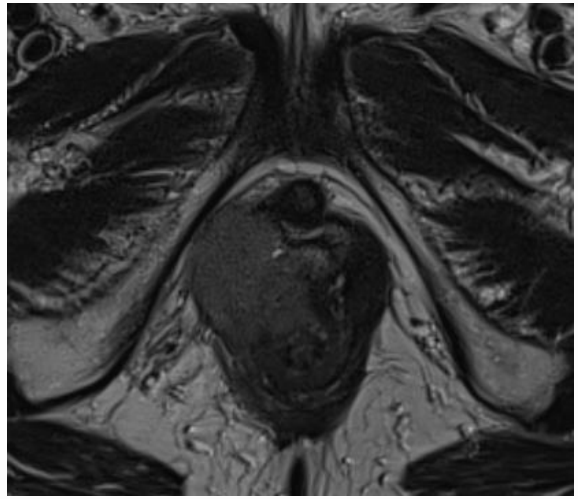
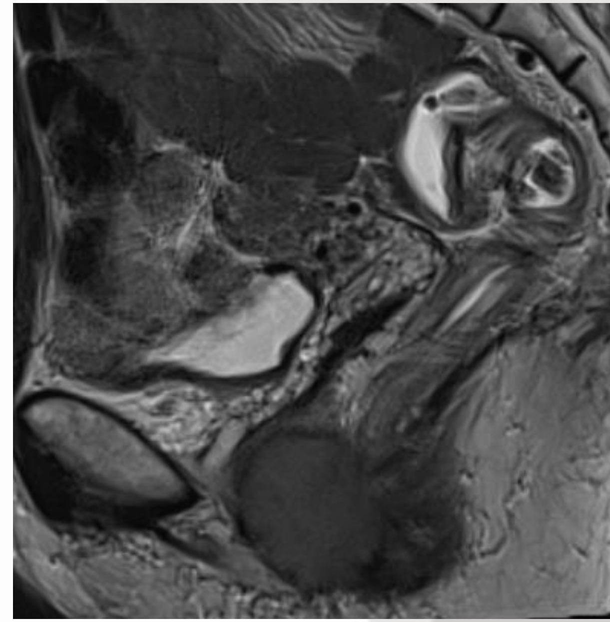
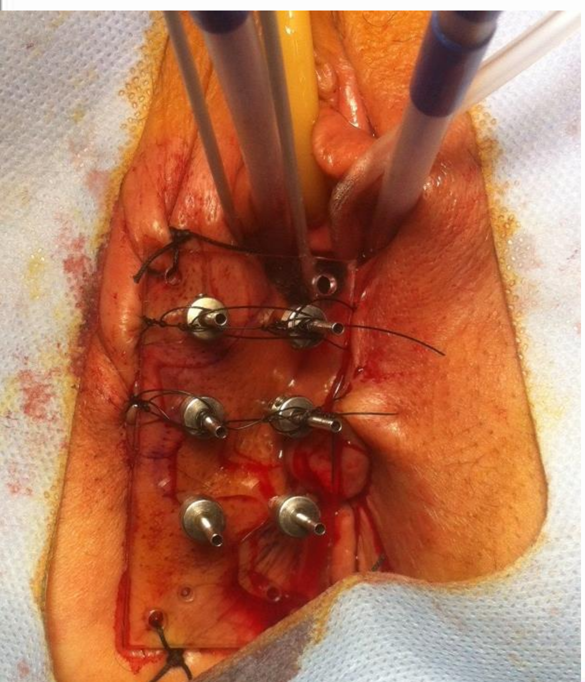
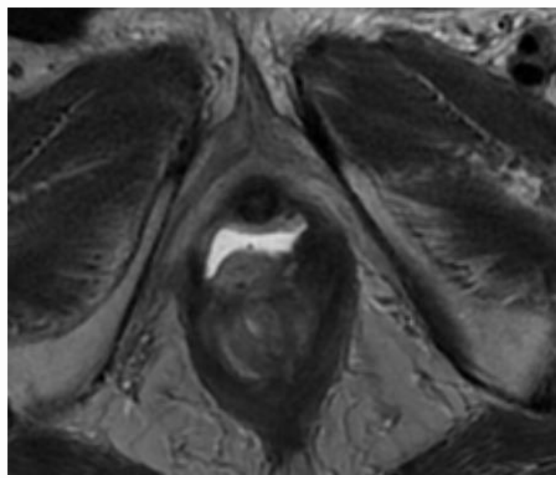
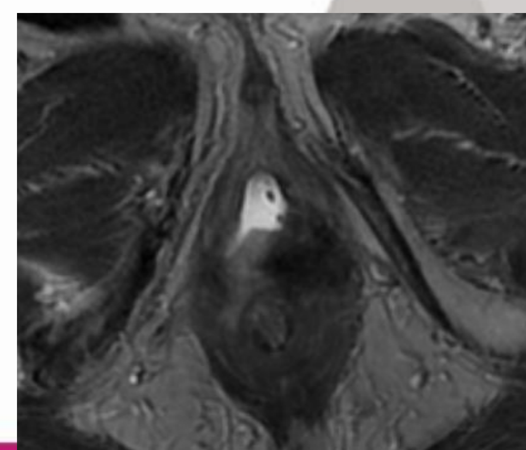


Interstitial techniques for vaginal cancers



Endocavitary + 3 needles

Dose : 80 Gy to the CTV_{HR}

Vaginal cancer: example n° 1

- 24 year-old patient
- VIH +
- Post-delivery vaginal bleeding
- Biopsy : moderately differentiated squamous cell ca.

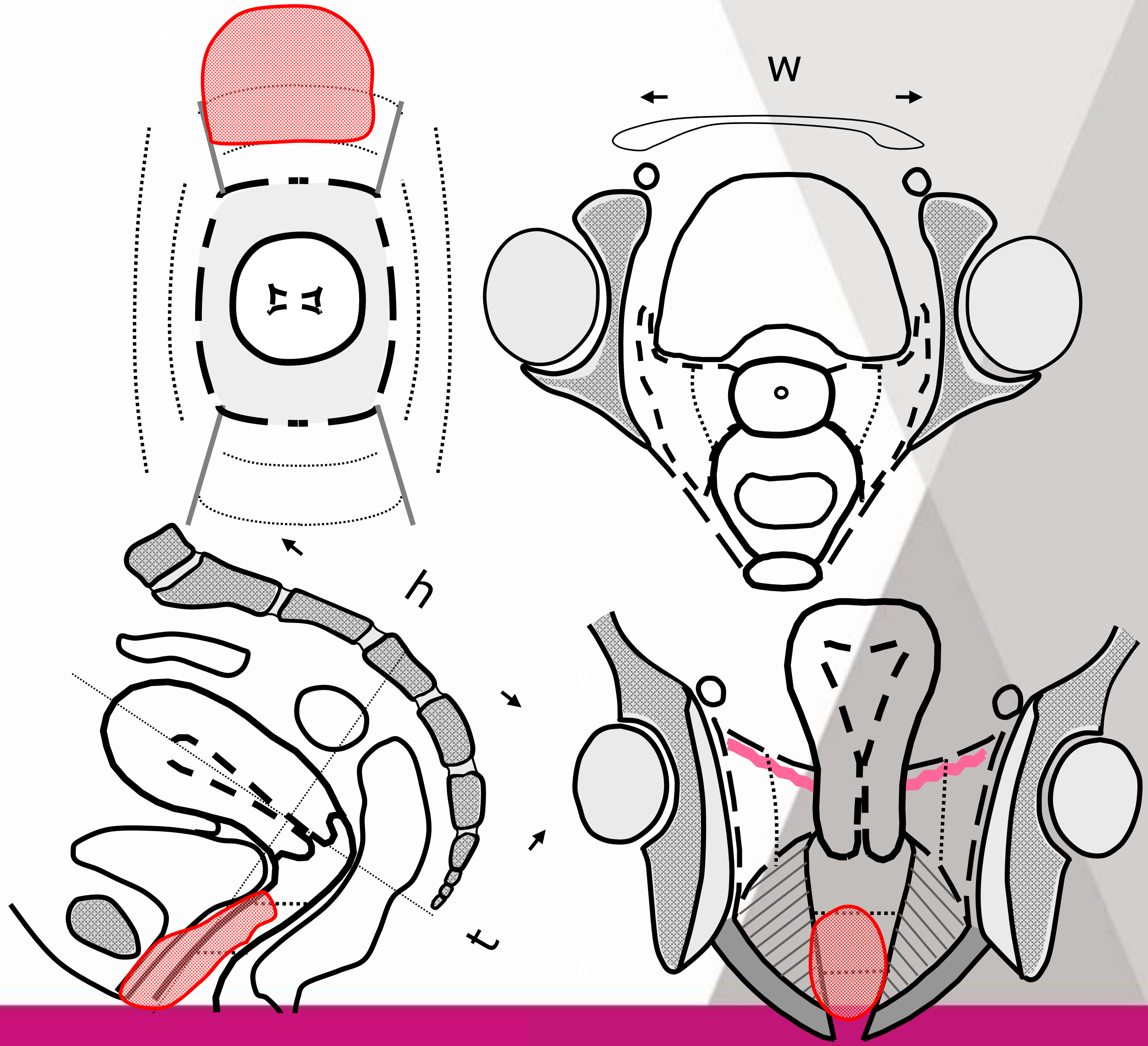
Initial clinical findings

__Dimensions (cm):__

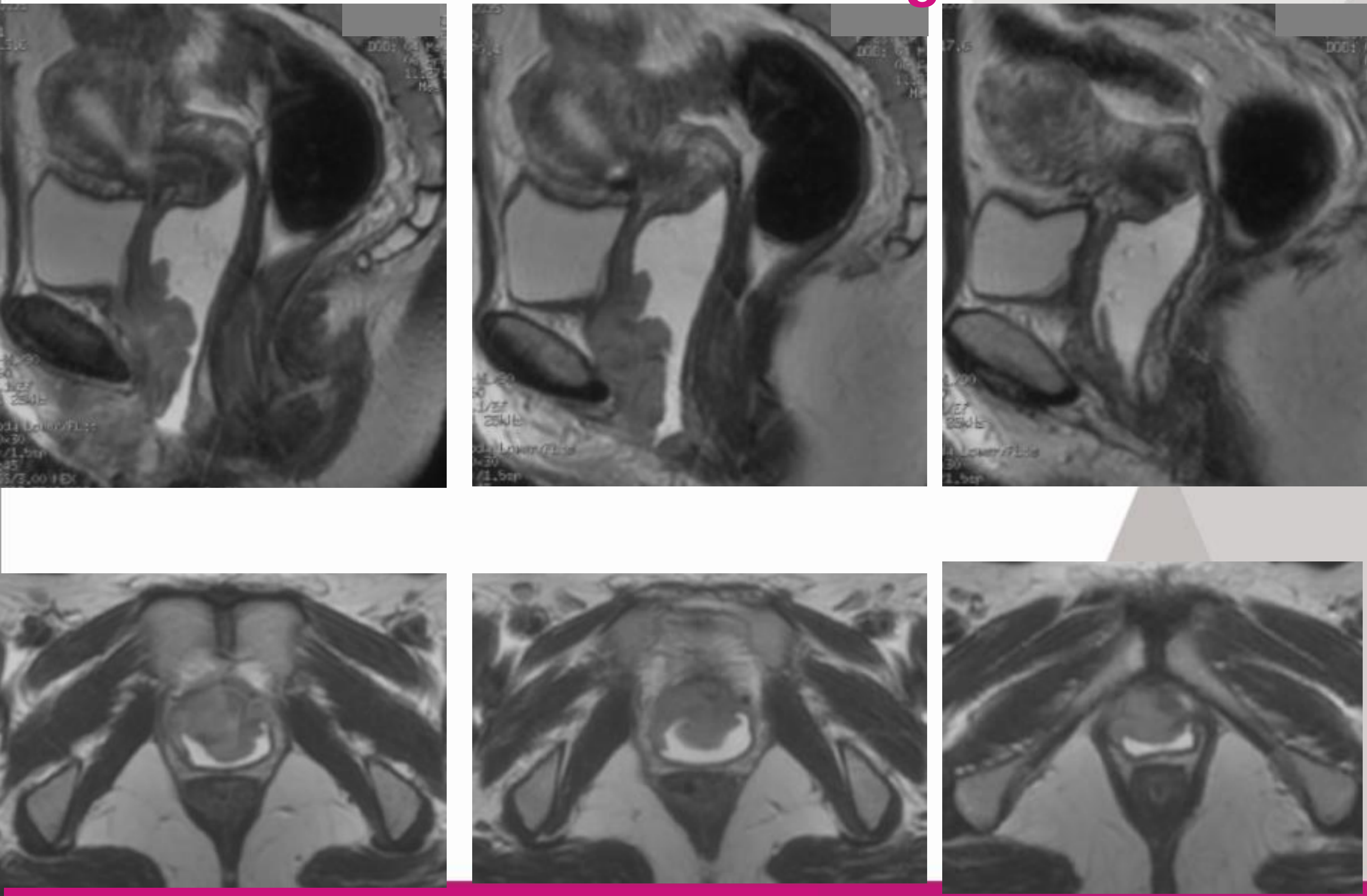
Width: 3.5 cm

Thickness: 2 cm

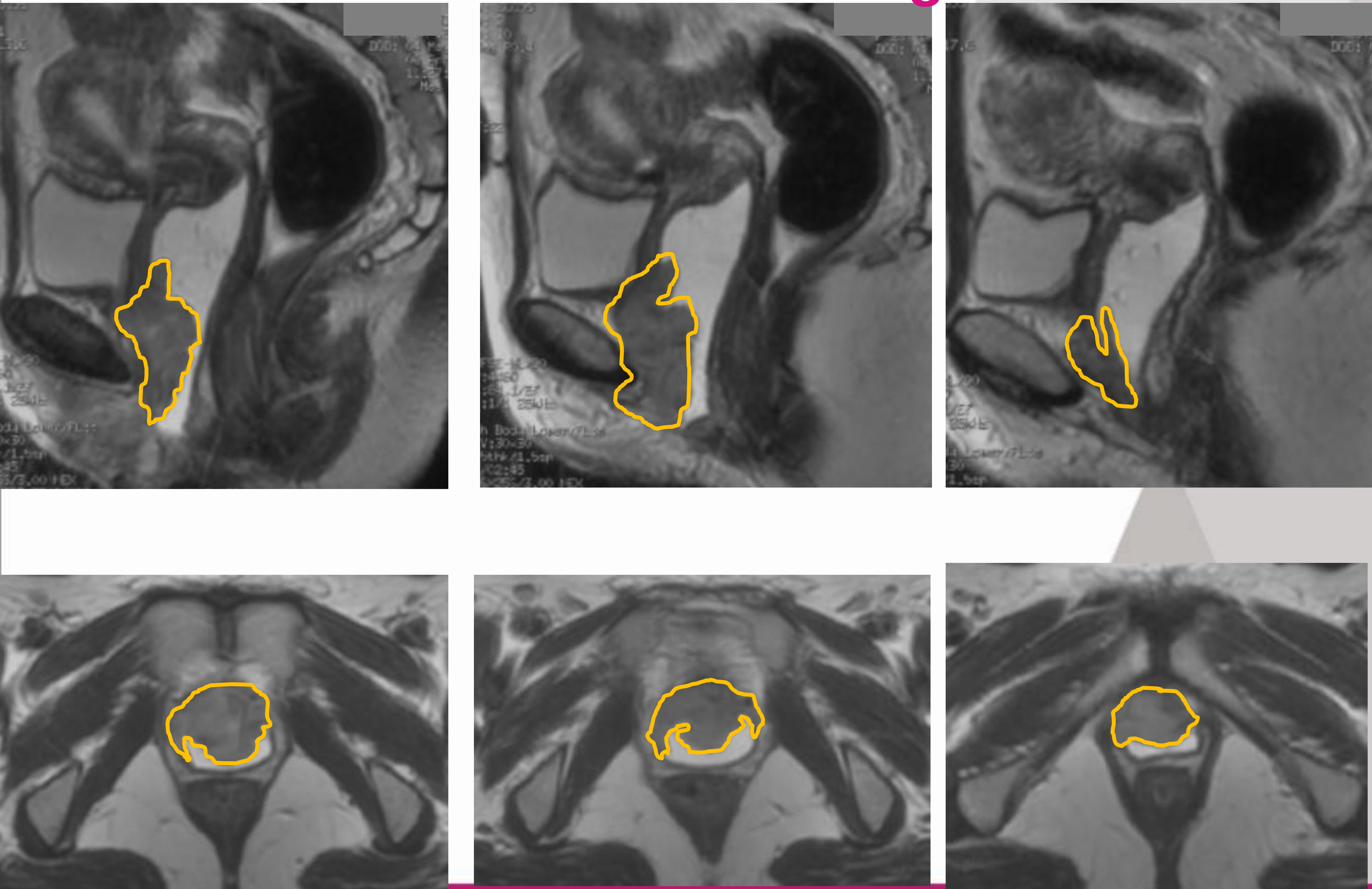
Height: 5.5 cm



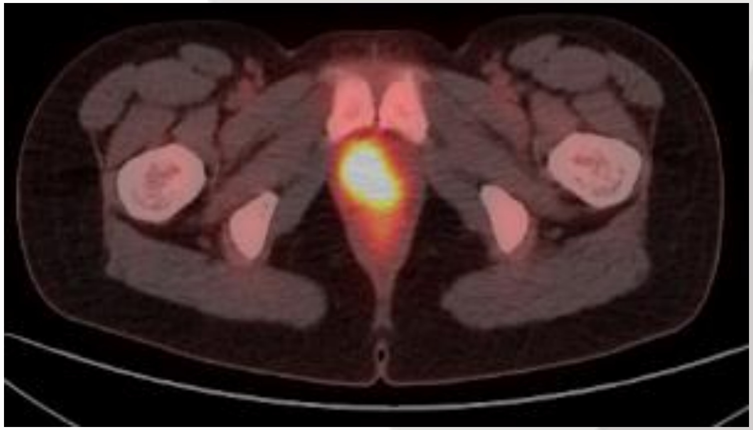
Initial MRI findings

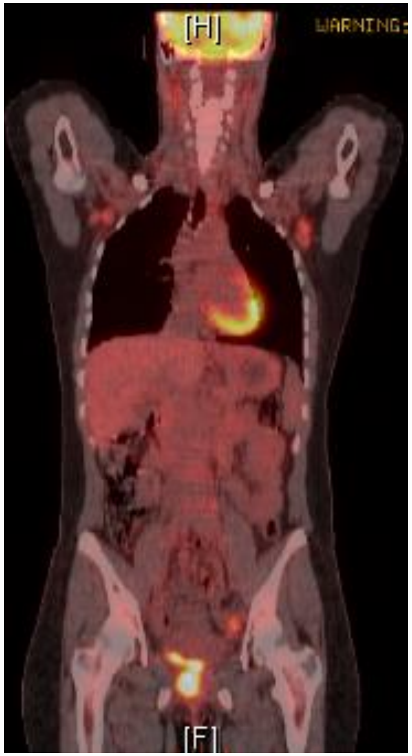


Initial MRI findings

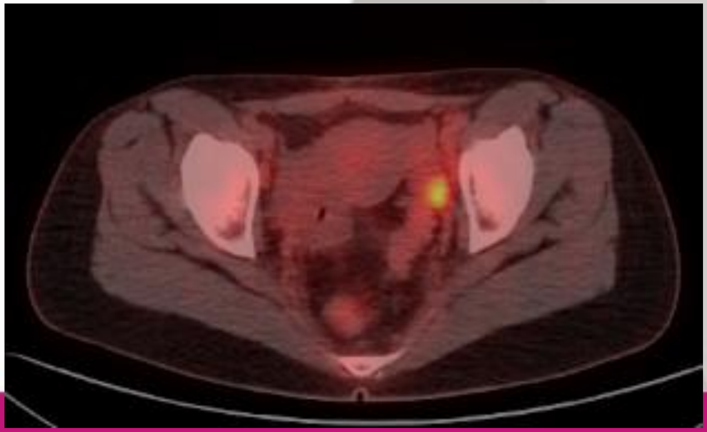


Vaginal cancer : PET-CT



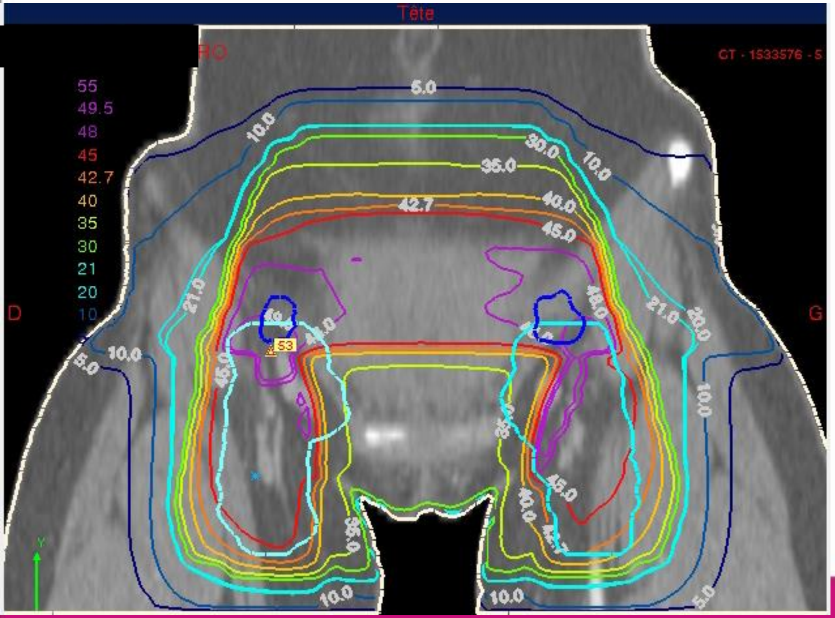


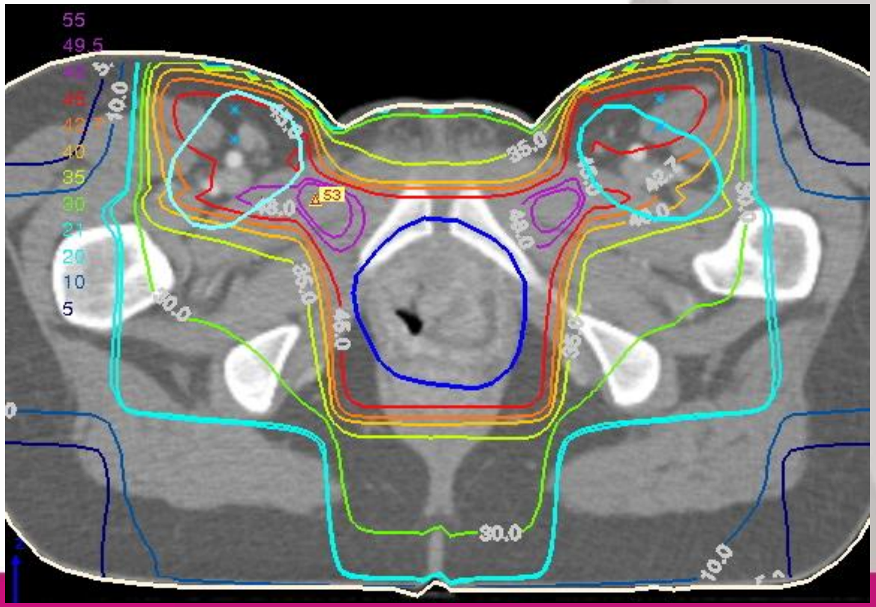
- tumour 53 mm height SUV 11.8
- internal left iliac node SUV 4.1



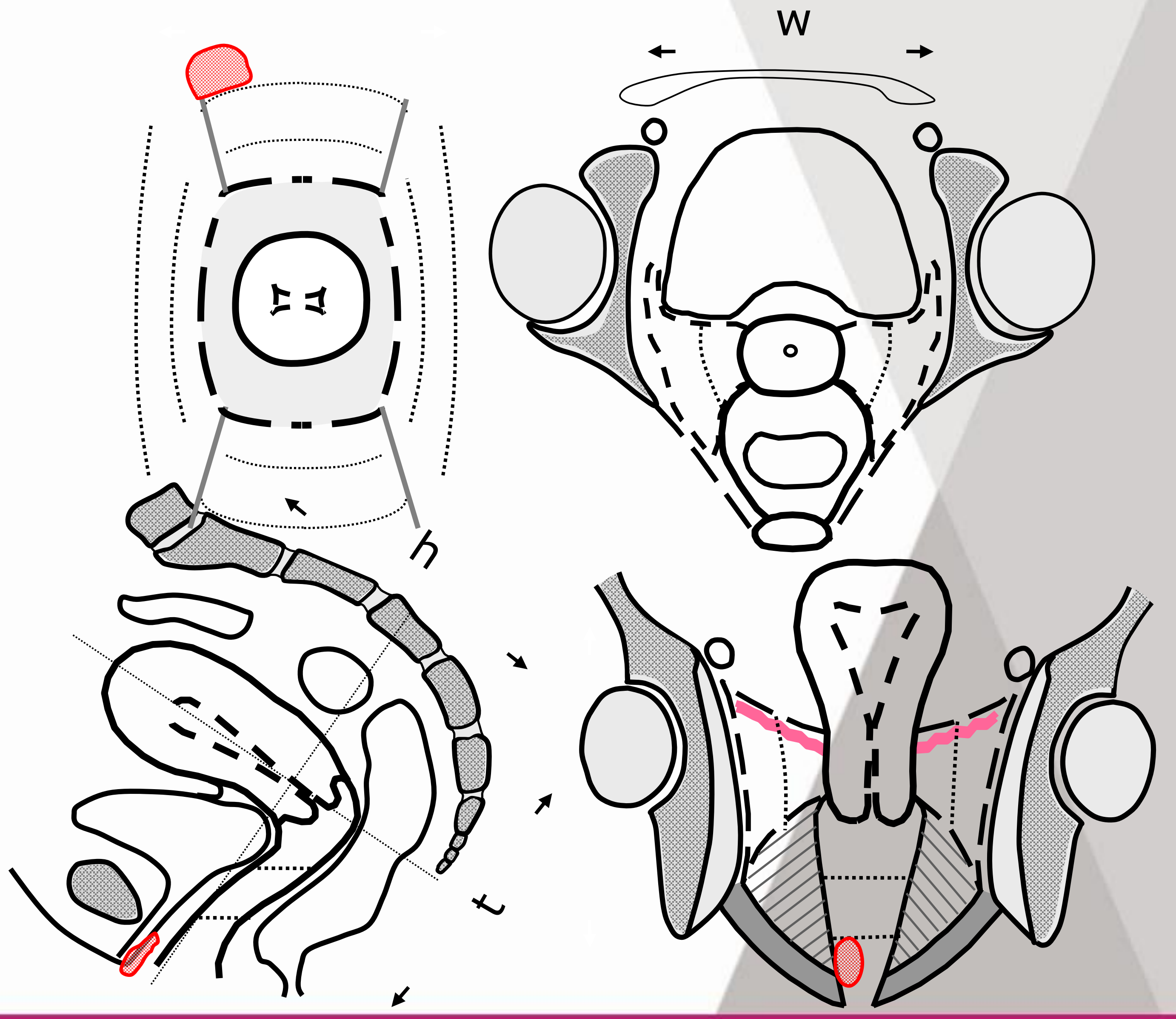
Vaginal cancer: treatment

- concomitant chemoradiation 45 Gy
- cisplatinum 40 mg/m2
- pelvis + inguinal nodes
- boost to the left iliac node : 60 Gy





Clinical findings at time of BT



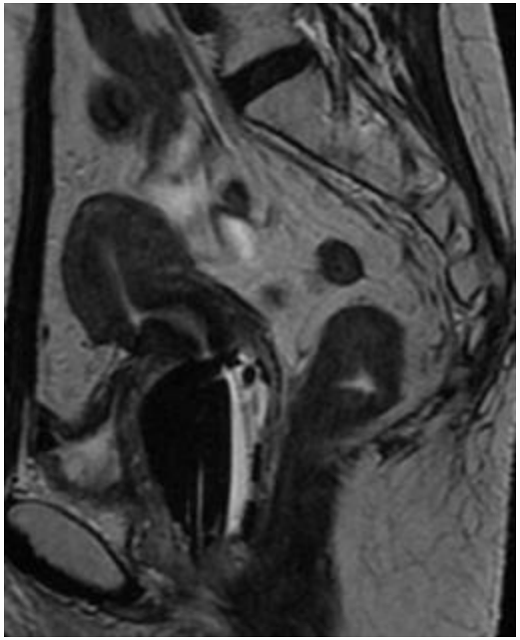
Dimensions (cm):

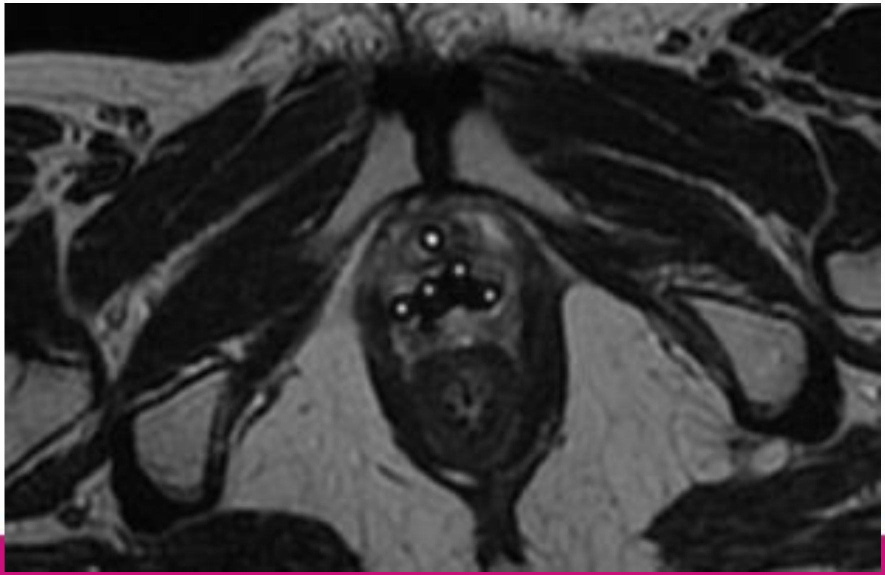
Width: 1 cm

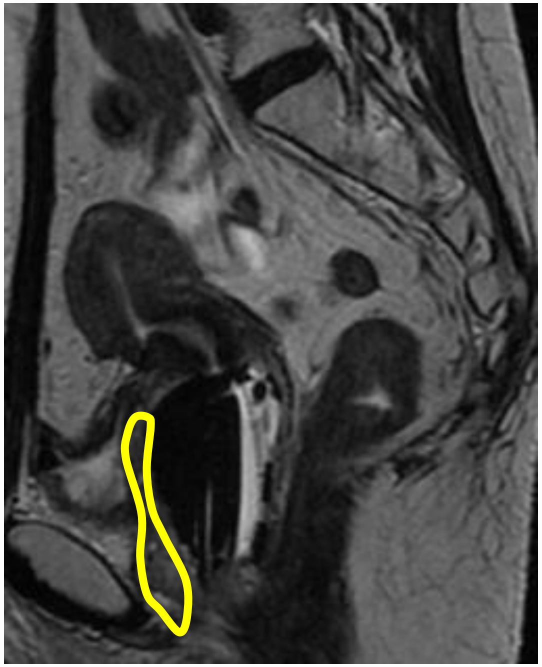
Thickness: 0.2 cm

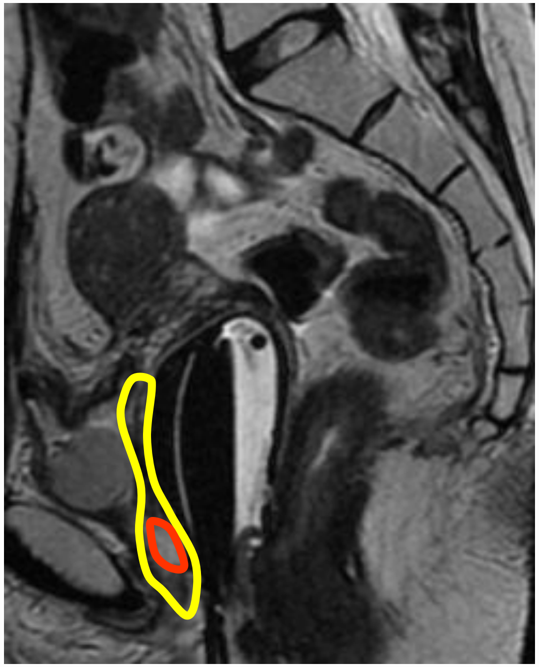
Height: 1 cm

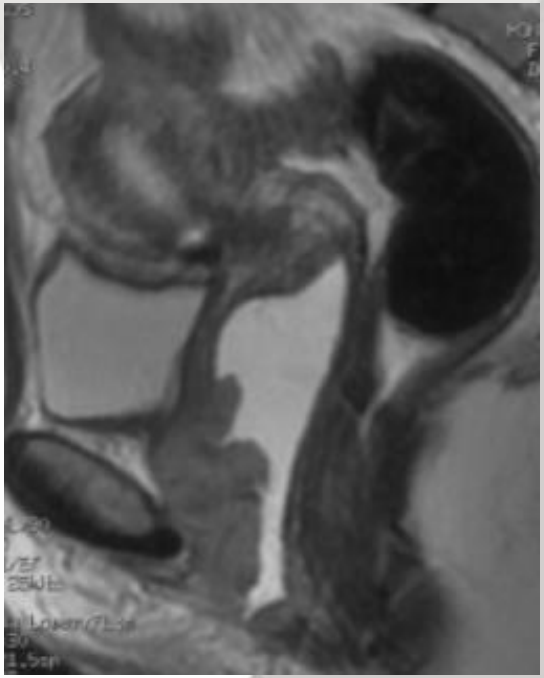
MRI at time of BT

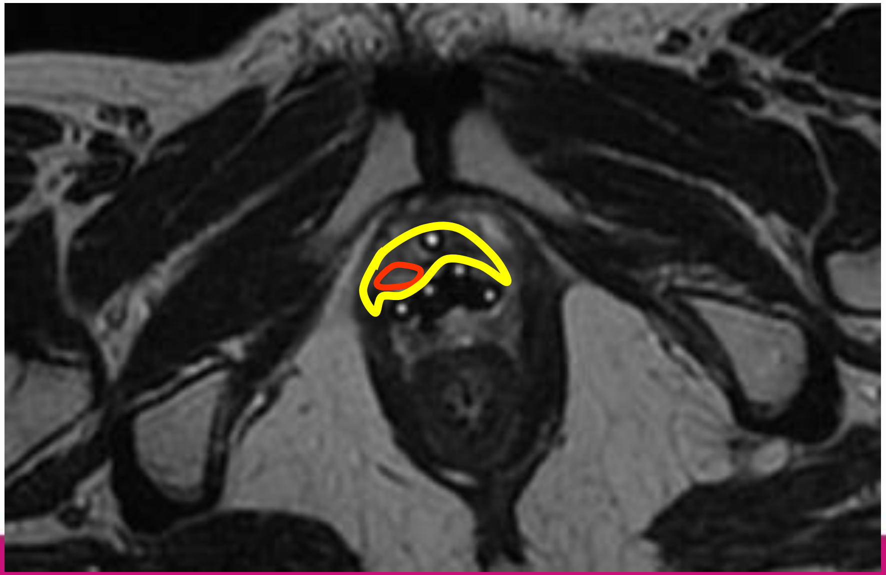


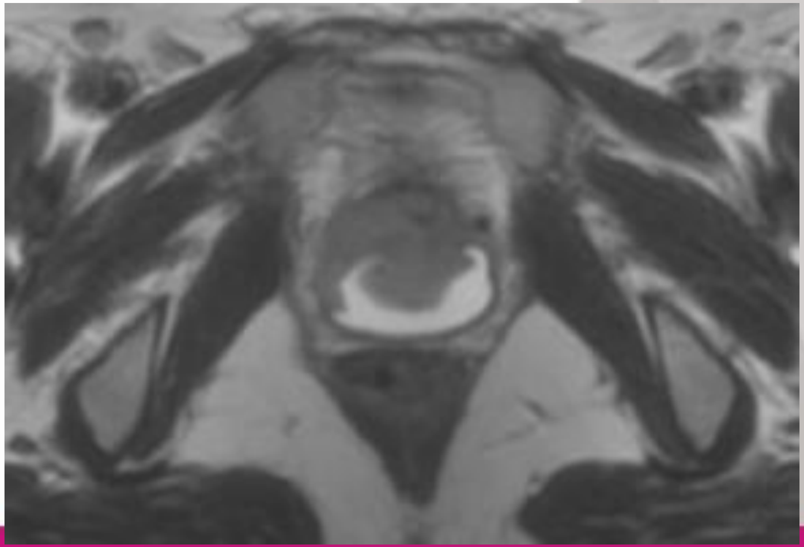






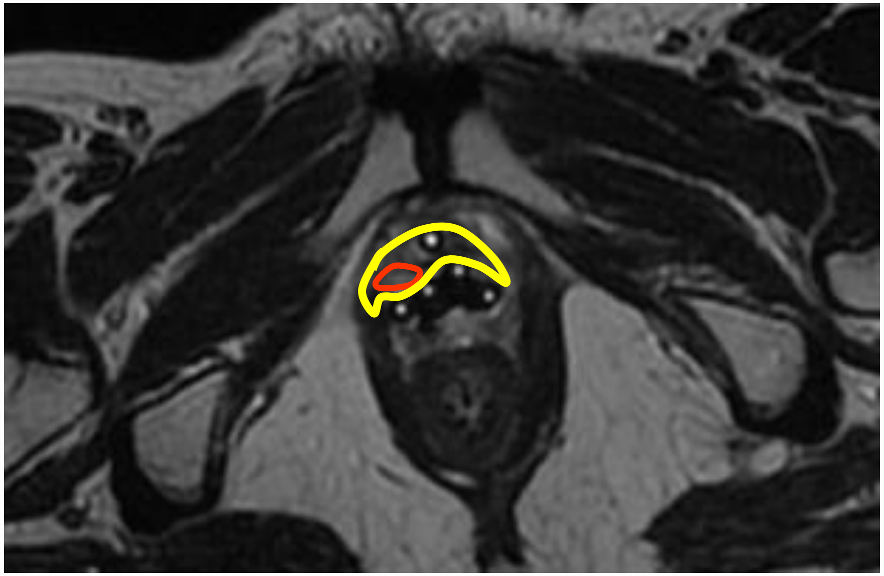


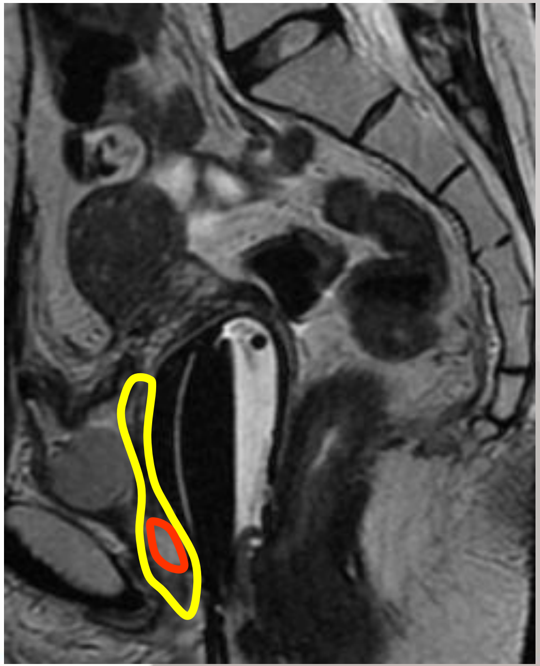


Vaginal cancer: brachytherapy

Planning aim :

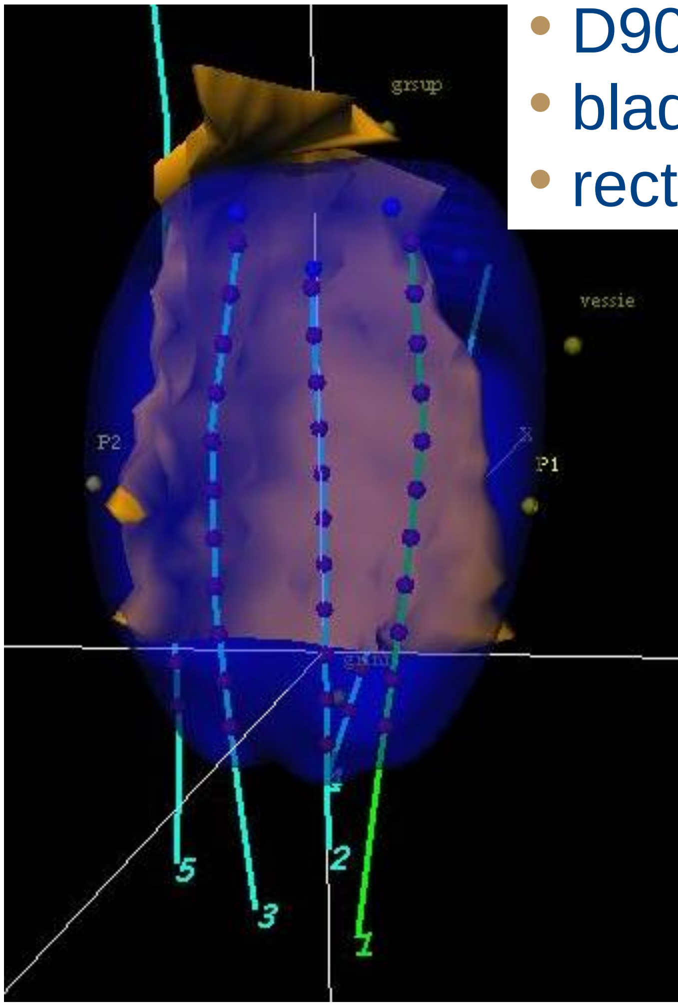
- 80 Gy+ to the HR-CTV
- 60 Gy+ to the IR-CTV
- 4 catheters vaginal mould 5cm length
- Endocavitary PDR BT

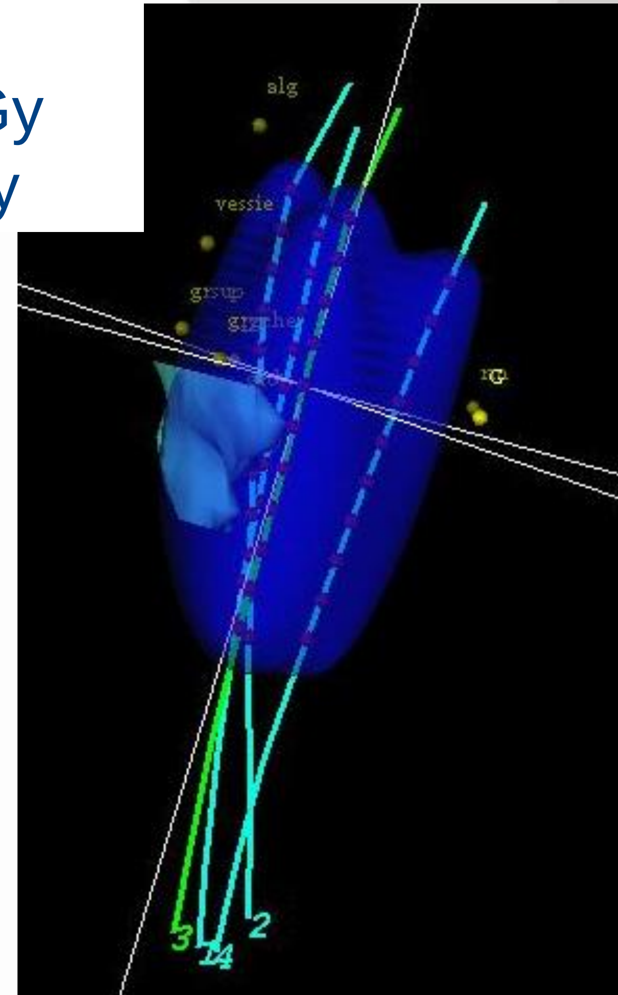




Planning results :

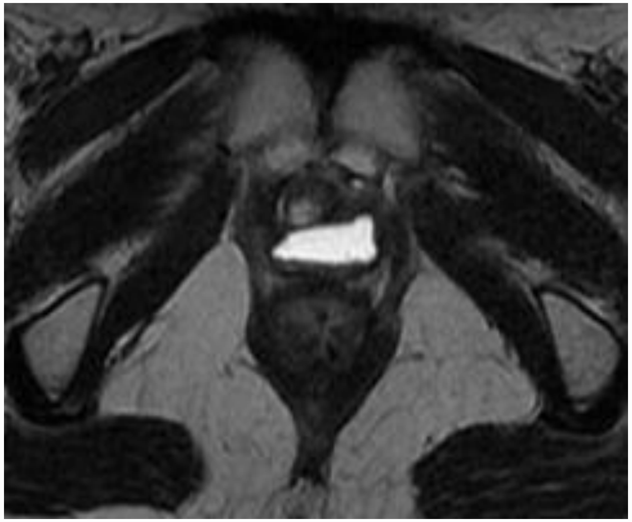
- D90 HR-CTV : 82 Gy
- D90 IR-CTV : 64 Gy
- bladder D2cm^3 : 17 Gy
- rectum D2cm^3 : 15 Gy

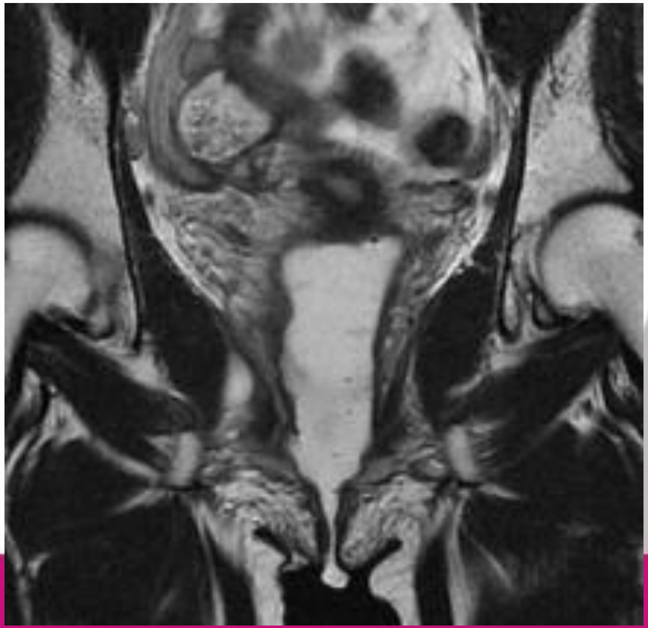




Vaginal cancer: result

MRI @ 2 years





Vaginal cancer: example n° 2

- 54 year-old patient
- Previous hysterectomy for microinvasive cervical tumor
- Vaginal bleeding
- Biopsy : moderately differentiated squamous cell ca.

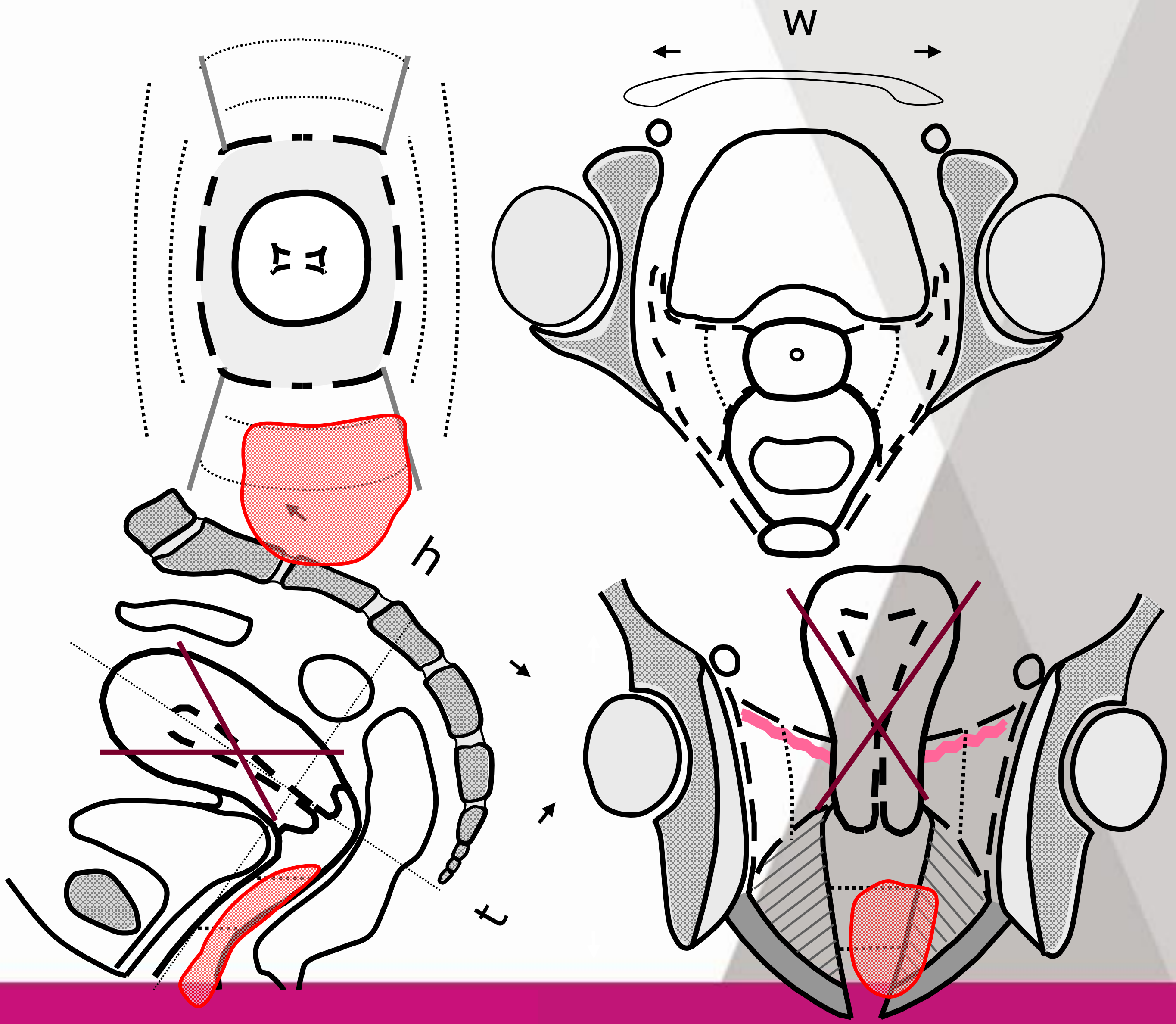
Initial clinical findings

Dimensions (cm):

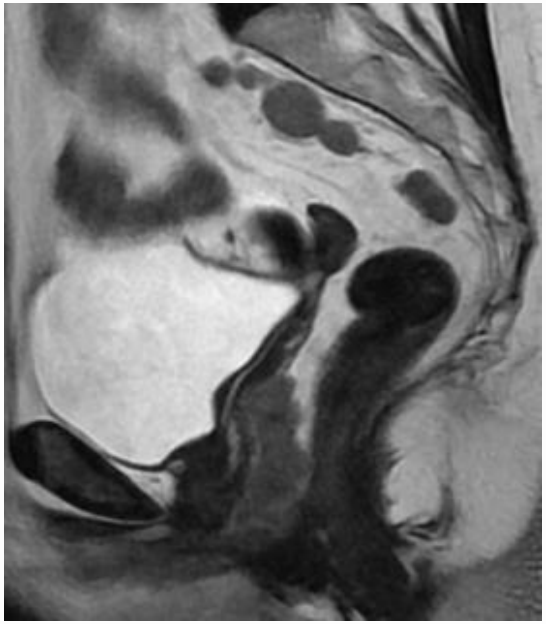
Width: 4 cm

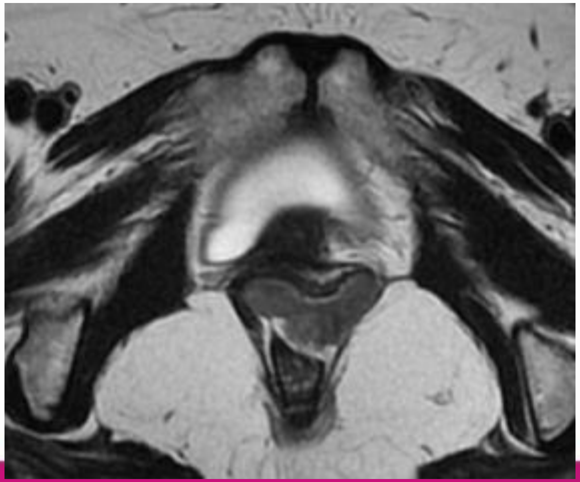
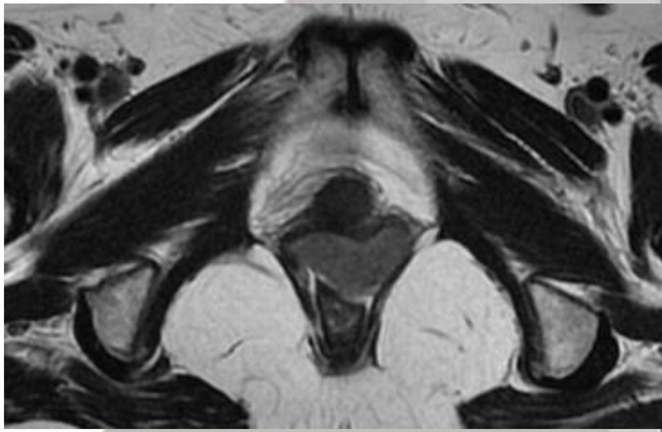
Thickness: 2 cm

Height: 5.5 cm

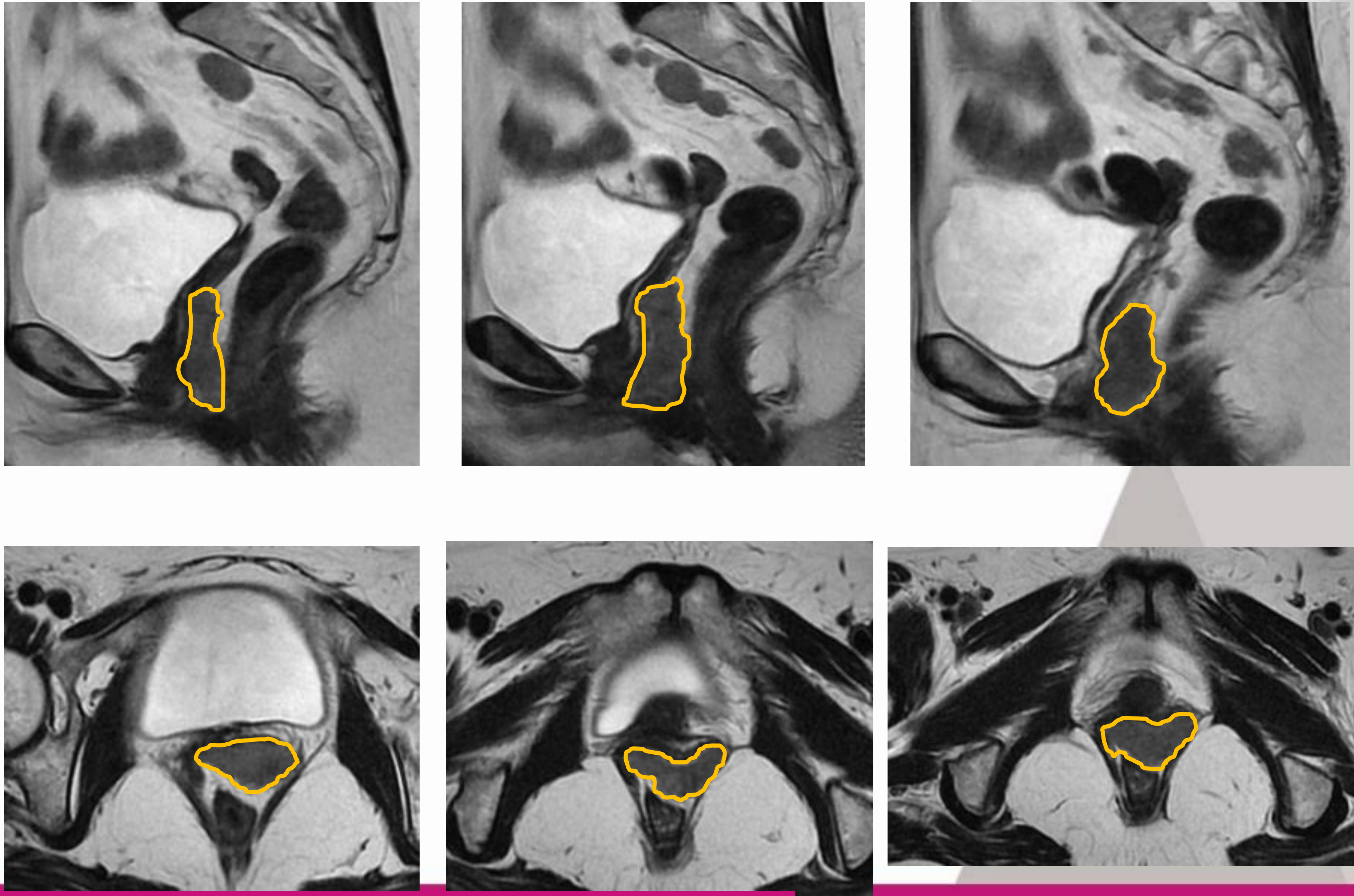


Initial MRI findings

Initial MRI findings

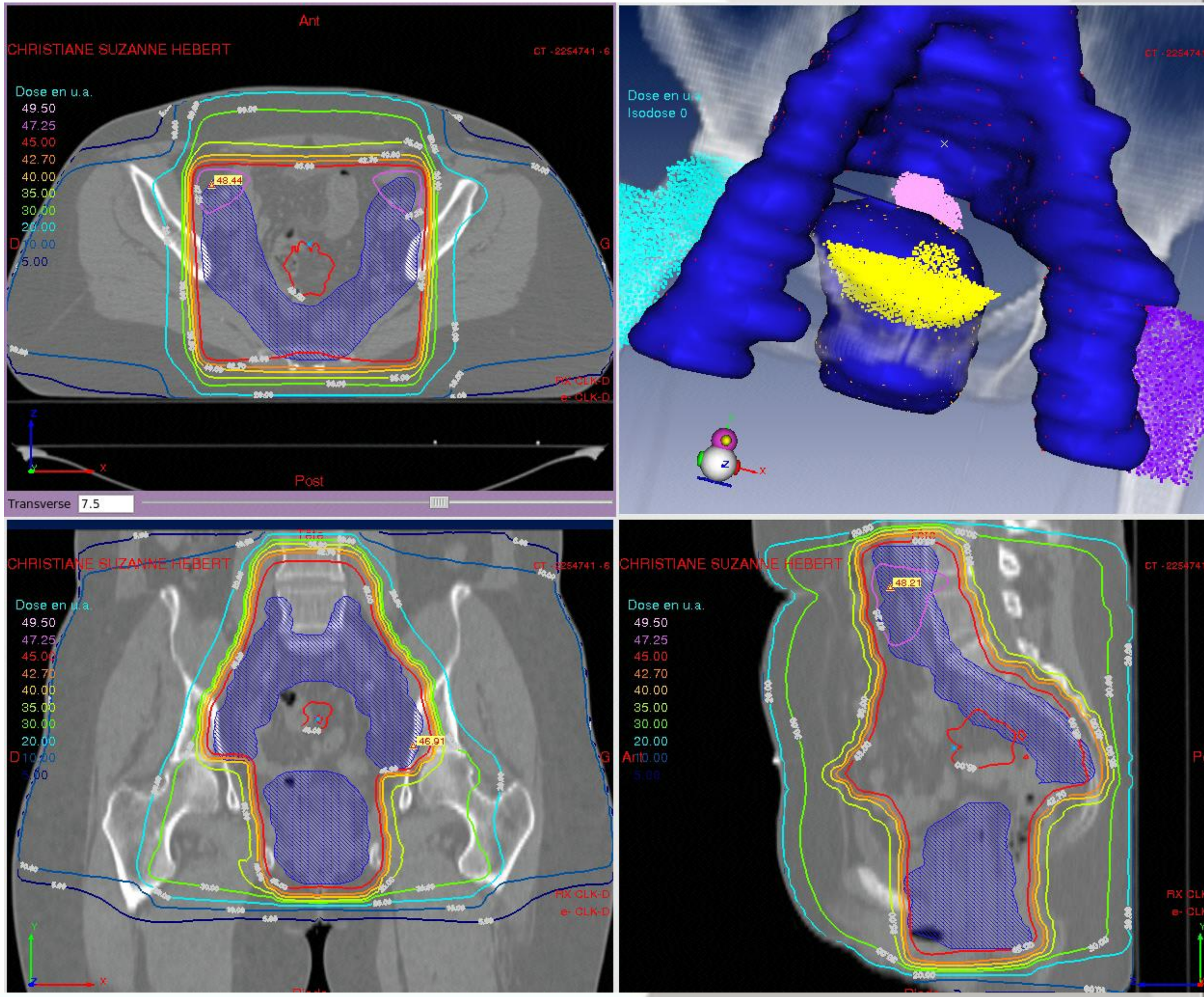


Vaginal cancer : PET-CT

- tumour 55 mm height SUV 10.5
- no inguinal nor pelvic nodes

Vaginal cancer: treatment

- concomitant chemoradiation 45 Gy
- cisplatinum 40 mg/m^2
- pelvis + inguinal nodes
- 1.8Gy/fraction



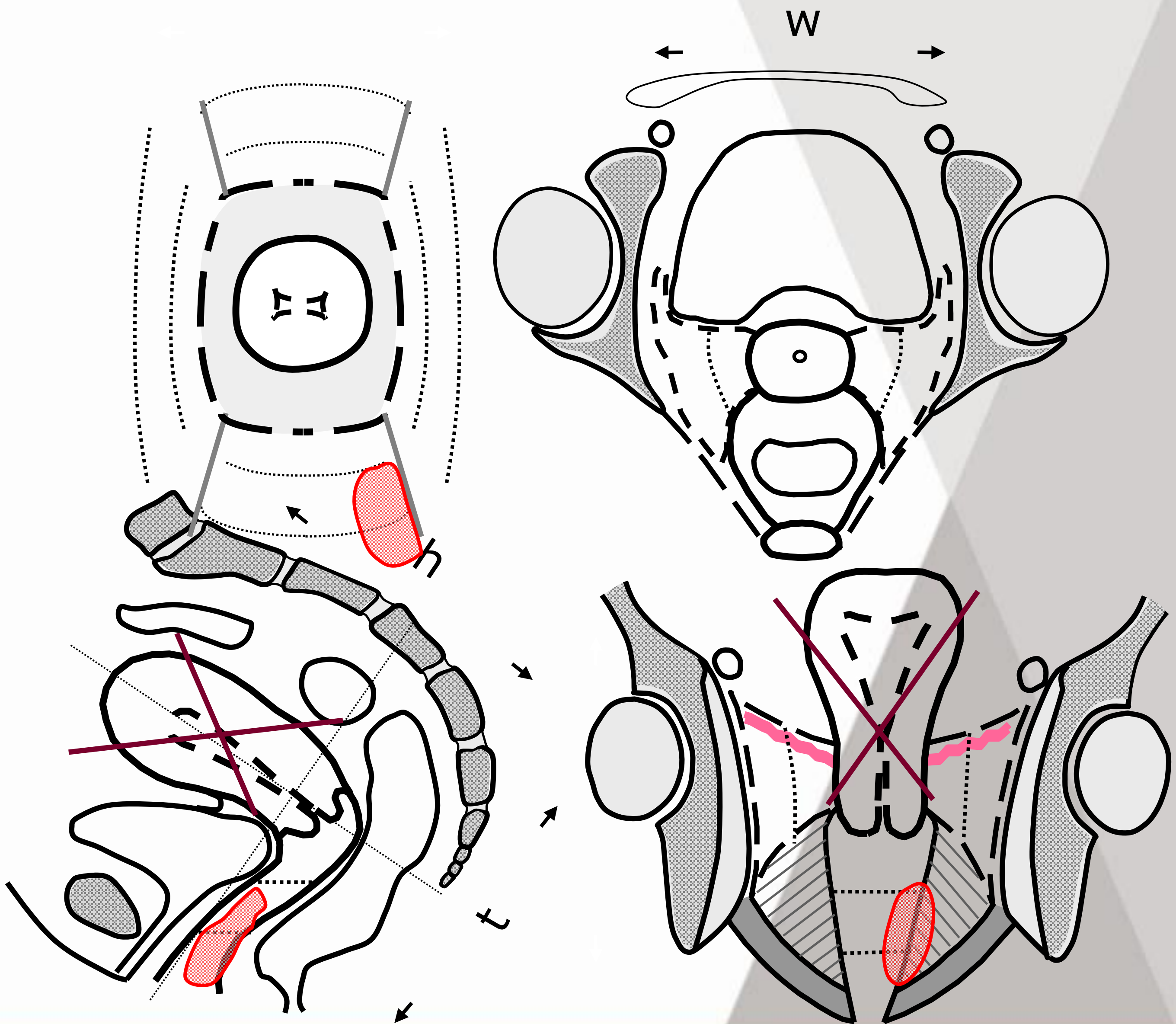
Clinical findings at time of BT

Dimensions (cm):

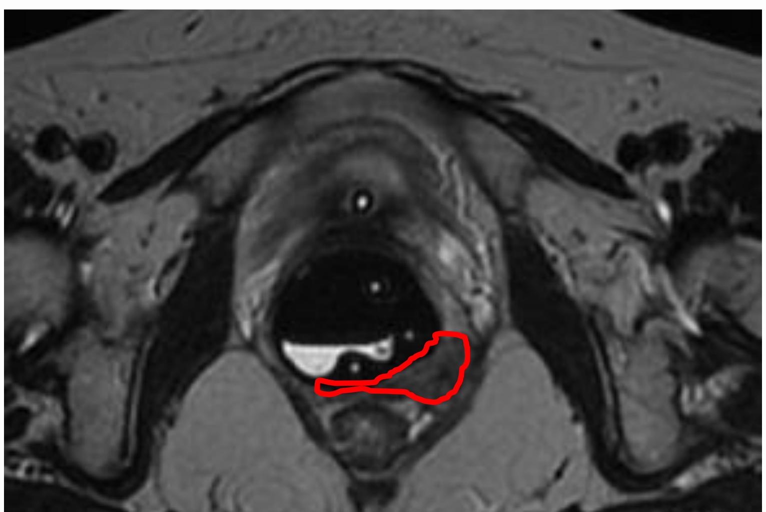
Width: 1 cm

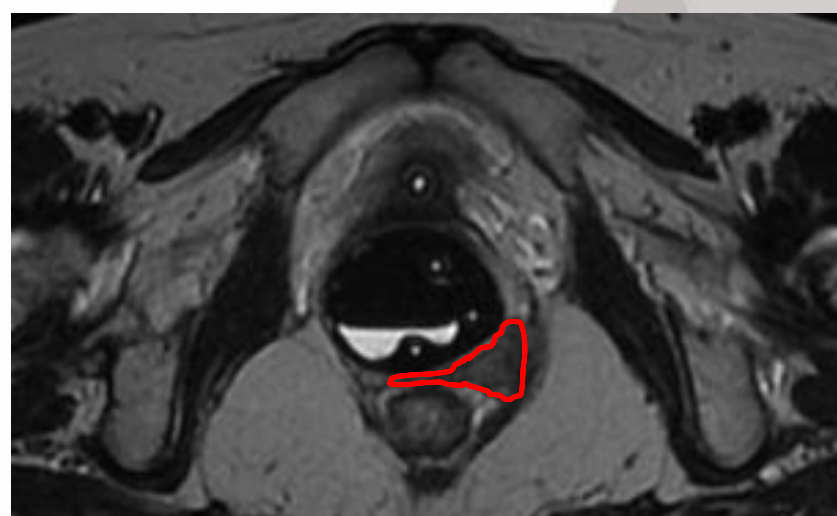
Thickness: 1 cm

Height: 3 cm



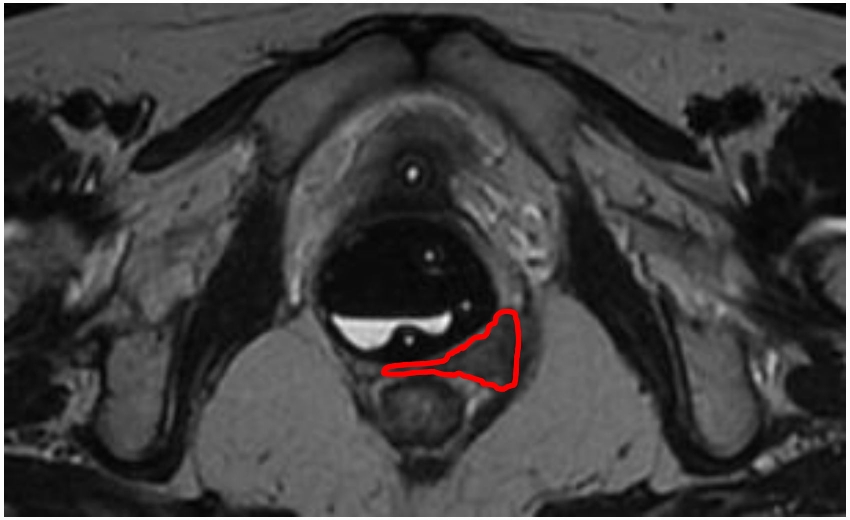
MRI findings at time of BT

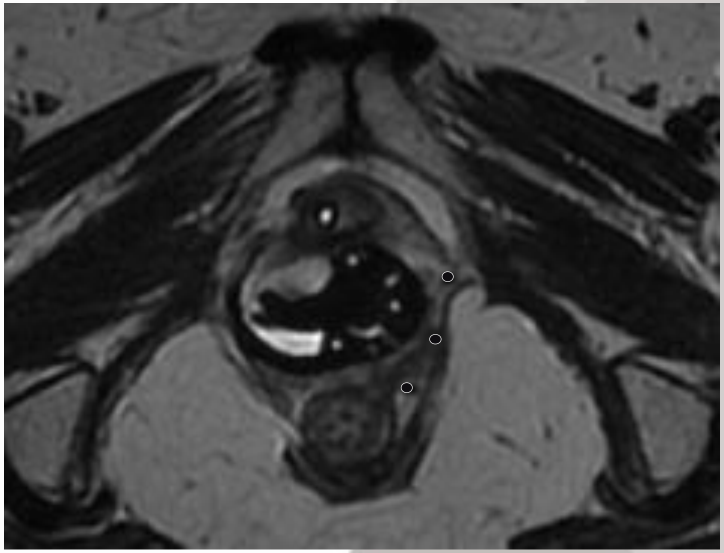




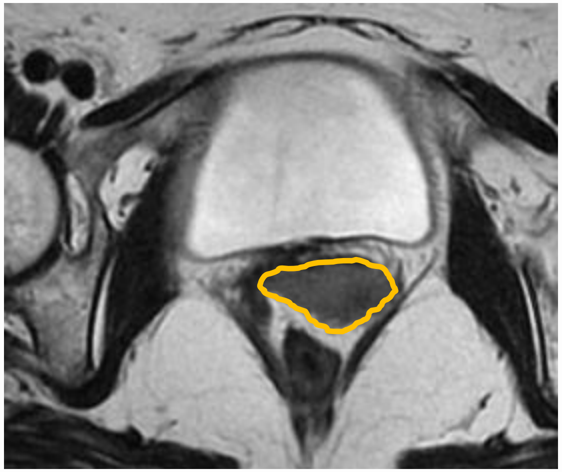
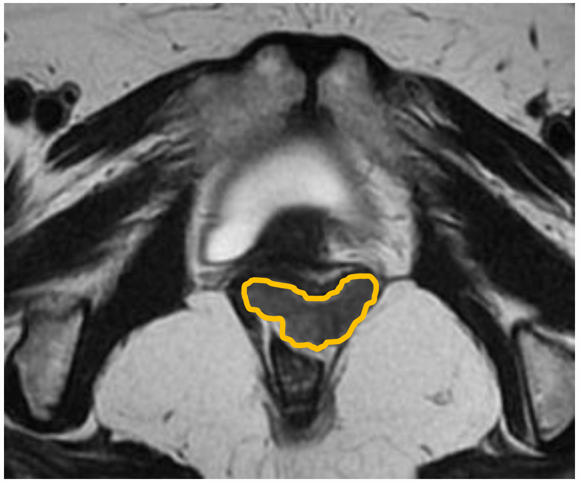
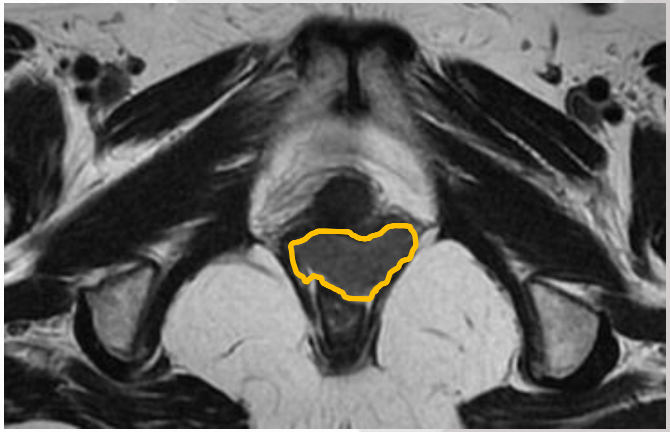
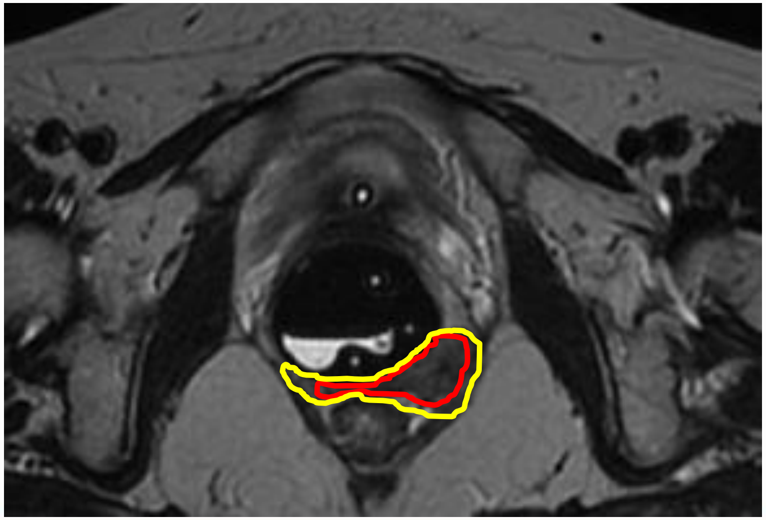
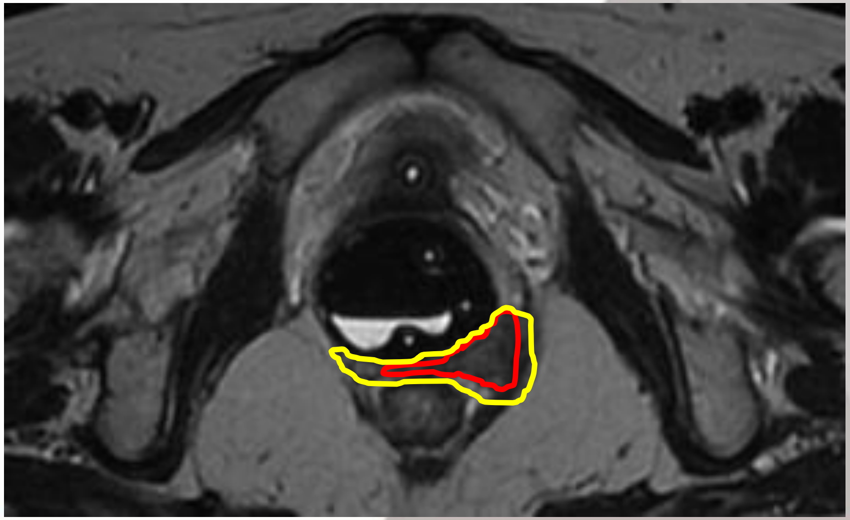
MRI findings at time of BT

Technique : endocavitary + interstitial

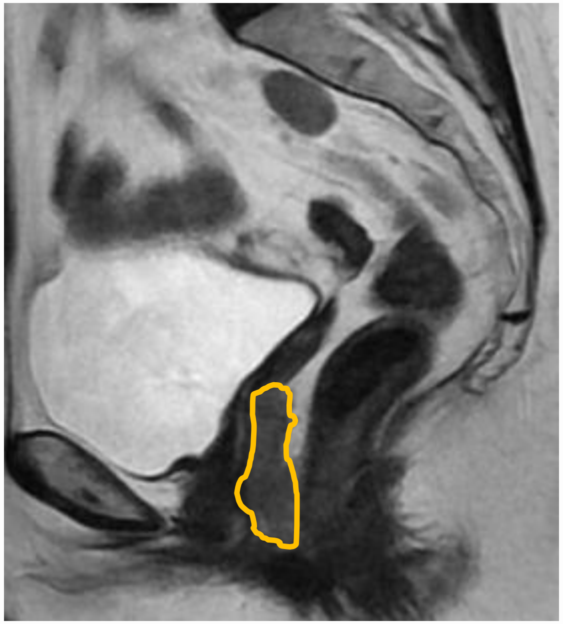


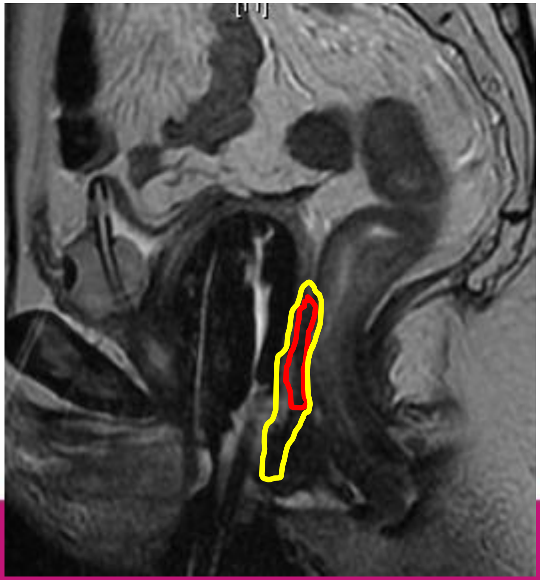


MRI findings at time of BT

MRI findings at time of BT





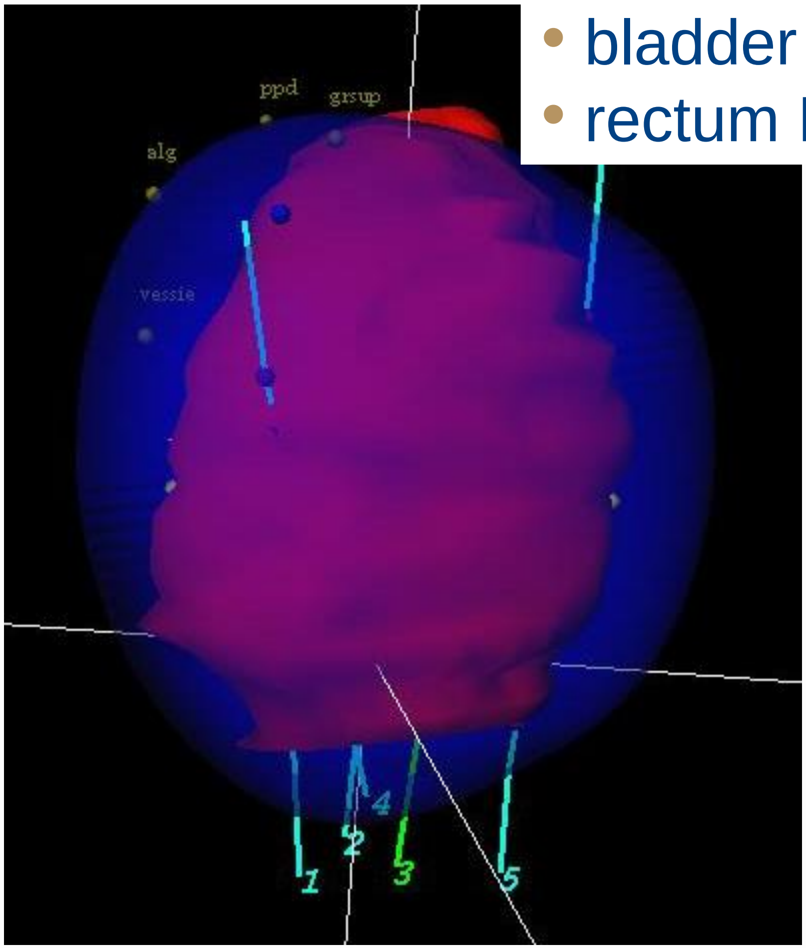
Vaginal cancer: brachytherapy

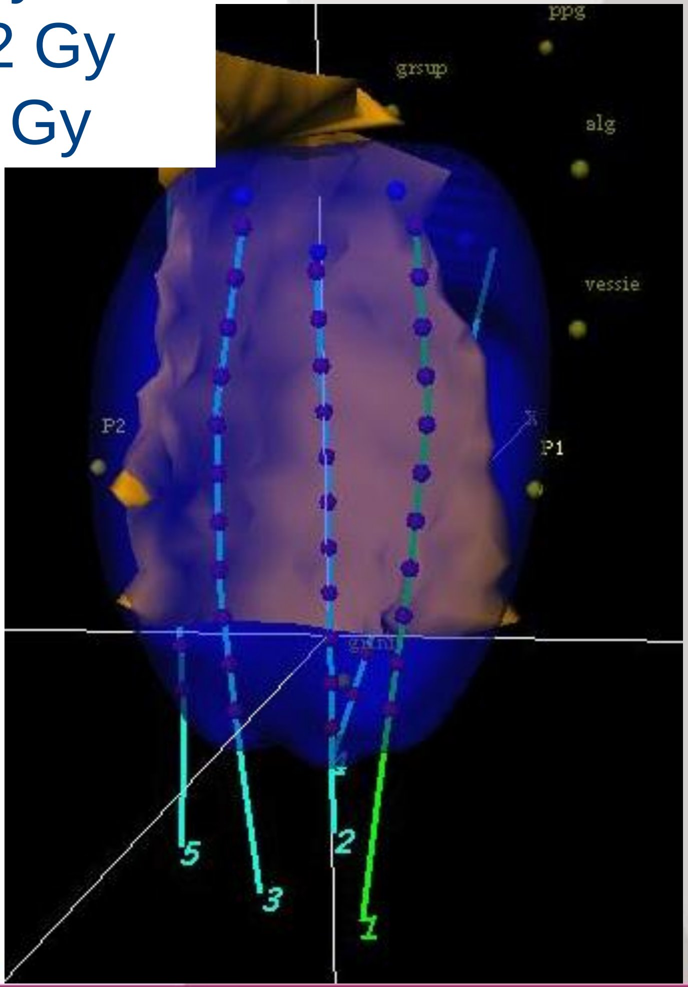
Planning aim :

- 80 Gy+ to the HR-CTV
- 60 Gy+ to the IR-CTV
- 3 catheters vaginal mould 5cm length
- 3 interstitial catheters (2 used) 4.5 cm
- PDR BT

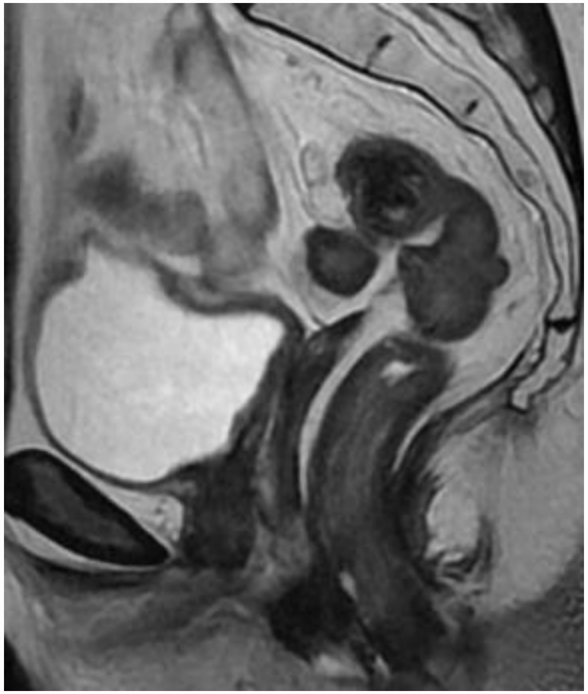
Planning results :

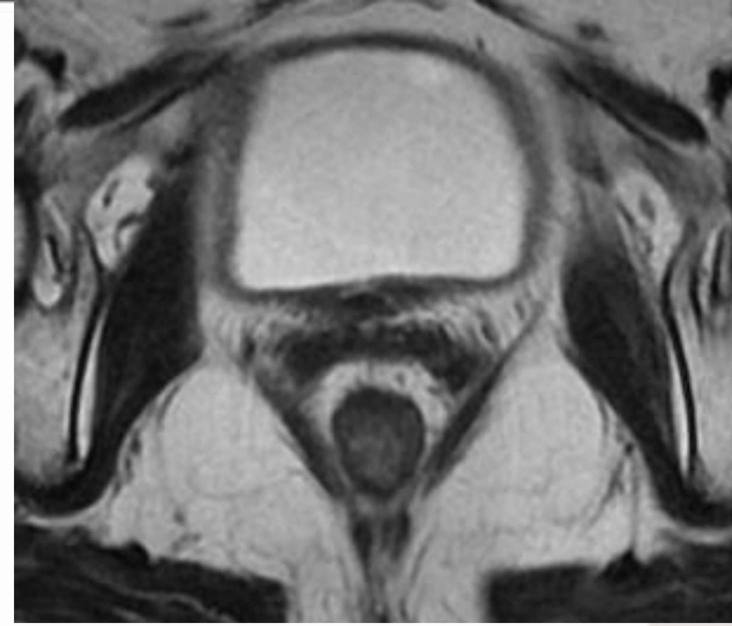
- D90 HR-CTV : 81 Gy
- D90 IR-CTV : 63 Gy
- bladder D2cm^3 : 22 Gy
- rectum D2cm^3 : 27 Gy



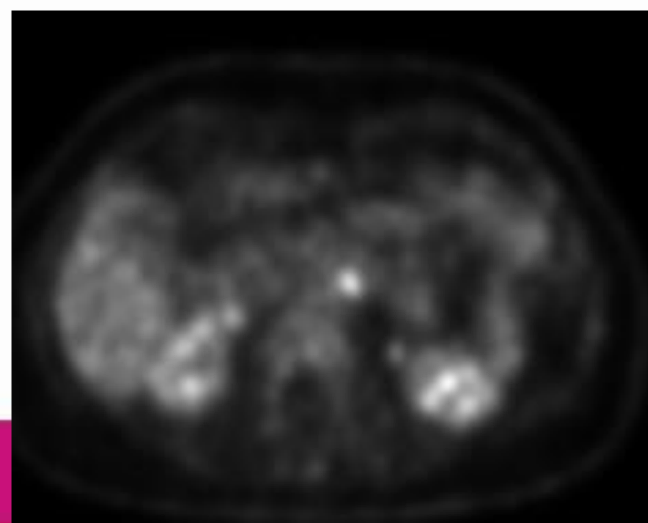


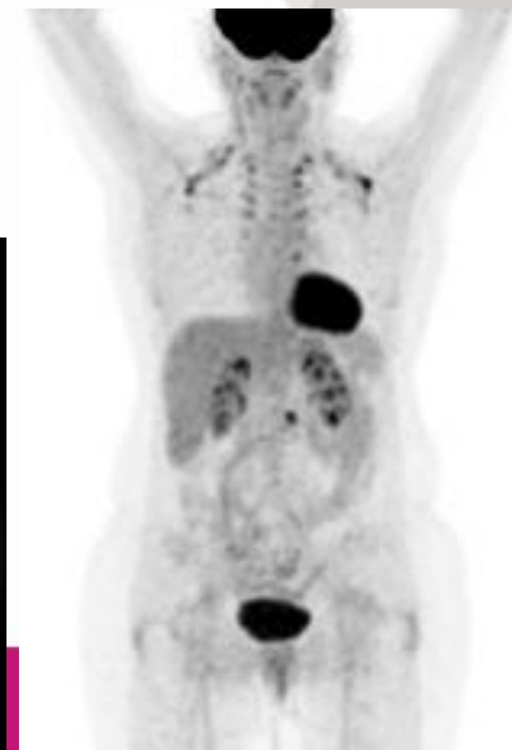
MRI 3 months
post treatment





PET-CT 7 months
post treatment





Paraaortic node L3
Concomitant
chemoradiation

TREATMENT OF LOCALLY ADVANCED VAGINAL CANCER WITH RADIOCHEMOTHERAPY AND MAGNETIC RESONANCE IMAGE-GUIDED ADAPTIVE BRACHYTHERAPY: DOSE–VOLUME PARAMETERS AND FIRST CLINICAL RESULTS

Johannes C. A. Dimopoulos, M.D.,* Maximilian P. Schmid, M.D.,† Elena Fidarova, M.D.,† Daniel Berger, Ph.D.,† Christian Kirisits, D.Sc.,† and Richard Pötter, M.D.†

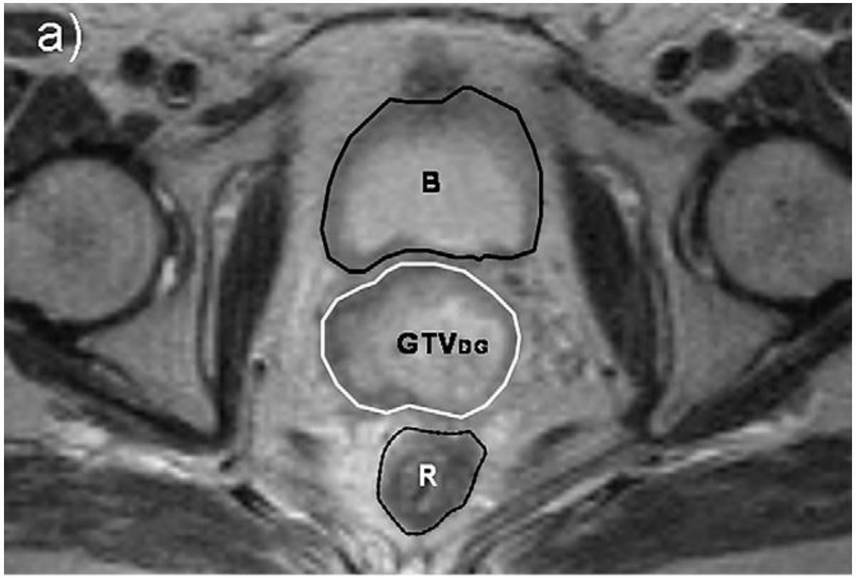
*Department of Radiation Oncology, Metropolitan Hospital, Athens, Greece; and †Department of Radiotherapy, Medical University of Vienna, Vienna, Austria

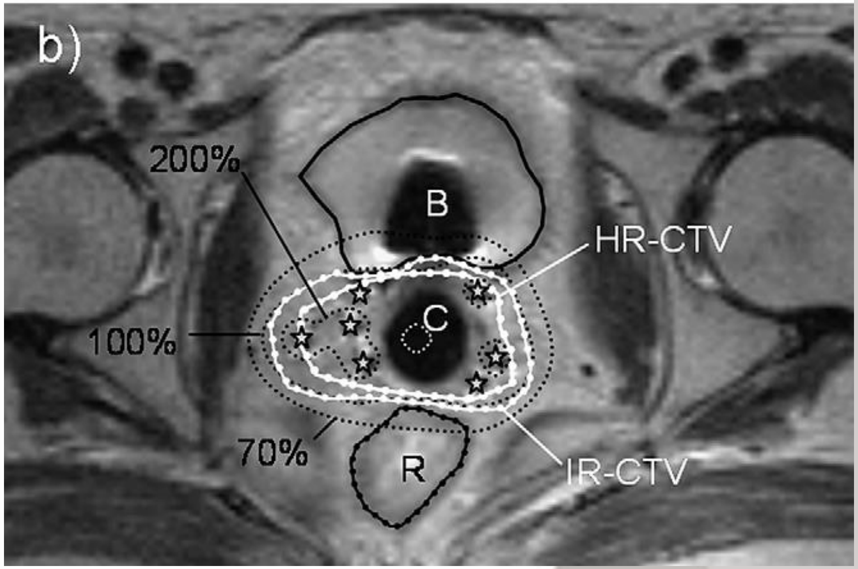
13 patients
1 endocavitary, 12 interstitial + endocavitary

- Mean GTV at diagnosis = 45 (+/-30) cm3
- Mean GTV at brachy = 10 (+/-14) cm3
- Mean D90 HR-CTV = 86 (+/-13) Gy
- Mean D2cm^3 bladder = 80 (+/-20) Gy
- Mean D2cm^3 urethra = 76 (+/-16) Gy
- Mean D2cm^3 rectum = 70 (+/-9) Gy
- Mean D2cm^3 sigmoid = 60 (+/-9) Gy

IJROBP 2012

Treatment results of primary vaginal cancer with the use of IGABT





Median FU : 43 (19-87) months
1 local recurrence
2 distant metastases

OAR constraints

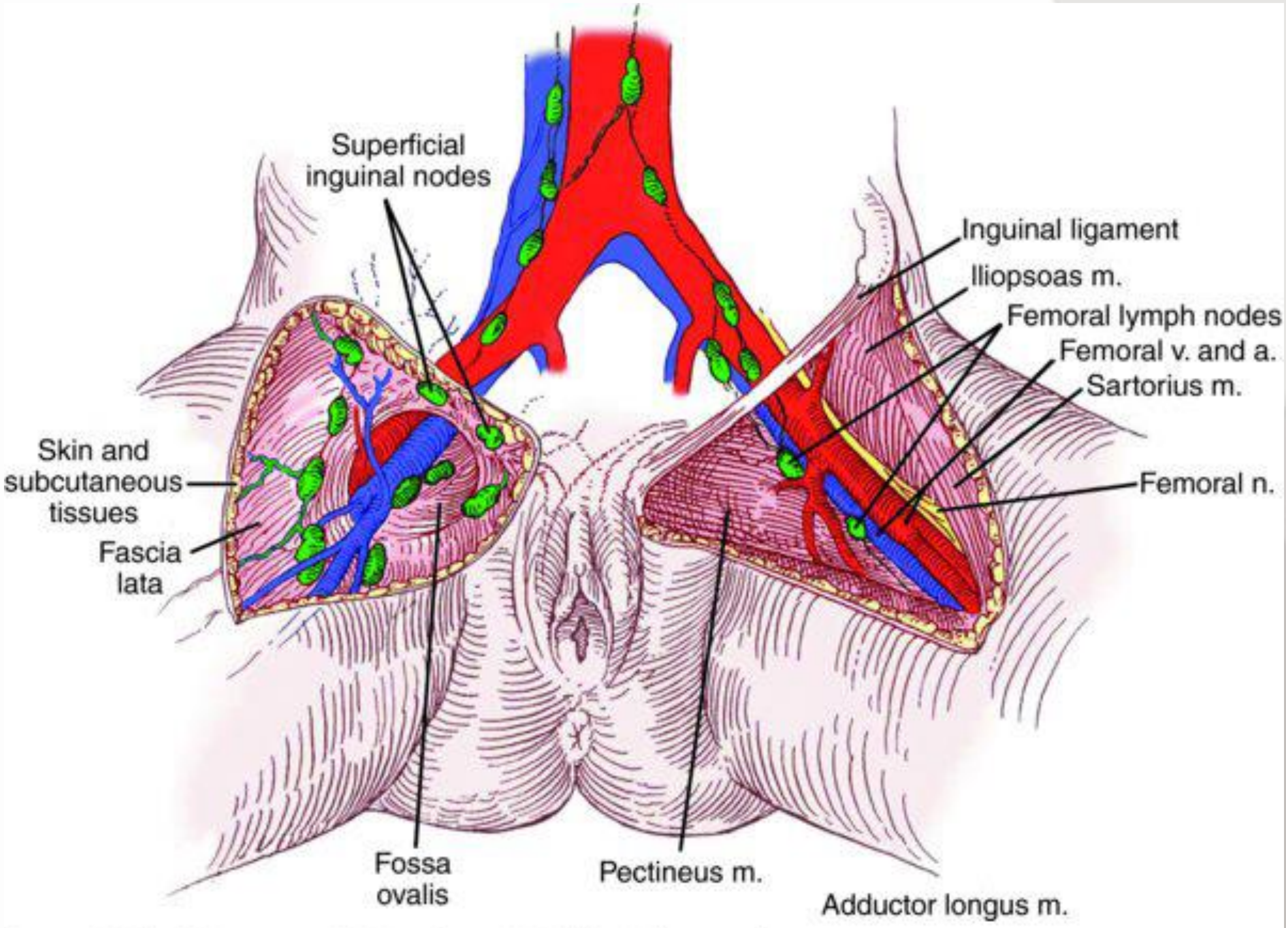
Anal canal : 70 Gy
Urethra : 80-85 Gy
Vagina : ??

Vulvar cancer

- Post-menopausal women
- Squamous cell carcinoma : 90%-95%
- Human papilloma virus not as often reported as in cervical cancer
- Lichen sclerosis

Vulvar cancer: natural history and pattern of spread

Vulvar cancer: lymph node



Source: DeVita VT, Lawrence TS, Rosenberg SA: *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 9th Edition:* www.lwwoncology.com

Vulvar cancer: FIGO classification 2009

Takes nodal status into account

- **Stage 0** : in situ tumour without nodal metastasis
- **Stage IA** : tumour ⩽ 2cm confined to the vulva or perineum and with stromal invasion ⩽ 1mm, no nodal metastasis
- **Stage IB** : tumour > 2cm or with stromal invasion > 1mm, confined to the vulva or perineum, with negative nodes
- **Stage II** : tumour of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes

Vulvar cancer: FIGO classification 2009

- **Stage III** : tumour of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes

  - **IIIA** : with 1 lymph node metastasis (≥ 5mm), or 1-2 lymph node metastasis(es) (< 5mm)

  - **IIIB** : with 2 or more lymph node metastases (≥ 5mm), or 3 or more lymph node metastases (< 5mm)

  - **IIIC** : with positive nodes with extracapsular spread

Vulvar cancer: FIGO classification 2009

- **Stage IV** : tumour invades other regional
  (2/3 upper urethra, 2/3 upper vagina),
  or distant structures

  - **IVA** : tumour invades any of the following :

    - upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or

    - fixed or ulcerated inguino-femoral lymph nodes

  - **IVB** : any distant metastasis including pelvic lymph nodes

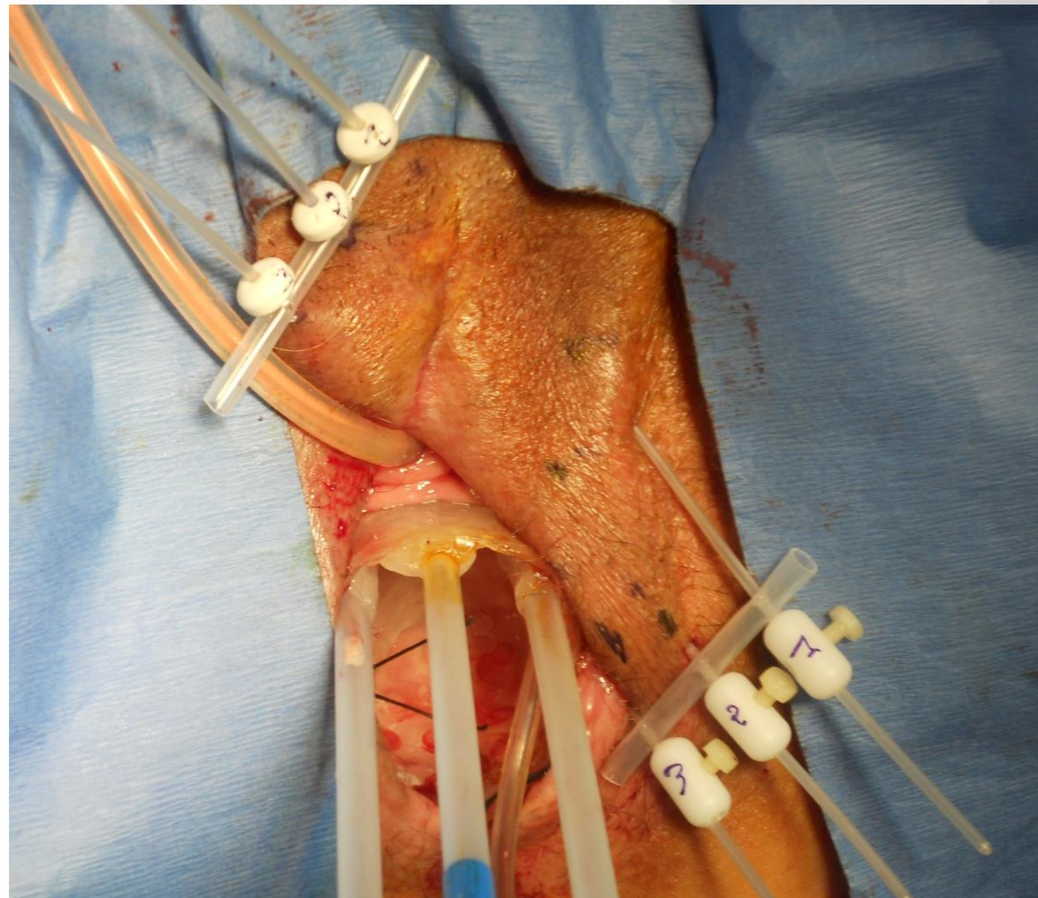
Vulvar cancer: treatment modalities

- Standard treatment = surgery
- ERT, BT or chemotherapy :
  - adjuvant treatment options
  - or exclusive treatment options in advanced disease

Vulvar cancer: surgery

- Standard surgery used to be :
  - Radical vulvectomy with “en bloc” bilateral inguinofemoral and pelvic lymphadenectomy
- Alternative nowadays :
  - wide excision if free microscopic margins of at least 8mm and preferably 20mm can be achieved
  - Sentinel node procedure

Vulvar cancer: irradiation

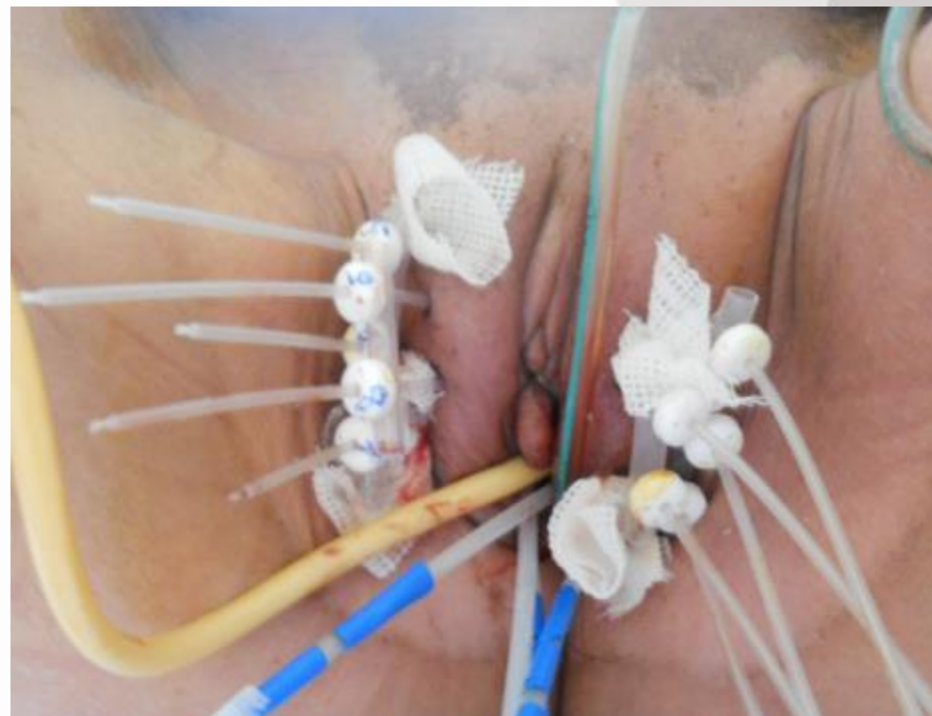


Vulvar cancer: exclusive radiation treatment

Indications

- Contra-indication to surgery or advanced tumours
- Total dose of 45 Gy to the pelvis ERT
- Interstitial BT total dose of 60 Gy-85 Gy
- Concurrent chemoradiation (cisplatinum or carboplatinum used alone or in combination with fluorouracil) → high response-rate (even in the absence of randomized trials)

Vulvar cancer: BT



Brachytherapy : dose / technique

Typical adjuvant doses : 45 to 50 Gy
Tumour in place : 45 Gy EBRT + boost to the primary tumor to 60-80 Gy

Technique : depends on tumour location:

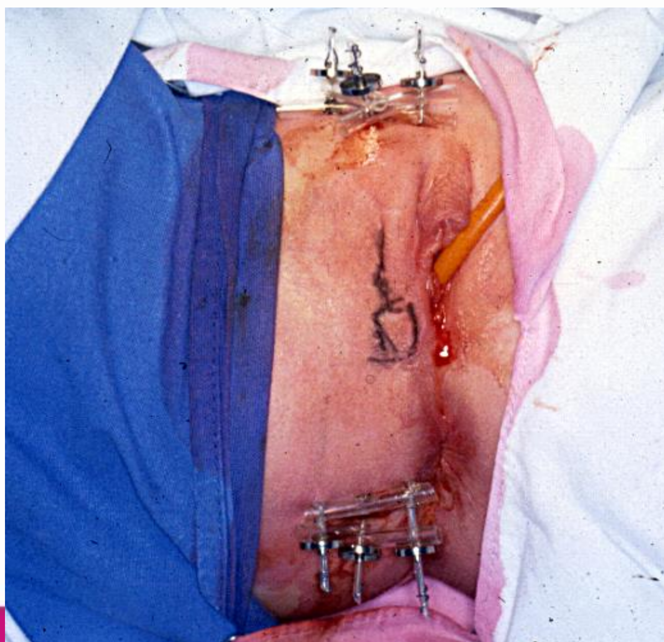
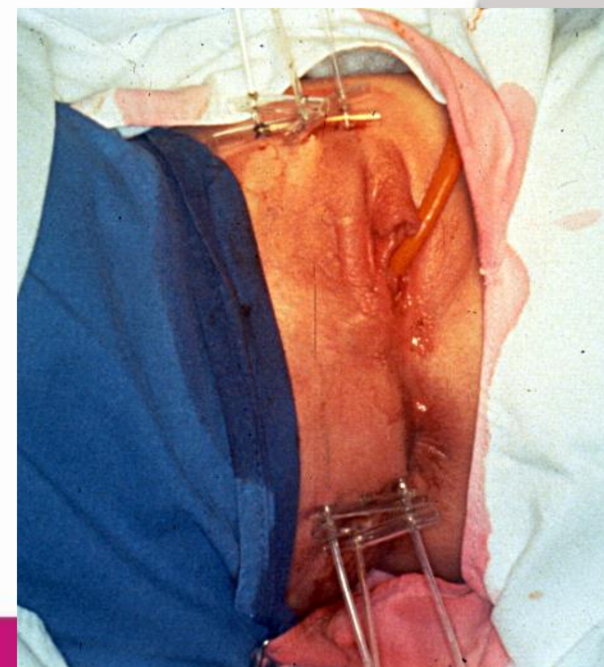
Labial tumour :

Interstitial
Plastic tube parallel to the labial axis, free hand placement

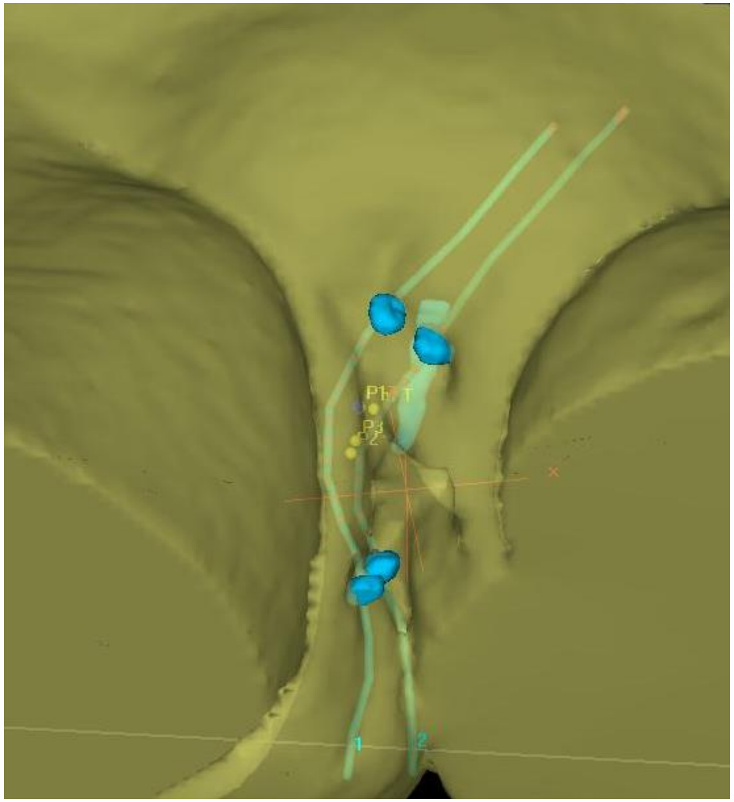
Para-urethral vaginal paravaginal involvement :

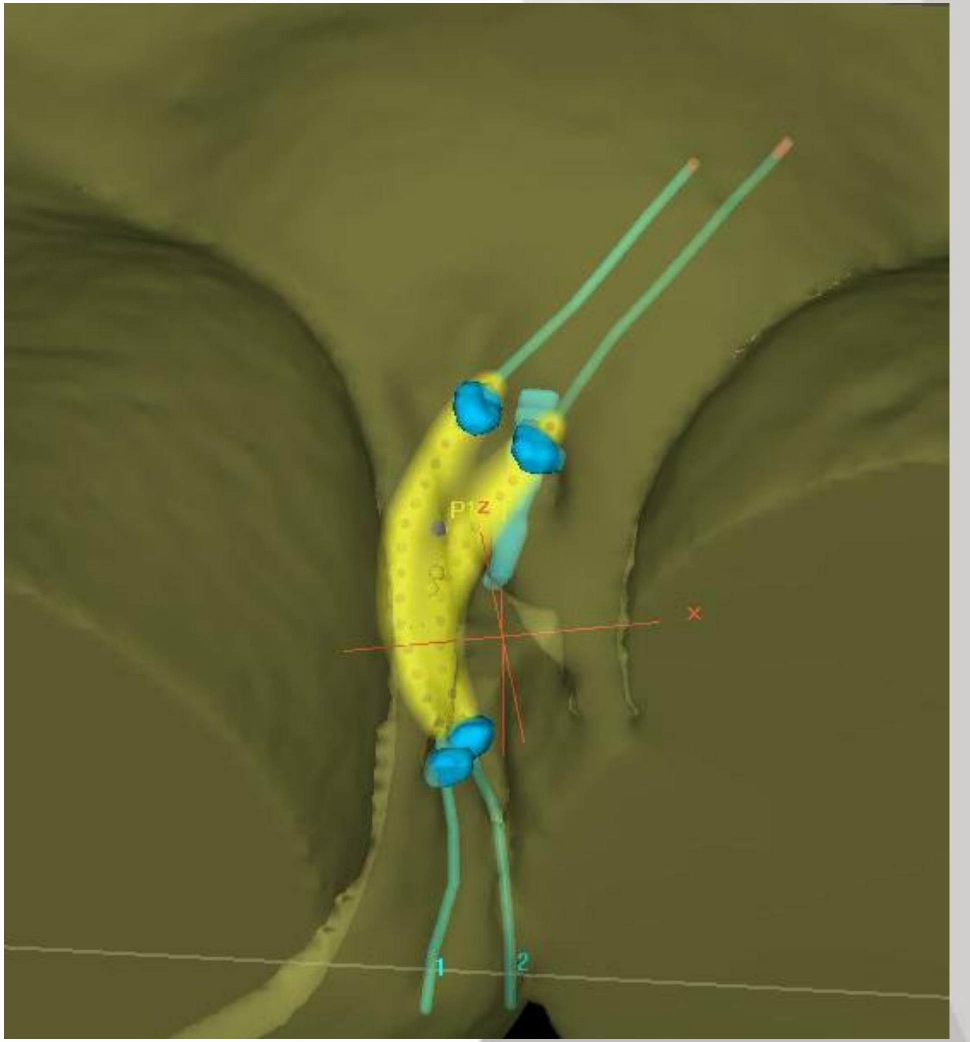
Plastic tube and/or needle parallel to the vaginal axis
Free hand or template
Interstitial +/- endocavitary

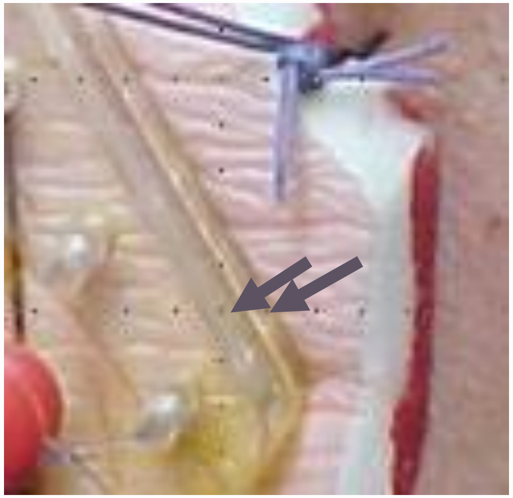


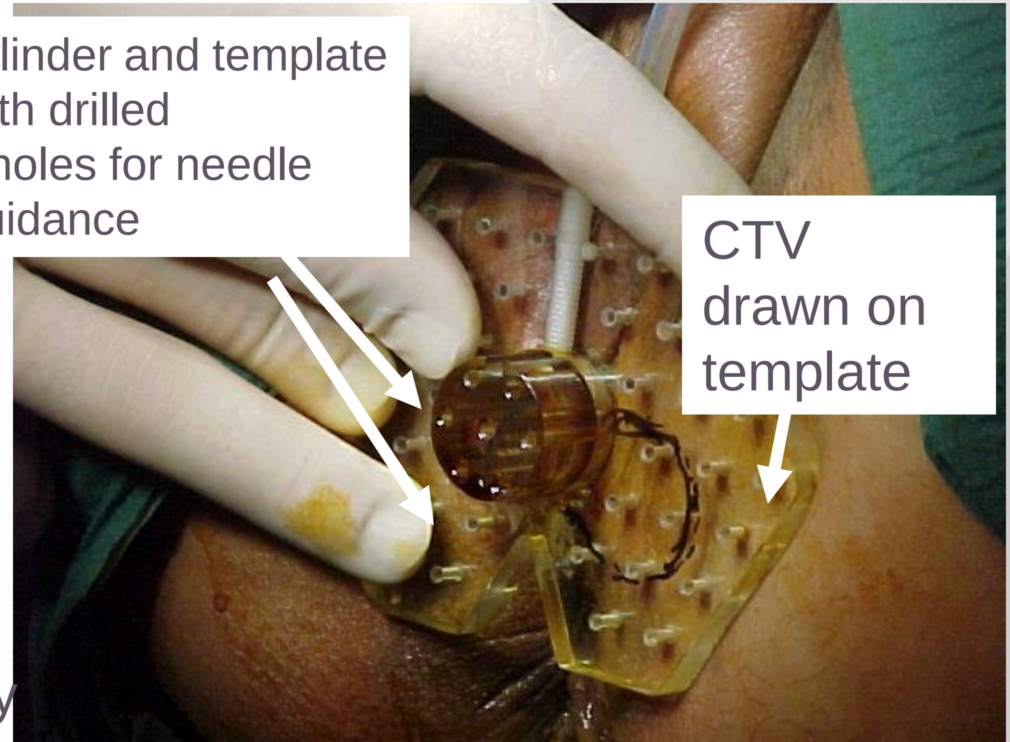





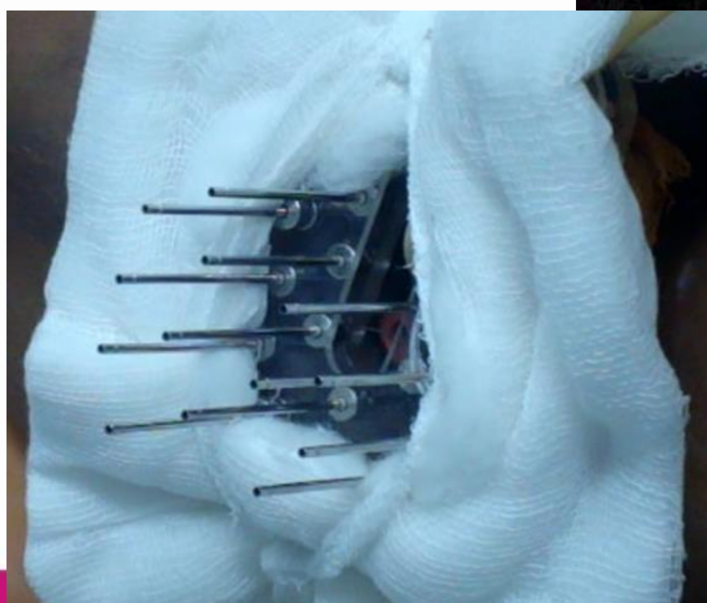

1
2

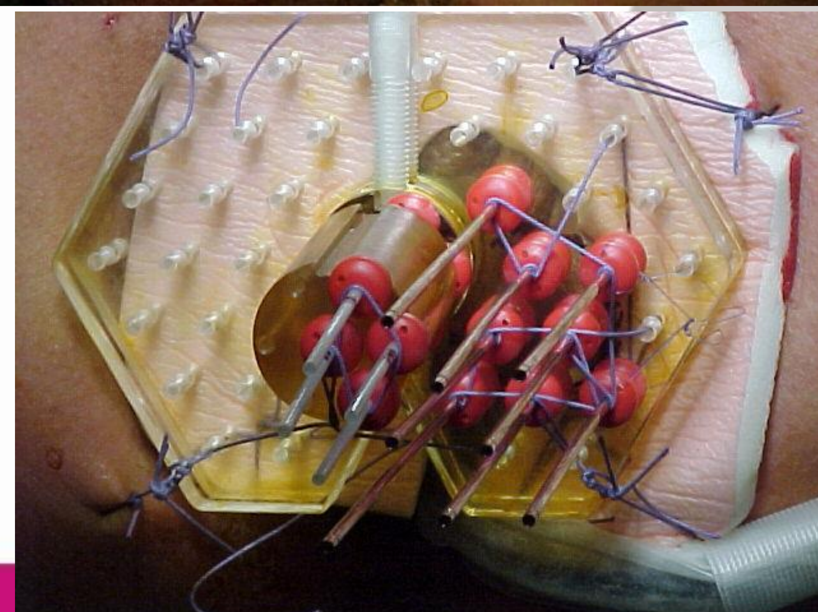

P1 Z
x
1
2



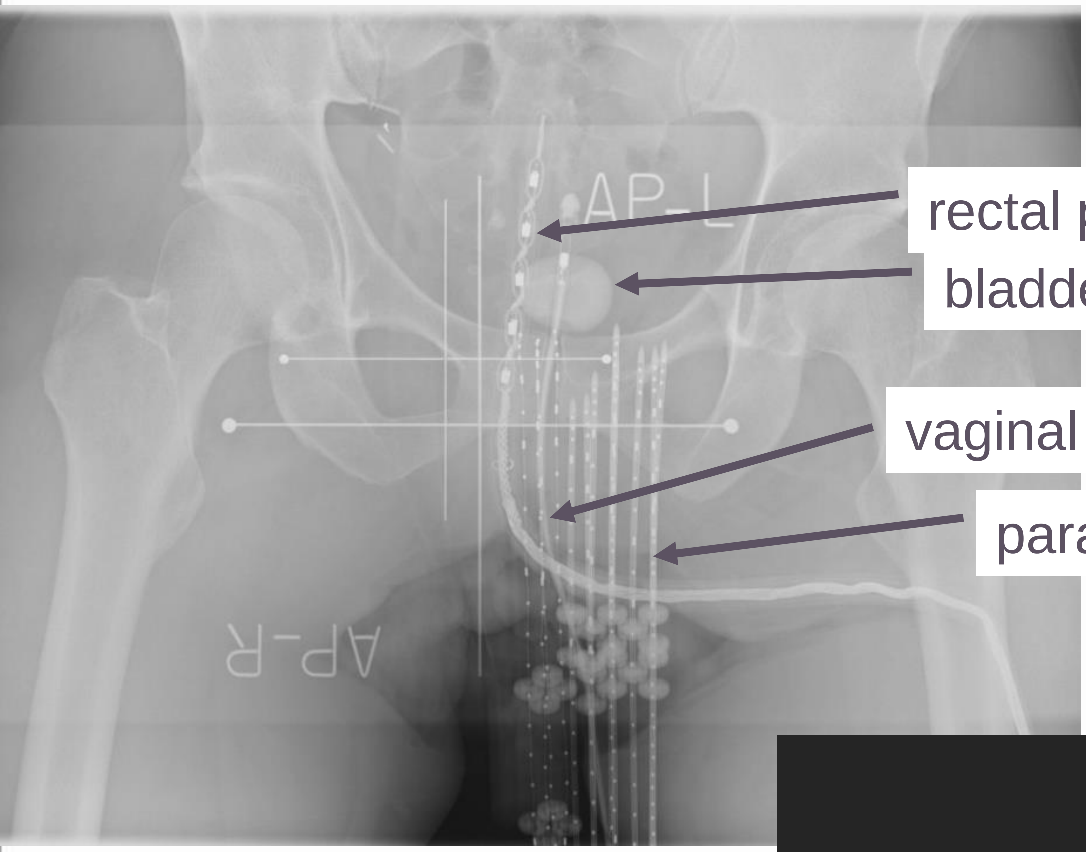


Courtesy Umesh Mahantshetty



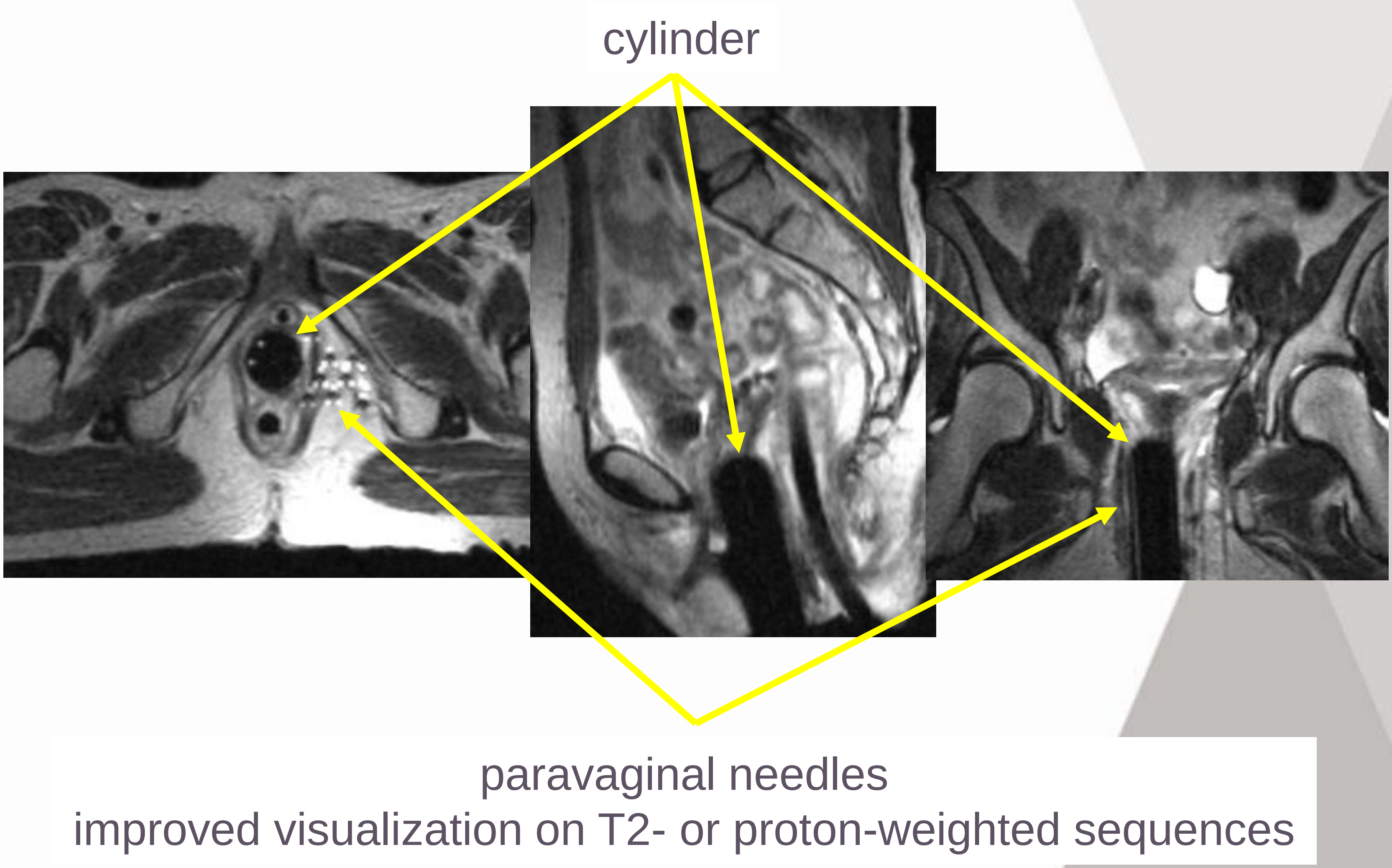


Orthogonal radiographs



Courtesy Umesh Mahantshetty

MRI-localization of the implant



Courtesy Umesh Mahantshetty

CTVs definition

- **So far no recommendations**
- **GEC-ESTRO recommendations adaptation ?**
  - Histopathological findings for postoperative treatment
  - Exclusive treatment
  - 10mm margin around HR-CTV or surgical margins
  - Different OAR :
    - Normal vulva
    - Urethra
    - Anus/peri-anal tissues
    - Vagina (if not involved)

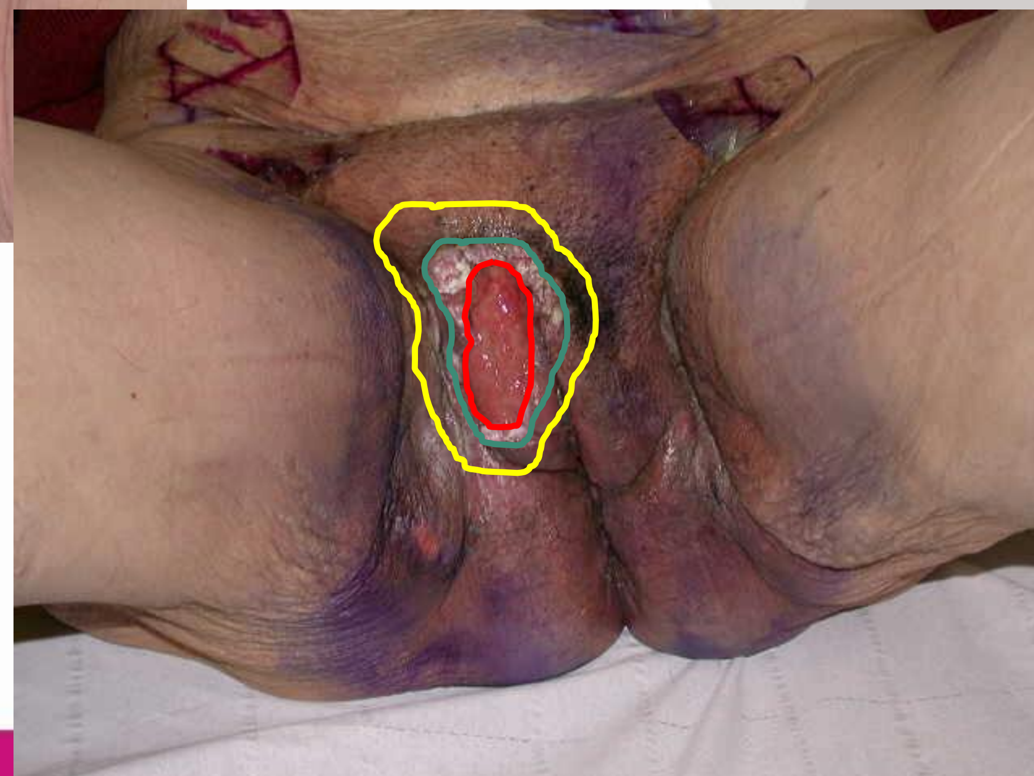
CTVs definition

- **Vulval specificities**
  - Lichen sclerosis

Tumour at diagnosis

After 45Gy ERT

Tumour at diagnosis



After 45Gy ERT

Challenges and pitfalls of image-guided vulval adaptive brachytherapy : Conclusion

- Exact knowledge of the disease :
  - Histopathological findings post surgical treatment
  - Disease mapping (before and after ERT) exclusive RT treatment
- Technical choice : tumour location
- More studies necessary to determine:
  - Dose to the tumour
  - Dose to OAR (urethra, anus, vagina)

Carcinoma Cervix IIIB (FIGO)

MR compatible Tandem and Ring with Interstitial needles (VIENNA - II applicator)

PRACTICAL EXAMPLE
TMH-33422-CN(SD)

Overview

- *Initial findings*
  - Initial clinical findings
  - Initial MRI findings
  - Other

- *EBRT, chemotherapy*

- *Findings at BRACHYTHERAPY (BT)*
  - Clinical findings at BT
  - MRI findings at BT

- *Delineation of GTV, CTV and Organs At Risk (OAR)*

Initial findings

Study ID: TMH-33422-CN(SD)

Patient & Tumour

Patient:

41 years old, Pre menopausal

No comorbidities

Tumour:

Histological type: SCC

FIGO Stage: III B, N1

Initial clinical findings:

Portio:

7x5 cm Large endophytic growth

Vagina: Upper 1cm

Fornices: Right and posterior involved

Parametria:

Right: up to LPW

Left: Medial half

Cystoscopy: Normal

MRI Pelvis:

Cervical mass lesion extending into vaginal cavity and lower uterine body.

Bilateral parametria involved.

Enlarged right obturator node (10mm)

(Images in subsequent slides)

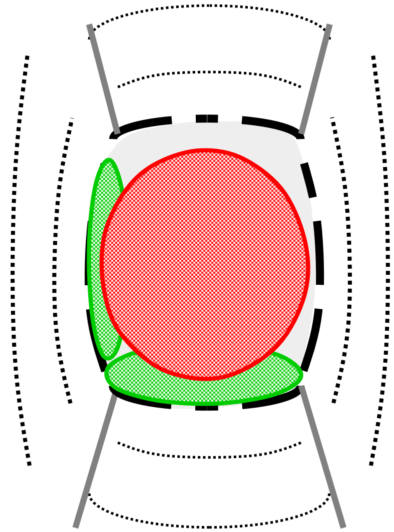
Details: see *Initial Clinical Drawings* (next slide)

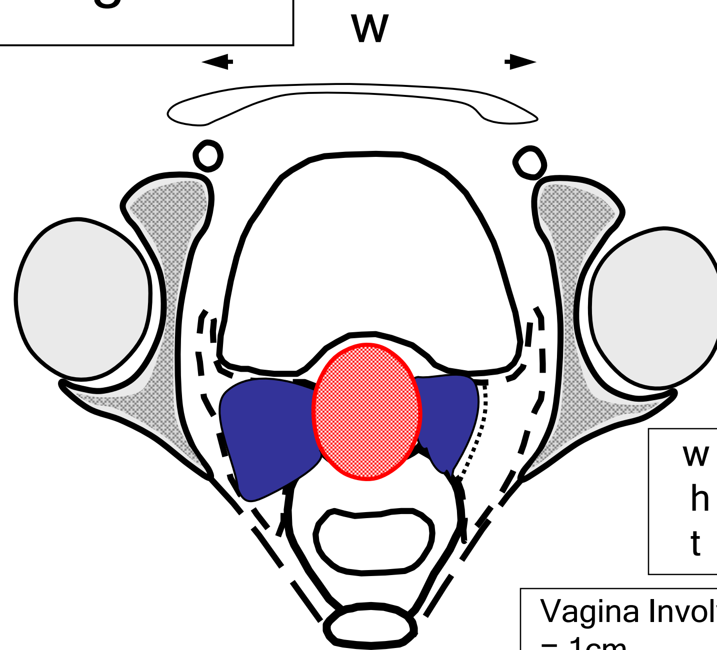
Study ID: TMH-33422-CN(SD)

Clinical Drawing

At Diagnosis

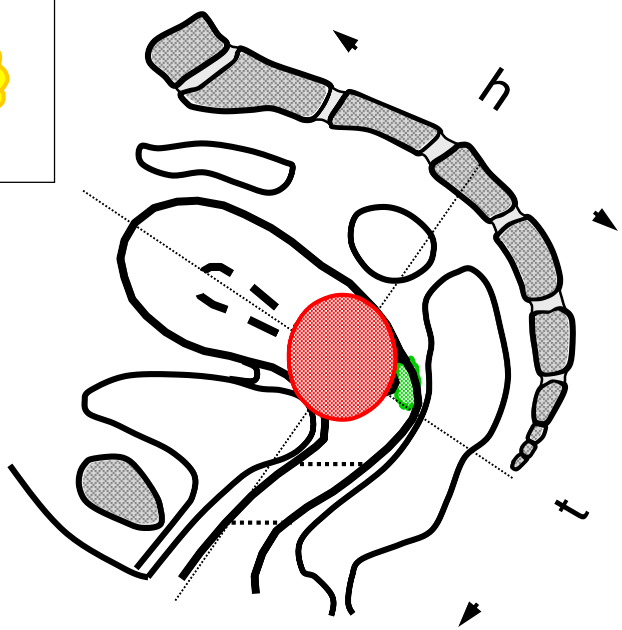
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

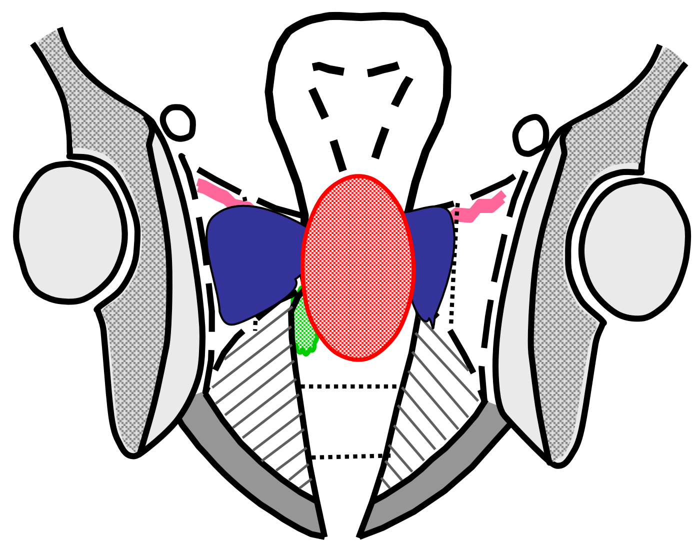




w = 7 cm
h = 5 cm
t = 5 cm

Vagina Involvement = 1cm





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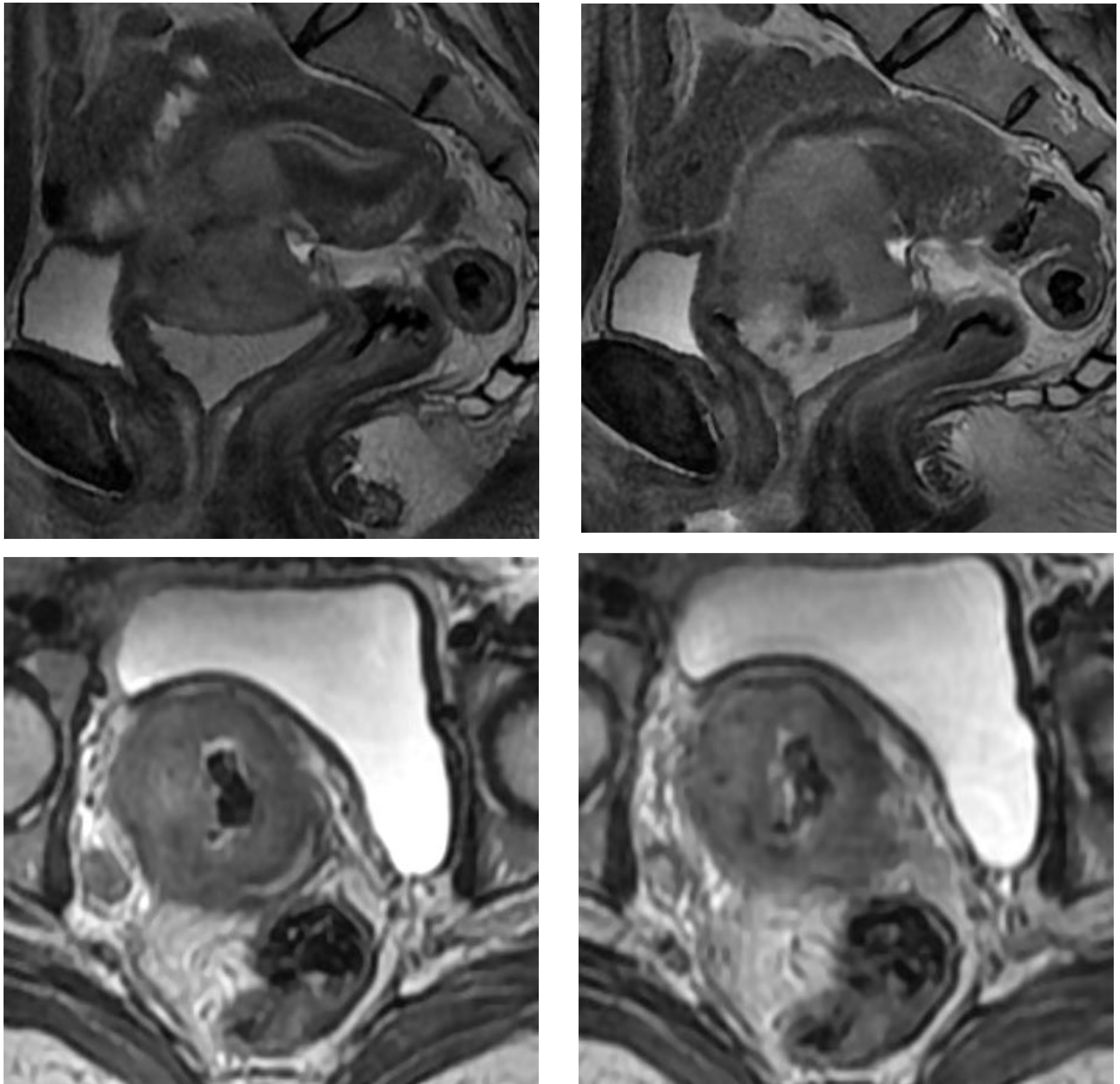
07.11.2016

Dr Umesh

Signature

Study ID: TMH-33422-CN(SD)

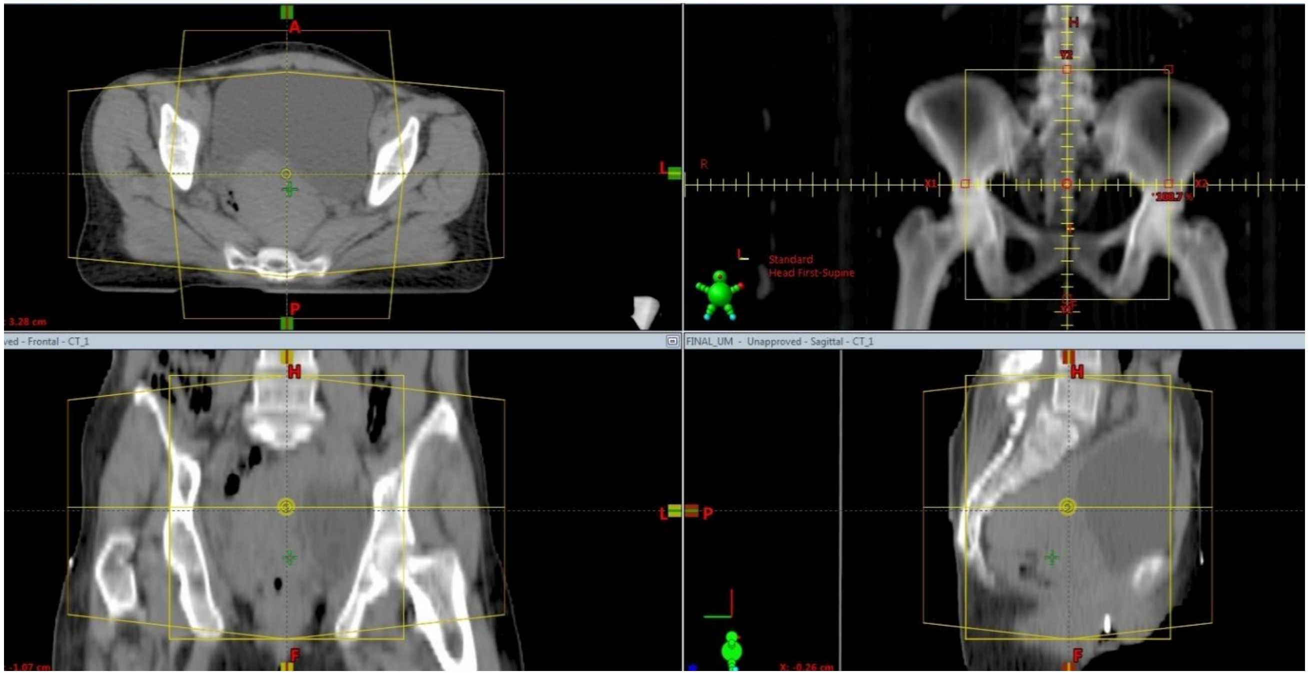
Initial



EBRT, Chemotherapy

EBRT & Chemotherapy

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



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

Findings at brachytherapy (immediately following EBRT)

Clinical findings at BT

Portio:

Residual endophytic growth eroding both lips of cervix

Vagina:

Right and posterior fornices involved.

Parametria:

Rt para involved up to LPW,

Lt para supple.

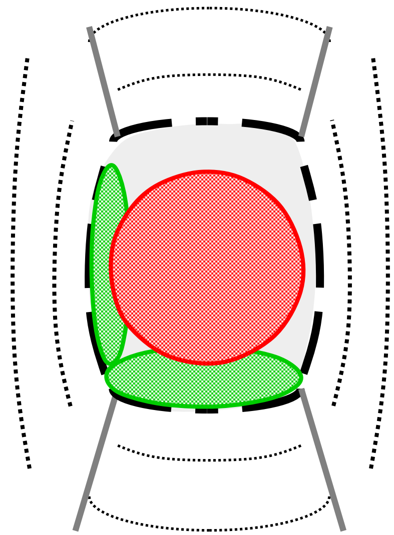
Details: see *Clinical Drawings at BT* (next slide)

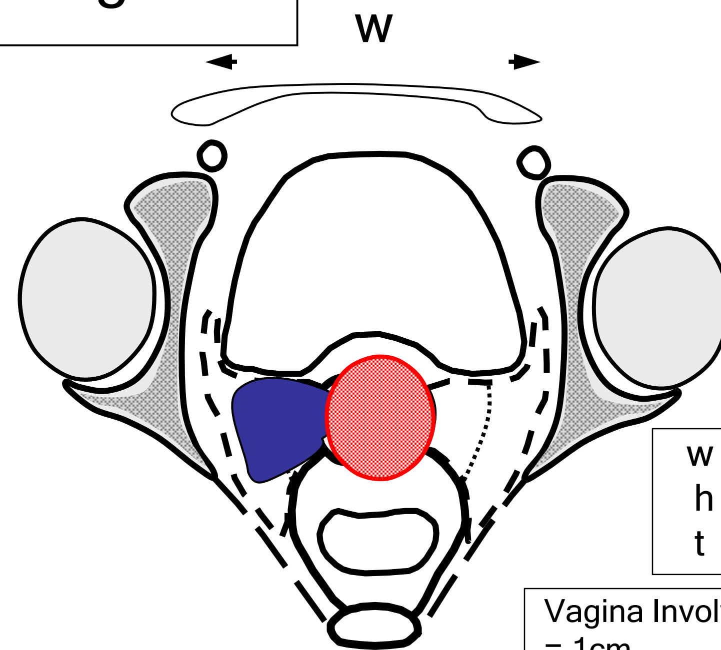
Study ID: TMH-33422-CN(SD)

Clinical Drawing

At Brachytherapy

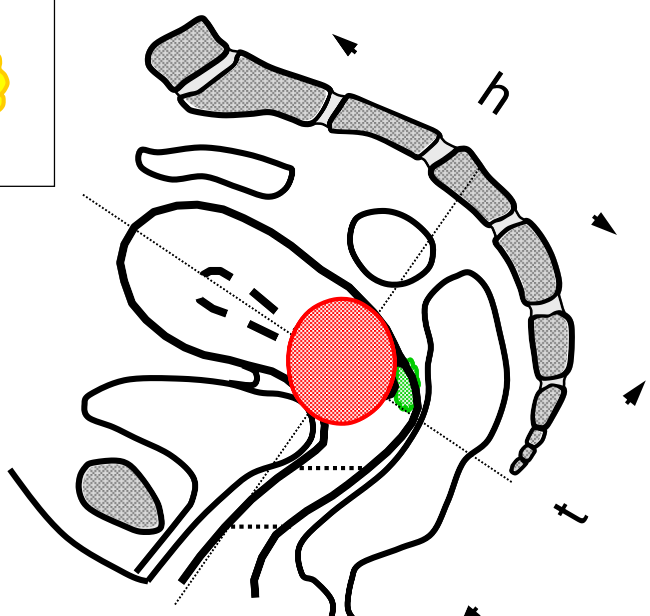
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

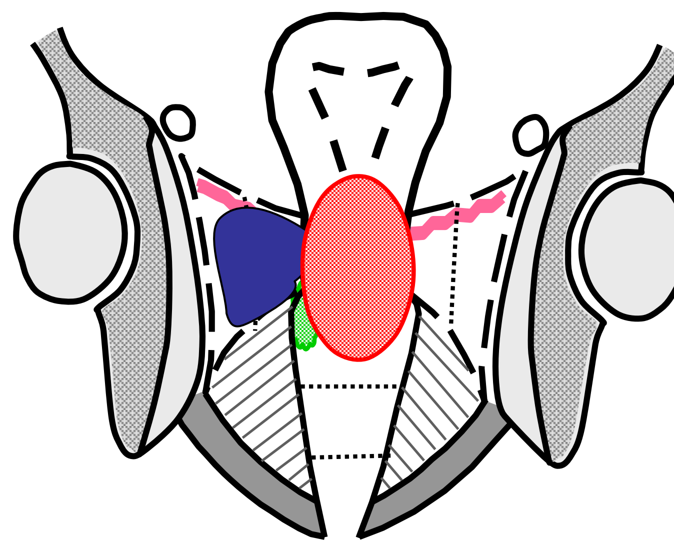




w = 5 cm
h = 3 cm
t = 3 cm

Vagina Involvement = 1cm





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27.12.2016

Dr Umesh

Signature

Insertion & imaging

Anaesthesia: General

Application:

Intracavitary component:

- Tandem length: 60 mm
- Tandem angle: 45º
- Ring diameter: 26 mm
- Material: plastic
- Comments: Water-filled plastic tube inside ring & tandem.

Interstitial component:

- N° of needles: 6 (3 straight + 3 divergent) in Rt parametrium
- Insertion depth: 5 cm
- Material: Titanium

Vaginal packing:

- Gauze impregnated with betadine

Imaging:

- MRI field strength: 1.5 T
- MRI configuration: closed
- Sequence(s): T2-weighted
- Imaging planes: transverse, sagittal, coronal
- Comments: Before imaging- Empty the bladder using Asepto syringe
  Inject 20cc saline in bladder

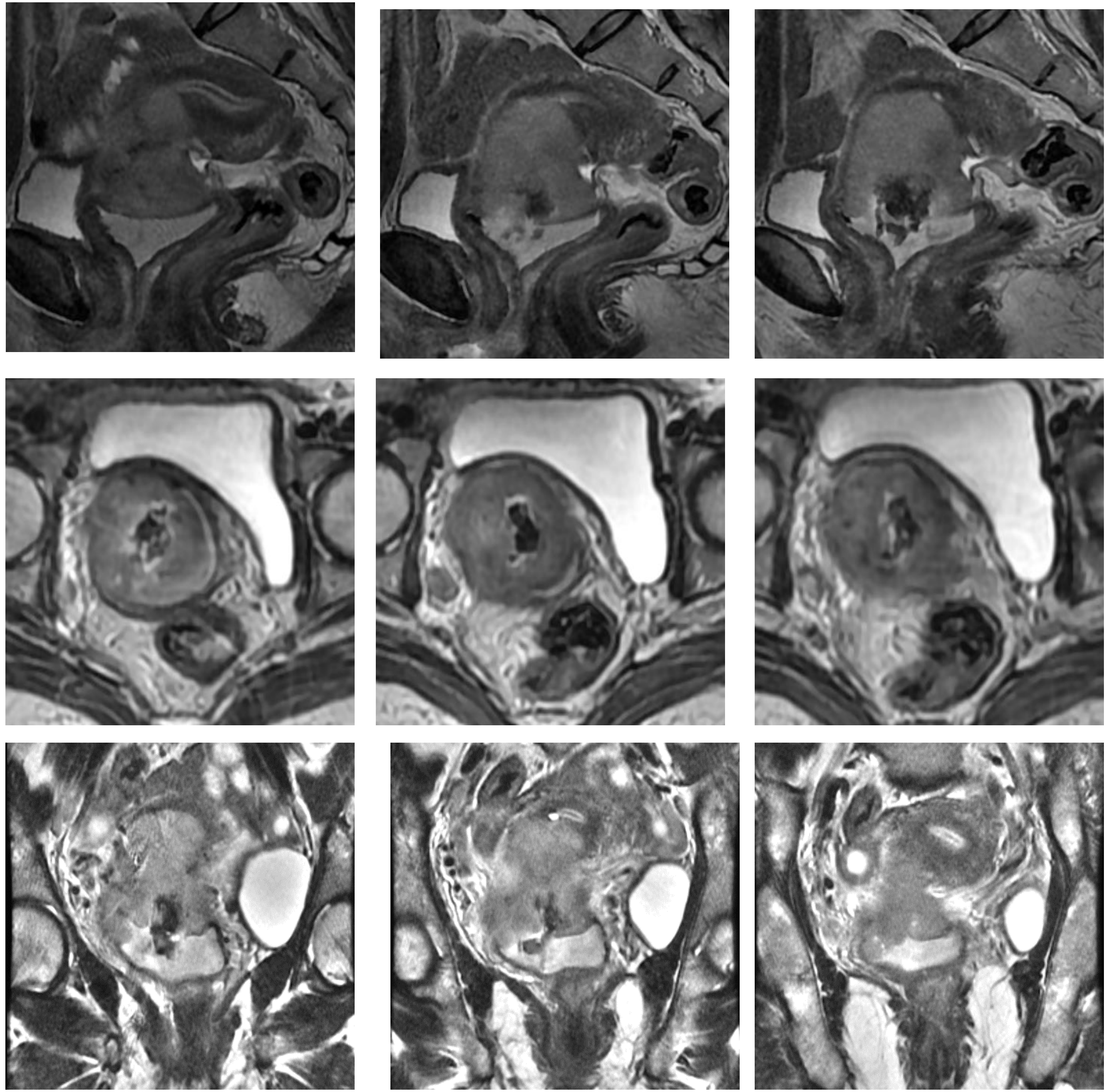
Study ID: TMH-33422-CN(SD)

Initial

Sag

Ax

Cor



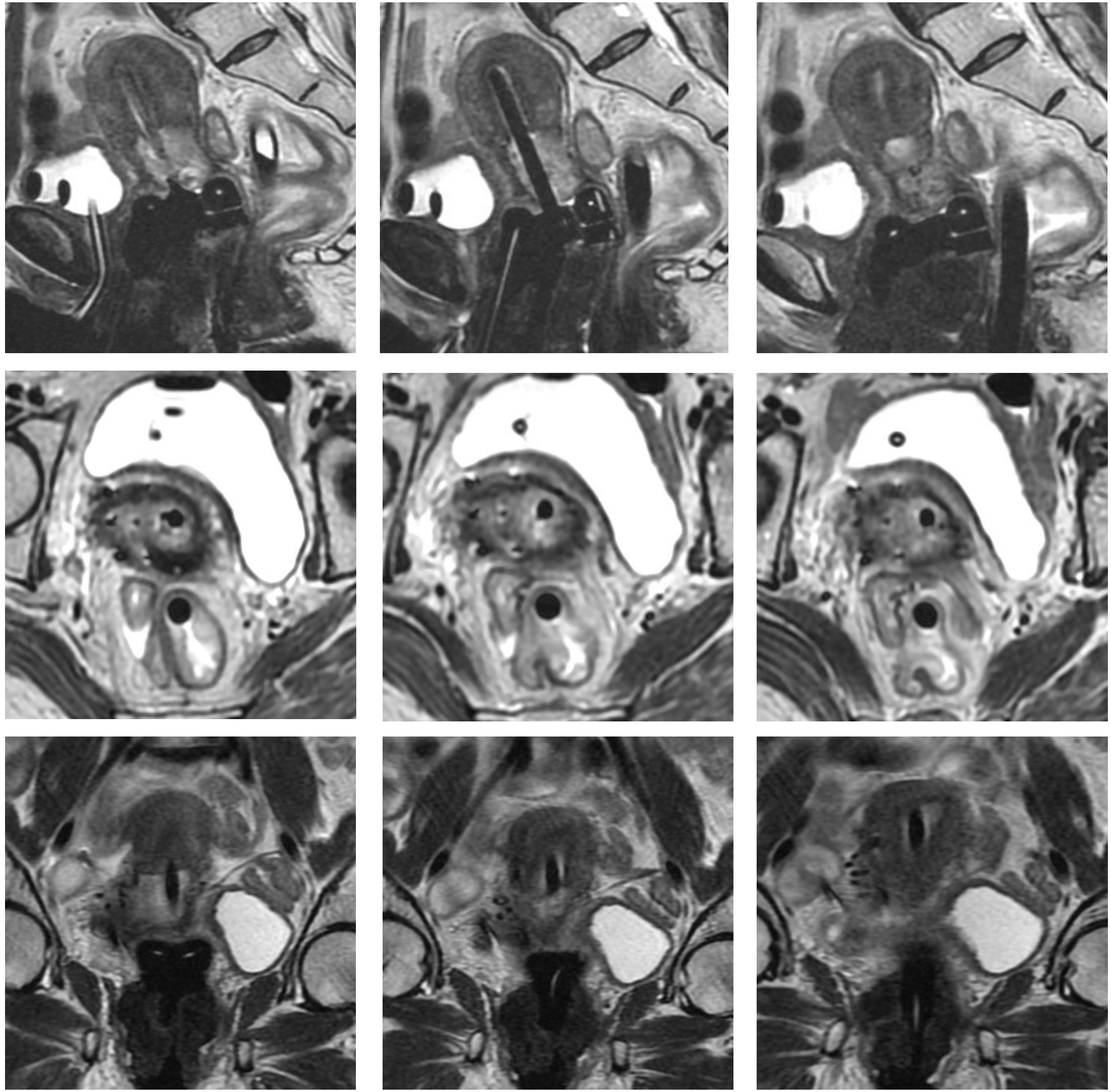
Study ID: TMH-33422-CN(SD)

At Brachy

Sag

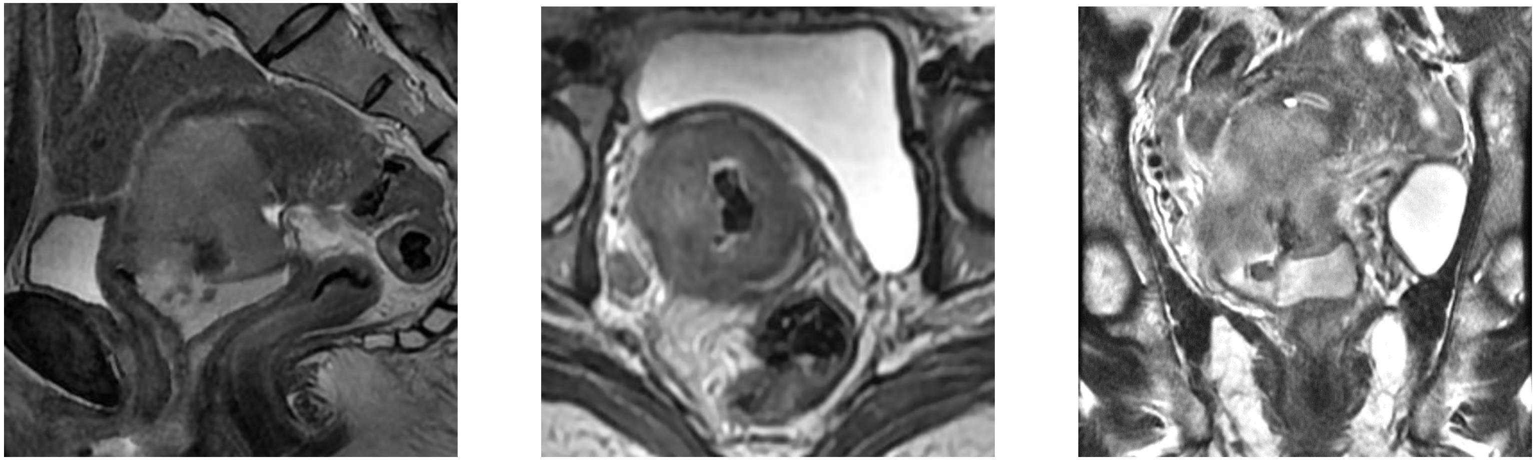
Ax

Cor

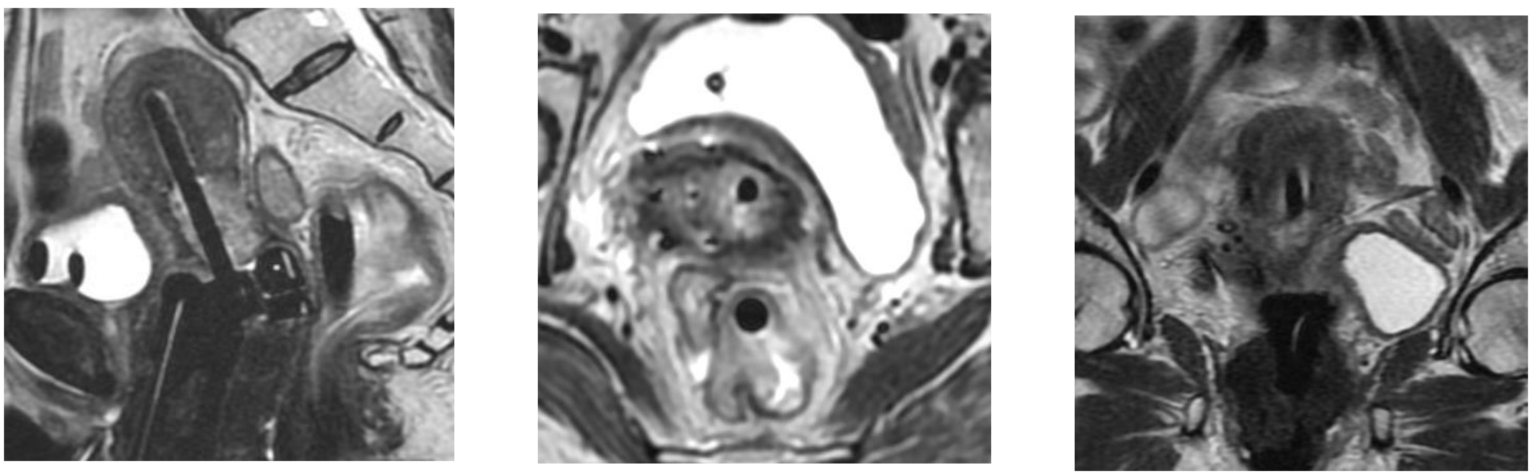


Study ID: TMH-33422-CN(SD)

Initial



At Brachy



Overview

- *Initial findings*
  - Initial clinical findings
  - Initial MRI findings
  - Other

- *EBRT, chemotherapy*

- *Findings at BRACHYTHERAPY (BT)*
  - Clinical findings at BT
  - MRI findings at BT

- *Delineation of GTV_{res}, $CTV\text{-}T_{HR}$, $CTV\text{-}T_{IR}$ and Organs At Risk (OAR)*

PLANNING

Session

Radiobiological models to combine dose from external beam radiotherapy
and
brachytherapy (HDR, MDR, LDR, PDR)

Taran Paulsen Hellebust
Associate Professor, Oslo University Hospital
Oslo, Norway

Thanks to
Daniel Berger, Kari Tanderup

Challenge

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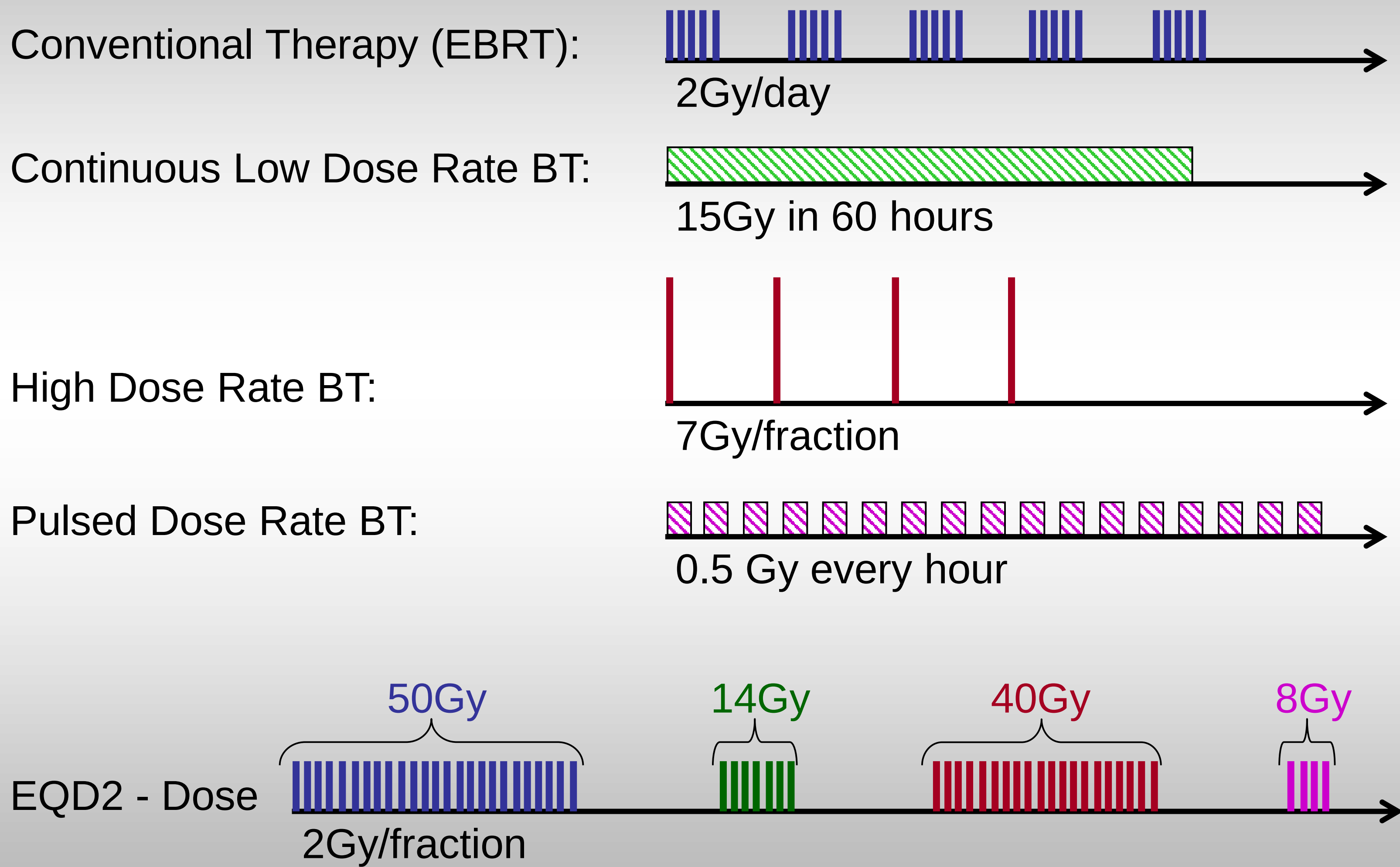
- We … s!

Different Fractionation Schedules



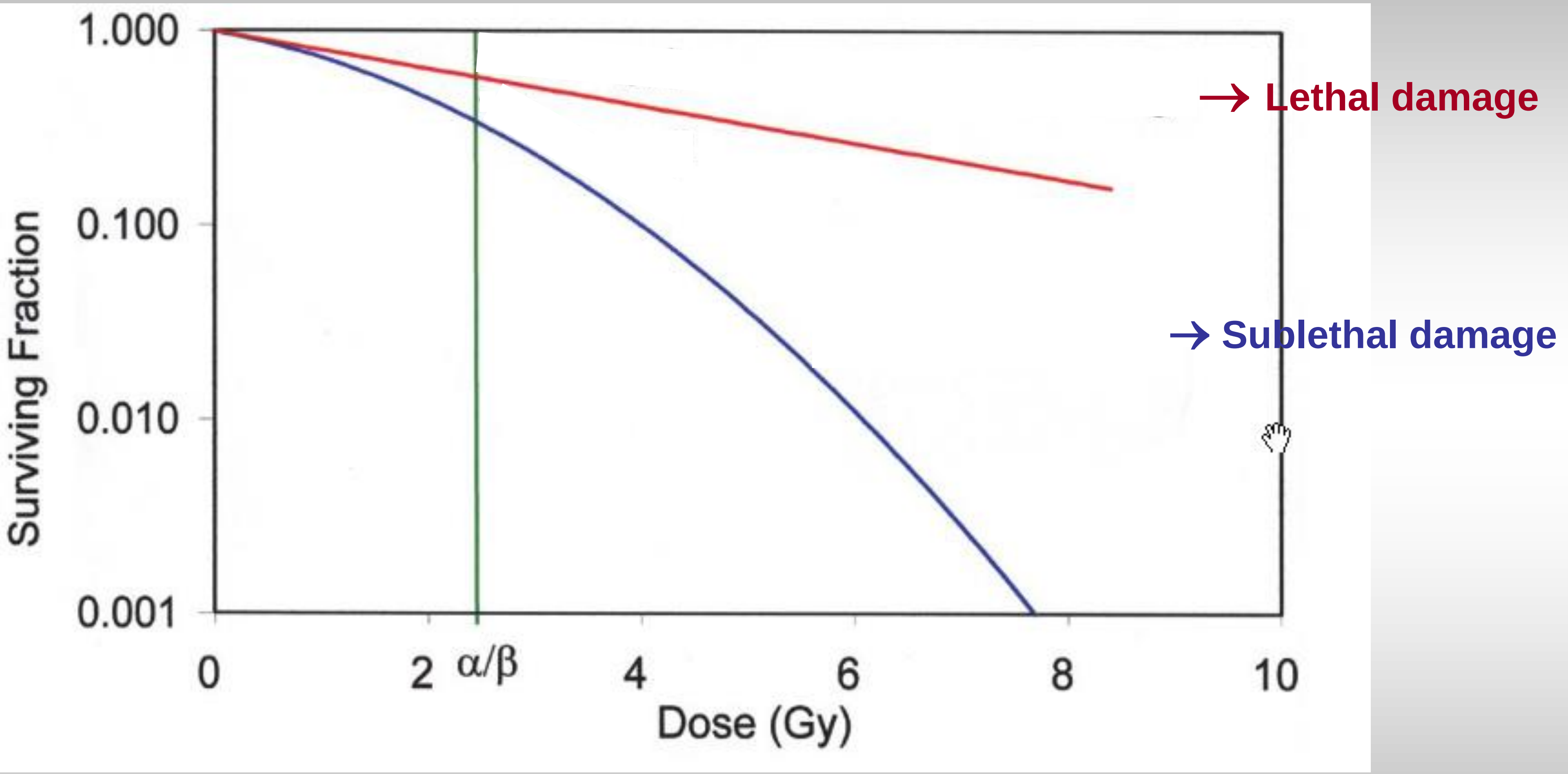
4 R’s of radiobiology

- Repair
  - Repair of sub-lethal DNA damage
- Redistribution
  - Radiosensitivity depends on phase in the cell cycle
- 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

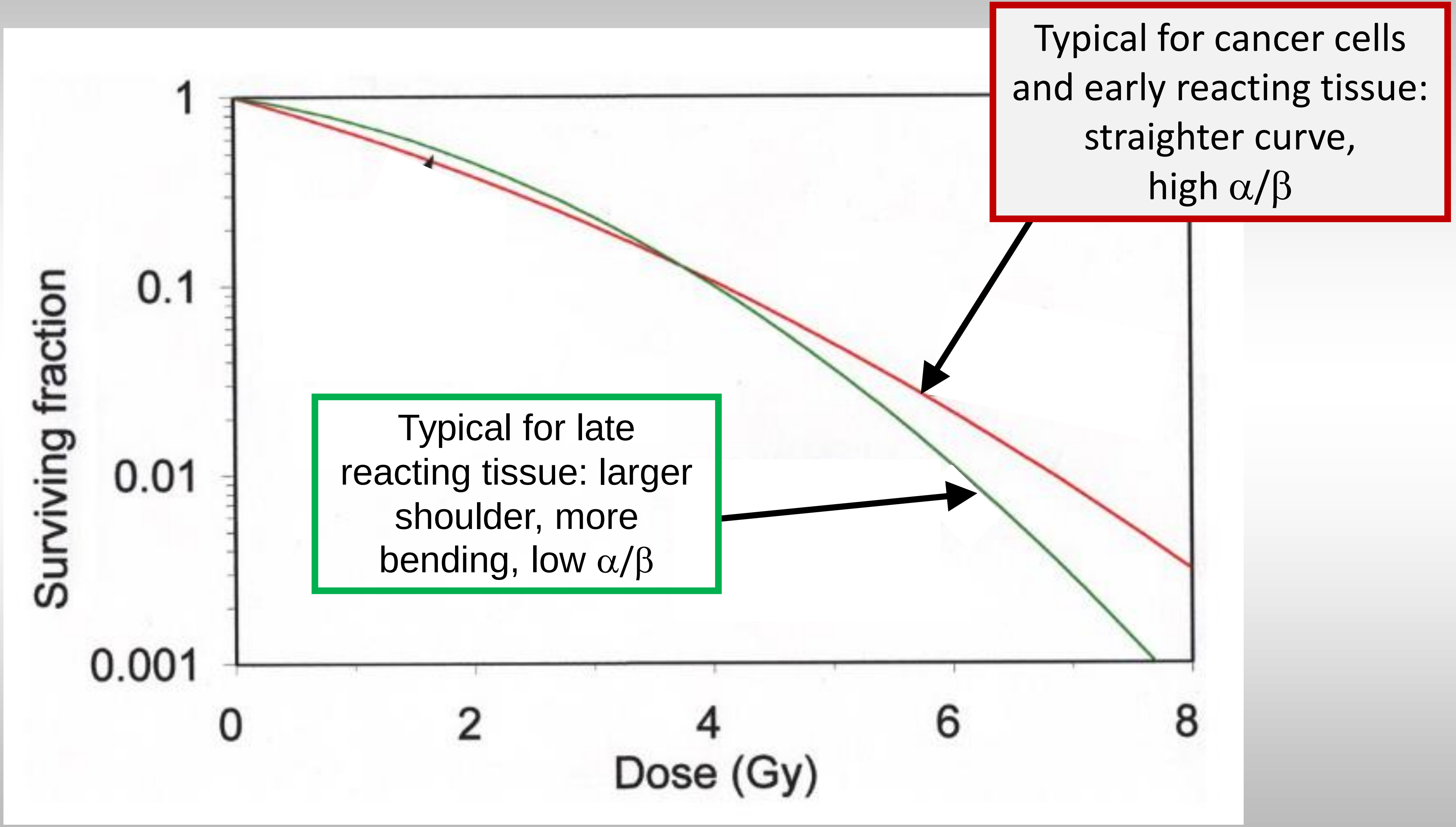
Linear-Quadratic Model



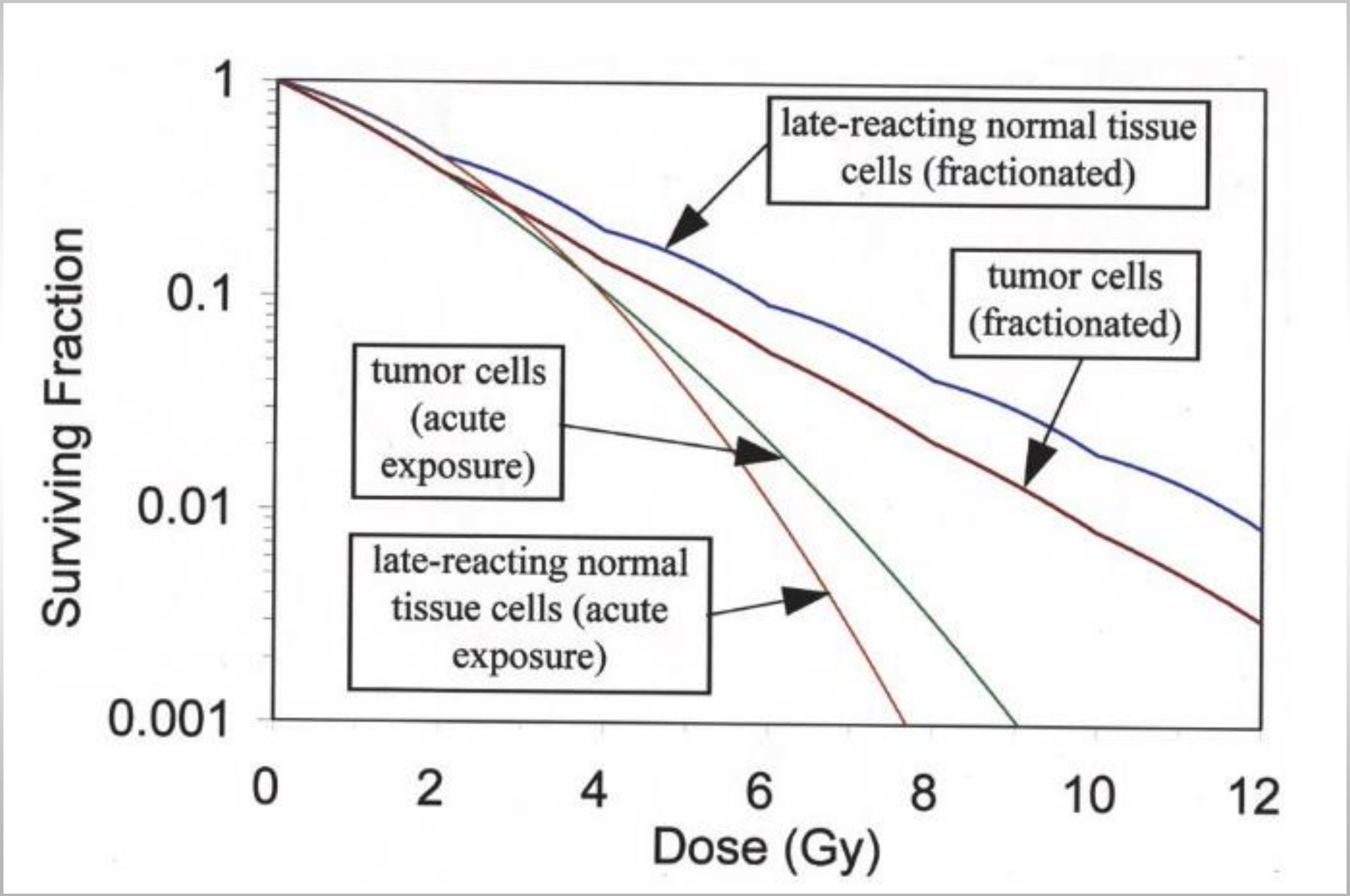
Of special interest is the dose where these two terms are equal:

$$\alpha D = \beta D^2 \quad \Rightarrow \quad D = \frac{\alpha}{\beta}$$

Linear-Quadratic Model



Fractionation



Limitation

4 Rs of Radiobiology

- **Recovery or Repair (half-time ~1hour)**
- ~~**Redistribution**~~
- ~~**Repopulation (< 1 day)**~~
- ~~**Reoxygenation**~~

Considered in the mathematical description (“equation”)

Linear - Quadratic model

- **Biologically Effective Dose:**

$$\mathbf{BED = nd\,[\,1 + \quad d\,/\,(\alpha/\beta)\,]}$$

- **BED ... virtual dose value 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

tissue dependent parameters :

α/β ...parameter describing lethal / sublethal lesions

Linear - Quadratic model for incomplete monoexponential sublethal damage repair

- **<u>Biologically Effective Dose:</u>**

$$\boxed{\mathrm{BED} = nd\,[\,1 + g\,d\,/\,(\alpha/\beta)\,]}$$

- **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>

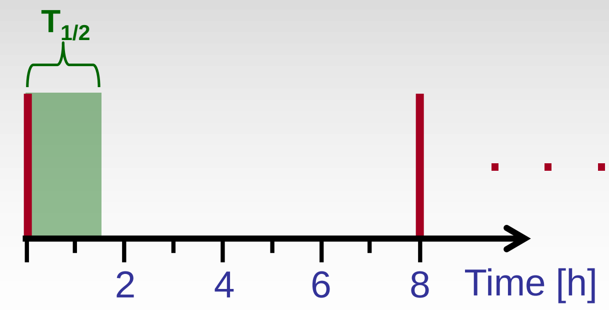
α/β ...parameter describing lethal / sublethal lesions
g ... repair function depending on - half time for cell repair $T_{1/2}$
- fractionation

Mathematical Description / Repair Function

- **External beam radiotherapy and HDR brachytherapy :**

no repair during irradiation (min)

repair function g = 1



- **LDR, MDR brachytherapy :**

repair during irradiation (hours - days) is significant

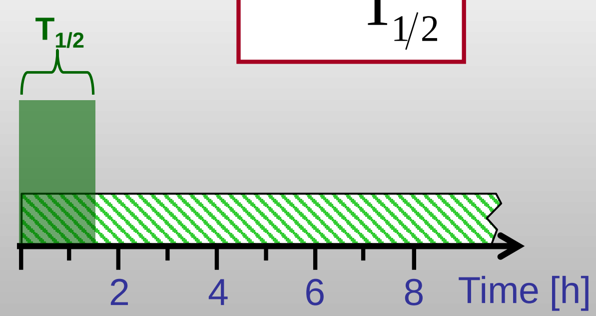
$$g(LDR, MDR) = \frac{2}{\mu t}\left[1 - \frac{1 - e^{-\mu t}}{\mu t}\right]$$

$$\mu = \frac{\ln 2}{T_{1/2}}$$

μ … repair rate

$T_{1/2}$ … half time for repair

t … irradiation time



Mathematical Description / Repair Function

- PDR brachytherapy :
- repair between successive pulses (hours) and during the whole fraction (hours - days) is significant

$$g(PDR) = \frac{2}{\mu t}\left[1 - \frac{ny - sy^2}{n\mu t}\right]$$

$$s = \frac{nk - k - nk^2 e^{-\mu t} + k^{n+1} e^{-\mu n t}}{\left(1 - k e^{-\mu t}\right)^2}$$

$$y = 1 - e^{-\mu t}$$

$$\mu = \frac{\ln 2}{T_{1/2}}$$

$$k = e^{-\mu x}$$

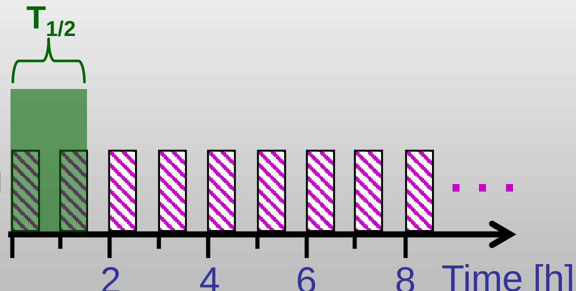
μ … repair rate

$T_{1/2}$ … half time for repair

t … irradiation time for each pulse

x … time between pulses without irradiation

n … number of equal pulses



Mathematical Description /Normalization - EQD2

- BED is the virtual dose value that produces the same biological effect as the physical dose with an infinite low dose rate

- Calculated BED values are normalized to conventional EBRT with 2 Gy / fraction (reference schedule) :

$$BED = D\,[\,1 + g \cdot d\,/\,(\alpha/\beta)\,] = D_{2Gy}\,[\,1 + 2\,/\,(\alpha/\beta)\,]$$

$$\boxed{EQD2 = D_{2Gy} = D\,\frac{gd+\alpha/\beta}{2Gy+\alpha/\beta}}$$

- To calculate the total isoeffective dose D_{2Gy} of a combined treatment, all isoeffective doses D_{2Gy} are added up :

$$D_{2Gy,TOTAL} = D_{2Gy,EXTERNAL} + D_{2Gy,BRACHY}$$

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 – 5 Gy for bladder, rectum, sigmoid

$T_{1/2}$ ~ 1.5 hours — **1 – 2 hours**

Clinical and experimental experience

Values of biological parameters

- Tumour and early reacting normal tissue:

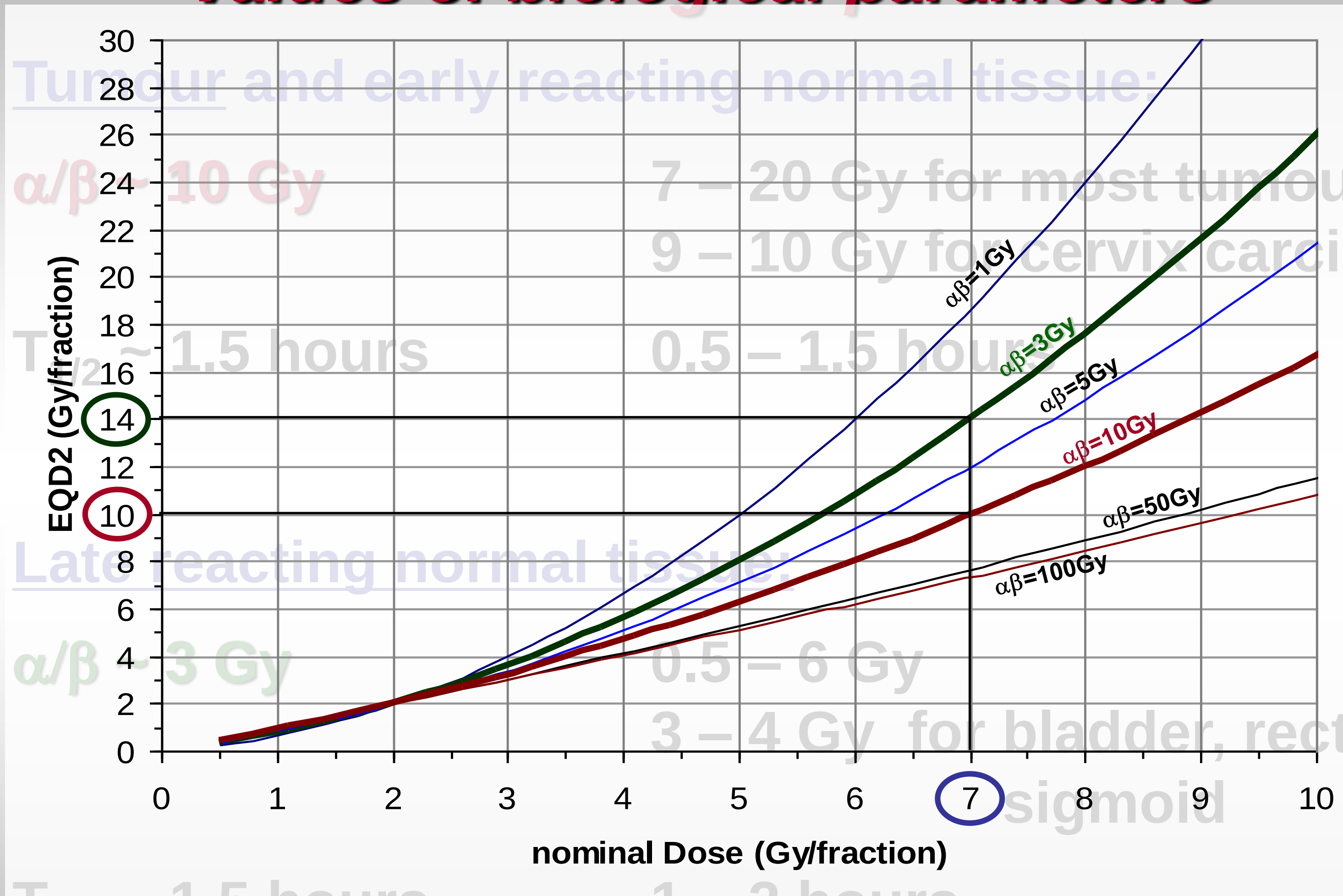
α/β ~ 10 Gy — 7 – 20 Gy for most tumours; 9 – 10 Gy for cervix carcinoma

$T_{1/2}$ ~ 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

Different fractionation schedules (EBRT)

Example for a external beam dose (25 x 1.8Gy):

$$BED = n \cdot d \left(1 + \frac{g \cdot d}{\alpha/\beta}\right) \qquad \alpha/\beta = 10Gy \qquad g = 1 \text{ (EBRT!)}$$

$$BED = 25 \cdot 1.8Gy \left(1 + \frac{1.8Gy}{10Gy}\right) = 53.1Gy_{10}$$

Normalize the dose in 2Gy per fraction:

$$EQD2 = \frac{BED}{\left(1 + \frac{2Gy}{\alpha/\beta}\right)} = \frac{53.1Gy}{\left(1 + \frac{2Gy}{10Gy}\right)} = 44.3Gy_{\alpha\beta 10}$$

Different fractionation schedules (EBRT)

Example for a external beam dose (25 x 1.8Gy):

$$EQD2 = D\,\frac{(g\,d + \alpha/\beta)}{(2Gy + \alpha/\beta)}$$

$\alpha/\beta = 10Gy$ $g = 1$ (EBRT!)

Normalize the dose in 2Gy per fraction:

$$EQD2 = 25x1.8Gy\,\frac{(1.8Gy + 10Gy)}{(2Gy + 10Gy)} = 44.3Gy_{\alpha\beta10}$$

Different fractionation schedules (EBRT)

Example for a a HDR brachy (4 x 7Gy):

$$EQD2 = D\,\frac{(g\,d + \alpha/\beta)}{(2Gy + \alpha/\beta)}$$

$\alpha/\beta = 10Gy$

$g = 1$ (HDR!)

Normalize the dose in 2Gy per fraction:

$$EQD2 = 4 \times 7Gy\,\frac{(7Gy + 10Gy)}{(2Gy + 10Gy)} = 39.7Gy_{\alpha\beta10}$$

Example EBRT + HDR-BT for cervical carcinoma

α/β = 10 Gy for cervical tumour

α/β = 3 Gy for OAR (bladder, rectum, sigmoid)

D90 HR-CTV		physical dose	EQD2
External beam	25 x 1.8 Gy =	(45 Gy)	$44\ Gy_{\alpha\beta 10}$
Brachytherapy	4 x 7.0 Gy =	(28 Gy)	$40\ Gy_{\alpha\beta 10}$
Total dose		~~73 Gy~~	$84\ Gy_{\alpha\beta 10}$

OAR	brachy dose to OAR D2cc		
External beam	25 x 1.8 Gy =	(45 Gy)	$43\ Gy_{\alpha\beta 3}$
Brachytherapy	4 x 4.9 Gy =	(20 Gy)	$31\ Gy_{\alpha\beta 3}$
Total dose		~~65 Gy~~	$74\ Gy_{\alpha\beta 3}$

Example EBRT + PDR-BT for cervical carcinoma

a/b = 10 Gy for cervical tumour

a/b = 3 Gy for OAR (bladder, rectum, sigmoid)

T1/2 = 1.5 h for cervical tumour and OAR

BT treatment time: 80h (PDR: pulse time = 15 min, interval = 1 h)

D90 HR-CTV		physical dose	EQD2		
External beam	25 x 1.8 Gy =	(45 Gy)	$44\ Gy_{ab10}$		HDR
BT 0.5Gy/h	80 x 0.5 Gy =	(40 Gy)	$40\ Gy_{ab10}$		
Total dose		~~85 Gy~~	$84\ Gy_{ab10}$	=	$84\ Gy_{\alpha\beta 10}$

OAR	brachy dose to OAR D2cc				
External beam	25 x 1.8 Gy =	(45 Gy)	$43\ Gy_{ab3}$		HDR
BT 0.35Gy/h	80 x 0.35 Gy =	(28 Gy)	$31\ Gy_{ab3}$		
Total dose		~~73 Gy~~	$68\ Gy_{ab3}$	<	$74\ Gy_{\alpha\beta 3}$

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

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 -

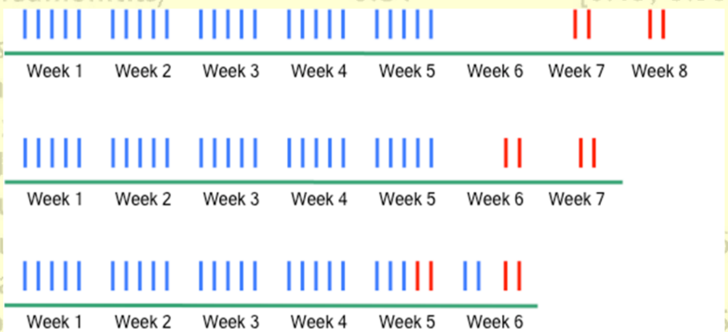
Influencing the local control rate

$$EQD_{2,T} = EQD_{2,t} - (T - t)D_{prolif}$$

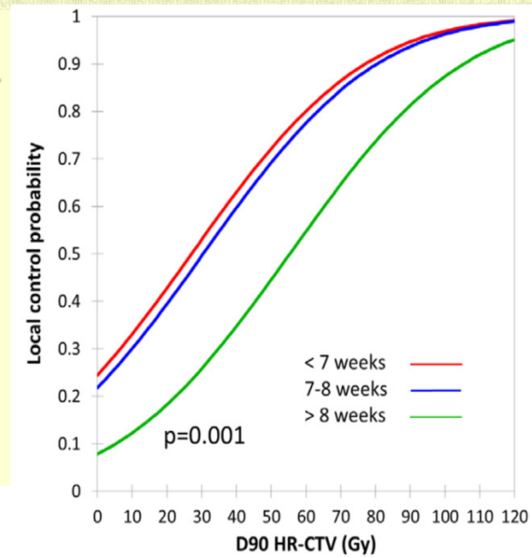
- Increasing OTT by one week is equivalent to a loss of 5 Gy in CTV_{HR} D90

Tanderup, retroEMBRACE, 2016, submitted

- Timing of the BT boost?



EBRT ⟷ BT



Mazeron et al, Radiother Oncol 2015

„Per day delay in overall treatment time results in loss of ~ 0.3 – 0.8 Gy/day“

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**
		D_{iso} [α/β=10Gy]	D_{iso} [α/β=3Gy]
dose per fraction	1,8		
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	TOTAL BT	TOTAL BT + EBT
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			*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 [cm^3]	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
0,1cm^3 - dose	8,0	8,0	9,5	7,5				
0,1cm^3 - D_{iso} [α/β=3Gy]	17,6	17,6	23,8	15,8	0,0	0,0	74,7	117,9
1cm^3 - dose	6,4	6,5	7,2	6,3				
1cm^3 - D_{iso} [α/β=3Gy]	12,0	12,4	14,7	11,7	0,0	0,0	50,8	94,0
2cm^3 - dose	6,0	6,0	6,4	5,9				
2cm^3 - D_{iso} [α/β=3Gy]	10,8	10,8	12,0	10,5	0,0	0,0	44,1	**87,3**
RECTUM [cm^3]	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
0,1cm^3 - dose	5,9	4,9	4,6	4,3				
0,1cm^3 - D_{iso} [α/β=3Gy]	10,5	7,7	7,0	6,3	0,0	0,0	31,5	74,7
1cm^3 - dose	4,8	4,2	3,7	3,6				
1cm^3 - D_{iso} [α/β=3Gy]	7,5	6,0	5,0	4,8	0,0	0,0	23,2	66,4
2cm^3 - dose	4,3	3,9	3,4	3,3				
2cm^3 - D_{iso} [α/β=3Gy]	6,3	5,4	4,4	4,2	0,0	0,0	20,2	**63,4**
SIGMOID [cm^3]	17,4	21,1	24,6	26,3			*22,4*	*3,4*
0,1cm^3 - dose	6,6	5,7	4,7	5,2				
0,1cm^3 - D_{iso} [α/β=3Gy]	12,7	9,9	7,2	8,5	0,0	0,0	38,4	81,6
1cm^3 - dose	5,4	4,7	3,8	4,2				
1cm^3 - D_{iso} [α/β=3Gy]	9,1	7,2	5,2	6,0	0,0	0,0	27,5	70,7
2cm^3 - dose	4,7	4,2	3,4	3,8				
2cm^3 - 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 take OTT time into account – remember loss of 5Gy per week at OTT>50 days
- Implement a spreadsheet in your department

$$\boxed{EQD2 = D_{2Gy} = D\,\frac{gd+\alpha/\beta}{2Gy+\alpha/\beta}}$$

BLADDER [cm^3]	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
0,1cm^3 - dose	8,0	8,0	9,5	7,5				
0,1cm^3 - D_{iso} [α/β=3Gy]	17,6	17,6	23,8	15,8	0,0	0,0	74,7	117,9
1cm^3 - dose	6,4	6,5	7,2	6,3				
1cm^3 - D_{iso} [α/β=3Gy]	12,0	12,4	14,7	11,7	0,0	0,0	50,8	94,0
2cm^3 - dose	6,0	6,0	6,4	5,9				
2cm^3 - D_{iso} [α/β=3Gy]	10,8	10,8	12,0	10,5	0,0	0,0	44,1	**87,3**
RECTUM [cm^3]	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
0,1cm^3 - dose	5,9	4,9	4,6	4,3				
0,1cm^3 - D_{iso} [α/β=3Gy]	10,5	7,7	7,0	6,3	0,0	0,0	31,5	74,7
1cm^3 - dose	4,8	4,2	3,7	3,6				
1cm^3 - D_{iso} [α/β=3Gy]	7,5	6,0	5,0	4,8	0,0	0,0	23,2	66,4
2cm^3 - dose	4,3	3,9	3,4	3,3				
2cm^3 - D_{iso} [α/β=3Gy]	6,3	5,4	4,4	4,2	0,0	0,0	20,2	**63,4**
SIGMOID [cm^3]	17,4	21,1	24,6	26,3			*22,4*	*3,4*
0,1cm^3 - dose	6,6	5,7	4,7	5,2				
0,1cm^3 - D_{iso} [α/β=3Gy]	12,7	9,9	7,2	8,5	0,0	0,0	38,4	81,6
1cm^3 - dose	5,4	4,7	3,8	4,2				
1cm^3 - D_{iso} [α/β=3Gy]	9,1	7,2	5,2	6,0	0,0	0,0	27,5	70,7
2cm^3 - dose	4,7	4,2	3,4	3,8				
2cm^3 - D_{iso} [α/β=3Gy]	7,2	6,0	4,4	5,2	0,0	0,0	22,8	**66,0**

Medical aspects of treatment planning and dose constraints: focus on BT

Clinical evidence for dose-effects

ESTRO Teaching Course

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

Prague October 2017

Richard Pötter

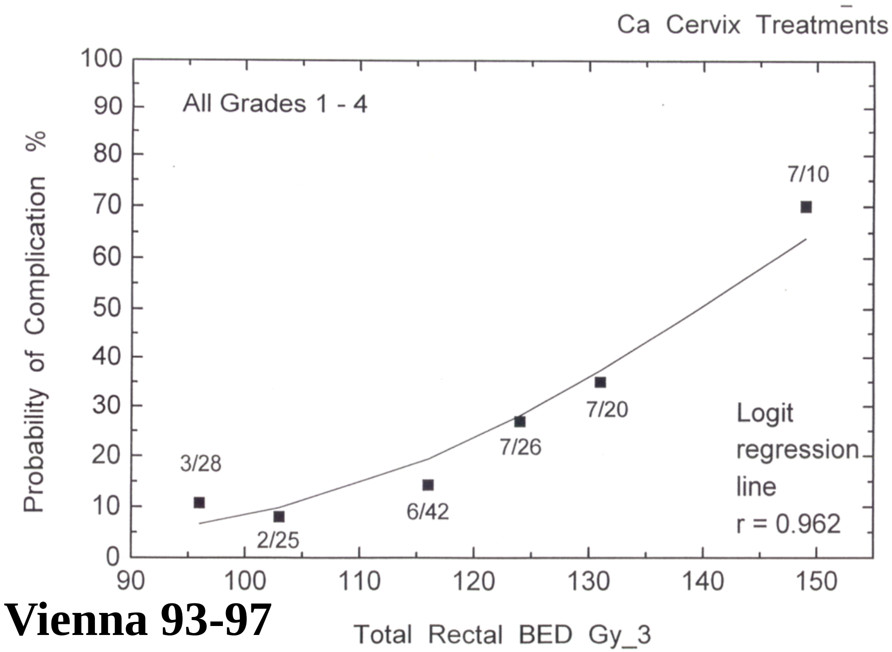
Kari Tanderup

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)

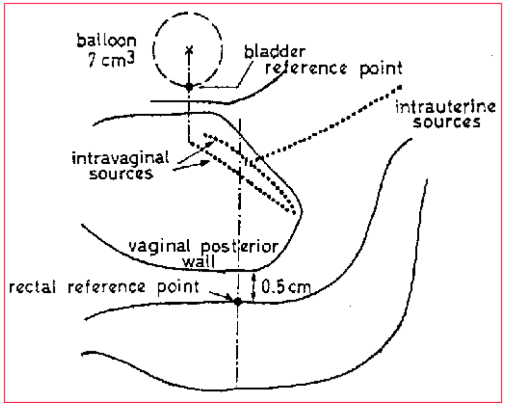


Vienna 93-97

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)

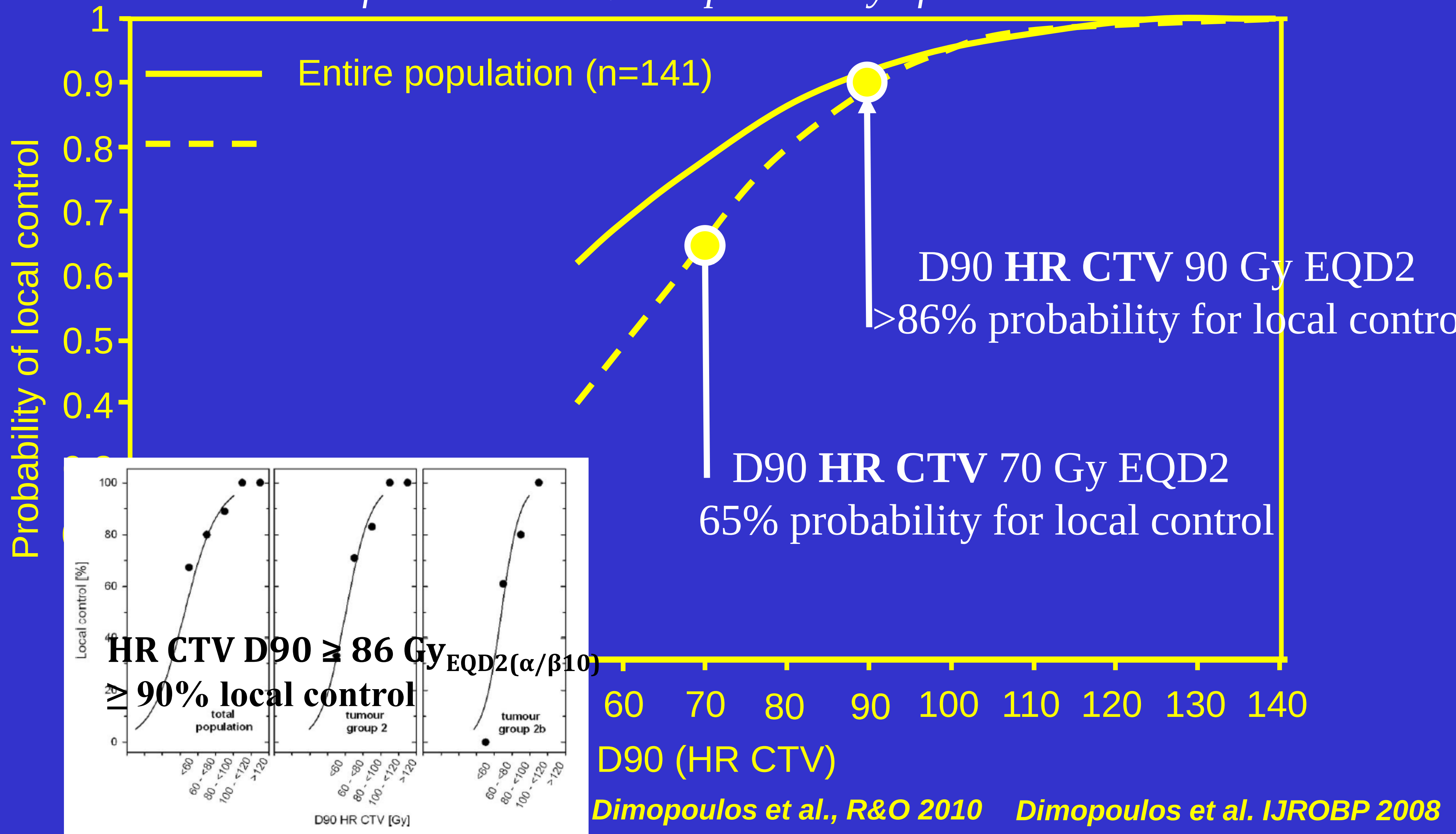
- **Vienna** (Dimopoulos 2008, 2010, Georg 2009,2011(Pötter 2007, 2011))
- **Seoul** (Kim et al. 2008)
- **Paris** (Mazeron 2014, 2015 (Castelnaud-Marchand 2015, Haie-Meder))
- **Aarhus** (Lindegaard, Tanderup 2014)
- **Leuven** (Ribeiro, Limbergen 2016)

Linking DVH-parameters to clinical outcome

HR CTV/Tumour

Analysis (n=141, FIGO: IB-IVA, median follow-up=51 months)

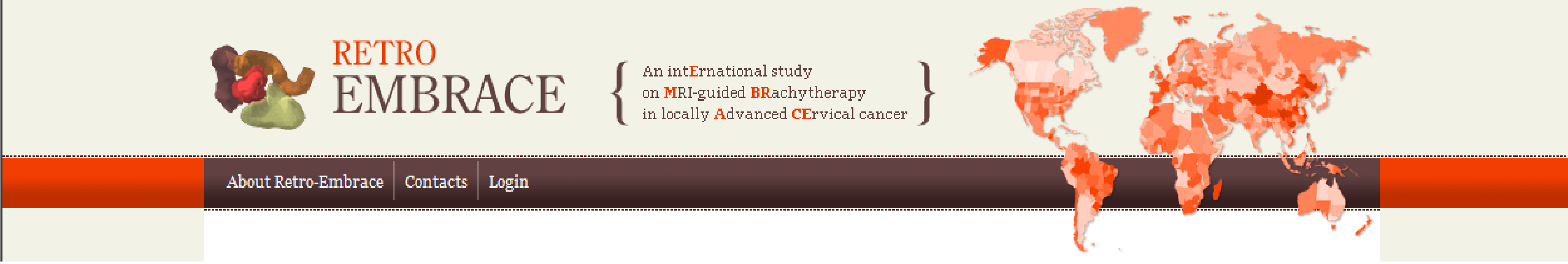
D90 for the HR-CTV and probability of local control



HR CTV D90 ≥ 86 Gy$_{EQD2(\alpha/\beta 10)}$

≥ 90% local control

Dimopoulos et al., R&O 2010 *Dimopoulos et al. IJROBP 2008*



- 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

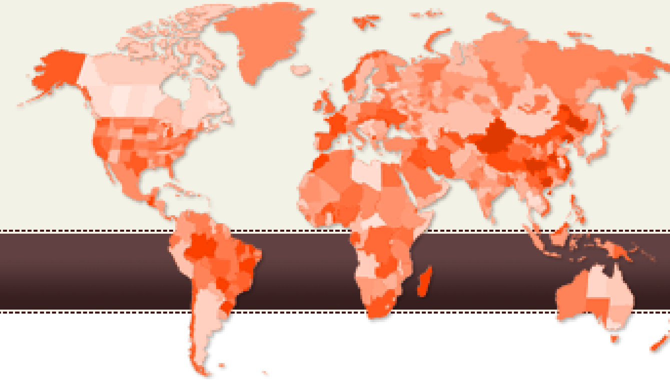
VARIAN medical systems | A partner for life

Nucletron Improving patient care

EMBRACE

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

About Embrace | Contacts | Participation | Login

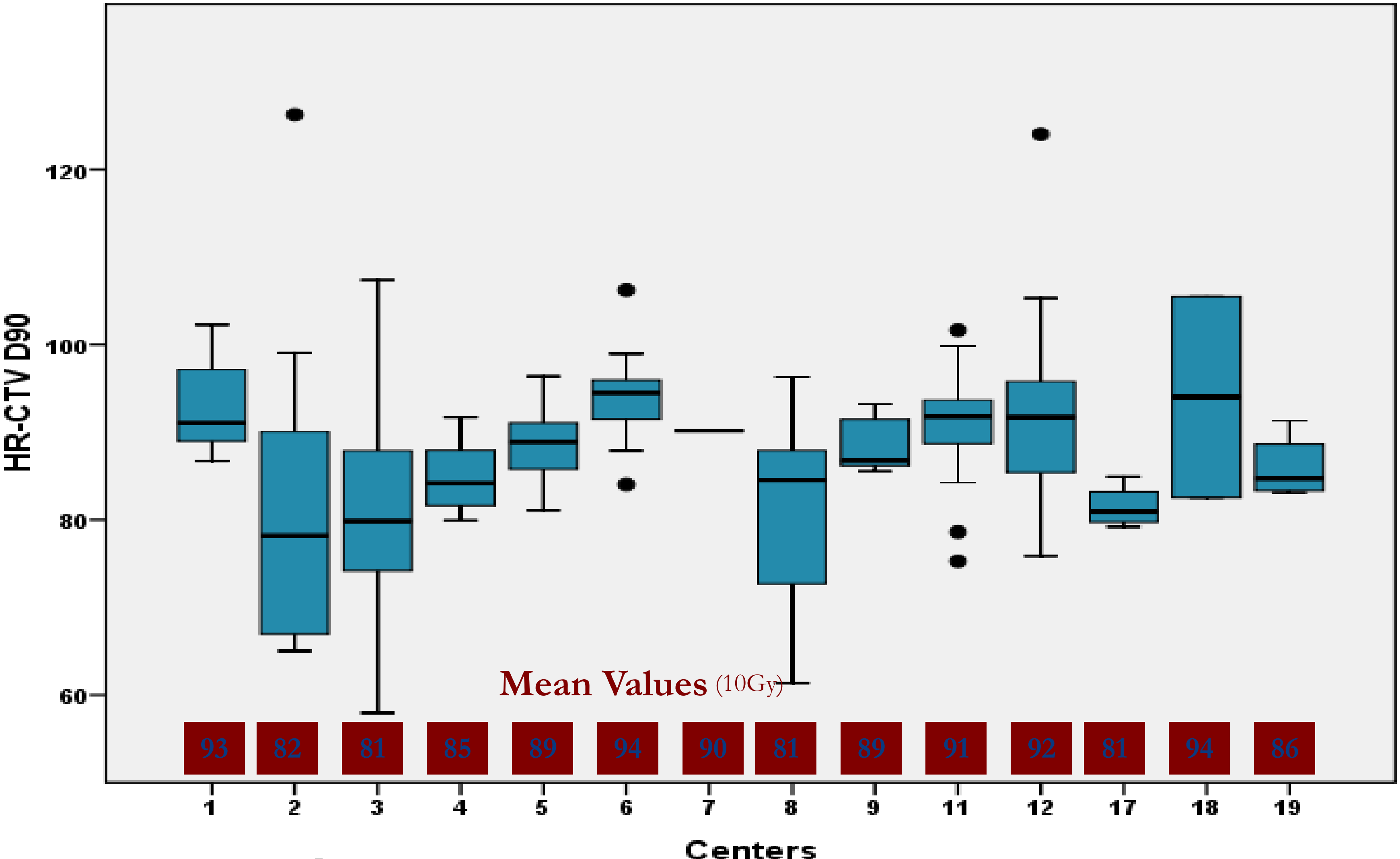


- **EMBRACE - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer**
- **A prospective observational multi-centre trial**
- **Major endpoint: local control;**
- **multiple hypotheses on dose volume effects**
- **Enrollment of patients 7/2008-12/2015, 1416 pts accrued**

VARIAN medical systems | A partner for life

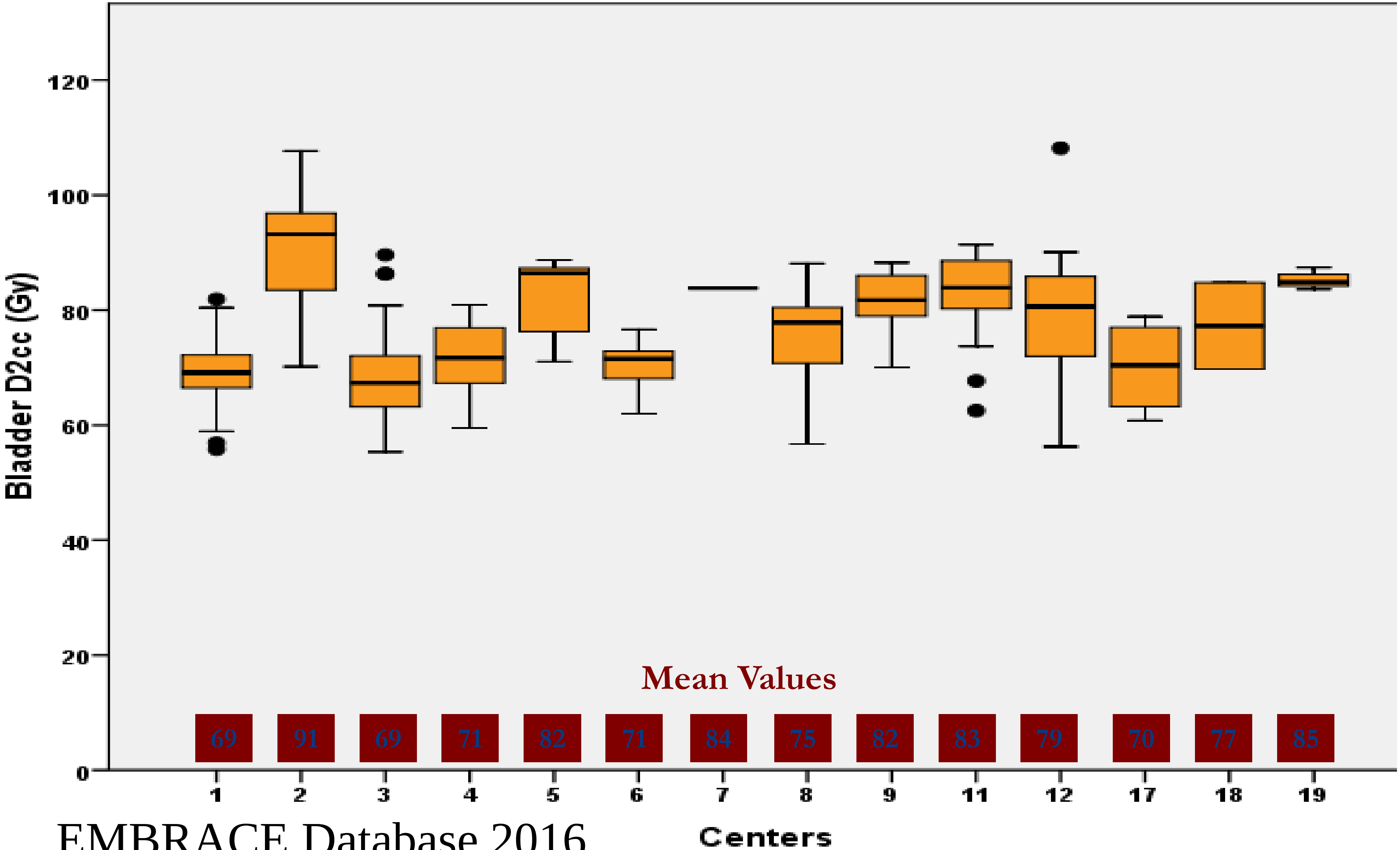
Nucletron Improving patient care

Heterogeneity of dose prescription: HRCTV D90



EMBRACE Database 2016

Heterogeneity of dose prescription: Bladder D2cc



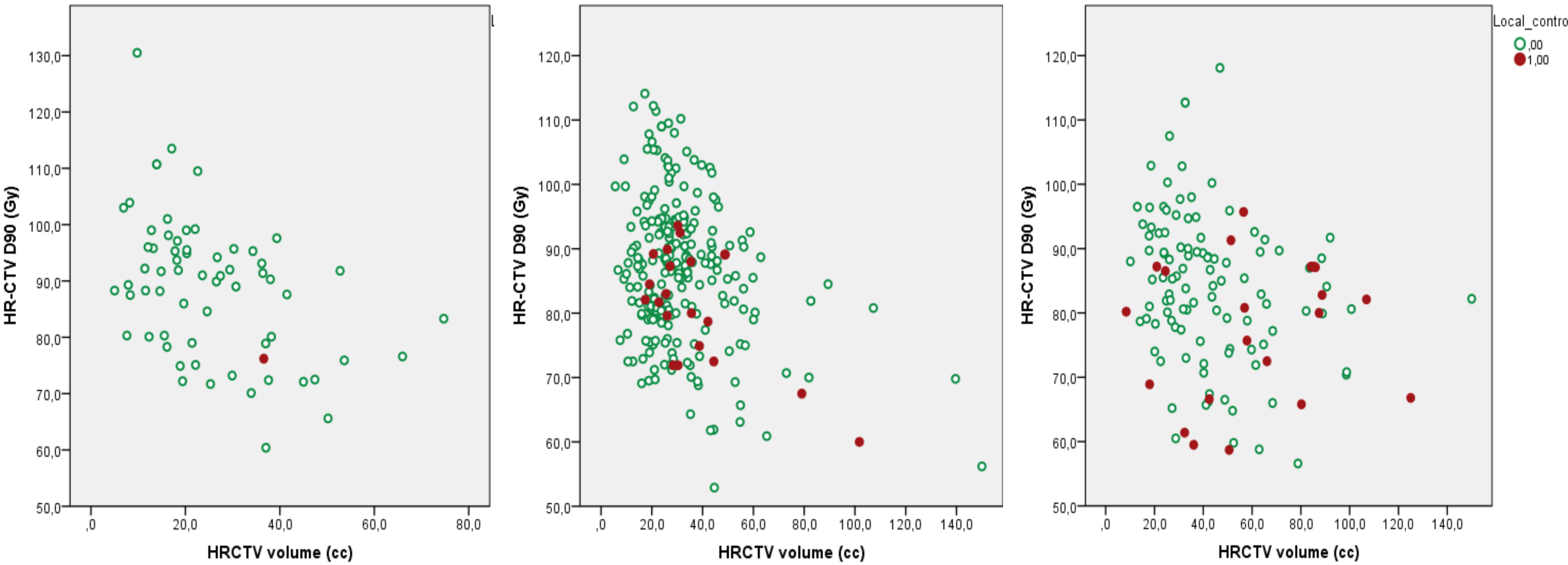
EMBRACE Database 2016

Recurrences according to dose and volume

Stage I

Stage II

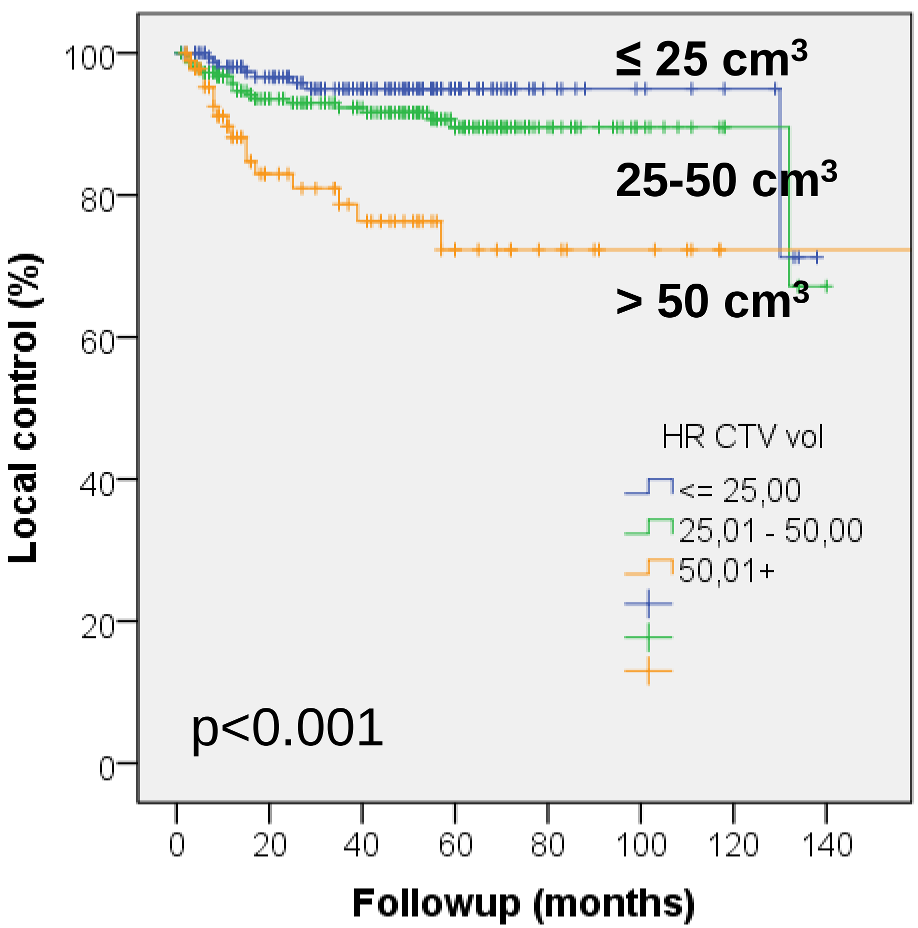
Stage III+IV



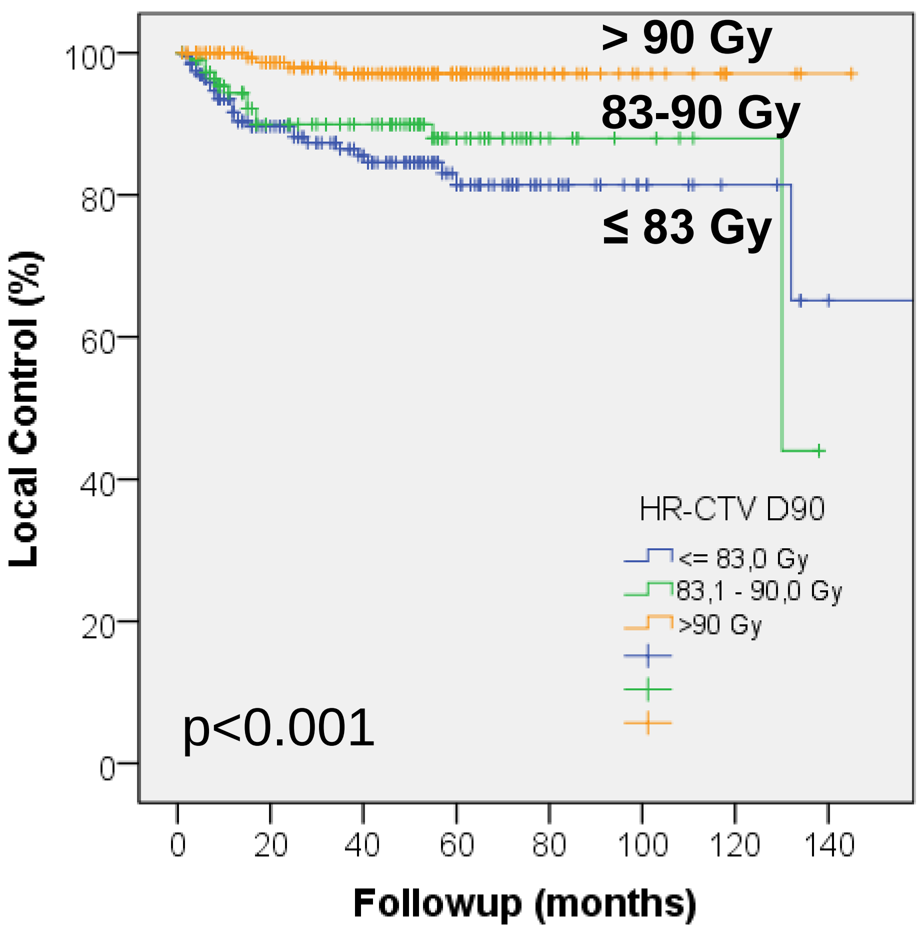
Tanderup et al. Radiotherapy and Oncology 2016

Actuarial local control: univariate analysis separate for HR CTV volume and dose

CTV_{HR} volume



CTV_{HR} dose



Tanderup et al 2015

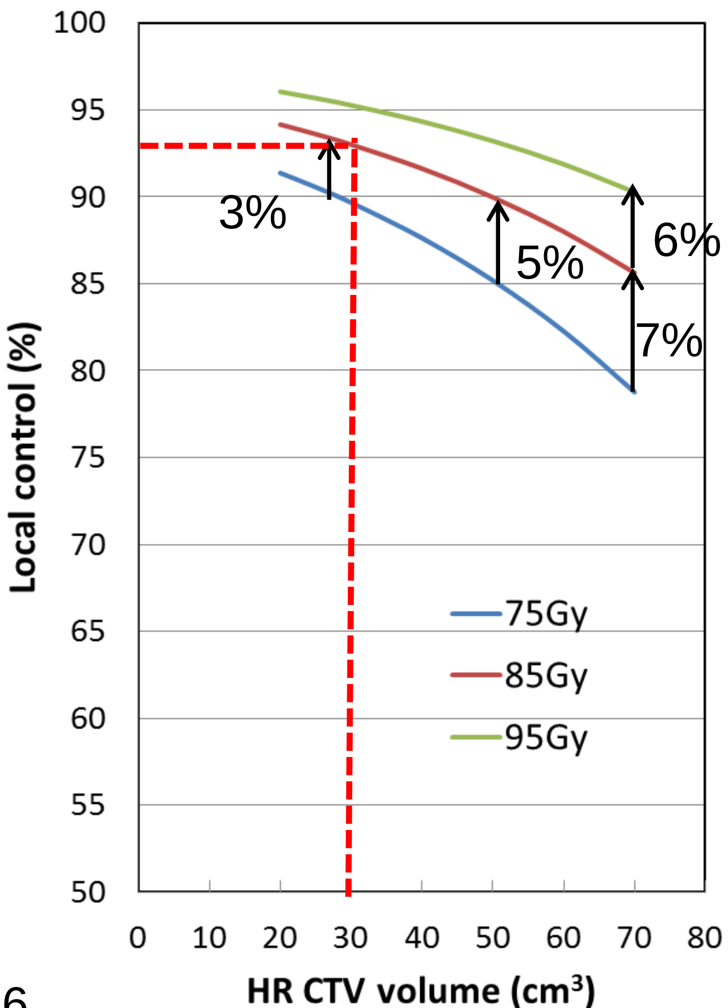
Dose, volume, and time effect

Effect of dose, volume and time:

Dose: 10Gy → 5% LC
Time: 7 days ~ 5Gy
Volume $10cm^3$ ~ 5Gy

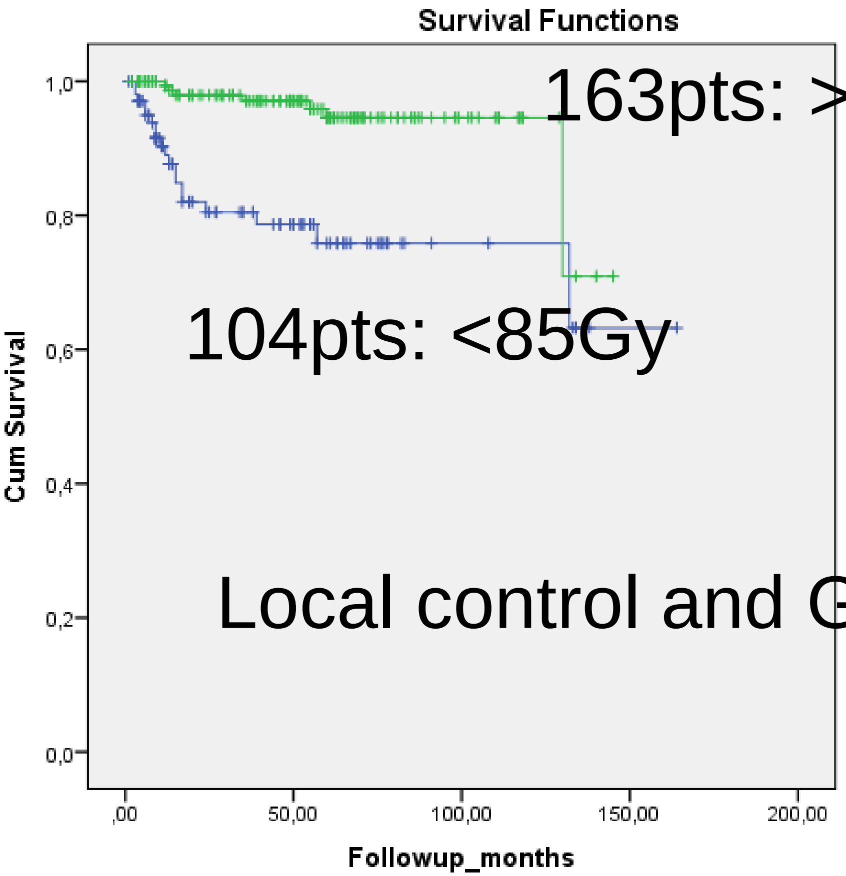
85Gy for $30cm^3$ CTV_{HR}: 93% LC

Local control at 3 years



Tanderup et al, Radiotherapy and Oncology 2016

Dose volume response for GTV

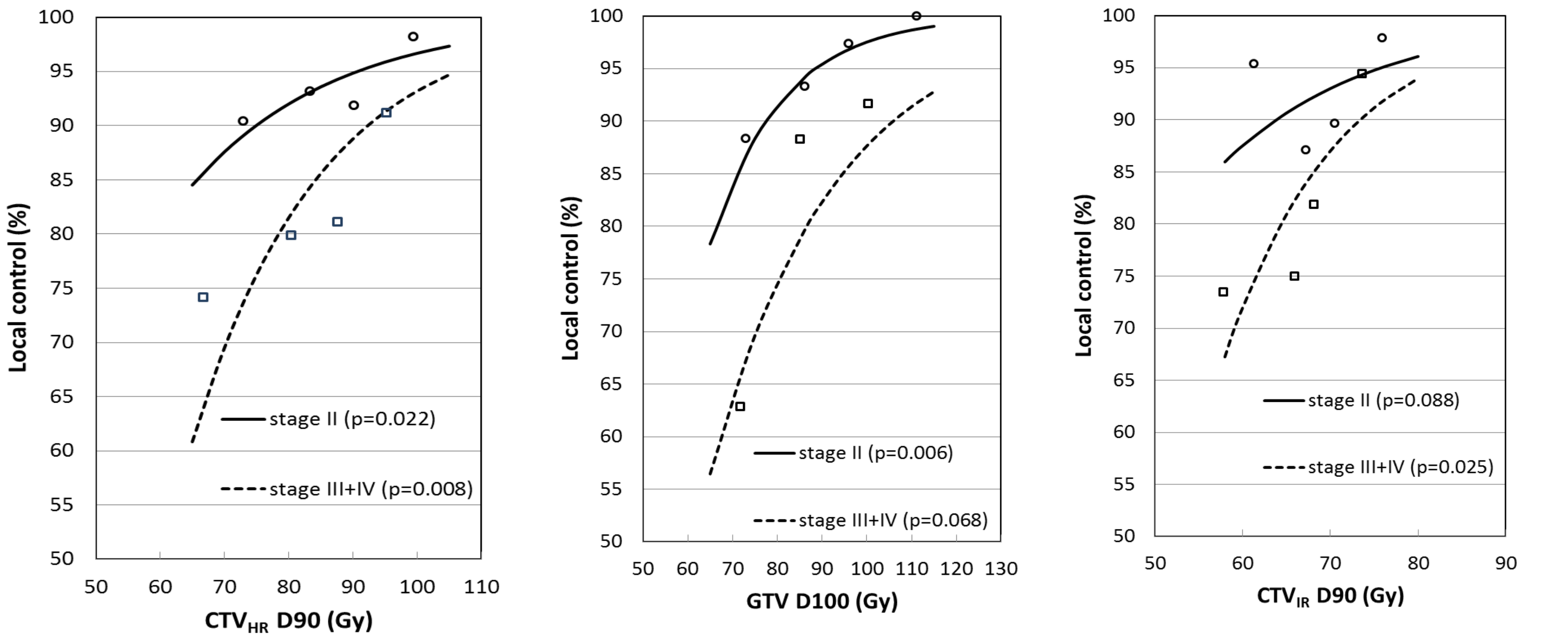


Local control and GTV dose

Tanderup 2015
Preparation for EMBRACE II

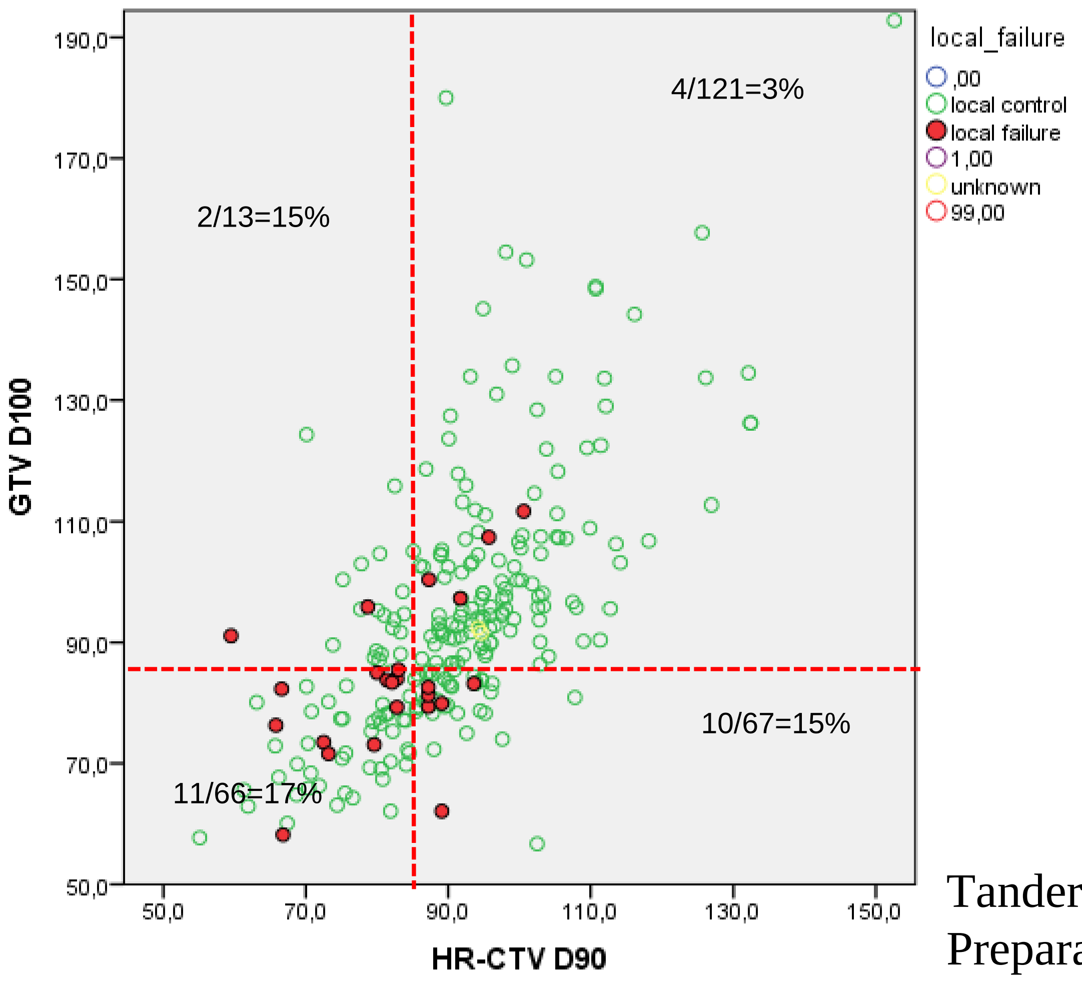
Dose effect GTV, CTV_{HR} and CTV_{IR}

Stage-related analysis



Tanderup et al. Radiotherapy and Oncology 2016

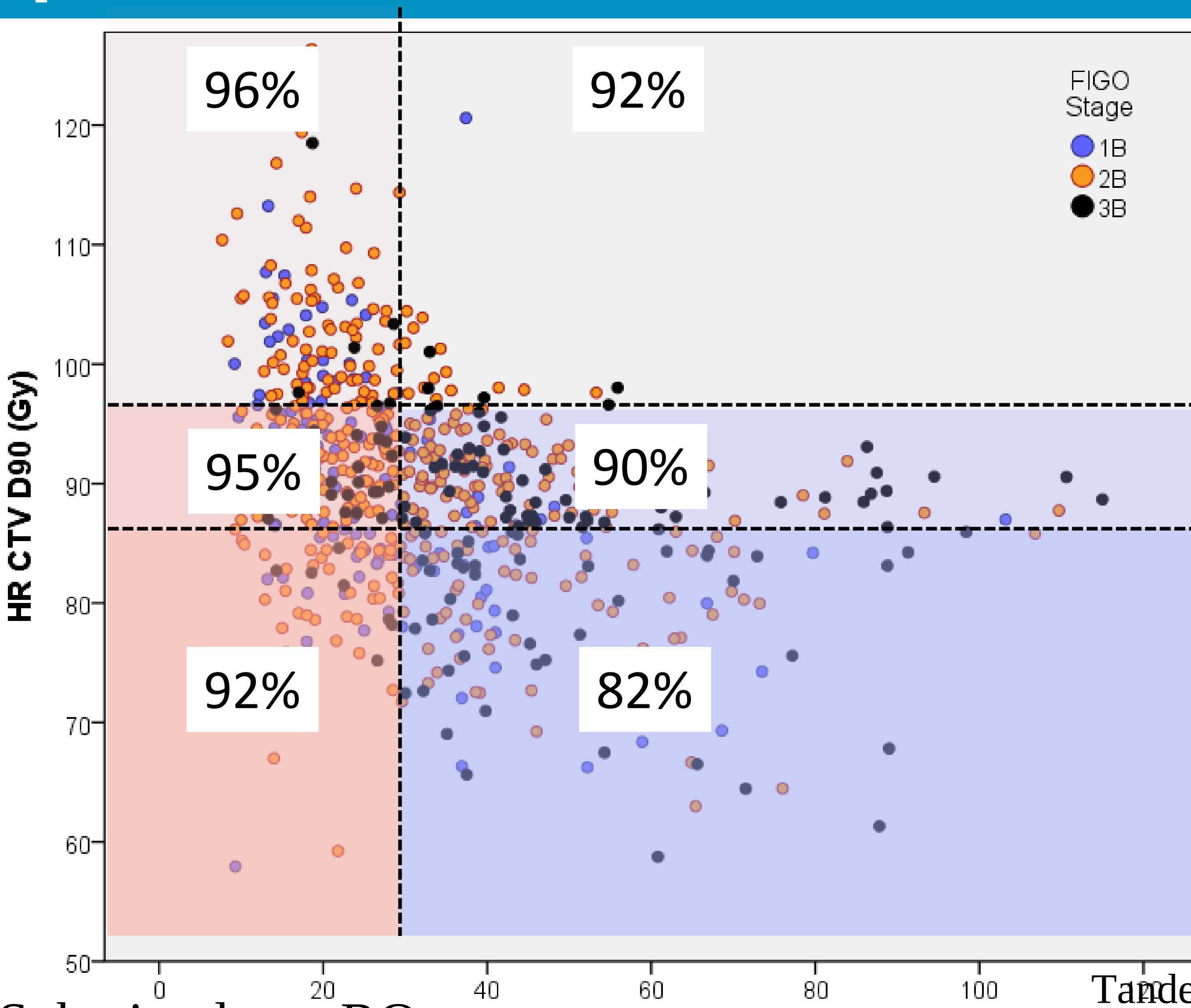
Combined constraints for GTV and CTV_{HR}



Tanderup 2015
Preparation for EMBRACE II

Practice in EMBRACE I and predicted local control from RetroEMBRACE

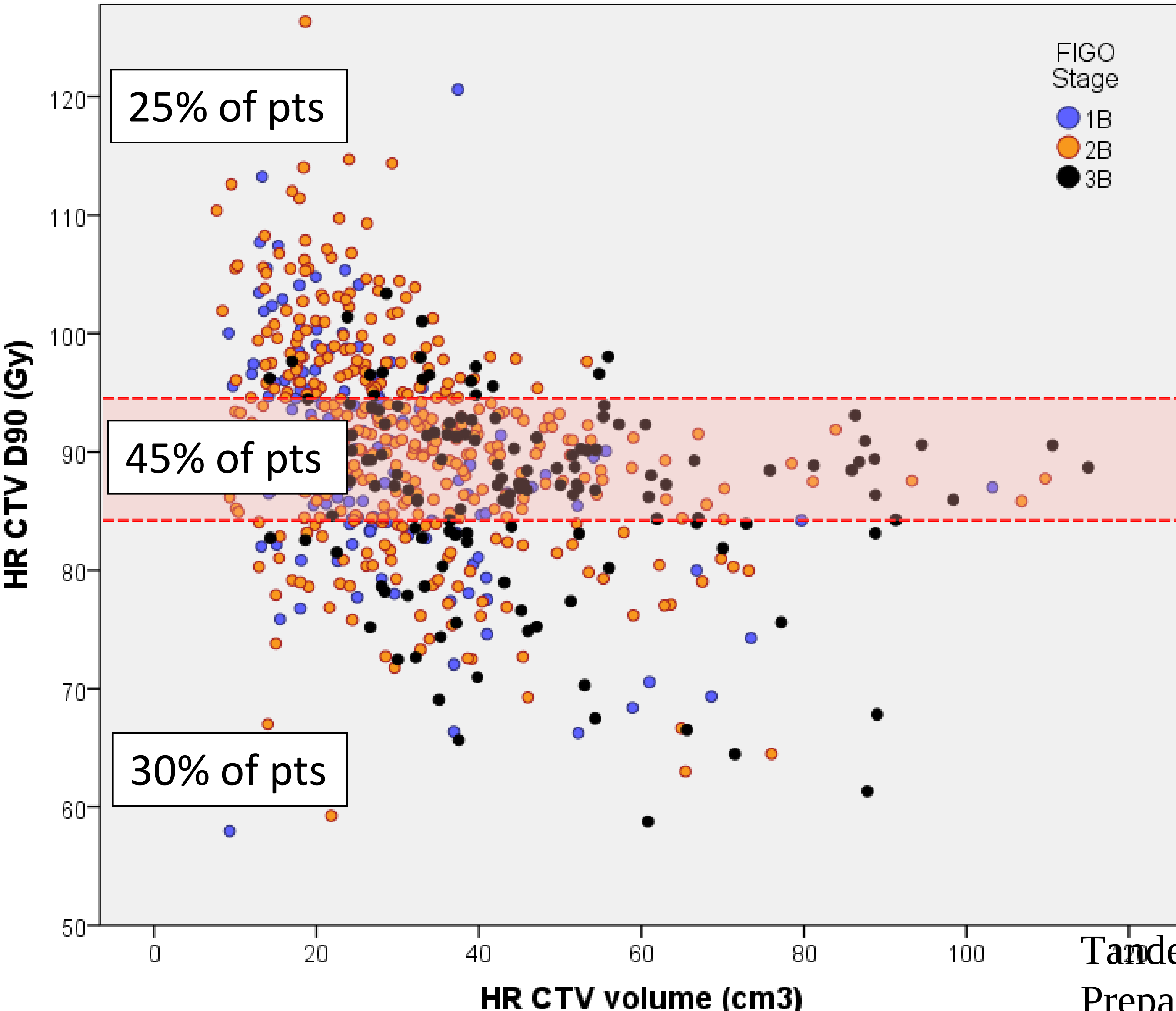
769 pts EMBRACE



Submitted to ctRO

Tanderup 2015
Preparation for EMBRACE II

EMBRACE I practice

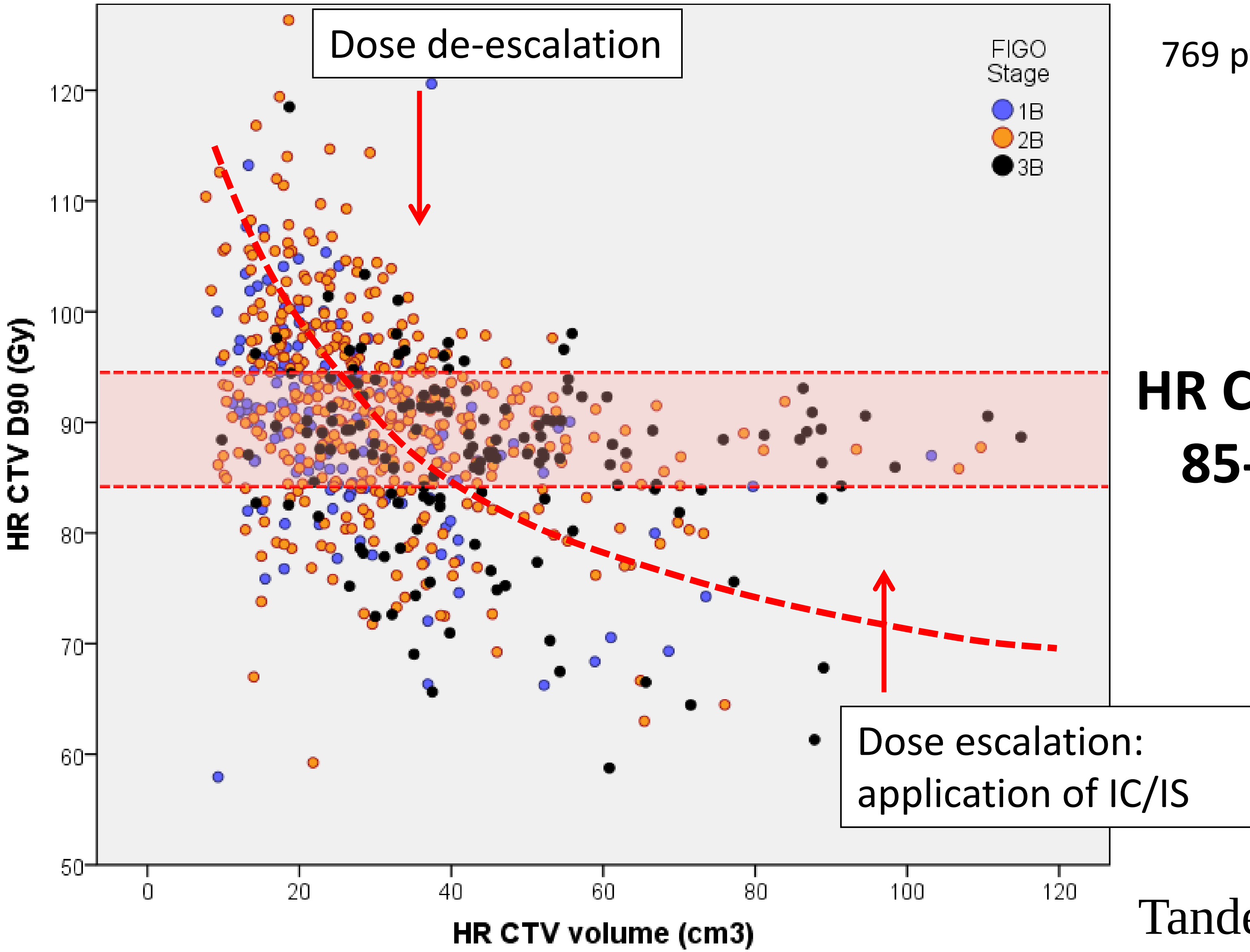


769 pts EMBRACE

HR CTV D90 85-95Gy

Tanderup 2015
Preparation for EMBRACE II

EMBRACE II dose prescription

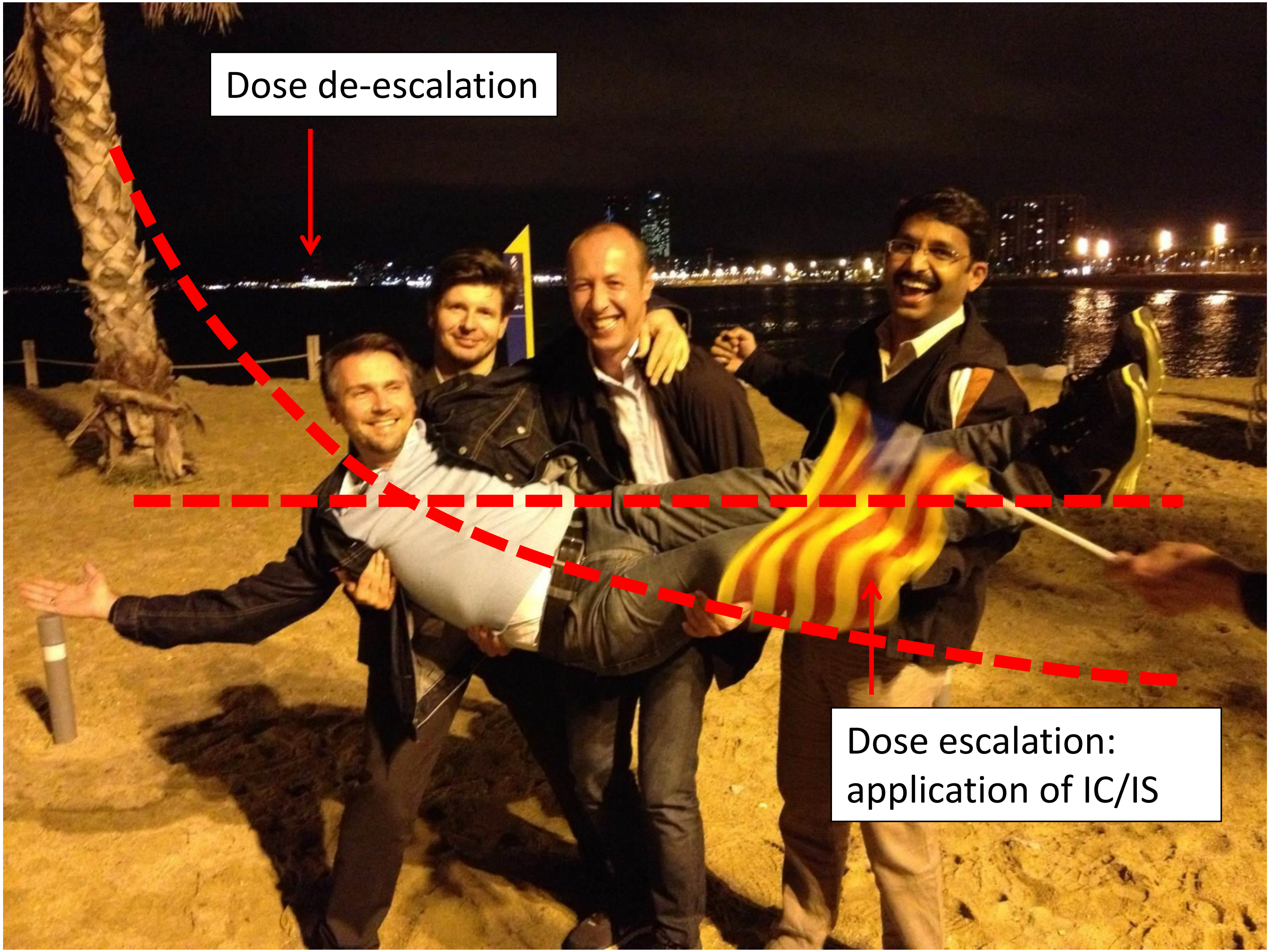


769 pts EMBRACE

HR CTV D90 85-95Gy

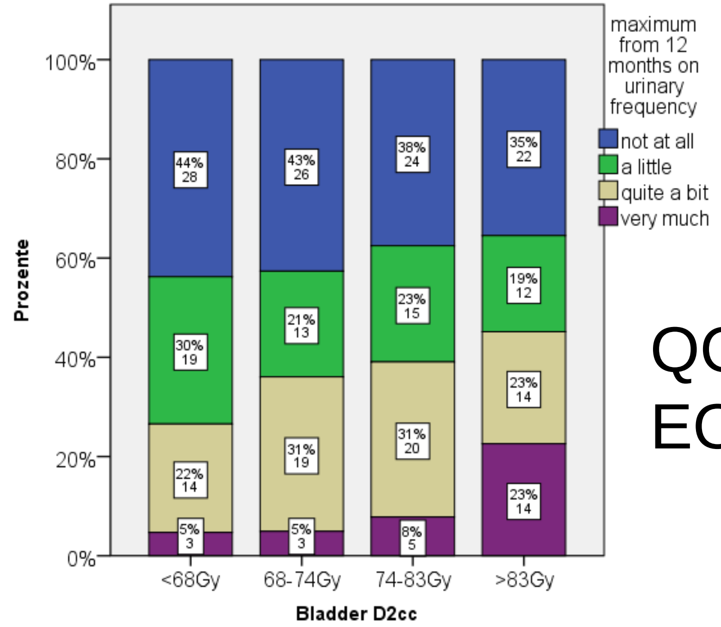
Tanderup 2015

Beach boy approach – Barcelona 2013

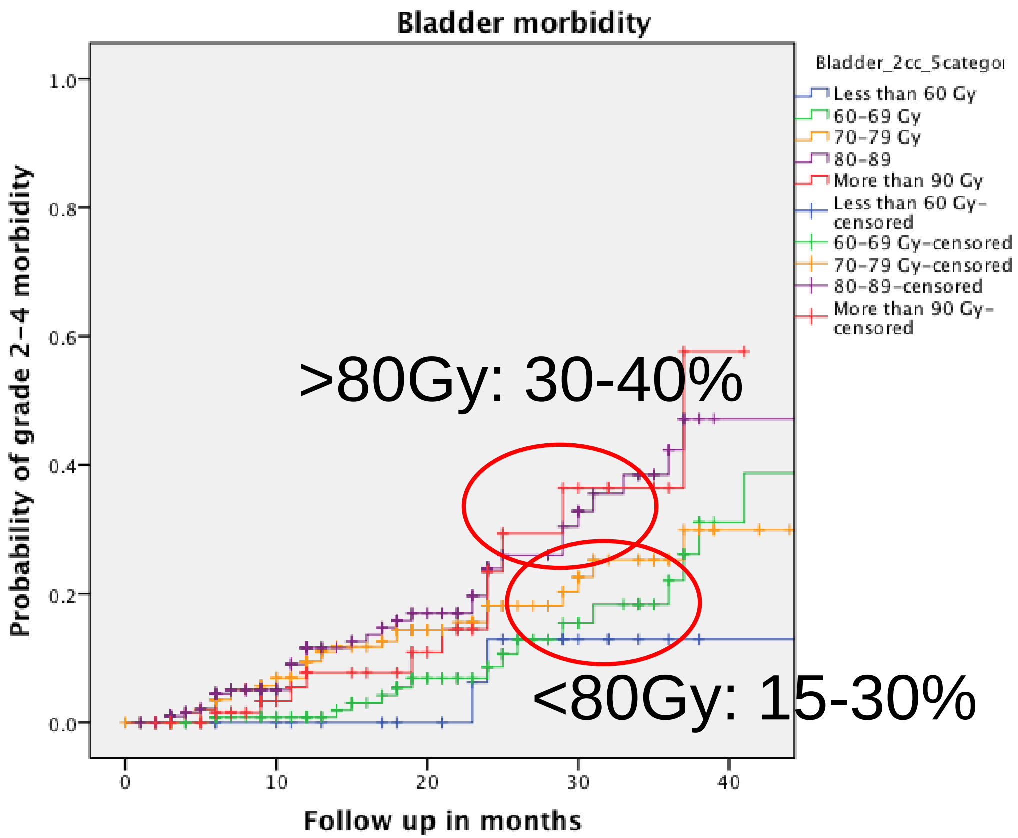


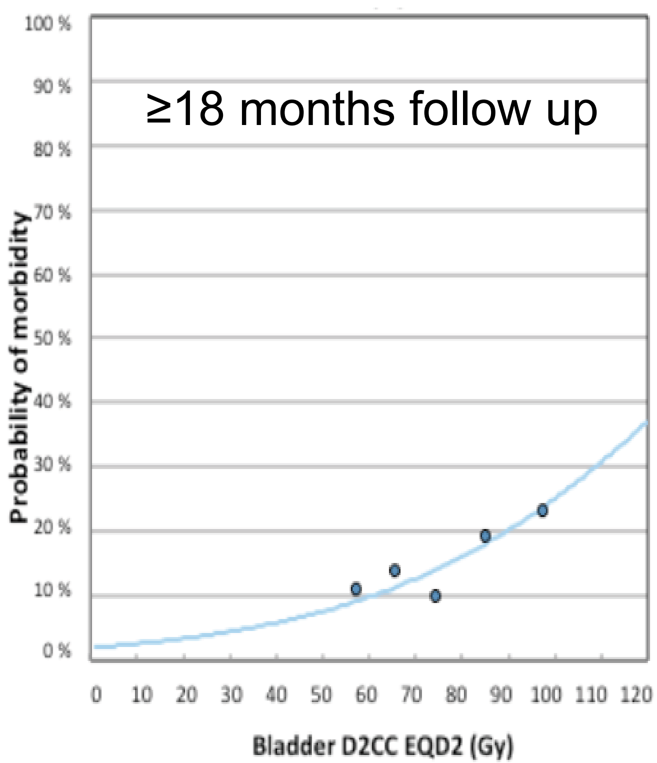
Bladder D_{2cm3}

- **EMBRACE CTCAE**
- **All endpoints except ureter stenosis G≥2**



QOL
EORTC

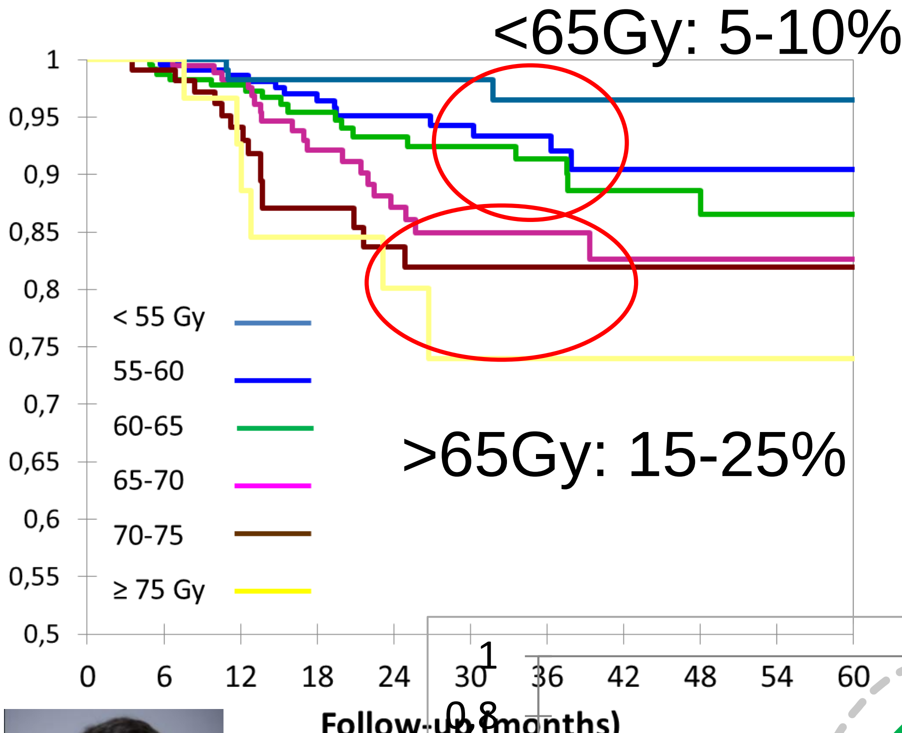




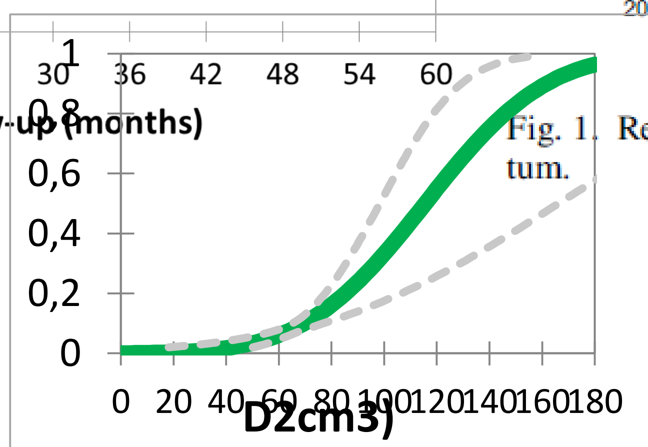
Fokdal et al 2015

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)

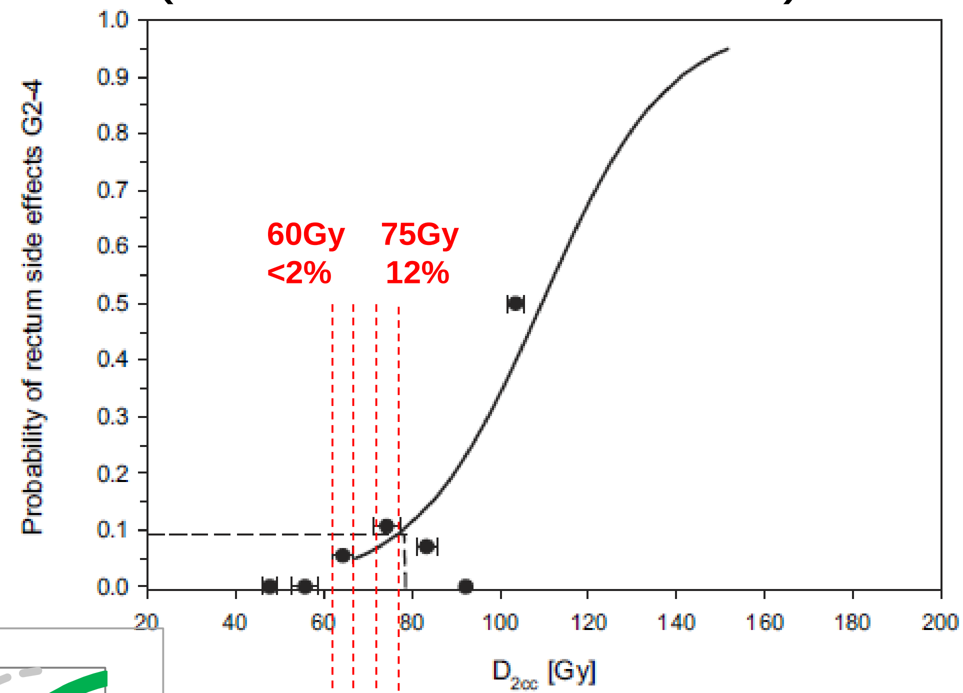
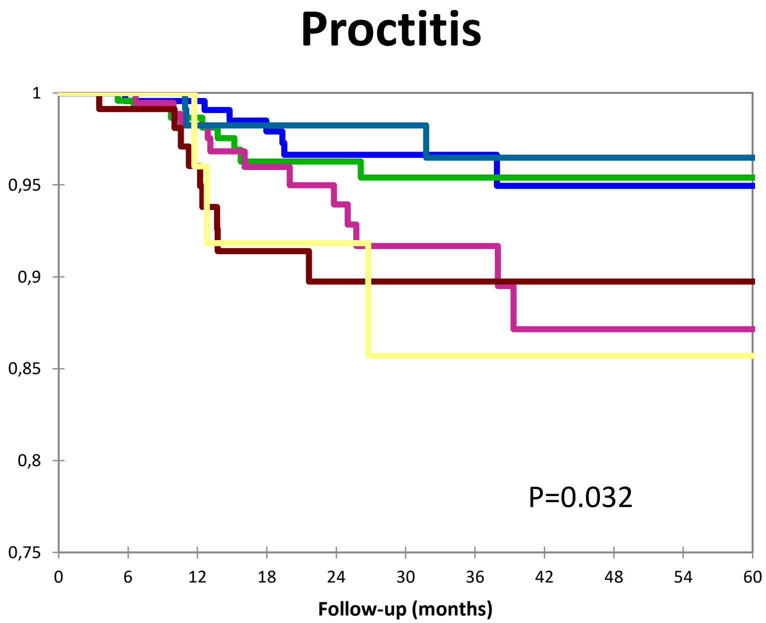
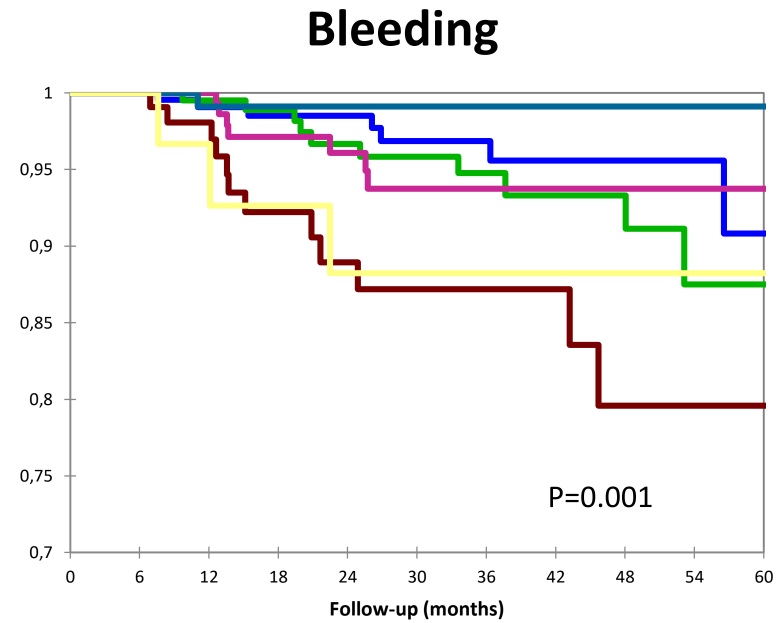


Fig. 1. Relationship between D_{2cc} and late side effects in the rectum.

P. Georg et al.,
IJROBP 2011





dose effects for different endpoints for rectal morbidity EMBRACE (n=960)

< 55 Gy

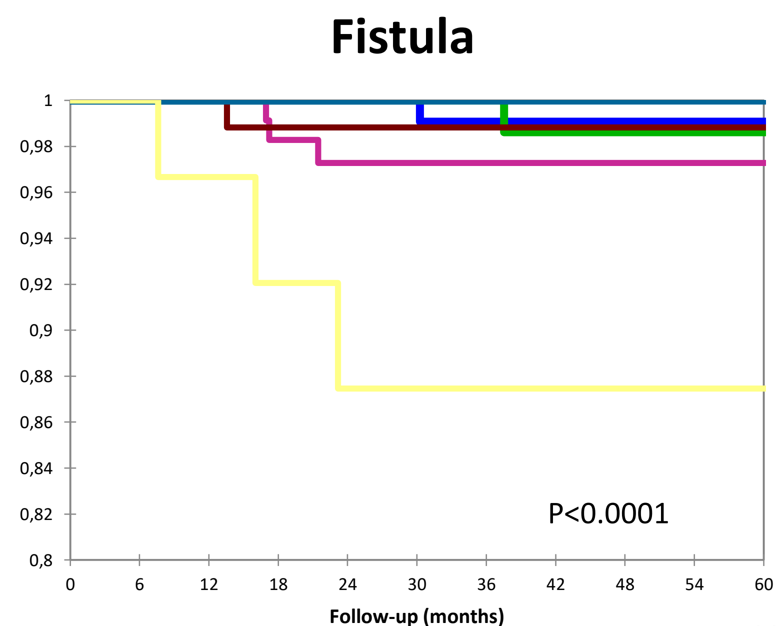
55-60

60-65

65-70

70-75

≥ 75 Gy

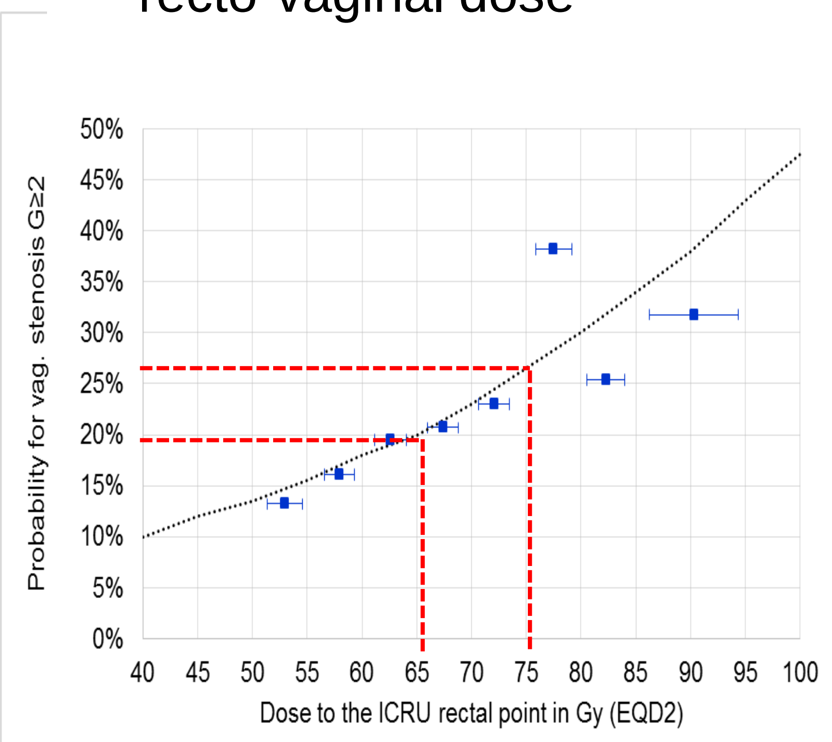


Mazeron et al, RadiothOncol 2016

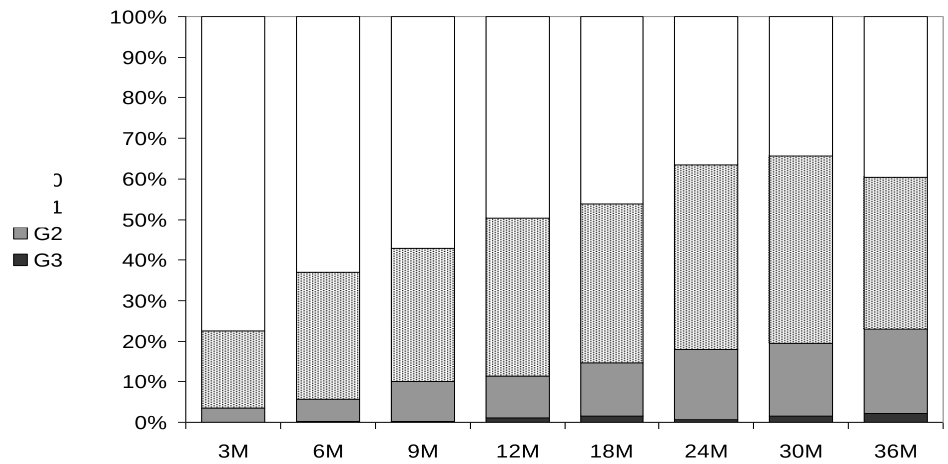
Vaginal stenosis and ICRU recto-vaginal point (630 pts)

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



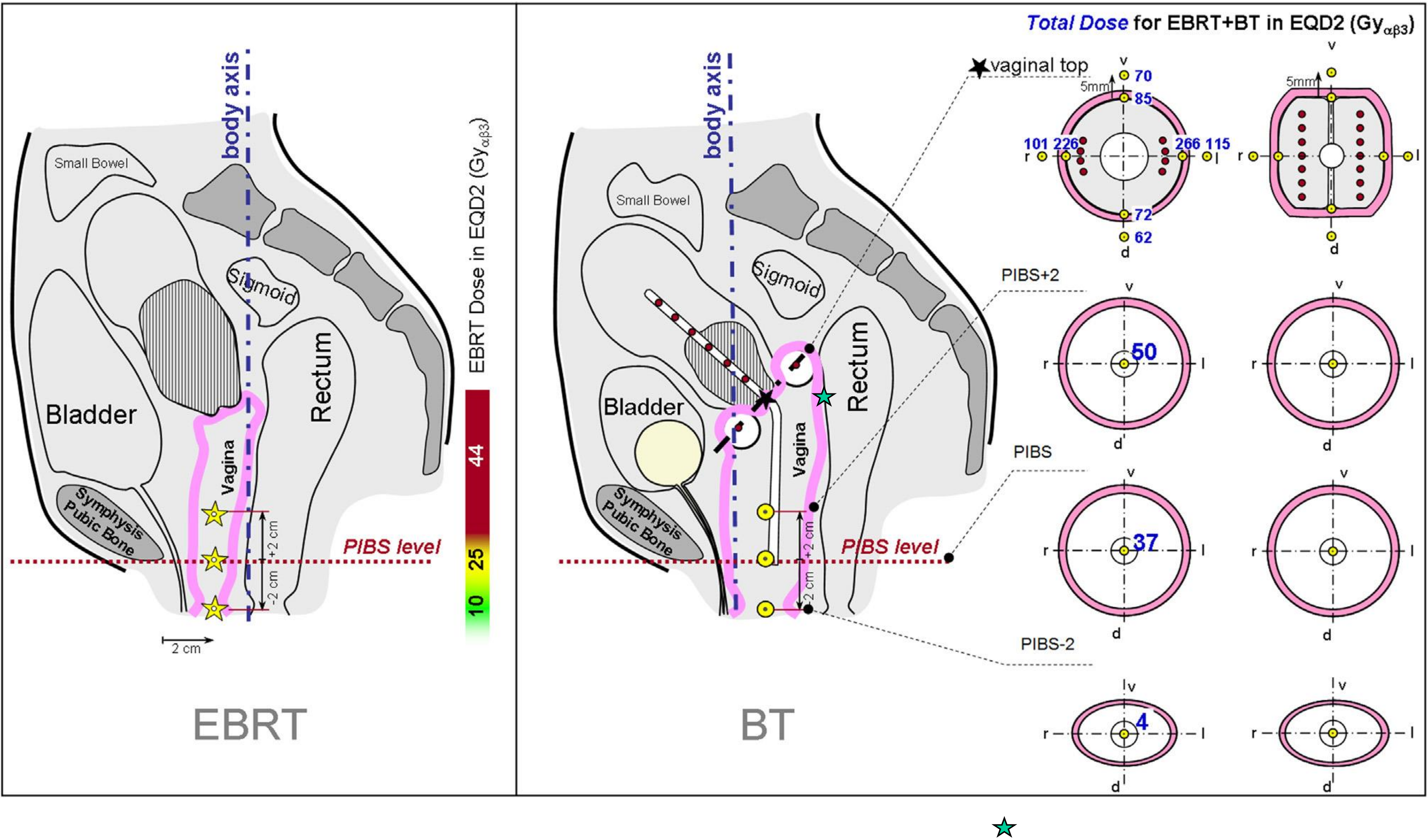
Prevalence vaginal stenosis



Kirchheiner K et al.Manifestation pattern of early-late vaginal morbidity. IJROBP 2014 May 1;89(1):88-95

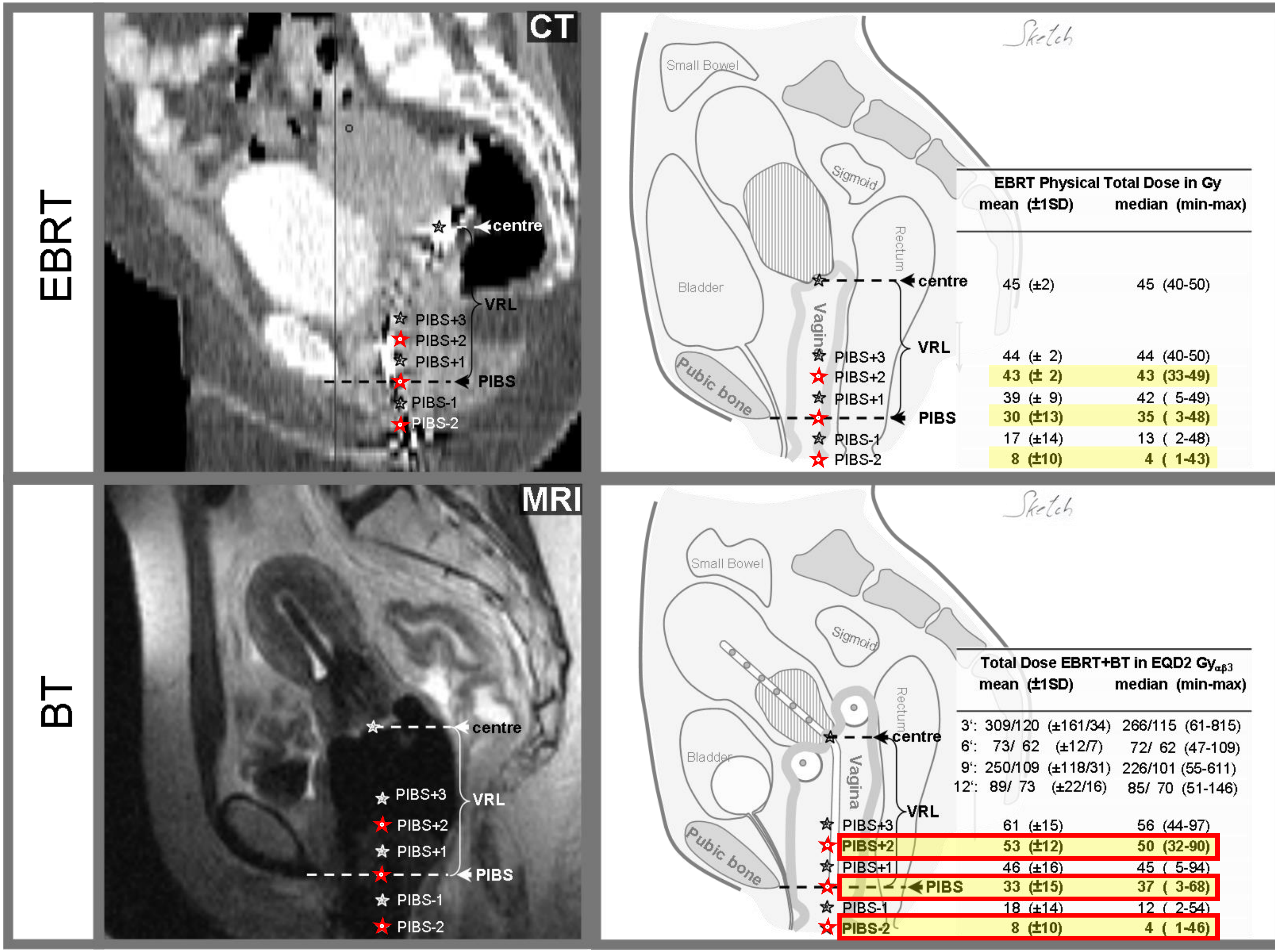
K Kirchheiner et al, EMBRACE data MUW/AUH, RadiothOncol 2016

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

Image guided brachytherapy in cervical cancer

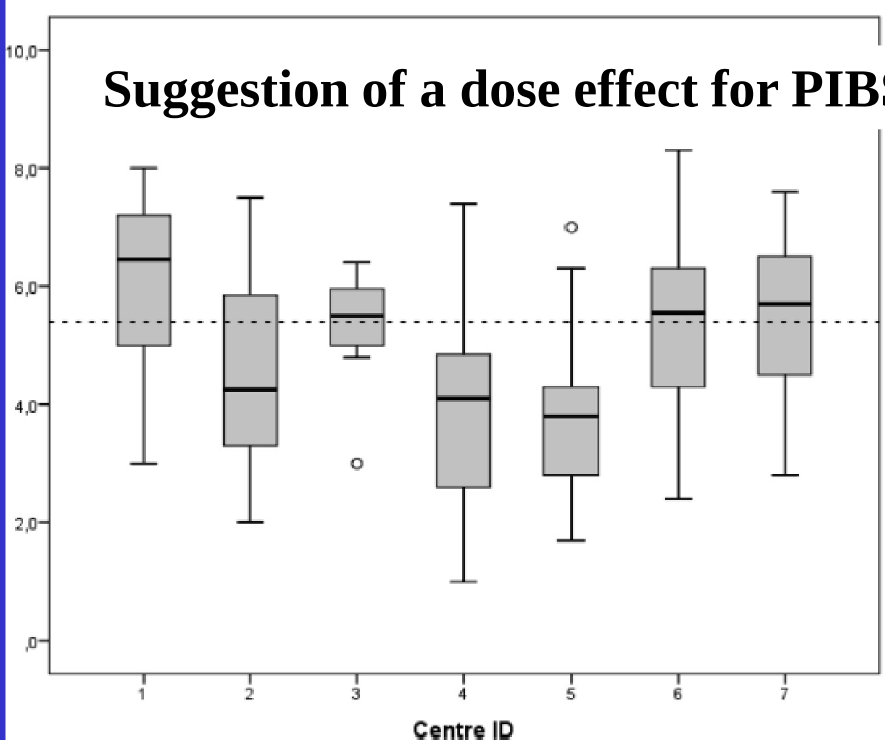
Multicentre evaluation of a novel vaginal dose reporting method in 153 cervical cancer patients

Henrike Westerveld [a,b,*], Astrid de Leeuw [c], Kathrin Kirchheiner [b], Pittaya Dankulchai [d], Bernard Oosterveld [e], Arun Oinam [f], Robert Hudej [g], Jamema Swamidas [h], Jacob Lindegaard [i], Kari Tanderup [i], Richard Pötter [b,j], Christian Kirisits [b,j], the EMBRACE Collaborative Group

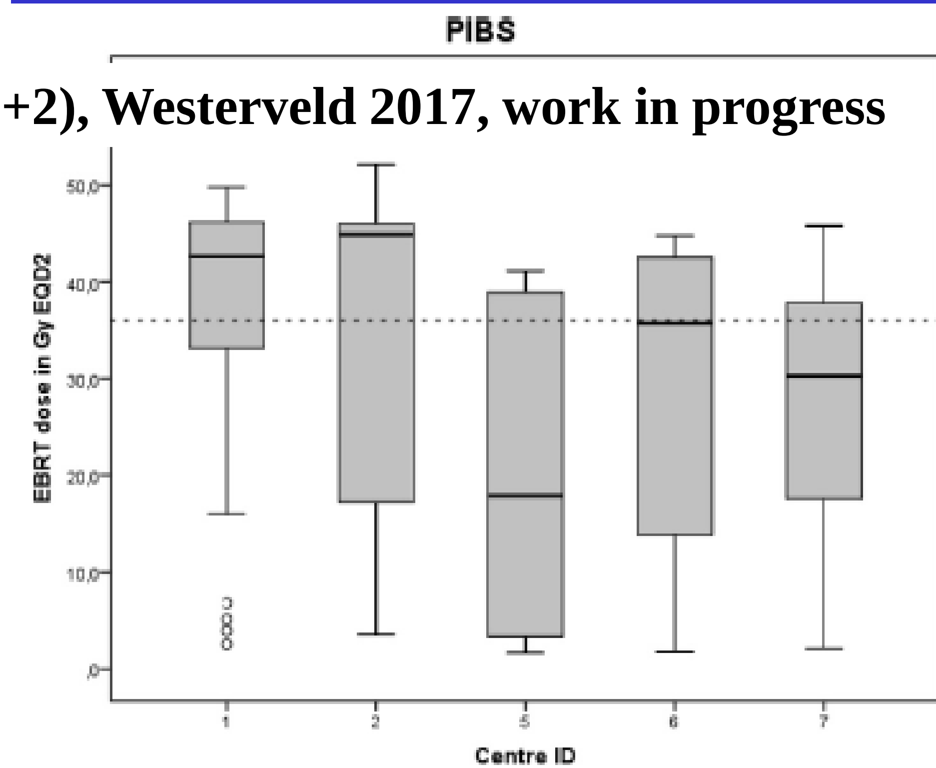
[a] *Department of Radiotherapy, Academic Medical Centre, University of Amsterdam, The Netherlands;* [b] *Department of Radiation Oncology, Comprehensive Cancer Centre, Medical University of Vienna, Austria;* [c] *Department of Radiation Oncology, University Medical Centre Utrecht, The Netherlands;* [d] *Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand;* [e] *Department of Radiation Oncology, Radiotherapiegroep, Arnhem, The Netherlands;* [f] *Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research, Chandigarh, India;* [g] *Department of Radiotherapy, Institute of Oncology Ljubljana, Slovenia;* [h] *Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India;* [i] *Department of Oncology, Aarhus University Hospital, Denmark; and* [j] *Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Austria*

Radioth and Oncol 2016

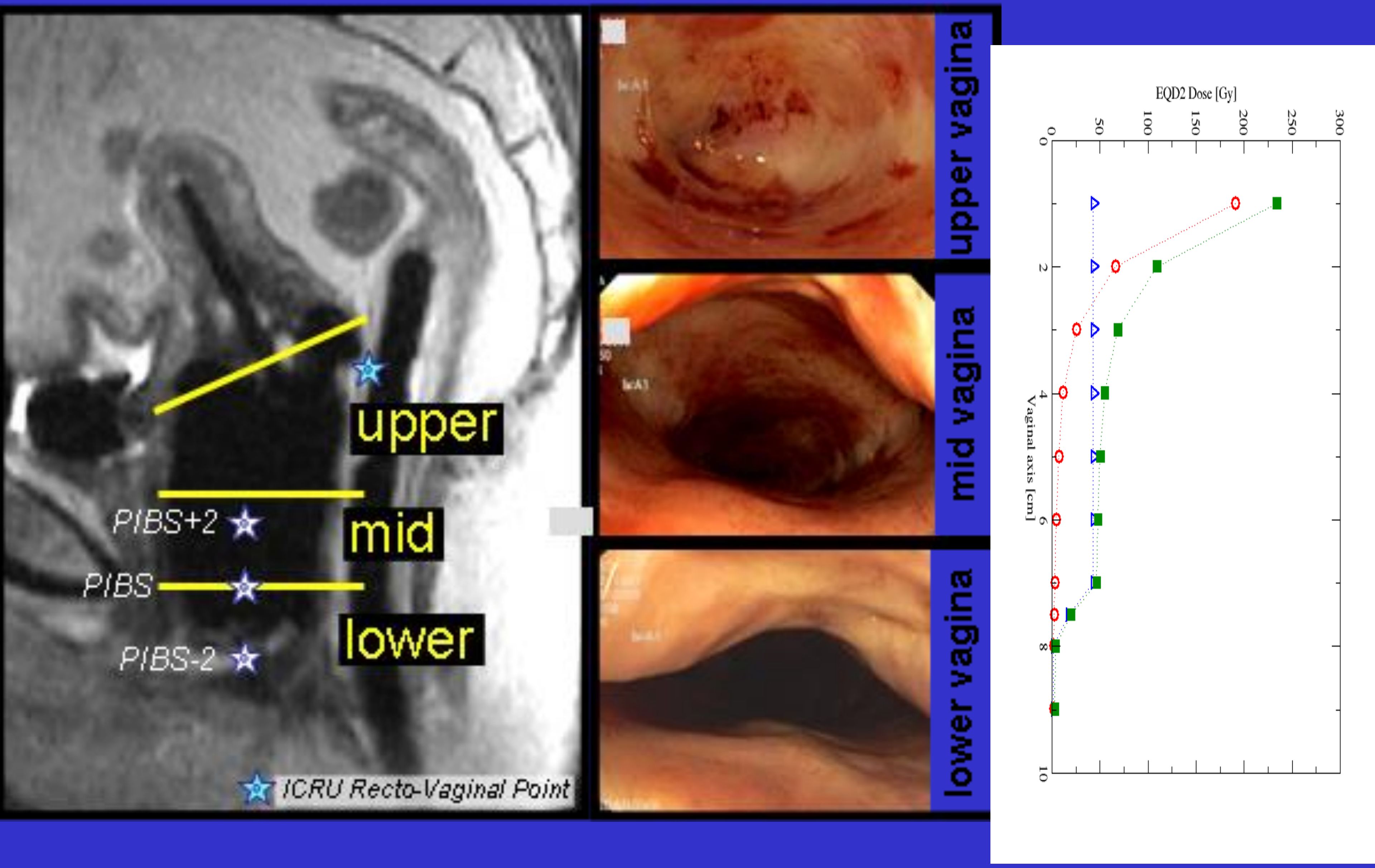
Suggestion of a dose effect for PIBS(+2), Westerveld 2017, work in progress



ginal reference length (VRL) in cm per centre. The dotted line represents the median length of the entire cohort.



Vaginal morbidity and radiation doses

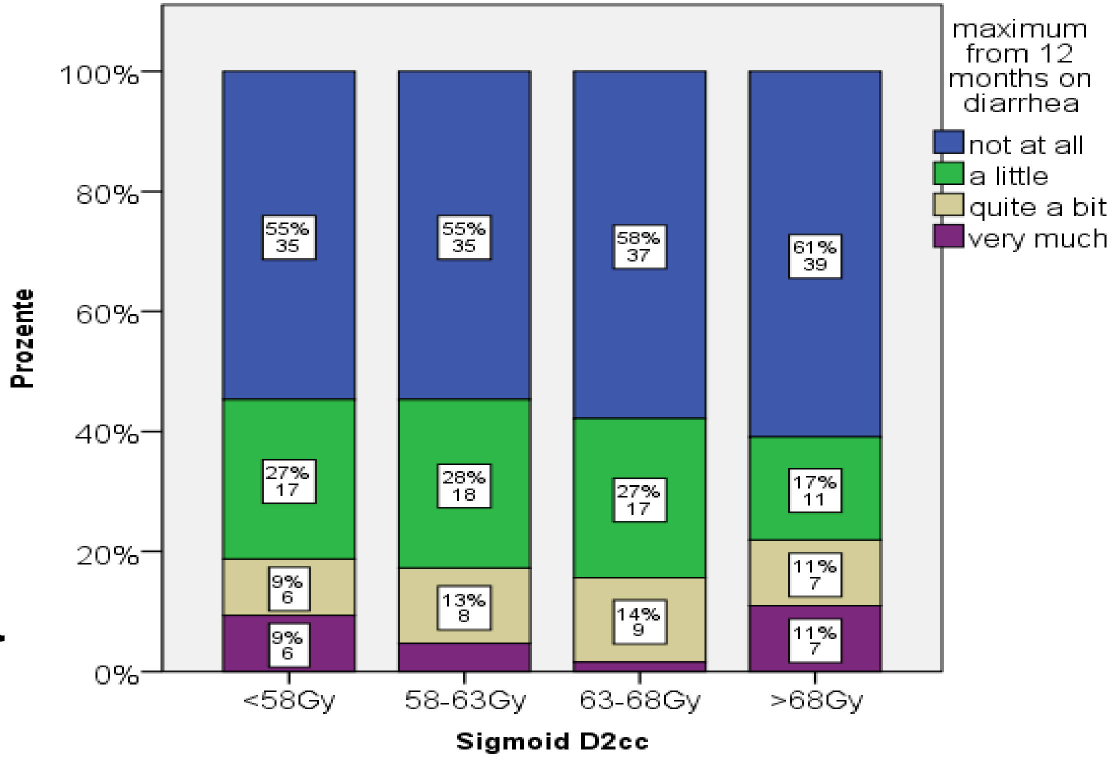


ICRU/GEC ESTRO Report 89 Fig. 6.1/Fig. 8.11

Sigmoid D_{2cm3}, preliminary data (2015)

- **No dose effect established – (so far)**

Diarrhea

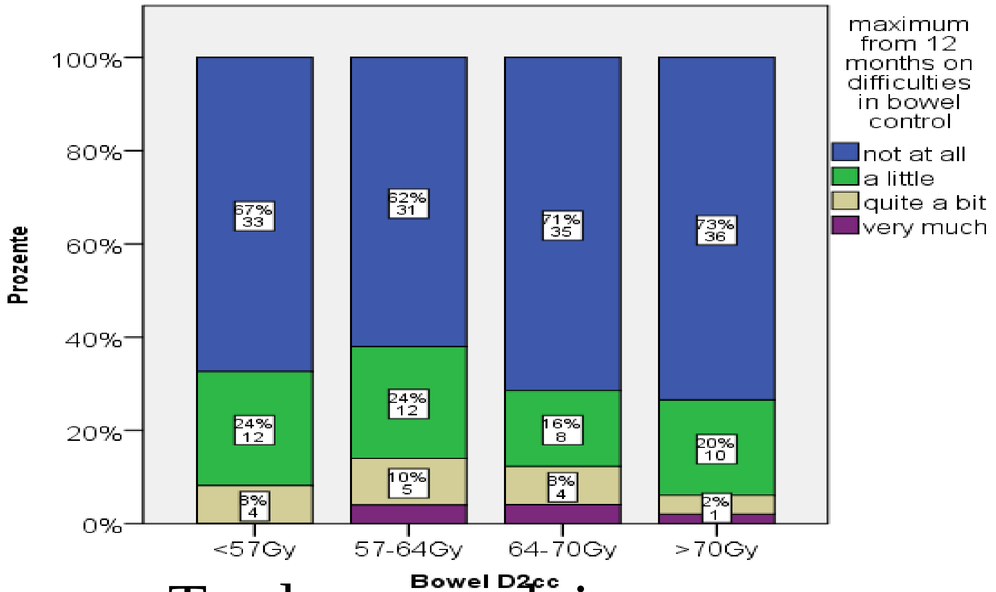


Bowel D_{2cm3}, and EBRT preliminary data

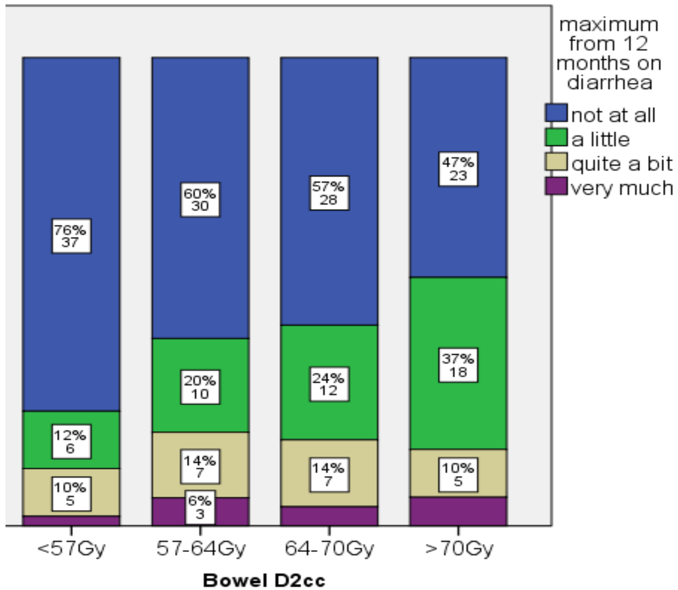
- **dose effect likely to become established for diarrhea**

2 cm³ (BT) and EBRT: dose (45/50Gy), boost, PA RT

Bowel control



Diarrhea

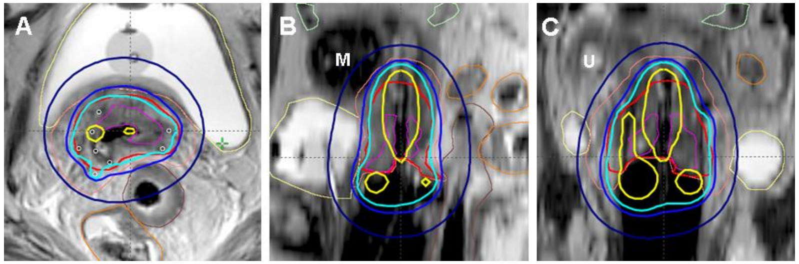


Jensen, Tanderup work in progress

Planning aim and prescription dose

- **Planning aim: what you want to obtain**
- **Prescribed dose: what you decide to treat**

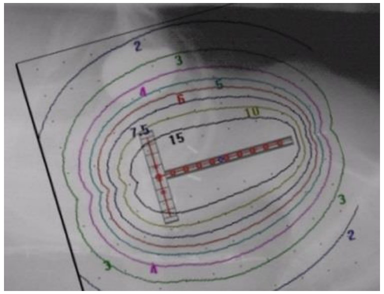
Example 1



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	$\leq$ 7Gy	6.8 Gy
Rectum	ICRU point	$\leq$ 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 (+2): 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

Physics aspects of treatment planning intracavitary +/- interstitial techniques in cervix cancer

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

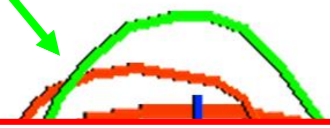
Prague 2017

Kari Tanderup, PhD

Aarhus University Hospital

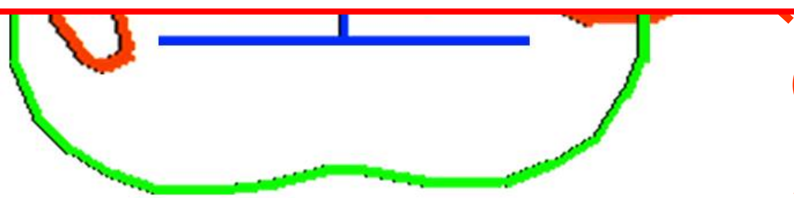
Limitation of point A and standard loading pattern

Point A isodose



Minimum HR-CTV dose relative to point A:

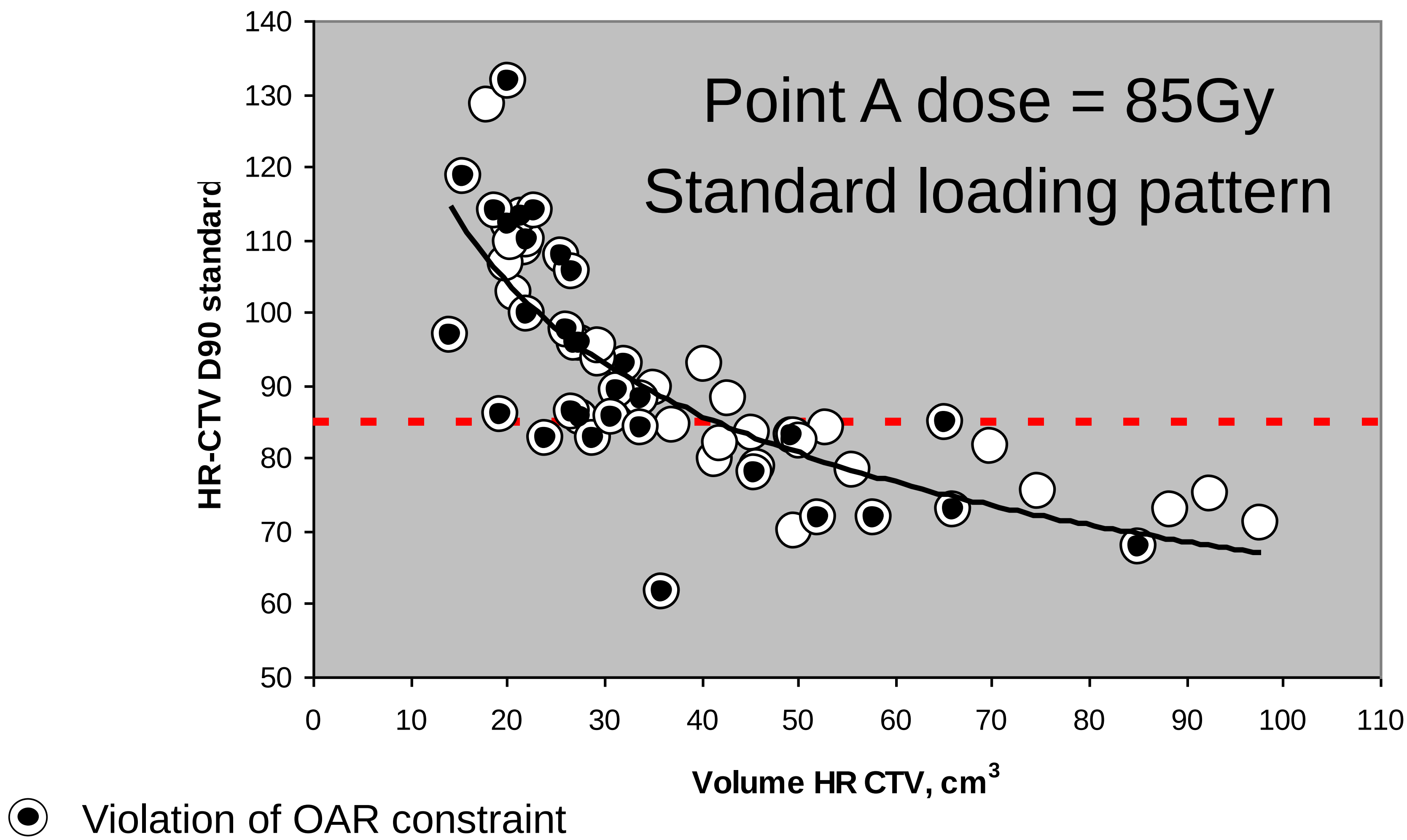
POINT A DOSE IS NOT A GOOD SURROGATE FOR TARGET DOSE



CTV's assessed from MRI

5 pt's

Limitation of standard loading pattern with dose prescription to point A



K Tanderup et al, Radiother Oncol 2010

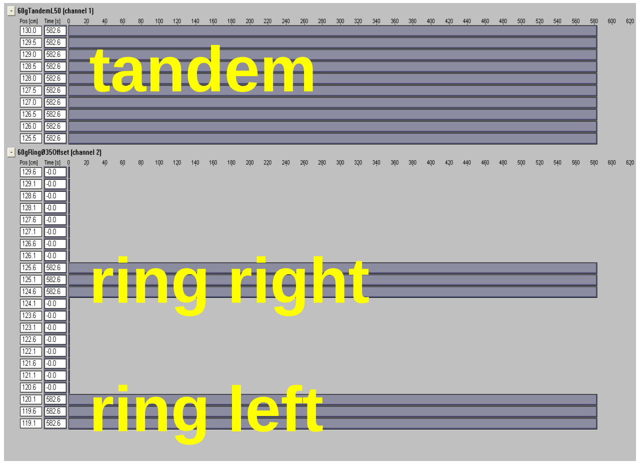
Tools for dose optimisation

- Manual dose optimisation
- Graphical optimization / Dose shaper
- Inverse planning

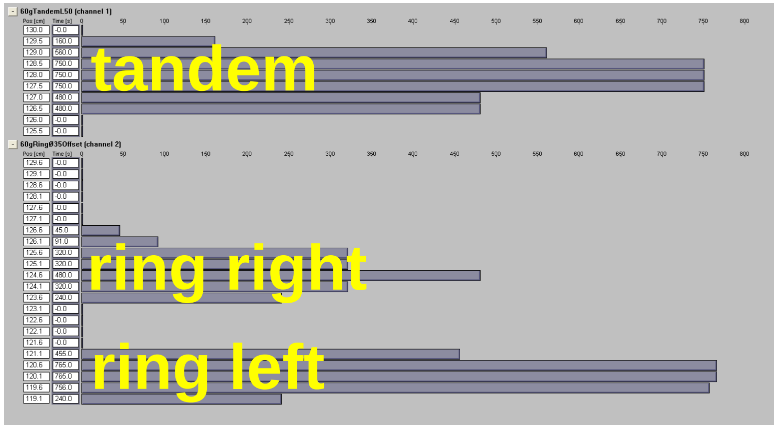
Manual optimisation

Dwell times

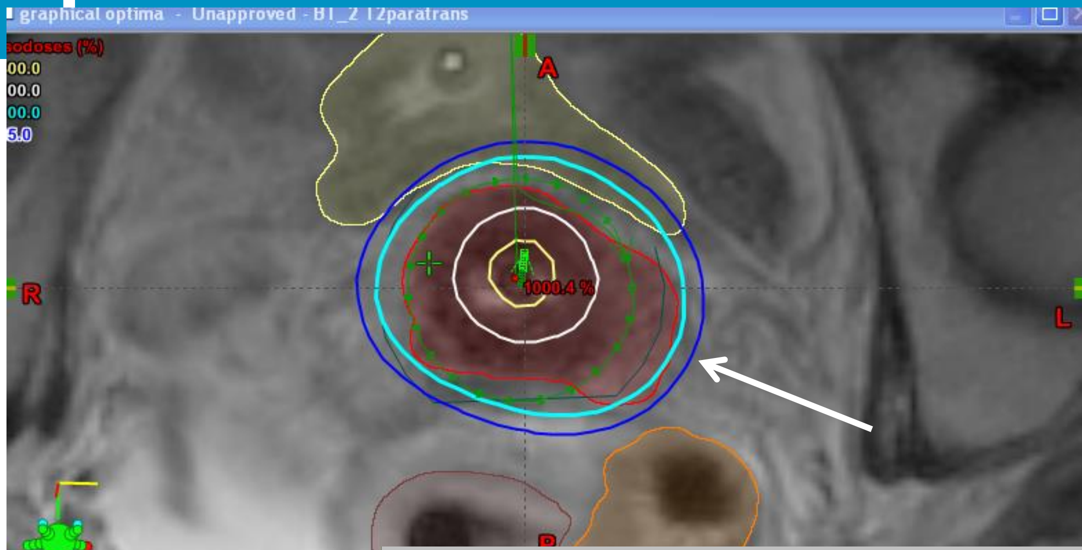
Standard

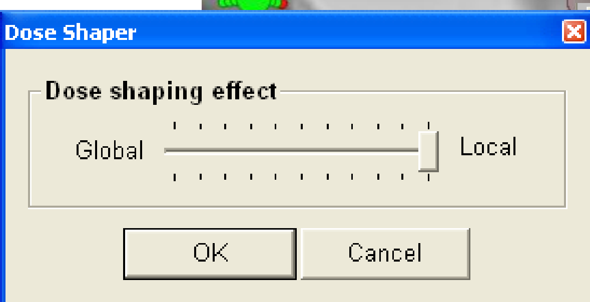


Manually optimised

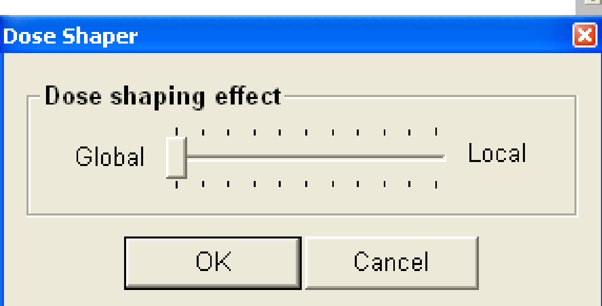


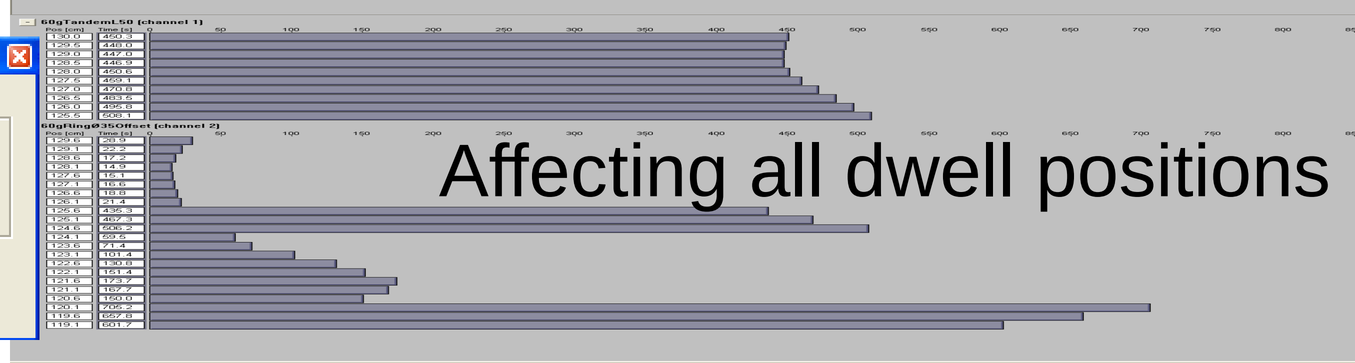
Graphical dose optimisation – “drag and drop”





Affecting nearby dwell positions

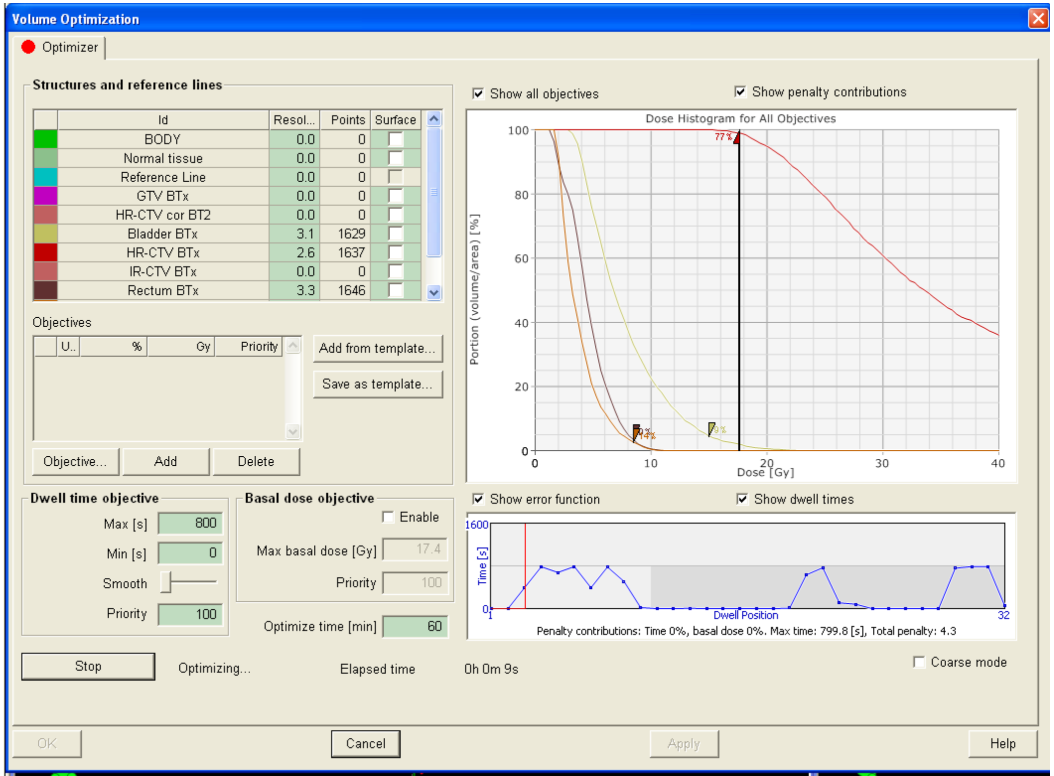




Affecting all dwell positions

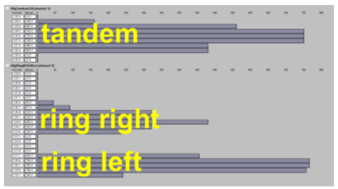
Inverse dose optimisation

- **Controlled by DVH constraints**
- **Weighting factors for different structures**



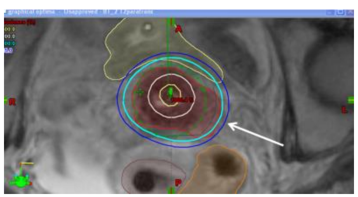
Which type do you prefer?

A. From scratch: manual



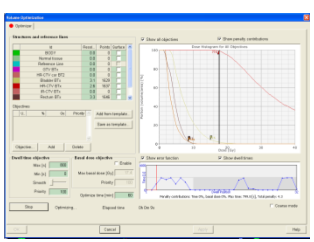
COOKED FROM SCRATCH

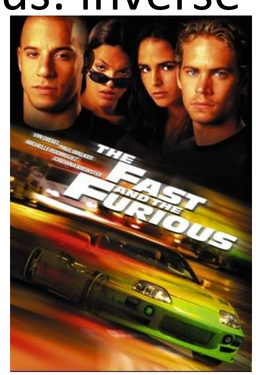
B. Elegant: drag and drop

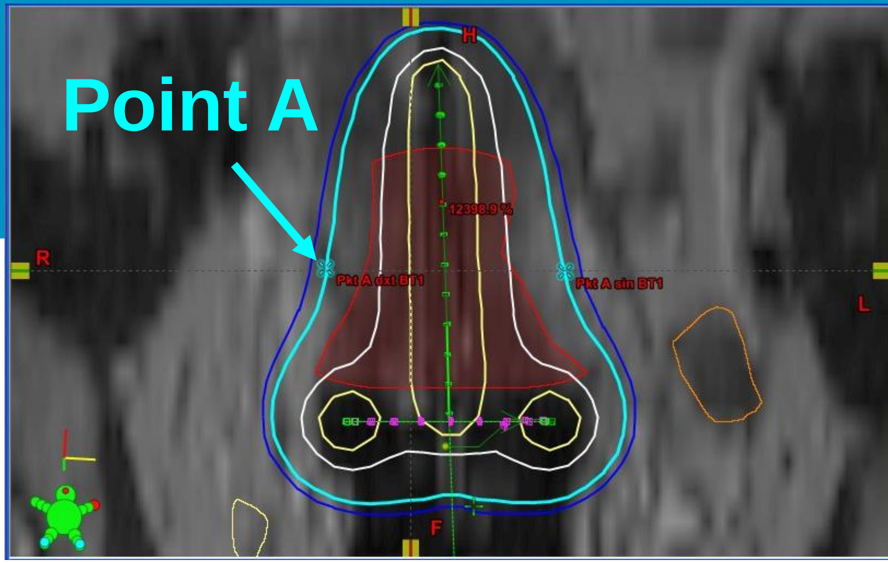


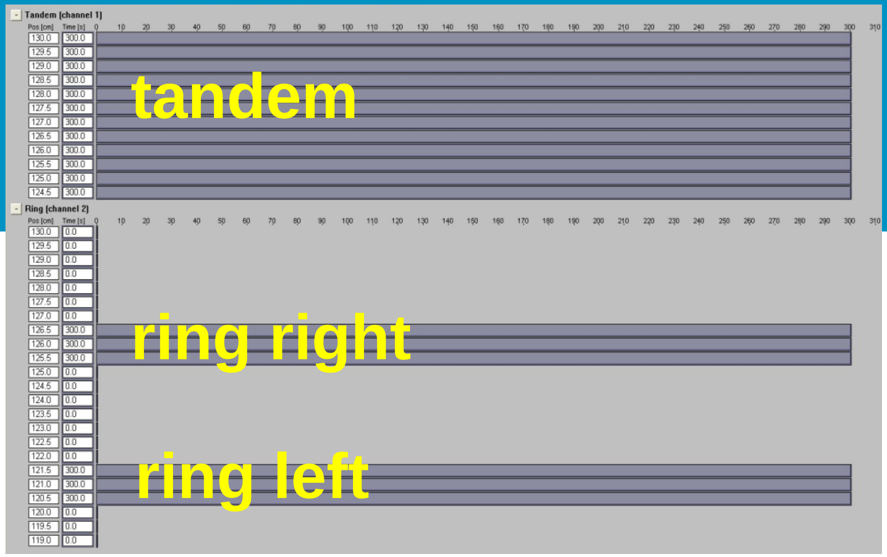
ELEGANT WOMAN
TIMELESS GRACE AND POISE FOR THE EVERYDAY WOMAN

C. Fast and furious: inverse









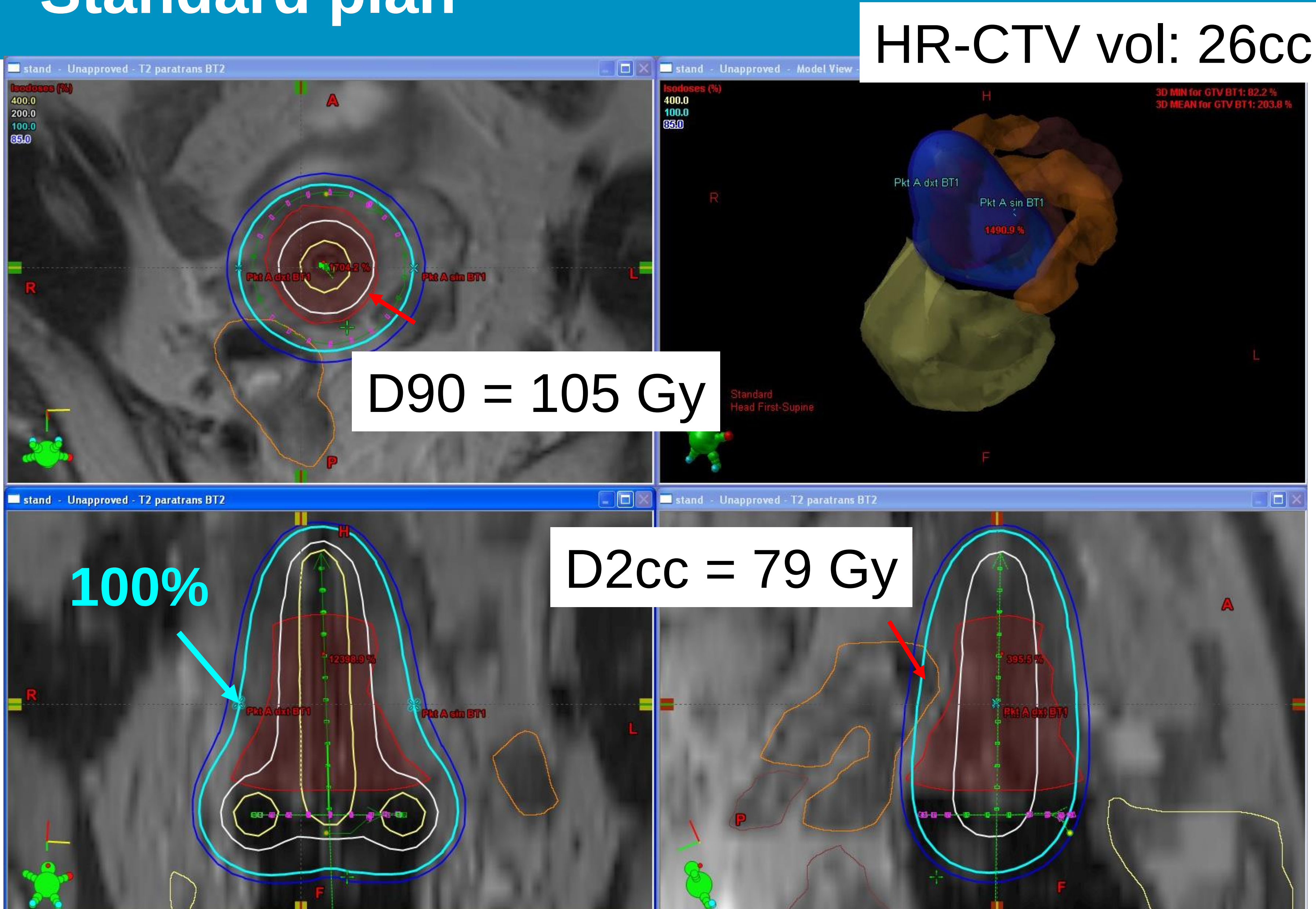
Always start optimisation

with

Standard loading pattern

Standard prescription

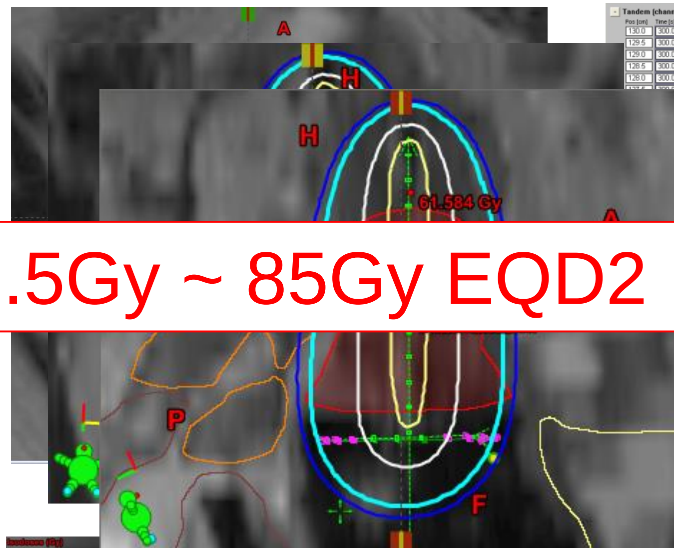
Example 1: good response stage IB2
Standard plan

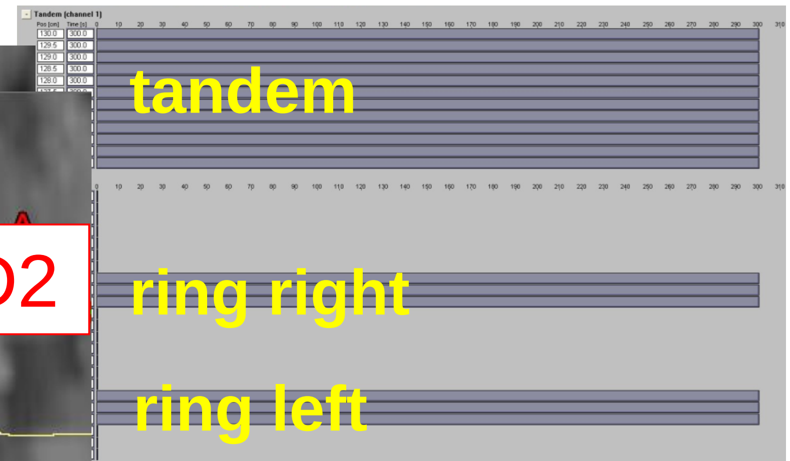


Example 1
Manual dose optimisation

Dose | **Dwell times**

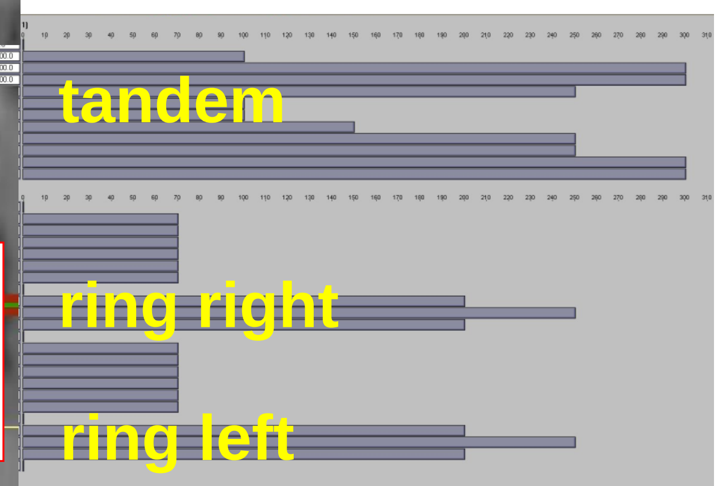
Standard





Point A = 17.5Gy ~ 85Gy EQD2

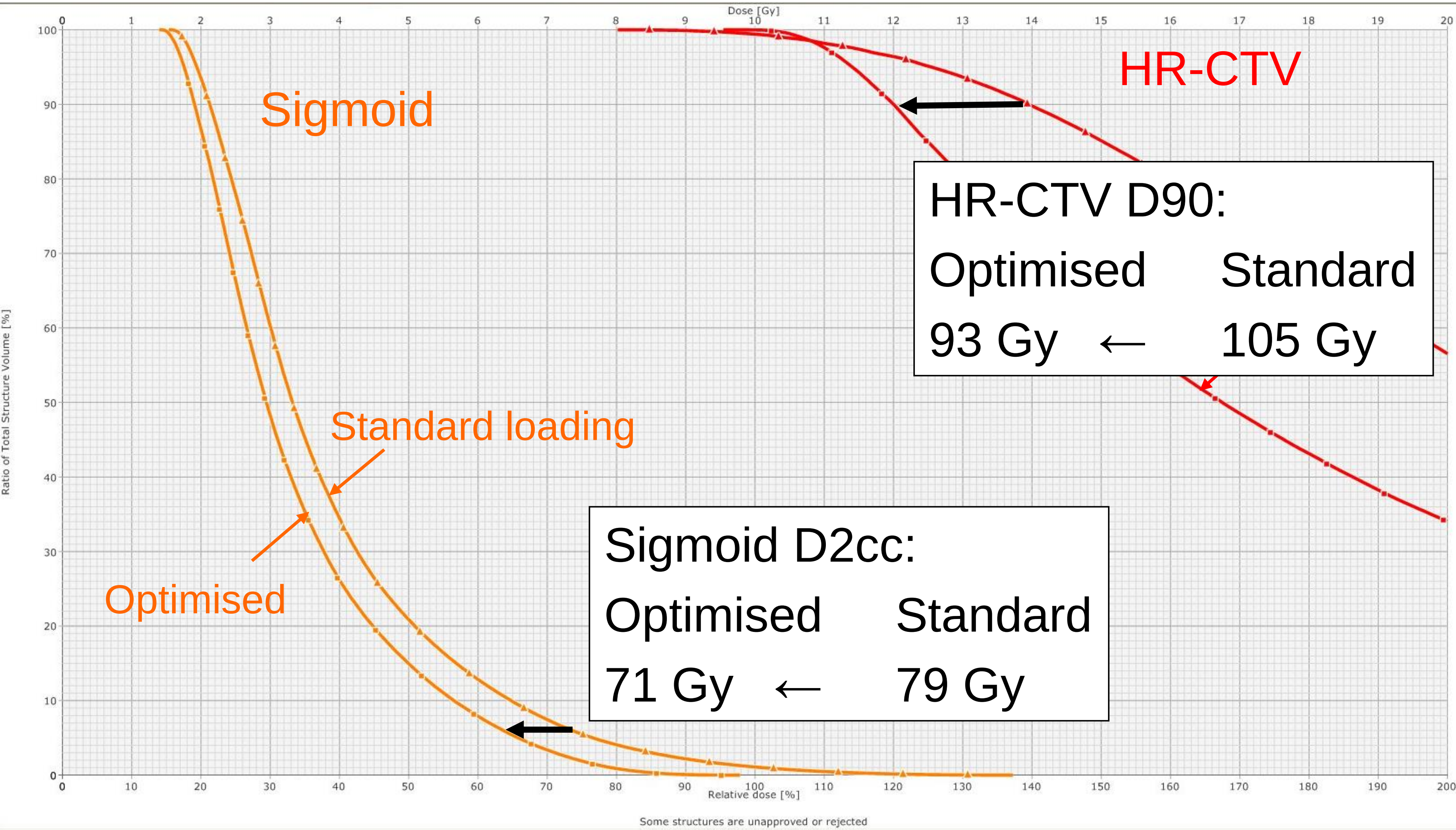
Manual optimisation



Point A = 13.1Gy ~ 72Gy EQD2

Reduction: 25%

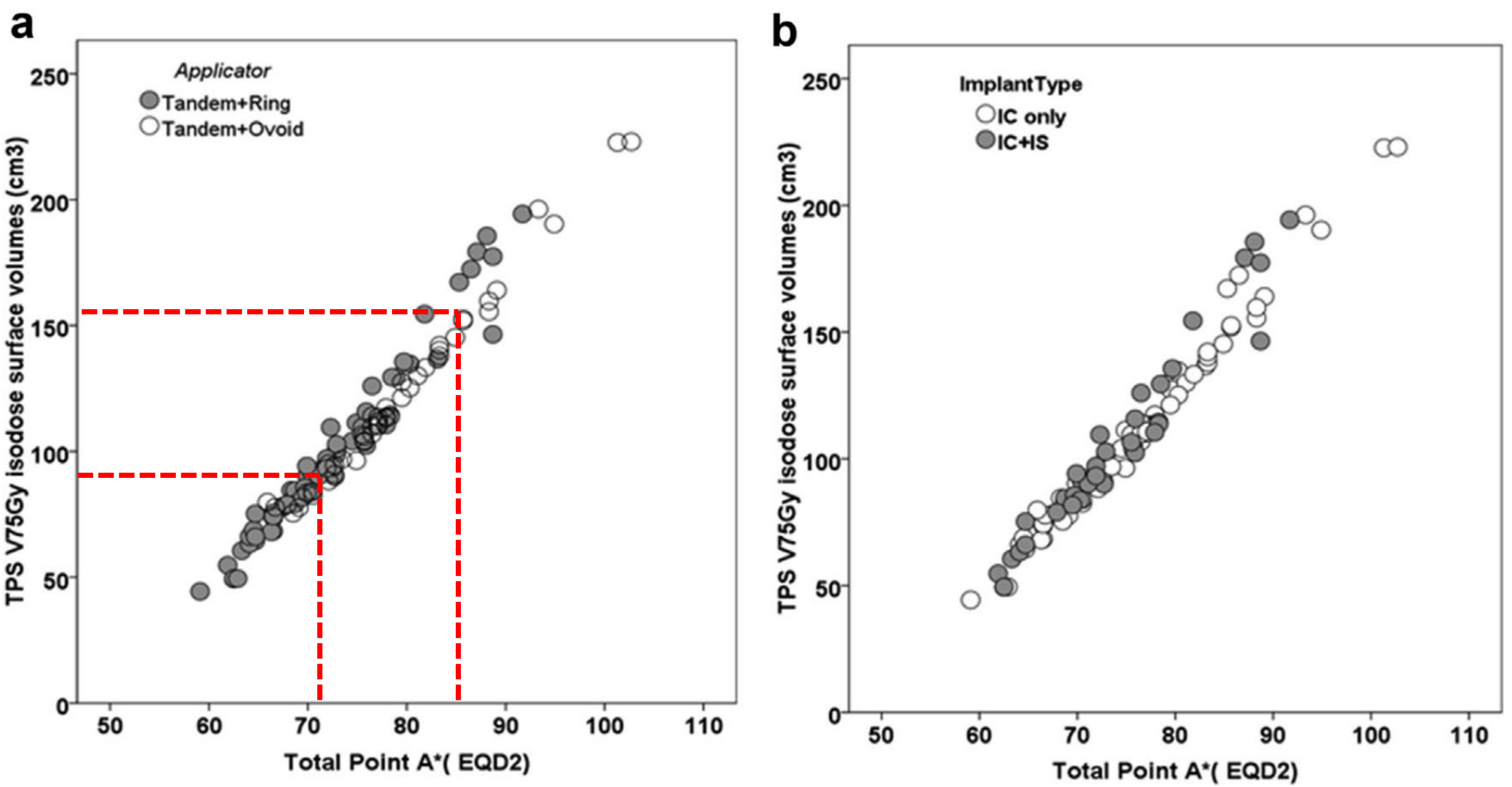
Example 1, DVH



Example 1, summary

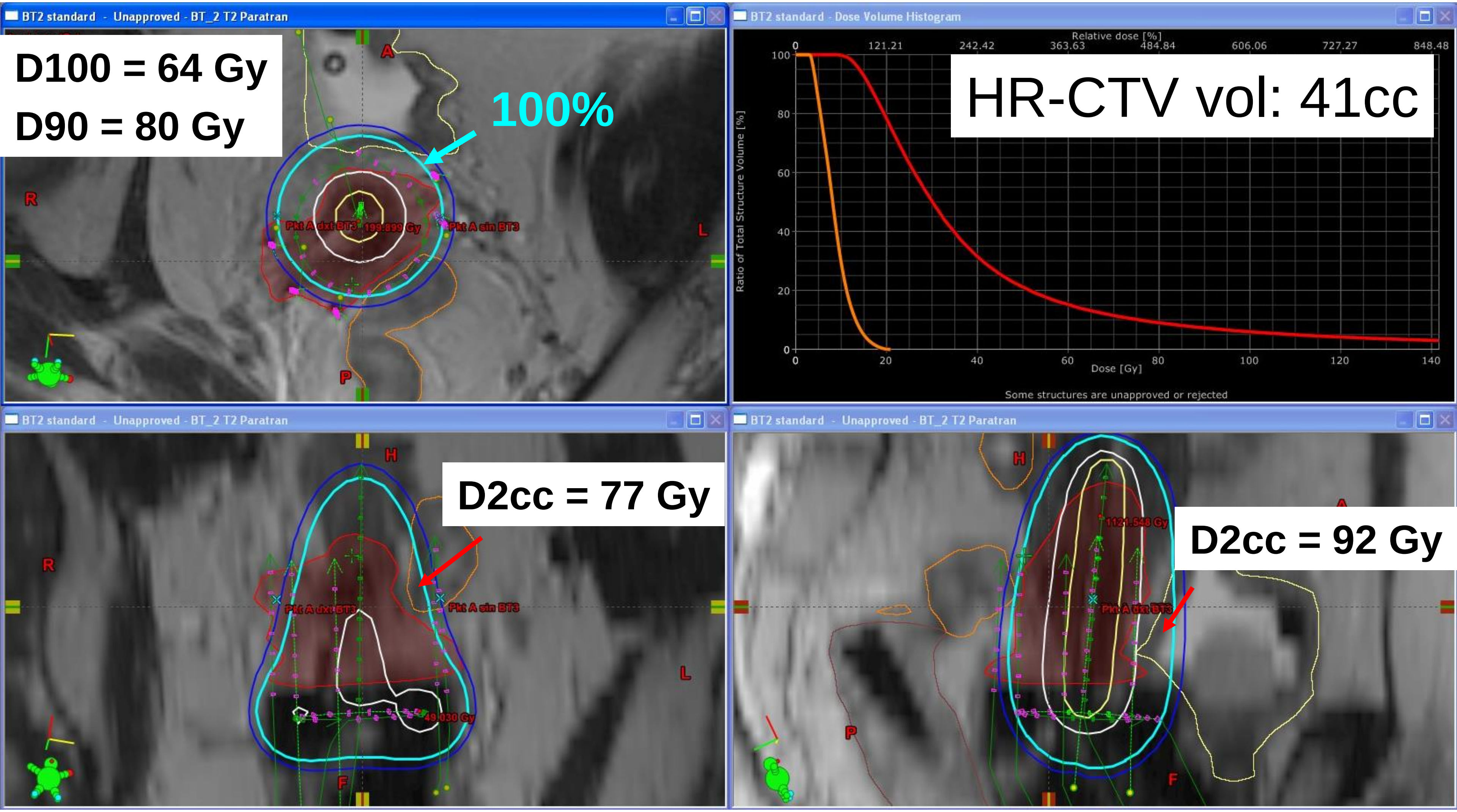
- Small tumour (HR-CTV vol 26cc)
- Decrease of pear (and point A dose)
- OAR dose decreased
- Planning aim: >85Gy
- Prescribed dose HR CTV D90: 93Gy
- 100% isodose adjusted by ~5mm

Why is point A still important in 3D image based brachytherapy?

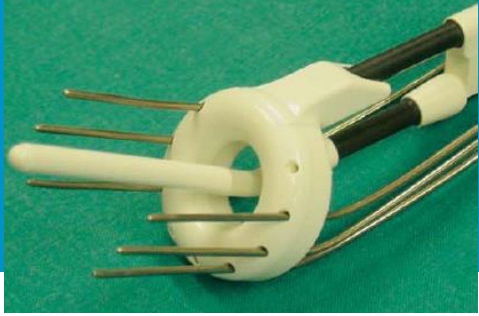


Nkiwane et al, Brachytherapy, in press

Example 2, Stage IIIB Standard dose plan



Example 2
Manually optimised plan



Dose | **Dwell times**

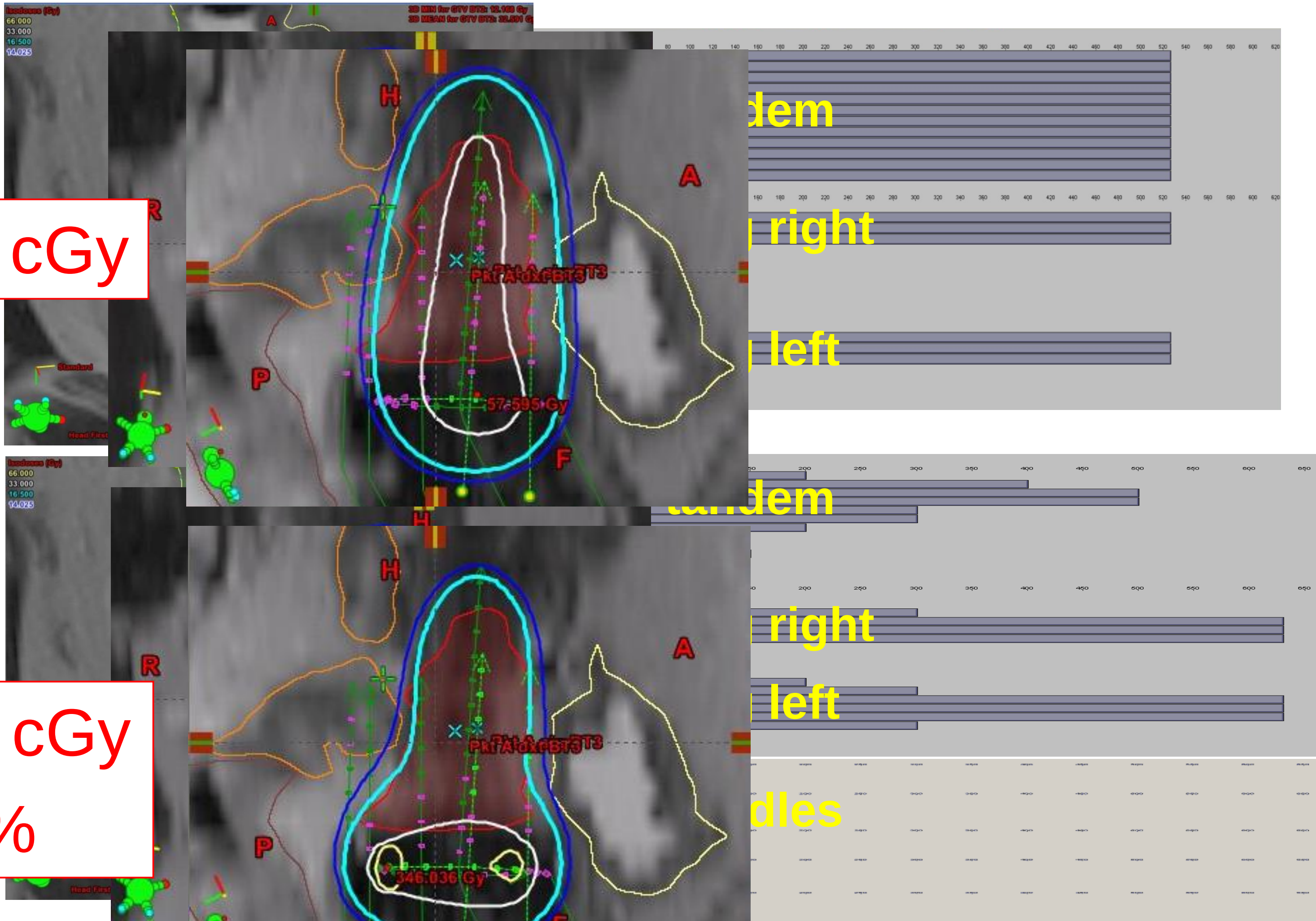
Standard

TRAK = 2.1 cGy

Manual optimisation

TRAK = 2.2 cGy

Increase: 7%

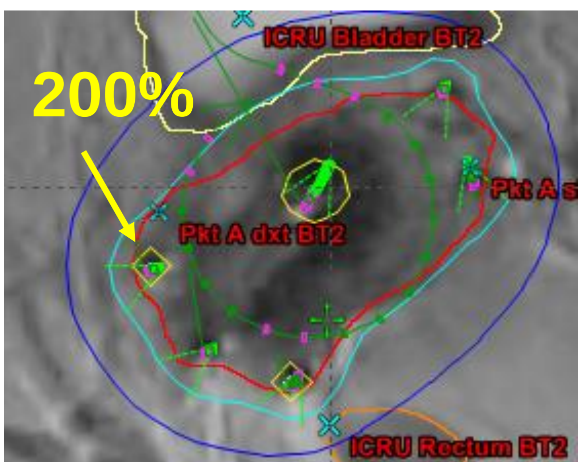


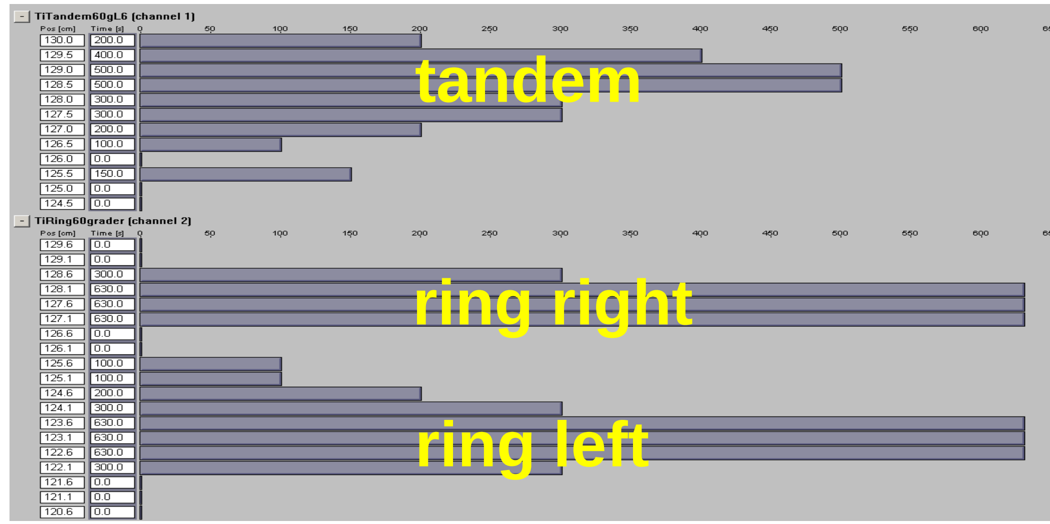
Loading of needles: dwell times and isodoses

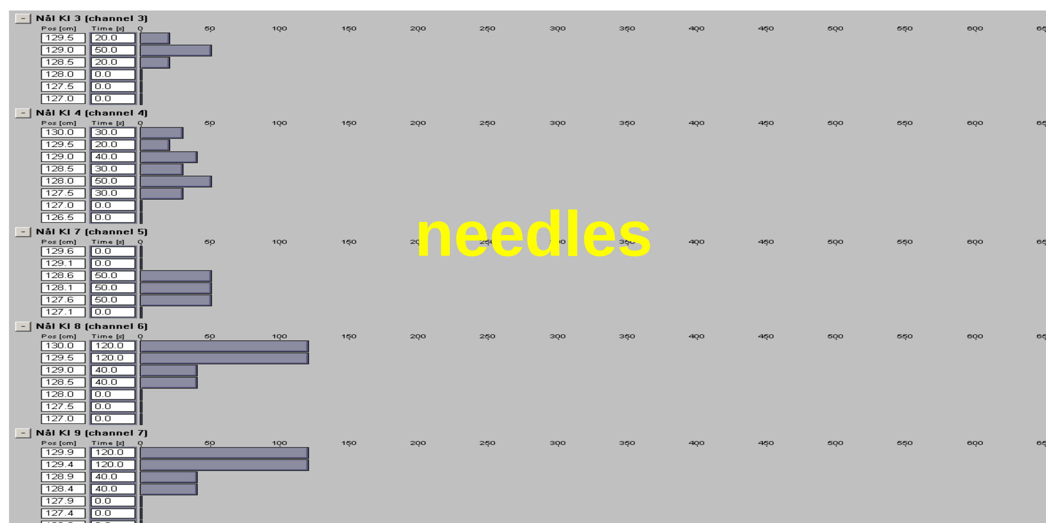
Dwell times needles:

10-20% of dwell time in tandem/ring

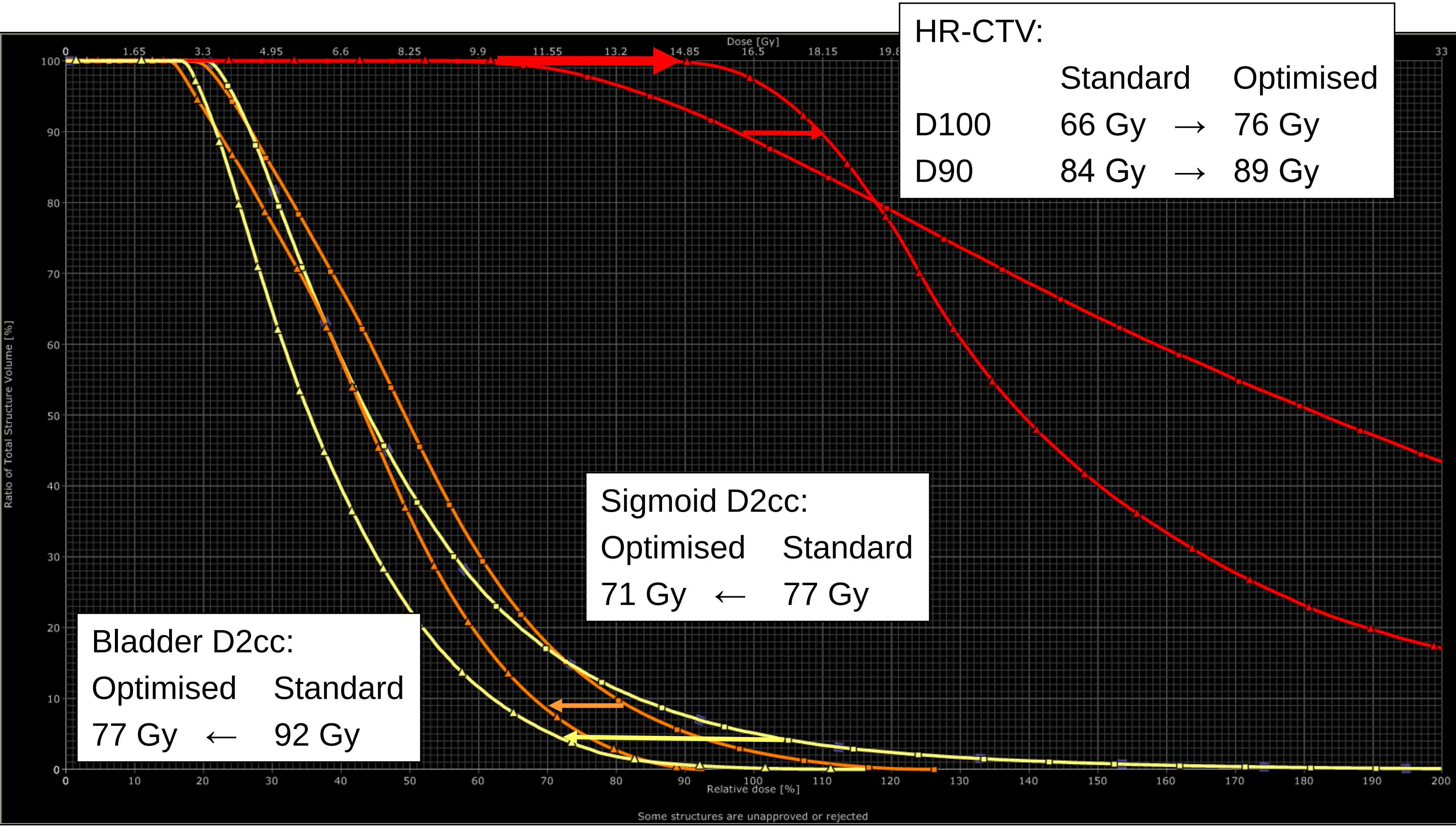
May be >20% if needle is placed directly in the GTV







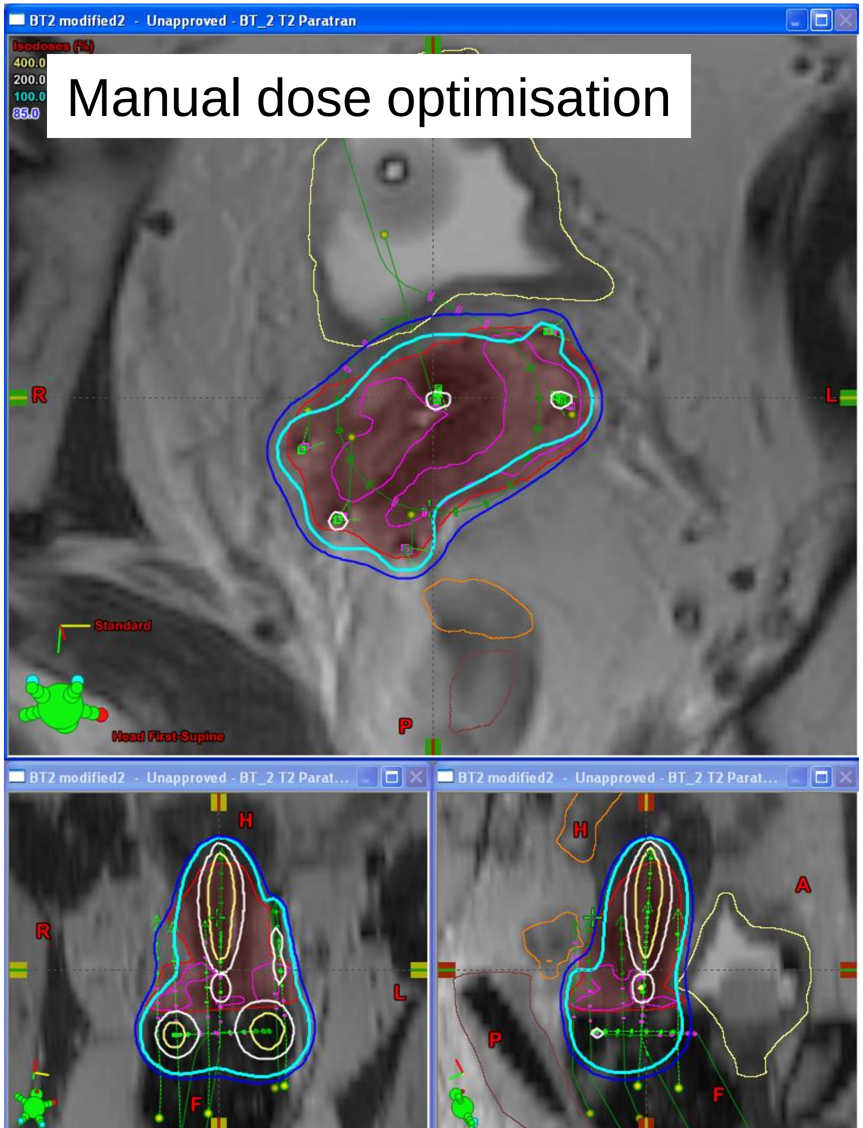
Example 3, DVH

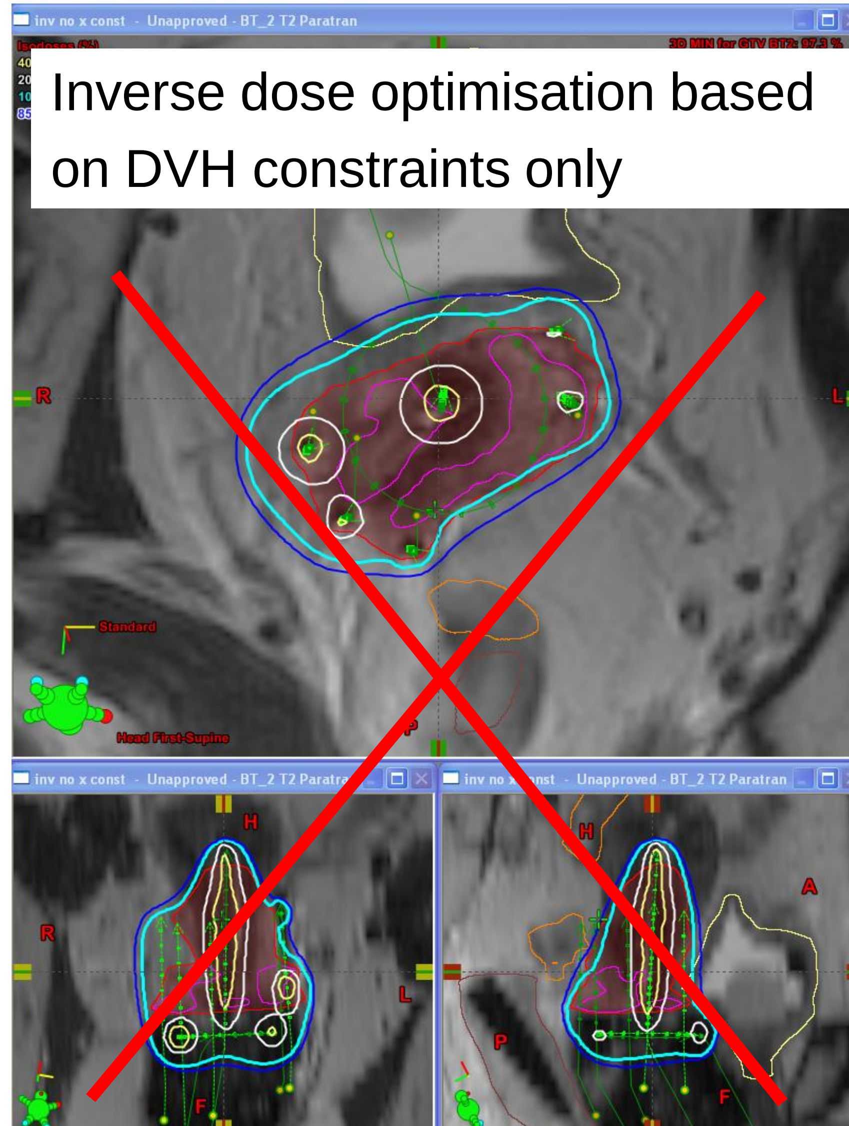


Example 3, summary

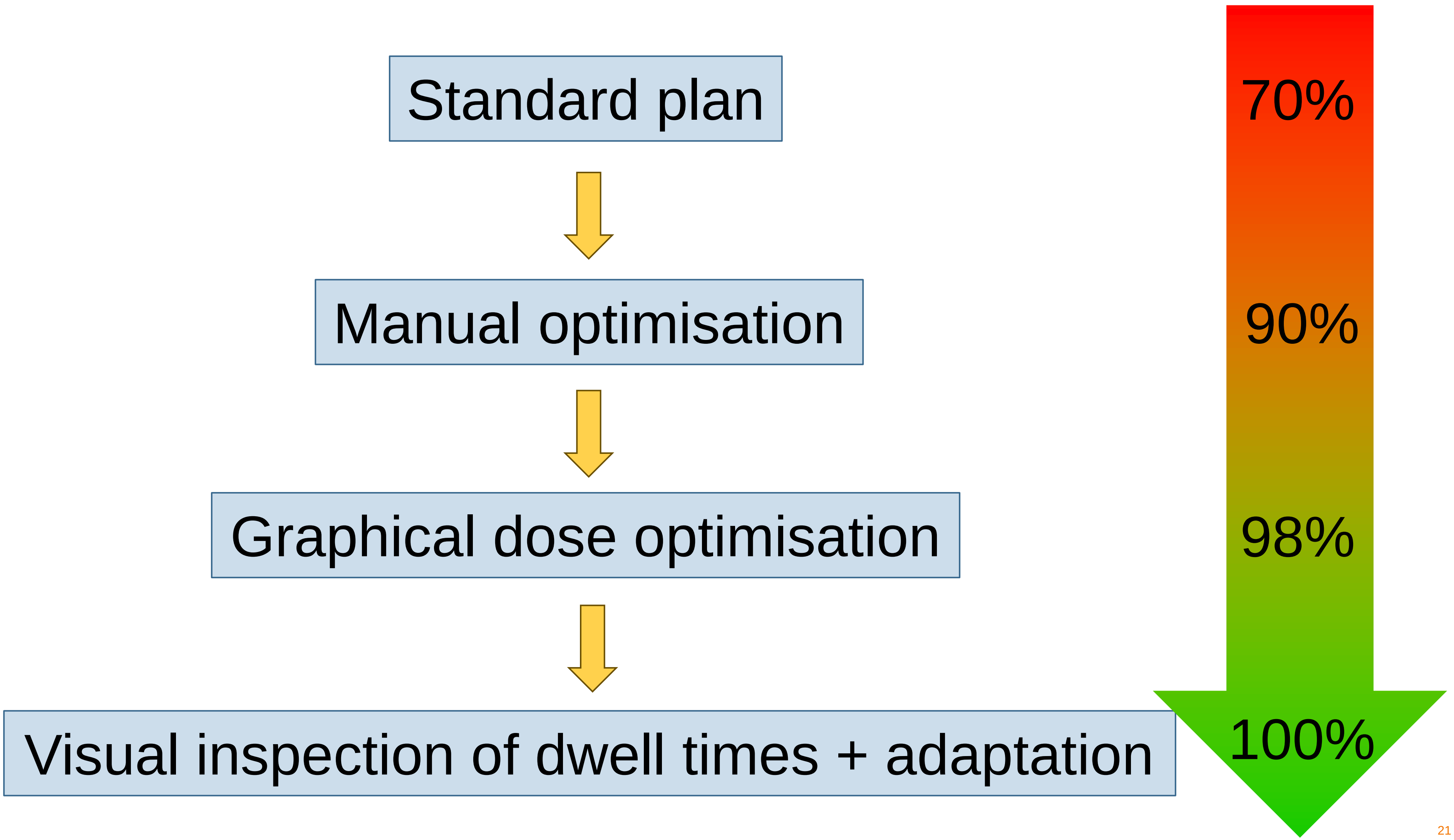
- Bad response (HR-CTV vol 41cc)
- Need of modified applicator (ring+needles)
- Needle loading: <20%
- Target coverage significantly increased – OAR dose significantly decreased
- Planning aim: >85Gy
- Prescribed dose HR CTV D90: 89Gy
- 100% isodose adjusted by ~ 10 mm

Example 3, inverse planning





When to use graphical dose optimisation (dose shaper)?



When to use graphical dose optimisation (dose shaper)?

~~Standard plan~~

↓

~~Graphical dose optimisation~~

↓

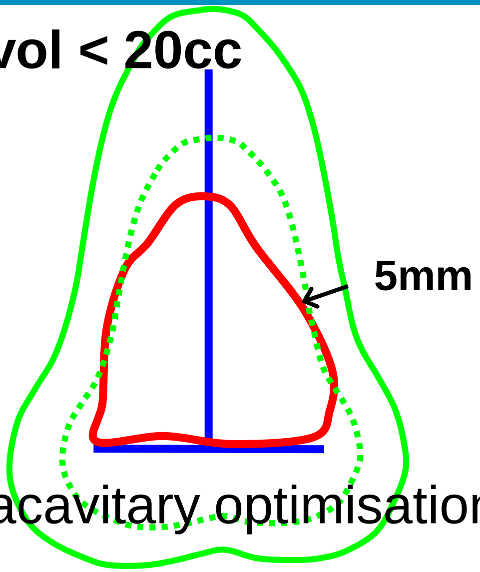
~~Visual inspection of dwell times + adaptation~~

Risk:

- Blowing up needle loading
- Loosing intuition of acceptable dwell times

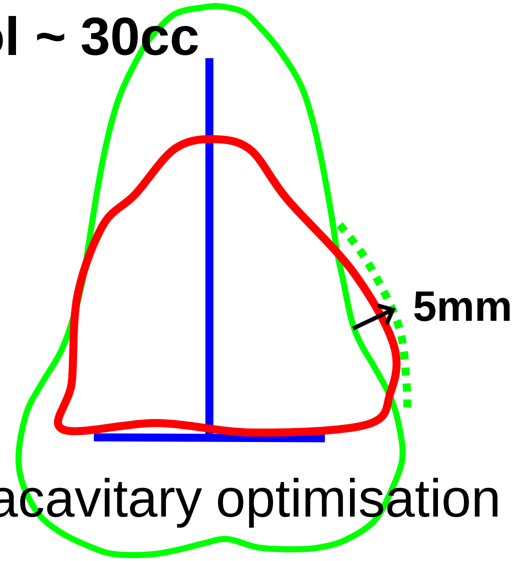
Typical scenarios of dose optimisation

HR-CTV vol < 20cc



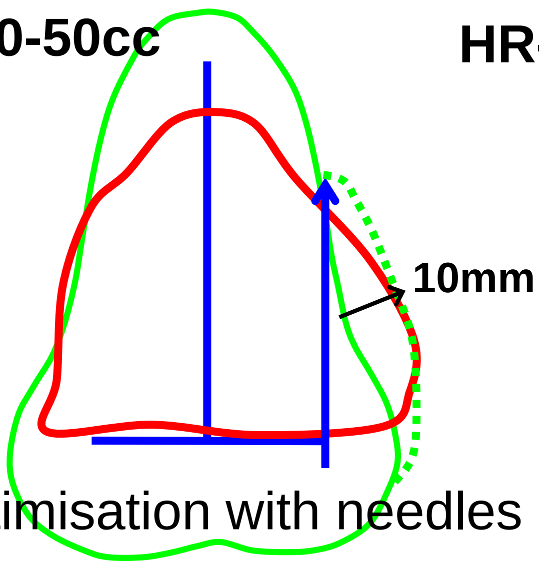
Intracavitary optimisation

HR-CTV vol ~ 30cc



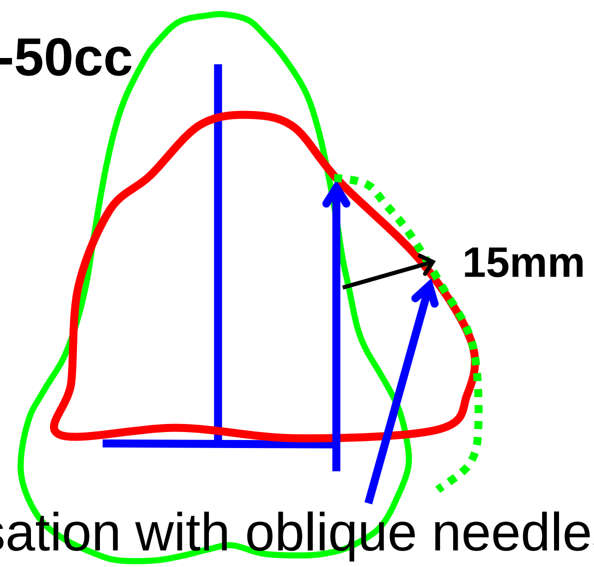
Intracavitary optimisation

HR-CTV vol > 40-50cc



Optimisation with needles

HR-CTV vol > 40-50cc



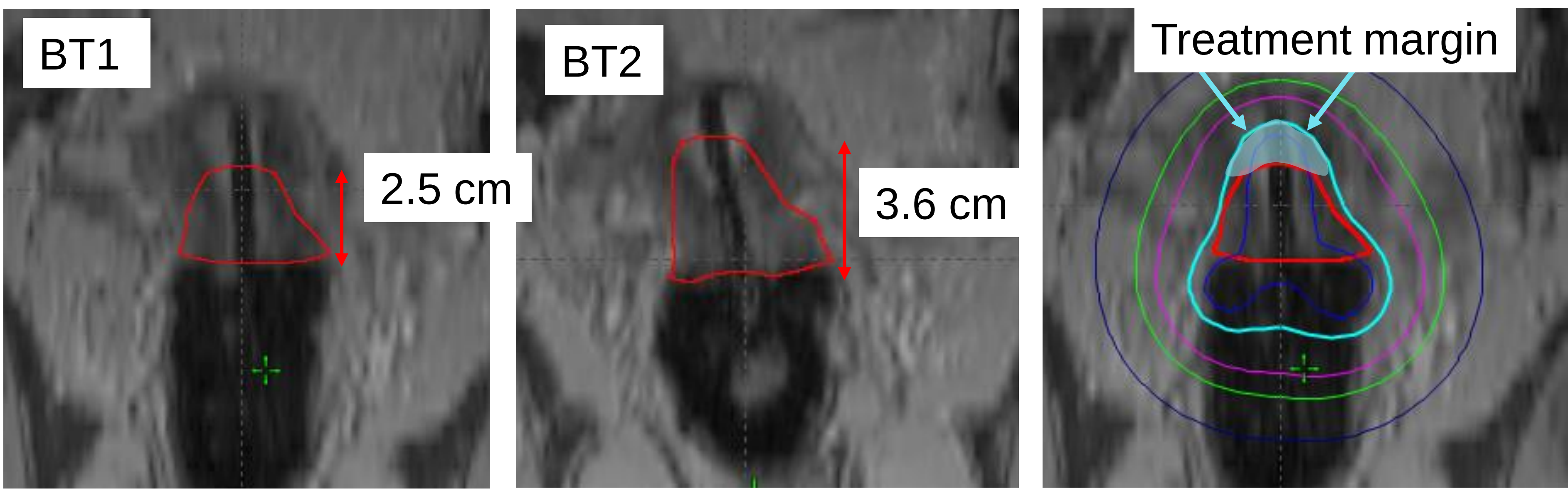
Optimisation with oblique needles

Conclusion – optimisation techniques

Manual	Conservative and "safe" Iterative procedure Dependent on experience of dose planner
Graphical	Fast for small adaptations and fine tuning after manual opt Beware of: -dwell times -deviations from standard loading
Inverse	Fast Requires extra contouring + manual adaptations Beware of: -dwell times -high dose regions -dose to non-contoured tissue -deviations from standard loading

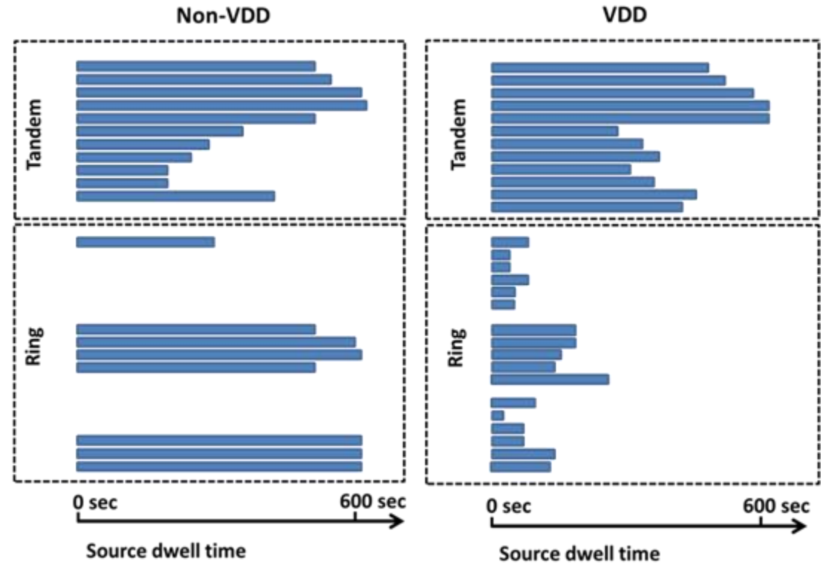
PTV???
Example contouring uncertainty

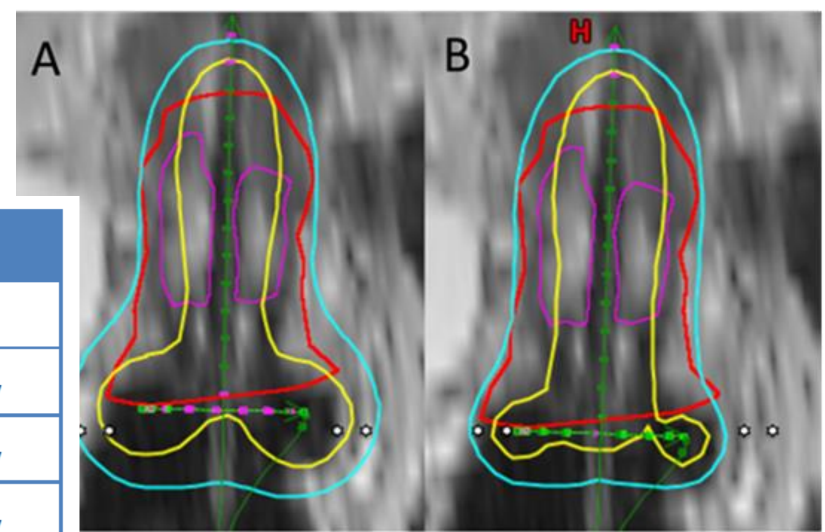
- **Variation in cranial border of HR-CTV**
- **Intra-observer variation!**
- **<u>Load the tandem above the CTV_{HR} when feasible</u>**



Vaginal dose de-escalation

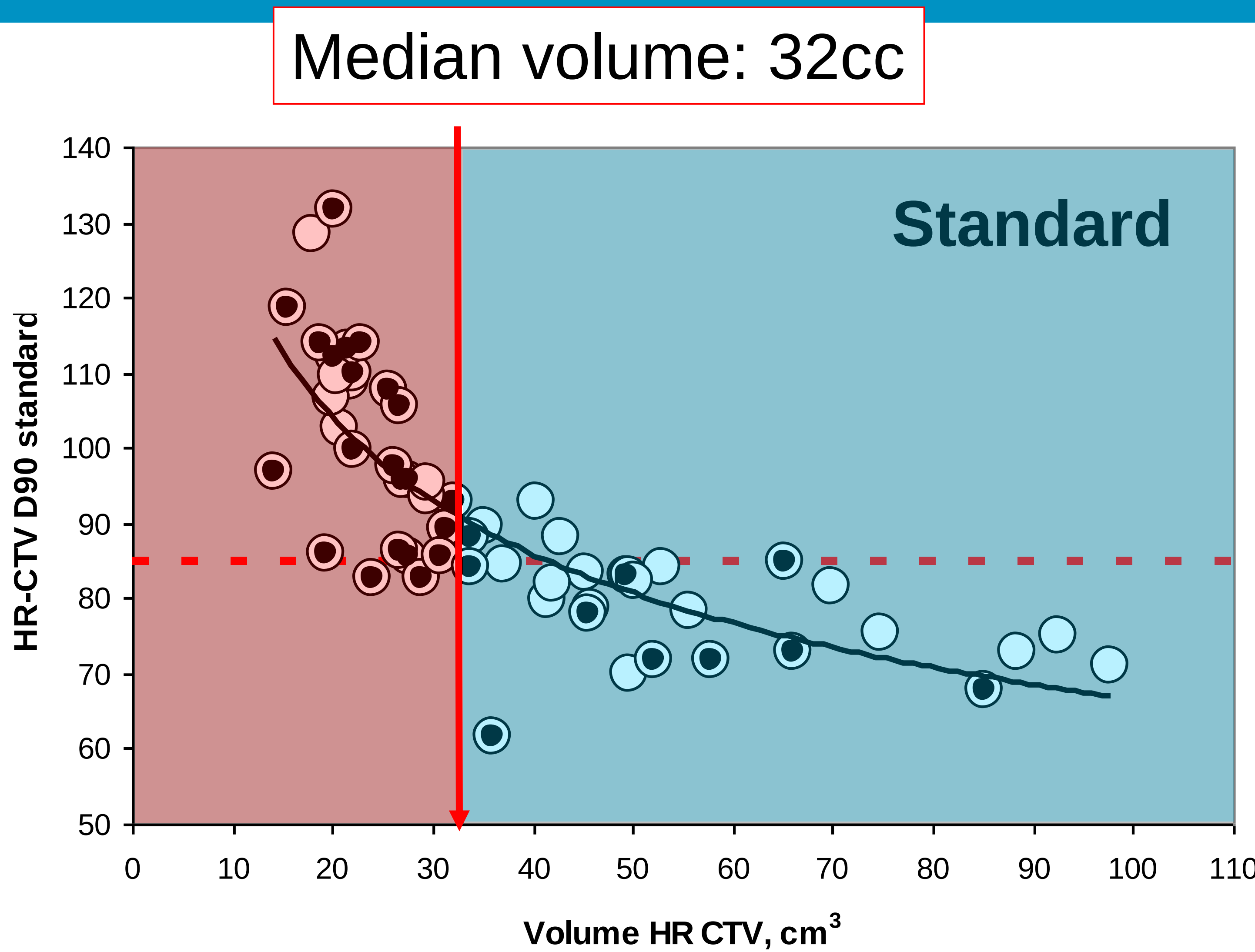
- **Change of loading pattern:**
  - **Shift of dwell time from vaginal sources to tandm/needles**
  - **E.g. 140% isodose out of vaginal mucosa**
  - **Aim for <30-40% loading in ring/ovoids**





	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!

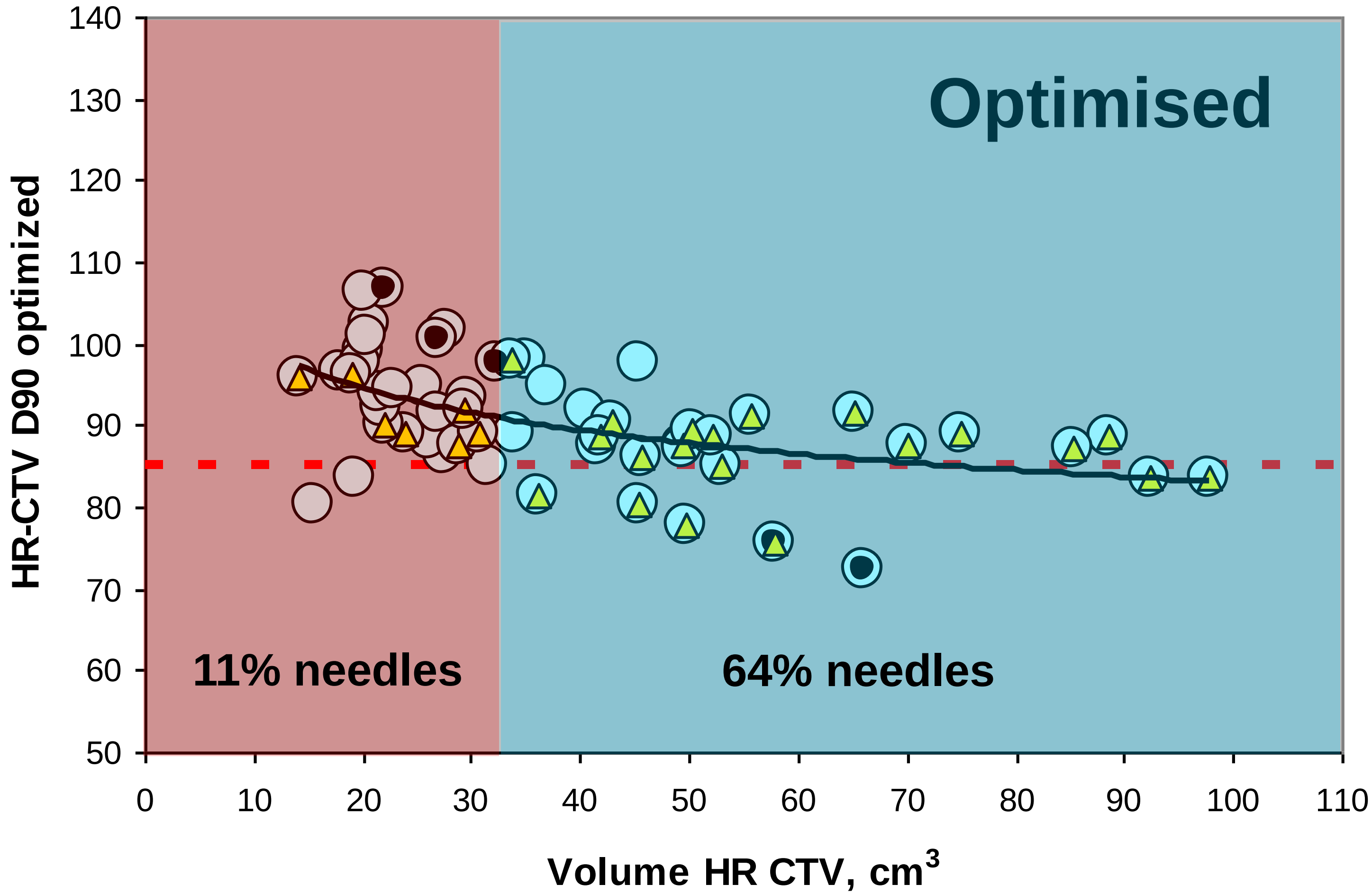


Violation of OAR constraint

K Tanderup et al, Radiother Oncol 2010

Volume is important!

K Tanderup et al, Radiother Oncol 2010

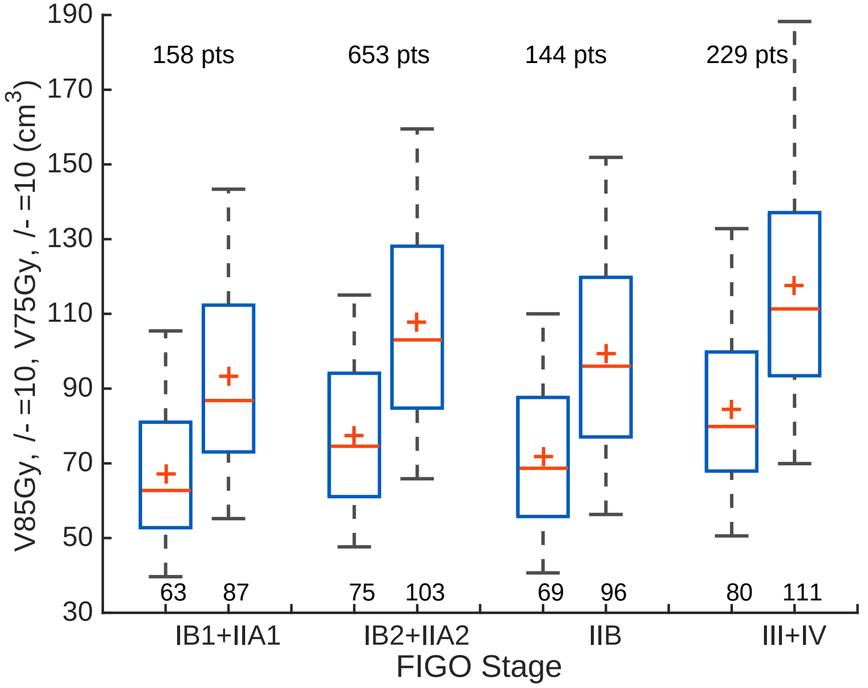


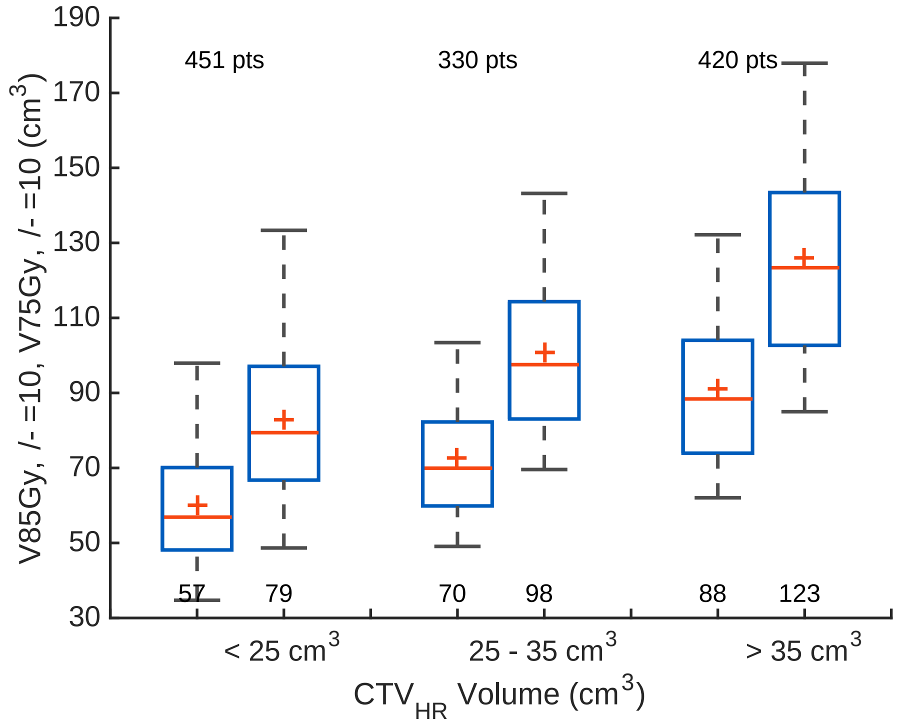
Violation of OAR constraint

Application of needles

Isodose surface volumes

V75Gy and V85Gy

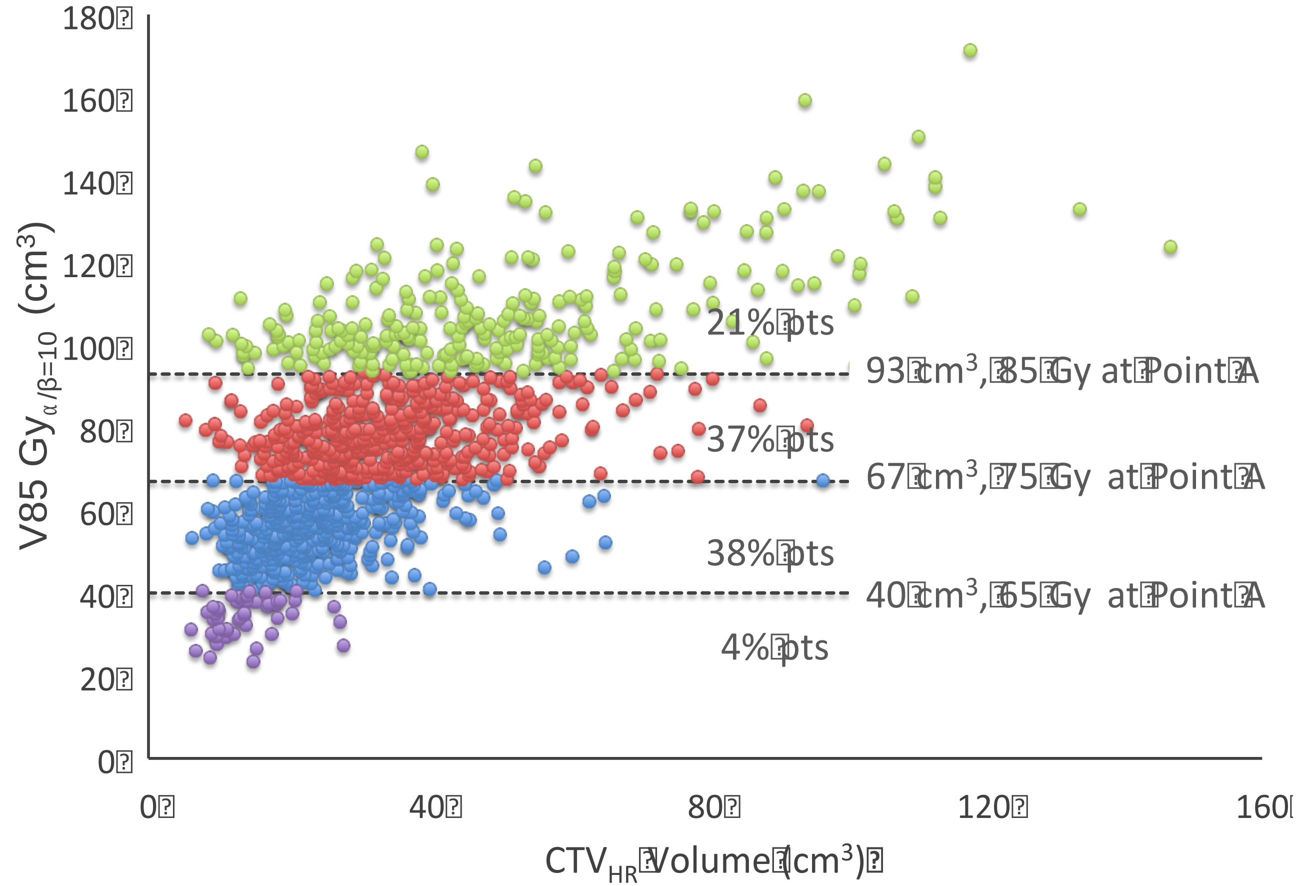




Monica Serban, EMBRACE data

Irradiated volumes

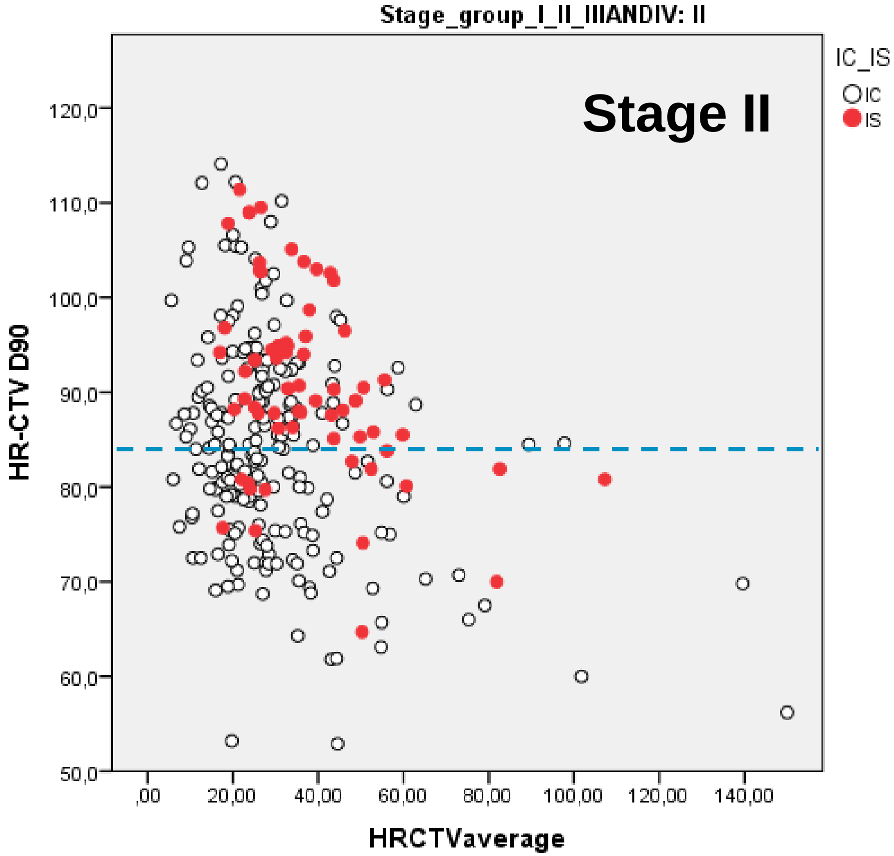
- **Individualised dose adaptation**
- **Overall dose de-escalation as compared to 85Gy to point A**

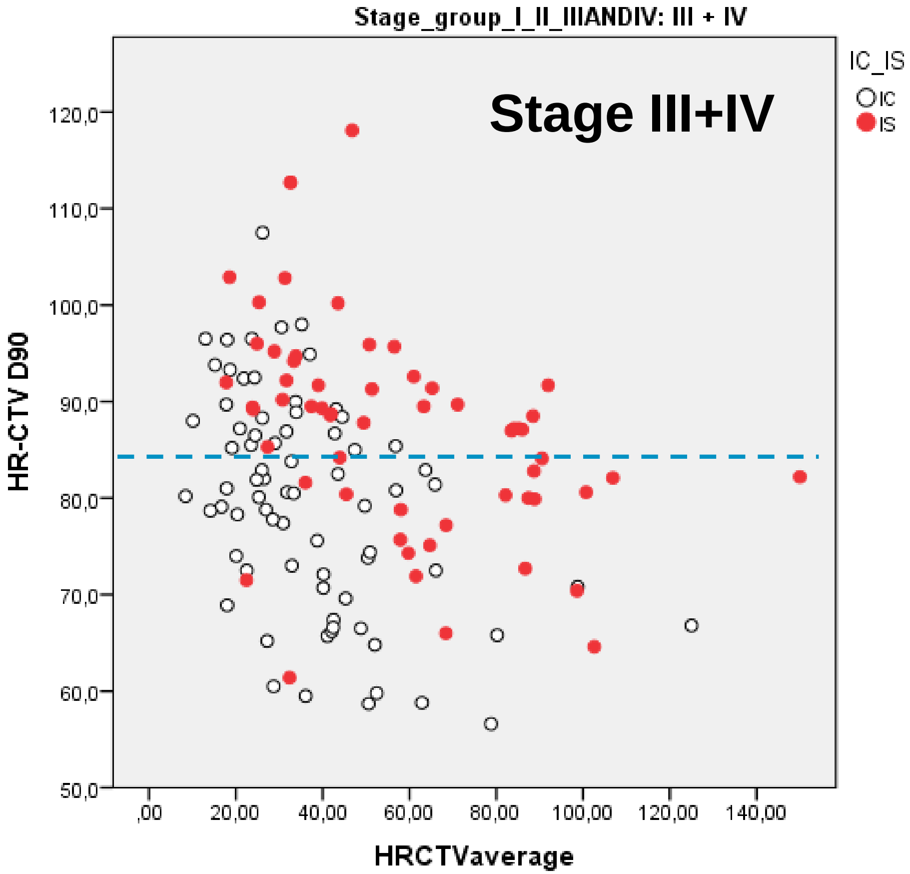


Monica Serban, EMBRACE data

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

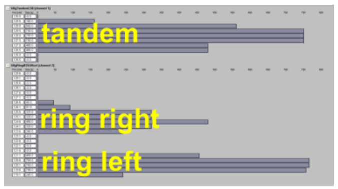
Standard plan
↓
Manual optimisation
↓
Graphical dose optimisation
↓
Visual inspection of dwell times + adaptation

B. Flow 2

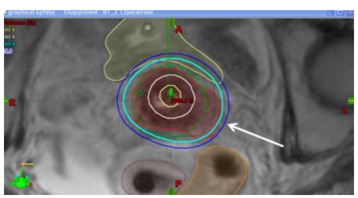
Standard plan
↓
Graphical dose optimisation
↓
Manual optimisation
↓
Visual inspection of dwell times + adaptation

Which type do you prefer?

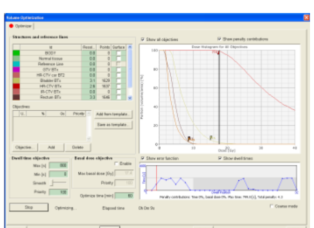
A. From scratch: manual

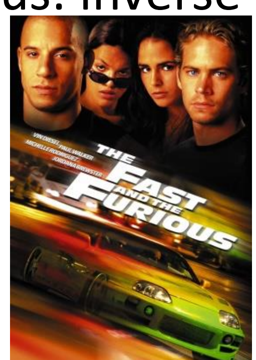


B. Elegant: drag and drop



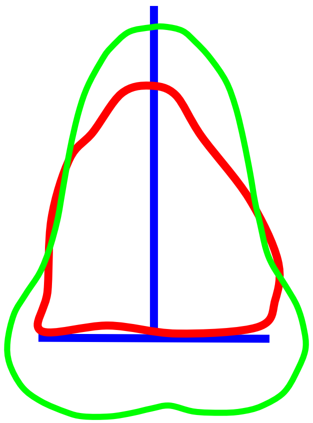
C. Fast and furious: inverse



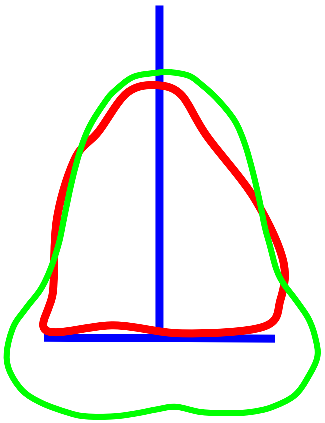


Which dose distribution do you prefer?

A. Plan 1



B. Plan 2



Session

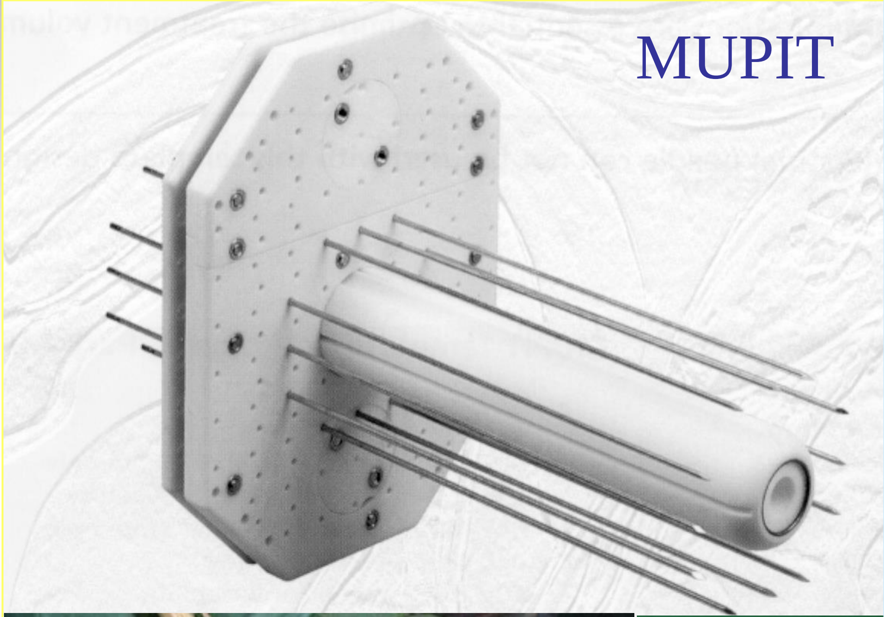
Physics aspects of Treatment Planning
Interstitial Techniques (other than cervix)

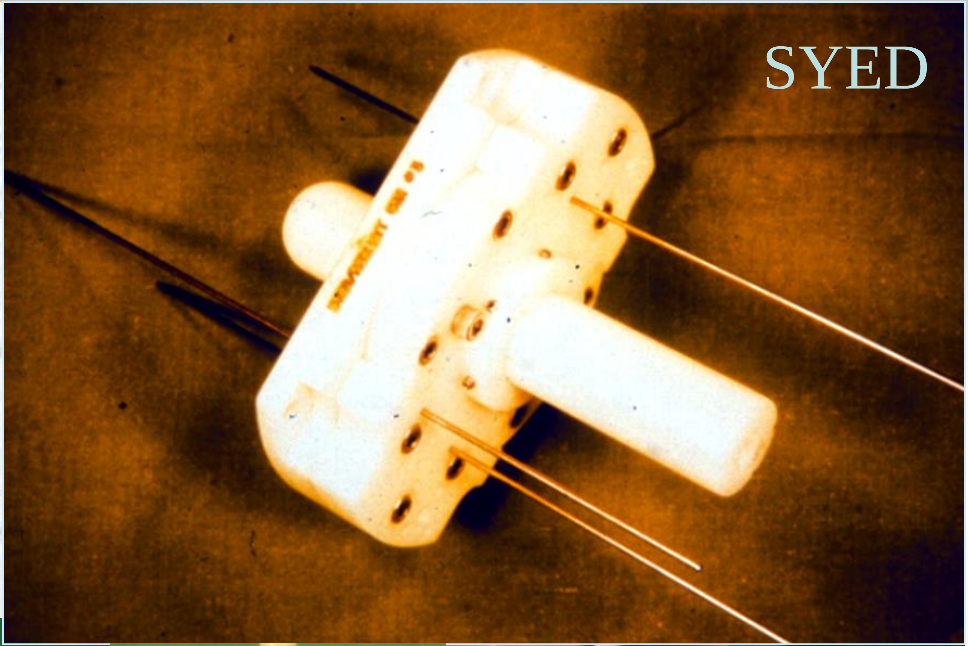
Nicole Nesvacil

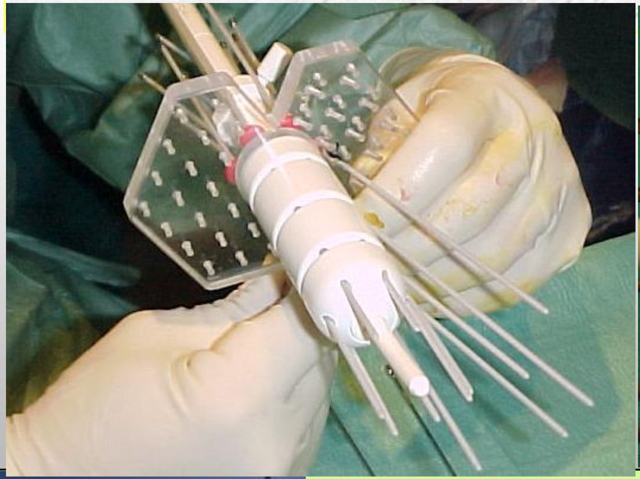
Presentation by Daniel Berger,
Christine Haie-Meder and Richard Pötter

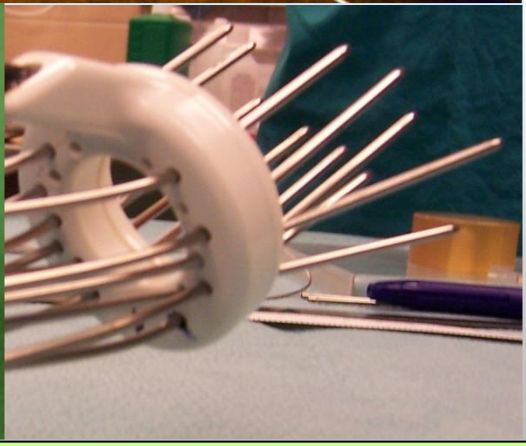
ESTRO Teaching Course on
Image-guided radiotherapy & Chemotherapy in
Gynaecological Cancer
- with a special focus on adaptive BT-

Interstitial Application Techniques

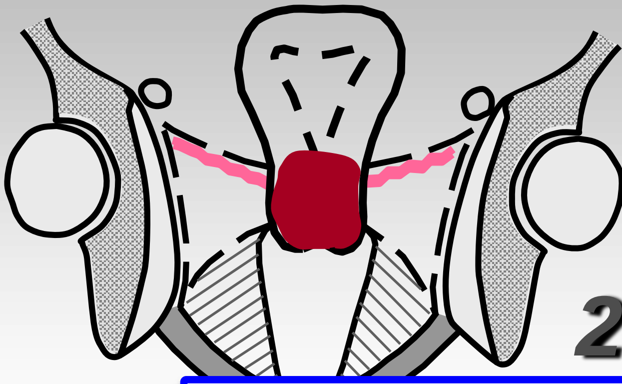






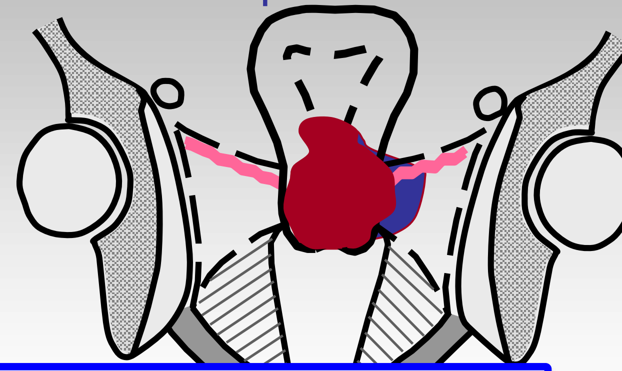


Tumour limited to cervix



28%/15%

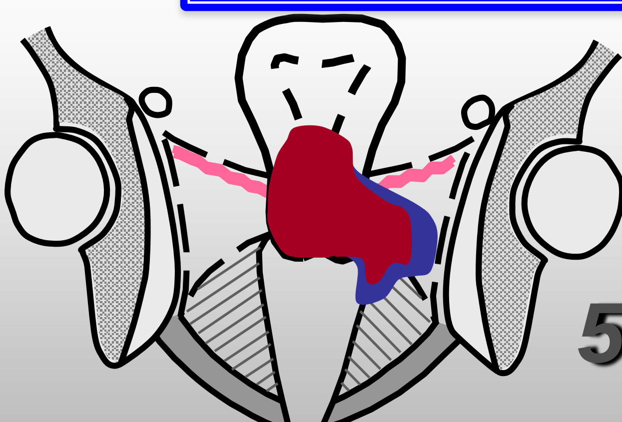
Cervical tumour with parametrial infiltration
inner third – half parametrium



%/40%

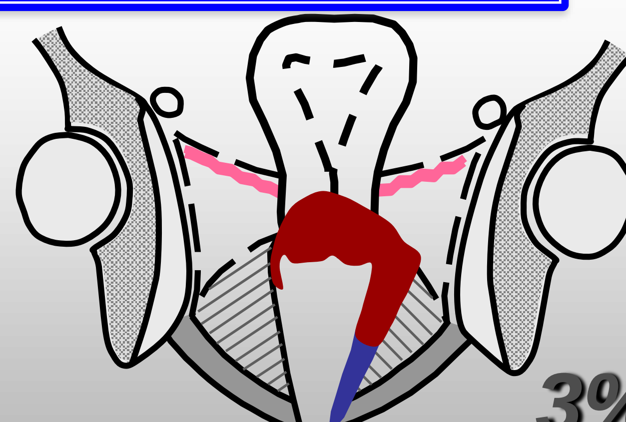
Vagina and Vulva: less than 5 %

Cervical tum
half paramet



5%/30%

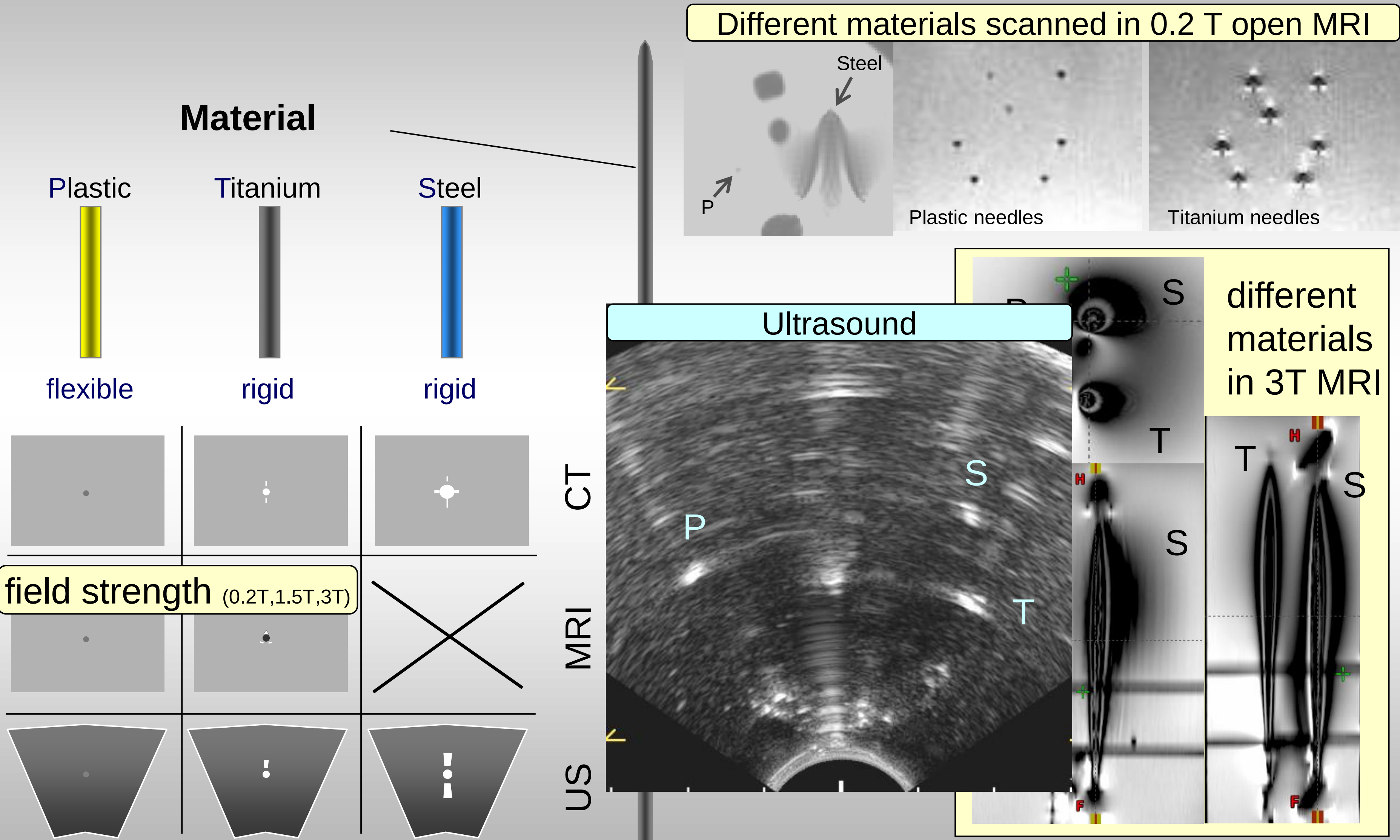
l infiltration
stal vagina



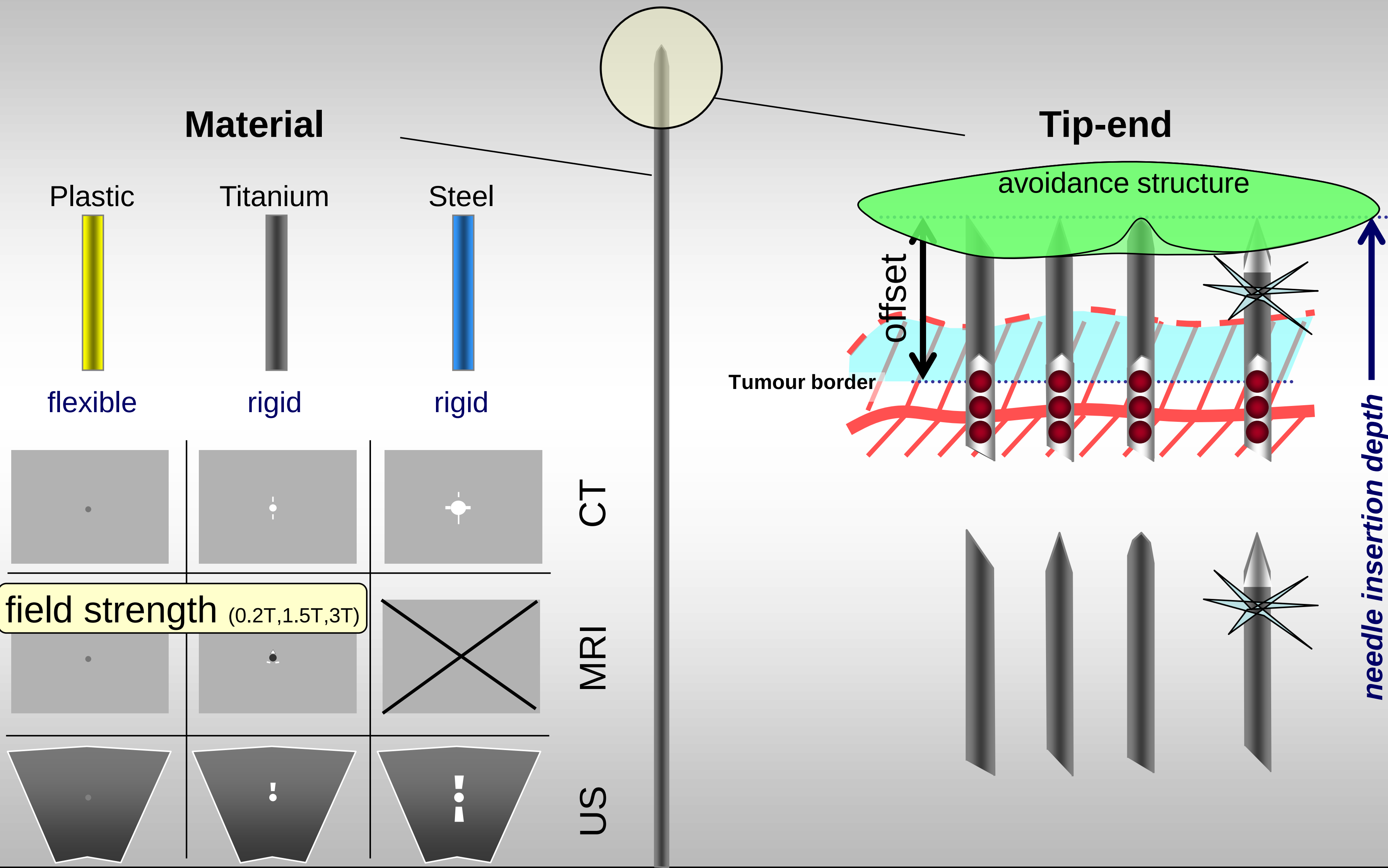
3%/15%

Frequency of tumor at BT for Europe/India

Know the tool you are using!



Know the tool you are using!



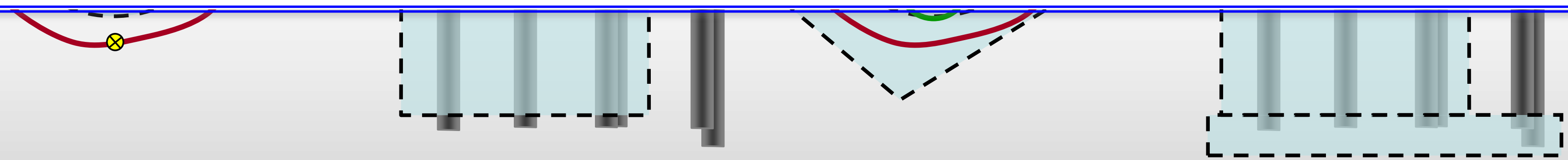
« Intracavitary » versus Interstitial treatment planning approach

achieved by Weighting/dwell times (and Normalization point) determined by location and target

⊗ Normalization/Reference point(s)

High dose region
The Paris system defines the high dose region (hyper dose sleeve) as the volume of tissue immediately surrounding the source which receives a dose equal or greater than twice the reference dose (see for example Fig 2.6 and Fig 2.14).
The clinical experience of those who developed the Paris system indicates that complications (e.g., necrosis) occur when the diameter of this region exceeds 8 - 10 mm (Pierquin et. al. (31)). This constraint will limit the separation between sources.

Taken from the GEC ESTRO Handbook



Dominant weighting in catheter 3
Dose normalized to Reference point
("reference" distance from applicator surface)

Balanced weighting between catheters 1-12
Dose normalized to ~85% basal dose (MCD)

Normalization Point – where to define the Reference point?

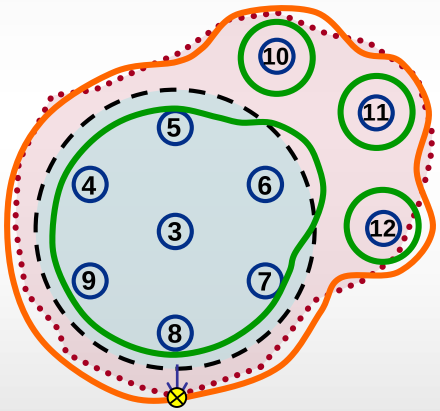
Target

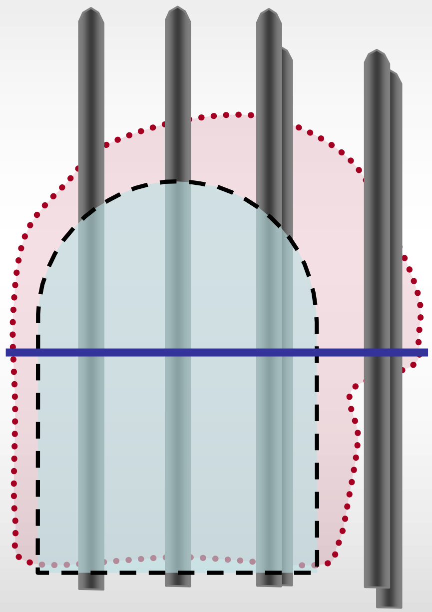
Normalization/Reference point(s)

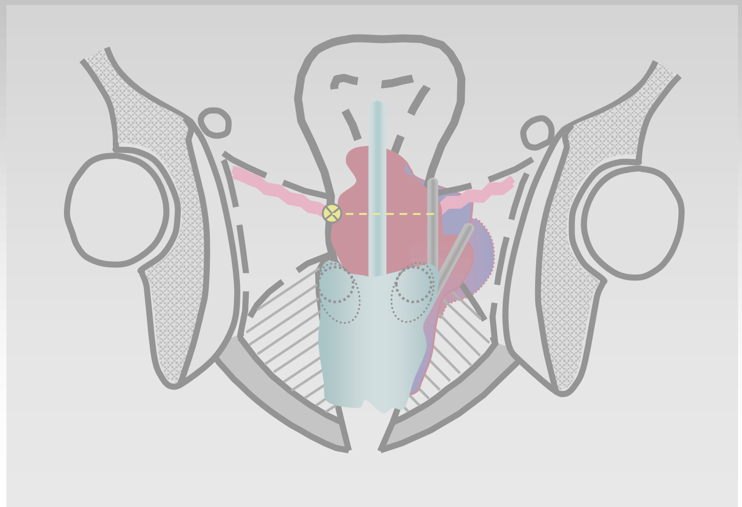
Nr Catheter Nr._

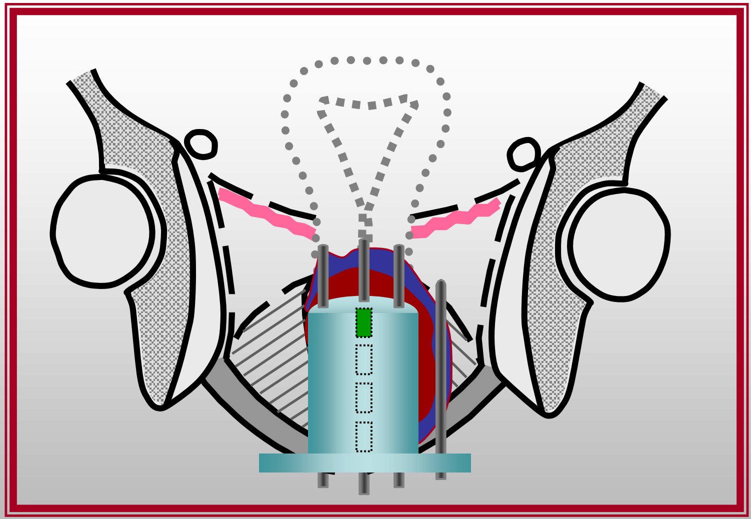
100% (=PD)

200%



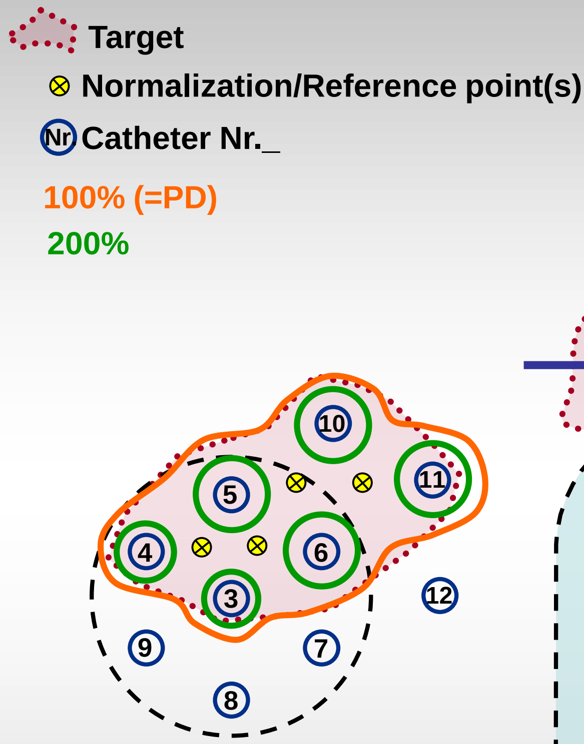


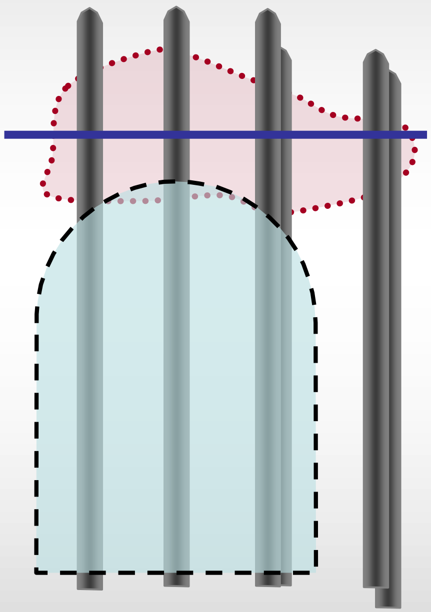


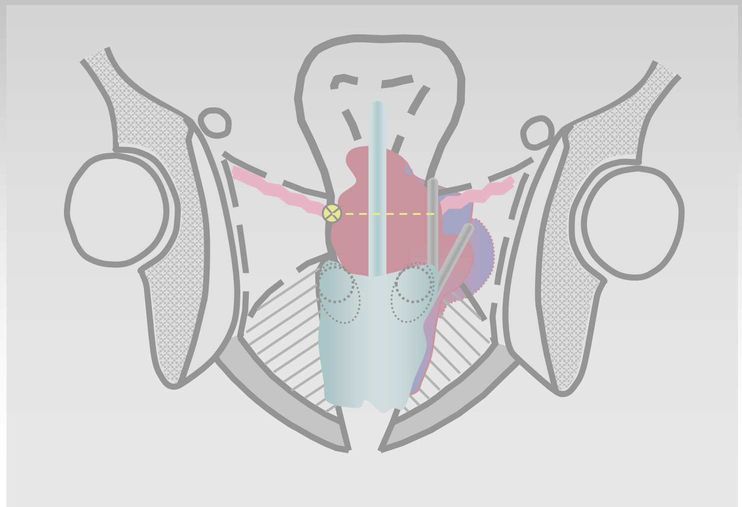


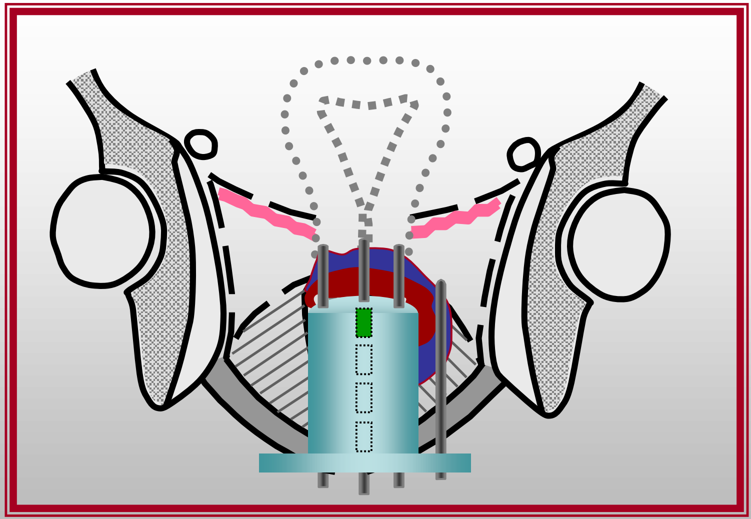
☒ Intracavitary ☐ Interstitial

Normalization Point – where to define the Reference point?









☐ Intracavitary ☒ Interstitial

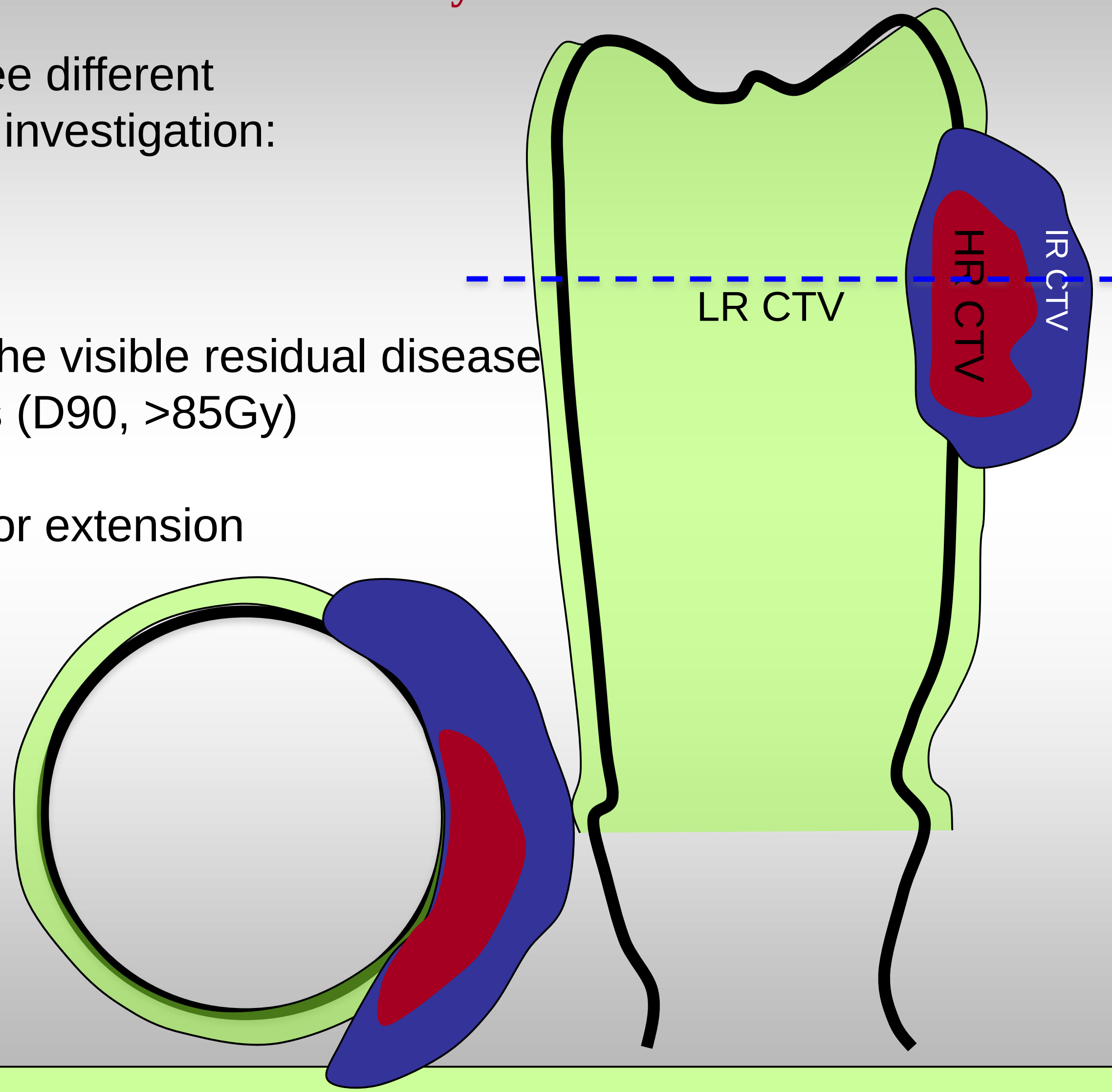
Treatment planning concept for locally advanced vaginal cancer currently used at the Medical University of Vienna

New target concept including three different target volumes is currently under investigation:

1) **HR CTV:** the clinically palpable disease and, on MRI, the visible residual disease plus the surrounding gray zones (D90, >85Gy)

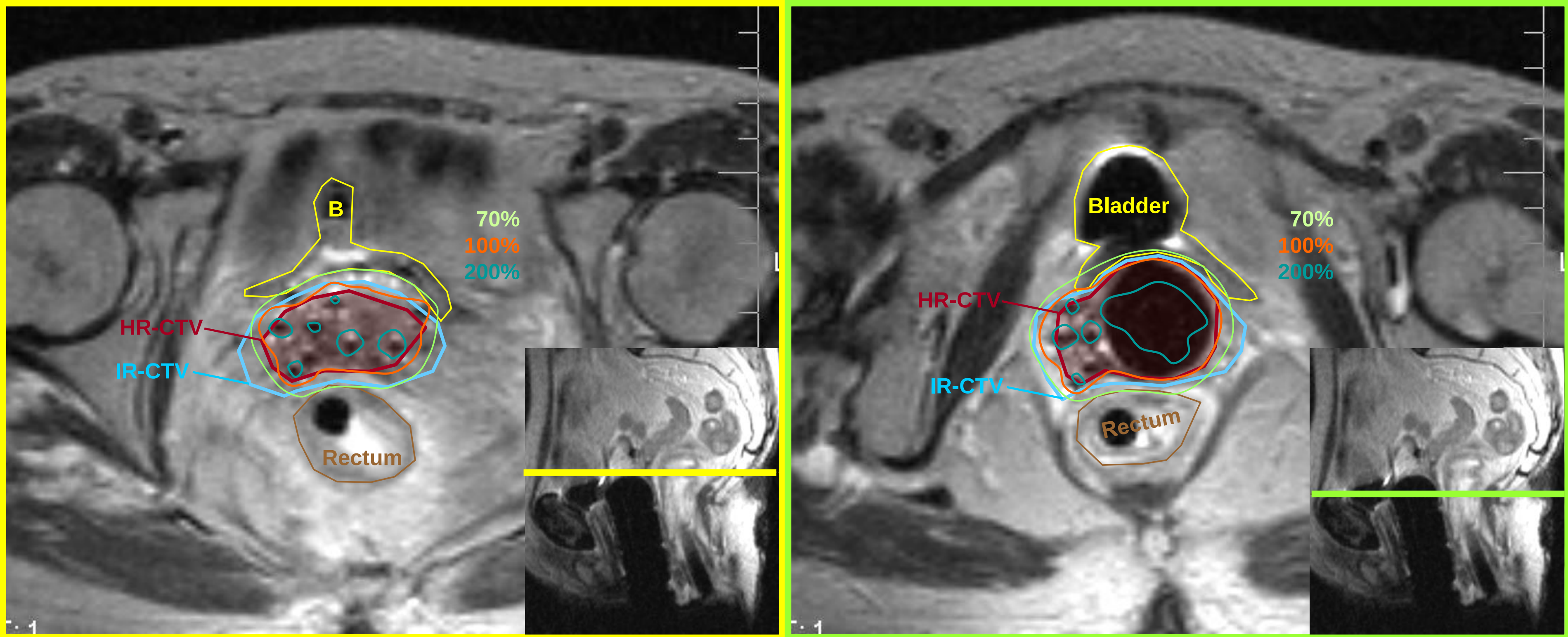
2) **IR CTV:** the region of initial tumor extension (D90, 60Gy)

3) **Low-Risk CTV:** complete remaining vagina (D90, 50 Gy).



Clinical results and DVH parameter in *Dimopoulos et al. 2011 IJROPB*

Clinical Example



HR-CTV D90 = 88 $Gy_{\alpha\beta10}$

IR-CTV D90 = 70 $Gy_{\alpha\beta10}$

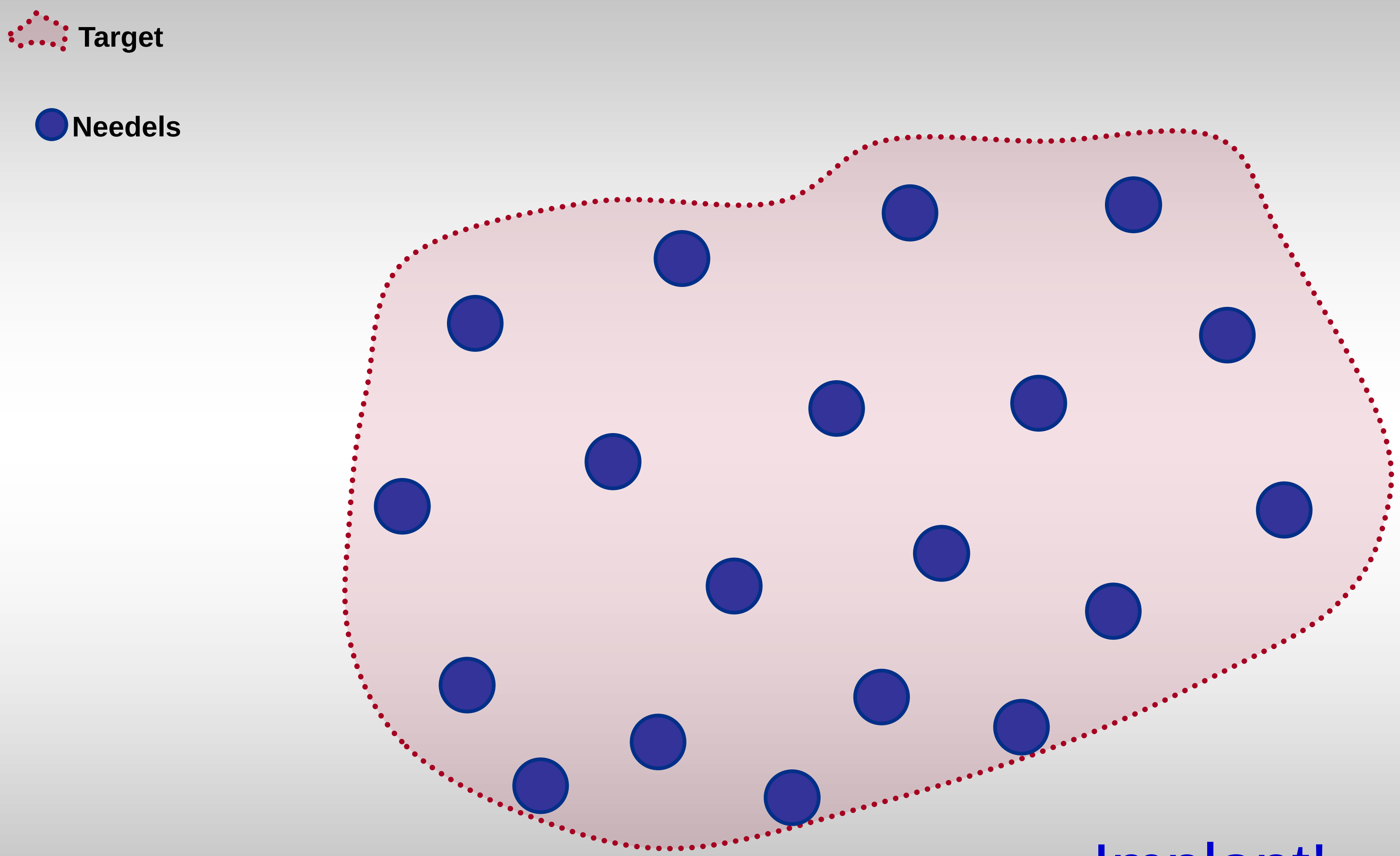
Bladder D_{2cc} = *70* $Gy_{\alpha\beta3}$

Rectum D_{2cc} = *67* $Gy_{\alpha\beta3}$

Sigmoid D_{2cc} = *55* $Gy_{\alpha\beta3}$

☒ **Intracavitary** ☒ **Interstitial**

Pre-treatment planning on the Implant before using any TPS



Implant!

Pre-treatment planning on the Implant before using any TPS

Table 2.8: Relationships between the Treated Volume and the implant geometry.

Ratio	*2 lines*	*Planar implant*	*Squares*	*Triangles*
Treated length / active length	0.69 – 0.81	0.69 – 0.78	0.66 – 0.73	0.65 – 0.76
Treated thickness / separation	0.54 – 0.58	0.57 – 0.69	1.55 –1.59	1.25 – 1.35
Safety margin / separation			0.26 – 0.28	0.18 – 0.21
Lateral margin / separation	0.37	0.33		

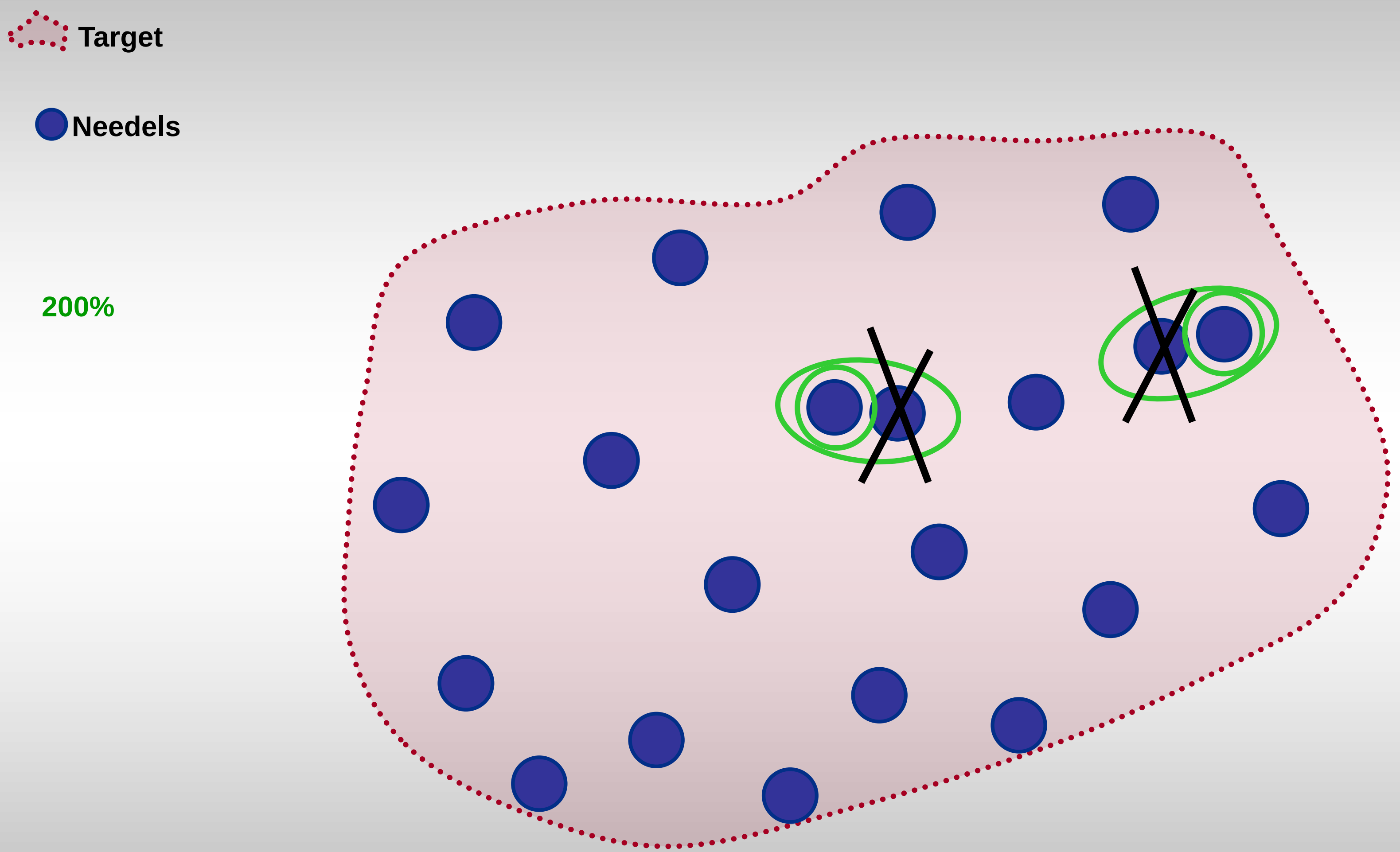
From Dutreix et al (8).

All of these relationships were established assuming that all lines in a given pattern have the same active length, but they are also valid, under certain conditions, for lines of slightly unequal length.

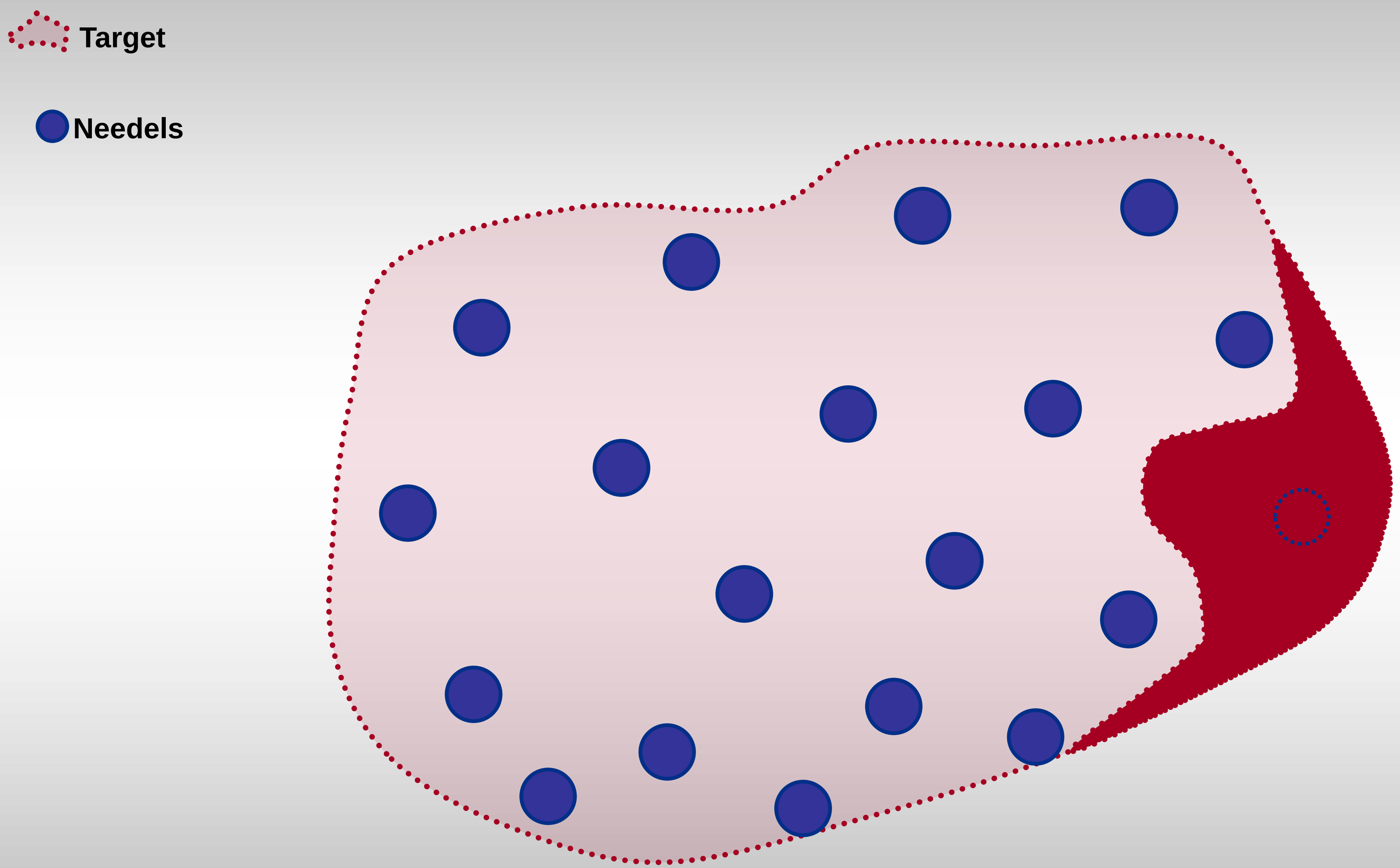
Table 2.8 can be summarised as follows:

* The ratio (length of the treated volume) / (active length) is close to 0.7.
* For one plane implants: the ratio (thickness of the treated volume) / (source separation) is about 0.6.
* For a two-plane implant this ratio is estimated as 1.3 for a triangular configuration and 1.6 for a square configuration.
* For more complex implants, the distance between the reference isodose and the outer lines of implants in the central plane (known as the safety margin) is equal to 0.2 times the separation for a triangular configuration and to 0.3 times the separation for a square configuration.

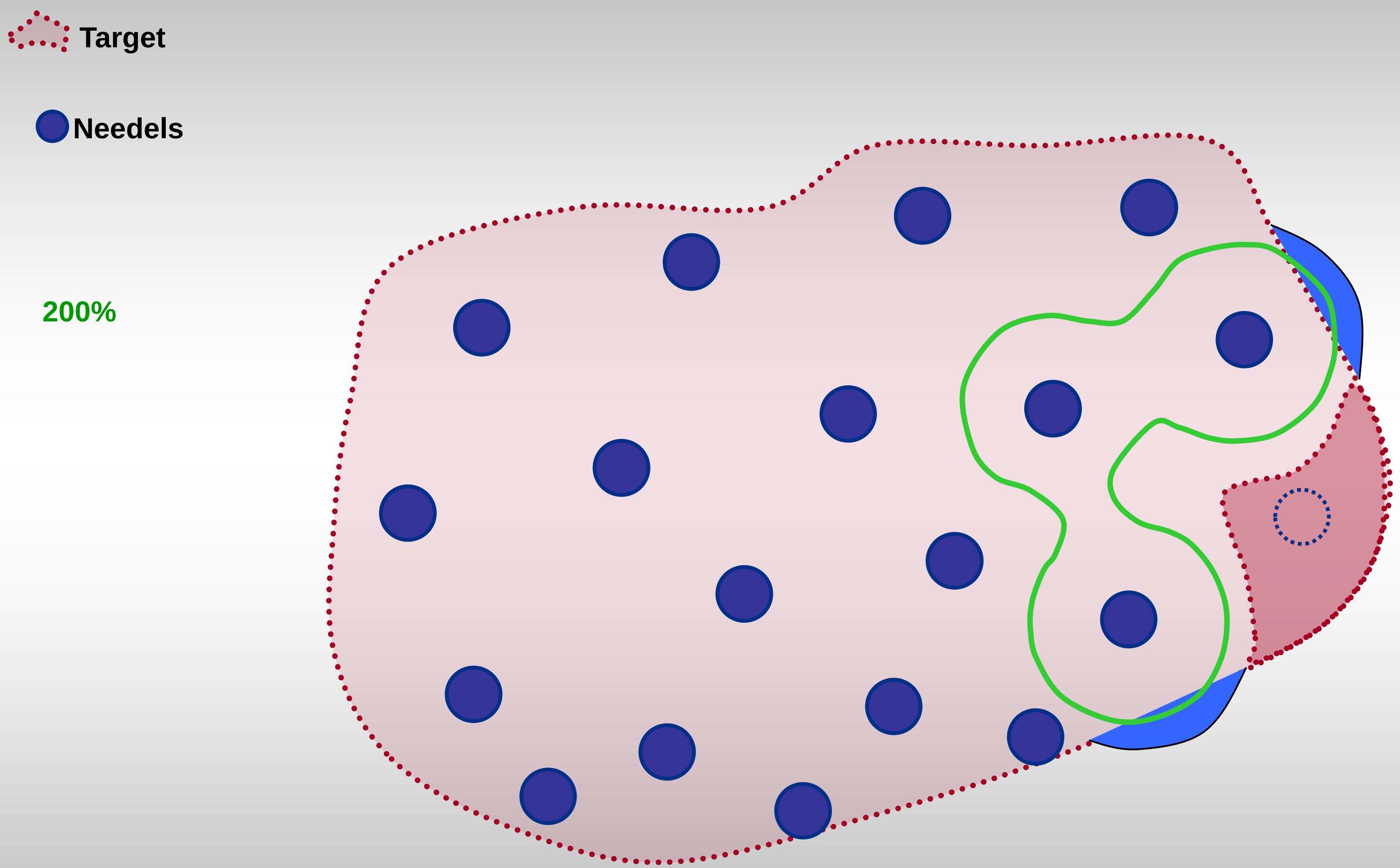
Pre-treatment planning on the Implant before using any TPS



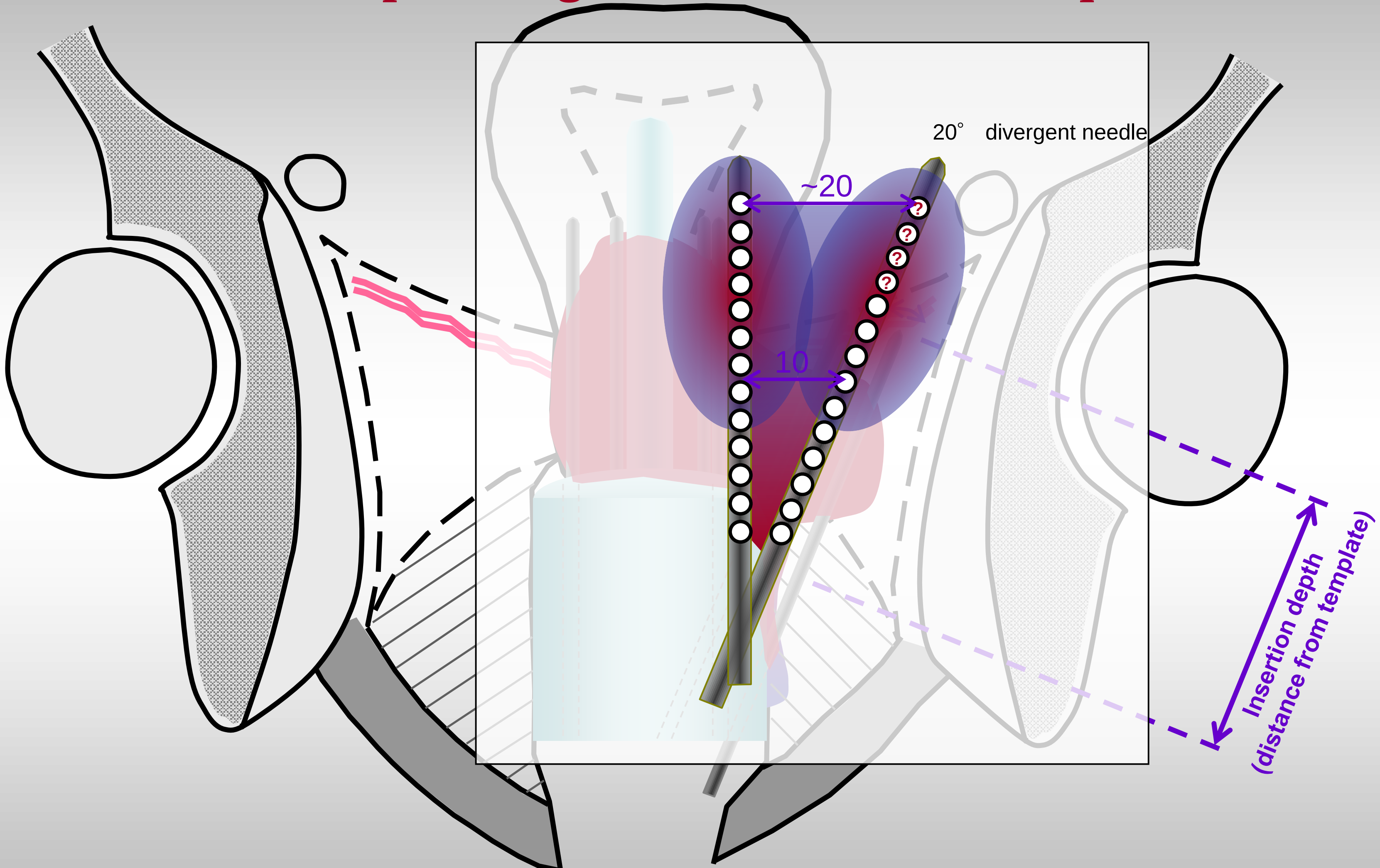
Pre-treatment planning on the Implant before using any TPS



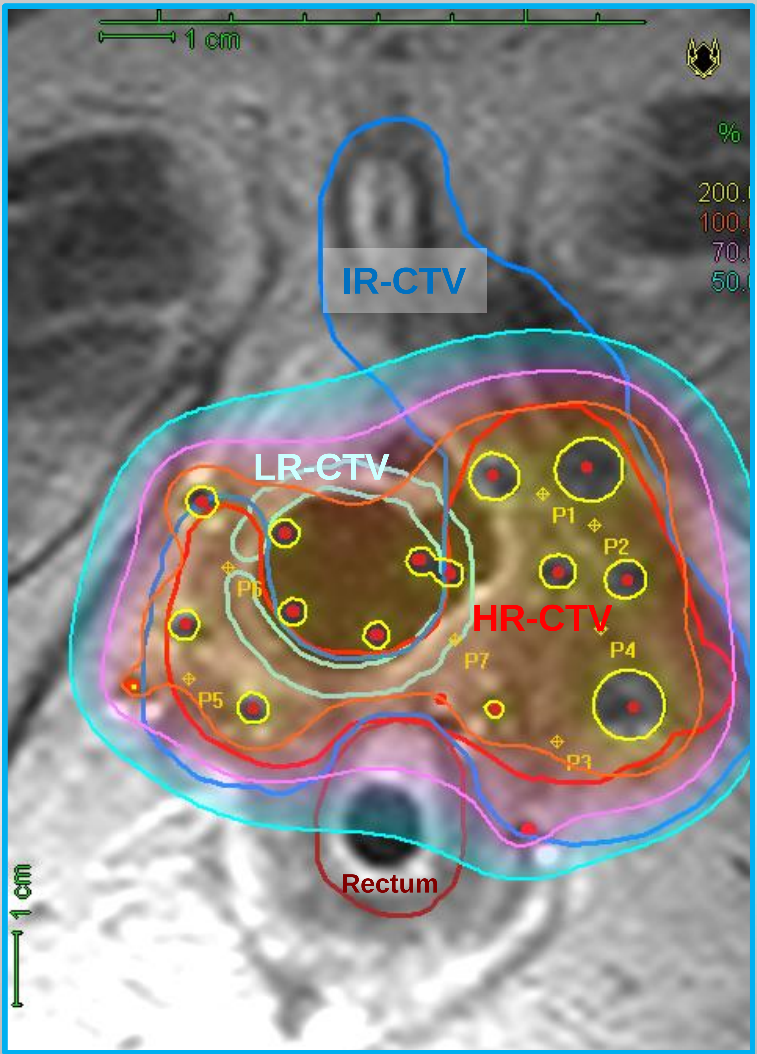
Pre-treatment planning on the Implant before using any TPS

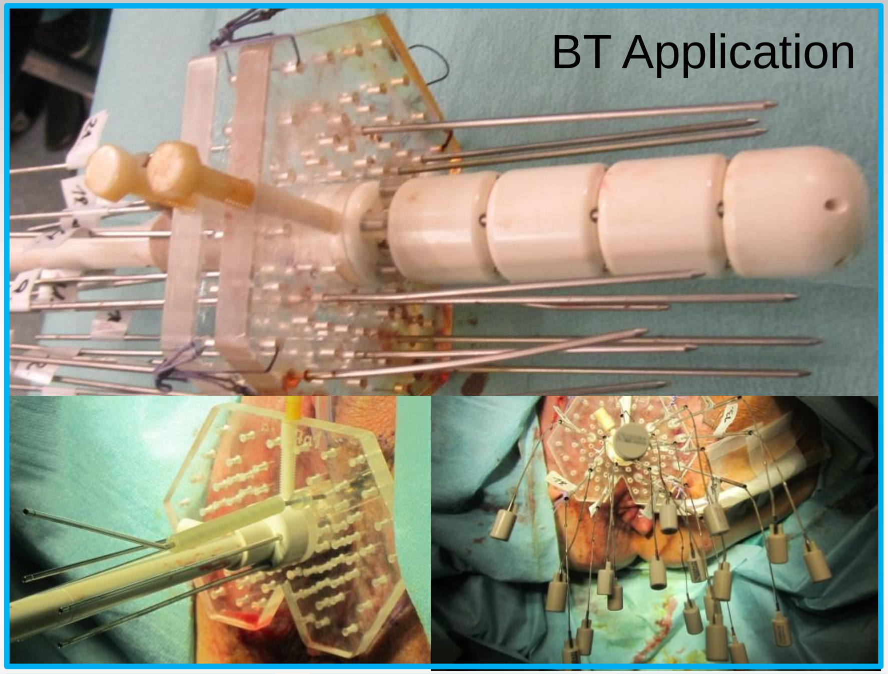


Treatment planning for interstitial techniques



Clinical case: N. Vulvae-Vaginal stage III (7cm max width!) 59.4 Gy EBRT + Cisplatin / 5-Fu
PDR-BT boost (0.5 Gy -> 20Gy D90= 80Gy Rectum: D2cc= 72Gy) CR after 1.5 years !



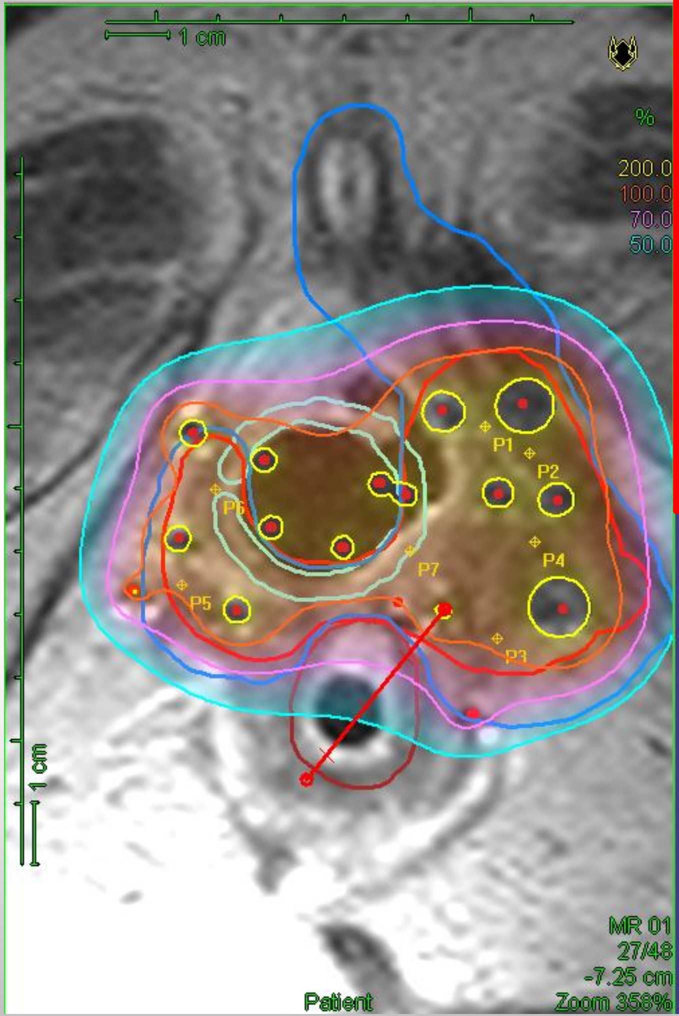


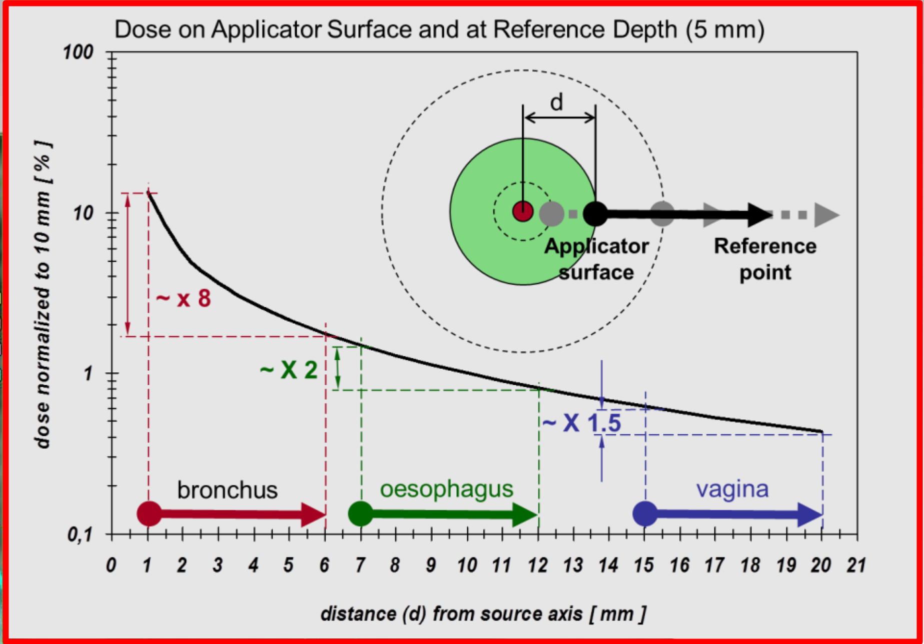
Jan 2012

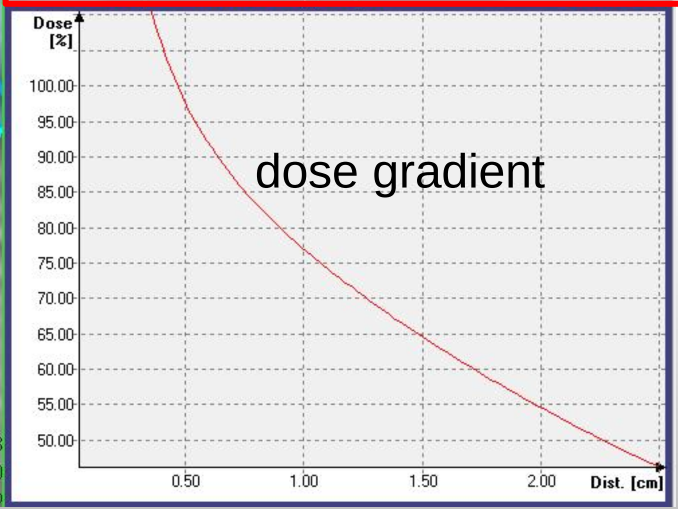
Apr 2012

May 2013

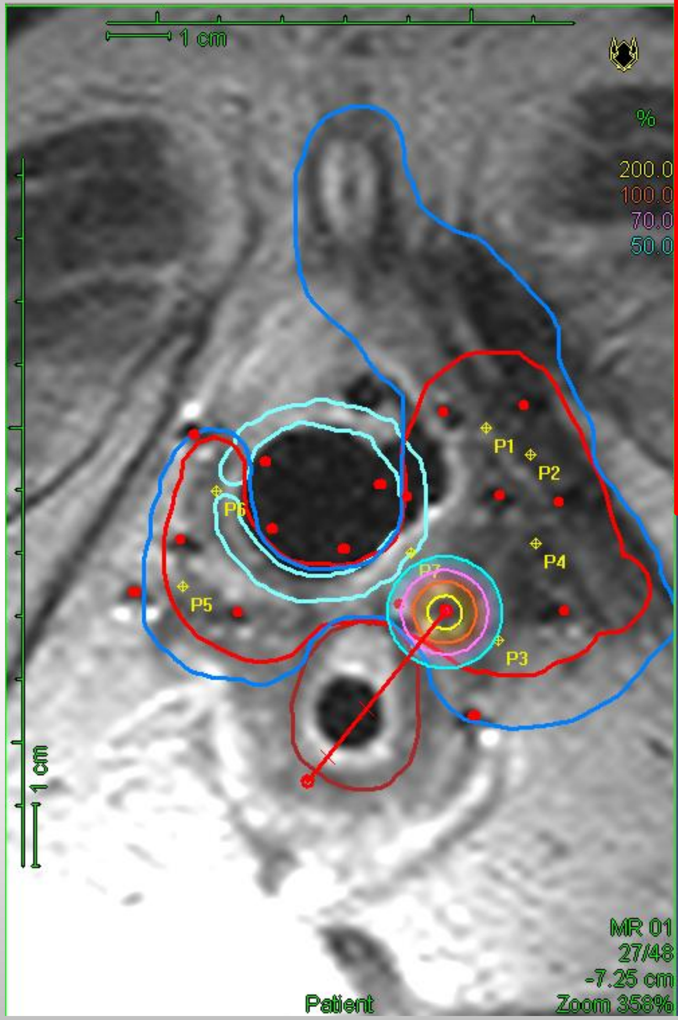
Dose gradient for adjacent OARs

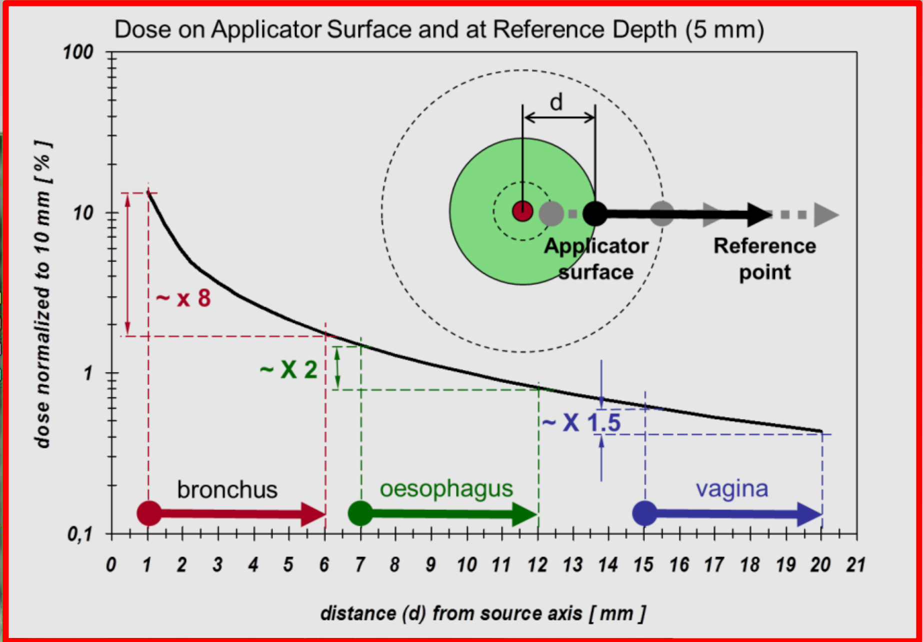


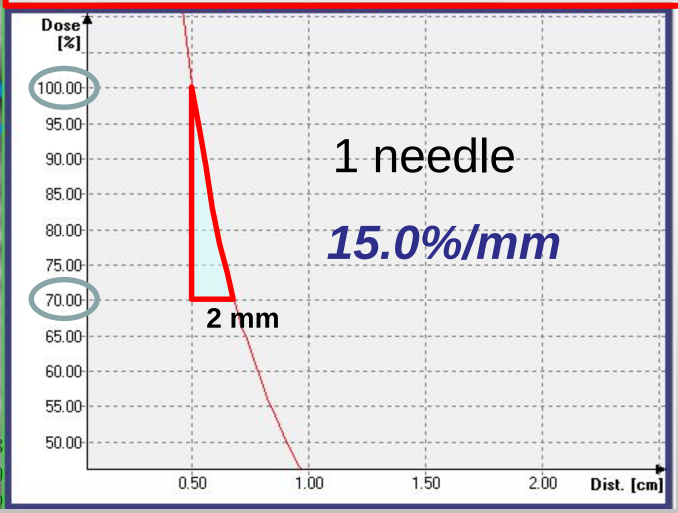




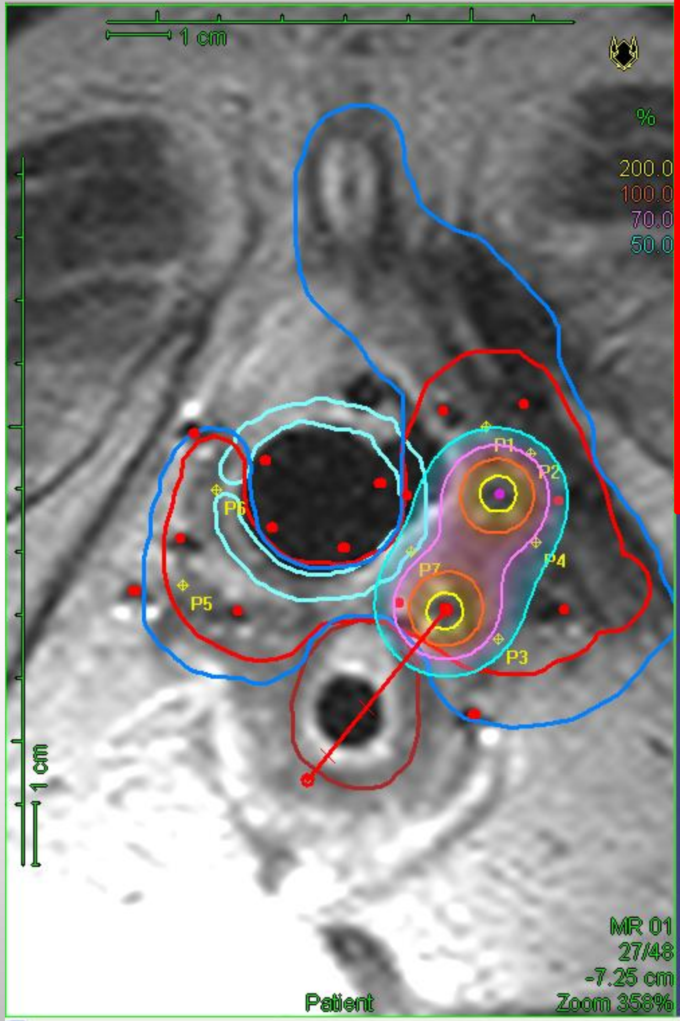
Dose gradient for adjacent OARs

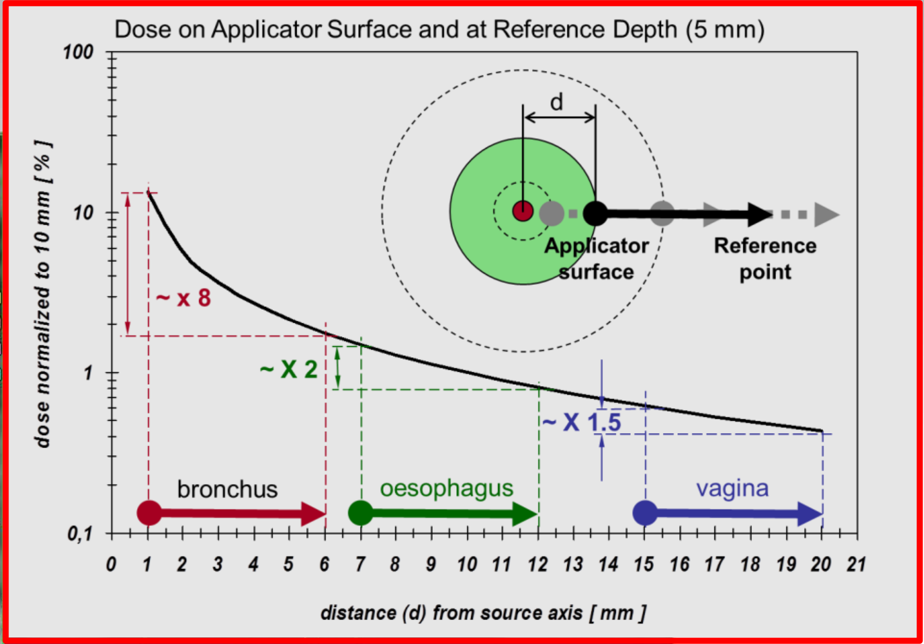






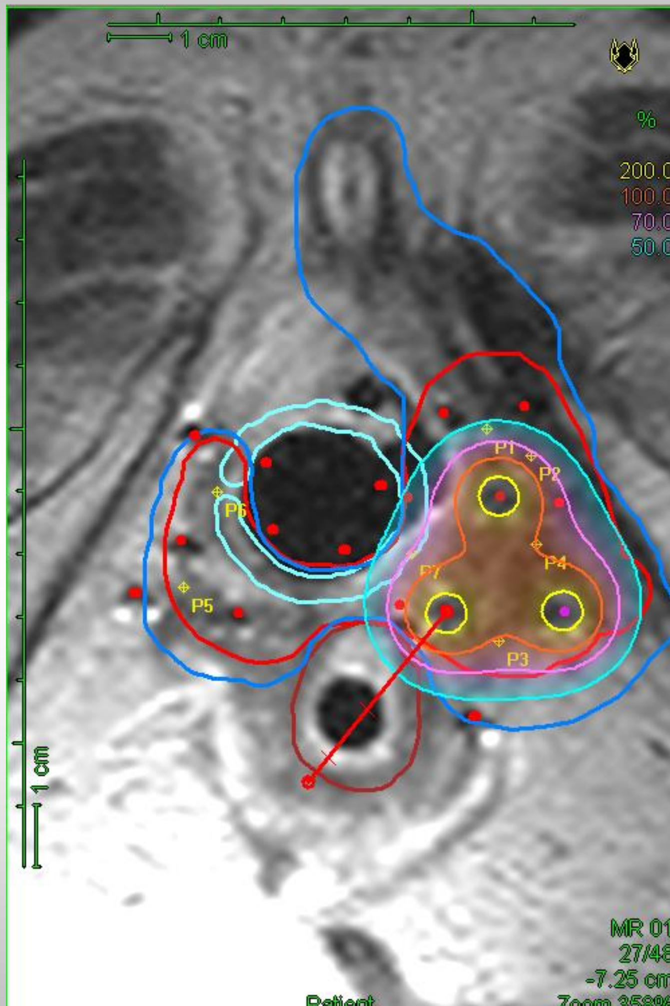
Dose gradient for adjacent OARs

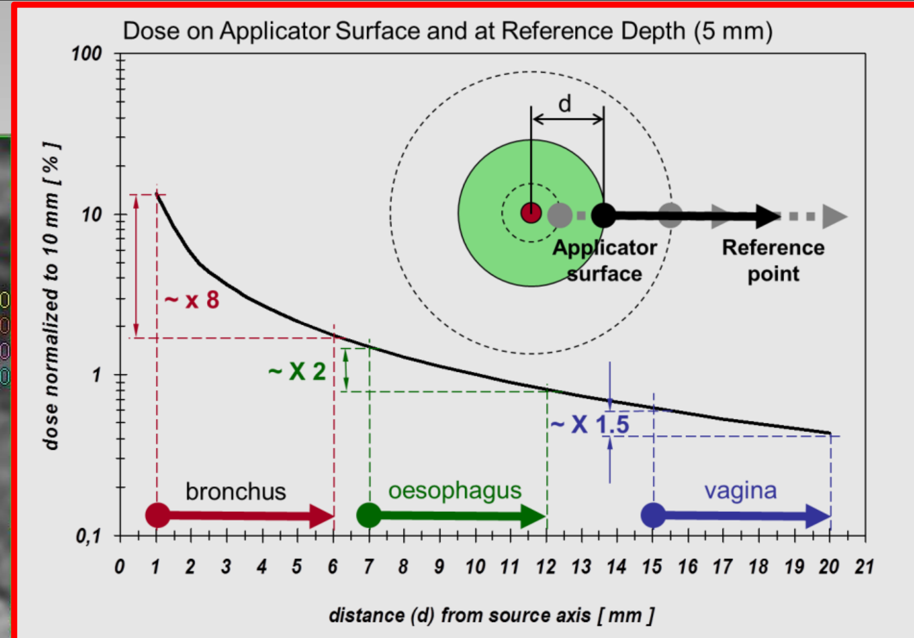


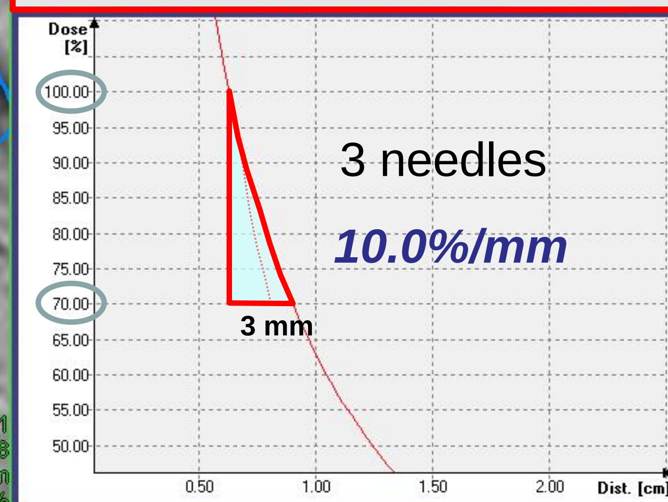


Time zone: W. Europe Star

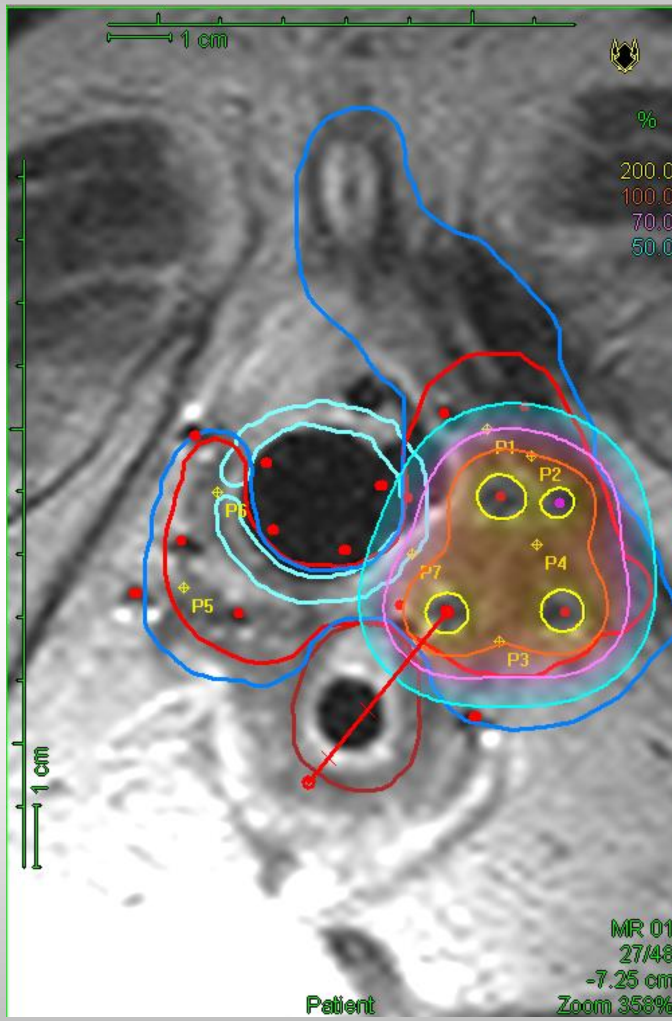
Dose gradient for adjacent OARs

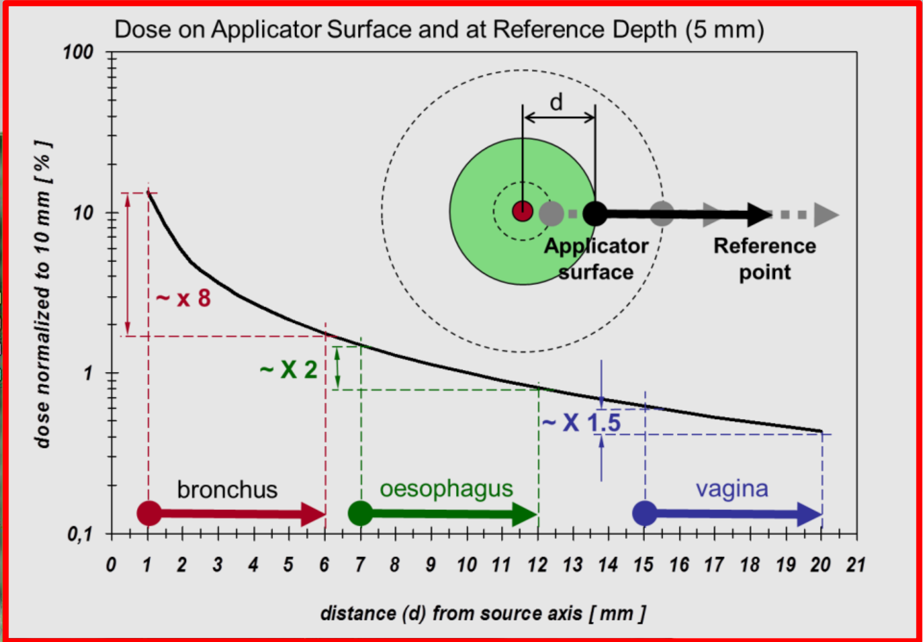


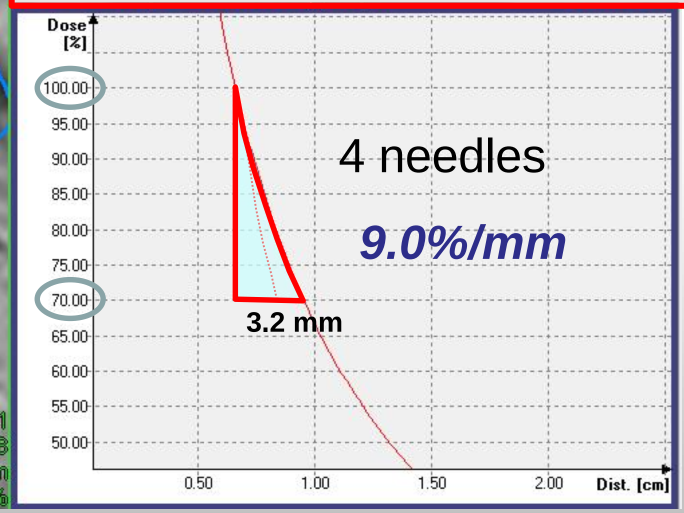




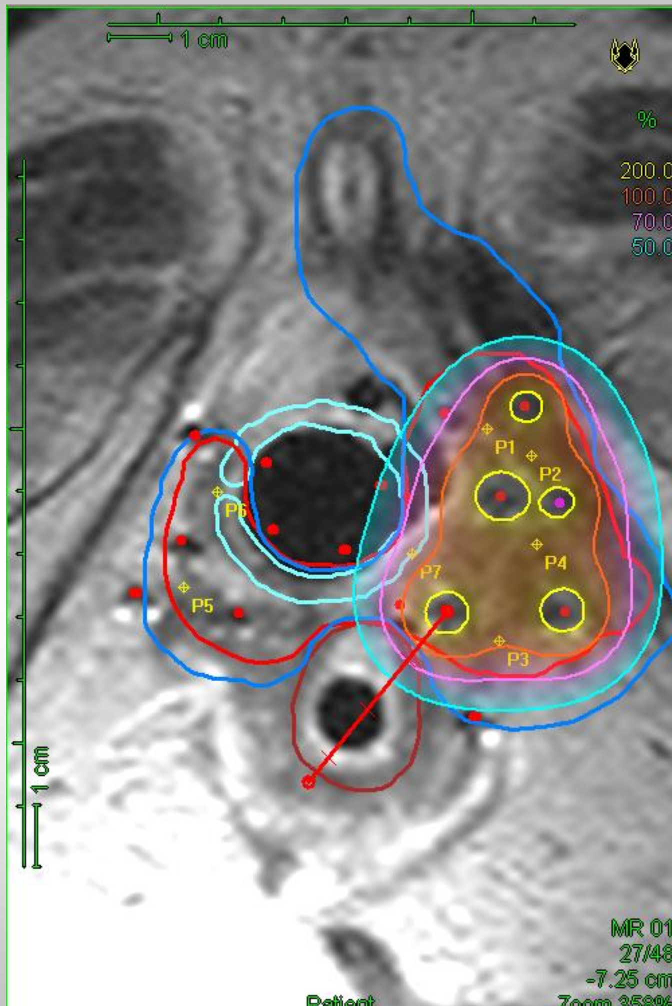
Dose gradient for adjacent OARs

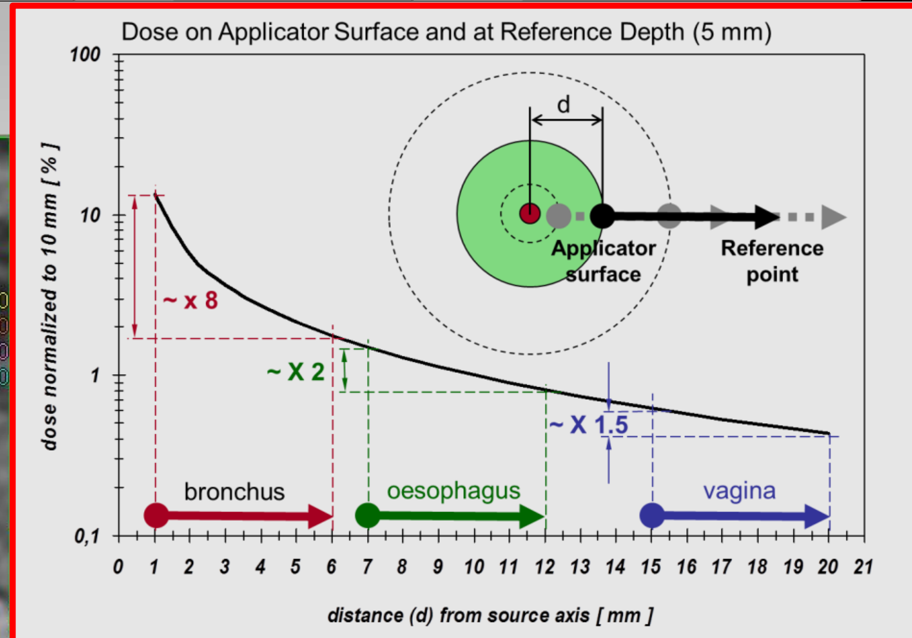


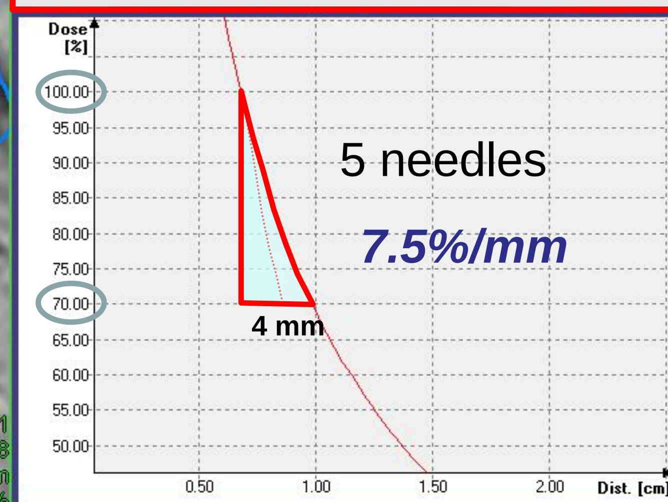




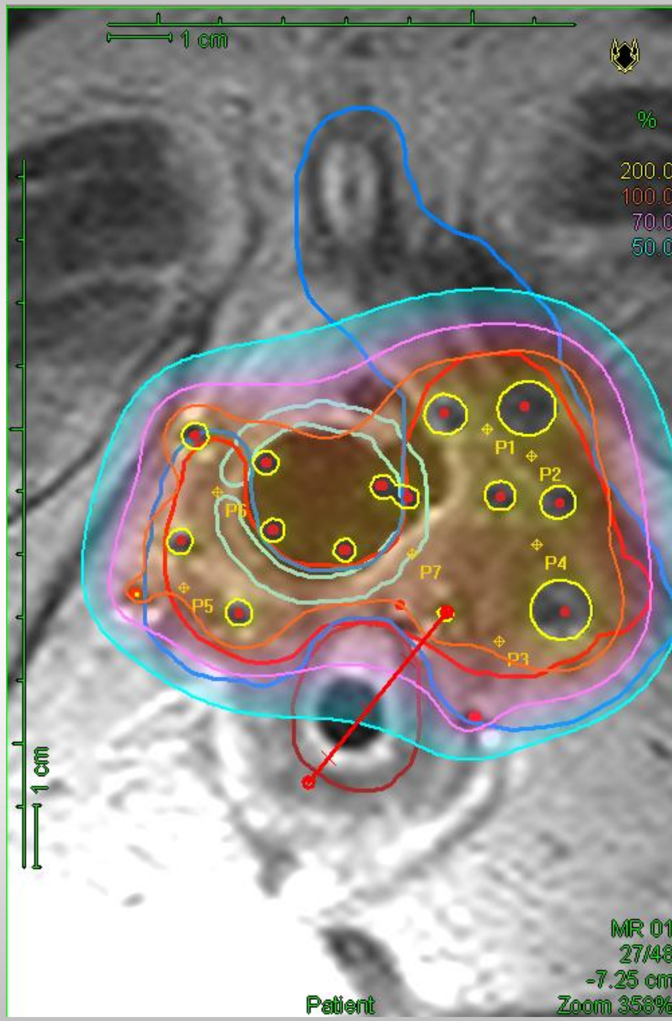
Dose gradient for adjacent OARs

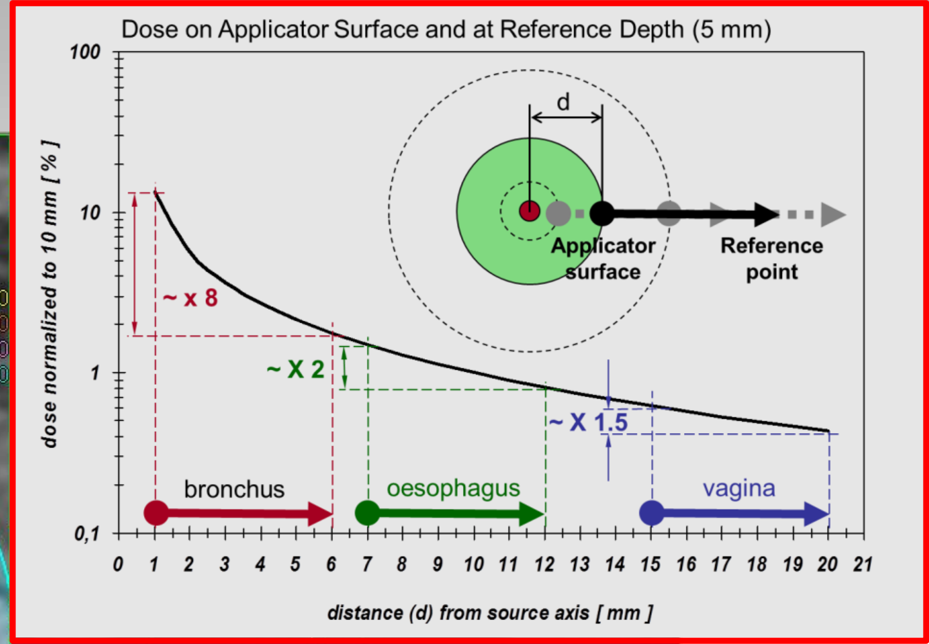


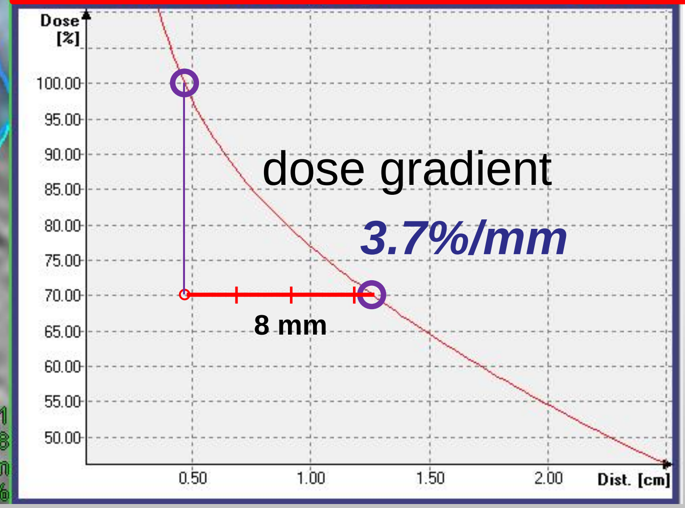




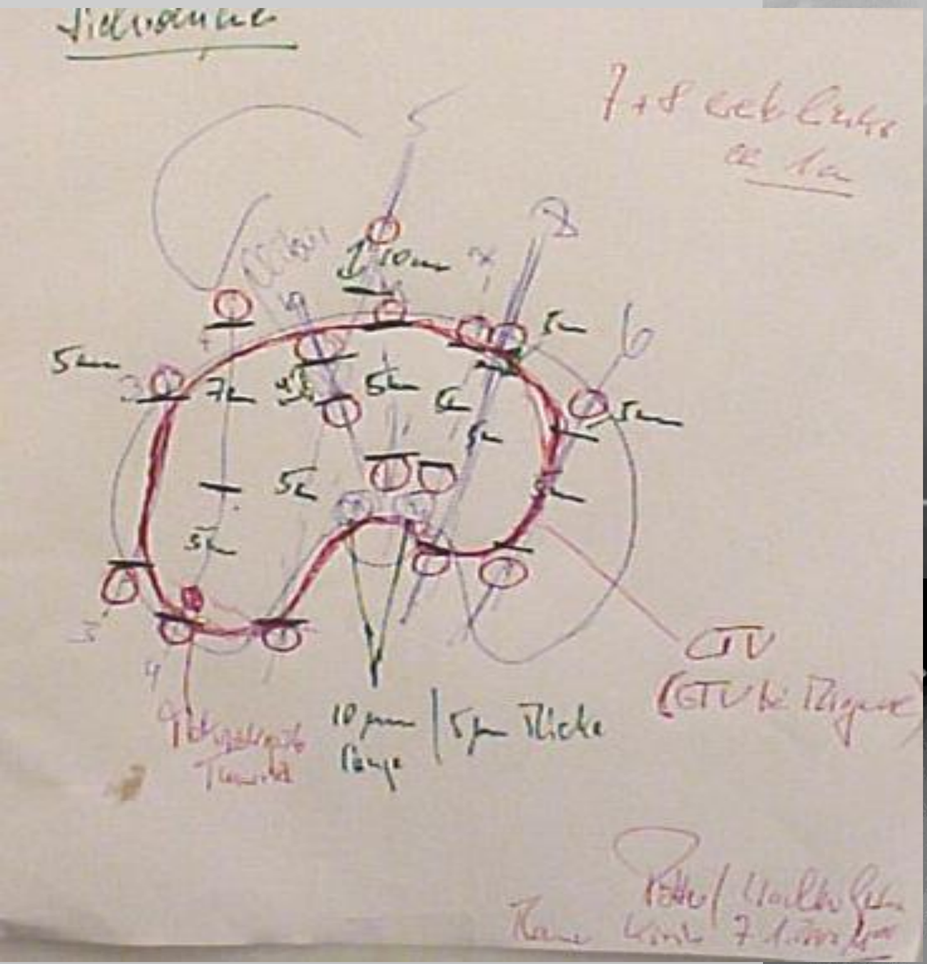
Dose gradient for adjacent OARs



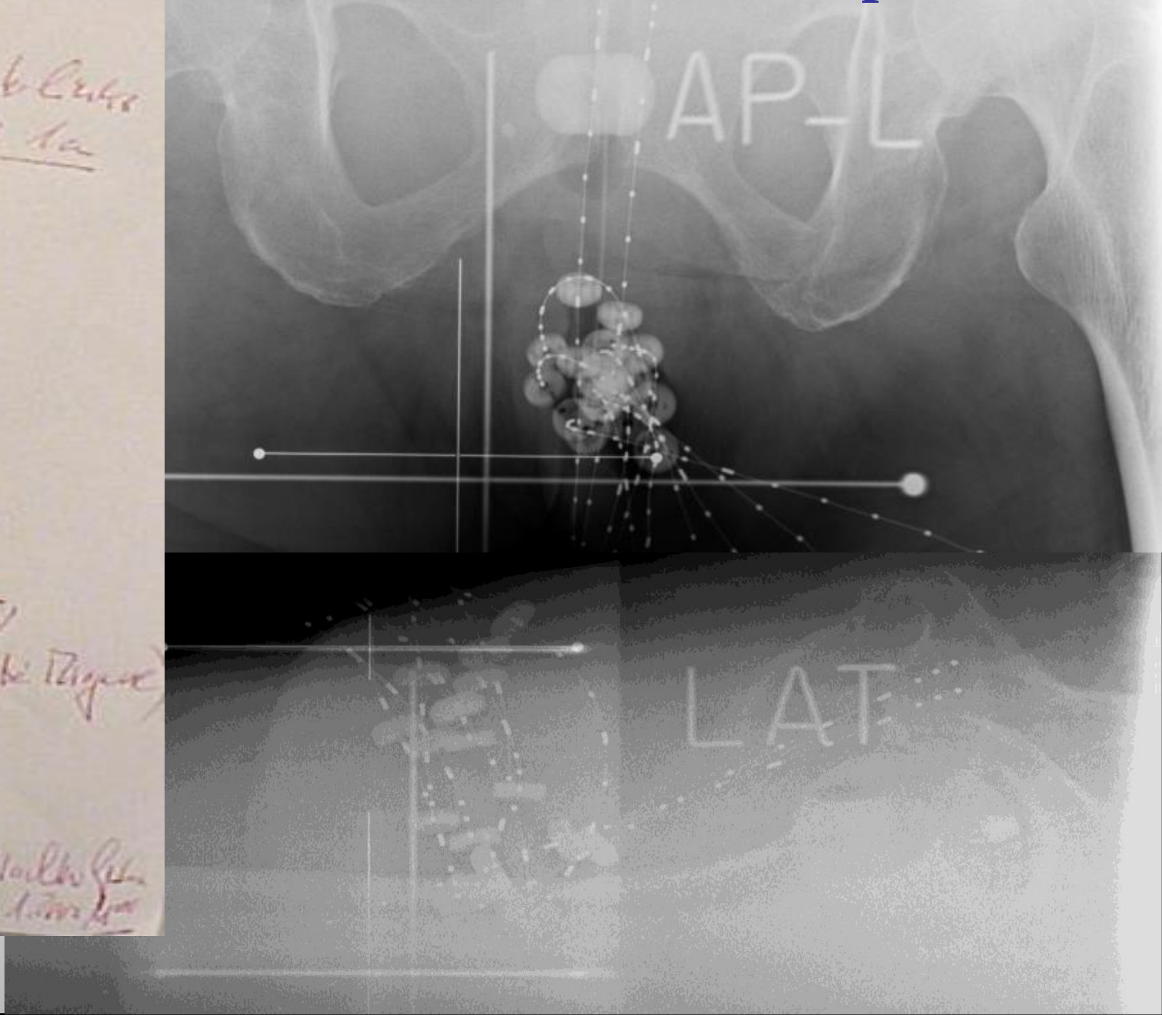




Interstitial Brachytherapy "Example Vulva"

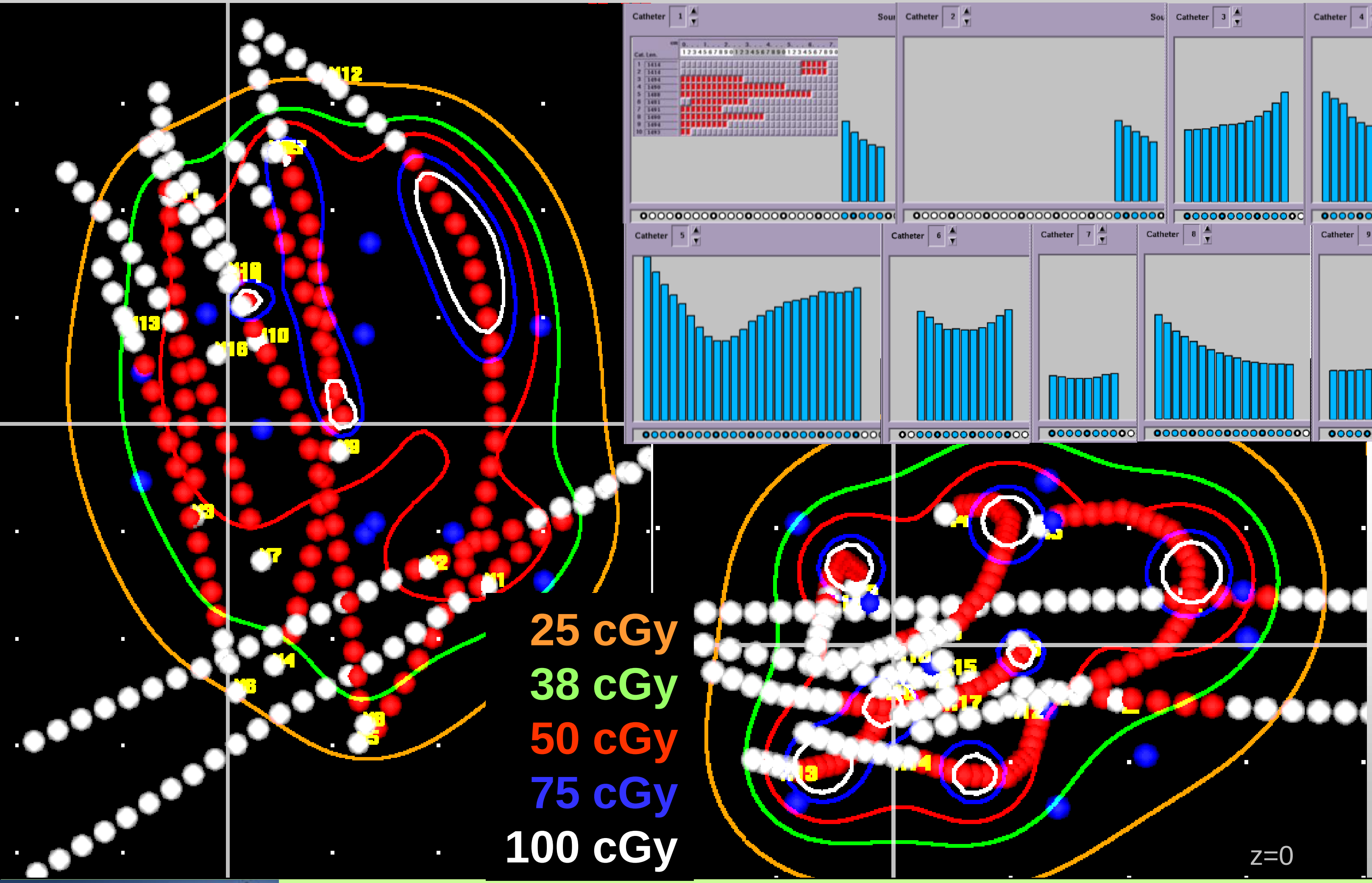


RTG control after implantation



Interstitial Brachytherapy “Example Vulva”

PDR BT- Treatment Planning

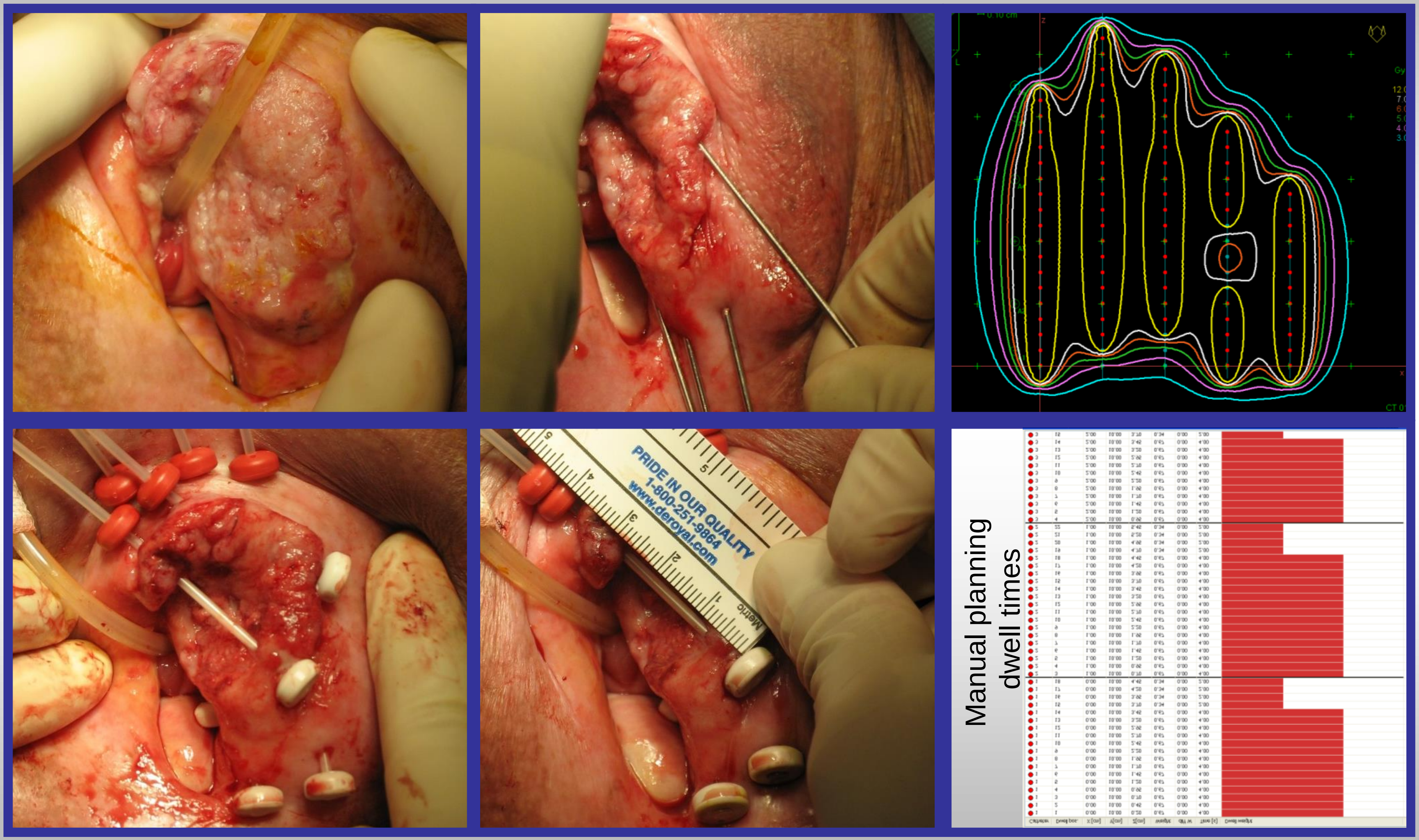


Volume:

$V(PD) = 30cm^3$

$V(2xPD) = 3.5cm^3$

Interstitial Brachytherapy "Example Vulva"



Reference- / Normalisation Points

- Interstitial using ICRU 58

  basal dose points

- Intracavitary + interstitial

  Points at level far from needle positions in addition to

  depth dose points for cylinder

  and/or basal points depending on location

- Interstitial (non parallel – E.g. vulva)

  Depth dose points

Tips

- Watch „High Dose Volumes“ – keep them small
- Take into account the “off-set” (distance: tip – 1st Dwell) when defining the needle insertion depth
- Review the implant on sectional images (MRI) to assure appropriate implant quality (target, OARs) before starting the TPS
- For complex implants: double-check the reconstruction and catheter to transfer-tube channel mapping
- *Keep the patient in the same position – for imaging and treatment delivery to minimize implant variations*

Thank You

Merci

Danke

Gracias

Dept. of Radiotherapy
Medical University of Vienna

Physics aspects of treatment planning in endometrium cancer

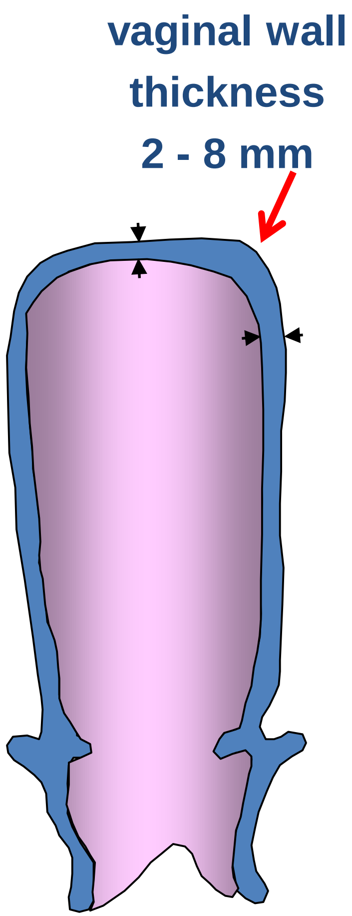
Taran Paulsen Hellebust

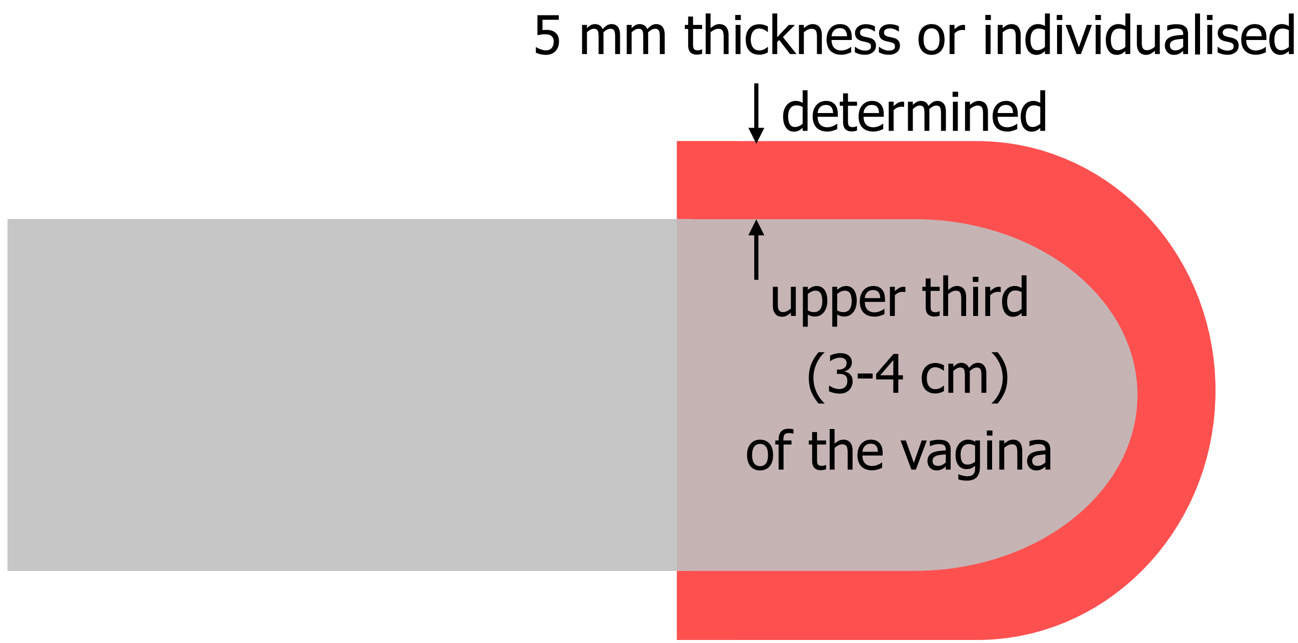
Associate professor

Oslo University Hospital/The Norwegian Radium Hospital

Oslo, Norway

Clinical Target Volume (CTV)



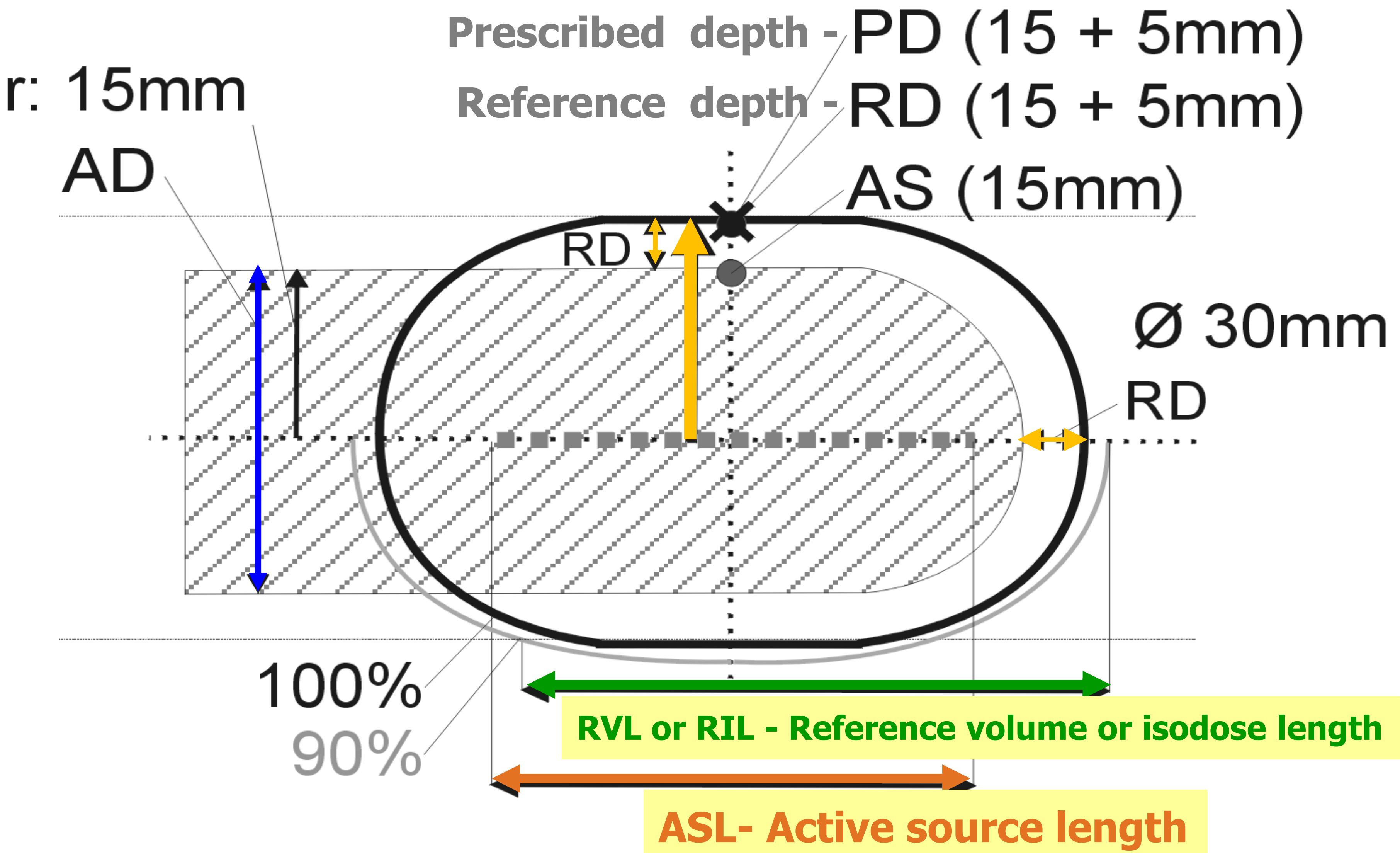


ABS survey regarding postopreative treatment for endometrium cancer

Applicator type	%*
Single channel vaginal cylinder	90.6
Shielded vaginal cylinder	13.0
Multichannel vaginal cylinder	10.9
Fletcher style colpostats	10.6
Henschke style colpostats	1.5
Other	2.1

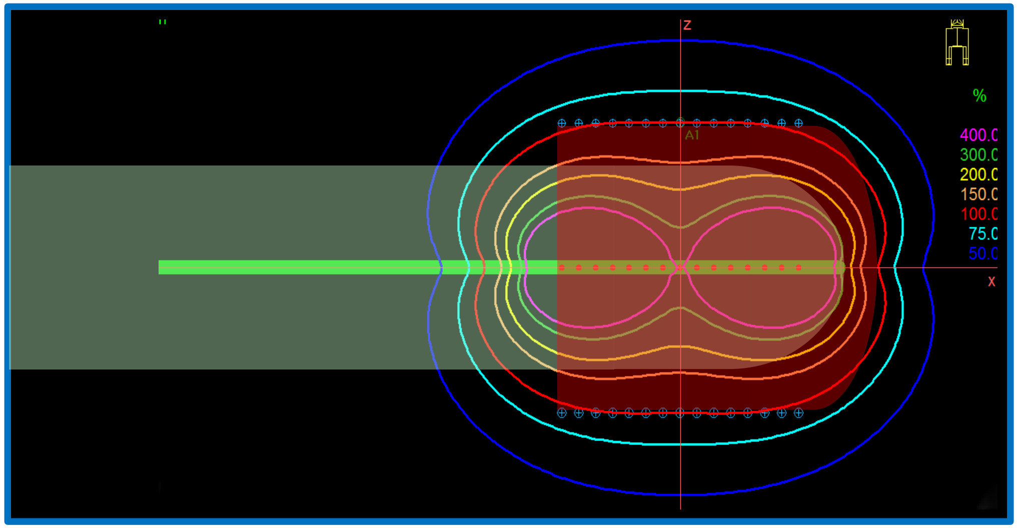
Small et al IJROBP 2005

Concept and terminology:



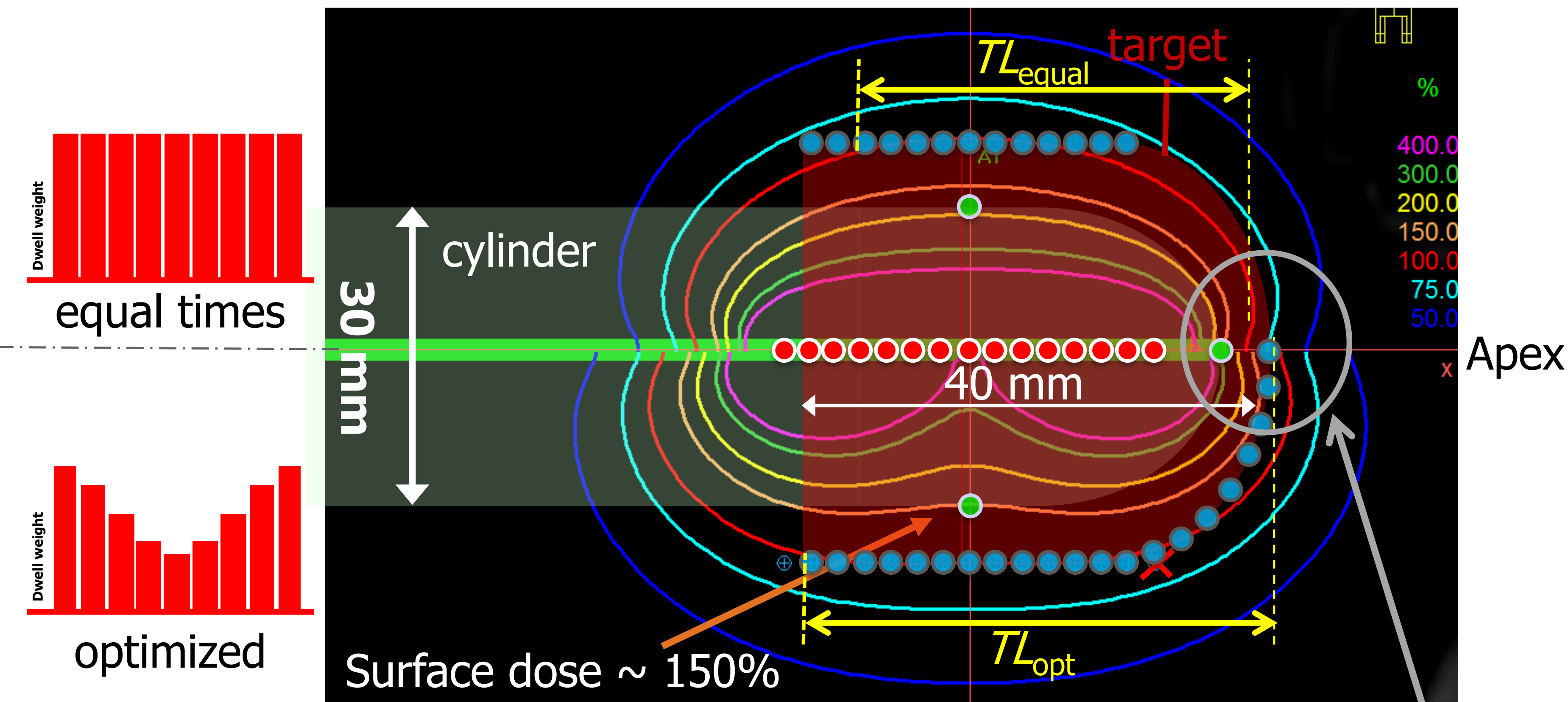
The dose distribution in CTV will depend on

- length to be treated
- applicator diameter
- prescription depth



- distance from the first dwell position to the tip of the applicator
- the shape of distal part of the applicator

Dose Optimization based on reference points/line



$ASL_{equal} = ASL_{opt}$

Dose at the applicator (apex) tip: $120\%_{equal} < 250\%_{opt}$

5mm (apex): $60\%_{equal} < 100\%_{opt}$

$RIL_{equal} < RIL_{opt}$

Vaginal Cylinder Treatment planning

Example: VagCyl.Ø30mm, VL=10cm TL=35cm, 2.5 mm step-size

DosePoints

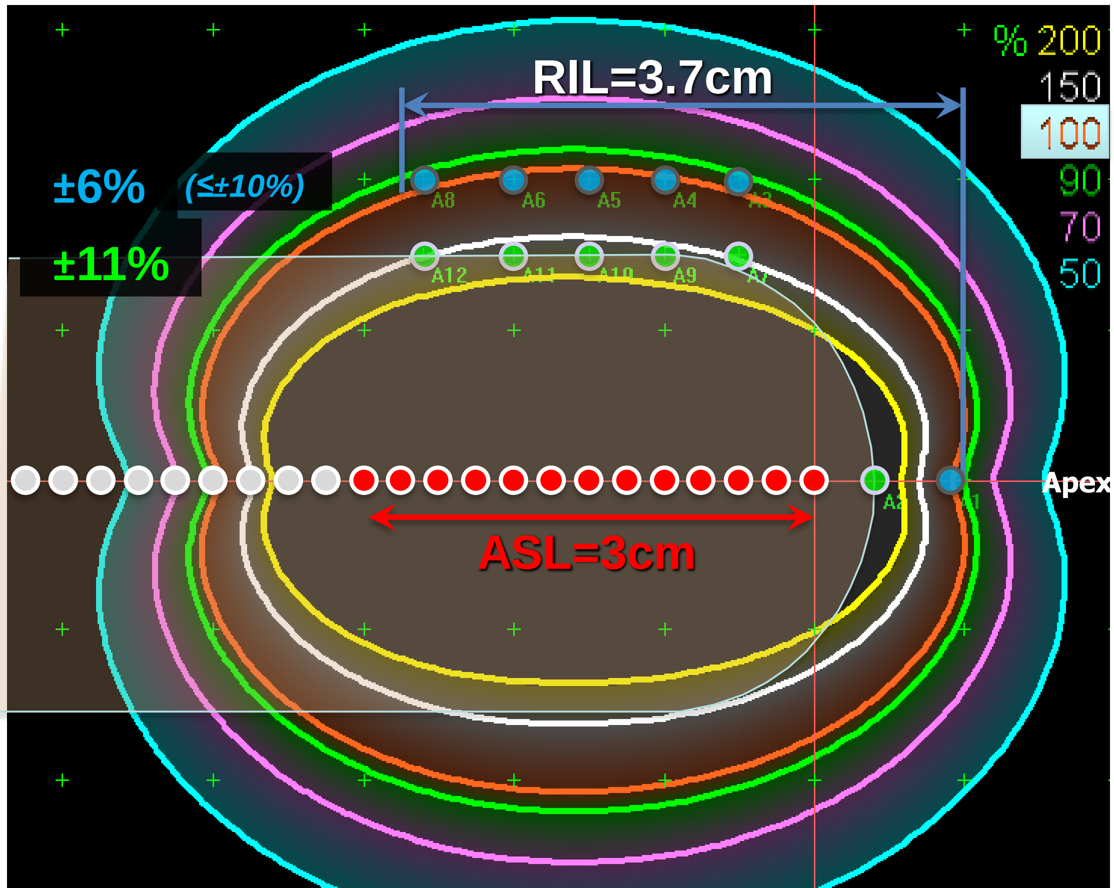
2.5mm step-size	
Apex DP [%]	
0mm	5mm
354,49	101,32
Lateral DP [%]	
0mm	5mm
143,98	92,66
161,30	101,82
168,74	105,76
165,98	104,04
147,87	94,40

TRAK= 0.23 cGy@1m

Dwells

Active Dwell	
Pos	time [s]
1	14,20
2	14,60
3	14,92
4	14,91
5	14,95
6	14,55
7	14,91
8	14,81
9	15,62
10	16,19
11	17,05
12	17,69
13	18,09

Σ202,5s



Vaginal Length: ~9 cm | TL: upper 1/3 : 3.5cm

Inactive — Active source pos.

Lat. dose points on applicator surface : 158% ±11% *Apex surface : 355%*

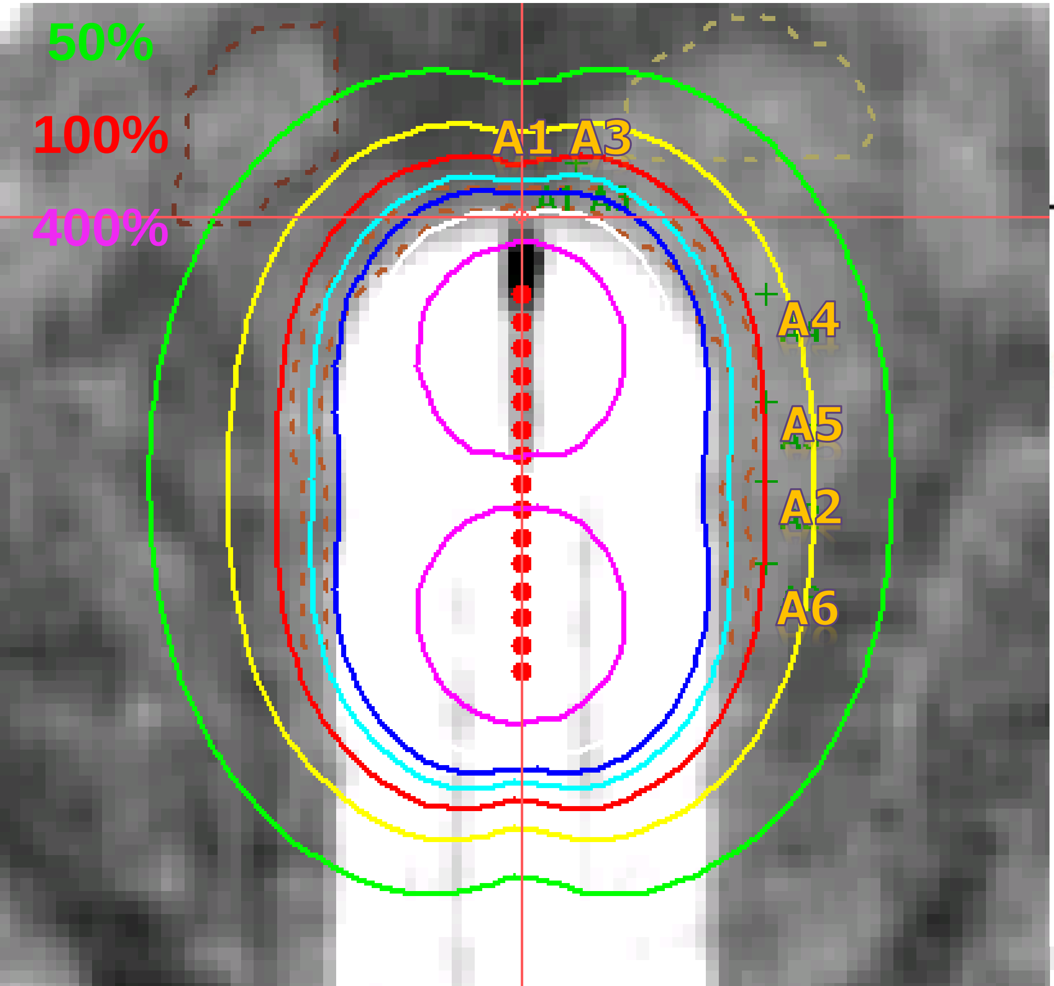
Lat. dose points in 5mm tissue depth : 100% ±6% *Apex 5mm : 101%*

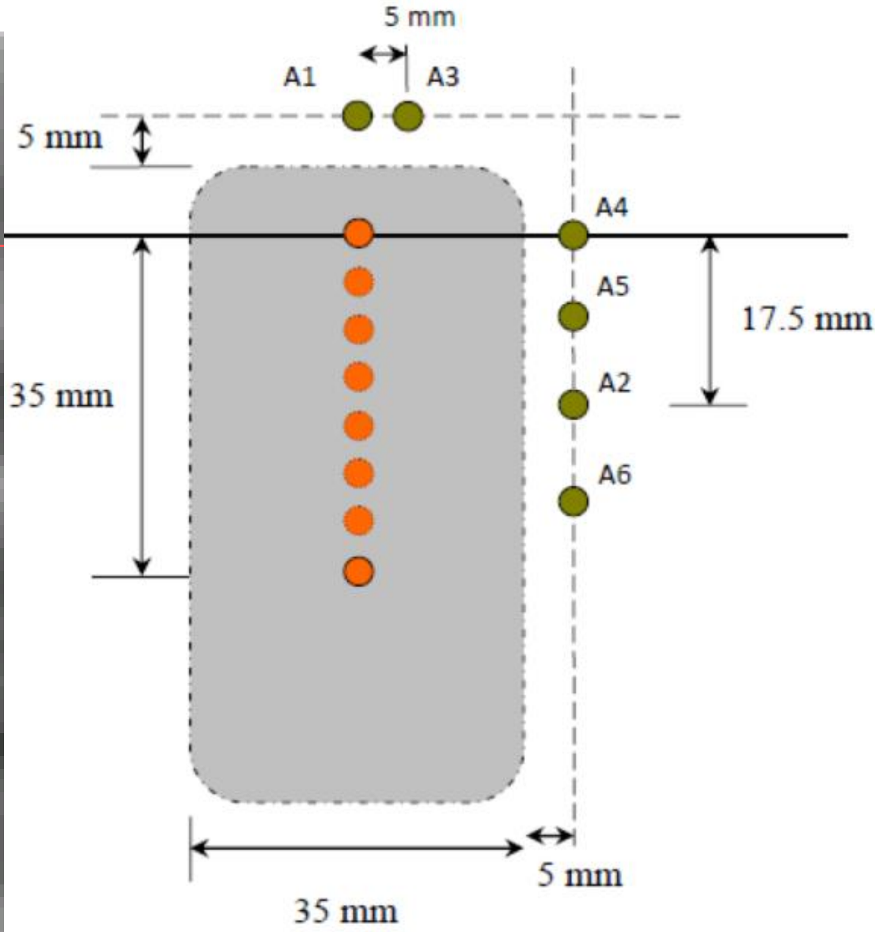
Methods - Dose planning

Prescription: 7 Gy (100%) at @ **A2**

Account for anisotropy: average **A1-A3= 100%**; **A1** min **90%**; **A3** max **110%**

A4-A5-A6 for dose recording, aiming for 100%

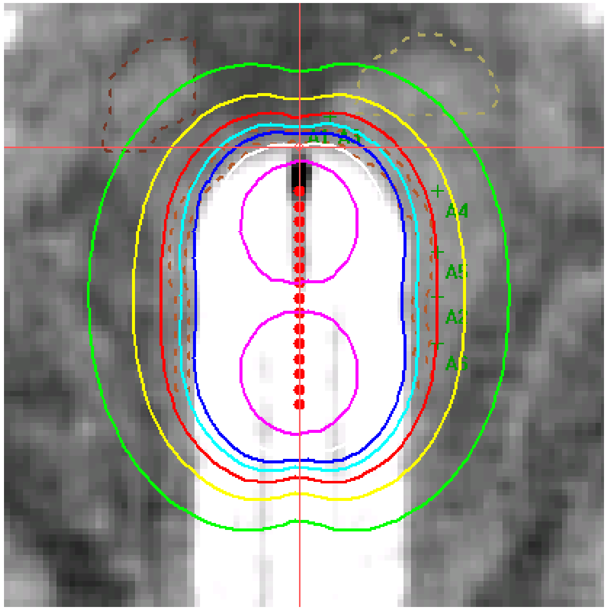




Cortesy: R. Nout

Cortesy: R. Nout

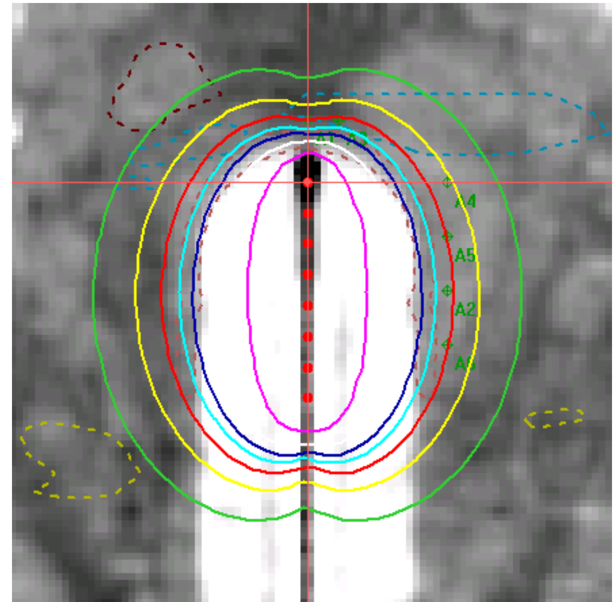
Dose planning



50%

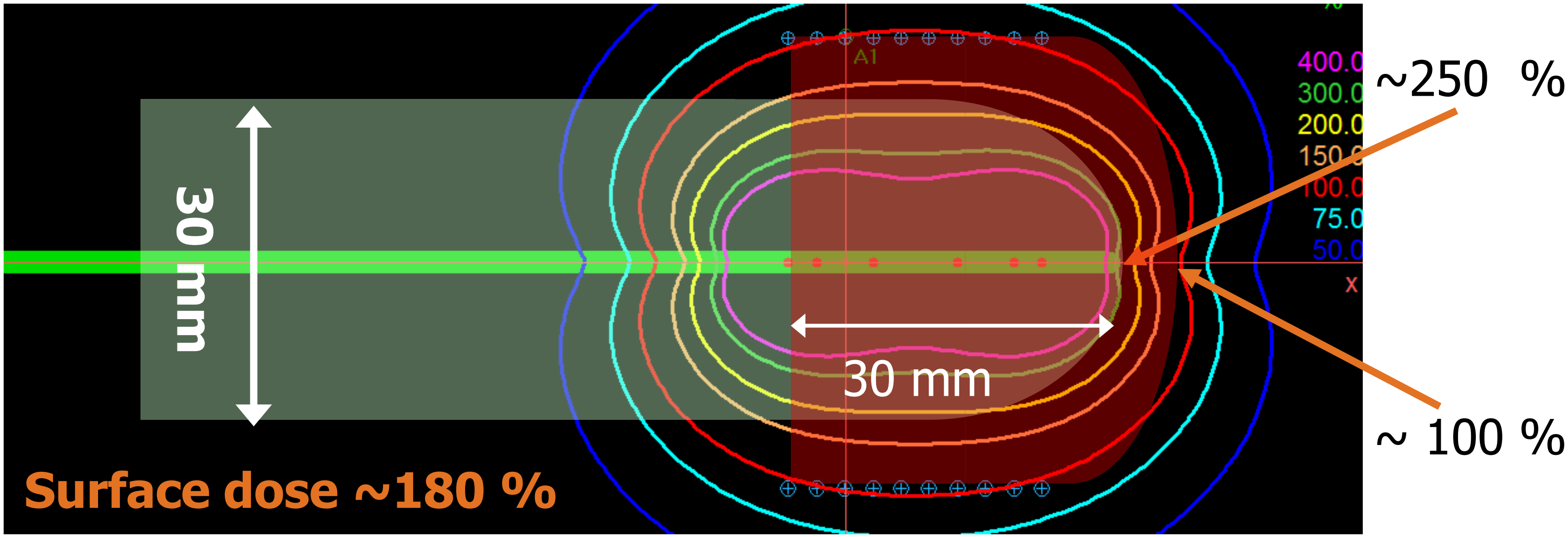
100%

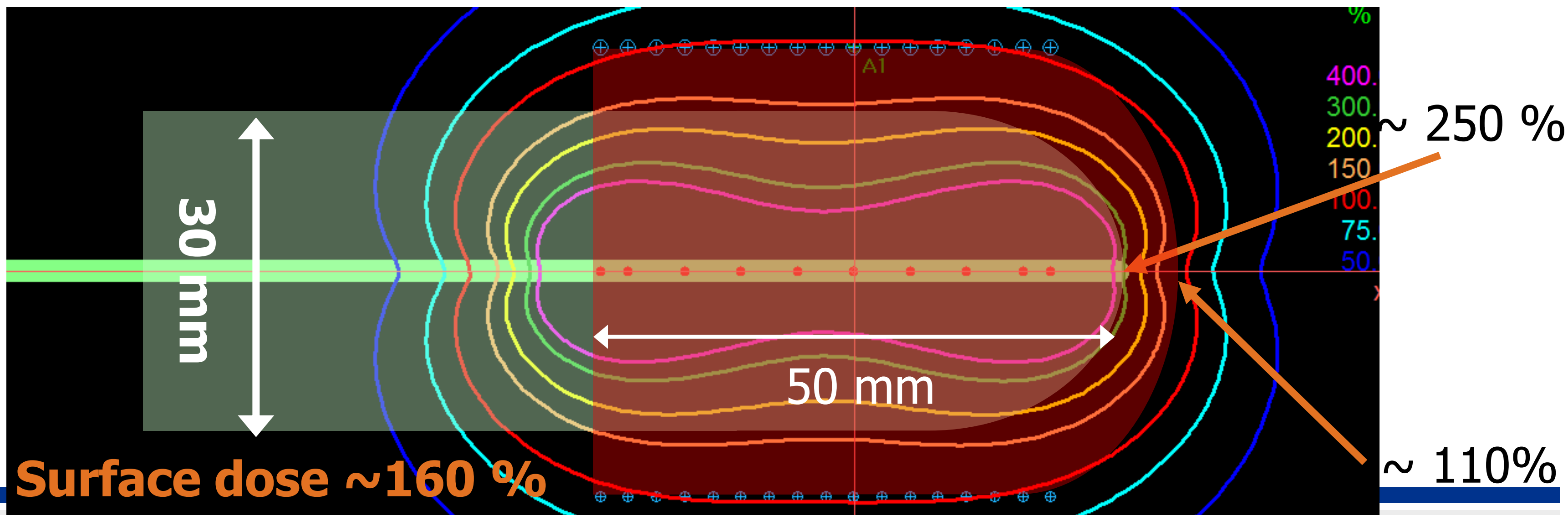
400%



A2 = 100%	A2 = 108%
A1: 93.4%, A3: 107.6%	A1: 94.3%, A3: 106.7%
Average A1/A3 = 100.5%	→ Average A1/A3: 100.5%
A4: 85.7%	A4: 79.4%
A5: 98.9%	A5: 99.6%
A6: 99.1%	A6: 102.1%

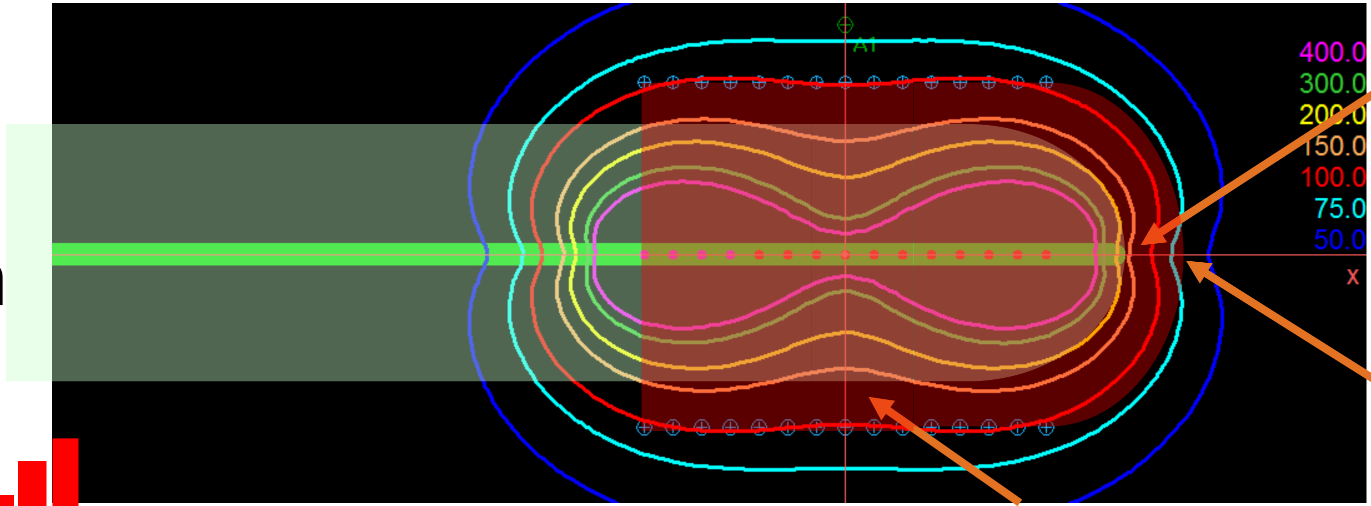
Length to be treated (3-5 cm)





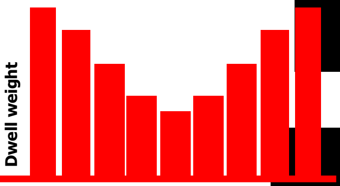
Cylinder diameter influences the dose

20 mm



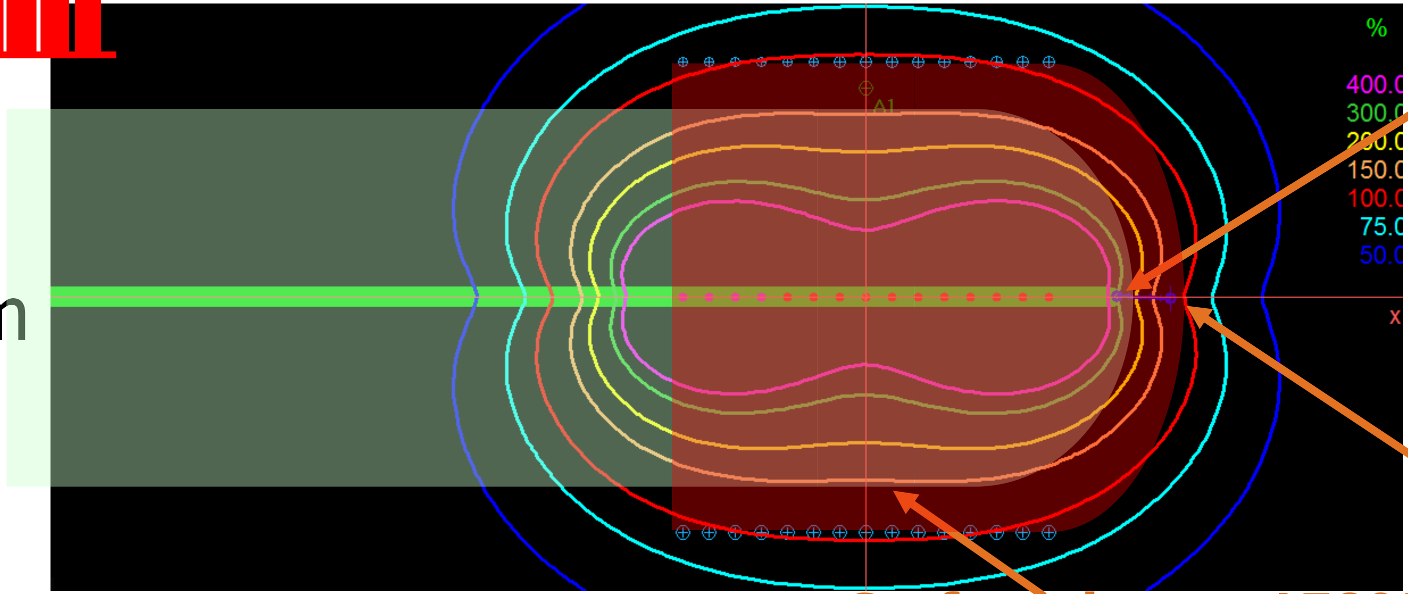
~ 150 %

~ 60 %



Surface dose ~ 170 %

35 mm

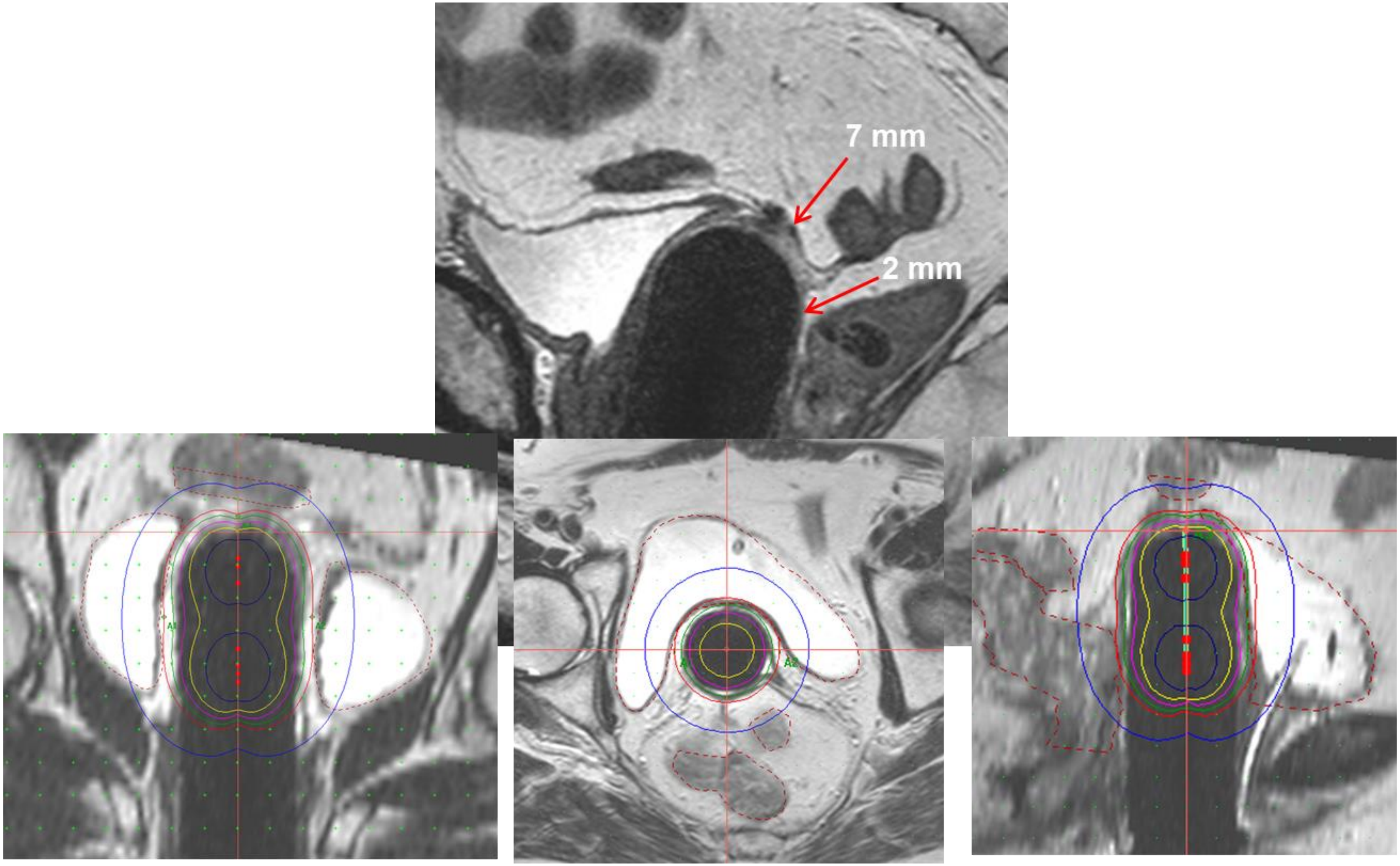


~ 300 %

~ 115%

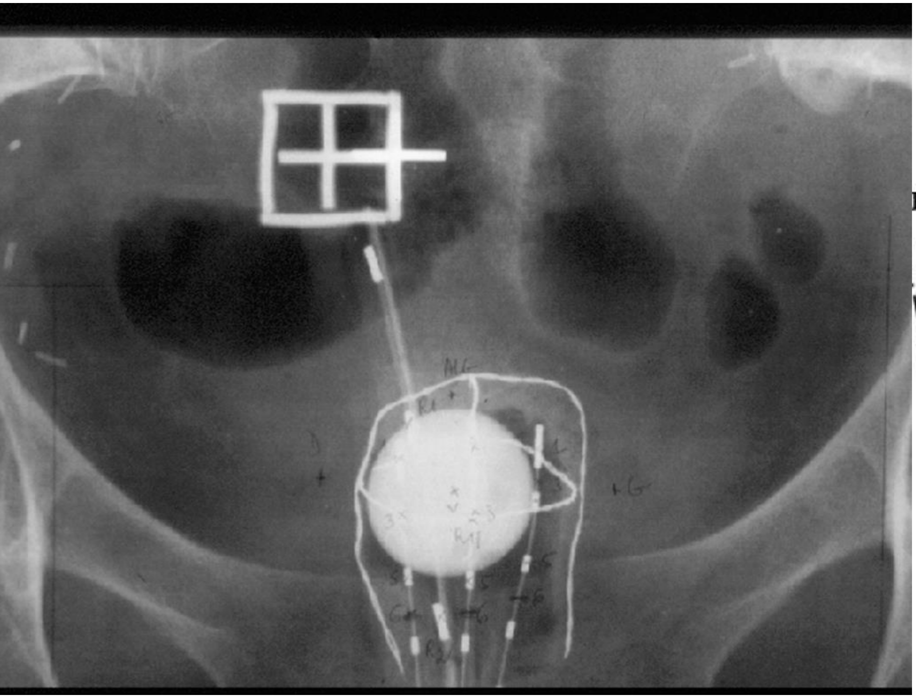
Surface dose ~ 150%

The Challenge

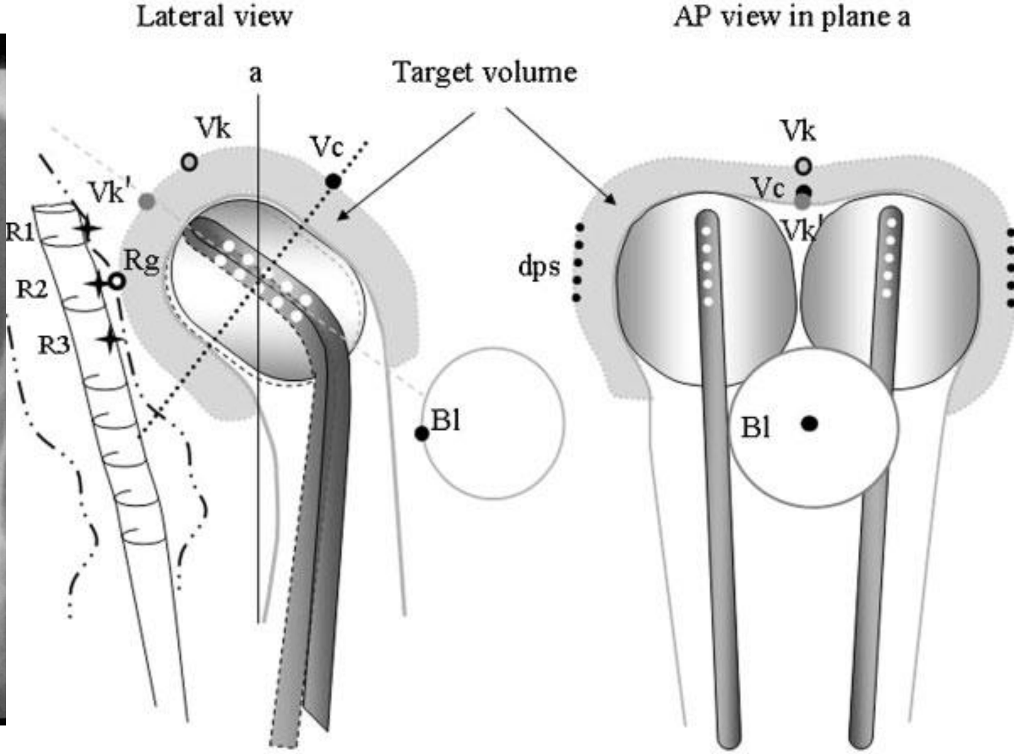


Other applicators

Mould

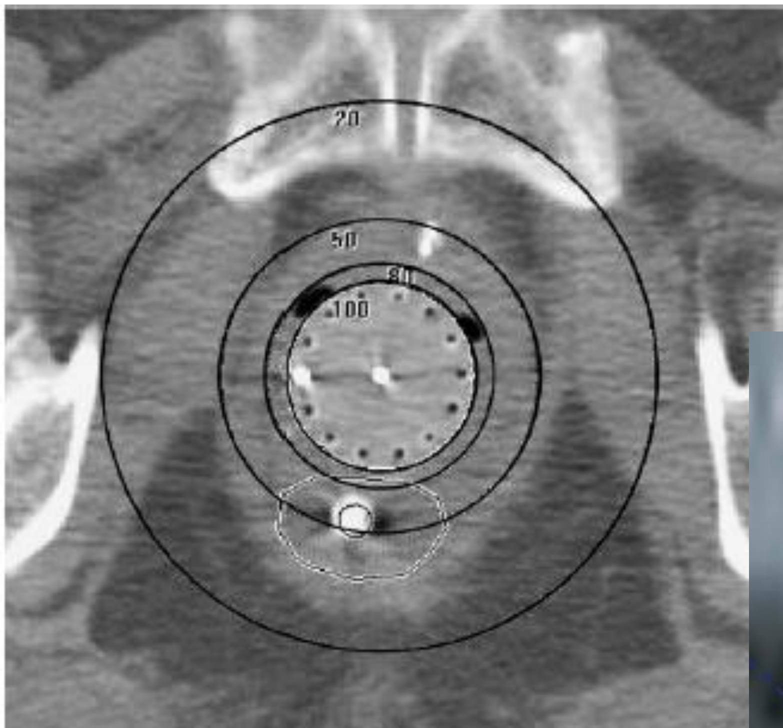


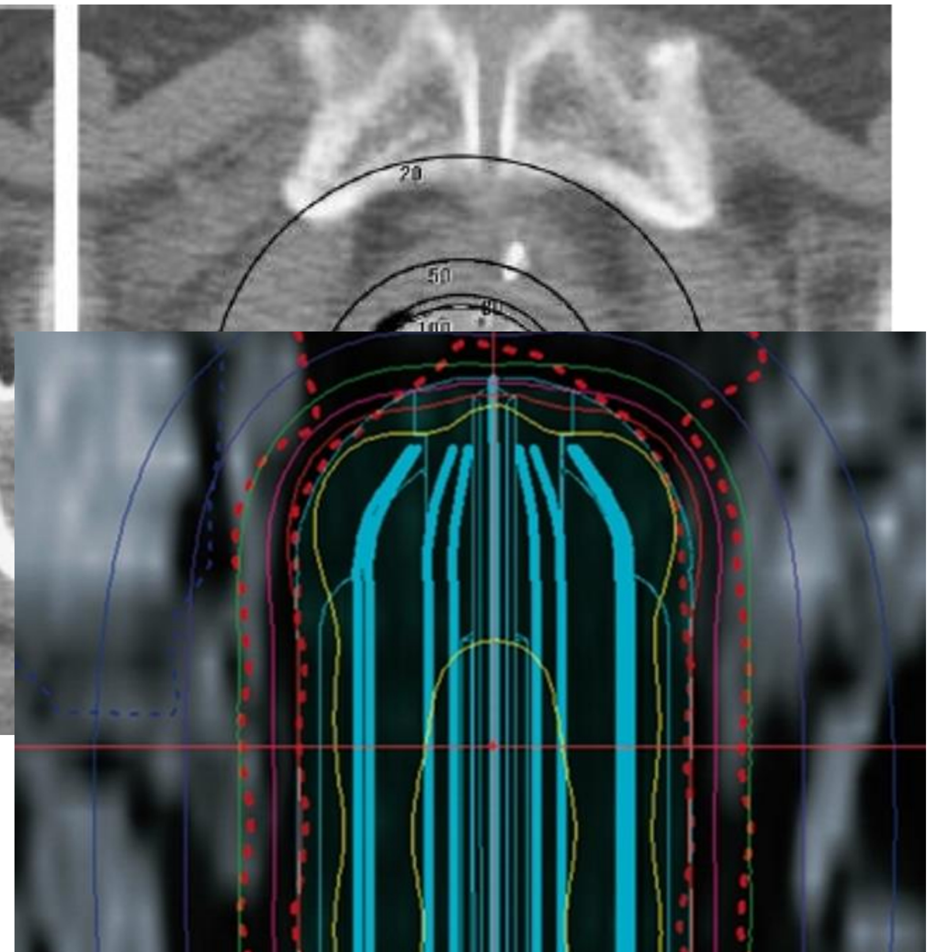
Fletcher ovoids



Tuncel et al BJR 2009

Multi-channel applicator





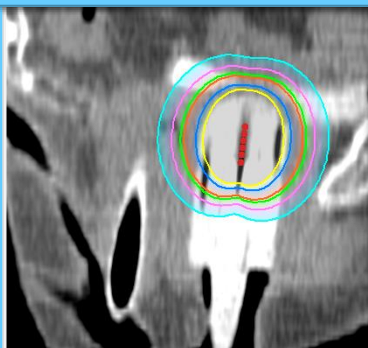
Central channel

Tanderup and Lindegaard RO 2004

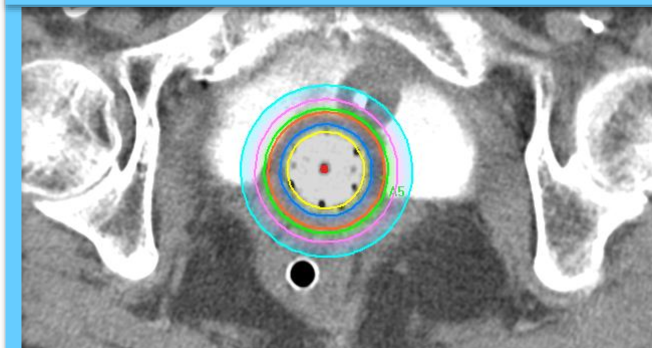
Treatment planning for Vaginal Cylinder

with or without imaging ?

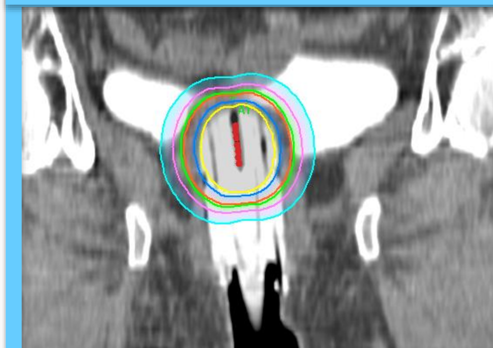
CT - sag



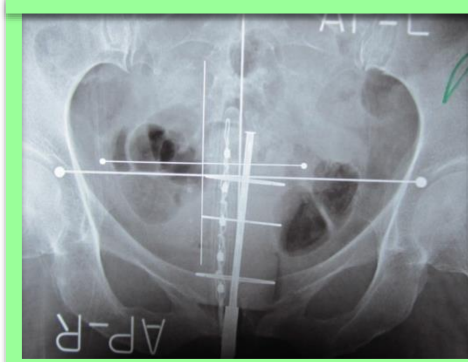
CT - transversal



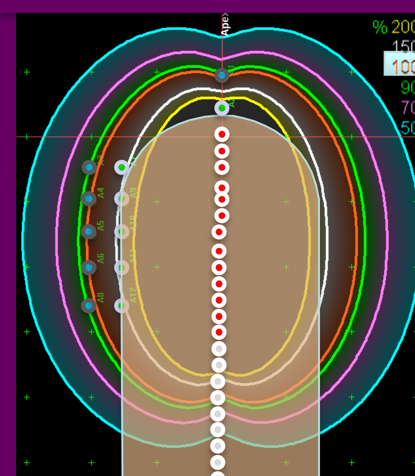
CT cor.



AP -radiograph



Template based



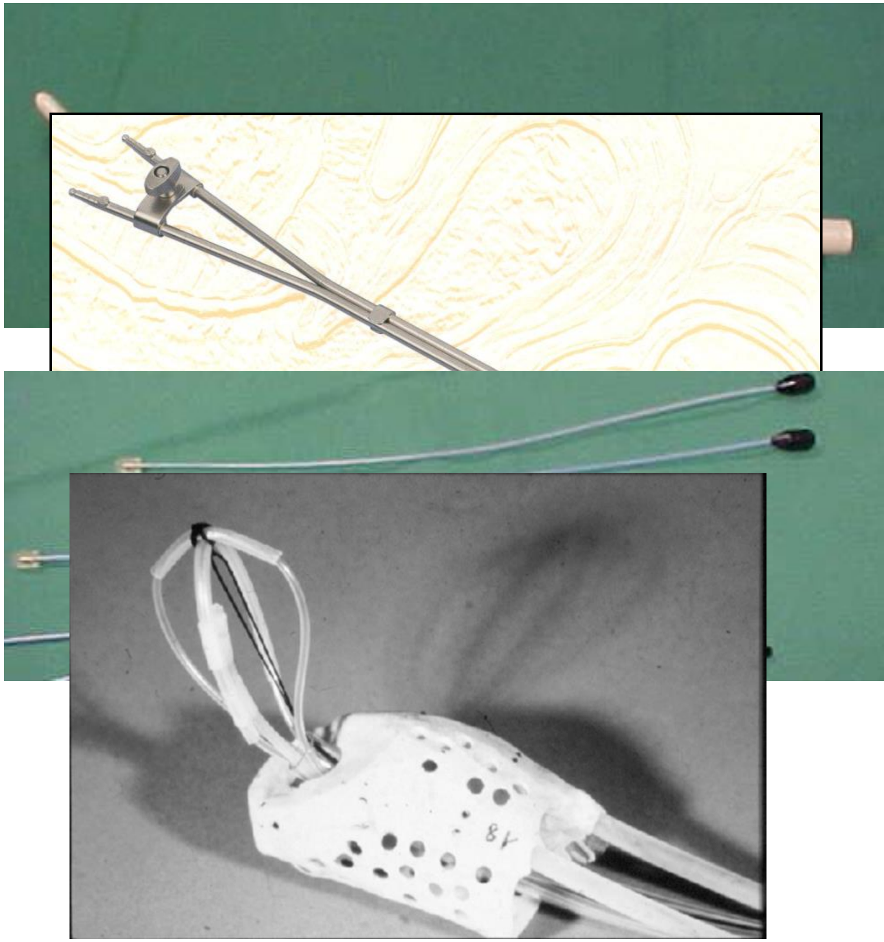
Treatment planning for definitive endometrium technique

The planning procedure

is depending on

type of applicator

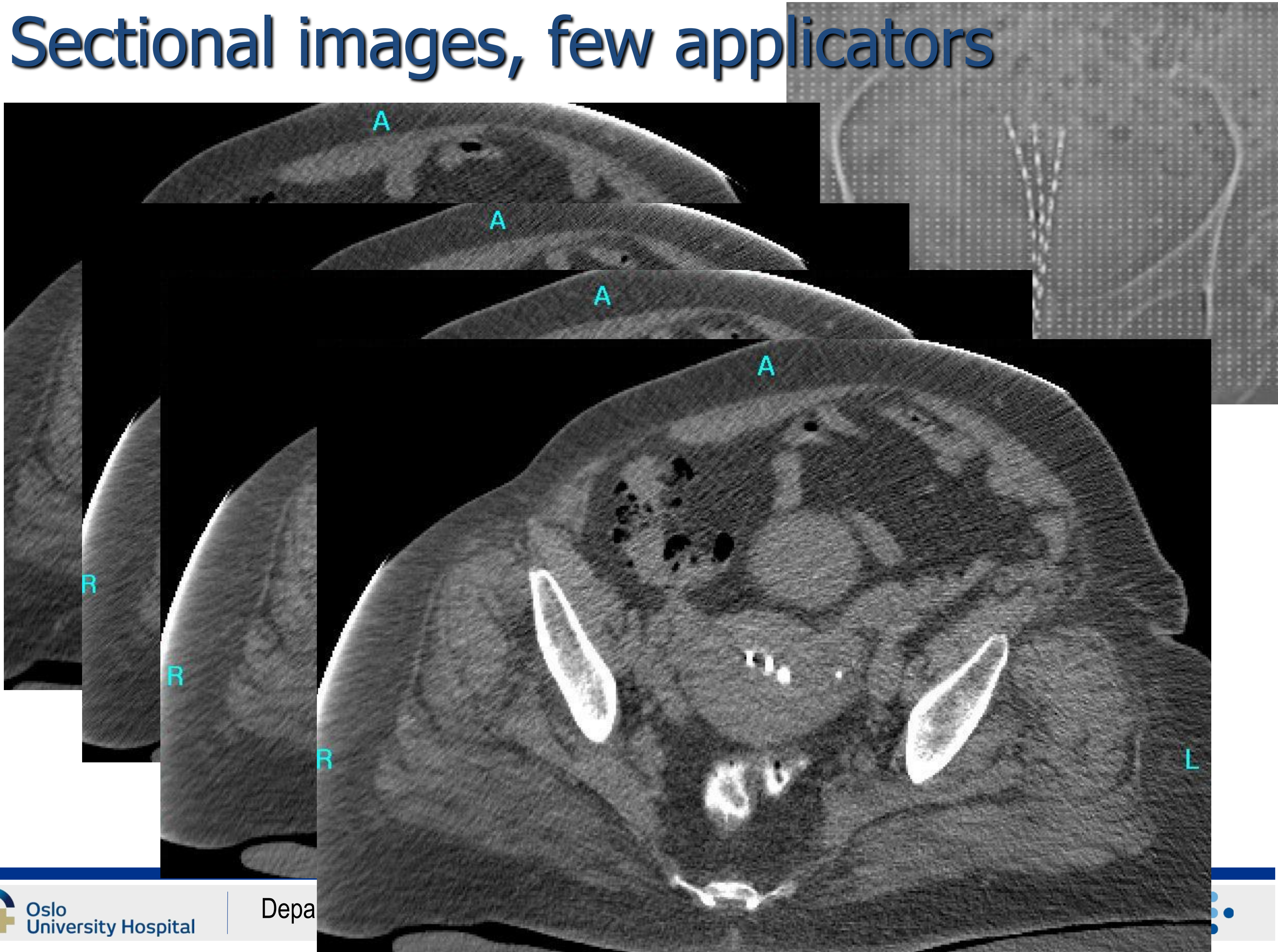
- one channel applicator
- two channel applicator
- Modified Heyman packing
- Norman-Simon-applicators
- Pernot umbrella technique



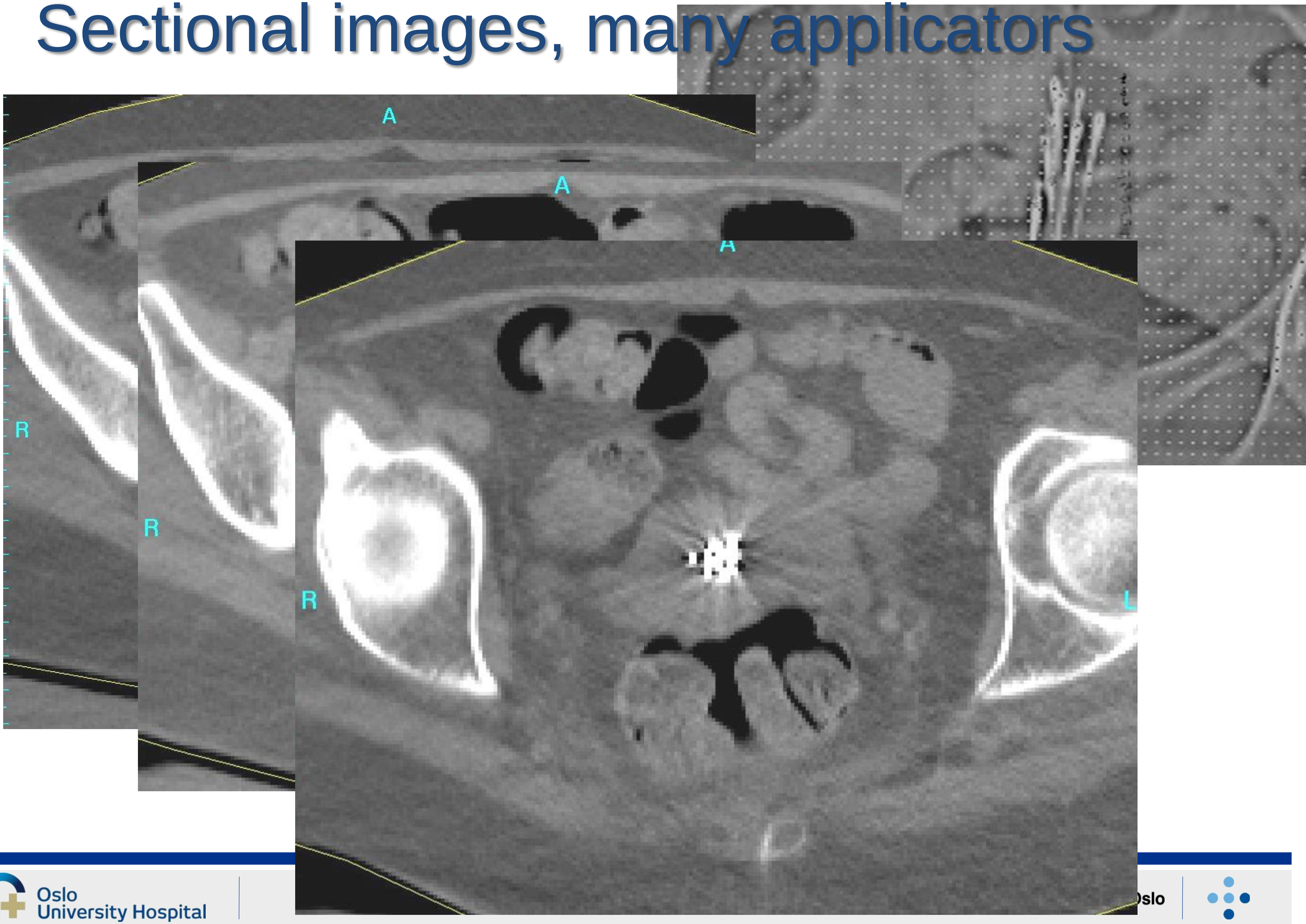
Reconstructing the applicator

- Rigid one- or two channel applicator – follow procedures described earlier.
- NS-applicators or packing – with many applicators it could be a complex procedure.

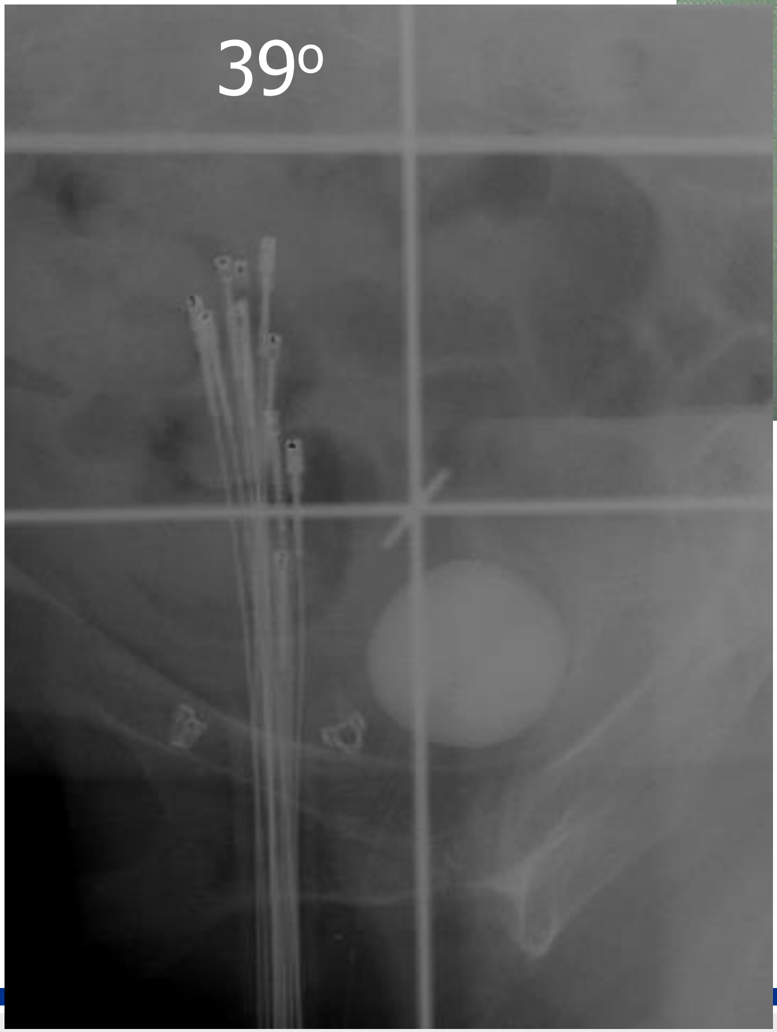
Sectional images, few applicators



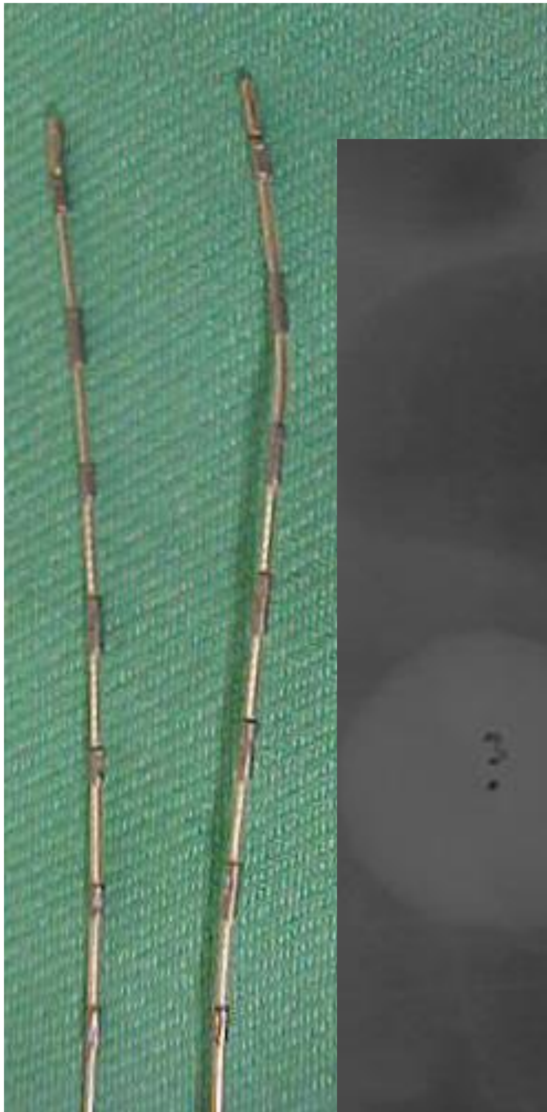
Sectional images, many applicators

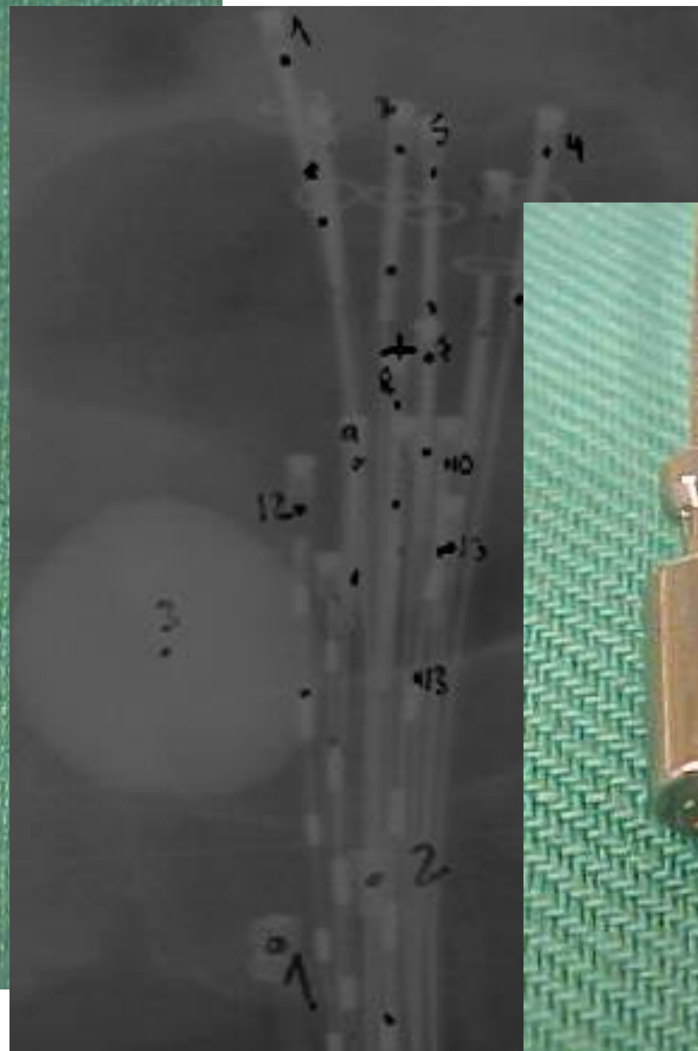


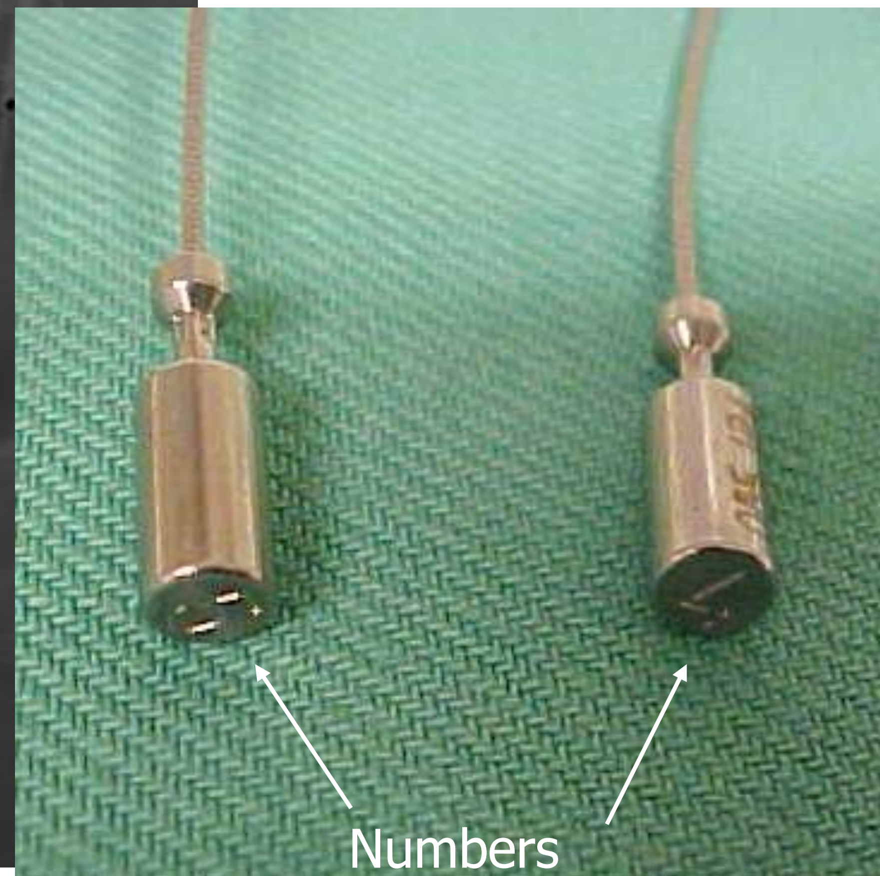
Norman Simon applicators



X-ray catheter to recognize each applicator



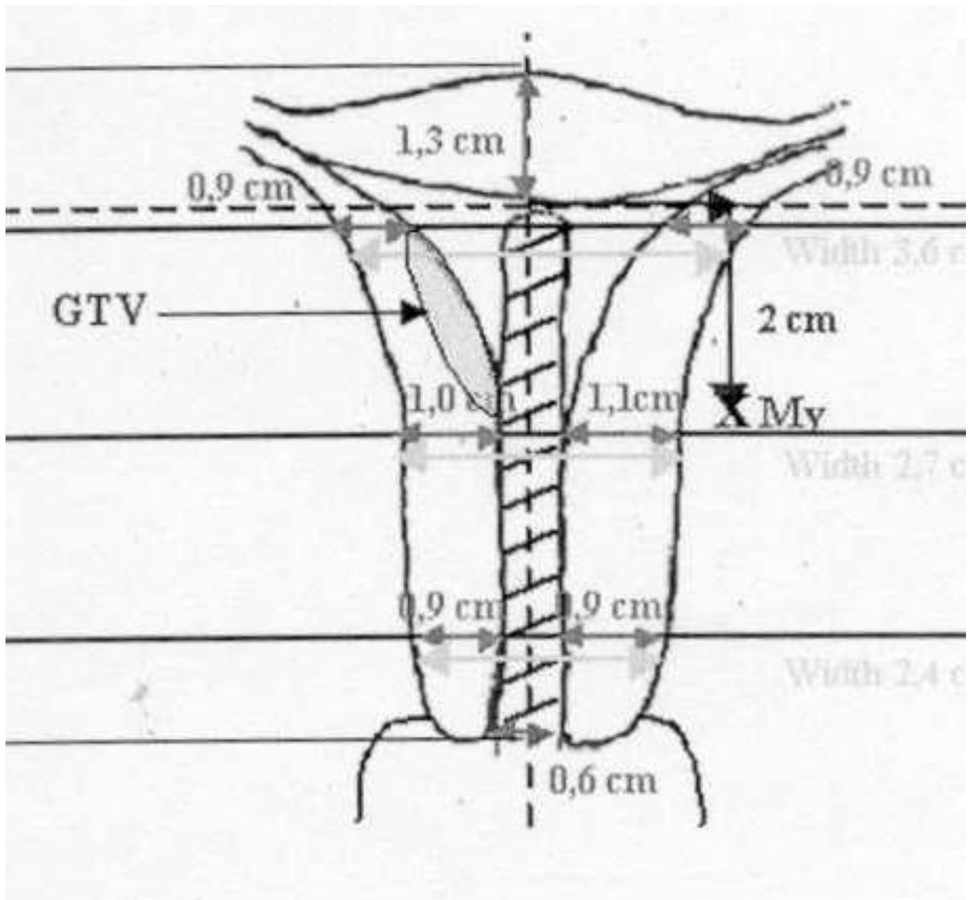




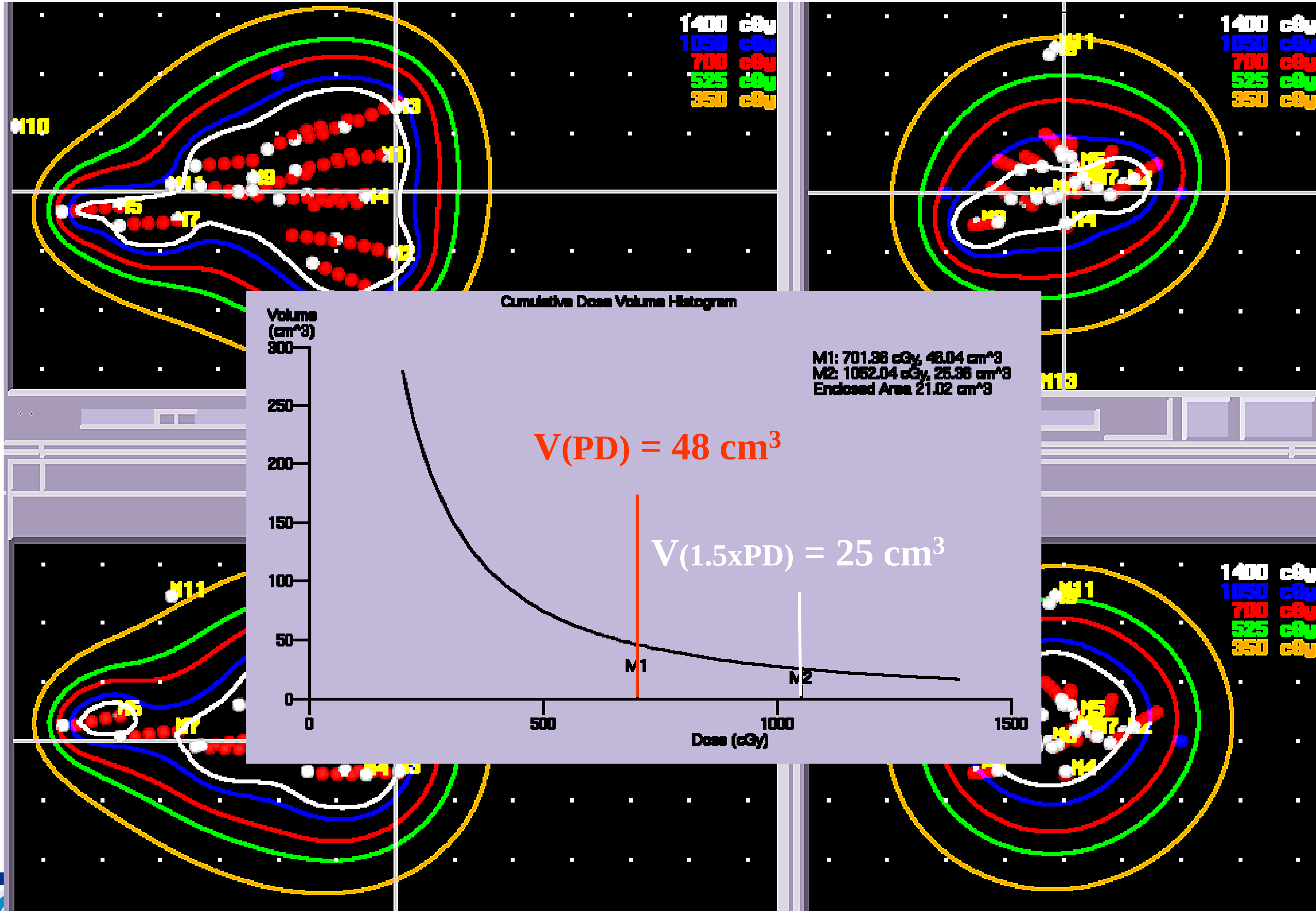
Reference points

- No consensus on which reference points to be used
- Proposed points
  - Point My, 2 cm caudal to the top of the most advanced applicator and 2 cm laterally
  - A-line, 2 cm from the tip of the applicator laterally
  - …
- Individualized approach, best achieved with CT or MRI

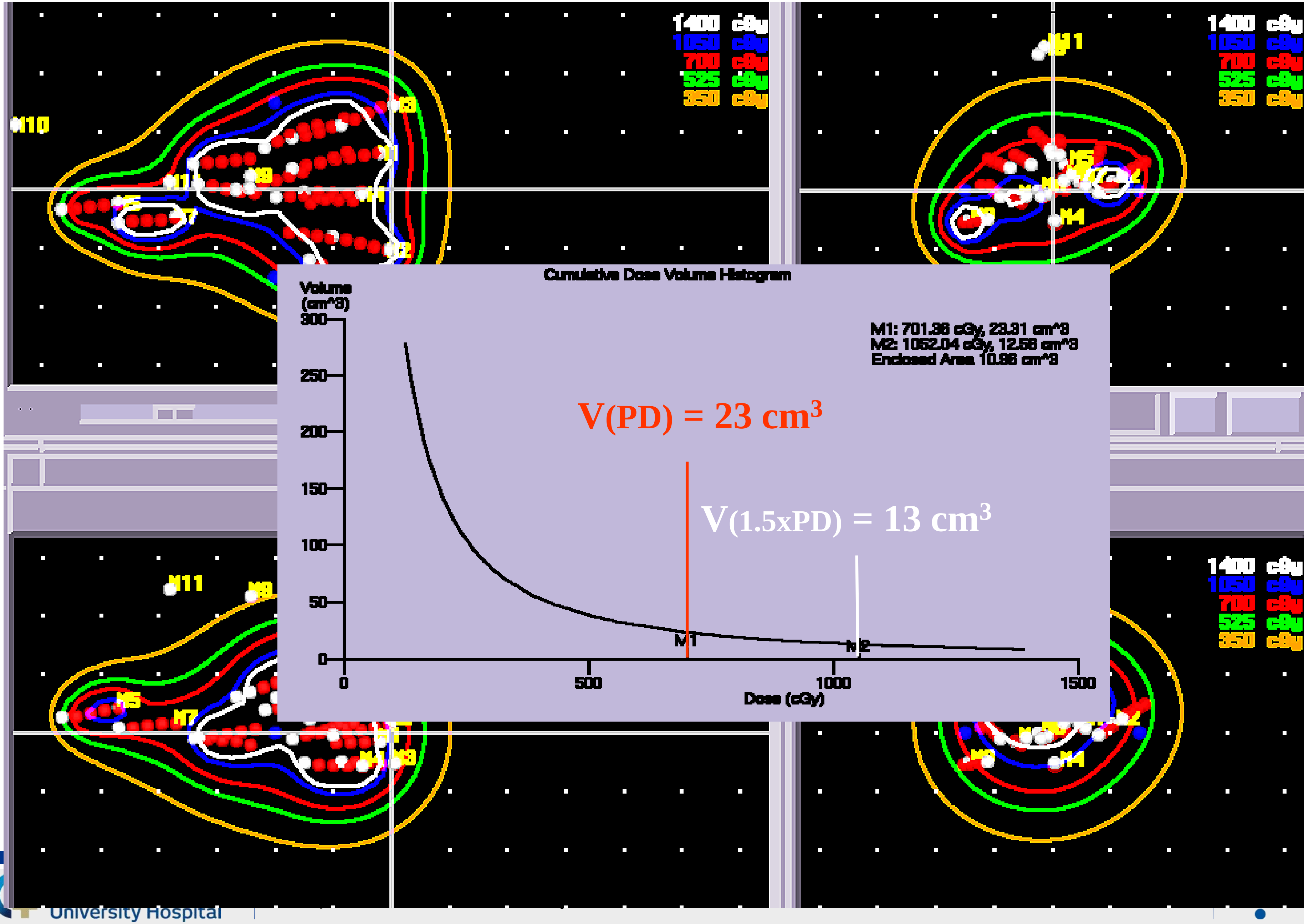
Small sized uterus



normalized to point My (caudal 20mm ; lateral 20mm)



normalized at level My (caudal 20mm ; lateral 15mm)

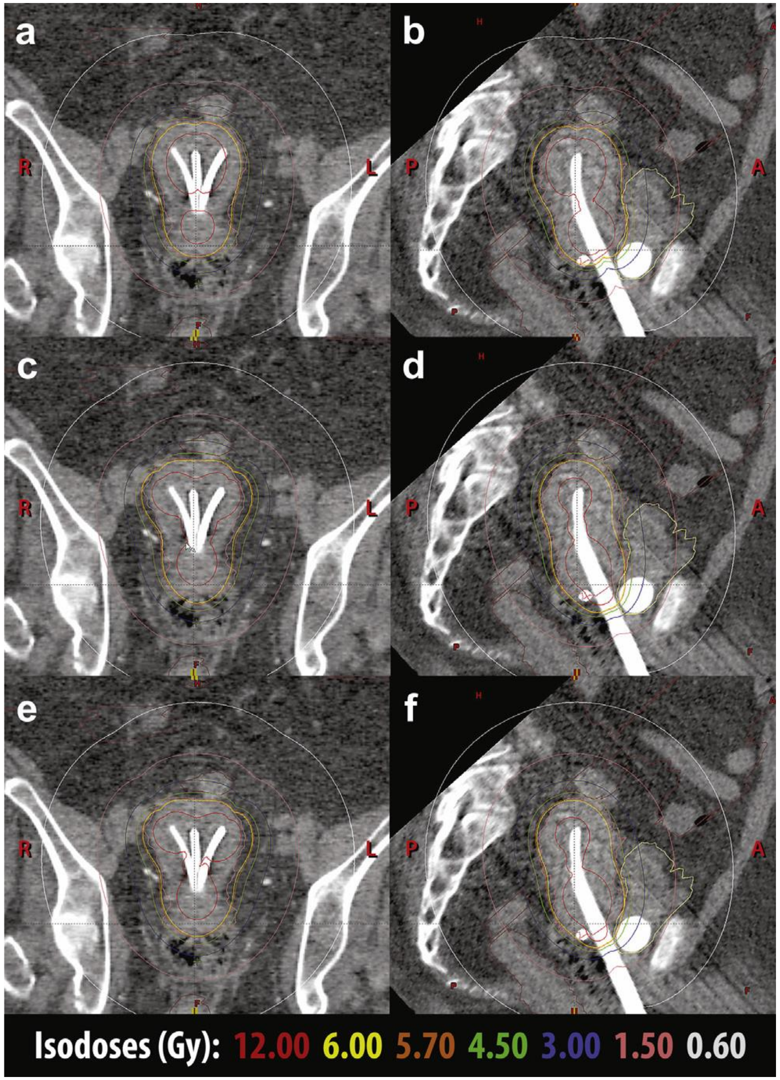


Single, dual and triple channel applicator

Single

Dual

Triple



Patient 1: 8cm long, 4.5 cm wide

Dose [Gy]	Single	Dual	Triple
CTV D90	96.0	97.3	97.9
Bladder D2cm^3	5.1	5.0	4.9
Rectum D2cm^3	1.6	1.8	1.7
Sigmoid D2cm^3	4.3	4.5	4.4

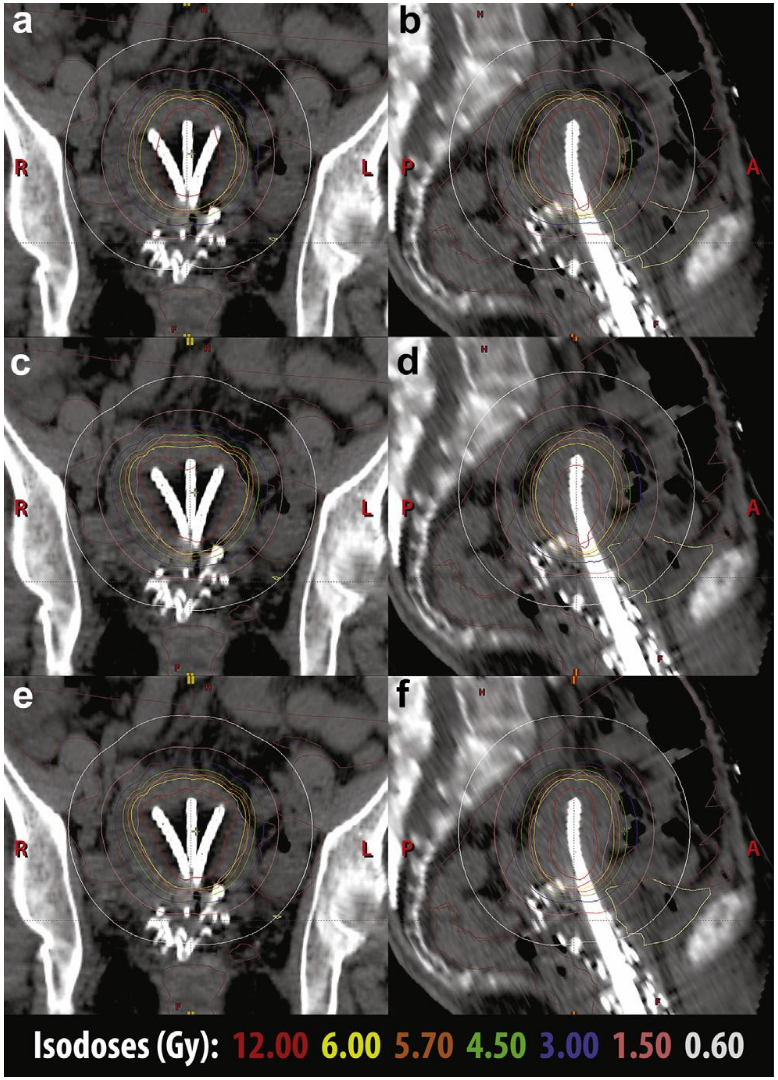
Johnsen et al
Brachytherapy 2014

Single, dual and triple channel applicator

Single

Dual

Triple



Patient 2: 5cm long, 5.4 cm wide

Dose [Gy]	Single	Dual	Triple
CTV D90	96.6	97.2	97.9
Bladder D2cm^3	2.6	2.6	2.4
Rectum D2cm^3	1.1	1.1	1.0
Sigmoid D2cm^3	5.5	5.0	4.7

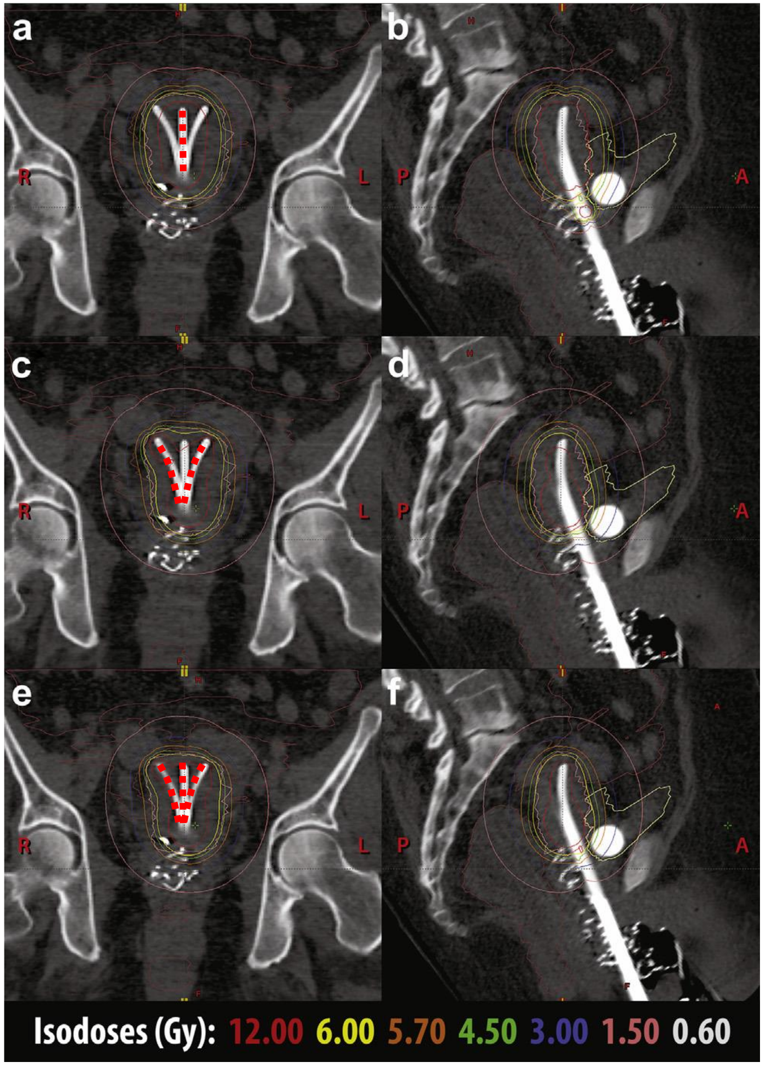
Johnsen et al
Brachytherapy 2014

Single, dual and triple channel applicator

Single

Dual

Triple

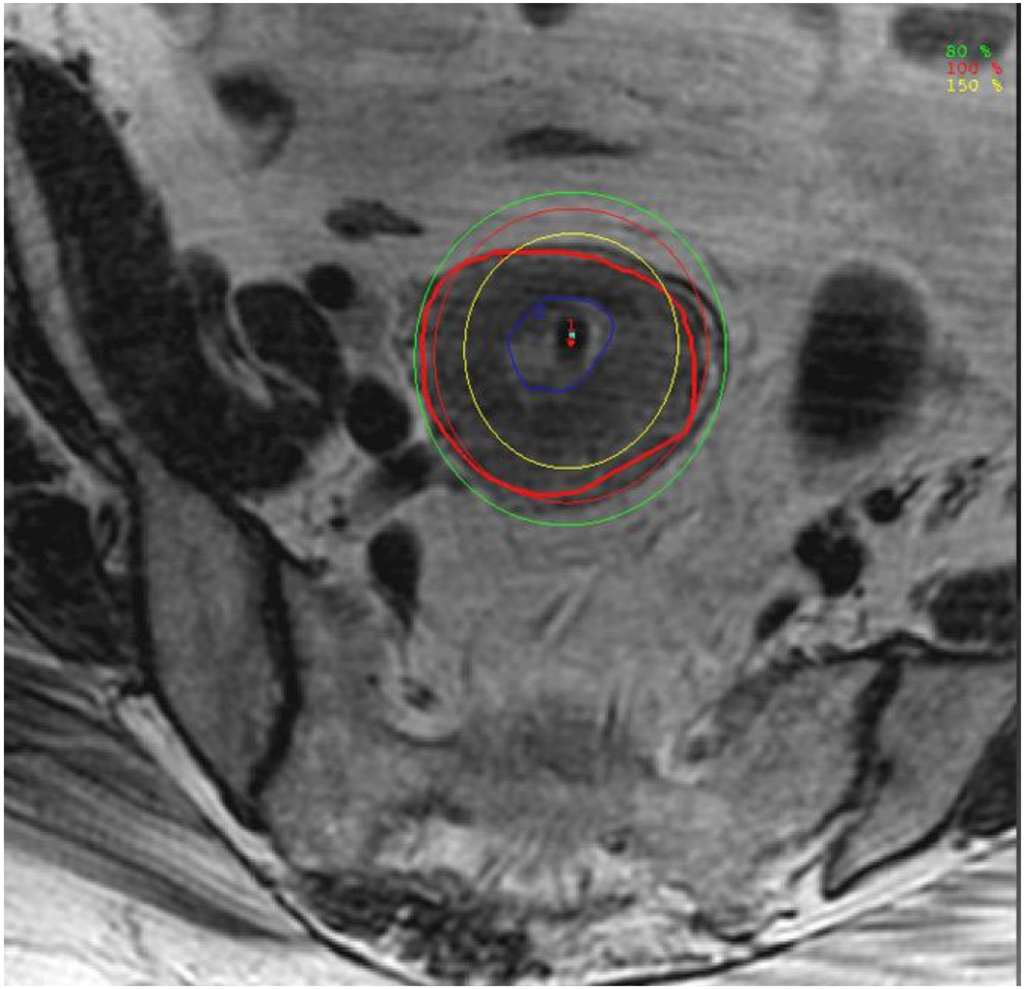


Patient 3: 6cm long, 5.5 cm wide

Dose [Gy]	Single	Dual	Triple
CTV D90	95.0	95.0	95.0
Bladder D2cm^3	8.5	5.7	5.6
Rectum D2cm^3	3.6	3.9	3.9
Sigmoid D2cm^3	6.9	4.9	4.8

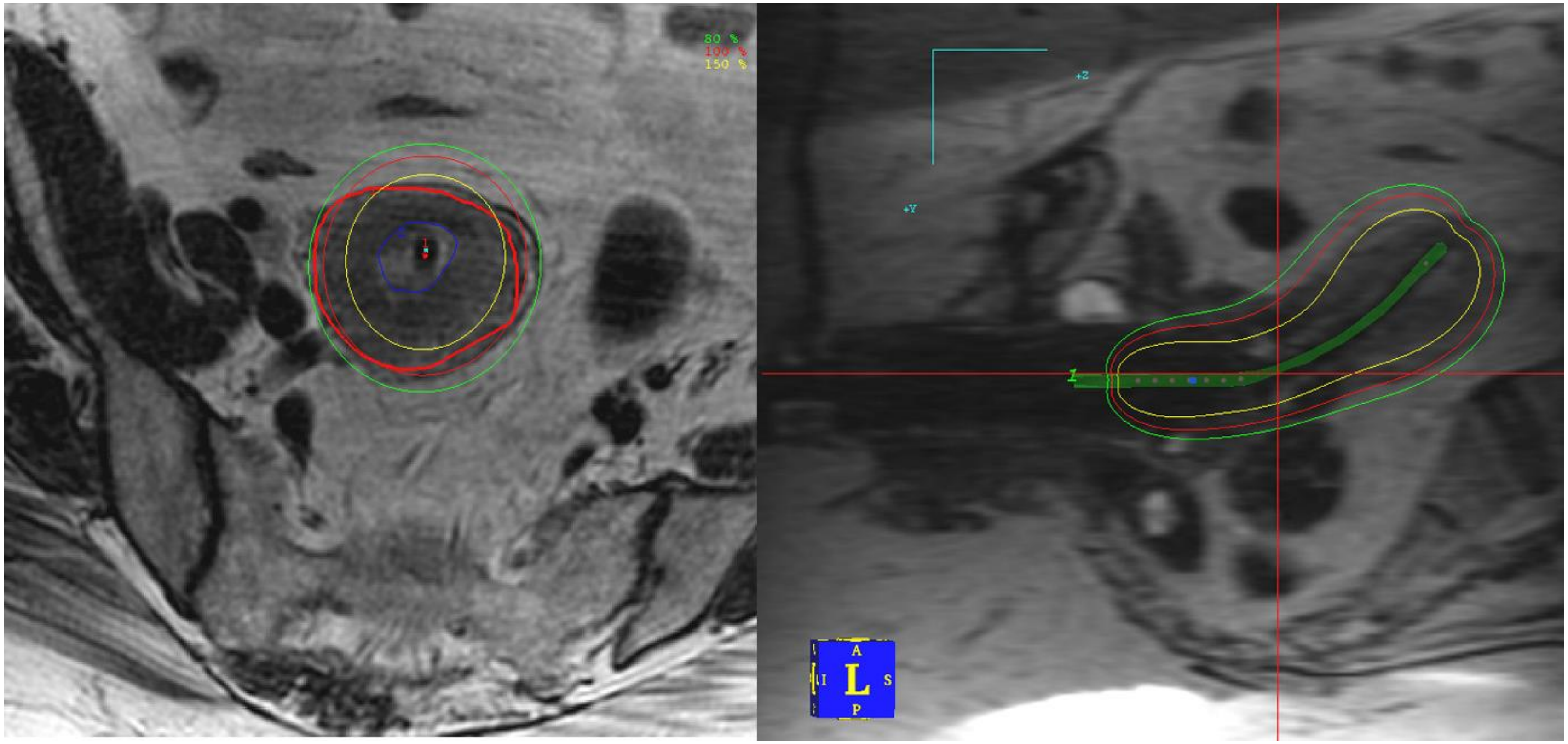
Johnsen et al
Brachytherapy 2014

Need MR to define GTV



Gill et al Brachytherapy 2014

Single channel applicator used for uterus with max with < 5 cm



Gill et al Brachytherapy 2014

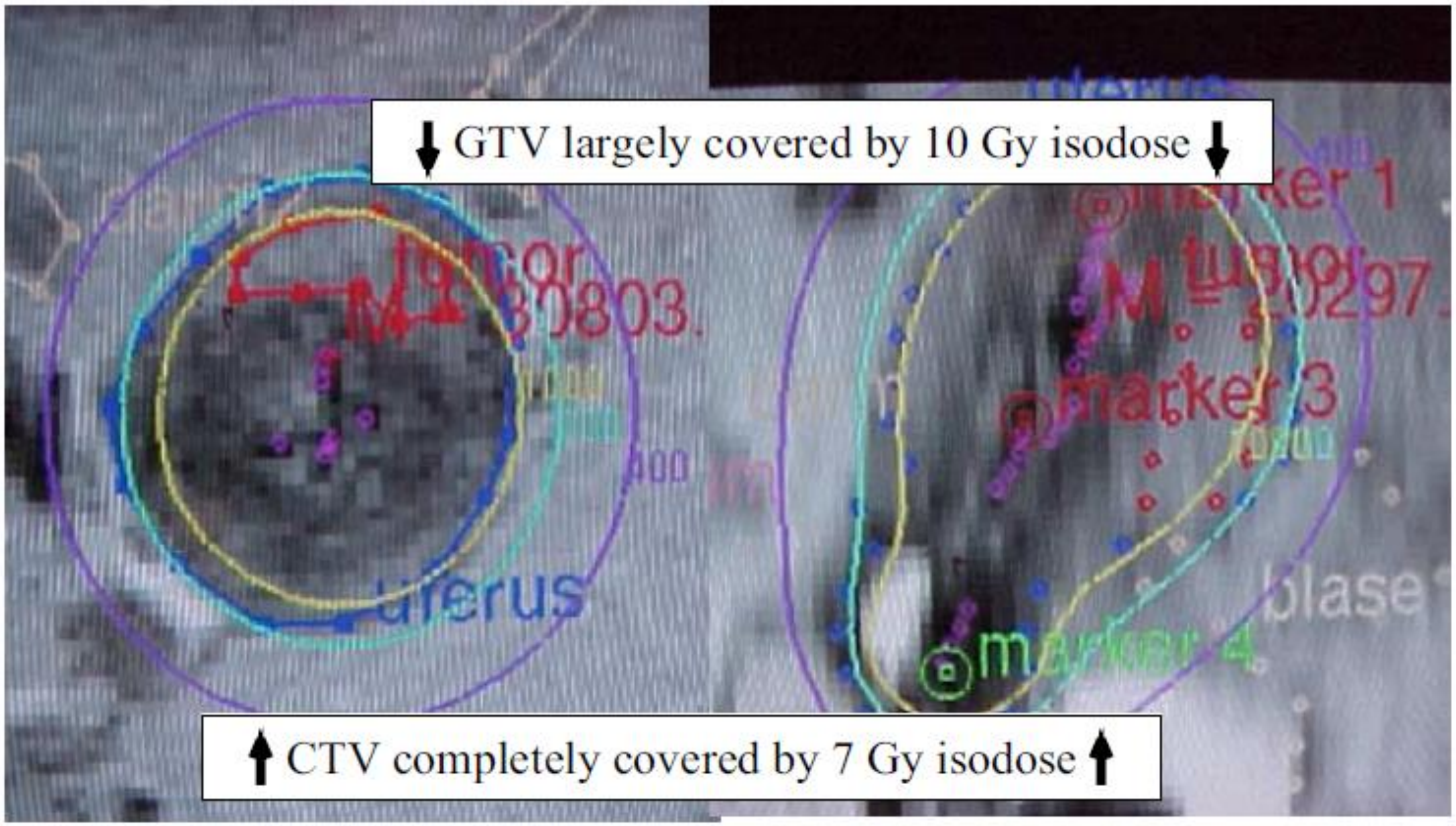
Single channel applicator used for uterus with max with < 5 cm

Summary of dosimetric findings for image-based HDR treatment planning

Characteristics	All patients (n = 38)	BT alone (n = 20)	EBRT + BT (n = 18)
GTV, mean ± SD			
Volume (cc)	6.8 ± 4.5	5.4 ± 1.9	8.9 ± 6.5
D_{90} EQD_2 (Gy)	160.0 ± 62.1	172.3 ± 59.6	138.0 ± 64.6
CTV, mean ± SD			
Volume (cc)	85.7 ± 25.9	82.0 ± 28.0	87.6 ± 24.0
D_{90} EQD_2 (Gy)	59.9 ± 13.3	48.6 ± 5.6	72.4 ± 6.0
Rectum D_{2cc} EQD_2 (Gy)			
Mean ± SD	42.2 ± 18.3	26.3 ± 8.9	59.8 ± 4.0
Sigmoid D_{2cc} EQD_2 (Gy)			
Mean ± SD	52.4 ± 13.6	41.5 ± 8.6	64.6 ± 4.9
Bladder D_{2cc} EQD_2 (Gy)			
Mean ± SD	58.6 ± 15.2	46.8 ± 10.4	71.7 ± 6.1

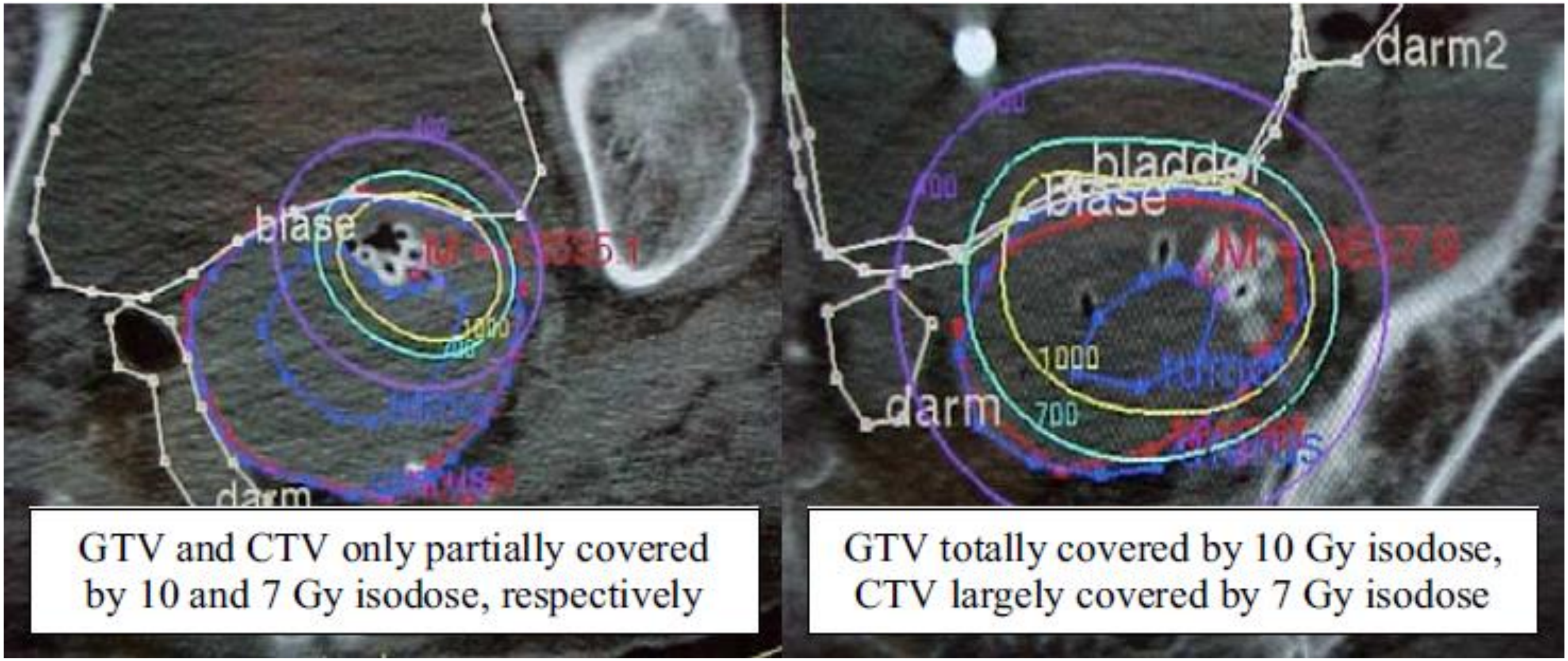
Gill et al Brachytherapy 2014

Norman-Simon applicators



Weitmann et al IJROBP 2005

Norman-Simon applicators



GTV and CTV only partially covered by 10 and 7 Gy isodose, respectively

GTV totally covered by 10 Gy isodose, CTV largely covered by 7 Gy isodose

Used from 3 to 18 applicators in 16 patients

Weitmann et al IJROBP 2005

Inter- and intra-fraction uncertainties and in brachytherapy

Nicole Nesvacil
Assistant Professor
Department of Radiotherapy, Comprehensive Cancer Center,
Christian Doppler Laboratory for Medical Radiation Research,
Medical University of Vienna

Based on material by K. Tanderup

Largest contribution to dose uncertainty for target?

A. Dose calculation

B. Applicator reconstruction

C. Target contouring

D. Target motion

Largest contribution to dose uncertainty for OARs?

A. Dose calculation

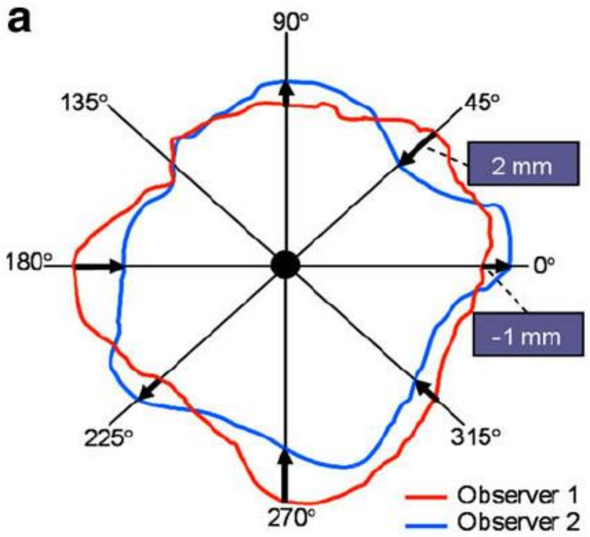
B. Applicator reconstruction

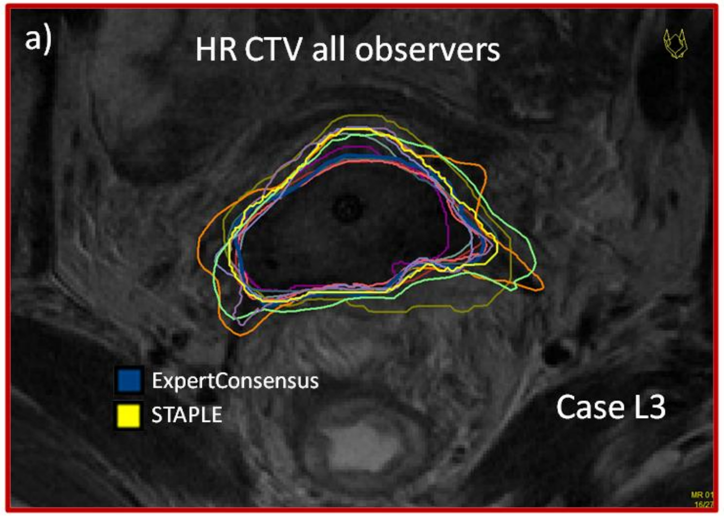
C. OAR contouring

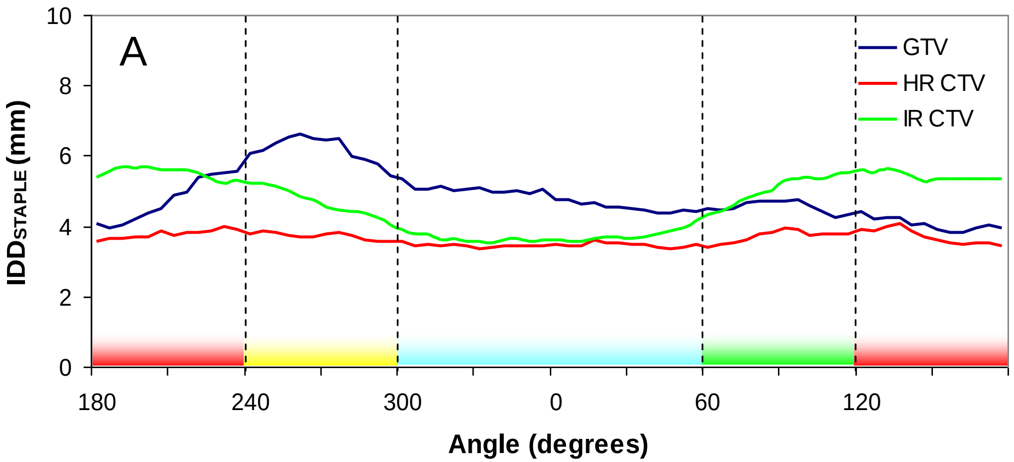
D. OAR motion

Contouring uncertainties CTV_{HR} on MRI

- CTV_{HR}:
  - Mean deviation <4mm
- GTV, CTV_{IR}:
  - Mean deviation <6-7mm



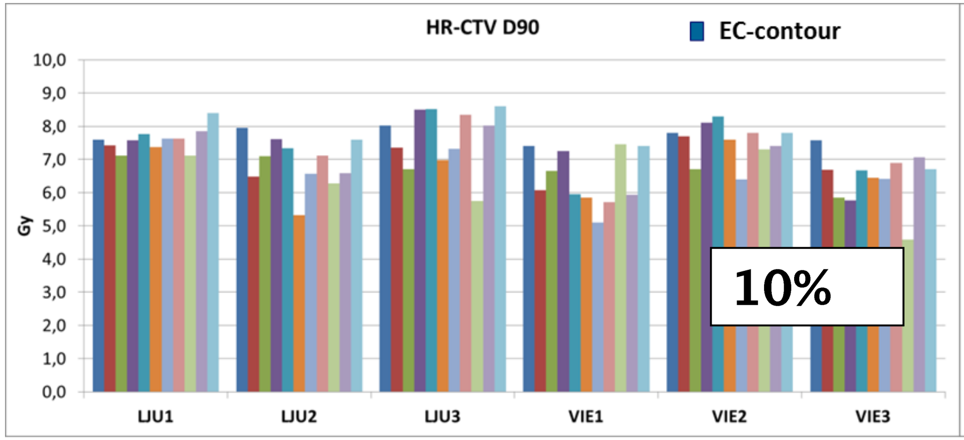




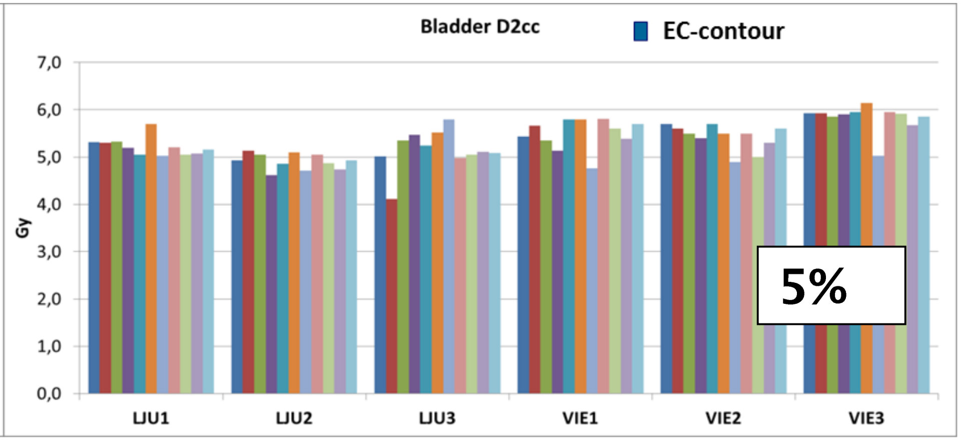
Petric et al, R&O 2008

Petric et al, RO 2013

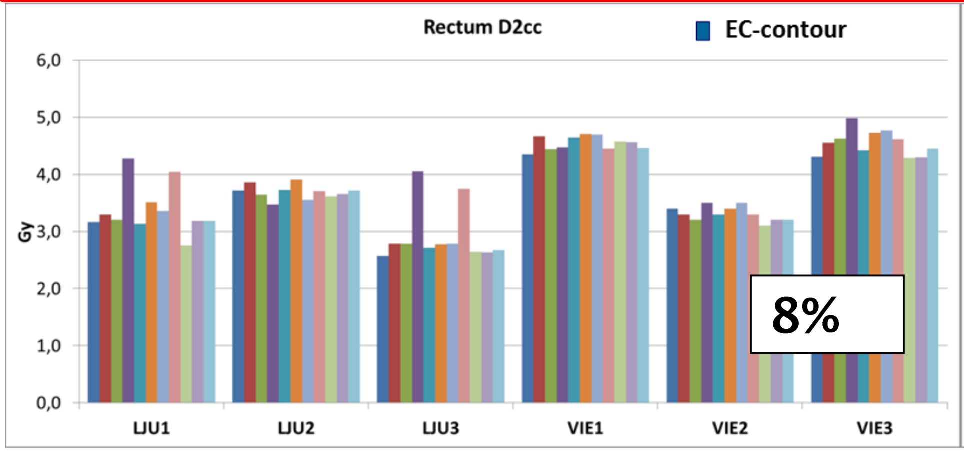
Impact of contouring uncertainties on dose



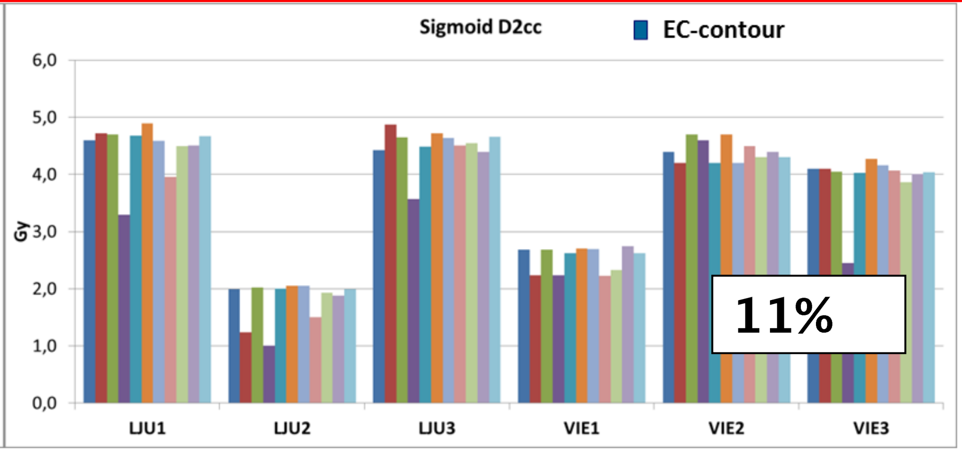
Mean (Gy)	7,59	6,80	7,61	6,34	7,51	6,31
SD (Gy)	0,38	0,70	0,95	0,81	0,59	0,74
Rel.SD (%)	5,0	10,3	12,5	12,7	7,9	11,7



Mean (Gy)	5,21	4,91	5,17	5,5	5,4	5,82
SD (Gy)	0,20	0,18	0,45	0,34	0,26	0,30
Rel.SD (%)	3,9	3,6	8,7	6,2	4,9	5,2



Mean (Gy)	3,39	3,68	2,96	4,57	3,30	4,57
SD (Gy)	0,45	0,13	0,51	0,11	0,13	0,22
Rel.SD (%)	13,3	3,6	17,1	2,4	4,0	4,8

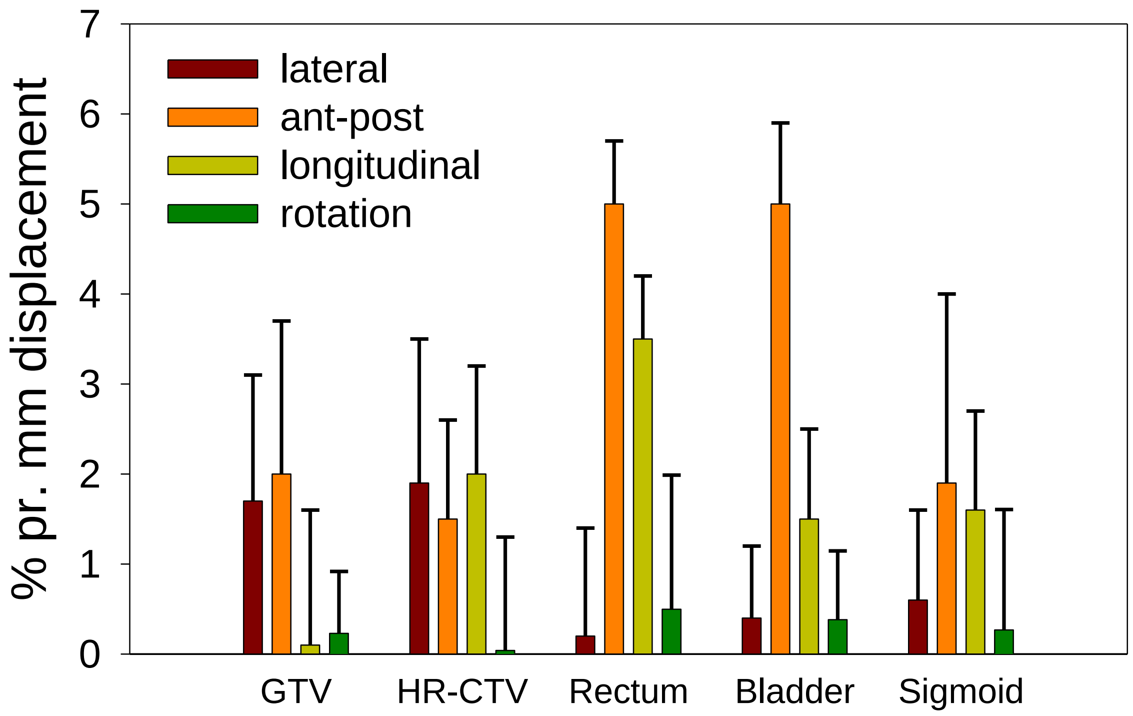


Mean (Gy)	4,45	1,77	4,51	2,51	4,41	3,91
SD (Gy)	0,47	0,38	0,35	0,22	0,20	0,52
Rel.SD (%)	10,6	21,6	7,9	8,9	4,6	13,4

Hellebust et al, RO 2013

Reconstruction uncertainties

- Evaluation of the impact of reconstruction uncertainties on DVH parameters (mean and standard deviation)

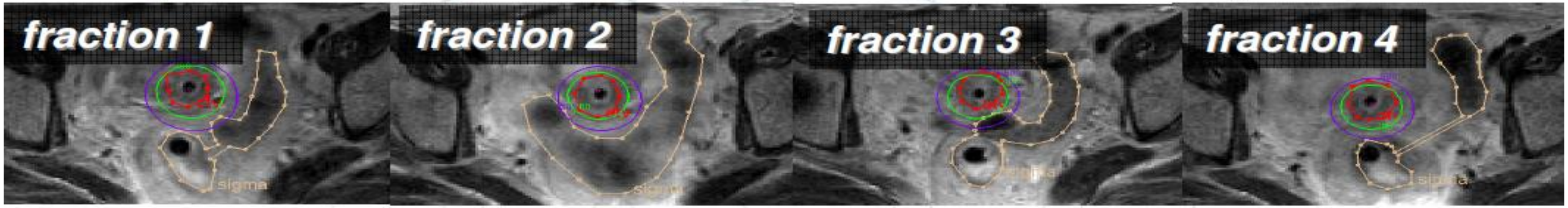


Tanderup et al, R&O 2008

Random dosimetric variations during Brachtherapy

Same plan used for 4 fractions, anatomical changes between irradiations may lead to large random dosimetric uncertainties

Lang et al. 2013, Radiother Oncol



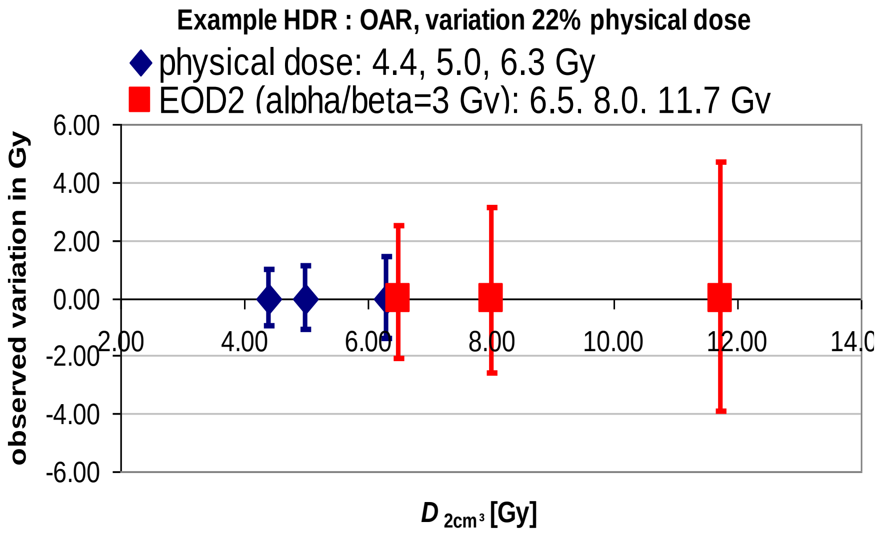
Results of a multicentre study between 6 centres with different treatment/ application techniques (Nesvacil et al. 2013, Radiother Oncol 107 and references therein) :

De Leeuw et al.; Hellebust et al.; Anderson et al.; Mohamed et al.; Lang et al.; Jamema et al.

			Bladder SD D2cc			Rectum SD D2cc			Sigmoid SD D2cc			HR CTV SD D90
total	2.7	1.5	20.3%	4.5	4.1	22.0%	1.6	-0.9	26.8%	-1.1	-1.7	13.1%
Intraaplication	1.3	1.5	17.7	3.8	2.3	20.5	-2.3	-3.7	23.5	-2.5	-4.3	10.8
interapplication	3.9	0.0	22.3	5.8	5.2	23.2	6.8	3.7	30.2	0.4	-0.8	15.1

Note: Changes correspond to physical dose change between 2 time points during course of BT. Effect on total EQD2 (EBRT+BT) depends on fractionation schedule (PDR, HDR, …)

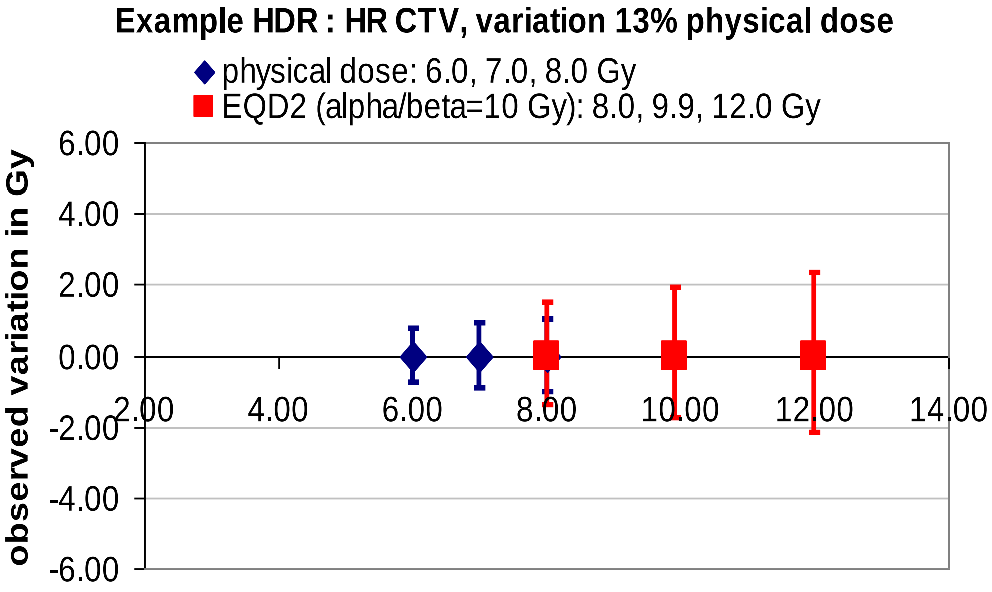
Translating random uncertainties to EQD2: single fraction dose



OAR
(SD 22%)

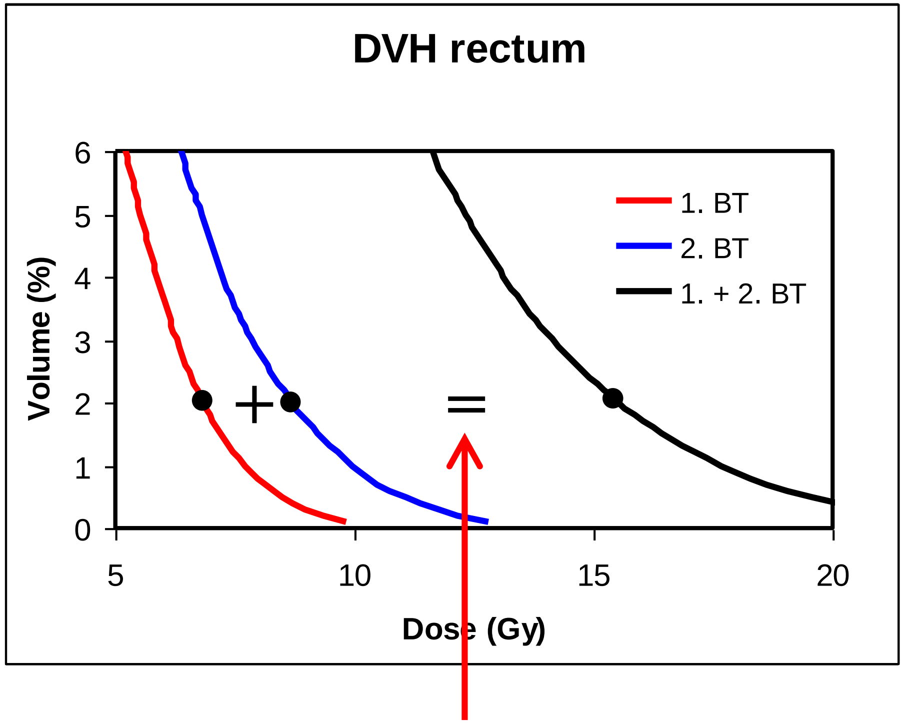
At higher EQD2 doses error bars become asymmetrical!

HR CTV
(SD 13%)



The impact of uncertainty on the total treatment dose depends on the fractionation scheme!

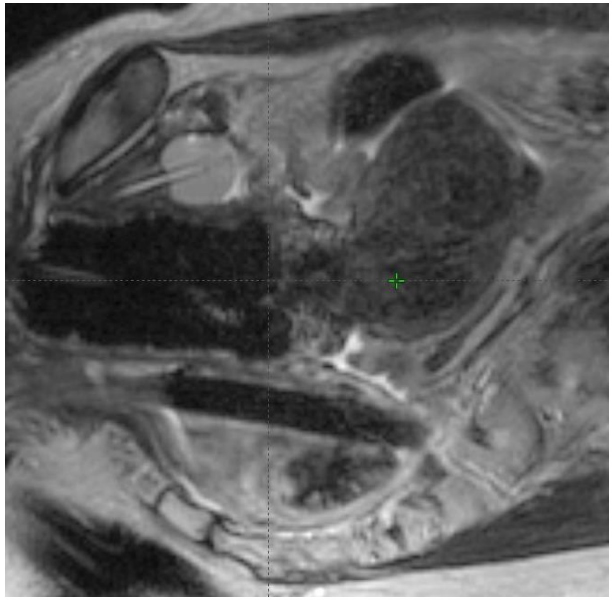
"Worst case assumption"
Calculation of DVH for several fractions

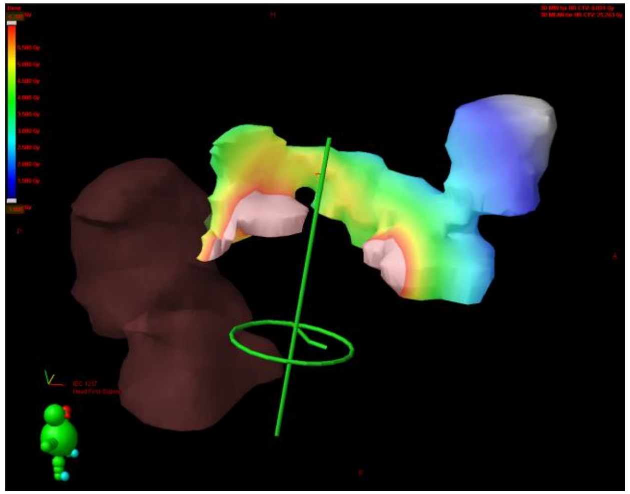


Approximation
"Worst case assumption" or DVH addition

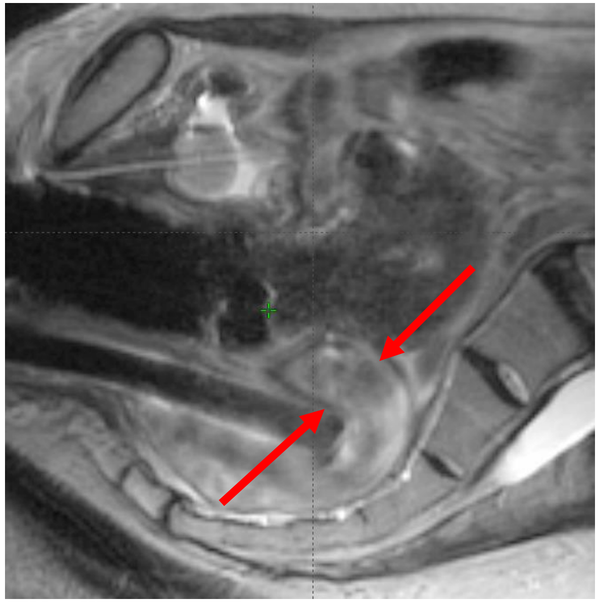
Different location of hotspots

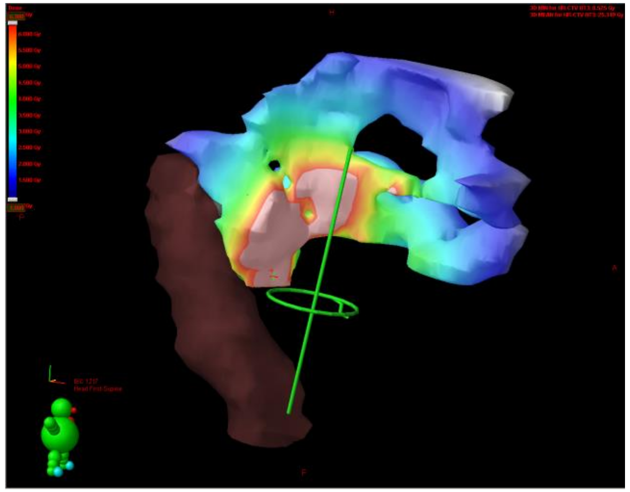
1. BT





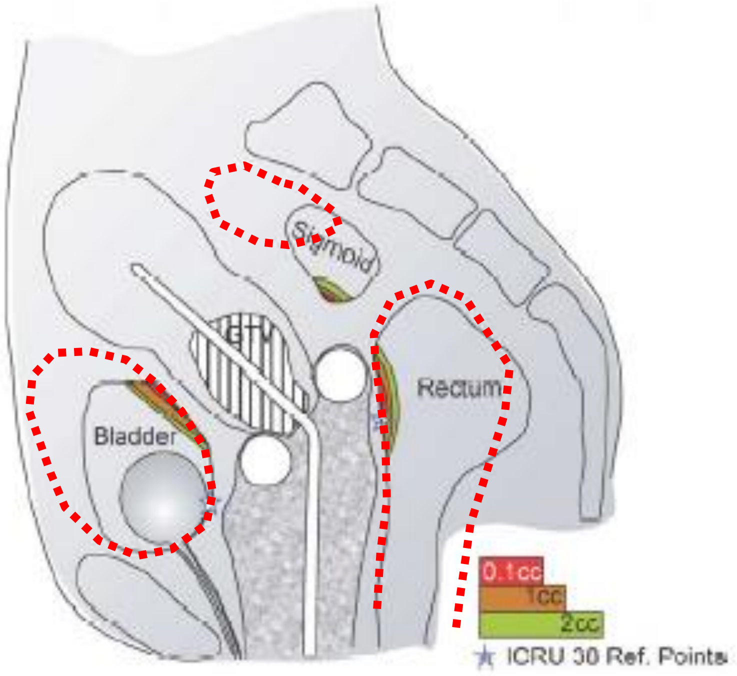
2. BT





Influence of organ deformation

- Sigmoid
  - Highly mobile
  - DVH calculation conservative



- Rectum and bladder
  - Less mobile

Table 2
Summary of results of spatial location of D_{2cm^3} hot spot region for each of the OAR.

Categories	Rectum ($n = 27$)	Bladder ($n = 27$)	Sigmoid ($n = 27$)
1. Overlapping region >50%	16	8	3
2. Overlapping region 10–50%	7	14	9
3. Overlapping region <10%/no overlap	4	5	15

Jamema S et al, vol 107, RO 2013

DVH addition

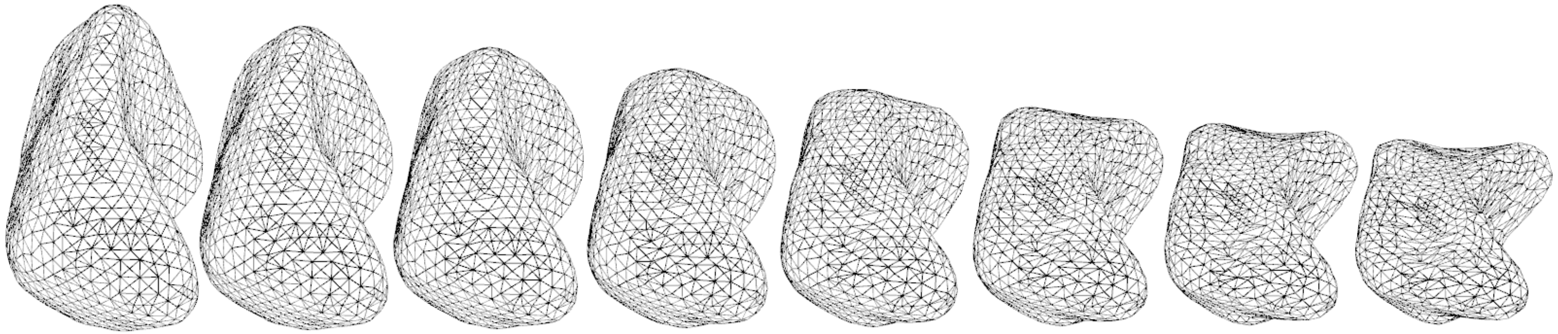
- Bladder and rectum dose:

$$BT_{total} = BT1 + BT2 + BT3 + BT4$$

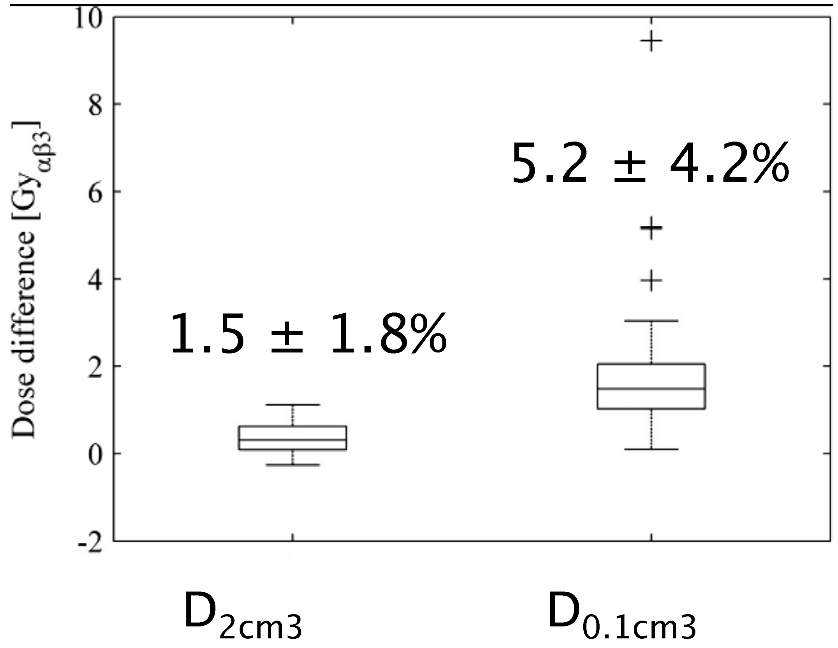
- Sigmoid dose potential over-estimation of dose:

$$BT_{total} < BT1 + BT2 + BT3 + BT4$$

Bladder dose accumulation with deformable registration (biomechanical)



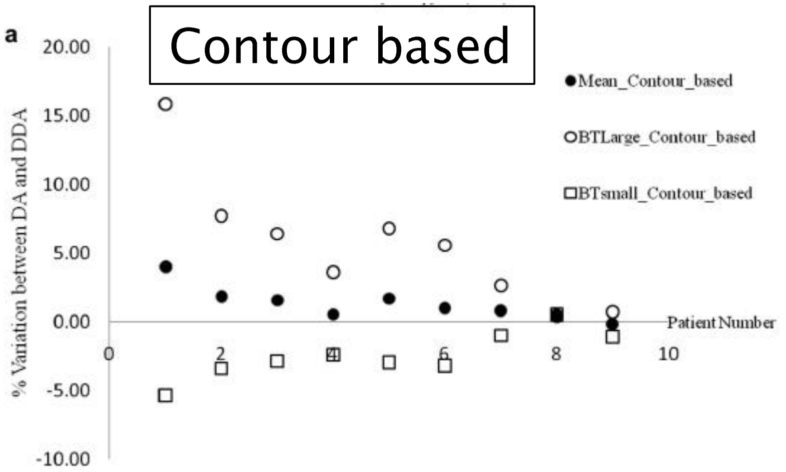
Difference between DVH addition and 3D dose accumulation:

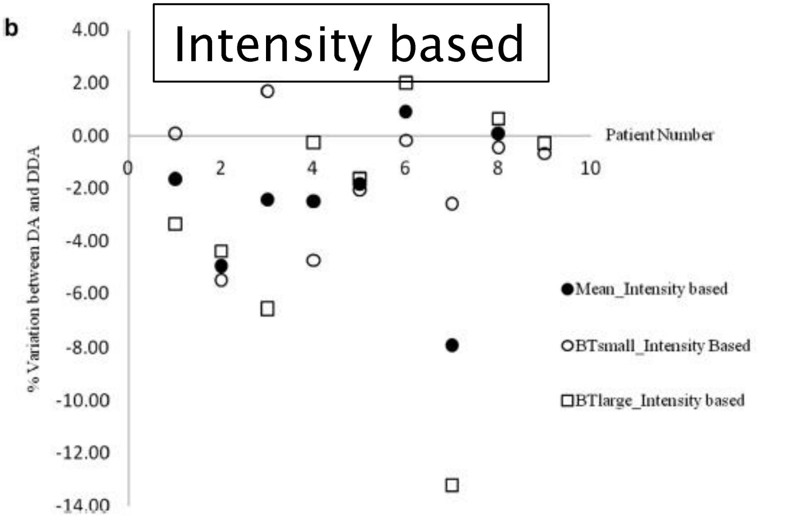


Pitfalls DIR based dose accumulation: Consistency of results

- Dose accumulation with intensity based DIR may not be consistent

- In-consistent DIR may systematically underestimate dose





-> DIR has currently very high, unknown uncertainties.
Clinically not advised to use it for decision making!!!!

Largest contribution to dose uncertainty for target?

A. Dose calculation

B. Applicator reconstruction

C. Target contouring

D. Target motion

Largest contribution to dose uncertainty for OARs?

A. Dose calculation

B. Applicator reconstruction

C. OAR contouring

D. OAR motion

The total uncertainty budget

- Radiotherapy and Oncology vol 107(1), 2013
- 19 papers on brachytherapy and mainly on uncertainties

Table 1
Uncertainty budget (SD) for one intracavitary brachytherapy fraction. The overall uncertainty for the entire treatment course is depending on the fractionation schedule and level of verification.

	Target (HR CTV D90)	OARs (D_{2cm^3})
Source strength	2%	2%
Dose and DVH calculation	3%	3%
Dwell position uncertainty (reconstruction and source positioning)	4%	4%
DVH addition across fractions (previously called "worst case assumption")	NA	1%[a]–?%
Contouring (inter-observer)	9%	5–11%
Intra- and inter-fraction (intra-application) uncertainties[b] (5)	11%	20–25%
Total[c]	12%	21–26%

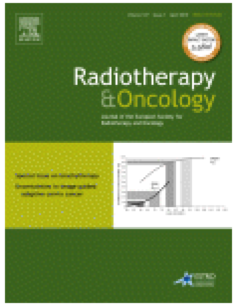
[a] For the bladder and likely rectum, whereas it has not been evaluated for sigmoid.
[b] Per se including intra-and inter-observer contouring variations.
[c] Contouring uncertainties included through intra- and inter-fraction uncertainties.

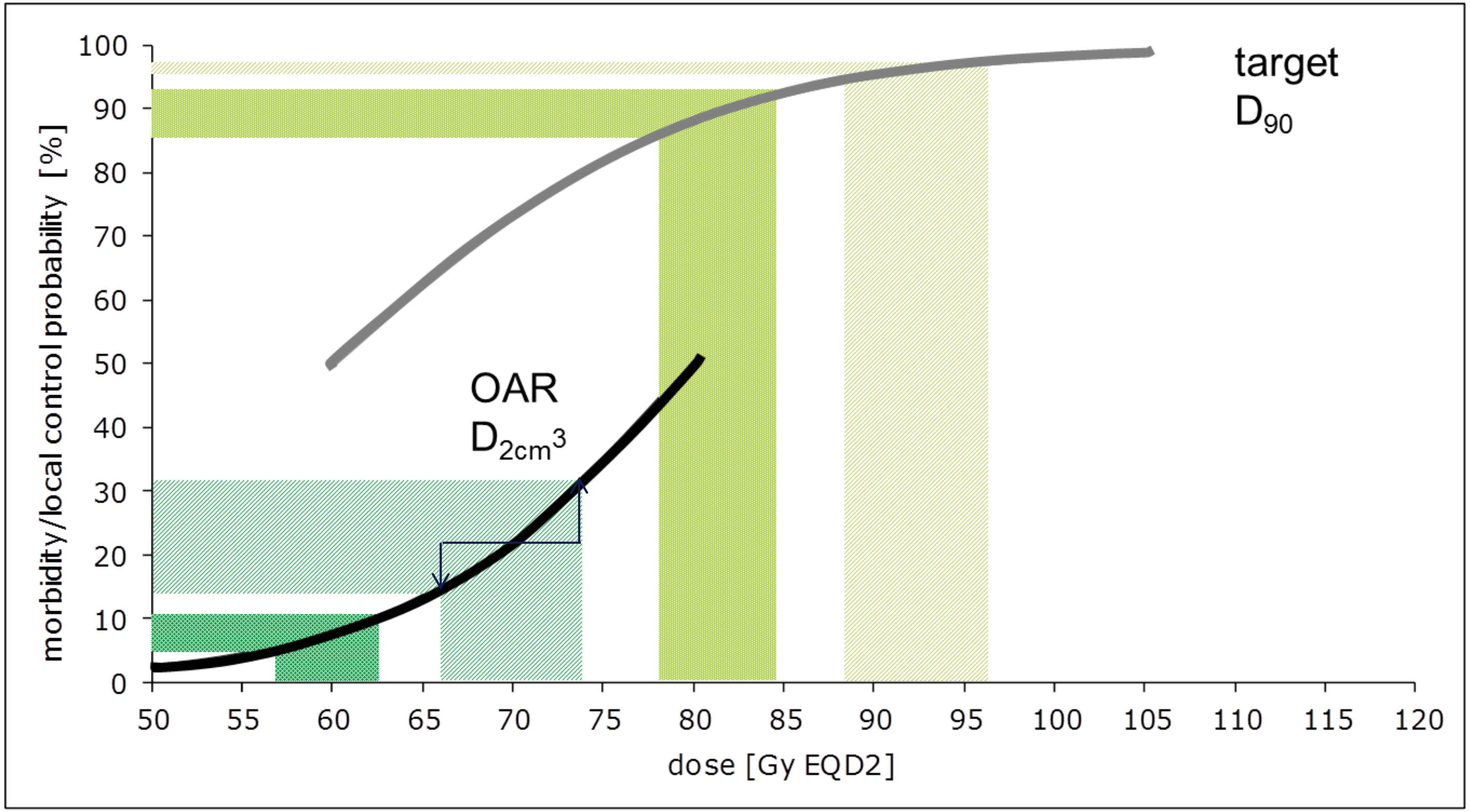
Tanderup, Nesvacil, Pötter, Kirisits, Editorial, RO 107(1) 2013

Examples total dose and uncertainty

- HR CTV: $D90 = 90 \pm 4Gy$
- Bladder: $D_{2cm3} = 85 \pm 7Gy$
- Rectum: $D_{2cm3} = 70 \pm 4Gy$
- Sigmoid: $D_{2cm3} = 70 \pm 7Gy$

Dosimetric uncertainties and dose-response relationships





Schematic illustration of the effect of dosimetric uncertainties of prescribed vs. delivered dose on response probabilities.

Tanderup et al. 2013, Radiother Oncol 107

Summary, Conclusion, Take Home Message?

- Systematic uncertainties can be minimized by refining our clinical protocols for
  - Applicator reconstruction,
  - organ filling,
  - image acquisition (optimal image quality for applicator reconstruction and delineation at the same time)

- Random inter-/intra-fraction uncertainties are a dominant factor for the total uncertainty budget in gyn BT. They can be large and can be monitored by use of repetitive imaging workflows.

Combinations of images and use of image registration in Brachytherapy

Nicole Nesvacil
Assistant Professor
Department of Radiotherapy, Comprehensive Cancer Center,
Christian Doppler Laboratory for Medical Radiation Research,
Medical University of Vienna

Thanks to K. Tanderup, C. Kirisits

Techniques for rigid registration in RT

- **Identity (DICOM)**

  automatic registration based on DICOM coordinate system

  - PET-CT, PET-MRI
  - **BT:** multiplanar MRI

- **Mutual information**

  automatic registration (CT, MRI-CT)

  - in EBRT: bony anatomy, external contour
  - in **BT**: head: bony anatomy, pelvis: BT applicator (≠ bony anatomy)
  - delineated structures

- **Landmark-based**

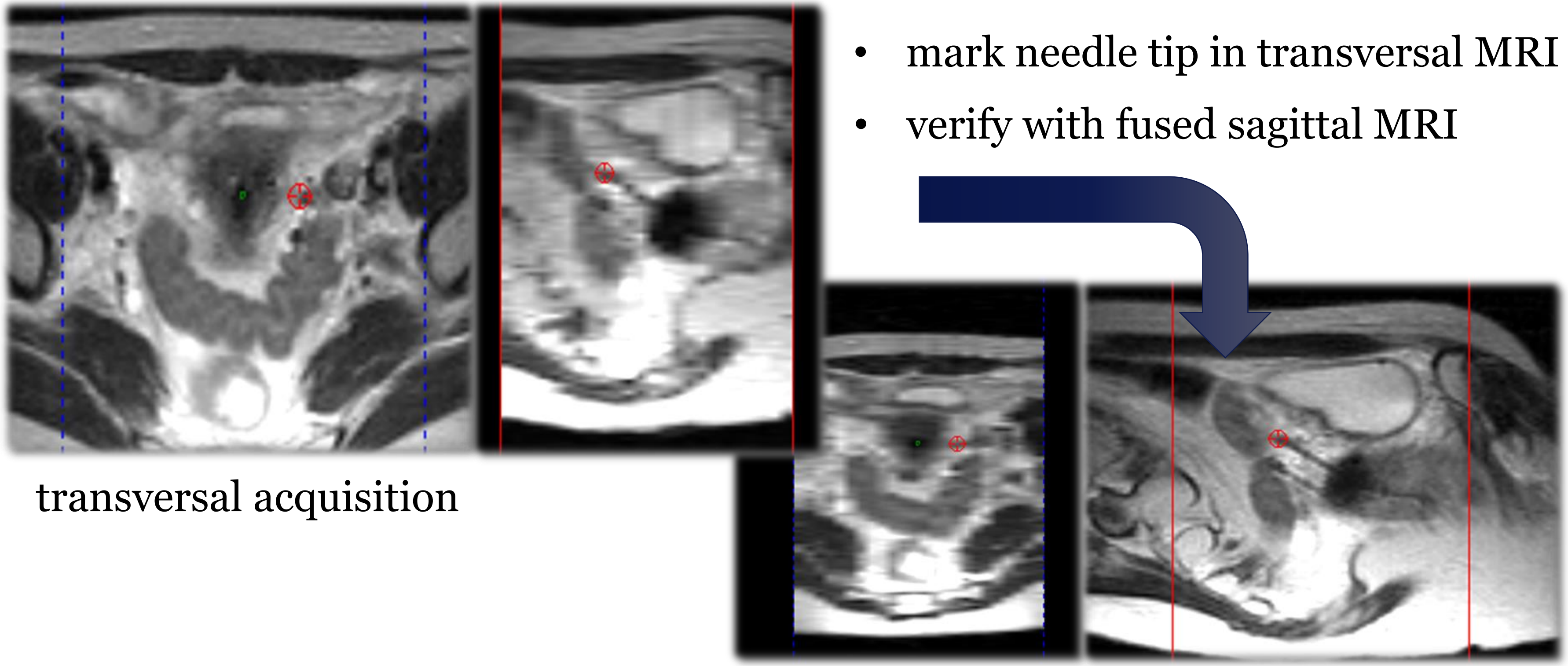
  manual definition of landmarks for registration

  - external markers, implanted markers, clips

- **Applicator-based (BT)**
  - manual: landmark definition based on applicator points
  - automatic: image volumes with reconstructed applicators (3D models) in place

DICOM Identity-based registration of multiplanar MRI:
applicator reconstruction, needle depth verification

- mark needle tip in transversal MRI
- verify with fused sagittal MRI



transversal acquisition

sagittal acquisition

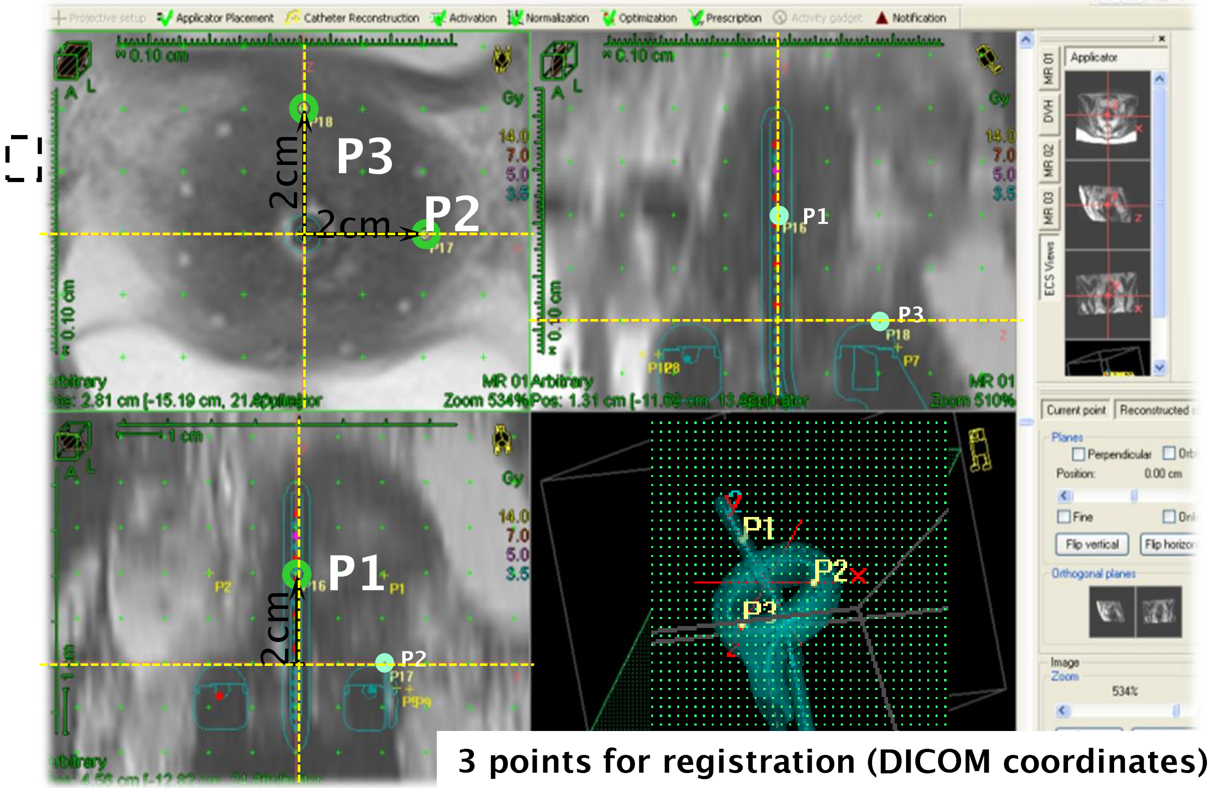
➕ Improved reconstruction precision for large MRI slice thickness available in TPS and/or DICOM viewers

▲ Uncertainty dominated by patient movement during acquisition (long scan times, anaesthesia)

Applicator-based registration (tandem-ring)

manual: landmark definition based on applicator points

automatic: image volumes with reconstructed applicators (3D models) in place



3 points for registration (DICOM coordinates)

If we know where the applicator is, we can define reproducible image registration points using the applicator as a reference coordinate system in all kinds of images!

<u>Example of manual method</u>: Align coordinate system according to applicator model and digitize 3 well defined points

Advantage of this method: uncertainty = reconstruction uncertainty, can be minimized and we know how! (If not, ask Jamema to repeat her lecture…)

Inter-/intra-fraction variations

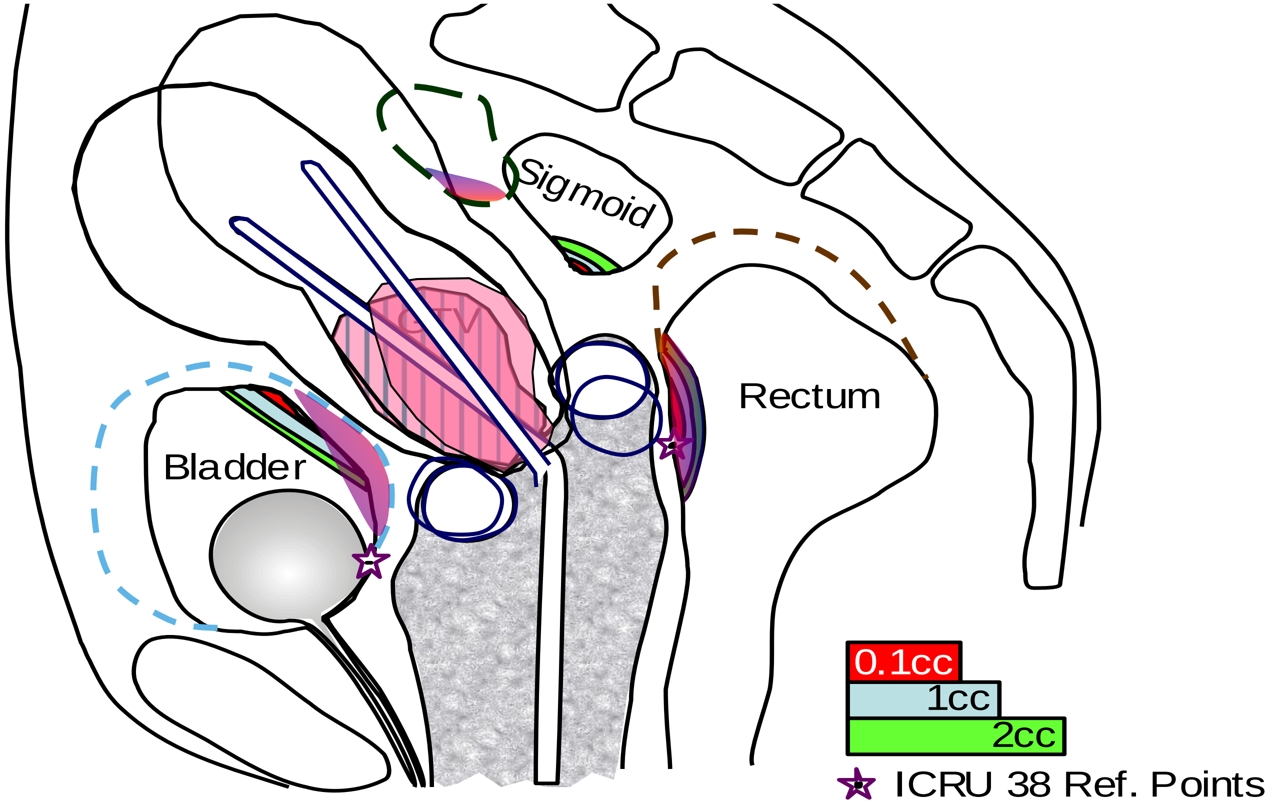
Cervix Cancer BT

Target
fixed to applicator

Rectum:
change of position or
filling with gas

Bladder:
change of filling
(use of bladder filling
protocol)

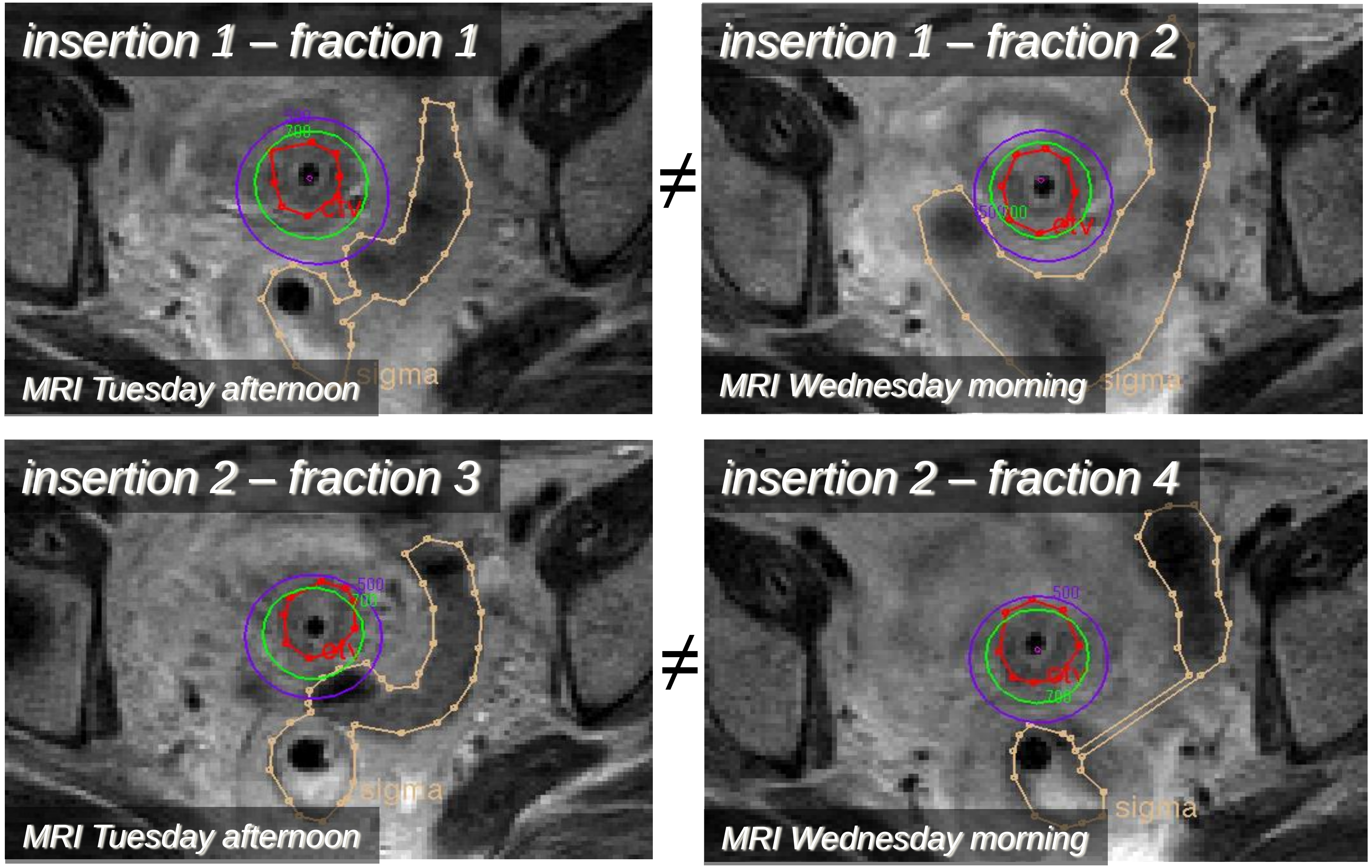
Sigmoid:
might change
its location



Impact on dose: fixed plan + variable anatomy

Plan 1

Plan 2



<------ inter-application variation ------>

<------ intra-application variation ------>

© Stefan Lang
Lang et al. 2013, Radiother Oncol

Solutions for 3D image guided adaptive planning

Is access to MRI with applicator in place available?

Yes, for each fraction/application

MRI for each HDR fraction

MRI for each application, CT before each fraction for OAR verification,…

Yes, but only for first application

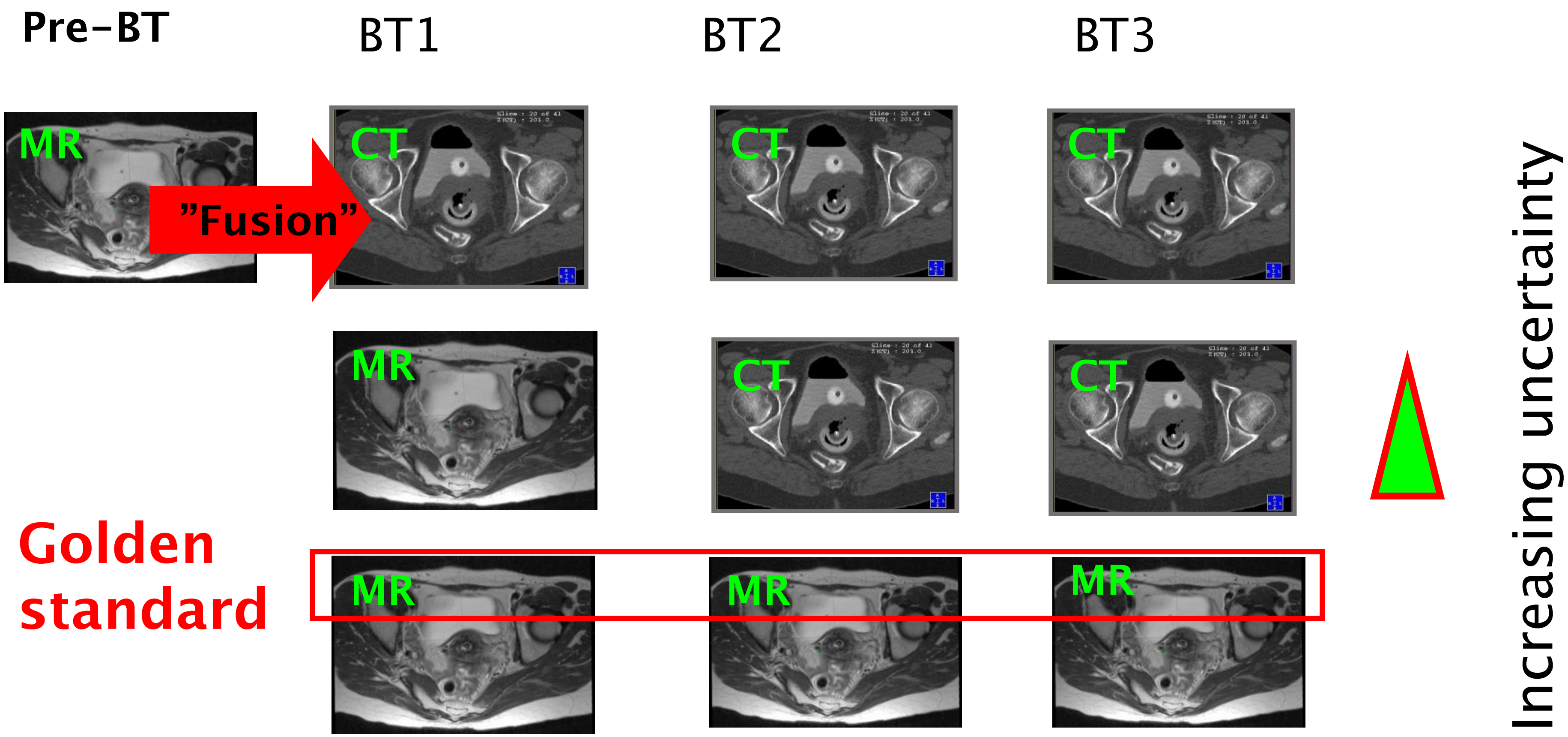
MRI for first application, CT for subsequent fractions (re-using MRI target from first fraction): software-based target transfer to avoid interobserver contouring uncertainties

No, not at all

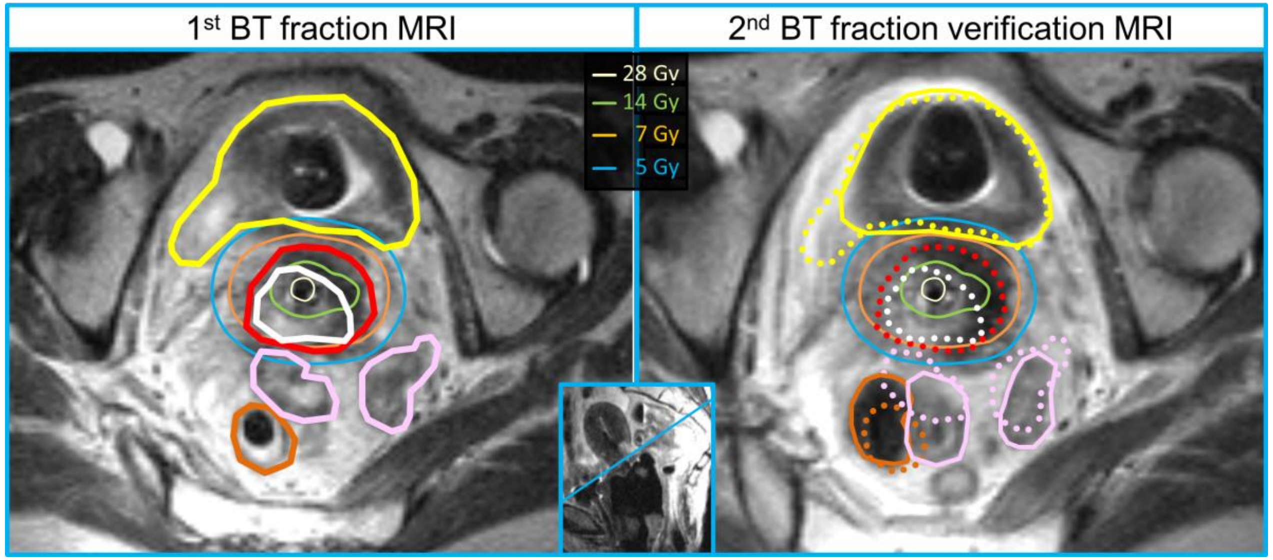
pre-BT MRI for target delineation on CT with applicator in situ at BT

or even: volumetric US scan after applicator insertion for target definition, and CT scan for OAR delineation (registration via applicator)

Image modality?



Example: day 1 – day 2 comparison

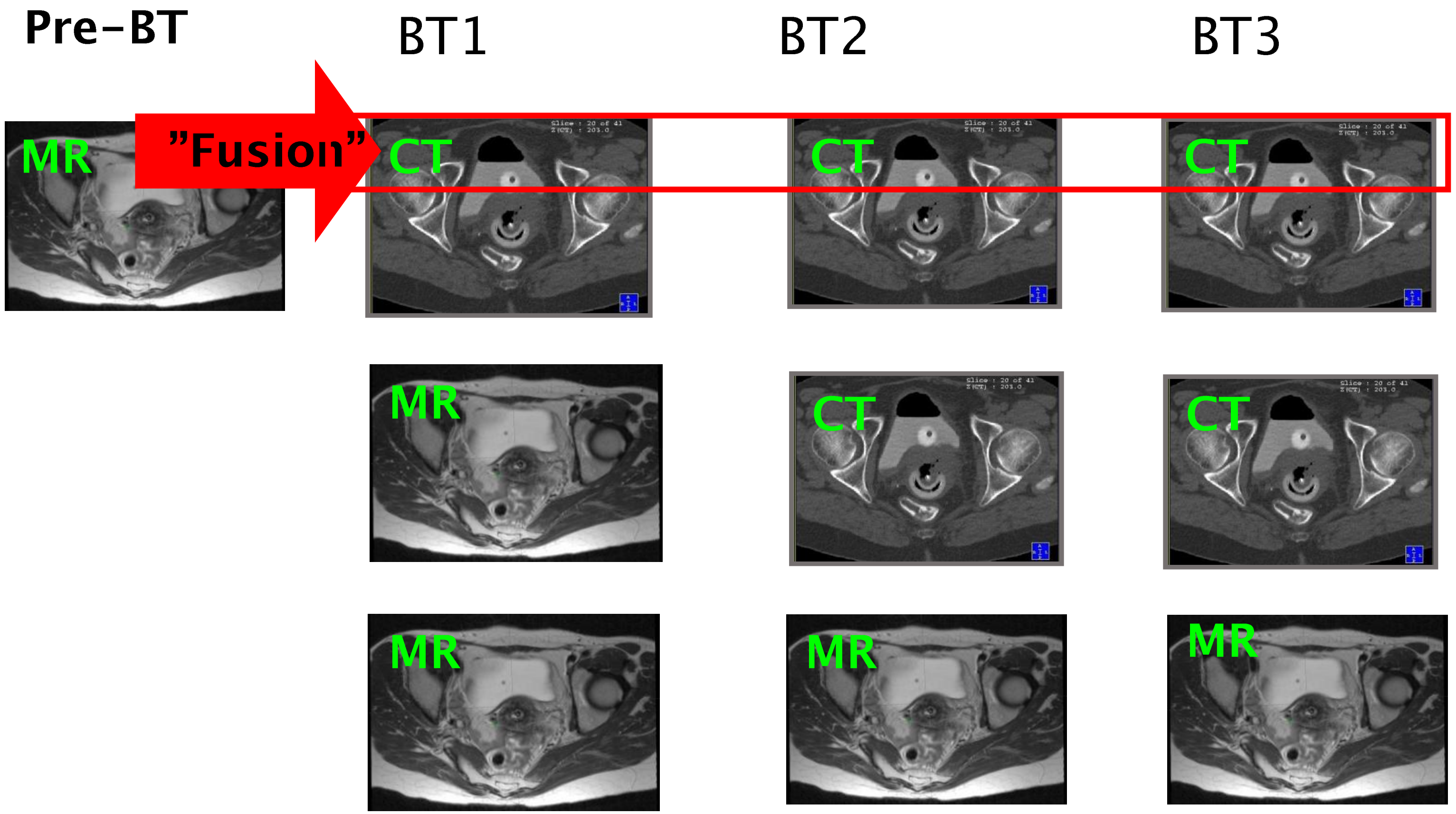


Bör et al. ESTRO 2014

Fast registration of MRI F1 and F2 via applicator coordinate system to

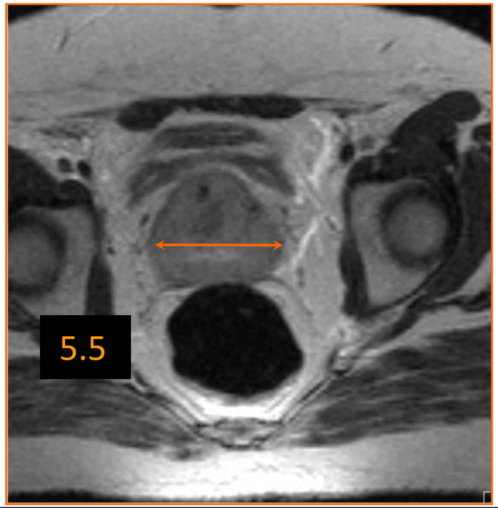
- check implant stability (relative position of applicators/needles and target)
- check organ variation
- decide to
  - » treat
  - » adapt organ filling
  - » recontour and re-evaluate DVH
  - » (rarely replan before treatment of F2)

Pre-BT MRI + CT

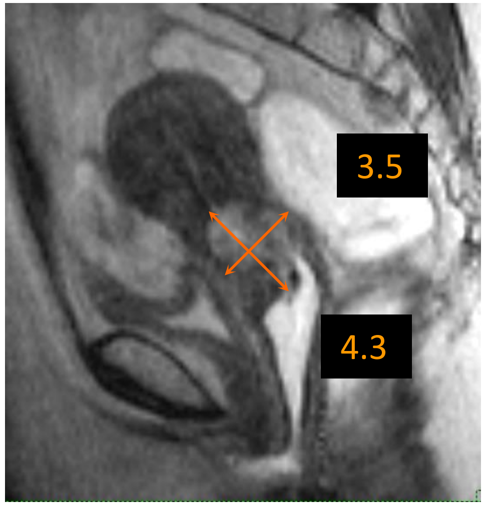


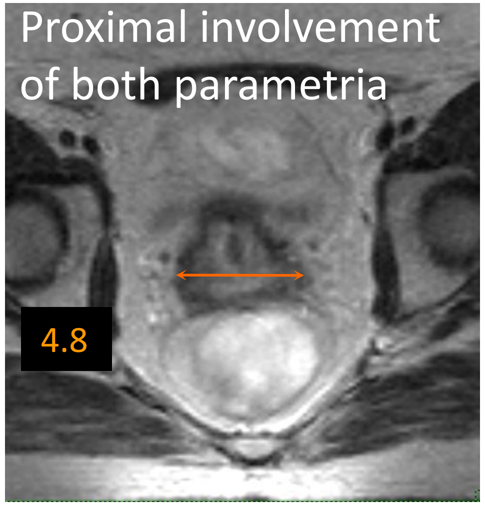
Example: CTV_{HR} „pre–BT MRI“ (CTV_{HR} 3)

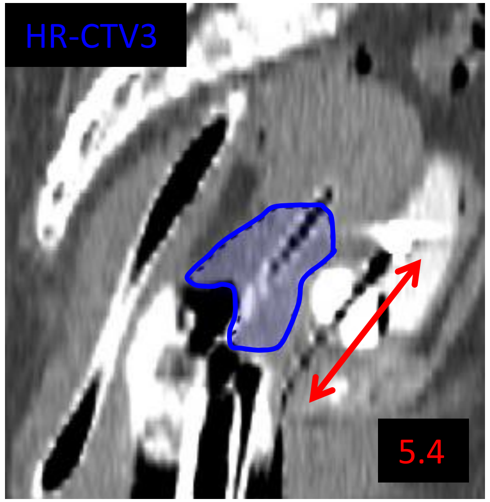
Diagnosis

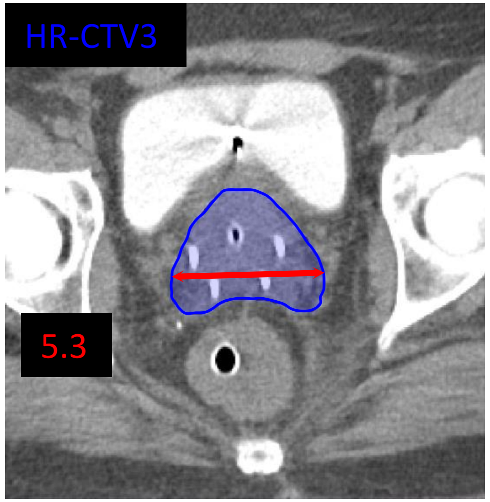


1st Brachytherapy

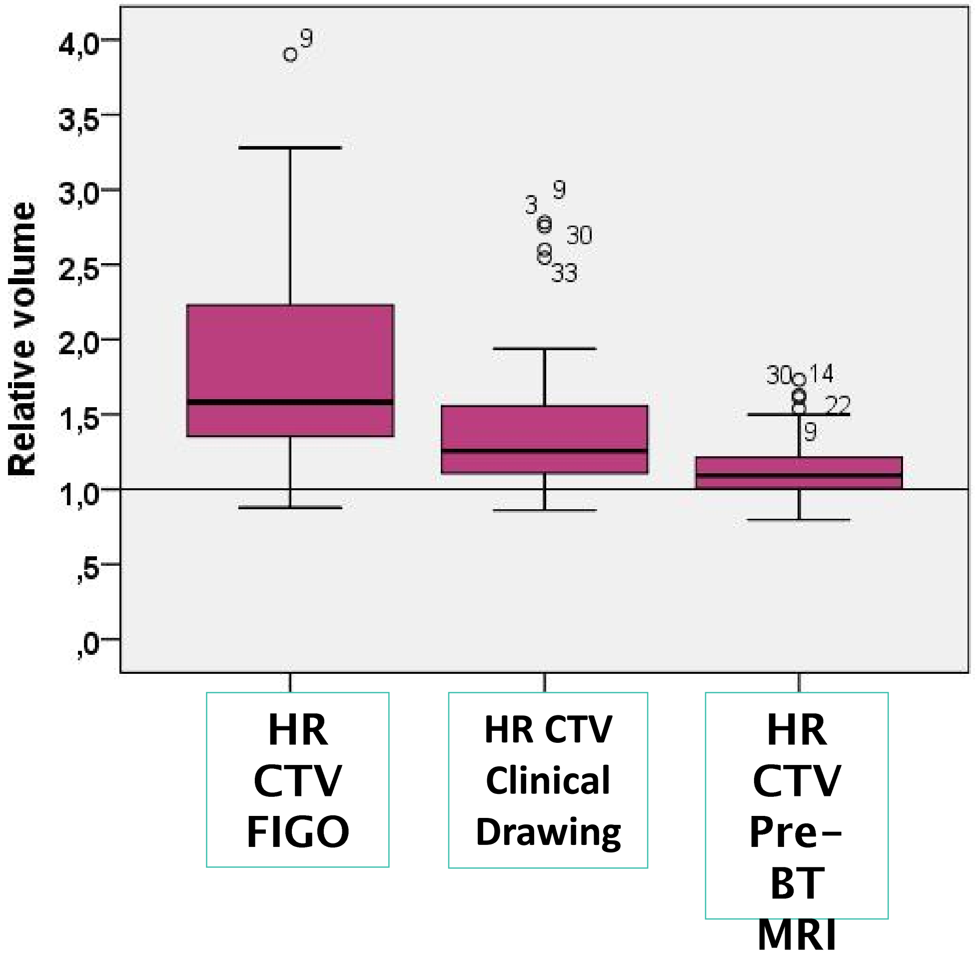






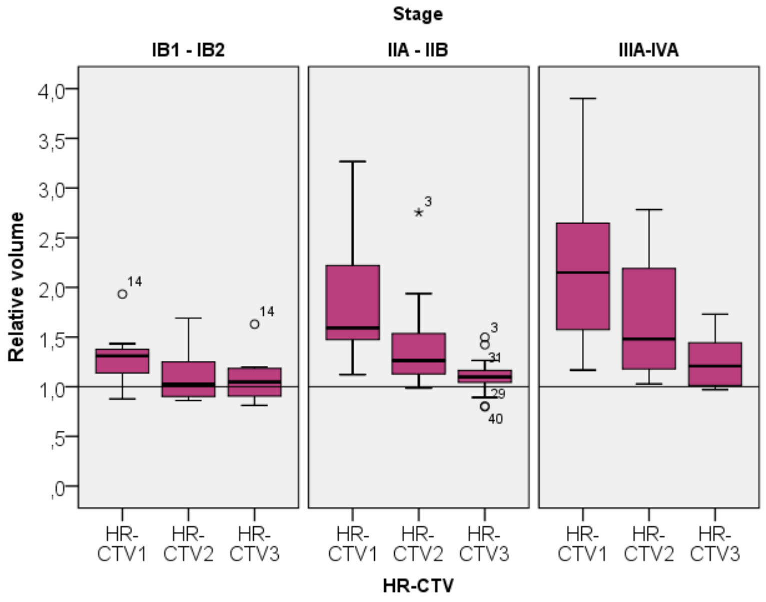


Delineation on CT according to three principles

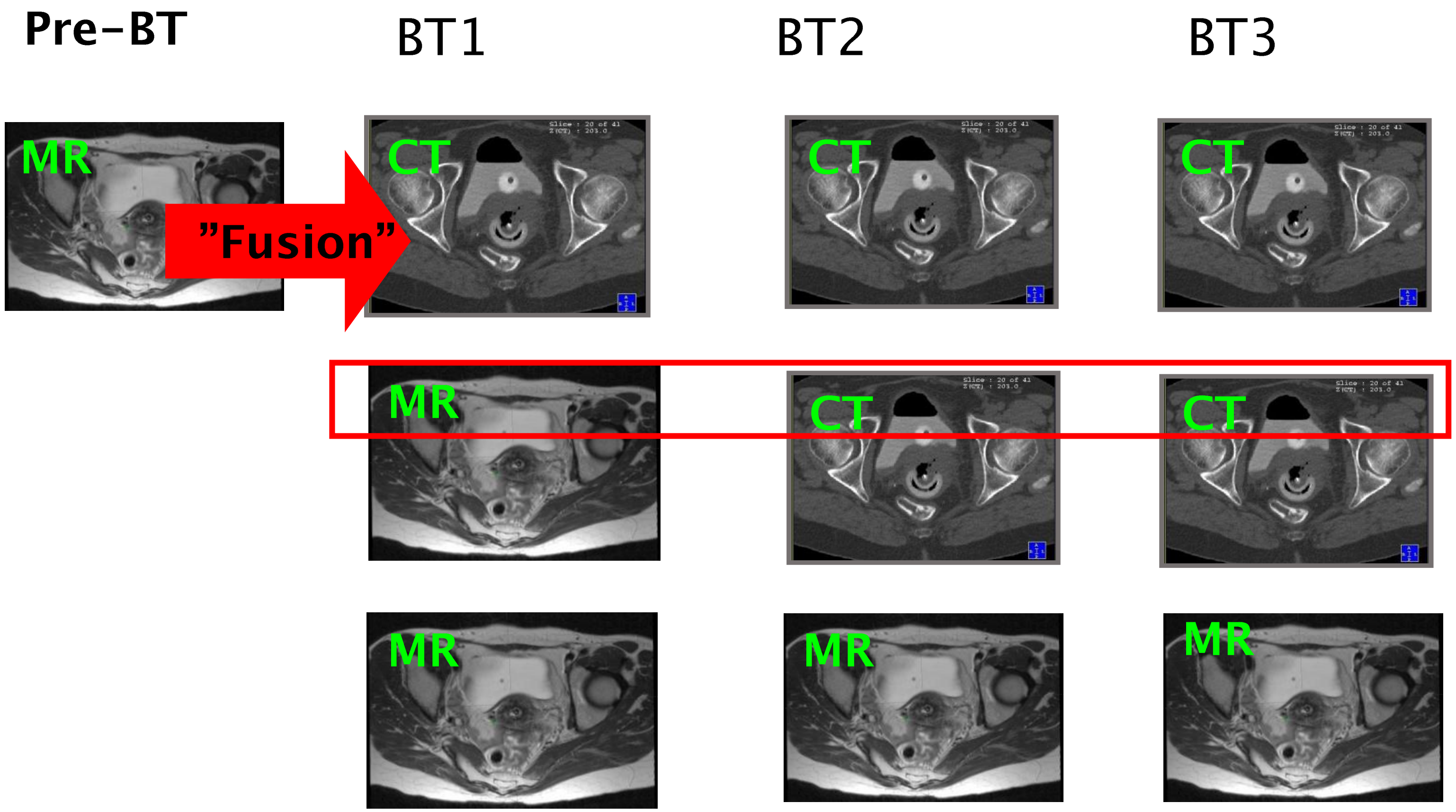


Three increasingly comprehensive principles for delineation on CT:

FIGO only
FIGO + clinical drawing
FIGO + clinical drawing + pre-BT MRI

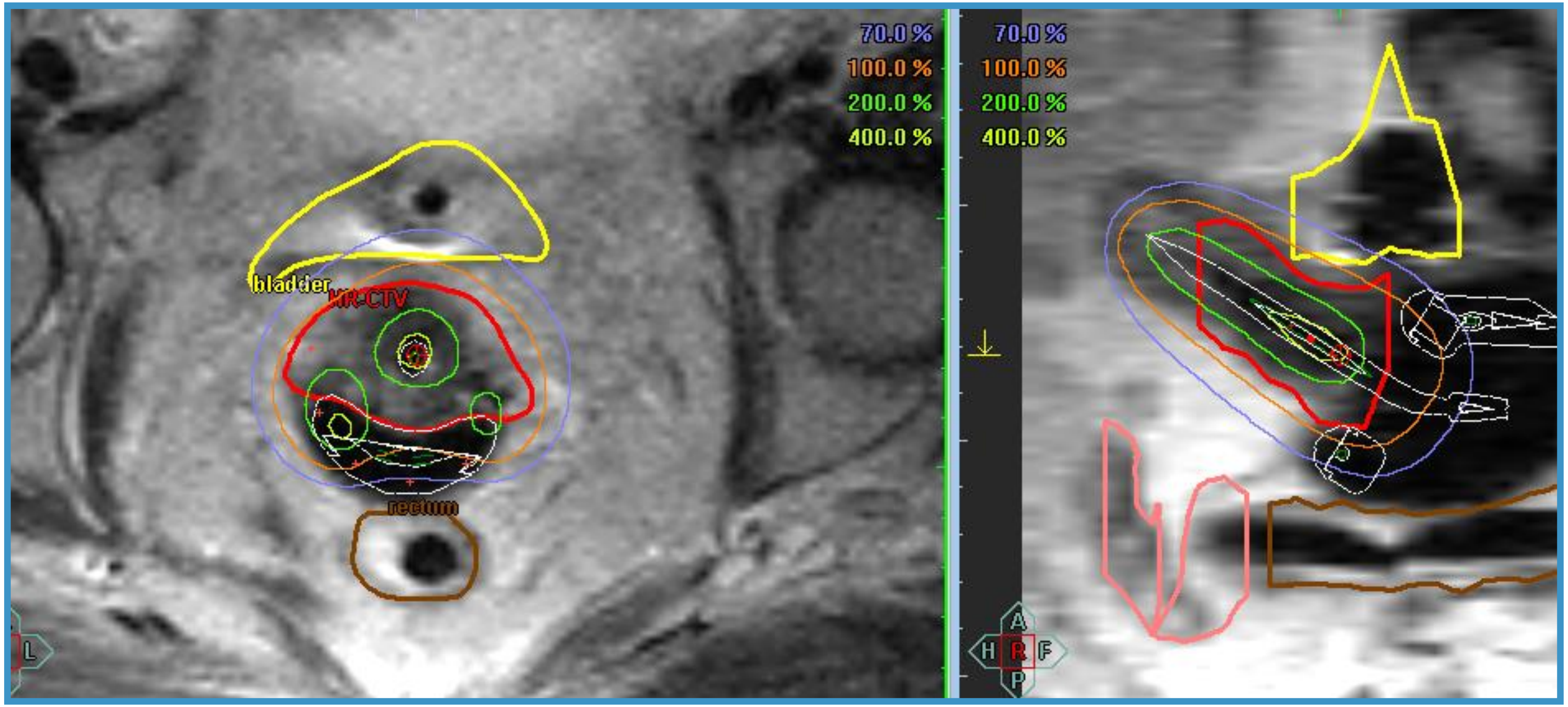


BT MRI + CT



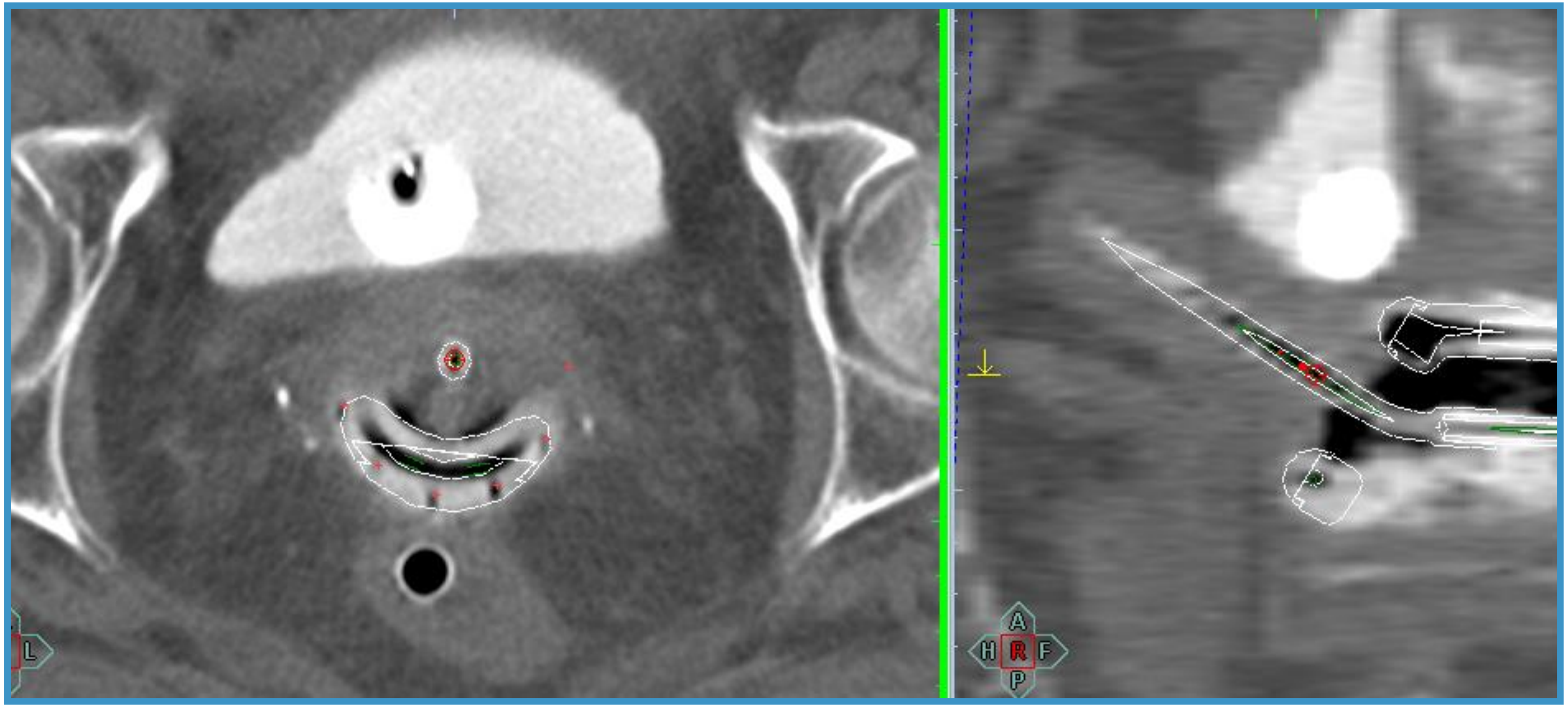
1st application: MRI

Applicator, target (HR CTV), OAR (rectum, bladder, sigmoid)
Dose planning and optimization on target+organ contours



2nd application: CT

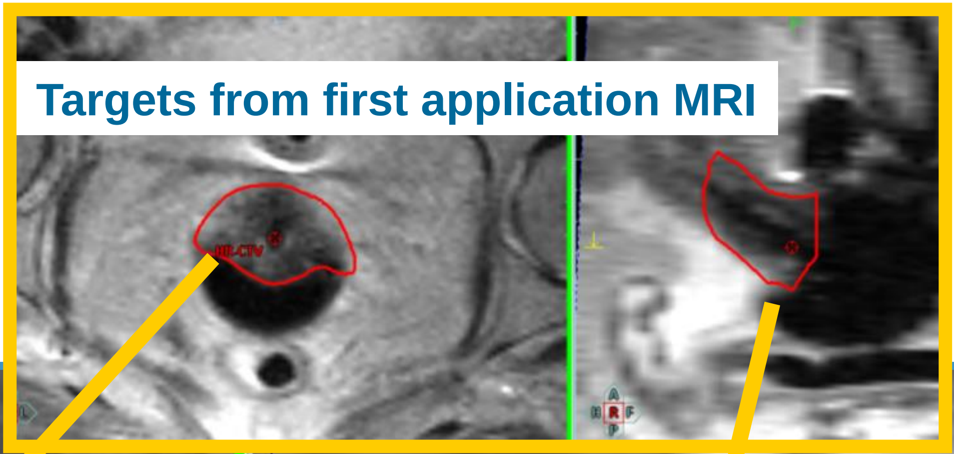
3D applicator reconstruction

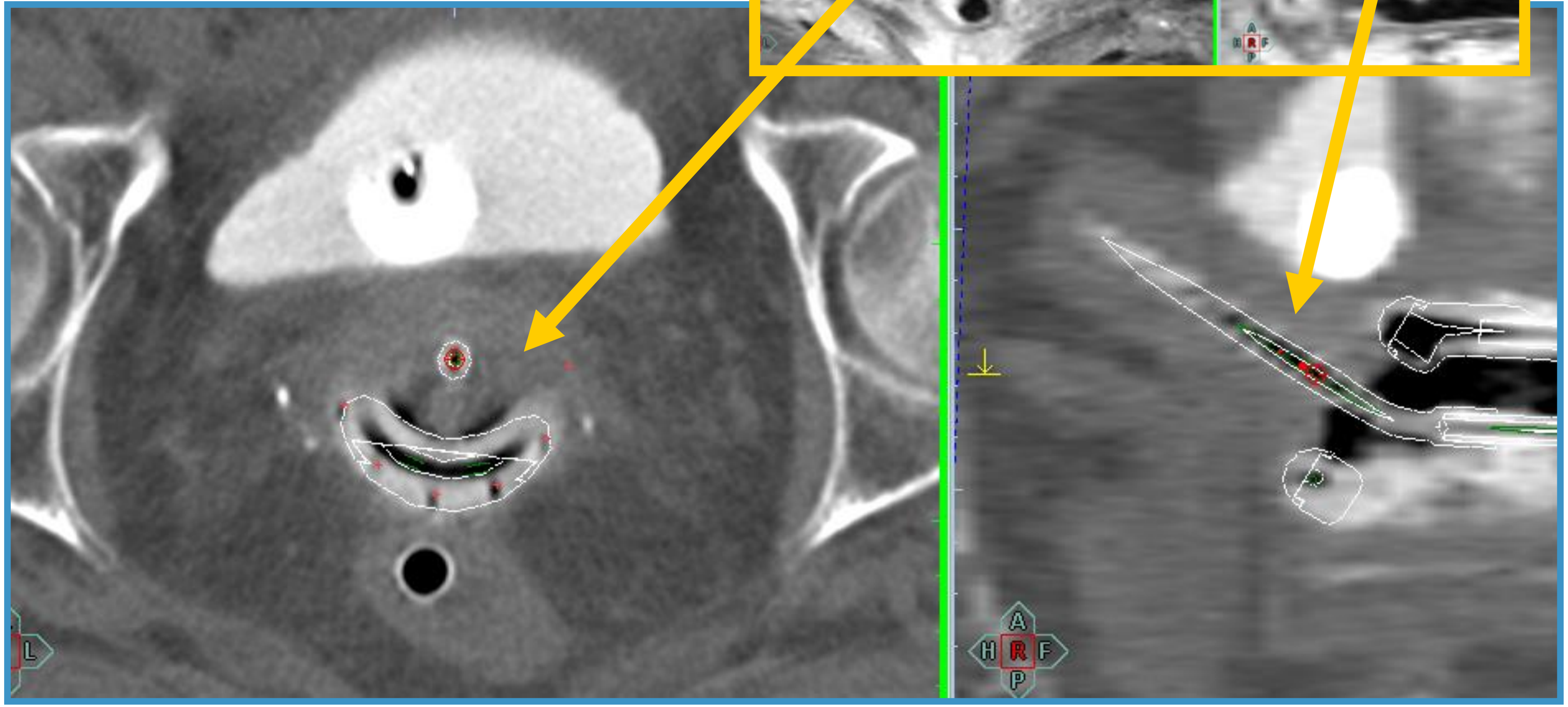


2nd application: CT

3D applicator reconstruction

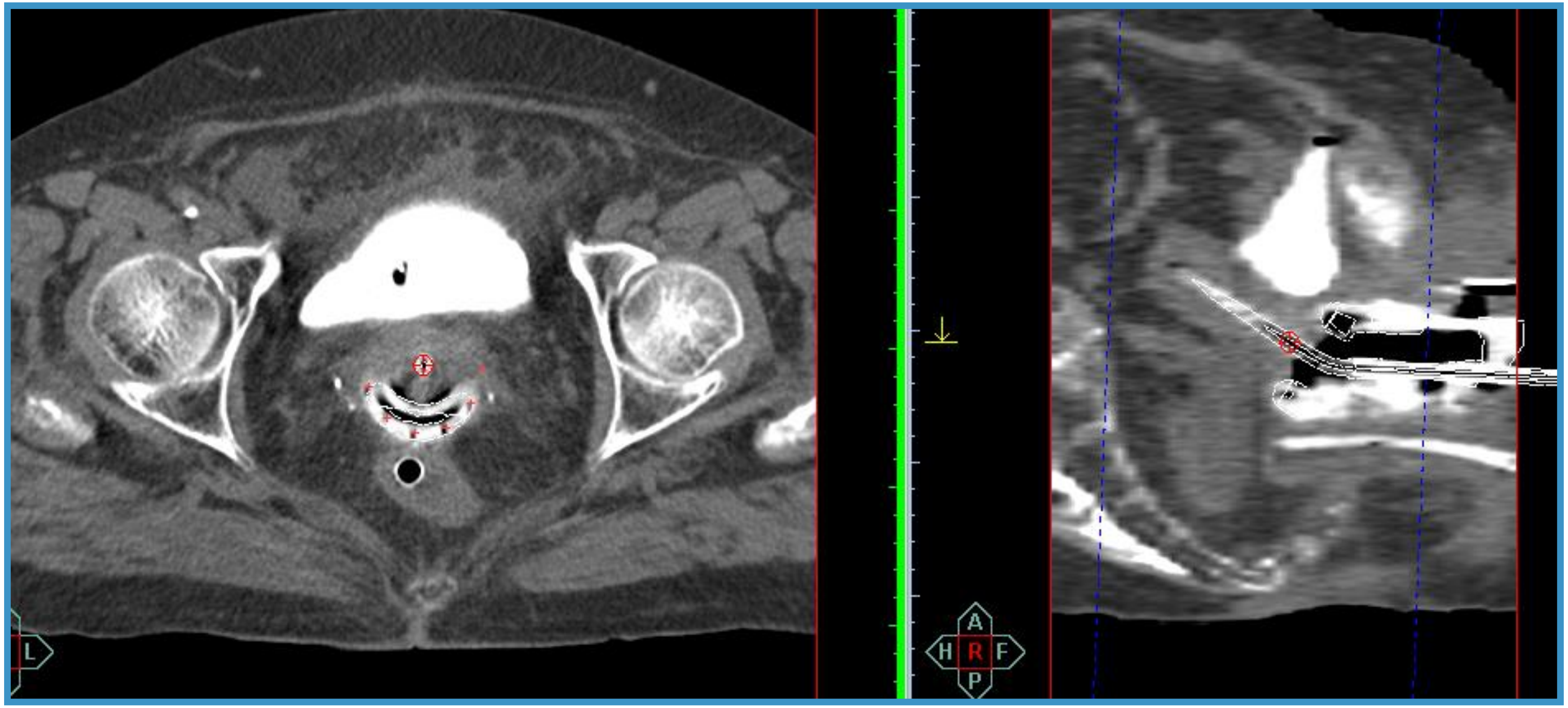
Target transfer





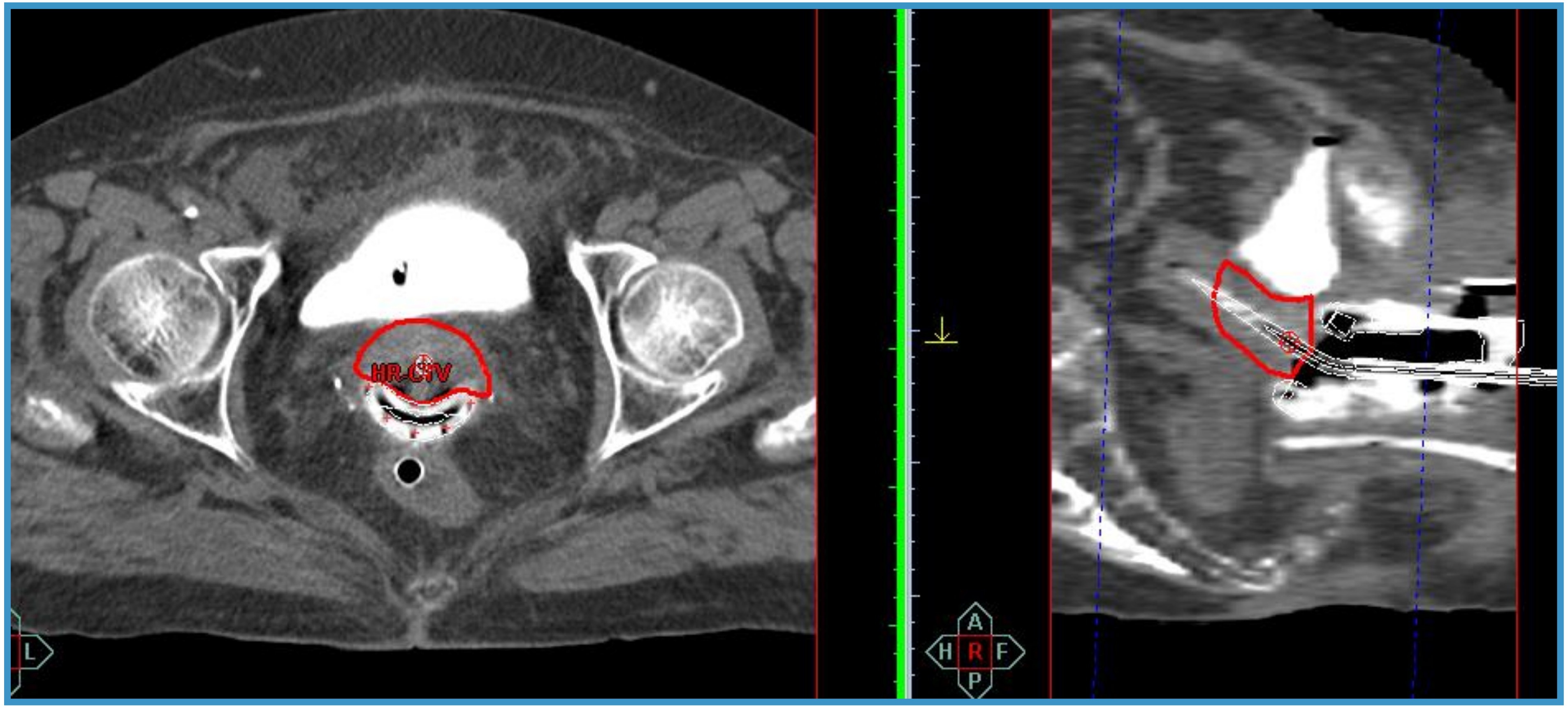
2^{nd} application: CT

Rigid image registration based on 3D applicator model



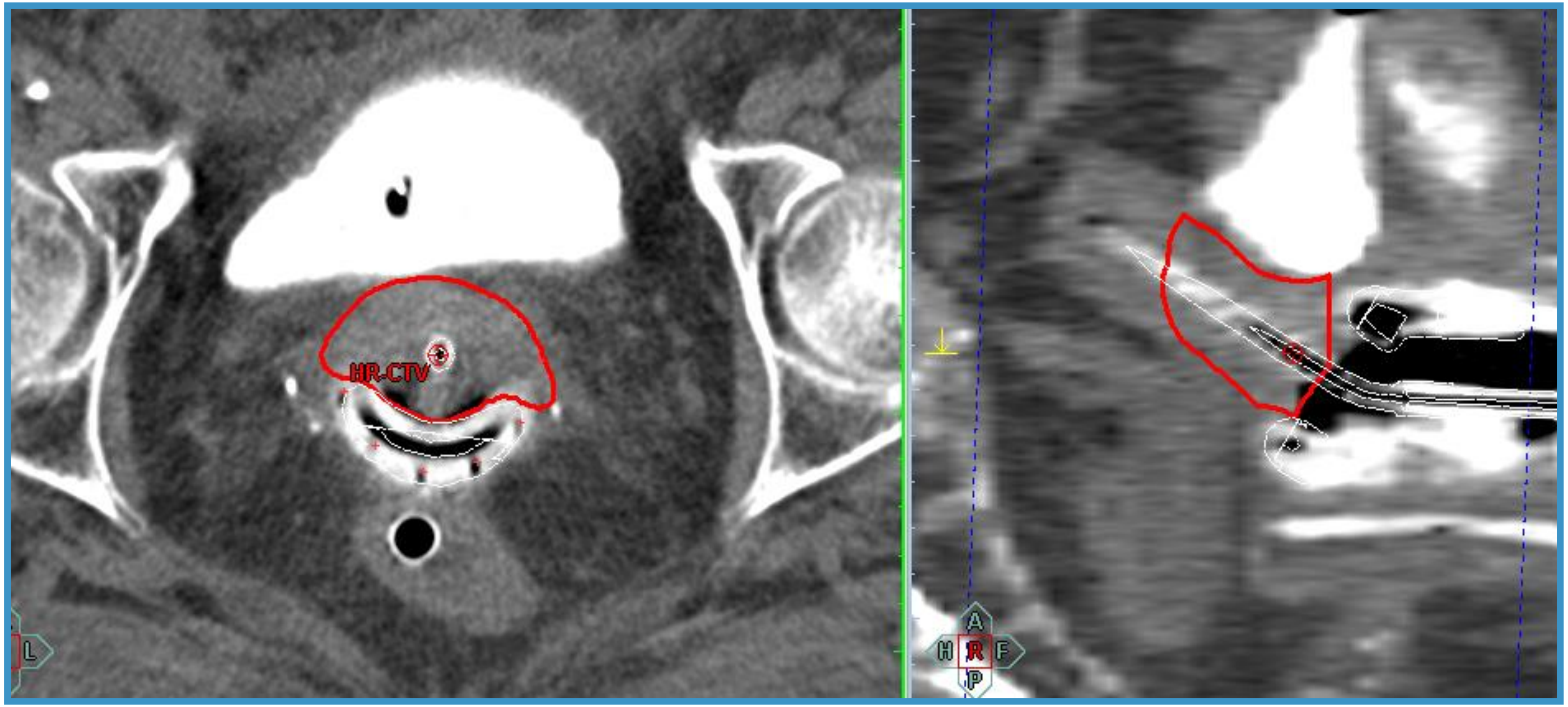
2nd application: CT

Automatic target transfer from MRI to CT with applicator as reference system



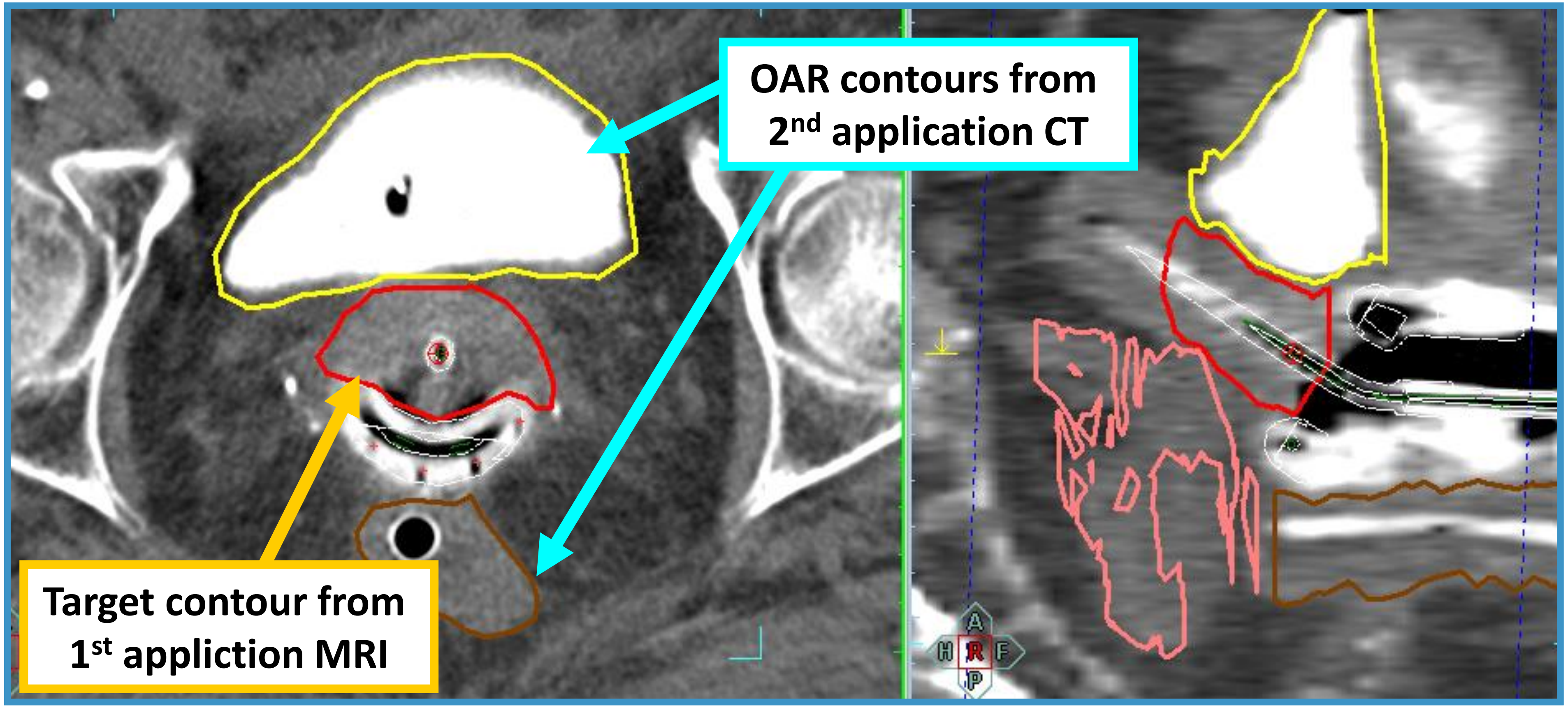
2nd application: CT

Contouring OAR on CT



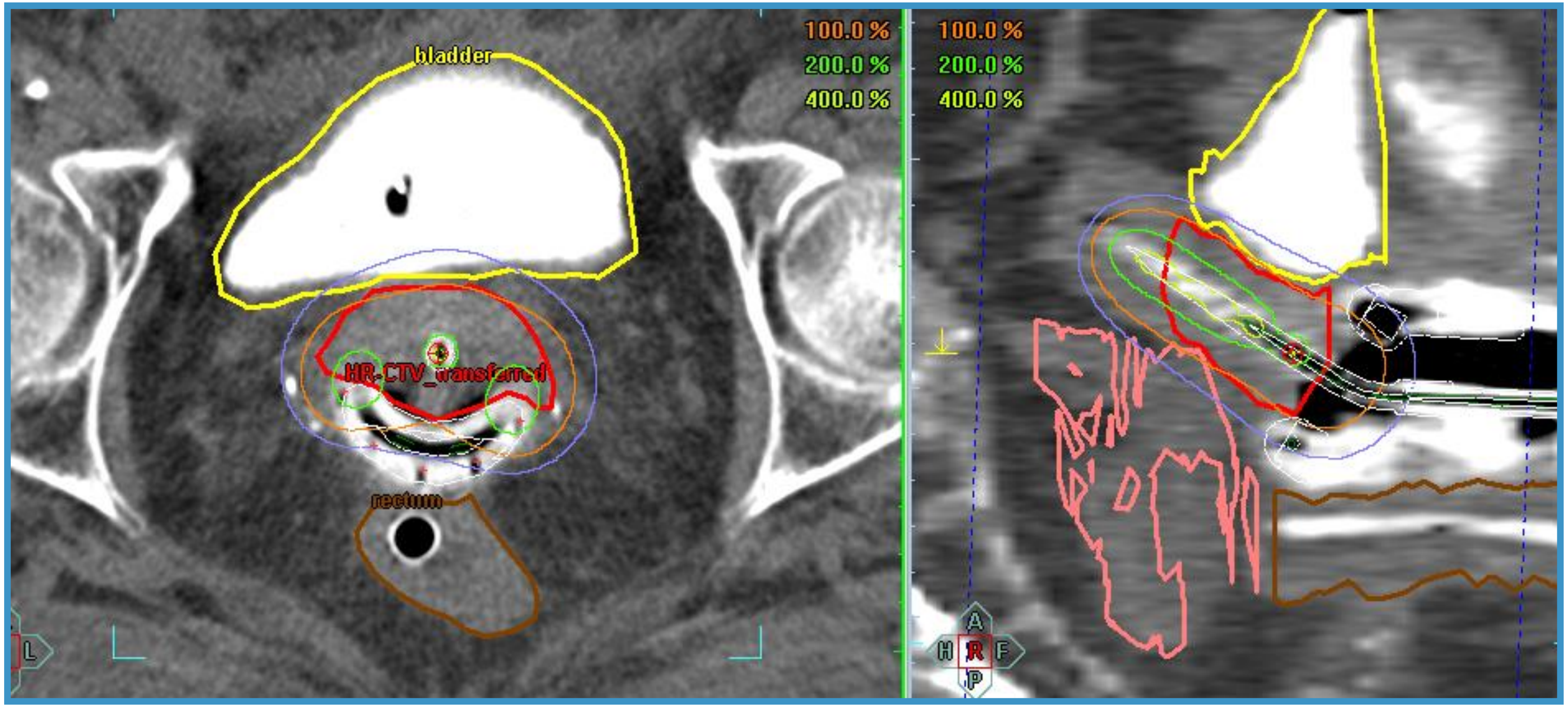
2nd application: CT

Contouring **OAR on CT**

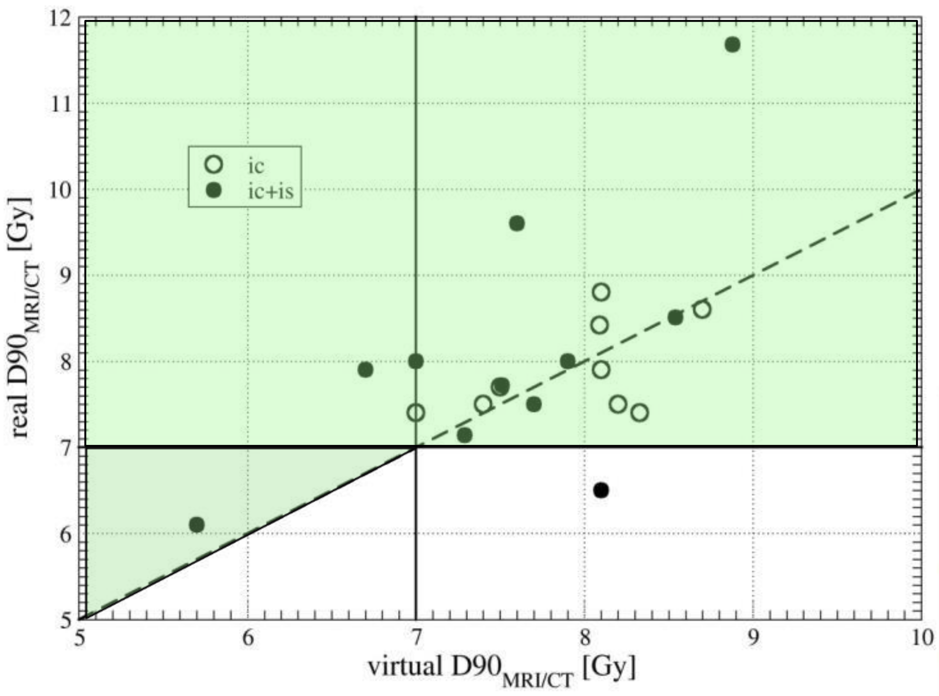


2nd application: CT

Dose planning and optimization based on copied target and individual OAR contours. All dose constraints for targets and OAR have to be achieved.

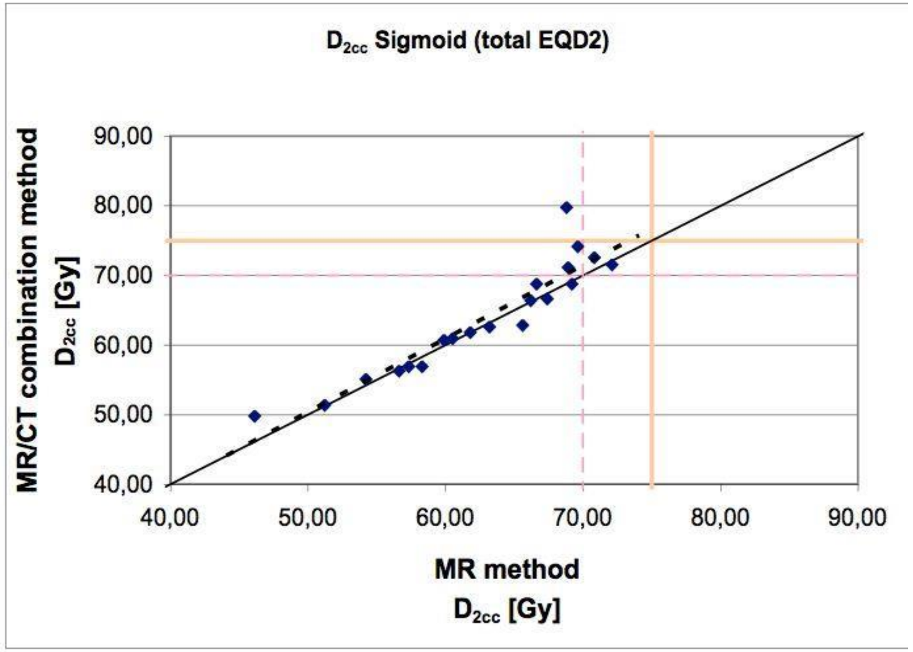


Results: D_{90} CTV_{HR}, D_{2cm^3} sigmoid



Planning aim D_{90} CTV_{HR}>7Gy per fraction was reached in all but one cases
(applicator position was different on MRI and CT)

Planning aim D_{2cm^3} sigmoid<80Gy EQD2(α/β=3Gy)
In total was reached in all but one cases
(intrafractionorgan motion, contouring uncertainties)



Solutions for 3D image guided adaptive planning

Is access to MRI with applicator in place available?

Yes, for each fraction/application

MRI for each HDR fraction

MRI for each application, CT before each fraction for OAR verification,…

Yes, but only for first application

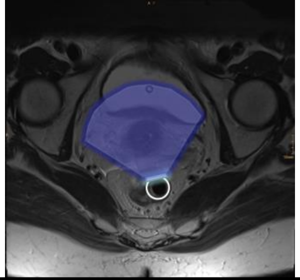
MRI for first application, CT for subsequent fractions (re-using MRI target from first fraction): software-based target transfer to avoid interobserver contouring uncertainties

No, not at all

pre-BT MRI for target delineation on CT with applicator in situ at BT

or even: volumetric US scan after applicator insertion for target definition, and CT scan for OAR delineation (registration via applicator)

No MRI? Use of transrectal US for target visualisation in cervix BT?



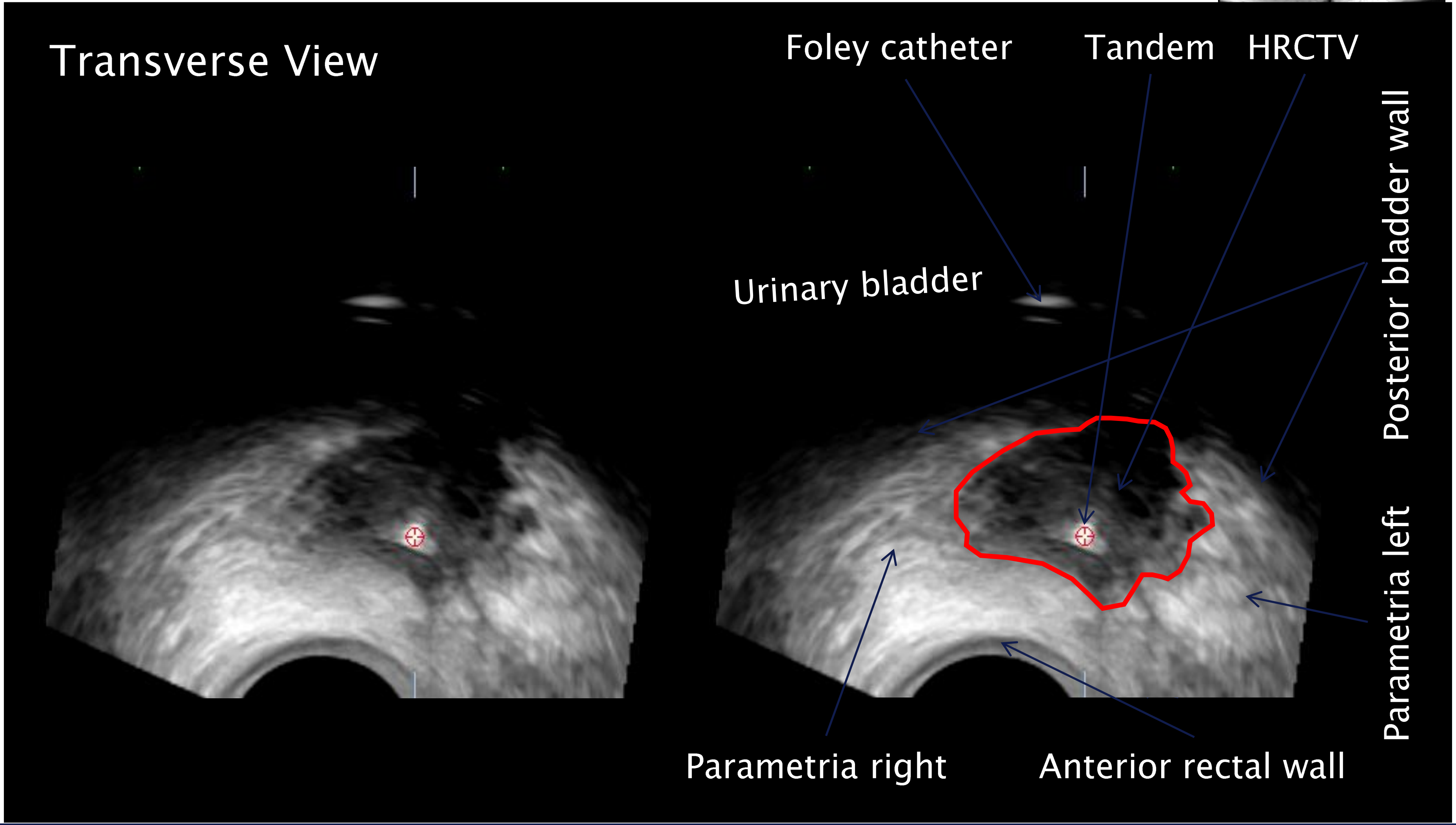
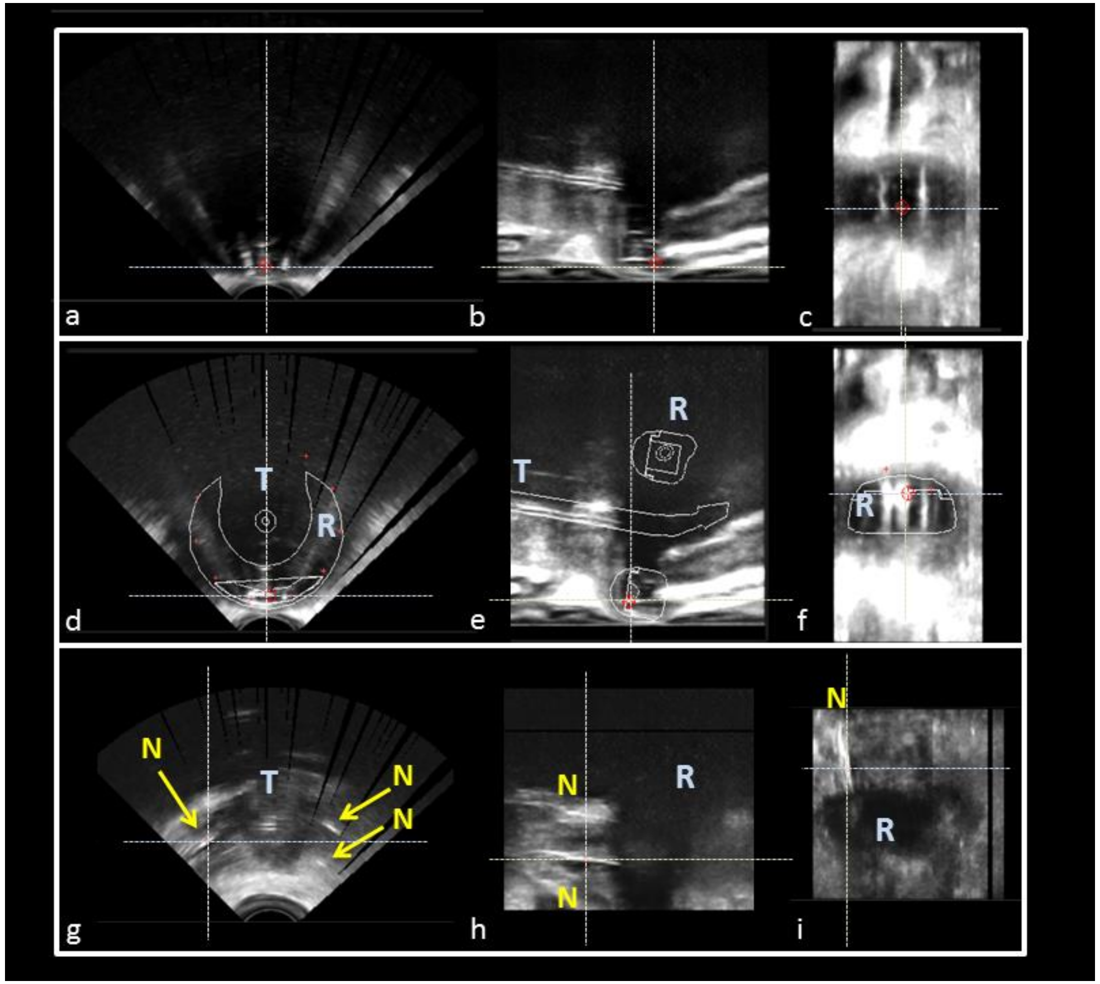


Image quality: TRUS-preBT: 2.9, TRUS-BT: 2.3, MRI-preBT: 2.9, MRI-BT: 2.7, CT-BT: 2.1

Direct applicator reconstruction on TRUS – large uncertainties



transversal sagittal coronal

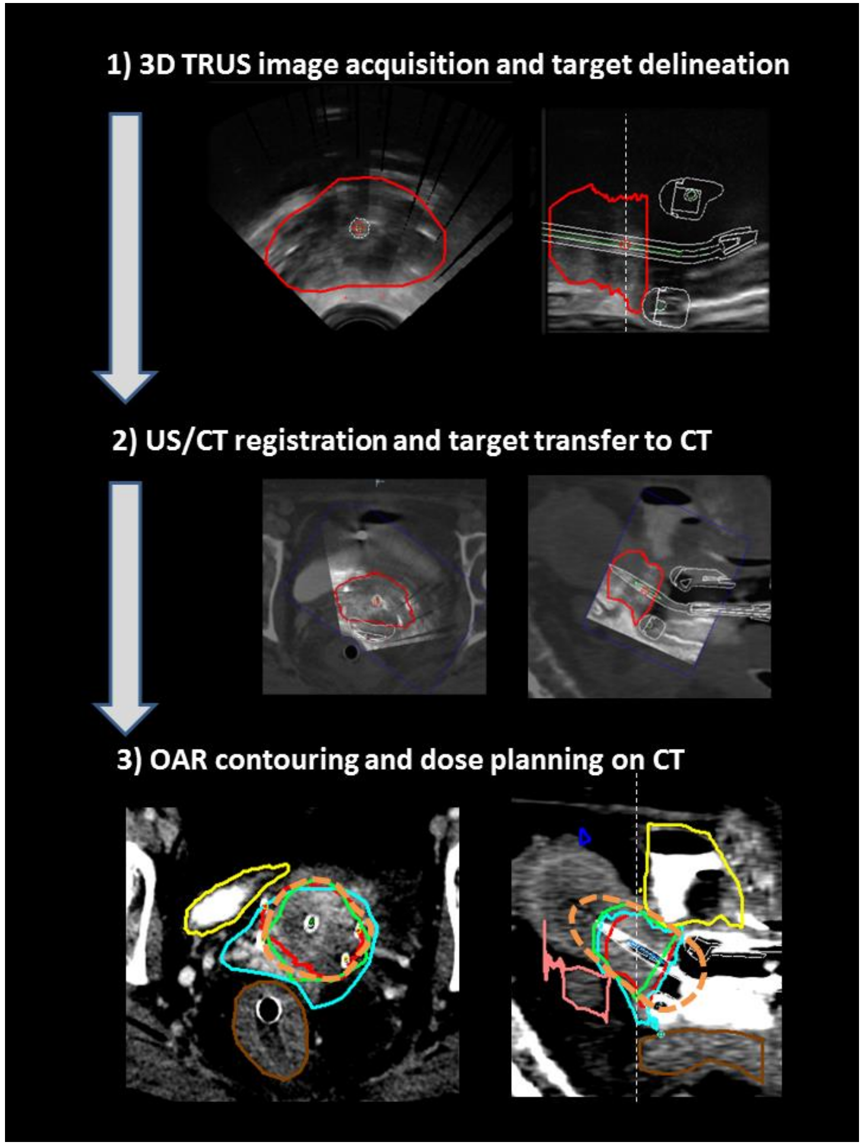
Ring applicator only partly visible

Tandem tip beyond FOV (probe dimensions optimized for prostate imaging)

Needle depiction quality as high as for prostate BT

Possible solution: TRUS acquisition + online applicator tracking

Nesvacil et al, Brachytherapy 2016,

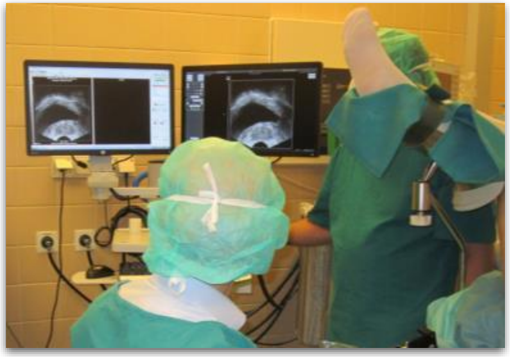


- Workflow for combination of TRUS and CT for treatment planning under investigation
    - Applicator reconstruction (automatic)
    - Fusion with CT
    - Delineation of target on TRUS/CT
    - OARs delineation on CT
- Method is expected to produce dose distributions that are more comparable with MRI-only, than the CT-only method.

Target volume comparison: blue (CT), green (MRI), red (TRUS)

Nesvacil et al, Brachytherapy 2016

Transrectal ultrasound for target definition in CT-based cervix cancer IGABT (no access to MRI @BT)



pre-implant scan, TRUS guidance of implantation

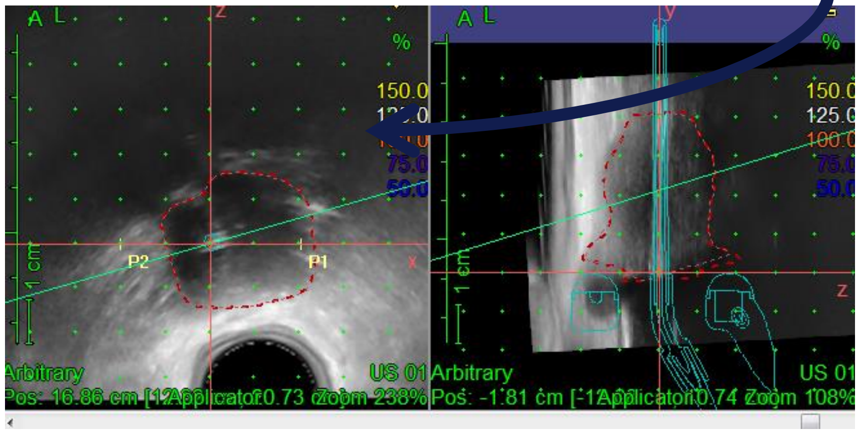
volumetric post-implant scan

applicator tracking

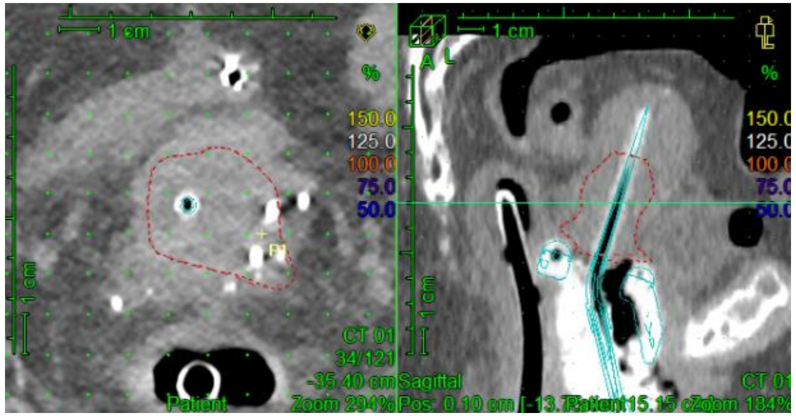
(ACMIT, Elekta)

main uncertainty: tracking, QA

TRUS target delineation



TRUS-CT registration via applicator



Schmid et al. R&O 2016, Nesvacil et al. Brachytherapy 2016

Other examples for applicator-based image registration:

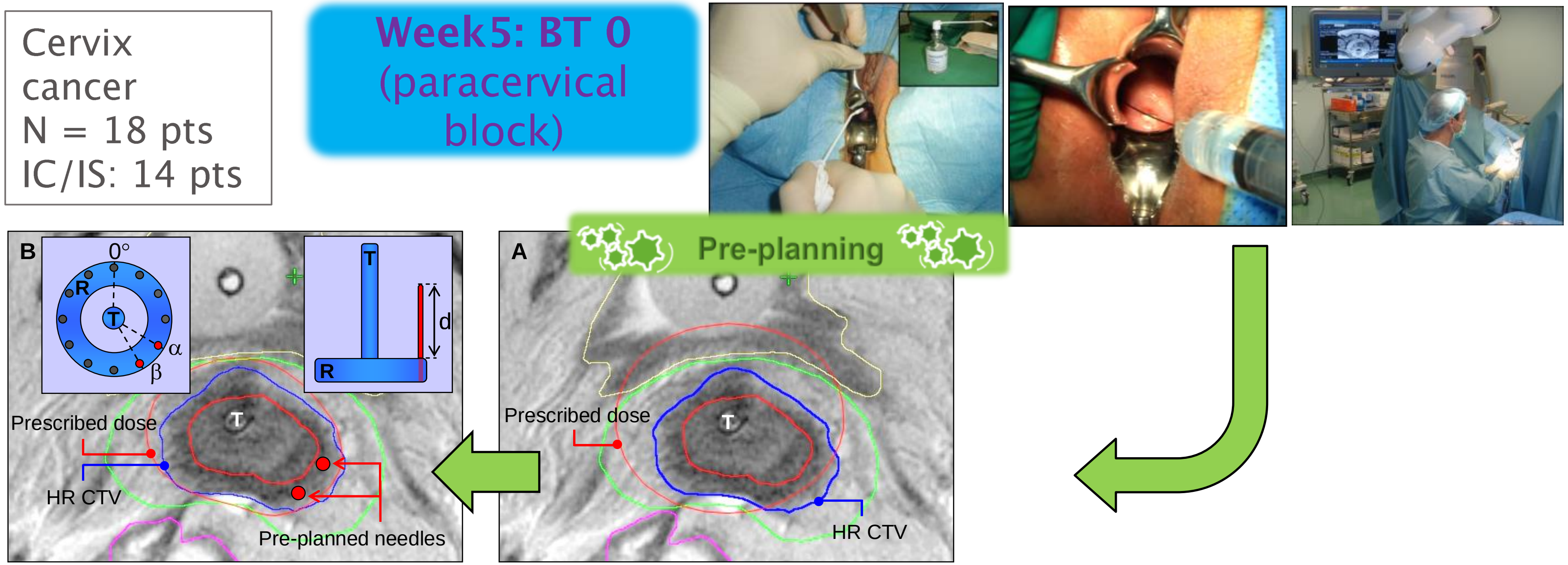
Pre-planning

Gyn Pre-planning: Intracavitary / Interstitial Insertion

Based on pre-brachytherapy MRI: **With applicator in place**

Cervix cancer
N = 18 pts
IC/IS: 14 pts

Week5: BT 0
(paracervical block)



Petric P, et al. Radiol Oncol 2014

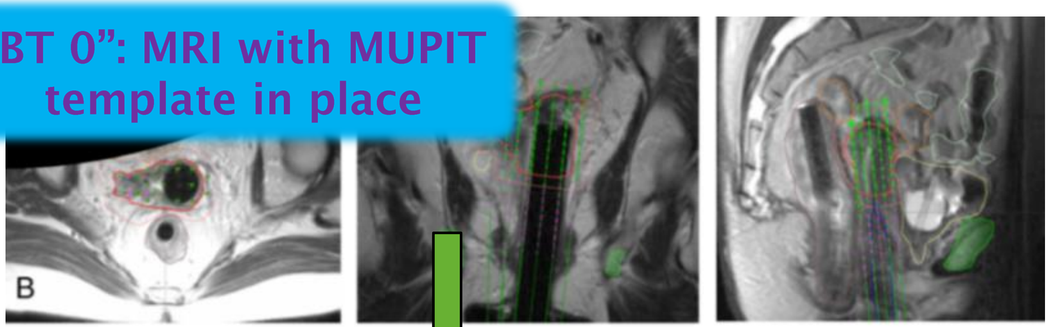
- BT implant preplanning with high geometrical reproducibility
- MRI target from pre-planning could be transferred to CT for planning at time of BT via applicator-based registration

Gyn BT Pre-planning: Intracavitary / Interstitial Insertion

Based on pre-brachytherapy MRI: **With applicator in place**

- Primary vaginal cancer
- Recurrent endometrial cancer
- Recurrent cervical cancer

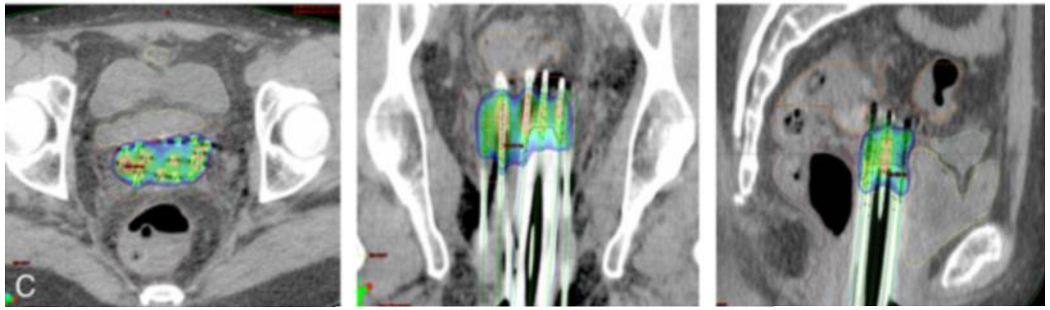
"BT 0": MRI with MUPIT template in place



Pre-planning

BT: IC + needles (LPSC)

MRI-CT registration on applicator for CT target definition



Preplanned No. of needles	(9–21)
Implanted No. of needles	(8–22)
Active No. of needles	(8–21)

Fokdal L, et al. Radiother Oncol 2011;100:473-479

Take home message:

Combination of images from different modalities is possible and often useful.

It might help to reduce inter- intra-fraction uncertainties, but can also introduce new ones!

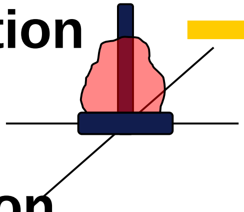
Therefore it should be done with caution, precision, standardized workflows and appropriate workflow QA.

Combined MRI-/CT- guided BT for cervical cancer

1st application

MRI- **based planning:**
3D applicator reconstruction

target delineation



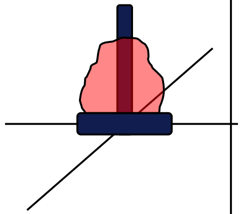
OAR delineation

Dose planning and optimization

2nd application

CT- **based planning:**
3D applicator reconstruction

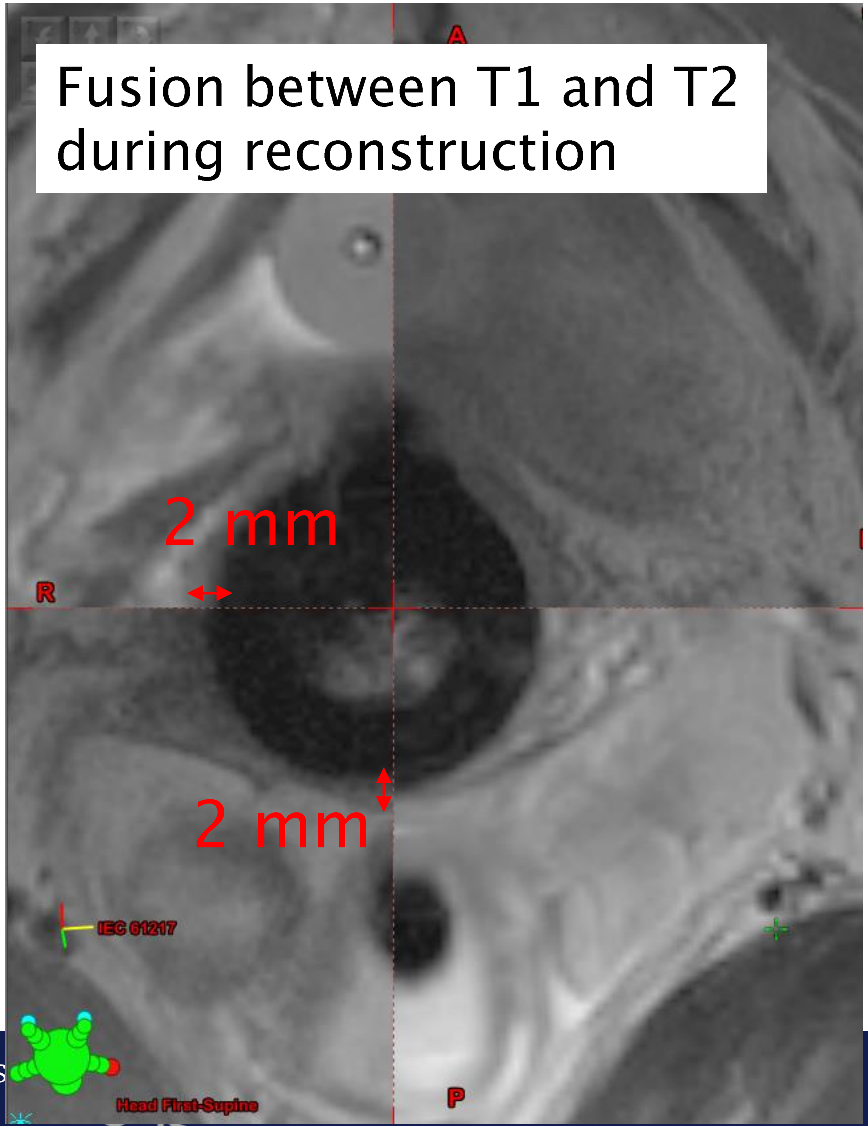
Target transfer from 1st MRI via applicator-based image registration



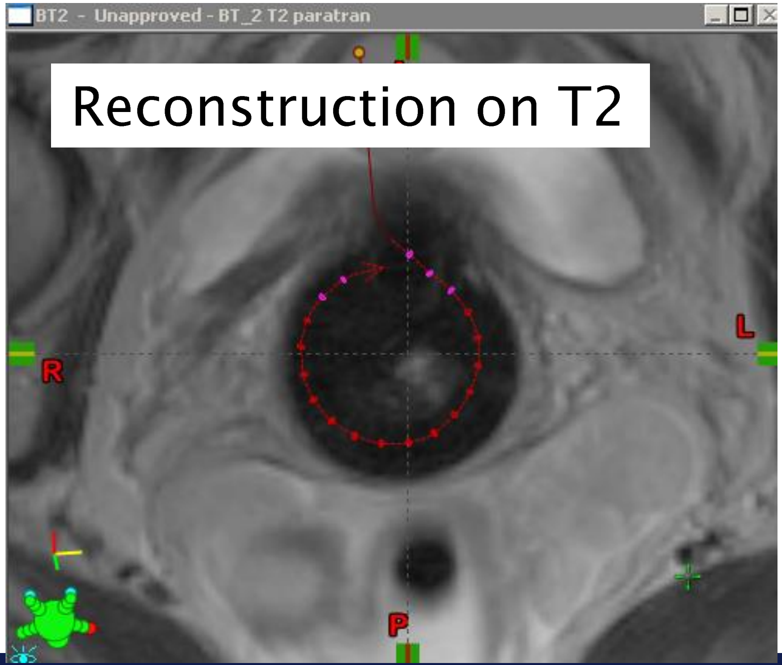
OAR delineation

Dose planning and optimization

Fusion uncertainties



Impact on DVH parameters:
HR CTV: 7% (underestimation)
Bladder: 10% (overestimation)
Rectum: 13% (underestimation)



MRI-based vs. combined MR-/CT- planning

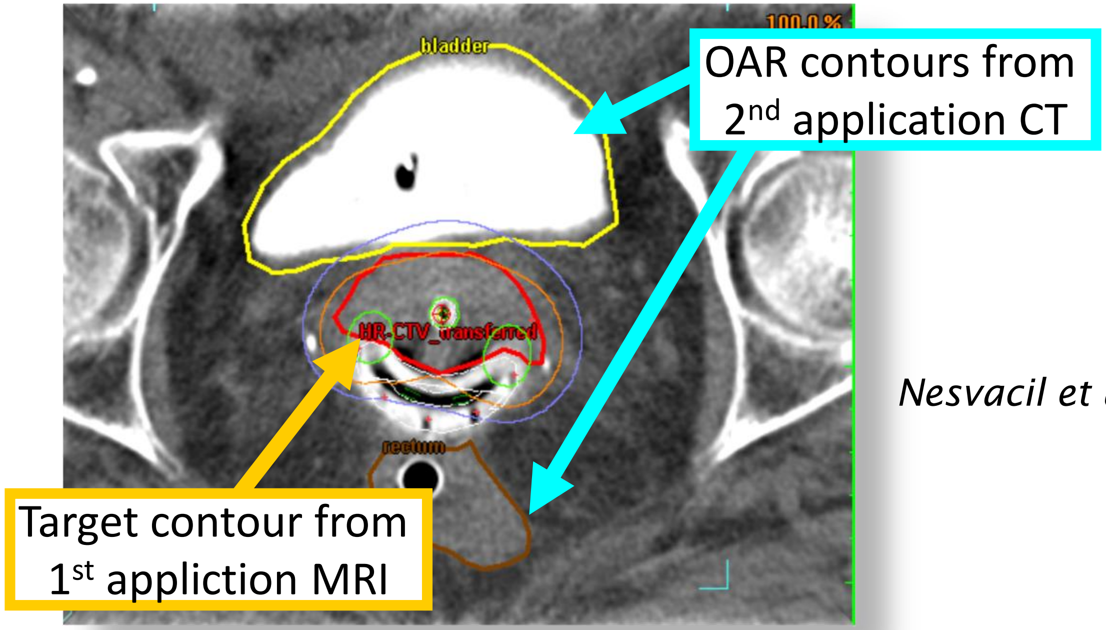
- Verification of the workflow by a retrospective study *(Nesvacil et al. 2013, Radiother Oncol 107:75-81)*

- 20 patients treated at AKH with fully MRI based BT were replanned using MRI for the 1st and CT for the 2nd application
  - HR CTV Volumes: 10-20 cm^3 (3), 20-40 cm^3 (12), 40-60 cm^3 (2), 60-90 cm^3 (3)
  - Applicator type: intracavitary (ic) tandem ring (9), ic+interstitial (11)

- The new plans for the 2nd application (loading pattern and dwell times) were reevaluated on the original MRI contours for the 2nd application

- Clinically acceptable plan quality was reached for most of the cases with the MRI/CT combination technique

Summary: Combined MRI/CT planning



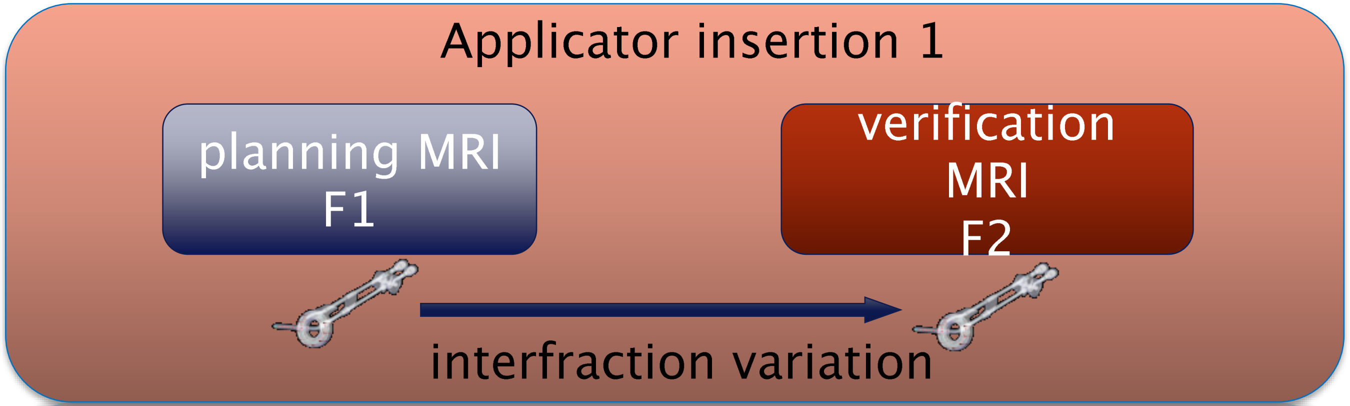
Nesvacil et al. R&O 2013

- allows use of MRI-based target concept and dose prescription protocols for adaptive CT planning -> better agreement with MRI-only planning *(Nesvacil et al. R&O 2013)*
- – fast if automatic applicator model-based registration implemented in TPS

- Automatic method not implemented in currently available commercial TPS

- Uncertainty dominated by applicator reconstruction, slice thickness, applicator rotation relative to target, time/target shrinkage between fractions

Applicator-based registration:
evaluation of inter-/intra-fraction variations



Fast registration of MRI F1 and F2 via applicator coordinate system to

- check implant stability (relative position of applicators/needles and target)
- check organ variation
- decide to
    - treat
    - adapt organ filling
    - recontour and re-evaluate DVH
    - (rarely replan before treatment of F2)

Time dose fractionation for EBRT + HDR BT

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

Prague 2017

Kari Tanderup

Richard Pötter

Aarhus University Hospital

Combination of EBRT and BT

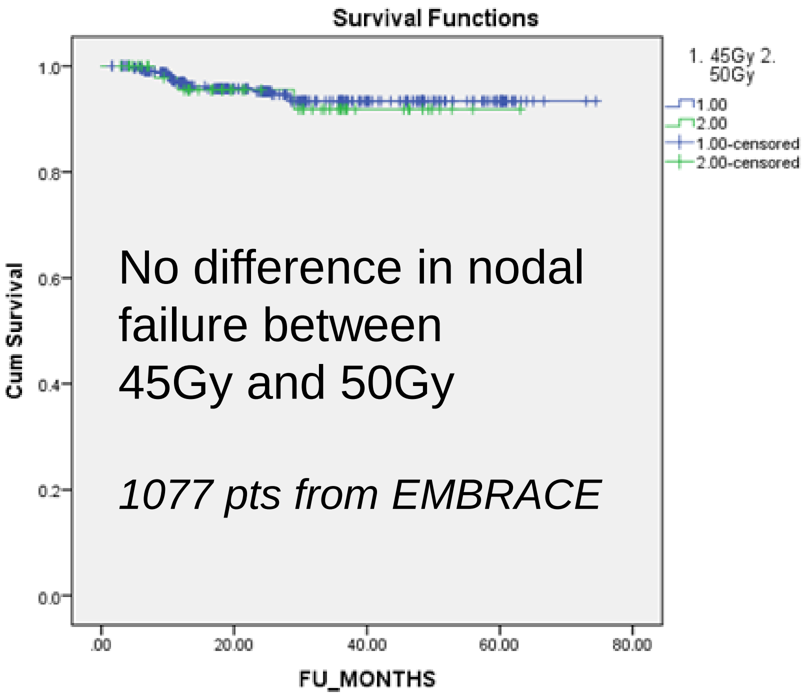
- **EBRT dose and fractionation**
- **BT dose and fractionation**
- **Timing of BT boost**
- **Overall treatment time**

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?**

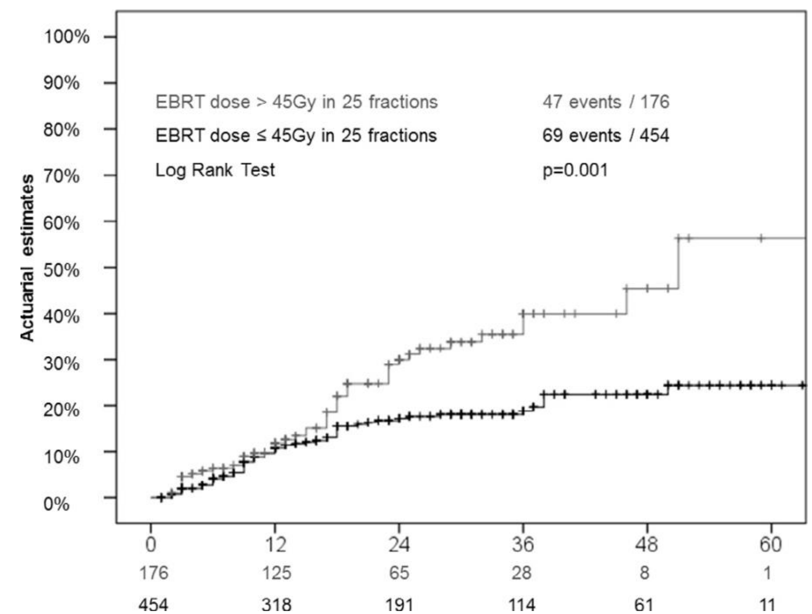


C Nomden, A de Leeuw, IM Jürgenliemk- Schultz, UMCU

- **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?

In literature still some uncertainty !

- Escalation typically recommended up to 55-60Gy

Grigsby PW, et al Int J Radiat Oncol Biol Phys 2001, 49(3):733–738.
Beadle BM, et al Int J Radiat Oncol Biol Phys 2010, 76(5):1396–1403.

- SIB IMRT – 55Gy/25# with option of sequential boost -10Gy/5#

Gynecologic Oncology 135 (2014) 239–243

- FDG avid nodal disease -62Gy/31# SIB

Cihoric *et al. Radiation Oncology* 2014, **9**:83

Pelvic nodal control in N1 EMBRACE patients: 7%

UMC Utrecht

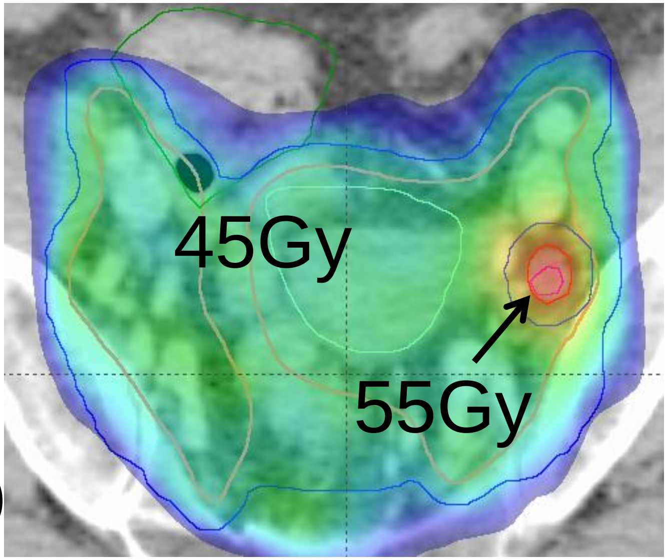
Courtesy Ina Jürgenliemk-Schulz

Post-boost with CRT

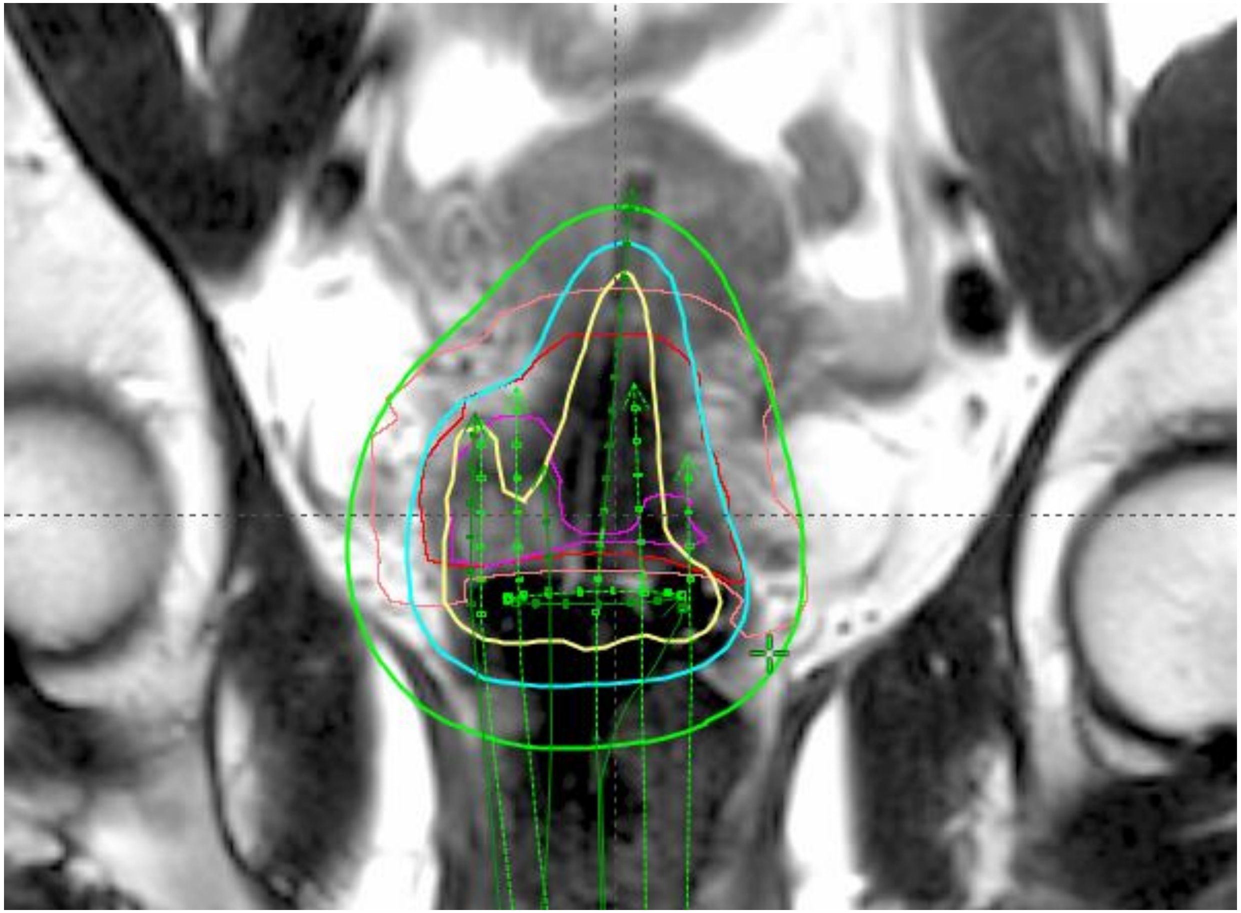
- AP-PA or 4 Field Box
- Avoid central pelvis irradiation
- Assessment of BT contribution (~0-6Gy)
- Examples of dose and fractionation:
  - Aim for total EBRT+BT dose of 55-60Gy
  - E.g. 50Gy whole pelvis + 5Gy
  - E.g. 45Gy whole pelvis + 10Gy

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

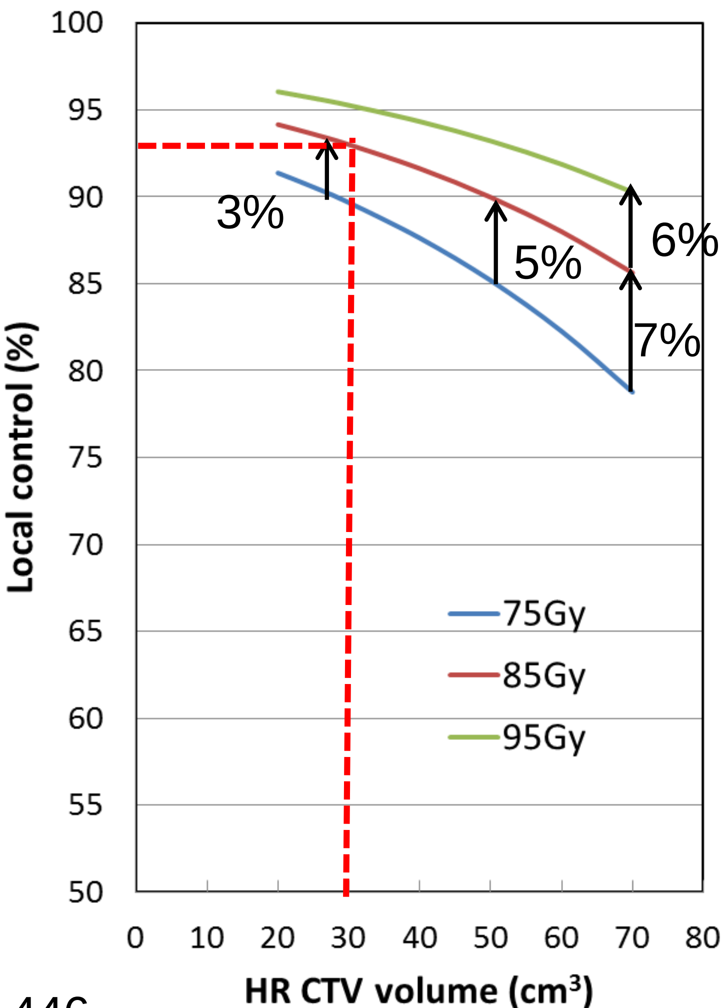
What do we know about dose and local control for CTV_{HR}?

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

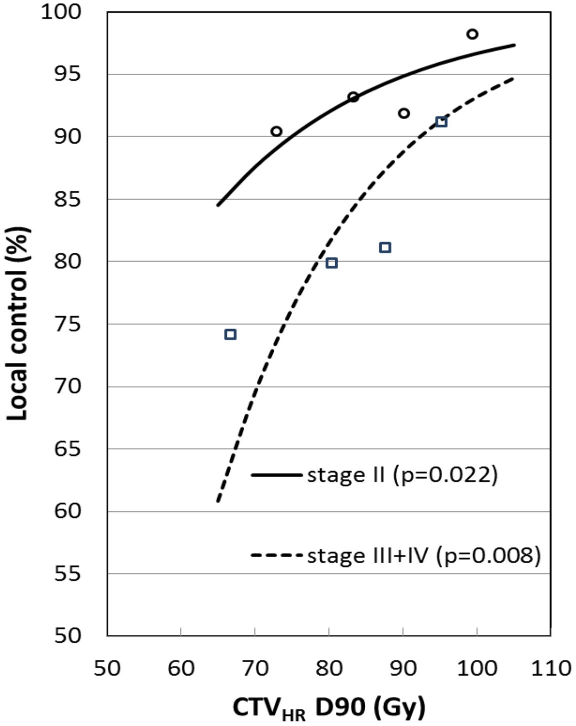
Local control at 3 years

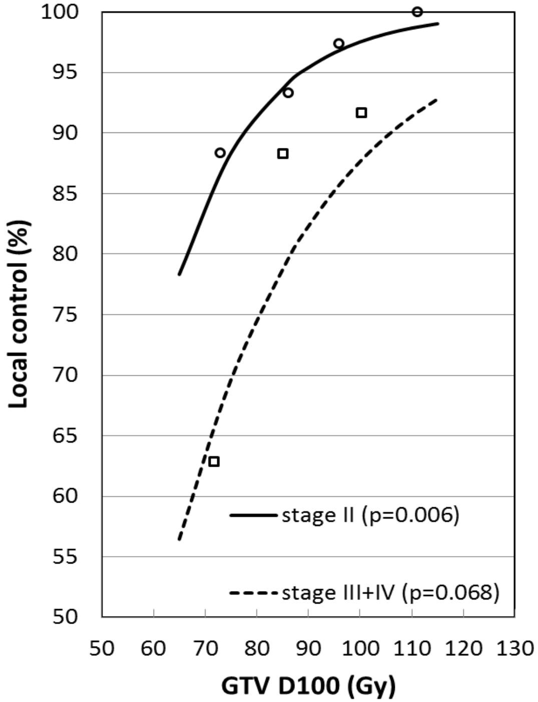


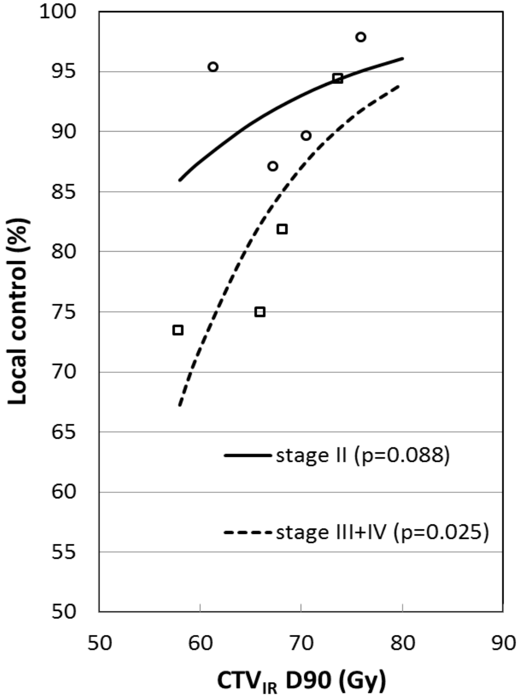
Tanderup et al, Radiother Oncol 120 (2016) 441–446

Dose effect GTV, CTV_{HR} and CTV_{IR}

Analysis according to stage



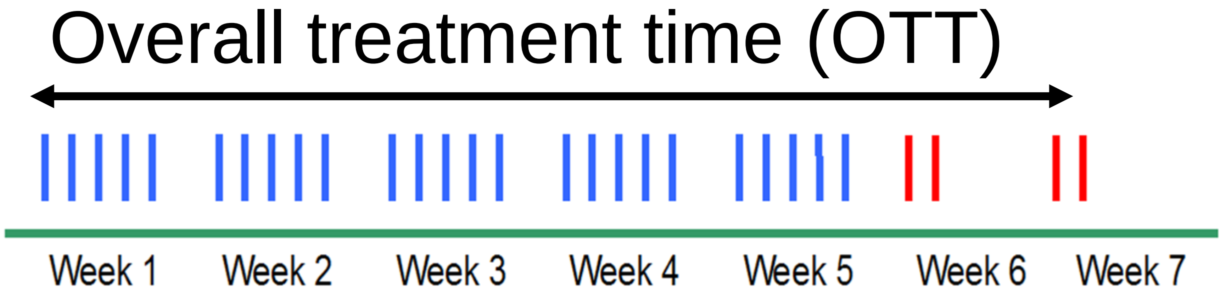




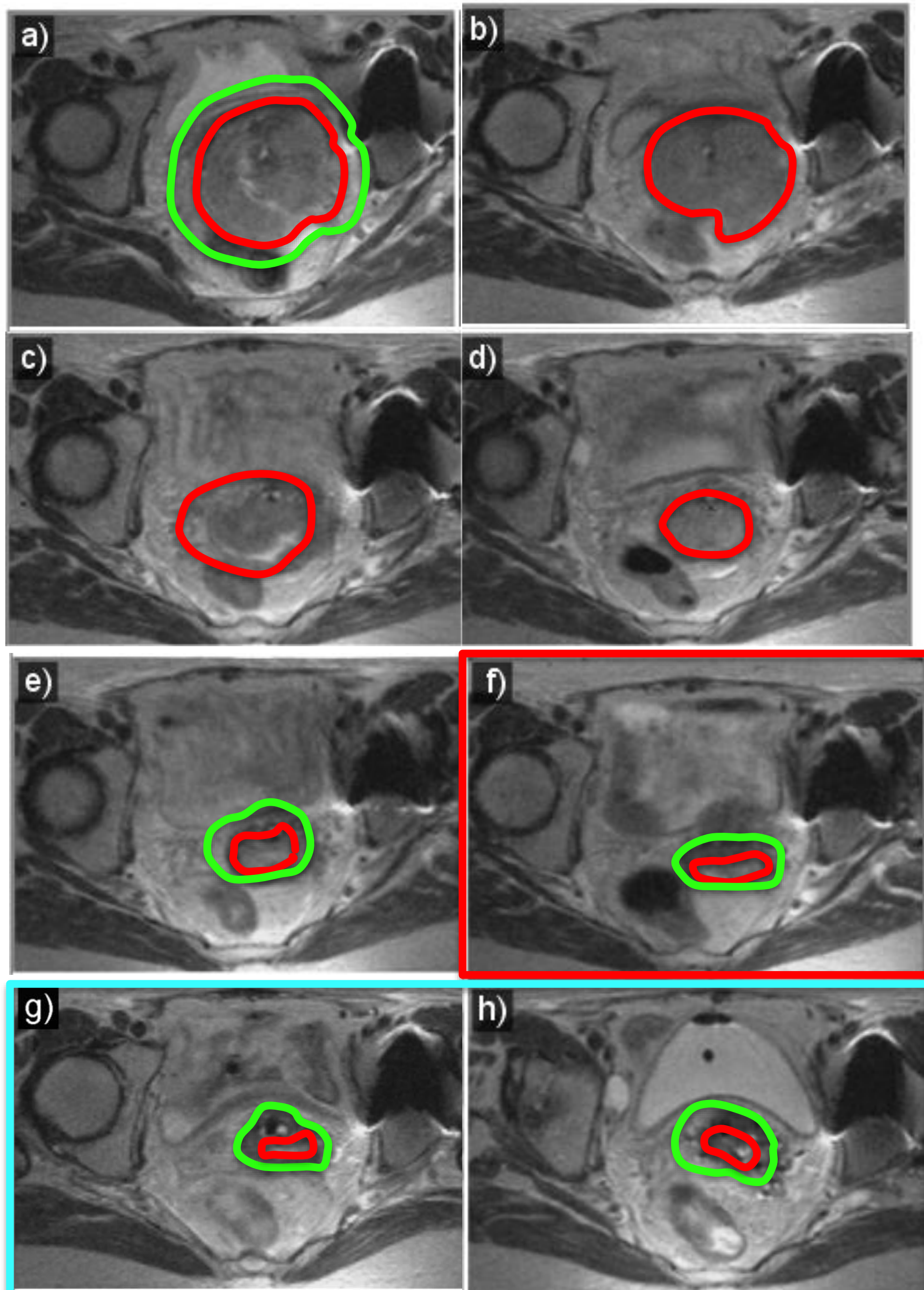
Tanderup et al, Radiother Oncol 120 (2016) 441–446

When do you preferentially start BT boost after initiation of EBRT for stage IIB?

- **A.** **Week 1**
- **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

EBRT dose

9 Gy

Cisplatin (40 mg/m^2) x1

18 Gy

Cisplatin (40 mg/m^2) x2

27 Gy

Cisplatin (40 mg/m^2) x3

36 Gy

Cisplatin (40 mg/m^2) x4

45 Gy

Pre-brachytherapy

EBRT45 Gy

Cisplatin (40 mg/m^2) x5

IGABT 45 Gy

Brachytherapy

GTV

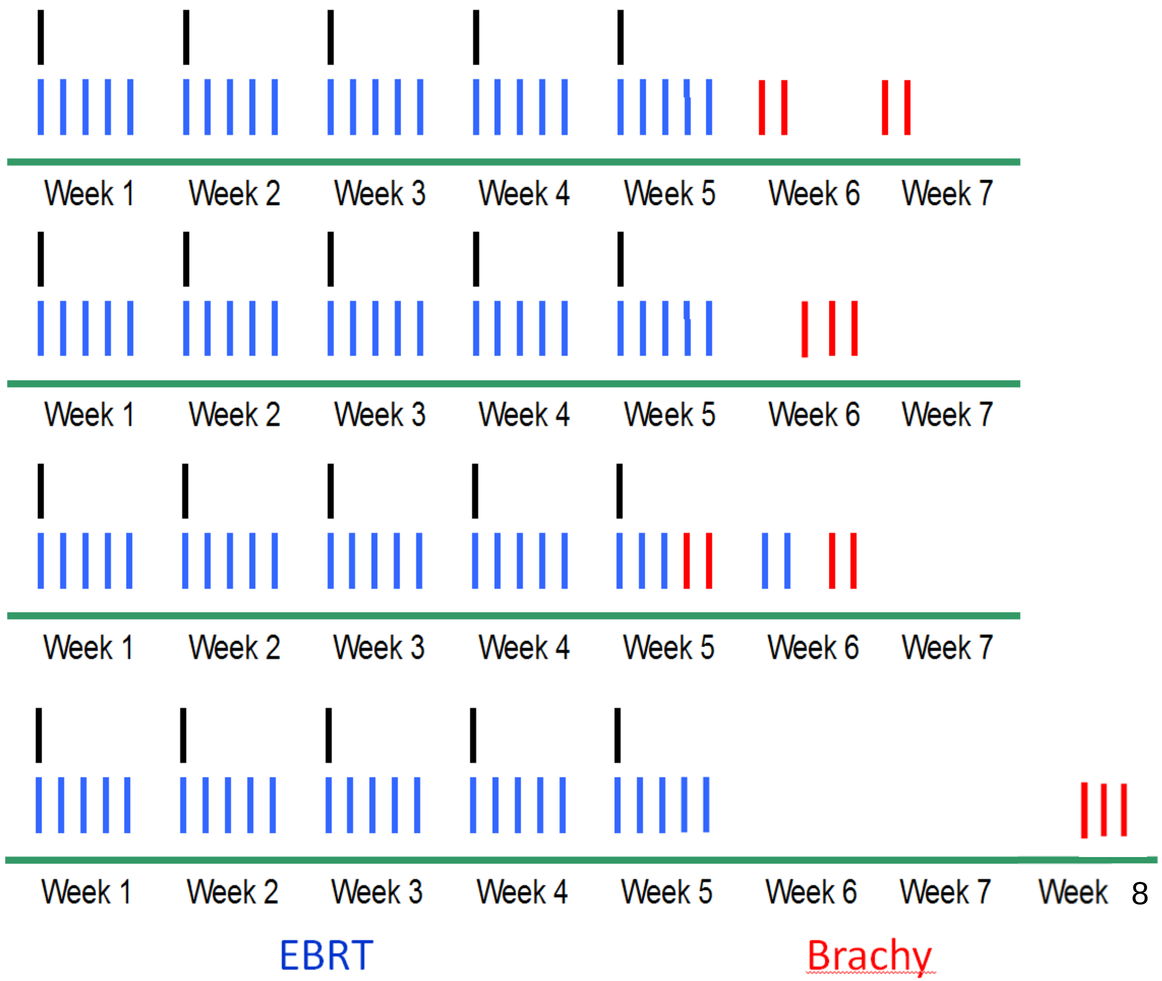
CTV

Impact of overall treatment time

1 week extra OTT ~ 5Gy less to CTV_{HR}
1 week extra OTT ~ loss of 2.5% local control

- **How to keep overall treatment time limited?**
- **Primary tumour:**
  - **Start BT towards the end of EBRT or immediately after end of EBRT**
  - **With the help of IC/IS it is not necessary to wait further for tumour shrinkage**
- **Pathological lymph nodes**
  - **Simultaneously integrated boost**

Equieffective dose and impact of overall treatment time



	EQD2	OTT correction
45Gy/25 fx EBRT 7Gy x 4 fx HDR BT	85Gy	+2Gy
50Gy/25 fx EBRT 7Gy x 3 fx HDR BT	80Gy	+5Gy
45Gy/25 fx EBRT 7Gy x 4 fx HDR BT	85Gy	+5Gy
50Gy/25 fx EBRT 7Gy x 3 fx HDR BT	80Gy	-5Gy

Take home messages

- **Elective lymph node target: 45-50Gy EBRT**
  - **Perspective of reducing morbidity with 45Gy**
- **Pathological lymph nodes: 55-60Gy EBRT**
  - **Balance between tumour control and morbidity**
- **Primary tumour (CTV_{HR}): >85-90Gy EBRT+BT**
  - **Balance between EBRT and BT**
  - **With more IC/IS BT it is possible to reduce EBRT dose to 45Gy**
- **Overall treatment time: <50 days**

Common dose planning aims for target structures

	EBRT dose	BT dose EQD2	Total EQD2 EBRT+BT
Elective lymph node target: CTV-E	45-50Gy	-	45-50Gy
Pathological lymph nodes	55-60Gy	0-4Gy	60Gy
Intermediate Risk CTV: CTV_{IR}	45-50Gy	15-20Gy	60-70Gy
High Risk CTV: CTV_{HR}	45-50Gy	35-45Gy	85-90Gy
GTV	45-50Gy	50-55Gy	95-100Gy
Point A	45-50Gy	25-40Gy	70-85Gy

Leiden University
Medical Center

Morbidity and QoL after IGABT for cervical cancer: Rectum, Sigmiod, Bladder, Vagina

ESTRO GYN teaching course,
Prague 2017

Remi Nout

With the help of: Richard Pötter and Johannes Dimopoulos

Learning Objectives

- Late morbidity patterns for rectum, bladder, bowel and vagina
- Mid & long-term impairments in quality of life (functional aspects in daily life and patient reported symptoms)
- Differential value of physician assessed morbidity and patient reported outcomes (symptoms and QoL).

Q: At my department…

A. We register all grades of late morbidity using a scoring system (e.g. CTCAE)
B. We register only severe morbidity (≥grade 3) morbidity using a scoring system)
C. We do not routinely register morbidity

Q: At my department…We register patient reported symptoms and QoL using questionnaires during follow-up:

A. Yes, as part of routine care
B. Yes, for studies / trials
C. No

Morbidity assessment in clinical trials (Kirchheiner)

objective ↕ subjective

clinical decision / medical intervention

Analytic outcomes (lab / imaging)	Anemia defined as reduction in the amount of hemoglobin in 100 ml of blood.
Physician assessed objective symptoms	Atrophy of the vaginal mucosa, ulceration, necrosis, fistula
Patient reported objective symptoms	Number of stools / day, consistency of stool
Patient reported subjective symptoms	Fatigue, pain, sexual functioning problems
Patient reported impact of symptoms on ADL	Impact of difficulties controlling bowel on activities of daily life / quality of life
Patient reported complex multidimensional concepts	Health-related quality of life, functioning aspects in daily life, psychological status

Physician assessed morbidity
Common Toxicity Criteria of AE

objective

Analytic outcomes
(lab / imaging)

Physician assessed
objective symptoms

Patient reported
objective symptoms

Patient reported
subjective symptoms

Patient reported impact of
symptoms on ADL

Patient reported complex
multidimensional concepts

subjective

clinical decision / medical intervention

Combined information is
translated by physician
into medical terms and grades

CTCAE v4. Proctitis G2

Symptoms e.g., rectal discomfort,
passing blood or mucus;

medical intervention indicated;

limiting instrumental activities of
daily life

Depends on the interpretation of
the physician
Translation problems may be
assumed!

Inter-rater reliability of CTCAE morbidity assessment

Atkinson et al. Qual Life Res 2012

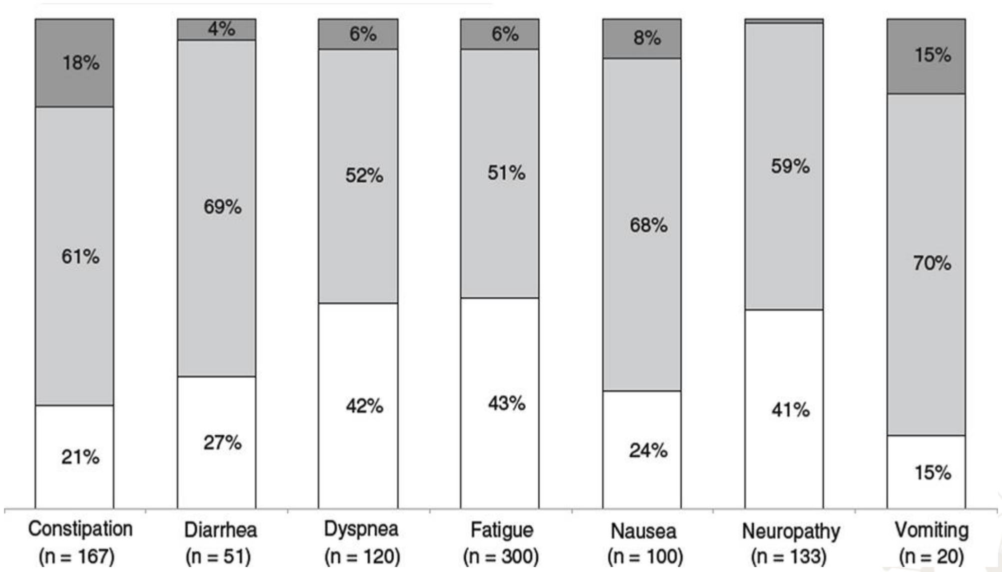
N=393 patients, mixed cancer type

CTCAE assessed by 2 independent physicians within ~1h

Results in symptomatic patients

- 15-43% agreement
- 51-70% 1 grade differences
- 1-18% 2 grades differences

CTCAE agreement between 2 physicians is moderate at best!



The lower the CTCAE grading, the more variation between physicians is observed.

Disagreement mainly between G0/G1/G2.

Chinnachamy et al. Jpn J Clin Oncol 2013

Patient reported outcomes (PRO)

objective

Analytic outcomes
(lab / imaging)

Physician assessed
objective symptoms

Patient reported
objective symptoms

Patient reported
subjective symptoms

Patient reported impact of
symptoms on ADL

Patient reported complex
multidimensional concepts

subjective

PRO considered as Gold standard

"…any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."
Final FDA PRO Guidance, Dec 2009

Objectifying the subjective experience
by questionnaires
with predefined response categories
and robust psychometric properties

Health-related quality of life assessment

EORTC QLQ C30
European Organization of Research and Treatment of Cancer Quality of Life Questionnaires
(Aaronson et al.) *Europe*

FACT-G
Functional Assessment of Cancer Therapy
(Cella et al.) *US*

SF 36
Short Form Health Survey 36
(Ware et al.) *beyond oncology*

Basic module and different disease- and treatment related modules available

Assessment

1. Overall quality of life
2. Aspects of functioning in daily life
   physical, social, emotional, role, cognitive functioning
3. Patient reported symptoms

EORTC / FACT QoL

Answer categories
- ❑ not at all
- ❑ a little
- ❑ (somewhat)
- ❑ quite a bit
- ❑ very much

Widely used for PRO symptom assessment

Answer categories not precise

No linear association with CTCAE grading

PRO-CTCAE

PRO assessment tool of the future

Compatible with CTCAE v4, covers 78 symptoms

Currently under development and validation

Frequency
- ❑ never
- ❑ rarely
- ❑ occasionally
- ❑ frequently
- ❑ almost constantly

Severity of symptoms
- ❑ none
- ❑ mild
- ❑ moderate
- ❑ severe
- ❑ very severe

Interference with usual activities
- ❑ not at all
- ❑ a little
- ❑ somewhat
- ❑ quite a bit
- ❑ very much

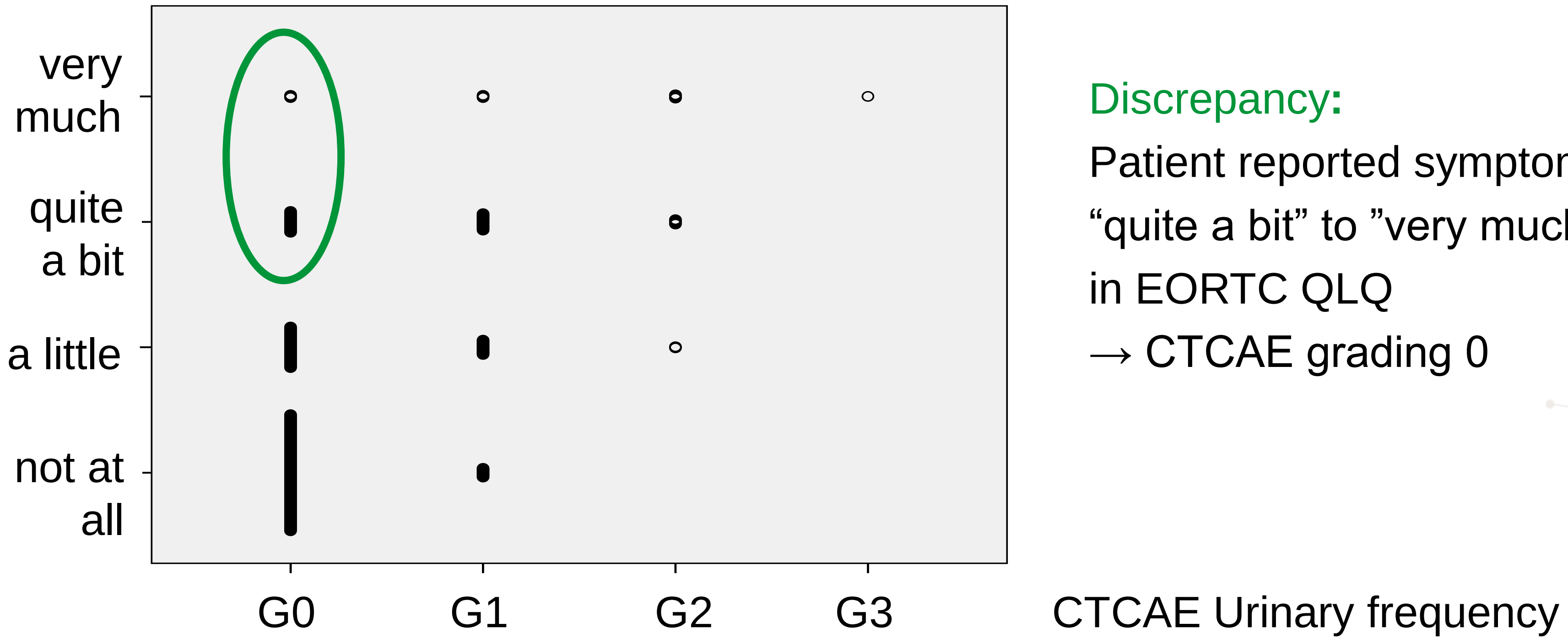
Agreement physician assessed vs. Patient reported symptoms

Kirchheiner et al. SUON 2012

N=223 cervical cancer, CTCAE v3 vs. EORTC C30 + CX24

3 months after end of definitive radiochemotherapy

EORTC : Did you pass water / urine frequently?



Discrepancy**:**
Patient reported symptom “quite a bit” to ”very much” in EORTC QLQ
→ CTCAE grading 0

12 overlapping symptoms CTCAE & EORTC QLQ	nr.of “quite a bit” or “very much” problems reported	nr.of discrepancies (CTCAE G0)
diarrhea	27	13
anal incontinence	17	15
bleeding hemorrhage GI	1	1
urinary frequency	52	23
urinary incontinence	15	7
bleeding hemorrhage GU	2	1
limb edema	21	10
fatigue	53	22
insomnia	53	26
hot flashes	73	19
vaginal dryness*	22	11
vaginal stenosis*	24	11
N=223 patients at 3 months FUP	In total 360 substantial problems reported	159 (44%) of substantial problems not recognized by physician assessed CTCAE

Possible explanations

Patients	Physicians
➢tendency to "please the doctor", based on gratitude ➢certain symptoms too embarrassing to report ➢level of distress caused by the symptoms is rated (highly subjective) ➢psychological coping strategies (dissimulating / aggravating symptoms)	➢ more emphasis on identifying severe G3/G4 morbidity than milder morbidity ➢ limited time to fully explore symptoms (general questions about any symptoms vs. systematical assessment of each symptom) ➢ continuum of severity along which a patient is put into context

Kirchheiner et al. 2012
Vistad et al. 2008
Atkinson et al. 2012

Summary I

- Technical developments in RT → less severe G3/G4 morbidity
  Focus to milder and moderate G1/G2 morbidity and impact on QoL,
  PRO are especially sensitive

- Physician assessed CTCAE morbidity has a wide range of interpretation and therefore a low inter-rater reliability
  (especially in mild to moderate morbidity)

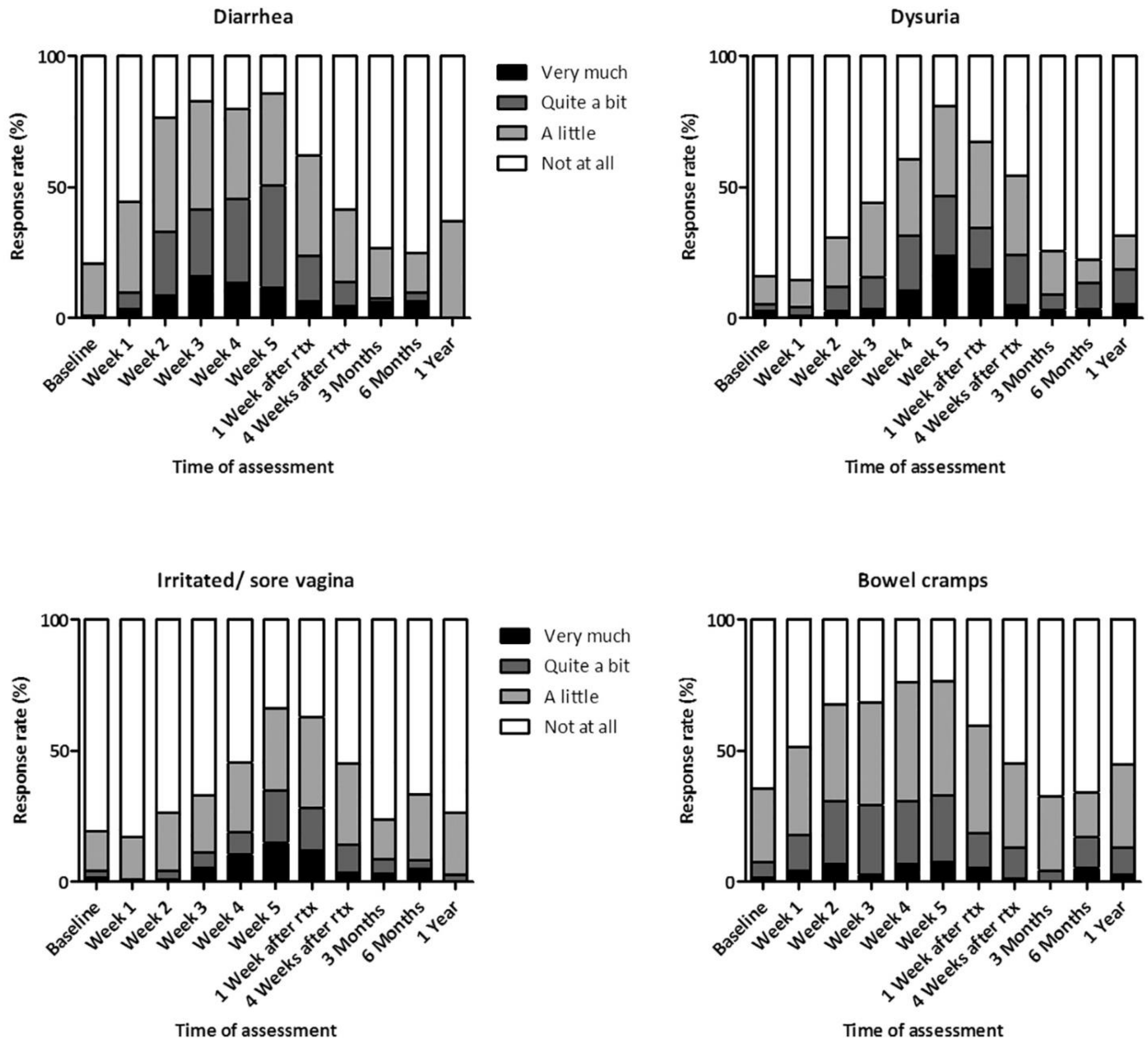
- Low associations between physician assessed and patient reported morbidity are consistently described in literature

- Both provide valuable information → combined reports or a collaborative approach provide a more accurate understanding of morbidity

Learning Objectives

- Late morbidity patterns for rectum, bladder, bowel and vagina
- Mid & long-term impairments in quality of life (functional aspects in daily life and patient reported symptoms)
- Differential value of physician assessed morbidity and patient reported outcomes (symptoms and QoL).

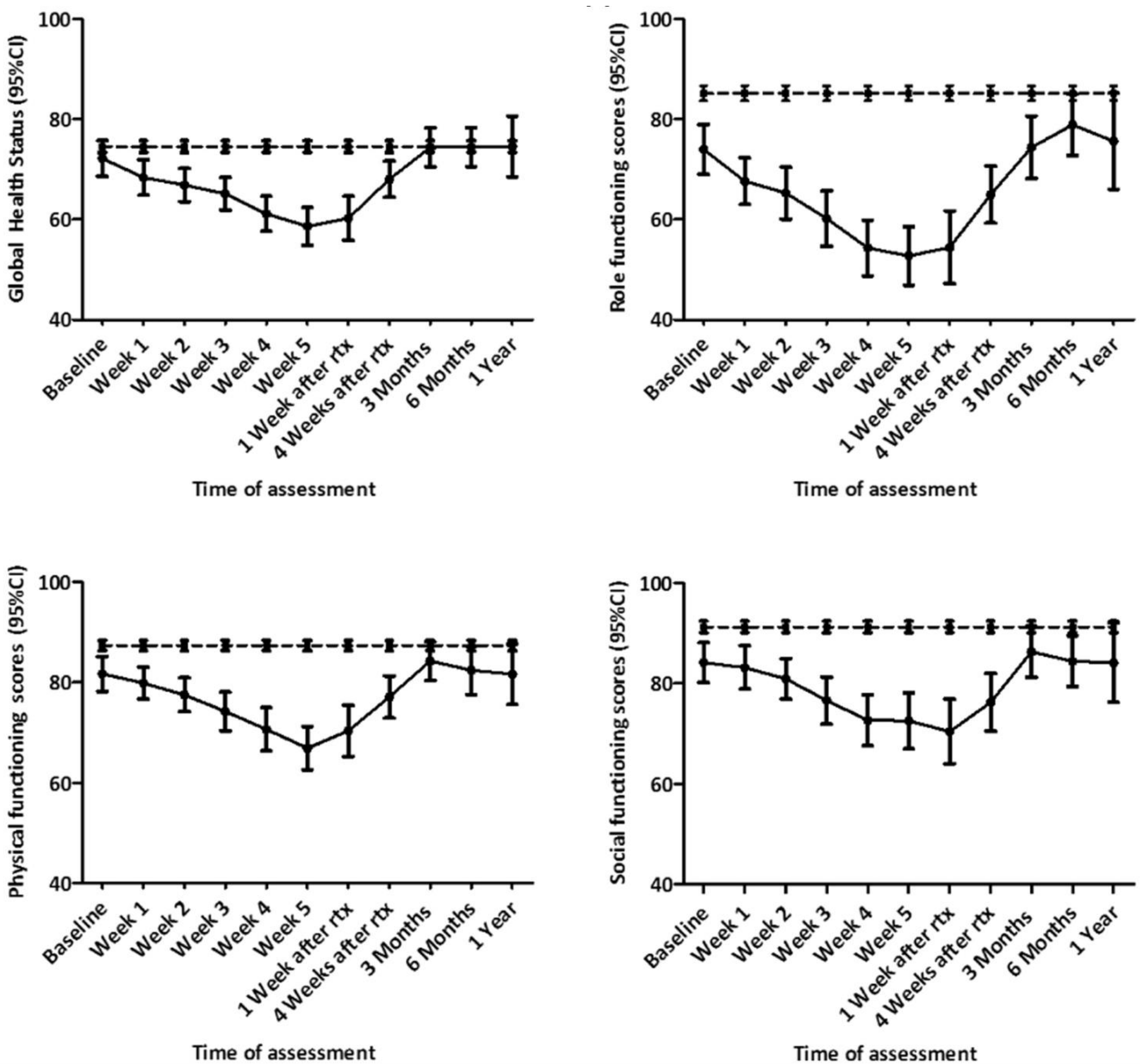
Most frequently reported symptoms during and shortly after treatment



- EORTC-C30 and CX24
- 137 patients
- Prospective weekly assessment

Heijkoop et al. Gyn Onc 2017

QoL and functioning during and shortly after treatment



- EORTC-C30 and CX24
- 137 patients
- Prospective weekly assessment

Heijkoop et al. Gyn Onc 2017

1129 pts. in database

- 50 pts. without baseline (BL) morbidity registered

1079 pts. with BL morbidity registered

- 107 pts. without follow up

972 pts. with ≥3 months follow up

Median follow up 22 months (1-67)

Late Morbidity: Bladder

EMBRACE I. CTCAE v3
Urinary frequency/urgency
Incontinence, urinary
Cystitis
Bladder spasm
Bleeding (Hemorrhage GU) – bladder, ureter, urethra
Stenosis/stricture – bladder, ureter, urethra
Fistula – bladder, ureter, urethra
Bladder other

Descriptive

crude incidence

actuarial incidence

prevalence

Fokdal and Kirchheiner

Maximum incidence of single bladder symptoms

Number of patients 970

	Frequency	Incontinence	Spasm	Bladder contracture	Ureter stenosis	Cystitis	Bleeding	Fistula
G0	482 (47.7%)	643 (66.3%)	898 (97.9%)	964 (92.6%)	930 (95.9%)	797 (82.2%)	916 (94.4%)	957 (98.7%)
G1	378 (30.0%)	225 (23.2%)	58 (6.0%)	58 (6.0%)	10 (1.0%)	109 (11.2%)	41 (4.2%)	3 (0.3%)
G2	96 (9.9%)	86 (8.9%)	13 (1.3%)	13 (1.3%)	9 (0.9%)	57 (5.9%)	11 (1.1%)	2 (0.2%)
G3	14 (1.4%)	12 (1.2%)	1 (0.1%)	1 (0.1%)	18 (1.9%)	5 (0.6%)	2 (0.2%)	5 (0.5%)
G4		4 (0.4%)	0 (0%)	0 (0%)	3 (0.3%)	1 (0.1%)	0 (0%)	3 (0.3%)

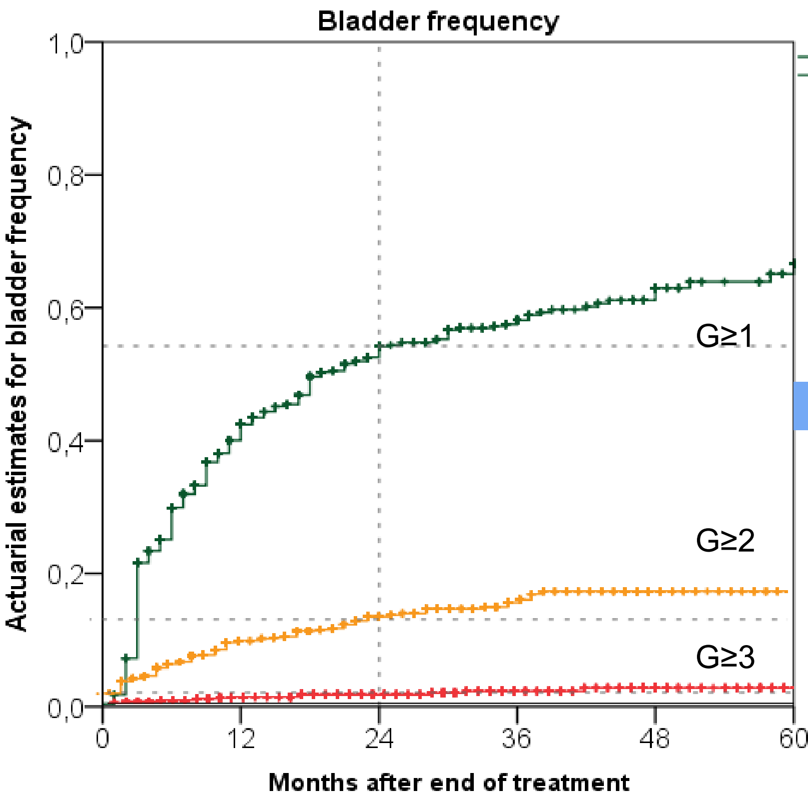
* 7 patients had tumor involvement of the bladder at time of diagnosis

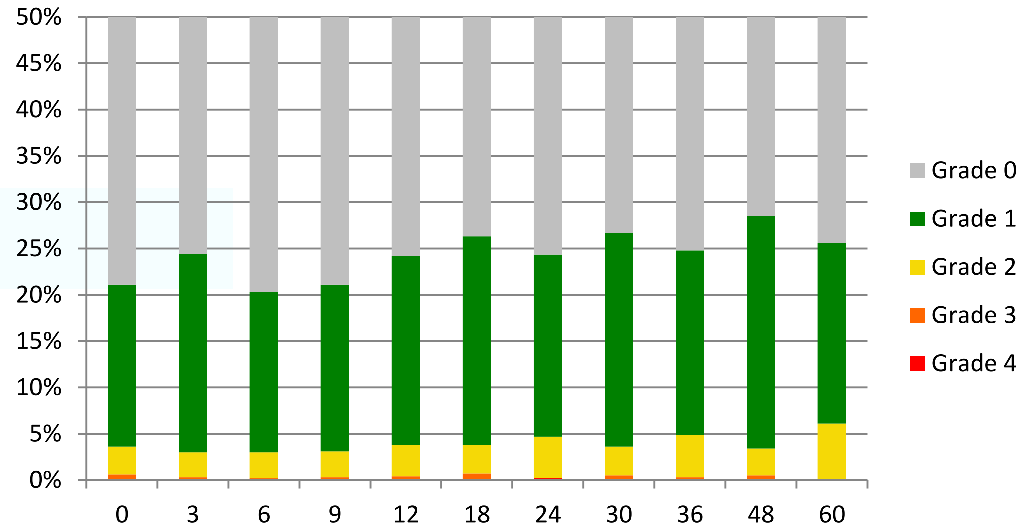
Maximum incidence PROM

Number of patients 852

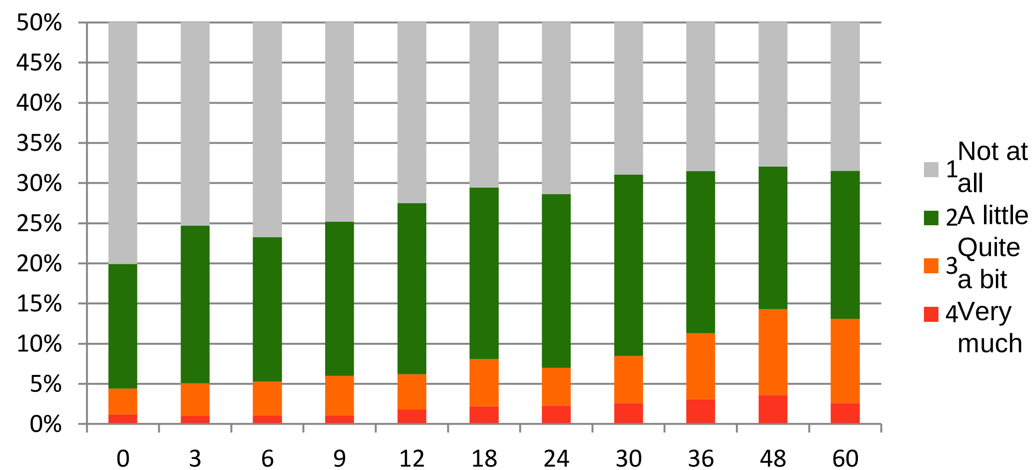
N= 852	frequency	Incontinence	Bladder emptying	Pain
Not at all	259 (30.4%)	442 (51.9%)	570 (66.9%)	534 (62.5%)
A little	262 (30.8%)	265 (31.1%)	182 (21.4%)	214 (25.1%)
Quite a bit	223 (26.2%)	102 (12.0%)	69 (8.1%)	64 (7.5%)
Very much	107 (12.6%)	43 (5.0%)	31 (3.6%)	42 (4.9%)

Bladder frequency



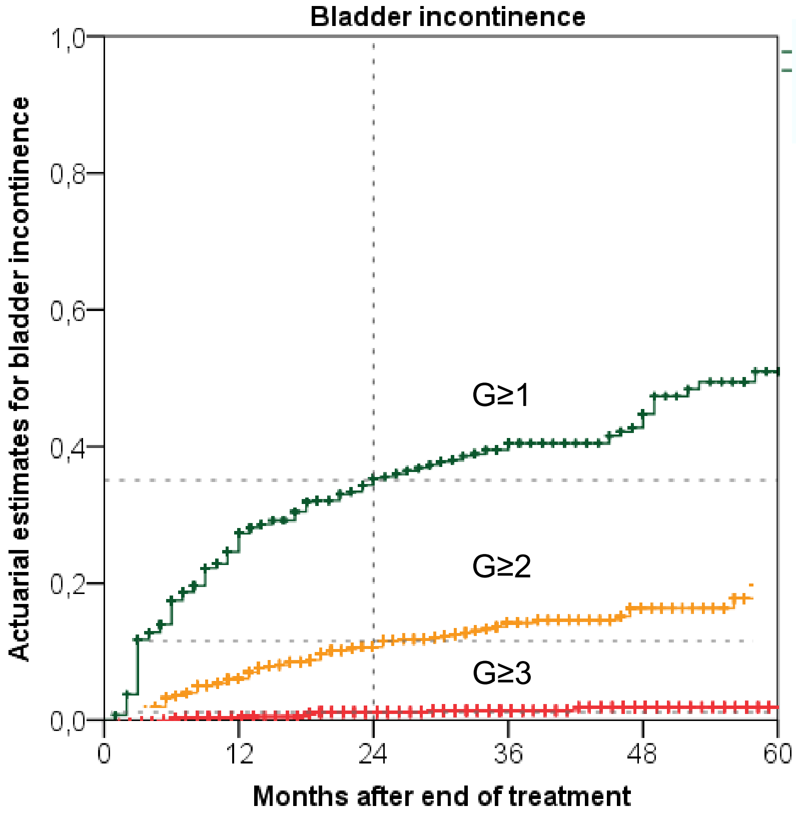


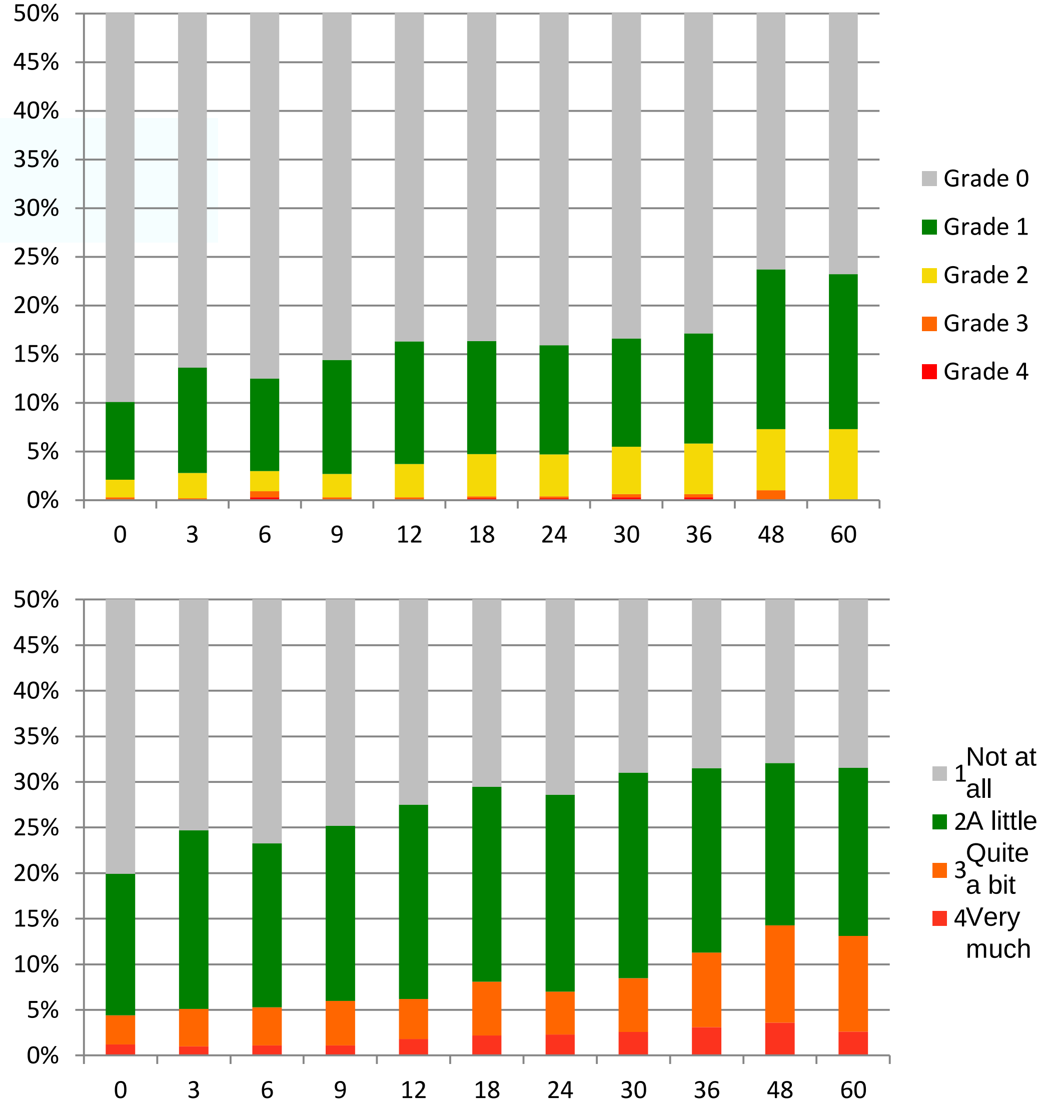
# patients	1081	918	864	755	732	604	498	386	326	207	82



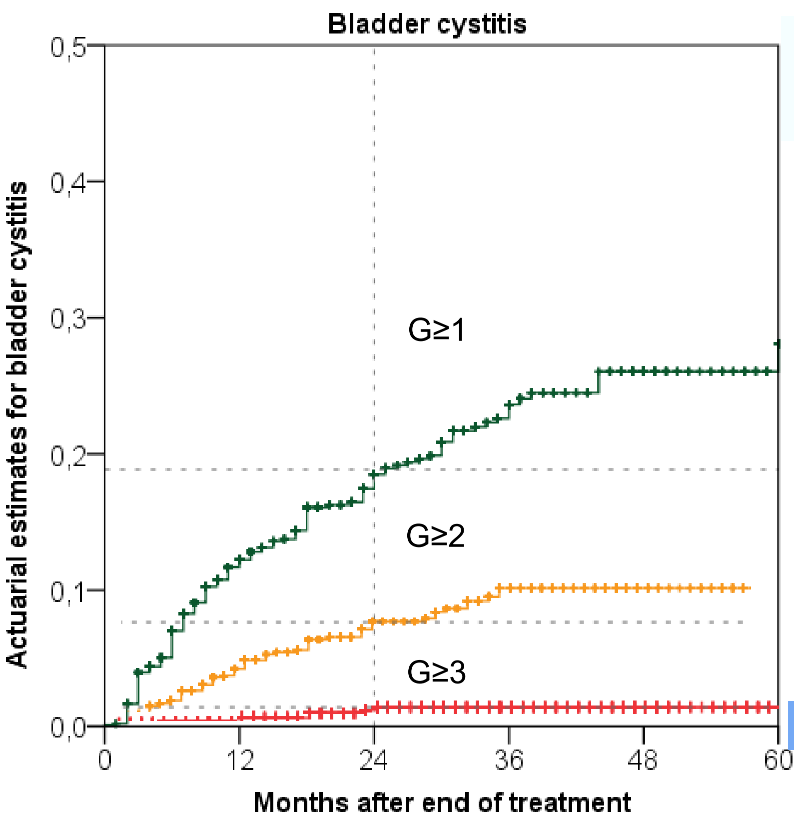
# patients	862	685	646	527	563	459	384	272	257	169	76

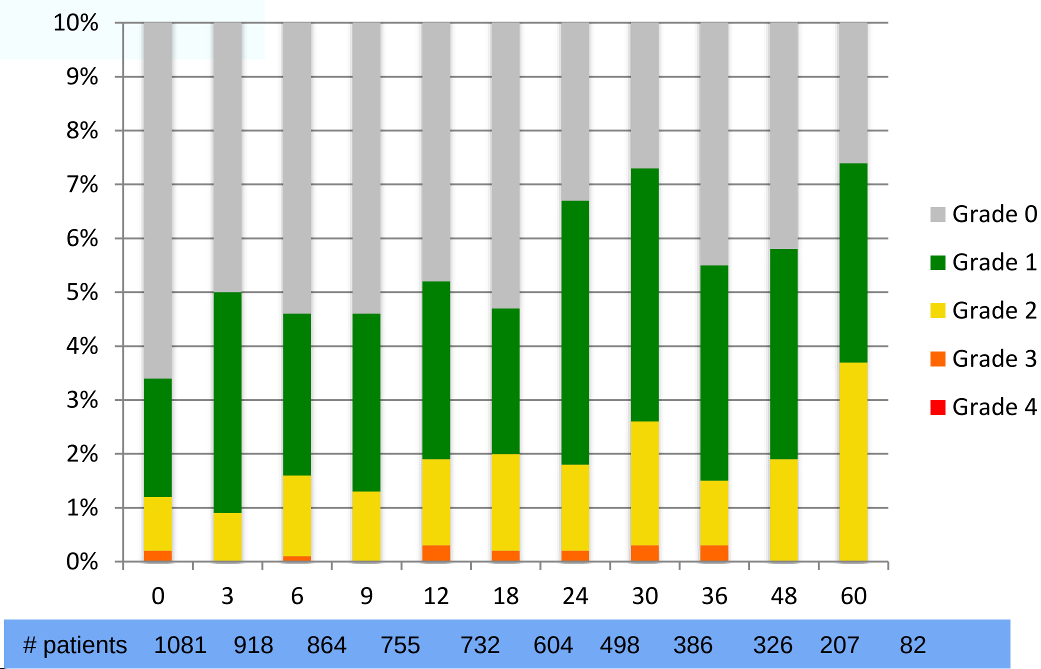
Bladder Incontinence





Bladder cystitis





Late Morbidity: GI, Rectum, Bowel

EMBRACE I. CTCAE v3
Diarrhea
Flatulence
Incontinence (anal)
Proctitis
Bleeding (hemorrhage GI, anus, rectum, sigmoid, colon, small bowel)
Stricture / stenosis (anus, rectum, sigmoid, colon, small bowel)
Fistula (anus, rectum, sigmoid, colon, small bowel)
Gastro-intestinal other

Descriptive

crude incidence

actuarial incidence

prevalence

Rectum (CTCAE overview)

	Proctitis		Bleeding		Stenosis		Fistula		ALL	
	N	%	N	%	N	%	N	%	N	%
Grade 0	782	81.5	805	83.8	949	98.9	951	99.1	694	72.3
Grade 1	135	14.1	114	12.0	5	0.5	0	0	193	20.1
Grade 2	39	4.1	31	3.2	6	0.6	5	0.5	58	6.0
Grade 3	4	0.4	10	1.0	0	0	3	0.3	14	1.6
Grade 4	0	0	0	0	0	0	1	0.1	1	0.1

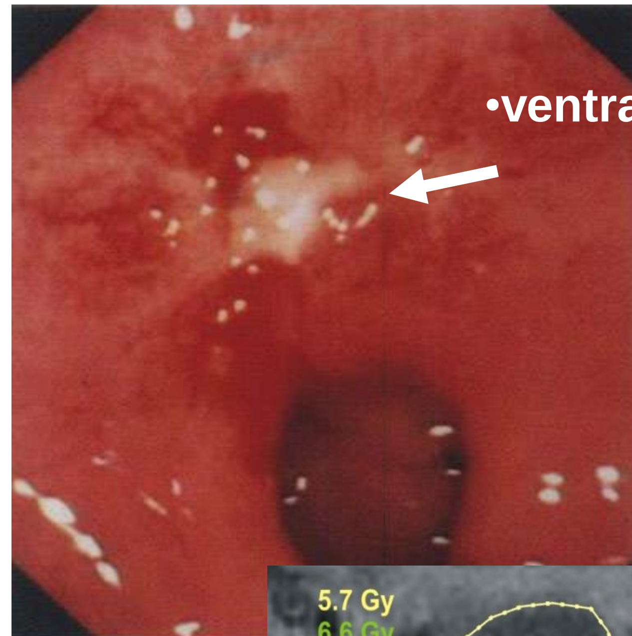
Median Follow-up: 25.4 months

Times to onset
From 1st fraction

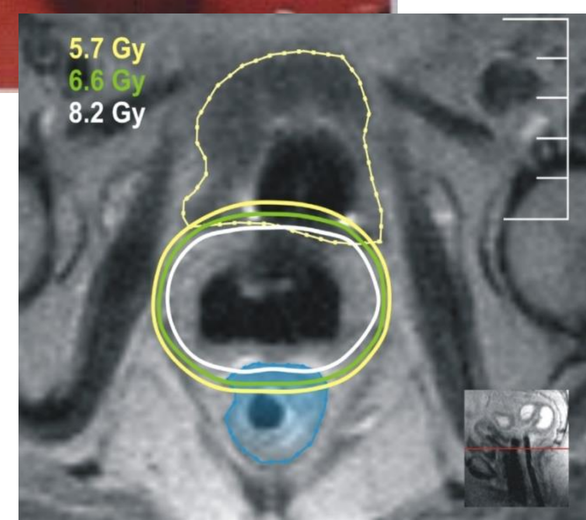
Grade 1-4	16.8+/-12.7
Grade 2-4	17.5+/-9.5
Grade 3-4	15.8+/-5.3

Rectum: Late telangiectasia and micro-ulceration

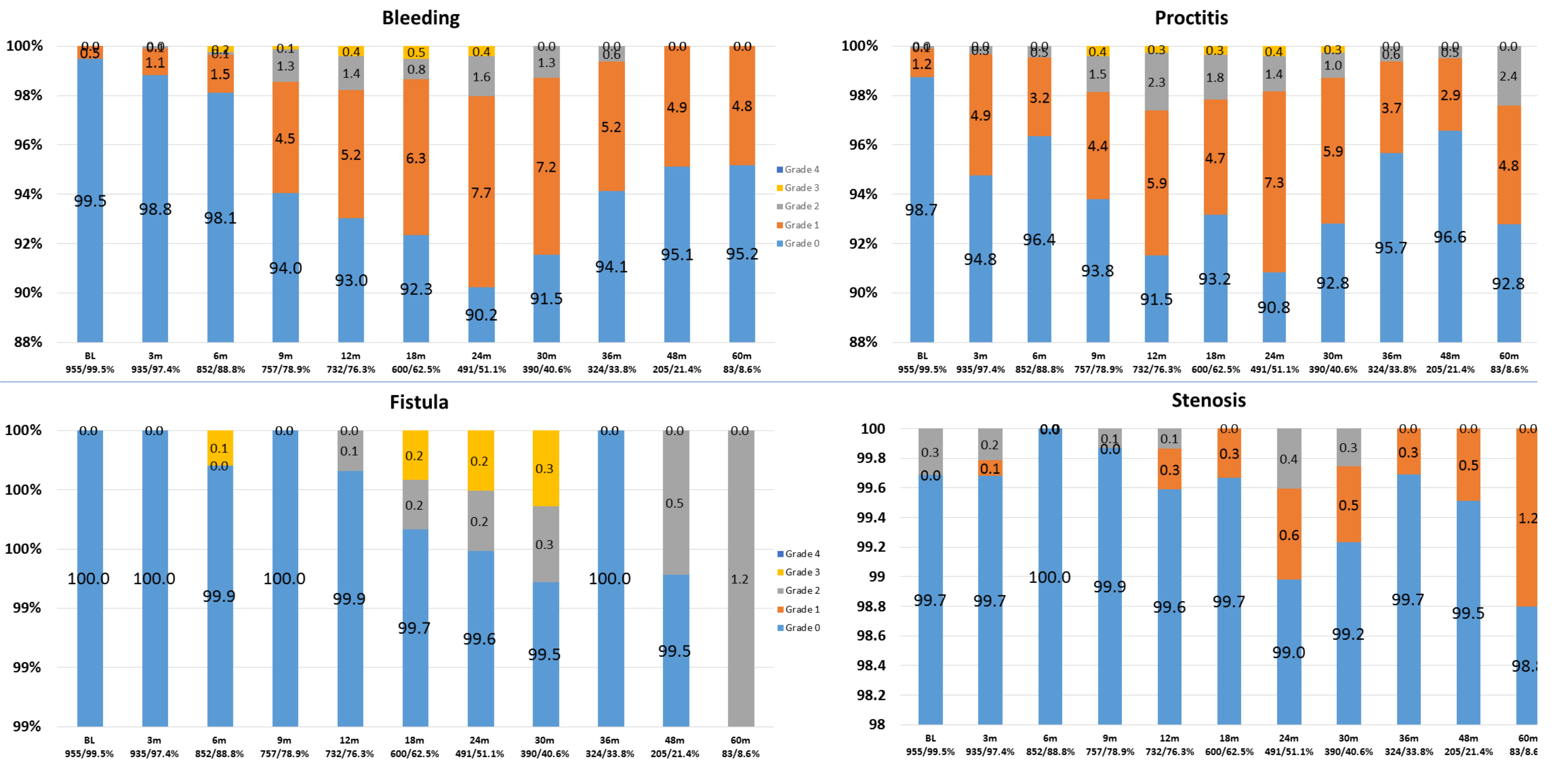
Endoscopy



•Georg P et al. R&O 2009

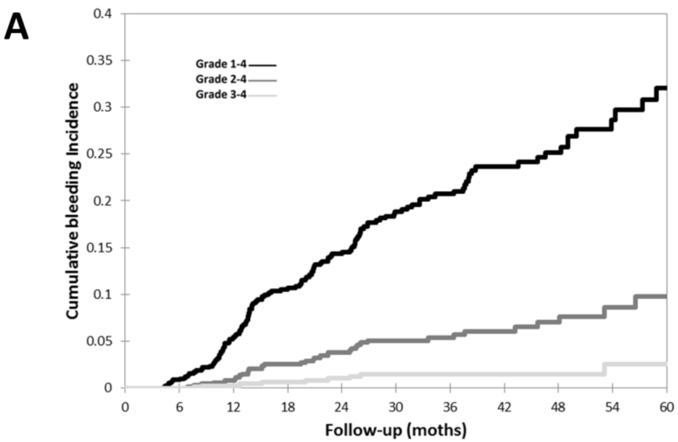


Prevalence for bleeding, proctitis, fistula, stenosis (rectum)

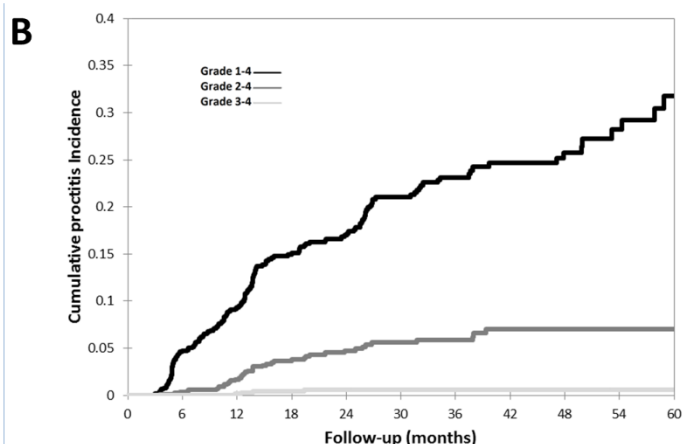


EMBRACE, Mazeron et al. R&O 2016

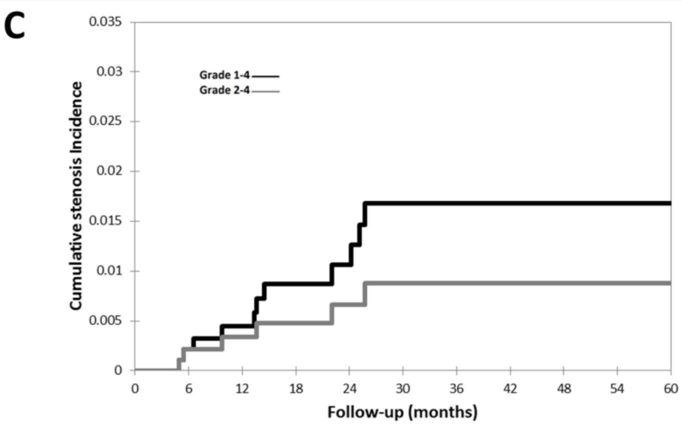
Actuarial estimate of bleeding, proctitis, stenosis, fistula



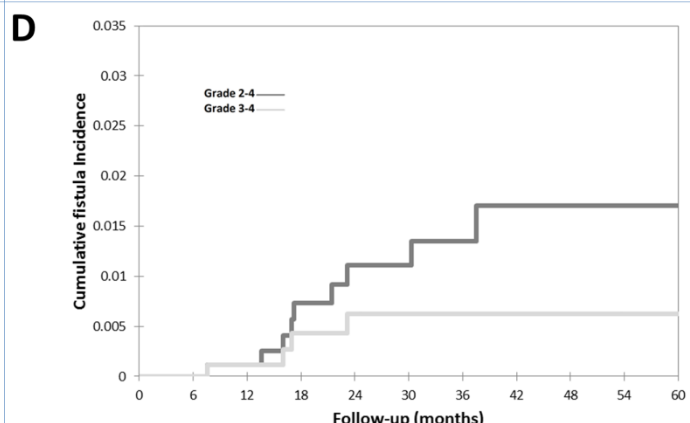
Number at risk						N events	Inc. at 3-y
Grade 1-4	960	722	436	260	137	155	20.7%
Grade 2-4	960	755	489	311	169	41	5.4%
Grade 3-4	960	759	501	319	175	10	0.6%



Number at risk						N events	Inc. at 3-y
Grade 1-4	960	695	426	257	136	175	23.1%
Grade 2-4	960	747	482	305	163	43	5.8%
Grade 3-4	960	760	504	322	177	4	0.6%



Number at risk						N events	Inc. at 3-y
Grade 1-4	960	760	503	319	174	11	1.7%
Grade 2-4	960	760	504	321	176	6	0.9%
Grade 3-4	960	761	507	324	179	0	0%



Number at risk						N events	Inc. at 3-y
Grade 1-4	960	760	503	322	178	9	1.4%
Grade 2-4	960	760	503	322	178	9	1.4%
Grade 3-4	960	760	504	322	178	4	0.6%

EMBRACE, Mazeron et al. R&O 2016

Late Morbidity: GI, Rectum, Bowel

EMBRACE I. CTCAE v3
Diarrhea
Flatulence
Incontinence (anal)
Proctitis
Bleeding (hemorrhage GI, anus, rectum, sigmoid, colon, small bowel)
Stricture / stenosis (anus, rectum, sigmoid, colon, small bowel)
Fistula (anus, rectum, sigmoid, colon, small bowel)
Gastro-intestinal other

Descriptive

crude incidence

actuarial incidence

prevalence

Nina Jensen

Maximum incidence of single bowel symptoms, CTCAE during all follow up

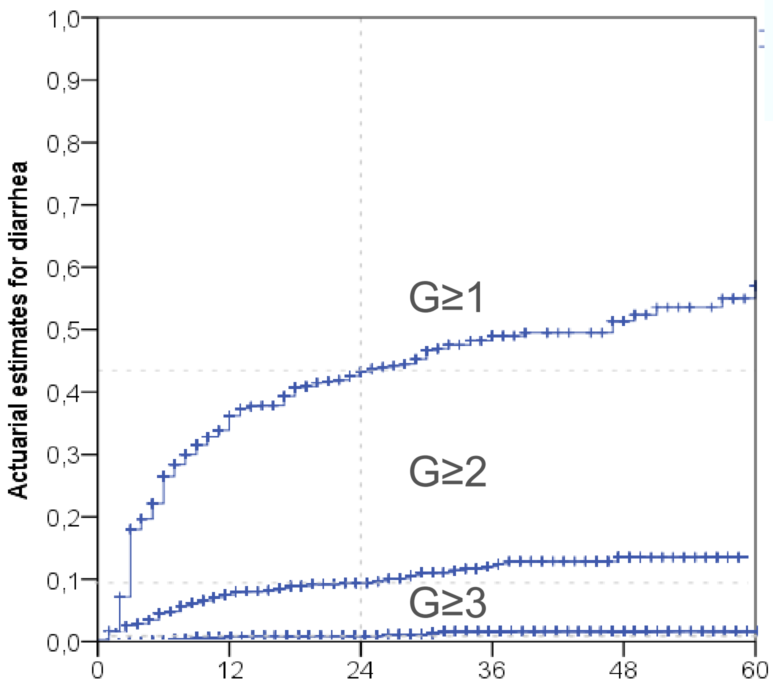
Number of patients 972 (missing 157)

	Diarrhea	Flatulence	Incontinence (anal)
G0	569 (58.5%)	593 (61.0%)	839 (86.3%)
G1	317 (32.6%)	298 (30.7%)	109 (11.2%)
G2	72 (7.4%)	81 (8.3%)	20 (2.1%)
G3	13 (1.3%)		2 (0.2%)
G4	1 (0.1%)		2 (0.2%)

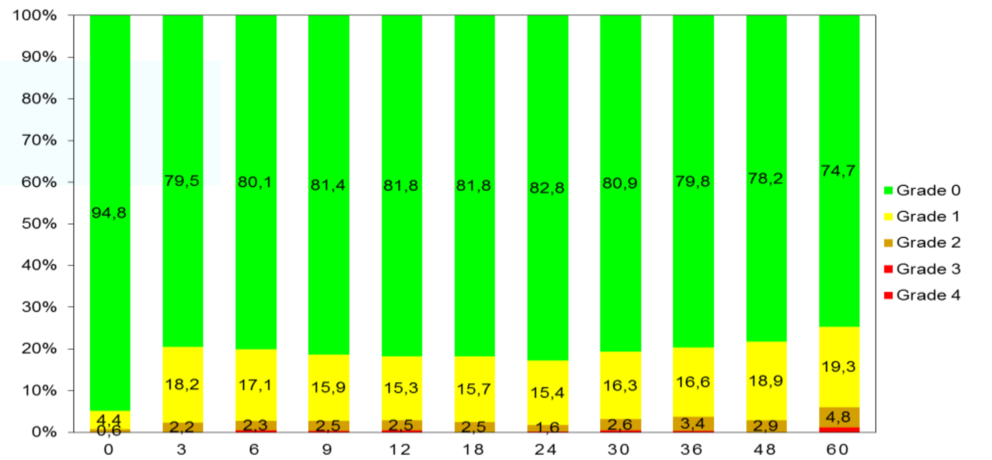
Maximum incidence of single bowel symptoms, EORTC C30+CX24

	Have you had diarrhea	Have you been constipated	Have you had cramps in your abdomen	Have you had difficulty in controlling your bowels
1="Not at all"	336 (39,3%)	484 (56,6%)	329 (38,5%)	433 (50,7%)
2="A little"	318 (37,2%)	249 (29,1%)	316 (37,0%)	276 (32,3%)
3="Quite a bit"	140 (16,4%)	91 (10,6%)	143 (16,7%)	102 (11,9%)
4="Very much"	61 (7,1%)	31 (3,6%)	66 (7,7%)	43 (5,0%)
Number of patients (Missing)	855 (274)	855 (274)	854 (275)	854 (275)

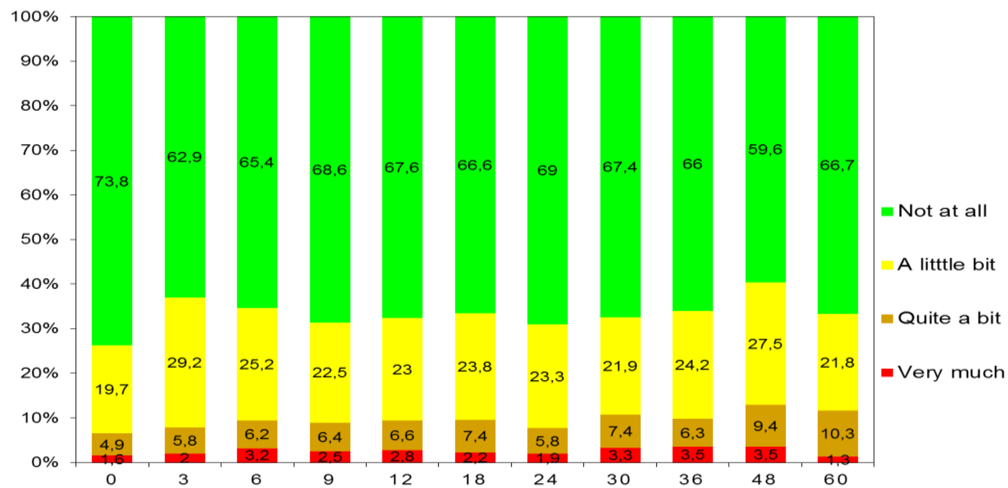
Diarrhea



Actuarial estimates for diarrhea
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0
12
24
36
48
60
G≥1
G≥2
G≥3

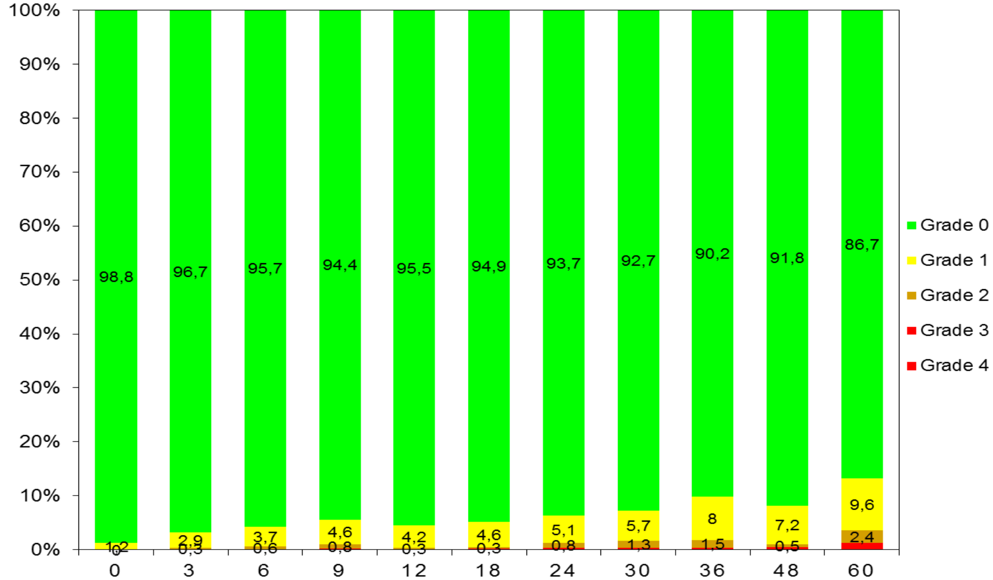


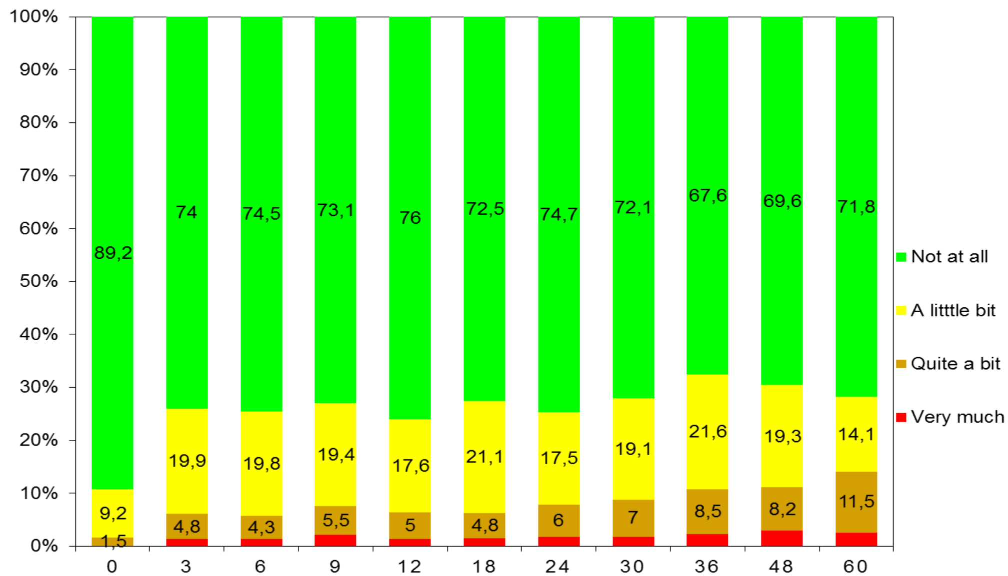
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
94,8
79,5
80,1
81,4
81,8
81,8
82,8
80,9
79,8
78,2
74,7
4,4
18,2
17,1
15,9
15,3
15,7
15,4
16,3
16,6
18,9
19,3
0,6
2,2
2,3
2,5
2,5
2,5
1,6
2,6
3,4
2,9
4,8
0
3
6
9
12
18
24
30
36
48
60
Grade 0
Grade 1
Grade 2
Grade 3
Grade 4



100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
73,8
62,9
65,4
68,6
67,6
66,6
69
67,4
66
59,6
66,7
19,7
29,2
25,2
22,5
23
23,8
23,3
21,9
24,2
27,5
21,8
4,9
5,8
6,2
6,4
6,6
7,4
5,8
7,4
6,3
9,4
10,3
1,6
2
3,2
2,5
2,8
2,2
1,9
3,3
3,5
3,5
1,3
0
3
6
9
12
18
24
30
36
48
60
Not at all
A litttle bit
Quite a bit
Very much

Incontinence – difficulty controling bowel





Late Morbidity: Vagina

EMBRACE I. CTCAE v3
Vaginal dryness
Vaginal stenosis/length
Vaginal mucositis
Bleeding (hemorrhage GU)
Fistula (Vagina cont.)
Vaginal other
Hormonal therapy
Regular vaginal dilatation

Descriptive

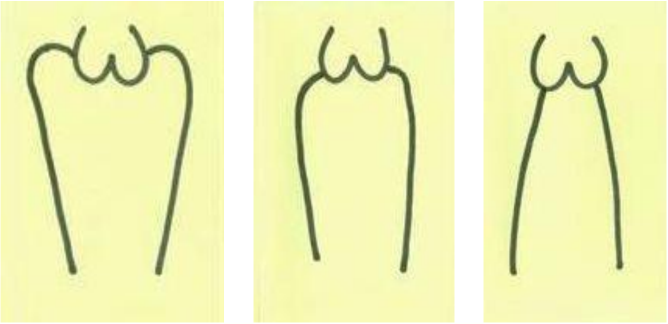
crude incidence

actuarial incidence

prevalence

Vaginal stenosis

Flattening of the fornices → „conical appearance“



Impact on sexuality:

Feeling of vaginal shortening

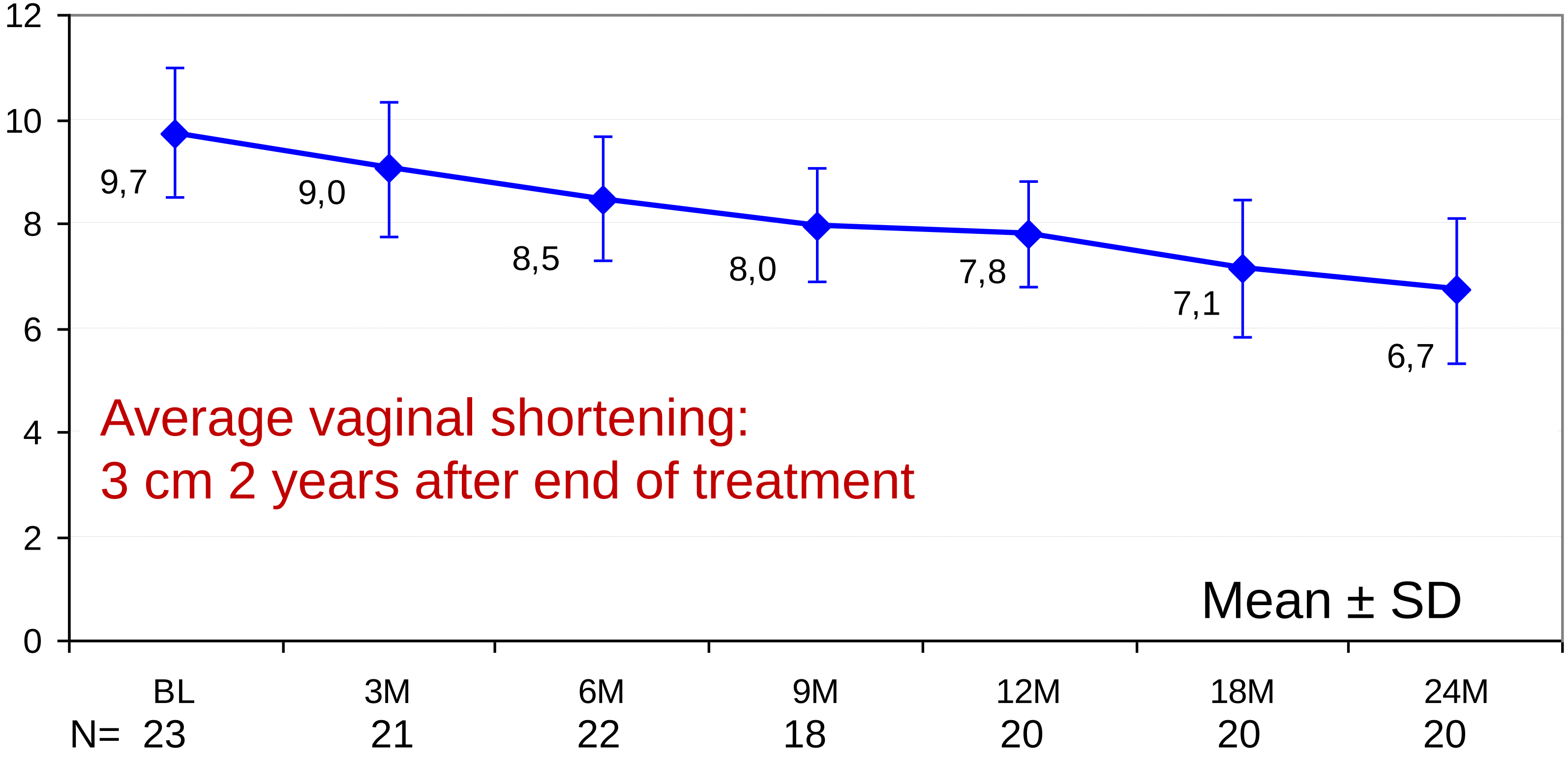
Feeling of vaginal tightening, esp. at the introitus

→ Pain during intercourse (dyspareunia)

Kirchheiner et. al. SUON 2012

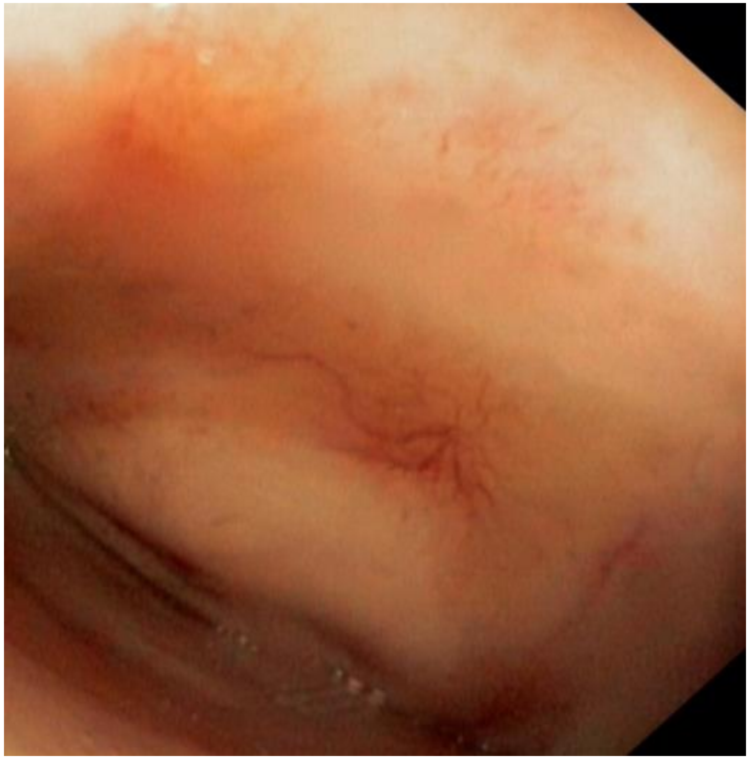
Vaginal length reduction

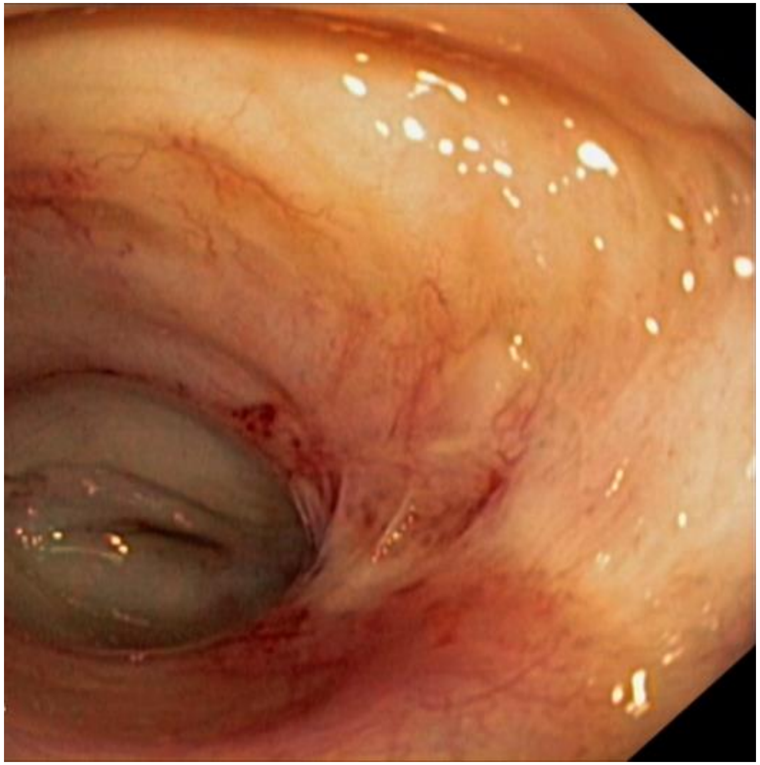
Fibrosis, loss of elasticity



Kirchheiner et al. abstract ESSM 2016

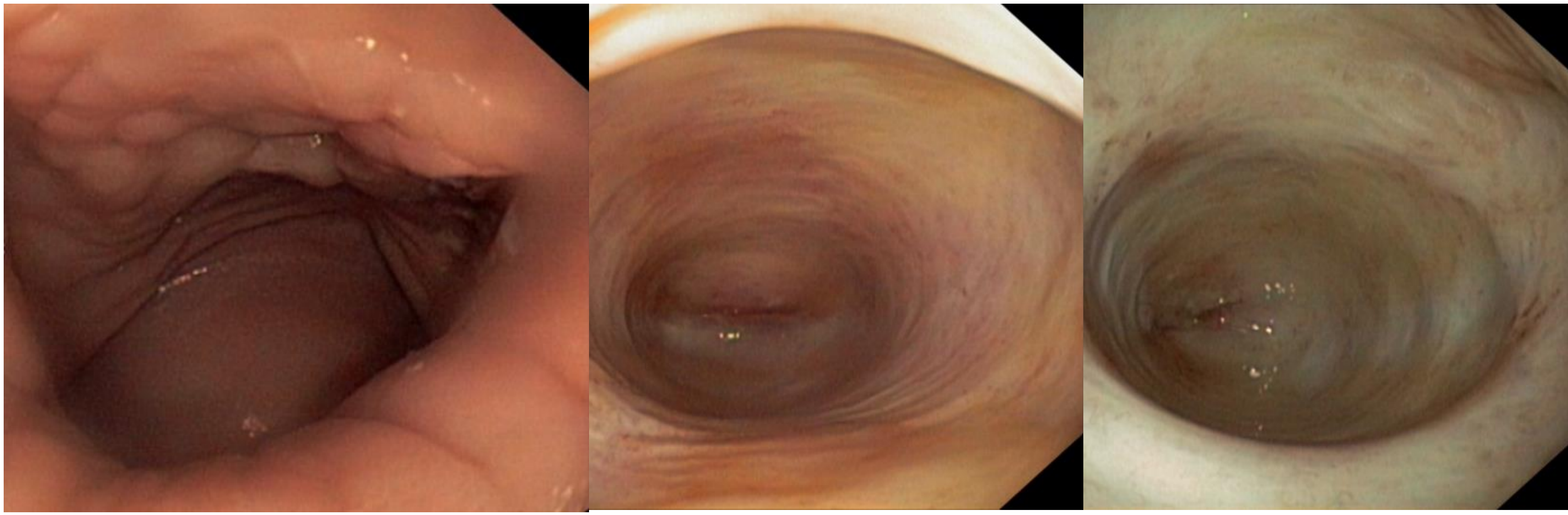
Telangiectasia





Impact on sexuality:
Contact bleeding during or after intercourse
(causes fear of recurrence)

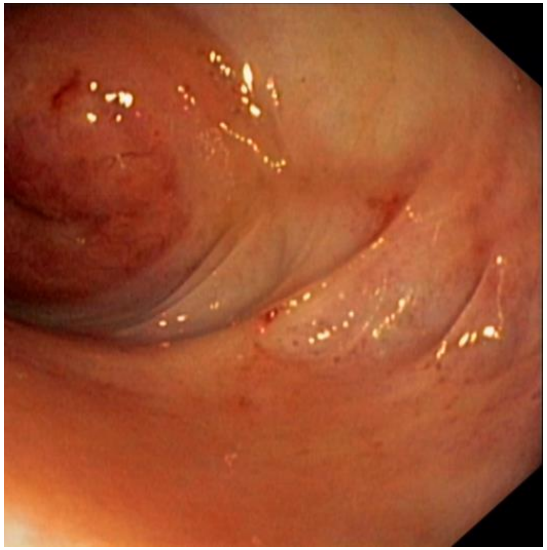
Atrophy of the mucosa

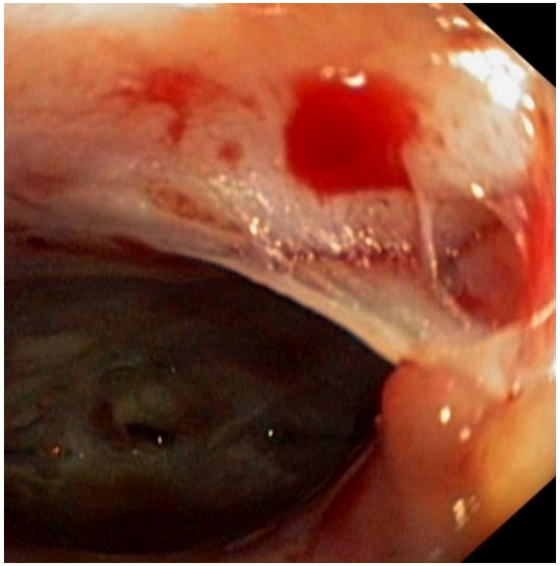


Impact on sexuality
Reduced lubrication despite sexual arrousal
→ painful friction and irritation of the mucosa,

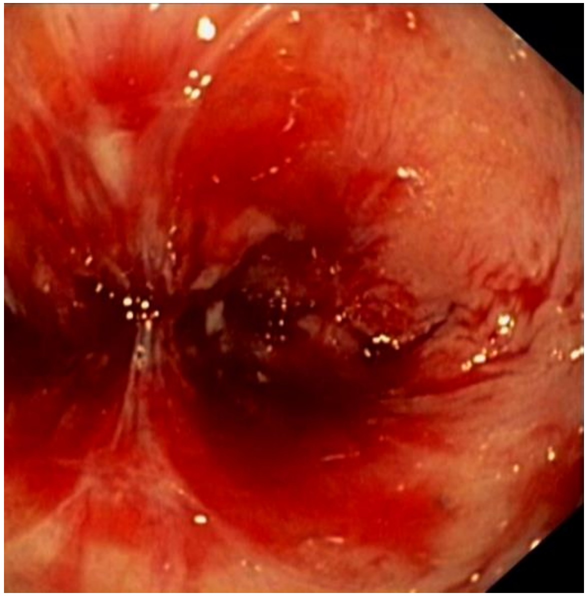
Feeling of soreness, itching, burning

Adhesions



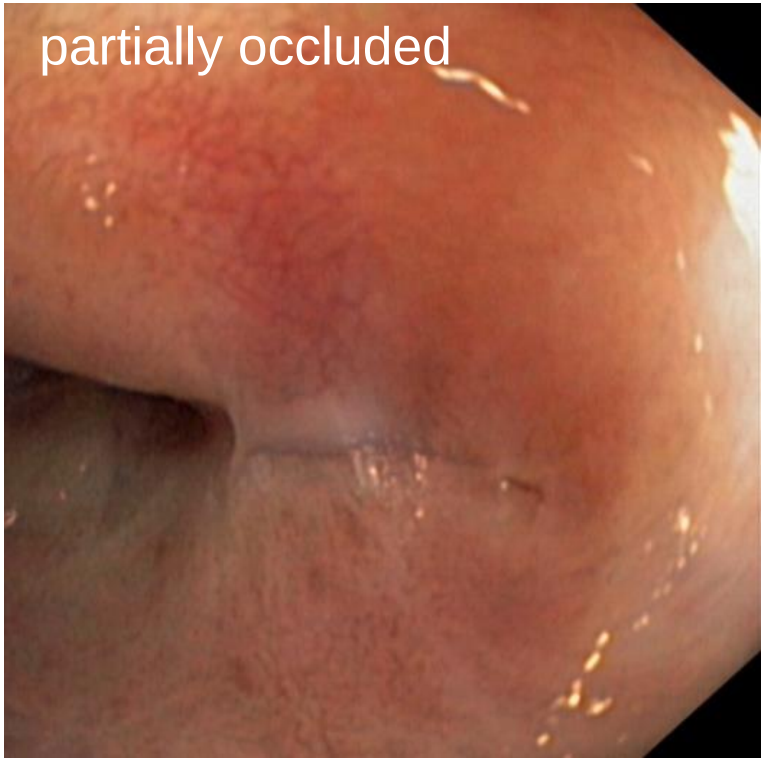


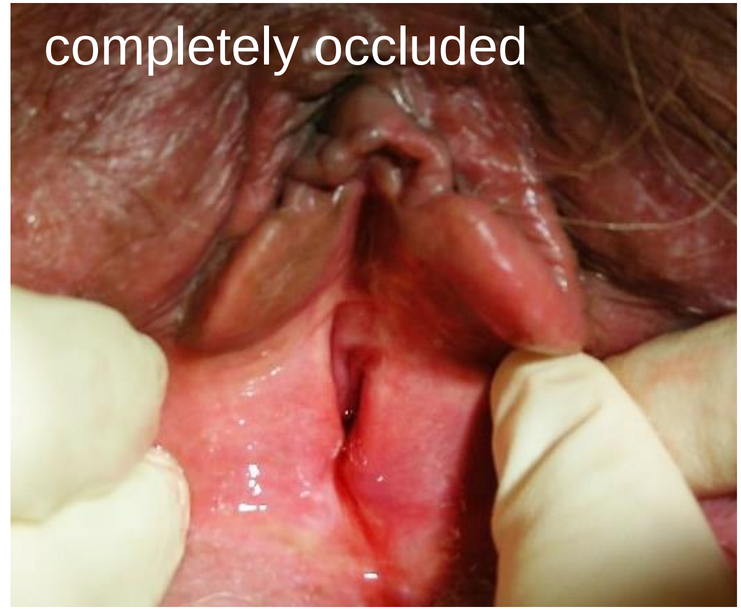
Resolvement during examination often painful



Impact on sexuality:
Rupture of adhesion during intercourse causes pain and bleeding

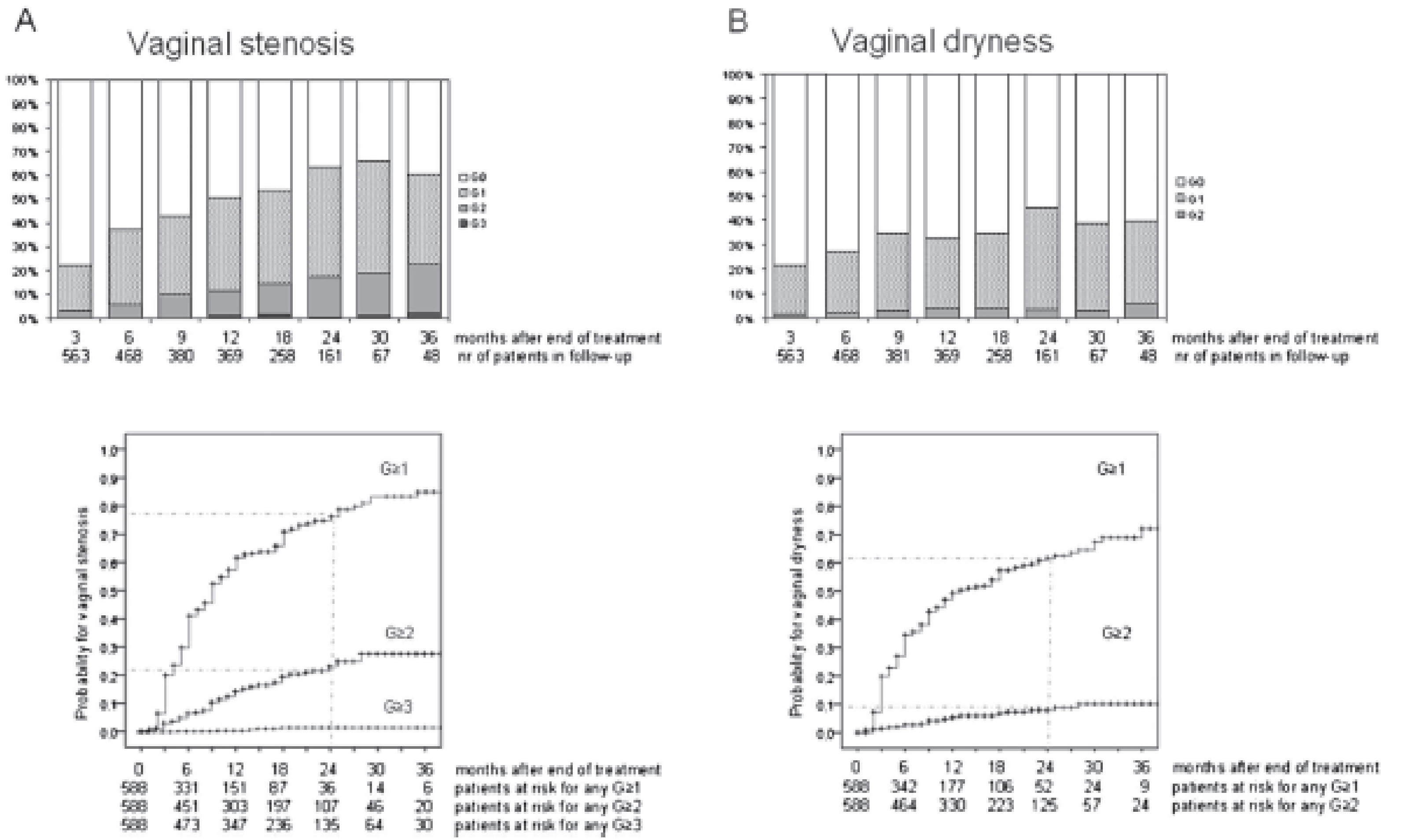
Vaginal occlusion





Prevention:
Regular dilation
and / or intercourse

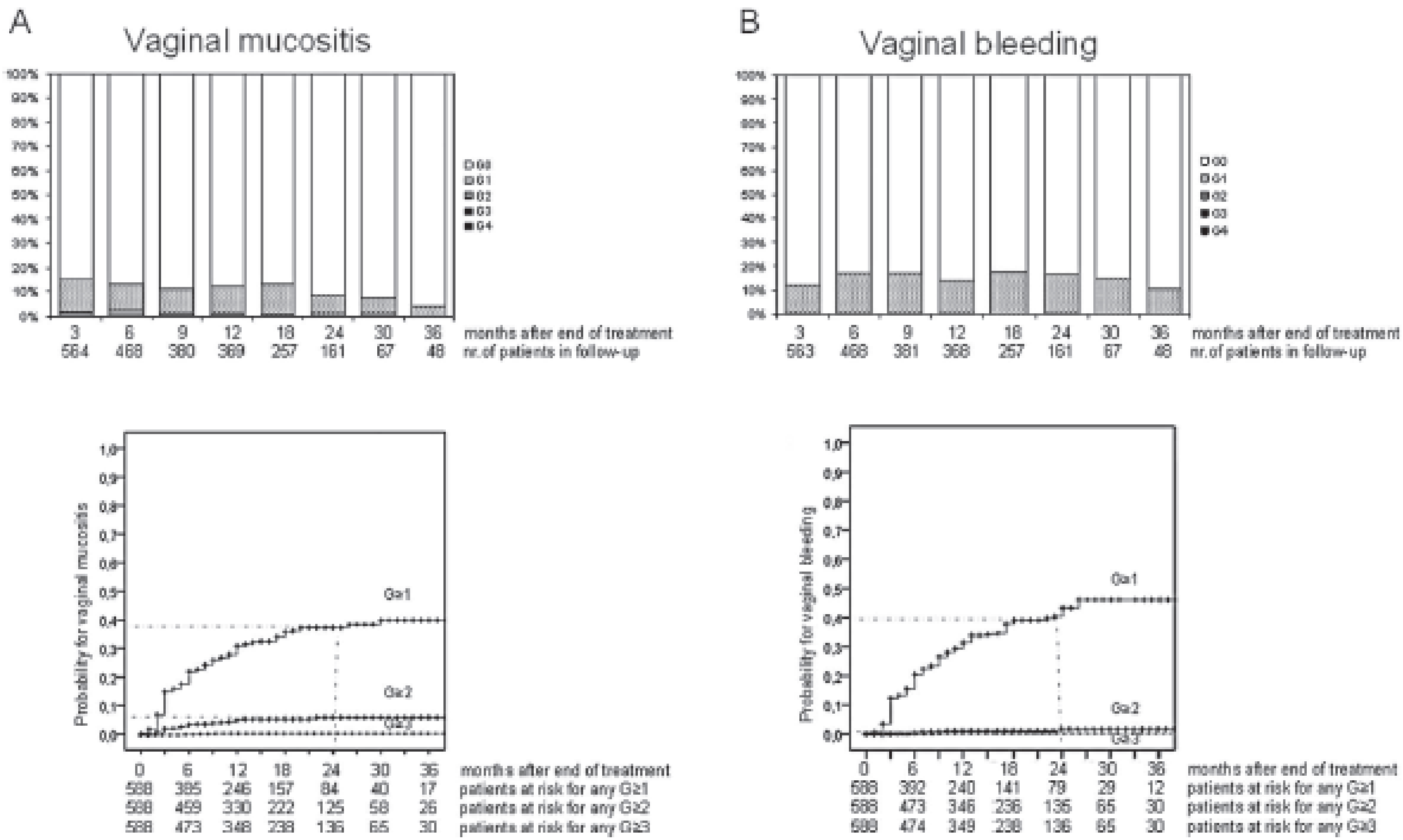
Patterns of manifestation: Prevalence rates and Actuarial estimates



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

Kirchheiner et al.
IJROBP 2014

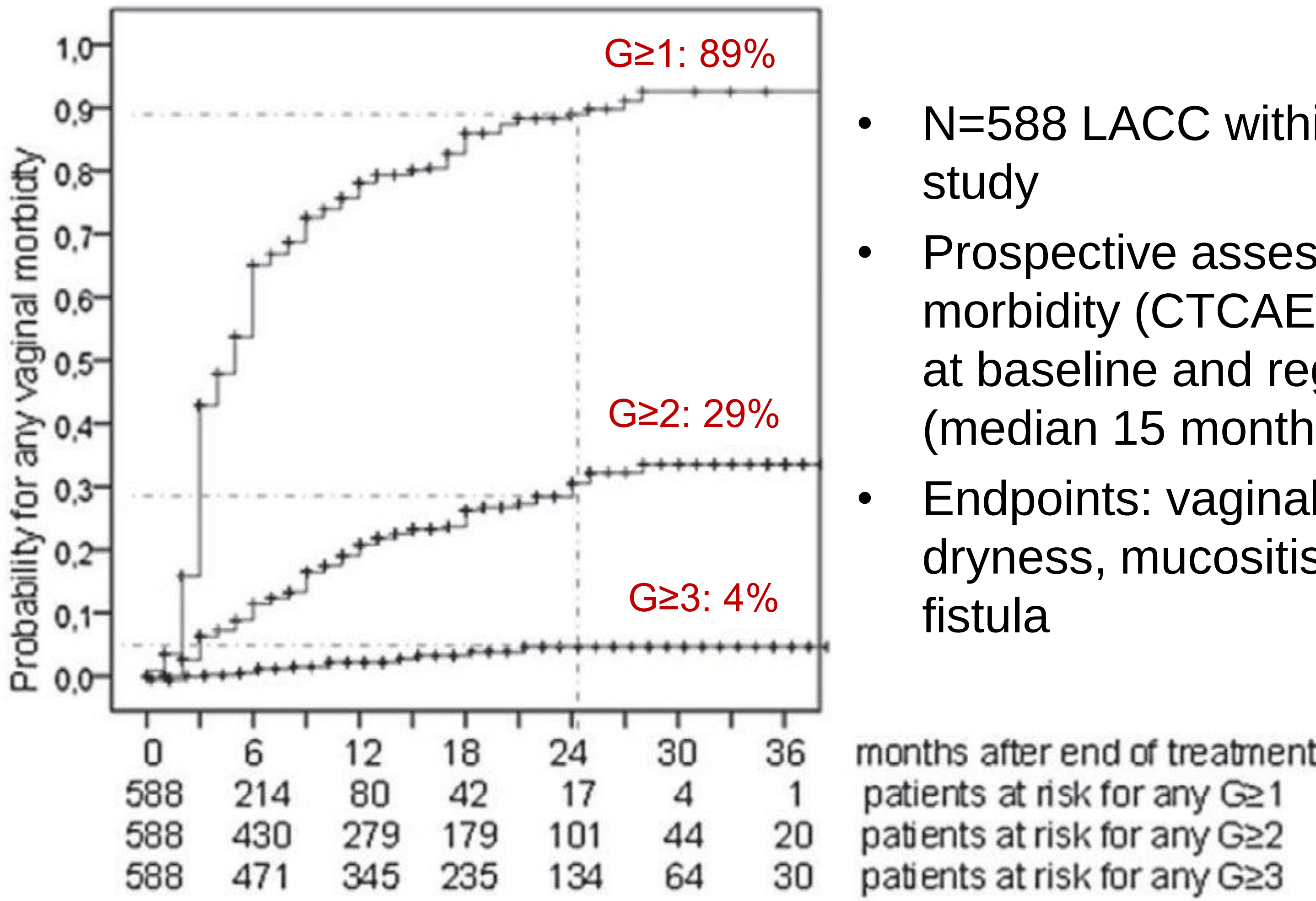
Patterns of manifestation:
Prevalence rates and Actuarial estimates



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

Kirchheiner et al.
IJROBP 2014

Vaginal morbidity after definitive radiochemotherapy + IGABT in LACC



- N=588 LACC within EMBRACE study
- Prospective assessment of morbidity (CTCAE 3) at baseline and regular follow-ups (median 15 months)
- Endpoints: vaginal stenosis, dryness, mucositis, bleeding, fistula

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

Kirchheiner et al.
IJROBP 2014

Table 3 Crude incidences of treatment-related individual vaginal symptoms and overall vaginal morbidity in 588 patients with a median follow-up time of 15 months

Grade	Vaginal stenosis	Vaginal dryness	Vaginal mucositis	Vaginal bleeding	Vaginal fistula	Other vaginal symptoms	Overall vaginal morbidity
G0	241 (41%)	312 (53%)	415 (71%)	407 (69%)	582 (99%)	523 (89%)	155 (26%)
G1	256 (43%)	244 (42%)	146 (25%)	175 (30%)	2	47 (8%)	309 (53%)
G2	86 (15%)	32 (5%)	23 (4%)	5 (1%)	0	14 (2%)	111 (19%)
G3	5 (1%)	N.A.	3	1	4 (1%)	4 (1%)	12 (2%)
G4	N.A.	N.A.	1	0	0	0	1
G5	N.A.	N.A.	0	0	0	0	0

Abbreviation: N.A. = not applicable.

Summary

Crude incidence, rates for single vaginal endpoints

At two years, actuarial probability of severe vaginal morbidity (G≥3) was 3.6%.

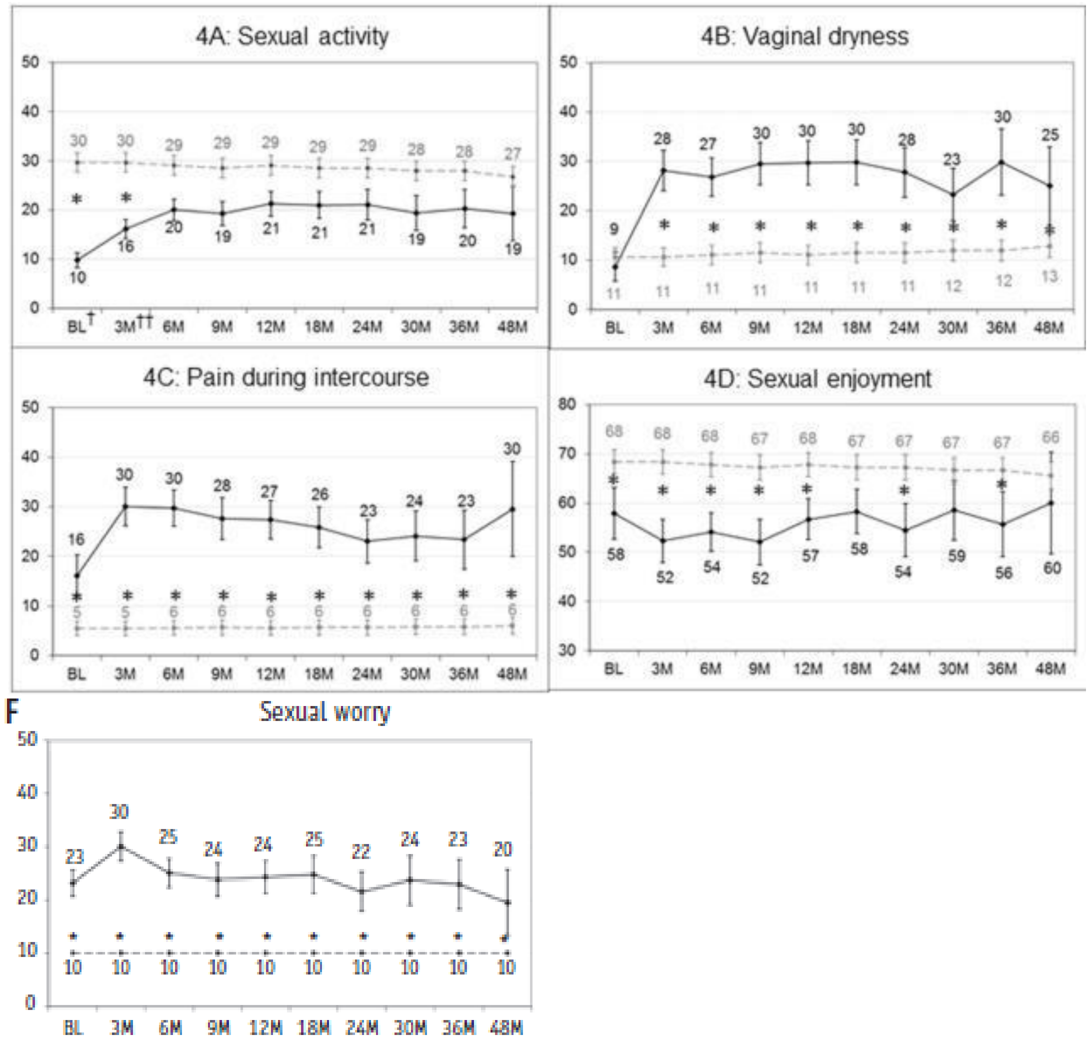
However, mild and moderate vaginal symptoms were still pronounced (G≥1: 89%, G≥2: 29%), of which the majority developed within 6 months.

Stenosis was most frequently observed, followed by vaginal dryness. Vaginal bleeding and mucositis was mainly mild and infrequently reported.

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

Kirchheiner et al.

IJROBP 2014



LONG-TERM IMPACT ON SEXUALITY

- Higher score represent higher symptom burden
- Comparison with age-matched, female normative reference population (dotted line).

Kirchheiner et al. IJROBP 2016

Stenosis: ICRU recto-vaginal referene point

With increasing dose to the recto-vaginal reference point, the probability of vaginal stenosis G≥2 increases significantly ($p=0.003$).

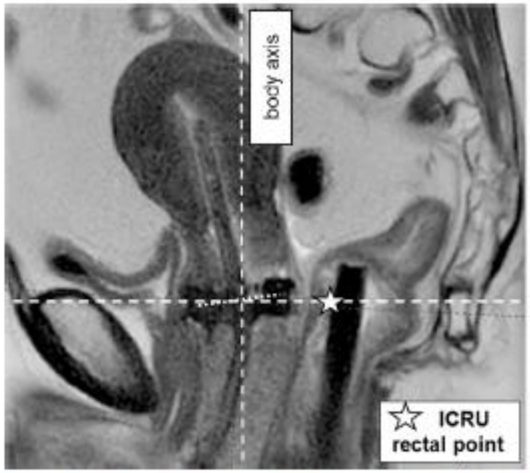


Fig. 1. ICRU rectal point depicted on sagittal T2 MRI, positioned at the intersection level between tandem and the source positions in the ring and 5 mm dorsal of the posterior vaginal wall on the axis perpendicular to the body axis.

Based on the model curve, the risk was 20% at 65Gy, 27% at 75Gy and 34% at 85Gy (recto-vaginal reference point dose).

Keeping the EBRT dose at 45Gy/25fractions and decreasing the dose contribution of brachytherapy to the vagina decrease the risk of stenosis.

A planning aim of ≤65Gy EQD2 (EBRT+brachytherapy dose) to the recto-vaginal reference point is therefore proposed.

Kirchheiner et al.

RO 2016

Late Morbidity: others

EMBRACE I. CTCAE v3
Fibrosis – deep connective tissue (pelvis right / left)
Fracture – insufficiency (Pelvic ring / Femoral head)
Muscle/soft tissue/bone other
Edema: limb
Edema: trunk/genital
Fatigue
Insomnia
Hot flashes
Other, specify category and grade

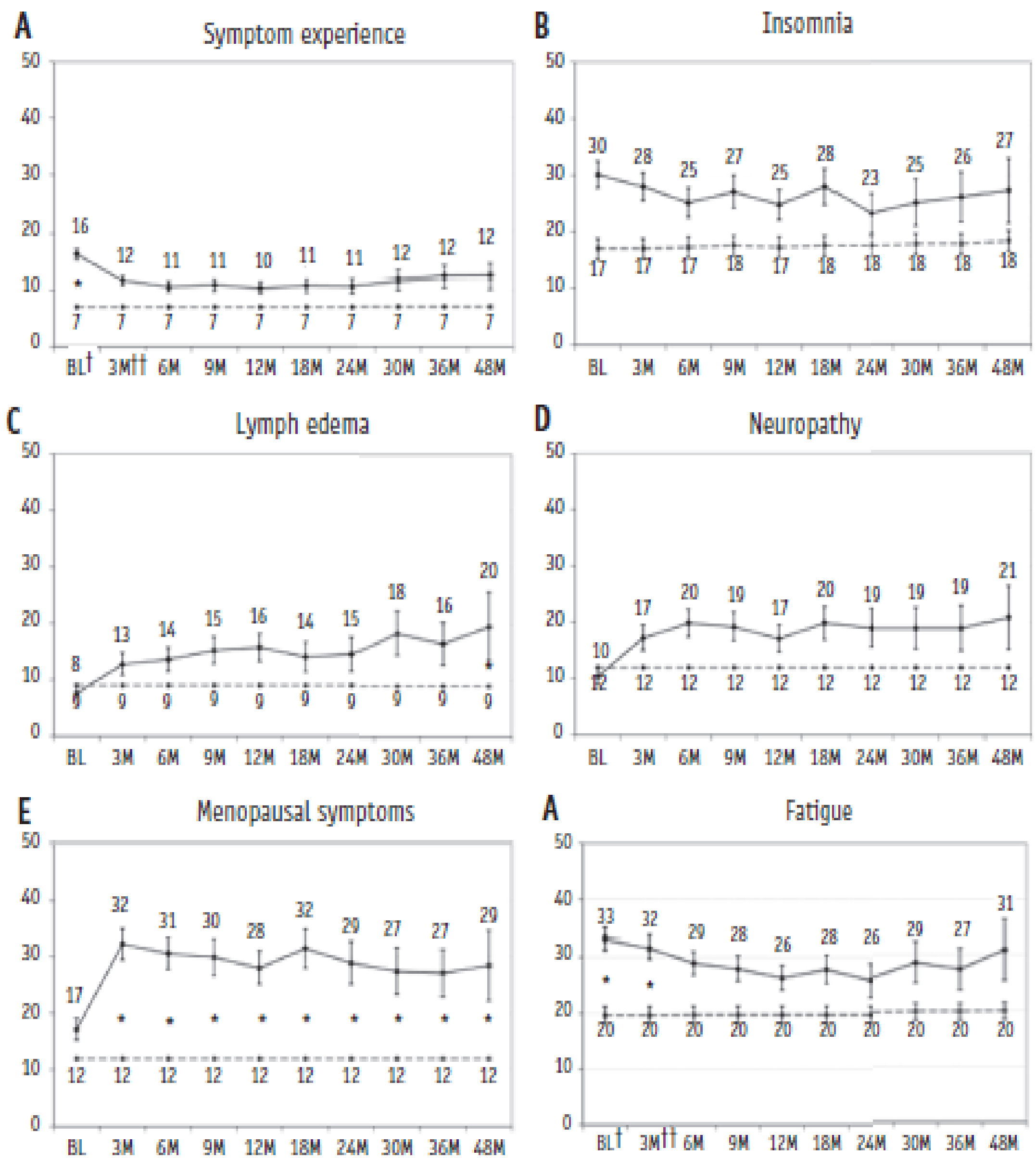
Descriptive

crude incidence

actuarial incidence

prevalence

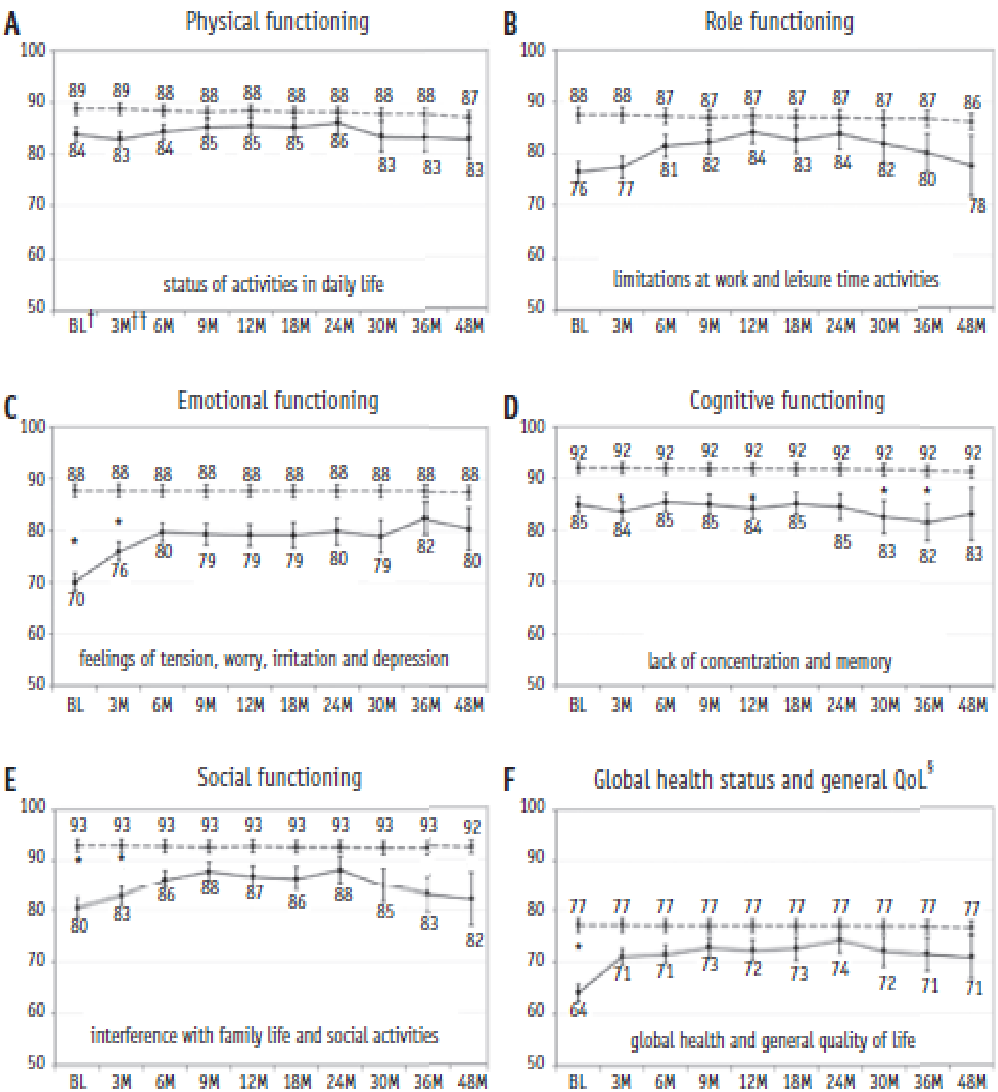
EMBRACE { An intErnational study on MRI-guided BRachytherapy in locally Advanced CErvical cancer }



LONG-TERM PATIENT REPORTED SYMPTOMS

- Higher score represent higher symptom burden
- Comparison with age-matched, female normative reference population (dotted line).

Kirchheiner et al. IJROBP 2016



LONG-TERM QUALITY OF LIFE

- 744, multi-institutional LACC patients (EMBRACE study)
- Prospective QoL assessment with EORTC-QLQ-C30+CX24
- Median follow-up 21 months
- Higher score represent better functioning and QoL
- Comparison with age-matched, female normative reference population (dotted line).

Kirchheiner et al. IJROBP 2016

Reported severe morbidity IGABT

RetroEMBRACE: Late toxicity recorded in 610/731 patients.

Actuarial rates of severe (G3-G5) at 5 years were:

•Bladder 5%

•GI-tract 7%

•Vagina 5%

Monocentric series MRI guided IGABT >100 patients (Vienna, Aarhus, Paris) report: 5.6% - 7% severe (G3-G5) morbidity

Sturdza et al. R&O 2016; Potter R&O 2011; Lindegaard Acta Onc 2013; Castelnau-Marchand Gyn Onc 2015

Summary II

- Retrospectively reported severe late morbidity 5-7% with MRI guided IGABT. However, mild and moderate are more frequent and may negatively affect QoL.

- Retrospective reporting has inherent limitations.

- Most frequently reported symptoms include:

- Bladder: frequency, incontinence
- Rectum: proctitis
- Bowel: diarrea, bowel cramps
- Vaginal: stenosis, dryness
- Other: hot flushes

Summary II

- Tumor-related symptoms (e.g. pain, appetite loss and constipation), which are present before treatment, decrease substantially at the first follow-up after treatment.

- Several treatment-related symptoms develop either immediately and persist over time (diarrhea, menopausal symptoms, peripheral neuropathy and sexual functioning problems) or develop gradually after treatment (lymph edema and dyspnea).

Thank you!

ESTRO-CARO Teaching Course
Image Guided Radiotherapy in cervix cancer
- with a special focus on adaptive brachytherapy -

Disease Outcome IGRT/IGABT
Cervix cancer

Richard Pötter

RESULTS OF DEFINITIVE RADIOTHERAPY IN LIMITED DISEASE

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		229	I MDAH	89 (89)	93 (95)
LDR		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

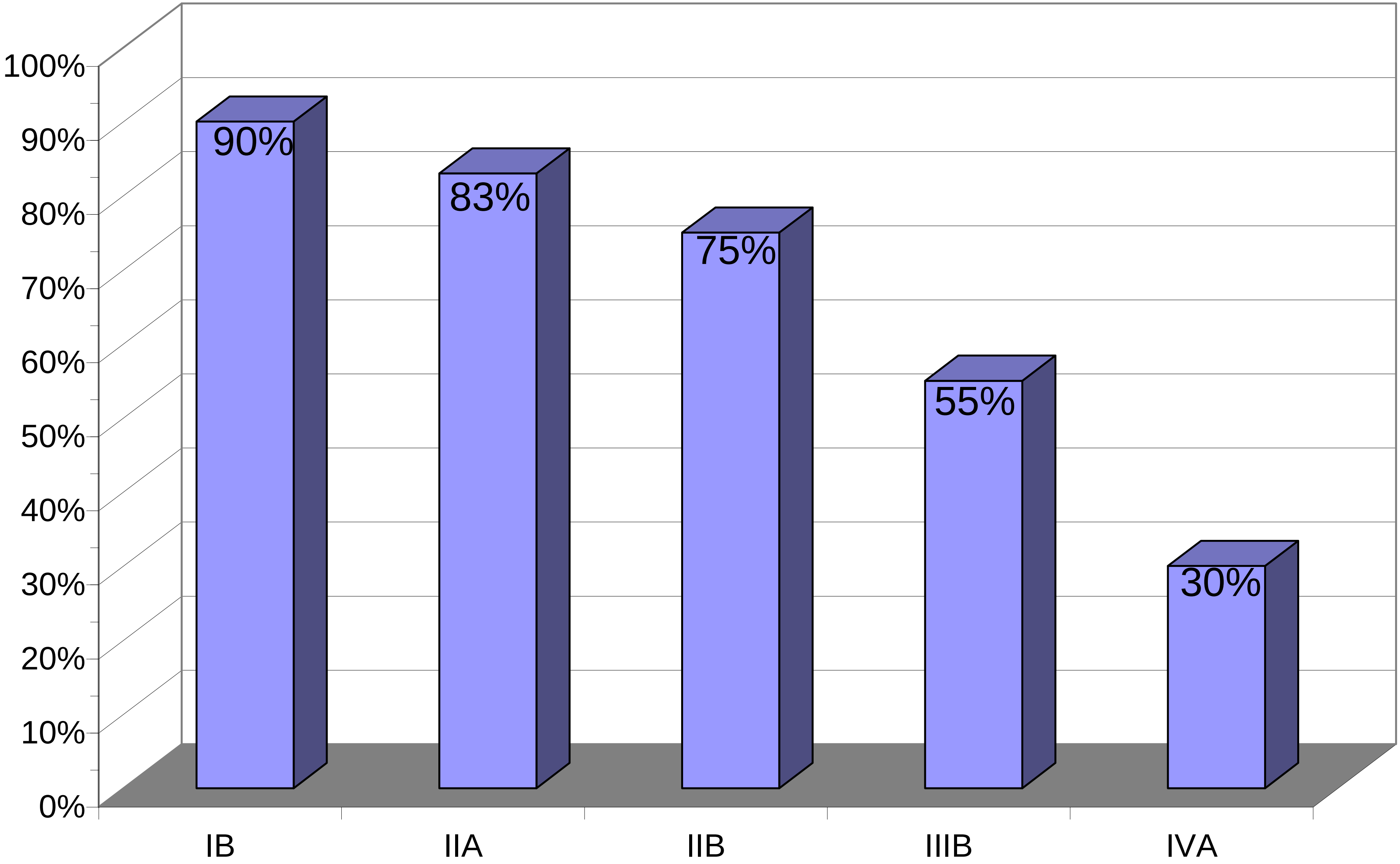
Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma.
In: Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Van Limbergen E, eds. (2002)
The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO

RESULTS OF DEFINITIVE RADIOTHERAPY IN EXTENDED DISEASE

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

TREATMENT RESULTS DEFINITIVE RADIOTHERAPY 2D X-RAY BASED PLANNING/POINT A



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

BENEFIT FROM CONCOMITANT RADIOCHEMOTHERAPY

SURVIVAL AND RECURRENCE AFTER CONCOMITANT CHEMOTHERAPY AND RADIOTHERAPY FOR CANCER OF UTERINE CERVIX: A SYSTEMATIC REVIEW AND META-ANALYSIS

3656 patients (19 studies)

LOCAL RECURRENCE RATE WAS SIGNIFICANTLY REDUCED BY CHEMORADIATION
OR 0.61, 95% CI 0.51-0.73, p< 0.0001

	RCHT	RT
OS	52%	40%
PFS	63%	47%
Toxicity Grade 3-4		
Haematological	16%	8%
Gastrointestinal	9%	4%

Green et al. Lancet 2001;358:781-86

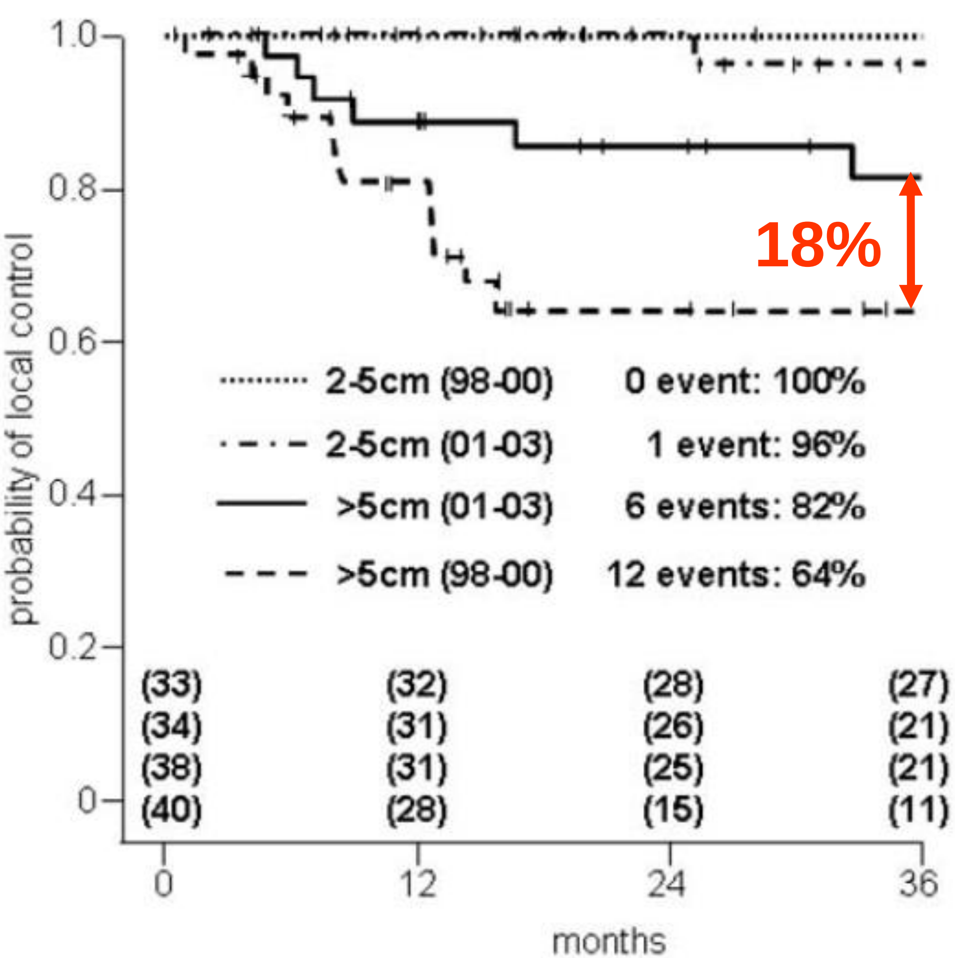
J Clin Oncol. 2002	RT	66% (p=0.42)

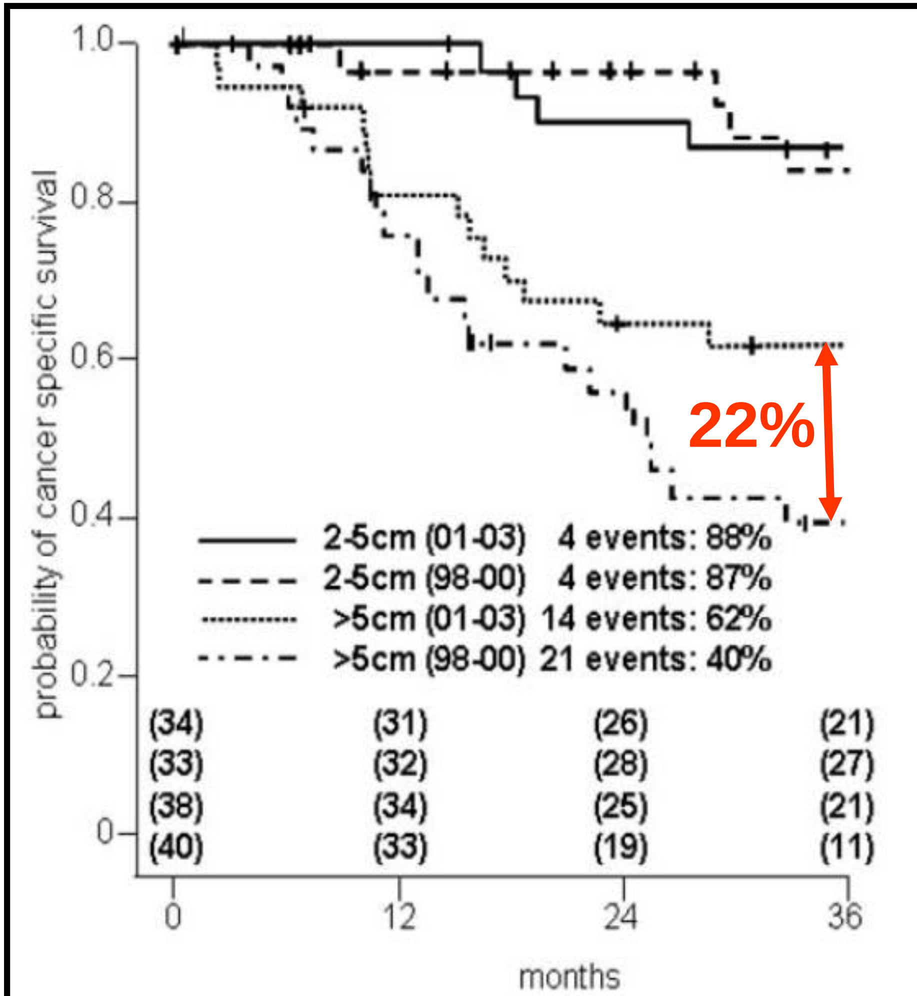
Clinical Evidence in IGABT Cervix Cancer

Upcoming Evidence

- Mono-intstitutional cohorts (ongoing, publicat. since 2007)
- Multi-center cohorts with retrospective evaluation
  RetroEMBRACE (publications expected for 2015+)
- Prospective Trials
  STIC: comparative 2D vs. 3D (published 2012)
  EMBRACE I: observational, 08/2008 - 12/2015
  EMBRACE II: interventional, start 01/2016

Image guided adpative brachytherapy (IGBT) cervix cancer
Local Control and Cancer Specific Survival (1998-2003)
TREATMENT PERIOD (-/+ IGABT) AND TUMOUR SIZE

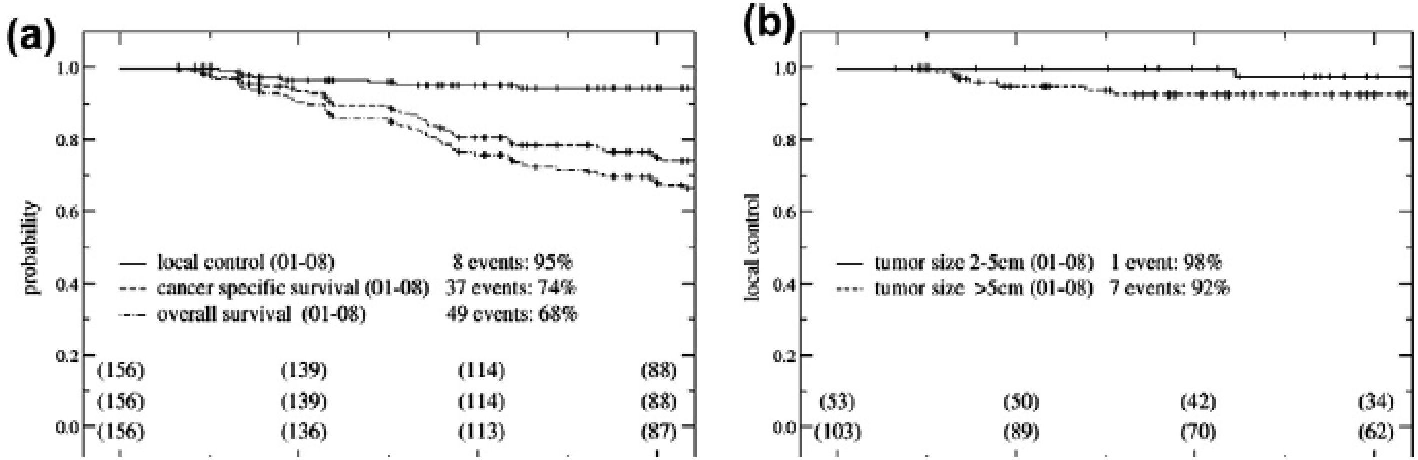




mean 81 Gy vs. 90 Gy in HR CTV

Pötter R. et al Radiother Oncol 2007

OUTCOME AFTER 3D BASED CERVICAL CANCER BT: Local Control, Cancer Specific Survival, Overall Survival



156 patients MRI guided BT, Vienna 2001-2008, mean D90 to HR CTV 92 Gy
7/156 with G3 and 4/156 G4 toxicity (LENT SOMA)

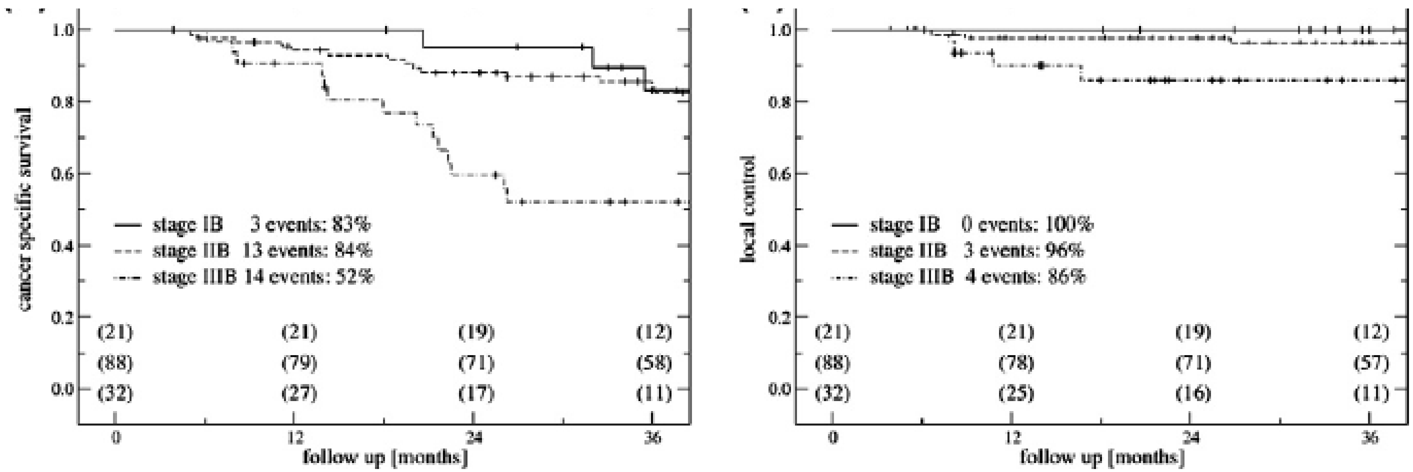


Fig. 1. Outcome after radiotherapy ± chemotherapy and image-guided adaptive brachytherapy. (a) Local control, cancer specific survival and overall survival for all 156 patients. (b) Local control and tumour size. (c) Cancer specific survival for FIGO stages IB, IIB, IIIB. (d) Local control for FIGO stages IB, IIB, IIIB.

Pötter et al. Radiother&Oncol 2011

CONTINUOUS COMPLETE REMISSION
3 YEARS*

VIENNA 1993-2003: 335 patients

TREATMENT PERIOD	CCR	
	2-5cm (REC.)	>5cm (REC.)
2001-2003**	**96%** (1/34)	**90%** (3/34)
1998-2000**	**96%** (1/33)	**71%** (9/37)
1993-1997***	**90%** (5/65)	**67%** (27/124)

** *Pötter et al. 2007 Radioth Oncol*

*** *Pötter et al. Cancer Radioth 2000*

* *Actuarial data (Kaplan Meier)*

Universitätsklinik für Strahlentherapie
und Strahlenbiologie Wien

CONCLUSIONS
(Vienna experience 1998-2008)

MRI assisted treatment planning
in defintive intracavitary cervical cancer brachytherapy
Plus risk adapted interstitial brachytherapy
plus 3D CRT +/- cis-PLATINUM (n=228)

- **Local control**

  tumours < 5 cm: ~95-100+% **D90: 90-95 Gy**

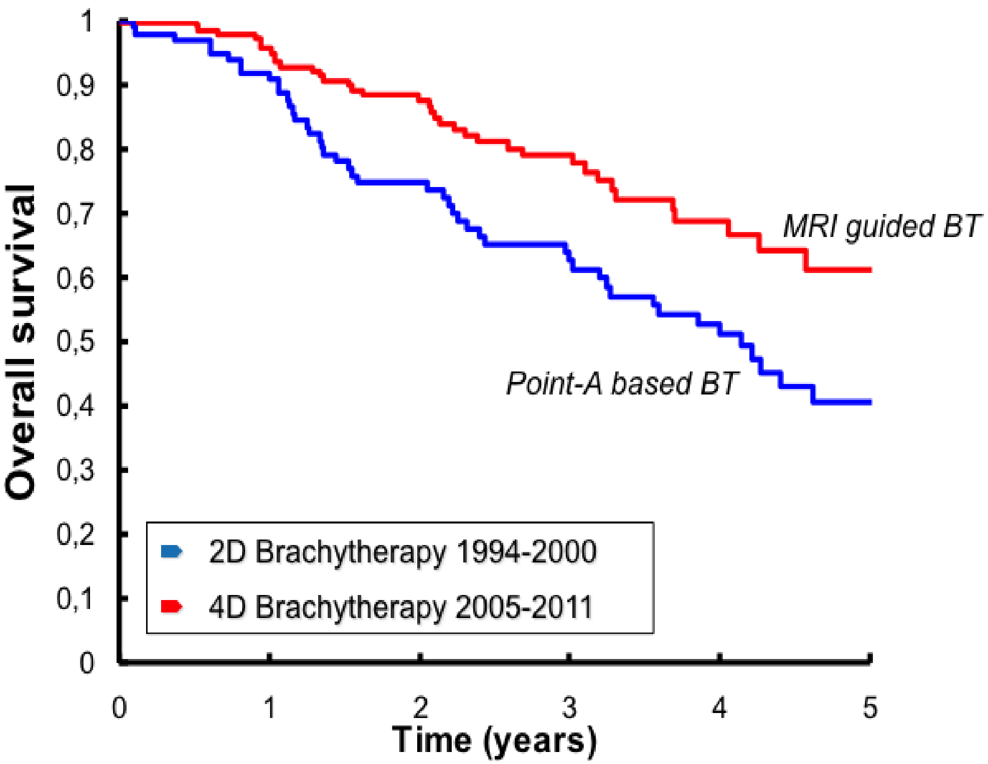
  tumours ≥ 5 cm: ~90% **D90: 90+ Gy**

- **Low rate of late side effects**

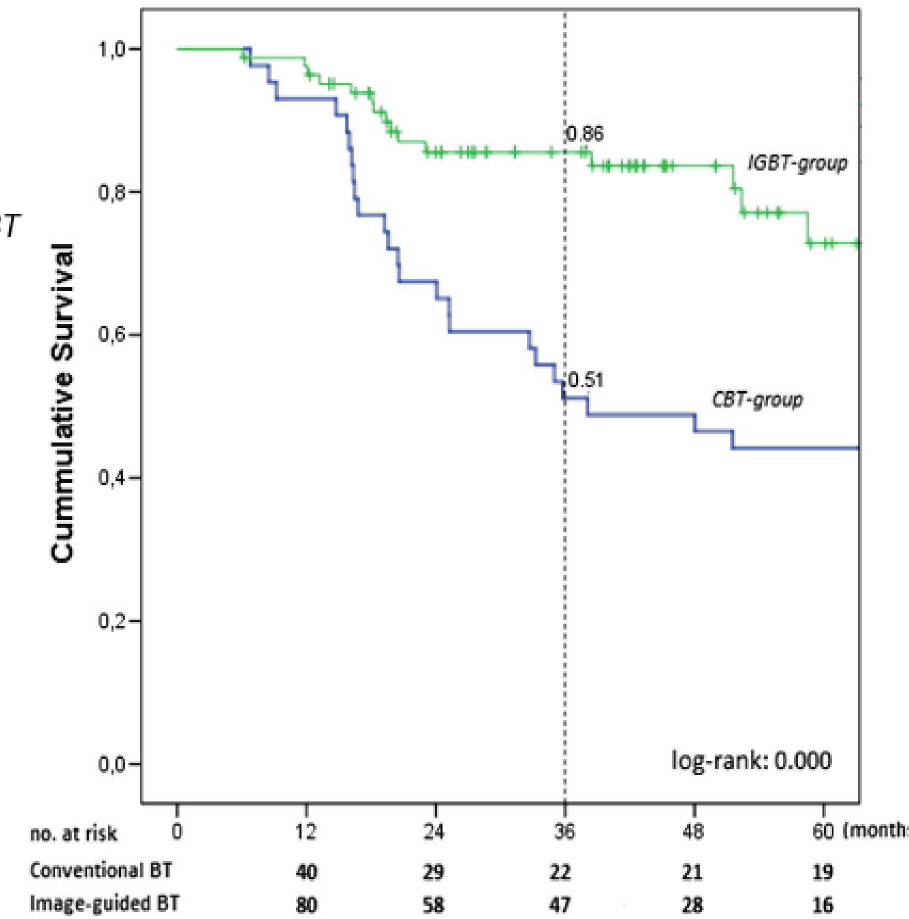
  Grade 3 and 4: <5% per organ site

Better local control = improved survival

Aarhus Experience



Leiden Experience



Lindegaard, Acta Oncologica 2013

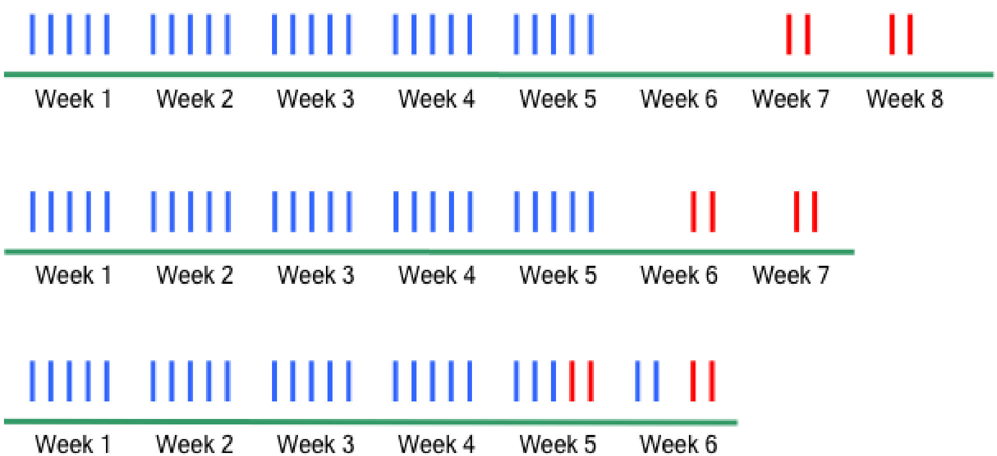
Rijkmans et el Gyn Oncol 2014

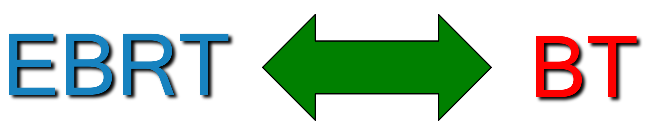
Overall treatment time (OTT)

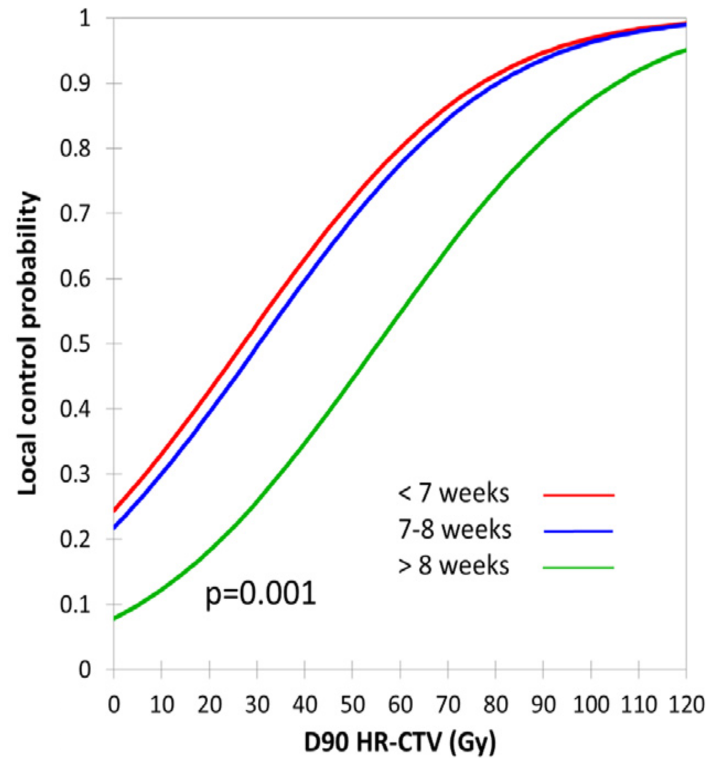
- **Increasing OTT by one week is equivalent to a loss of 5 Gy in CTV_{HR} D90**

Tanderup et al. , RetroEMBRACE, 2016, RadiothOncol

- **Timing of the BT boost?**







Mazeron et al, Paris data, Radiother Oncol 2015

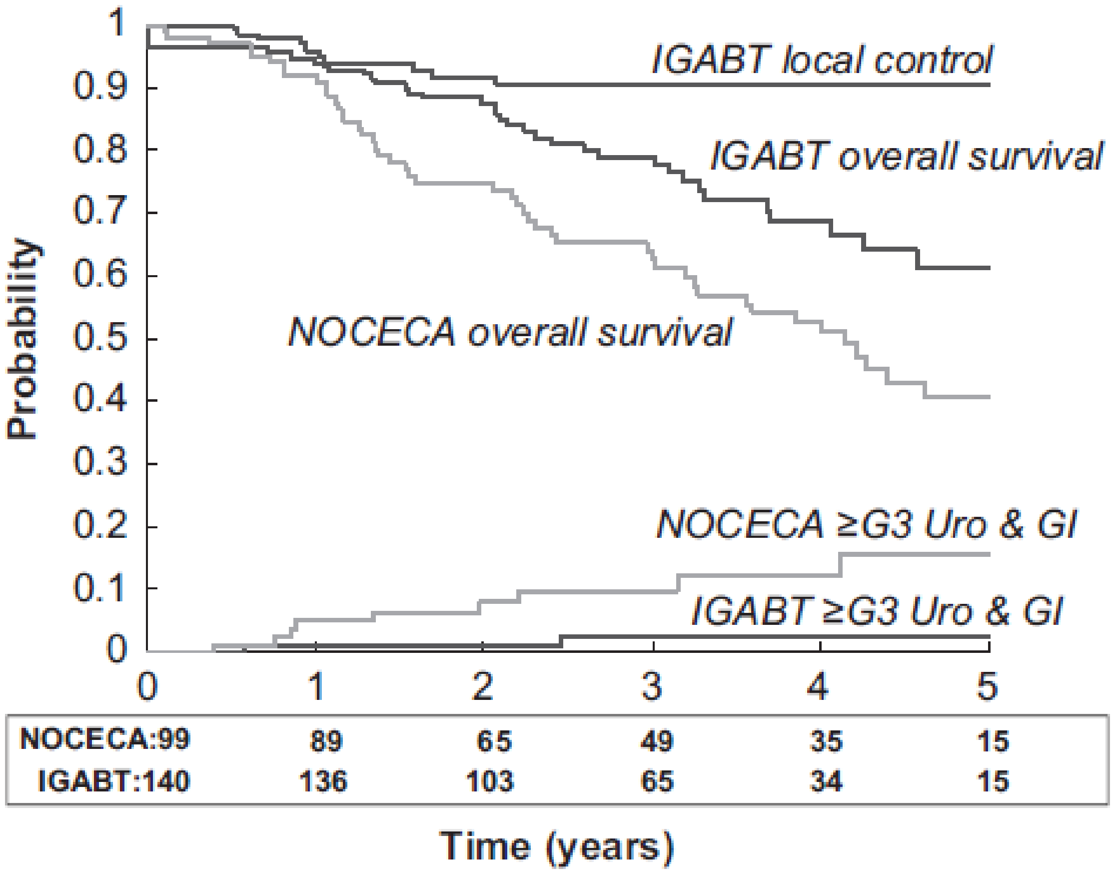


Figure 3. Actuarial local control, overall survival and ≥grade 3 combined urological-gastrointestinal morbidity in 140 patients treated with IGABT (black lines). For comparison the curves for overall survival and morbidity in 99 patients treated with 2D x-ray-based brachytherapy (NOCECA) are indicated (grey lines). Patient number at risk for overall survival is indicated below the x-axis.

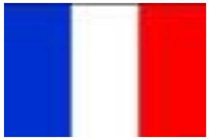
LC 3 y: 90%

OS 3 y:
IGABT/ChTh: 79%
NOCECA: 63%

morbidity 3y ≥G3:
10%
3%

Lindegaard et al.
Acta Oncologica 2013

Multicenter studies with IGABT in cervix ca.

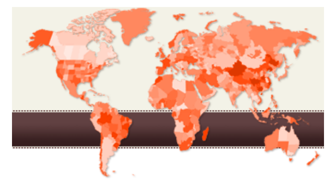


STIC

- Prospective
- 2D vs. 3D (CT)
  - **Non random.**
  - **Availability**
- Completed
- 2005-2008
- 20 centers
- 705 pts
- **Def. EBRT+BT**
- **Preop BT**
- **Preop. EBRT+BT**

Embrace

- Prospective
- Phase "IV" (MRI)



- Accruing
- 2008-2015
- 23 centers
- 1416 pts
- **Def. EBRT+BT**

Retro Embrace

- Retrospective
- Before Embrace
- Collecting
- 2011-2013
- 12 centers
- 780 pts
- **Def. EBRT+BT**

From 2D – 3D
X Ray vs CT/MRI (STIC trial)

At 24 months	Group 1 BT followed by surgery		Group 2 EBRT BT surgery		Group 3 EBRT BT		P*
	2D	3D	2D	3D	2D	3D	
LRFS	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

LRFS: local free relapse survival; RLRFS: loco regional relapse free survival; DFS: disease free survival

* 2D-3D brachytherapy comparison : Cox proportional hazard model adjusted for regimens.

Table 6: 24-month Relapse Survivals

Charra-Brunaud

705 Pts available for analysis

Group 1: BT followed by surgery; 165 patients (2D arm: 76; 3D arm: 89);
Group 2: EBRT (+/- chemotherapy), BT, then surgery; 305 patients (2D arm: 142; 3D arm: 163);
Group 3: definitive radiotherapy: EBRT (+/- chemotherapy), then BT; 235 patients, (2D arm: 118; 3D arm: 117).

Charra-Brunaud et al, 2012 Radioth and Oncol

Results:

Variable		No of patients
Median Age (years)	53 (23 – 91)	731
FIGO Stage	1A	2 (0.3 %)
	1B	123 (16.8%)
	2A	42 (5.7 %)
	2B	368 (**50.3 %**)
	3A	23 (3.1 %)
	3B	145 (**19.8 %**)
	4A	23 (3.1 %)
	4B	5 (0.7 %)
Histology	Squamous cell Ca	620 (84.8%)
	Adenocarcinoma	71 (9.7%)
	Adenosquamous	29 (4%)
	Others	11 (1.5%)
Median tumour width	Clinically: 50 mm	MRT @ diagnosis: 47 mm
Nodal status	N+	296 (40%)
	N-	436 (60%)
CHT	Yes: 566 (76.5%)	No: 165 (22.5%)
dian FU	47 months	

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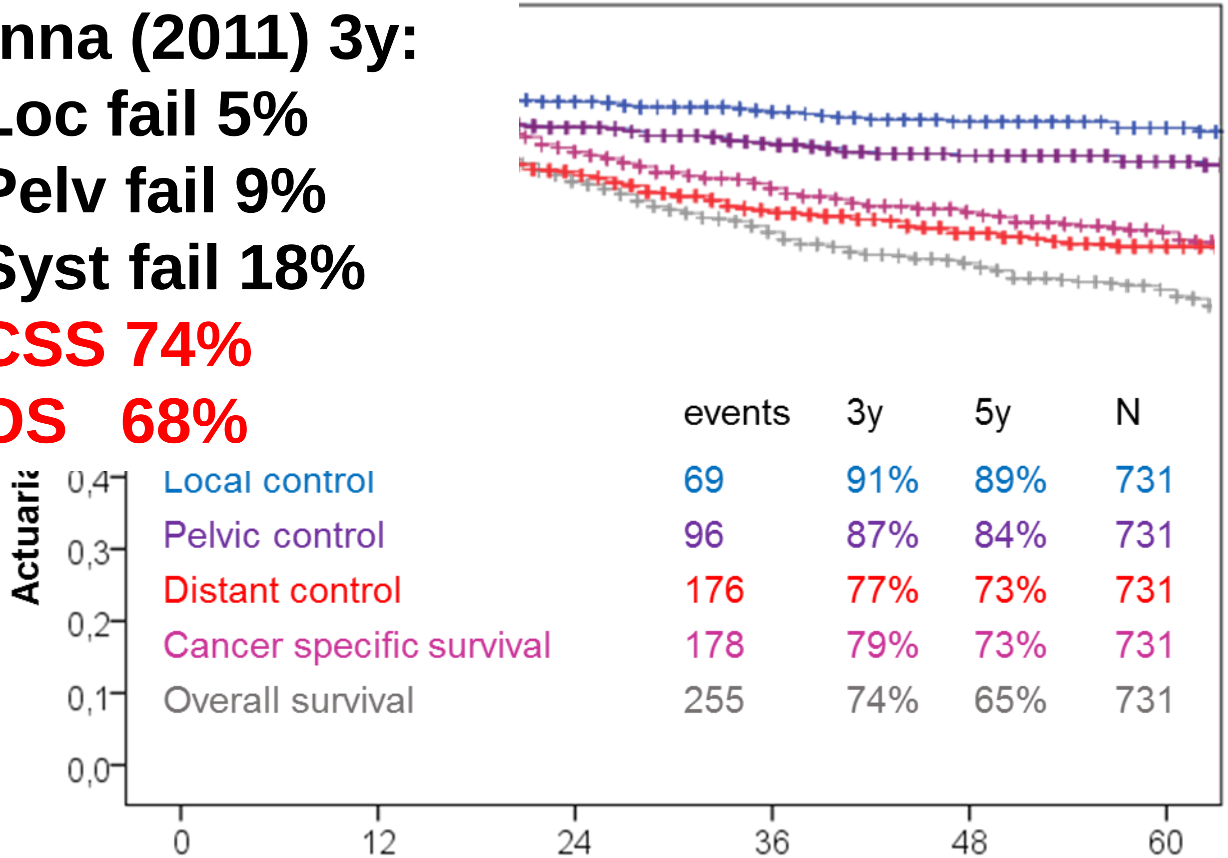
COMPREHENSIVE CANCER CENTER VIENNA

Local, pelvic and distant control, cancer specific and overall survival

Vienna (2011) 3y:

- **Loc fail 5%**
- **Pelv fail 9%**
- **Syst fail 18%**
- **CSS 74%**
- **OS 68%**



	events	3y	5y	N
Local control	69	91%	89%	731
Pelvic control	96	87%	84%	731
Distant control	176	77%	73%	731
Cancer specific survival	178	79%	73%	731
Overall survival	255	74%	65%	731

Vienna: mean 92 Gy HR CTV

LC	731	603	491	384	294	187
PC	731	603	491	384	294	187
DC	731	603	491	384	294	187
CSS	731	651	537	429	332	220
OS	731	651	537	429	332	220

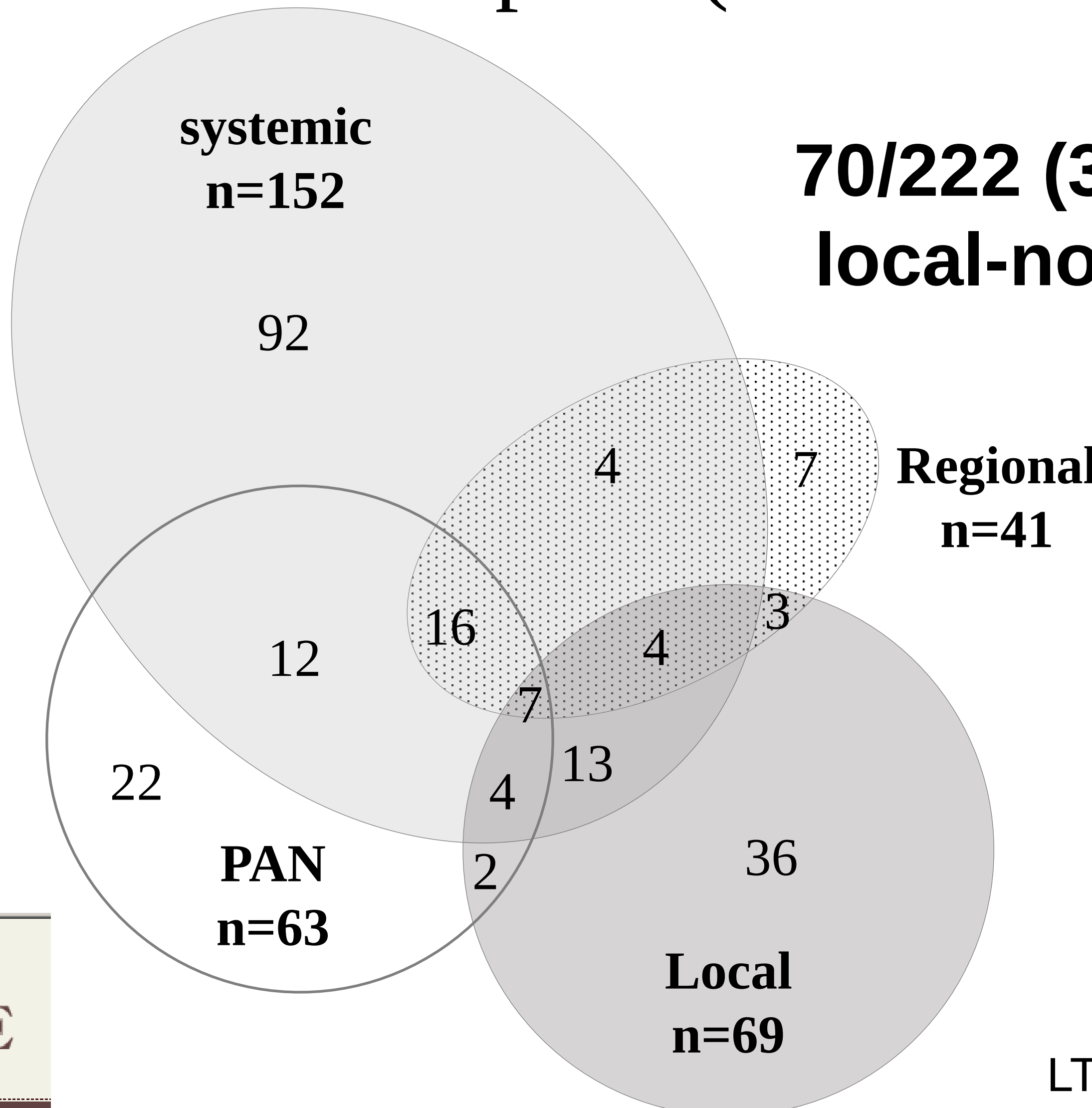
- **731 patients**
- **12 institutions**
- **Loc fail 9-11%**
- **Pelv fail 13-16%**
- **Syst fail 23-27%**
- **CSS 79-73%**
- **OS 74-65%**

Mean D90
In HR CTV
84 Gy

Sturdza et al. 2016

crude number of failures

n=325 events in 222 pats. (out of 731): 30%



70/222 (32%) local-nodal only

RETRO EMBRACE

About Retro-Embrace | Contacts | Login

LT Tan et al.
submitted to R&O

Local control and FIGO stage (RetroEMBRACE)

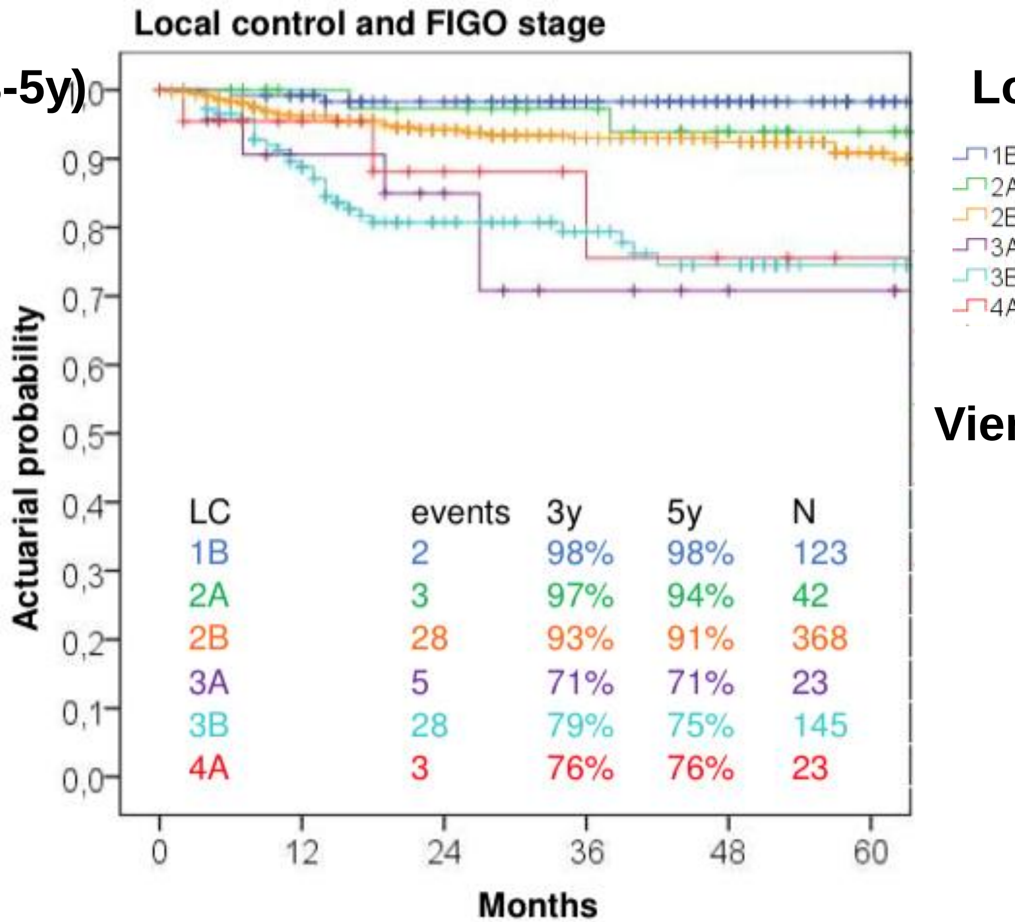
Loc failure (Retro 3-5y)

IB	2%
IIB	7-9%
IIIB	21-25%
IVA	24%

RetroEMBRACE 3y:

IB:	98%*
IIB	93%
IIIB	79%

*2 events in IB2



Loc failure (Vienna 3y

IB	0%
IIB	4%
IIIB	14%
IVA	2/6 (n)

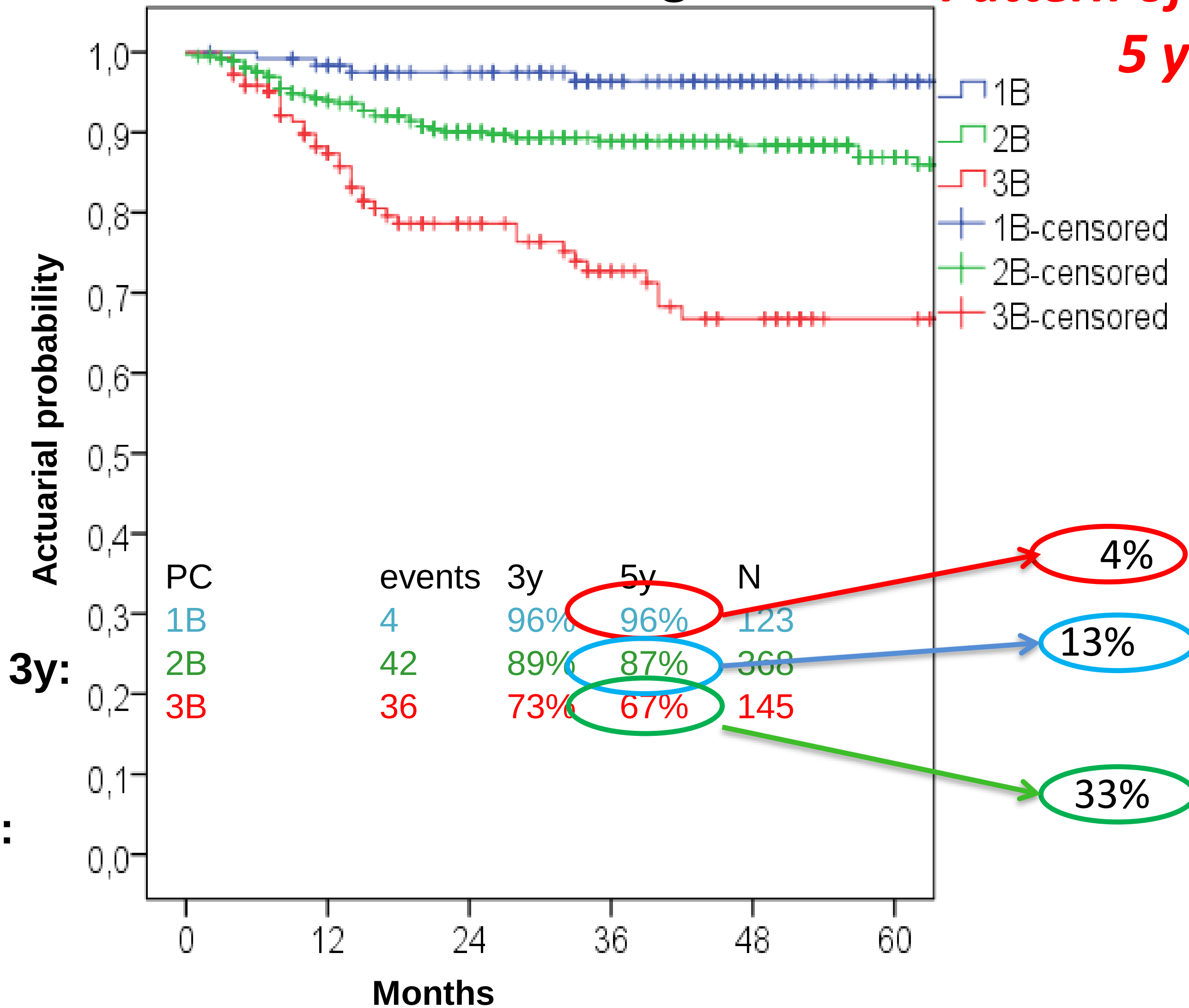
Vienna (2011) 3y:

IB:	100%
IIB	96%
IIIB	86%

Sturdza et al. 2016

Pelvic control and FIGO stage

Pattern of Relapse
5 years



PC	events	3y	5y	N
1B	4	96%	96%	123
2B	42	89%	87%	368
3B	36	73%	67%	145

123	116	100	75	53	30
368	303	256	205	164	107
145	108	72	53	40	26

RetroEMBRACE 3y: overall 87%

Vienna (2011) 3y: overall 91%

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RetroEMBRACE Outcome Sturdza et al. 2016

Universitätsklinik für Strahlentherapie und Strahlenbiologie Wien

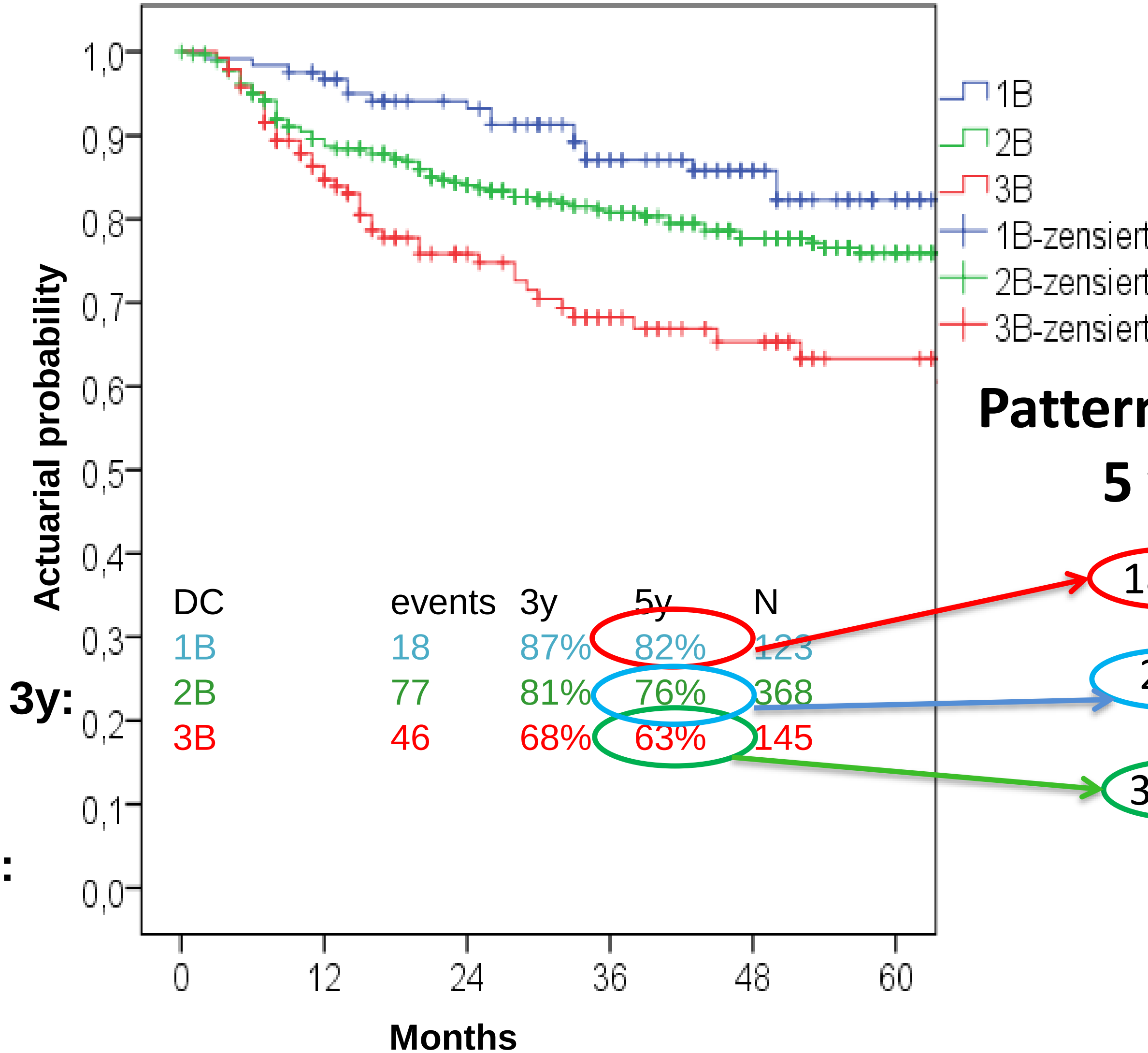
Local control – advanced treatment adaptation including interstitial brachytherapy (RetroEMBRACE)

Width in MRI at diagnosis	Local control at 5 year (%)	
	Limited adaptation	Advanced adaptation
Tumor <**5cm**	95%	94%
Tumor **≥5cm**	77%	86%

The use of advanced adaption including interstitial BT improves local control in large tumors

Fokdal et al. 2016. Fortin et al.to be submitted

Distant control and FIGO stage



123	116	100	75	53	30
368	303	256	205	164	107
145	108	72	53	40	26

Pattern of Relapse 5 years

18%

24%

37%

RetroEMBRACE 3y: overall 77%

Vienna (2011) 3y: overall 82%

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RetroEMBRACE Outcome Sturdza et al. 2015 (unpublished)

Subgroup analysis (distant control)

- 394 consecutive patients from 7 centres treated with RCHT and IGBT

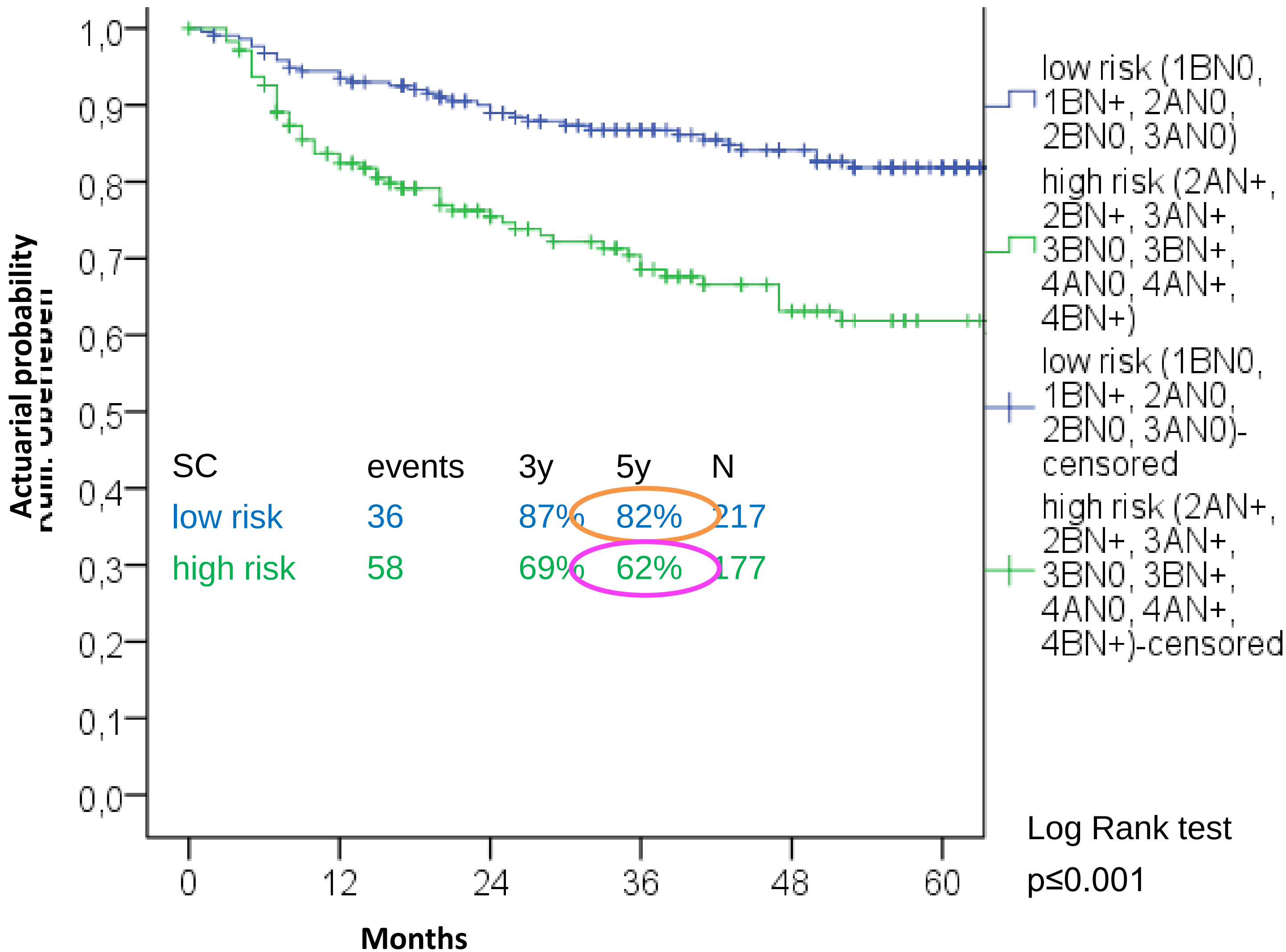
  (5 centers enrolled selected patients)

- Two groups based on univariate analysis

  Low risk: 1B, 2A, 2B, 3A &N0, 1BN+

  High risk: 2A-2B & N+, any 3B-4A

Distant control in consecutive patients treated with radiochemotherapy



SC	events	3y	5y	N
low risk	36	87%	82%	217
high risk	58	69%	62%	177

18%

38%

Log Rank test

p≤0.001

217	199	172	142	115	80
177	134	97	76	54	40

Low risk: 1B, 2A, 2B, 3A &N0,

High risk: 2A-2B&N+, any3B4A

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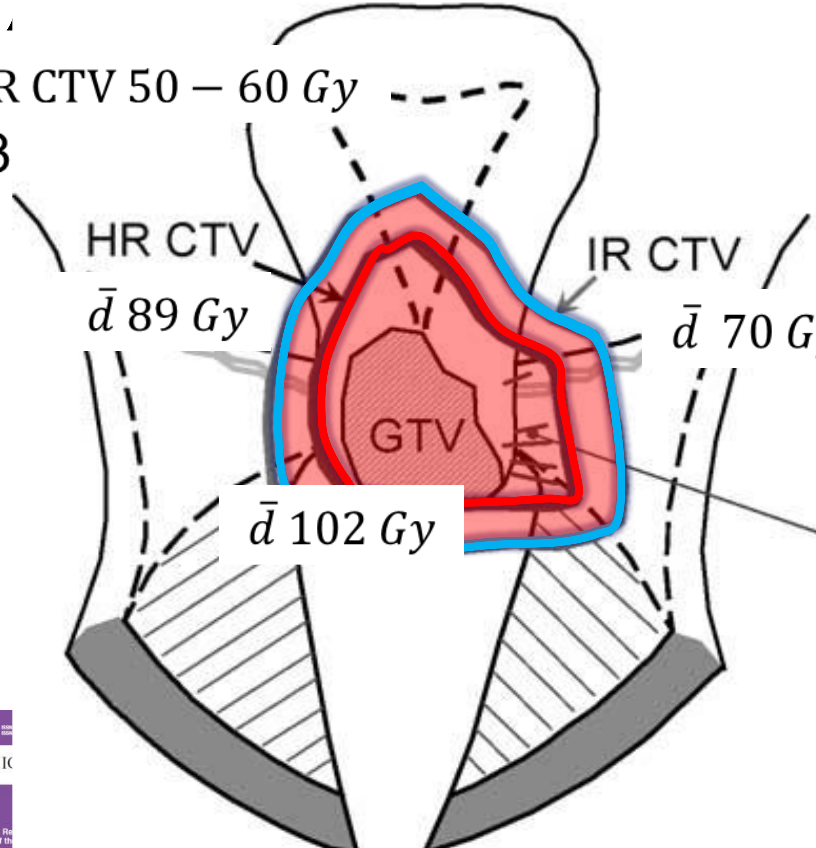
RetroEMBRACE Outcome Sturdza et al. 2015 (unpublished)

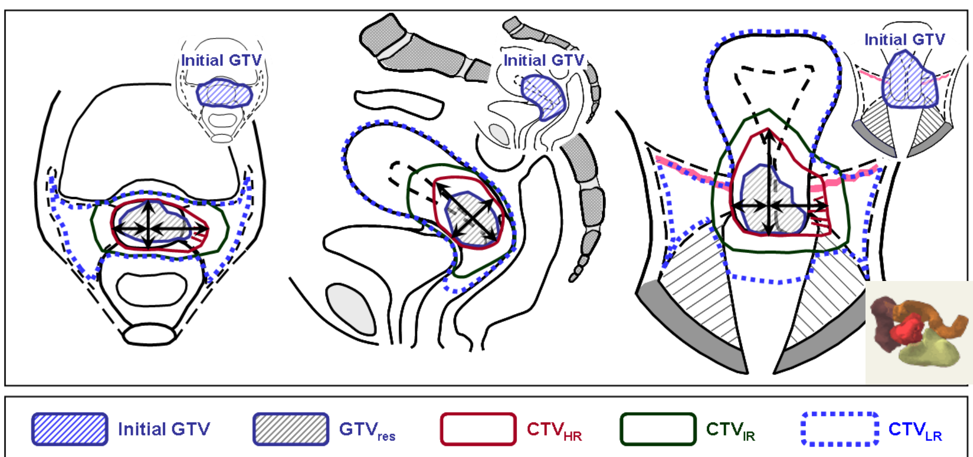
Dose prescription according to risk

large variations in initial/adaptive volumes and doses

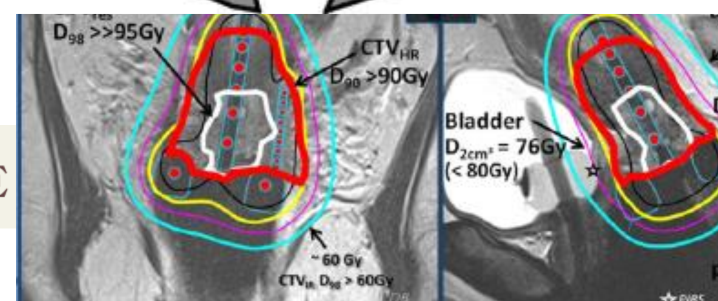
(EMBRACE studies (06/2017)

Initial CTV-T_{LR}	Ø 230 cm^3
Initial GTV-T	Ø 55 cm^3
Adaptive CTV-T_{IR}	Ø 78 cm^3
Adaptive CTV-T_{HR}	Ø 33 cm^3
Residual GTV	Ø 9 cm^3





EMBRACE



Crude failure patterns EMBRACE *
(total: n=1416) median at 2 year follow-up

- 6.5% local (80 out of 1230) (Schmid et al. 2017)
- 8% nodal (86 out of 1077) (Nomden et al. 2017)
- 18% distant (133 out of 753) (Fortin et al. 2015)

*Preliminary data 06/2017

About 50% of failures occur synchronous

Clinical evidence: Overall local outcome

EMBRACE cohort (n=1230)

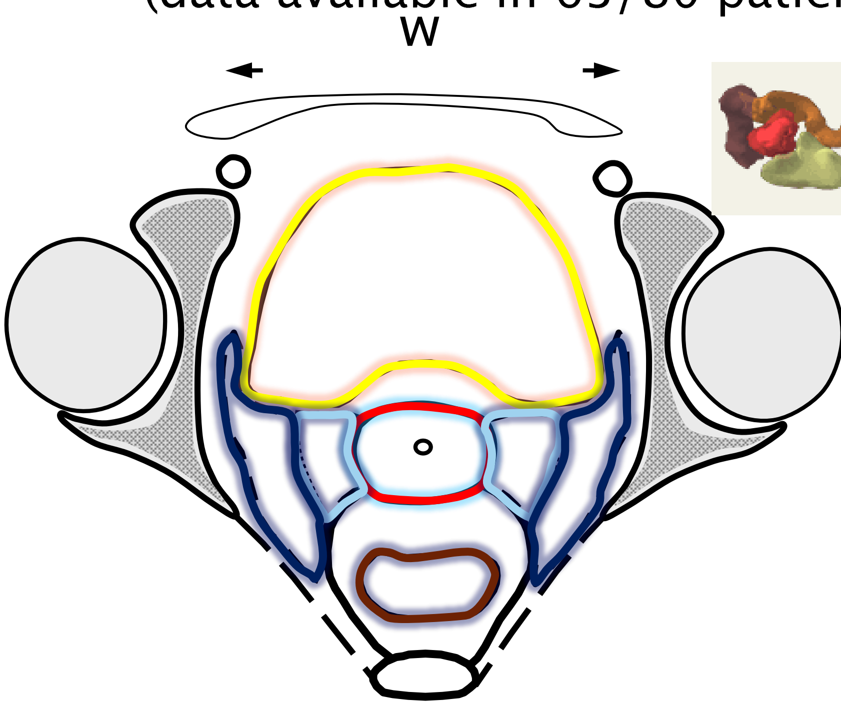
- **24 incomplete remissions (IR)** (98% complete remission rate)
  (72 incomplete remissions (IR) at 3 months, 48 resolved at 6-9 months)
- **56 local recurrences (LR)** (at median 25 months FUP)
  - Median time to local recurrence: 11.5 months
    (86% of local recurrences occured within 24months)
- **80 local failures (IR+LR) (6.5%)**
  - 42 (52%) synchronous nodal or distant failures

M. Schmid et al. ESTRO 2017

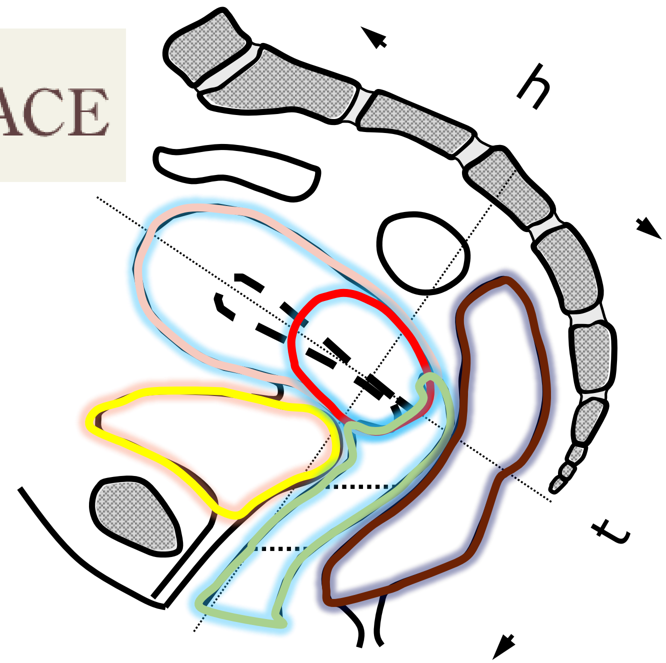
Anatomical location of local failures (n=1230)

108 locations in 63 patients with local failure

(data available in 63/80 patients (79%), multiple locations possible)



EMBRACE



Cervix and uterus: 80% (n=50)

Proximal parametria: 13% (n=8)

Distal parametria / pelvic wall: 29% (n=18)

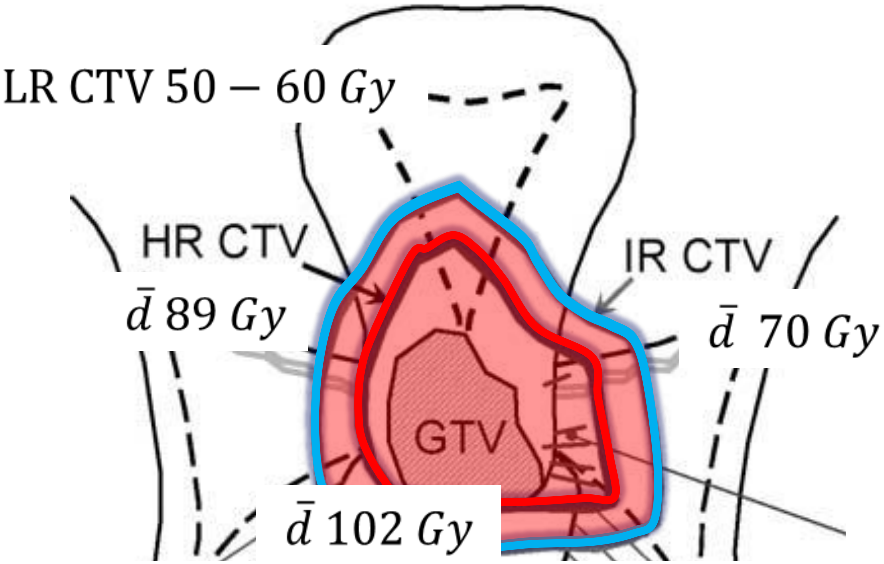
Vagina: 29% (n=18)

Urinary bladder: 19% (n=12)

Rectum: 3% (n=2)

Local failures
in regard to boost brachytherapy target volumes

data available in 53/80 patients (66%)



EMBRACE

Inside HRCTV: 51% (n=27 (+16))

Inside IRCTV: 17% (n=9)

Inside HR & IRCTV: 30% (n=16)

Not related: 2% (n=1)

Failure pattern provides
prospective clinical validation of adaptive target concept
For locally advanced cervix cancer applying BT boost
(one major aim of the EMBRACE study)

Pattern of nodal spread and recurrence
EMBRACE cohort, n=1077

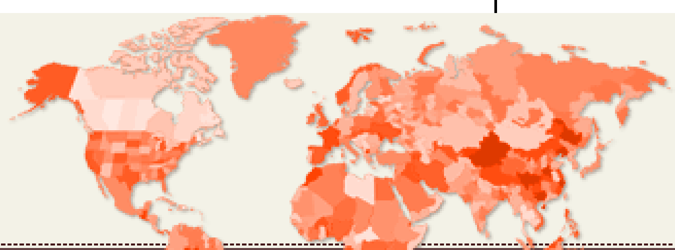
Table 2 Location of nodes at diagnosis and at nodal failure in 1077 patients; multiple nodal sites per patient are possible; crude rates are given

n = 1077 pat.	All = 1077 pat. N+ at diagnosis = 516 (48%)	All = 1077 NF = 86 (8%) pat.	N- = 516 pat. NF = 25* (5%) pat.	N+ = 516 pat. NF = 60* (12%) pat.
Pelvic	512 (48%) (99%)	50 (5%) (58%)	14 (3%) (56%)	35 (7%) (58%)
Comon iliac	146 (14%) (28%)	22 (2%) (26%)	4 (0.8%) (16%)	17 (3%) (28%)
Int/Ext ilac	477 (44%) (92%)	40 (4%) (47%)	10 (2%) (40%)	29 (6%) (48%)
Parametrial	55 (5%) (11%)	3 (0.3%) (3%)	2 (0.4%) (8%)	1 (2%) (2%)
PAO	66 (6%) (13%)	61 (6%) (71%)	16 (3.2%) (64%)	44 (9%) (73%)
Inguinal	18 (2%) (3%)	12 (1.2%) (14%)	3 (0.6%) (12%)	9 (2%) (15%)

N- = no nodes at diagnosis, N+ = nodes at diagnosis, NF = patients with nodal failure

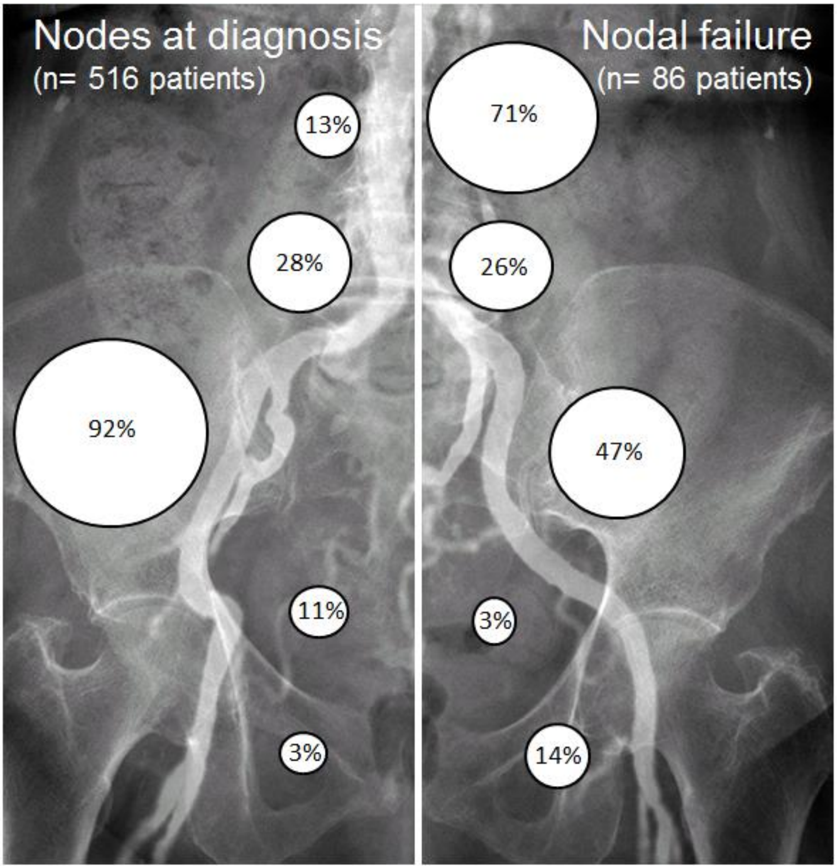
* For one patient with nodal failure no information on nodal status at diagnosis was available

Nomden et al. under submission



Nodal Recurrence and pattern of nodal recurrence EMBRACE and RetroEMBRACE

EMBRACE cohort 1077 pats.:



RetroEMBRACE cohort

296/731 N+ at diagnosis

Nodal Relapse

81/731 (11%)

41 pelvic (39%)
63 paraaortic (61%)

LT Tan submitted R&O

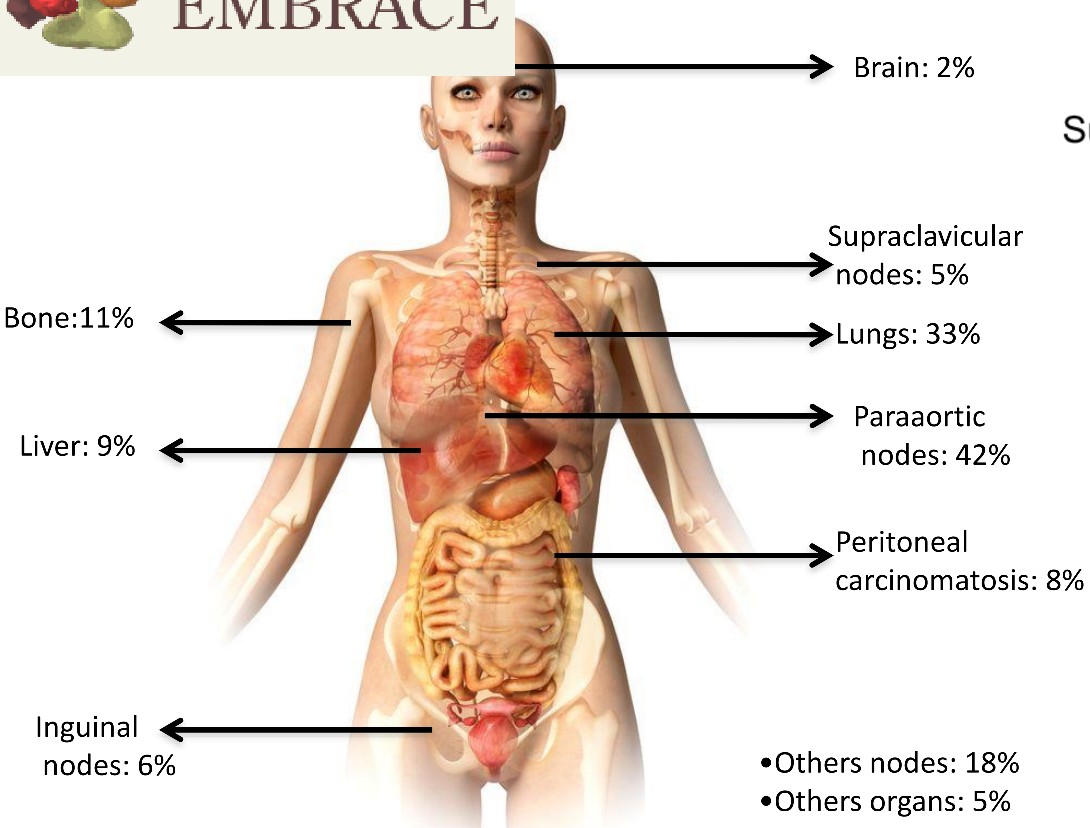
nodal recurrence: overall 86/1077 (8%)

Nomden et al. under submission

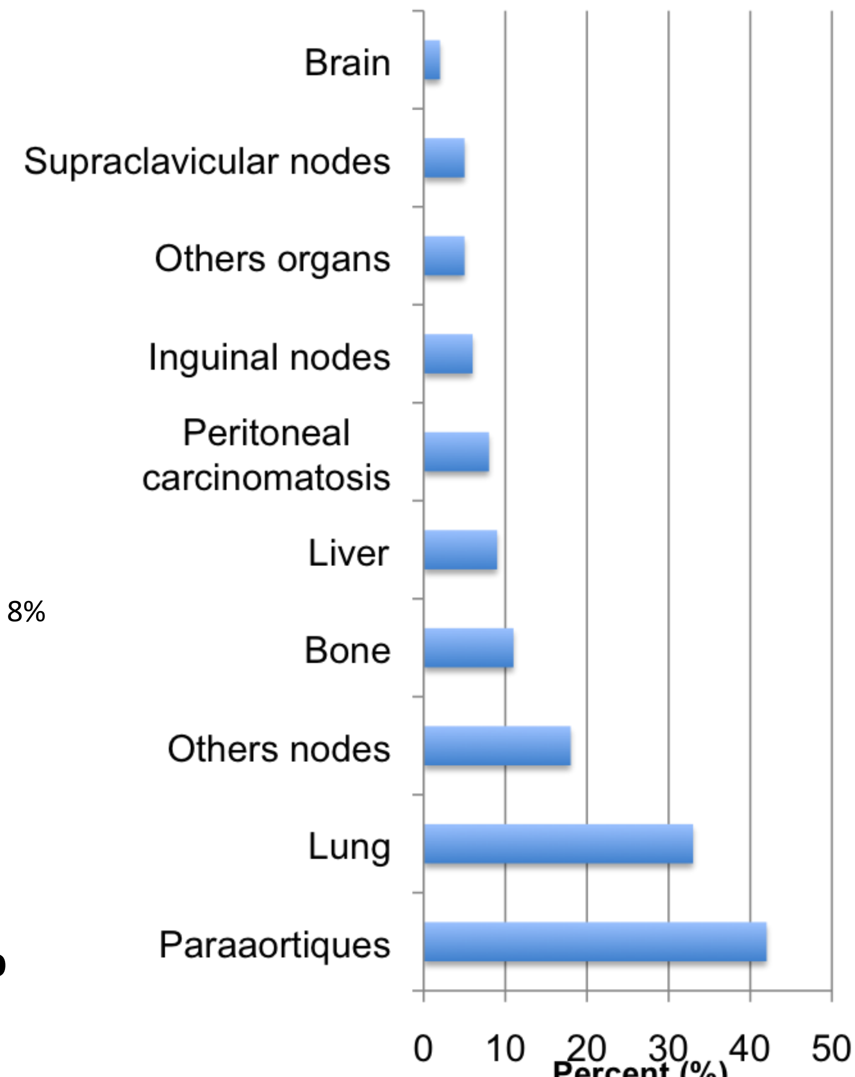
Systemic (distant) recurrence analysis
(EMBRACE data, 133 events in 753 patients)

Systemic recurrences at first event

EMBRACE



- Others nodes: 18%
- Others organs: 5%



Major lymph node component in distant recurrence: LN 64%, organ 57%

Fortin et al. ASTRO 2015

Interpretation of RetroEMBRACE results

(IGABT compared to large population based cohorts using 2D BT)

Pelvic failure (crude)	Concomitant chemo	IB	IIB	IIIB	total
retroEMBRACE (n=731)	77%	4%	11%	25%	**13%**
Perez 1998	0%	12%	21%	41%	
Barillot 1997	0%	13%	24%	49%	**23%**
Improvement		**Δ8-9%**	**Δ10-13%**	**Δ16-24%**	**Δ10%**

Overall Survival Radio-chemo	retroEMBRACE Consecutive 3D/4D IGABT	UK Survey Vale 2010 2D BT	US SEER 2000-2009 2D BT	US NCDBA 2004-2011 2D BT
No of pts	394	471	3246	2571
5y OS	67%	55%	55%	54%
Improvement	**Reference**	**Δ12%**	**Δ12%**	**Δ13%**

BENEFIT FROM CONCOMITANT RADIOCHEMOTHERAPY

AUTHOR	RANDOMISATION ARMS	STAGE	LOCOREGIONAL RECURRENCE	3 YEAR OVERALL SURVIVAL
Keys *et al* *N Engl J Med. 1999*	RT + Cisplatin + HE RT+ HE	Bulky IB	9% 21% RR 0.51 (95% CI)	83% 74% (p=0.008)
Whitney *et al* *J Clin Oncol. 1999*	RT + Cis/5-FU RT + HU	IIB,III, IVA	24.9% 30.4% RR 0.79 (90% CI)	67% 57% (p=0.018)
Rose *et al* *N Engl J Med. 1999*	RT + Cisplatin RT + Cis/5-FU+HU RT + HU	IIB,III, IVA	Not reported	65% 65% 47% (p=0.004)
Morris *et al* *N Engl J Med. 1999*	RT + Cis/5-FU RT (pelvis + paraaortal)	IB-IVA (~70% IB-IIB in each group)	19% 35% RR 0.47 (95% CI)	75% 63% (p=0.004)
Peters *et al* *J Clin Oncol. 2000*	HE + RT + Cis/5-FU HE + RT	IA2,IB, IIA	5.5% 17%	81% 71% (p=0.007)
Pearcey *et al* *J Clin Oncol. 2002*	RT+Cisplatin RT	IB-IVA	Not reported	69% 66% (p=0.42)

Interpretation of RetroEMBRACE results
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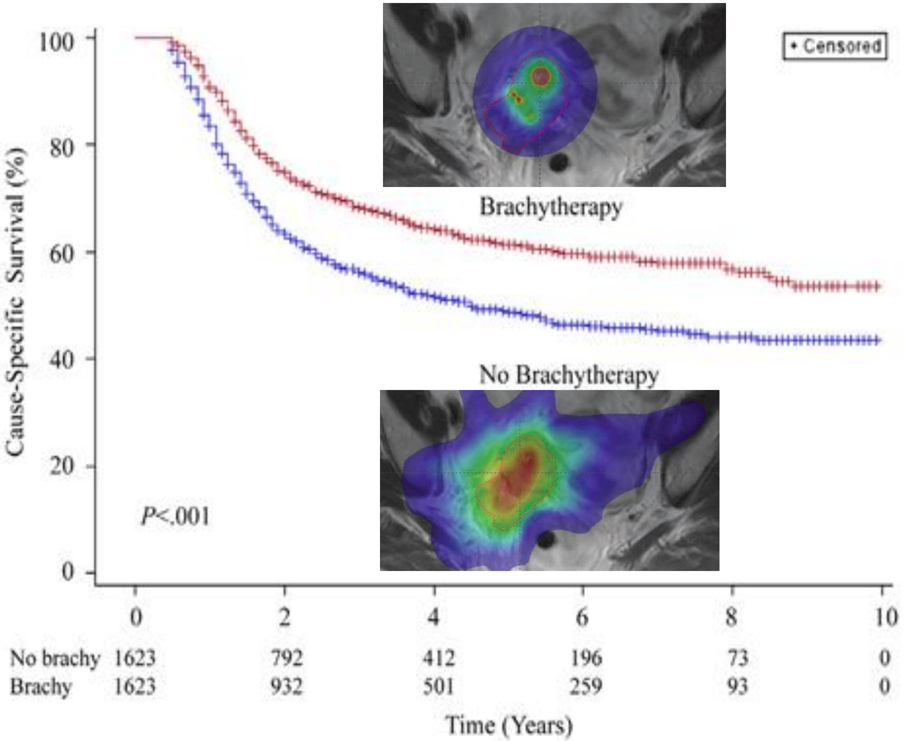
Paradoxon!

- **Advances in brachytherapy are (more) important**
- **Understanding the limitations of EBRT: volume and dose**

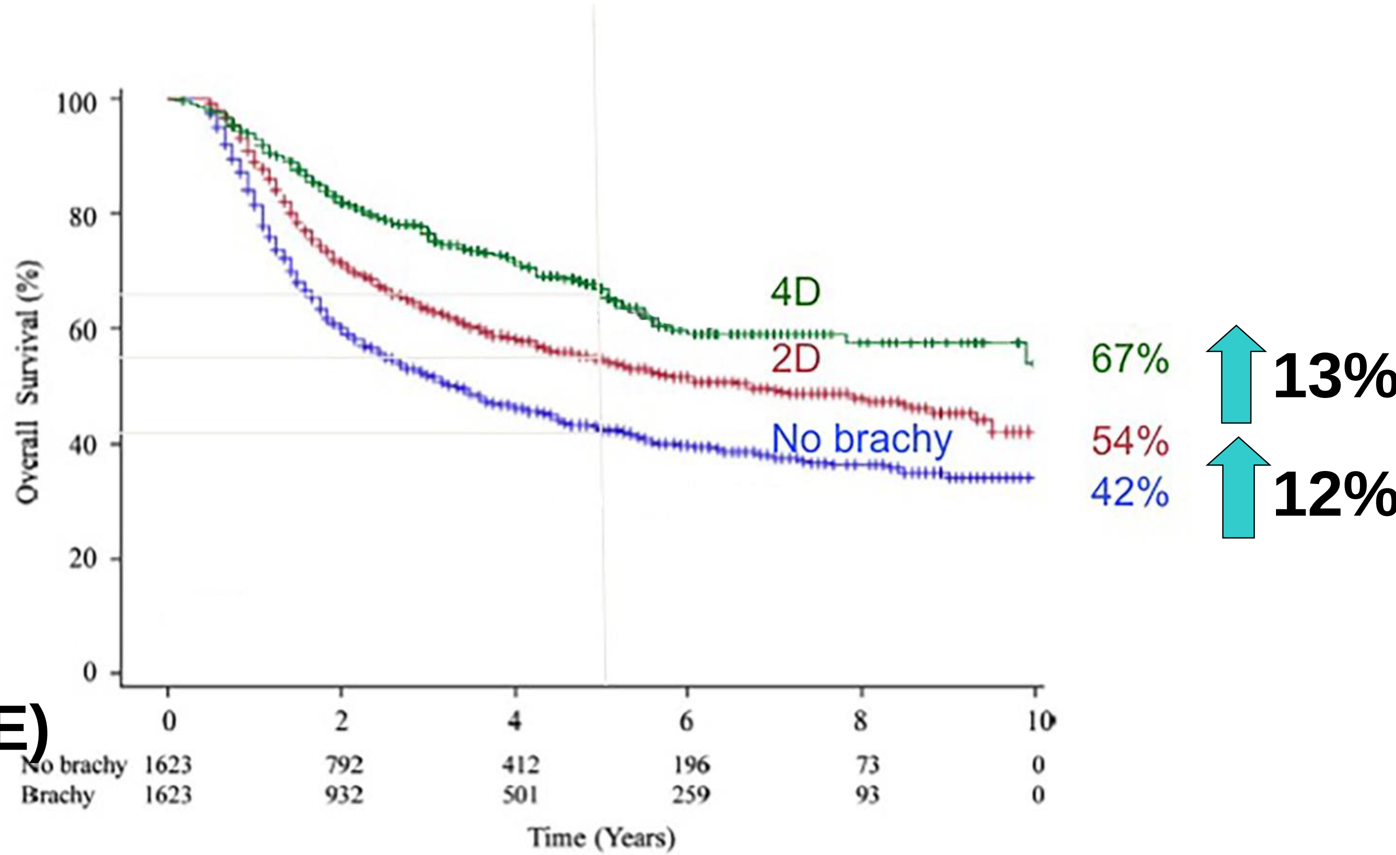


Han et al, IJROBP, 2013

Overall Survival locally advanced cervical cancer: the impact of brachytherapy

Total
25% increase in Overall Survival

from
„no brachy“
(Han)
to
„4D brachy“
(RetroEMBRACE)



Han et al Int J Radiation Oncol Biol Phys 2013;87:111-119
Sturdza et al. Improved local control and survival in LACC thruough Imae guided adaptive brachytherapy, Radiotherapy and On

Next generation of clinical trials
based on IGABT + IGRT as CCRT
- Hypothesis driven -

- Comparative Trials on IGABT vs. 2D (randomized)
- Dose escalation for advanced disease HR CTV (LC, OS)
- Dose de-escalation for limited and favourable advanced disease (good response,…) (Morb/QoL)
- Systematic Introduction of IMRT/IGRT (Morb/QoL
- Para-aortic RT, SIB (Lymphnode) (NC, OS)
- Systematic concomitant radiochemotherapy min. 5 cycl. for subgroups with high risk of distant metastases (OS)
- Testing Dose/Volume constraints for Target and OARs
- Biomarker investigation (Hypoxia, HPV, EGFR)

MEDIZINISCHE UNIVERSITÄT WIEN

Acknowledgements

Gyn GEC ESTRO network
EMBRACE study and research group,
ICRU group (ESTRO)

Sponsored by:

MEDIZINISCHE UNIVERSITÄT WIEN

Facilitated through

ESTRO

Support:

Nucleatron
Improving patient care

VARIAN
medical systems

EMBRACE kick-off meeting Brussels 04/2008

6th Gyn G ... ris 06/2010

Core Group of EMBRACE+ICRU89 2008-2015

4th Annual EMBRACE meeting Vienna 12/2012

Patient preparation and principles of BT Application

Counseling, Anesthesia, Procedure, Removal, Bleeding

Richard Pötter, Vienna

MEDIZINISCHE UNIVERSITÄT WIEN

modified from Umesh Mahantshetty, DMRT, MD, DNBR

Professor, Radiation Oncology

TATA MEMORIAL HOSPITAL, MUMBAI, INDIA

OUTLINE

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

PREPLANNING

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

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 (or more e.g. X-prep)
  - Vaginal Douche
  - Nil by mouth at-least 4-6 hours prior to procedure

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

- medication history (avoid drugs with impact on blood coagulation)
- Appropriate medications for existing co-morbidities
- Thrombosis Prophylaxis, compressions socks, Heparin 40 mg
- Review latest blood investigations (anemia & electrolyte imbalance) and correct 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 (spinal, general, epidural, local)
- ✧ 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 applicator 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.

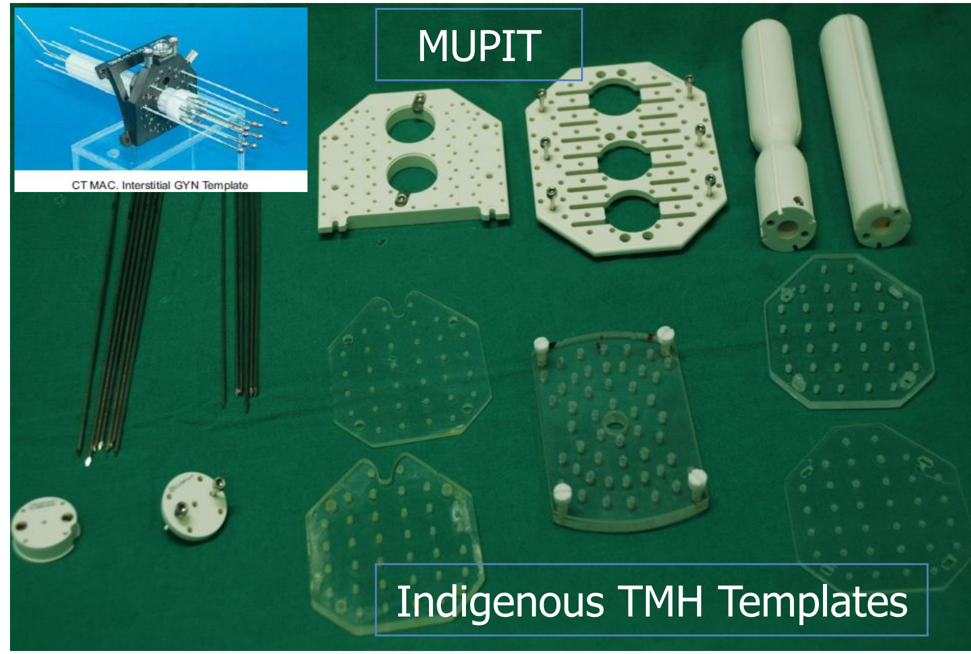
- **Combined Intracavitary and Interstitial (IC + IS)**

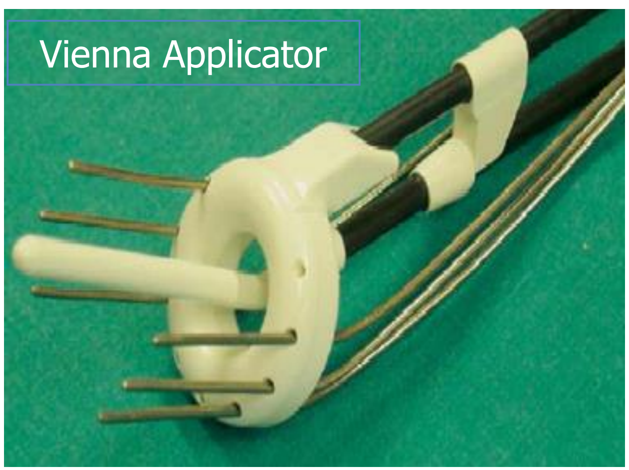
    - Vienna Applicator, Utrecht applicator, etc.

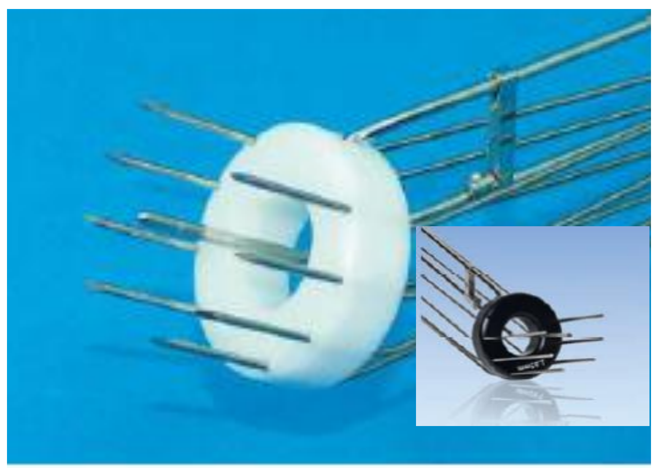
- **Interstitial (IS)**

    - MUPIT, Indigenous Templates with needles / tubes

Brachytherapy Applicators for GYN Cancers







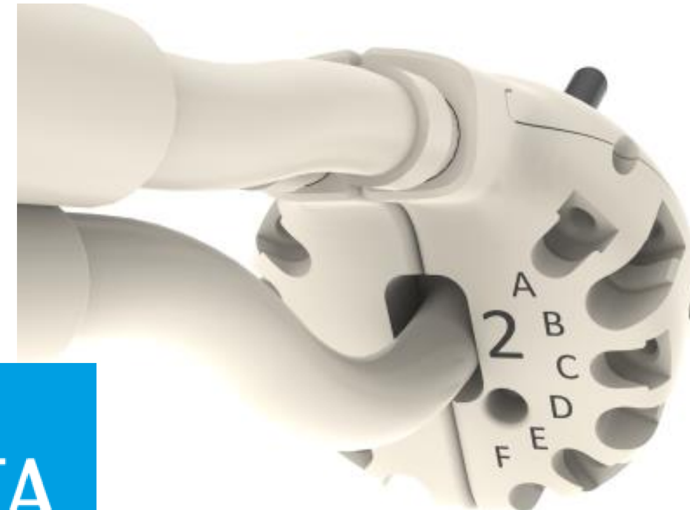
CT Vienna System with Titanium Needles

Tandem - Ring with needles/tubes

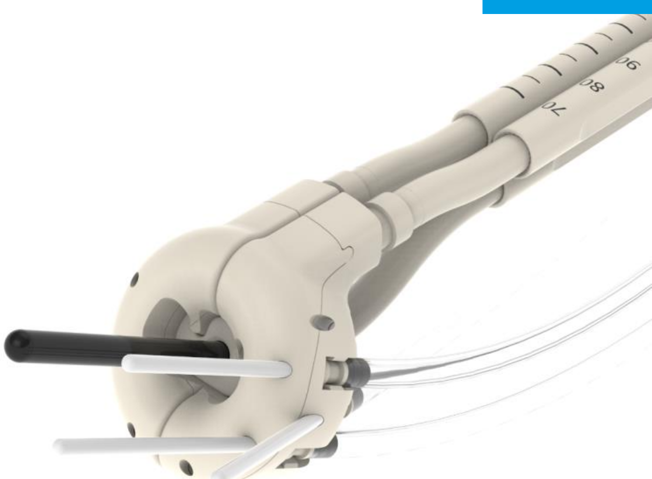
Tandem - Ovoid with tubes

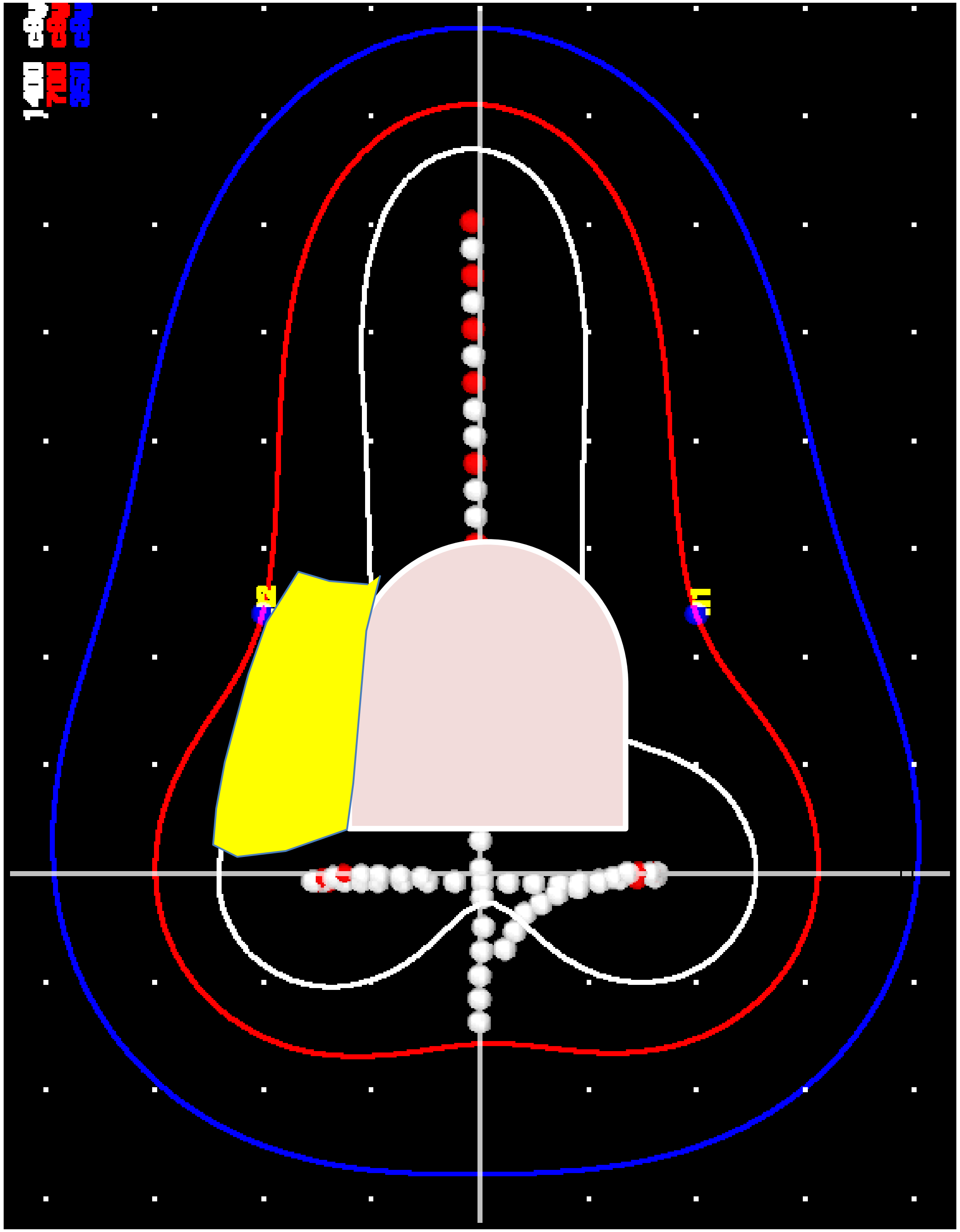
Latest Development in Applicators

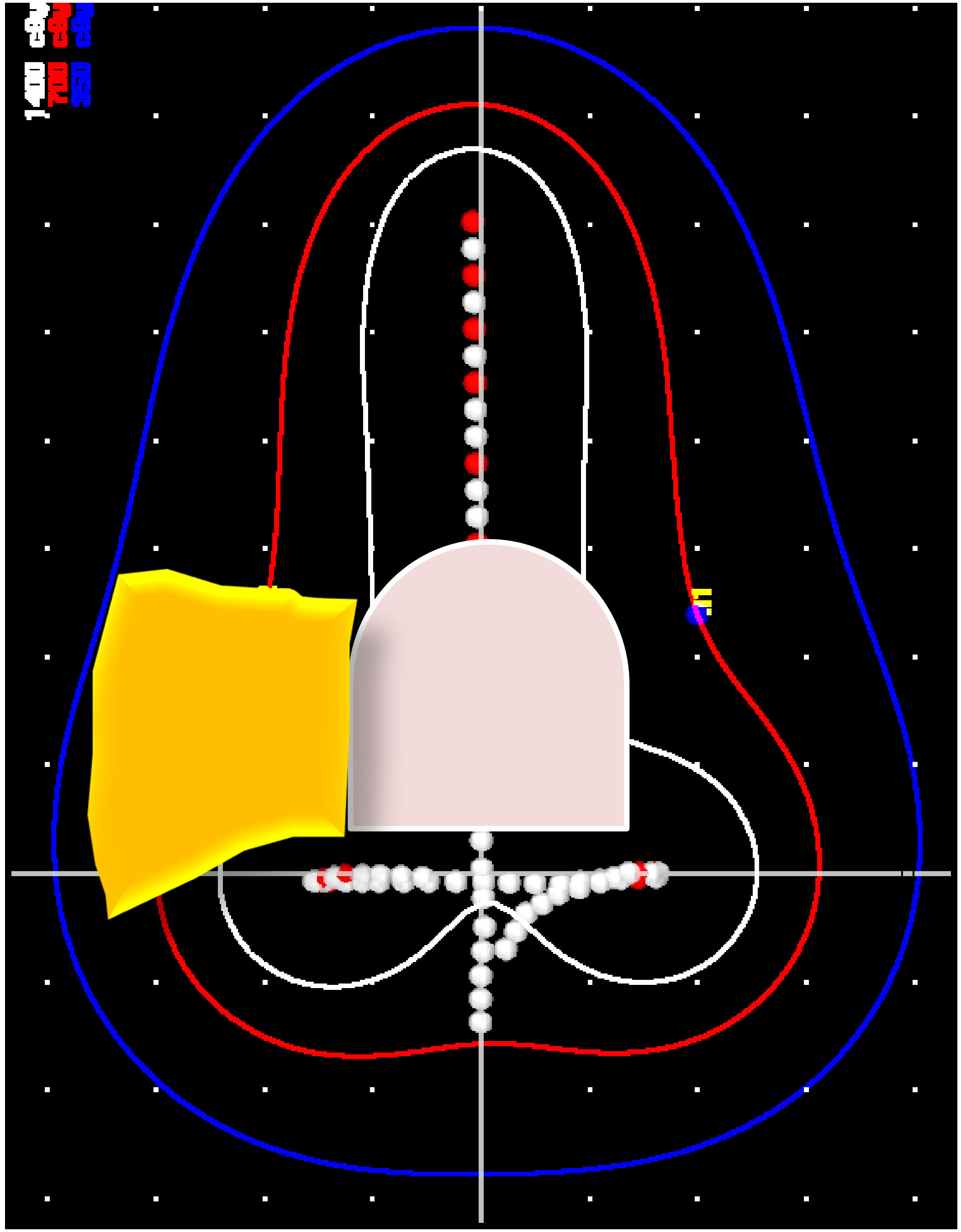
VENEZIA GYN APPLICATOR



ELEKTA




1400
700
350


1400
700
350

Vaginal Packing Is essential!

Gauze has to be visible on MRI/CT
With a clear contrast to the cervix/tumor regions

Quality control through volumetric imaging encouraged!

VIDEO PRESENTATION
OF
BT PROCEDURE

Umesh Mahantshetty,
Tata Memorial Hospital

Treatment delivery & Care in the Ward

- 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 major patient movements (applicator displacement)
- Medications, (Antibiotics, anti-inflammatory as appropriate) , Analgesia (epidural)
- Intake – Output charting,
- Regular monitoring of Vital parameters

REMOVAL OF THE APPLICATOR: under sedation/anaesthesia in operation thea

Intracavitary Alone:

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

Management of acute bleeding after removal

Do not panic!!!

- Removal of applicator parts:
  look at the needle / tube tips when removing,
  e.g. with speculum support
- Bleeding……
  clean the vagina and identify the location of the bleeding
  Differentiate between venous and arterial bleeding!!!
- Arterial bleeding: secure the IV access and start IV fluids
- Nurse/anasthesiologist : TO monitor the vitals
- Focussed compression with your pointing figure
  on the spot where the bleeding comes from, against the pelvis (bone).
  Maintain the compression for at least 7- 10 minutes
- To perform CT pelvis after patient is stable to assess pelvic collection
- To monitor Hemoglobin directly after the procedure and after 3 hours

"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?

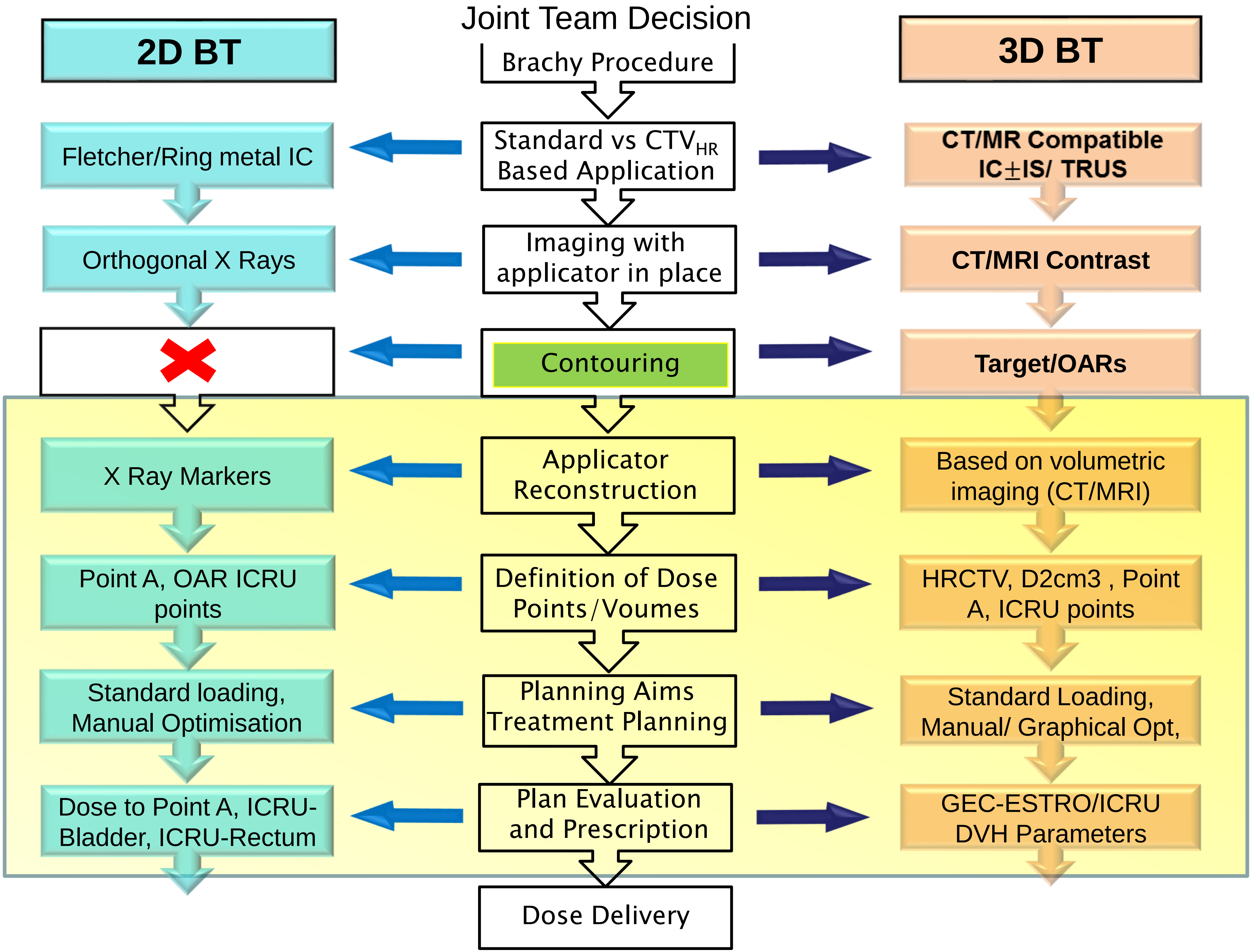
Work hard to Strengthen your skills – technology will follow you

Umesh Mahantshetty

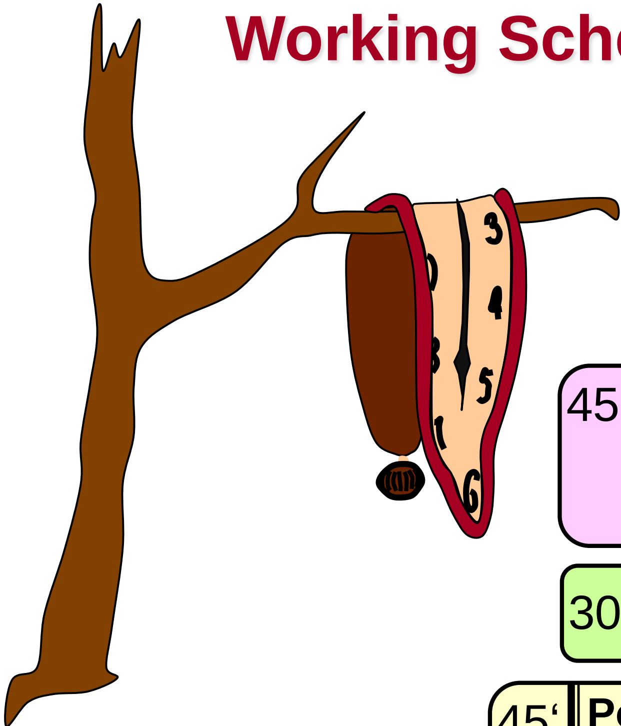
ESTRO Teaching Course on
Image-guided radiotherapy & Chemotherapy in Gynaecological Cancer
- with a special focus on adaptive BT-

Tips and Tricks

Richard, Daniel, Umesh, Ina


2D BT
Joint Team Decision
Brachy Procedure
3D BT
Fletcher/Ring metal IC
Standard vs CTV_{HR} Based Application
CT/MR Compatible IC±IS/ TRUS
Orthogonal X Rays
Imaging with applicator in place
CT/MRI Contrast
Contouring
Target/OARs
X Ray Markers
Applicator Reconstruction
Based on volumetric imaging (CT/MRI)
Point A, OAR ICRU points
Definition of Dose Points/Voumes
HRCTV, D2cm3 , Point A, ICRU points
Standard loading, Manual Optimisation
Planning Aims Treatment Planning
Standard Loading, Manual/ Graphical Opt,
Dose to Point A, ICRU-Bladder, ICRU-Rectum
Plan Evaluation and Prescription
GEC-ESTRO/ICRU DVH Parameters
Dose Delivery

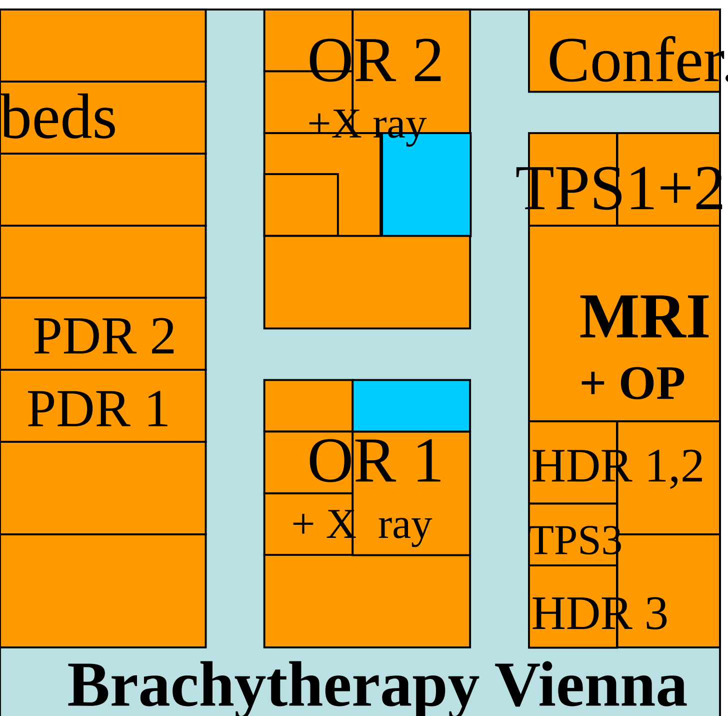
Working Schedule Brachytherapy of Cervix Cancer



15‘	**Preparation**	
	Patient	Surgical-nurse /Physician
	med.tech. Documents	RTT
	DVH pre-planning	Physician and Physicist
45‘	**Anaesthesia**	
	Spinal/Epidural or General	Anaesthetist / Anaesthesia-nurse
30‘	**Application IC±IS (TRUS)**	Physician / surg.-nurse/RTT
45‘	**Post Intervention Imaging**	
	MR / CT	RTT (diagnostic)
	supervision + discussion	Physician and Physicist
30‘	**Contouring**	
	Organs at Risk	RTT / Physician
	Target Volume	Physician
45‘	**Treatment Planning**	
	Reconstruction / Constraints	RTT / Physicist
	Discussion and Validation	Physicist and Physician
15‘	**Radiation Treatment**	RTT

Multidisciplinary Team approach

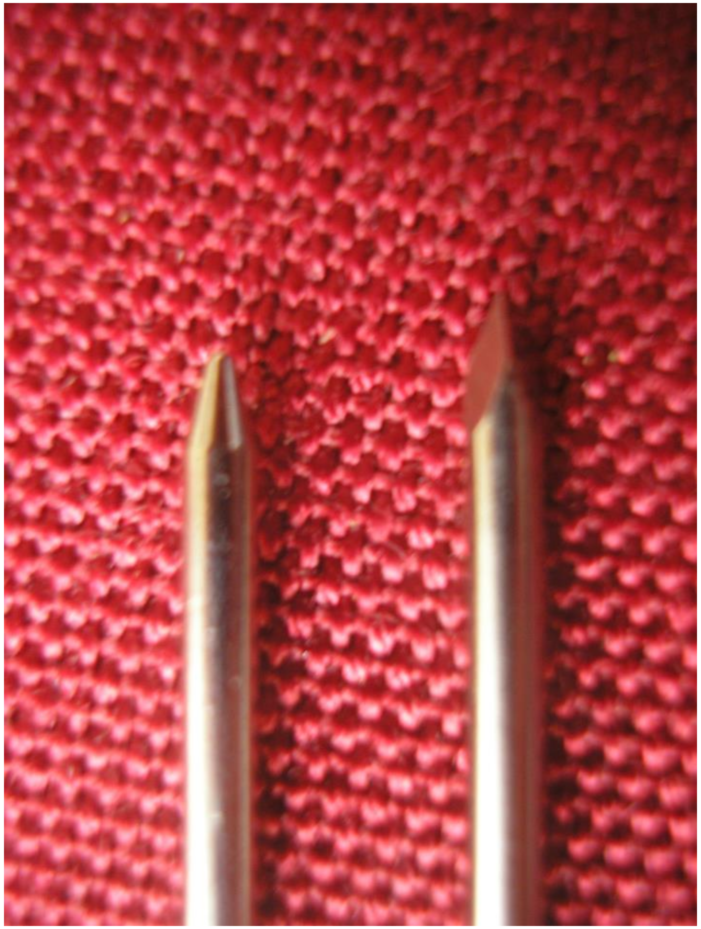
Total Time 3h 45min



Costs for open MRI: ~500.000 €

PRE-REQUISITES

- Check list
- Dummy run
- Workflow and various processes
- Applicators
- Treatment planning principles
- Analgesics
- Removal of application
- Manage the bleeding after removal
- Do not use sharp needles
- Optimization tools
- Learning Curve



Preconditions - Management

- *Peri-operative Management (bowel preparation, measurements against thrombosis and infection, iv. hydration)*
- *Pain management - anaesthesia (spinal / epidural / general)*
- *Sectional imaging (CT / MRI)*

  -at diagnosis and before brachytherapy (alternative 1)
  -at diagnosis and at first brachytherapy (alternative 2)
  -at diagnosis and at every brachytherapy (alternative 3)
- *Equipment (appropriate set of applicators)*
- *Learning curve*

TMH - AKH Vienna Collaboration: 2008 – 2009

Bilateral Exchange Program

Teaching Courses!

Hands on

Workshops!

Cadeveric

workshops!

COMMITMENT!

BE OPTIMISTIC!

HURDLES

TRANSITION FROM 2D TO 3D

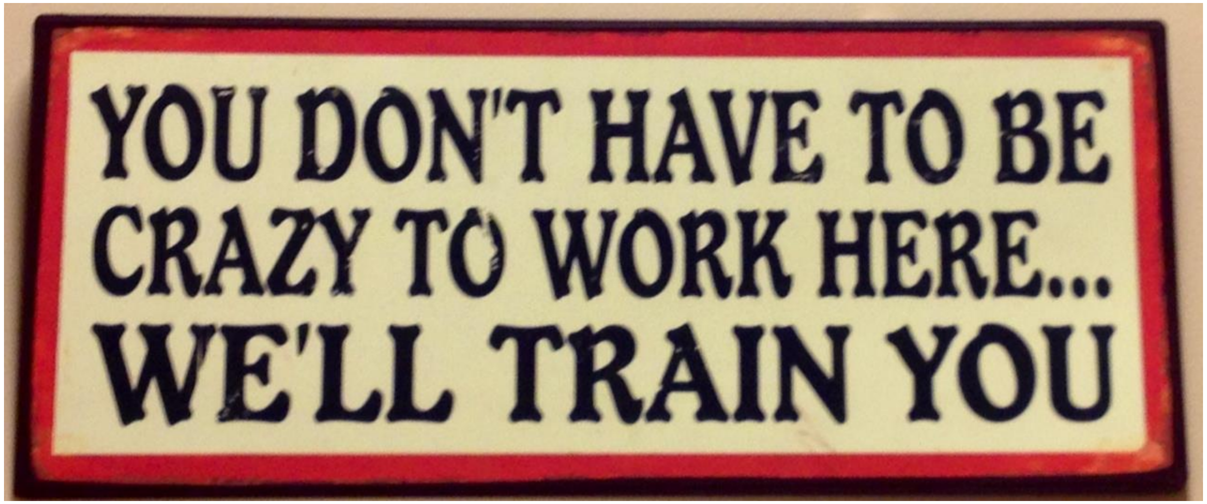
SECRET TO A SUCCESSFUL JOURNEY!

- 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!!



Communication, Co-ordination and Leadership

Co-ordination with Radiologist , Anesthetist, Physicist,Technologist and others

Discussion

Interaction

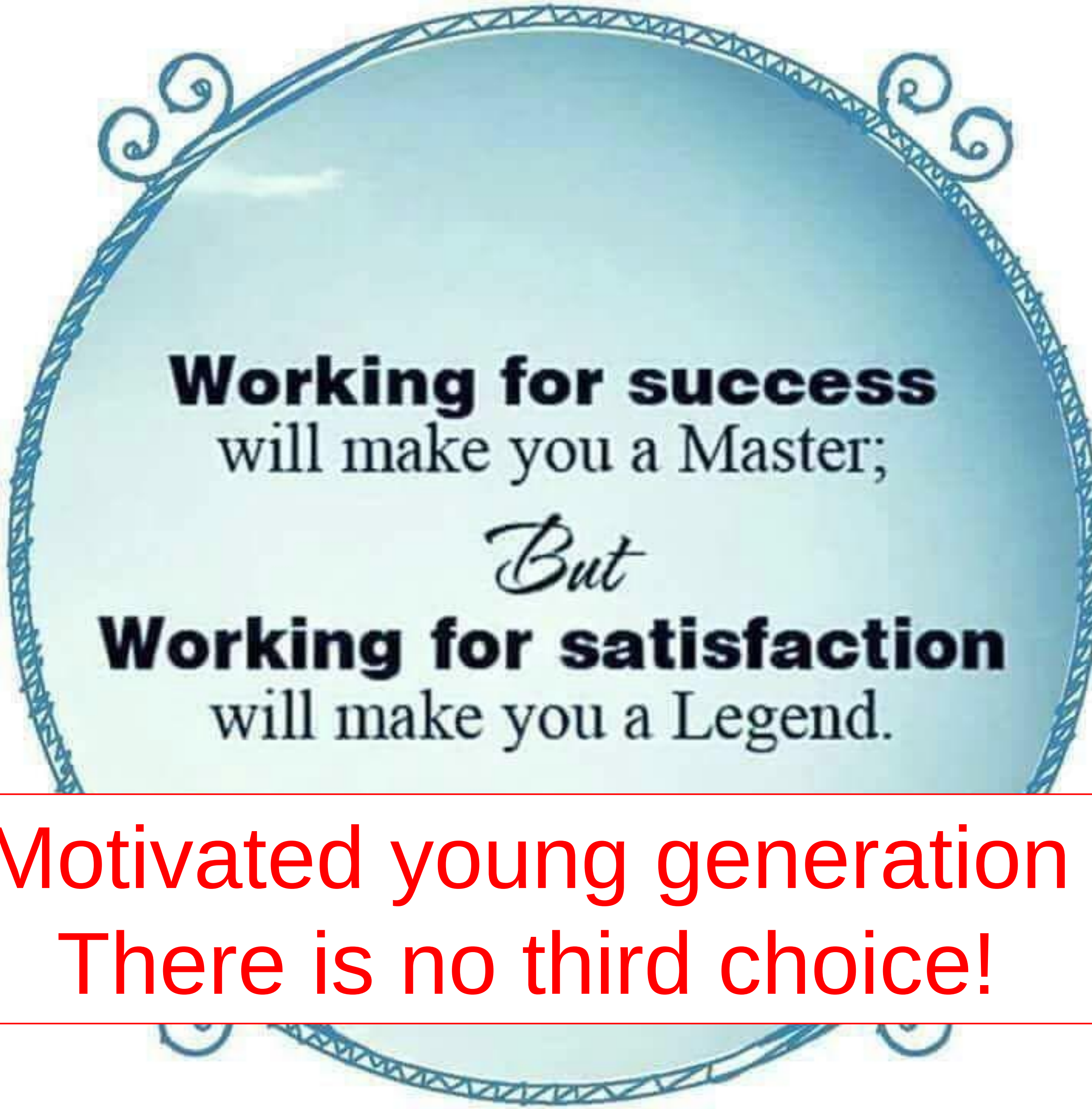
Teaching

PARTY!

Merci - Thank you

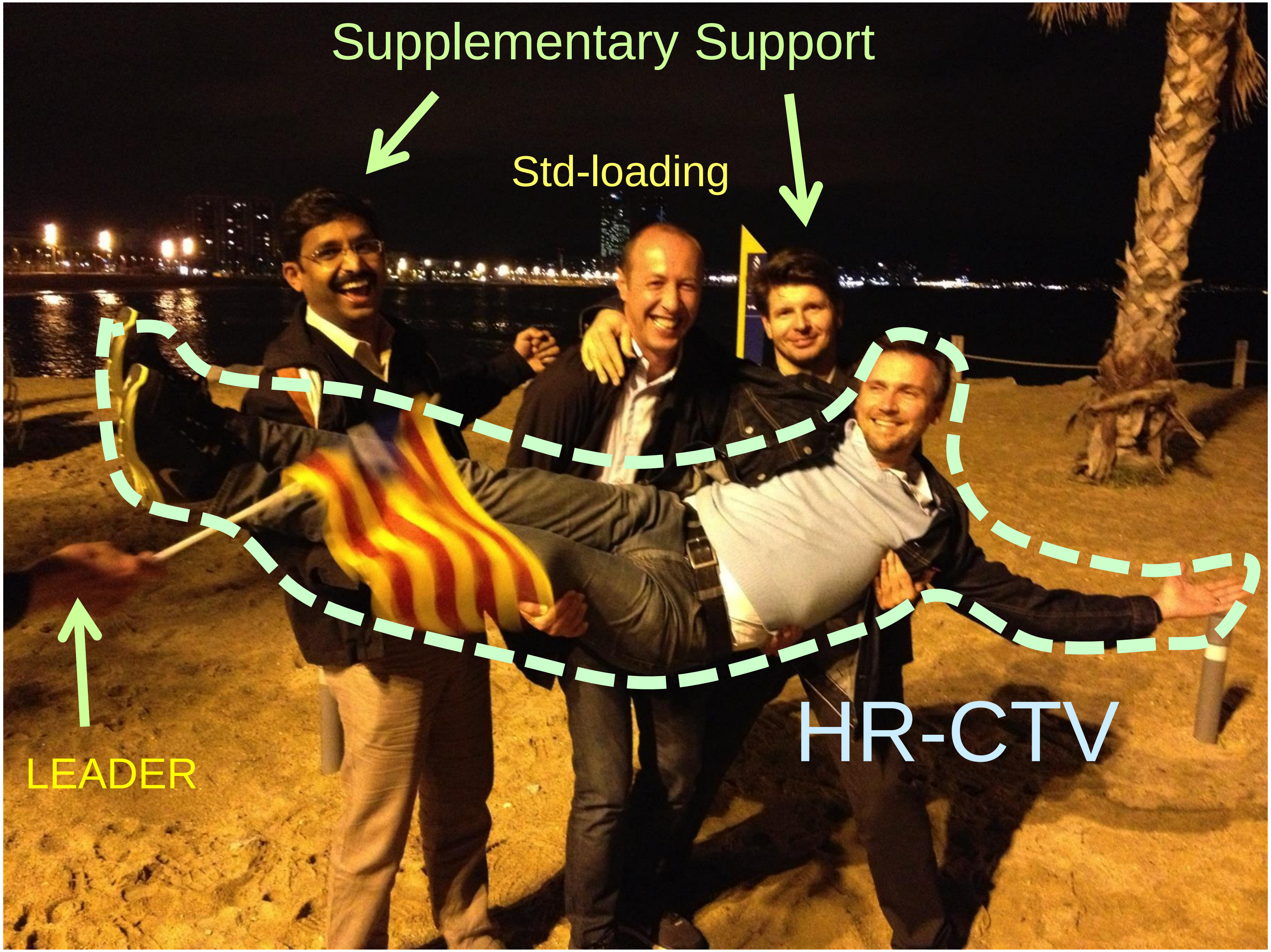
Committed hard working faculty!
Sleeping, tired and freeeeeezing faculty

17th Edition of TC, Toronto 2016



Motivated young generation
There is no third choice!

Team work at TC Barcelona 2013



With permission

GEC ESTRO gyn network

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

Prague 2017

Richard Pötter
Kari Tanderup

ESTRO committee structure

ESTRO
European SocieTy for
RADIOTHERAPY
& ONCOLOGY

Contact | Bec

HOME **ABOUT US** MEMBERS EVENTS SCHOOL CAREERS

About us > Governance / organisation > Scientific Council > Committees

MISSION & VALUES

GOVERNANCE / ORGANISATION

- **General Assembly**
- **Board**
- **Policies**
- **Executive Council**
- **Education Council**
- **Stakeholders' Council**
- **Scientific Council**
  - **Committees**
  - **Task Forces**
- **Nominating Council**
- **Committees activities**

COMMITTEES

The Board of ESTRO creates and determines the mission of standing and ad-hoc committees as required to conduct the business of the Society. The committees report to the Council to which their purpose is linked.

Current standing committees reporting to the Scientific Council:

- Advisory Committee on Radiation Oncology Practice - ACROP
- Clinical Committee
- Education & Training Committee
- GEC-ESTRO Brachytherapy Committee
- Physics Committee
- Radiobiology Committee
- RTT Committee
- Young ESTRO Committee

GEC ESTRO working groups

Contact | Becor

HOME ABOUT US MEMBERS EVENTS SCHOOL CAREERS

About us > Governance / organisation > Committees activities > GEC-ESTRO Brachytherapy Committee

MISSION & VALUES

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- **Executive Council**
- **Education Council**
- **Stakeholders' Council**
- **Scientific Council**
- **Nominating Council**
- **Committees activities**

HISTORY

AWARDS

HERO

EU PROJECTS

NATIONAL SOCIETIES

GEC-ESTRO BRACHYTHERAPY COMMITTEE

Over the years, GEC-ESTRO has substantially increased its work, initiating new activities such as organ-related working groups, an executive committee, teaching courses and publications and it is now an integral part of ESTRO. Further information on these activities can be found here.

Working groups

There are six brachytherapy working groups. Please click on the links below or on the right hand side of this page for further information about the activities of the group.

GEC-ESTRO Breast - Chair: Vratislav Strnad
GEC-ESTRO Head and Neck - Chair: György Kovacs
GEC-ESTRO Urology - Chair: Peter Hoskin
GEC-ESTRO Gynaecology - Chair: Kari Tanderup
GEC-ESTRO BRAPHYQS - Chair: Frank-André Sieber
GEC-ESTRO Anal - Chair: Arthur Sun Myint

Brachytherapy publications

GEC ESTRO Handbook of Brachytherapy

The GEC ESTRO Handbook of Brachytherapy is aimed at clinicians, physicists and radiotherapy technologists worldwide, this textbook covers the basics of brachytherapy, including the physics and radiobiology and also describes in detail all aspects of clinical practice.

First published in 2002, this valuable handbook is currently under review. The new version of the GEC ESTRO Handbook of brachytherapy will be included in DOVE, the current version of the book can be found here.

Guidelines and recommendations

Brachytherapy guidelines and recommedations issued by ESTRO and other organisations can be found through the search portal. These comprehensive books present a full review of the state of the art of brachytherapy and clinical radiobiology and are widely regarded as essential reading for all those involved in the delivery of radiation oncology therapies.

GEC ESTRO gyn working group and network

Working group and network chairs:
2000-2005 (Working group): Christine Haie-Meder

2005-2007: Richard Pötter and Christian Kirisits

2007-ongoing: Kari Tanderup and Richard Pötter

GEC ESTRO gyn network core institutions:

Participation and contact:
The GEC ESTRO gyn network is an open network, and we welcome all colleagues who have specific interest in gyneacological brachytherapy. Please email Kari Tanderup (karitand@rm.dk) if you are interested in joining the network.

Past meetings and workshops
Ressources:

- Reporting spreadsheet from Vienna (HDR) and Aarhus (PDR)
- www.EMBRACESTUDY.dk
- ICRU report 89 (www.ICRU.org; **http://jicru.oxfordjournals.org**)

Selection of publications from the Gyn GEC ESTRO network and EMBRACE

GEC ESTRO workshop

5TH GEC-ESTRO WORKSHOP

30 November-01 December, 2017
Rome, Italy

Venue

Faculty of Medicine and Surgery "A. Gemelli"
Centro Congressi Europa (Conference Center)
Largo Francesco Vito no. 1
00168 Rome
Italy

"The Strength of Brachytherapy"

In November 2016 the GEC-ESTRO Workshop was successfully held for the fourth time in Poznań, Poland. Planned by the GEC-ESTRO Committee and organised by the ESTRO Office, this event has become a hallmark platform for networking with the seven GEC-ESTRO working groups:

GYN network meeting:

- November 30, 2017
- Sign-up: Kari Tanderup

GEC ESTRO gyn network
Step by step process - over the last 20 years...

- **Pioneering experiences: from 1998**
- **Recom I: Target concepts (RO 2005)**
- **Recom II: Reporting (RO 2006)**
- **Recom III: Applicator reconstruction (RO 2010)**
- **Recom IV: Requirements for imaging (RO 2012)**
- **ICRU report 89 (2016)**
- **Uncertainties in contouring, treatment planning, treatment delivery: 15 papers (RO vol 107, 2015)**
- **Retrospective and prospective multicenter clinical studies (2008→)**
- **Clinical outcome of IGABT (RO vol 120, 2016)**

- **ESTRO teaching course since 2004 (>1500 participants)**
- **Annual hands-on workshops (education of >100 institutions)**
- **Web-based contouring teaching**

Gyn GEC ESTRO NETWORK

chair Kari Tanderup, AUH, co-chair Richard Pötter, MUW

Aarhus | Cambridge | Leeds | Leiden | Leuven | Ljubljana | Milwaukee | Mount Vernon | Mumbai | Oslo | Paris IGR | Utrecht | Vienna

ESTRO

N E T W O R K

Contouring of CTV, GTV, OAR WP1	Applicator reconstruction WP2	Treatment planning WP3	Applicator development WP4	MR imaging WP5

W O R K P A C K A G E S

EMBRACE Study (since 2008)

supported by Nucletron/Varian/Bebig

A C T I V I T I E S

- 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 2011→

PUBLICATIONS ON:

- CONTOURING
- DOSE REPORTING
- MR IMAGING
- INTER-OBSERVER VARIATIONS
- APPLICATOR RECONSTRUCTION
- TREATMENT PLANNING
- UNCERTAINTIES

Current task groups

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)

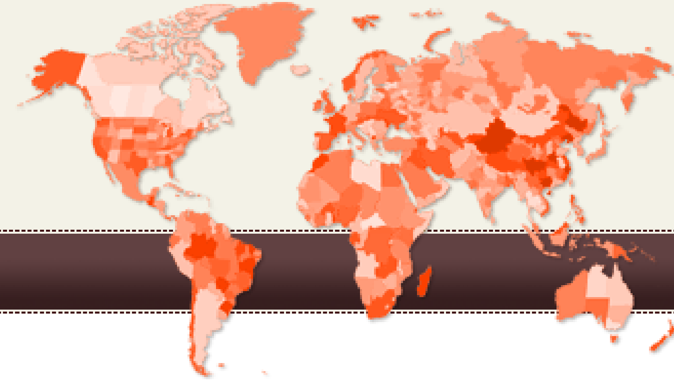
Task group on vaginal brachytherapy (coordinator Remi Nout)

Task group on image registration (coordinators Jamema Swamidas, Christian Kirisits, Kari Tanderup)

EMBRACE

{ 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**

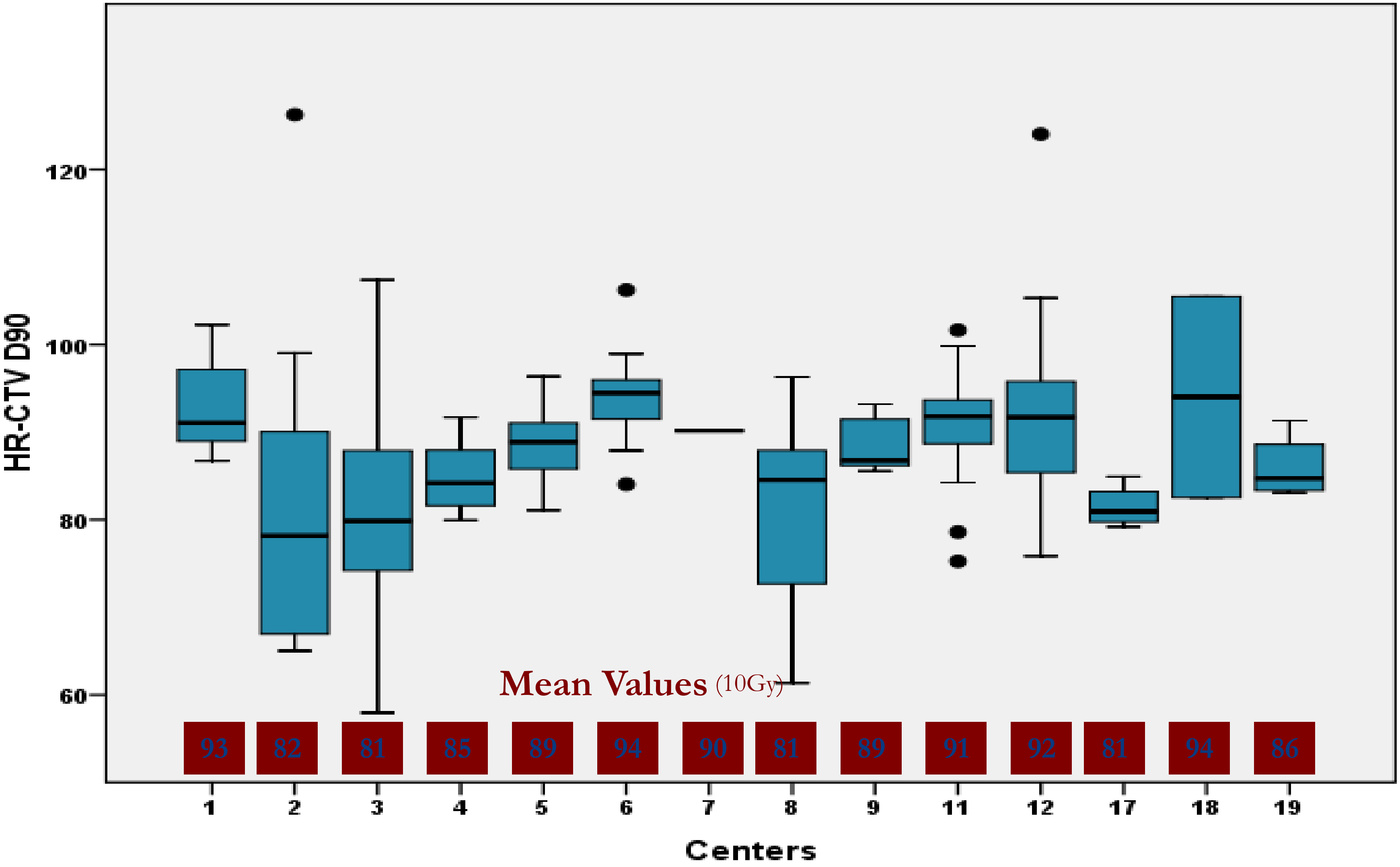
- **Fractionation, planning and prescription according to institutional practice**

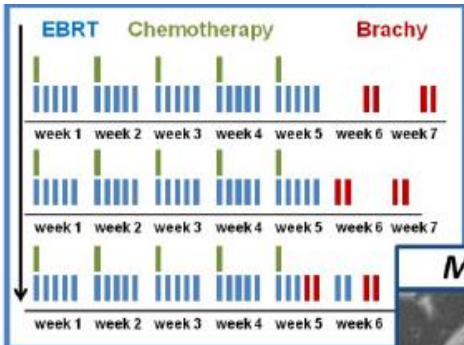
- **Enrollment of patients in 2008-2015, 1419 pts accrued**

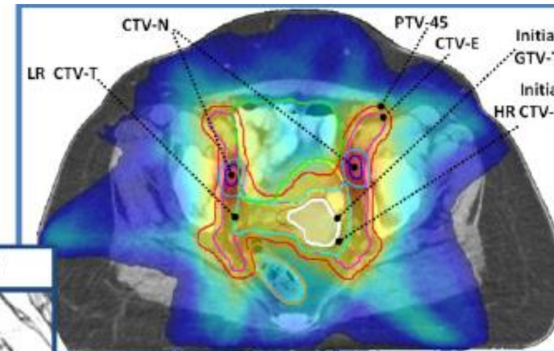
VARIAN medical systems | A partner for life

Nucletron Improving patient care

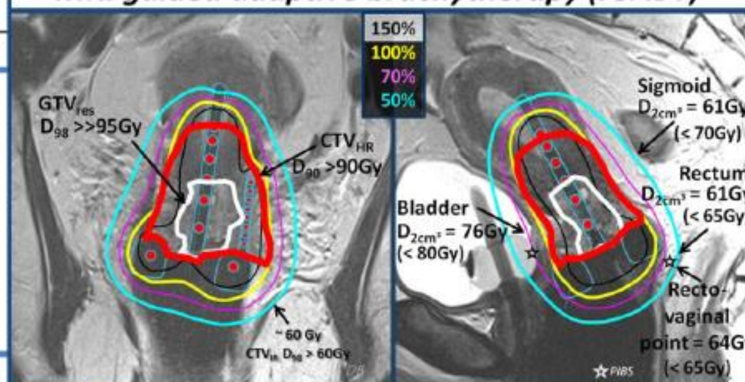
Heterogeneity of dose prescription: HRCTV D90

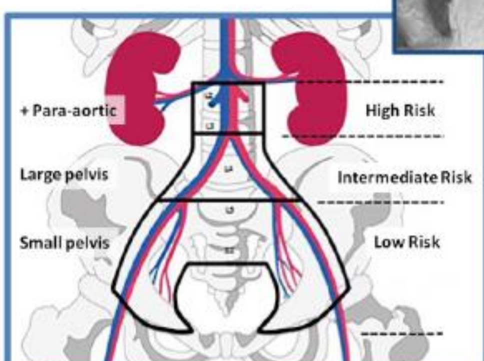




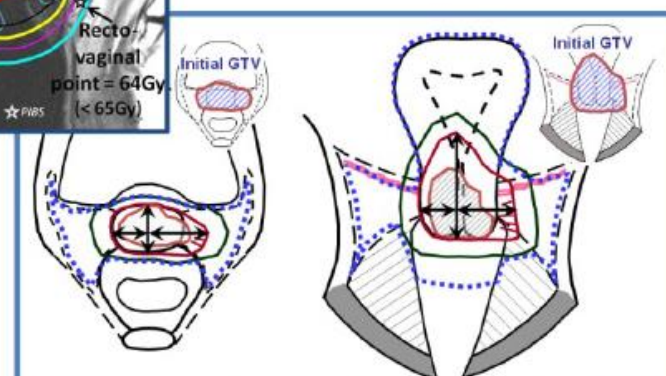


MRI guided adaptive brachytherapy (IGABT)





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 interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading (<33% of total loading (51% in EMBRACE I)
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

EMBRACE II interventions

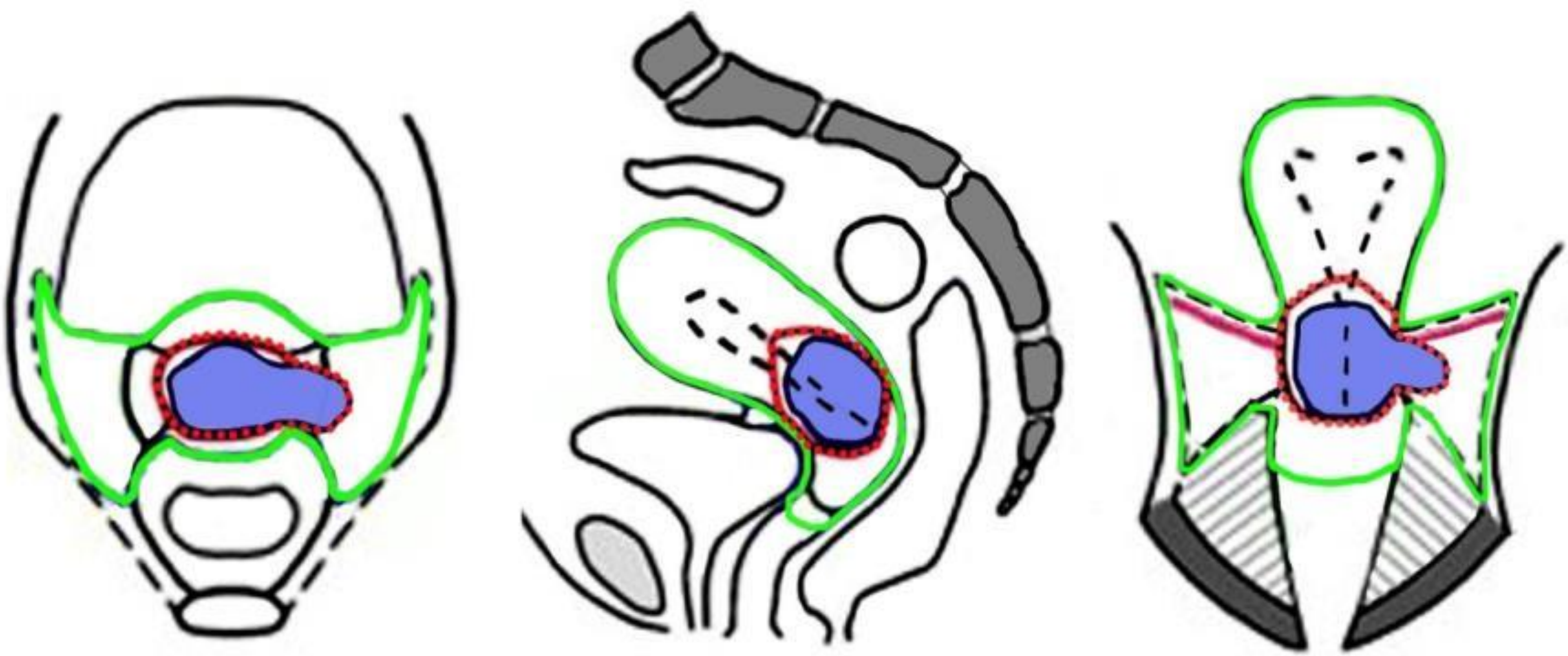
- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT + Utilisation of daily IGRT (reduction of V43Gy by 1000cm3 (from 2500cm3 to 1500cm3 pelvis)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

EMBRACE II interventions

- **Increased use of IC/IS technique in BT**
- **Reduction of vaginal source loading**
- **Systematic utilisation of IMRT**
- **Utilisation of daily IGRT (set-up according to bony structures)**
- **EBRT target concept related to the primary tumour; concepts for OAR contouring**
- **EBRT dose prescription (45Gy/25fx) and reporting**
- **Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence**
- **Systematic application of simultaneous chemotherapy**
- **Reduction of overall treatment time**

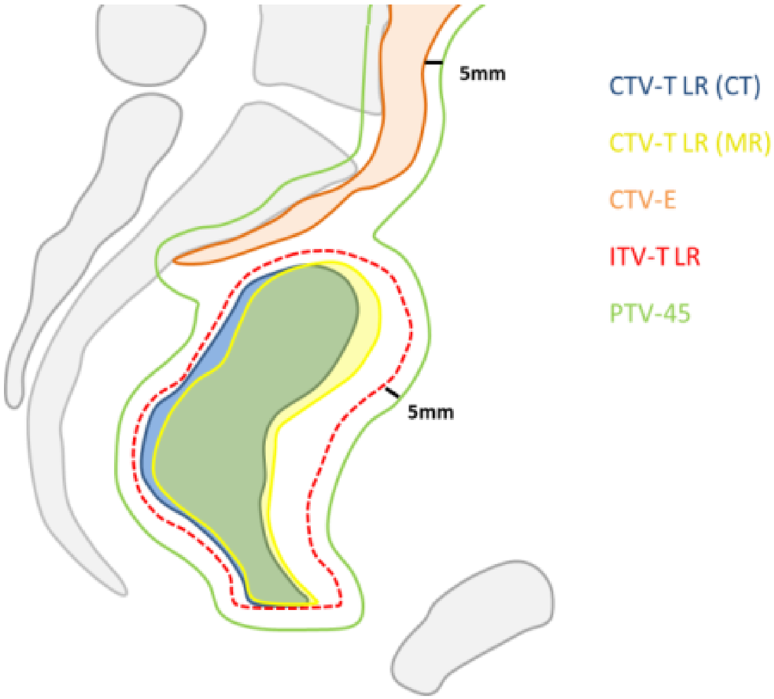
Target concept related to primary tumour

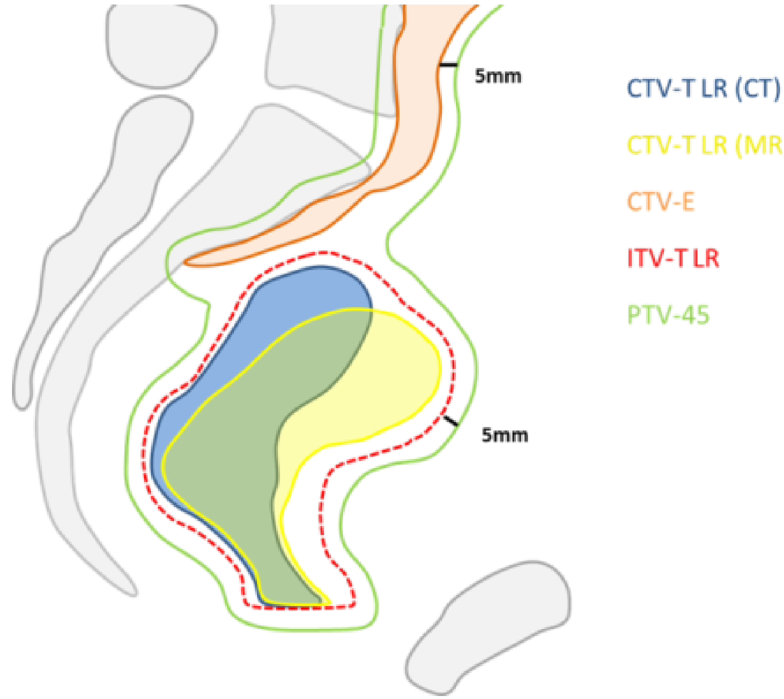
- **Initial GTV (blue)**
- **Initial HR CTV-T (red): GTV+cervix**
- **LR CTV-T (green): HR CTV + uterus + parametria + vagina**



Internal target volume

- **Combined appearance on CT and MRI**
- **Taking organ motion into account**





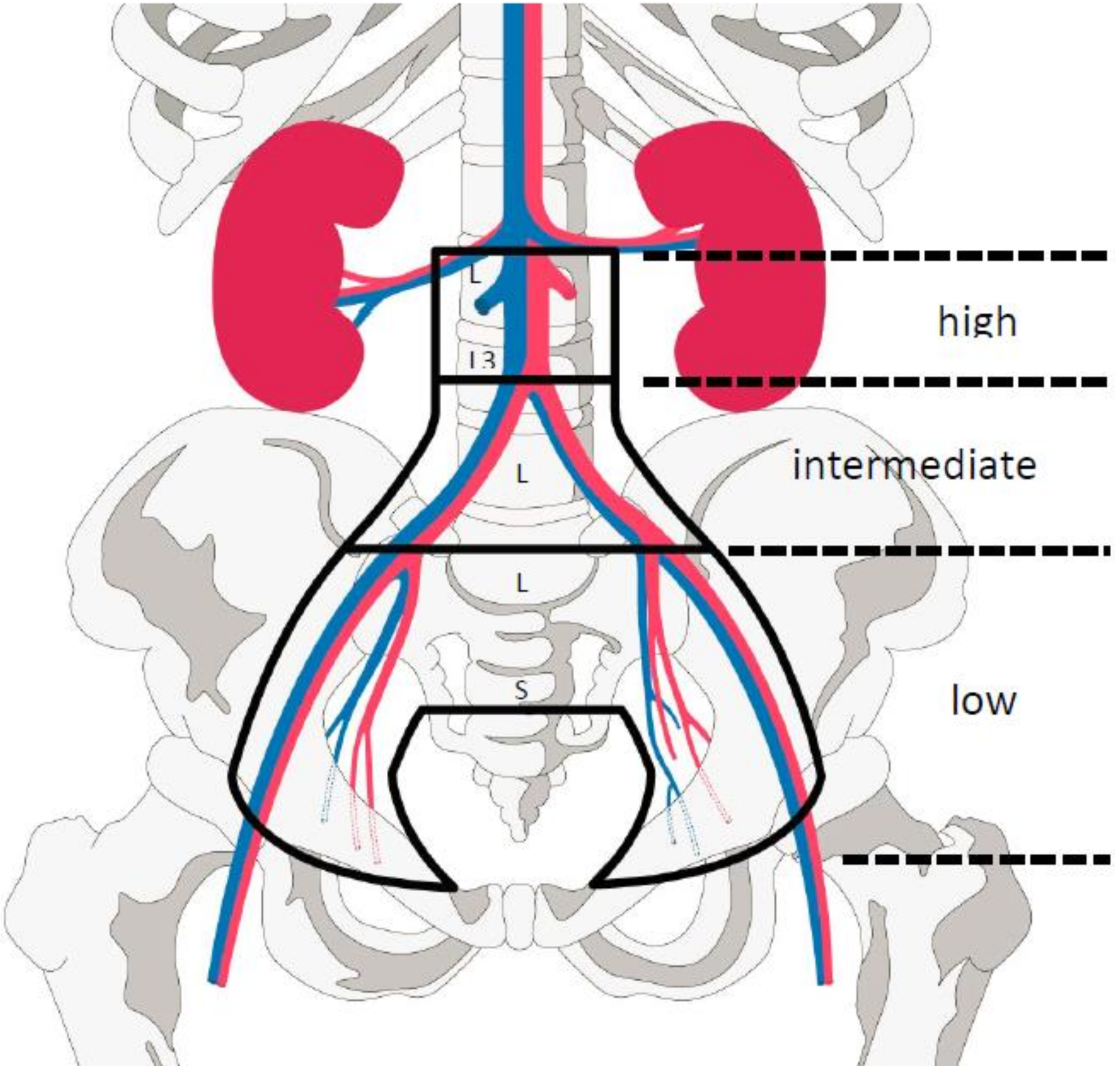
EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription and reporting (45Gy/25 fx in all fractions (30% patients with >45Gy in EMBRACE I)
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

EMBRACE II interventions

- **Increased use of IC/IS technique in BT**
- **Reduction of vaginal source loading**
- **Systematic utilisation of IMRT**
- **Utilisation of daily IGRT (set-up according to bony structures)**
- **EBRT target concept related to the primary tumour; concepts for OAR contouring**
- **EBRT dose prescription (45Gy/25fx) and reporting**
- **Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence (application of PAN irradiation in 55% of N+ patients (25% in EMBRACE I))**
- **Systematic application of simultaneous chemotherapy**
- **Reduction of overall treatment time**

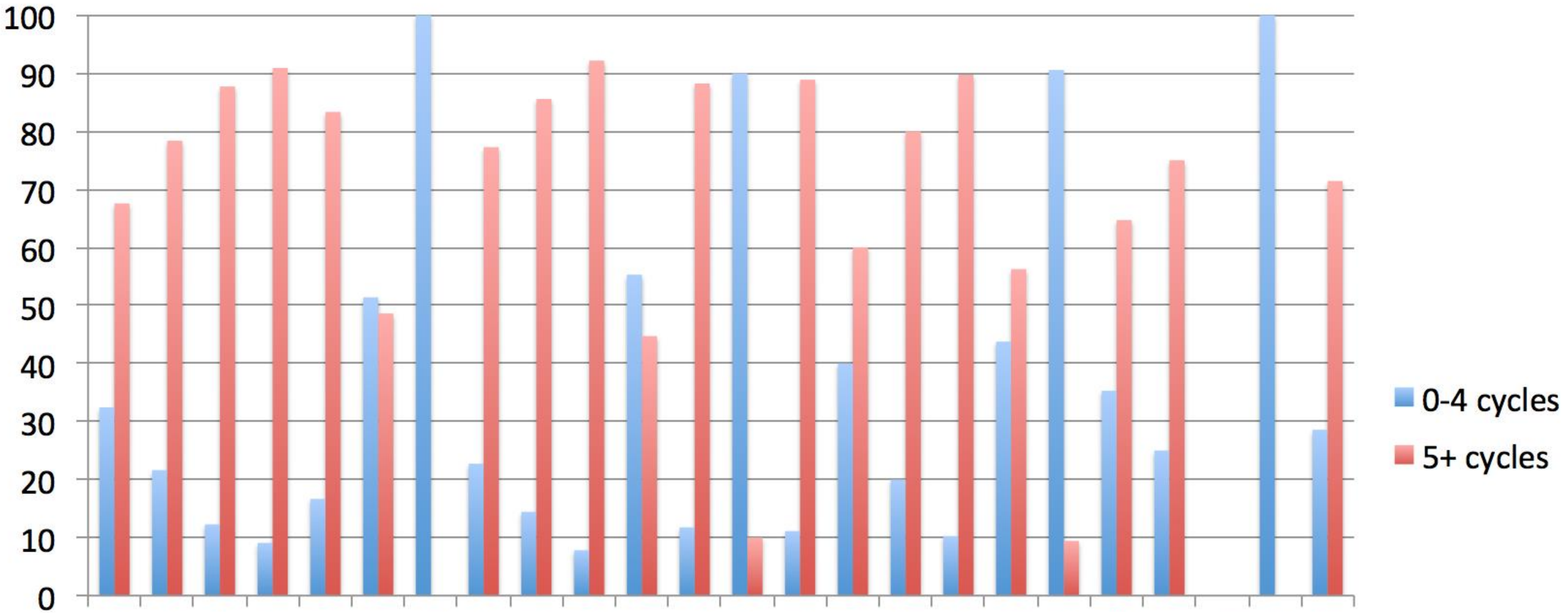
Target concept related to elective lymph nodes



EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy (administration of 5 cycles in 80% of patients (69% in EMBRACE I)
- Reduction of overall treatment time

Administration of chemotherapy in EMBRACE I



EMBRACE II interventions

- **Increased use of IC/IS technique in BT**
- **Reduction of vaginal source loading**
- **Systematic utilisation of IMRT**
- **Utilisation of daily IGRT (set-up according to bony structures)**
- **EBRT target concept related to the primary tumour; concepts for OAR contouring**
- **EBRT dose prescription (45Gy/25fx) and reporting**
- **Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence**
- **Systematic application of simultaneous chemotherapy**
- **Reduction of overall treatment time (OTT<50 days in 80% of patients (50% of patients in EMBRACE I)**

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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