Welcome to
2nd AROI - ESTRO GYN Teaching Course

3D Radiotherapy with a Special Emphasis on

Implementation of

"MRI & CT Based Brachytherapy in Cervical Cancer"

8 - 11 March 2018

Lucknow

ASSOCIATION OF RADIATION ONCOLOGISTS OF INDIA

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ESTRO School

MOU – Torino Italy

ESTRO – AROI : April 2016

AROI - ESTRO GYN TEACHING COURSES IN INDIA 2017- 2019

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

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

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

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

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

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

1st ESTRO-AROI GYN Teaching Course

8-11 March 2017
Bengaluru, India

ROADMAP

RADIOTHERAPY TREATMENT PLANNING AND DELIVERY

RADIATION ONCOLOGIST, MEDICAL PHYSICIST, RADIATION THERAPIST, OTHER SPECIALIST

FACULTY

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

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

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

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

Richard Pötter | Kari Tanderup | Umesh Mahantshetty | Jamema Swamidas

ESTRO COURSES : So far!

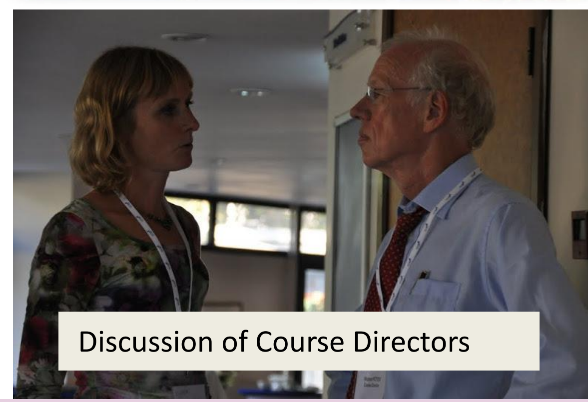
Image-guided cervix radiotherapy – with a special focus on adaptive brachytherapy

In the ESTRO school for more than 13 years:

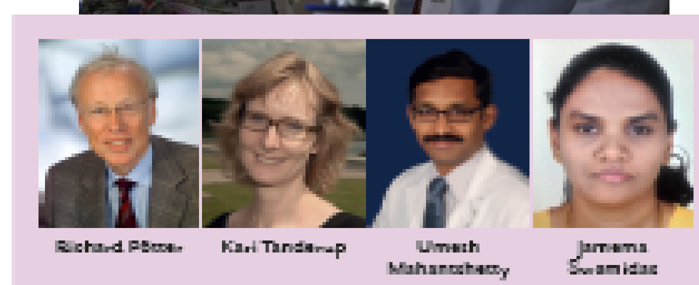
- 1st edition Vienna 08 2004: 80 participants
- 2nd edition Paris 08 2005: 100 participants
- 3rd edition Vienna 08 2006: 130 participants
- 4th edition Copenhagen 08 2007: 106 participants
- 5th edition London 08 2008: 158 participants
- 6th edition (1st intern.) Manila 01 2009: 160 participants ESTRO-SEAROG
- 7th edition Amsterdam 09 2009: 120 participants
- 8th edition Warsaw 08 2010: 110 participants
- 9th edition Chandigarh (2nd intern.) 03 2011: 102 particip. AROI-ESTRO
- 10th edition Izmir 09 2011: 104 participants
- 11th edition Beijing (3rd intern.) 03 2012: 128 participants ESTRO-CSRO
- 12th edition Budapest 10 2012: 102 participants
- 13th edition Moscow (4th intern.) 06 2013: 180 participants
- 14th edition Barcelona 09 2013: 90 participants
- 15th edition Florence 10 2014: 99 participants
- 16th edition Utrecht 11 2015: 82 participants
- 17th edition Toronto (5th intern.) 04 2016: 110 particip. ESTRO-CARO
- 18th edition Bengaluru (6th Itern) 03 2017: 80 parti.cip. AROI ESTRO
- 19th edition Prague 11 2017: 105 participants
- 20th edition Lucknow 03 2018: 96 participants

In total ~ 2200 participants

Discussion of Course Directors



Discussion of Course Directors



WORLD CONGRESS OF BRACHYTHERAPY

San Francisco
June 2016

MEETING AT STARBUCK'S CORNER

1st AROI ESTRO GYN TC at MS Ramaiah Medical College March 2017

1st AROI ESTRO GYN TC at MS Ramaiah Medical College March 2017

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- Kari Tanderup, Physicist, University Hospital, Åarhus (DEN)

AROI Course Directors:

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

ESTRO & AROI Teaching Faculty:

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

Local Organizer

Madhup Rastogi, Radiation Oncologist, RMLIMS, Lucknow

Guest faculty:

- Ajeet K Gandhi, Radiation Oncologist, RMLIMS, Lucknow
- Anoop K Srivastava, Medical Physicist, RMLIMS, Lucknow
- Abhishek Basu, Assistant Professor, Radiation Oncology, RG Kar Med. Coll. , Kolkota
- P K Shrivastava, Professor, Radiology, KGMU, Lucknow

PROJECT MANAGER

- **Melissa Vanderijst, ESTRO**

7th March 2018 at the Venue


PASSION
CHANGES

Program Highlights

3 D Radiotherapy with a Special Emphasis on Implementation of MRI / CT Based Brachytherapy

Program customized for year 1 & 2 participants : Common & Separate Sessions

- **Day 1:**
  - External Beam RT : 2D to State of the art RT
  - EBRT Contouring and Planning Workshop
- **Day 2:**
  - Basics of cervical brachytherapy
  - **Videos on Advanced BT Application from various Institutions**
  - BT Commissioning Workshop
- **Day 3:**
  - Transition from 2D to 3D BT, **CT based Contouring**
  - Principles of Advanced BT planning
  - **Discussion and feedback Sessions for Year 2 participants**
  - BT Contouring and Applicator Reconstruction workshop
- **Day 4:**
  - Treatment planning workshop
  - Practical implementation
  - Setting goals

- *On behlaf of AROI and ESTRO,*
  - *RMLIMS and their Staff*
  - *The Enthusiastic Teaching Staff*
  - *The Enthusiastic participants*
  - *The Sponsors*

2nd ESTRO – AROI GYN Teaching Course

"Image Guided Brachytherapy"

8 – 11 March, 2018

Dr.RMLIMS, Lucknow (U.P) INDIA

PRE-WORKSHOP QUESTIONNAIRE RESULTS

Dr Ajeet Kumar Gandhi

MD (AIIMS), DNB, UICCF (MSKCC,USA)

Assistant professor, Radiation oncology

Dr RMLIMS, Lucknow

Participants

- **Total=97**
- **Physicians=57**
- **Physicians + Physicist =38 (19 pairs)**
- **Respondents= 55 (Year 1) + 13 (Year 2) ~70%**


ONE

Years since graduation as a medical doctor/ other education:

- 40/54: $\geq$ 5 years since graduation (2-30 years experience in the subject)

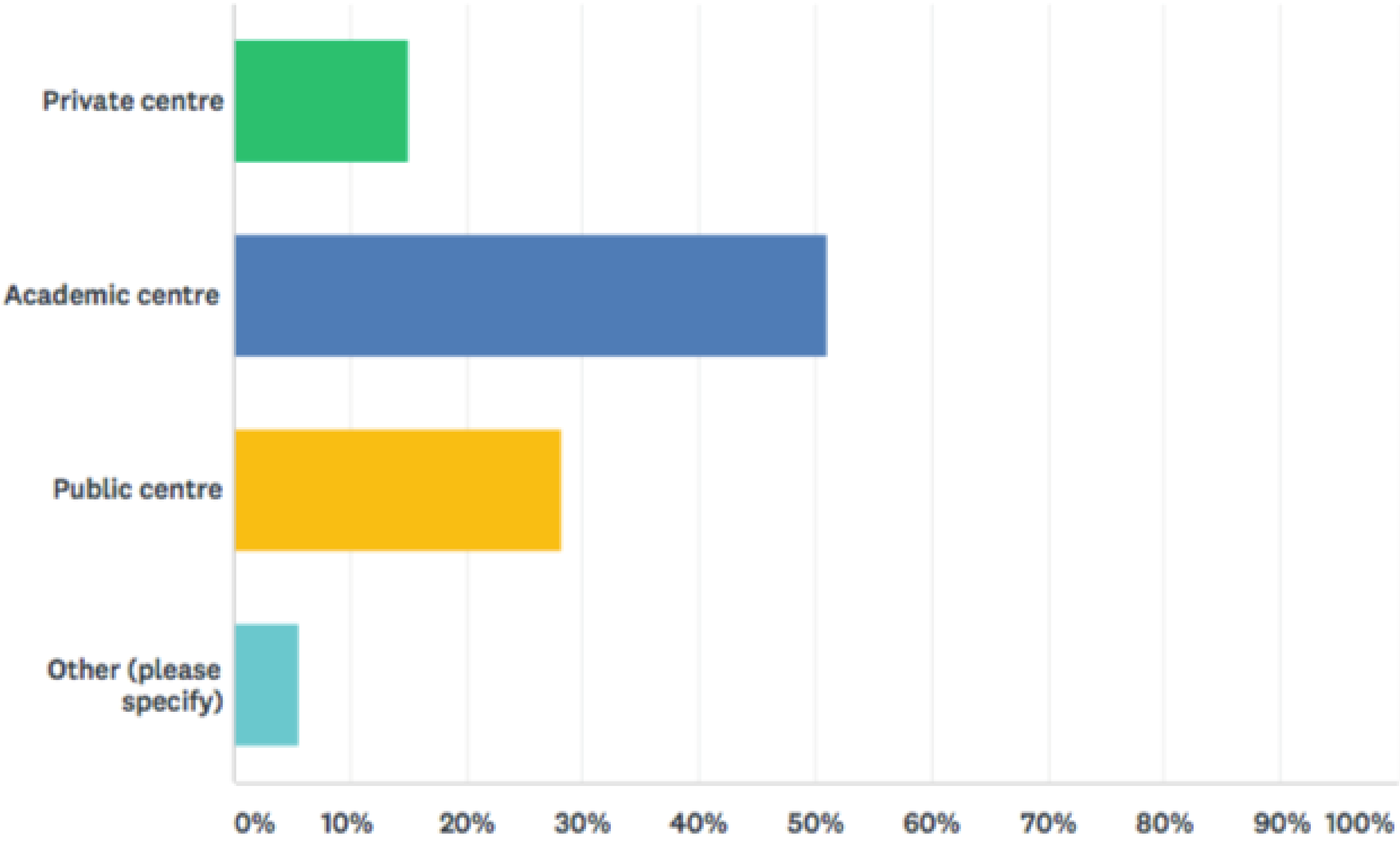
Years since graduation as a medical doctor/ other education:

- 38/54 : $\geq$ 5 years in Oncology Department
- Rest have less than 5 years experience
- Range: 5-30 years

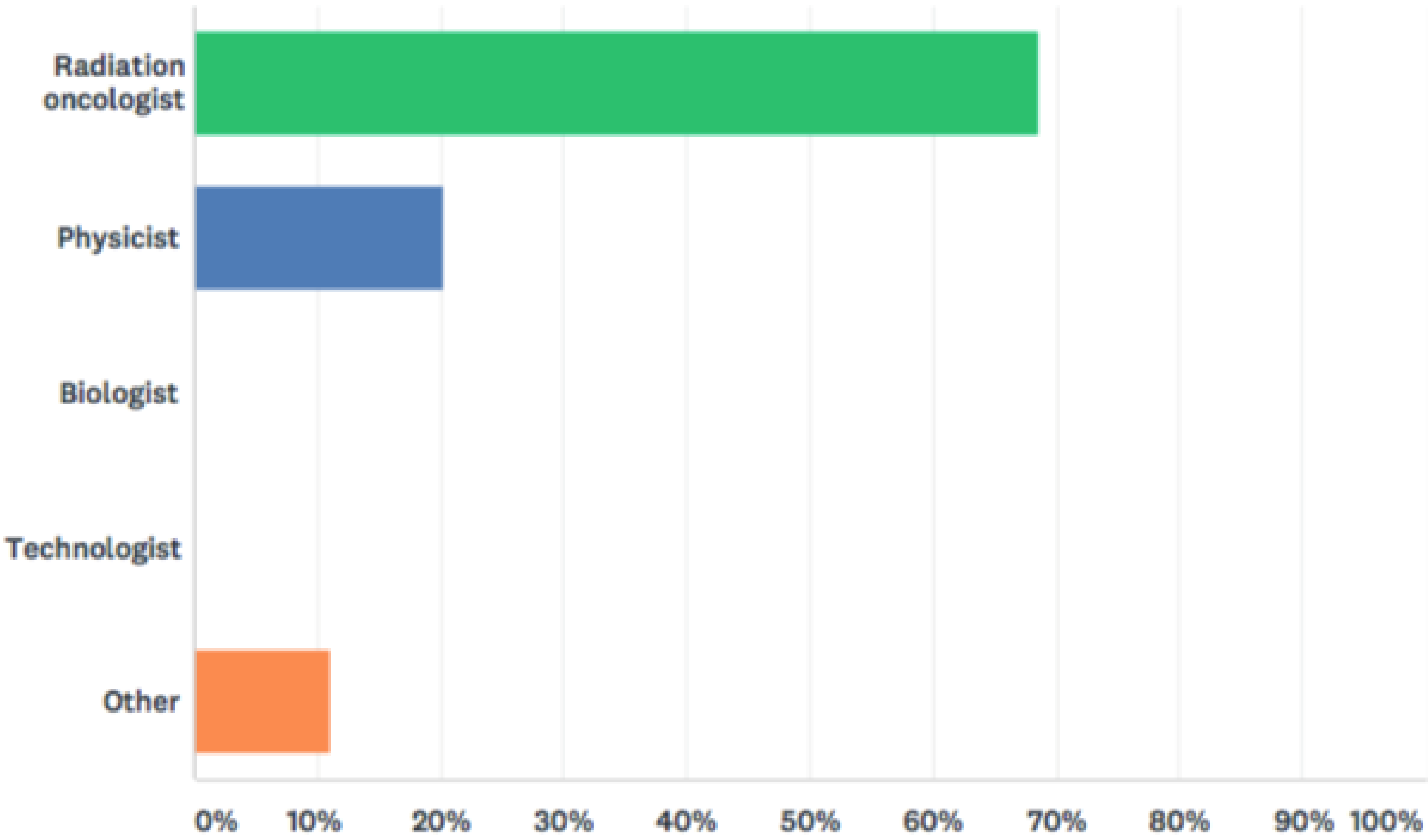
Number of active treatment units (brachytherapy, cobalt and LINACs):

- Almost all of the institutions have a functional brachytherapy unit
- Around 95% of the institutions have LINACs

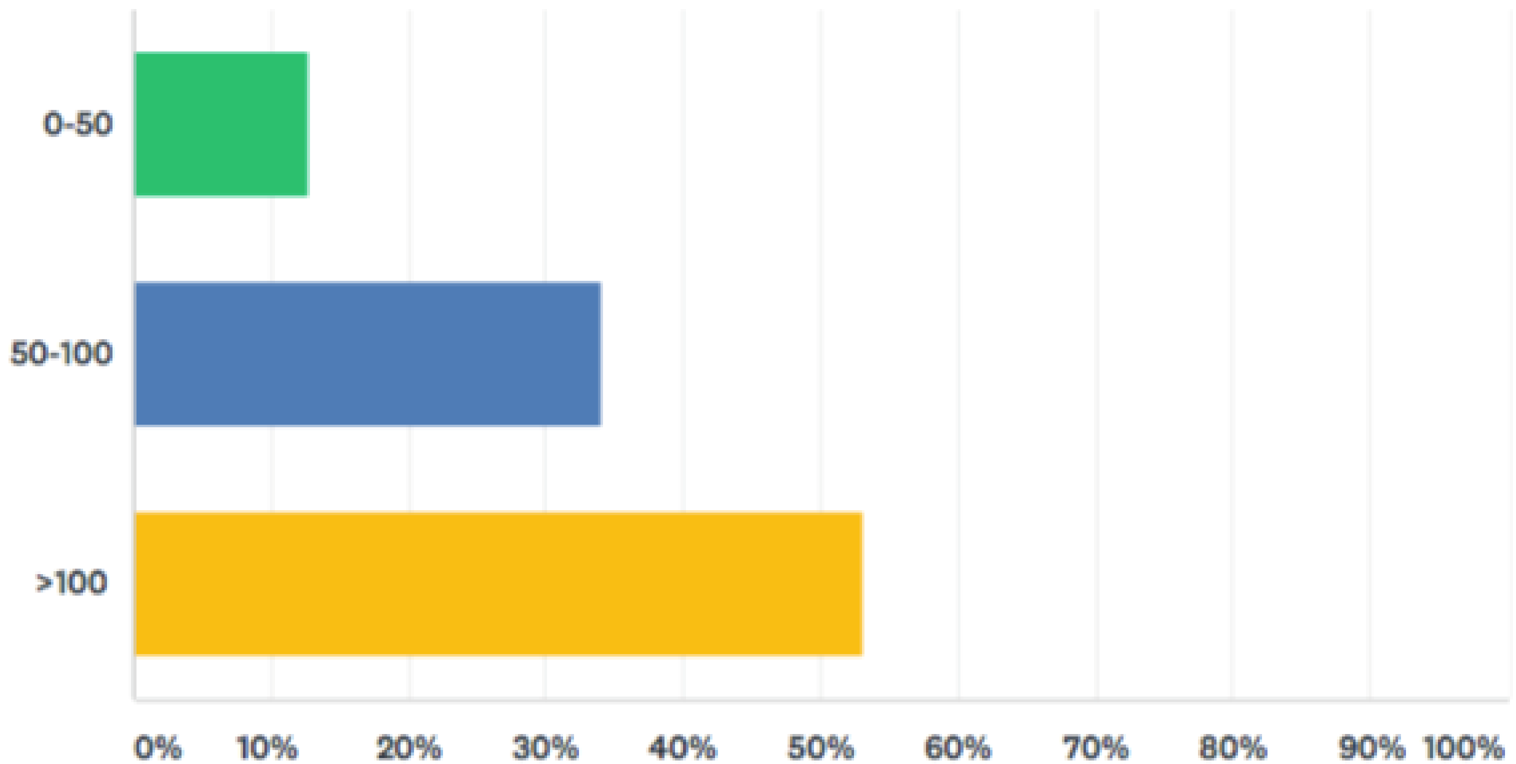
Institutional type (53)



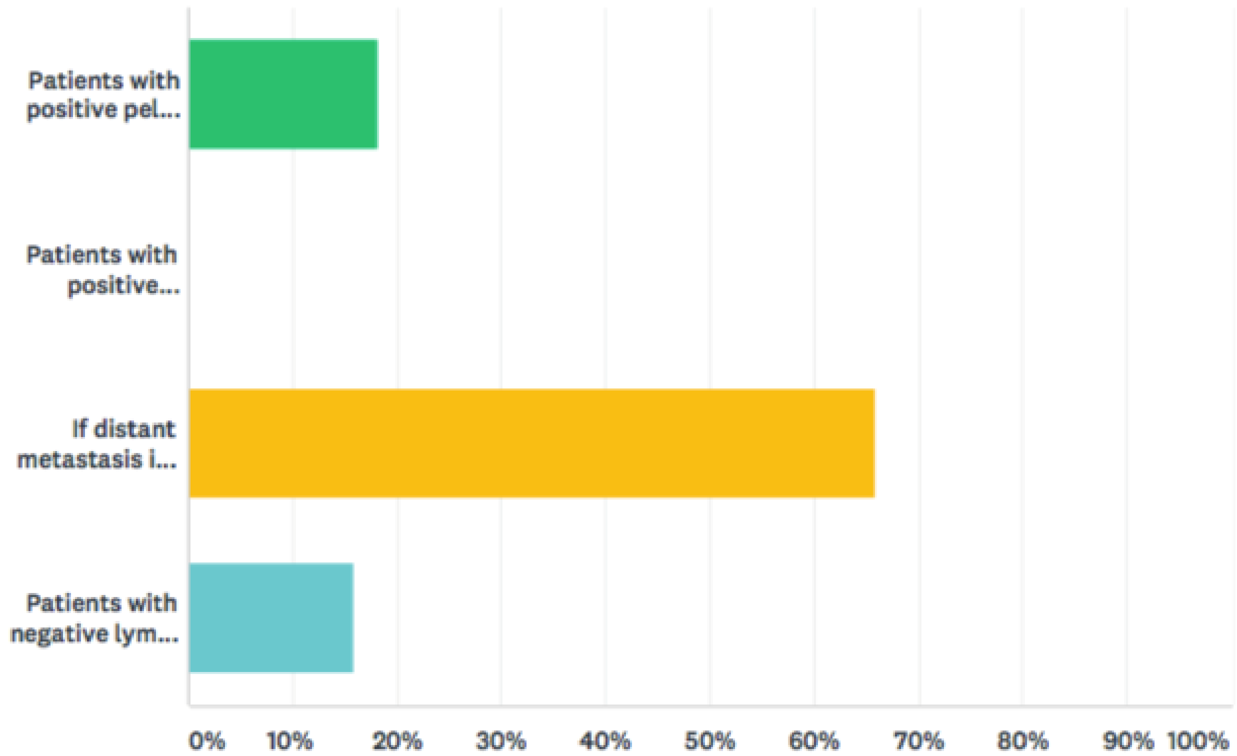
Education (54)



Number of carcinoma cervix treated definitively (47)



Cervix cancer patients treated with definitive radio(chemotherapy) [44]



ANSWER CHOICES	RESPONSES
Patients with positive pelvic and/or para-aortic lymph nodes	18.18%
Patients with positive para-aortic lymph nodes	0.00%
If distant metastasis is excluded I treat all patients with tumour stages I-Iva	65.91%
Patients with negative lymph nodes if local tumor stage is IIb or greater	15.91%

EBRT techniques employed (47)

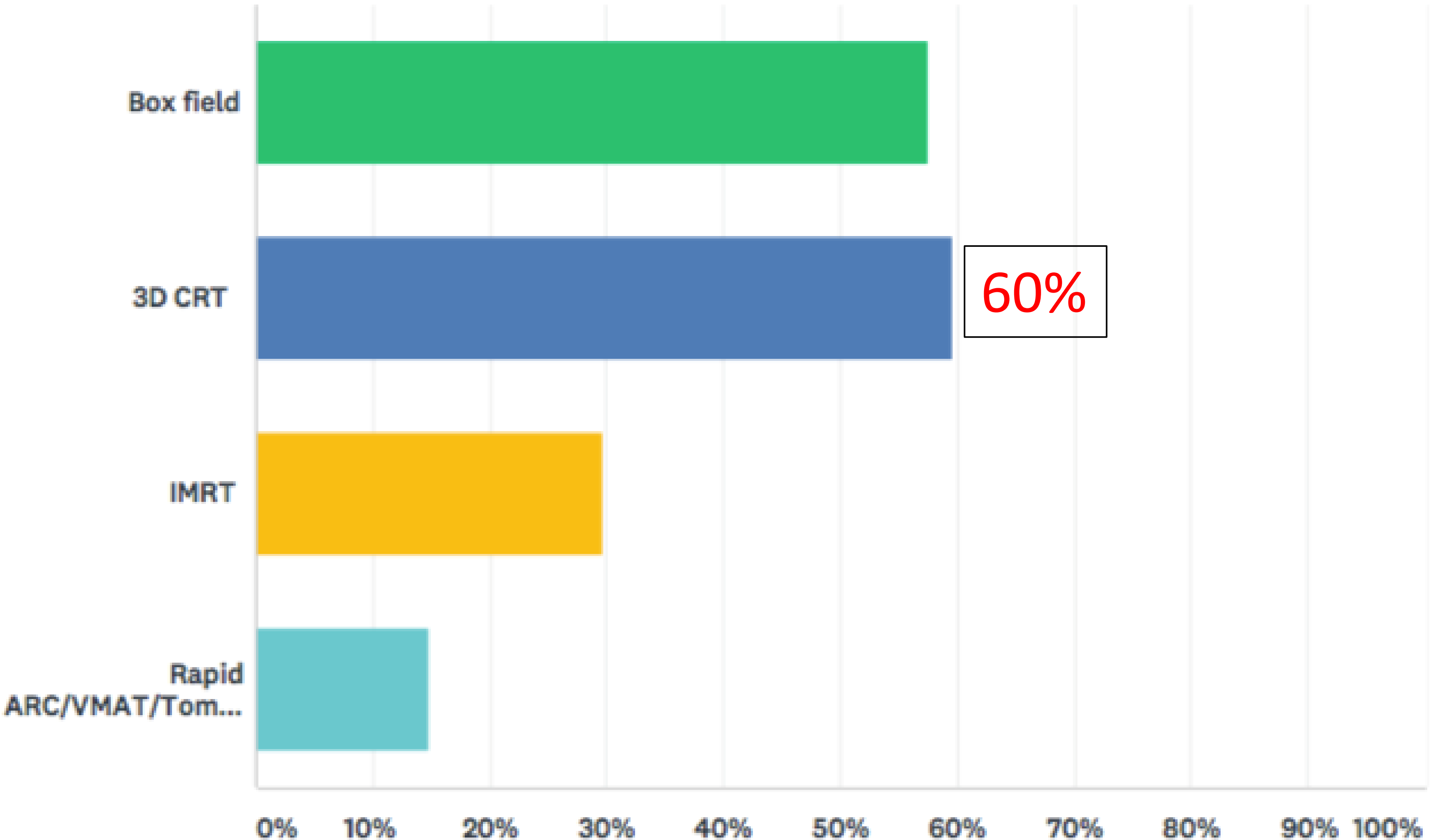
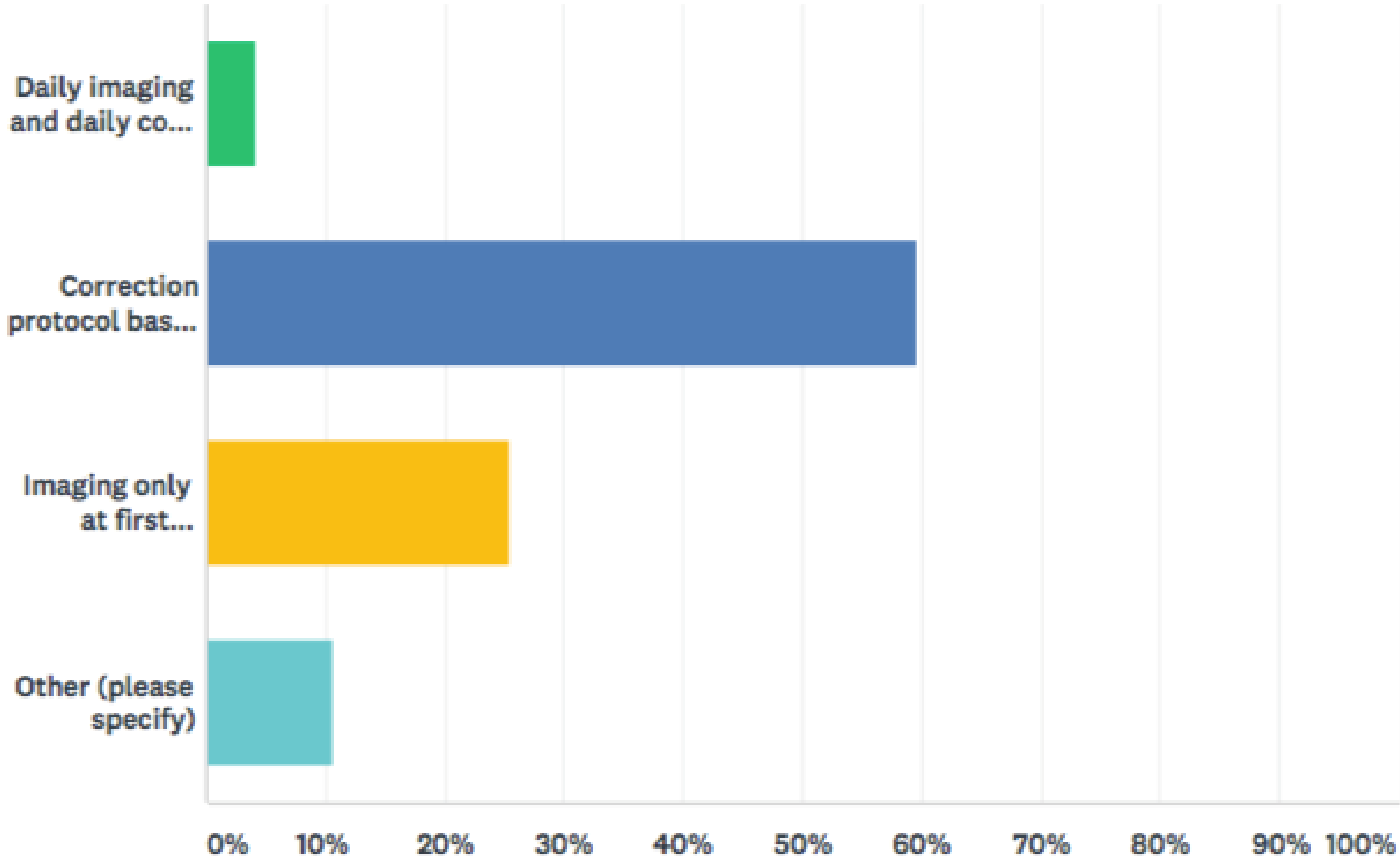
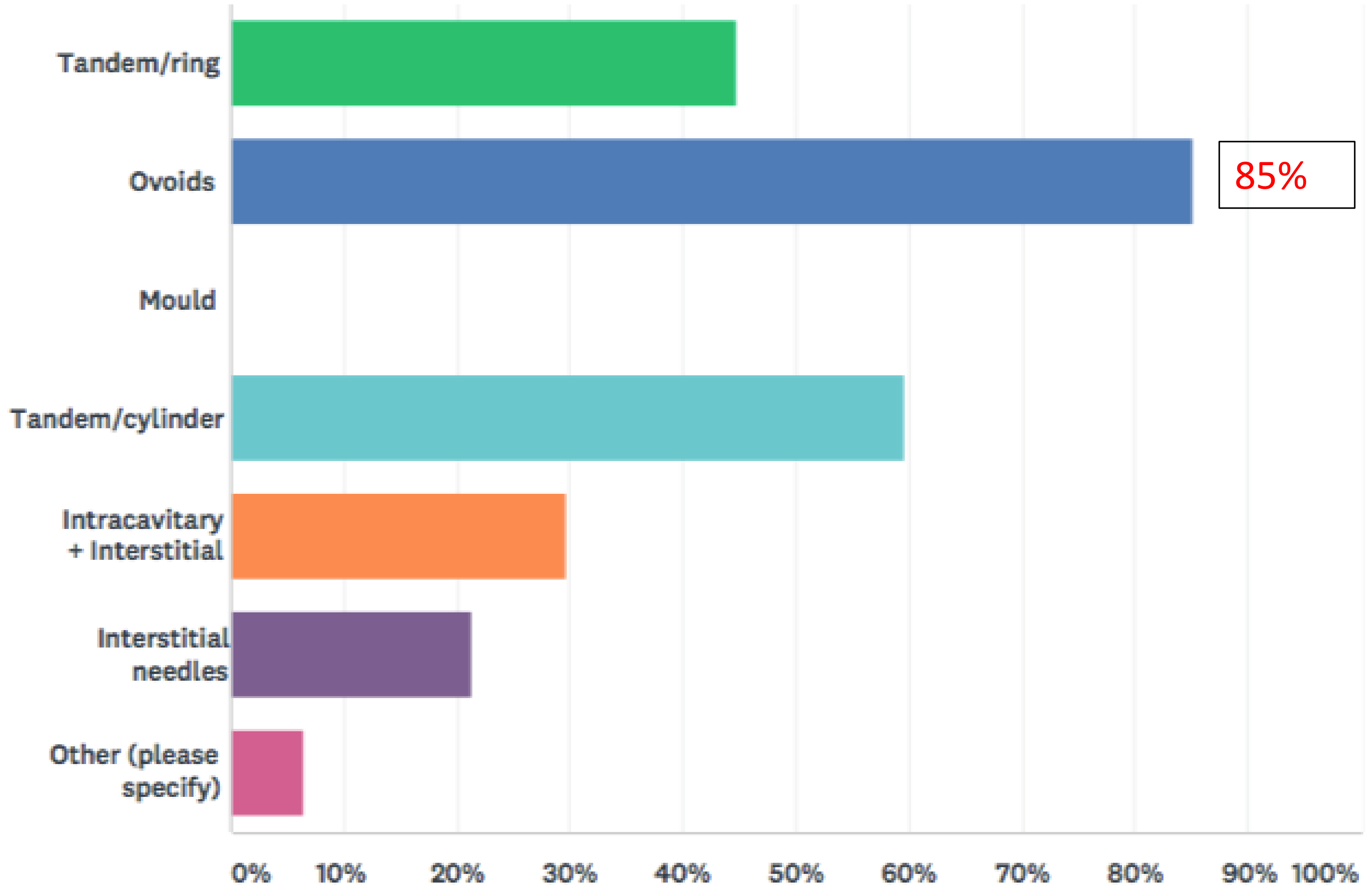


Image guidance for EBRT (47)

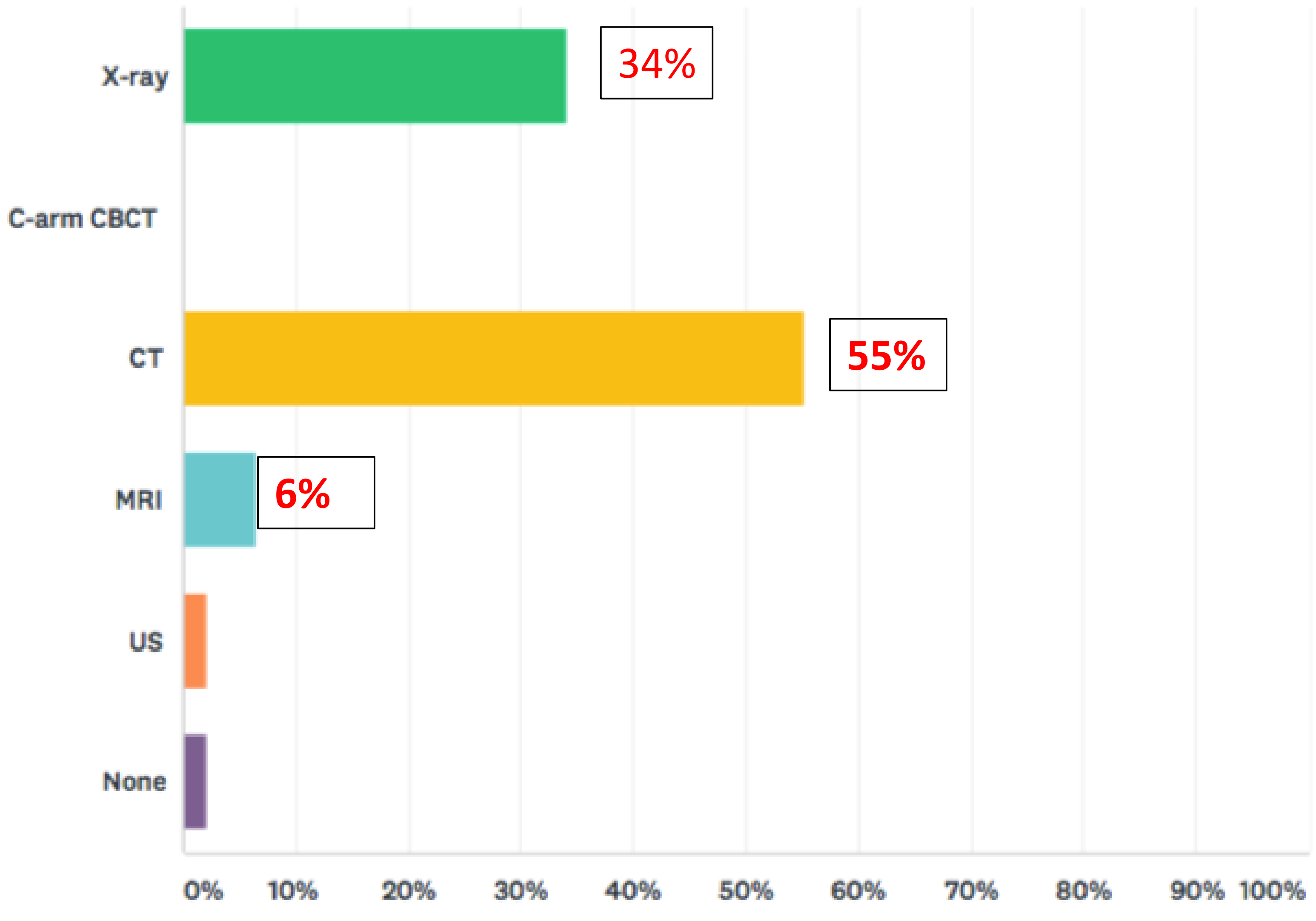


- Correction protocol based on e.g. imaging at first fractions or at weekly fractions – 60%
- Imaging only at first fraction – 30%

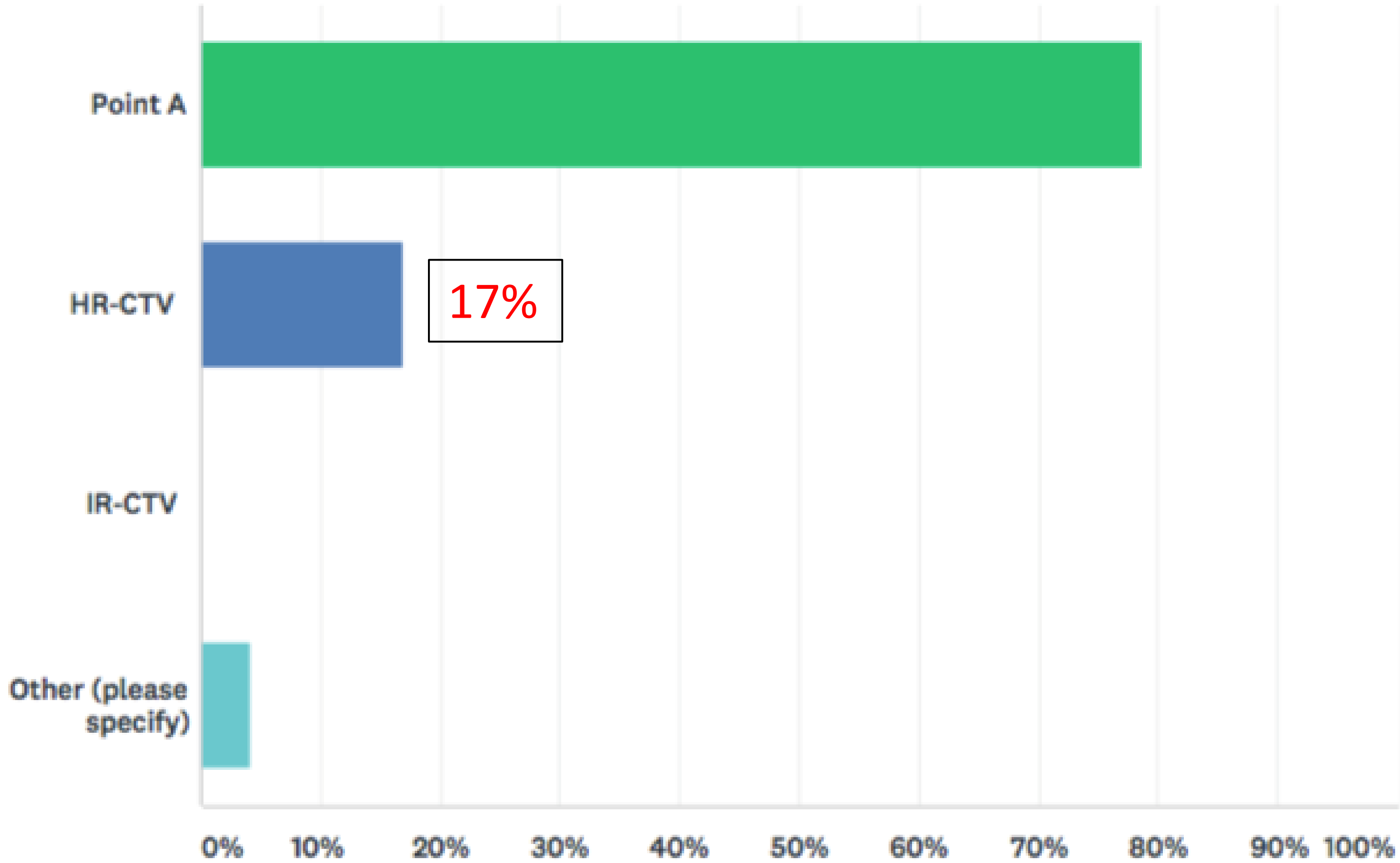
Applicator: Brachytherapy (47)



Imaging at brachytherapy
47 Replies



Volume/point of brachytherapy dose prescription [47 Replies]

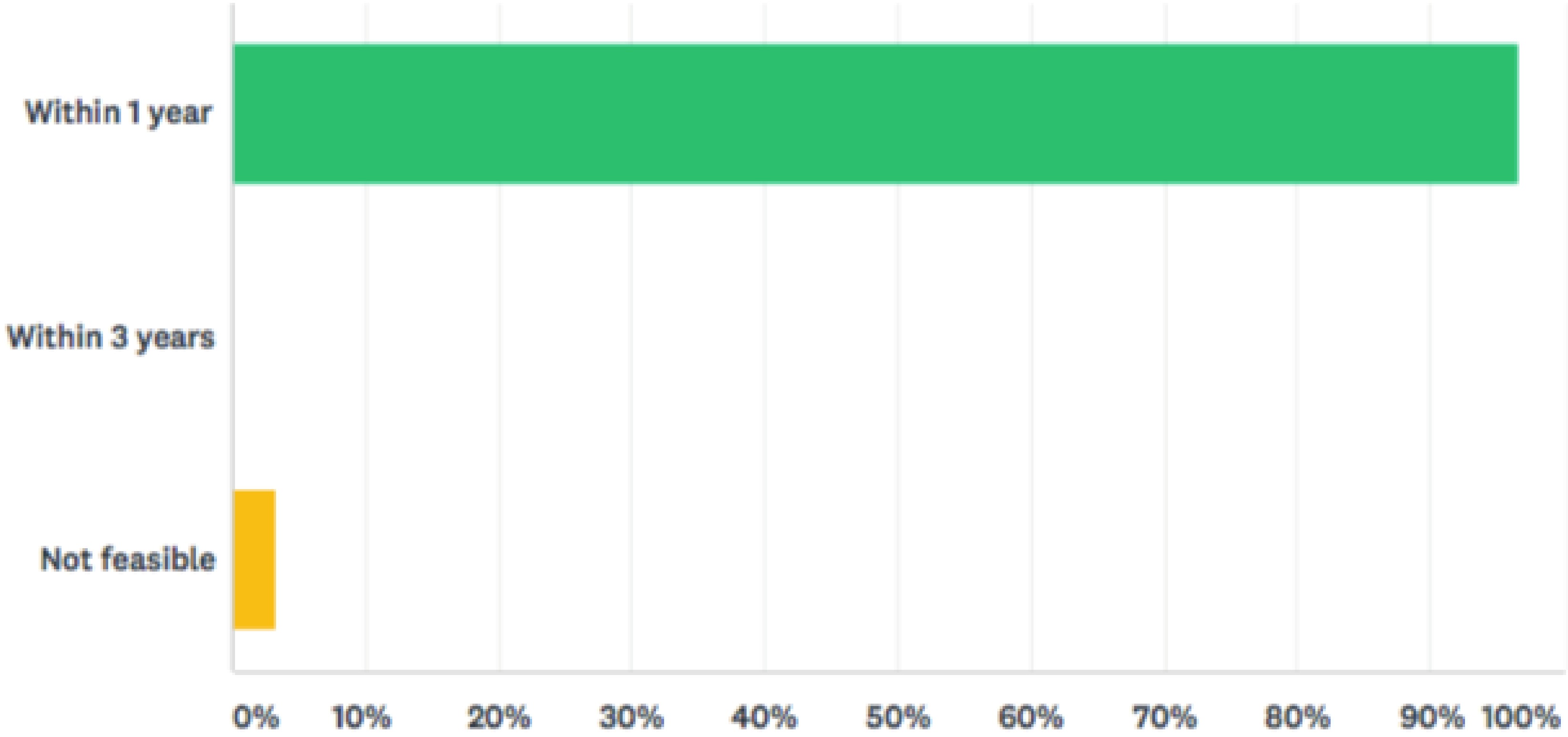


Common dose fractionation schedules utilized for BT treatment of cervical cancers

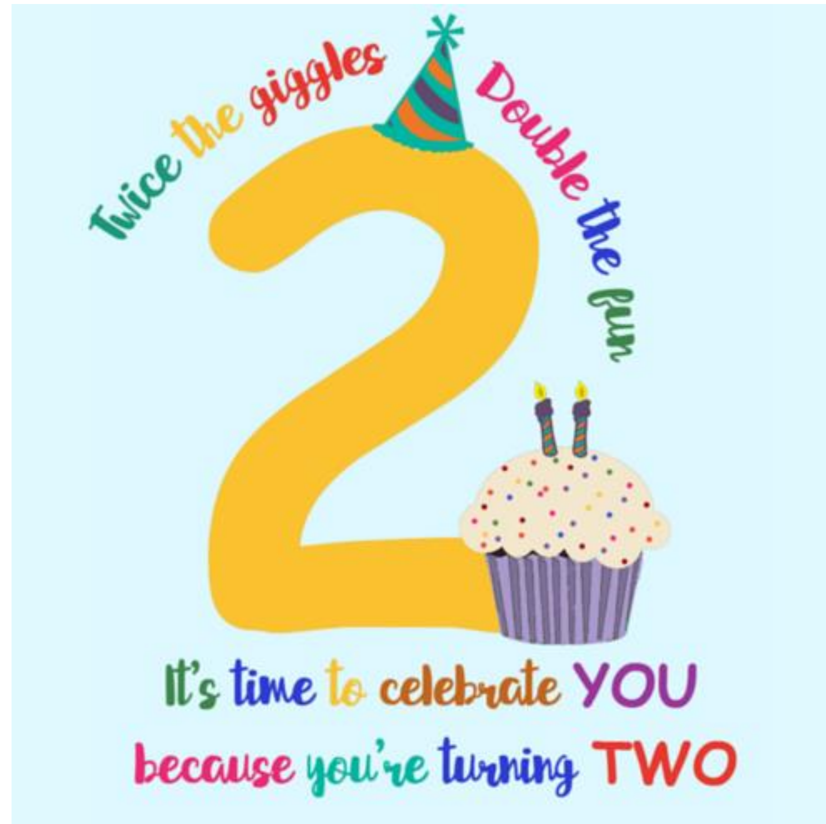
- Twice weekly fractionation – 13% [6/46]
- 7 Gy X 3# - Most commonly used fractionation schedule (6 Gy X 3 - 4 # and 9 Gy X 2#)
- Most participants using
  - 85-90Gy (locally advanced)
  - 75-85Gy (early stage)
- Total brachytherapy doses : 18-21 Gy

Plan to start 3D image based dose planning

Answered: 30 Skipped: 25



2017: 63 total and 20 teams
2018: 13



- **Years since graduation as a medical doctor/other education:** All except one, have at least 7 years of experience

- **Years employed at an Oncology department**: 5-18 years

- **Number of active treatment units at your department (brachytherapy, cobalt and LINACs):** All the centers are equipped with brachytherapy units and LINACs

- **Academic centers:** 70%
- **Physician: physicist**=60:40

Technique of EBRT: 3DCRT/IMRT

- **3D CRT/IMRT** – 8/11
- **Bladder protocol during EBRT:** (500 ml of water, used 30 minutes before simulation most commonly practiced)
- **CTV to PTV margins:** Varied from 5 mm – 10 mm, most participants use 7 mm
- **IGRT imaging protocol** [10/13]:All except one, use CBCT at least once weekly
- **Adaptive protocol & Re-planning** : None

Brachytherapy (9/13)

- **BT procedures:** IC Vs IC+ IS applicator
  - 5/9 used interstitial applicators.
- **Anesthesia:** General – 4; Spinal – 5
- **Imaging and sequencing**

  At BT: CT (6); MRI (4)

BT dose and fractionation (9/13)

- **Volume contouring**: HR-CTV (7)
- **Applicator Commissioning**: 9
- **Applicator reconstruction**: Manual (7); Library (2)
- **Offset for manual reconstruction**: 0.33-6 mm
- **Prescription point**: HR-CTV (7)
- **Optimization**: Manual (6)
- **Plan Evaluation parameters** (GEC ESTRO/ICRU 89): 4/6 used GEC ESTRO based parameters

Happy Studies!!

ESTRO School

Anatomical considerations
Role of clinical gynaecological examination
Staging

C. Haie-Meder
Brachytherapy Unit

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

GUSTAVE ROUSSY
COMPREHENSIVE CANCER CENTER

Cervix cancer : generalities

- 500,000 new cervical cancer cases each year
- 80% of the new cases in developing countries
- 3rd most common cause of female cancer mortality
- 274,000 deaths each year
- Human papillomavirus is responsible for virtually all cases of cervical cancer
- HPV-16 and -18 = the most prevalent of the oncogenic types

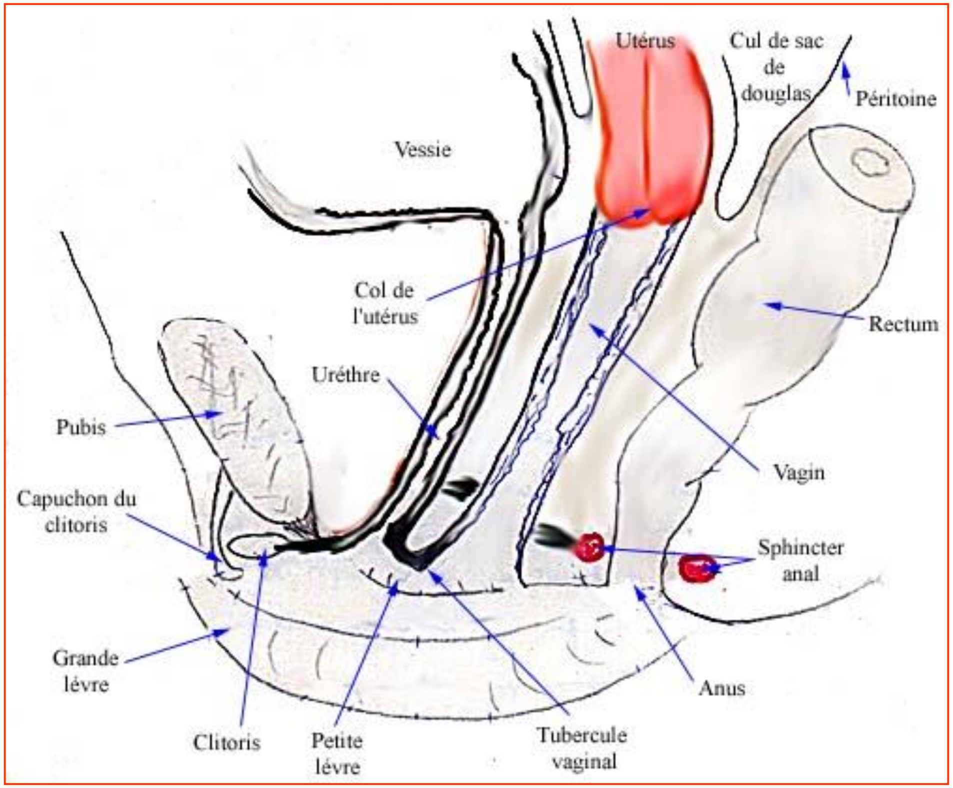
Cervix cancer : generalities

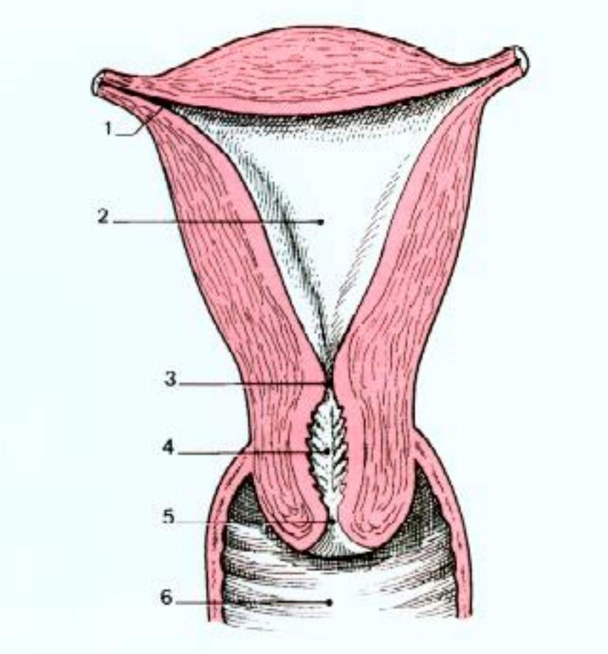
- Curable disease

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

Anatomical considerations

Uterus





Configuration interne de l'utérus (coupe frontale)

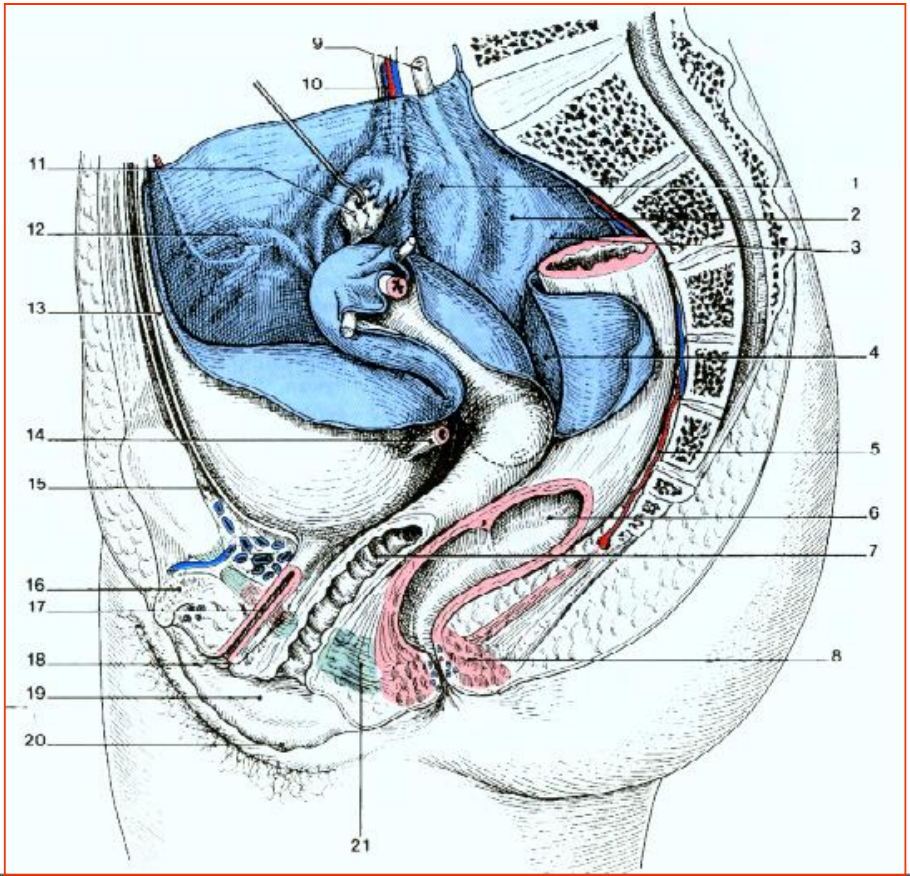
Hollow muscle

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

Anatomical considerations

Uterus

Supravaginal part
Bladder and rectum faces covered with peritoneum

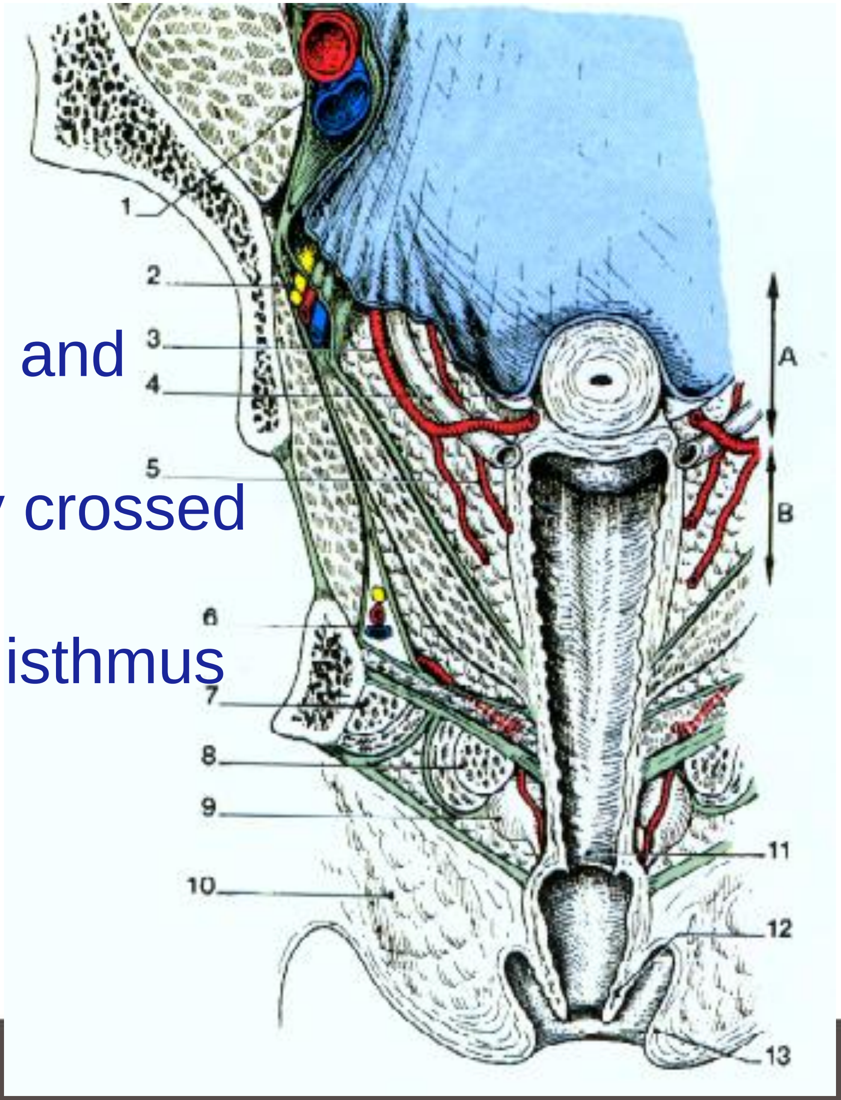


Vaginal part
Separated from the vagina
by vaginal fornices

Anatomical considerations

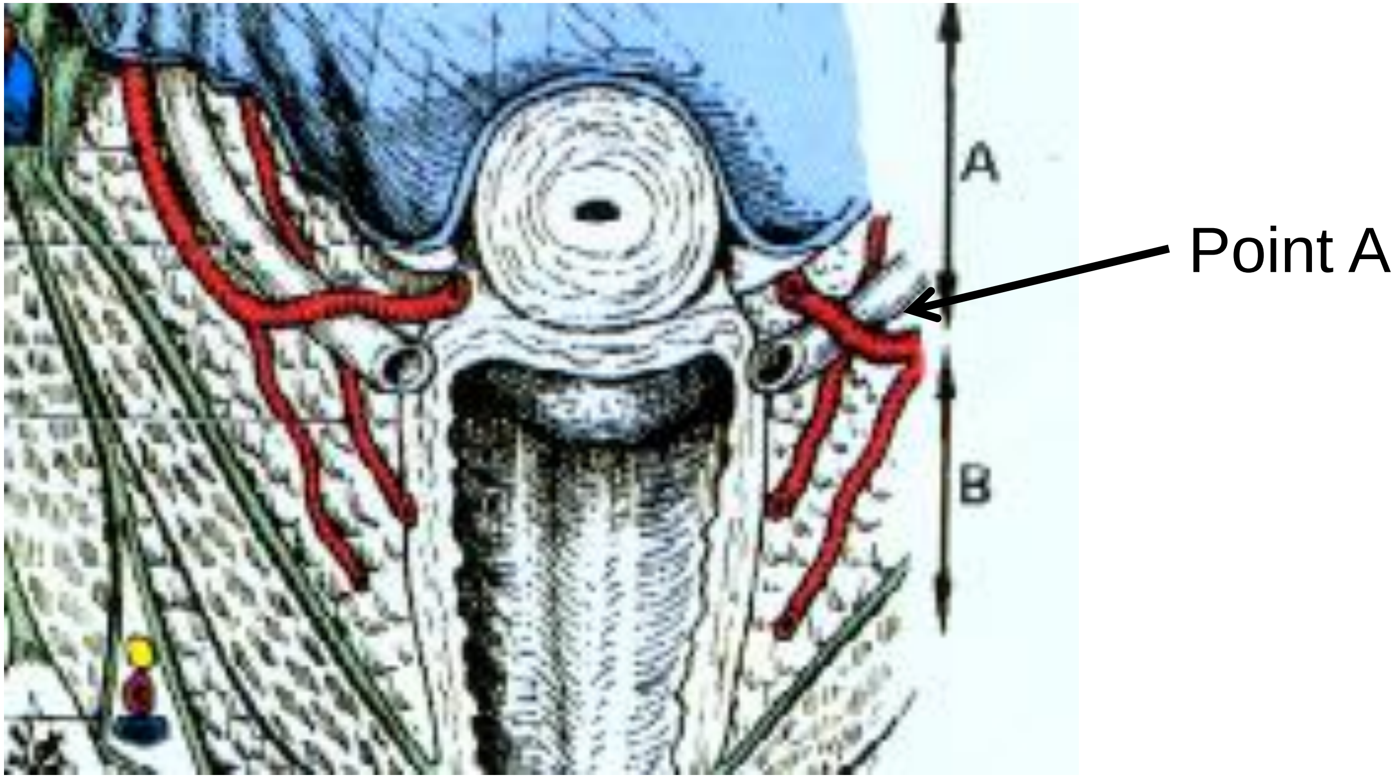
Uterus

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



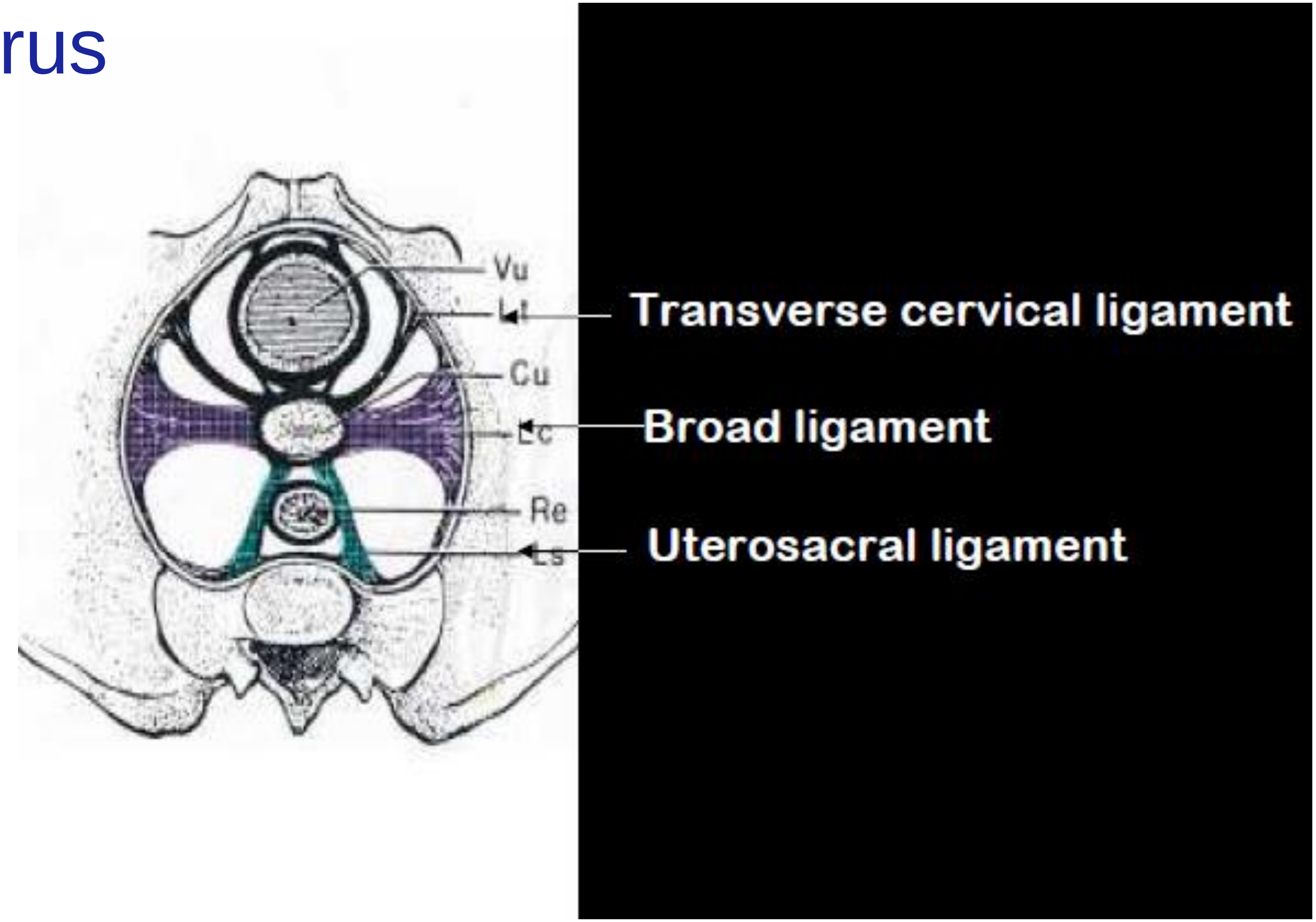
Anatomical considerations

Uterus



Anatomical considerations

Uterus



Anatomical considerations

Uterus

Parametrial Limits:

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

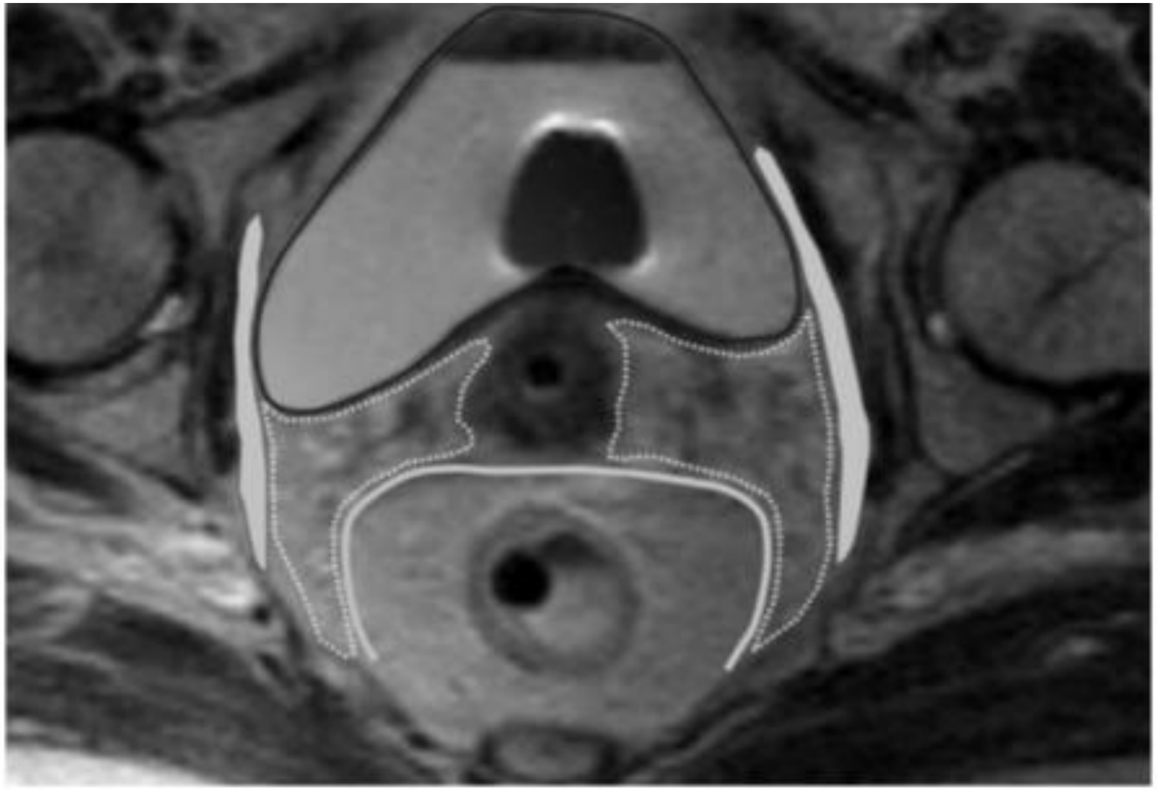


Fig. 2. Definition of parametria according to visible and reproducible radiologic criteria at its borders: ventral = bladder, dorsal = perirectal fascia, medial = tumor/cervical rim, lateral = pelvic wall (PW). At the PW, the space that contains vessels and lymph nodes is particularly indicated. For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

Anatomical considerations

Classification of radical hysterectomy

Denis Querleu, C Paul Morrow

Lancet Oncol 2008; 9: 297–303

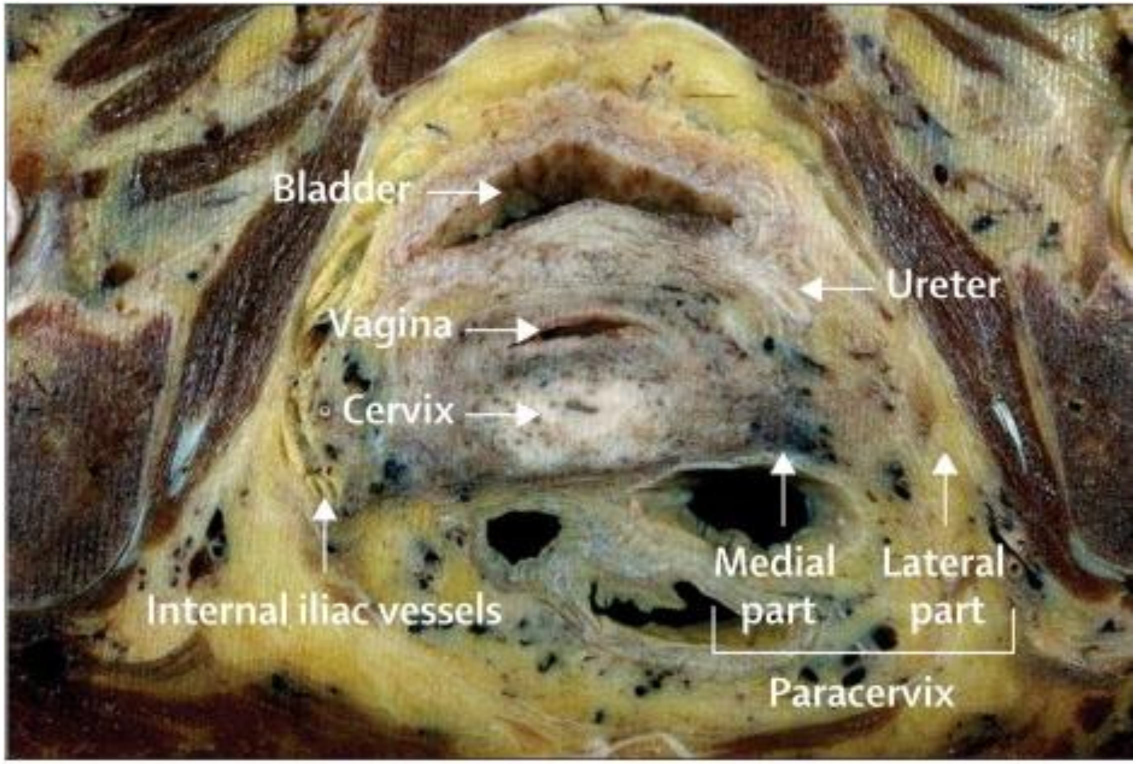


Figure 1

Transverse section of pelvis

Anatomical considerations

Classification of radical hysterectomy

Denis Querleu, C Paul Morrow

Lancet Oncol 2008; 9: 297–303

Figure 4

Type A radical hysterectomy

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

Anatomical considerations

Classification of radical hysterectomy

Denis Querleu, C Paul Morrow

Lancet Oncol 2008; 9: 297–303

Figure 5

Type B1 radical hysterectomy

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

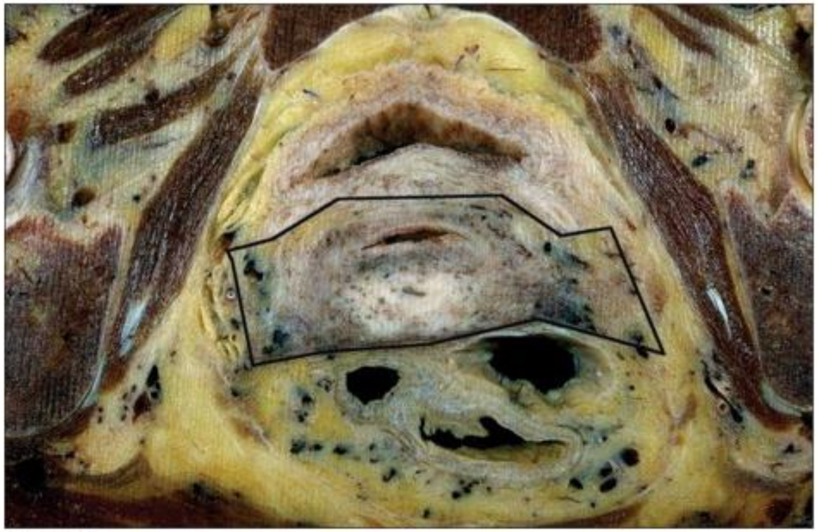


Figure 6

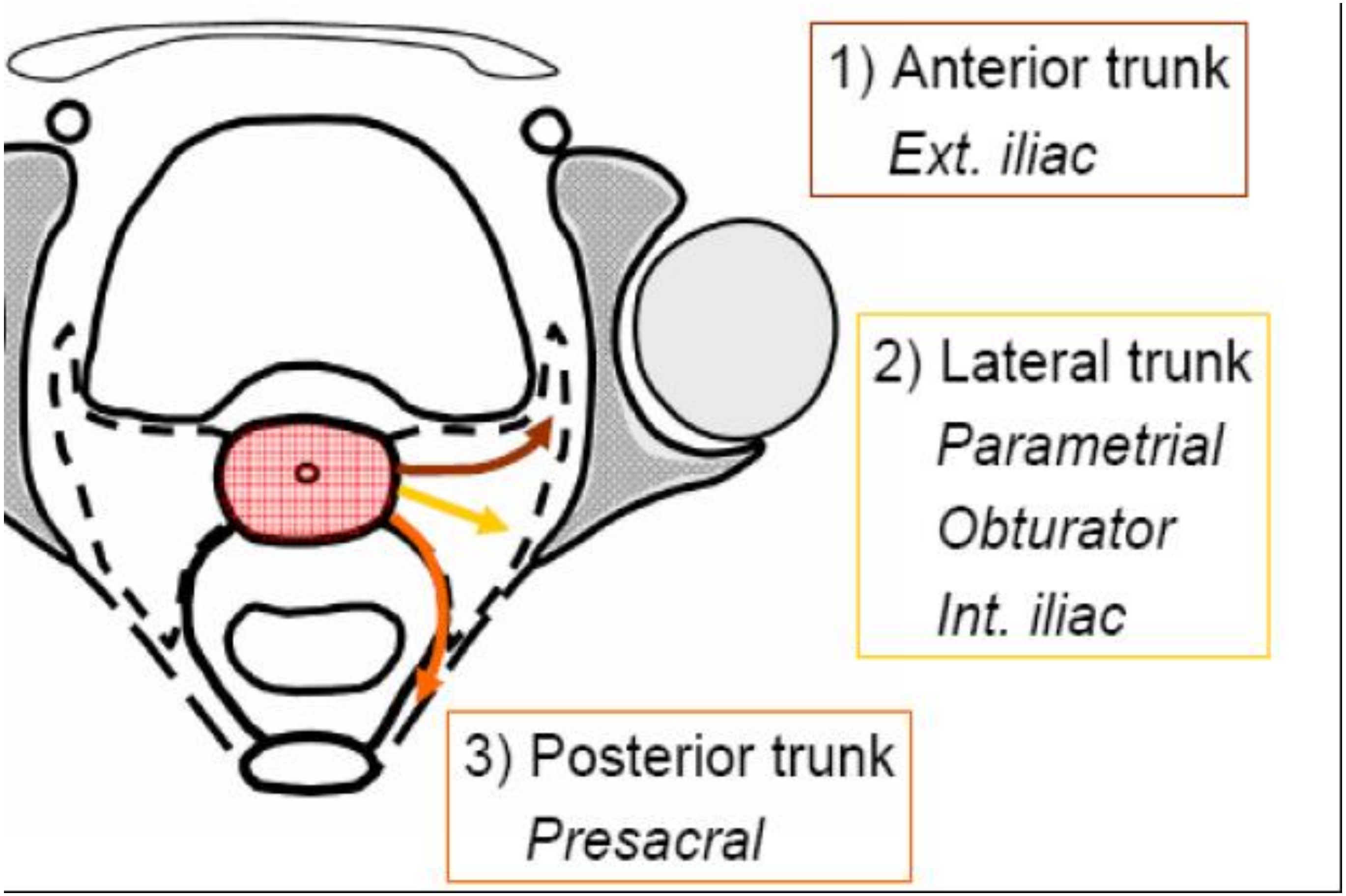
Type C2 radical hysterectomy

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

Anatomical considerations

Lymphatic drainage

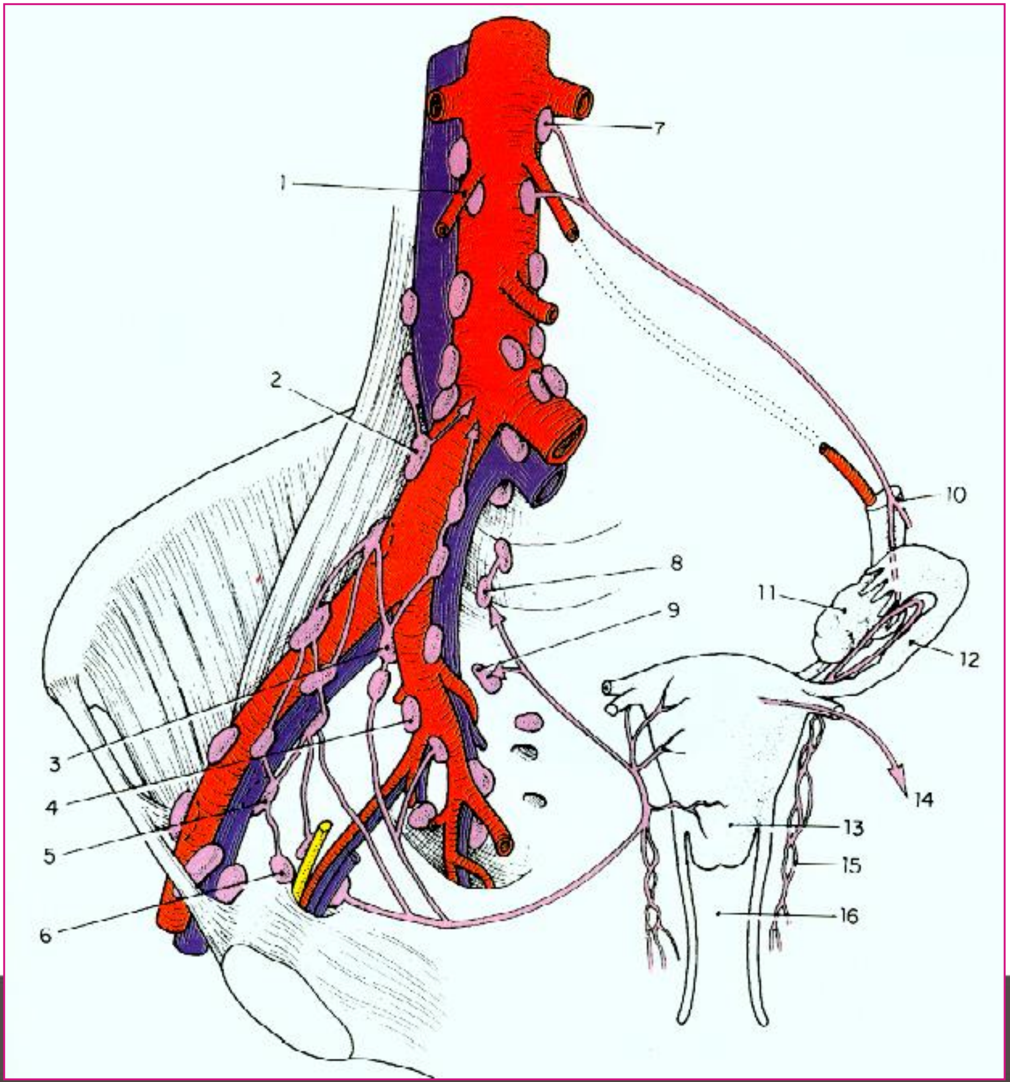
Uterus



Anatomical considerations

Lymphatic drainage

Uterus



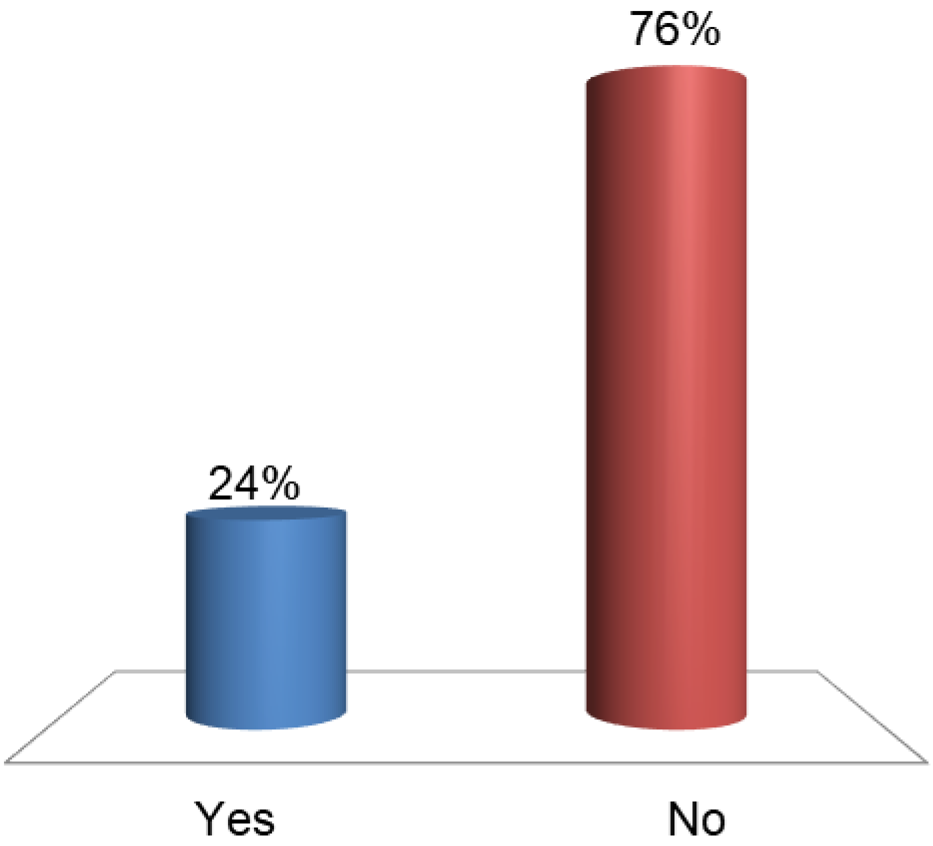
Lymph nodes	Anatomical boundaries					
	Cranial	Caudal	Medial	Lateral	Anterior	Posterior
Common iliac nodes	Bifurcation of abdominal aorta (at the inferior border of L4)	Bifurcation of the common iliac vessels (at the inferior border of L5, at the level of the superior border of the ala of sacrum)	Loose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

Role of clinical examination

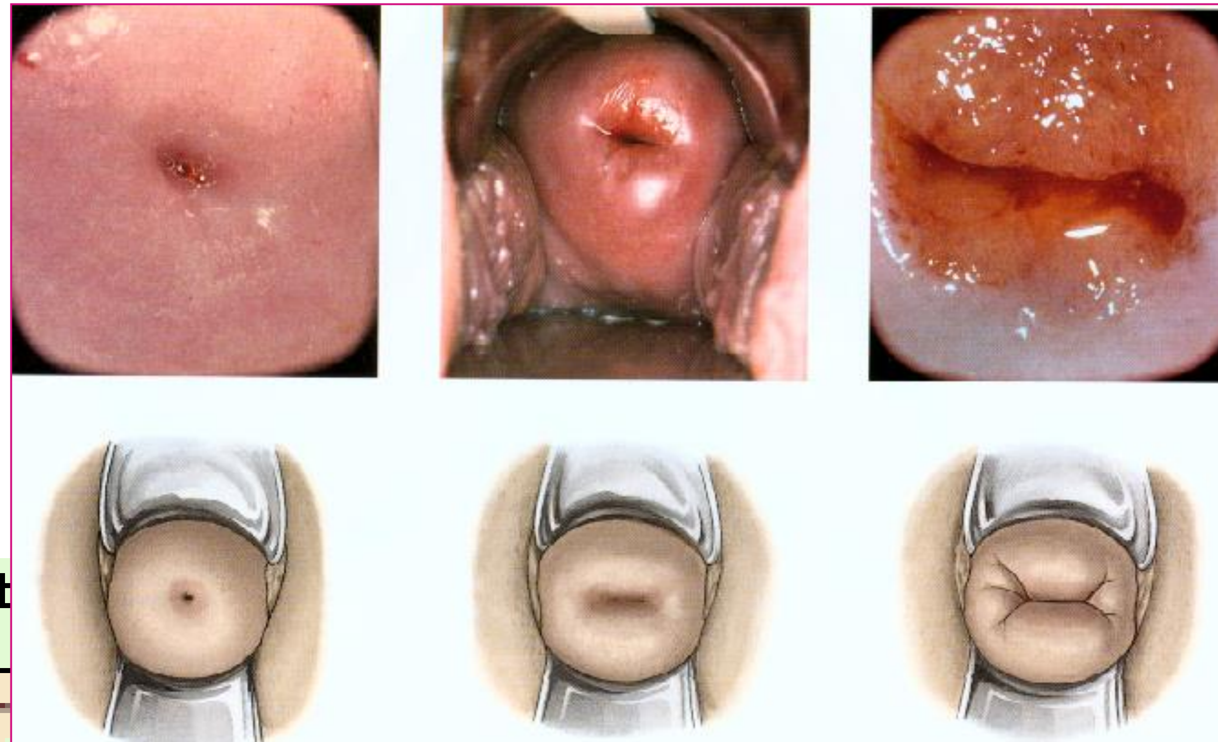
- Accurate tumor characteristics
- Staging
- General condition and fitness for radical treatment

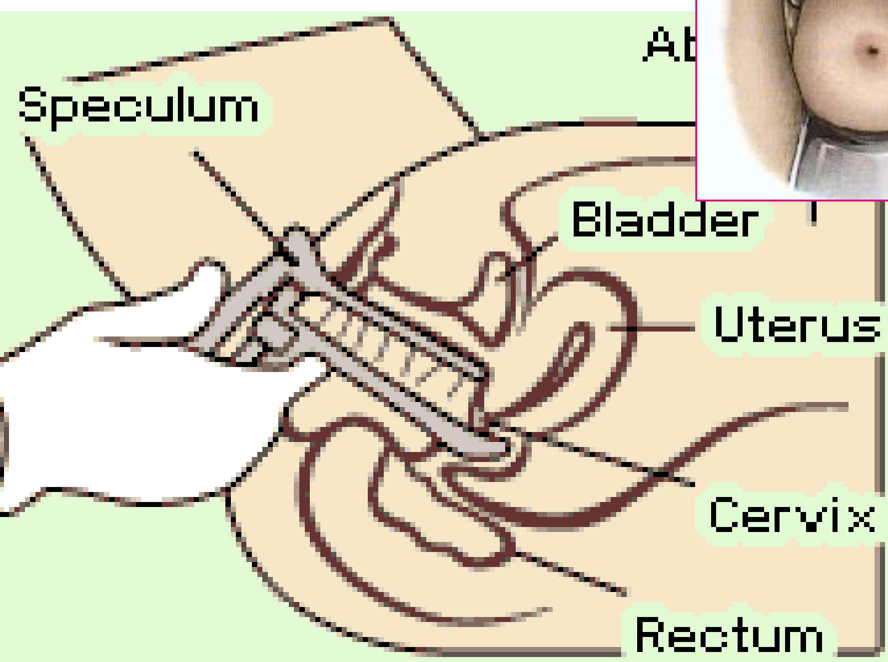
Do you do gynaecological examination under general anaesthesia?

A. Yes
B. No



Clinical examination





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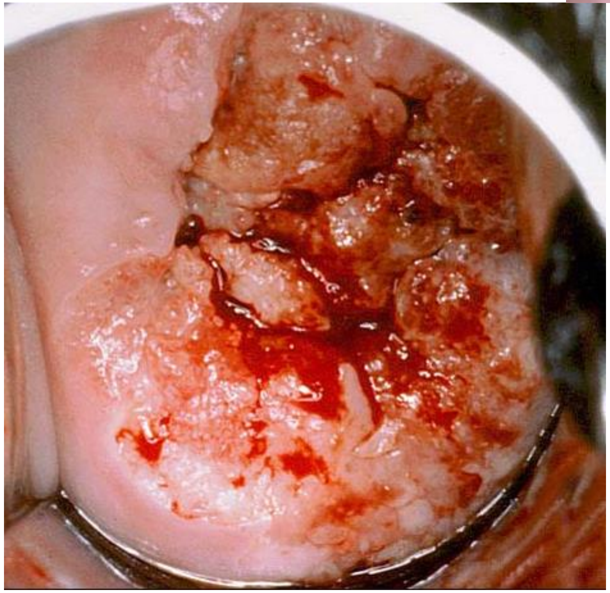
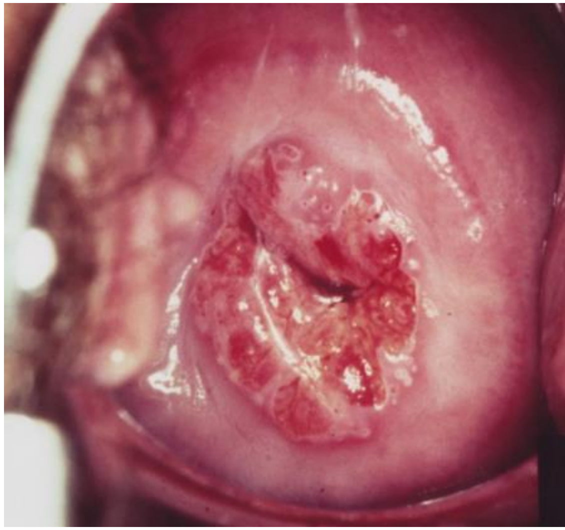
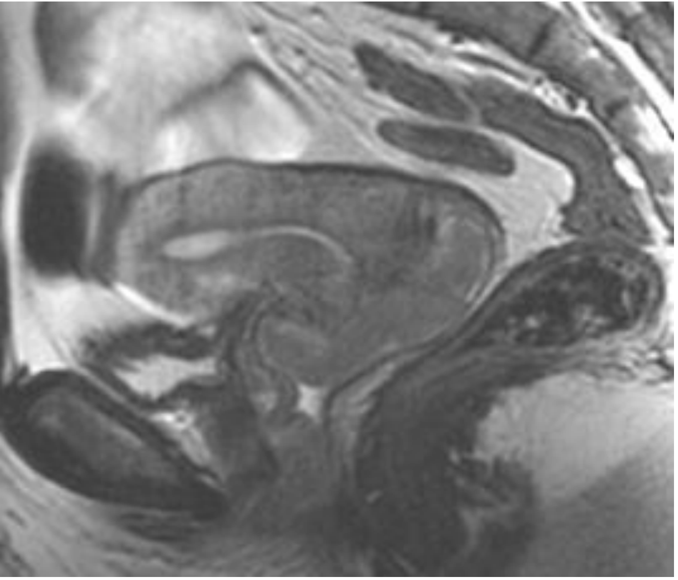
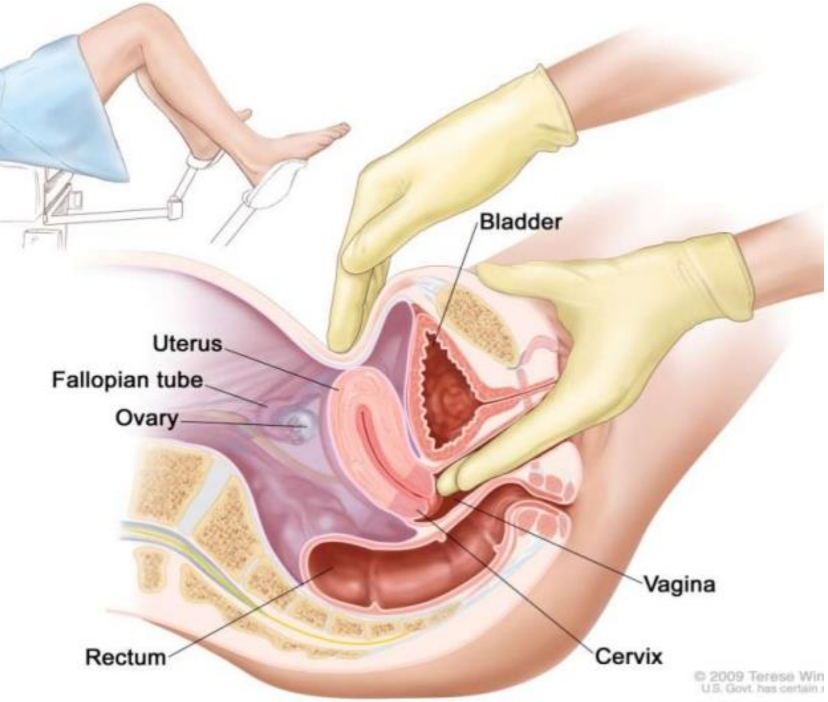






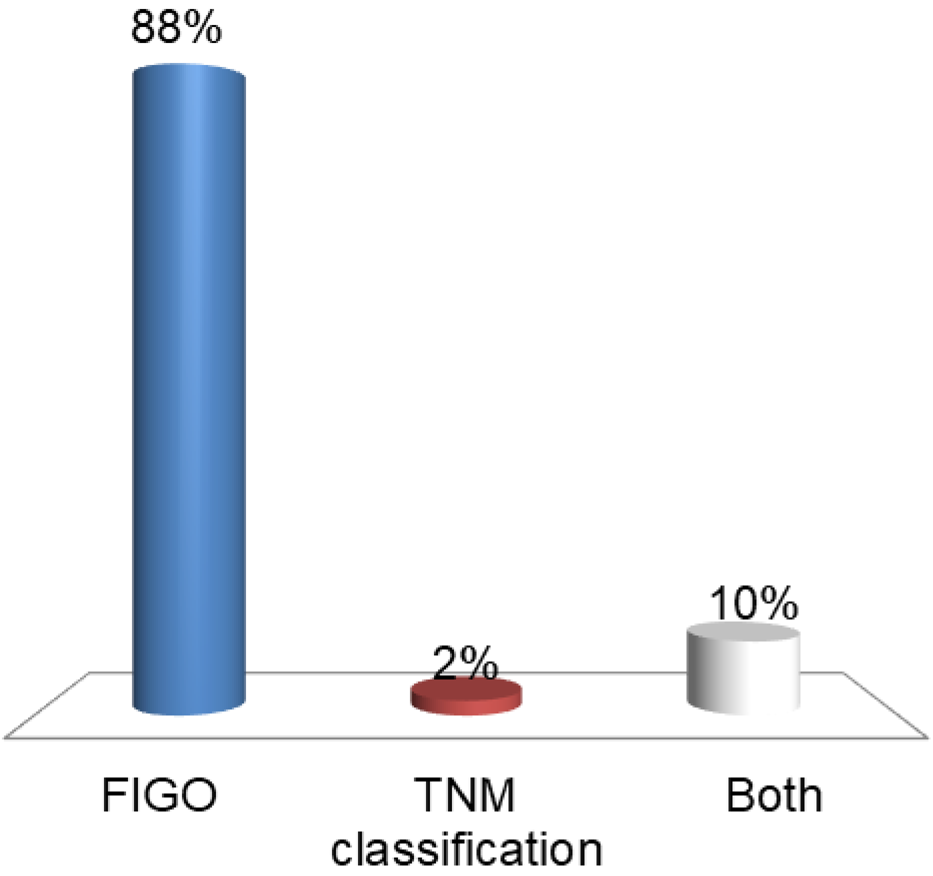
Clinical examination

Tumor measurement
Tumor extension:
vagina (vaginal impression)
parametrium



Staging
Which staging do you use?

A. FIGO
B. TNM classification
C. Both



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

ELSEVIER

Seminars in Diagnostic Pathology

Issues and inconsistencies in the revised gynecologic staging systems

Lisa Cole, MD, Mark H. Stoler, MD

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

FIGO staging 2008

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

5-year survival: 89.1%

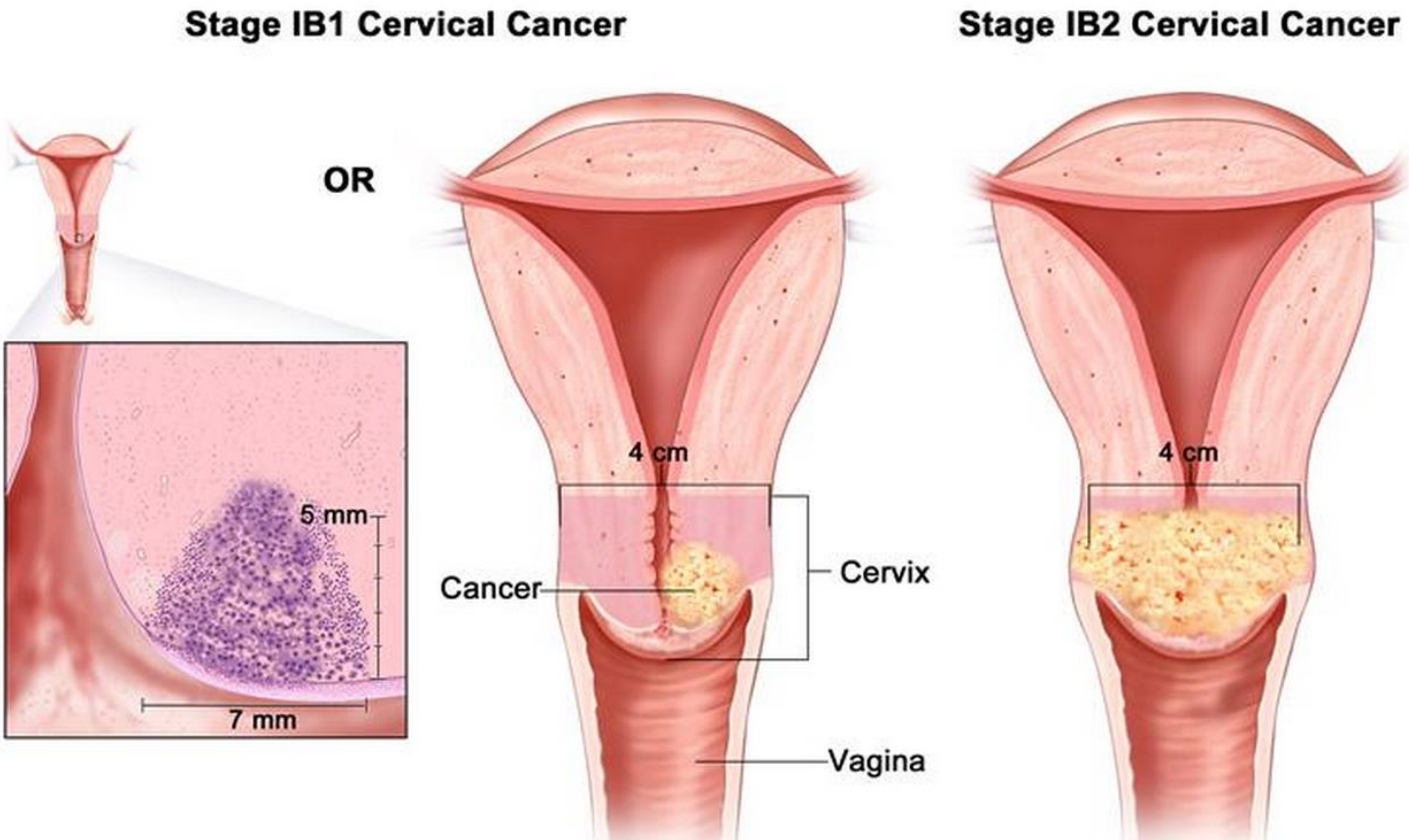
5-year survival : 75.7%

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

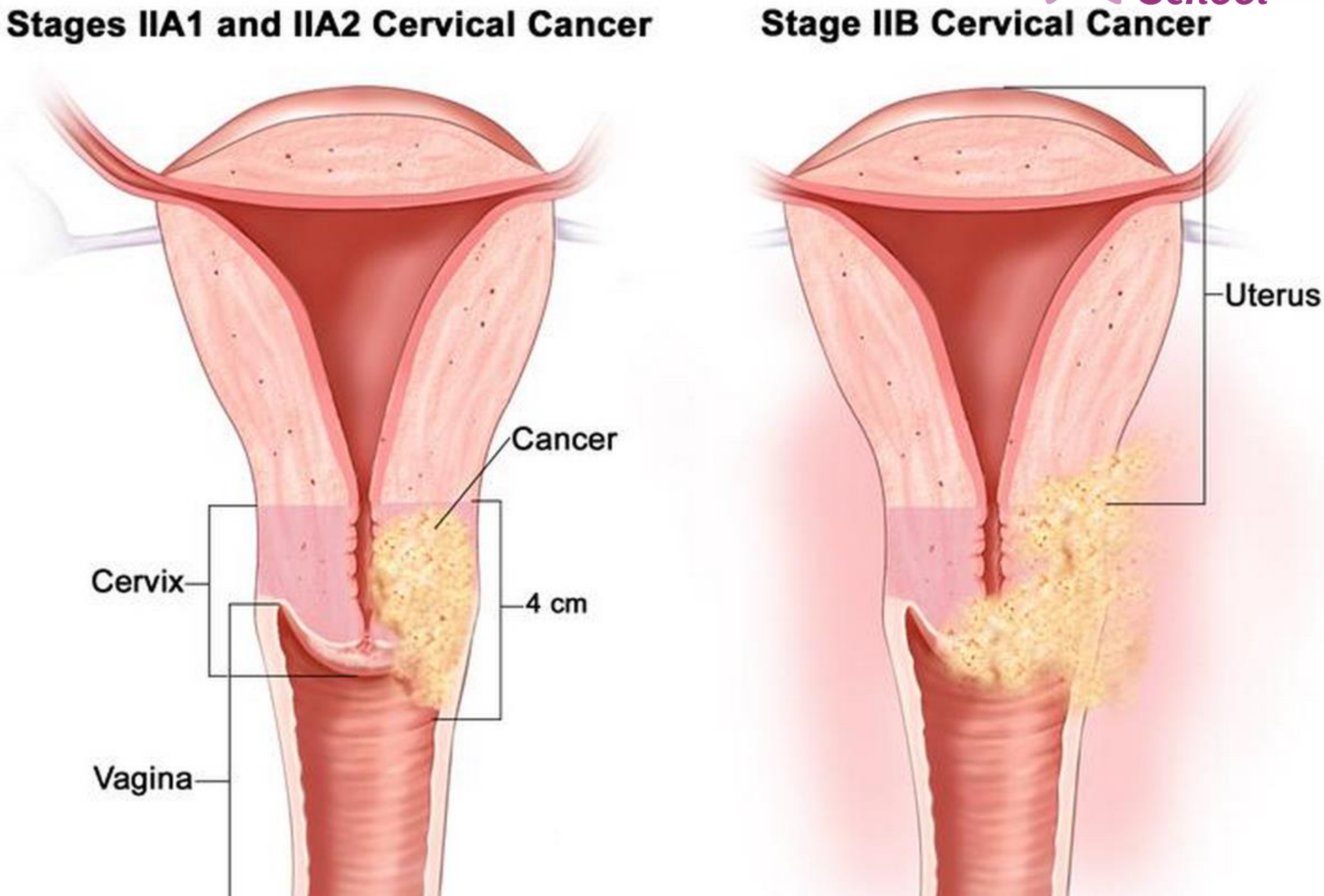
- **Stage III: tumour extends to pelvic sidewall and/or lower third of vagina or causes hydronephrosis or non-functioning kidney**
  - IIIa: lower third of vagina, no pelvic side wall extension
  - IIIb: involving pelvic side wall or causing hydronephrosis

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

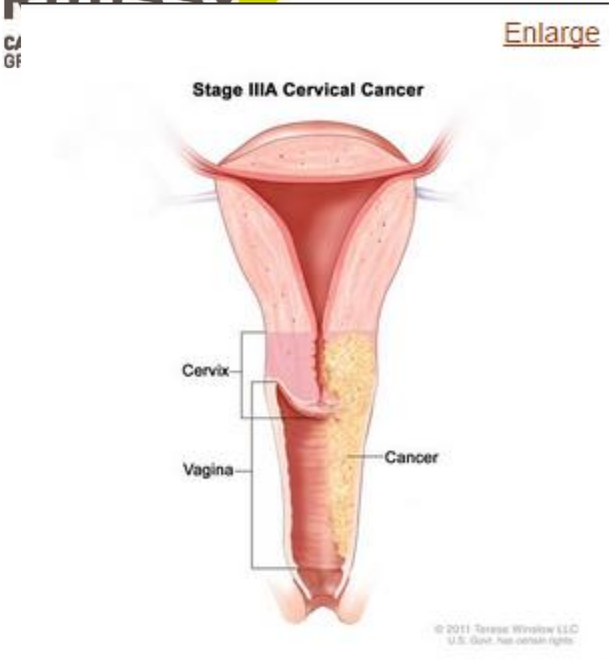
FIGO stage I 2008



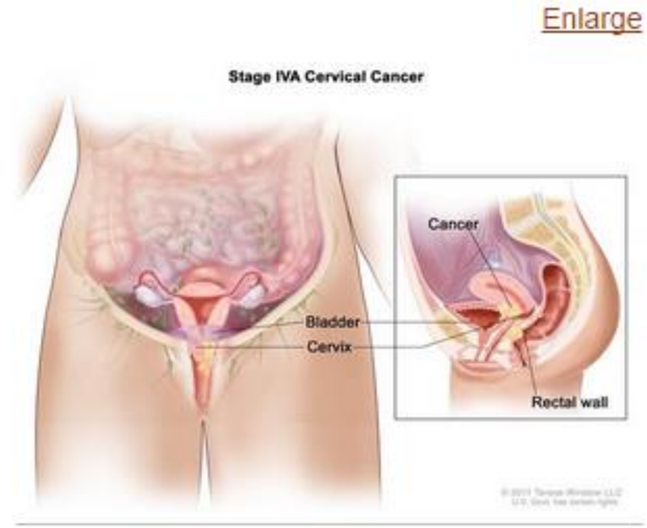
FIGO stage II 2008



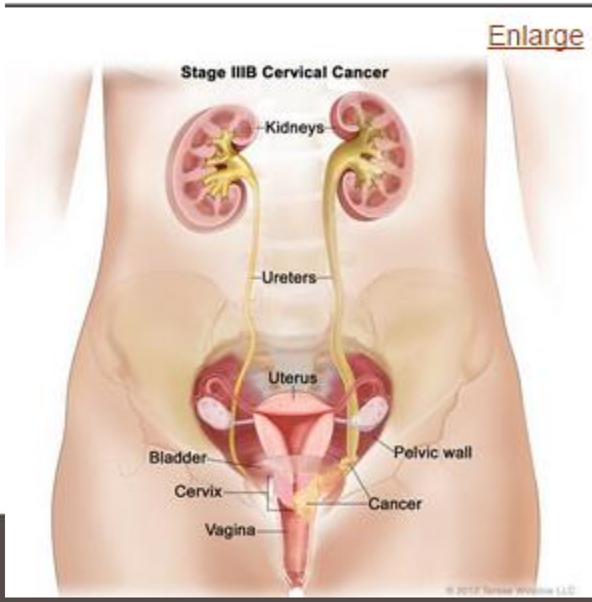
FIGO stage III/IV 2008



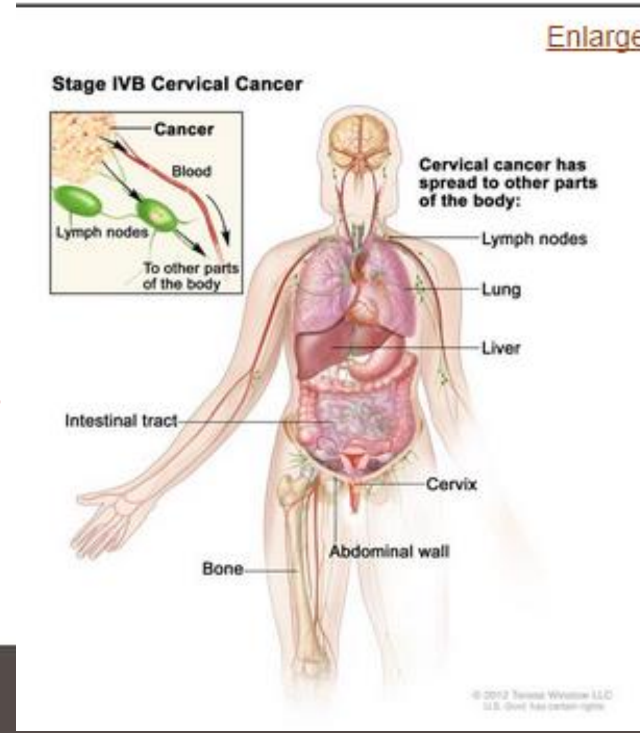
IIIA



IVA

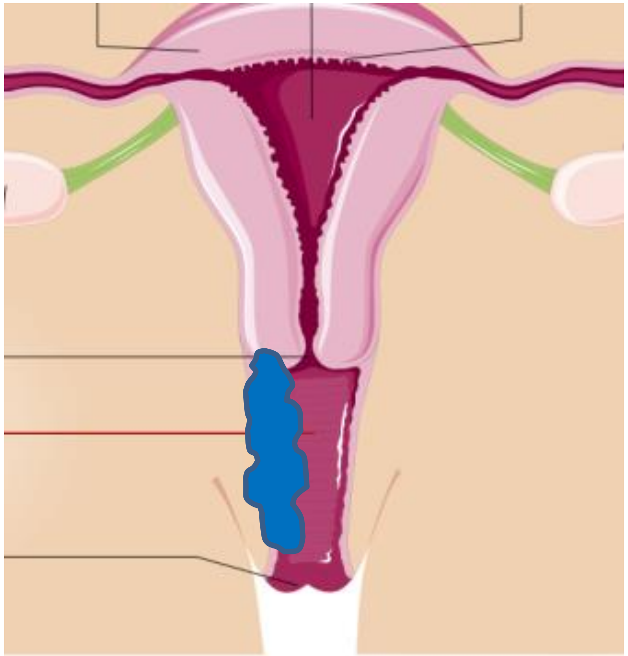


IIIB



IVB

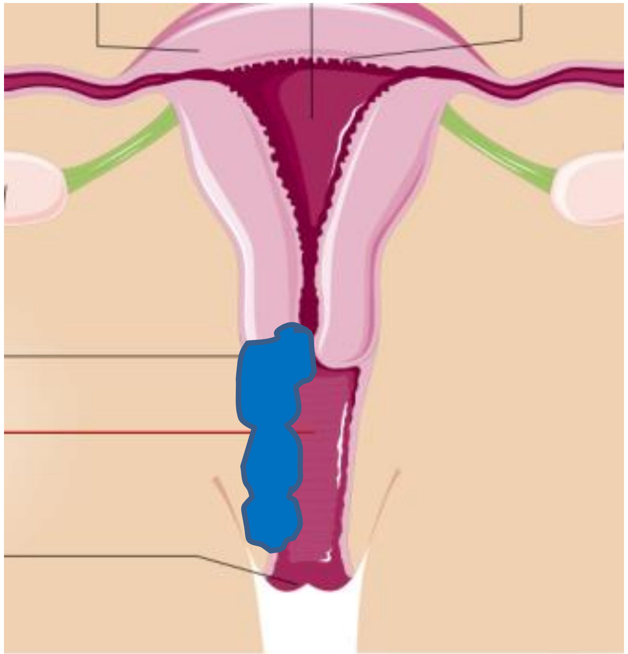
FIGO classification: How would you classify this tumor using FIGO staging rules?



A. Primary vaginal cancer with cervical extension

B. Primary cervical cancer with vaginal extension

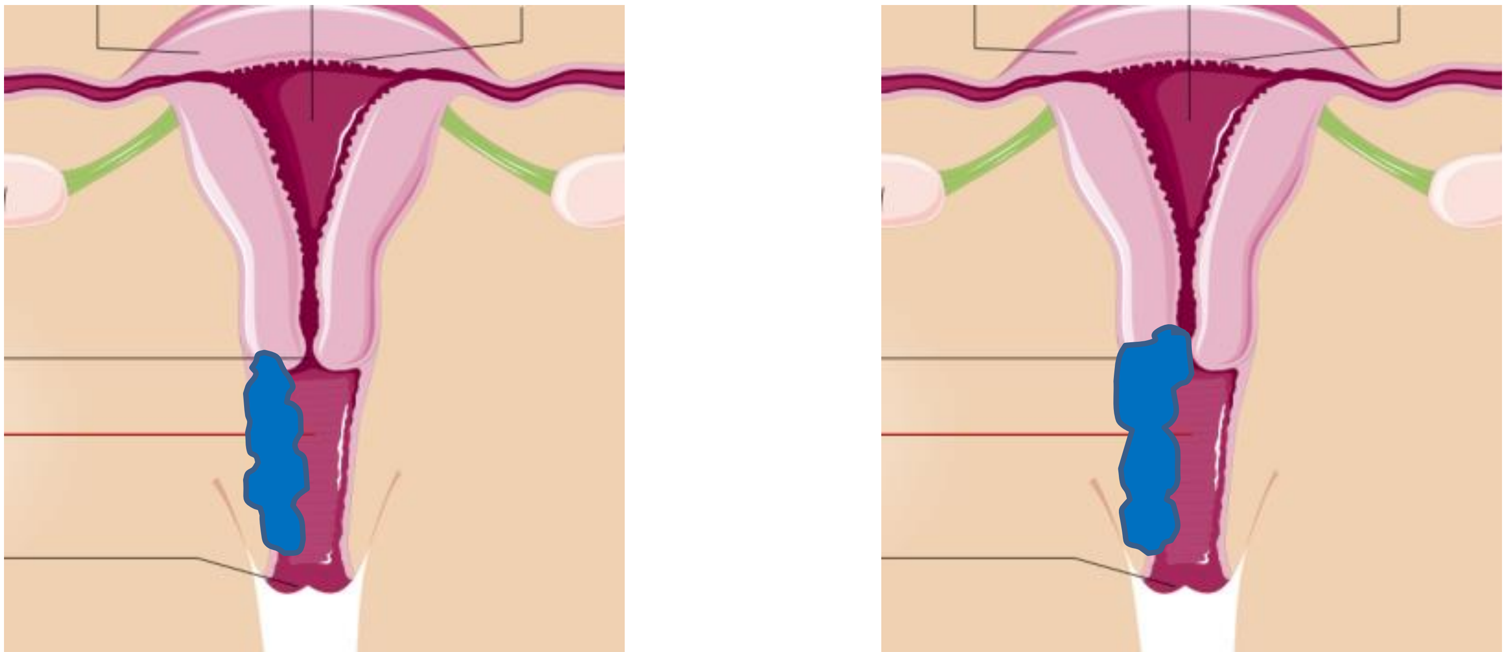
FIGO classification: How would you classify this tumor using FIGO staging rules?



A. Primary vaginal cancer with cervical extension
B. Primary cervical cancer with vaginal extension

FIGO classification

A B



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

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

FIGO staging / TNM classification

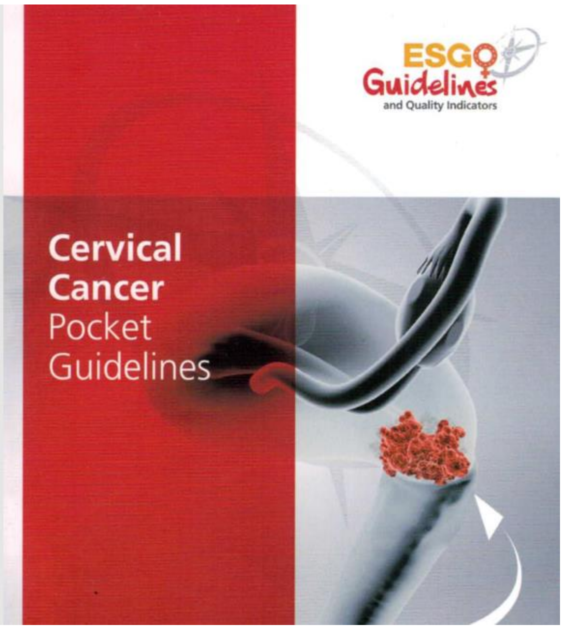
Regional Lymph Nodes (N)

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 paraortic 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



ESGO
European Society of
Gynaecological Oncology

POCKET GUIDELINES
CERVICAL CANCER

based on

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

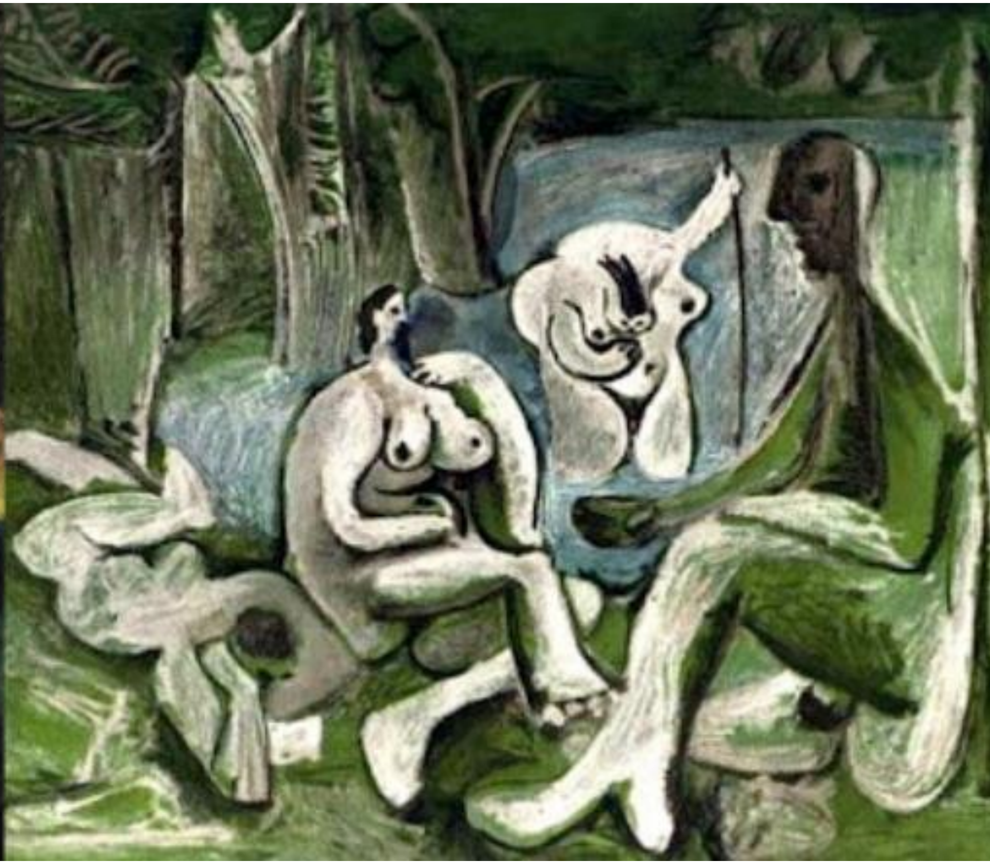
STAGING

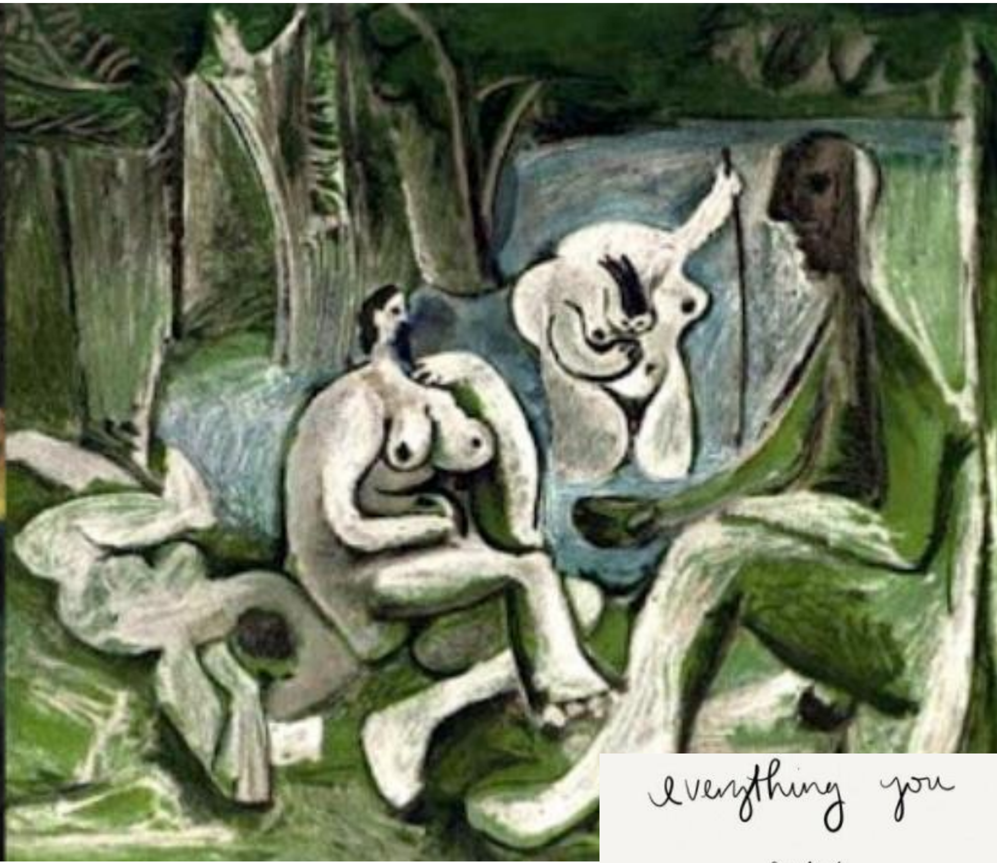
FIGO staging and TNM classification

✓	Patients with cervical cancer should be staged according to the TNM classification. Clinical staging (FIGO) should also be documented *(see Table 1)*.
C	TNM should be based on a correlation of various modalities (integrating physical examination, imaging, and pathology) after discussion in a multidisciplinary forum.
✓	The method used to determine tumour status (T); lymph node status (N); and systemic status (M), i.e., clinical (c), imaging (i), and/or pathological (p) should be recorded.
✓	Lymph node metastases should be classified according to the TNM classification *(see Principles of pathological evaluation)*.

Conclusion

- Importance of clinical examination
- Knowledge of lymphatic drainage
- FIGO classification $\longrightarrow$ TNM

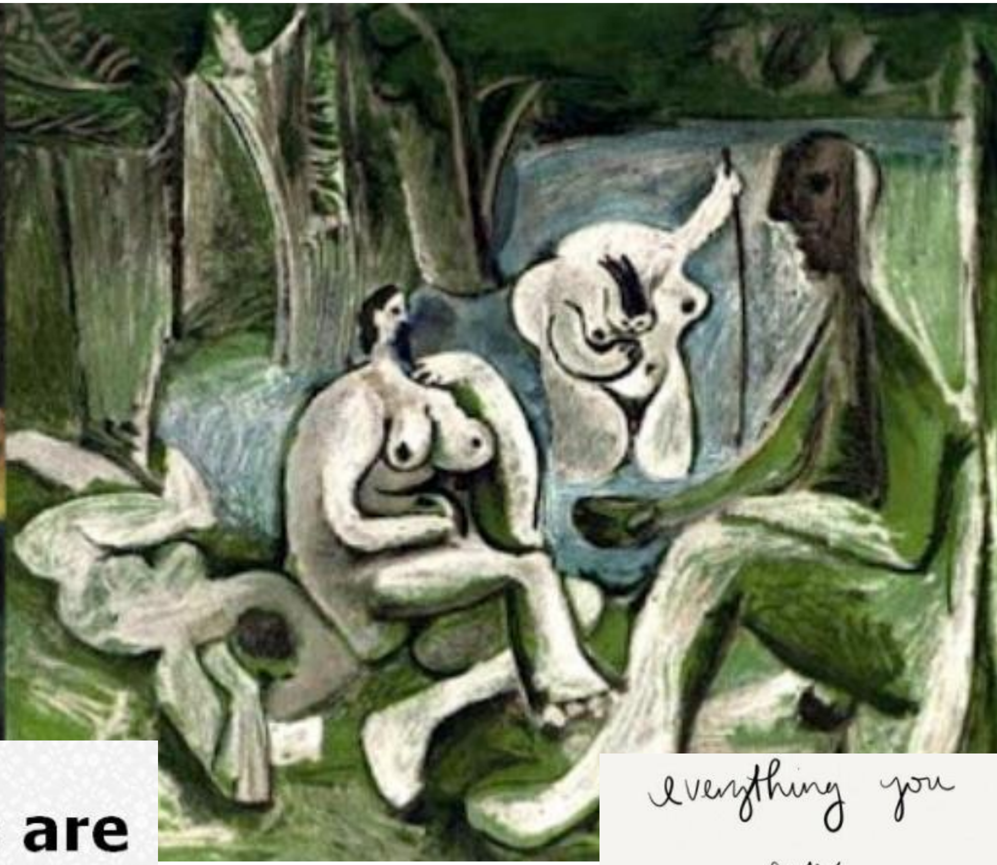





everything you
can
IMAGINE
is
real.
-pablo picasso

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

ESTRO School



"Computers are useless. They can only give you answers."
— Pablo Picasso

everything you can IMAGINE is real
-pablo picasso

IMAGING PATHOLOGY OF CERVICAL CANCER

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

At the time of Diagnosis/ Brachytherapy

Umesh Mahantshetty

Professor,

Department of Radiation Oncology

&

GYN Disease Management Group Member

Tata Memorial Hospital, Mumbai, India

2nd AROI - ESTRO TEACHING COURSE Lucknow 2018

IMAGING PATHOLOGY OF CERVICAL CANCER

RADIATION ONCOLOGIST'S PERSPECTIVE

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

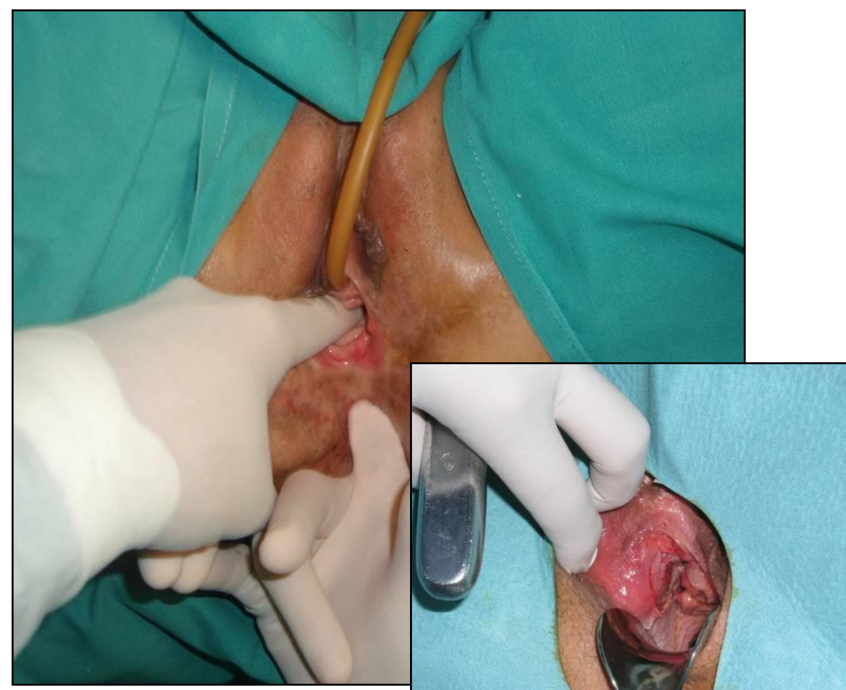
At Brachytherapy ……….. Prof. Richard Poetter

Basic imaging level

Clinical Examination : Inspection & Palpation

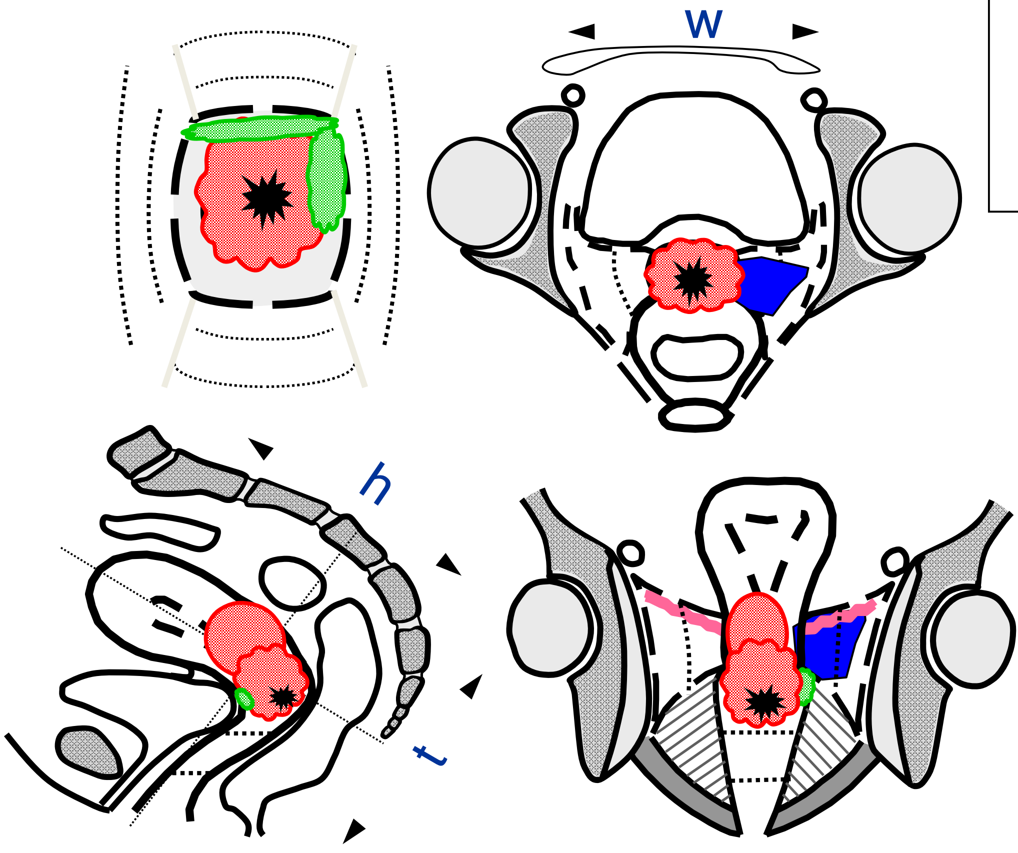
Imaging device: Eye & Finger

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

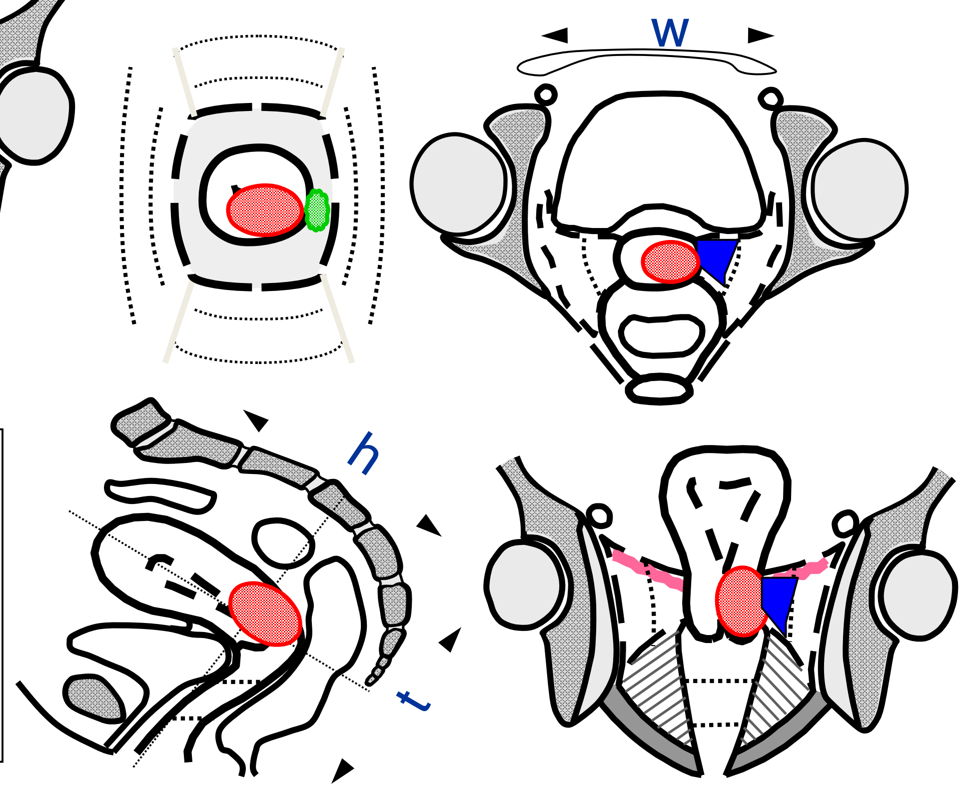


Documentation by Clinical Drawings

At Diagnosis



At Brachytherapy



- **Complimentary to other imaging modalities**
- **Cannot be replaced**

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

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

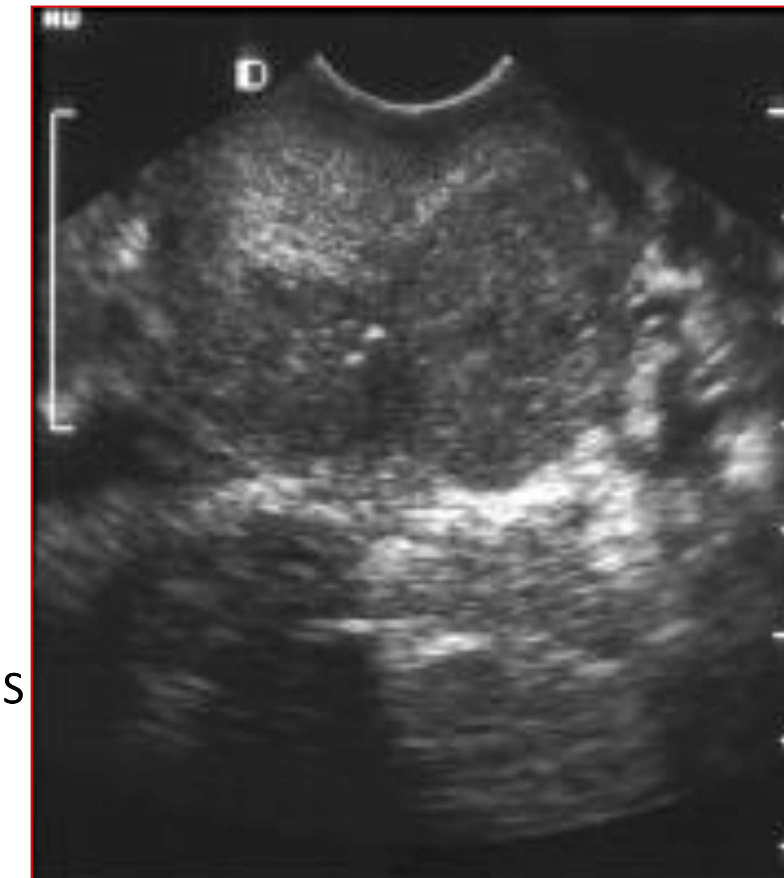
Signs

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

LIMITATIONS OF US

- OPERATOR DEPENDEDNT

- INTER OBSERVER VARIATION



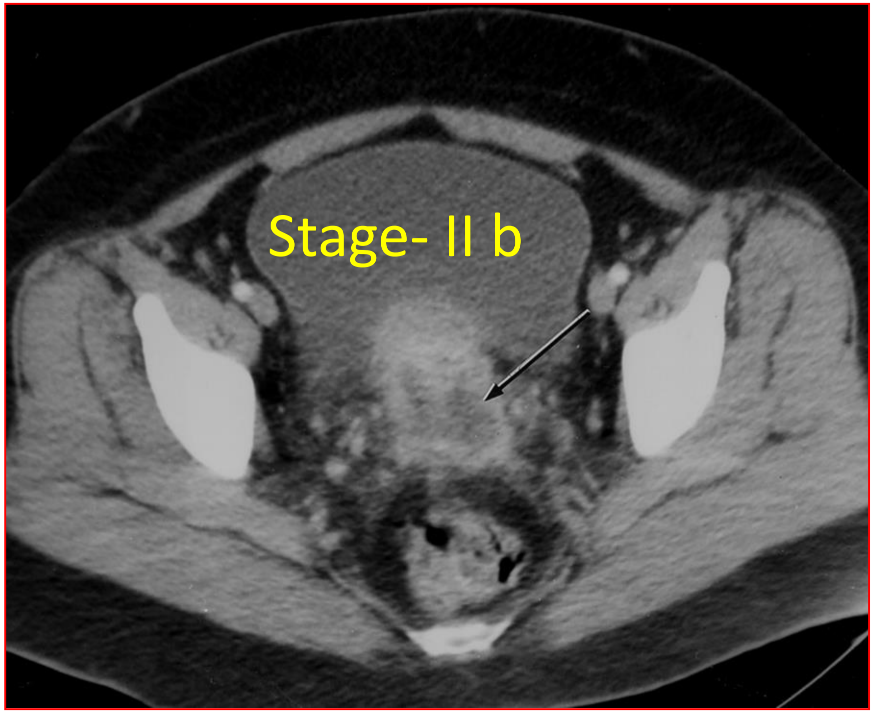
US IN BT

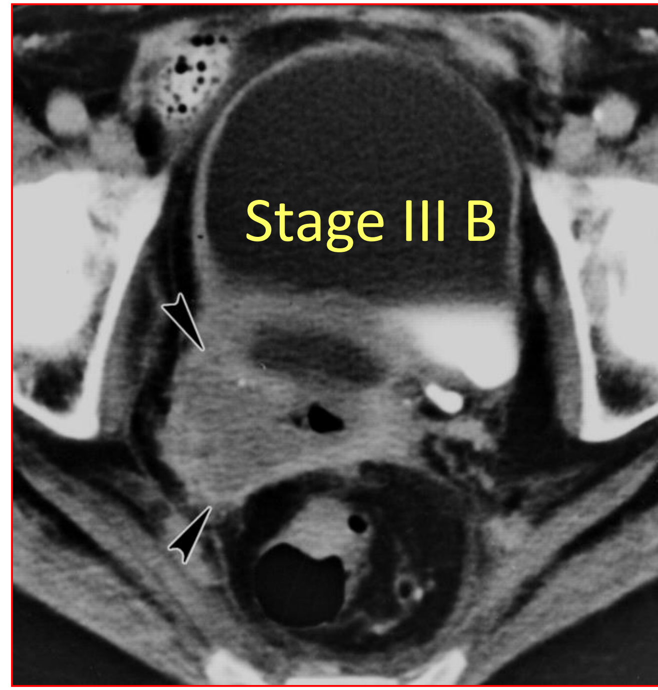
- REAL TIME IMAGING TO PREVENT PERFORATIONS

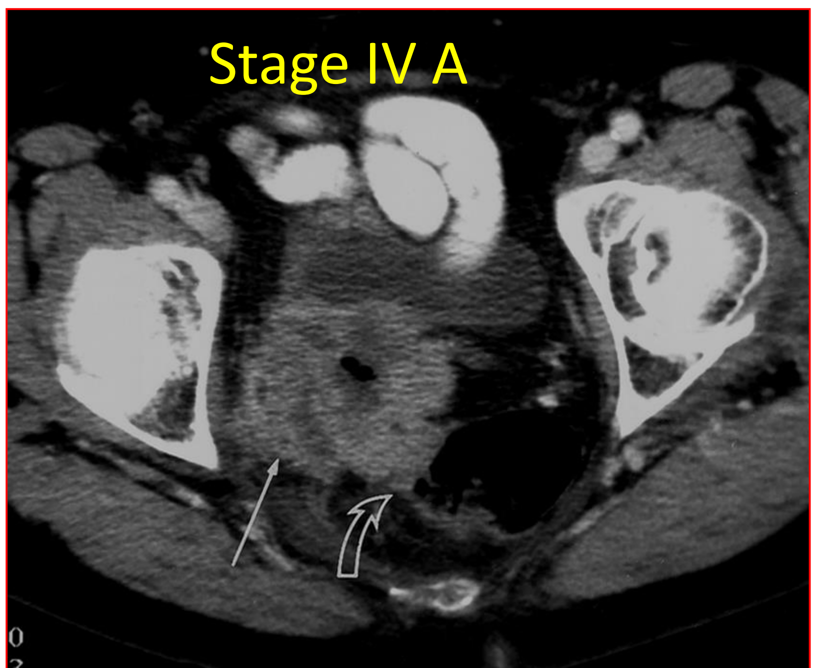
- GUIDE BT APPLICATION

CT

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

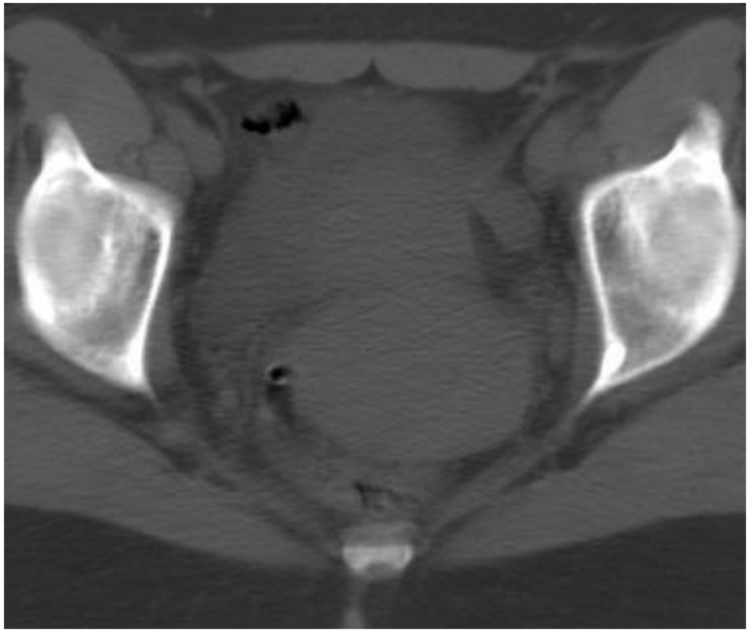

Stage- II b


Stage III B


Stage IV A

Computed Tomography

Non-enhanced CT simulator images



Advantages

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

Limitations

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

CT for EBRT- Image acquisition

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

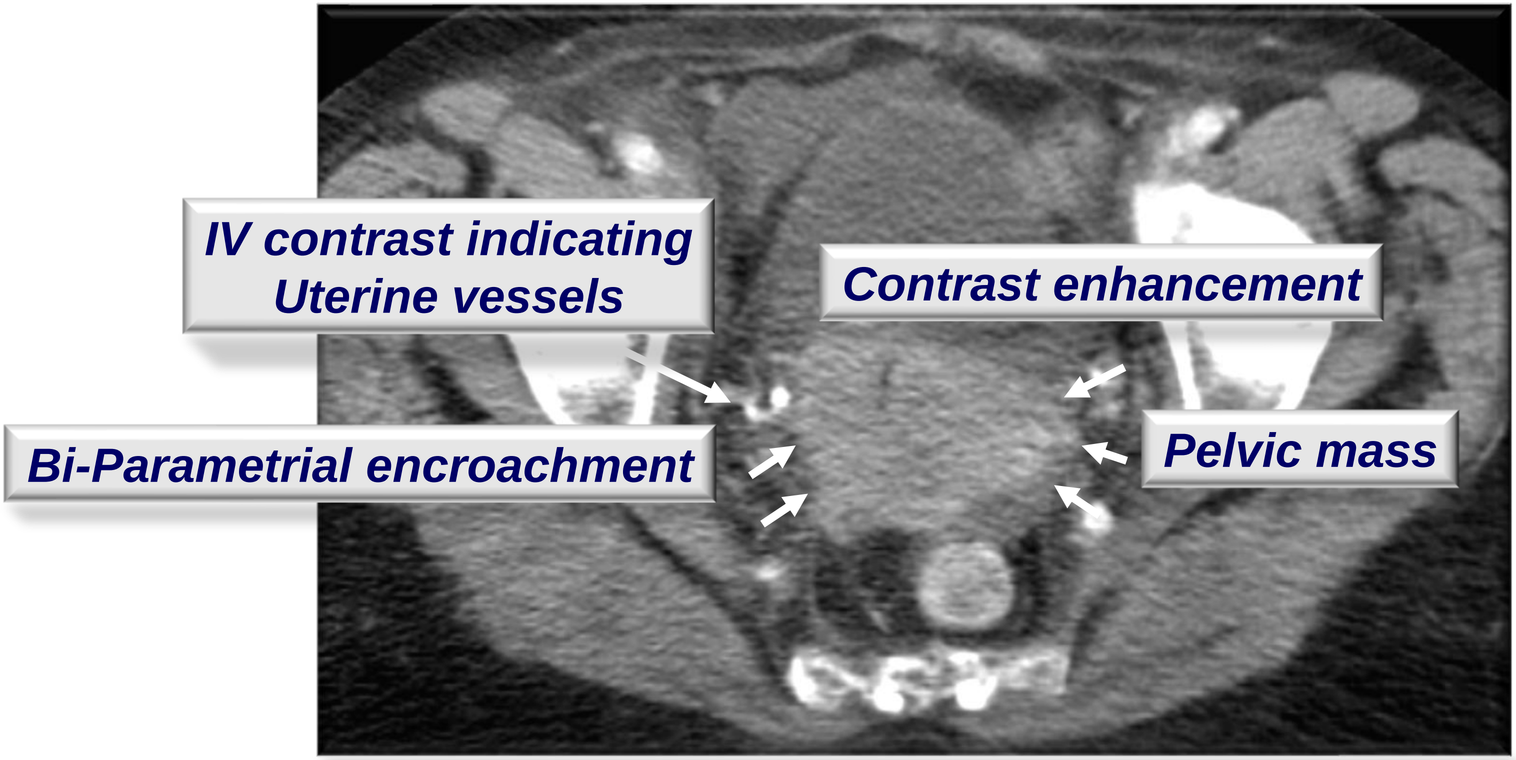
- ***administration of iv contrast***

- ***Delayed image acquisition for bladder visualisation***

- ***administration of oral iodine based contrast***

- ***patient positioning***

CT: IV contrast for EBRT imaging



CT: IV contrast delayed image acquisition

IV contrast – delayed image acquisition for bladder

Computed Tomography

Improvement of images through specific protocols

- Contrast enhanced CT simulator images
- Delayed images or retrograde injection of contrast for improved bladder delineation
- Specific protocols required regarding contrast flow, image aquisition delay
- Safety precautions (allergic reactions, resuscitation equipment, presence of physician during imaging).

Bladder contrast: influence on dose distribution In conformal radiotherapy can be avoided

Treatment planning systems: contouring of the contrasted bladder and asigning density value

Imaging protocols MRI and CT

General characteristics

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

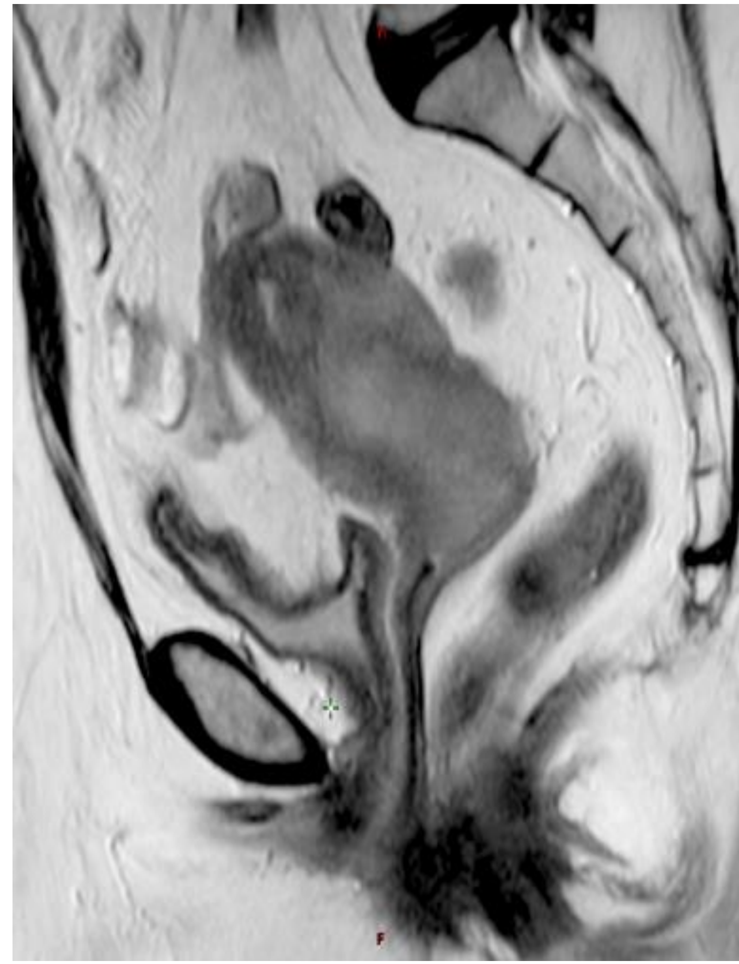
Diagnostic scan

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

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

Endometrial invasion of cervical disease

Vs



CT

MRI

Indications for MRI in cervical cancer

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

Advantages of MRI

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

Radiotherapy and Oncology 103 (2012) 113–122

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GEC-ESTRO Recommendations

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

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

[a] Metropolitan Hospital, Athens, Greece; [b] Institut Curie, Paris, France; [c] Aarhus University Hospital, Denmark; [d] Institute of Oncology Ljubljana, Slovenia; [e] Comprehensive Cancer Center, Medical University of Vienna, Austria; [f] Universitaire Ziekenhuis Gasthuisberg Leuven, Belgium; [g] Institut Gustave Roussy, Villejuif, France

ABSTRACT

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

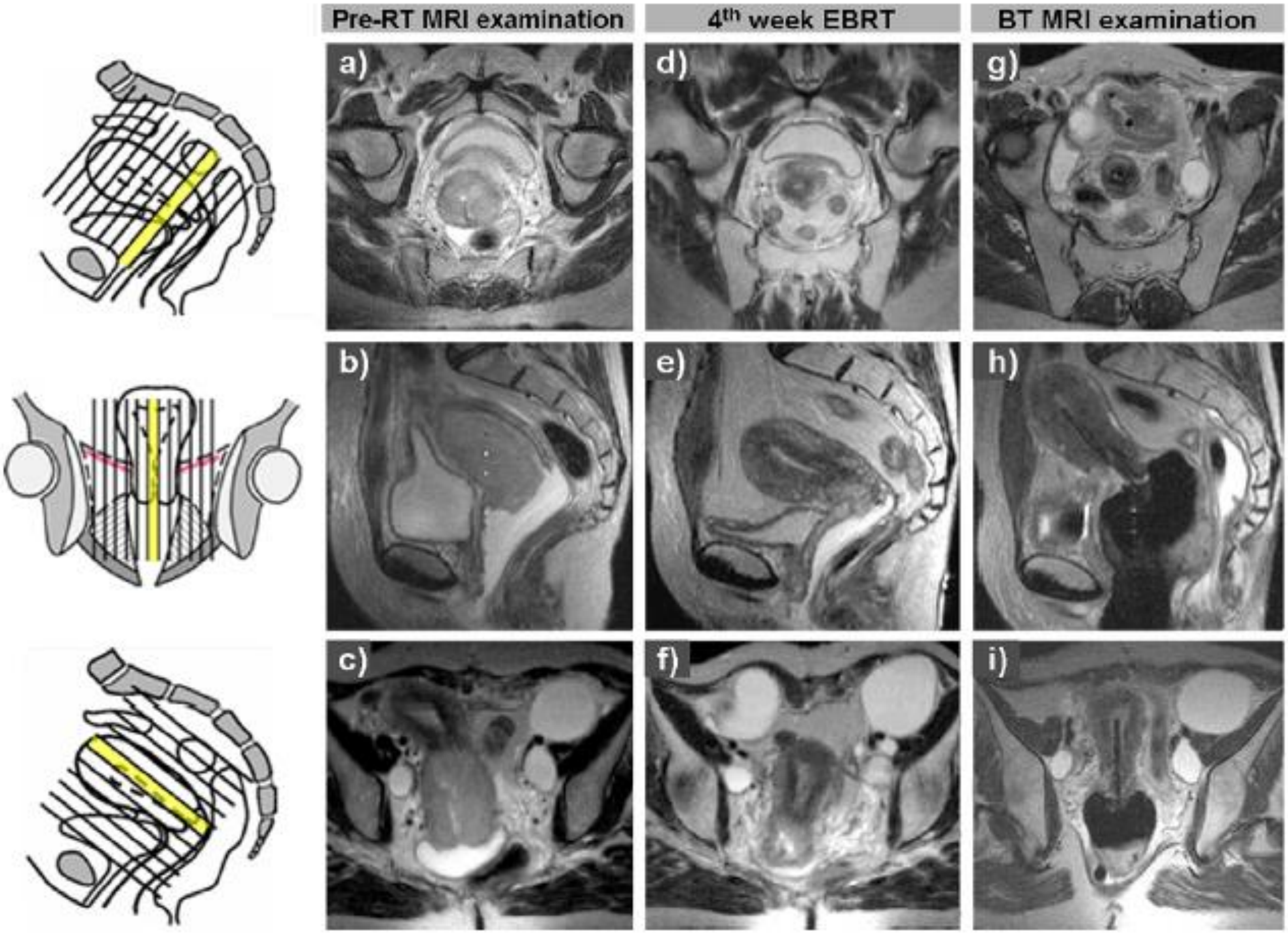
Methods and parameters have been developed and progressively validated from clinical experience from different institutions (IGR, Universities of Vienna, Leuven, Aarhus and Ljubljana) and successfully applied during expert meetings, contouring workshops, as well as within clinical and interobserver studies.

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

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

 Radiotherapy and Oncology 103 (2012) 113–122

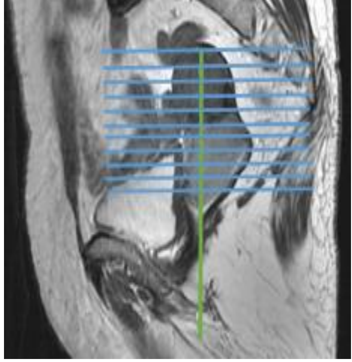
IMAGE PLANE, ORIENTATION AND COVERAGE



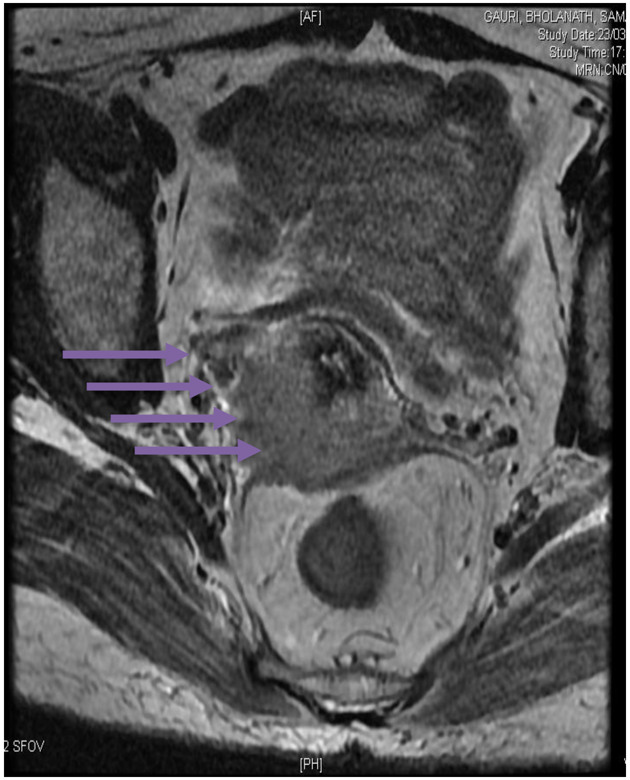
Para – transverse , para-coronal, para-saggital

RO 2012; GEC-ESTRO RECOMMENDATION-IV

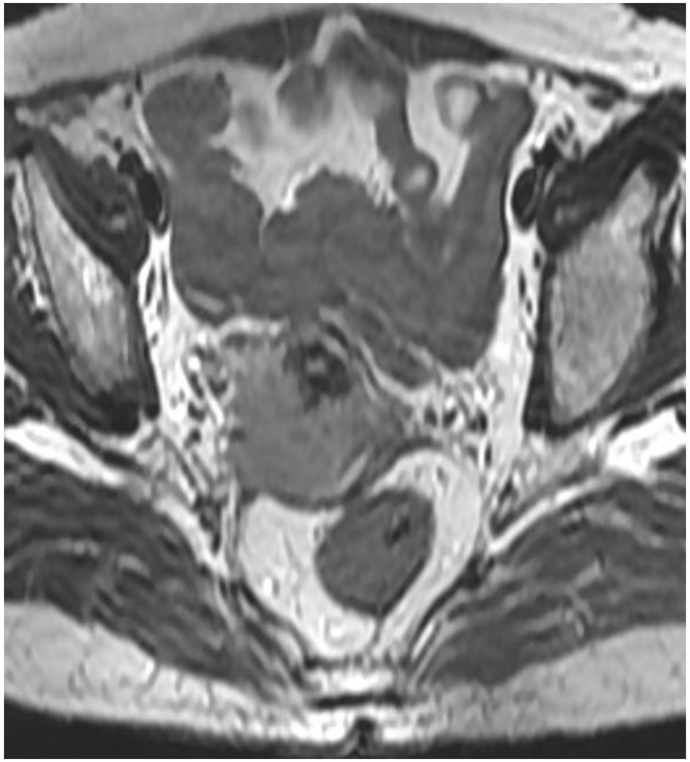
Right parametrial invasion



Para-axial



True-axial



Technical Requirements:

1. **Magnetic Field Strength:**

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

   - 3T for Pre Rx MR (Experience growing)

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

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

3. **Coils:** Pelvic coil

4. **Patient Preparation:**

   - Bowel preparation and reduction in bowel movements

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

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

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

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

   - Rectal dosimeters - optional

RO 2012; GEC-ESTRO RECOMMENDATION-IV

Table 2

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

Protocol			Sequence parameters									
	Number		Fatsat	TR (ms)[a]	TE (ms)[b]	ETL[c]	FOV (cm^2)[d]	M(f)[e]	M(p)[e]	Nex[f]	SW[g]	NPW[h]
Pre-RT MRI scan	1		No	2000–5000	90–120	4–20	35 × 20	512	256	2	3–4	Yes
	2		No	2000–5000	90–120	4–20	35 × 40	512	256	2	5	Yes
	3		No	2000–5000	90–120	4–20	35 × 20	512	256	2	3–4	Yes
	4		No	2000–5000	90–120	4–20	35 × 40	512	256	2	5	Yes
	5	TSE	Optional	500–700	10–20	NA	35 × 20	512	256	2	5–7	Yes
		3D GRE[i]	Optional	5–10	2–5	[i]	37 × 30	[i]	[i]	[i]	1–4	[i]
	6	TSE	Optional	500–700	10–20	NA	35 × 20	256	256	2	3–5	Yes
	7	TSE	Optional	500–700	10–20	NA	35 × 20	256	256	2	3–5	Yes
		3D GRE[i]	Optional	5–10	2–5	[i]	37 × 30	[i]	[i]	[i]	1–4	[i]
BT MRI scan	8		No	2000–5000	90–120	4–20	35 × 20	512	256	2	3–5	Yes
	9		No	2000–5000	90–120	4–20	35 × 40	512	256	2	3–5	Yes
	10		No	2000–5000	90–120	4–20	35 × 20	512	256	2	3–5	Yes
	11		No	2000–5000	90–120	4–20	35 × 40	512	256	2	3–5	Yes
	12		No	See Refs. [22,48–56] for sequence parameters								
	13		No									

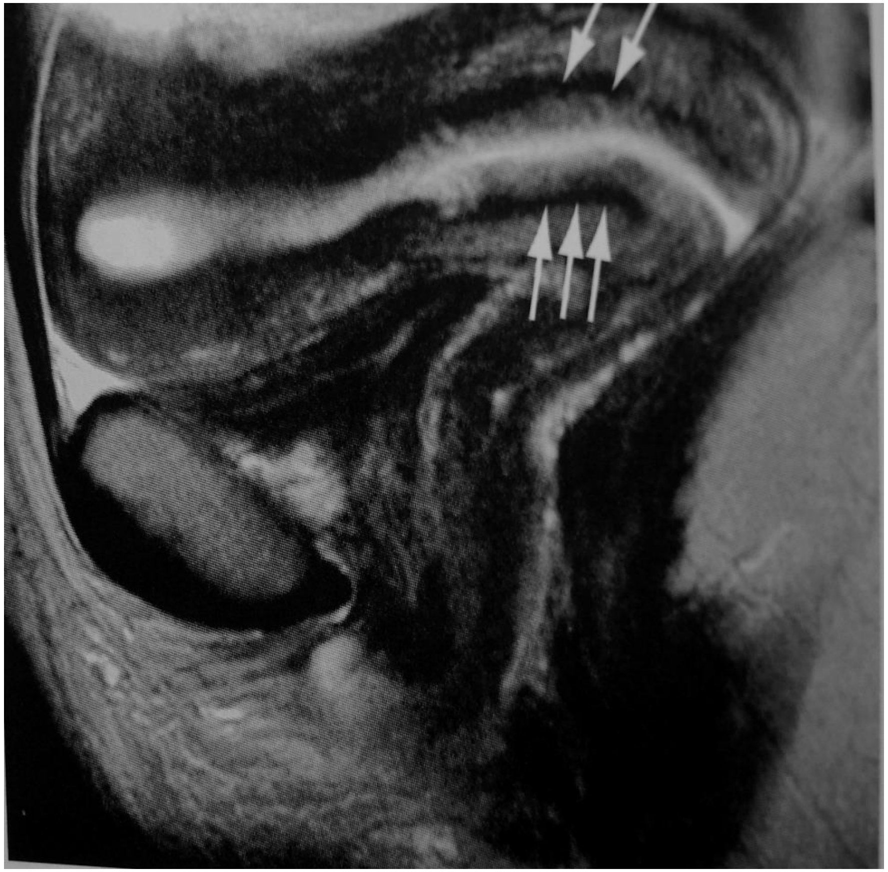
[a] TR = time of repetition.
[b] E = time of echo.
[c] ETL = echo train length or turbo factor.
[d] FOV = minimum field of view.
[e] M = matrix: (f) = frequency, (p) = phase.
[f] Nex = number of excitations.
[g] SW = slice width.
[h] NPW = no phase wrap.
[i] Exact parameters depending on vendor, gradient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

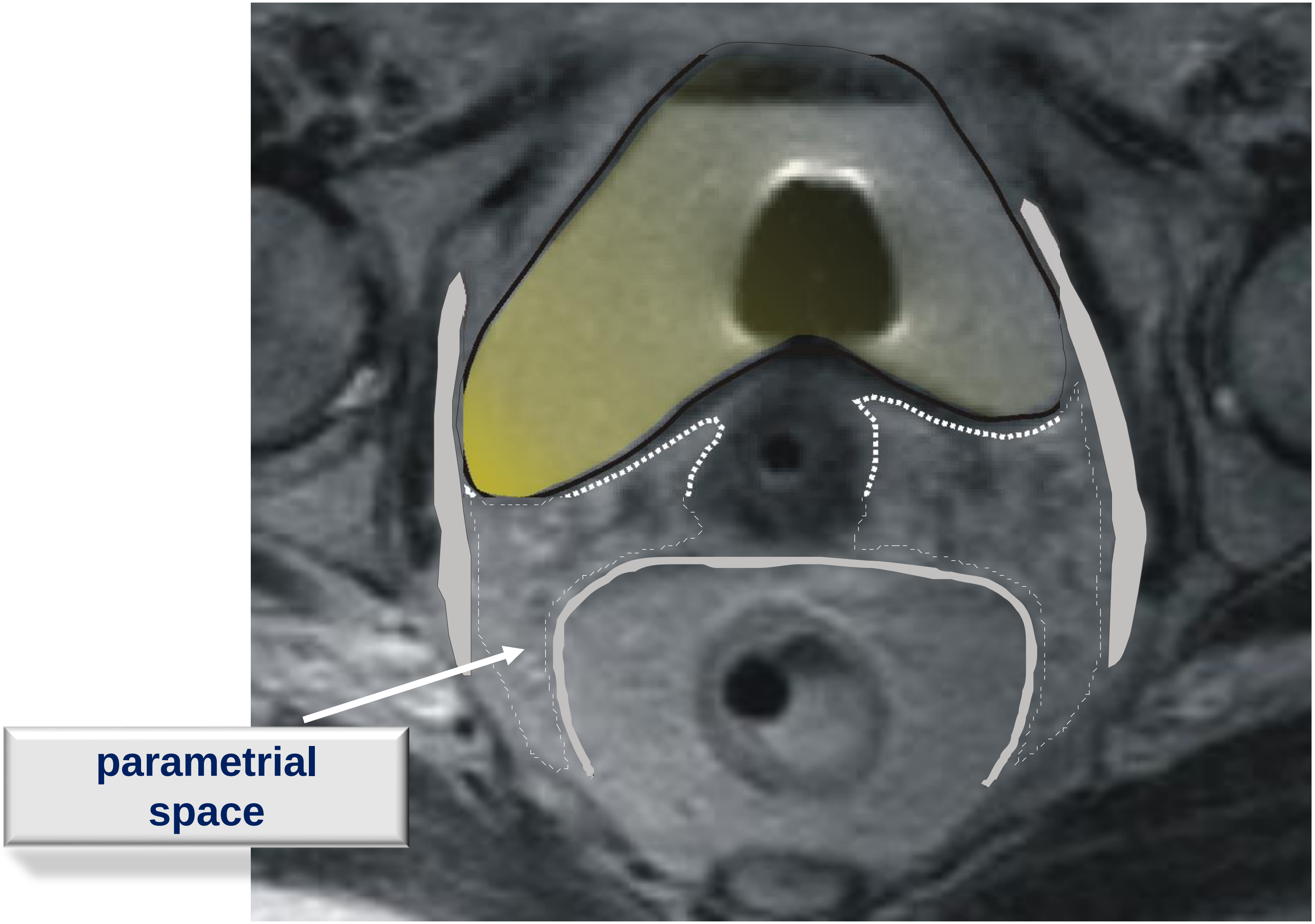
Interaction with Radiologist, Radiology and Brachytherapy Technologist

Standardize a protocol for your MR

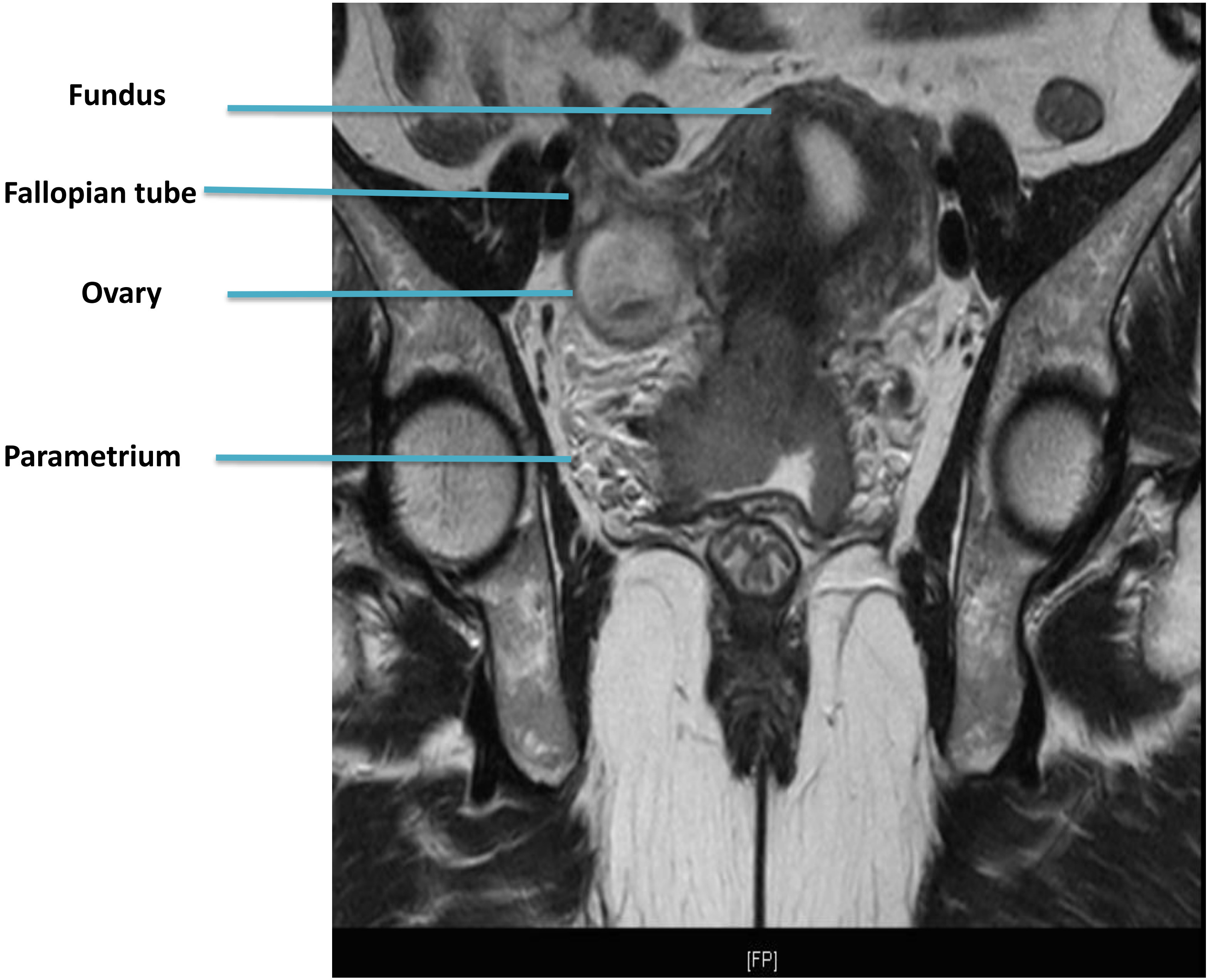
RO 2012; GEC-ESTRO RECOMMENDATION-IV

Normal Anatomy



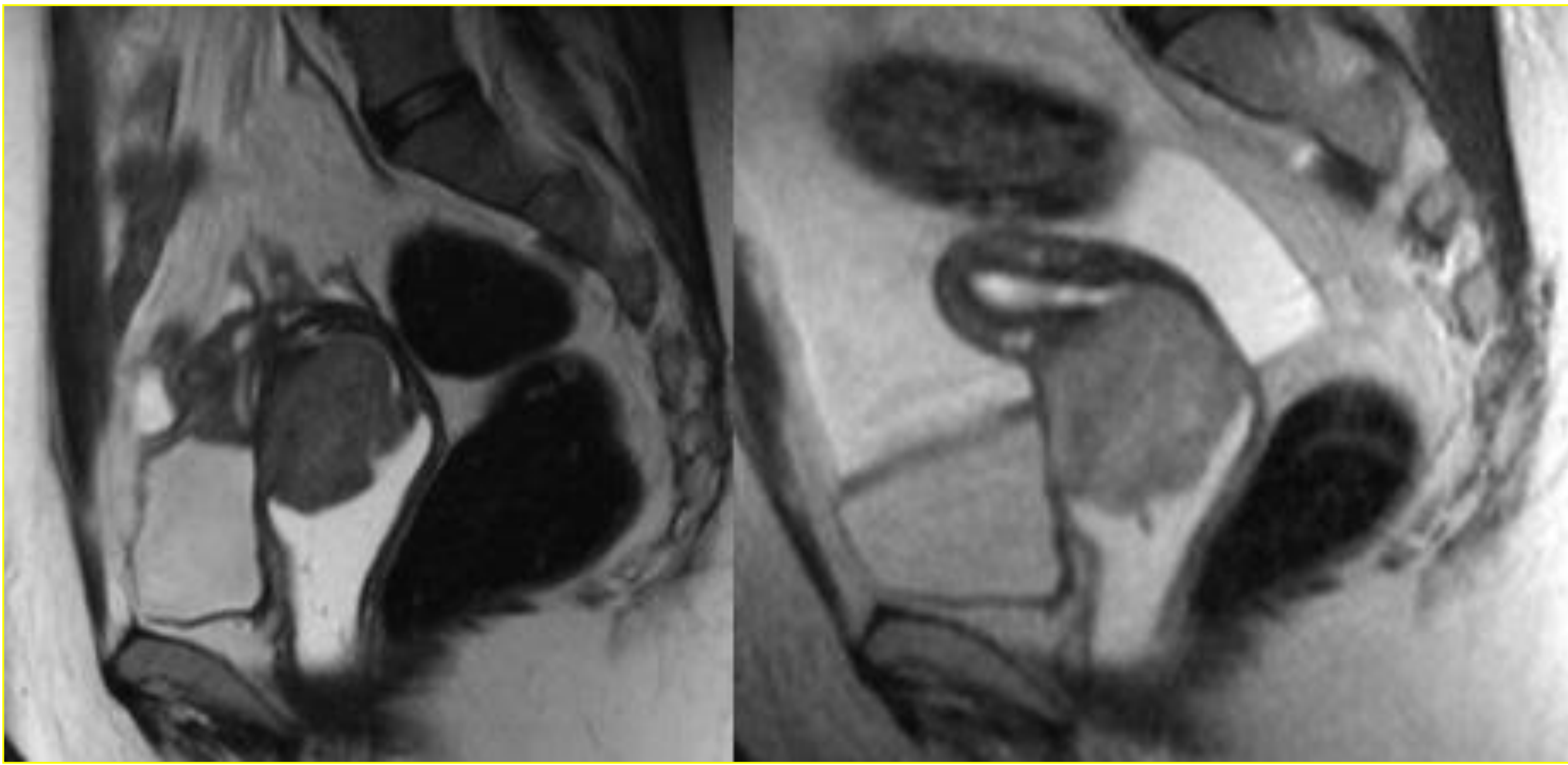


Dimopoulos et al. IJROBP 2006



Fundus
Fallopian tube
Ovary
Parametrium
[FP]

MR FIELD STRENGTH

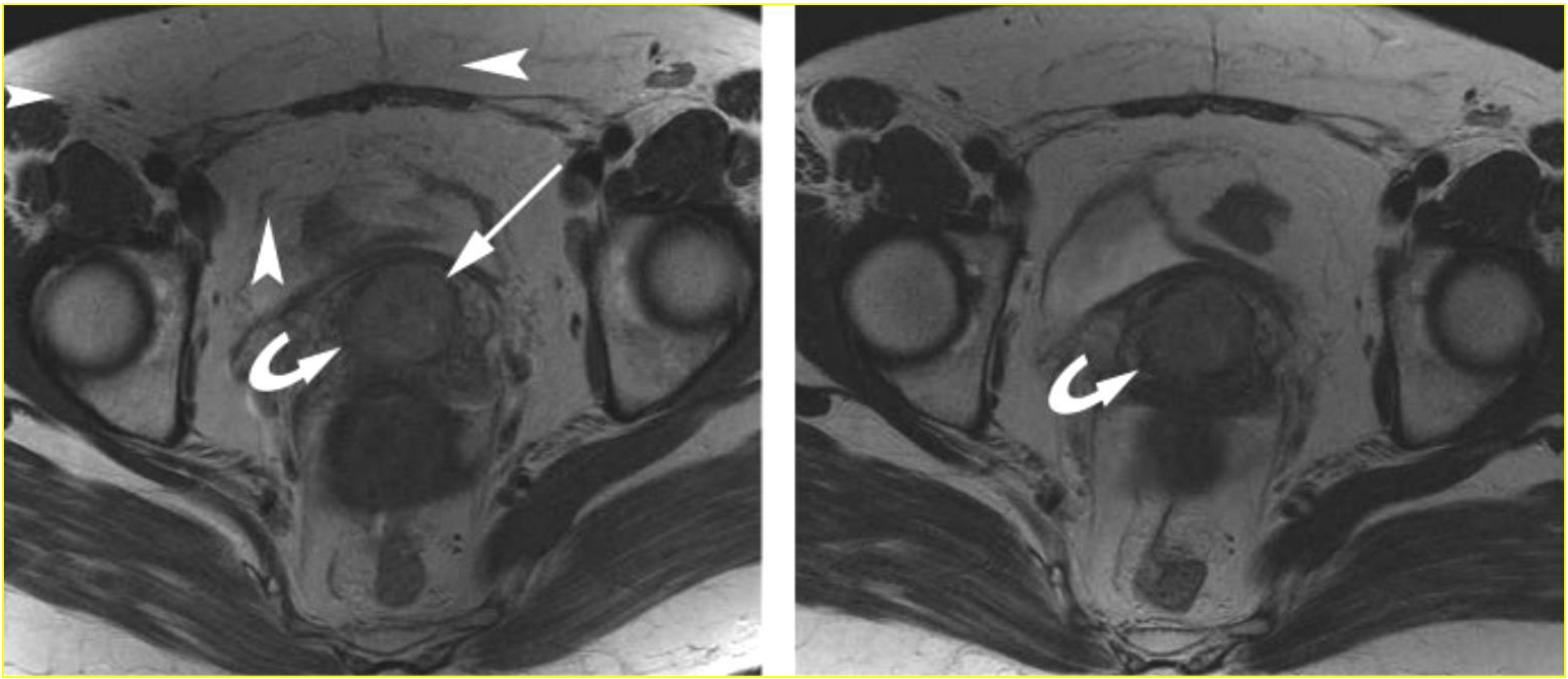


1.5 T

0.23 T

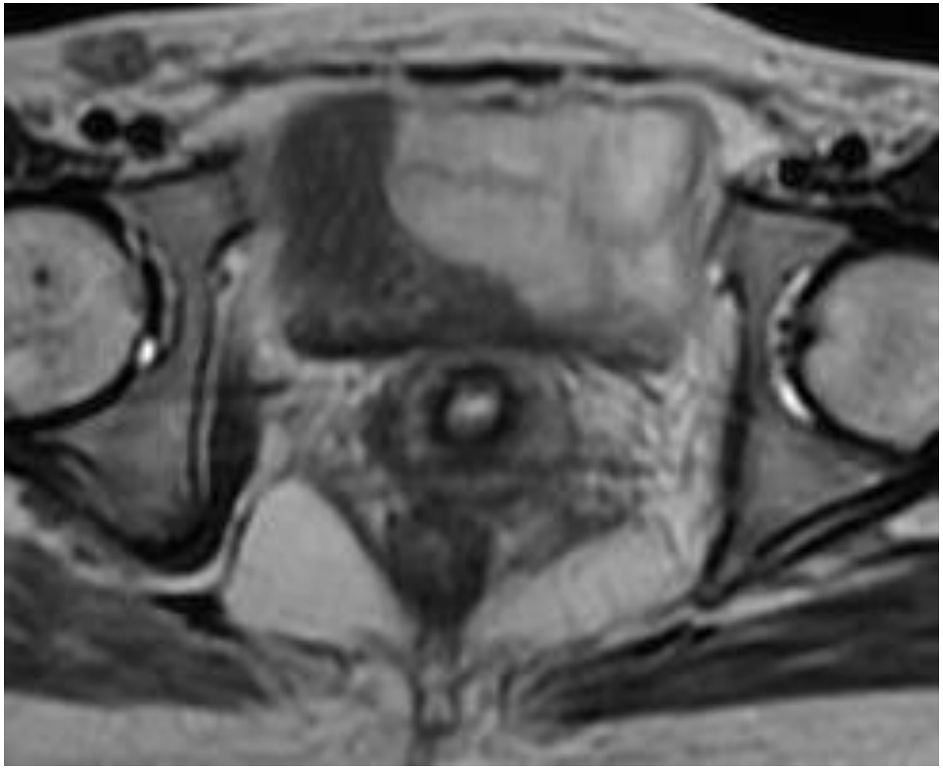
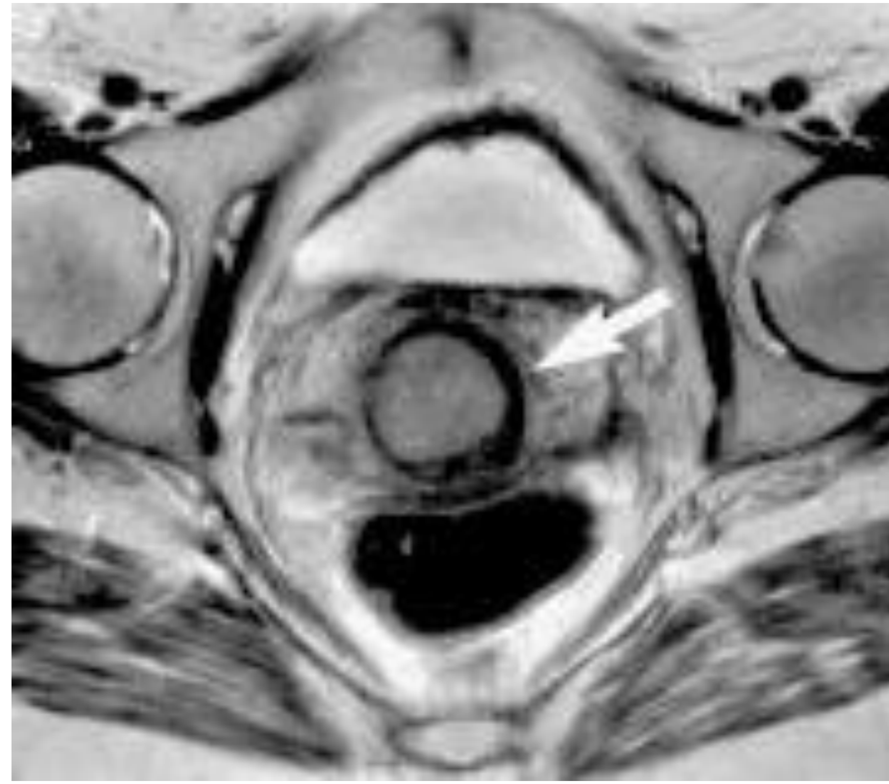
MR IMAGING : GYN GEC ESTRO RECOMMENDATIONS

FIELD STRENGTH

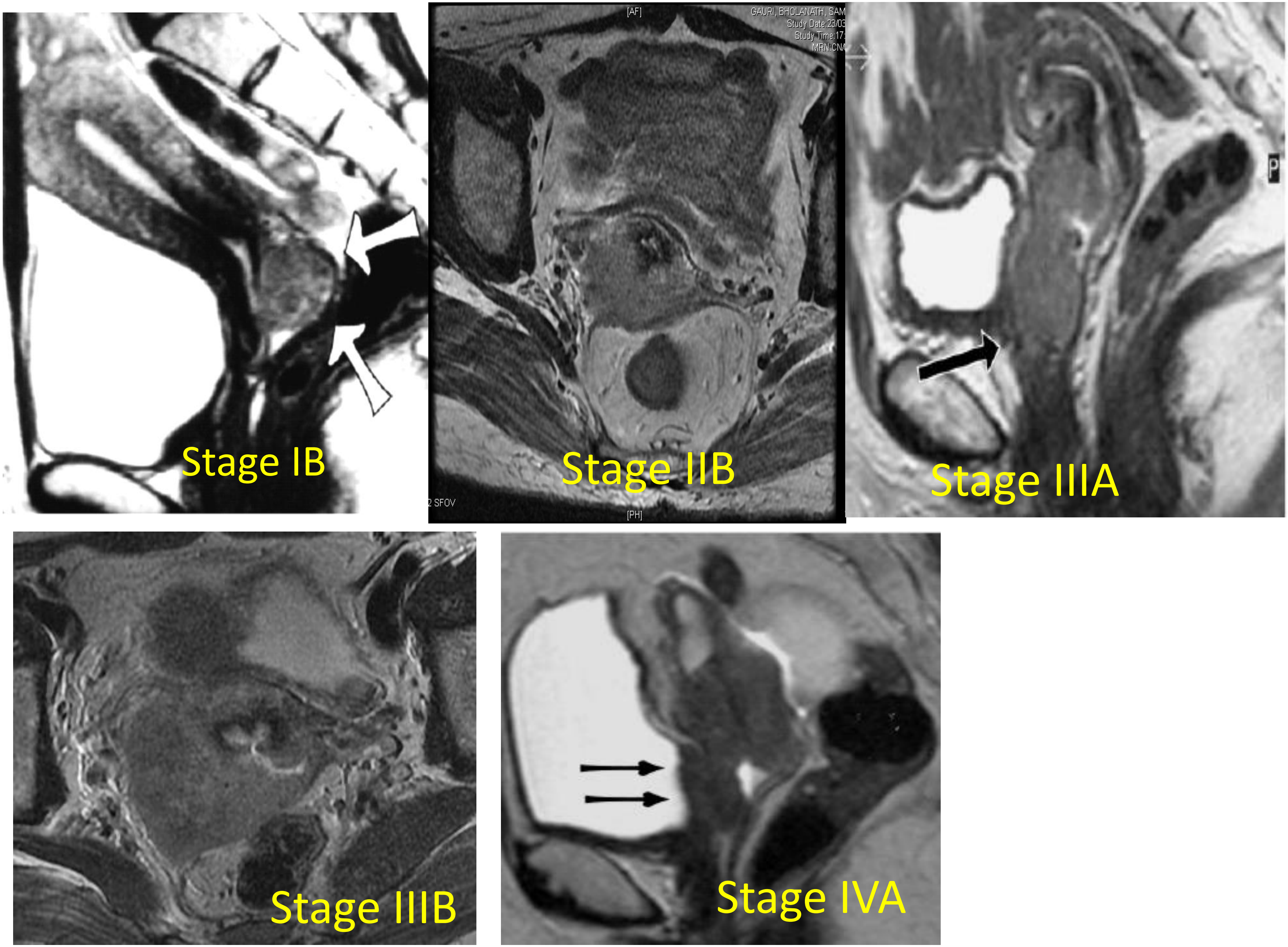


3 T **1.5 T**

Masatoshi et al Radiology 2009

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


Stage IB
[AF]
Stage IIB
[PH]
Stage IIIA
P
Stage IIIB
Stage IVA

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

expansive with spiculae

→ no remnants in PM

expansive with spiculae + infiltrating parts

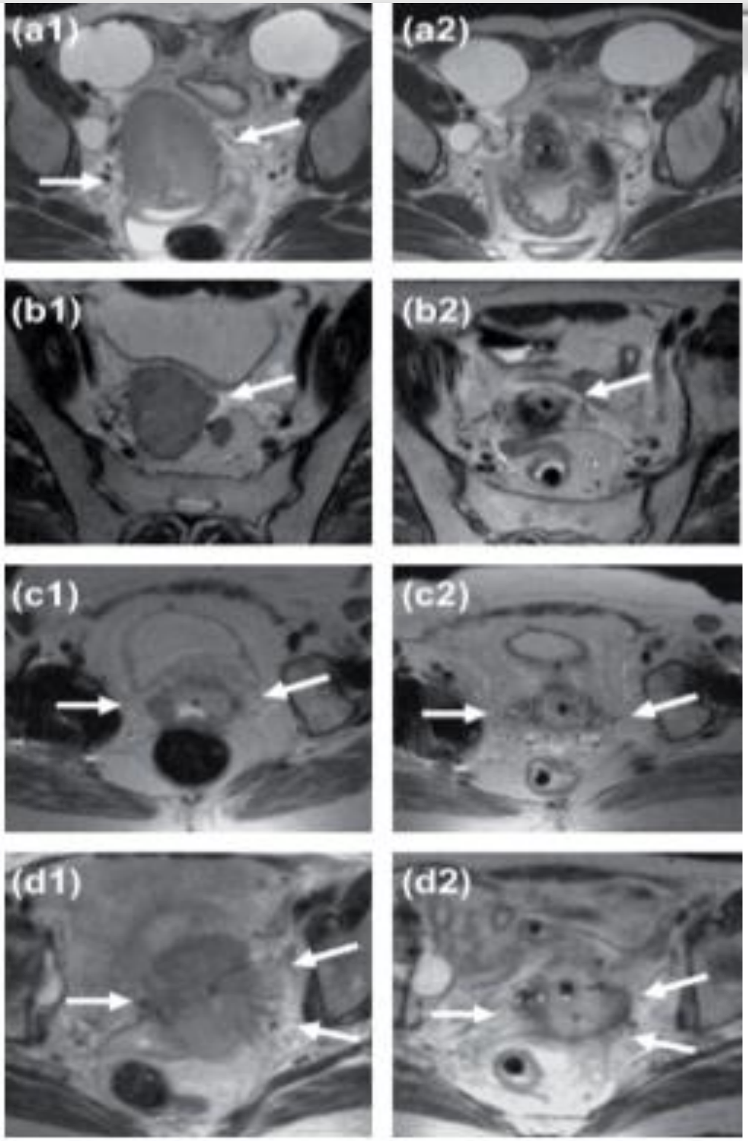
→ grey zones in the PM

infiltrative parts in both PM

→ grey and bright zones

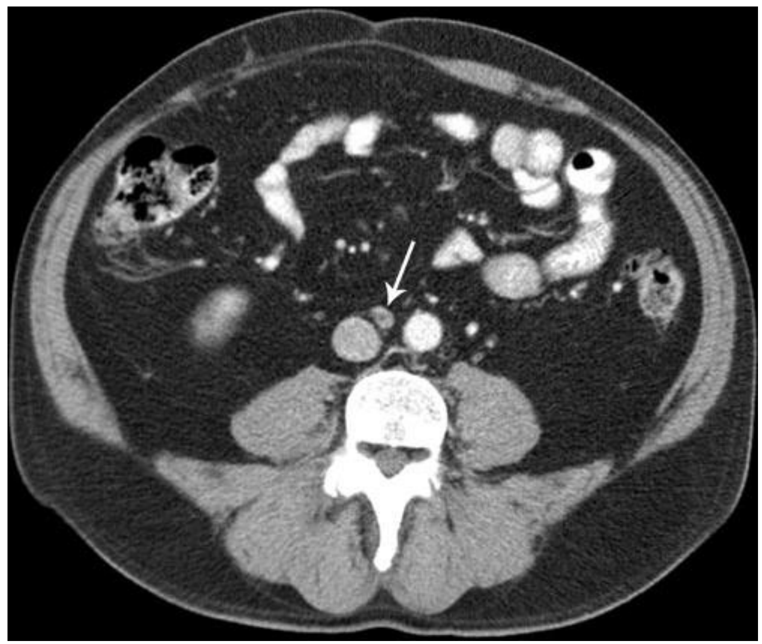
infiltrative parts in both PM

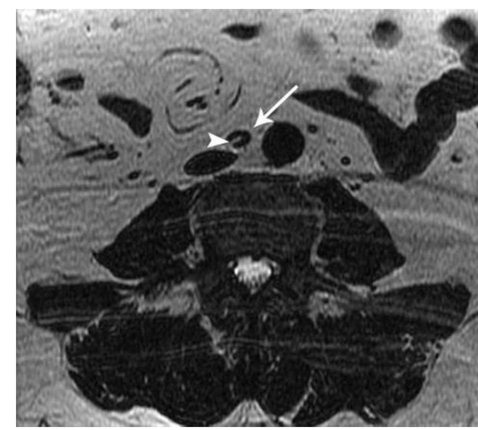
→ grey and bright zones



Schmid et al. Acta Oncologica 2013

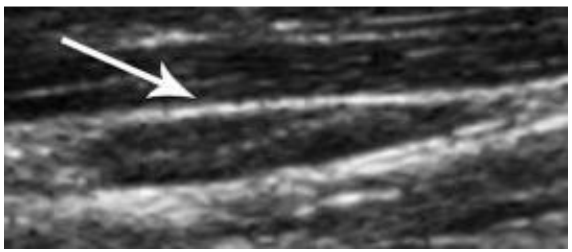
ASSESSMENT OF NODAL PATHOLOGY

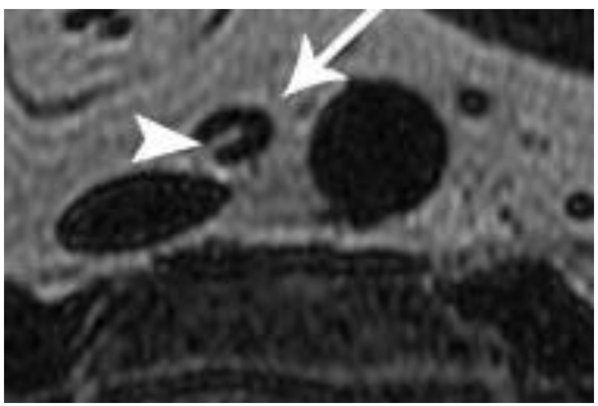


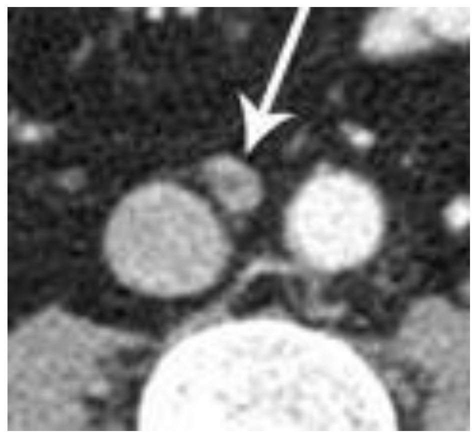


Torabi M, J Nucl Med 2004 ; 45 : 1509-18

ASSESSMENT OF NODAL PATHOLOGY







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

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

Size criterion : < 10 mm

FDG PET- CT

BIOLOGICAL & ANATOMICAL DATA

FDG Uptake in Pelvic Organs

Normal Pelvic Organs & Benign Lesions

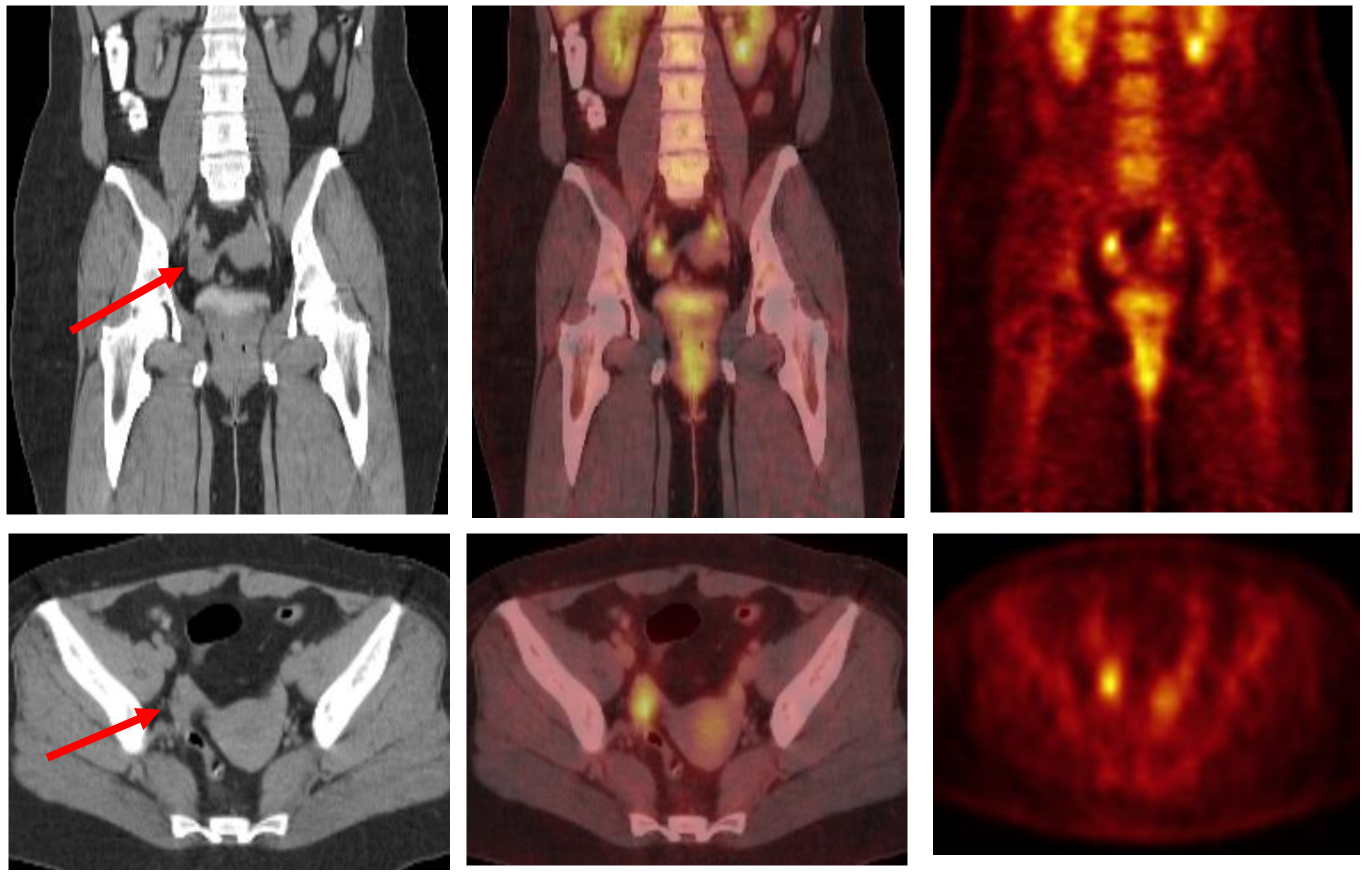
1. Urinary tract
2. Menstruating
3. Ovarian follicular cysts
4. Cystadenoma
5. Endometriosis
6. Leiomyoma
7. Infection/inflammation

PET in Gynecologic Cancer

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

FDG-PET

FDG-PET/CT



PET and Cervical Cancers

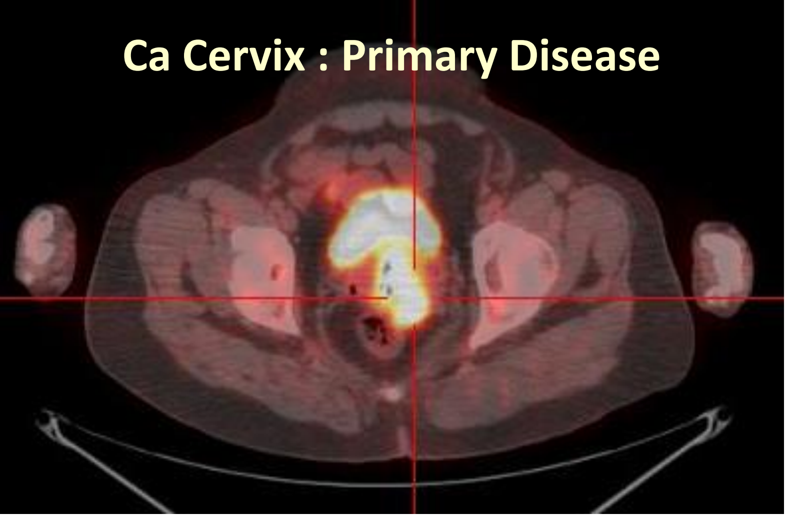
NEWLY DIAGNOSED

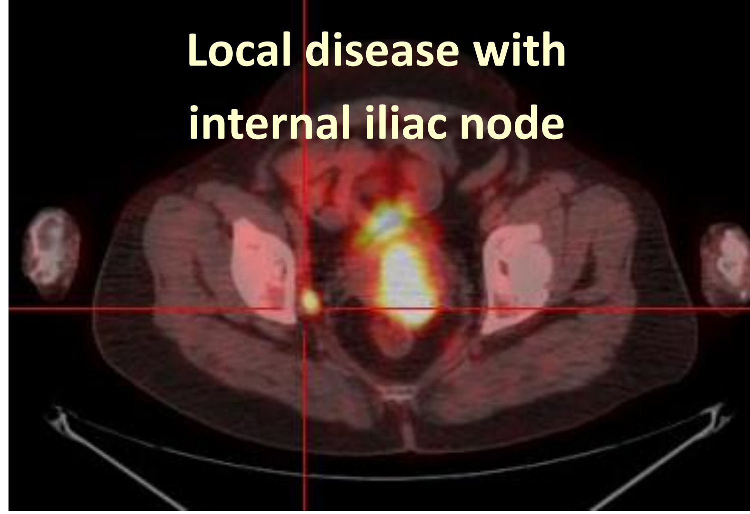
Early Stage (I-IIA)	Advanced Stage (IIB-IIIB)
➢ Surgery / RT	➢ Radical RT + CT
➢ >50 % require Adj. Rx	➢ Pelvic Radiation
➢ 20-30 % pelvic node +ve	➢ 30-45% para aortic node+ve
➢ CT/MRI limitations	➢ CT/MRI limitations
➢ Can PET identify these 20-30 % patients?	➢ Can PET identify at least 30%
➢ Avoid morbidity of multi-modality Rx	➢ Tailor multi-modality treatment Rx

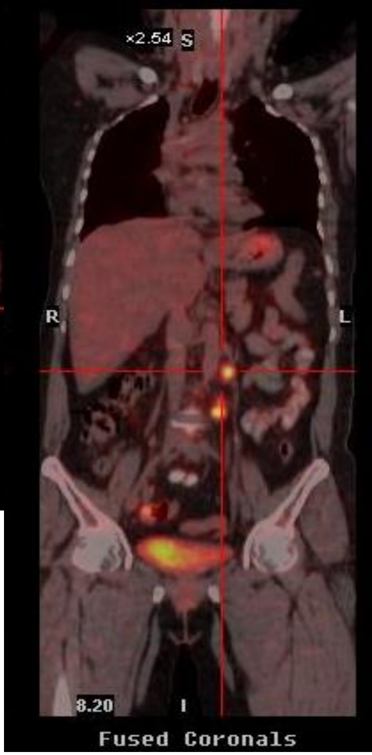
Knowledge of natural history of GYN Cancers and Lymph Nodal Spread : Vital

PET and Cervical Cancers

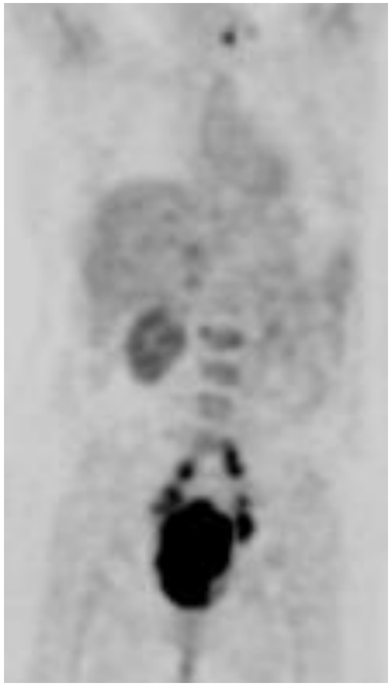
- **Primary Tumor Staging**
- **Lymph Nodal Staging : Early Vs Advance Stages**
- **Pre-treatment Prognostic Value**
- **Treatment Plan Optimization : Single modality, Aggressive Rx …**
- **Post-therapy Surveillance**
  - **Local**
  - **Regional (Pelvic / Para-aortic)**
  - **Distant Metastasis**







PET and Cervical Cancers



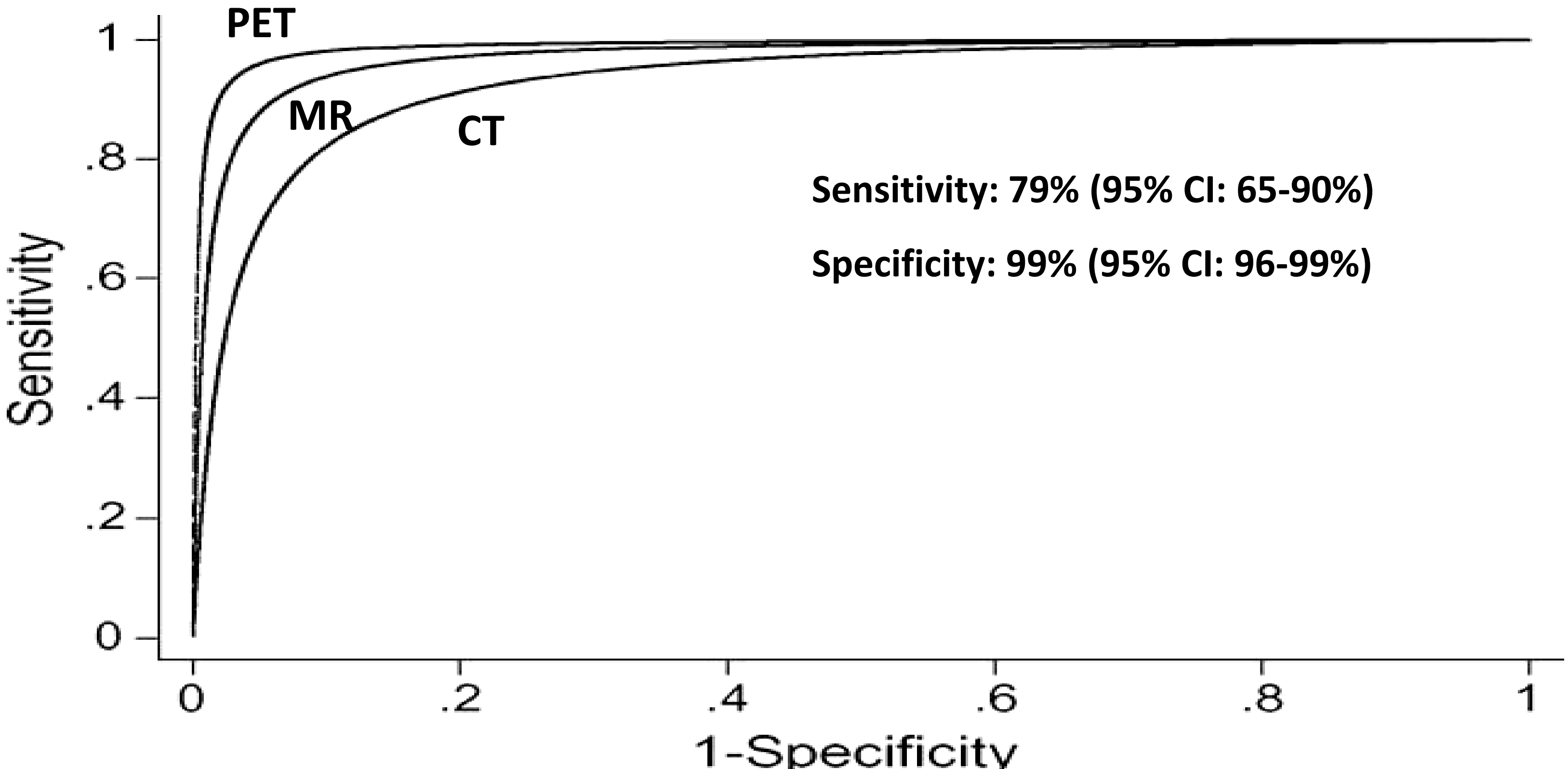
Ca Cervix IIIb with
SCF node

Ca Cervix IIIb with
Liver Metastasis

PET / PET-CT and Cancer Cervix

Lymph Nodal Staging

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



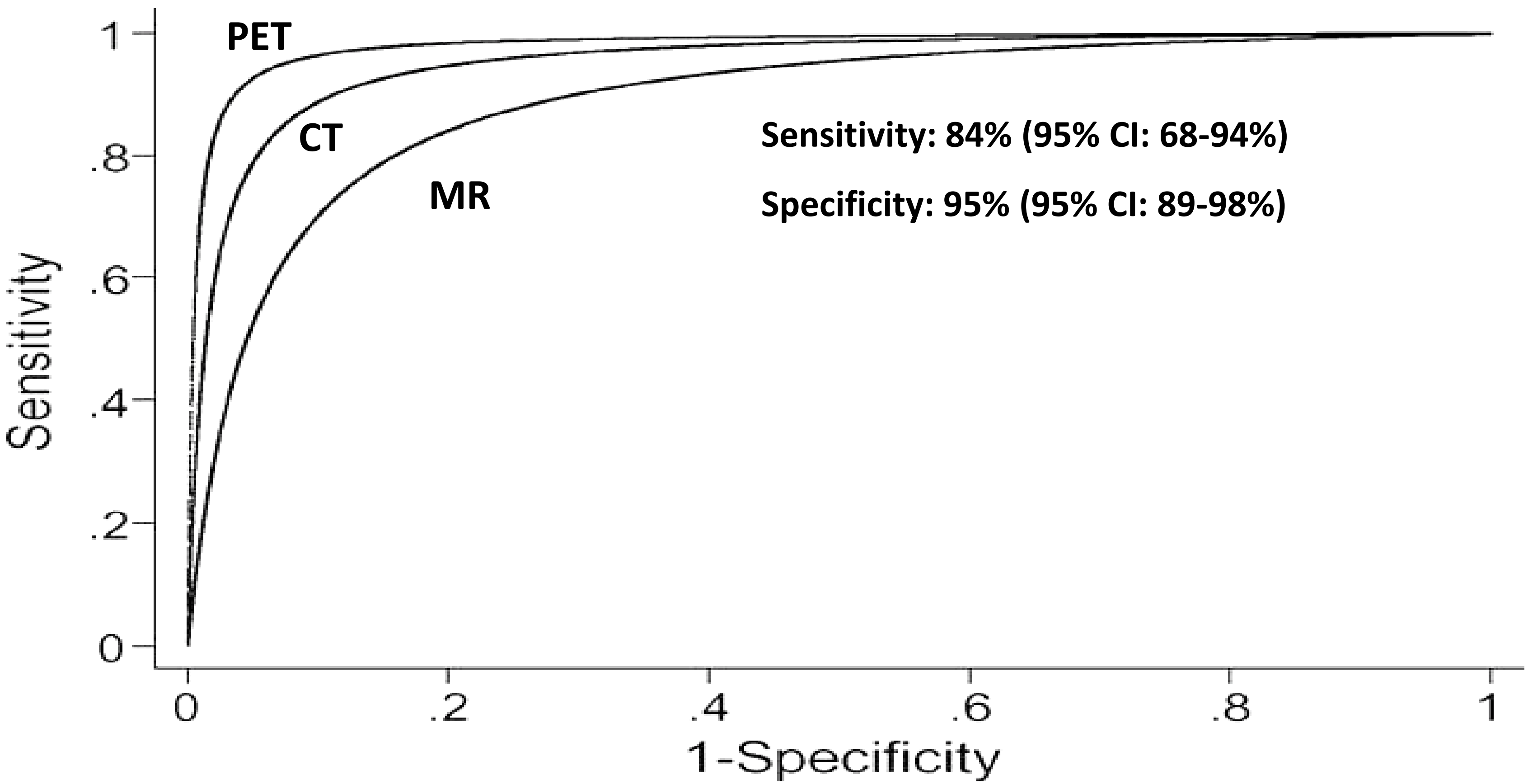
No enough evidence exists for detection of nodal disease in early Cx cancer and cannot replace lymph nodal dissection

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

PET / PET-CT and Cancer Cervix

Para-aortic Lymph Nodal Staging

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



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

PET / PET-CT and Cancer Cervix

Post Therapy Surveillance

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

PET / PET-CT and Cancer Cervix

Response and Outcome

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

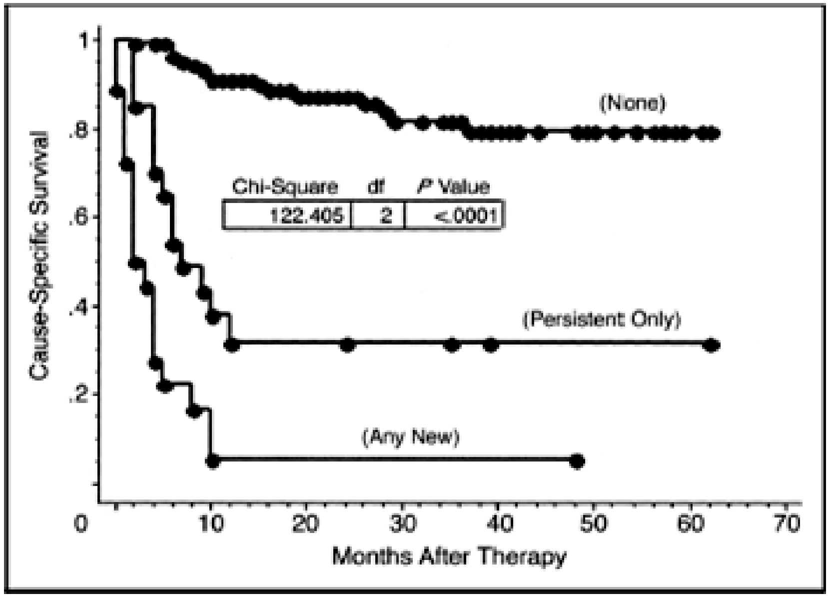


Fig 1. Cause-specific survival.

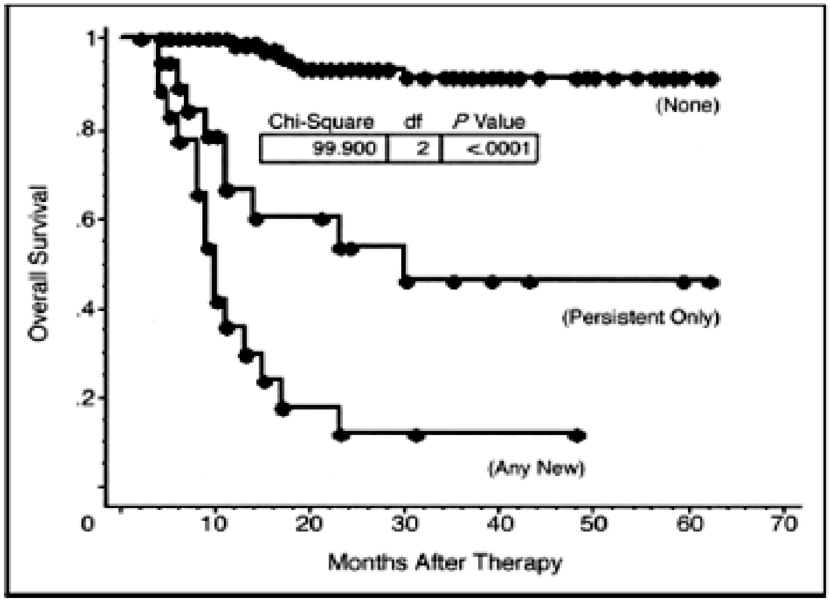


Fig 2. Overall survival.

Grigsby et al JCO 2004

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

SUMMARY

- **Natural history of Cervical Cancer : Thorough Understanding**
- **Clinical Evaluation and Drawings : Mandatory**
- **Knowledge & Interpretation of Imaging Modalities : Essential**
- **Training and Learning Curve**
- **Interaction with Radilogist and Nuclear Medicine physcian**

THANK YOU

Acknowledgement s

ESTRO Teaching Material

GYN ESTRO Teaching Faculty

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

Primoz Petric, MD, Msc
Senior Consultant

Department of Radiation Oncology
NCCCR, HMC
Doha, Qatar

Adapted and Presented by

Richard Pötter, Medical University Vienna

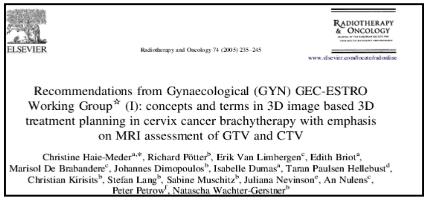
Lucknow, March 2018

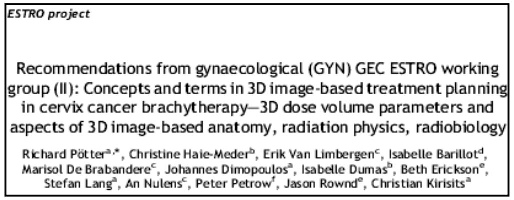
20’

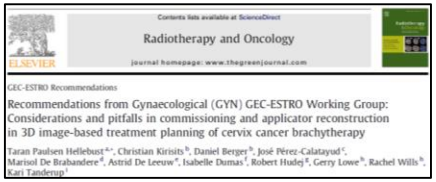
Gold standard I : T2W MRI

Magnetic Resonance Imaging

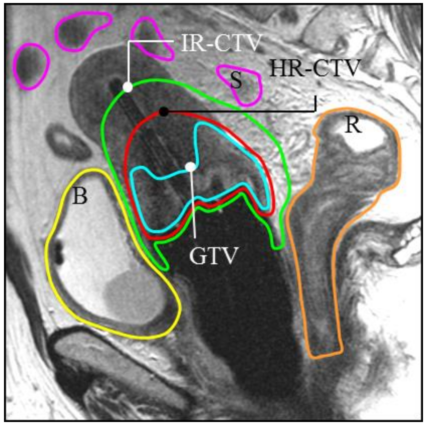
- Soft tissue depiction
- Multiplanar imaging
- Published Recommendations
- Clinical Results

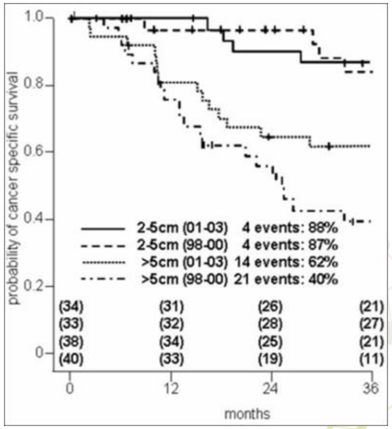

ELSEVIER
Radiotherapy and Oncology 74 (2005) 235–245
Radiotherapy & Oncology
www.elsevier.com/locate/radonline
Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group* (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment 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]


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


Contents lists available at SciVerse ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com
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
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De Brabandere M. Radiother Oncol 2008
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Boss EA. Obstet Gyn 1995

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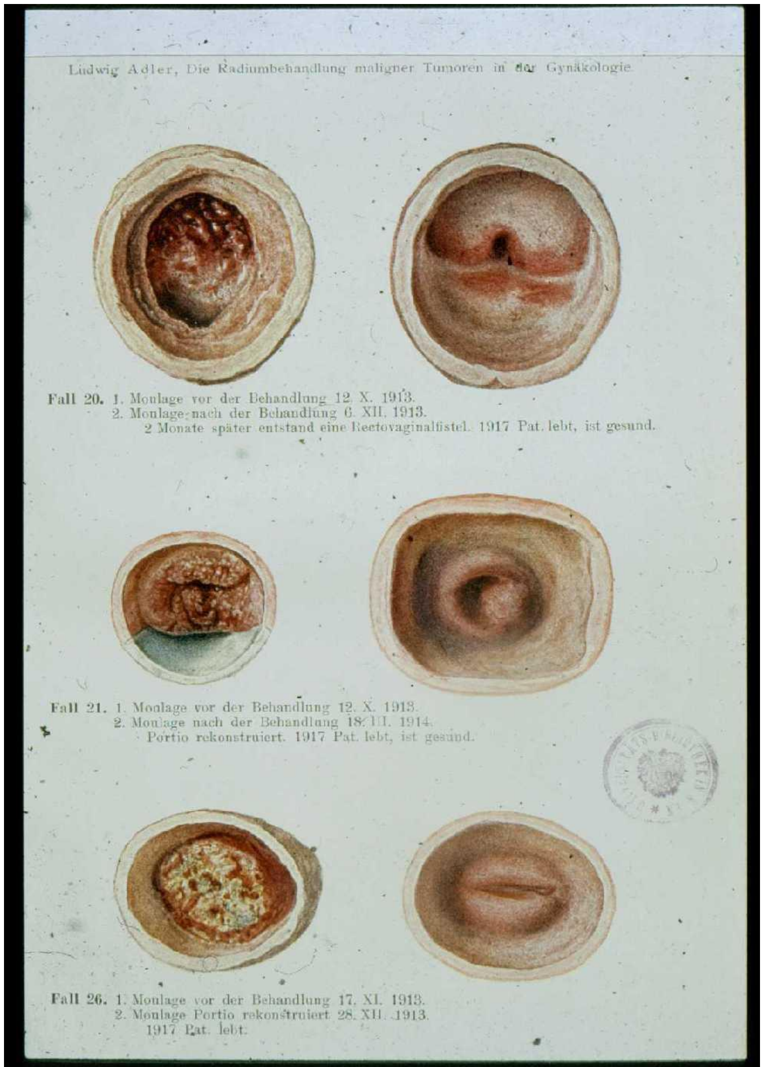
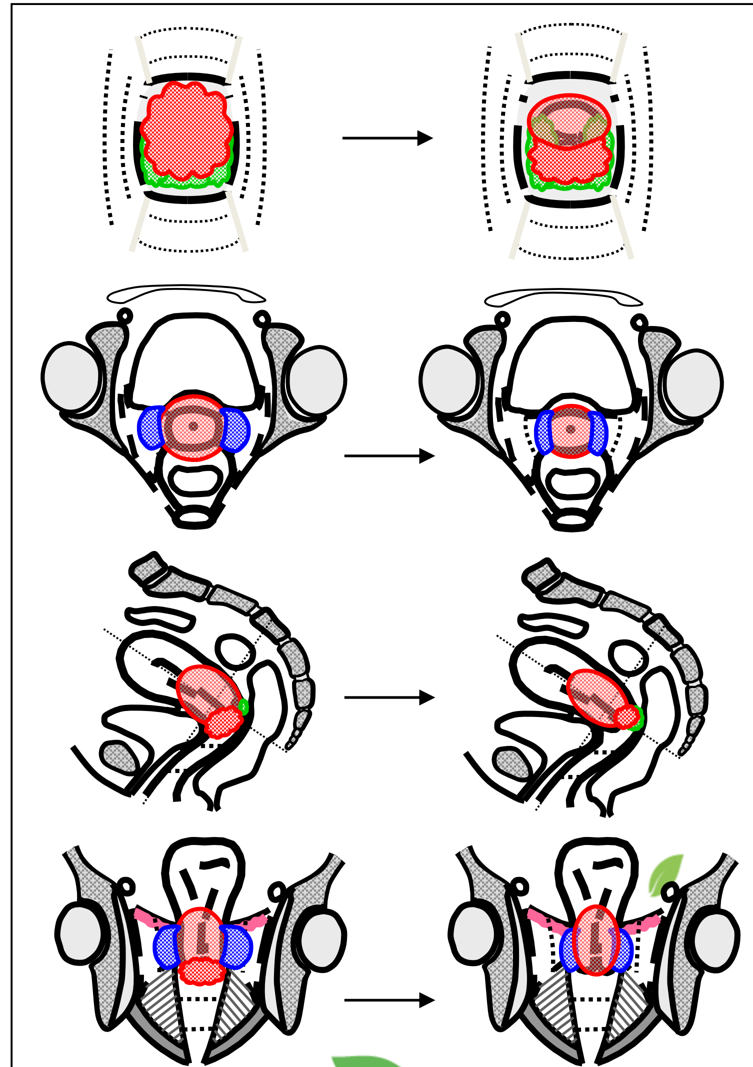
Hricak H. Radiology 2007
Yu KK. Radiology 1997
Sala E. Radiology 2006
Yu KK. Radiology 1999

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

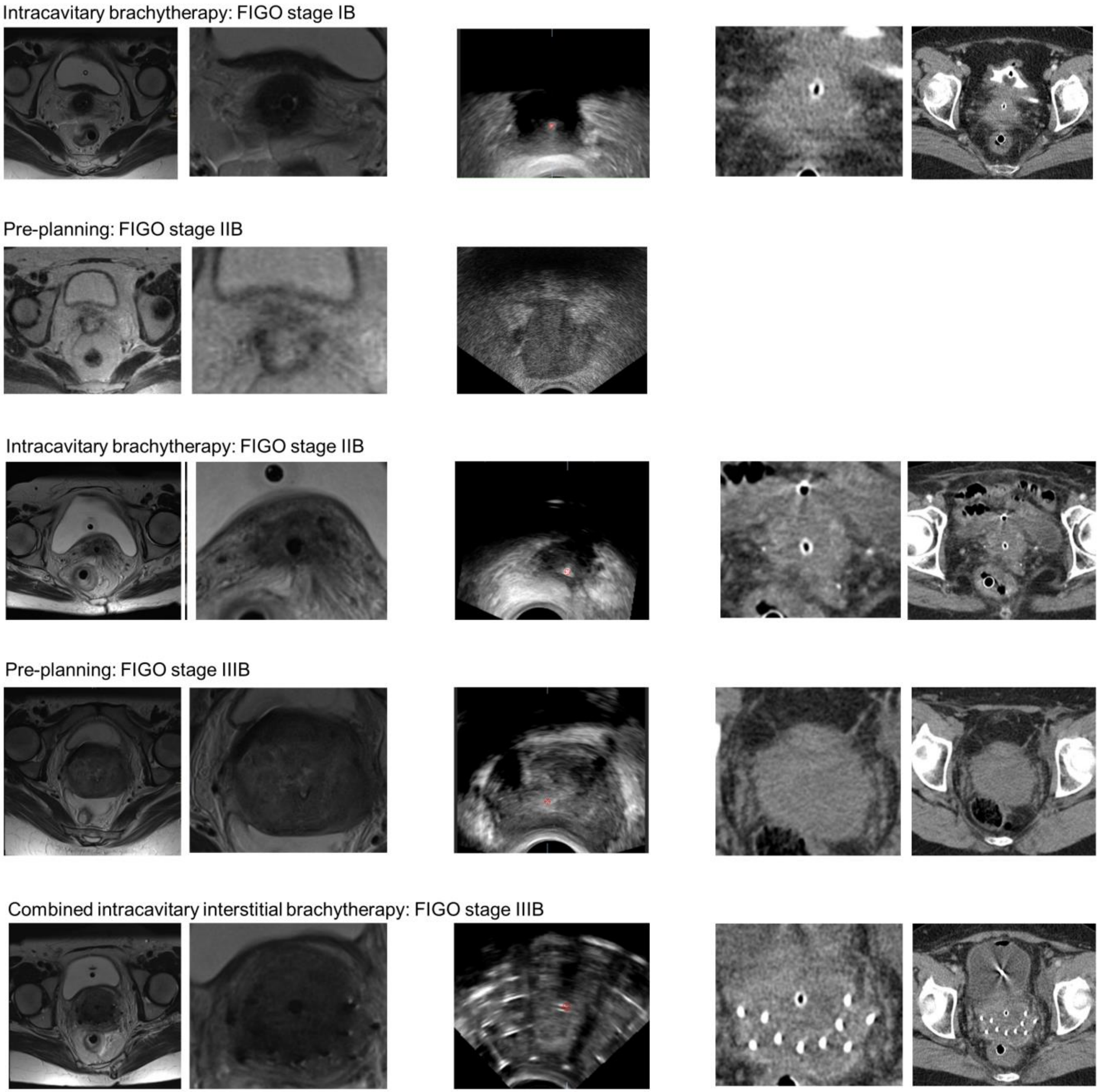
Adler: Strahlentherapie, 1918

EMBRACE study protocol, 2011





Courtesy: R. Pötter, MUW



M. Schmid, Vienna, ongoing clinical study

Imaging at BT

MRI (gold)

US (silver+)

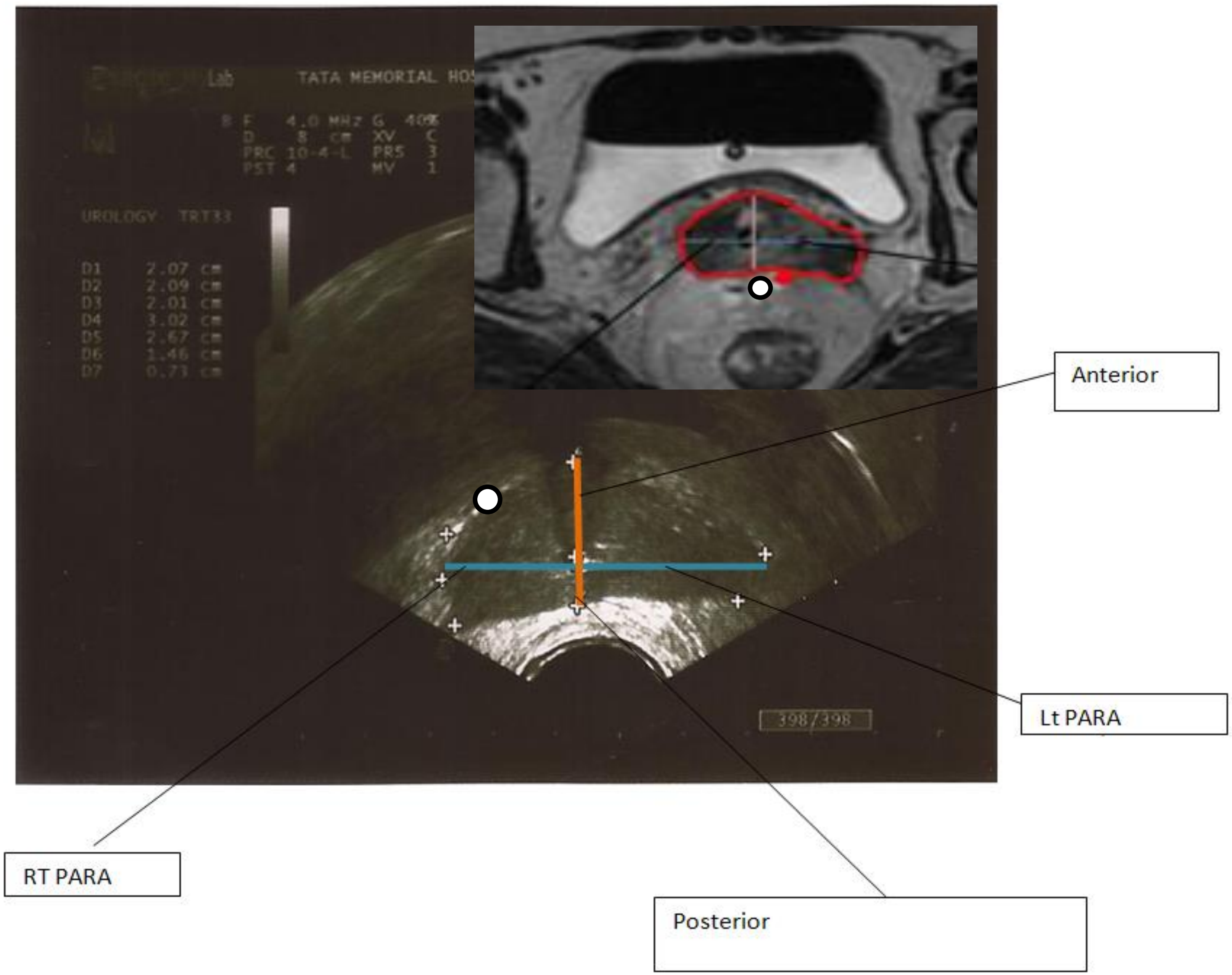
CT (bronze)

Clinical drawing (gold)

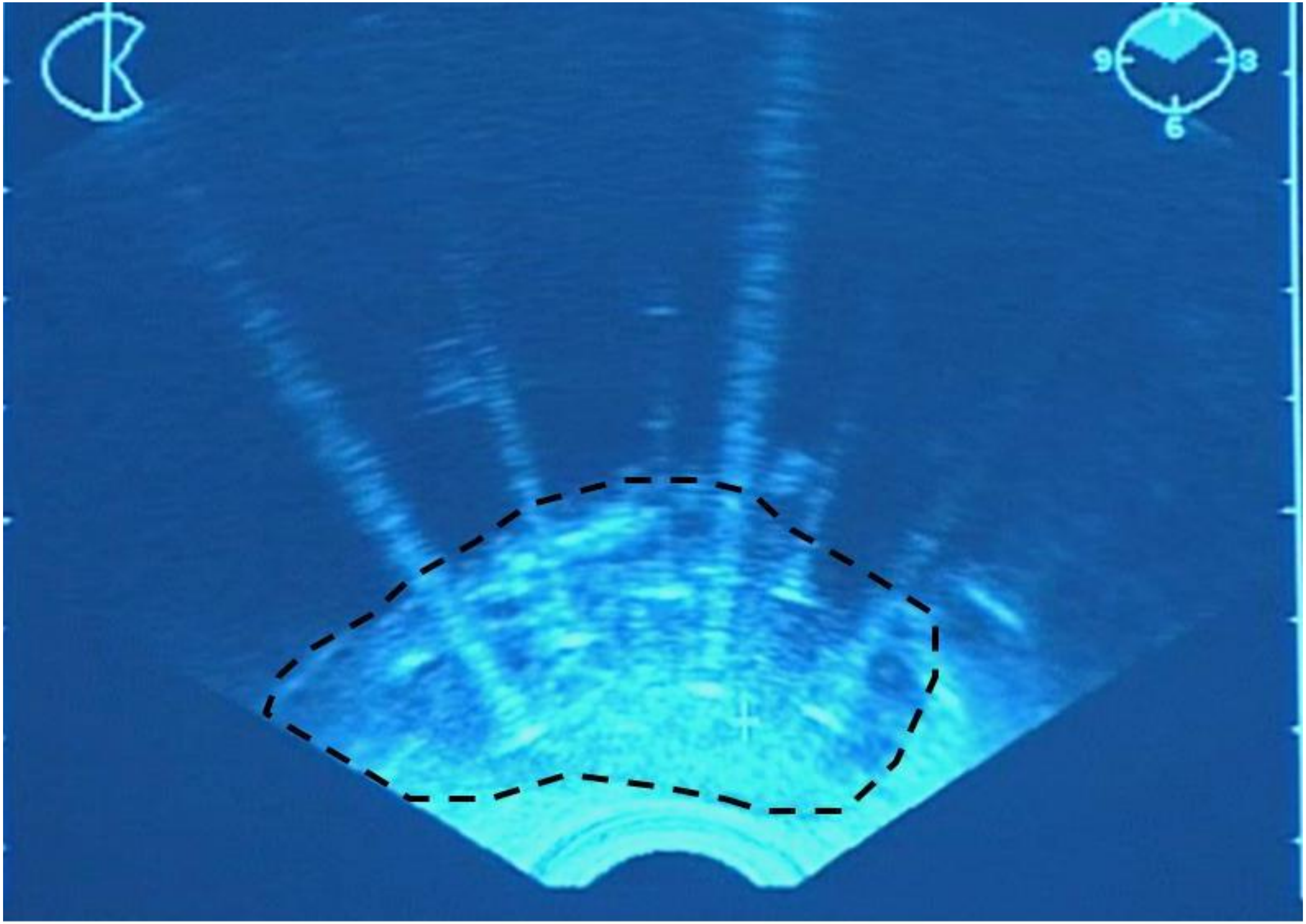
RESEARCH : TRUS Guided Target Volume Definition

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

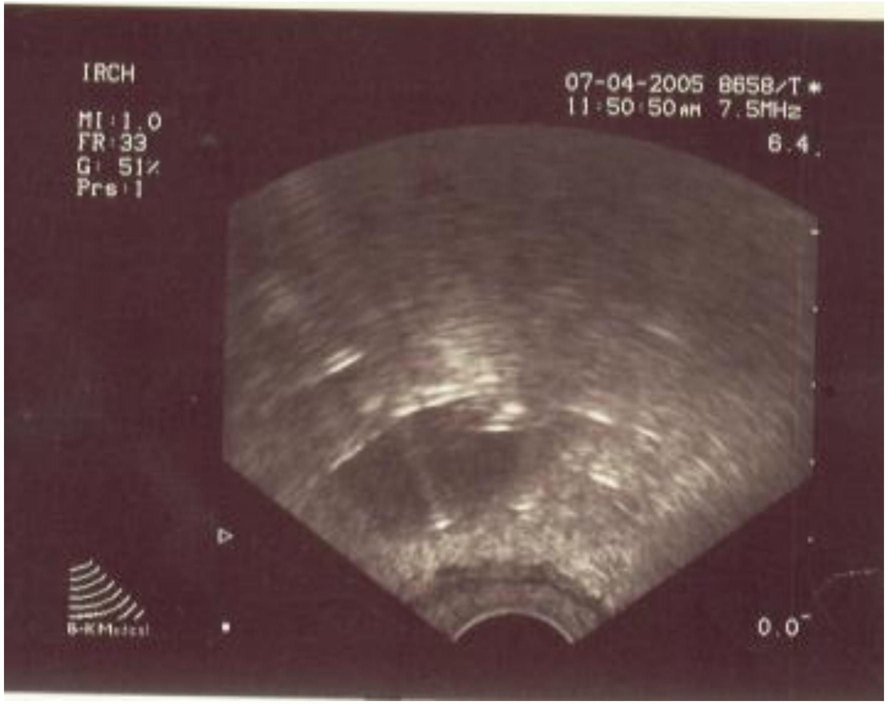
MRI-TRUS Correlation

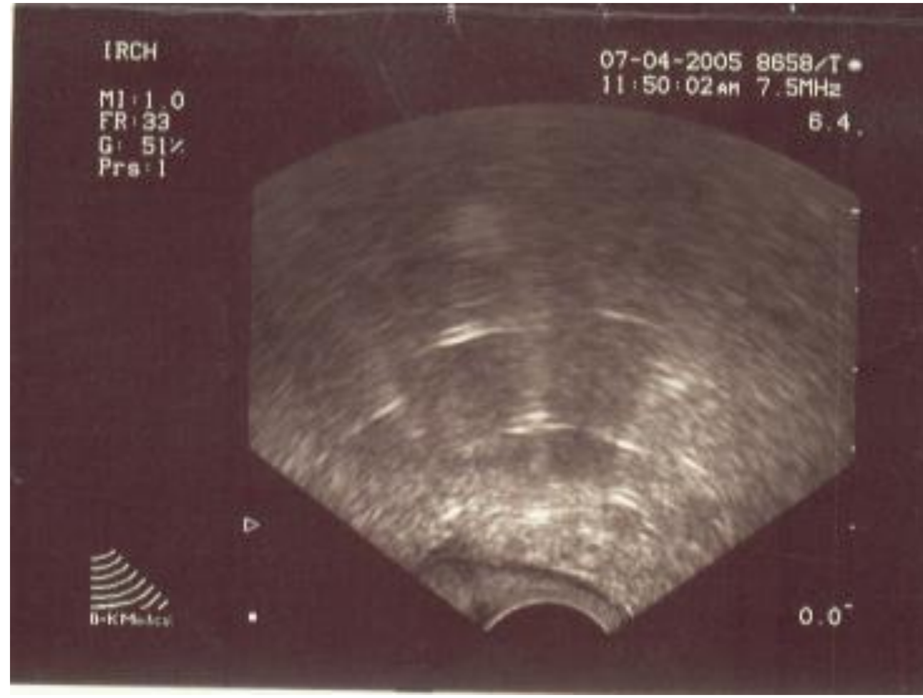


TRUS image showing IBT needles in cervical cancer



By courtesy of D. Sharma





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

Original Article

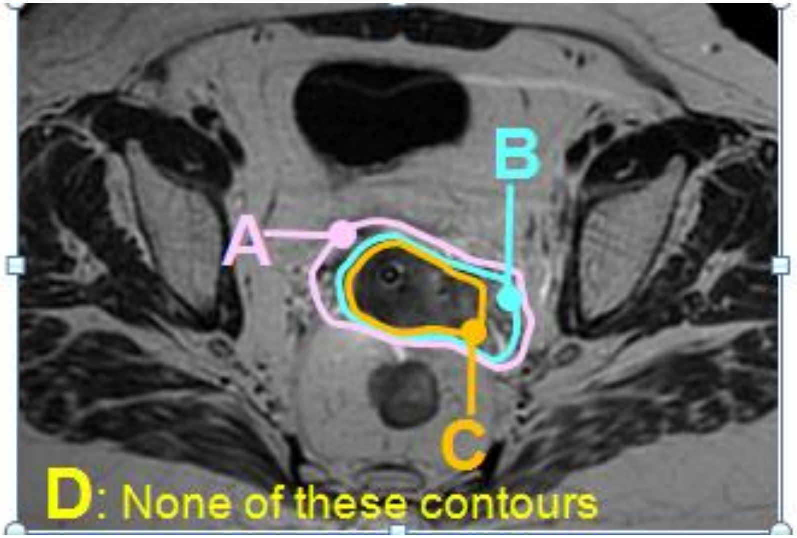
Use of transrectal ultrasound for high dose rate interstitial brachytherapy for patients of carcinoma of uterine cervix

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

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

Interpretation of imaging findings at BT

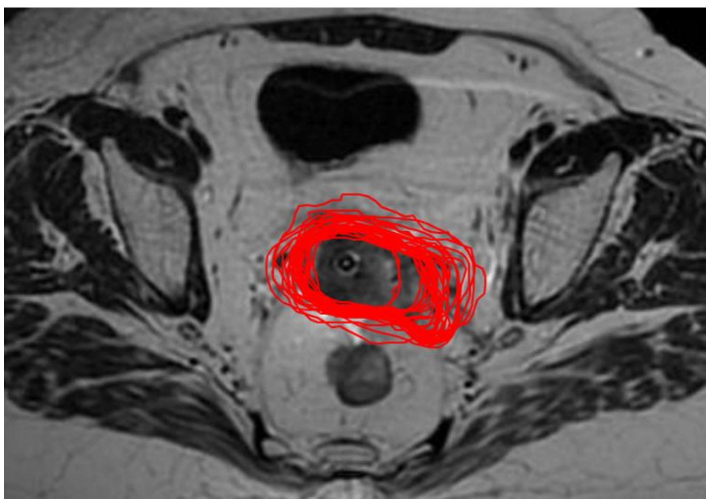
What is the High Risk CTV on this slice? (your best guess)



A. A
B. B
C. B
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

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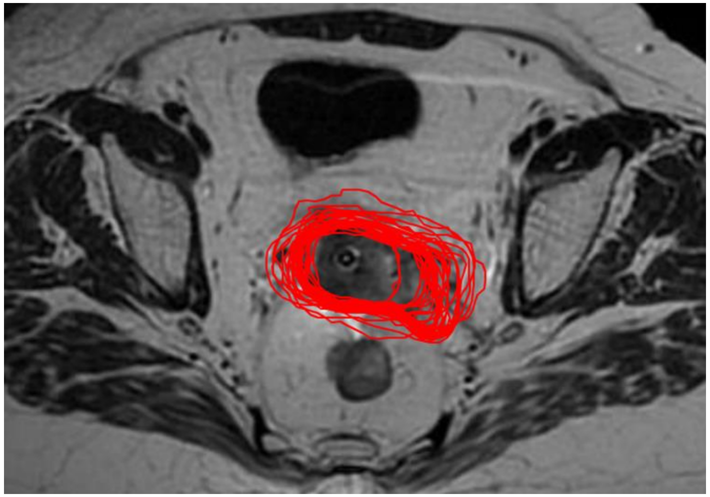

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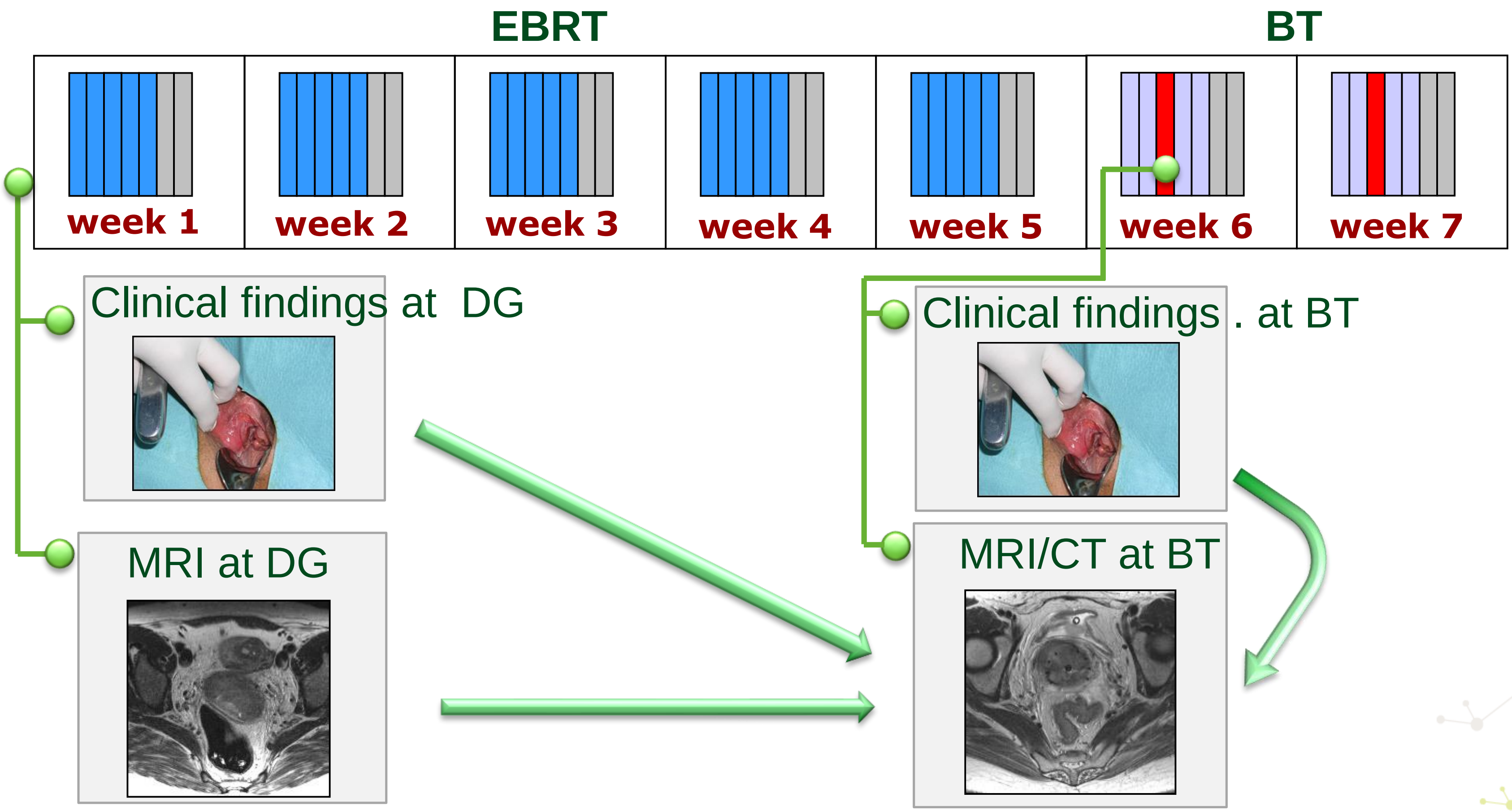
Hellebust TP, et al. Radiother Oncolo 2013
Petric P, et al. Radiother Oncol 2013

Assessment of sectional imaging at time of BT

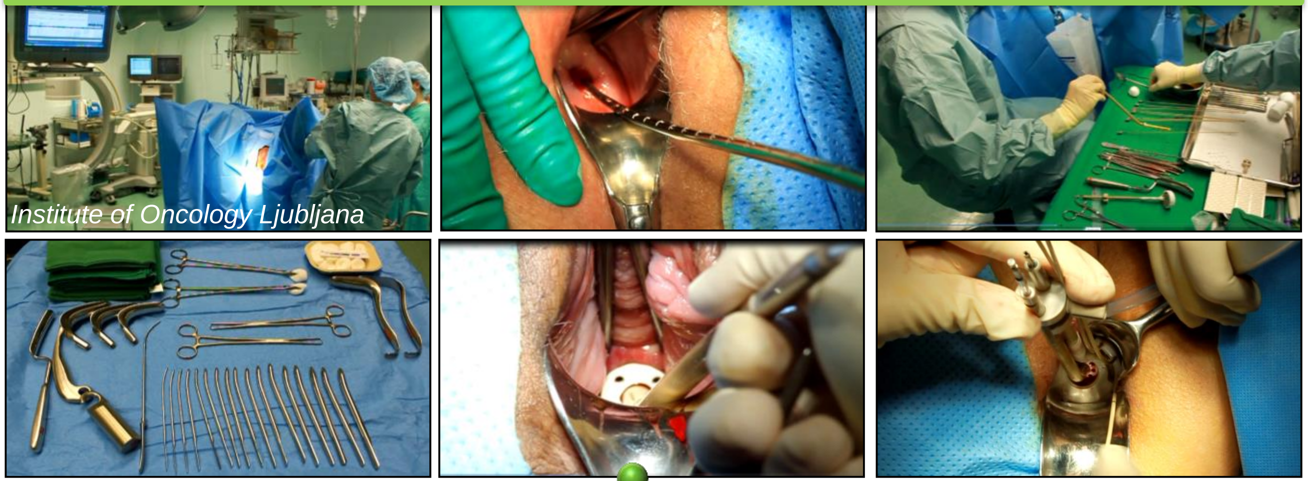
General principles



MRI and/or CT/US with clinical drawings

STEPS of Assessment of MRI/CT at BT

THEATRE



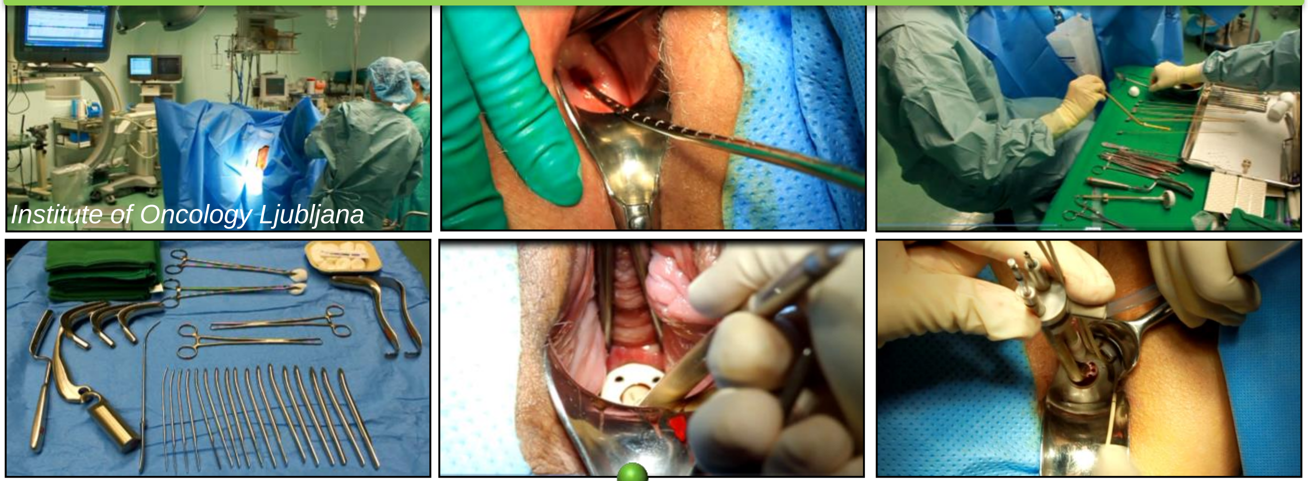
MRI and/or CT/US with clinical drawings

1. Rule out ***FLOP***

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

STEPS of Assessment of MRI/CT at BT

THEATRE



MRI and/or CT/US with clinical drawings

1. Rule out ***FLOP***

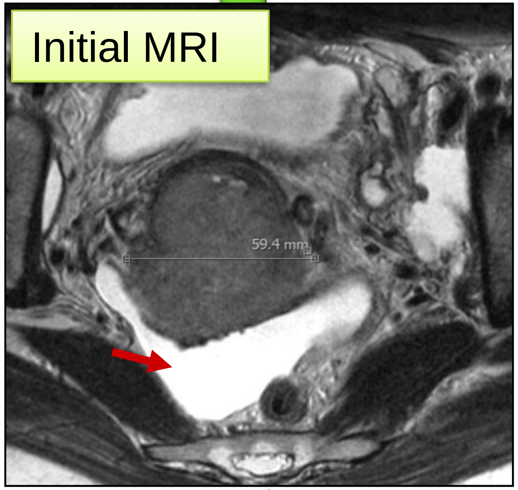
2. Set the ***STAGE*** for contouring

1. Rule out **FLOP**

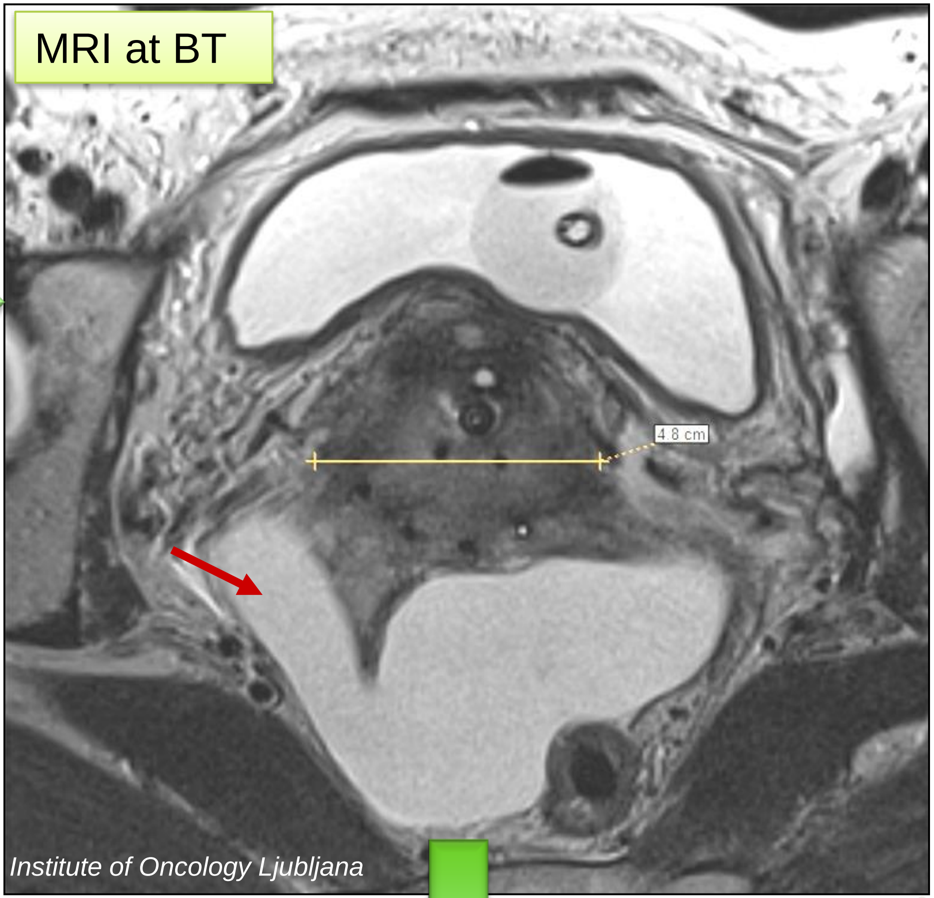
FL **FL**uid in abdomen?

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

Initial MRI



MRI at BT

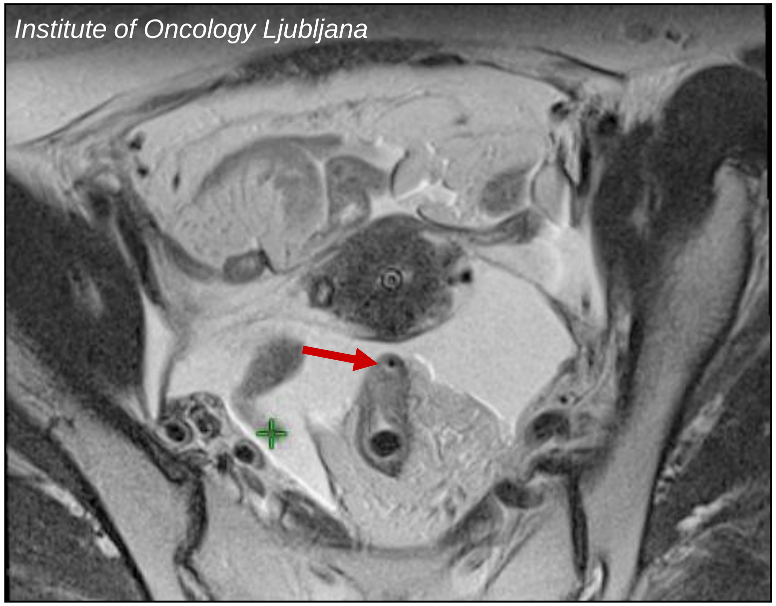


Compare with initial findings!

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**

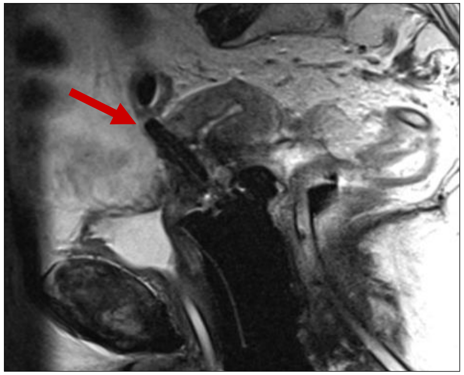
FL **FL**uid in abdomen?

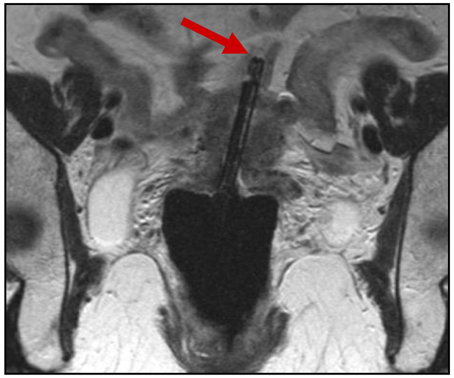
OP **O**rgan **P**erforation?

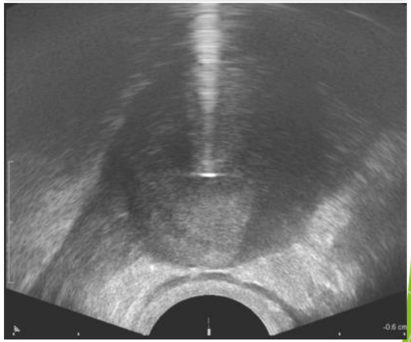
Uterine perforations

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
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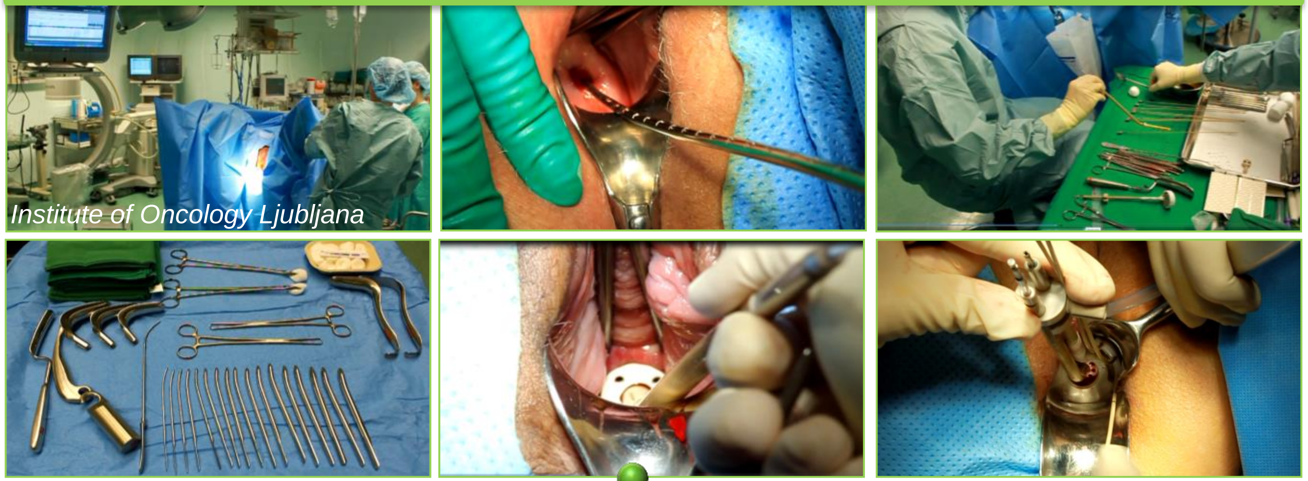
Granai CO, et al. Gyn Oncol 1984
Segedin B, et al. Radiol Oncol 2013

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

Systematic Assessment of MRI/CT at BT

THEATRE



MRI and/or CT/US with clinical drawings

1. Rule out ***FLOP***

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

Set the **STAGE** for contouring

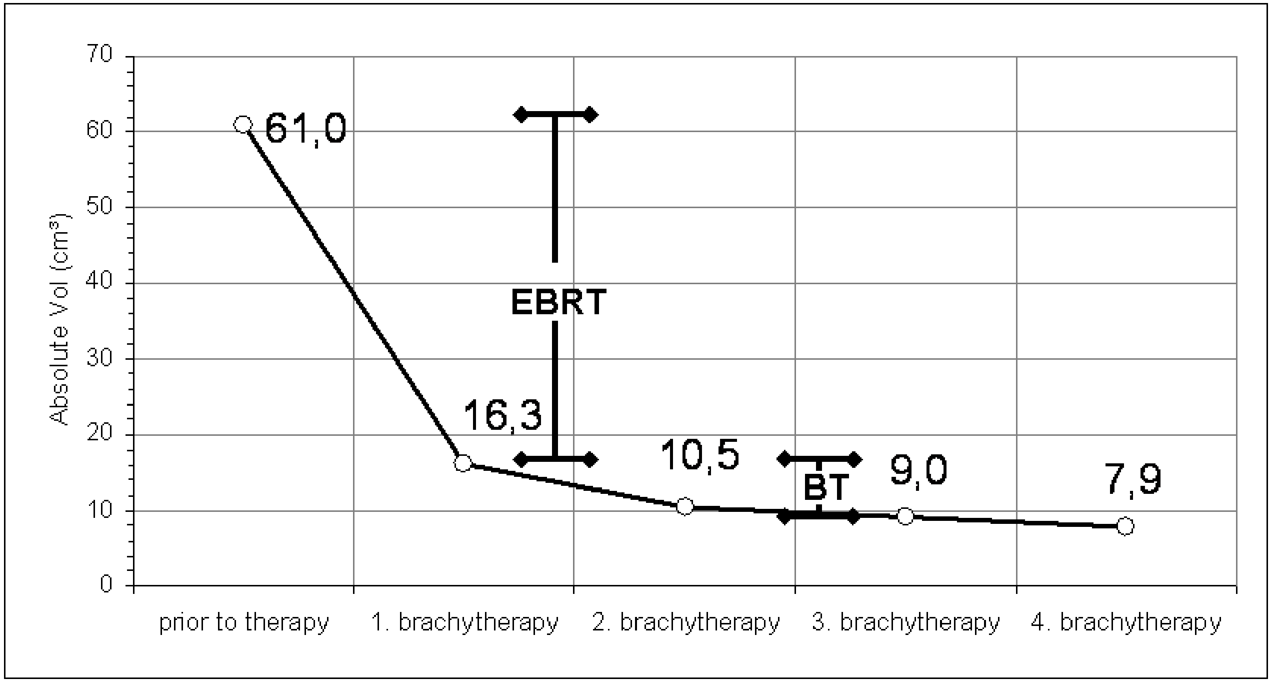
- **S**ize of the residual tumor?
- **T**opography of the target Volume?
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

Set the **STAGE** for contouring

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

Size of the tumor at Brachytherapy

Volume change during treatment

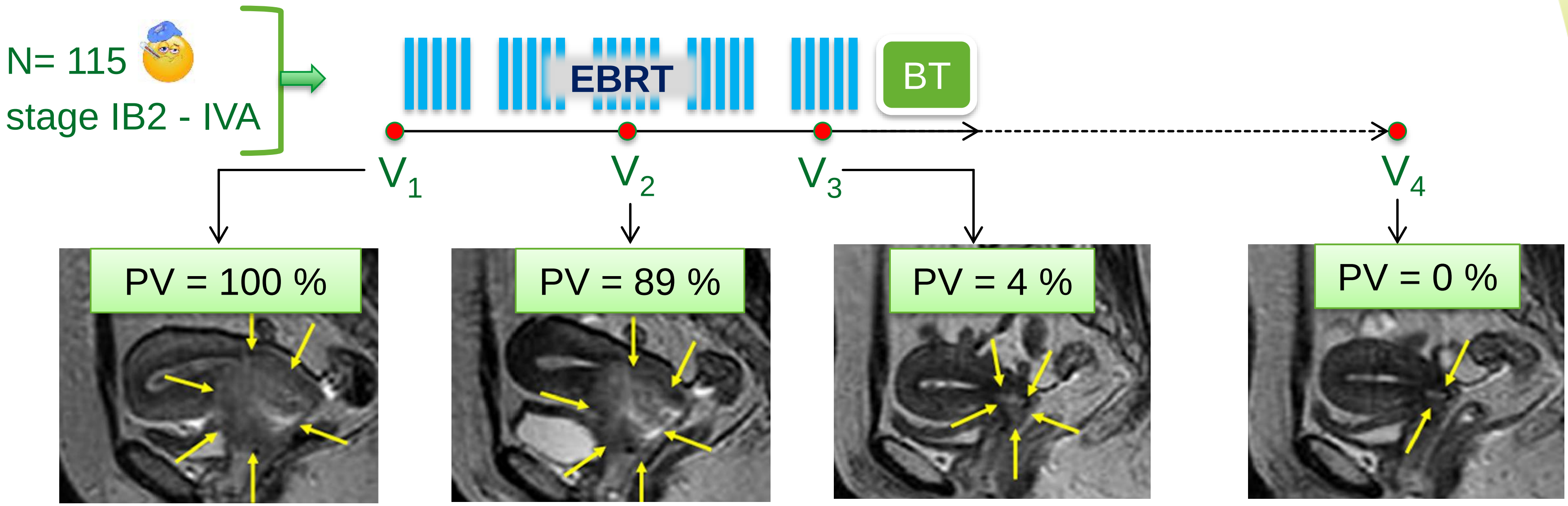


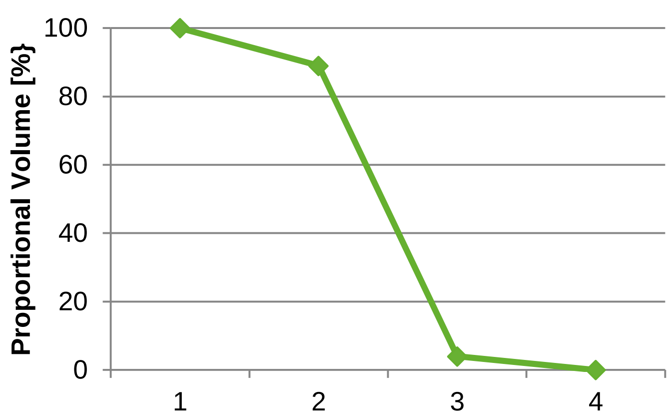
Dimopoulos J, et al.Strahlenther Onkol 2009

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

Size of the tumor at Brachytherapy

Volume change during treatment





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

Alive & well at 7 y

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

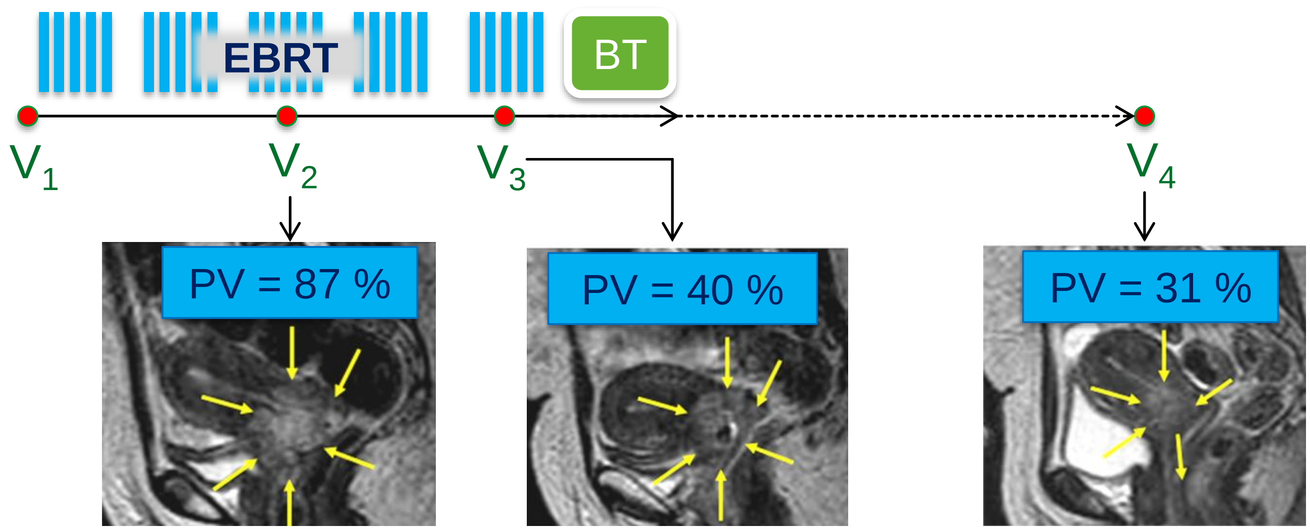
Size of the tumor at Brachytherapy

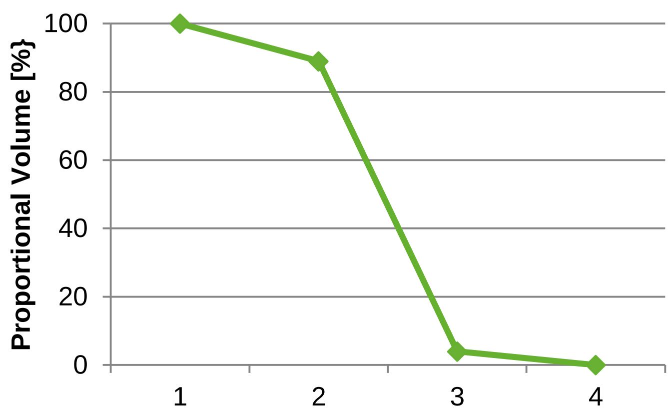
Volume change during treatment

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

N= 115

stage IB2 - IVA





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

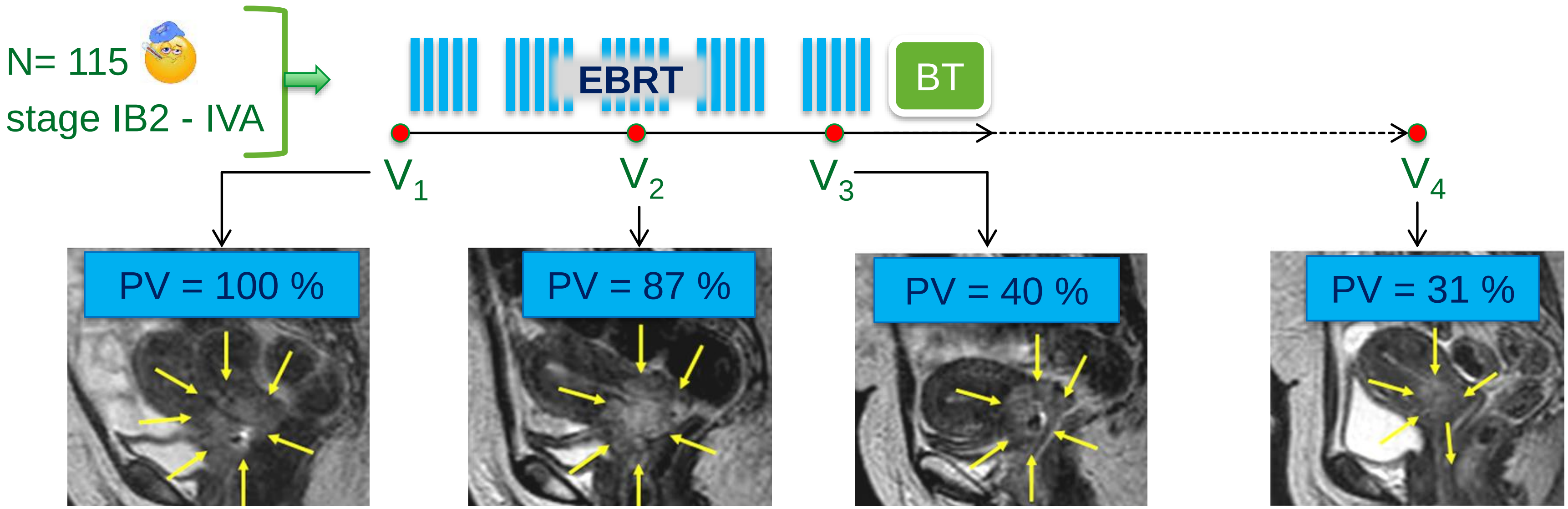
Alive & well at 7 y

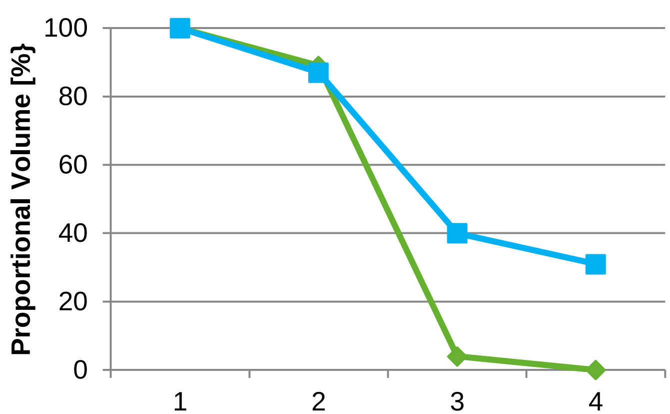
Mayr NA, et al. Int J Radiat Oncol Biol Phys 2010
Wang JZ, et al. Cancer 2010

Size of the tumor at Brachytherapy

Volume change during treatment

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





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

→ Alive & well at 7 y

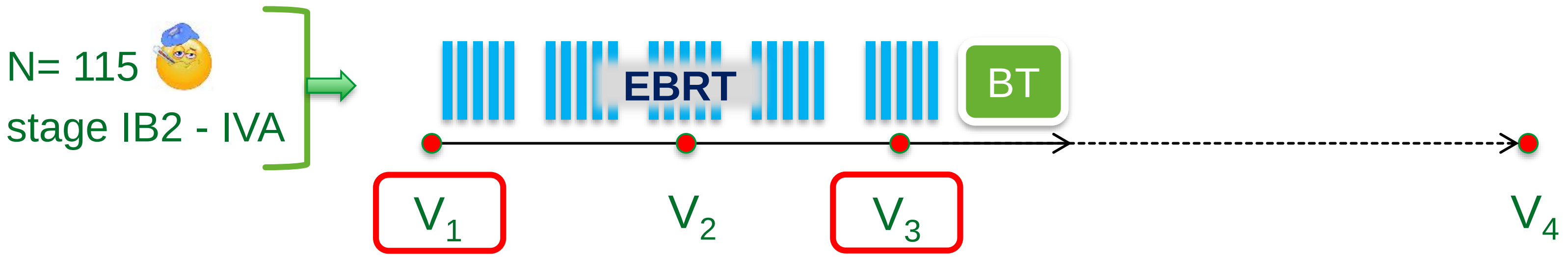
- Slow response: 0.8% / Gy
- Low slope
- High AUC (50 %)

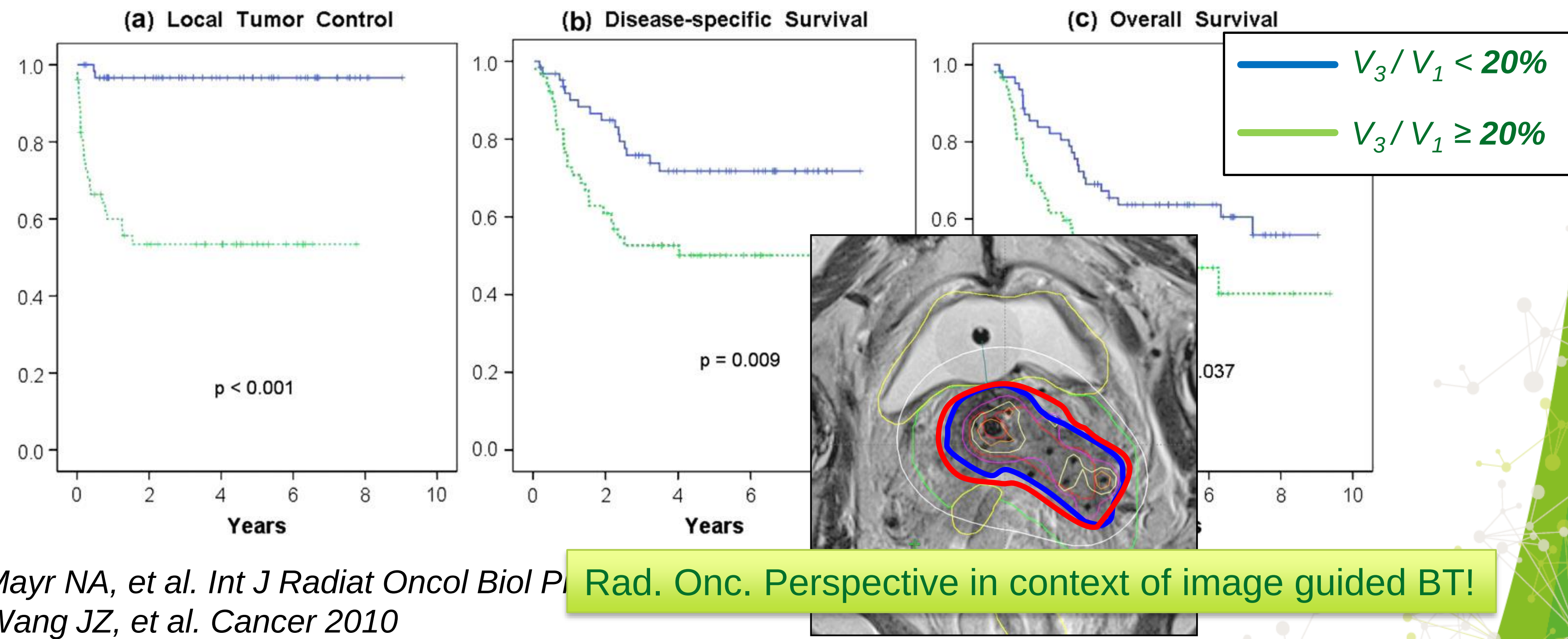
→ LR at 1 y
Death at 2 y

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





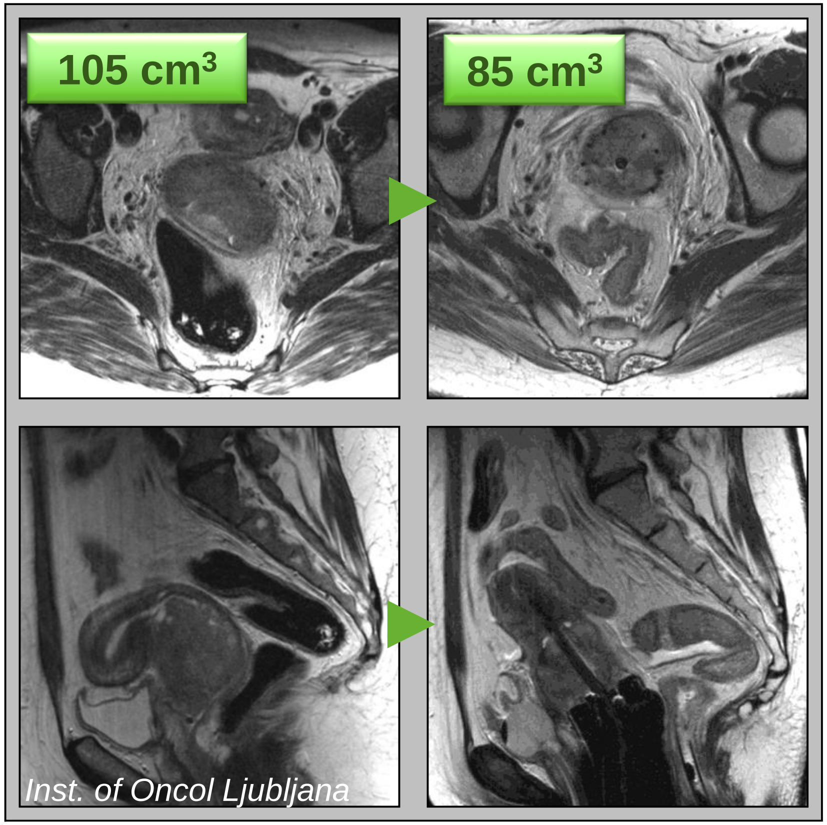
Rad. Onc. Perspective in context of image guided BT!

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

Size of the tumor at Brachytherapy

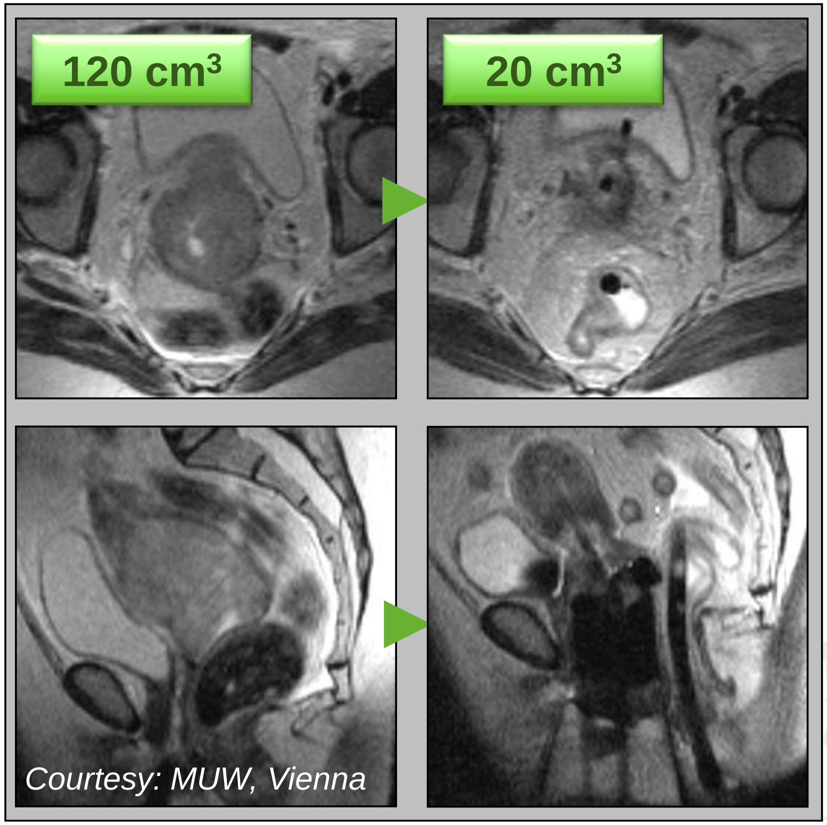
Qualitative vs. quantitative

Bad response



81 %

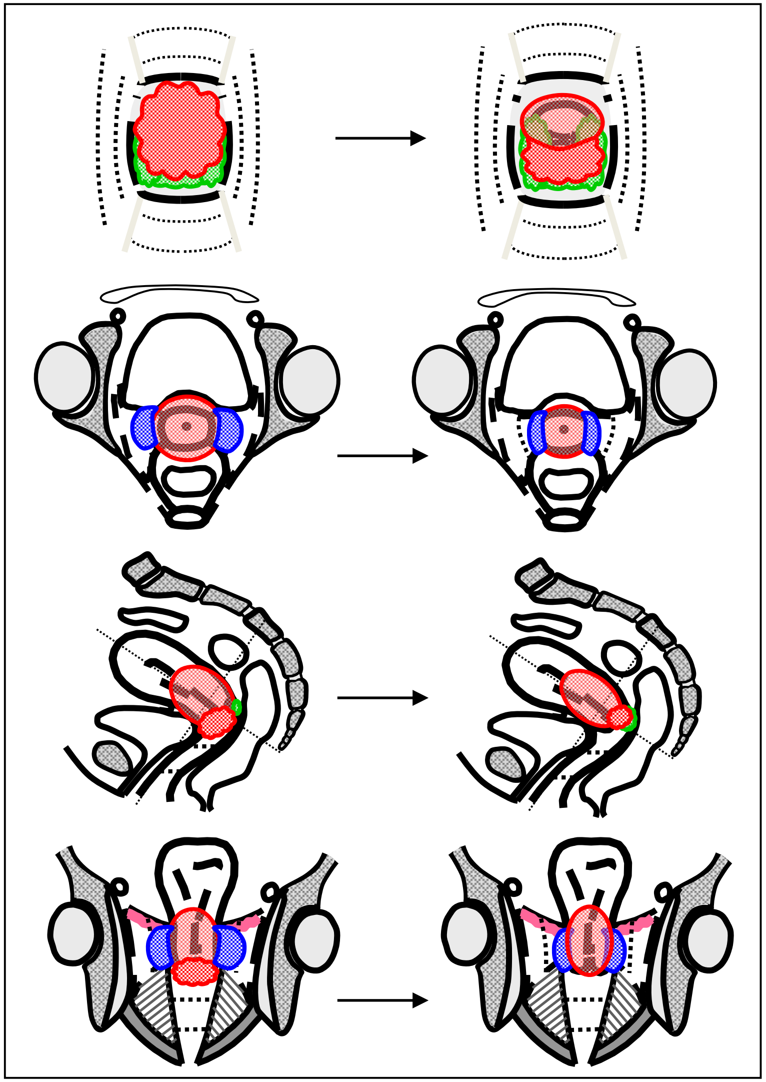
Good response

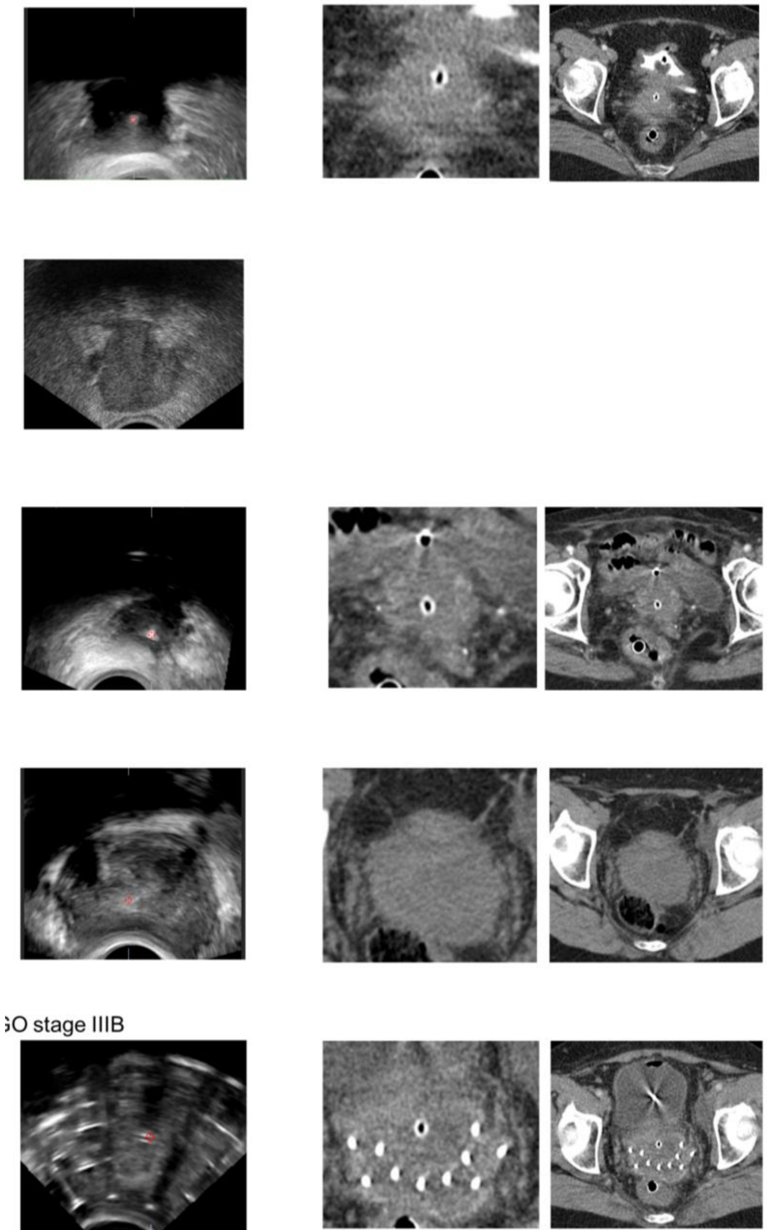


17 %

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

EMBRACE study protocol, 2011



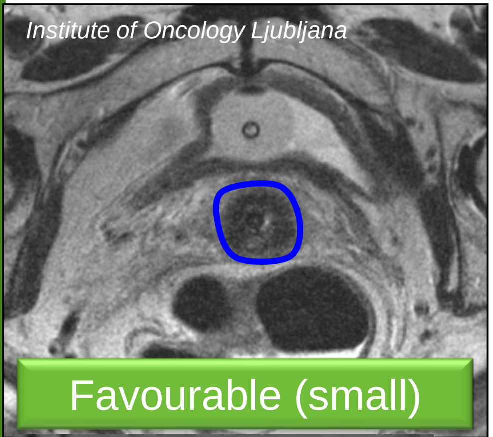


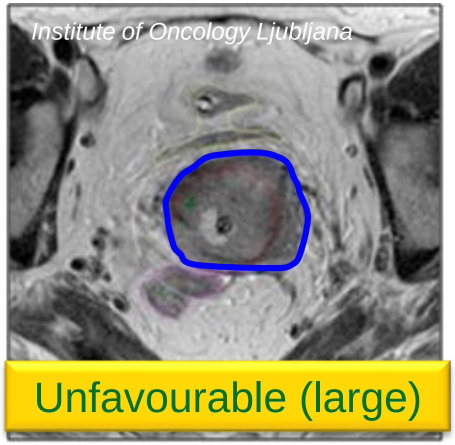
Set the **STAGE** before contouring

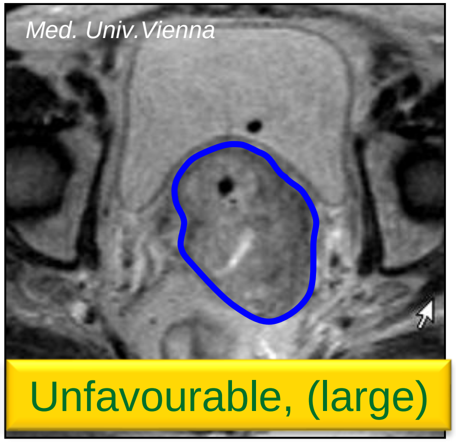
- **S**ize of the residual tumor?
- **T**opography of the target V?
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

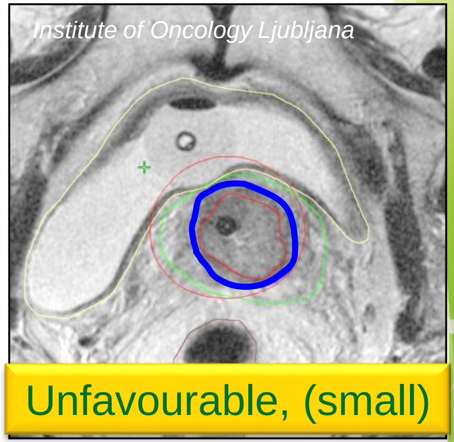
Topography of the tumour

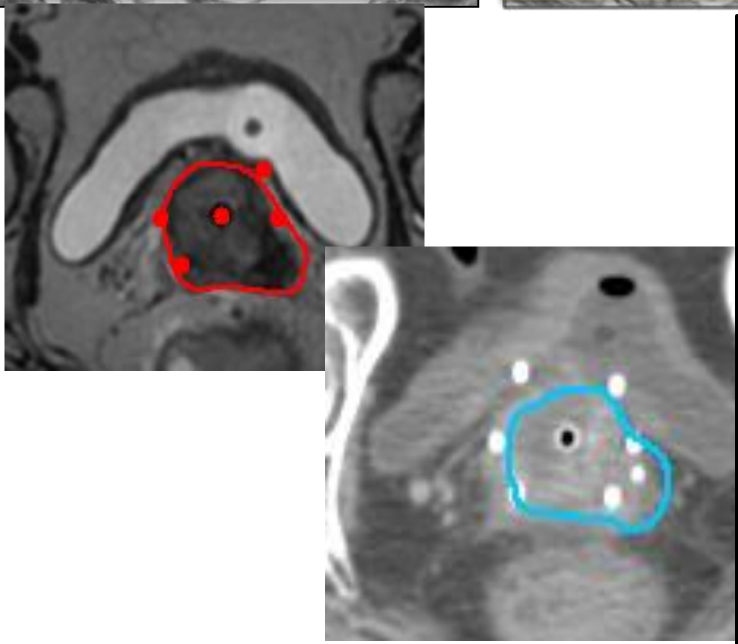
Tumour and Target shape and extent: symmetry related to tandem

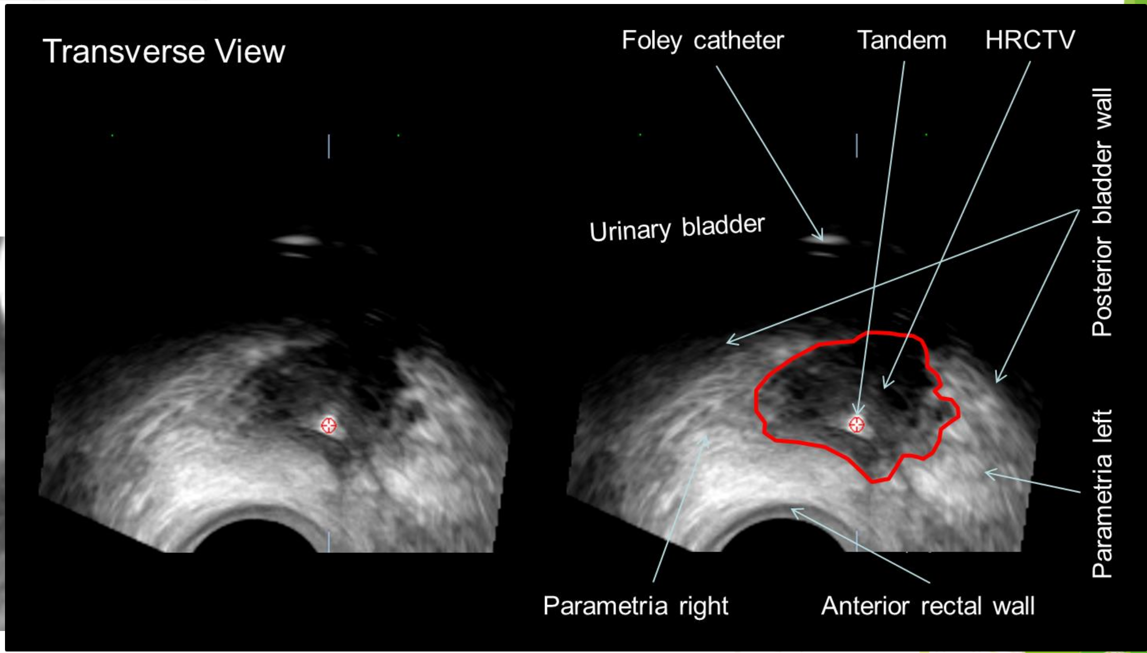




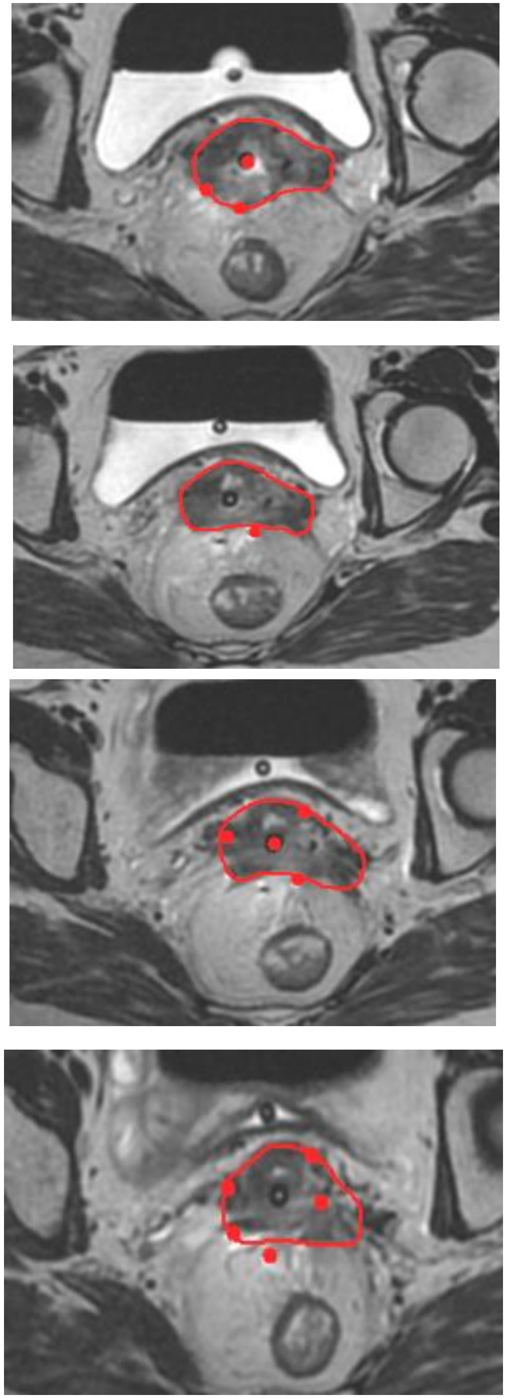


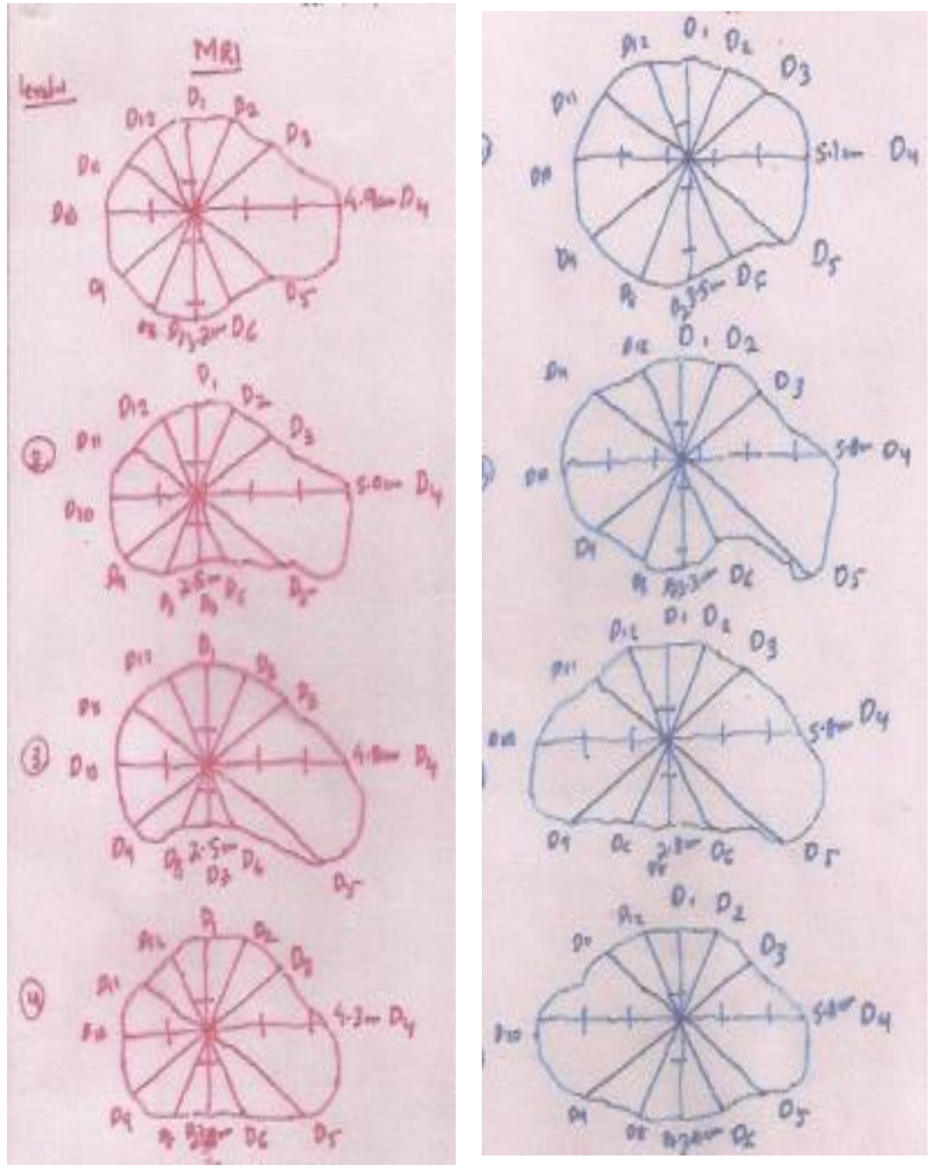


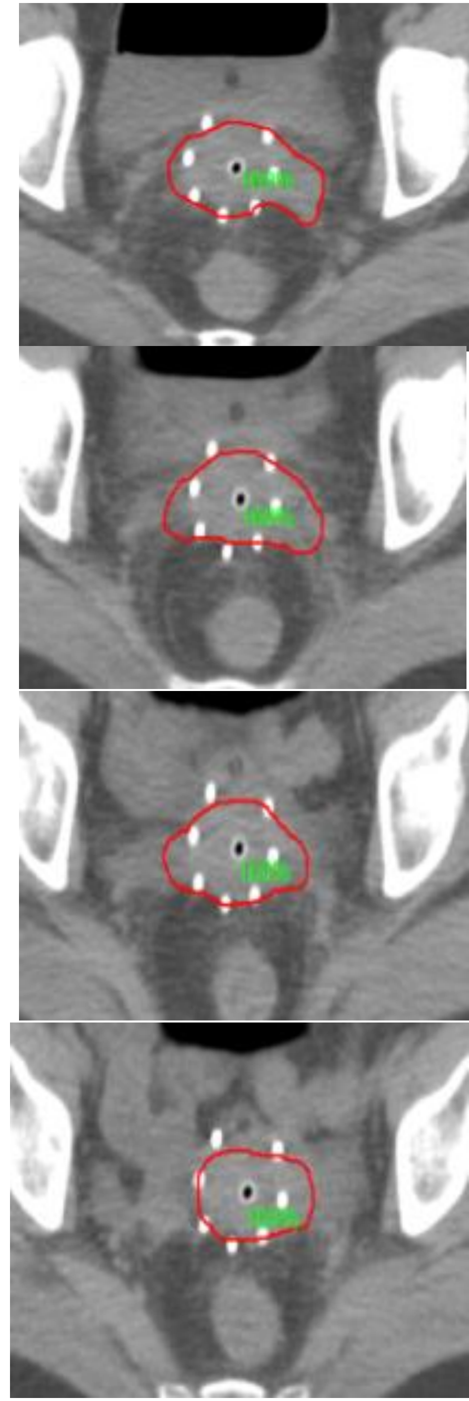




Ca Cervix-IIIB,
HRCTV includes para involved at BT







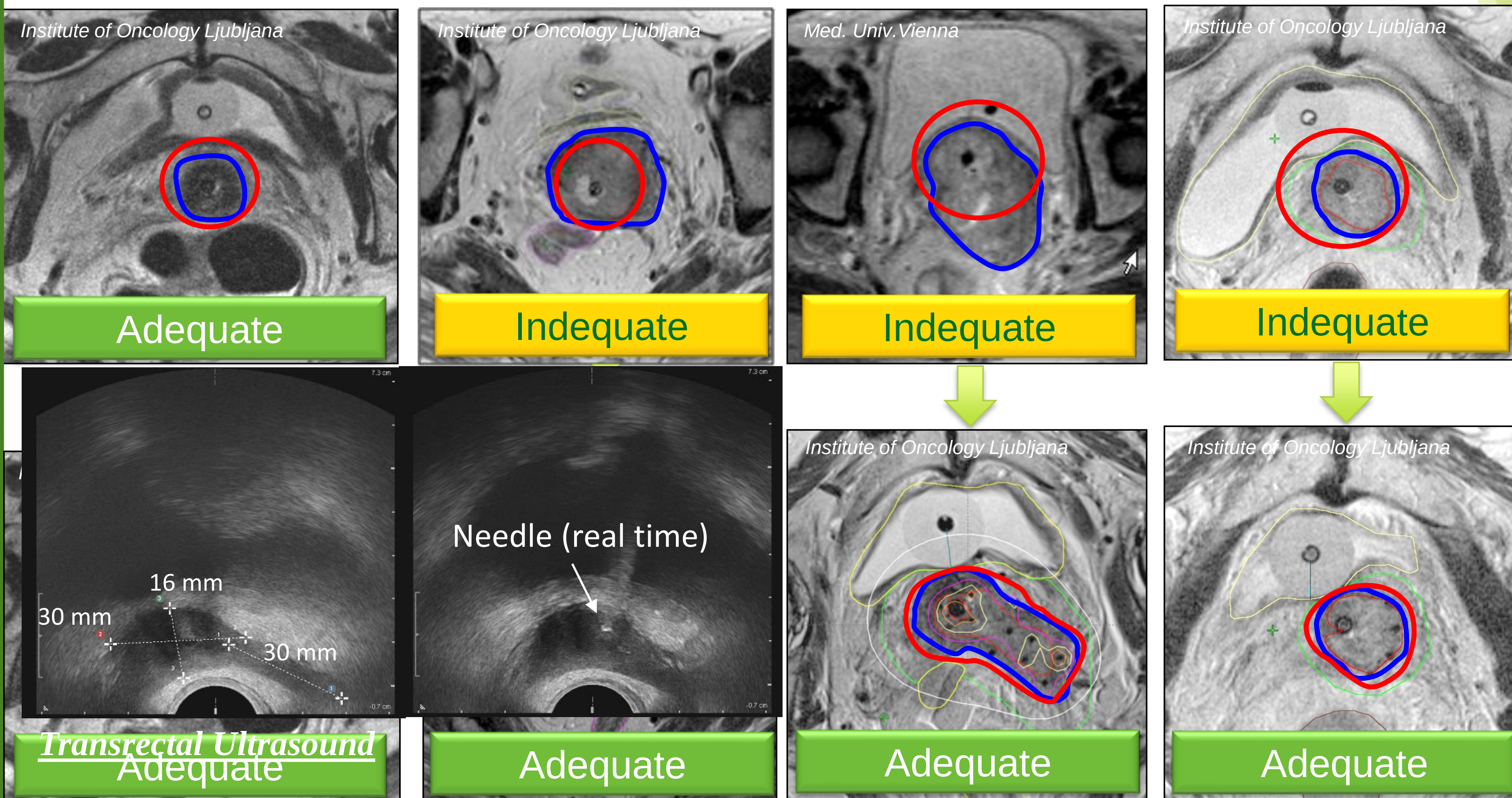
Ongoing TMH Clinical Study

Set the **STAGE** before contouring

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

Adequacy of the implant

Relation: Applicator(s) - Target V - Organs



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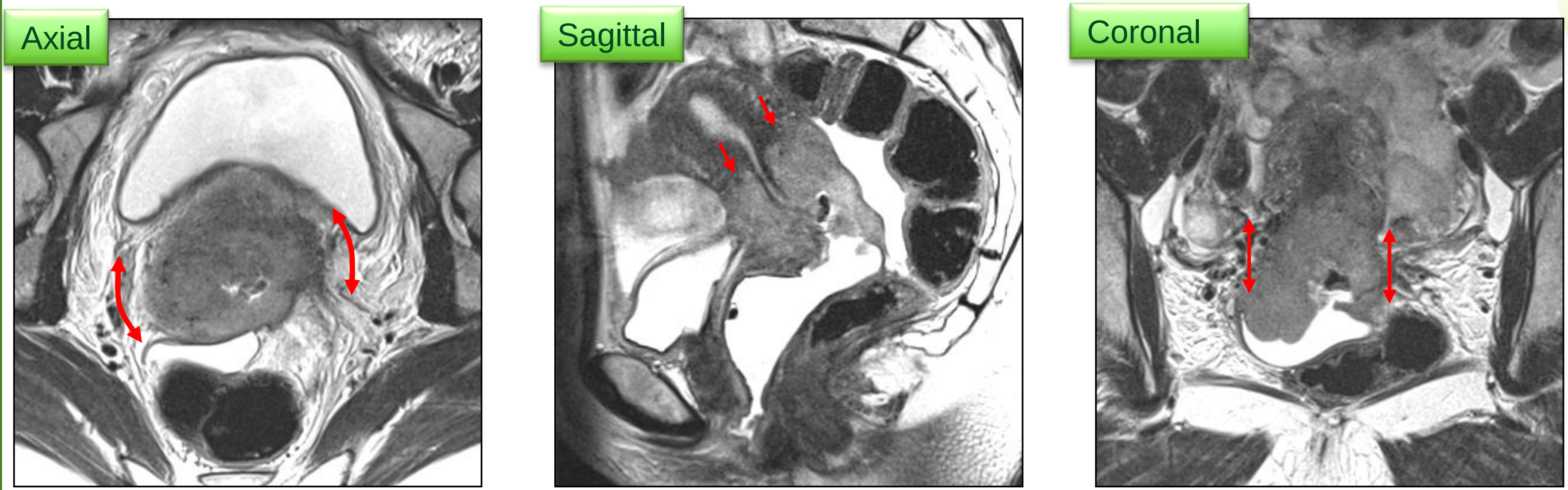
- **E**xtra findings?

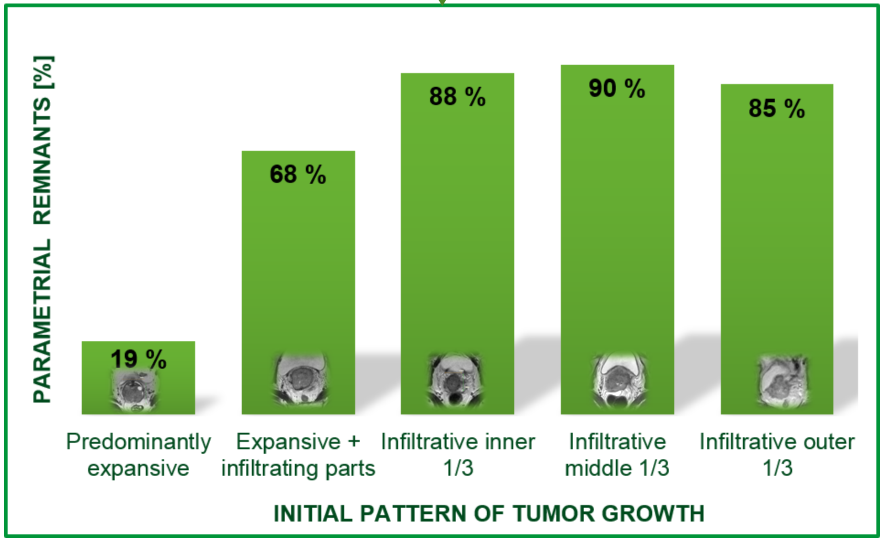
Grey zones

Grey zones at BT correlate with *Initial spread*

Grey zones

Grey zones at BT correlate with *Initial spread*

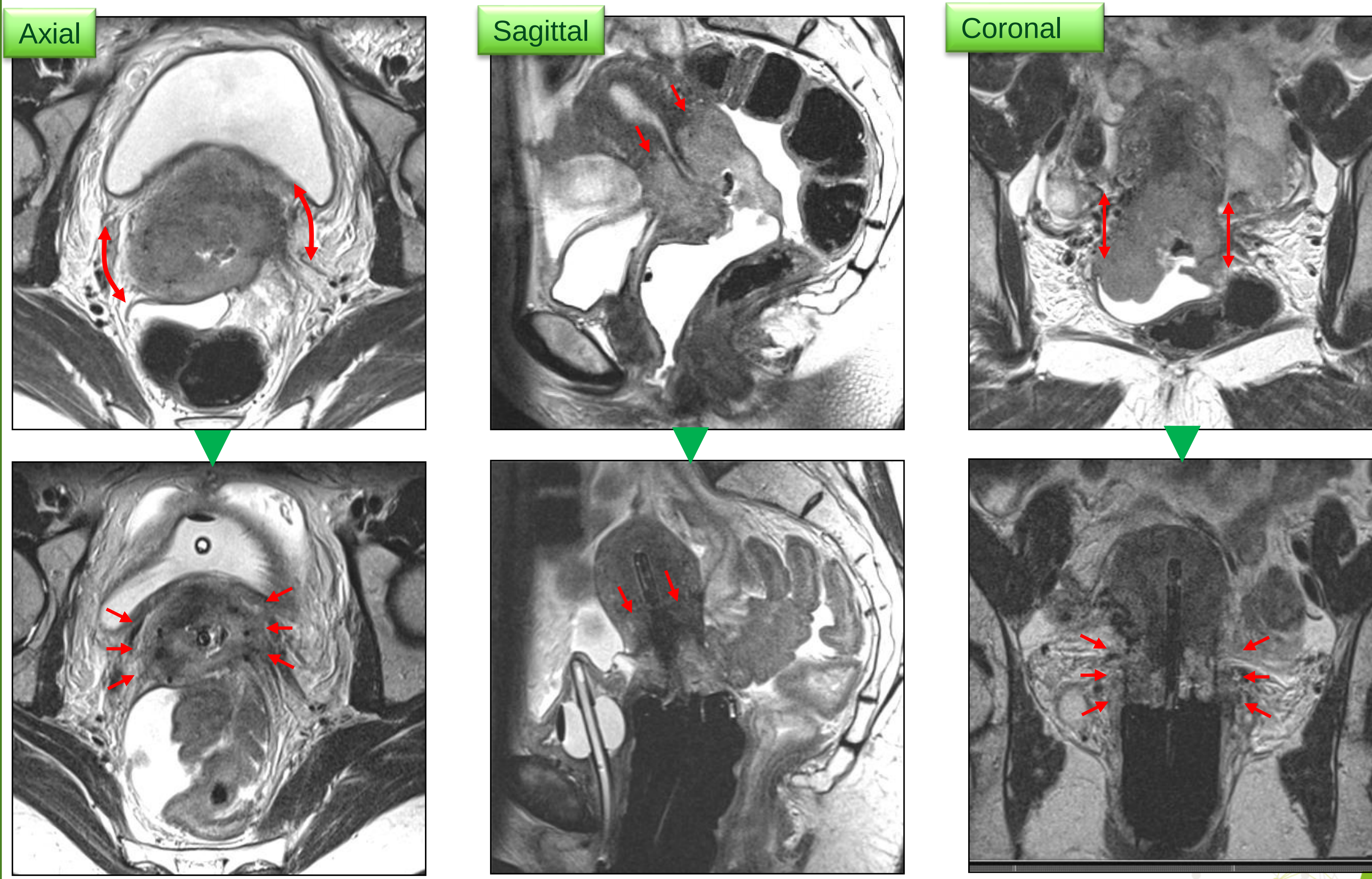




Schmid MP, et al. Acta Oncol 2013
Yoshida K, et al. IJROBP 2016

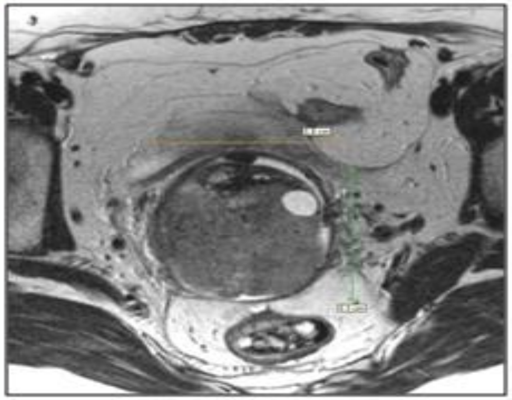
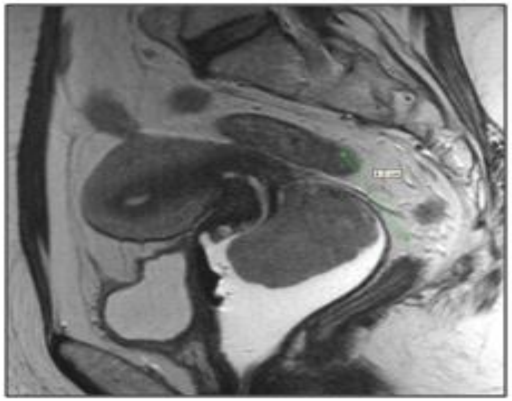
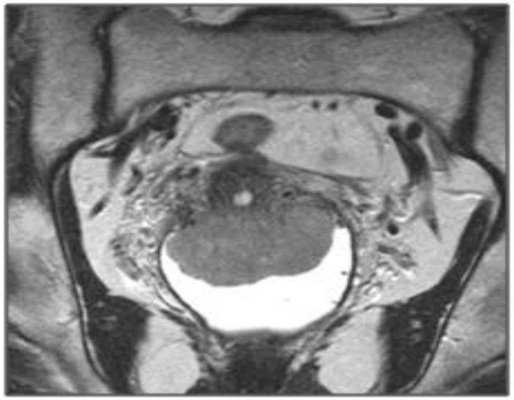
Grey zones

Grey zones at BT correlate with *Initial spread*



Grey zones

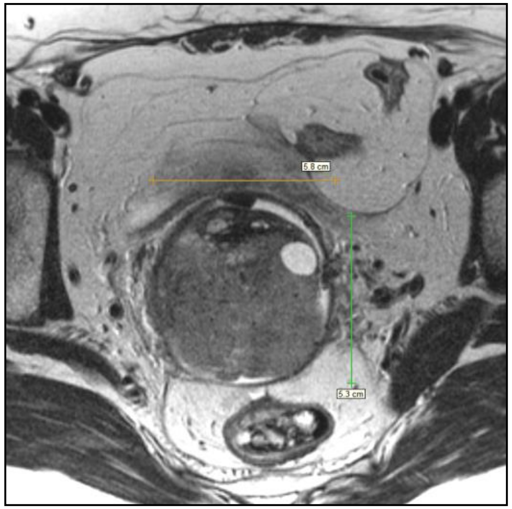
Grey zones at BT correlate with *Initial spread*

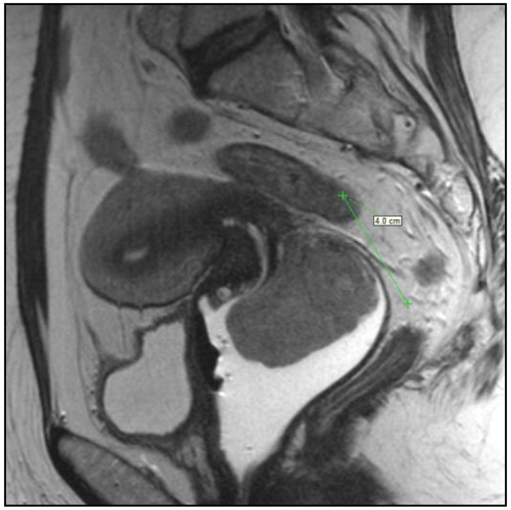




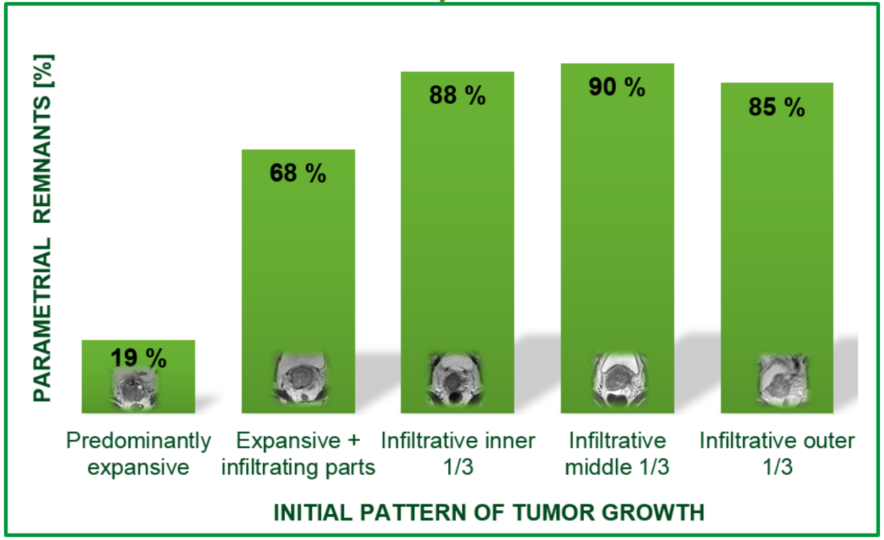
Estimate probability for residual pathological tissues in parametria after EBRT for this patient:

Grey zones

Grey zones at BT correlate with *Initial spread*



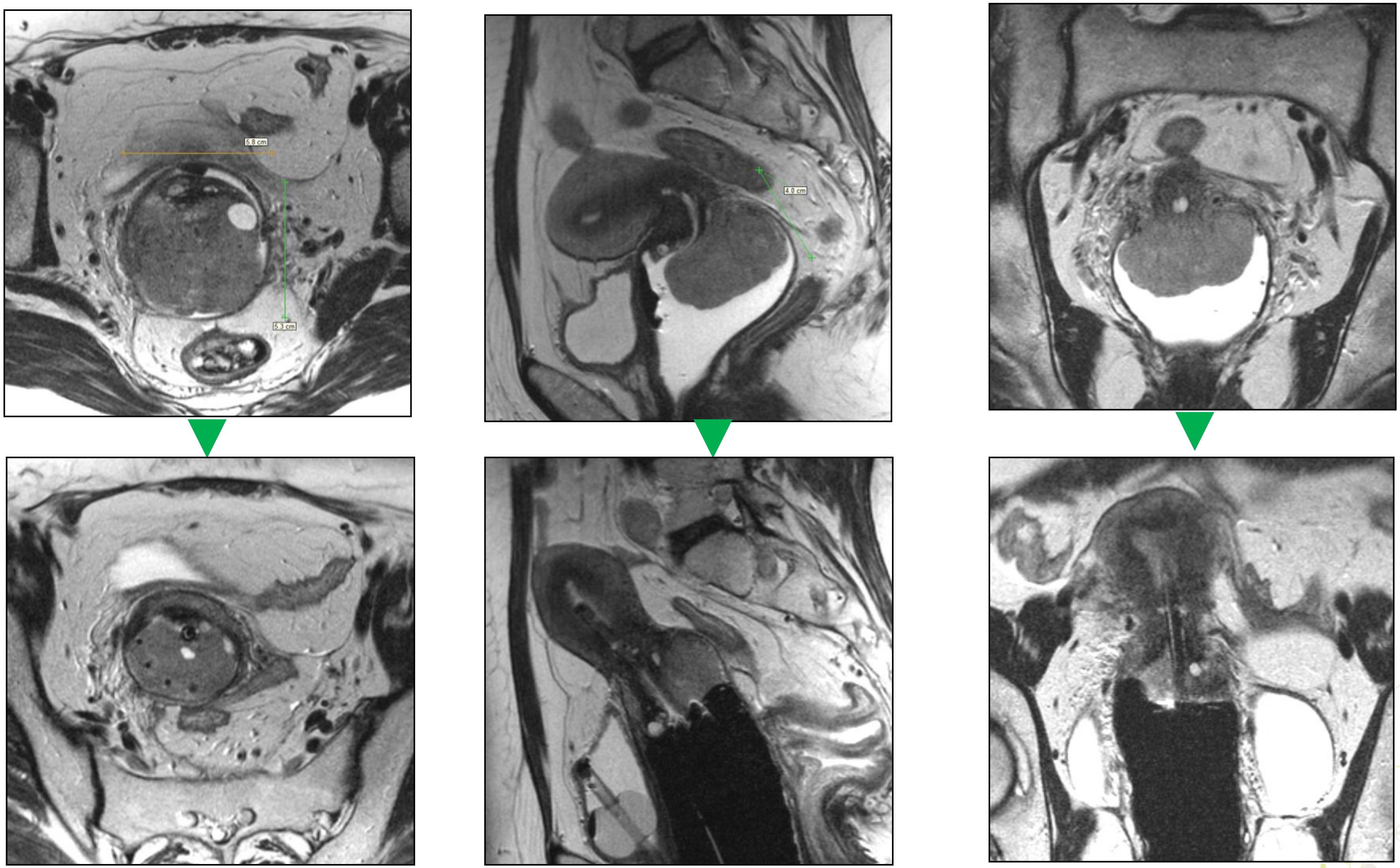




Schmid MP, et al. Acta Oncol 2013
Yoshida K, et al. IJROBP 2016

Grey zones

Grey zones at BT correlate with *Initial spread*



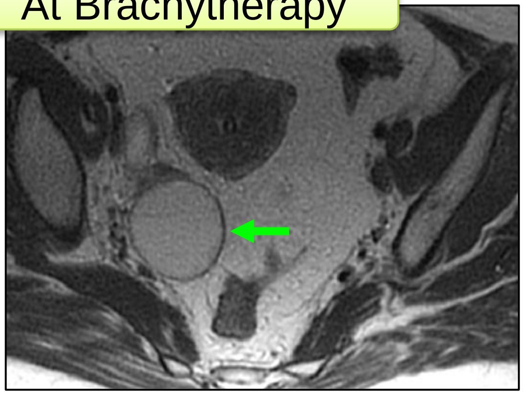
Set the **STAGE** before contouring

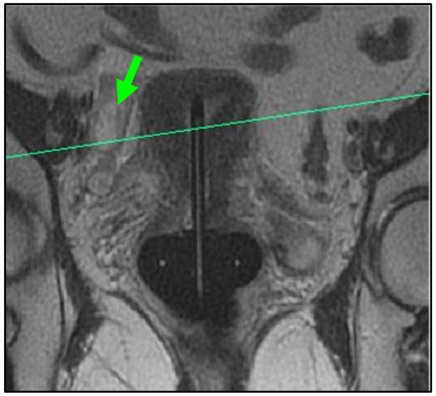
- **S**ize of the residual tumor?
- **T**opography of the target V?
- **A**dequacy of the implant?
- **G**rey zones in relation to GTV_{DG}?
- **E**xtra findings?

"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)

Rule out **FLOP**

Set the **STAGE** for contourig

MRI and/or CT/US with clinical drawings

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

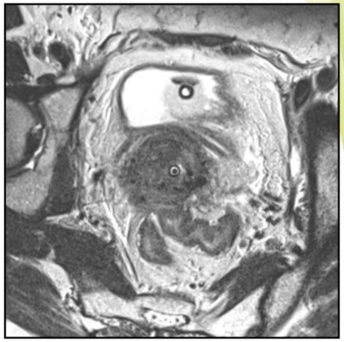
1. **S**ize of the tumor:
   - 8 cm^3 (ellipsoid formula)
   - Regression to Proportional V: PV = 20 % initial V

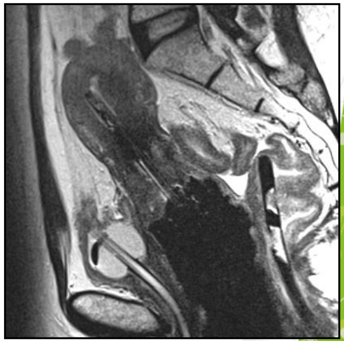
2. **T**opography: unfavourable due to right parametrial extension.

3. **A**dequate insertion geometry.

4. **G**rey zones correspond to initial infiltrative tumor: proximal third of right parametrium, dorsally. (fibrosis in clin exam)

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



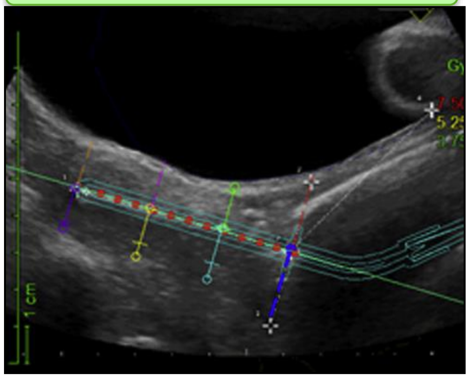


Petric P Journal of Contemporary Brachytherapy 2014

Choice of imaging modality for IGABT

ULTRASOUND

Transabdominal

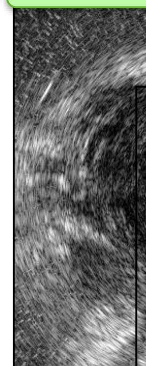


Van Dyk et al. Brachytherapy 2015

Transrectal

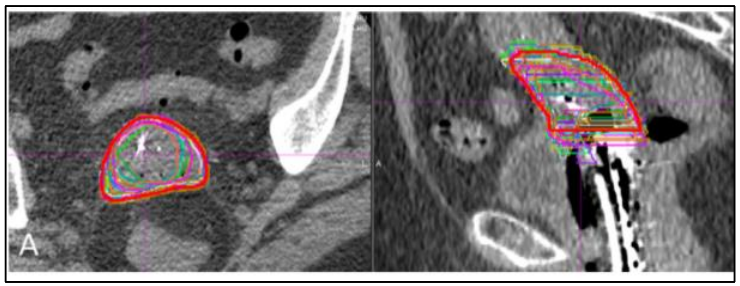
Schmid MP, et al. Radiother Oncol 2016

Rotatir



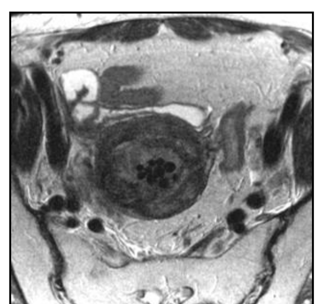
Petric P, Kir

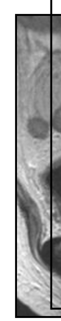
CT



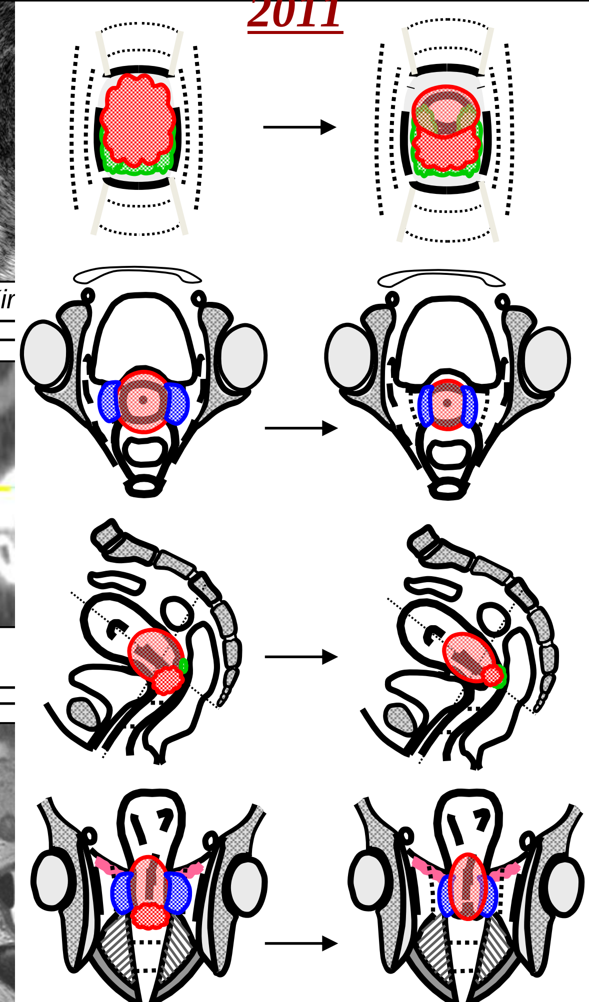
Viswanathan AN, et al Int J Radiat Oncol Biol Phys 2014

MRI





EMBRACE study protocol, 2011



Patient Preparation for Treatment Planning

EBRT

Immobilization, Organ Filling / Reproducibility

Umesh Mahantshetty

Professor, Department of Radiation Oncology

Tata Memorial Hospital, Mumbai, India

European Society for Therapeutic Radiology and Oncology

2nd AROI - ESTRO TEACHING COURSE LUCKNOW 2018

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

Counseling & Patient preparation Instructions

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

  - preparation of the parts (perineum)

- Dietary instructions & Rx of constipation

Pre-planning Audit

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

  - Radical / Postoperative / Palliative

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

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

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

Positioning & Immobilization

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

SUPINE POSITION

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

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

SUPINE WITH KNEE REST & ALIGNMENT

LASER ALIGNMENT

Immobilisation

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

Thermoplastic molds

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

Immobilization: Other methods

Elekta Body Frame

Body Fix system with Vacloks

Prone Versus Supine

Prone vs. supine position in endometrial cancer IMRT

47 patients; adjuvant RT

- 21 pts: prone
- 26 pts: supine

Small Bowel dosimetric and clinical results:

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

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

Conclusion: no difference in dose and toxicity.

Beriwal S, et al. 2007, IJROBP

Prone versus supine

Systematic review

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

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

Department of Radiation Oncology, University of Groningen, The Netherlands

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

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

Wiesendanger-Wittmer EM, et al. Radiother Oncol 2012

Positioning & Immobilization - Summary

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

  - Are now generally used and provide excellent reproducibility

  - Comfortable to patient

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

ORGAN FILING PROTOCOLS

- **Bladder filing**

  - Some bladder filing protocol

  - Various protocols utilized (500 – 1000 ml)

- **Rectal filing**

  - Empty bowels daily before planning / treatment

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

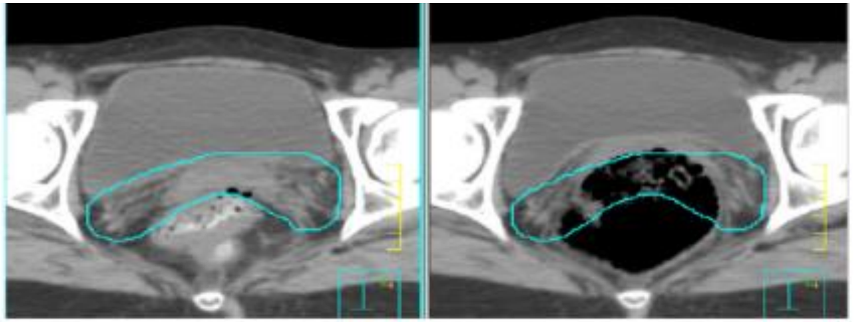


Fig. 2. Effect of rectal filling comparing the planning scan (left) to pretreatment scan (right). Cyan contour represents the CTV. (CTV - clinical target volume).

Organ filing: Bladder

Jhingran A, et al. IJROBP 2012

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

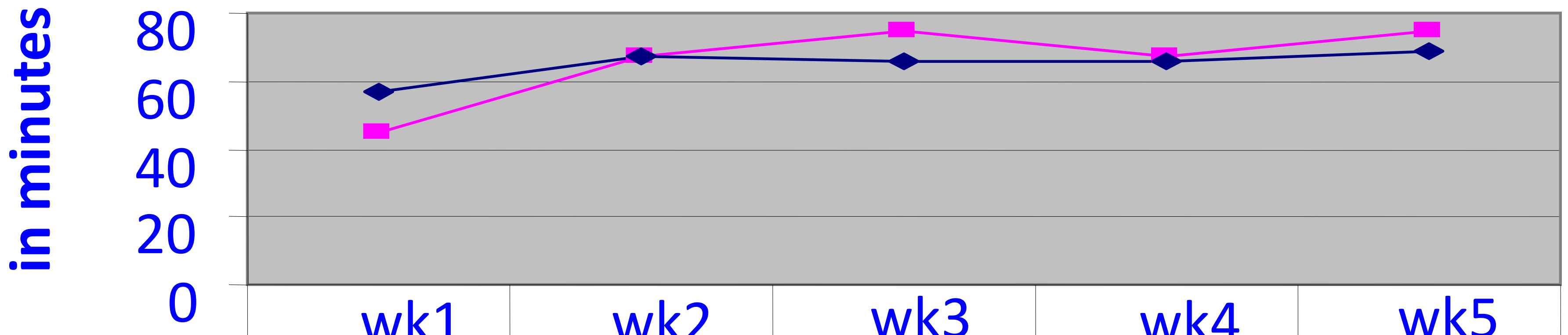
Jhingran A, et al. IJROBP 2012

TMH Study (N = 46 patients)

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

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

Methodology : Volume assessed by serial Trans-Abdominal US

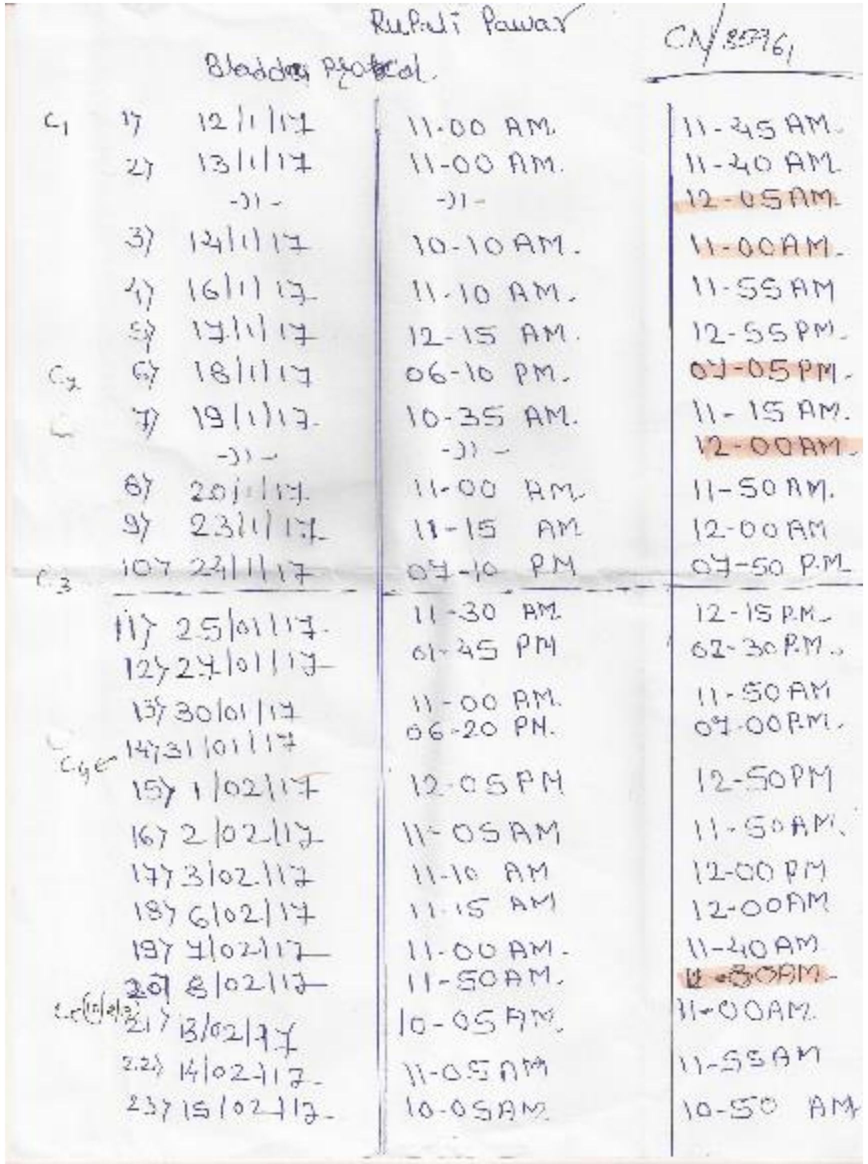


	wk1	wk2	wk3	wk4	wk5
Median filling time	45	67.5	75	67.5	75
Mean filling time	57	67	66	66	69

Mahantshetty et al ; TCRT 2017

Bladder protocol Compliance: Quick Assessment

Patient Record



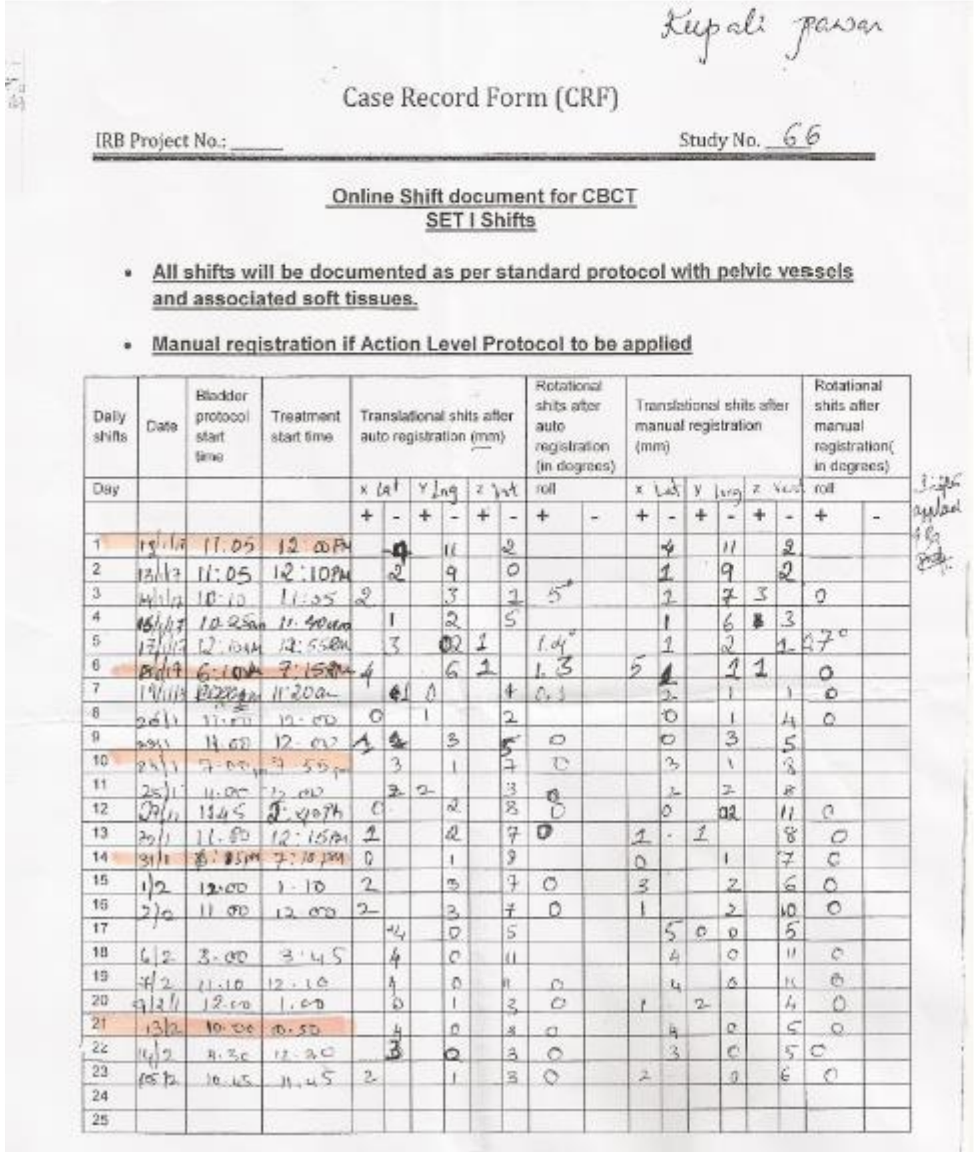
Rupali Pawar

CN/35796

Bladder Protocol.

C1	1)	12/1/17	11.00 AM.	11-45 AM.
	2)	13/1/17	11-00 AM.	11-40 AM.
		-"-	-"-	12-05 AM.
	3)	14/1/17	10-10 AM.	11-00 AM.
	4)	16/1/17	11-10 AM.	11-55 AM
	5)	17/1/17	12-15 AM.	12-55 PM.
C2	6)	18/1/17	06-10 PM.	07-05 PM.
	7)	19/1/17.	10-35 AM.	11-15 AM.
		-"-	-"-	12-00 AM.
	8)	20/1/17.	11-00 AM.	11-50 AM.
	9)	23/1/17.	11-15 AM	12-00 AM
C3	10)	24/1/17	07-10 PM	07-50 P.M.
	11)	25/01/17.	11-30 AM.	12-15 P.M.
	12)	27/01/17	01-45 PM	02-30 P.M.
	13)	30/01/17	11-00 AM.	11-50 AM
C4	14)	31/01/17	06-20 PM.	07-00 P.M.
	15)	1/02/17	12-05 PM	12-50 PM
	16)	2/02/17.	11-05 AM	11-50 AM.
	17)	3/02/17	11-10 AM	12-00 PM
	18)	6/02/17	11-15 AM	12-00 AM
	19)	7/02/17	11-00 AM.	11-40 AM
	20)	8/02/17	11-50 AM.	12-30 PM.
C5 (13/2/17)	21)	13/02/17	10-05 AM.	11-00 AM.
	22)	14/02/17.	11-05 AM	11-55 AM
	23)	15/02/17.	10-05 AM.	10-50 AM.

Technologist Record



Rupali pawar

Case Record Form (CRF)

IRB Project No.: ______ Study No. 66

Online Shift document for CBCT

SET I Shifts

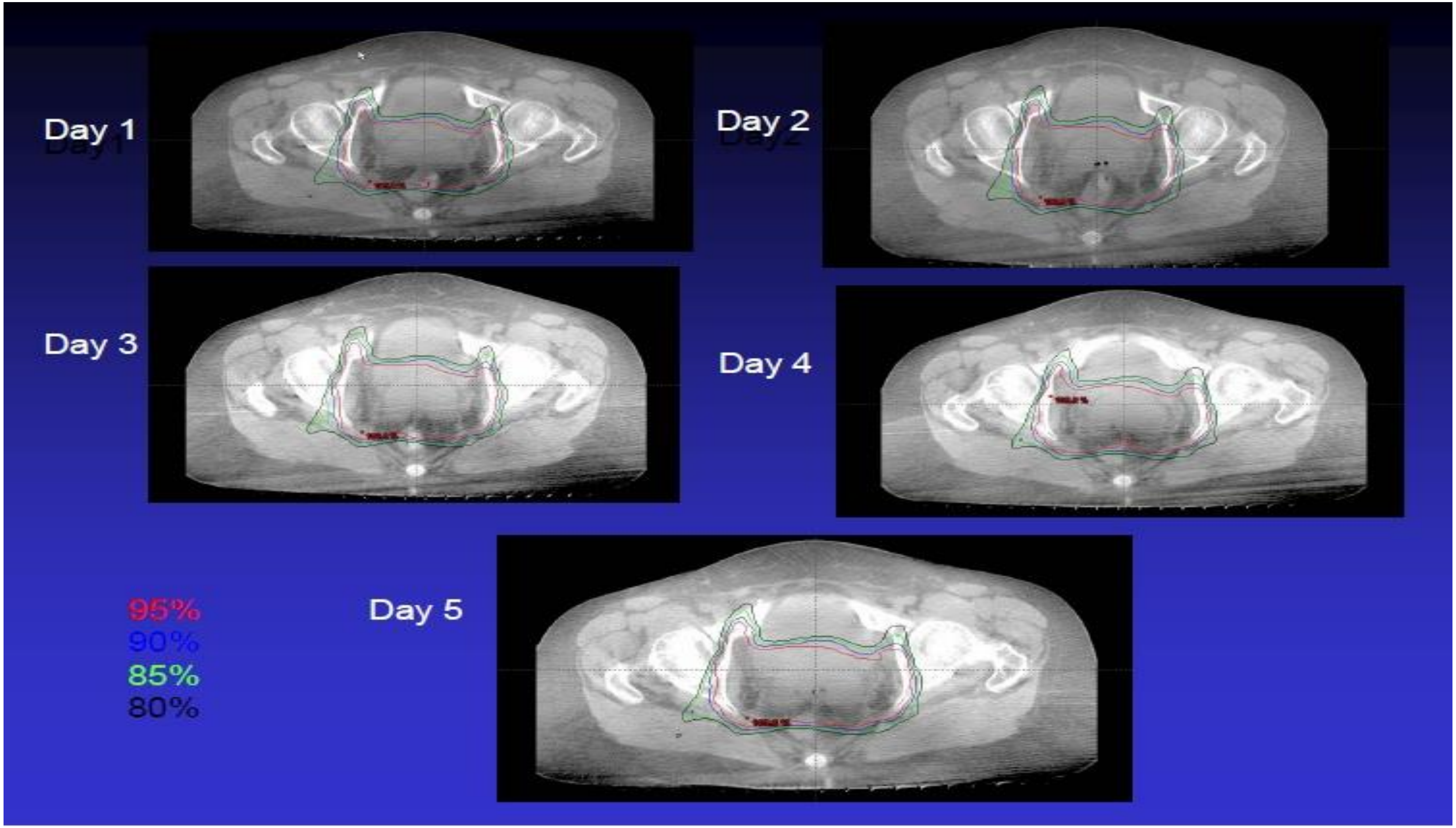
- **All shifts will be documented as per standard protocol with pelvic vessels and associated soft tissues.**
- **Manual registration if Action Level Protocol to be applied**

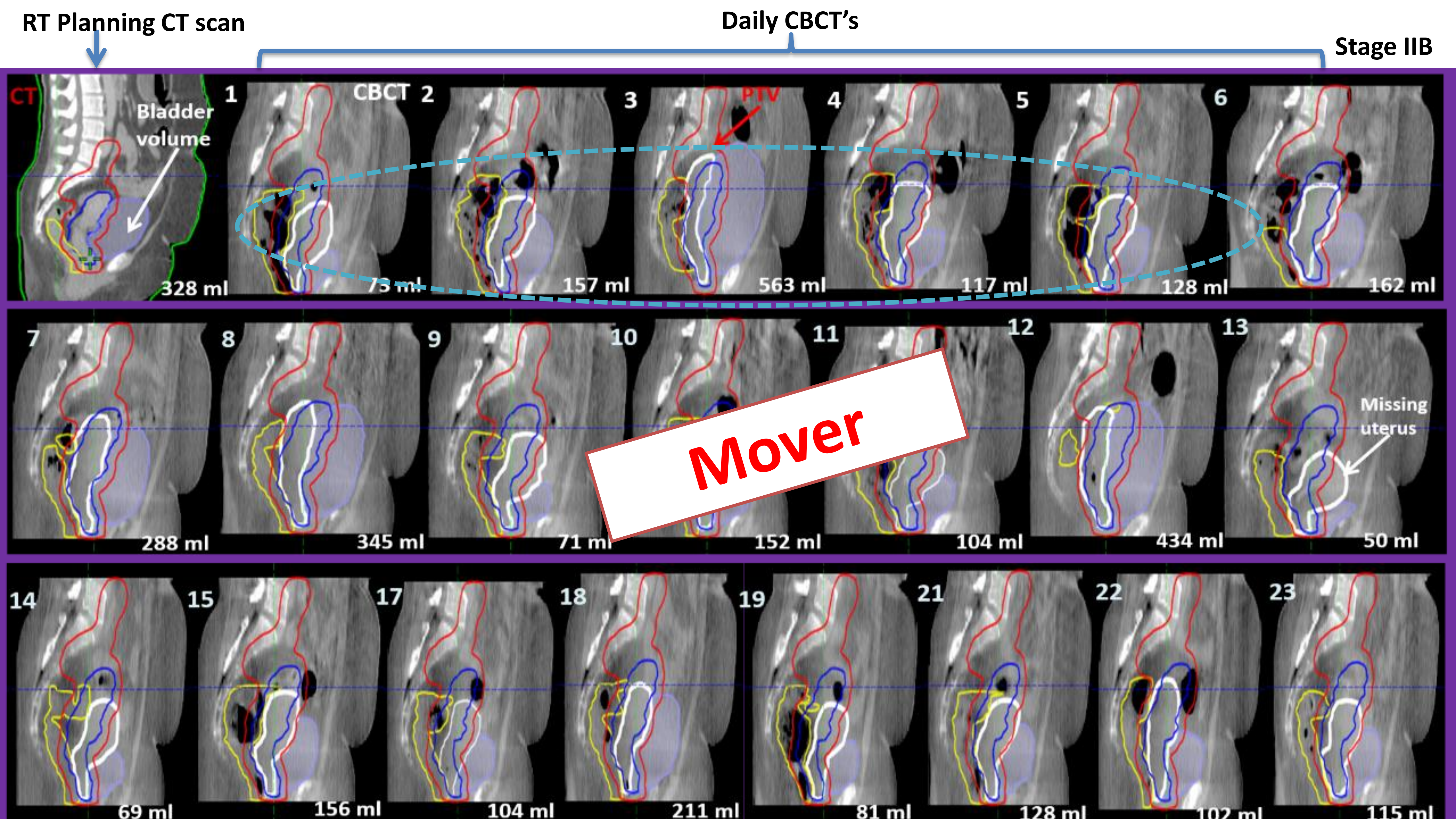
Daily shifts	Date	Bladder protocol start time	Treatment start time	Translational shits after auto registration (mm)						Rotational shits after auto registration (in degrees)		Translational shits after manual registration (mm)						Rotational shits after manual registration(in degrees)	
Day				x lat		Y lng		z vert		roll		x lat		y lng		z vert		roll	
				+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
1	13/1/17	11.05	12.00PM		4		11		2				4		11		2		
2	13/1/17	11:05	12:10PM		2		9		0				1		9		2		
3	14/1/17	10.10	11:35	2			3		1	5°			1		7	3		0	
4	16/1/17	10.25am	11.40am		1		2		5				1		6	[illegible]	3		
5	17/1/17	12.10AM	12:55PM		3		02	1		1.4°			1		2		1.	37°	
6	18/1/17	6:10PM	7:15PM	4			6	1		1.3		5	1		1	1		0	
7	19/1/17	[illegible]	11:20am		1	0			4	0.1			2		1		1	0	
8	20/1	11.00	12.00	0		1			2				0		1		4	0	
9	23/1	11.00	12.00	1	4		3		5	0			0		3		5		
10	24/1	7.00pm	7.55pm		3		1		7	0			3		1		3		
11	25/1	11.00	12.00		2	2			3	0			2		2		8		
12	27/1	11.45	12.40pm	0			2		8	0			0		02		11	0	
13	30/1	11.50	12:15PM	1			2		7	0		1	.	1			8	0	
14	31/1	6:45PM	7:10PM	0			1		9			0			1		7	0	
15	1/2	12.00	1.10	2			3		7	0		3			2		6	0	
16	2/2	11.00	12.00	2			3		7	0		1			2		10	0	
17					4		0		5				5	0	0		5		
18	6/2	3.00	3.45		4		0		11				4		0		11	0	
19	7/2	11.10	12.10		4		0		11	0			4		0		11	0	
20	9/2/17	12.00	1.00		0		1		3	0		1		2			4	0	
21	13/2	10.00	10.50		4		0		8	0			4		0		5	0	
22	14/2	11.30	12.20		3		0		3	0			3		0		5	0	
23	15/2	10.45	11.45	2			1		3	0		2			0		6	0	
24																			
25																			

1.37° applied [illegible]

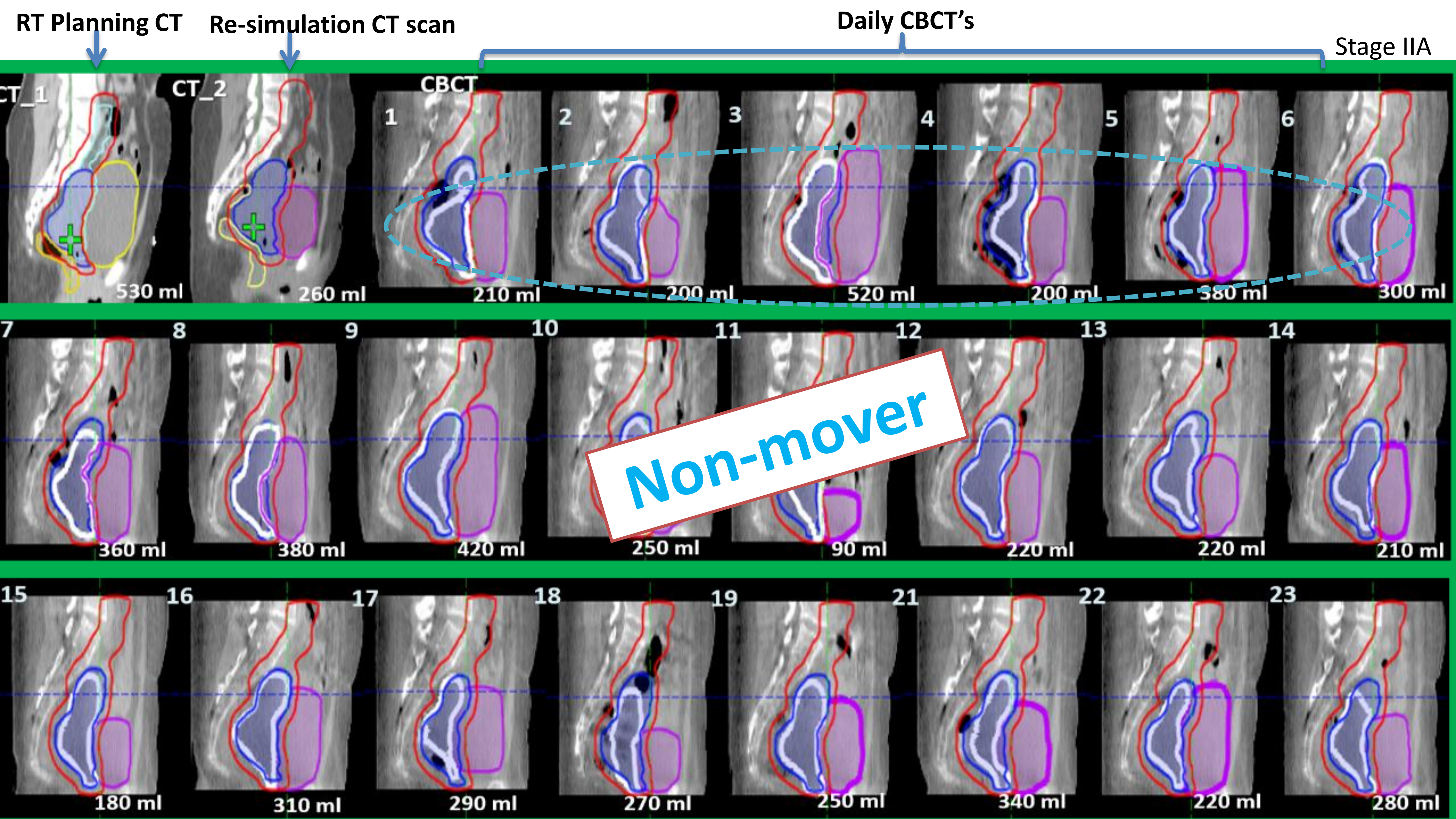
An example of Image Guided Radiation therapy (IGRT)

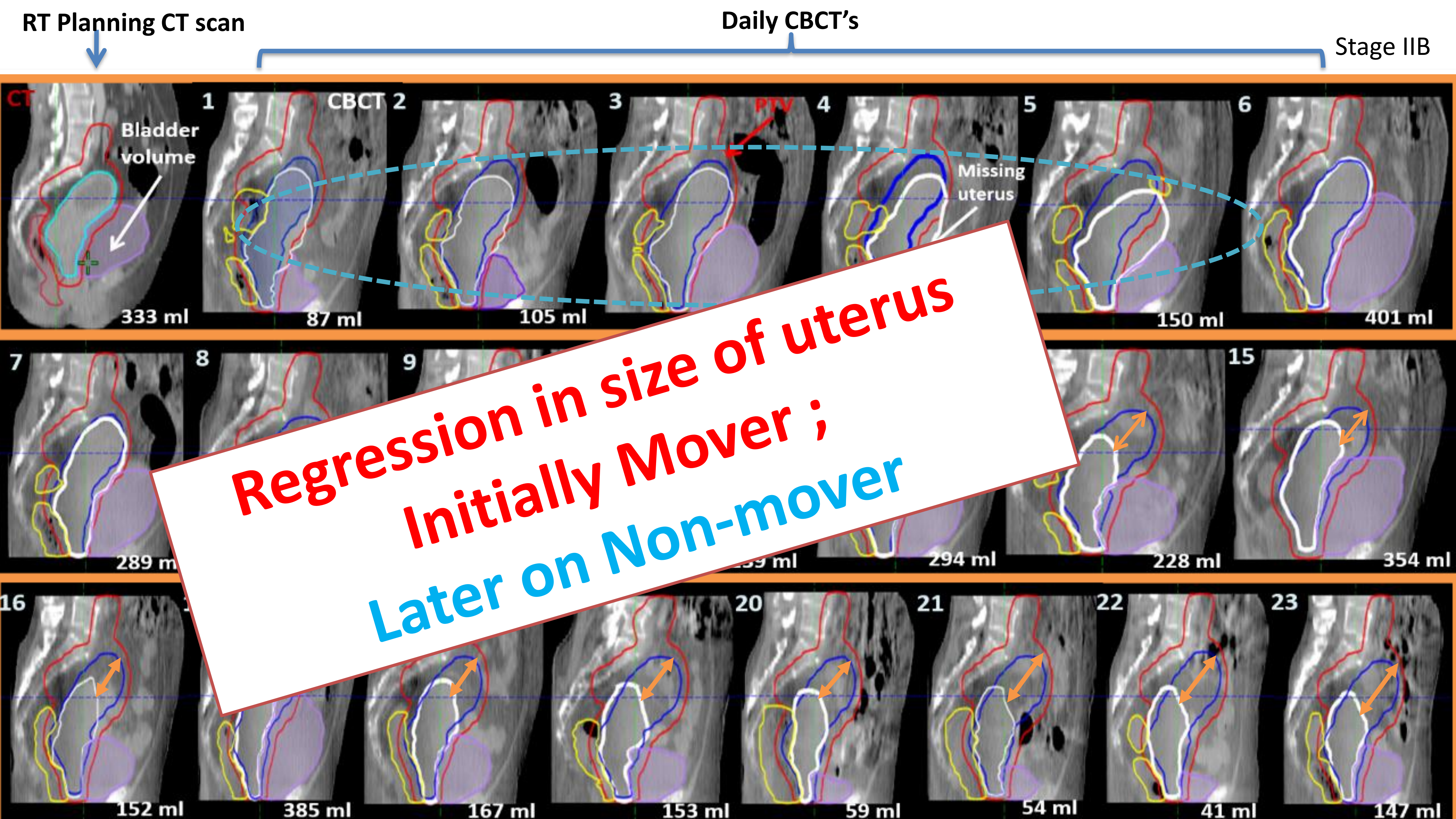
Bladder Filling Status





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


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



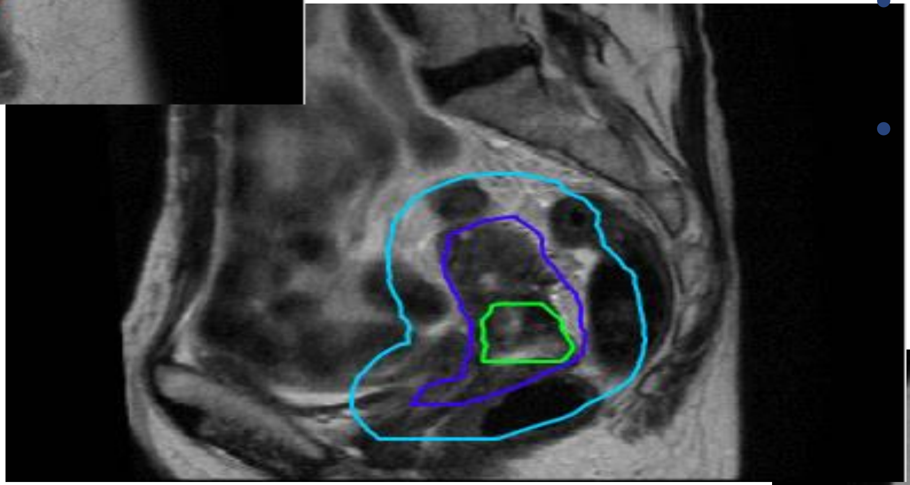
RT Planning CT scan
Daily CBCT's
Stage IIB
CT
Bladder volume
1
CBCT 2
3
PTV
4
Missing uterus
5
6
333 ml
87 ml
105 ml
150 ml
401 ml
7
8
9
15
289 ml
294 ml
228 ml
354 ml
16
20
21
22
23
152 ml
385 ml
167 ml
153 ml
59 ml
54 ml
41 ml
147 ml
Regression in size of uterus
Initially Mover ;
Later on Non-mover

Target motion & Bladder filing effect during EBRT

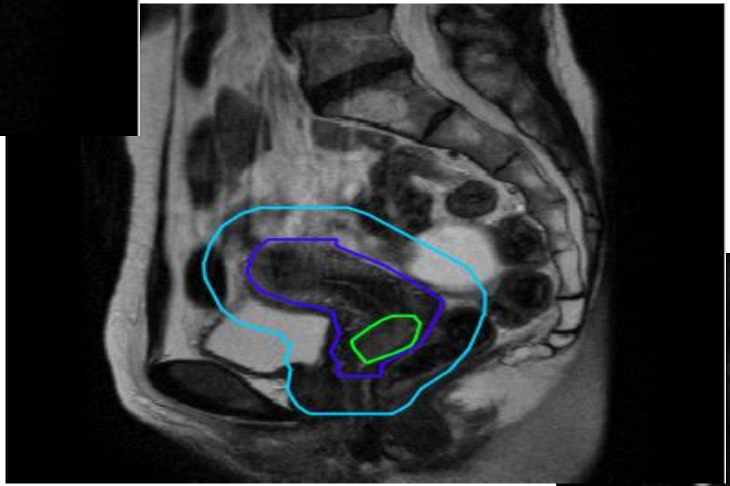
Van de Bunt et al 2008

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

Low impact



Low impact



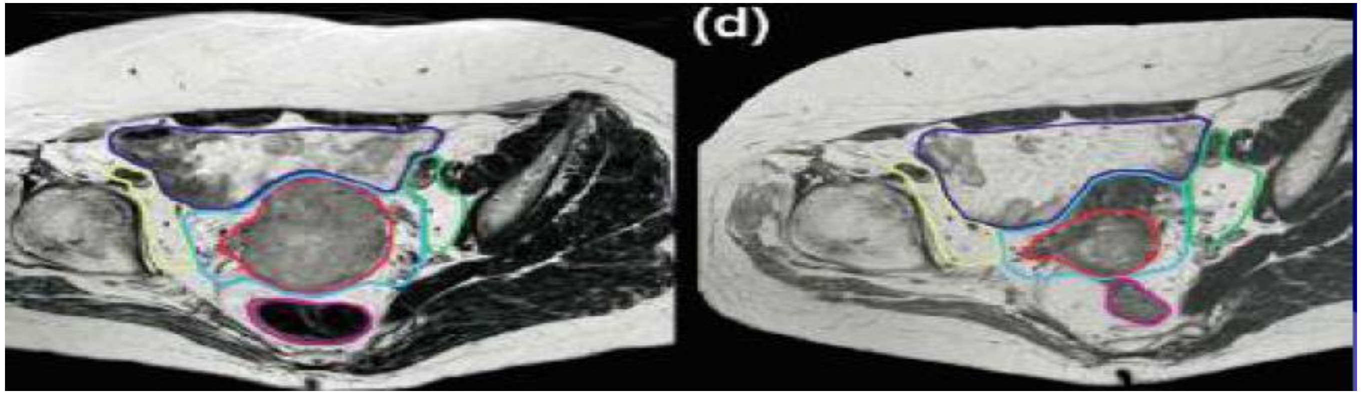
High impact of bladder and bowel

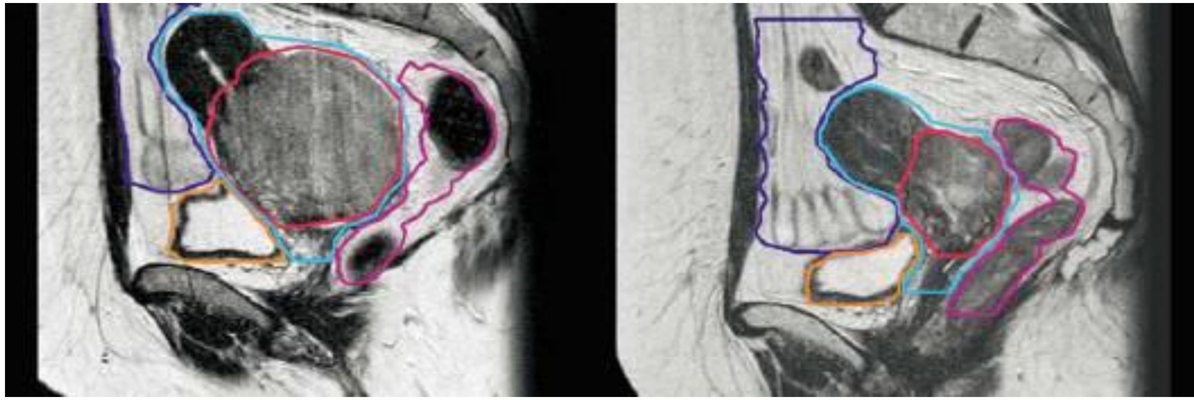
High impact of bladder

GTV
CTV
PTV

Courtesy : Ina Schulz, Utrecht

TUMOR REGRESSION DURING EXTERNAL RADIATION THERAPY





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

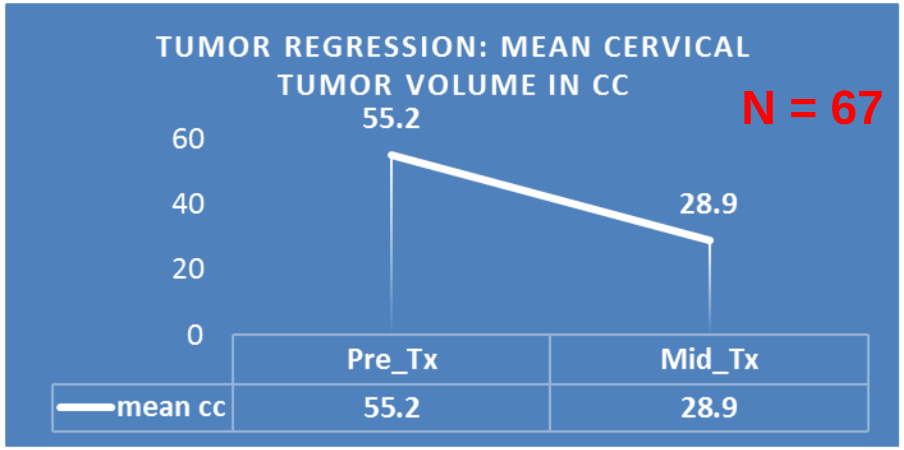
➢ University of Utah used physical exam measurements and found by 30.8 Gy tumors reduced by 50%

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

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

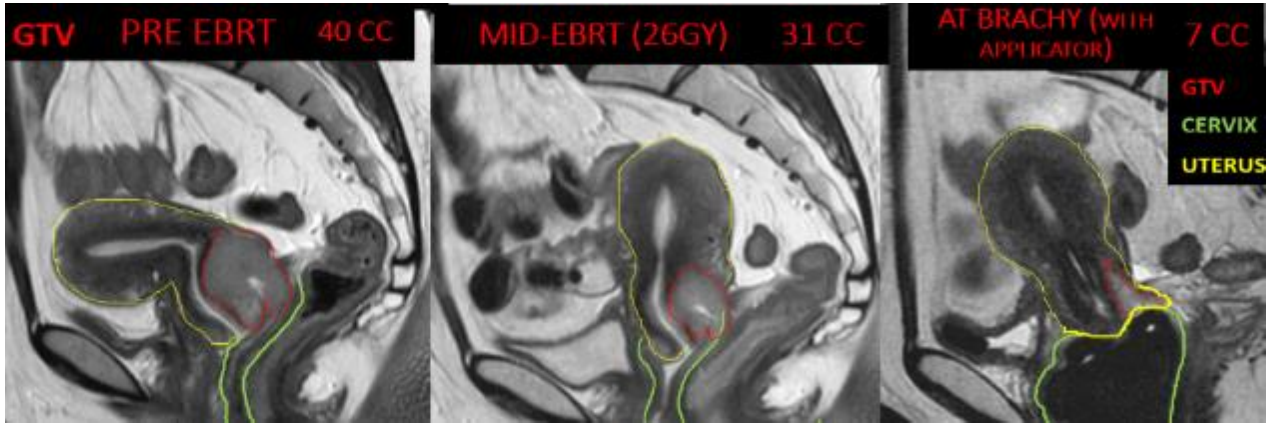
Quantification of tumor regression, Set-up errors and Internal Organ Motion in locally advanced Cervical cancer treated with radical radiation - results from a prospective study

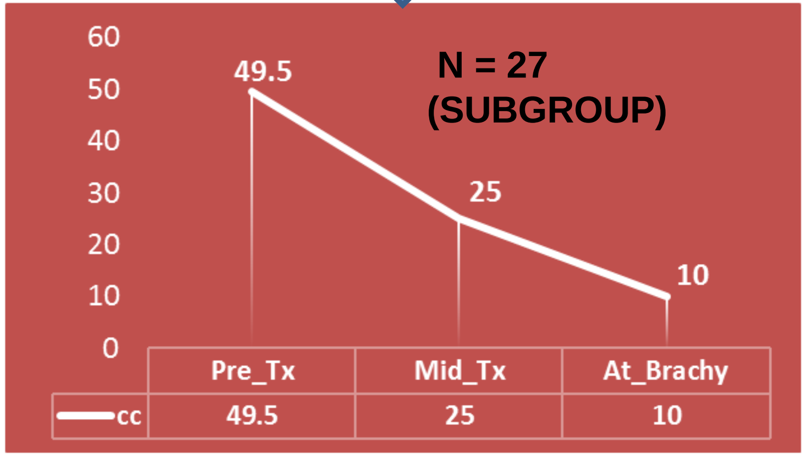
- **Cervical cancer with intact Uterus**
- **N = 70 patients with FIGO IIB-IIIB** (3 out of trial)
- **May 2011- March 2017**
- **Daily CBCT- IGRT (3DCRT/IMR plan)**
- **Online/Offline: CTV nodal/primary mid-cervix and uterine matching**
- **Baseline MRI and Mid-RT MRI = To evaluate tumor Regression**



Mean cervical tumor volume reduced from 55.2 cc at diagnosis to 28.9 cc at mid treatment.

Tumor regression





TMH data (unpublished)

TMH data (unpublished)

Set-up errors and organ motion

CBCT Matching Workflow

Set I Registration (Nodal CTV/Bony matching)

Match to Pelvic lymph nodes CTV/Vessels

Set II Registration (Soft-tissue matching)- Surrogate organ motion

Taking **Set I** shifts as a starting point, **matching is done for CTV Primary (at mid-cervix and mid-uterus)**

Systematic (∑), Random (σ) error distribution and calculated safety margin (Van herk's Recipe)

Nodal region				Cervix				Uterus			
	Σ	σ	Margin		Σ	σ	Margin		Σ	σ	Margin
X +	2.0	2.8	7.0	X +	2.1	3.0	7.3	X +	2.2	2.7	7.3
X -	2.7	3.3	8.9	X -	2.3	2.9	7.7	X -	2.3	2.7	7.6
Y +	3.0	4.1	10.3	Y +	2.3	4.0	8.5	Y +	2.7	4.8	10.2
Y -	1.9	3.5	7.2	Y +	1.8	3.1	6.7	Y -	3.0	4.3	10.4
Z +	2.4	3.5	8.5	Z +	2.7	3.9	9.5	Z +	6.6	6.2	20.9
Z -	2.9	3.6	9.8	Z -	2.3	3.8	8.5	Z -	4.0	3.8	12.6

Intra-fraction organ motion

Pre-treatment MR GTV (n=67)								
Organ motion (mm)	<45.6 cc (n=34)				>45.6 cc (n=33)			
Translational couch shifts	Cervix		Uterus		Cervix		Uterus	
	Mean Shifts (±SD)	Van Herk's margin	Mean Shifts (±SD)	Van Herk's margin	Mean Shifts (±SD)	Van Herk's margin	Mean Shifts (±SD)	Van Herk's margin
Left-lateral (X+)	2.8 (±1.3)	4.6	2.7 (±2.2)	6.9	4.3 (±2.4)	7.7	3.0 (±2.0)	6.2
Right-lateral (X-)	3.5 (±1.8)	5.8	3.9 (±2.2)	6.7	4.8 (±2.5)	7.9	4.4 (±2.3)	7.2
Anterior (Y+)	3.8 (±2.1)	6.8	5.6 (±2.6)	8.6	4.6 (±2.2)	7.5	5.9 (±2.7)	9.3
Posterior (Y-)	4.7 (±1.6)	5.9	6.5 (±3.2)	10.0	4.1 (±1.9)	6.0	6.8 (±2.7)	9.0
Superior (Z+)	4.7 (±3.5)	10.9	5.6 (±6.5)	19.1	4.3 (±1.7)	5.9	9.2 (±6.2)	19.0
Inferior (Z-)	4.0 (±2.3)	7.8	6.1 (±4.6)	13.5	4.3 (±2.3)	7.5	5.2 (±3.1)	9.6

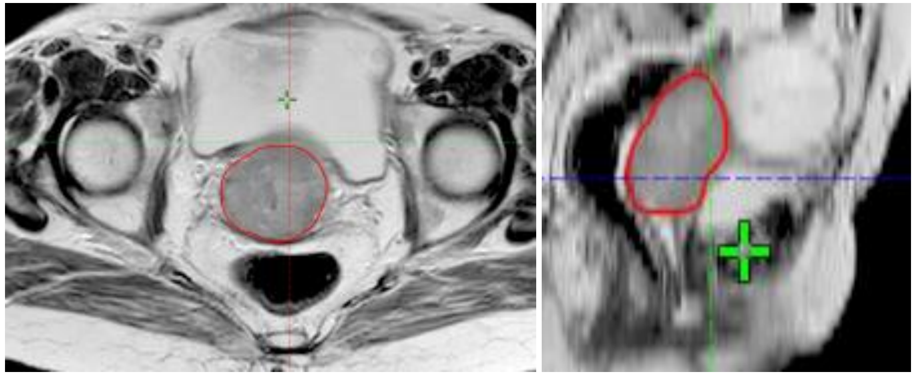
Mid-treatment MR GTV regression (n=67)							
<50% reduction (n=33)				>50% reduction (n=34)			
Cervix		Uterus		Cervix		Uterus	
Mean Shifts (±SD)	Van Herk's margin	Mean Shifts (±SD)	Van Herk's margin	Mean Shifts (±SD)	Van Herk's margin	Mean Shifts (±SD)	Van Herk's margin
3.5 (±2.3)	7.0	2.8 (±2.5)	7.7	3.5 (±1.9)	6.4	2.9 (±1.6)	5.3
4.1 (±2.0)	6.4	4.3 (±2.5)	6.4	4.2 (±2.5)	7.8	4.0 (±2.0)	6.3
4.2 (±2.5)	8.1	5.8 (±2.5)	8.3	4.2 (±1.8)	6.3	5.6 (±2.9)	9.6
4.7 (±1.9)	6.3	6.7 (±3.3)	6.3	4.2 (±1.6)	5.7	6.7 (±2.6)	8.4
4.9 (±3.2)	10.1	8.4 (±8.0)	23.1	4.1 (±2.3)	7.2	6.5 (±4.9)	15.2
3.7 (±2.5)	8.1	5.3 (±4.6)	8.1	4.6 (±2.0)	7.0	6.1 (±3.2)	10.2

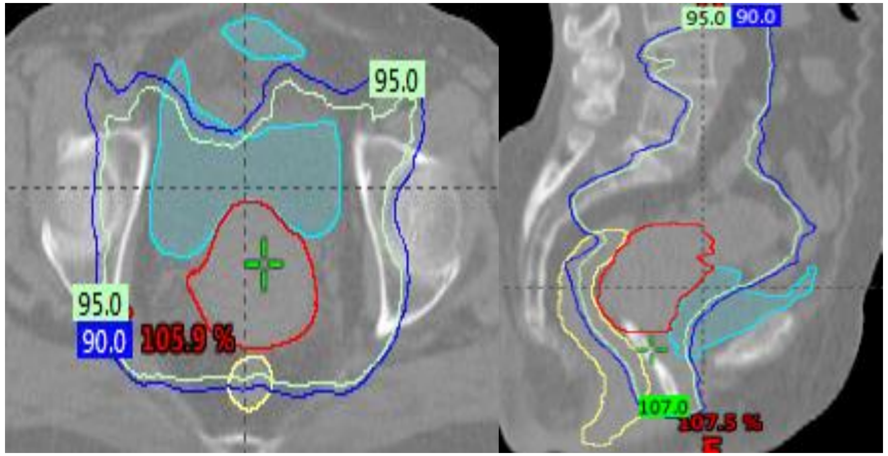
No difference in organ motion irrespective of ***pre-treatment tumor volume or mid-treatment tumor regression***

Our experience

Adaptive / mid RT Replan – *Dosimetric advantage!*

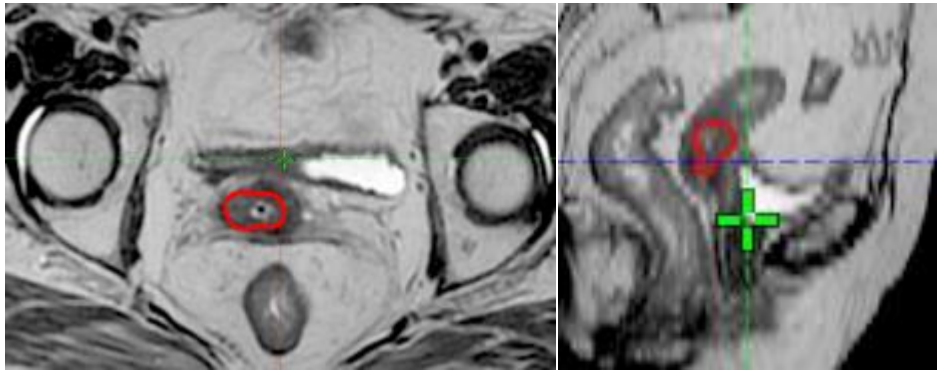
PRE EBRT GTV VOLUME

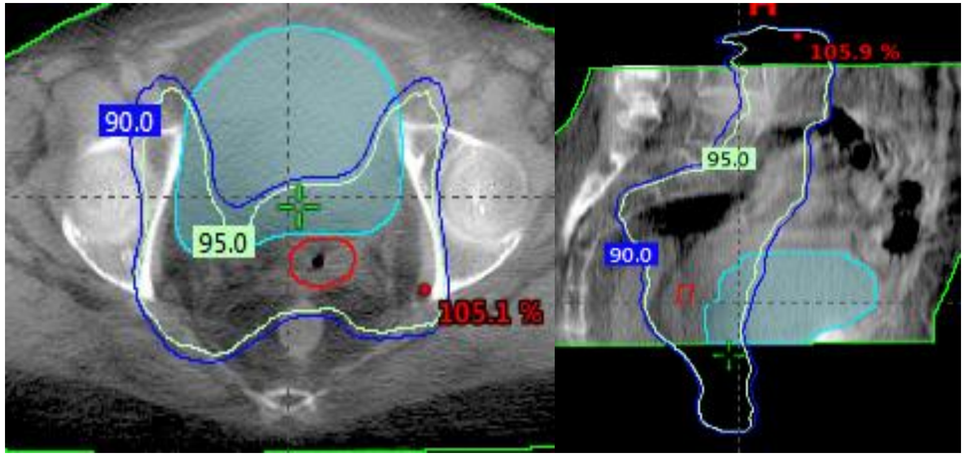




Dose distribution with representative PreTx_GTV on planning CT image

MID EBRT (26GY) GTV VOLUME

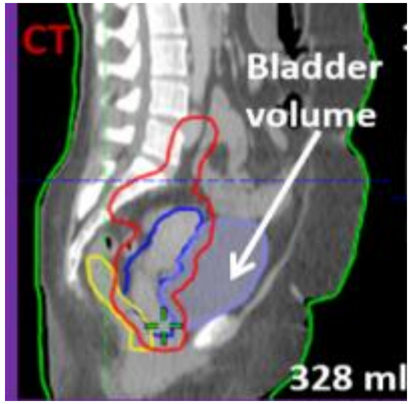




Dose distribution with representative Mid RT_GTV on planning CBCT D-13 image

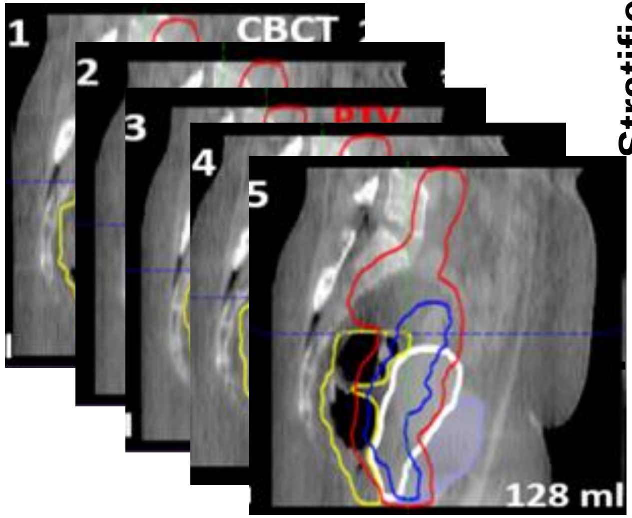
With Adaptive plan

Movers Vs Non-movers



Planning CT

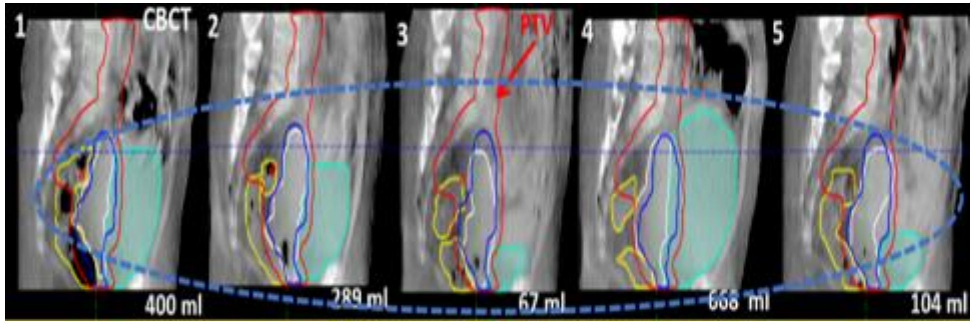
+



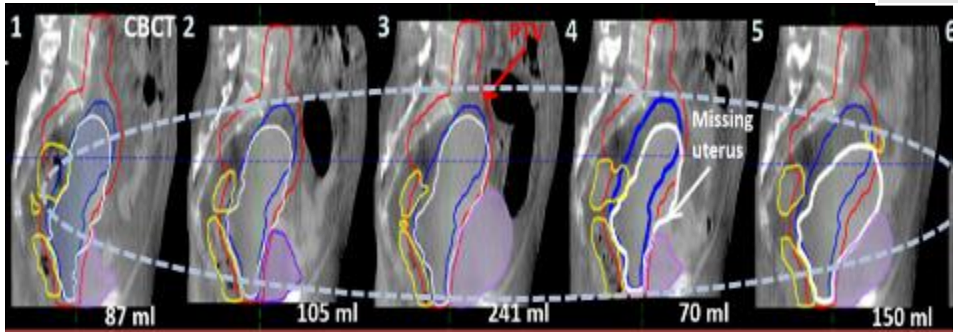
5 Daily CBCTs Week1

Stratified as Movers/Non-movers

Non-movers



Movers



Grouping	N (%)	Stage distribution	
Mover	18 (25%)	Stage II -11 Stage III - 7	Adaptive plan done in 9 patients
Non mover	49 (75%)	Stage II -23 Stage III - 26	

SUMMARY

- Patient Position & Immobilization:

  - Supine with Knee rest and laser alignment

  - Whole body vacloks / body fix: as an alternative

- Organ filing:

  - Rectum: Preferably empty through out the planning and Rx

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

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

Dr. D.N. Sharma
Professor,
Department of Radiation Oncology,
All India Institute of Medical Sciences, New Delhi

Outline

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

I will not discuss

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

Patient preparation, Immobilization,

↓

Imaging, Simulation etc.

↓

Target /OAR delineation

↓

DRR, Beam placement, Plan generation, Evaluation

↓

Treatment verification, Treatment delivery

Role of Simulation in RT process

- The simulation belongs to the most important st
  of whole treatment process
- Mimic the radiation th
  diverge

Target coverage & OAR sparing

he beam

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

Simulation Team

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

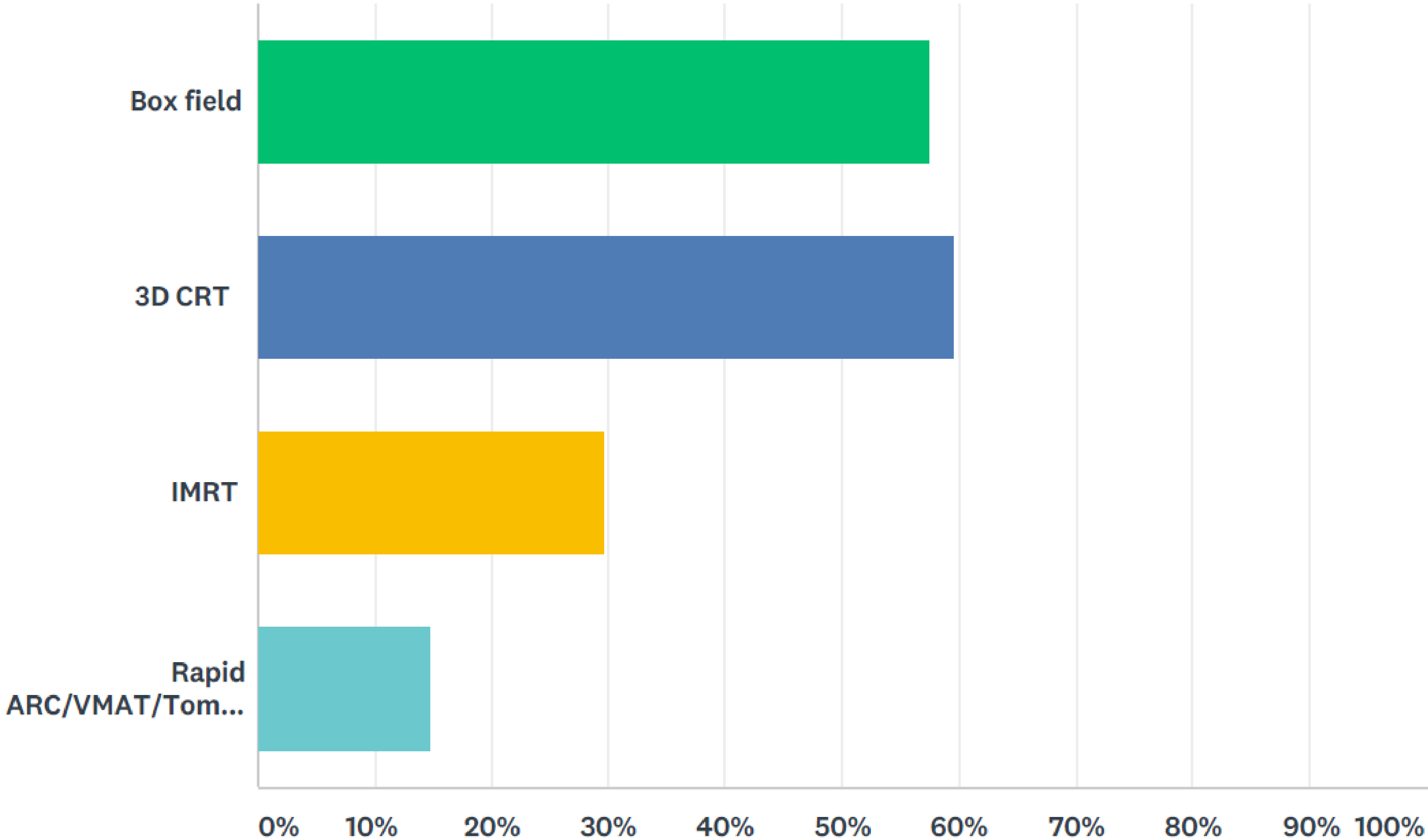
- ***Radiologist***

Conventional Simulator

X-ray/Fluoroscopy

Q10 What external RT techniques are commonly utilized?

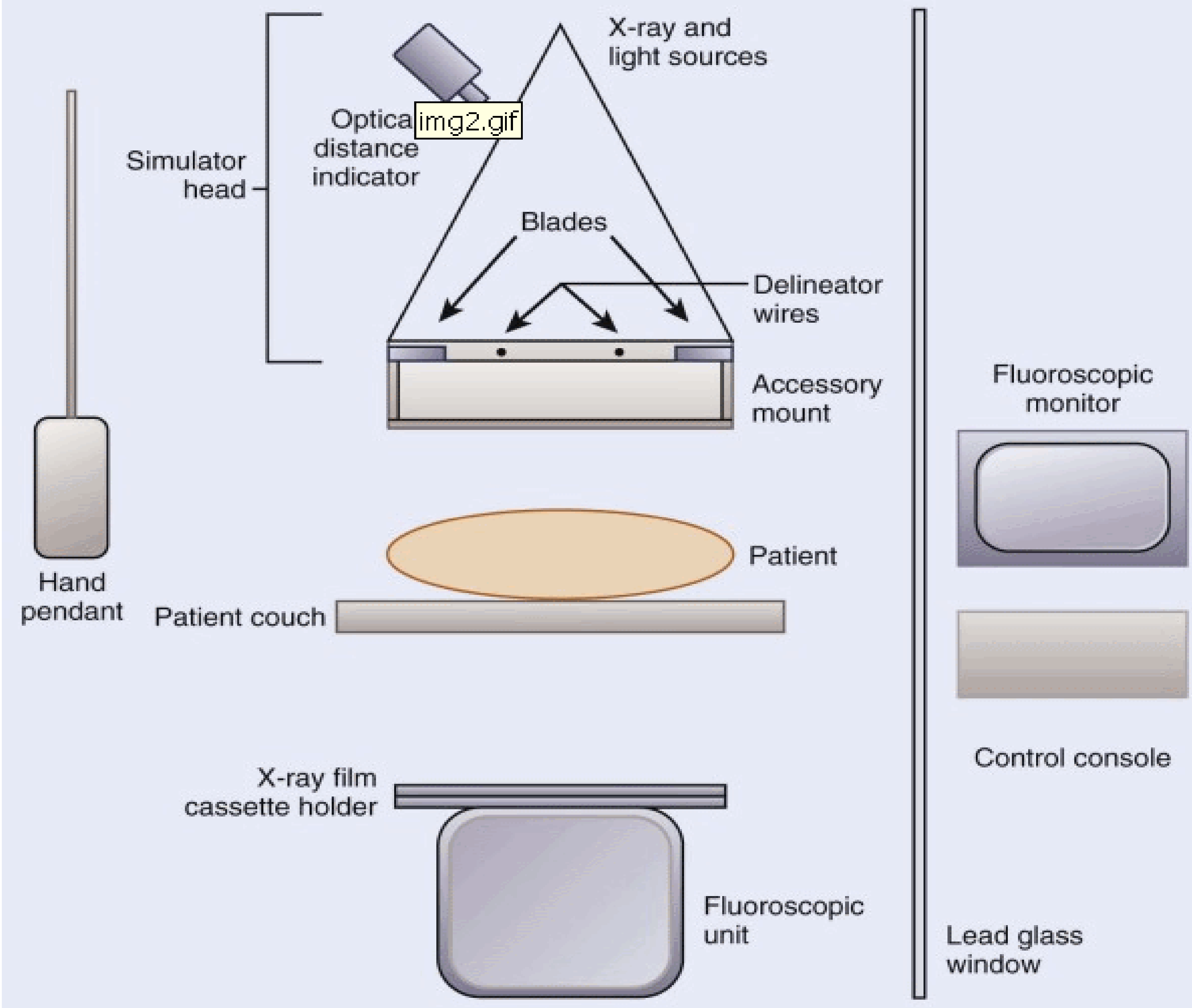
Answered: 47 Skipped: 8



Conventional Fluoroscopic Simulator

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

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

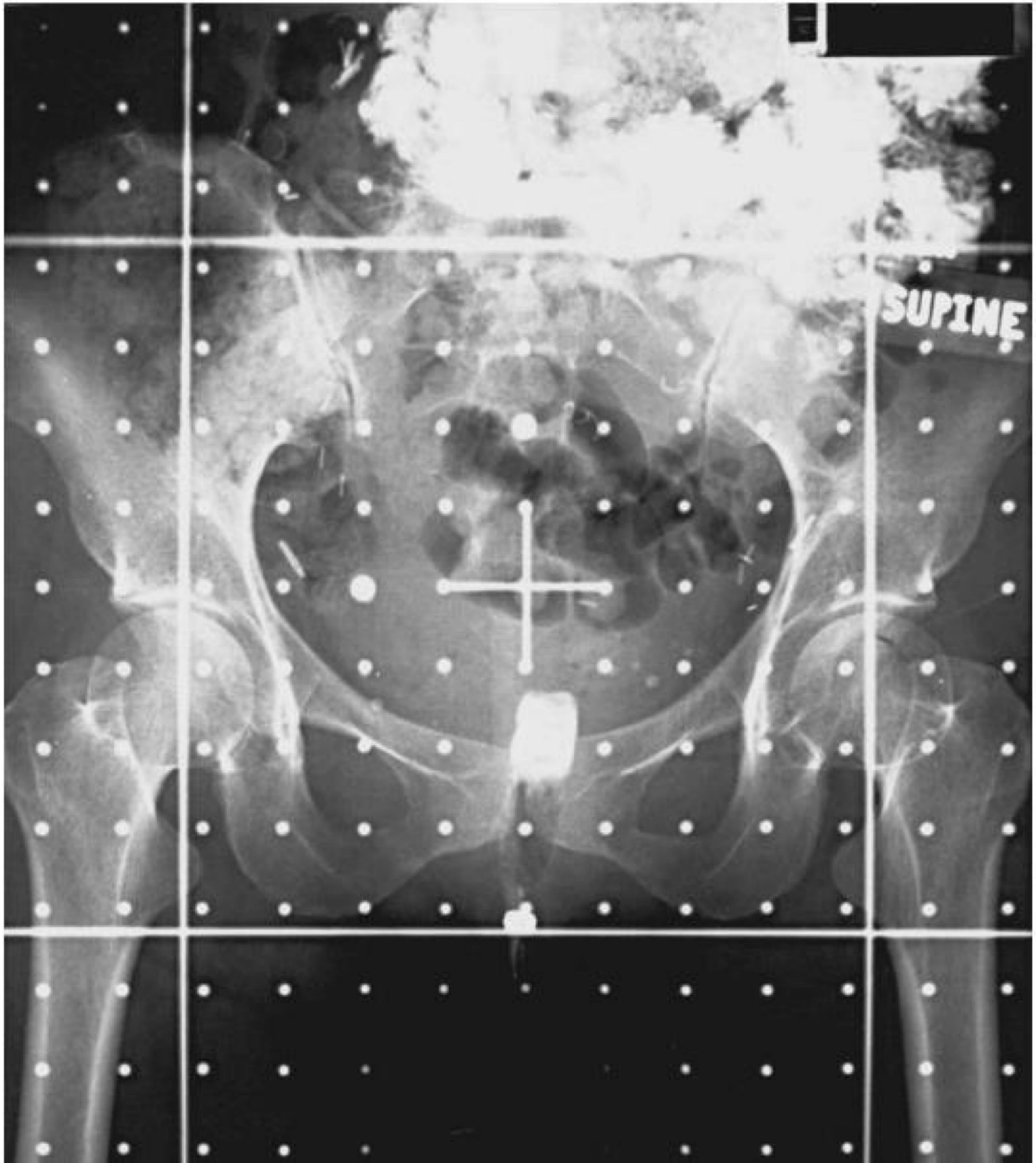

X-ray and light sources
img2.gif
Optical distance indicator
Simulator head
Blades
Delineator wires
Accessory mount
Fluoroscopic monitor
Patient
Hand pendant
Patient couch
Control console
X-ray film cassette holder
Fluoroscopic unit
Lead glass window

Conventional Simulator

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

Procedure

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


SUPINE

Field borders [AP-PA field]

- Superior border- L4-L5 junction (to encompass the common iliac node)

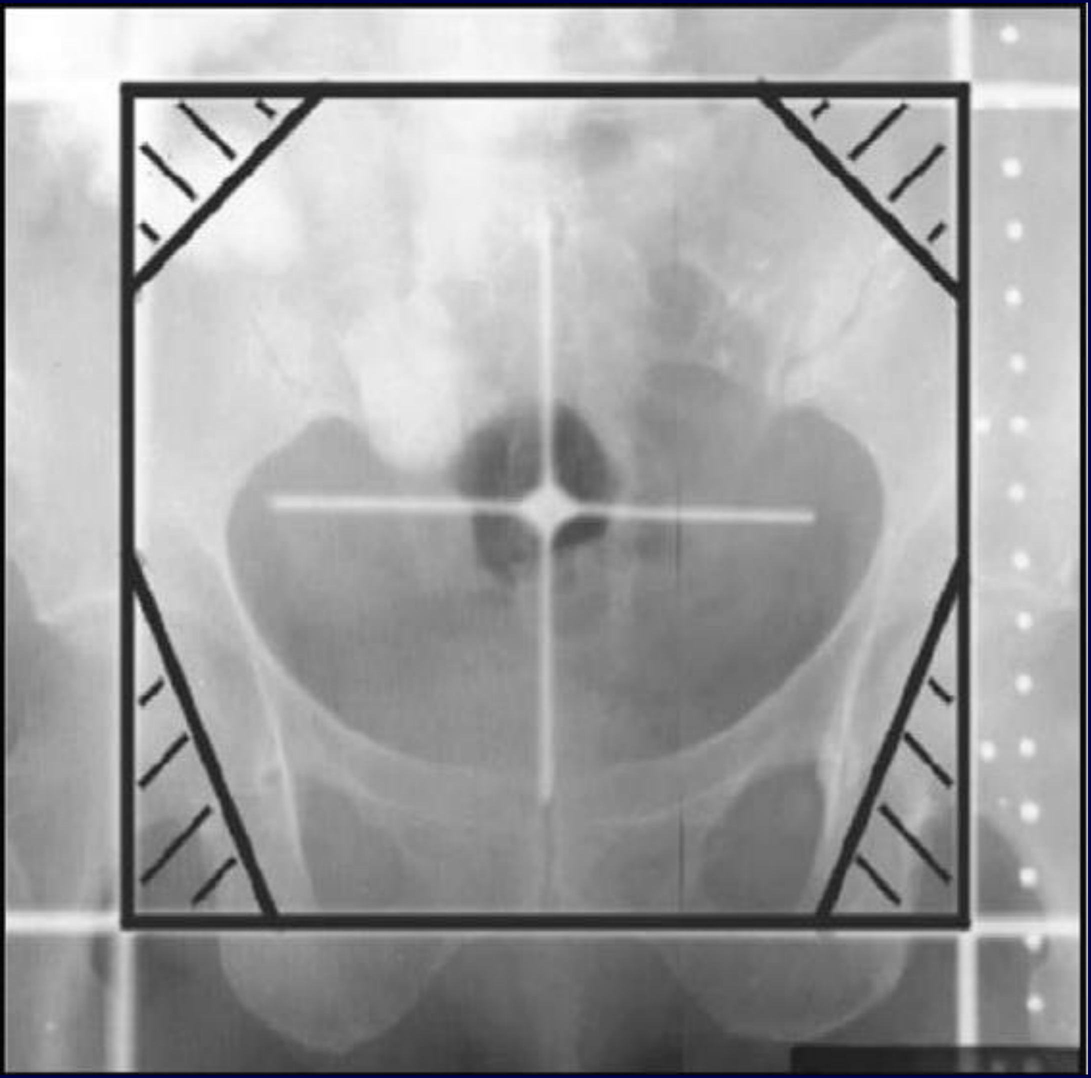
- Lateral border- 1.5 cm from the widest pelvic part of the pelvic brim

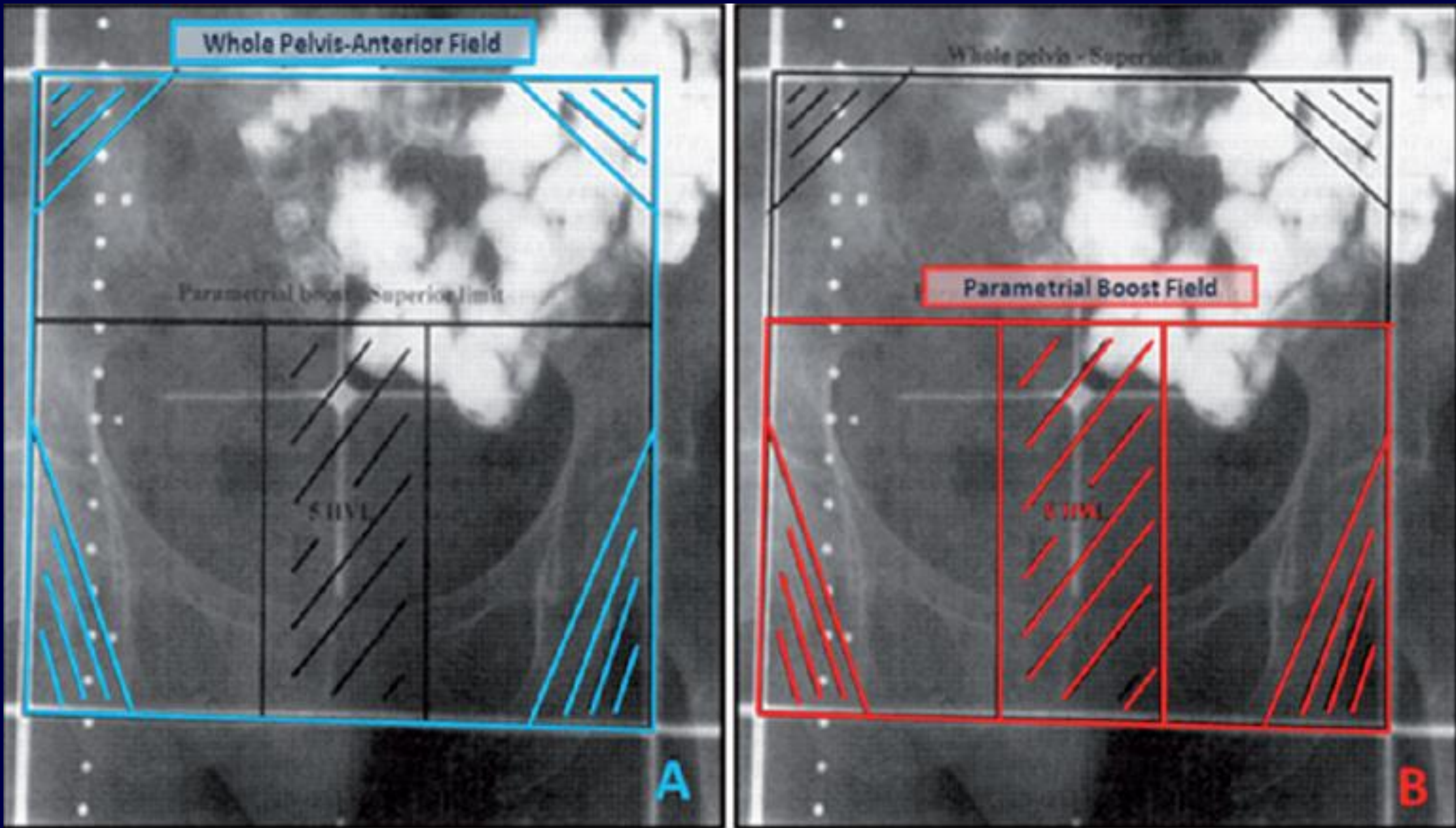
- Inferior-no vaginal wall involved- lower border of the obturator foramen.

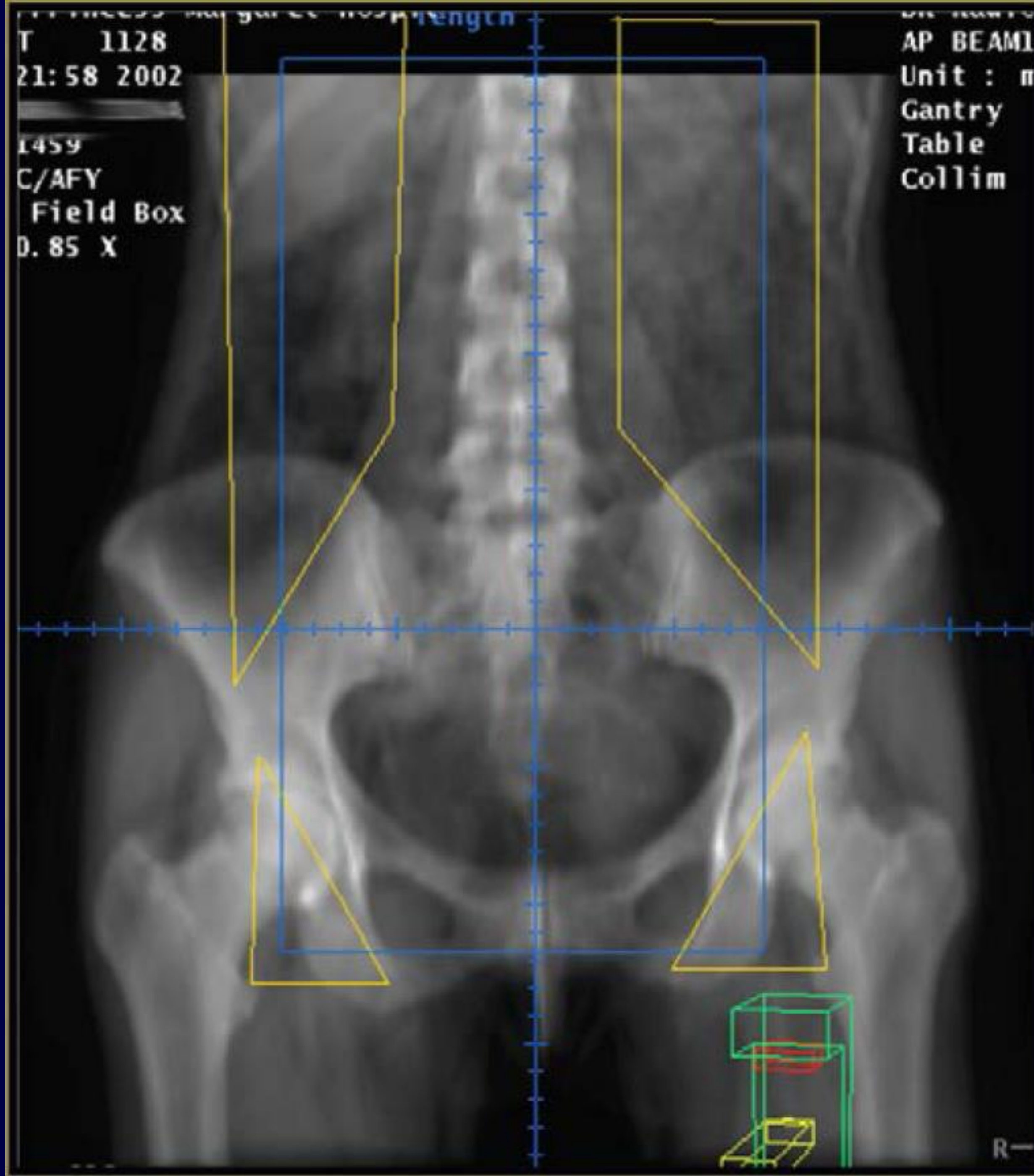
- If they are then – 2cm below the lower most point of disease

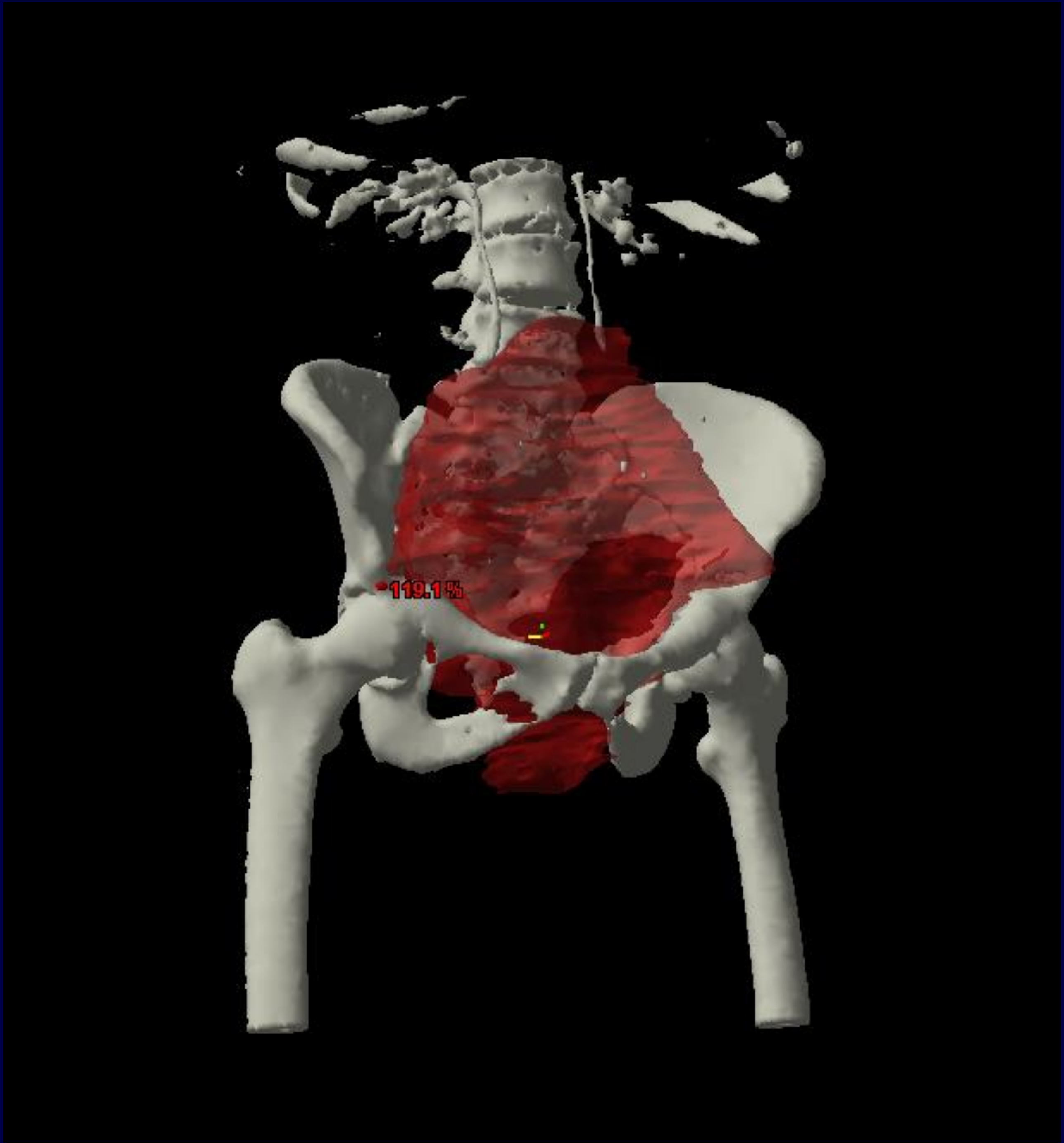
Lateral fields

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

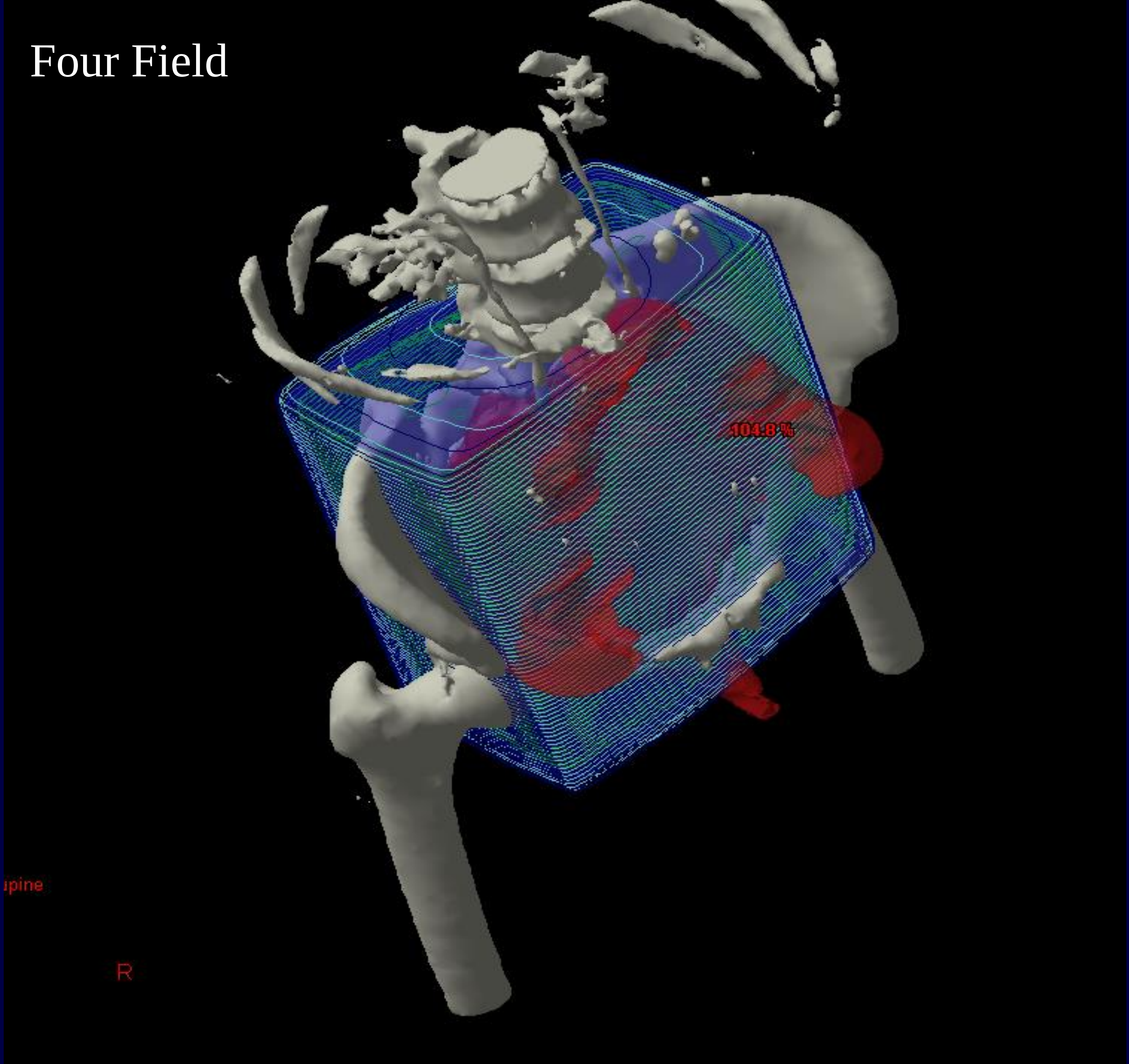


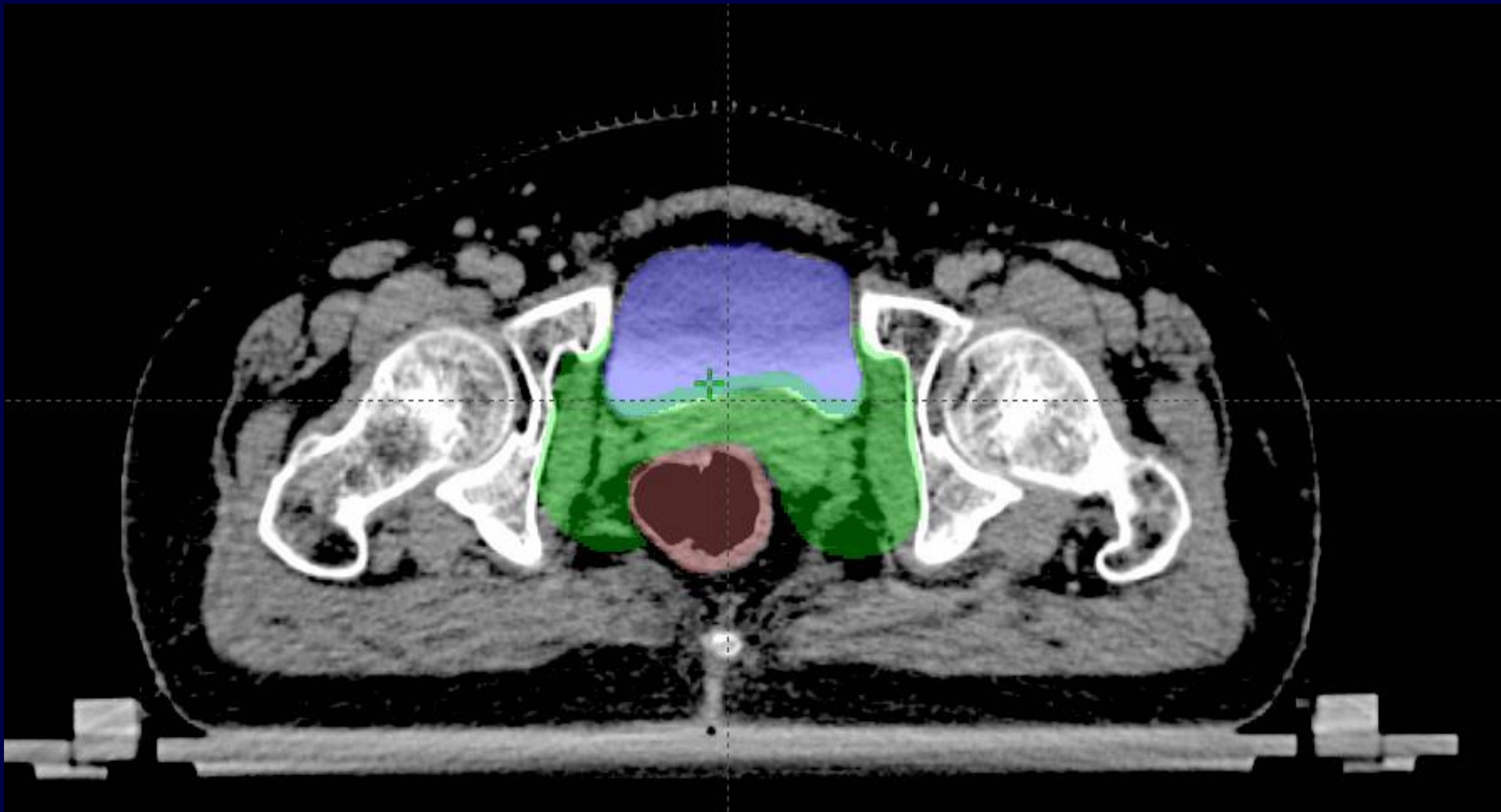


Whole Pelvis-Anterior Field
5 HVL
A
Whole pelvis - Superior limit
Parametrial Boost Field
B

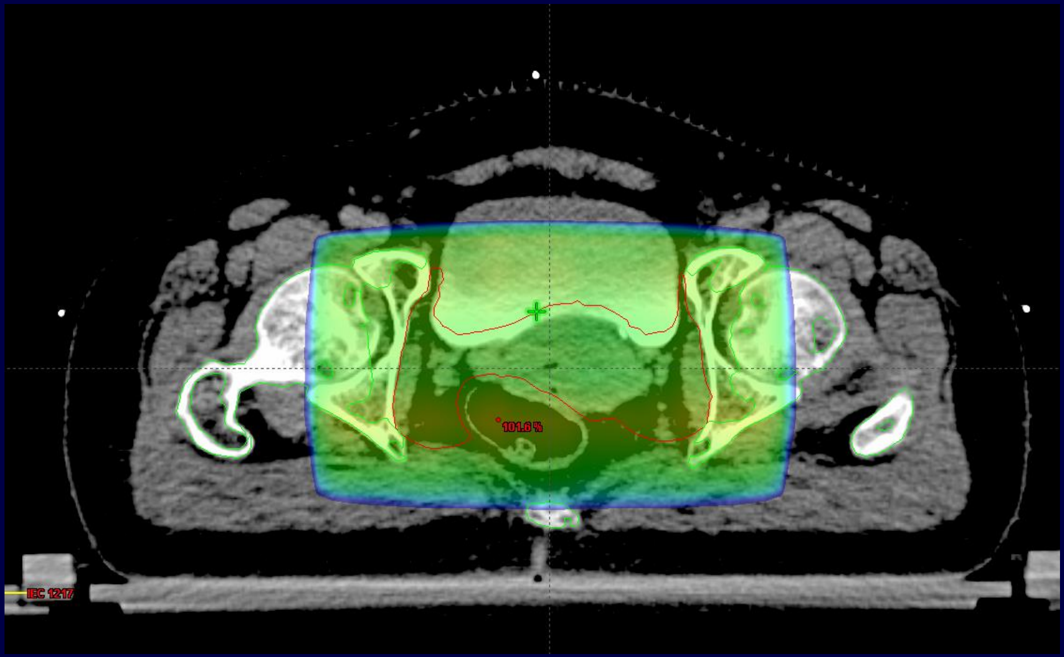

T 1128
21:58 2002
1459
C/AFY
Field Box
D.85 X
AP BEAM1
Unit : m
Gantry
Table
Collim
R

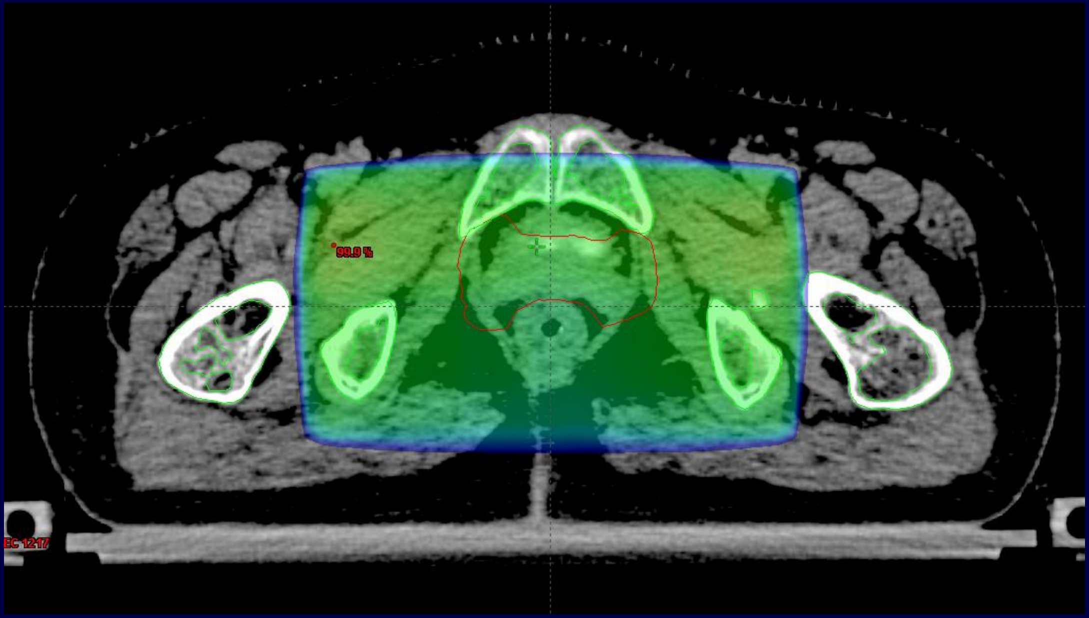

119.1 %

Four Field






101.6 %
IEC 1217


99.9 %
EC 1217

Int J Radiat Oncol Biol Phys. 1999 Apr 1;44(1):53-9.

Anatomic study of the pelvis in carcinoma of the uterine cervix as related to the box technique.

Zunino S[1], Rosato O, Lucino S, Jauregui E, Rossi L, Venencia D.

Author information

Abstract

PURPOSE: To review the radiation therapy "box" technique for cancer of the cervix by means of magnetic resonance imaging (MRI), lymphangiography, and anatomic studies on cadavers.

METHODS AND MATERIALS: From 1993 to 1996, the anatomic borders of the "box" technique used at our Radiation Oncology Department-the superior border of the AP-PA fields at the inferior edge of L4; the inferior border at the inferior edge of the ischium; the lateral borders placed 2.5 cm outside of the bony pelvis rim; the anterior border of the lateral fields over the anterior edge of the pubic symphysis; and the posterior at the S2-S3 interspace-were reviewed in 35 sagittal MRI and 10 lymphangiographies of patients with FIGO IB (6), IIA (6), IIB (19), IIIB (3), and IVA (1). An anatomic revision was conducted on 30 cadavers to identify aortic bifurcation, lymphatic nodes, and uterus flexion.

RESULTS: In 50% of the patients with FIGO IB, the posterior border of the lateral field was inadequate to encompass the planning target volume (PTV), and in 67% with Stage IIA. In IIB, the anterior border was inadequate in 1 patient, and the posterior in 8 (42%). In IIB and IVA patients, the PTV was not encompassed. When correlating the anterior and posterior borders of the lateral field and the treatment volume in the 35 sagittal MRIs, the posterior border of the lateral field was inadequate in 49%, and the anterior border in 9% of the cases. According to the lymphangiography, the portals encompassed the external iliac nodes. Dissected female pelvises revealed that the aortic bifurcation occurred at the level of the inferior L4 edge in 80% of the cadavers. There was no correlation between uterus flexion in MRIs and in cadavers.

CONCLUSION: The design of the lateral fields of the four-field technique for the irradiation of the uterine cervix based on anatomic bone references failed to encompass the planning-target volume in a significant number of patients.

Int J Radiat Oncol Biol Phys. 2006 Jan 1;64(1):205-9. Epub 2005 Sep 29.

Use of CT simulation for treatment of cervical cancer to assess the adequacy of lymph node coverage of conventional pelvic fields based on bony landmarks.

Finlay MH[1], Ackerman I, Tirona RG, Hamilton P, Barbera L, Thomas G.

Author information

Abstract

PURPOSE: To assess the adequacy of nodal coverage of "conventional" pelvic radiation fields for carcinoma of the cervix, with contoured pelvic vessels on simulation computed tomography (CT) as surrogates for lymph node location.

METHODS AND MATERIALS: Pelvic arteries were contoured on non-contrast-enhanced CT simulation images of 43 patients with cervix cancer, FIGO Stages I-III. Vessel contours were hidden, and conventional pelvic fields were outlined: (1) anterior/posterior fields (AP): superior border, L5-S1 interspace; inferior border, obturator foramina; lateral border, 2 centimeters lateral to pelvic brim. (2) Lateral fields (LAT): Anterior border, symphysis pubis; posterior border, S2-S3 interspace. Distances were measured between the following: (1) bifurcation of the common iliac artery and superior border, (2) external iliac artery and lateral border of the AP field, and (3) external iliac artery and anterior border of the LAT field. The distances were considered as "inadequate" if <15 mm, "adequate" if 15-20 mm, and "generous" if >20 mm.

RESULTS: Superiorly, 34 patients (79.1%) had inadequate coverage. On the AP, margins were generous in 19 (44.2%), but inadequate in 9 (20.9%). On the LAT, margins were inadequate in 30 (69.8%) patients. Overall, 41 (95.4%, CI, 84.2%-99.4%) patients had at least 1 inadequate margin, the majority located superiorly. Twenty-four (55.8%; CI, 39.9%-70.9%) patients had at least 1 generous margin, the majority located laterally on the AP field.

CONCLUSION: Conventional pelvic fields based on bony landmarks do not provide optimal lymph node coverage in a substantial proportion of patients and may include excess normal tissue in some. CT simulation with vessel contouring as a surrogate for lymph node localization provides more precise and individualized field delineation.

CT Simulation

CT simulation

- CT Imaging is used for simulation
- Provides good imaging quality of Target and OAR
- Available in most RT departments
- Cost effective
- Compatibility with TPS

Issues

- Exposure
- Imaging quality compromise in certain sites

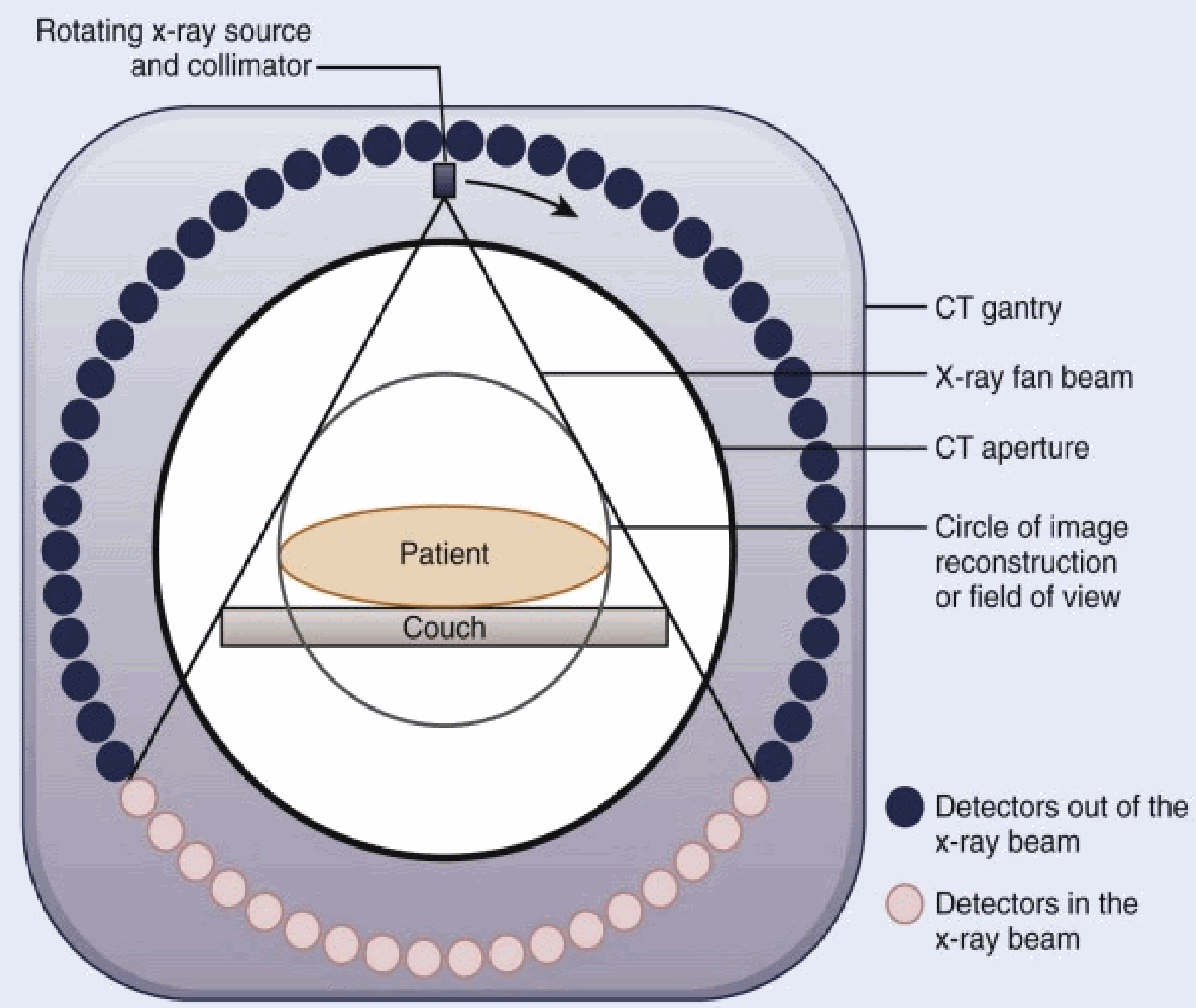
CT simulation

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

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

CT Simulator Components

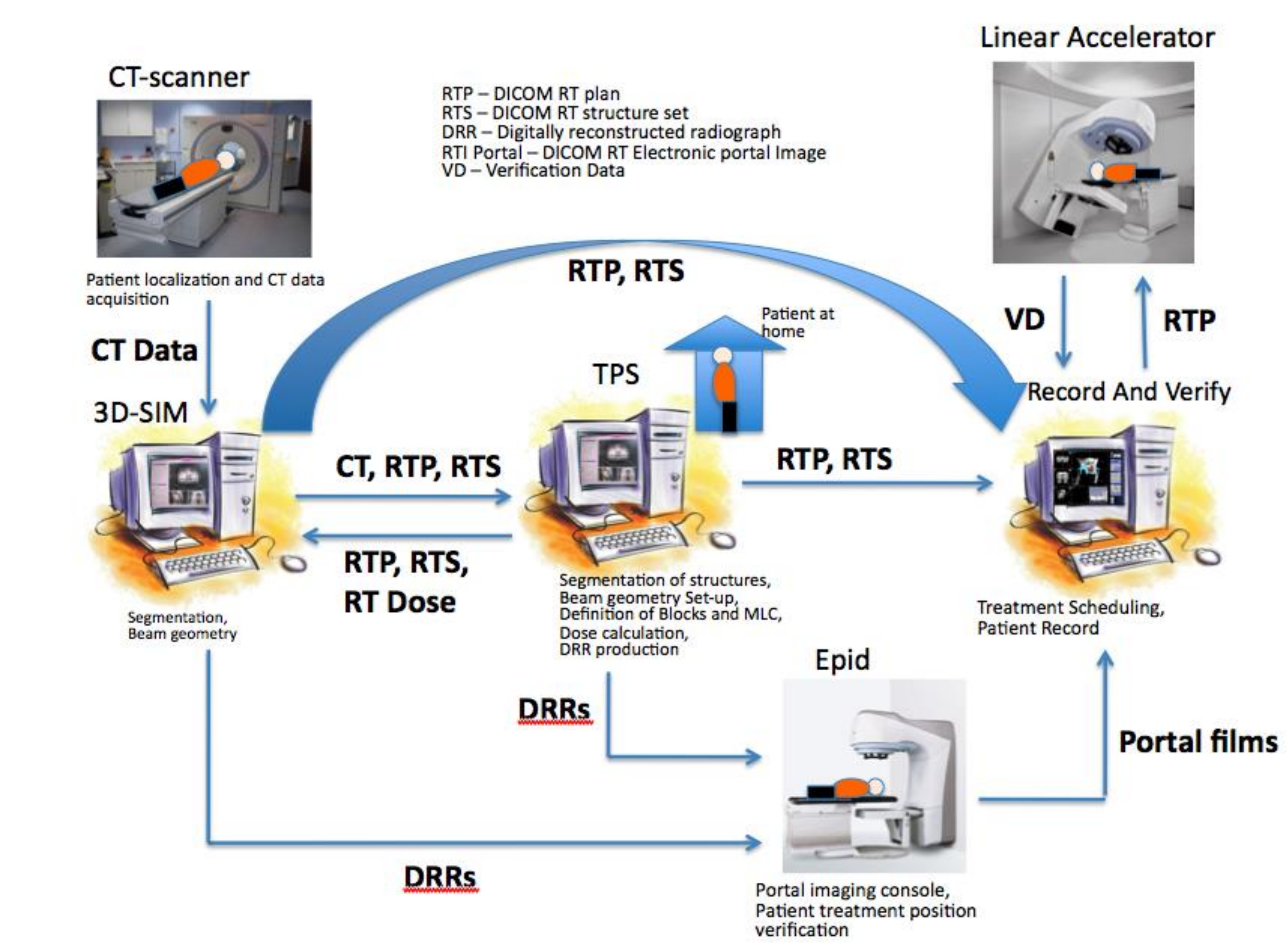
- X-ray tube
- Large bore CT-scanner with opening of up to 85cm
- Detectors systems
- Collimators and attenuator
- Patients couch
- Laser
- Computer and work station
- Control console


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


LightSpeed
28 1:24PM

Features of Multislice CT scanner

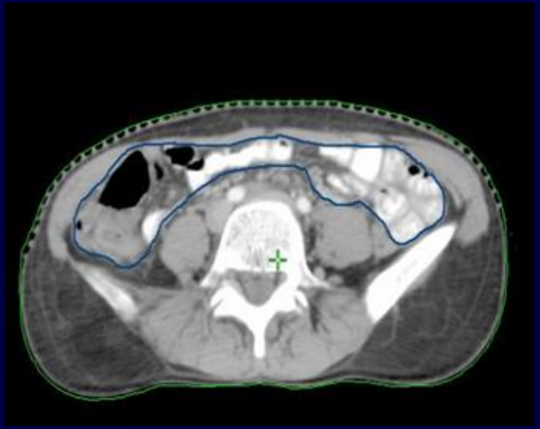
- Faster scan times
- Lower tube heat loading
- Longer volume covered per rotation
- Improved temporal resolution - faster scan times
- Improved spatial resolution – thinner slices
- Decreased image noise – more mA available



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

CT Simulation

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



CT Simulation

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

Virtual Simulation

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

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

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

- Thus it also called as Virtual simulation

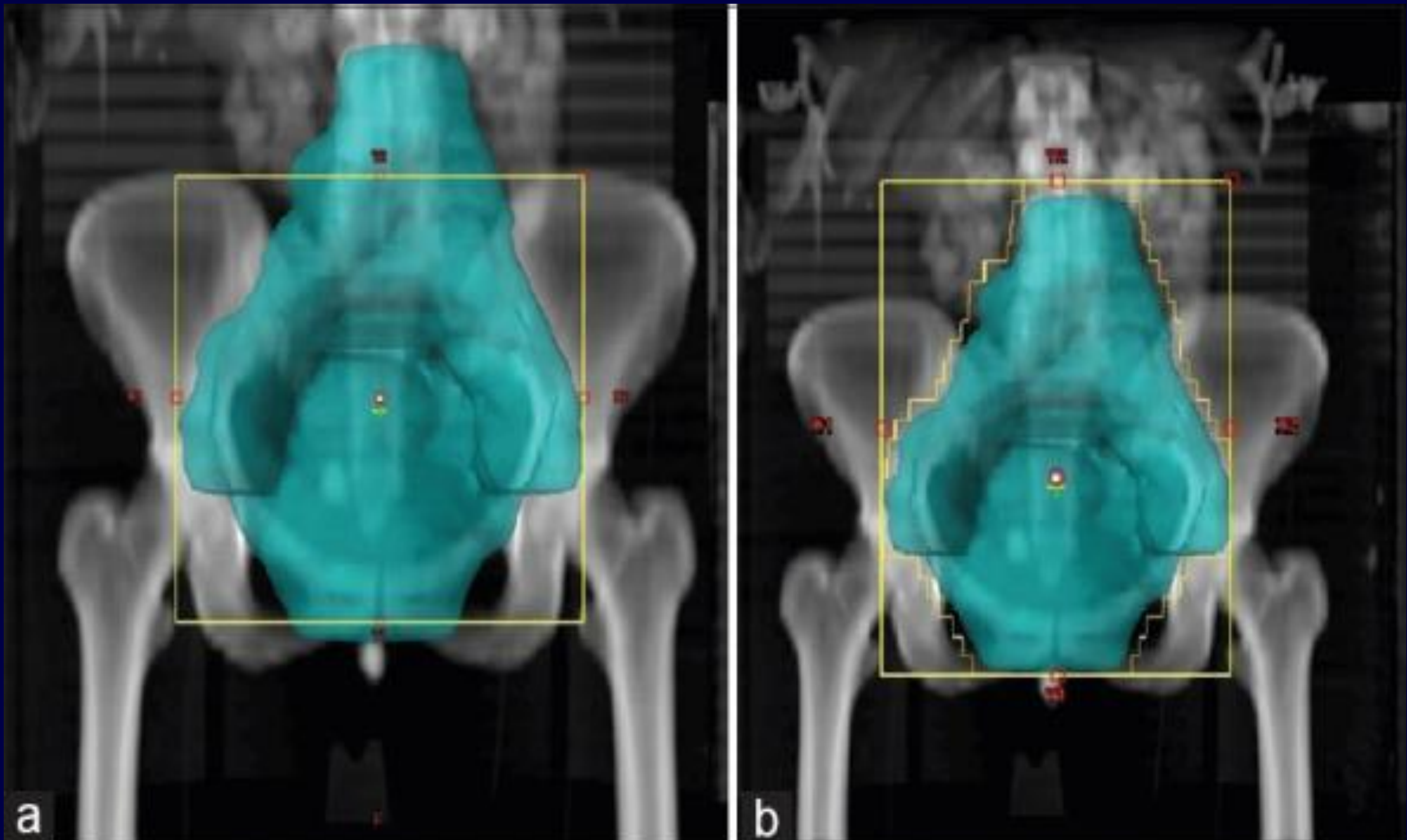
George W. Sherouse, PhD, DABR, FAAPM, Univ North Carolina

Virtual Simulation: Workflow

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

Advantages of Virtual-Simulation

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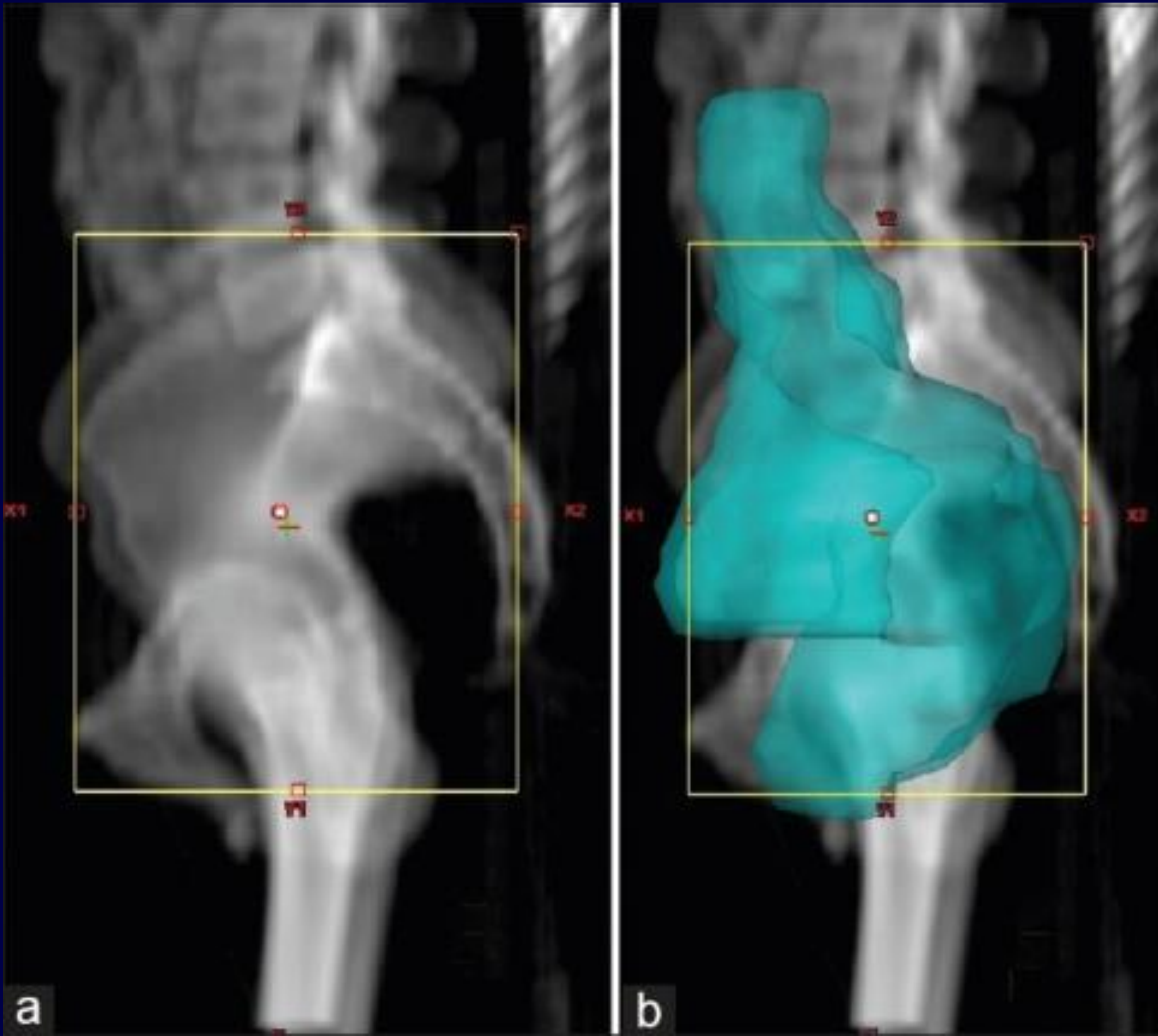
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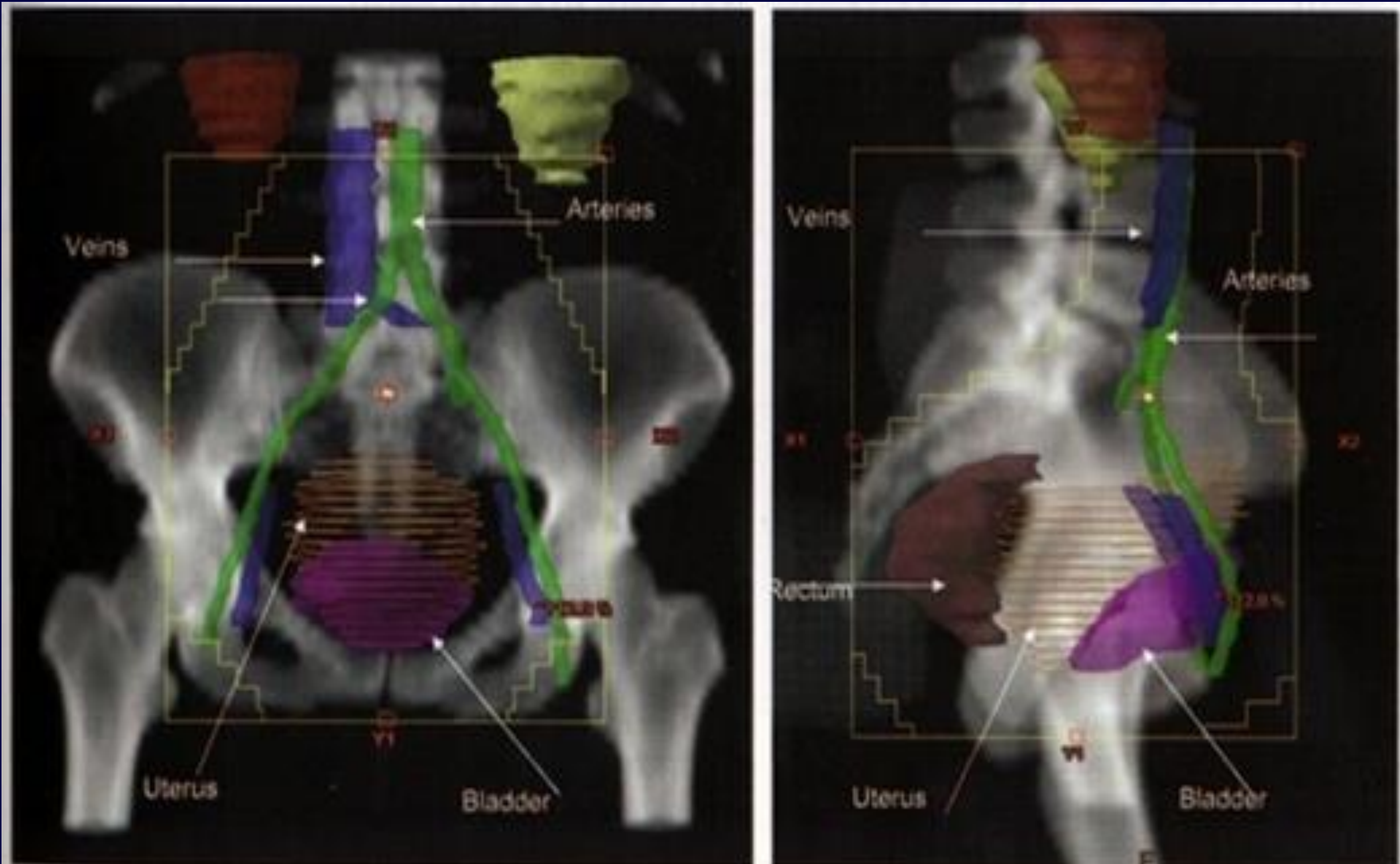
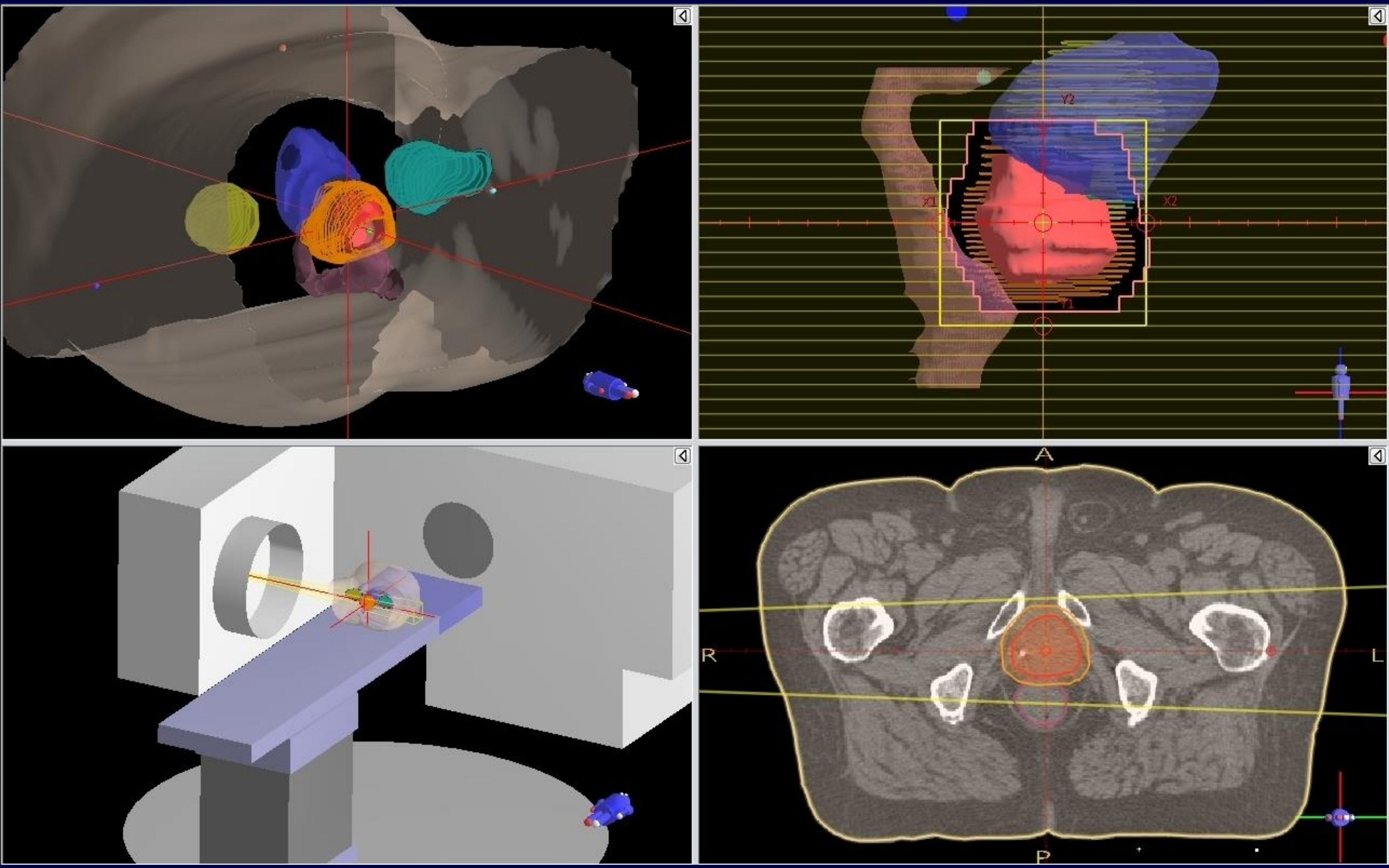


DDR – Anterior beam

DDR – Right Lateral beam

BEV and REV: Virtual Simulation



To Summarize ....

- Simulation is a crucial step in the RT planning
- X-ray/Flouroscopic simulation is still useful
- CT simulation is most practical

  3D imaging

  Virtual simulation
- CT simulator should be preferred modality in the current era

Thank you

CTV delineation
For External Beam RadioTherapy (EBRT)

Ina Jürgenliemk-Schulz
University Medical Centre Utrecht, The Netherlands
Primoz Petric
National Center for Cancer Care and Research, Doha, Qatar

Modified and Presented by
Richard Pötter,
Medical University of Vienna

2nd AROI ESTRO Gyn teaching course
3D Radiotherapy with a Special Emphasis on Implementation of MRI/CT Based Brachytherapy In Cervical Cancer

Lucknow, India, March 2018

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

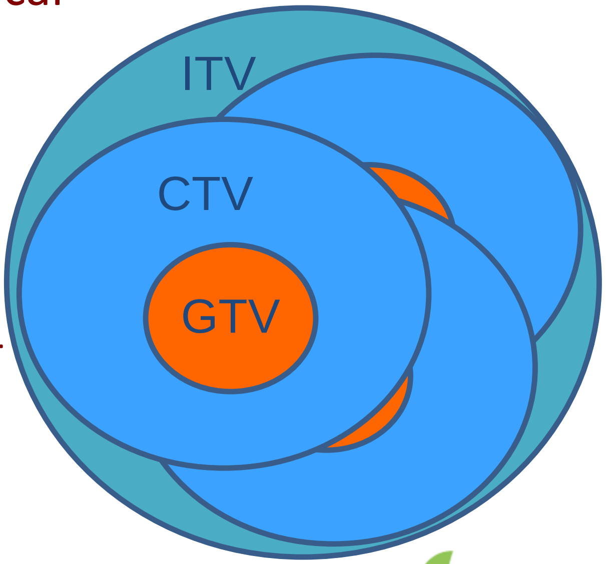
GTV = Gross Tumor Volume

- Macroscopic tumor, visible clinically and with imaging

ICRU reports 50-83

CTV = Clinical Target Volume

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



ITV = Internal target volume

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

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

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

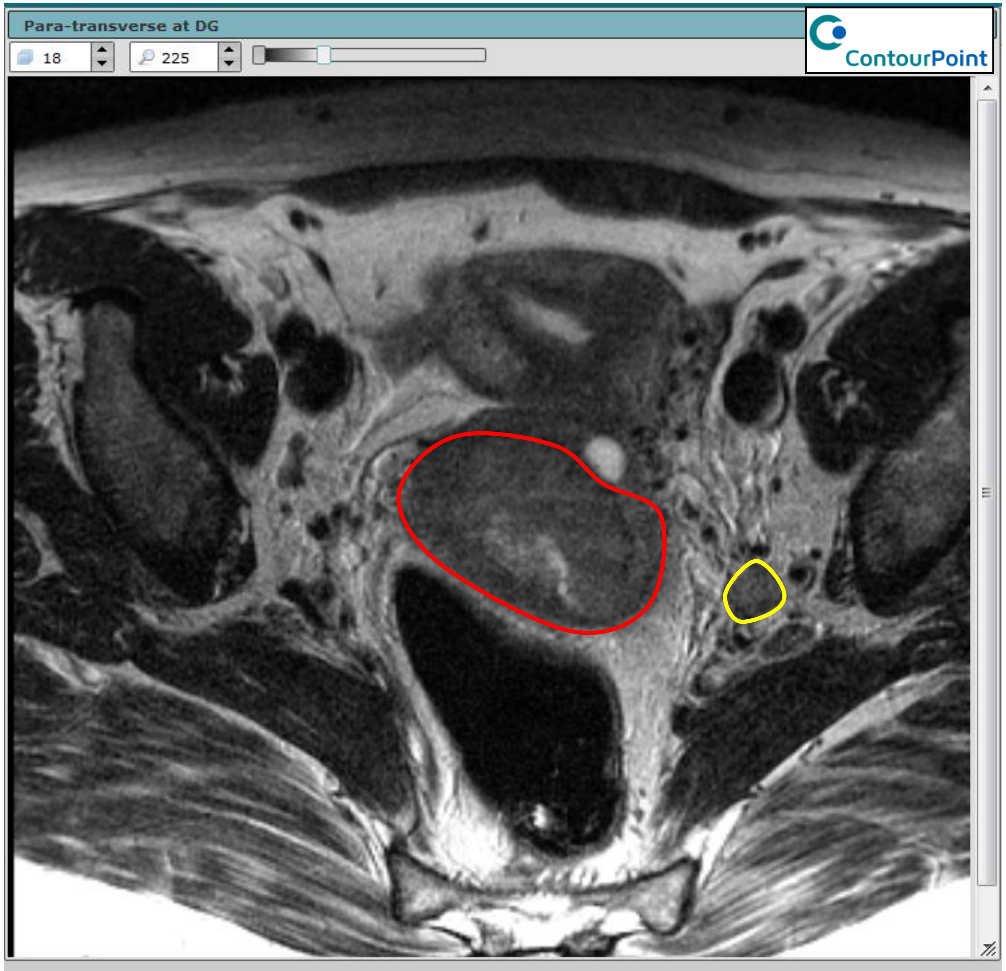
A. GTV +Cervix+Uterus +Parametria+upper vagina
B. GTV + cervix only
C. GTV, Cervix + Parametria only
D. GTV + whole Uterus only
E. GTV + cervix + Upper Vagina only
F. Adjacent organs
G. Ovaries

GTV-T *(GTV initial)*

GTV is in principal composed of:

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

High signal intensity on T2 weighted MRI



GTV

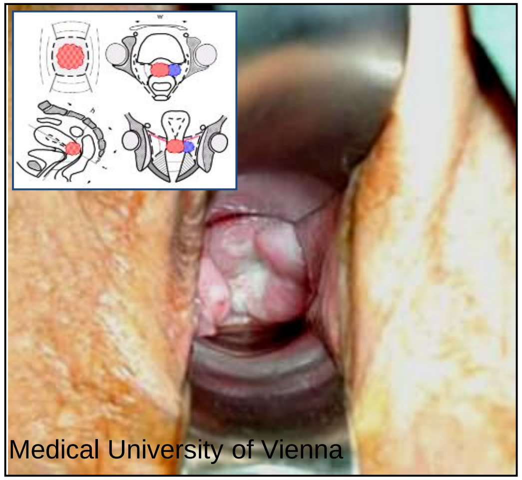
Consists of *Primary* and *Nodal* GTV *(GTV-T initial and GTV-N initial)*

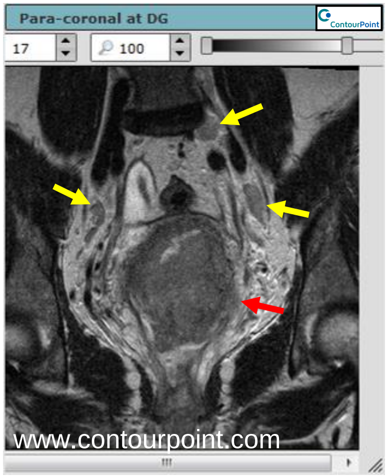
Investigation modality needs to be reported

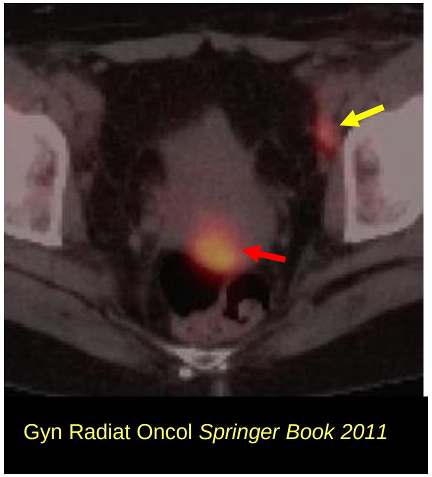
Clinical Examination

Imaging (MRI, CT, PET CT, US)

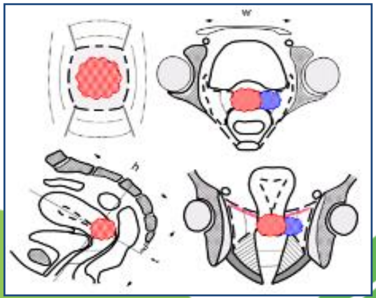
Invasive







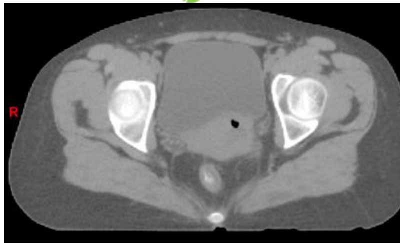
GTV contouring: combine information from different modalities



In case of GTV-T and CT only available,

clinical examination

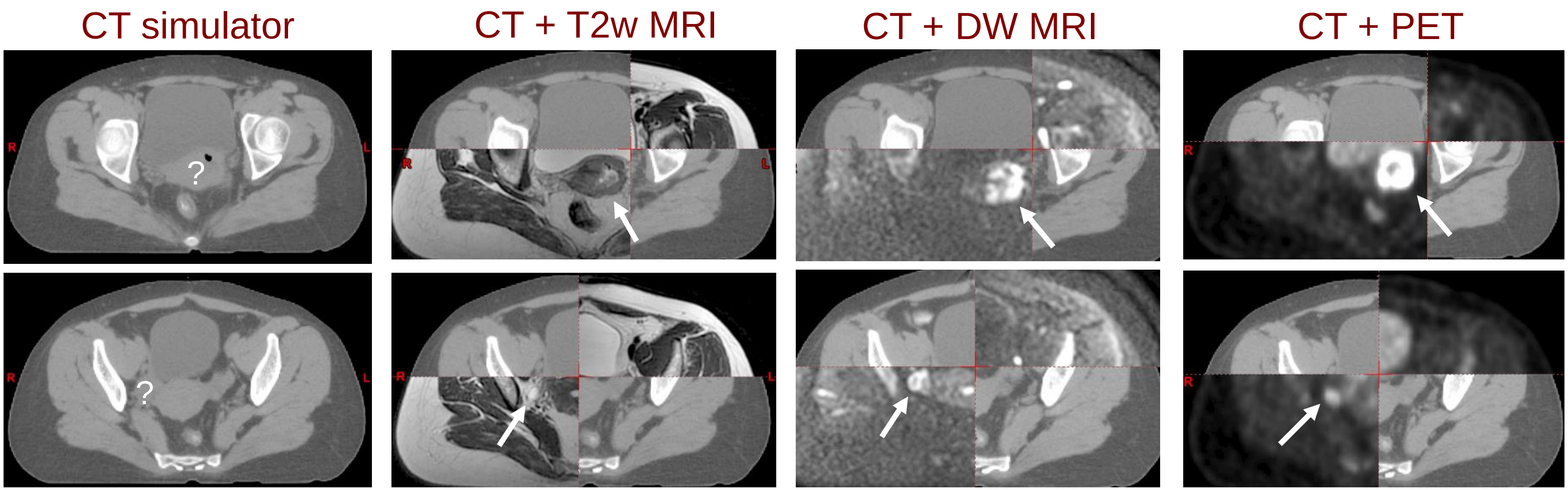
is essential plus full documentation



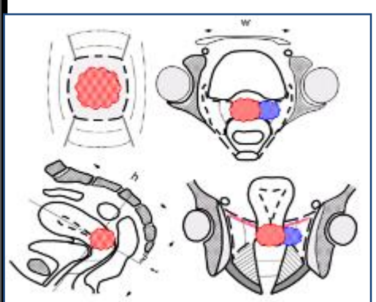
Initial GTV-T contouring (composite GTV)

Co-registration of different imaging modalities?

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



Example; NCCCR, Doha, Qatar



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

Clinical judgement remains essential in the era of imaging epidemics!

CTV contouring (Tumor and Nodes related)

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

Initial CTV-T:

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

GTV and Remaining unaffected cervix: *HR-CTV-T $_{initial}$*

All of the above: *LR-CTV-T $_{initial}$*

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

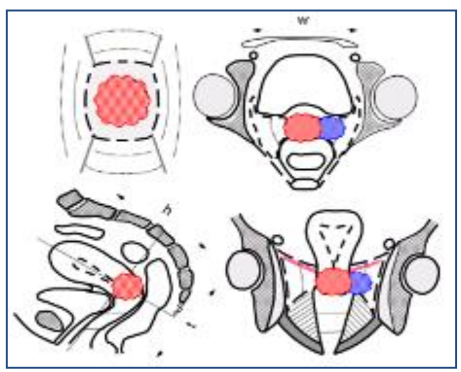
- Lymph node regions at risk (vessel orientated)
- Affected lymph-nodes: CTV-N

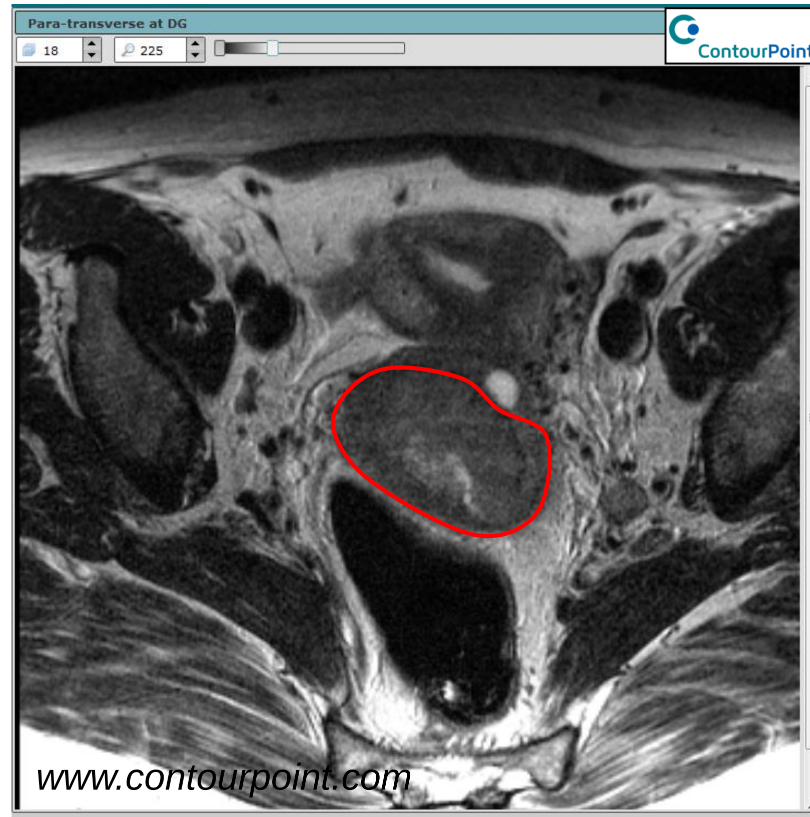
Initial CTV-T

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

Initial CTV-T

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

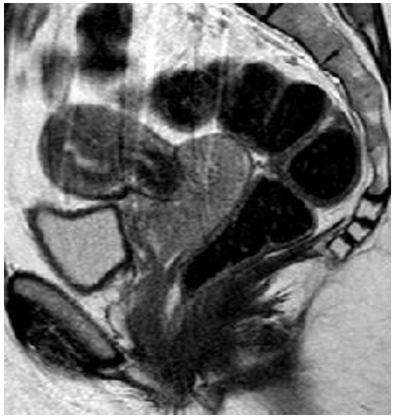


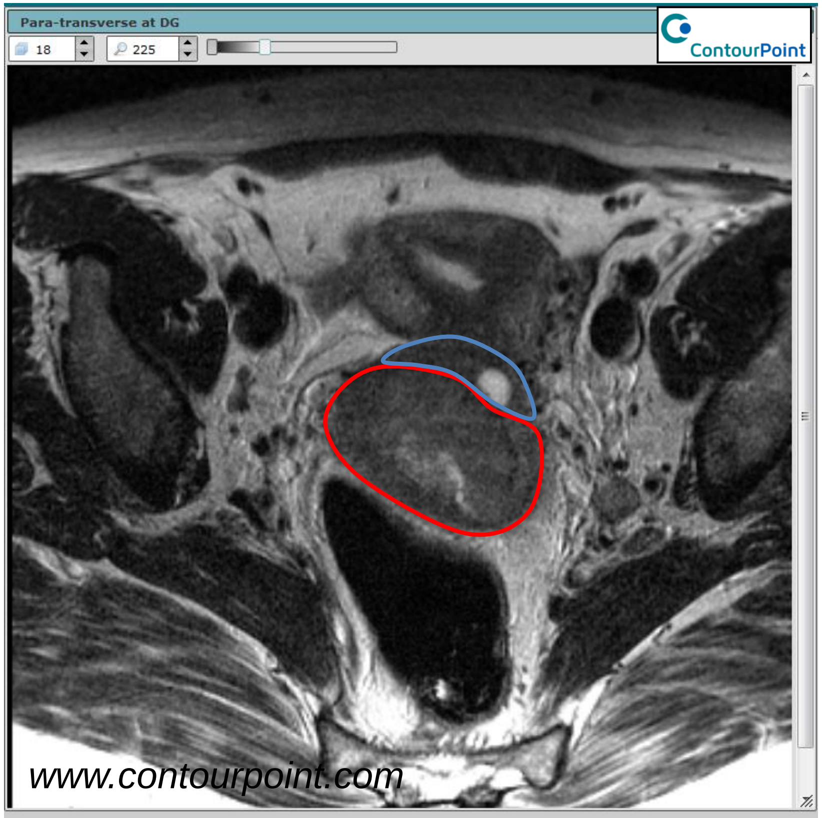


Initial CTV-T: HR CTV-T$_{initial}$

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

HR-CTV-T initial

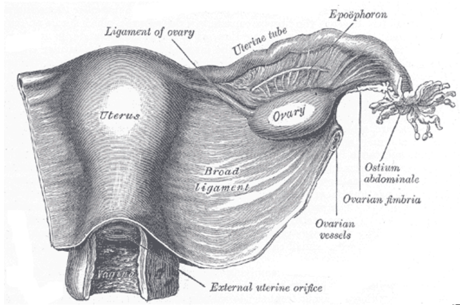


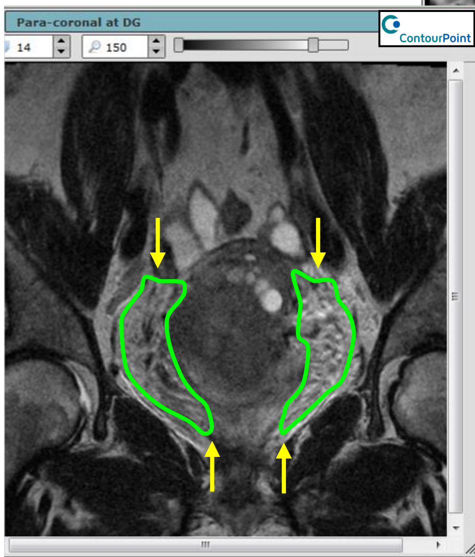


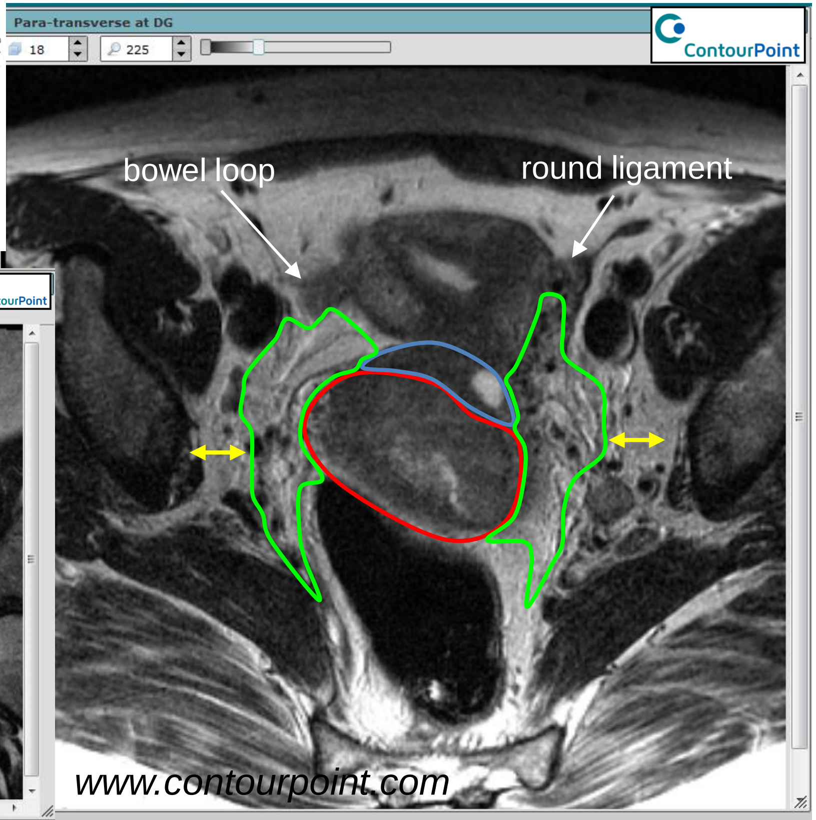
Initial CTV-T: LR CTV-T$_{initial}$

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

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

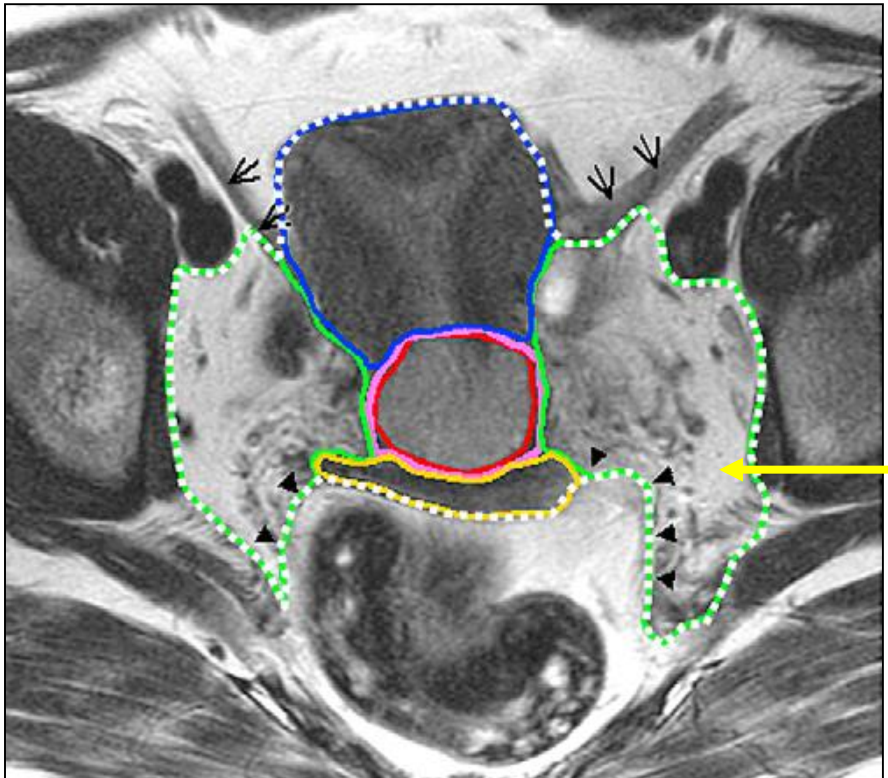


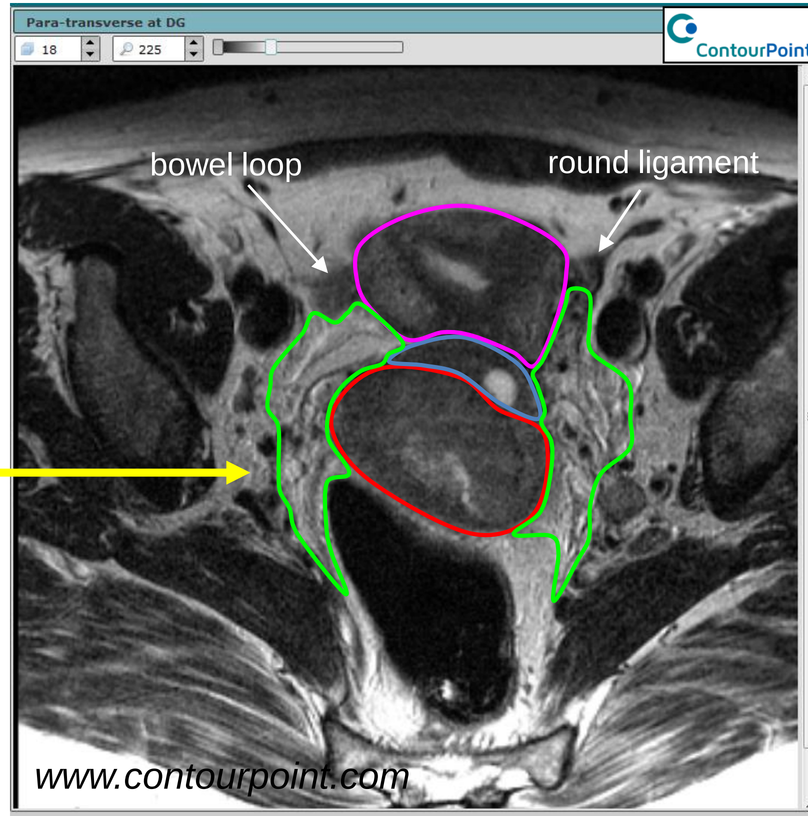




Anatomical boundaries	
Anteriorly	*Posterior wall of bladder/bowel loops or posterior border of external iliac vessel*
Posteriorly	*Uterosacral ligaments and mesorectal fascia*
Laterally	*Medial border of internal obturator muscle/ pelvic sidewall*
Superiorly	*Top of fallopian tube/ broad ligament*
Inferiorly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

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

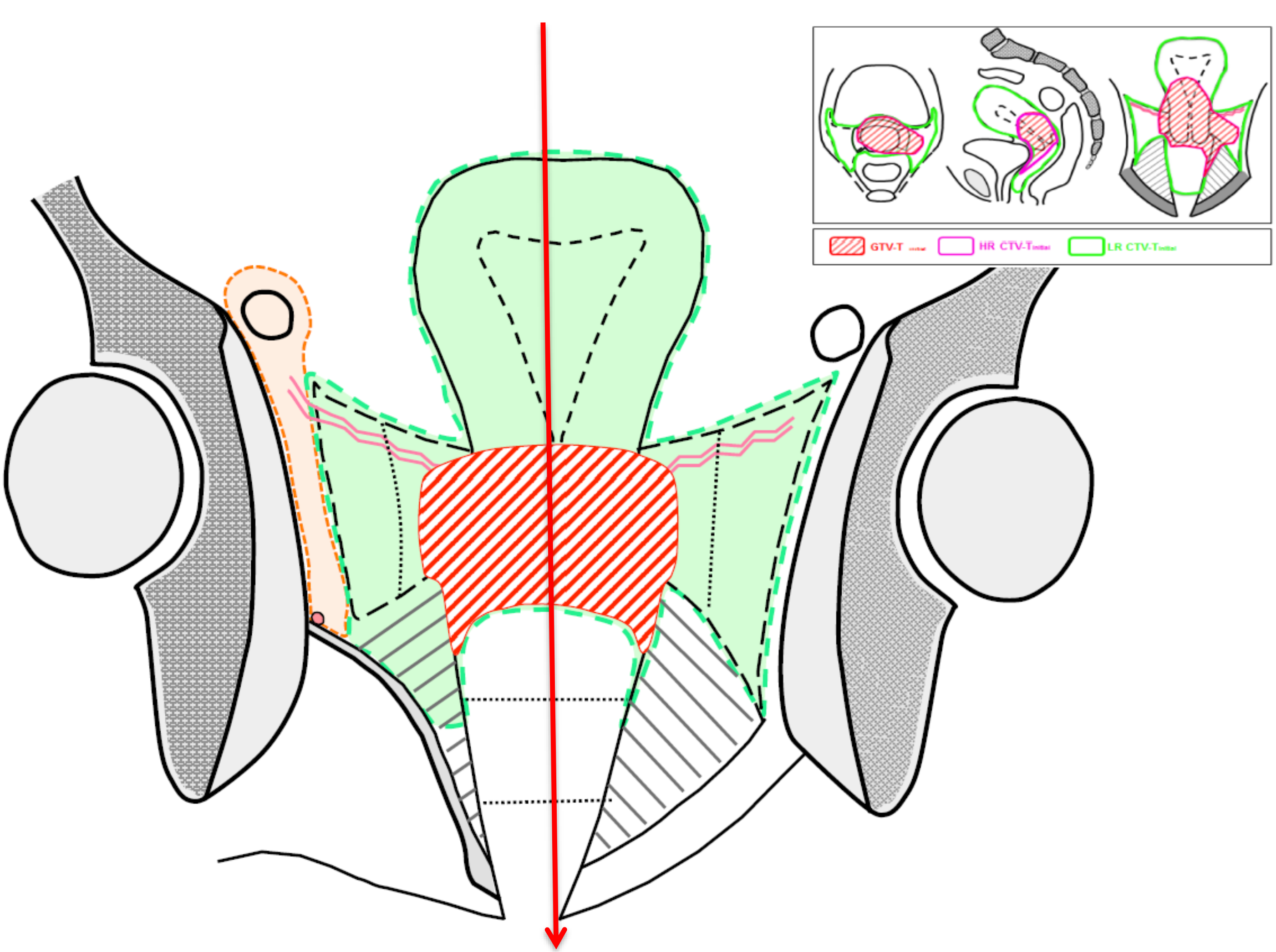




From original publication: Lim K, et al. IJROBP 2010:

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

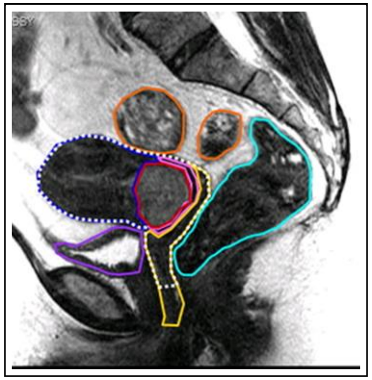
Future LR-CTV-$T_{initial}$ and CTV-T-E

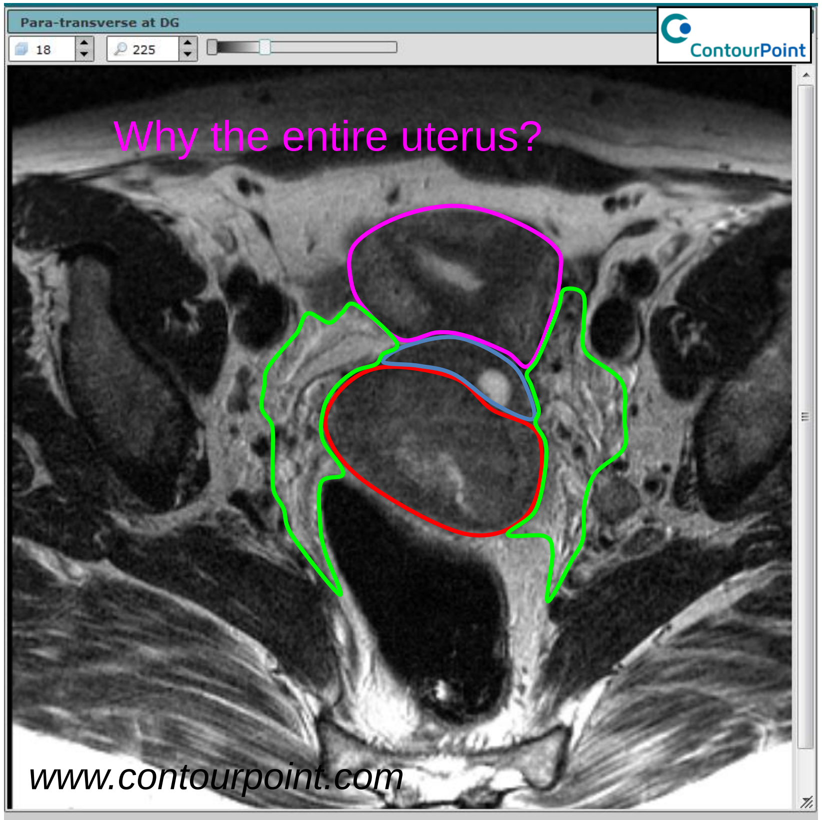


Courtesy Remi Nout

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

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





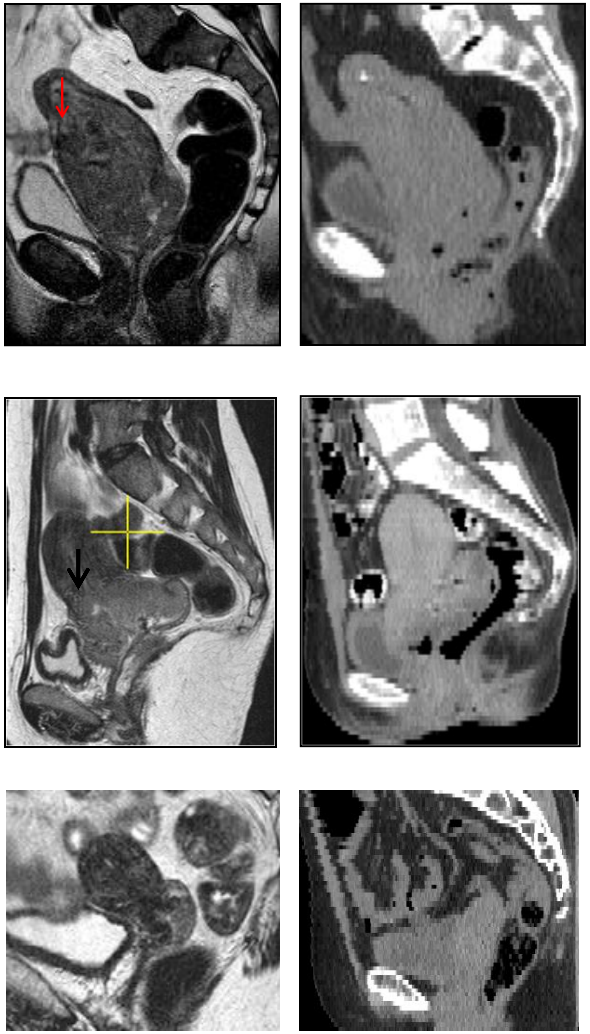
Lim K, et al. IJROBP 2010

Why the entire uterus?

Rationale

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

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

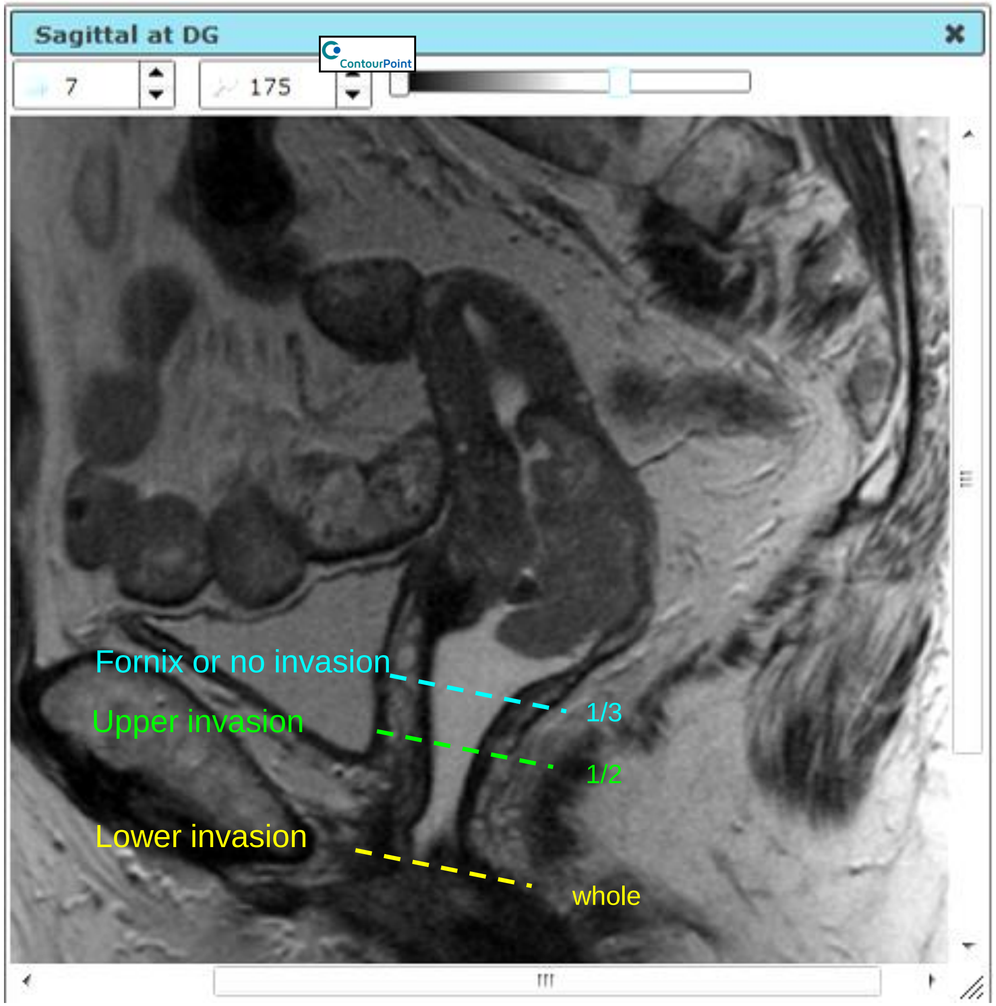


Lim K, et al. IJROBP 2010
[a]Plante M. Gynecol Oncol 2008
[b]Bali A, et al. Gynecol Oncol 2008
[c]Diaz JP, et al. Gynecol Oncol 2008
[d]Hertel H, et al. Gynecol Oncol 2006
[e]Nishio H, et al. Gynecol Oncol 2009

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

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

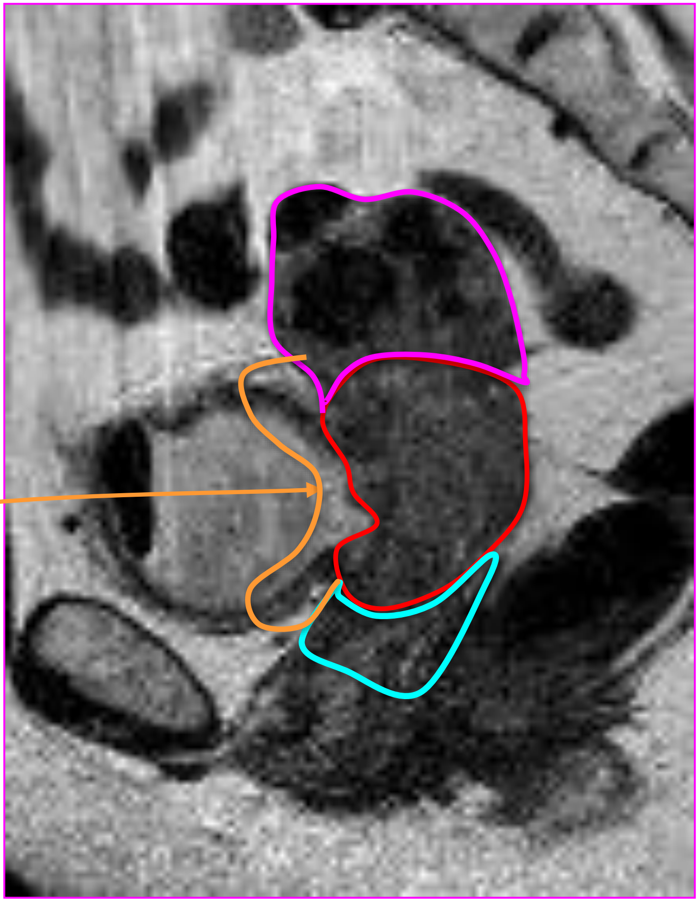
- GTV
- Cervix
- Parametria
- Uterus
- Varying Vaginal length
- Involved organs (FIGO IVA)



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

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

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



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

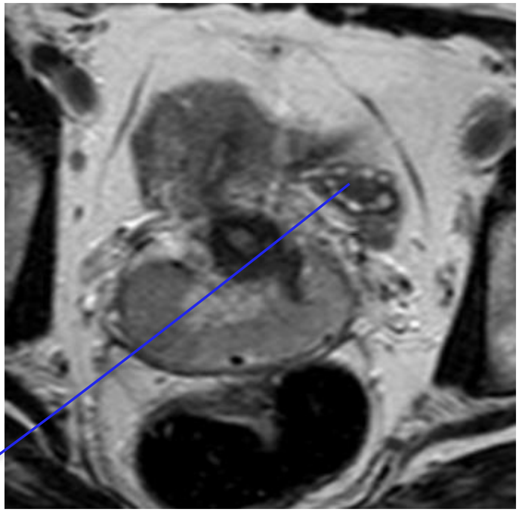
Overall risk of ovarian metastases is small, increased risk reported for:

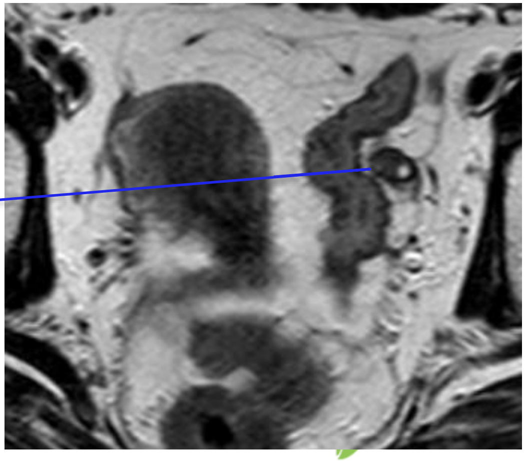
- adeno/adenosquamous histology, even micro-invasive
- high grade and LVSI
- extension into the uterine corpus
- ovaries can be highly mobile !

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

LR-CTV-T *initial*

- Ovaries ?

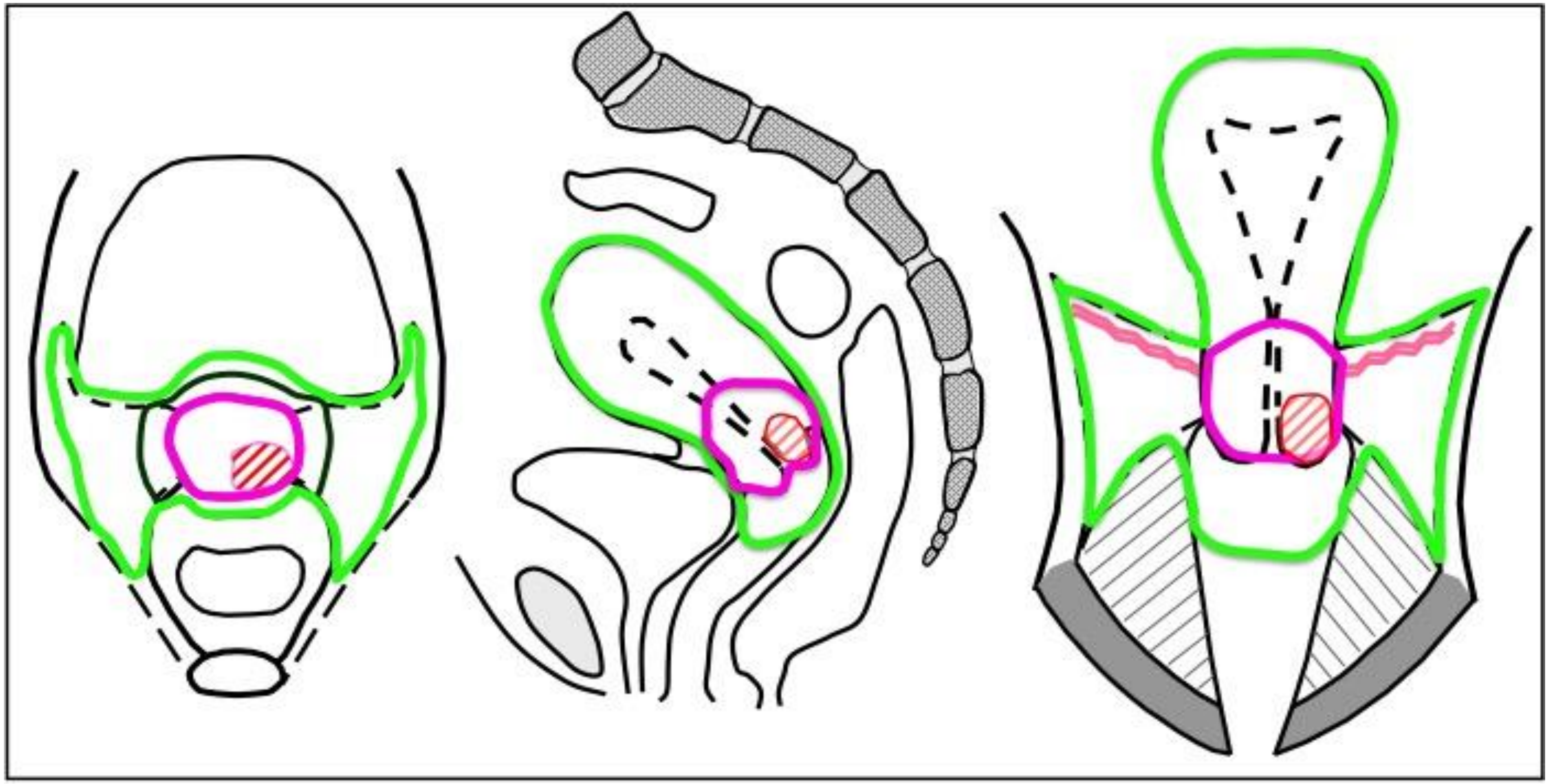




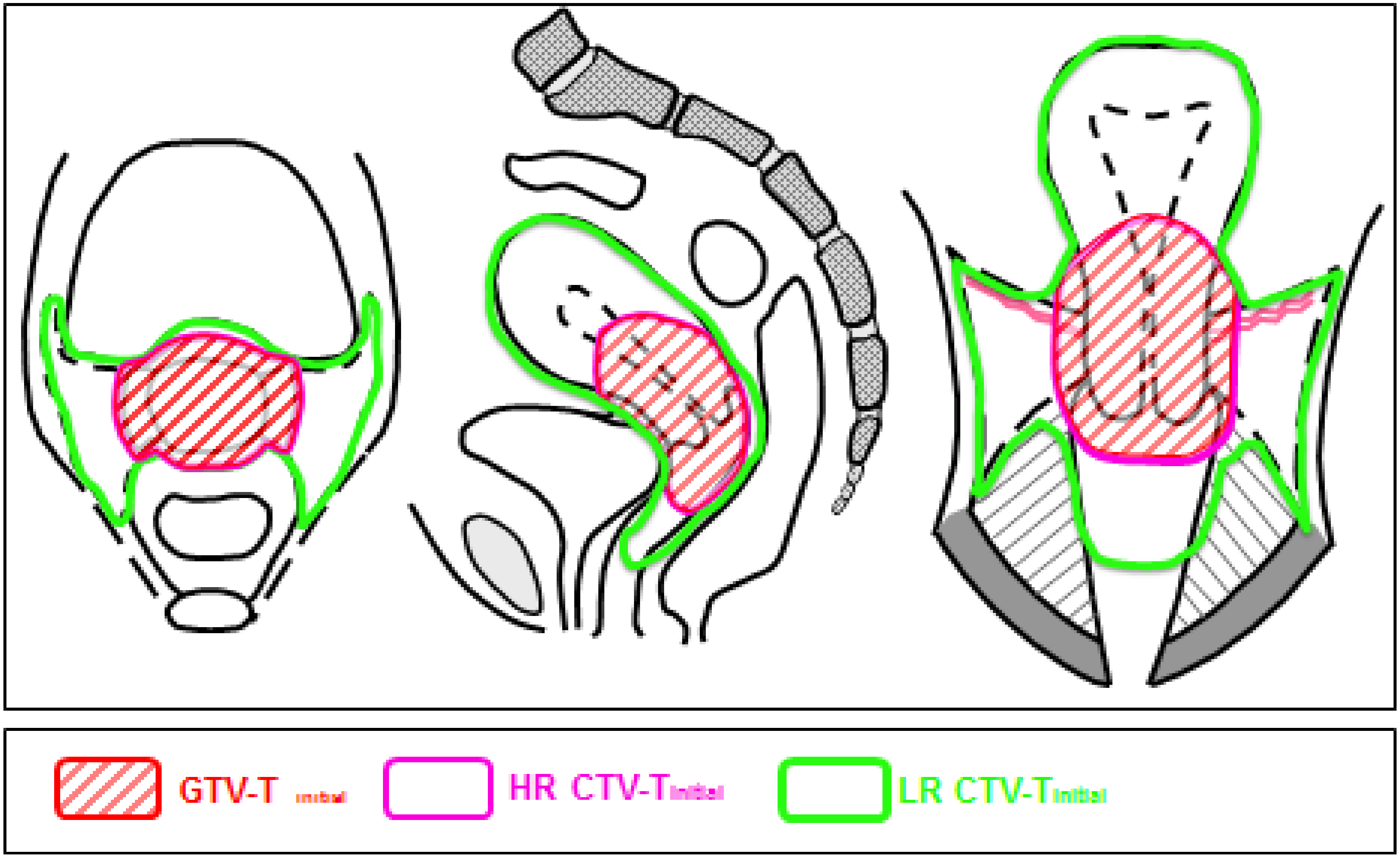
The overall CTV of the primary tumor for EBRT always includes ?

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

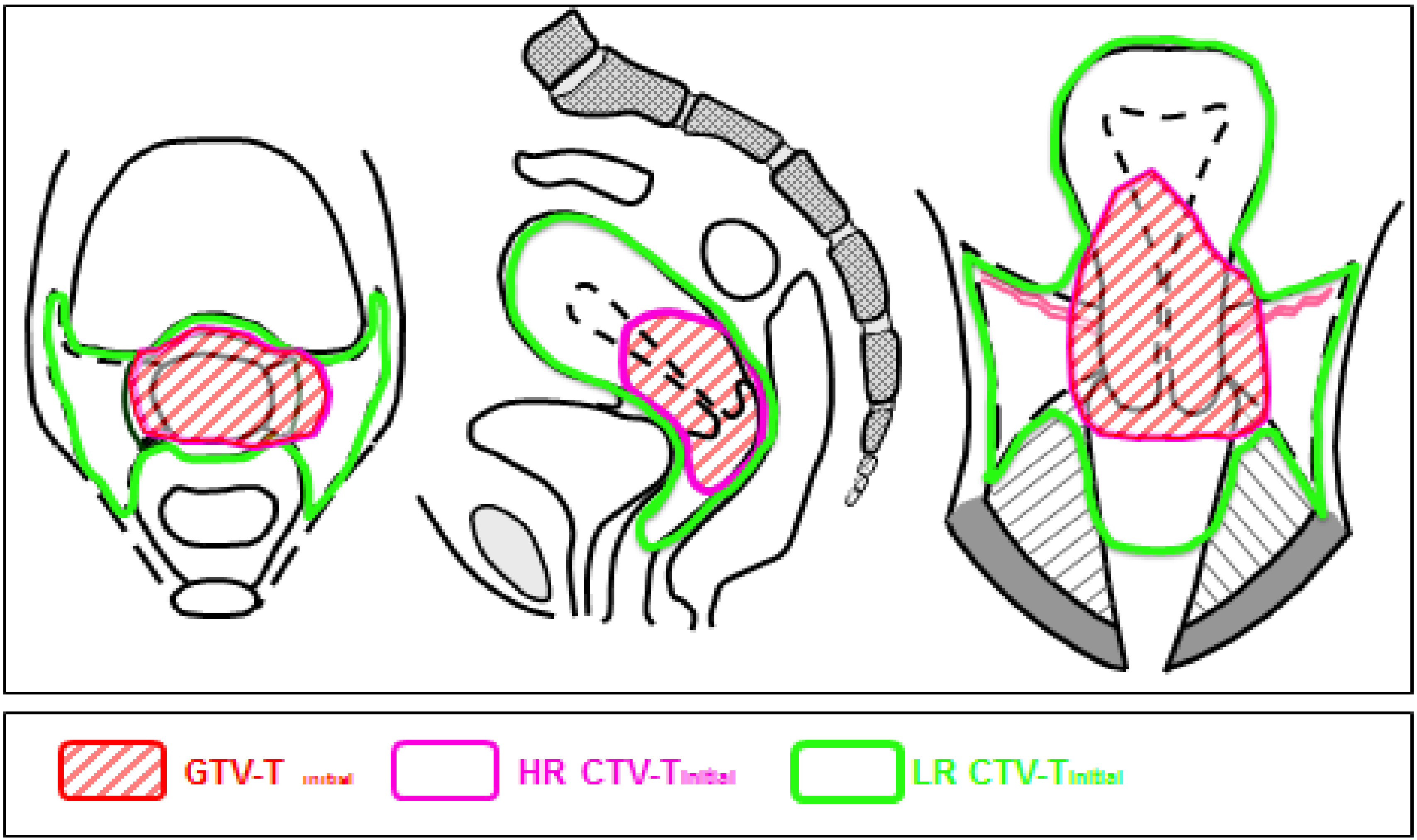
EMBRACE II: CTV-T: initial GTV, HR CTV, LR CTV: Stage IB1



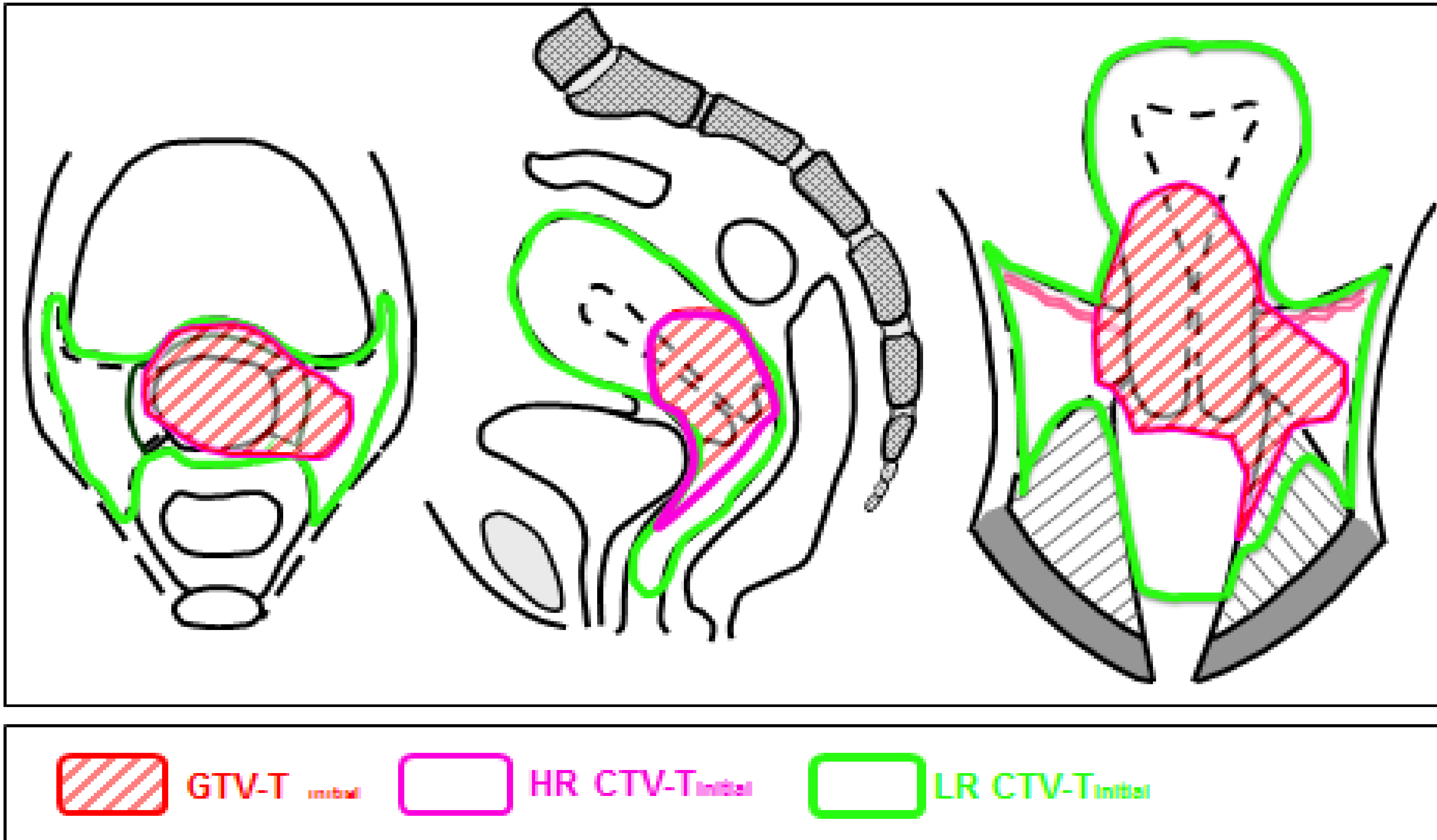
EMBRACE II: CTV-T: initial GTV, HR CTV, LR CTV: Stage IB2



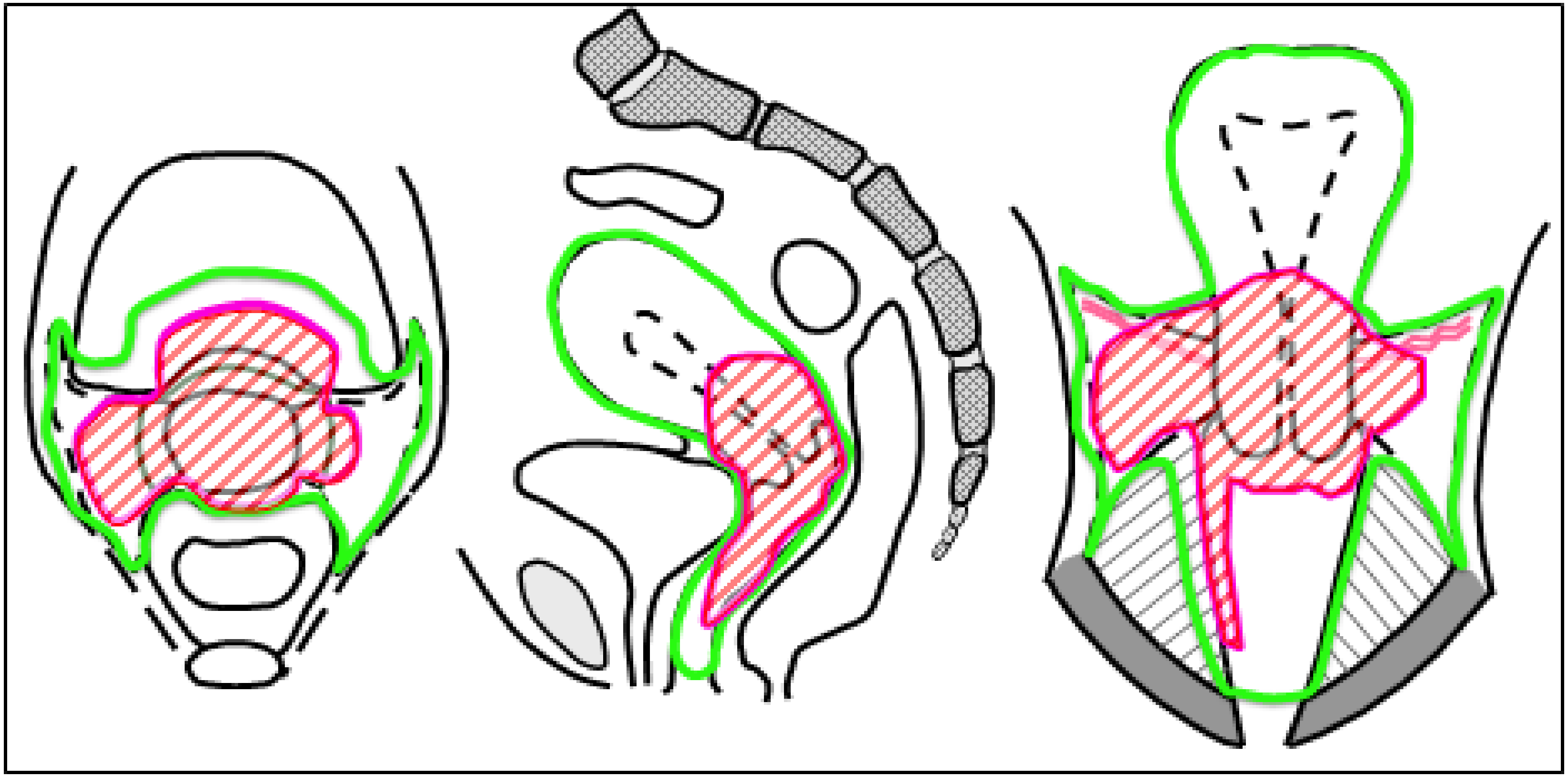
EMBRACE II: CTV-T: initial GTV, HR CTV, LR CTV: stage IIB



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



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

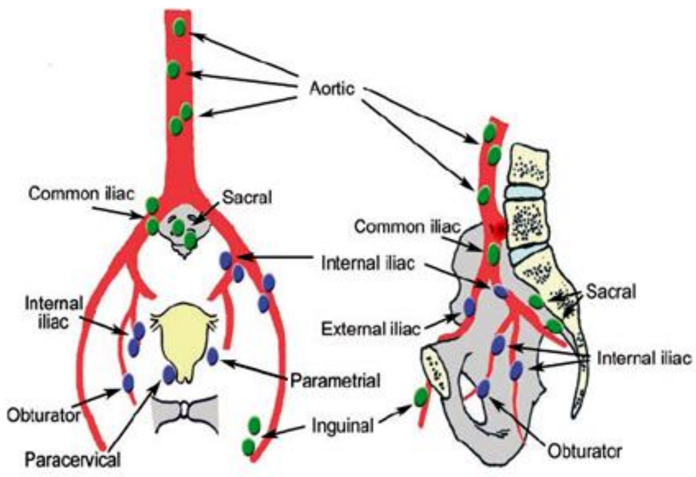


GTV-T initial HR CTV-T initial LR CTV-T initial

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

Lymph nodes are located around vessels

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



Nodal CTV contouring = Delineation of vessels with margins

Which margin/s are necessary ?

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

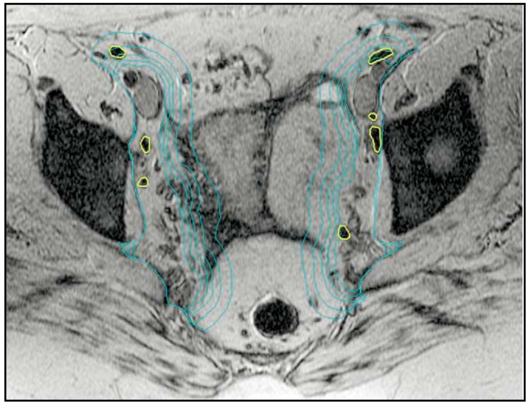
A. 5 mm
B. 7 mm
C. 10 mm
D. 5 mm with small adaptations
E. 7 mm with small adaptations
F. 10 mm with small adaptations

Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

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



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

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

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

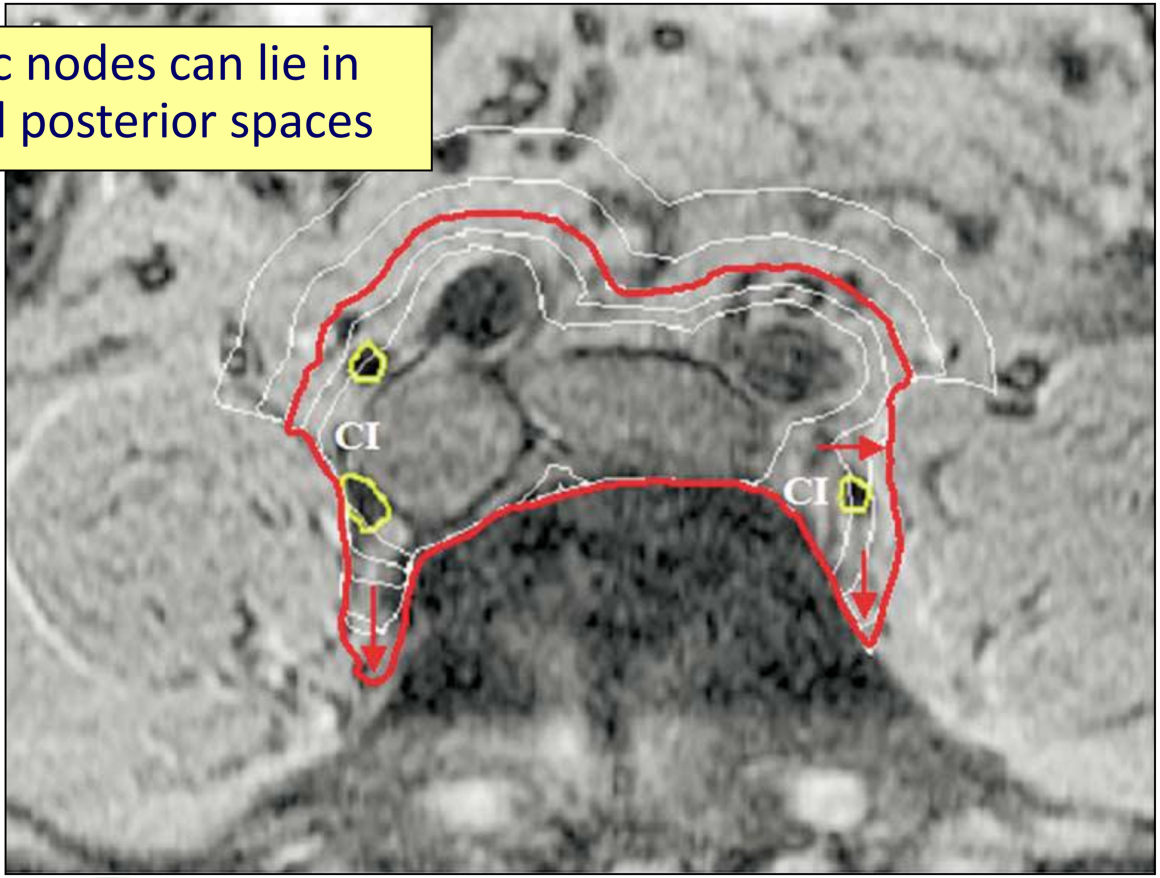
Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

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

Common iliac nodes can lie in lateral and posterior spaces



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

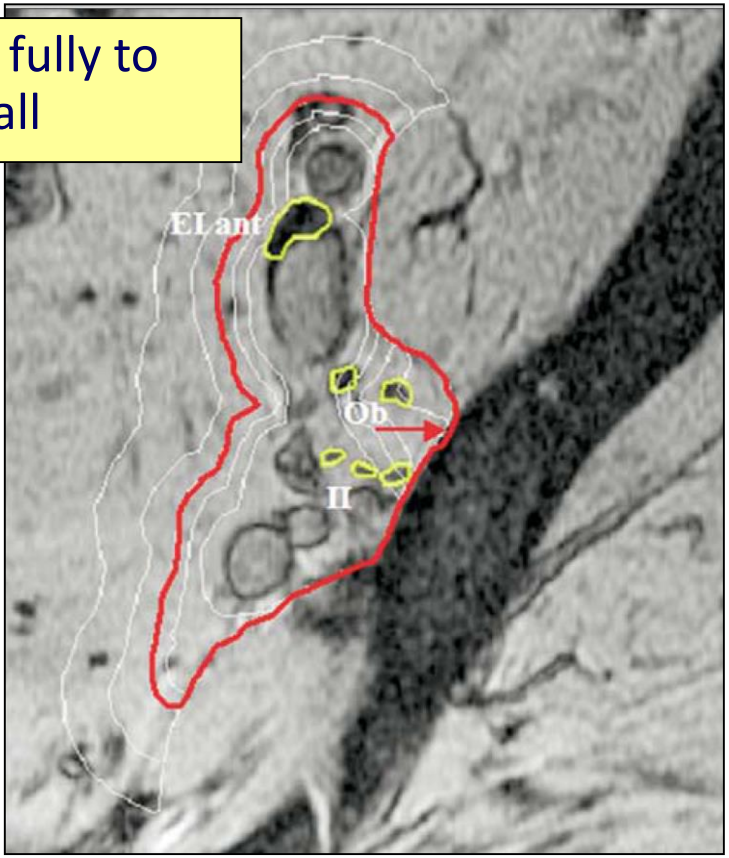
Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

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

Contour must extend fully to pelvic sidewall



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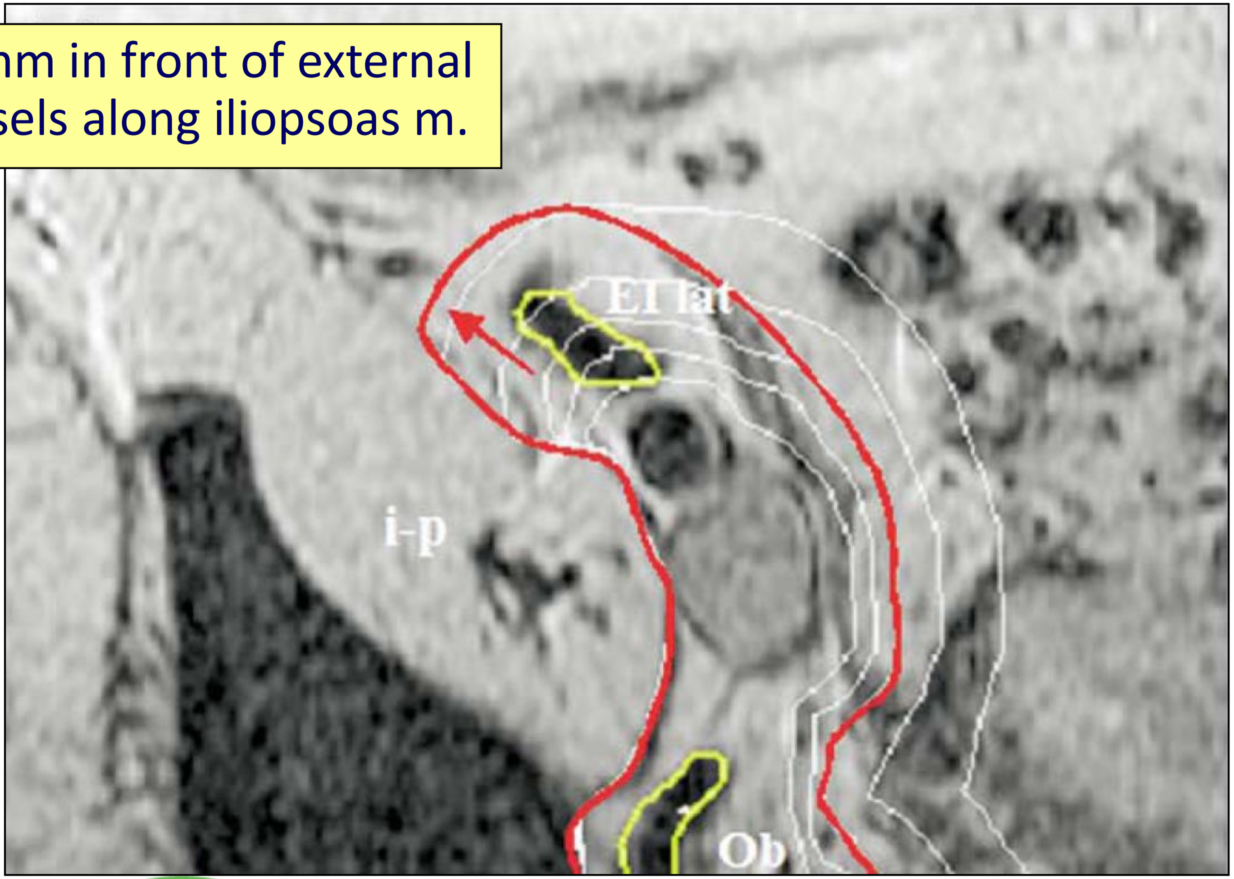
Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

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

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



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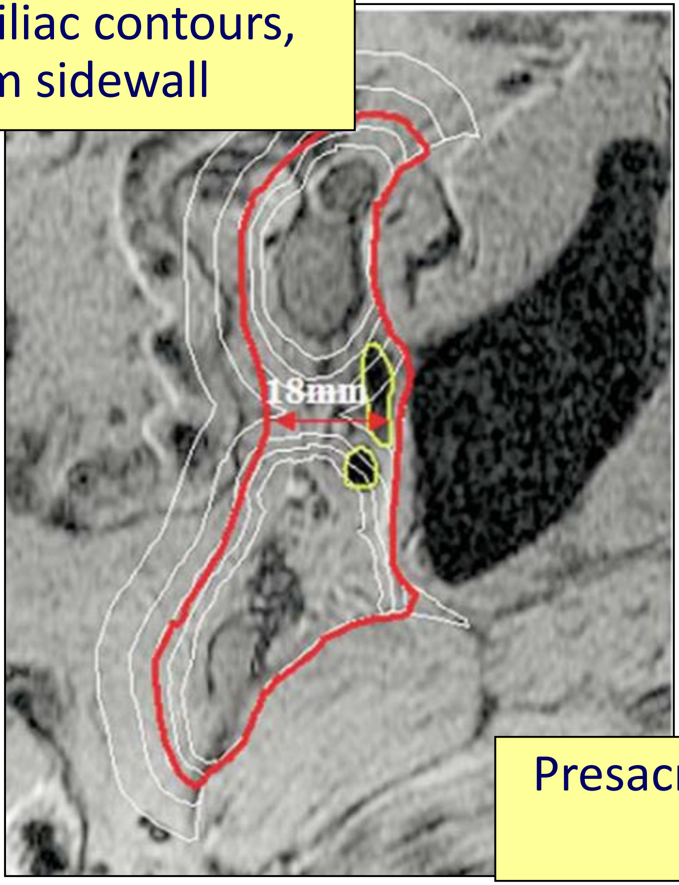
Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

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

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



Presacral nodes: keep 10 mm in front of sacrum

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

Nodal CTV

Ultrasmall Particles of Iron Oxide (USPIO) data

Taylor A et al., IJROBP 2005

Recommendations for pelvic nodal CTV delineation

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

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

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

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

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

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

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

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

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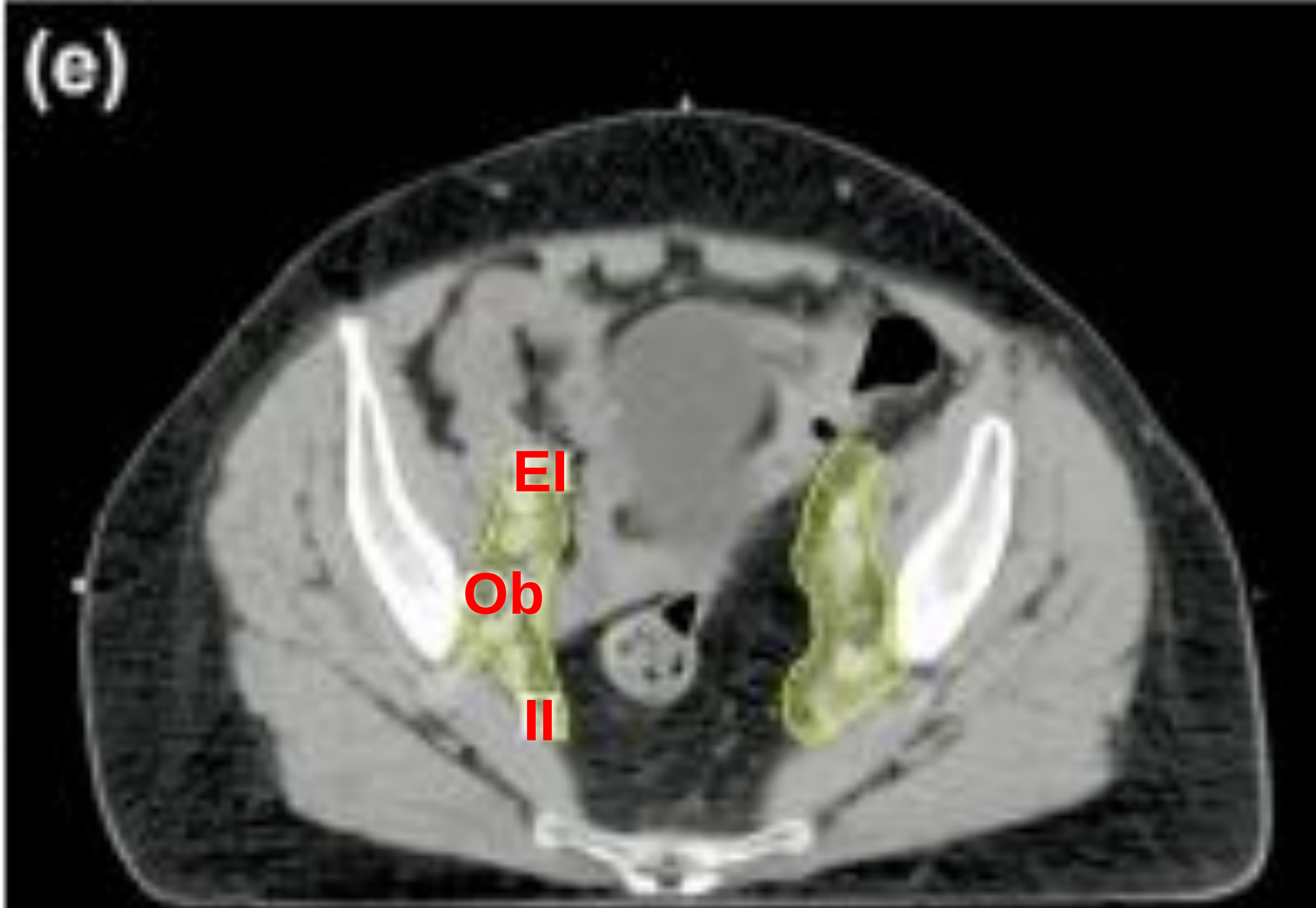

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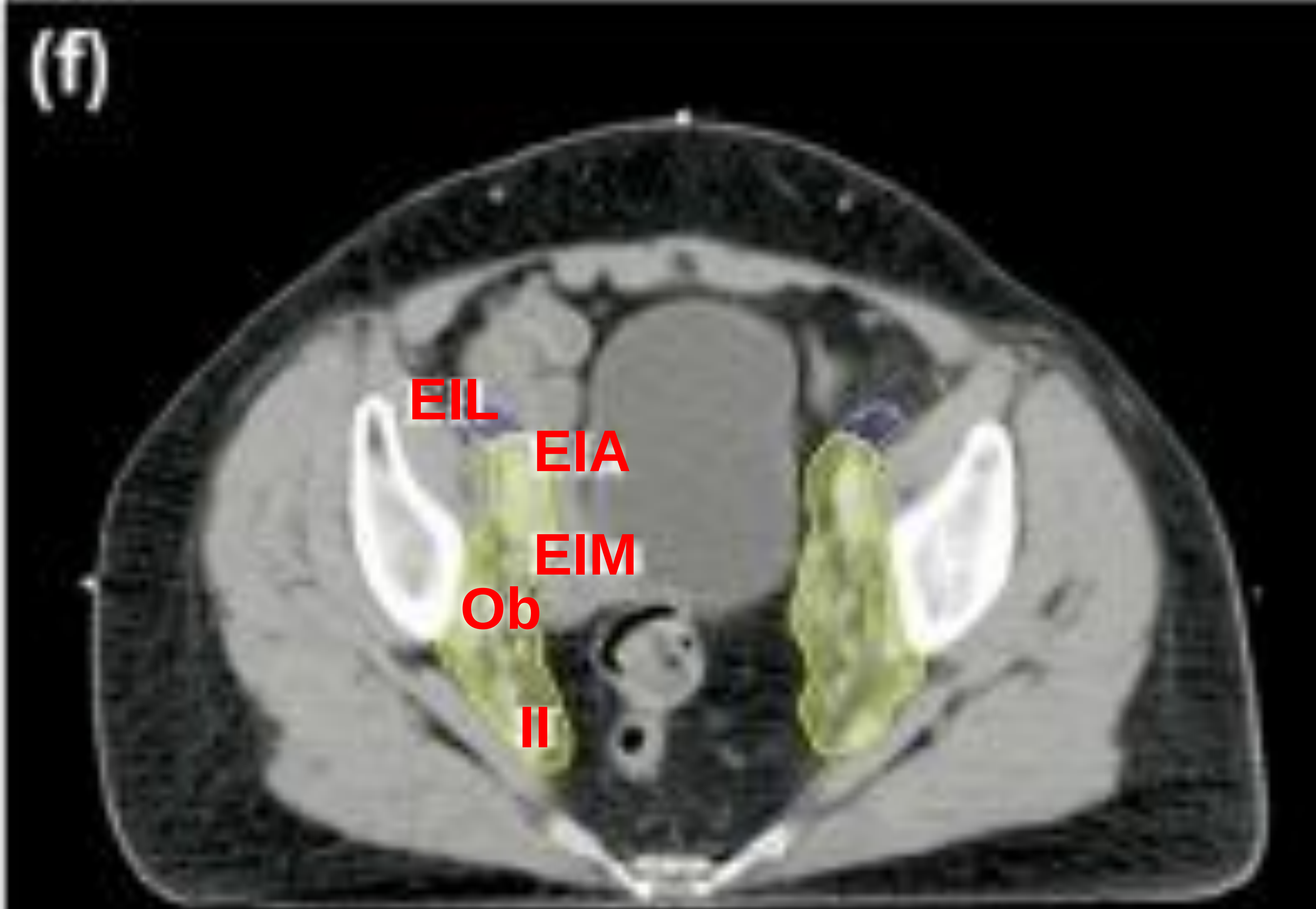

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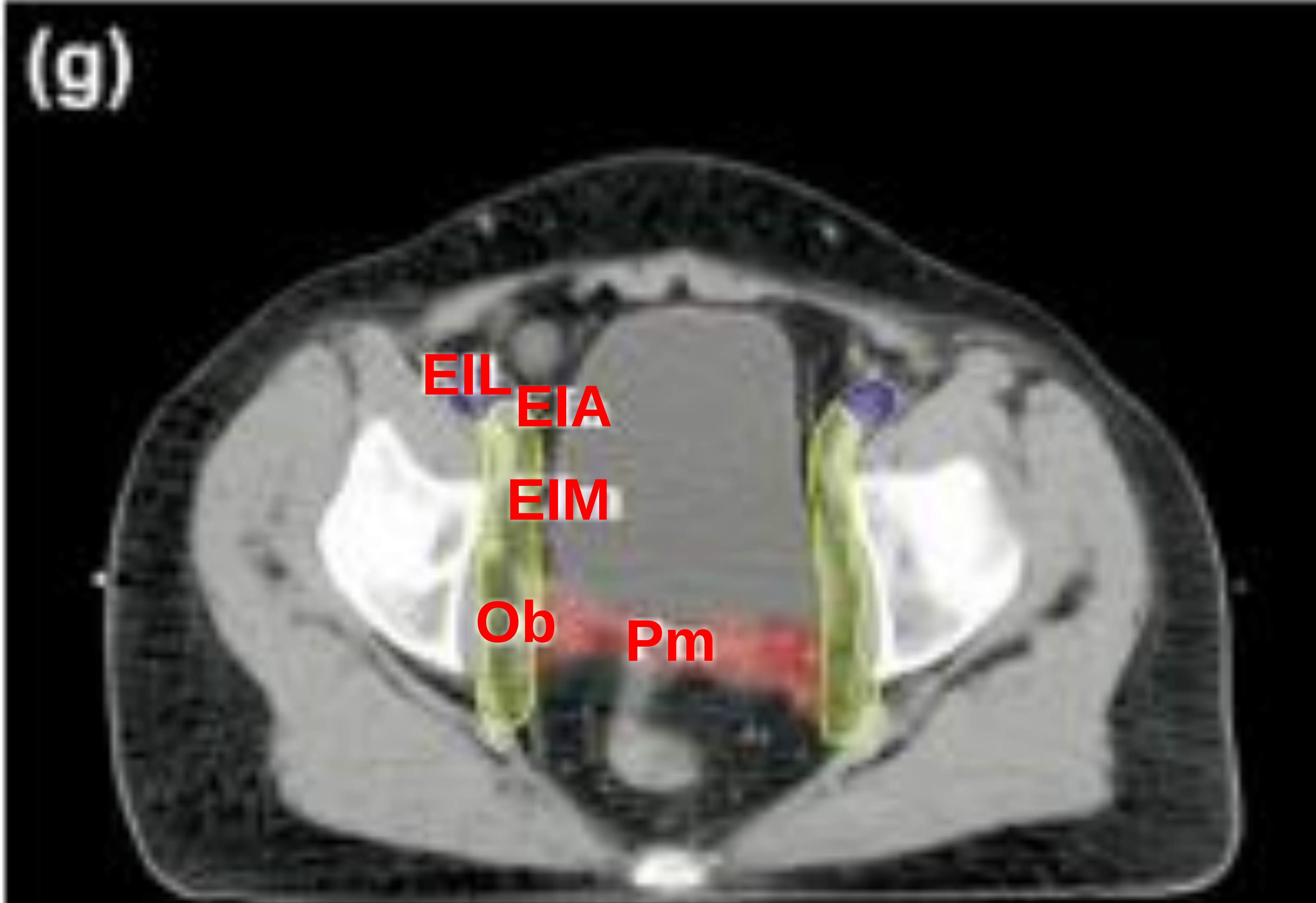

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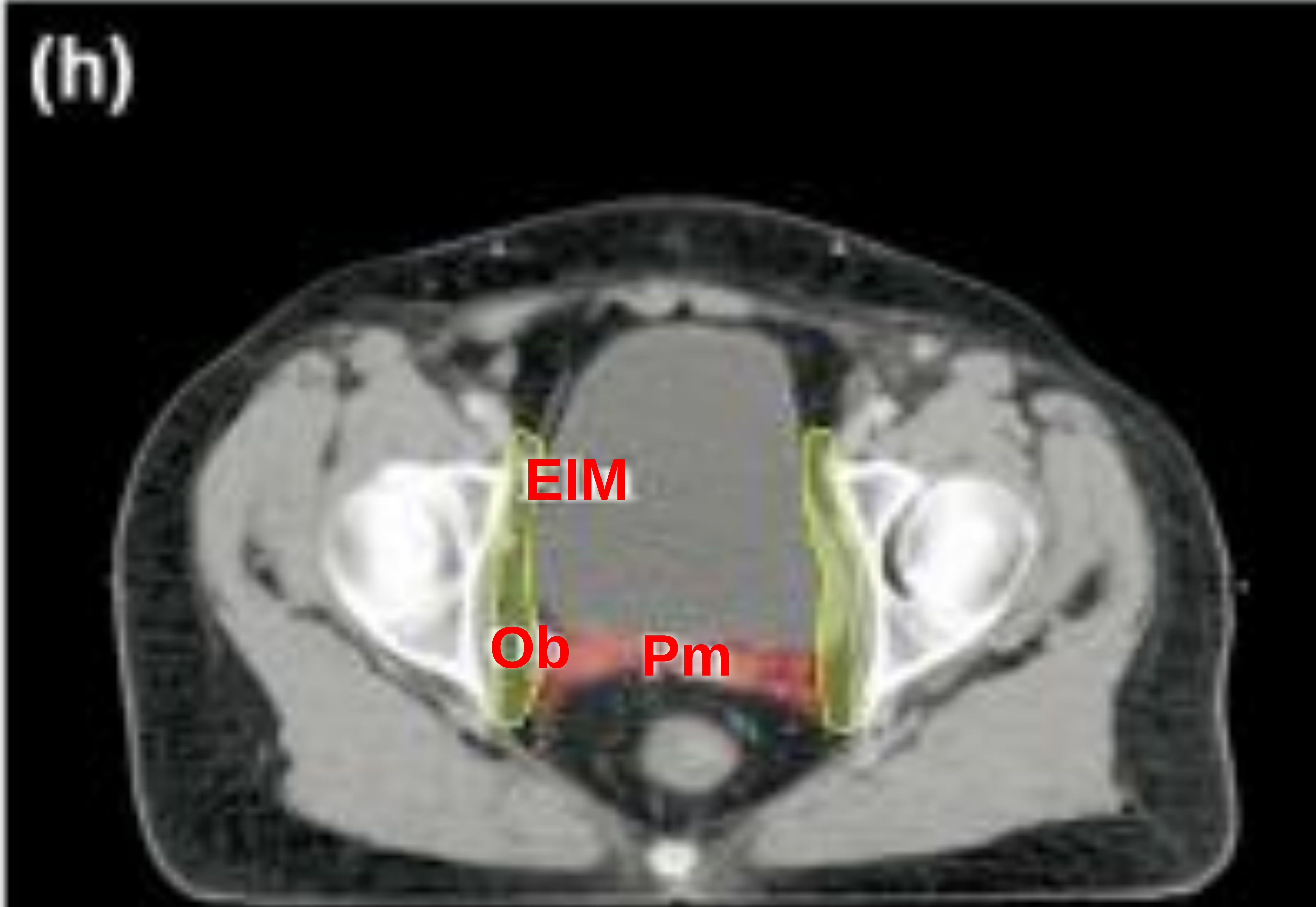


Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol 63.no.5, 1604-1612, 2005.

RTOG, GOG, NCIC, ESTRO, ACRIN Consensus

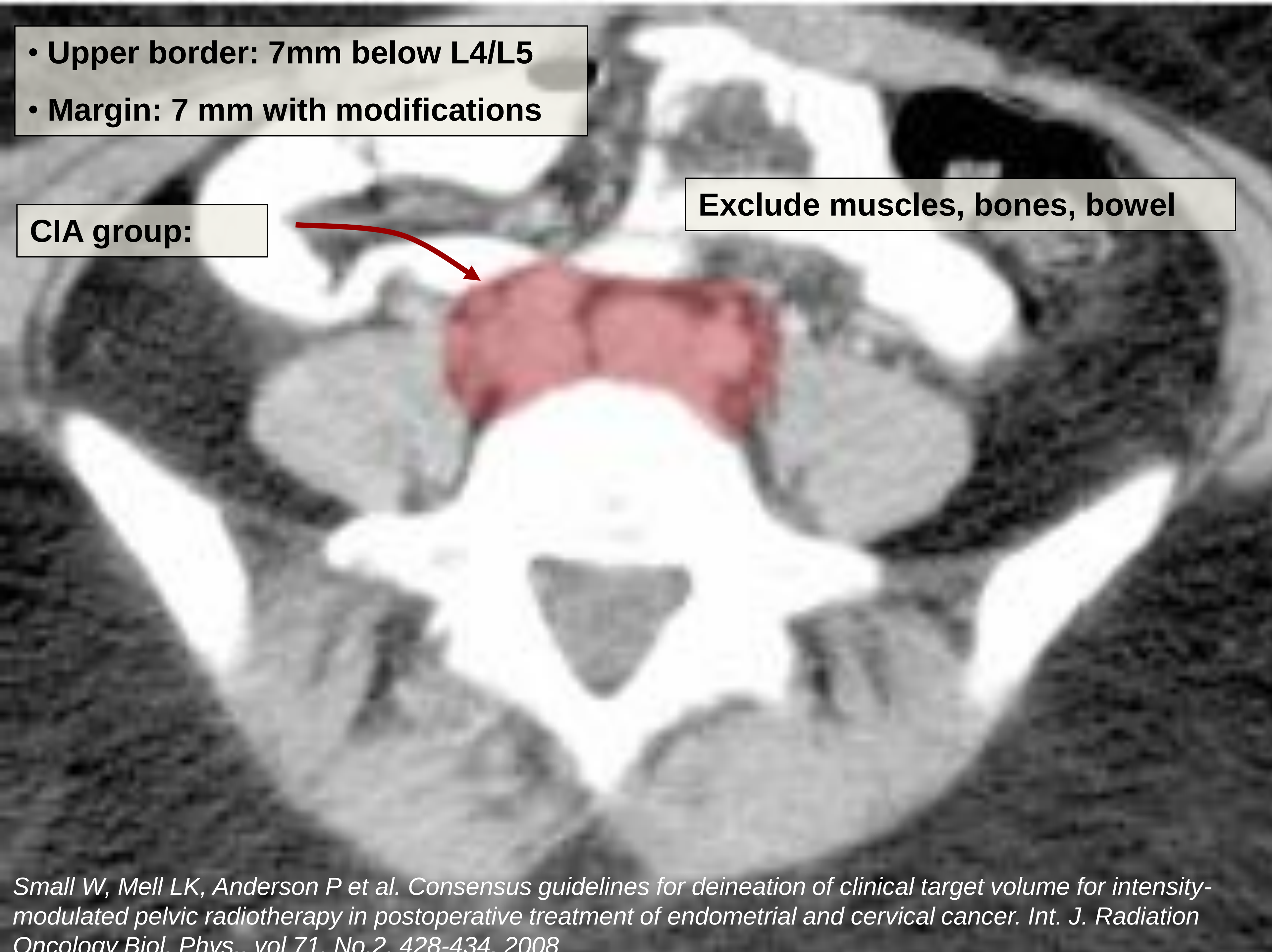
Small W, et al. IJROBP, 2008

(postoperative setting)

Pelvic nodal groups for cervix and endometrial cancer contouring:

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

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



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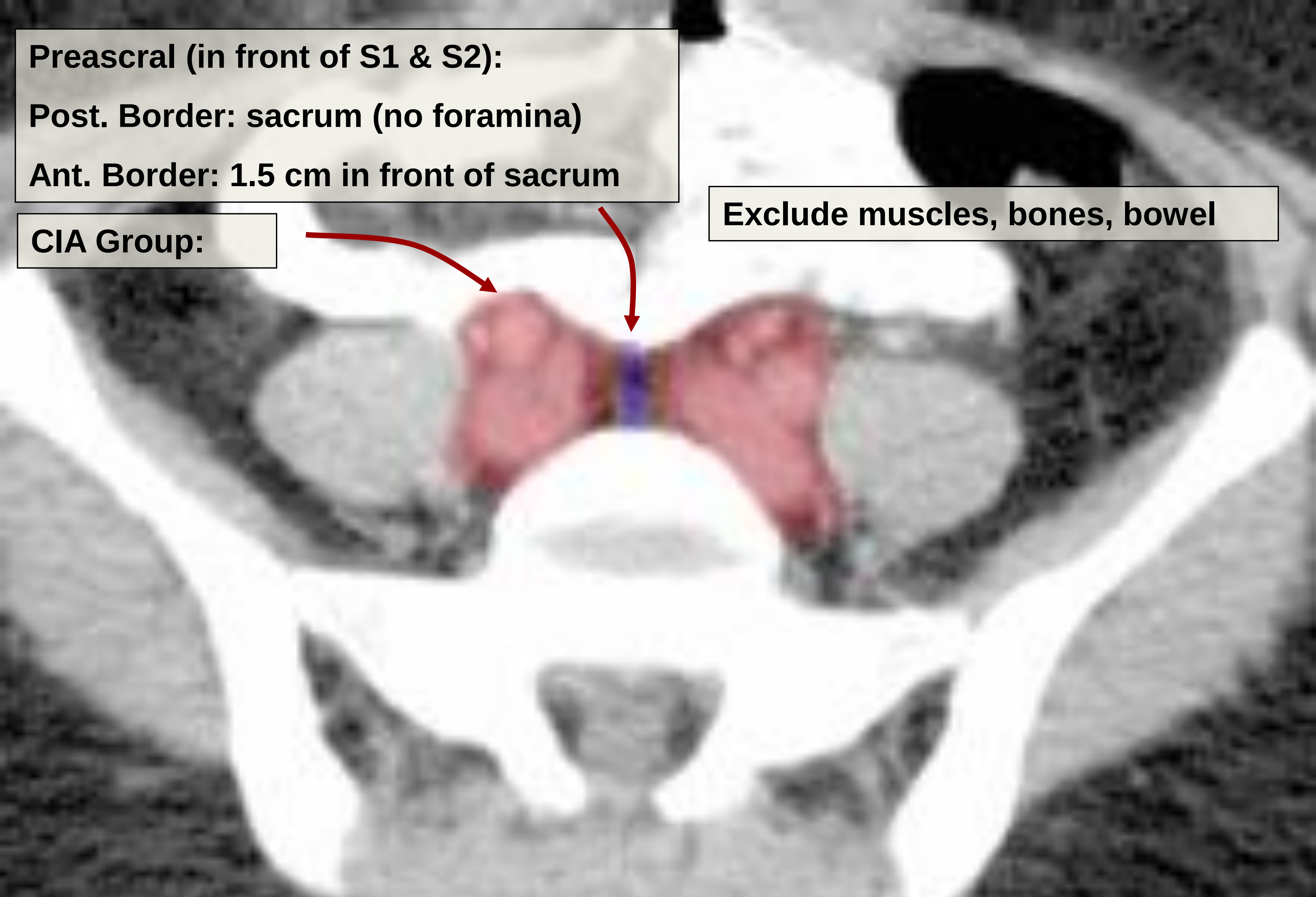

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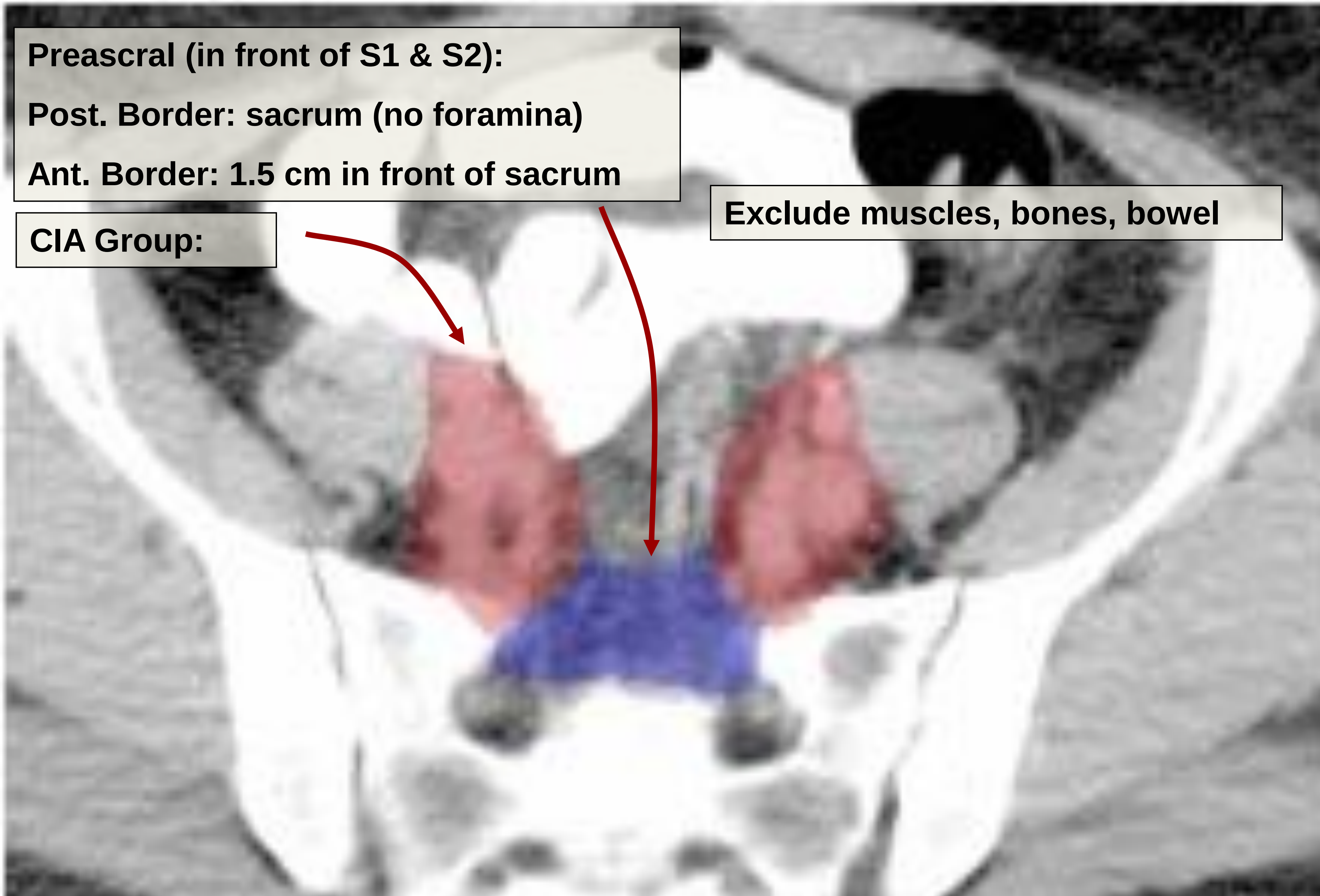

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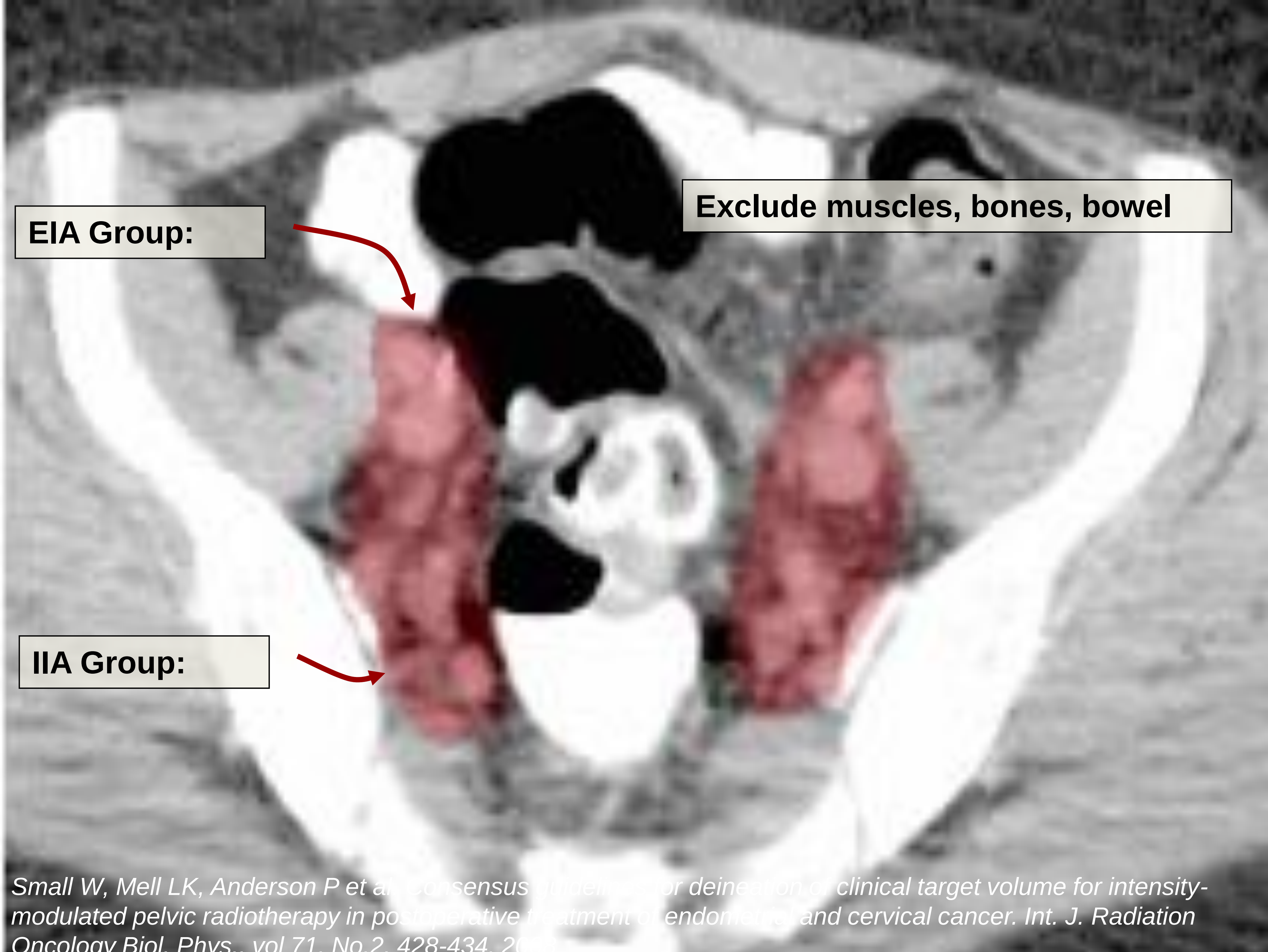
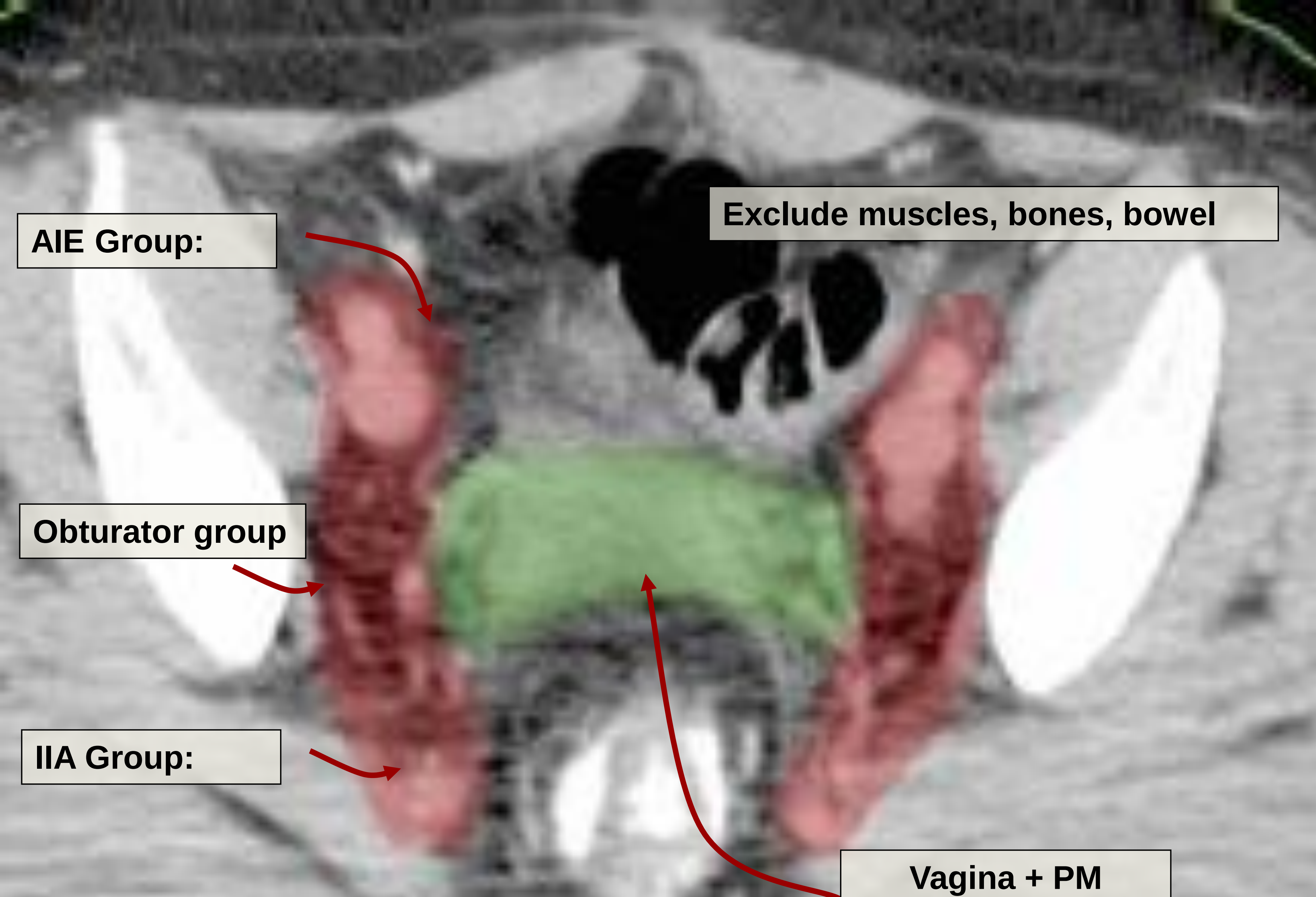


Small W, Mell LK, Anderson P et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int. J. Radiation Oncology Biol. Phys., vol 71, No.2, 428-434, 20



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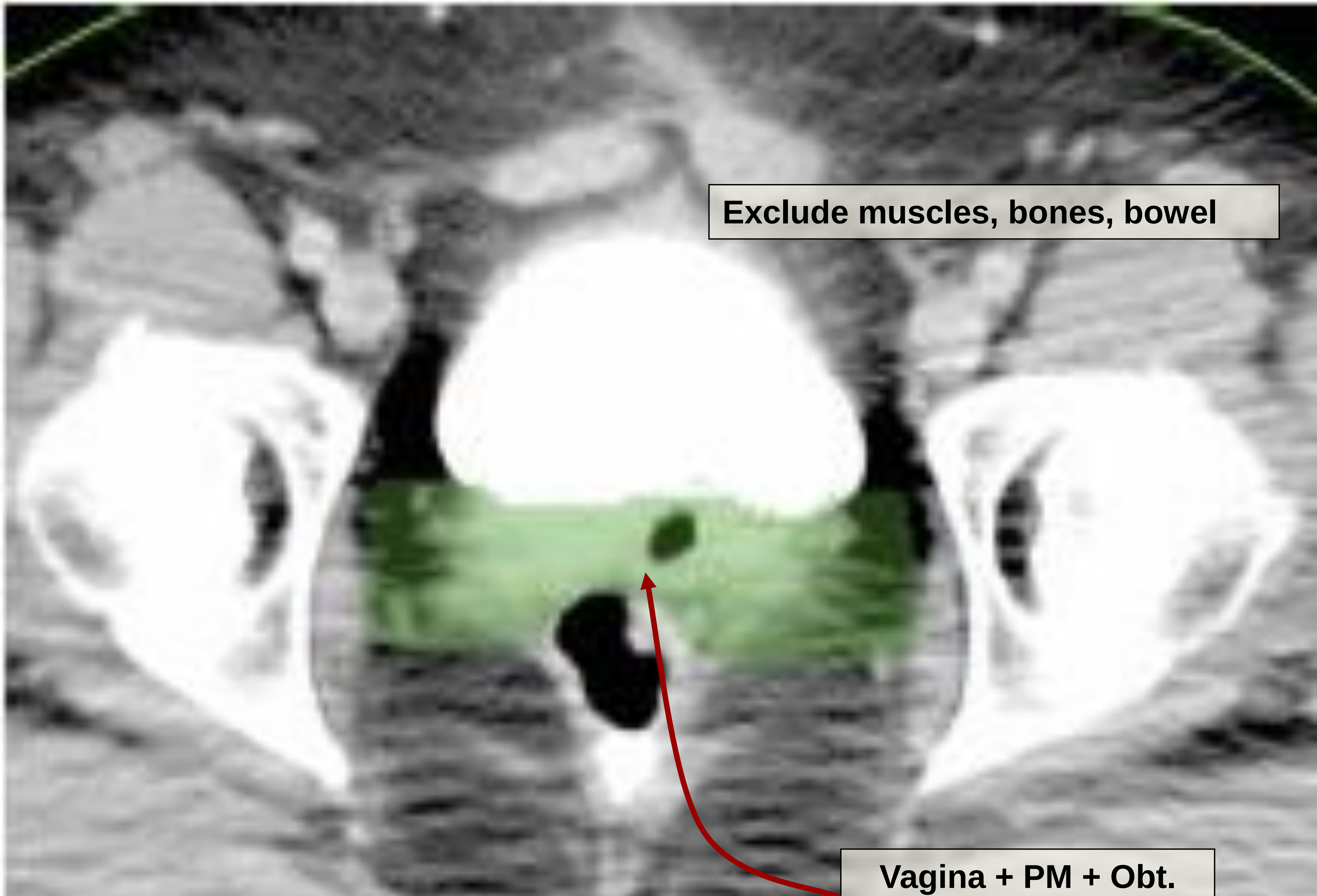
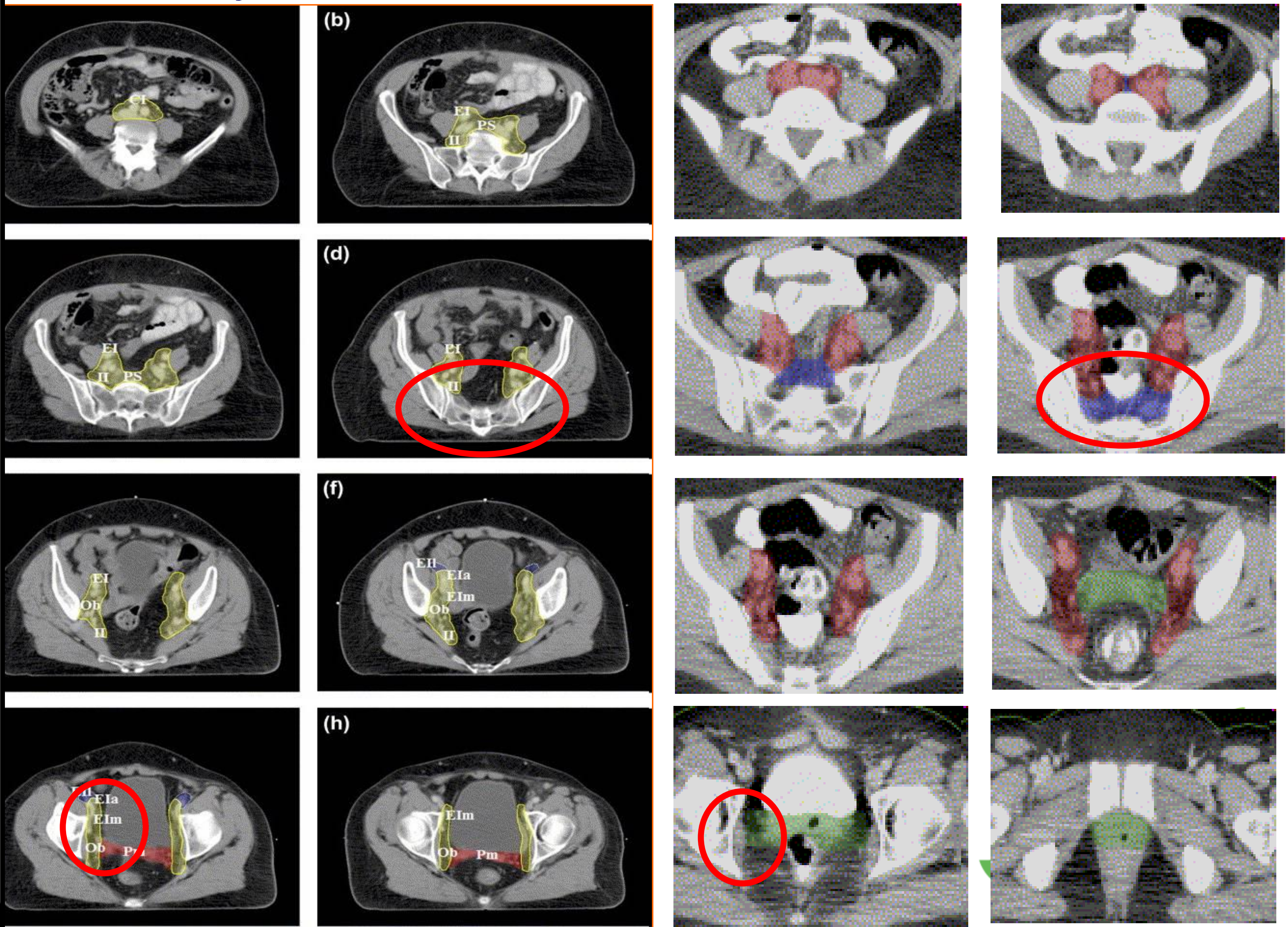


Small W, Mell LK, Anderson P et al. Consensus guidelines for deineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int. J. Radiation Oncology Biol. Phys., vol 71, No 2, 428-434, 2008

Taylor vs. Small

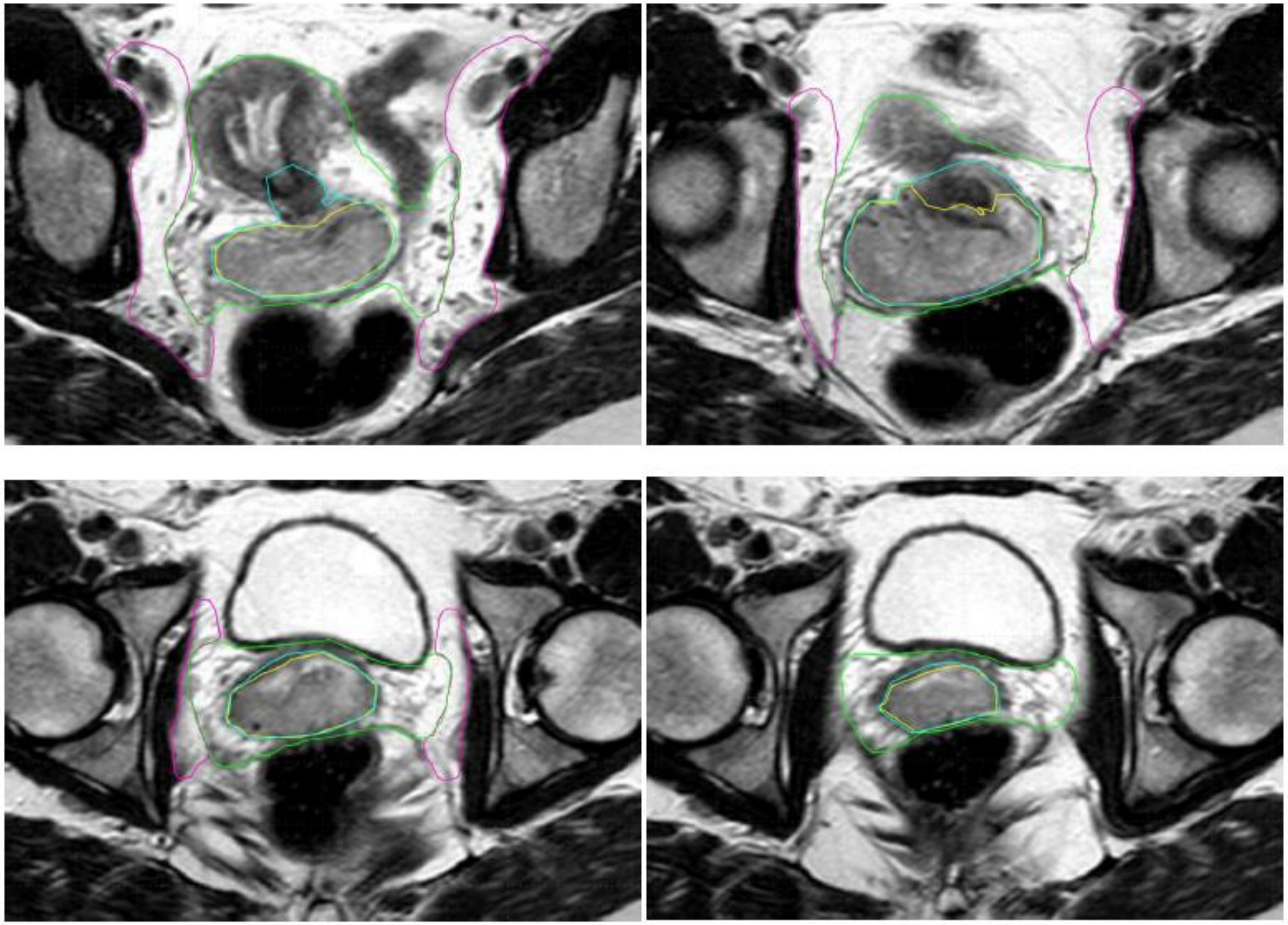
Taylor 2007

Small 2008



Elective nodal CTV: Caudal extension

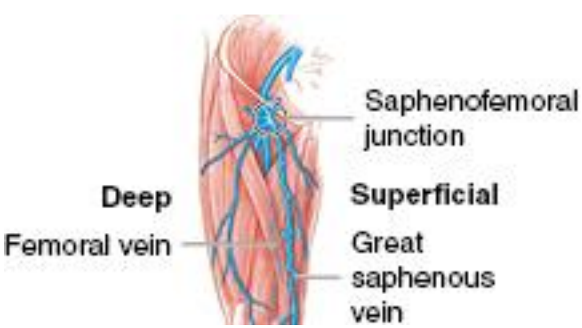
- Transition zone goes down to the pelvic floor (usually at the upper part of the obturator foramen, below femoral head, were internal iliac vessels enter or leave the true pelvis)

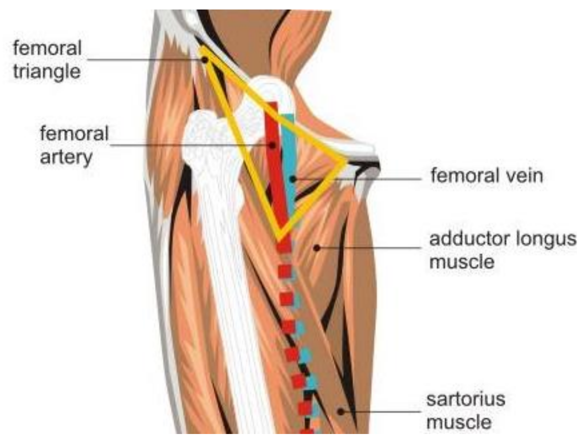


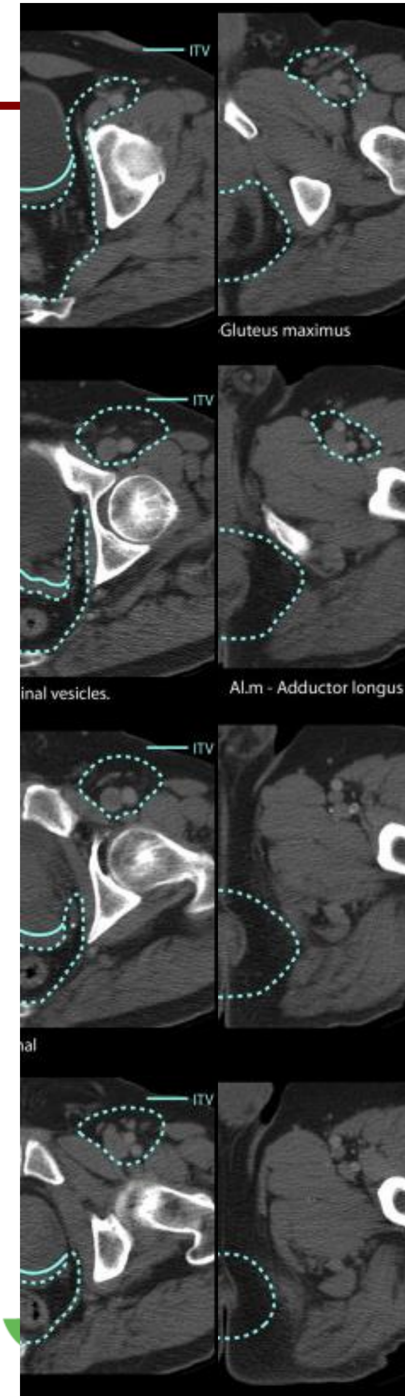
From EMBRACE II protocol

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





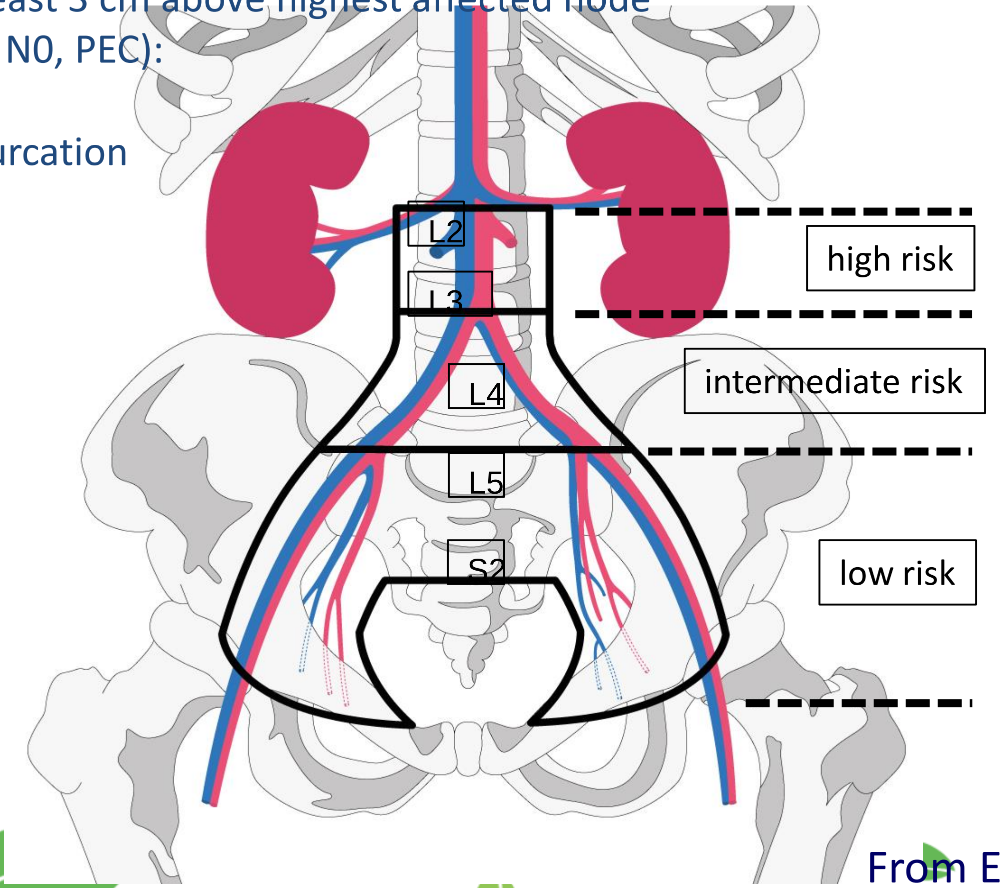


Ng et al., Australasian Gastrointestinal Trials Group (AGITG) Contouring Atlas and Planning Guidelines for Intensity-Modulated Radiotherapy in Anal Cancer, Int. J. Radiation Oncology Biol. Phys., Vol 83, 1455-1462, 2005.

Elective nodal CTV: Cranial extension

Ongoing investigations and discussion (EMBRACE II)

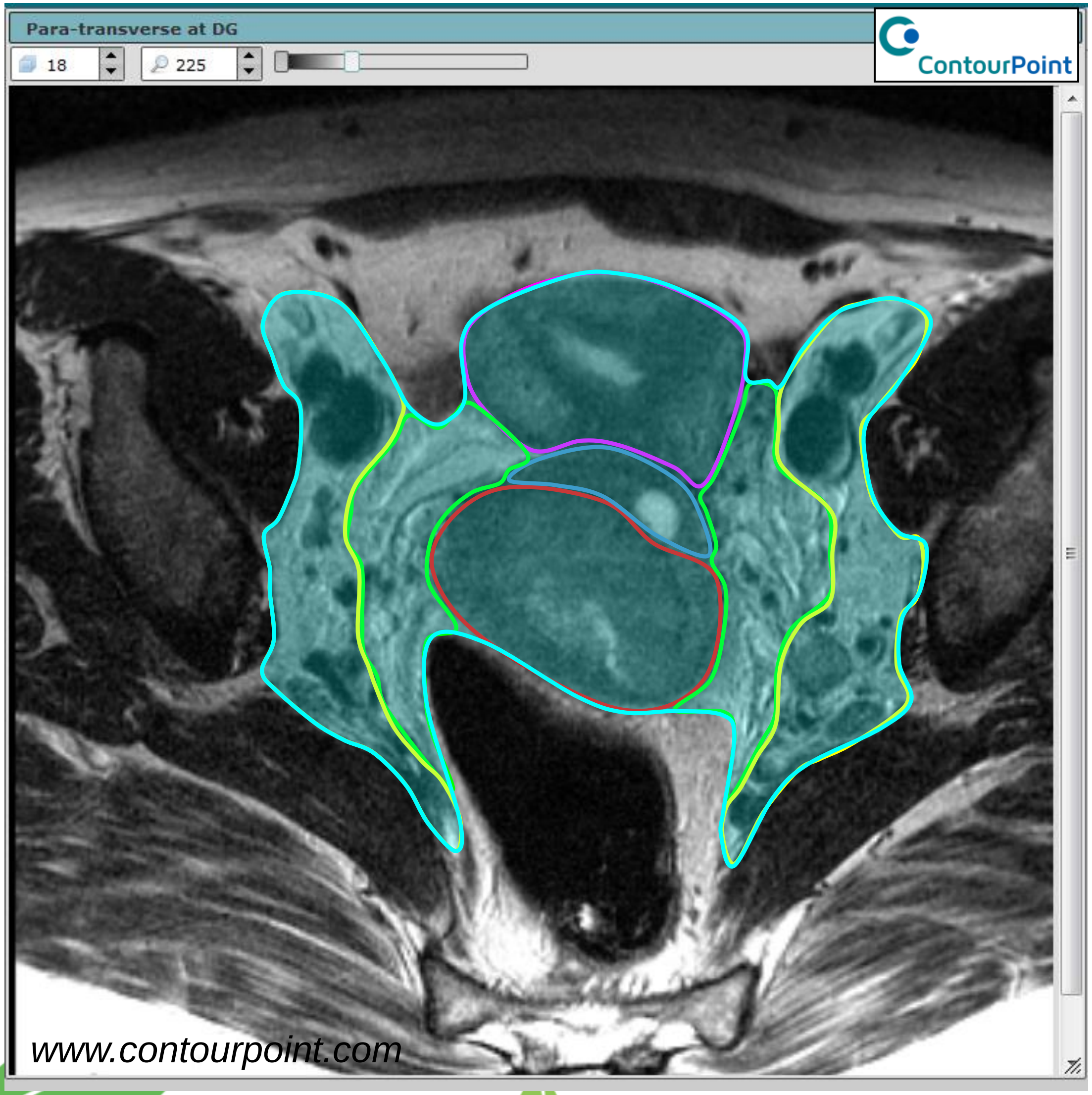
- Intermediate risk: upper border level of aortic bifurcation or defined by bony anatomy (L3/34)
- High risk: Depending on extension of nodal disease into common iliac region consider or ≥ 3 pelvic nodes:
  inclusion of low PAO region up to renal vessels (L2),
  extension of at least 3 cm above highest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



From EMBRACE II protocol

Total CTV for definitive cervix cancer EBRT

Initial CTV-T + Nodal CTV



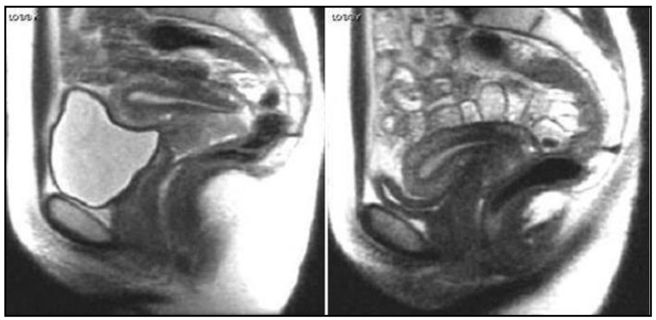
The margin needed to include 99% of detectable lymph nodes is?

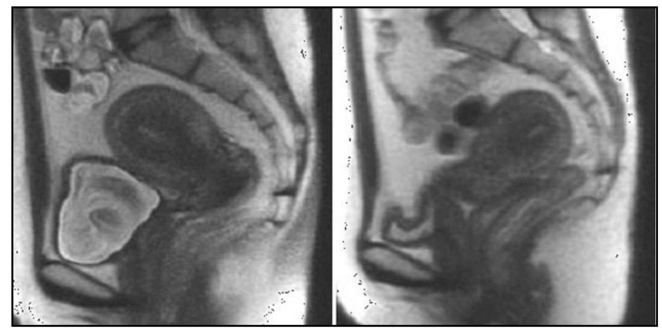
A. 5 mm
B. 7 mm
C. 10 mm
D. 5 mm with small adaptations
E. 7 mm with small adaptations
F. 10 mm with small adaptations

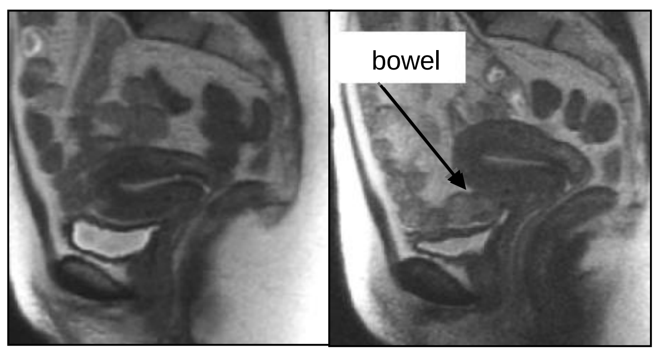
ITV-T – Internal Target Volume

= 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

= 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		Cervix cancer		
	MRI baseline & weekly		MRI & cine MRI – done baseline & weekly during standard EBRT		
	Target motion not directly measured. Margins required to encompass GTV & CTV from week to week used as a surrogate for target shifts		Point of interest study – uterine fundus, uterine canal & cervical os		
Inter-fraction motion	GTV	CTV	Uterine fundus	Uterine canal	Cervical os
Sup/					
Ant/post (mm)	Ant = 12	Ant = 24	AP = 14.5	AP = 13.1	AP = 11.2
	Post = 14	Post = 17			
Left/right (mm)	Rt = 12	Rt = 12	–	–	–
	Lt = 11	Lt = 6			
Comments	Bladder & bowel prep. not specified		Bladder & bowel prep. specified		
	CTV-PTV margins recommendation:		Suggested inter-fraction margins – fundus (10–40 mm); canal (10–25 mm), os (10–15 mm)		
	Ant = 24 mm; Post = 17 mm; Rt = 12 mm; Lt = 16 mm; Sup = 11 mm; Inf = 8 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

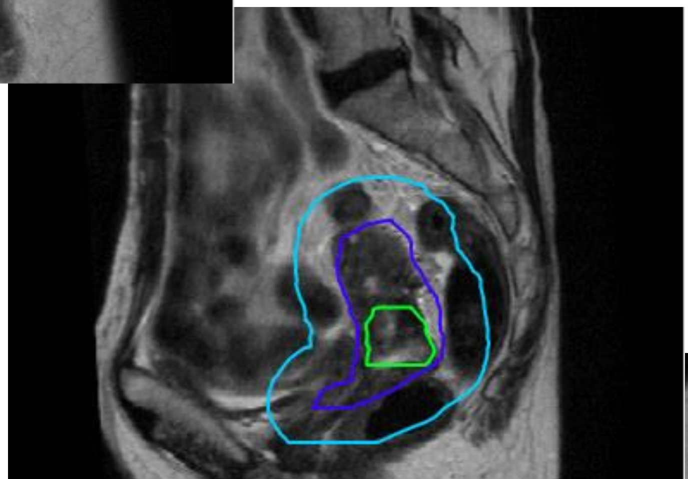
Lim K, et al. Image guidance...In: Viswanathan et al., eds. Gyn Radiat Oncol. Springer 2011

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

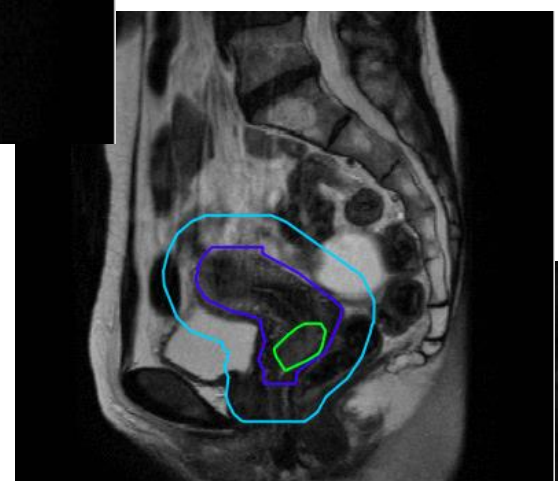
Target (CTV-T) motion during EBRT

- 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

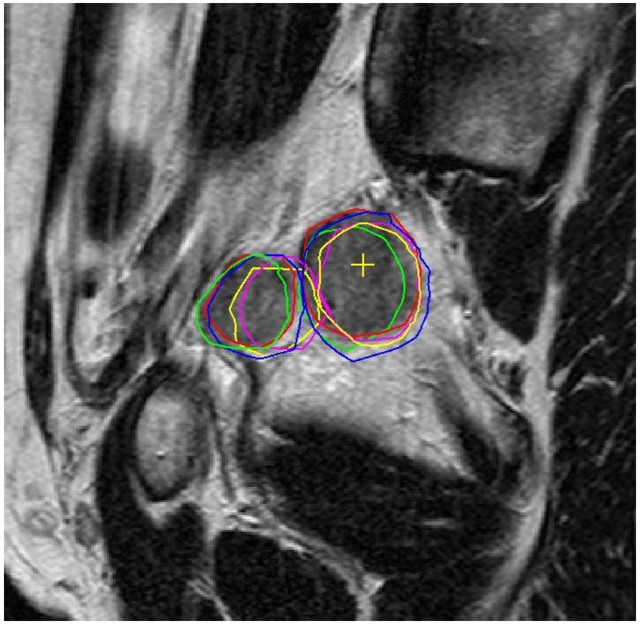
GTV
CTV
PTV

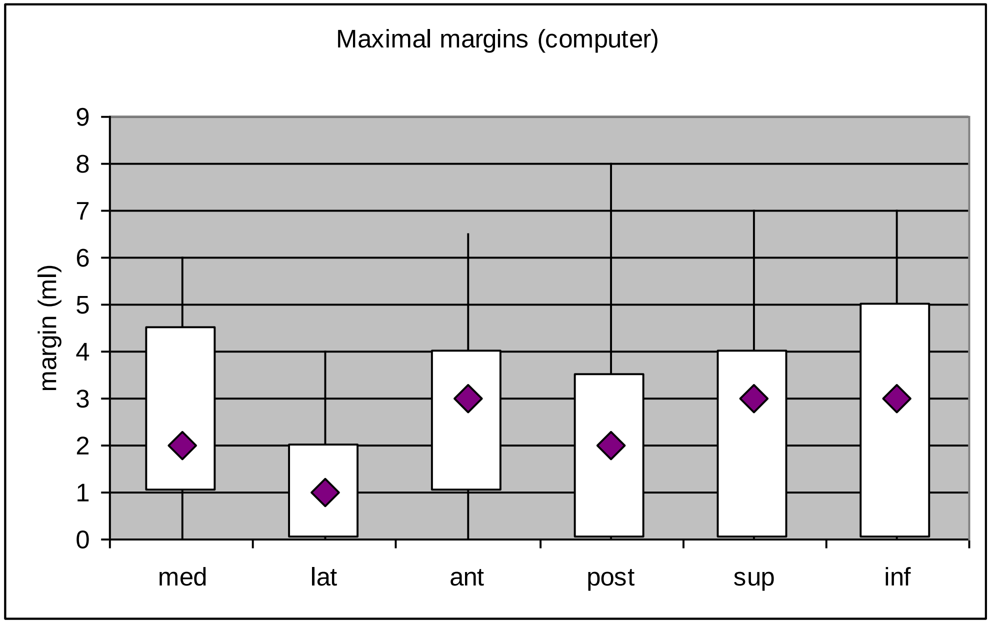
Van de Bunt et al 2008

Inter-fraction motion of nodal CTV

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

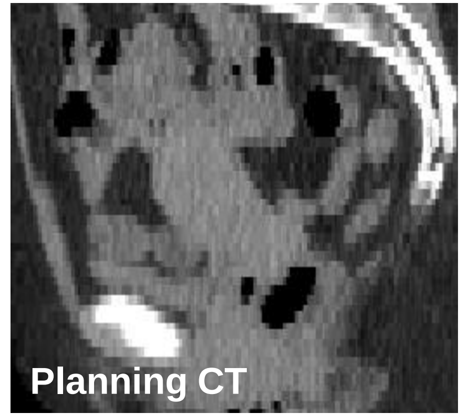
"Mover or non-mover" ?

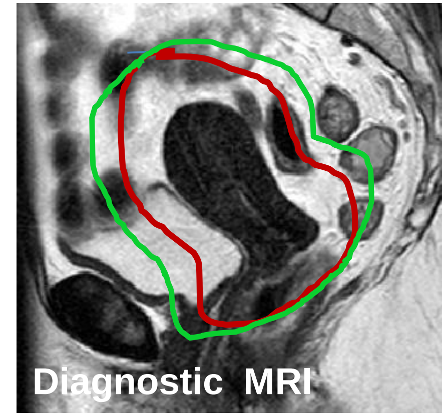
Repeated MRI with changing bladder fillings

To detect "Movers and Non-movers"

Work in progress

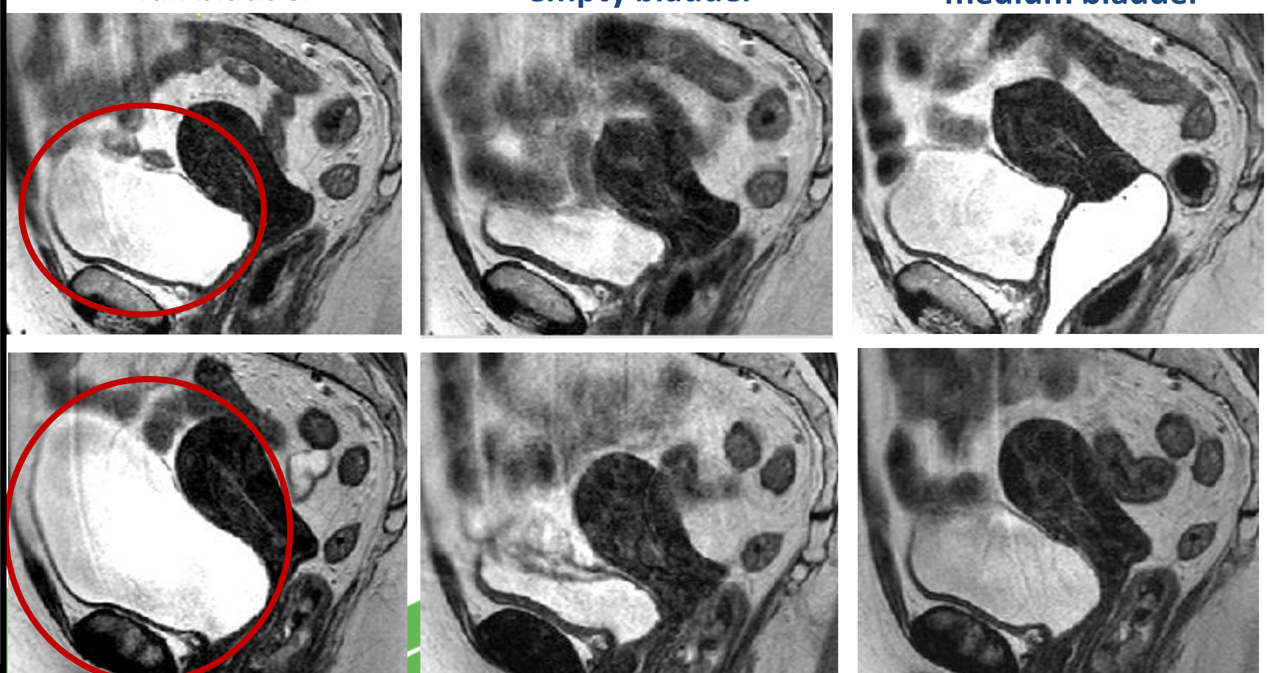
Check: rectal filling!





medium bladder filling intended

full bladder | **empty bladder** | **medium bladder**

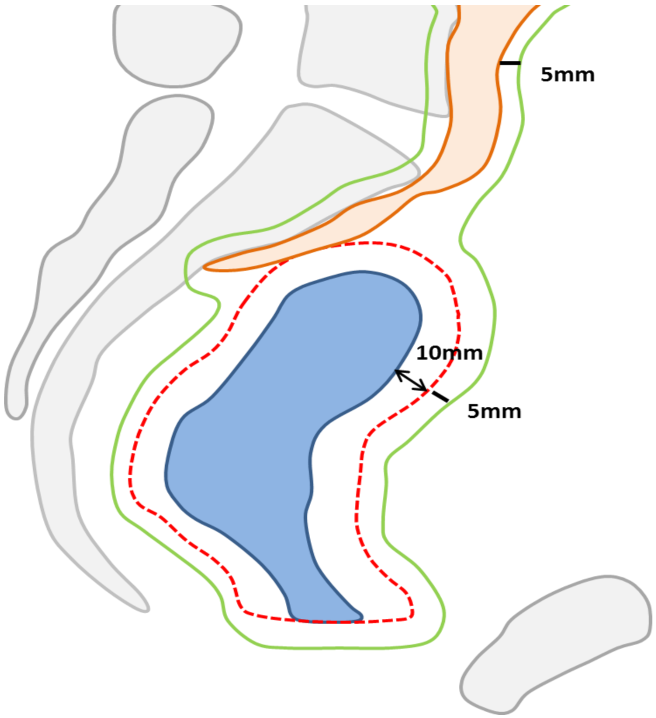


Pre-treatment

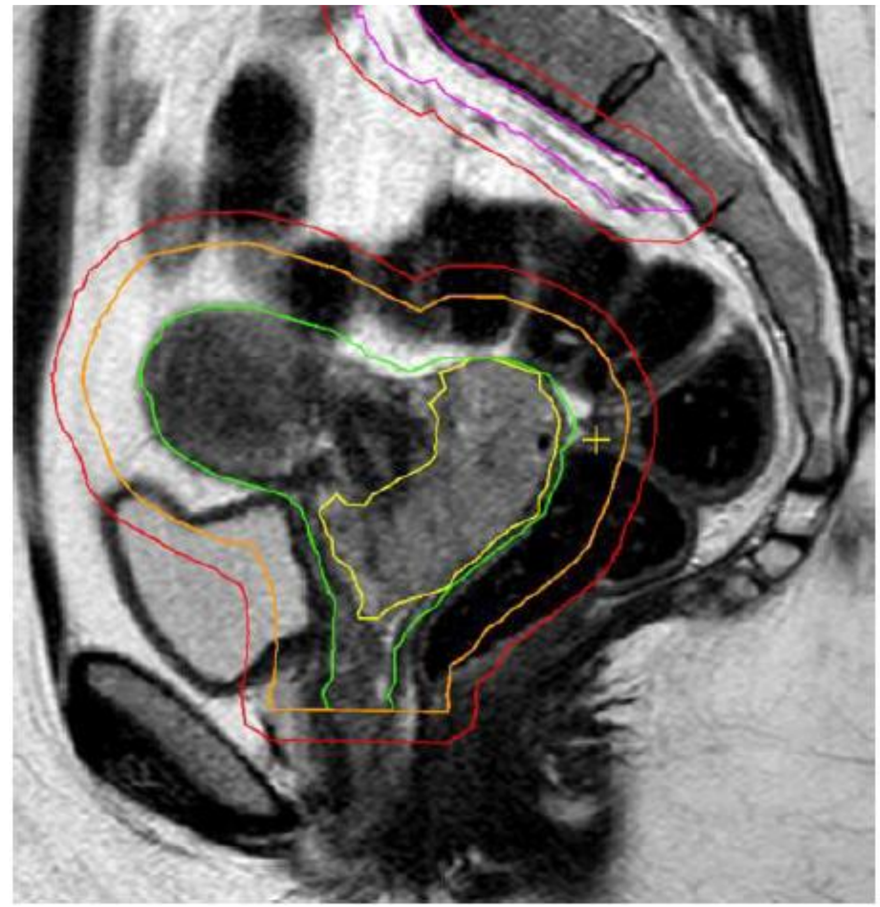
Week 1 EBRT

Courtesy
Petra Kroon-van Loon
Jochem Hes

ITV-T based on standard margin approach

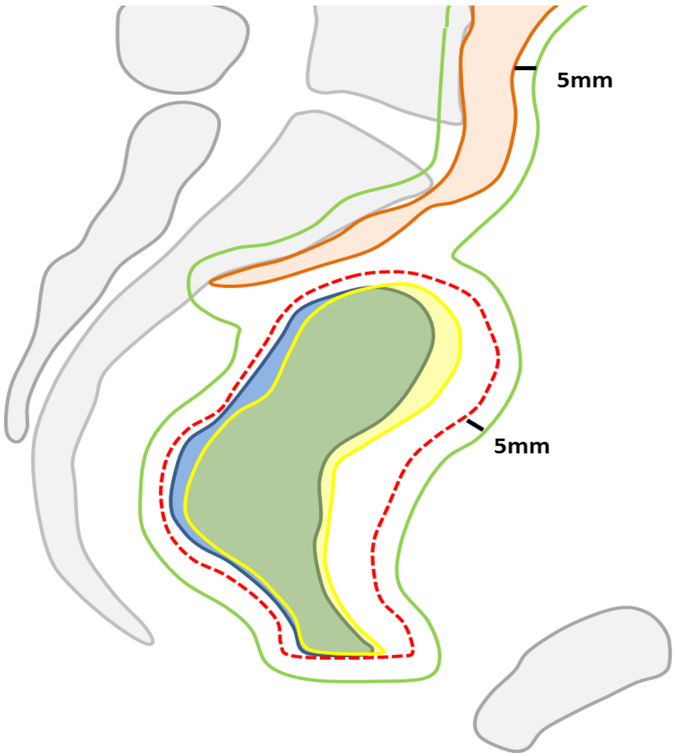


CTV-T LR (CT)
CTV-E
ITV-T LR
PTV-45

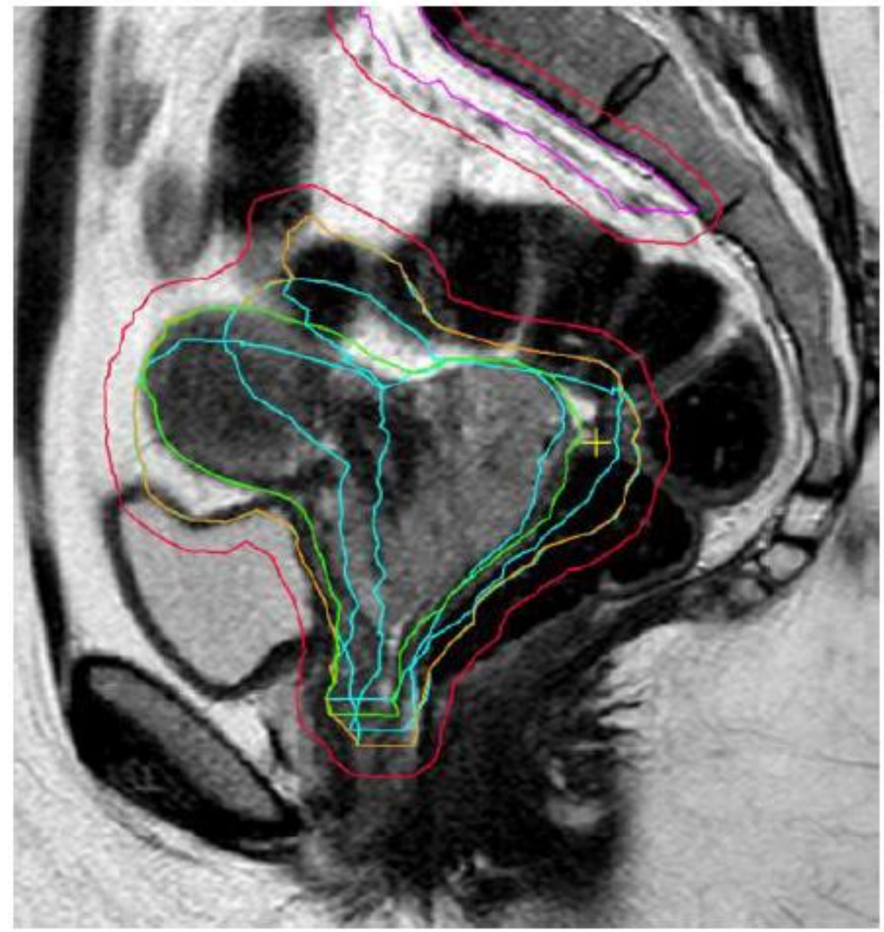


From EMBRACE II protocol

Individualized ITV-T



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

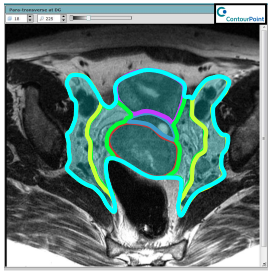


From EMBRACE II protocol

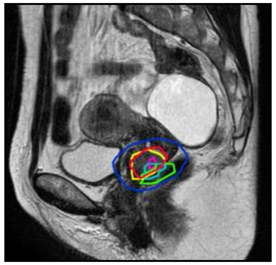
Conclusions

- GTV-T, CTV-T, ITV-T concept is complex
- CTV-ITV-T margin for internal motion & deformation
- Recommendations for standard ITV margin

  at the uterus for CTV-T: min 10-15



- Margins may differ betwen patients
- CTV-ITV-T margin depends on position verification method



- No ITV concept for CTV-E and CTV-N

Management and treatment planning of paraaortic node area

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

Paraaortic (PAo) node involvement: **To your knowledge, what is the rate of involved paraortic nodes in advanced cervical cancer FIGO IB2-IVA:**

A. **1-15%**
B. **15-35%**
C. **35-50%**
D. **>50%**

Paraaortic (PAo) node involvement

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

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

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

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

Radiother Oncol 11 (1988) 101-12

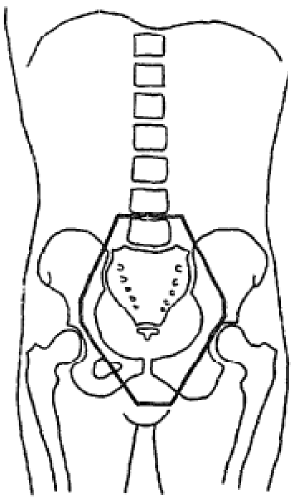


Fig. 1. Pelvic irradiation.

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

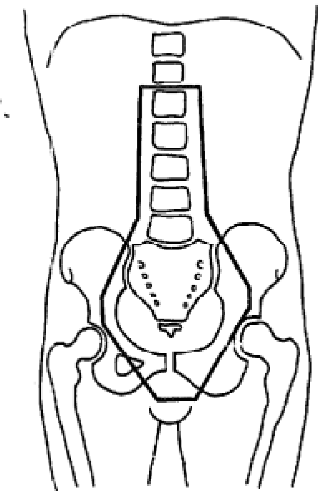


Fig. 2. Pelvic and para-aortic irradiation.

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

13%

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

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

VOLUME 22 · NUMBER 5 · MARCH 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

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

Table 3. Survival and Recurrence Rates

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

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

The Oncologist®

Gynecologic Oncology

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

The Oncologist 2013;18:415–22

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

163 patients
11% had paraaortic failure

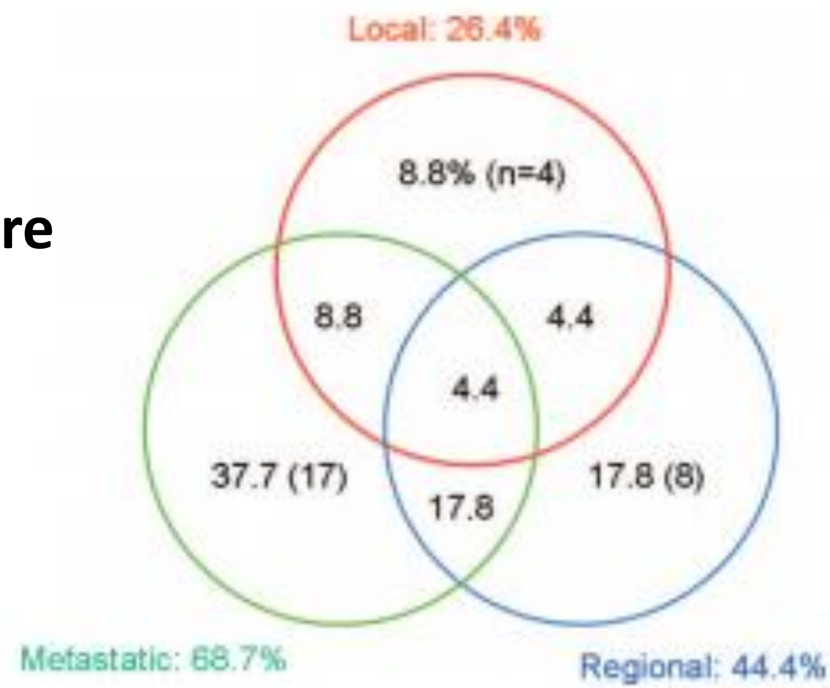
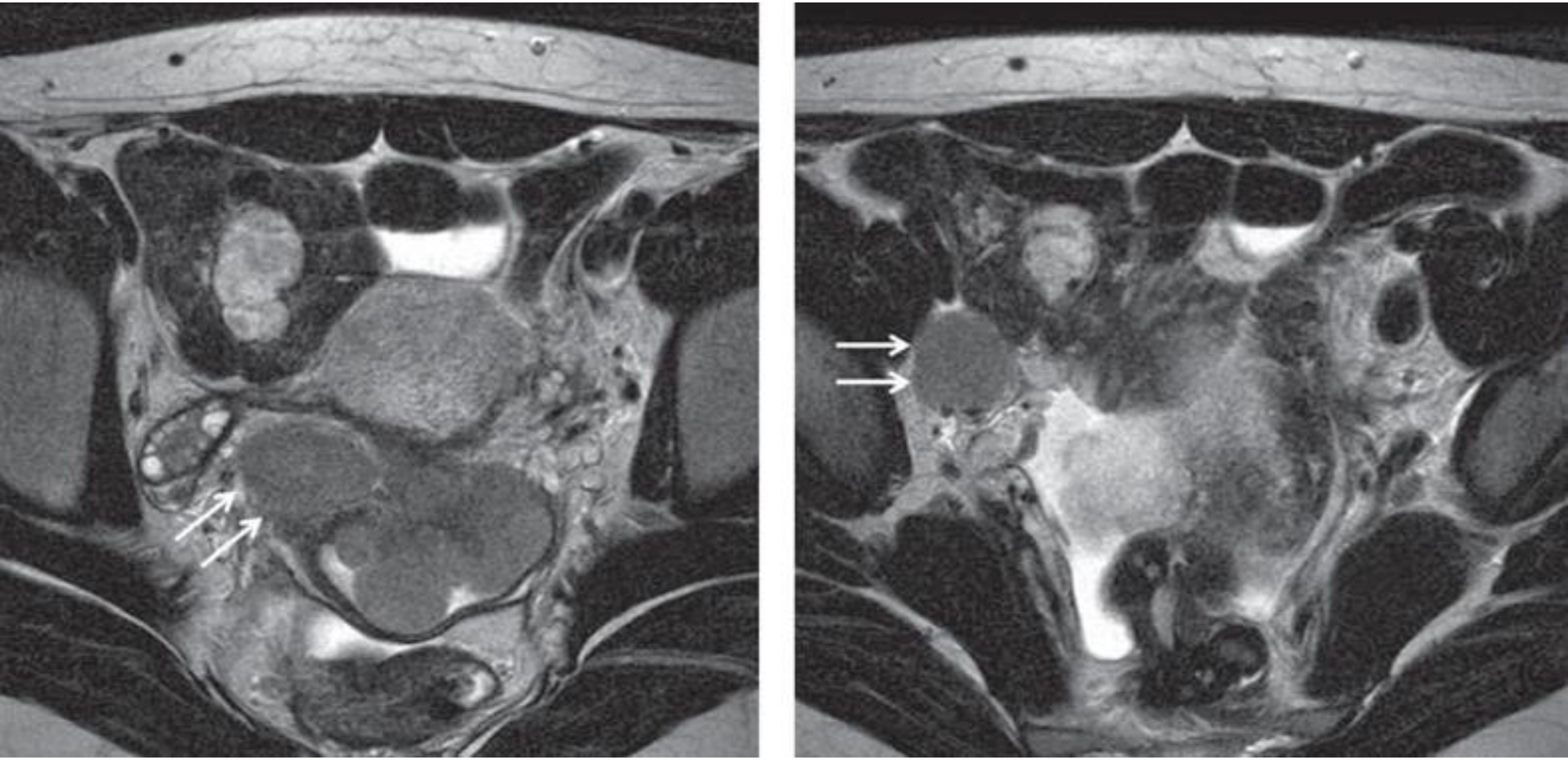


Figure 1. Pattern of relapses.

How can one better assess paraaortic node status?

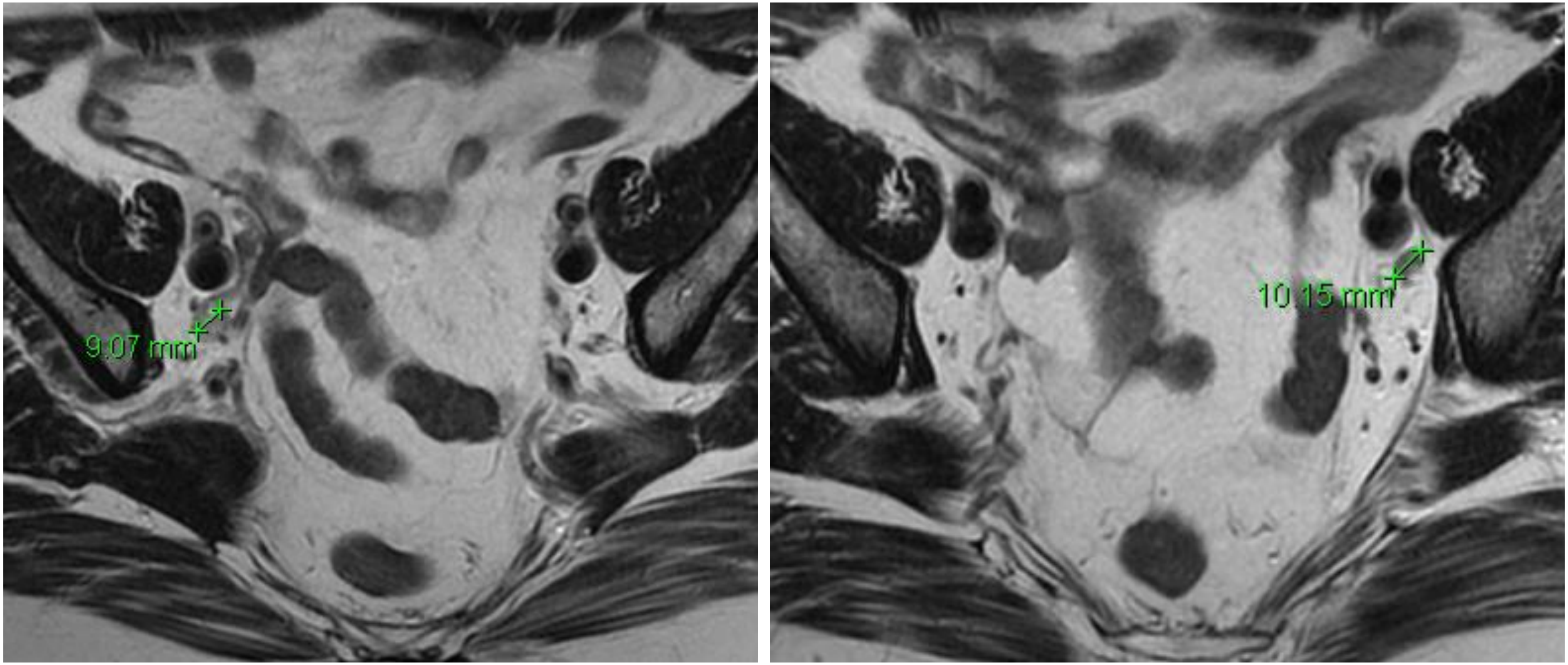
Nodal assessment

MRI ≥ CT-scanning for nodal involvement assessment



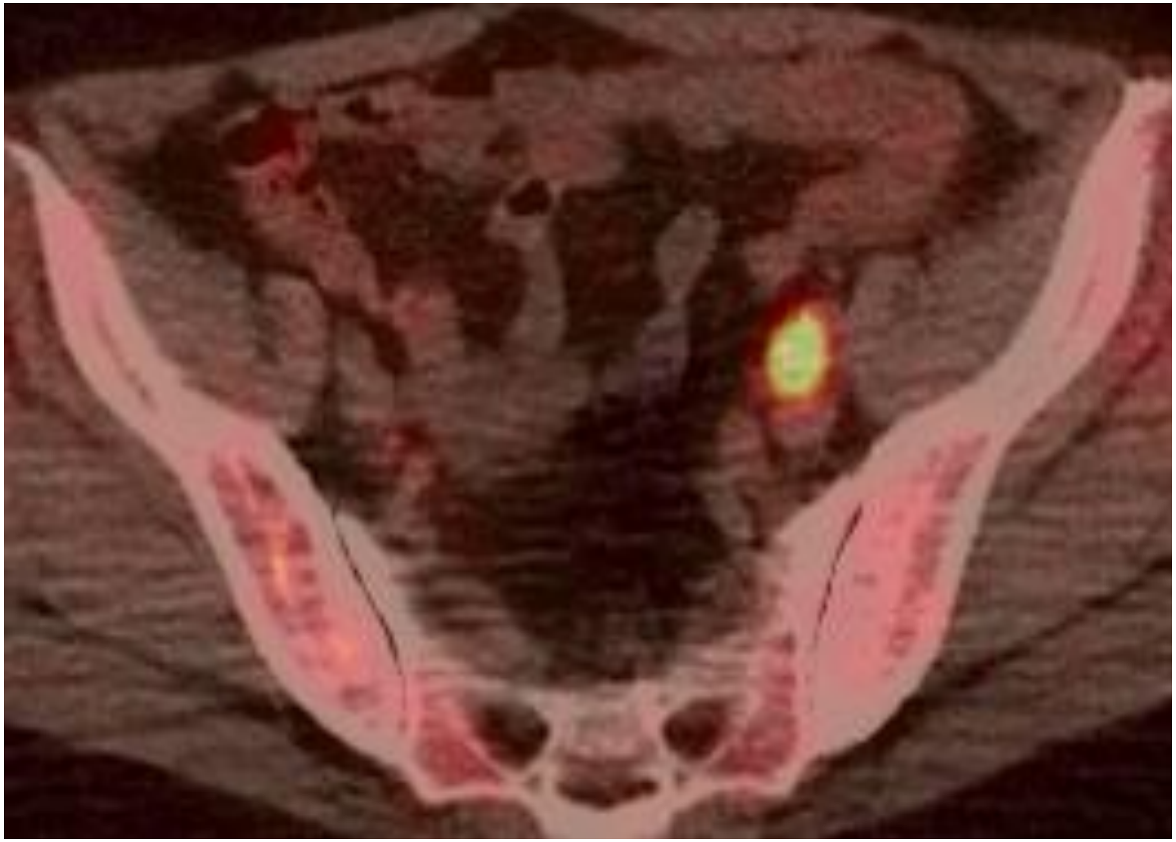
Nodal assessment

MRI ≥ CT-scanning for nodal involvement assessment



Nodal assessment

Role of PET-CT



Role of PET-CT advanced stage

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

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

Cancer Treatment Reviews (2008) 34, 671–681

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

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

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

Prognostic value of PET-CT

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

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

July 2000-March 2009 560 patients

J Clin Oncol 2010;28:2108-13

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

FIGO Stage	Total No. of Patients	No. of Lymph Nodes		Lymph Node Type: Pelvic		Para-Aortic		Supra-clavicular	
		No.	%	No.	%	No.	%	No.	%
IA1	1	1	100	0		0		0	
IA2	11	10	91	1	9	0		0	
IB1	146	118	81	28	19	3	2	0	
IB2	81	40	49	41	51	7	9	1	1
IIA	14	7	50	7	50	3	21	1	7
IIB	161	74	46	87	54	27	17	6	4
IIIA	4	2	50	2	50	1	25	1	25
IIIB	111	36	32	75	68	37	33	12	11
IVA	11	5	45	6	55	3	27	0	
IVB	20	3	15	17	85	12	60	10	50
All	560	199	34	264	47	93	17	31	6

Prognostic value of PET-CT

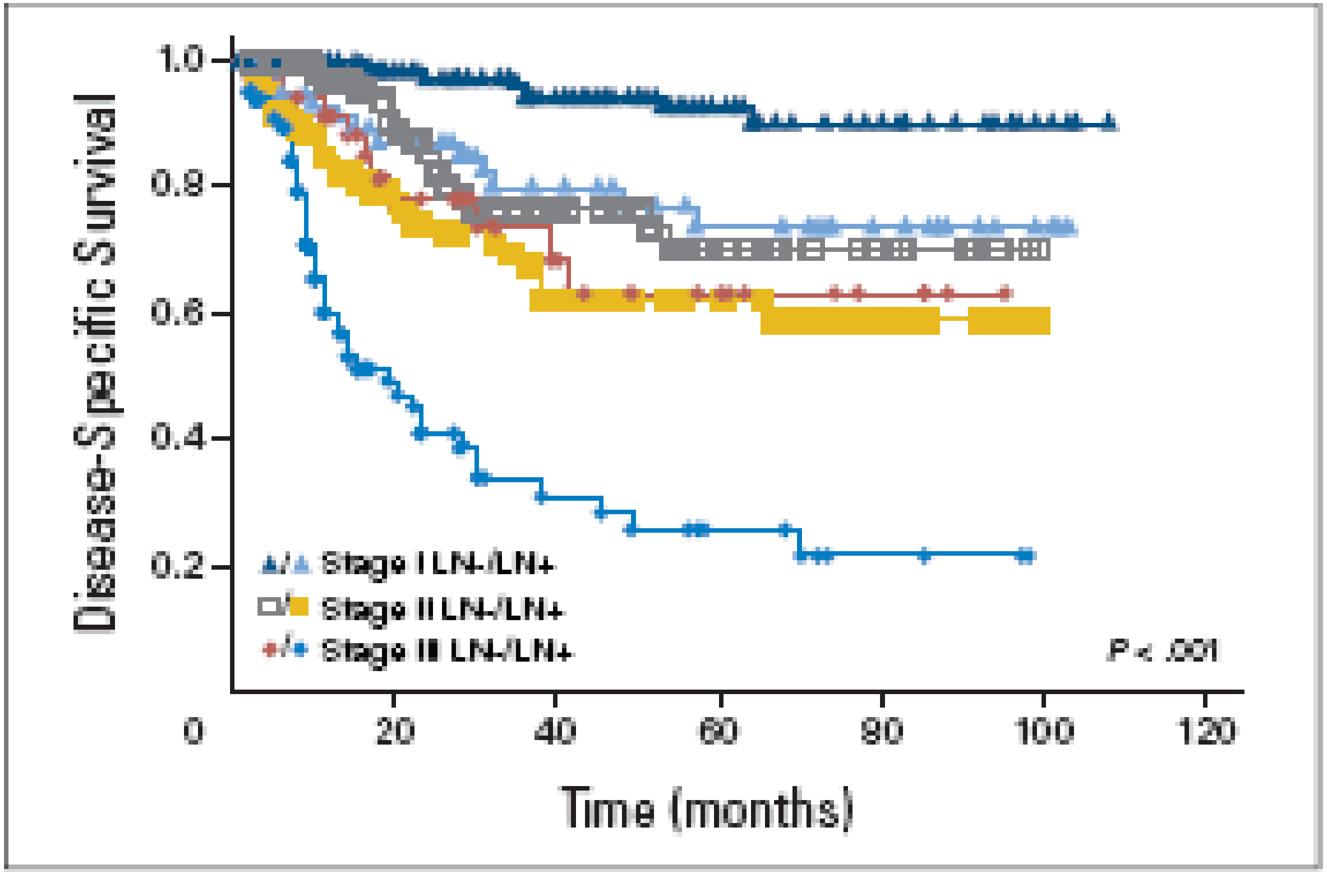


Fig 1. Kaplan-Meier disease-specific survival divided by International Federation of Gynecology and Obstetrics stage and positron emission tomography (PET) lymph node (LN) status: stage I, PET negative (dark blue triangle); stage I, PET positive (light blue triangle); stage II, PET negative (gray square);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

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

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

Lancet Oncol 2012; 13: e212–

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

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

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

Lancet Oncol 2012 13:212-20

VOLUME 31 · NUMBER 24 · AUGUST 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

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

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

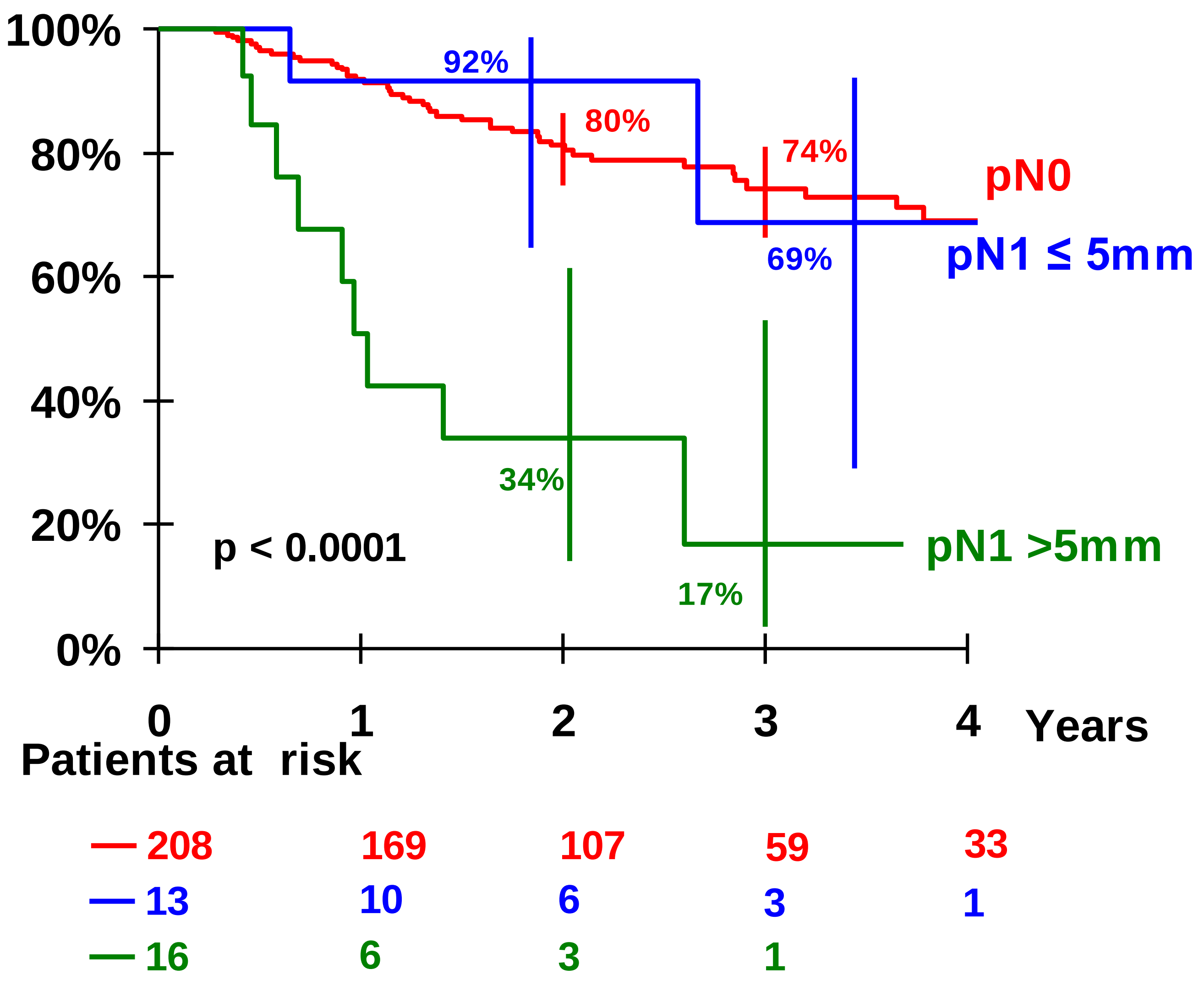
Patient characteristics

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

88 %

29 (11%) PA+ : False negative rate

EFS according to the size of + PA nodes



Questions

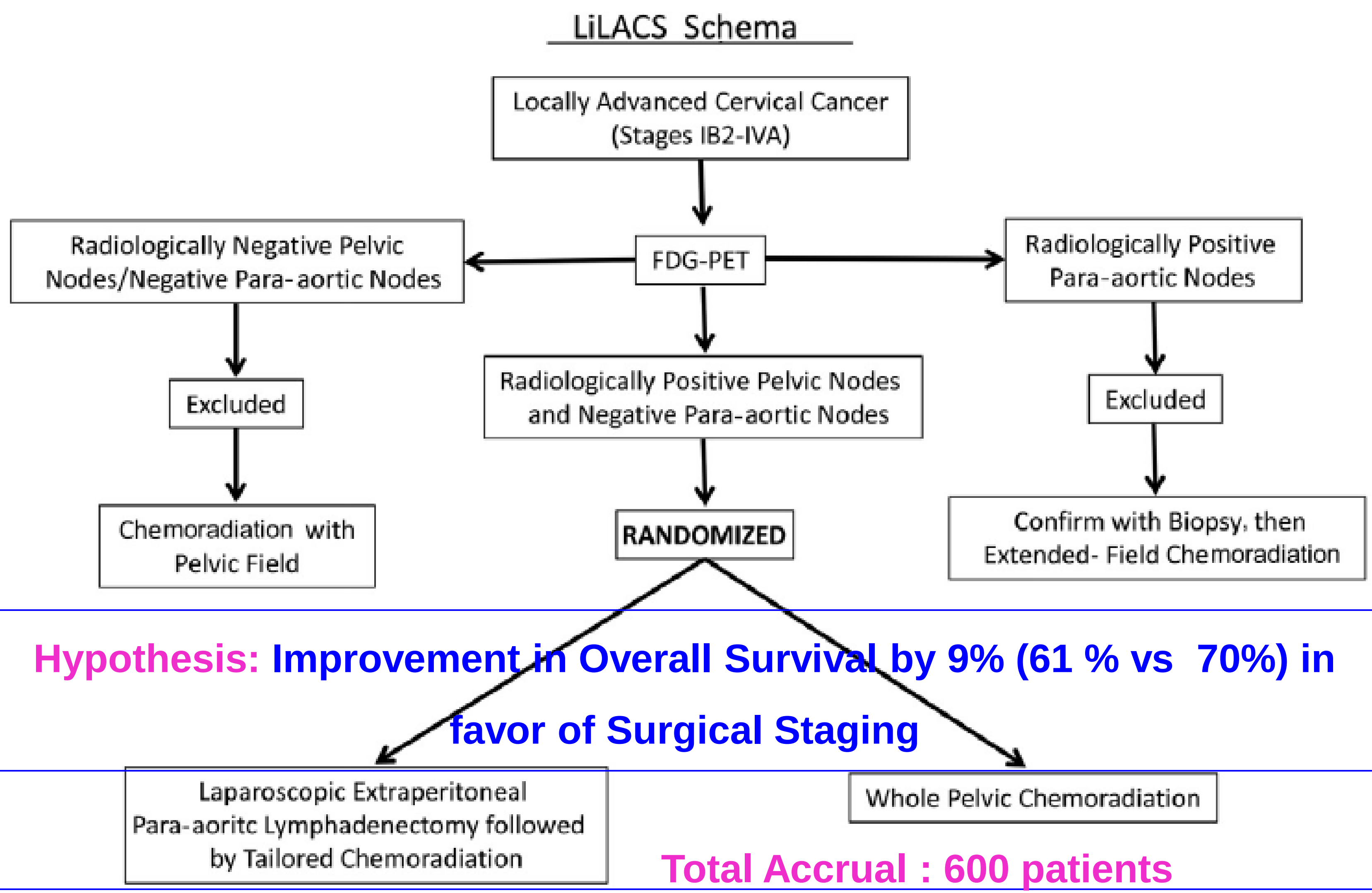
- Is it really necessary to irradiate paraaortic lymph nodes in case of mets < 5mm?

- Is chemotherapy alone able to potentially sterilize paraaortic micro metastases?

- What is the real potential benefit of paraaortic lymphadenectomy?

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

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

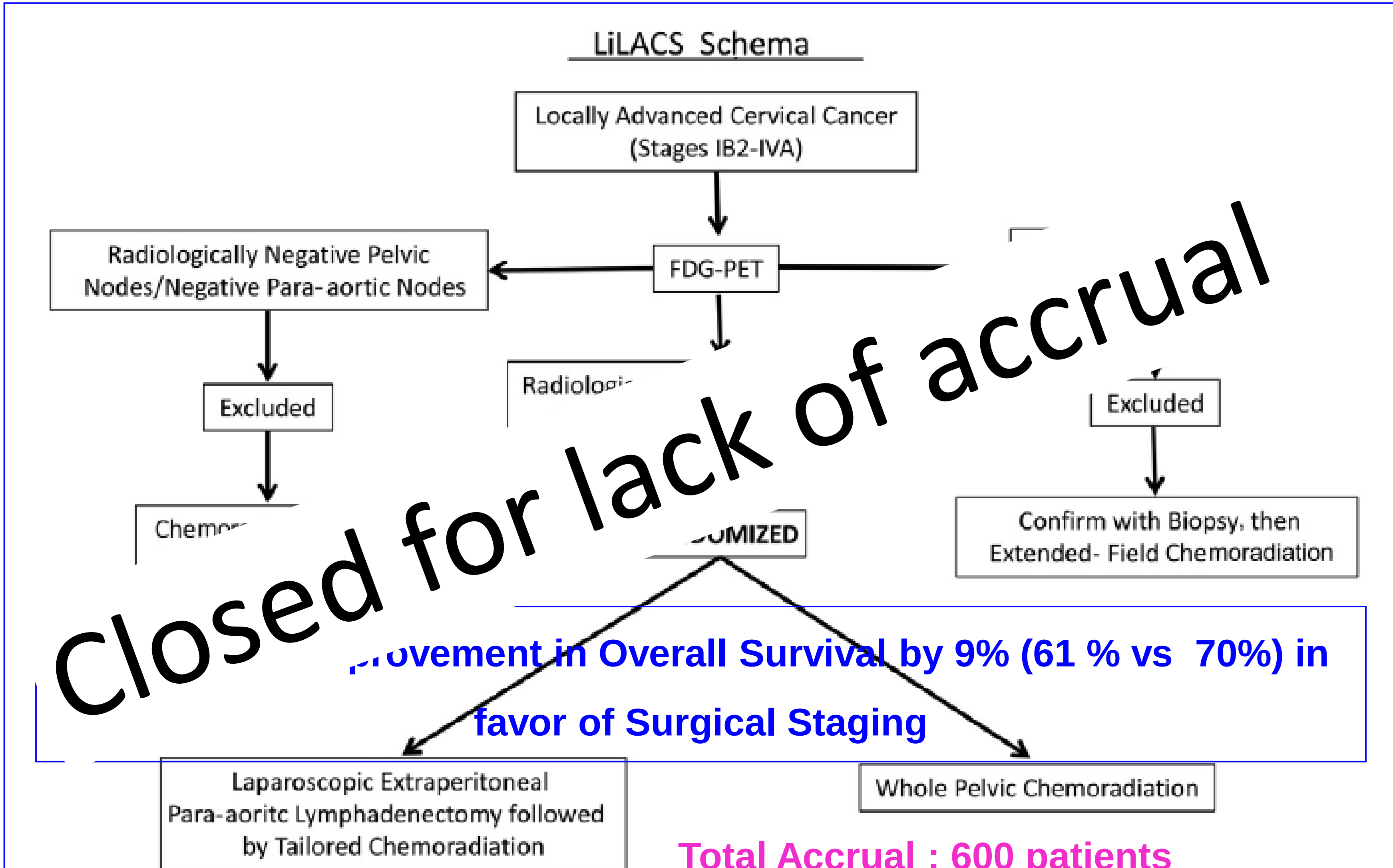


Hypothesis: Improvement in Overall Survival by 9% (61 % vs 70%) in favor of Surgical Staging

Total Accrual : 600 patients

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

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



Multicenter Phase III Intergroup Trial of the German Radiation Oncology Group and the Gynecologic Cancer Group

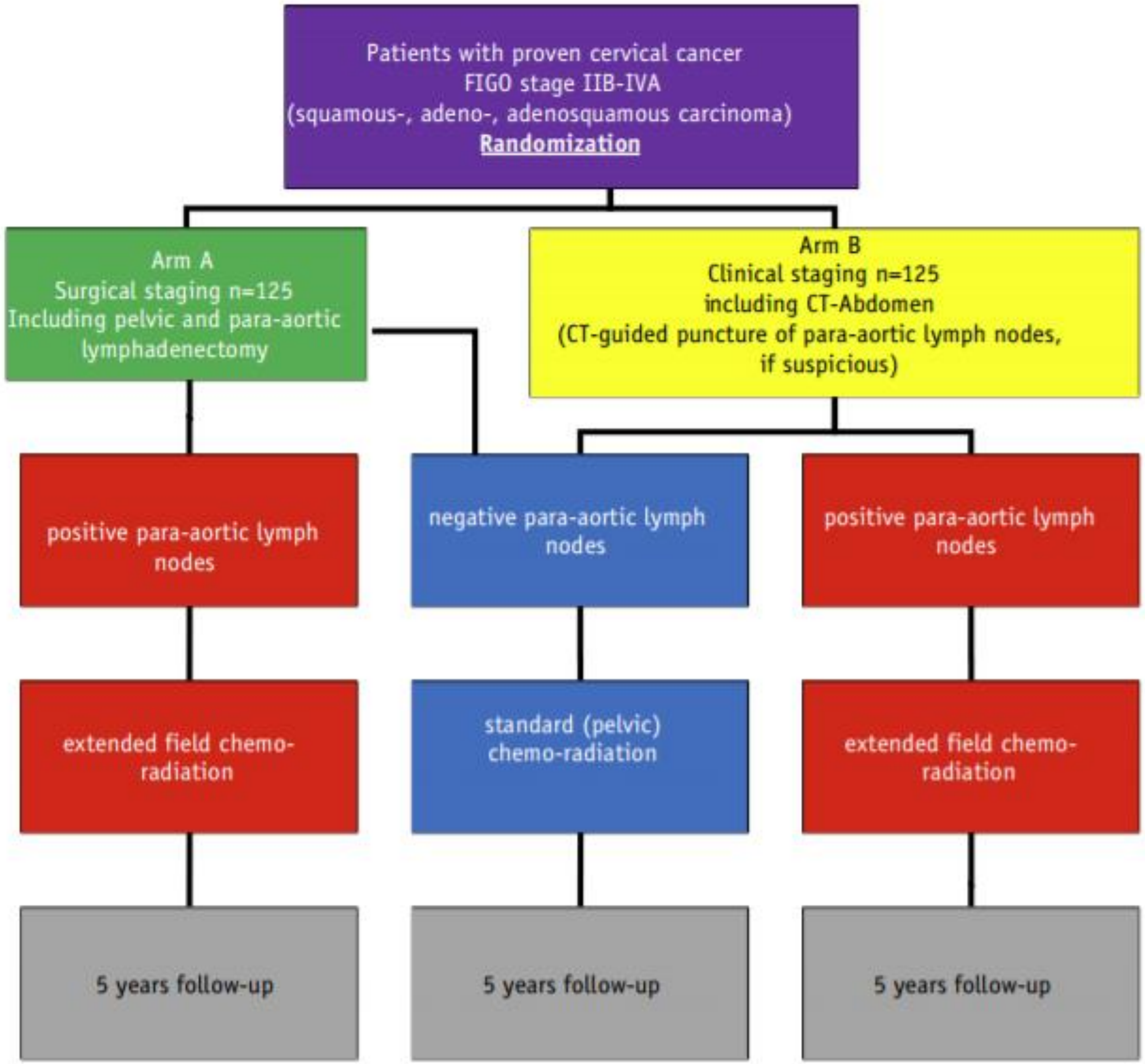


Fig. 1. Flow chart of Uterus-11 trial. *Abbreviations:* CT = computed tomography; FIGO = International Federation of Gynecology and Obstetrics.

Role of Surgical Versus Clinical Staging in Chemoradiated FIGO Stage IIB-IVA Cervical Cancer Patients—Acute Toxicity and Treatment Quality of the Uterus-11 Multicenter Phase III Intergroup Trial of the German Radiation Oncology Group and the Gynecologic Cancer Group

Simone Marnitz, MD,[*] Peter Martus, PhD,[†] Christhardt Köhler, MD,[‡] Carmen Stromberger, MD,[*] Elke Asse, MD,[§] Peter Mallmann, MD,[||] Heinz Schmidberger, MD,[¶] Renato José Affonso Júnior, MD,[#] João Soares Nunes, MD,[**] Jalid Sehouli, MD,[††] and Volker Budach, MD[*]

Int J Radiation Oncol Biol Phys 94:243-53; 2016

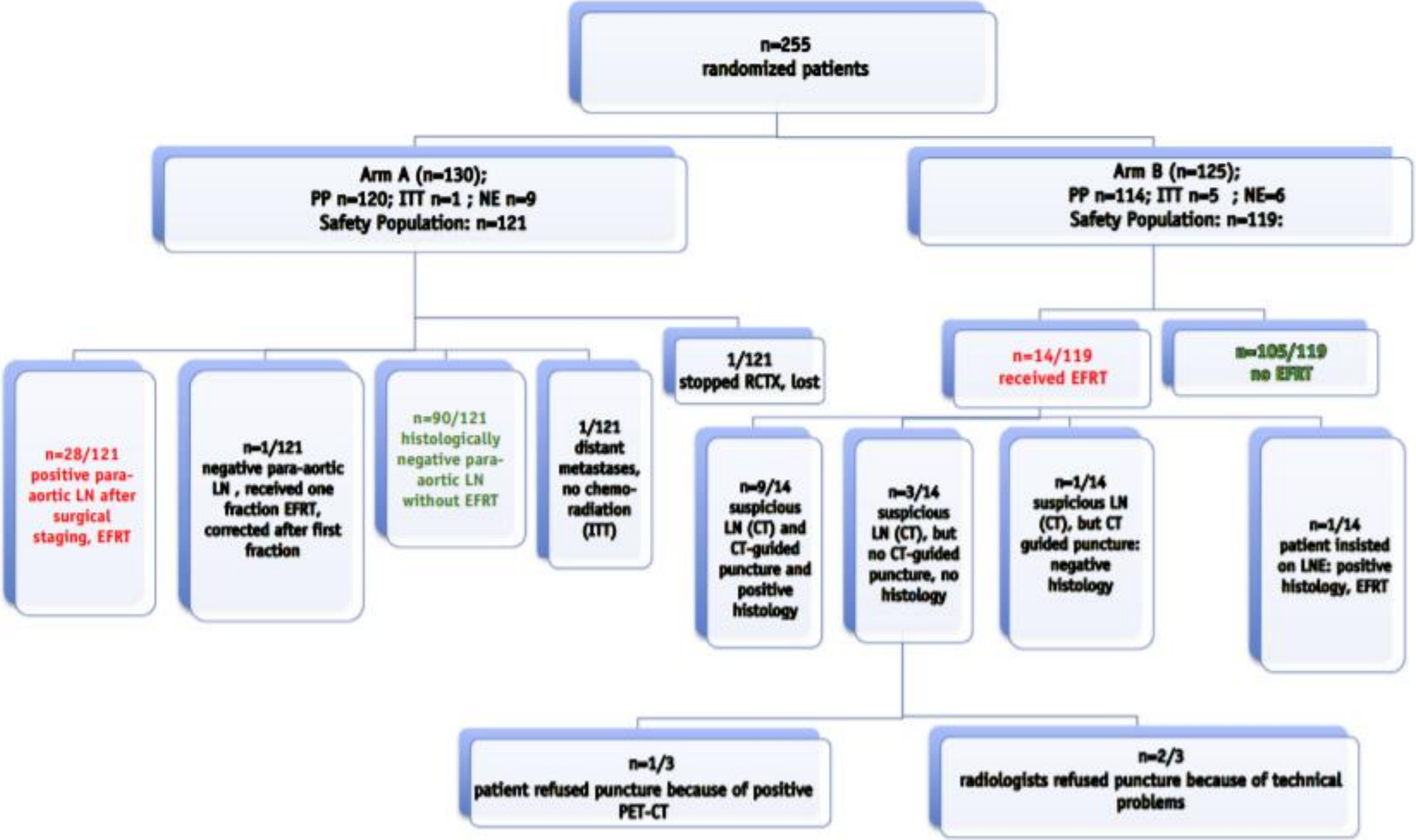


Fig. 3. Para-aortic upstaging according to randomization result. *Abbreviations:* CT = computed tomography; EFRT = extended field radiation therapy; ITT = intention to treat; LN = lymph nodes; LNE = lymphonodectomy; NE = not eligible; PET-CT = positron emission tomography computed tomography; PP = per protocol; RCTX = chemoradiation therapy.

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

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

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

Int J Gynecol Cancer 2016;26: 169-75

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

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

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

Int J Gynecol Cancer 2016;26: 169-75

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

Pretherapeutic staging of locally advanced cervical cancer: Inframesenteric paraaortic lymphadenectomy accuracy to detect paraaortic metastases in comparison with infrarenal paraaortic lymphadenectomy

Gynecol Oncol 147:340 –4;2017

Henri Azaïs [a,1], Louise Ghesquière [a], Clothilde Petitnicolas [a], Yves Borghesi [a], Emmanuelle Tresch-Bruneel [b], Abel Cordoba [c], Fabrice Narducci [a], Lucie Bresson [a], Eric Leblanc [a,*]

Table 3
Lymph nodes characteristics.

	IM (N = 56)	IR (N = 63)	p
	n (%)	n (%)	
Lymphadenectomy para-aortic	56/56 (100)	63/63 (100)	
Positive lymph nodes	10/56 (17.9)	10/63 (15.9)	0.77
Total number of para-aortic lymph nodes	N = 56	N = 62	
Median – [range]	13 [4–37]	21 [9–46]	
Mean	13.6 ± 6.3	23.7 ± 9.1	<0.001
Total number of positive para-aortic lymph nodes	N = 10	N = 10	
Median – [range]	2 [1 – 22]	5 [1 – 10]	
Mean	4.9 ± 6.7	5.2 ± 3.8	0.40

5. Conclusion

Through this series, we can confirm that IM-PALND appears to be as effective as IR-PALND to assess paraaortic nodal status in locally advanced cervical cancer, whatever its pathological subtype (glandular or squamous cell carcinoma). Cervical cancer histological subtype should not influence surgical decisions regarding para-aortic lymph node dissection strategies among patients with negative PET/CT imaging at paraaortic level.

Table 5
Lymph nodes, PET/CT and surgery subtype characteristics.
Histological subtypes comparison.

	Squamous tumor (N = 86)	Glandular tumor (N = 27)	p
	n (%)	n (%)	
All patients (IM ± IR)			
PALND +	15/85 (17.7)	5/27 (18.5)	1.00
PET/CT + in PLN	23/74 (31.1)	4/24 (16.7)	0.17
PALND +/PET/CT + in PLN	7/23 (30.4)	1/4 (25)	1.00
PALND +/PET/CT − in PLN	6/51 (11.8)	4/20 (20)	0.45
IM patients			
PALND +	7/42 (16.7)	3/12 (25)	0.67
PET/CT + in PLN	8/37 (21.6)	2/11 (18.2)	1.00
PALND +/PET/CT + in PLN	2/8 (25)	0/2 (0)	1.00
PALND +/PET/CT − in PLN	3/29 (10.3)	3/9 (33.3)	0.13
IR patients			
PALND +	8/43 (18.6)	2/15 (13.3)	1.00
PET/CT + in PLN	15/37 (40.5)	2/13 (15.4)	0.17
PALND +/PET/CT + in PLN	5/15 (33.3)	1/2 (50)	1.00
PALND +/PET/CT − in PLN	3/22 (13.6)	1/11 (9.1)	1.00

*Positive PET/CT = abnormal FDG ([^{18}F]-fluoro-2-deoxy-D-glucose) uptake.
**Negative PET/CT = normal FDG ([^{18}F]-fluoro-2-deoxy-D-glucose) uptake.
IM = infra mesenteric.
IR = infra renal.
PALND = para-aortic lymph node dissection.
PLN = pelvic lymph nodes.

PAo irradiation :
Which technique?
Which dose?

Extended field radiation with PAo node inclusion

Previous studies of irradiation to paraaortic metastasis[a]

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

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

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

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

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

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

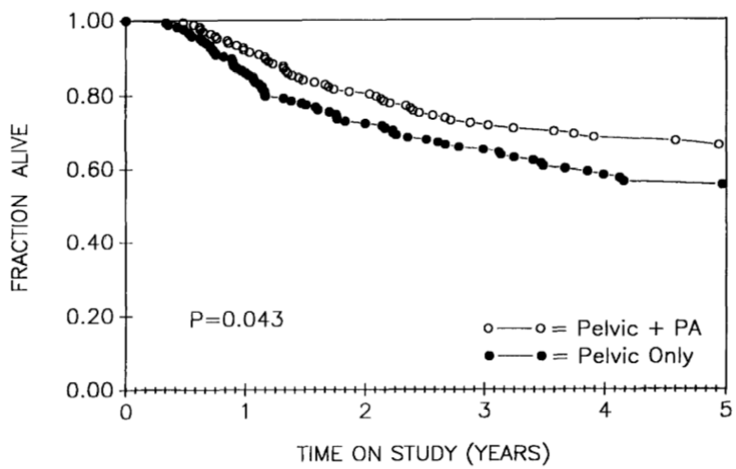
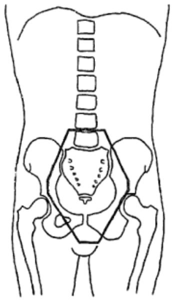
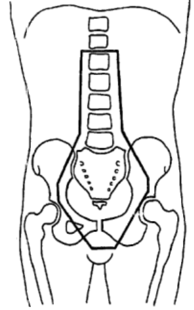


Fig. 1. RTOG 79-20 survival by assigned treatment (Kaplan-Meier).



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



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

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

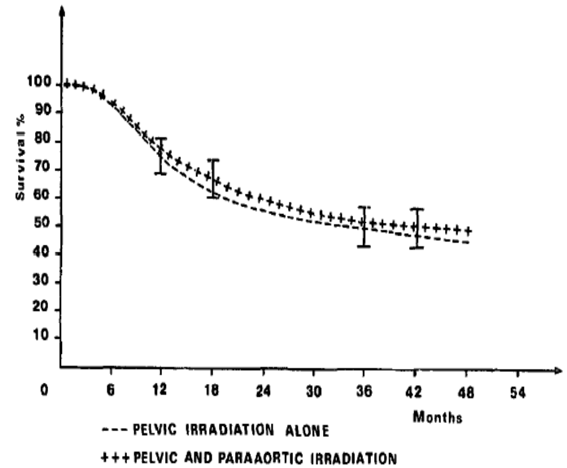


Fig. 3. Disease-free survival (lifetable method).

Conclusions:

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

Role of IMRT

IMRT for PAo RT

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

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

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

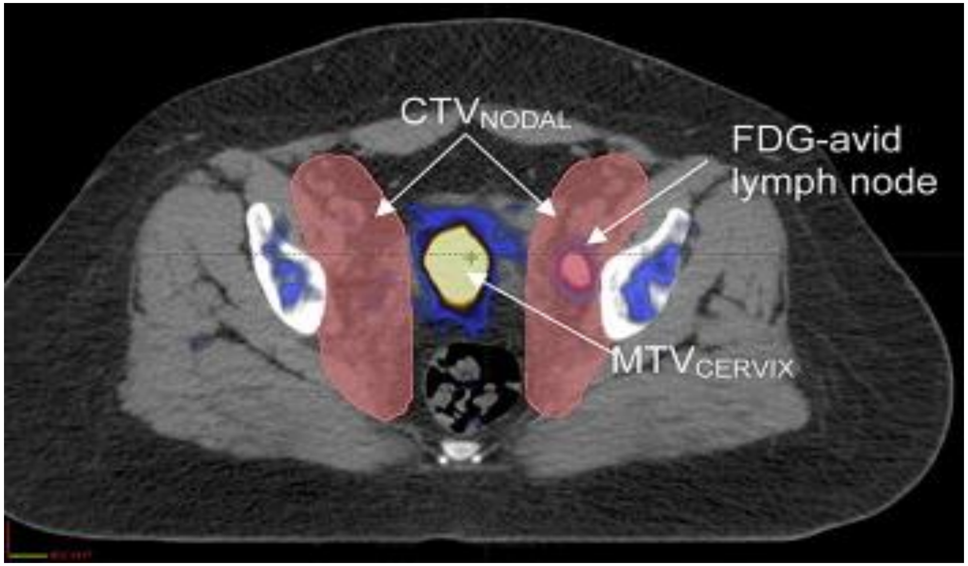
Gouy Lancet Oncol 2012;13: 212-20

PET- CT Based IMRT

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

Kidd et al., IJROBP 2010

PET-CT Based IMRT: Outcome



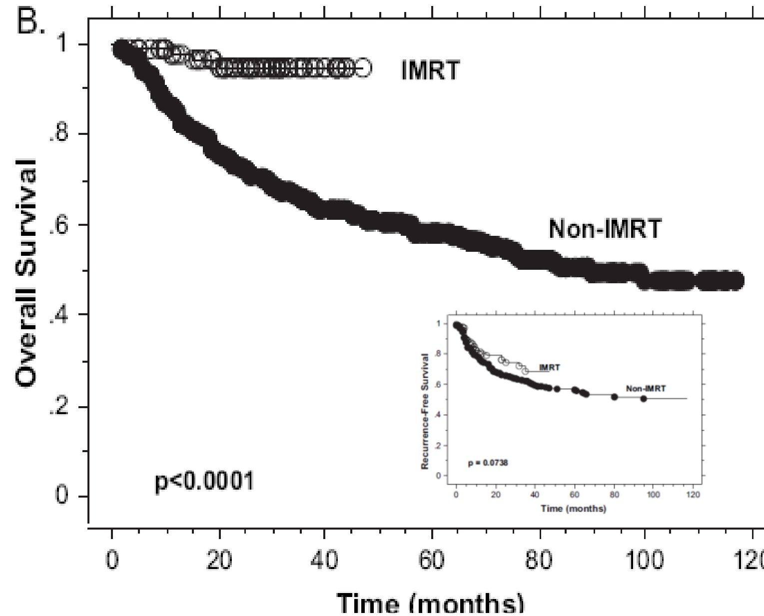


Table 2. Distribution of recurrences for the IMRT, non-IMRT, and total groups

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

Kidd et al., IJROBP 2010

PET-CT Based IMRT: Toxicities

ACUTE toxicities

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

LATE toxicities: Grade 3 or more GI and GU toxicities

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

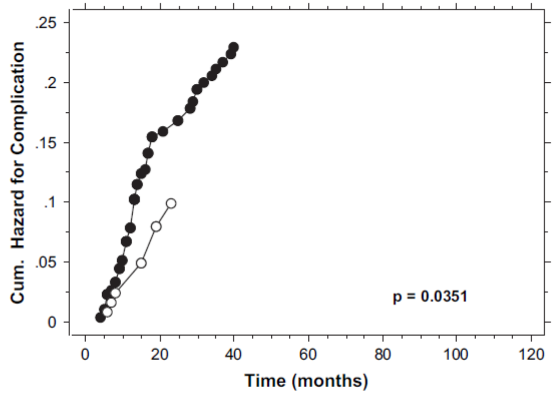


Fig. 4. Cumulative hazard function rates of bowel or bladder complication for the intensity-modulated radiation therapy (IMRT) (○) and non-IMRT (●) groups.

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

Grigsby et al., IJROBP 2010

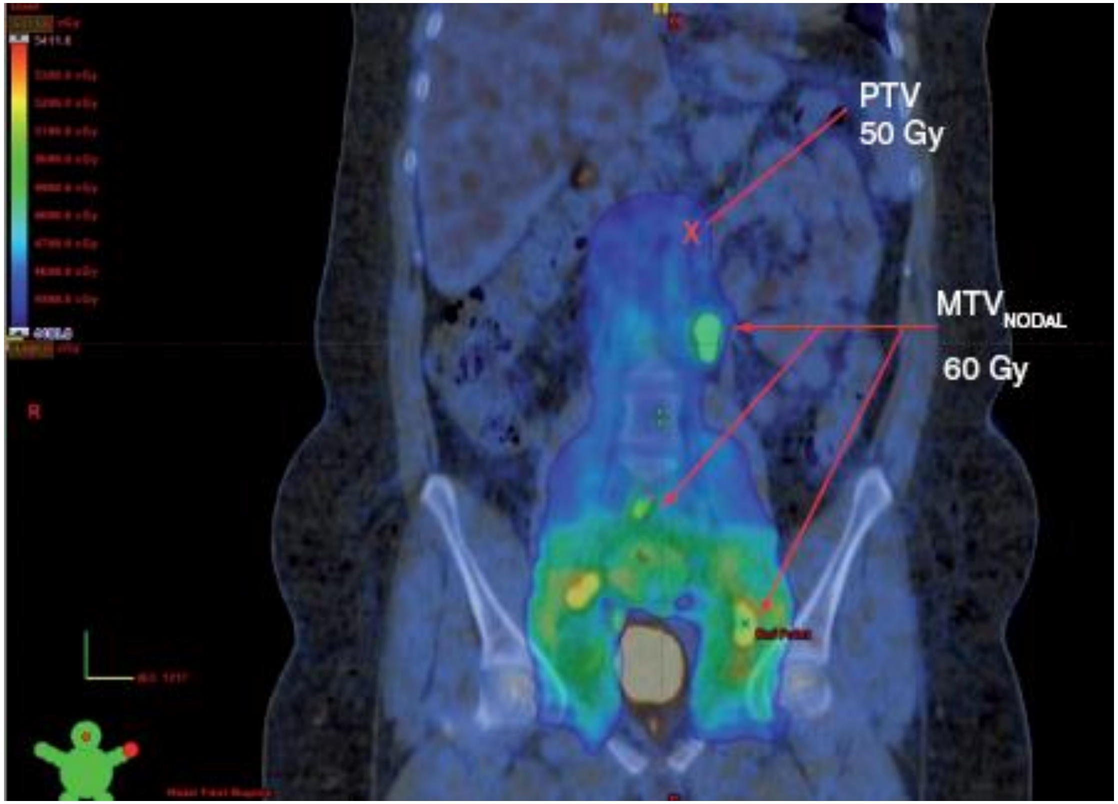
Role of Surgical Versus Clinical Staging in Chemoradiated FIGO Stage IIB-IVA Cervical Cancer Patients—Acute Toxicity and Treatment Quality of the Uterus-11 Multicenter Phase III Intergroup Trial of the German Radiation Oncology Group and the Gynecologic Cancer Group

Simone Marnitz, MD,* Peter Martus, PhD,† Christhardt Köhler, MD,‡ Carmen Stromberger, MD,* Elke Asse, MD,§ Peter Mallmann, MD,|| Heinz Schmidberger, MD,¶ Renato José Affonso Júnior, MD,# João Soares Nunes, MD,** Jalid Sehouli, MD,†† and Volker Budach, MD*

Int J Radiation Oncol Biol Phys 94:243-53; 2016

Technique	3D (n=78)	IMRT (n=92) 60%	P value
grade 3 toxicity			
leucocytopenia	30 (32.6%)	27 (36.0%)	P=0.487
thrombocytopenia	3 (3.3%)	2 (2.7%)	P=0.020
anemia	0 (0%)	6 (8.0%)	P<0.00
diarrhea	3 (3.3%)	1 (1.3%)	P=0.322
nausea	13 (14.1%)	1 (1.3%)	P<0.00
vomiting	7 (7.6%)	0 (0%)	P<0.00
GU	0 (0%)	0 (0%)	n.s.
VAG	0 (0%)	0 (0%)	n.s.
NEURO	0 (0%)	0 (0%)	n.s.
OTO	0 (0%)	0 (0%)	n.s.

Which dose to the PAo nodes?



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

Which dose to the PAo nodes?

LYMPH NODE CONTROL IN CERVICAL CANCER

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

208 patients

Table 2. Para-aortic lymph nodes

Lymph node status	Patients (no.)	Mean lymph node dose (Gy)	Paraaortic lymph node failure
PET negative	175	0	1/175
PET positive/CT ≤1 cm	24	43.9*	0/24
PET positive/CT >1 cm to ≤2 cm	5	45*	0/5
PET positive/CT >2 cm to ≤3 cm	4	33.9	0/4
Total	208	—	1/208

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

Which dose to the PAo nodes?

Lymph node as the only failure rate <2%

Table 4. Pelvic lymph nodes

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

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

Table 5. Paraaortic lymph nodes

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

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

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

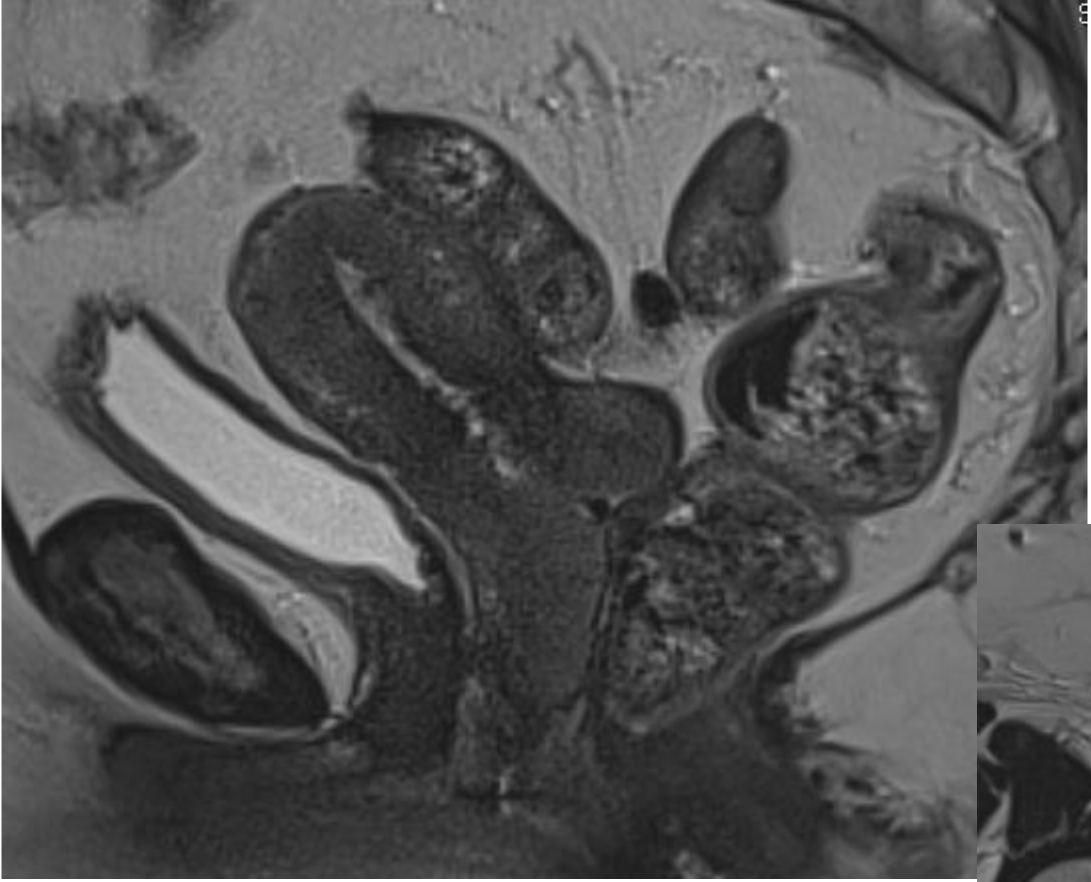
Which dose to the PAo nodes if macroscopic disease?

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

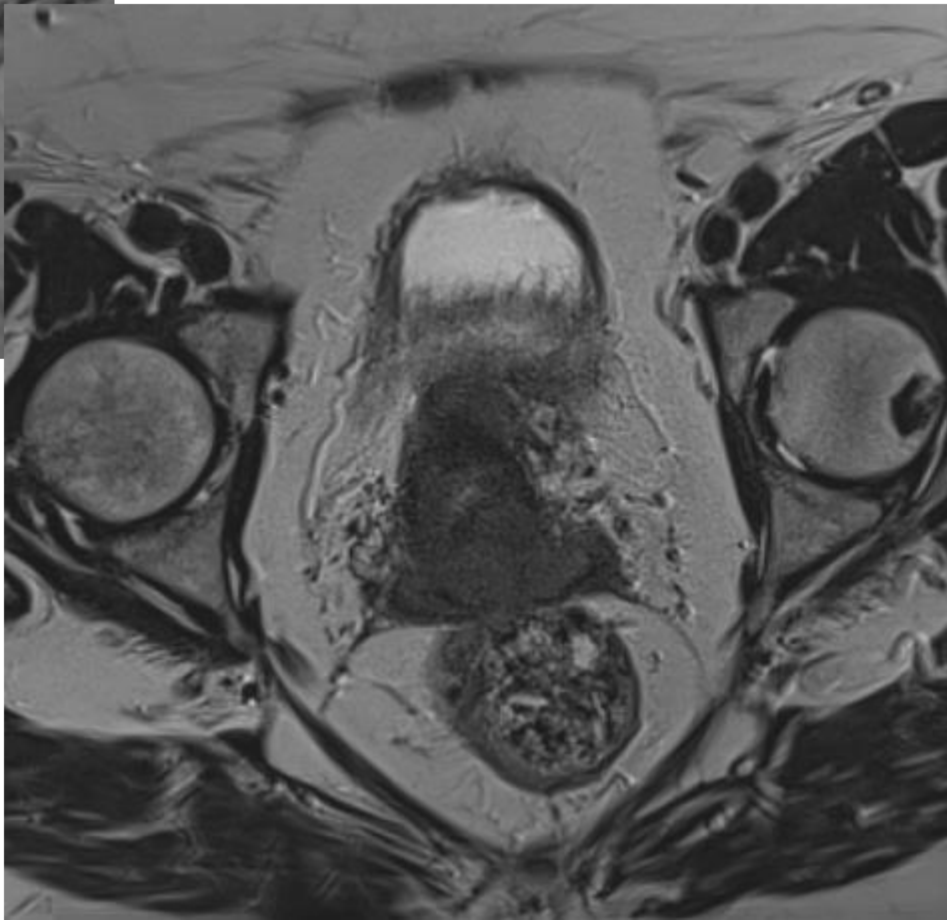
Nodal assessment in advanced cervix cancer : Conclusions

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

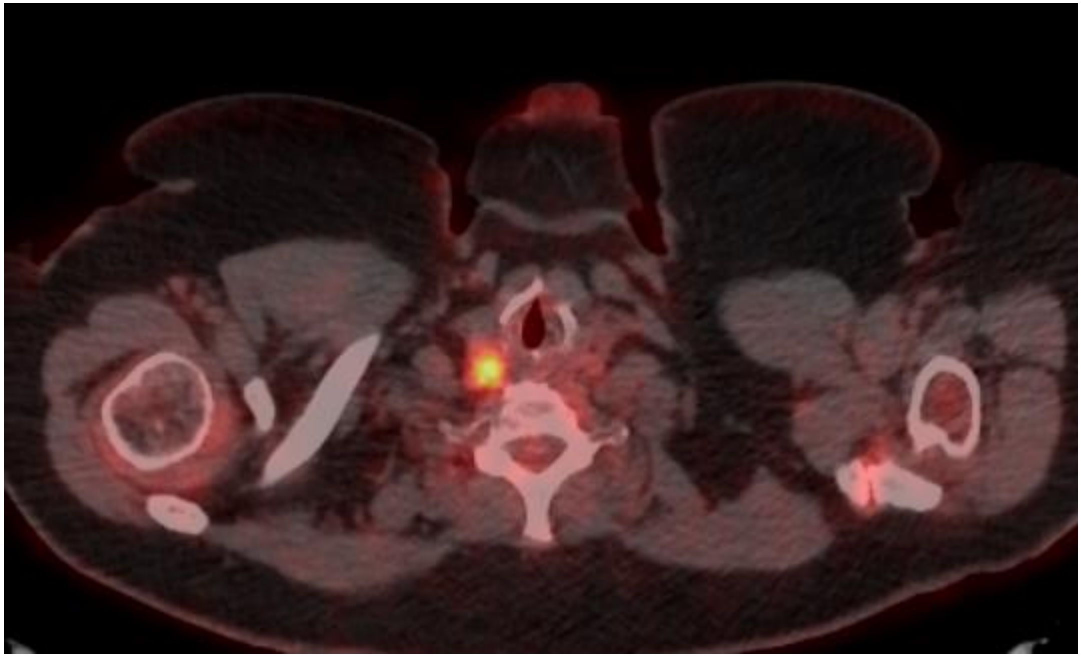

Ceci n'est pas une pomme



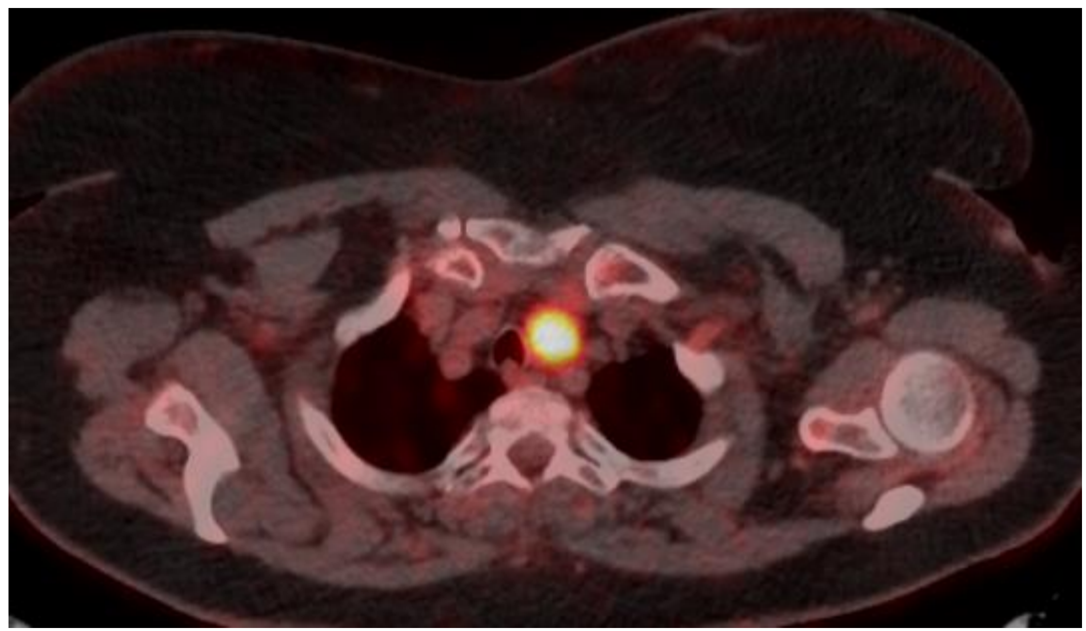
35 year old patient
Stage IIB
No lymph node at MRI



Mind PET-CT conclusions



Bilateral supra-clavicular lymph nodes



Mind PET-CT conclusions

Chirico The tired troubadour

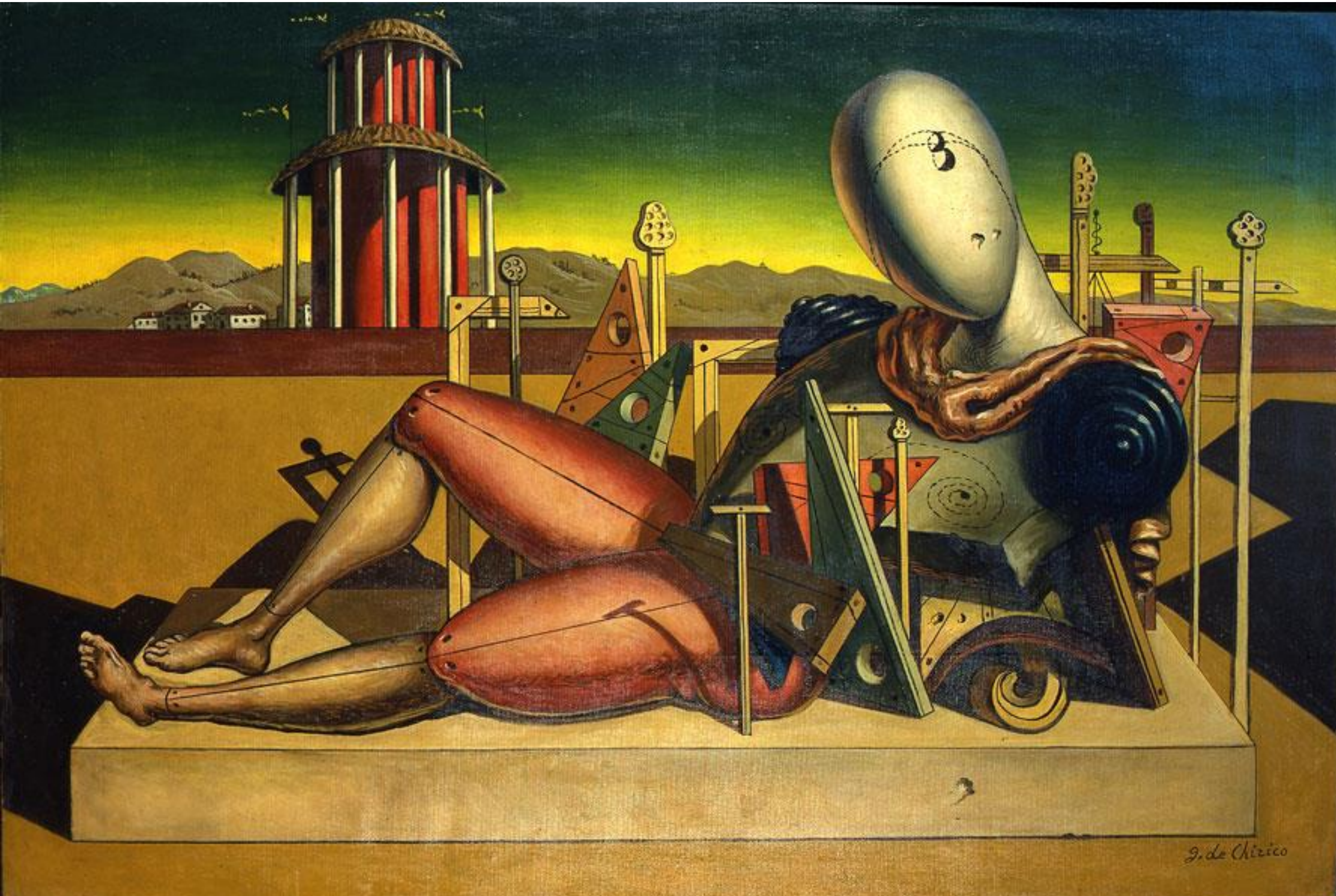


Image guidance, organ motion and ITV/PTV

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

Lucknow 2018

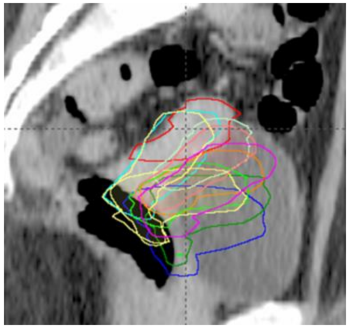
Prof Kari Tanderup

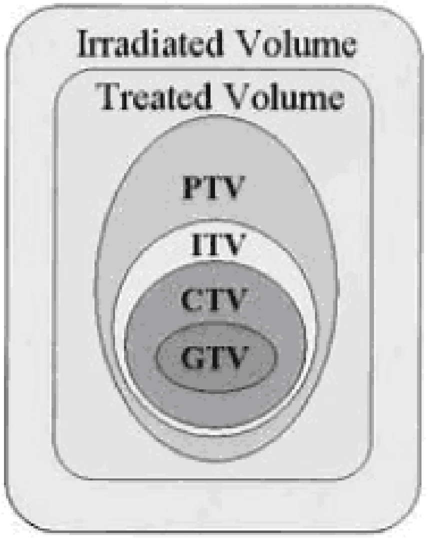
Prof Richard Pötter

Aarhus University Hospital

ITV and PTV

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

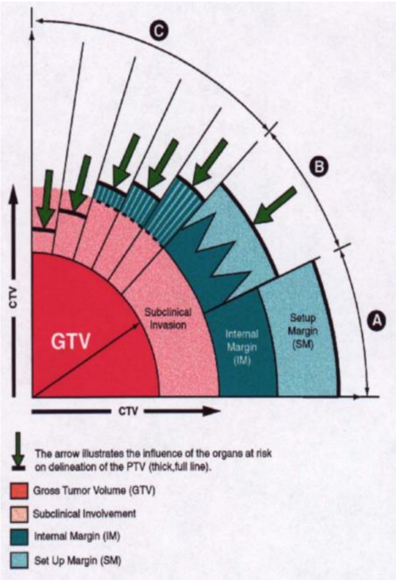




- **PTV: External variations**
  - **Beam positioning**
  - **Patient set-up (e.g. uncertainties when setting up according to skin marks)**

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

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



Do you use ITV margins in cervix cancer EBRT in your department?

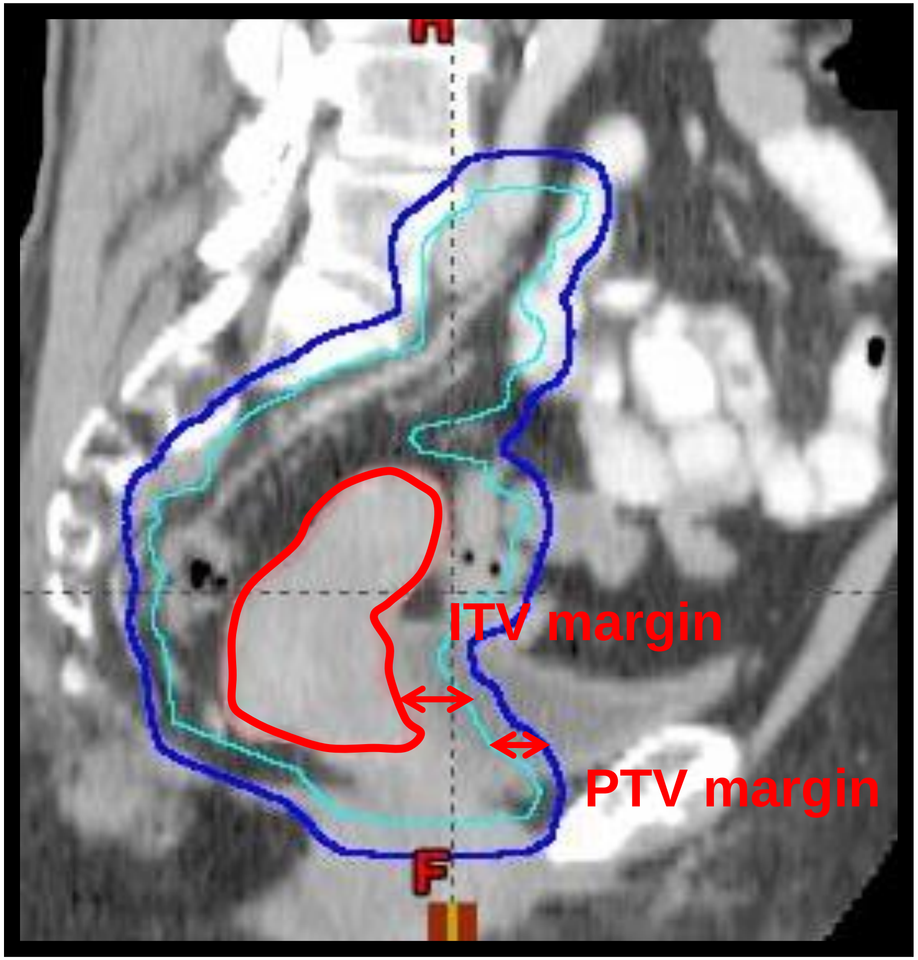
A. Yes
B. No

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

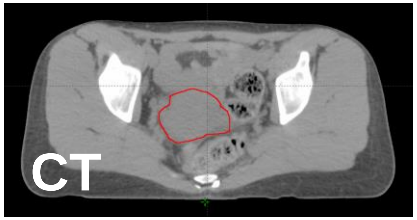
Margins in cervix cancer

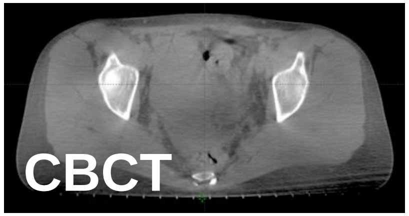
- Primary CTV
  - ITV margin
  - PTV margin
- Pathologic nodes
  - PTV margin
- Elective CTV
  - PTV margin
- Role of on-board imaging?



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

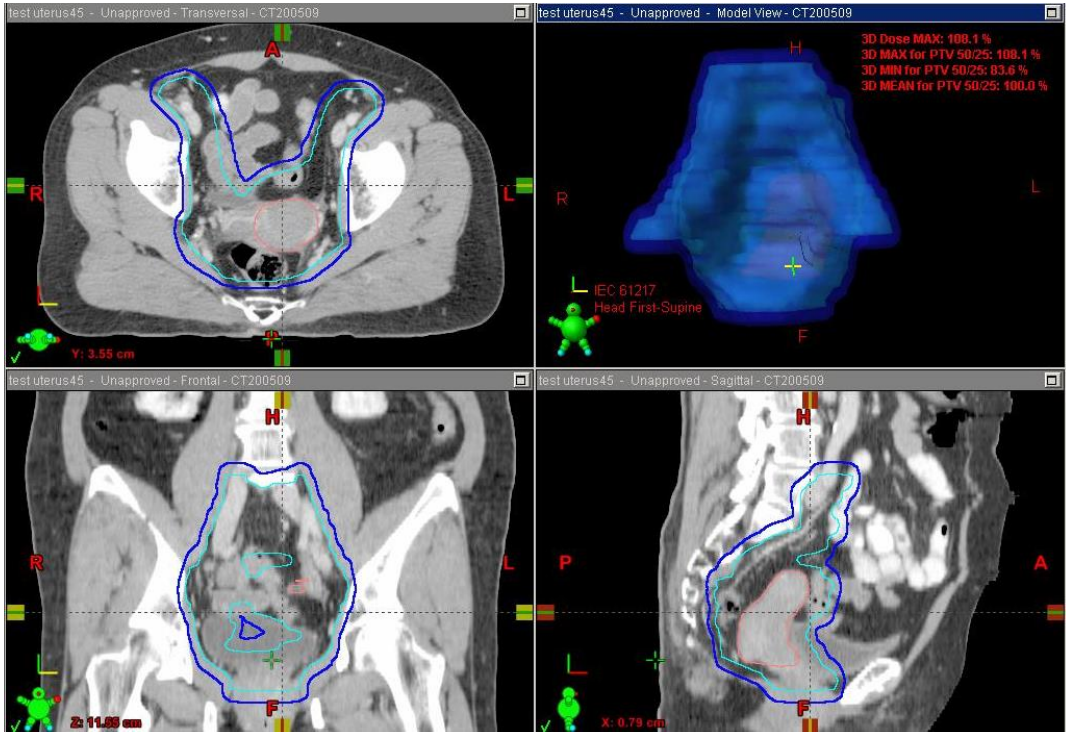
A. Bony fusion/evaluation
B. Fusion/evaluation on cervix
C. Fusion/evaluation on markers in cervix





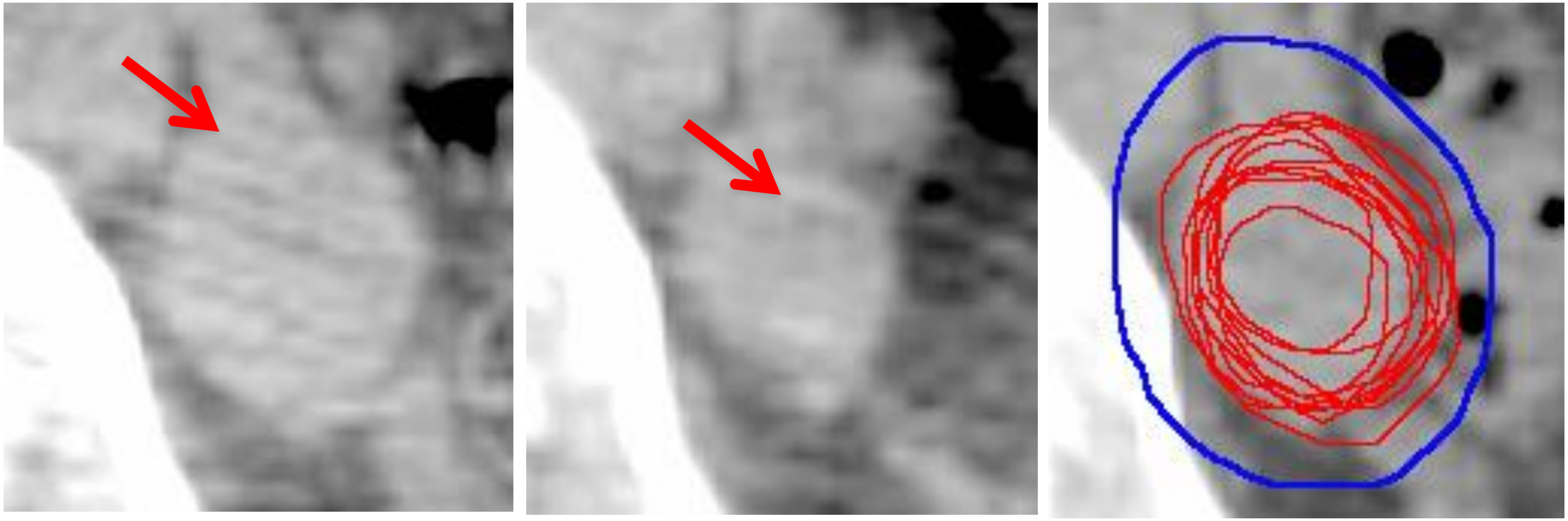
PTV elective target volume

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



PTV pathological lymph nodes

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



CBCT 1st treatment | CBCT 24th treatment | PTV (blue) GTV on 10 CBCT (red)

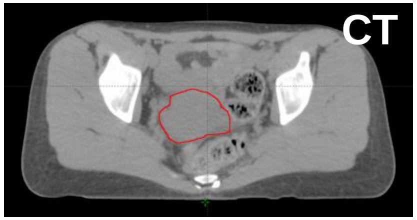
Anne Ramlov, Radiother Oncol, 2017

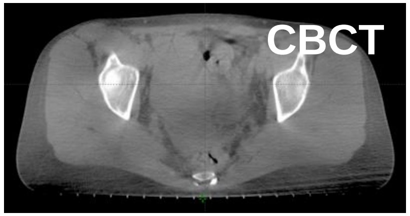
Which PTV margin do you apply for CTV-E?

A. ≤5 mm
B. 6-9 mm
C. ≥10 mm

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

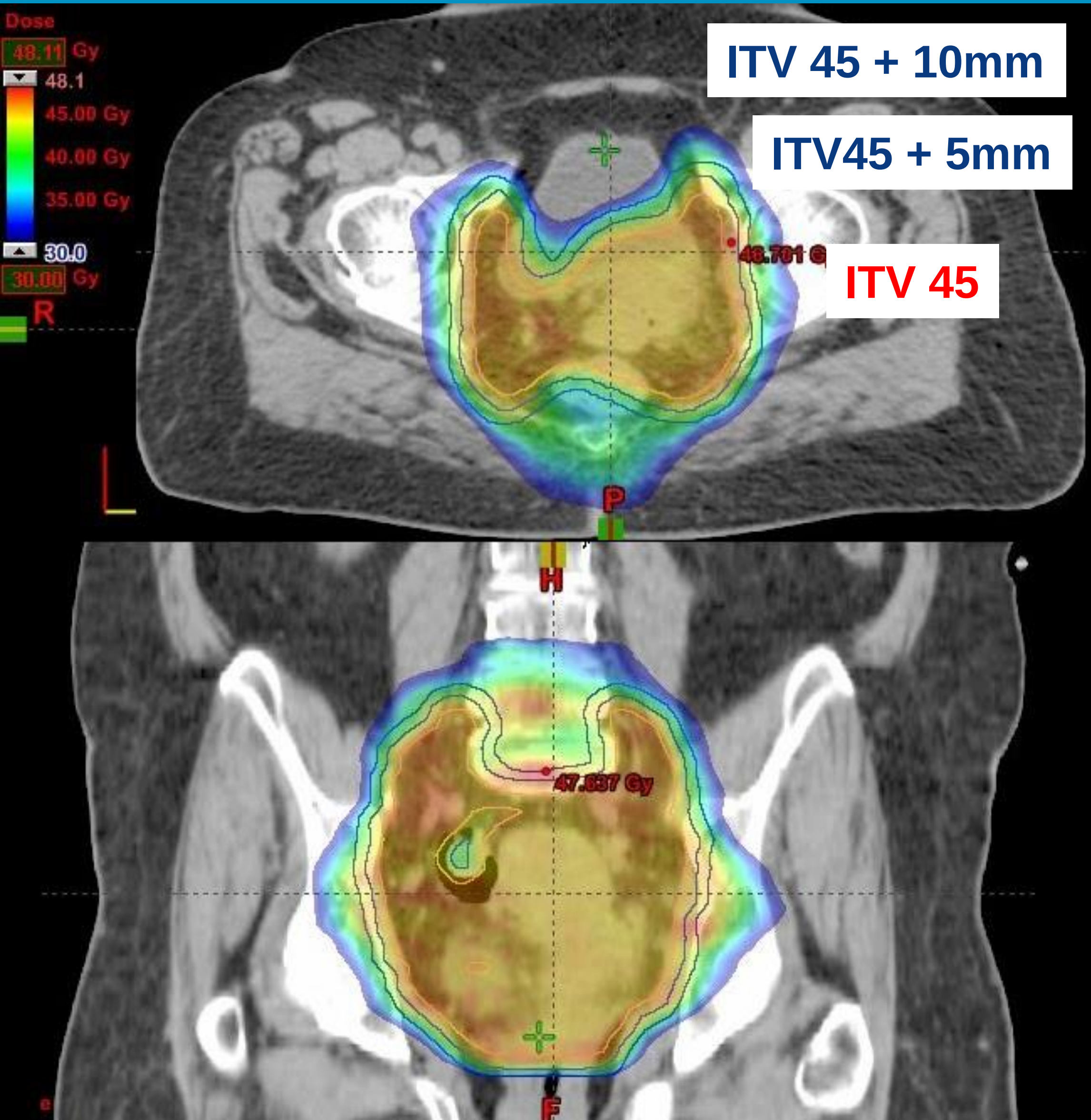
L.Laursen, RO 105 (2012) 220–225

Why does the margin matter?

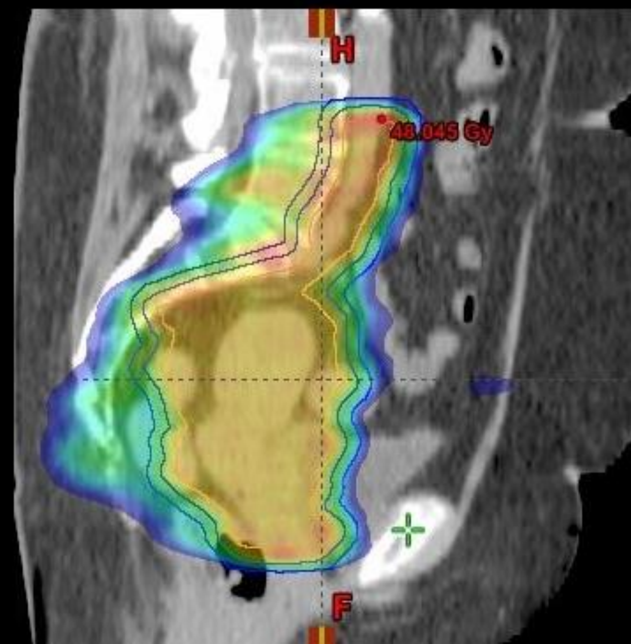
D. Verellen *et al.*, Nature Reviews Cancer 2007

$$\boxed{\begin{array}{c} r \\ \downarrow \\ \pi r^2 \\ \downarrow \\ 4/3\pi r^3 \end{array}}$$

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



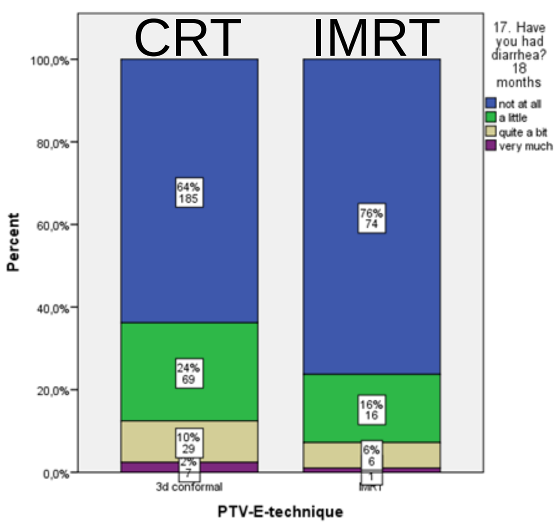
ITV 45	ITV 45 + 5mm	ITV 45 + 10mm
1000 cc	1500 cc	2000 cc

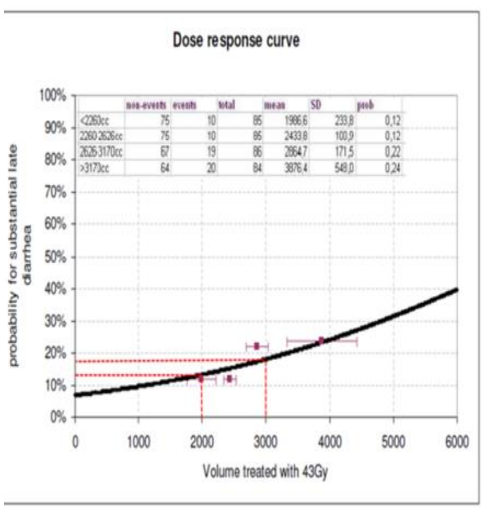


Is it important to reduce irradiated volume?

- Evidence that bowel irradiation is related with acute morbidity
- Evidence that bowel irradiation is related with late morbidity
- Randomised trials (Chopra et al (TMH) Klopp et al (MDACC)

Late toxicity: diarrhea





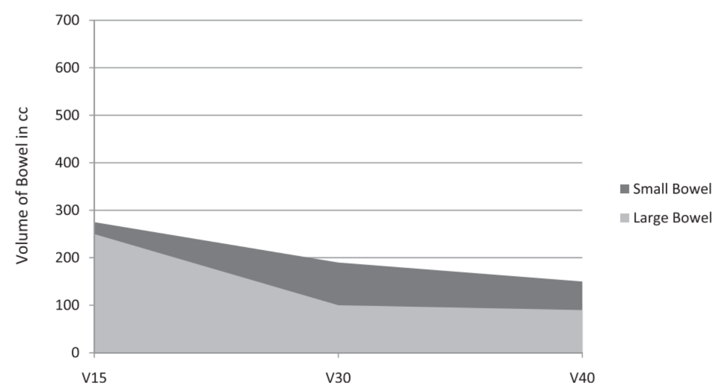
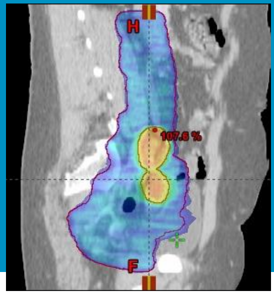


Fig. 1. Recommended dose–volume histogram. Restricting small bowel and large bowel volume doses within the recommended area under curve can restrict late bowel toxicity to within 5%.

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

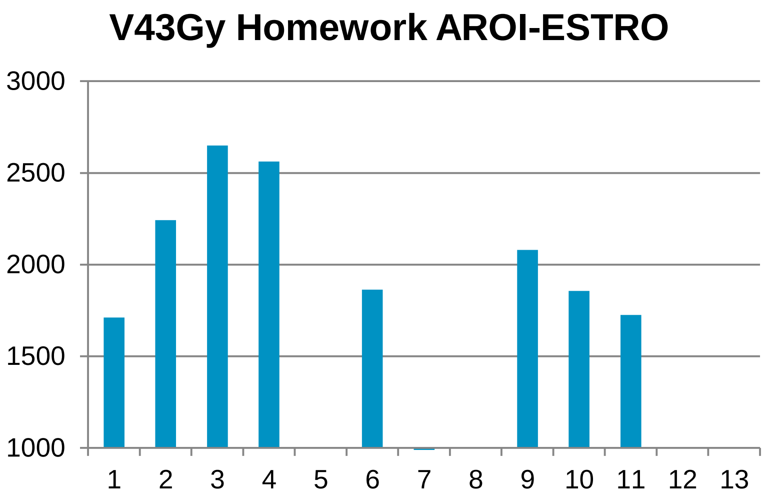
Nodal boost	Pelvic
V57 (cc) EMBRACE I	160 cm^3
CTV-N vol (cc)	10cc per node
PTV-N vol (cc) 5mm margin	30cc per node
V50Gy (cc) EMBRACE II	120 cm^3

Change of practice: EMBRACE I → EMBRACE II

CRT → IMRT : ↘ 500cm^3 (V43)

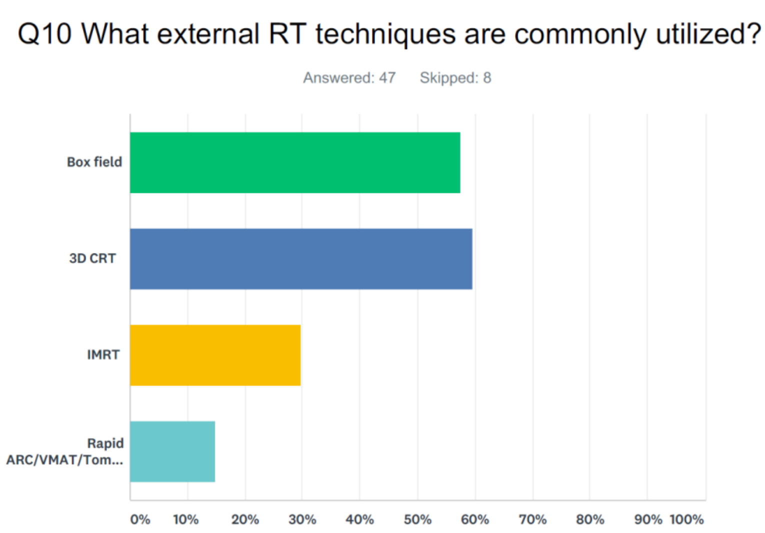
50Gy → 45Gy : ↘ 400cm^3 (V43)

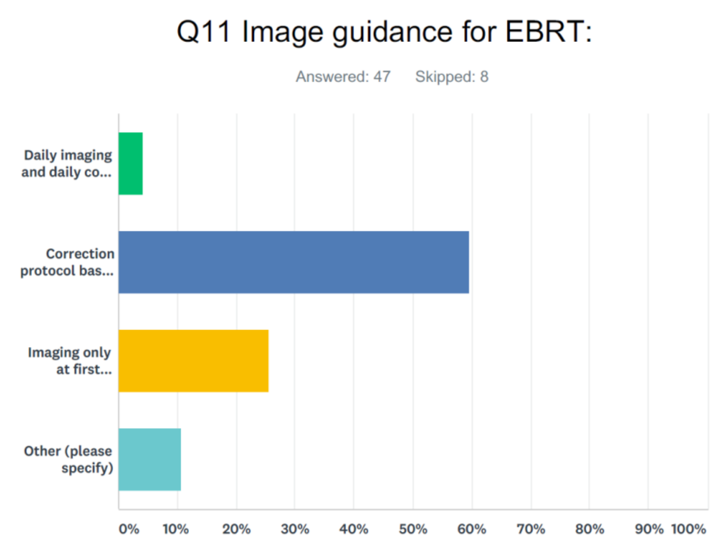
xmm → 5mm : ↘ 100 cm^3 pr mm (V43)



What are your priorities?

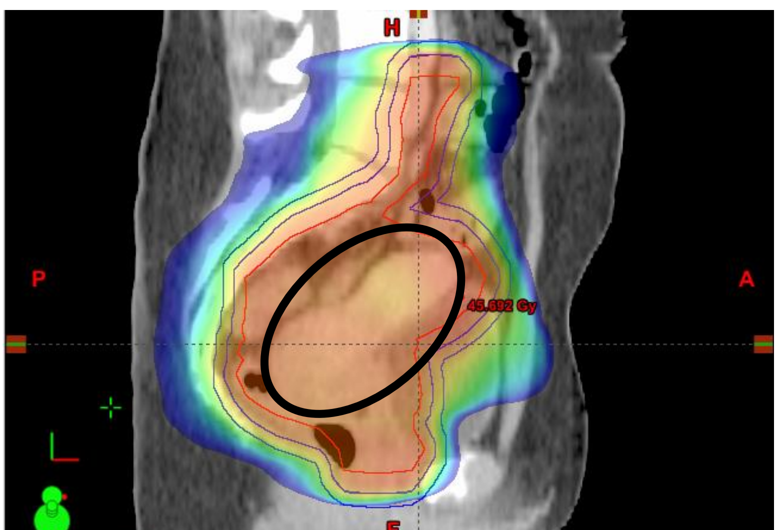
A. IMRT/VMAT
B. Daily IGRT
C. Both





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

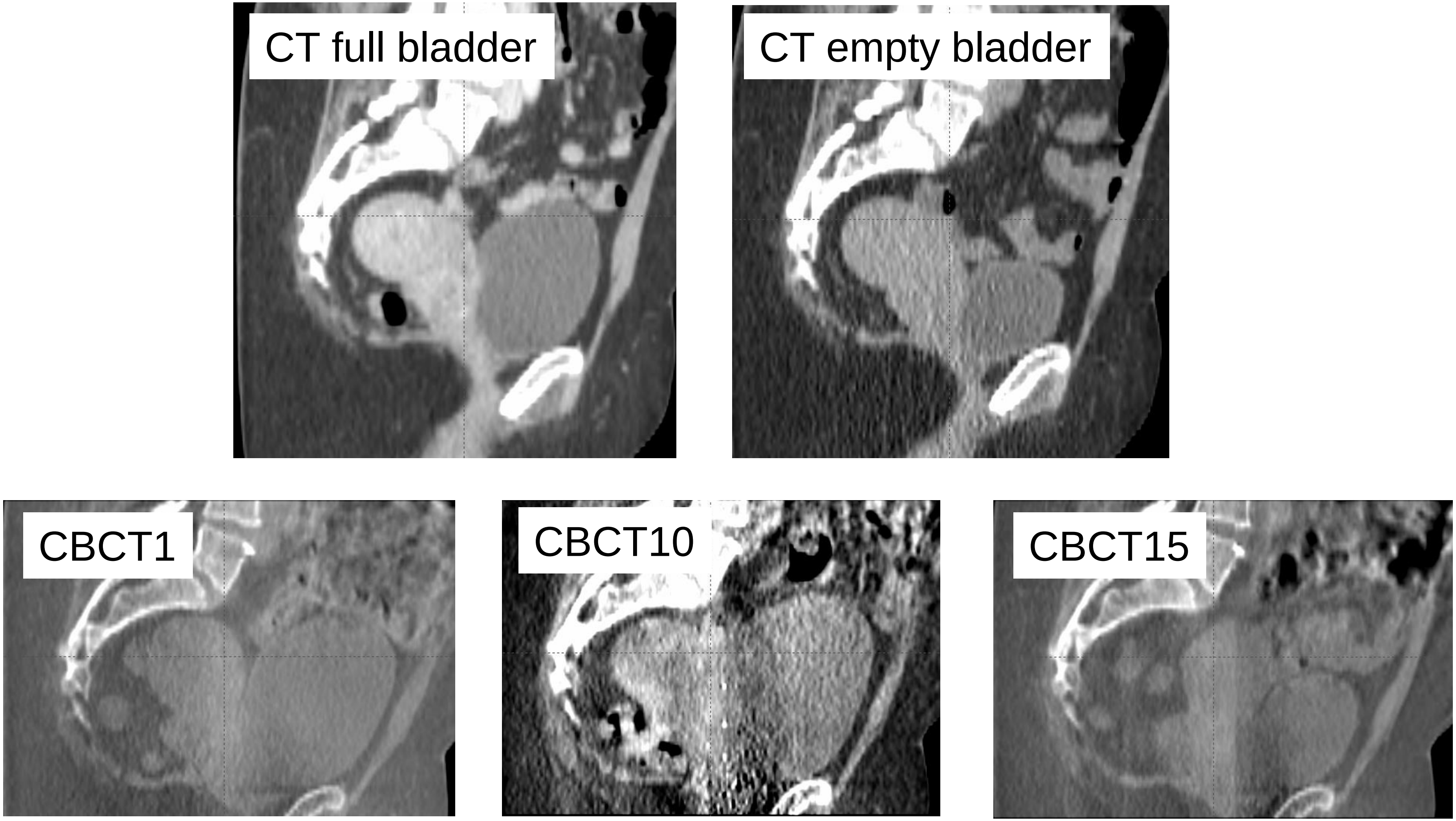


Motion and dose – primary target

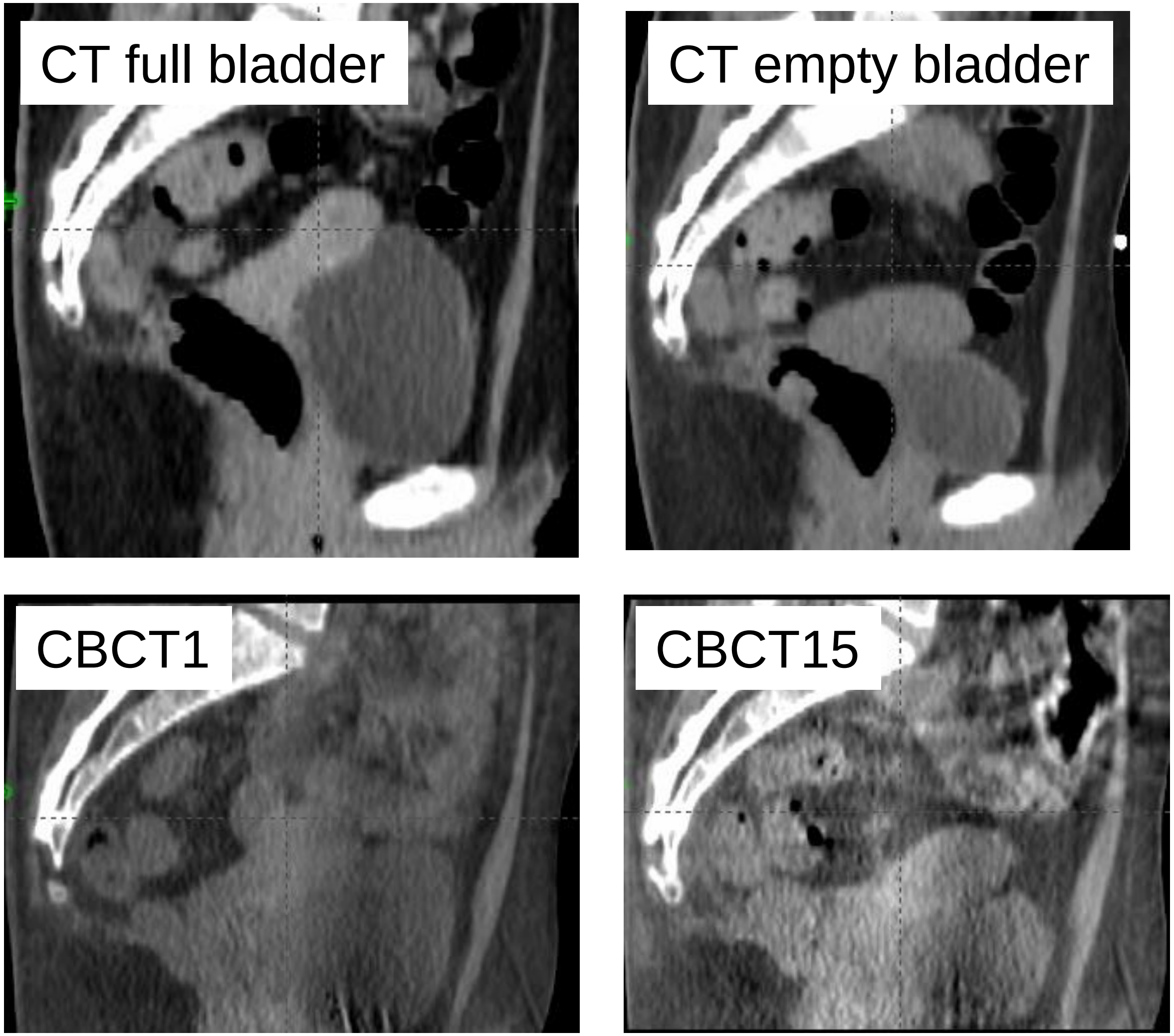
- Jadon et al. A systematic review of organ motion and image-guided strategies in external beam radiotherapy for cervical cancer. Clin Oncol (R Coll Radiol). 2014 Apr;26(4):185-96
  - 39 relevant studies
  - Patient specific motion: 5-40mm
  - Population based margins would be large (up to 40mm)

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

Example of primary tumour motion pattern



Example of primary tumour motion pattern

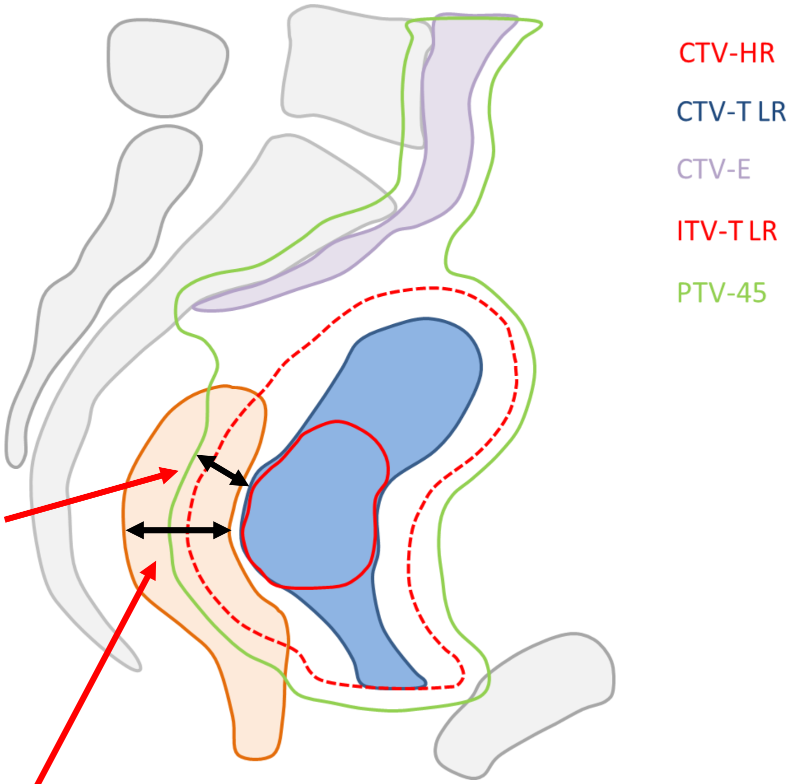


ITV-T LR and PTV-T LR

Standard:

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

CTV to PTV: 20mm



Maximum rectal filling at treatment planning scan: 40mm

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

Patient case:

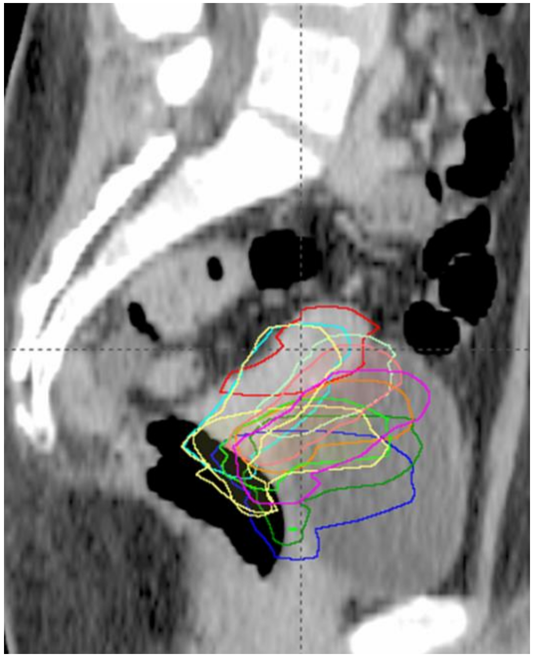
- 45/25fx EBRT
- 1.5cm CTV-PTV margin
- 50% of fractions: uterus outside PTV
- 40Gy EQD2 BT prescribed to CTV_{HR}

A. 20Gy

B. 30Gy

C. 35Gy

D. >40Gy



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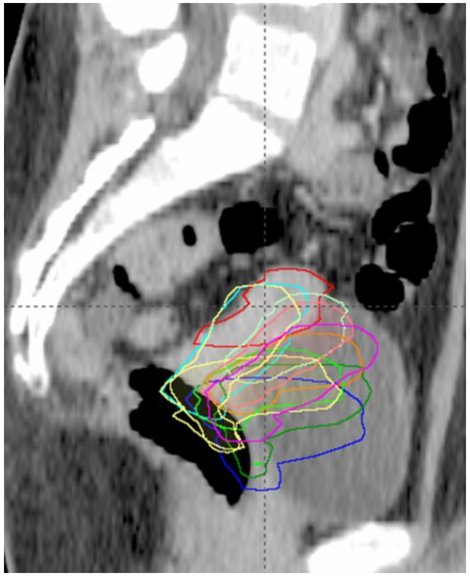


EBRT dose: **38Gy**

BT dose: **6Gy**

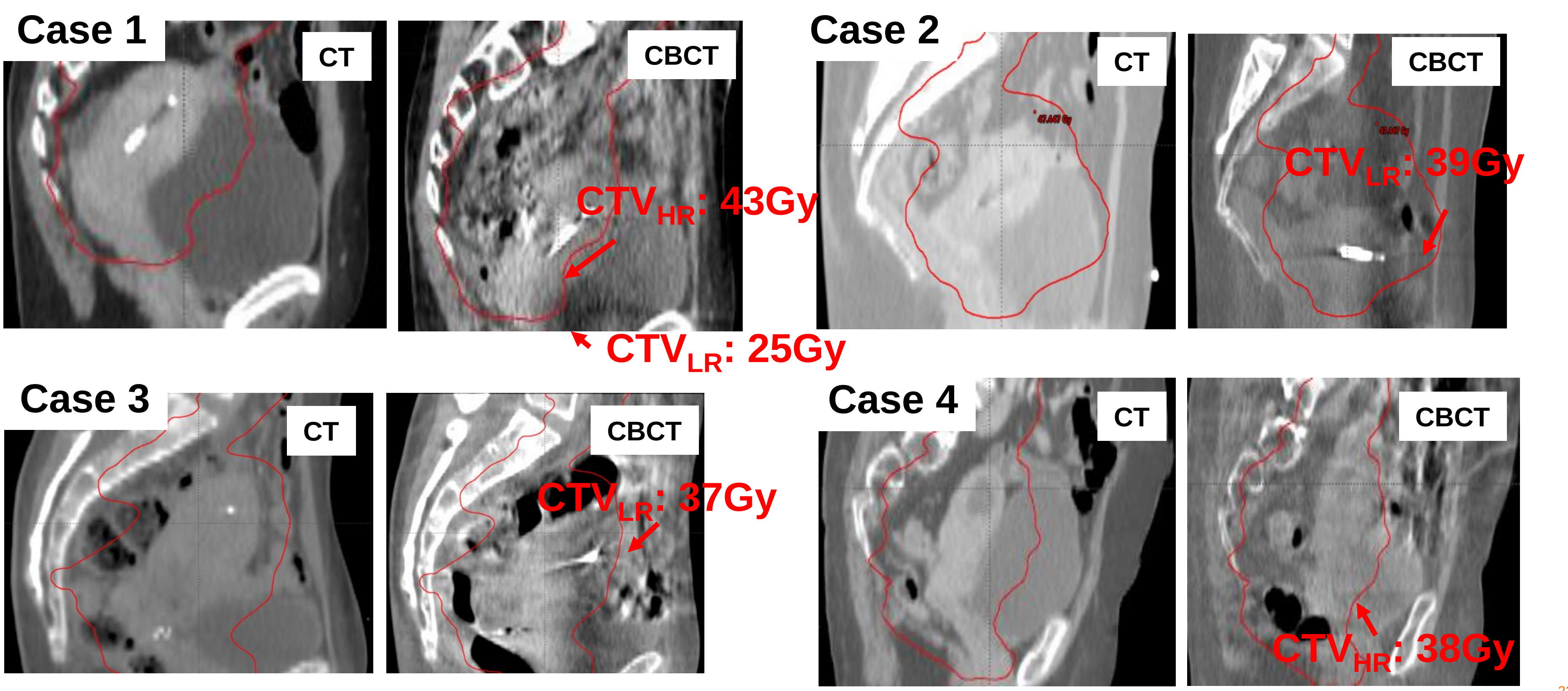
EBRT+BT dose: **44Gy**

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

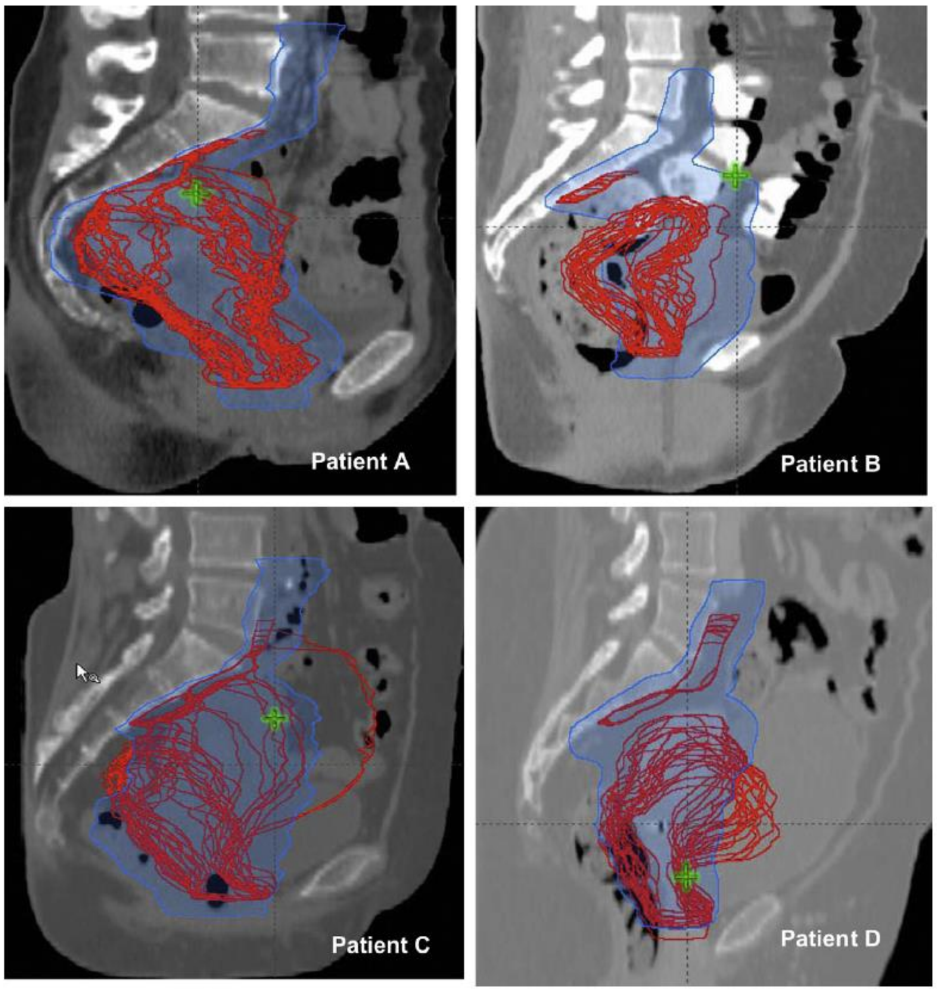
Sapru et al, Radither Oncol 107 (2013) 93–98

Worst cases (15% of patients) from Aarhus

- **Full and empty bladder planning CT + MRI**
- **Individualised ITV margin**
- **Prescribed EBRT: 45Gy in 25 fx**



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

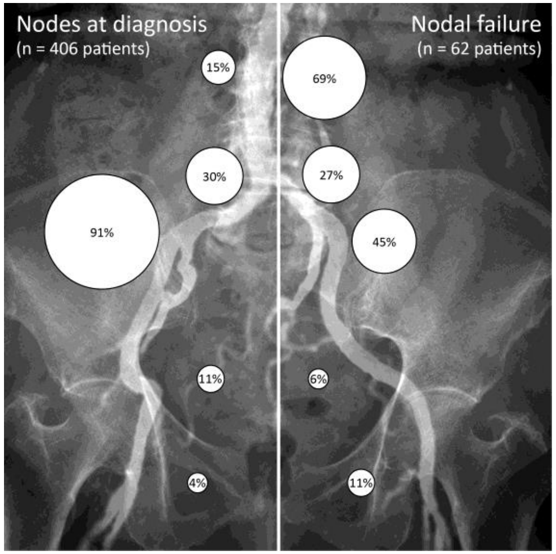


Tyagi et al, DAILY ONLINE CONE BEAM COMPUTED TOMOGRAPHY TO ASSESS INTERFRACTIONAL MOTION IN PATIENTS WITH INTACT CERVICAL CANCER, IJROBP 2011

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

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)**



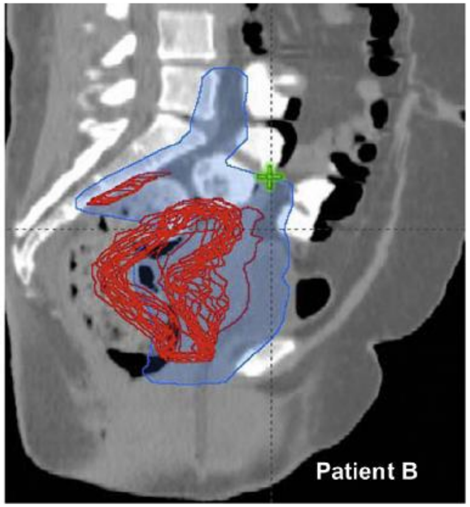
Pattern of nodal failure (EMBRACE)

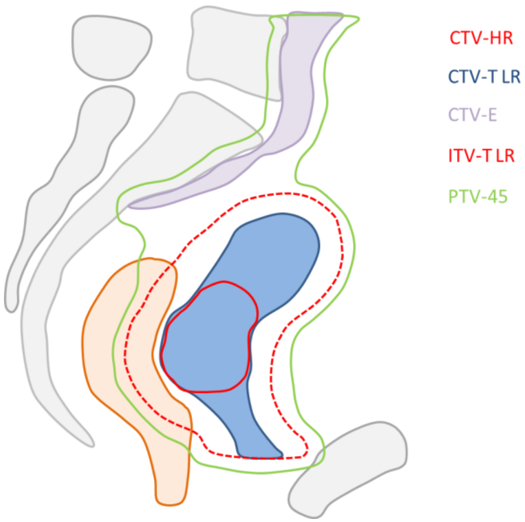
152 failures in 1338 pts (11%)

- Inside elective target volume: 41%
- Outside elective target volume: 41% (39% PAO)
- In boosted nodes: 35%

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.





External Beam Treatment Techniques and Optimization – Physics aspects

Jamema Swamidas
Kari Tanderup

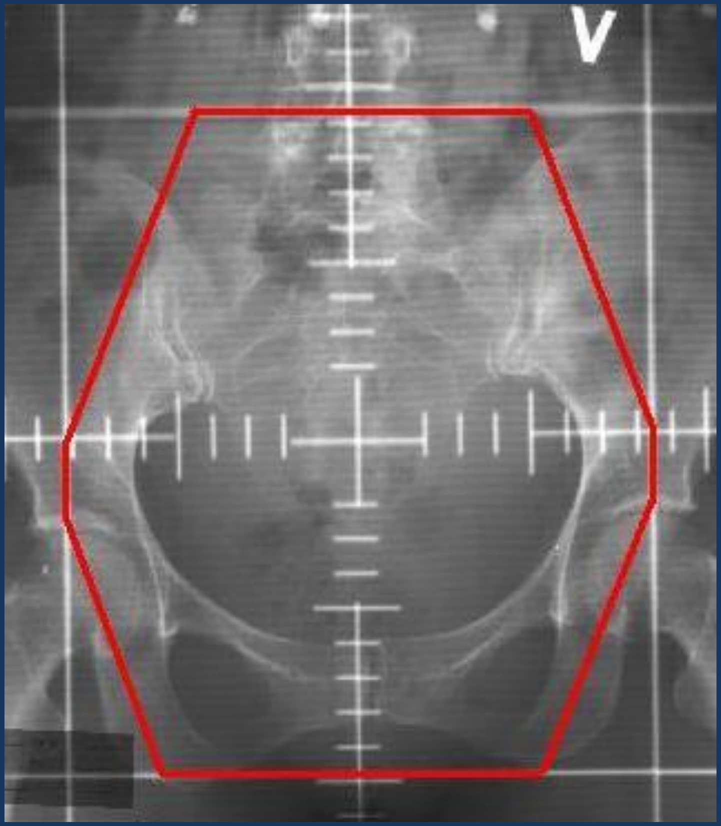
ESTRO School

ESTRO teaching course
Prague 22-26 Oct 2017

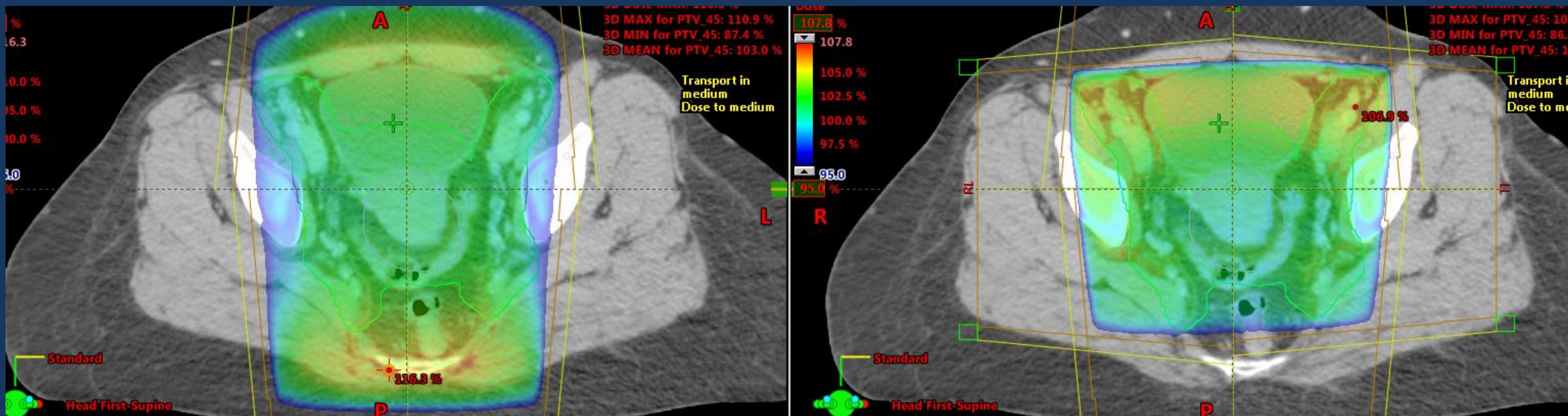
What kind of techniques do we have?

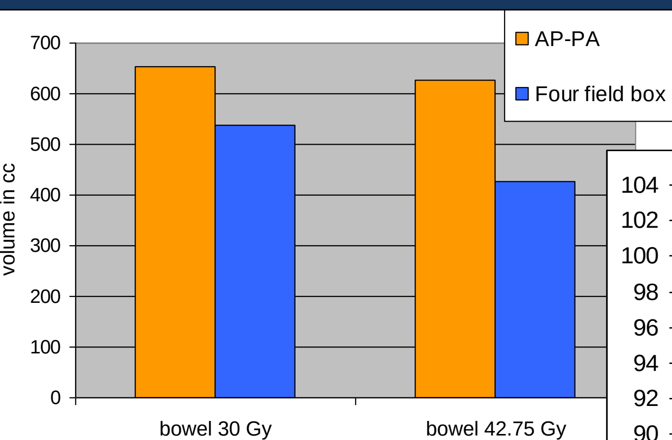
- AP-PA / Four Field Box – Radiograph based
- 3DCRT
- IMRT
- VMAT
- Helical Tomotherapy
- Proton Therapy

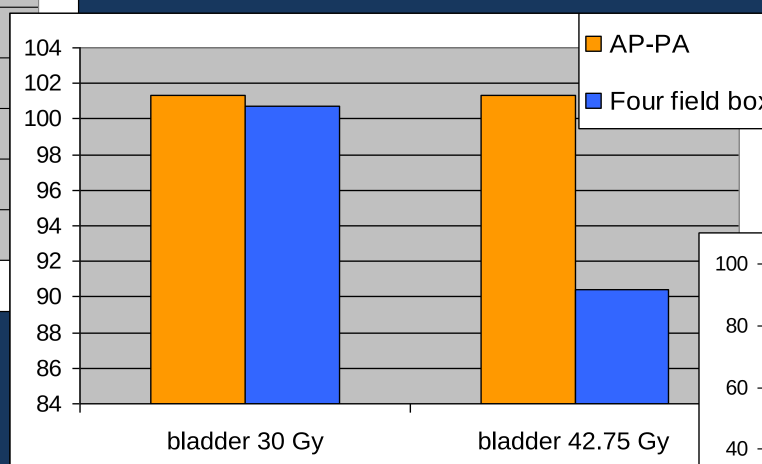
AP/PA or 4F box – Radiograph based

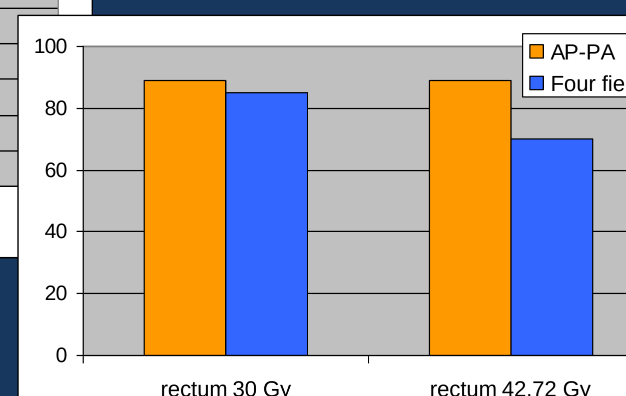


AP/PA vs 4F Box





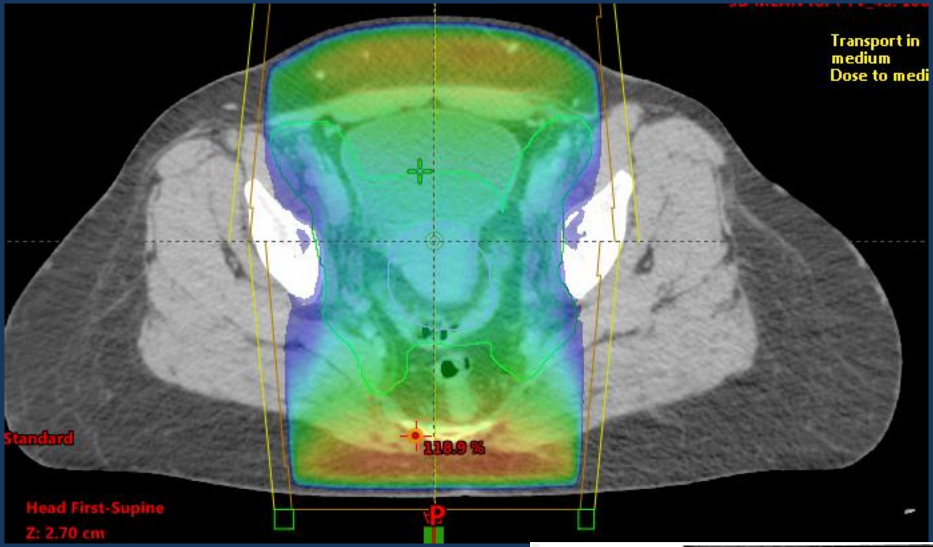




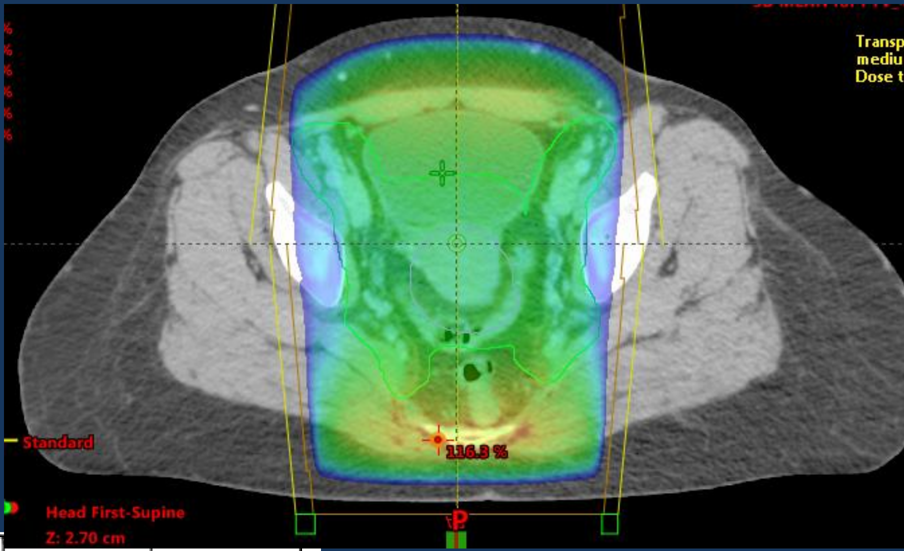
Van de Bunt et al 2006

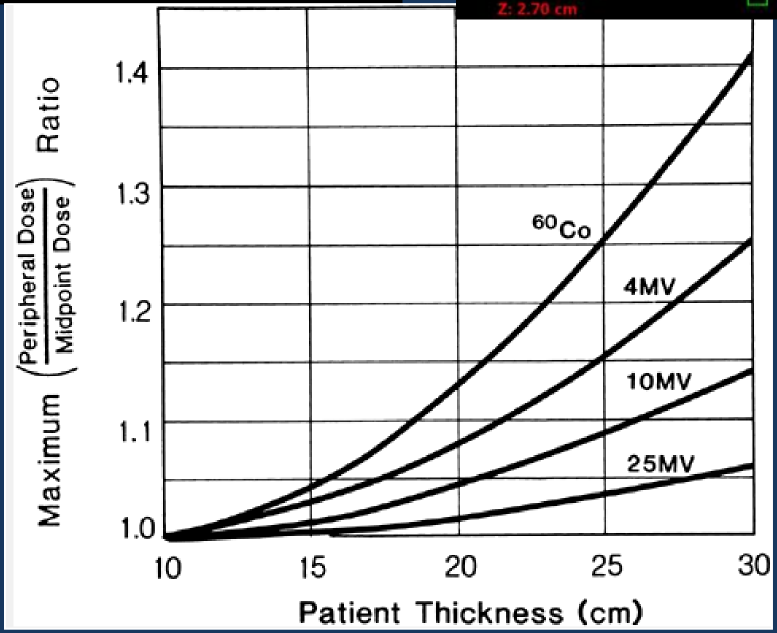
Choice of energy

6MV



15 MV

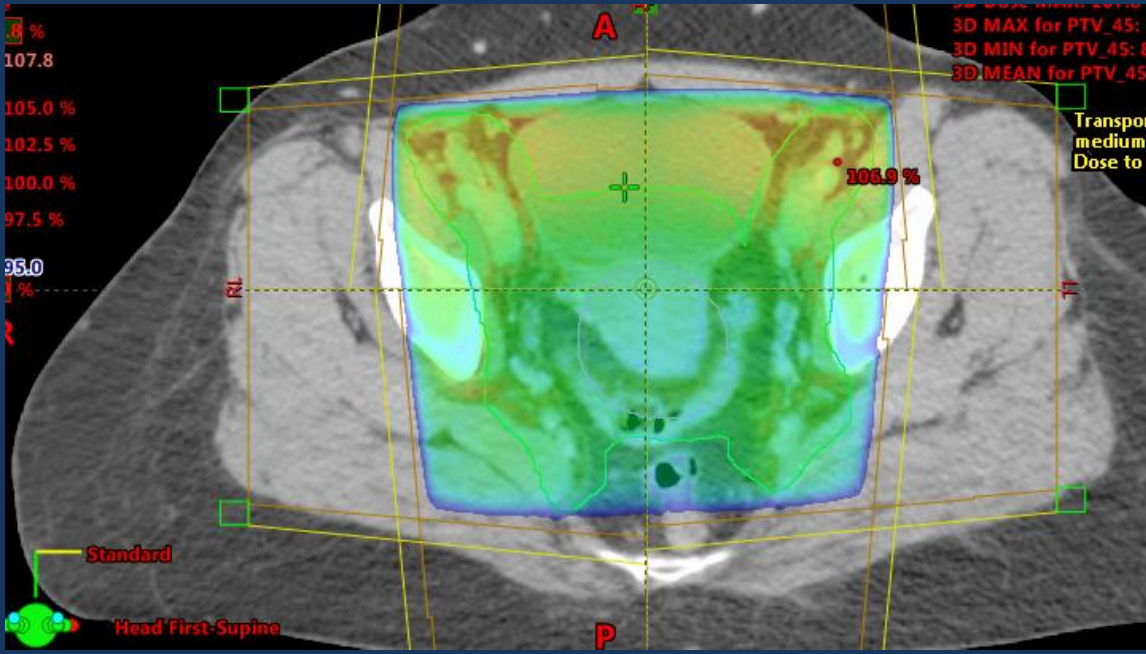




Khan 1994

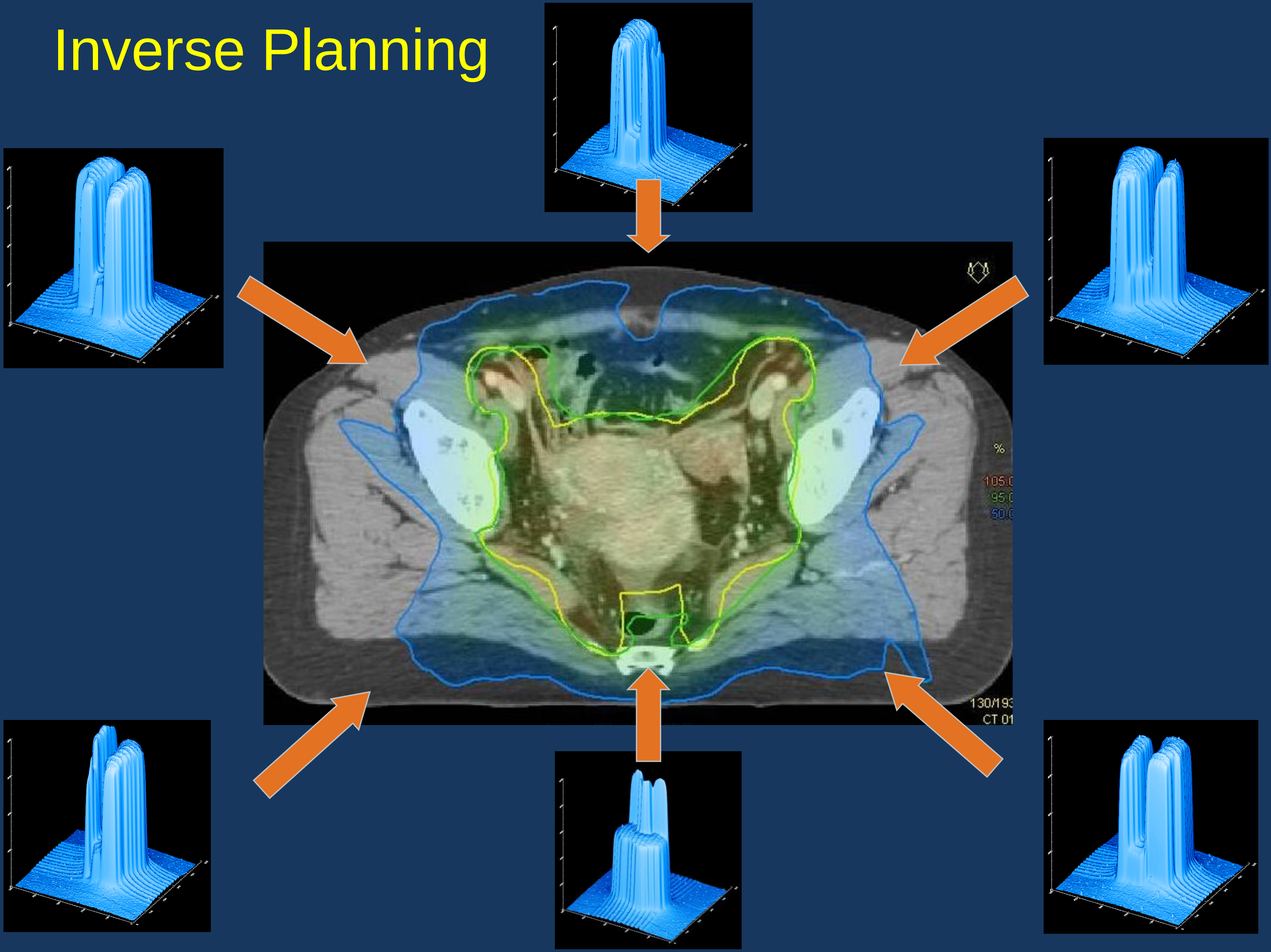
Forward planning

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



- Iteratively change

Inverse Planning



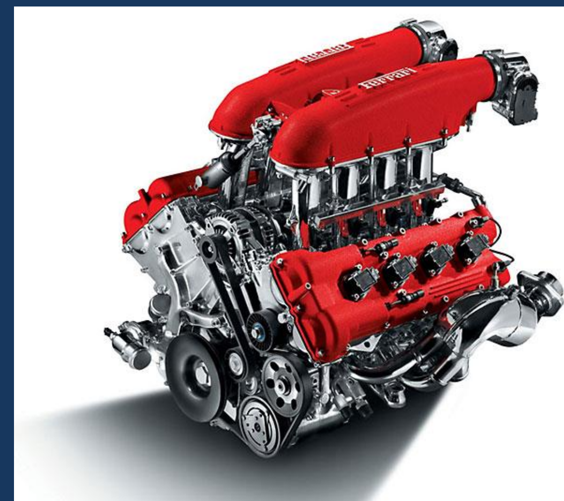
Inverse Planning – what is available

- 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
- CTV-(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 < 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 (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 < 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 D0.01

* 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. **V95% > 95%**
B. **V100% > 95%**
C. **V90% > 95%**
D. **V95% > 100%**

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

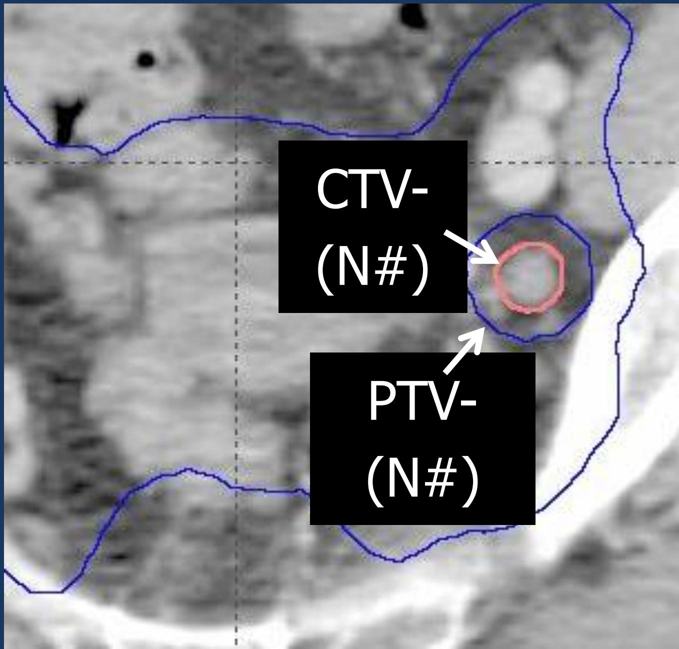
o PTV-(N#) = PTV-(N#) subtract CTV-(N#)

Purpose:

press down the dose around CTV-(N#)

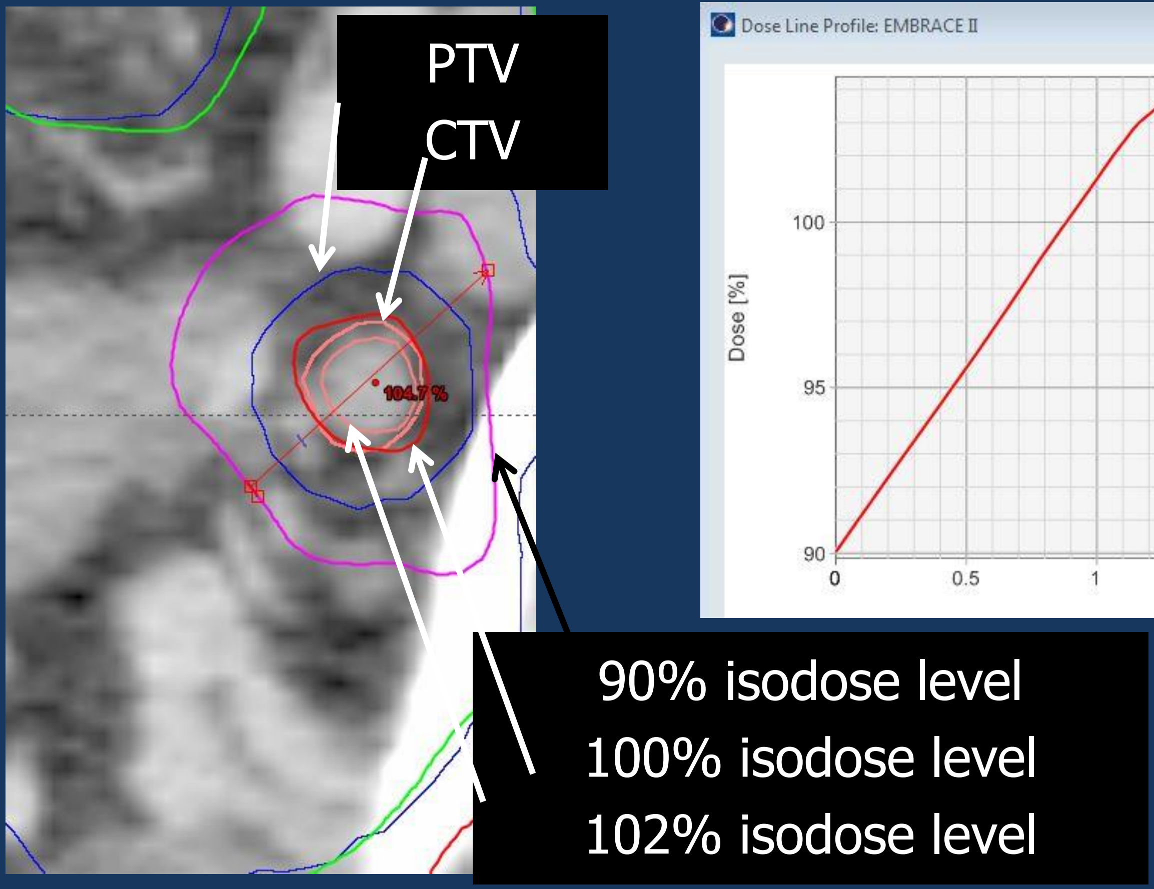
Dmax ≈ 100% of prescribed dose

Dmin ≈ 90% of prescribed dose.



Courtesy :Marianne S Assenholt

Coverage Probability - CoP



Courtesy :Marianne S Assenholt

Coverage Probability Principle aims

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

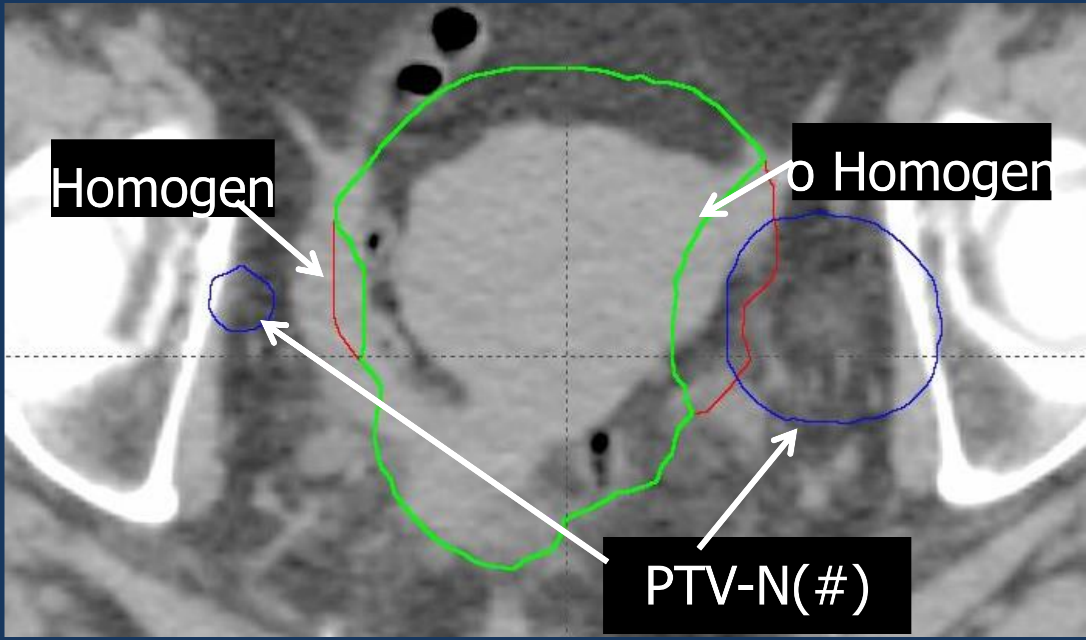
Optimization volume: **o Homogen**

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

Purpose:

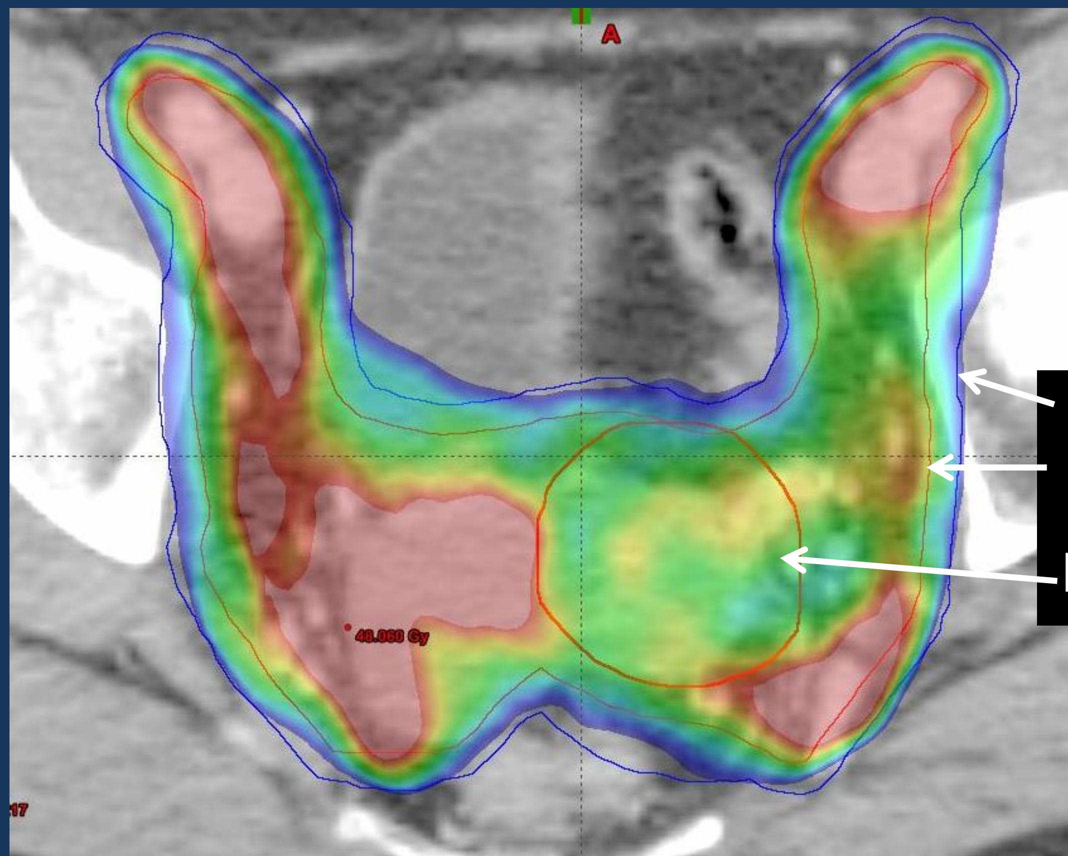
To avoid dose higher than 103% of 45Gy.

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

Aware of BT region during IMRT – Avoid hot spots



PTV45

ITV45

Homogen

Red area: Dose > 103% of 45Gy

Colored area: Dose > 95% of 45Gy

Courtesy :Marianne S Assenholt

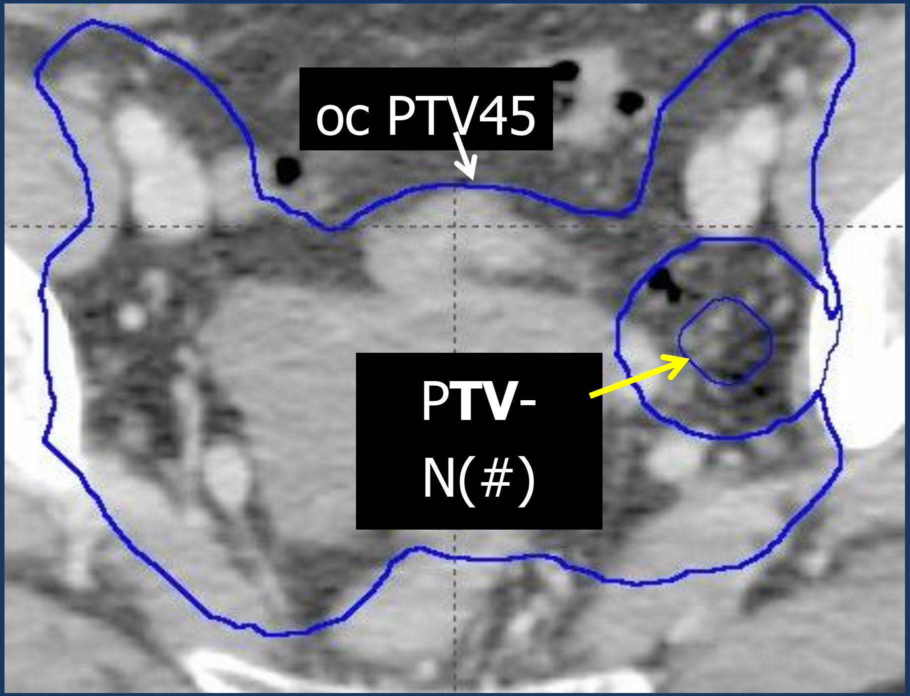
Optimization volumes e.g : **oc PTV45**

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

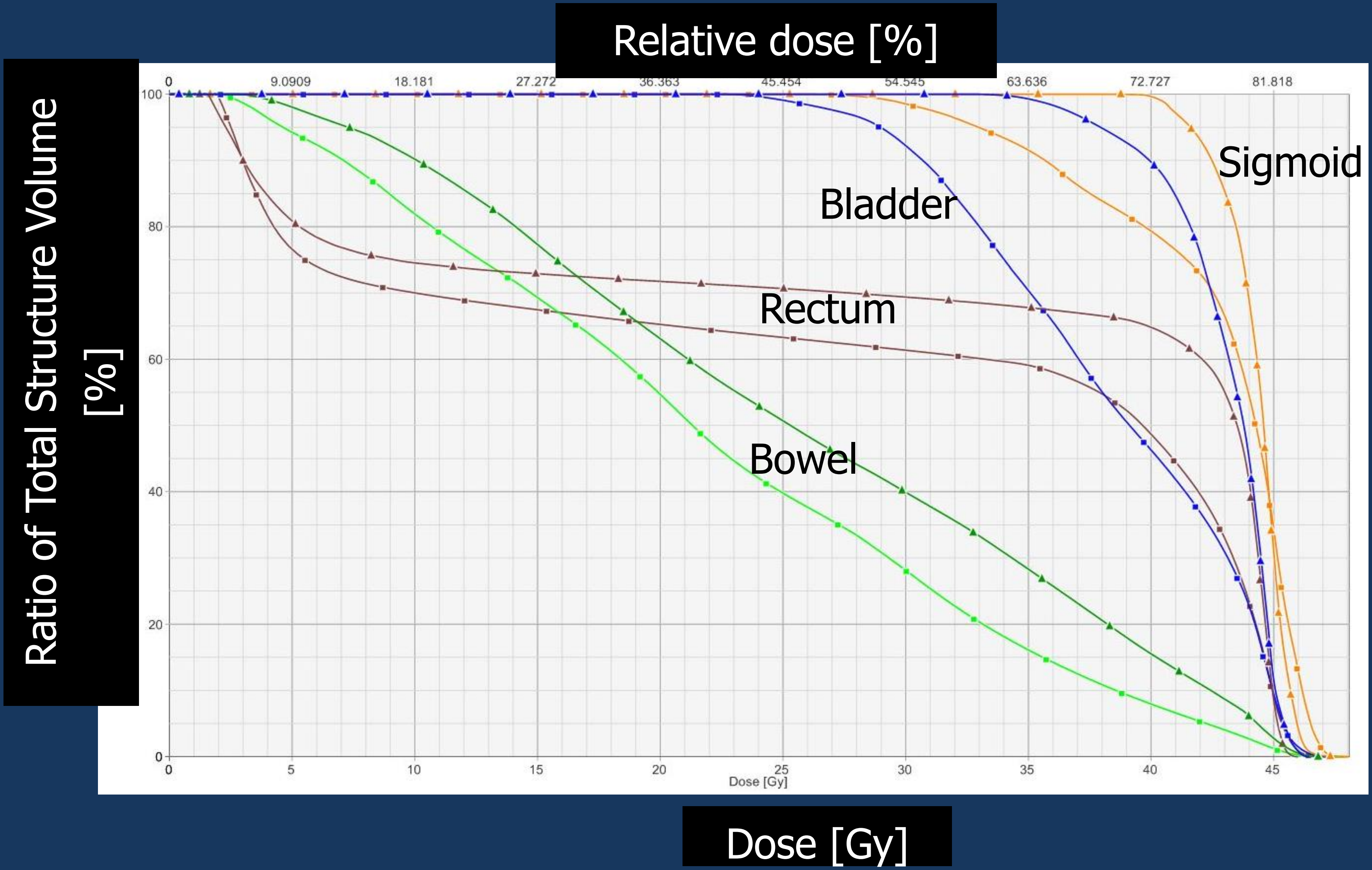
Organs at risk – ALARA

- 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

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*	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

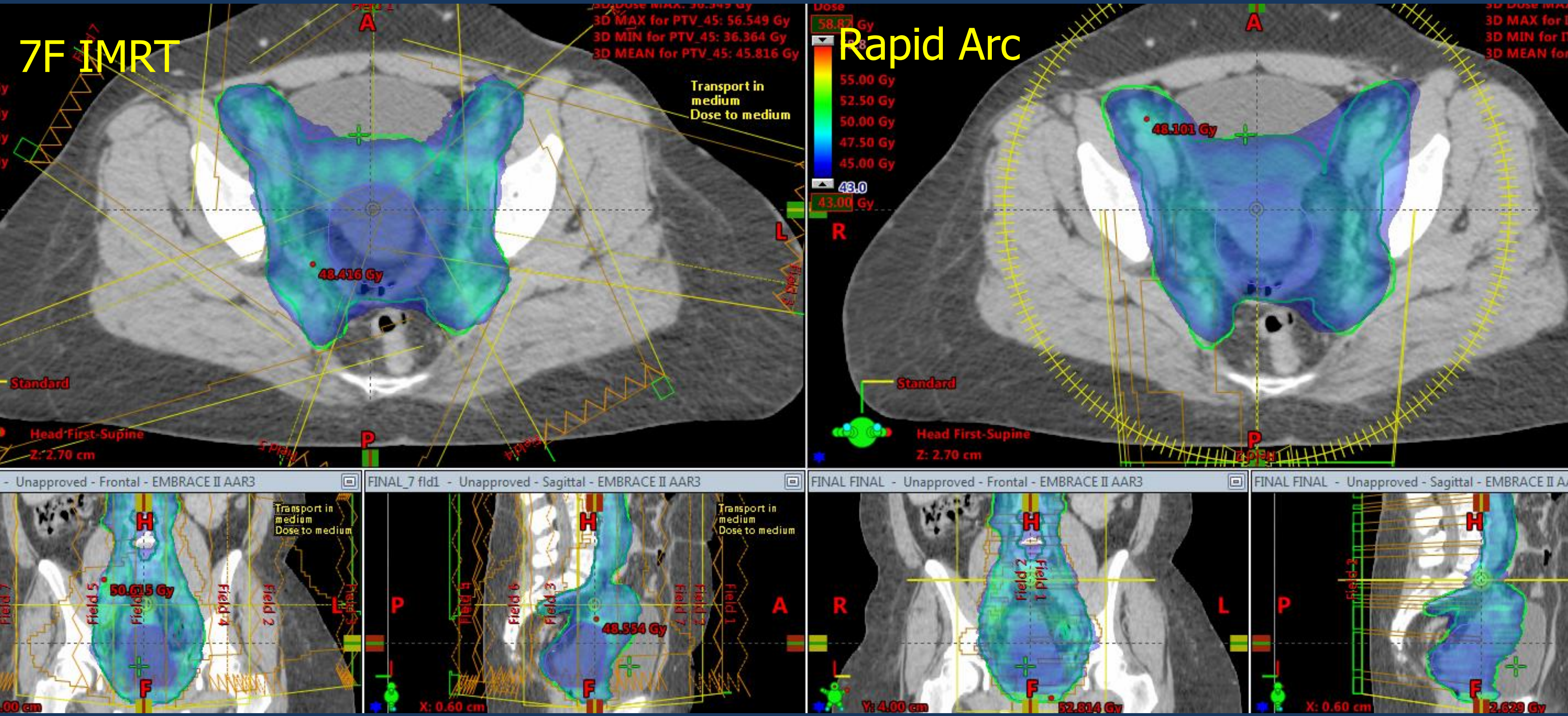
* intensity modulated radiotherapy; +

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

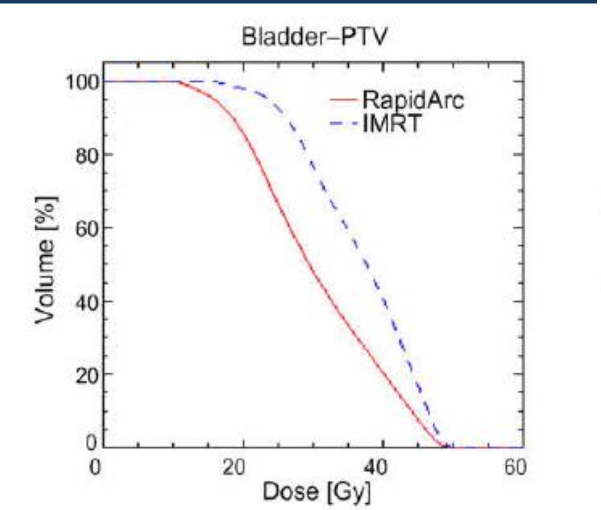
IMRT vs VMAT

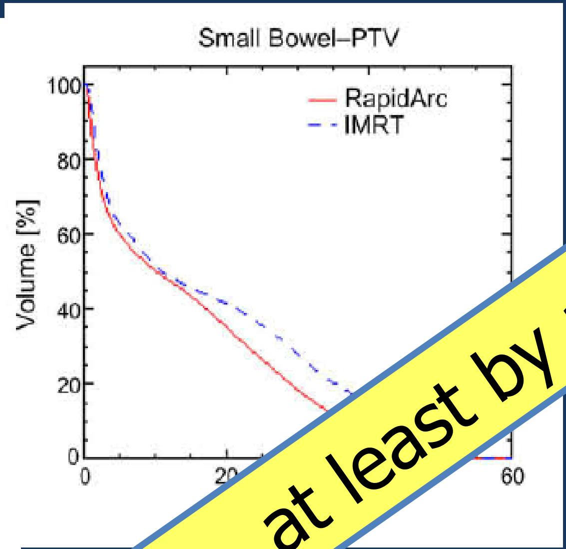


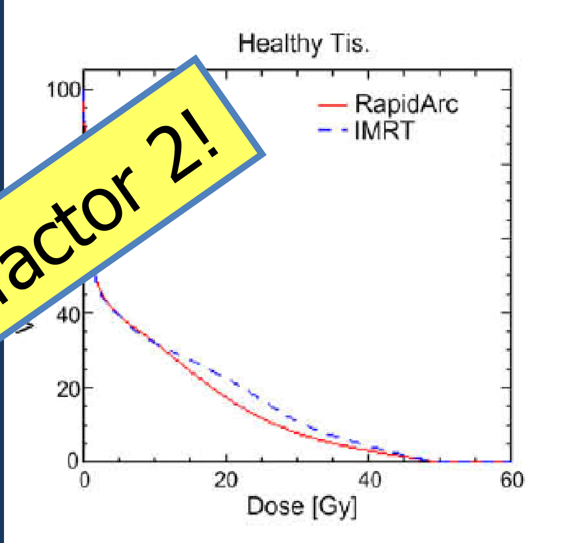
7F IMRT
3D MAX for PTV_45: 56.549 Gy
3D MIN for PTV_45: 36.364 Gy
3D MEAN for PTV_45: 45.816 Gy
Transport in medium
Dose to medium
48.416 Gy
Standard
Head First-Supine
Z: 2.70 cm
Rapid Arc
55.00 Gy
52.50 Gy
50.00 Gy
47.50 Gy
45.00 Gy
43.0
43.00 Gy
48.101 Gy
Unapproved - Frontal - EMBRACE II AAR3
FINAL_7 fld1 - Unapproved - Sagittal - EMBRACE II AAR3
50.615 Gy
48.554 Gy
X: 0.60 cm
FINAL FINAL - Unapproved - Frontal - EMBRACE II AAR3
FINAL FINAL - Unapproved - Sagittal - EMBRACE II A
Y: 4.00 cm
52.814 Gy
2.629 Gy

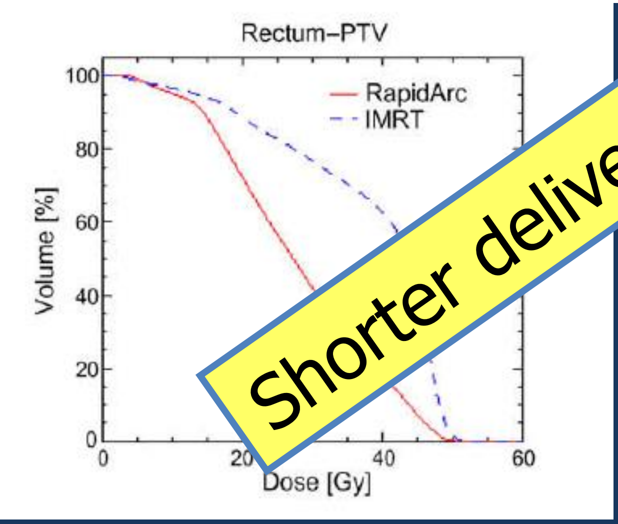
IMRT vs VMAT (RapidArc)

8 patients with ca. cervix







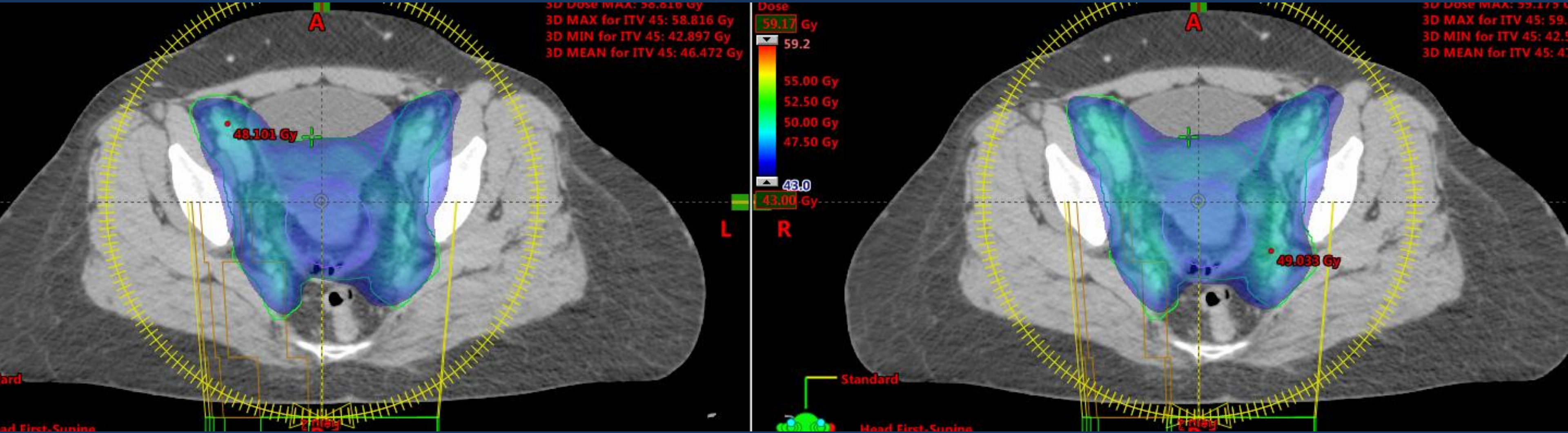


Shorter delivery time, at least by a factor 2!

	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

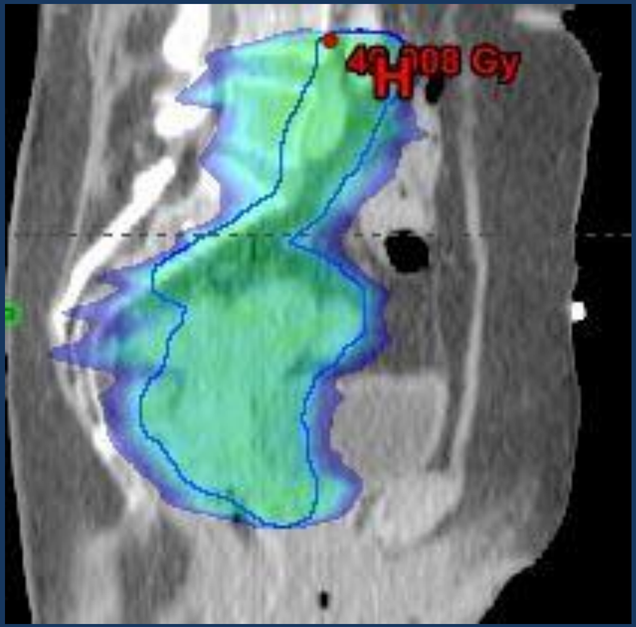
  11% less for 6FFF-VMAT and 16% less for 10FFF - VMAT

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

Conformity

- Low dose spillage
- Volume receiving 43 Gy, 50 Gy
- Ratio of $V43/V_{PTV}$ ~ 1.1
- $V36/V_{PTV}$ ~ 1.6

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



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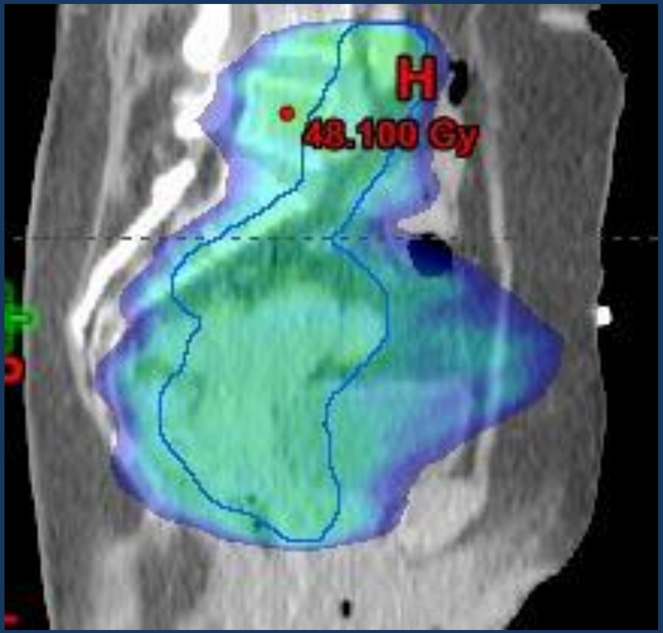
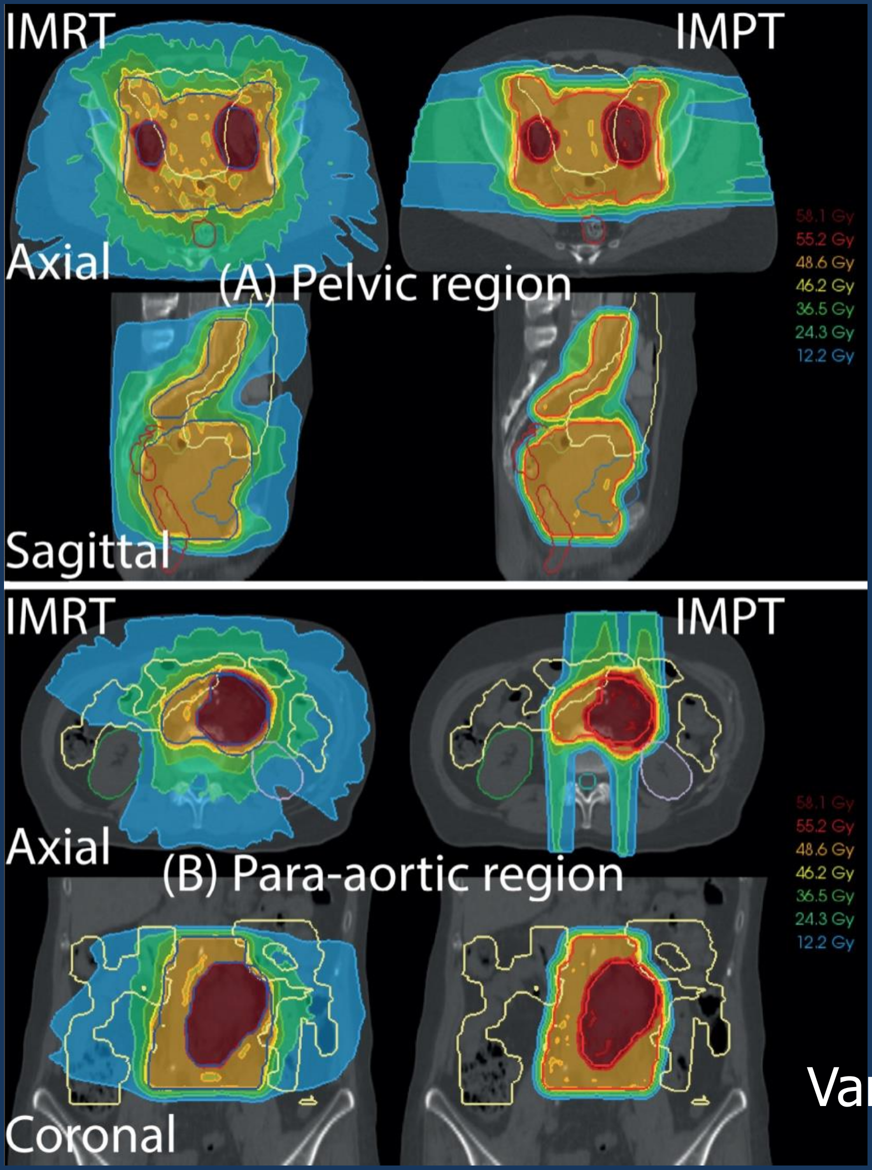


2

A. 1

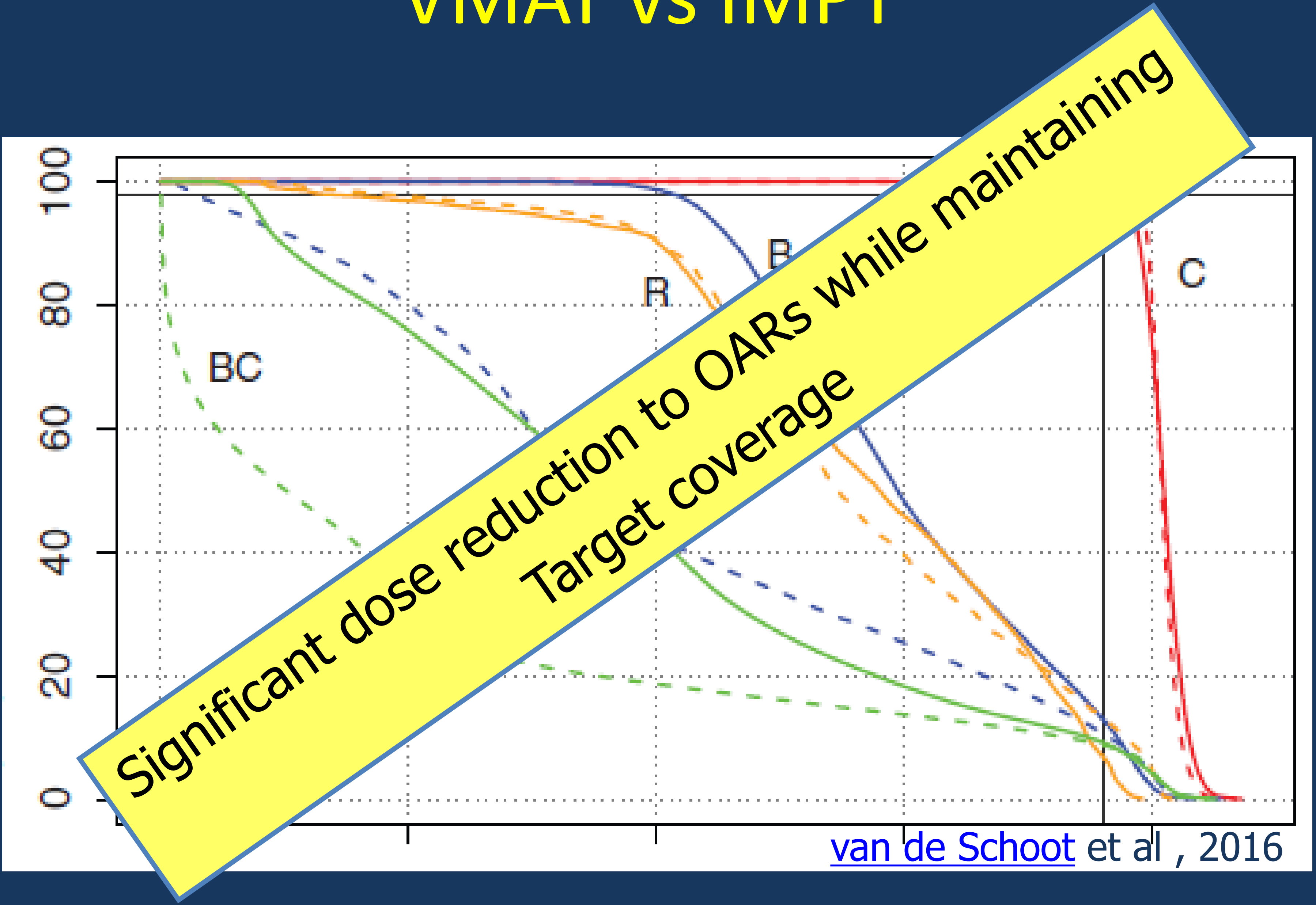
B. 2

IMRT vs IMPT



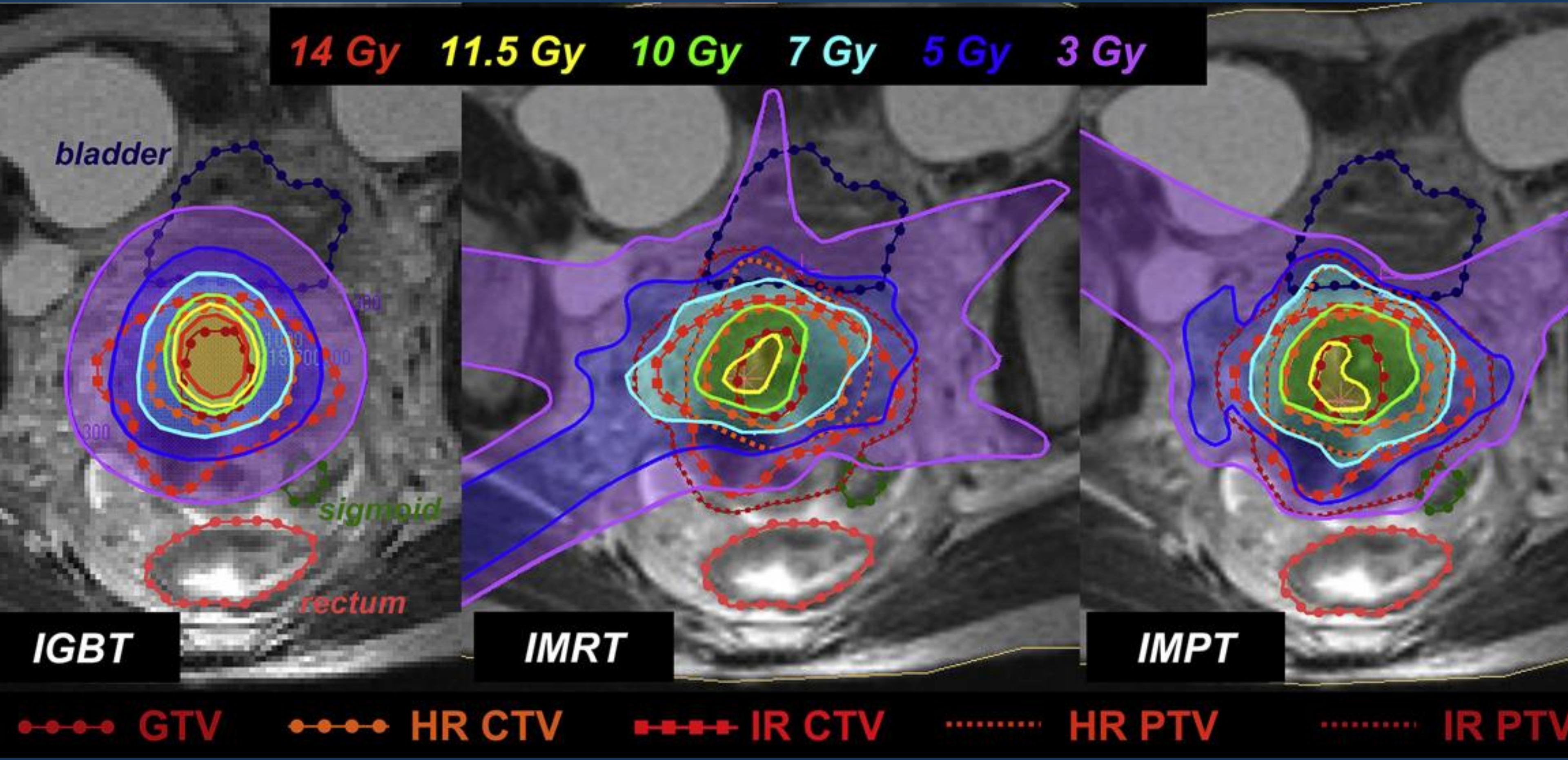
Vande san de et al, 2016

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

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

Umesh Mahantshetty, *TMC Mumbai*

Ina Schulz, *Universtity Medical Centre Utrecht*

Outline

- Evidence for EBRT dose constraints & DVH parameters
- Evidence for dosimetric and clinical gain IMRT
- Incorporation on Newer Imaging Modalities
- Impact of DVH parameters on treatment planning

EBRT for GYN Cancer treatment

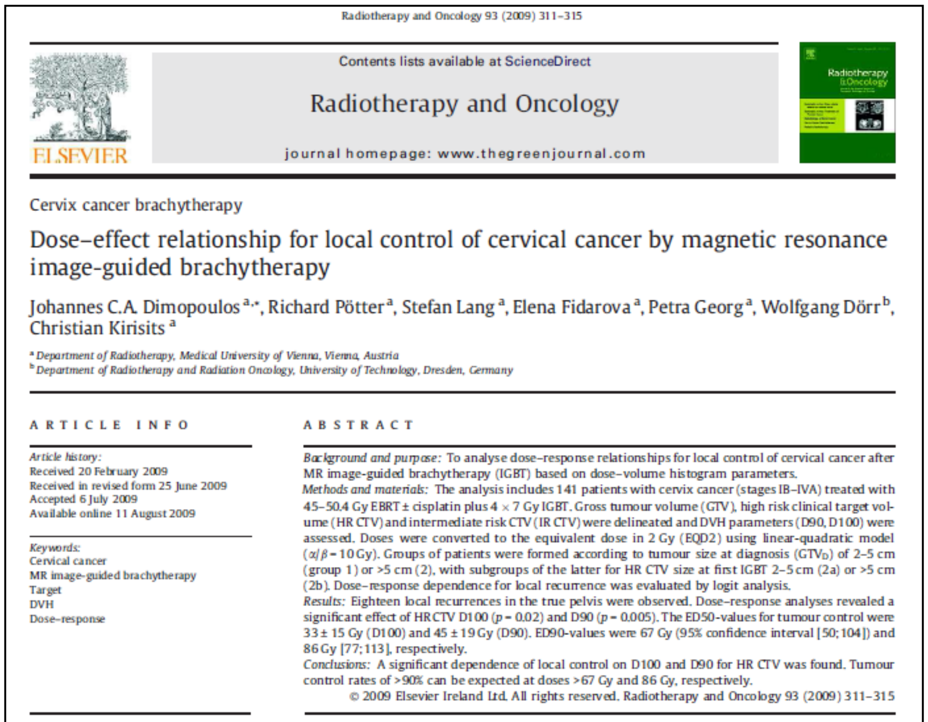
- Elective dose including draining lymphatic system
- Boost to regional pathologic nodes
- Boost to primary tumor if brachytherapy is not feasible
- Dose needed for tumor control too high for surrounding OAR
- Reduction according to ALARA, as low as reasonably achievable
- Dose constraints and DVH parameters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

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

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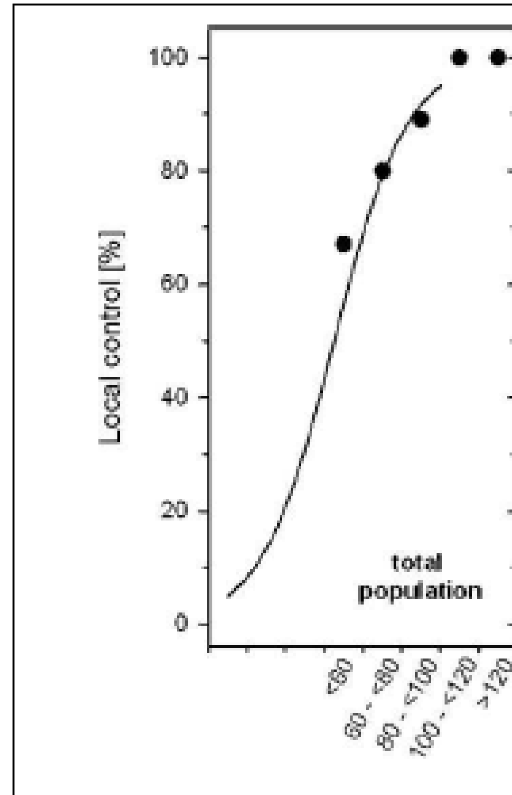
Dose–response

ABSTRACT

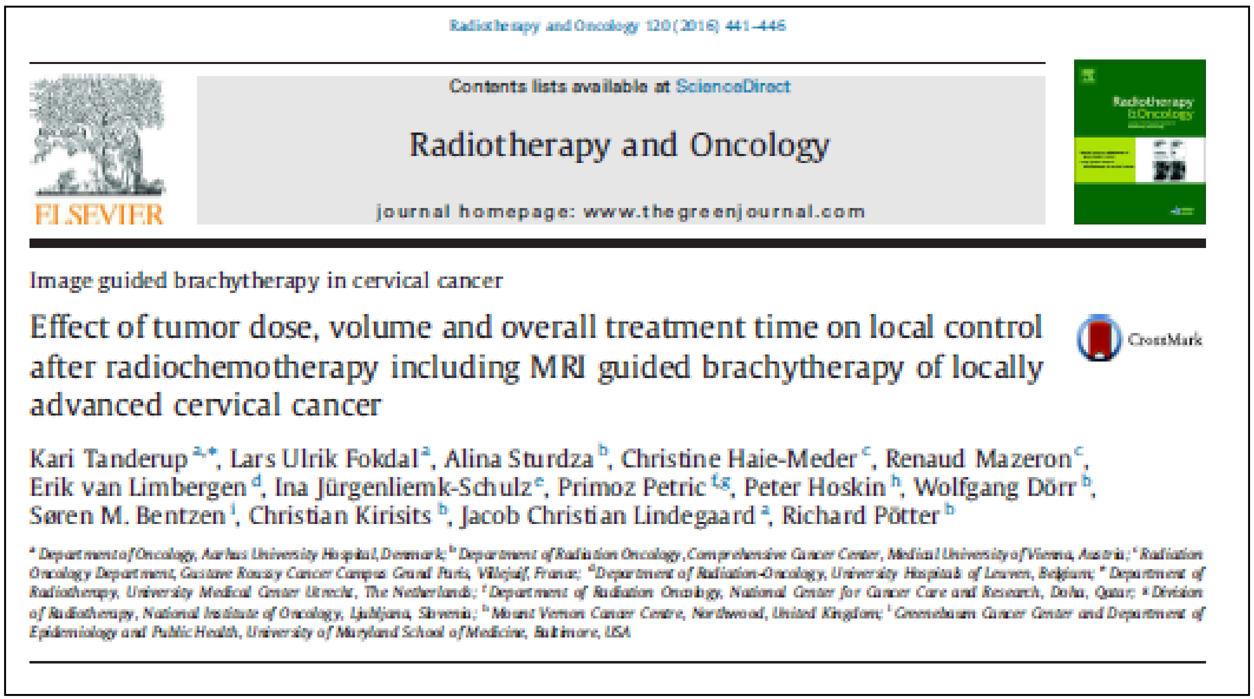
Background and purpose: To analyse dose–response relationships for local control of cervical cancer after MR image-guided brachytherapy (IGBT) based on dose–volume histogram parameters.
Methods and materials: The analysis includes 141 patients with cervix cancer (stages IB–IVA) treated with 45–50.4 Gy 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.



Evidence for dose needed to control primary tumor

Bigger tumors need more dose

- Local control depends on applied dose in a certain volume


Radiotherapy and Oncology 120 (2016) 441–446

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Image guided brachytherapy in cervical cancer

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

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

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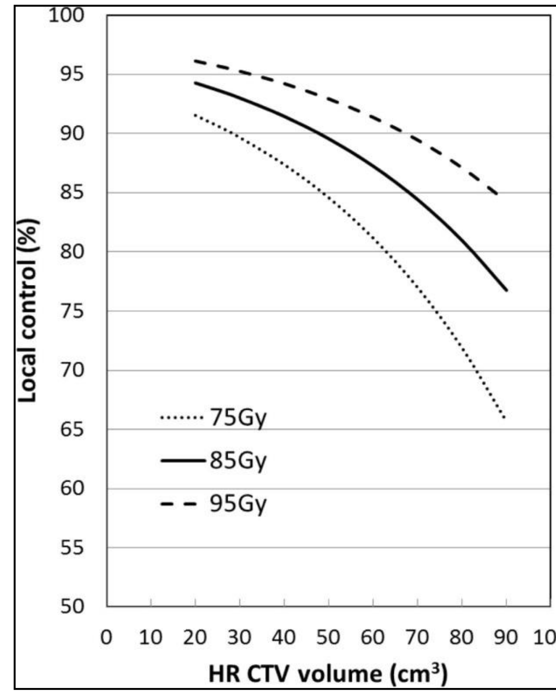

Tanderup 2016

Evidence for dose needed to control primary tumor

Preliminary results with SBRT, no brachy

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

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

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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

Mendez 2016

Evidence for dose needed to control primary tumor

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

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

Mendez 2016

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, Elzbieta van de Steen-Banasik, Henk Beerman, Mat van Lent, for the PORTEC Study Group**

Perez 1998

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 42, No. 2, pp. 335–344, 1998

0360-3016/98 $19.00 + .00

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

Evidence for dose to elective region & 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

CrossMark

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.

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#

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

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

Gynecologic Oncology 135 (2014) 239–243

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

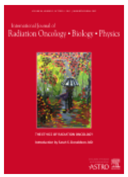
As high as intended and reasonably achievable

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 !

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 LATE Radiographical: anatomical, functional Biochemical (blood test, functional test) Degree of severity Degree of frequency Impact on quality of life (QOL)
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

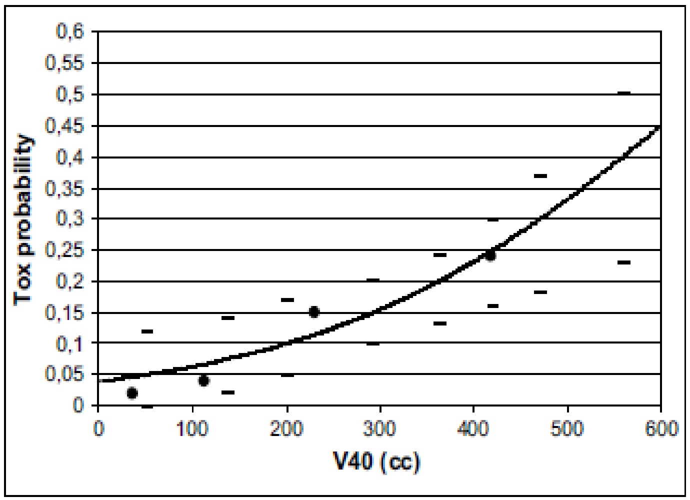


Fig. 1. The relationship between the V40 of the intestinal cavity (outside the planning target volume) and the risk of Grade 2–3 acute bowel toxicity is plotted, together with 95% confidence intervals (lo-

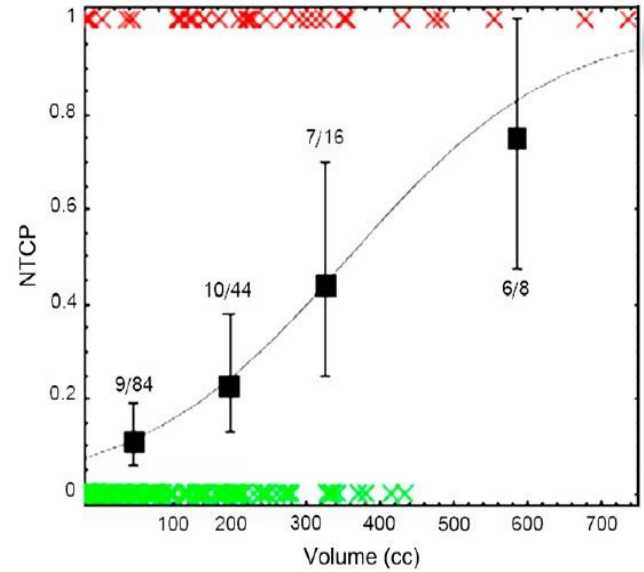
Incidence of toxicity drops from 21% to 3% when:

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

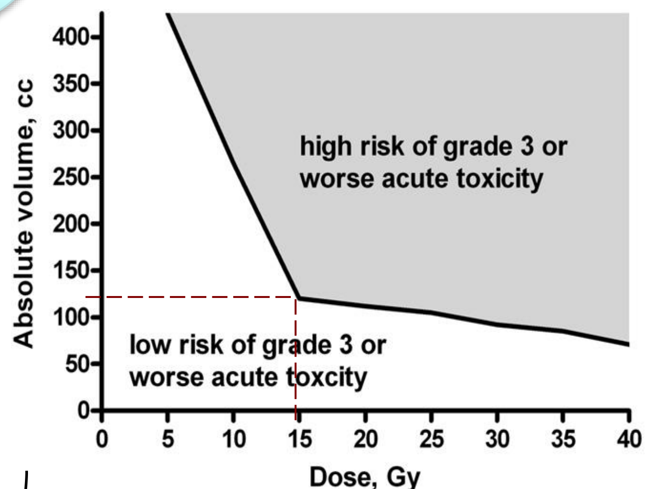
V15 should however be seen as a geometrical surrogate for the high dose volumes and not used alone for optimizing IMRT dose distribution

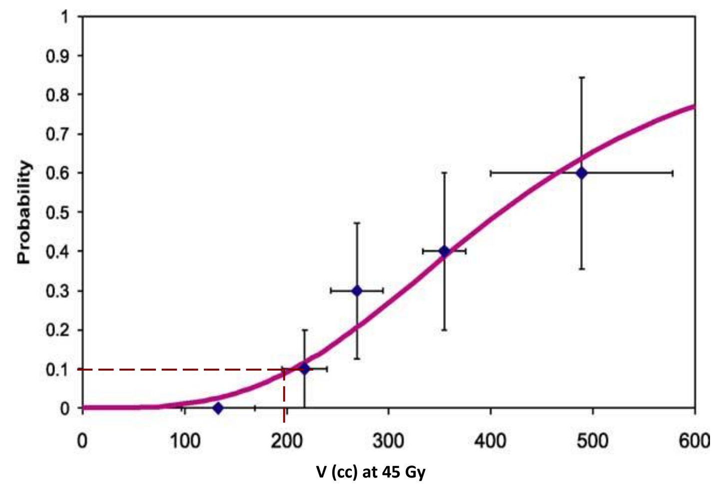
Dose constraints depend on contouring approach

Baglan
IJROBP, 2002

Treshold – based risk models

Roeske
Radiother Oncol 2003





Based on delineation of Bowel Loops

Based on delineation of Bowel bag

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

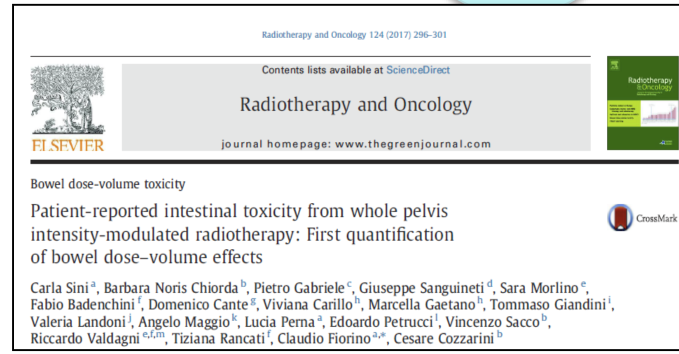
Review: Kavanagh DB, IJROBP 2010 (QUANTEC)

Marks: IJROBP 2010 (QUANTEC)

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]

300 *Bowel dose–volume ef*

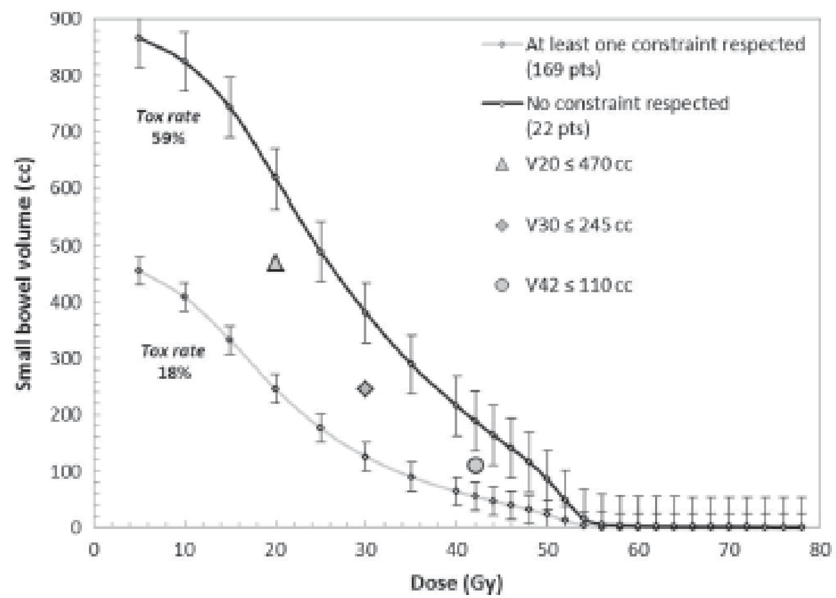


Fig. 4. Absolute average DVHs for patient with/without liquid evacuation (endpoint ΔIBDQ5 < −2) for high risk (V20 > 470 cm^3, V30 > 245 cm^3, V42 > 110 cm^3, n = 22) and low risk (the others, n = 169) patients. Error bars denote standard error.

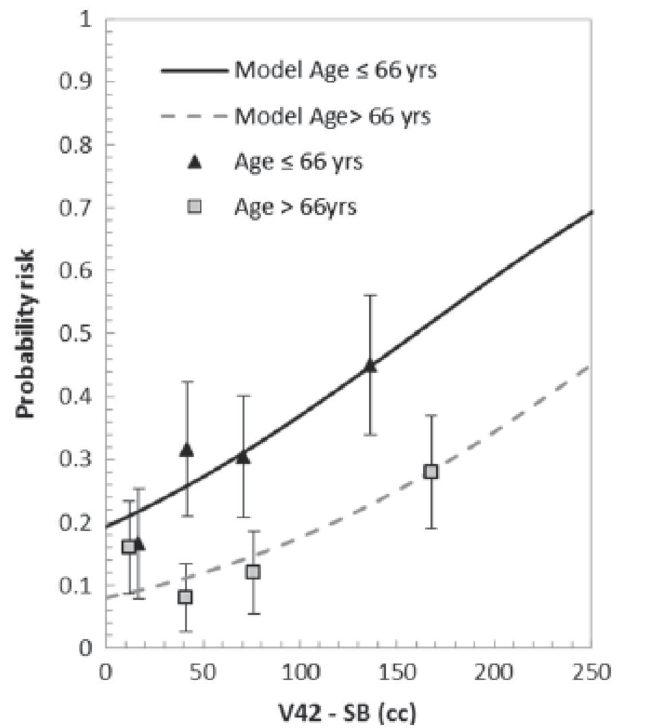


Fig. 3. Risk of acute liquid evacuation vs bowel V42 for patients older and younger than 66 years.

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 LATE Radiographical: anatomical, functional Biochemical (blood test, functional test) Degree of severity Degree of frequency Impact on quality of life (QOL)
VI	Issues on reporting of toxicity	

Bowel including duodenum
Extended field RT

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 60 – 65 Gy

Literature data dose constraints rectum & bladder

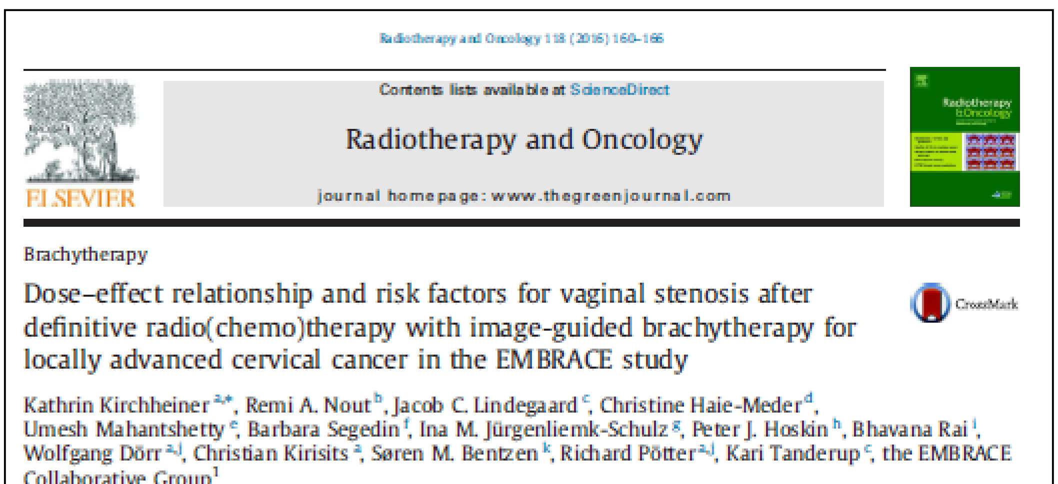
Study	Bladder constraints	Rectum constraints	Sigmoid constraints	Femoral heads
Jhingran *et al.*(RTOG 0418)	V45<35%	V45<60%		V30<15%
Gandhi *et al.*(AIIMS)	V40<40% Dmax <50Gy	V40<40% Dmax <50Gy		
Mouttet –Audouard *et al* (Centre Oscar Lambret)	V40<50% V45<20% Dmax<60Gy	V40<50% V45<20% Dmax<60Gy	V40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

Vagina

Also vagina does not like EBRT dose

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

Kirchheiner 2016



Radiotherapy and Oncology 118 (2016) 160–166

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Brachytherapy

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

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

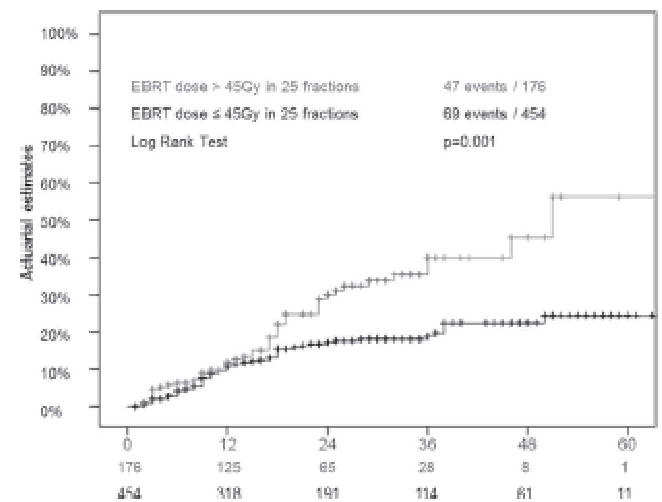


Fig. 3. Actuarial estimates for vaginal stenosis G ≥ 2 in patients according to the EBRT dose.

Do we need dose constraints and DVH parameters?

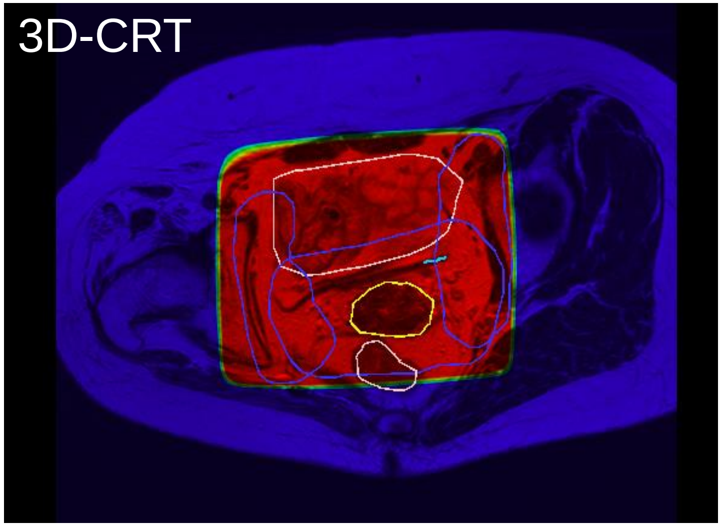
Yes !

- 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”

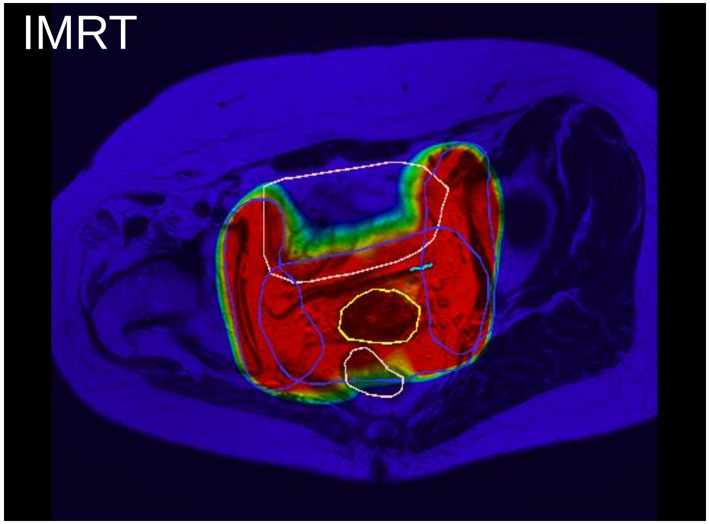
How to achieve the required dose gradients ?

Modern EBRT planning; IMRT

3D conformal



7 beam IMRT

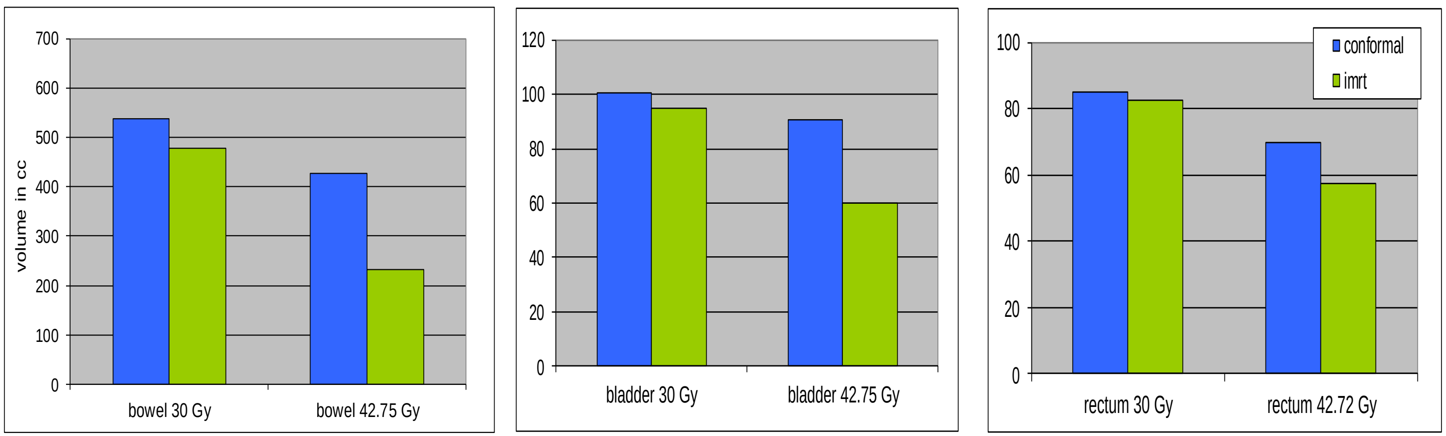


IMRT versus 3D-CRT

Single institution experience

•Advantage IMRT over 3D Conformal for organ sparing

•Volume of OAR receiving high dose significantly smaller with IMRT



Van de Bunt 2006

CLINICAL INVESTIGATION Cervix

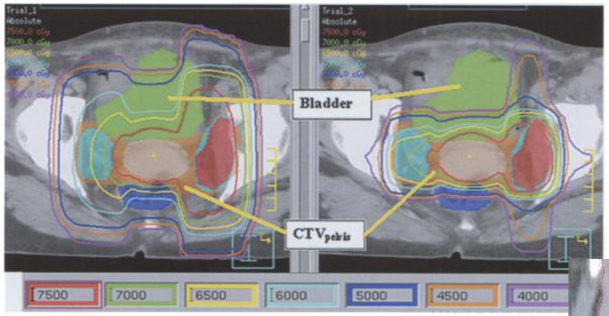
CONVENTIONAL, CONFORMAL, AND INTENSITY-MODULATED RADIATION THERAPY TREATMENT PLANNING OF EXTERNAL BEAM RADIOTHERAPY FOR CERVICAL CANCER: THE IMPACT OF TUMOR REGRESSION

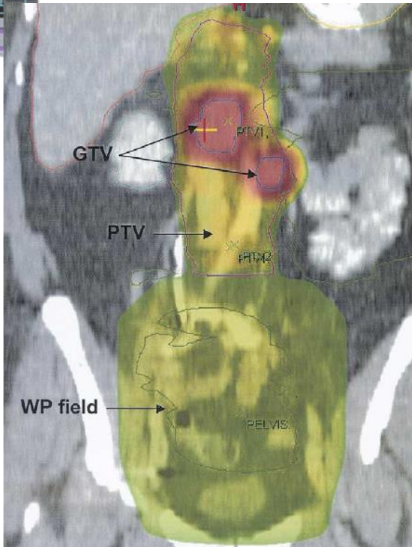
LINDA VAN DE BUNT, M.D.,* UULKE A. VAN DER HEIDE, PH.D.,* MARTIJN KETELAARS, PH.D.,* GERARD A. P. DE KORT, M.D.,† AND INA M. JÜRGENLIEMK-SCHULZ, M.D., PH.D.*

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

Use of IMRT Techniques in GYN Cancers- Clinical Evidence

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





Sem Rad Oncol. 2002

Yang Radiation Oncology 2012, 7:197

Dosimetric meta-analysis

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

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

Yang Radiation Oncology 2012, 7:197

Dosimetric meta-analysis Summary

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

Pooled averages

Yang Radiation Oncology 2012,7:197

Increasing utilization of IMRT

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

Smith 2015

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Clinical Investigation

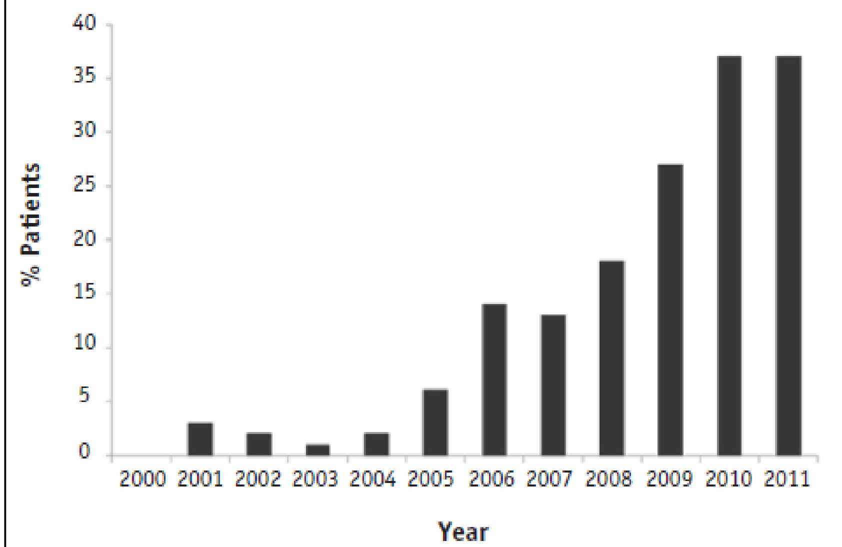
Trends in the Quality of Treatment for Patients With Intact Cervical Cancer in the United States, 1999 Through 2011

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

Received Nov 6, 2014, and in revised form Jan 23, 2015. Accepted for publication Jan 27, 2015.



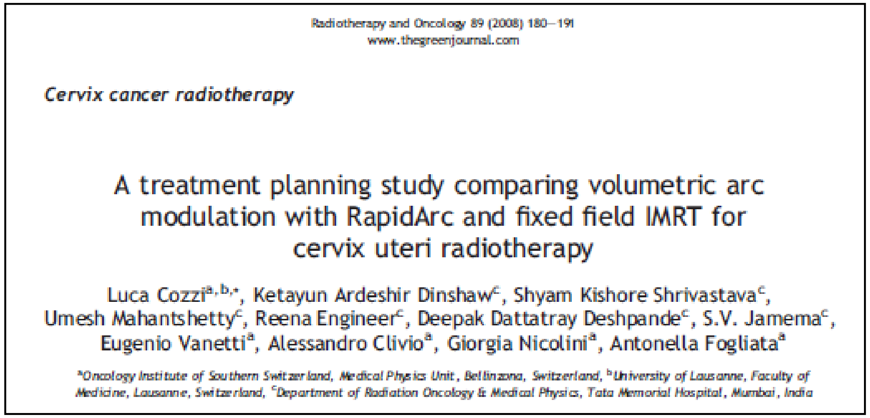
Developments in IMRT technique

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

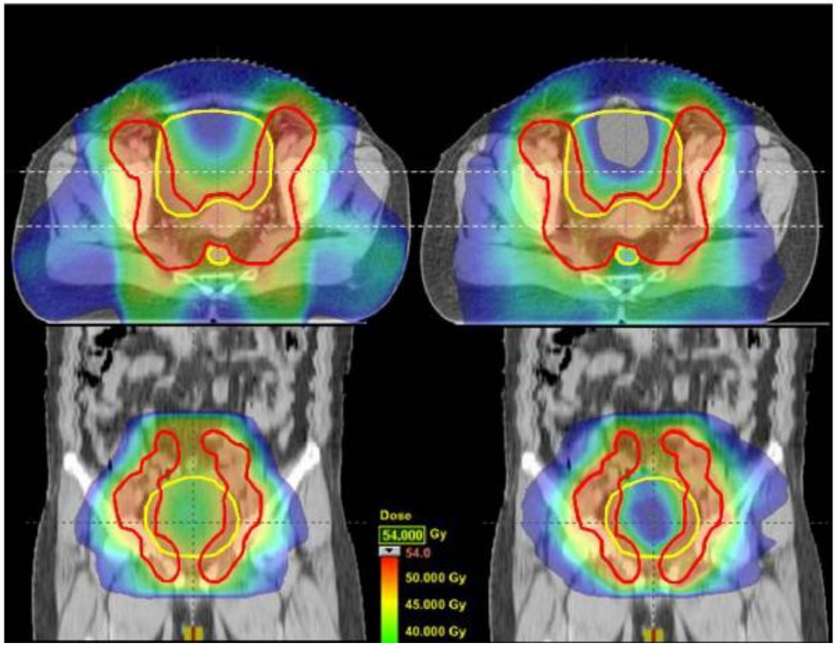
Cervix cancer radiotherapy

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

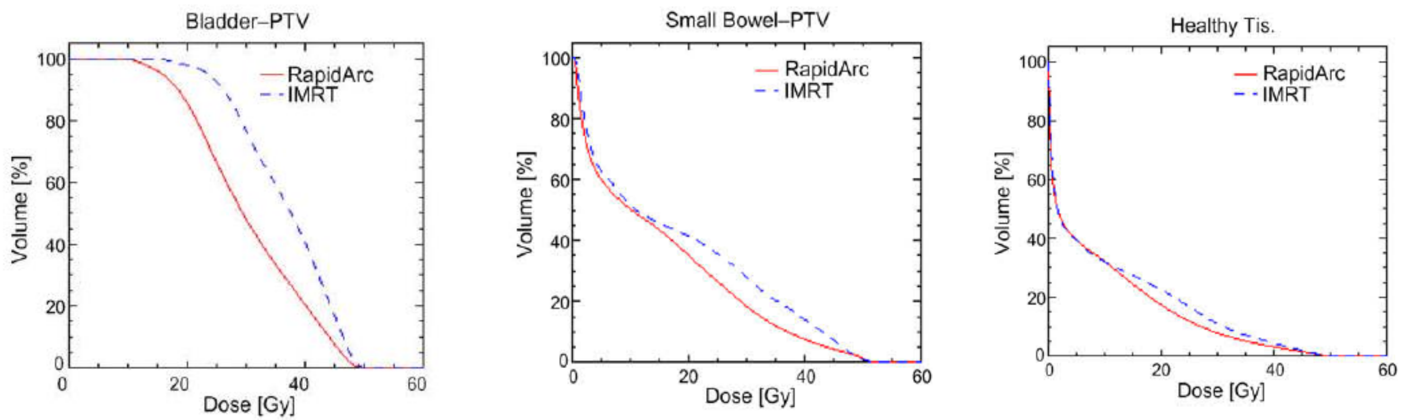
Luca Cozzi[a,b,*], Ketayun Ardeshir Dinshaw[c], Shyam Kishore Shrivastava[c], Umesh Mahantshetty[c], Reena Engineer[c], Deepak Dattatray Deshpande[c], S.V. Jamema[c], Eugenio Vanetti[a], Alessandro Clivio[a], Giorgia Nicolini[a], Antonella Fogliata[a]

[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

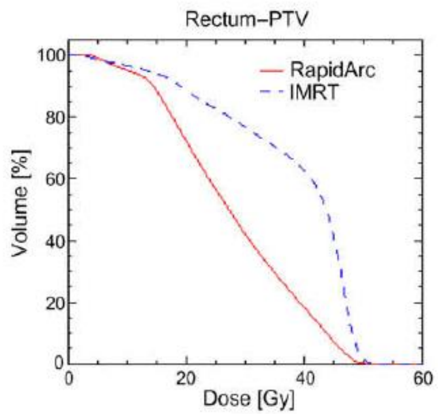
IMRT **VMAT**



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!

Developments in proton therapy for gyn cancers

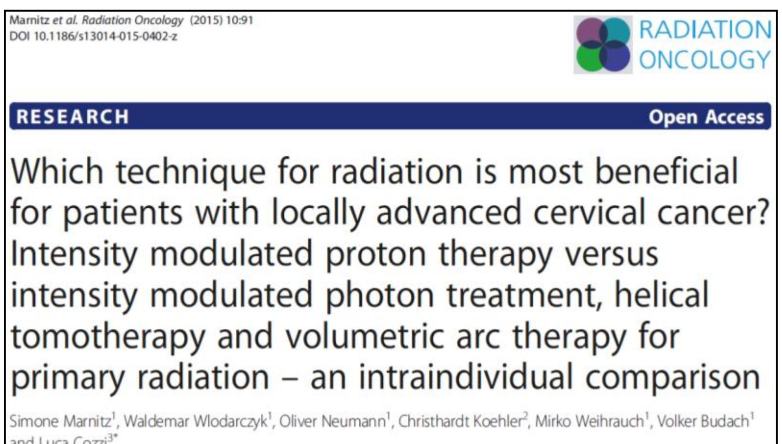
Proton IMRT versus photon IMRT/VMAT/Tomotherapy

•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*]

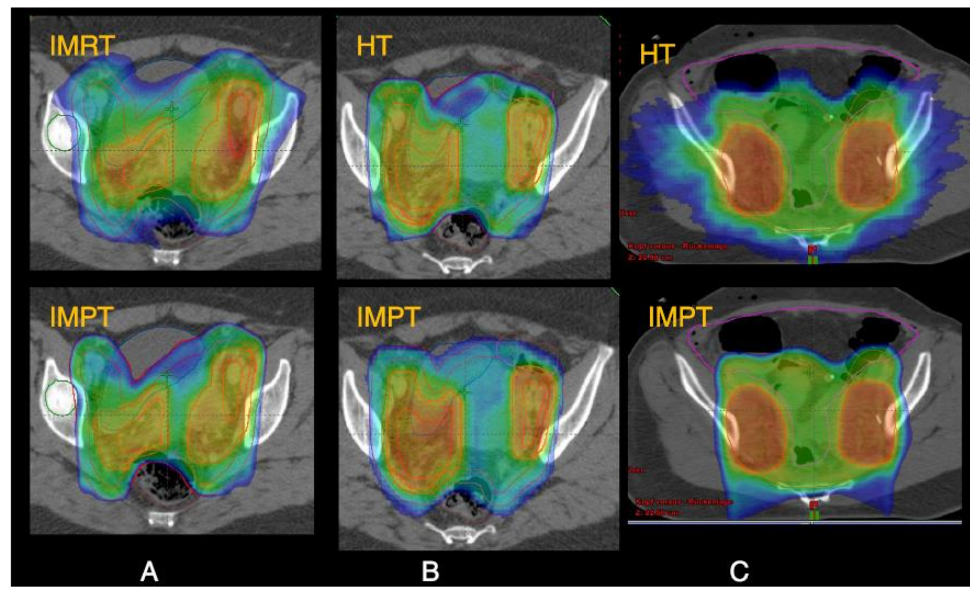
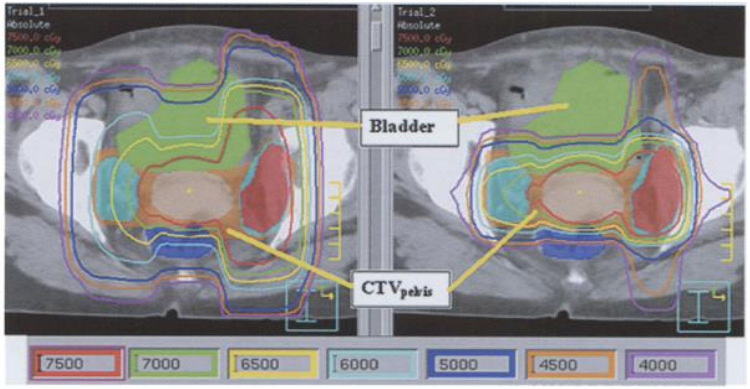
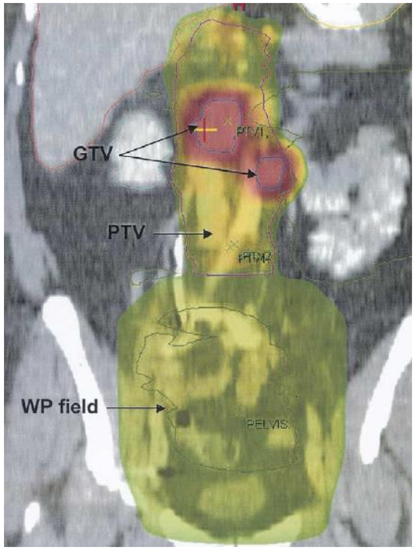


Figure 3 Examples of rectum and bowel sparing potential between techniques. **A** and **B**: rectum, colorwash is at 45 Gy; **B**: SB, colowash is at 30 Gy.

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





AIIMS INDIA STUDY

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

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

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

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

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

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

Significant reduction in V40 for Rectum, bladder and small bowel

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

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

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

GI Chronic toxicity

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

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

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

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	100 patients
Conventional External RT (40 Gy /20#)	IMRT Pelvis (50 Gy/25#)
+ ICA – HDR (7 Gy x 5#)	+ ICA – HDR (7 Gy x 5#)
with Concomitant Chemo-radiation	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

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
- Final analysis will be presented in ESTRO 2018 Conference

Post Operative IMRT in GYN Cancers

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

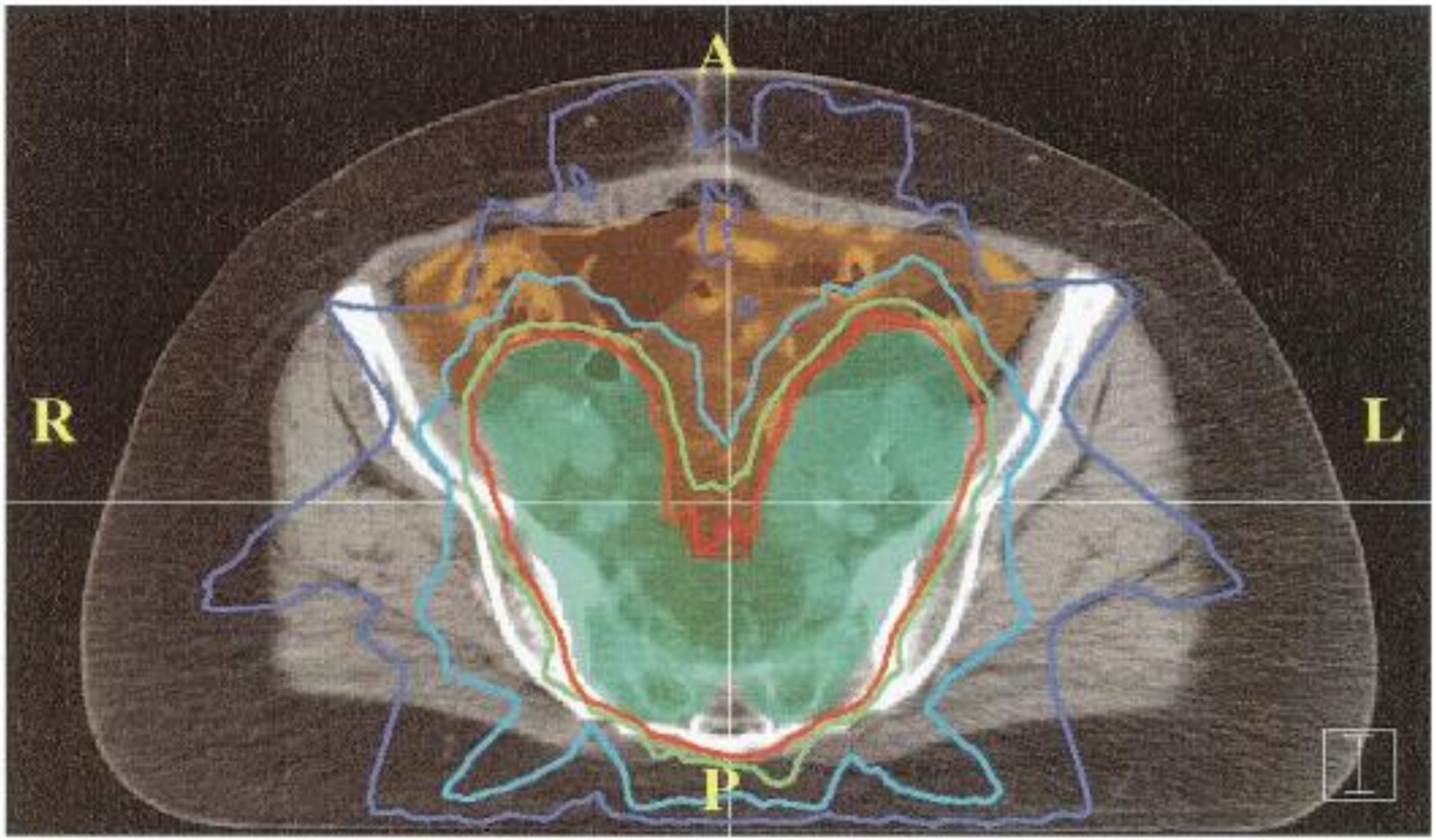


Fig. 2. Isodose curves from an IM-WPRT plan superimposed on an axial CT slice through the upper pelvis. The small bowel and PTV are shaded in orange and green, respectively. Highlighted are the 100% (red), 90% (green), 70% (light blue), and 50% (dark blue) isodose curves.

RTOG 0418

A phase II study of post op IMRT in gynecological cancer

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

IJROBP 2013

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

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

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

IJROBP 2013

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

Post Hysterectomy
Needs Adjuvant RT

Hypothesis: IMRT will significantly reduce grade ≥ II late bowel toxicity with postoperative radiation

Stratified Randomization
Type of Hysterectomy
Use of Concurrent Chemotherapy

N=120
Standard RT

N=120
IG-IMRT (Tomotherapy)

CTCAE version 3.0, QOL (EORTC QLQ C30 & Cx-24)

Interim Analysis Planned : 50% complete F/up of 18 mths.

Bowel Doses : 3DCRT vs. IMRT

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

IMRT led to significant reduction in Bowel and PC doses

S Chopra et al; ASTRO 2015

Primary Endpoint

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

Median Follow Up = 20 months

14% absolute difference; statistically insignificant at interim analysis

S Chopra et al; ASTRO 2015

Dose Constraints : Literature

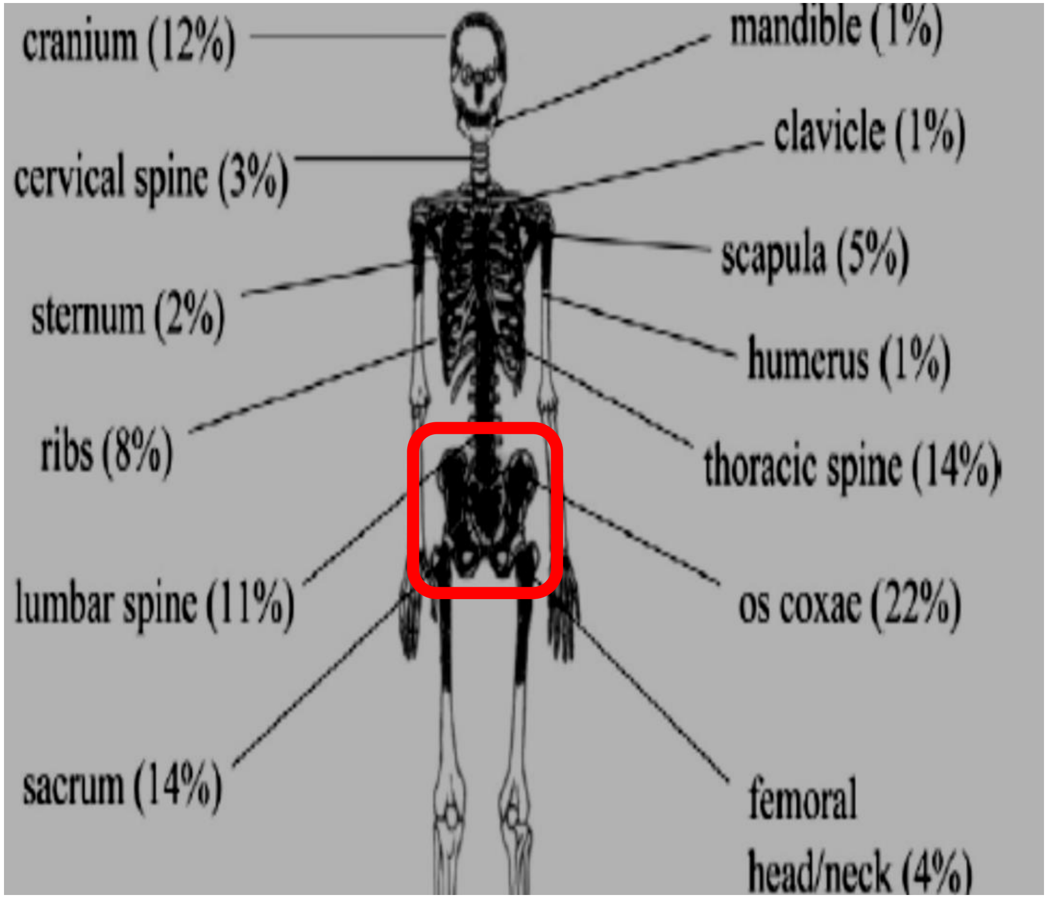
Study	Bladder Constraints	Rectum constraints	Sigmoid constraints	Femoral Heads
Jhingran *et al.*(RTOG 0418)	V45<35%	V45<60%		V30<15%
Gandhi *et al.*(AIIMS)	V40<40% Dmax <50Gy	V40<40% Dmax <50Gy		
Mouttet – Audouard *et al* (Centre Oscar Lambret)	V40<50% V45<20% Dmax<60Gy	V40<50% V45<20% Dmax<60Gy	V40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

Bowel Bag :V45 < 200 cc for <10% probability for $\geq$ Gr 3 toxicity

PET-CT Based Active Bone Marrow as a potential OAR

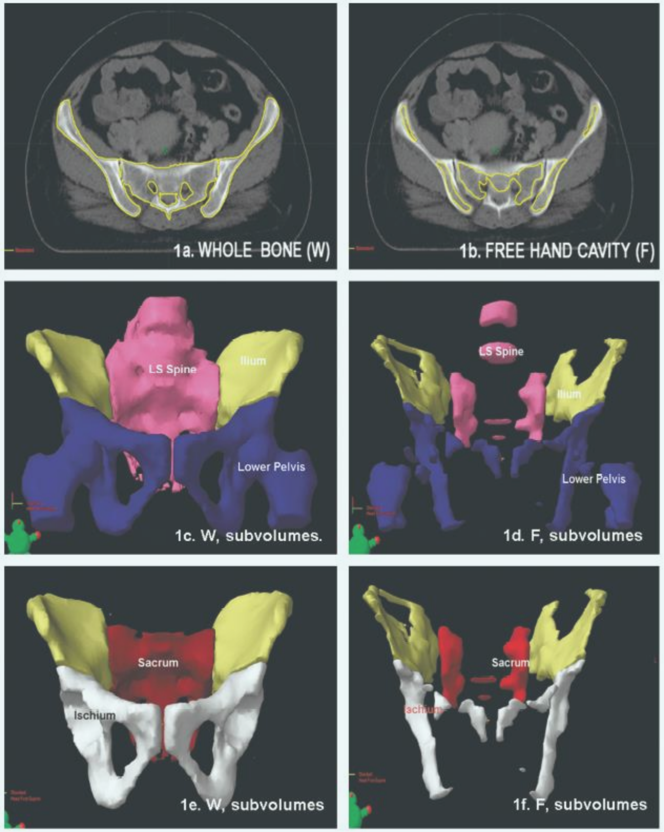
Bone marrow : Organ at risk for haematological toxicities

Adult: Haematopoietic Tissue Distribution

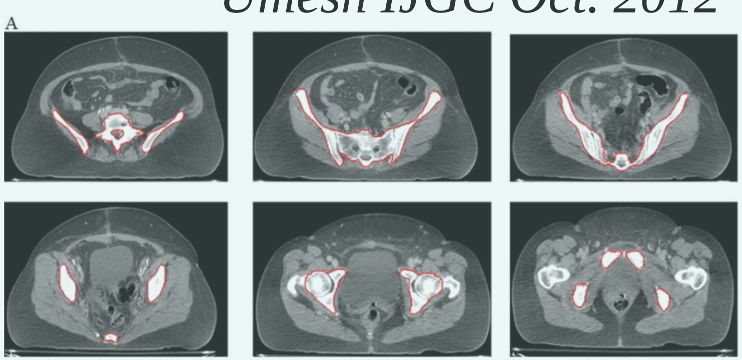


- **Approx. 45-50% of active marrow in pelvic field**
- **Constitutes critical mass for toxicities**

CT Based

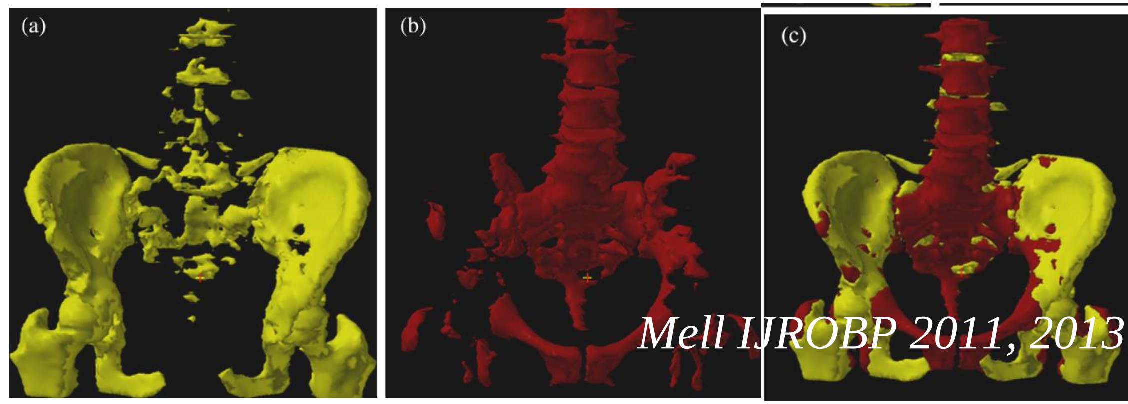


Umesh IJGC Oct. 2012

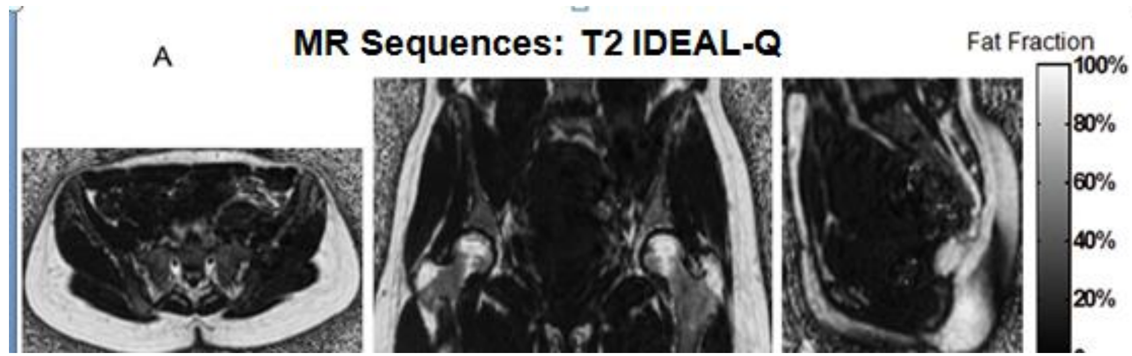


IJROBP 2013

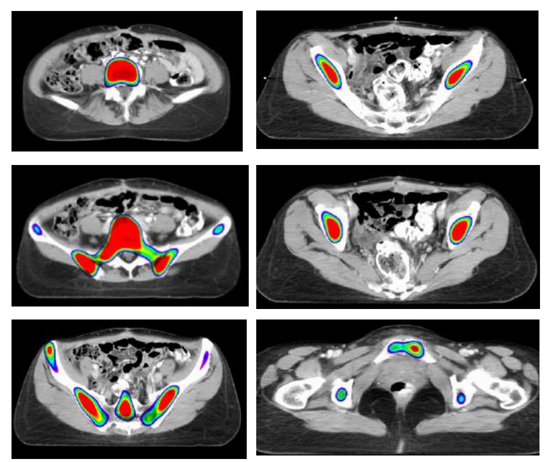
FDG PET: SUV > Mean corrected for body weight



Mell IJROBP 2011, 2013

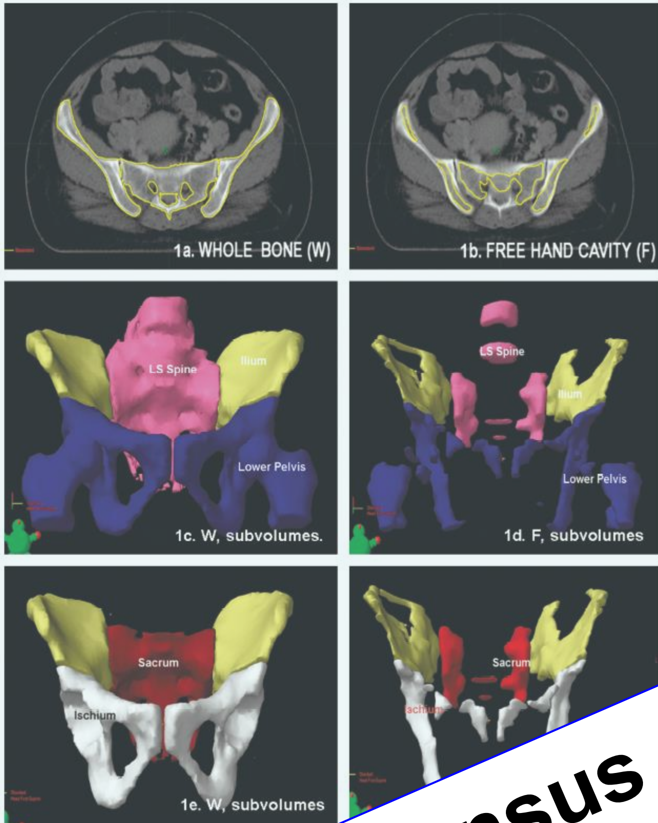


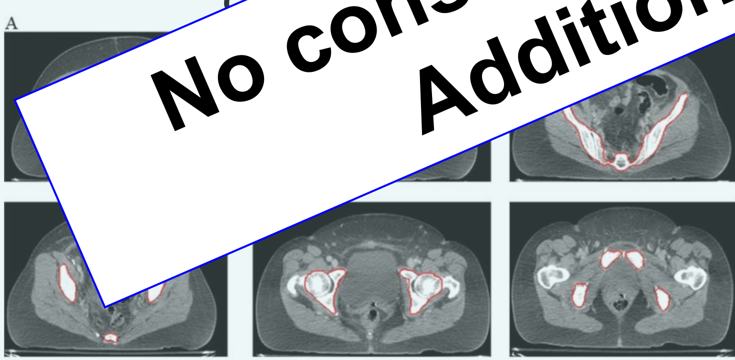
SPECT-CT: Tc 99m sulphur colloid defined hot-spots



Roeske et al; Rad. Oncol 2005

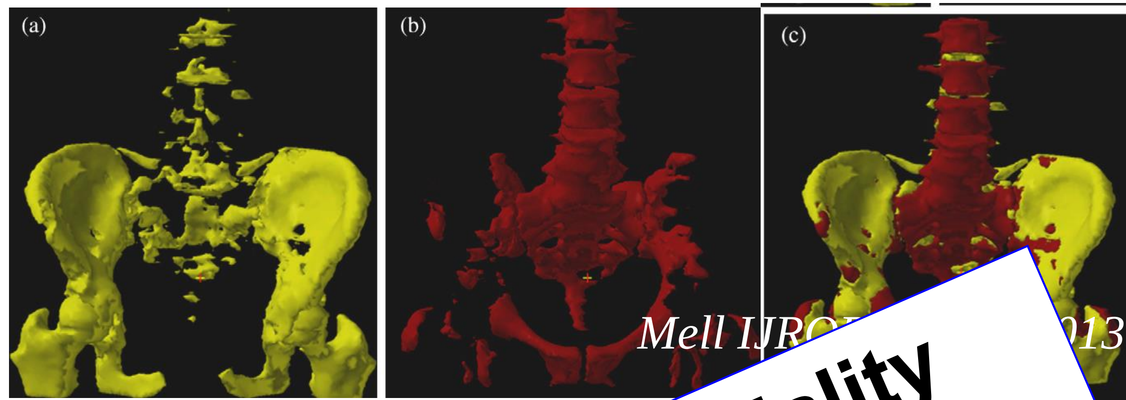
CT Based





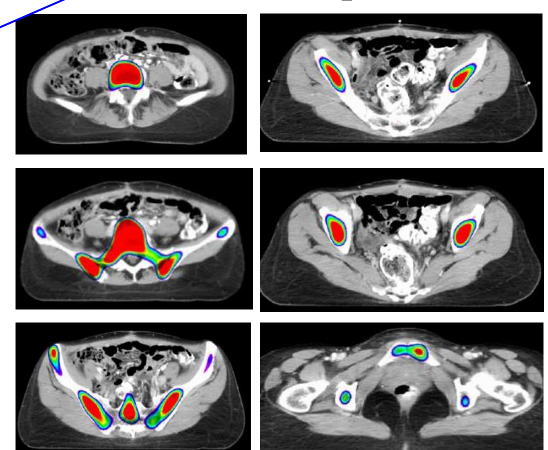
IJROBP 2013

FDG PET: SUV > Mean corrected for body weight



Mell IJR... 013

... 1c 99m sulphur colloid defined hot-spots



Roeske et al; Rad. Oncol 2005

No consensus on optimal single modality
Additional Research Required

Comparison of various studies

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

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

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

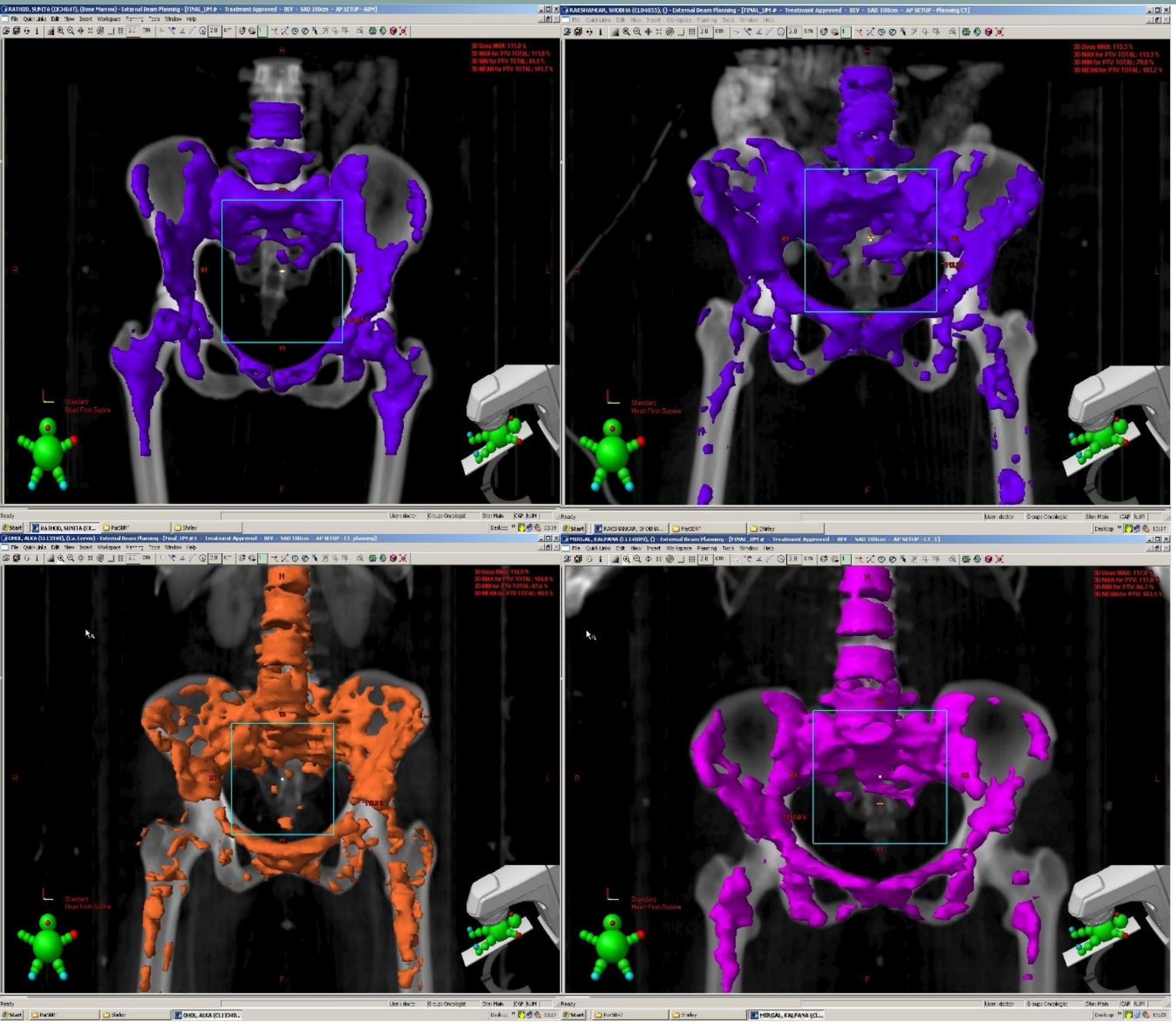
International Evaluation of Radiotherapy Technology Effectiveness in Cervical Cancer (INTERTECC): Phase II/III Trial of Intensity Modulated Radiotherapy

UC San Diego
RADIATION ONCOLOGY

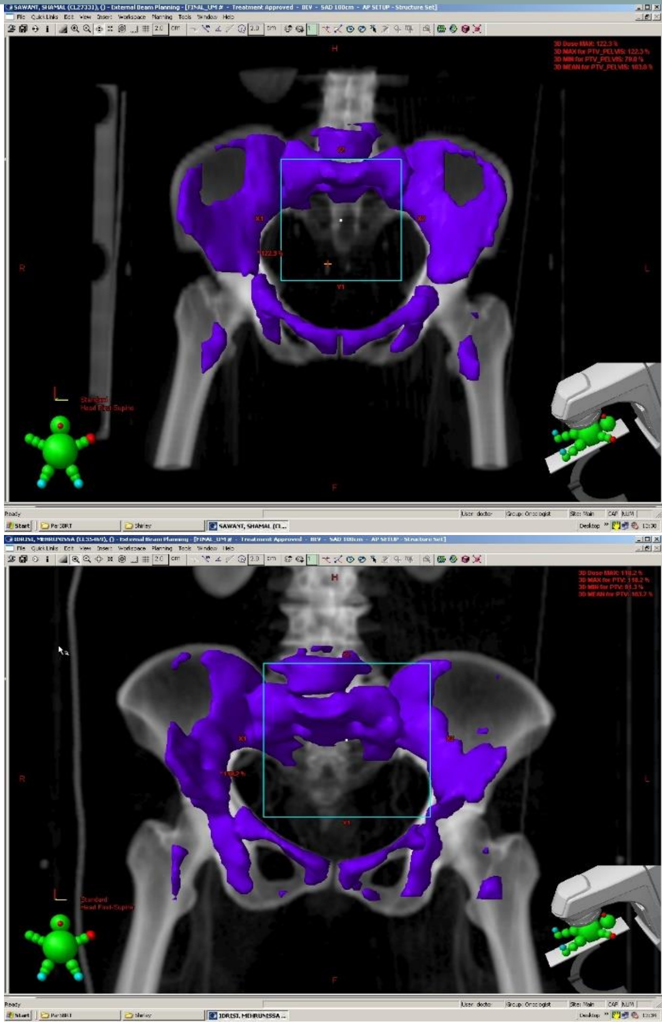
CART UCSD
CENTER FOR ADVANCED RADIOTHERAPY TECHNOLOGIES

INTERTECC Trial: Multi-centric International Study

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



FDG PET based contouring



FLT PET based contouring

TMH Experience : 9 pts recruited in phase II study

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

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

INTERTECC Preliminary Data: Jan 2015

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

Courtesy: Loren Mell UCSD; PI INTERTECC

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

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

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

RESULTS:

- October 2011 to April 2015, (median follow-up was 26.0 months)
- 83 patients
- The incidence of any primary event was 26.5% (95% [CI] 18.2%-36.9%), significantly lower than the 40% incidence hypothesized a priori from historical data (P=.012).

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

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

CONCLUSIONS:

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

Ongoing evidence for improving treatment planning – EMBRACE II

Clinical and Translational Radiation Oncology 9 (2018) 48–60

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

Review Article

The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies

Richard Pötter [a,1], Kari Tanderup [b,1,*], Christian Kirisits [a], Astrid de Leeuw [c], Kathrin Kirchheiner [a], Remi Nout [d], Li Tee Tan [e], Christine Haie-Meder [f], Umesh Mahantshetty [g], Barbara Segedin [h], Peter Hoskin [i], Kjersti Bruheim [j], Bhavana Rai [k], Fleur Huang [l], Erik Van Limbergen [m], Max Schmid [a], Nicole Nesvacil [a], Alina Sturdza [a], Lars Fokdal [b], Nina Boje Kibsgaard Jensen [b], Dietmar Georg [a], Marianne Assenholt [b], Yvette Seppenwoolde [a], Christel Nomden [c], Israel Fortin [a,o], Supriya Chopra [g], Uulke van der Heide [n], Tamara Rumpold [a], Jacob Christian Lindegaard [b], Ina Jürgenliemk-Schulz [c], the EMBRACE Collaborative Group [2]

[a] Department of Radiation Oncology, Comprehensive Cancer Center, Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Austria

- 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

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	

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%

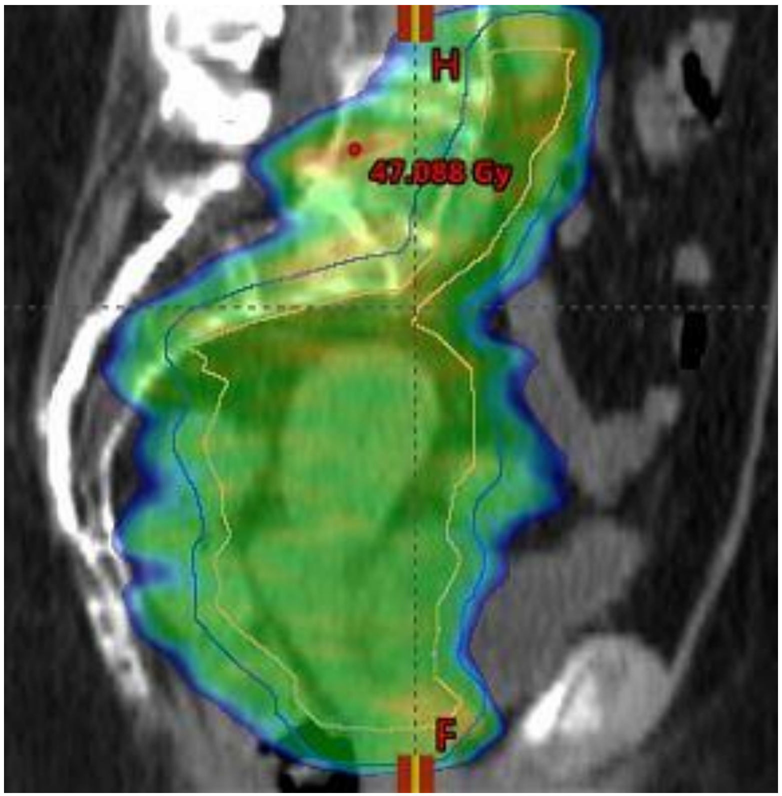
* Soft constraints which can be used in the treatment plan optimisation. Values are based on the clinical data of EMBRACEII patients entered in the study before June 2017. The constraints are not supposed to be fulfilled by all patients, but rather by ~70-80% of the patients.

Impact on dose distribution

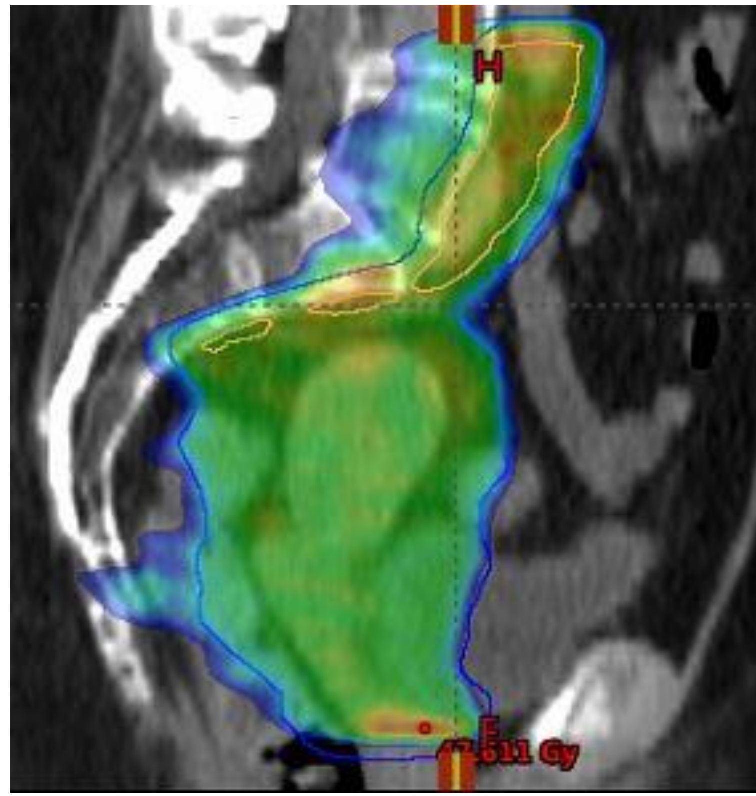
Comparison EBRT volumes treated in EMBRACE I and EMBRACE II

- V 40 Gy

EMBRACE I



EMBRACE II



Courtesy Thomas Berger

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 by offering more degrees of freedom
- Pre-defined 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 !

Homework EBRT planning

ESTRO GYN BT course

Lucknow 2018

Find your institution number

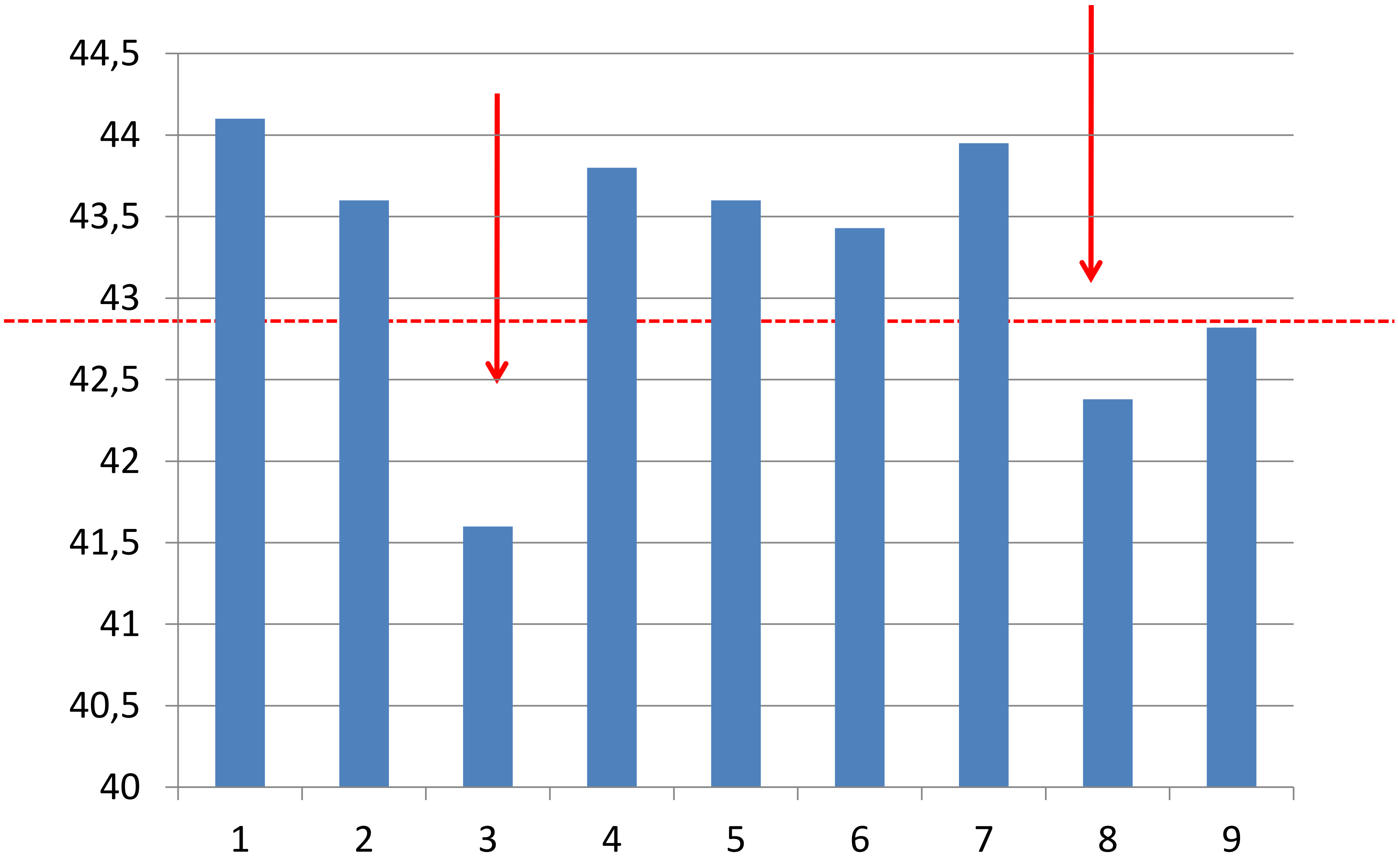
Tata reference plan EMBRACE II	1
BHU	2
Guru Gobind Singh MC&H, Faridkot	3
Indo American, Hyderabad	4
Max Hospital, Delhi (Masanta)	5
University Hospital , Malaysia	6
Apollo Cancer Institute, (Kasirajan)	7
Sharma	8
Rajesh	9
MSR, Bangalore	10

Targets - Evaluation criteria

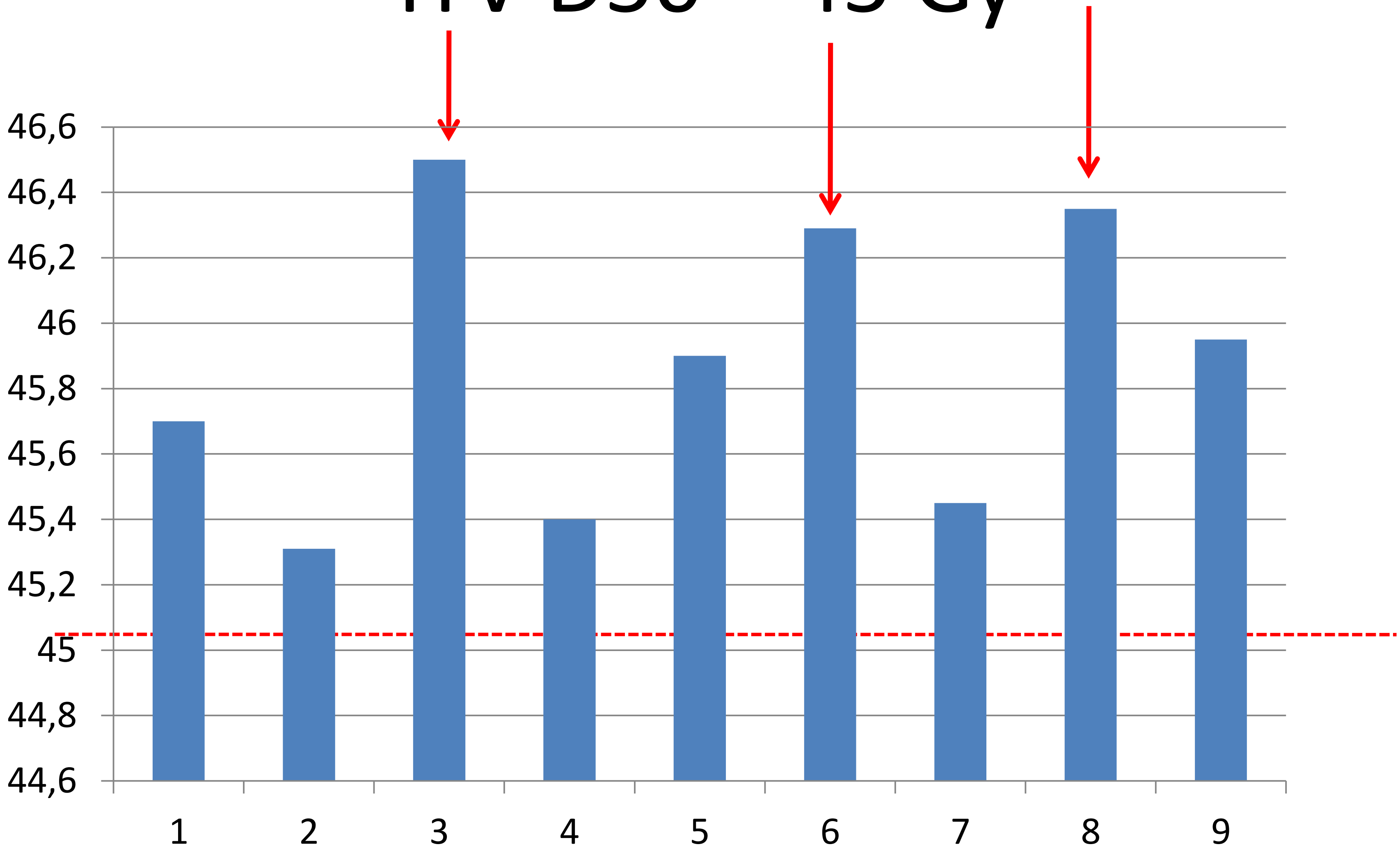
- Hard dose plan criteria must be fulfilled

		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



ITV D50 ~ 45 Gy



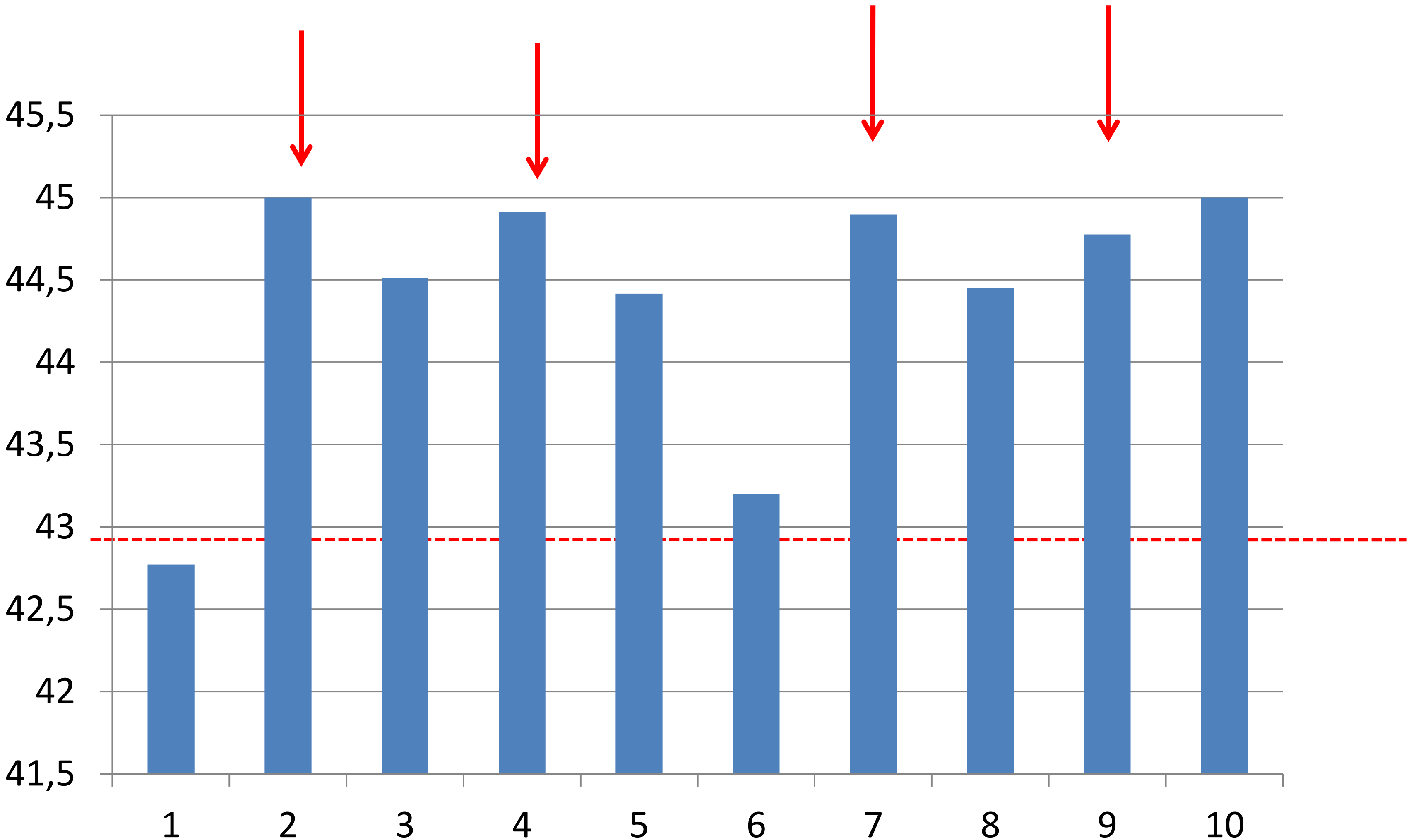
ITV45

- ITV45 coverage
  - 2/8 institutions did not fulfill Dmin ≥ 95%
- ITV45 D50 too high
  - 3 institutions had D50>46.0Gy

PTV45

- Coverage criteria for PTV45: V95% ≥ 95%
  - The spirit and aim in EMBRACE II is to spare normal tissue as much as possible
  - A better coverage than the constraints is NOT a better dose plan ☺

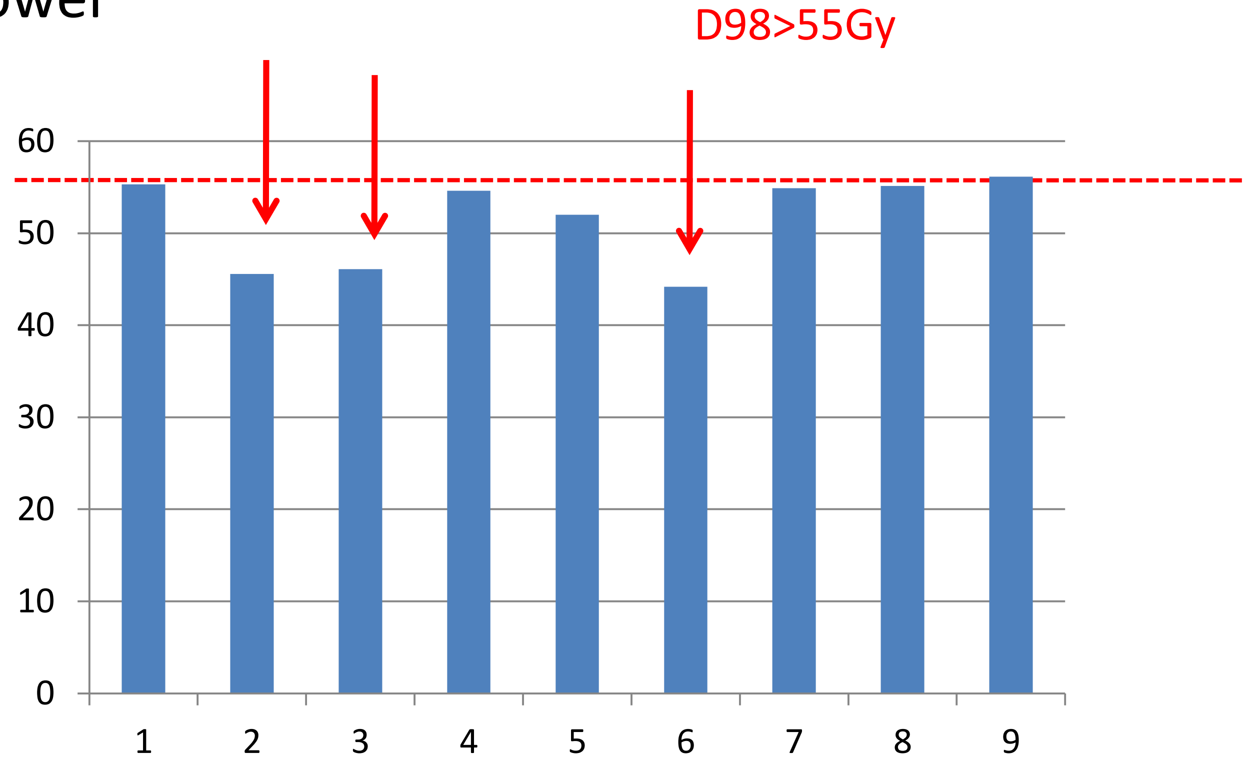
PTV45: V42.75Gy ≥ 95%



Nodal boosting

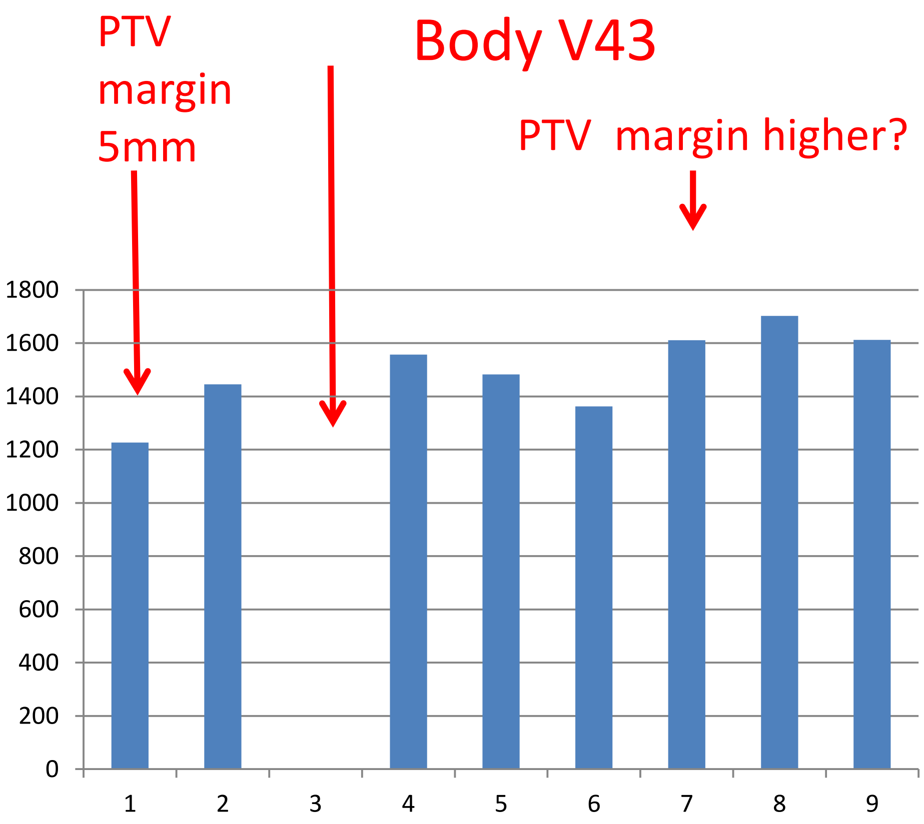
CTV N1 D98

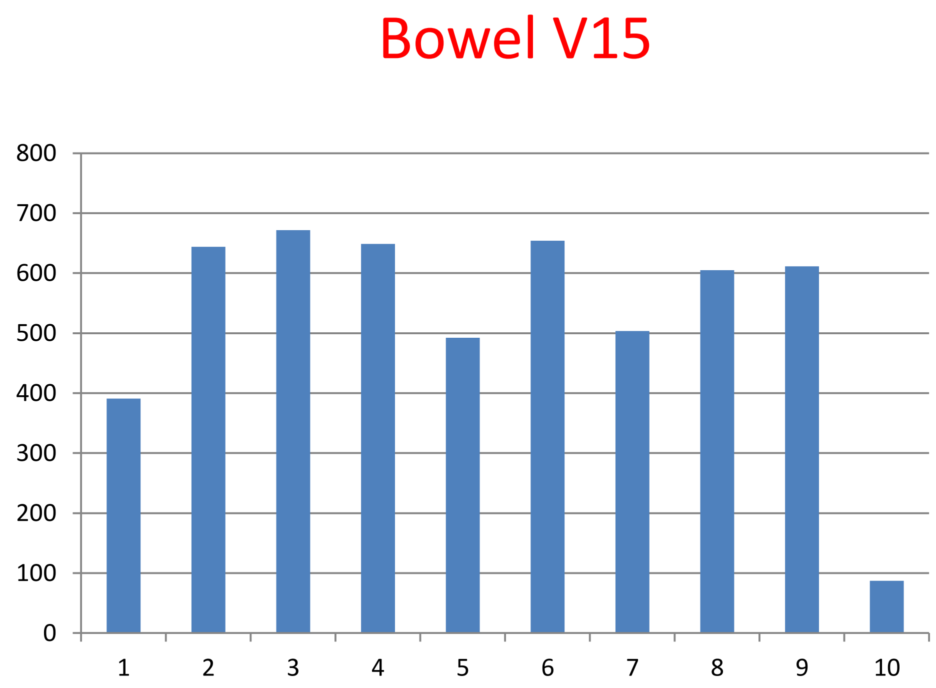
- CTV-N D98>100% of prescribed dose is a hard constraint since the coverage on the edge of PTV-N can be as low as 90% and the margins are small.
- Hard target coverage constraints overrules soft constraints e.g. Bowel



Irradiation of normal tissue

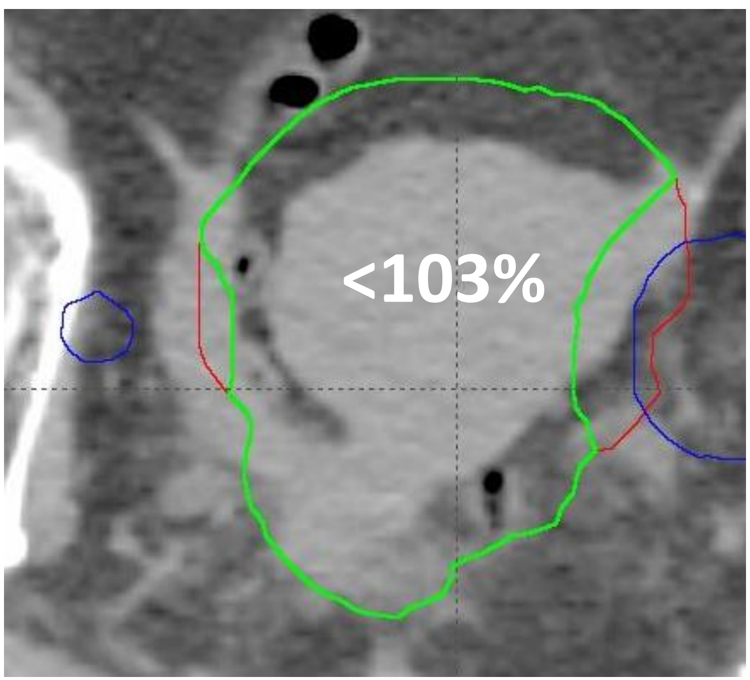
- Difference in irradiated body volume of 1000cm3
- Question of PTV margin
  - 5mm margin expands irradiated volume by 500cm3
  - 10mm margin expands irradiated volume by 1000cm3

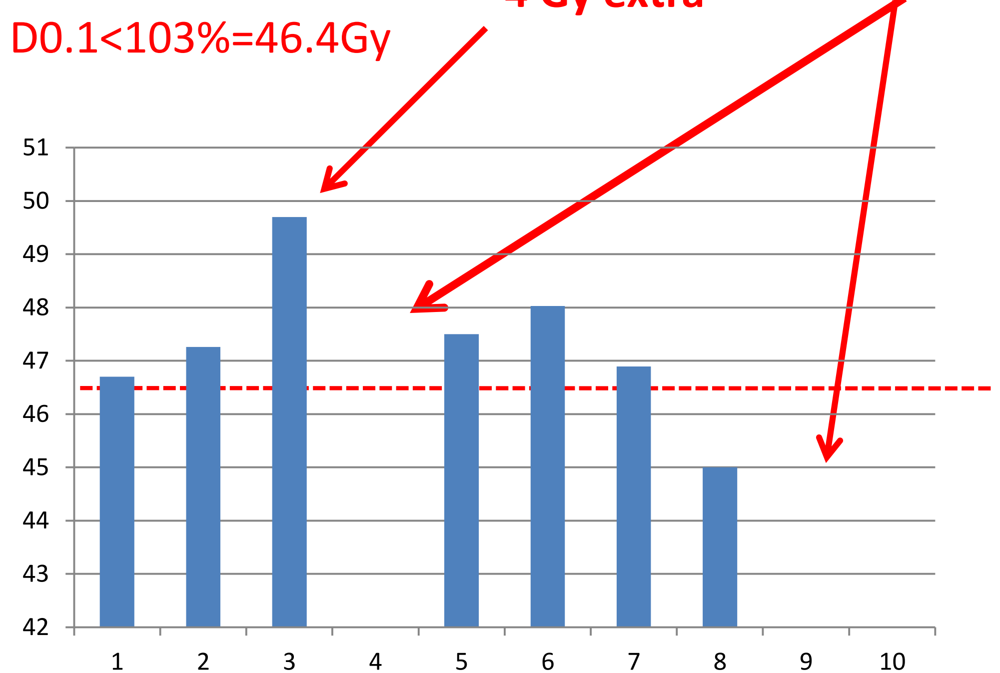




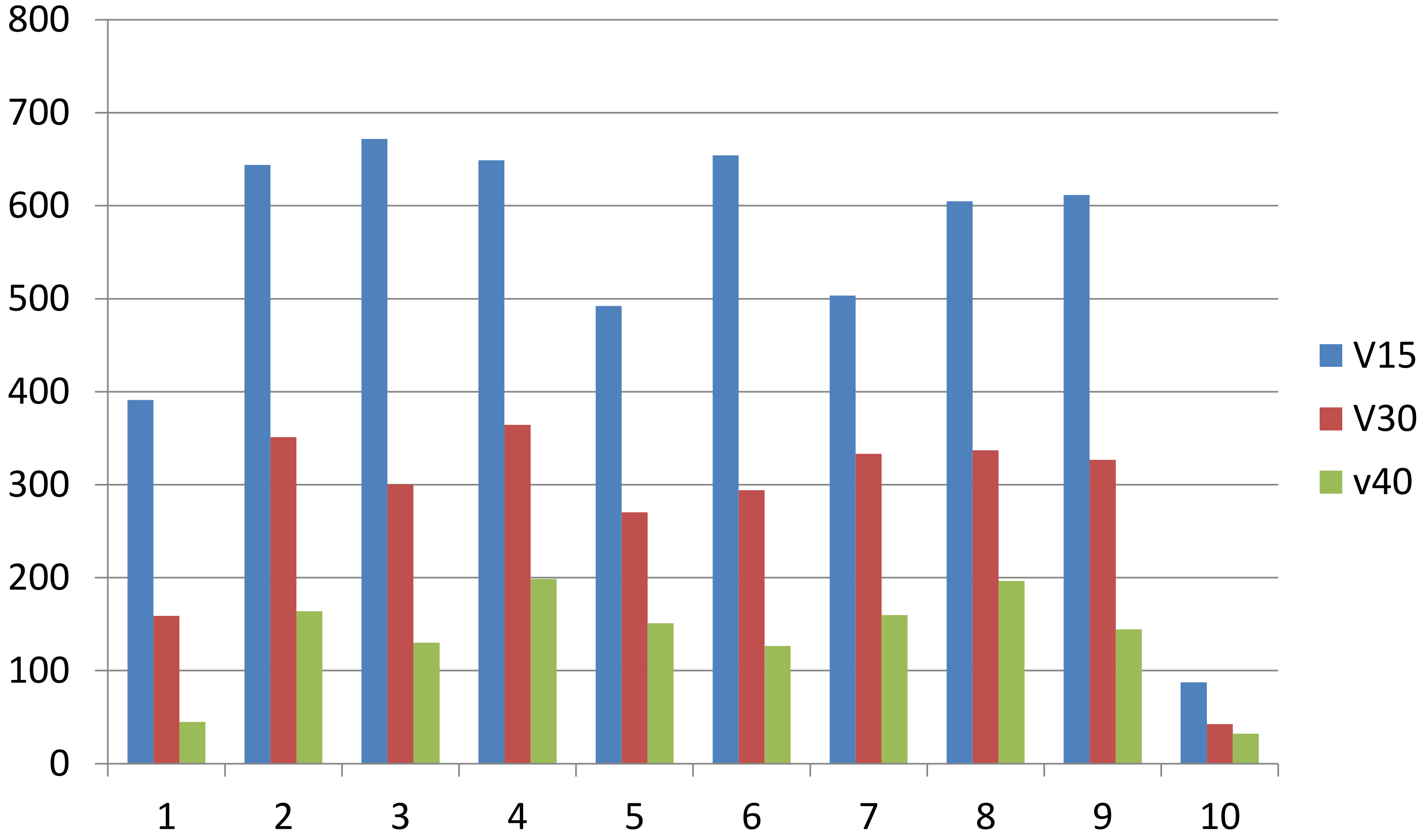
Help contour for homogenity

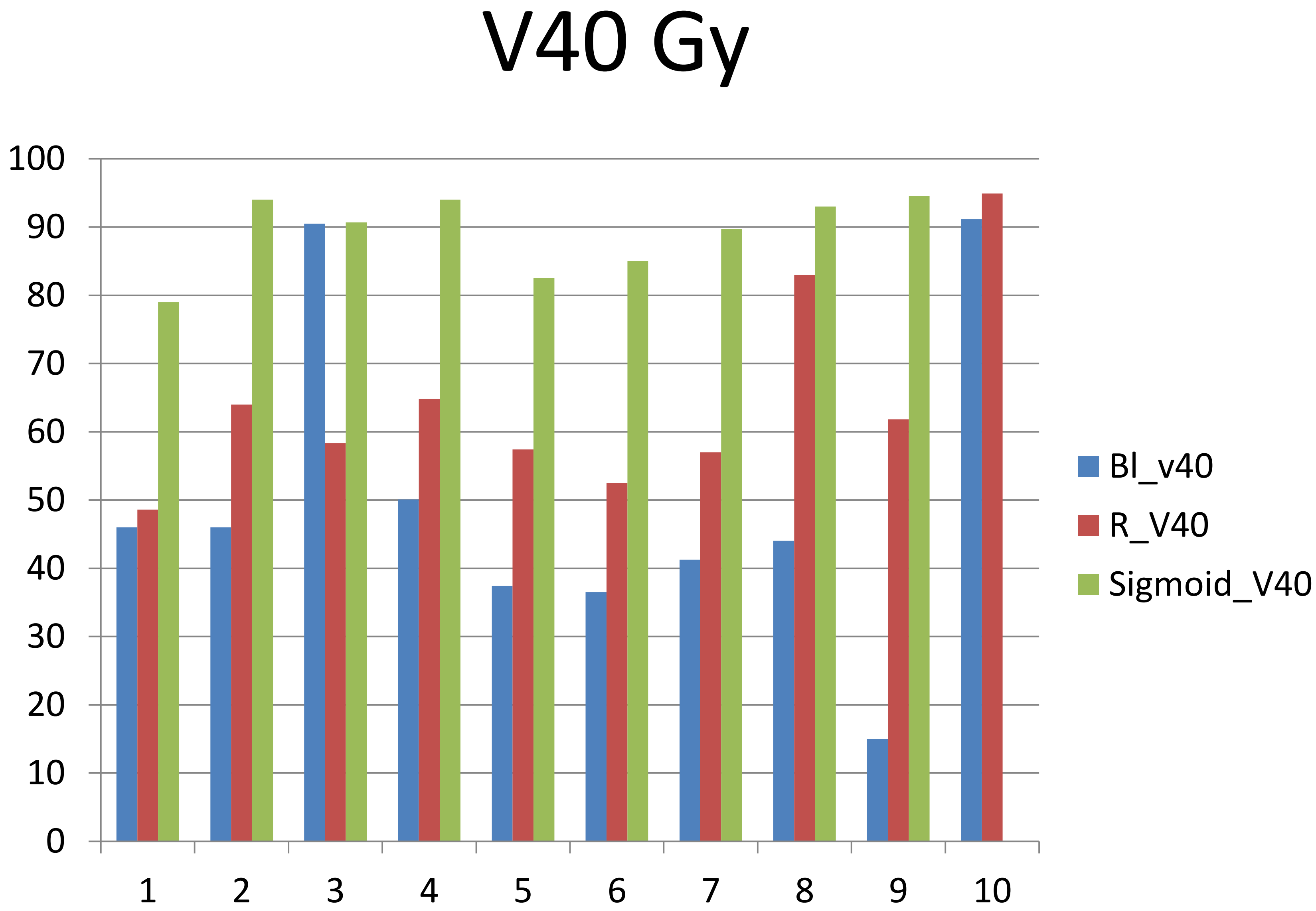
- Control of dose in the region where BT is delivered
- In particular relevant when boosting lymph nodes with simultaneous integrated boost



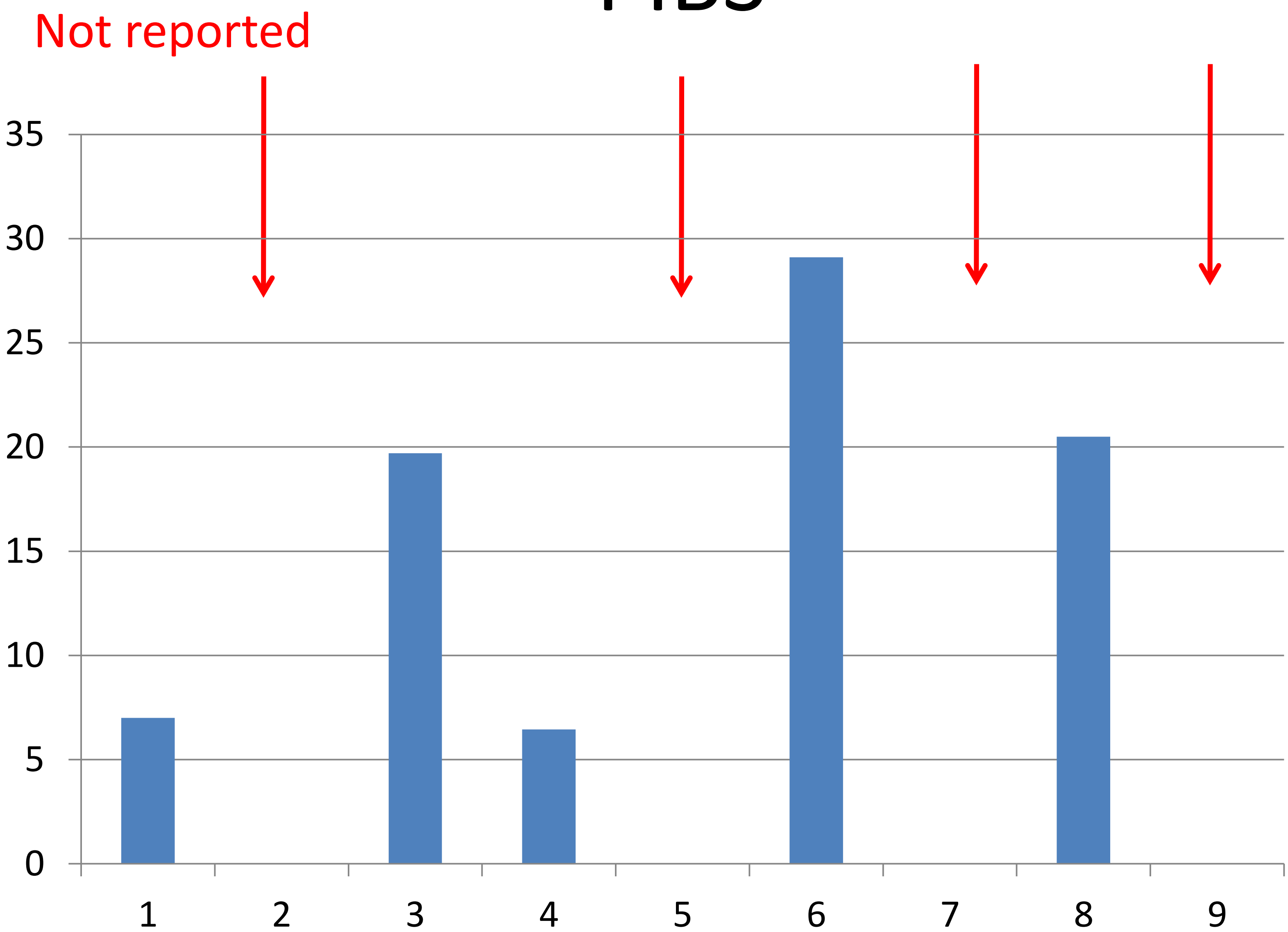


Bowel



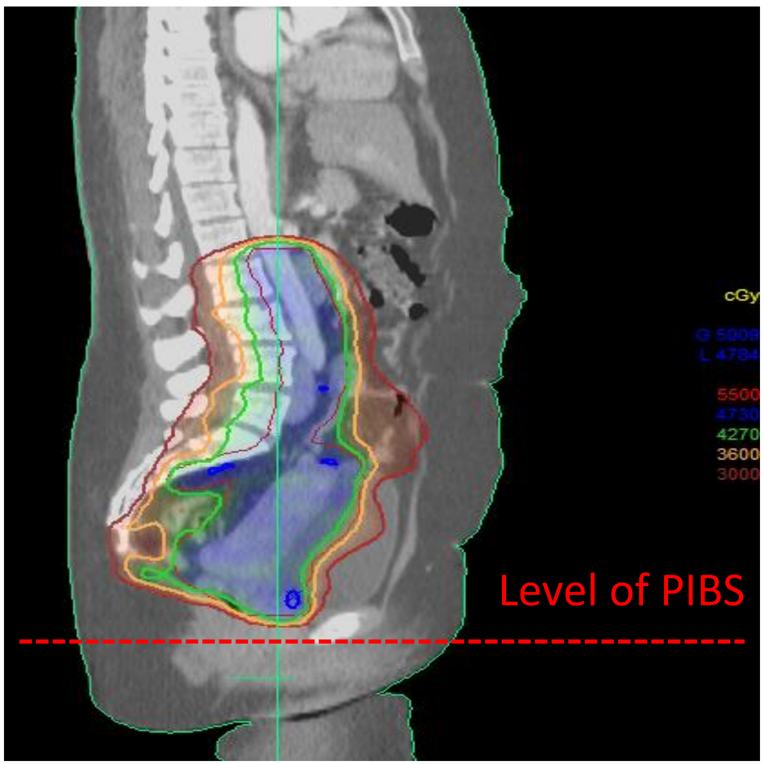

V40 Gy
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
Bl_v40
R_V40
Sigmoid_V40

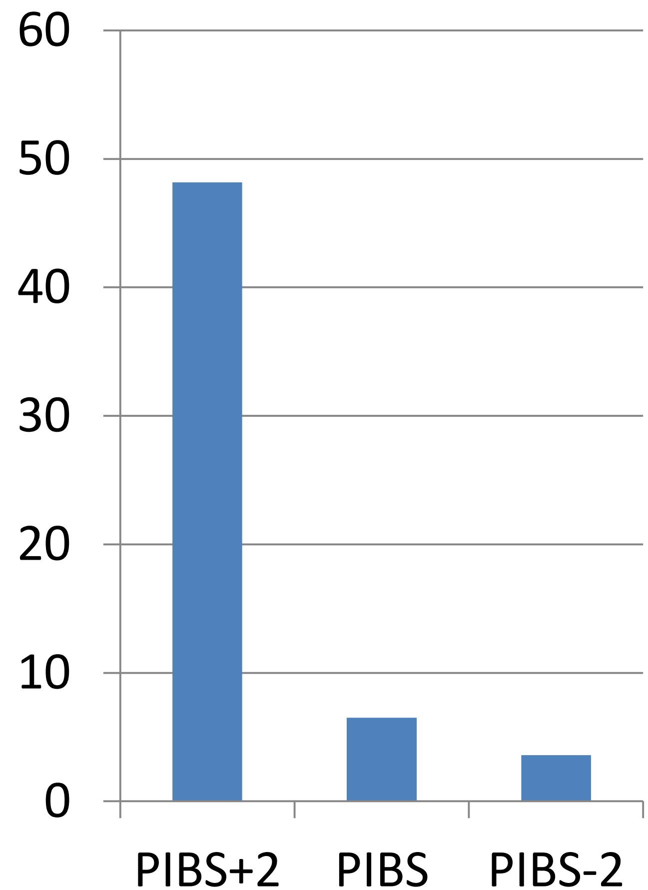
PIBS



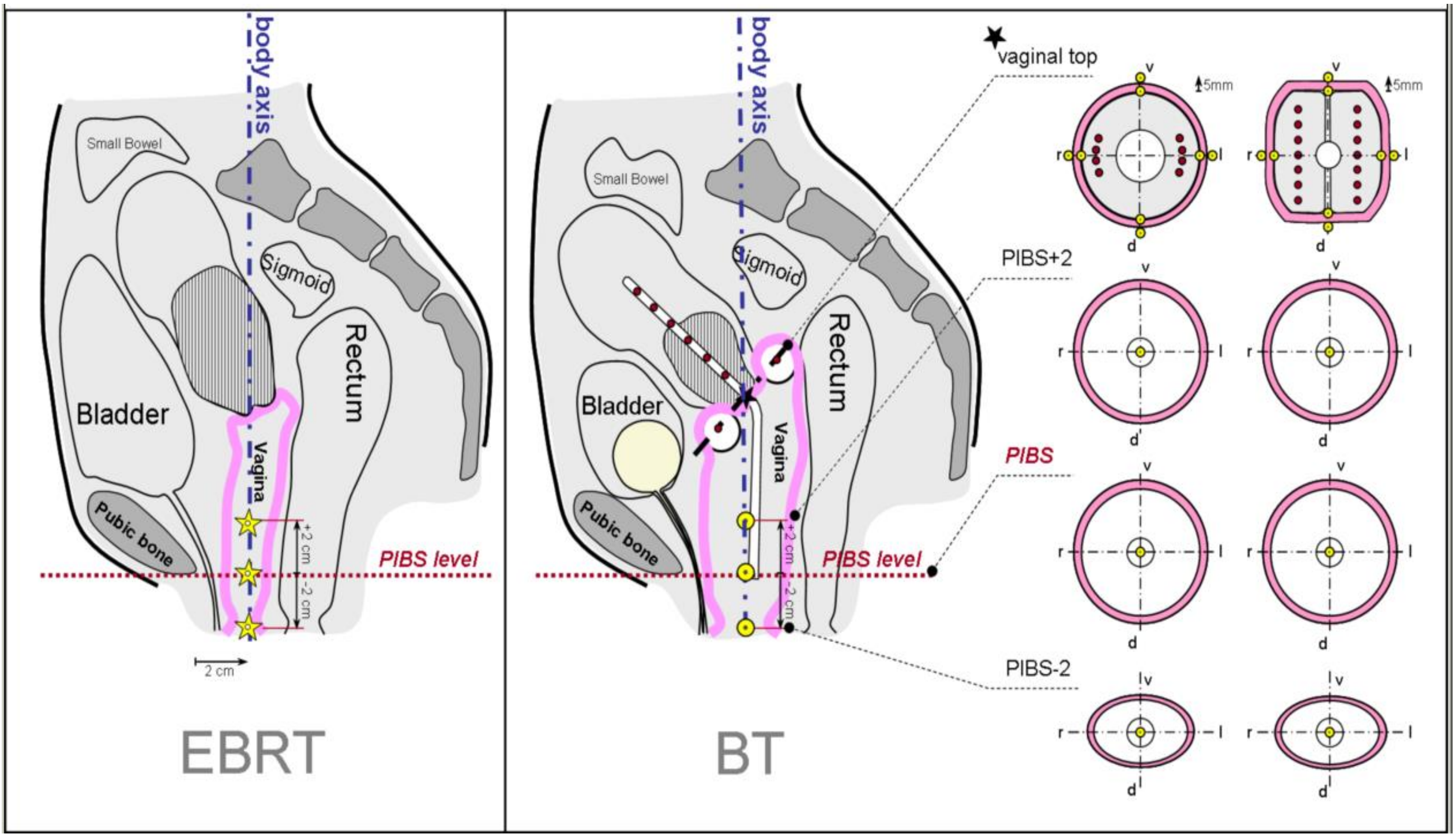
PIBS points

- Indicative of lower field border





Vaginal Reference Points



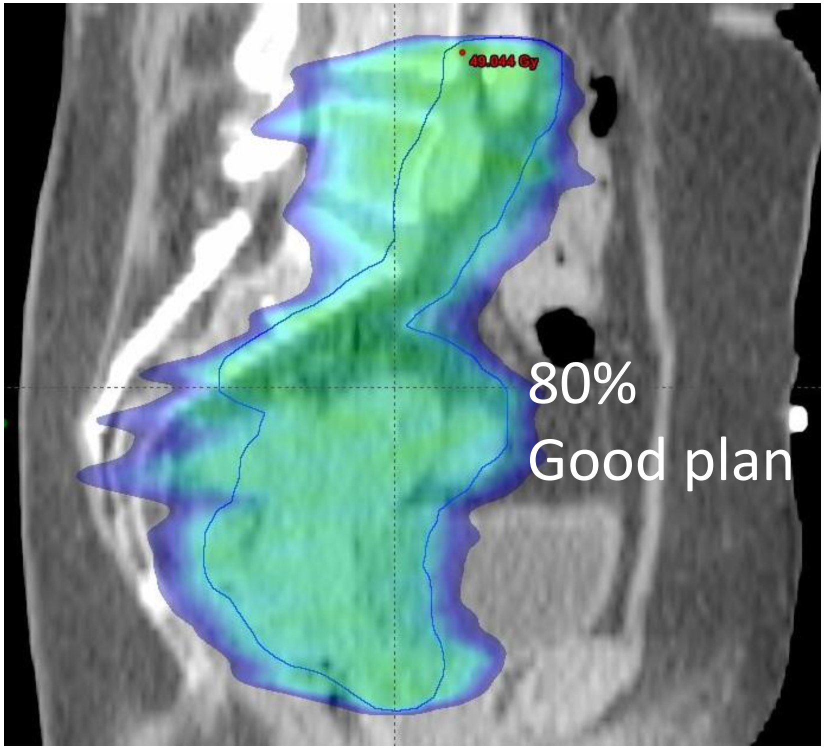
PIBS: Posterior-Inferior Border of Symphysis

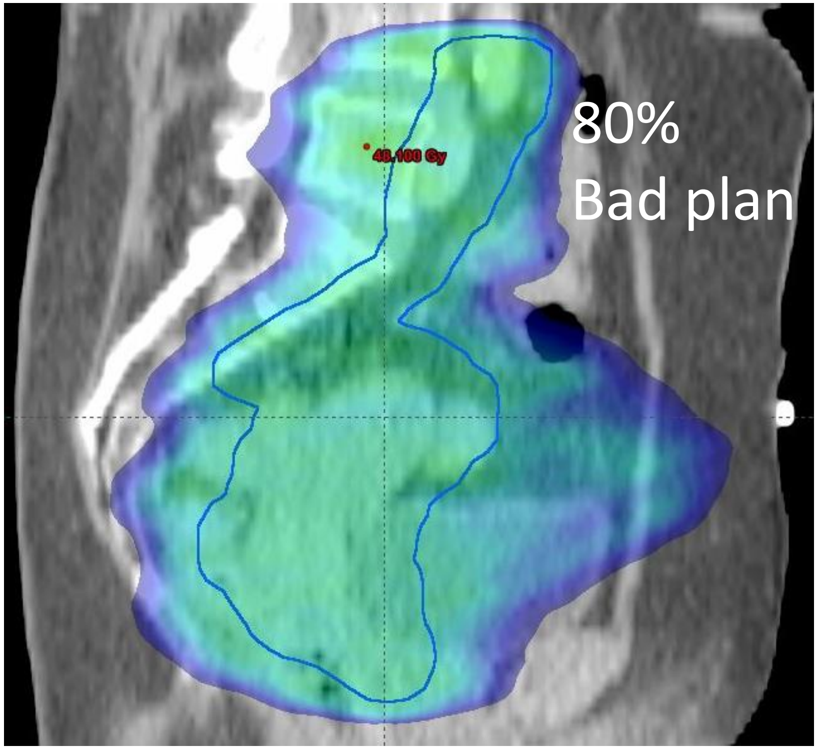
Summary

- PIBS and BT help contour - not reported by many.
- Mean(sd) V43Gy is 1396(366). The conformality is = 1.3 vs 1.04 (Tata_Ref)
- Nodal boosting not done by 4/8 ?
- Coverage and organ sparing – Bowel to be improved, bladder, rectum are ok ?.

Conformality of lower doses

- 80% isodose around 1.5cm from 100% in direction towards critical normal tissue such as bowel





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

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Professor, Radiation Oncology

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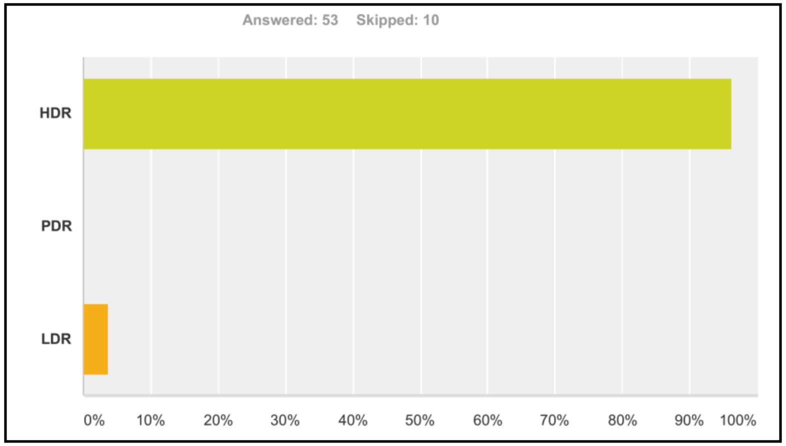
GYN GEC – ESTRO TEACHING FACULTY

OUTLINE

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

Patient Selection (1)

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



Patient Selection (2)

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

Imaging protocols MRI and CT

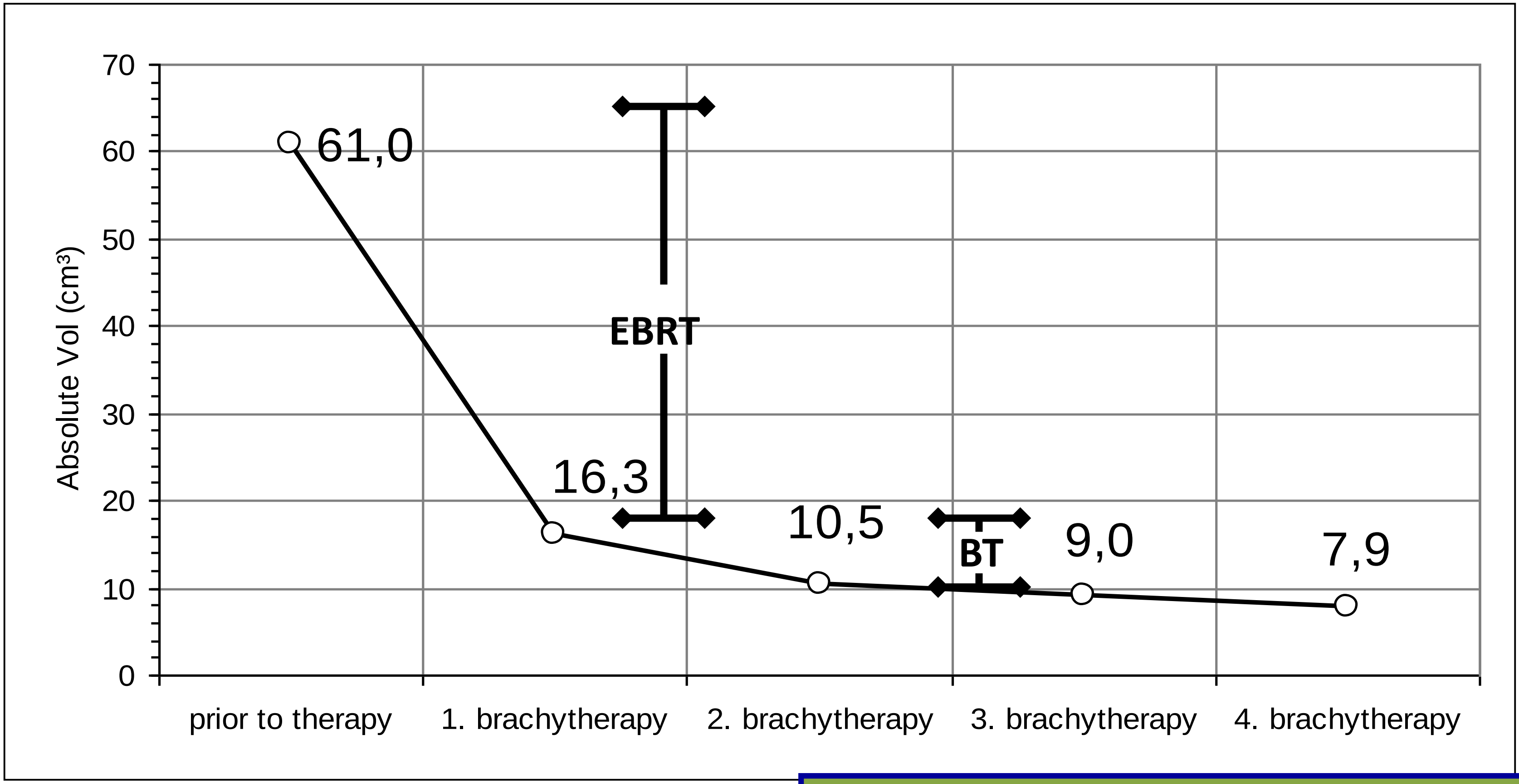
Key issues for image-guided radiotherapy

Quantitative tumor regression

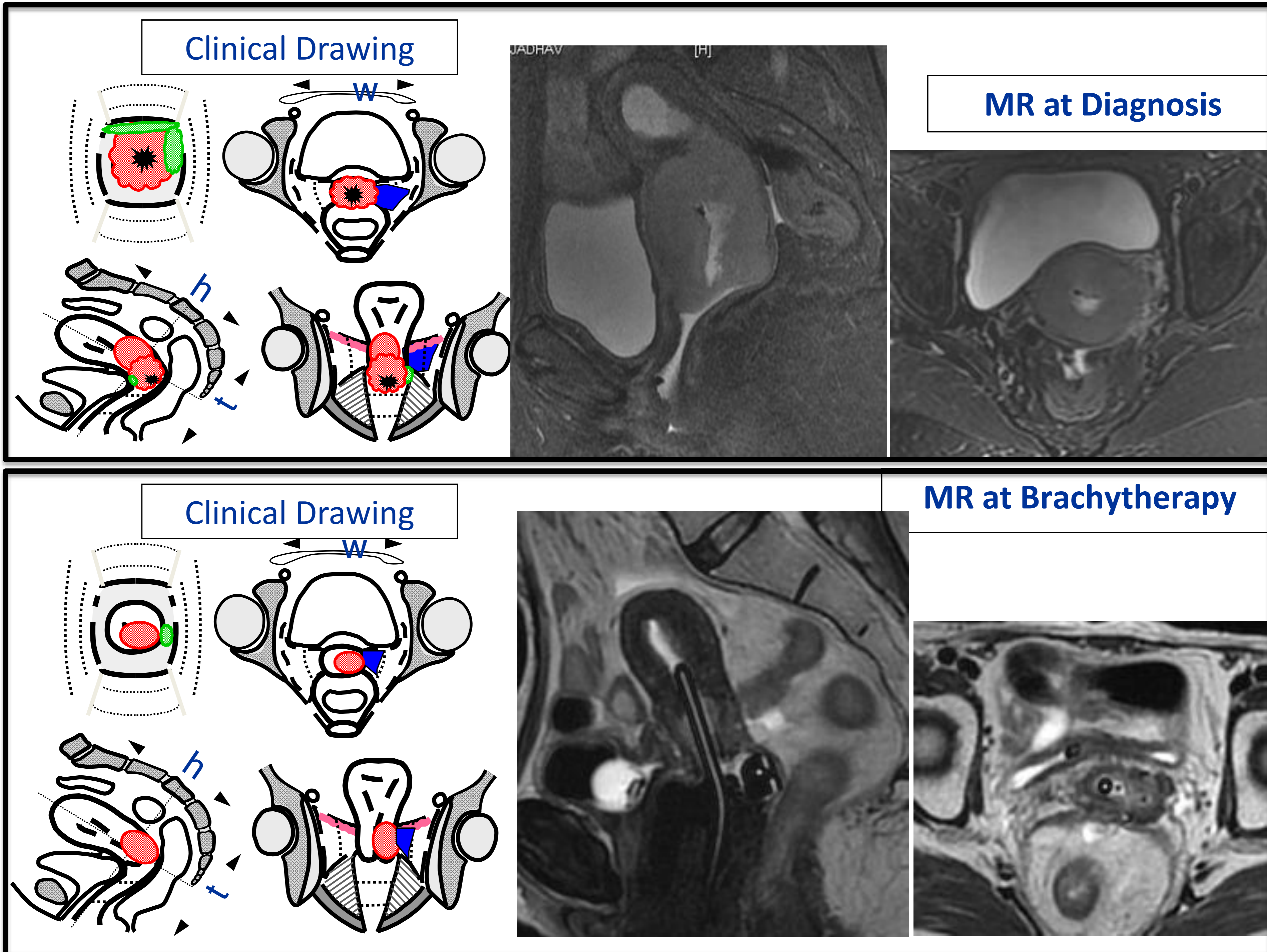
Courtesy : Johannes Dimopoulos

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

easy to predict



Dimopoulos et al. Strahlenther Onkol 2009


Clinical Drawing
w
h
t
JADHAV
[H]
MR at Diagnosis
Clinical Drawing
w
h
t
MR at Brachytherapy

PREPLANNING

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

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

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

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

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

Principles of the BT Procedure - 1

✧ Secure intravenous access.

✧ Check for the desired Instrumentation before BT procedure starts

✧ Short Anesthesia

✧ Position patient in lithotomy position.

✧ Parts painted and draped.

✧ Foley's catheterization and 7 ml of Radio opaque contrast

✧ Bladder protocol

✧ EUA: response to external RT

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.

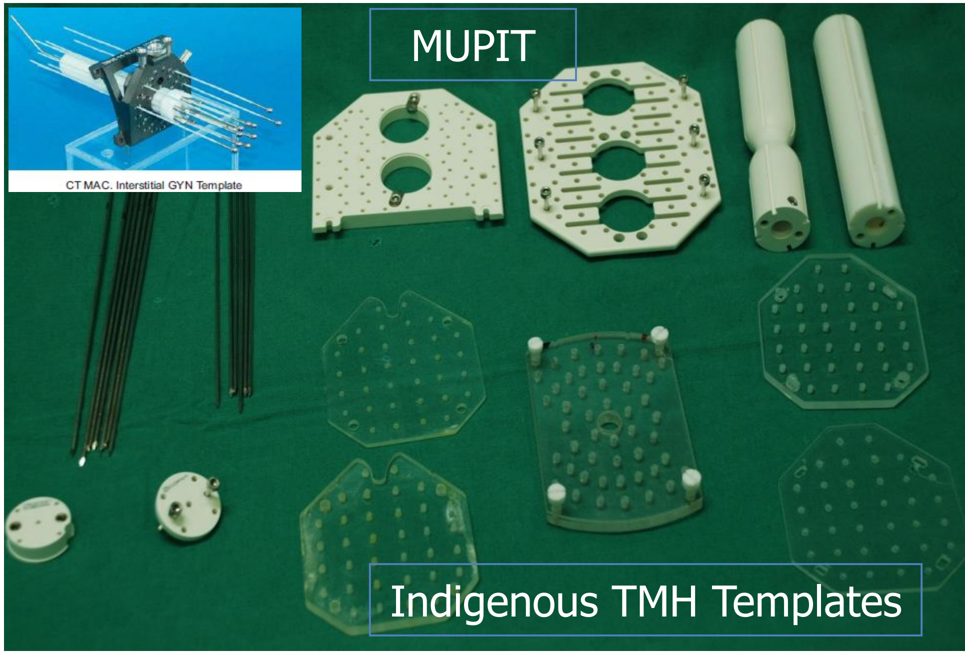
- **Combined Intracavitary and Interstitial (IC + IS)**

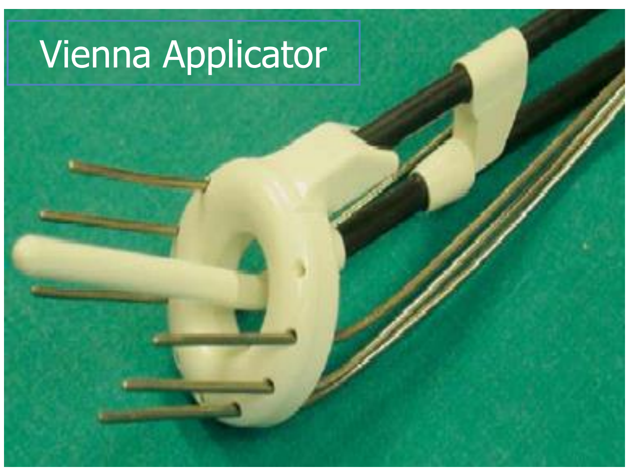
  - Vienna Applicator, Utrecht applicator, etc.

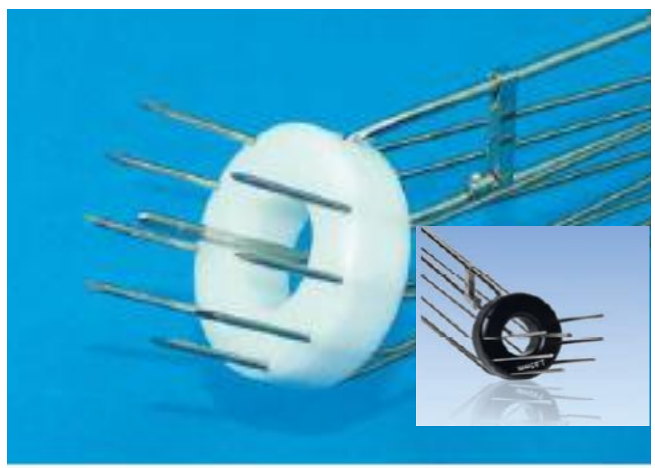
- **Interstitial (IS)**

  - MUPIT, Indigenous Templates with needles / tubes

Brachytherapy Applicators for GYN Cancers







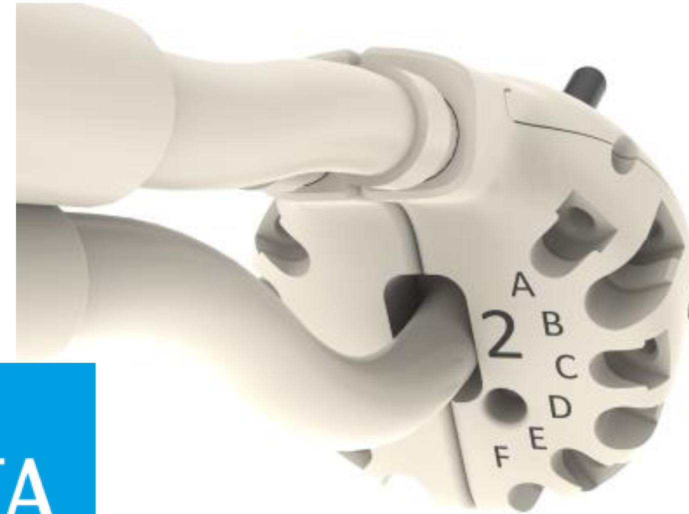
CT Vienna System with Titanium Needles

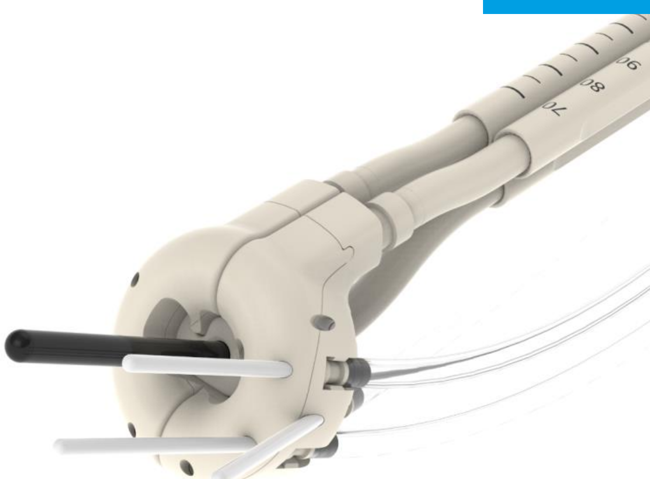
Tandem - Ring with needles/tubes

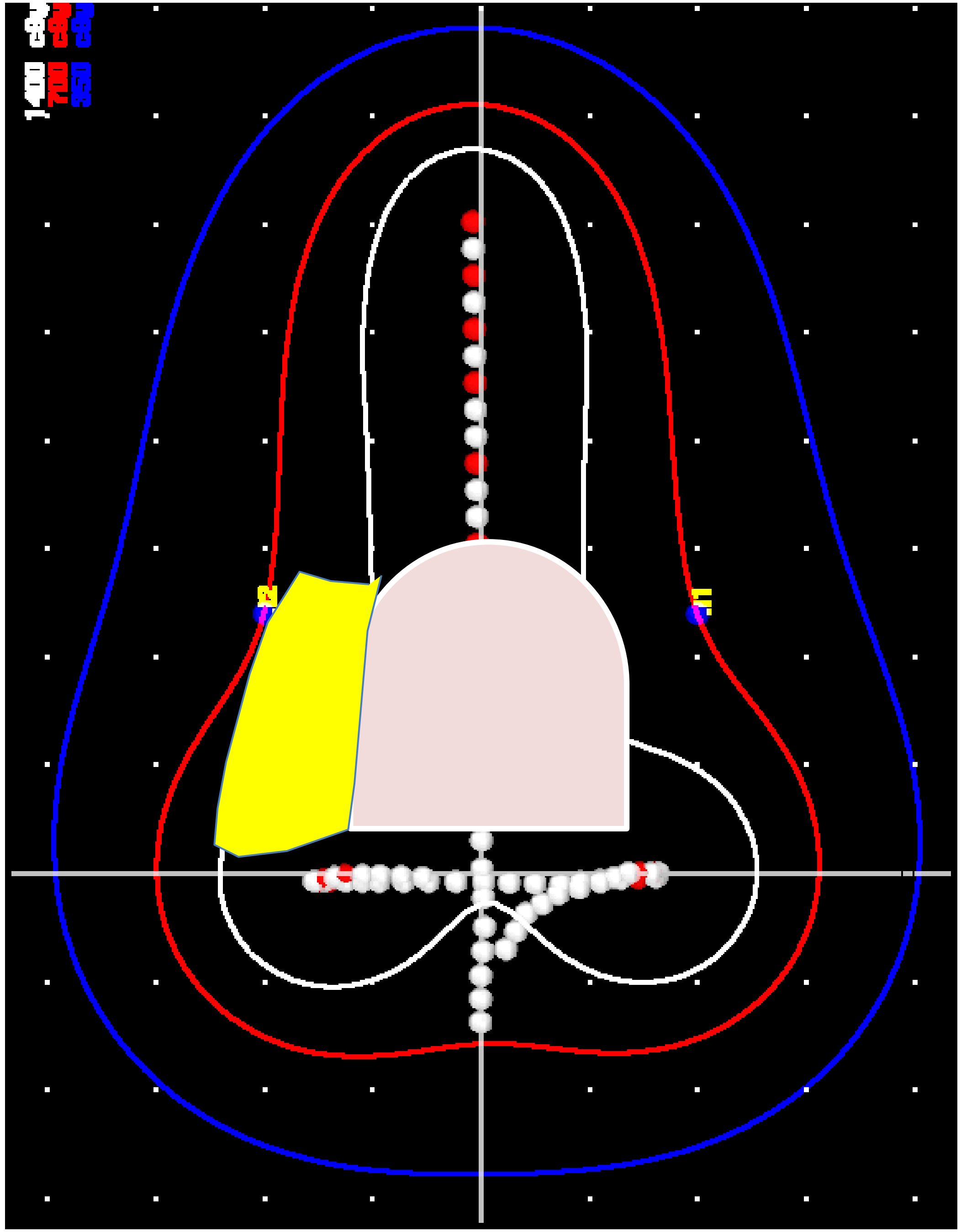
Tandem - Ovoid with tubes

Latest Development in Applicators

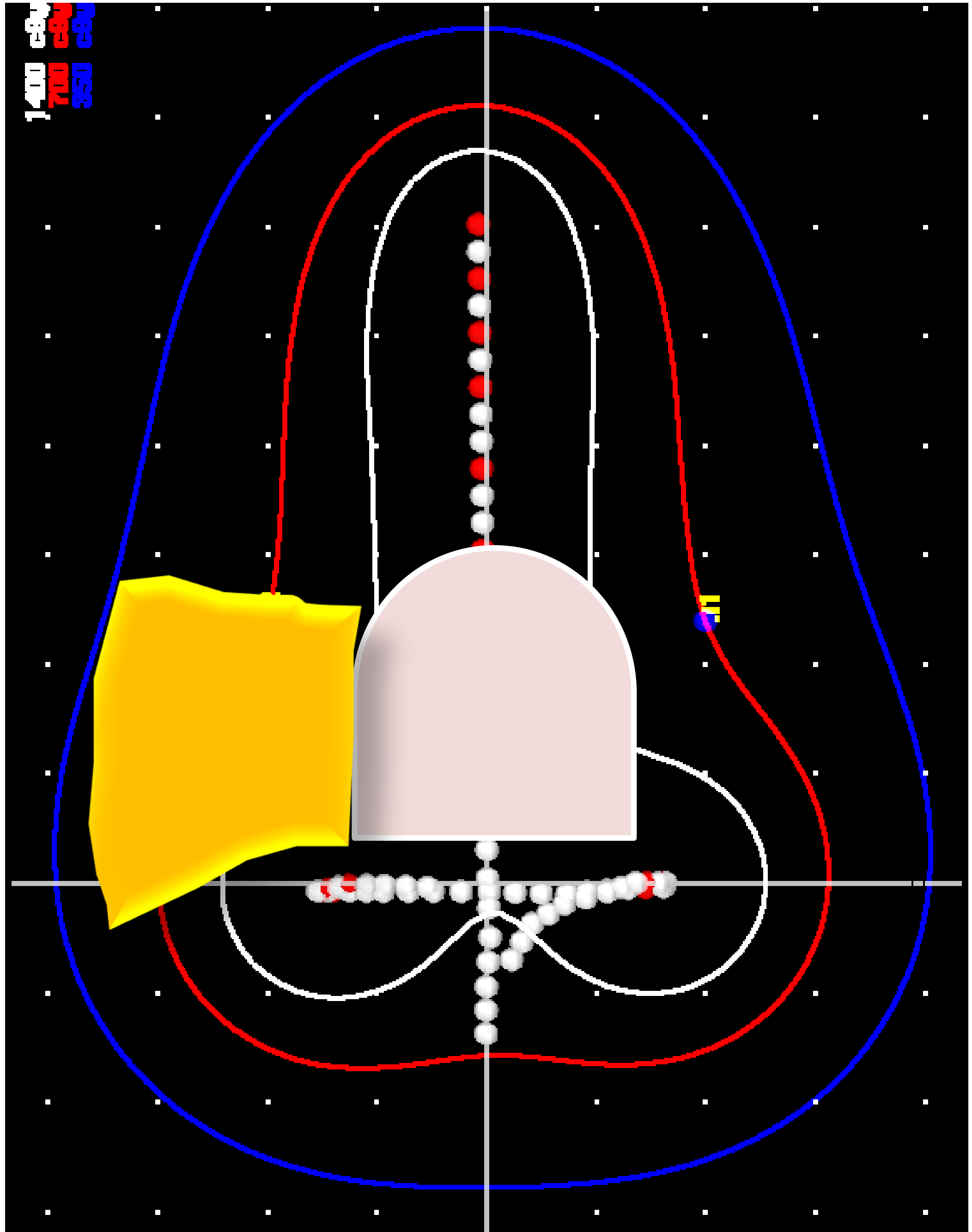
VENEZIA GYN APPLICATOR







1400
700
350


1400 cGy
700 cGy
350 cGy

VIDEO PRESENTATION OF BT PROCEDURE

Treatment delivery & Care in the Ward

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

REMOVAL OF THE APPLICATOR

Intracavitary Alone:

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

IC + IS

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

Management of acute bleeding after removal

Do not panic!!!

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

"Man often becomes what he believes himself to be.

If I keep on saying to myself that I cannot do a certain thing, it is possible that I may end by really becoming incapable of doing it.

On the contrary, if I have the belief that I can do it, I shall surely acquire the capacity to do it even if I may not have it at the beginning." — Mahatma Gandhi

Brachytherapy Skills?

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

THANK YOU

FOR YOUR ATTENTION !

المركز الوطني
لعلاج وأبحاث السرطان
National Center for
Cancer Care & Research

2nd AROI/ESTRO Gyn Teaching Course

ESTRO School

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

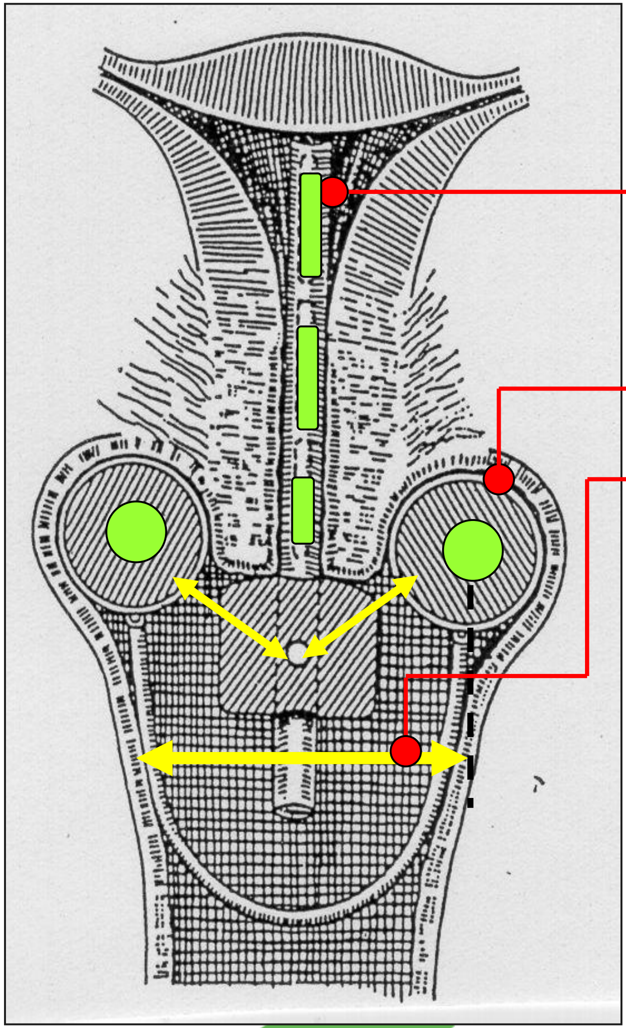
Lucknow, 2018

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

not connected; distance not fixed → no fixed geometry

^{226}Ra preloading

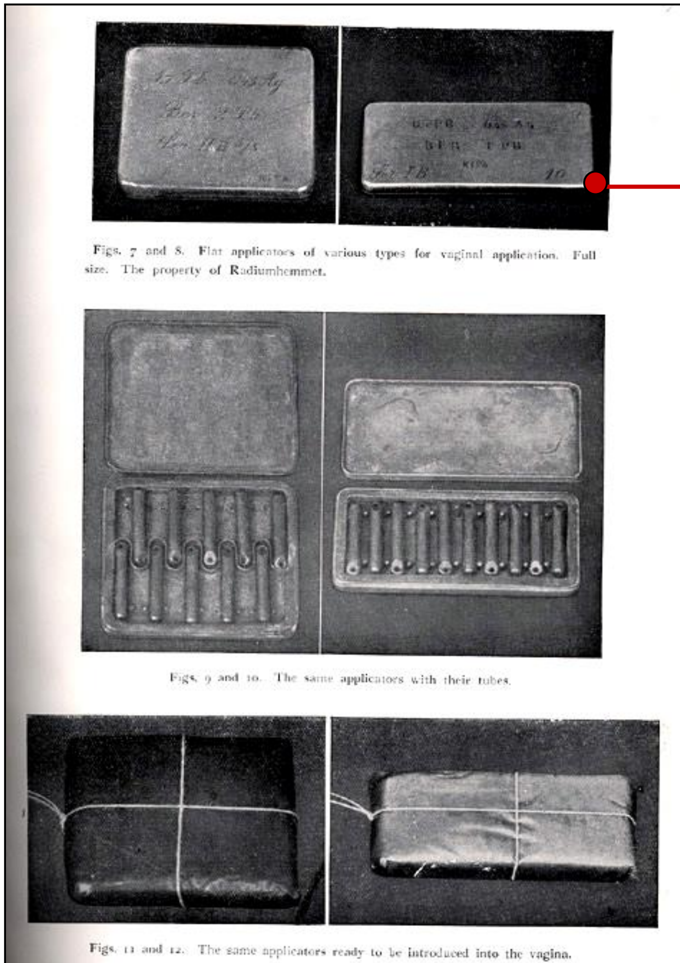
- X mg of ^{226}Ra for Y hours

Typical application

- ≈ 5 days (*120 h*)
- 7000-8000 mgh

Classical Stockholm method

1913-1914: Radiumhemmet, Stockholm, Sweden

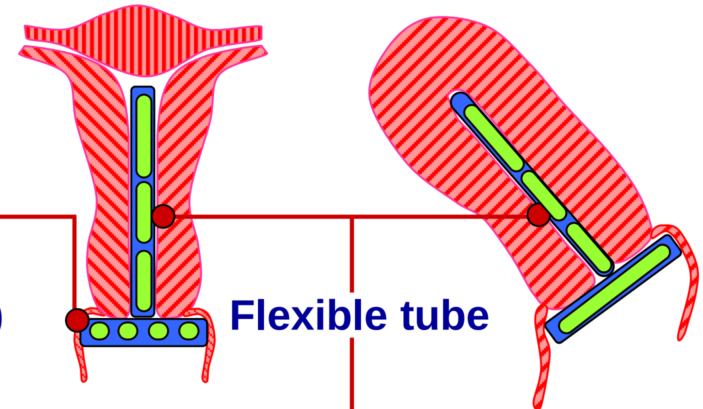


Figs. 7 and 8. Flat applicators of various types for vaginal application. Full size. The property of Radiumhemmet.

Figs. 9 and 10. The same applicators with their tubes.

Figs. 11 and 12. The same applicators ready to be introduced into the vagina.

Applicator:



Flat box (plate) — Flexible tube

not connected → No fixed geometry

^{226}Ra preloading

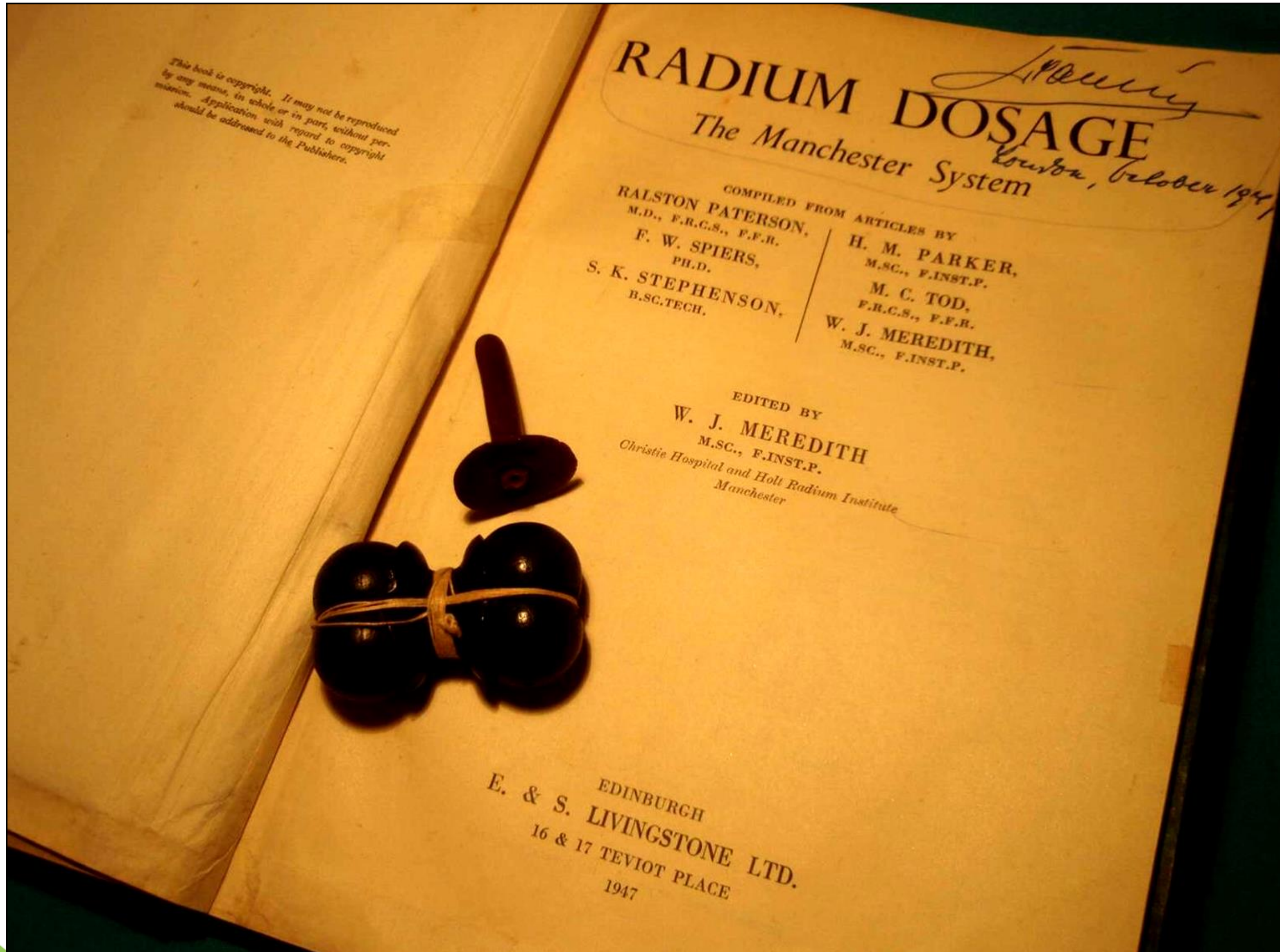
- X mg of ^{226}Ra for Y hours

Typical treatment

- 2 – 3 applications (á 20-30 h)
- ≈ 7000 mgh

Historical Manchester System

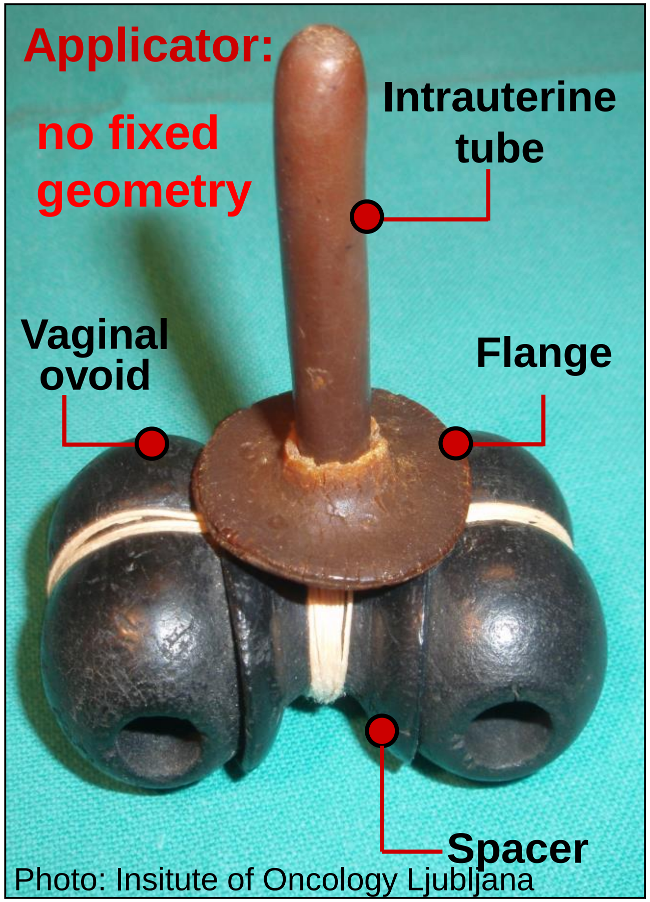
1938: Holt Radium Institute, Manchester, England



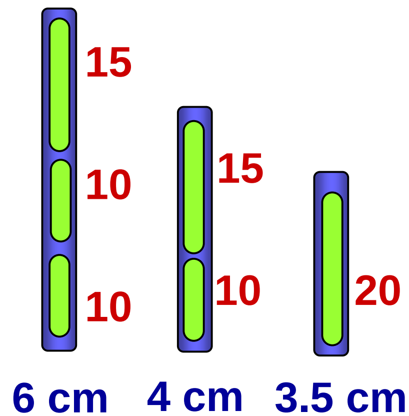
Historical
Paris
Stockholm
Manchester
Fletcher
Modern
Stockholm
Manchester & Fletcher
Mould
Limitations of IC Applicators
Emerging Technologies

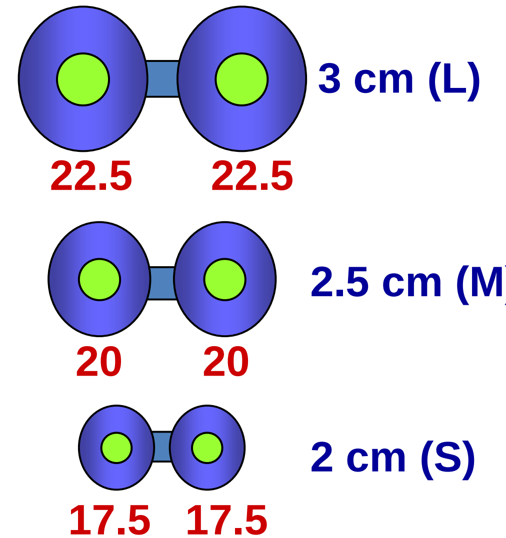
Historical Manchester System

Related to historical Paris technique

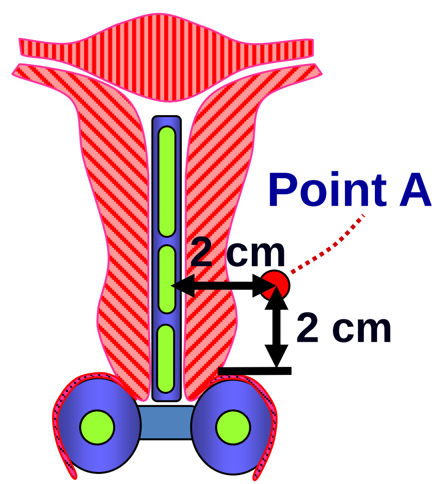


^{226}Ra preloading (mg):





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

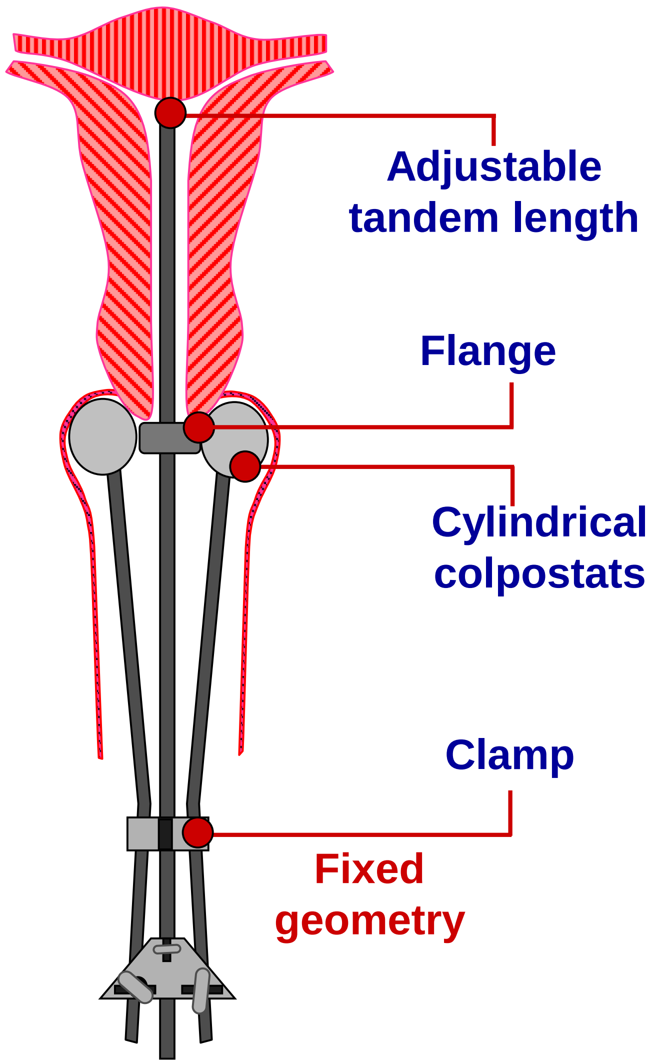
↓

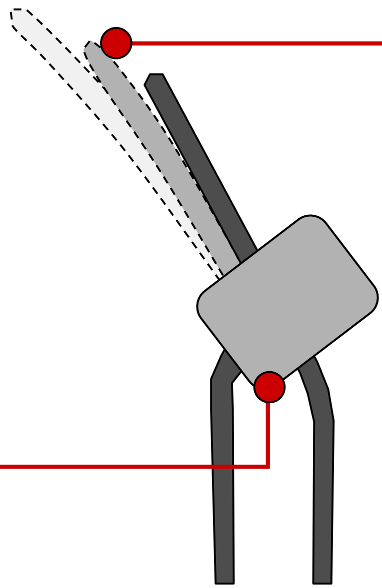
Certain point A dose

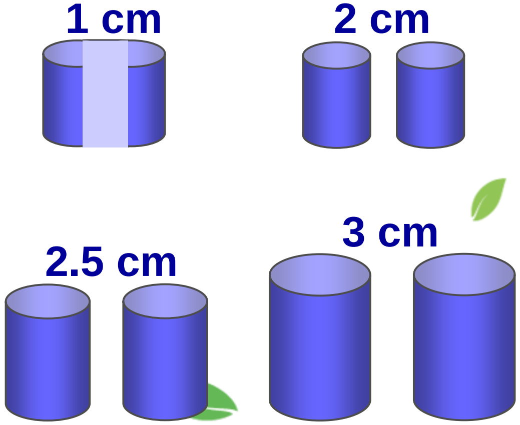
Meredith WJ, ed.. Radium dosage. The Manchester system. Edinburgh;1947.

Fletcher–Suit–Delclos–Horiot Technique

1950's: Fletcher





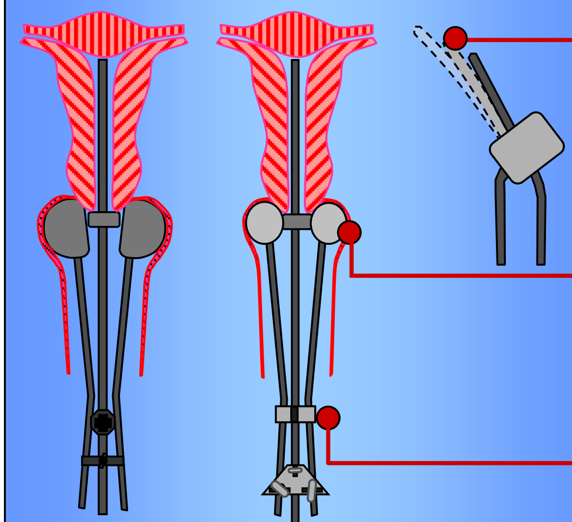


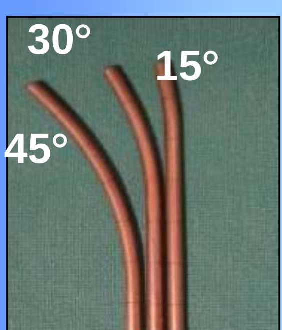
Modern Intracavitary Techniques

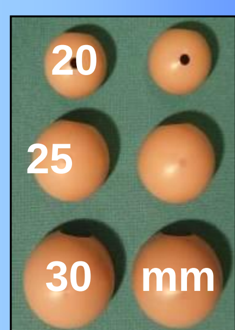
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style







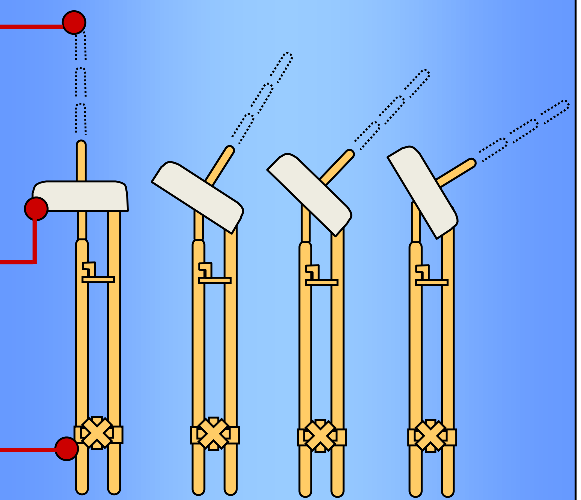
Common features:

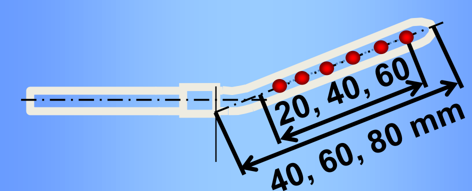
Uterine Tandem:
various lengths, angles or curvatures

Ovoids, cylinders, rings
various outer & source path diameters

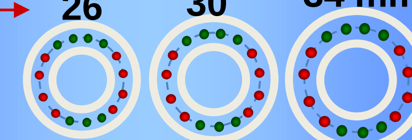
Clamp

Stockholm style





Source path Φ → 26 30 34 mm

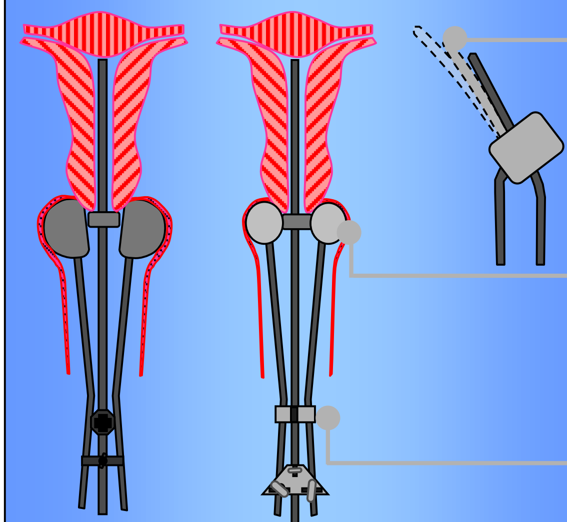


Outer Φ → 38 42 47 mm

Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



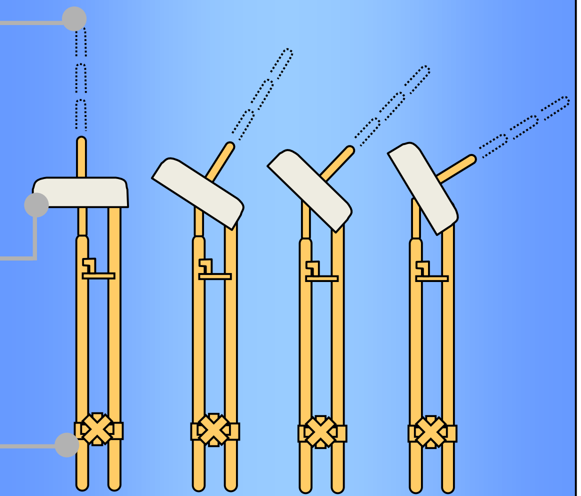
Common features:

Uterine Tandem: various lengths, angles or curvatures

Ovoids, cylinders, rings various outer & source path diameters

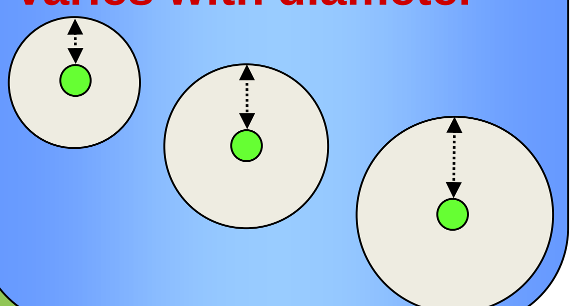
Clamp

Stockholm style



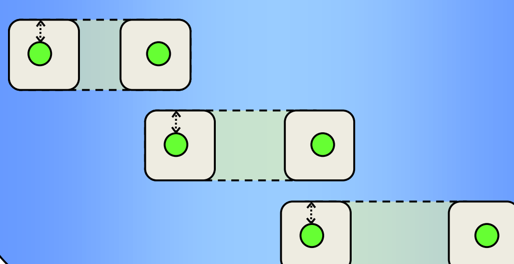
Differences:

Varies with diameter



Thickness of ovoids and rings

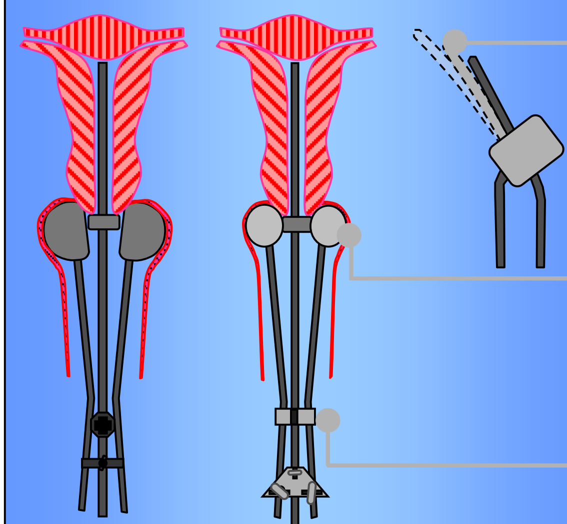
Constant



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



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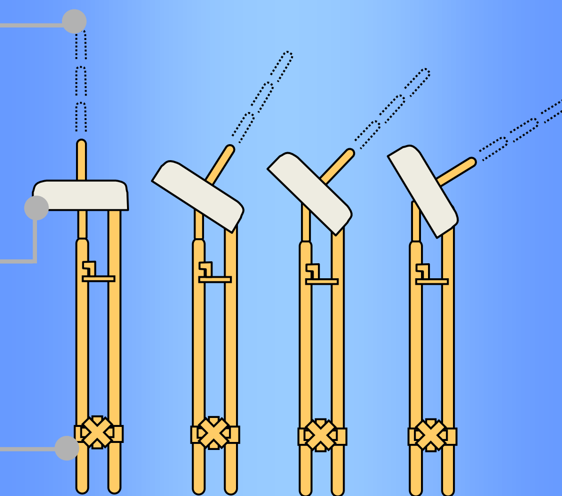
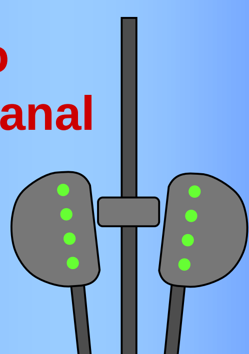
Clamp

Stockholm style



Differences:

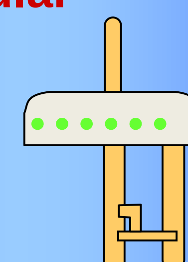
Parallel to cervical canal



Manchester style

Source path orientation

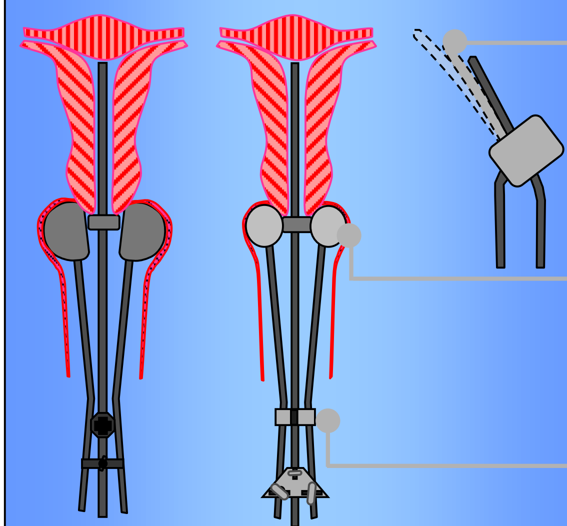
Perpendicular to cervical canal



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



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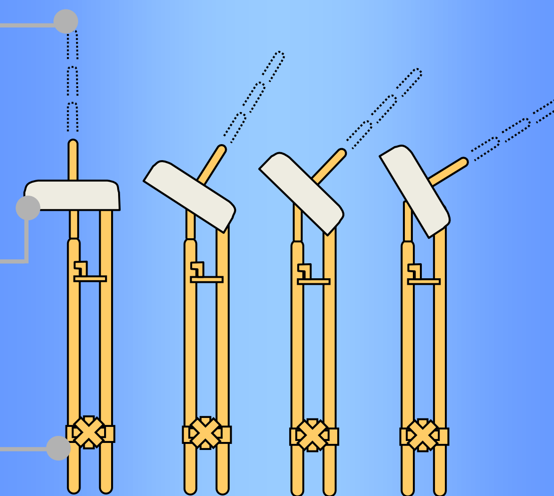
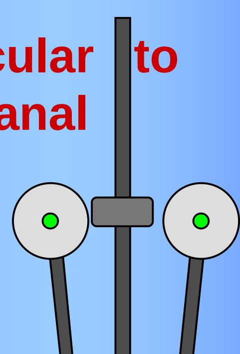
Stockholm style



Perpendicular to cervical canal

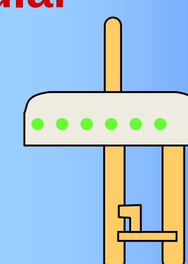


Fletcher style

Differences:

Source path orientation

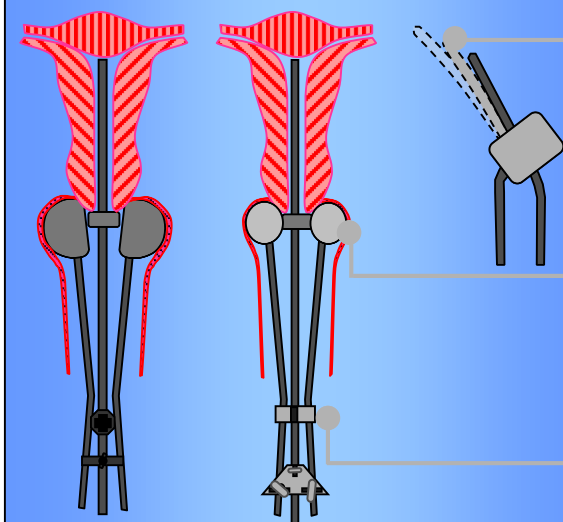
Perpendicular to cervical canal



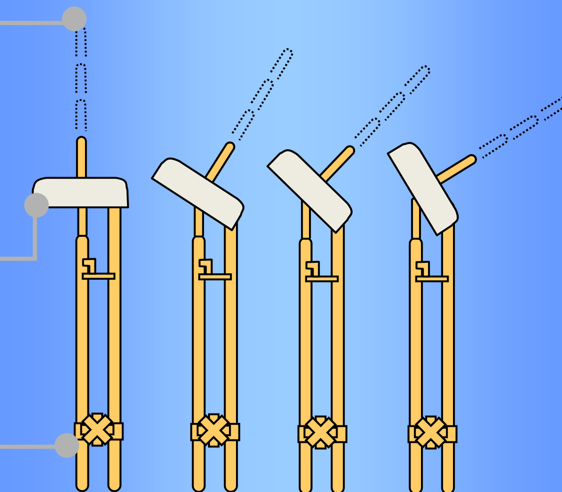
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Stockholm style



Common features:

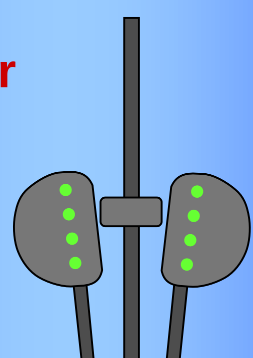
Uterine Tandem: various lengths, angles or curvatures

Ovoids, cylinders, rings various outer & source path diameters

Clamp

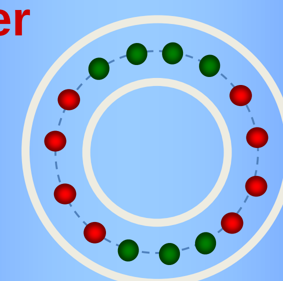
Differences:

Lower



Loading flexibility

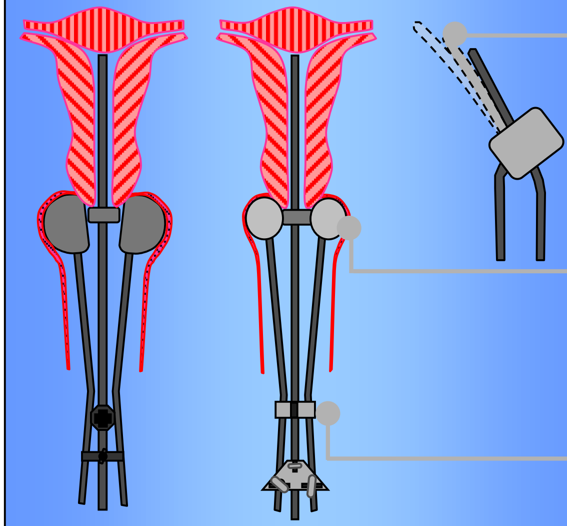
Higher



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



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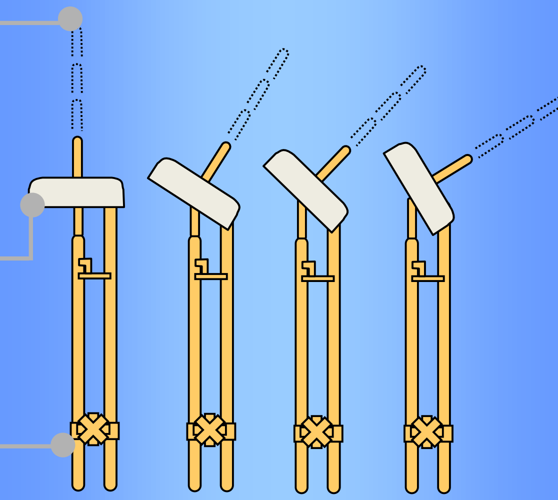
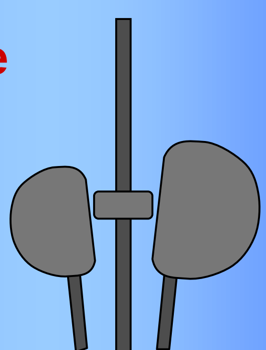


Differences:

Asymetric insertion

Possible

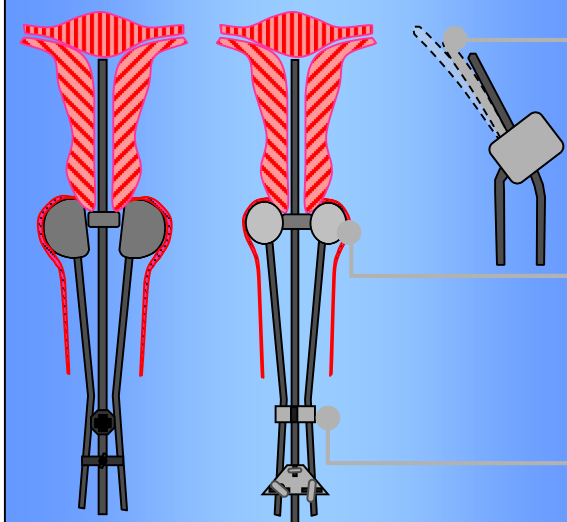


Not applicable

Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



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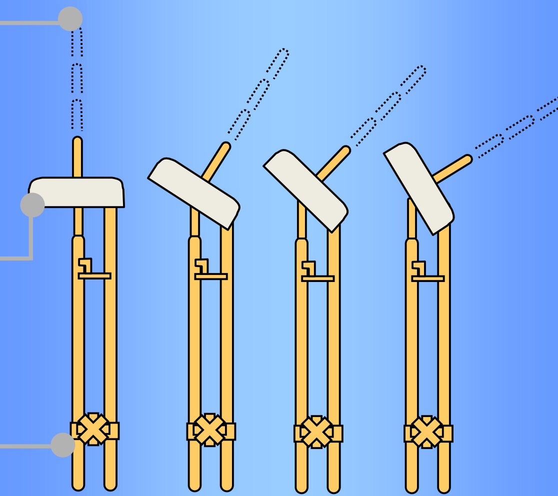
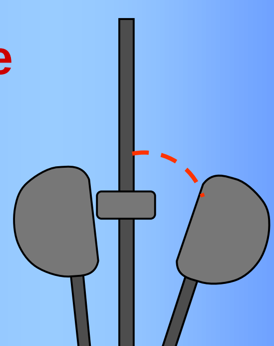


Differences:

Possible



Adjustable spacing

Not applicable

Historical

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

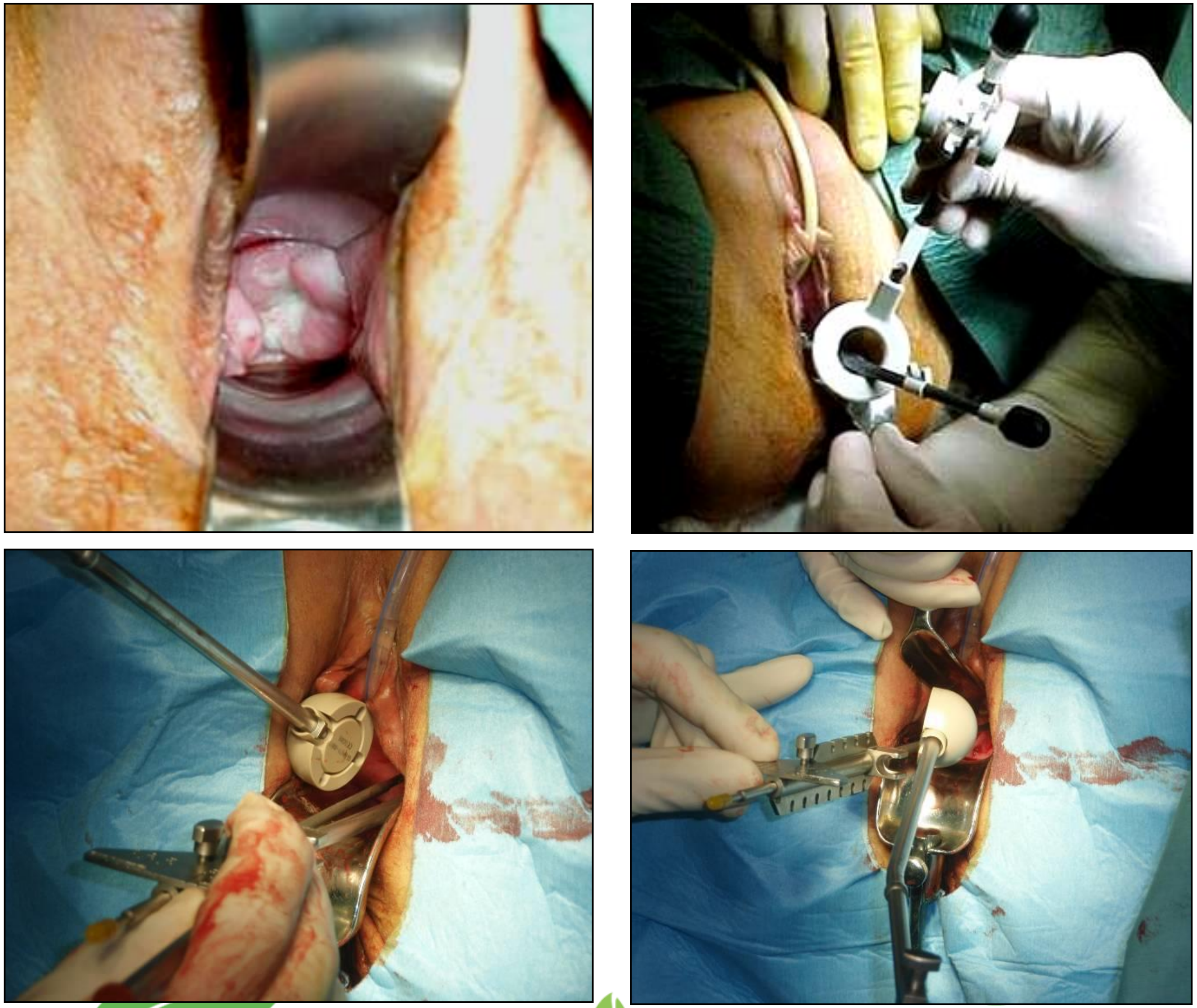
Mould

Limitations of IC Applicators

Emerging Technologies

Modern Intracavitary Techniques

Applicator insertion



Modern Intracavitary Techniques


Concept: same as 100 years ago…

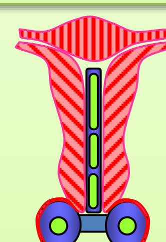
Modern IC techniques

Materials: Imaging…

Channel diameters: Smaller

Loading patterns: Mimicking historical

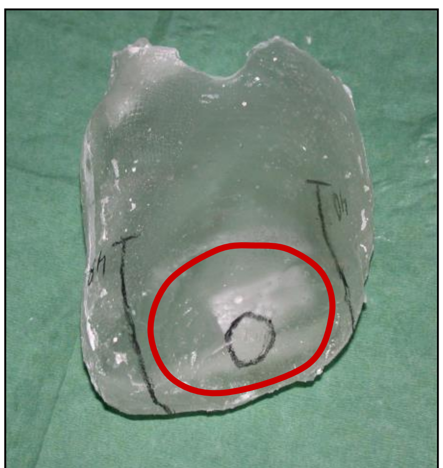


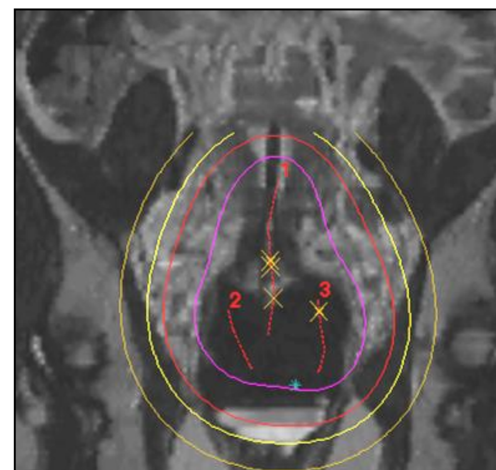


Mould Technique

Personalized applicators

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

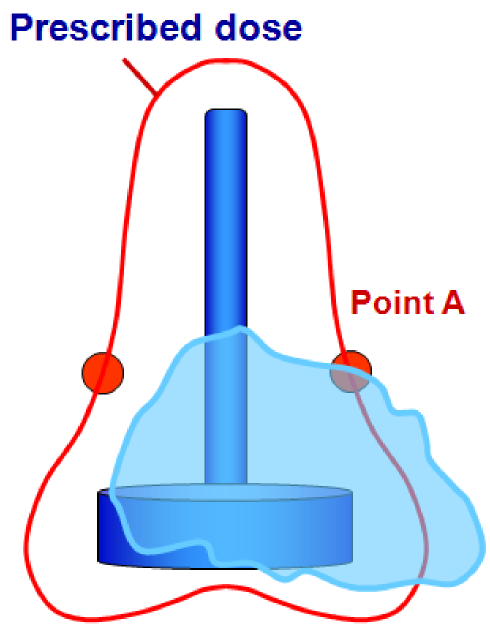




Courtesy: C. Haie-Meder, IGR, Paris, France

Limitations of modern IC applicators

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



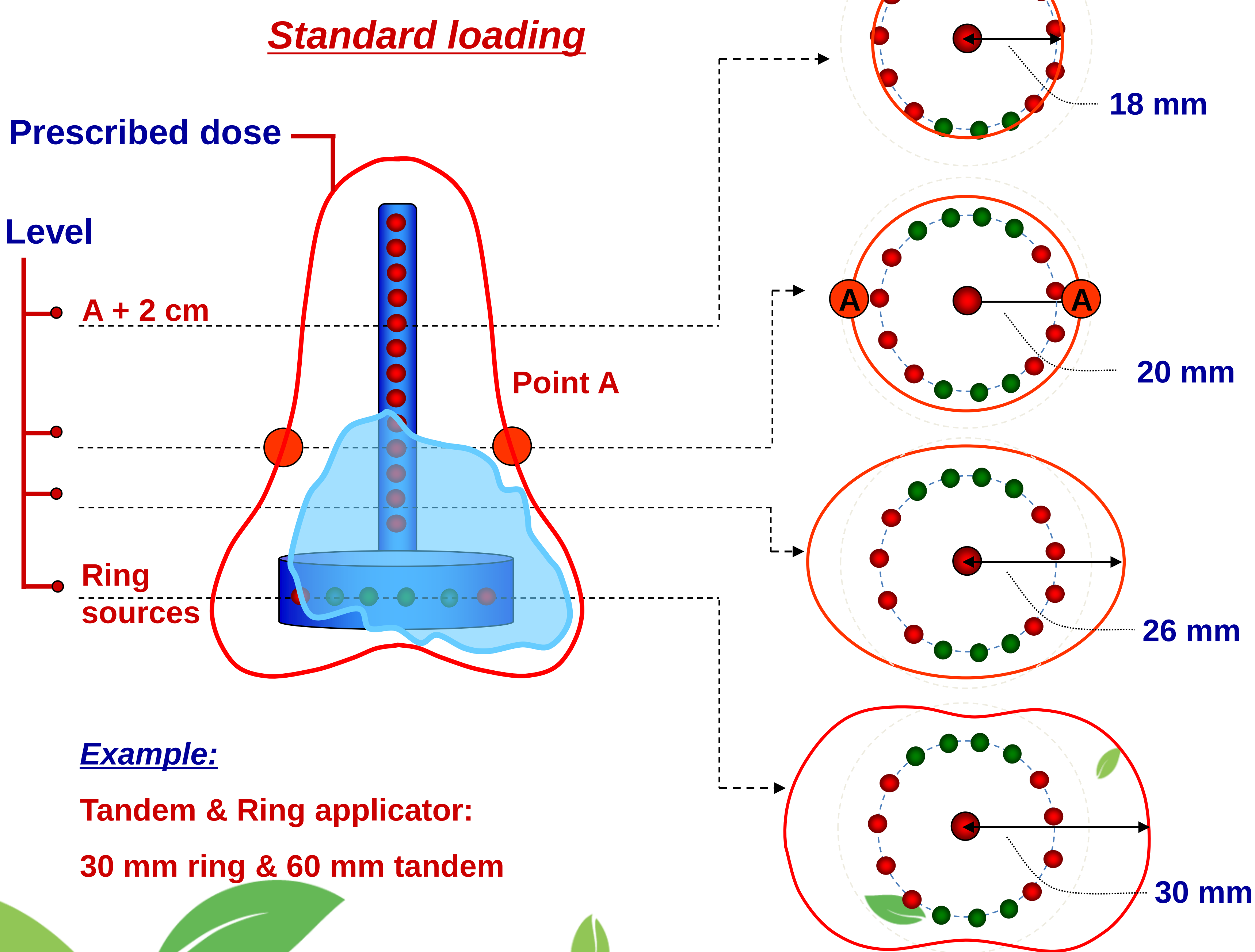
A. Up to ~1 mm

B. Up to ~ 5 mm

C. Up to ~ 10 mm

D. Up to ~ 20 mm

Dimensions of prescribed dose: different levels

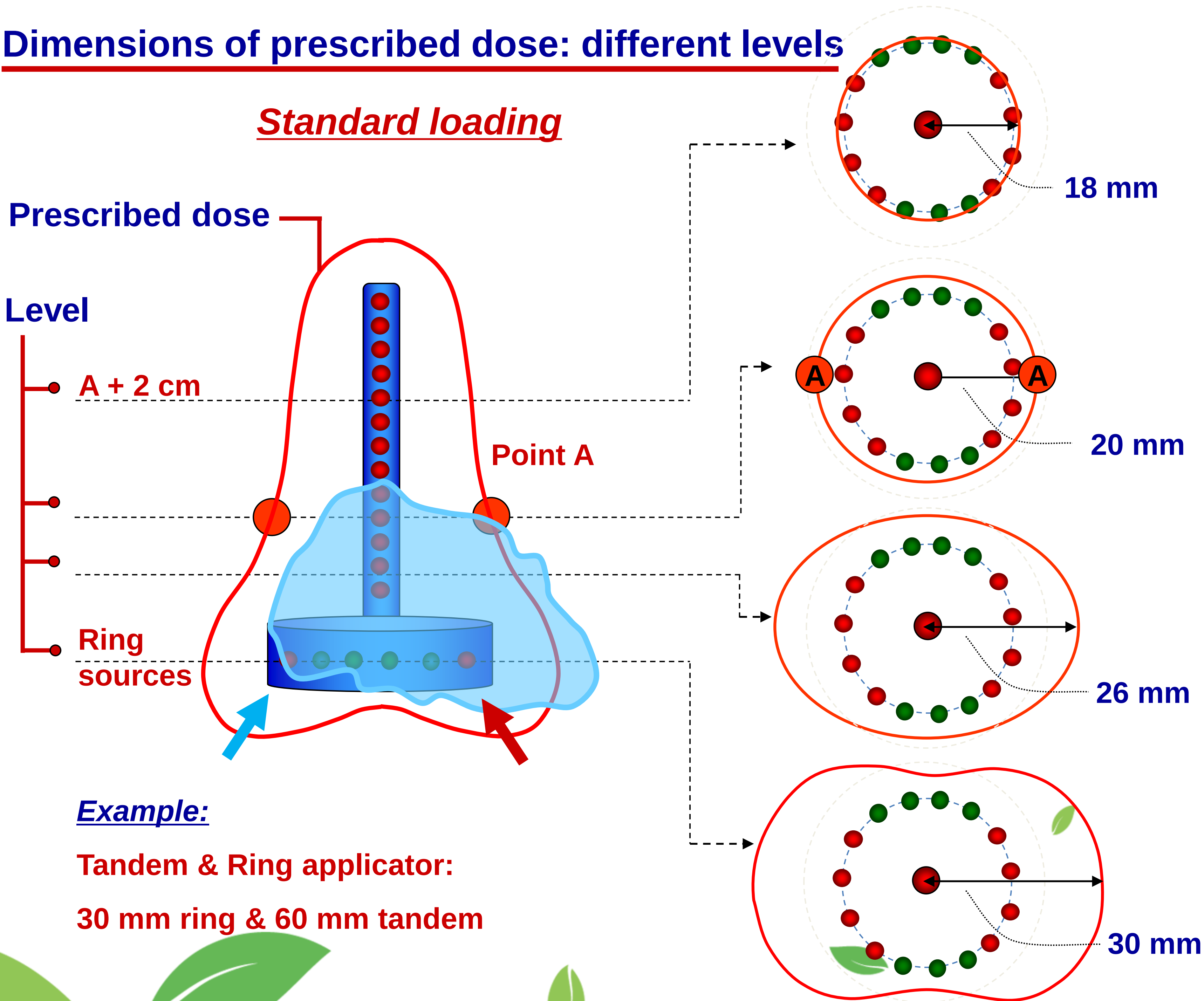


Example:

Tandem & Ring applicator:

30 mm ring & 60 mm tandem

Dimensions of prescribed dose: different levels

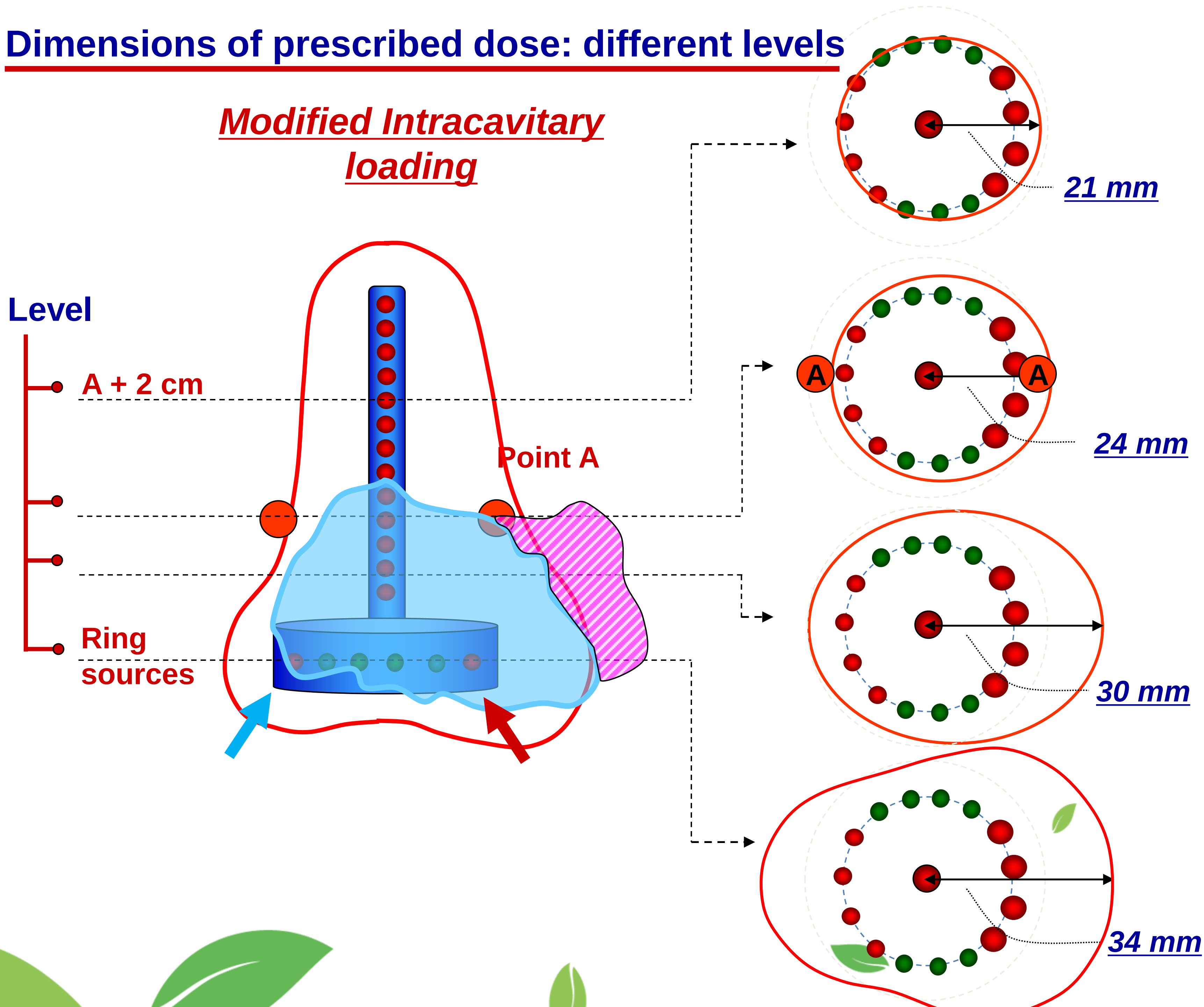


Example:

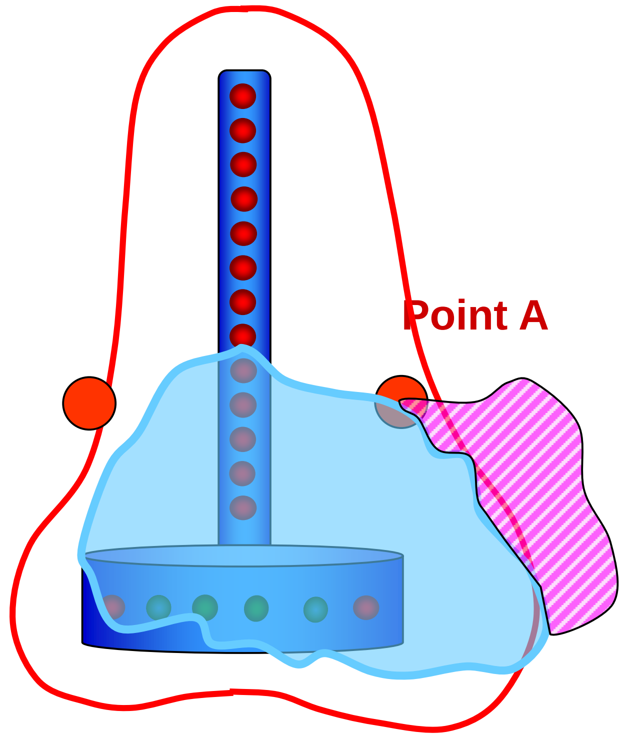
Tandem & Ring applicator:

30 mm ring & 60 mm tandem

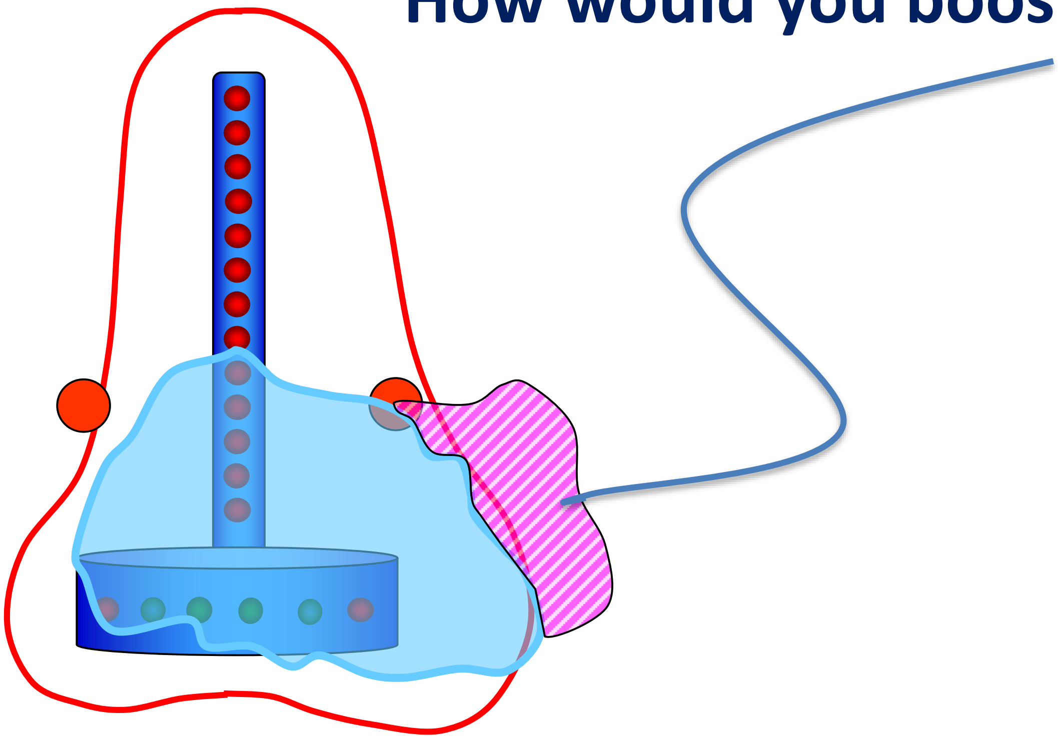
Dimensions of prescribed dose: different levels



Overcoming limitations of IC applicators



Overcoming limitations of IC applicators
How would you boost this area?



A. By expansion of dose from IC applicator

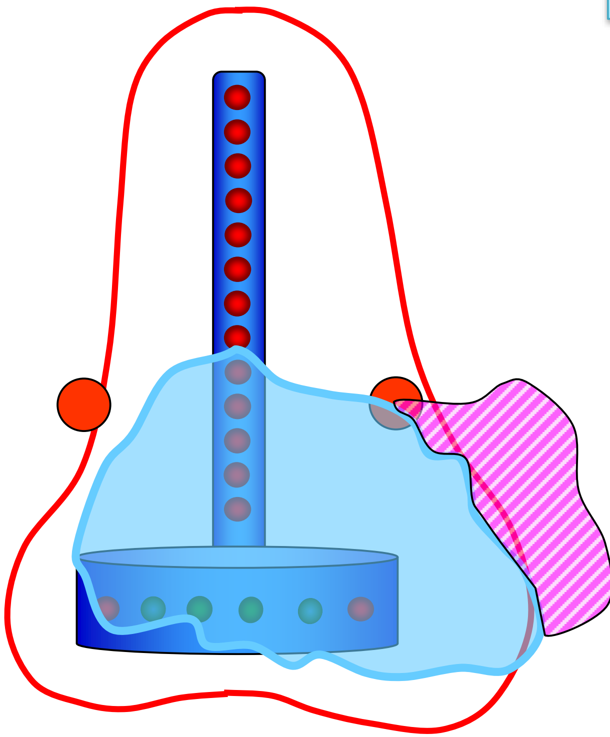
B. By EBRT boost with midline shielding

C. By adding Interstitial to Intracavitary BT

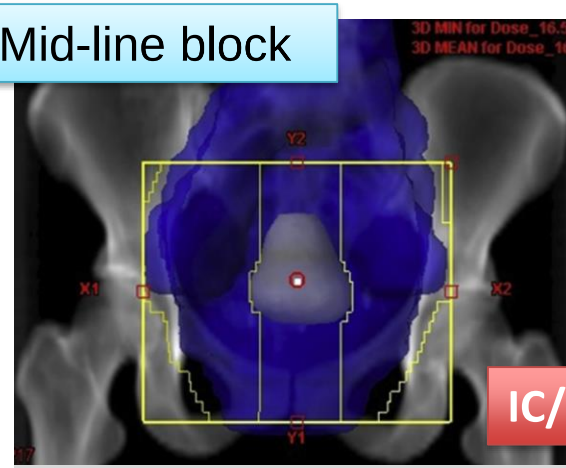
D. Other

Overcoming limitations of IC applicators

External beam boost with midline "shielding"



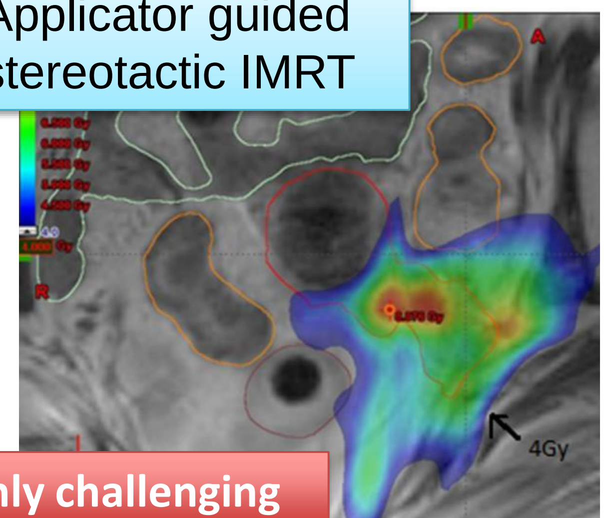
Mid-line block



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

IC/IS boost > EBRT boost

Applicator guided stereotactic IMRT



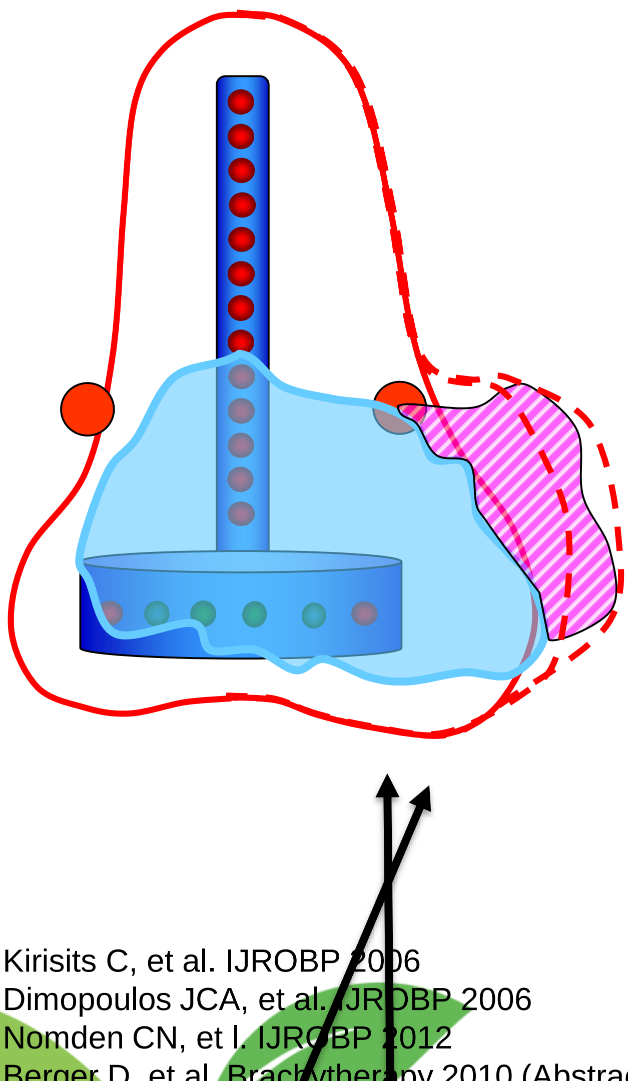
When IC/IS BT is highly challenging

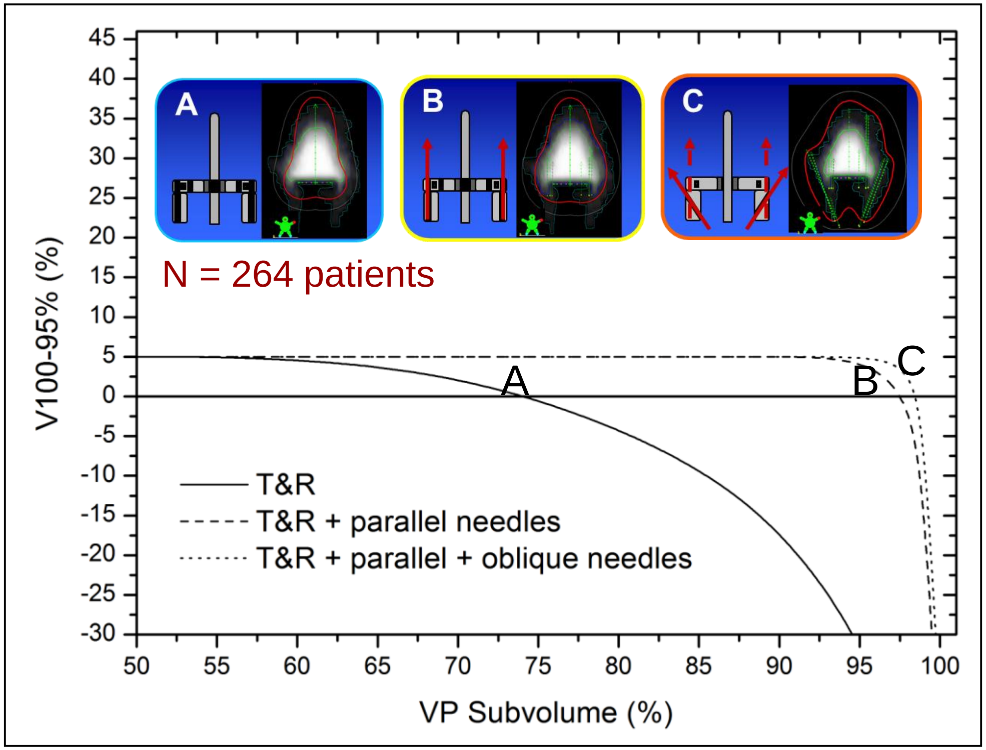
Assenholt MS, et al Brachytherapy 20114

Historical
Paris
Stockholm
Manchester
Fletcher
Modern
Stockholm
Manchester & Fletcher
Mould
Limitations of IC Applicators
Emerging Technologies

Overcoming limitations of IC applicators

Combined Intracavitary & Interstitial brachytherapy





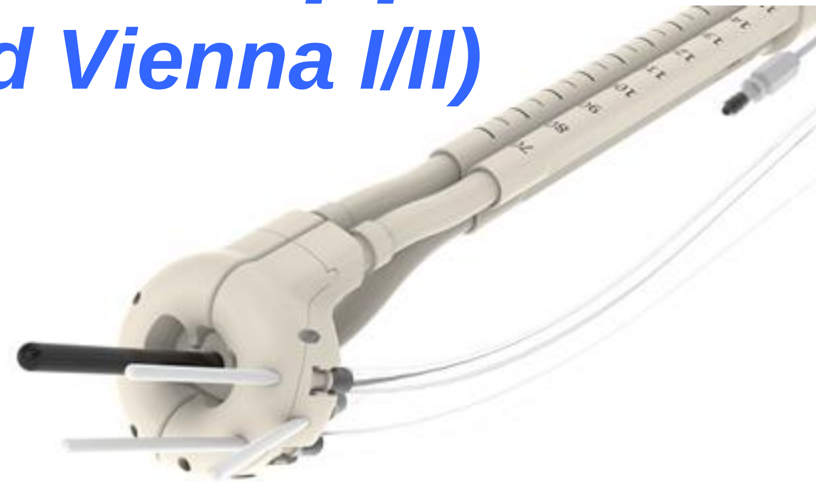
Petric P, et al. Radiother Oncol 2010 (Abstract)

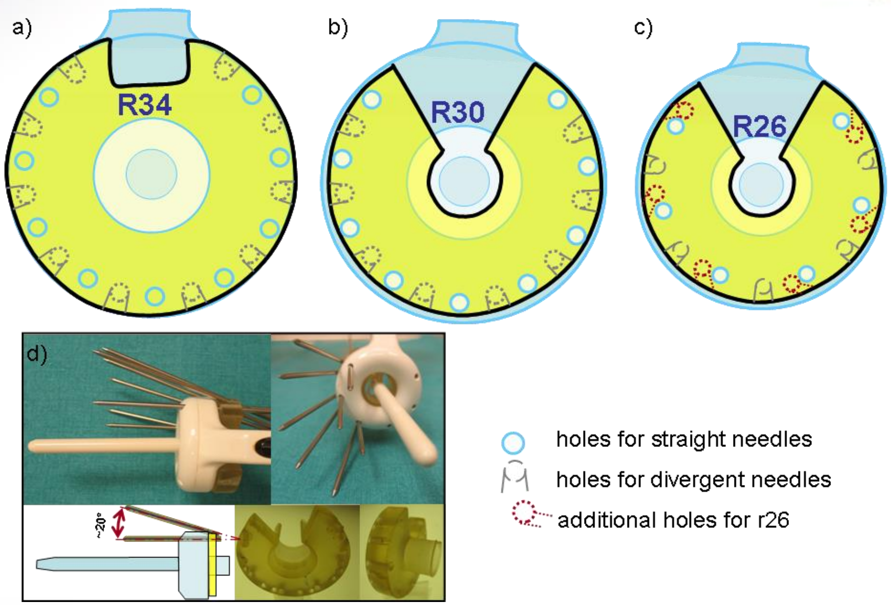
Mohamed S, et al Brachytherapy 2015:

IC/IS boost superior to EBRT boost

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

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





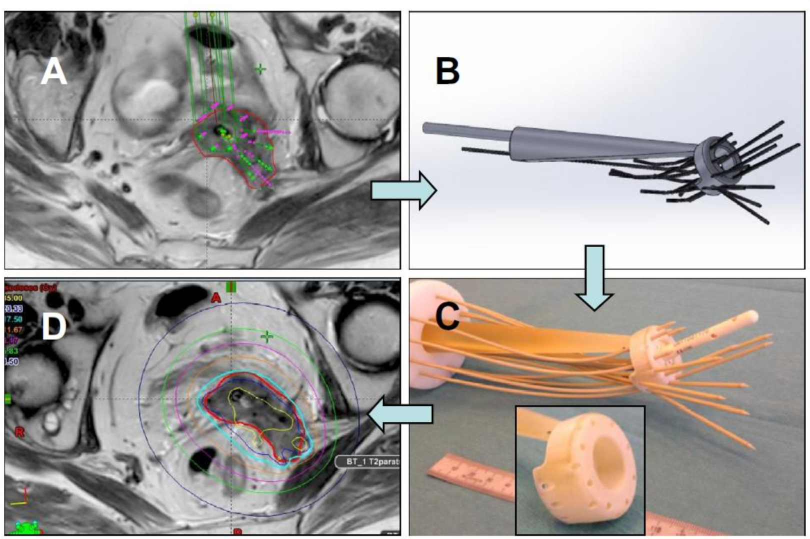
Berger, Kirisits,
Mahantshetty et al. .
Vienna II, 2016,
(submitted to R&O)

MEDIZINISCHE
UNIVERSITÄT
WIEN

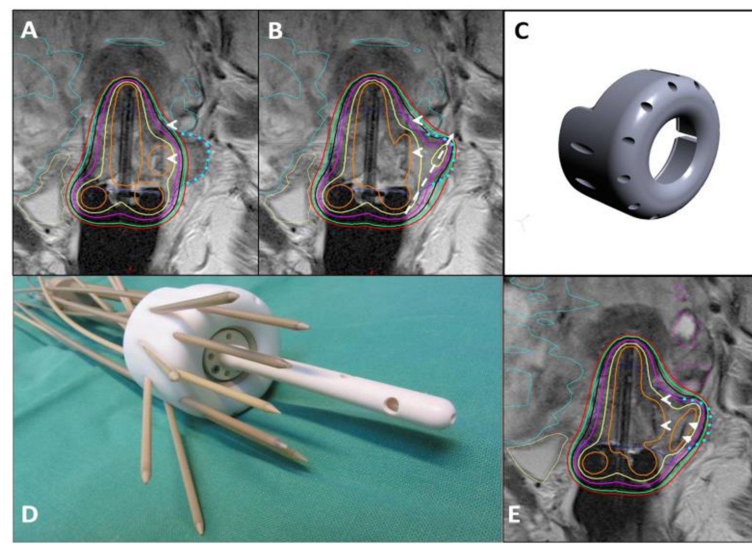
Linking research and education

3D printing technology (IC or IC/IS)

Classic Moulage technique



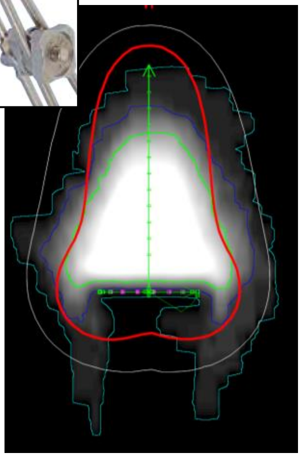
Lindegaard J, et al. Radiother Oncol 2016



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

Summary

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

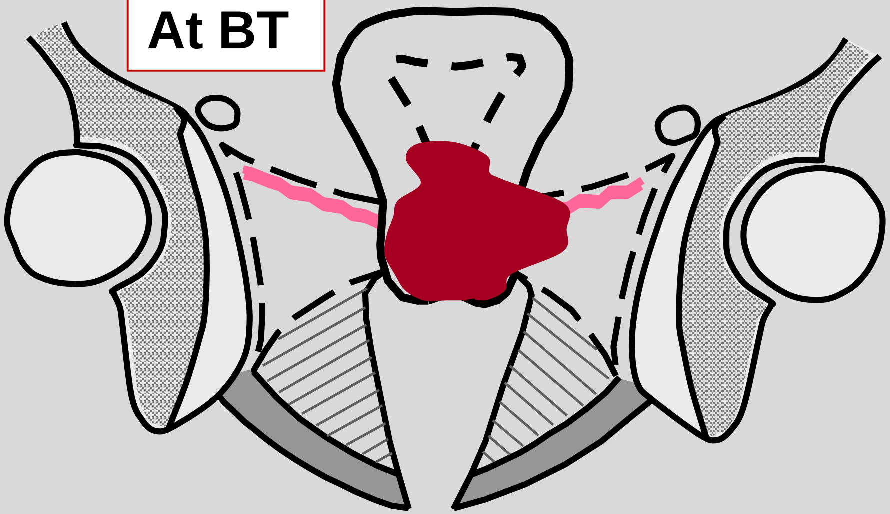


Combined intracavitary-interstitial technique for cervix cancer

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

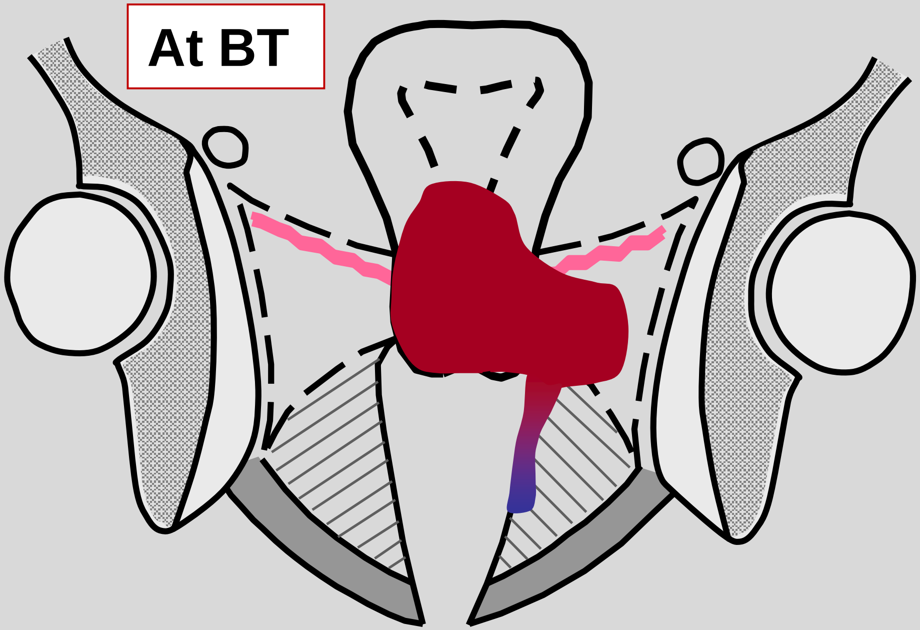
Johannes C. Athanasios Dimopoulos, Head, Radiation Oncology
Metropolitan Hospital, Athens, Greece

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



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

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



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

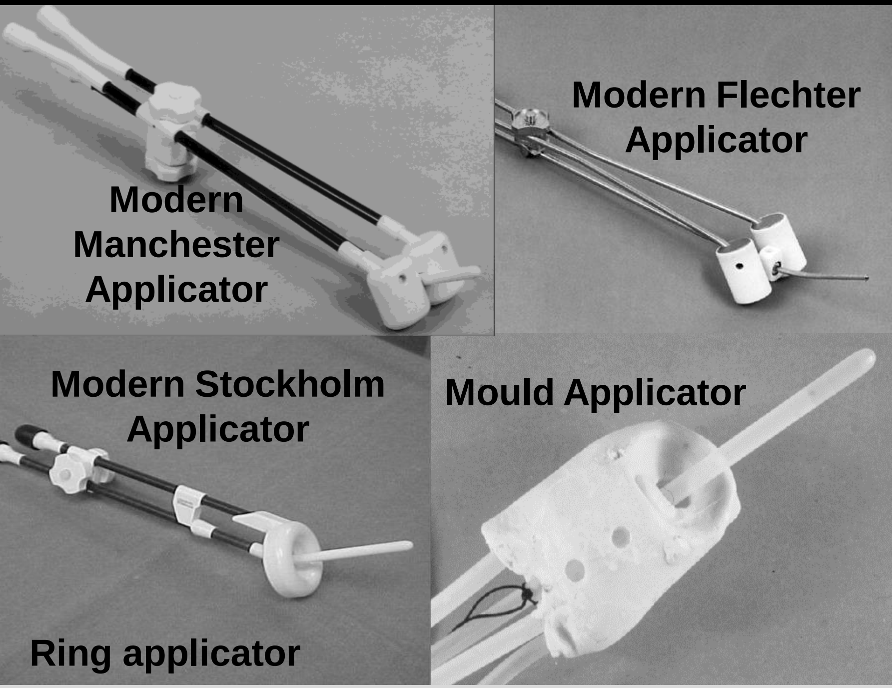
OUTLINE

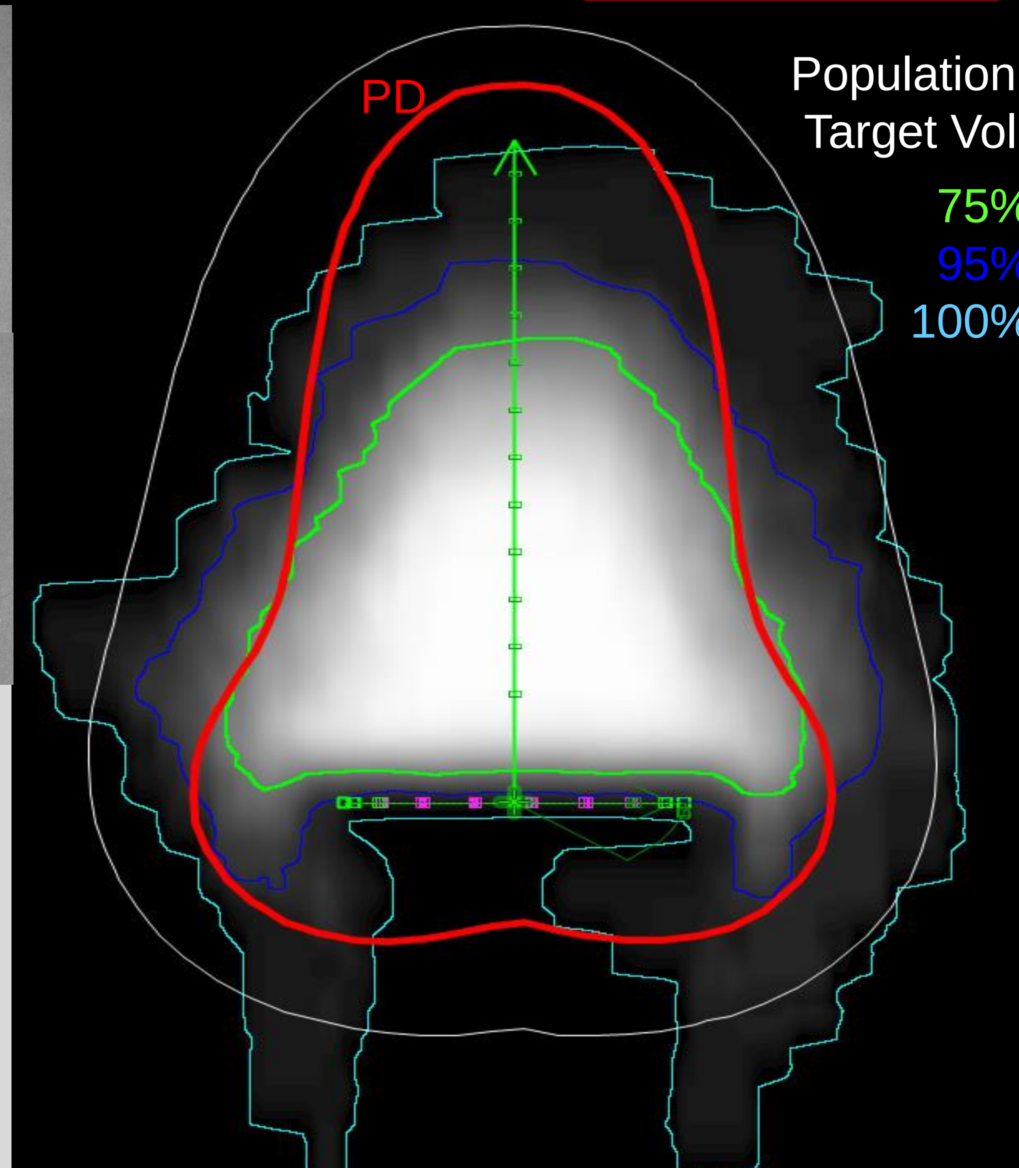
- *Limitations of STD Intracavitary Applicators*
- *Conventional Interstitial Techniques*
- *Modern Intracavitary + Interstitial Techniques*
- *Optimizing Applicator placement by Image guidance*
- *Principles of Selection of Appropriate Technique*

Limitations of pure intracavitary techniques

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

264 patients





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

Courtesy: P. Petric,D. Berger

Indications for combined intracavitary/interstitial

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

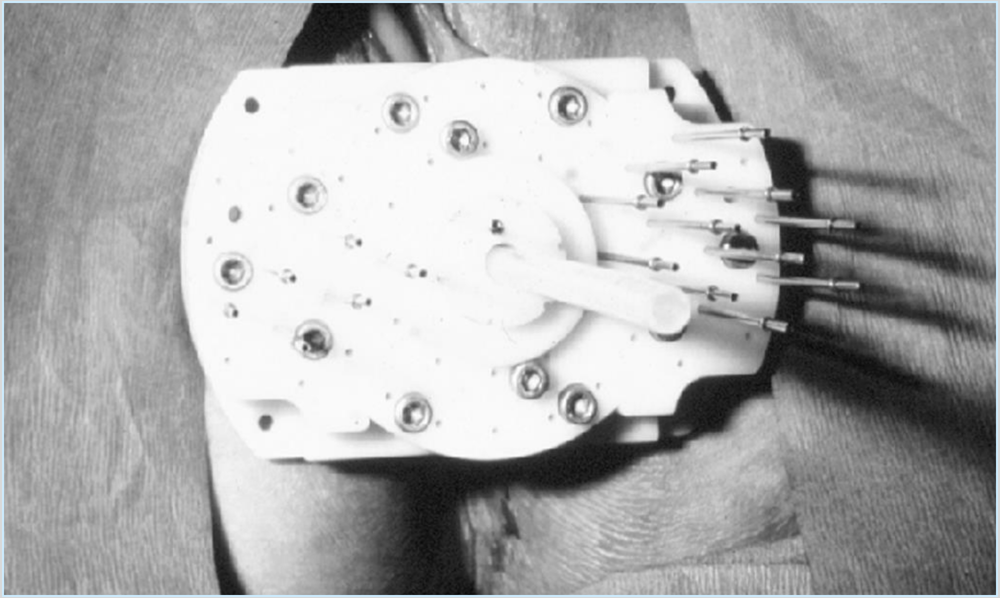
INTERSTITIAL TECHNIQUES
AIMS IN LOCALLY ADVANCED DISEASE

- *accurate and reproducible placement of needles*
- *tailor positions of needles to the target*
- *tailor dose distribution to target and OAR*
  - *adequate target coverage*
  - *Optimal sparing of OAR*

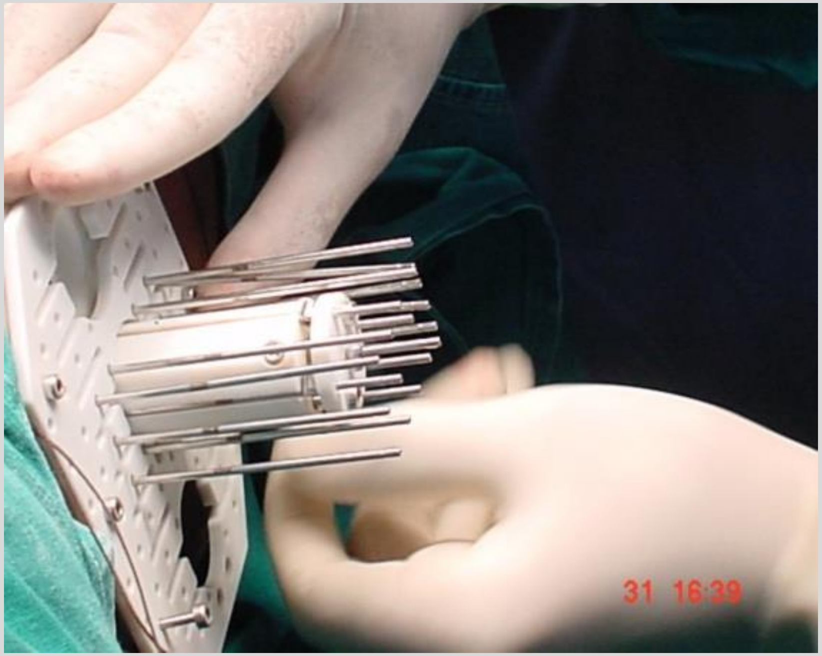
CLASSICAL INTERSTITIAL TECHNIQUES
FREEHAND PLACEMENT

CLASSICAL INTERSTITIAL TECHNIQUES
PERINEAL TEMPLATES

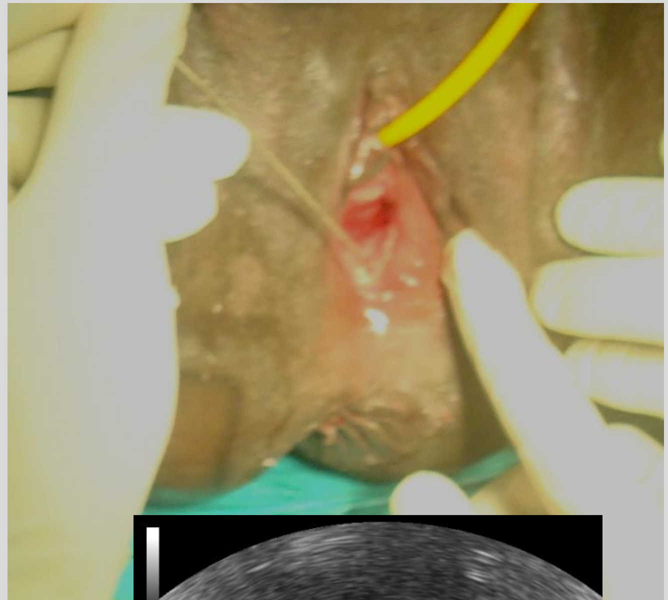
SYED

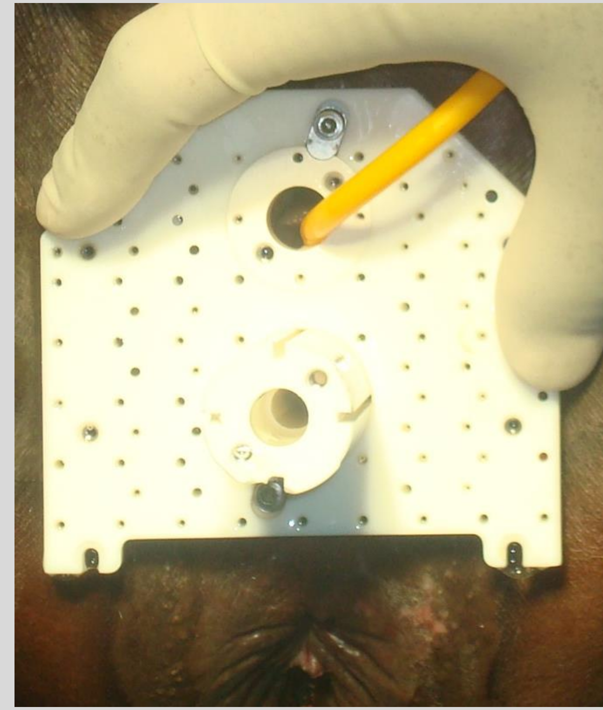


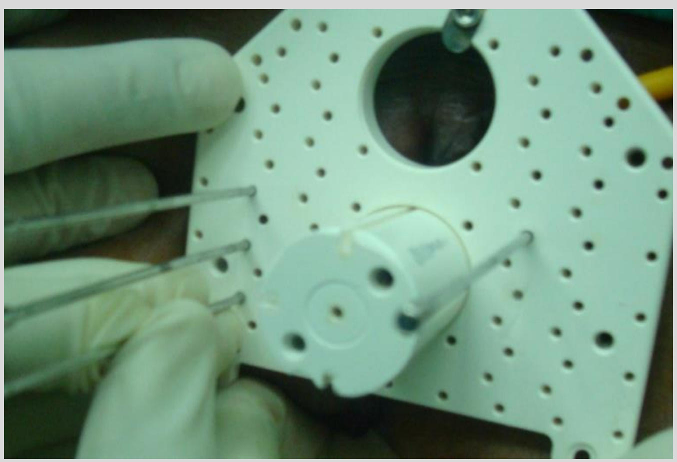
MUPIT

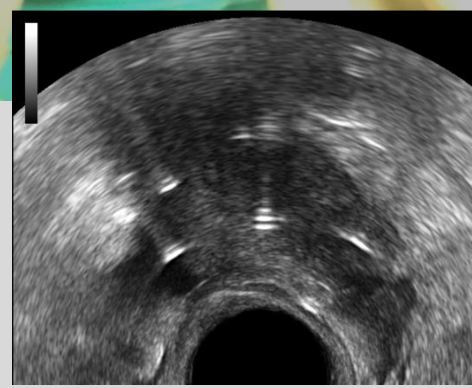


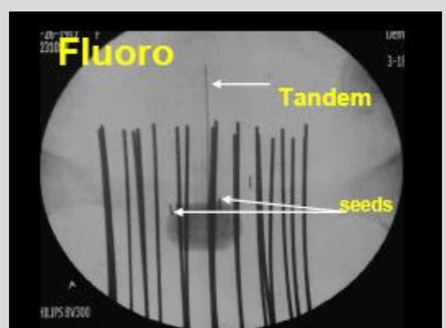
PRINICPLES OF MUPIT PROCEDURE

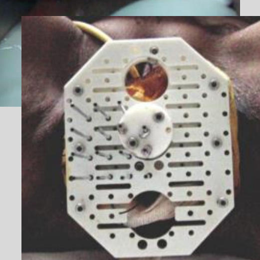


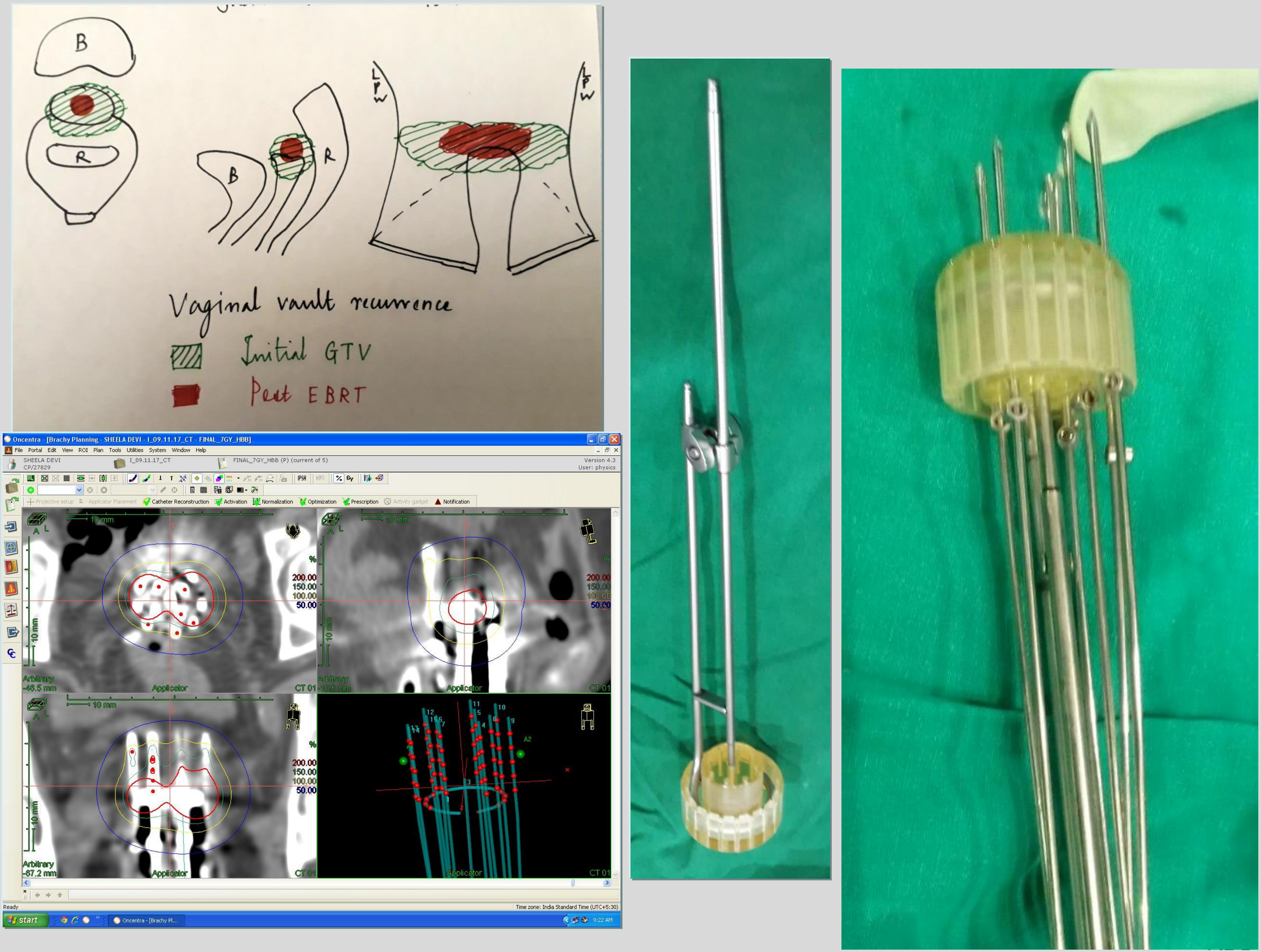






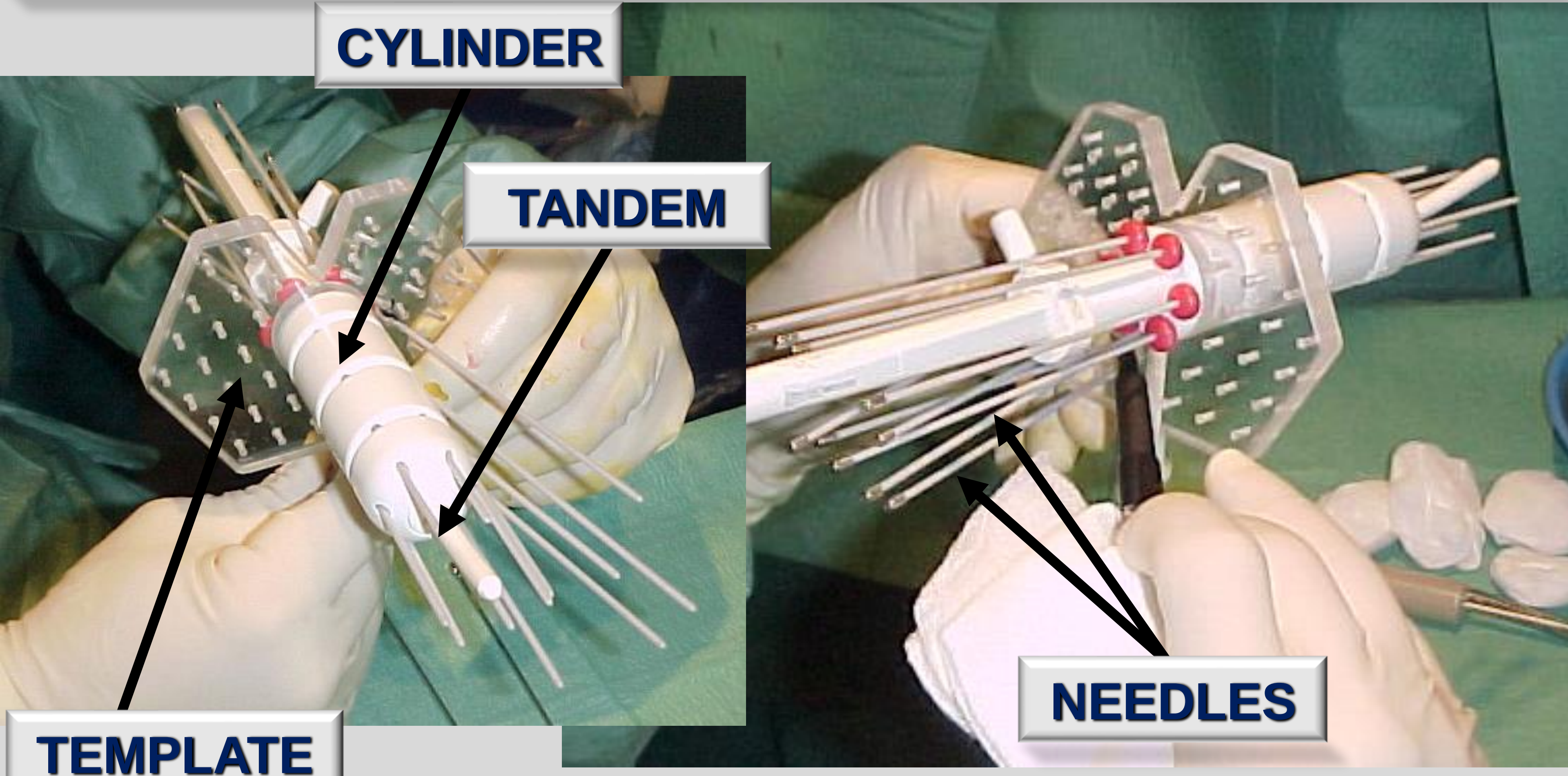


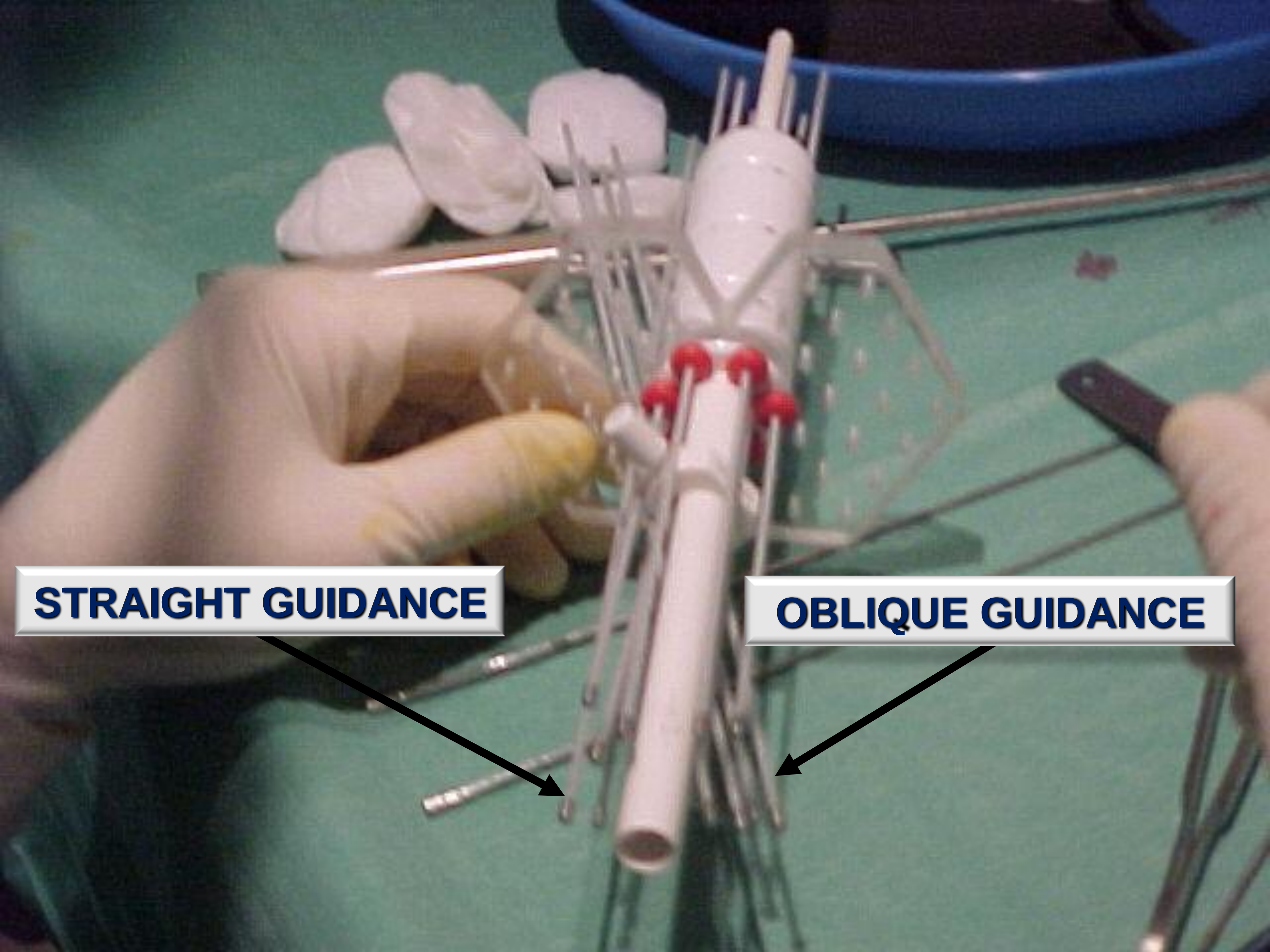



B
R
B
R
LPW
LPW
Vaginal vault recurrence
Initial GTV
Post EBRT
Oncentra - [Brachy Planning - SHEELA DEVI - I_09.11.17_CT - FINAL_7GY_HBB]
File Portal Edit View ROI Plan Tools Utilities System Window Help
SHEELA DEVI
CP/27829
I_09.11.17_CT
FINAL_7GY_HBB (P) (current of 5)
Version 4.3
User: physics
Projective setup
Applicator Placement
Catheter Reconstruction
Activation
Normalization
Optimization
Prescription
Activity gadget
Notification
10 mm
%
200.00
150.00
100.00
50.00
Arbitrary
-46.5 mm
Applicator
CT 01
-10.6 mm
Arbitrary
-67.2 mm
A2
Ready
Time zone: India Standard Time (UTC+5:30)
start
Oncentra - [Brachy Pl...
9:22 AM

MODIFIED CLASSICAL INTERSTITIAL TECHNIQUES

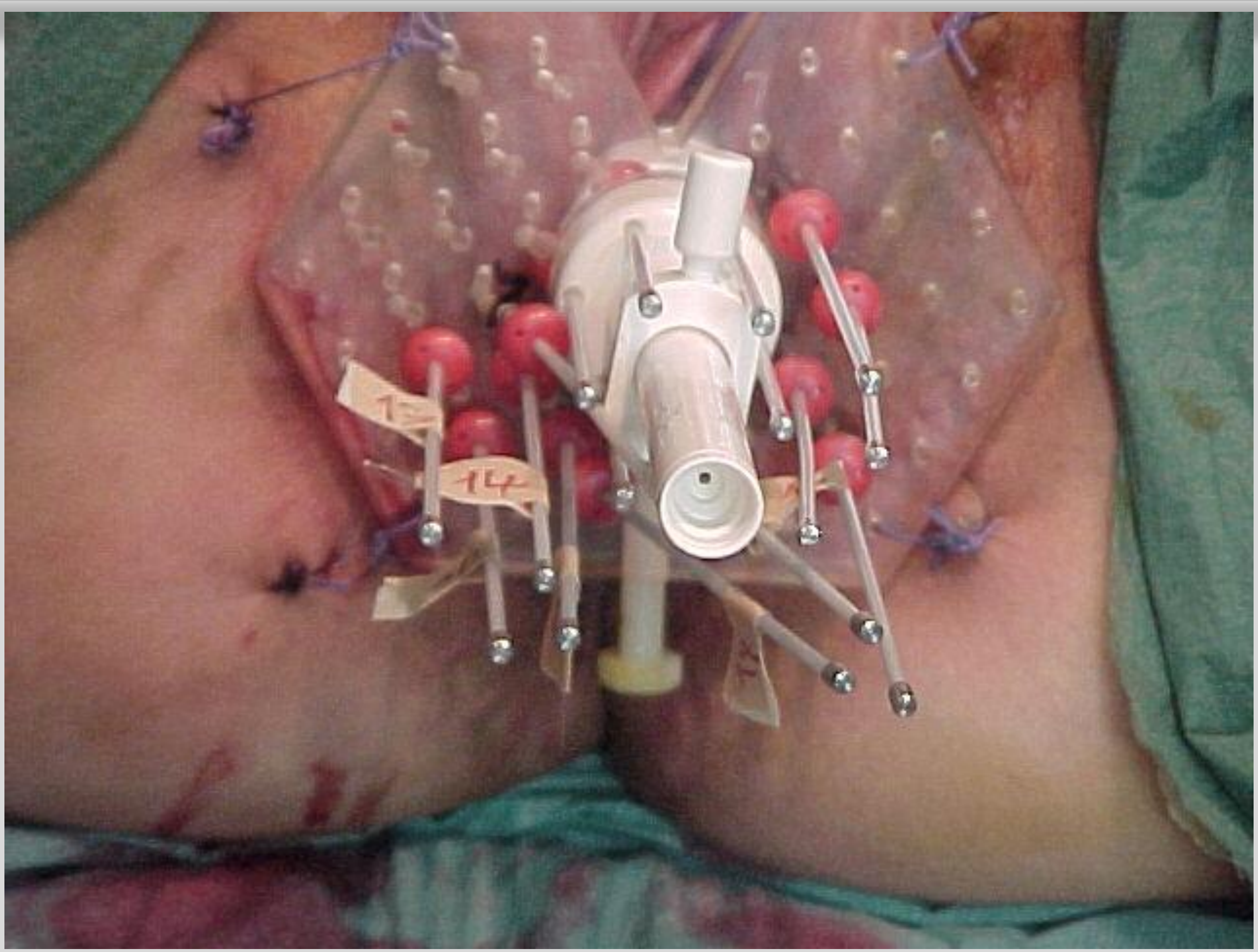
MRI-compatible cylinder + tandem + template




STRAIGHT GUIDANCE
OBLIQUE GUIDANCE

MODIFIED CLASSICAL INTERSTITIAL TECHNIQUES

COMPLETED IMPLANT



CLASSICAL & MODIFIED INTERSTITIAL TECHNIQUES

DRAWBACKS

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

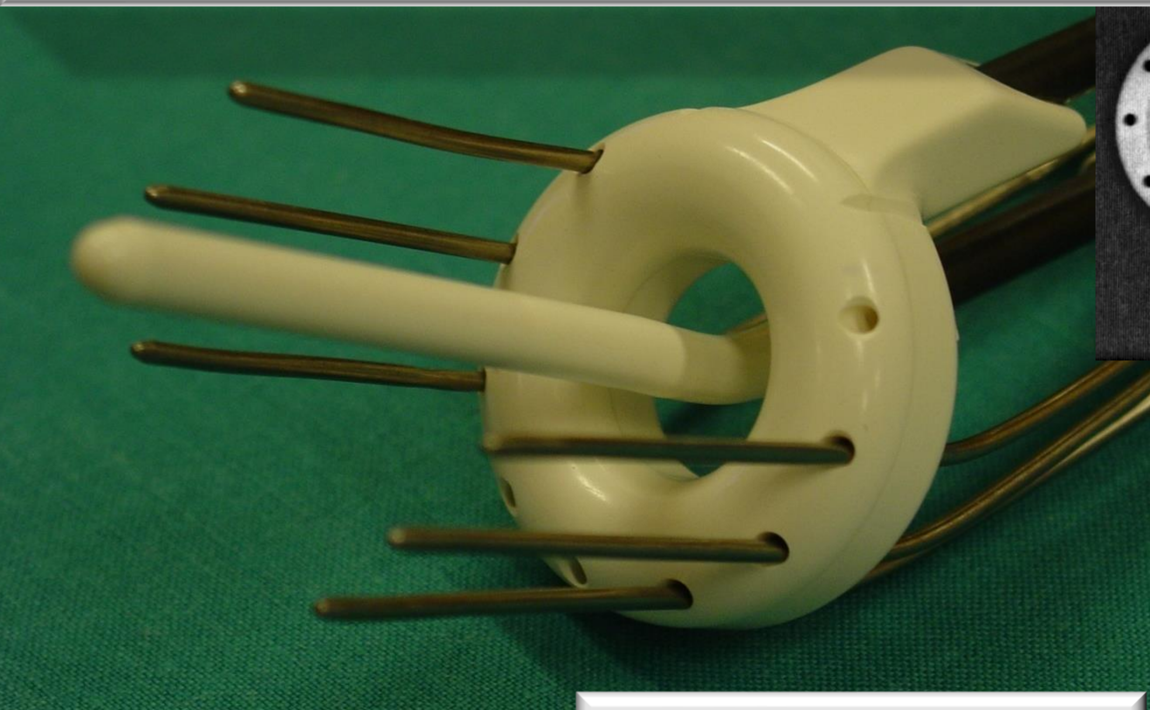
- *Perineal templates (Syed, MUPIT, others)*
  - *high number of needles used*
  - *long distances between template and target (loss of parallelism, inaccurate positioning)*
  - *impediment for general acceptance: considerable risk of serious acute/late complications*

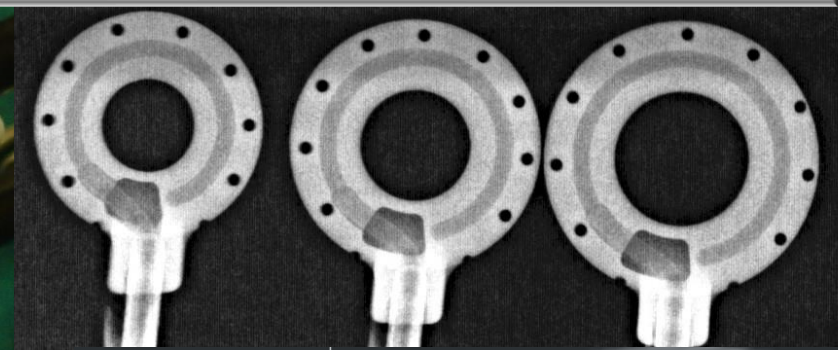
INTRACAVITARY + INTERSTITIAL TECHNIQUES

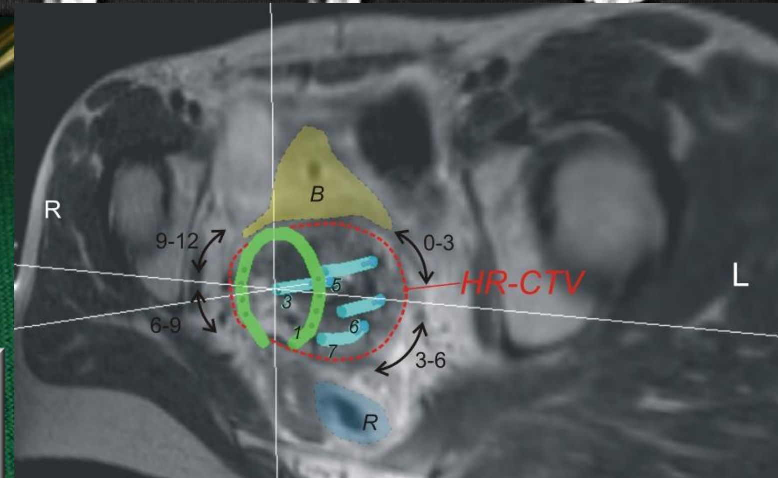
TASKS

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

MODERN INTERSTITIAL TECHNIQUES







The Vienna Applicator

Intercavitary / interstitial Tandem-Ring Applicator

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

Kirisits et al. IJROBP 2006 (technical note)
Dimopoulos et al. IJROBP 2006 (clinical results)

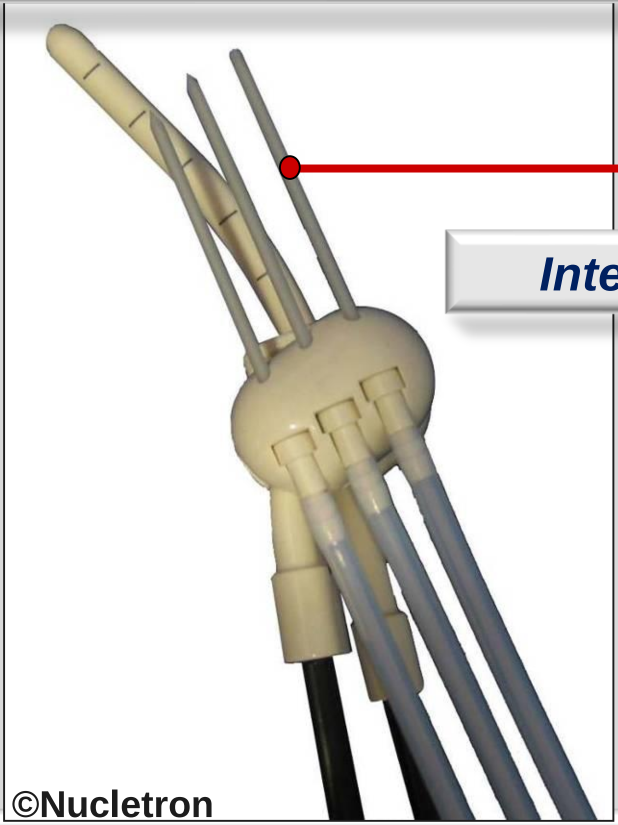
MODERN INTERSTITIAL TECHNIQUES

Applicators – special situations

Cervical cancer with moderate lateral expansion: modified principles of treatment

The Utrecht Applicator

Intracavitary / interstitial Fletcher Applicator



Interstitial tubes/needles

Schulz I, et al. Radiother Oncol., with permission

INTRACVITARY +INTERSTITIAL TECHNIQUES

VIDEO PRESENTATIONS

VIENNA APPLICATION AT AKH VIENNA

VIENNA APPLICATION AT TATA

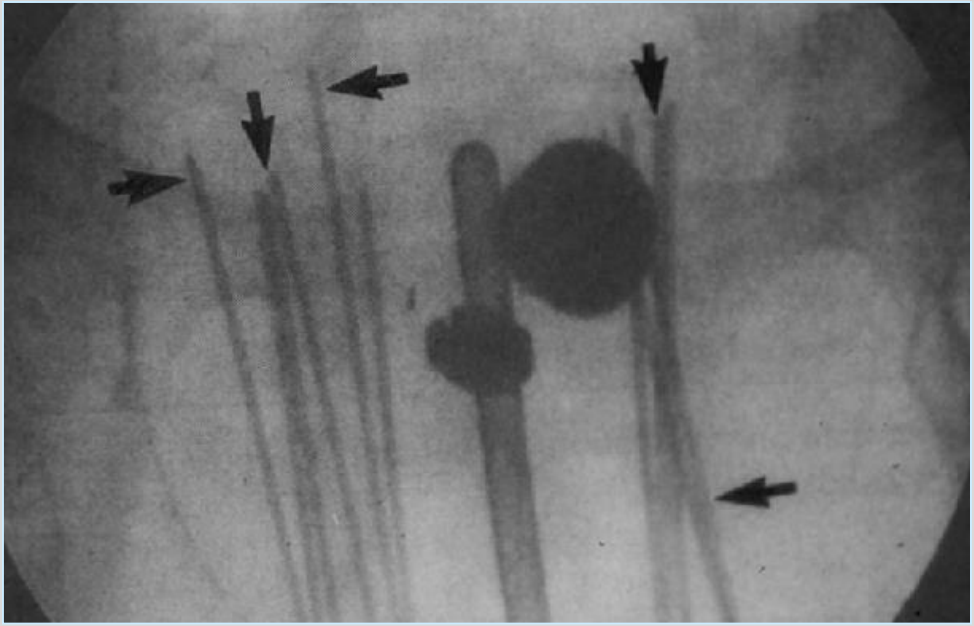
INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

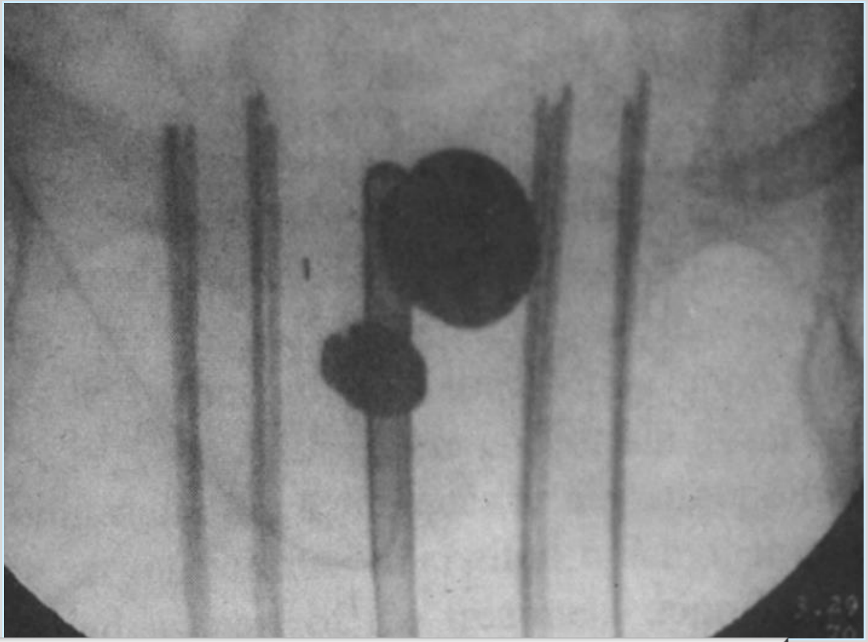
NEEDLE PLACEMENT ACCURACY

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

INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

NEEDLE PLACEMENT ACCURACY: FLUOROSCOPY





REPOSITIONING: ACCURATE

LIMITATIONS: TARGET VISUALIZATION & COVERAGE

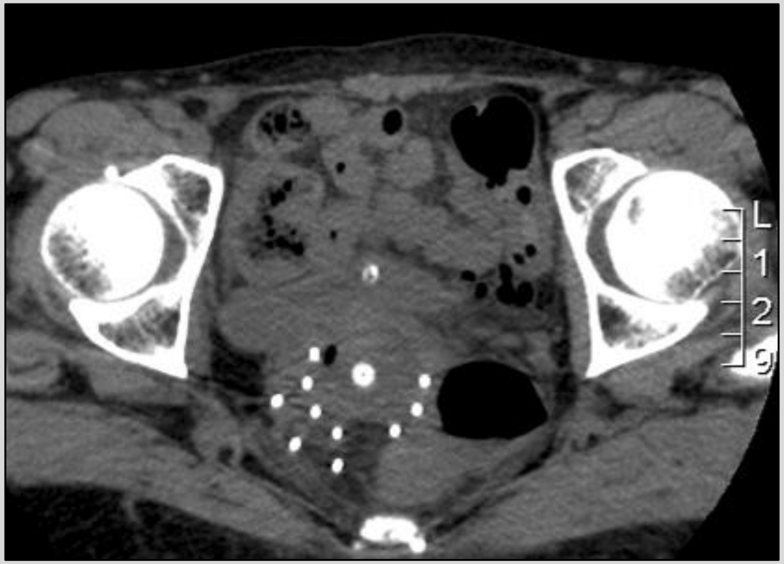
Nag IJROBP 40:415-20;1998

Computed Tomography

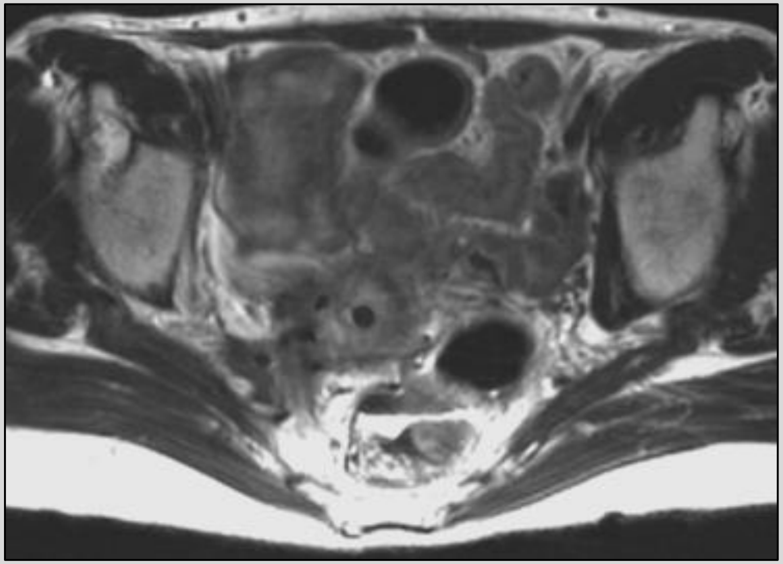
Findings at Brachytherapy

Example: cervix cancer

Assess Tumour size & Topography



Native CT (no contrast)



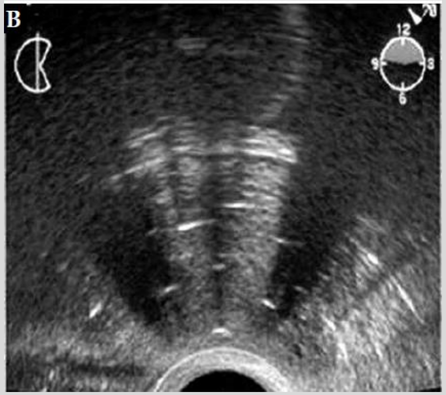
T2W FSE MRI (same patient)

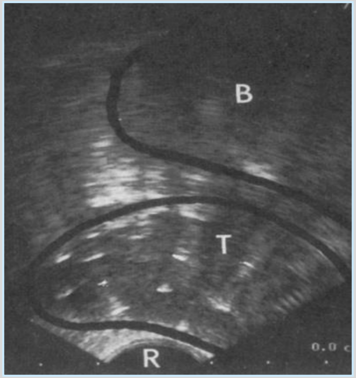
Courtesy; Jacob C Lindegaard, Aarhus University Hospital

INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT

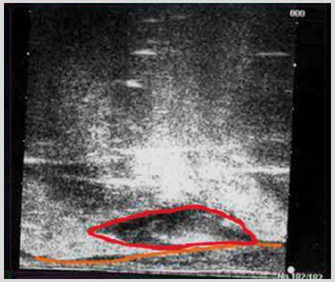
	Ultrasound	MRI
Accessibility in the operating room	High	Low
Real-time image guidance	High	Low
Catheter visualization	High	High
Target visualization	High	High
Volume based evaluation	Low	High
Treatment planning	Low	High
Experience with technique	Low	High
Clinical evidence	Low	High

Kamrava M. J Contemp Brachytherapy 2014





Weitmann HD et al. Strahlenther Onkol 2006; 182: 86-95.
Wenzel W. J Clin Ultrasound 1975; 3: 311-312.
Brascho DJ et al. Radiology 1978; 129: 163-167.
Stock RG et al. IJROBP 1997; 37: 819-825.
Sharma DN et al. J Gynecol Oncol 2010; 21: 12-17.

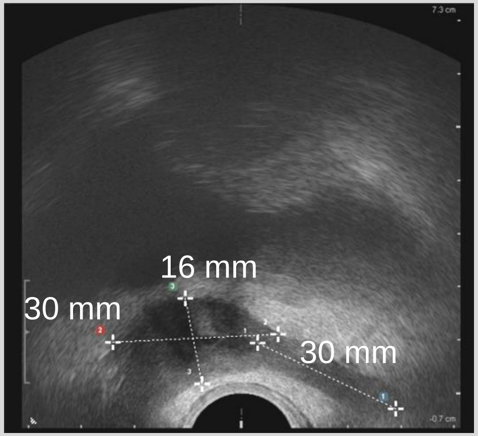


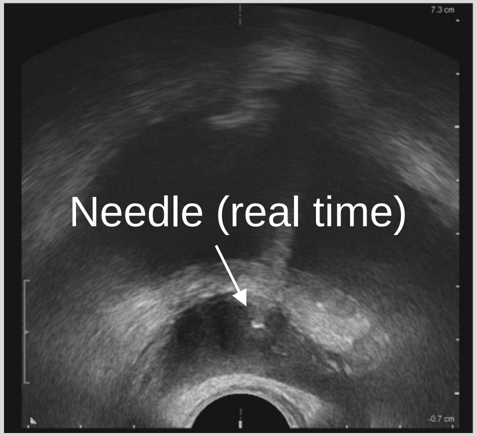
Ultrasound

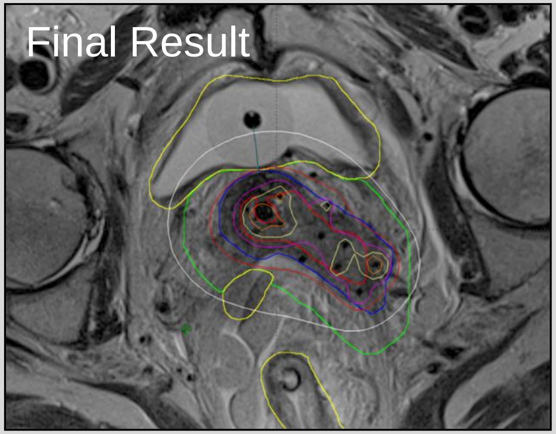
Findings at Brachytherapy

Cervix cancer

Assess Tumour size & Topography







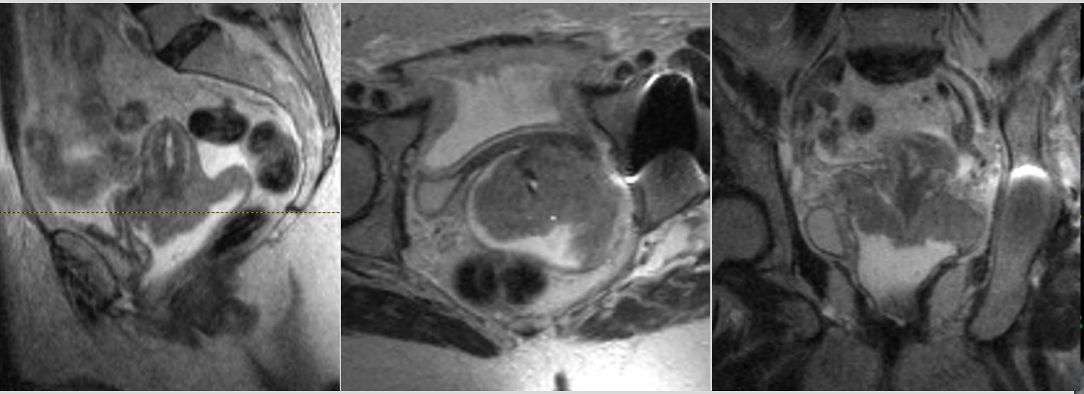
Transrectal Ultrasound

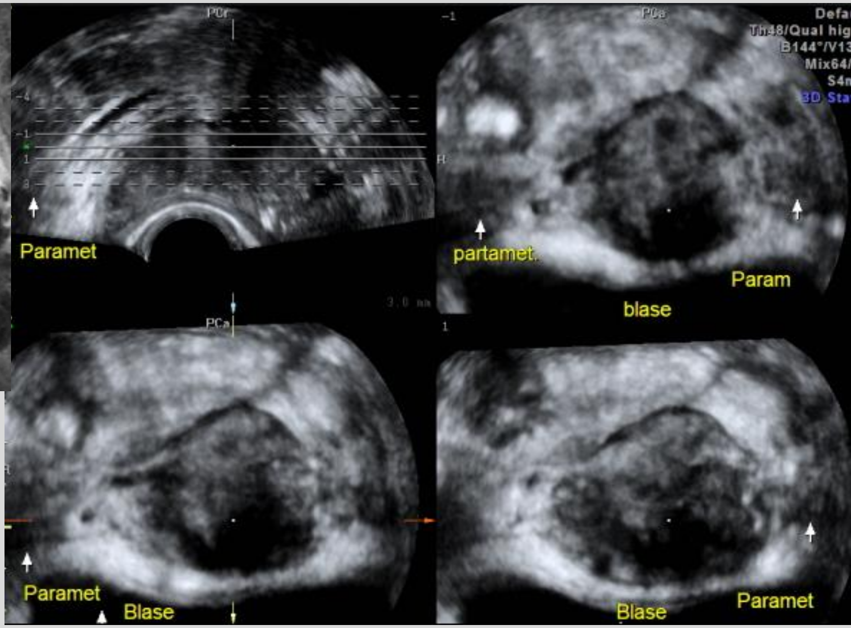
T2W FSE MRI (same patient)

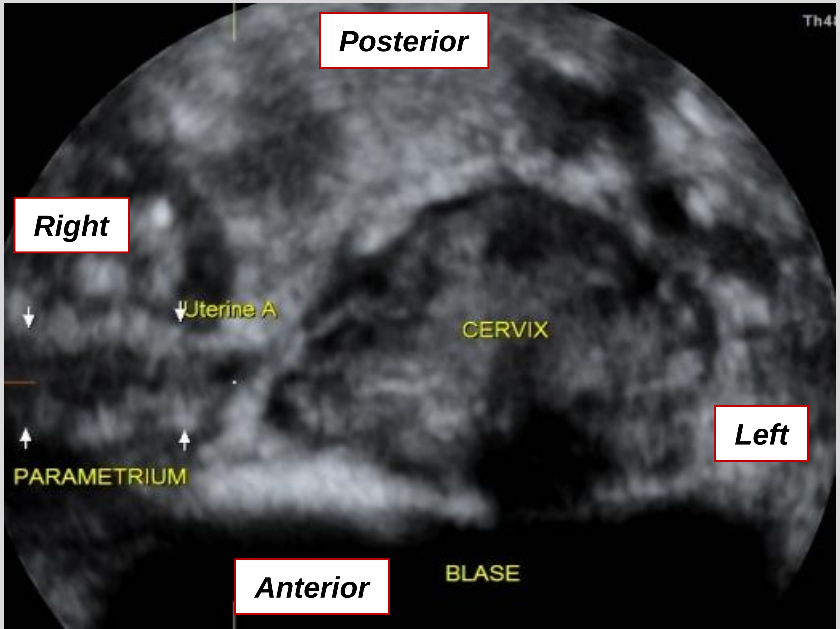
→ *Decide on application technique, Guide insertion, Aid treatment planning*

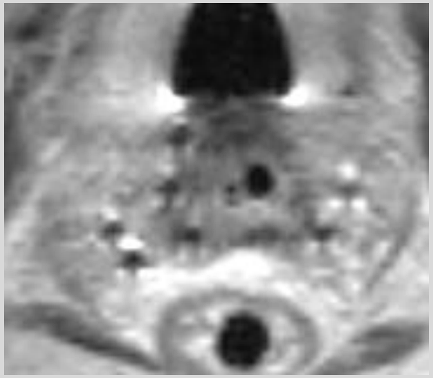
Source: Institute of Oncology Ljubljana

INTERSTITIAL TECHNIQUES
POTENTIAL OF MODERN US TECHNIQUES





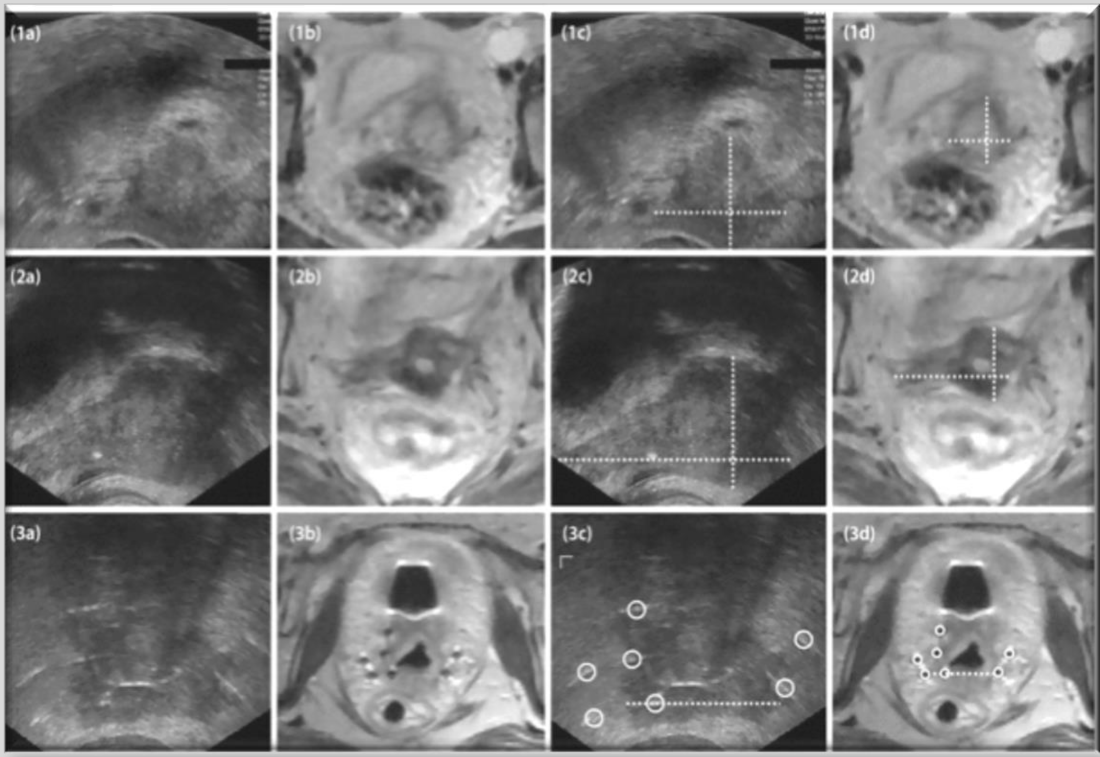




INTERSTITIAL TECHNIQUES
POTENTIAL OF MODERN US TECHNIQUES

US

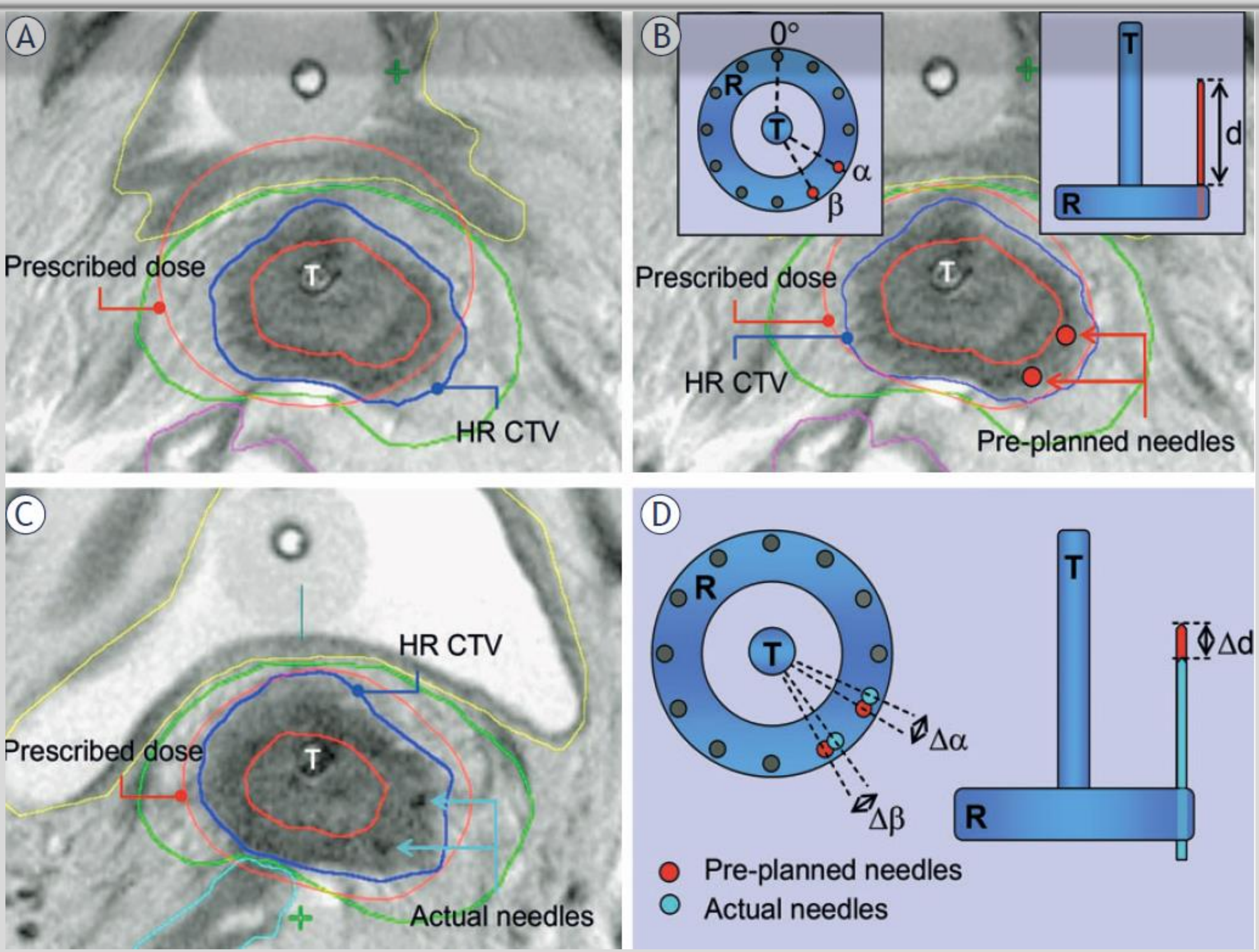
GYN BRACHY IMAGING MODALITIES



Schmid et al. Strahlenther Onkol 2013

Good correlation between US and MRI

INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT



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

COMBINED INTRACAVITARY & INTERSTITIAL TECHNIQUES

SELECTION OF APPLICATION TECHNIQUE

Based on clinical examination and sectional imaging:

At the time of diagnosis

- Initial tumor extension

During EBRT

-Quantitative and qualitative tumor regression

At the time of brachytherapy

-Topography of residual tumor in relation to the applicator

Selection of Brachytherapy Technique

- In General: depending on residual disease at brachytherapy

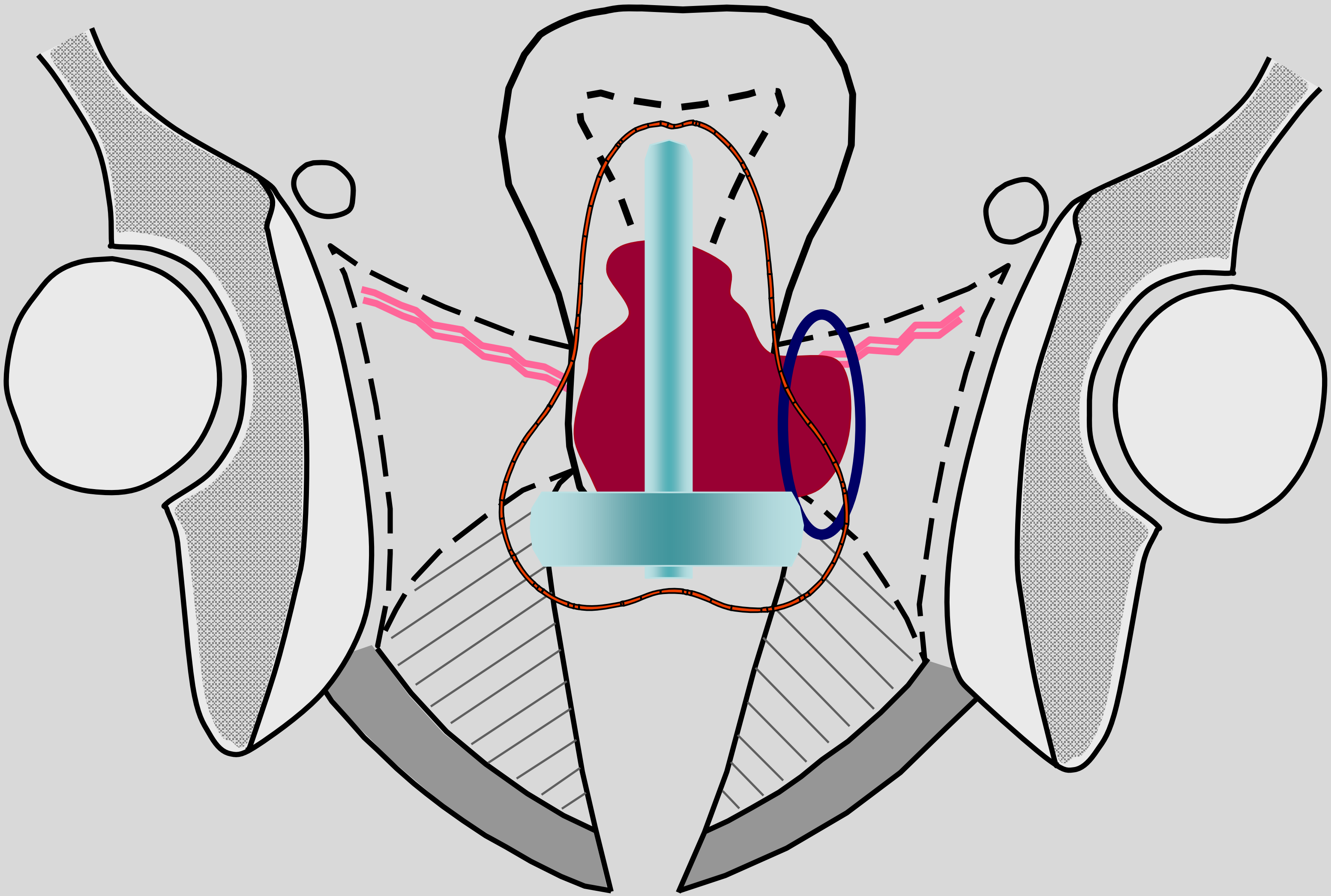
  - Disease confined to cervix and medial third parametrium: IC alone

  - Extensions beyond medial third parametrium: IC + IS combination

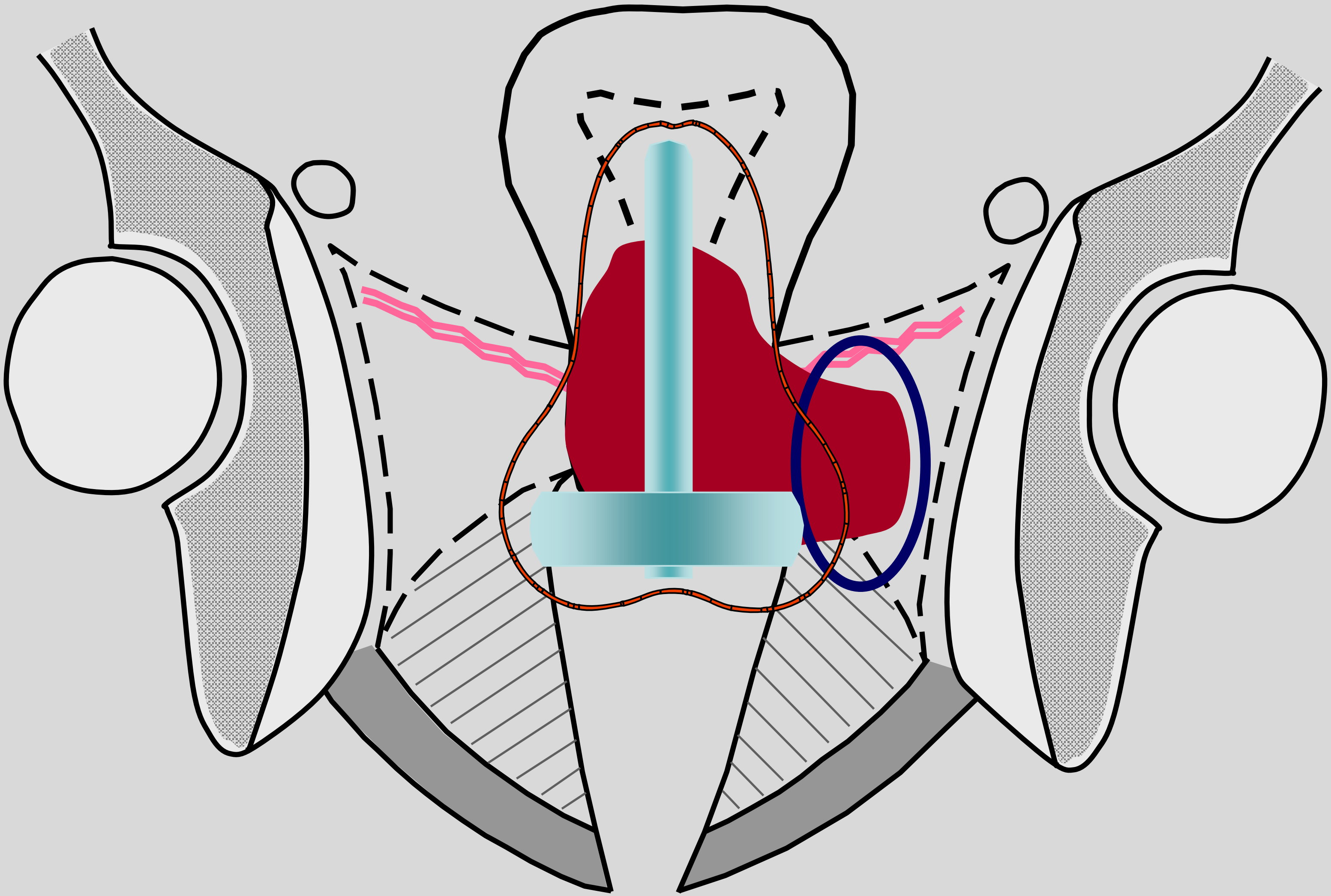
  - Extensive disease not amenable to IC + IS: IS

- Applications can be modified in subsequent fractions (esp. HDR)

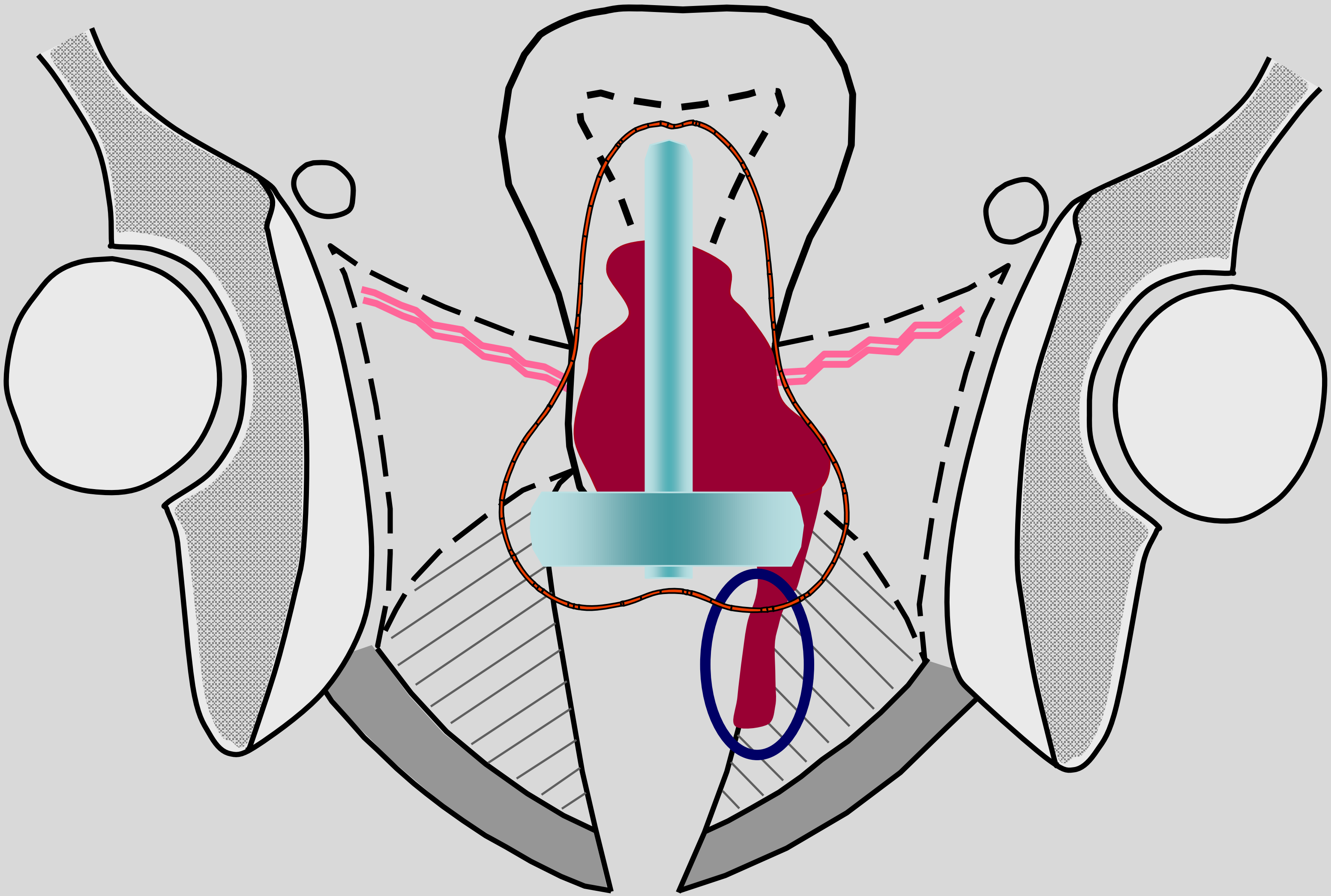
DETECTION OF INAPPROPRIATE COVERAGE: 1



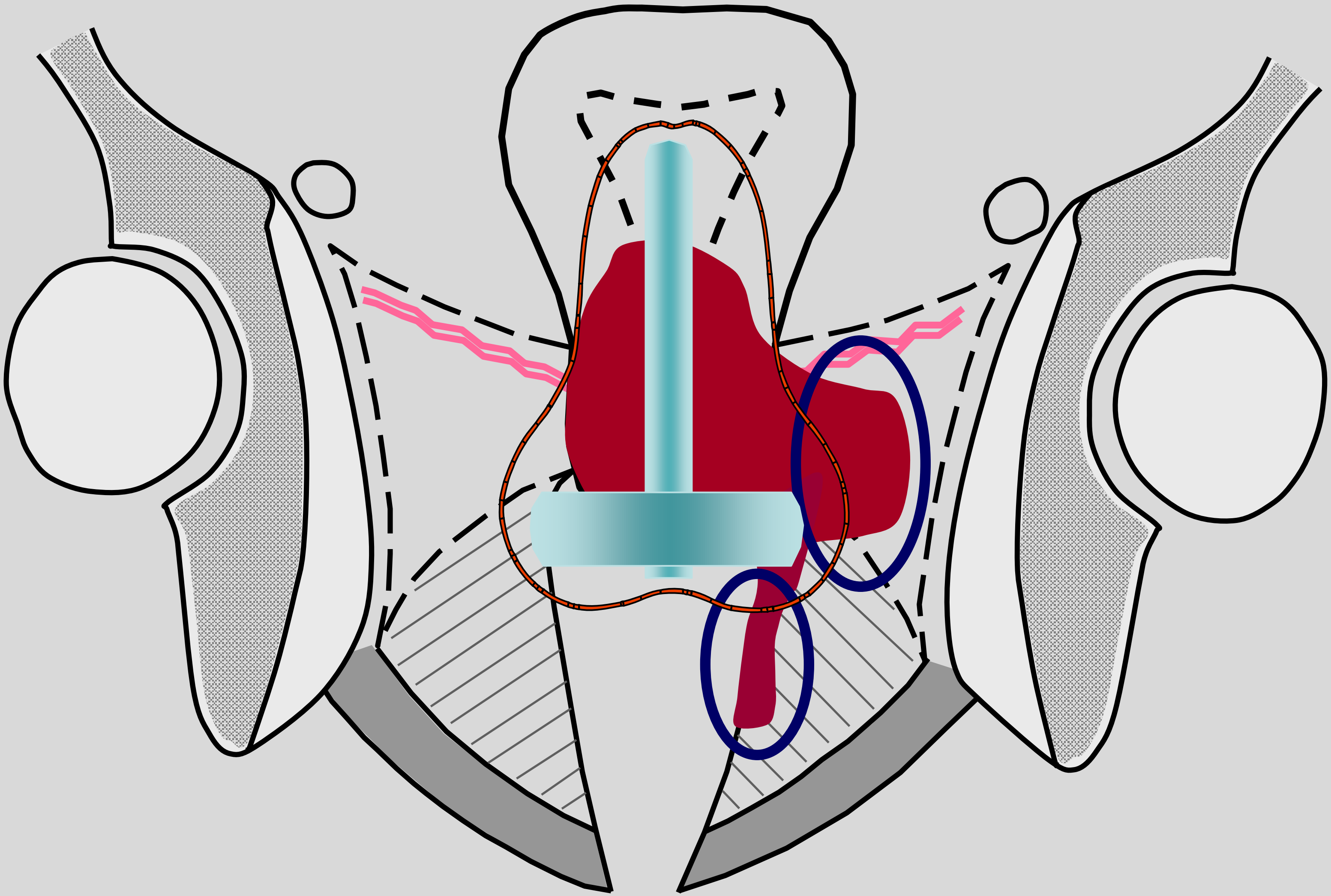
DETECTION OF INAPPROPRIATE COVERAGE: 1A



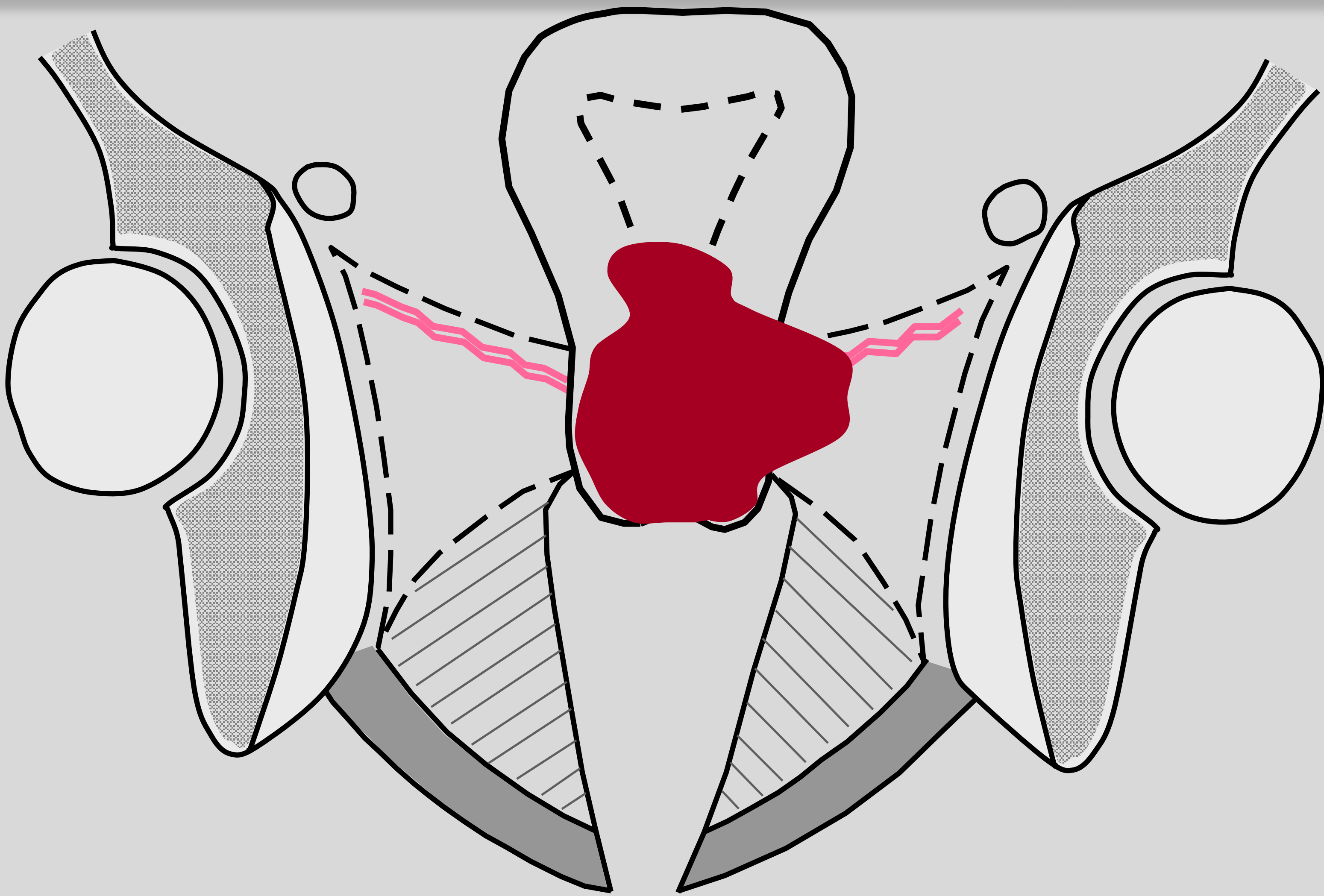
DETECTION OF INAPPROPRIATE COVERAGE: 2



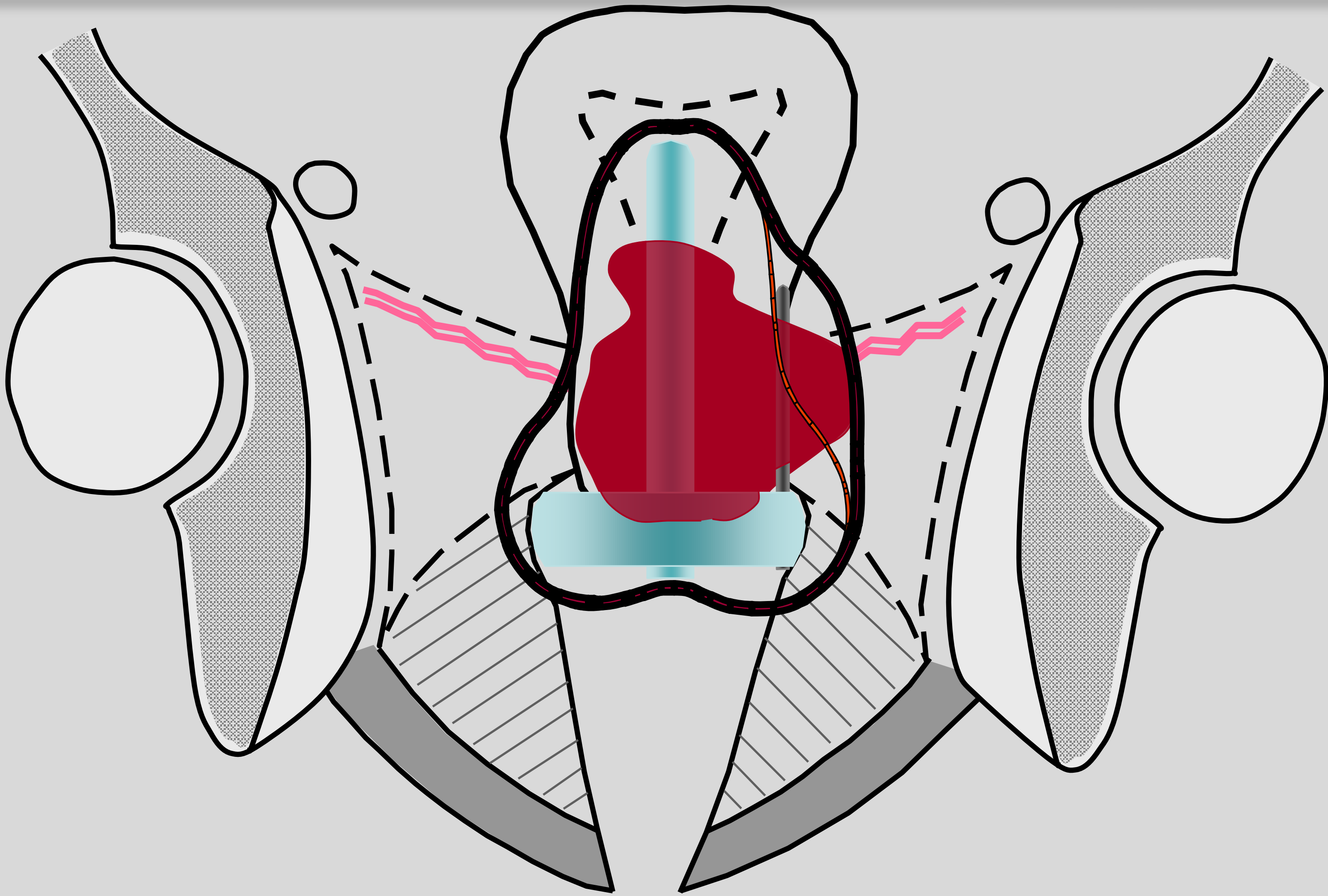
DETECTION OF INAPPROPRIATE COVERAGE: 2A



Pattern of tumor regression: 1

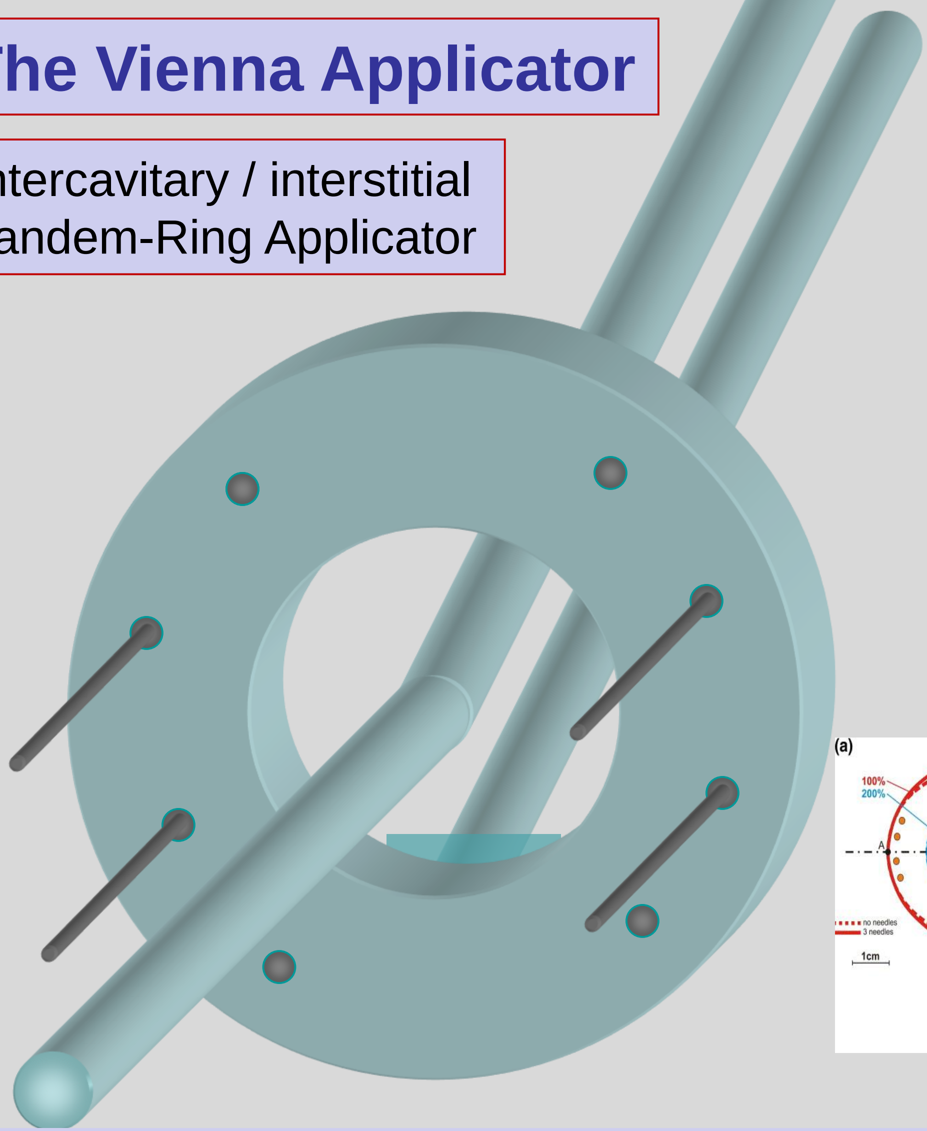


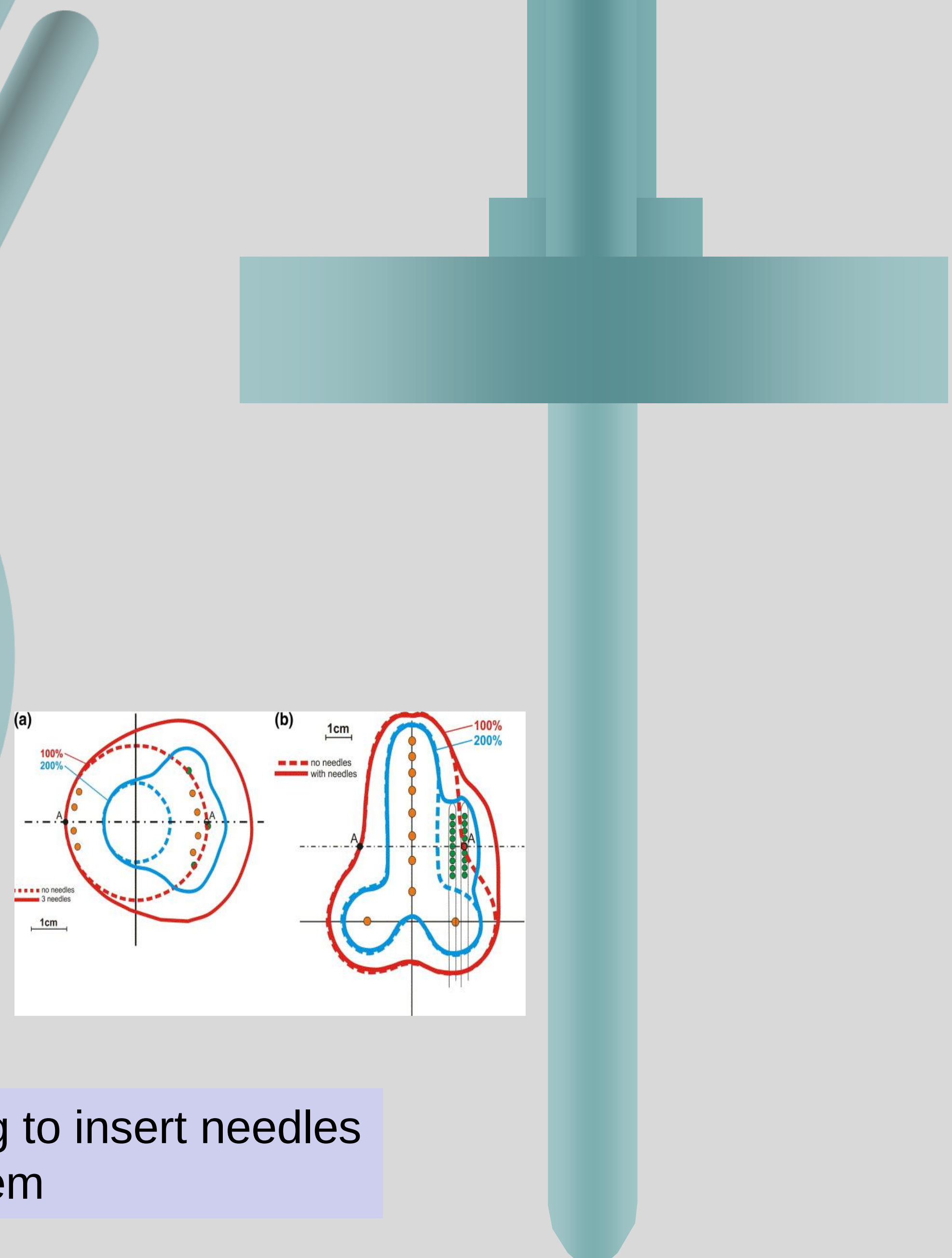
Pattern of tumor regression: 1



The Vienna Applicator

Intercavitary / interstitial
Tandem-Ring Applicator



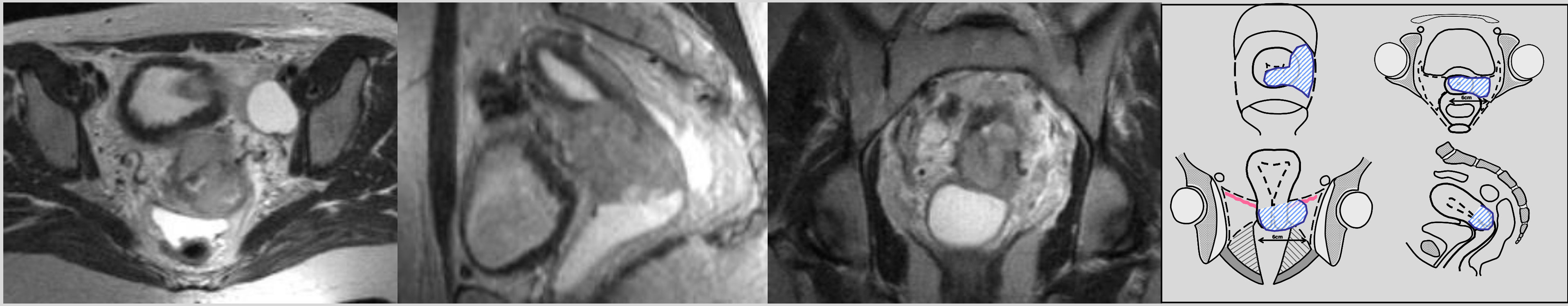


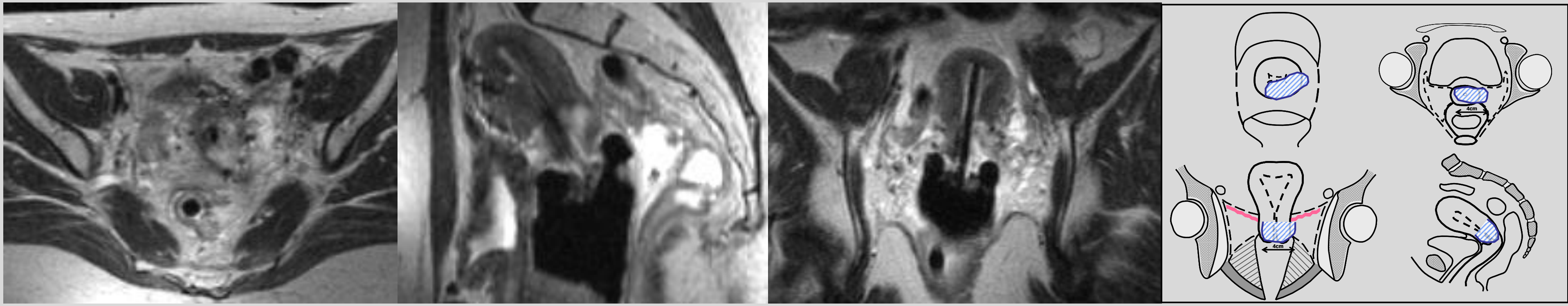
Modified Applicator: drilled holes into ring to insert needles parallel to the Tandem

Kirisits et al. IJROBP 2006 (technical note)

Dimopoulos et al. IJROBP 2006 (clinical results)

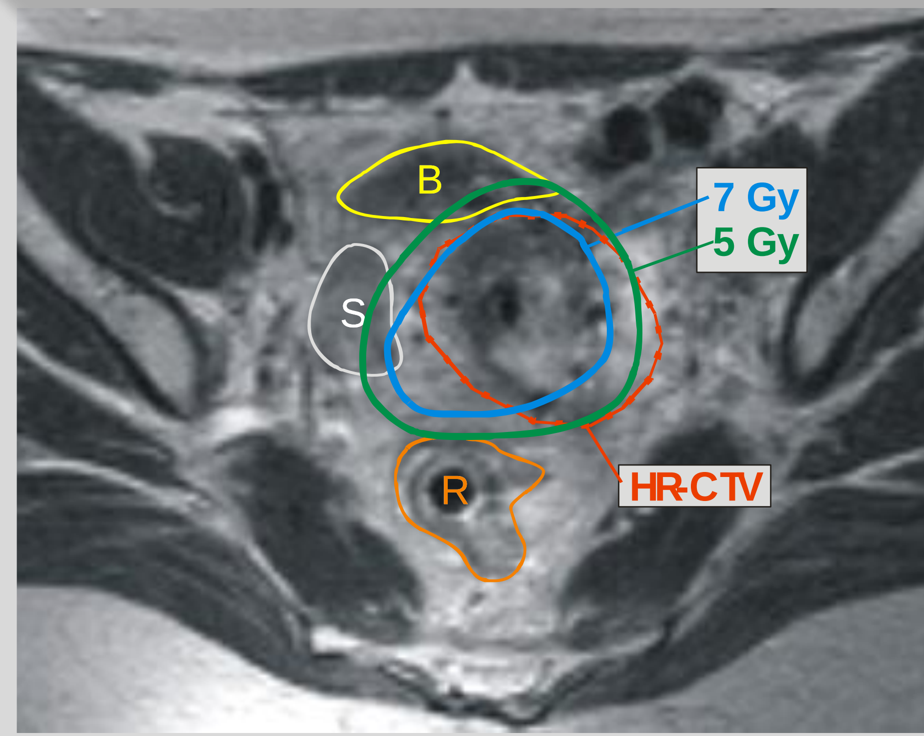
Clinical example
Stage IIB / distal / insufficient response

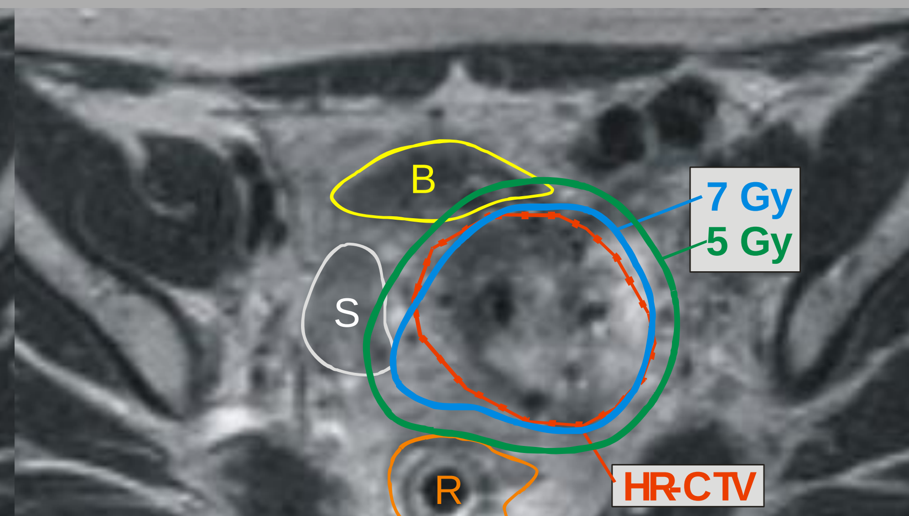


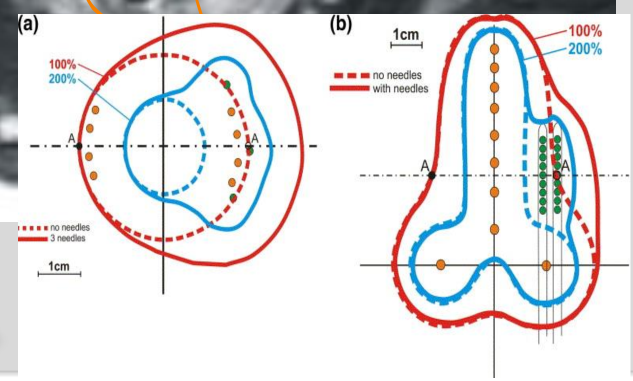


Clinical example - Interstitial Treatment MRI Based Treatment Planning plus Novel Application Technique

standard treatment plan **optimized interstitial**







INTRACAVITARY PLUS NEEDLES LEFT PARAMETRIUM

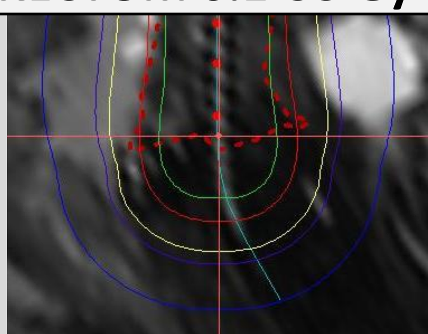
Improved placement control - Low number of needles – Combined with MRI based treatment planning

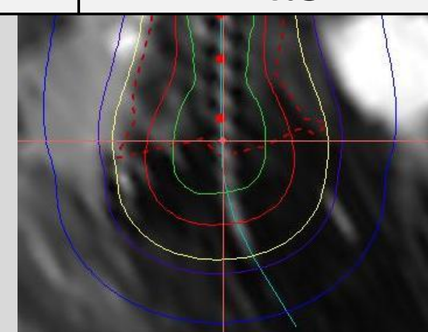
UNFAVORABLE TOPOGRAPHY FOR OAR'S: 1- 2A

STD INTRA-CAVITARY BT

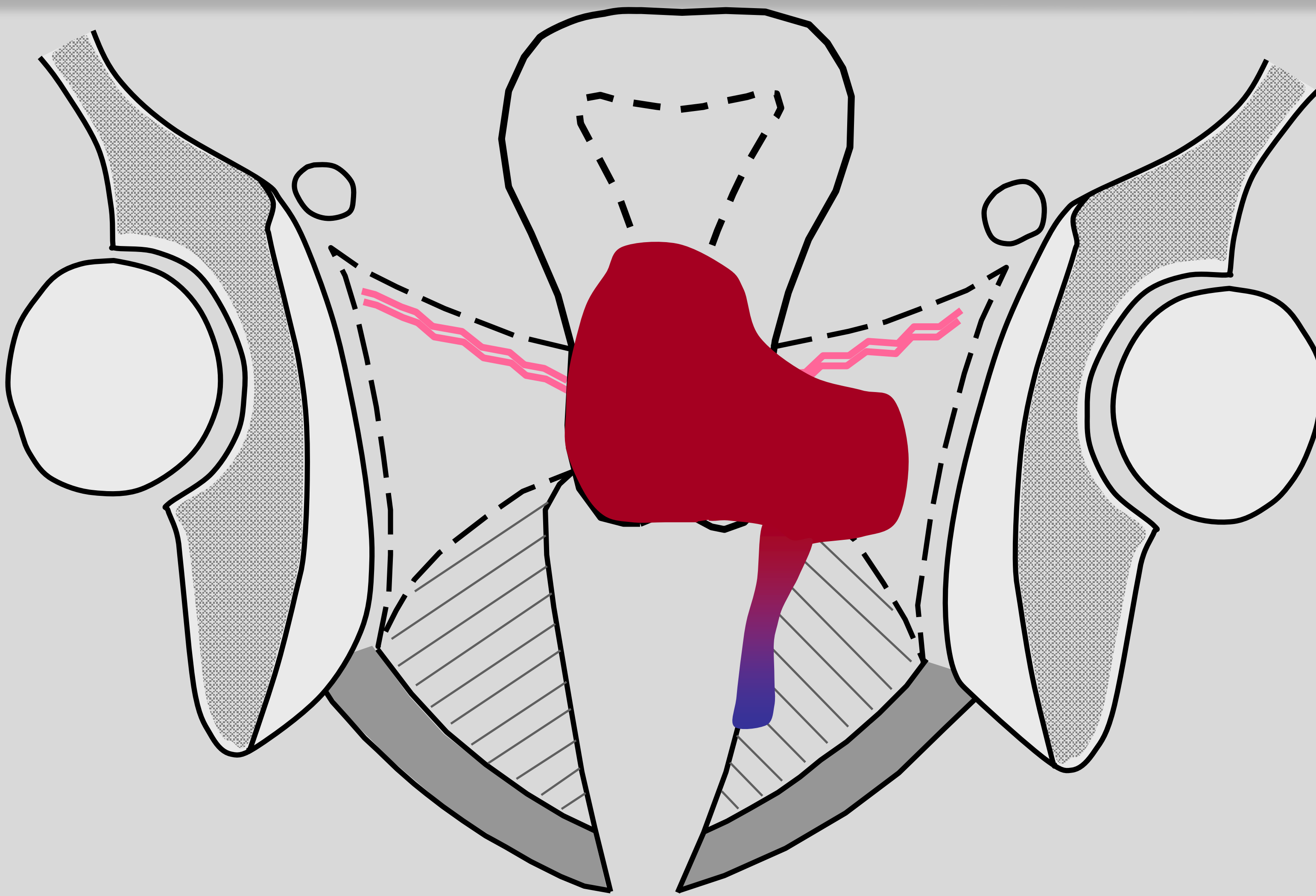
Vienna

Parameters	Ring	Vienna
HRCTV D98 (Gy)	7.6	7.3
HRCTV D90 (Gy)	10.2	8.3
HRCTV V100 (%)	99	99
SIMOID 2CC-Gy	5	4
SIMOID 0.1CC-Gy	7	5.5
BLADDER 2CC-Gy	9	6.3
BLADDER 0.1CC-Gy	11.8	7.8
RECTUM 2CC-Gy	3.9	3.4
RECTUM 0.1 CC-Gy	5.2	4.5

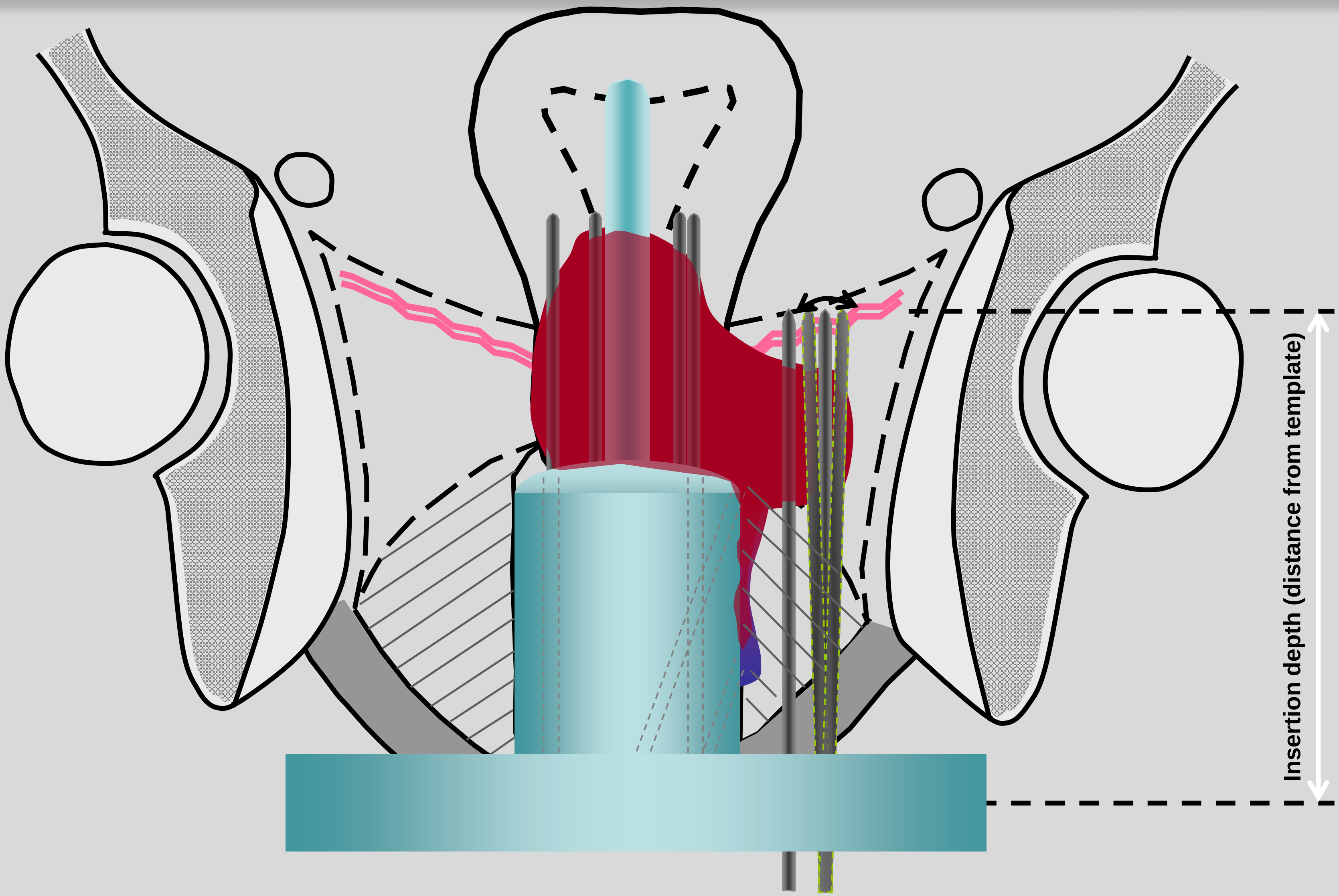




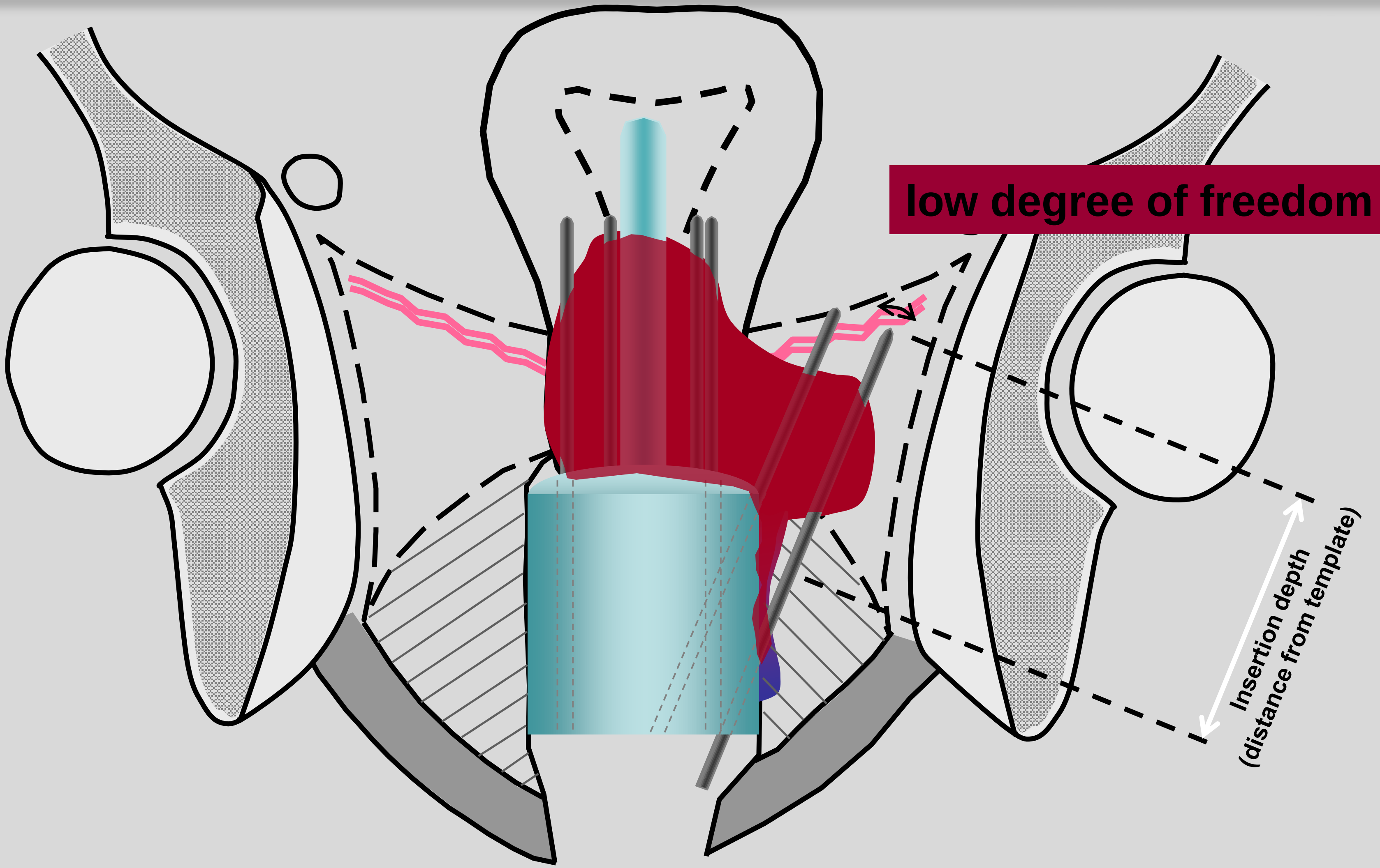
Pattern of tumor regression: 2-2A



Pattern of tumor regression

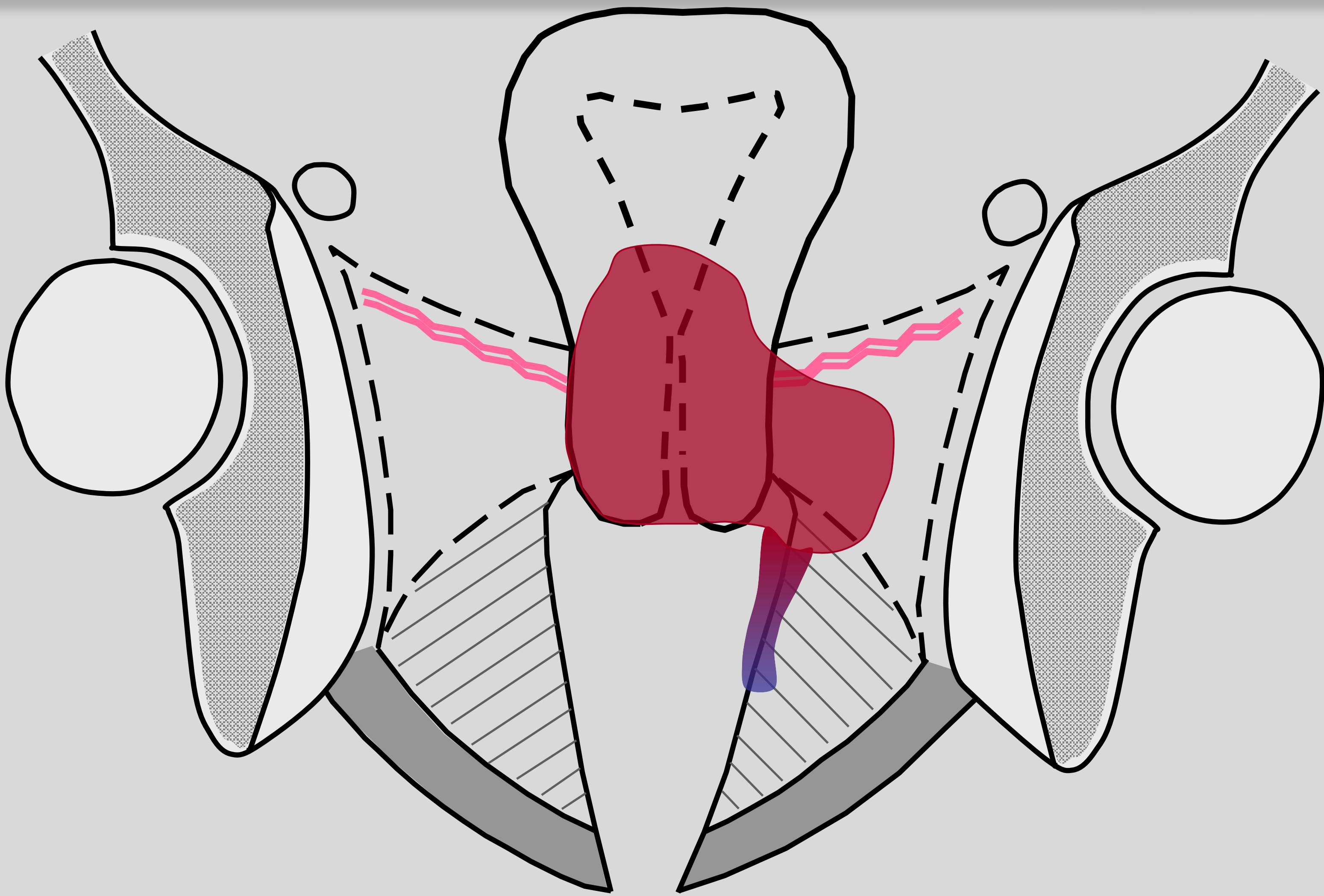


Pattern of tumor regression



Tandem + Cylinder + Needles

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

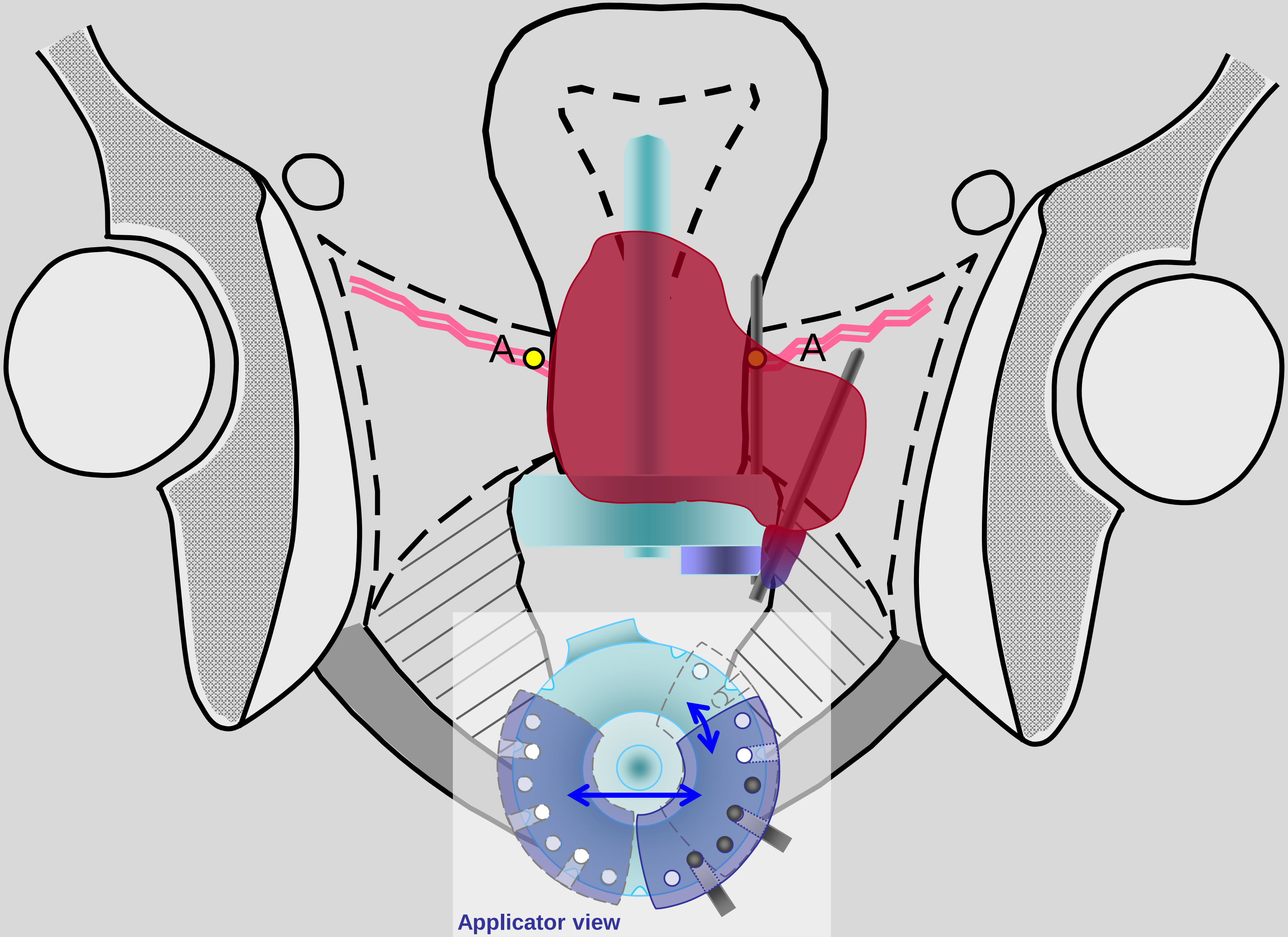


The Vienna II Applicator

Berger et al. ABS 2010

Applicator for distal parametrial disease

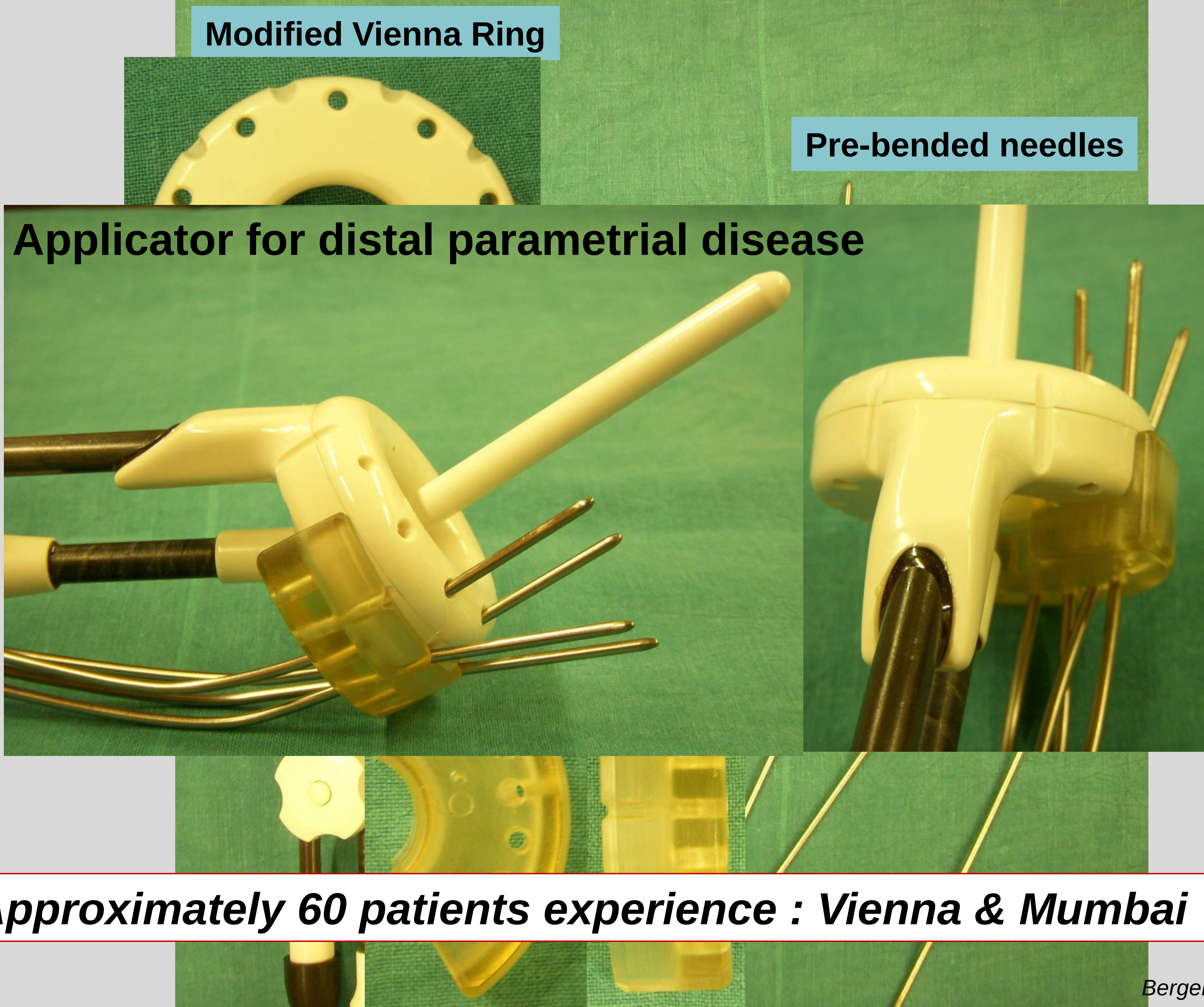
additional parallel and divergent template guided needles



The Vienna II Applicator

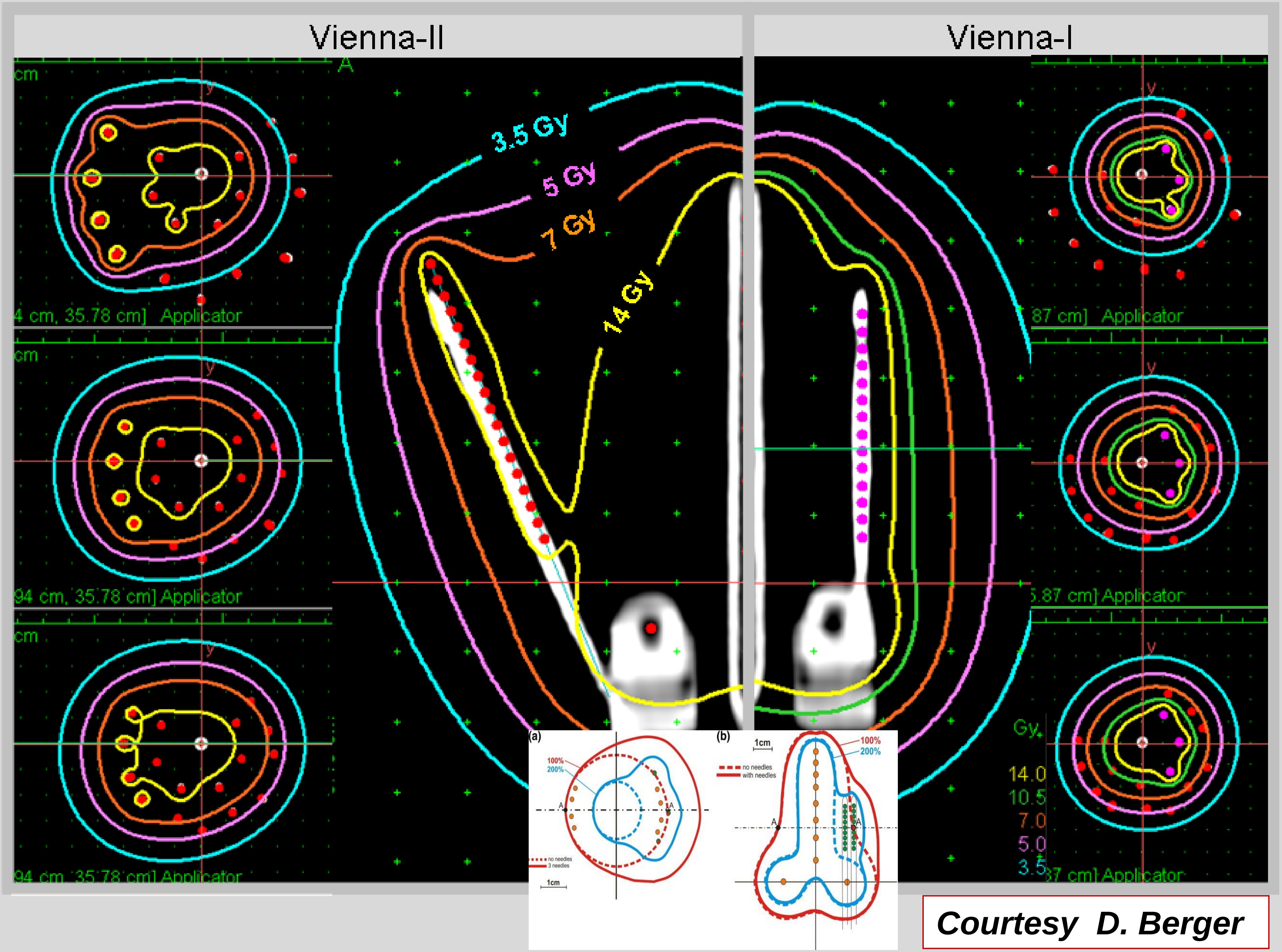
Berger et al. ABS 2010

Applicator for distal parametrial disease



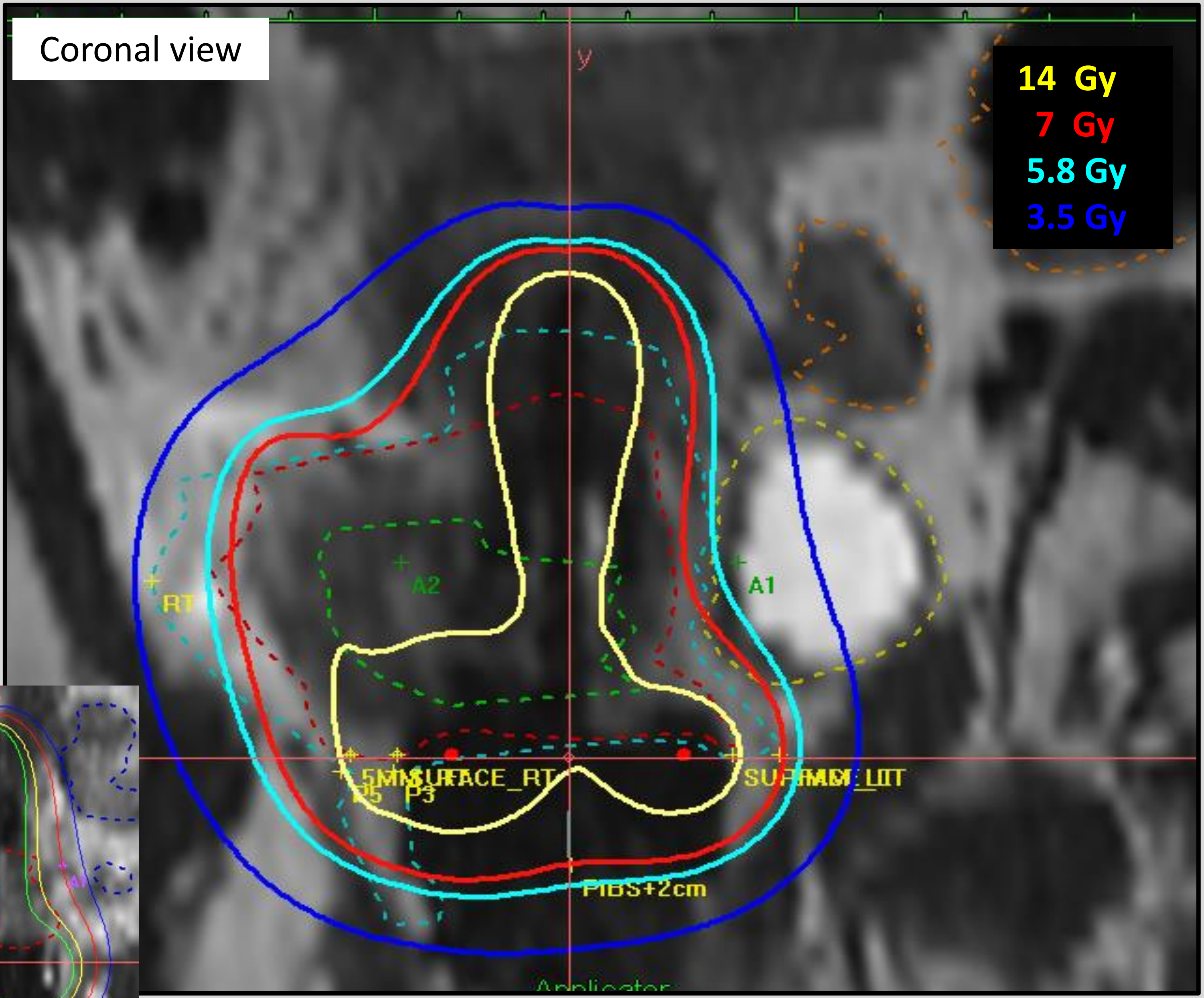
Approximately 60 patients experience : Vienna & Mumbai

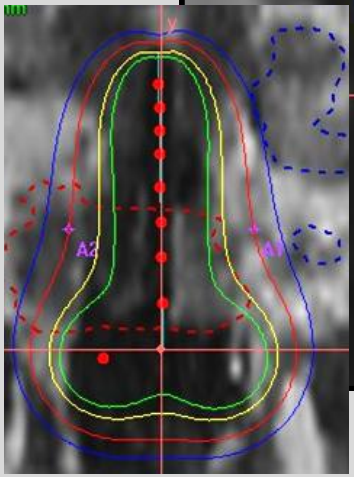
Berger et al.



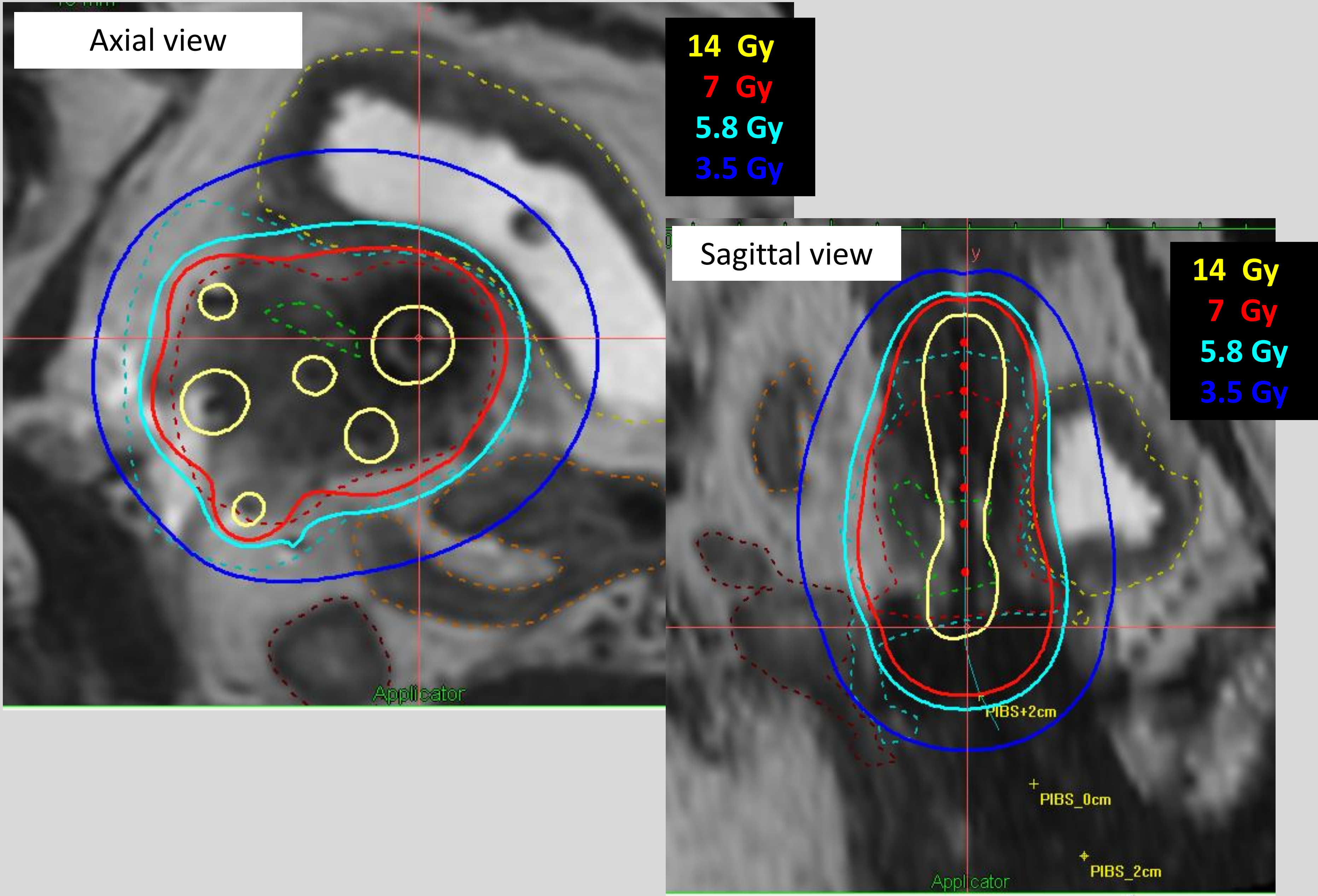
Courtesy D. Berger

PLAN EVALUATION





PLAN EVALUATION



PIBS:Postero-inferior border of pubic symphysis

GEC –ESTRO / ICRU (89)

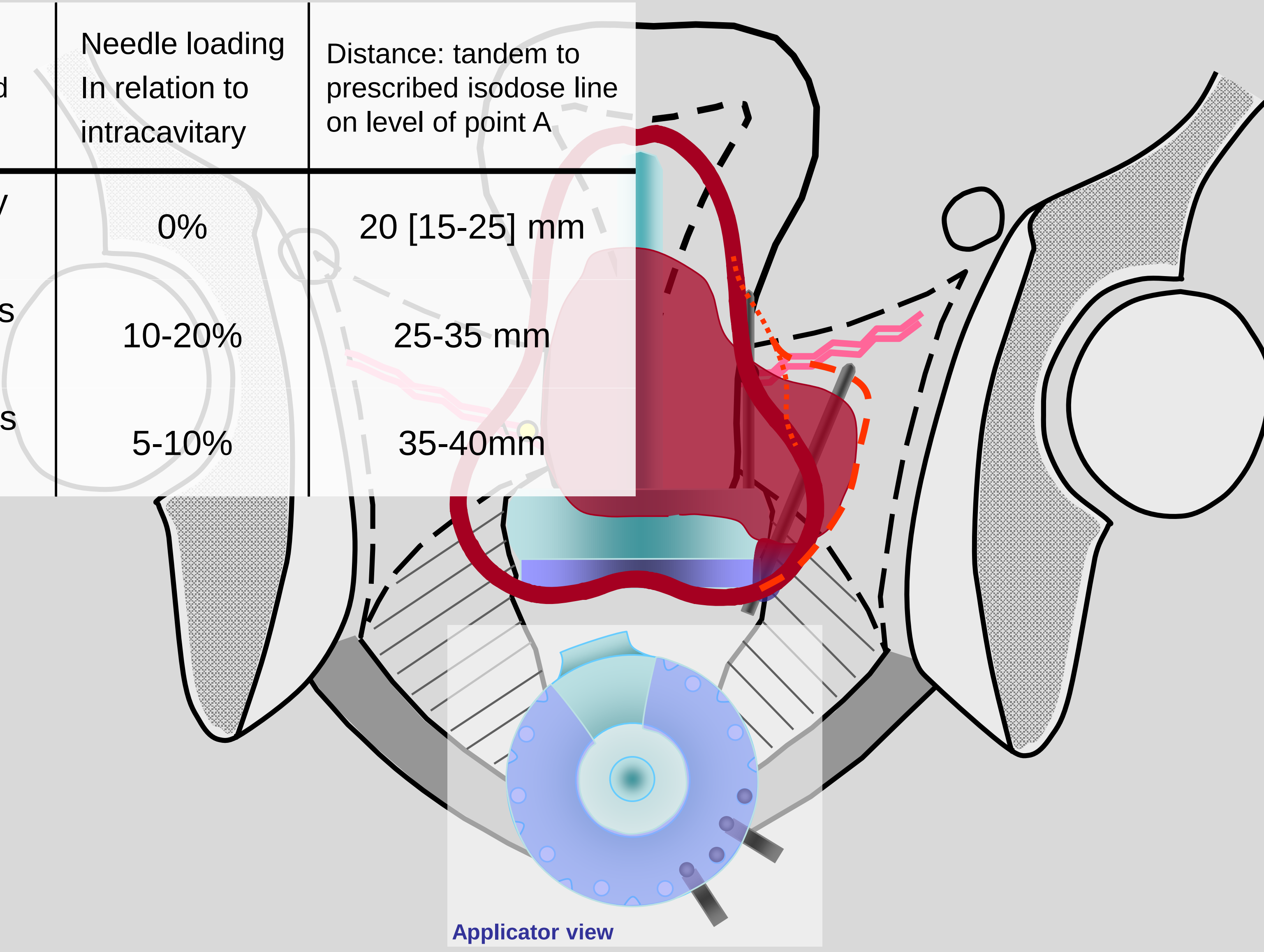
REPORTING OF DOSE VOLUME PARAMETERS

External (45 Gy/ 25#) + HDR-BRT (7 Gy x 4# in 2 Applications)

			Planning aim	**Prescribed dose**
CTV_{HR}	**D_{90}**	$EQD2_{10}$	≥ 85 Gy	96.2 Gy
Bladder	**D_{2cm^3}**	$EQD2_3$	≤ 90 Gy	82.9 Gy
Rectum	**D_{2cm^3}**	$EQD2_3$	≤ 70 Gy	68.3 Gy
Sigmoid	**D_{2cm^3}**	$EQD2_3$	≤ 70 Gy	67.4 Gy

Joint Vienna-II project Vienna and Mumbai

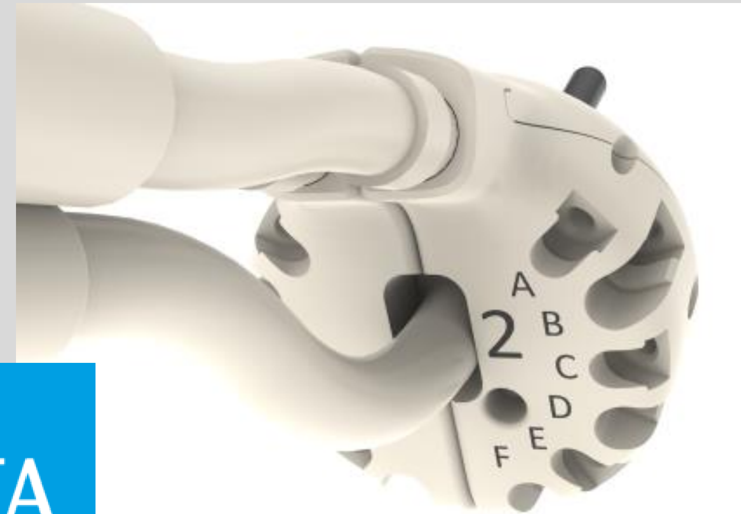
Physical distance between tandem and needle	Needle loading In relation to intracavitary	Distance: tandem to prescribed isodose line on level of point A
Intracavitary only No needles	0%	20 [15-25] mm
+ Parallel needles 20mm	10-20%	25-35 mm
+ Oblique needles 20° (23-27mm)	5-10%	35-40mm



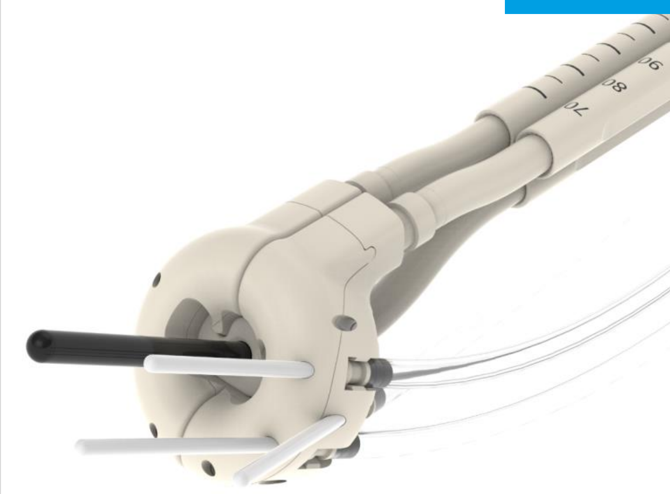
D. Berger et al.

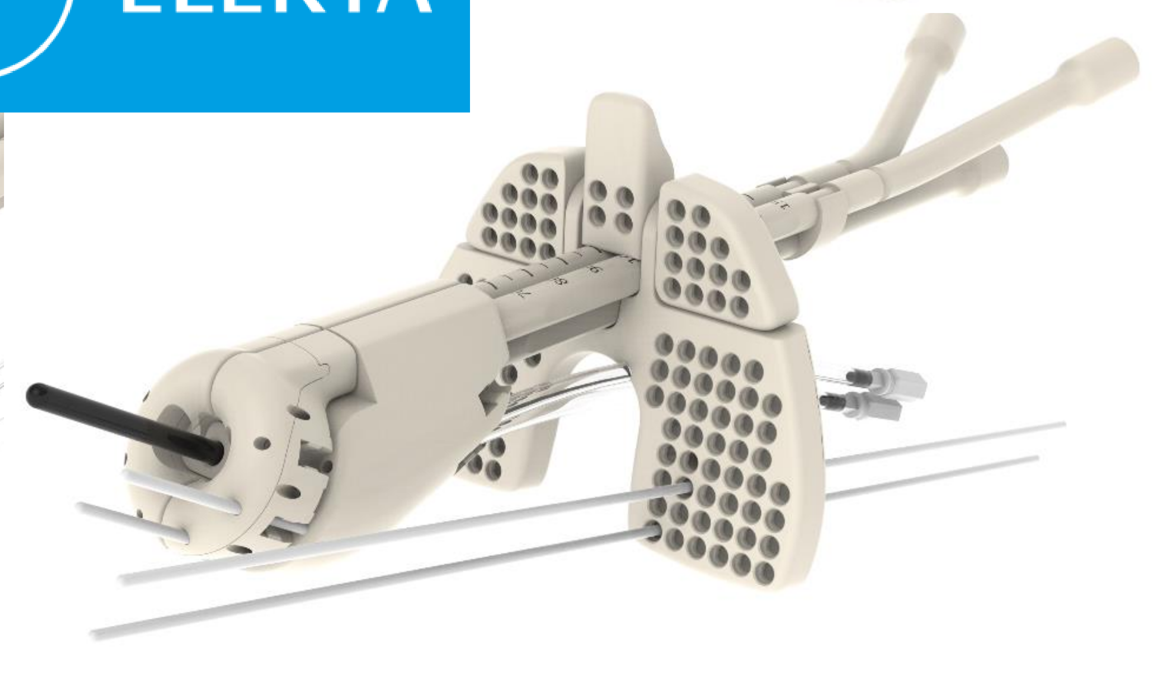
Latest Development in Applicators

VENEZIA GYN APPLICATOR



ELEKTA

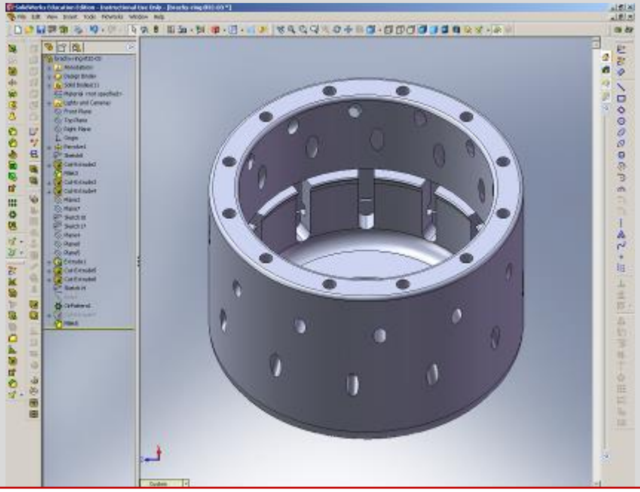


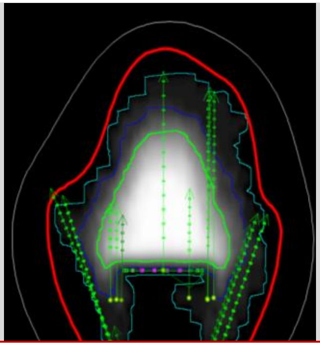


Adaptive BT applicators

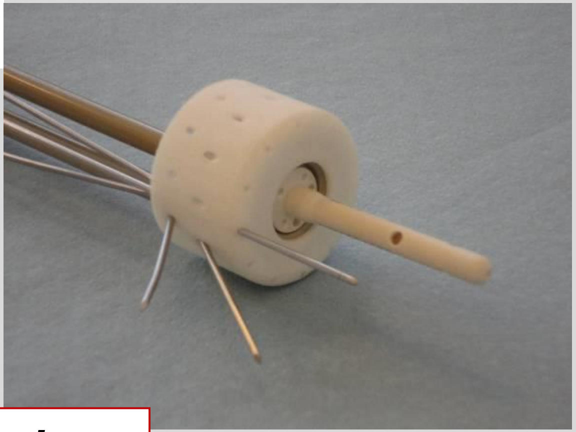
3D Printing

Virtual applicator





New applicator

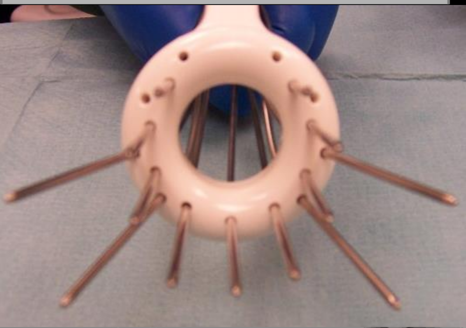


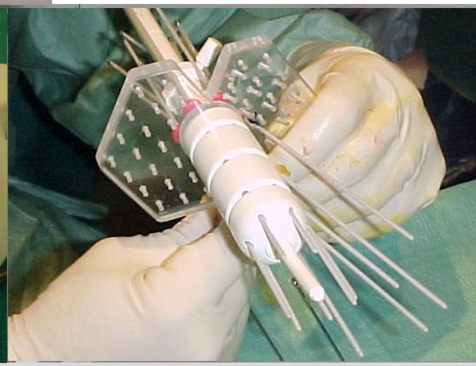
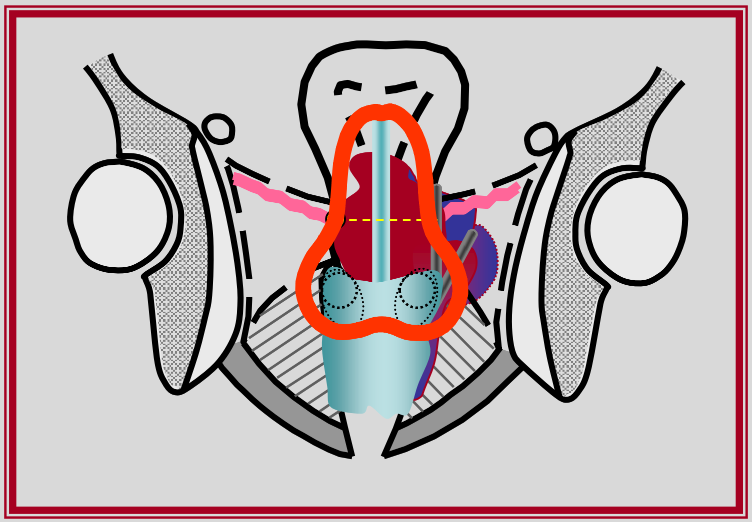
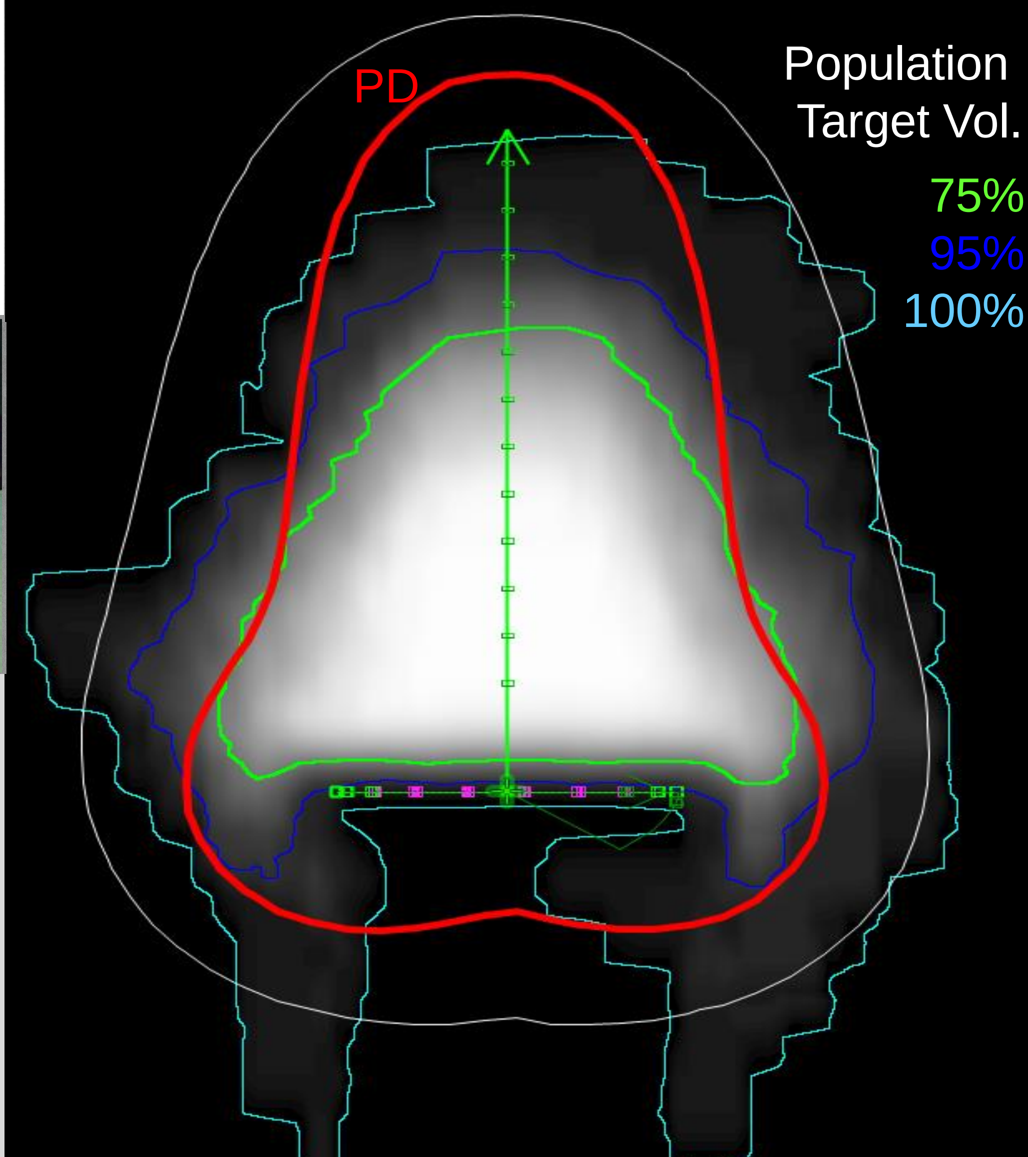
264 patients with tumour mapping Ljubljana, Vienna, Aarhus

Provided by Primoz Petric and Jacob Lindegaard Ljubljana/Aarhus

Mission

264 patients



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

Courtesy: P. Petric,D. Berger

SUMMARY & CONCLUSIONS

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

CLINICAL DIAGRAMS: CERVICAL CANCER

Umesh Mahantshetty

Professor,

Department of Radiation Oncology

&

GYN Disease Management Group Member

Tata Memorial Hospital, Mumbai, India

Q: Clinical drawings aid in

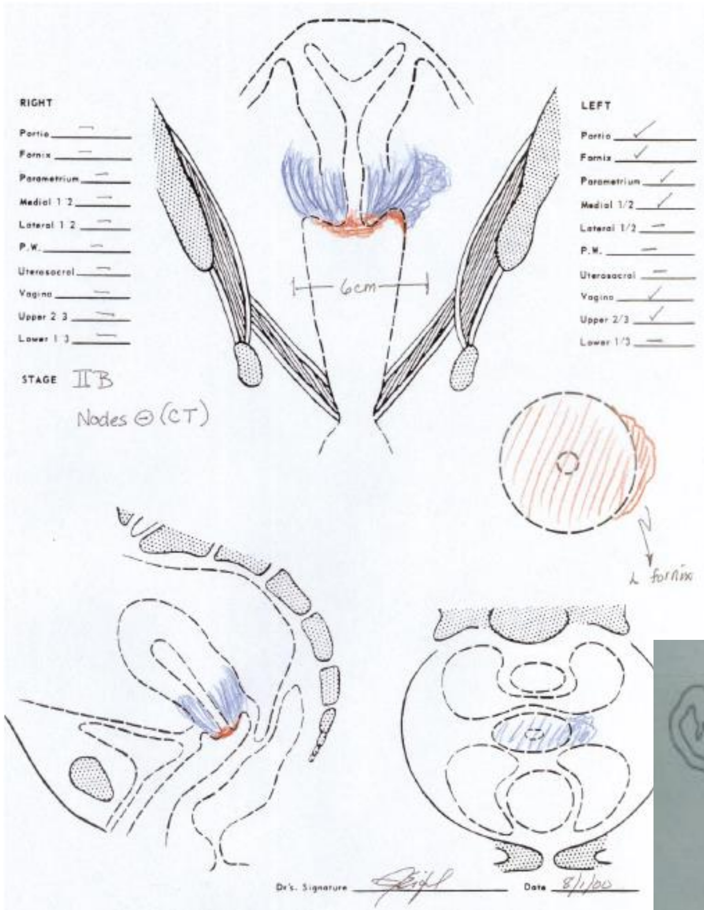
A. A: 3D Documentation
B. B: Evaluation of Disease Remission
C. C: Selection of BT technique
D. D. All of the above

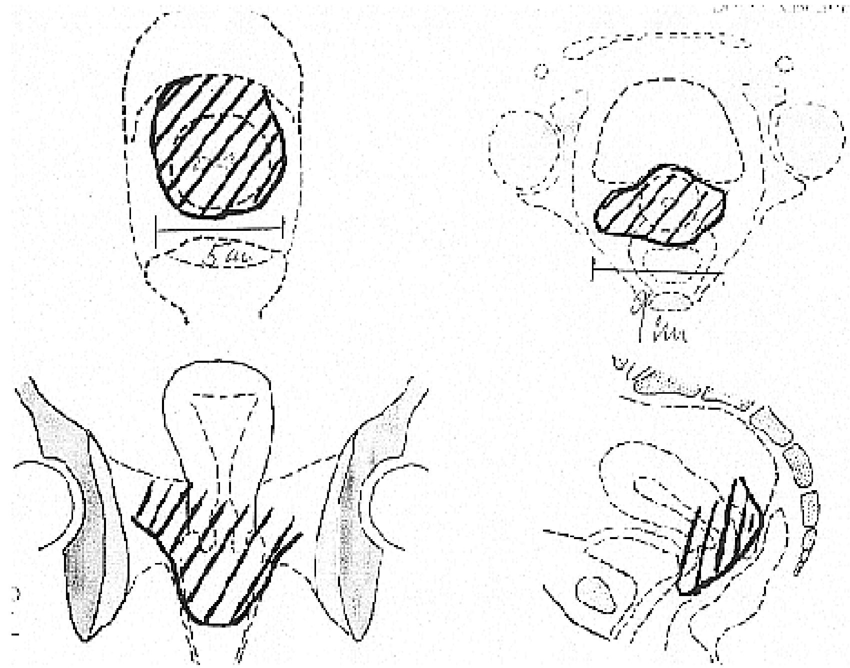
Clinical drawings

Vienna

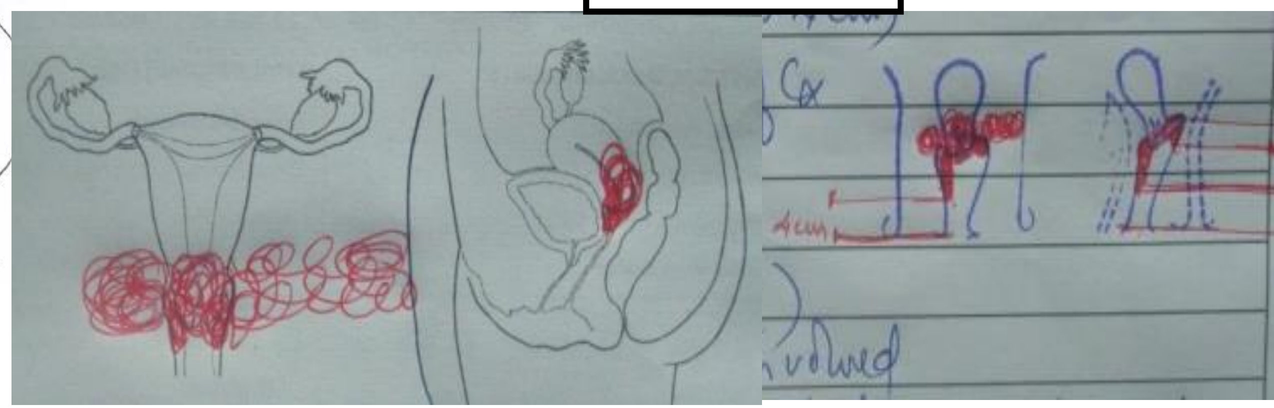
Eifel-Levenback (ed)

Atlas of clinical oncology 2001





TMH, Mumbai



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

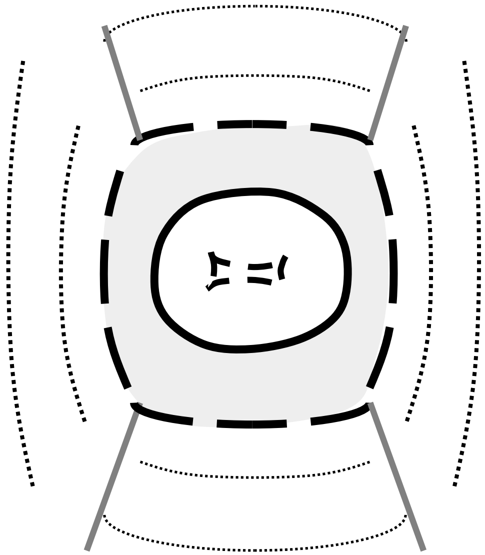
Patient : ABC

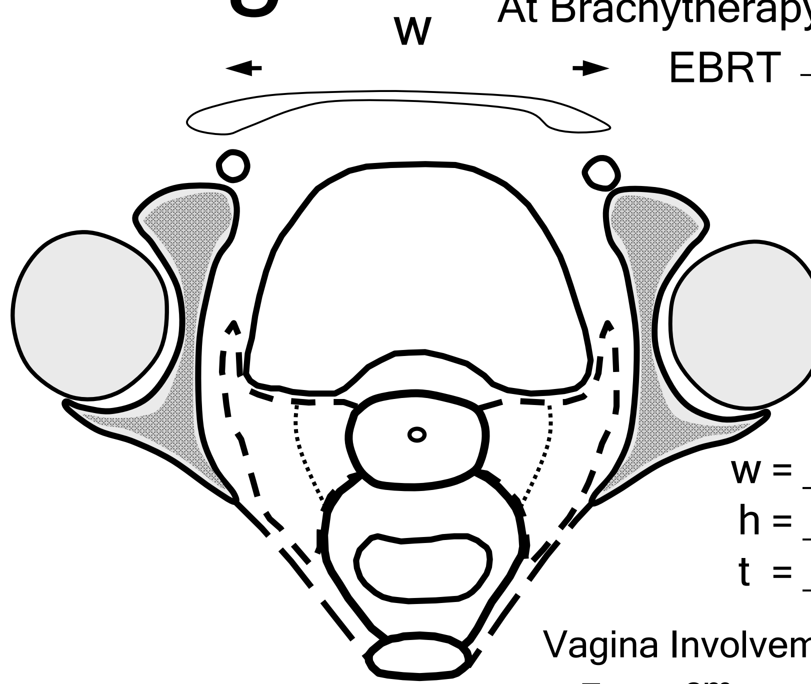
Clinical Drawing

At Diagnosis ☐

At Brachytherapy ☐

EBRT ____ Gy



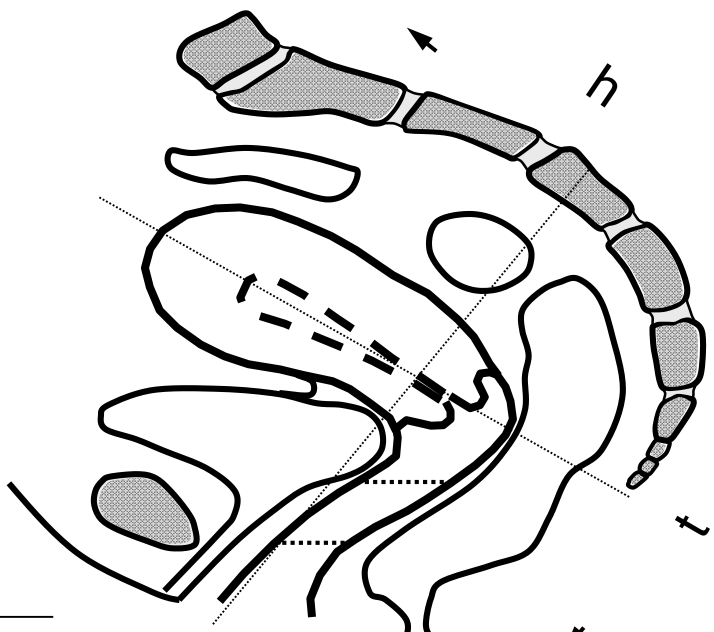


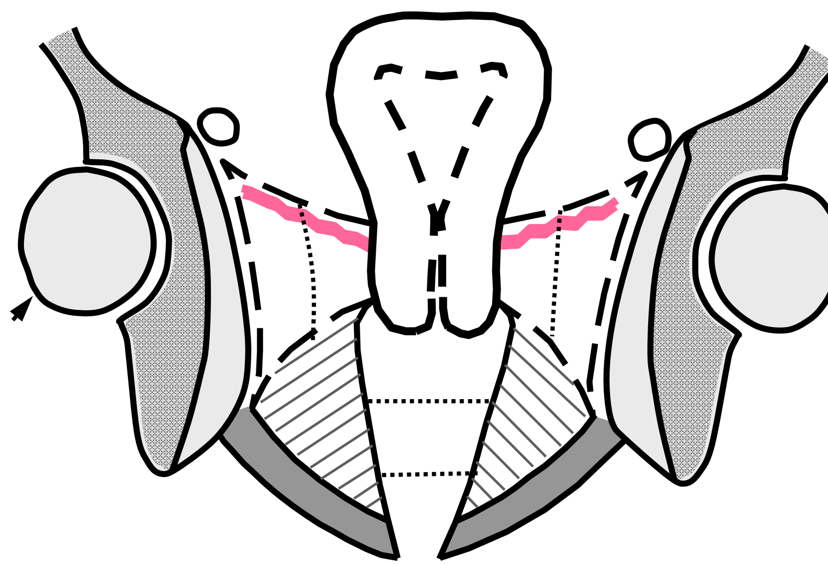
w = ____ cm

h = ____ cm

t = ____ cm

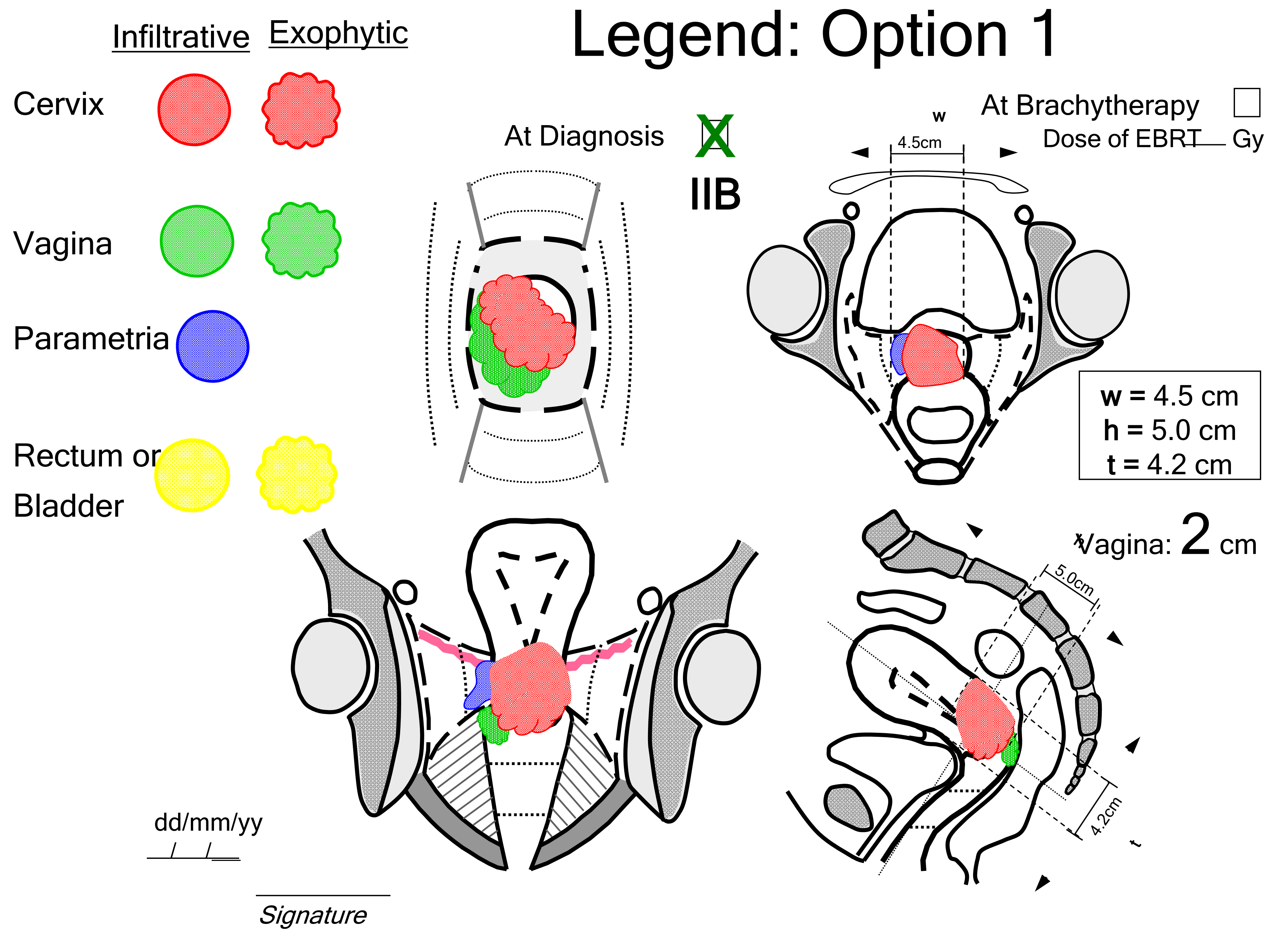
Vagina Involvement
= ____ cm





dd/mm/yy
____/____/____

Signature


Legend: Option 1
Infiltrative
Exophytic
Cervix
Vagina
Parametria
Rectum or
Bladder
At Diagnosis
X
IIB
At Brachytherapy
Dose of EBRT ___ Gy
w
4.5cm
w = 4.5 cm
h = 5.0 cm
t = 4.2 cm
Vagina: 2 cm
5.0cm
4.2cm
t
dd/mm/yy
__/__/__
Signature

Legend: Option 2

At Diagnosis X

At Brachytherapy

Dose of EBT ____ Gy

or Cervix

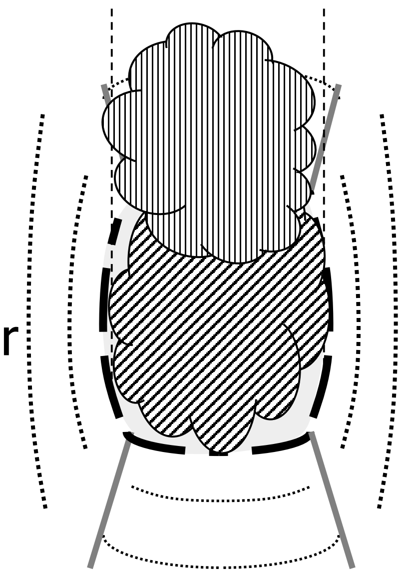
Vagina

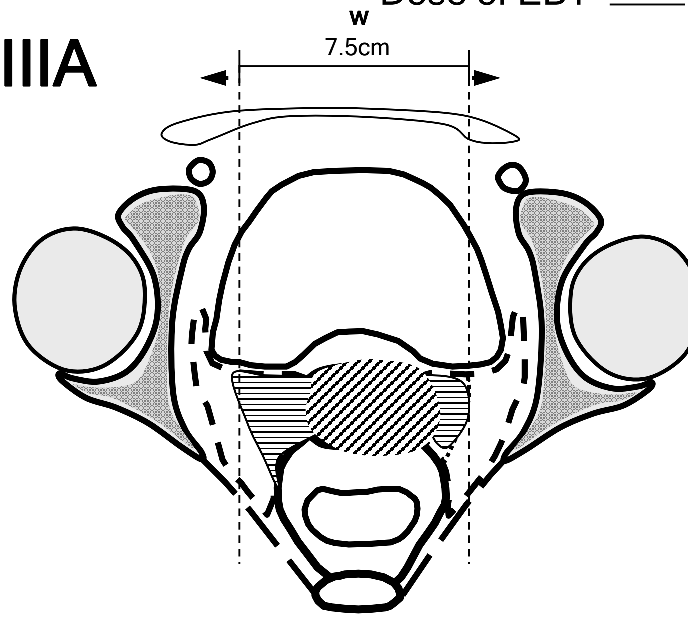
Parametria

Rectum or Bladder Infiltration

Exophytic

IIIA





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

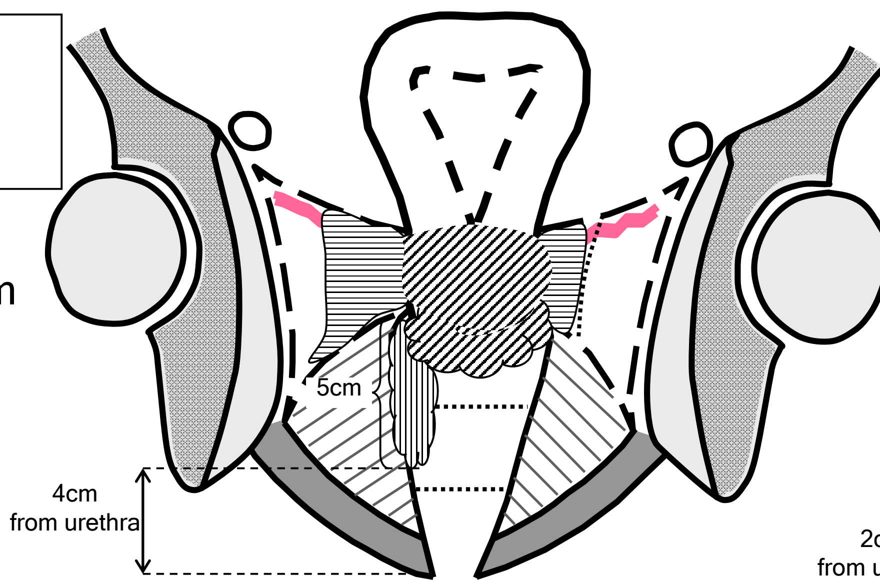
Vagina: 7 cm

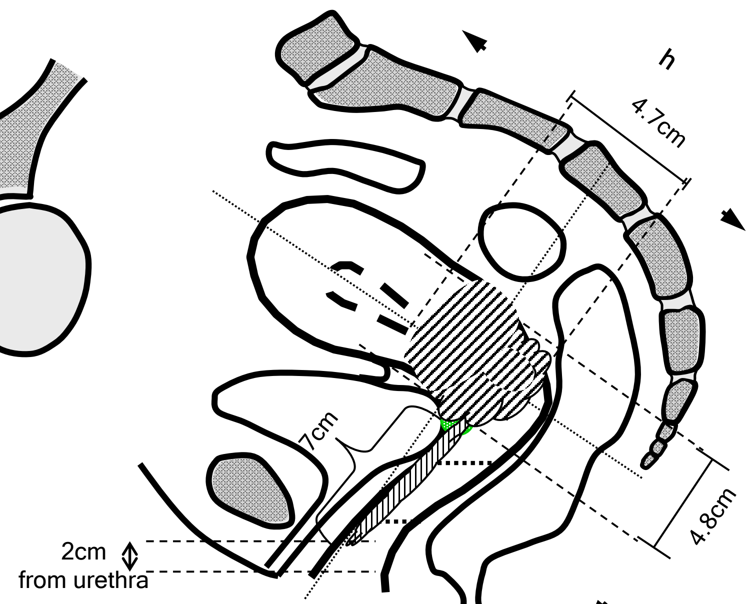
dd/mm/yy

___/___/___

____

Signature





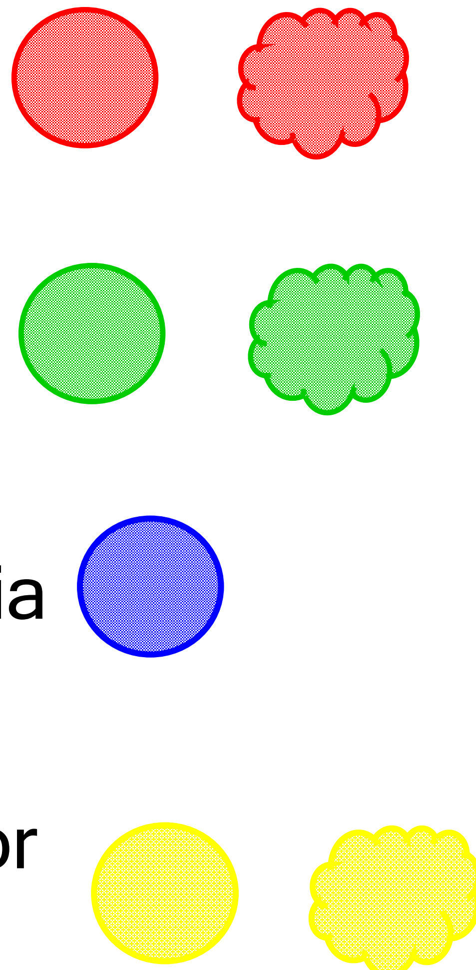
Option 3: Copy and Paste

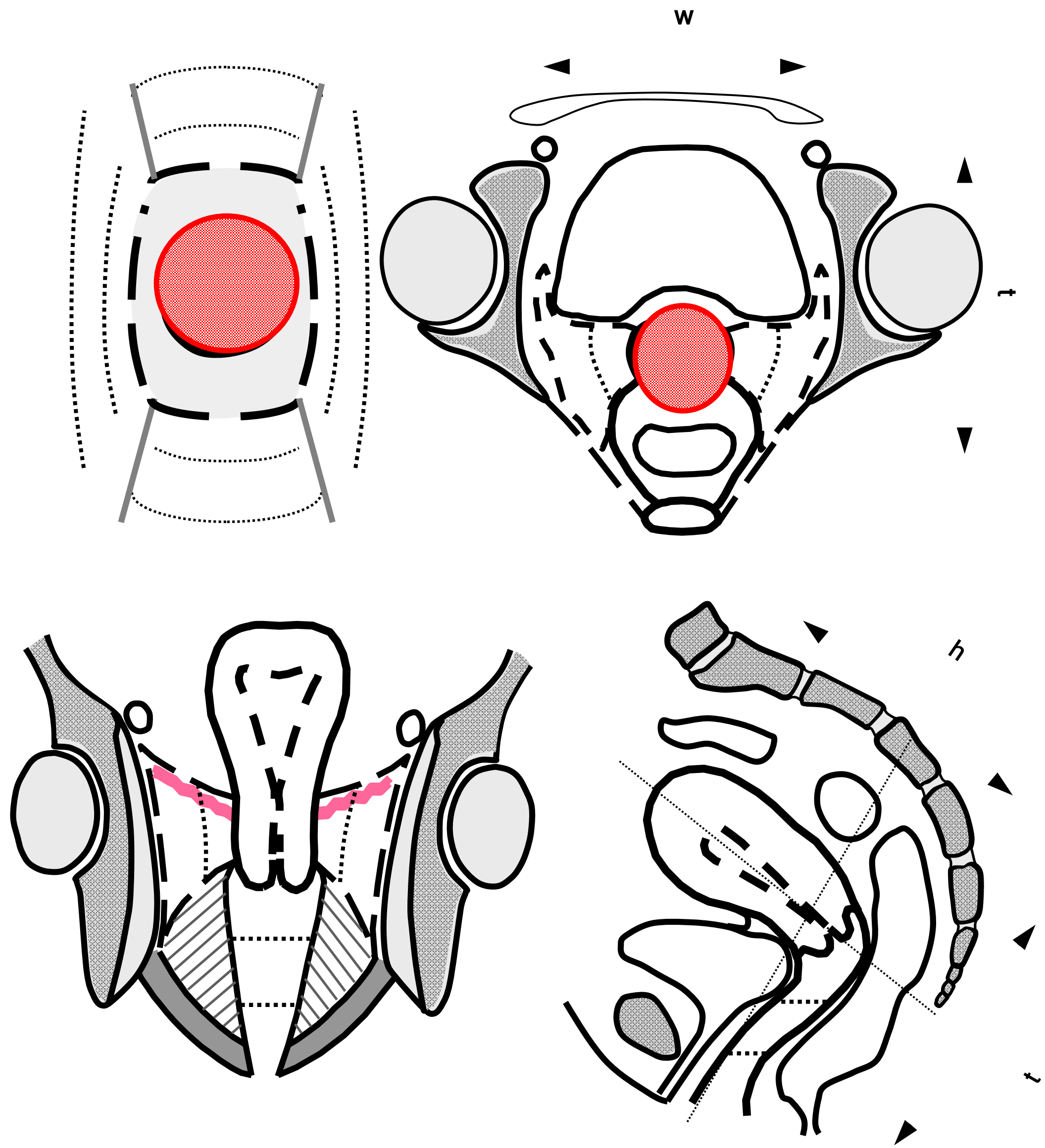
Cervix

Vagina

Parametria

Rectum or Bladder





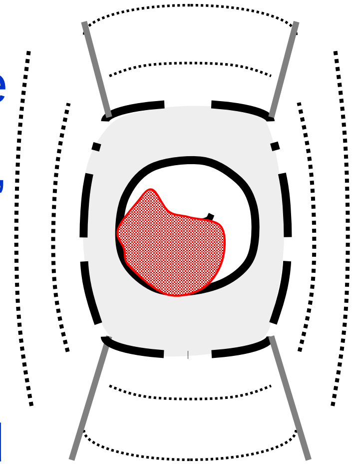
At Diagnosis ☒

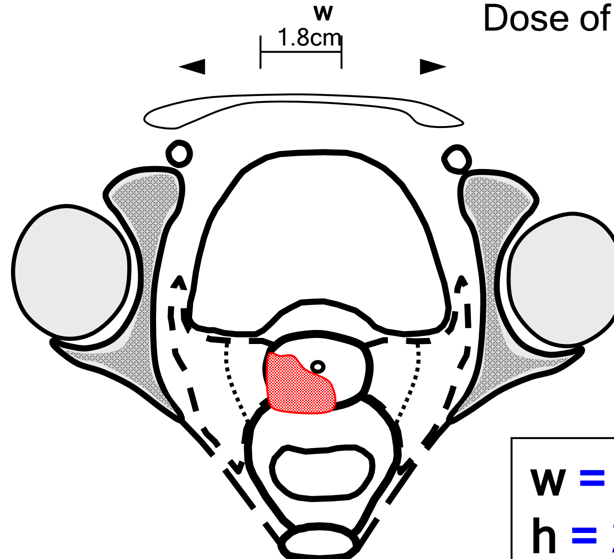
IB1

At Brachytherapy ☐

Dose of EBRT Gy

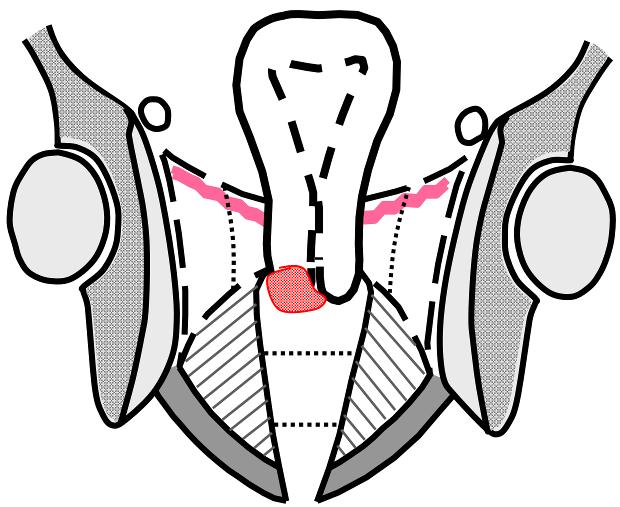
- Cervix: tumour at the posterior and right lip, from 5 to 10h
- Vagina: not involved
- Parametria: not involved

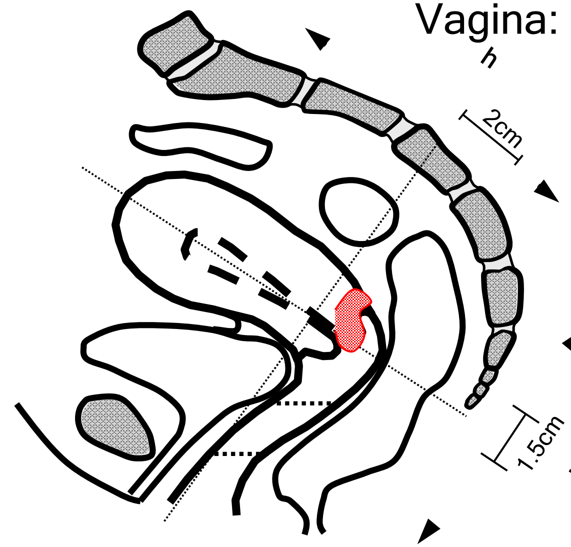




w = 1.8 cm
h = 2.0 cm
t = 1.5 cm

Vagina: 0 cm





dd/mm/yy
___/___/___

Signature

At Diagnosis ☐

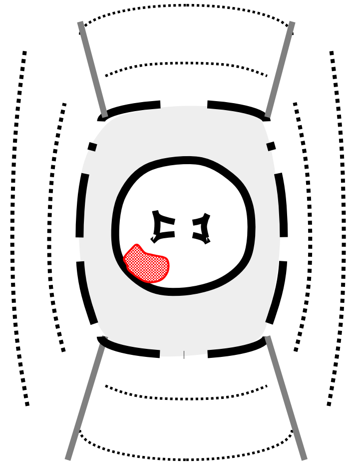
IB1

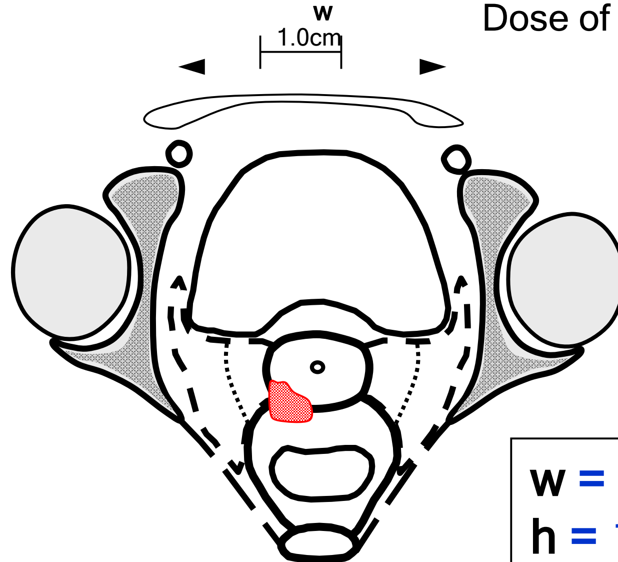
At Brachytherapy ☒

Dose of EBRT Gy

Good response

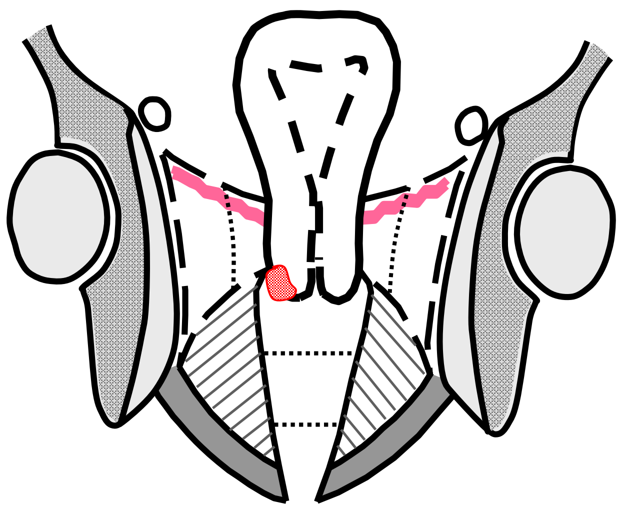
- Cervix: residual tumour from 7 to 9h
- Vagina: not involved
- Parametria: not involved

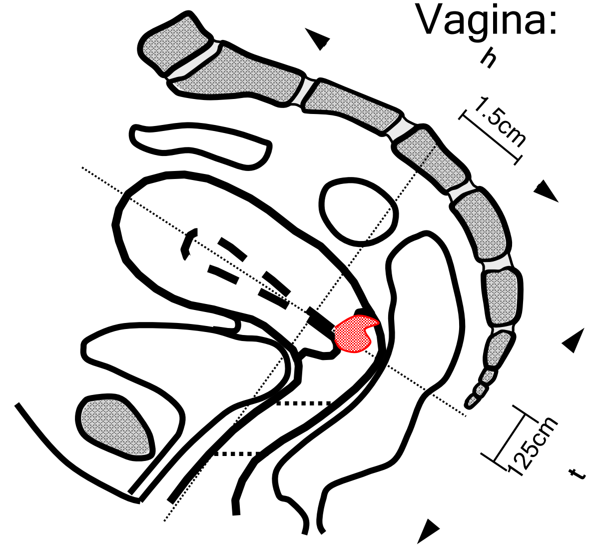




w = 1.0 cm
h = 1.5 cm
t = 1.2 cm

Vagina: 0 cm





dd/mm/yy

___/___/___

Signature

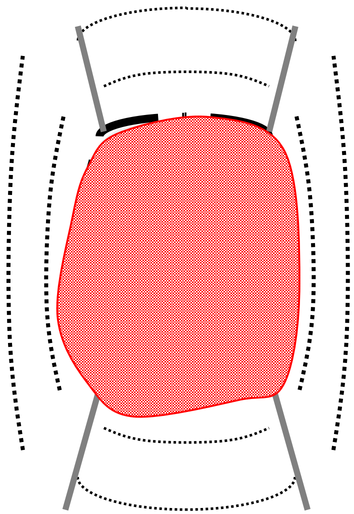
At Diagnosis ☒

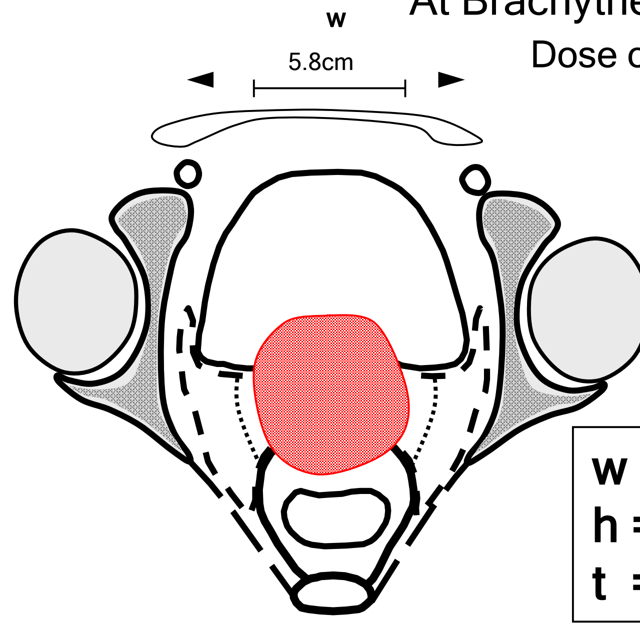
Special Case
IB2 - Bulky

At Brachytherapy ☐

Dose of EBRT ____ Gy

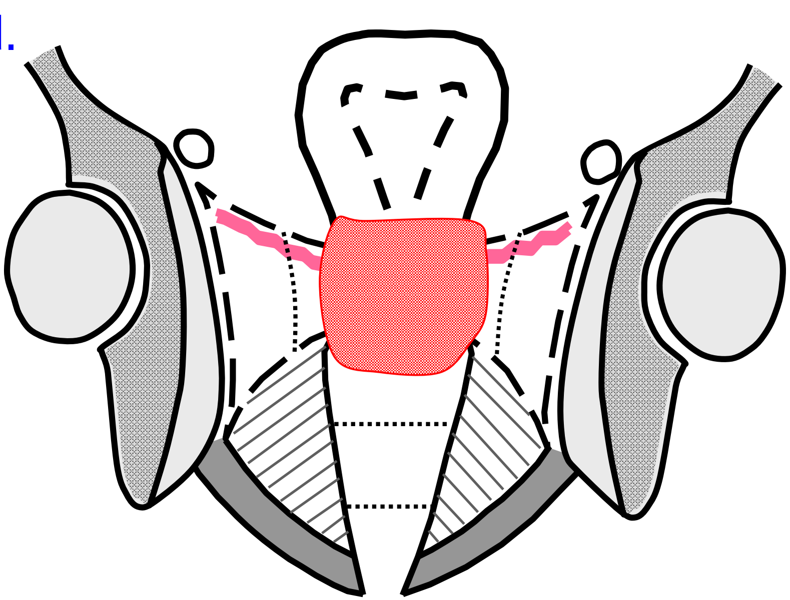
bulky cervical tumour where the tumour bulges towards the vaginal, bladder and rectal walls, but these structures are not involved.

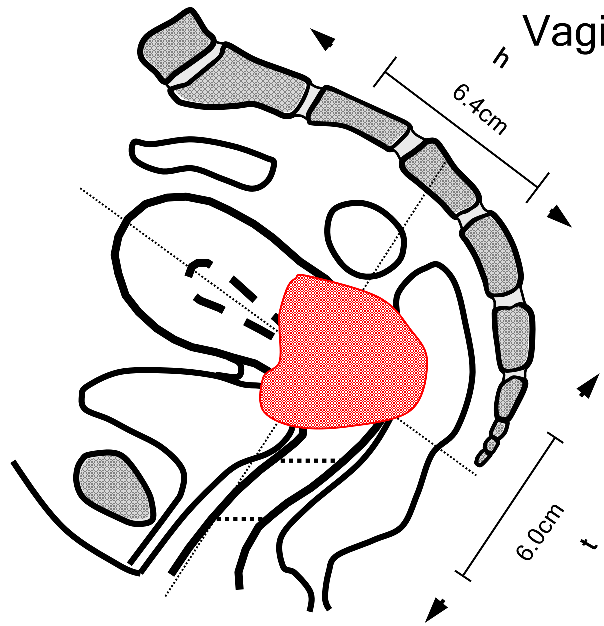




w = 5.8 cm
h = 6.4 cm
t = 6.0 cm

Vagina: 0 cm





dd/mm/yy
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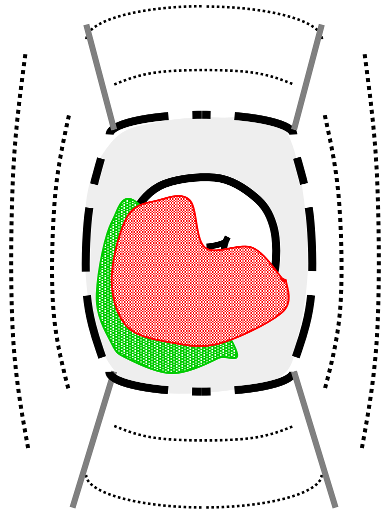
____
Signature

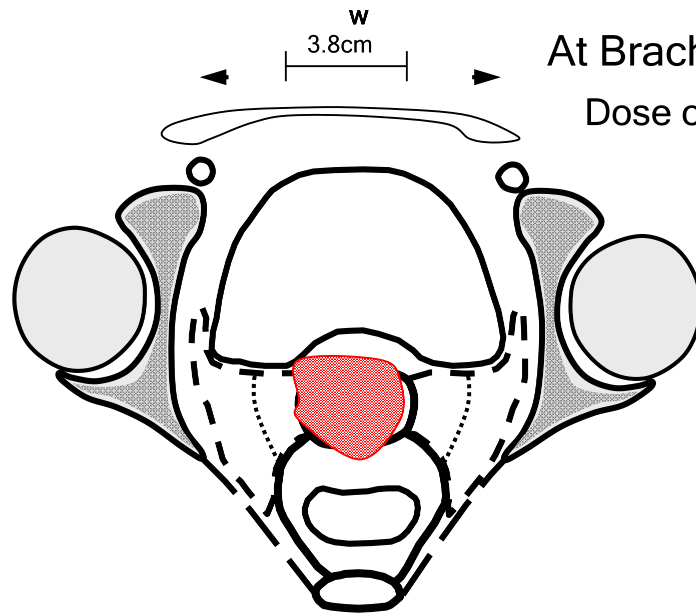
At Diagnosis ☒

IIA

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

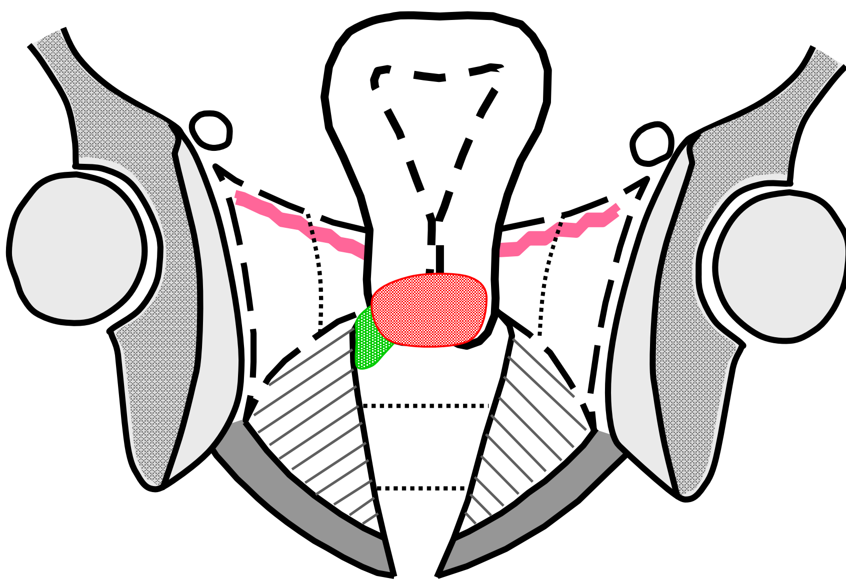
Vagina: 1.5 cm

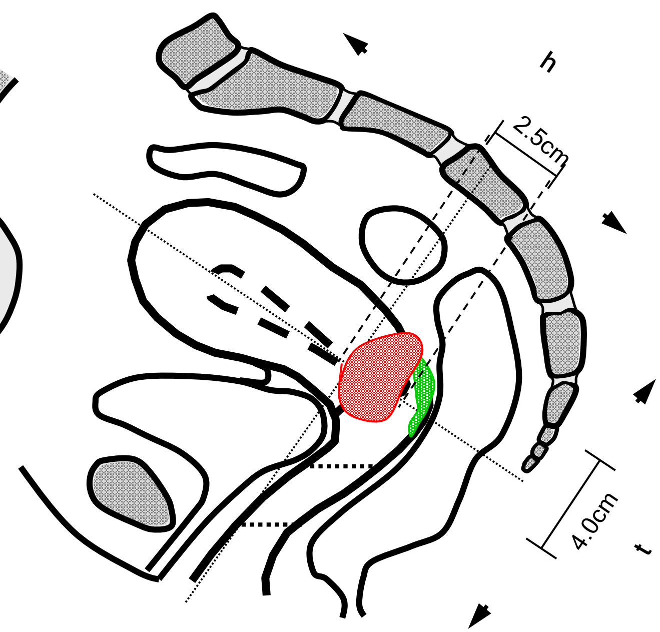




At Brachytherapy ☐

Dose of EBRT____ Gy





dd/mm/yy
___/___/___

____
Signature

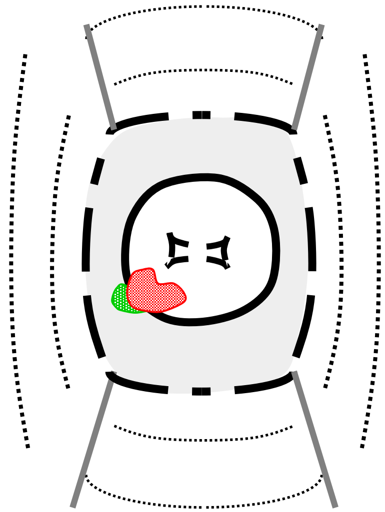
Note: extension of vaginal involvement is specified separately, and should **not** be included in **h**

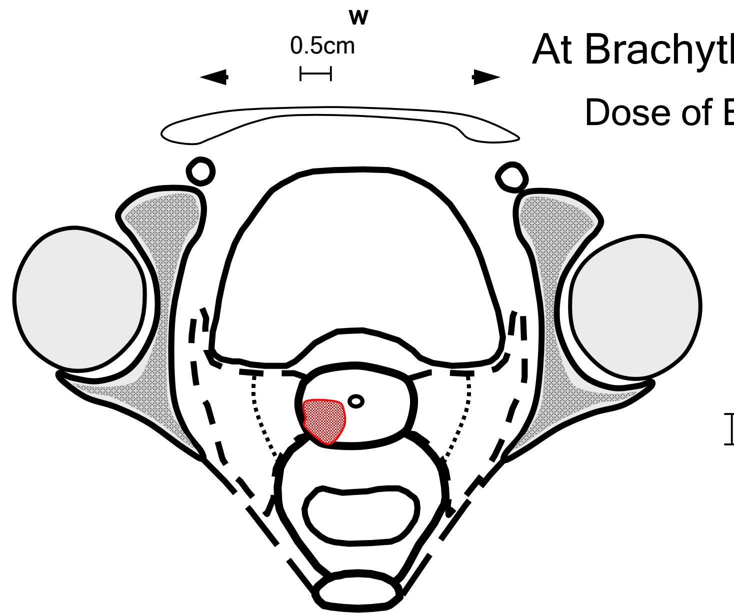
At Diagnosis ☐

IIA

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

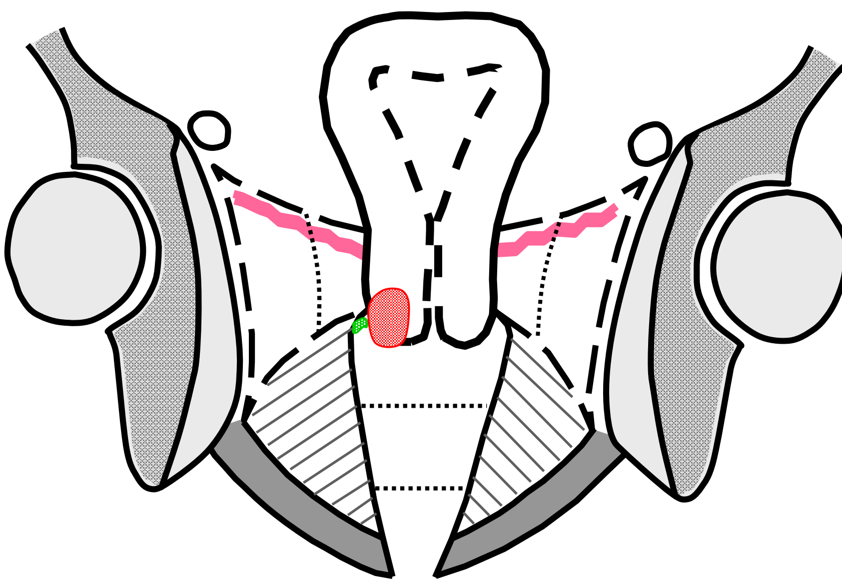
Vagina: 0.3 cm

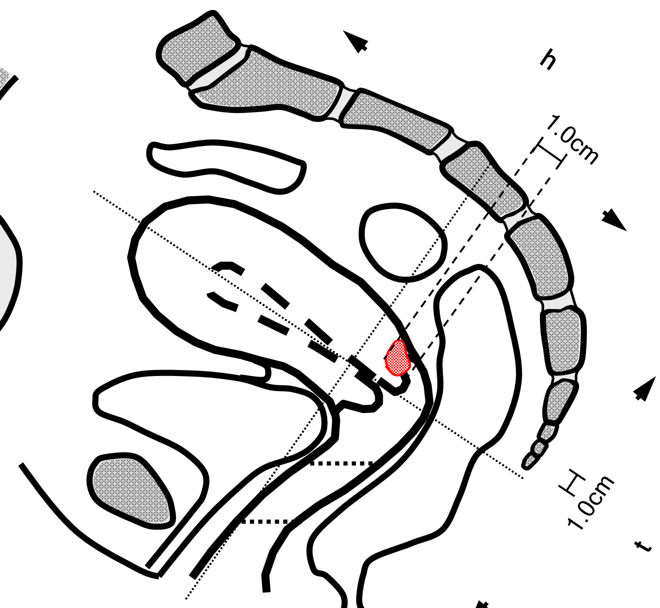




At Brachytherapy ☒

Dose of EBRT 45 Gy





dd/mm/yy

___/___/___

____

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 ☒

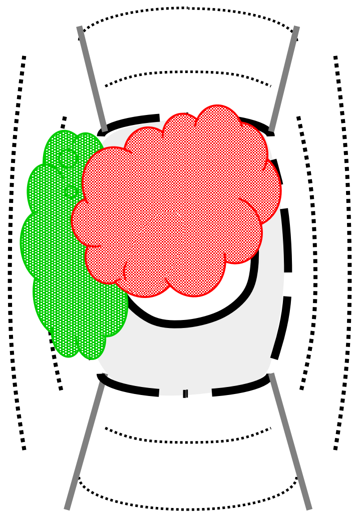
At Brachytherapy ☐

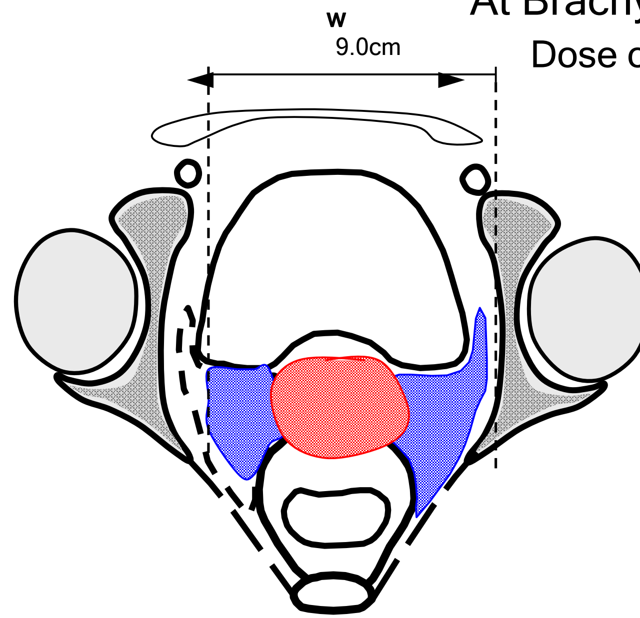
Dose of EBRT ____ Gy

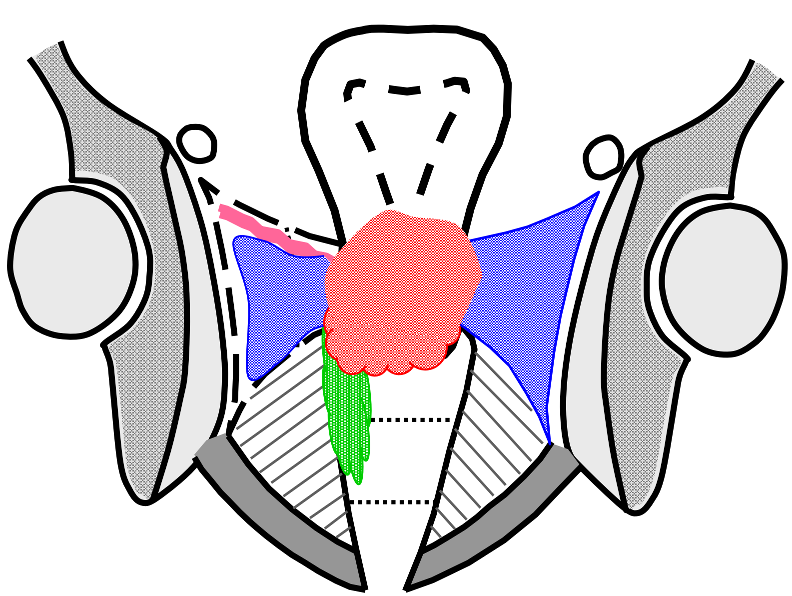
IIIB

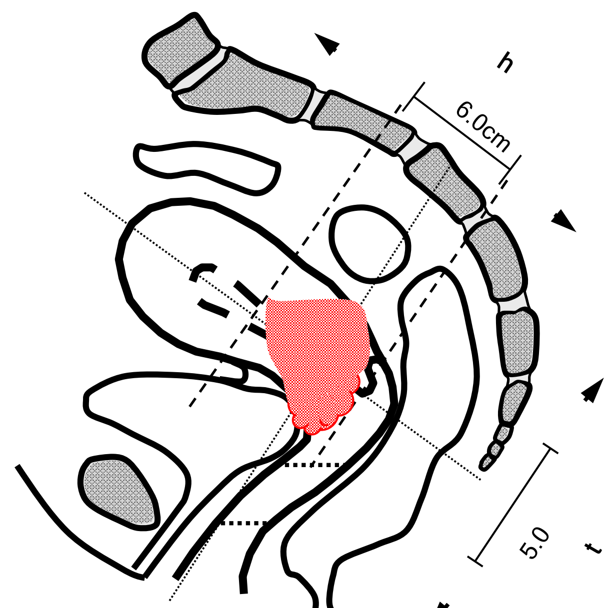
w = 9.0 cm **h** = 6.0 cm **t** = 5.0 cm

Vagina: 5 cm









dd/mm/yy

___/___/___

____

Signature

Note: vagina and parametria not included in h

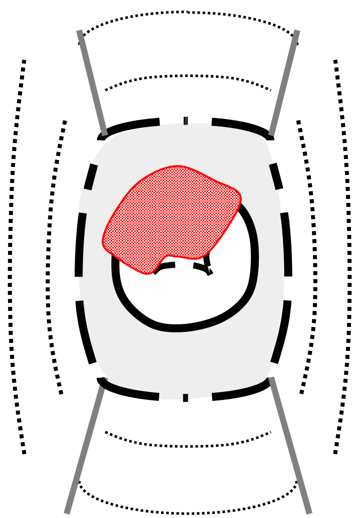
At Diagnosis ☐

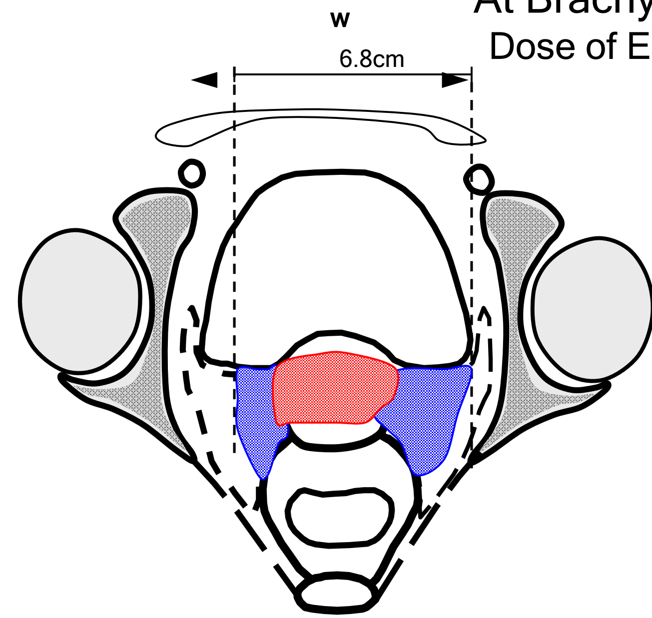
At Brachytherapy ☒
Dose of EBRT 50.4 Gy

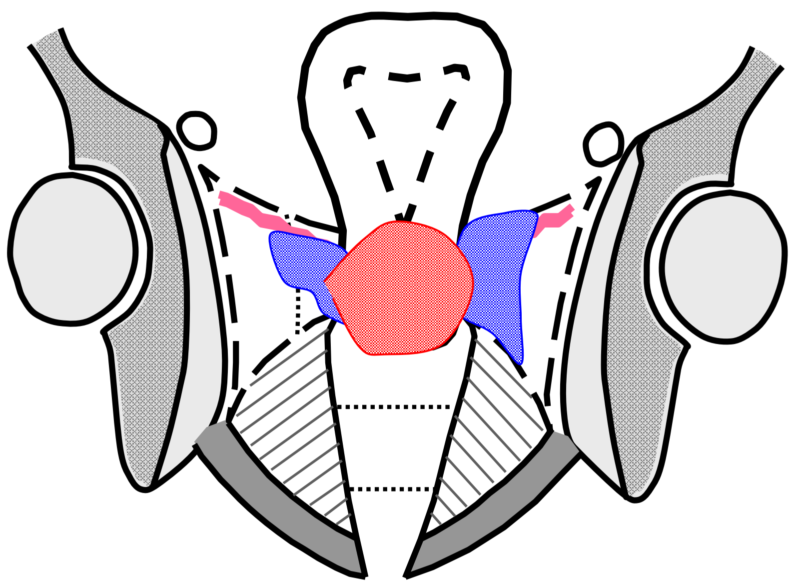
IIIB

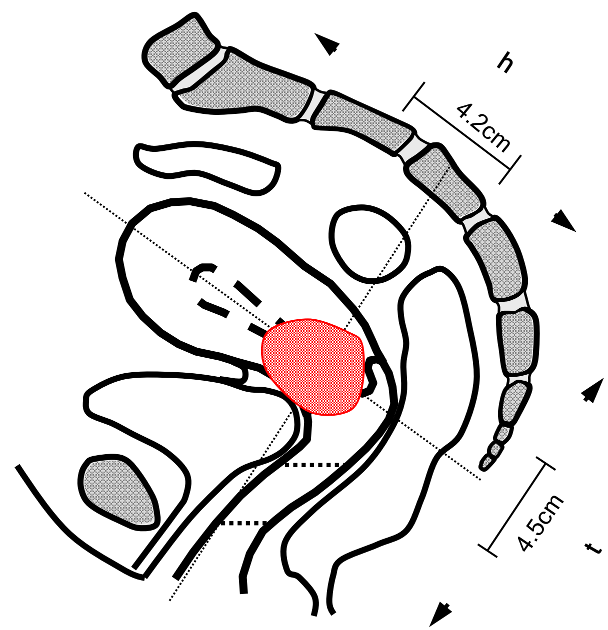
w = 6.8 cm
h = 4.2 cm
t = 4.5 cm

Vagina: 0 cm









dd/mm/yy
/ /

Signature

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

At Diagnosis ☒

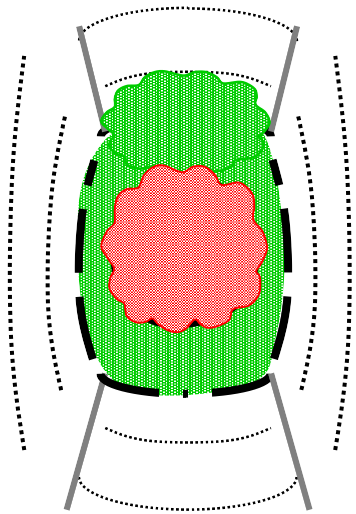
At Brachytherapy ☐

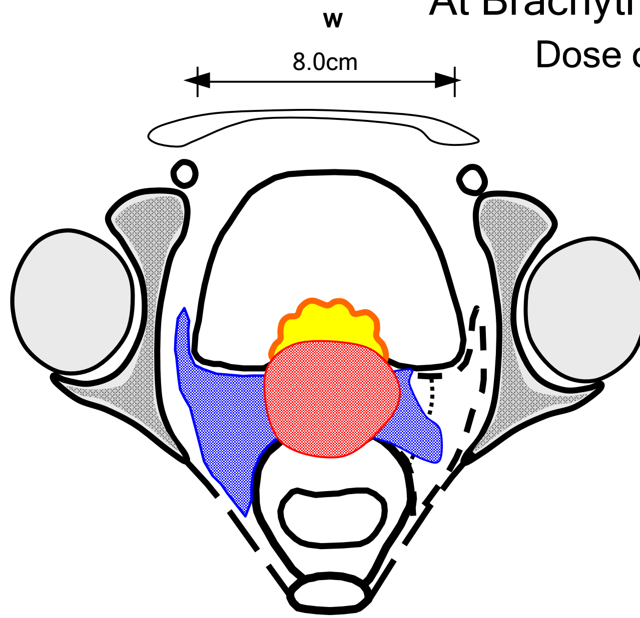
Dose of EBT____ Gy

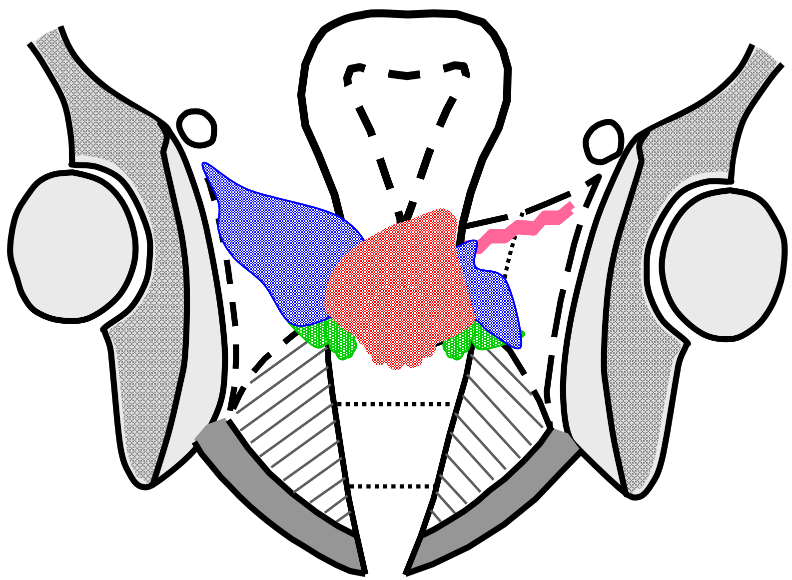
IVA - Bladder

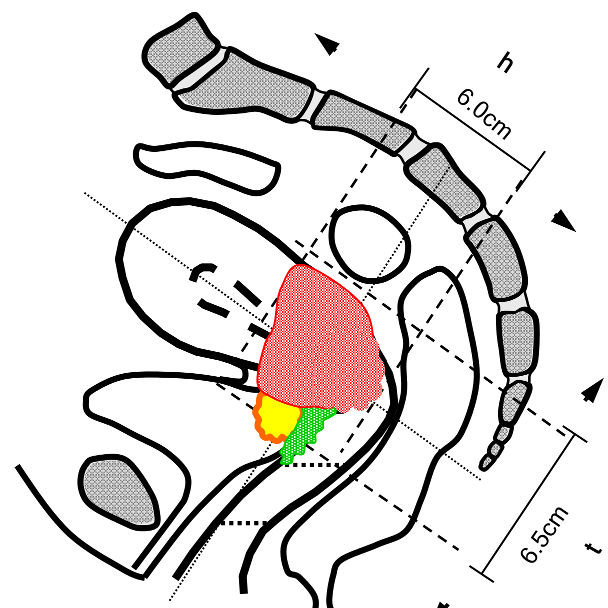
w = 8.0 cm
h = 6.0 cm
t = 6.5 cm

Vagina: 5 cm









dd/mm/yy

___/___/___

____

Signature

At Diagnosis ☐

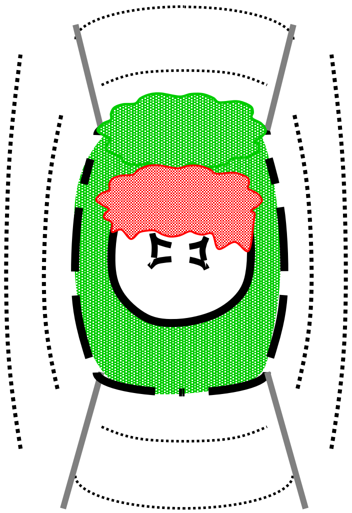
At Brachytherapy ☒

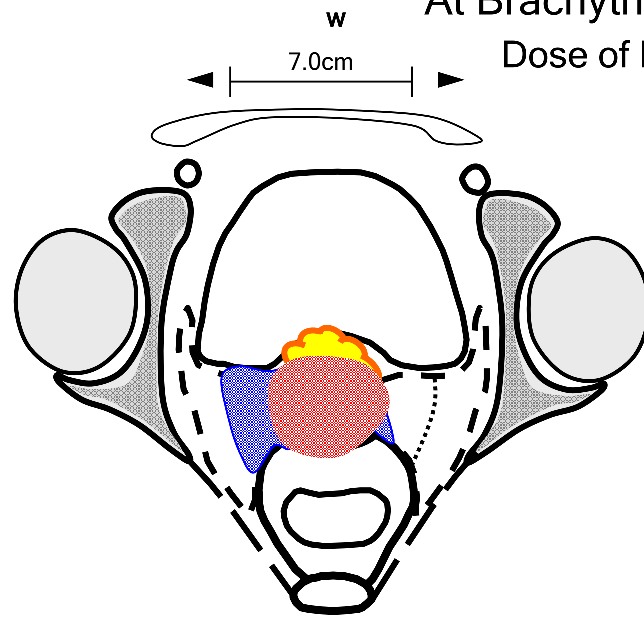
Dose of EBRT 45 Gy

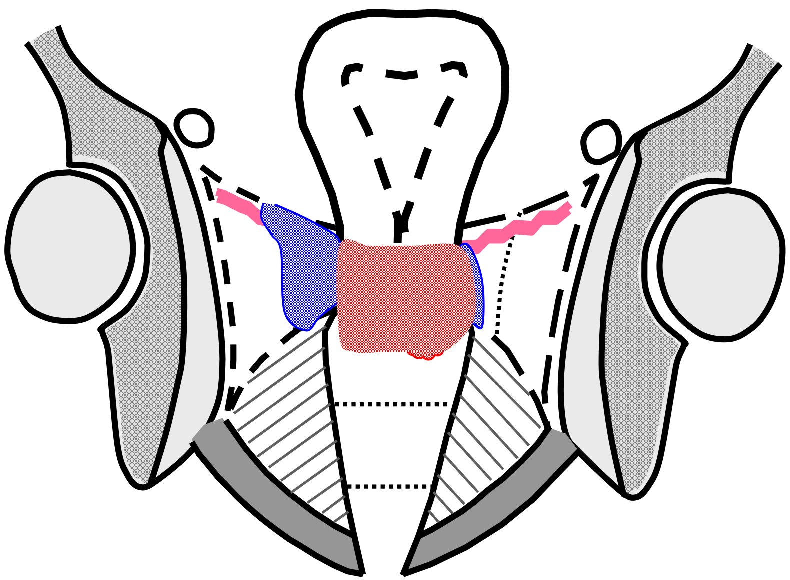
IVA - Bladder

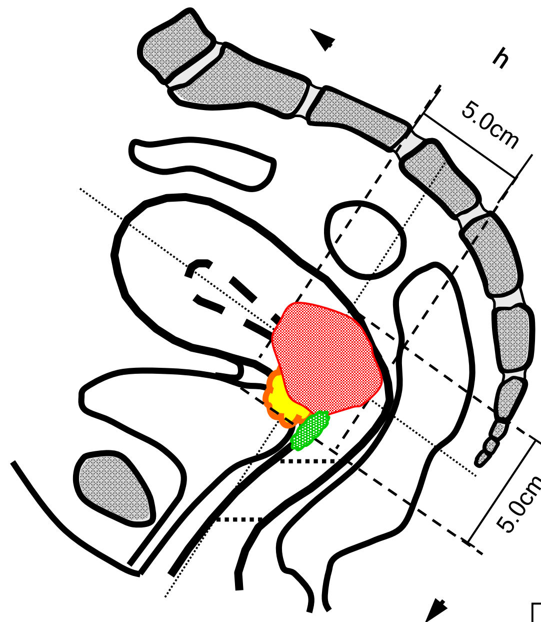
w = 7.0 cm
h = 5.0 cm
t = 5.0 cm

Vagina: 2.5 cm







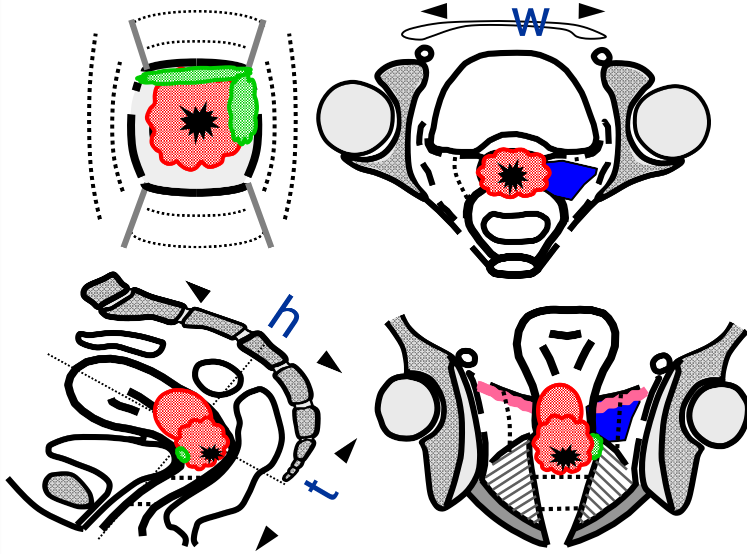


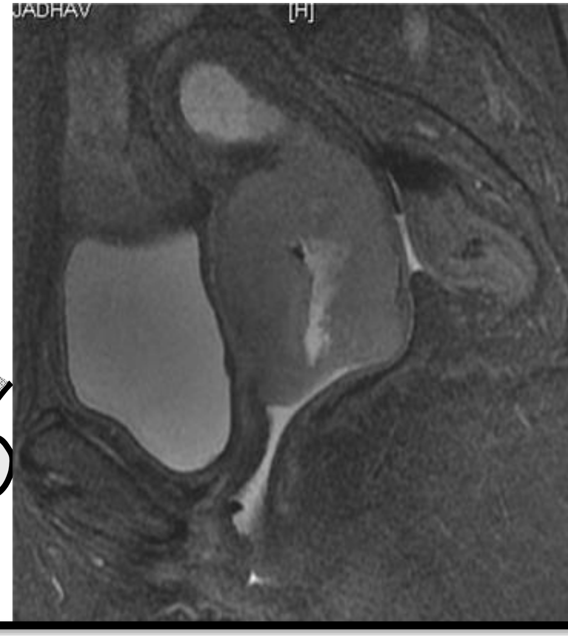
dd/mm/yy
___/___/___

Signature

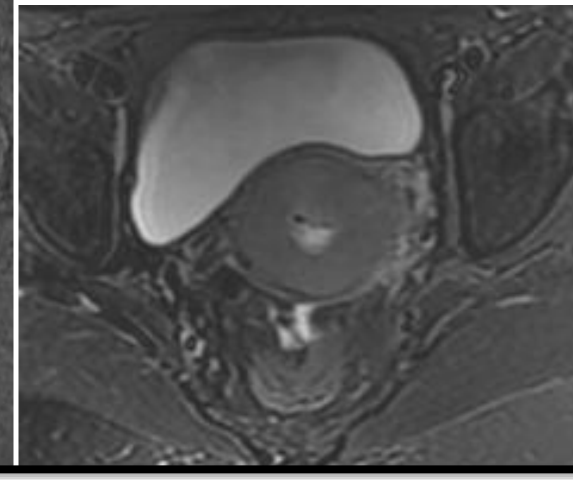
Case V

Clinical Drawing

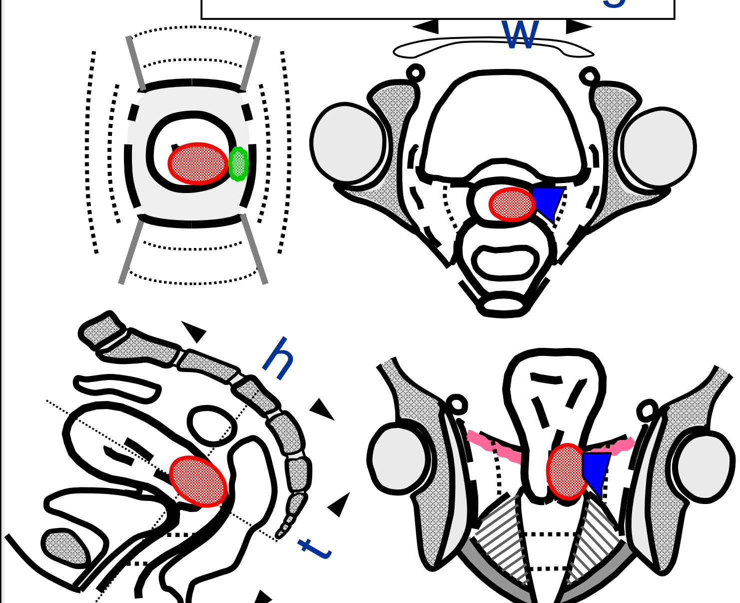




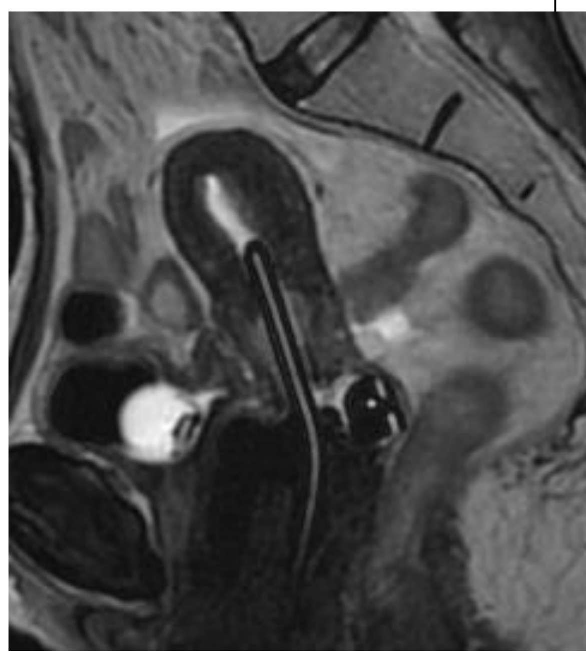
MR at Diagnosis

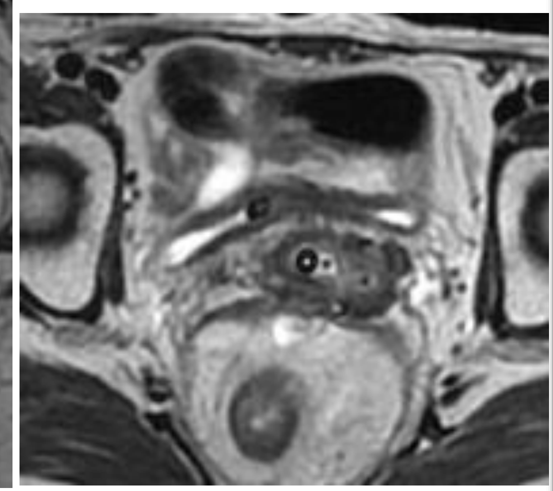


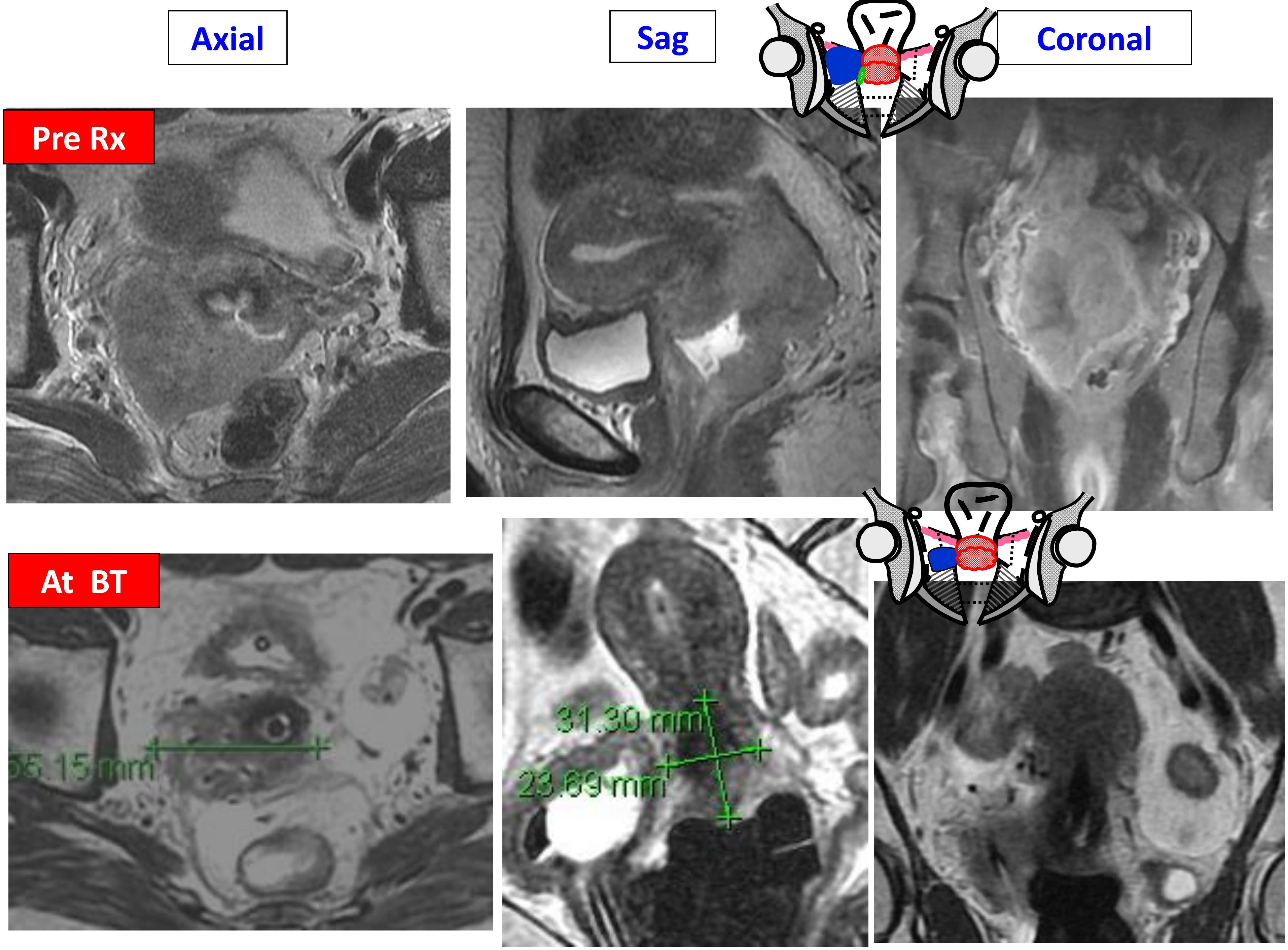
Clinical Drawing



MR at Brachytherapy






Axial
Sag
Coronal
Pre Rx
At BT
55.15 mm
31.30 mm
23.69 mm

Clinical versus MRI dimensions Correlation

100 patients of locally advanced cervical cancer (2 excluded for analysis).

Aug 2009- Dec 2013

FIGO stage- IIB (n=31), IIIB (n=55), IVA (n=8)

3D- disease mapping with clinical examination at diagnosis and at brachytherapy (under EUA)

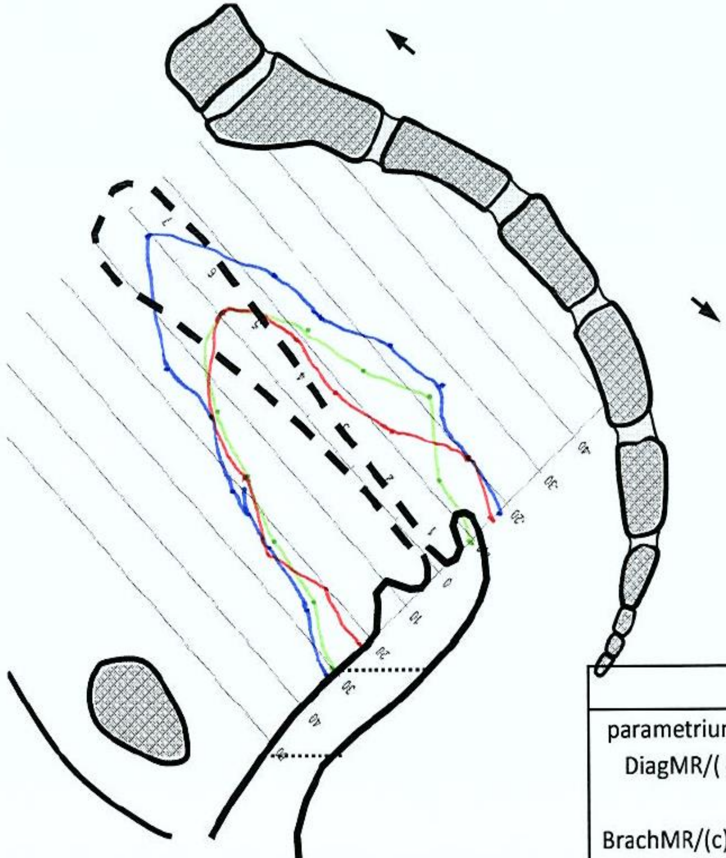
MRI at diagnosis and MRI at brachytherapy

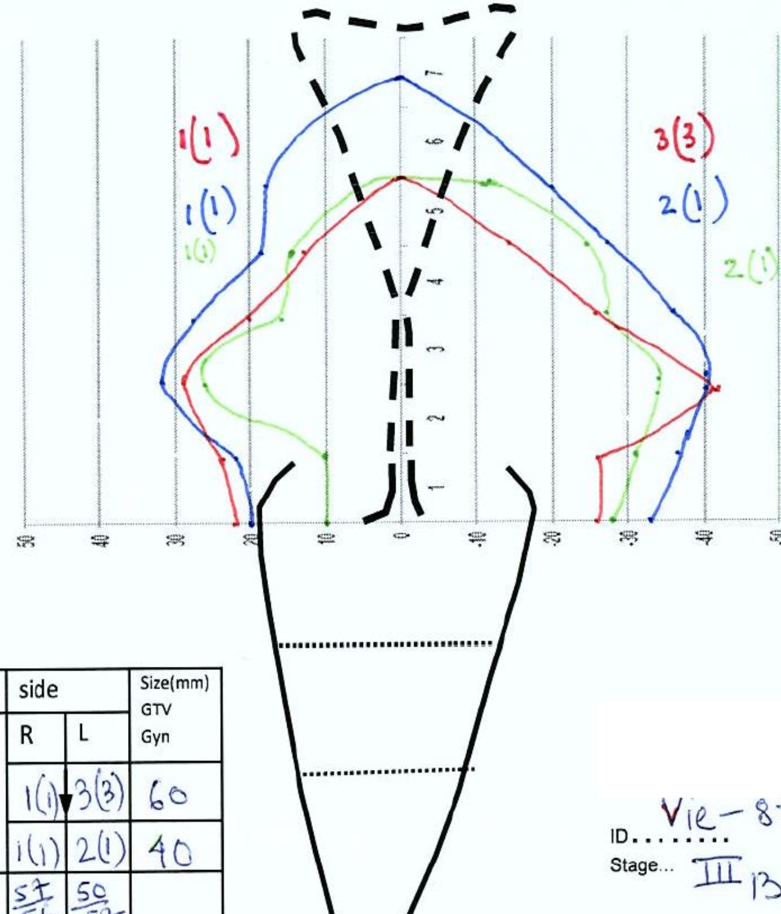
Variable (n=98)	Parameter (in cm)	Clinical Mean (±SD)	MRI Mean (±SD)
At diagnosis	Height	4.7 (±0.8)	4.7 (±1.3)
	Width	6.4 (±1.3)	5.7 (±1.2)
	Thickness	4.6 (±1.0)	4.3 (±1.1)
At Brachytherapy	Height	3.1 (±0.9)	4.4 (±0.9)
	Width	4.4 (±1.4)	4.6 (±0.9)
	Thickness	2.8 (±0.8)	3.3 (±0.8)

TMH Cohort of EMBRACE

10

MR
HR CTV
IR CTV





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

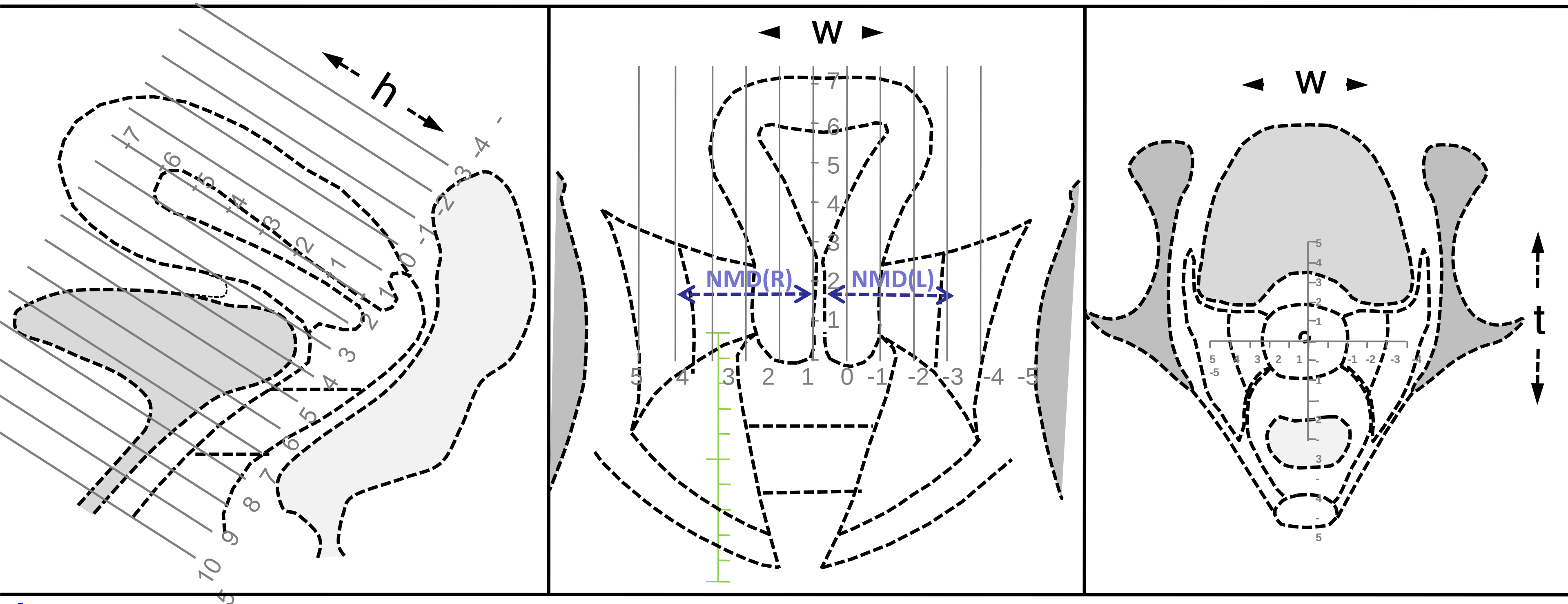
ID....... Vie-87
Stage... III B.

	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	20	16	28	13	14	19	-	~~14~~	18		Date Brachy ....
LT	26	28	33	23	32	37	42	33	40	26	27	37	15	25	27	-	~~12~~	20		
ANT	22	30	30	20	24	26	24	21	23	19	18	21	16	13	15	-	~~11~~	16		
POST	15	9	18	20	12	20	11	22	26	08	15	23	08	12	16	-	~~13~~	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. __]

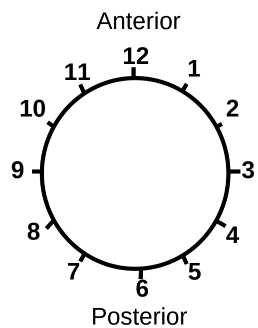


h = ____ cm **t = ____ cm** **w = ____ cm** **NMD (R) =____cm** **NMD (L) =____cm**

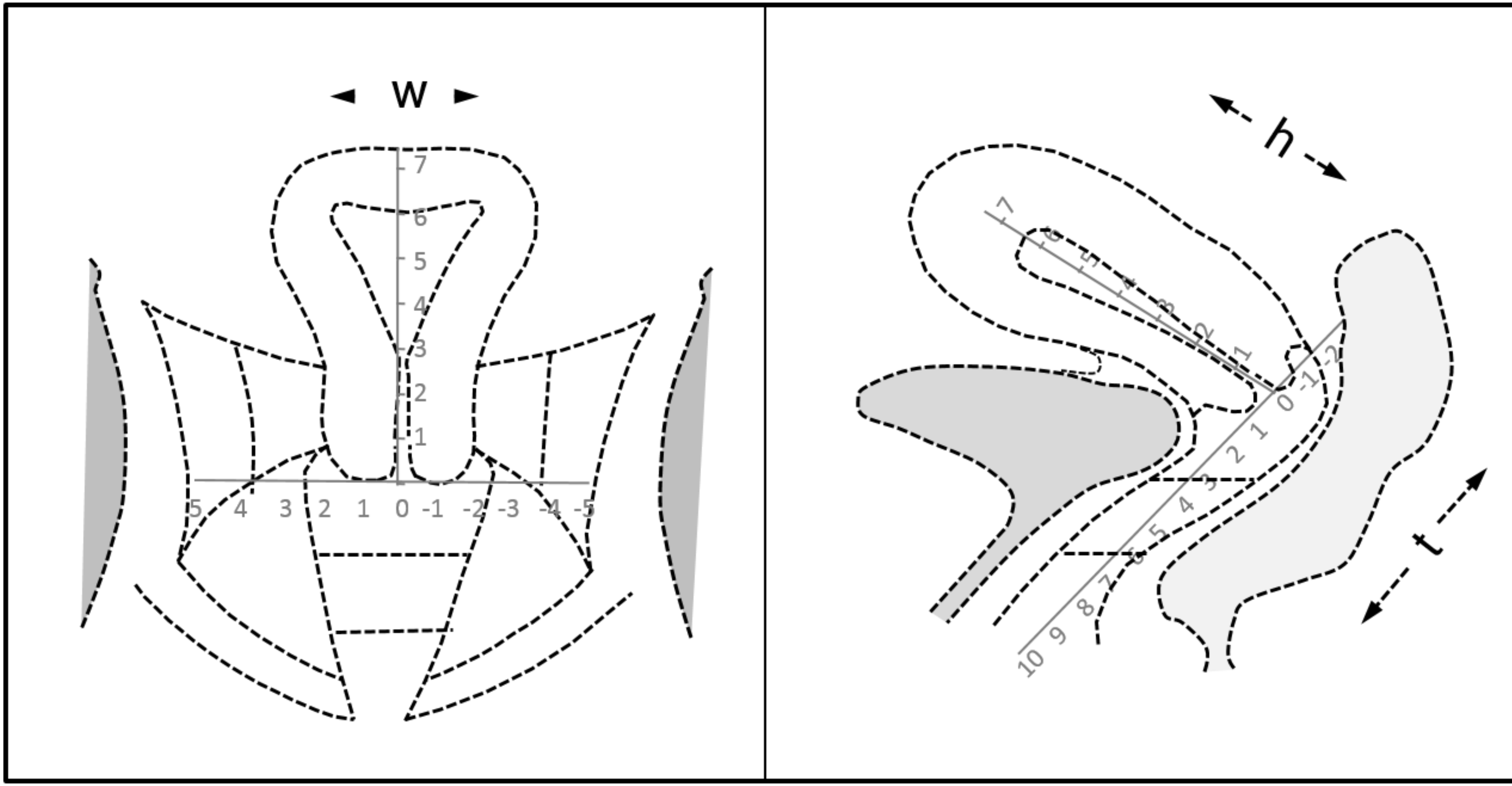
[NMD-Near Minimum Distance with respect to central canal]

Vaginal Disease

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



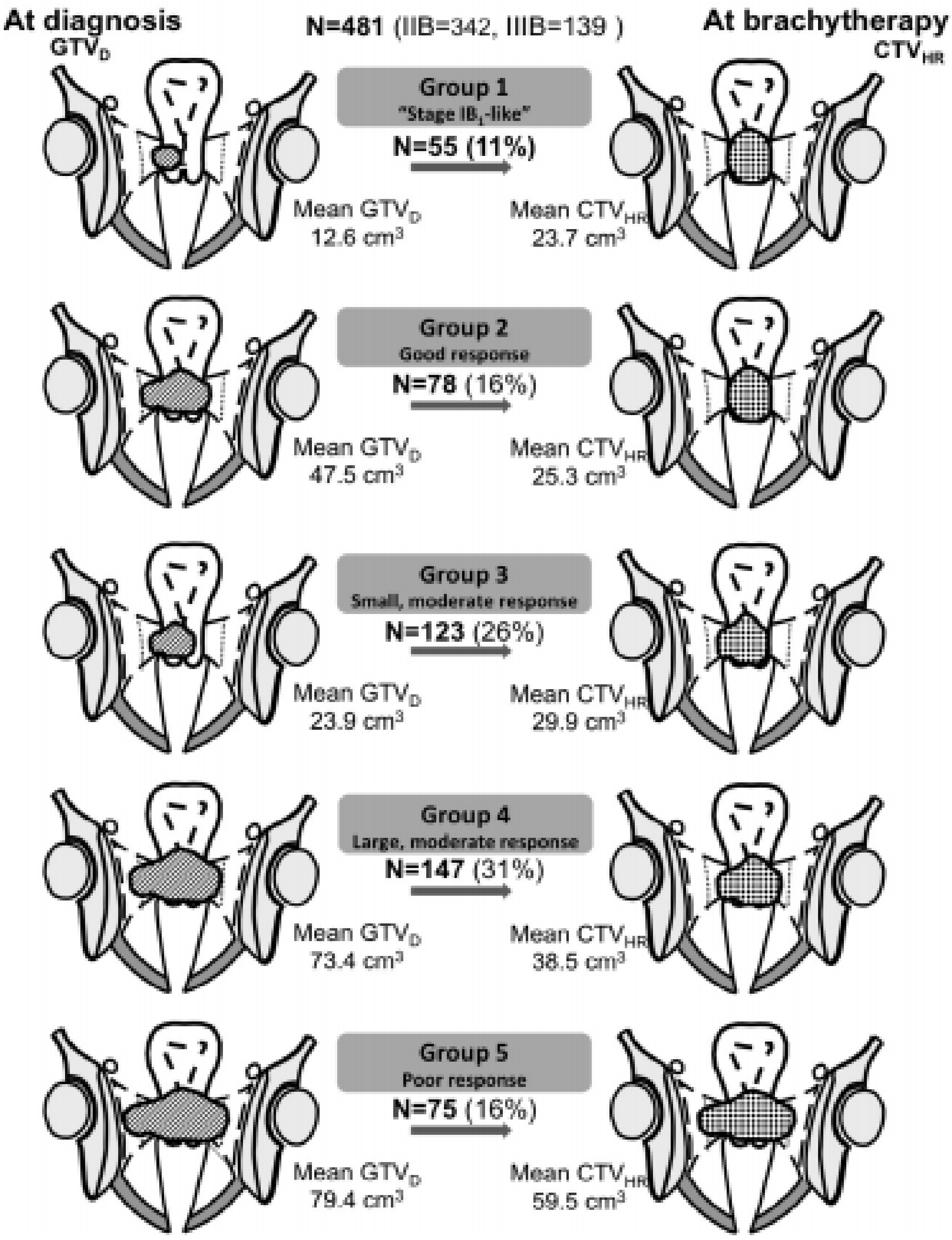
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		



w
7
6
5
4
3
2
1
5 4 3 2 1 0 -1 -2 -3 -4 -5
h
t
7
6
5
4
3
2
1
0
-1
-2
10 9 8 7 6 5 4 3 2 1

PATTERNS OF DISEASE AT DIAGNOSIS AND HRCTV AT BT

N. Jastaniyah et al. / Radiotherapy and Oncology 120 (2016) 404–411



IJROBP 2016

SUMMARY

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

EMBRACE

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

Appendix

- Extended CRF 60-120 Month Follow-ups
- Clinical Drawings (PowerPoint)
- Updated CRF July 2013
- CTCAE v3.0(PDF)
- Instructions for dummy-run (PDF)
- GYN GEC-ESTRO Guidelines I (PDF)
- GYN GEC-ESTRO Guidelines II (PDF)
- Applicator reconstruction catalogue (PDF)

ABOUT EMBRACE

- Synopsis
- Protocol PDF download
- Amendments
- Appendix
- Quality of Life sub-study
- Embrace study commitee
- Participants
- FAQ
- Sponsors

www.embracestudy.dk/AboutAppendix.aspx

Will you implement clinical documentation with 3D drawings in your routine clinical practice?

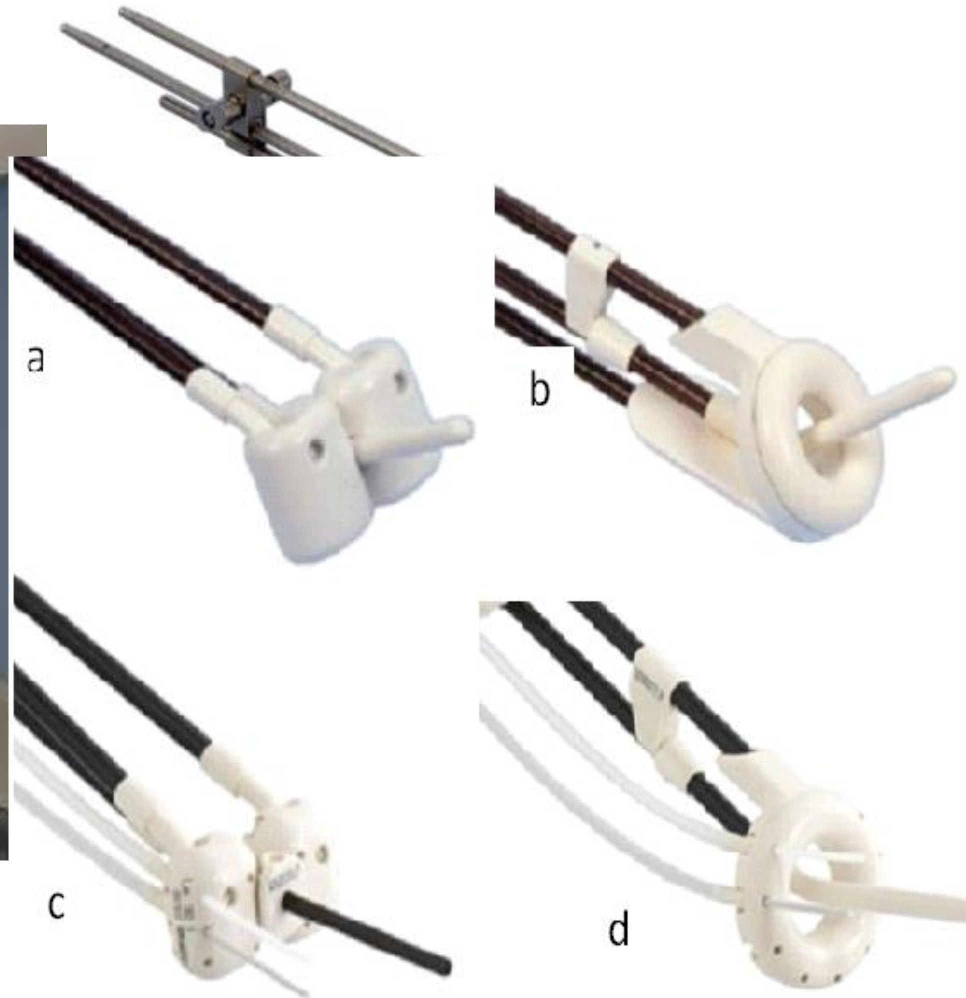
A. Yes
B. No
C. Not sure

Applicator commissioning, reconstruction, geometry and fusion

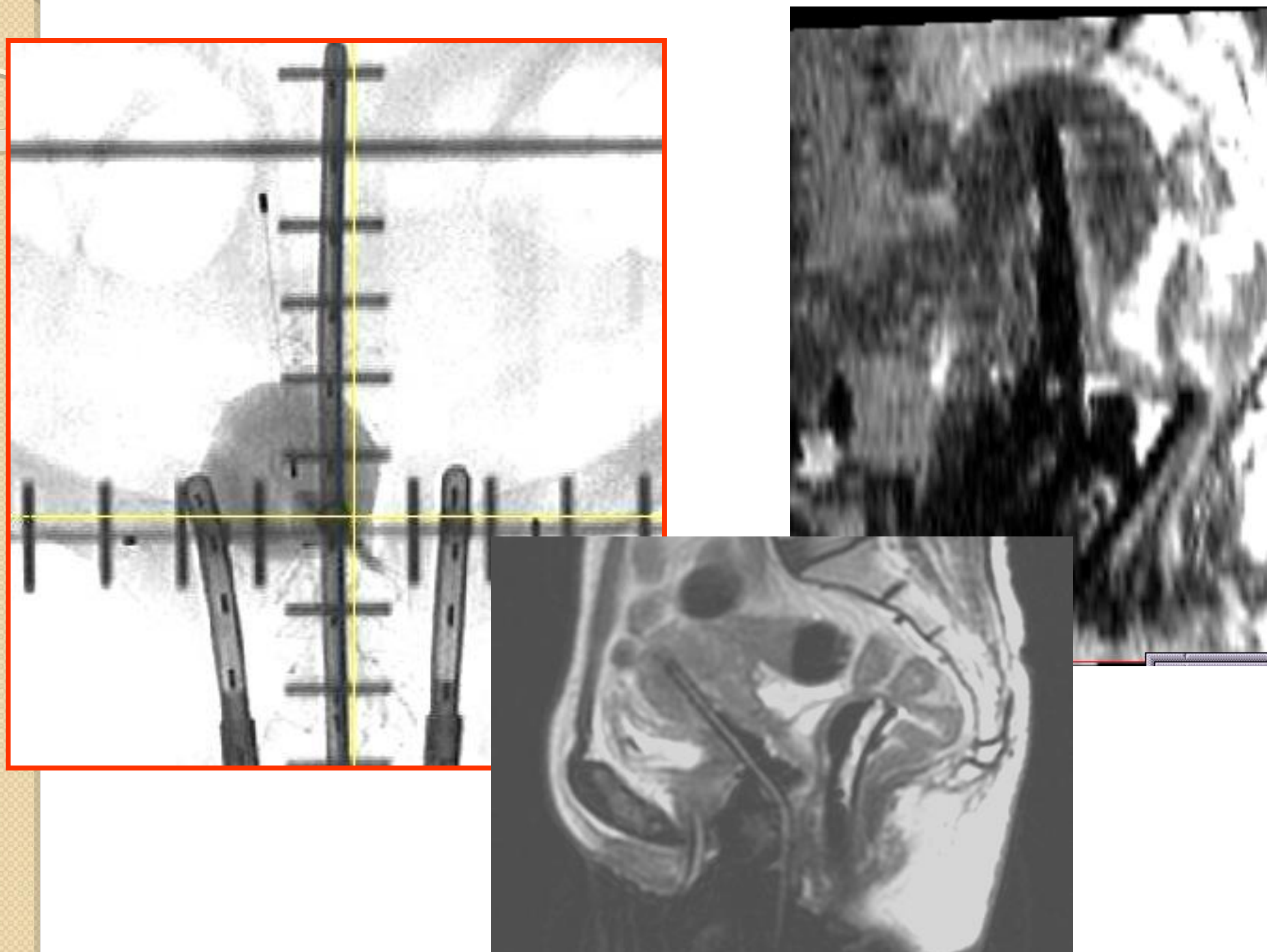
Jamema Swamidas PhD,
Assistant Professor
Department of Medical Physics
Tata Memorial Hospital,
Mumbai,
India

ESTRO
European Society for Therapeutic Radiology and Oncology

Commissioning

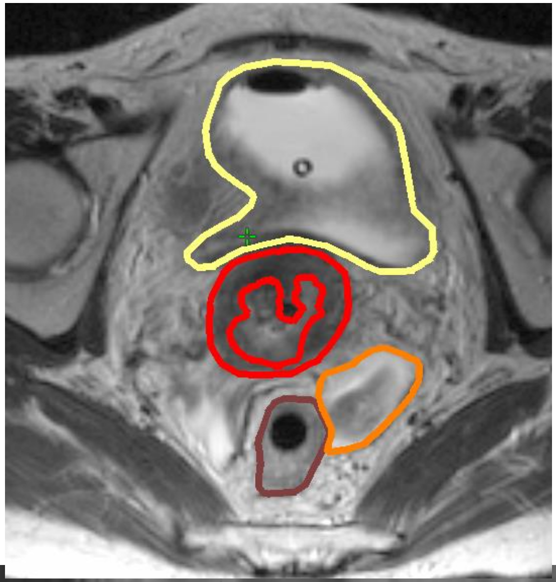


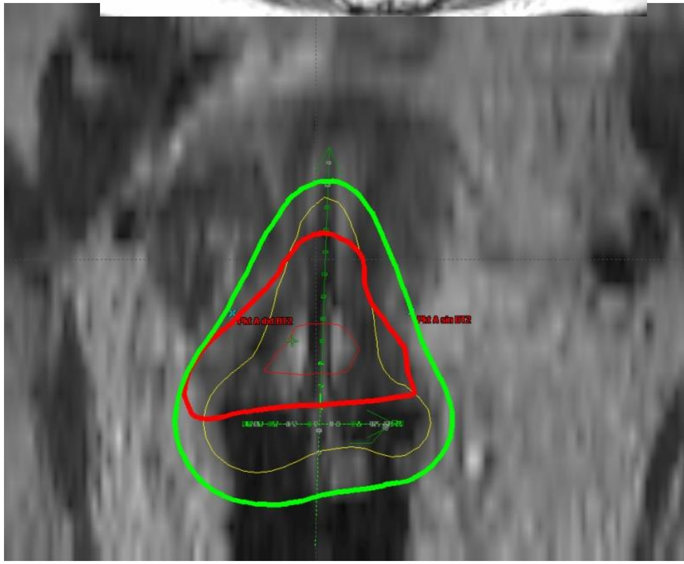
Why so much fuss about Applicator commissioning /reconstruction in 3D BT?



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



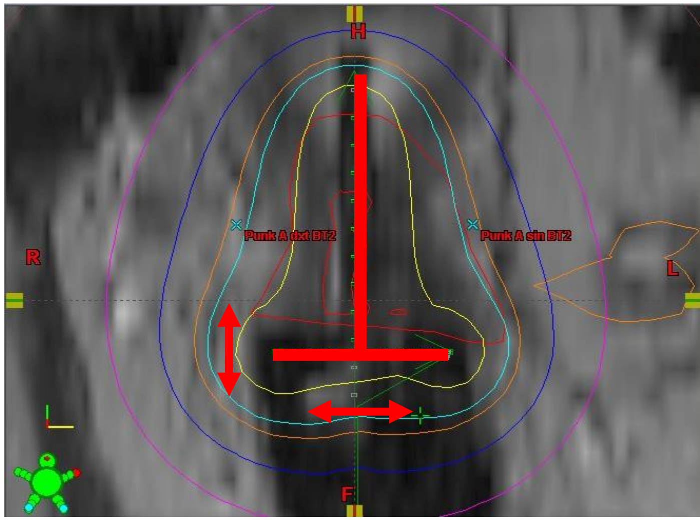


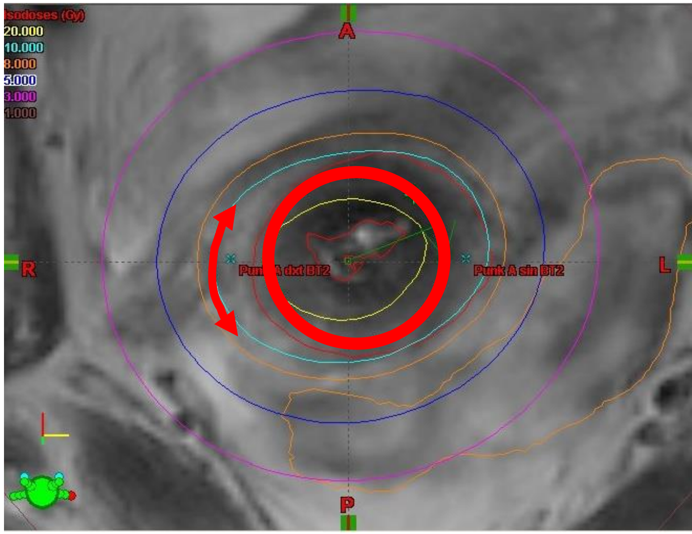
Tanderup et al, R&O 2008

Simulation of un-certainty

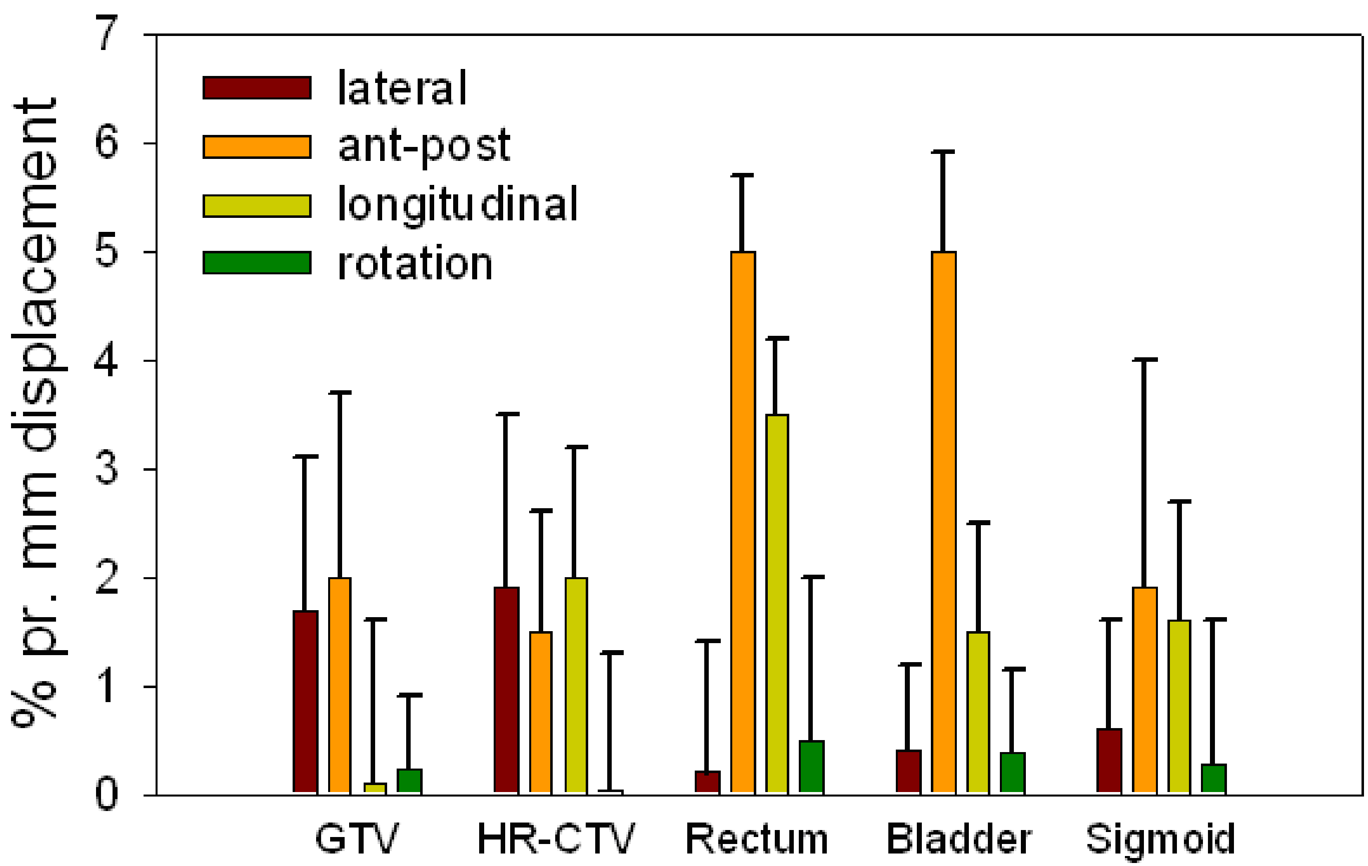
- Displacement in directions:
  - Longitudinal (along tandem):
    - ± 3 mm, ± 5 mm
  - Lateral:
    - ± 3 mm
  - Ant-post
    - ± 3 mm
- Rotation of ring:
  - ± 15 dgr (4 mm)

Tanderup et al, R&O 2008





Mean DVH shifts (%) pr mm



Tanderup et al, R&O 2008

Reading material

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

GEC-ESTRO Recommendations

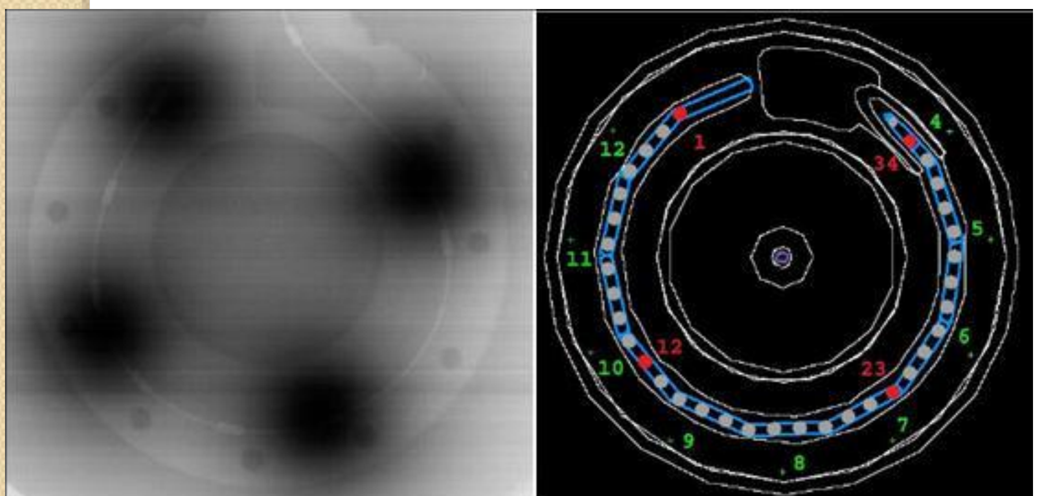
Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group: Considerations and pitfalls in commissioning and applicator reconstruction in 3D image-based treatment planning of cervix cancer brachytherapy

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.

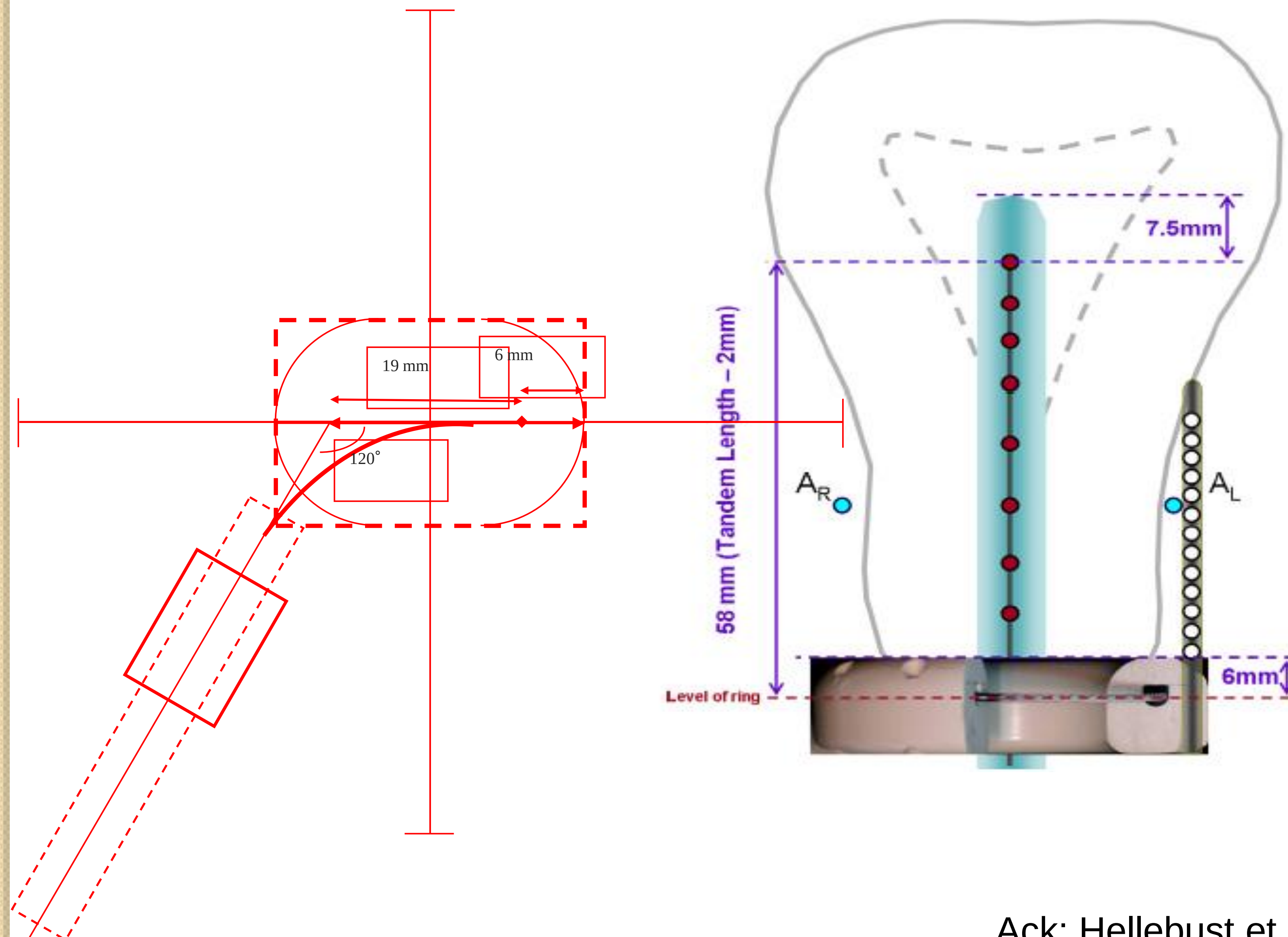
Commissioning of applicator



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

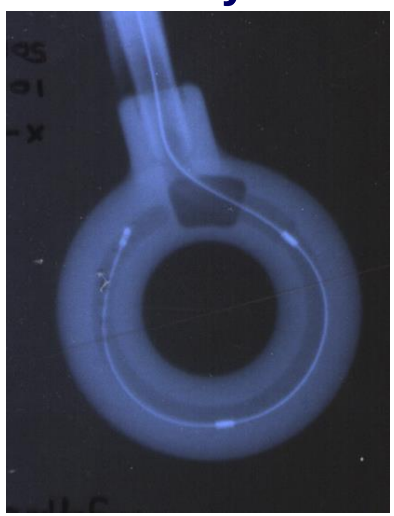


Ack: Hellebust et al

Step 1/5: Understand the geometry

The ring applicator from Bebig vs Elekta

X-ray



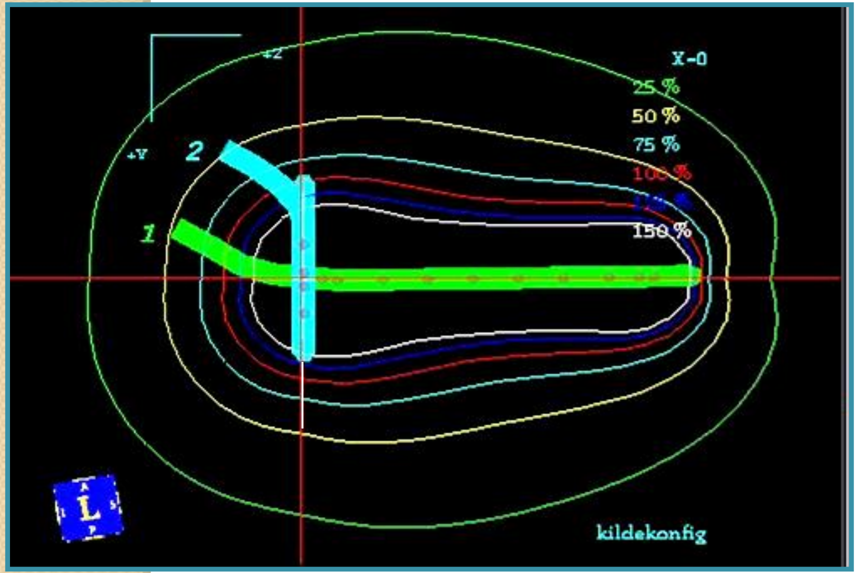
X-ray

Elekta **Bebig**

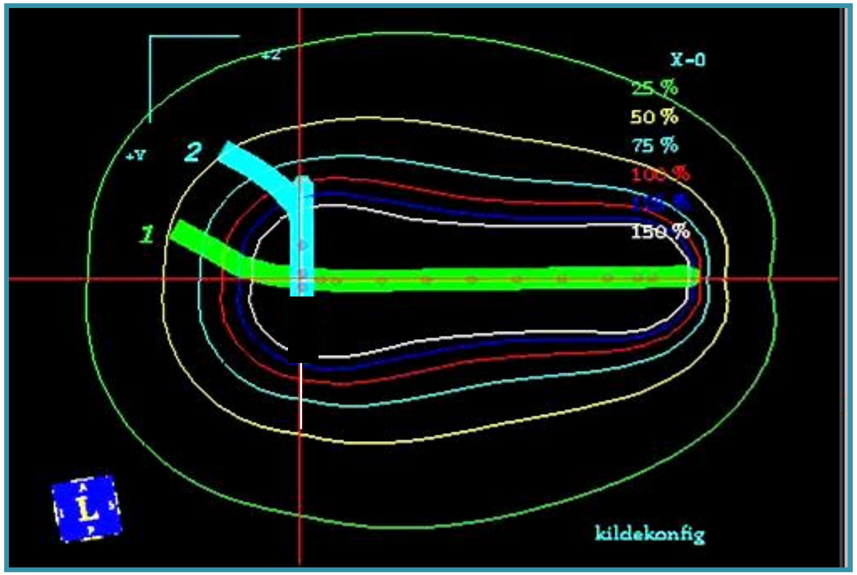
Slide courtesy :TP Hellebust

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

Elekta



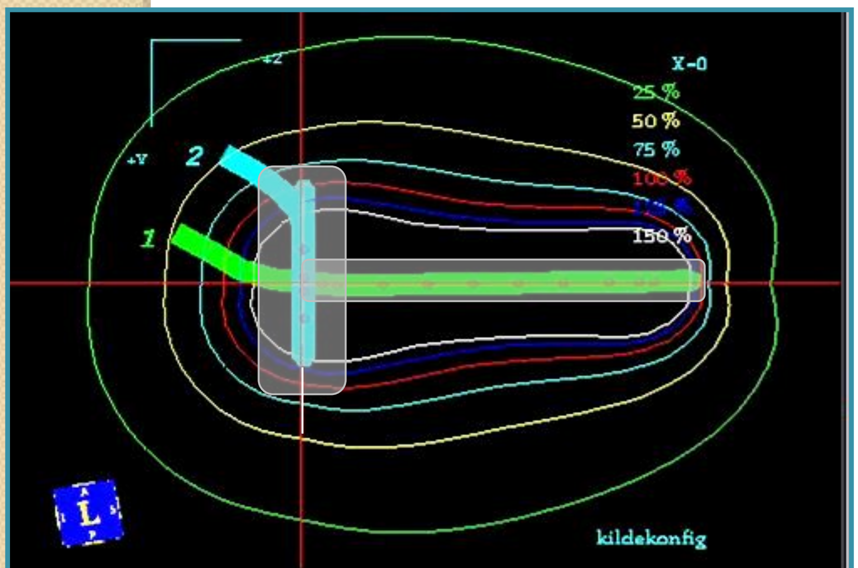
Bebig



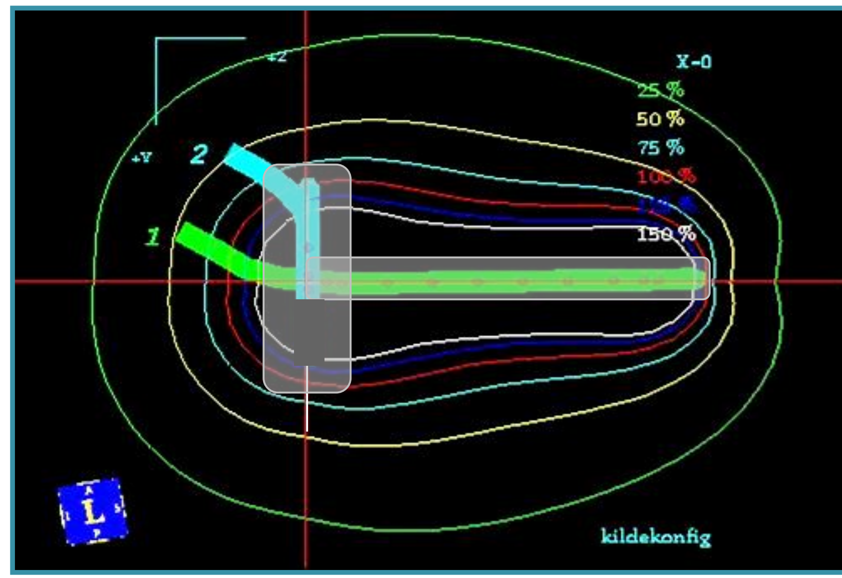
Slide courtesy :TP Hellebust

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

Elekta

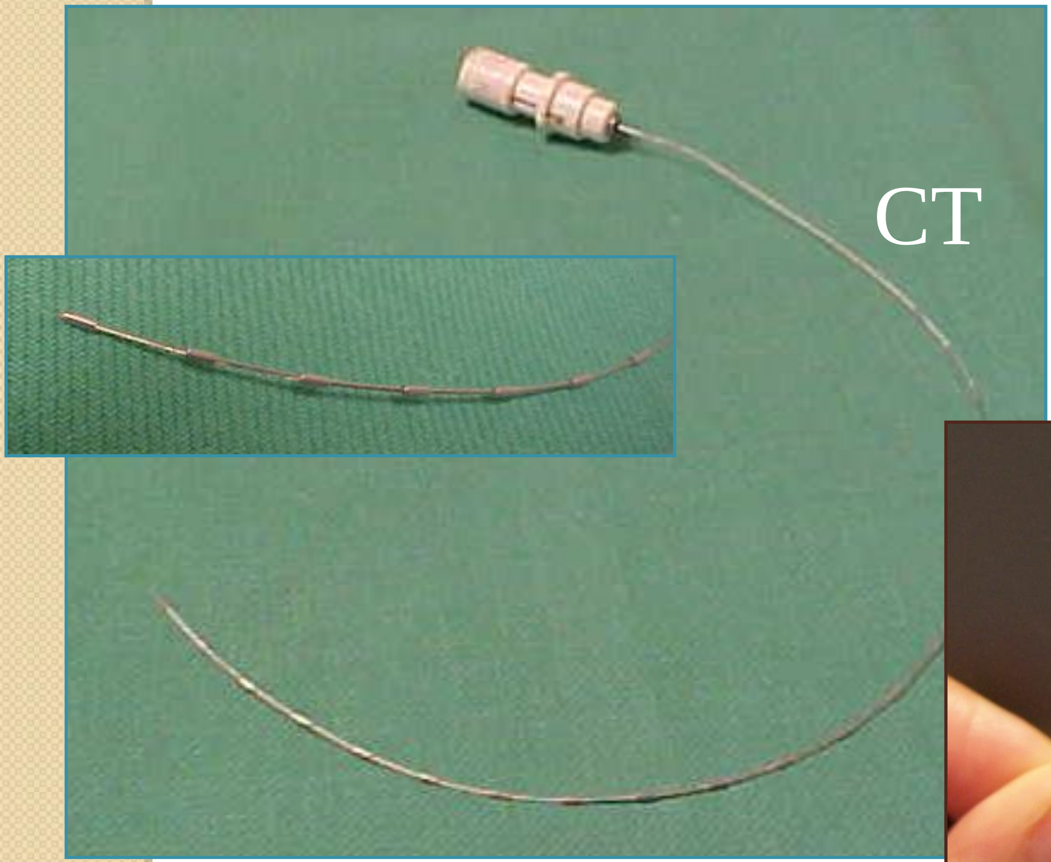


Bebig

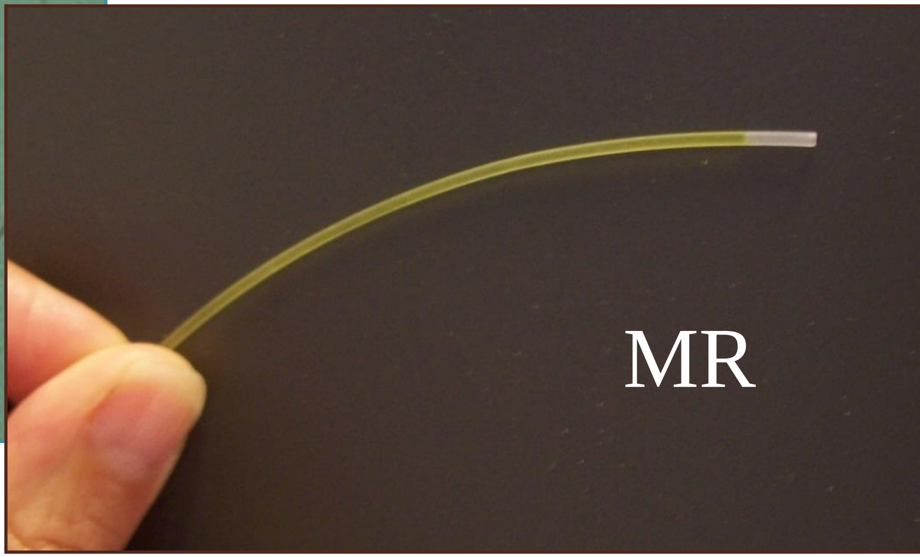


Slide courtesy : Hellebust

Step 2/5: Choose the Markers

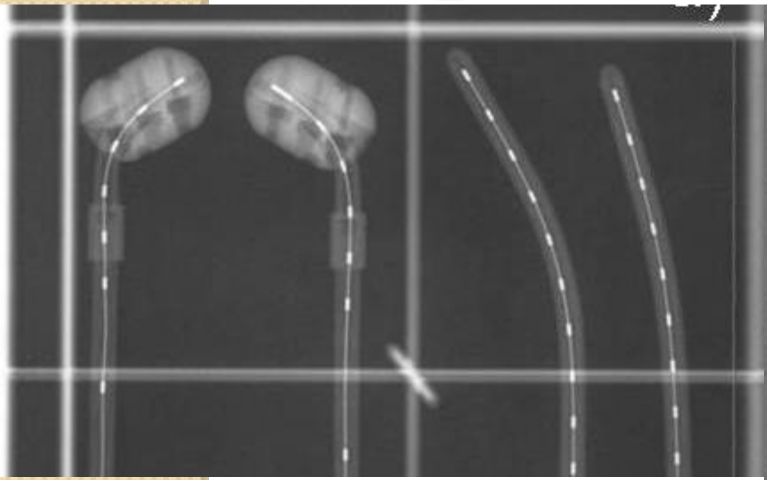


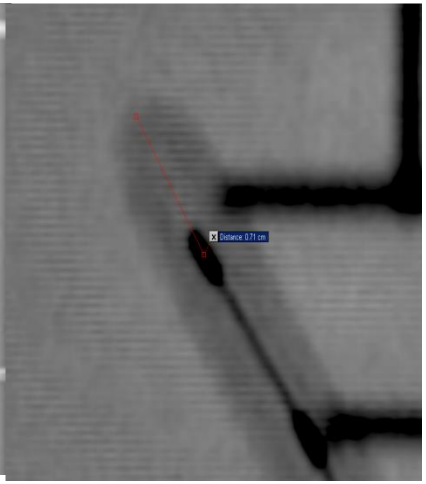
important: Dedicated for each type of applicator, check for locking!!

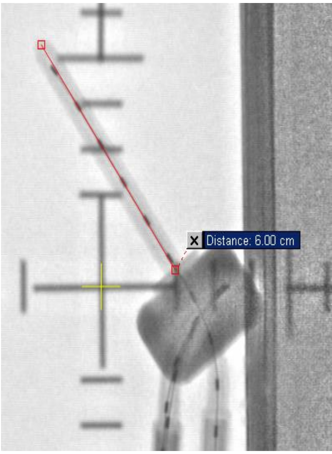


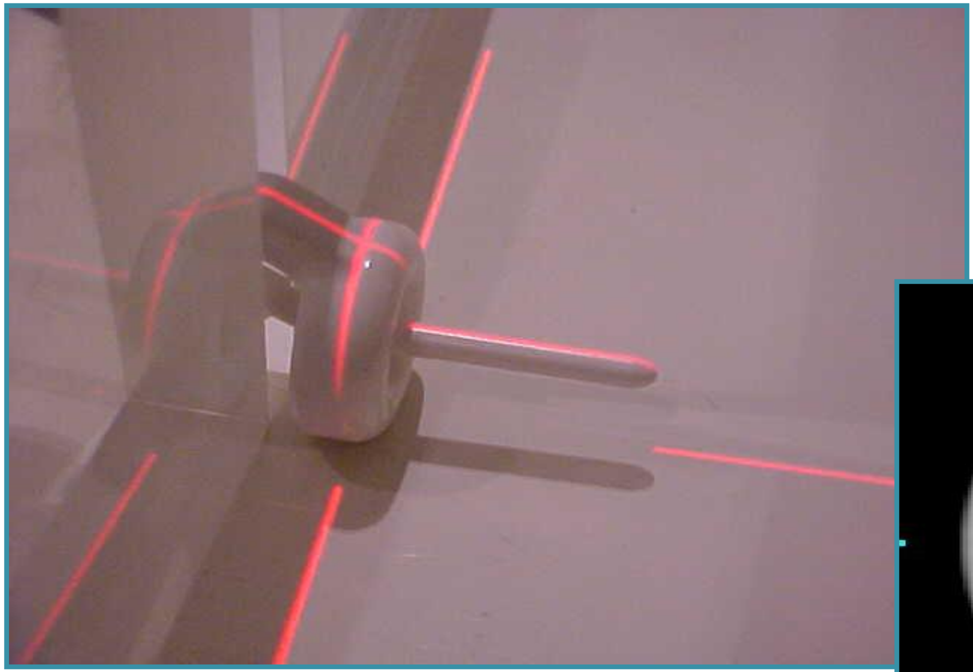
Ack: Hellebust

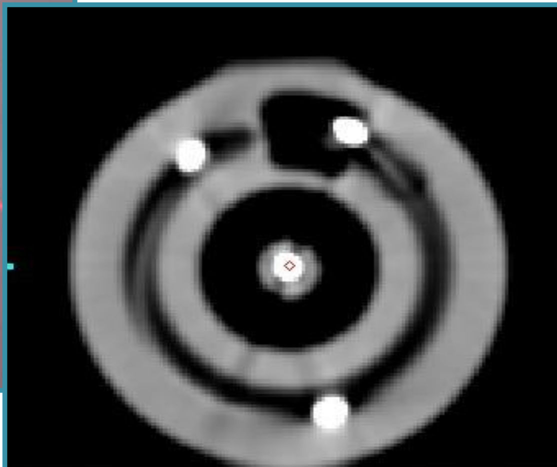
Step 3/5: Radiograph / CT / MR





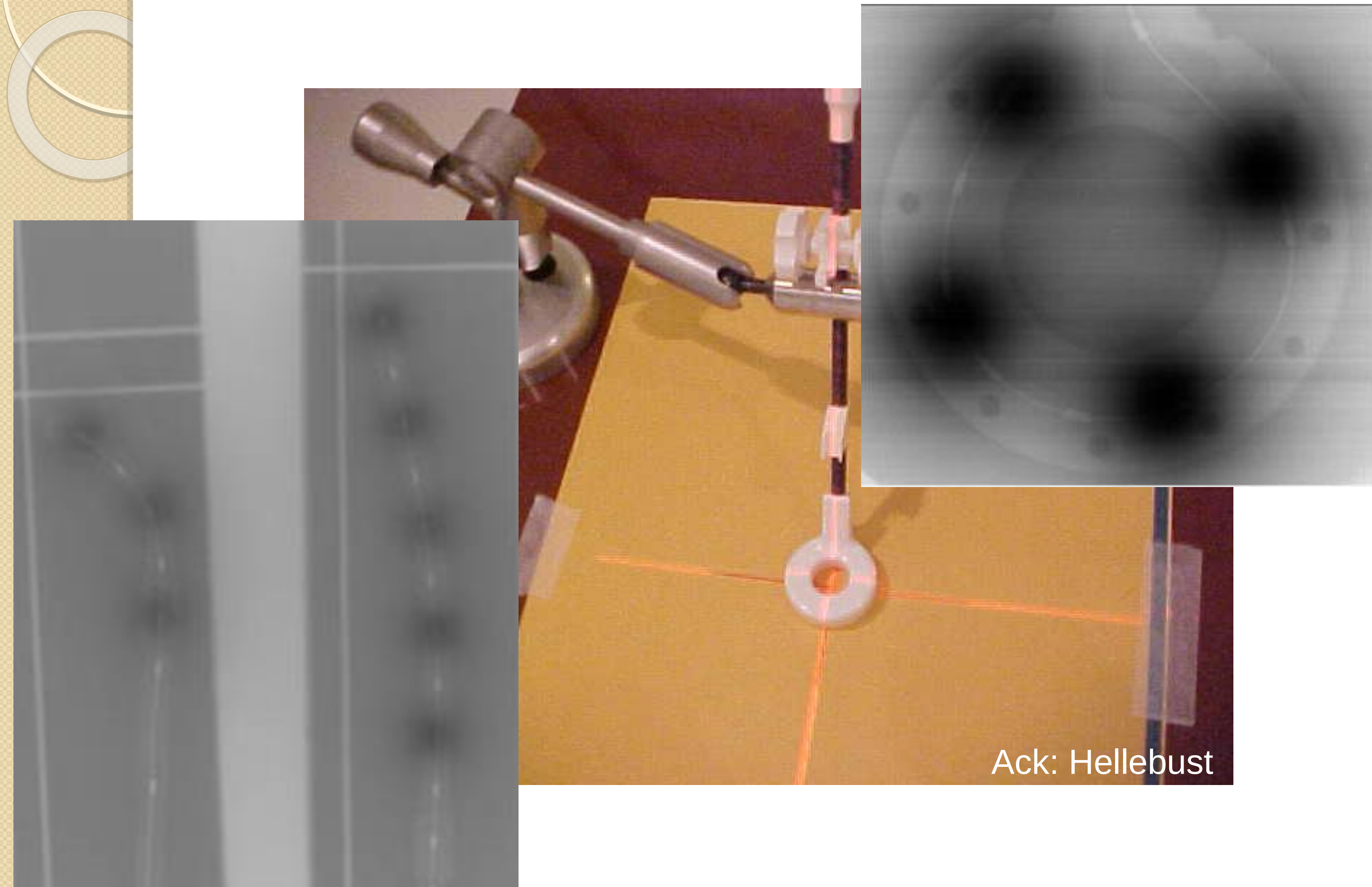






Ack: Hellebust TP

Step 4 /5 : Auto radiograph

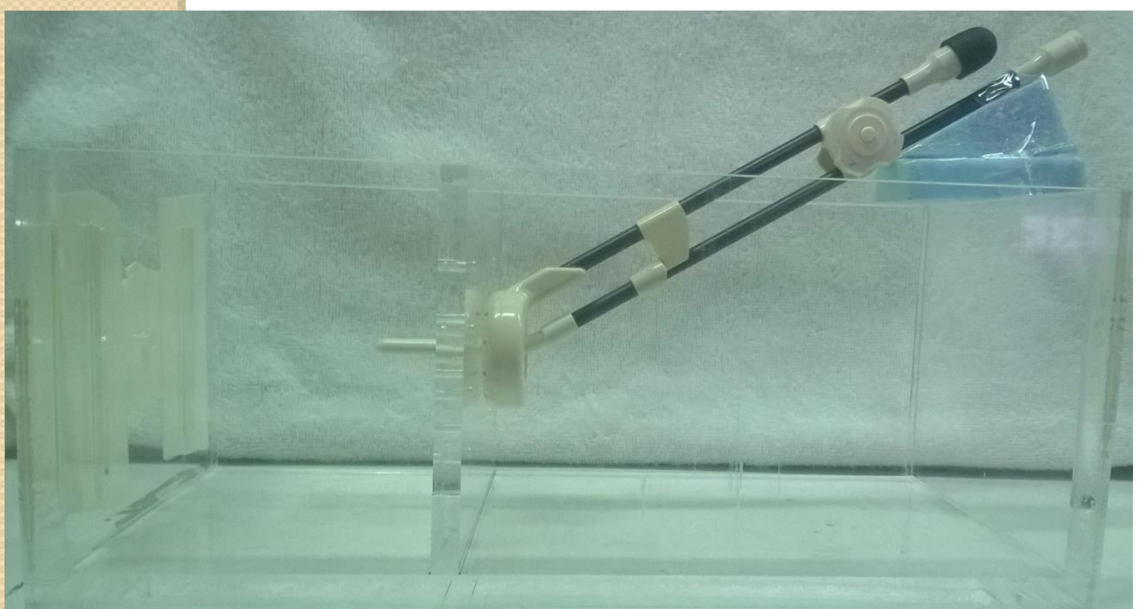


Step 5/5 : Analysis

- Compare the auto radiograph with the manufacturer specifications
- Comparing step 1 with 3&4

Phantom

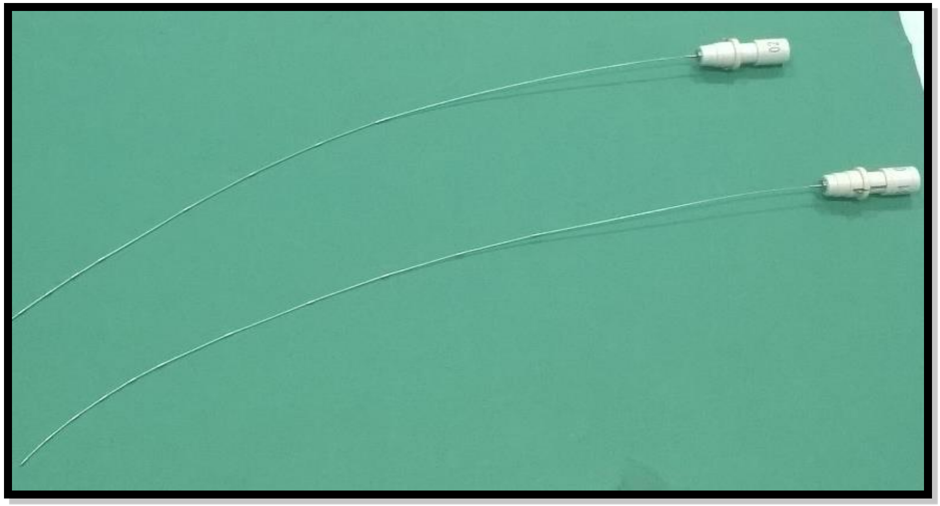
- Should facilitate accurate positioning of the applicator
- External setup markers for proper setup during imaging



Vienna Applicator

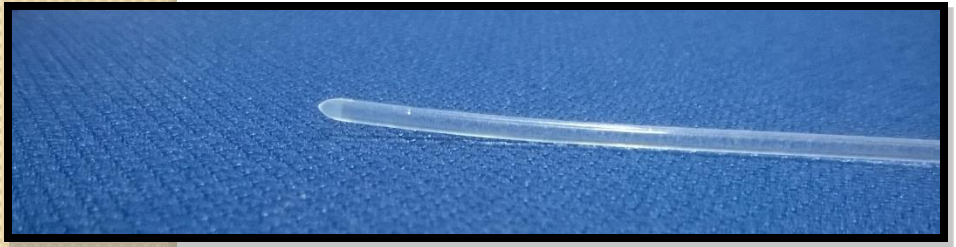
Medium:

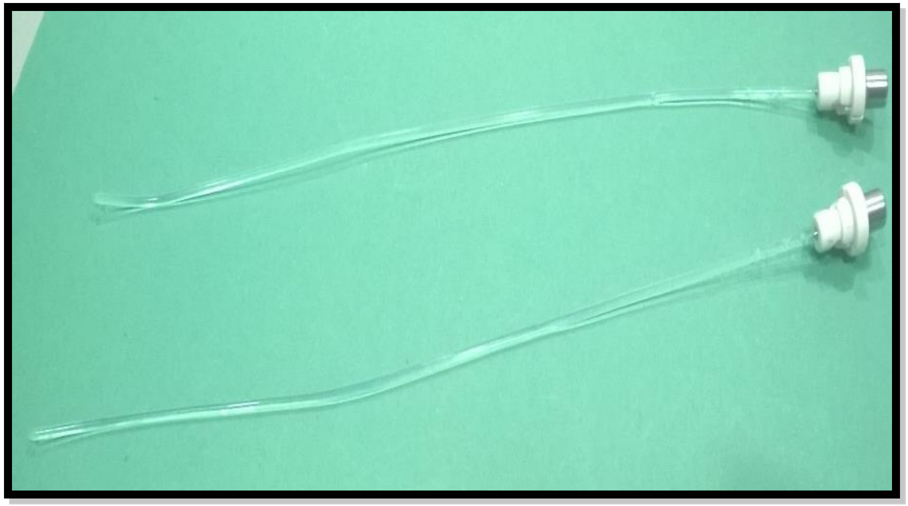
- Preferable if it resembles human tissue imaging qualities.
- Ideal for CT/ MR applicator is Agarose gel (3%) with $CuSO_4$ (1 g/L)



X-ray markers for CT/MR applicator.

DO NOT USE X-RAY MARKER DURING MRI.

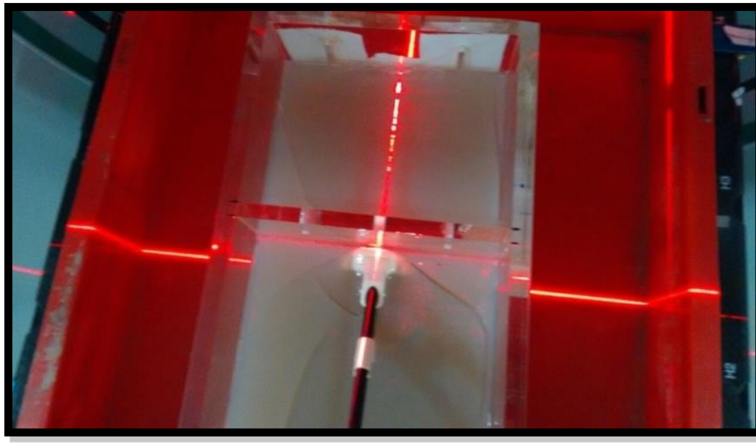




MR markers for CT/MR applicator.
They are filled with water.
$CuSO_4$ can also be used.

Imaging

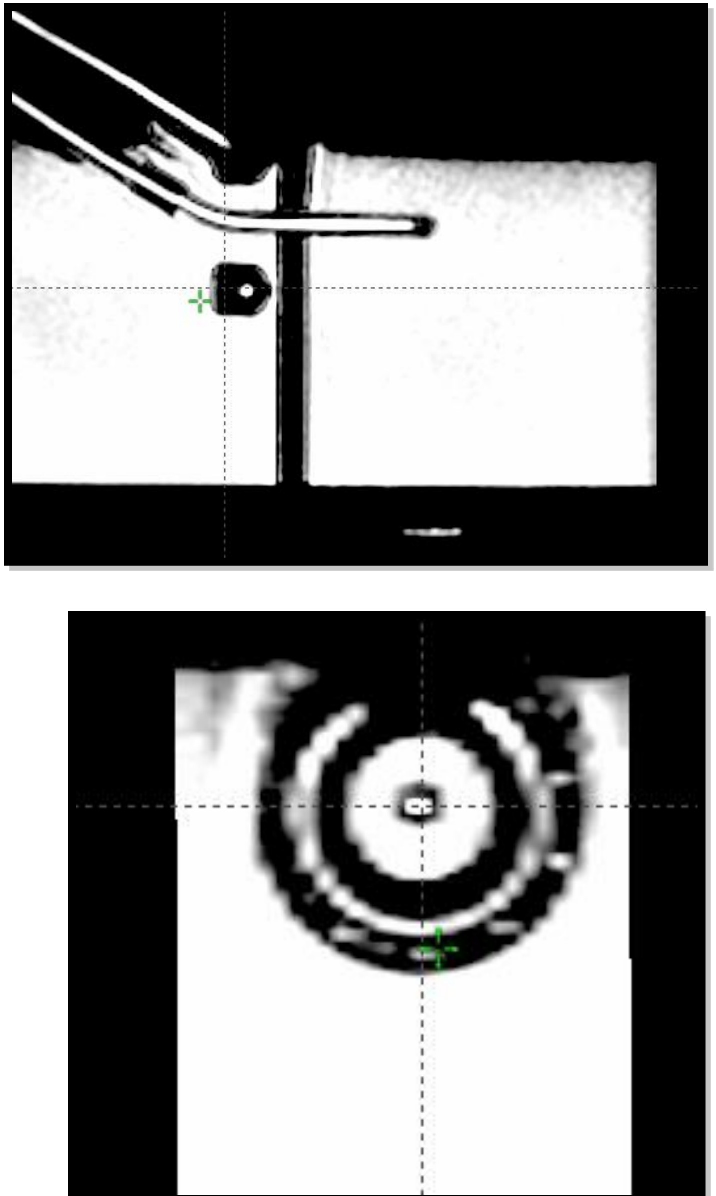
- Setup according to the external markers.
- Align the axis of the applicator along the saggital Laser.

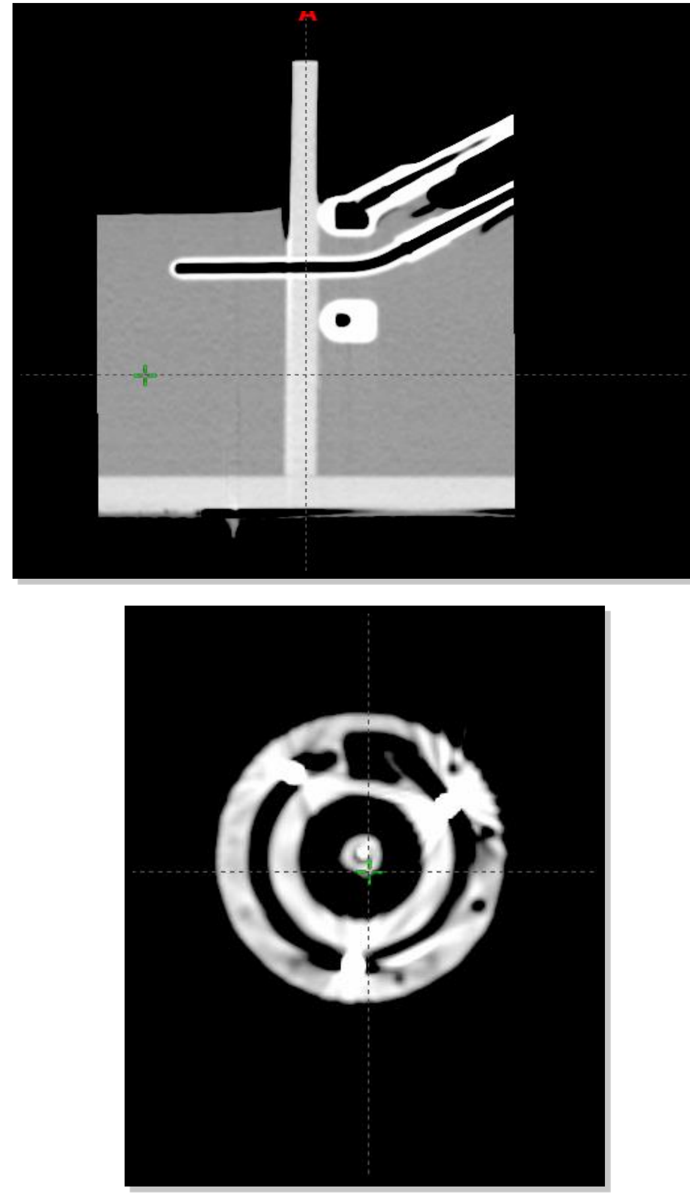


- Imaging Series
  - CT – <1 mm slice thickness
  - MRI – T1, T2 para-axial, para-saggital and para- coronal. 2- 3 mm slice thickness. Zero overlap

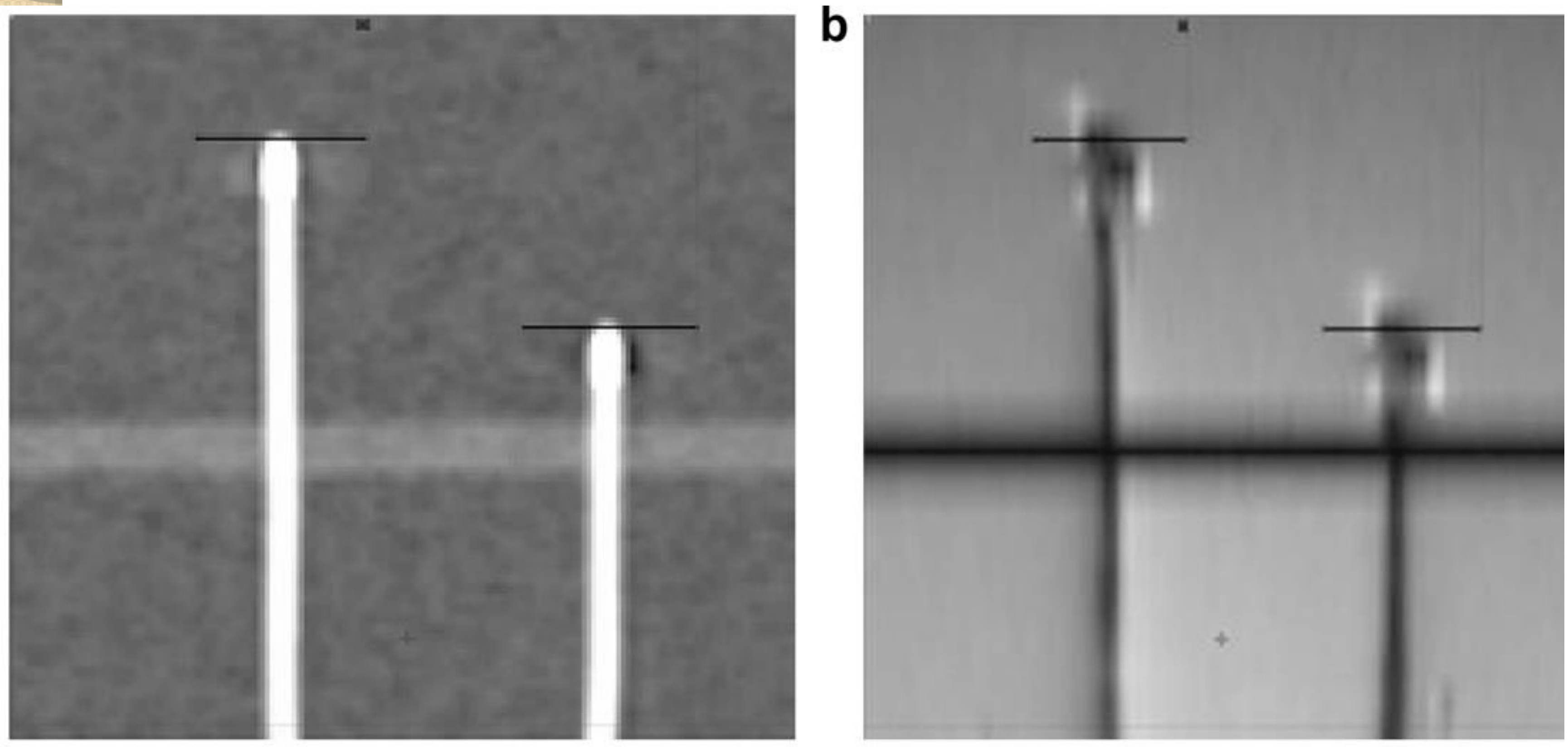
MRI

CT

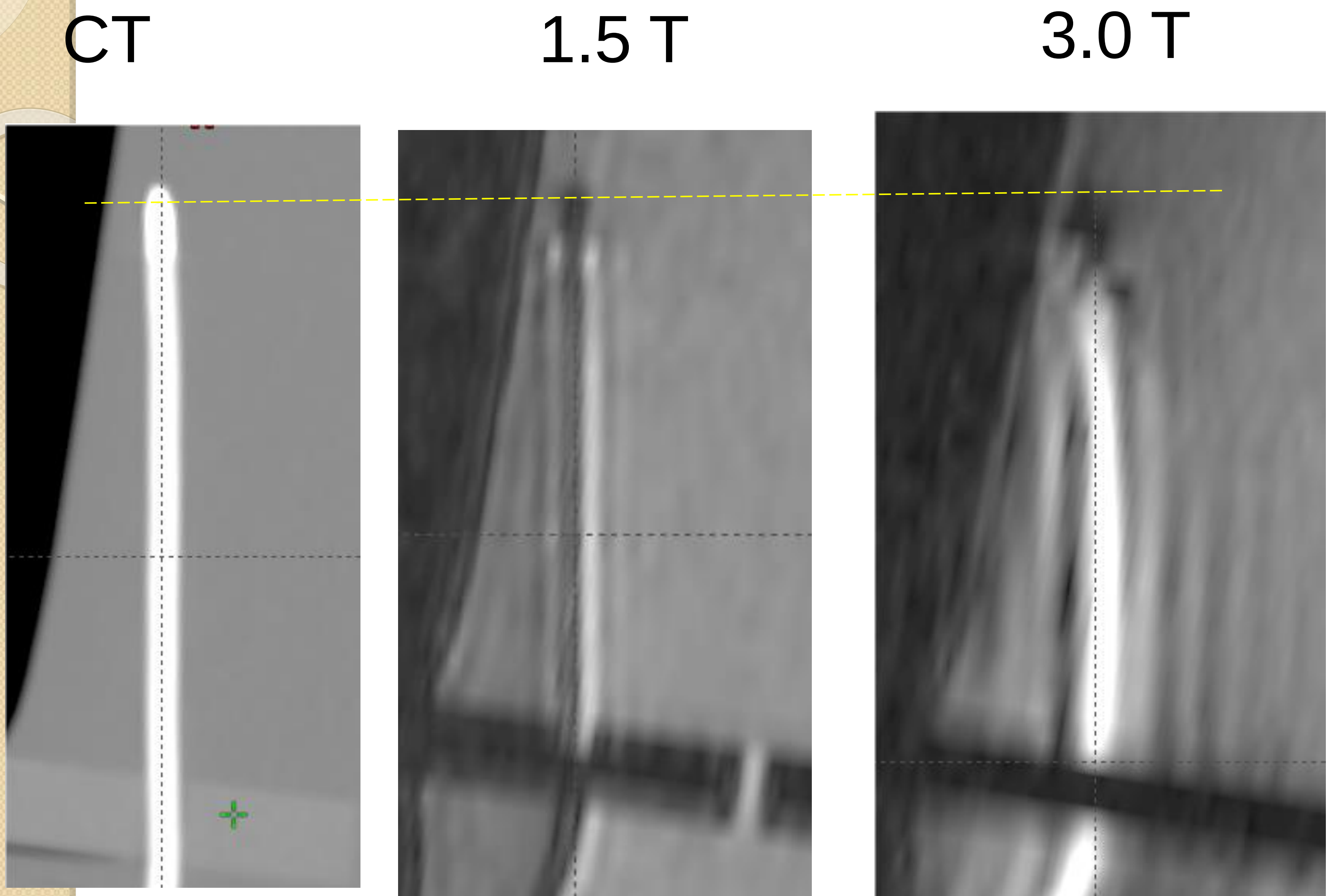




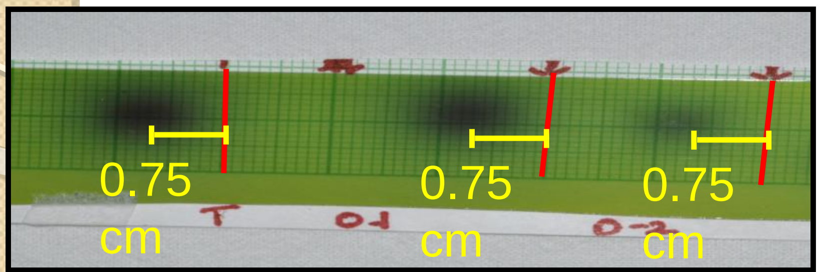
Titanium Needles

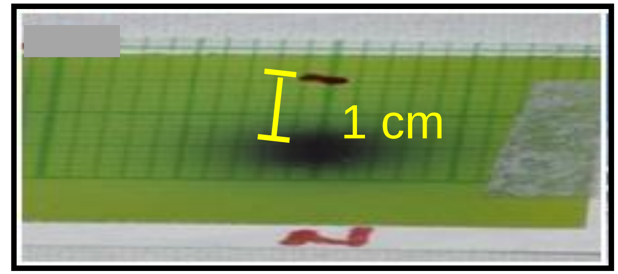


Haack et al, RO 2006

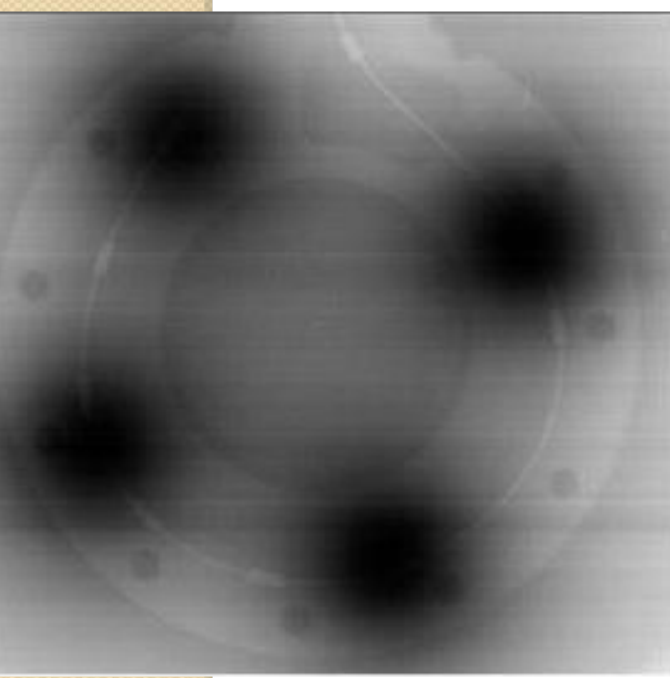

CT
1.5 T
3.0 T

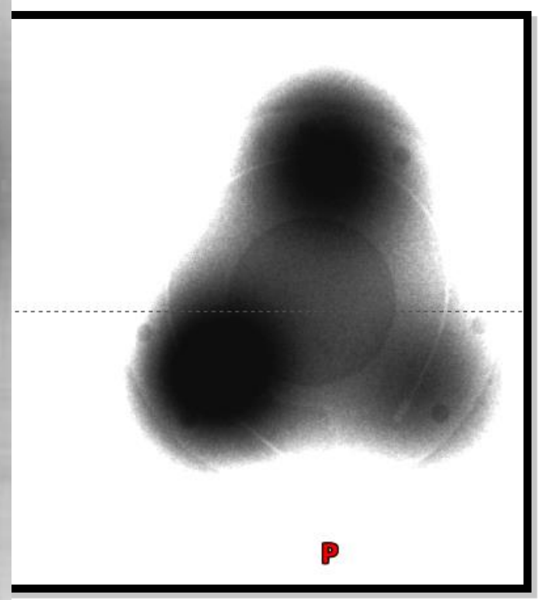
Auto Radiograph

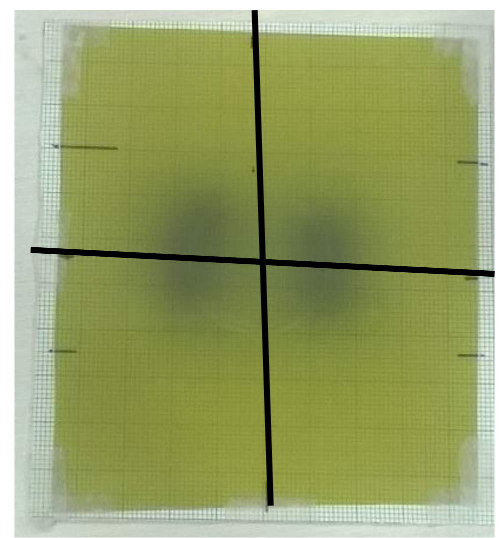




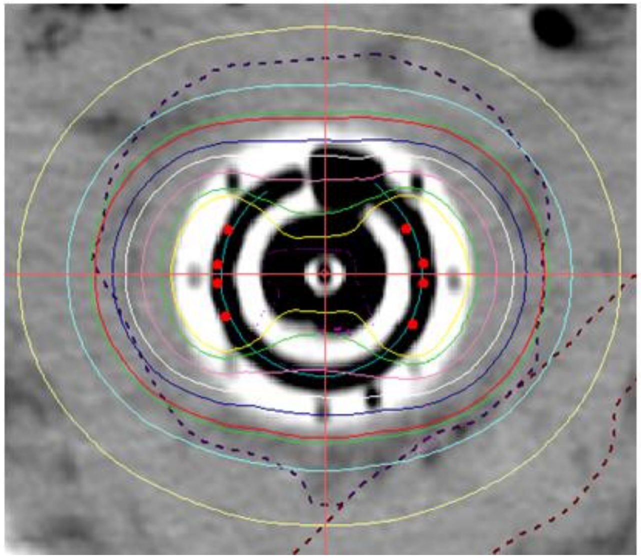
Red line indicates the physical tip

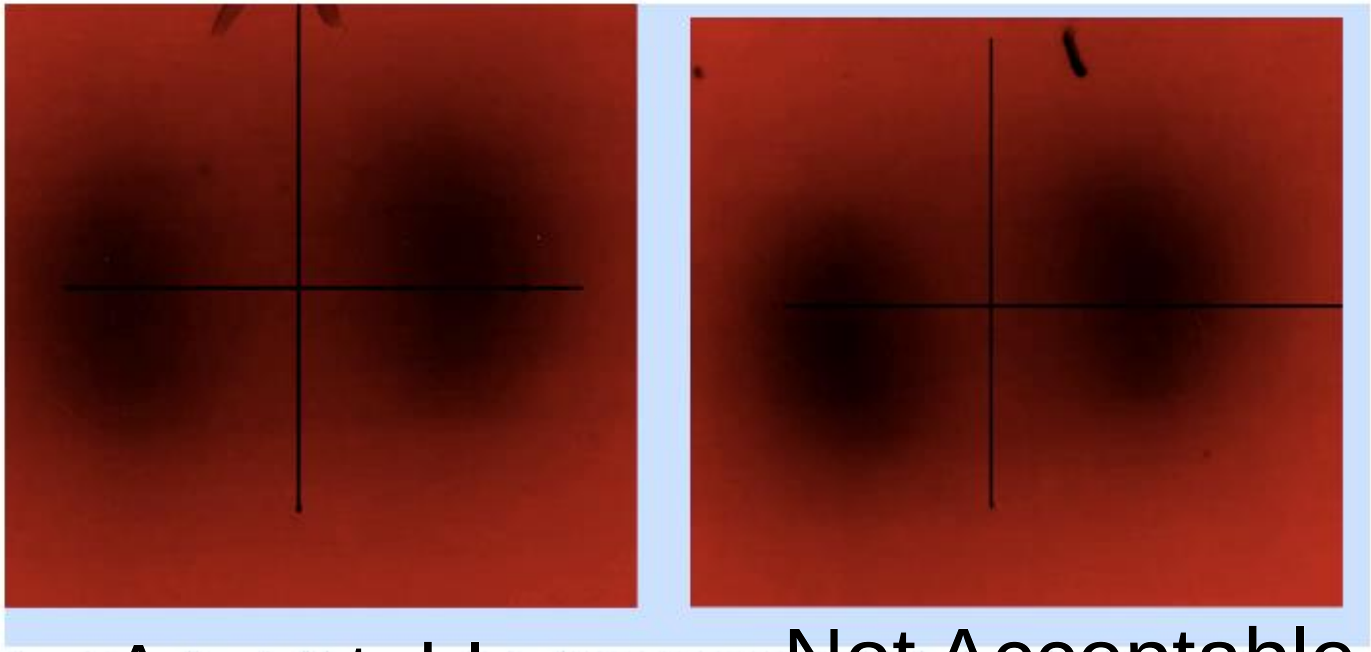






Ring Applicator



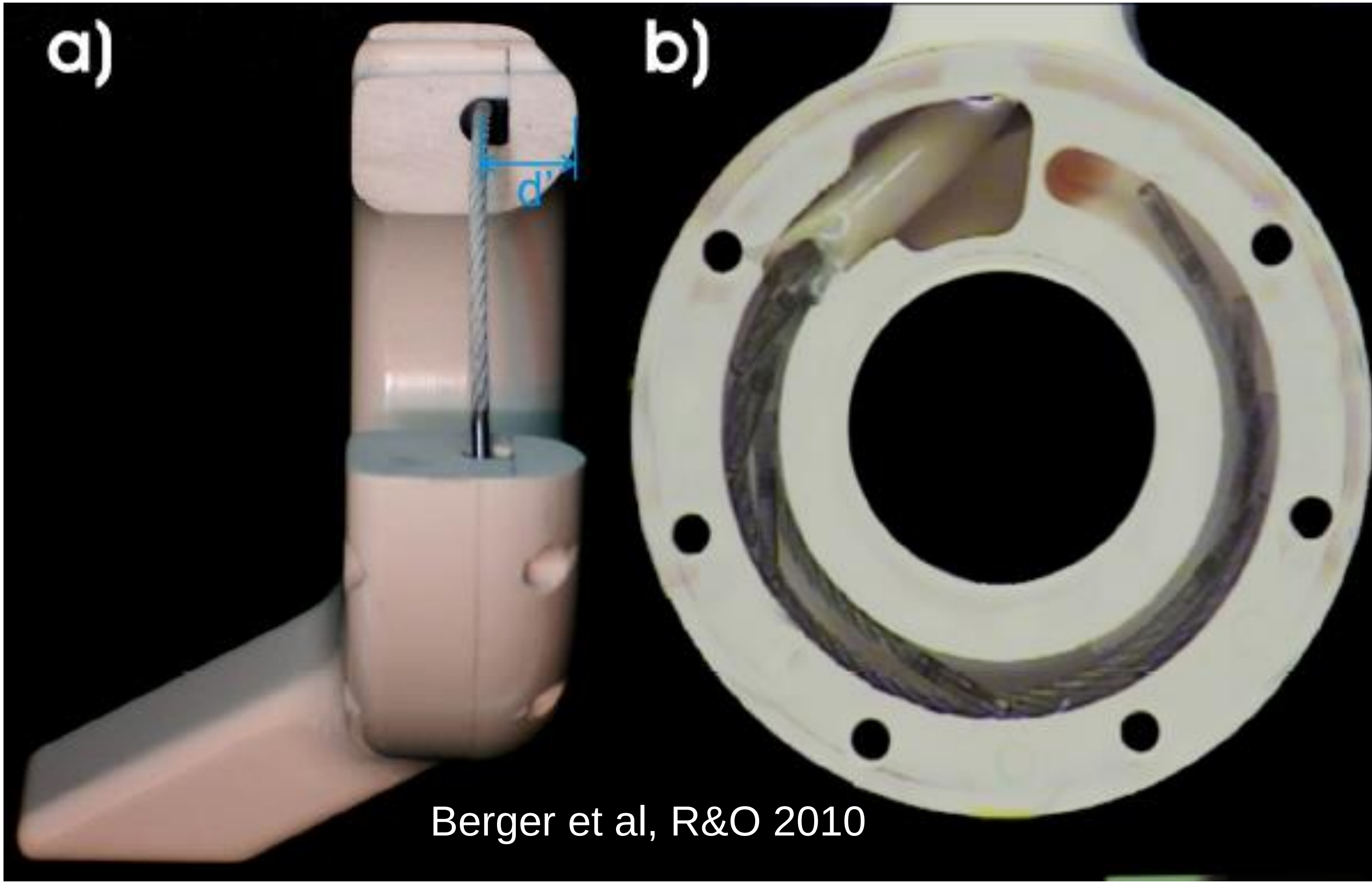


Acceptable

Not Acceptable

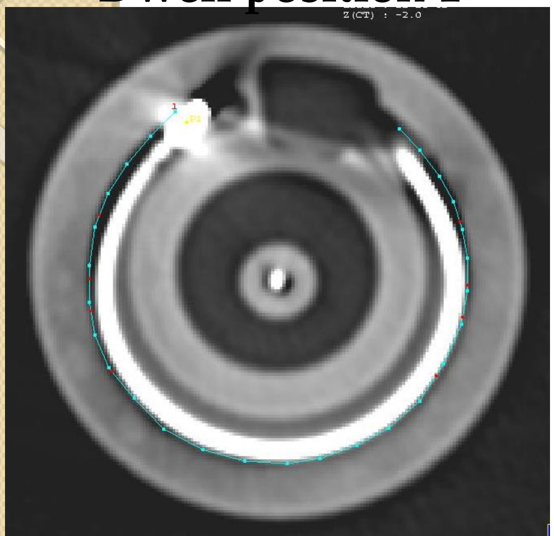
Images : Hellebust

Photo of the ring with the source

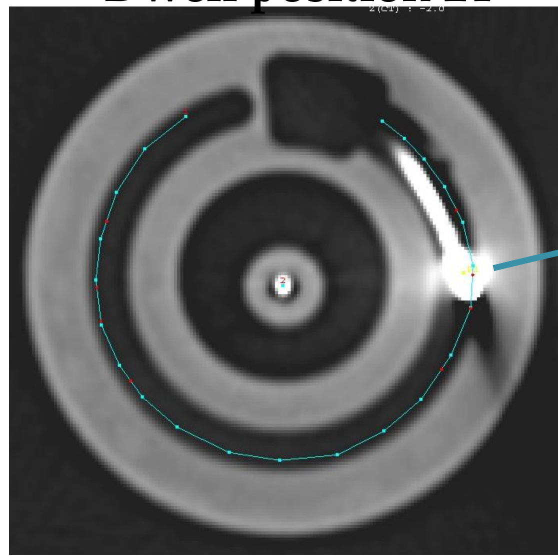


CT images of the ring with the source

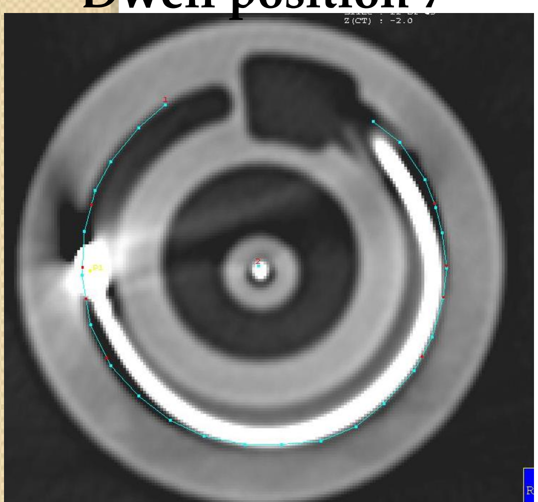
Dwell position 1

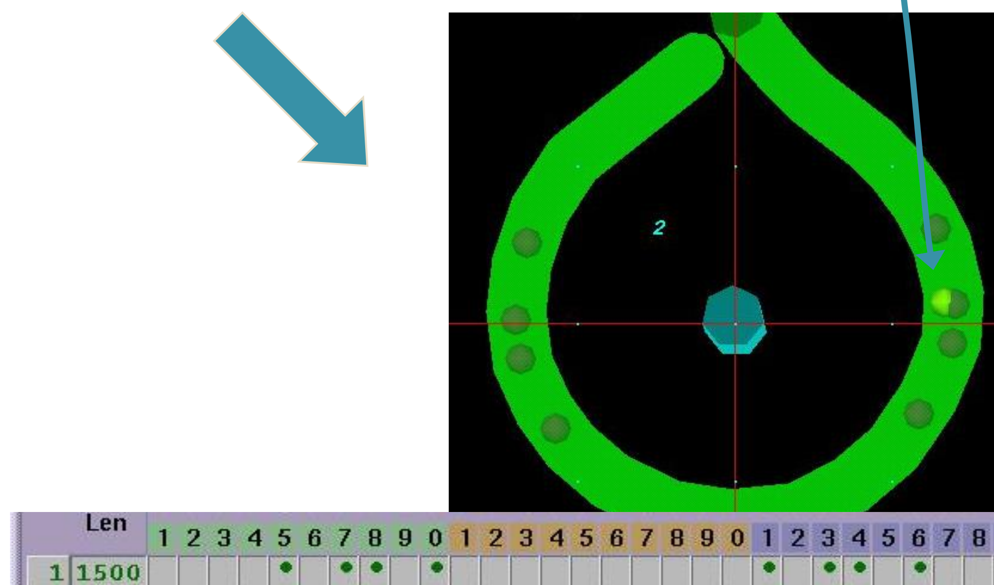


Dwell position 24



Dwell position 7





Hellebust et al, PMB 52 (2007)

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 applicator geometry
  - Choose the markers
  - CT/MR
  - Image Registration - Analyze the images
  - Auto radiograph

Applicator Reconstruction

Localization techniques

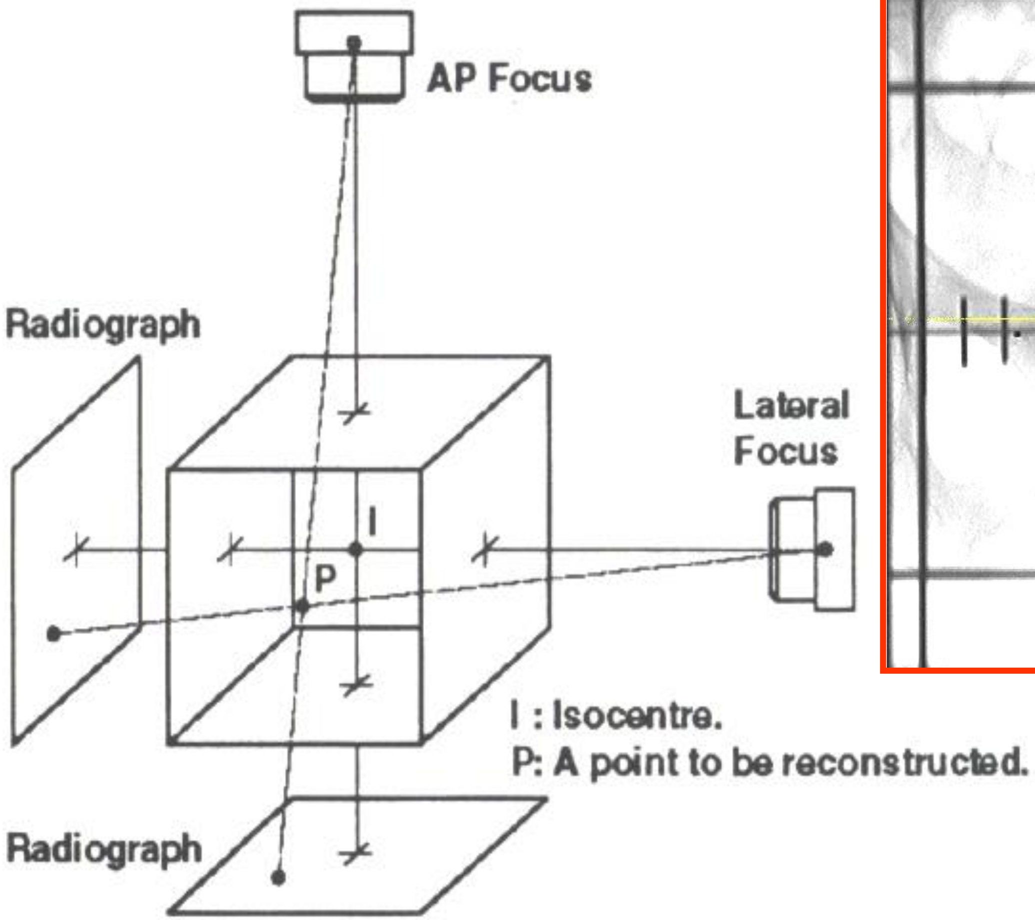
Conventional simulator, C-arm

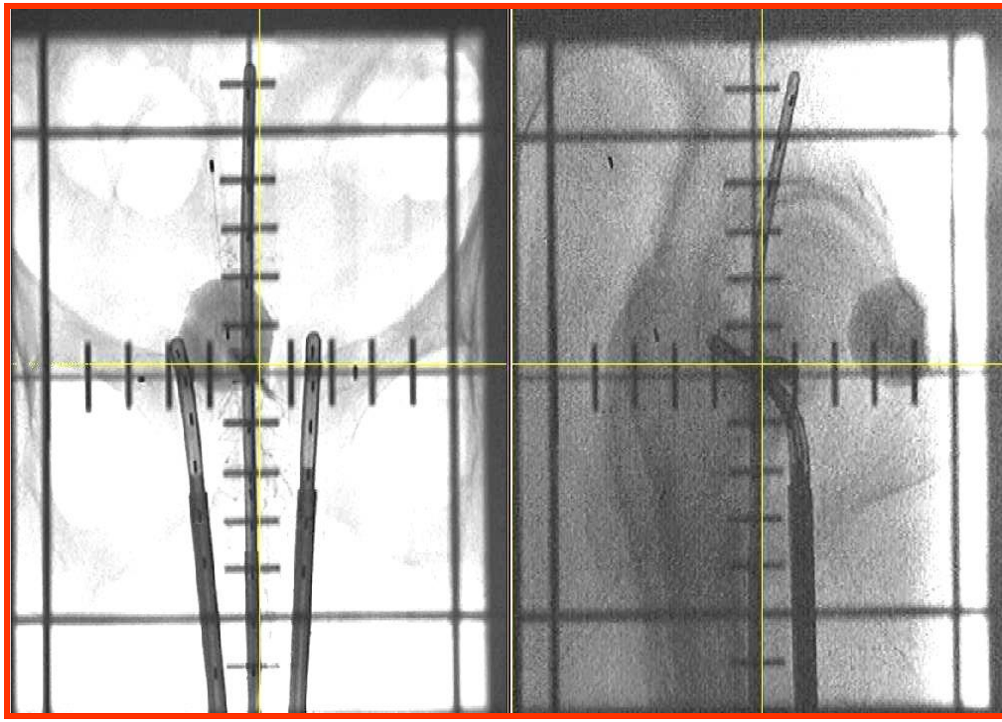
- Orthogonal images
- Semi-orthogonal
- Variable angle
- Stereo-shift

3D sectional images

- CT
- MR

Orthogonal images





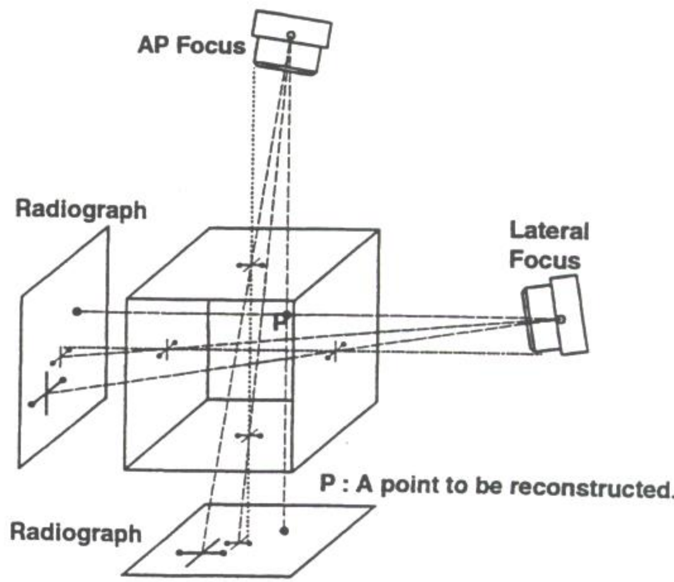
- Magnification = FFD/FAD
- Markers locked
- may not be useful for Ring applicators

From: Plato user manual

Semi-orthogonal

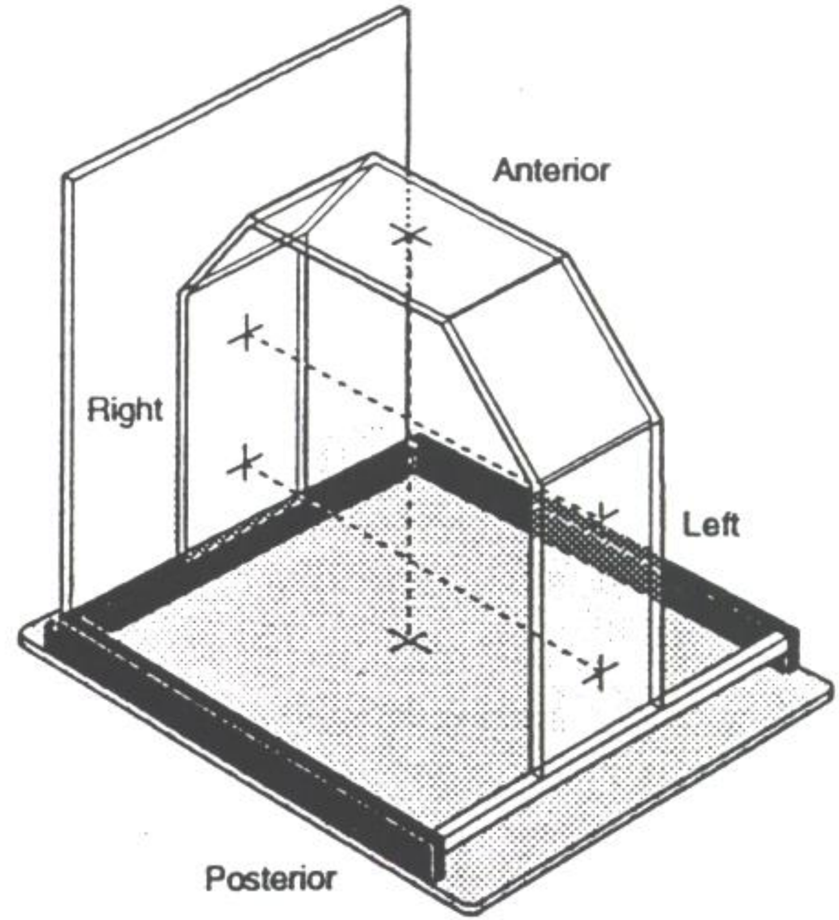
Note

If there is only a portable or mobile radiographic unit available, the semi-orthogonal reconstruction method is the only technique for treatment planning .



Reconstruction Box

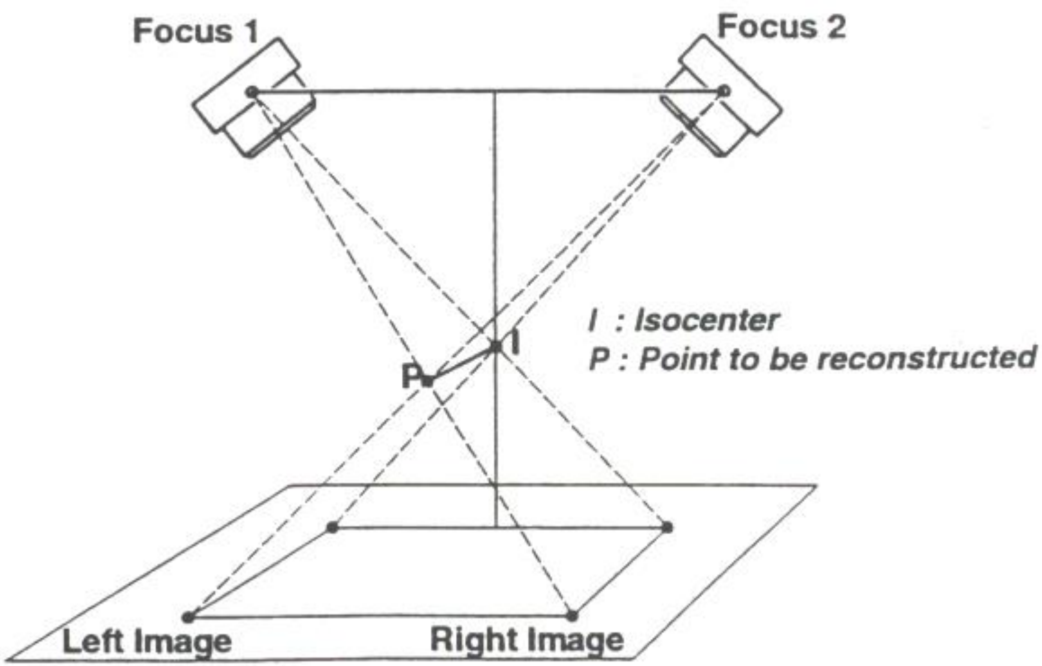
The reconstruction box is constructed with radiopaque initials AP and LAT within the appropriate sides of the box. These initials will appear on the radiograph as a large AP image which corresponds



From: Plato user manual

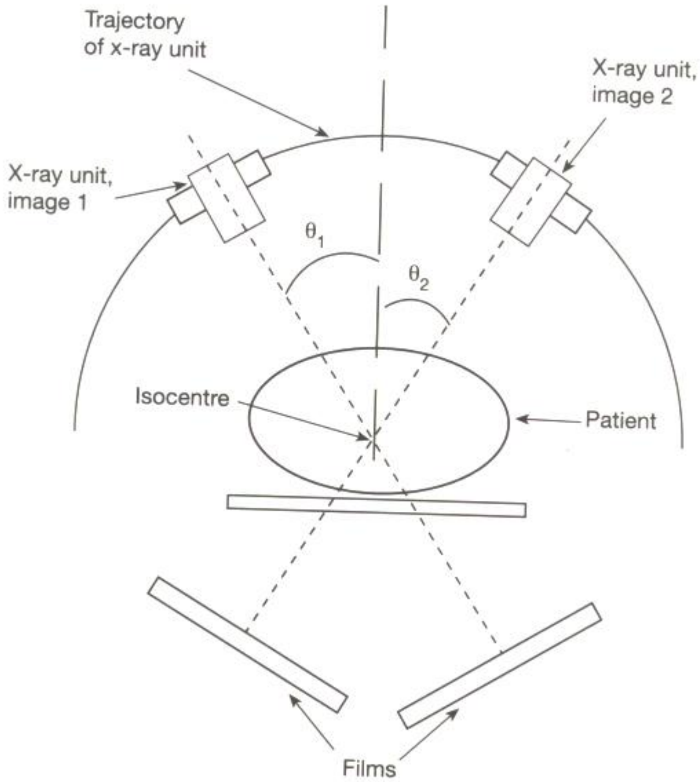
Stereo-shift

This method is particularly useful
when only an X-ray unit is available for localization

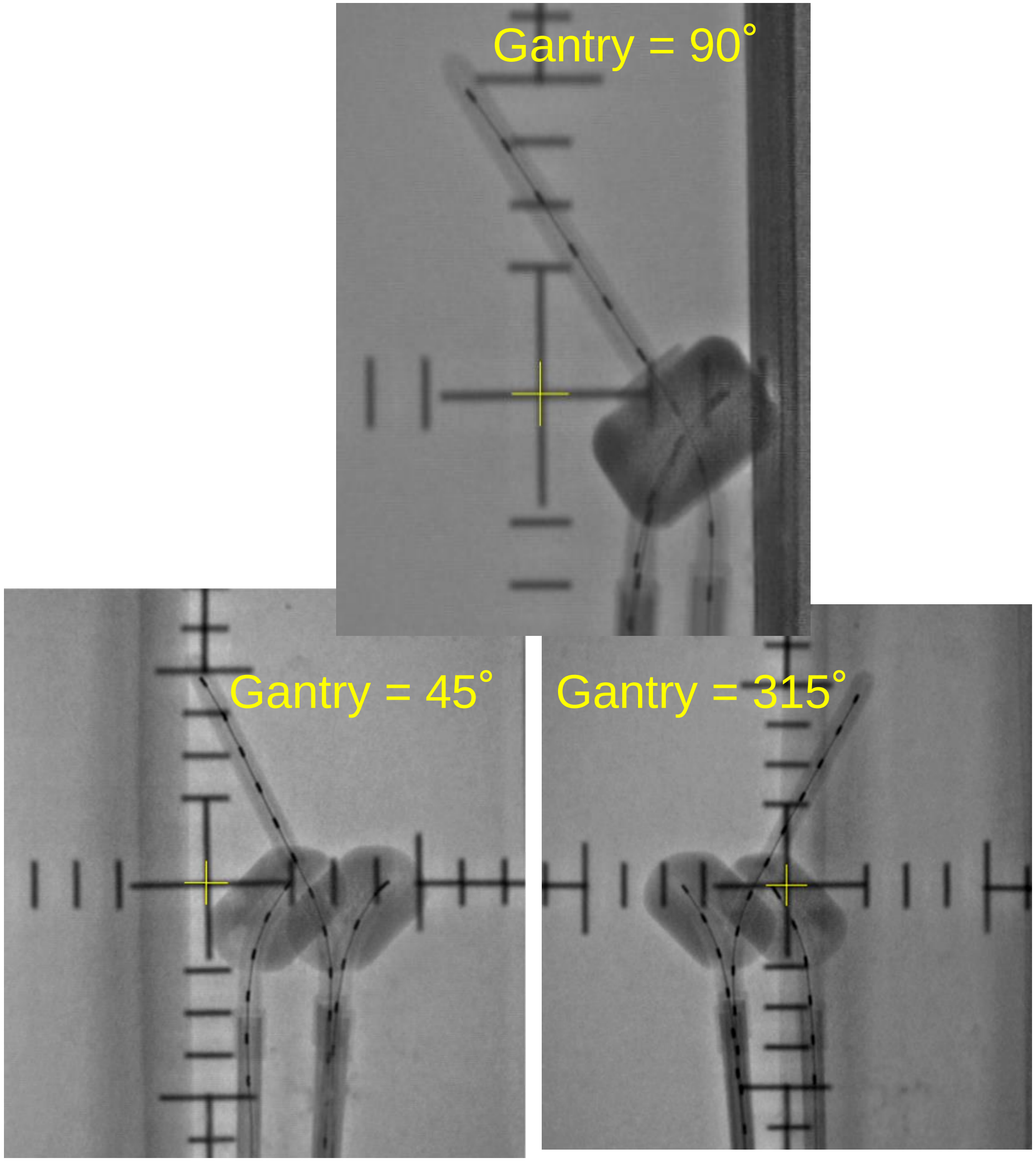


From: Plato user manual

Variable angle



From: Thomadsen "Achieving quality in brachytherapy", IoP 2000

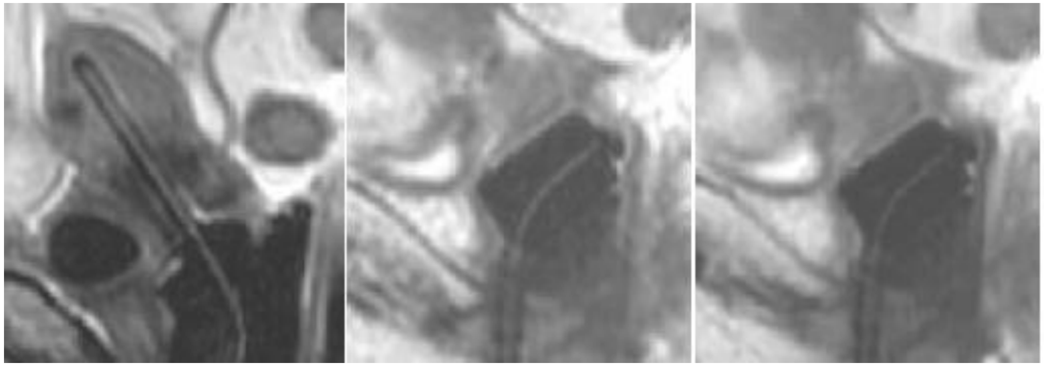


Reconstruction

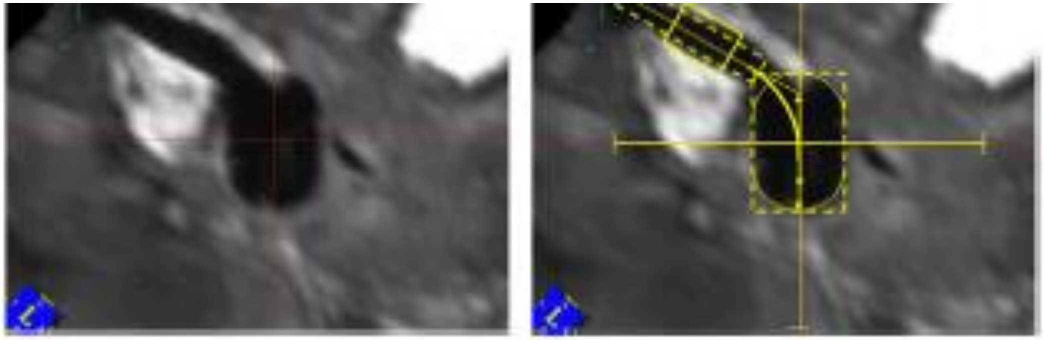
- Direct reconstruction
- Library of applicators

Direct Reconstruction

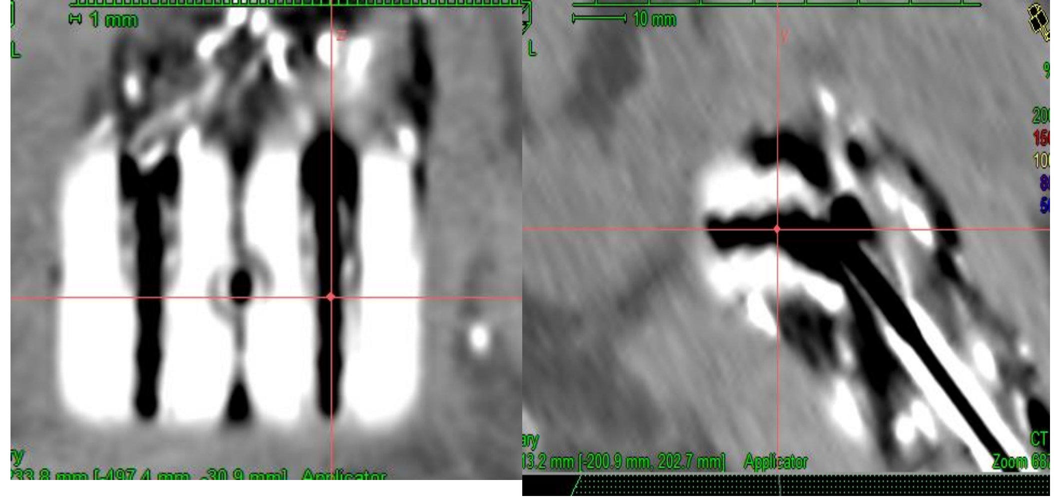
- Clear visualization of the source channels in a single plane.
- Check the geometry of the applicator verified during commissioning.
- Especially useful for curved applicators (ovoid/ring)

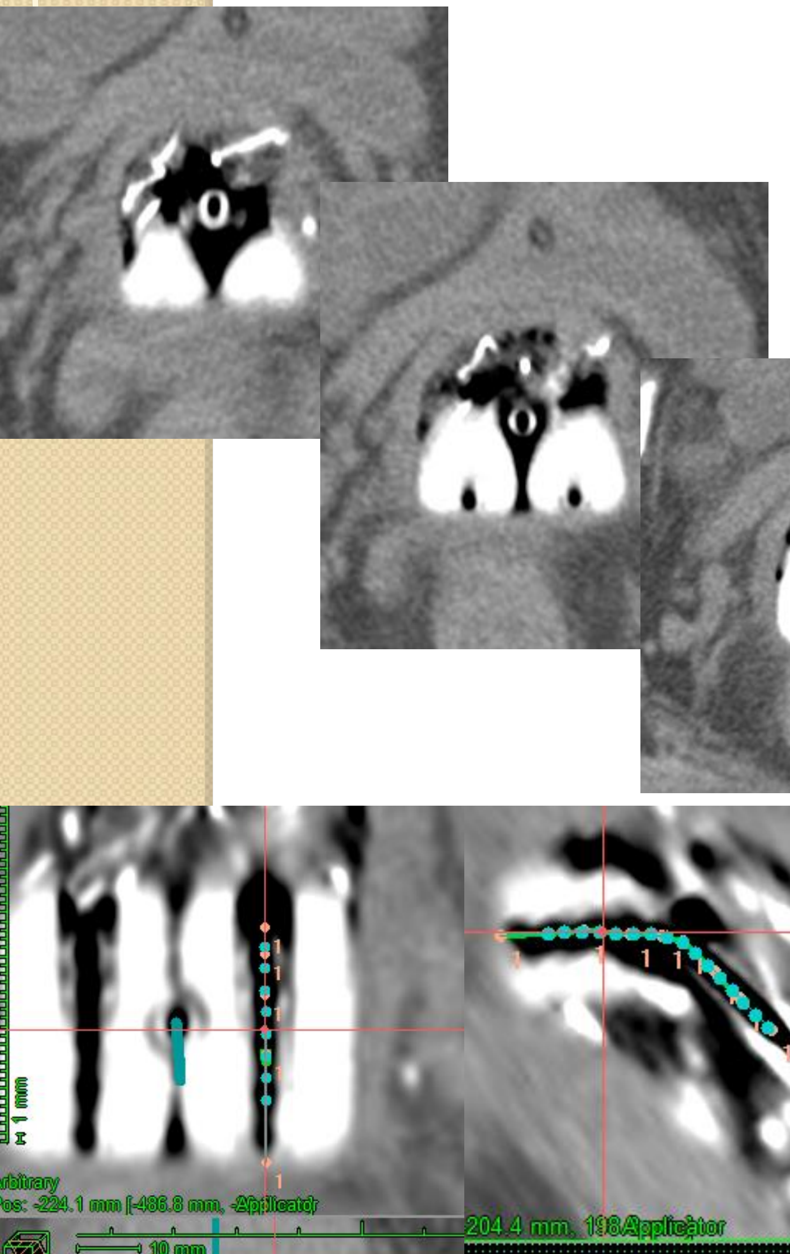


Leeuw et al, RO,2009



DR - T/O





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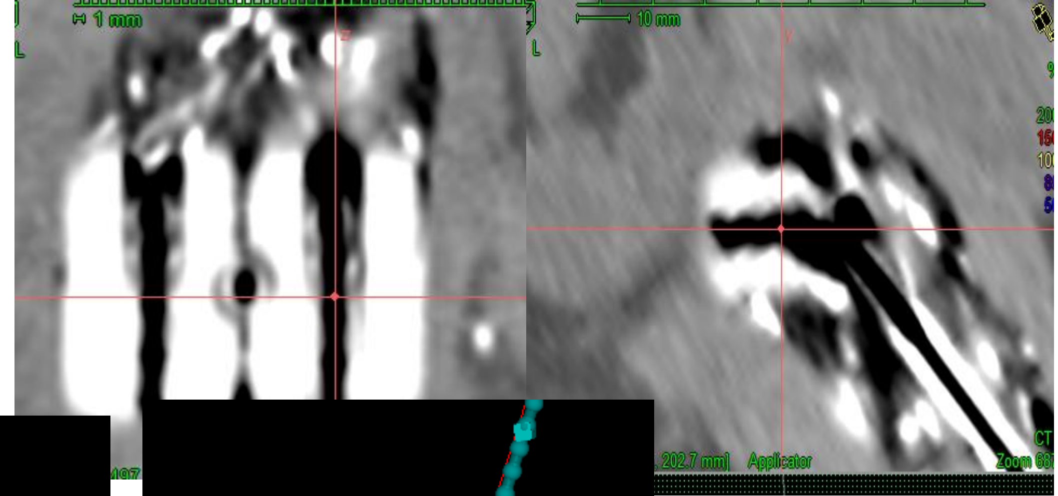
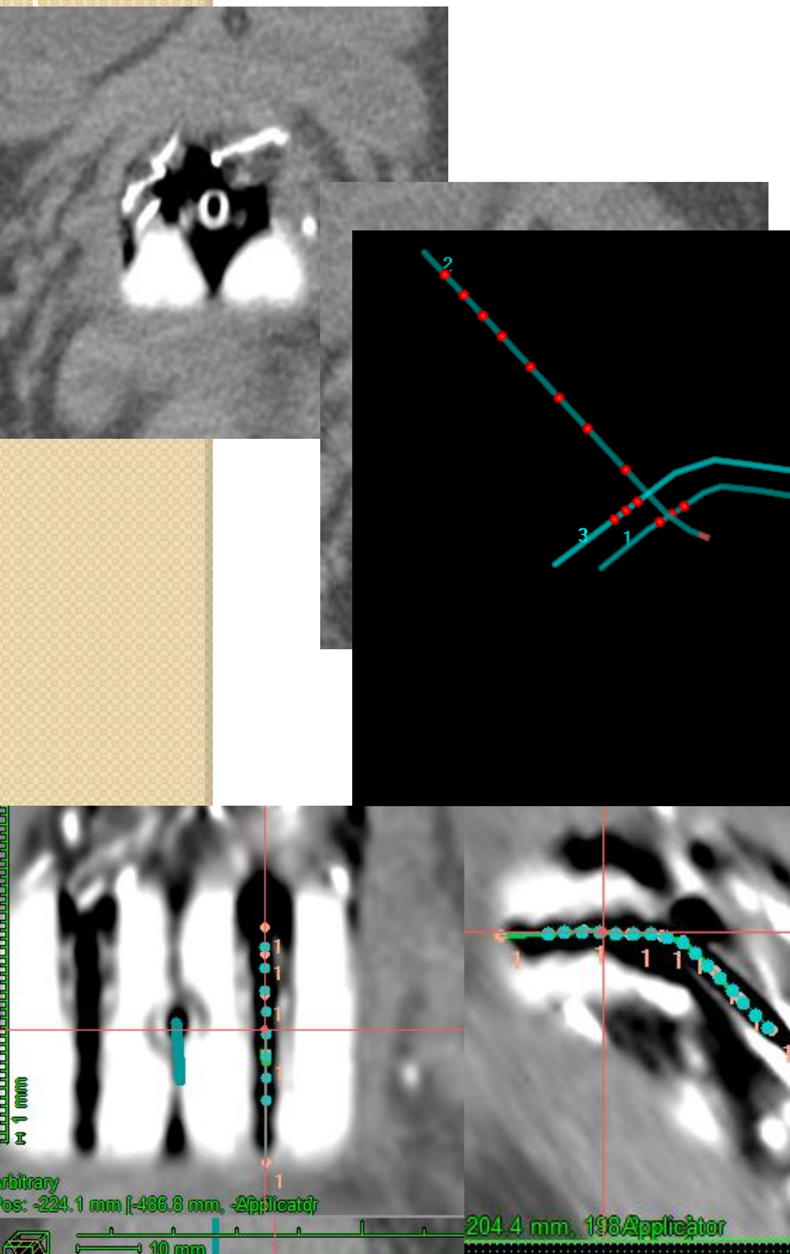
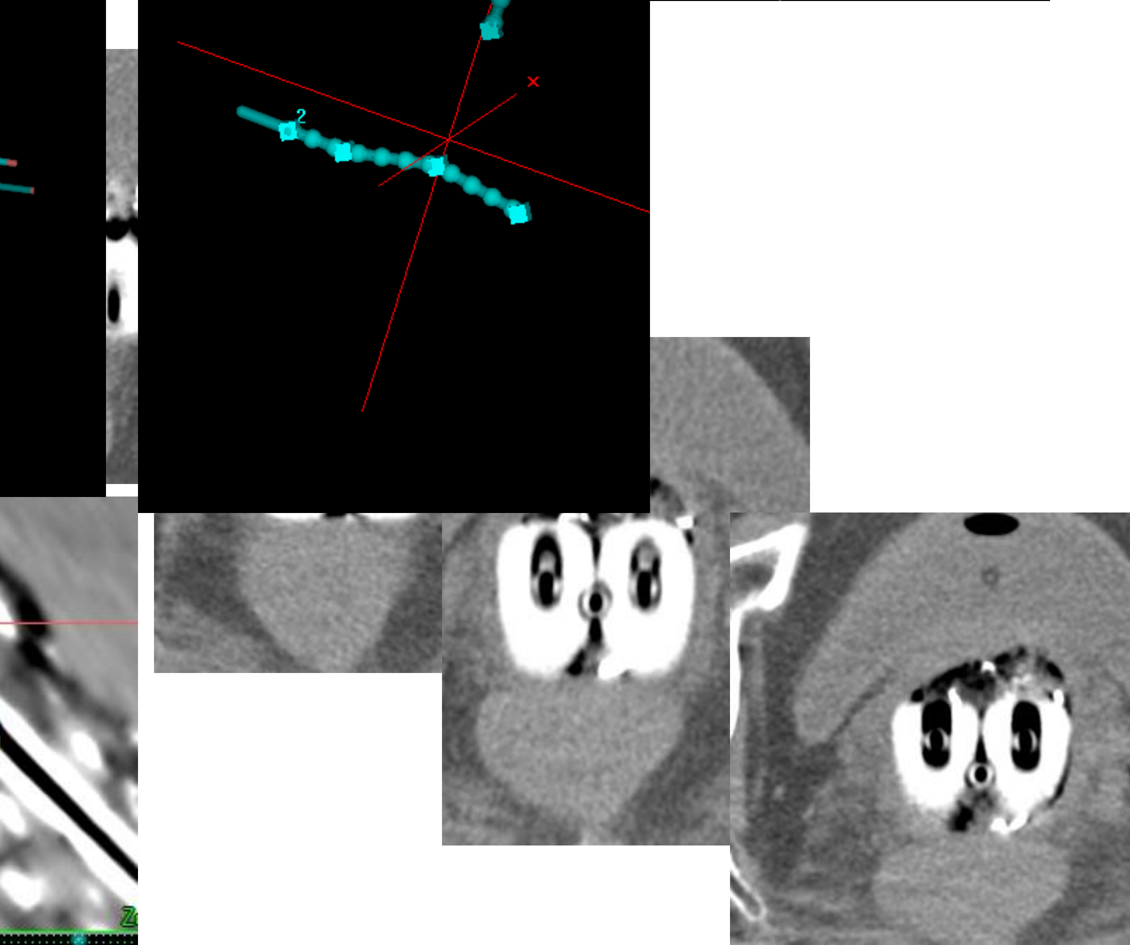
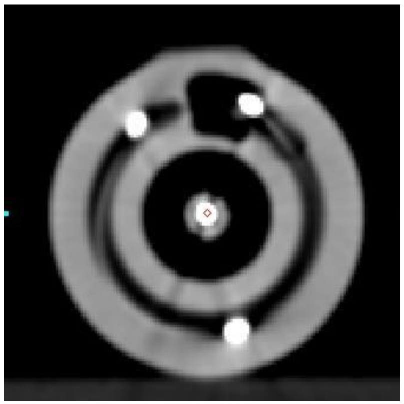


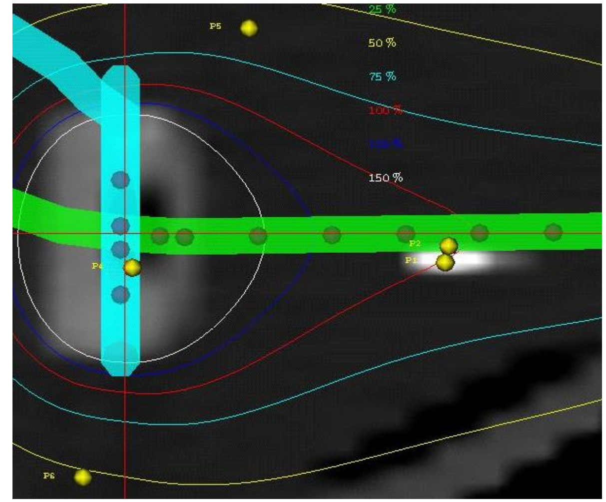




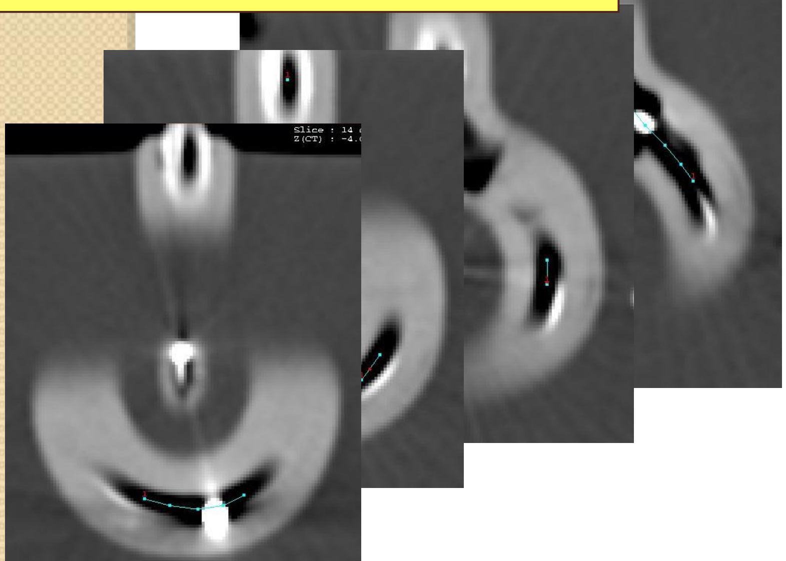
DR - Ring

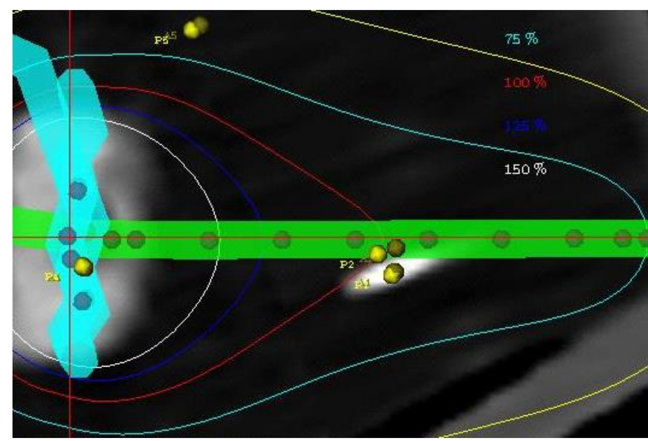
Ring in one slice





Ring in several slices

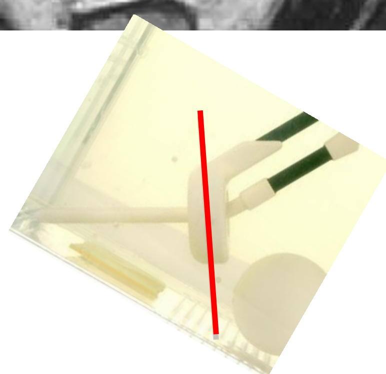




Ack: Hellebust

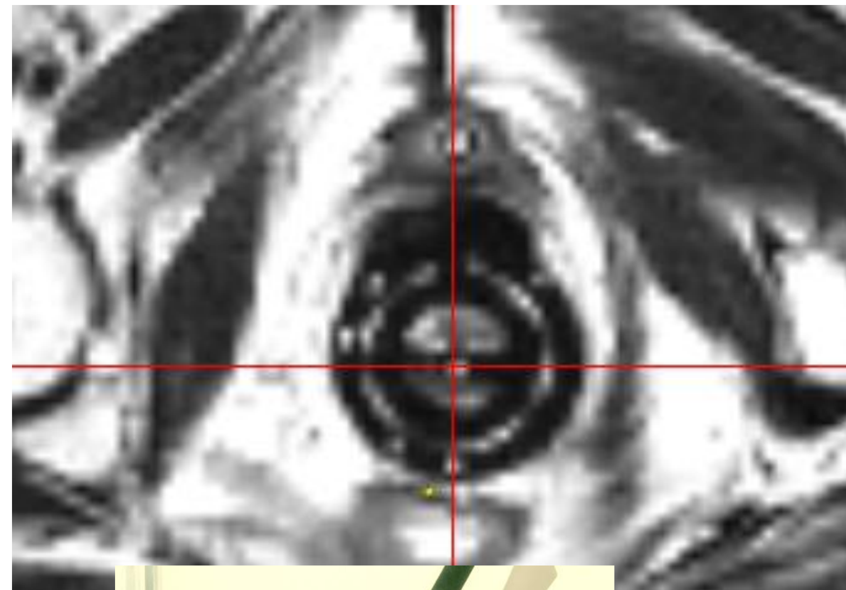
Orientation of the imaging sequence

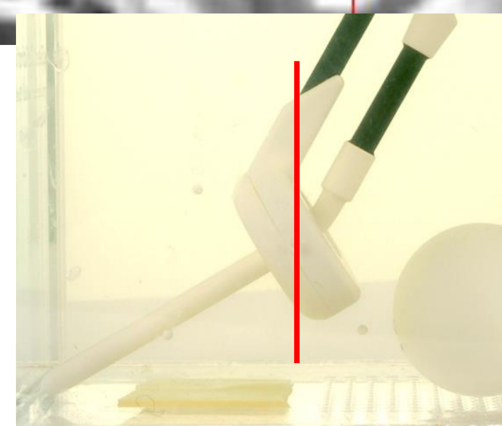
- Para transverse



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

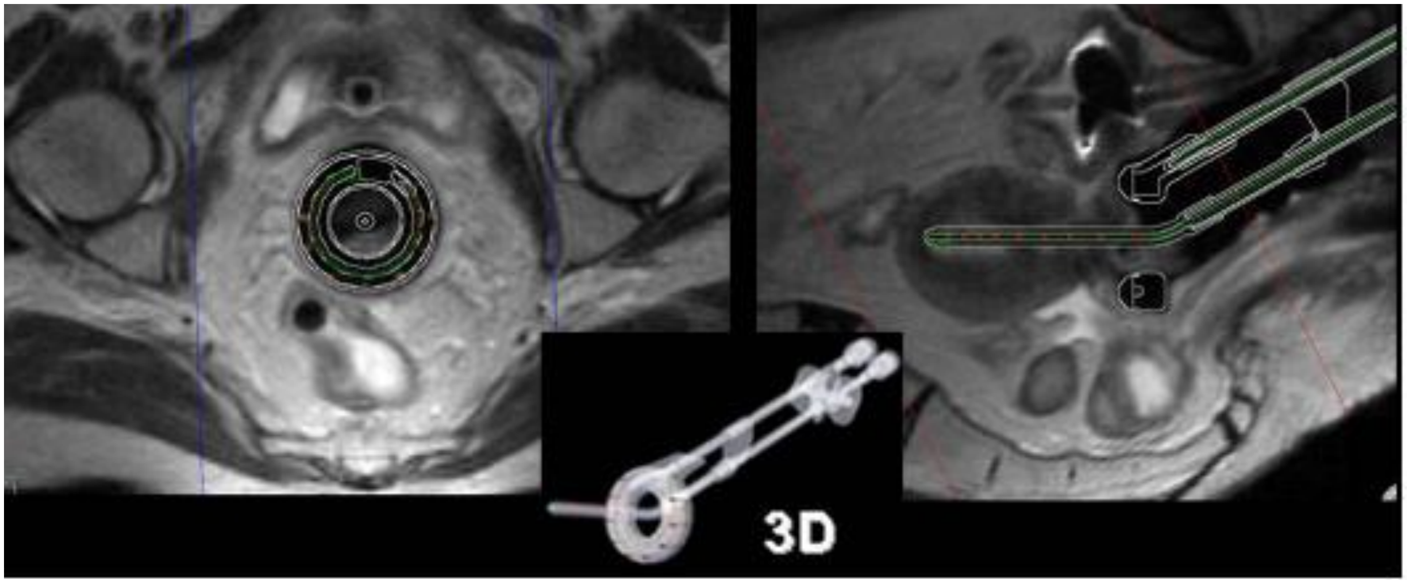
- Transverse (MP Reconstructed)



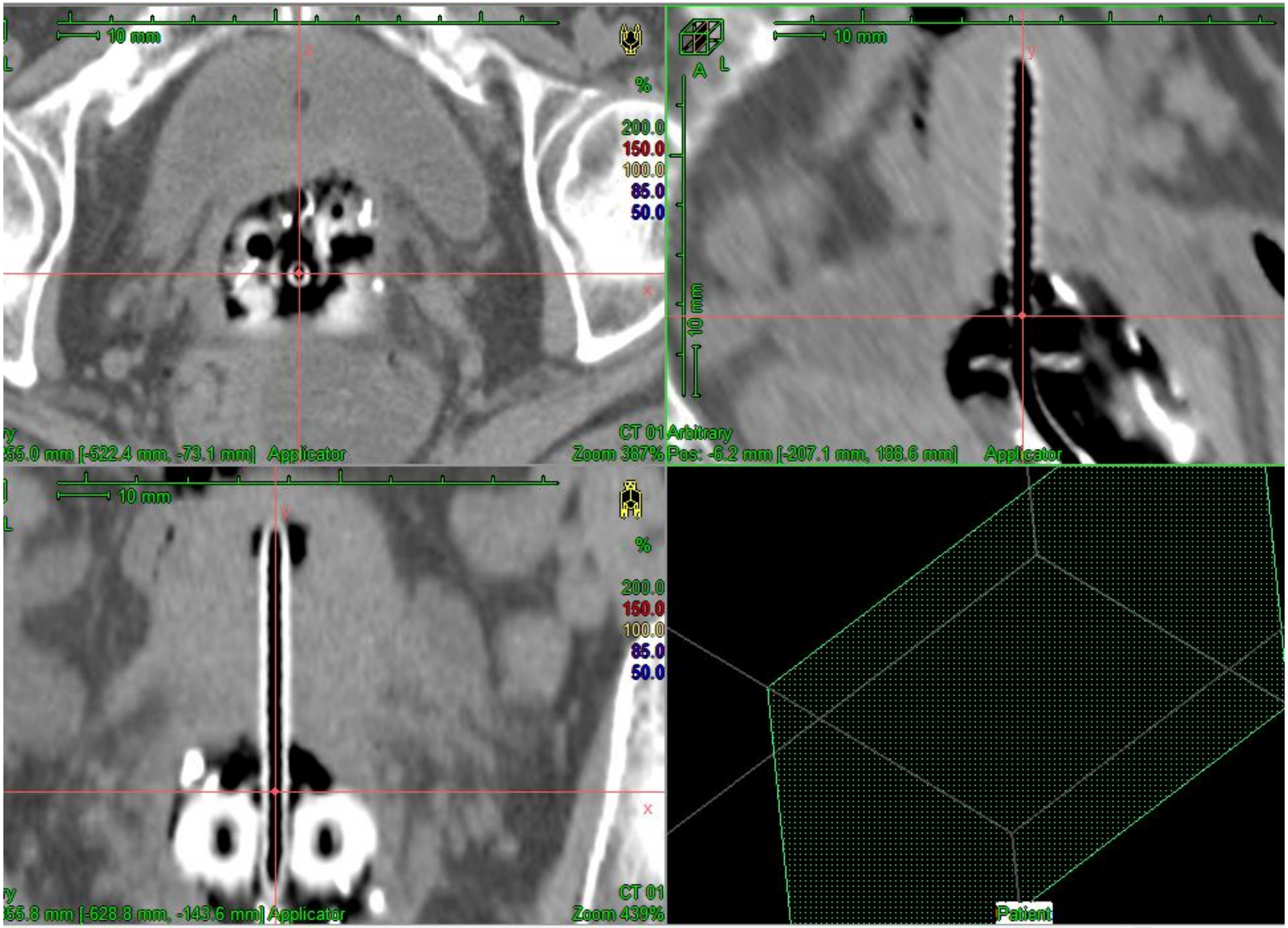


Library of applicators

- 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

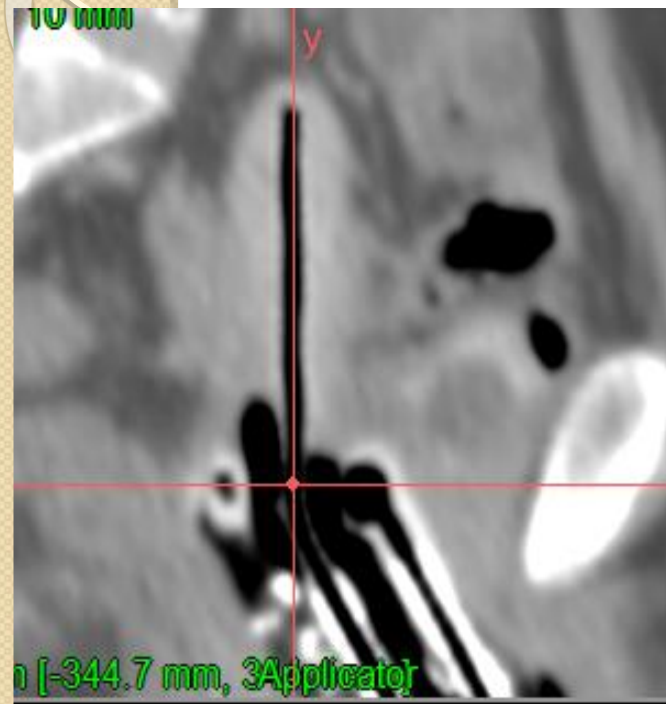


Applicator reconstruction using MR images

Markers: water filled 6F catheters

Role of Registration in applicator reconstruction

Role of registration: applicator Reconstruction

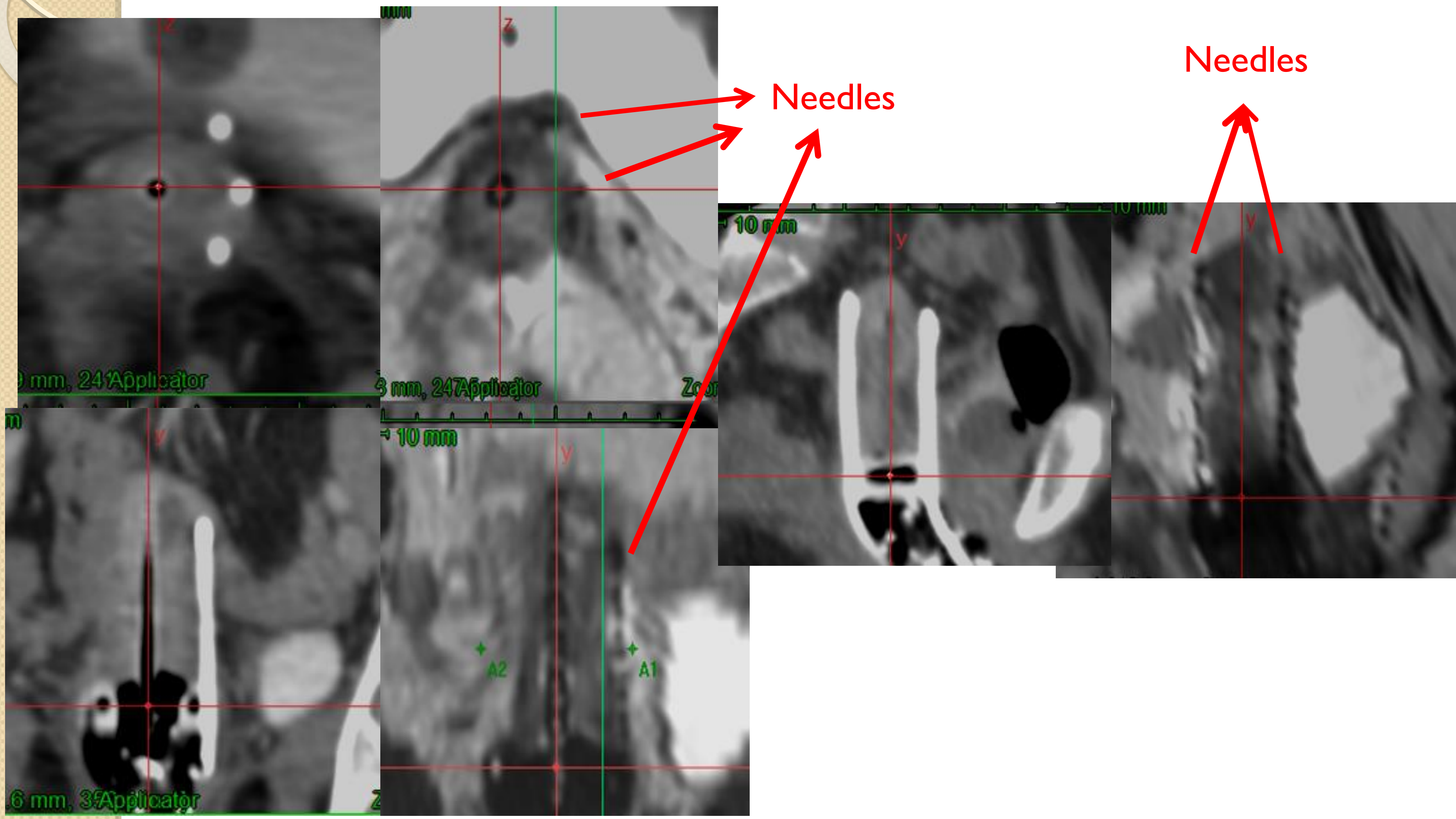


CT – No marker

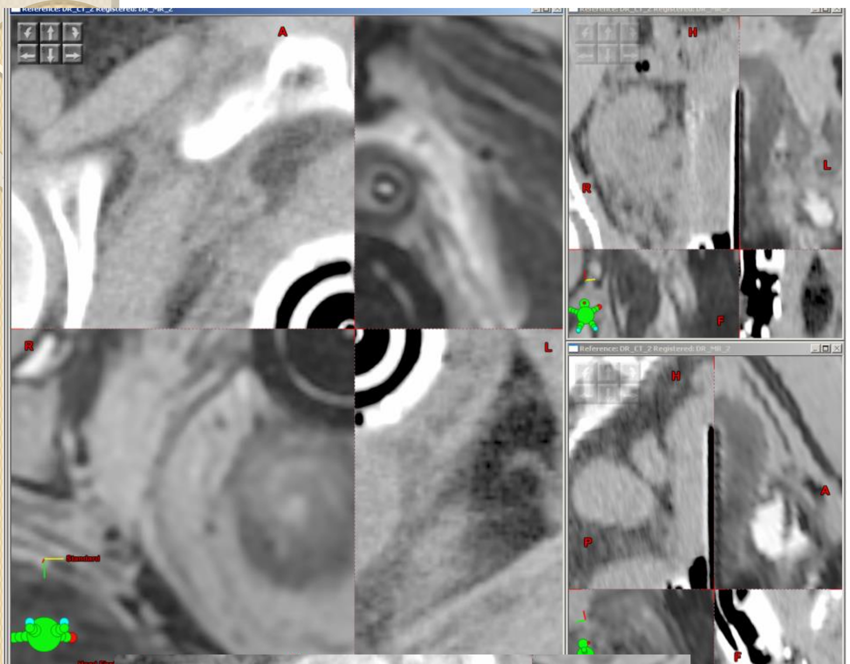
MR – No marker

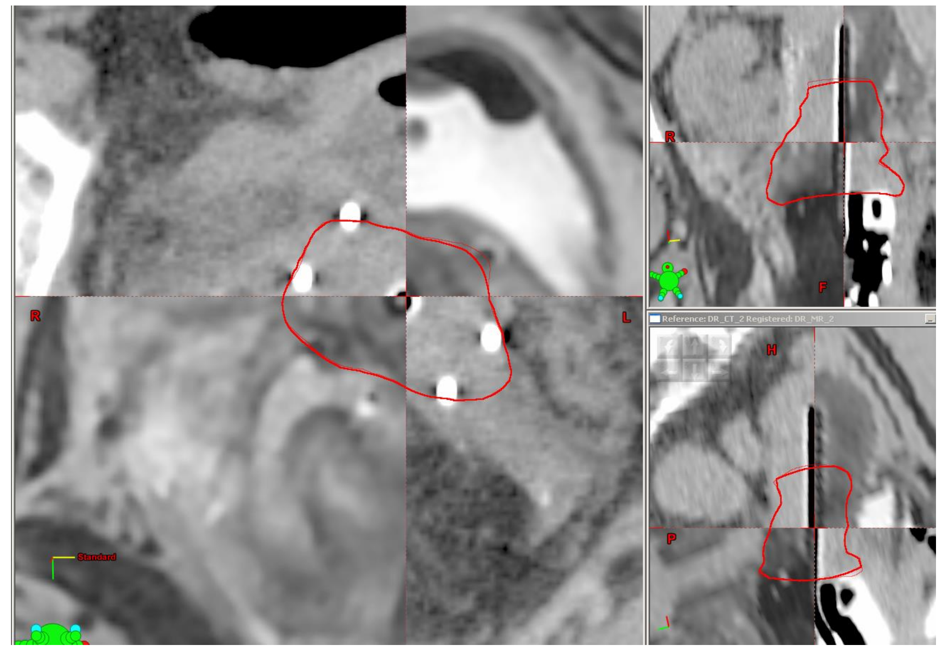
MR – Water marker

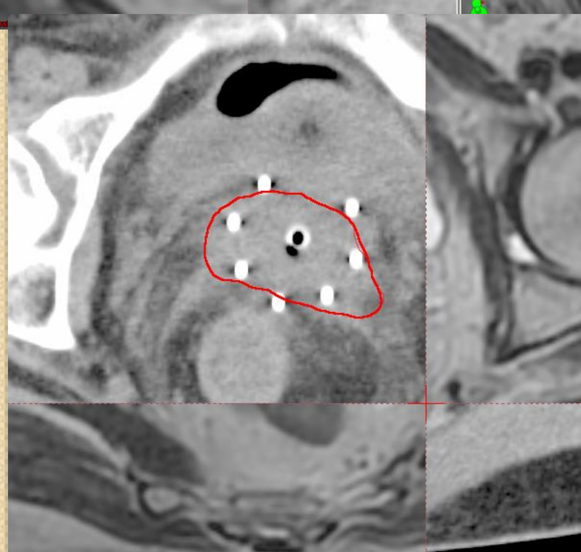
Role of registration: applicator Reconstruction : needles

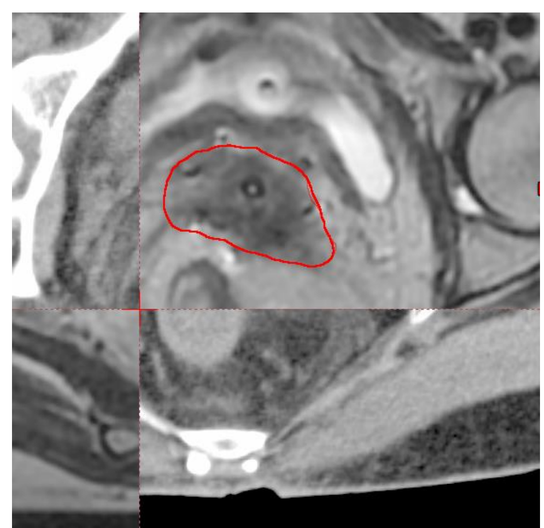


CT vs MR

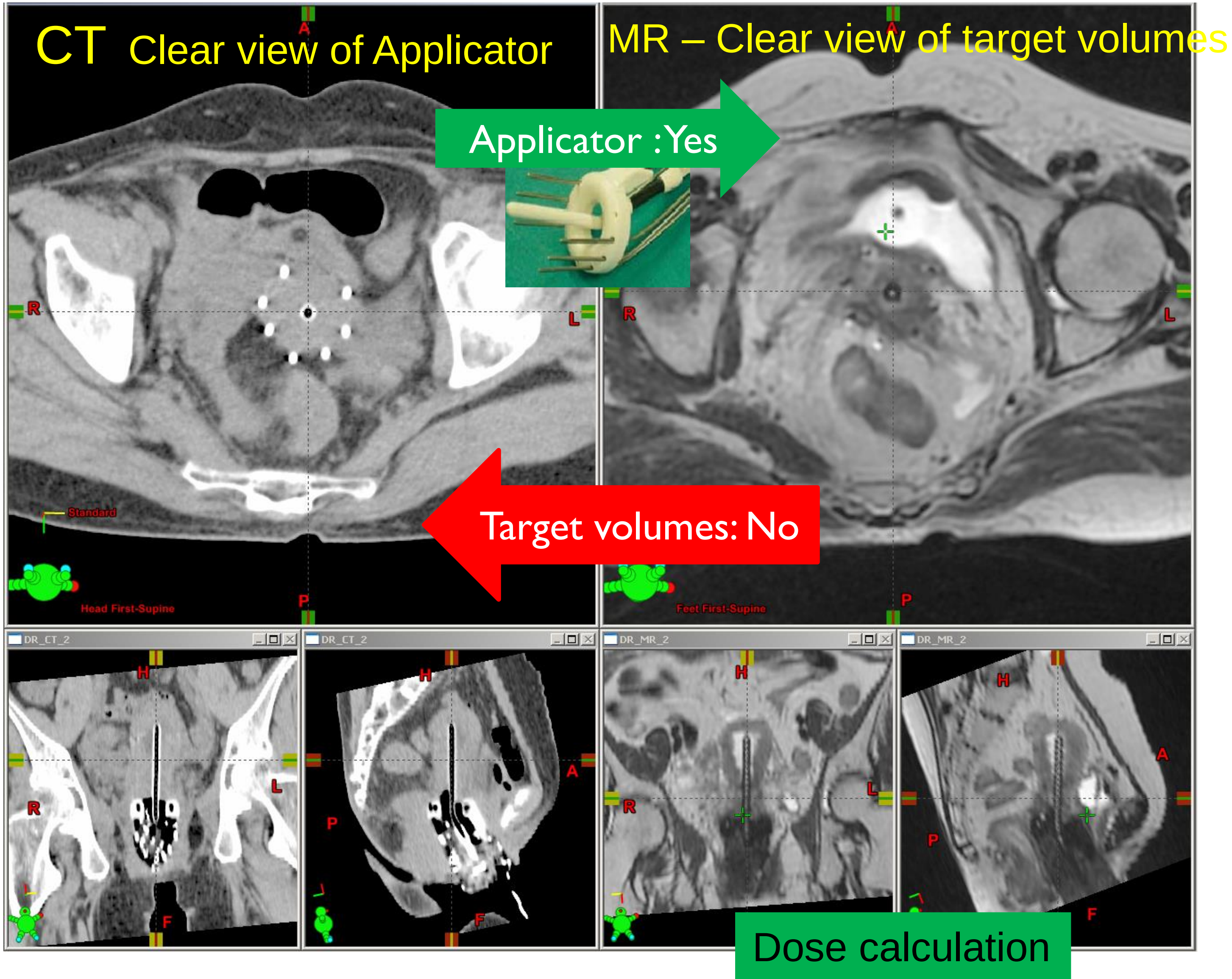




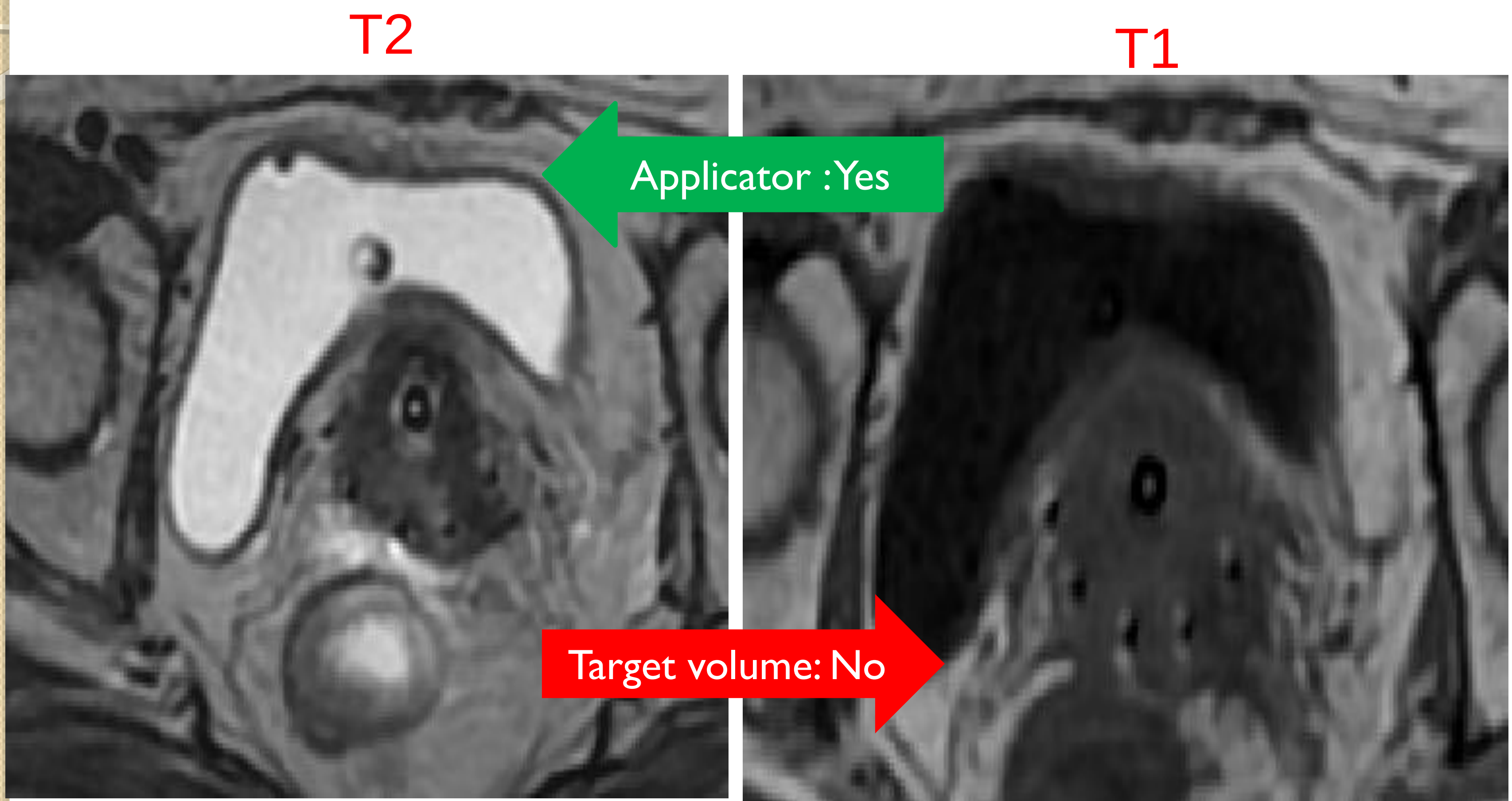




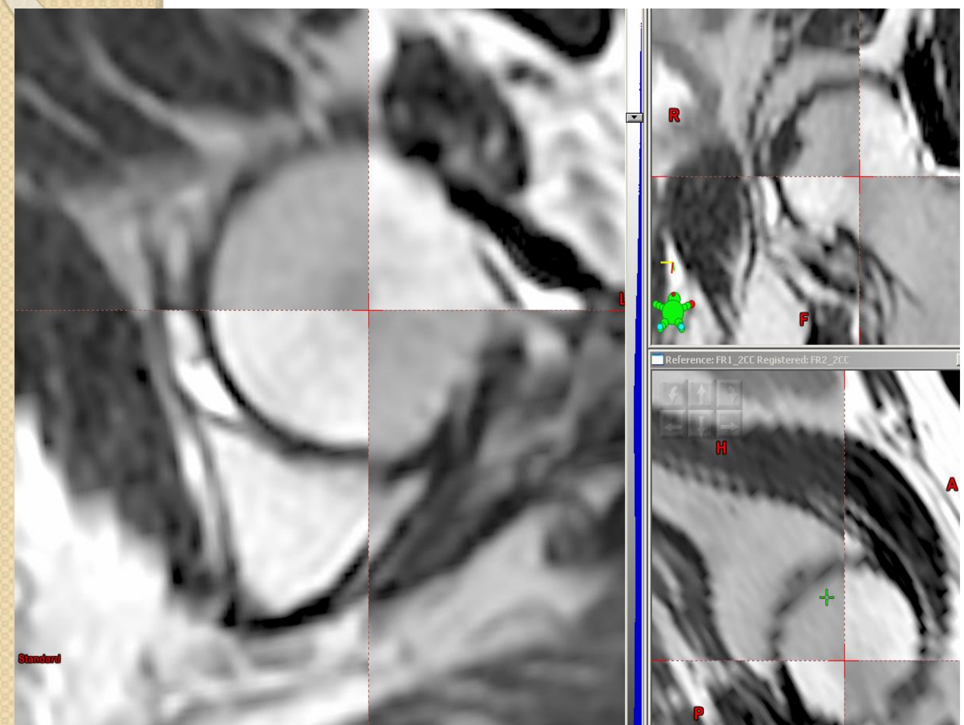
Registration of CT vs MR – Reconstruction



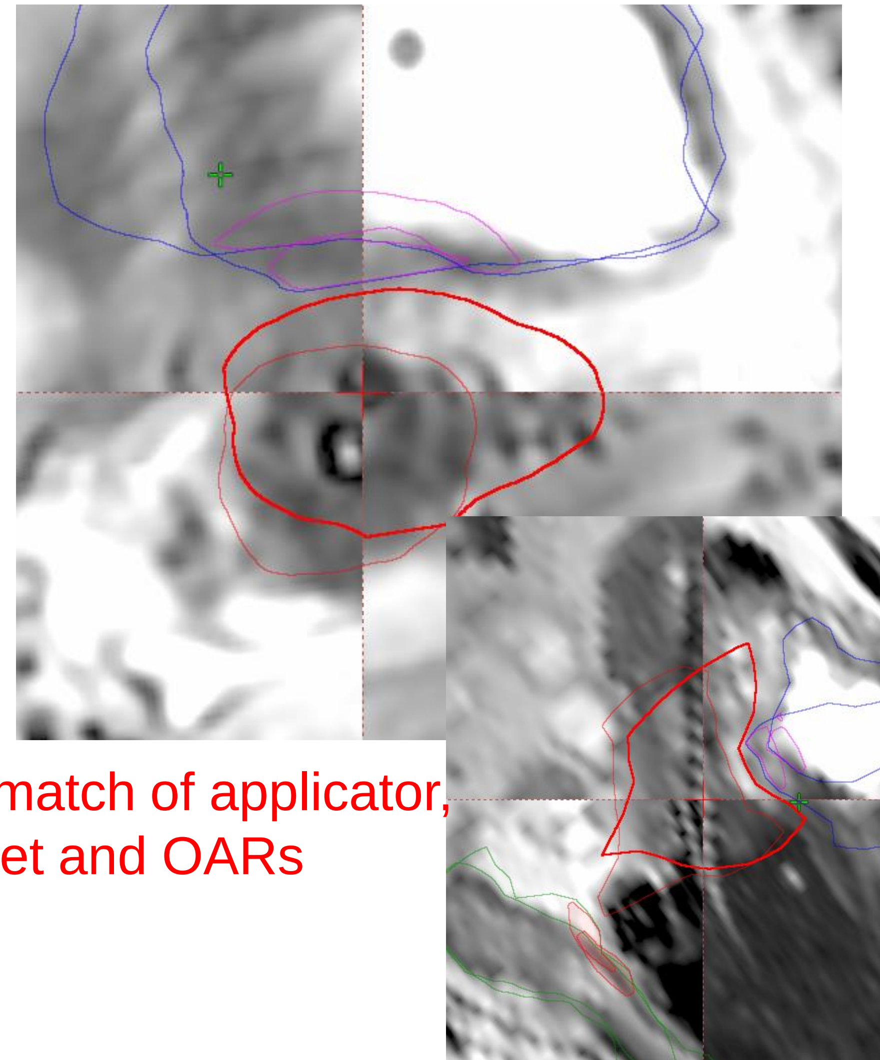
Registration of T1 vs T2 for Reconstruction



Registration in Brachytherapy – Bone as a reference ? No

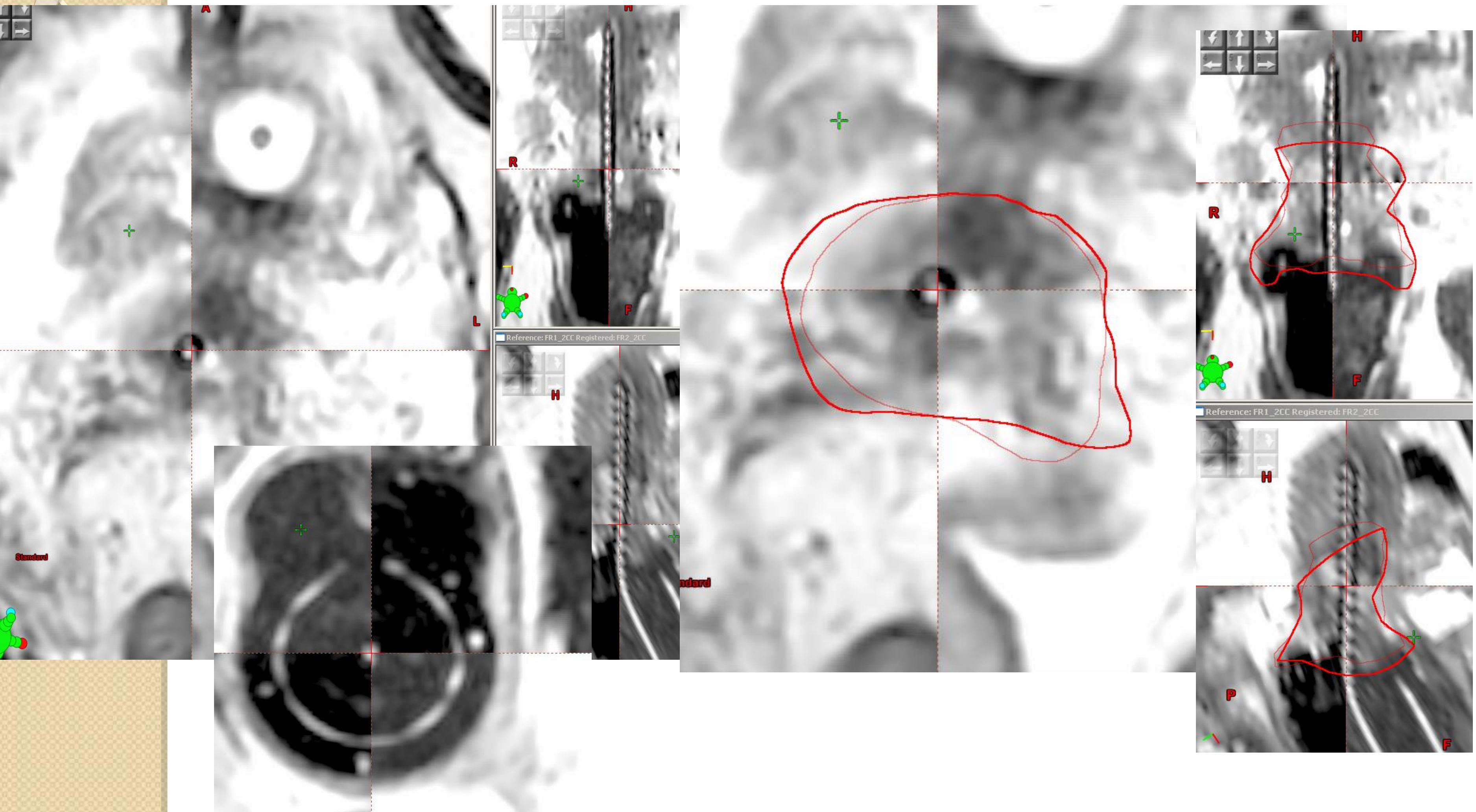


Good matching of bones



Mismatch of applicator, target and OARs

Registration in Brachytherapy – applicator as a reference? -Yes



Anatomy moves with the applicator in BT

Summary

- Applicator reconstruction
  - Direct reconstruction
  - Library of applicators

- Registration
  - Applicator reconstruction based on bony anatomy

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

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

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ESTRO European Society for RADIOTHERAPY & ONCOLOGY

I C R U

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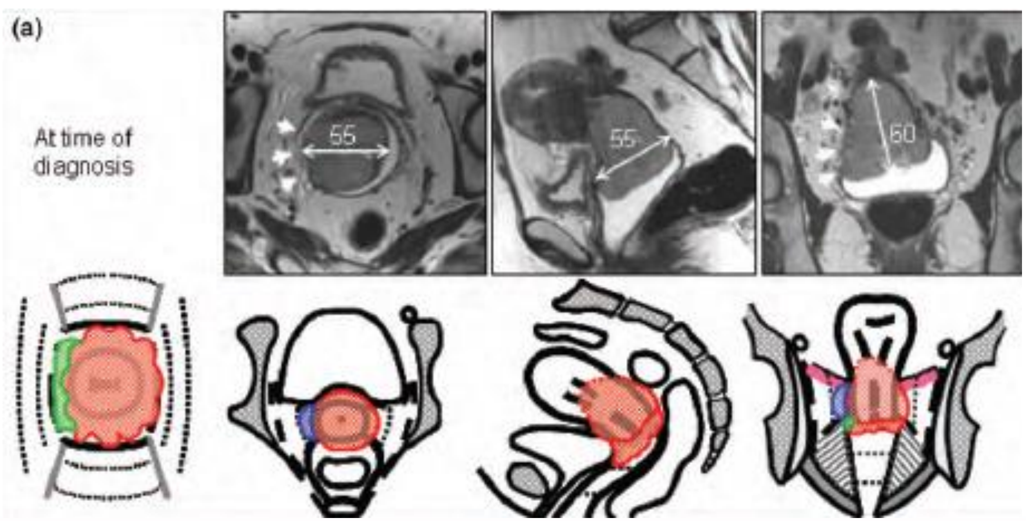
INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS

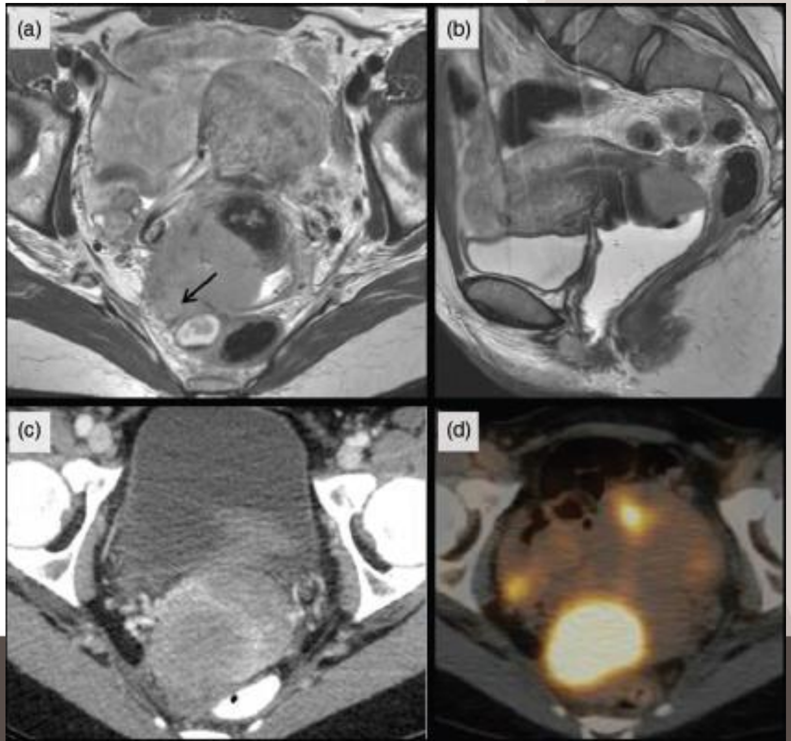
Tumor and target volume definitions for the primary tumor

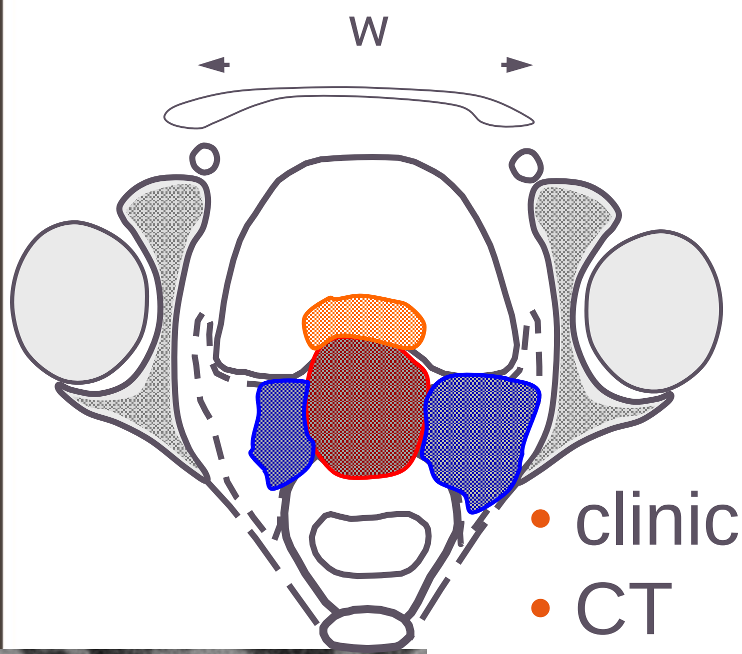
- GTV for the primary tumor (GTV-T)
- CTV for the primary tumor (CTV-T)
- Residual GTV-T ($GTV\text{-}T_{res}$)
- Adaptive CTV-T ($CTV\text{-}T_{adapt}$)
- High-Risk CTV-T ($CTV\text{-}T_{HR}$)
- Intermediate-Risk CTV-T ($CTV\text{-}T_{IR}$)
- Low-Risk CTV-T ($CTV\text{-}T_{LR}$)
- Planning Target Volume (PTV-T)

GTV for the primary tumor (GTV-T)

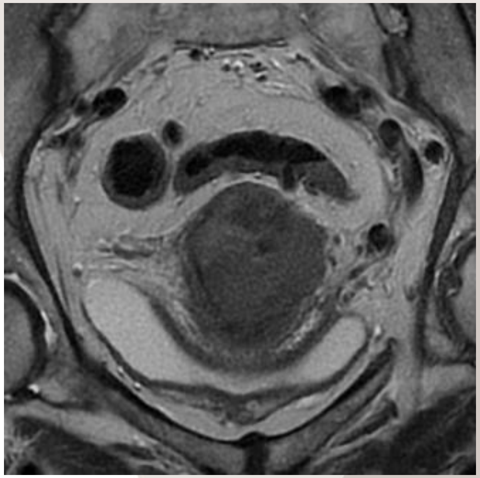
- basis for treatment prescription and planning
- clinical, imaging, and/or pathology investigations assessment
- represents macroscopic demonstrable disease for the primary tumor according to the UICC TNM classification
- composite GTV-T
- context of adaptive radiotherapy : GTV-T_{init} to distinguish this from the GTV-T_{res}



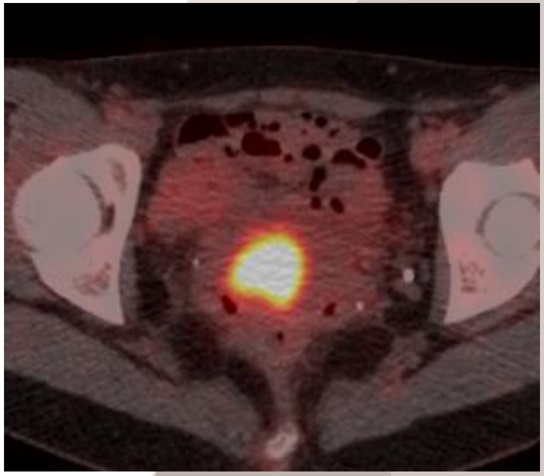




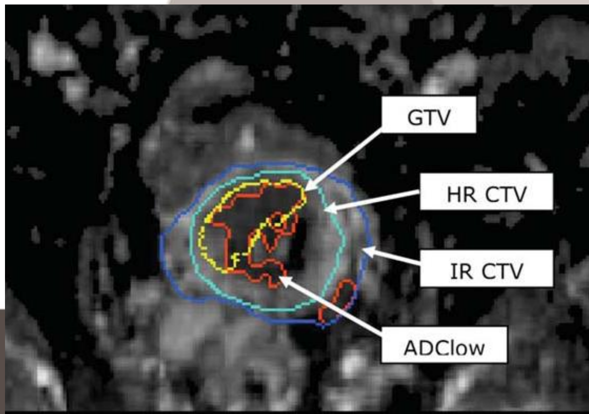
GTV_{init}



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

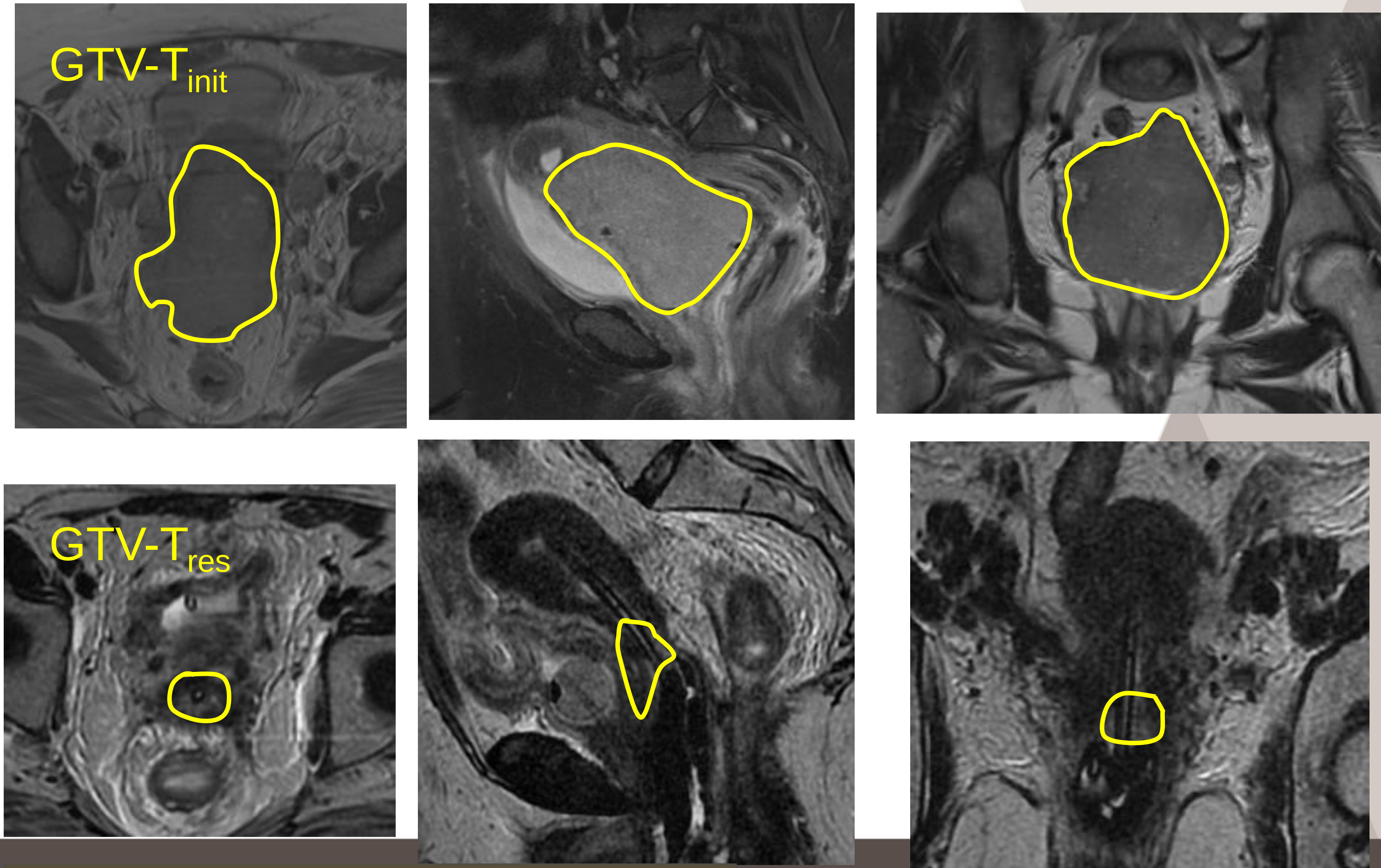


Composite GTV



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

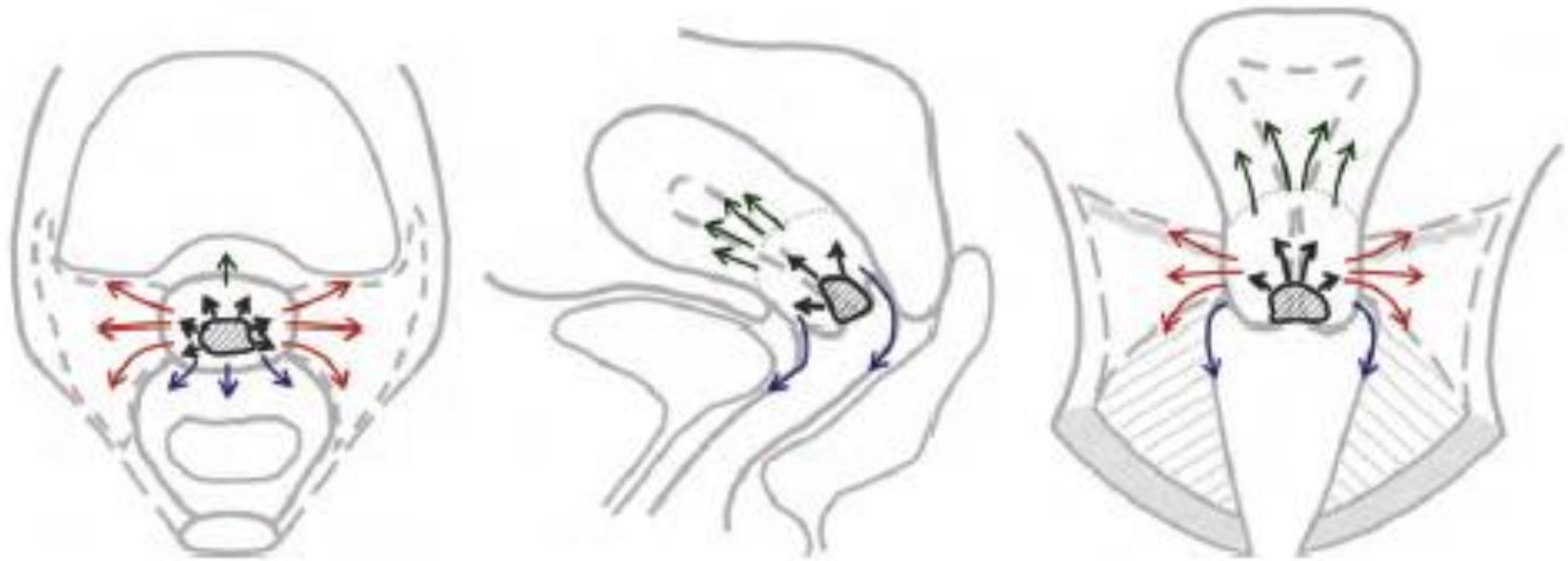


Figure 5.5. Schematic axial (left) mid-sagittal (middle) and mid-coronal (right) views of typical cervix cancer growth in—and outside—th cervix with extra-cervical infiltration into adjacent structures such as parametria, uterine corpus, vagina [see also electronic appendi Gyn GEC ESTRO Rec II (Lim *et 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”

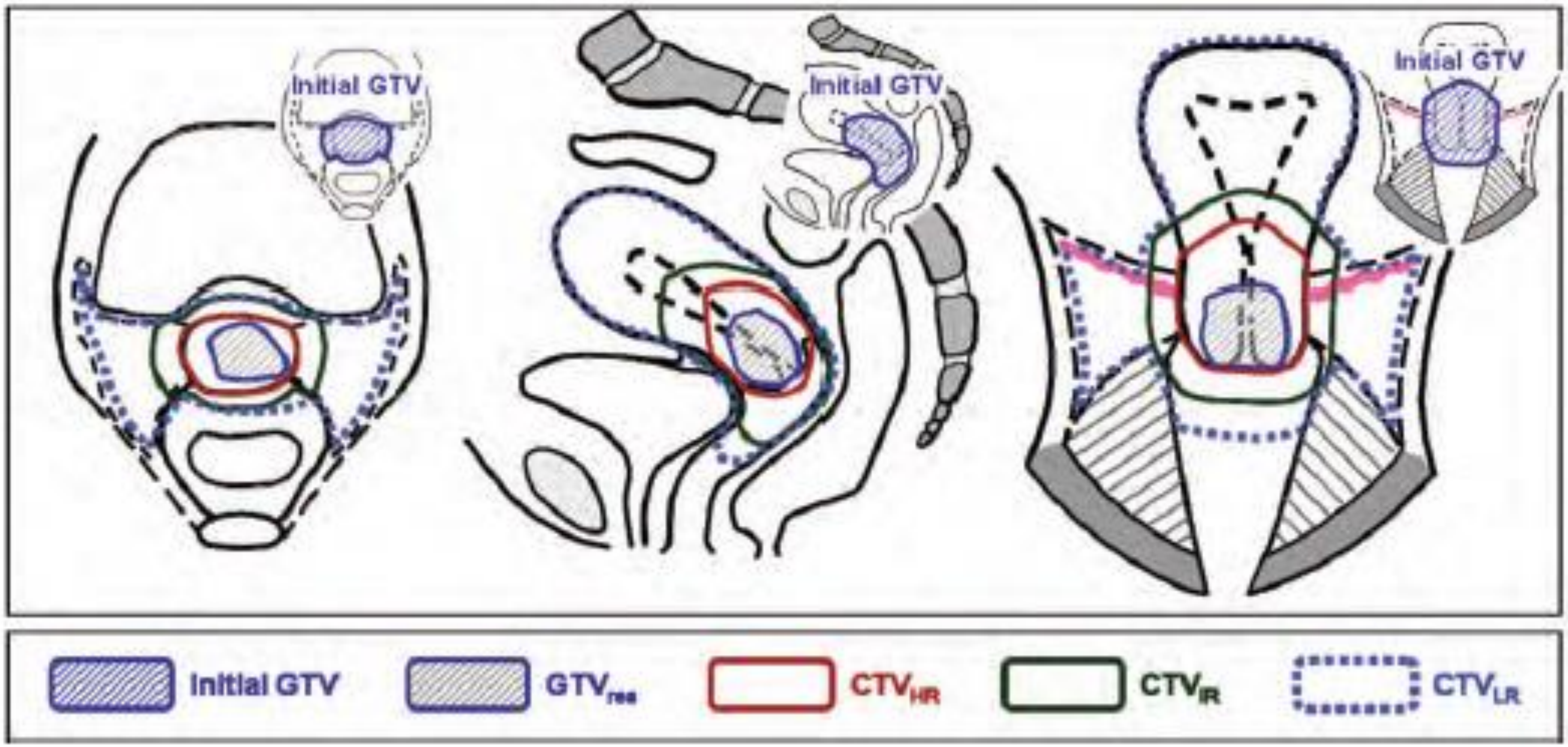
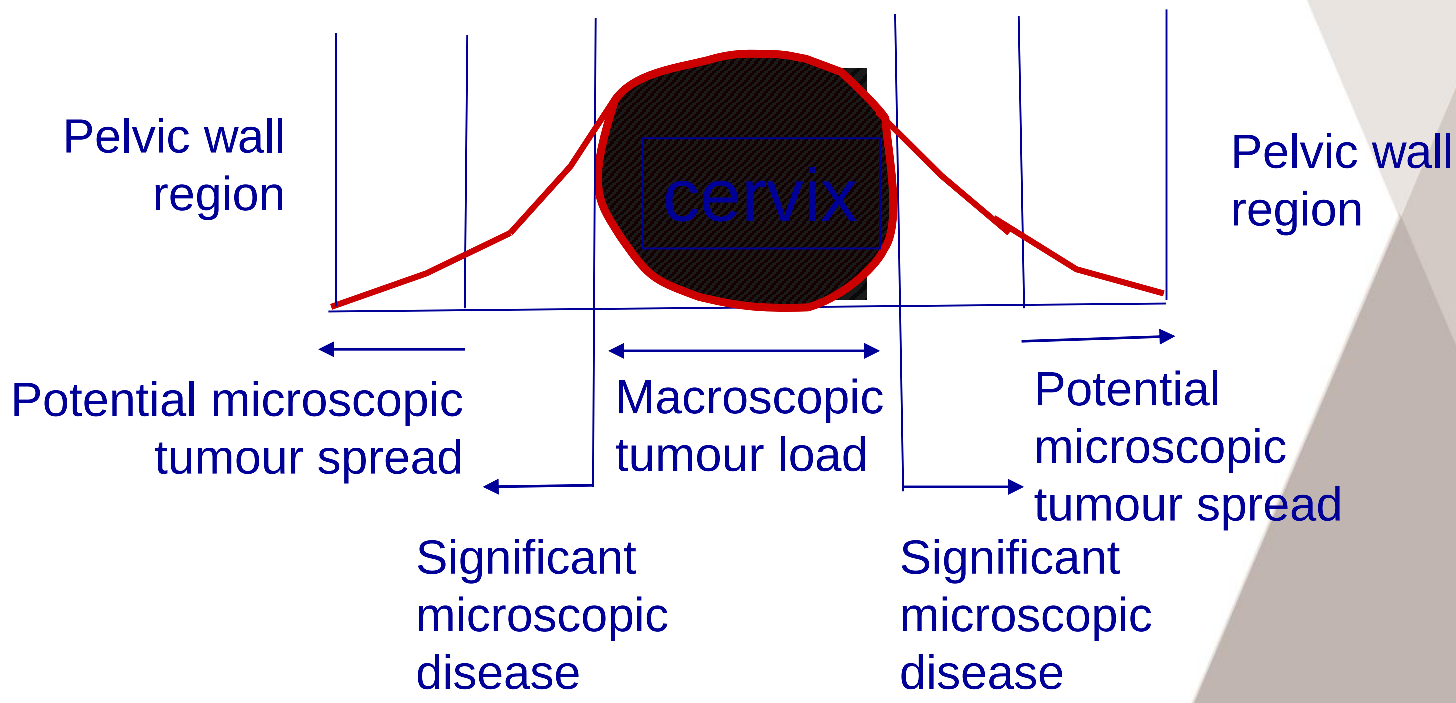


Figure 5.9. Schematic diagram for cervical cancer, Stage IB_2 (bulky disease), good response after chemo-radiotherapy: residual GTV-T ($GTV\text{-}T_{res}$), adaptive CTV-T ($CTV\text{-}T_{HR}$), initial GTV-T ($GTV\text{-}T_{init}$), intermediate risk CTV-T ($CTV\text{-}T_{IR}$) ($GTV\text{-}T_{init}$ 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)

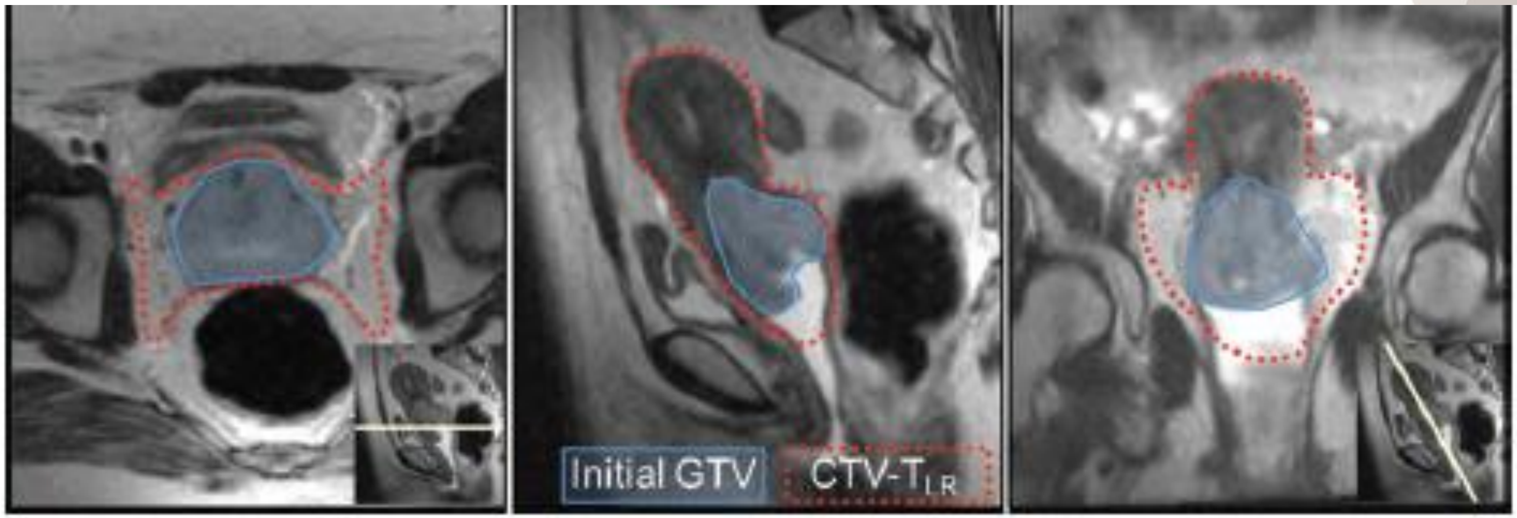
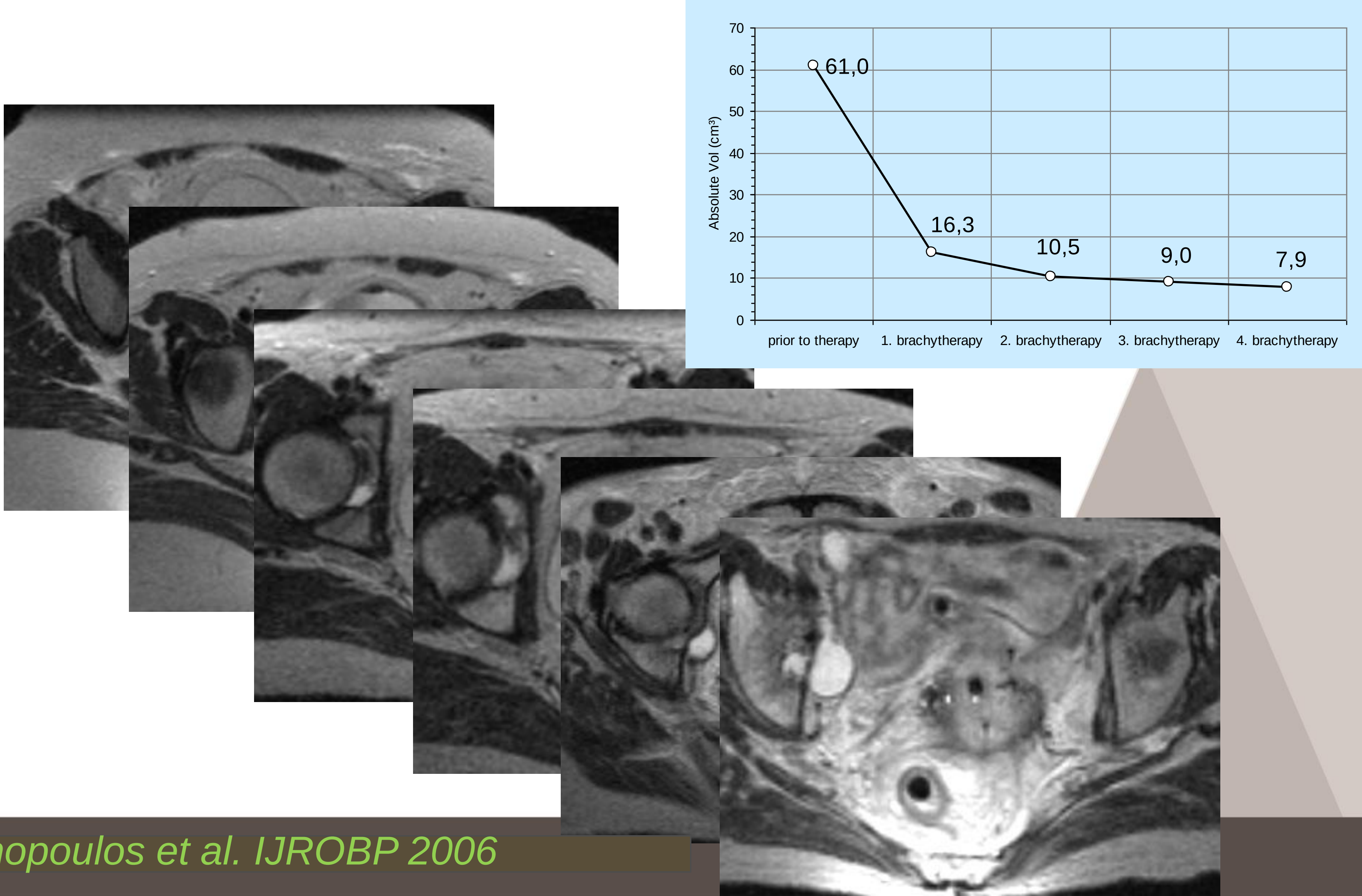


Figure 5.7. Magnetic resonance imaging at diagnosis of Stage IIB cervical cancer infiltrating both parametria with GTV-T_{init} and CTV-T_{LR} (CTV-T_3) including both parametria, uterine corpus, and upper vagina, contoured for treatment planning of EBRT.

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

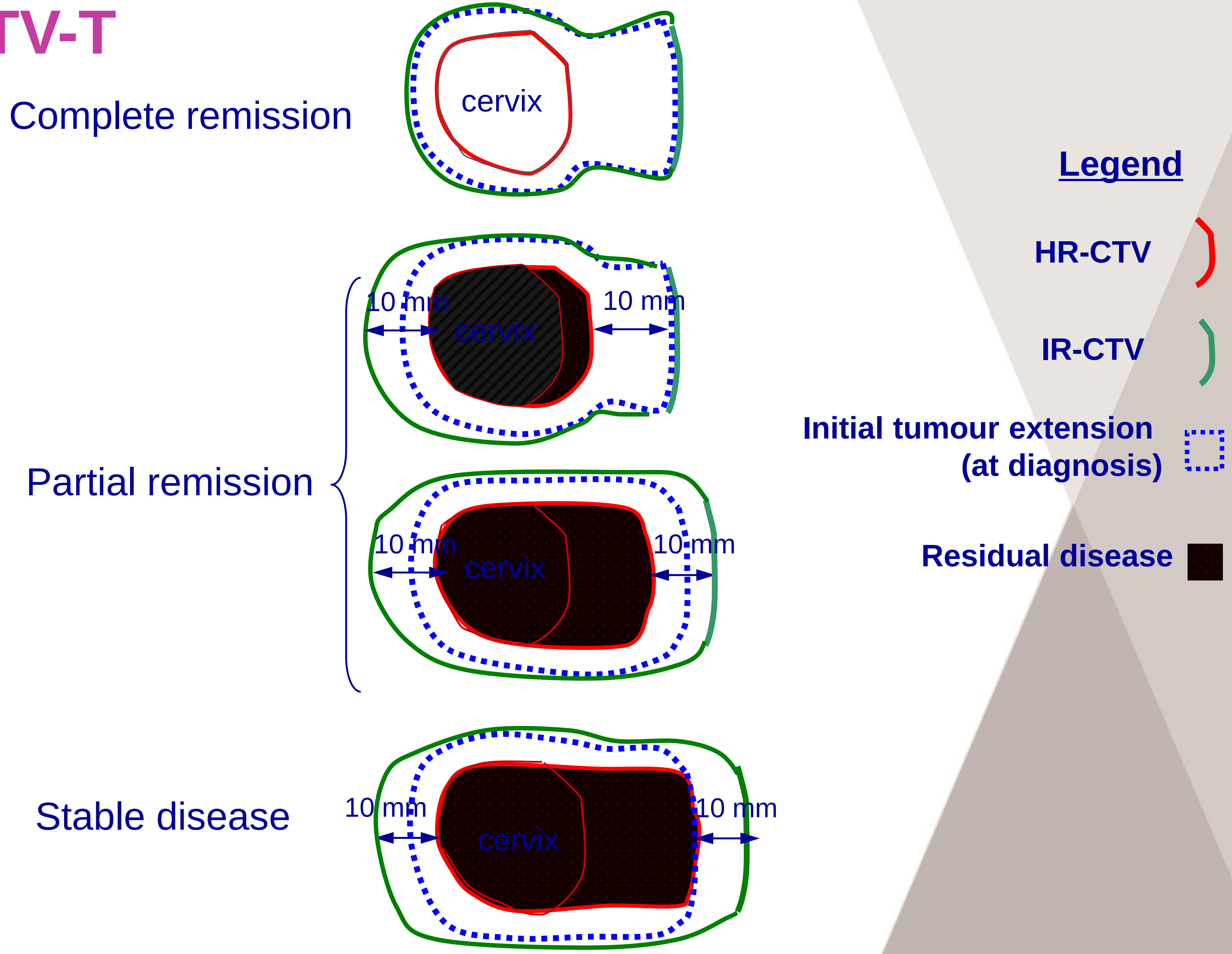
In all cases includes:

- 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

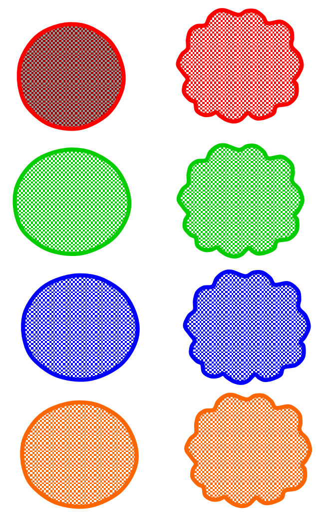
Cervix

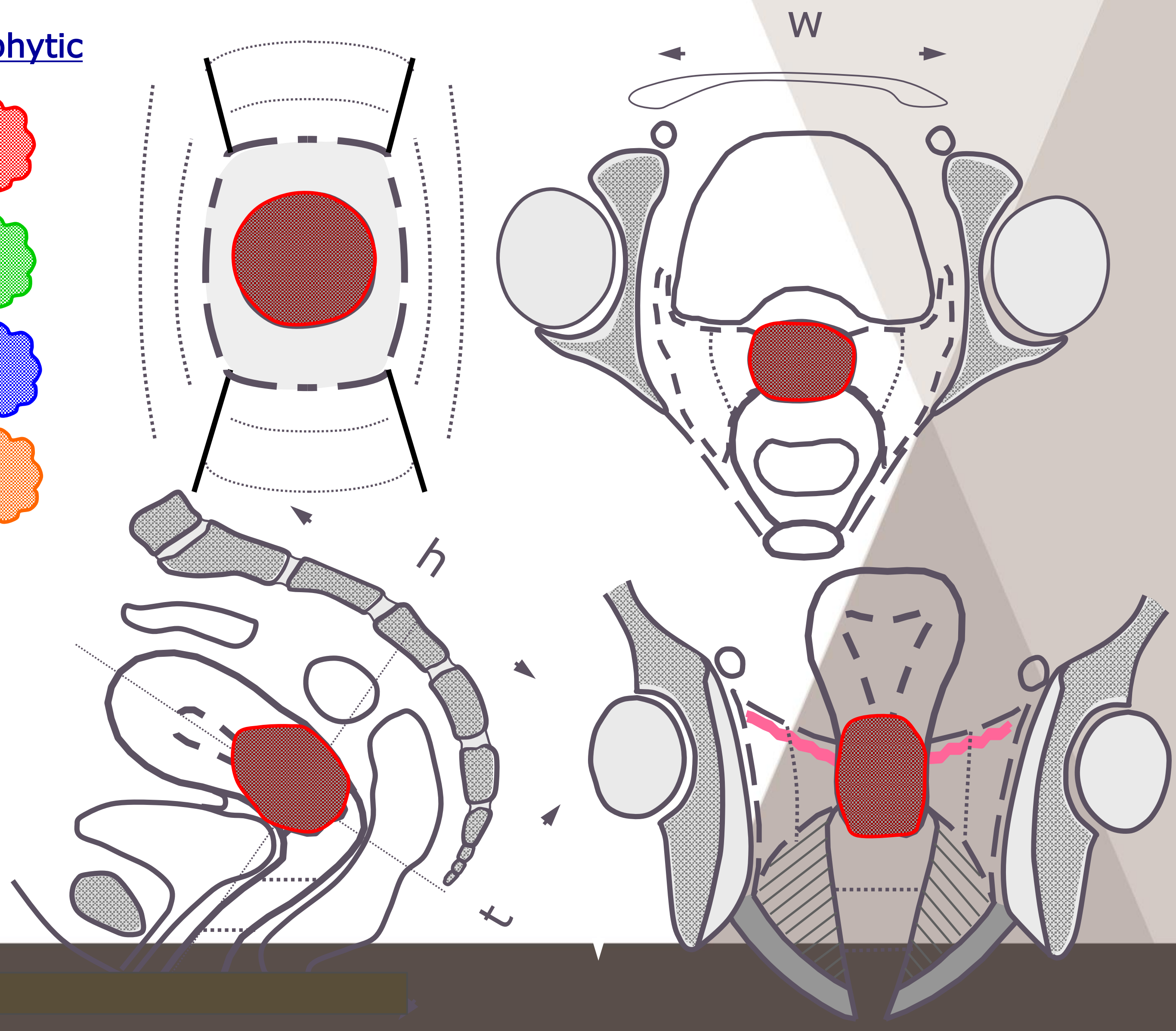
Vagina

Parametrium

Rectum or

Bladder





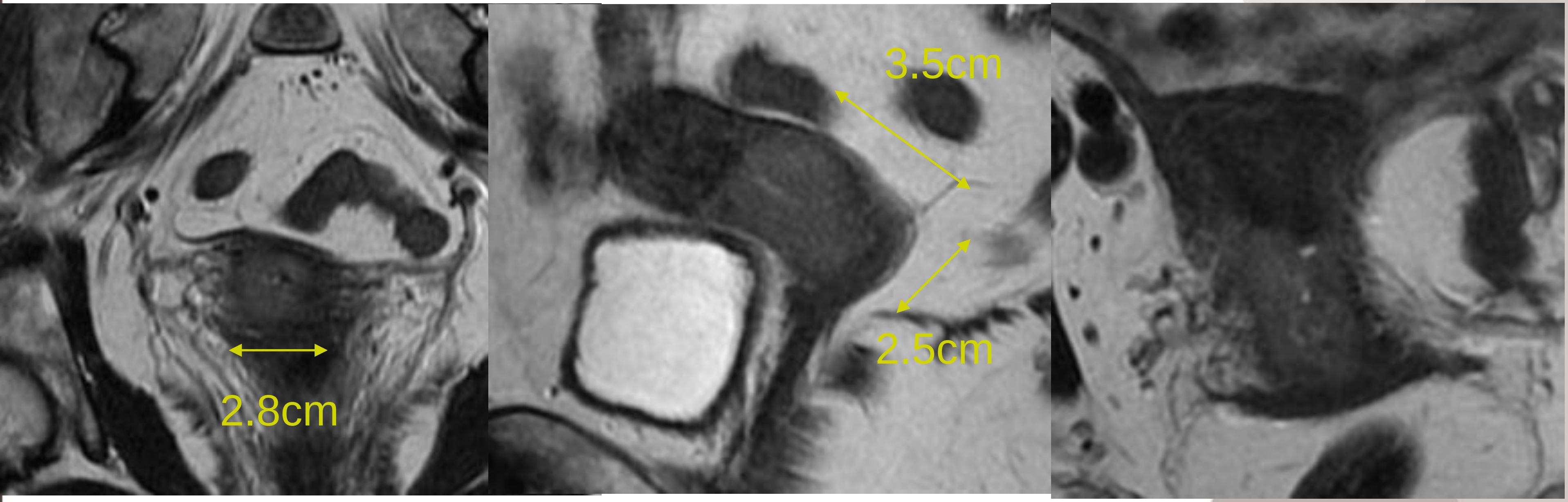
Dimensions (cm):

Width : 3

Thickness : 2.5

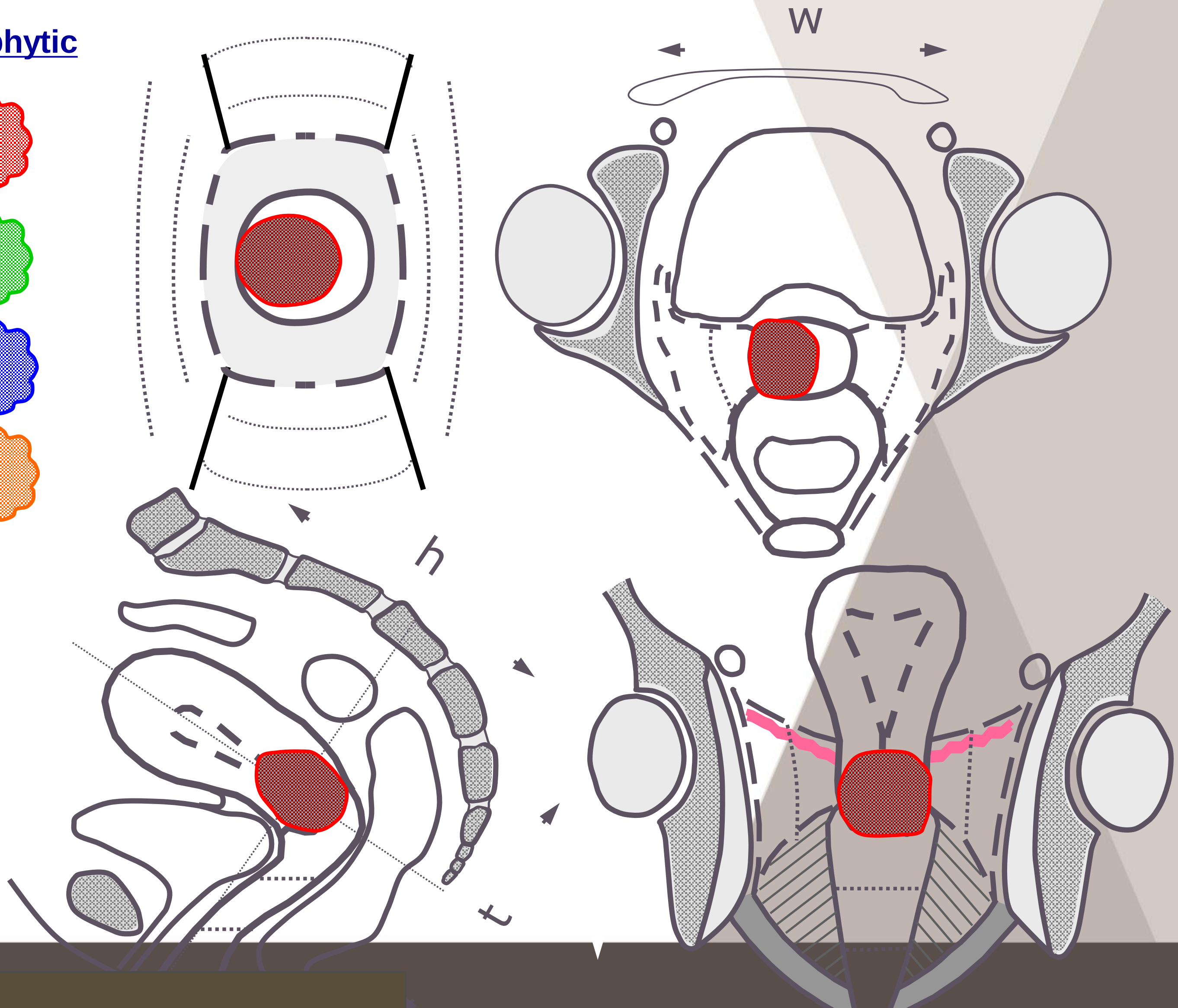
Height : 3

Stage IB1



Stage IB1 : at the time of brachytherapy

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		



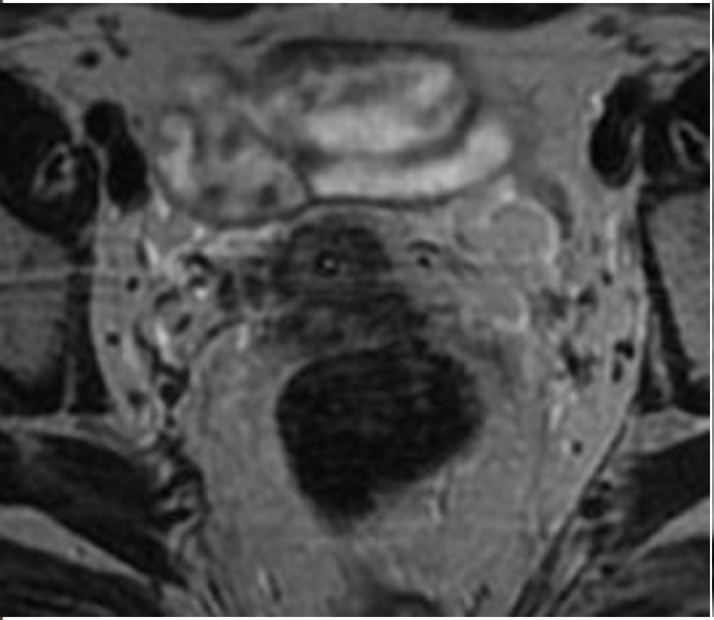
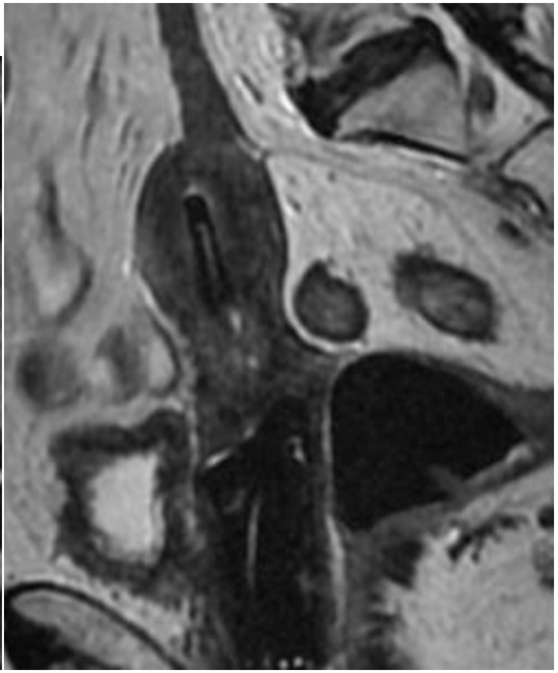
Dimensions (cm):

Width : 1.5

Thickness : 2

Height : 1.5

Stage IB1

Target volume concepts

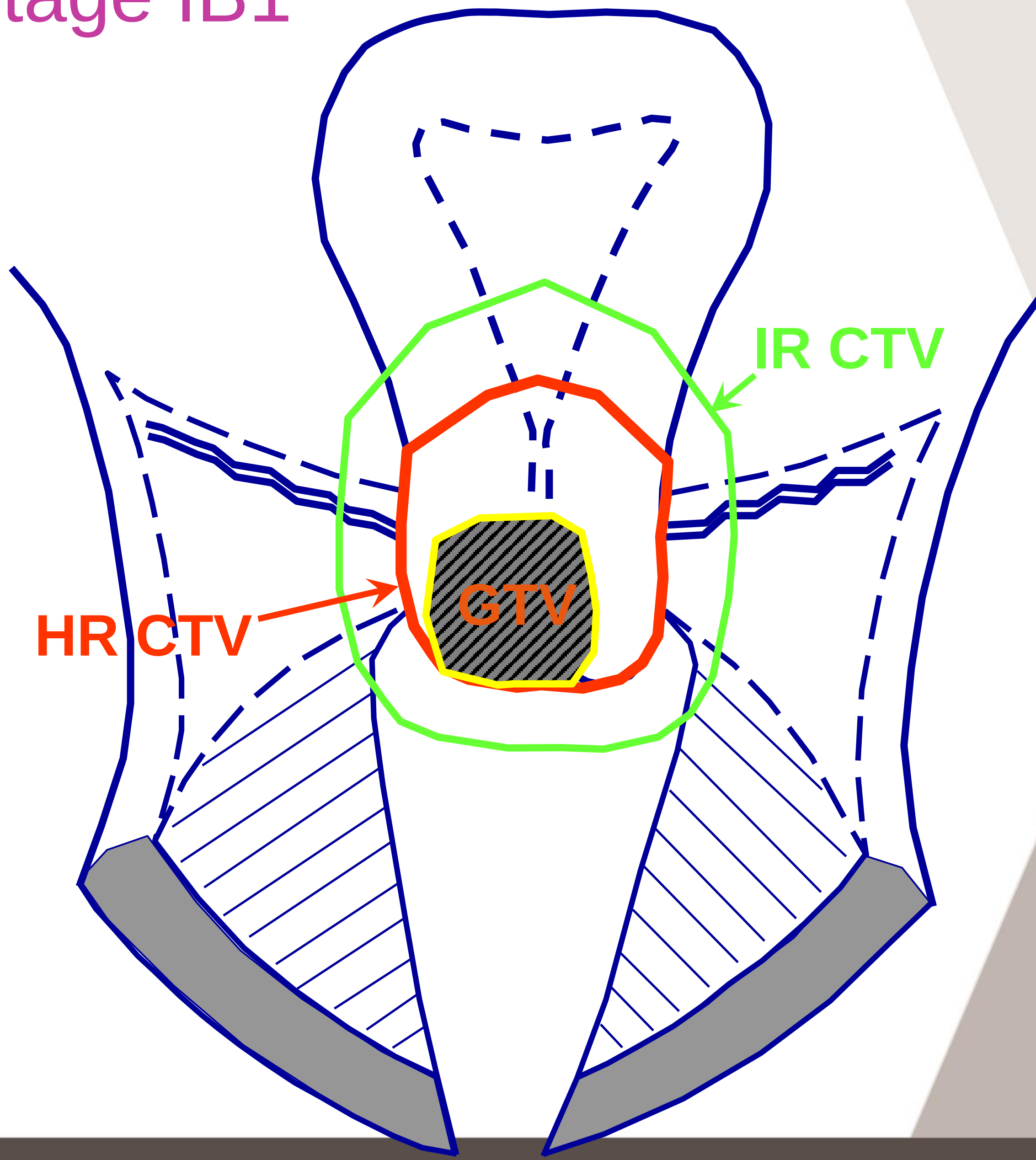
High Risk CTV :
GTV at time of brachytherapy
In all cases includes:
- Whole cervix
- [Presumed tumour extension (=0)]
- Clinical assessment
- [Residual grey zones on MRI]

NO SAFETY MARGINS

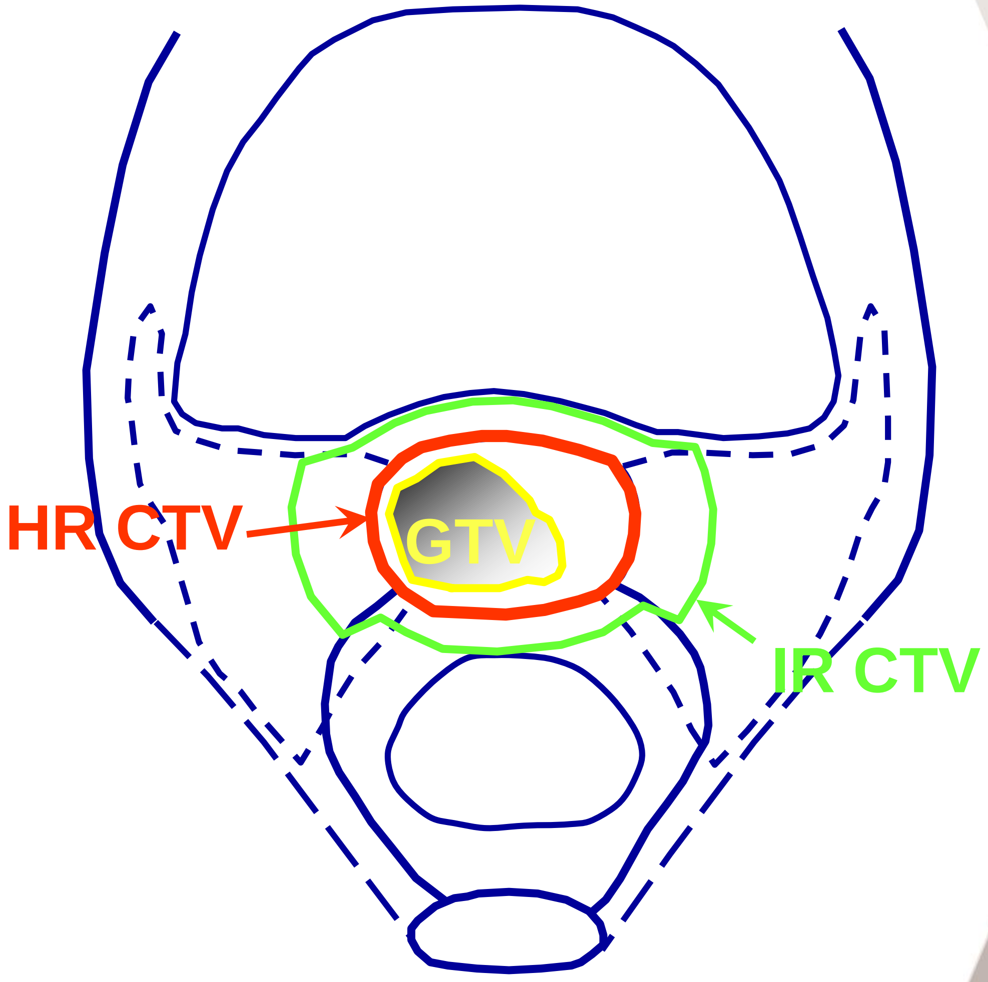
Intermediate Risk CTV :
GTV at time of diagnosis
In all cases includes:
- HR-CTV
- integrates initial CTV

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

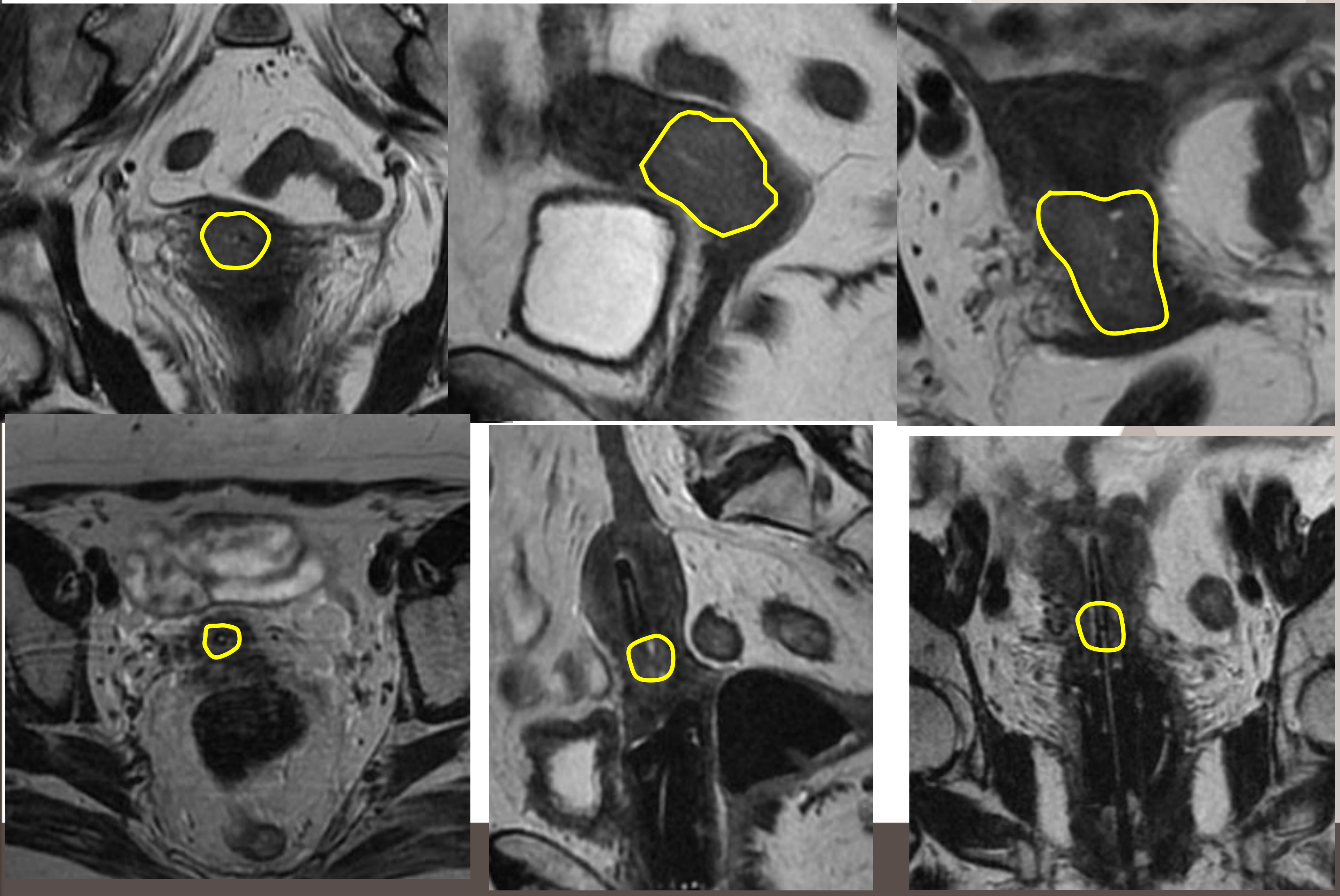
Stage IB1



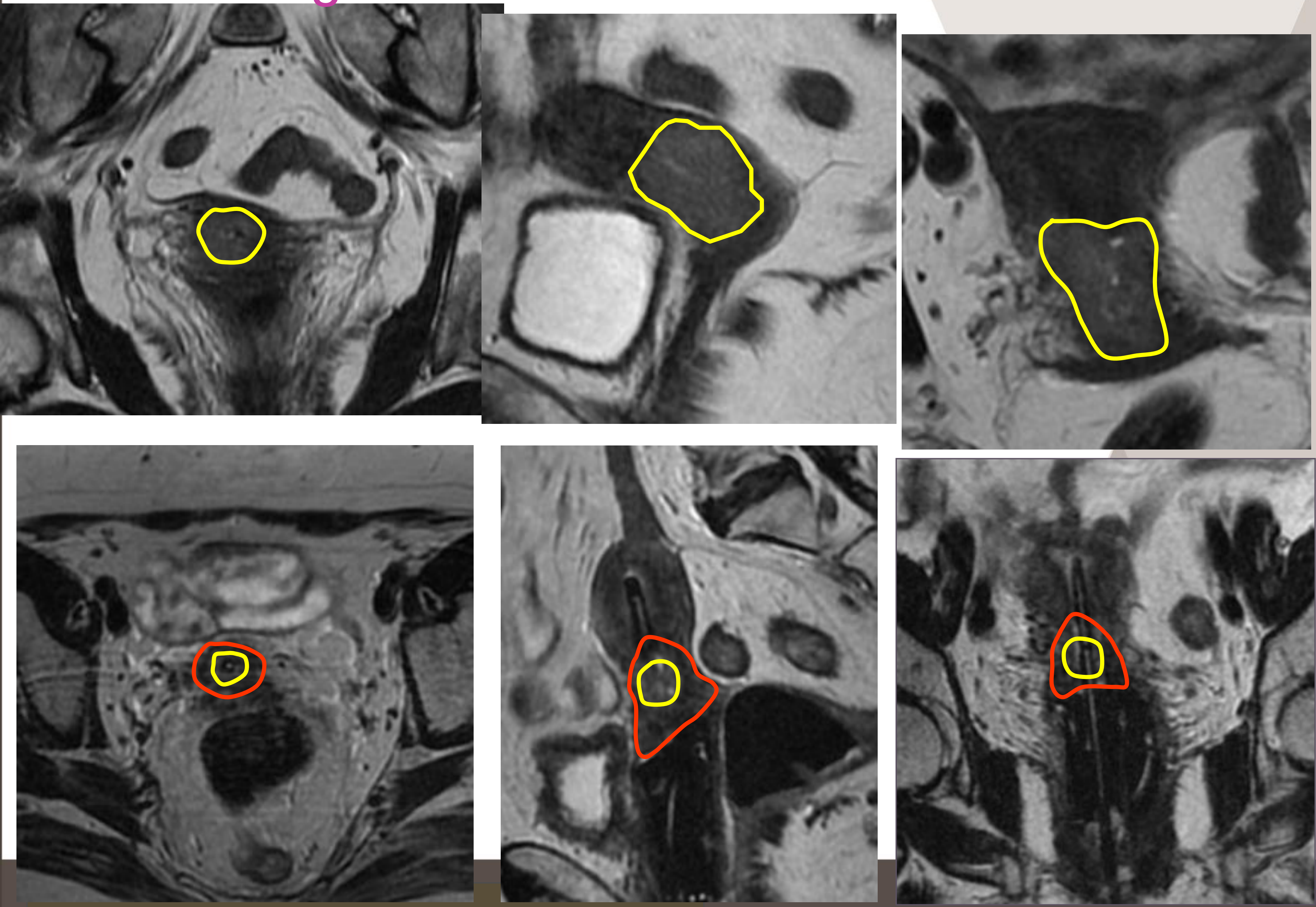
Stage IB1



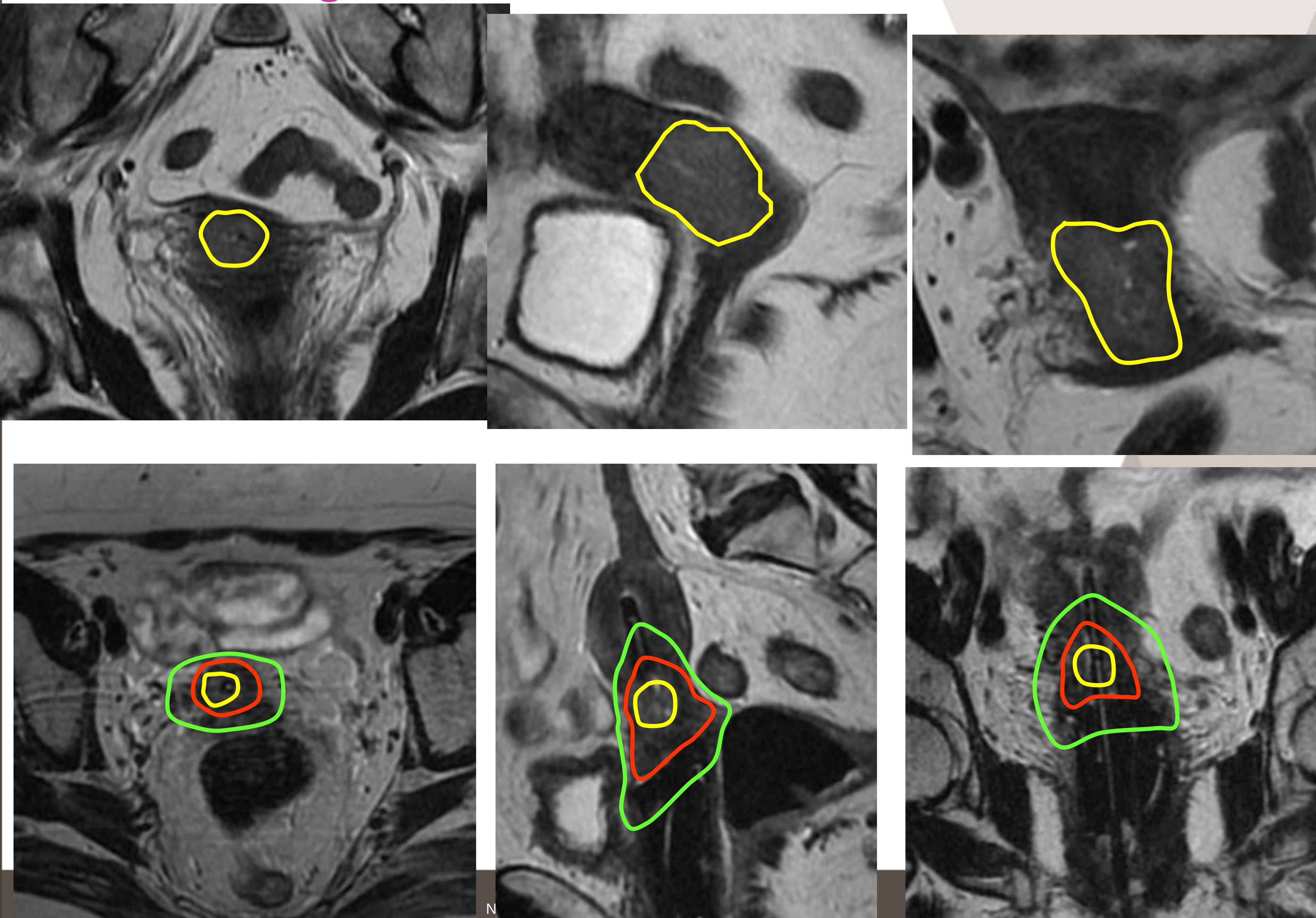
Stage IB1



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

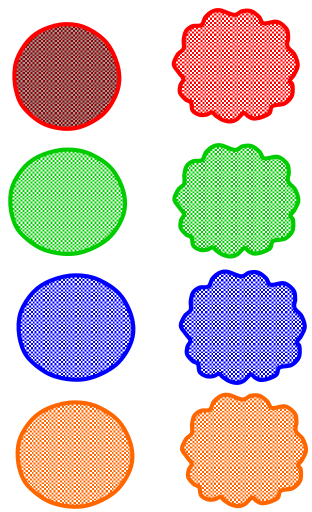
Infiltrating Exophytic

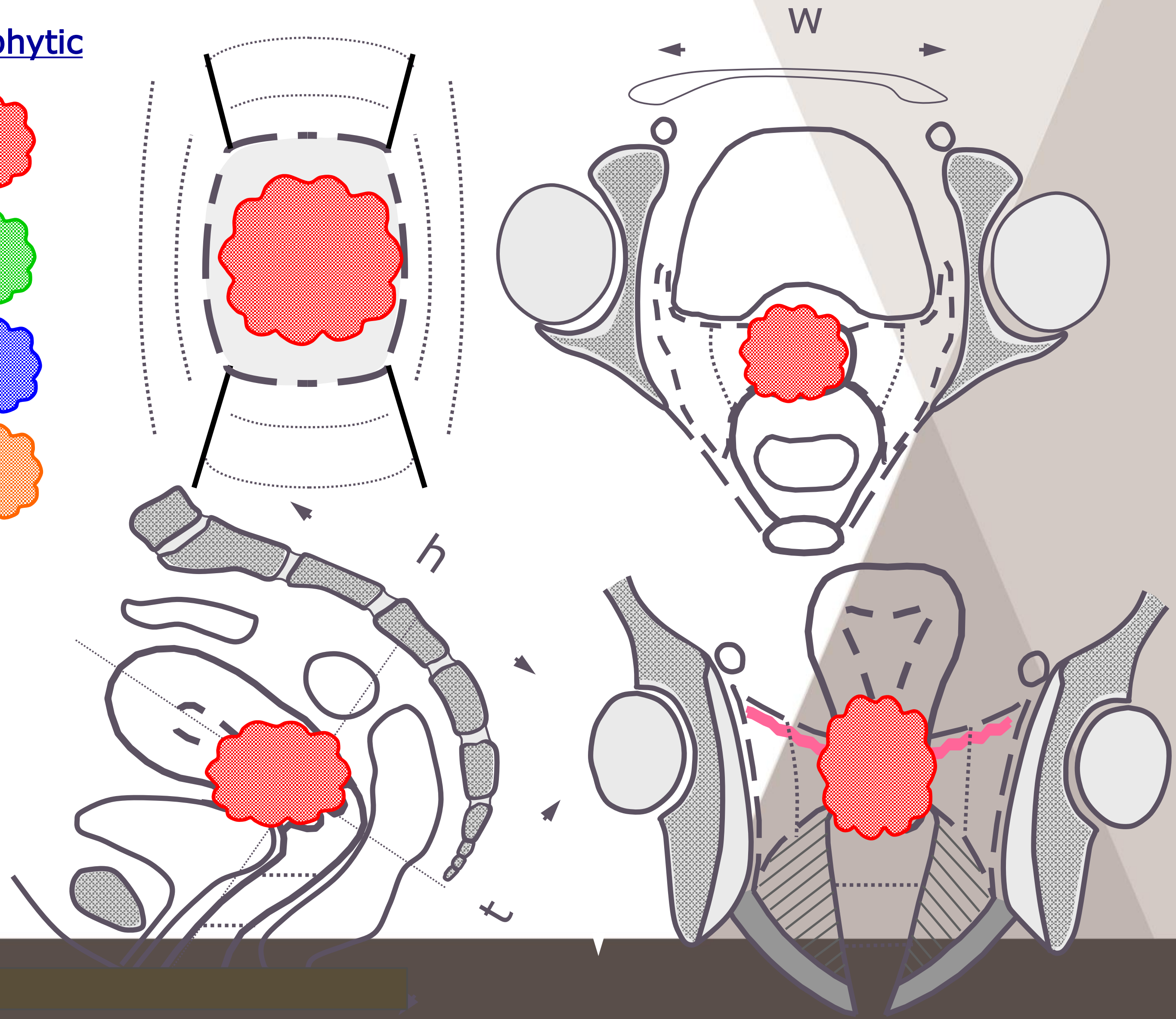
Cervix

Vagina

Parametrium

Rectum or Bladder





Dimensions (cm):

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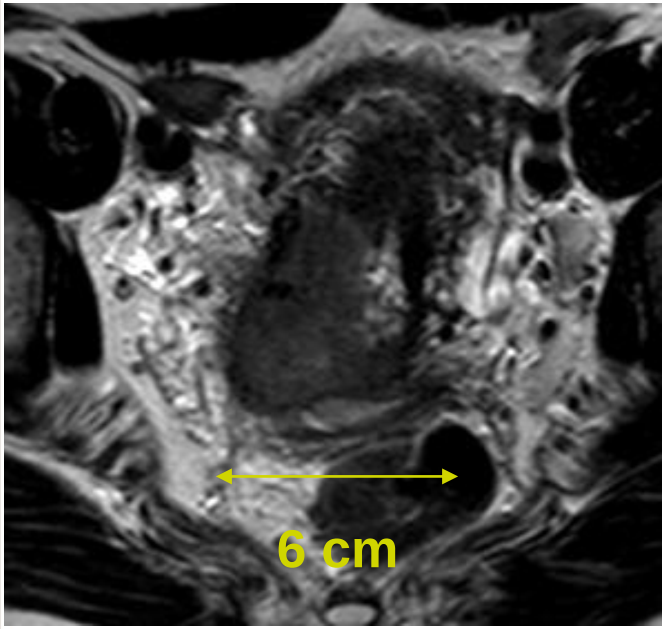
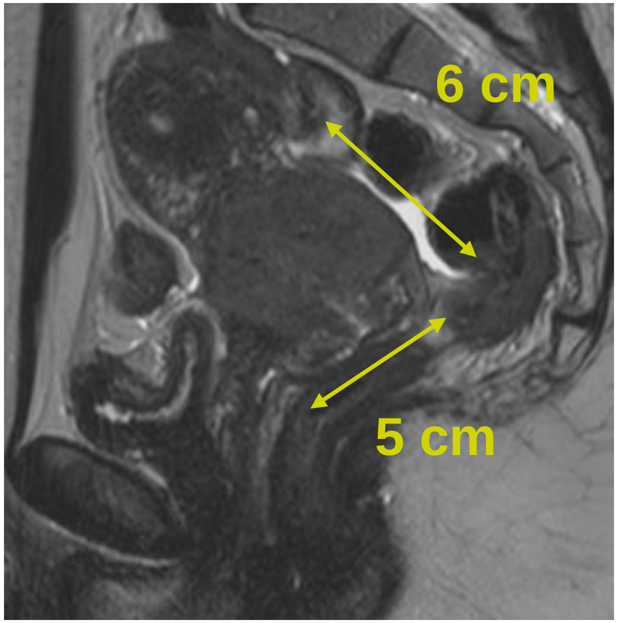
Thickness : 5

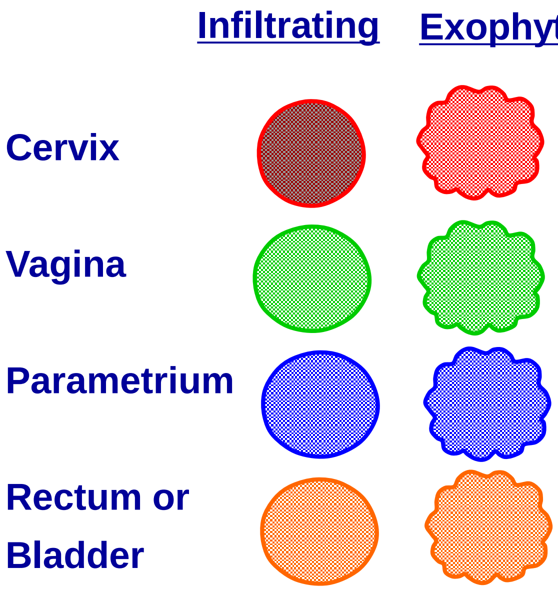
Height : 5

Stage IB2 : initial MRI





Stage IB2 : at the time of brachytherapy

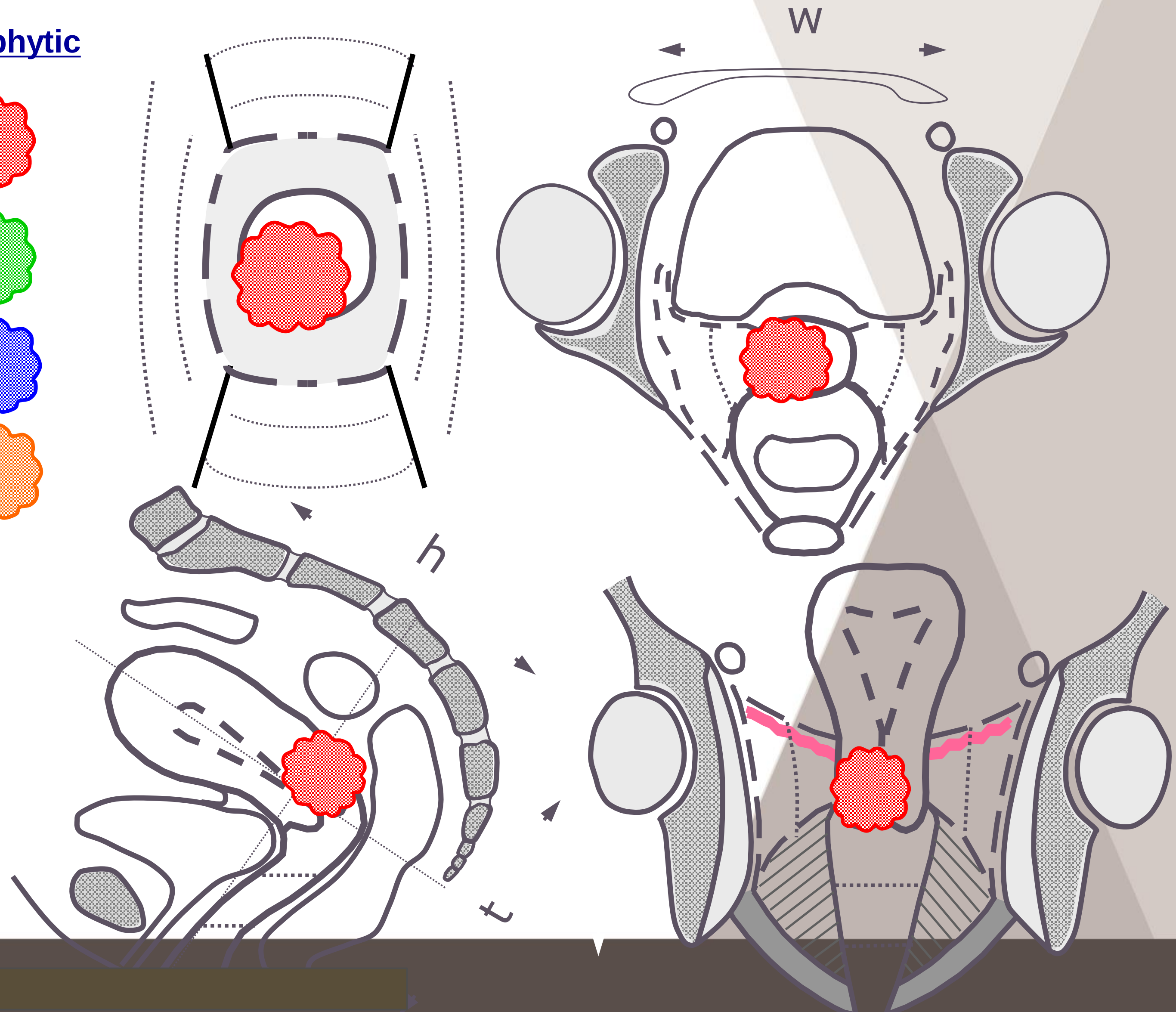


Dimensions (cm):

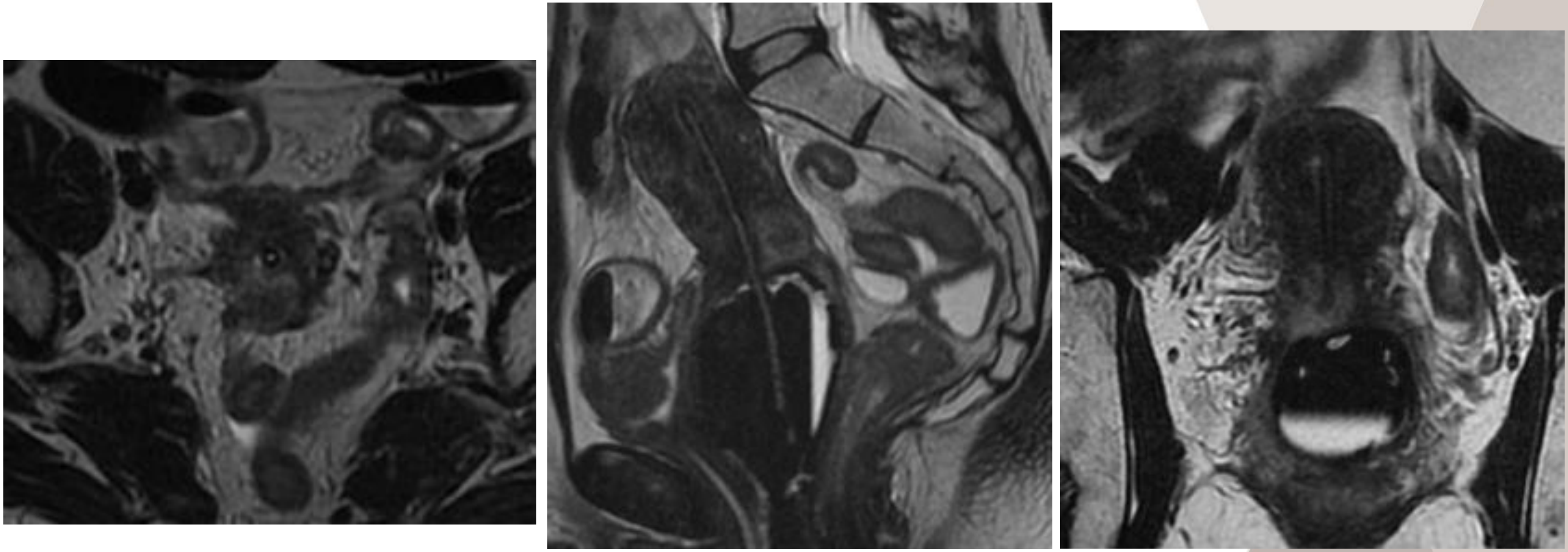
Width : 2.5

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

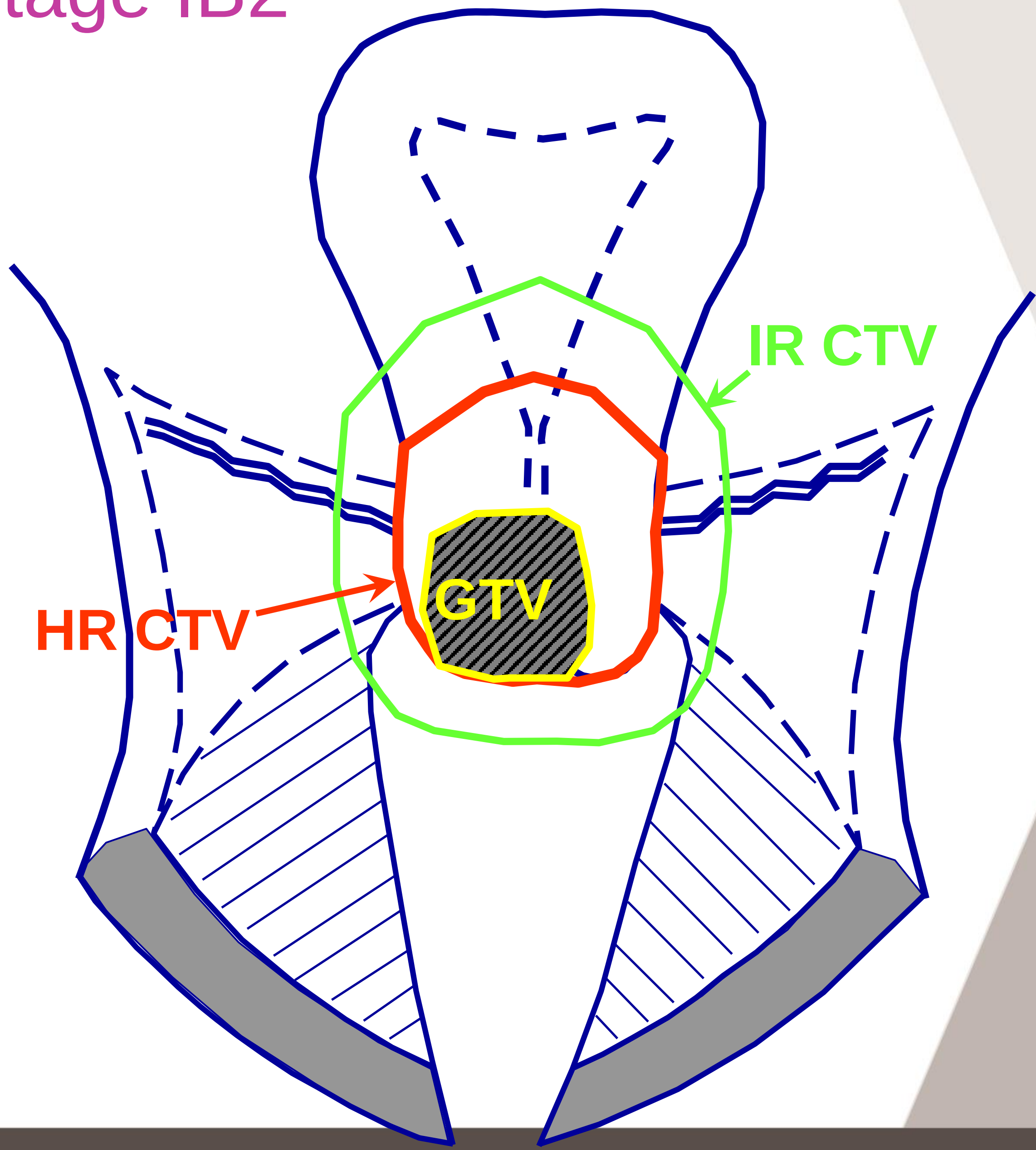
High Risk CTV :
GTV at time of brachytherapy
In all cases includes:
- Whole cervix
- Presumed tumour extension (=0)
- Clinical assessment
- (Residual grey zones on MRI)

NO SAFETY MARGINS

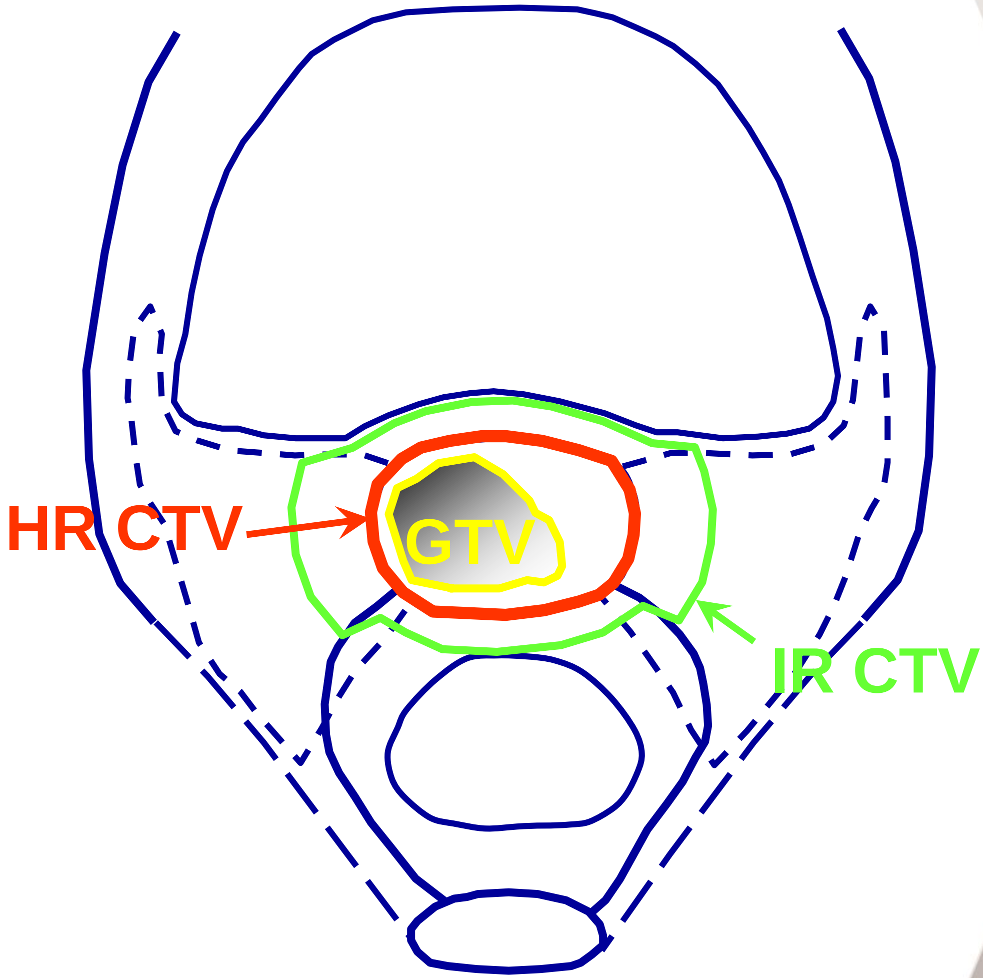
Intermediate Risk CTV :
GTV at time of diagnosis
In all cases includes:
- HR-CTV
- integrates initial CTV

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

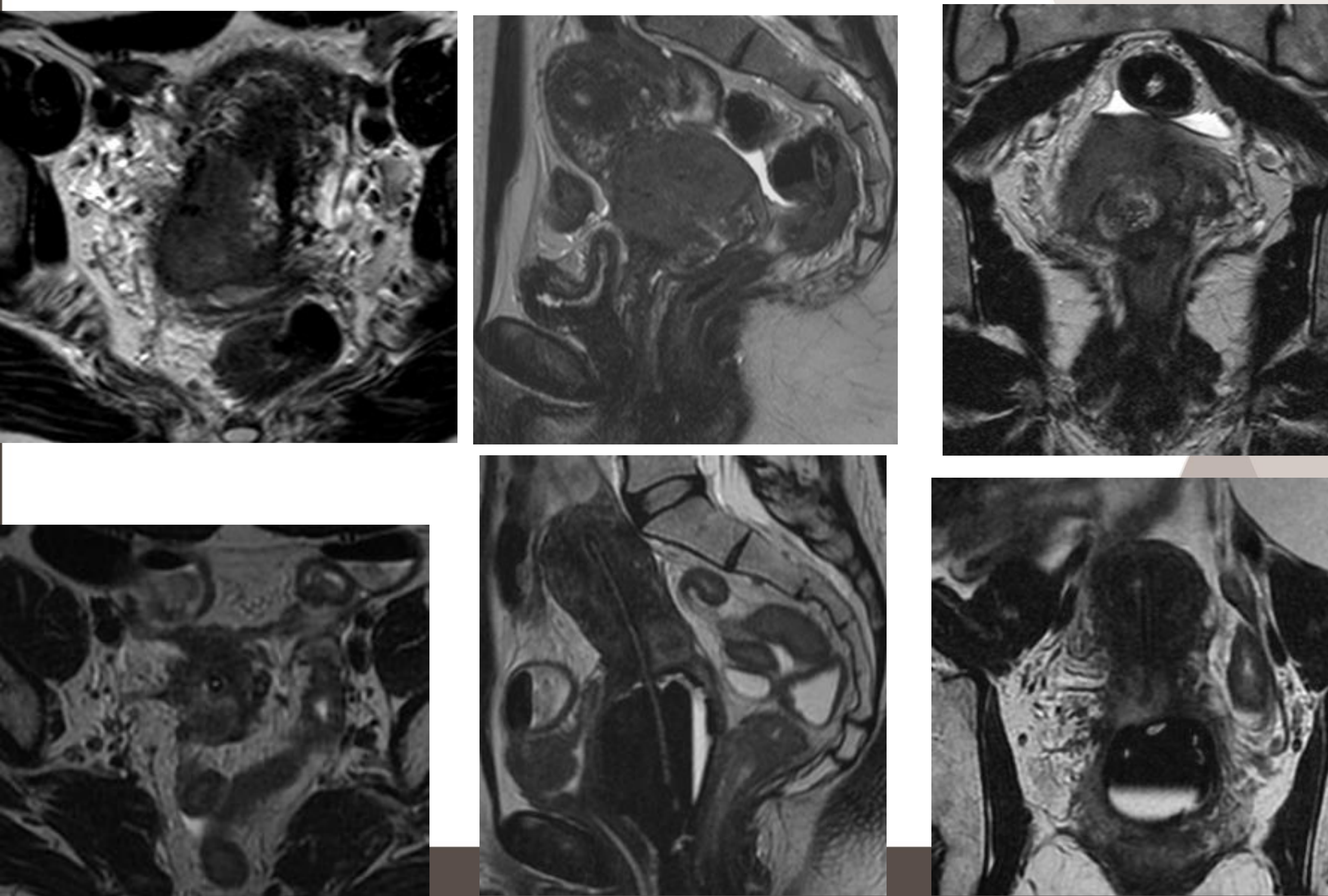
Stage IB2



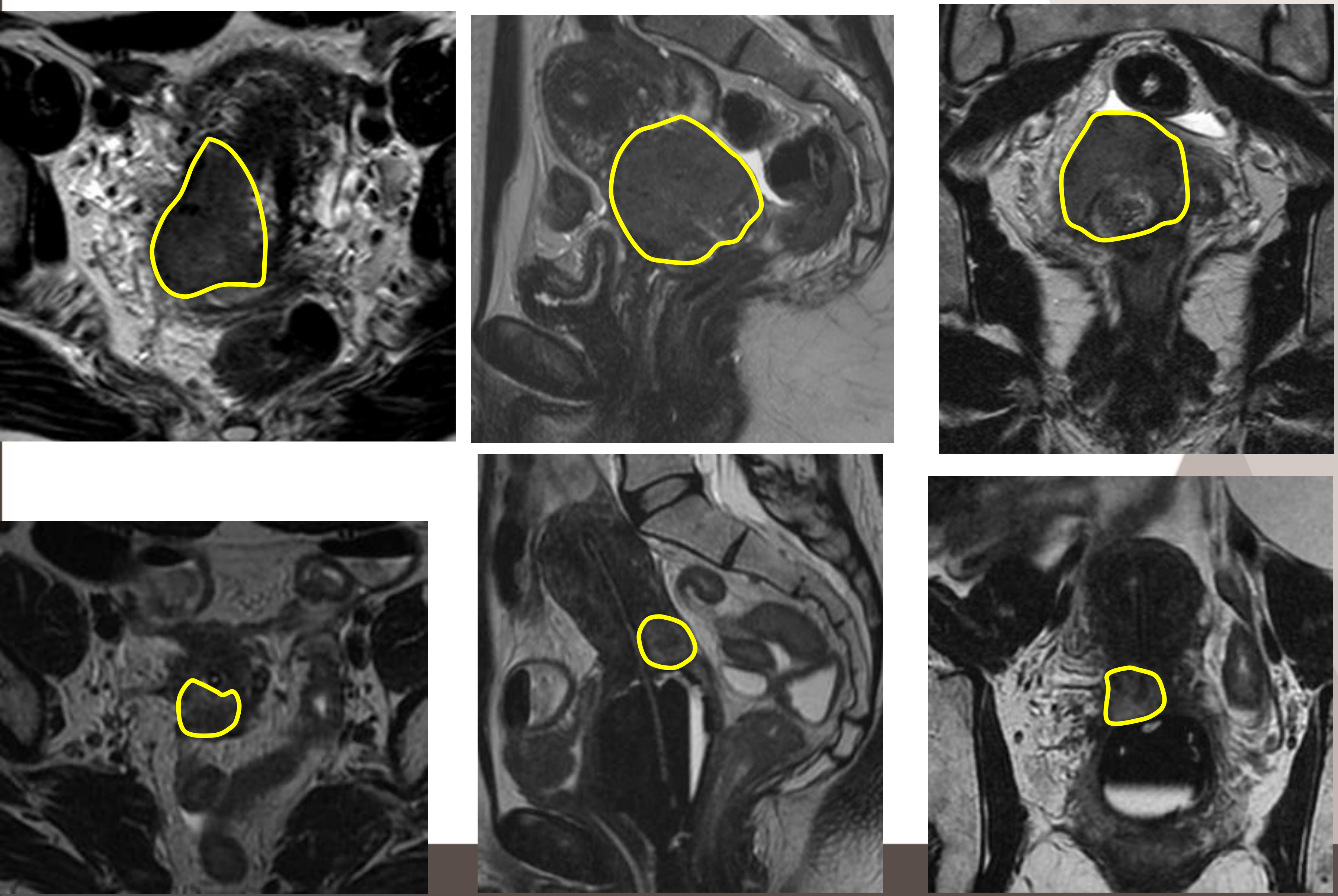
Stage IB2



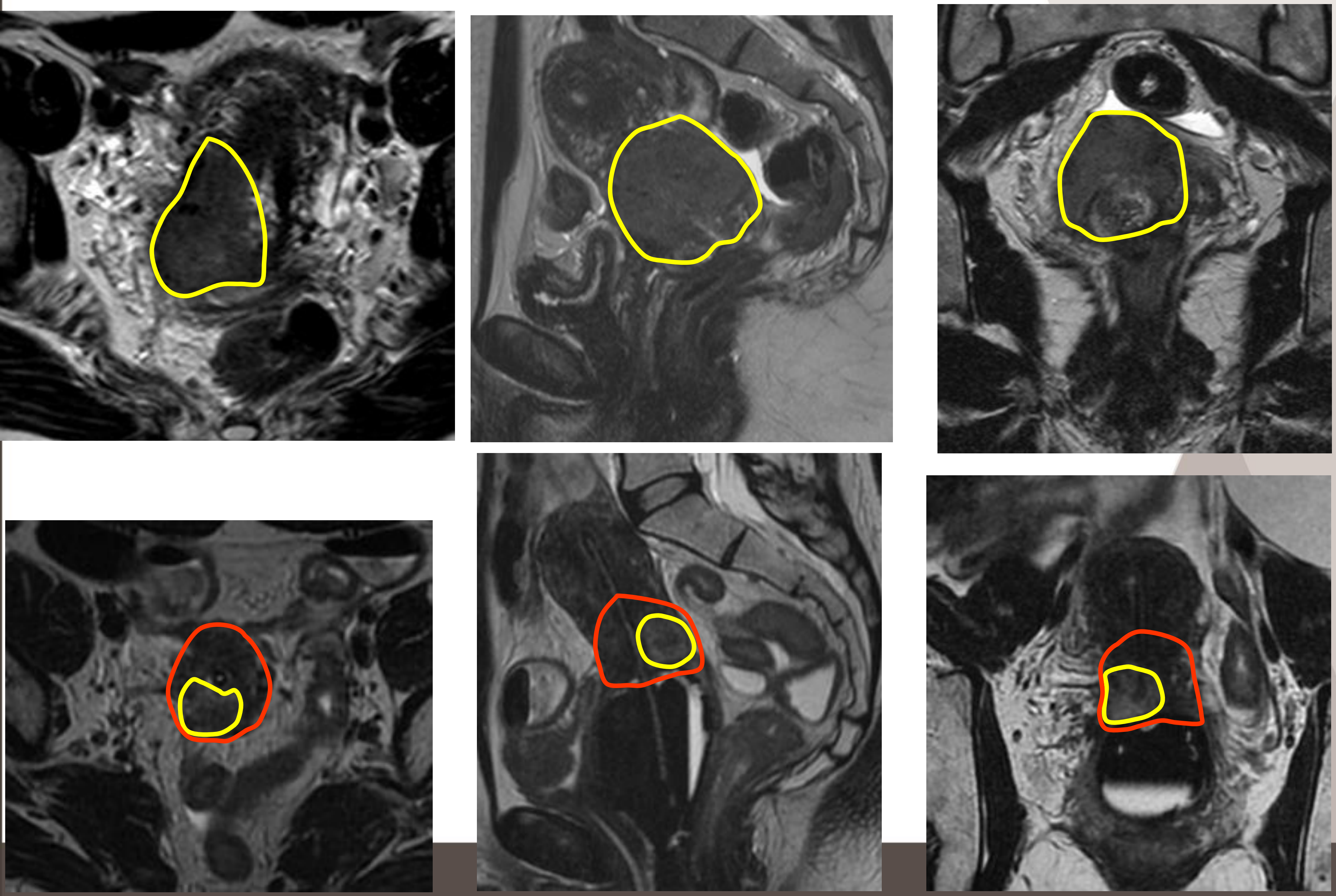
Stage IB2



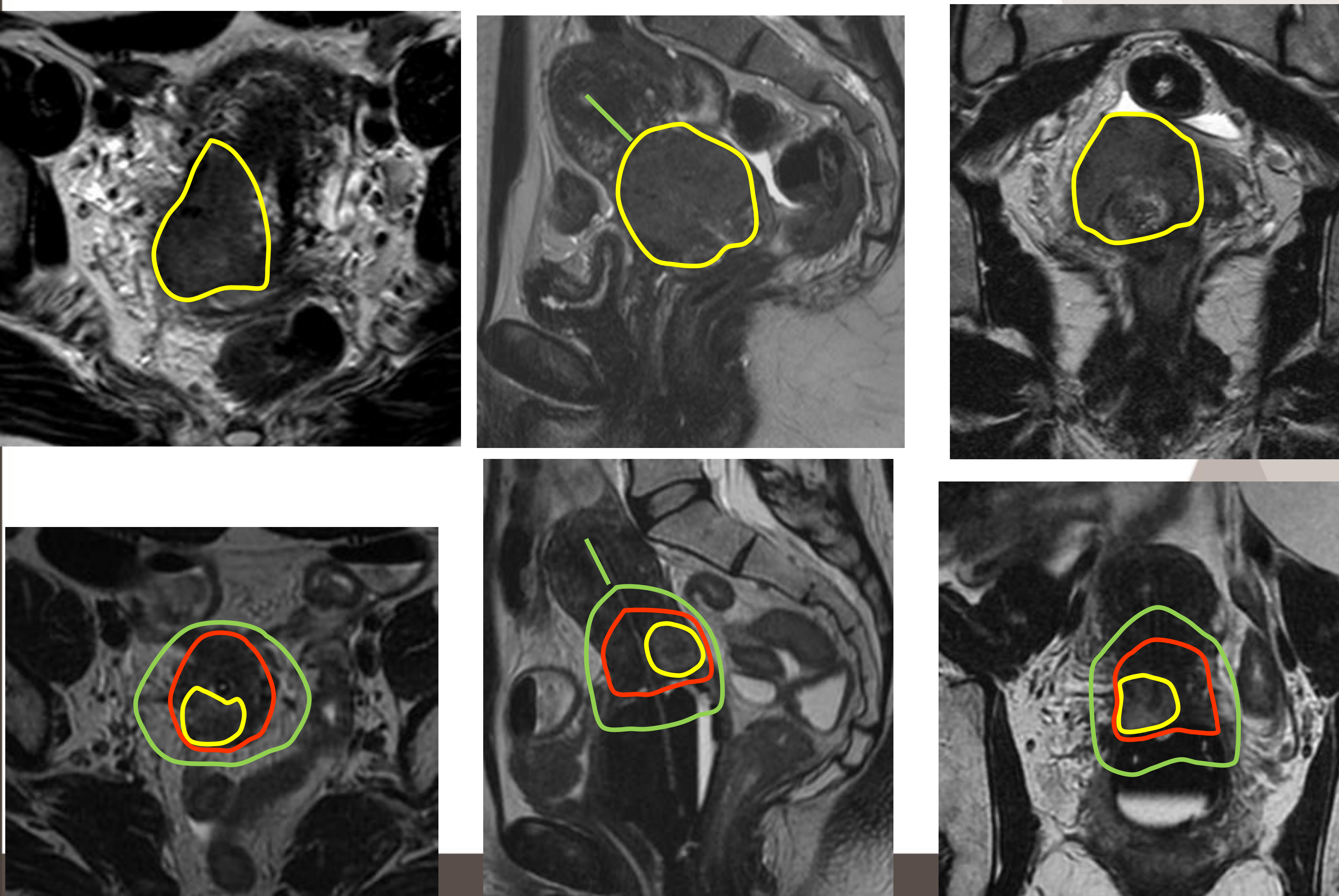
Stage IB2



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

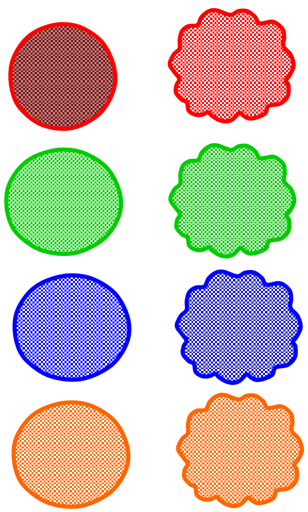
Infiltrating Exophytic

Cervix

Vagina

Parametrium

Rectum or Bladder



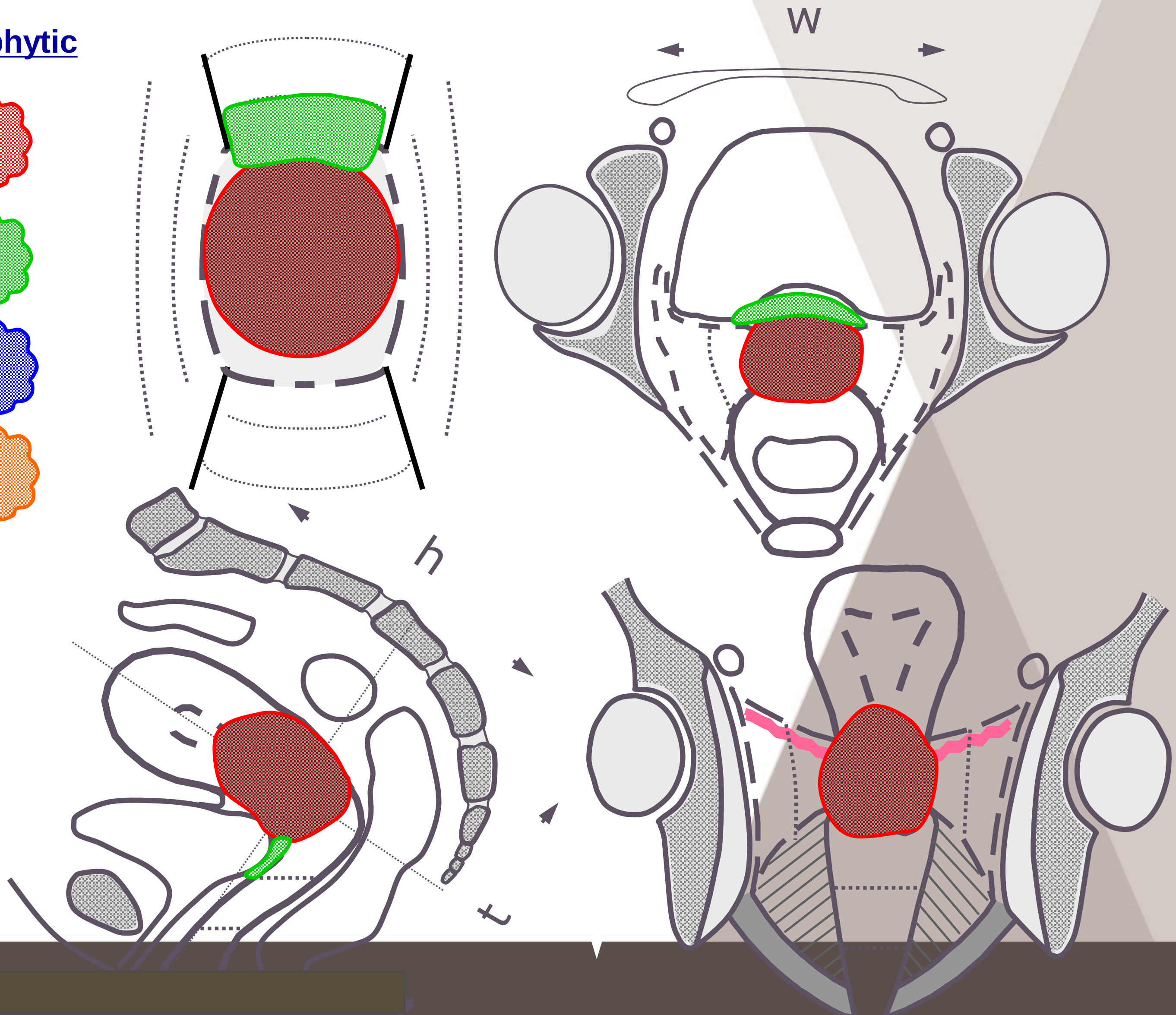
Dimensions (cm):

Width : 5

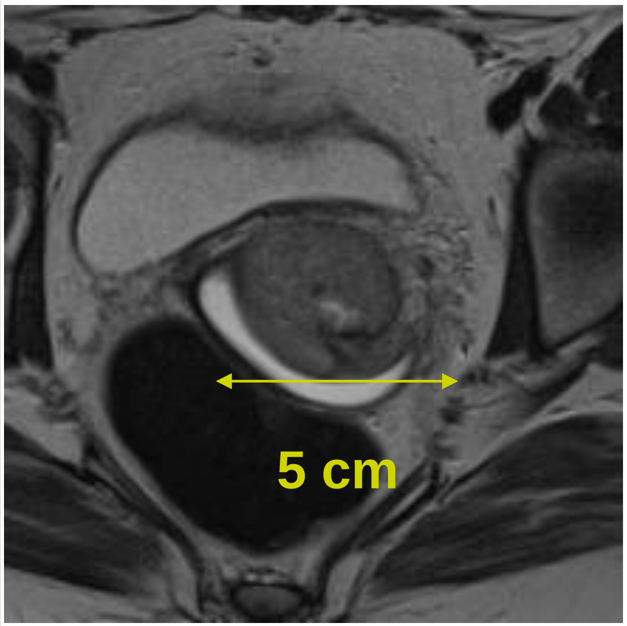
Thickness:4.5

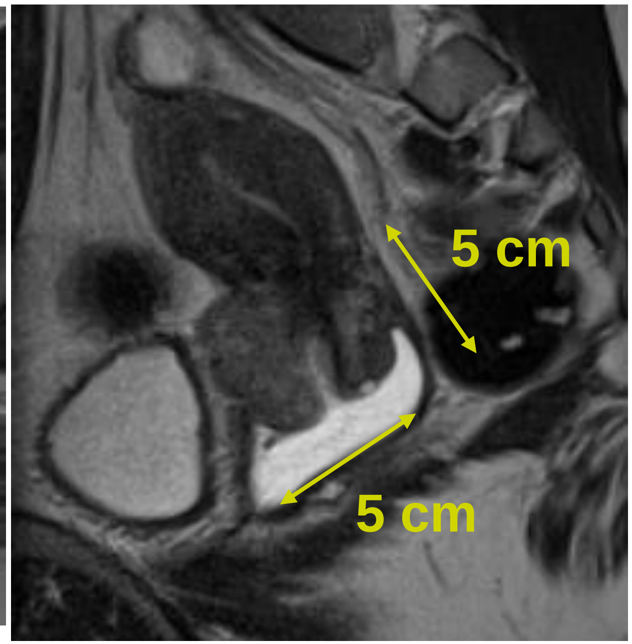
Height : 5

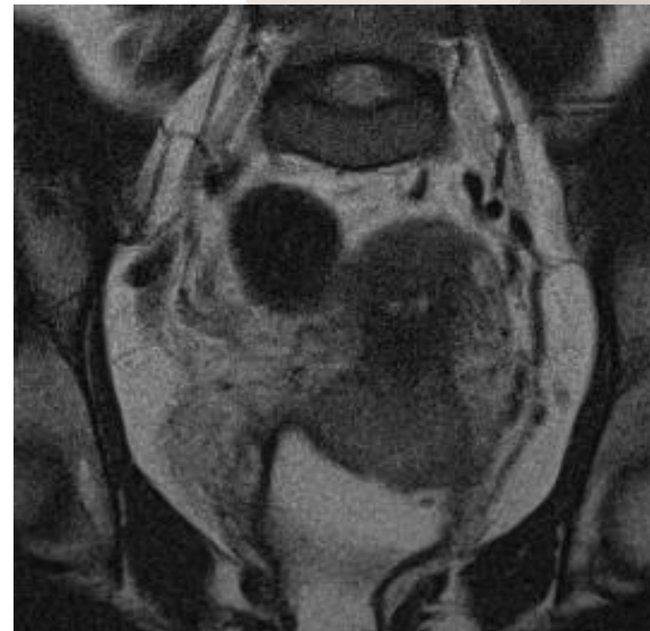
Vaginal involv 1.5



Stage IIA : initial MRI

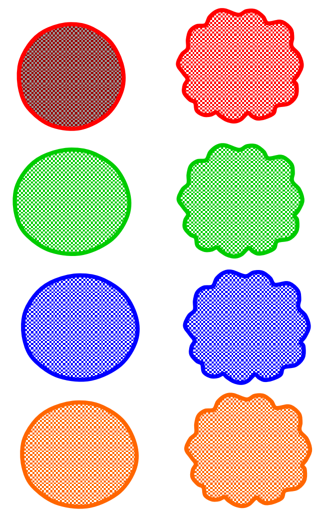






Stage IIA : at time of brachytherapy

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		



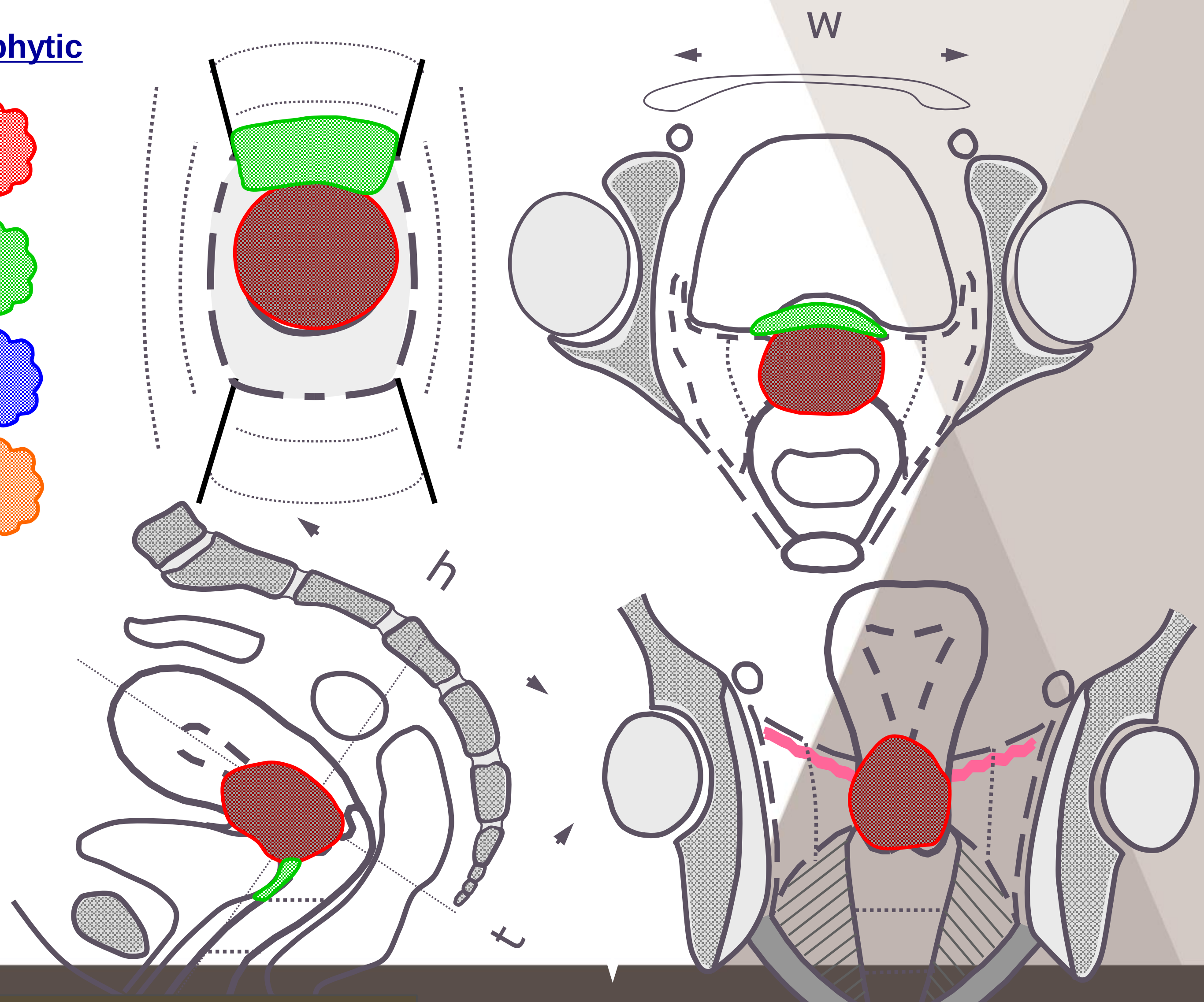
Dimensions (cm):

Width : 3.5

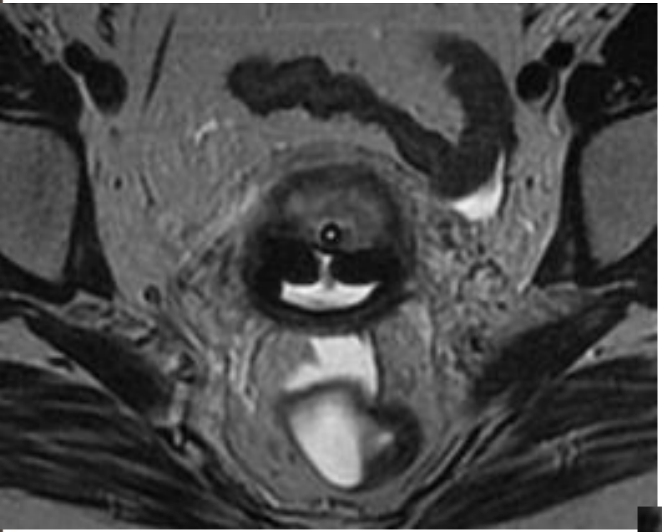
Thickness:3.5

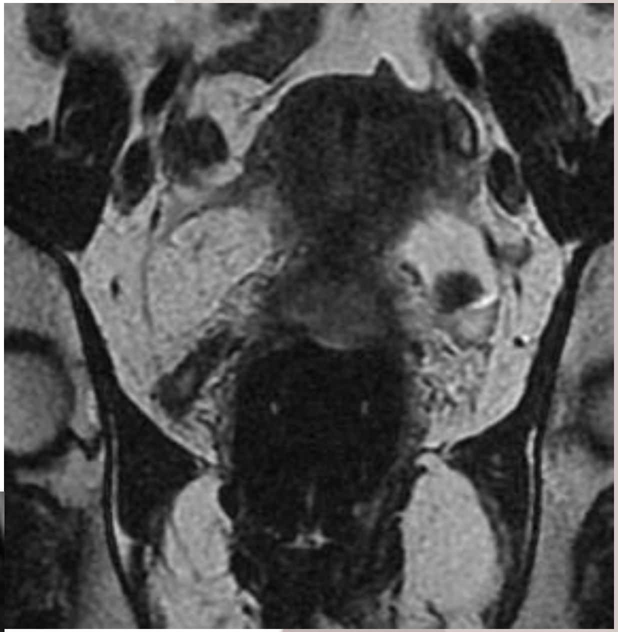
Height : 3

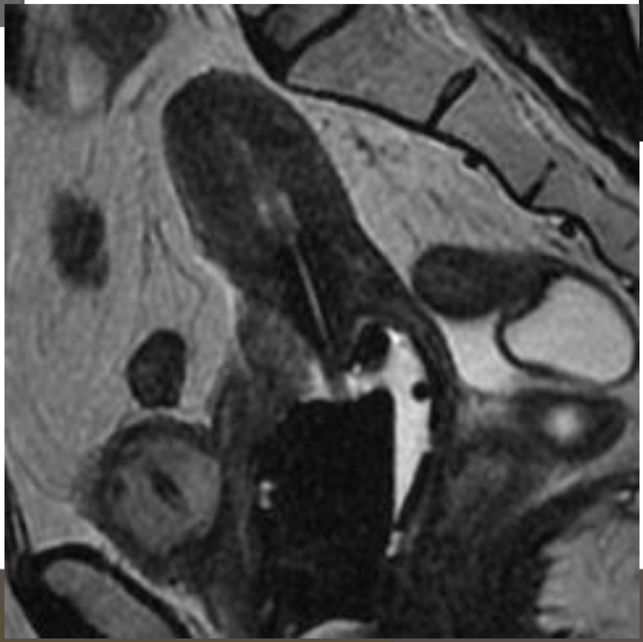
Vaginal involv :1



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

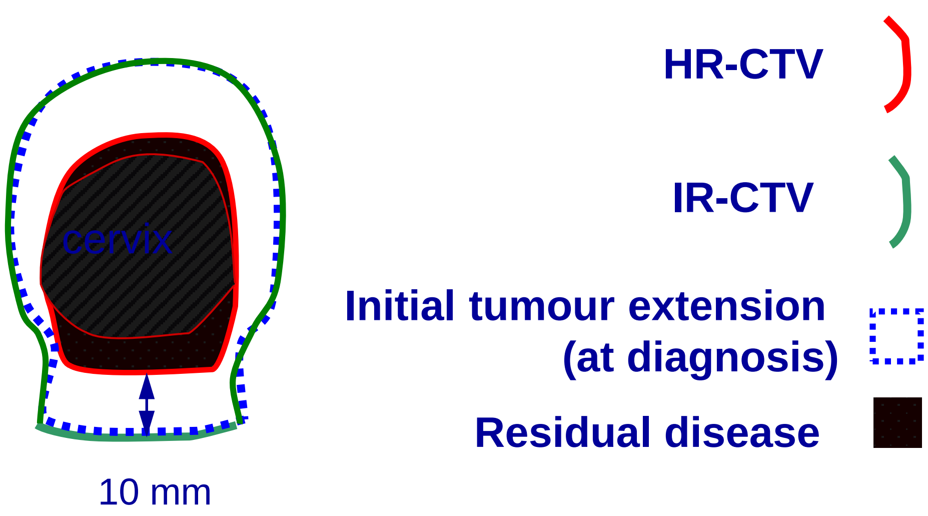
High Risk CTV :

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

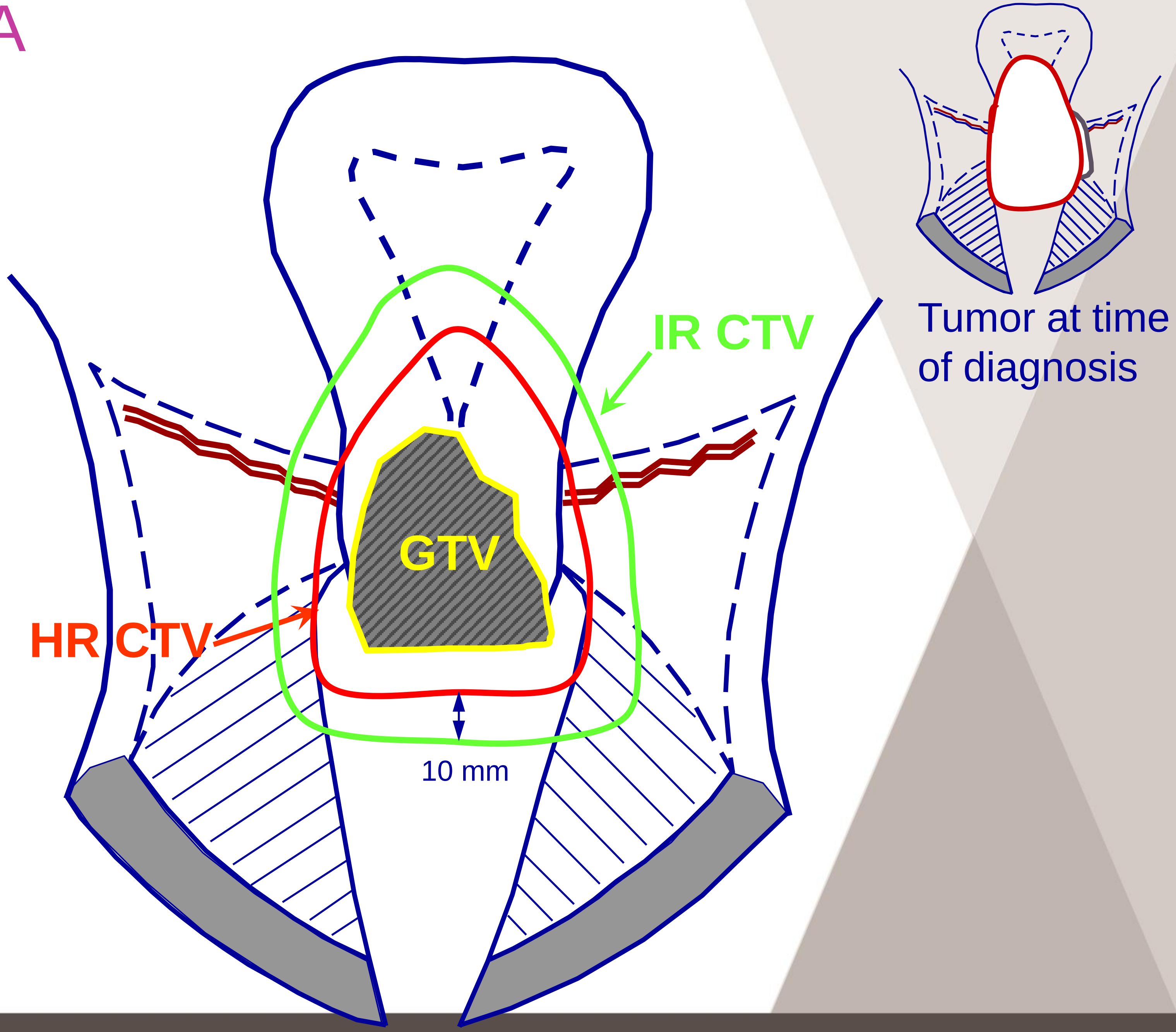
SAFETY MARGINS :

1-1.5 cm cranially

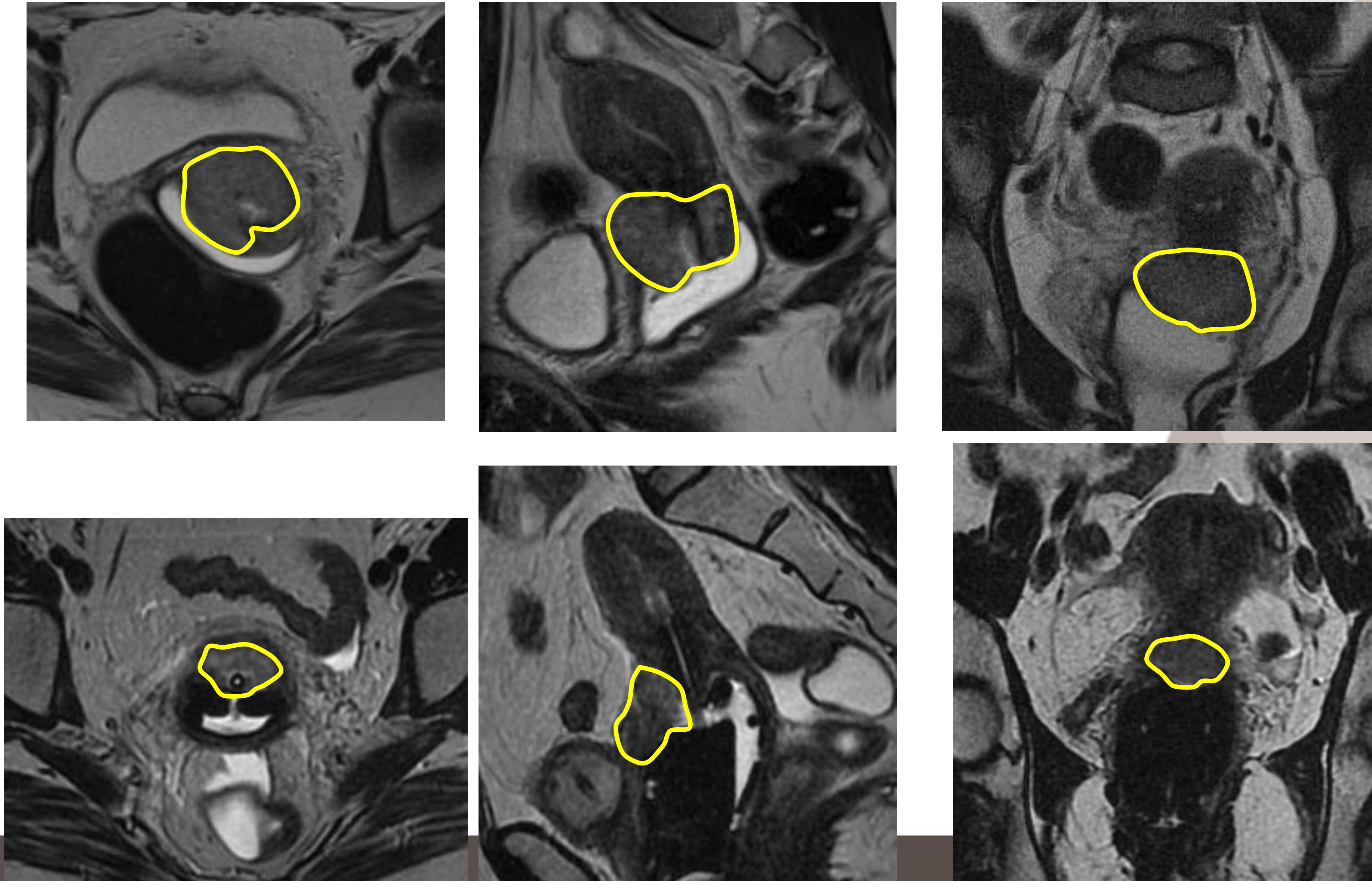
0.5cm antero-posteriorly

1cm laterally

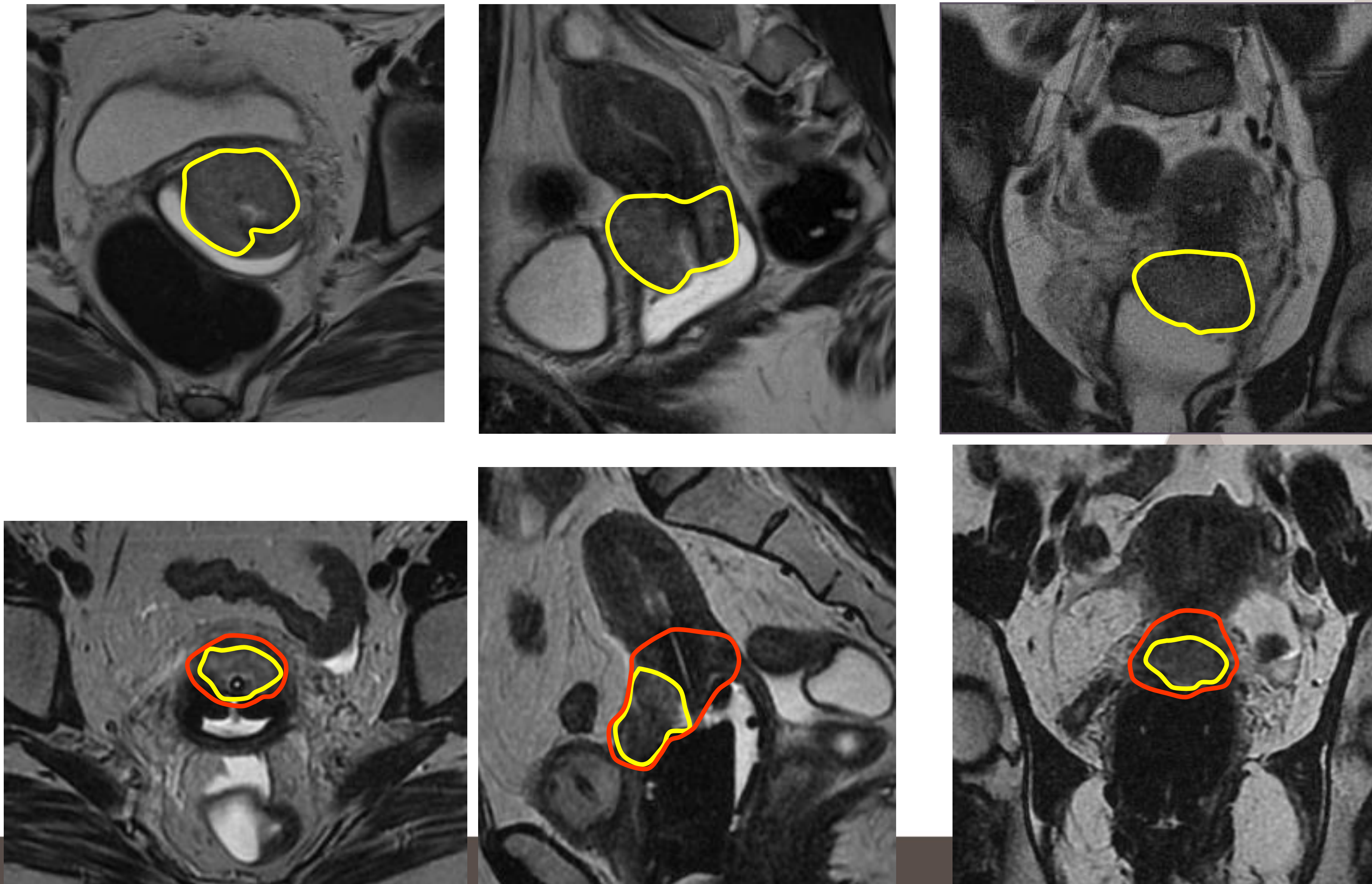
Stage IIA



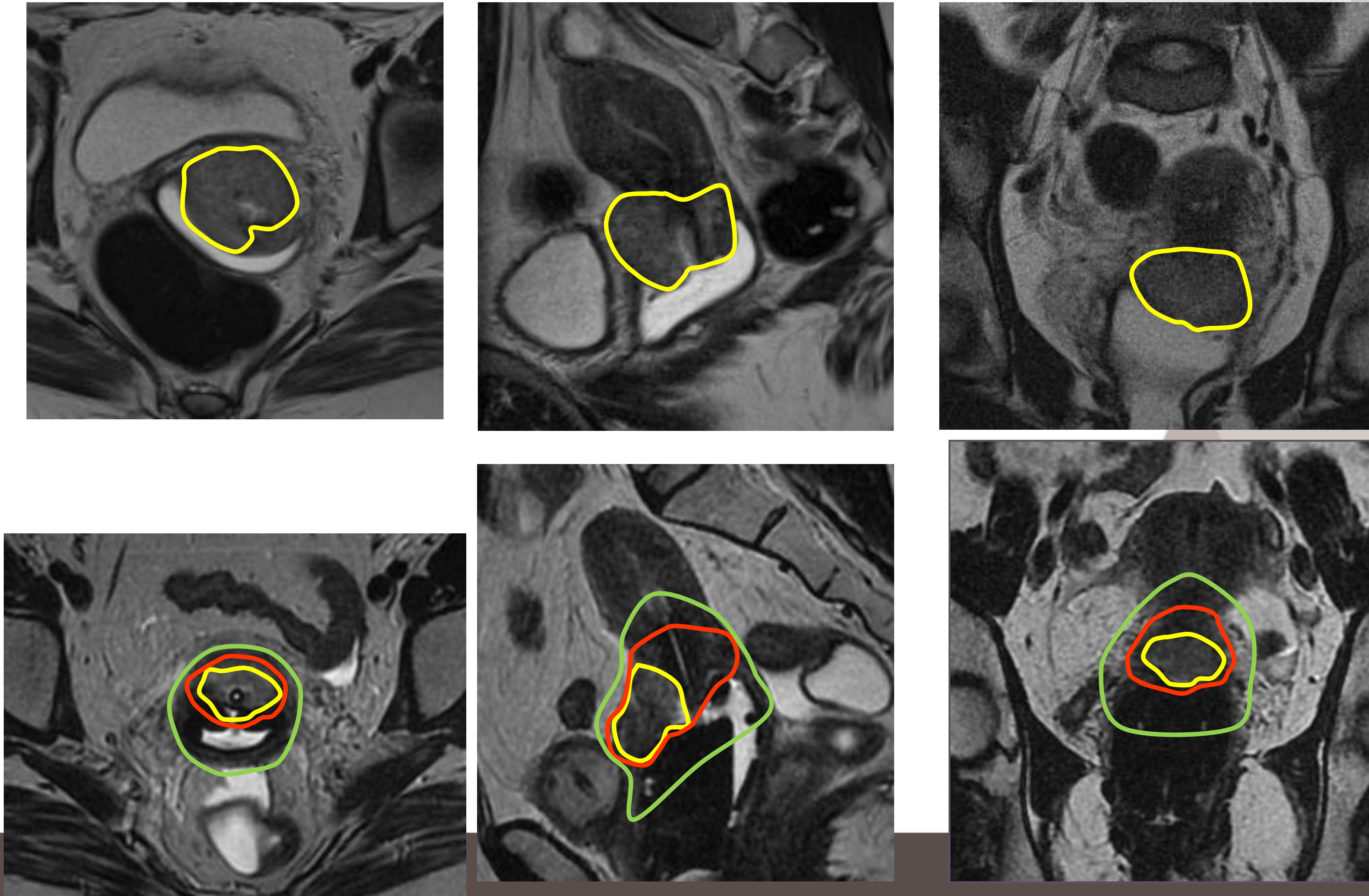
Stage IIA



Stage IIA



Stage IIA



Patient n° 4

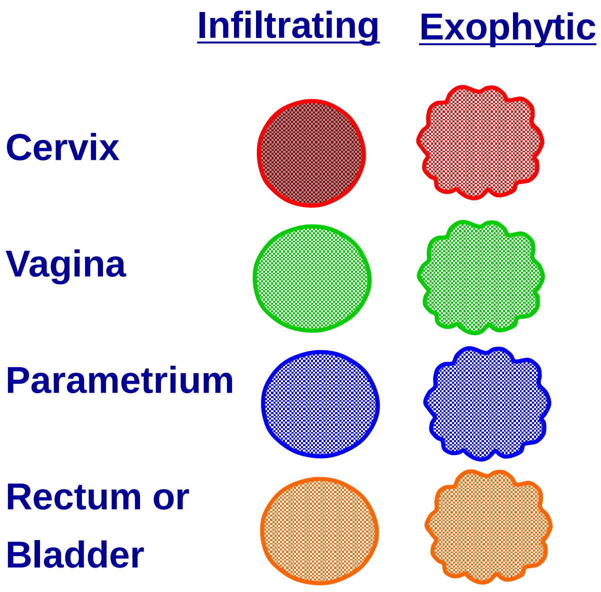
Mrs Evelyn BOR…
46 year-old
WHO=0, 72 kg, 1m67

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



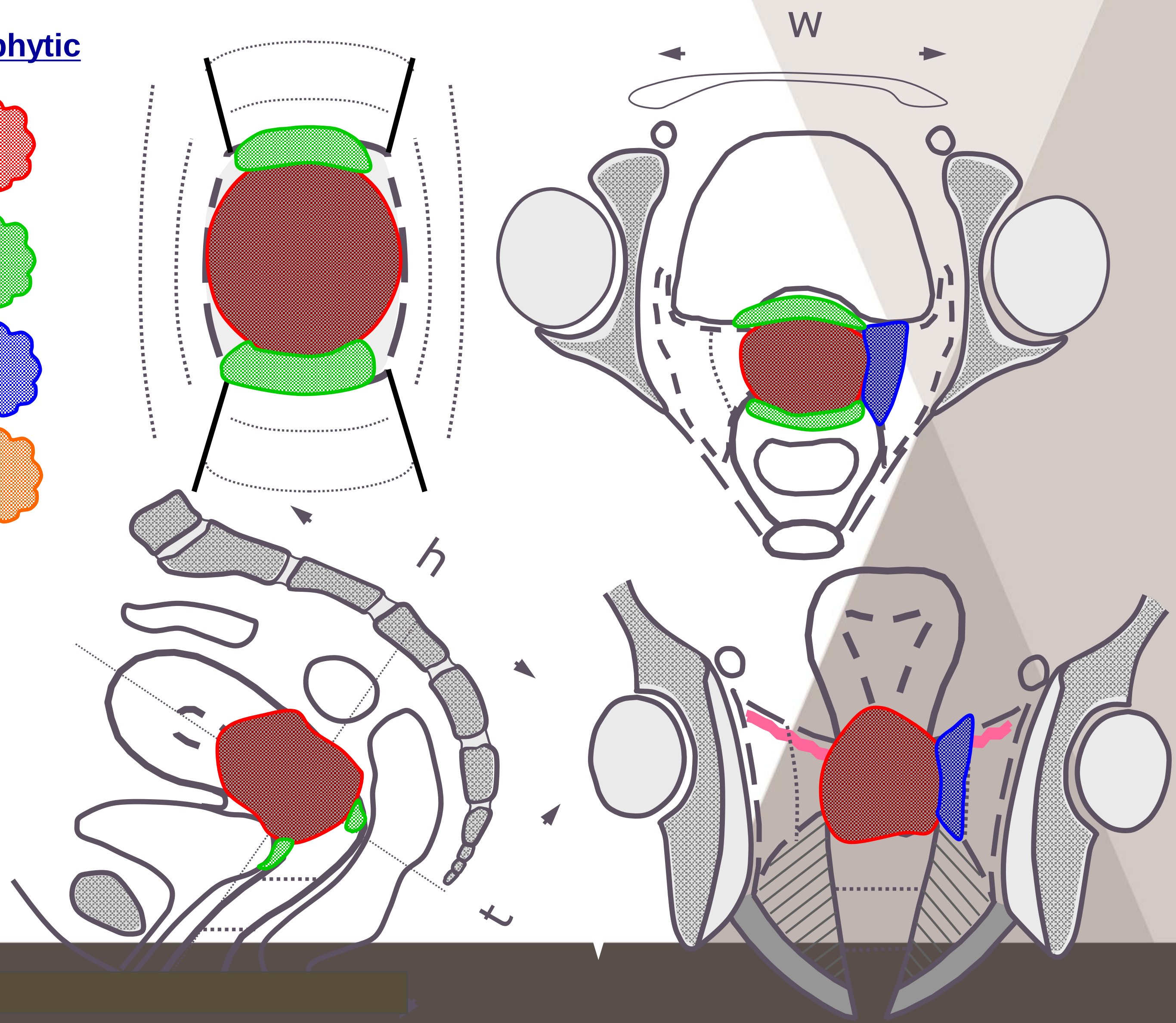
Dimensions (cm):

Width : 5

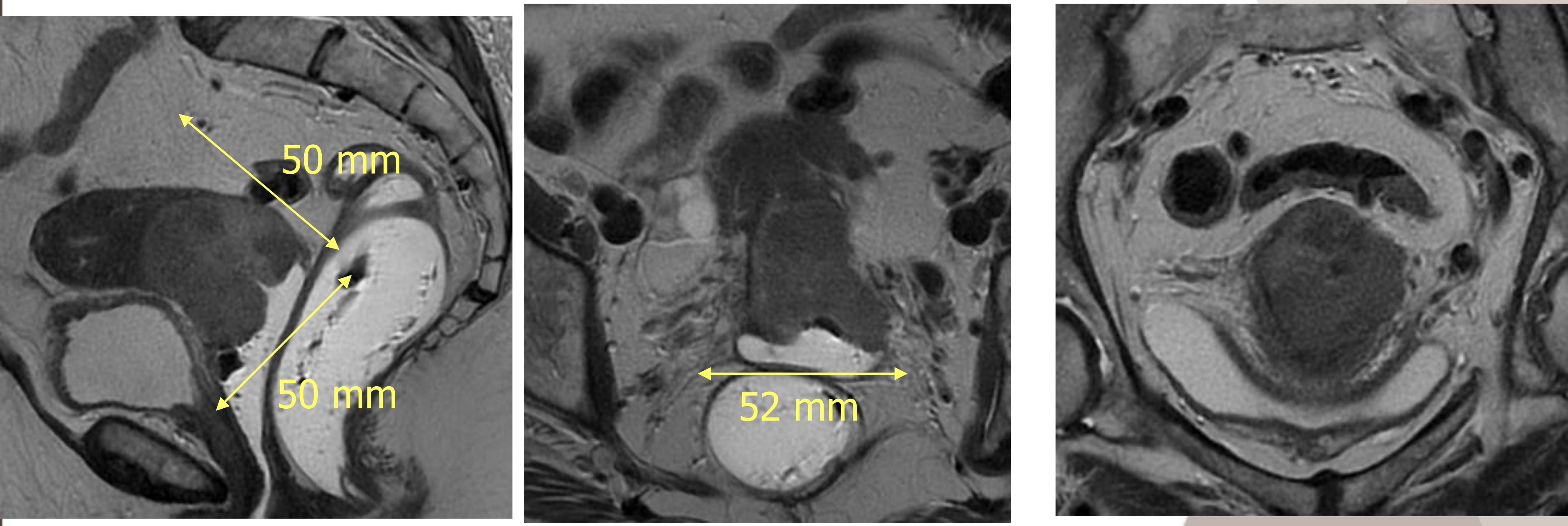
Thickness:5

Height : 5

Fornix involv 1

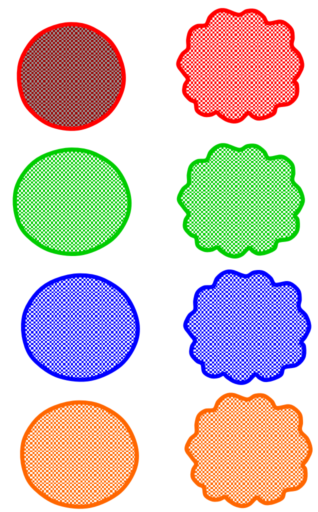


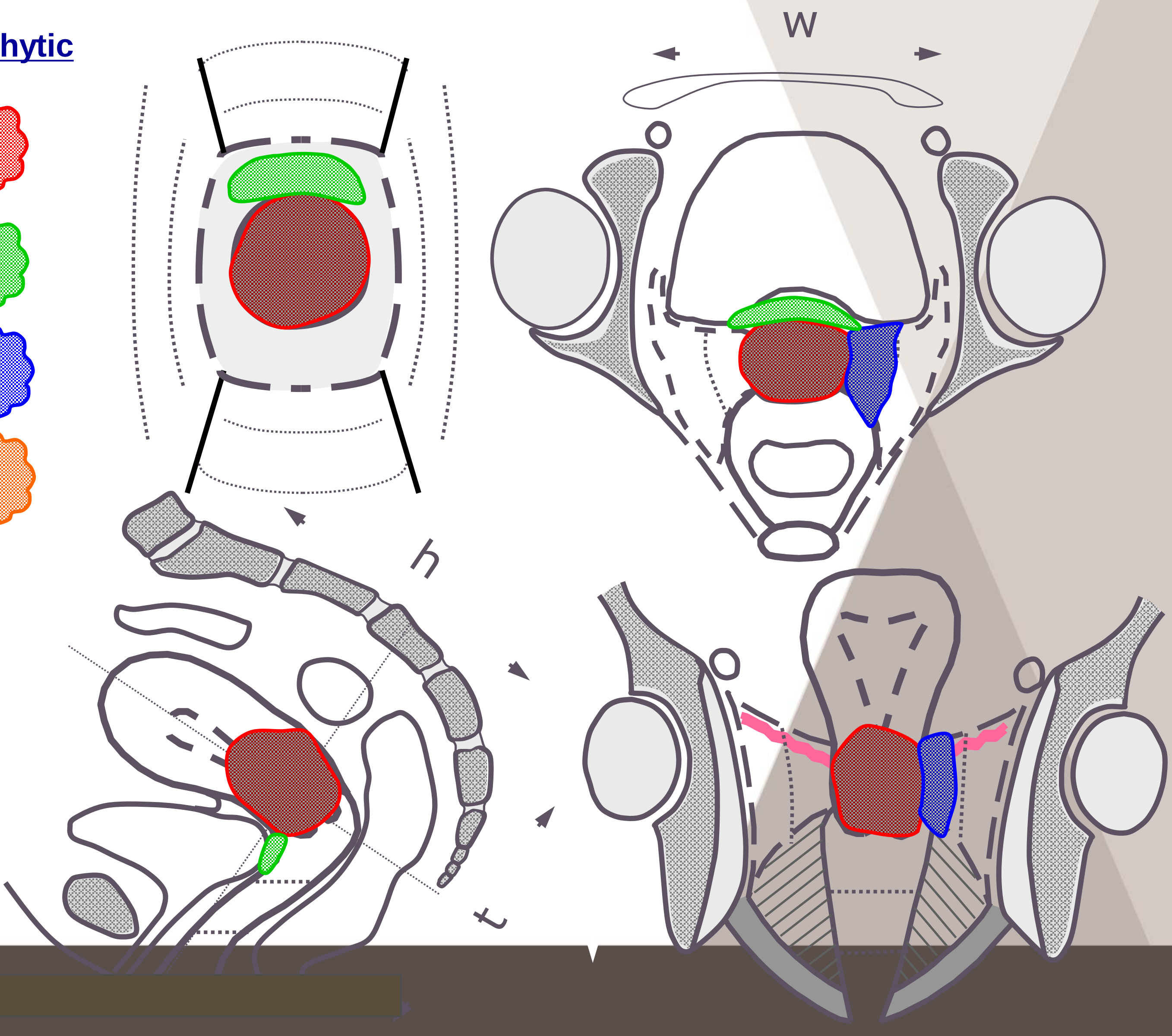
Stage IIB : initial MRI



Stage IIB : at the time of brachytherapy

	Infiltrating	Exophytic
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		





Dimensions (cm):

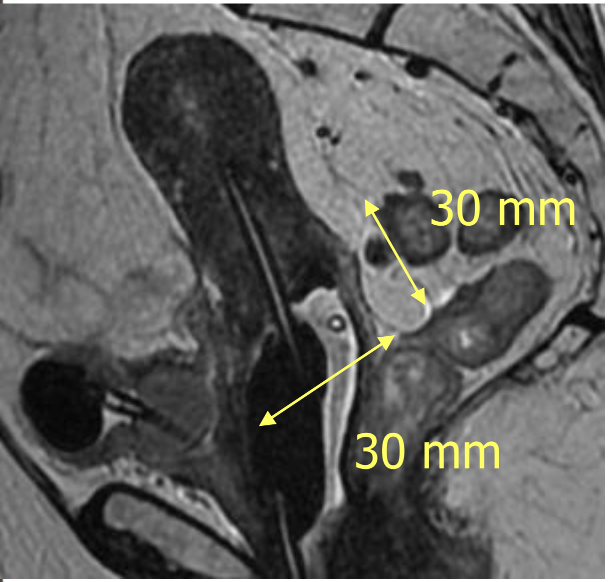
Largeur : 3

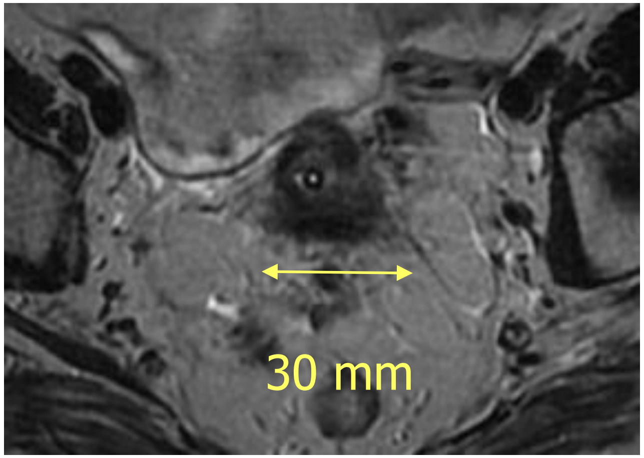
Epaisseur : 3

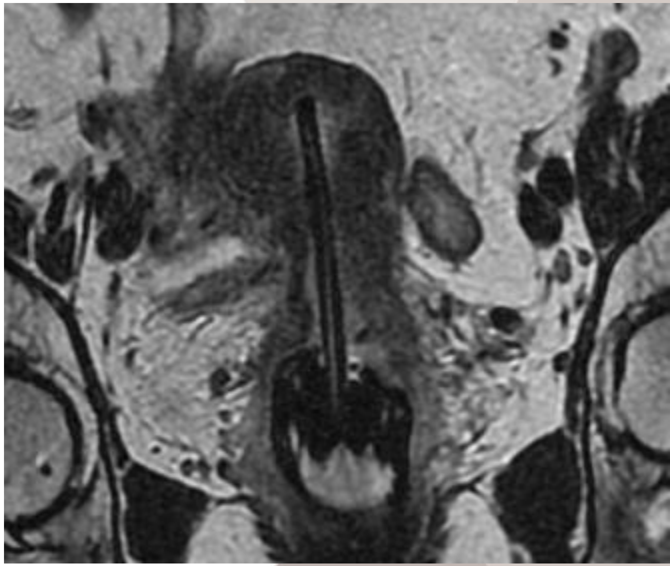
Hauteur : 3

Env. vaginal : 1

Stage IIB : MRI at the time of brachytherapy







Target volume concepts

High Risk CTV :
GTV at time of brachytherapy
In all cases includes:

- GTV + whole cervix
- Presumed tumour extension in adjacent tissues
  - **Clinical assessment**
  - **Residual grey zones on MRI**

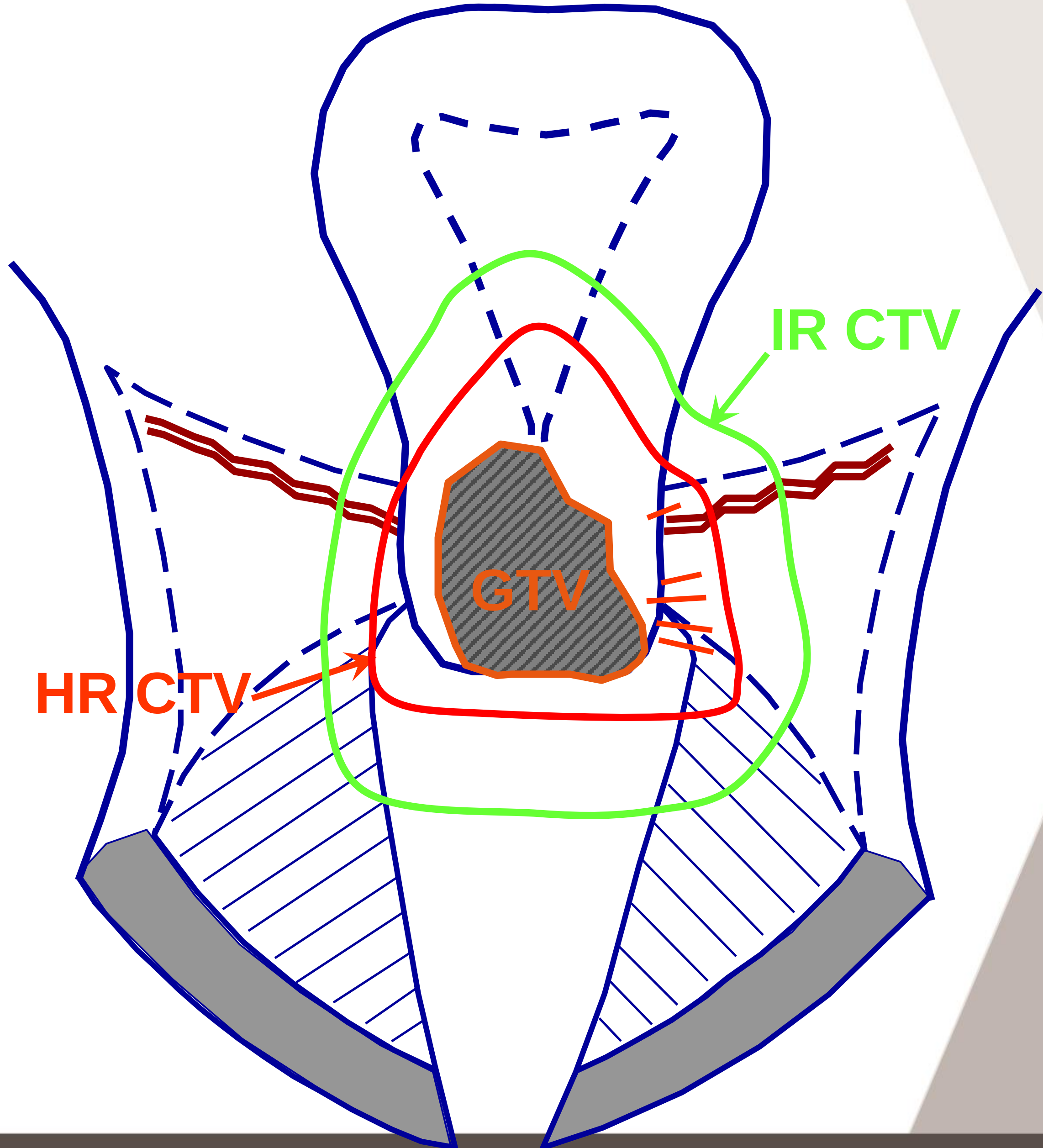
NO SAFETY MARGINS

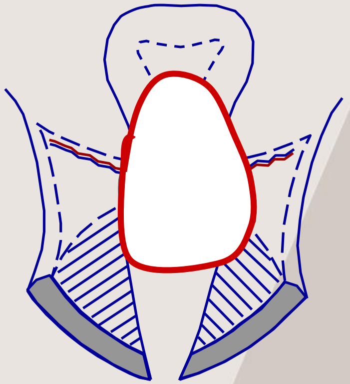
Intermediate Risk CTV :
GTV at time of diagnosis
In all cases includes:

- HR-CTV
- integrates initial CTV

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

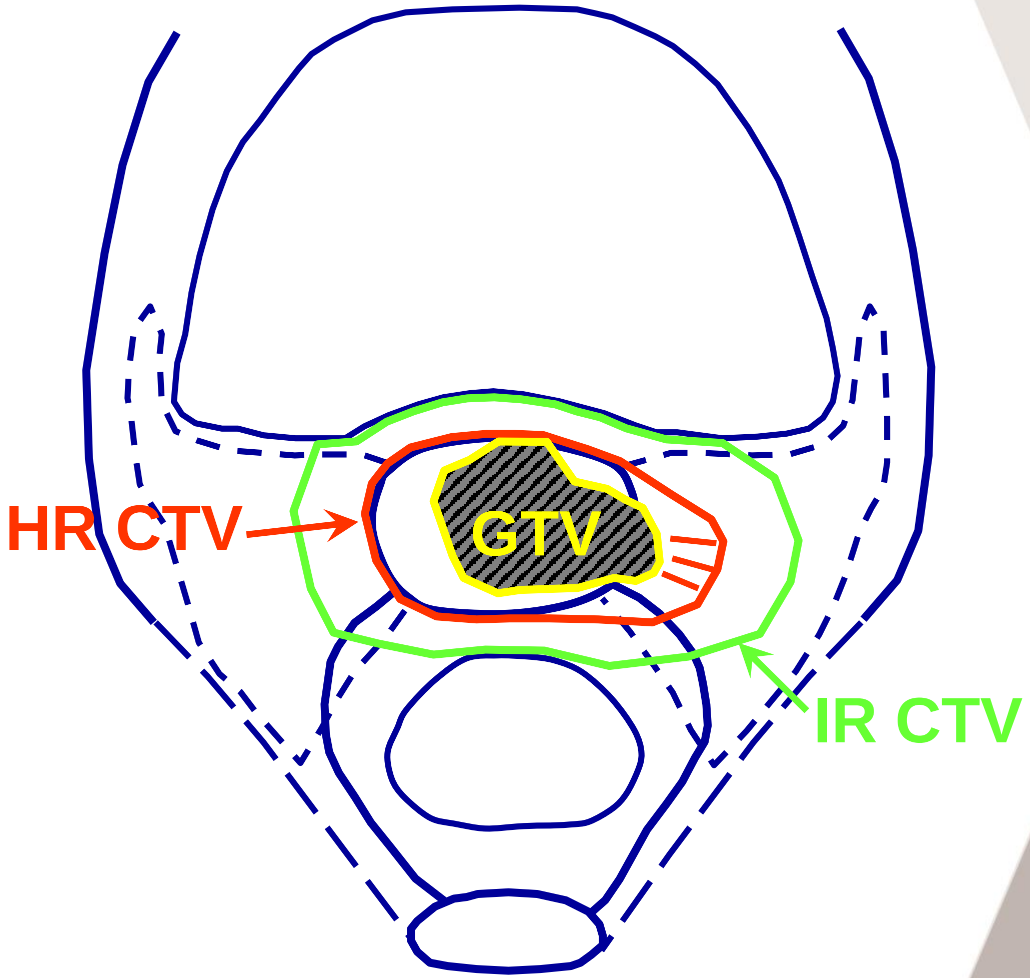
Stage IIB

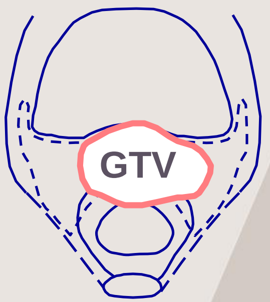




Tumor at time of diagnosis

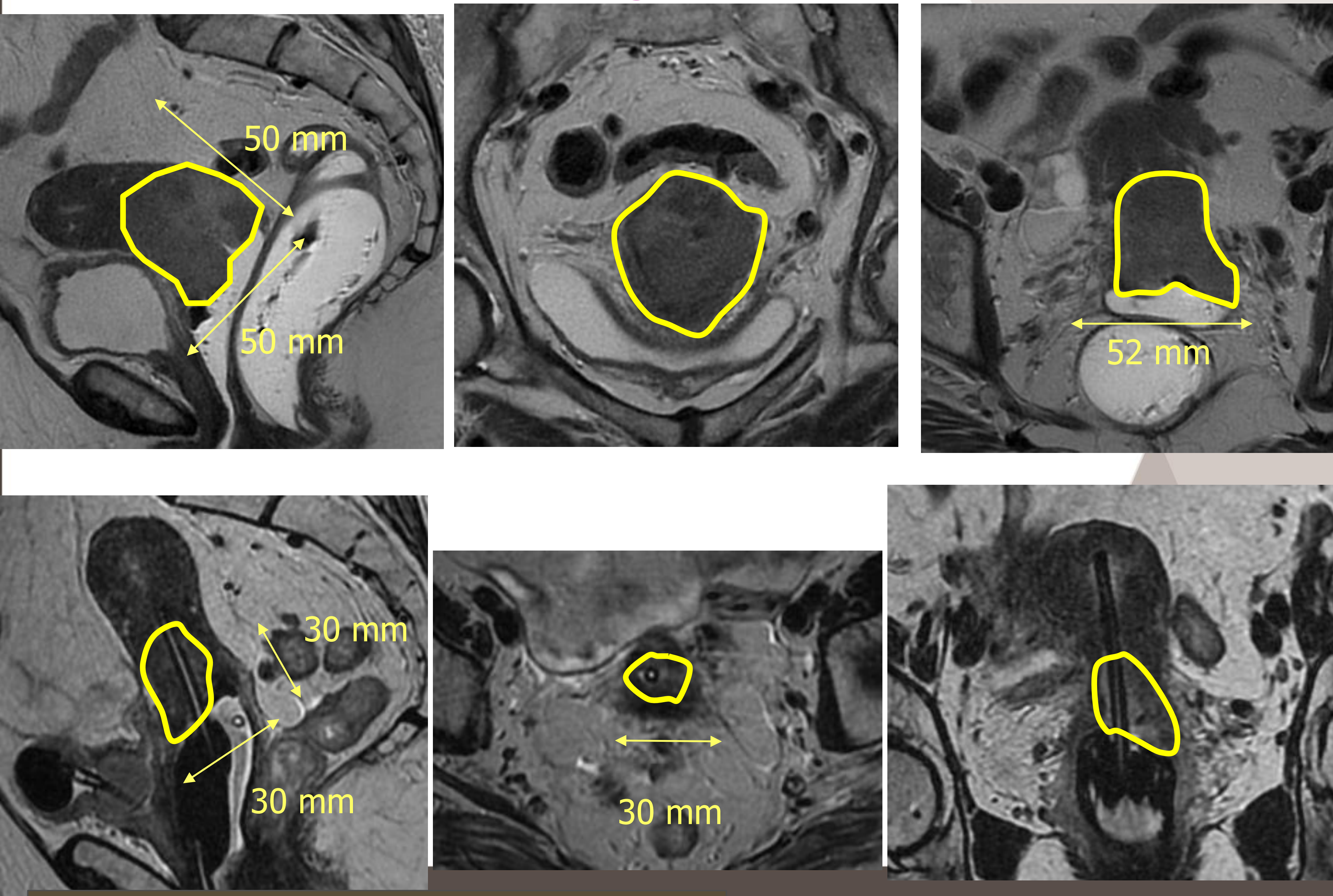
Stage IIB



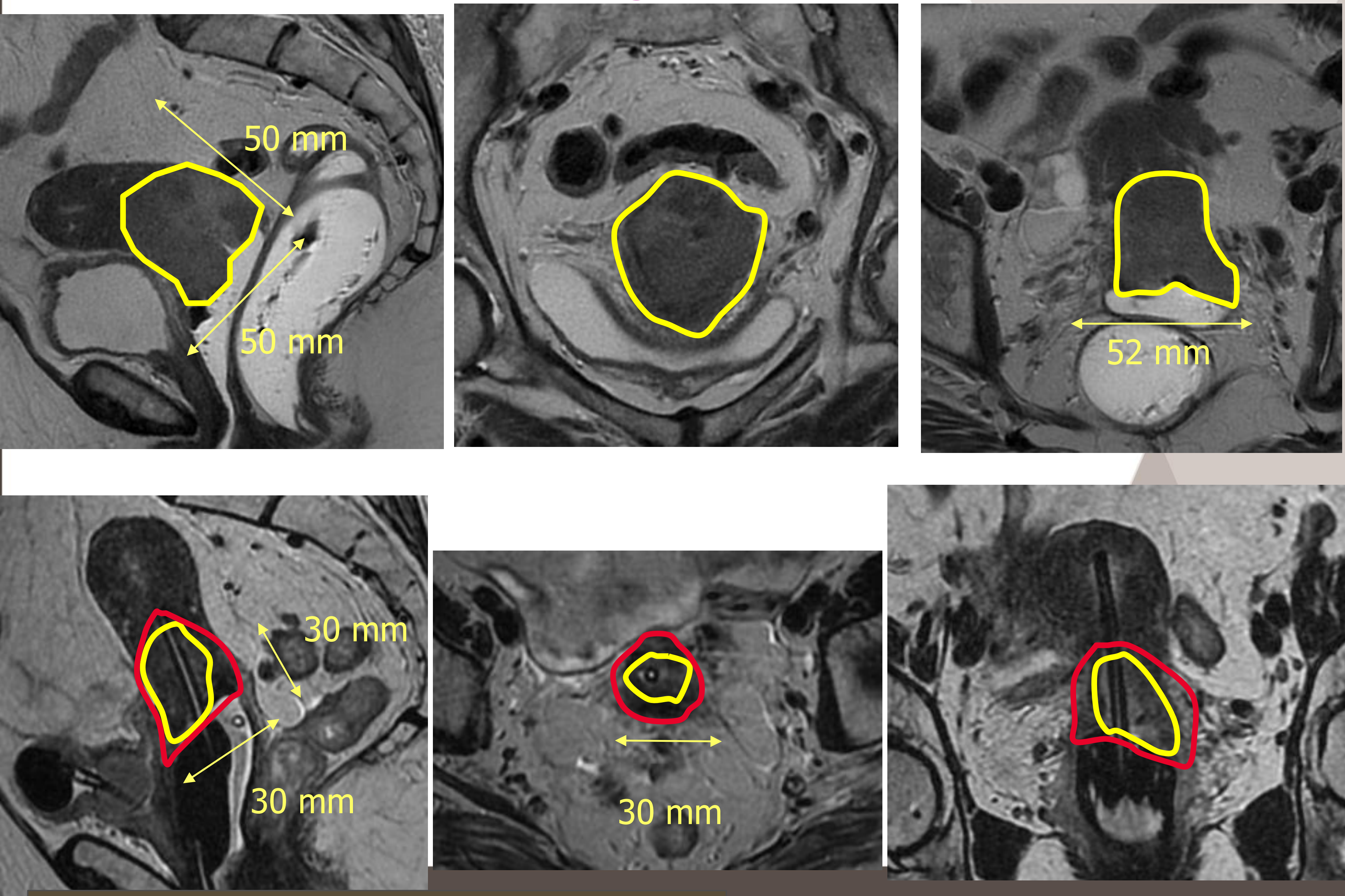


Tumor at time of diagnosis.

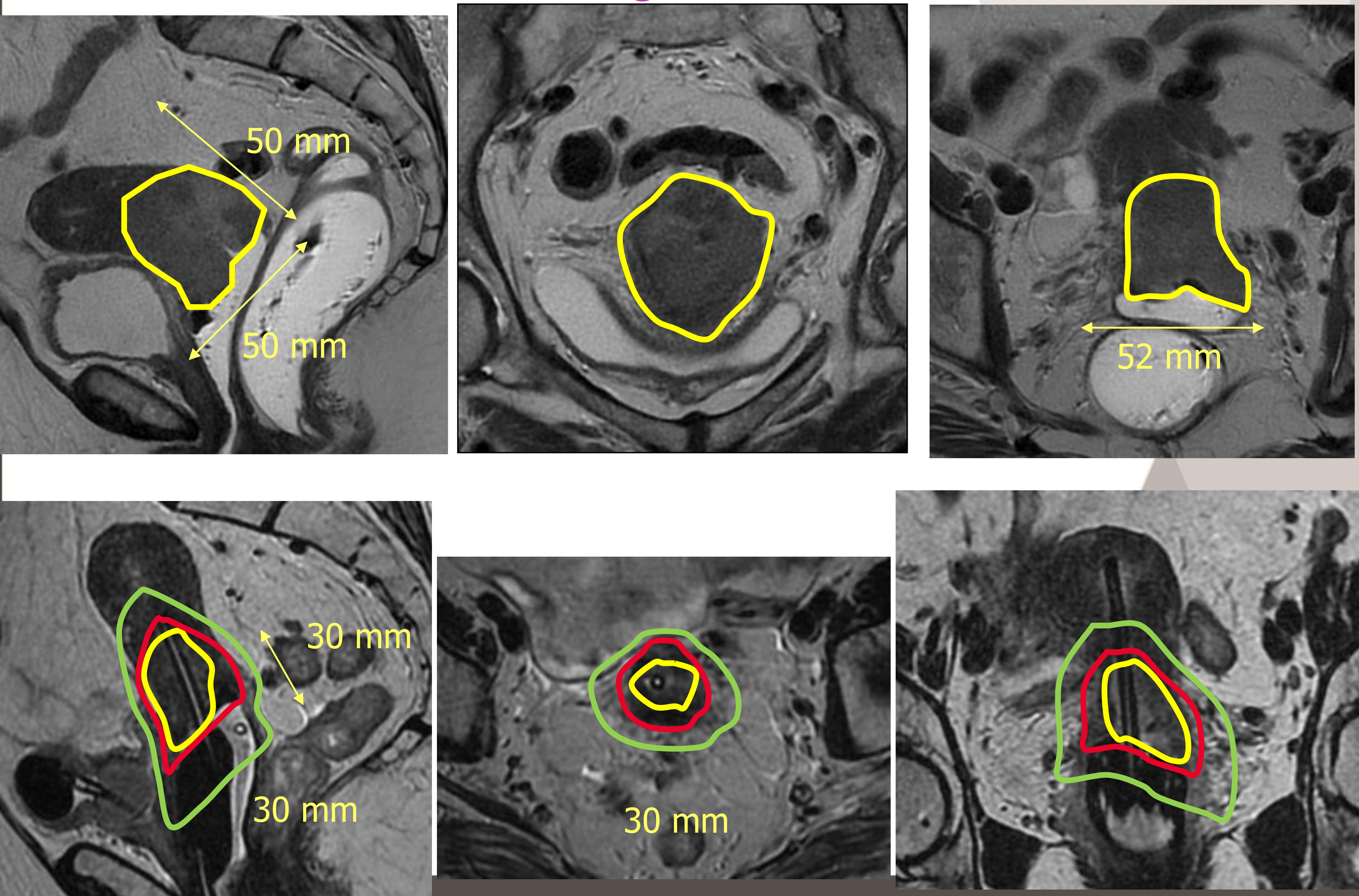
Stage IIB



Stage IIB



Stage IIB



Patient n° 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

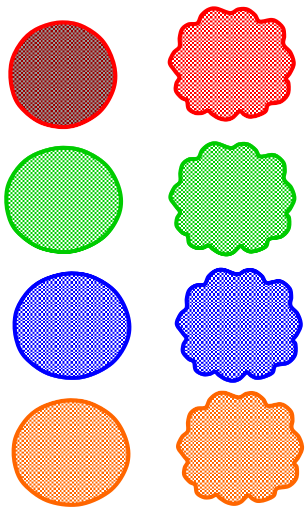
Infiltrating **Exophytic**

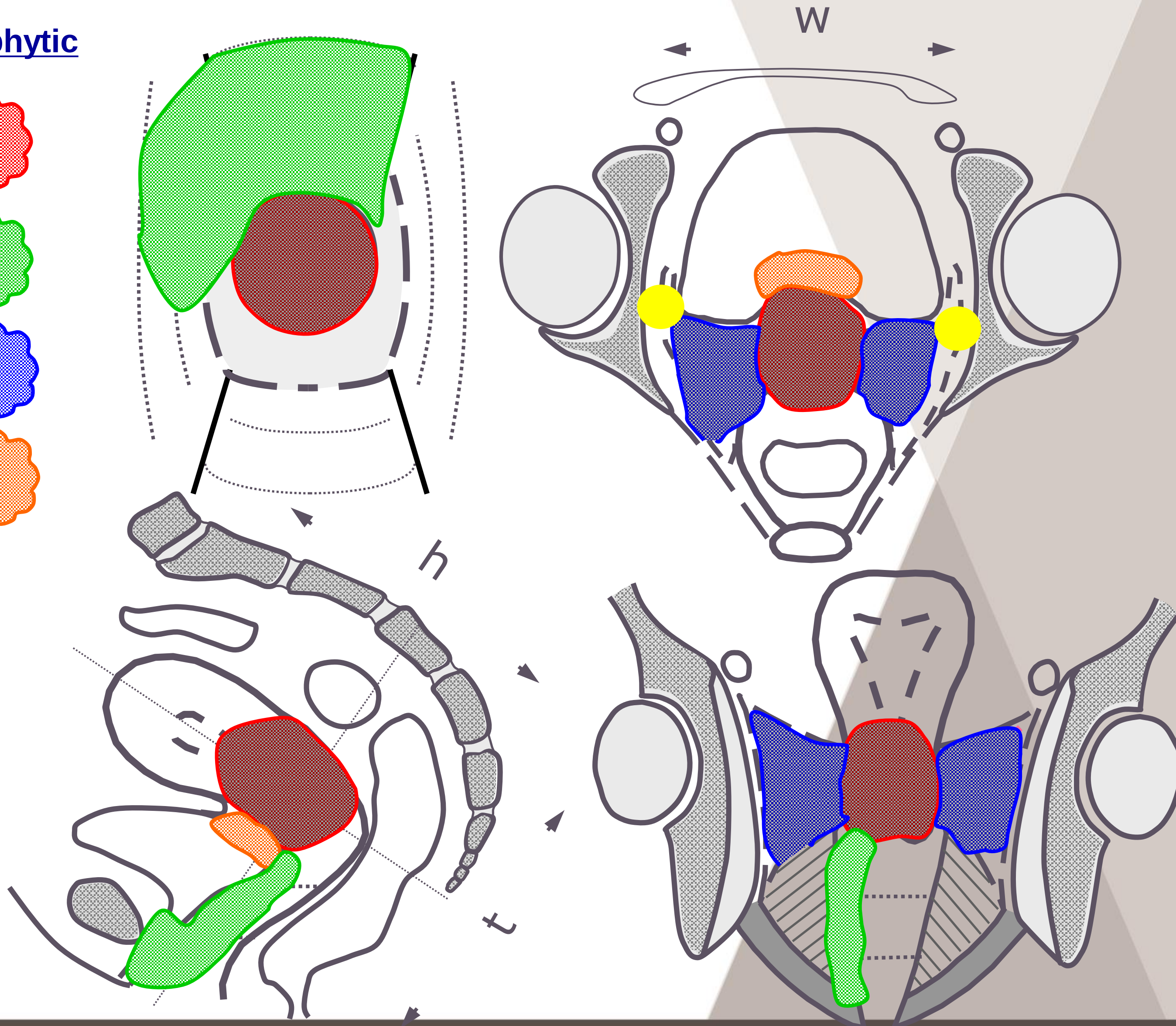
Cervix

Vagina

Parametrium

Rectum or Bladder





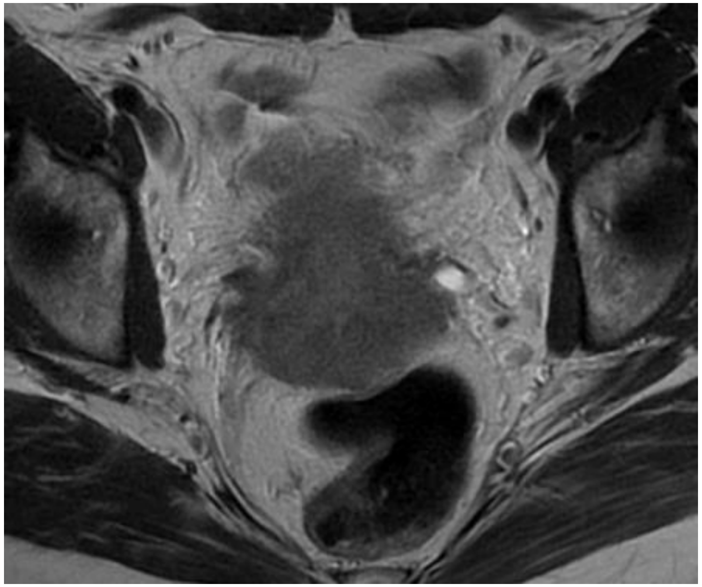
Dimensions (cm):

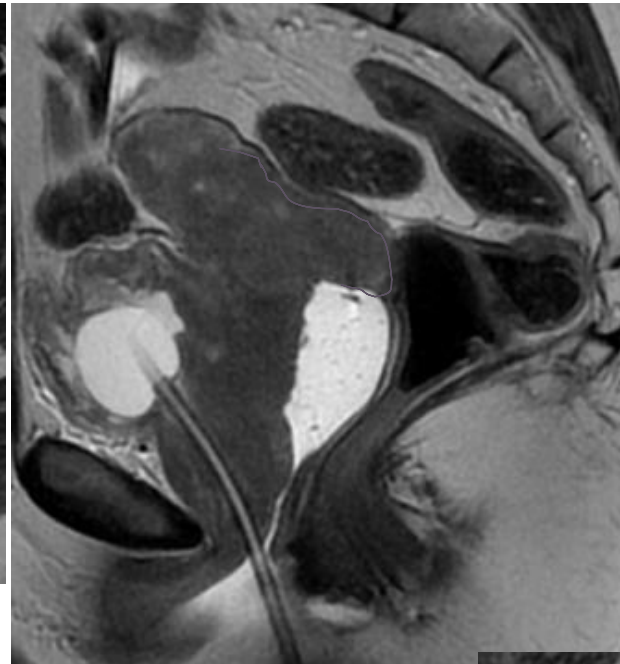
Width : 8

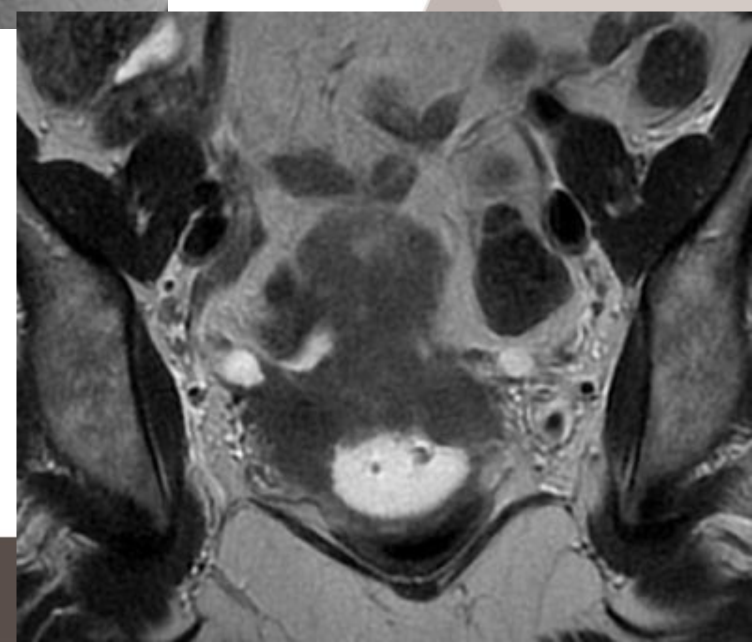
Thickness :6

Height : 7

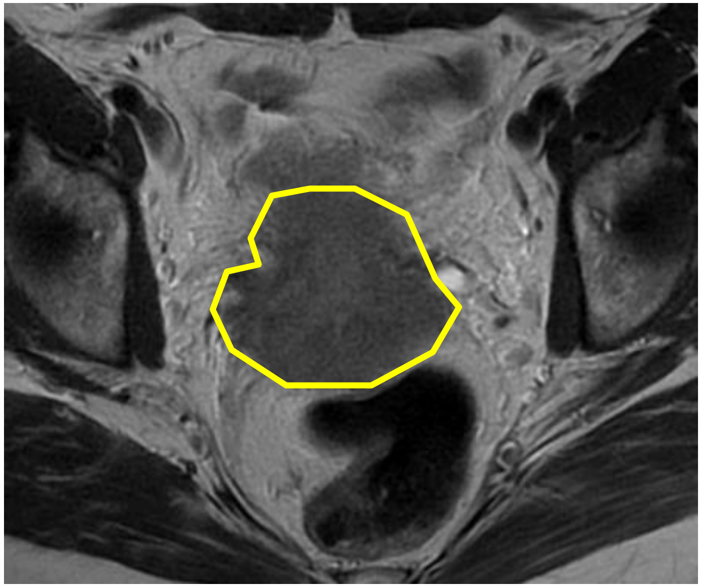
Stage IVA : initial MRI

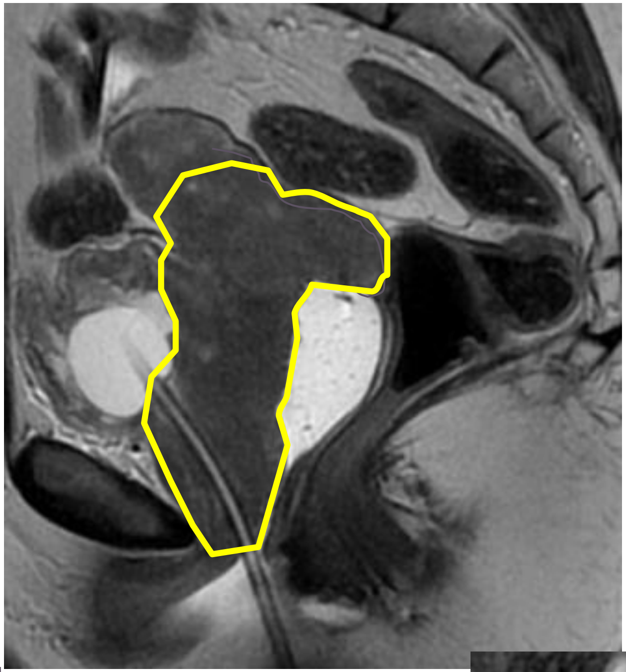


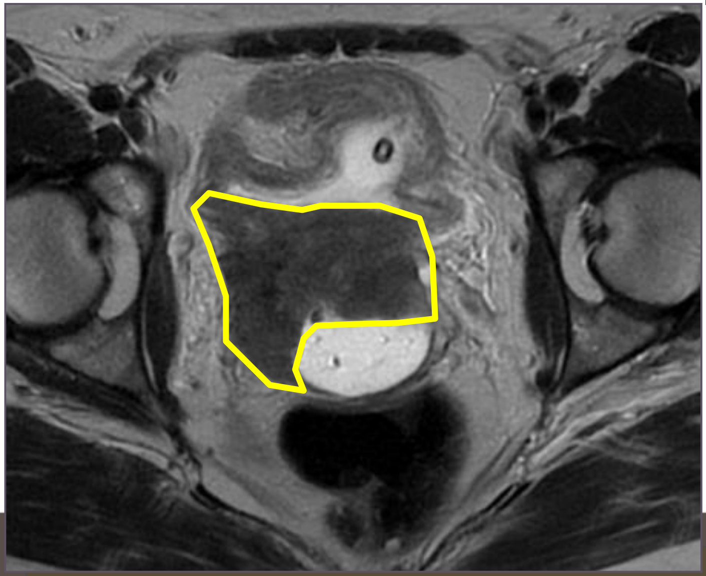


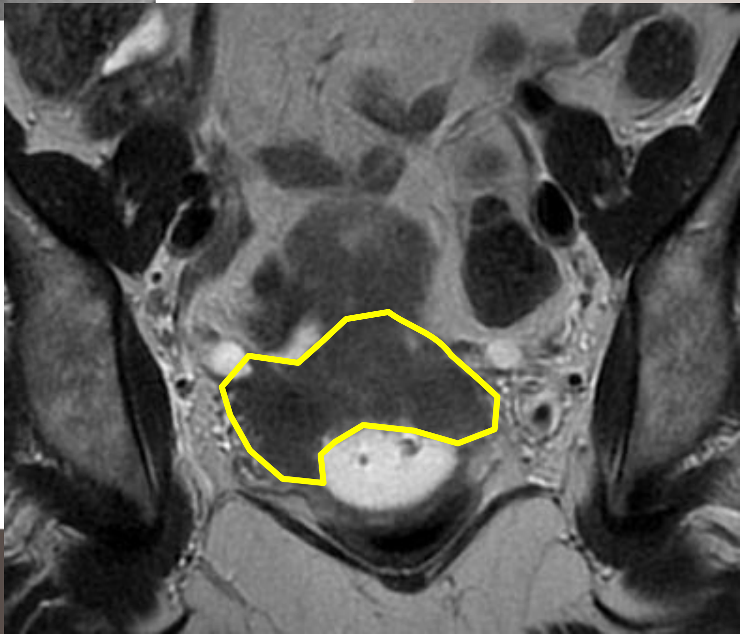


Stage IVA : initial MRI



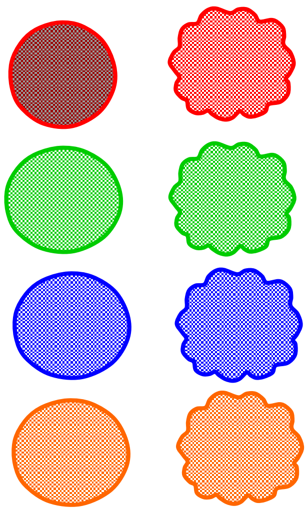






Stage IVA : at time of brachy

	Infiltrating	**Exophytic**
Cervix		
Vagina		
Parametrium		
Rectum or Bladder		

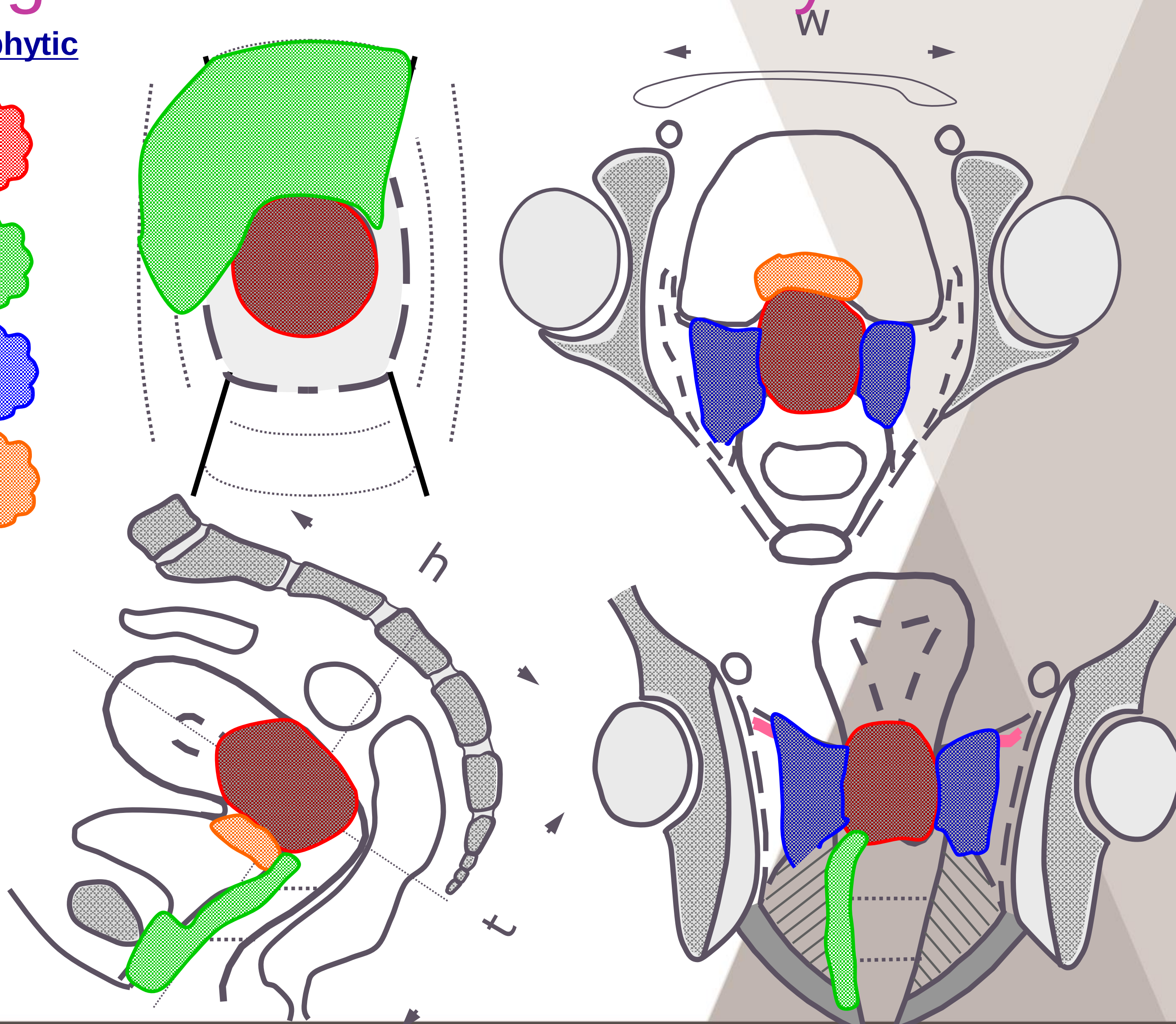


Dimensions (cm):

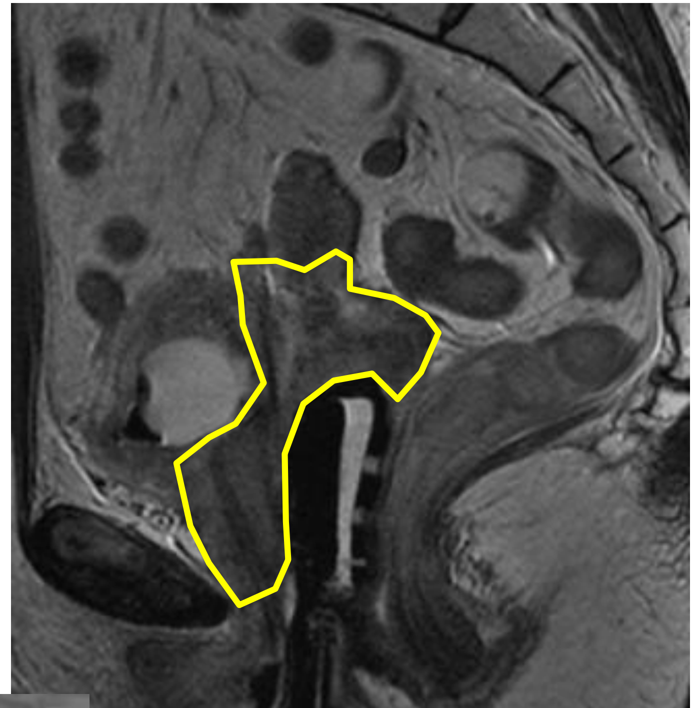
Width : 8

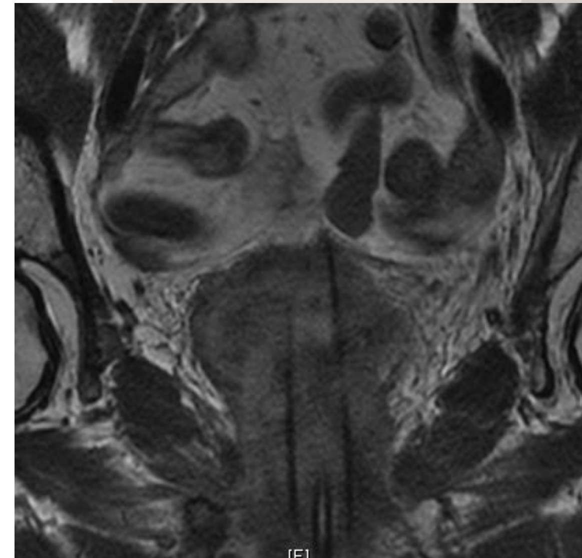
Thickness :6

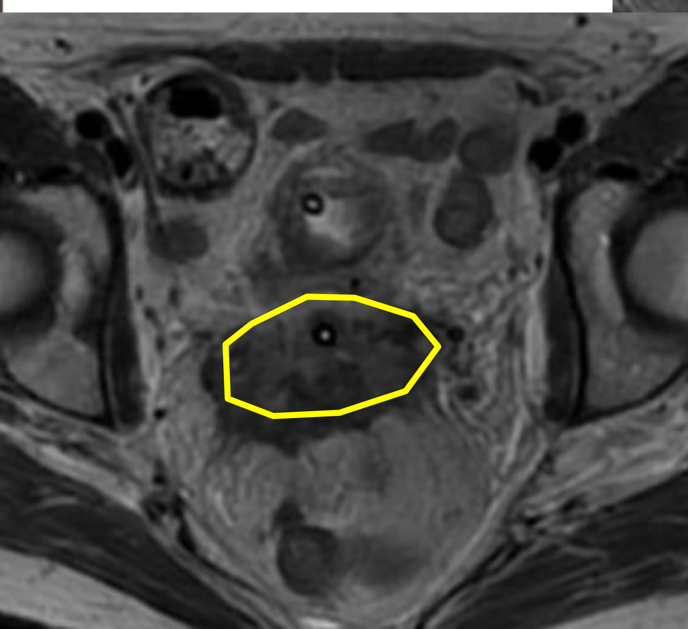
Height : 7



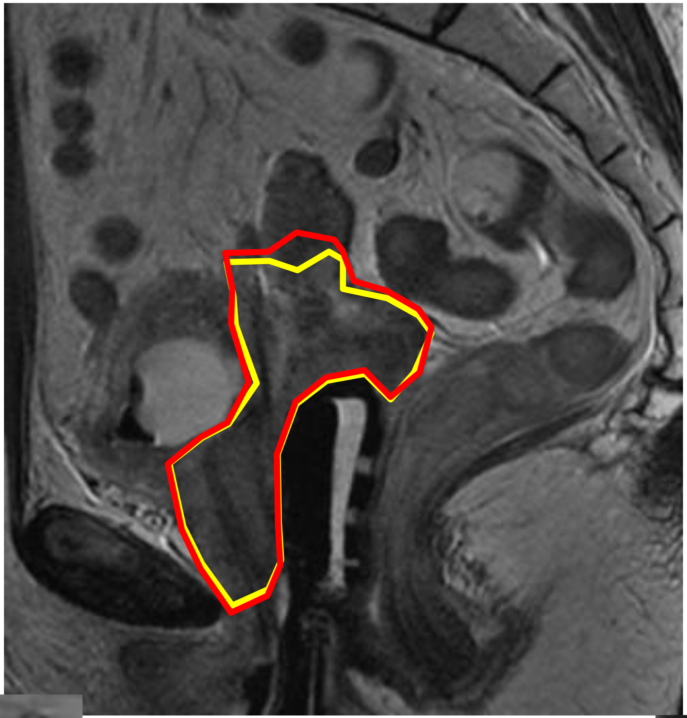
Stage IVA : at time of brachytherapy

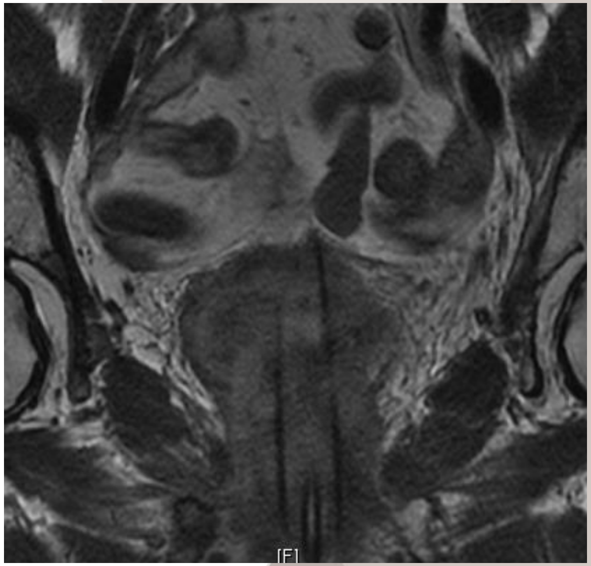


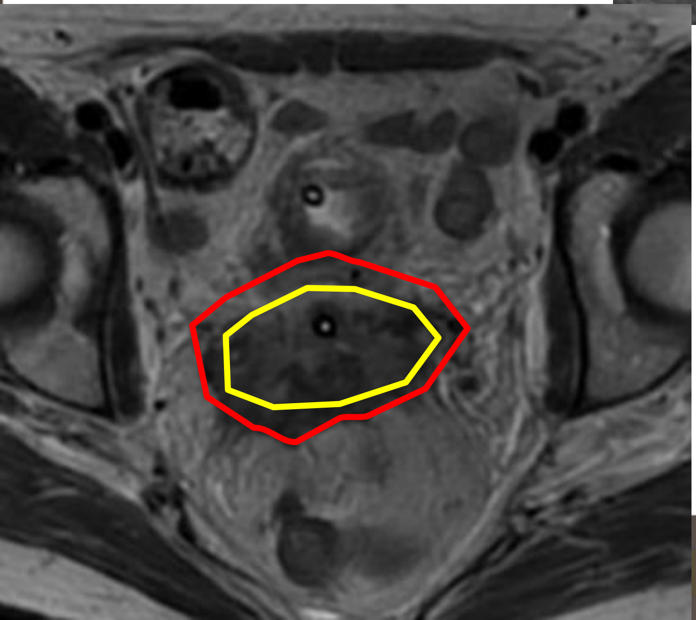


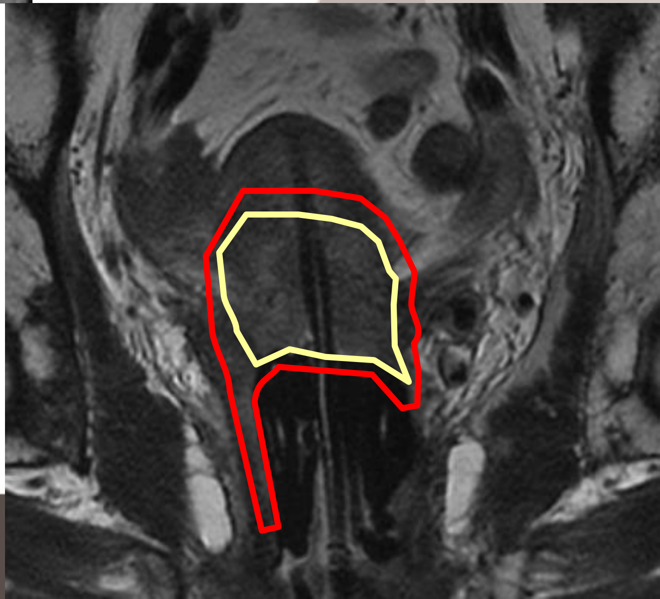


Stage IVA : at time of brachytherapy

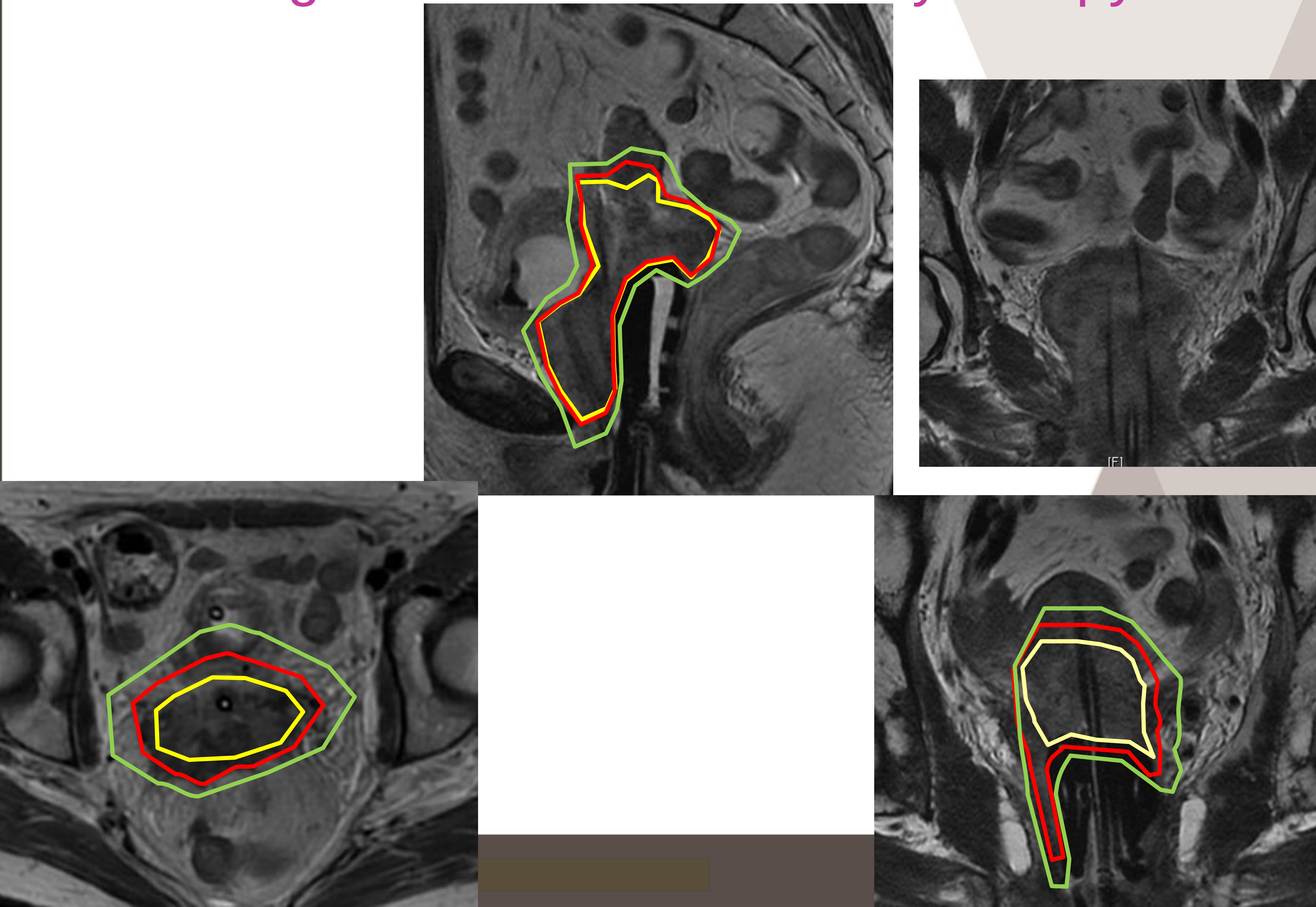








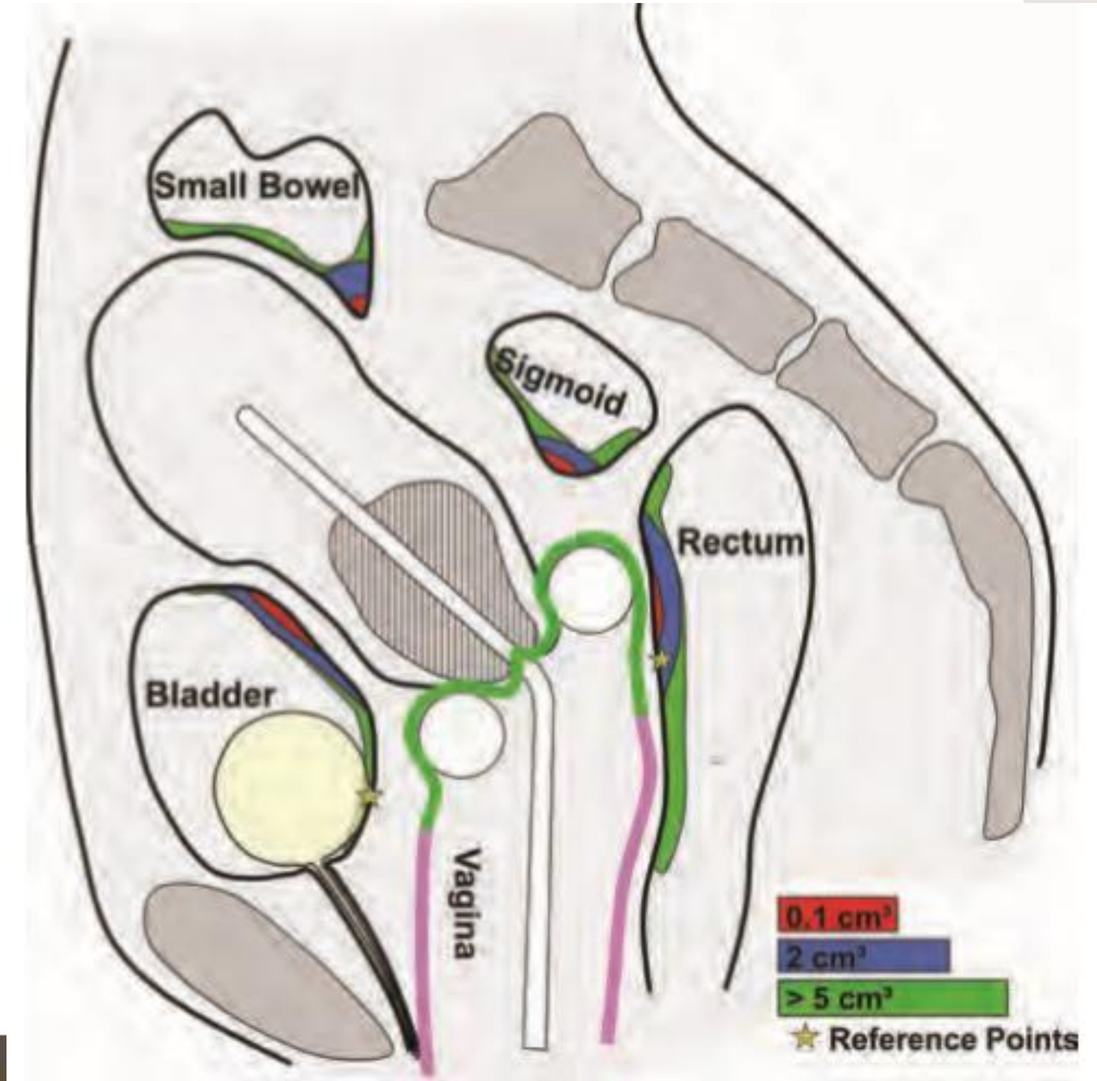
Stage IVA : at time of brachytherapy



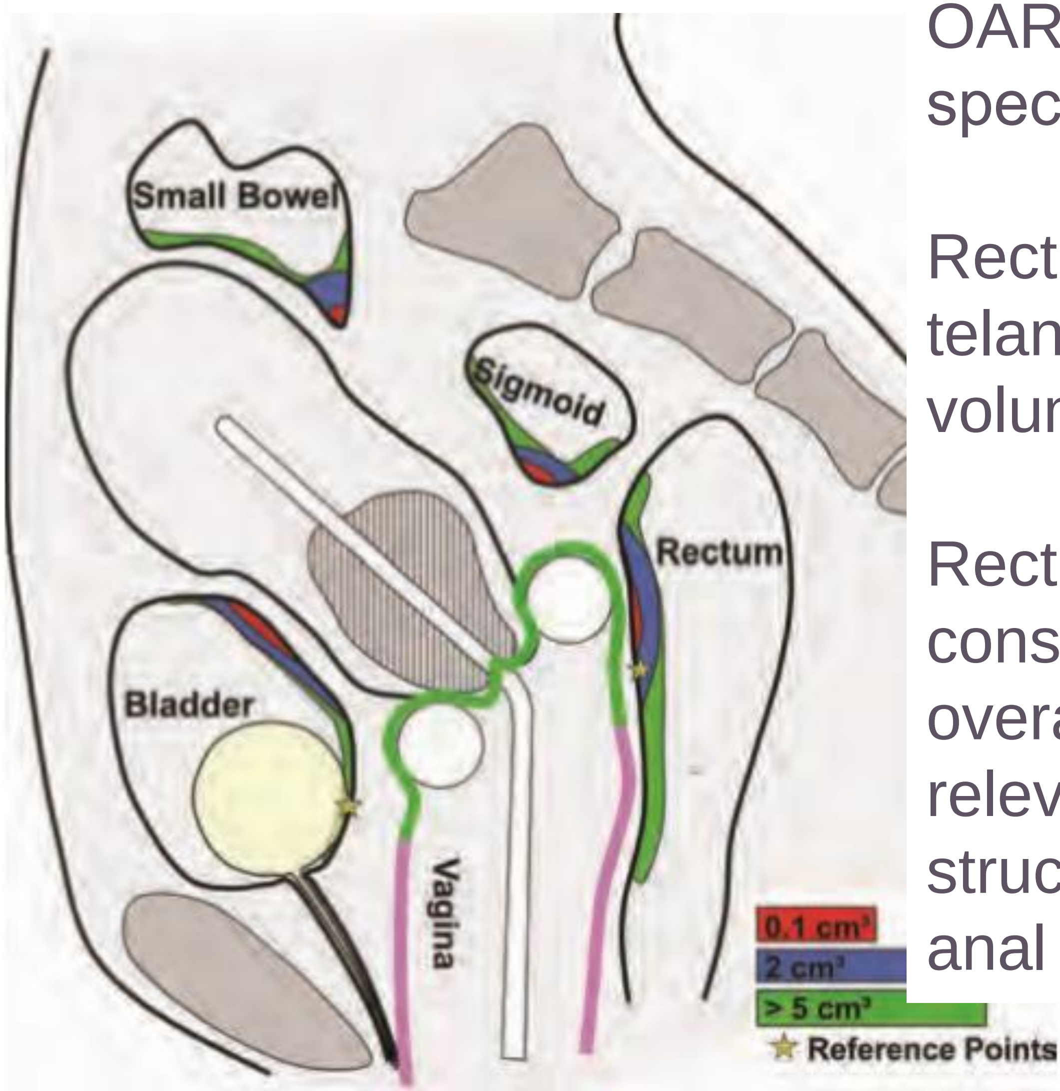
Organs at risk

Organs at risk

Small organ-wall volumes up to 2 cm^3–3cm^3 represent typical targets for brachytherapy-related morbidity



Organs at risk



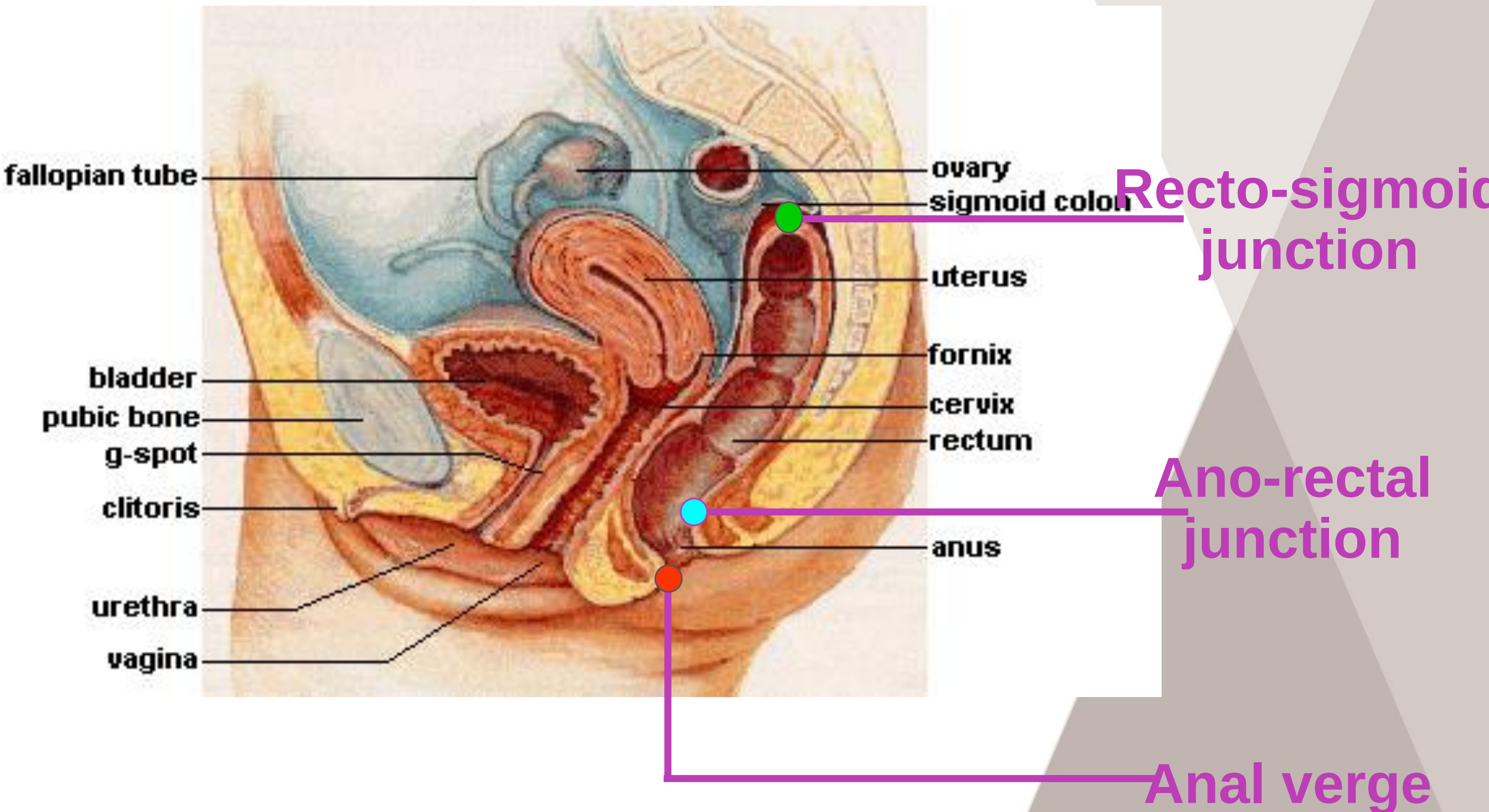
OAR-specific or OAR-sub-volume specific types of morbidity

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

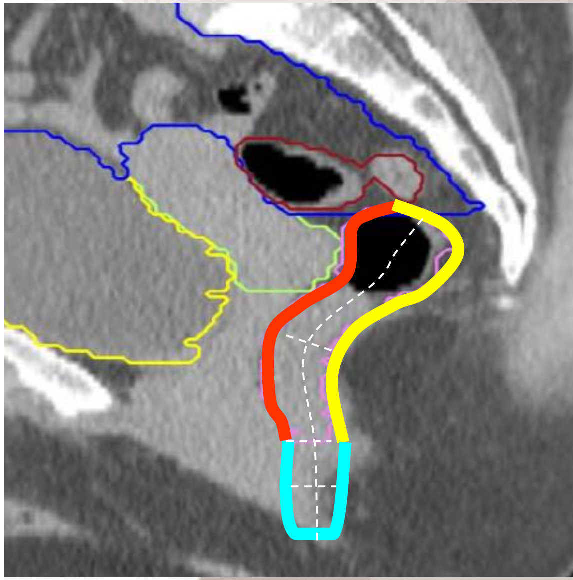
Perspectives

Separate delineation of ano-rectal regions

Separate assessment of DVH to different regions

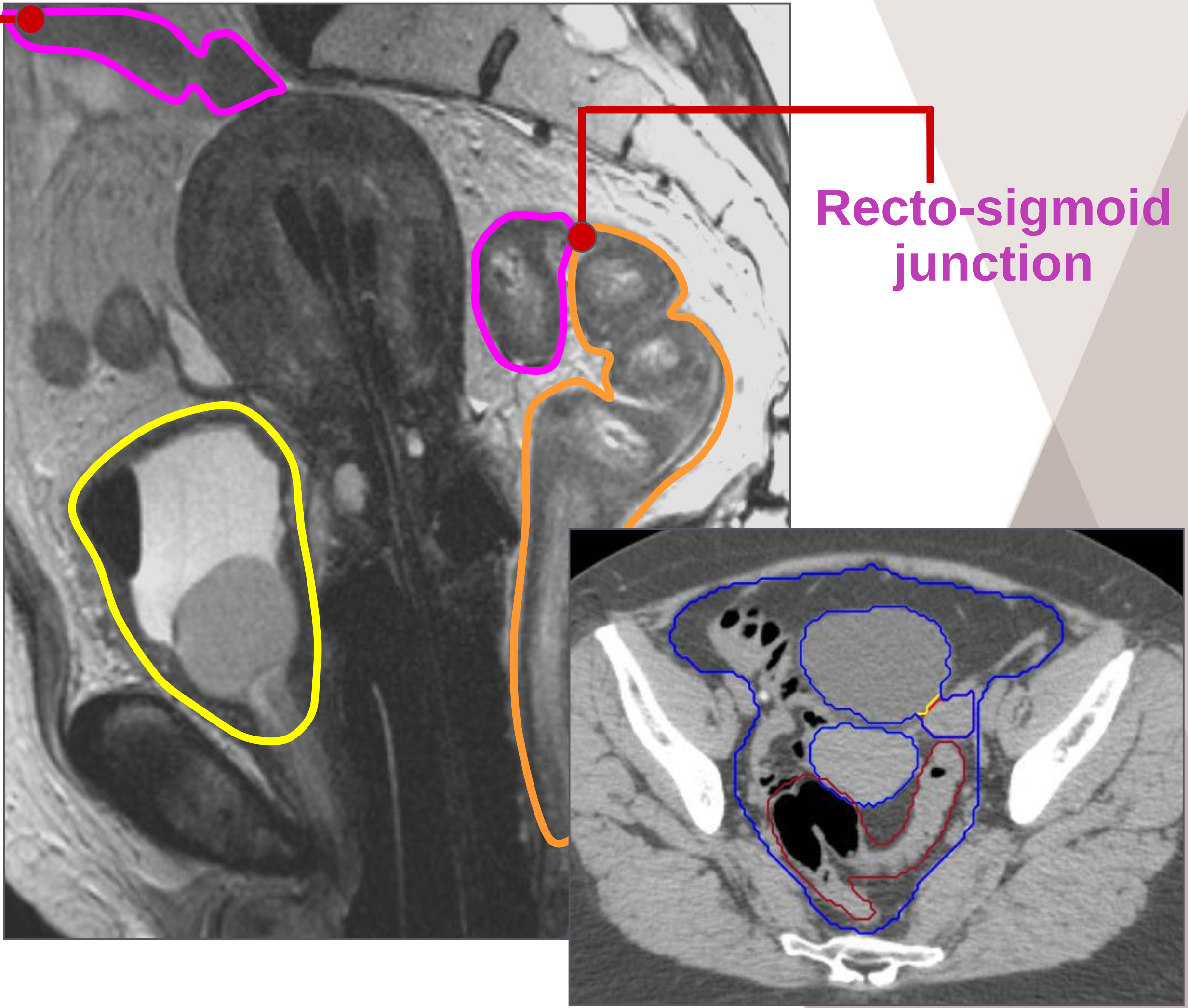
Separate scoring & modelling of different endpoints

Determination of relevant structures for different endpoints



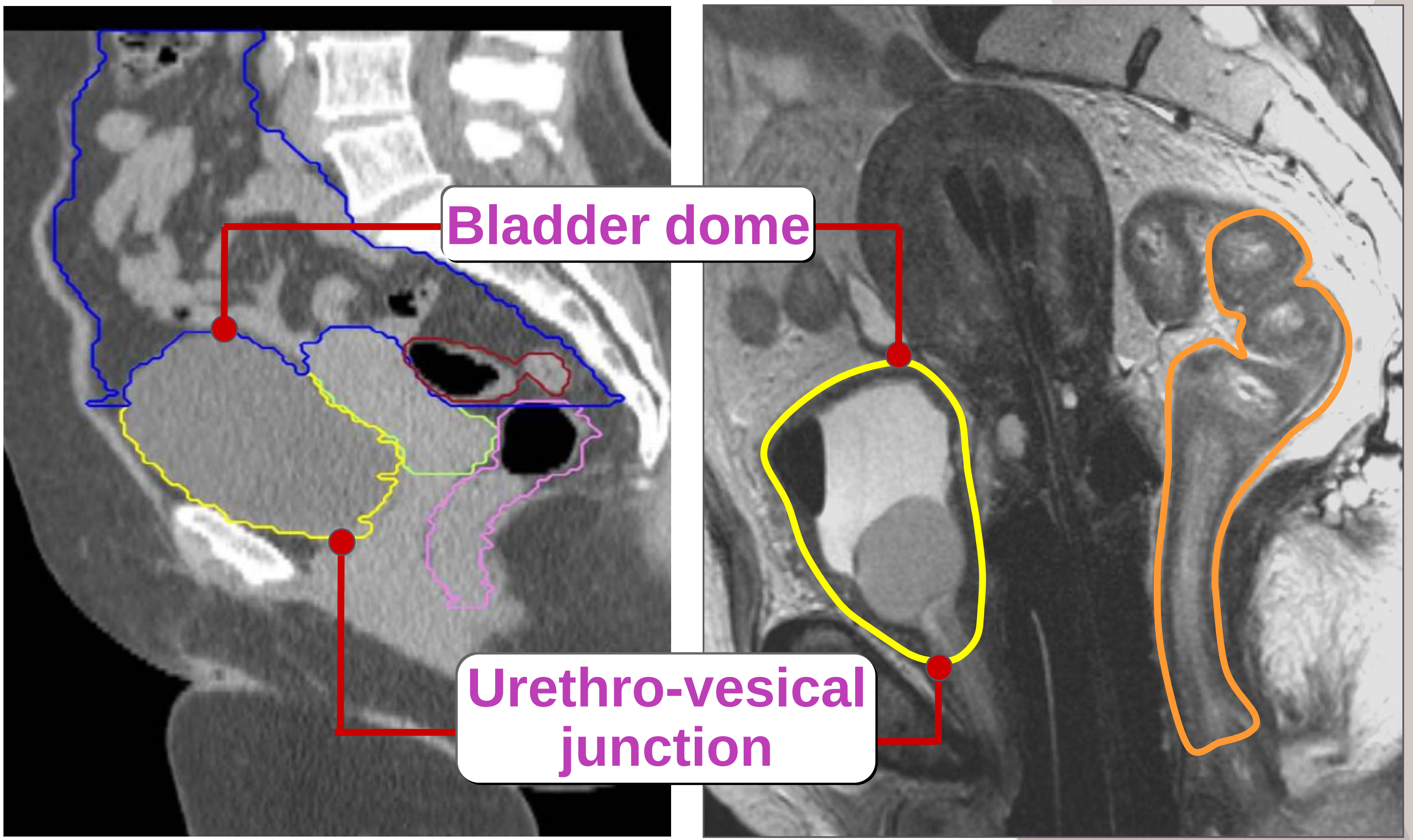
High D regions

Sigmoid colon



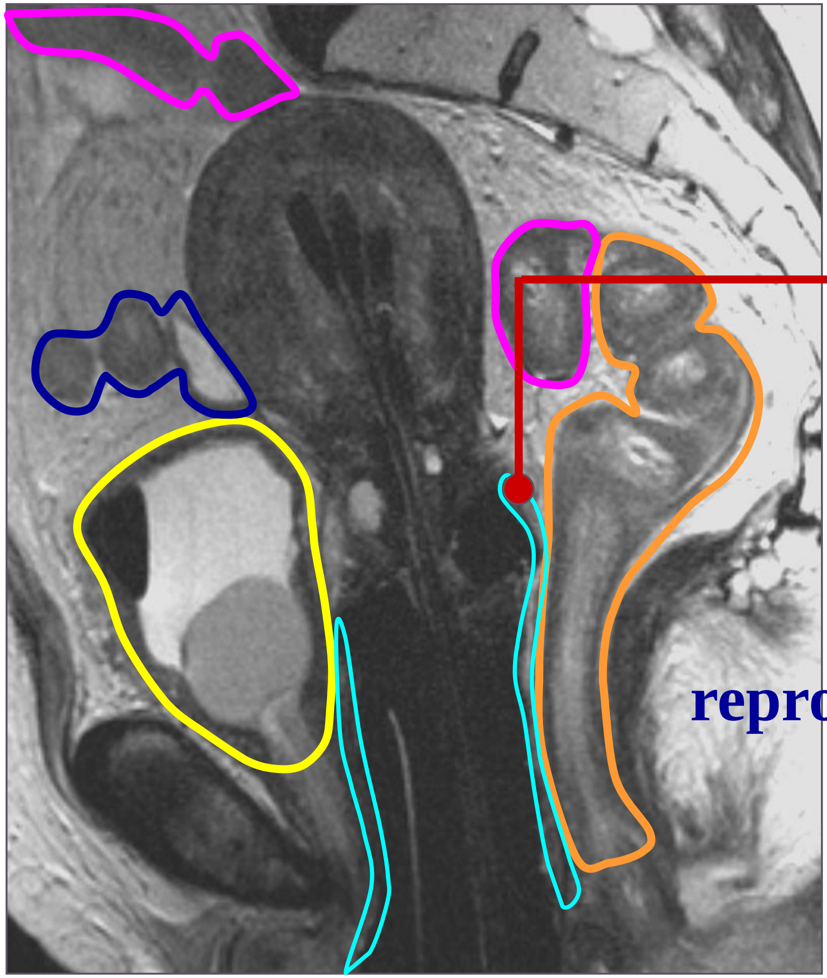
Bladder

What to delineate?



Viswanathan AN, et al. IJROBP 2010

Vagina



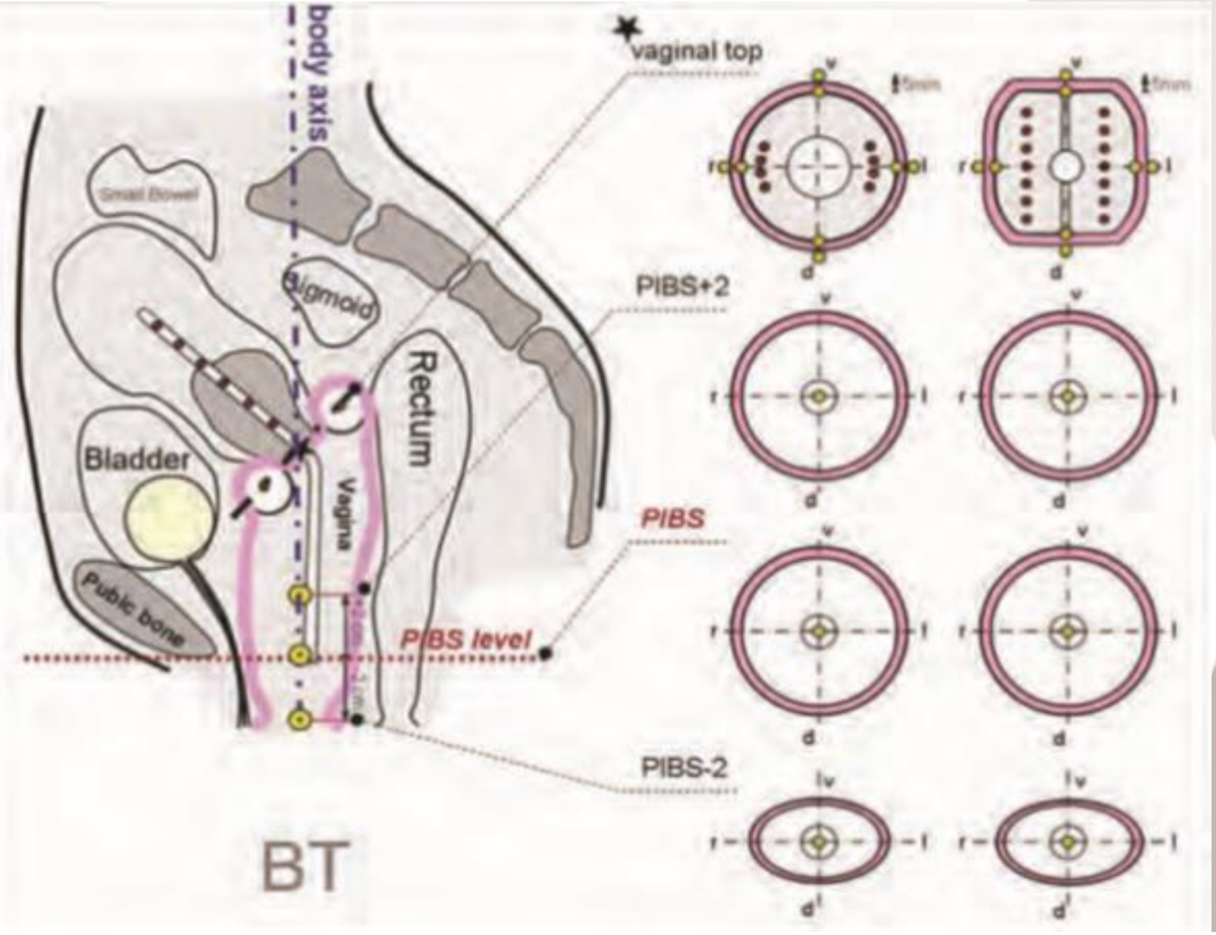
Vaginal wall

Delineation, DVH, Reporting:

- **↑ uncertainties**
- **↓ reproducibility**

Berger D, et al. IJROBP 2007

Vagina

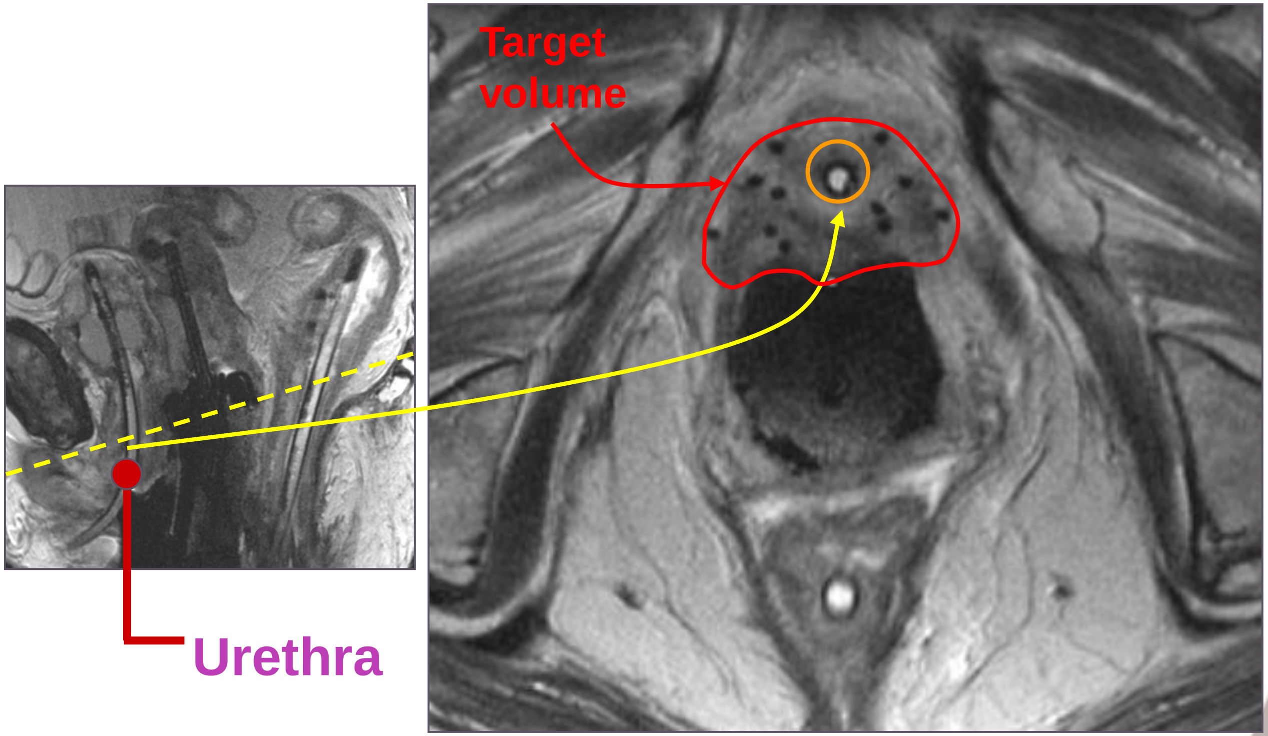


PIBS vaginal-dose point definition : 2 cm posterior from the posterior-inferior border of the pubic symphysis at the point of this line where it crosses the applicator tandem

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

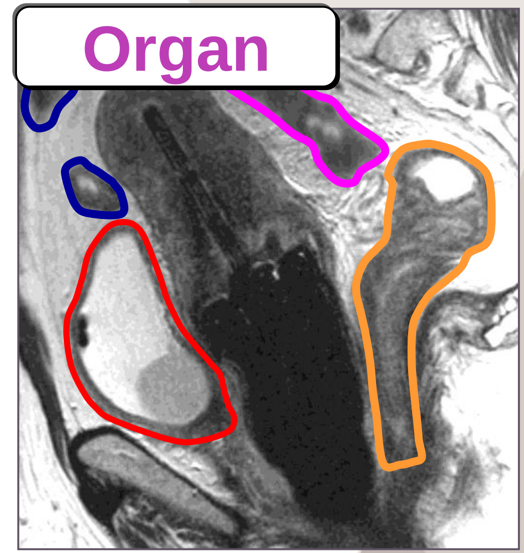


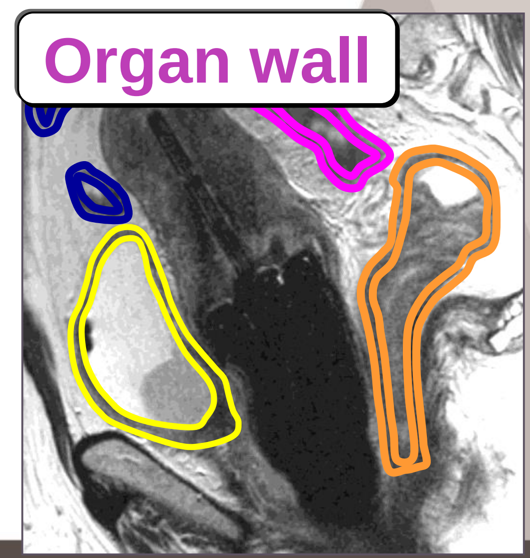
Delineate Organ or Organ wall?

Situation in Brachytherapy

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

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

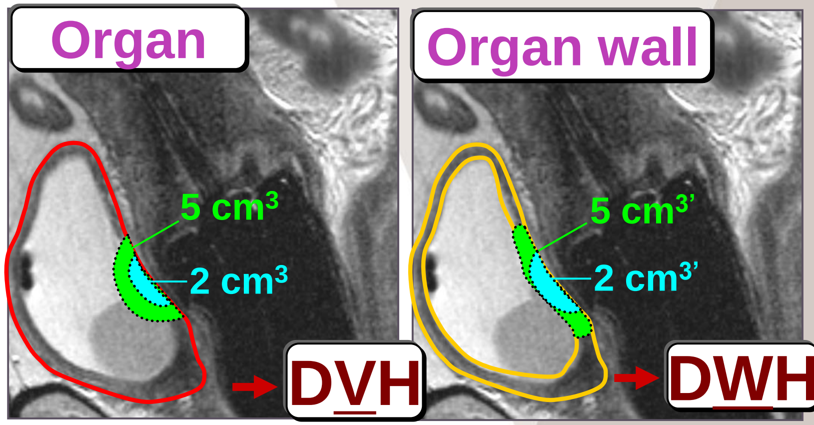




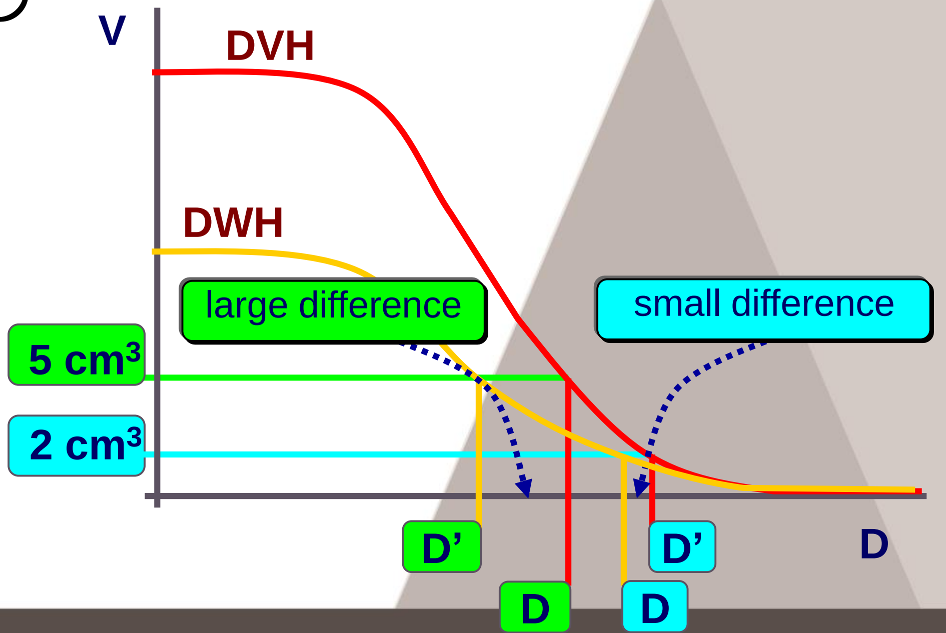
Delineate Organ or Organ wall?

Situation in Brachytherapy

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



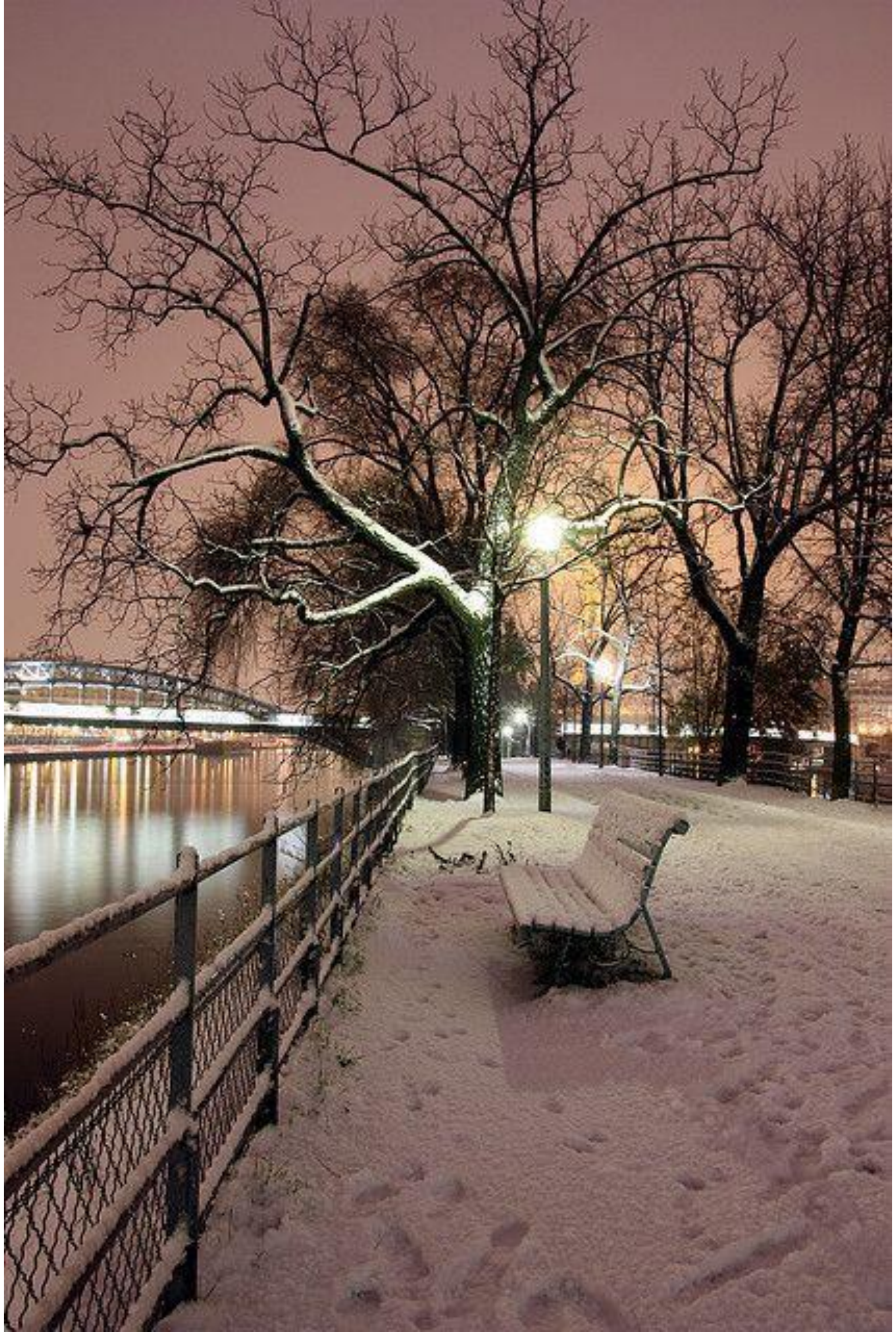
Yes, if doses up to 2 cm³ are evaluated



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

Conclusion

- Importance of GTV and CTV for the primary tumor
- Residual GTV-T (GTV-T_{res})
- Adaptive CTV-T (CTV-T_{adapt})
- High-Risk CTV-T (CTV-THR)
- Intermediate-Risk CTV-T (CTV-TIR)
- OAR delineation



2D and 3D delineation of Organs at Risk

Dr. D.N. Sharma
Professor
Department of Radiation Oncology
All India Institute of Medical Sciences, New Delhi

Organs at Risk (OAR): Definition

- Introduced first in the ICRU report 50 *"Prescribing, Recording, and Reporting Photon Beam Therapy"(1993)*

- OARs defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose

Why should we draw OARs ?

- **Treatment planning System has no "common sense" – what you do not draw, the TPS does not consider**

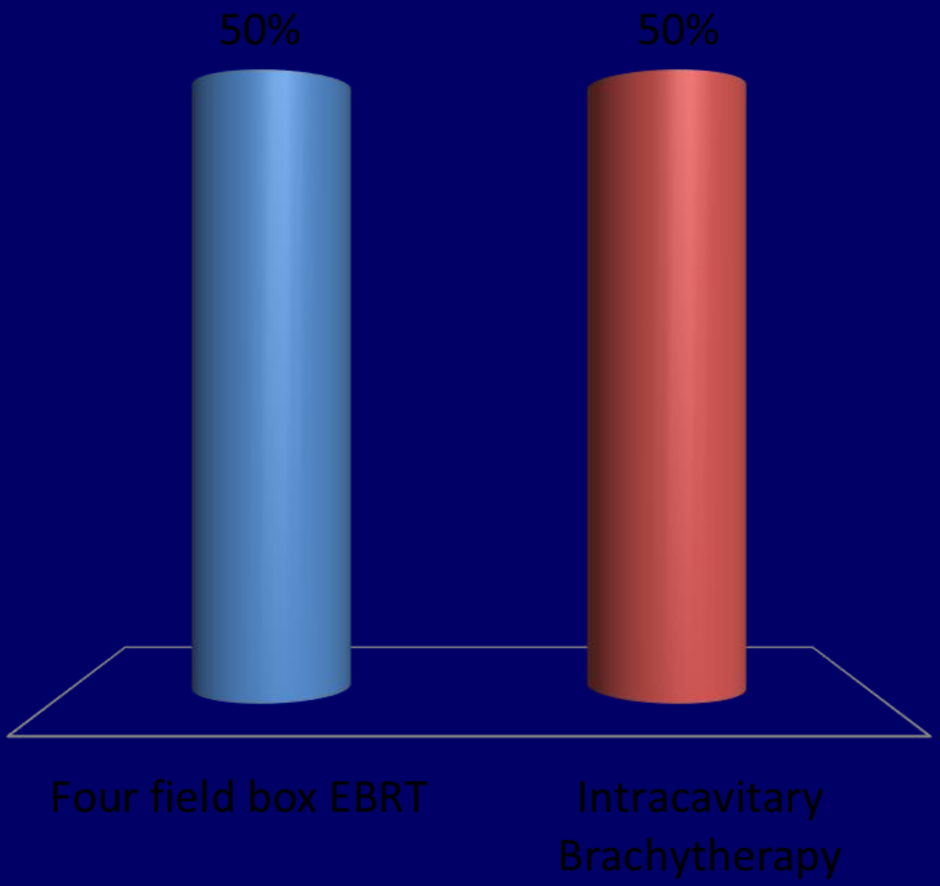
- To save some structure, we need to feed it to TPS

- Dose constraints can be given only to (and assessed for) identified structures

- Compare results between institutions

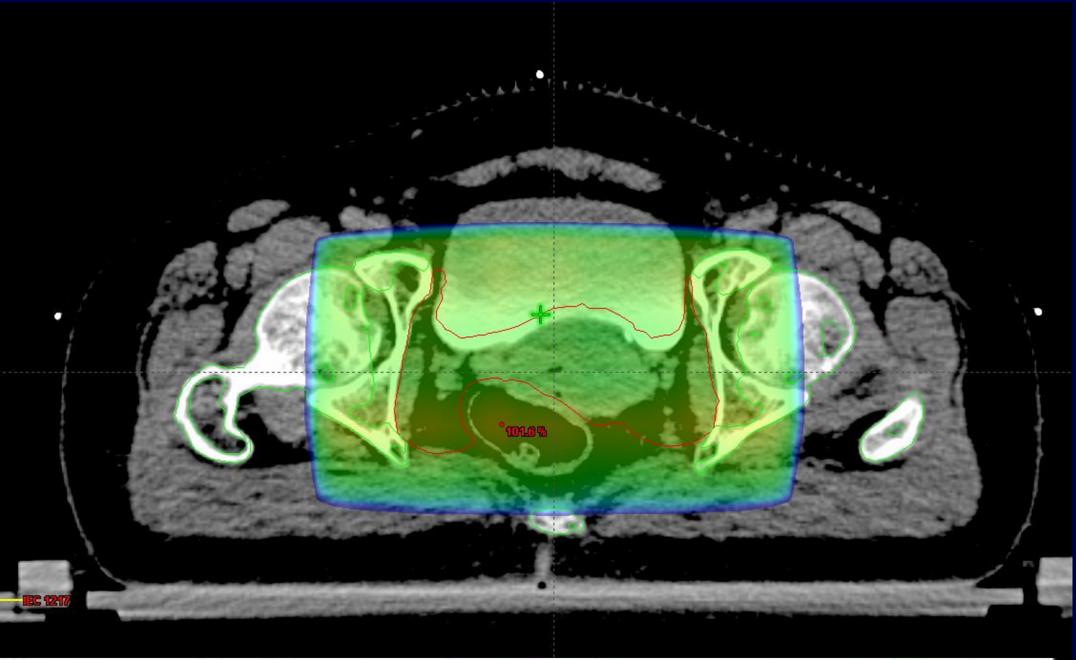
OARs are more important in

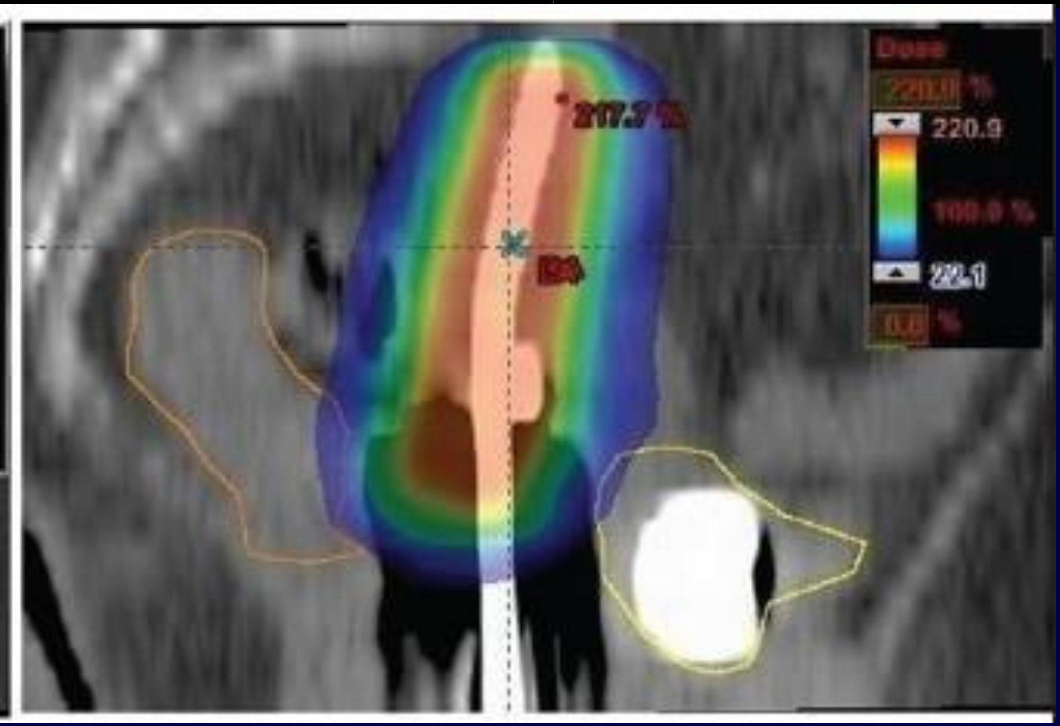
A. Four field box EBRT
B. Intracavitary Brachytherapy

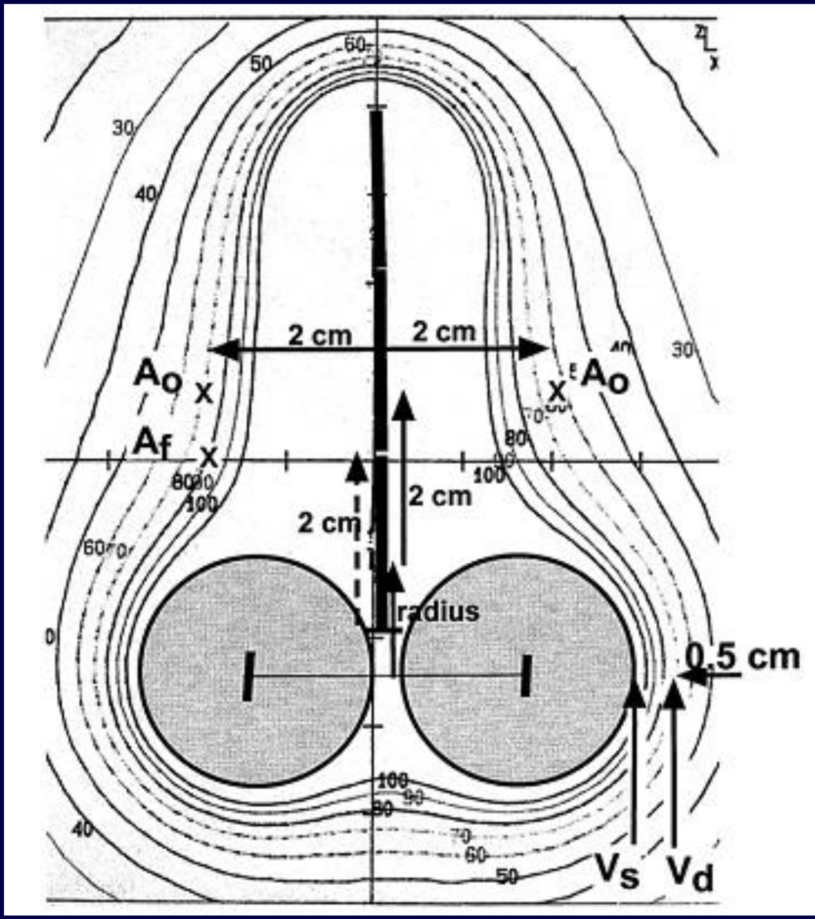


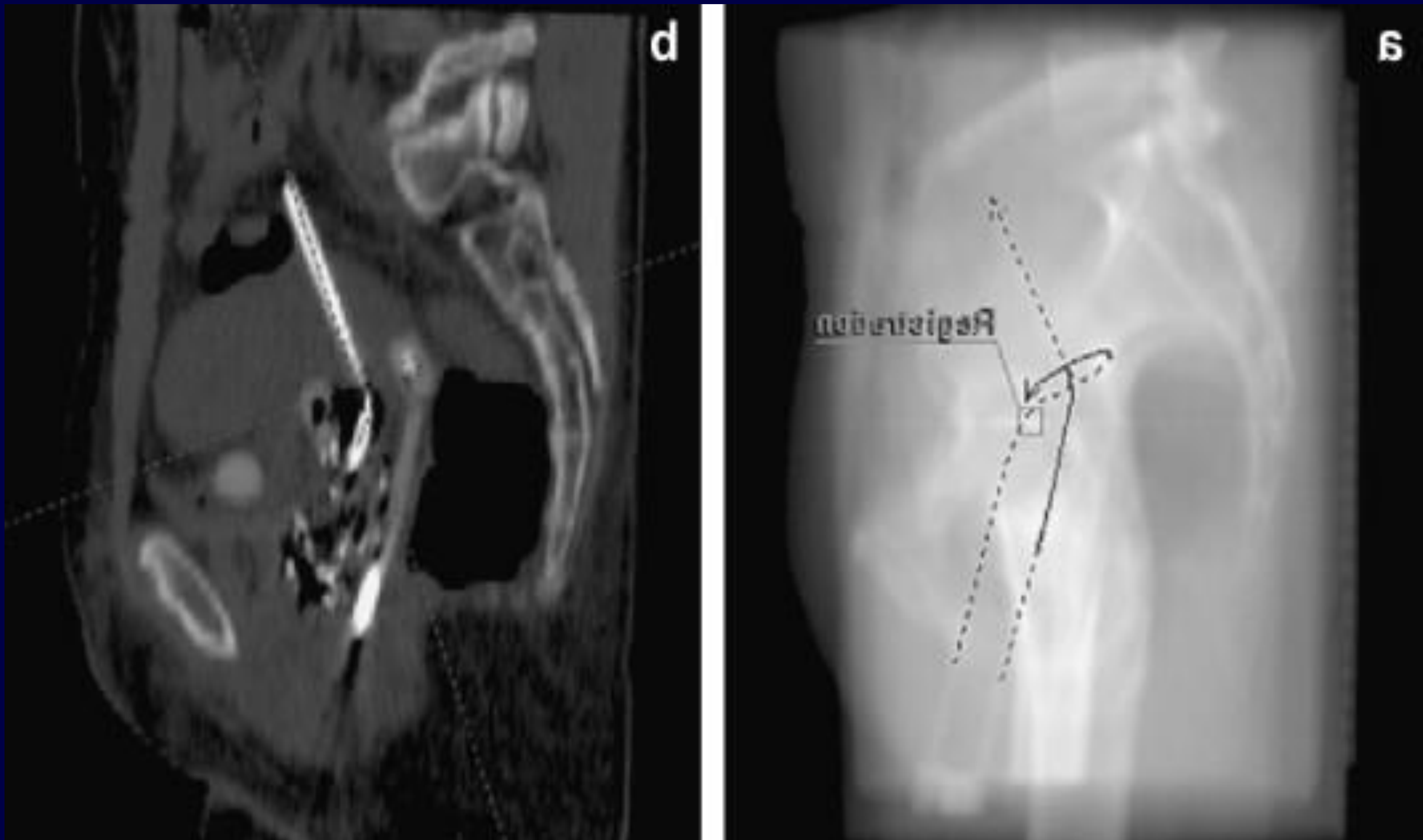
Radiation treatment of cervical cancer

- Total intended dose : 80-90 Gy
- Considerable dose is delivered by brachytherapy (WPRT= 45 Gy + 40-45 by ICRT)
- Almost equal to EBRT dose
- OARs lie very close to the target volumes
- Dose intensity is higher in brachytherapy
- Sharp dose fall off : strength of brachytherapy



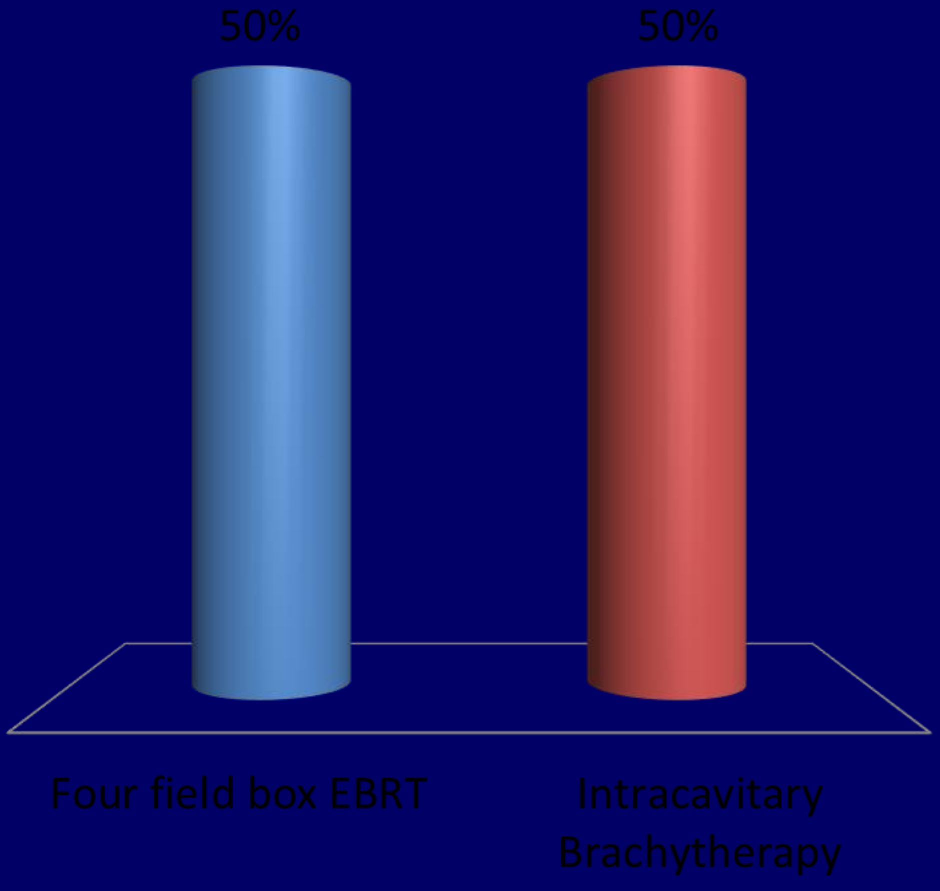

Dose
220.9
100.0 %
22.1
%


2 cm
2 cm
Ao
Ao
Af
2 cm
2 cm
radius
0.5 cm
Vs
Vd


b
a
Registration

OARs are more important in

A. Four field box EBRT
B. Intracavitary Brachytherapy



Morbidities and QOL

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

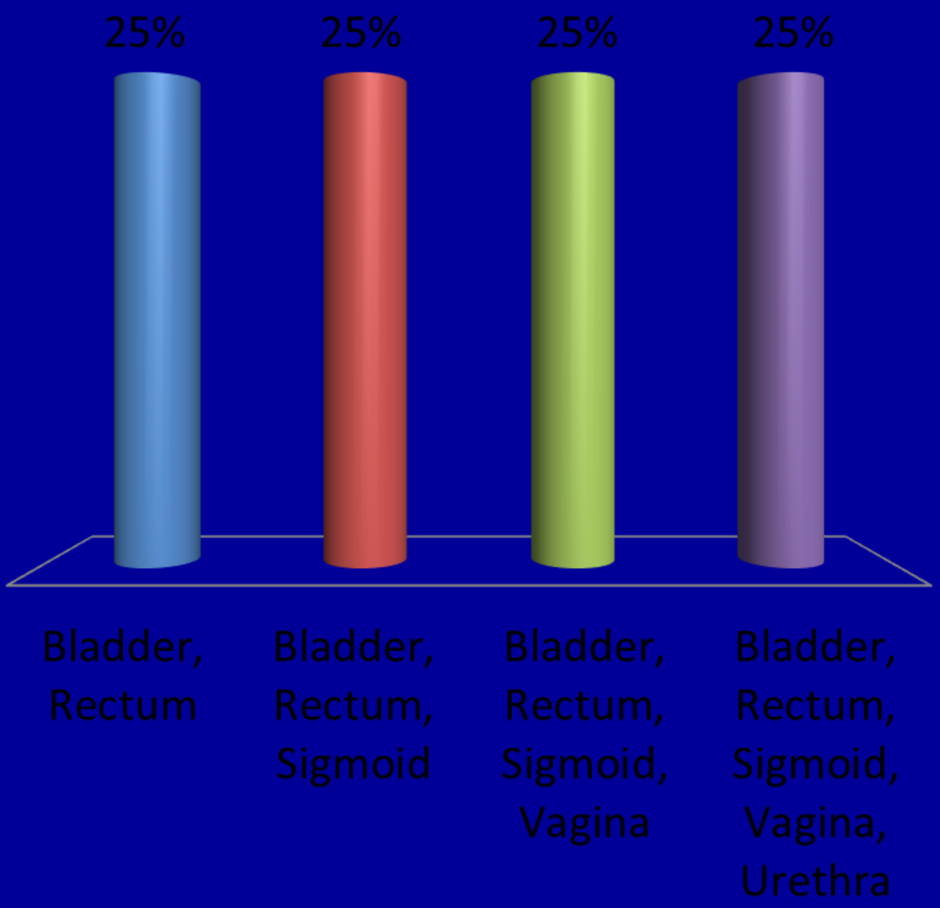
OARs in pelvic Irradiation

	Acute	Late
Small bowel	√	√
Large bowel	√	√
Sigmoid colon	√	√
Rectum	√	√
Anal canal	√	√
Urinary bladder	√	√
Bone marrow (pelvic bones, femur head, sacrum)	√	√
Ovaries		√
Lumbosacral plexus		√
Kidneys		√
Skin & subcutaneous tissue		√

OARs in Brachytherapy

What are the relevant OARs in ICRT ?

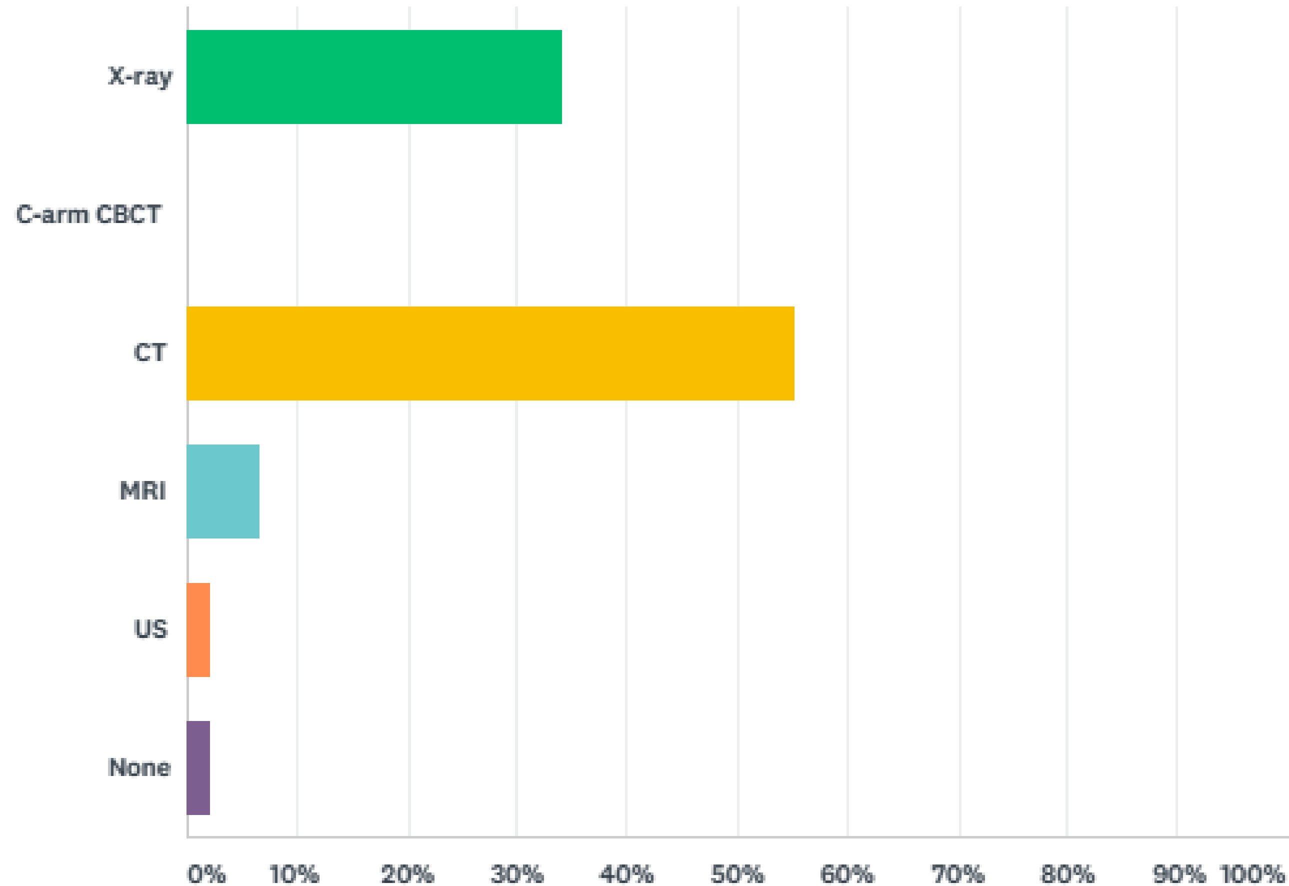
A. Bladder, Rectum
B. Bladder, Rectum, Sigmoid
C. Bladder, Rectum, Sigmoid, Vagina
D. Bladder, Rectum, Sigmoid, Vagina, Urethra



2D delineation of OARs

Q14 Which kind of imaging do you perform with the applicator in place at the time of brachytherapy?

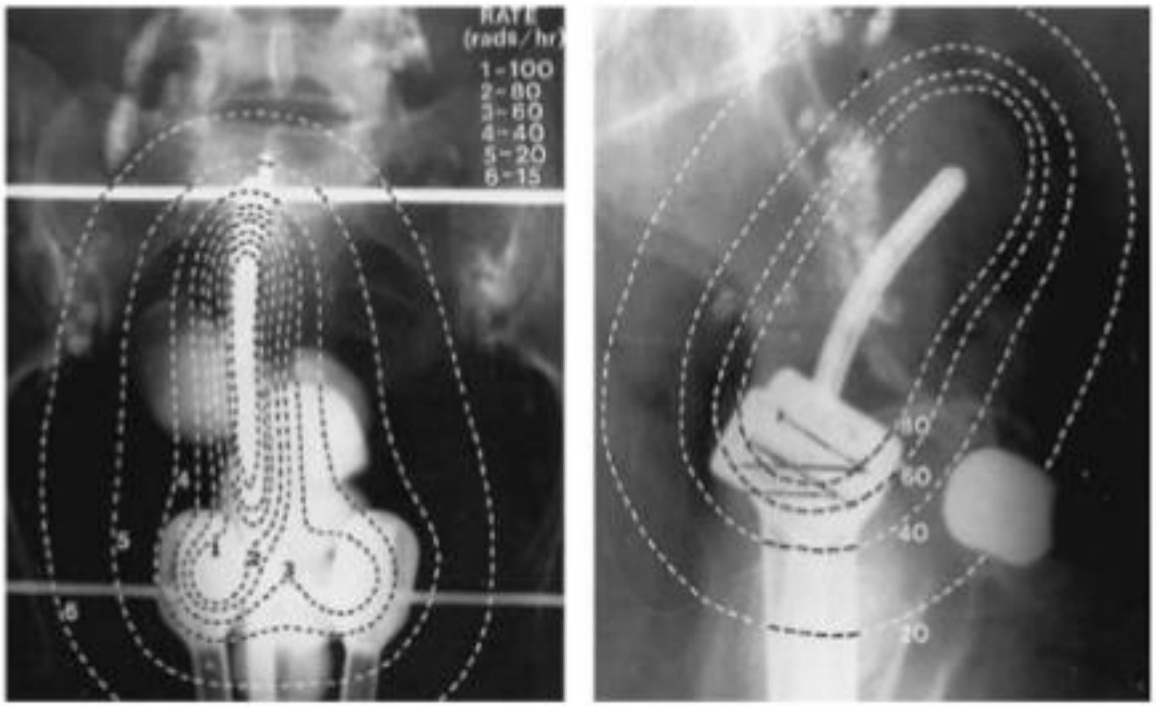
Answered: 47 Skipped: 8



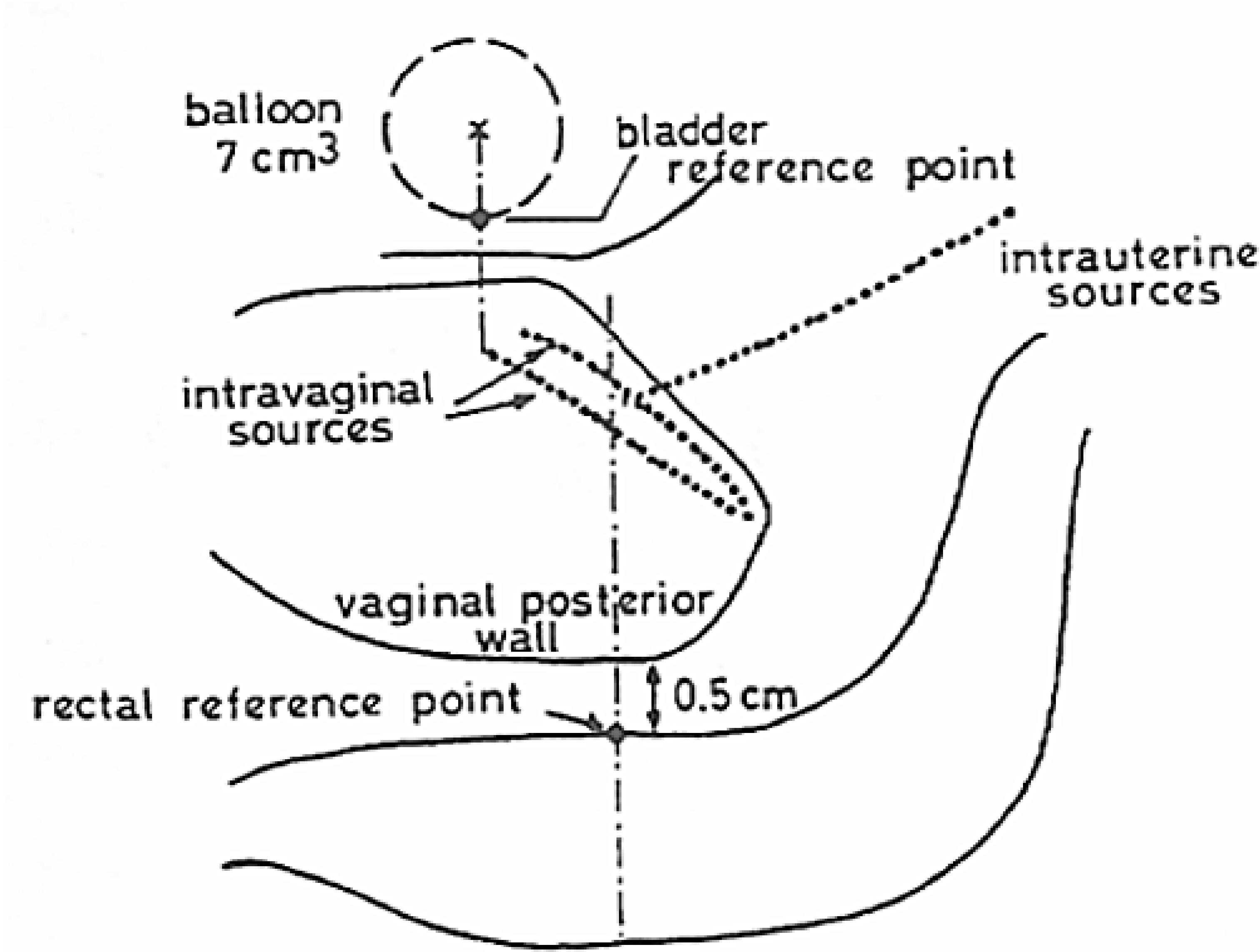
2D delineation of OARs

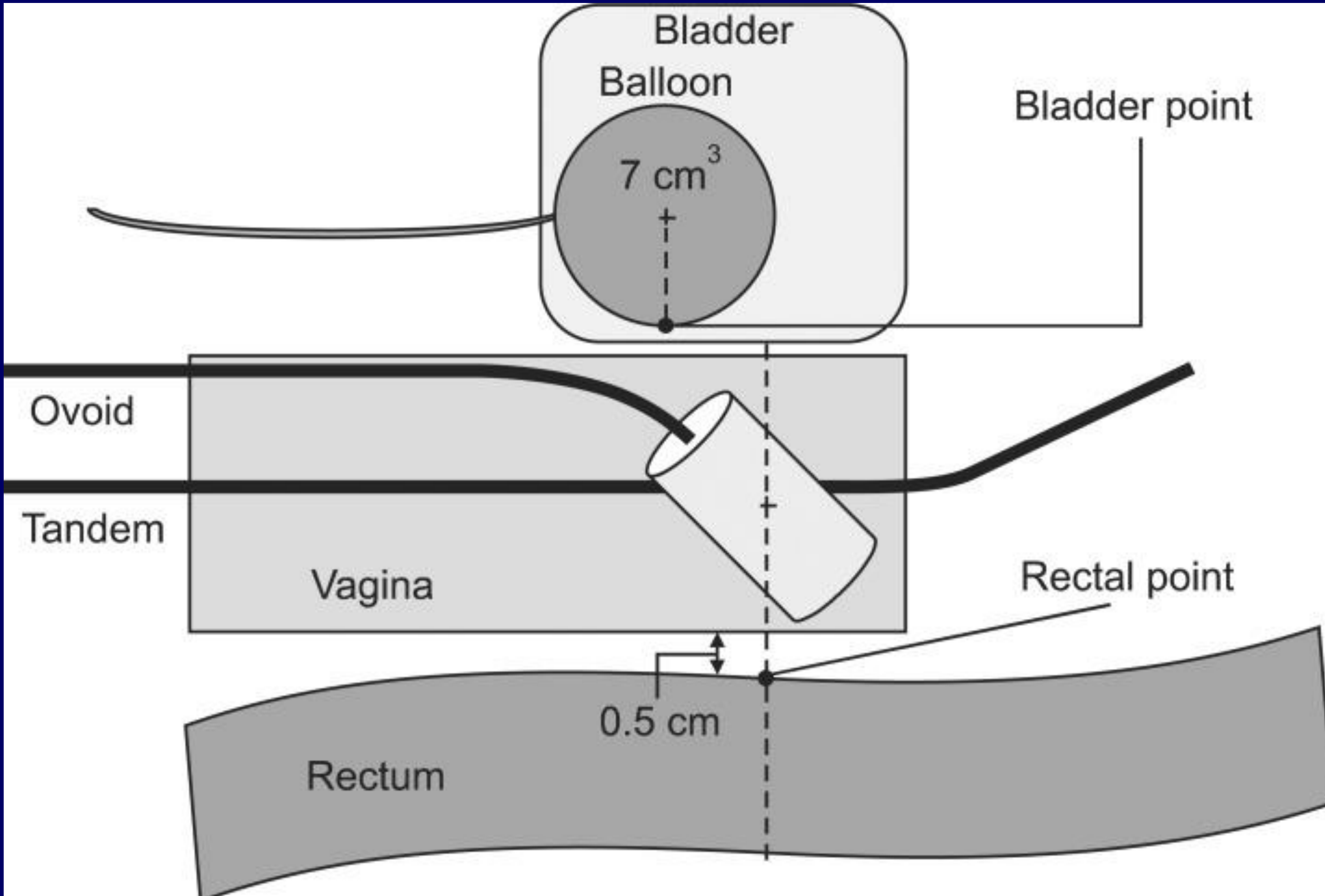
- Based on radiographic imaging
- Most guidelines do not recommend radiographic image
- OARs are localized based on points
- Only few organs are localized
- The toxicity correlation is poor
- If volumetric imaging is not available, X-ray based simulation may be practiced but certainly not encouraged

2D brachytherapy planning



ICRU 38: Bladder and Rectal points



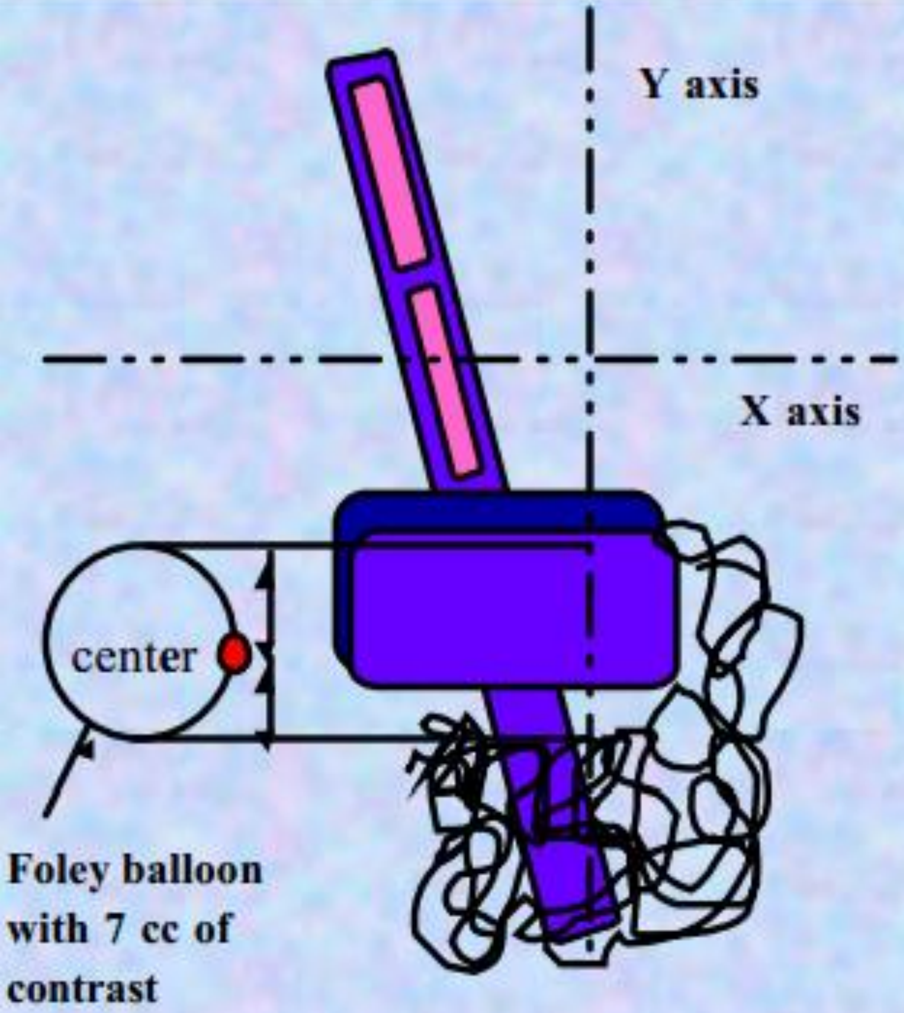

Bladder
Balloon
Bladder point
7 cm3
Ovoid
Tandem
Vagina
Rectal point
0.5 cm
Rectum

Bladder reference point

Bladder point is obtained in following way:

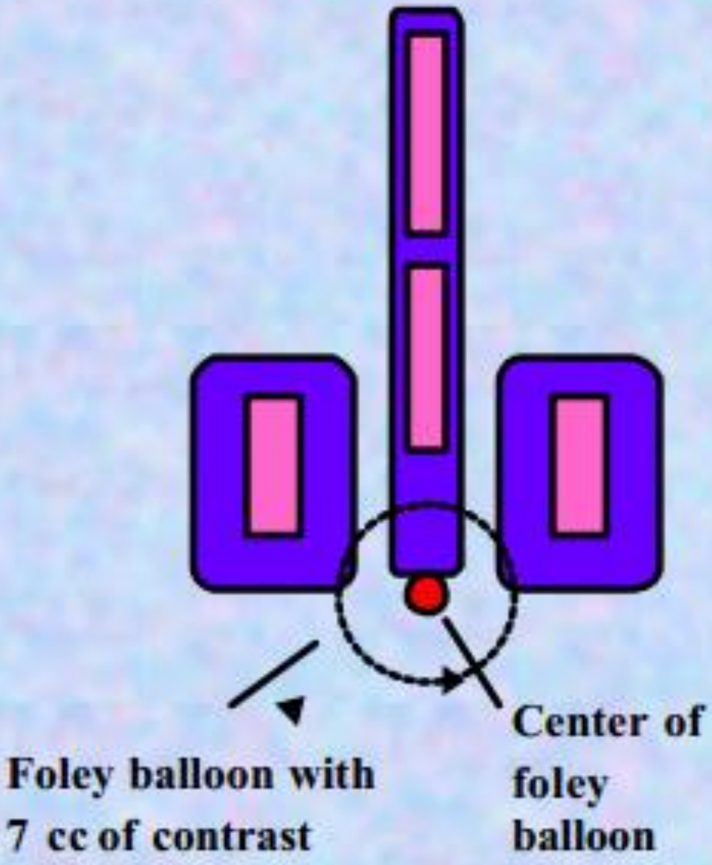
- Foley's catheter balloon is filled with 7 cm^3 of radio-opaque fluid
- Catheter is pulled downward to bring the balloon against the urethra
- On lateral radiograph, reference point is at the posterior surface of balloon
- On frontal radiograph reference point is taken at the centre of balloon

Bladder reference point: Lateral view



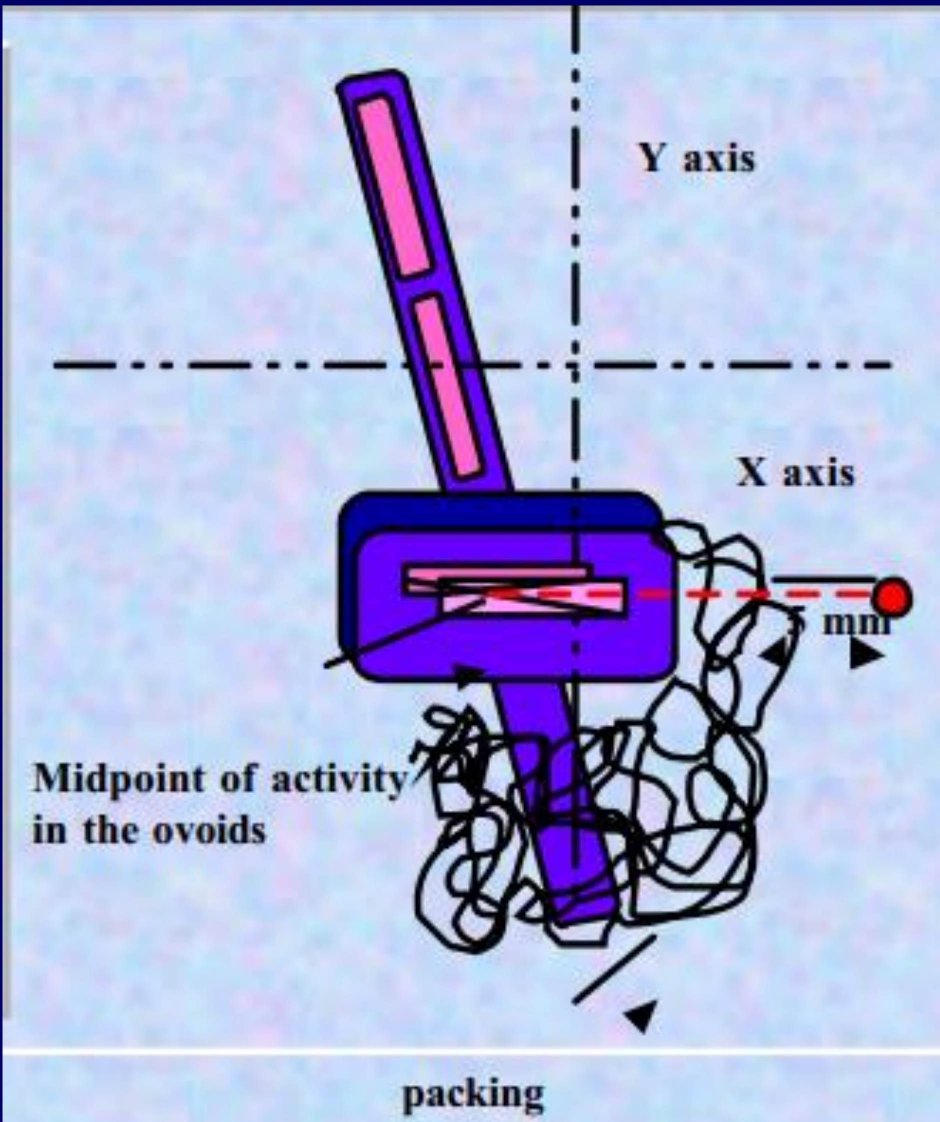
On the Lateral film the bladder point is obtained on a line drawn anteroposteriorly through the center of the balloon at the posterior surface.

Bladder reference point: AP view



On the AP film the bladder point is marked at the center of the balloon.

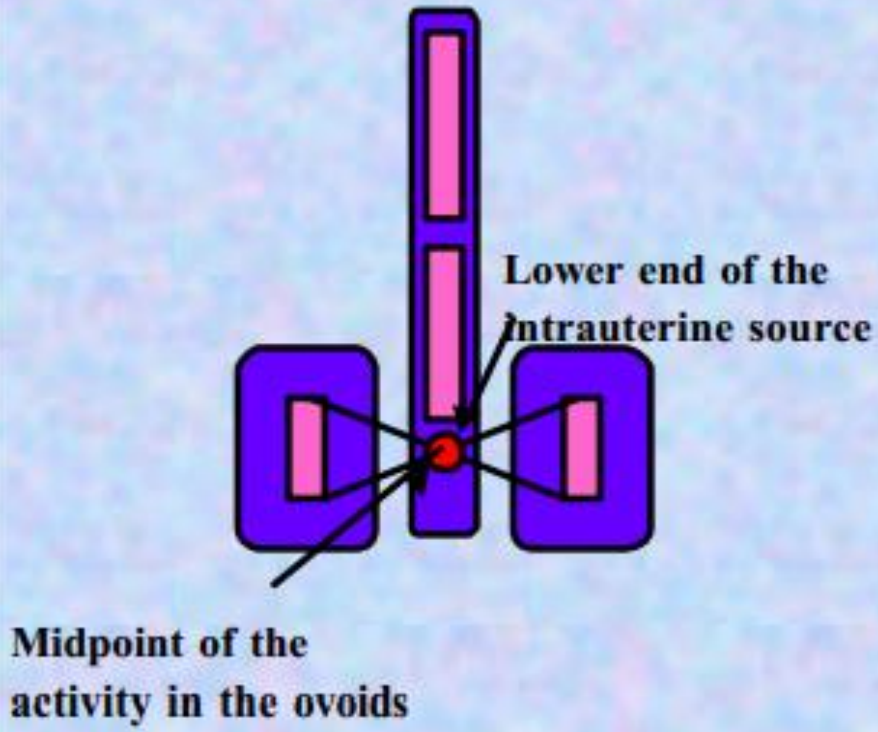
Rectal reference point: Lateral view



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

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

Rectal reference point: AP view



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

Limitations of 2D delineation

- Only points are visualized
- No target, no OAR
- Doses to these points does nor correctly predicts the morbidity
- So we need axial imaging for 3D delineation

3D delineation of OAR

3D delineation of OAR

- Based on the volumetric imaging
- Various imaging devices used

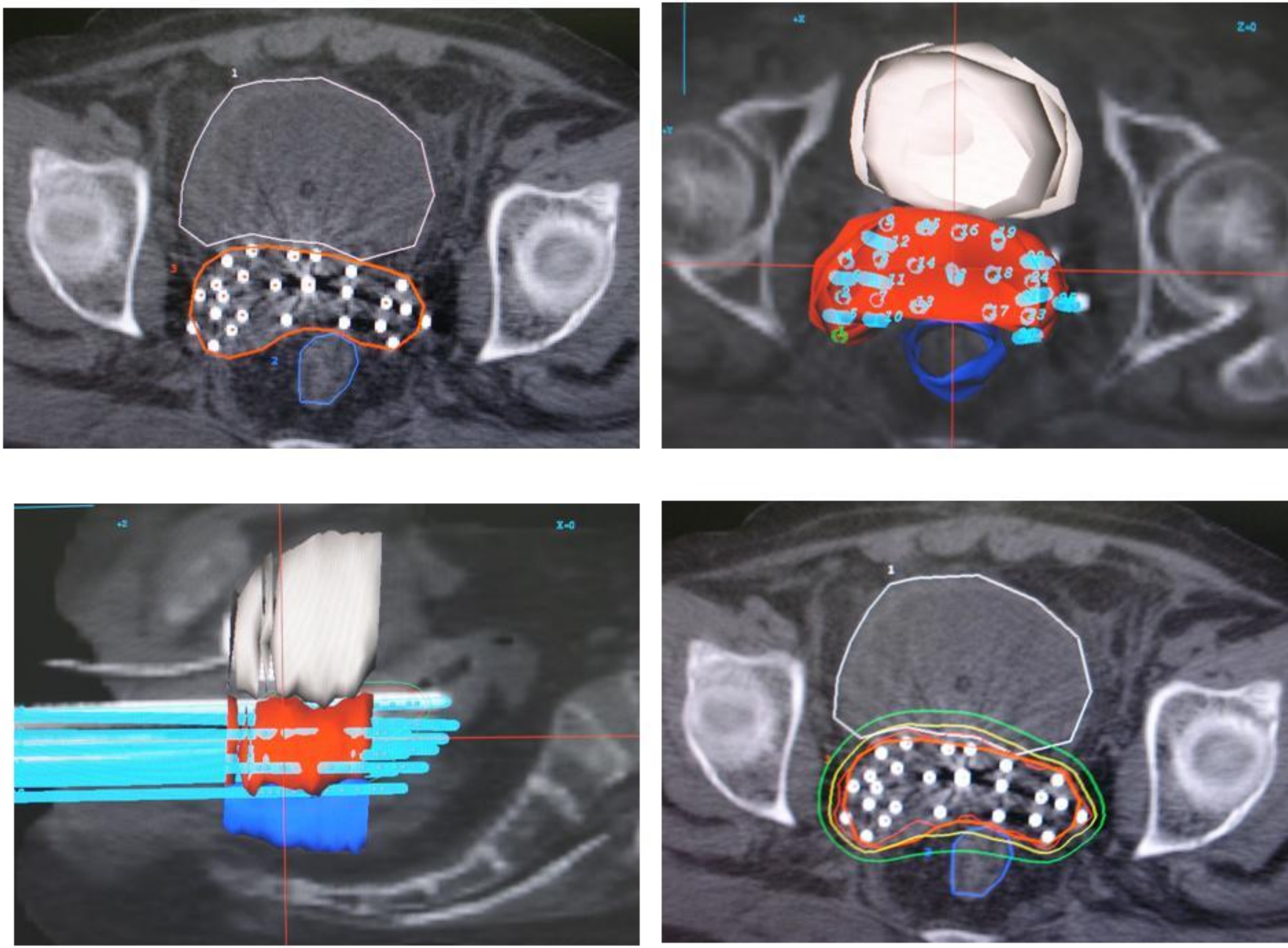
- MRI	: Standard
- CT Scan	: Practical
- USG	: Investigational
- PET-CT Scan	: Investigational

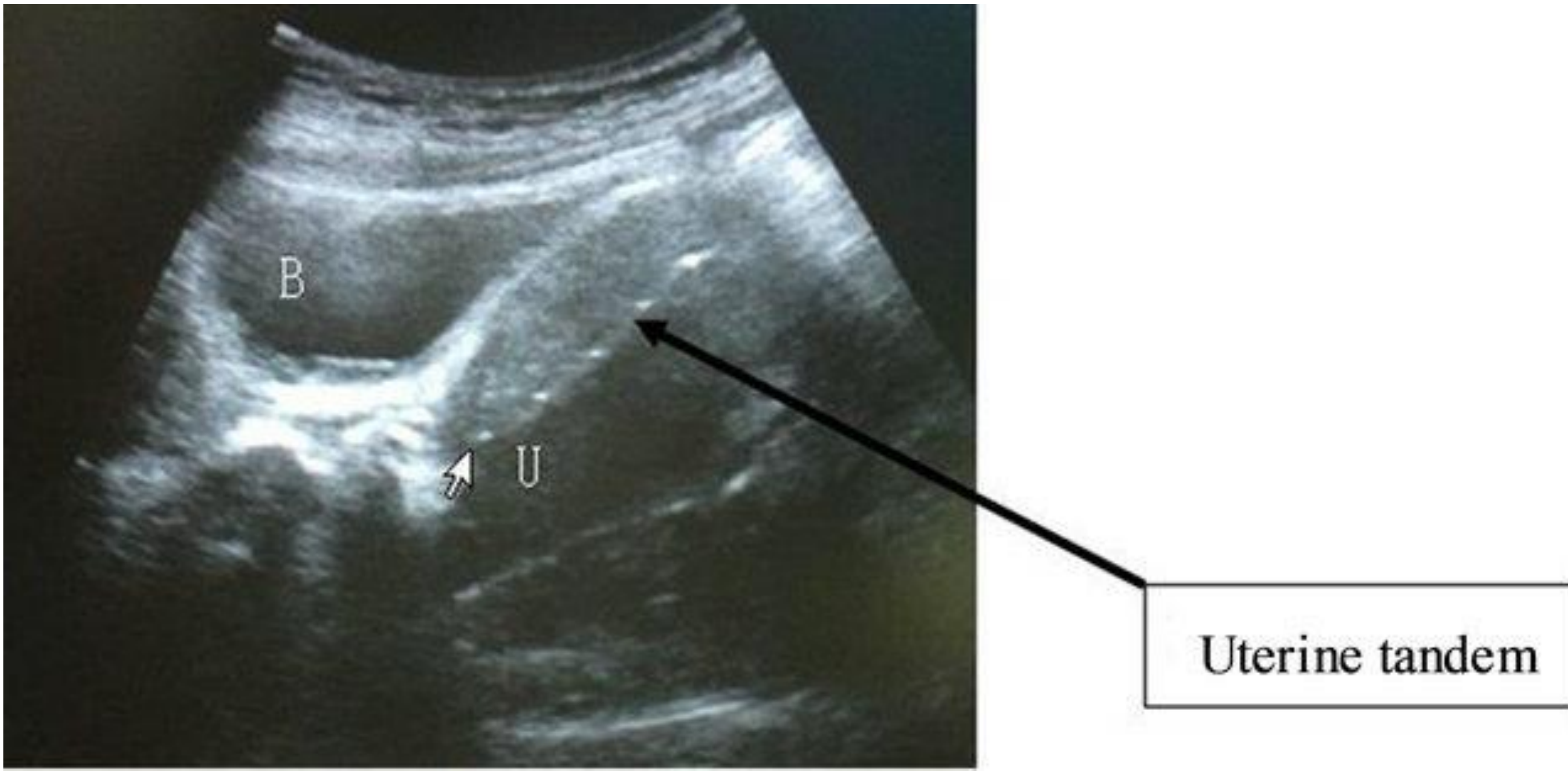
Delineation of OARs

- **Sigmoid colon:** Should be clearly identified, and the whole structure should be contoured, with specific focus on the areas adjacent to the uterus. Length up to the junction with the descending colon.

- **Rectum :** This implies the entire length from the ano-rectum to the recto-sigmoid junction

- **Bladder:** The whole posterior, posterior-caudal (trigone), and posterior-cranial bladder wall should be included till bladder neck


1
2
3
+X
Z=0
X=0
12
16
19
14
18
11
10
17
13
1
2


B
U
Uterine tandem

BRACHYTHERAPY

Brachytherapy 15 (2016) 839−844

Gynecologic Oncology

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

Nicole Nesvacil[1,2,*], Maximilian P. Schmid[1], Richard Pötter[1,2], Gernot Kronreif[3], Christian Kirisits[1,2]

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

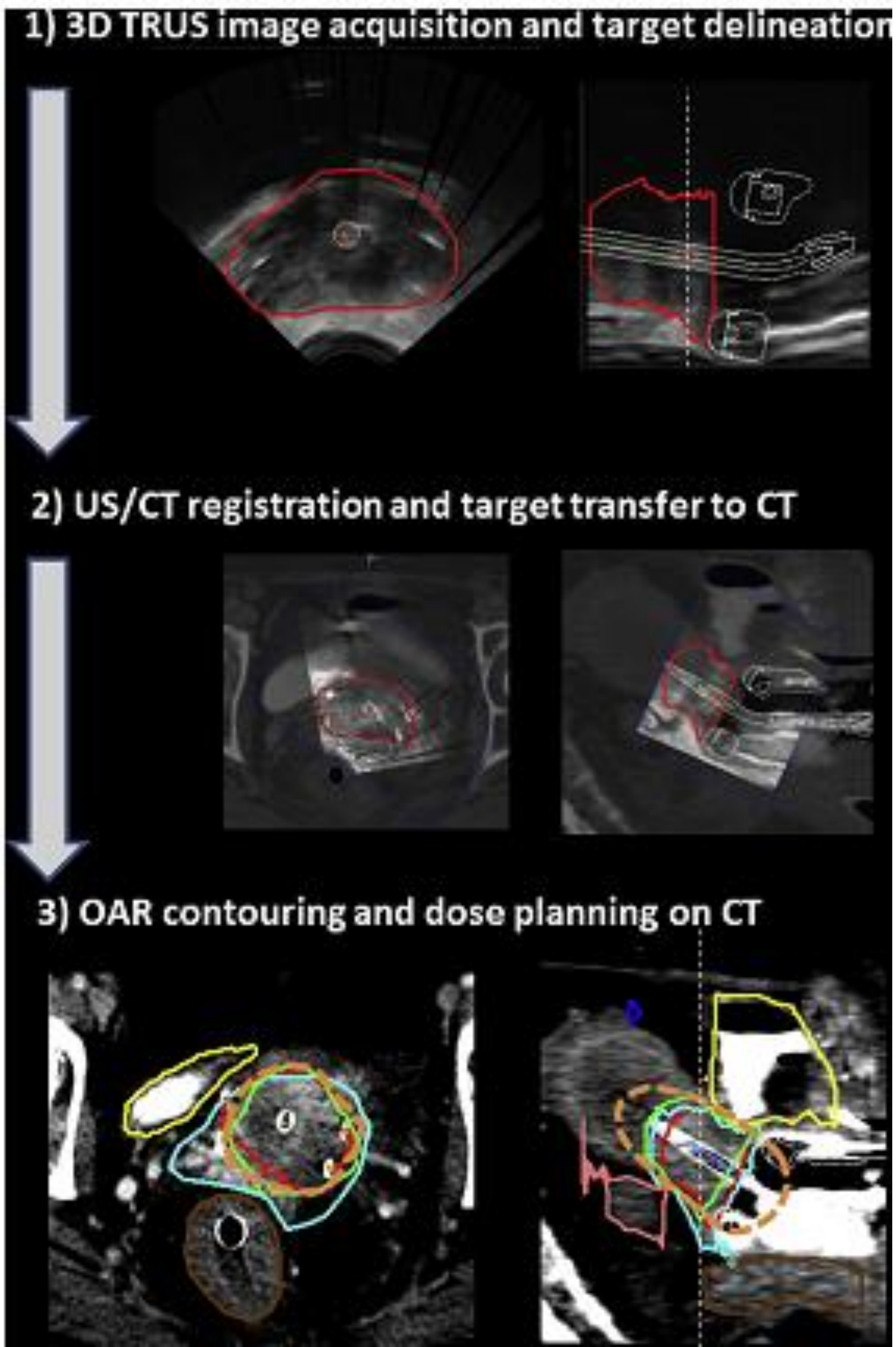
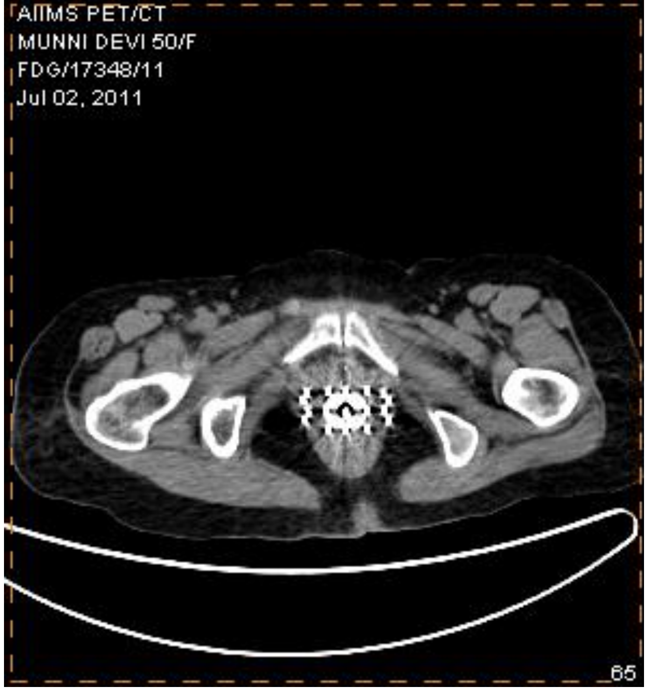
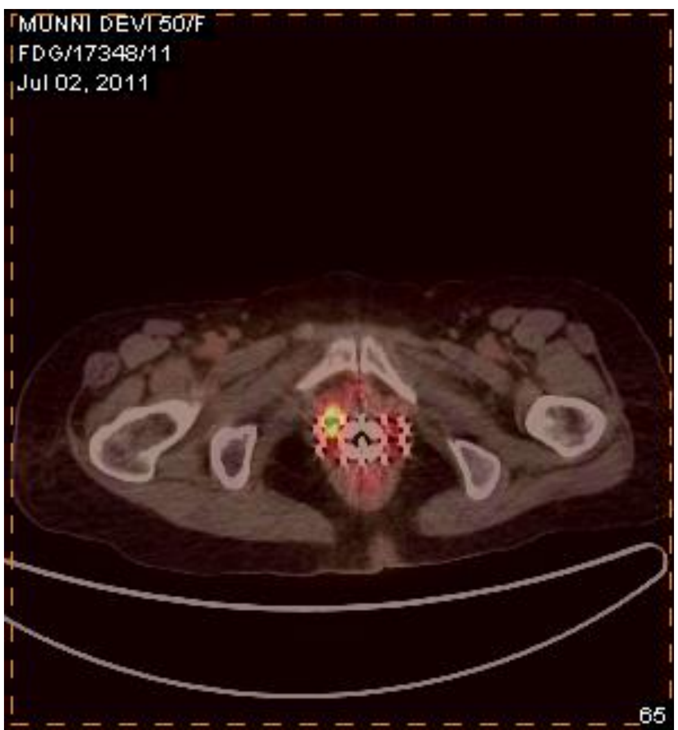
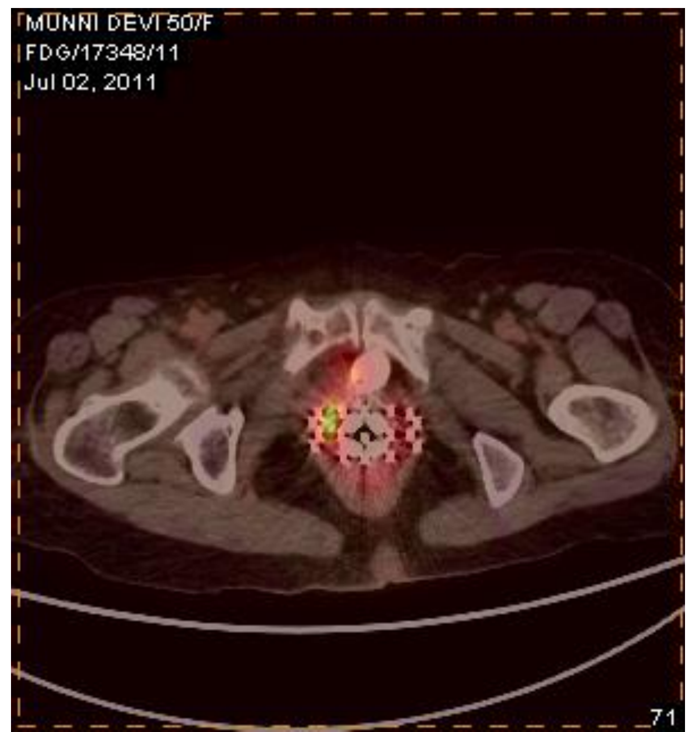
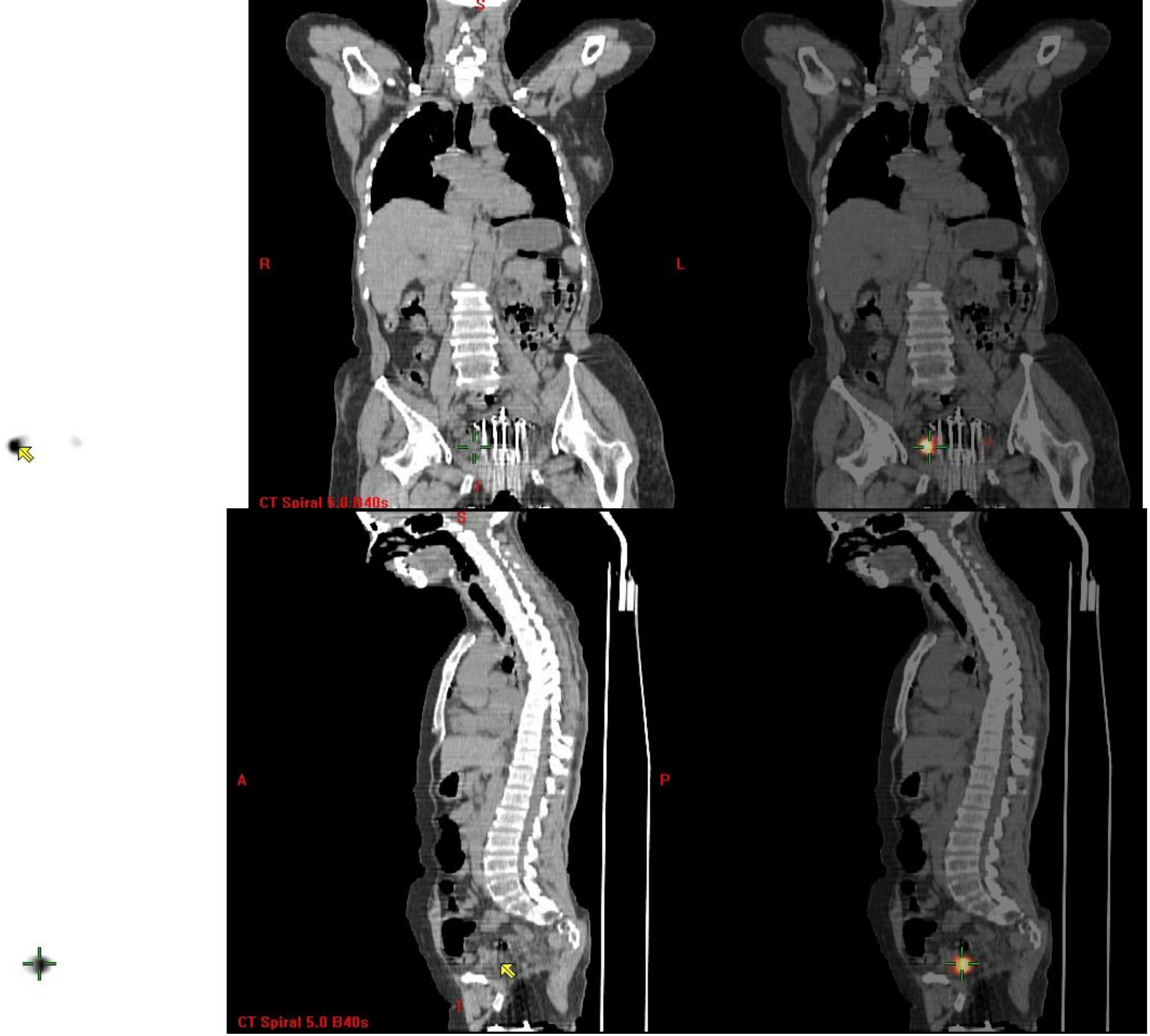

1) 3D TRUS image acquisition and target delineation
2) US/CT registration and target transfer to CT
3) OAR contouring and dose planning on CT

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

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

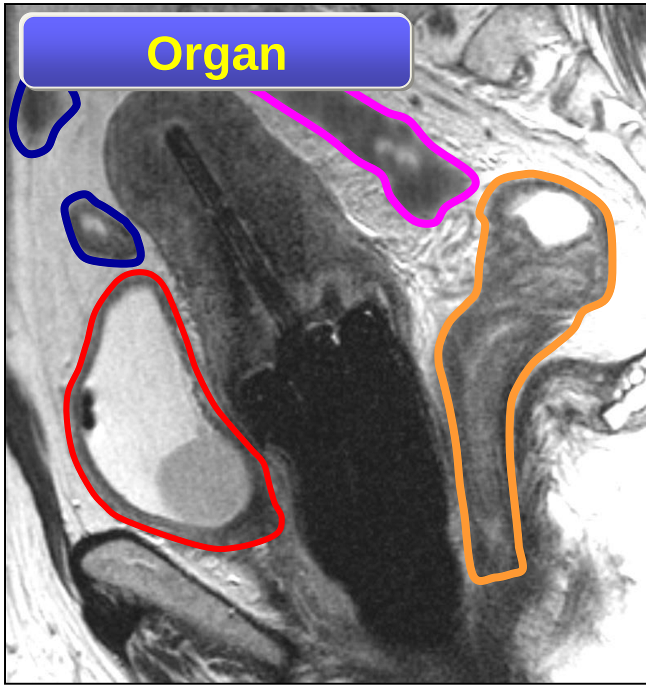

AIIMS PET/CT
MUNNI DEVI 50/F
FDG/17348/11
Jul 02, 2011
65

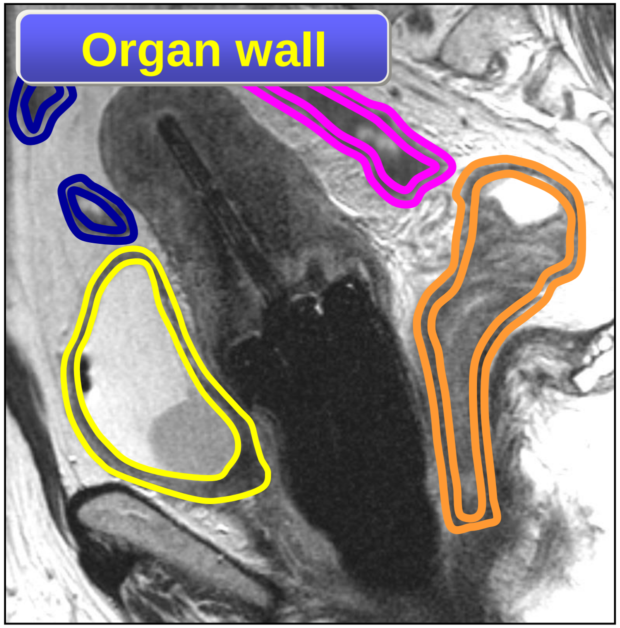
AIIMS PET/CT
MUNNI DEVI 50/F
FDG/17348/11
Jul 02, 2011
71

MUNNI DEVI 50/F
FDG/17348/11
Jul 02, 2011
65

MUNNI DEVI 50/F
FDG/17348/11
Jul 02, 2011
71


S
R
L
CT Spiral 5.0 B40s
S
A
P
I
CT Spiral 5.0 B40s

Delineate Organ or Organ wall?

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

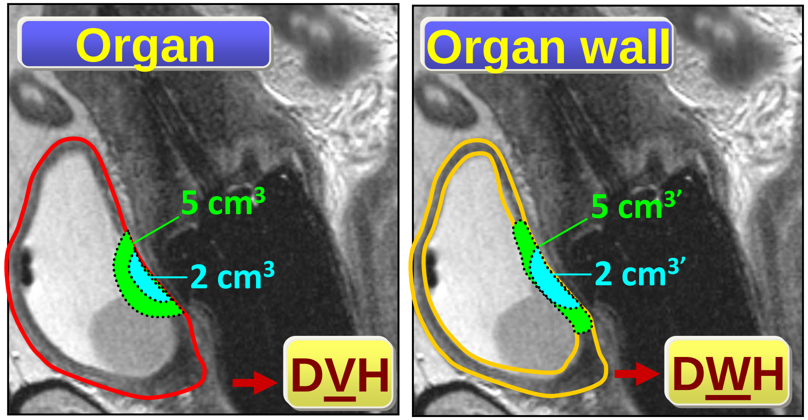




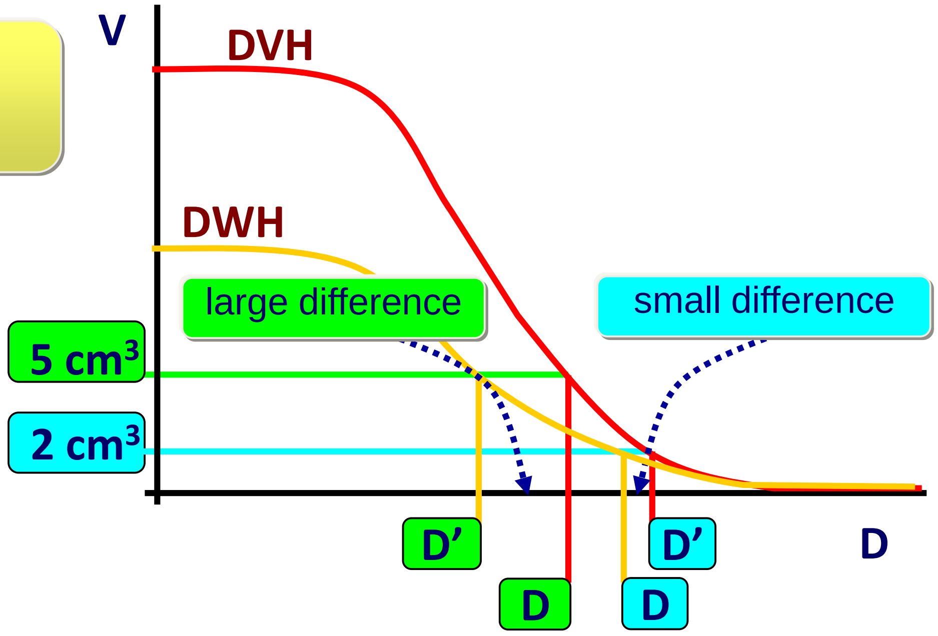
Can we contour organs instead of organ walls?

Delineate Organ or Organ wall?

I. Situation in Brachytherapy



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

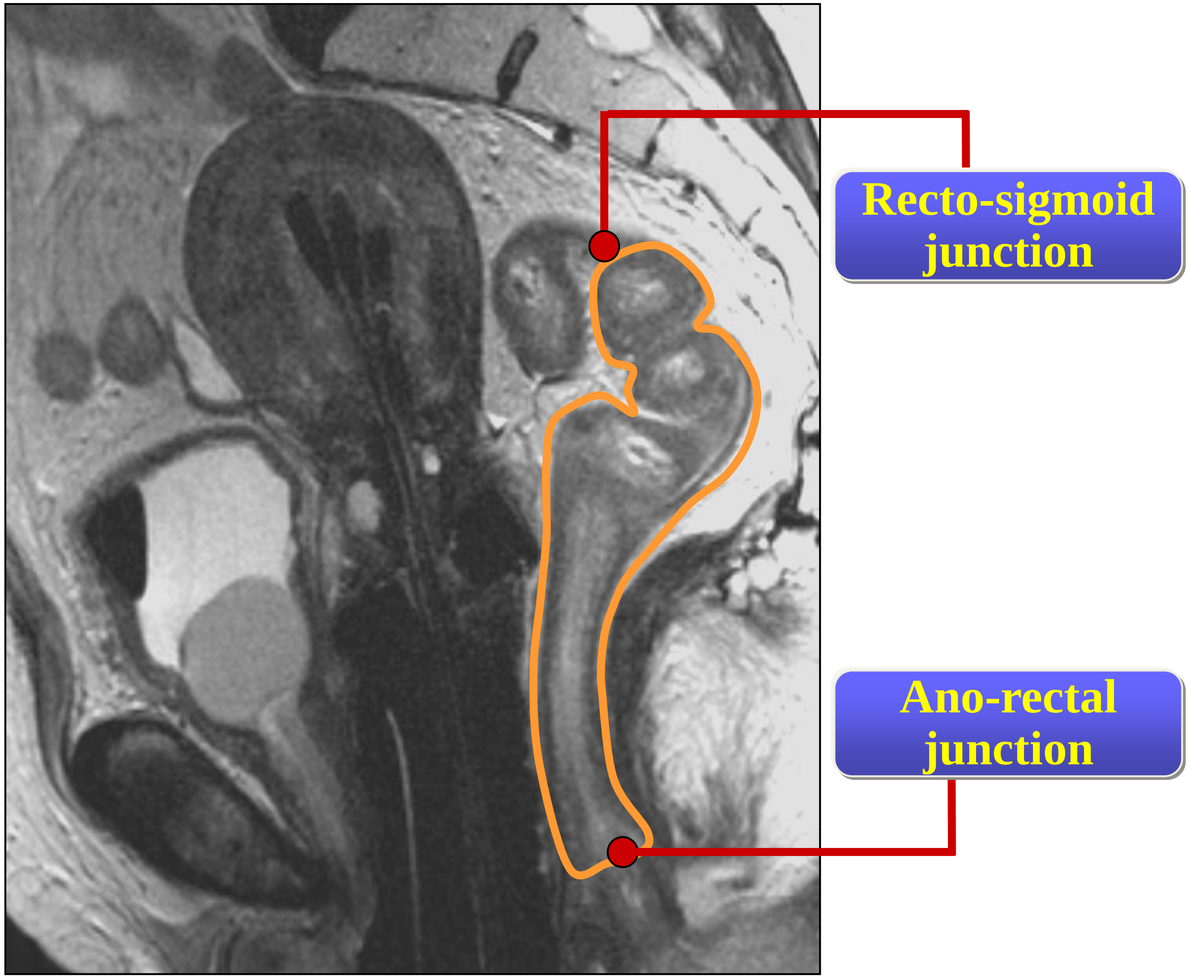


<u>Yes, if</u> doses to $2\ cm^3$ are evaluated.

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

Clear Definitions of Organs at risk

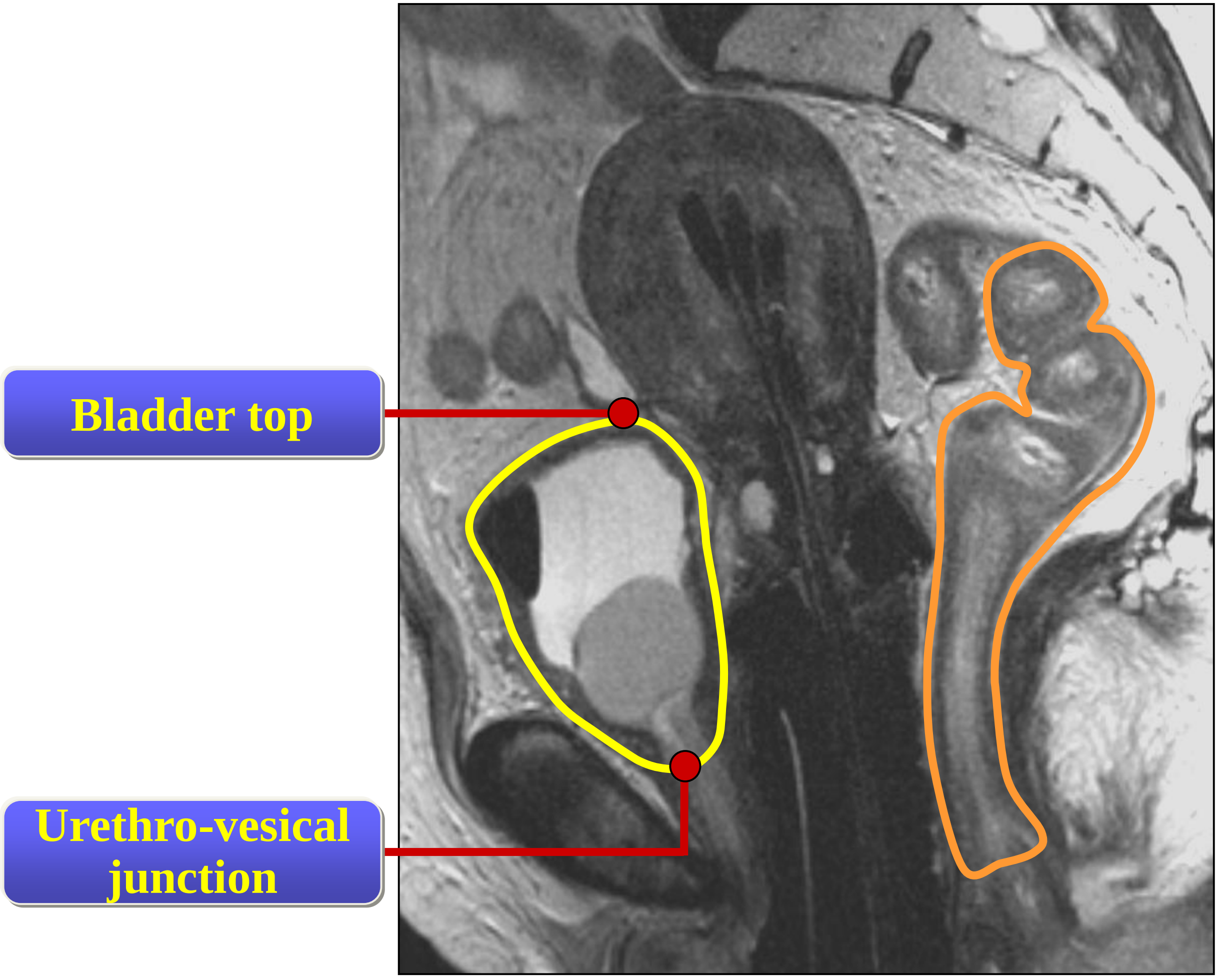
Rectum



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

Clear Definitions of Organs at risk

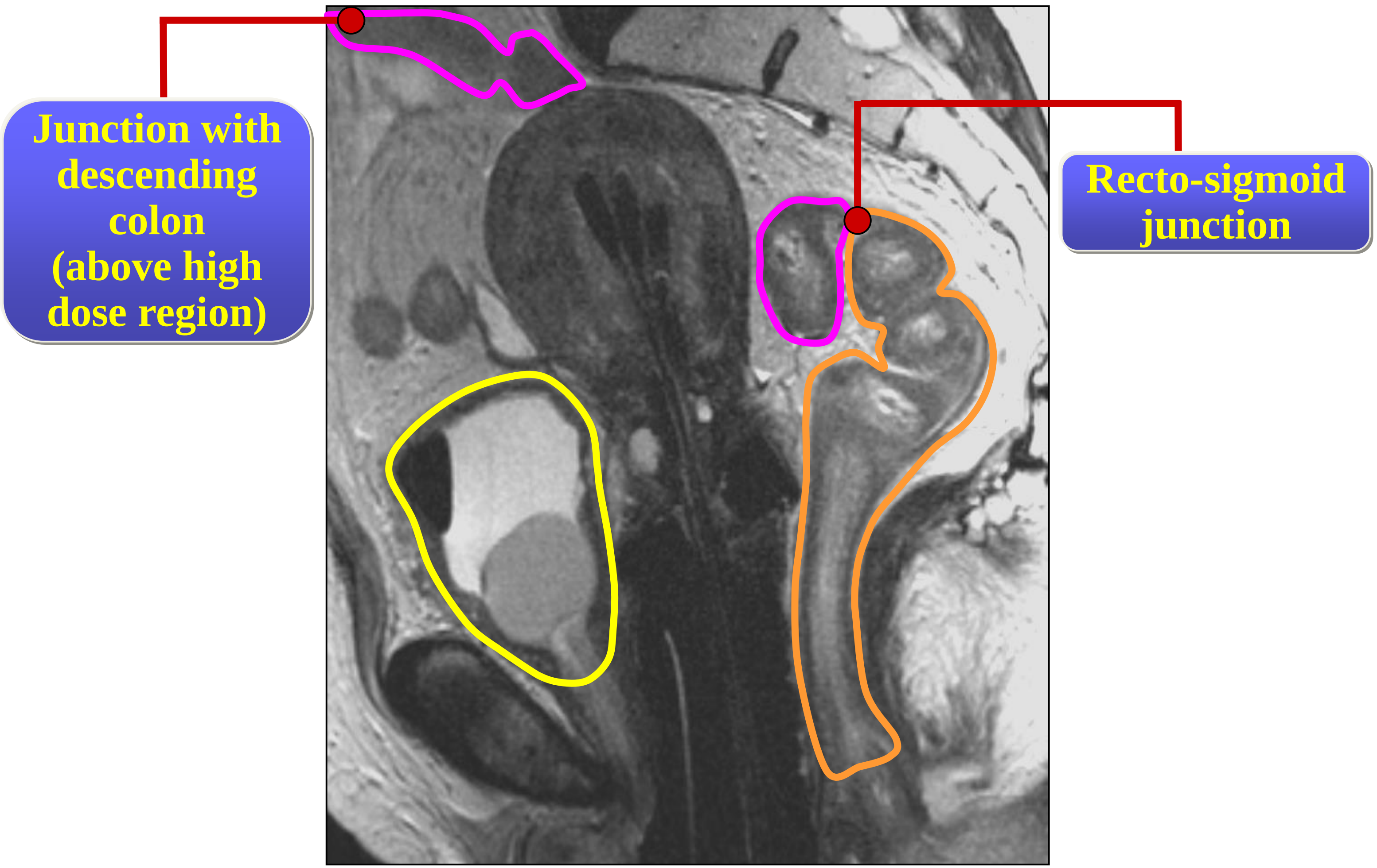
Bladder



Viswanathan AN, et al. IJROBP 2010

Clear Definitions of Organs at risk

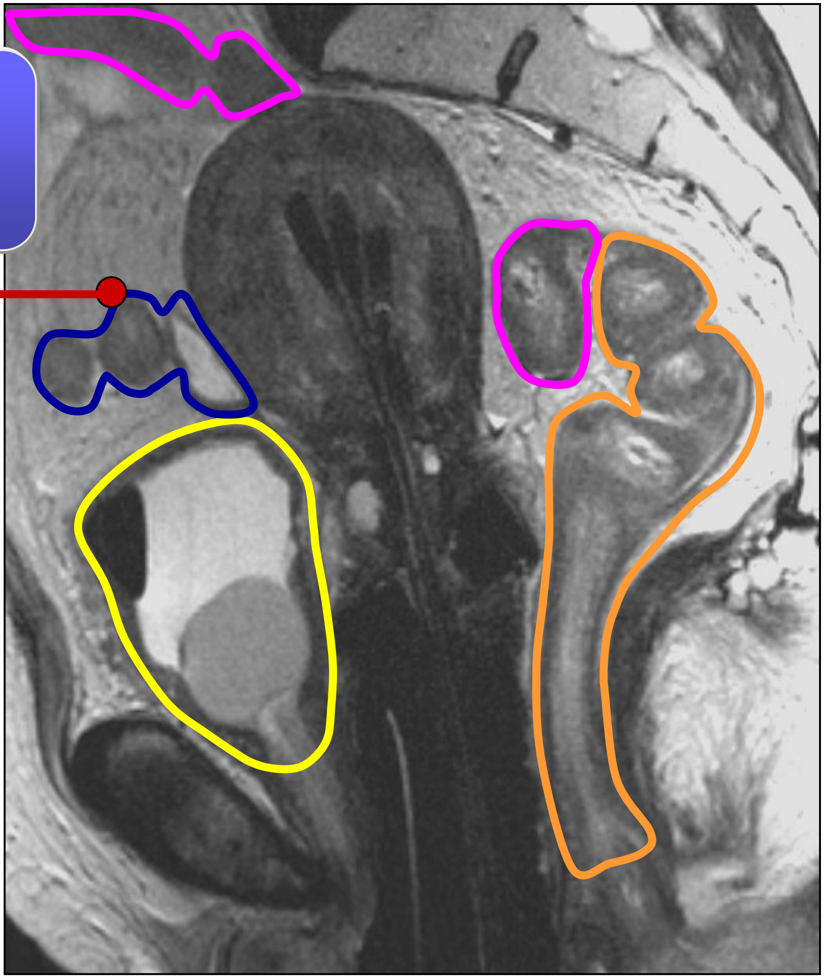
Sigmoid colon



Clear Definitions of Organs at risk

Small bowel

Loops in vicinity of high dose region



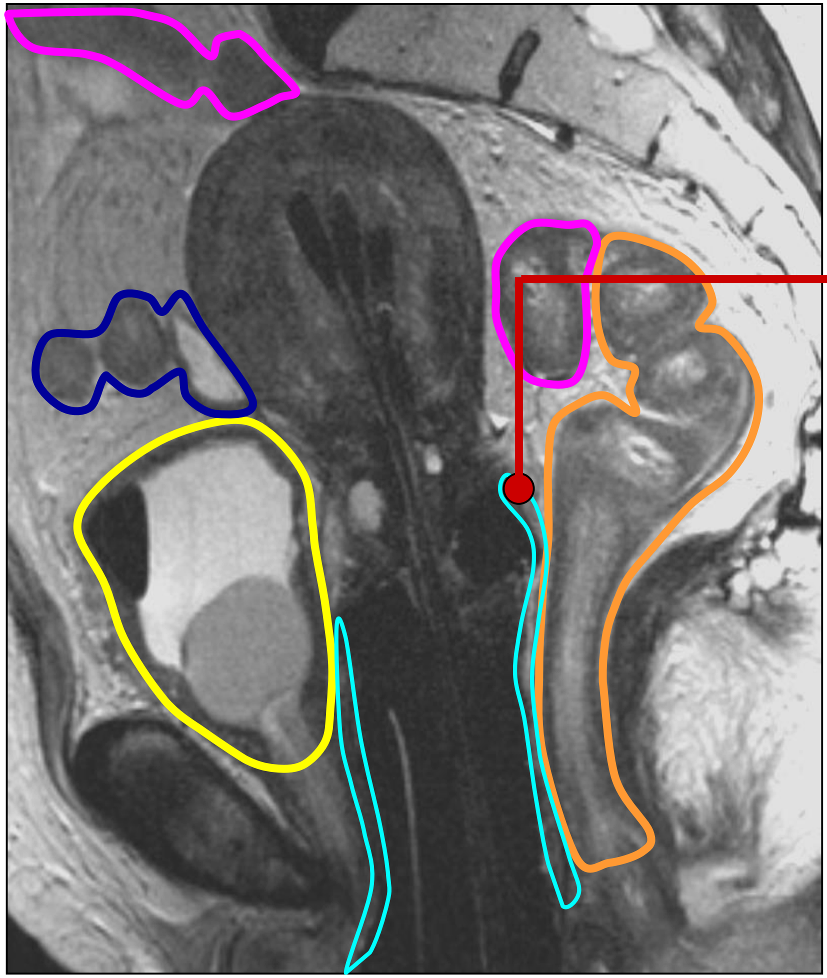
Kavanagh BD, et al. IJROBP 2010
Muren LP. Radiother Oncol 2003

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

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

Clear Definitions of Organs at risk

Vagina



Vaginal wall

Delineation, DVH, Reporting:

- ↑ uncertainties
- ↓ reproducibility

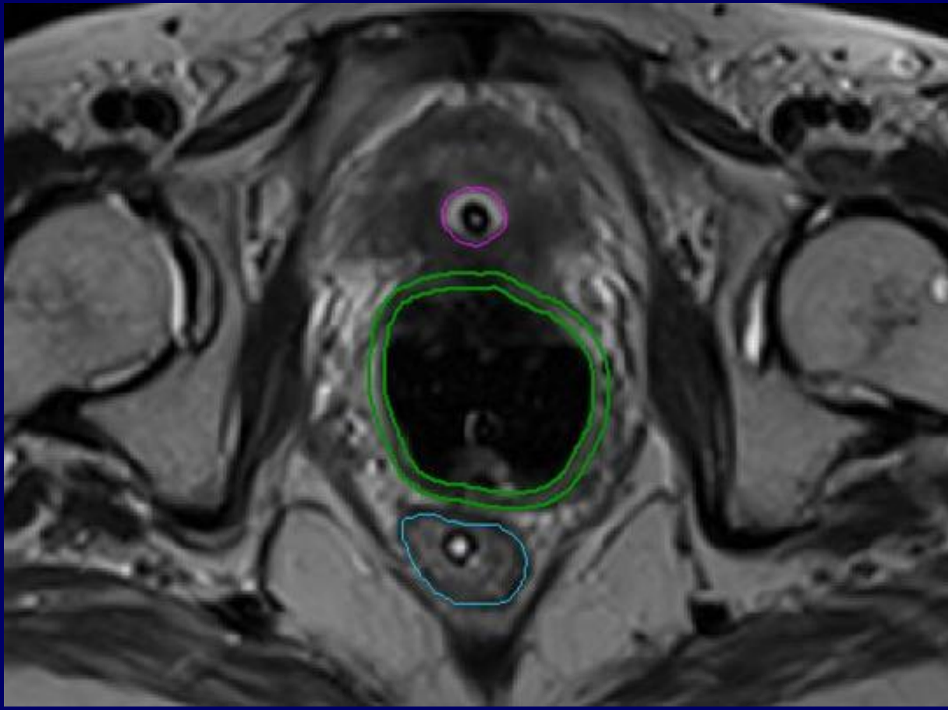
SUBJECT OF FURTHER STUDIES

Berger D, et al. IJROBP 2007

Vaginal wall Contouring

- Contour vaginal wall according to visible low signal intensity of vaginal wall.

- If not accurately distinguished: Take 3 mm as overall organ wall thickness and contour from fornices till introitus in three parts as per ICRU 89



Other OARs

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

Summary

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

CT Guided Contouring & Planning

Umesh Mahantshetty

Professor,

Department of Radiation Oncology

&

GYN Disease Management Group Member

Tata Memorial Hospital, Mumbai, India

2nd AROI - ESTRO TEACHING COURSE Lucknow 2018

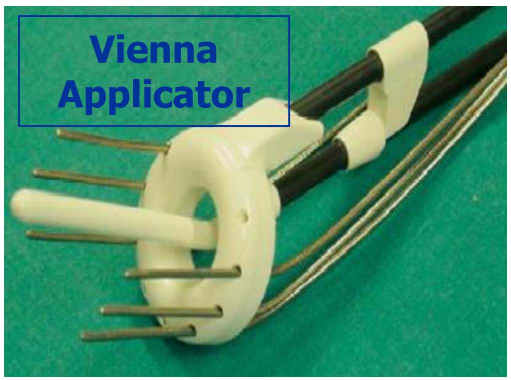
Specific Learning Objectives

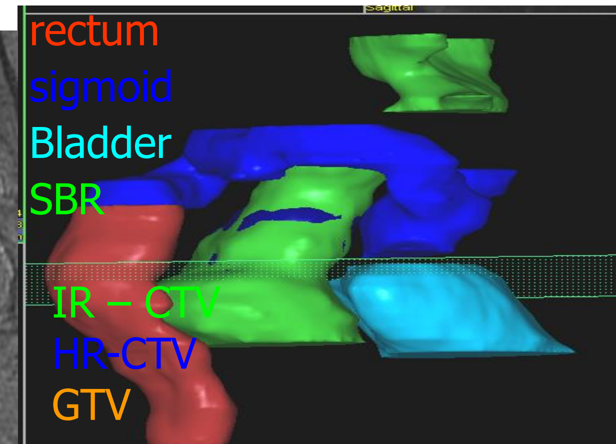
- To understand the GYN Pelvic CT anatomy and Standardization for CT based contouring
- To delineate target on CT Imaging
- To delineate OAR's namely bladder, rectum and sigmoid

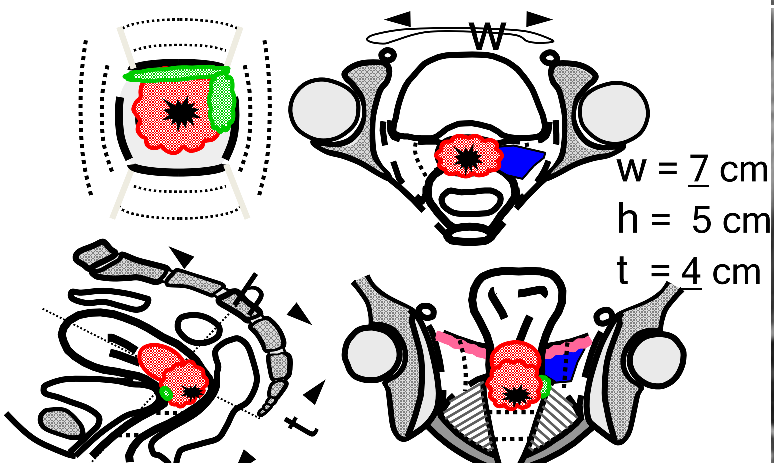
INTRODUCTION / BACKGROUND

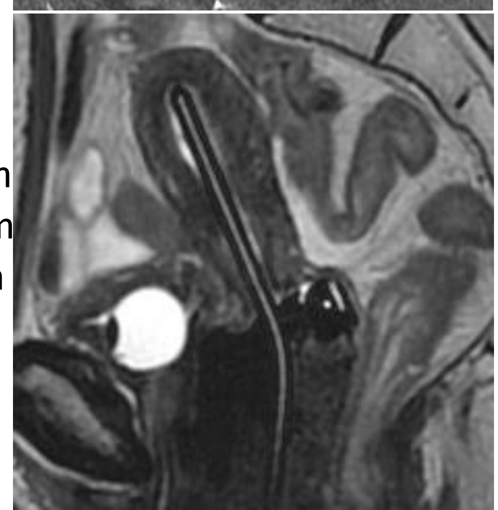
- **Applicators**
- **Imaging: MRI**
- **Planning systems**

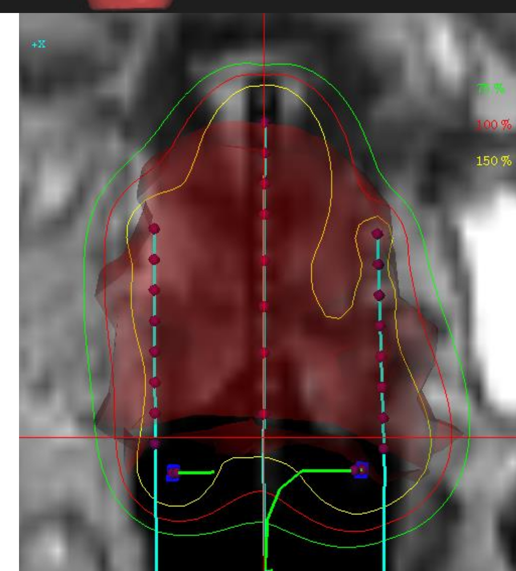
"GOLD STANDARD"
MRI Based Approach

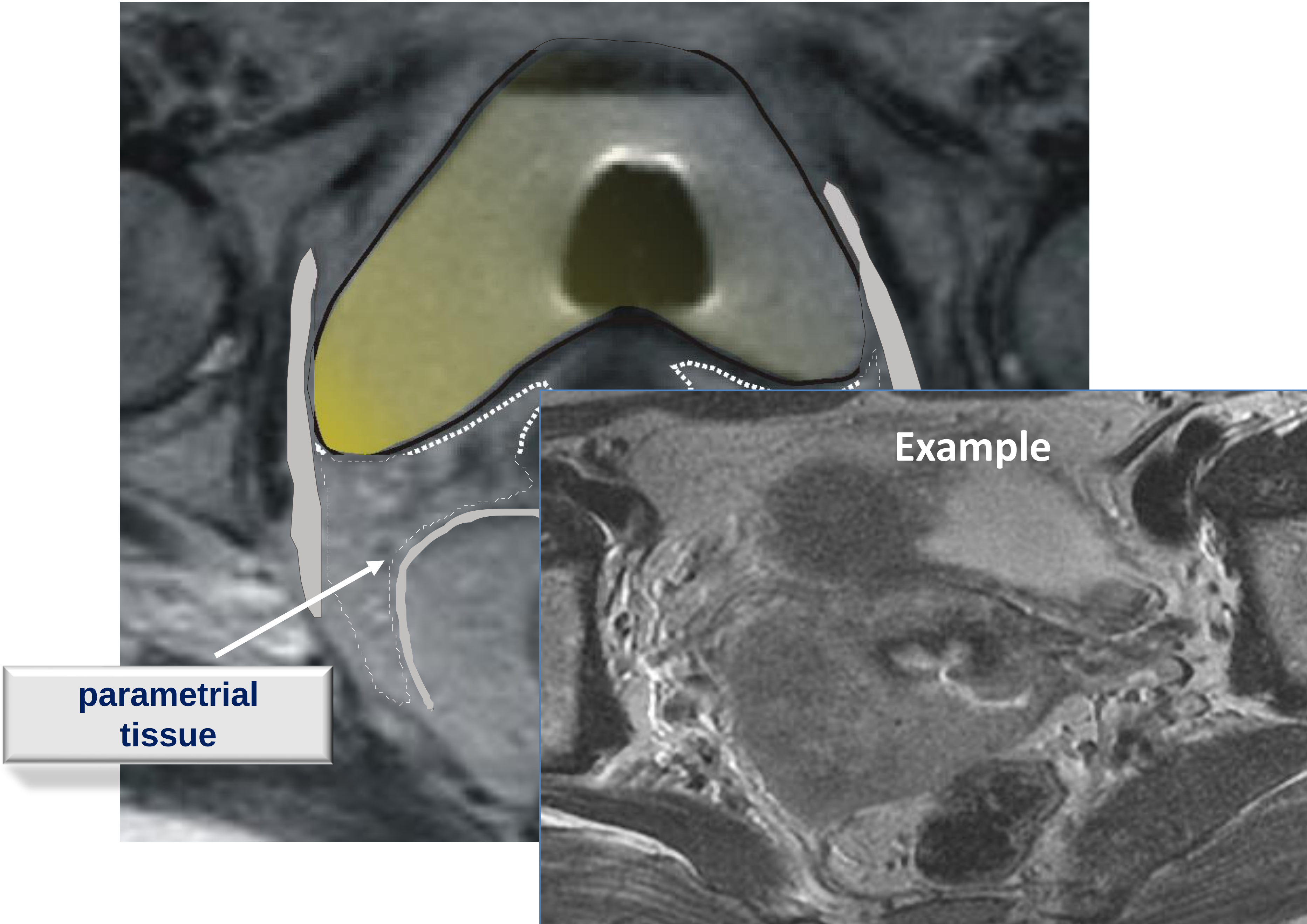




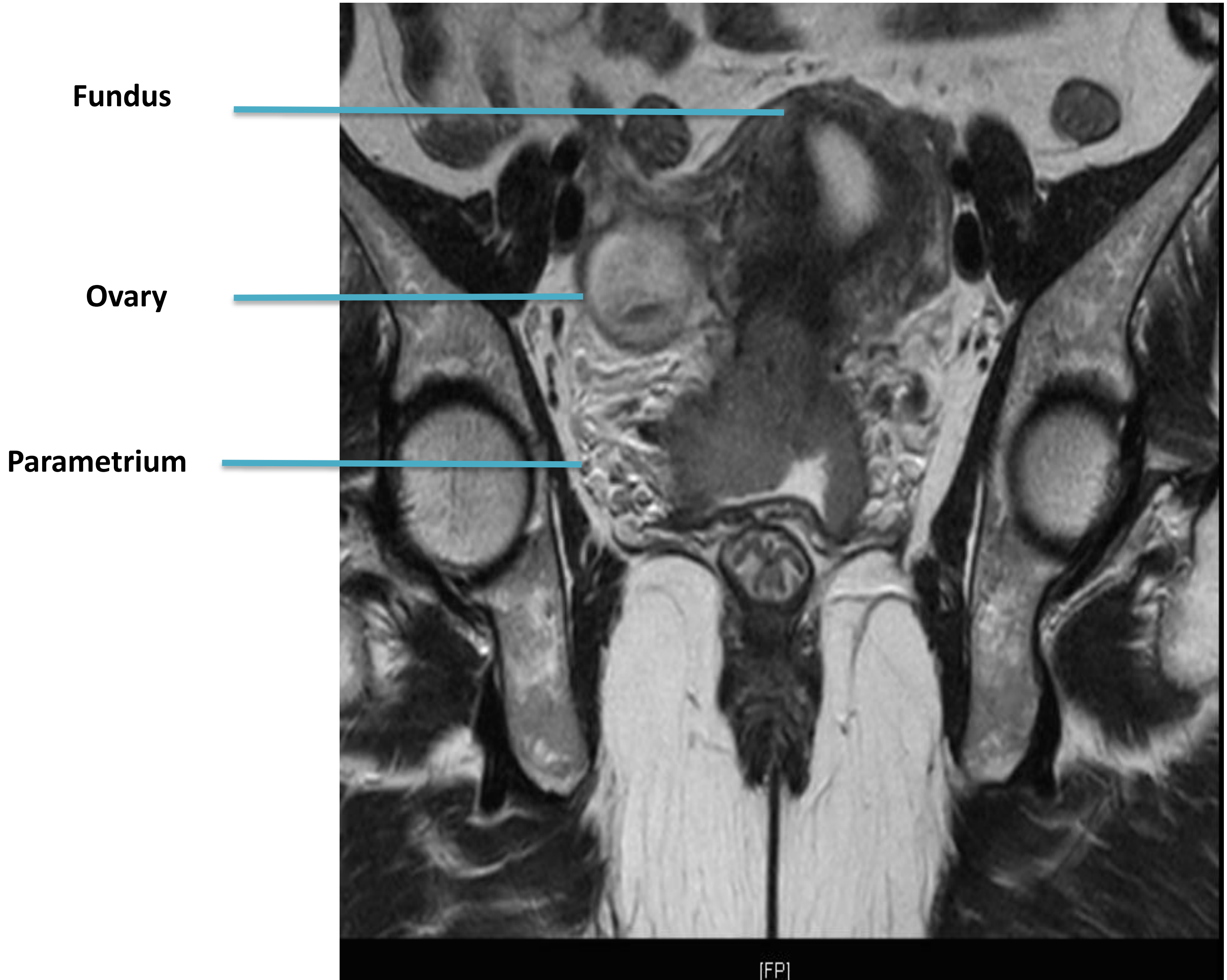




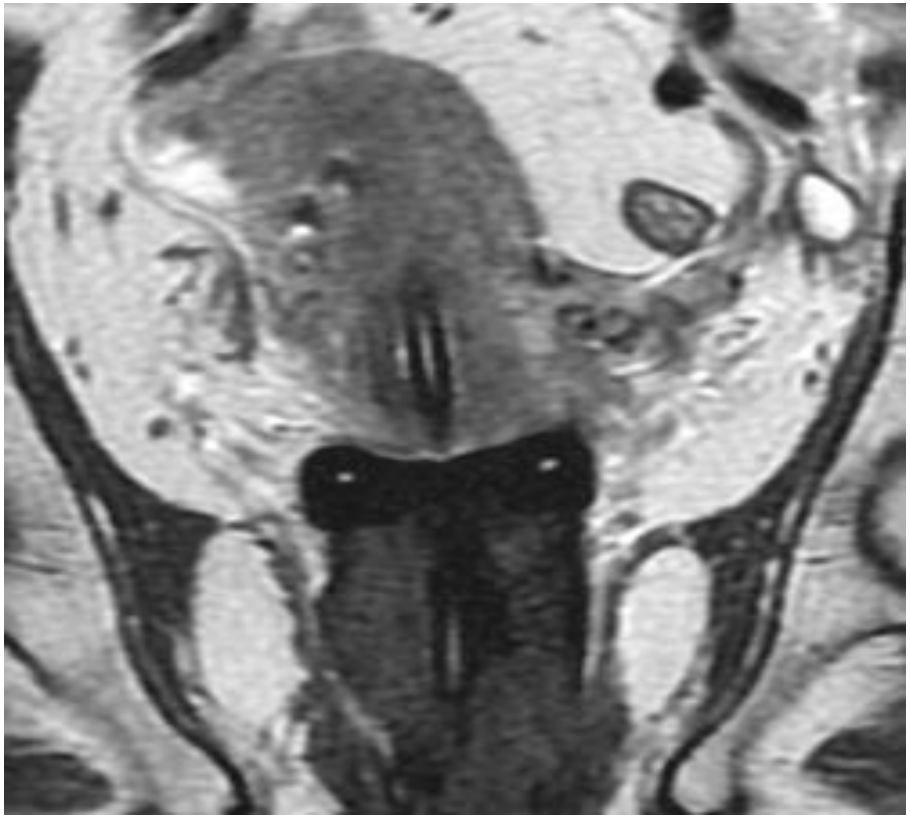


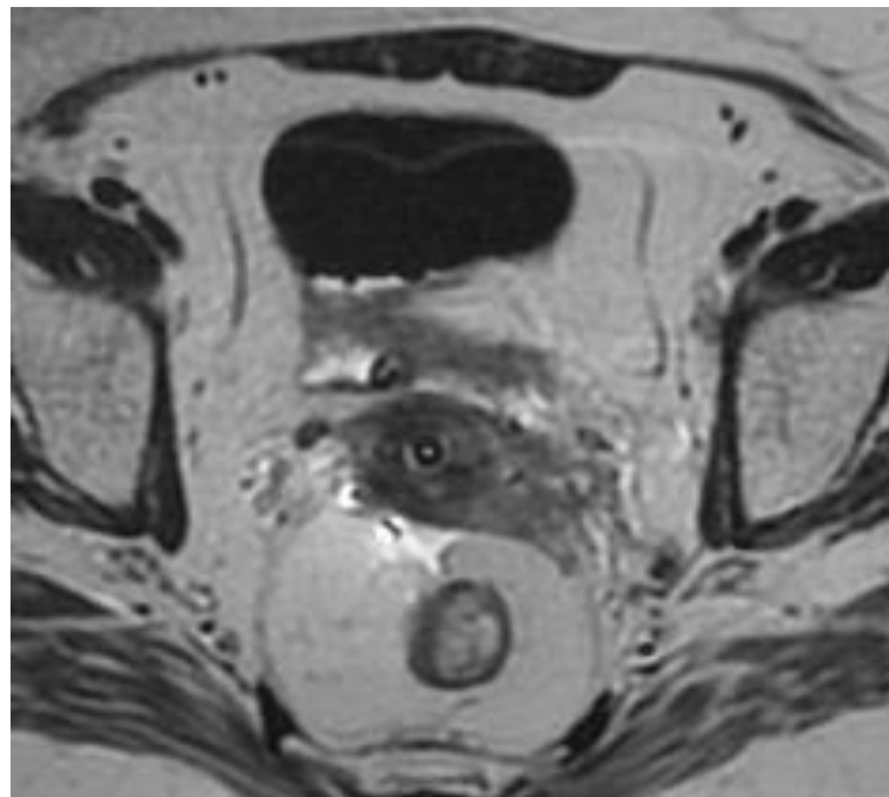


Dimopoulos et al. IJROBP 2006

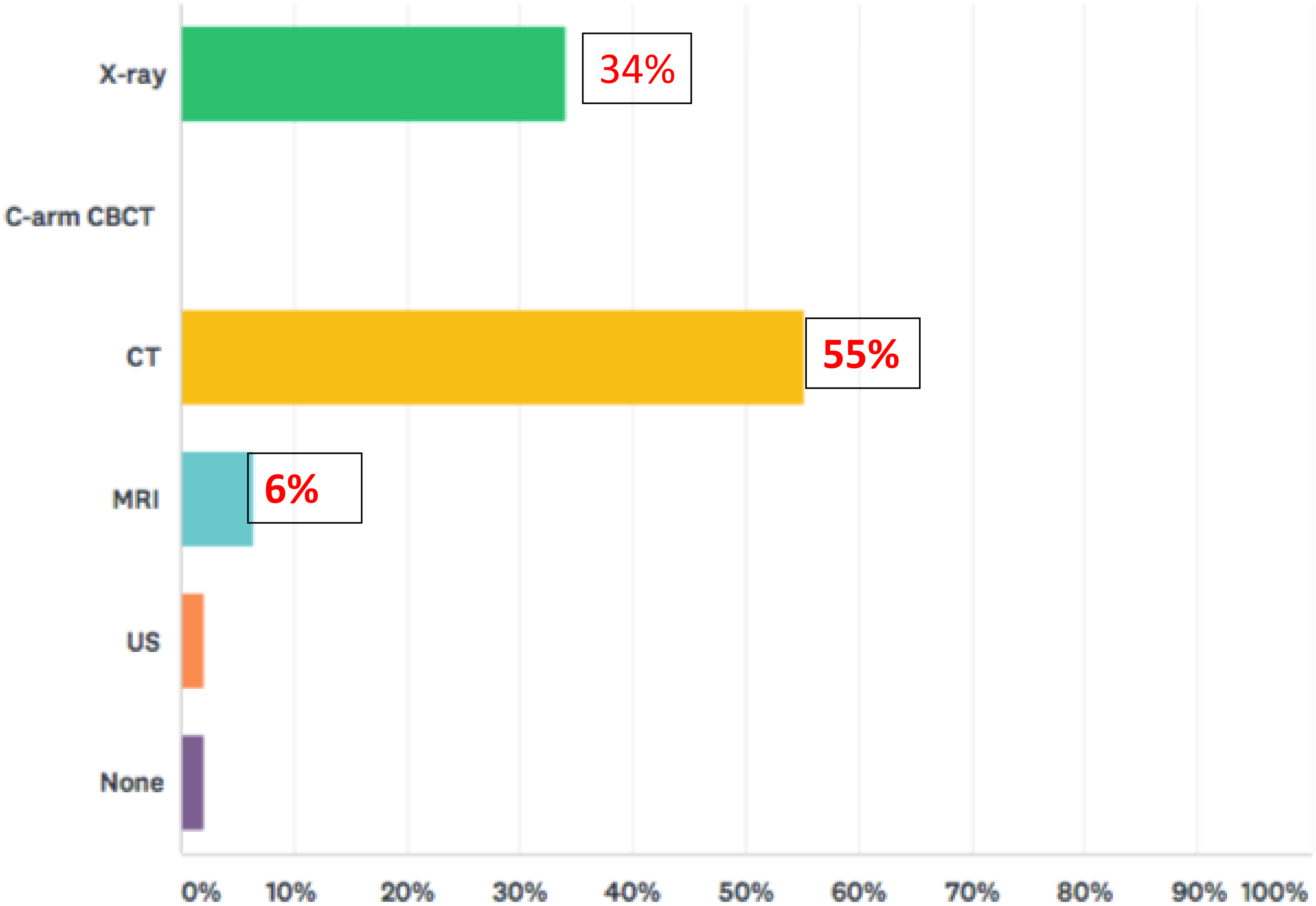


Fundus
Ovary
Parametrium
[FP]





Imaging at brachytherapy
47 Replies

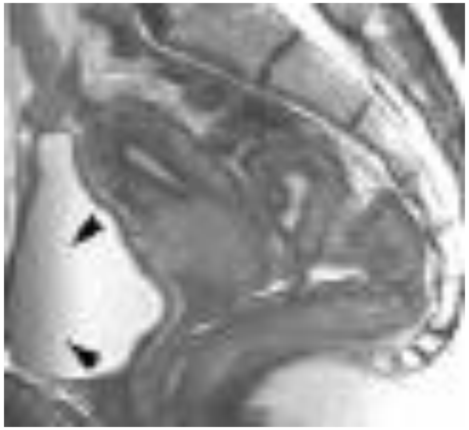


SURVEY REPORTS

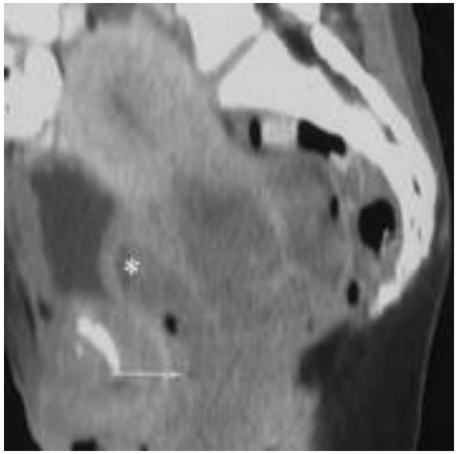
	2D	CT	MR	Others
United States (IJROBP 2010)	43%	55%	2%	US for insertion (55%)
Canada (Brachy 2013)	63%	66%	13%	9% (Cone beam CT)
Australia & NZ (JMIRO 2010)	30%	65%	-	20% (combination US+MR)
UK (Clin. Oncol. 2011)	29%	51%	20%	--
GYN ESTRO TC Survey (AVG)				
European Teaching Courses	45%	50%	30%	US (10%)
Outside Europe Courses	60%	40%	10%	US (15%)

Overall : > 50% use CT Imaging

Why CT for "At Brachy Contouring"



- CT Imaging : Gold STD for RT planning!
- Vast experience with CT based contouring for EBRT!
- Availability : CT Vs MR in Radiotherapy Depts.
- CT Based Contouring is practiced for all the tumor sites during external radiation therapy planning.



CT Guided Contouring

Don’t s

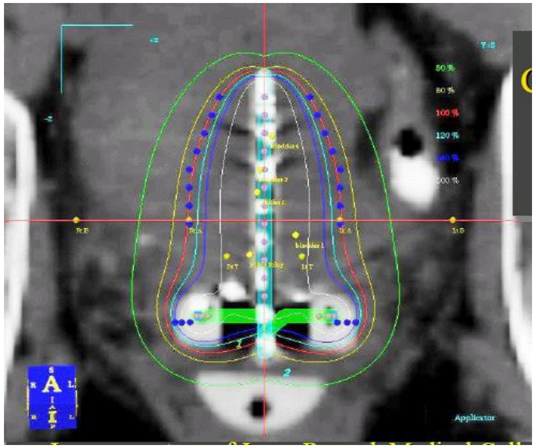
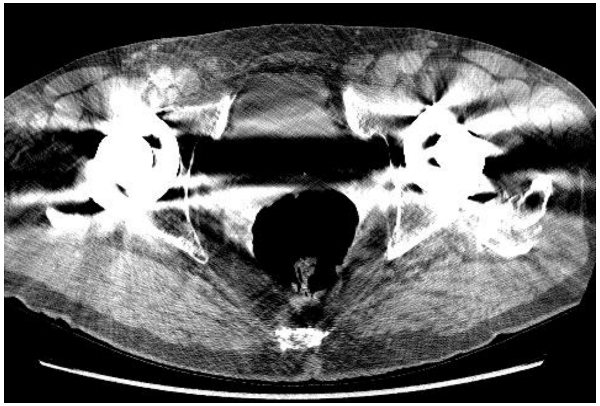
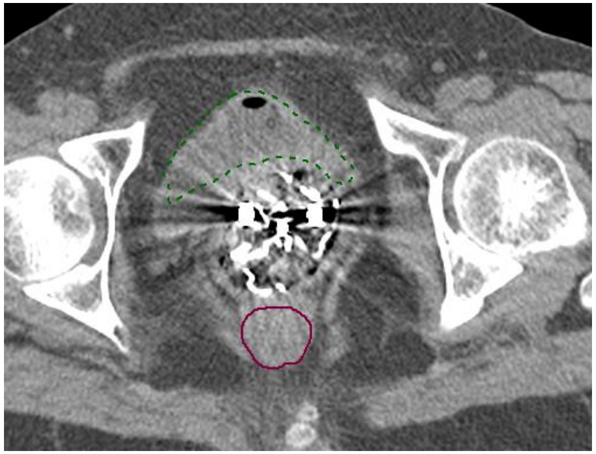
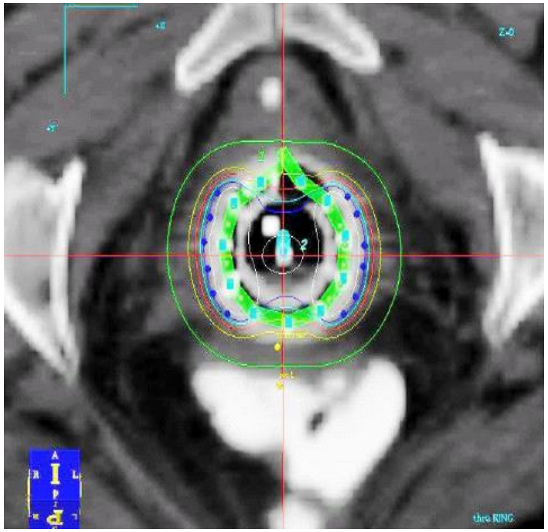
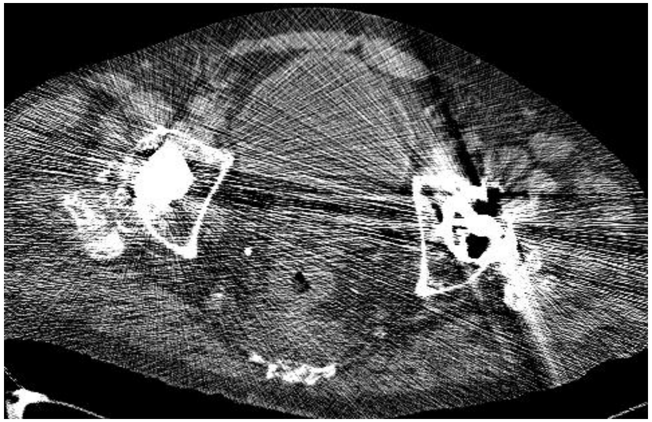
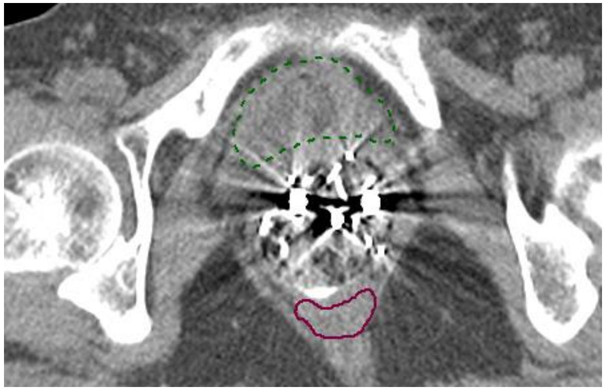
- Do not use the metallic applicators made of stainless steels
- Do not use conventional contrast agents in foley’s bulb / rectum / sigmoid
- Do not use radio-opaque gauze / rectal seperator (SS) for vaginal packing
- Do not use dummies meant for X-rays based planning

Do’s

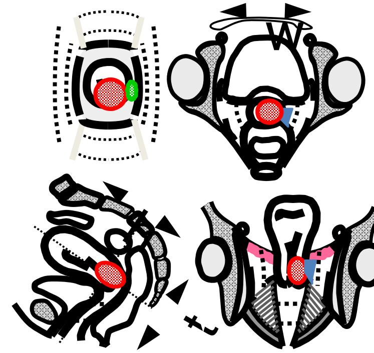
- CT / MR Compatible Brachy Applicators
- Use saline/ water as contrast in foley’s bulb & dilute urograffin for rectum/ sigmoid/ bladder
- CT protocol: 2-3 mm slice axial sections with / without IV Contrast
- Dummies : Copper / low density metal
- Proper Documentation and mapping of disease : Clinical / Imaging

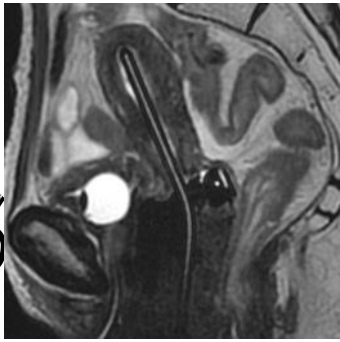
CT Artifacts

Applicators , Bowel contrast, Hip prosthesis, Foley's catheter, Dummies, Rectal retractors

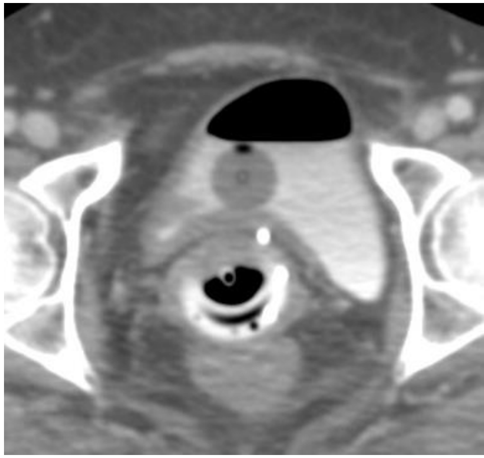
Pre - requisites





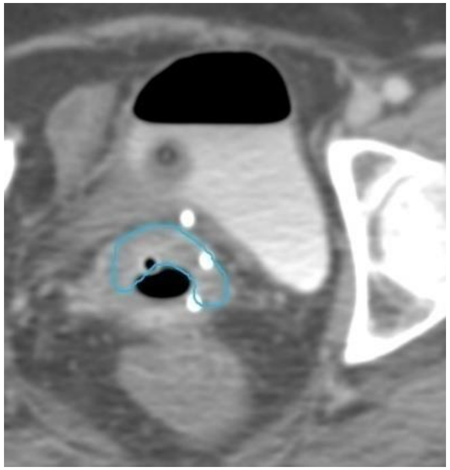
- *Experience of MR Based Approach: Mandatory*

- *At Diagnosis: Clinical drawings, MR +/- CT*



- *At Brachytherapy: Standardization of the CT protocol*
  - *- CT compatible applicators*
  - *- bladder filling protocol with dilute contrast*
  - *- Intravenous contrast*

- *Adopt the MR based definitions*



Comparison of various parameters required for target definition / contouring

	Clinical examination	MR	CT
GTV	**good**	**excellent**	**poor**
Outline of cervix	**good**	**excellent**	**good**
Uterine corpus invasion	poor	**excellent**	poor
Parametrium (normal & abnormal)	**(good) Learning curve**	**good**	poor
Vaginal disease	**excellent**	**Excellent for para-vaginal disease**	poor

Various targets at brachytherapy on CT:

- GTV at brachy: no visualization of residual tumor on CT
- **HR-CTV: on CT feasible with Clinical & CT protocol**
- IR-CTV: safety margins to HR-CTV
- OAR: rectum, bladder and sigmoid

CT guided Target Definition / Contouring
High Risk CTV:

STD: Clinical + MR Based (Pre Rx +Brachy)

- GTV-B + Whole cervix
- Presumed tumour extensions
  - Local extent
  - Residual grey zones on MR
- NO SAFETY MARGINS

Clinical + Pre Rx MR + CT Based

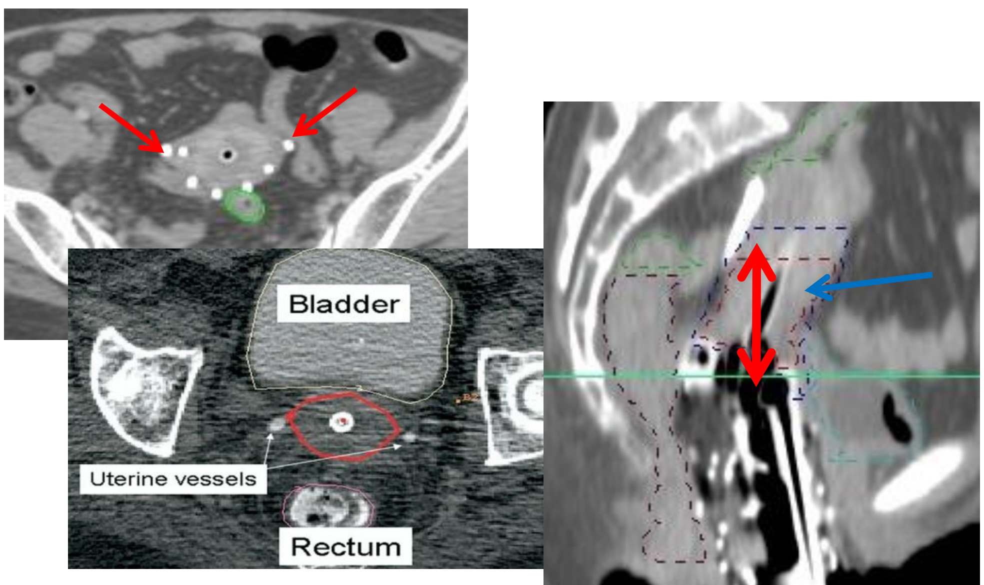
- **Whole of Cervix**
- **Presumed extensions at brachy**
- Parametrium: Clinical + CT imaging *(Trans rectal US*)* + Pre Rx MR
- Endocervical: Clinical + Pre-Rx MR
- Vagina: Disease at Diagnosis + EUA at Brachy
- ***Safety margins: superiorly along the uterus (lower 2/3rds of uterus)***

** Intra-operative TRUS Imaging findings if available*

HR-CTV Delineation On CT
Some landmarks for Whole Cervix

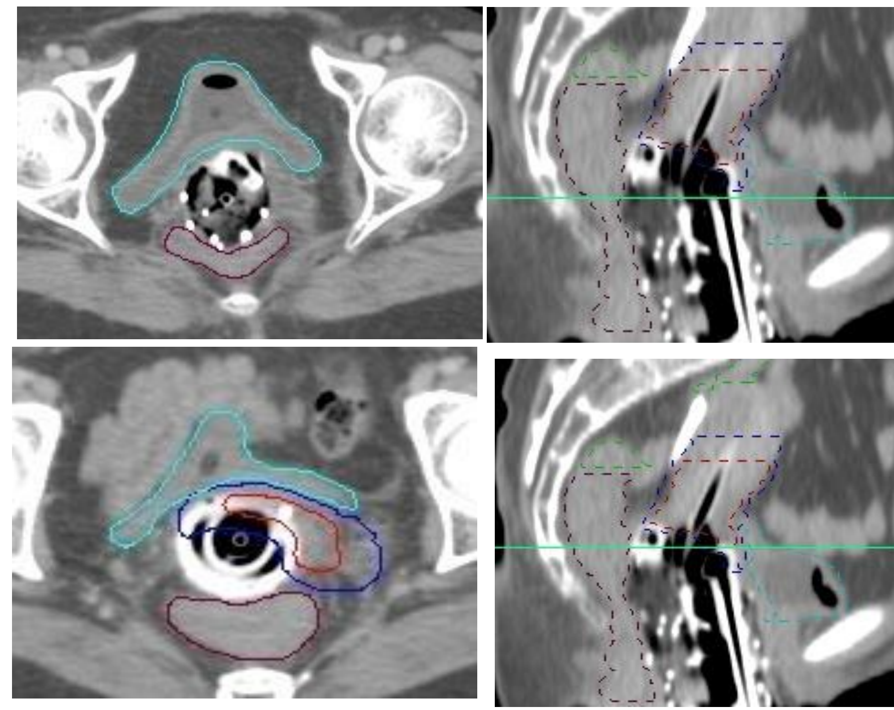
Superior extent

- Level of uterine vessels first abut cervical tissue (need i/v contrast)
- Point of volume expansion
- Point of uterine cavity appearance
- Conical cervical apex or the isthmus

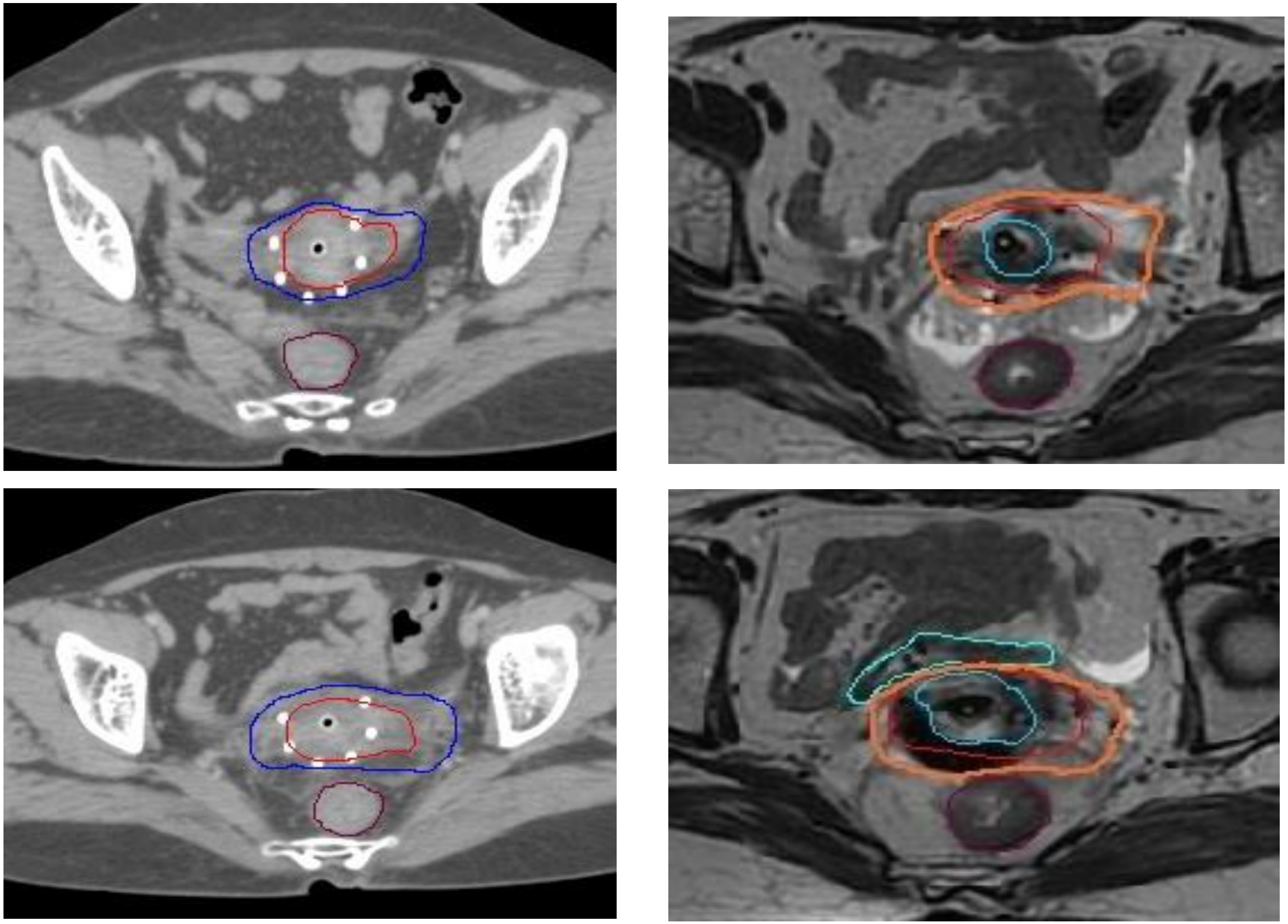


Inferior extent

At superior level of Ring/Ovoid

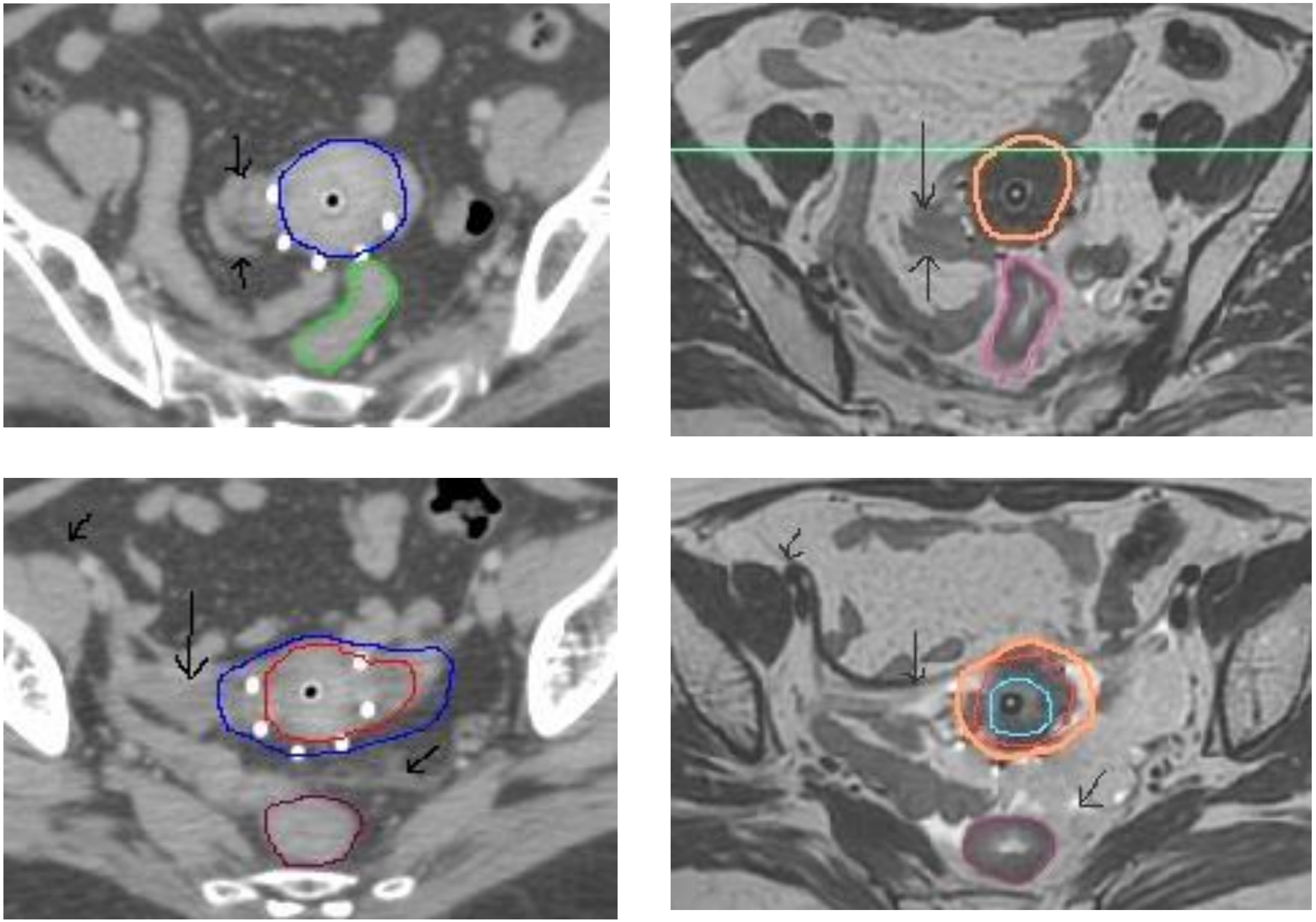


HR-CTV: Lateral width
Abnormal Parametrium???

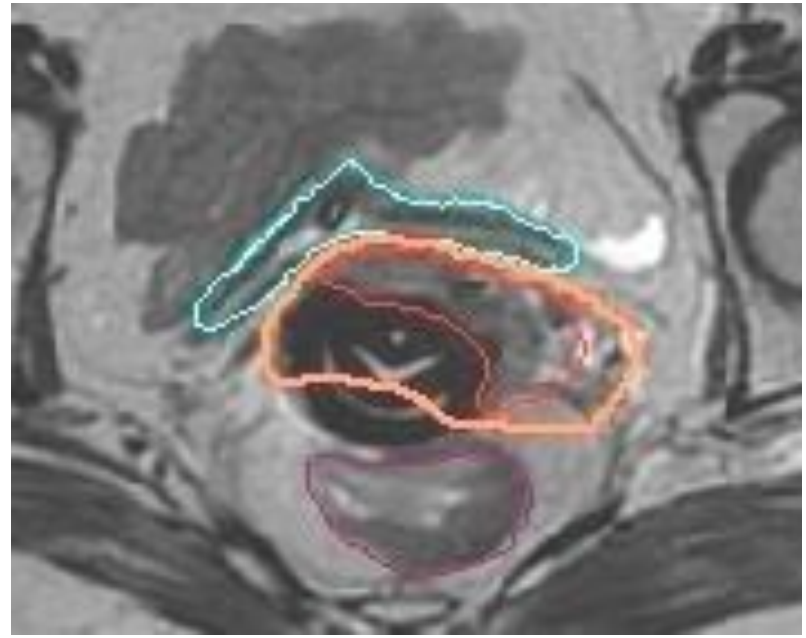


Lateral width of HR-CTV on CT : Clinical examination and objective documentation

HR-CTV Lateral width Limitations:
Bowel/ovary/else?



Special situations : Practical difficulties
Anterior / Posterior Extent

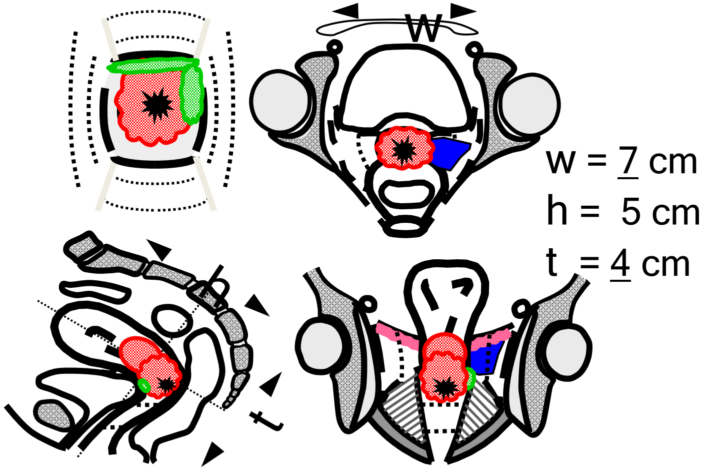


- At the level of ring / ovoid’s & cervix difficult boundaries
- Especially in empty Bladder & Rectum
  - Need good information of anatomy and correlation with clinical findings
  - Thorough orientation of CT images
  - MRI image studies experience is vital

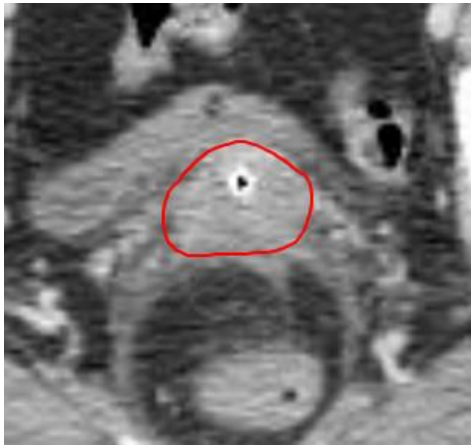
HR-CTV Delineation On CT

Extensions: Clinical examination + CT findings

- Whole cervix
- Parametrium: over-estimated
- Endocervical: under-estimated
- Vagina : clinical examination



- none can be truly estimated on CT



Summary: HR-CTV contouring seems feasible with clinical examination and CT findings and assisted by pre-Rx MRI

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

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

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

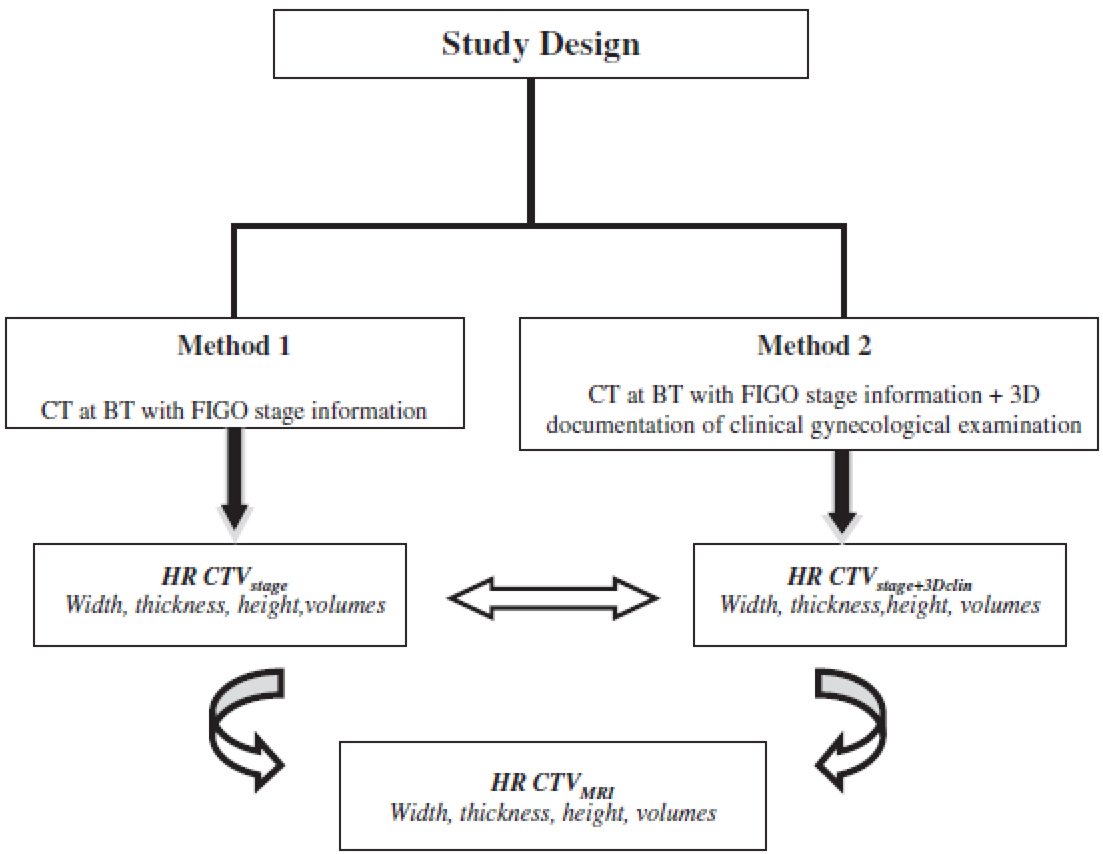


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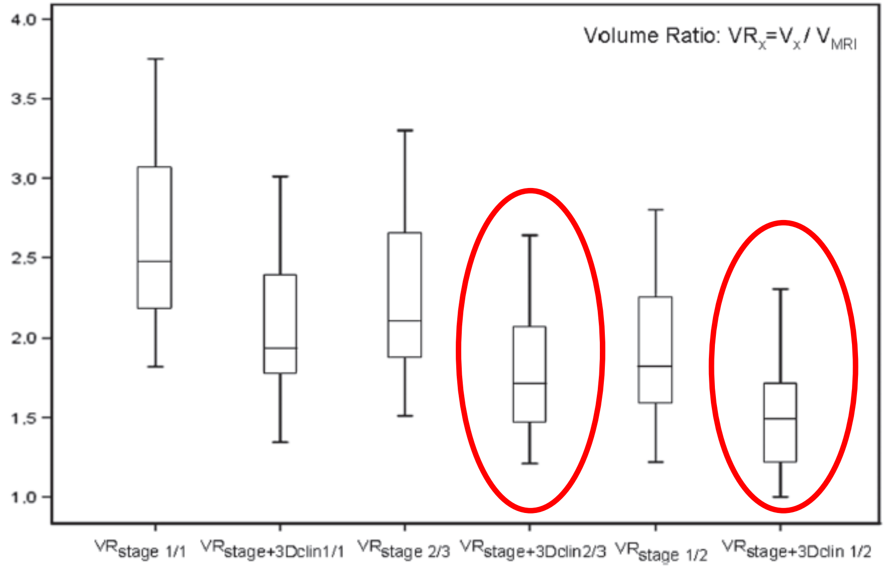
Table I. Mean, standard deviations and ranges of volume, height, width, and thickness of HR CTV_{stage}, HR $CTV_{stage+3Dclin}$ and HR CTV_{MRI}.

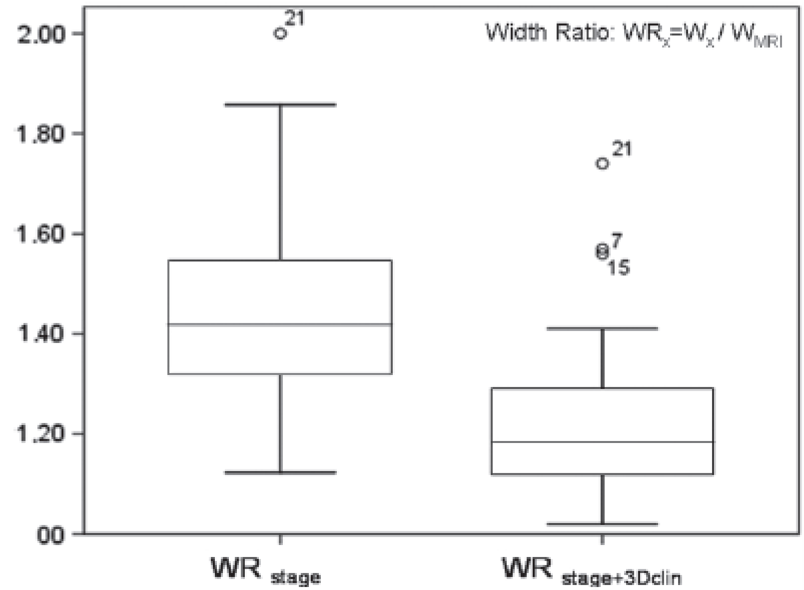
Parameters (mean ± SD [range])	Height (cm)	Width (cm)	Thickness (cm)	Volume (cm^3)
HR CTV_{stage} 1/1 uterine height	6.6 ± 1.5 [4.0–10.8]	6.2 ± 0.8 [4.8–7.9]	3.9 ± 0.5 [2.9–4.8]	82 ± 27 [38–164]
HR CTV_{stage} 2/3 uterine height	5.1 ± 1.3 [3.2–9.2]	*	*	71 ± 23 [32–149]
HR CTV_{stage} ½ uterine height	4.3 ± 1.1 [2.8–8.4]	*	*	60 ± 20 [28–131]
HR $CTV_{stage+3Dclin}$ 1/1 uterine height	6.6 ± 1.5 [4.0–10.8]	5.4 ± 0.6 [4.2–6.5]	3.7 ± 0.5 [2.3–4.6]	66 ± 23 [32–141]
HR $CTV_{stage+3Dclin}$ 2/3 uterine height	5.1 ± 1.3 [3.2–9.2]	*	*	56 ± 20 [27–127]
HR $CTV_{stage+3Dclin}$ 1/2 uterine height	4.3 ± 1.1 [2.8–8.4]	*	*	47 ± 17 [21–111]
HR CTV_{MRI}	4.1 ± 1.5 [2.0–8.0]	4.4 ± 0.7 [3.0–5.7]	3.2 ± 0.6 [2.0–4.1]	34 ± 15 [12–73]

*Asterisks indicate that width and thickness values are independent of uterine height. The heights for the two different CT-based HR CTV groups are identical when the same uterine standard length is used.

Table II. Mean and standard deviations of the CT/MRI width ratios ($WR_x = W_x/W_{MRI}$) thickness ratios ($TR_x = T_x/T_{MRI}$) for all HR CTV_{stage} and HR $CTV_{stage+3Dclin}$, and heights ratios ($HR_x = H_x/H_{MRI}$) for all standard uterine heights used for both CT-based contour types, grouped by different FIGO stages.

		FIGO stage			
	x	IB (n = 8)	IIB (n = 18)	III (n = 9)	All (n = 35)
CT/MR width ratio WR_x	HR CTV_{stage}	1.5 ± 0.3	1.4 ± 0.1	1.4 ± 0.2	1.5 ± 0.2
(mean ± SD)	HR $CTV_{stage+3Dclin}$	1.3 ± 0.2	1.2 ± 0.1	1.2 ± 0.2	1.2 ± 0.2
CT/MR thickness ratio TR_x	HR CTV_{stage}	1.2 ± 0.1	1.3 ± 0.2	1.1 ± 0.1	1.2 ± 0.2
(mean ± SD)	HR $CTV_{stage+3Dclin}$	1.2 ± 0.1	1.2 ± 0.2	1.1 ± 0.1	1.2 ± 0.1
CT/MR height ratio HR_x	1/1 uterine height	1.7 ± 0.2	1.9 ± 0.2	1.7 ± 0.6	1.7 ± 0.4
(mean ± SD)	2/3 uterine height	1.3 ± 0.1	1.5 ± 0.2	1.3 ± 0.4	1.3 ± 0.3
	1/2 uterine height	1.1 ± 0.1	1.2 ± 0.2	1.1 ± 0.4	1.1 ± 0.3





Conclusion. CT-based HR CTV contouring based on FIGO stage alone leads to large overestimation of width and volume. Target delineation accuracy can systematically improve through incorporation of additional information from comprehensive 3D documentation of repetitive gynecological examination in the contouring protocol, and thus help to improve the accuracy of dose optimization in settings with limited access to imaging facilities at the time of brachytherapy. If CT information is only available, minimum 2/3 of uterine height may be a good surrogate for the height of HR CTV.

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OAR's Delineation on CT

- Robust experience of OAR contouring for EBRT
- All studies show equivalent results for standard OARs
  - Rectum
  - Bladder
  - Sigmoid

Table 3. Volume and dose to organs at risk after importing to Plato, normalized to 7 Gy/fraction

OARs	MRI	CT
Bladder		
Volume (cm^3)	62.5 ± 31.6	84.5 ± 57.5
$D_{0.1cm^3}$	7.5 ± 1.0	6.5 ± 1.5
D_{1cm^3}	6.1 ± 0.6	5.5 ± 1.4
D_{2cm^3}	5.6 ± 0.6	5.0 ± 1.2
Rectum		
Volume (cc)	45.3 ± 15.3	62.8 ± 16.8*
$D_{0.1cm^3}$	5.0 ± 0.9	5.0 ± 1.1
D_{1cm^3}	4.2 ± 0.7	4.2 ± 0.9
D_{02cm^3}	3.9 ± 0.7	3.9 ± 0.8
Sigmoid		
Volume (cc)	36.5 ± 25.2	29.8 ± 16
$D_{0.1cm^3}$	5.5 ± 1.1	5.5 ± 1.9
D_{1cm^3}	4.5 ± 0.9	4.3 ± 1.5
D_{2cm^3}	4.0 ± 0.8	3.9 ± 1.4

OAR	CT (mean ± SD)	MRI (mean ± SD)	*P* value
Bladder			
Volume (cc)	83.9 ± 34.74	76.6 ± 39	0.089
ICRU Pt (Gy)	6.1 ± 2.4	6.3 ± 2.9	0.435
2 cc	9.0 ± 2.8	9.0 ± 2.1	0.911
1 cc	10.0 ± 3.21	10.0 ± 2.37	0.783
0.1 cc	13.0 ± 4.59	12.4 ± 3.06	0.549
Rectum			
Volume (cc)	48.7 ± 17.01	45.6 ± 10.16	0.377
ICRU Pt (Gy)	4.3 ± 1.4	4.3 ± 1.21	0.964
2 cc	4.5 ± 1.2	4.6 ± 0.9	0.67
1 cc	4.9 ± 1.4	5.1 ± 1.0	0.603
0.1 cc	6.1 ± 1.9	6.4 ± 1.6	0.443
Sigmoid			
Volume (cc)	44.22 ± 15.94	50.42 ± 25.92	0.288
2 cc (Gy)	5.6 ± 1.8	6.1 ± 1.9	0.377
1 cc	6.3 ± 2.1	6.9 ± 2.2	0.392
0.1 cc	8.0 ± 2.5	8.4 ± 3.7	0.699

Viswanathan et al.; IJROBP 2007
Krishnatry et al JJCO 2012

SUMMARY
High Risk CTV : Target definition / Contouring on CT

Based on Clinical examination, single MRI (at diagnosis preferable) and CT Imaging at Brachytheapy

- **Whole of Cervix**
- **Presumed extensions at brachytherapy**

  - Width: parametrium clinically & (TRUS)

  - Height: to be generous to include a larger volume of uterus superiorly (? Safety margins: 2/3rds) while vaginal disease to be delineated based on clinical findings at brachy

  - Thickness: anatomical boundaries (rectum/ bladder)

- **CT Based Target Definition: Current area of Research**

Comparison of Various Parameters required for Target Definition / Contouring

	Clinical examination	MR	CT
GTV	good	excellent	V poor
Outline of cervix	good	excellent	good
Uterine corpus invasion	poor	excellent	poor
Parametrium (normal & abnormal)	(good)	good	poor
Vaginal disease	excellent	Excellent for para-vaginal disease	poor

Various targets at brachytherapy on CT:

- GTV at Brachy: No visualization of residual tumor on CT
- **HR - CTV: on CT feasible with Clinical & CT findings**
- IR - CTV: safety margins to HR-CTV

Prospective Ongoing Study at TMH, MUMBAI

PROTOCOL

Evaluation of CT Imaging Assisted Contouring for Image Based Brachytherapy in Carcinoma of the Uterine Cervix

DATA SET - I

- Pre Rx Clinical Cartoon and Clinical measurements
- Pre Rx MR Pelvis : Primary tumor topography and measurements
- Dimensions of Disease: GTV-D and $IRCTV_B$ Concept

DATA SET - II

- Clinical Cartoon at 1st Brachytherapy
- CT Imaging: 3mm slices (Contrast)
- MR planning
- GTV_B, HR-CTV, IR-CTV at 1st Brachytherapy on CT and MR

END POINTS

- Correlation between CT Vs MR Based HR-CTV & IR-CTV contouring
- Correlation between CT Vs MR Based OAR contouring

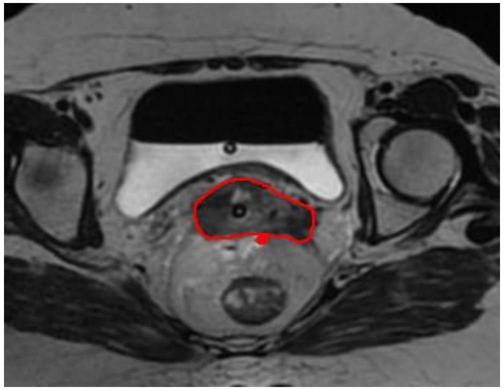
- **TRUS after tandem insertion at 3 levels**
- **Bladder filling protocol**
- **HR-CTV contoured on CT with the knowledge of Clinical + Pre Rx MR**
- **STD MR based contouring**

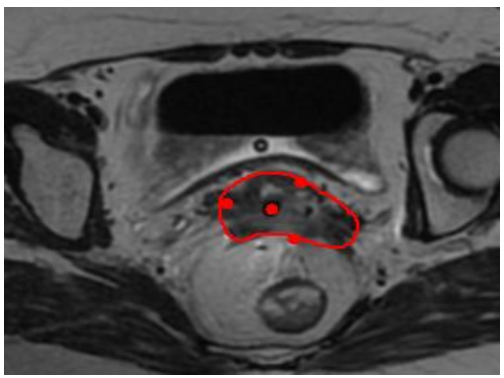
27 pts recruited so far
STUDY: Ongoing

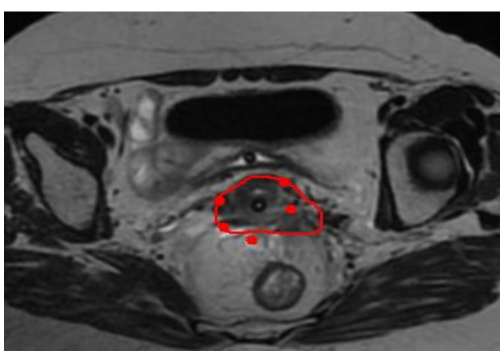
Bladder Protocol

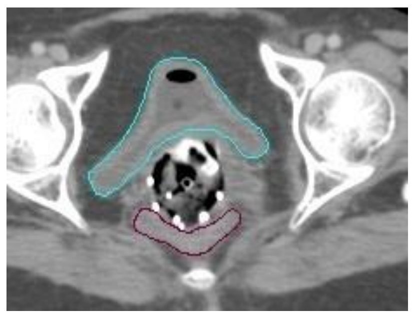
CT / MR Imaging

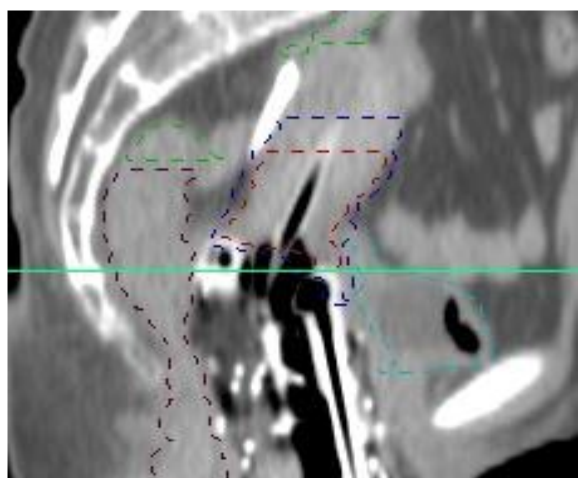
- Empty bladder before start of procedure
- Maintain a negative pressure by Asepto pump
- Push 20- 50 ml of fluid at Imaging and delivery

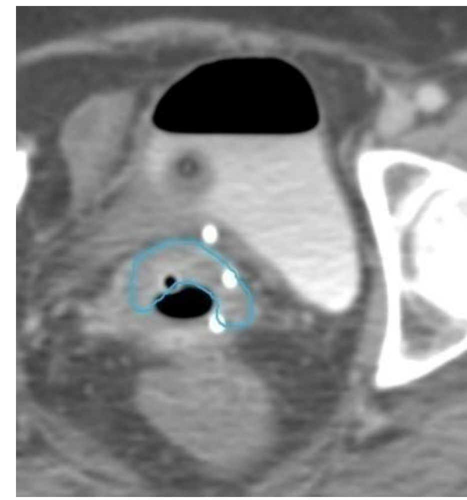


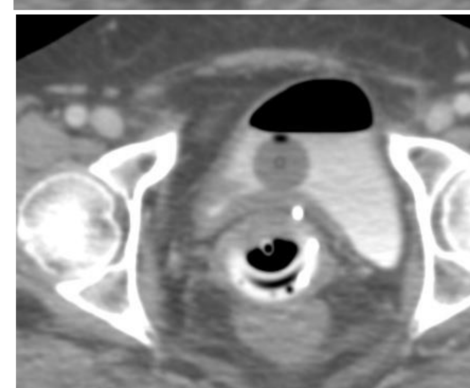








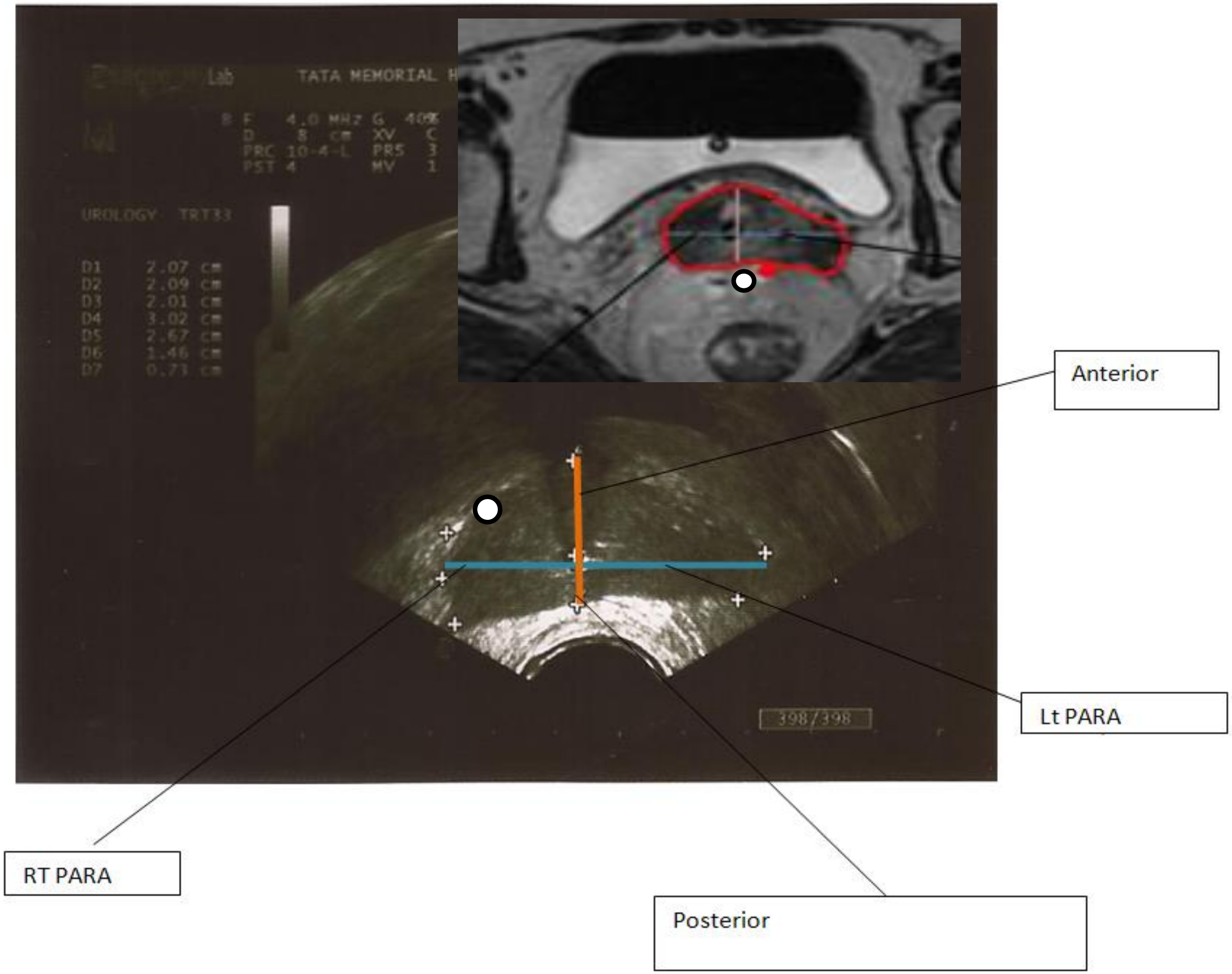




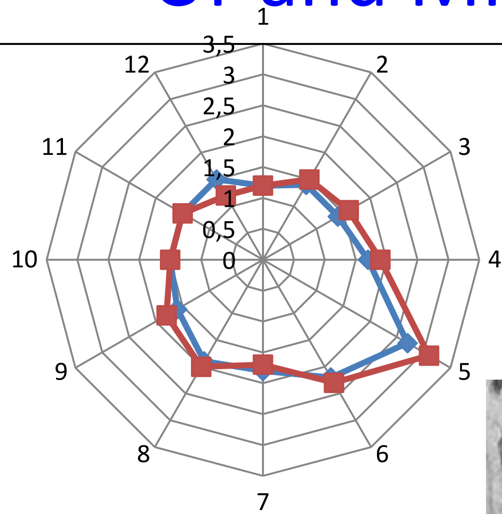
TRUS Guided Target Volume Definition

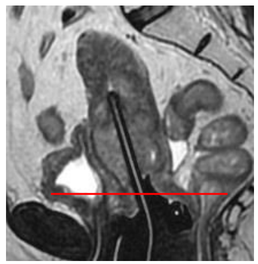
TMH STUDY: ONGOING RESEARCH (N=27 pts so far)

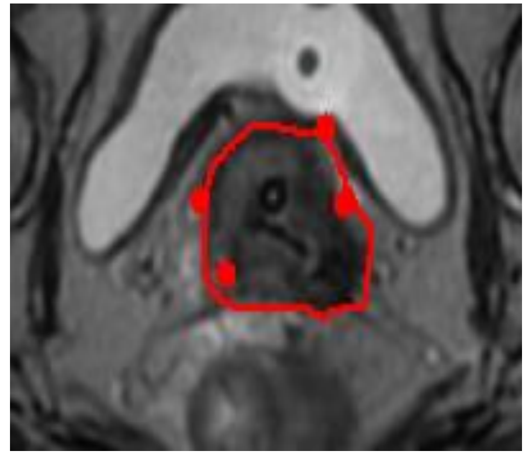
MRI-TRUS Correlation

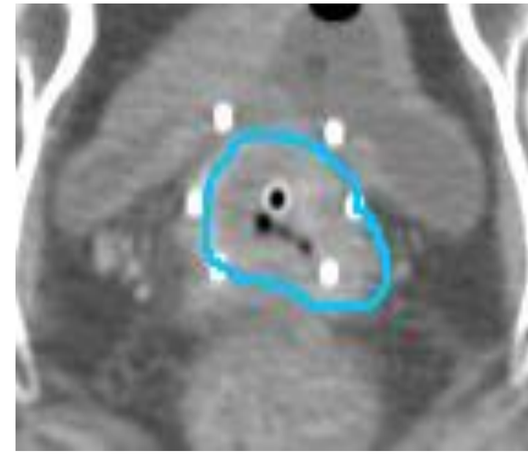


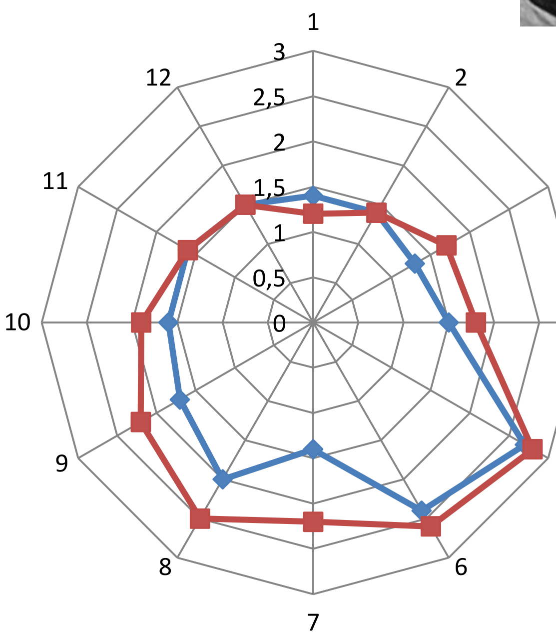
CT and MRI correlation: Ongoing Research

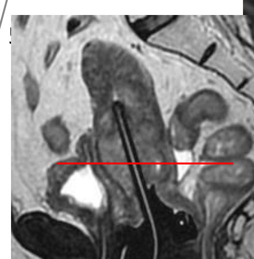


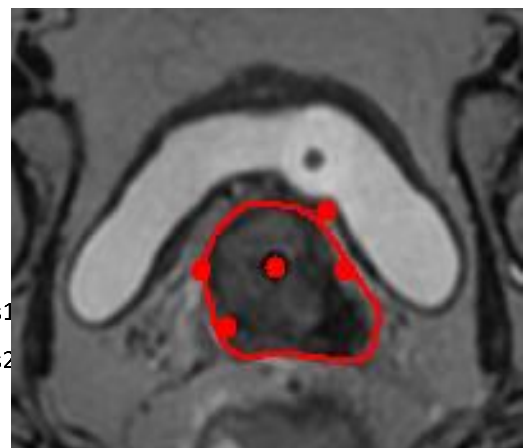


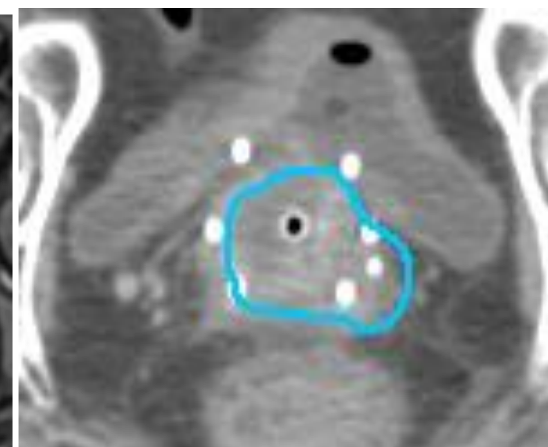






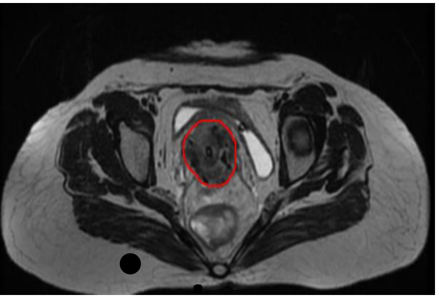
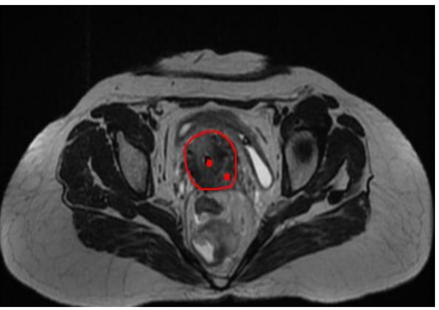
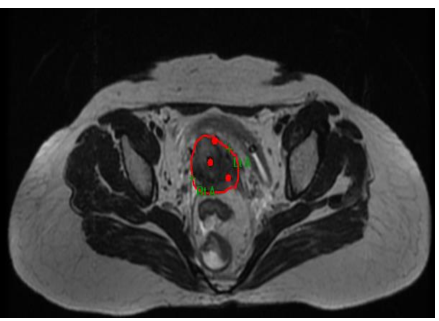
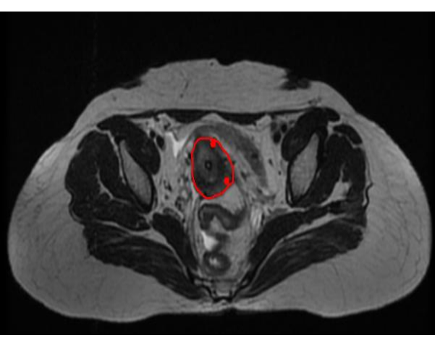
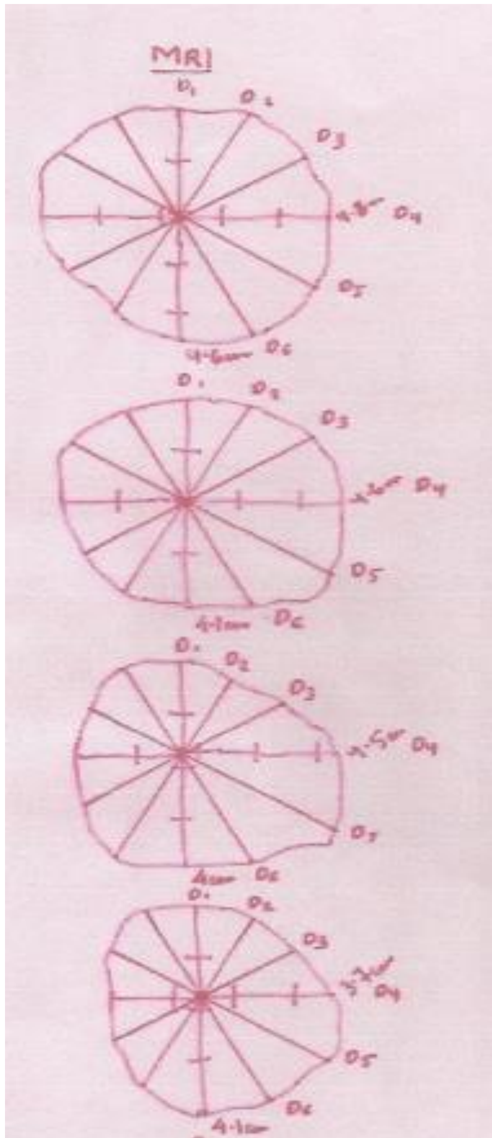


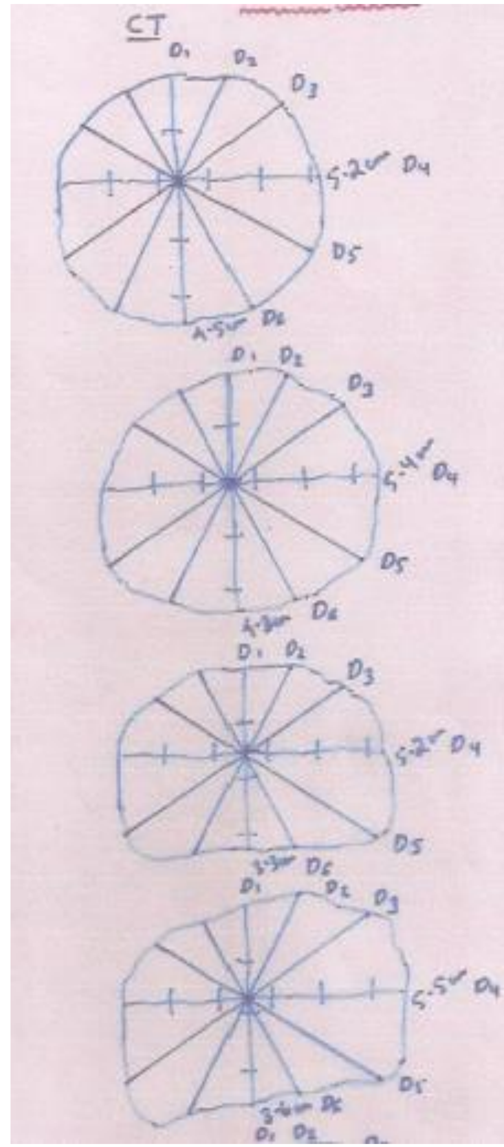


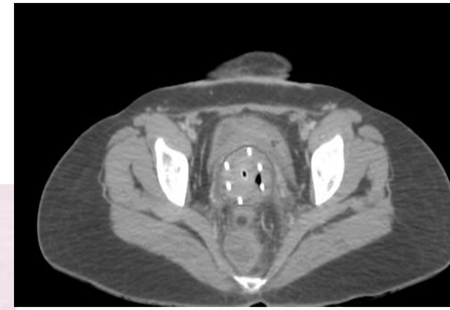
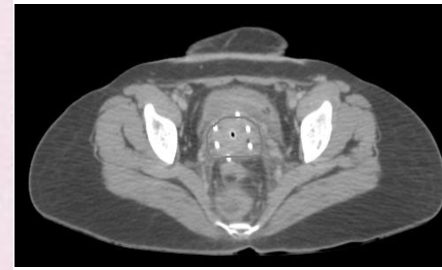
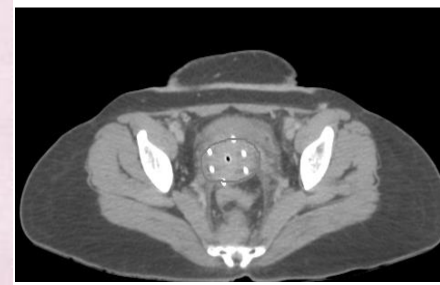
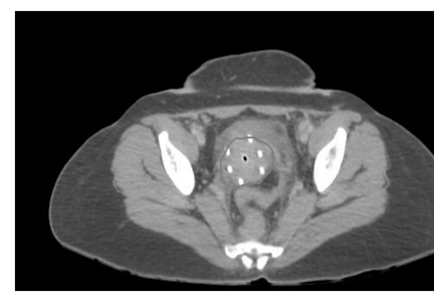


TMH Study

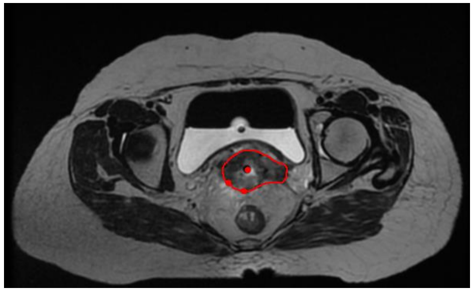
Ca Cervix - IIB
HRCTV includes Cervix only NO PARA Invasion at BT

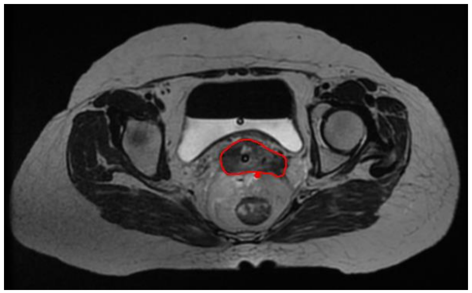






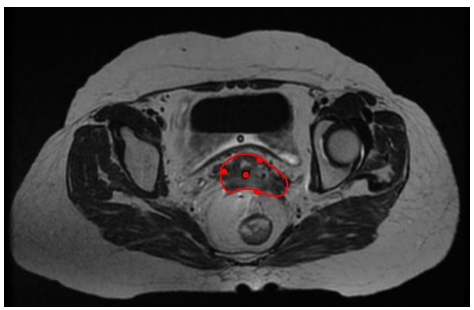


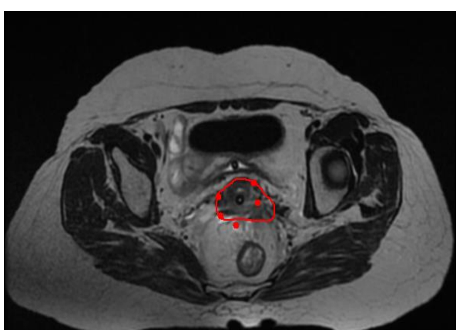





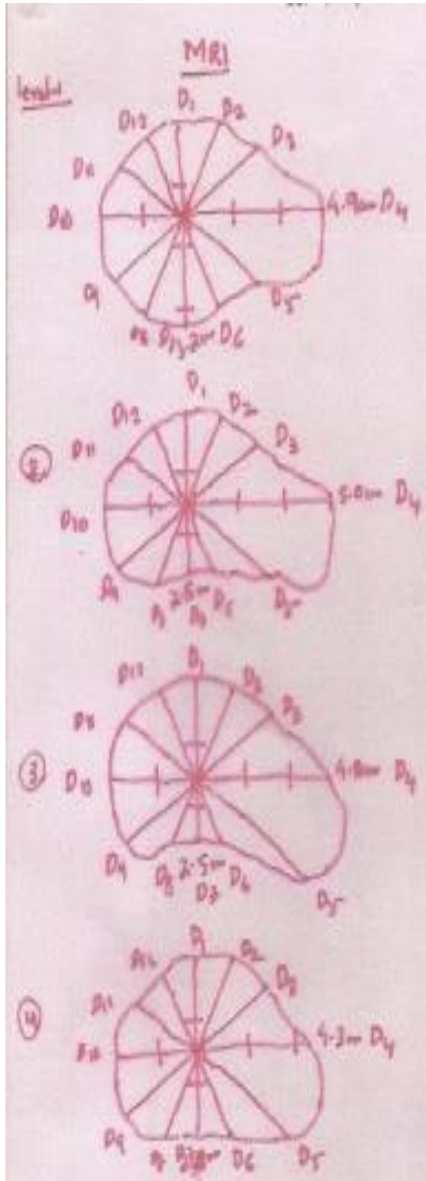
Ca Cervix-IIIB,
HRCTV includes para involved at BT

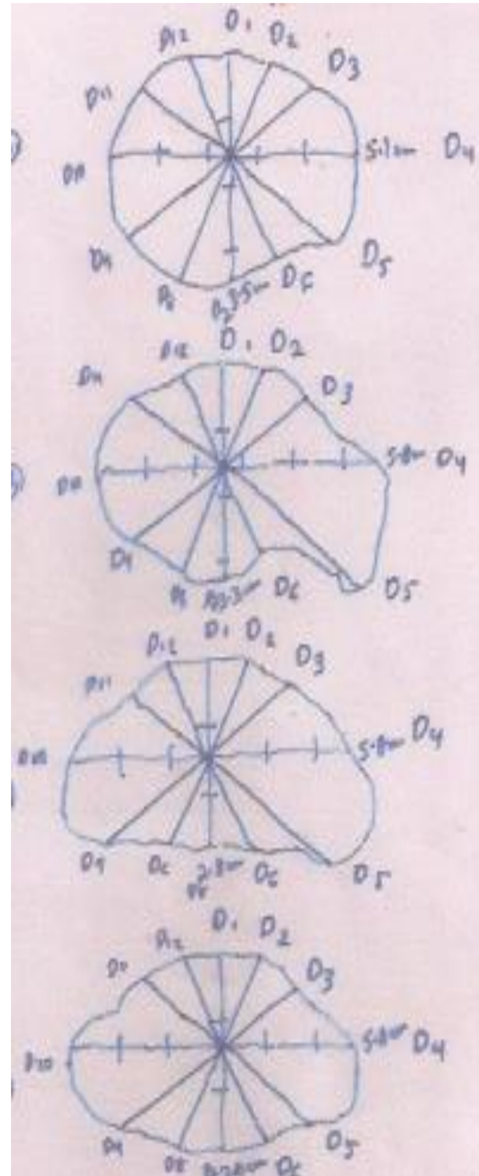


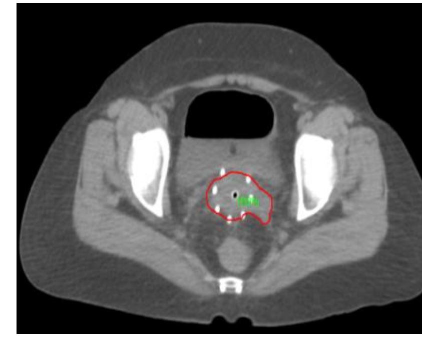


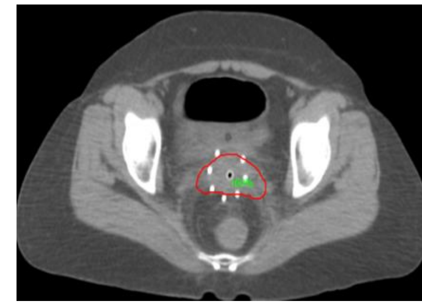


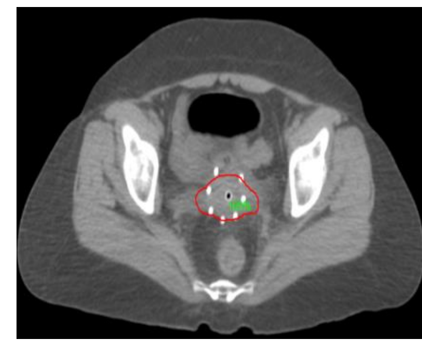




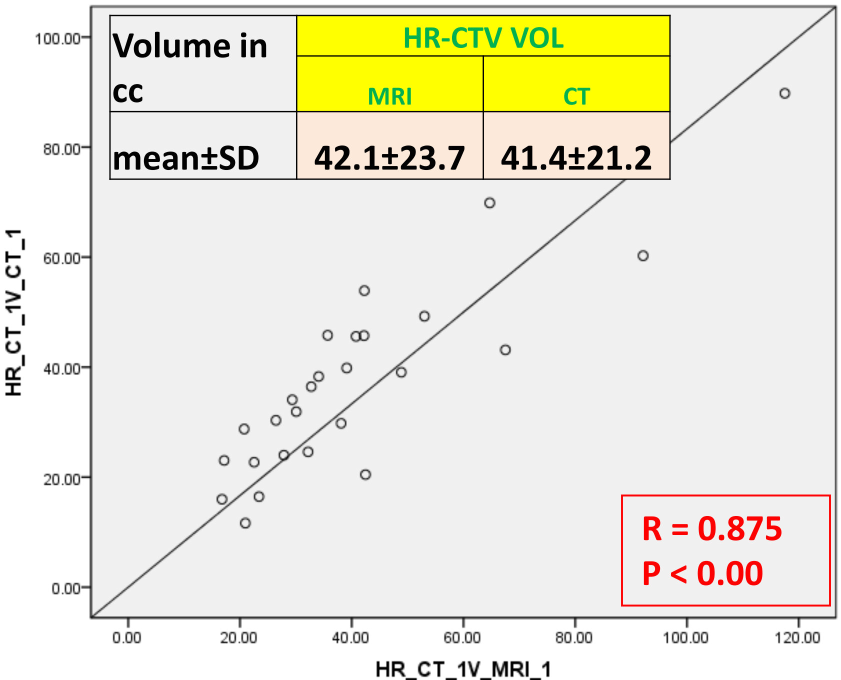




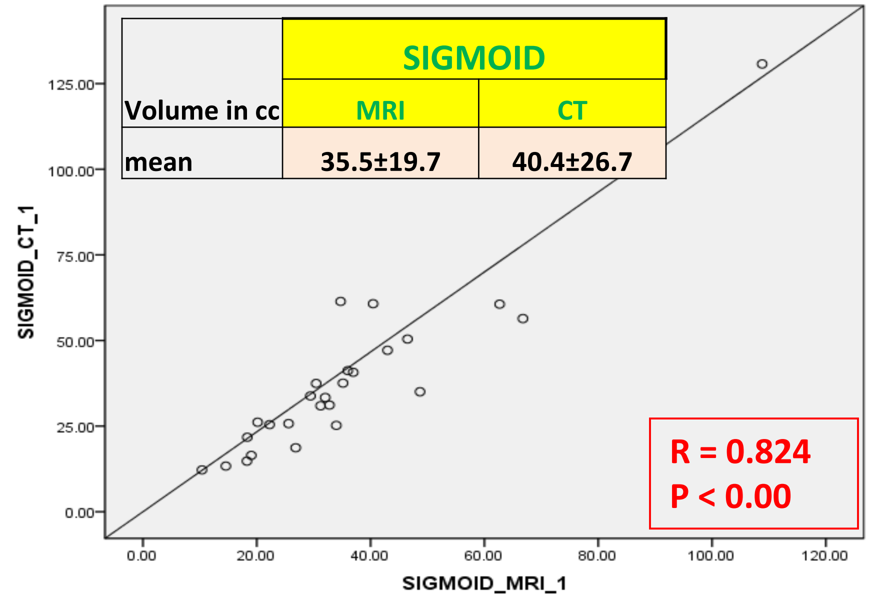




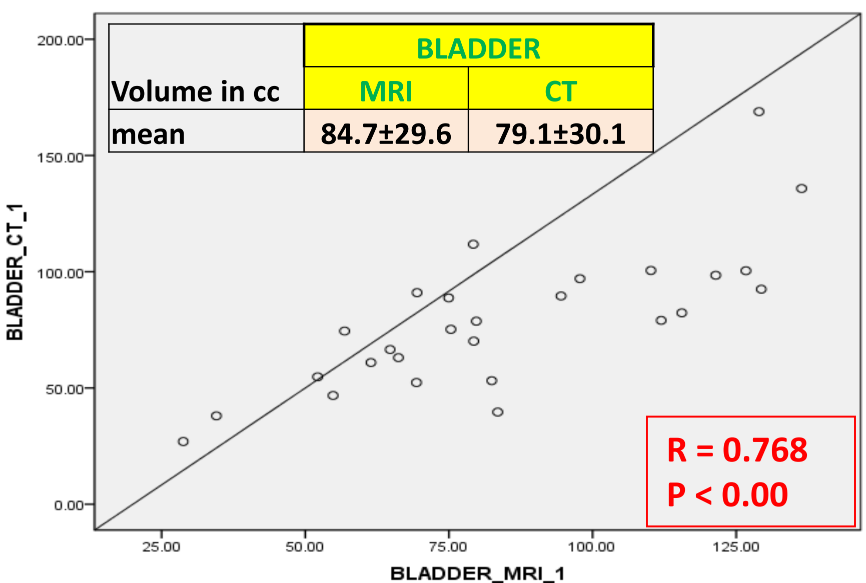
Volumes : CT Vs MR
N = 27 patients



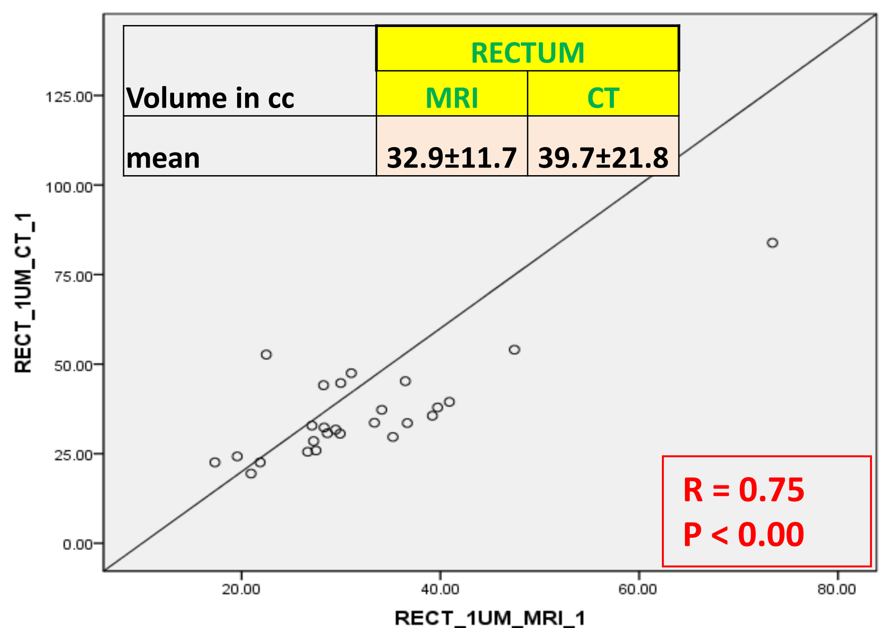
Volume in cc	HR-CTV VOL	
	MRI	CT
mean±SD	42.1±23.7	41.4±21.2



Volume in cc	SIGMOID	
	MRI	CT
mean	35.5±19.7	40.4±26.7



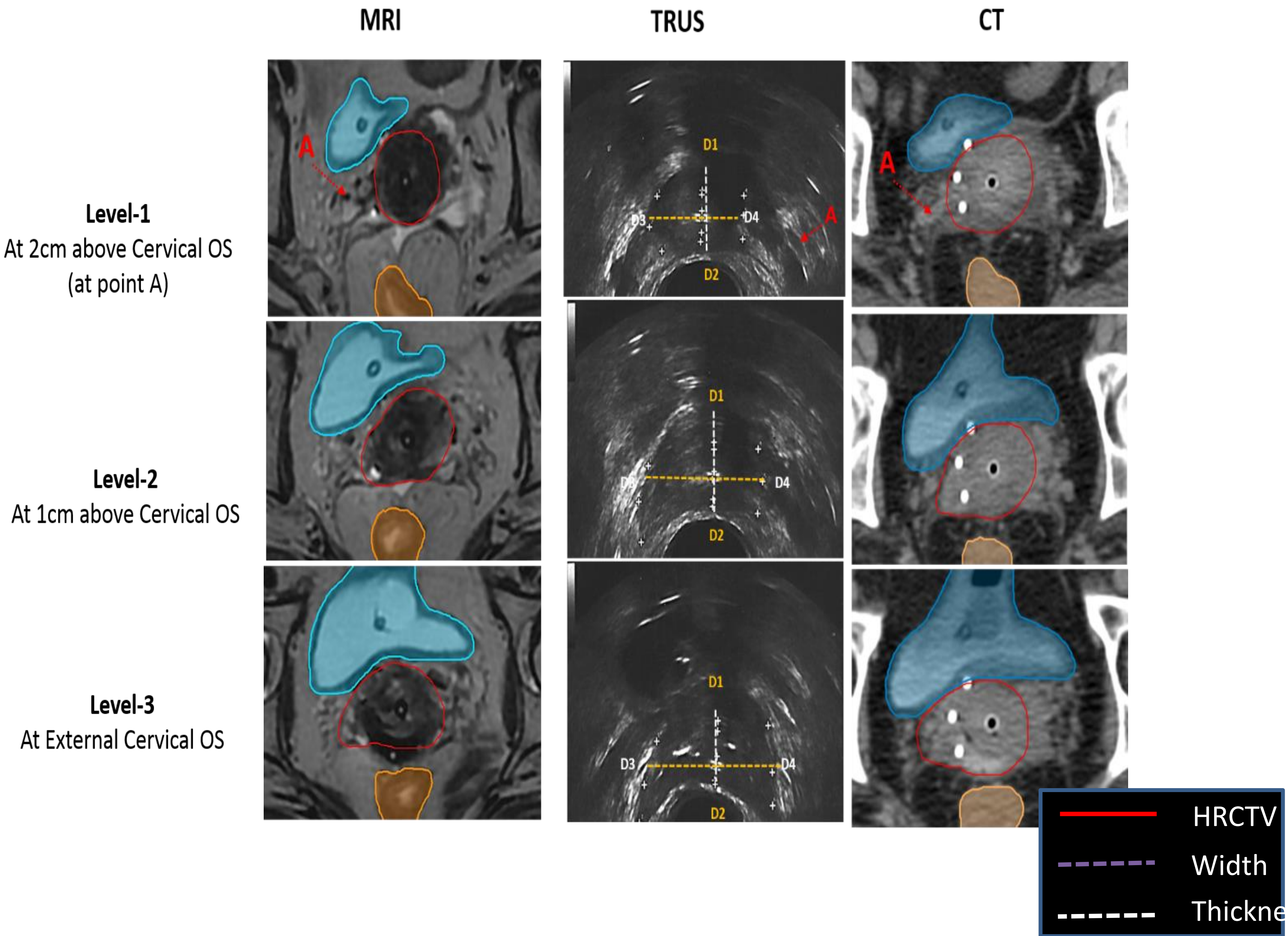
Volume in cc	BLADDER	
	MRI	CT
mean	84.7±29.6	79.1±30.1



Volume in cc	RECTUM	
	MRI	CT
mean	32.9±11.7	39.7±21.8

At BT

No para involvement (Left side)



At BT

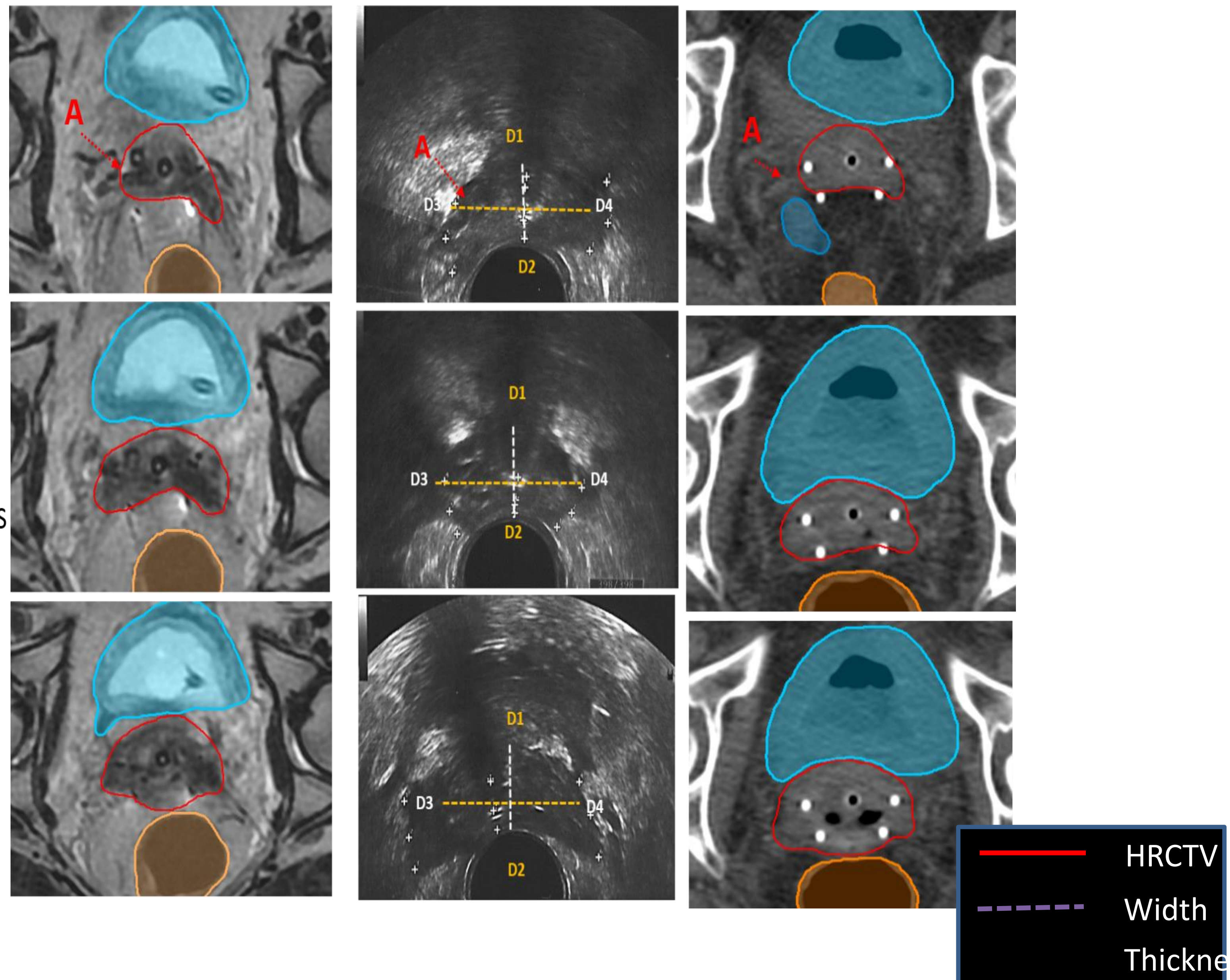
Medial para (both side)

MRI | TRUS | CT

Level-1
At 2cm above Cervical OS
(at point A)

Level-2
At 1cm above Cervical OS

Level-3
At External Cervical OS



At BT

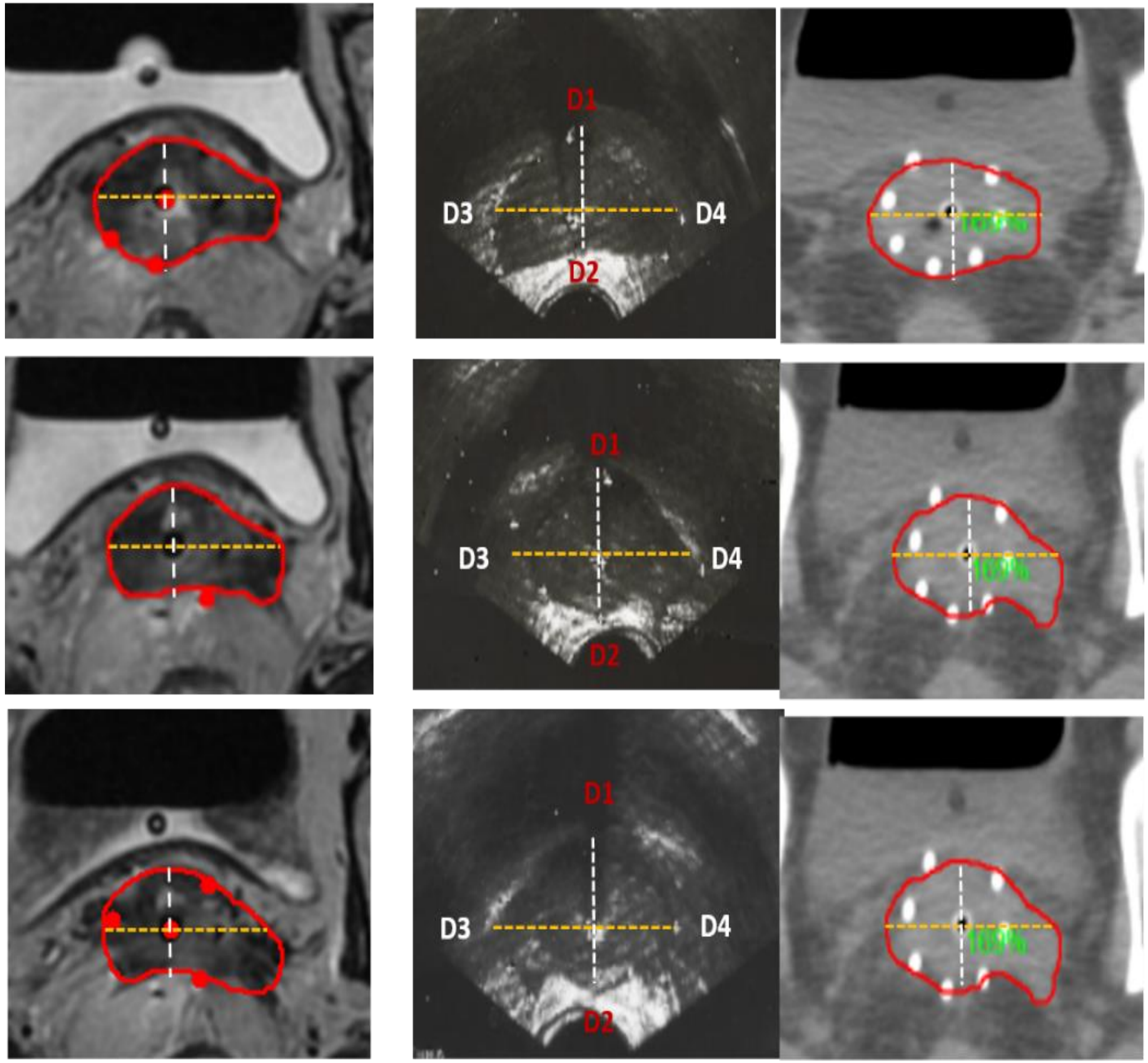
Lateral para (left side)

MRI | TRUS | CT

Level-1
At 2cm above Cervical OS
(at point A)

Level-2
At 1cm above Cervical OS

Level-3
At External Cervical OS



HRCTV
Width
Thickne

TRUS assisted HRCTV delineation on CT images

- 25 patients, stage IIB (11) and IIIB (14)
- MRI at diagnosis, TRUS images during BT, 3D- clinical information's $=HRCTV_{CT}$
- Compared $HRCTV_{CT}$ with $HRCTV_{MR}$

Parameter	**Variables**		**MRI** Mean (±SD)	**CT** Mean (±SD)	**Pearson correlation coefficient (r)**	**P-value**
HR-CTV	Volume(*cm³)*		39 (±19)	39.1 (±20)	0.92	0.000*
	Dimensions (cm)	Height	4.4 (±0.9)	4.4 (±1.1)	0.76	0.000*
		Width	4.6 (±0.7)	4.7 (±0.6)	0.77	0.000*
		Thickness	3.5 (±0.7)	3.4 (±0.5)	0.74	0.000*

TRUS assisted HRCTV delineation on CT images

	HR-CTV	MRI	TRUS-CT	Mean difference of MRI-CT	Pearson correlation coefficient (r)	P-value
Level 1 (Point A) Mean (±SD)	Width	3.4 (±1.0)	3.9 (±0.9)	0.1 (±0.0)	0.75	0.000*
	Thickness	3.1 (±1.0)	3.0 (±0.7)	0.2 (±0.6)	0.80	0.000*
Level 2 Mean (±SD)	Width	3.7(±1.0)	4.0 (±0.8)	-0.5 (±0.6)	0.69	0.000*
	Thickness	3.2 (±1.0)	3.1 (±0.7)	0.2 (±0.6)	0.70	0.000*
Level 3 Mean (±SD)	Width	3.8 (±0.8)	4.1 (±0.7)	-0.3 (±0.5)	0.80	0.000*
	Thickness	3.3 (±0.7)	3.1 (±0.8)	-0.4 (±0.7)	0.73	0.000*

- **Correlation was good when para disease defined at BT**
- **With Para Invasion: Overestimation of width on CT**
- **Dosimetric Impact: Ongoing**

SUMMARY AND CONCLUSIONS

- MR Based Approach: Gold Standard for IGABT Practice
- CT Guide Contouring is feasible provided
  - MR Based Approach Experience : 20 -25 patients experience
  - Assisted by one Pre-Rx MR Imaging
  - Standardized CT Protocol: IV contrast, slice thickness etc..
  - HR-CTV & OAR's only
- CT Based Contouring Guidelines : 2018-2019
- No robust clinical data with the CT Image Based/ Guided Brachytherapy

GEC-ESTRO – Indian Brachytherapy Society

CT Based Contouring Recommendations

Prof. Umesh Mahantshetty

Prof. Richard Pötter

PRE REQUISITES
FOR
CT BASED TARGET DEFINITION AND CONTOURING

1. Clinical Assessment: Clinical diagrams and documentation of disease at diagnosis and BT

2. CT Imaging Protocol: IV contrast, rectal/ bladder filling etc…

3. Response Evaluation: External Beam & Chemotherapy prior to BT

1. Clinical Assessment:

Clinical diagrams and documentation of disease

at diagnosis and BT

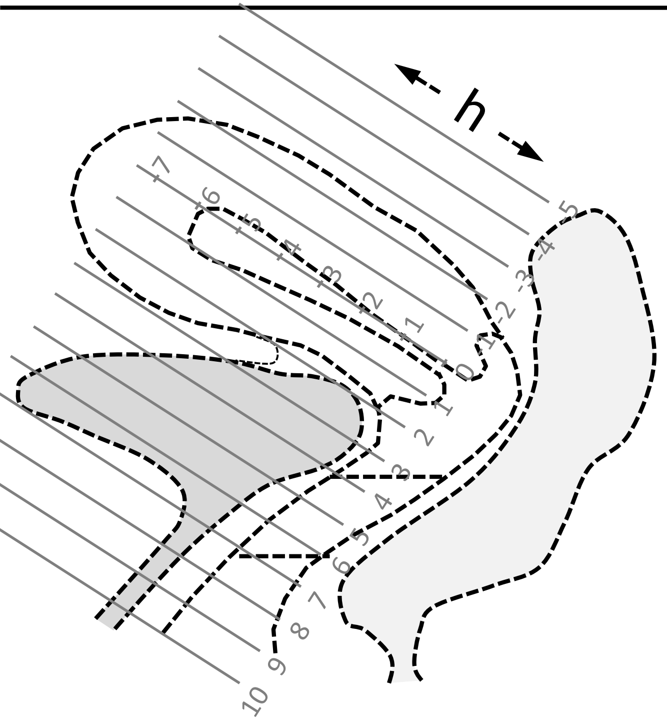
- Definition of Near Minimum Distance (NMD)

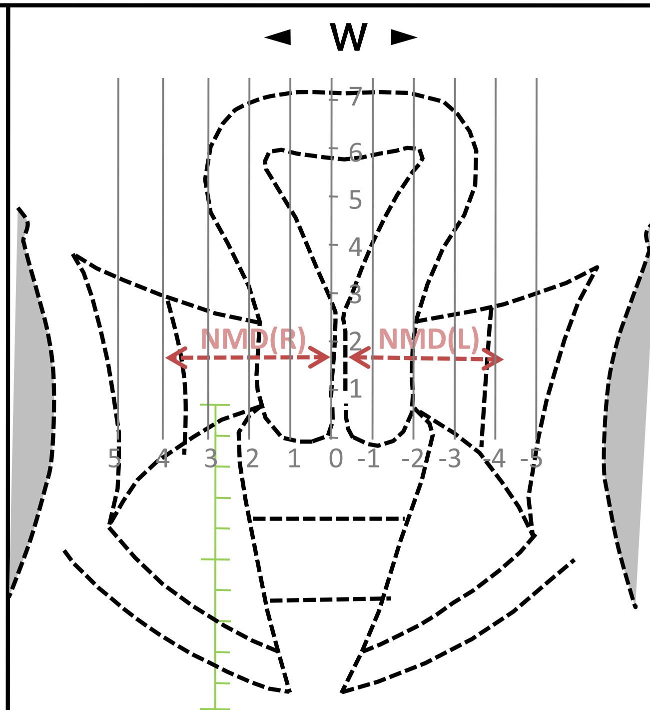
- Documentation of tumor dimensions

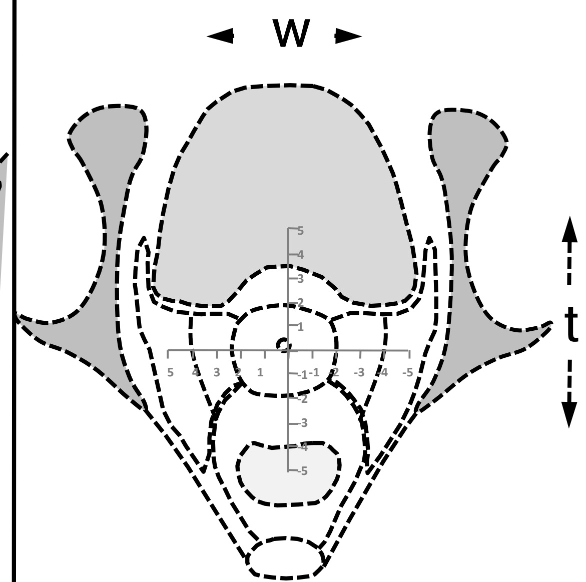
  - height, thickness and NMD’s

Revised Clinical Drawings

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





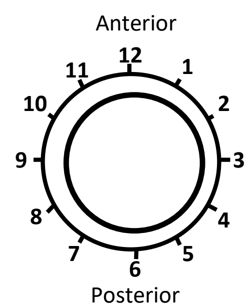


h = ____ cm **t = ____ cm** **w = ____ cm** **NMD (R) =____cm** **NMD (L) =____cm**

[NMD-Near Maximum Distance]

Vaginal Disease

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

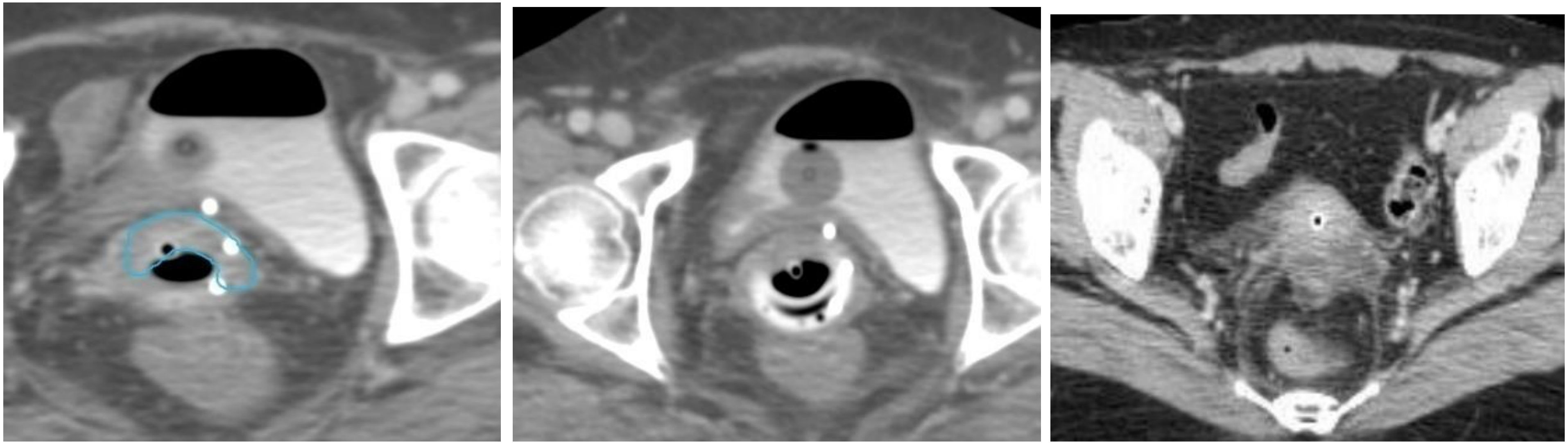


	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

2. CT Imaging Protocol

Standardization of the CT protocol

- *CT compatible applicators: follow the do's and don't s*
- *Bladder filling protocol with dilute contrast*
- *Rectal filling: preferably empty with dilute contrast if required*
- *Intravenous contrast : arterial phase*
- *Axial scans : 2-3 mm slices*
- *Anatomical landmarks: for eg. Uterine artery / ureters ..*



3. RESPONSE to EBRT + CT

PATTERNS OF REMISSION

- ***Clinical mapping:***

- Disease at diagnosis & BT

- **Patterns depending on remission**

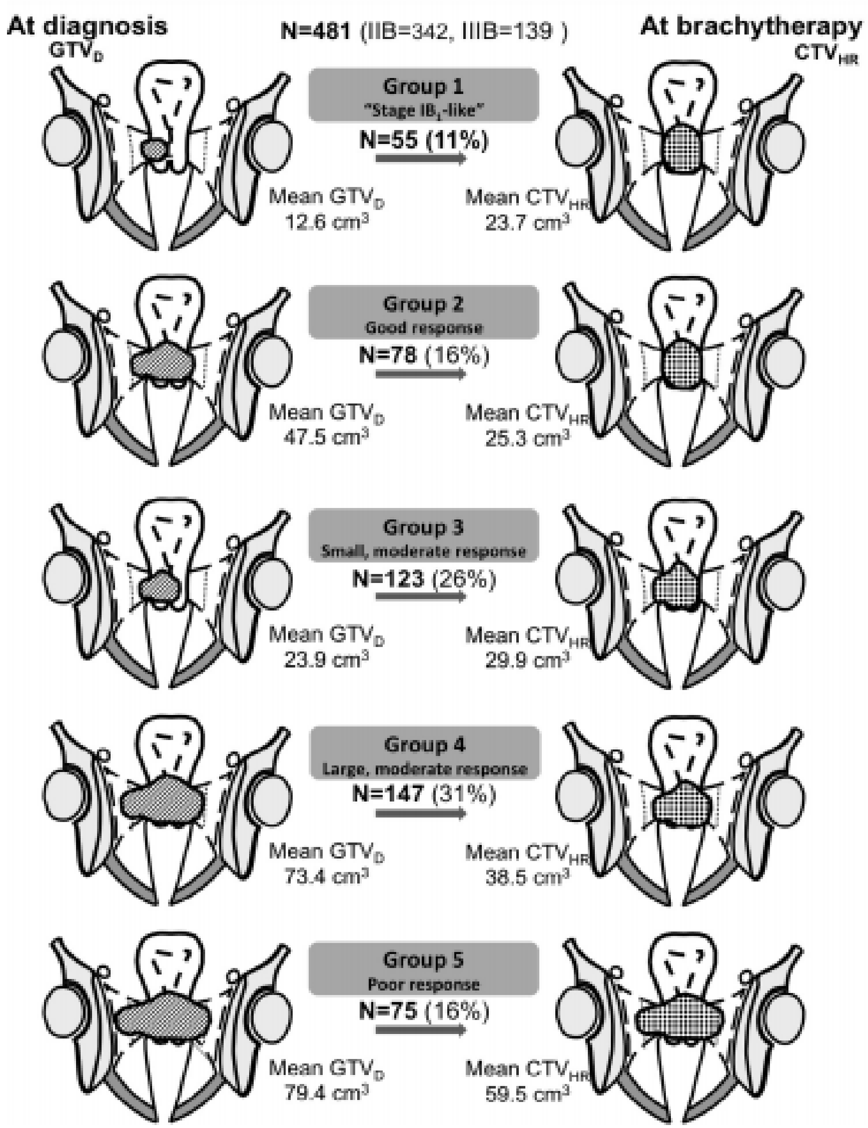
- **HR-CTV into 3 subgroups:**

  - No para invasion

  - Medial para invasion

  - Lateral para invasion

N. Jastaniyah et al./Radiotherapy and Oncology 120 (2016) 404–411



3. RESPONSE to EBRT + CT

PATTERNS OF REMISSION

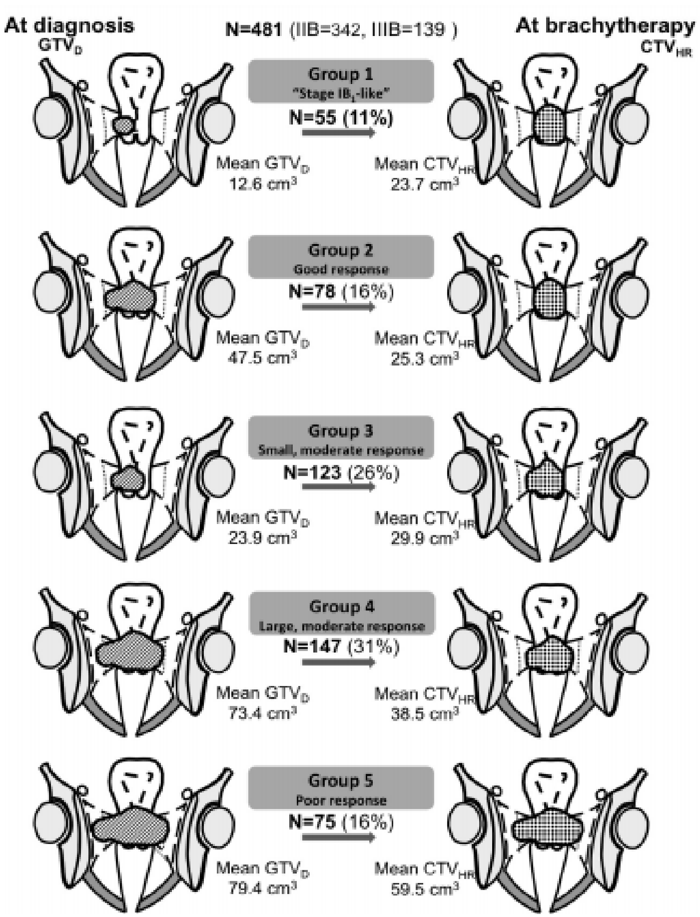
Clinical Remission at the time of BT

- Complete: anatomical boundaries of cervix

- Partial: Clinical NMD's at diagnosis and at BT in various environments

- Poor response: Clinical NMD's at Diagnosis adapted to the anatomy on CT at BT.

N. Jastaniyah et al. / Radiotherapy and Oncology 120 (2016) 404–411



Definition of target volumes in different clinical environments

- GTV_{CT} : Not possible and discuss limitations
- **$HRCTV_{CT}$: in detail**
- $IRCTV_{CT}$: similar to the GEC ESTRO recommendations
- OAR s' : Rectum, Bladder, Sigmoid, small bowel

CT Based HR- CTV Definition In different Environments

Clinical Examination and documentation as above mandatory followed by one of the environments:

1. CT at diagnosis (CT – CT Environment)

- CT Only
- Real time TRUS during BT application and CT

2. MR at Diagnosis (MR – CT Environment)

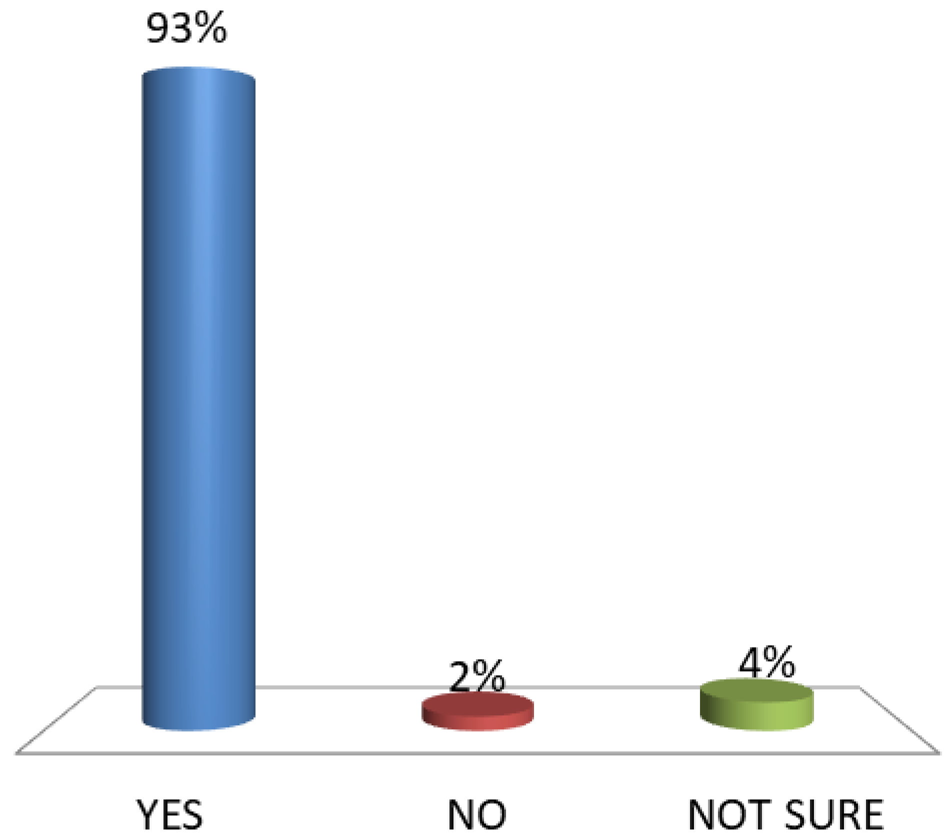
- CT Only
- Real time TRUS during BT application and CT

3. MR at diagnosis & Pre BT MR (Pre BT MR – CT Environment)

- CT Only
- Real time TRUS during BT application and CT

How many of you would be interested in prospective evaluation and validation of CT based target Contouring in IGABT for Cervical Cancer?

A. YES
B. NO
C. NOT SURE



DISCUSSION ON ROADMAP TOMORROW AFTERNOON!!!

THANK YOU!

CLINICAL IMPLICATIONS OF RADIOGRAPHY BASED BT PLANNING

Umesh Mahantshetty

Professor,

Department of Radiation Oncology

&

GYN Disease Management Group Member

Tata Memorial Hospital, Mumbai, India

2nd AROI - ESTRO TEACHING COURSE Lucknow 2018

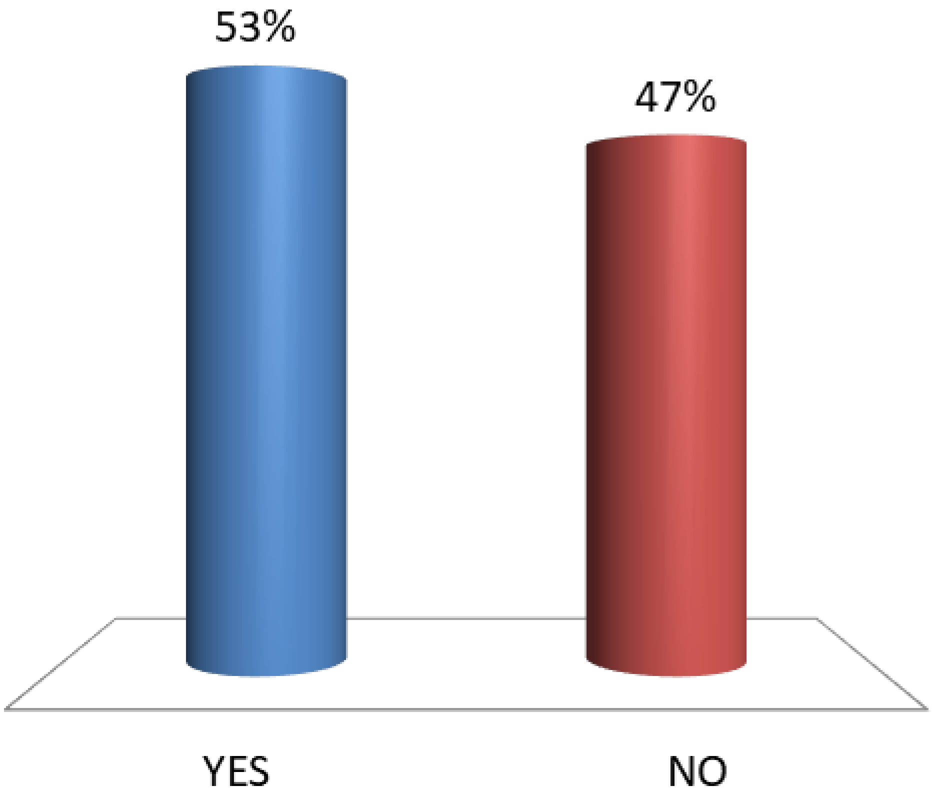
Tata Memorial Hospital

ROUTINE GYN BRACHYTHERAPY PRACTICE

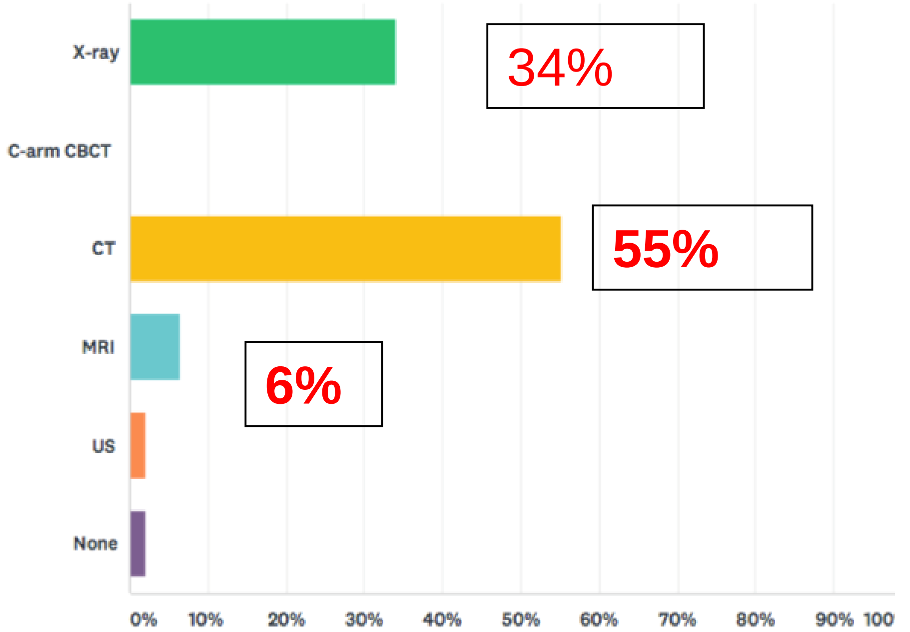
- GYN BT Applications: 4 - 10 (Avg. 6)
- BT procedures under anesthesia per day : 4-8 (Avg: 6) includ,. IC+ IS
- Vault BT (Endometrium /Cervix post-op): 1 - 2
- Interstitial Templates : 1-2 Interstitial /wk
- Planning Details* : 3-4 orthogonal X-ray based ; 2-3 CT; 1 MR Based
- All patient undergo CT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

How many of you have both C-Arm / Conventional Simulator and CT Simulator in your Department / Hospital

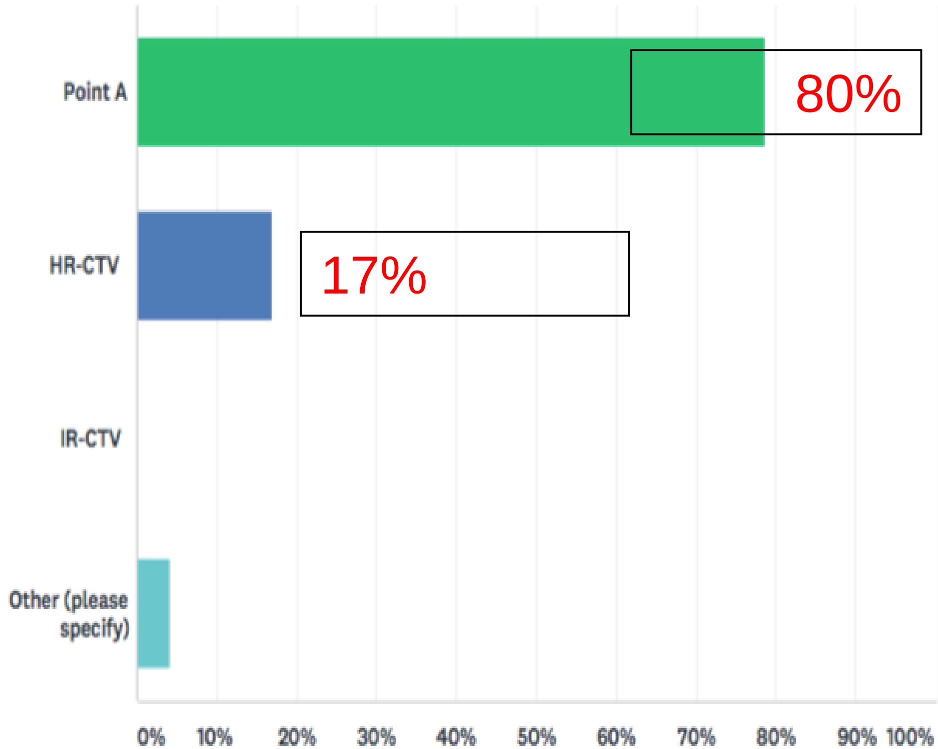
A. YES
B. NO



Imaging at brachytherapy
47 Replies



Volume/point of brachytherapy dose prescription [47 Replies]



TRANSITION FROM 2D to 3D

INCORPORATION OF CT IMAGING FOR ROUTINE BT PLANNING

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

TRANSITION FROM 2D to 3D

2 Approaches in CT Environment

1. INCORPORATION OF CT IMAGING

FOR ROUTINE BT PLANNING WITHOUT TARGET CONCEPT

2. CT BASED TARGET CONCEPT

TRANSITION FROM 2D to 3D

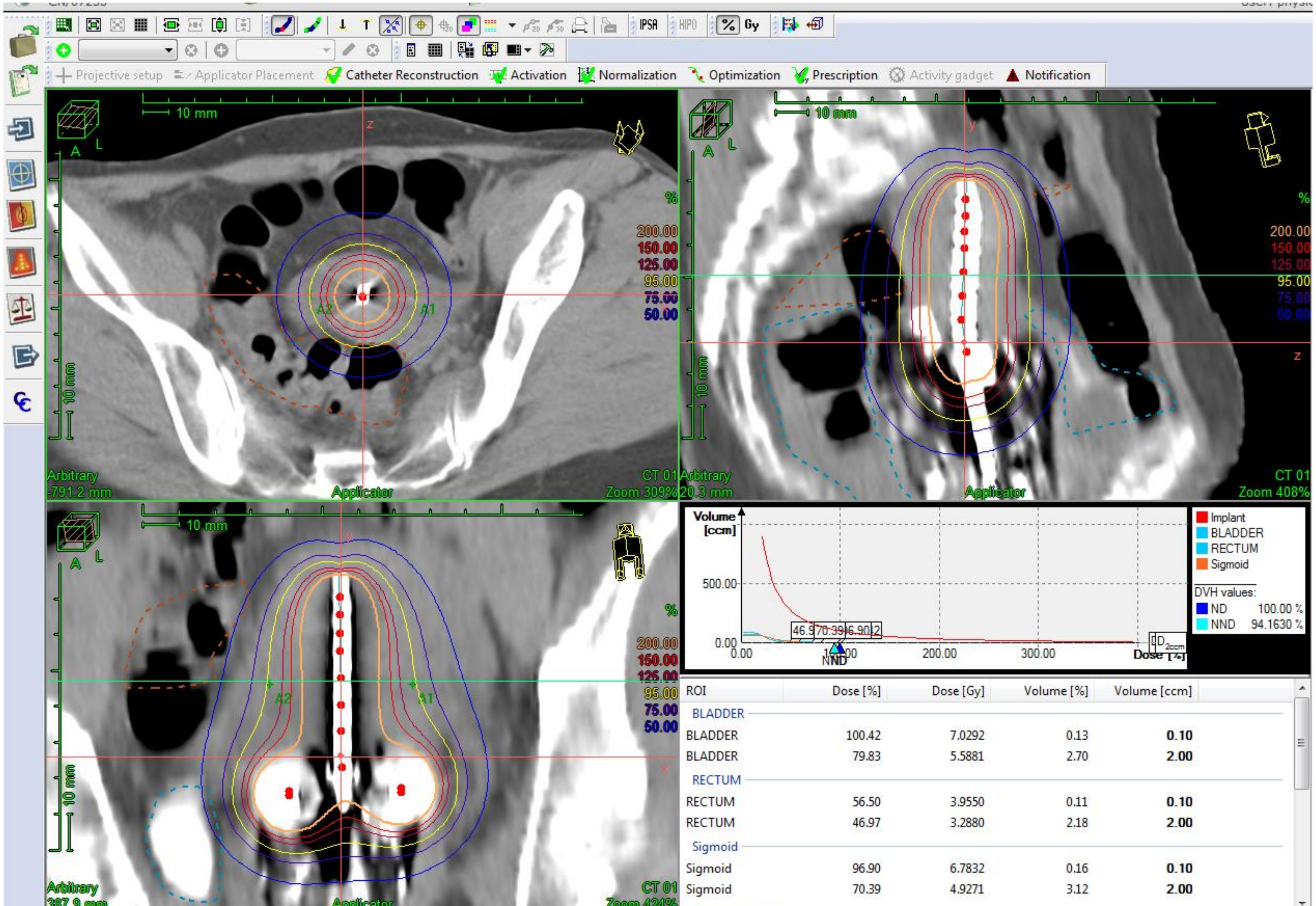
1. INCORPORATION OF CT IMAGING FOR ROUTINE BT PLANNING

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

1st ICA

EXAMPLE NO. 1

PT ID: ***CN/07253***



POINT A: 7.1 / 6.9 Gy

ICRUR: 3.7 Gy / 2 cm3 : 3.3 Gy

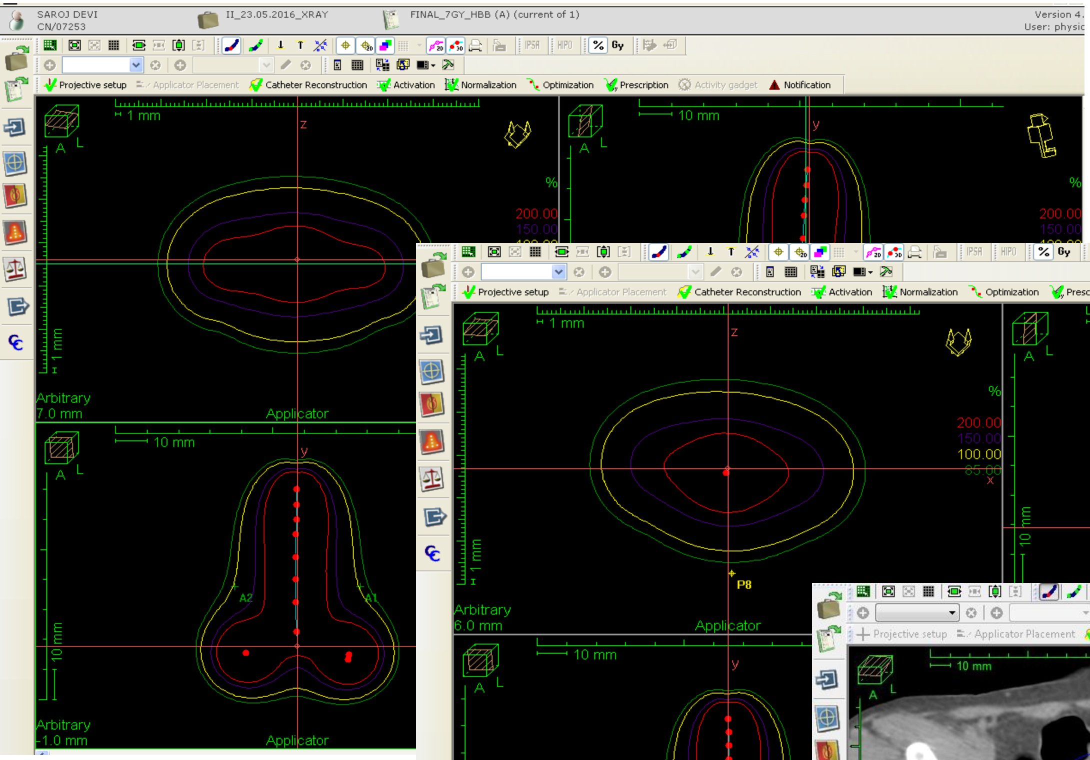
ICRUB: 2.6 Gy / 2 cm3 : 5.6 Gy

Sigmoid: 4. 0 Gy (2 cm3)

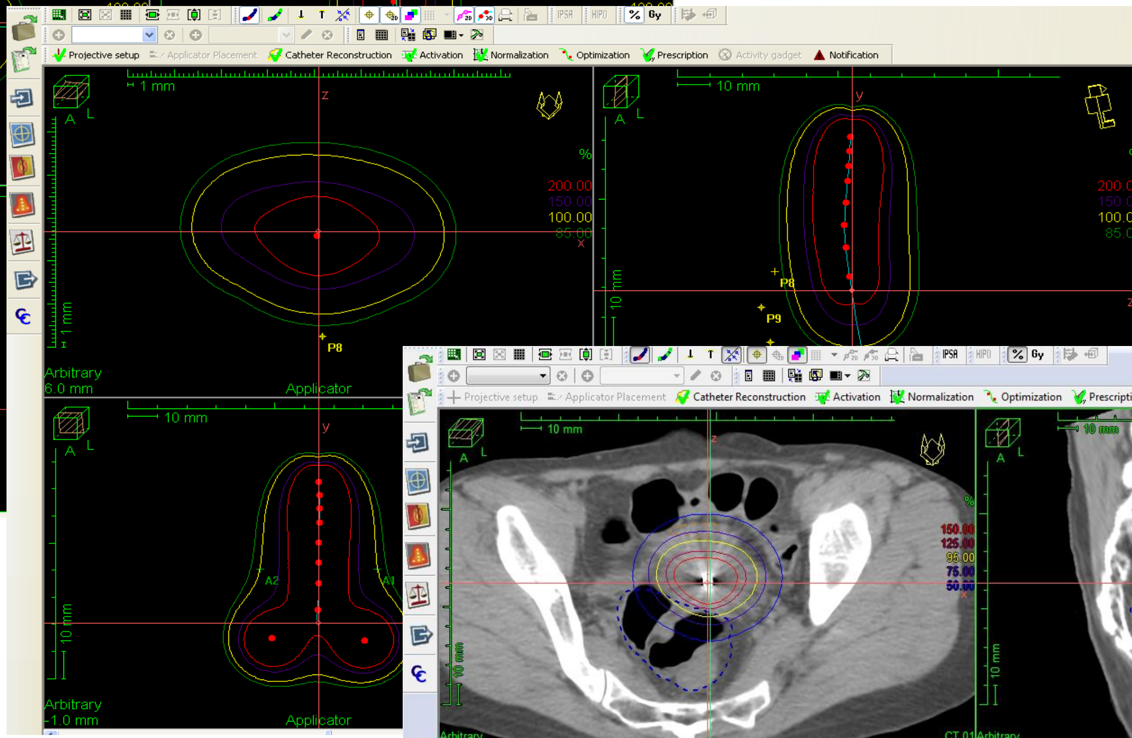
2nd ICA

EXAMPLE NO. 1

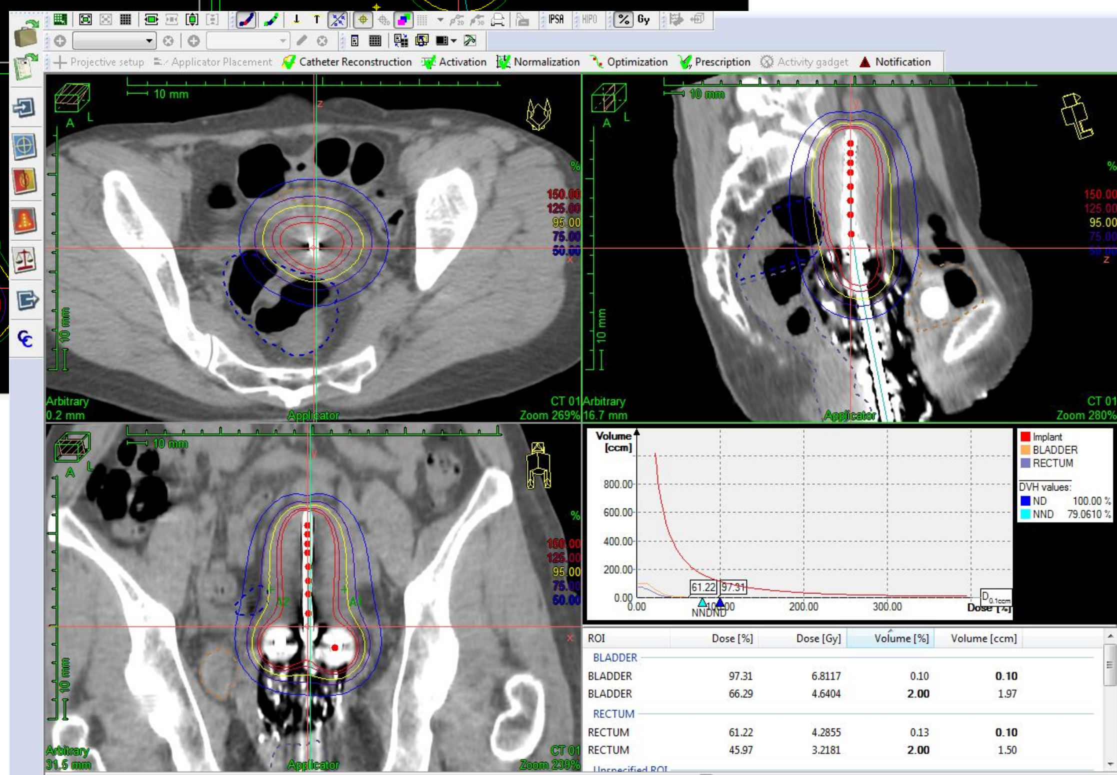
PT ID: CN/07253



3rd ICA



4th ICA



PT ID: CN/07253

EXAMPLE NO. 1

Total doses in EQD2

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

AT BT : RESIDUAL DISEASE AT CERVIX & MEDIAL THIRD PARA

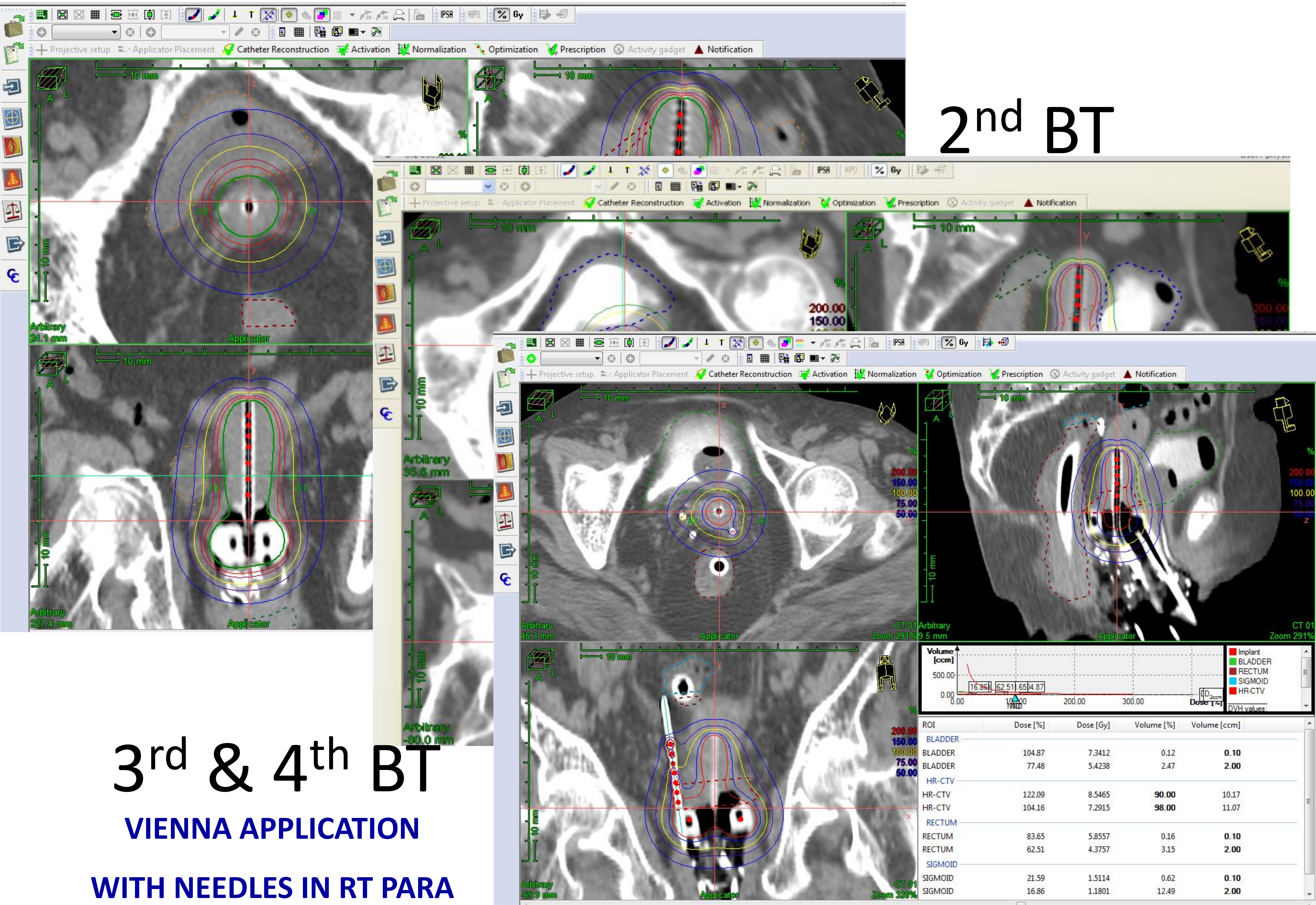
BT#	PLANNING IMAGING	Point A (Left /Right)		ICRU Bladder	ICRU Rectum
I	CT	7.1	6.9	2.6 (2 cm3 : 5.6)	3.7 (2cm3 : 3.3)
II	X-RAY	6.8	7.2	2.1	2.7
III	X-RAY	7	7	1.8	5.2
IV	CT	7.1	6.9	2.7 (2 cm3 : 4.6)	5 (2cm3 : 3.1)
TOTAL	EQD2	85.6 Gy	85.8 Gy	66.6 Gy (2 cm3: 80 Gy)	65.4 Gy (2cm3: 64 Gy)

1st BT

EXAMPLE NO. 2

PT ID: CN/03032

2nd BT



ROI	Dose [%]	Dose [Gy]	Volume [%]	Volume [ccm]
BLADDER				
BLADDER	104.87	7.3412	0.12	0.10
BLADDER	77.48	5.4238	2.47	2.00
HR-CTV				
HR-CTV	122.09	8.5465	90.00	10.17
HR-CTV	104.16	7.2915	98.00	11.07
RECTUM				
RECTUM	83.65	5.8557	0.16	0.10
RECTUM	62.51	4.3757	3.15	2.00
SIGMOID				
SIGMOID	21.59	1.5114	0.62	0.10
SIGMOID	16.86	1.1801	12.49	2.00

3rd & 4th BT

VIENNA APPLICATION

WITH NEEDLES IN RT PARA

PT ID: CN/03032

EXAMPLE NO. 2

Total doses in EQD2

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

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

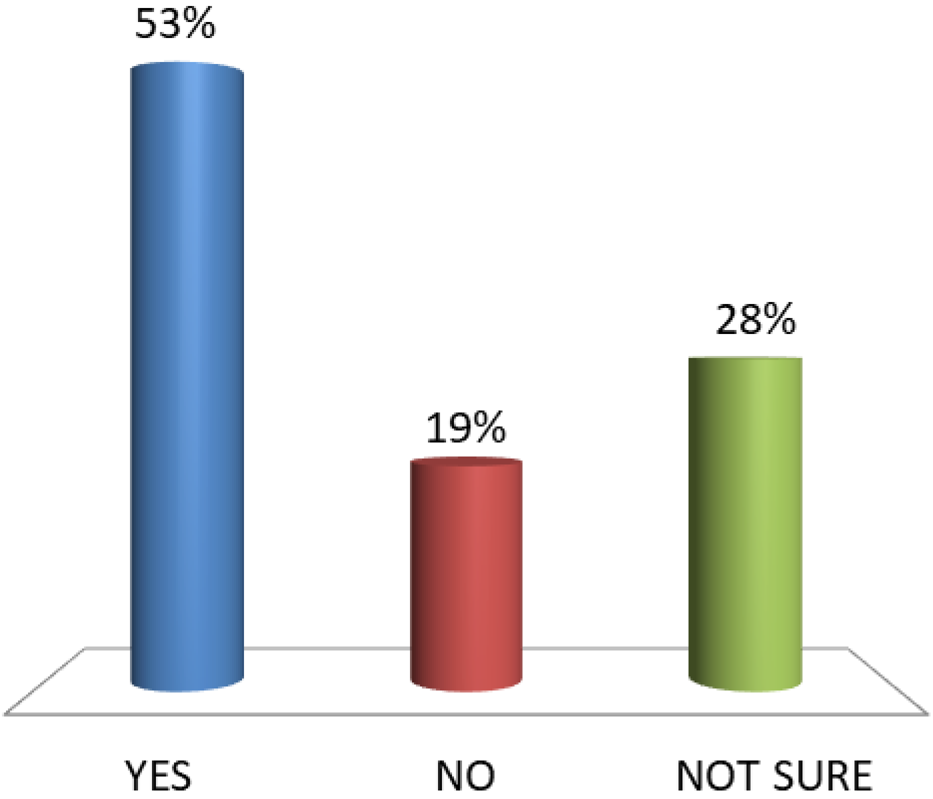
CT PLANNING EVERY FRACTION

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

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

How many of you would be interested in prospective evaluation and validation of THIS APPROACH CT – X - RAY …..for Cervical Cancer?

A. YES
B. NO
C. NOT SURE



TRANSITION FROM 2D to 3D

2 Approaches in CT Environment

1. INCORPORATION OF CT IMAGING
FOR ROUTINE BT PLANNING

2. CT BASED TARGET CONCEPT

TRANSITION FROM 2D to 3D

2. CT BASED TARGET CONCEPT

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

Further Details & Disucssion during the Contouring Session in the afternoon

2nd AROI ESTRO AROI Gyn Teaching Course
Lucknow, March 2018

ICRU89-GEC-ESTRO recommendations on dose points and volume reporting

Richard Pötter

Recommendations, DVH parameters

Radiotherapy and Oncology 78 (2006) 67–77
www.thegreenjournal.com

ESTRO project

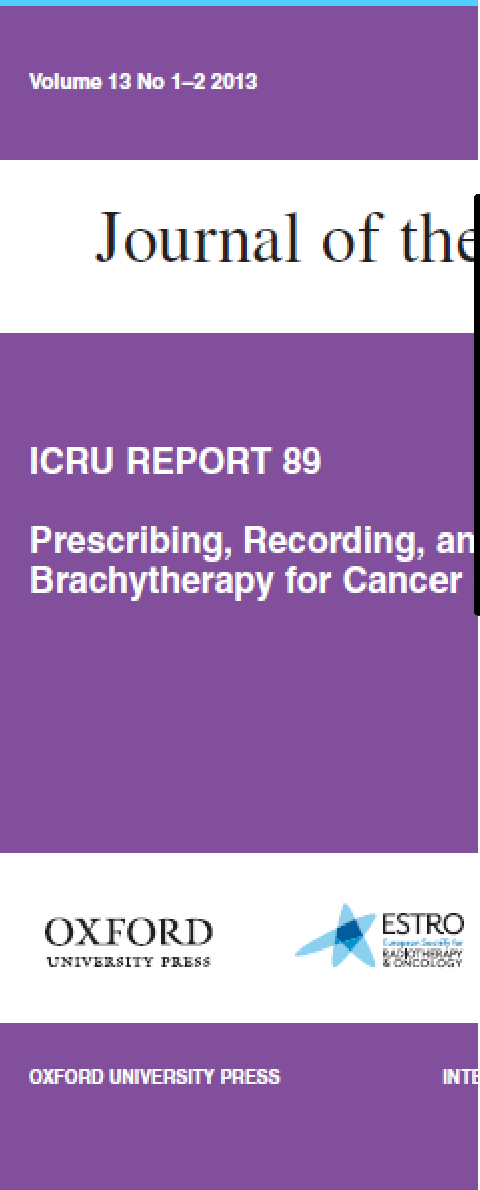
Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology

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

[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*

ICRU GEC ESTRO 89 (published 062016)

Website Oxford University Press: http://jicru.oxfordjournals.org/



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

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E. Rosenblatt, International Atomic Energy Agency, Vienna, Austria
A. N. Viswanathan, Harvard Medical School, Boston, MA, USA

ICRU/GEC ESTRO recommendations for gyneacological brachytherapy

- 1 - INTRODUCTION
- 2 - PREVENTION, DIAGNOSIS, PROGNOSIS, TREATMENT AND OUTCOME
- 3 - BRACHYTHERAPY TECHNIQUES AND SYSTEMS
- 4 - BRACHYTHERAPY IMAGING FOR TREATMENT PLANNING
- 5 - TUMOR AND TARGET VOLUMES AND ADAPTIVE RADIOTHERAPY
- 6 - ORGANS AT RISK-AND-MORBIDITY-RELATED CONCEPTS AND VOLUMES
- 7 - RADIOBIOLOGICAL CONSIDERATIONS
- 8 - DOSE AND VOLUME PARAMETERS FOR PRESCRIBING, RECORDING, AND REPORTING OF BRACHYTHERAPY ALONE AND COMBINED WITH EXTERNAL BEAM RADIOTHERAPY
- 9 - 3D VOLUMETRIC DOSE ASSESSMENT
- 10 - RADIOGRAPHIC DOSE ASSESMENT
- 11 - SOURCES AND DOSE CALCULATION
- 12 - TREATMENT PLANNING
- 13 - SUMMARY OF THE RECOMMENDATIONS
- APPENDIX – EXAMPLES, SPREADSHEETS, DRAWINGS

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

Learning Objectives (I)

- Understand the concepts and learn the terms
  of dose volume and dose point parameters
  for planning, prescribing, recording and reporting
  the GTV and the CTV doses for 3D IGABT;

- Understand the concepts and learn the terms
  of dose volume and dose point parameters
  for planning, prescribing, recording and reporting
  the OAR doses for 3D IGABT;

Learning Objectives (II)

- Be able to use brachytherapy related
  dose volume and dose point parameters
  for planning aims and dose prescription
  for GTV, CTV, and the relevant OARs in IGABT.

Three levels of reporting

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

Level 1 - *Minimum standard for reporting*

Source and dose calculation:

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

Level 1 – *minimum standard for reporting*

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

At Diagnosis ☒

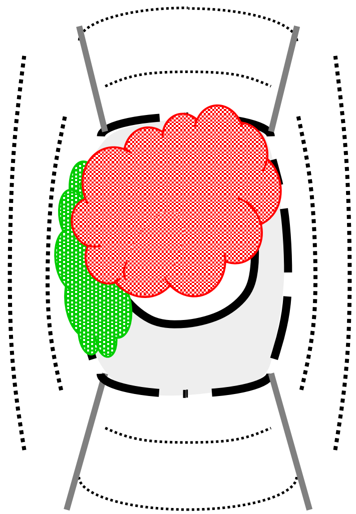
At Brachytherapy ☐

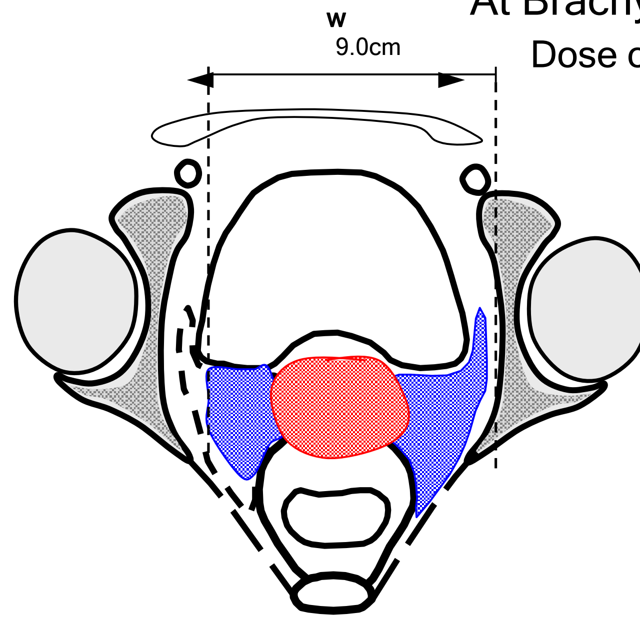
Dose of EBRT ____ Gy

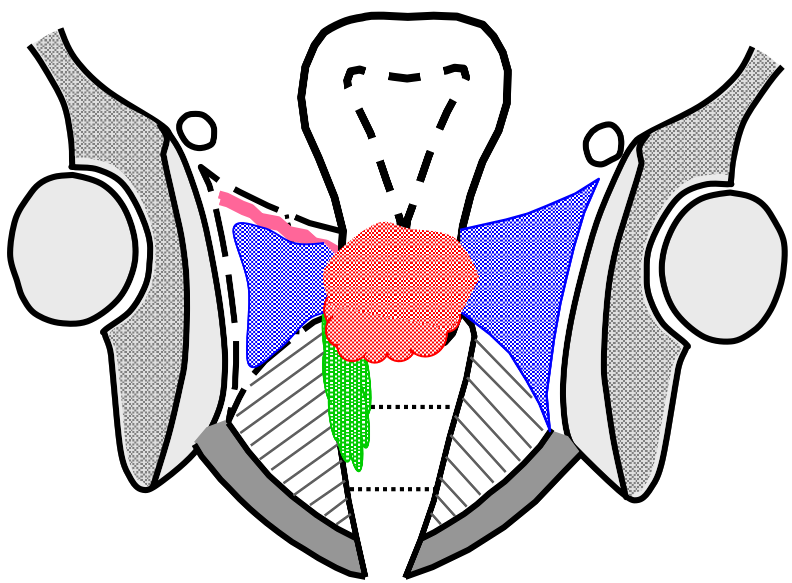
IIIB

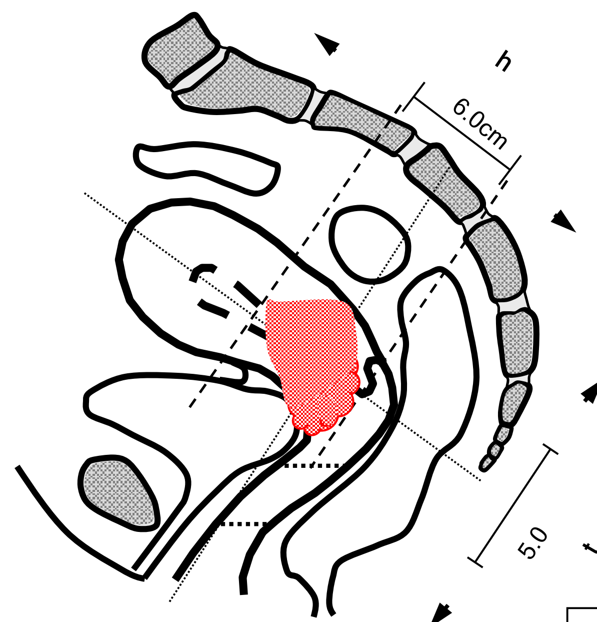
w = 9.0 cm	
h = 6.0 cm	
t = 5.0 cm	

Vagina: 5 cm









dd/mm/yy
___/___/___

____
Signature

Note: vagina and parametria not included in h

Case IV

At Diagnosis ☐

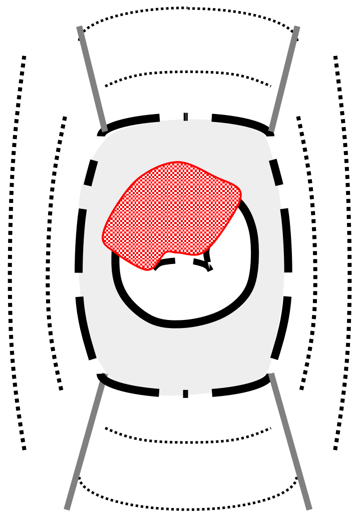
At Brachytherapy ☒

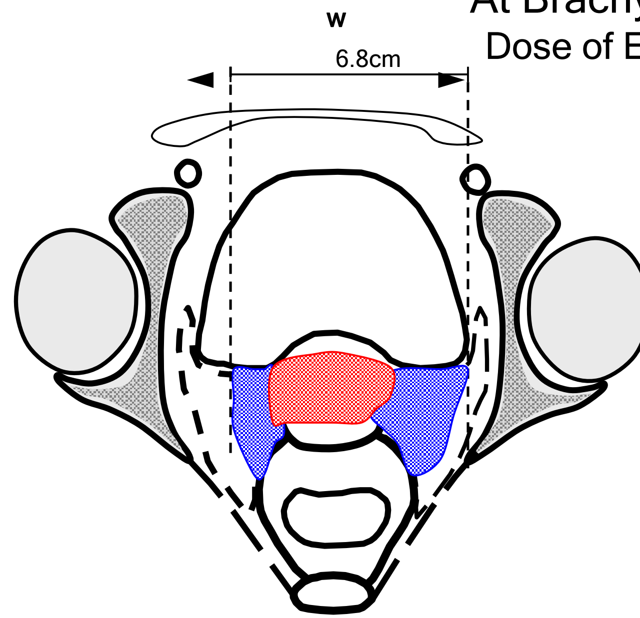
Dose of EBRT 50.4 Gy

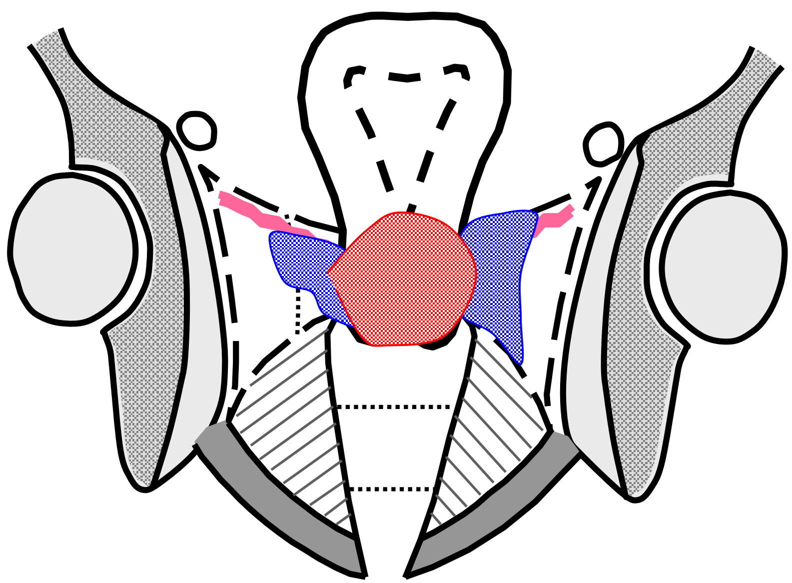
IIIB

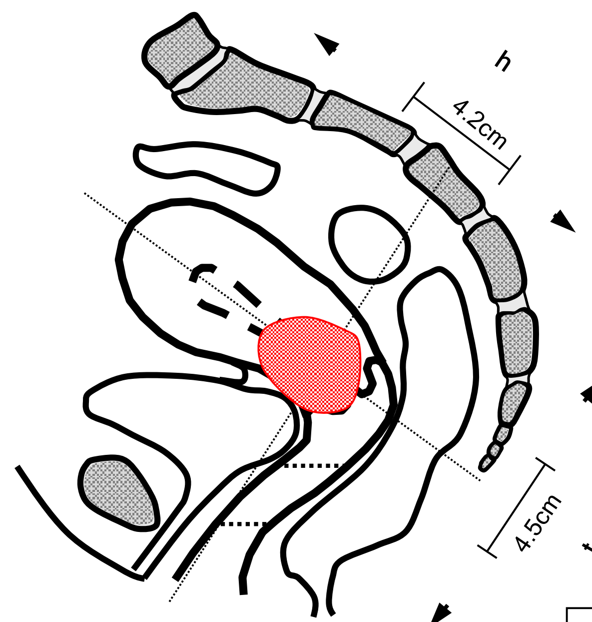
w = 6.8 cm
h = 4.2 cm
t = 4.5 cm

Vagina: 0 cm









dd/mm/yy
__/__/__

____
Signature

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

Case IV

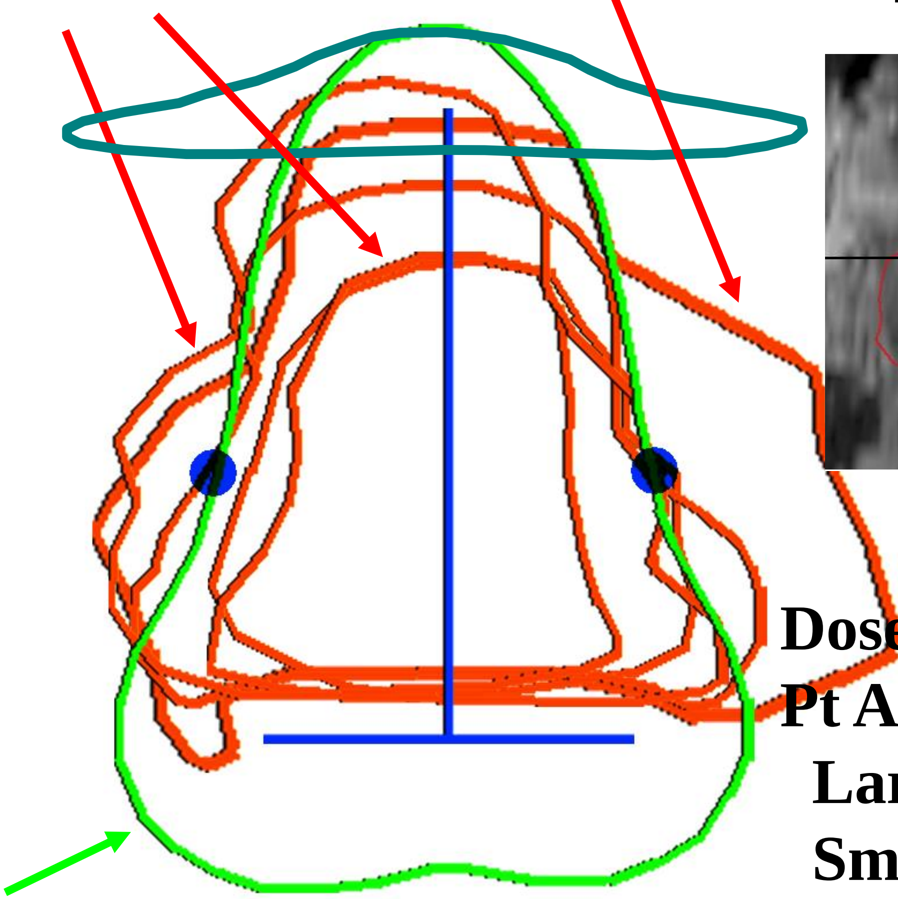
Level 1 – *minimum standard for reporting*

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**

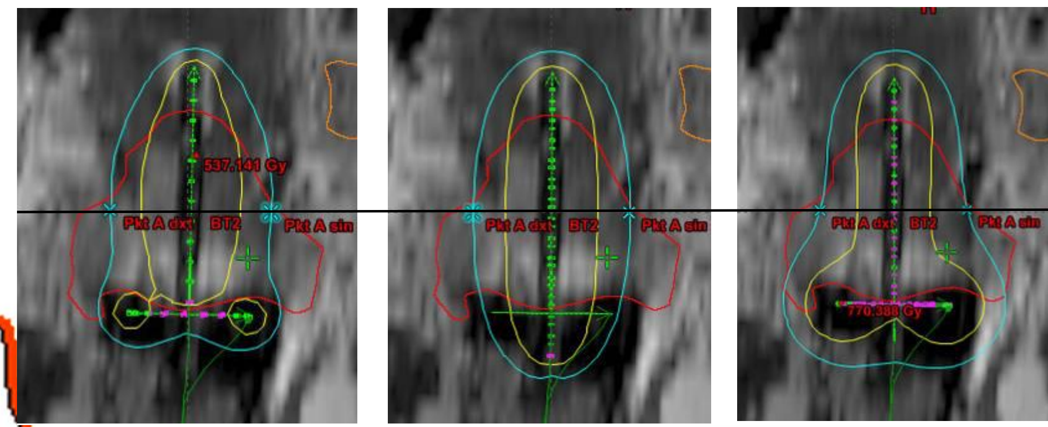
Point-A based brachytherapy: the dilemma facing a target volume

Small to large HR CTVs



Point A standard isodose

Milwaukee Toronto Vienna

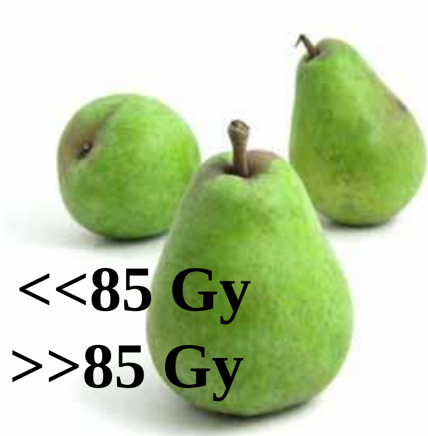


Doses:

Pt A: 85 Gy

Large HR CTVs: <<85 Gy

Small HR CTVs: >>85 Gy



Dose Delivery Pattern ICRU 89

Absorbed dose rate/dose per fraction

Number of fractions

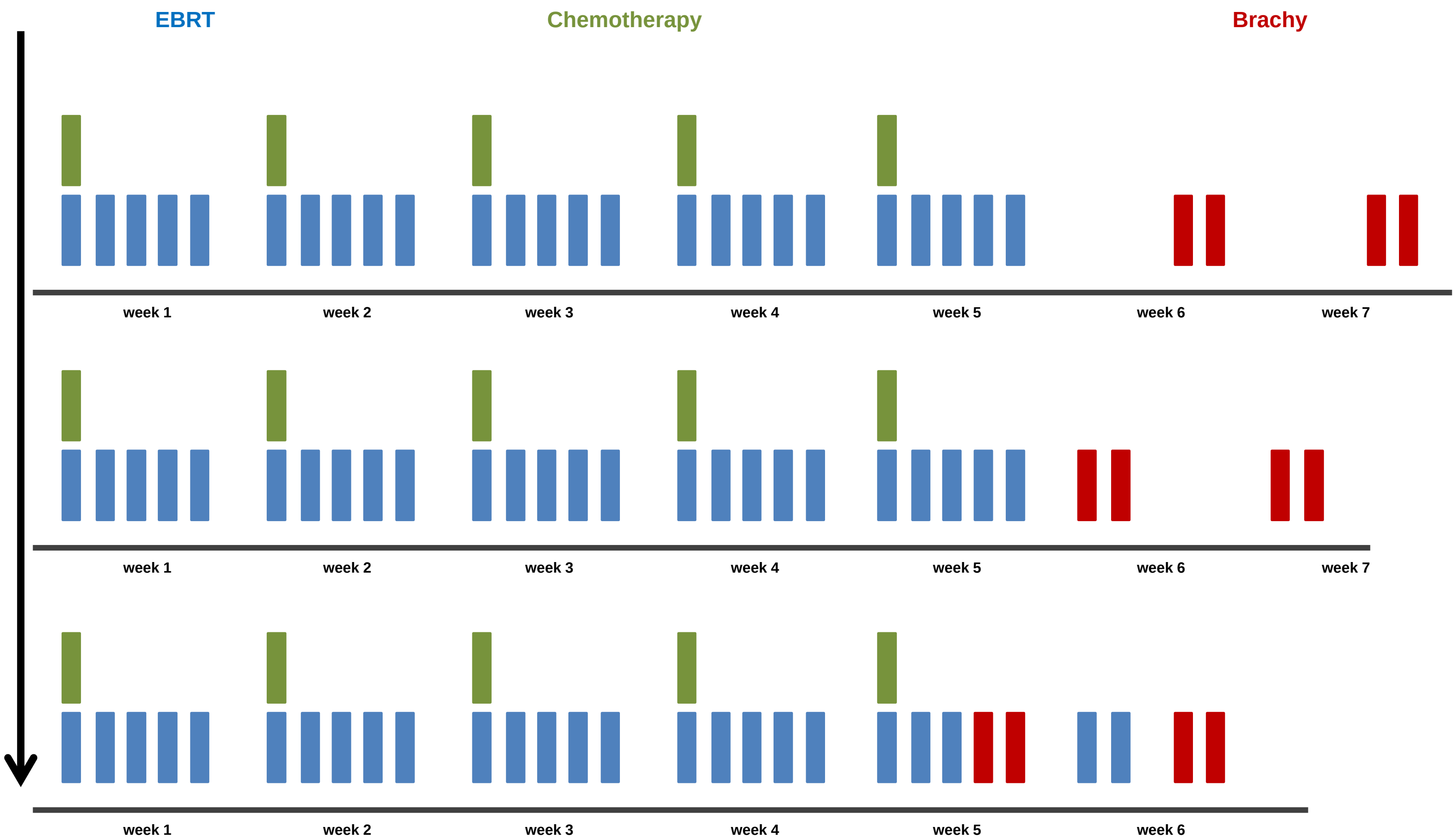
Time between fractions

(Pulse number, size, time, if PDR)

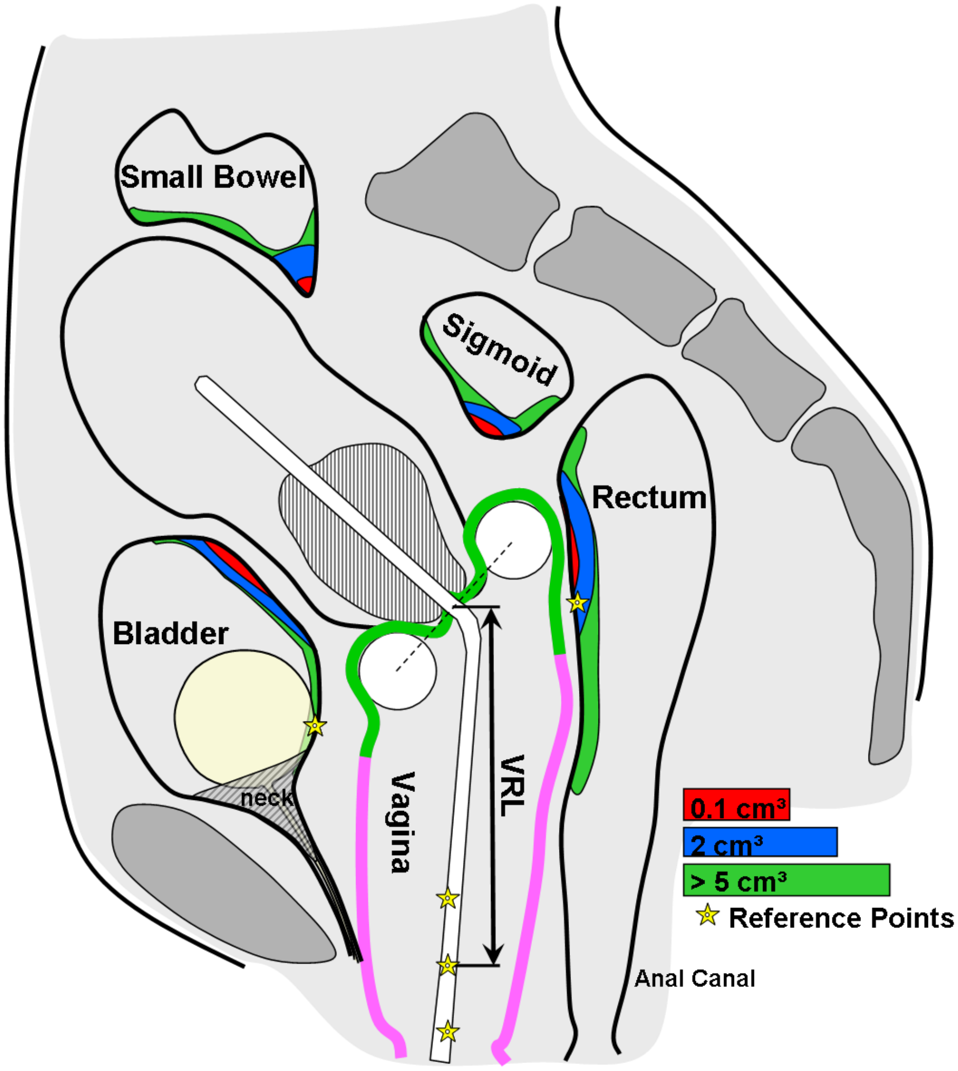
Overall treatment time

Total EQD2

Overall Treatment Time (BT, EBRT, total)



DVH Parameters and Reference Points,



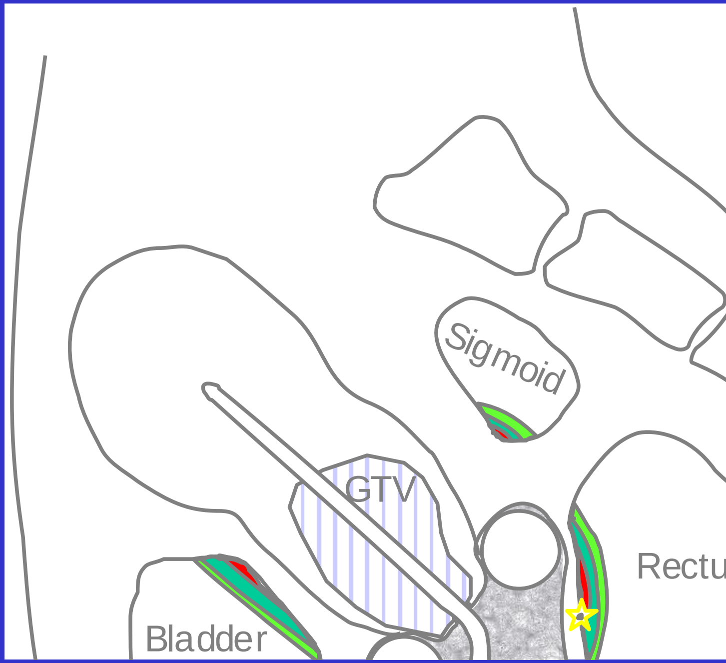
ICRU/GEC ESTRO
report 89, 2016

Fig. 6.4, Fig. 8.8

3D-based Dose Volume Parameters for OAR

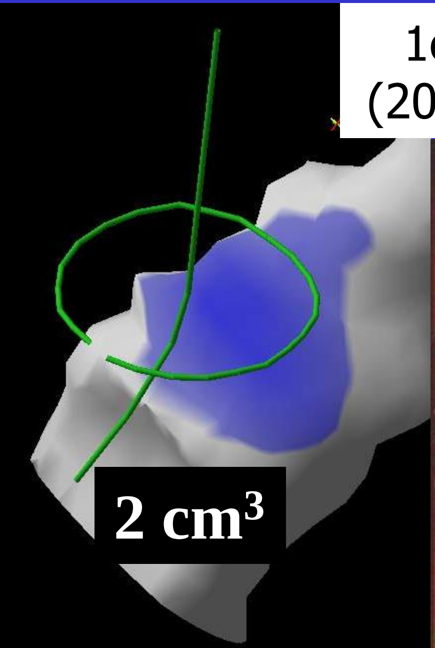
CLASSICAL MAX DOSE in 2D:
in 3D a voxel is no clinical relevant endpoint

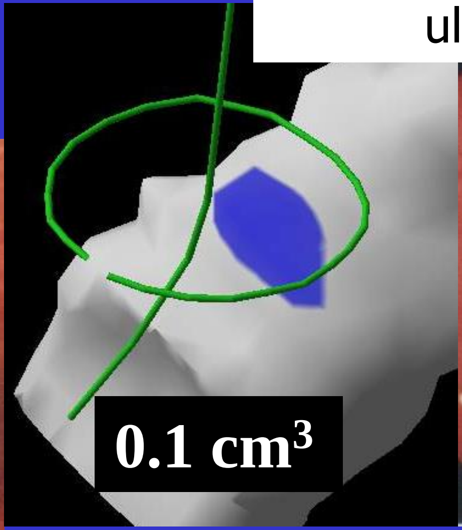
FIXED VOLUME: tolerance dose (total dose)- "minimum dose to the most exposed tissue"*

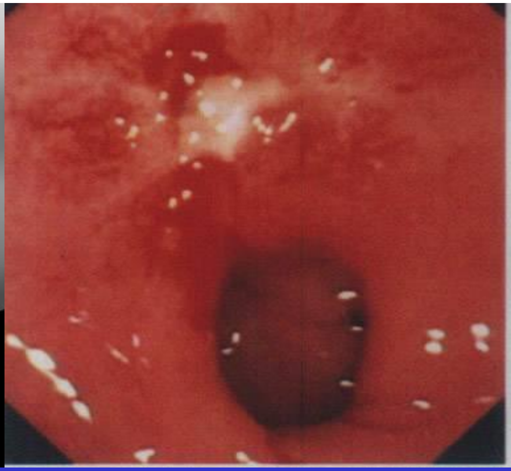


0.1 cc: 3D"maximum dose": ulceration(fistula)

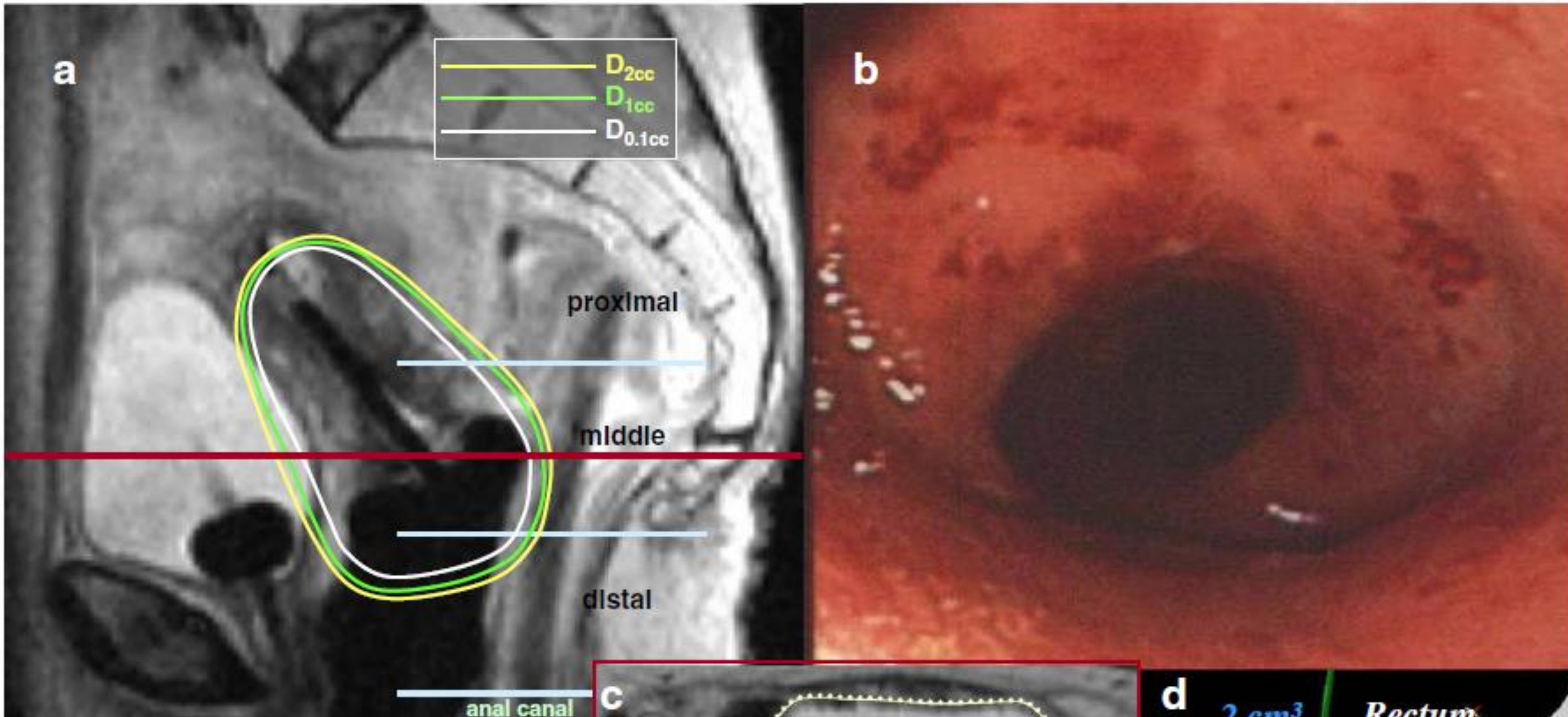
1cc/2cc:teleangiectasia (20 mm x 20 mm x 5 mm)





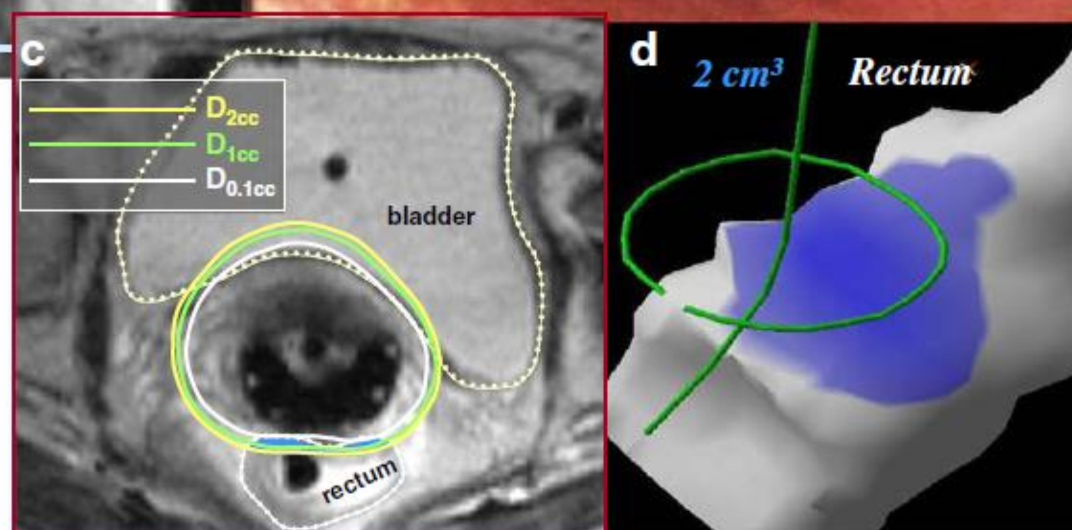


**GYN GEC ESTRO Recommendations(II) Radiother Oncol 2006*

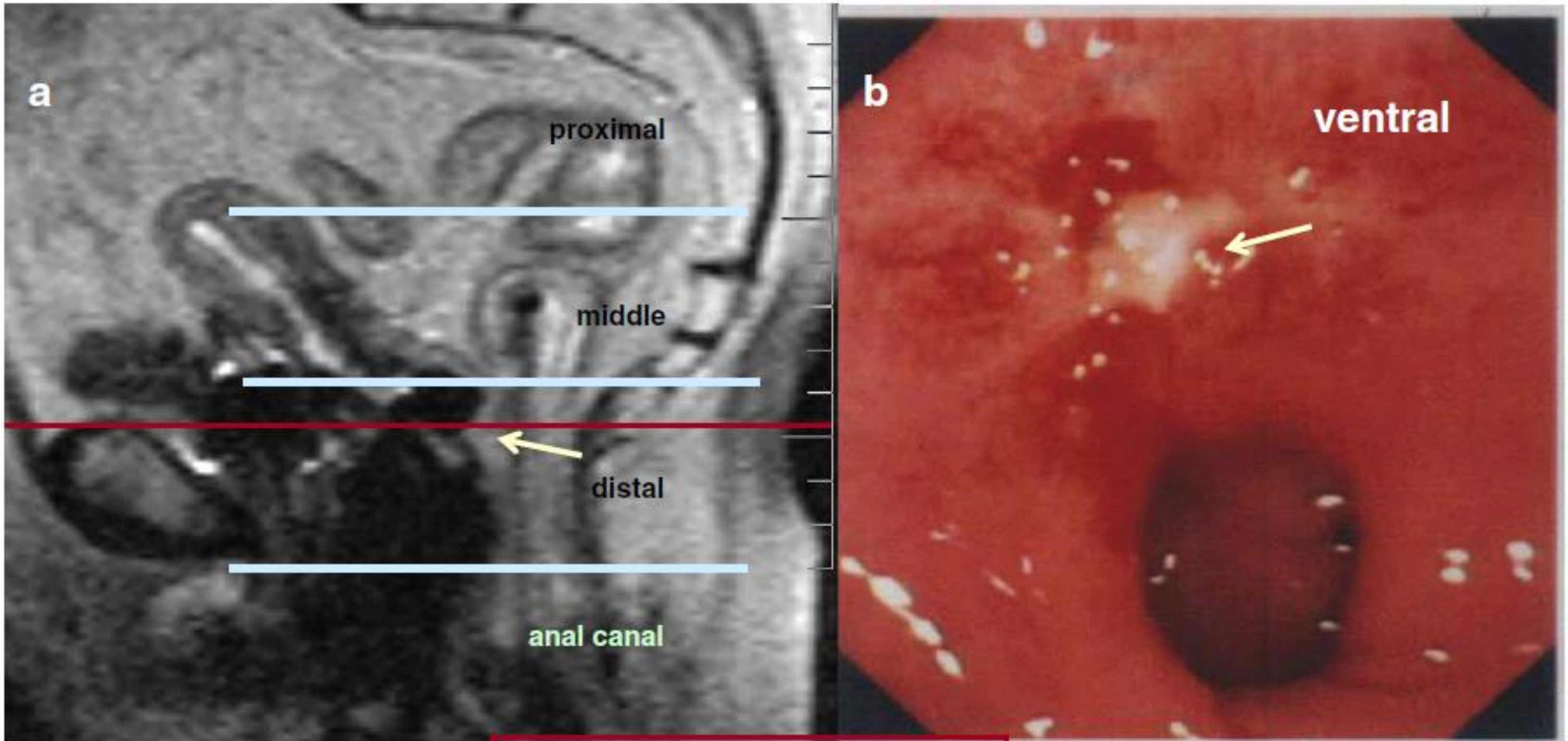


Total DVH parameters
(calculated taking into account all
4 fractions)

D_{2cc}= 75 Gy EQD2
D_{1cc}= 82 Gy EQD2
$D_{0.1cc}$= 103 Gy EQD2



Georg P et al. Radiother and Oncol 2009

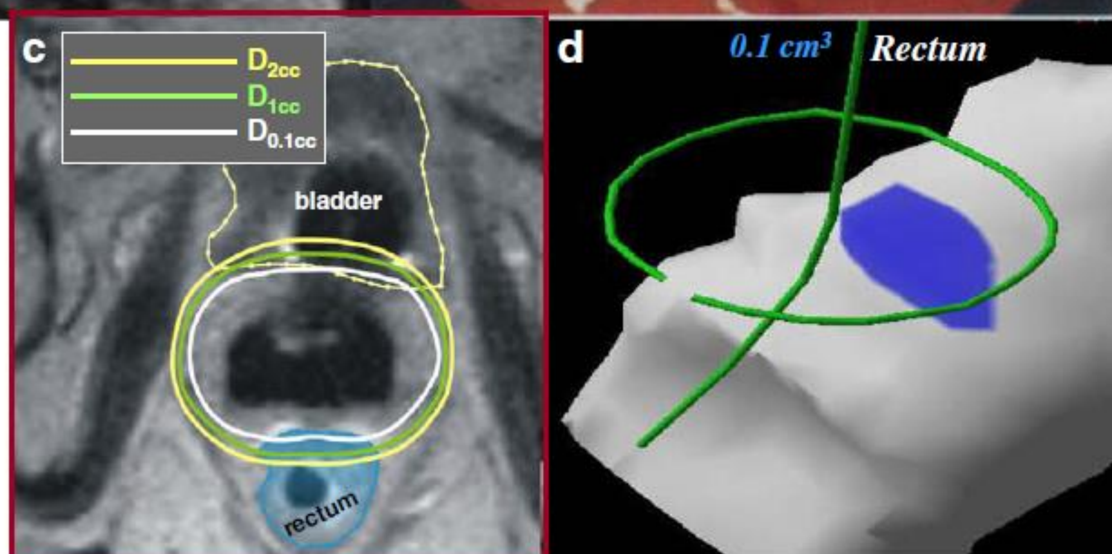


Total DVH parameters
(calculated taking into account all 4 fractions)

D_{2cc}= 81 Gy EQD2

D_{1cc}= 90 Gy EQD2

$D_{0.1cc}$= 108 Gy EQD2

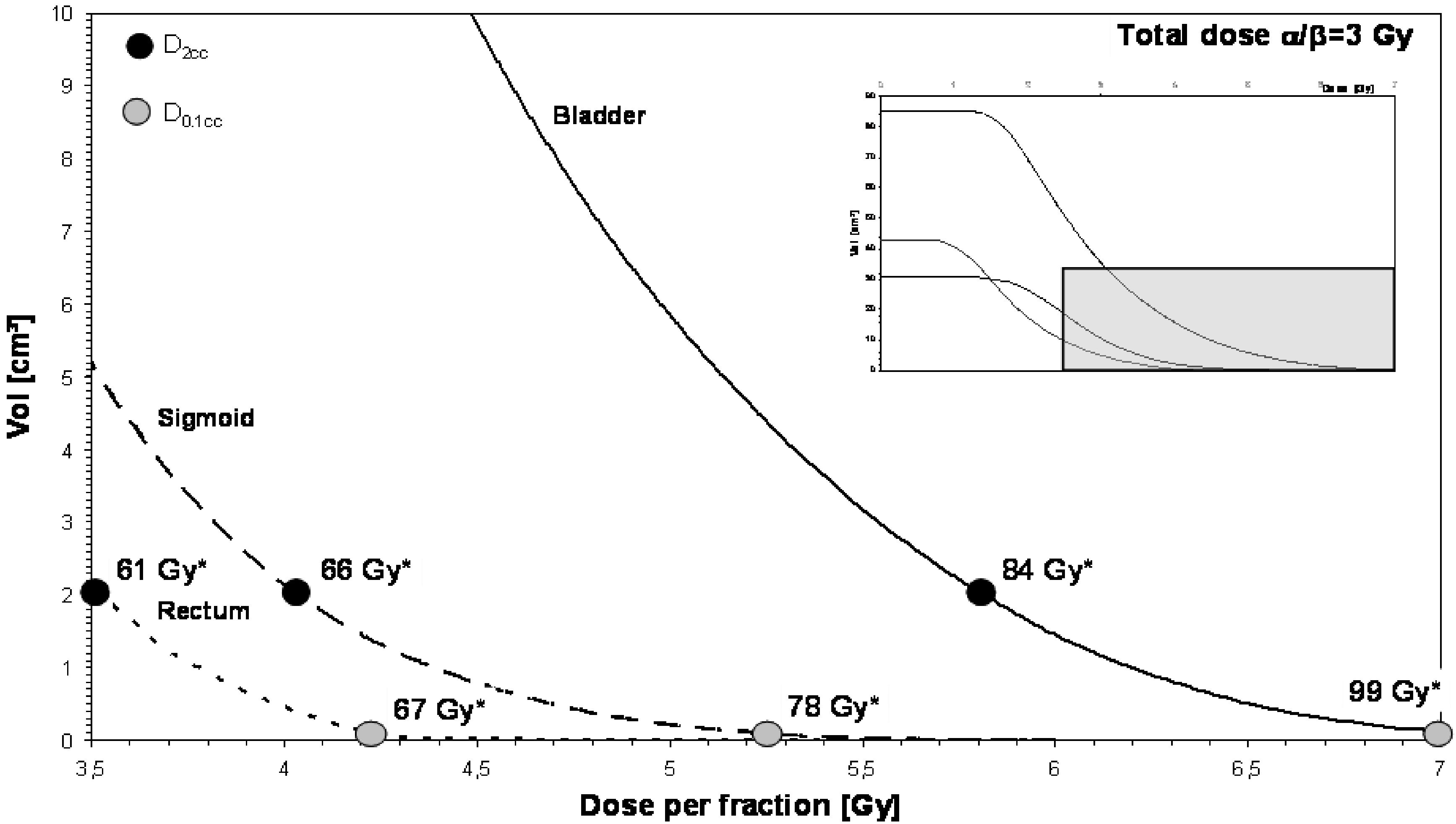


Georg P et al. Radiother and Oncol 2009

D_{2cm3} for rectum is endpoint for

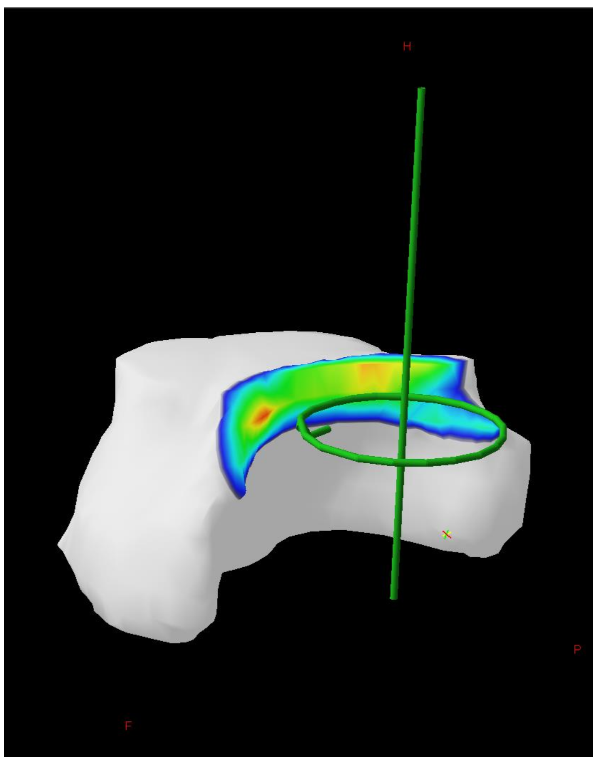
A. Rectum stenosis
B. Anal incontinence
C. Rectal bleeding, ulceration, fistula

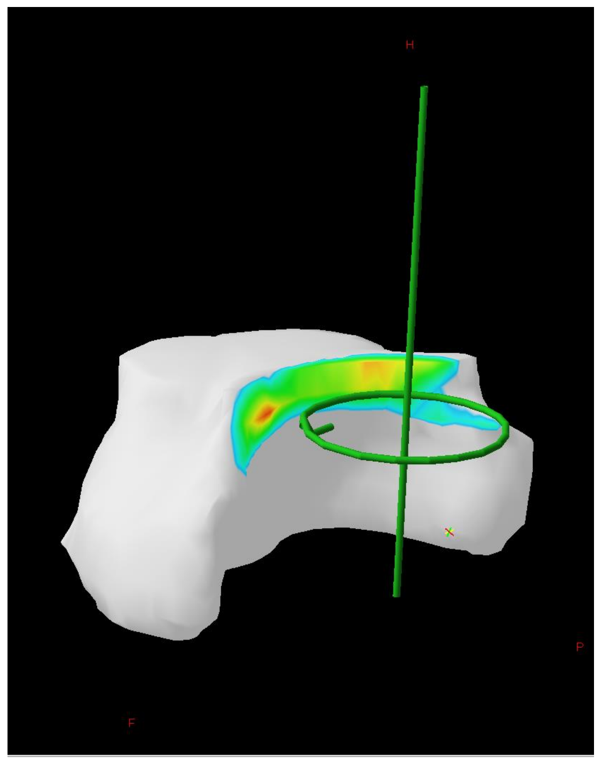
DVH Parameters for organs at risk
(ICRU 89)

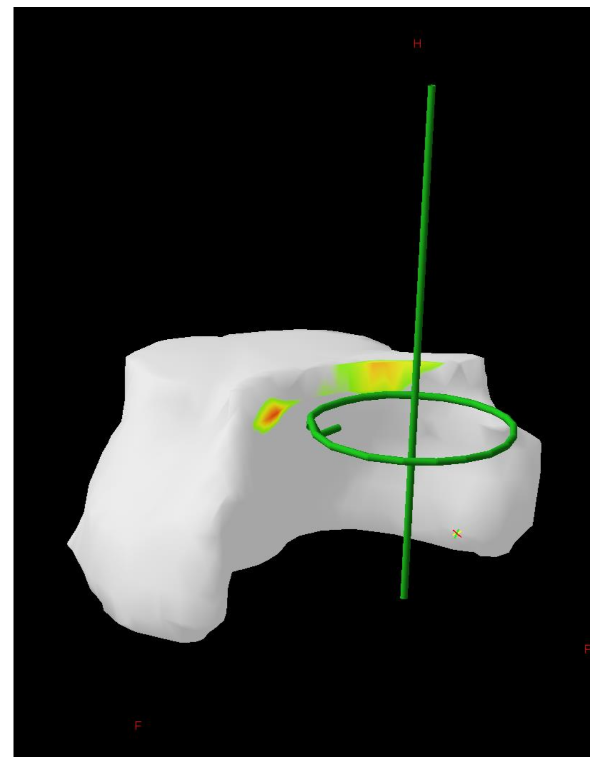


Bladder

D_{2cc}	D_{1cc}	$D_{0.1cc}$
w x h:		
40mm x 20mm		**20mm x 10mm**





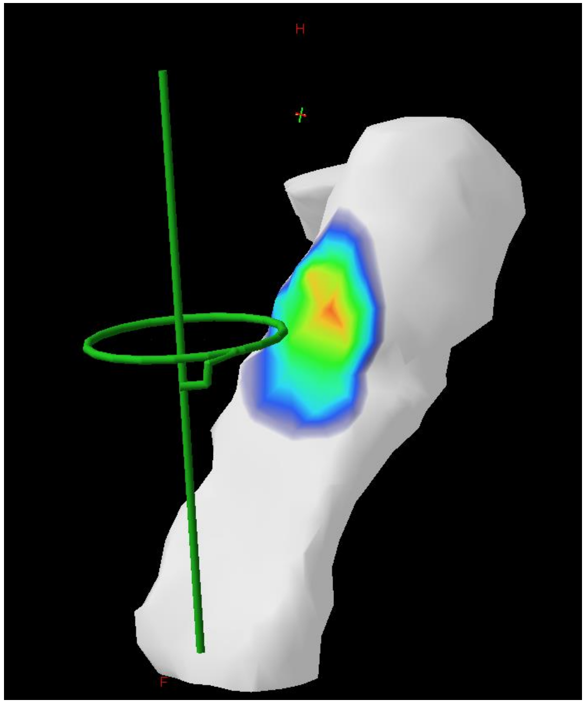


Rectum

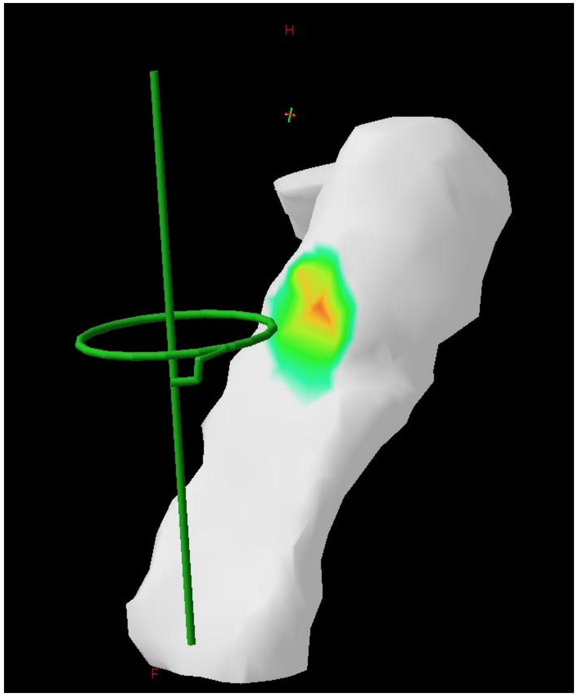
D_{2cc}

w x h:

30mm x 30mm

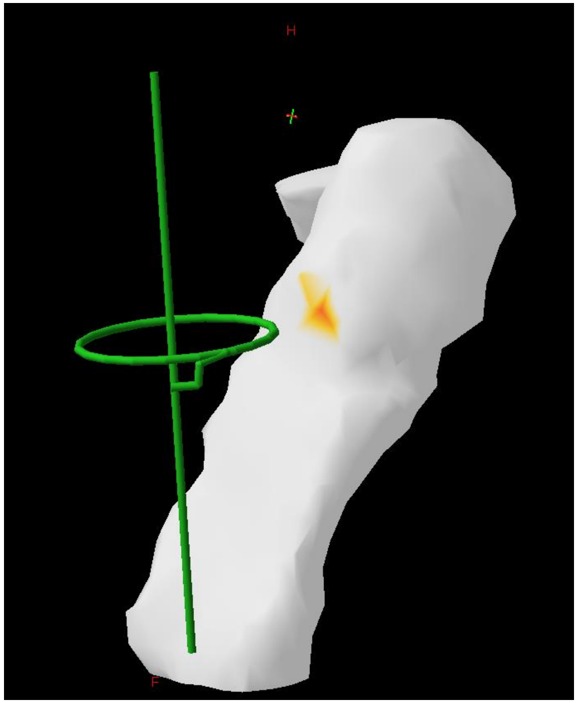


D_{1cc}



$D_{0.1cc}$

10mm x 10mm

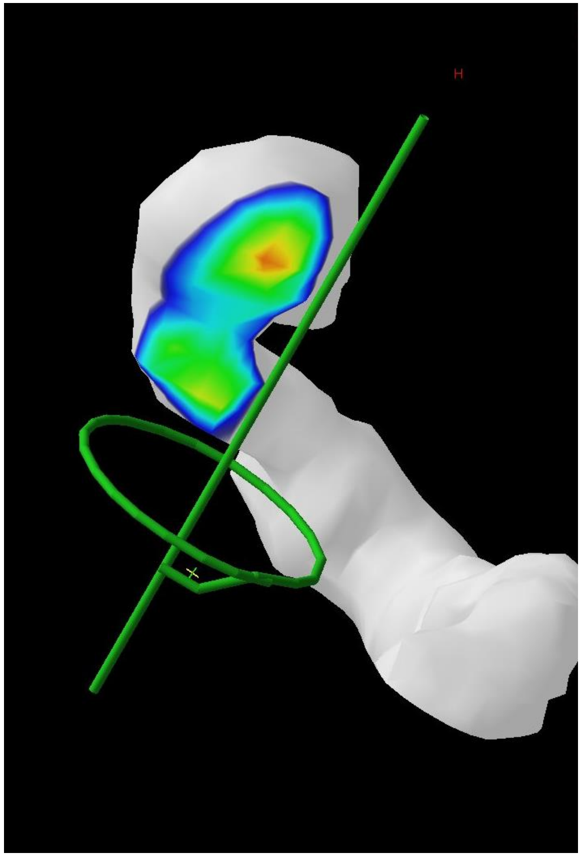


Sigmoid

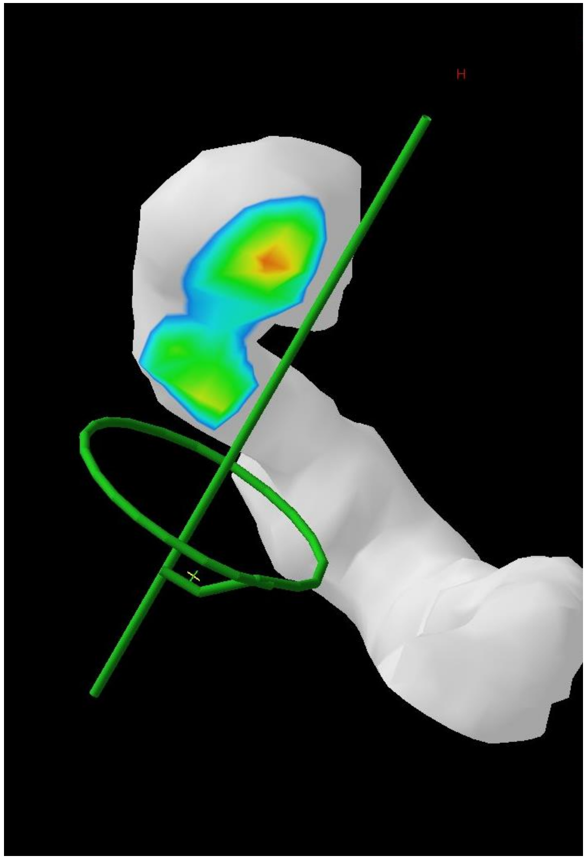
D_{2cc}

w x h:

25mm x 20mm

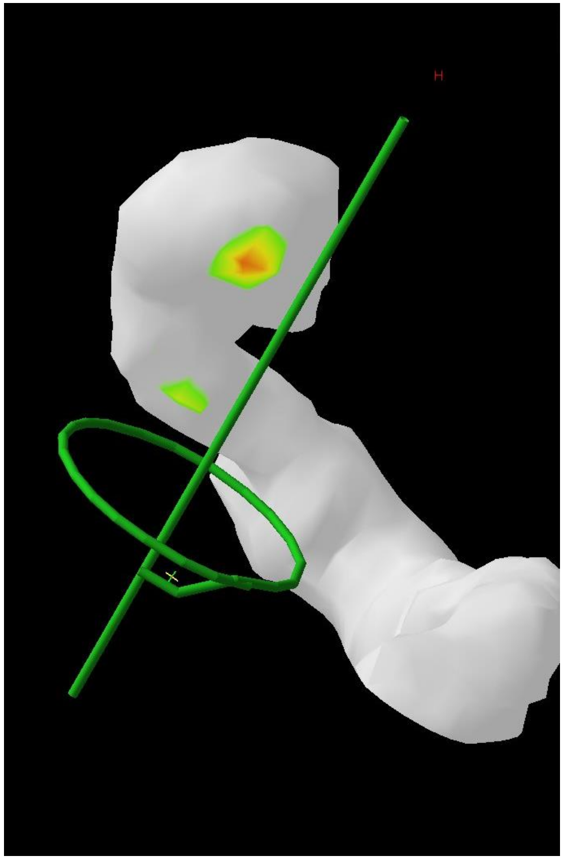


D_{1cc}

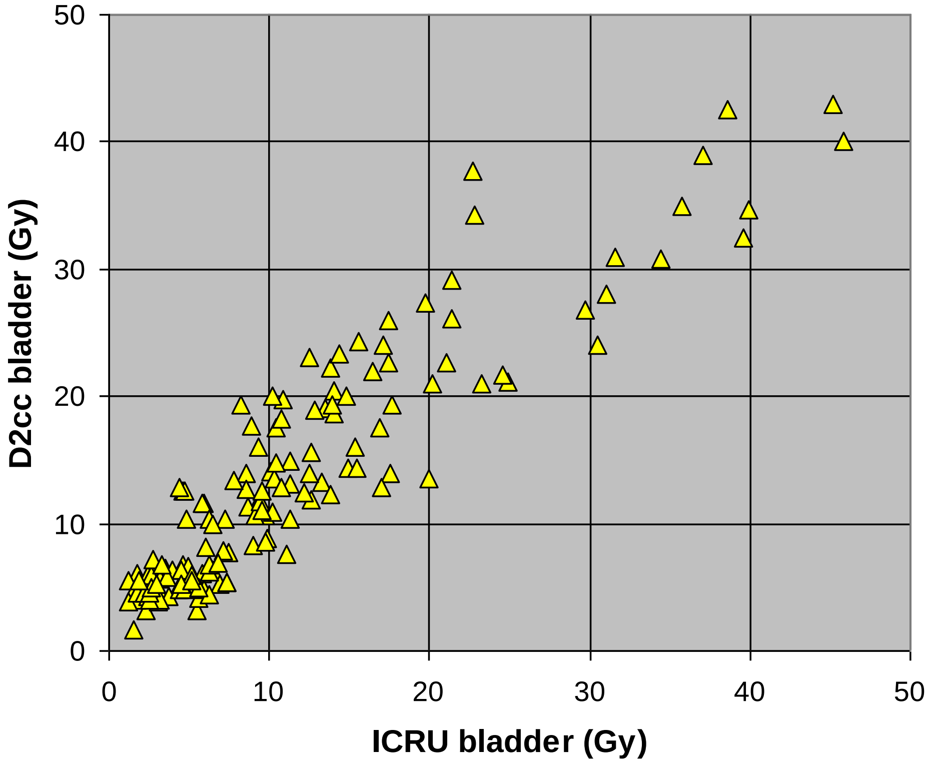


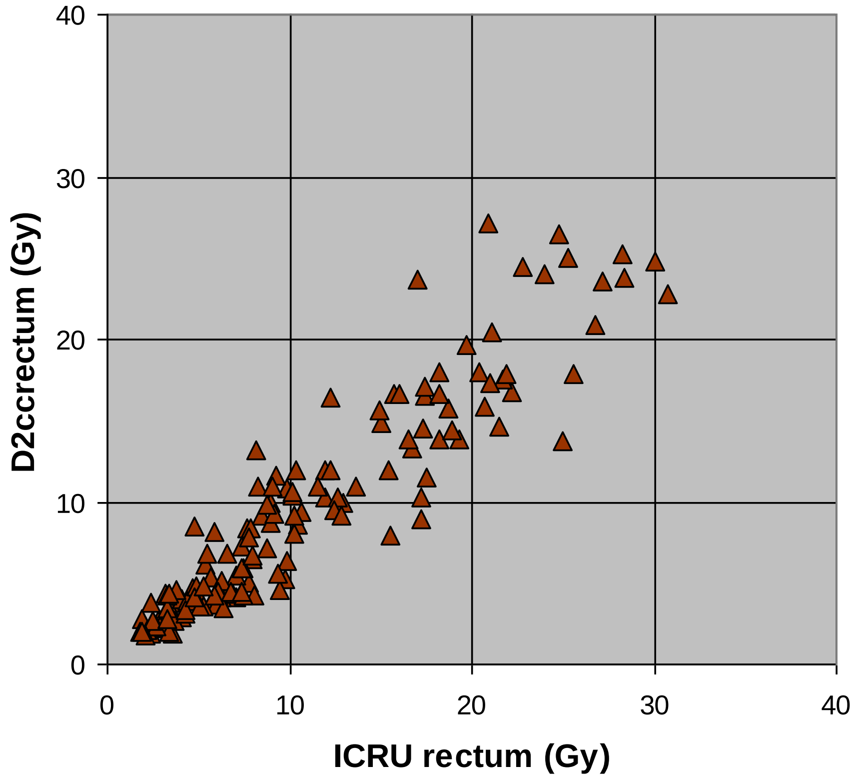
$D_{0.1cc}$

10mm x 10mm



ICRU point dose and D2cc doses



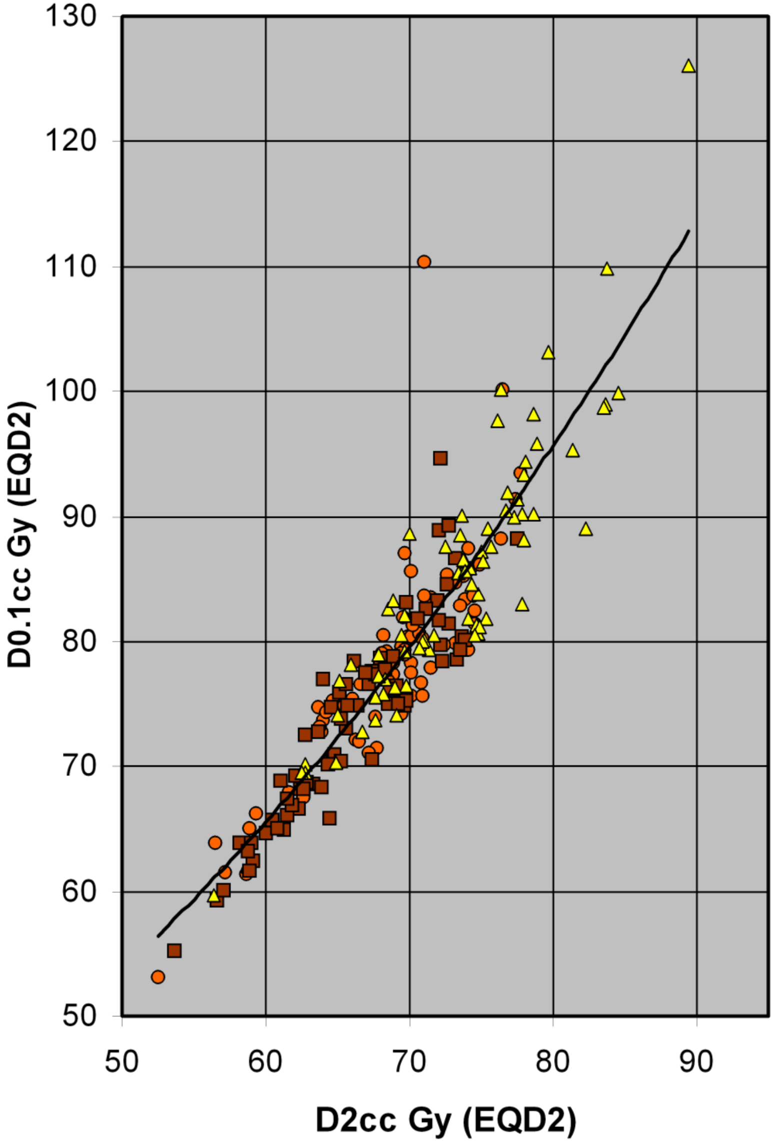


EMBRACE data, Tanderup et al.

D2cc and D0.1cc

	D2cc Gy EQD2	D0.1cc Gy EQD2
Bladder	71 ± 7	81 ± 13
Rectum	65 ± 6	72 ± 8
Sigmoid	67 ± 6	74 ± 12

$D_{0.1cc} / D_{2cc}$: 134% ± 9%
(Physical doses)



Aarhus University Hospital: PDR BT

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

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

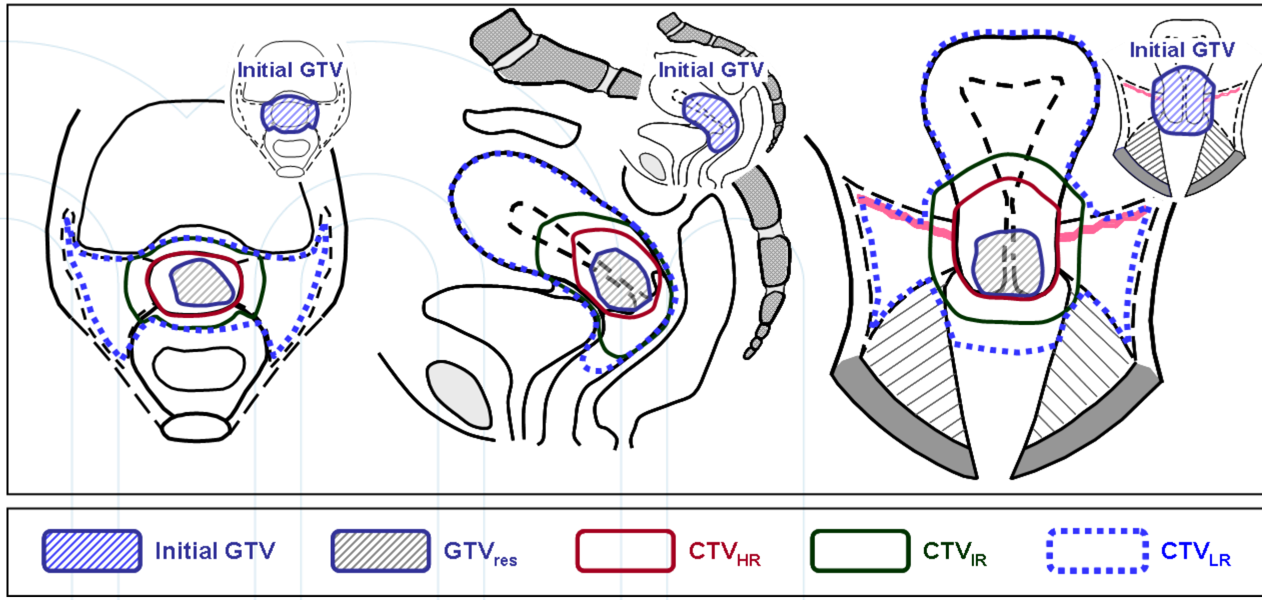
Level 2 - *Advanced standard for reporting* All that is reported in level 1 plus (ICRU 89):

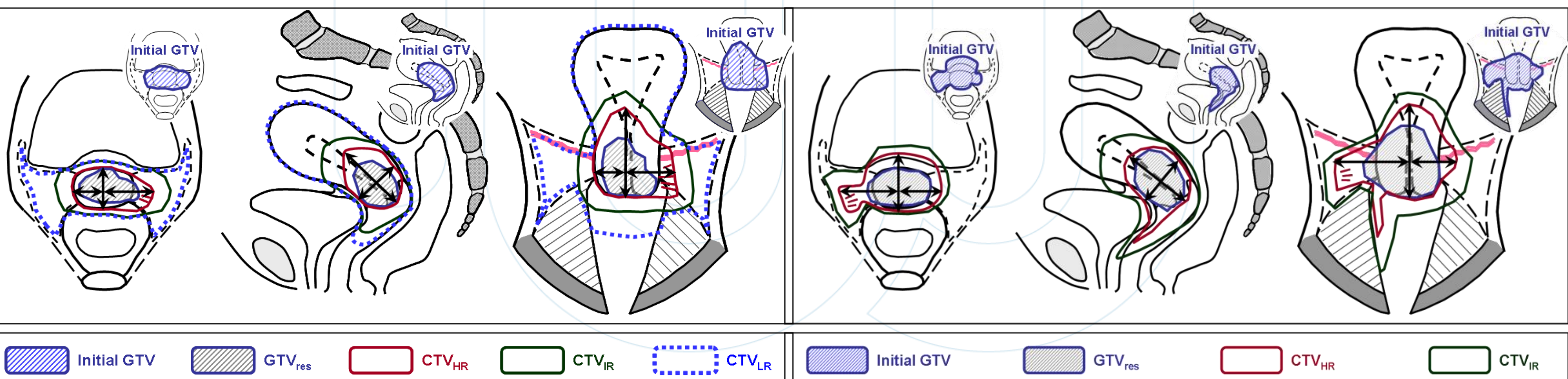
3D delineation of volumes (on volumetric images with applicator and on clinical diagrams):

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

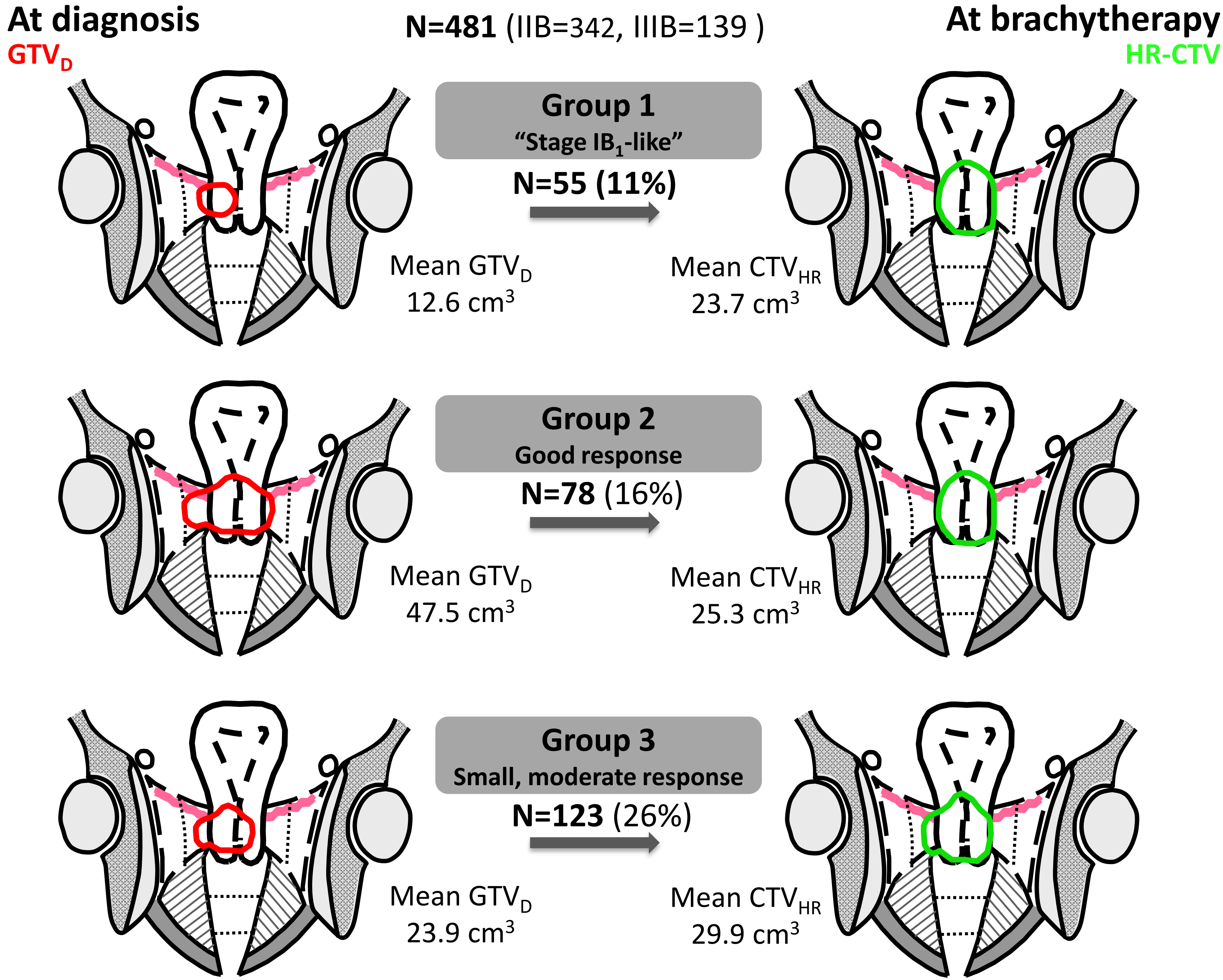
Overview of the adaptive target concept in cervix cancer stage IB, IIB, IIIB

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





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



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

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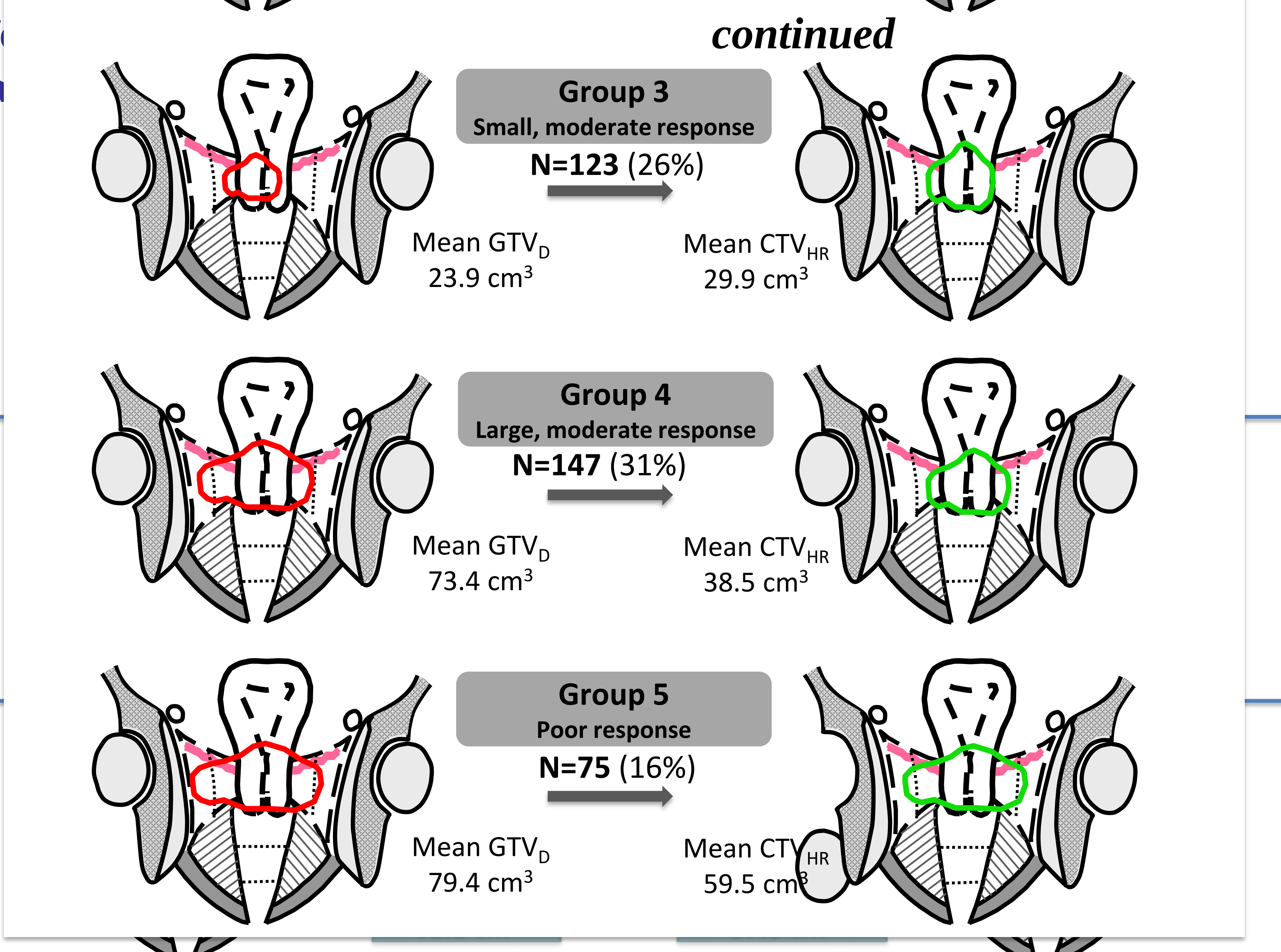


Jastaniyah N, Yoshida K *et al*; fellows at MUW/AKH Vienna, ASTRO 2014, IJROBP 2016

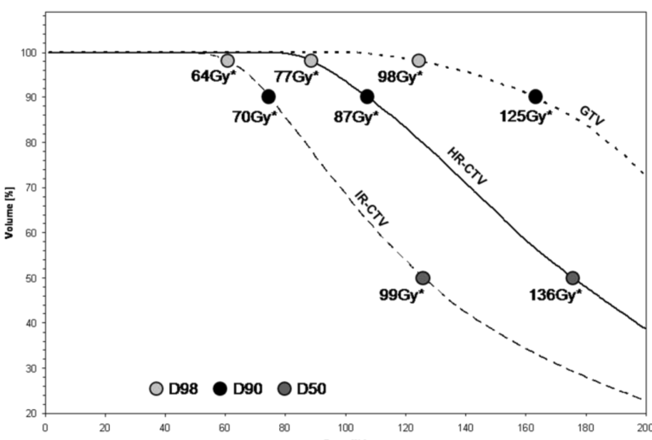
Level 2 - *Advanced standard for reporting* All that is reported in level 1 plus (ICRU 89):

Dose reporting for defined volumes based on volumetric imaging:

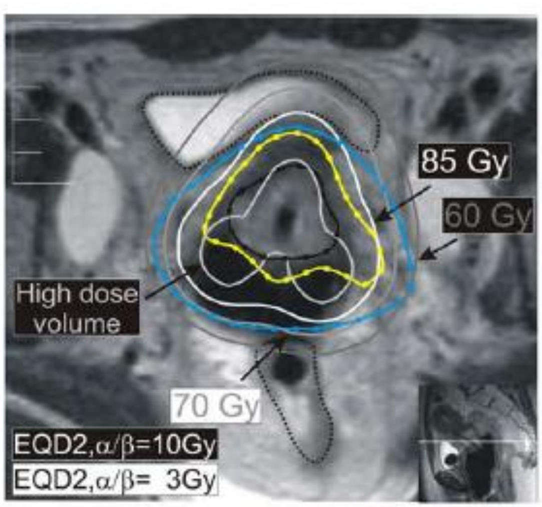
- **D_{98}, D_{90}, D_{50} for CTV_{HR}**
- **(D_{98}, D_{90}, D_{50} for CTV_{IR} if used for prescription)**
- **D_{98} for GTV_{res}**
- **D_{98} for pathological lymph nodes**

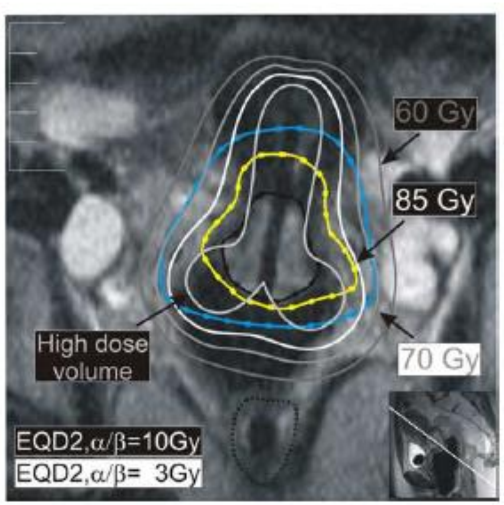
DVH-parameters CTV-T_{HR} (ICRU 89)

- **D90: Minimum dose within most exposed 90% of volume of interest**
  - **reliable and reproducible, but 10% „neglected“ (clin relevance)**
- **D 98: Minimum dose within most exposed 98% of volume of interest**
  - **reliable and reproducible, 2% not included**
- **[V100: Volume recieving prescribed physical dose (V150%/V200%)]**
  - **indicates target coverage;**
    only relevant within a specific dose (rate) and fractionation schedule
- **D50: Minimum dose within most exposed 50% of volume of interest**



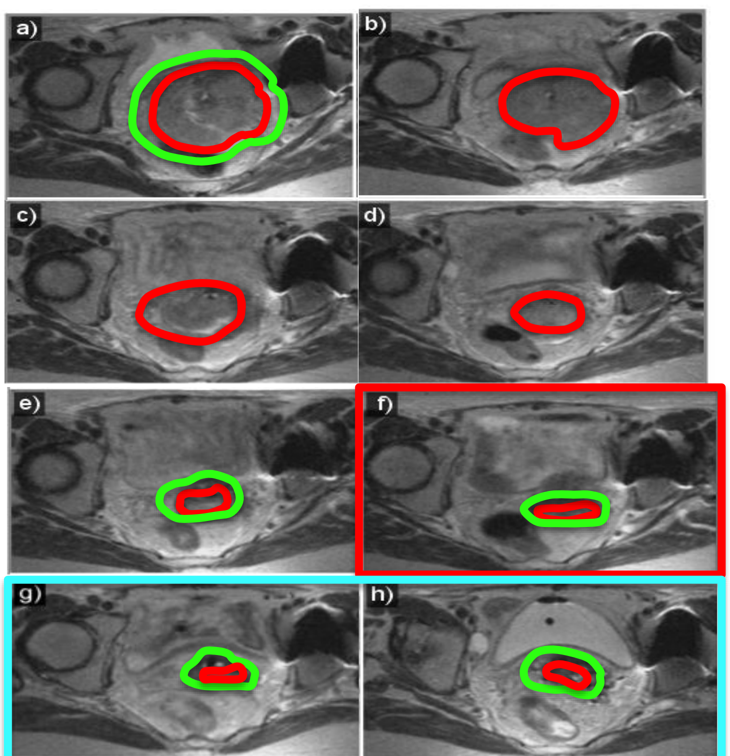
GEC ESTRO Rec II, 2006

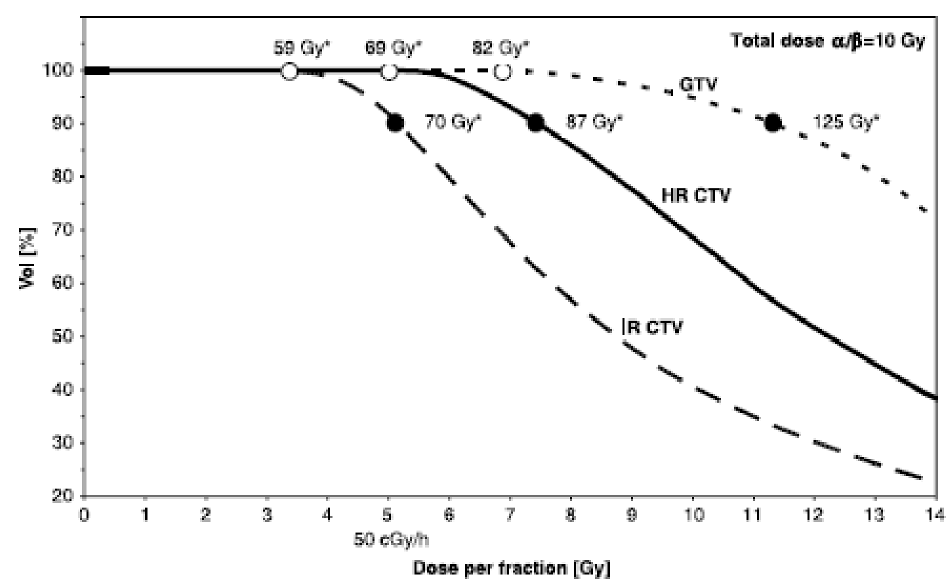




Dose and Volume Parameters (Vienna data 1998-2008)

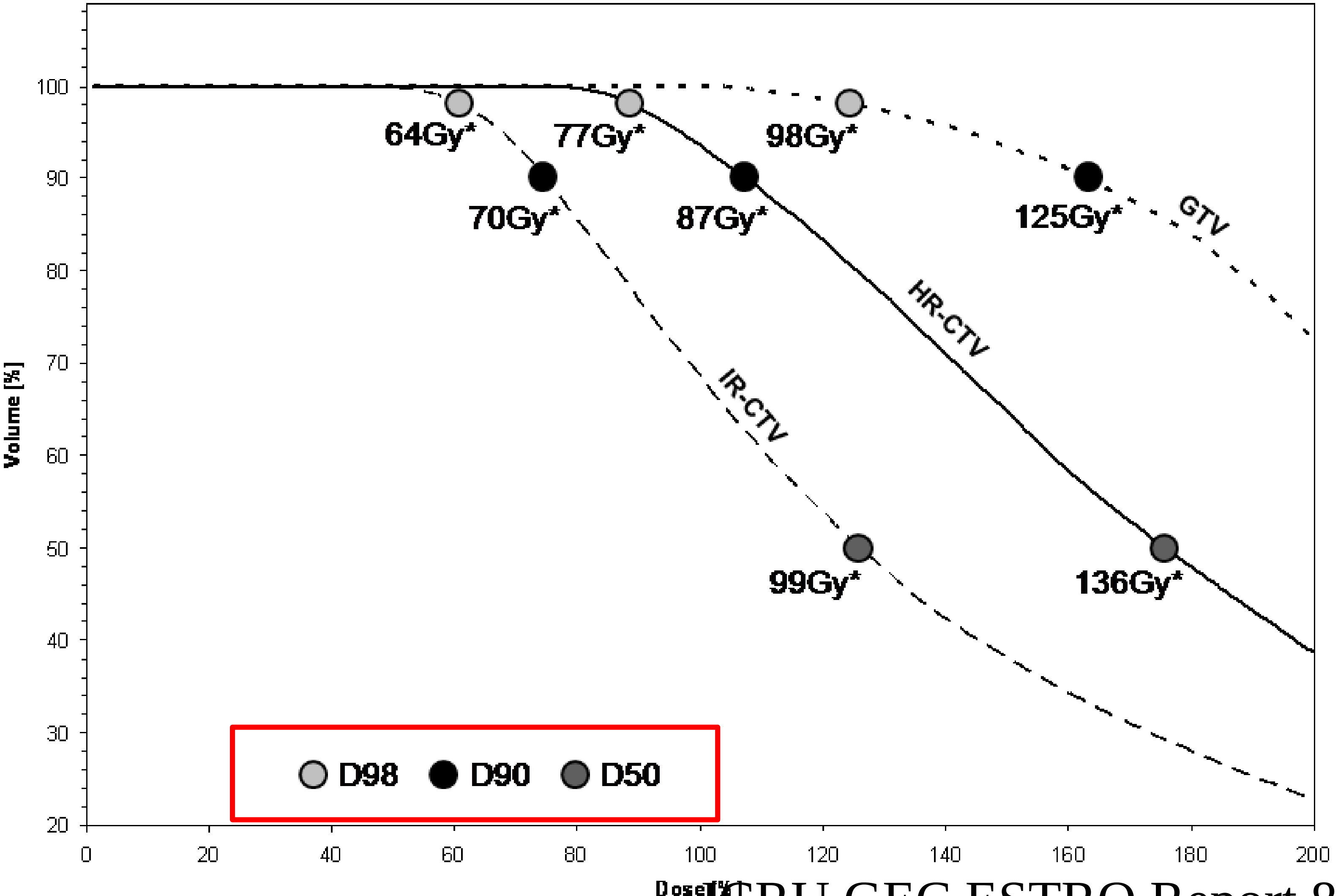
IR CTV-T	~ 100 cm^3	~ 66 Gy EQD2	(D90)
HR CTV-T	~ 39 cm^3	~ 89 Gy EQD2	(D90)
Res. GTV-T	~ 9 cm^3	~ 119 Gy EQD2	(D100)





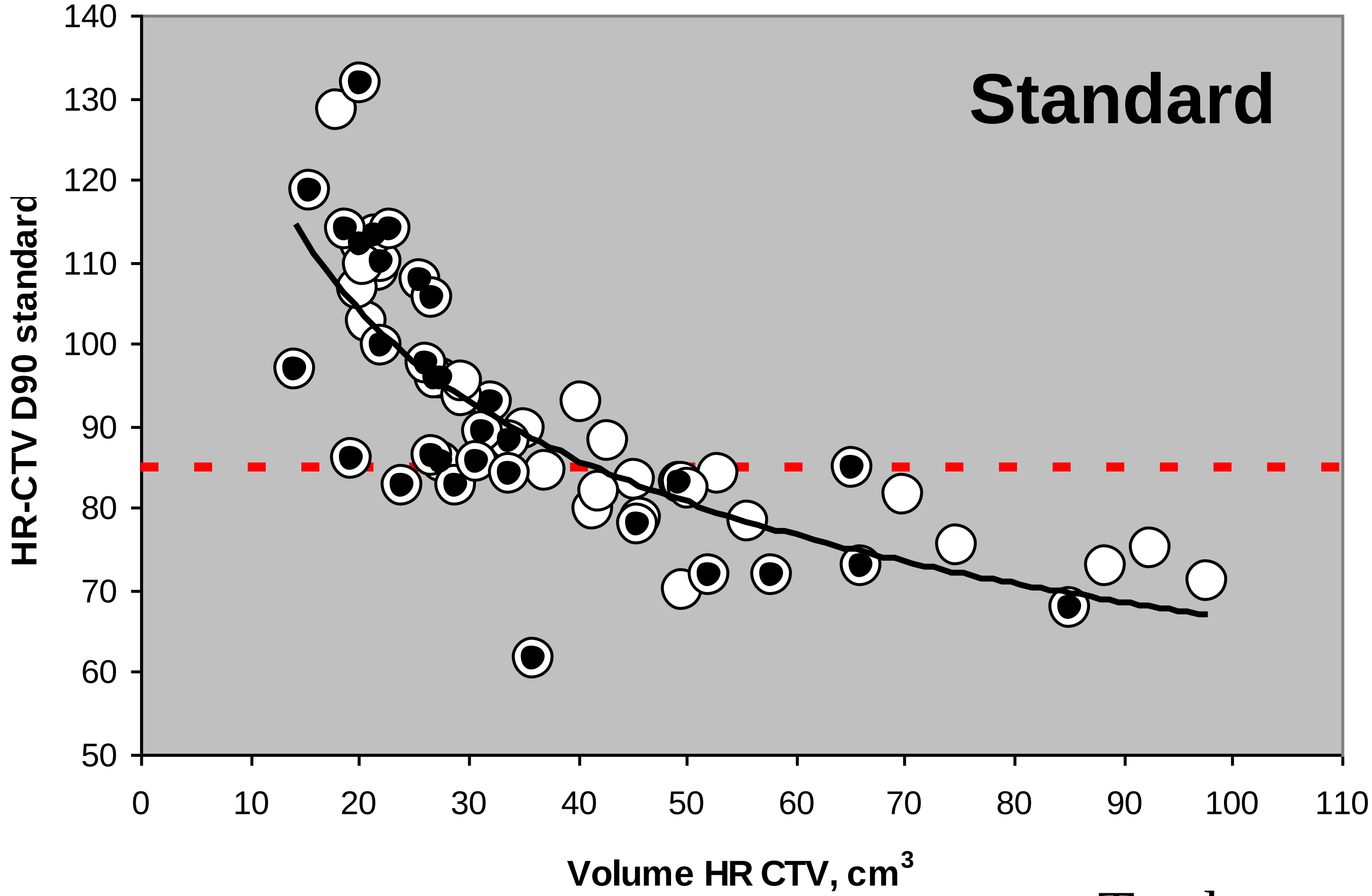
GEC ESTRO Rec II, 2006

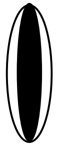
DVH parameters targets:
GTV, CTV-HR, CTV-IR



ICRU GEC ESTRO Report 89, 2016

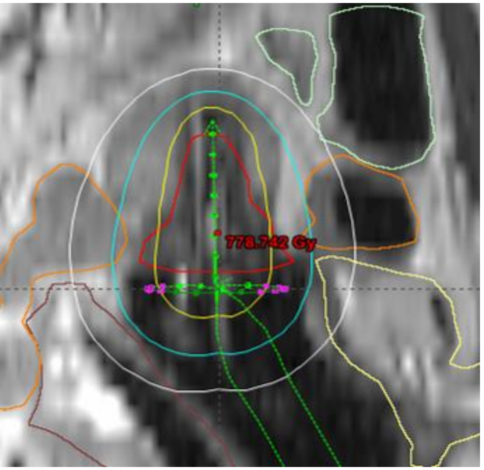
Dose in D90 and HR CTV for point A prescription: the dilemma
High Target Doses in small tumours
Low Target Doses in large tumours
Violation of OAR constraints



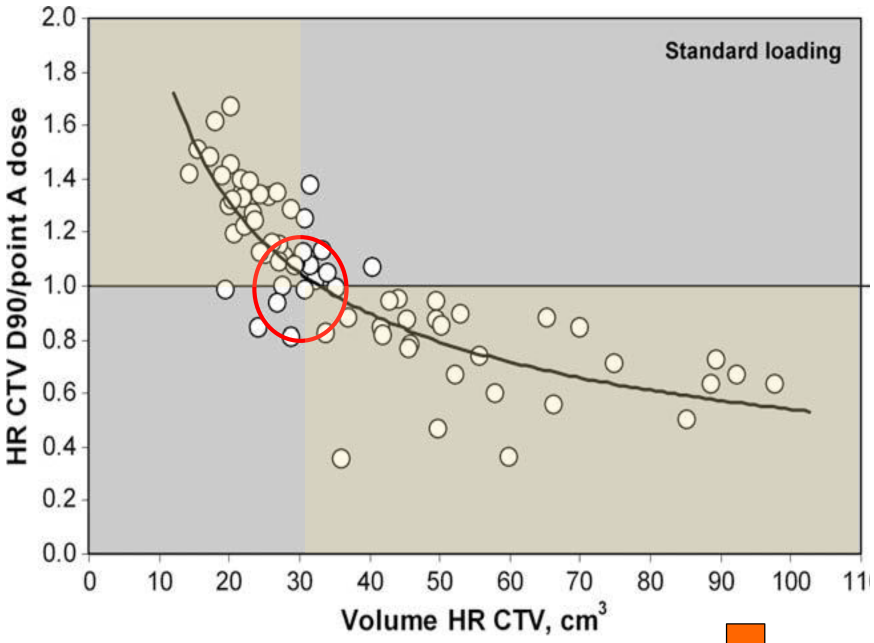

Violation of OAR constraint

Tanderup et al.

Consequences of prescribing to Point-A

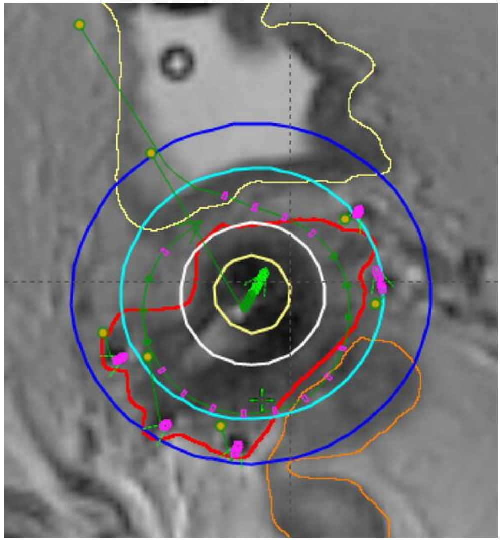


Overdosing organs at risk



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):

.

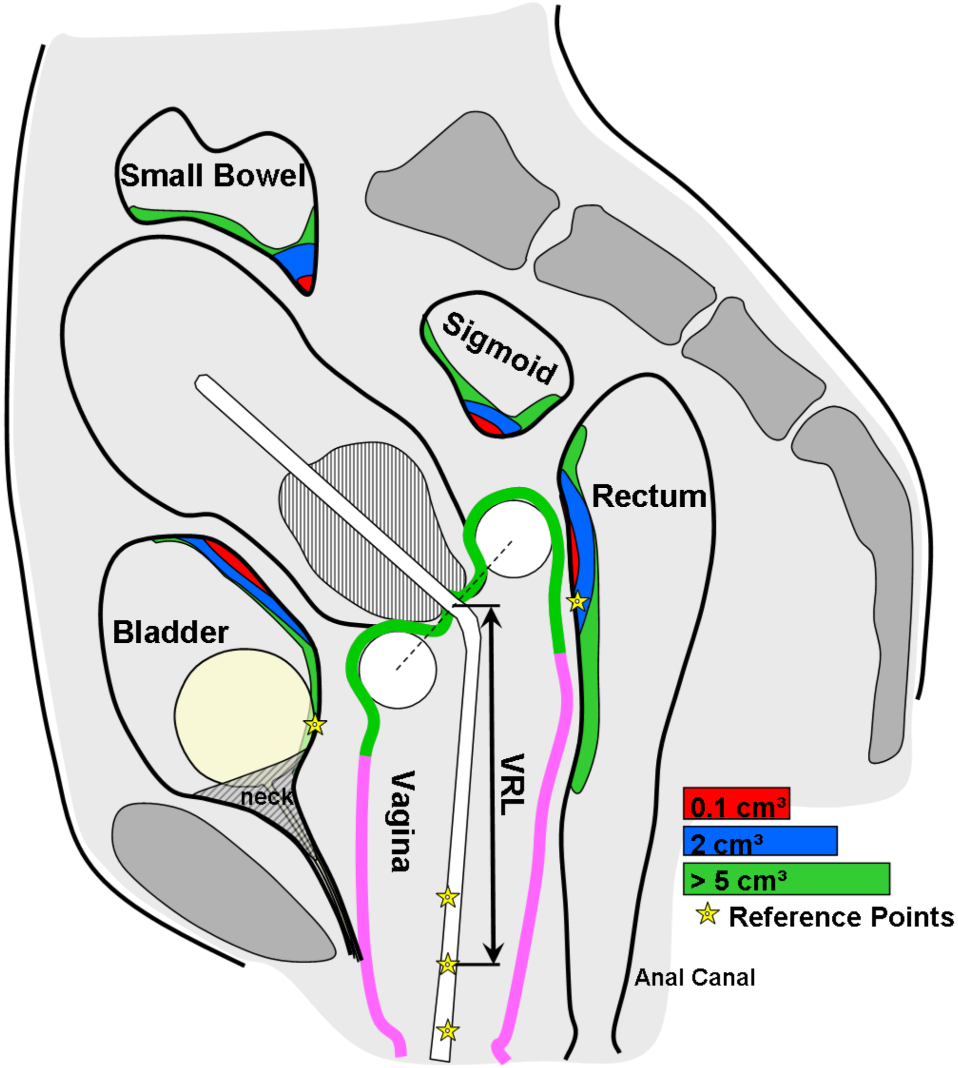
Dose reporting based on volumetric imaging for OARs:

- **Bladder/Rectovaginal reference point dose**
- **$D_{0.1cm^3}$,D_{2cm^3} for sigmoid**
- **D_{2cm^3} bowel**
- **Intermediate and low dose parameters in bladder, rectum, sigmoid, bowel (e.g. V_{15Gy}, V_{25Gy}, V_{35Gy}, V_{45Gy} or $D_{98\%}$, $D_{50\%}$, $D_{2\%}$)**
- **Vaginal point doses at level of sources (lateral at 5 mm)**
- **Lower and mid-vagina doses (PIBS, PIBS ±2cm)**

DVH Parameters and Reference Points,

ICRU/GEC ESTRO
report 89, 2016

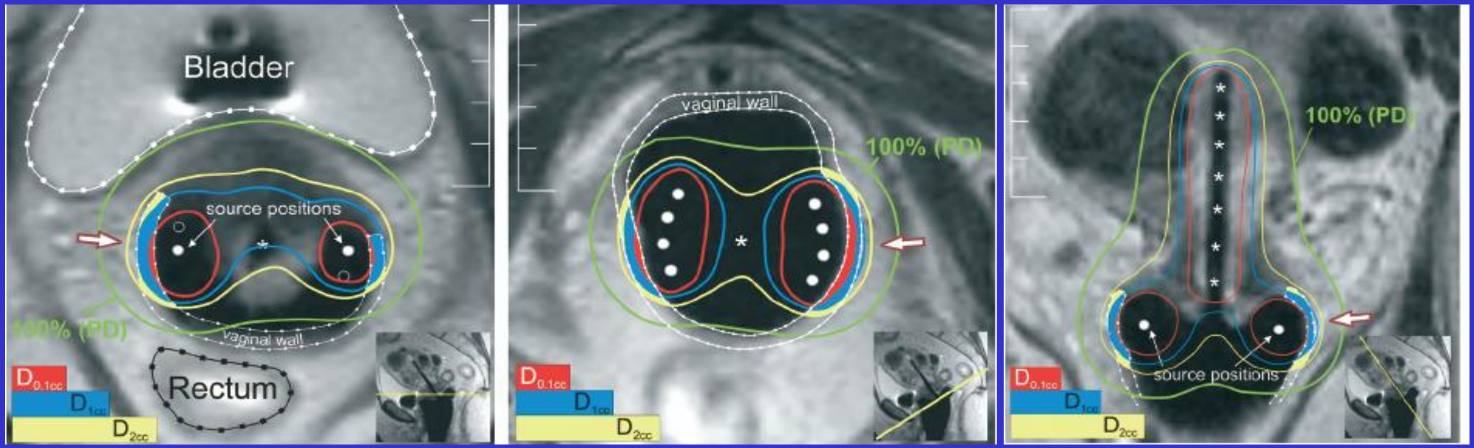
Fig. 6.4, Fig. 8.8



Vaginal dose assessment and reporting

UNCERTAINTIES IN ASSESMENT OF THE VAGINAL DOSE FOR INTRACAVITARY BRACHYTHERAPY OF CERVICAL CANCER USING A TANDEM-RING APPLICATOR

Daniel Berger, M.Sc., Johannes Dimopoulos, M.D., Petra Georg, M.D., Dietmar Georg, Ph.D., Richard Pötter, M.D., and Christian Kirisits, Sc.D.

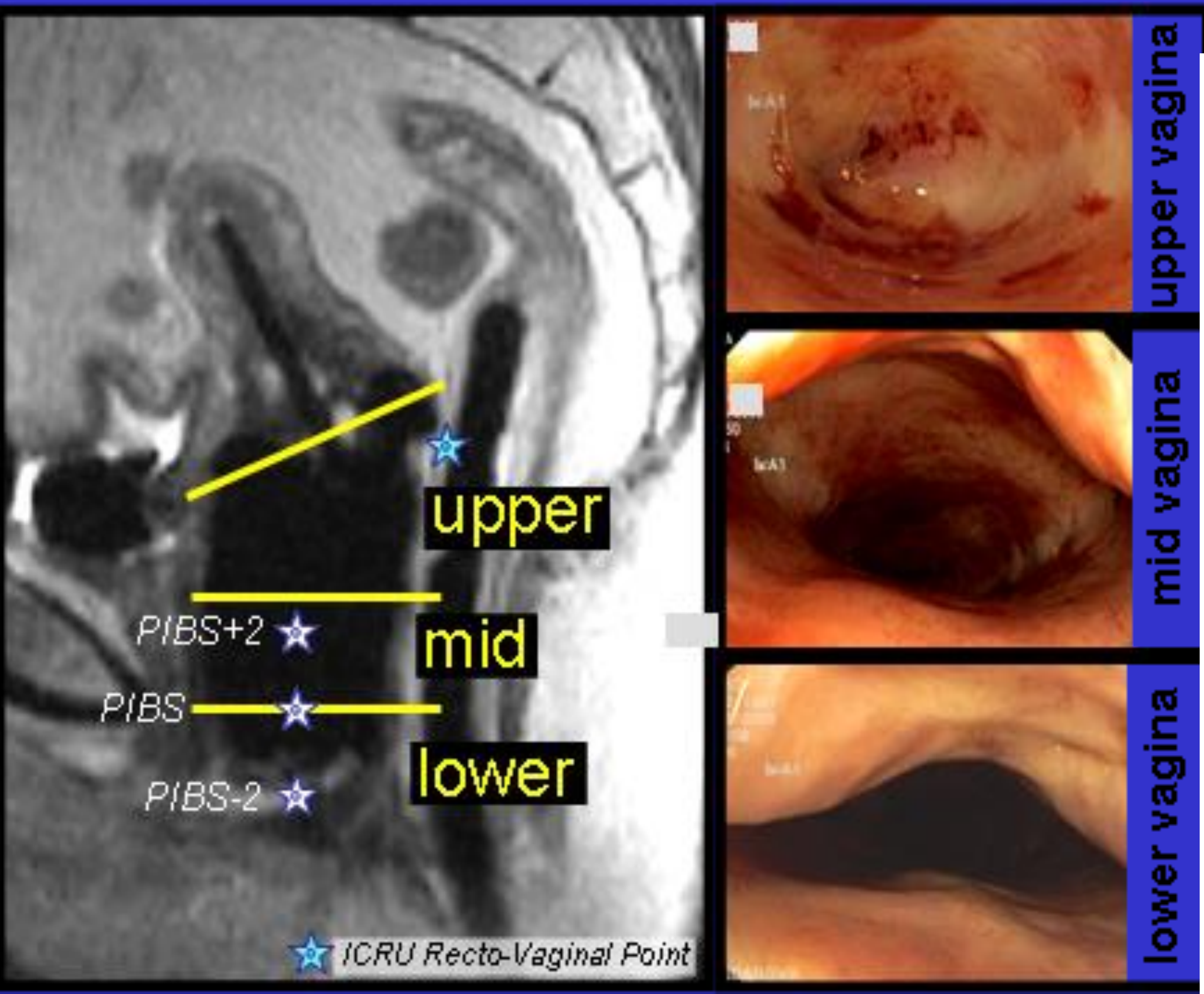


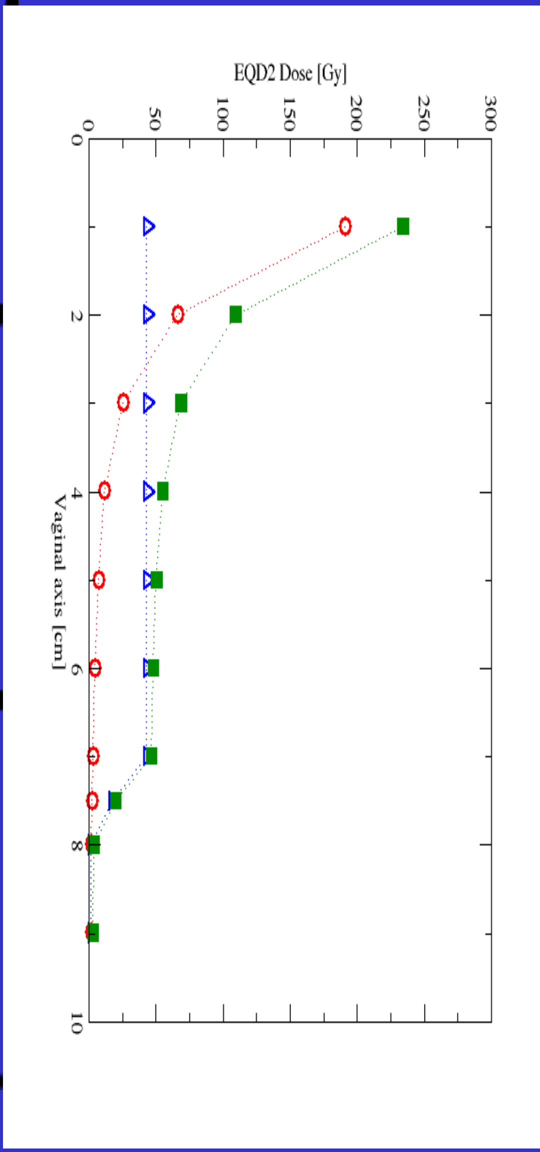
<u>**DVH parameters have HIGH uncertainty for representative vaginal dose estimation**</u>

They are influenced by the resolution of sectional imaging, contouring accuracy and applicator reconstruction

Berger et al, IJROBP 2007

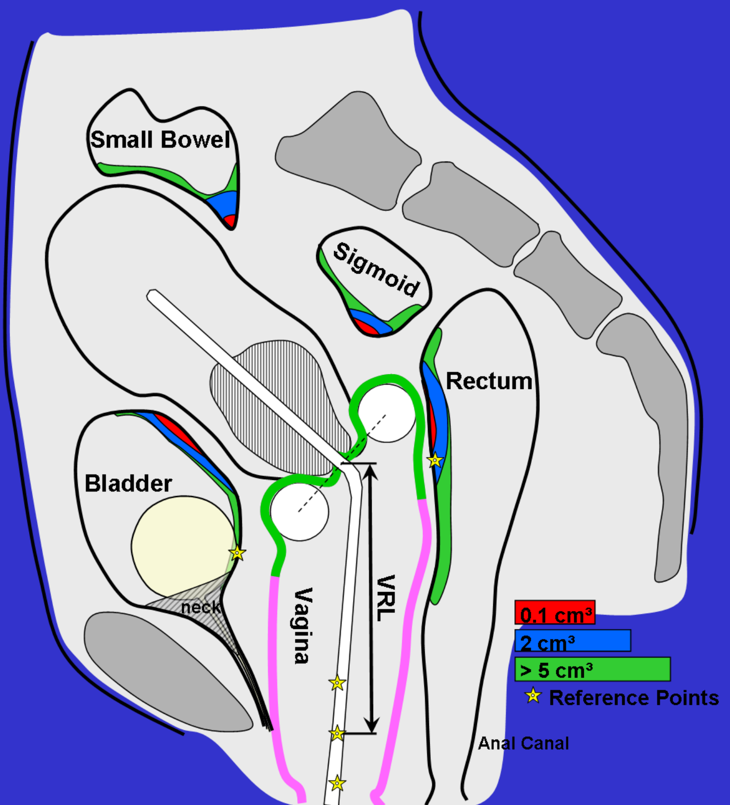
Vaginal morbidity and radiation doses





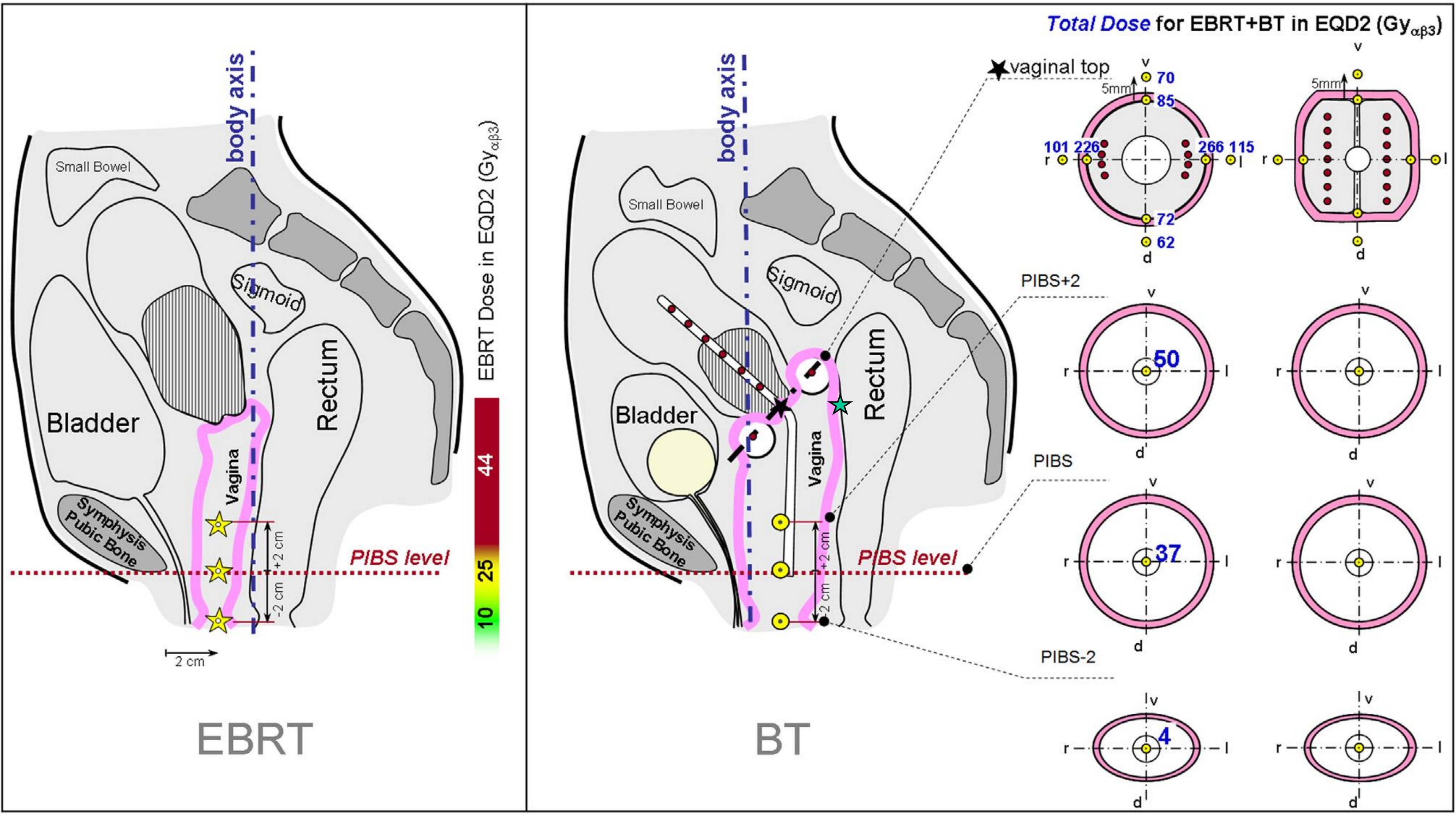
ICRU/GEC ESTRO Report 89 Fig. 6.1/Fig. 8.11

DVH Parameters and Reference Points, Vaginal point: *variations in application*



ICRU/GEC ESTRO
report 89, 2016
Fig. 6.4, Fig. 8.8

Vaginal Dose Points: PIBS, PIBS+2, PIBS-2:
no clinical evidence (too early): contribution from BT and EBRT



Westerveld et al. RadiothOncol 2013

Vaginal Reference Length (VRL)

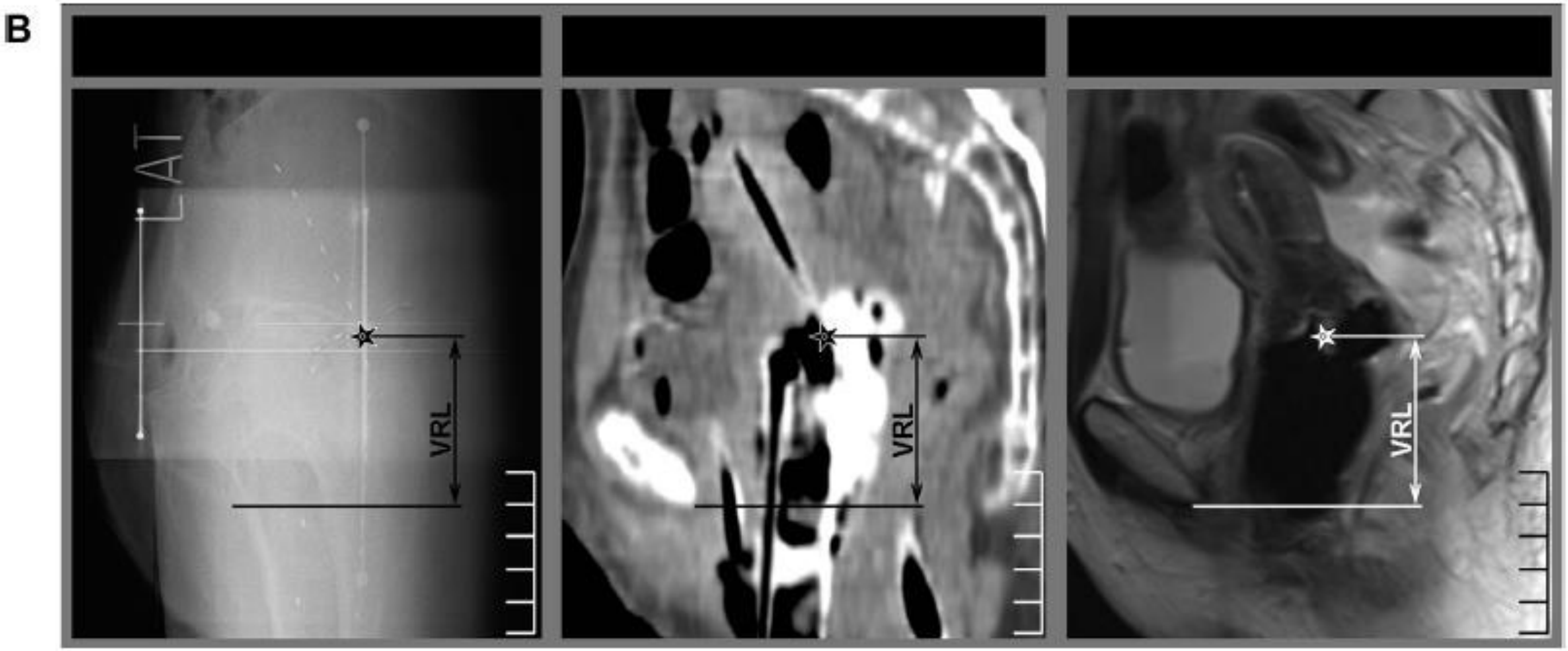


Fig. 1. Definition of vaginal dose points and vaginal reference length (VRL). (A) Vaginal dose points are defined in relation to a point at the level of the posterior–inferior border of the symphysis (PIBS) on sagittal (reconstructed) CT or MR images used for EBRT and BT treatment planning. The star at PIBS level represents the vaginal reference point. In the table on the right side mean (SD) and median (min–max) values are given for each level in EBRT and for total dose in EQD2. Additionally, total doses to the top are given for all four clockwise positions at the vaginal surface and 5 mm depth (e.g. median total dose at 3 o'clock is respectively 266 and 115 Gy for surface and 5 mm depth). (B) VRL at time of BT with a ring applicator in situ on a lateral radiograph, sagittal MPR CT image and sagittal MRI view. VRL is measured from centre of the ring (indicated by a star) to the PIBS level, indicated by the solid line orthogonal to the body axis.

D_{2cm3} and $D0.1_{cm3}$ for OAR are recommended

A. for the vagina
B. for the bladder only
C. for rectum, sigmoid, bladder

General principles for reporting of physical and equieffective EBRT and BT dose (ICRU/GEC ESTRO report 88)

Physical dose and number of fractions is assessed for target, OARs, dose points:

- BT

- EBRT

Total equi-effective dose (EQD2) is calculated according to the linear quadratic model through the following steps:

- BT EQD2 for each fraction
- Total BT EQD2
- Total EBRT EQD2
- Accumulated total EBRT+BT EQD2*

**Based on current assumptions outlined in ICRU 88 chapter 9*

Reporting of radiobiological parameters:

α/β values for tumour and OARs*

In addition $T_{1/2}$ and recovery model for LDR and PDR treatments*

*At present: α/β=3 Gy for late effects in OAR and 10 Gy for tumour, and $T_{1/2}$=1.5h

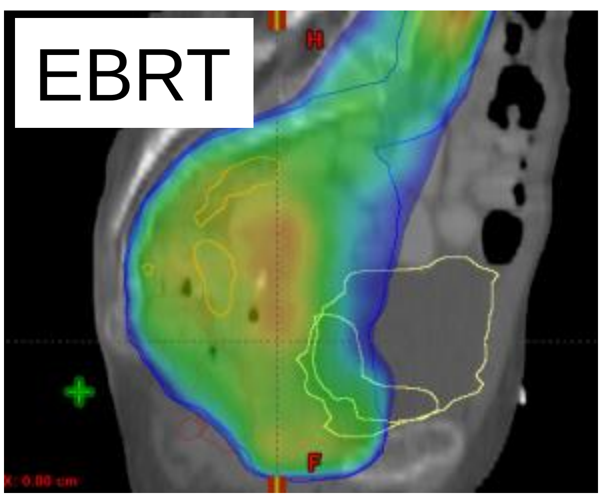
Pelvic EBRT (elective) + BT

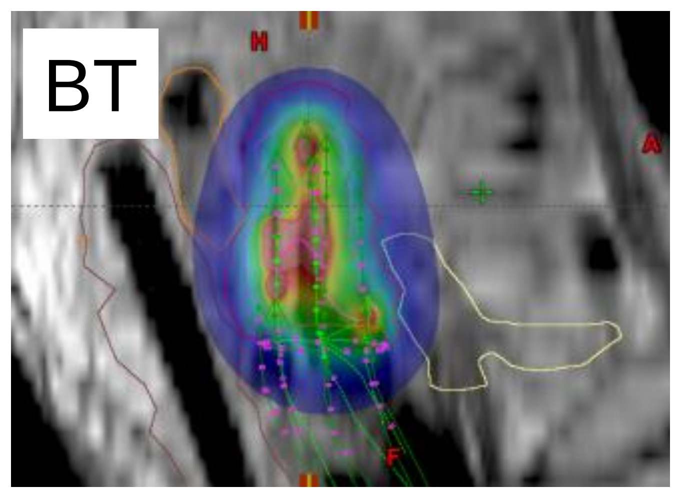
- **Elective target volume and CTV-T:**
  - **Normally homogeneous dose within 95%-107% of PD**

Recommended assessment of total EQD2 dose:

Target (HR CTV-T): $D90_{EQD2}$ (total) = PD_{EQD2}(EBRT) + $D90_{EQD2}$(BT)

OAR: $D_{2cm3,\ EQD2}$ (total) = PD_{EQD2}(EBRT) + $D_{2cm3,\ EQD2}$ (BT)





Calculation of EQD2 in spreadsheet

- **EBRT+BT**
- **EQD_2 calculations**
  - **Tumor: α/β = 10 Gy**
  - **OAR: α/β = 3 Gy**
  - **T½ = 1.5 h**

DVH analysis of MR-guided intracavitary PDR brachytherapy

Pt. ID								
Optimized plan		Variable	Unit	BT_1	BT_2	BT_3	Sum BT	EBRT+BT
		Date		29-12-06	05-01-06	12-01-06	*Mean*	*Stddev*
Applicator		Tandem length	mm	50	50	50		
		Ring diameter	mm	30	30	35		
Time/dose pattern		Number of pulses	no.	10	10	10		
		Puls duration	min	24	24	7		
		Puls interval	min	36	36	53		
		Source strength factor		266	284	94		
		Total treatment time	sek	5310	5128	4268	14706	
		TRAK (Gy at 1m)	cGy	0,60	0,58	0,48	1,66	
TUMOR		Prescribed Dose (PD)	Gy	10,0	10,0	10,0	30,0	80,0
α/β (Gy) =	10,0	**PD_{iso} (EQ2)**	Gy	11,2	11,2	11,2	33,6	83,6
T½ (h) =	1,5	Volume of PD	cm^3	89,3	86,2	66,3	*80,6*	*10,2*
EBRT dose	50,0	PD*2	Gy	20,0	20,0	20,0		
EBRT fx	25	**$PD{*}2_{iso}$ (EQ2)**	Gy	28,1	28,1	28,3	84,5	134,5
EBRT EQ2	50,0	Volume of PD*2	cm^3	32,7	30,4	22,9	*28,7*	*4,2*
		PD Point-A level left	mm	21,1	19,6	15,4	*18,7*	*2,4*
		PD Point-A level right	mm	19,4	19,2	16,5	*18,4*	*1,3*
Point-A		Dose point A_{left}	Gy	10,7	9,9	7,4		
		D_{iso} point A_{left} (EQ2)	Gy	12,1	11,0	7,7	30,9	80,9
		Dose point A_{right}	Gy	9,6	9,3	8,1		
		D_{iso} point A_{right} (EQ2)	Gy	10,6	10,2	8,6	29,4	79,4
		Dose point A_{mean}	Gy	10,1	9,6	7,7		
		D_{iso} point A_{mean} (EQ2)	Gy	11,4	10,6	8,2	30,1	80,1
Clinical tumor size		Width	mm	40	40	40		
		Height	mm	30	30	25		
		Thickness	mm	40	40	40		
		Clinical tumor volume	cm^3	25,1	25,1	20,9	*23,7*	*2,0*
GTV		Volume of GTV	cm^3	6,6	4,5	4,9	*5,3*	*0,9*
		D100 =MTD	Gy	11,5	15,1	13,9		
		$D100_{iso}$	Gy	13,4	19,2	17,1	49,8	99,8
		D90	Gy	18,5	20,7	18,3		
		$D90_{iso}$	Gy	25,3	29,6	25,0	79,9	129,9
		V100	%	100,0%	100,0%	100,0%	*100,0%*	*0,0%*
HR CTV		Volume of HR CTV	cm^3	29,5	29,1	24,5	*27,7*	*2,3*
		D100 =MTD	Gy	9,4	9,6	9,3		
		$D100_{iso}$	Gy	10,4	10,6	10,2	31,3	81,3
		D90	Gy	13,7	14,9	13,3		
		$D90_{iso}$	Gy	16,7	18,7	16,2	51,7	101,7
		V100	%	99,9%	100,0%	100,0%	*100,0%*	*0,1%*

When adding doses from EBRT and BT You assume for the HR CTV for BT that

A. 50% of the ICRU point dose of EBRT has been applied (or of median EBRT dose)
B. 90% of the dose of the ICRU point dose of EBRT has been applied (or of median EBRT dose)
C. 100% of the dose of the ICRU point dose of EBRT has been applied (or of median EBRT dose)

When adding doses from EBRT and BT You assume for the 2 cm3 for OAR that

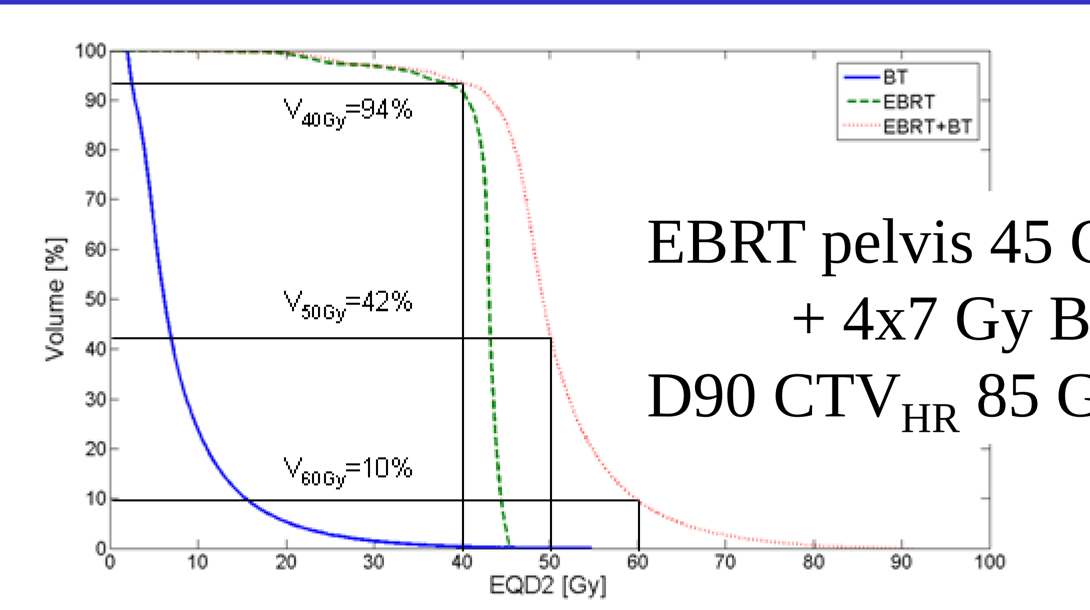
A. 50% of the EBRT ICRU point dose has been applied (or of median EBRT dose)
B. 90% of the EBRT ICRU point dose has been applied (or of median EBRT dose)
C. 100% of the EBRT ICRU point dose EBRT has been applied (or of median EBRT dose)

Limitations of adding doses according to „ICRU point-3D model" both for CTV and OAR

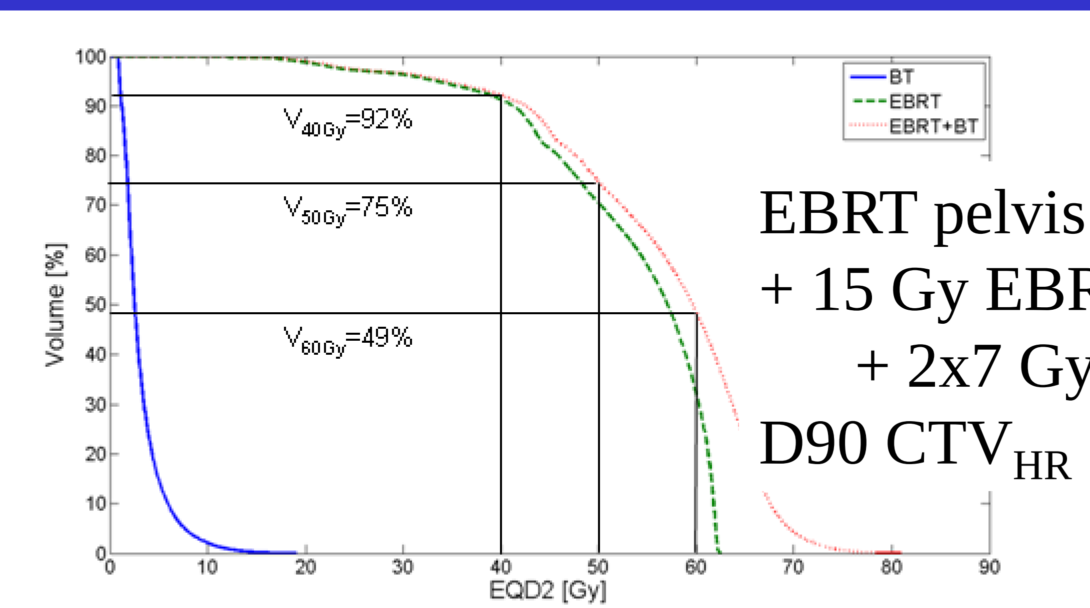
- **Non-homogenous dose distribution EBRT**
  e.g. IMRT, VMAT…
- **Parametrial boost**
- **Lymph node boost**
- **Limitations of the linear-quadratic model**

- **Future solution for complex adding doses….**

DVHs Rectum for different contributions of EBRT and BT *and* specific morbidity endpoints



EBRT pelvis 45 Gy
+ 4x7 Gy BT
D90 CTV_{HR} 85 Gy



EBRT pelvis 45 Gy
+ 15 Gy EBRT boost
+ 2x7 Gy BT
D90 CTV_{HR} 85 Gy

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**

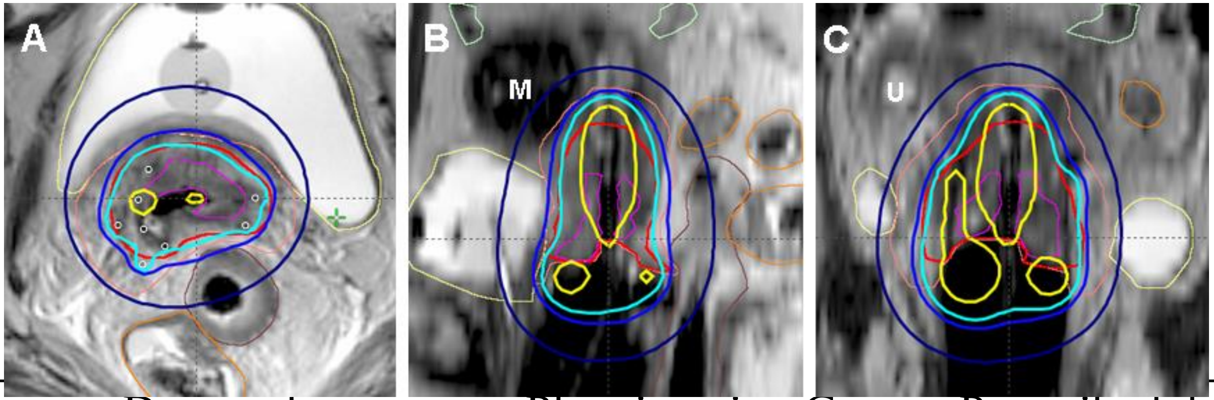
Case 6,

IIIB, IC/IS BT

Appendix,

ICRU 89,

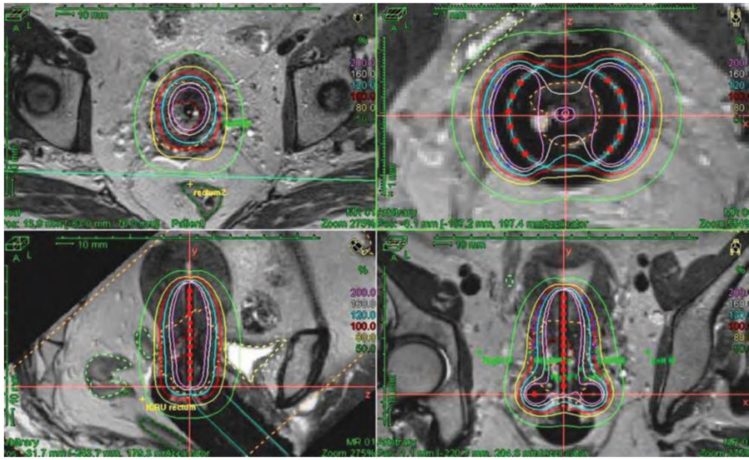
PP201-207



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

Structure	Dose parameter	Planning aim, Gy	Prescribed dose Gy
Target	Point A	7Gy	6.5Gy
Bladder	ICRU point	≤ 7Gy	6.8 Gy
Rectum	ICRU point	≤ 75% of 7Gy	5.3 Gy

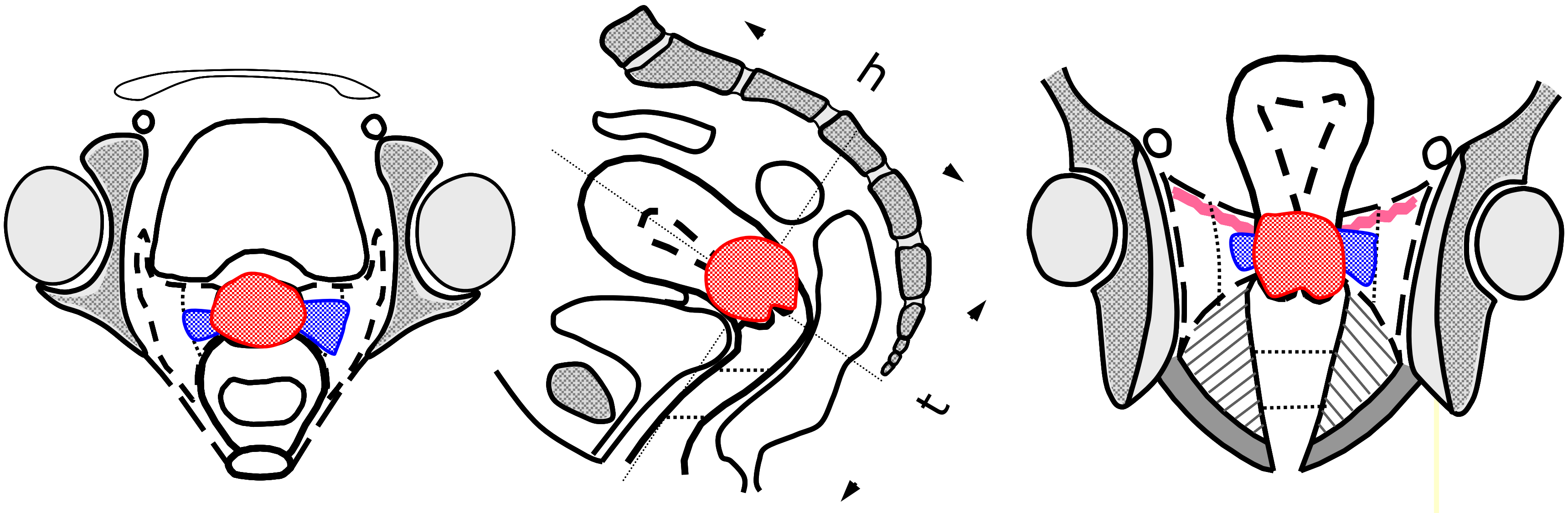
Example: Cervical Cancer Stage IIB (6 cm), N0, CCRT (3D CRT), MRI, Ring and Needles, HDR BT

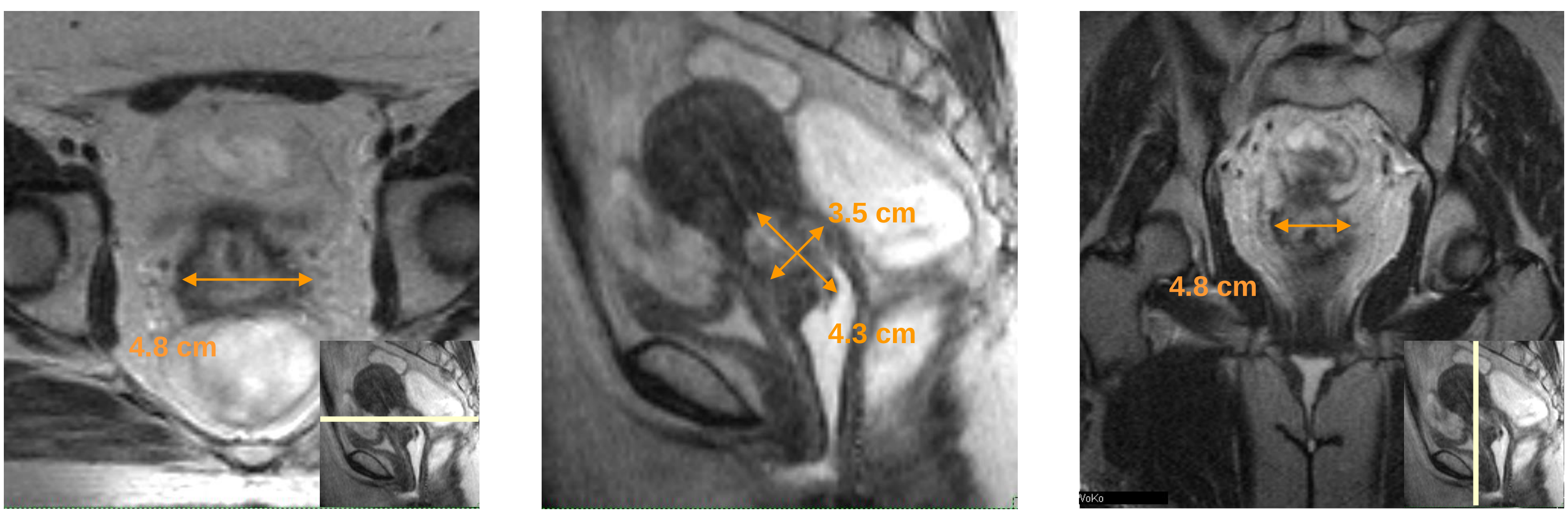
(case 5, ICRU 89, page 193-199)

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

	1st application	2nd application
Nominal tandem length	60 mm	60 mm
Nominal ring diameter	30 mm	30 mm
Number of active needles	3	3
TRAK	2 x 4.3 mGy	2 x 4.2 mGy
60 Gy volume	*262 cm^3*	*250 cm^3*
75 Gy volume	*181 cm^3*	*168 cm^3*
85 Gy volume	*85 cm^3*	*83 cm^3*

Example (dose points) (Appendix case 5, ICRU 89)

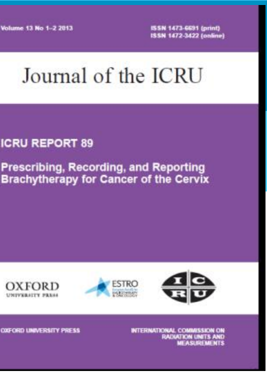
			1st application		2nd application		Total dose
			BT1	BT2	BT3	BT4	EBRT+BT
			(Gy)	(Gy)	(Gy)	(Gy)	(Gy in EQD2)
Point	A	right	x*	x*	x*	x*	x*
		left	7.0	7.0	7.8	7.8	87.2
Pelvic Wall	Point	right	1.1	1.1	1.0	1.0	48.2
		left	1.0	1.0	1.1	1.1	48.2
Bladder	ICRU	point	2.8	2.8	5.5	5.5	68.4
Recto-Vaginal	ICRU	point	2.4	2.4	3.5	3.5	57.5
Vagina	5 mm	right	7.5	7.5	7.6	7.6	106.9
		left	7.3	7.3	7.2	7.2	102.7
	PIBS**	+2 cm	5.9	5.9	6.3	6.3	88.8
		0 cm	2.6	2.6	2.4	2.4	53.4
		- 2 cm	0.6	0.6	0.7	0.7	7.3

Example (DVH parameters) (Appendix case 5, ICRU 89)

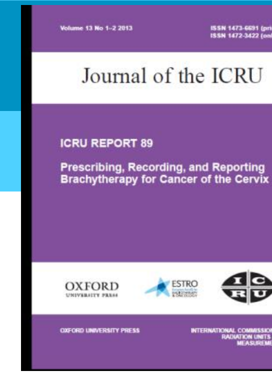
		1st application		2nd application		Total dose
		BT1	BT2	BT3	BT4	EBRT+BT
		(Gy)	(Gy)	(Gy)	(Gy)	(Gy in EQD2)
GTV_{res}	D_{98}	10.1	10.1	10.7	10.7	115.0
	D_{90}	11.9	11.9	12.4	12.4	134.0
CTV_{HR}	D_{98}	6.5	6.5	6.7	6.7	80.8
	D_{90}	7.9	7.9	8.1	8.1	92.3
	D_{50}	11.7	11.7	11.5	11.5	127.8
CTV_{IR}	D_{98}	3.7	3.7	4.1	4.1	62.3
	D_{90}	4.6	4.6	5.3	5.3	69.0
	D_{50}	8.5	8.5	8.7	8.7	97.6
Bladder	$D_{0.1cm^3}$	7.2	7.2	7.2	7.2	102.0
	D_{2cm^3}	5.6	5.6	5.4	5.4	80.6
Rectum	$D_{0.1cm^3}$	4.8	4.8	5.0	5.0	74.2
	D_{2cm^3}	3.8	3.8	3.9	3.9	64.3
Sigmoid	$D_{0.1cm^3}$	1.9	1.9	4.4	4.4	59.9
	D_{2cm^3}	1.5	1.5	2.6	2.6	51.7

OUTLINE Summary:

Point and Dose volume reporting in cervix cancer brachytherapy



available through: www.oxforduniversitypress (258 pp)



- **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 reporting (9-30)**
- **Advanced standards for reporting (31-47)**
- **Equi-effective Doses and total dose reporting (48-50)**
- **Limitations (51-54)**
- **From Planning Aims to Prescription (55-58)**
- **Examples ICRU report 89: IIB, HDR BT ring/needles, (59-64)**

Applicator reconstruction, geometry and fusion

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Localization techniques

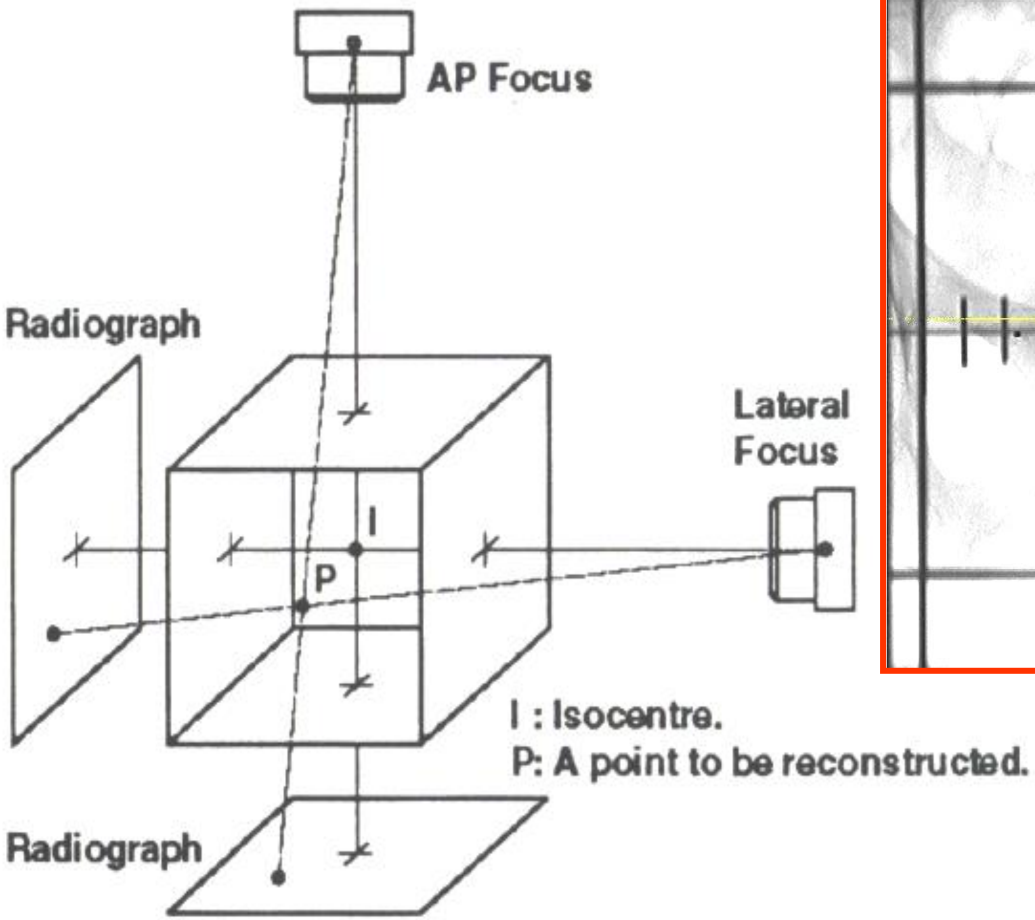
Conventional simulator, C-arm

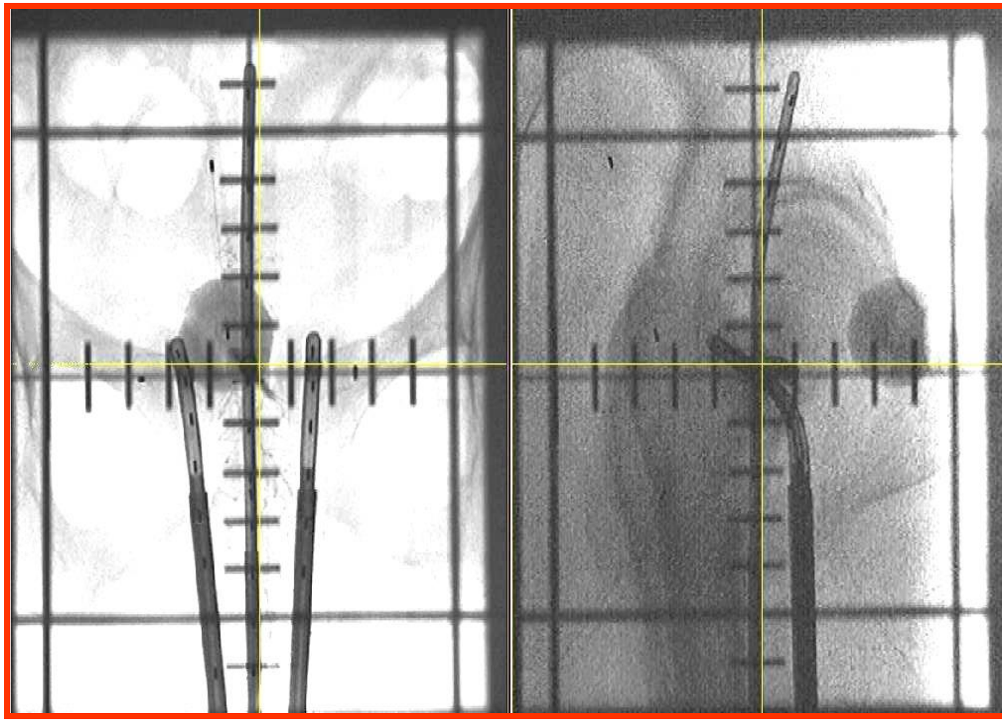
- Orthogonal images
- Semi-orthogonal
- Variable angle
- Stereo-shift

3D sectional images

- CT
- MR

Orthogonal images





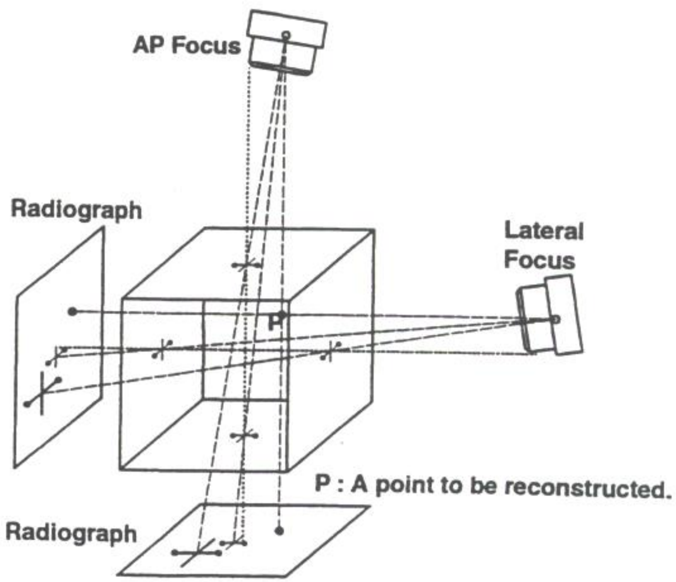
- Magnification = FFD/FAD
- Markers locked
- may not be useful for Ring applicators

From: Plato user manual

Semi-orthogonal

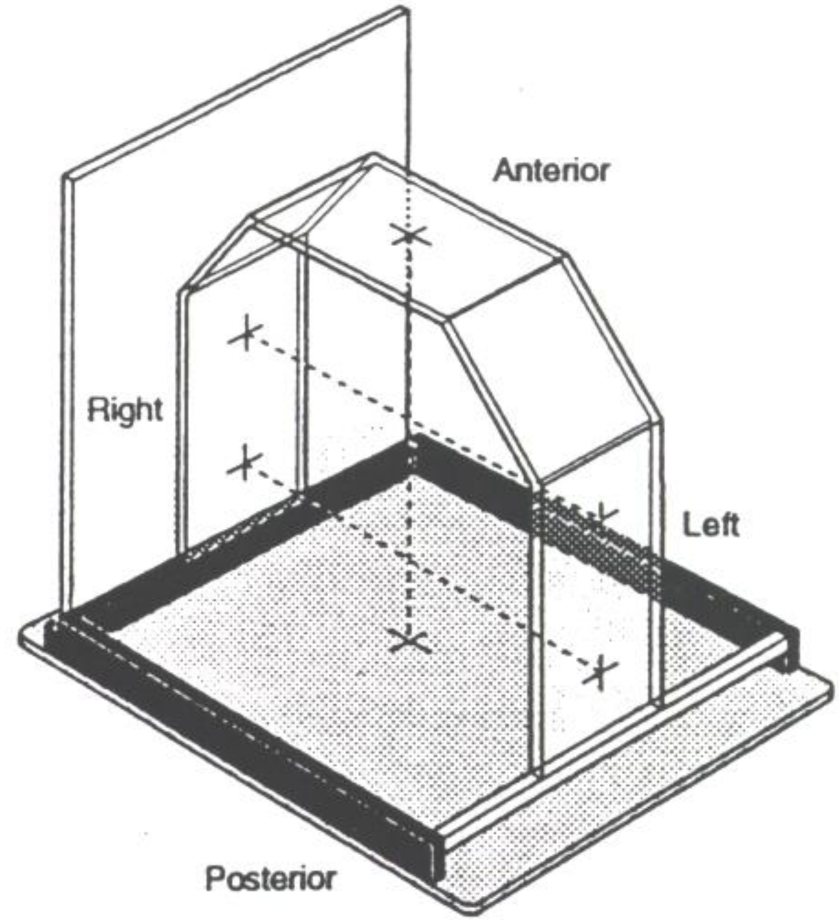
Note

If there is only a portable or mobile radiographic unit available, the semi-orthogonal reconstruction method is the only technique for treatment planning .



Reconstruction Box

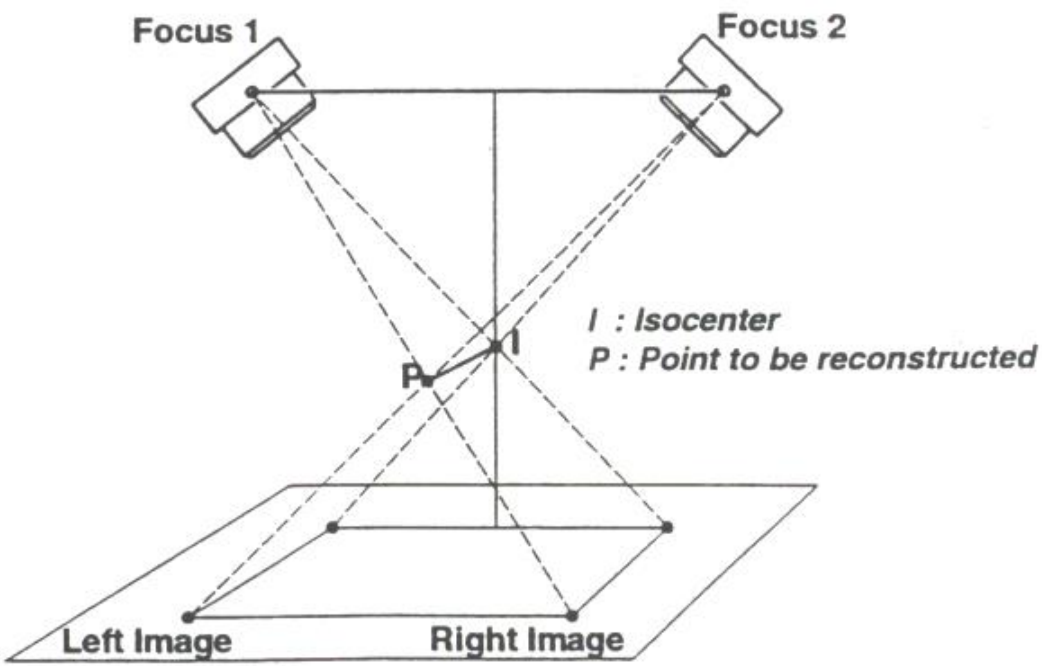
The reconstruction box is constructed with radiopaque initials AP and LAT within the appropriate sides of the box. These initials will appear on the radiograph as a large AP image which corresponds



From: Plato user manual

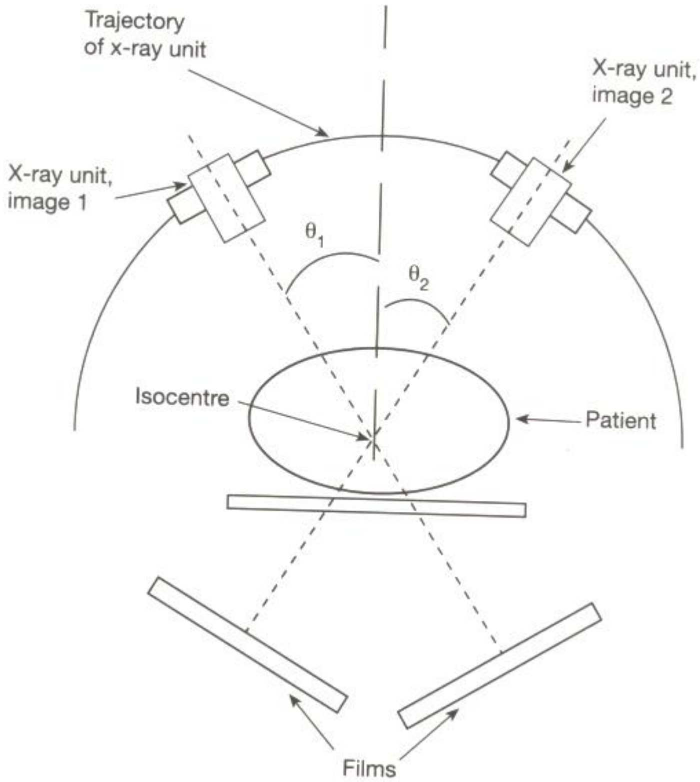
Stereo-shift

This method is particularly useful
when only an X-ray unit is available for localization

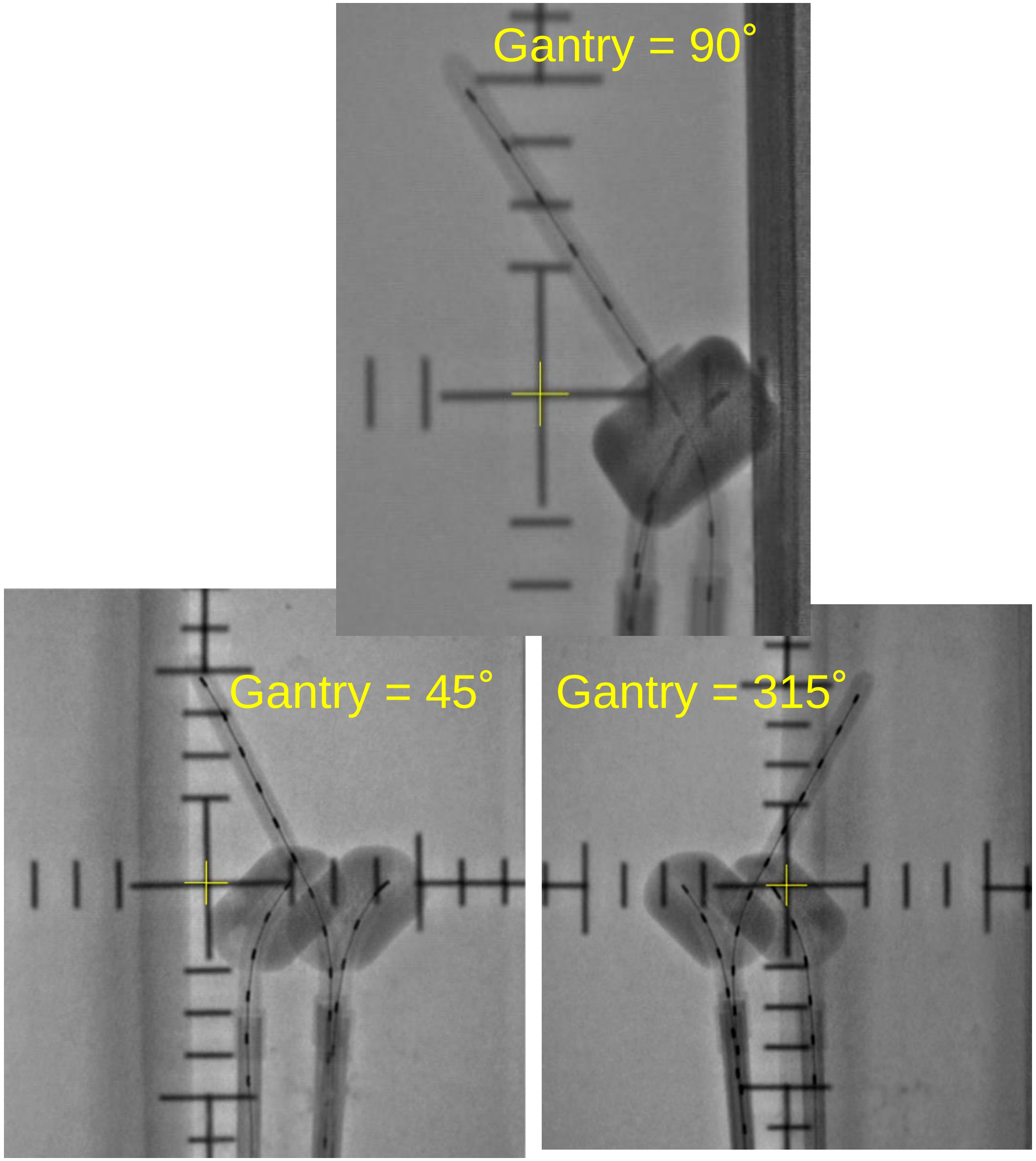


From: Plato user manual

Variable angle



From: Thomadsen "Achieving quality in brachytherapy", IoP 2000

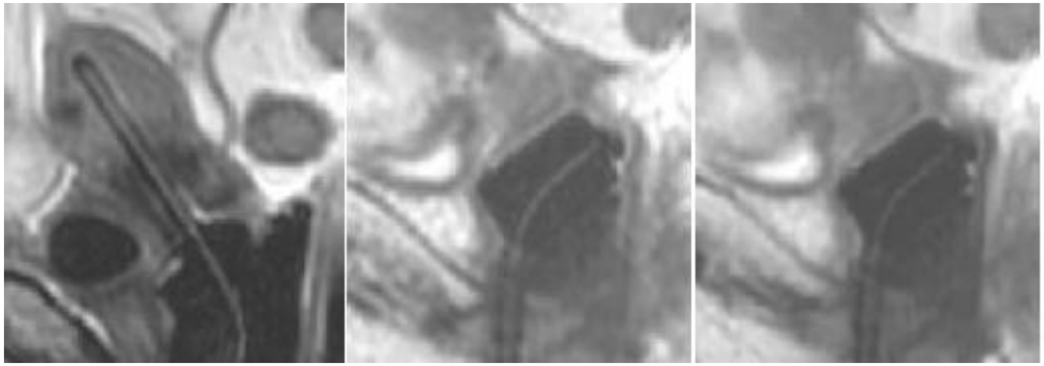


Reconstruction

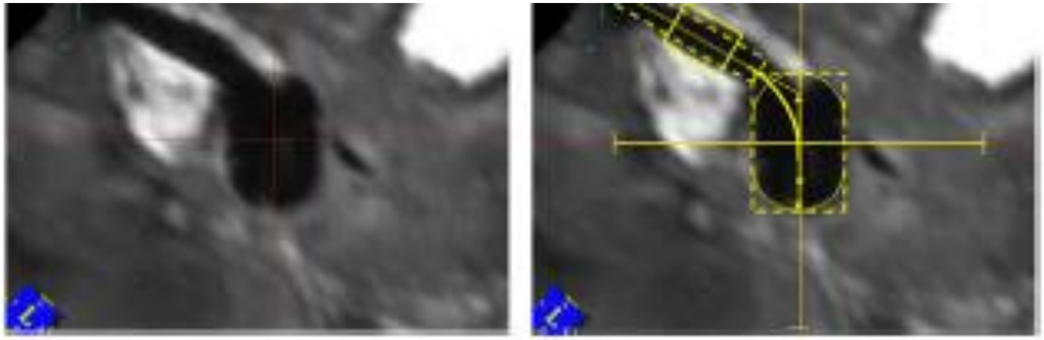
- Direct reconstruction
- Library of applicators

Direct Reconstruction

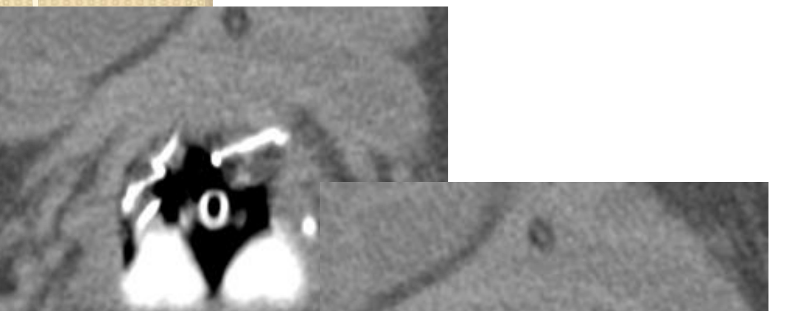
- Clear visualization of the source channels in a single plane.
- Check the geometry of the applicator verified during commissioning.
- Especially useful for curved applicators (ovoid/ring)

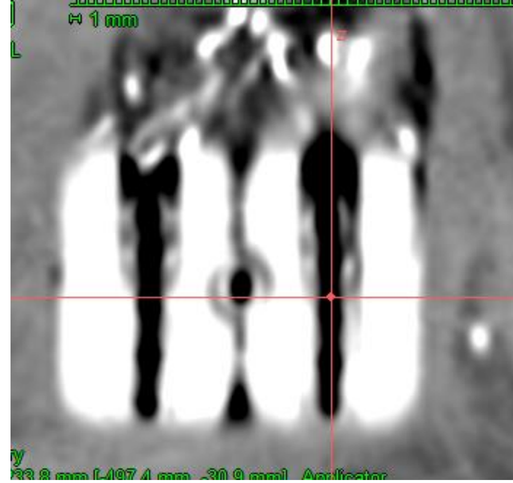


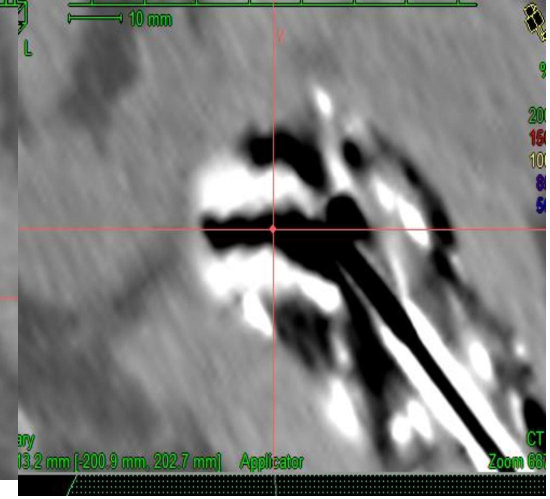
Leeuw et al, RO,2009

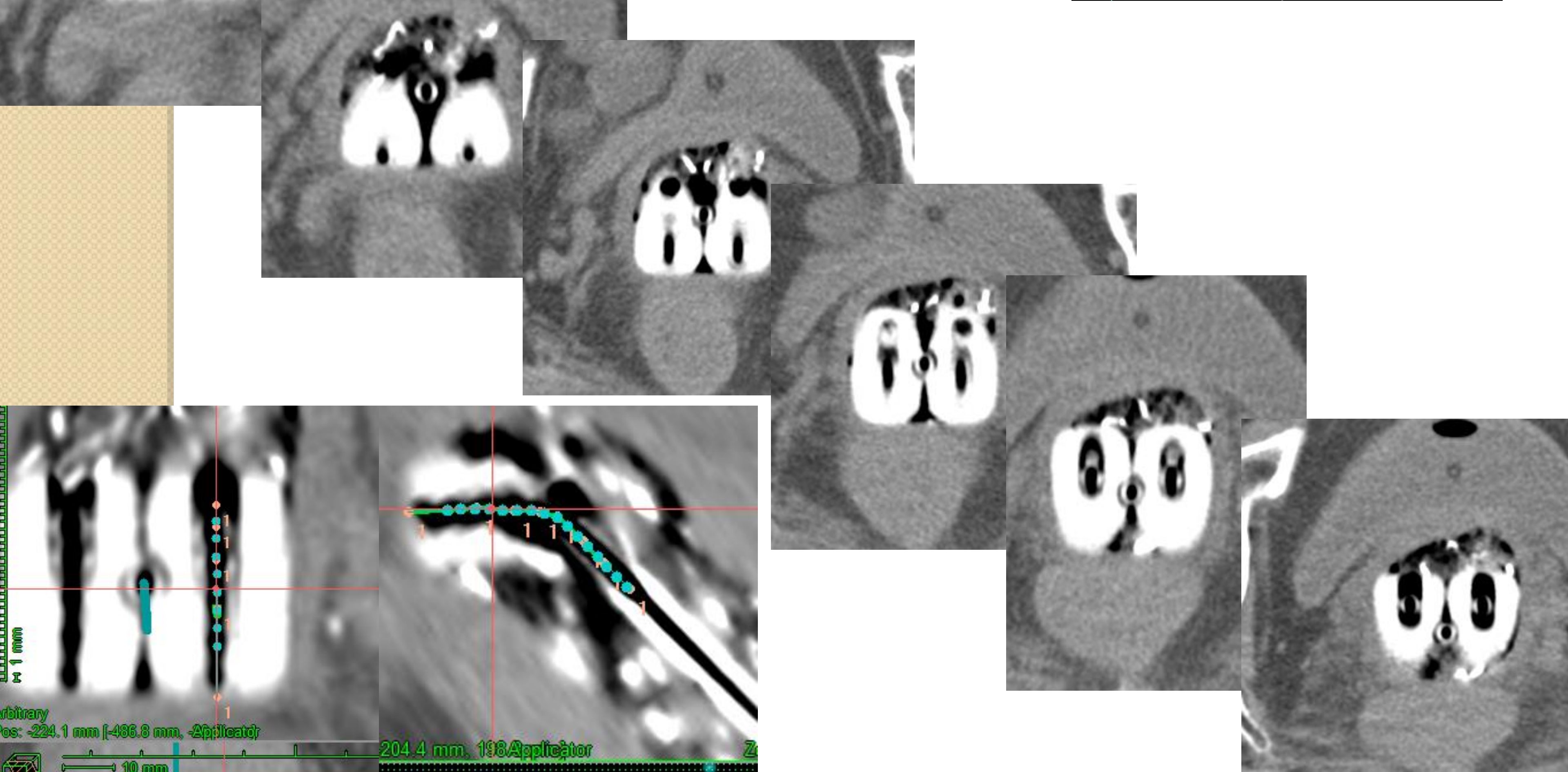


DR - T/O

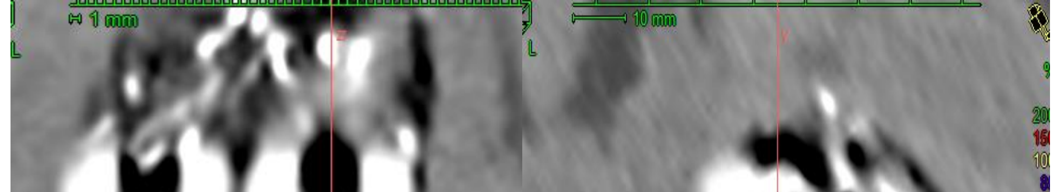


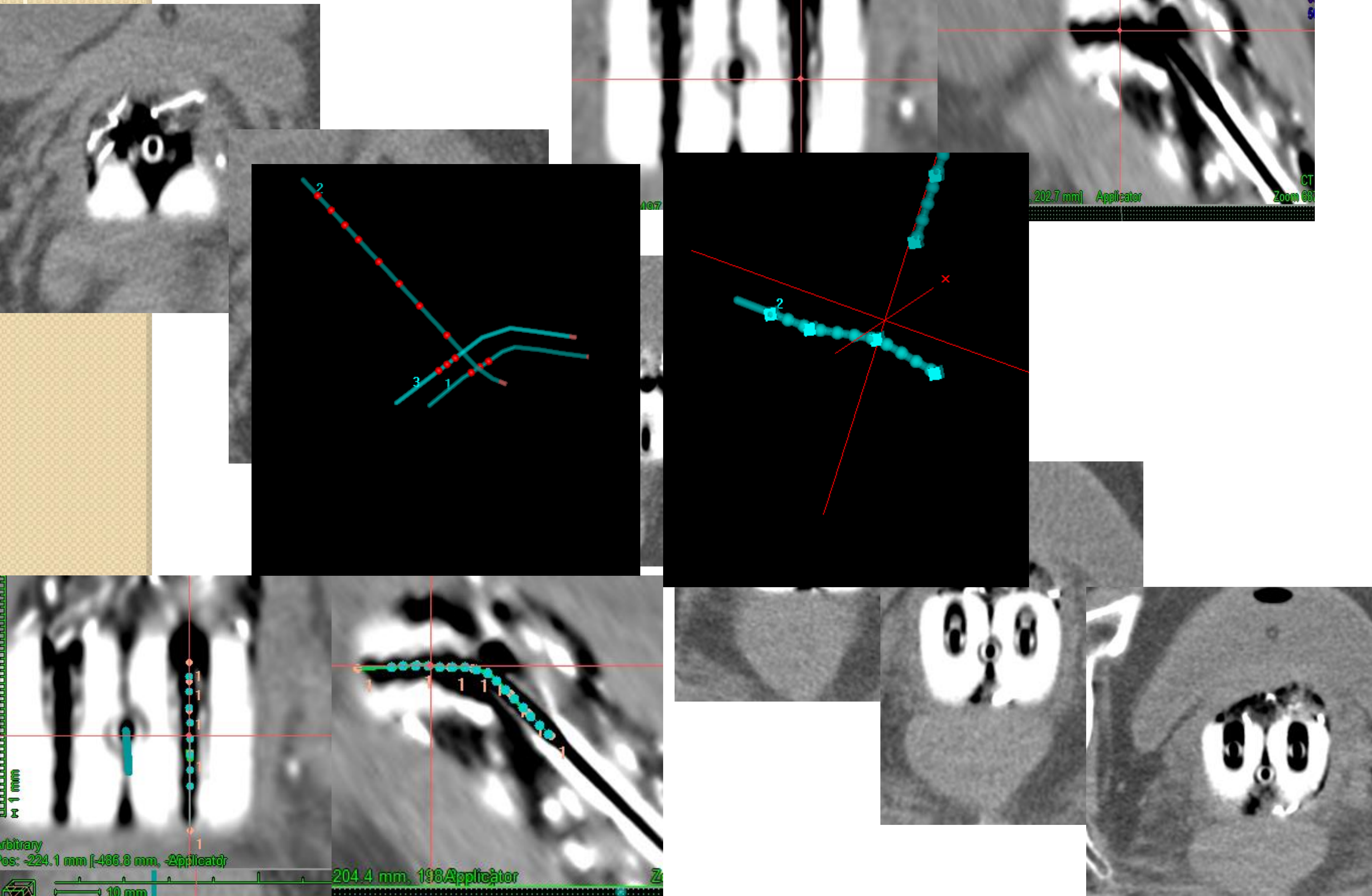






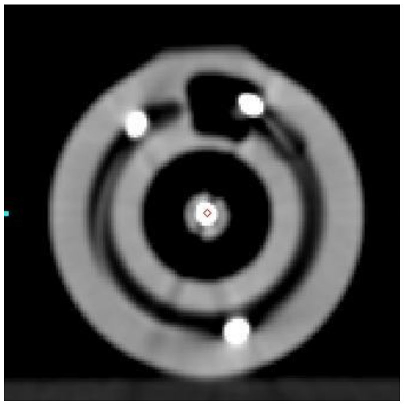
DR – T/O

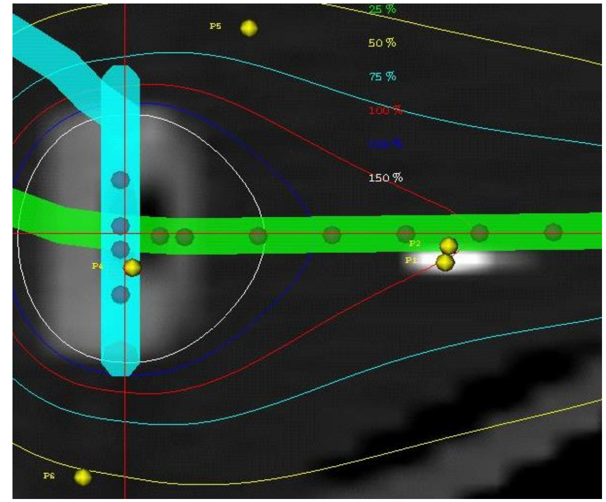




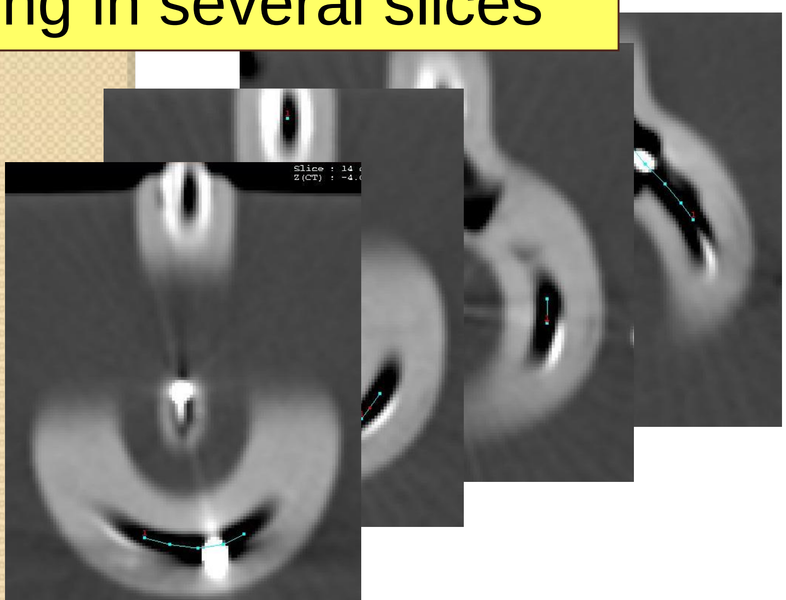
DR - Ring

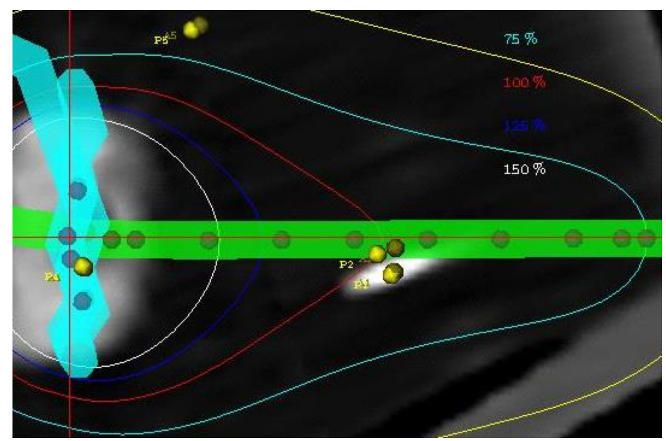
Ring in one slice





Ring in several slices

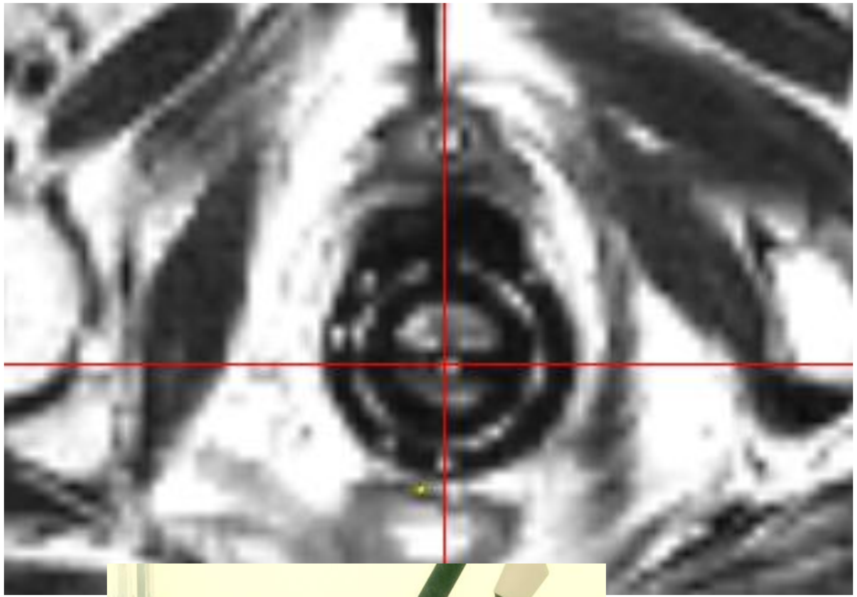


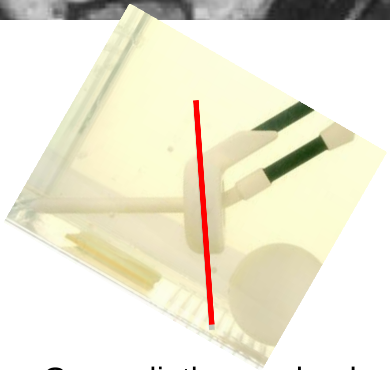


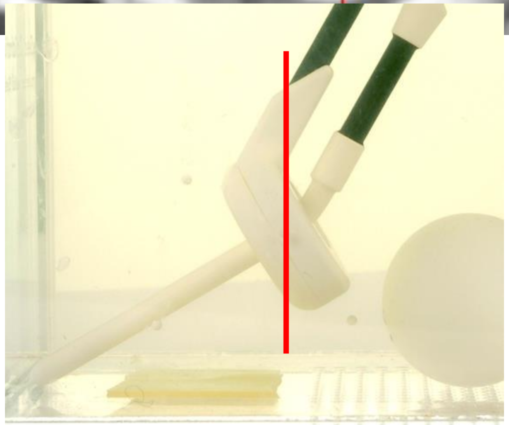
Ack: Hellebust

Orientation of the imaging sequence

- Para transverse
- Transverse (MP Reconstructed)



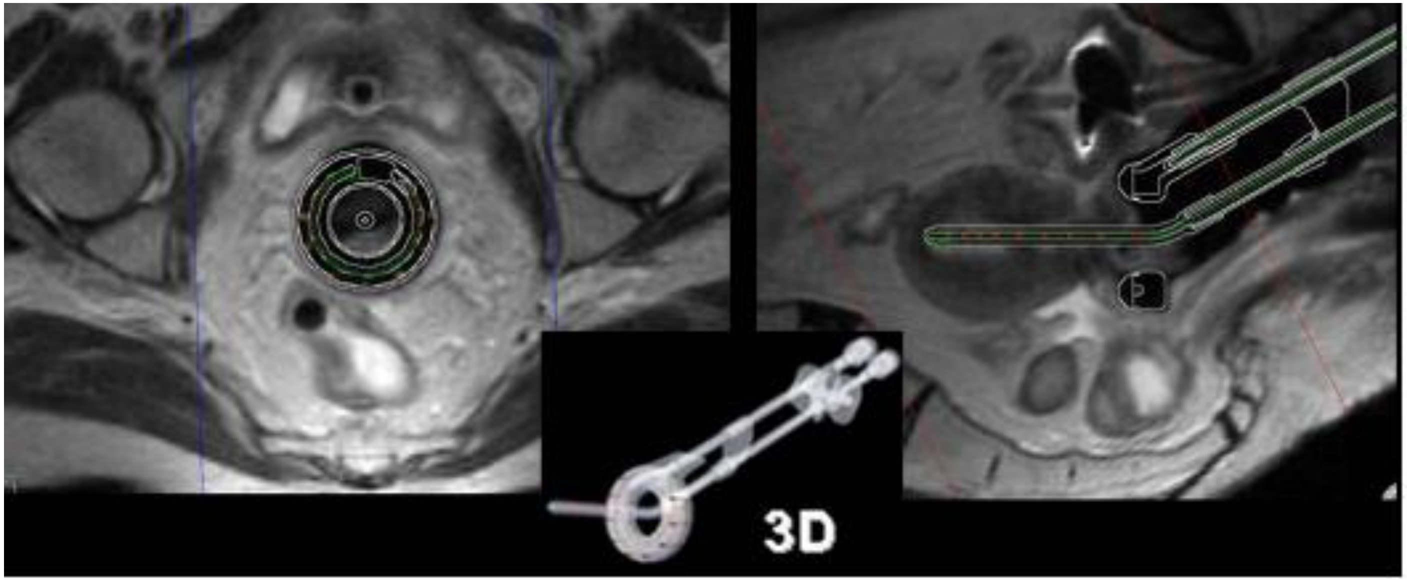




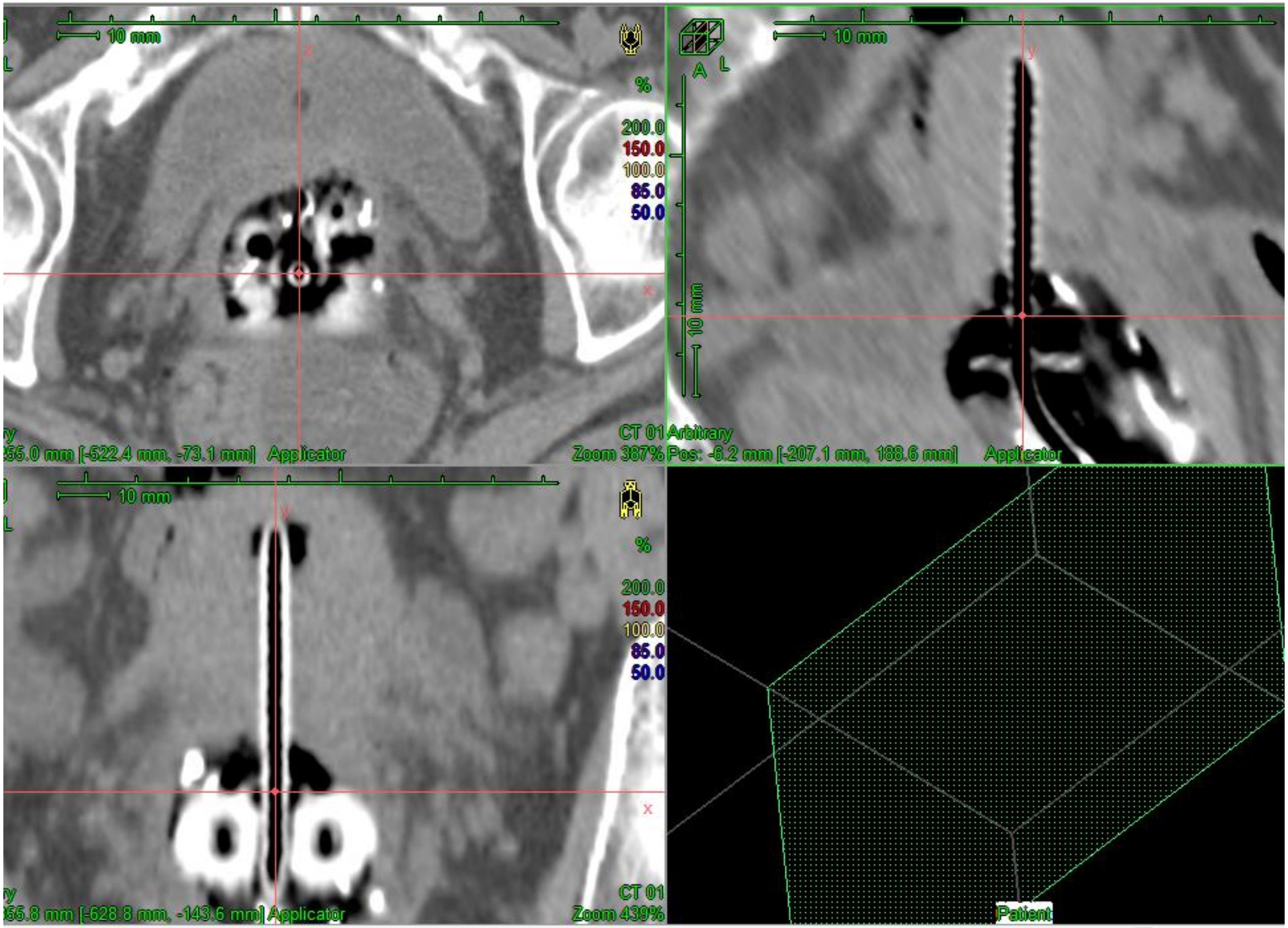
From Gyn radiotherapy book,
Editor: A viswanathan,
Kirisits C, Erickson B, Potter P

Library of applicators

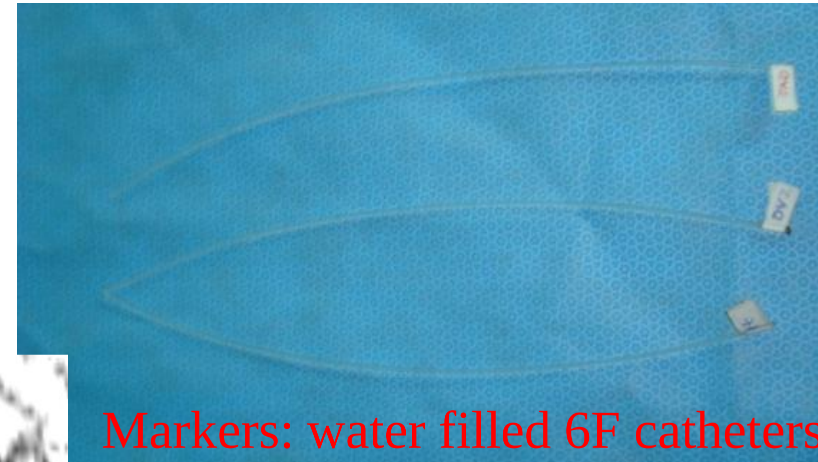
- Some TPSs contain an applicator library which includes information about the physical outer applicator dimensions, an applicator file can be imported and rotated and translated until it matches the black area in the patient MR images
- Fast, simple, and less prone to reconstruction errors.



Applicator reconstruction using CT images



Applicator reconstruction using MR images

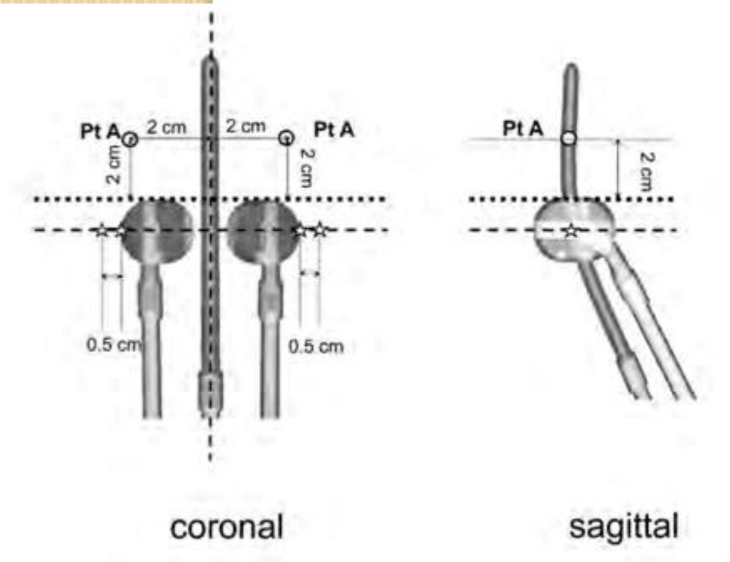


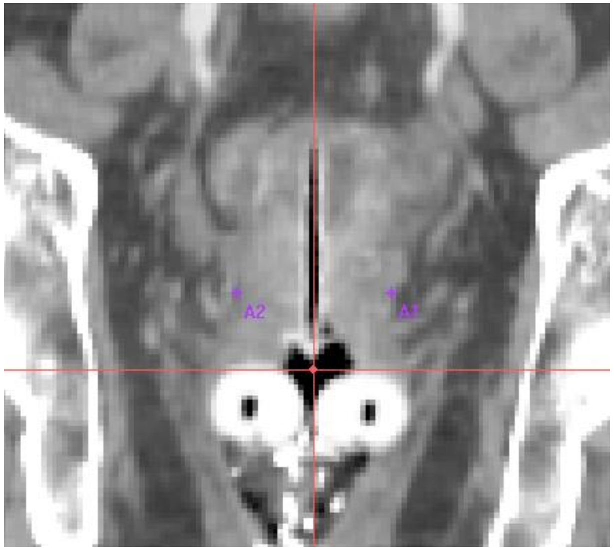
ICRU 89 Reference points

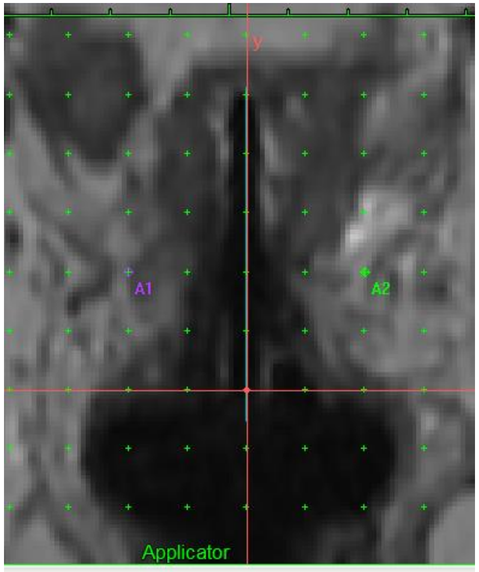
- Point A
- ICRU Bladder
- ICRU Recto Vaginal
- PIBS
- Vaginal points

Point A - Tandem/Ovoid

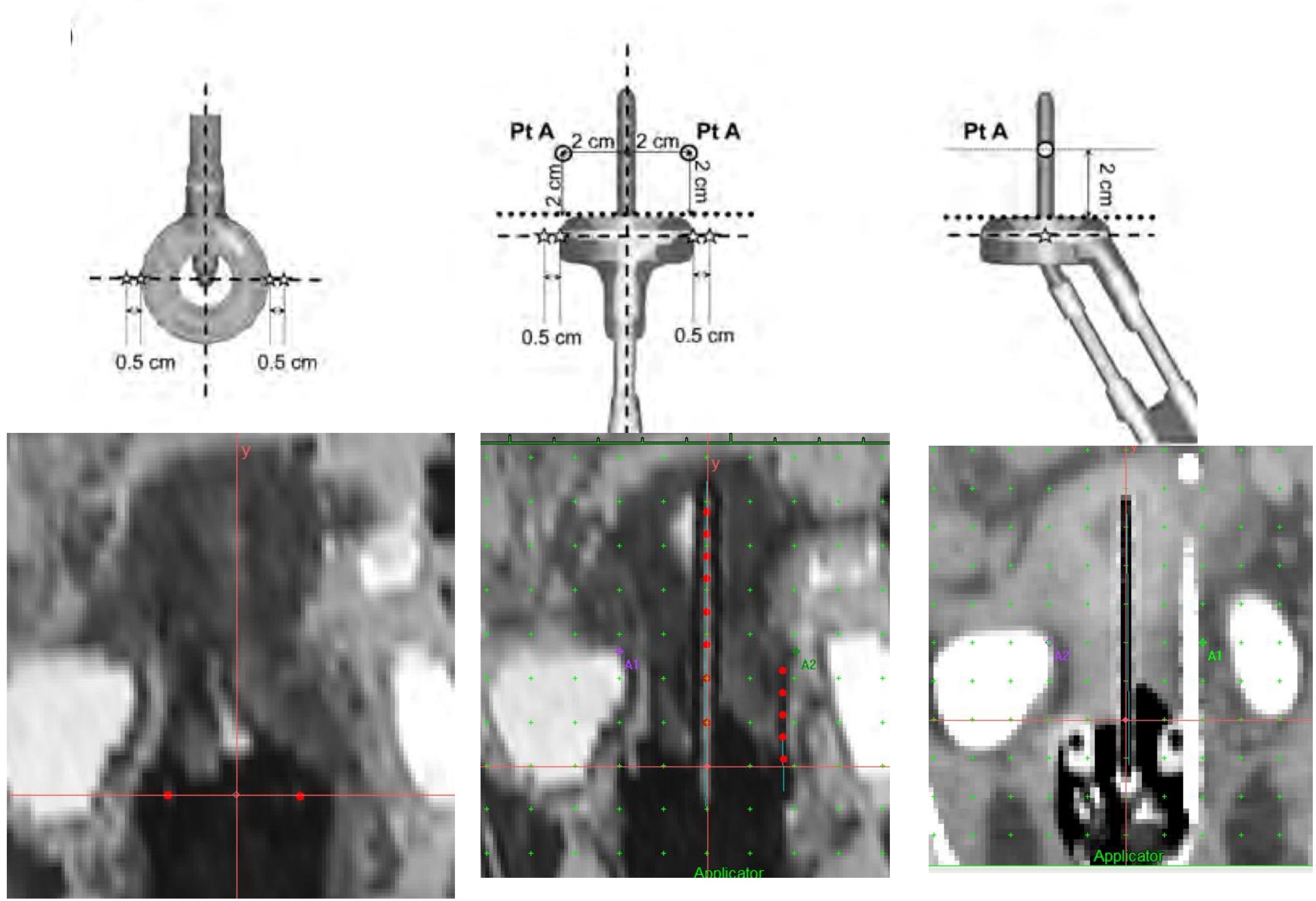
- 2cm lateral to the center of uterine canal and 2 cm above from the mucosa of the lateral fornix



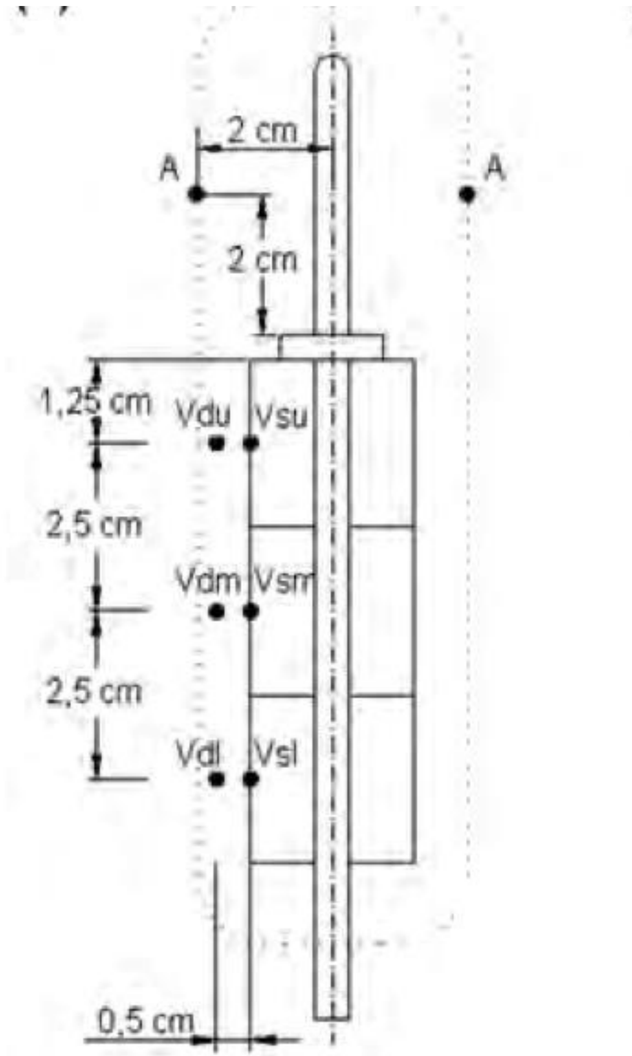




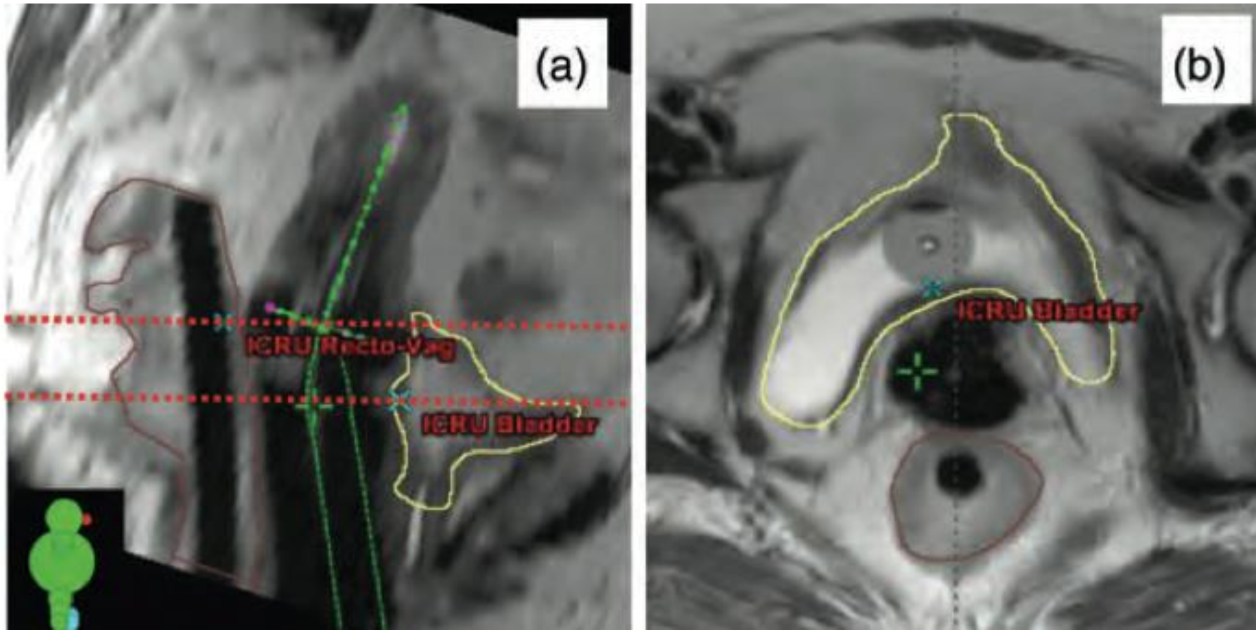
Point A - Tandem/Ring

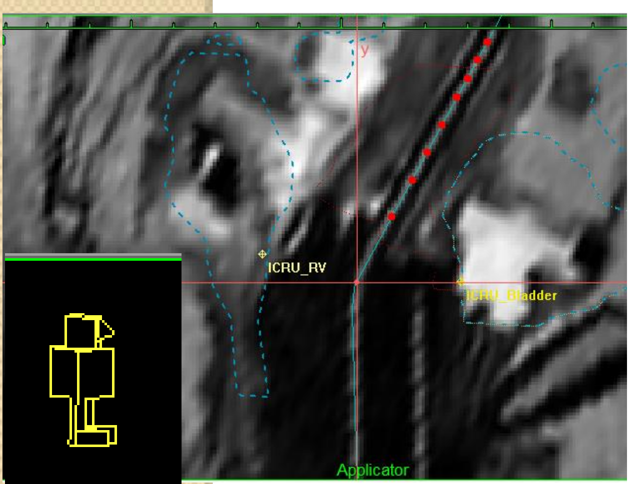


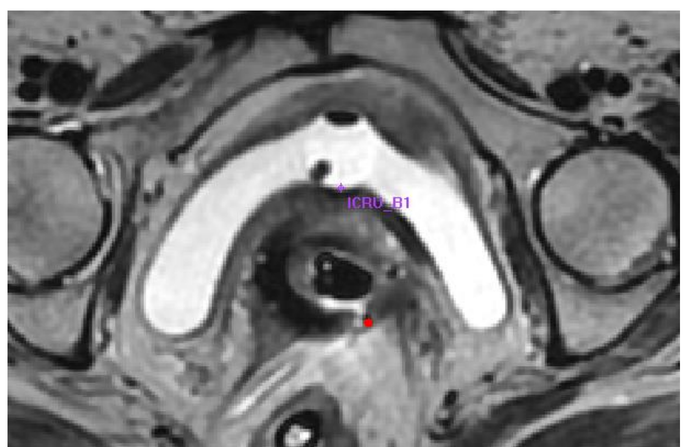
Point A – Vaginal cylinder & tandem

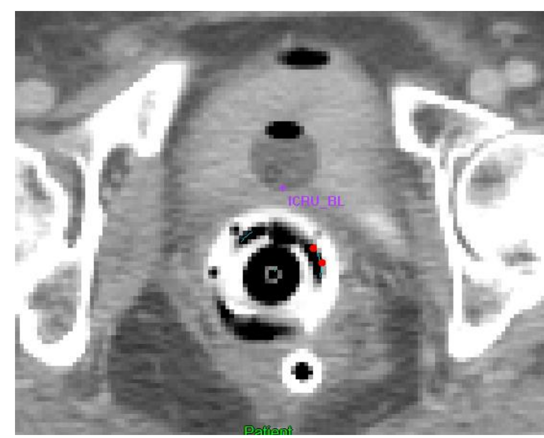


ICRU 89 Bladder point

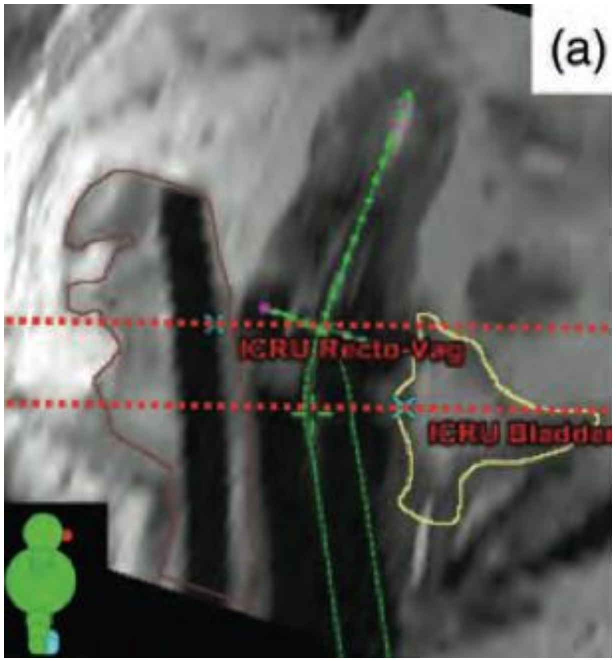


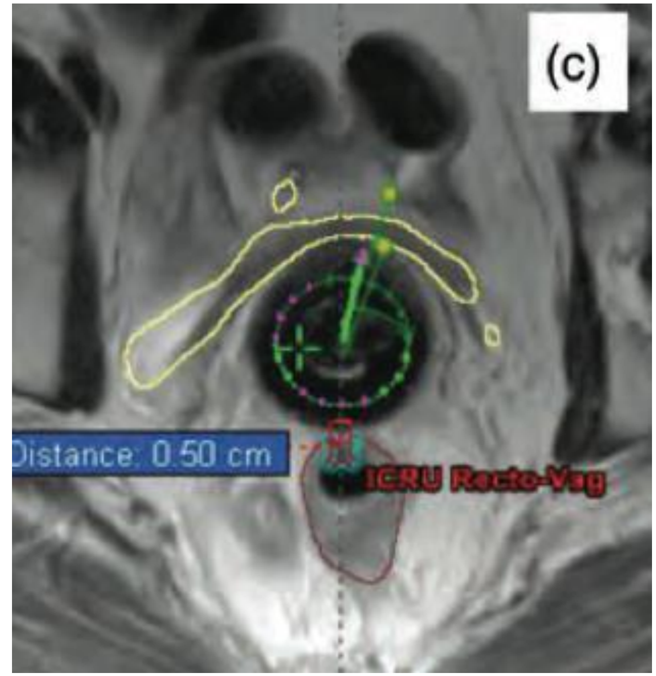


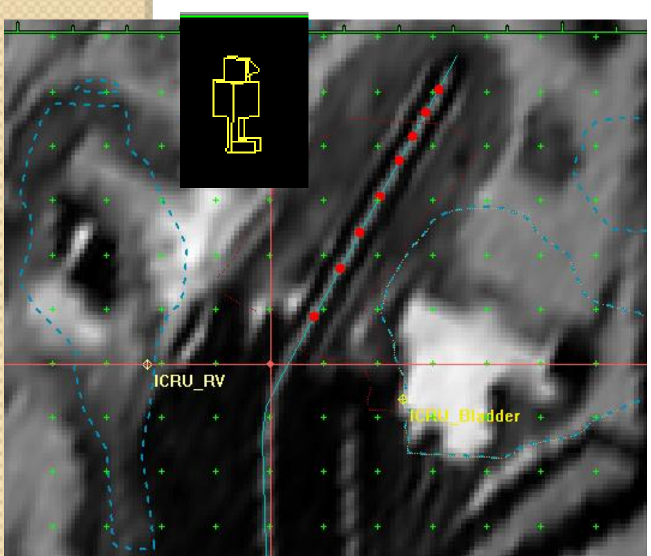


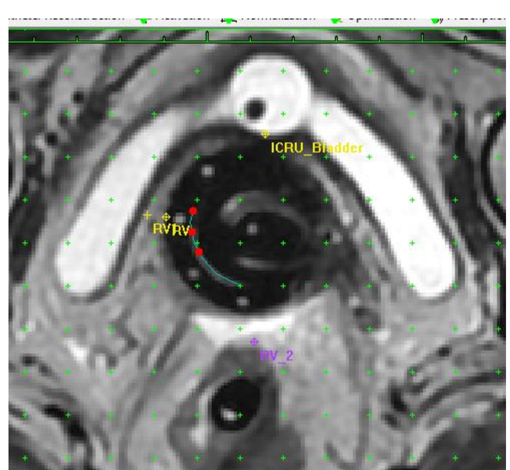


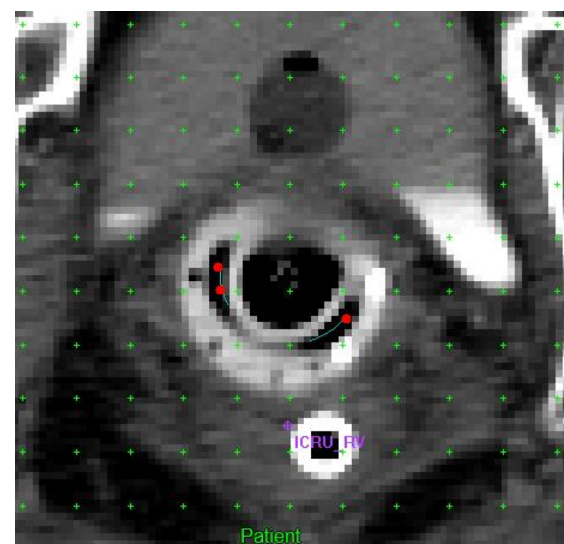
ICRU 89 Recto Vaginal point



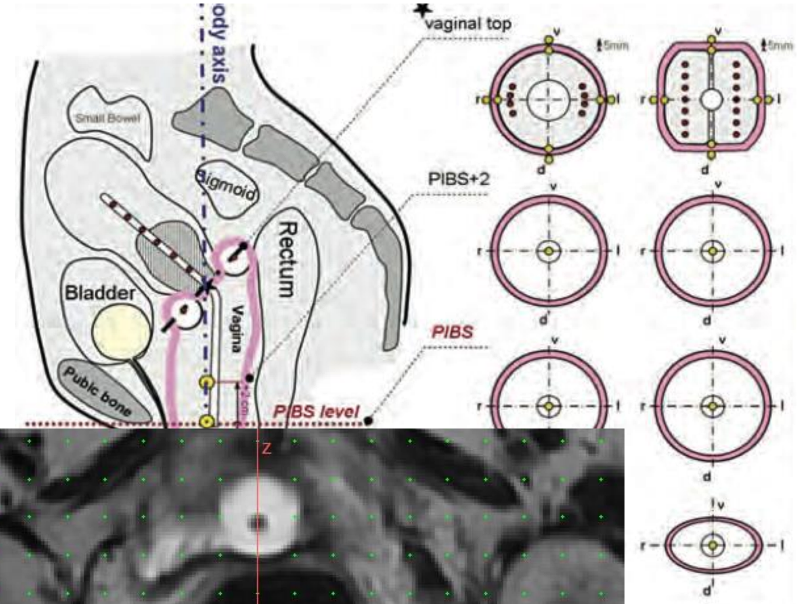


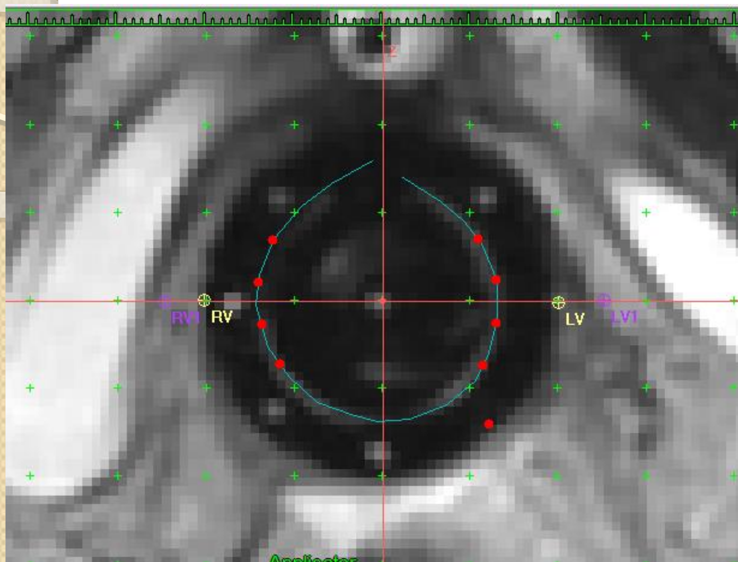


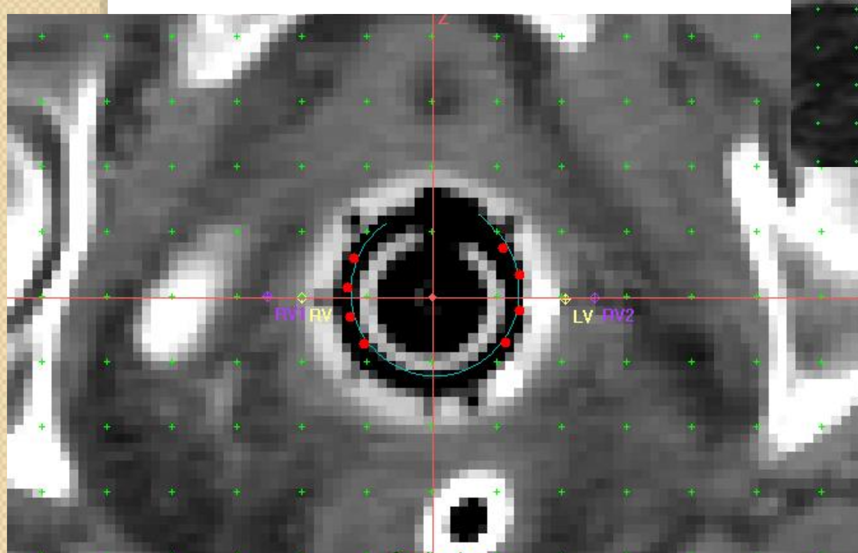


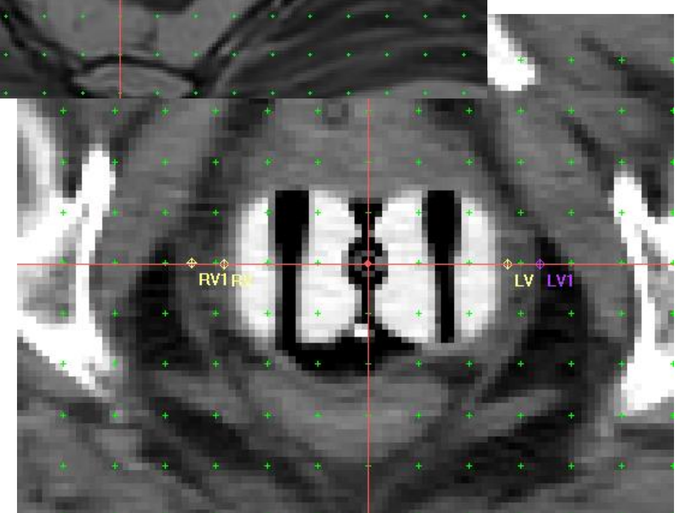


Vaginal points

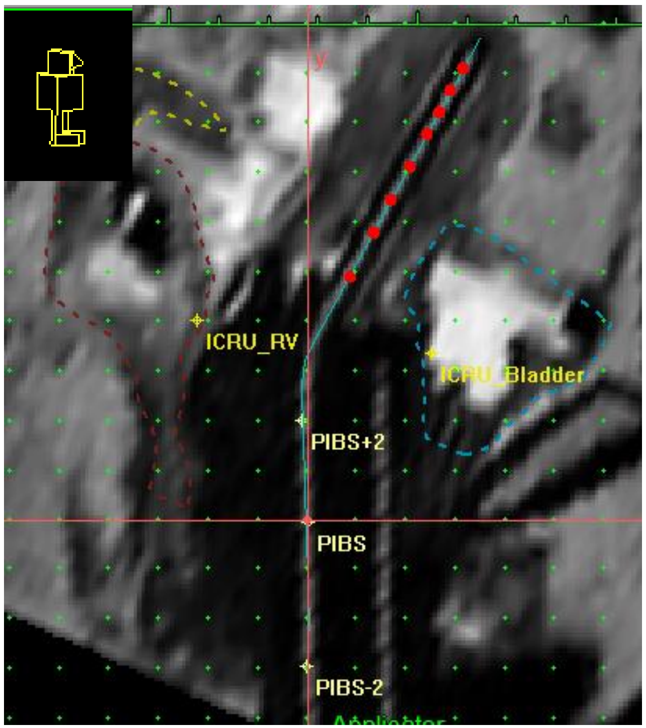


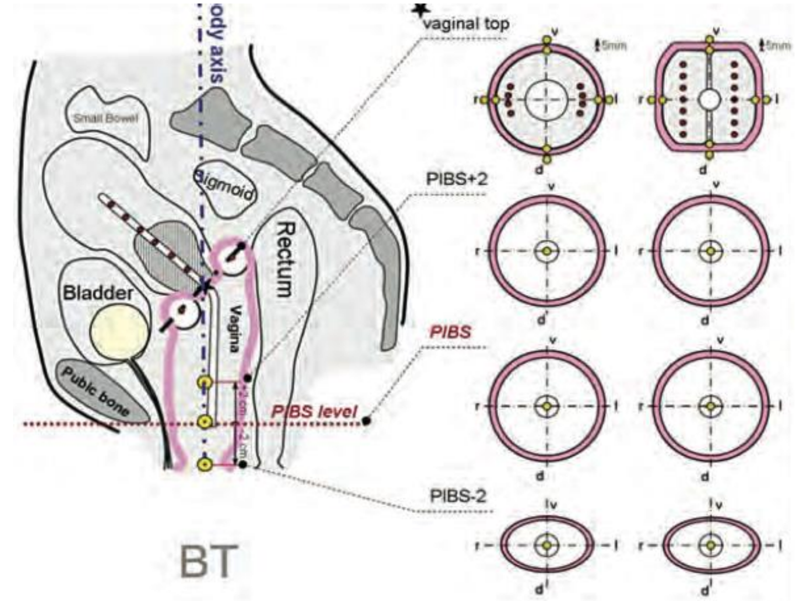


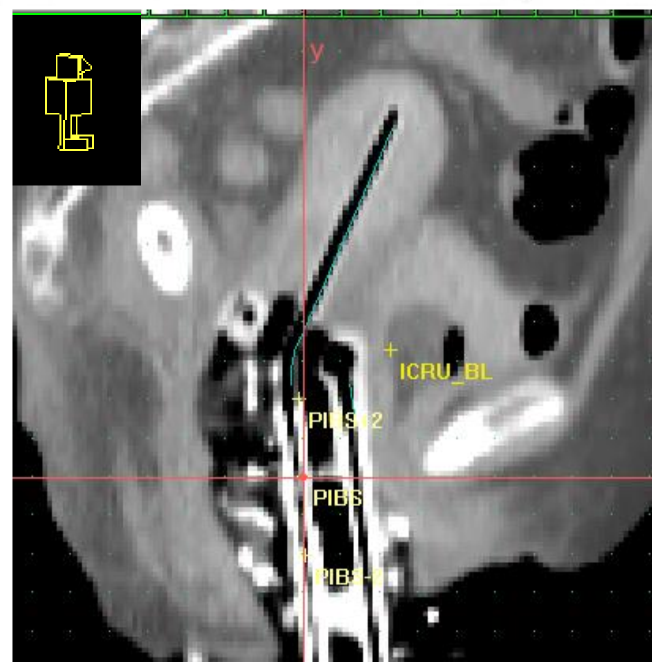




PIBS

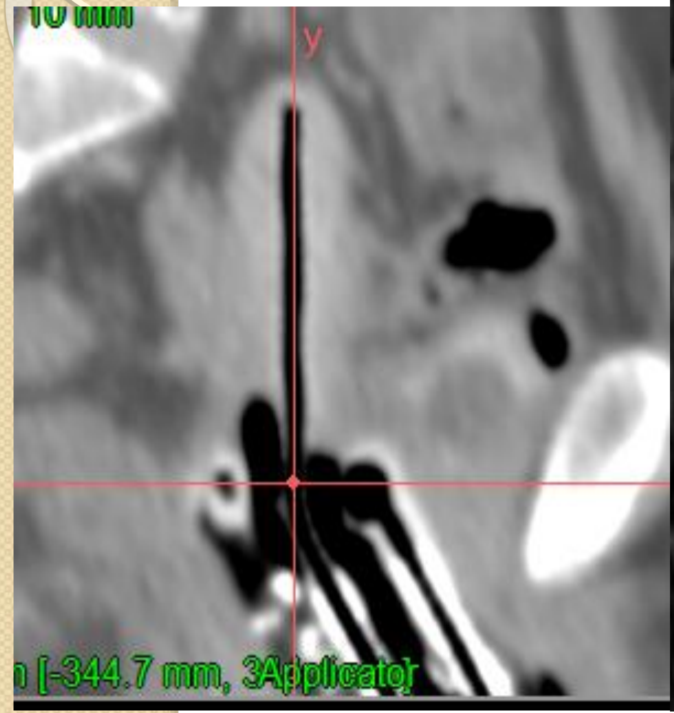

ICRU_RV
ICRU_Bladder
PIBS+2
PIBS
PIBS-2


vaginal top
Small Bowel
Sigmoid
Rectum
Bladder
Vagina
Pubic bone
PIBS level
PIBS+2
PIBS
PIBS-2
BT


ICRU_BL
PIBS+2
PIBS
PIBS-2

Role of Registration in applicator reconstruction

Role of registration: applicator Reconstruction

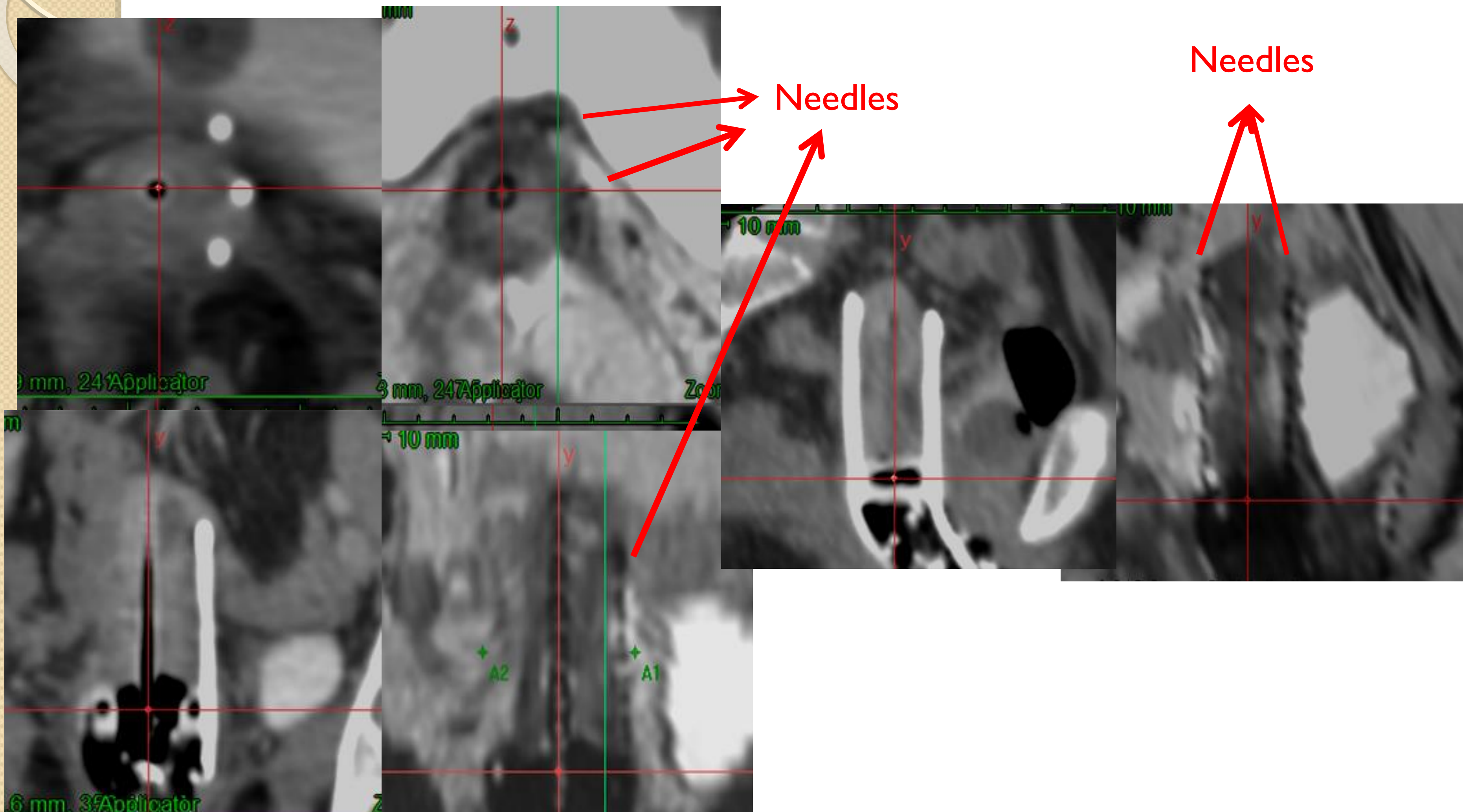


CT – No marker

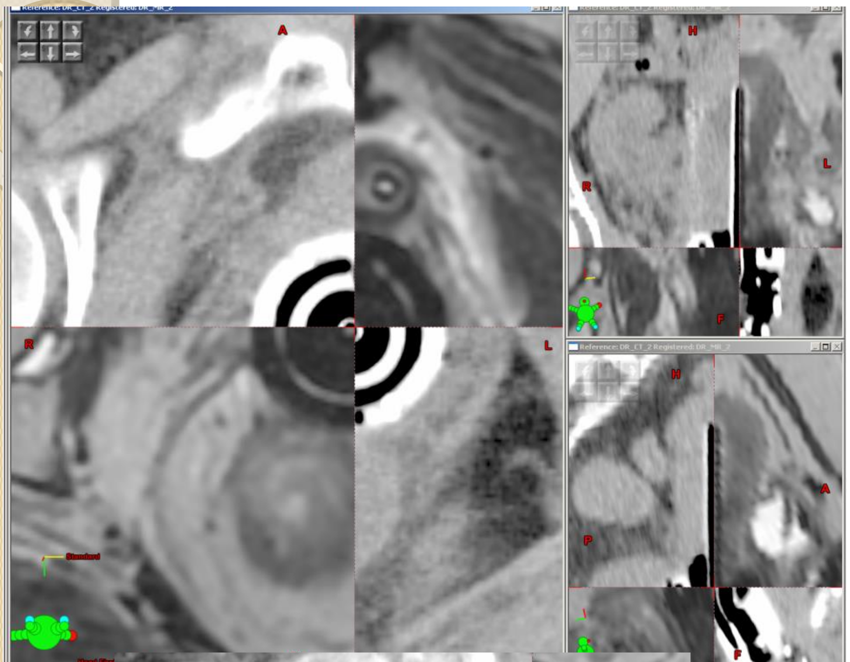
MR – No marker

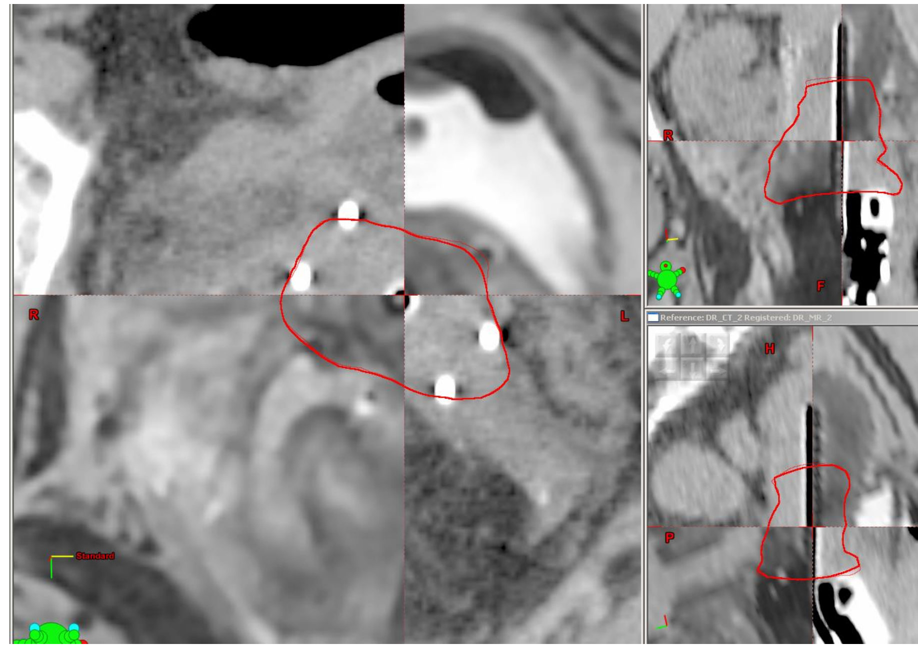
MR – Water marker

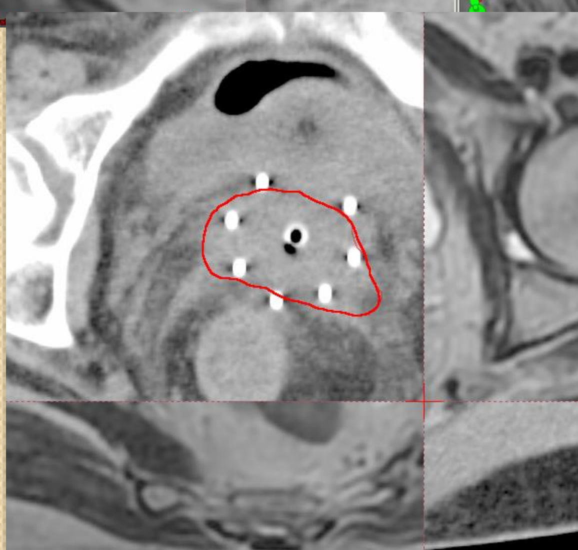
Role of registration: applicator Reconstruction : needles

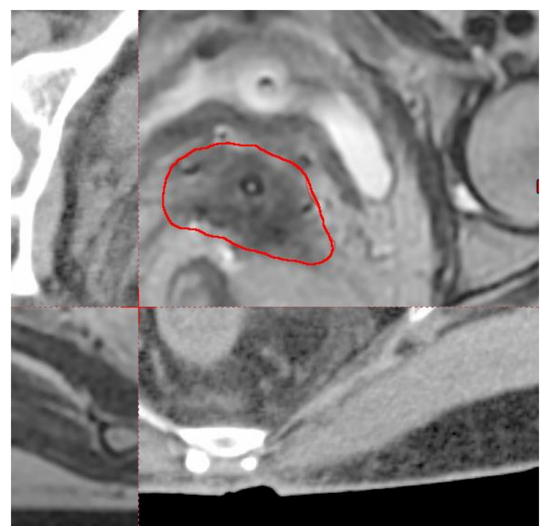


CT vs MR

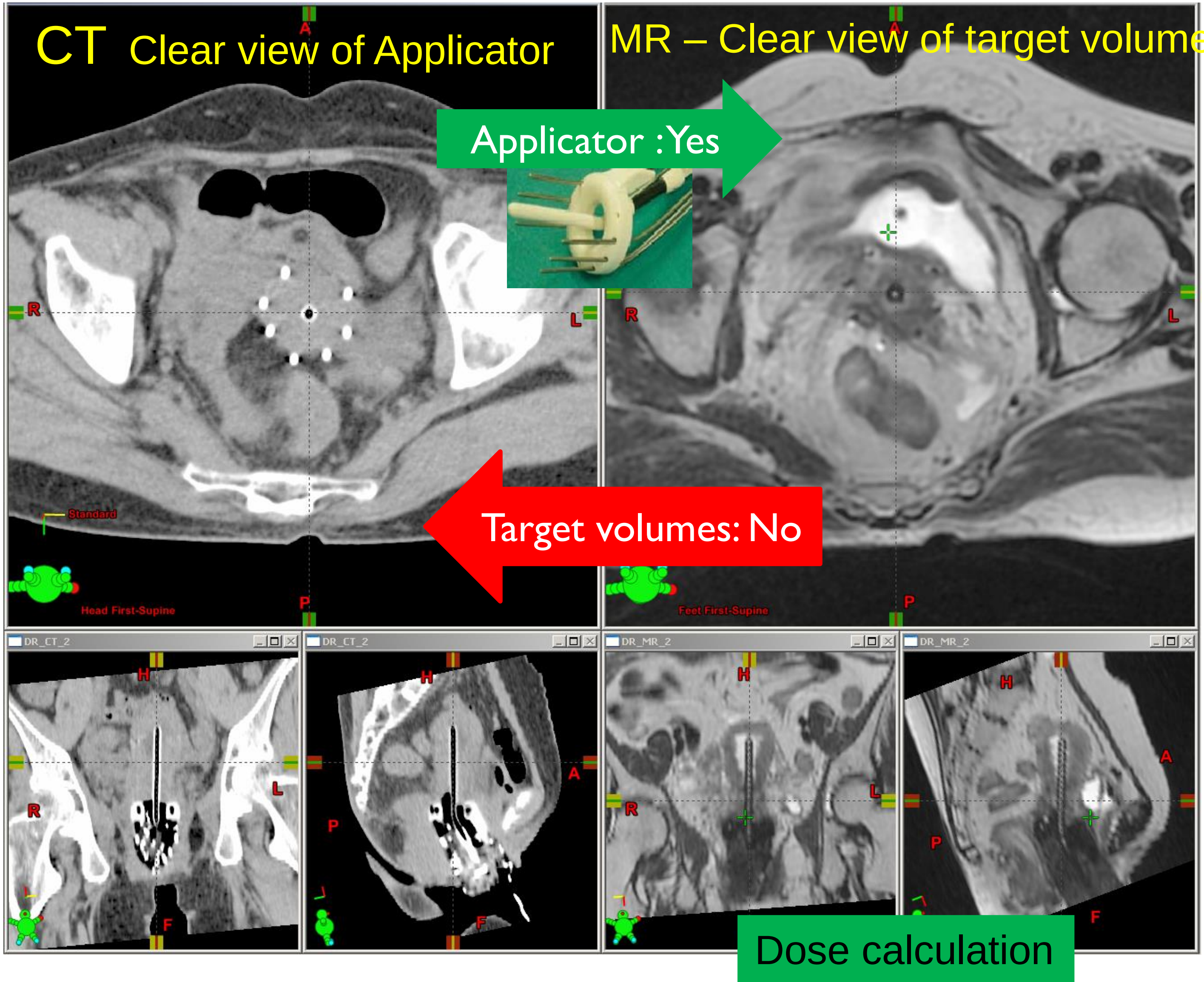






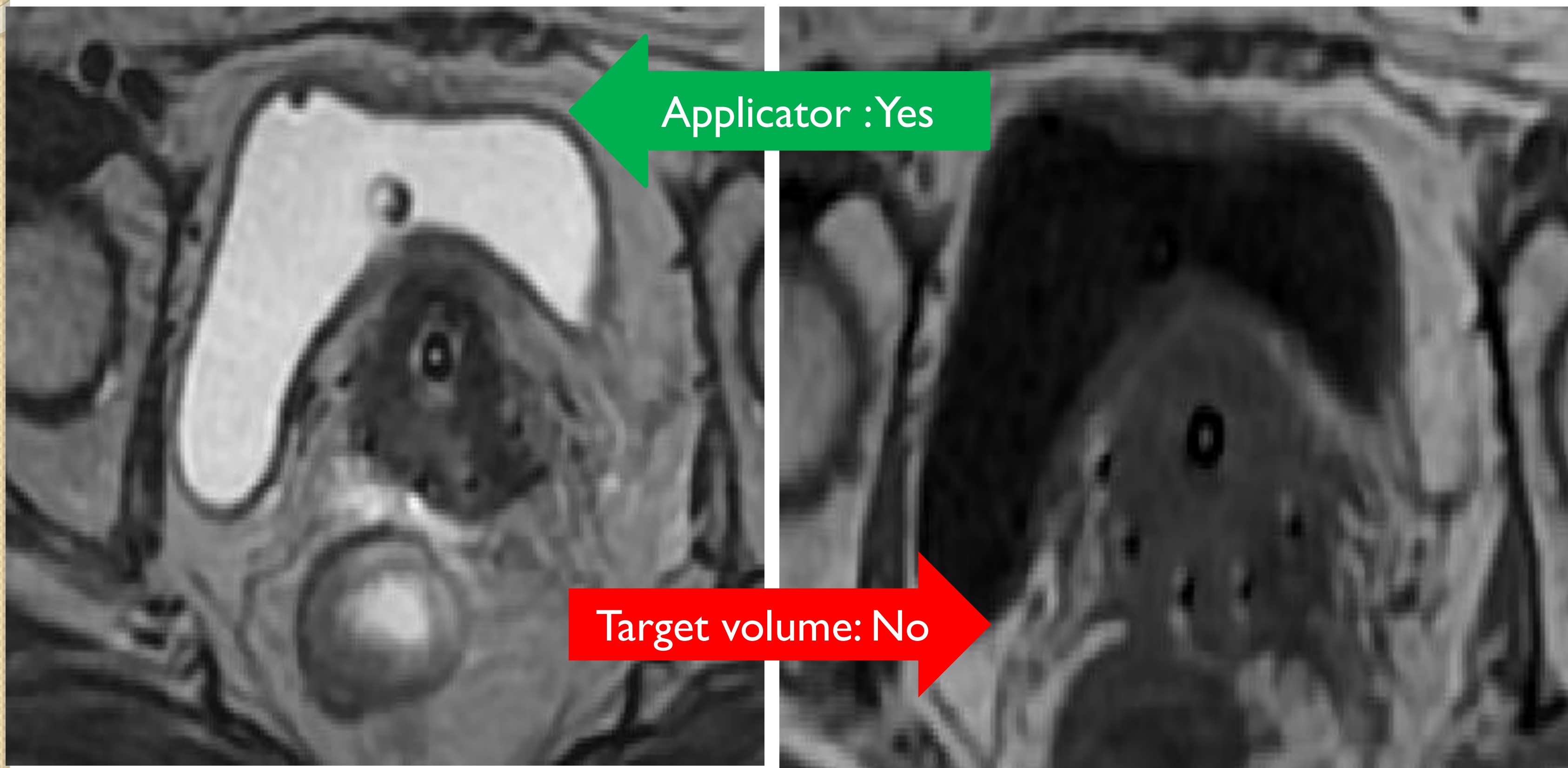


Registration of CT vs MR – Reconstruction

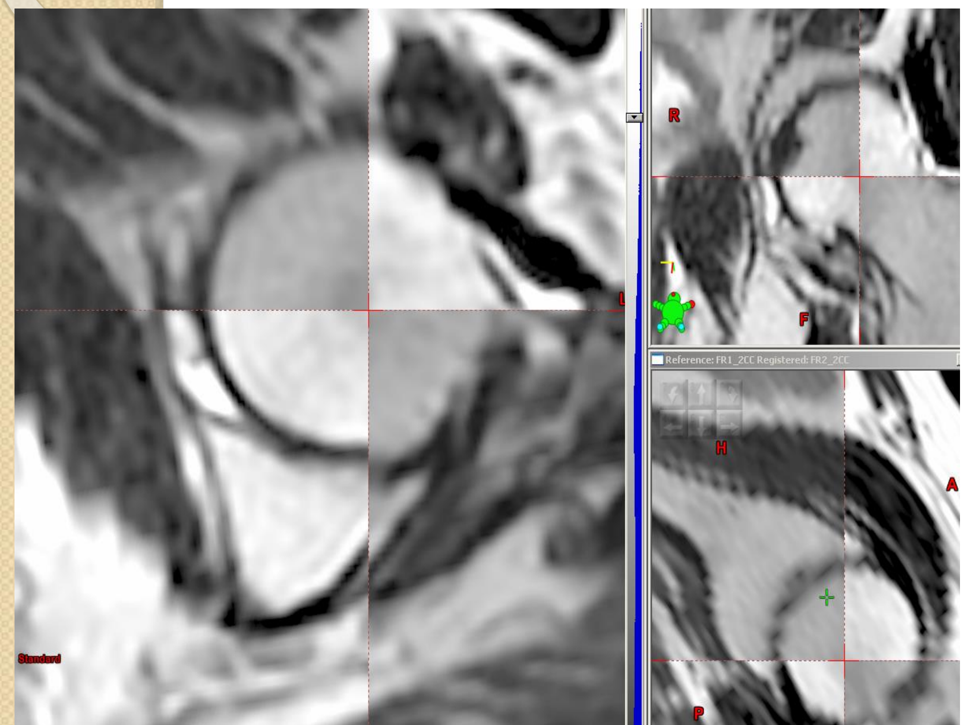


Registration of T1 vs T2 for Reconstruction

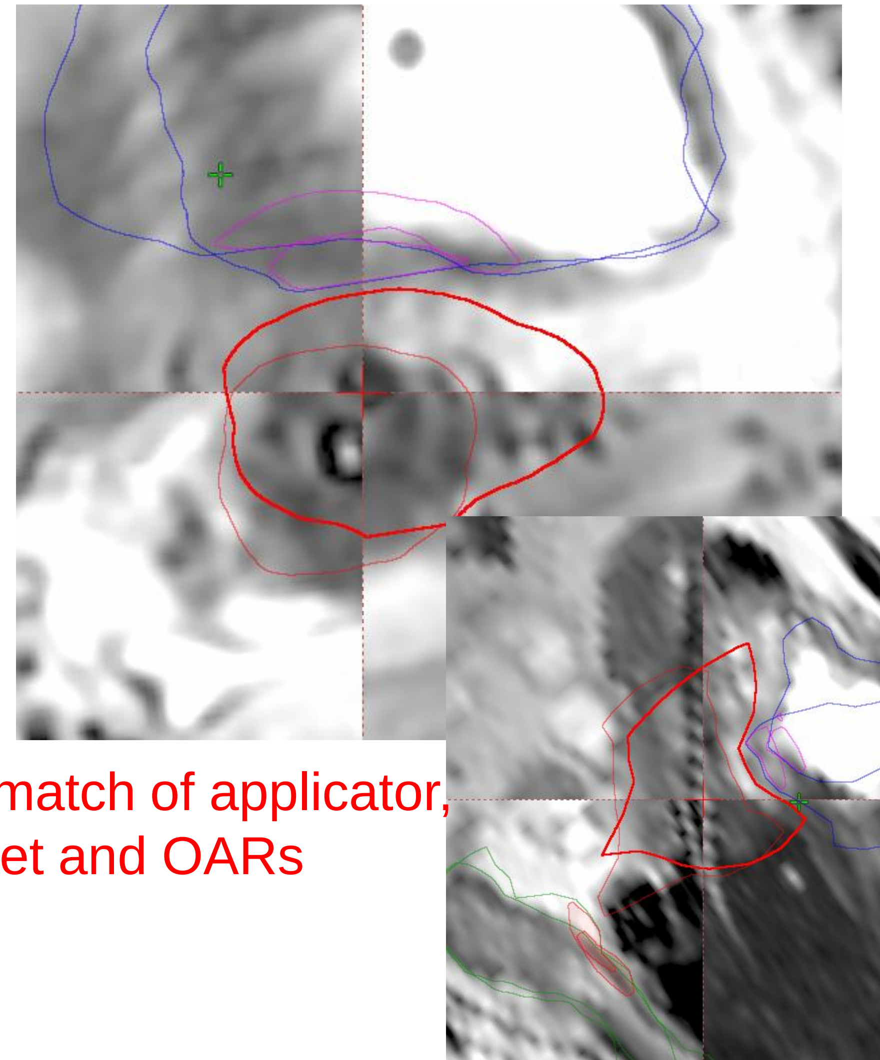
T2 T1



Registration in Brachytherapy – Bone as a reference ? No

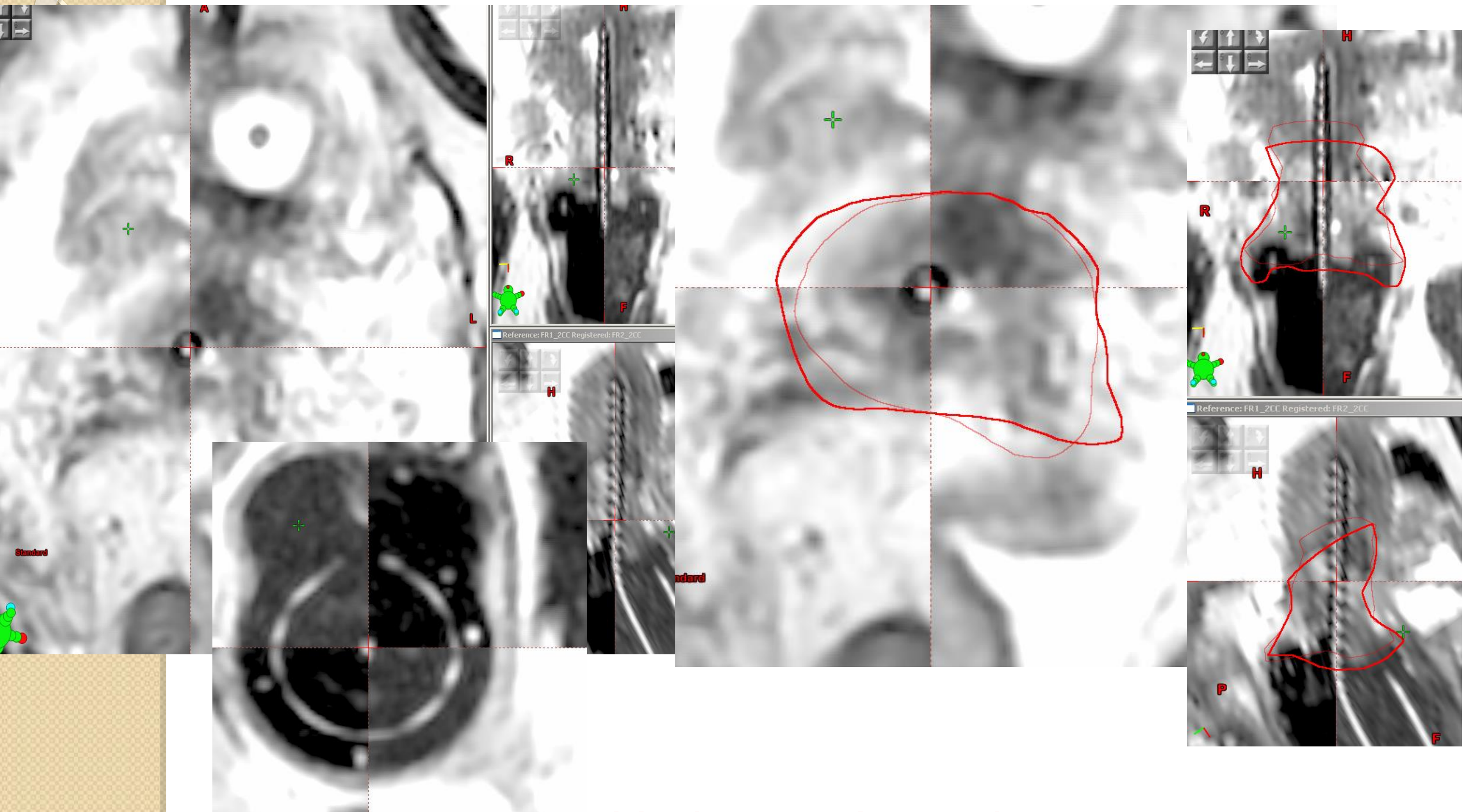


Good matching of bones



Mismatch of applicator, target and OARs

Registration in Brachytherapy – applicator as a reference? -Yes



Anatomy moves with the applicator in BT

Summary

- Applicator reconstruction
  - Direct reconstruction
  - Library of applicators

- Registration
  - Applicator reconstruction based on bony anatomy

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

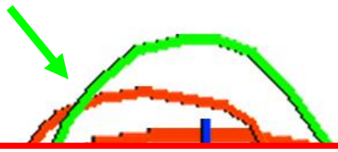
Prague 2017

Kari Tanderup, PhD

Aarhus University Hospital

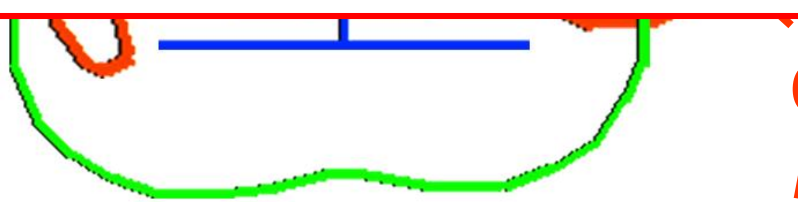
Limitation of point A and standard loading pattern

Point A isodose



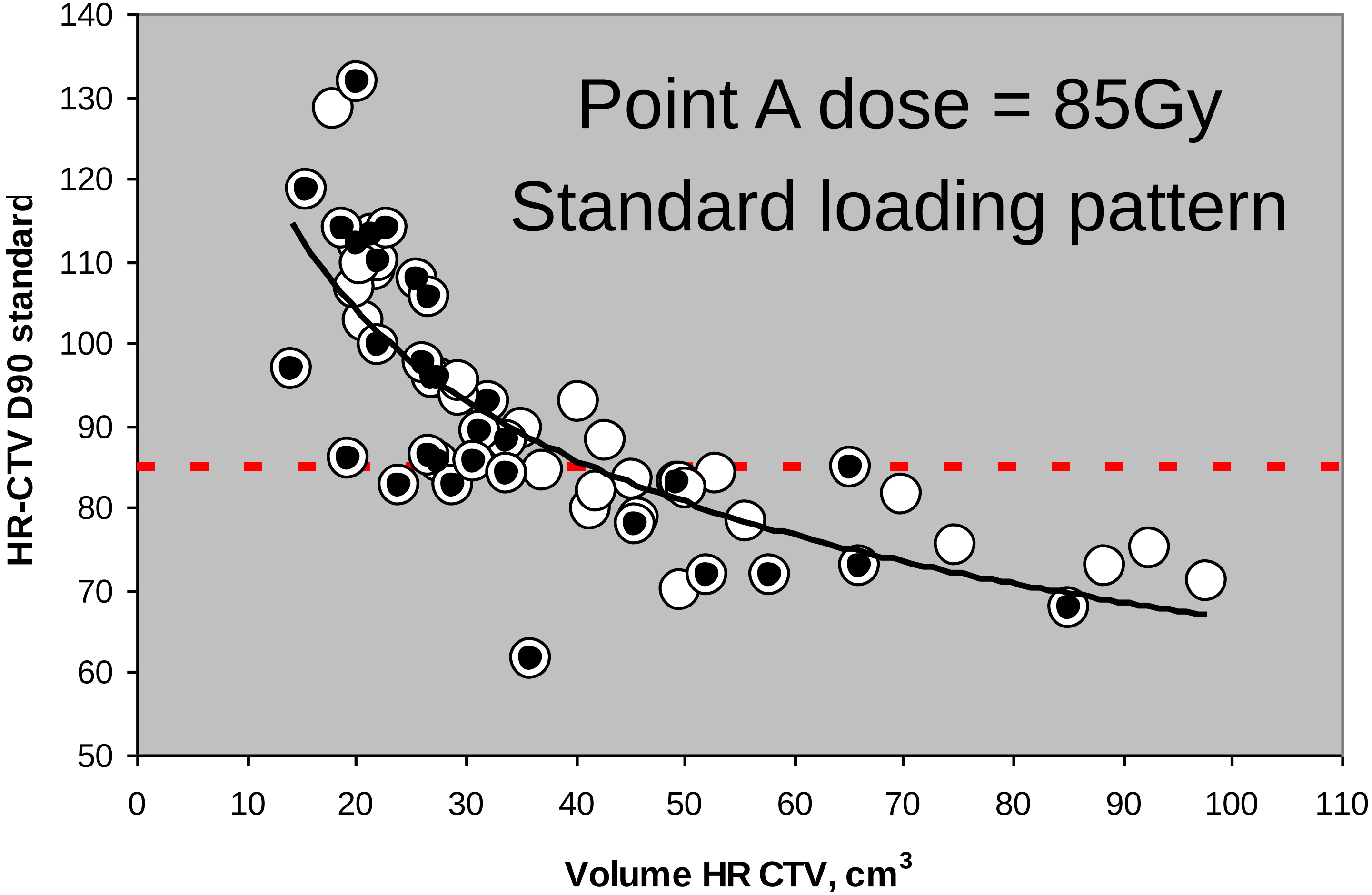
Minimum HR-CTV dose relative to point A:

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



Violation of OAR constraint

K Tanderup et al, Radiother Oncol 2010

Tools for dose optimisation

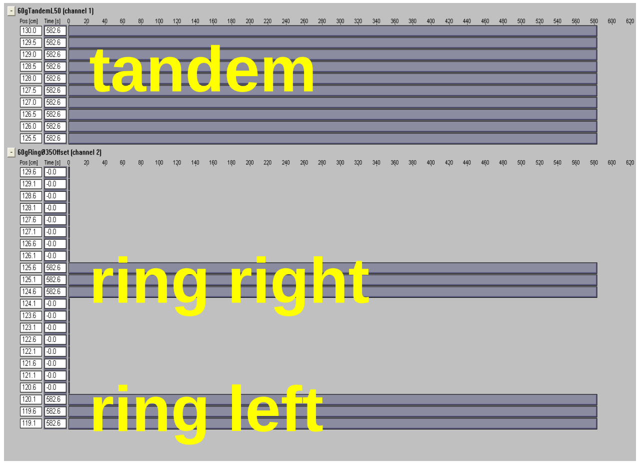
- **Manual dose optimisation**
- **Graphical optimization / Dose shaper**
- **Inverse planning**

Manual optimisation

Dwell times

Standard

Normalised to point A

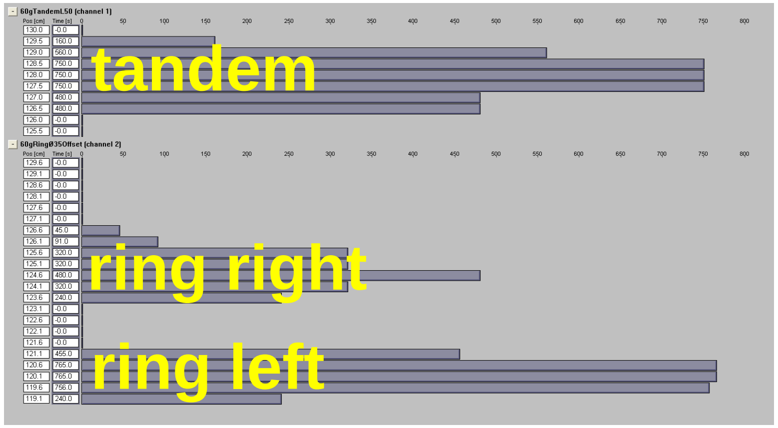


50%

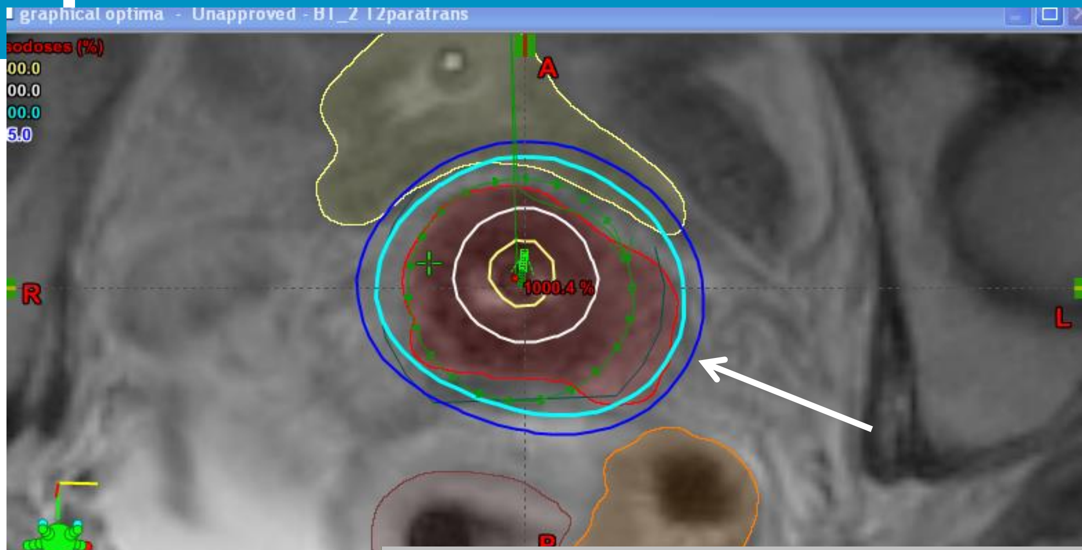
25%

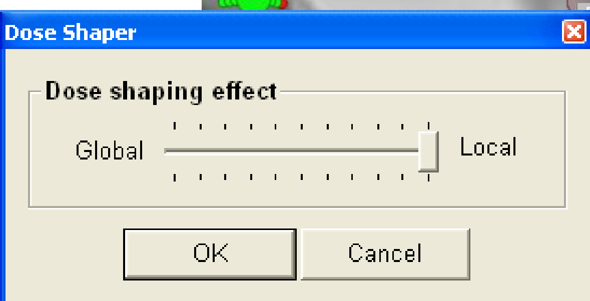
25%

Manually optimised

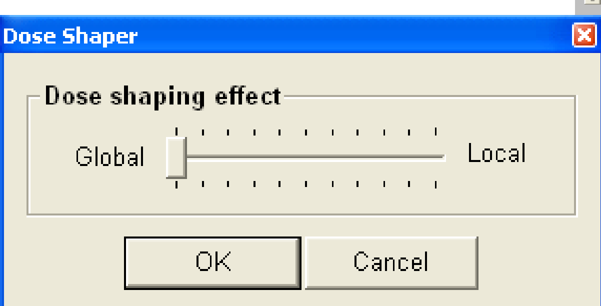


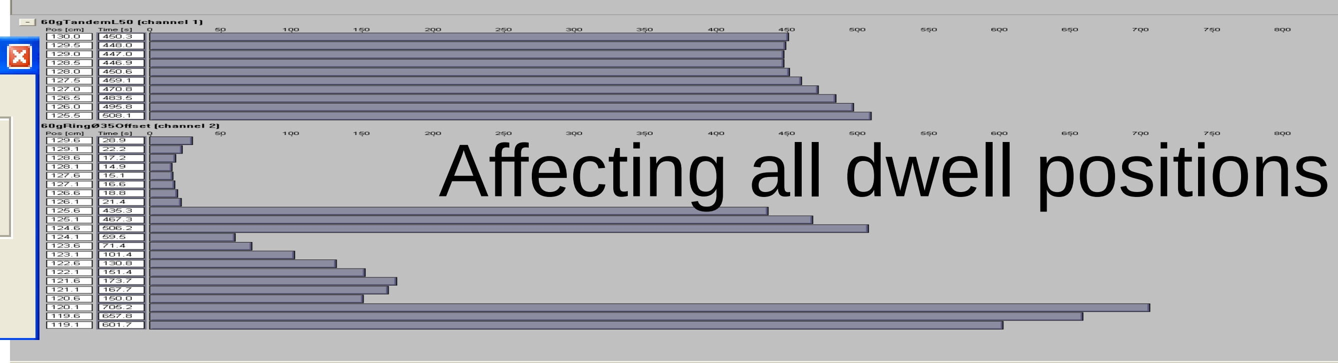
Graphical dose optimisation – “drag and drop”





Affecting nearby dwell positions

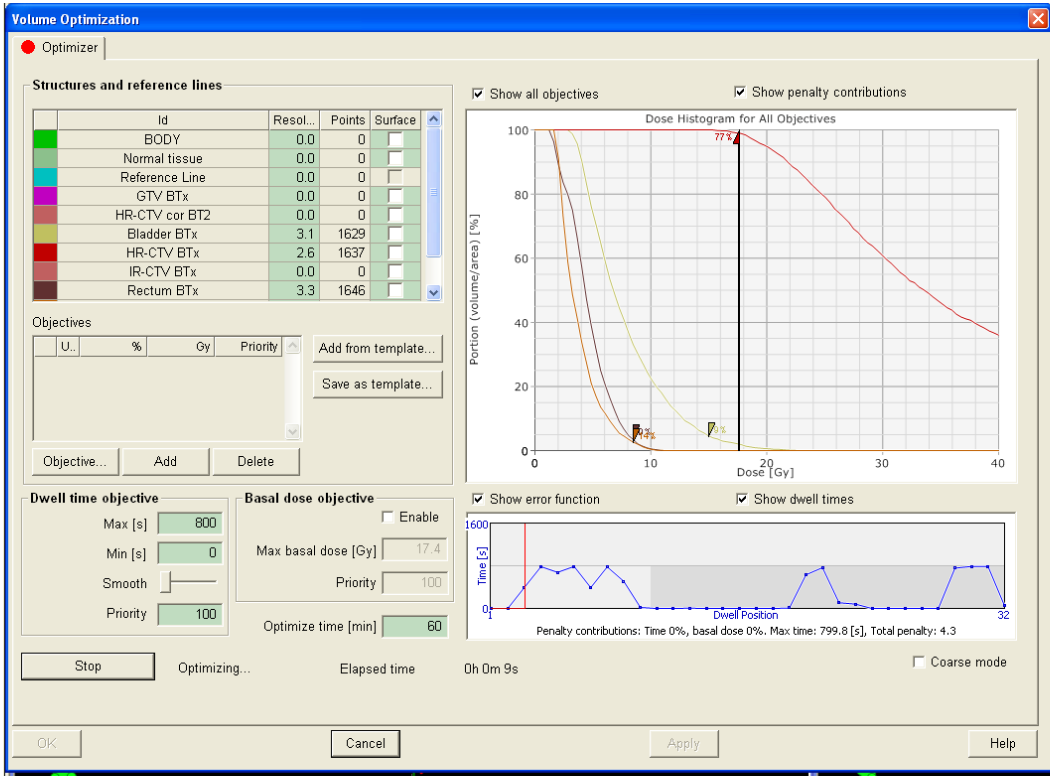




Affecting all dwell positions

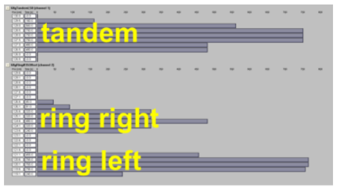
Inverse dose optimisation

- Controlled by DVH constraints
- Weighting factors for different structures



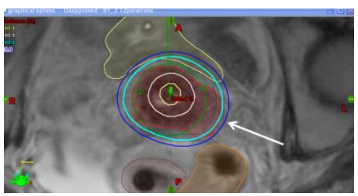
Which type do you prefer?

A. From scratch: manual



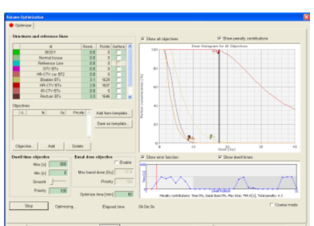
COOKED FROM SCRATCH

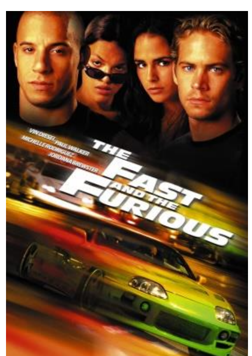
B. Elegant: drag and drop

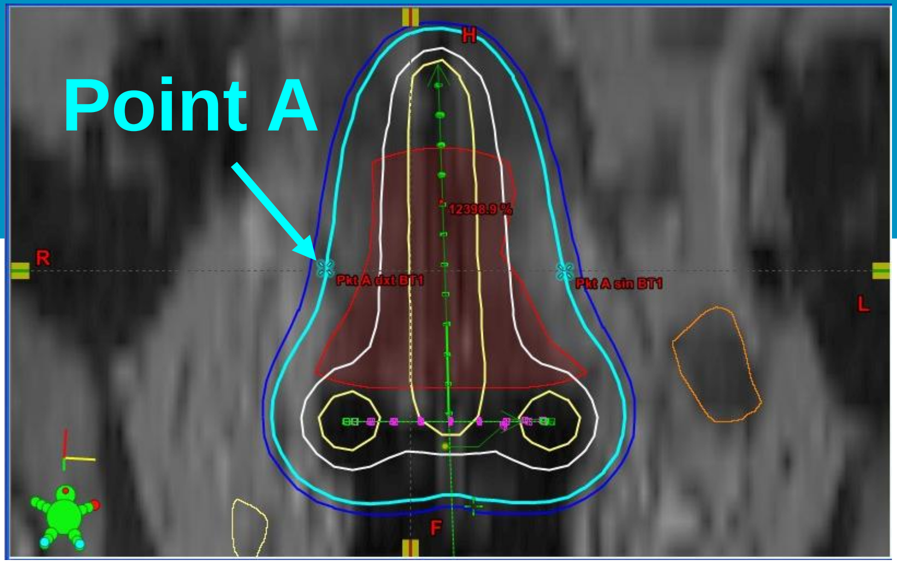


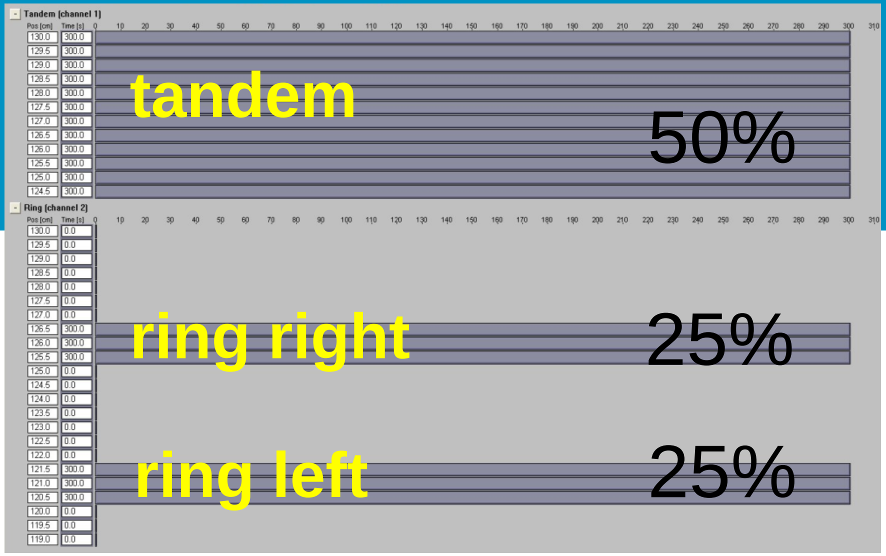
ELEGANT WOMAN
TIMELESS GRACE AND POISE FOR THE EVERYDAY WOMAN

C. Fast and furious: inverse









Always start optimisation

with

Standard loading pattern

Standard prescription e.g. 7Gy to point A

Calculation on MRI? It is OK!

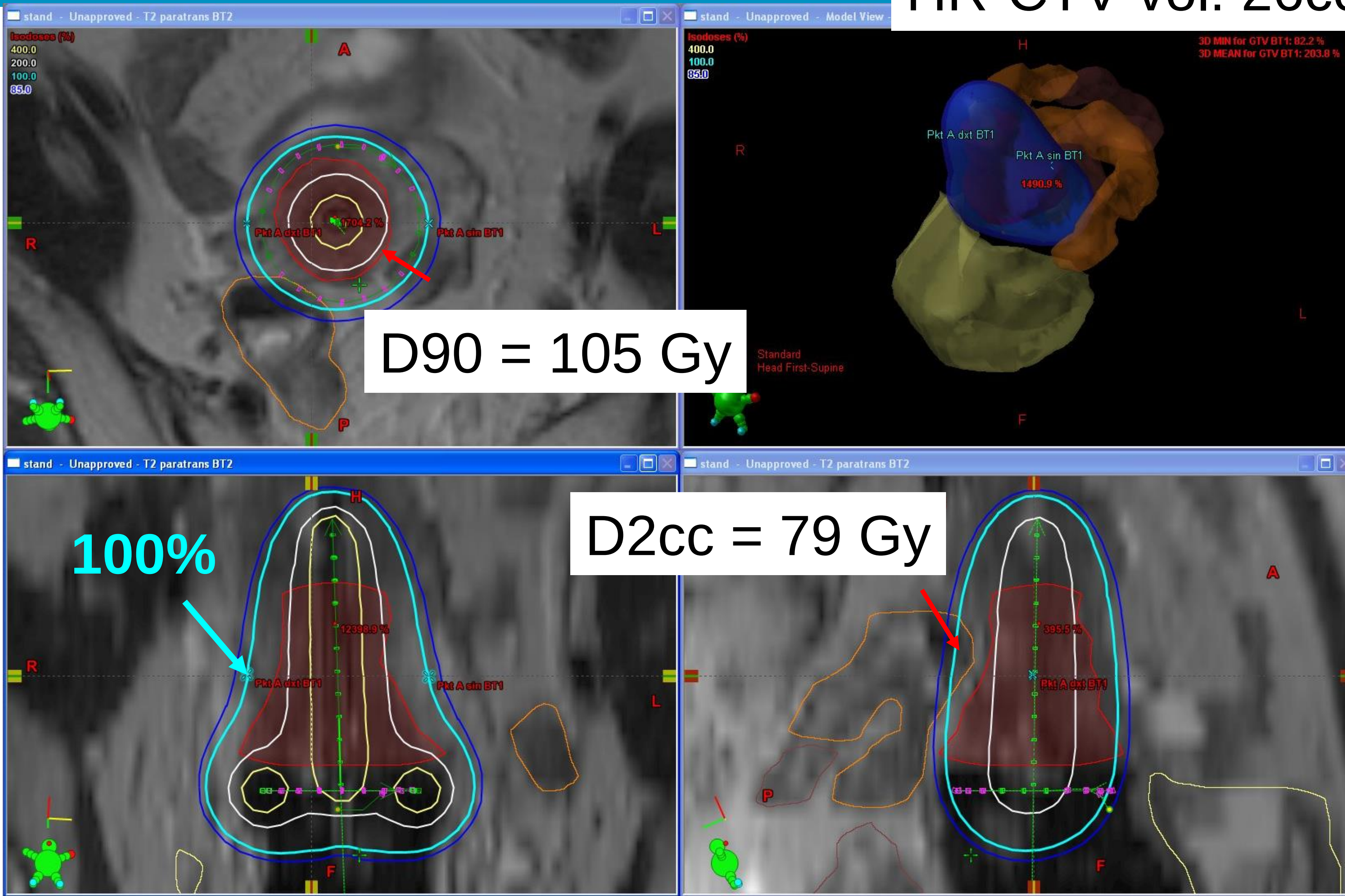
- **TG43 algorithm is based on water calculation and can be done on CT, MRI and US**
- **Model based algorithms take tissue into account (based on CT), but has limited impact for gyn brachy**

Implant	% Variation
Surface Mould (Nose)	9 ± 7
Head and Neck (Base of Tongue)	8 ± 8
Breast APBI –Multi Catheter	8 ± 2.0
Lip Implant	11 ± 14
Eye Lid	22 ± 37
Gynaecology – Vienna applicator (Polymer)	1 ± 0.2
Gynaecology – Ring applicator (SS)	4 ± 0.7

Courtesy Jamema Swamidas

Example 1: good response stage IB2
Standard plan

HR-CTV vol: 26cc



D90 = 105 Gy

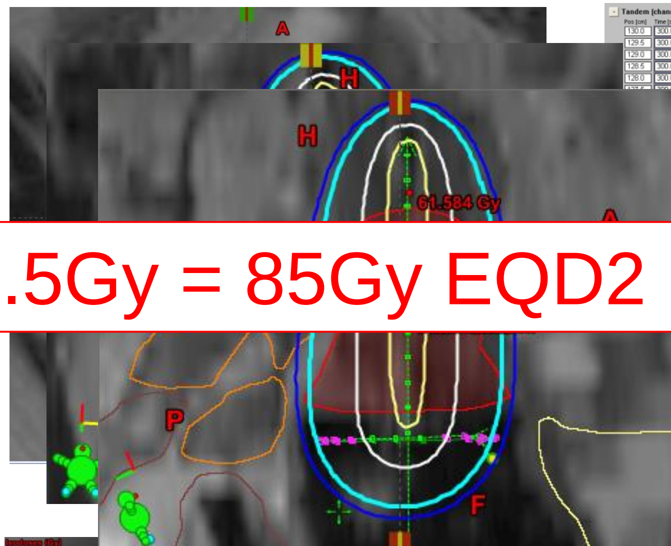
100%

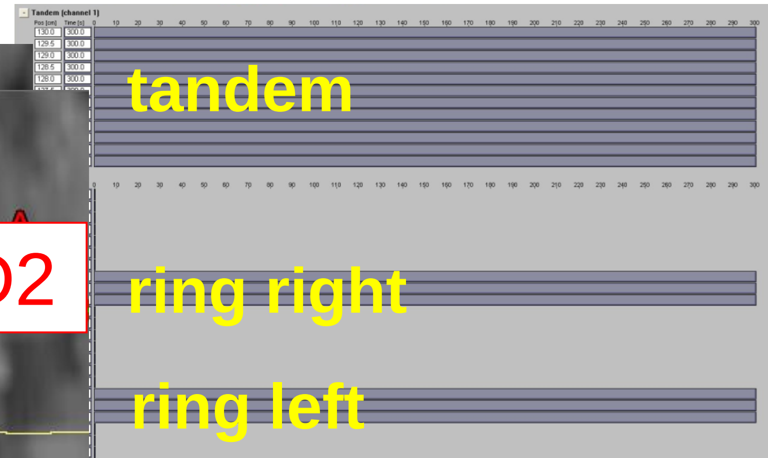
D2cc = 79 Gy

Example 1
Manual dose optimisation

Dose | **Dwell times**

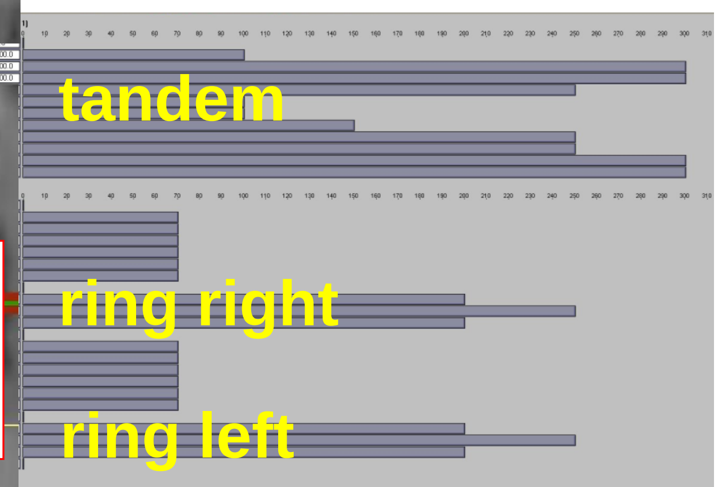
Standard





Point A = 17.5Gy = 85Gy EQD2

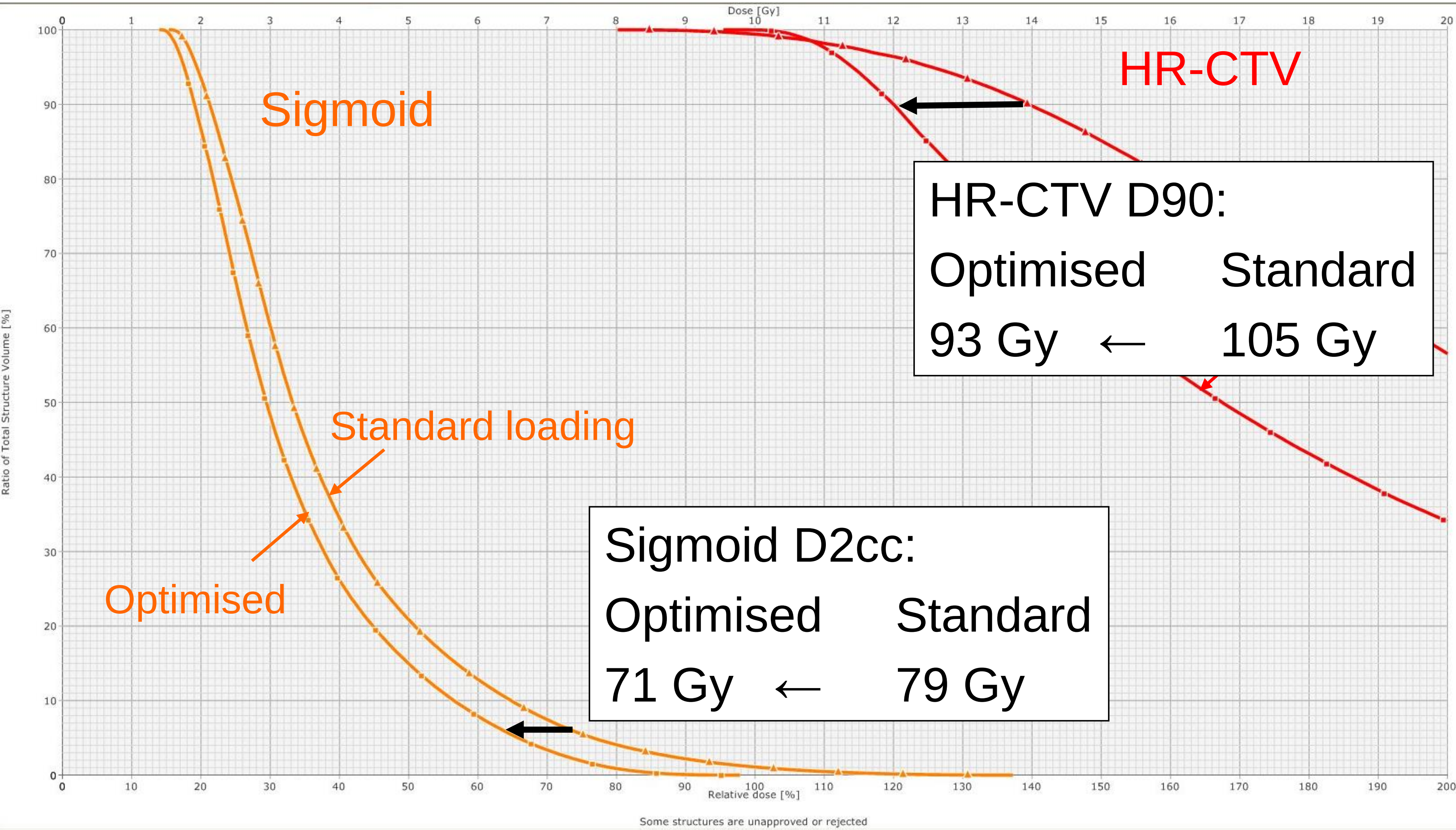
Manual optimisation



Point A = 14.5Gy = 75Gy EQD2

Reduction: 20%

Example 1, DVH



Example 1, summary

- **Small tumour (HR-CTV vol 26cc)**

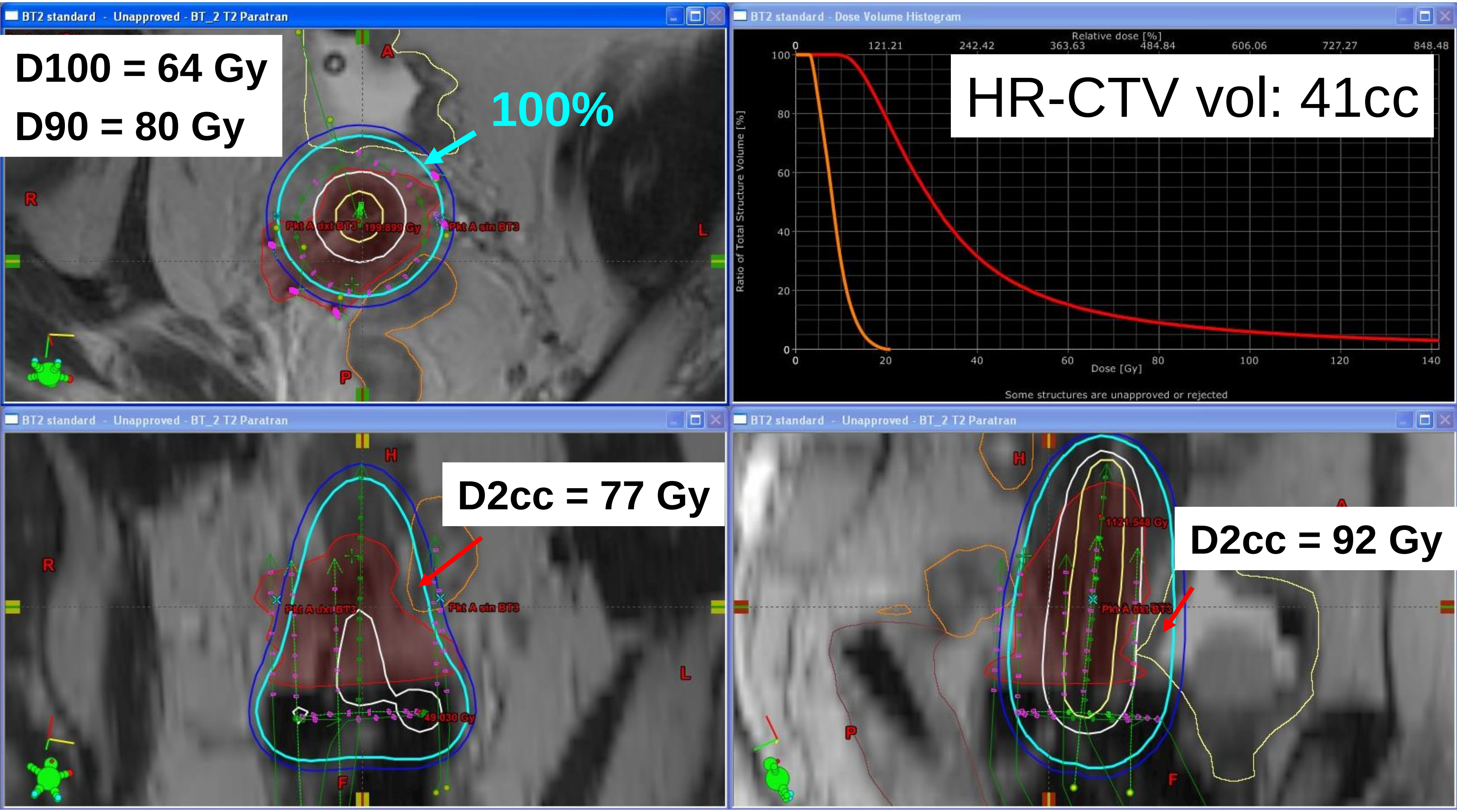
- **20% reduction of Point A dose (to 75Gy) and reduction of volume of pear (85Gy isodose)**

- **OAR dose decreased**

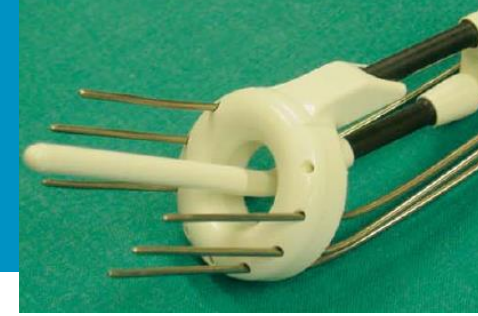
- **Planning aim: >85Gy**
- **Prescribed dose HR CTV D90: 93Gy**

- **100% isodose adjusted by ~5mm**

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

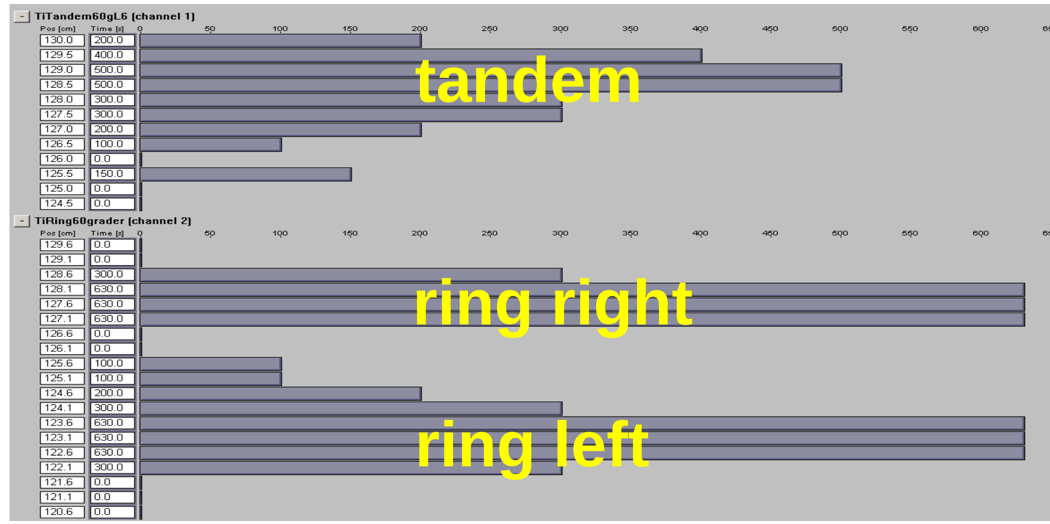
Increase: 7%

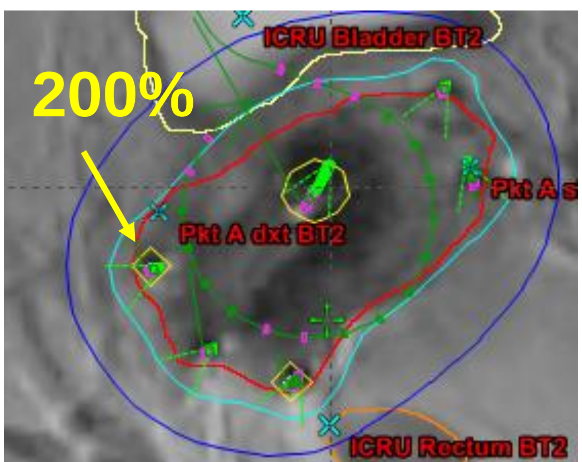
Loading of needles: dwell times and isodoses

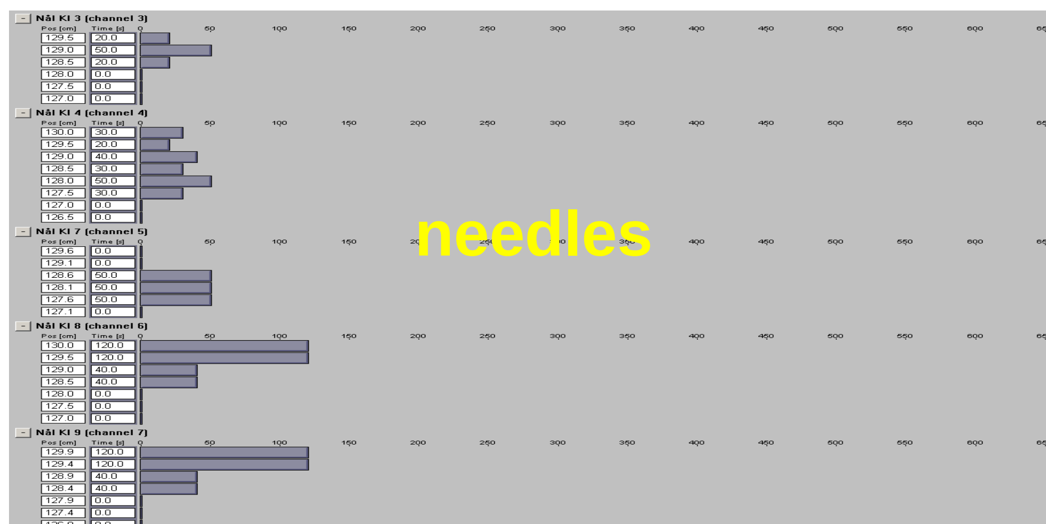
Dwell times needles:

10-20% of dwell time in tandem/ring

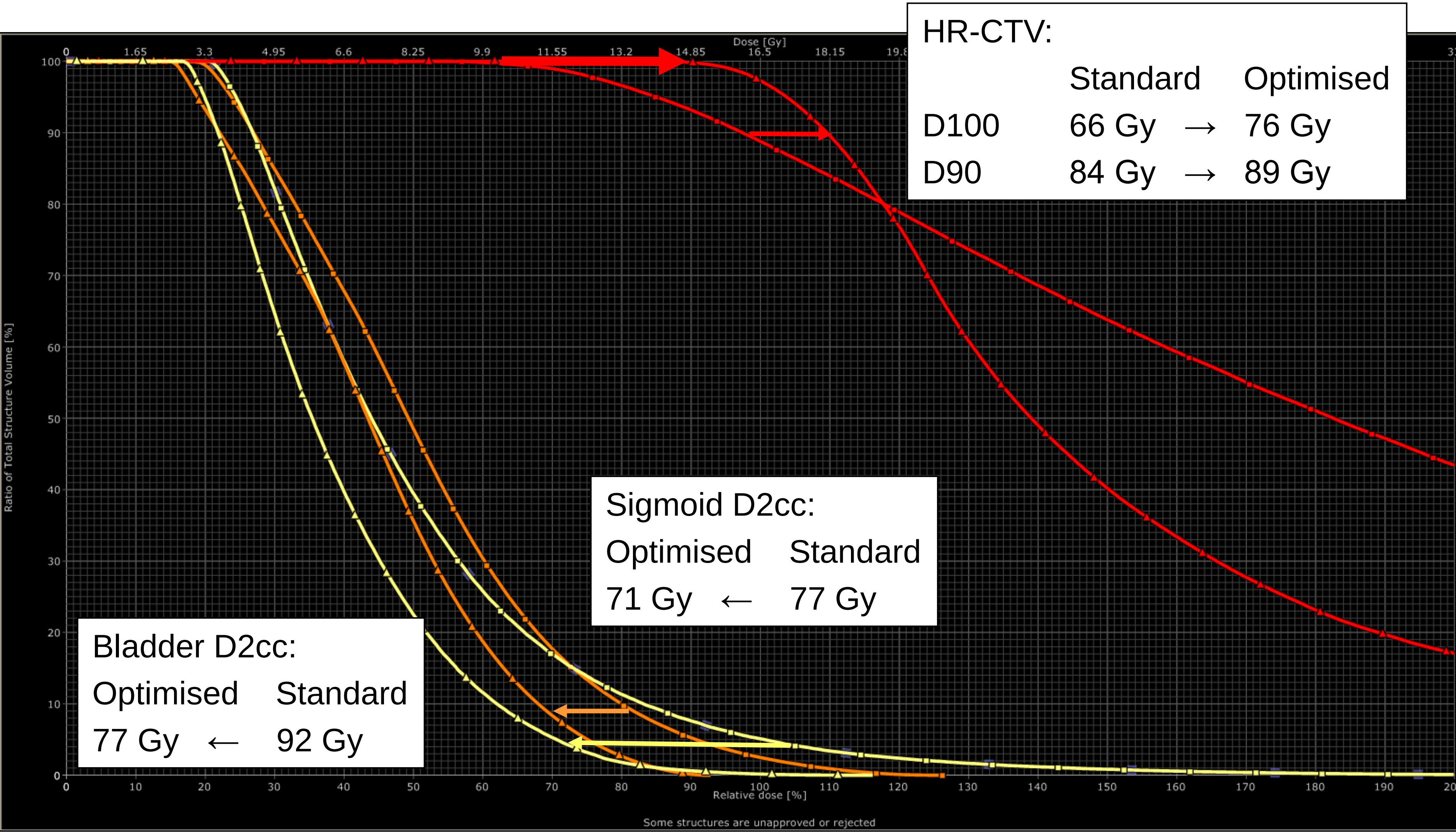
May be >20% if needle is placed directly in the GTV







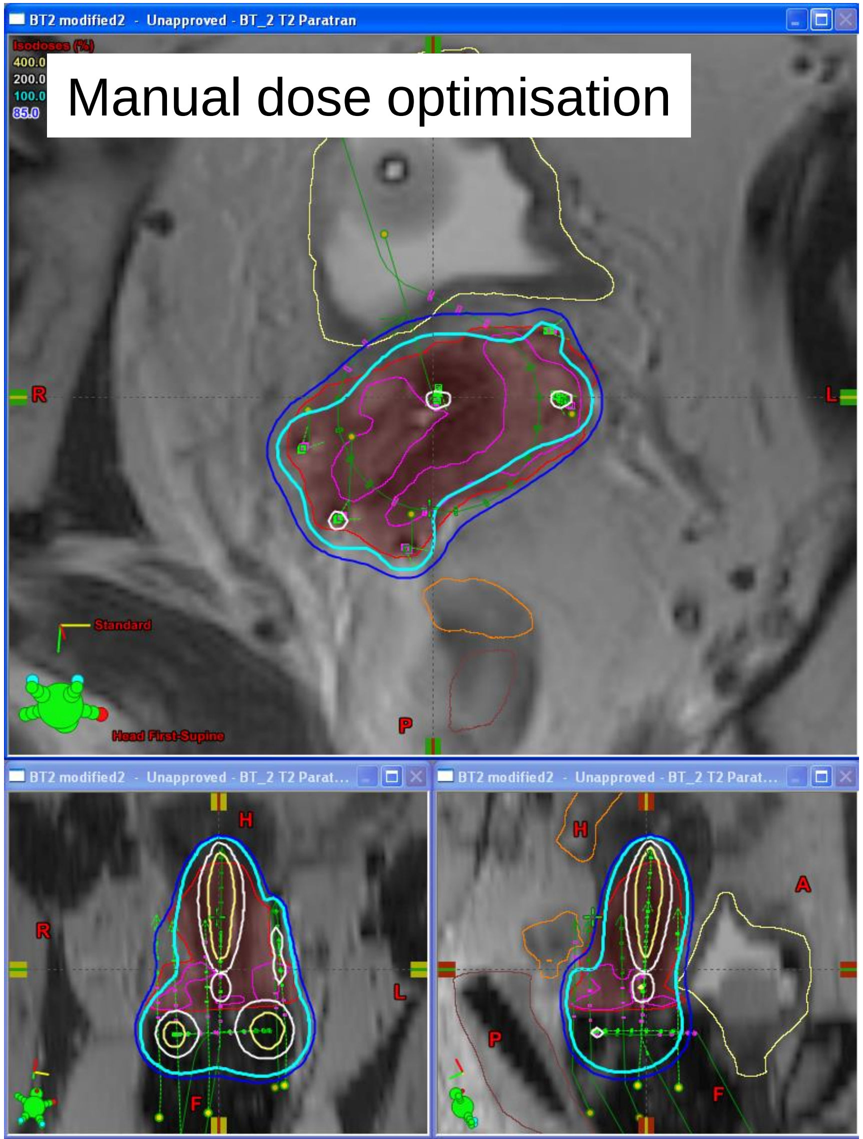
Example 2, DVH

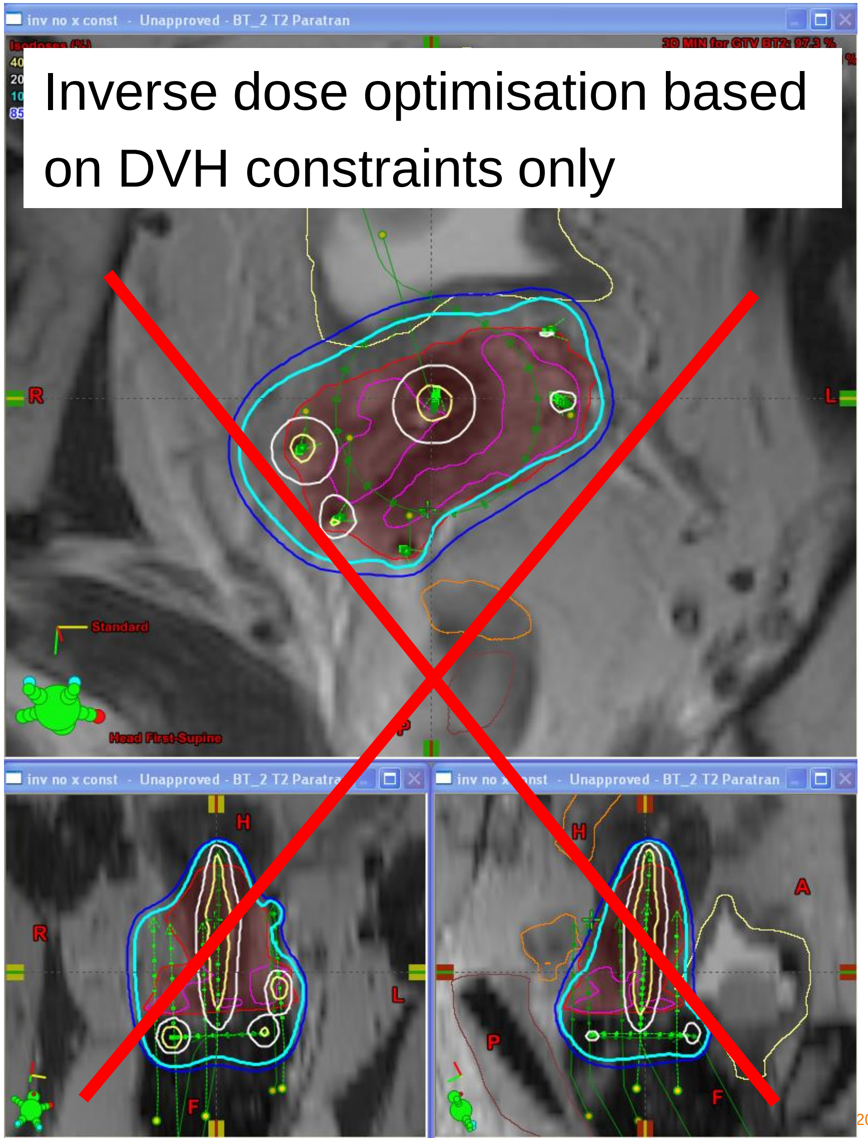


Example 2, summary

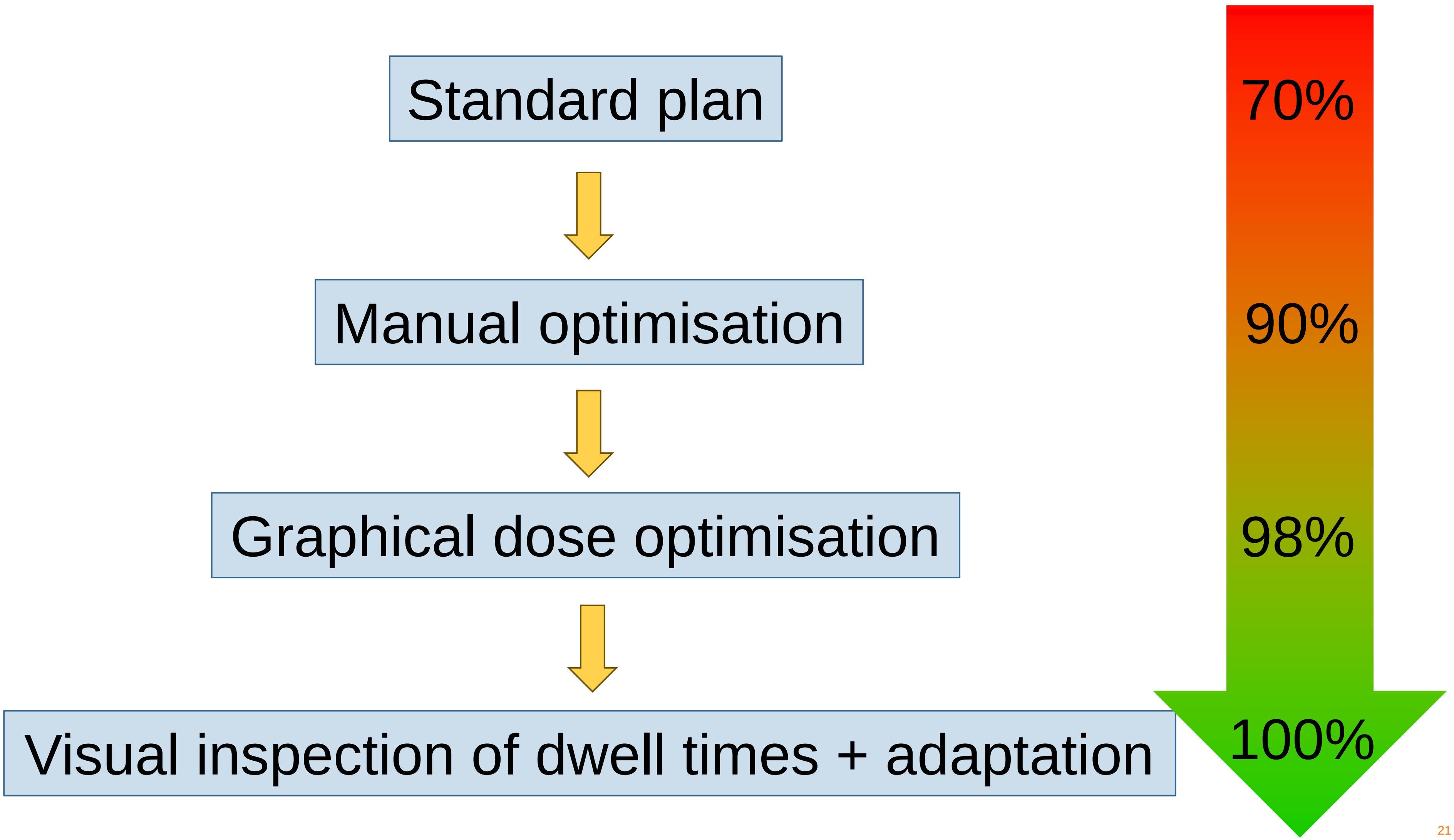
- **Bad response (HR-CTV vol 41cc)**
- **Need of modified applicator (ring+needles)**
- **Needle loading: <20%**
- **Target coverage significantly increased – OAR dose significantly decreased**
- **Planning aim: >85Gy**
- **Prescribed dose HR CTV D90: 89Gy**
- **100% isodose adjusted by ~ 10 mm**

Example 2, inverse planning





When to use graphical dose optimisation (dose shaper)?



When to use graphical dose optimisation (dose shaper)?

Standard plan

↓

Graphical dose optimisation

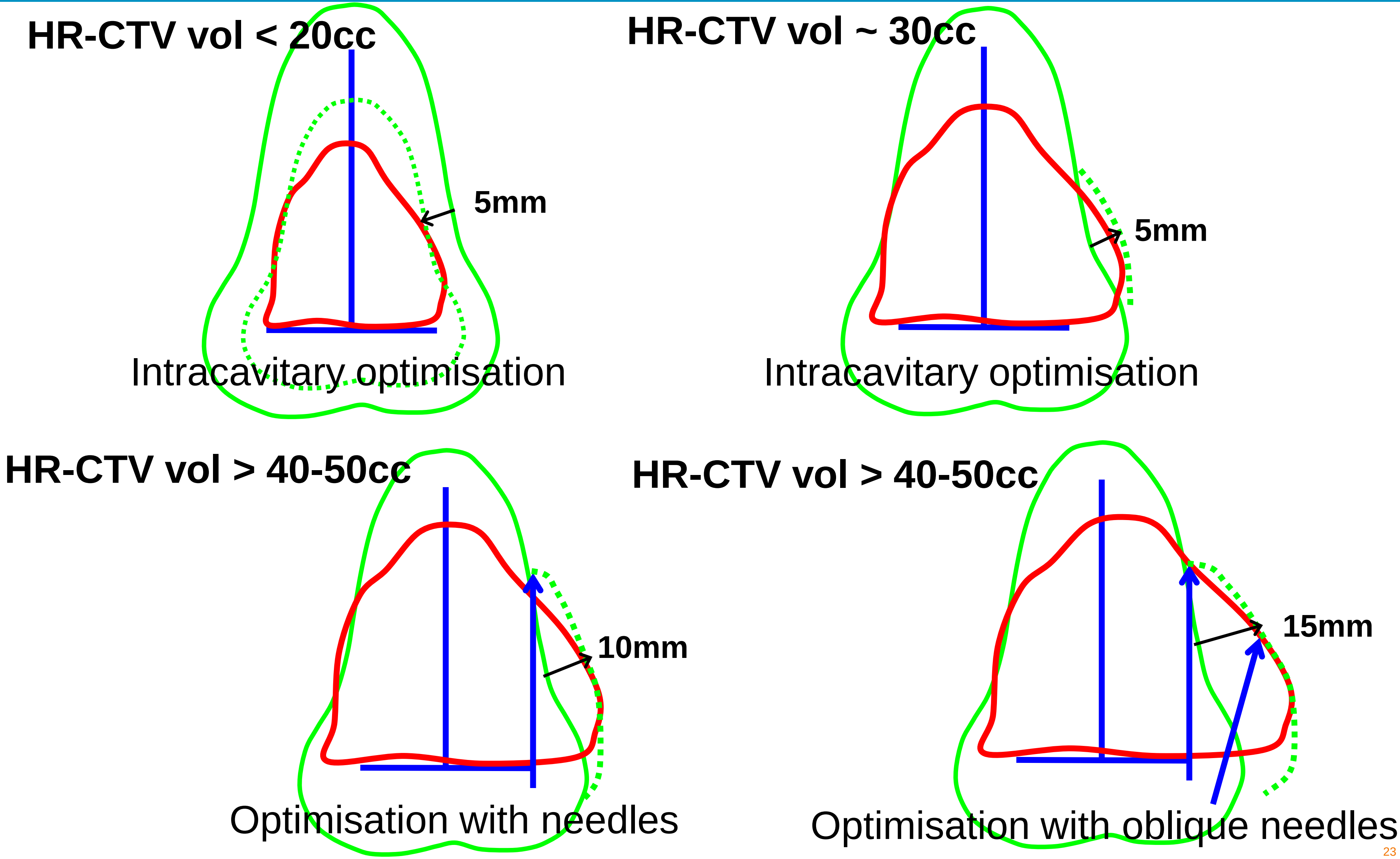
↓

Visual inspection of dwell times + adaptation

Risk:

- Blowing up needle loading
- Loosing intuition of acceptable dwell times

Typical scenarios of dose optimisation

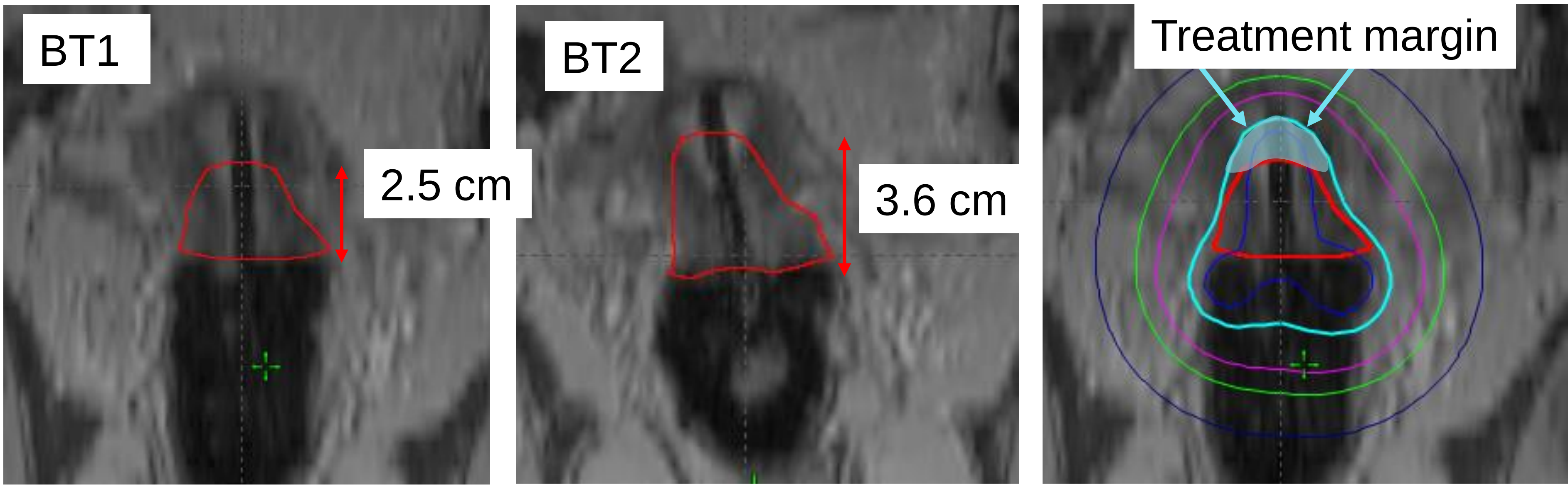


Conclusion – optimisation techniques

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

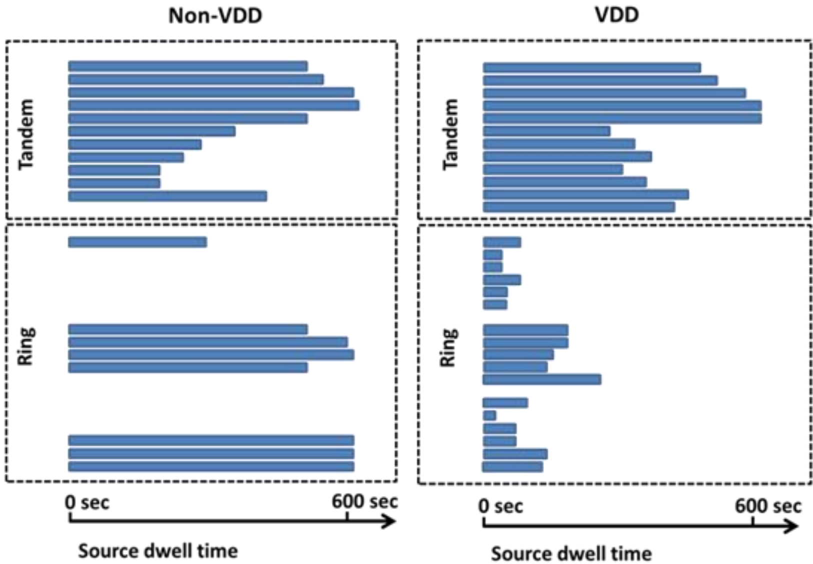
PTV???
Example contouring uncertainty

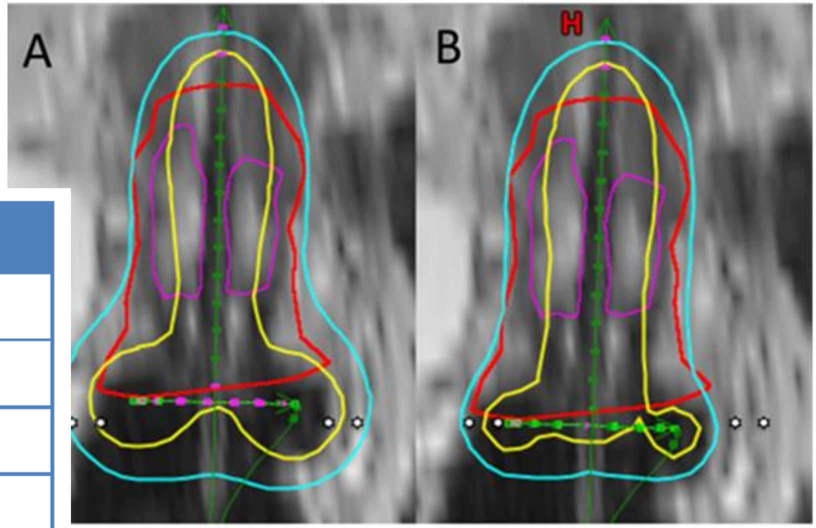
- **Variation in cranial border of HR-CTV**
- **Intra-observer variation!**
- **<u>Load the tandem above the CTV$_{HR}$ when feasible</u>**



Vaginal dose de-escalation

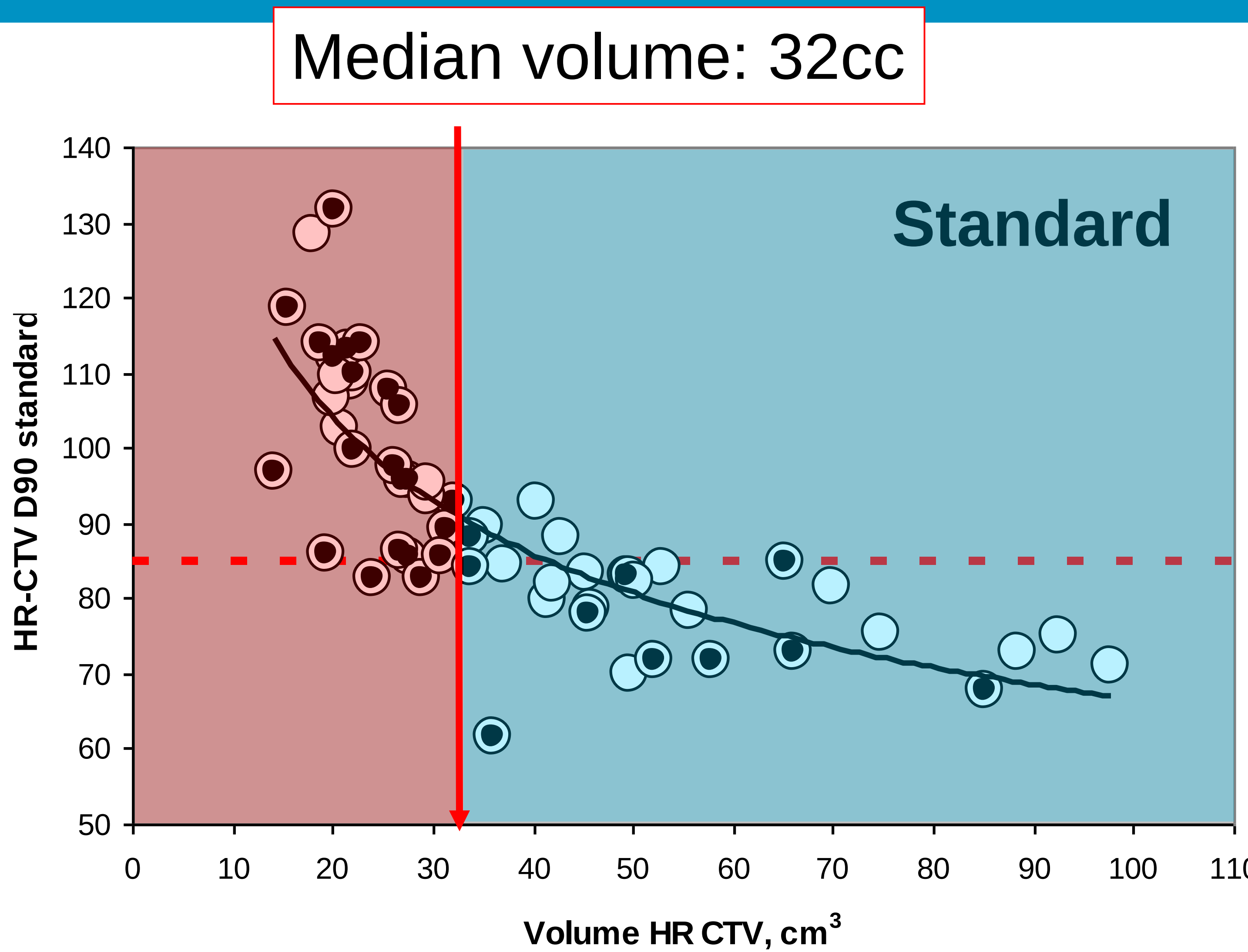
- **Change of loading pattern:**
  - **Shift of dwell time from vaginal sources to tandm/needles**
  - **E.g. 140% isodose out of vaginal mucosa**
  - **Aim for <30-40% loading in ring/ovoids**





	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!

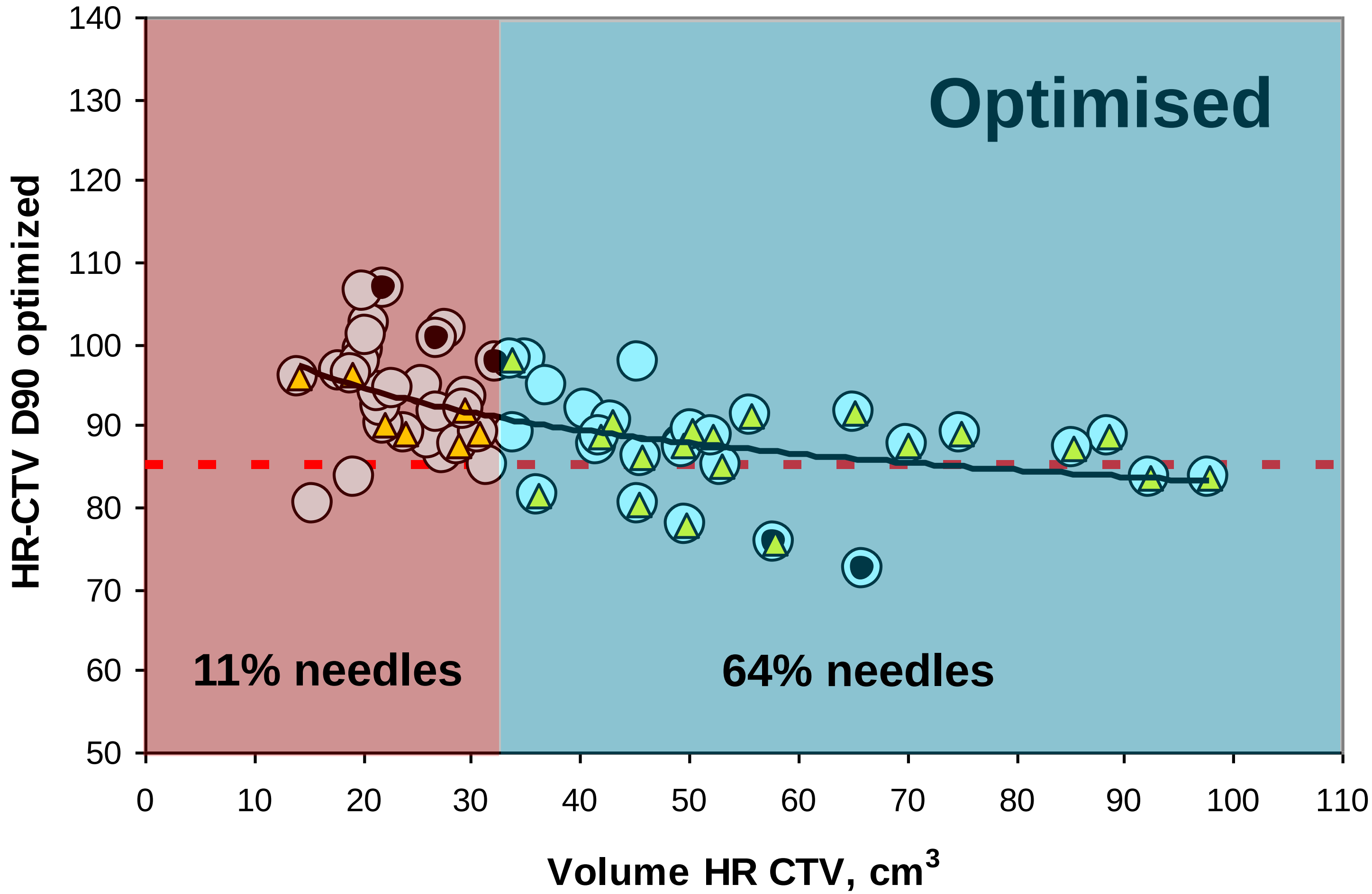


Violation of OAR constraint

K Tanderup et al, Radiother Oncol 2010

Volume is important!

K Tanderup et al, Radiother Oncol 2010



Violation of OAR constraint

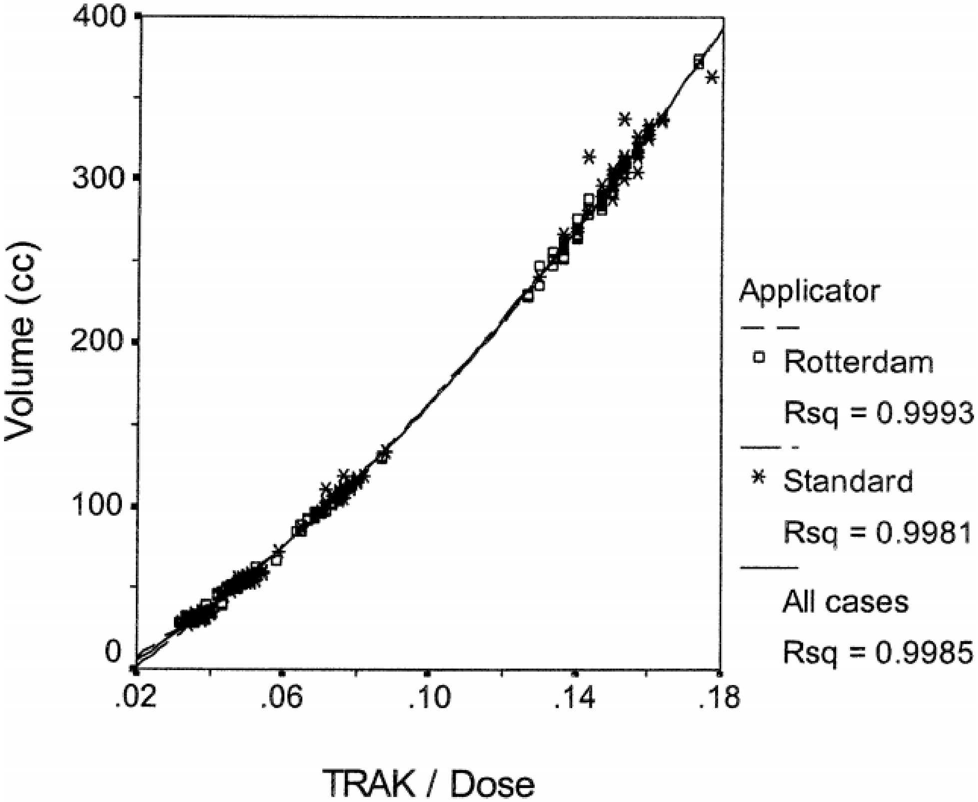
Application of needles

Keep track of your TRAK!
Total Reference Air Kerma

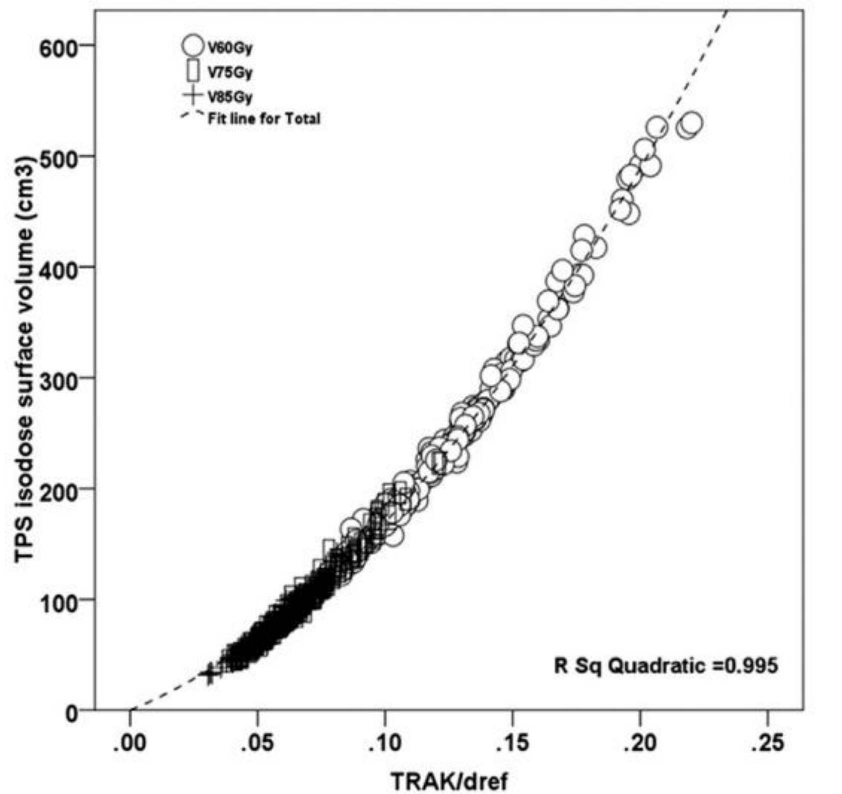
TRAK = $\sum t_i$ * RAKR

RAKR = 4.07 cGy/s (10Ci Ir-192)

$$Vref = 4965\left(\frac{TRAK}{d_{ref}}\right)^{3/2} + \left(\frac{TRAK}{d_{ref}}\right) - 1.5$$

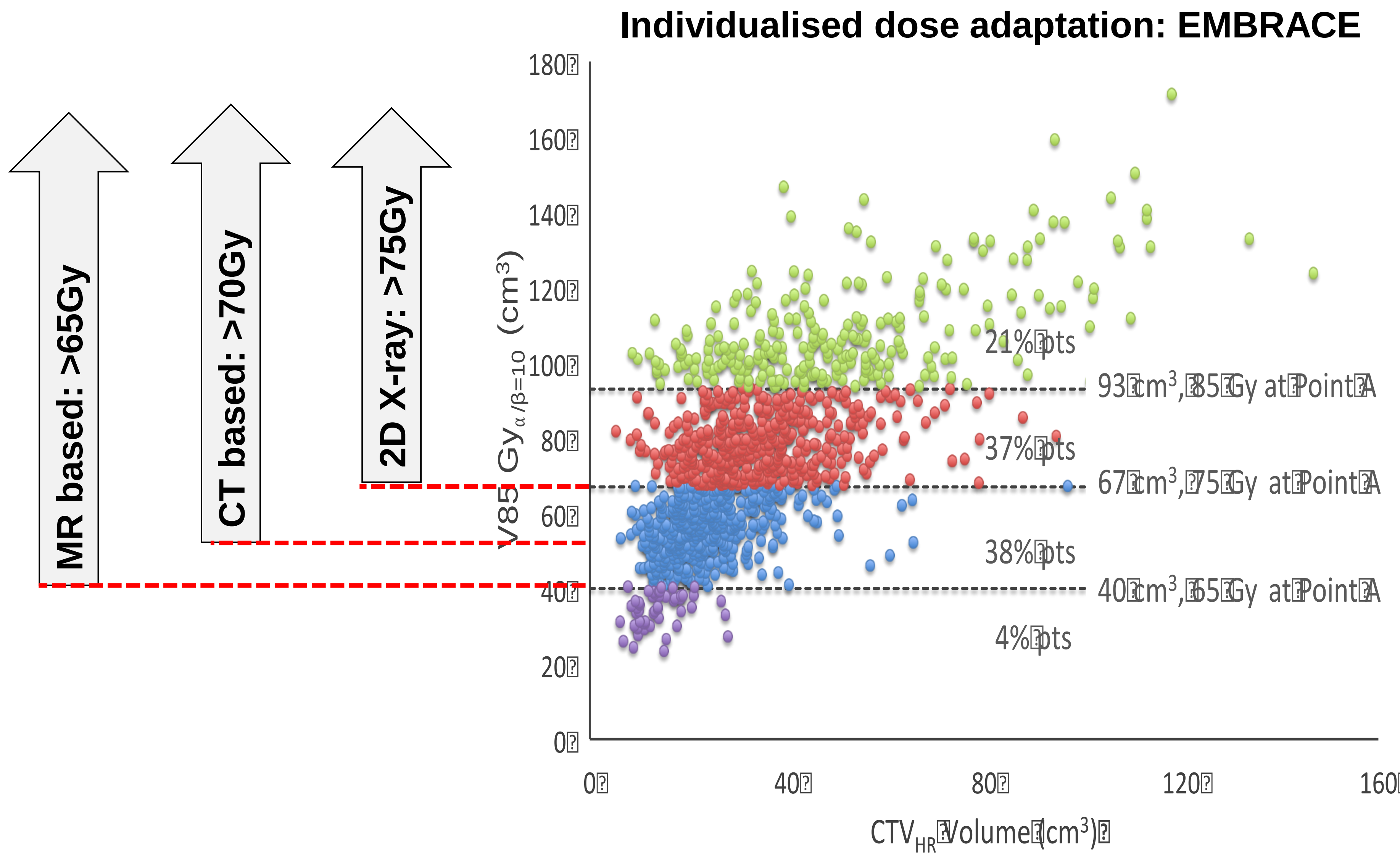


Datta et al, Brachytherapy 2:91–97, 2013

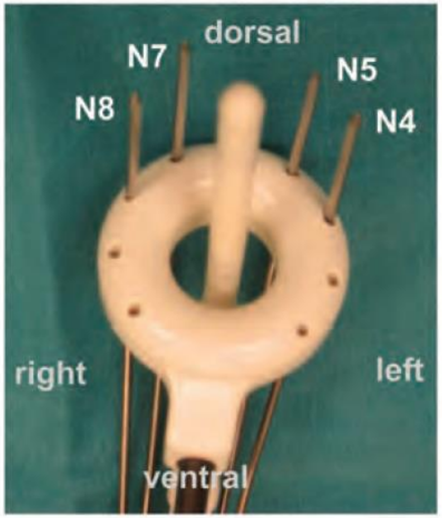


Nkiwane et al, Brachytherapy 16(6):1184-1191, 2017

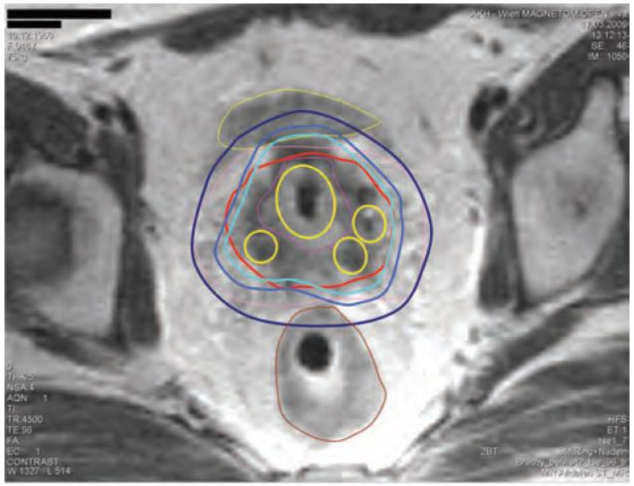
Volumes treated to 85Gy
Be Careful:Thresholds of point A dose



Example IIB (ICRU89)



- CTV_{HR} volume $43cm^3$
- 45Gy EBRT + 4 fx BT
- TRAK 0.43cGy (x4)
- V85Gy = $85cm^3$



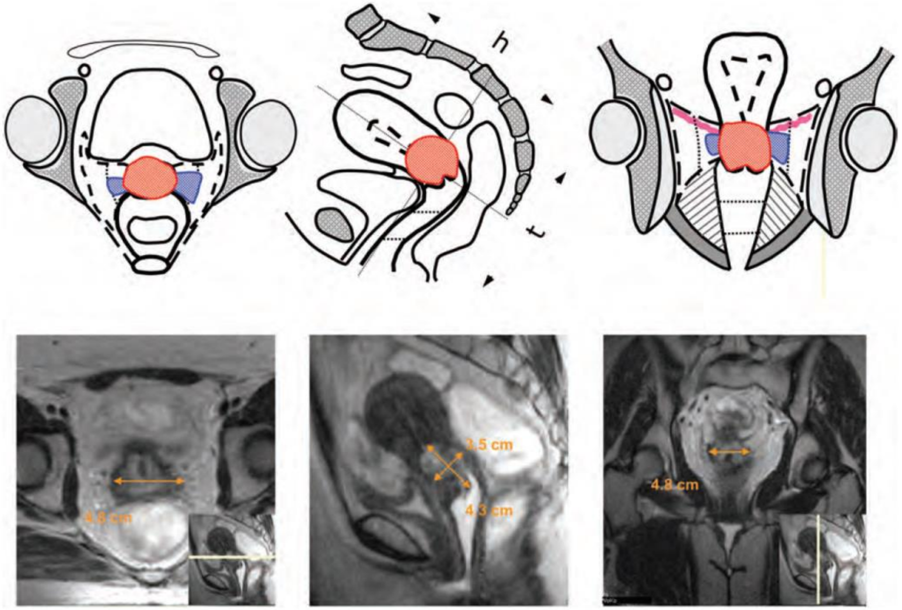
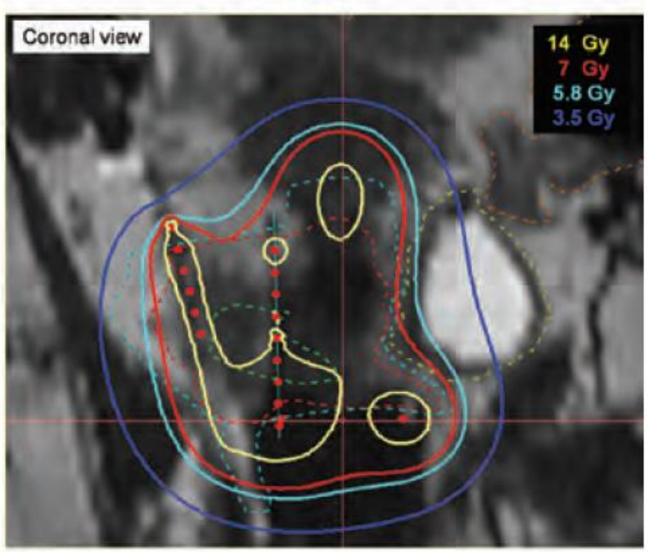


Figure A.5.4. Residual GTV and residual pathological tissue at the time of first brachytherapy: clinical drawings (upper) and corresponding MRI images (lower) at the time of first brachytherapy without applicator in place.

Example IIIB (ICRU89)

- CTV$_{HR}$ volume 66cm^3
- 45Gy EBRT + 4 fx BT
- TRAK 0.50cGy (x4)
- V85Gy = 70cm^3



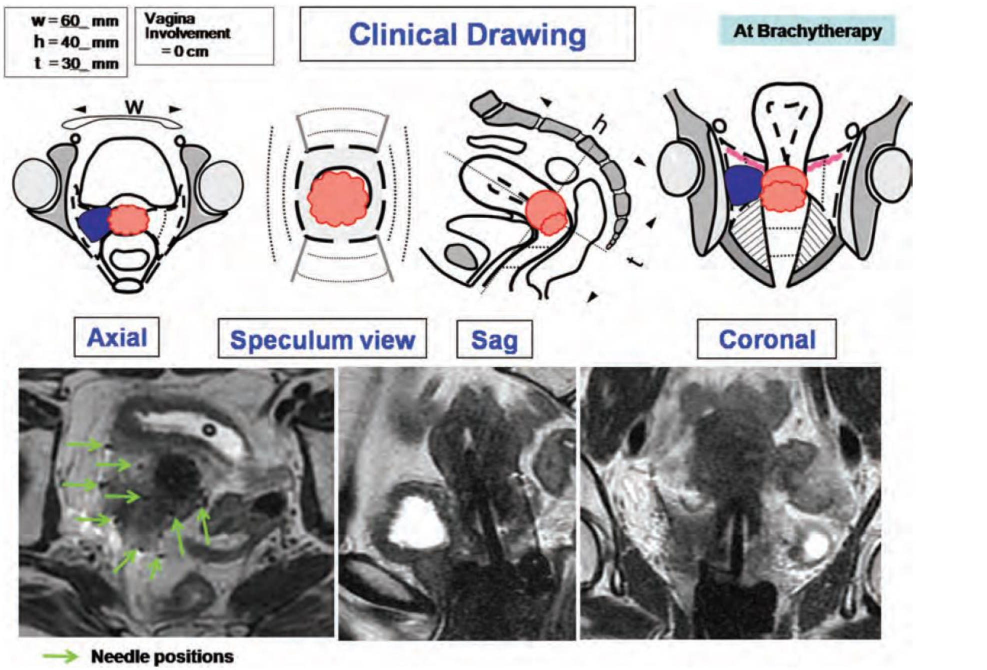


Figure A.8.4. Residual GTV and residual pathological tissue at the time of first brachytherapy: Clinical drawings (upper) and corresponding MRI images (lower) at the time of brachytherapy with applicator in place.

Take home message – dose optimisation

- **Always start dose optimisation with standard loading pattern**
- **Use manual dose optimisation for major changes**
- **Use graphical optimisation for minor adaptation**
- **Needle loading: start with 10-20%**

- **Application of combined intracavitary-interstitial applicator: increased therapeutic window by ~10Gy**

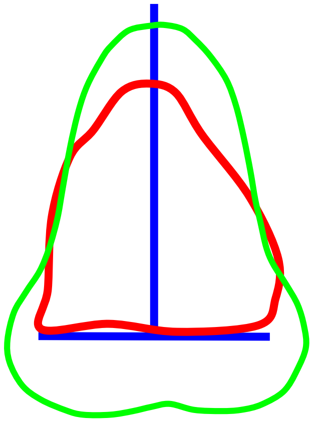
Which dose planning constraints are correct (several answers possible)?

CT based brachytherapy planning

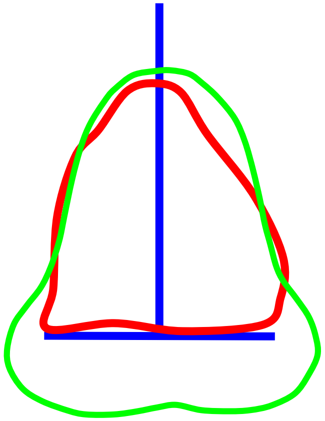
A. CTV_{HR} D90 should be at least 85Gy
B. Point A should be at least 85Gy
C. Point A should be at least 70Gy

Which dose distribution do you prefer?

A. Plan A



B. Plan B



I prefer to do optimisation

A. Flow 1

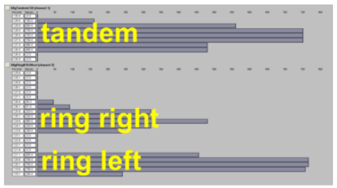
Standard plan
↓
Manual optimisation
↓
Graphical dose optimisation
↓
Visual inspection of dwell times + adaptation

B. Flow 2

Standard plan
↓
Graphical dose optimisation
↓
Manual optimisation
↓
Visual inspection of dwell times + adaptation

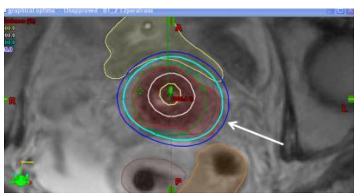
Which type do you prefer?

A. From scratch: manual



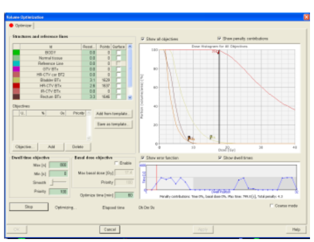
COOKED FROM SCRATCH

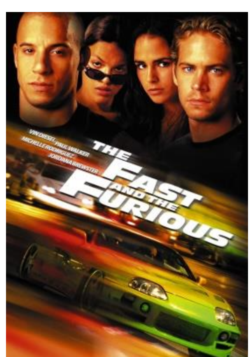
B. Elegant: drag and drop



ELEGANT WOMAN
TIMELESS GRACE AND POISE FOR THE EVERYDAY WOMAN

C. Fast and furious: inverse





Radiobiological models to combine dose from external beam radiotherapy
and
brachytherapy (HDR, MDR, LDR, PDR)

Daniel Berger, Kari Tanderup

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

Lucknow 2018

Challenge

- Brachytherapy is hypo-fractionated
- A variety of schedules exist:
  - 7Gy x 3
  - 9Gy x 2
  - 7Gy x 4
- How to communicate doses between institutions?
- We need biologically equieffective doses!

Prescribing, Recording and reporting: GEC ESTRO and ICRU

GEC ESTRO recommendations II

Radiotherapy and Oncology 78 (2006) 67–77
www.thegreenjournal.com

ESTRO project

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

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

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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

ICRU

OXFORD UNIVERSITY PRESS

INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS

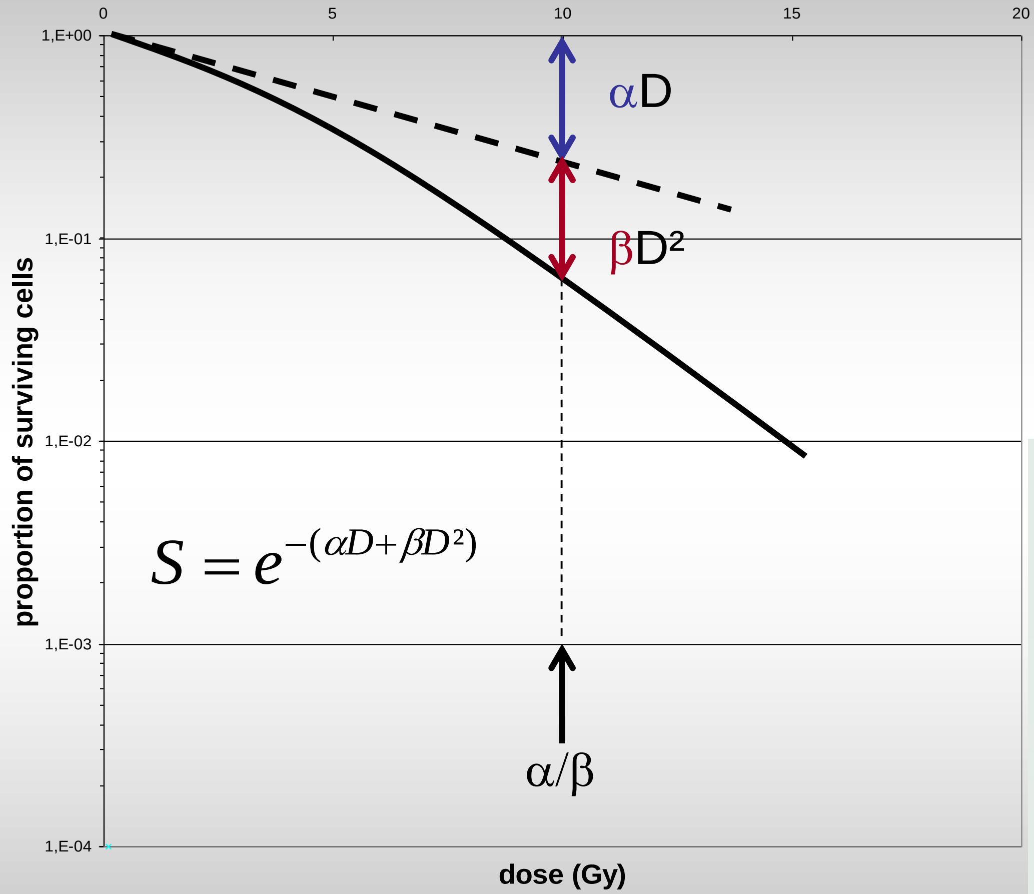
4 R's of radiobiology

- Repair
  - Repair of sub-lethal DNA damage
- Redistribution
  - Radiosensitivity depends on phase in the cell cycle → redistribution changes radiosensitivity
- Repopulation
  - Cell divide during a radiotherapy treatment
- Reoxygenation
  - Radiosensitivity changes due to change in oxygenation

Which of the following radiobiological effect(s) is(are) taken into account in the EQD2 calculation when using the LQ-model?

A. Repair
B. Redistribution
C. Repopulation
D. Reoxygenation
E. all

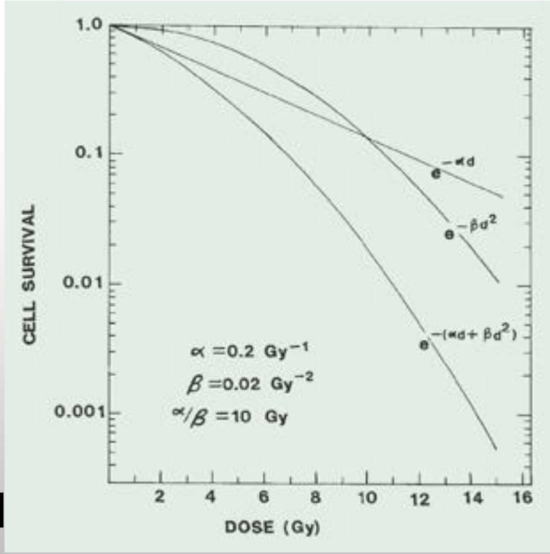
Linear-Quadratic Model



Survival curve according to the LQ-model

-> Lethal damage

-> Sublethal damage

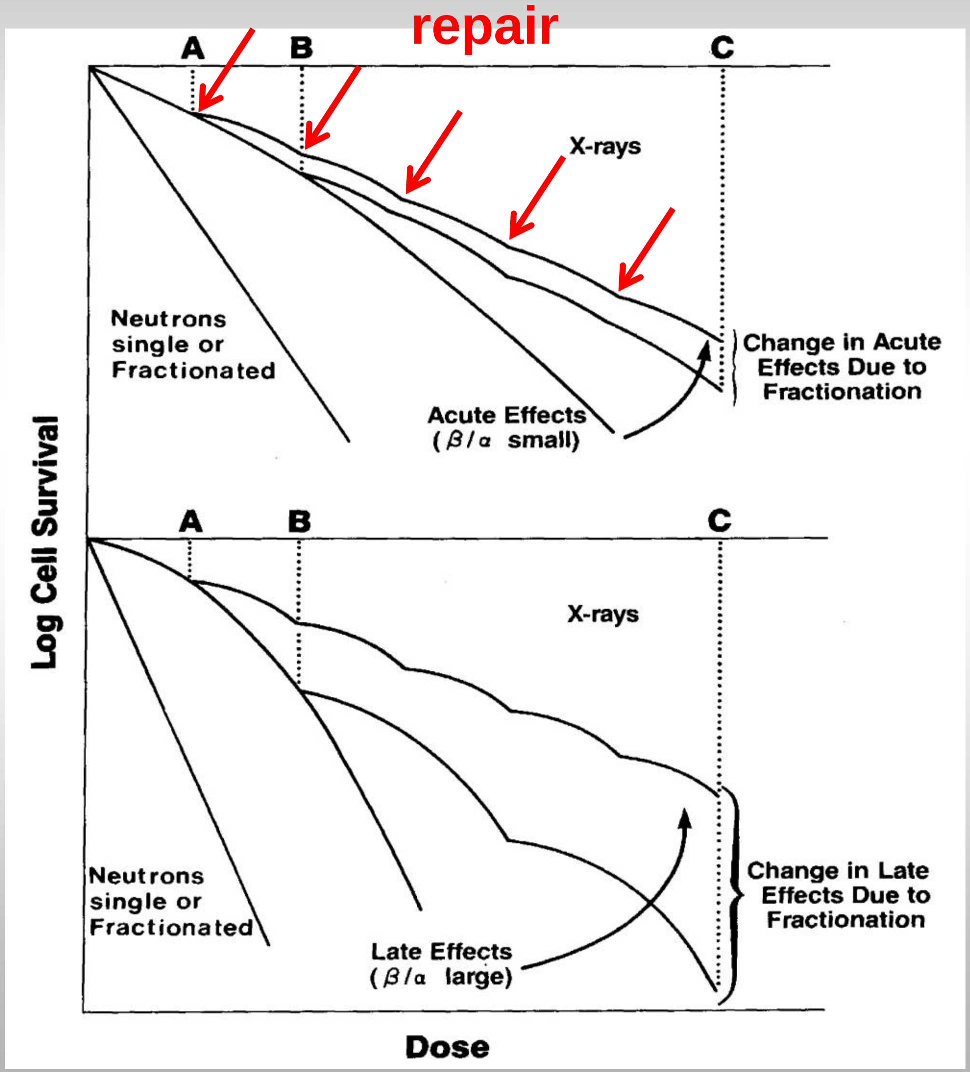


This can be used to fit a continuously bending curve to cell survival data

remember survival curve by Puck and Marcus

Fractionation & acute and late reacting tissue

Repair between fractions:
- The shape of curve starts over again!



LQ model

- Recovery or Repair (half-time ~1.5hour)
- ~~Redistribution~~
- ~~Repopulation (< 1 day)~~
- ~~Reoxygenation~~

Considered in the mathematical description ("equation")

Equi-effective dose for HDR
Use of the LQ model

EQD2: Absorbed doses that, when delivered with 2Gy per fraction, would produce the same biologic effect

$$EQD_2 = n \cdot d \, \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

- n: number of fractions
- d: fractional dose
- Tumor $\alpha/\beta = 10$
- Late morbidity $\alpha/\beta = 3$

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

EXAMPLE: Calculation of EQD2 for HDR 1 fraction of 7Gy

- D: total dose
- d: fractional dose
- Tumor $\alpha/\beta=10$
- Late morbidity $\alpha/\beta=3$

$$EQD_2 = n \cdot d \, \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

Tumour

$$EQD_2 = 7 \cdot \frac{7+10}{2+3} Gy = 10Gy$$

Organ at risk

$$EQD_2 = 7 \cdot \frac{7+3}{2+3} Gy = 14Gy$$

EXAMPLE: Calculation of EQD2 for HDR 3 fractions of 7Gy

- D: total dose
- d: fractional dose
- Tumor $\alpha/\beta=10$
- Late morbidity $\alpha/\beta=3$

$$EQD_2 = n \cdot d \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

Tumour

$$EQD_2 = 7 \cdot 3 \cdot \frac{7+10}{2+3} Gy = 30 Gy$$

Organ at risk

$$EQD_2 = 7 \cdot 3 \cdot \frac{7+3}{2+3} Gy = 42 Gy$$

EBRT + BT dose

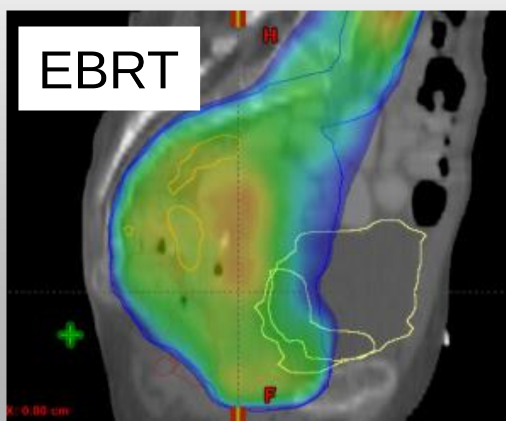
- Dose in elective target volume:
  - Homogeneous dose 95%-103% of prescribed dose (PD)

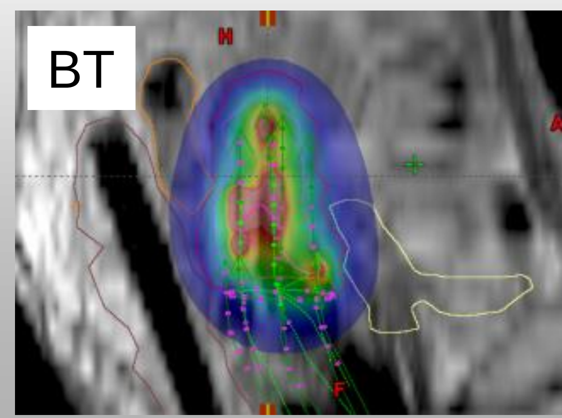
Good approximation:

Target: $D90\ (total) = PD_{(EBRT)} + D90(BT)$

OAR: $D_{2cm3}\ (total) = PD_{(EBRT)} + D_{2cm3}(BT)$

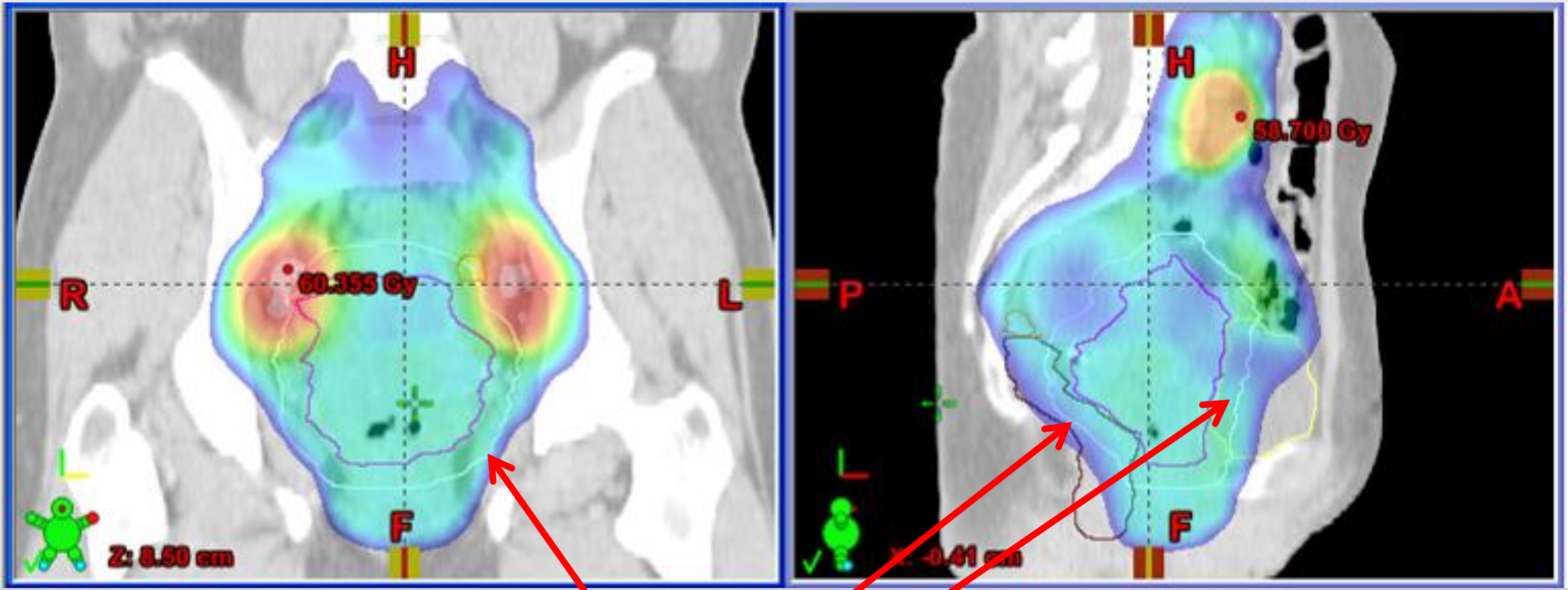
~~**NOT:** $D_{2cm3}\ (total) = D_{2cm3\ (EBRT)} + D_{2cm3}(BT)$~~





Be aware of IMRT hot spots in the BT region!

Lymph node boost: Create homogeneous dose during planning!

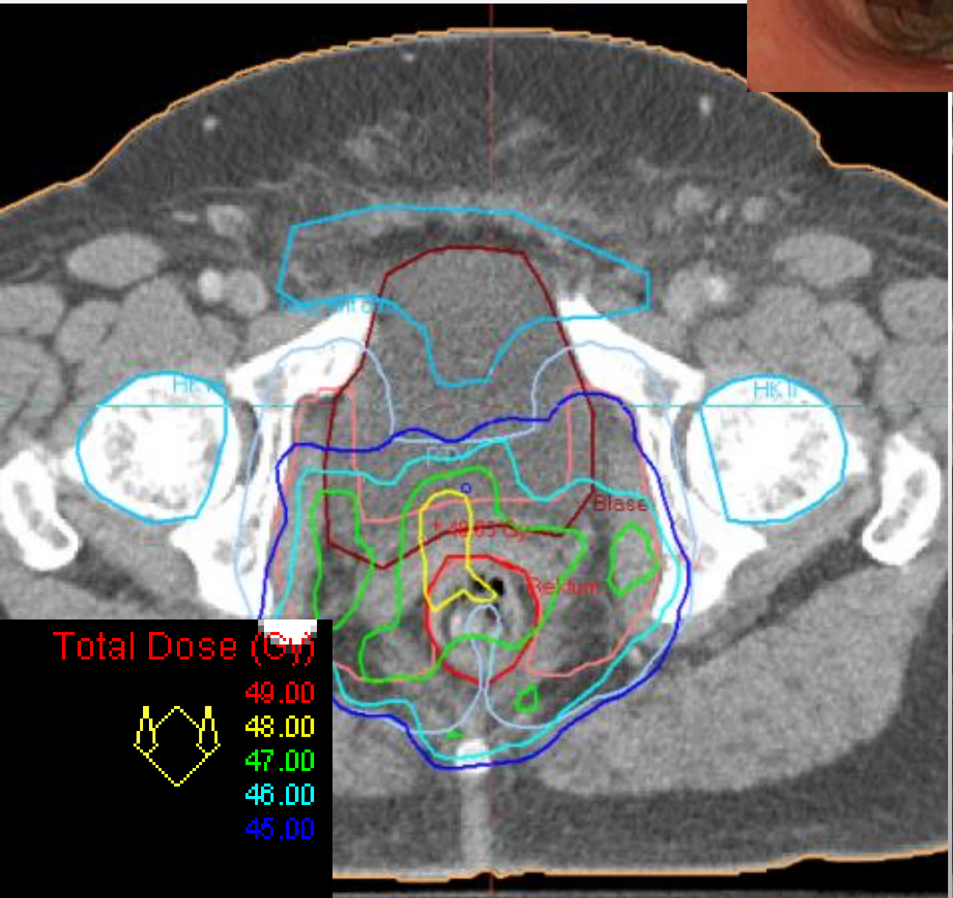


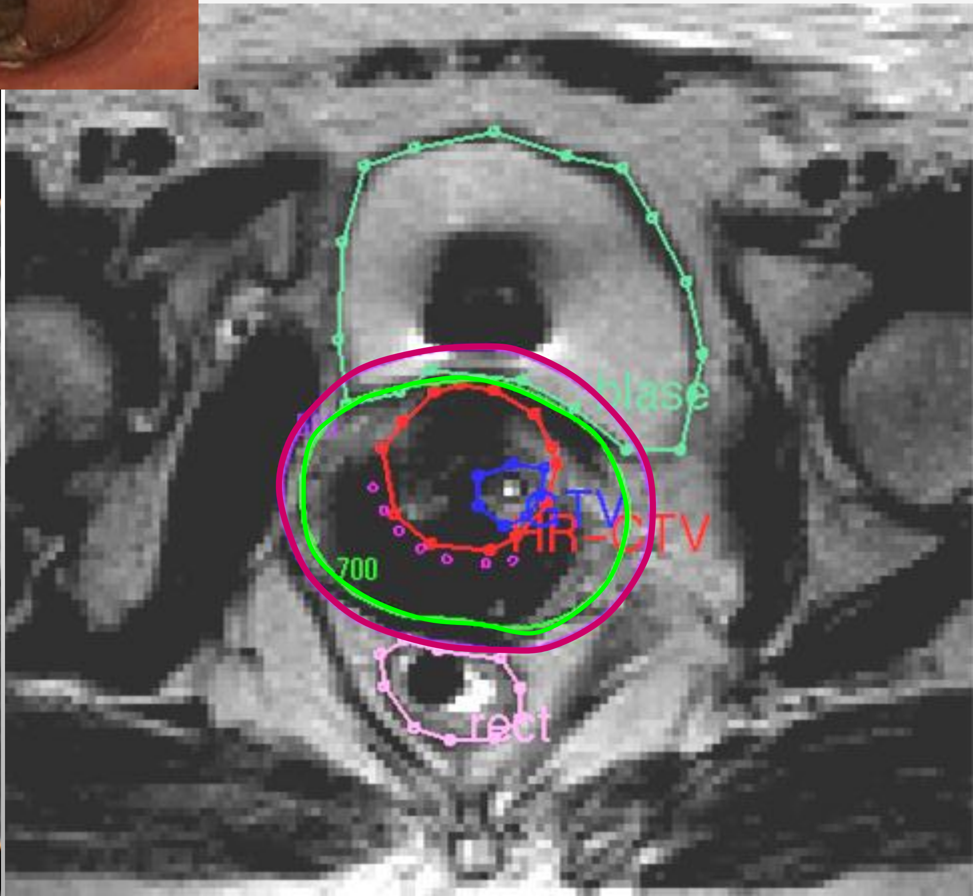
Homogenous volume for inverse dose planning

How could this happen?

D2cm3 = 65.7 Gy EQD2$_{(\alpha/\beta=3)}$

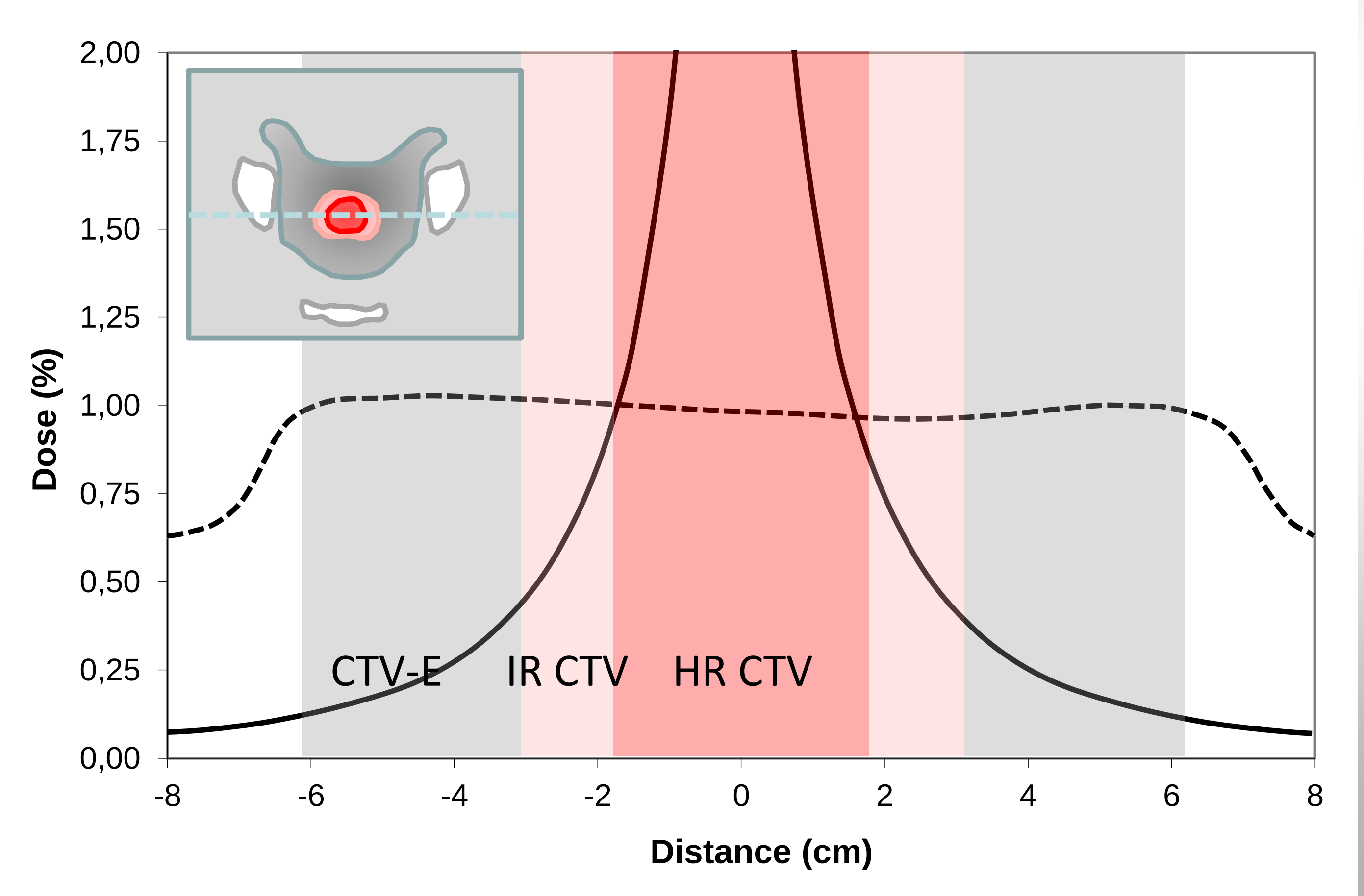
D2cm3 = 79.2 Gy EQD2$_{(\alpha/\beta=3)}$



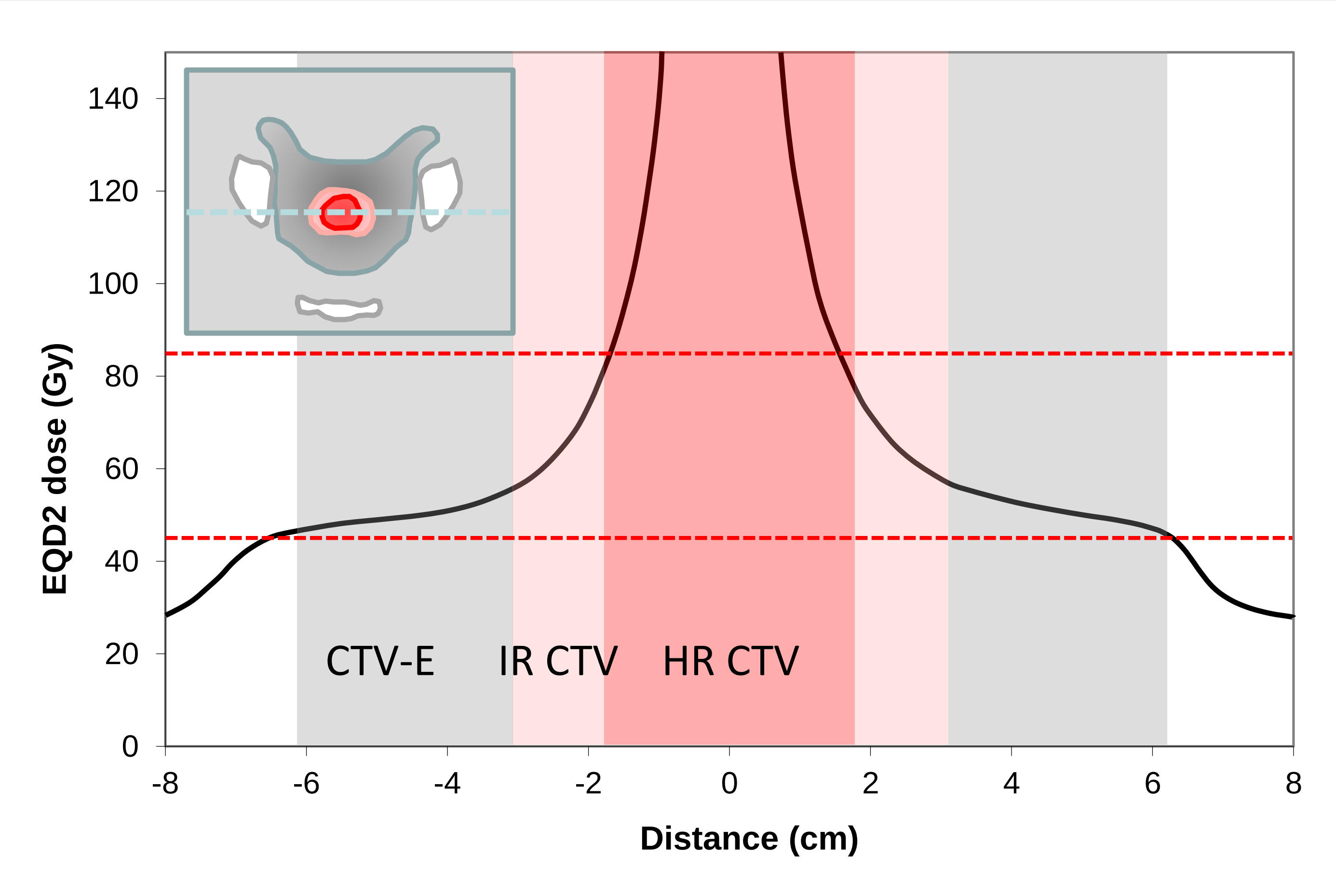


Depth dose: physical dose

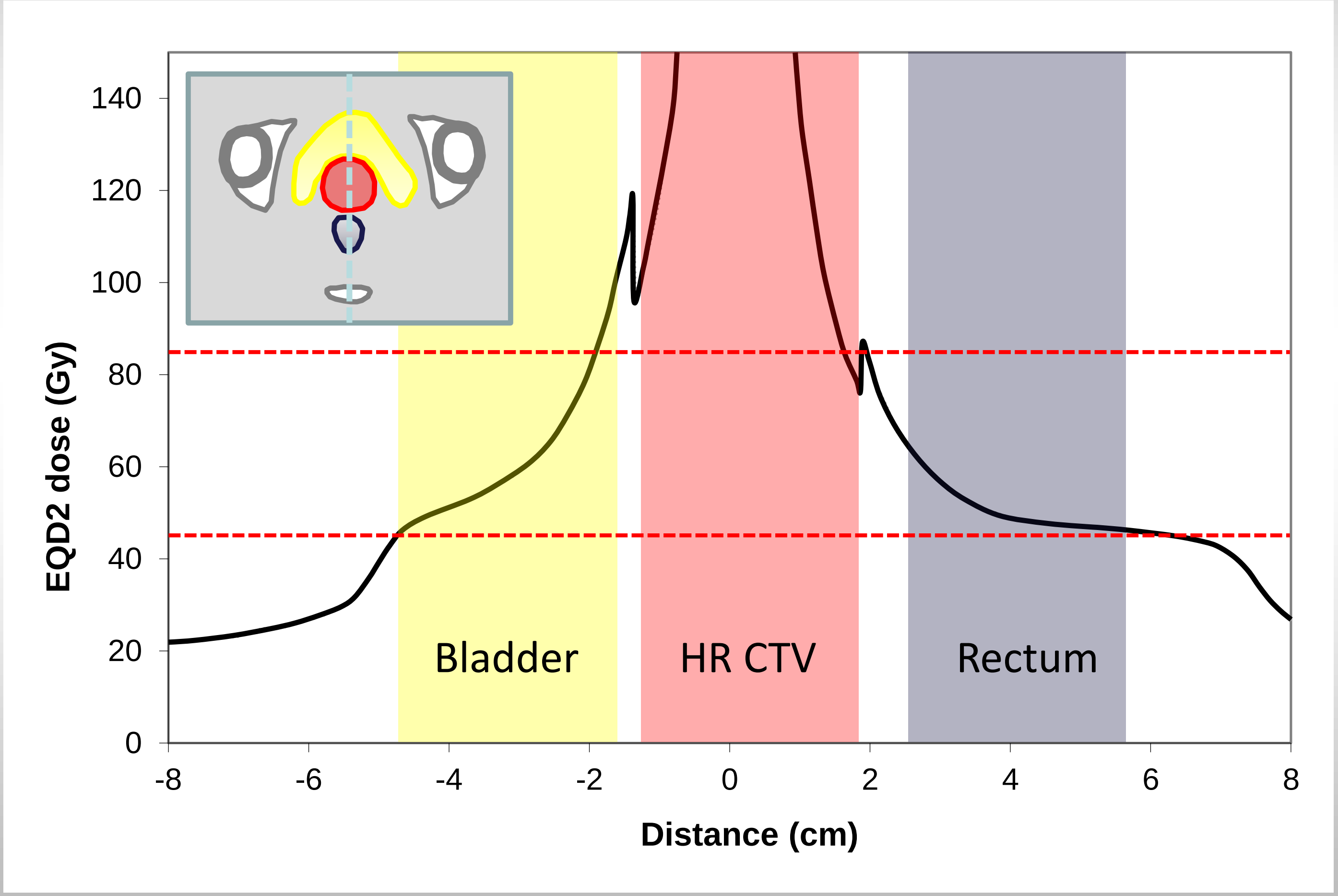
High, intermediate, low doses within mm
Dose gradient: 6% pr mm at point A



EBRT+BT: total EQD2 tumour



EBRT+BT: total EQD2 OARs



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~~

Limitations of the EQD2 model for BT

- **Chemotherapy is not taken into account**
- **Uncertainty increases for single fraction dose values >7-10Gy**
- **Only cell repair is considered**
- **α/β values and $T_{1/2}$ are under discussion (E.g. tumour type prostate, OAR etc.)**
- **Repopulation not taken into account (while we know that overall treatment time is important)**

Repopulation
– changing the overall treatment time -

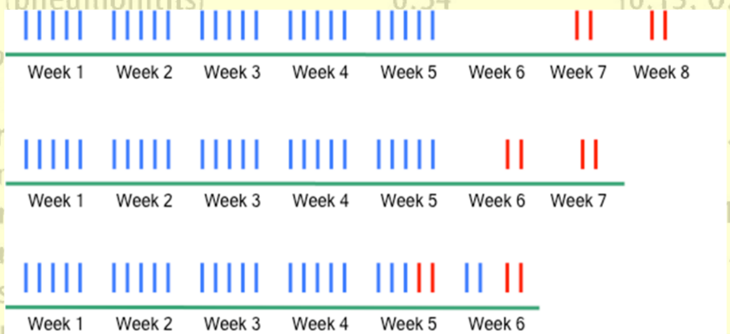
Influencing the local control rate

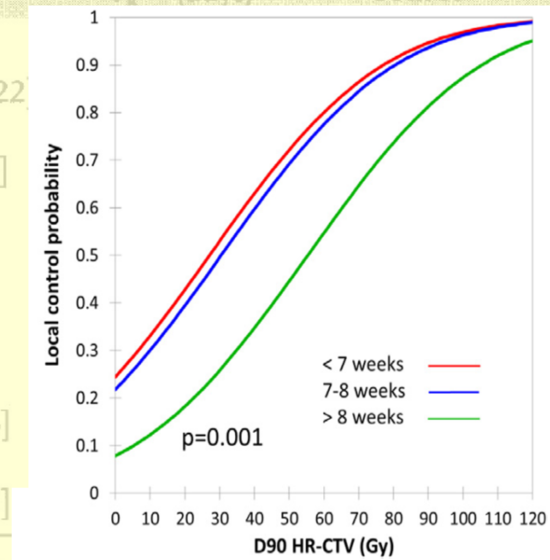
$$EQD_{2,T} = EQD_{2,t} - (T - t)D_{prolif}$$

- Increasing OTT by one week is equivalent to a loss of 5 Gy in CTV_{HR} D90

Tanderup et al Radiother Oncol, 2016

- Timing of the BT boost?





EBRT ⟷ BT

Mazeron et al, Radiother Oncol 2015

„Per day delay in overall treatment time results in loss of ~ 0.3 – 0.8 Gy/day“

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** **cPT2b pN0**
GTV at diag.	**88 cm^3**
chemoth.	**cisplatin**

EXTERNAL BEAM THERAPY		**TUMOUR**	**OAR**
dose per fraction	1,8	D_{iso} [α/β=10Gy]	D_{iso} [α/β=3Gy]
fractions without central shield	25	44,3	43,2
fractions with central shield		0,0	0,0
total dose	**45,0**	**44,3**	**43,2**

BRACHYTHERAPY	**F 1**	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**
date						
physicist						
MR / CT	MR	MR	MR	MR		
applicator(s): type	tandem-ring	tandem-ring	tandem-ring	tandem-ring		
applicator(s): dimensions	r34i60	r34i60	r34i60	r34i60		
eval plan, remarks	2	2	3	2		

dose values in Gy

TOTAL BT	**TOTAL BT + EBT**
mean	*stddev*

Treatment planning documentation of fractionated gynaecological BT (HDR)

TRAK [cGy at 1m]	0,54	0,49	0,47	0,44			**1,94**	
prescribed dose PD	7	7	7	7				
PD $_{iso}$ [α/β=10Gy]	9,9	9,9	9,9	9,9	0,0	0,0	39,7	**83,9**
volume of PD [cm^3]	121,1	106,9	97,7	89,5			***103,8***	*11,7*
PDx2	14,0	14,0	14,0	14,0	0,0	0,0		
PDx2 $_{iso}$ [α/β=10Gy]	28,0	28,0	28,0	28,0	0,0	0,0	112,0	156,3
volume of PDx2 [cm^3]	41,6	33	30	26,1			*32,7*	*5,7*
pres. point level (A / My / [mm])	A	A	A	A				
pres. point [mm $_{left}$ / mm $_{right}$]	22 / -22	A	A	19 / -19				
dose to + A left	7,6	7,1	6,7	6,5				
A_{left} - D_{iso} [α/β=10Gy]	11,1	10,1	9,3	8,9	0,0	0,0	39,5	**83,8**
dose to - A right	7,8	6,9	7,3	6,7				
A_{right} - D_{iso} [α/β=10Gy]	11,6	9,7	10,5	9,3	0,0	0,0	41,1	**85,4**
dose to A mean	7,7	7,0	7,0	6,6	0,0	0,0		
A_{mean} - D_{iso} [α/β=10Gy]	11,4	9,9	9,9	9,1	0,0	0,0	40,3	**84,6**
GTV [cm^3]	8,8	7,8	5,5	6,1			*7,1*	*1,3*
D 100 = MTD	9,3	8,9	6,9	6,2				
D 100 $_{iso}$ [α/β=10Gy]	15,0	14,0	9,7	8,4	0,0	0,0	47,1	91,3
D 90	13,3	12,0	11,7	10,6				
D 90 $_{iso}$ [α/β=10Gy]	25,8	22,0	21,2	18,2	0,0	0,0	87,2	**131,4**
V 100 = volume of PD [%]	100,0%	100,0%	99,9%	99,1%			***99,8%***	*0,4%*
CTV [cm^3]	53,5	51,5	40	40,4			*46,4*	*6,2*
D 100 = MTD	5,0	5,0	3,5	3,8				
D 100 $_{iso}$ [α/β=10Gy]	6,3	6,3	3,9	4,4	0,0	0,0	20,8	65,1
D 90	8,1	7,0	6,9	6,4				
D 90 $_{iso}$ [α/β=10Gy]	12,2	9,9	9,7	8,7	0,0	0,0	40,6	**84,8**
V 100 = volume of PD [%]	95,9%	90,4%	89,3%	86,8%			***90,6%***	*3,3%*
volume of mean A-dose [%]	92,7%	90,4%	89,3%	88,9%			*90,3%*	*1,5%*

Treatment planning documentation of fractionated gynaecological BT (HDR)

BLADDER [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
- LQ model does not tage OTT time into account – remember loss of 5Gy per week at OTT>50 days
- Implement a spreadsheet in your department

$$EQD_2 = n \cdot d \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

$$EQD_2 = 7 \cdot \frac{7+10}{2+3} Gy = 10Gy$$

BLADDER [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**

Parametrial and nodal boost including midline block: combination of EBRT and BT

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

Lucknow 2018

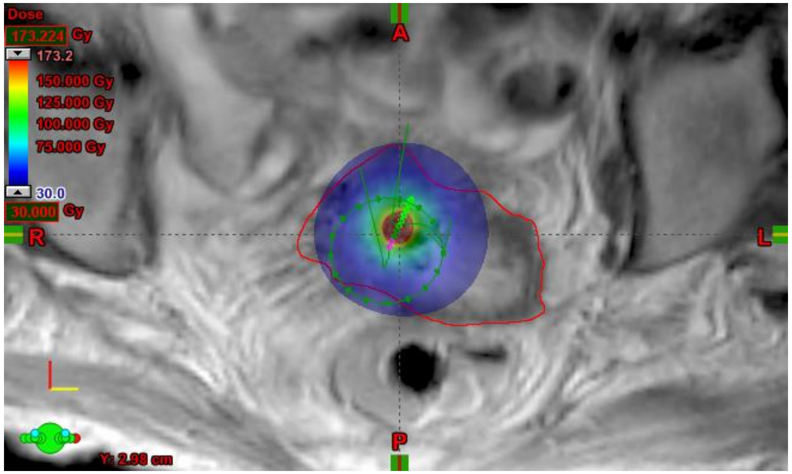
Kari Tanderup

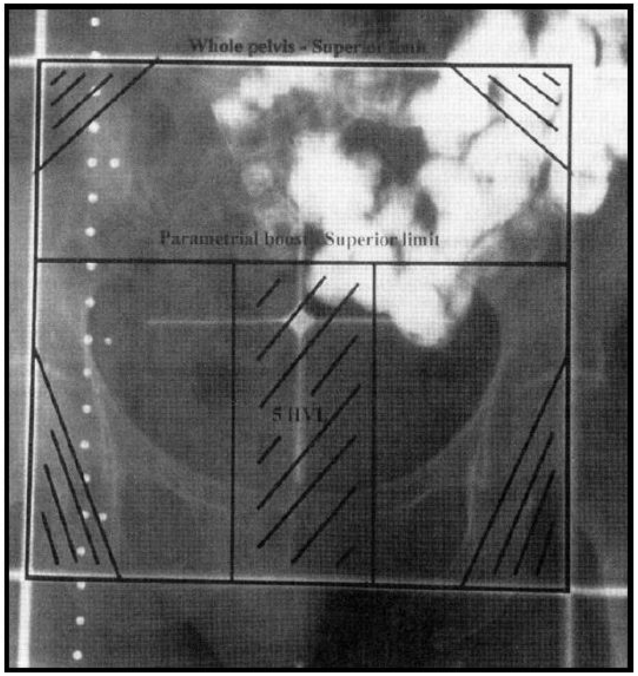
Ina Jürgenliemk-Schulz

Aarhus University Hospital

Indication for parametrial boost

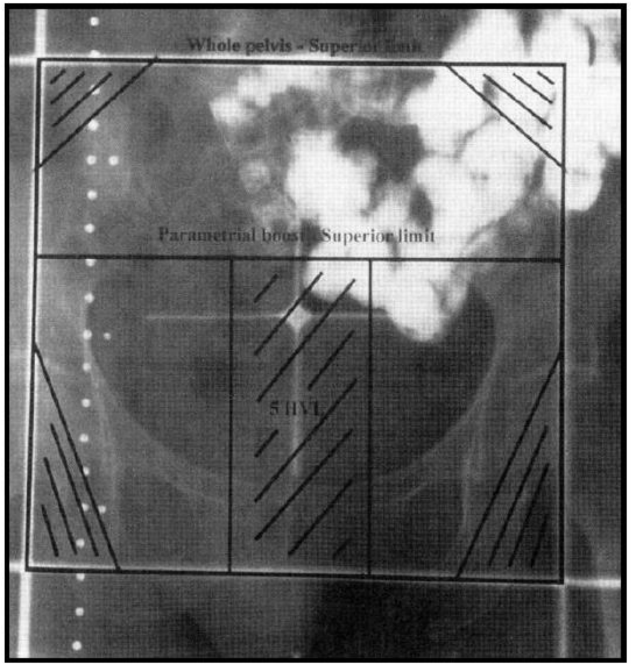
- Bulky stage IIB and IIIB
- Insufficient coverage of BT dose





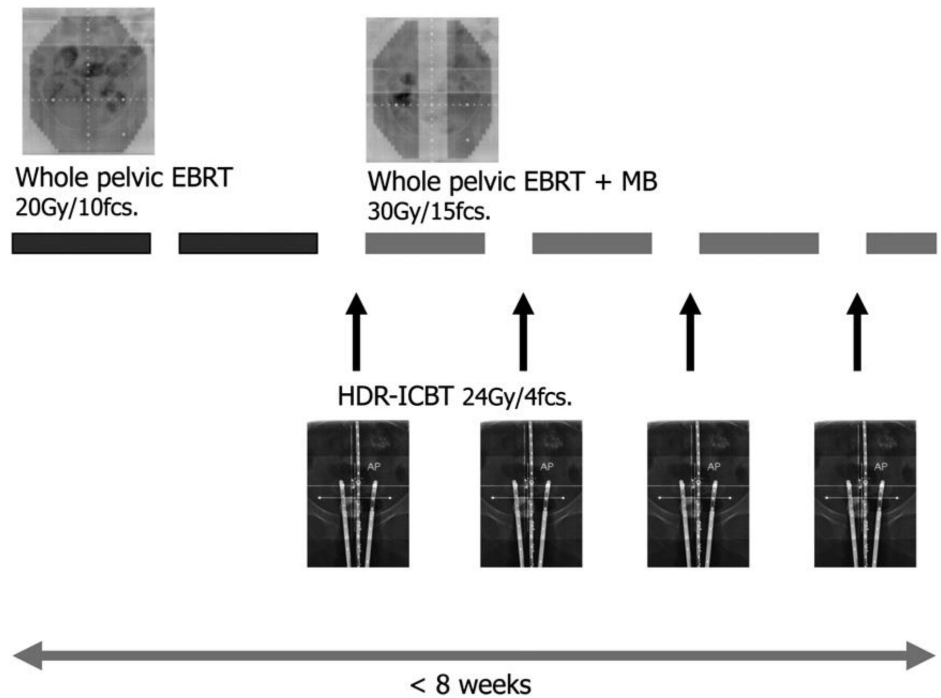
Standard technique

- Delivered after 45-50Gy EBRT
- Midline block of 4cm
- Upper border: bottom of sacroiliac joints
- 3-5 fractions of 1.8Gy
- GOG standard:
  - 5.4Gy in stage IIB
  - 9Gy in stage IIIB



Midline block

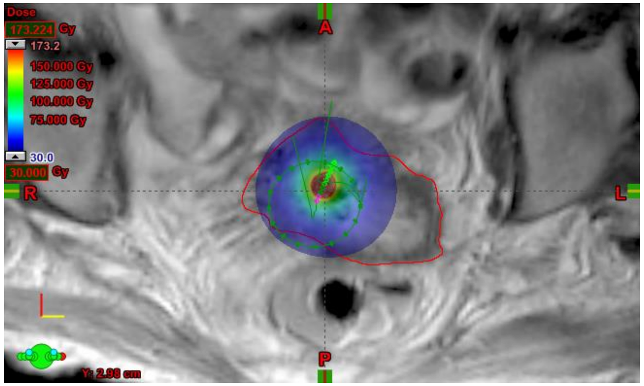
- **EBRT pelvis to e.g. 50Gy**
- **Application of midline block after e.g. 20Gy**
- **Higher amount of BT applied**
  - **e.g. 6.5Gy in 6 fractions**
- **BT is started early during EBRT**
  - **e.g. week 1 or 2**
- **Widely used in Japan**
  - **70% of patients in Japan, Patterns of care 1999-2001, Toita et al IJROBP 70(3) 2008**



Toita et al, IJROBP, Vol. 82, No. 1, 49–56, 2012

Challenge: Midline block dose calculation

- Which dose does midline block fields deliver to HR-CTV and IR-CTV (D90 and D100)?
- Does midline blocked fields deliver dose to bladder, rectum and sigmoid (D2cc)?
- Challenge for dose calculation:
  - BT and EBRT physical doses cannot be directly added and transformed to EQD2 dose
  - Anatomy changes between EBRT and BT



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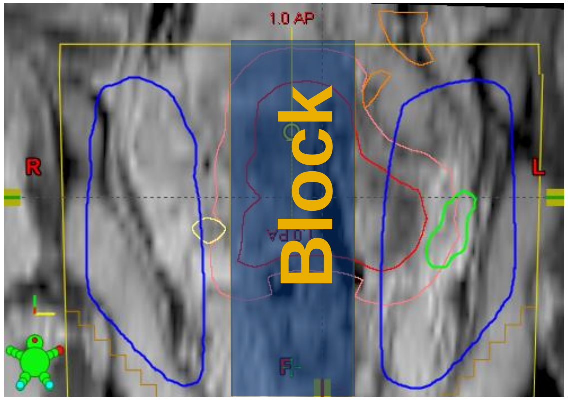

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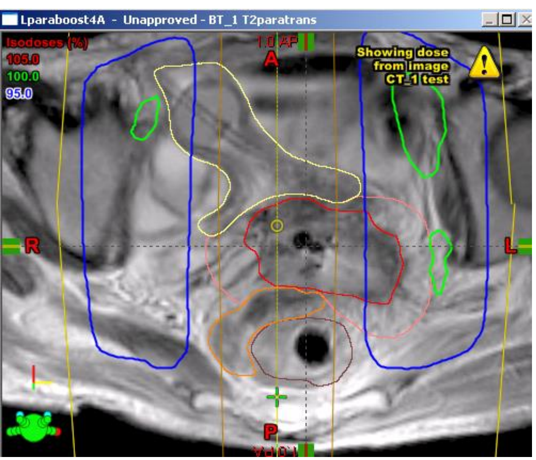
Accumulation of dose

- **6 patients with large tumours and/or unfavourable topography were analysed**
- **HR-CTV volumes of 31-100 ccm**
- **Radiotherapy schedule:**
  - **45 Gy (25fx) whole pelvis EBRT**
  - **9 Gy (5fx) midline block boost**
  - **4x7 Gy HDR intracavitary BT**

Midline block



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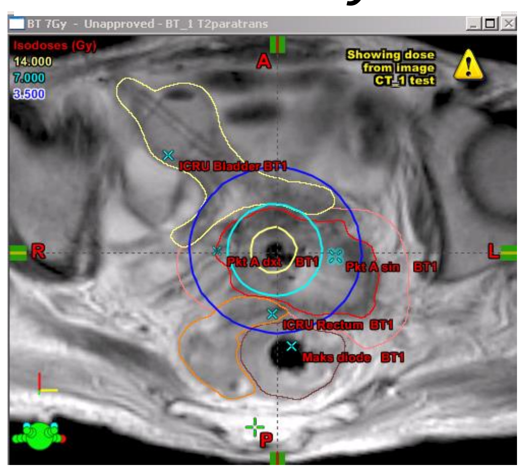
Intracavitary BT



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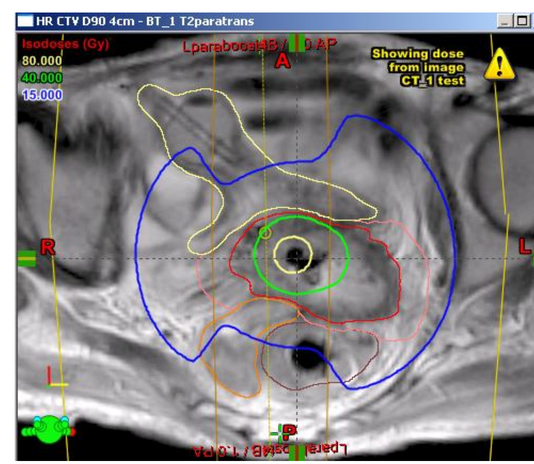
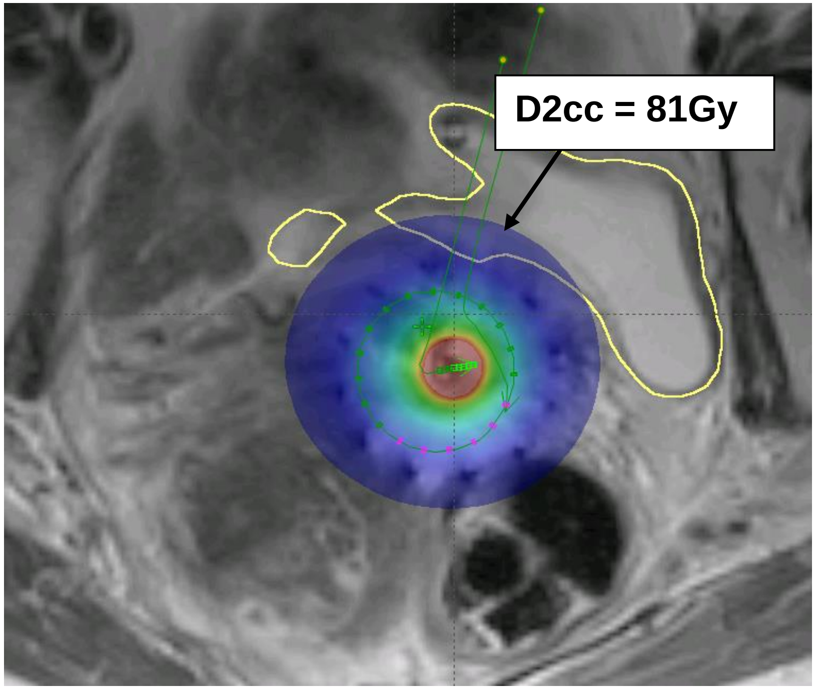
Midline block + BT



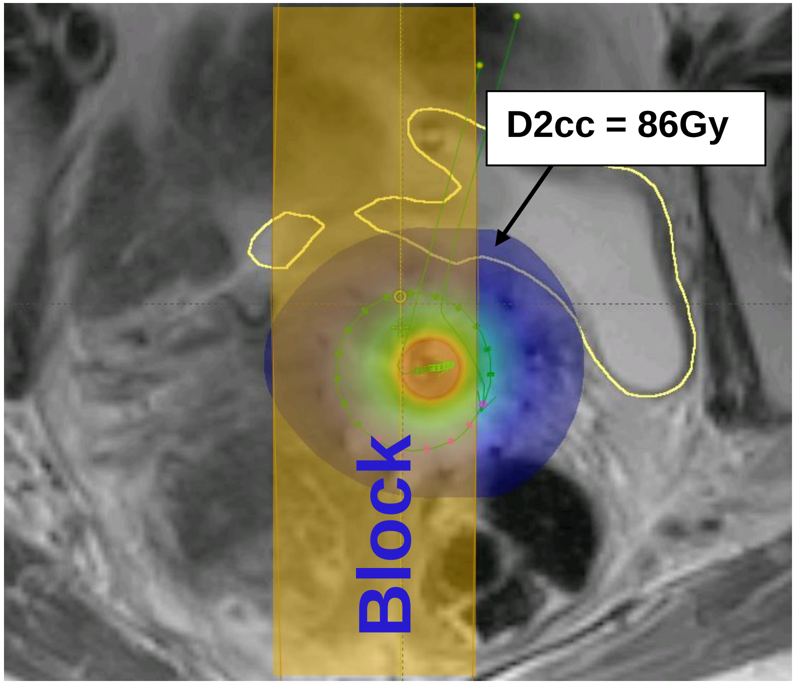
L. Fenkell et al, IJROBP 2011

Example, dose to OAR

BT

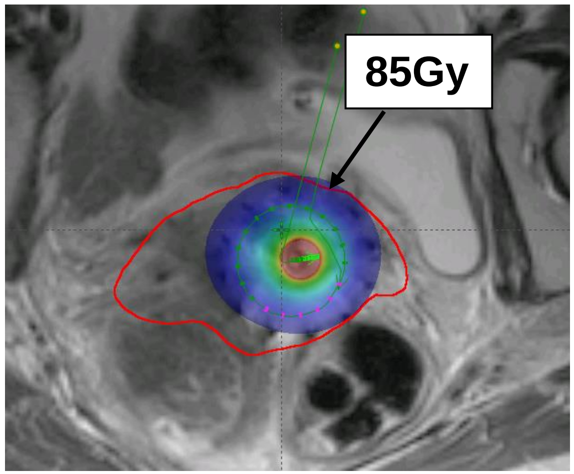
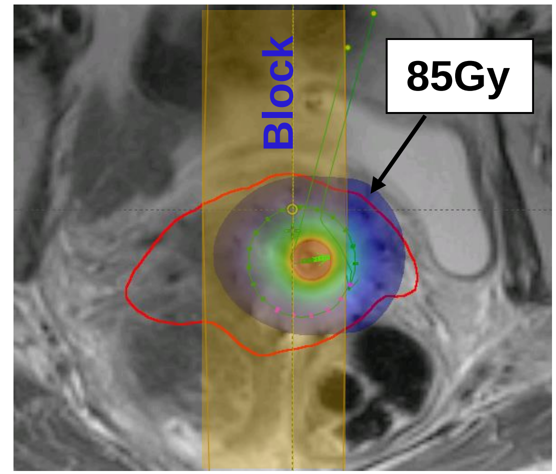
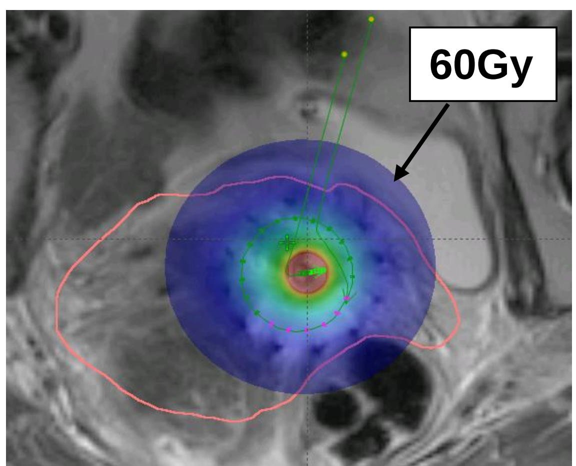
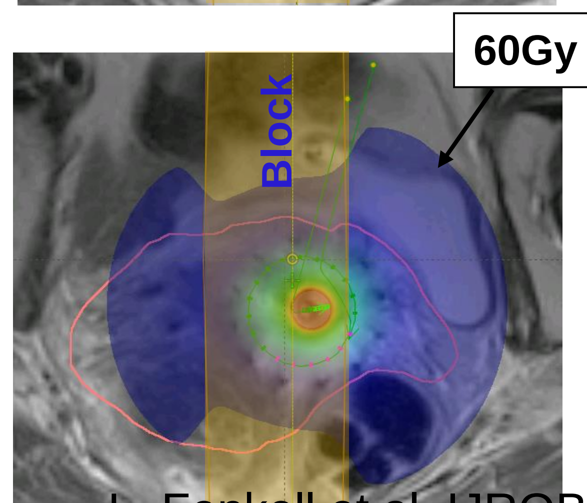


BT + midline boost



L. Fenkell et al, IJROBP 2011

Example, dose to HR and IR CTV

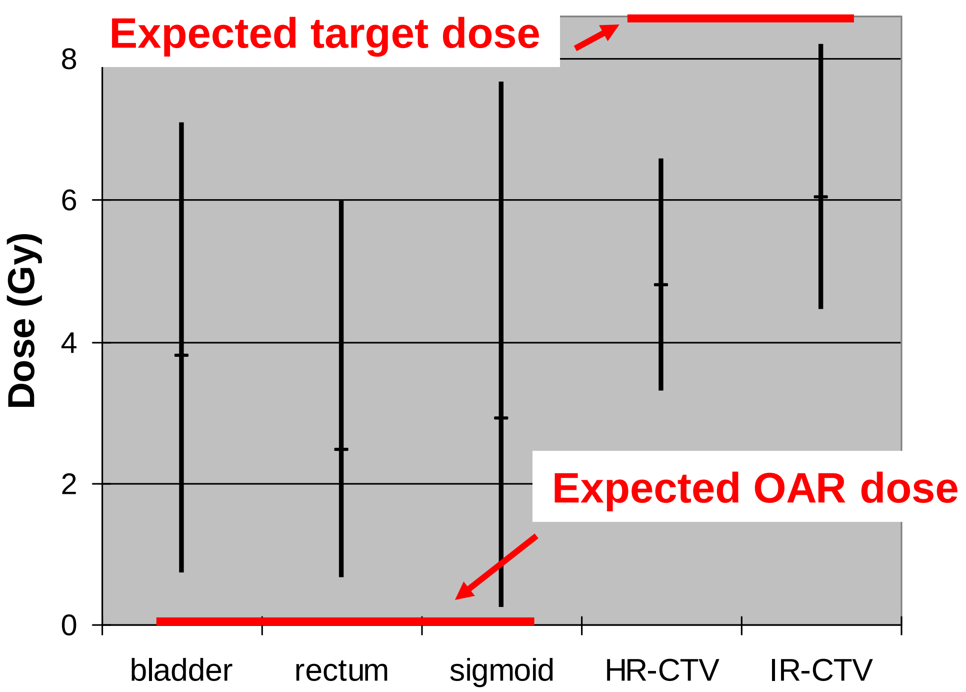
	BT	BT + midline boost
HR CTV		
IR CTV		

L. Fenkell et al, IJROBP 2011

Addition of BT dose and EBRT parametrial boost dose

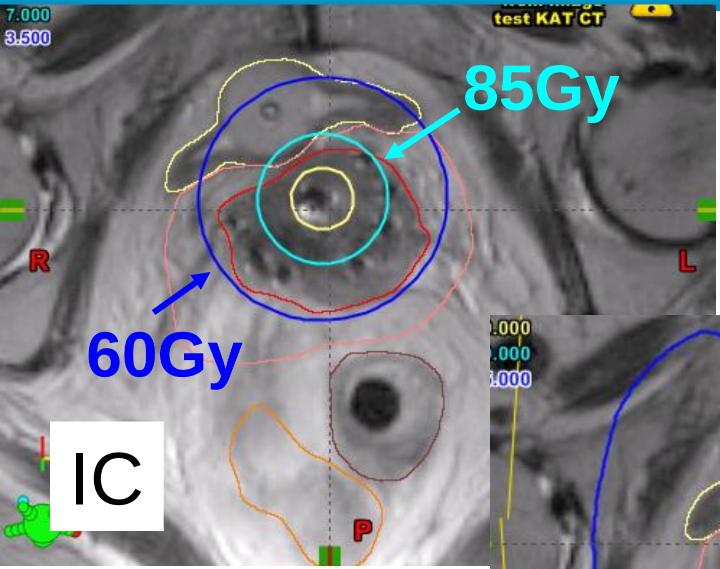
Significant uncertainties for addition of BT and parametrial boost!!

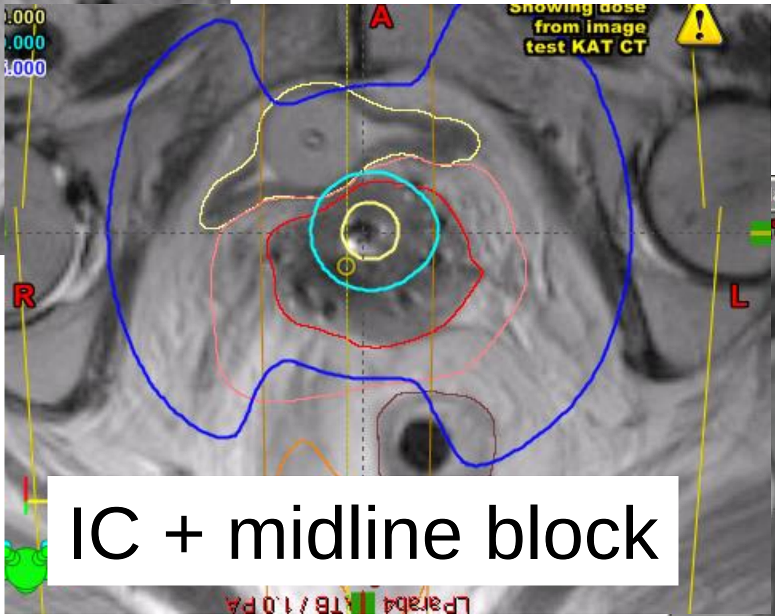
- 9 Gy parametrial boost
- Target dose << 9Gy
- Significant OAR dose

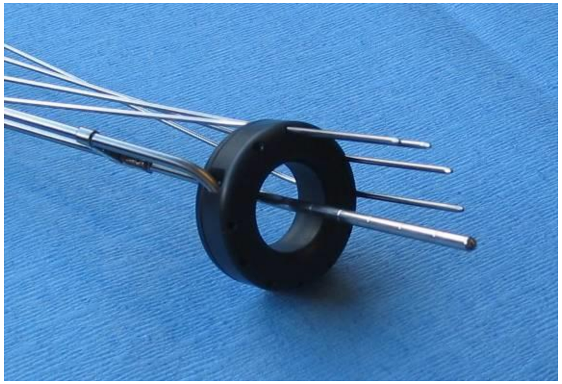


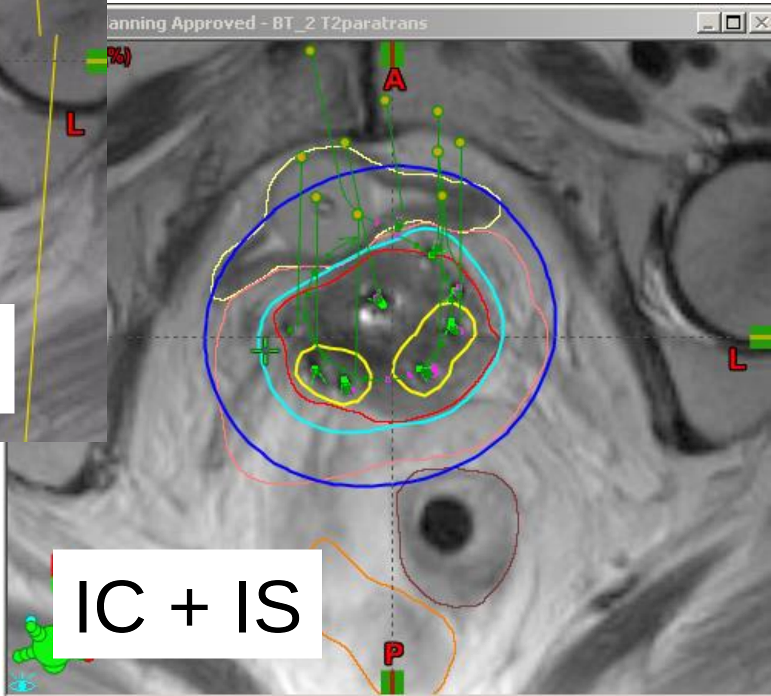
L. Fenkell et al, IJROBP 2011

Midline block boost compared to interstitial needles









Comparison between IC+BT and IC/IS

A number of 23 patients (stage II, III, IV) with parametrial involvement at time of BT

EQD2 (Gy)	IC+PB Mean (SD)	IC/IS Mean (SD)	Diff IC+PB - IC/IS	p value
GTV D90	110.7 (15.7)	106.5 (10.5)	4.0 (11.2)	0.10
HR CTV D90	88.7 (5.3)	89.0 (3.4)	-0.3 (4.8)	0.79
D_{2cm3} Bladder	77.2 (5.9)	71.8 (5.0)	5.4 (4.0)	<0.001
D_{2cm3} Rectum	68.1 (6.3)	64.1 (4.8)	4.4 (2.7)	<0.001
D_{2cm3} Sigmoid	67.5 (5.5)	62.6 (5.2)	5.0 (2.9)	<0.001
D_{2cm3} Bowel	68.3 (6.9)	62.1 (6.7)	6.2 (3.5)	<0.001

Mohamed et al, Brachytherapy 2014

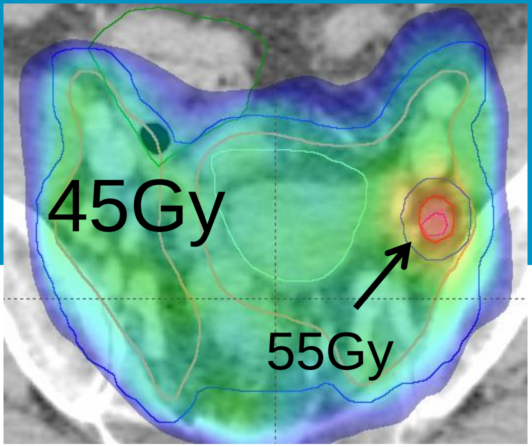
Techniques for boosting of pathologic lymph nodes

- **Techniques:**
  - **Post boost with CRT**
  - **Simultaneous integrated boost with IMRT**

Post-boost with CRT

- AP-PA or 4 Field Box
- Avoid central pelvis irradiation
- Assessment of BT contribution (~0-6Gy)
- CTV according to residual GTV (taking shrinkage into account)
- Examples of dose and fractionation:
  - Aim for total EBRT+BT dose of 55-60Gy
  - E.g. 50Gy whole pelvis + 5Gy
  - E.g. 45Gy whole pelvis + 10Gy

Simultaneously integrated lymph node boost (SIB)



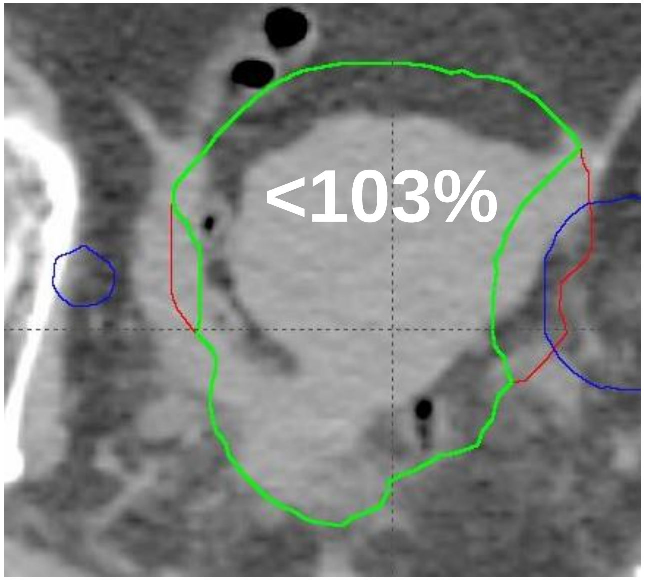
- **SIB lymph node boost:**
  - **IMRT/VMAT/Tomotherapy**
  - **Dose planning with two dose levels**
    - **Elective target**
    - **Pathological lymph node target**
- **Recommended lymph node dose in EMBRACE II:**
  - **45Gy/25fx to elective CTV**
  - **Aim for a total of 60Gy EBRT+BT to CTV-N**
    - **55Gy/25fx (within pelvis)**
    - **57.5Gy/25fx (outside pelvis)**

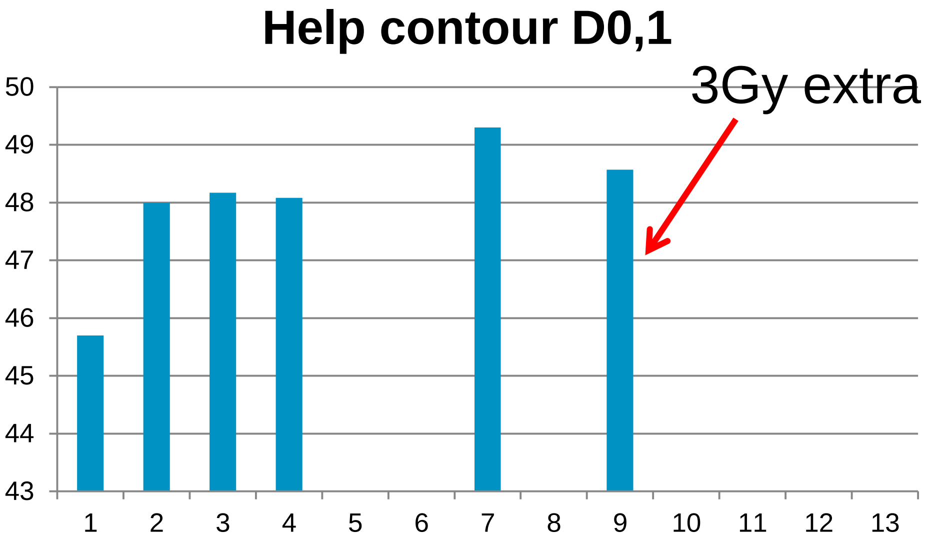
Advantages and disadvantages of SIB boost

- **Advantages:**
  - **Limits overall treatment time of nodal target (hypo-fractionation of small volumes)**
  - **Limits irradiation of normal tissue as compared to AP-PA post boost**
  - **Is robust to inter-fraction motion**
- **Disadvantages:**
  - **In case of large lymph nodes, the boost volume becomes higher – can be modified through replanning after e.g. 20-25Gy**

Help contour in the region of the primary tumour where BT is delivered

- Homogeneity is particularly relevant when boosting lymph nodes
- Control of dose in the BT region
- Help contour:
    - Margin of 1cm to initial GTV or CTV_{HR}
    - Strict constraint on max dose: 103%





Conclusion

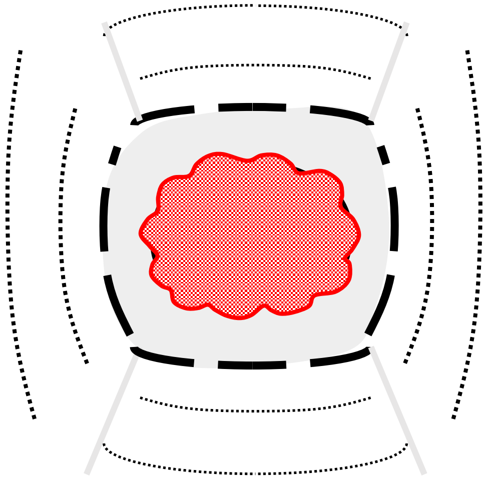
- **Combination of parametrial boost and BT:**
  - **High EBRT and BT gradients in the same region**
  - **Difficult to predict target dose**
  - **Difficult to predict OAR dose**
  - **Large normal tissue volume irradiated to a significant dose**
- **Combination of interstitial BT and intracavitary BT:**
  - **Higher target dose (compared with para-boost)**
  - **Reduced OAR dose (compared with para-boost)**
  - **Better conformality with HR-CTV and IR-CTV**
- **Simultaneous integrated boost**
  - **Limits overall treatment time**

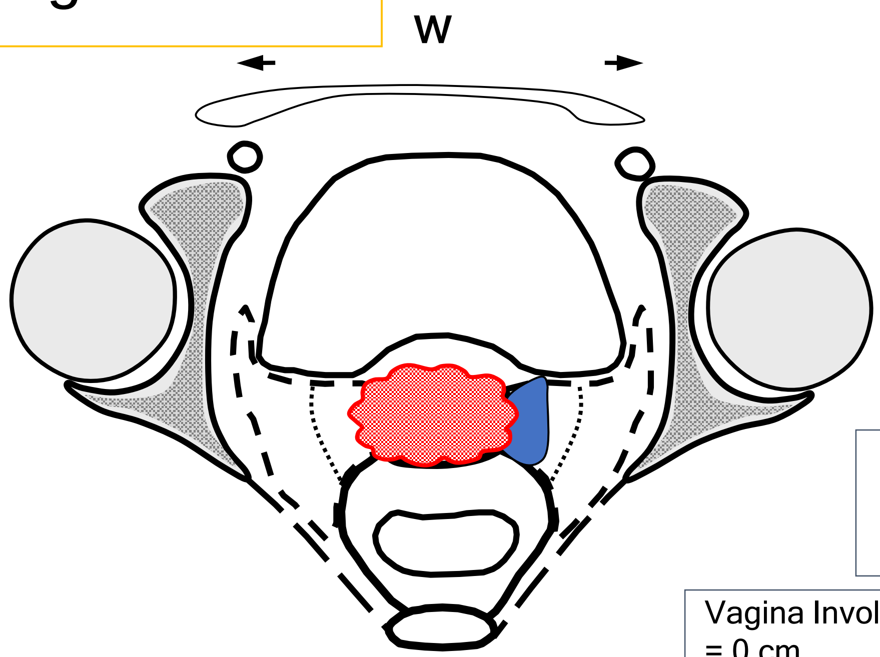
EBRT CONTOURING EXERCISE : HOME WORK

Clinical Drawing

At Diagnosis

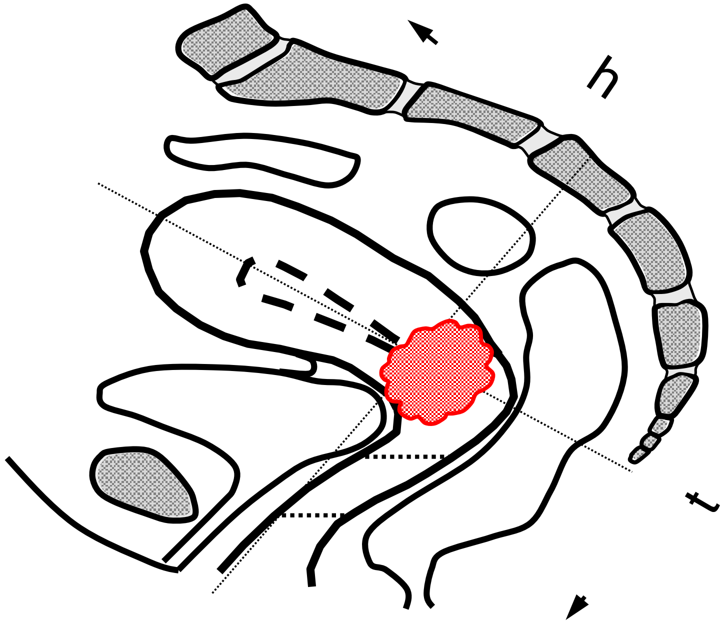
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

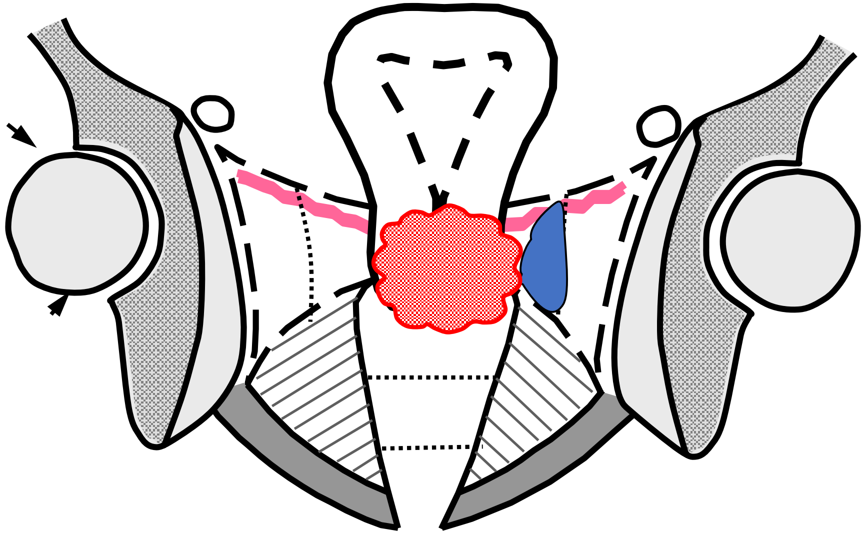




w = 35 mm
h = 35 mm
t = 35 mm

Vagina Involvement
= 0 cm

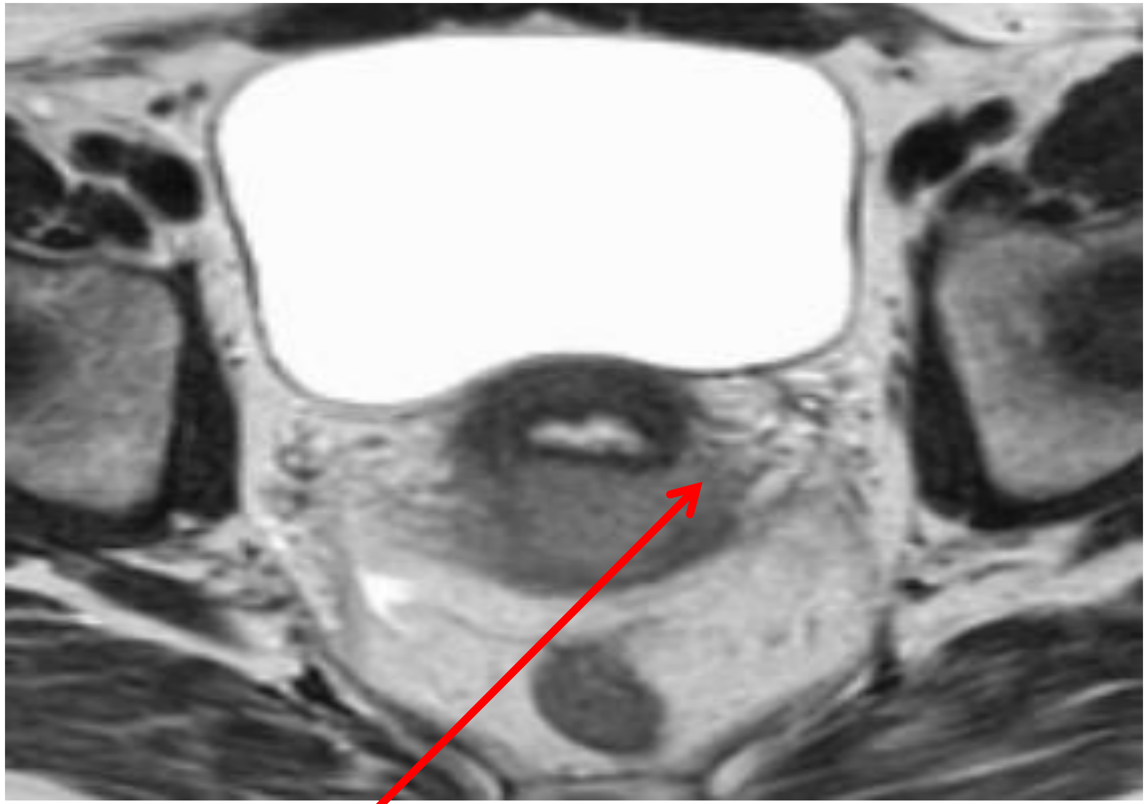


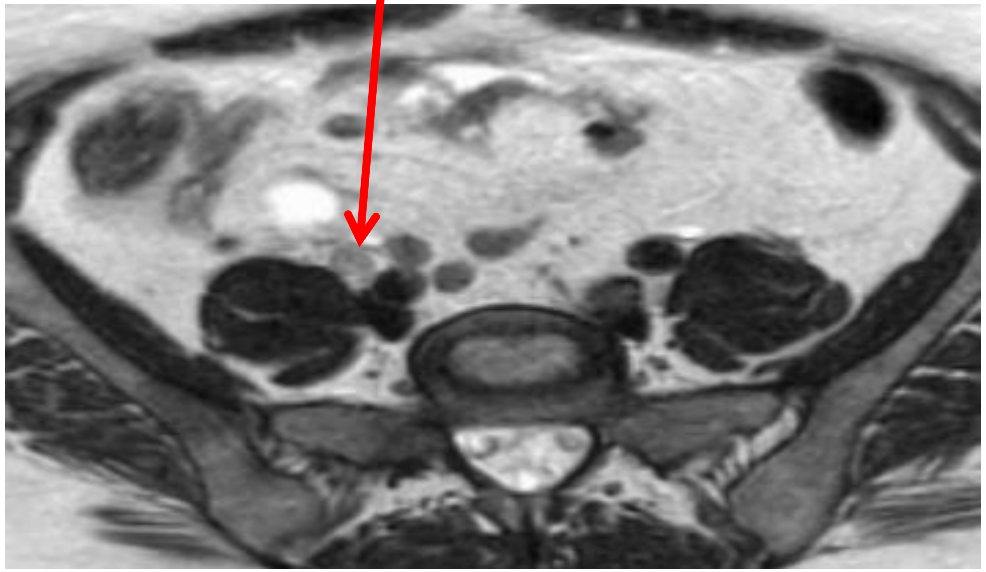


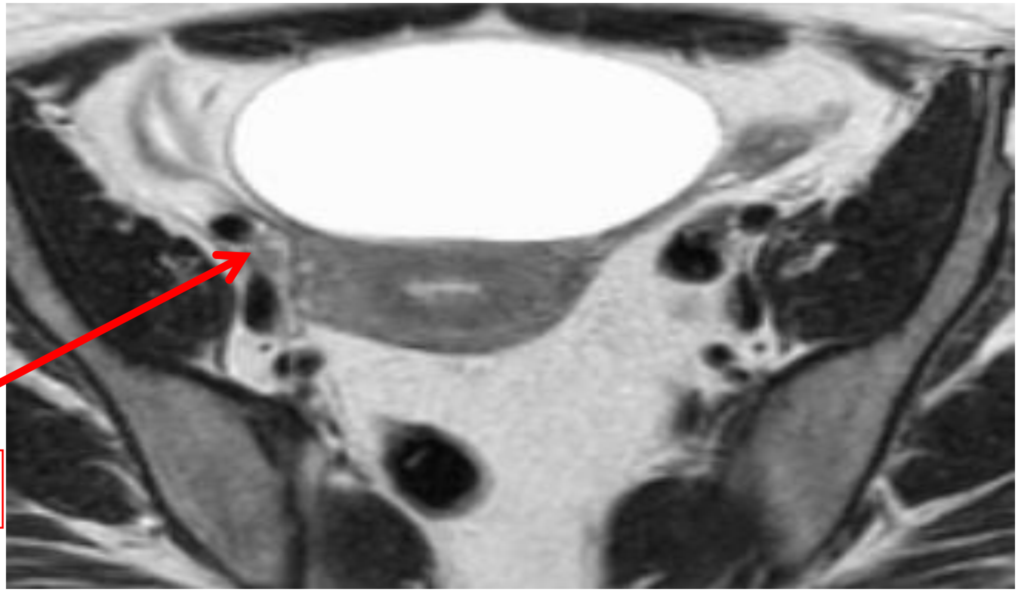
dd/mm/yy

Signature

Initial







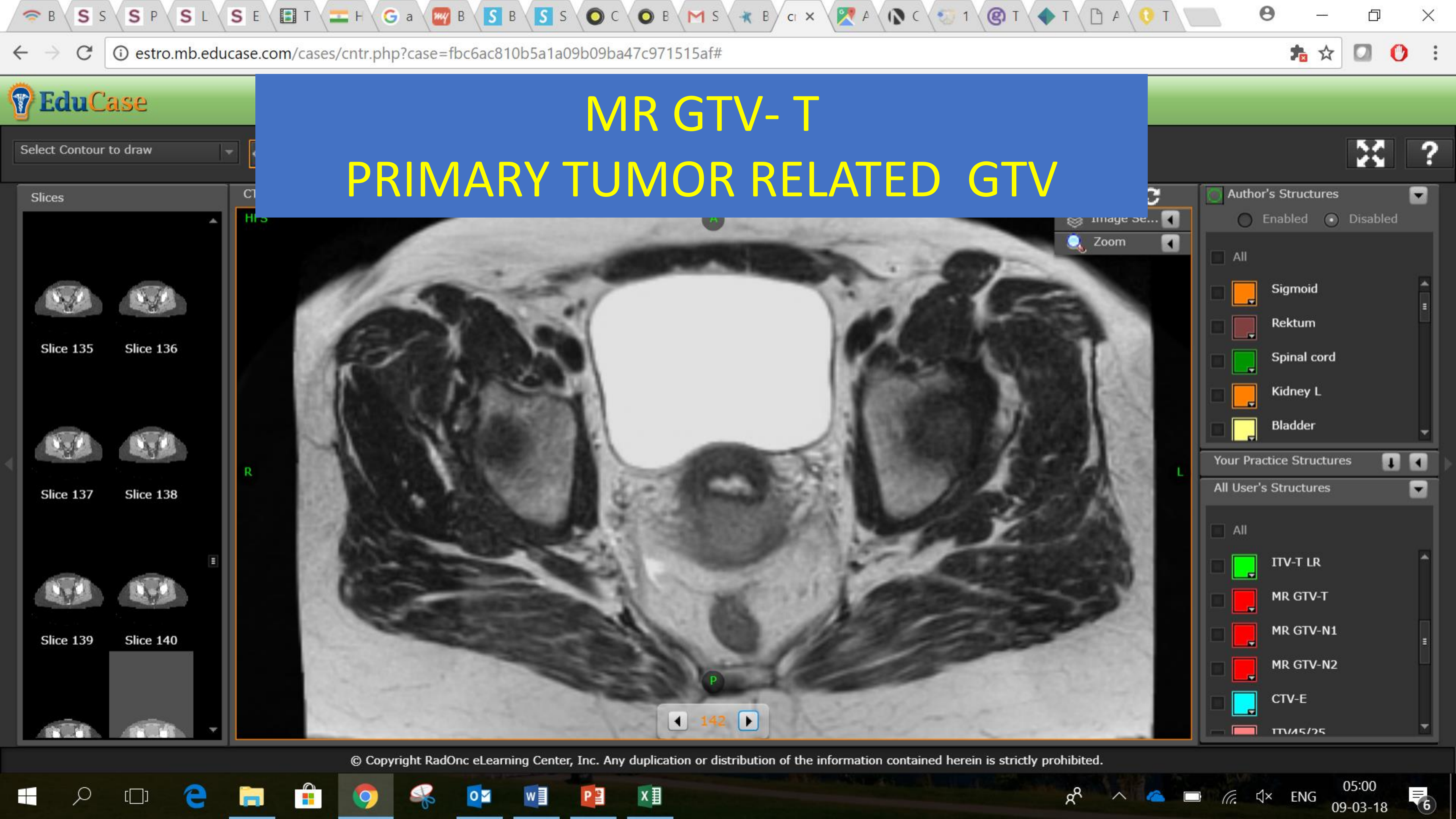
RT Common Iliac node

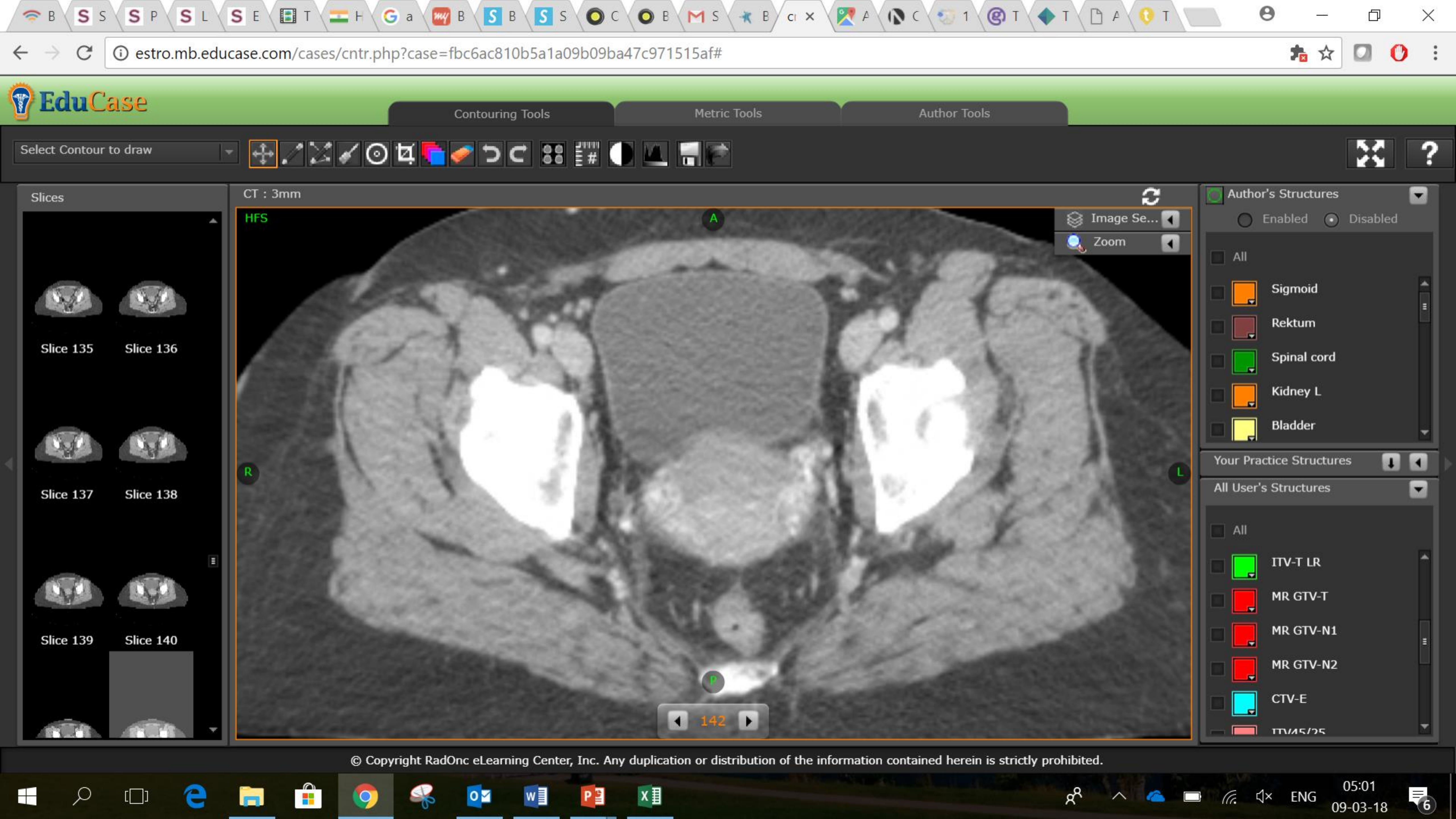
RT para invasion

RT Ext Iliac node

MR GTV- T

PRIMARY TUMOR RELATED GTV

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Contouring Tools
Metric Tools
Author Tools
Select Contour to draw
Slices
Slice 135
Slice 136
Slice 137
Slice 138
Slice 139
Slice 140
CT : 3mm
HFS
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Zoom
142
Author's Structures
Enabled
Disabled
All
Sigmoid
Rektum
Spinal cord
Kidney L
Bladder
Your Practice Structures
All User's Structures
All
ITV-T LR
MR GTV-T
MR GTV-N1
MR GTV-N2
CTV-E
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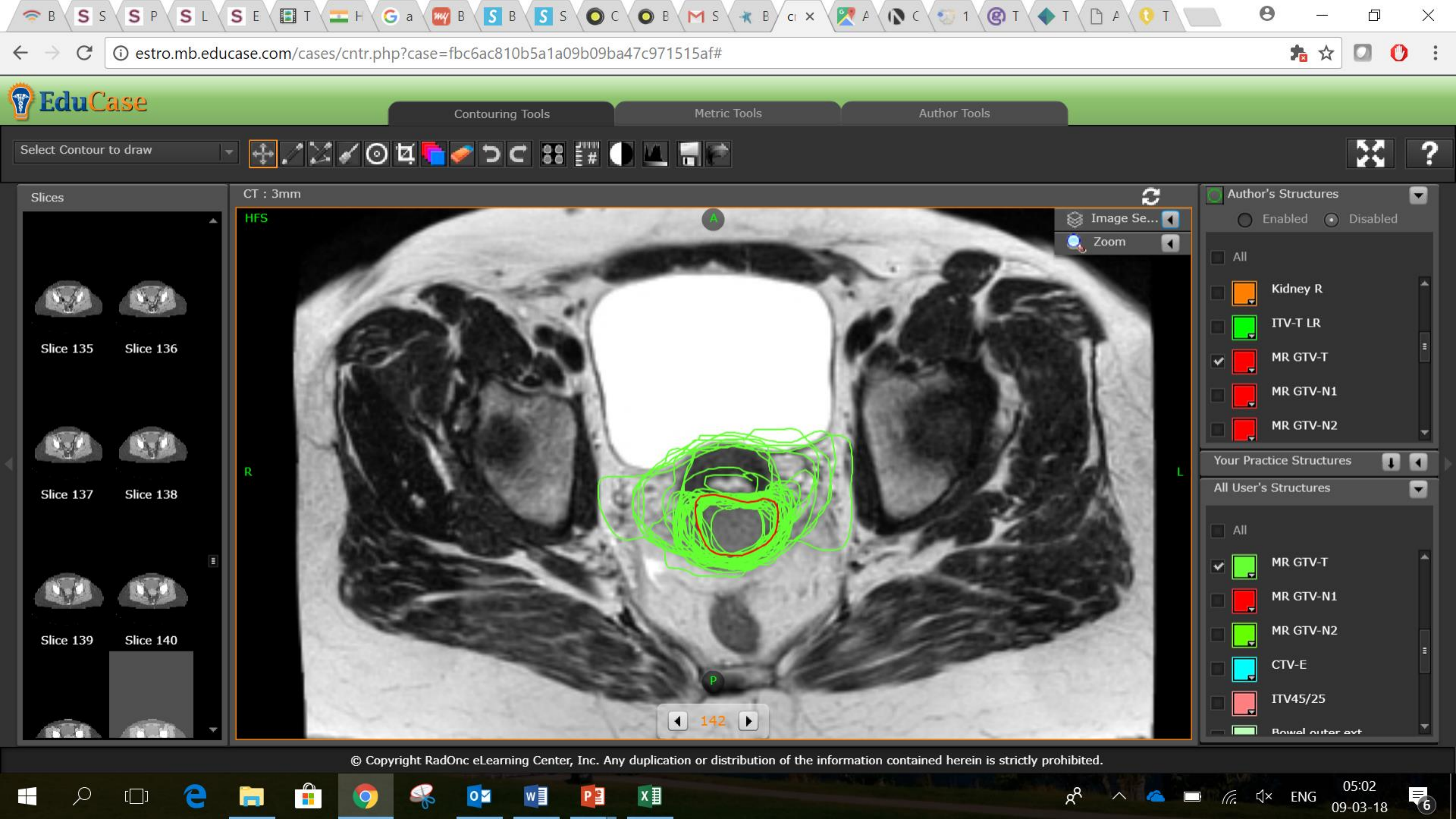
ENG
05:01
09-03-18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Slice 137
Slice 138
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142
Author's Structures
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ITV-T LR
MR GTV-T
MR GTV-N1
MR GTV-N2
Your Practice Structures
All User's Structures
All
MR GTV-T
MR GTV-N1
MR GTV-N2
CTV-E
ITV45/25
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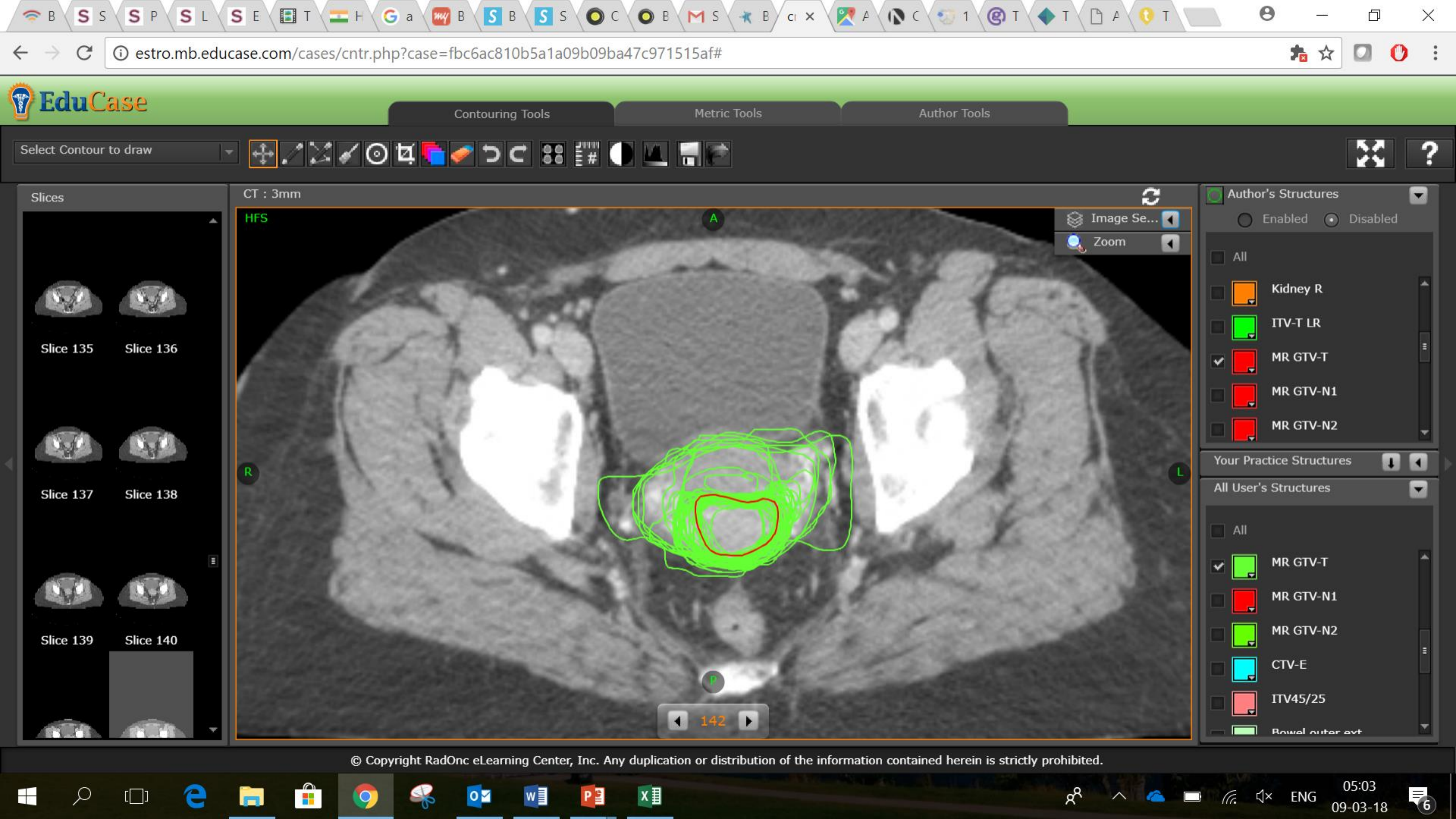
ENG
05:02
09-03-18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CT : 3mm
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142
Author's Structures
Enabled
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All
Kidney R
ITV-T LR
MR GTV-T
MR GTV-N1
MR GTV-N2
Your Practice Structures
All User's Structures
All
MR GTV-T
MR GTV-N1
MR GTV-N2
CTV-E
ITV45/25
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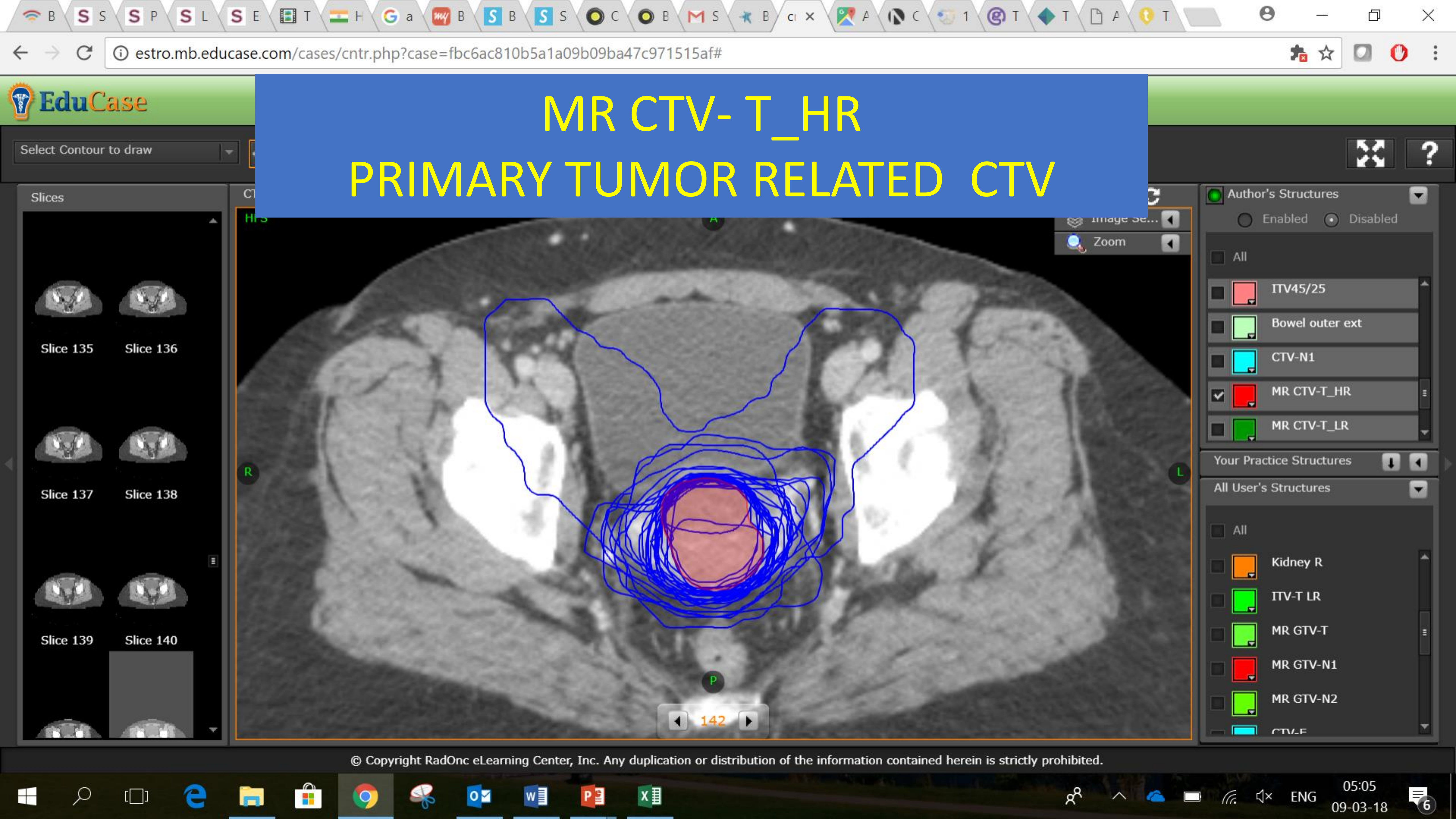
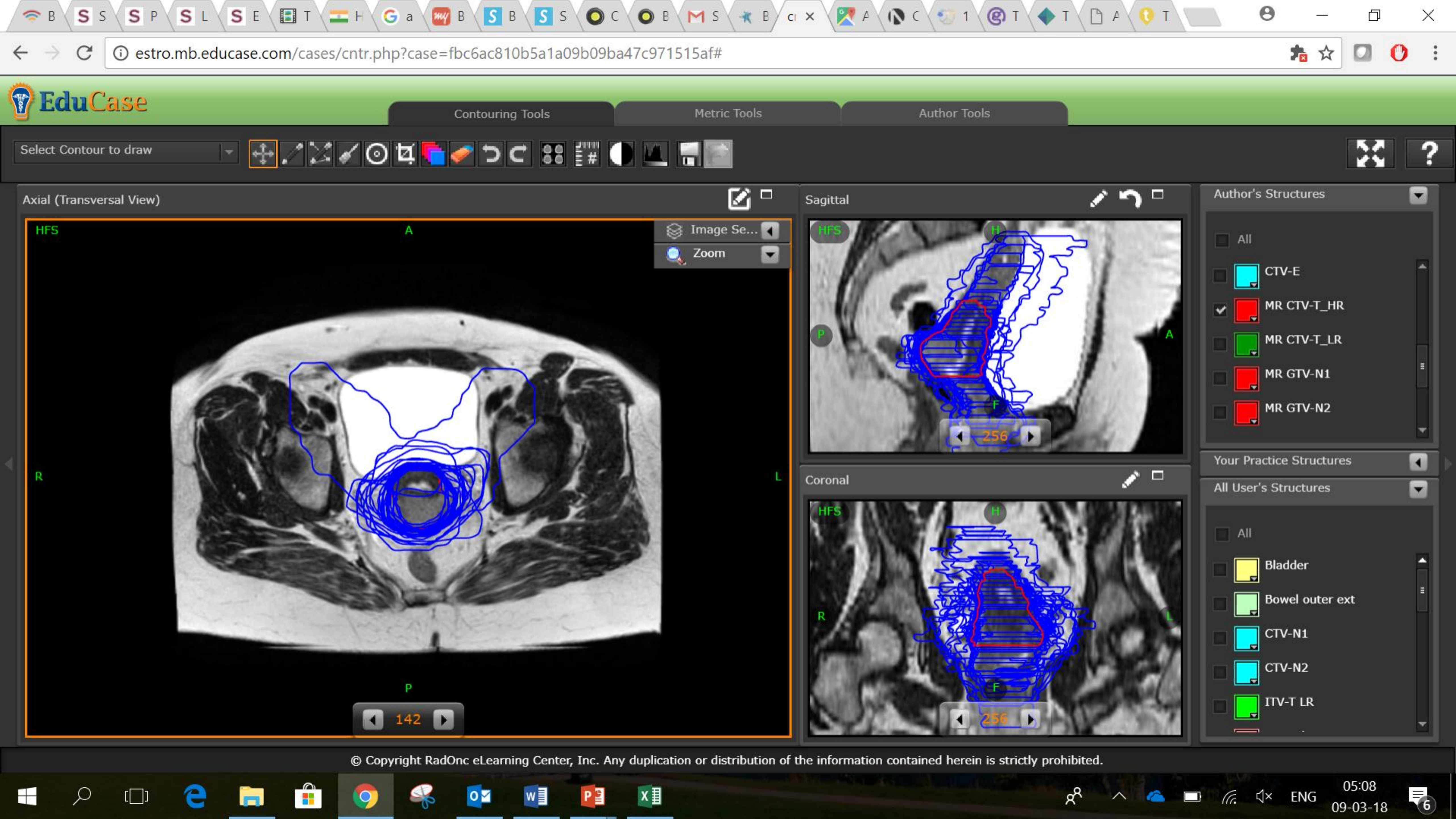
ENG
05:03
09-03-18

MR CTV- T_HR
PRIMARY TUMOR RELATED CTV

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Sagittal
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Author's Structures
All
CTV-E
MR CTV-T_HR
MR CTV-T_LR
MR GTV-N1
MR GTV-N2
Your Practice Structures
All User's Structures
All
Bladder
Bowel outer ext
CTV-N1
CTV-N2
ITV-T LR
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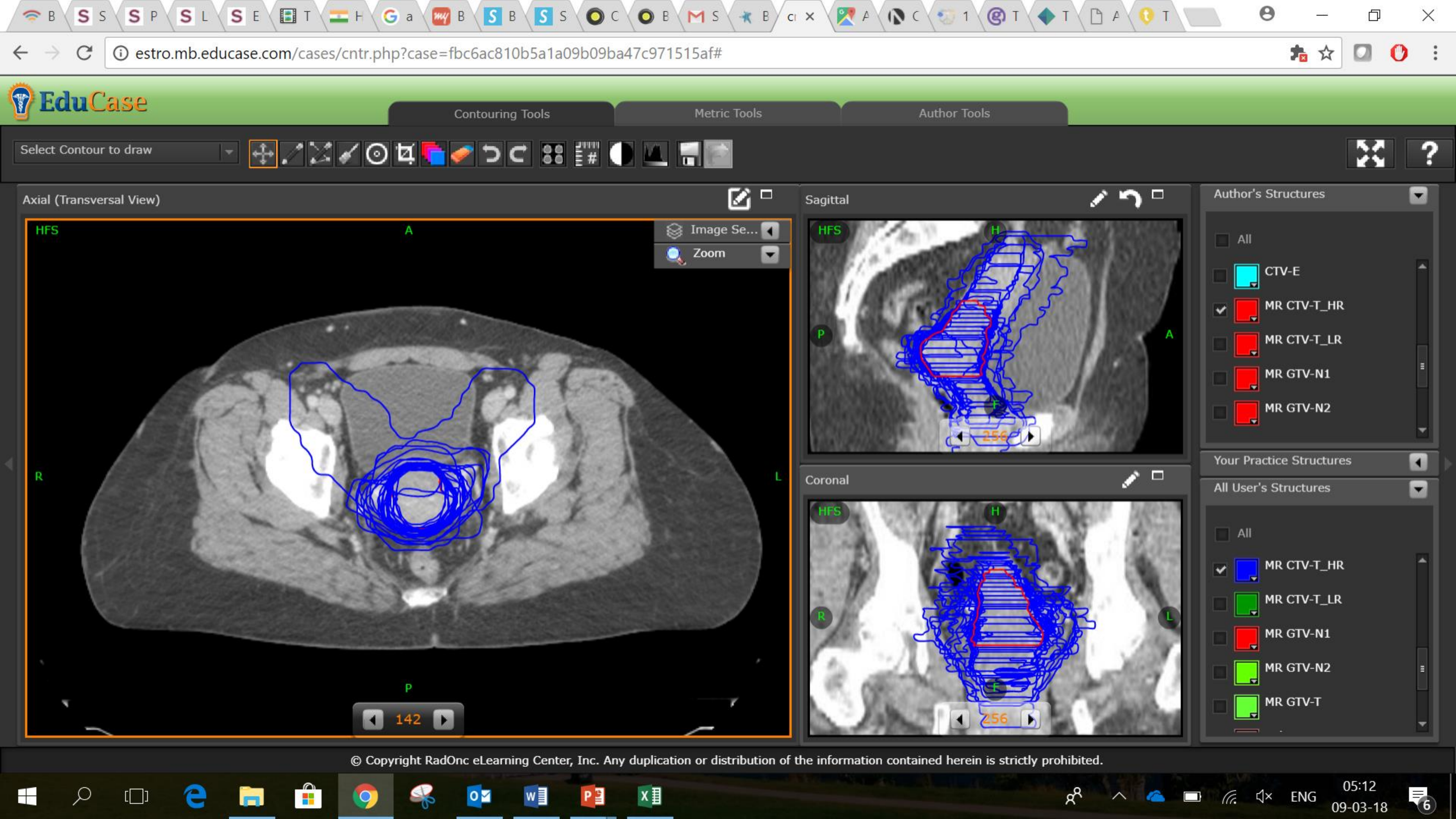
ENG
05:08
09-03-18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Author's Structures
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MR CTV-T_LR
MR GTV-N1
MR GTV-N2
Your Practice Structures
All User's Structures
All
MR CTV-T_HR
MR CTV-T_LR
MR GTV-N1
MR GTV-N2
MR GTV-T
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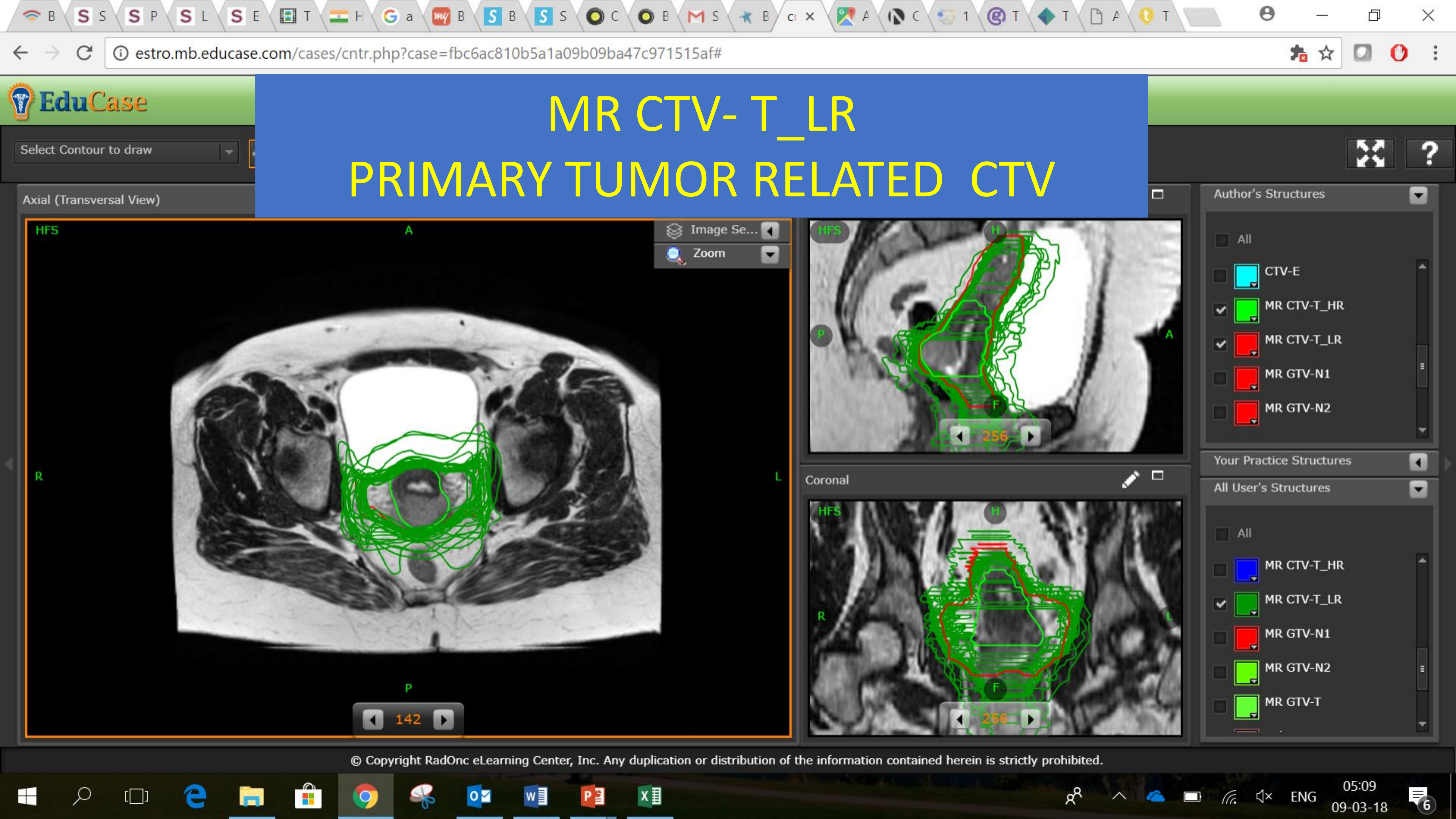
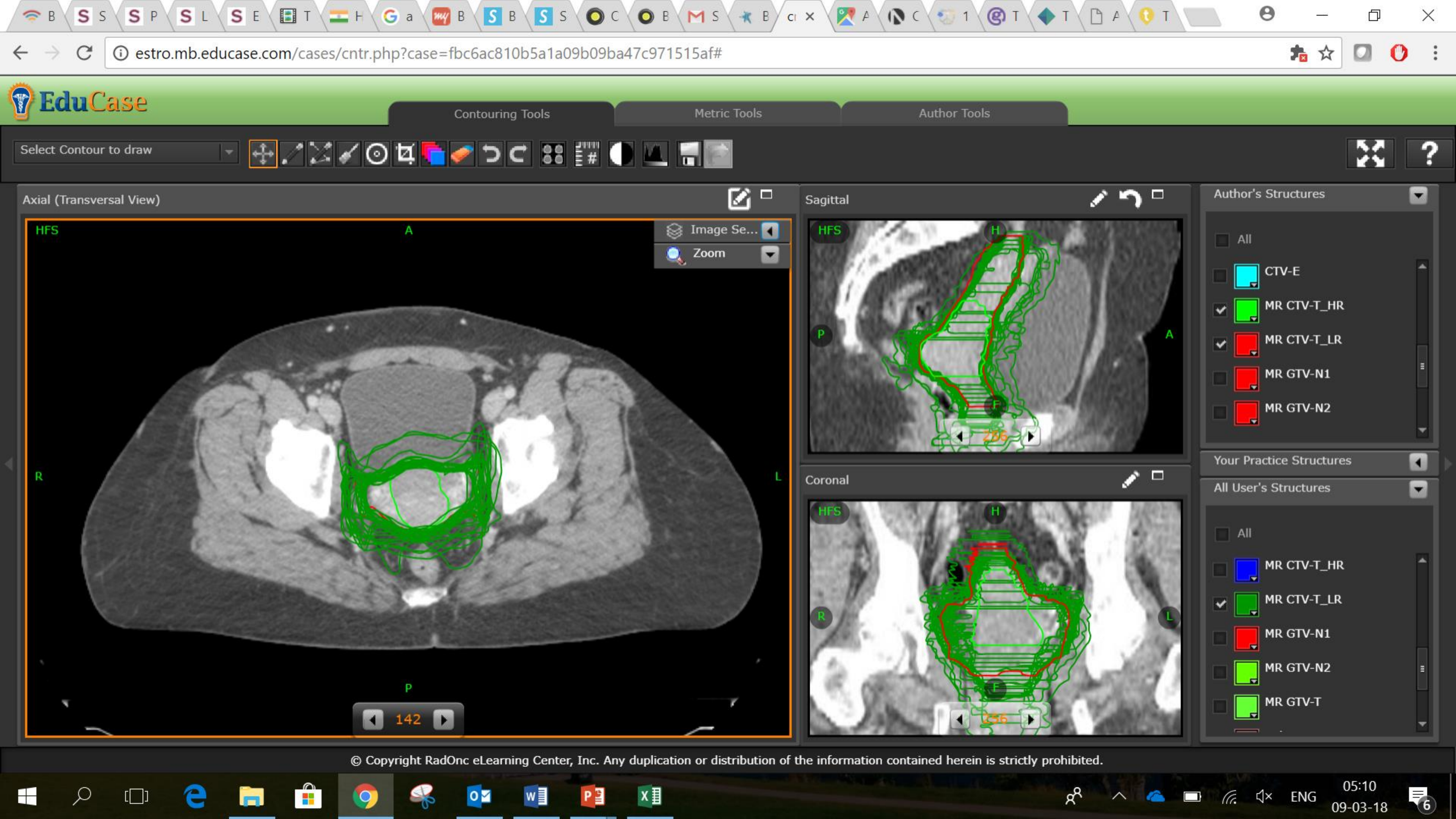
ENG
05:12
09-03-18

MR CTV- T_LR
PRIMARY TUMOR RELATED CTV

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Author's Structures
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CTV-E
MR CTV-T_HR
MR CTV-T_LR
MR GTV-N1
MR GTV-N2
Your Practice Structures
All User's Structures
All
MR CTV-T_HR
MR CTV-T_LR
MR GTV-N1
MR GTV-N2
MR GTV-T
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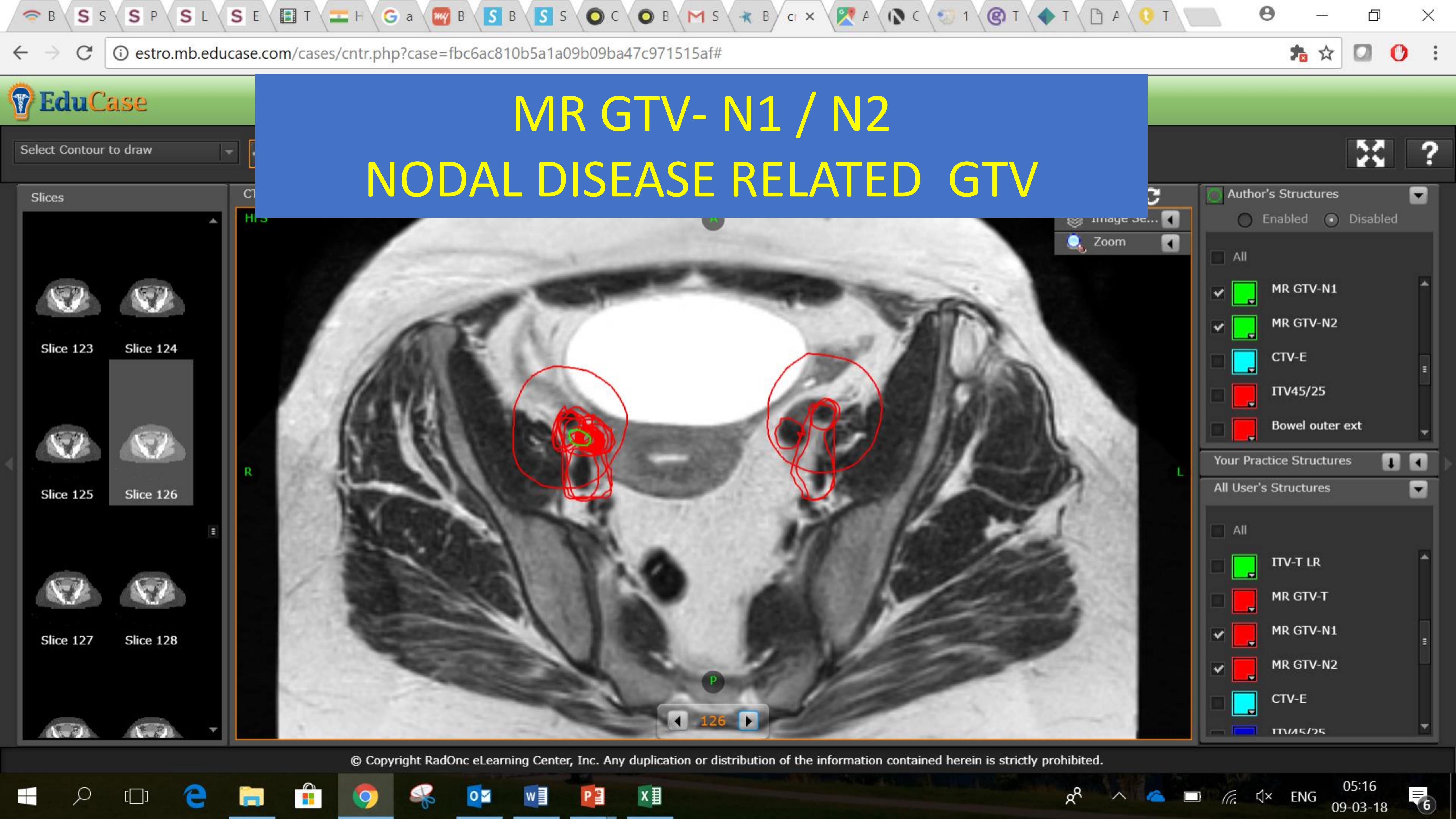
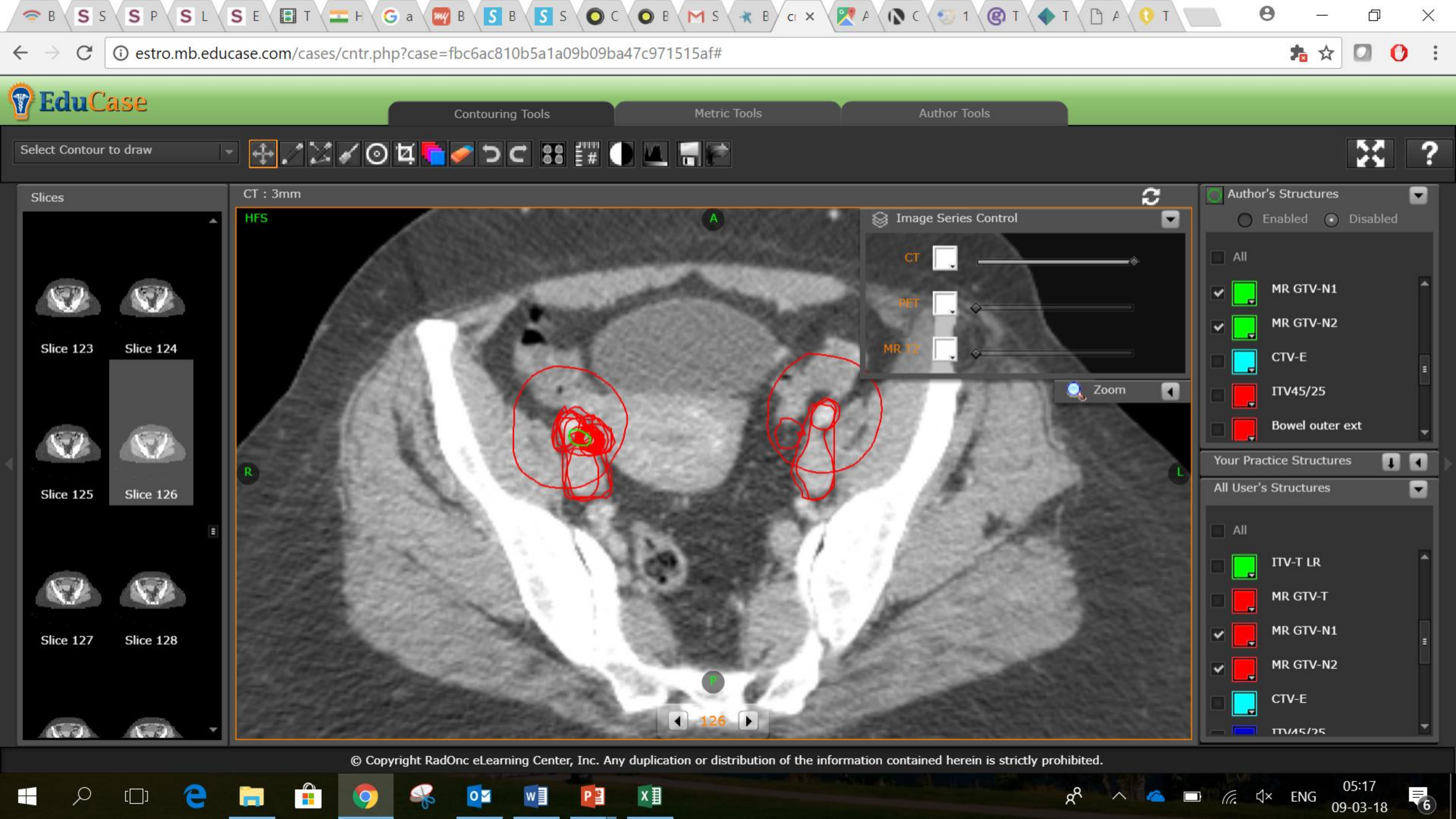
ENG
05:10
09-03-18

MR GTV- N1 / N2
NODAL DISEASE RELATED GTV





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CT : 3mm
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Image Series Control
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Author's Structures
Enabled
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MR GTV-N1
MR GTV-N2
CTV-E
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Your Practice Structures
All User's Structures
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ITV-T LR
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MR GTV-N1
MR GTV-N2
CTV-E
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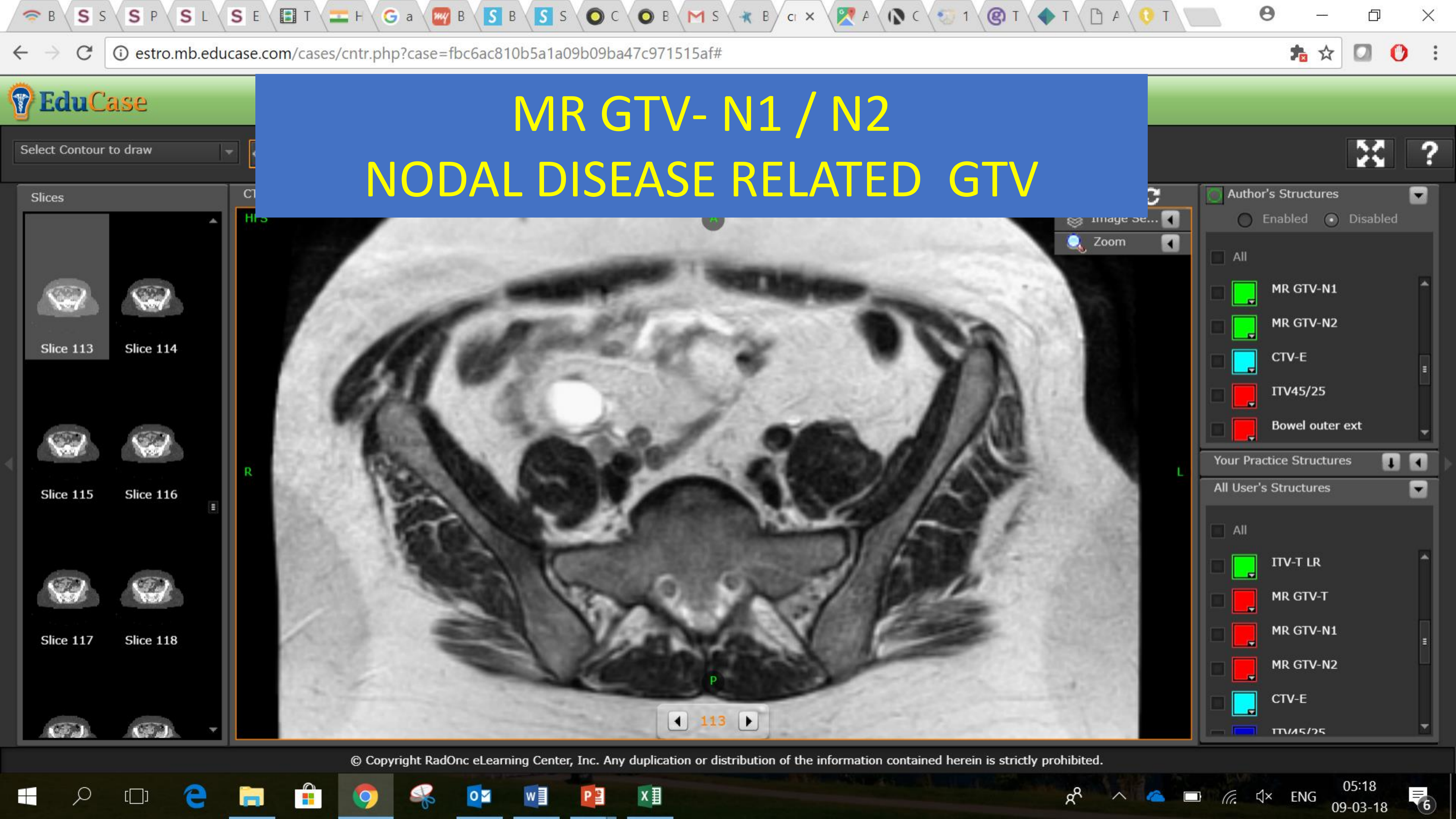
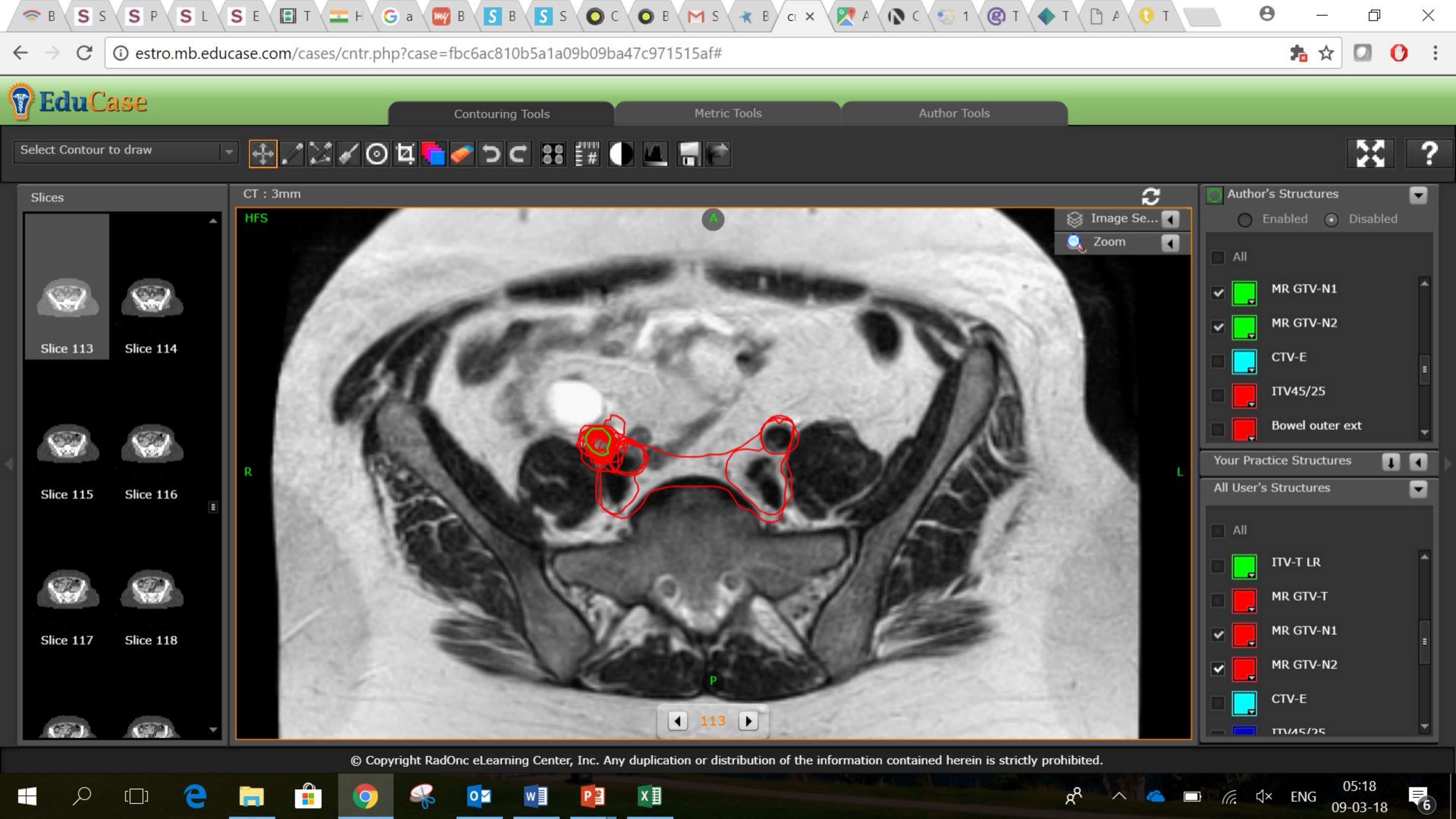
ENG
05:17
09-03-18

MR GTV- N1 / N2

NODAL DISEASE RELATED GTV





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CT : 3mm
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Author's Structures
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MR GTV-N2
CTV-E
ITV45/25
Bowel outer ext
Your Practice Structures
All User's Structures
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ITV-T LR
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ENG
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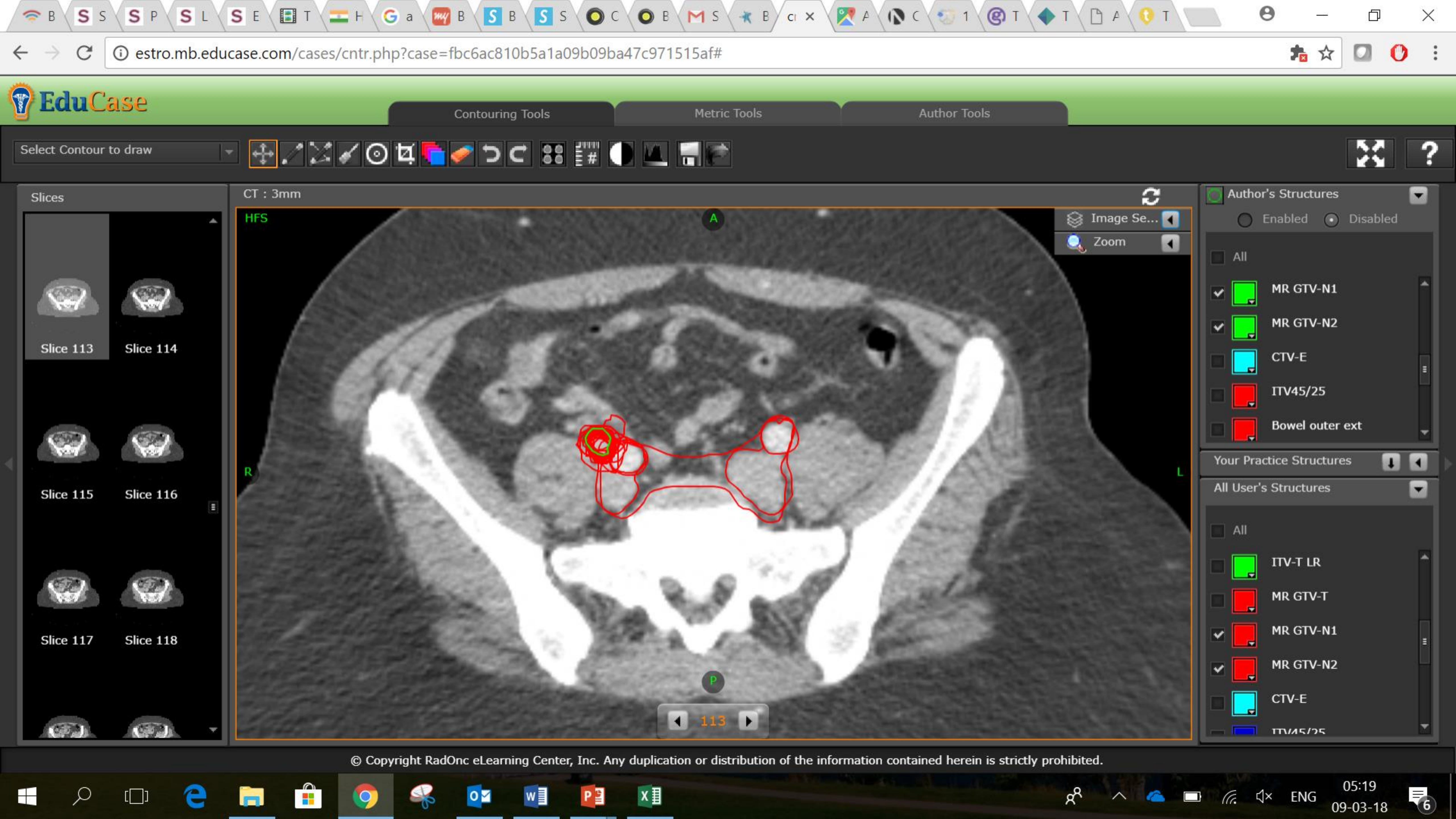
09-03-18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Your Practice Structures
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ITV-T LR
MR GTV-T
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MR GTV-N2
CTV-E
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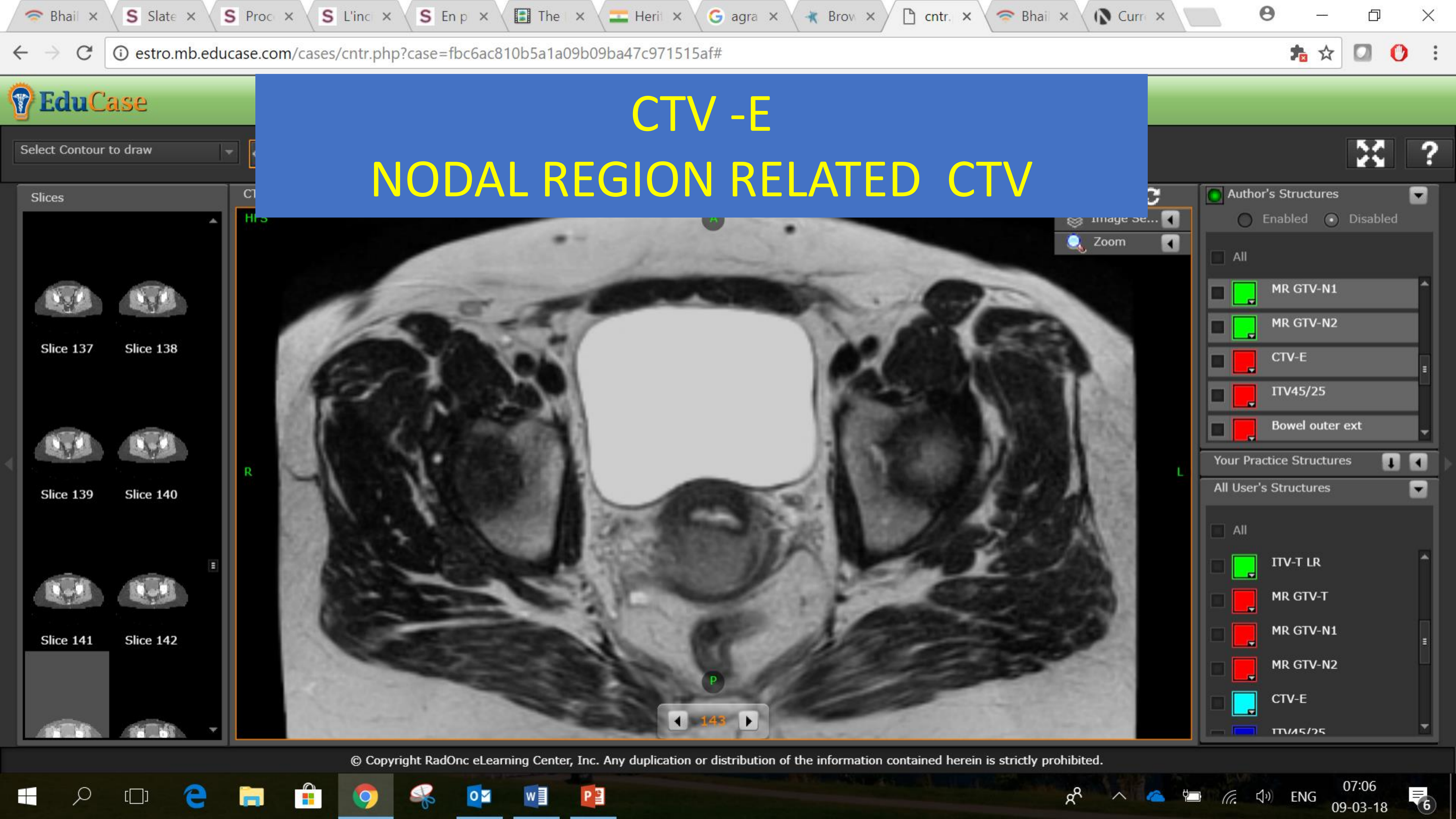
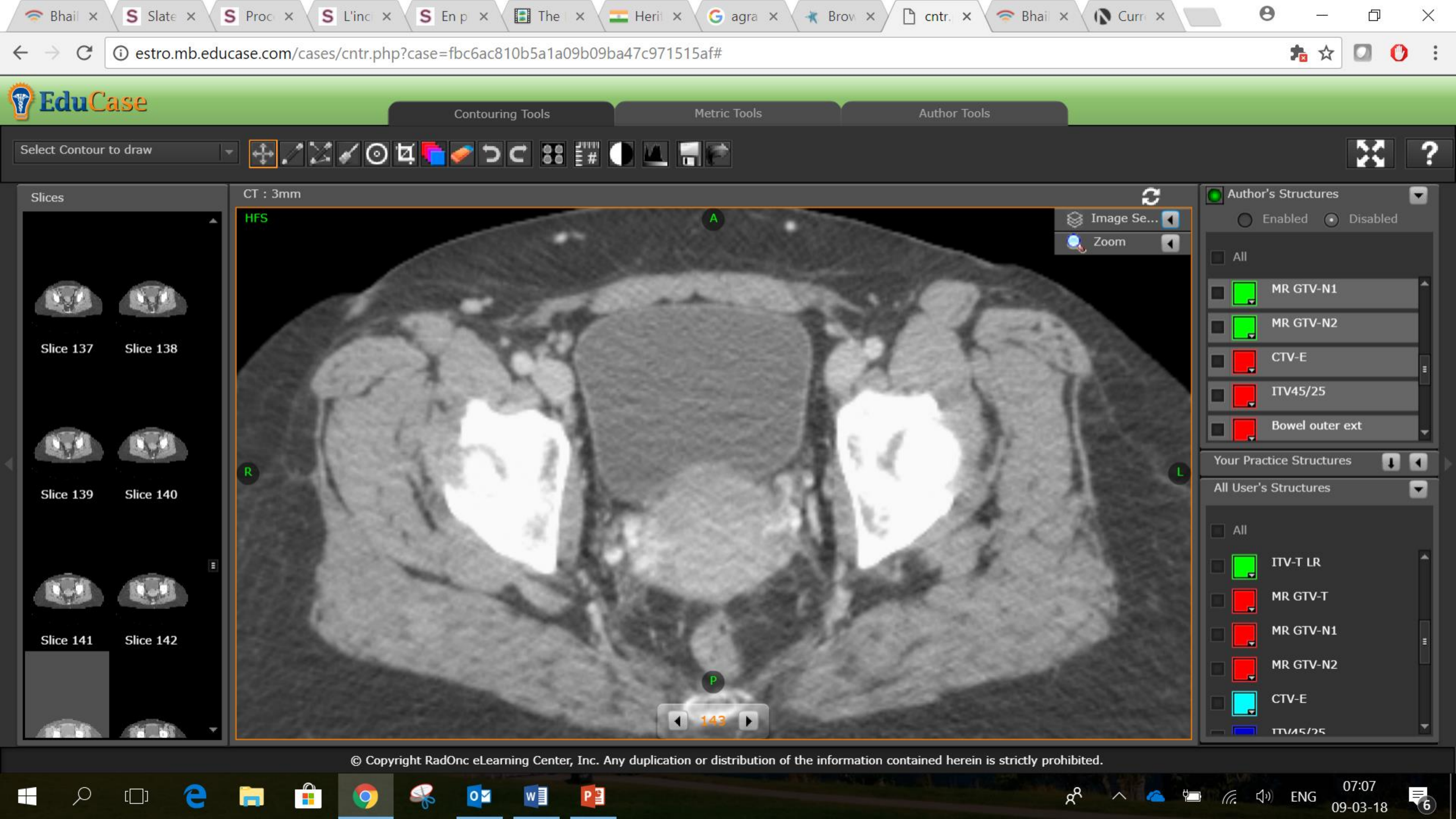
ENG
05:19
09-03-18

CTV -E
NODAL REGION RELATED CTV

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Slice 138
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Slice 141
Slice 142
Author's Structures
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All
MR GTV-N1
MR GTV-N2
CTV-E
ITV45/25
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Your Practice Structures
All User's Structures
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ITV-T LR
MR GTV-T
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ENG
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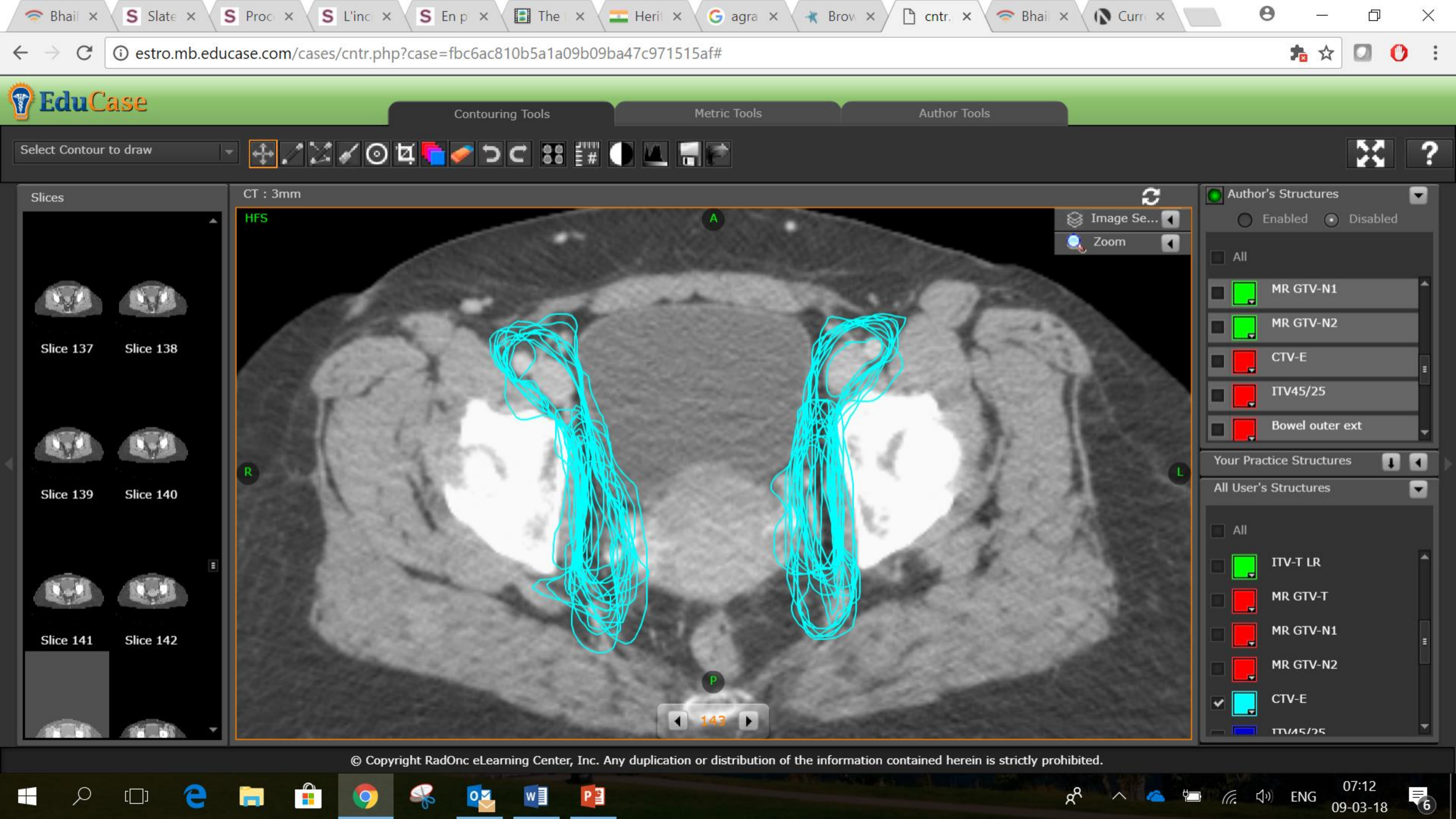
09-03-18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CT : 3mm
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Author's Structures
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All
MR GTV-N1
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ITV-T LR
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ENG
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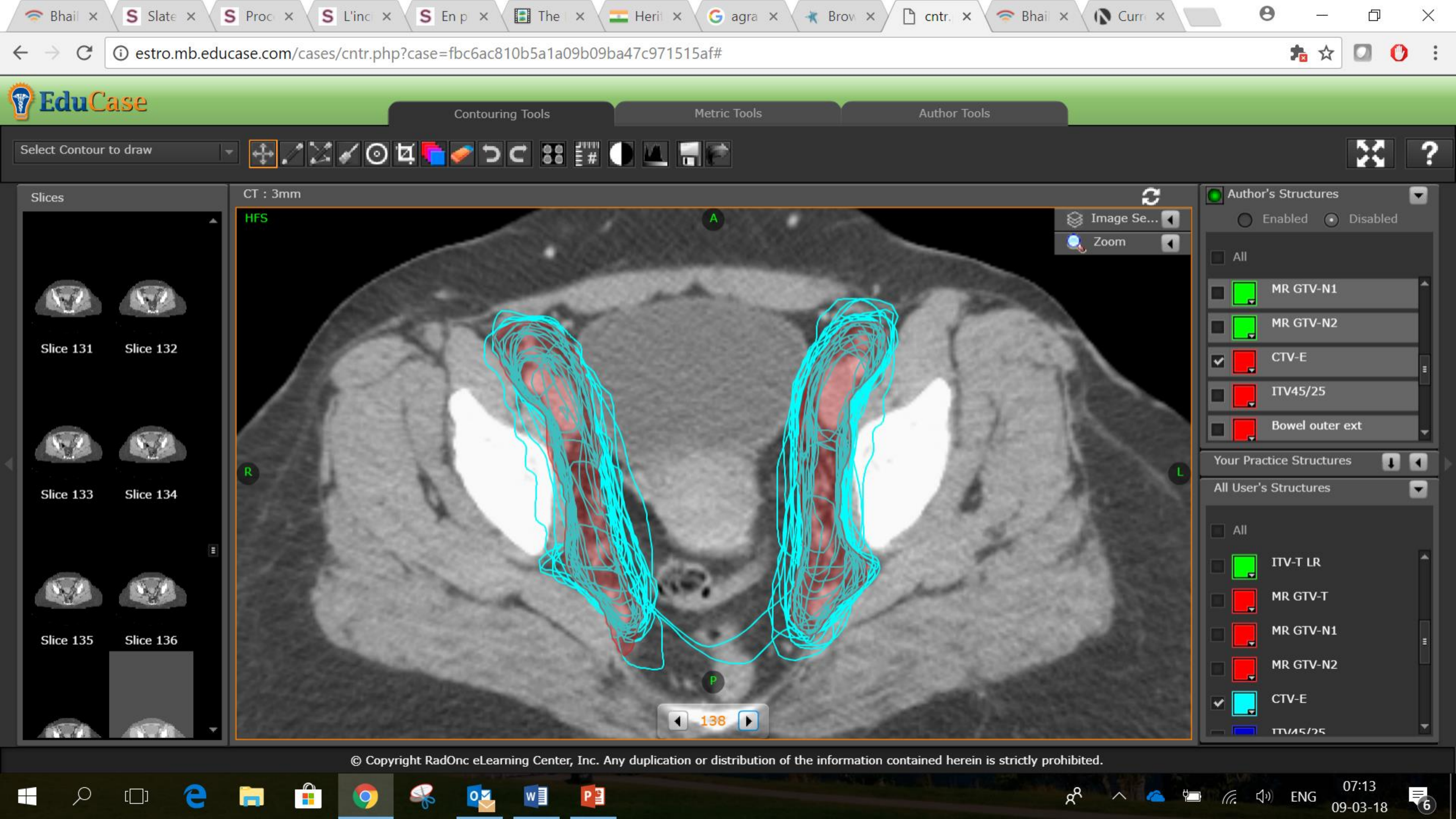
09-03-18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Author's Structures
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MR GTV-N1
MR GTV-N2
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Bowel outer ext
Your Practice Structures
All User's Structures
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ENG
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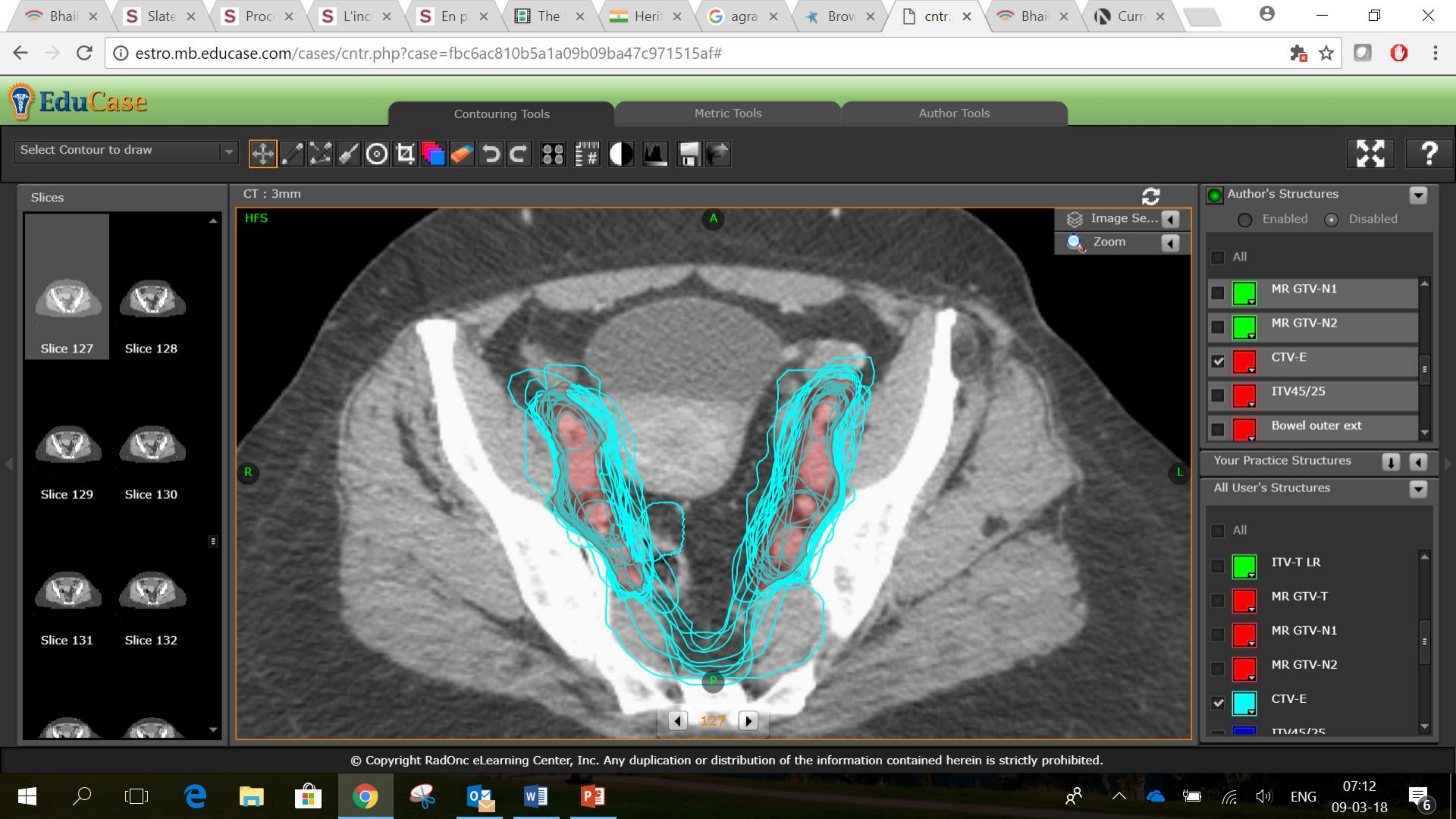
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Author's Structures
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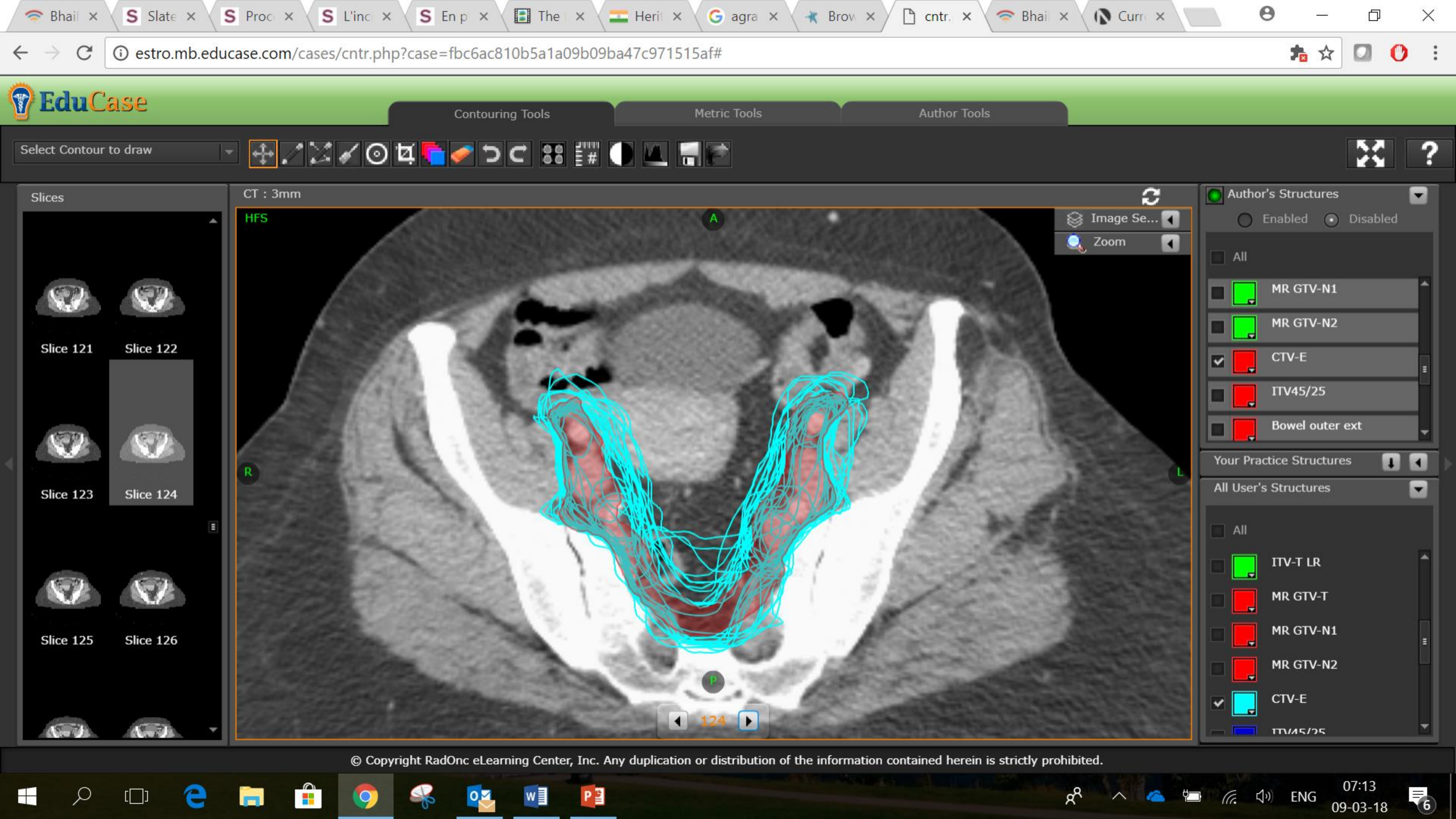
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Author's Structures
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MR GTV-N2
CTV-E
ITV45/25
Bowel outer ext
Your Practice Structures
All User's Structures
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ENG
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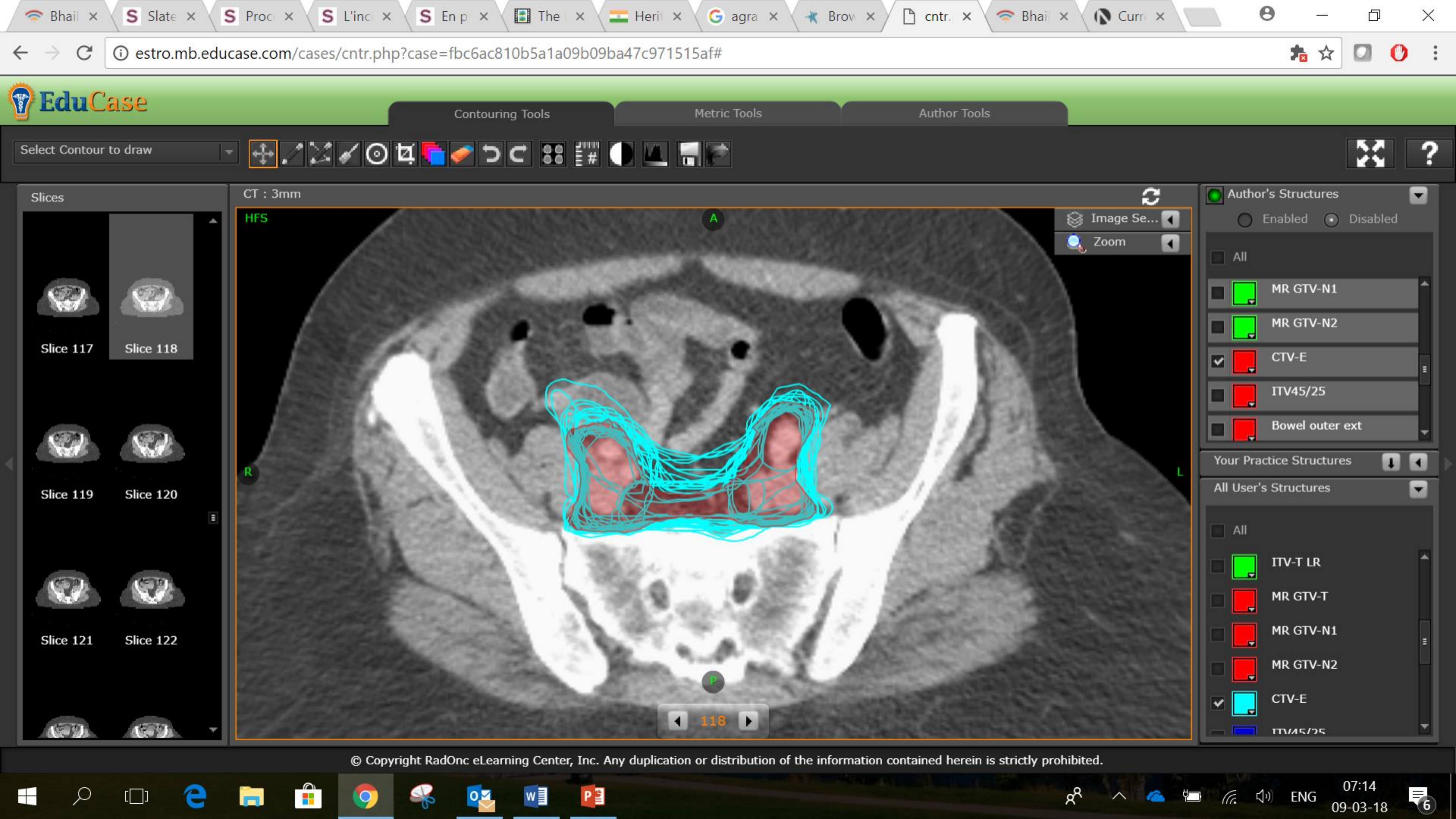
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CT : 3mm
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118
Author's Structures
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MR GTV-N1
MR GTV-N2
CTV-E
ITV45/25
Bowel outer ext
Your Practice Structures
All User's Structures
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ITV-T LR
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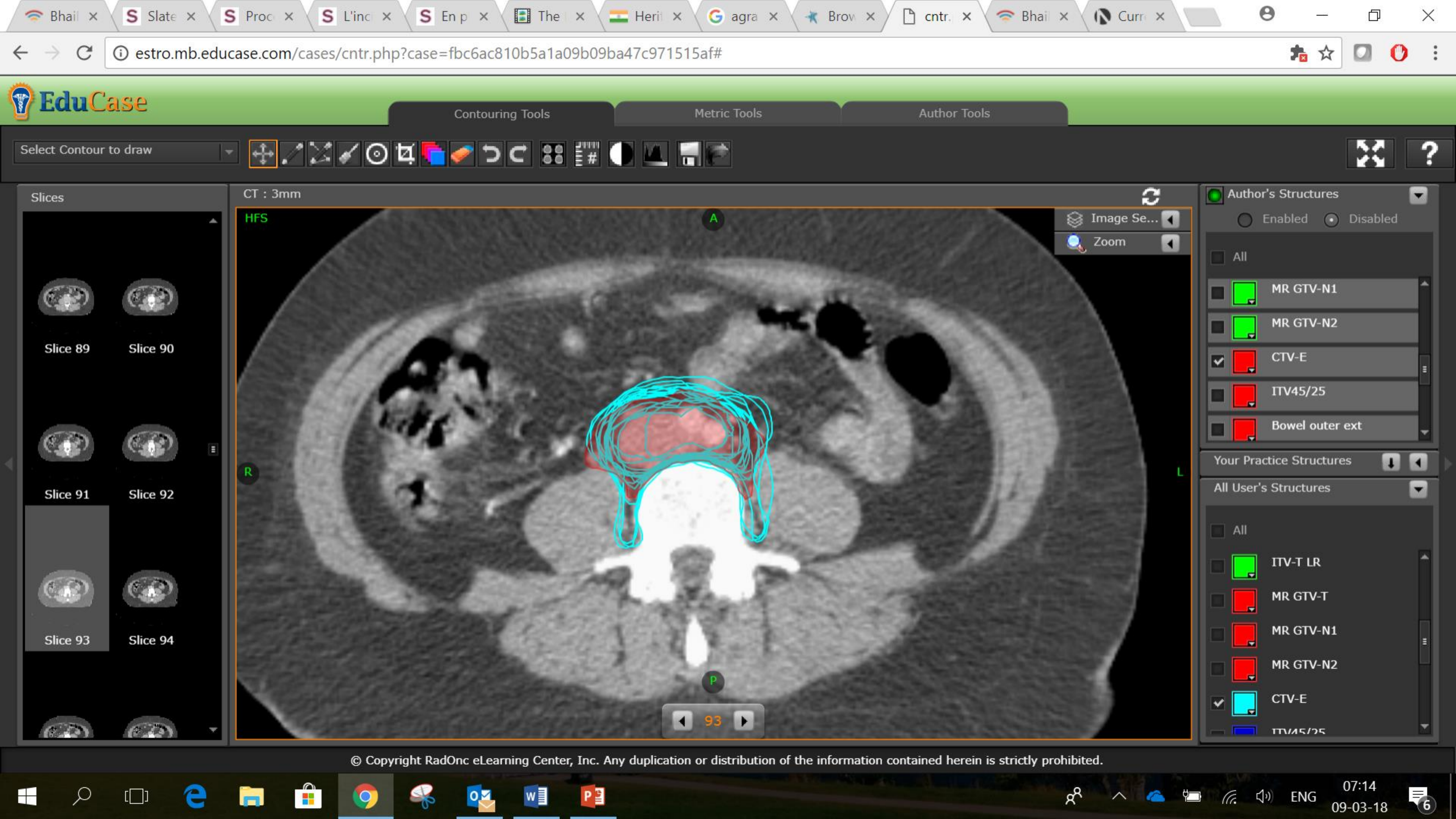
09-03-18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CT : 3mm
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Author's Structures
Enabled
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MR GTV-N1
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Bowel outer ext
Your Practice Structures
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MR GTV-N2
CTV-E
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ENG
07:14
09-03-18

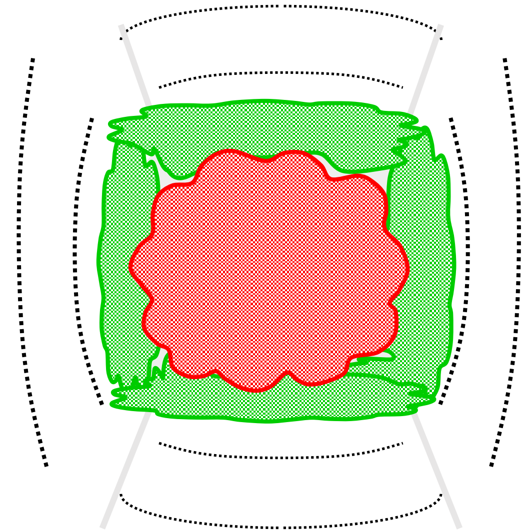
BT CONTOURING EXERCISE
TATA03_MR : HOME WORK

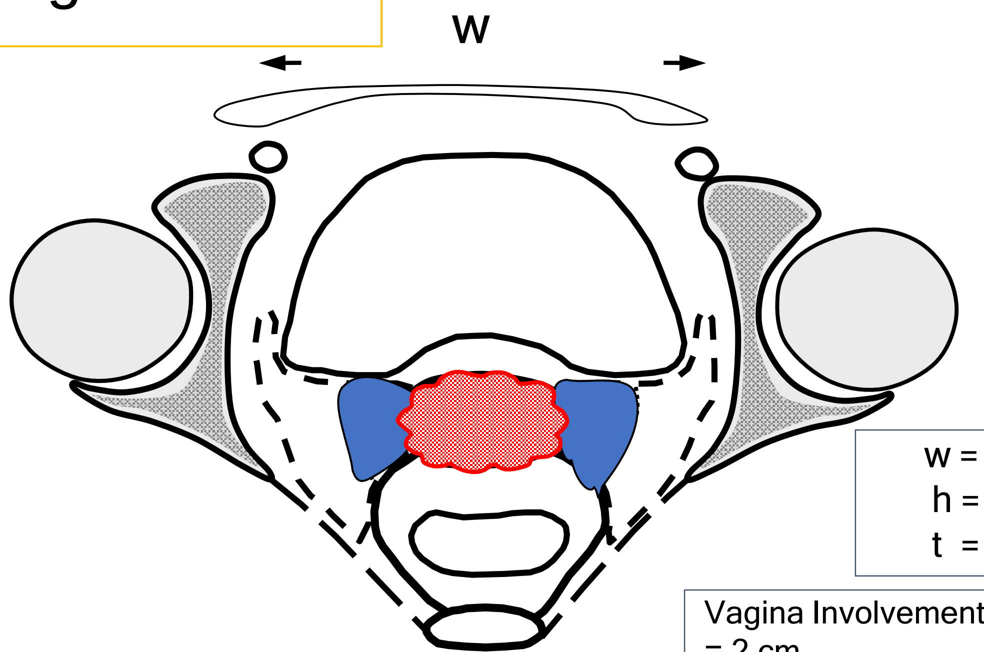
Study ID: TMH-30196-CN(PK)

Clinical Drawing

At Diagnosis

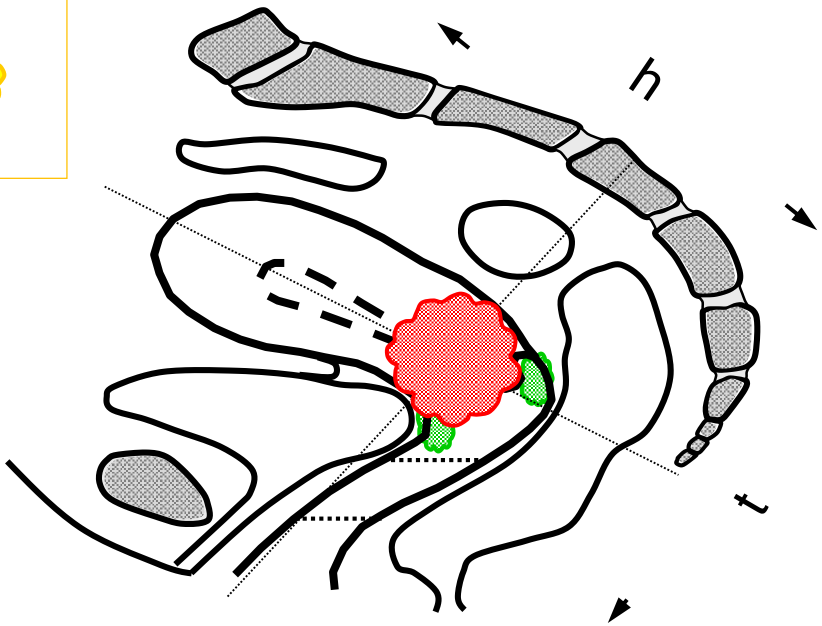
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

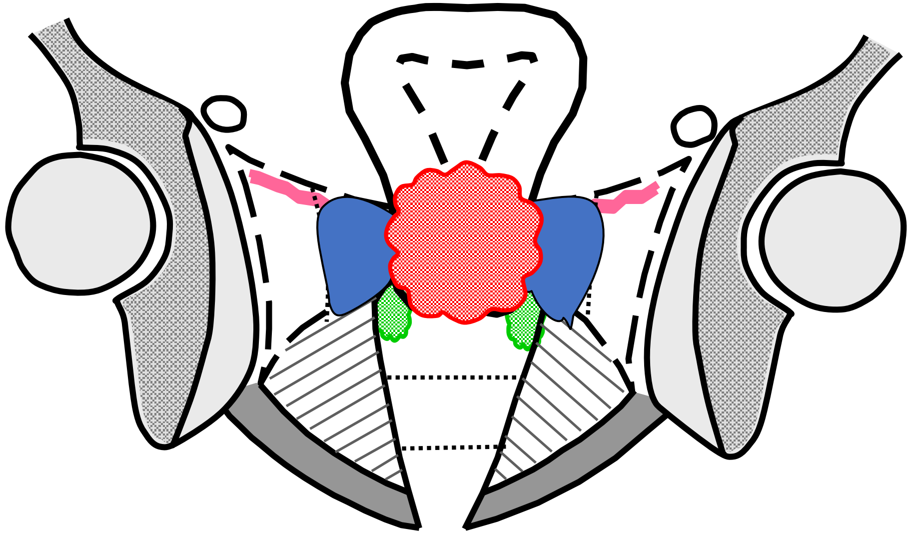




w = 7 cm
h = 5 cm
t = 5 cm

Vagina Involvement
= 2 cm





dd/mm/yy
10.10.2016

Dr Umesh

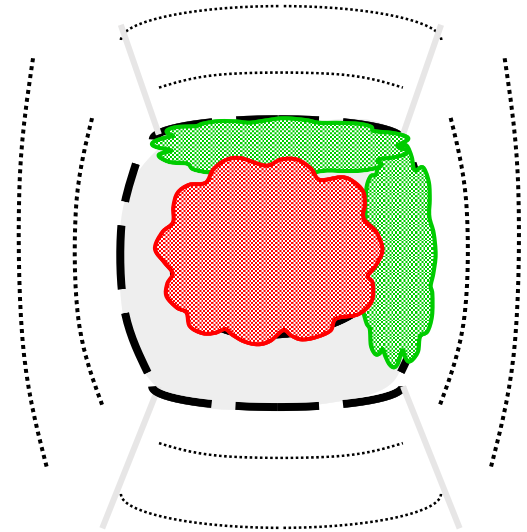
Signature

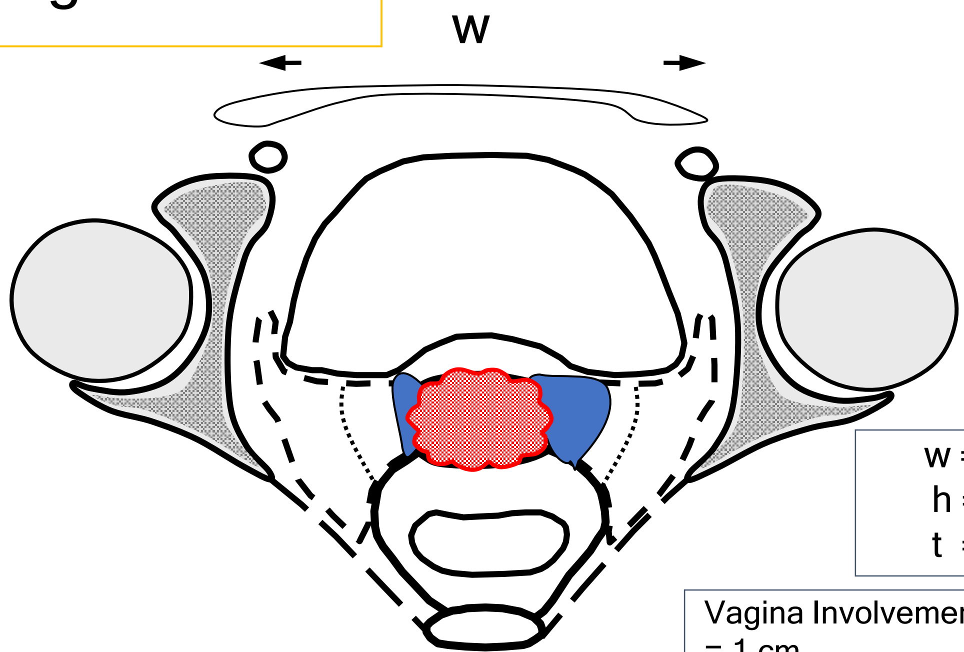
Study ID: TMH-30196-CN(PK)

Clinical Drawing

At Brachytherapy

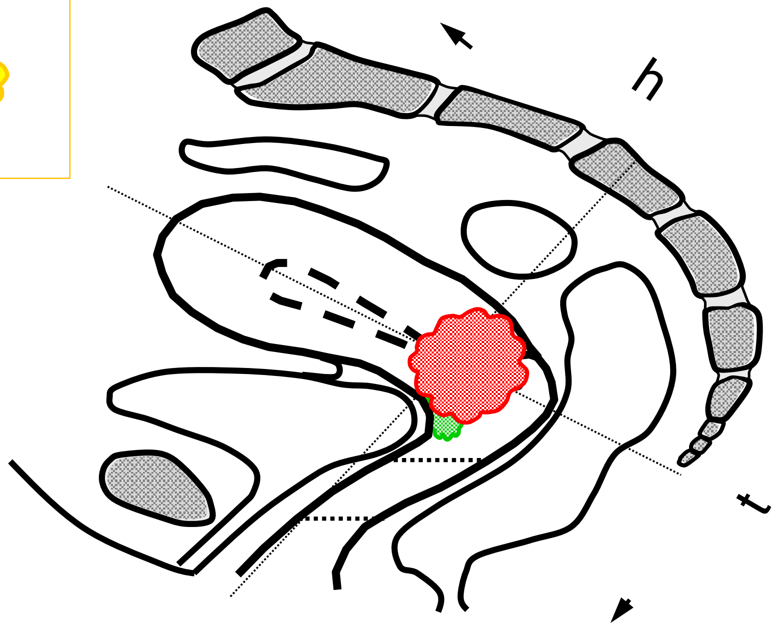
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		

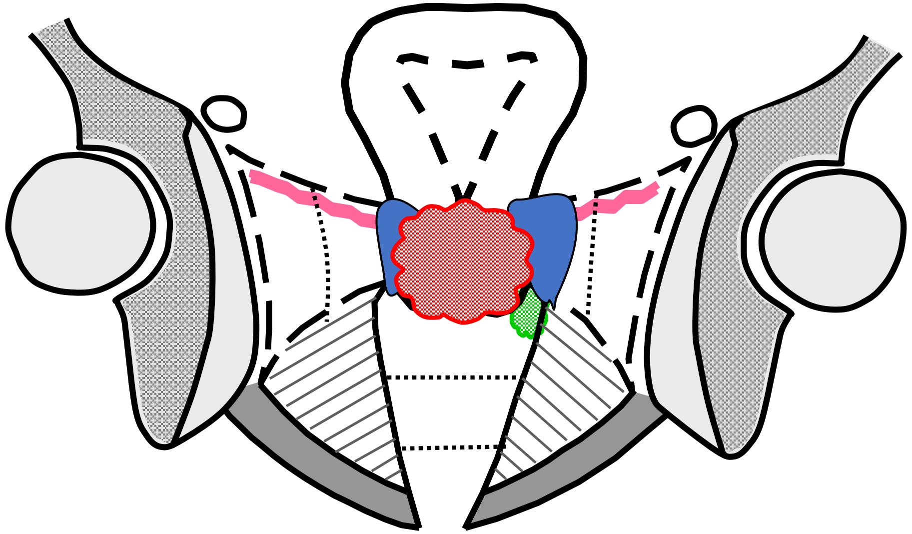




w = 5 cm
h = 3 cm
t = 3 cm

Vagina Involvement = 1 cm





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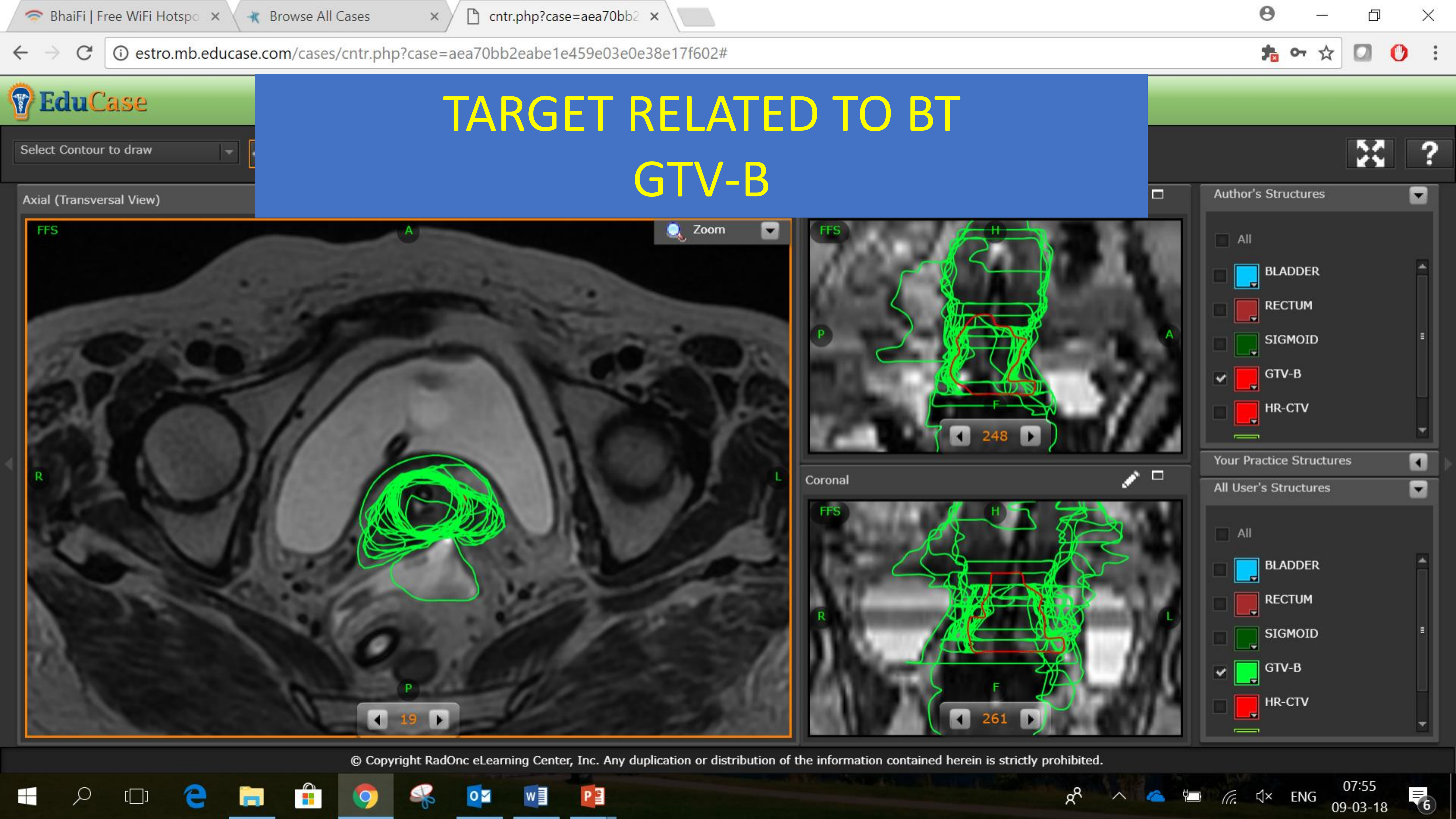
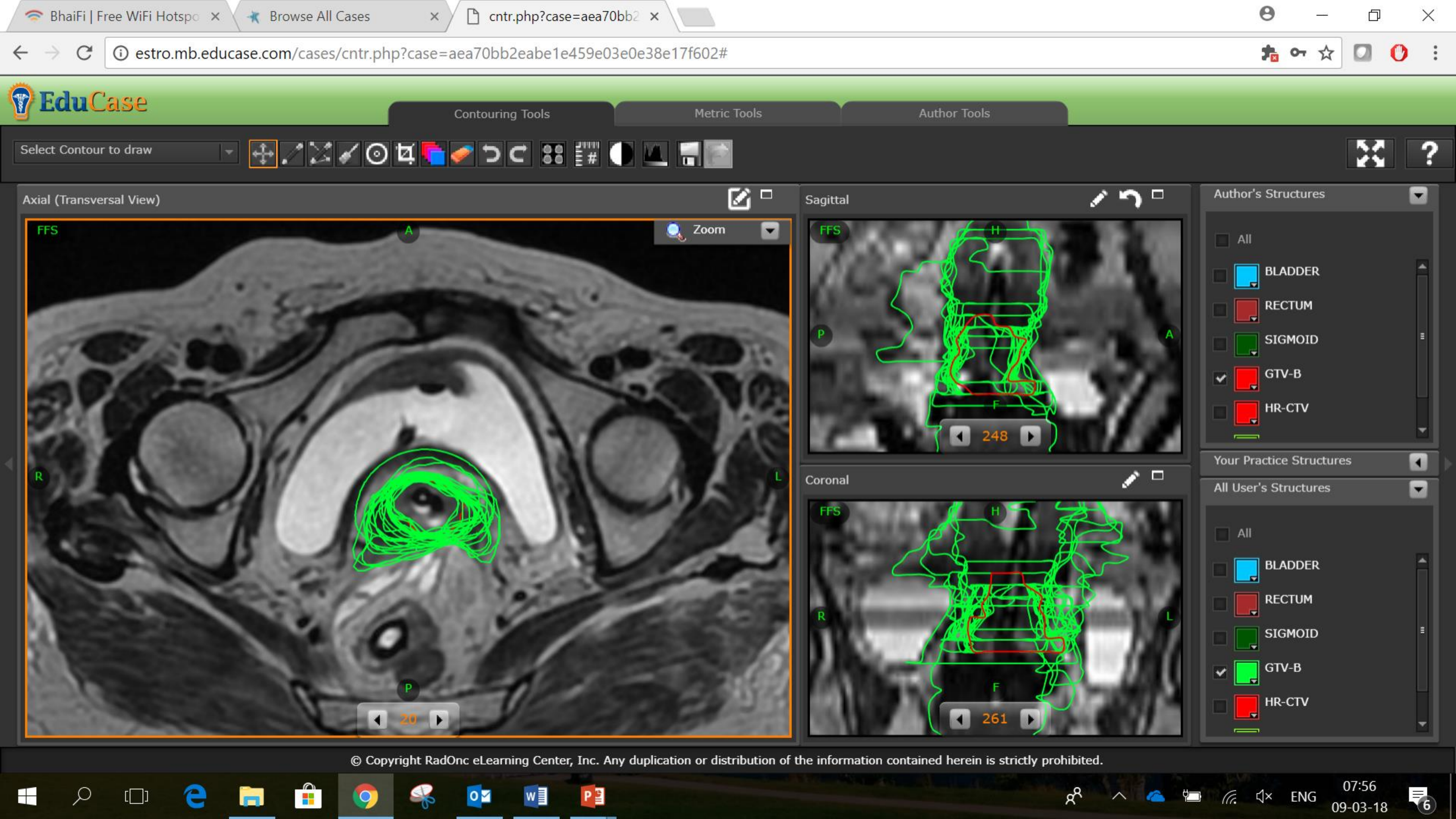
18.11.2016

Dr Umesh
Signature

TARGET RELATED TO BT
GTV-B

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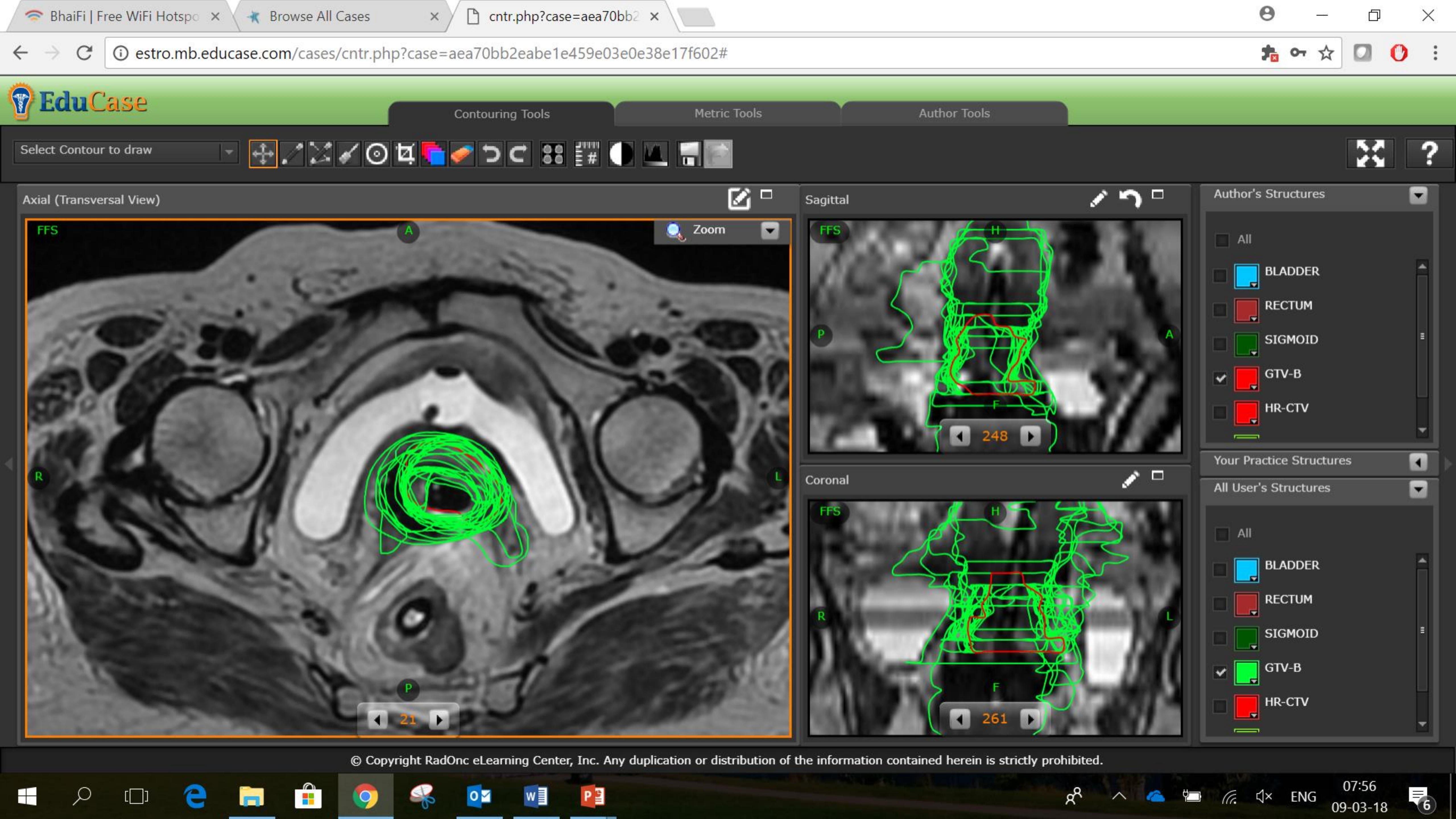
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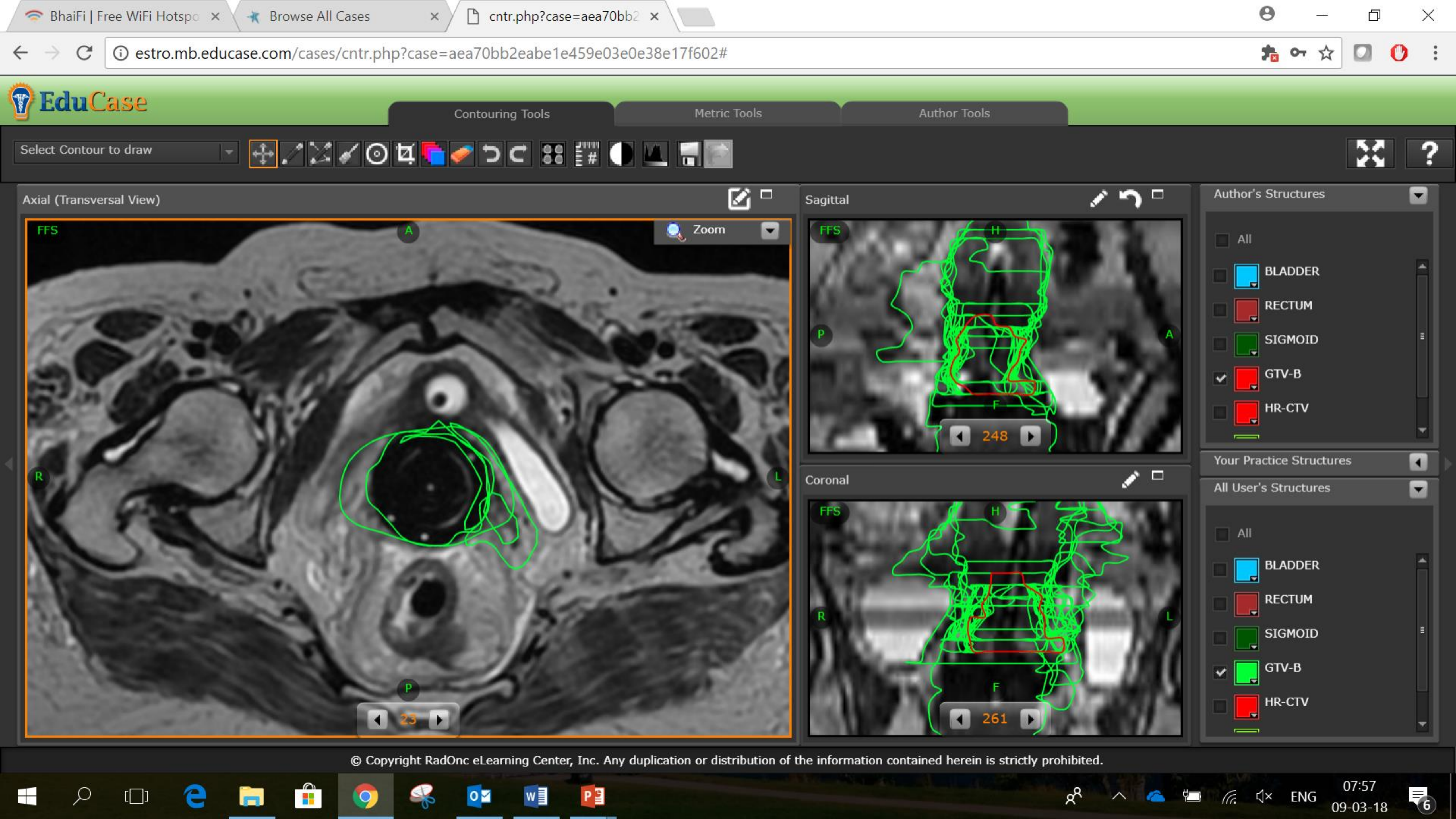
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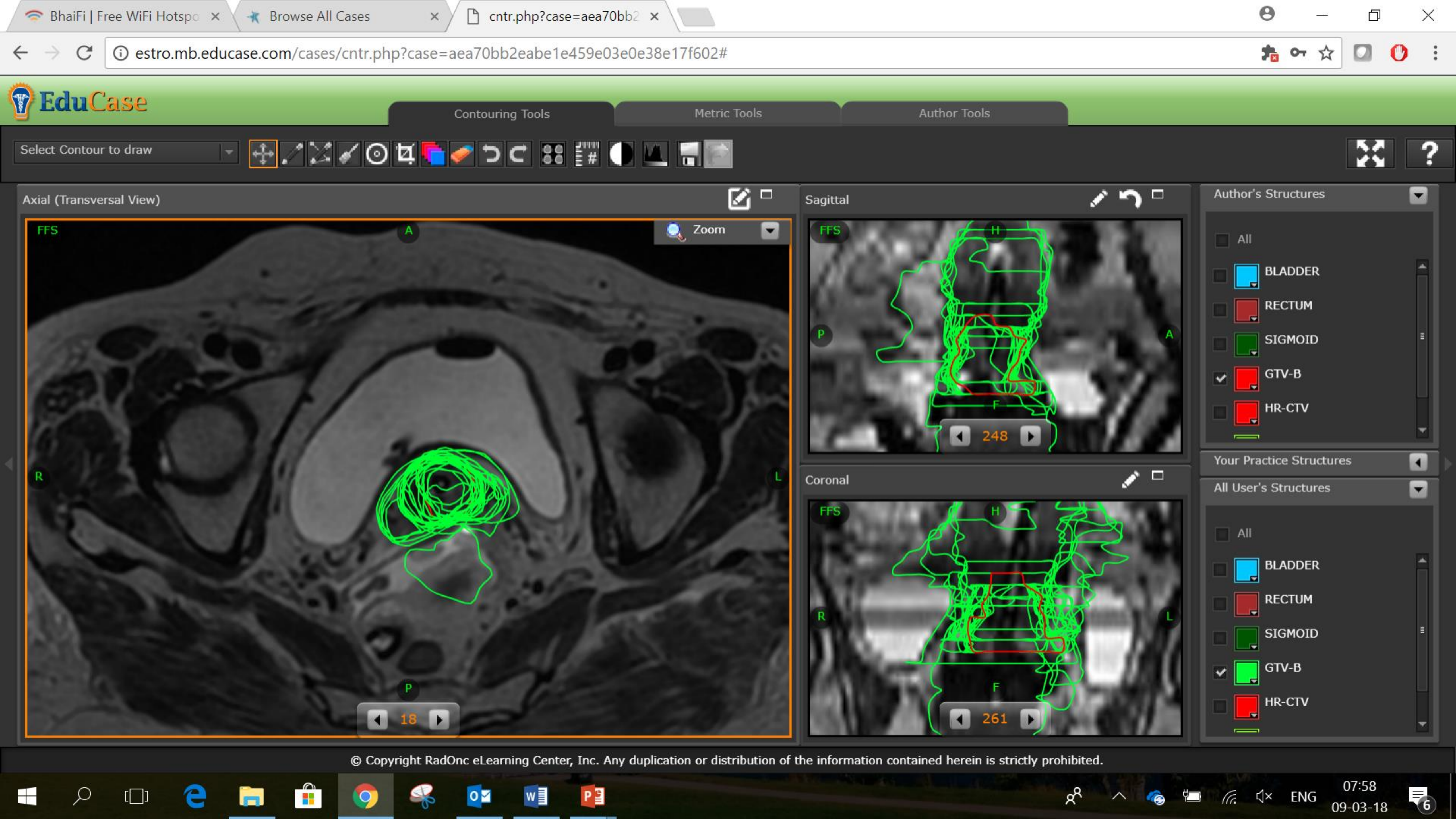
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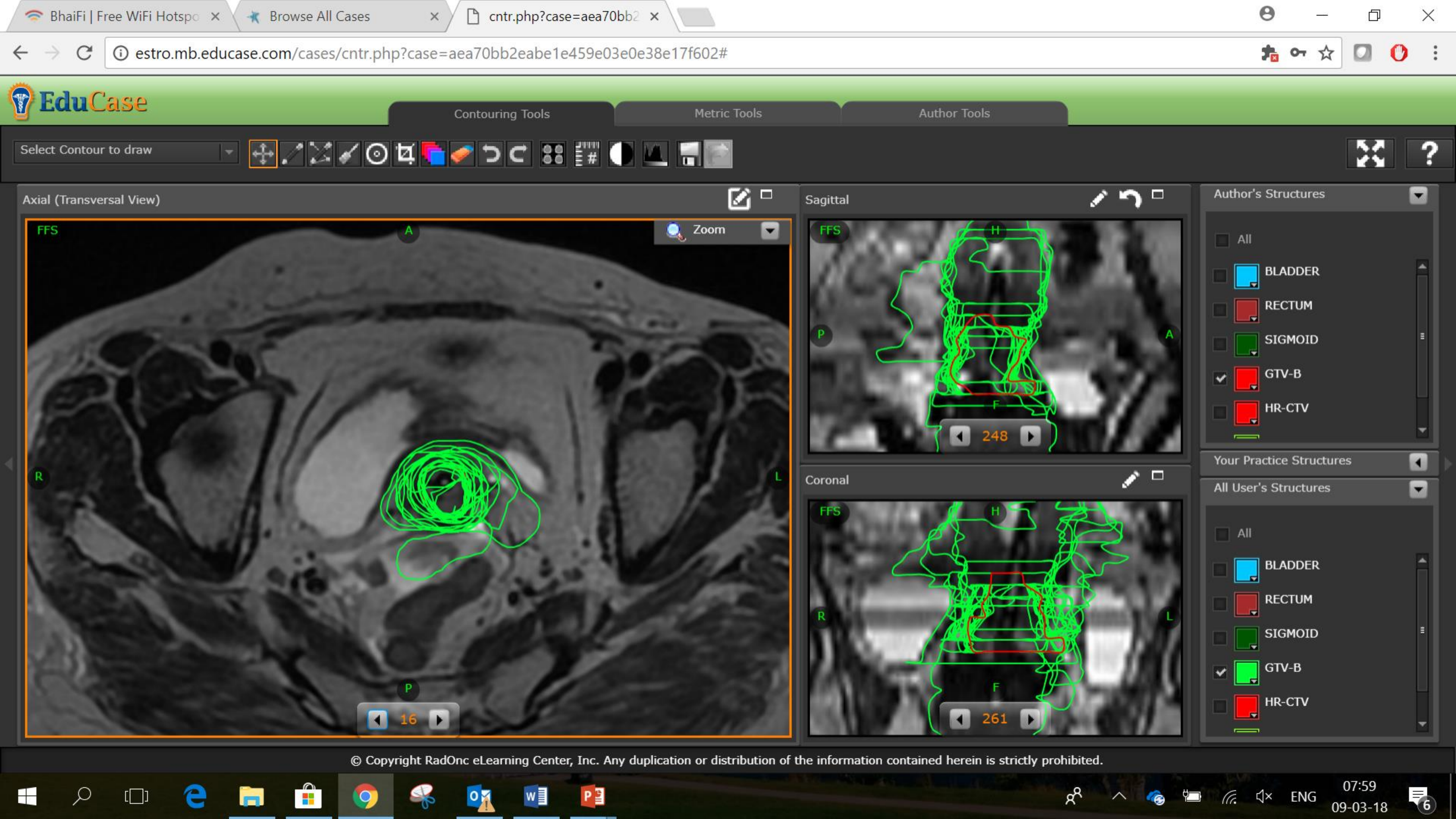
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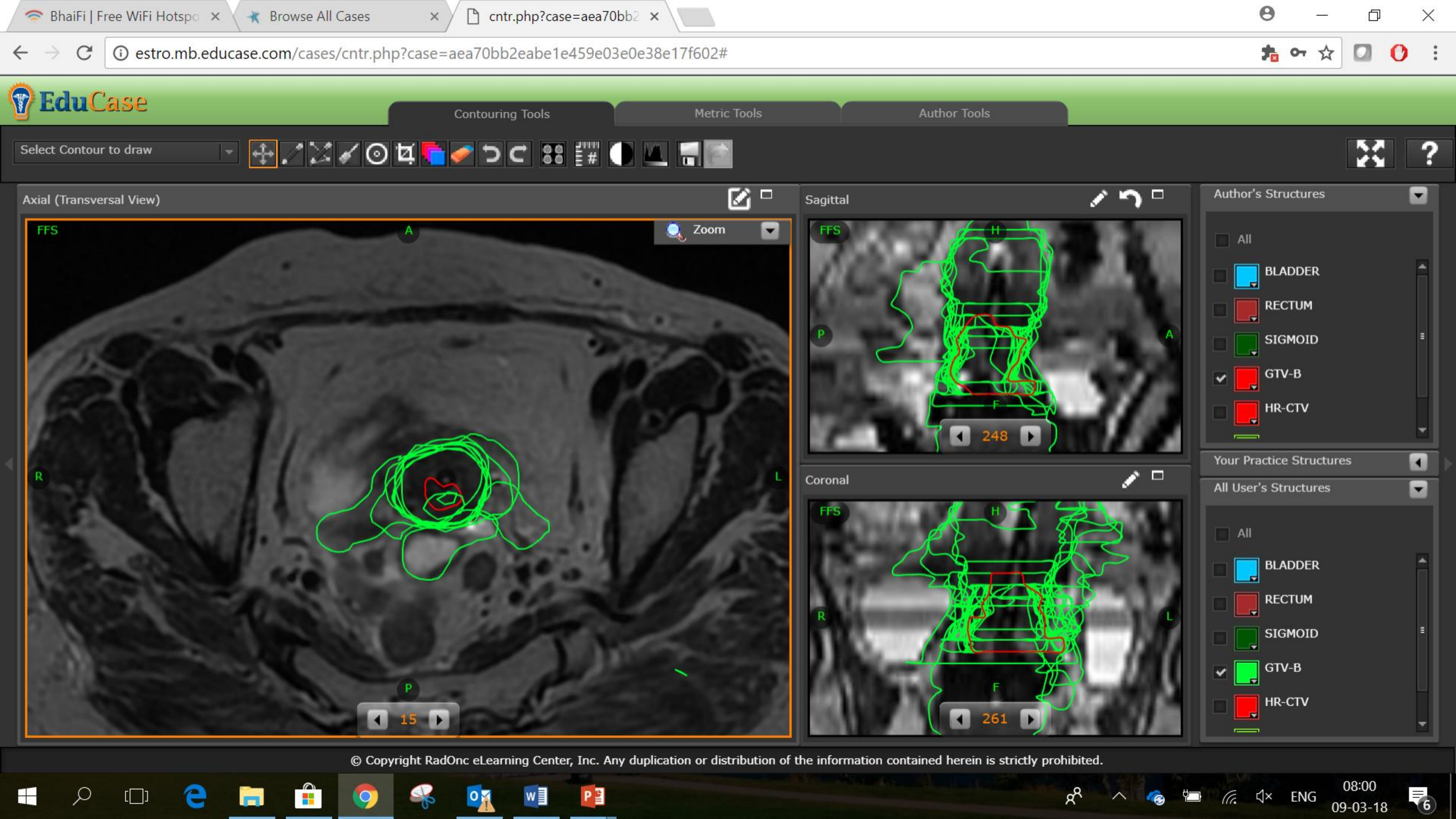
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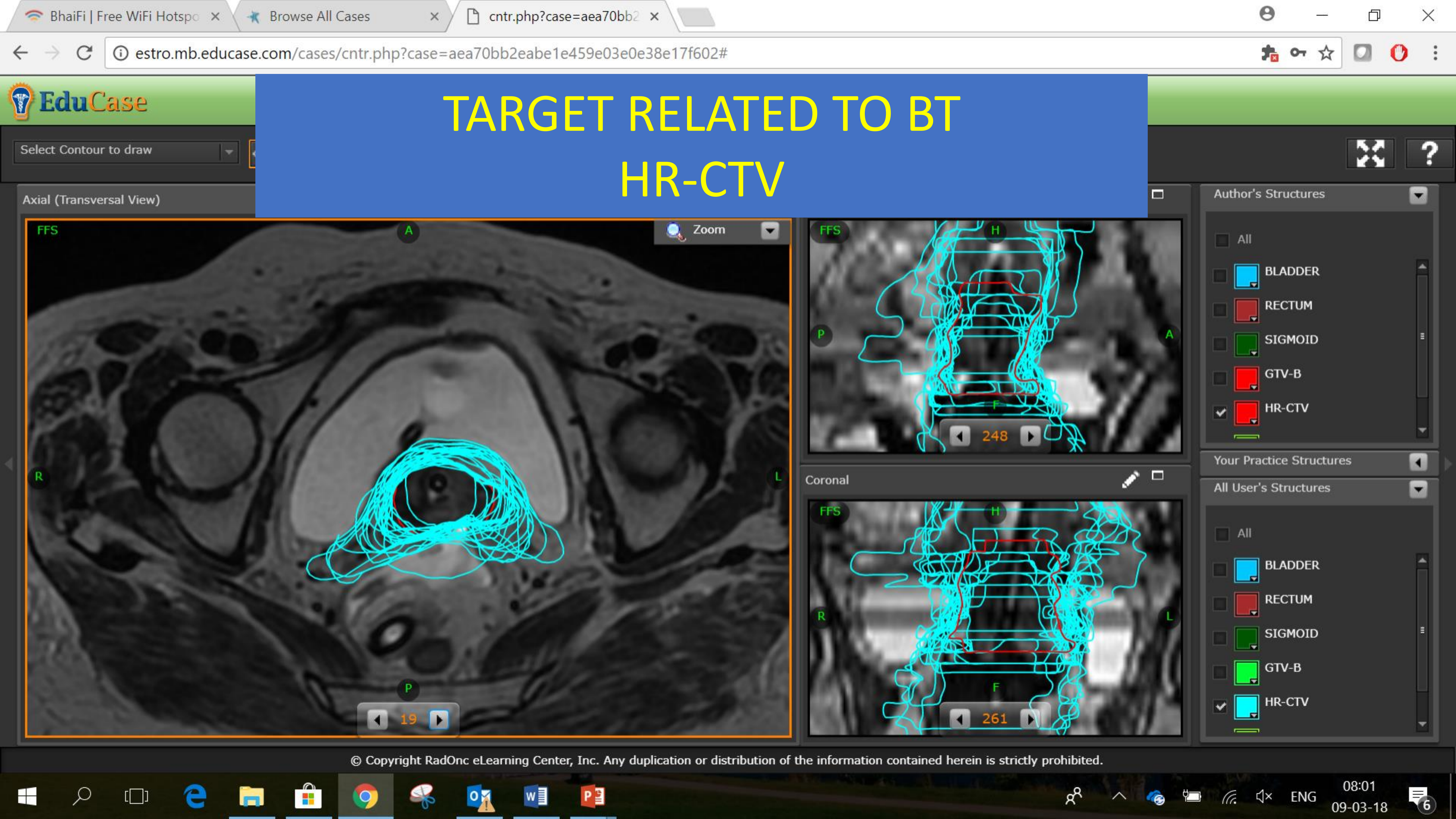

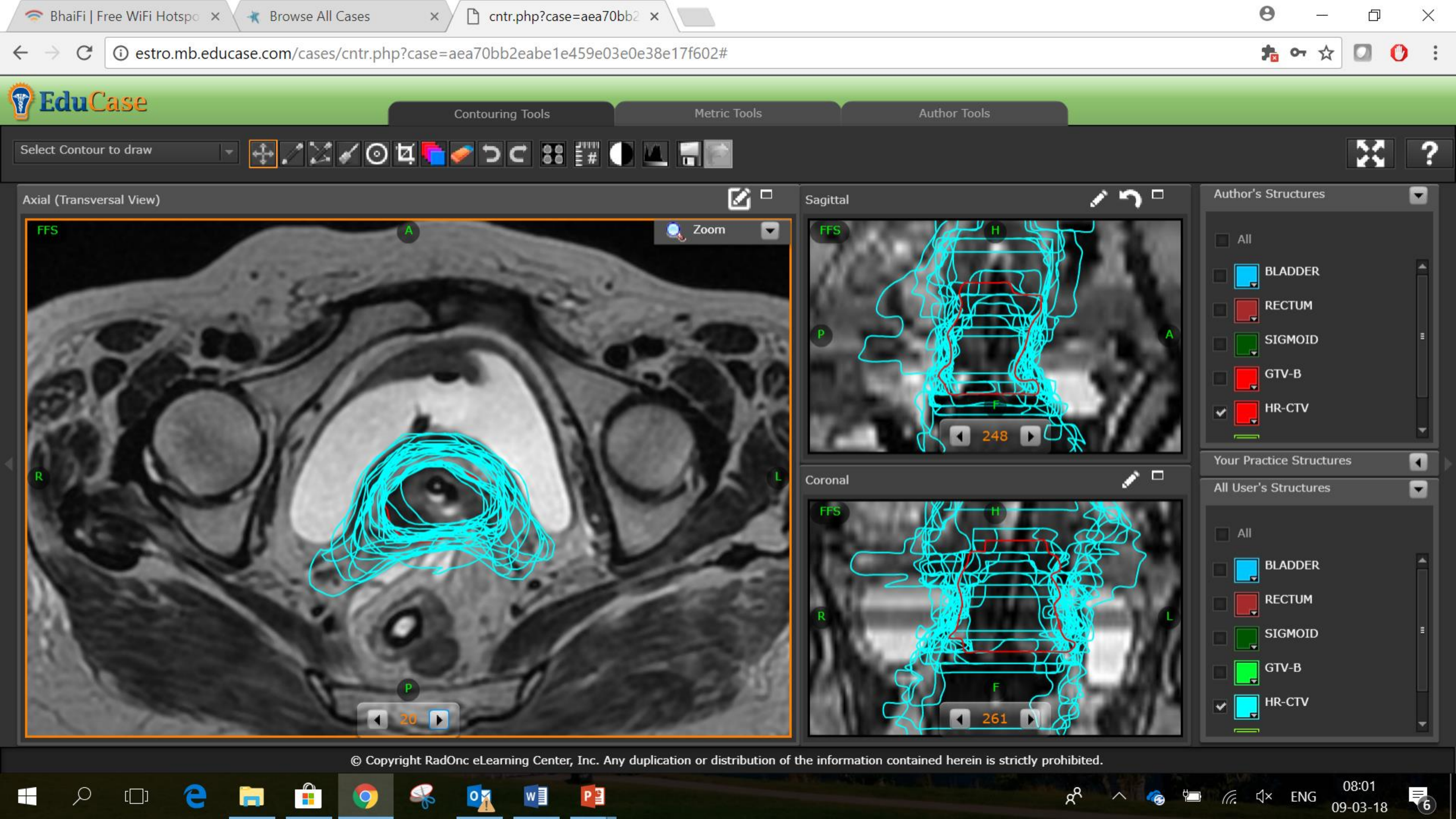
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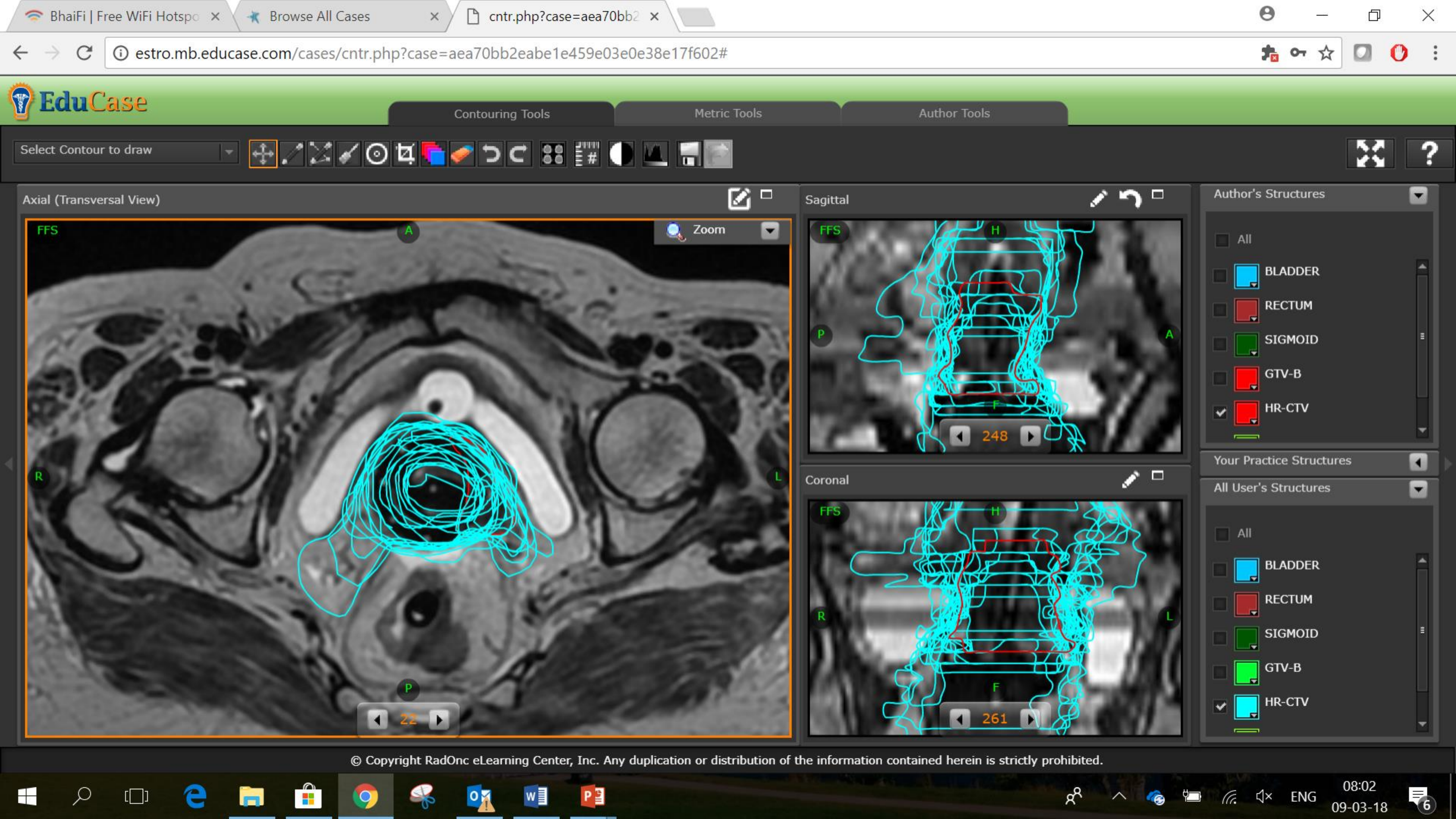
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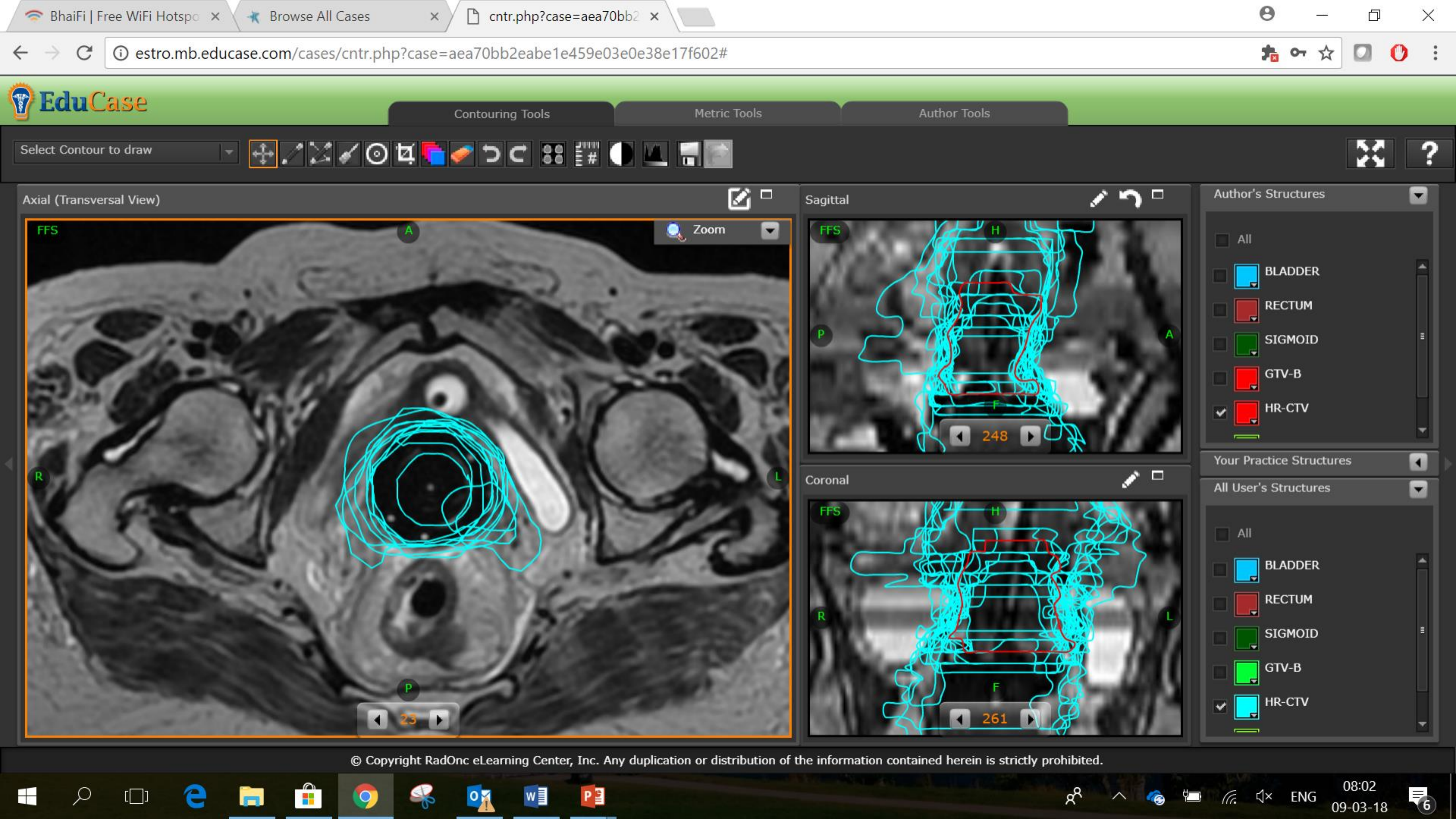

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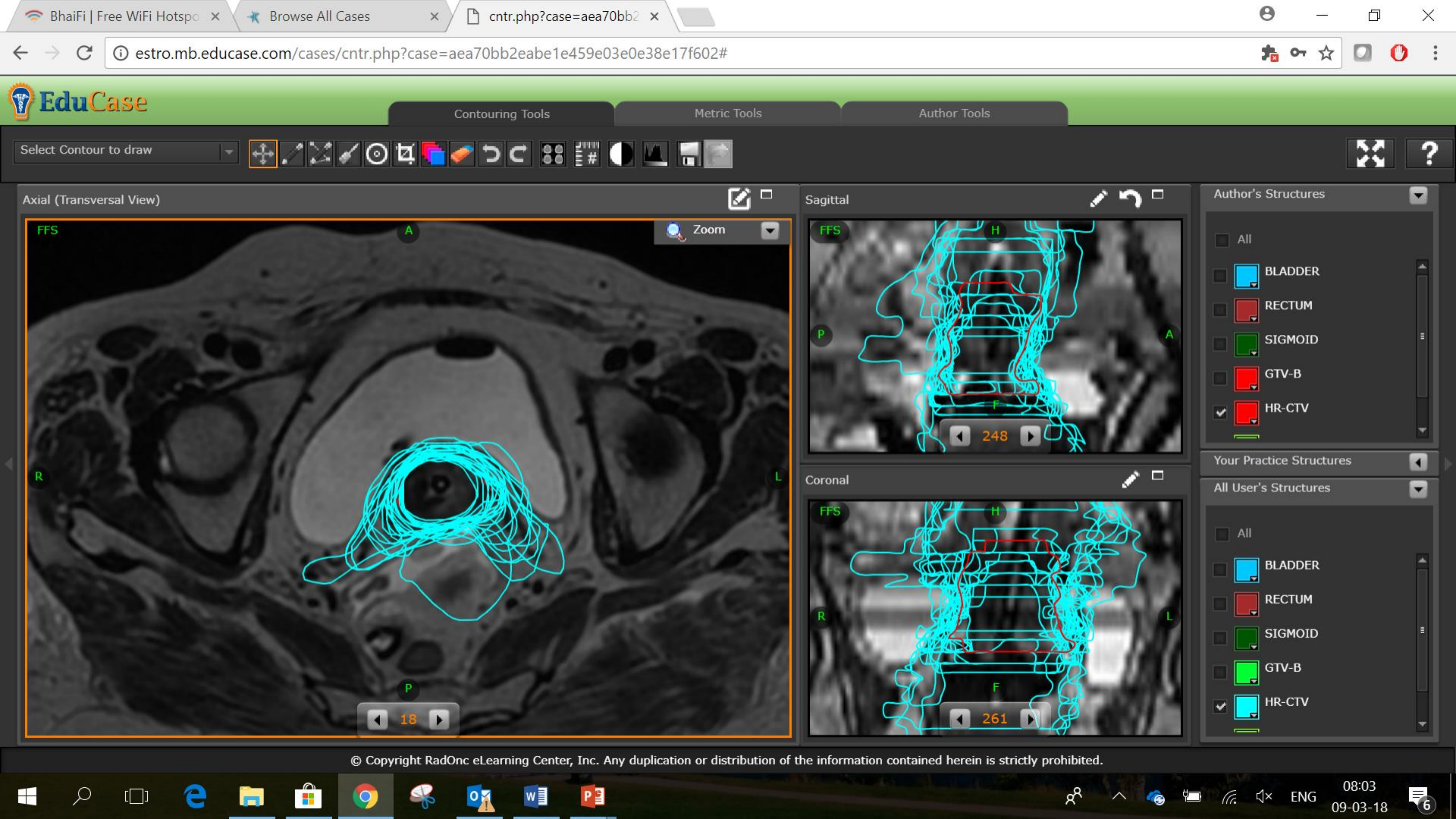
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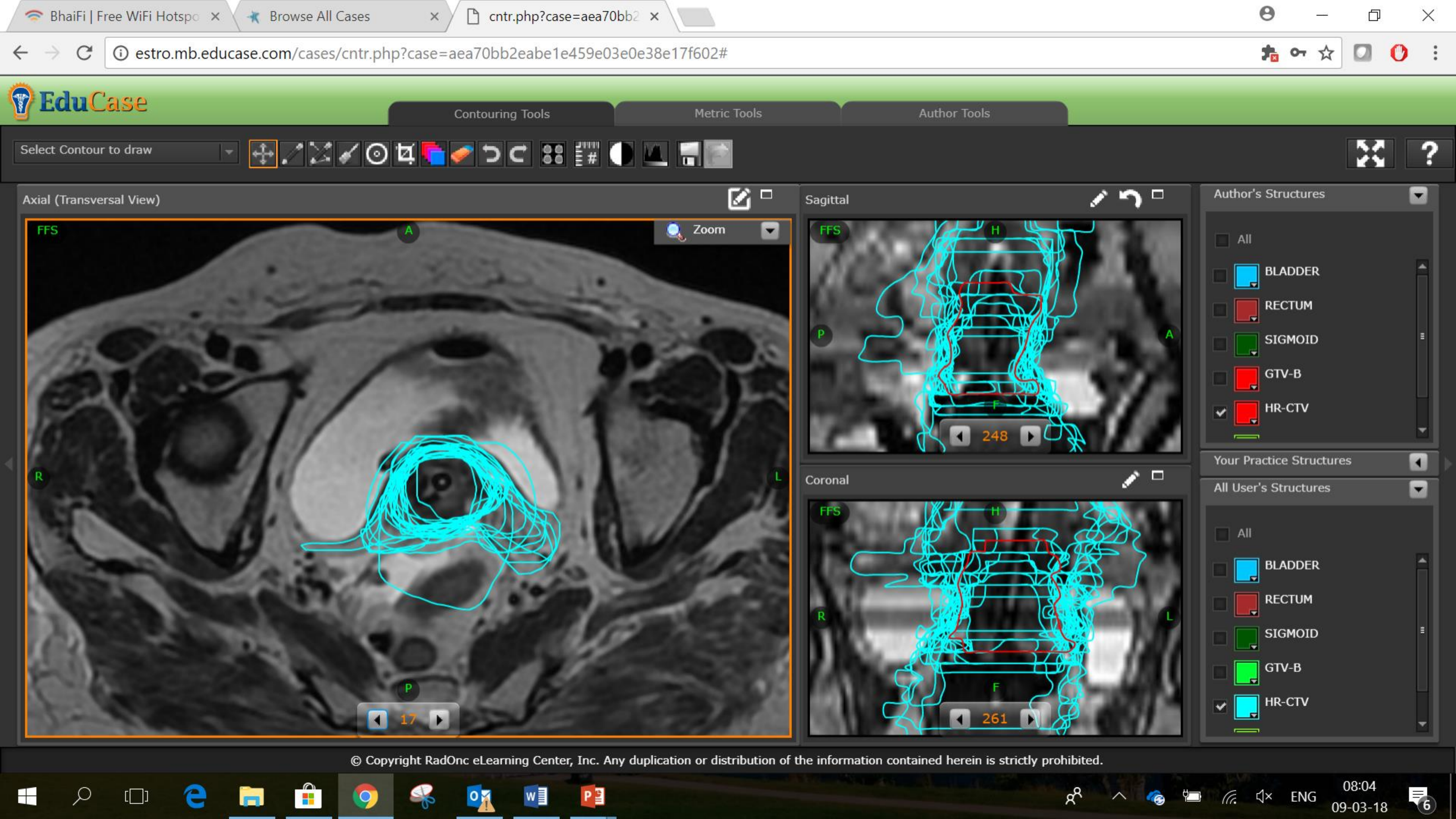

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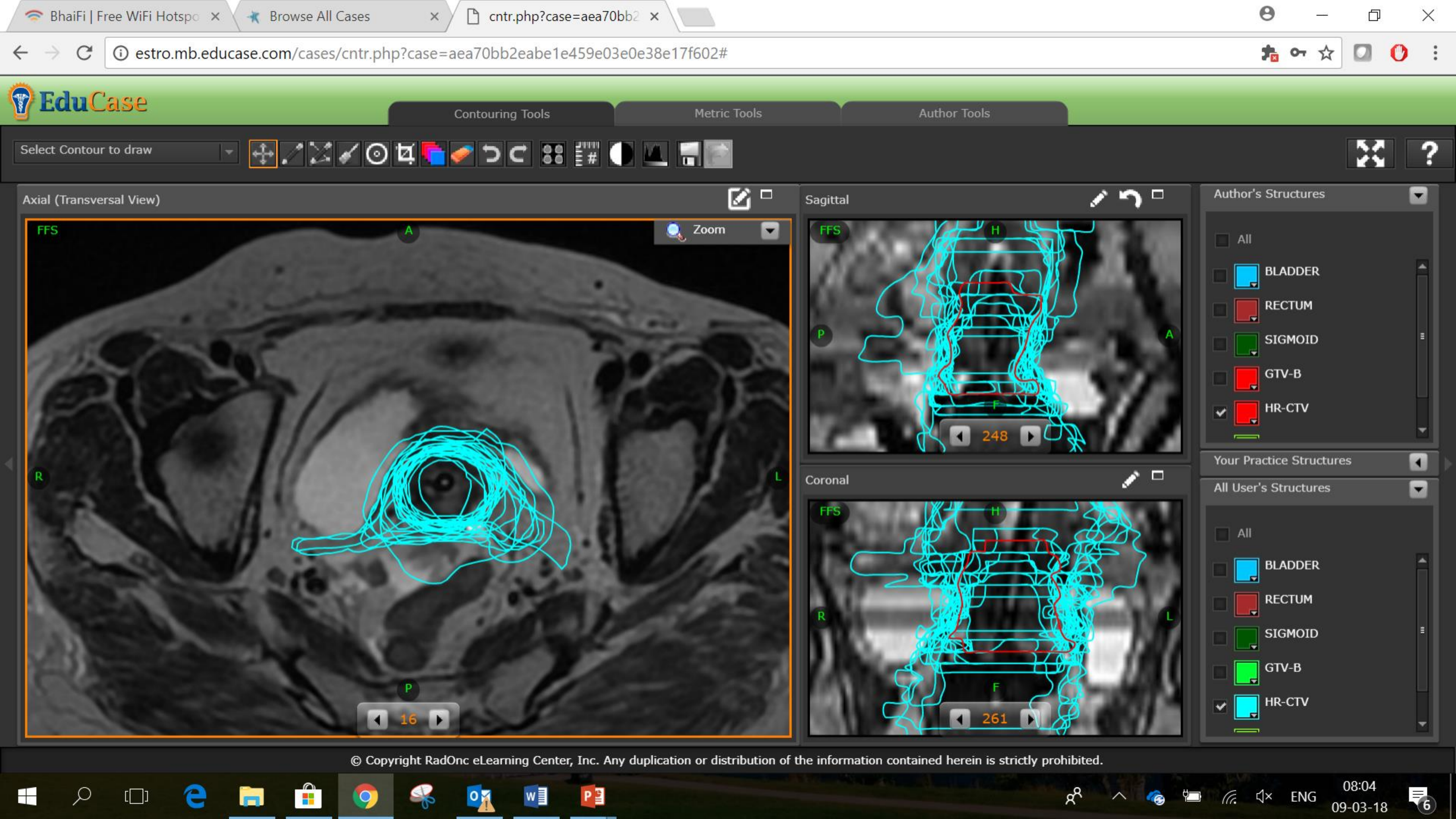
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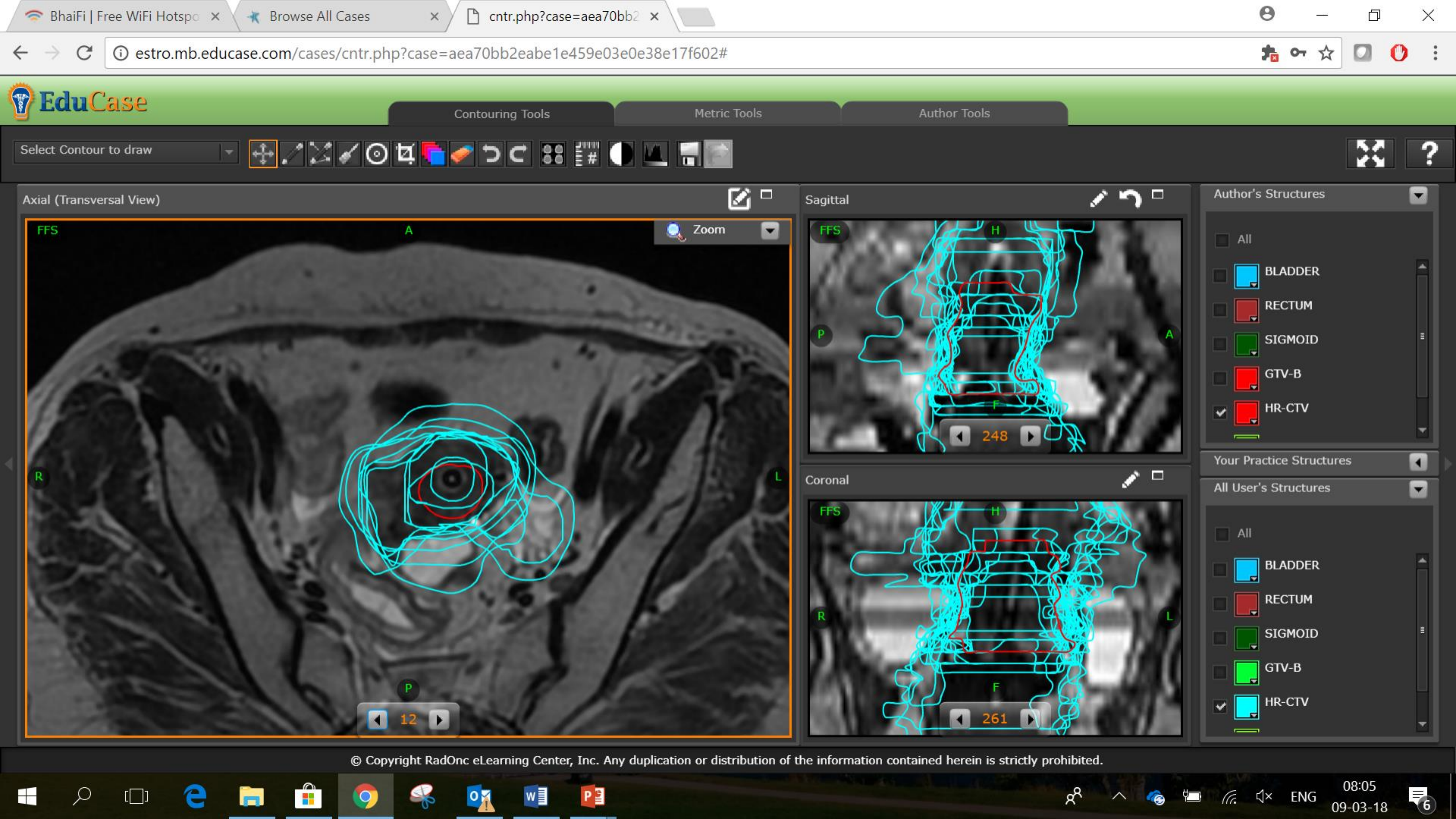
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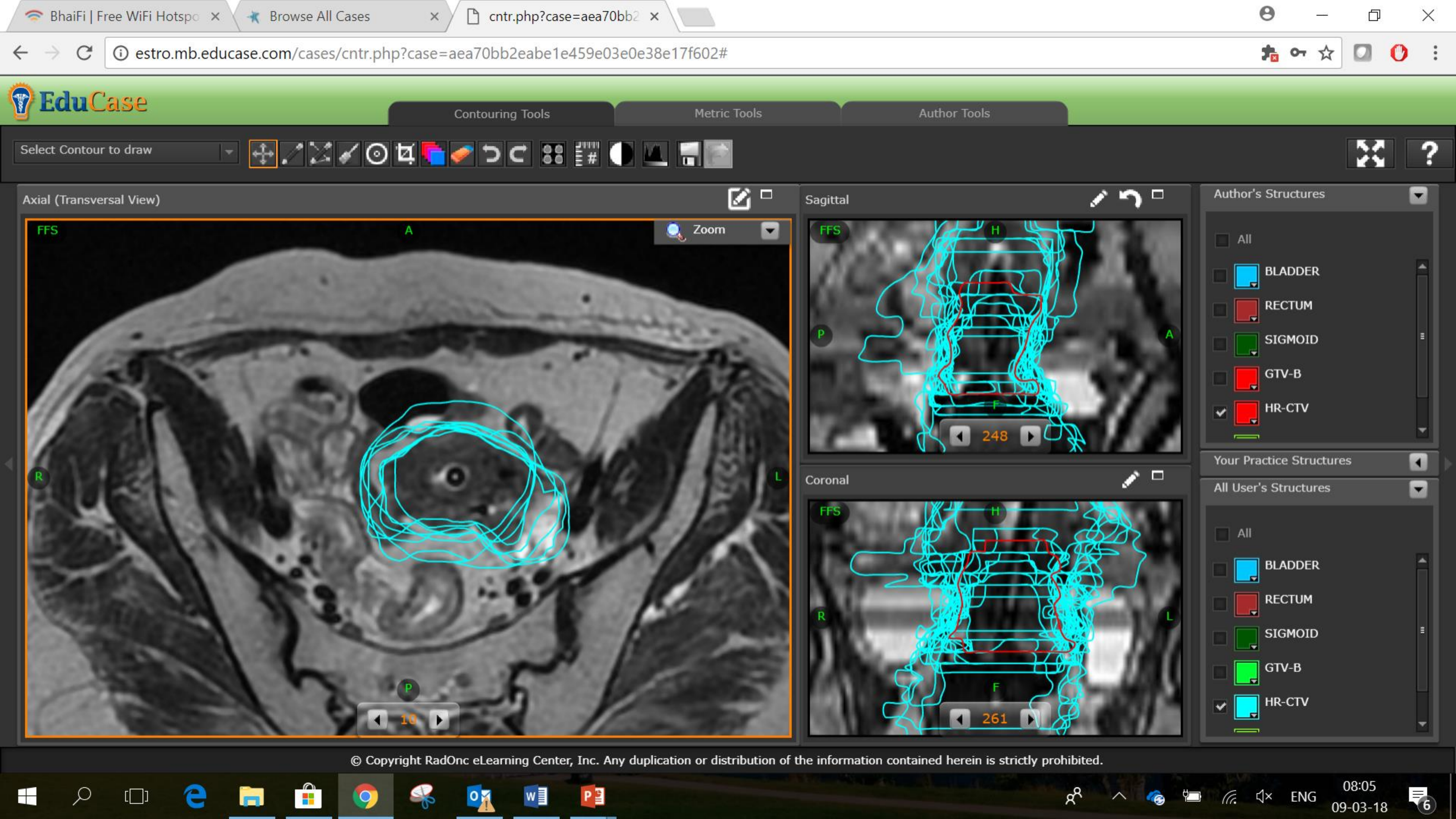
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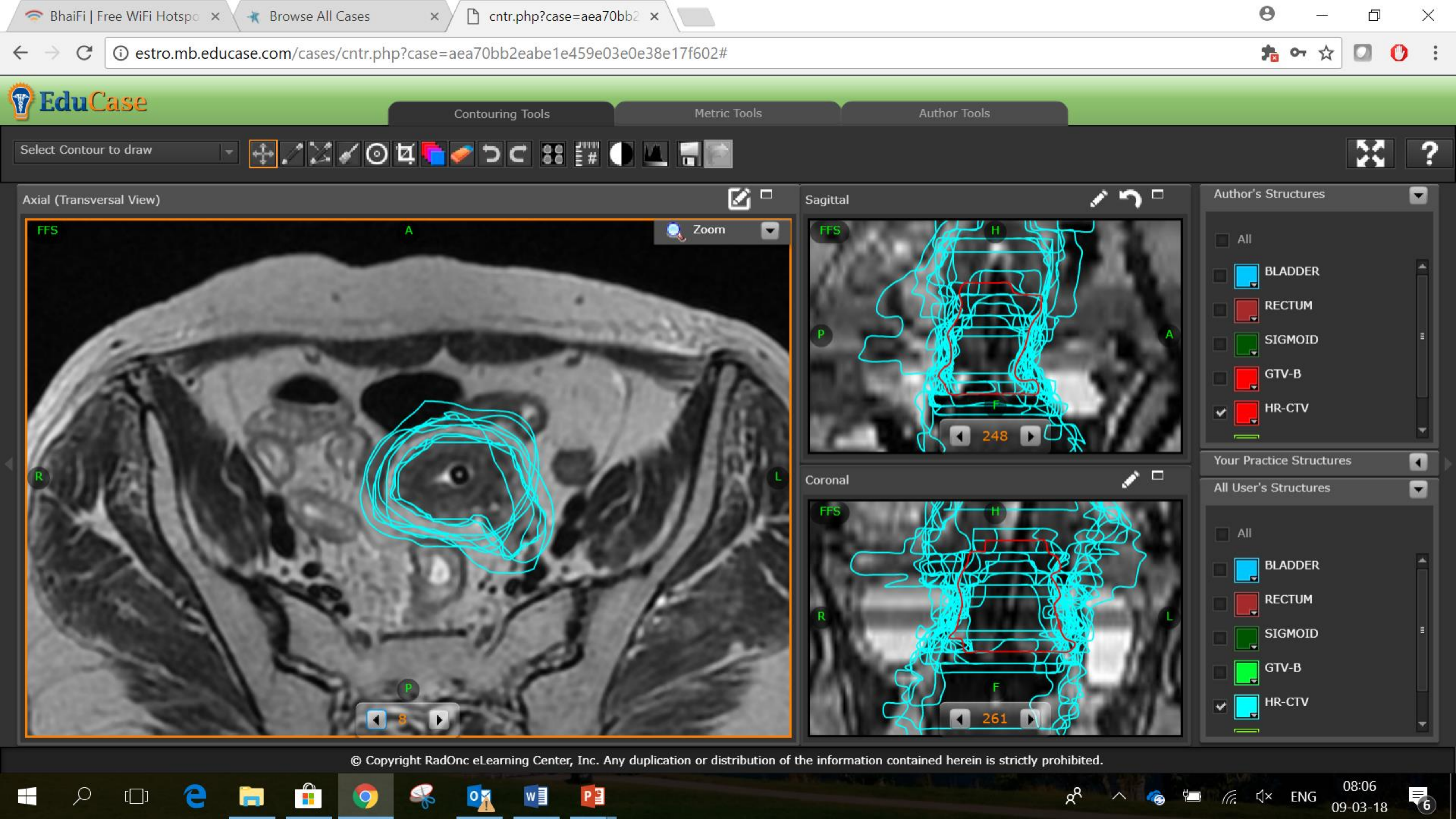
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Homework Brachytherapy planning (Tata 03)

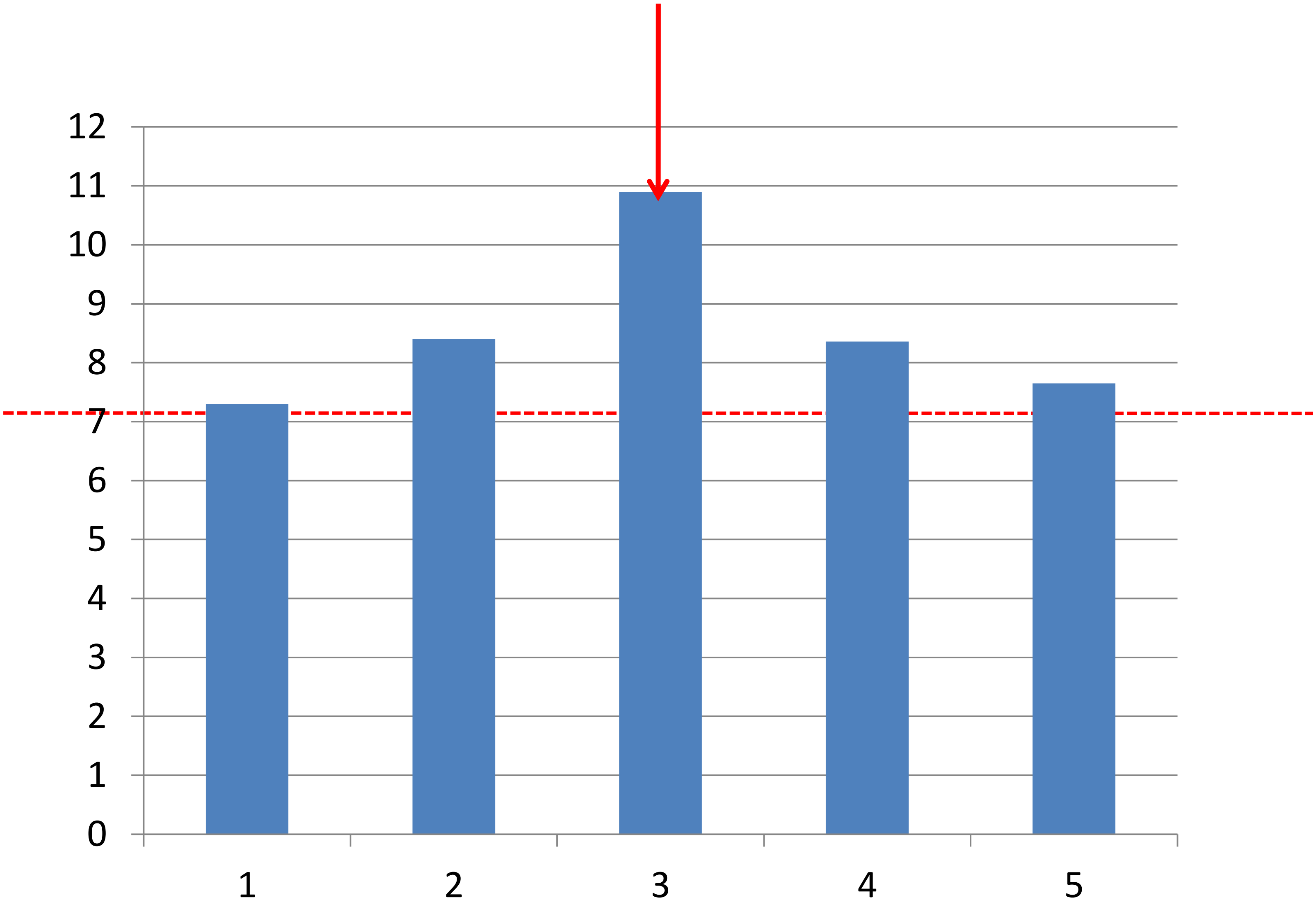
ESTRO GYN BT course

Lucknow 2018

Institutions

Reference plan	
Guru Gobind Singh MC&H, Faridkot	
BHU	
Kasirajan	
Malaysia	
Indo American, Hyderabad	

D90 CTV_{HR} > 7.0 Gy



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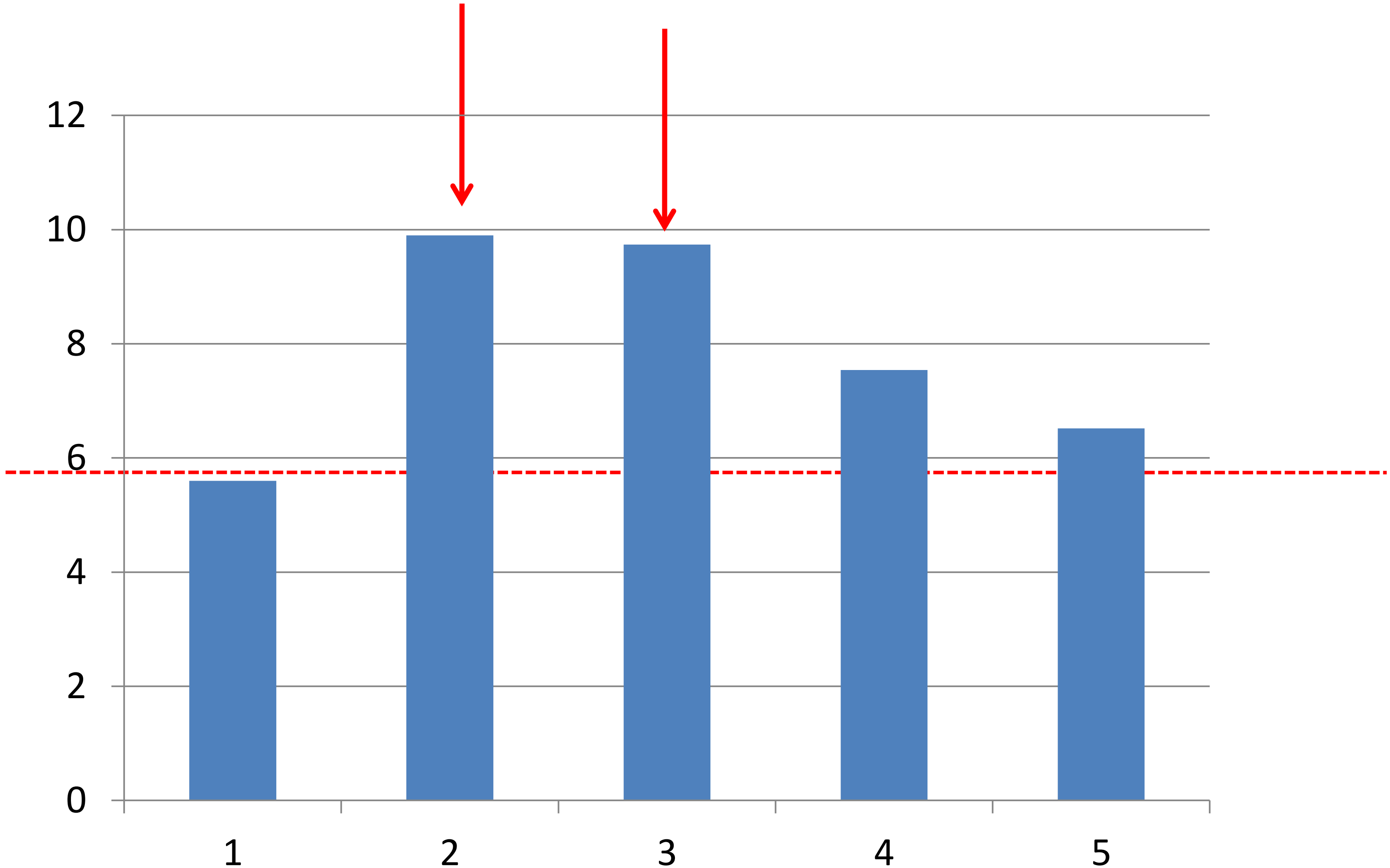

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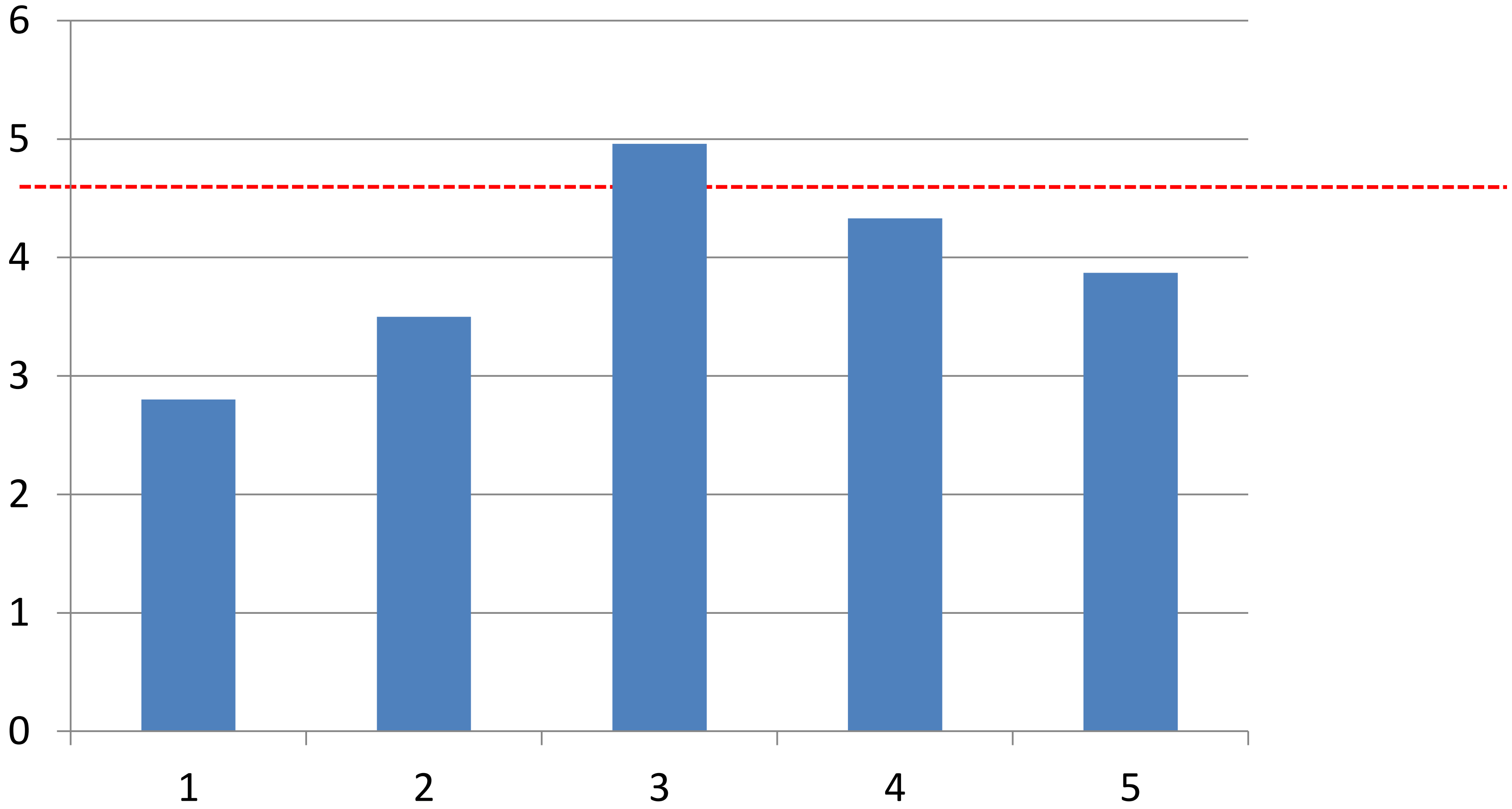

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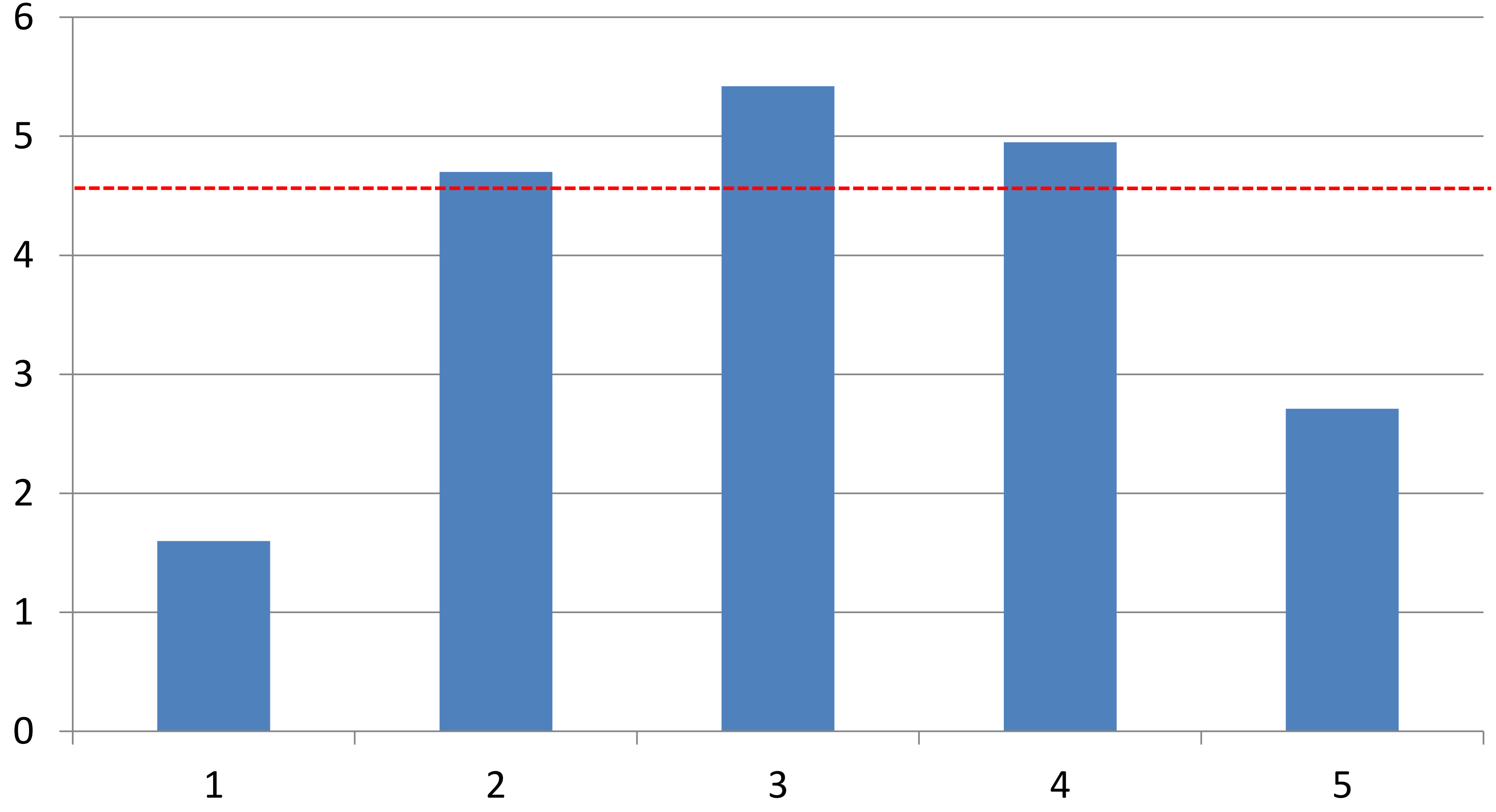

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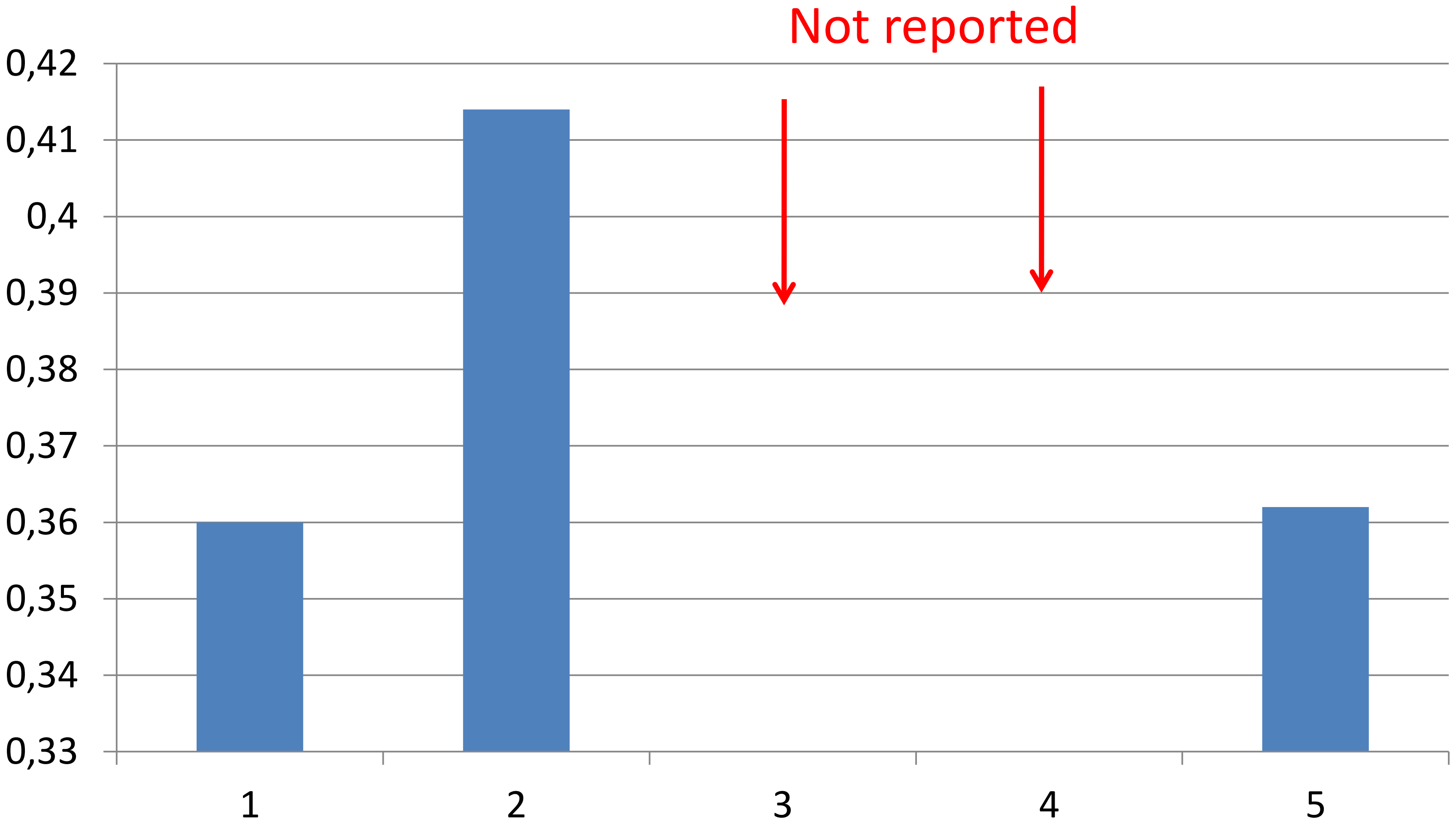

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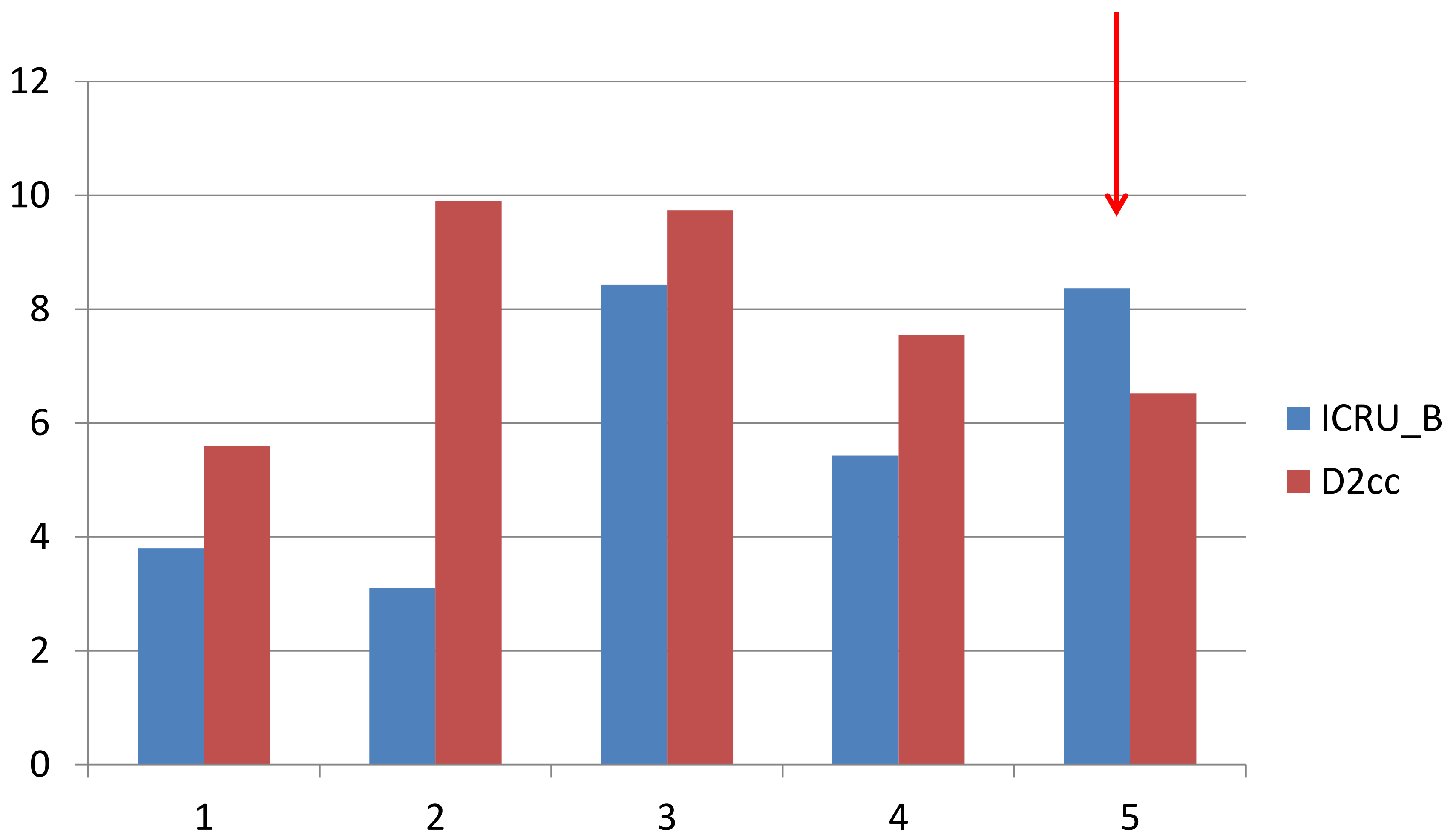

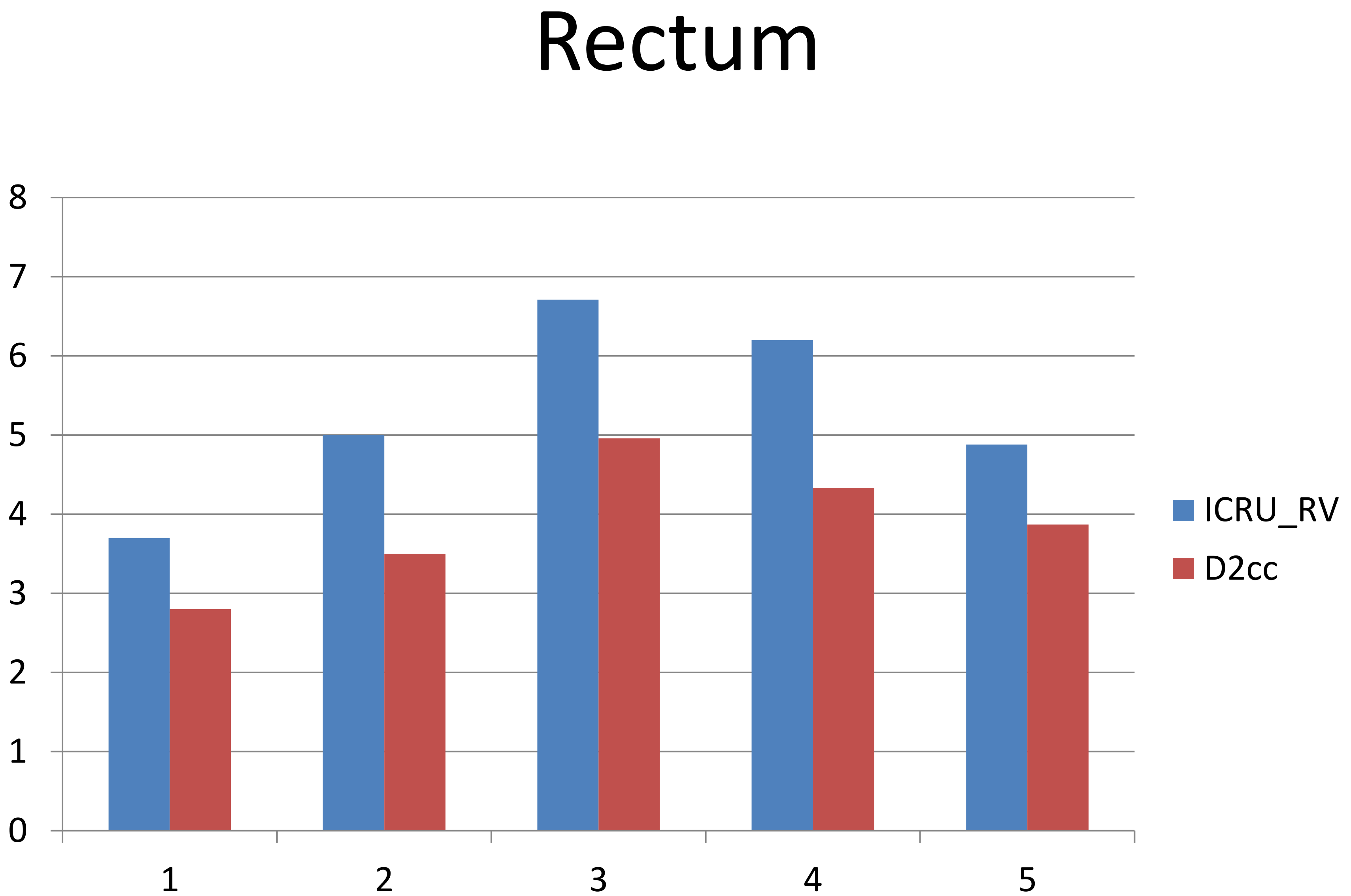
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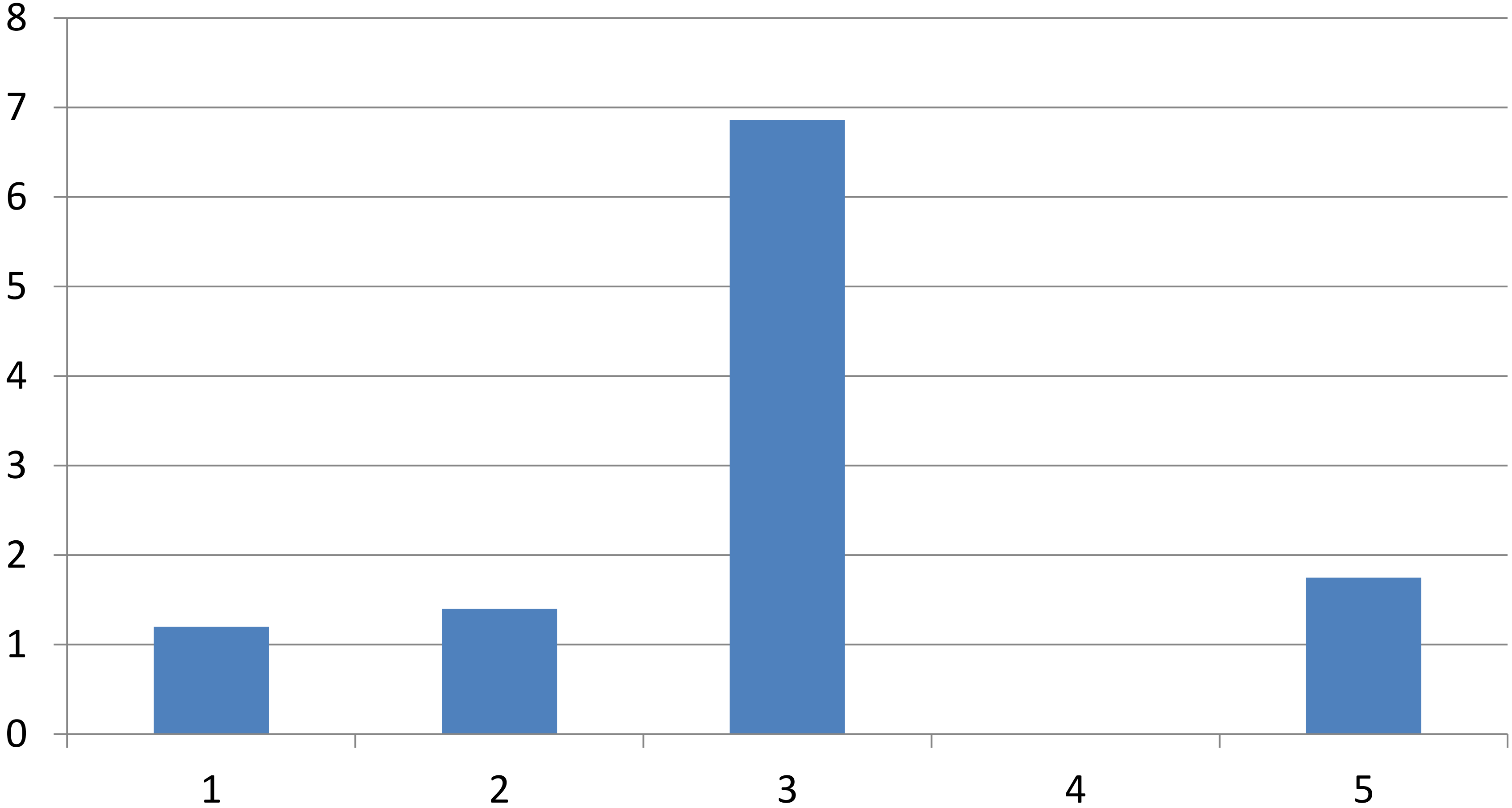

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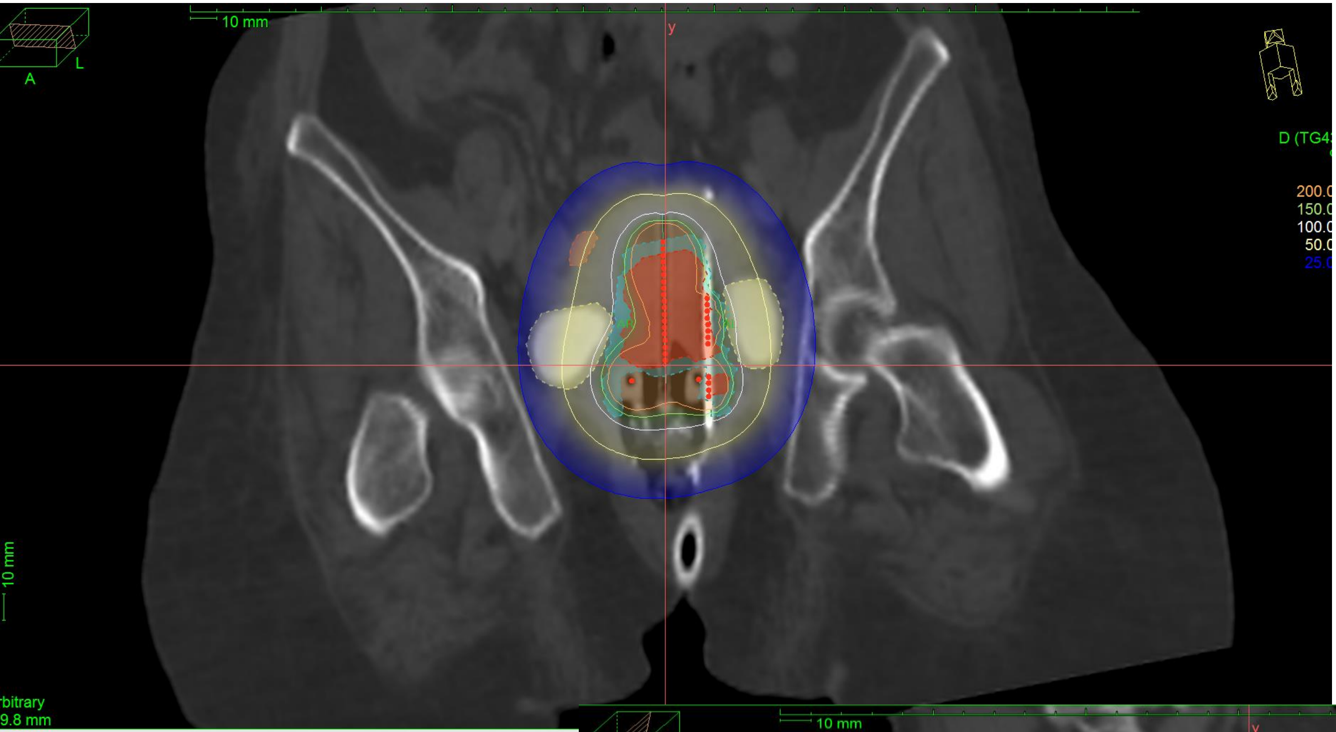

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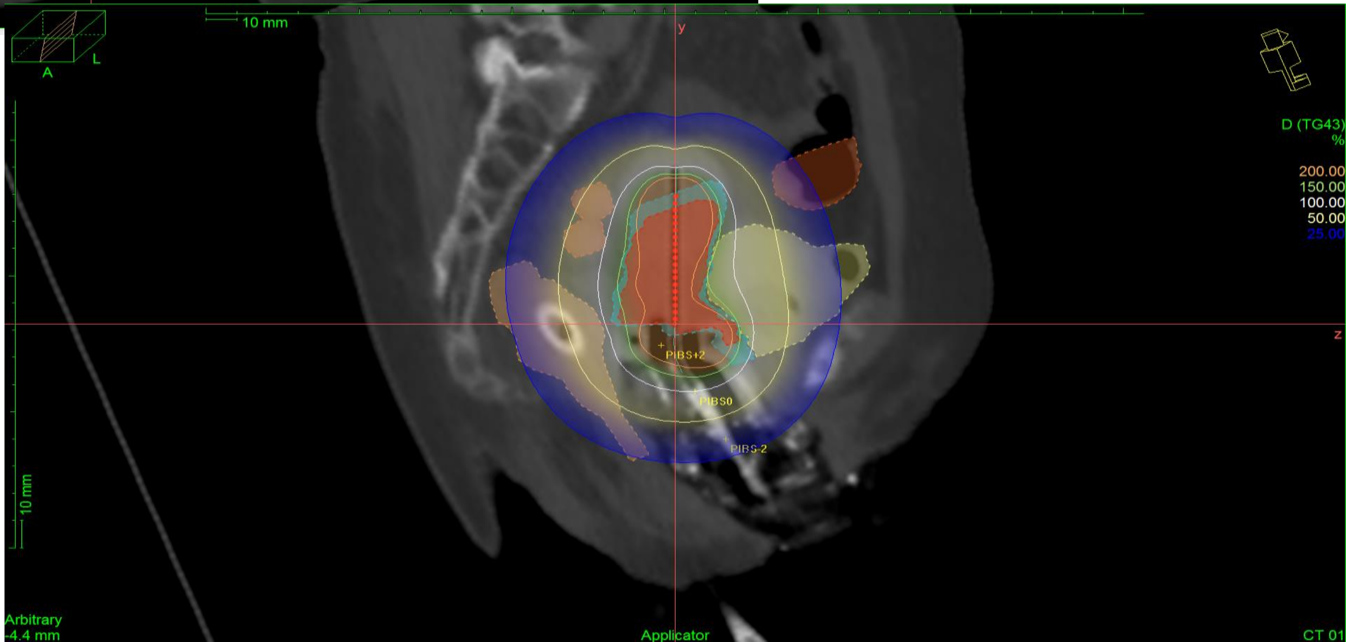
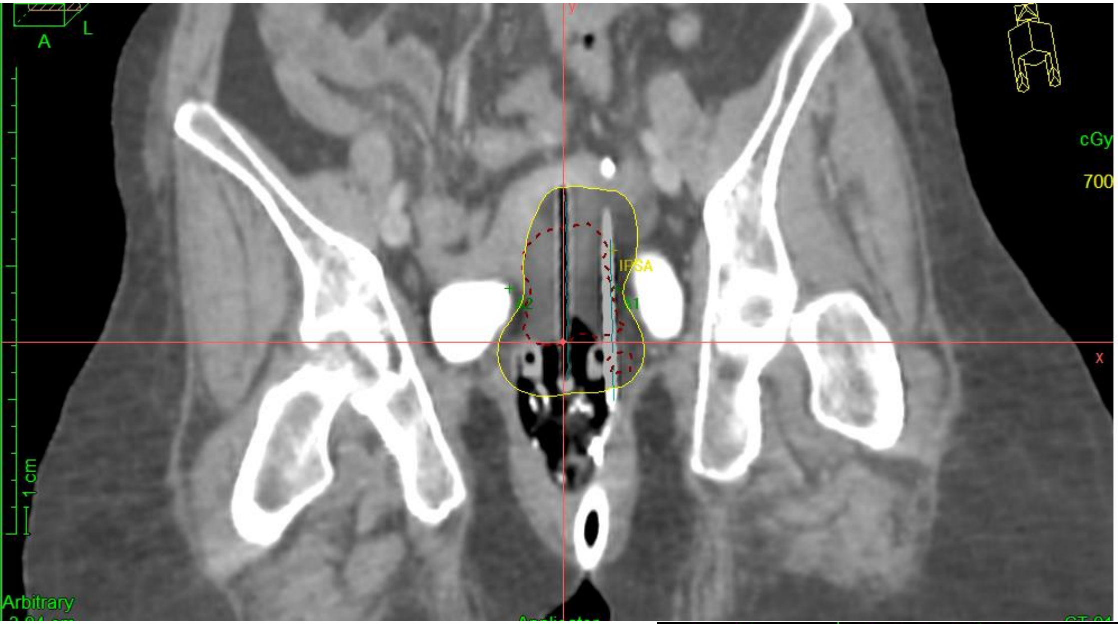
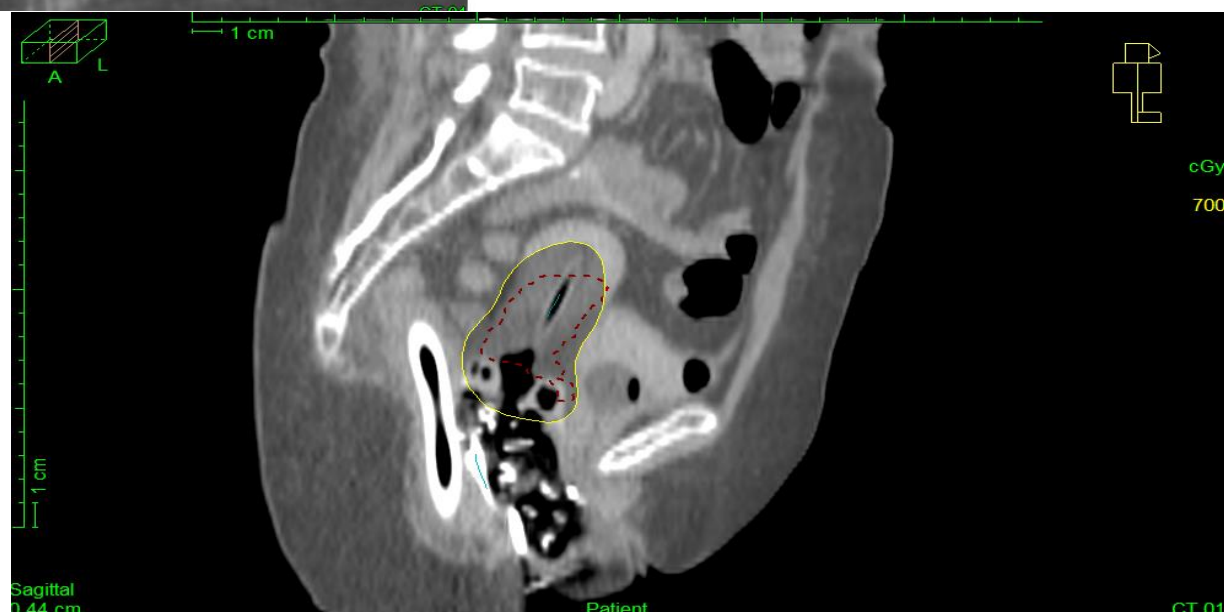
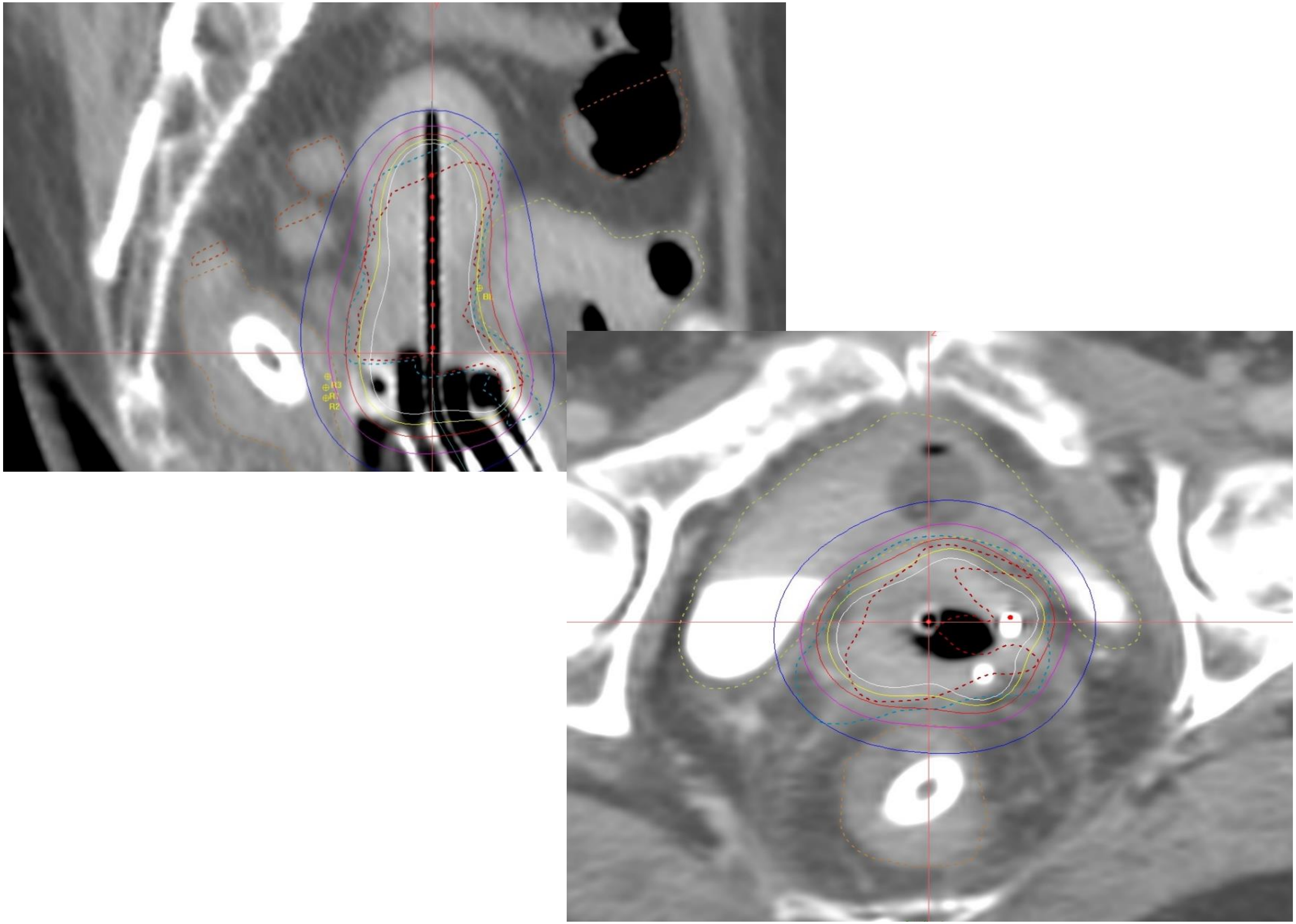
100.0
50.0
25.0
10 mm
bitrary
9.8 mm

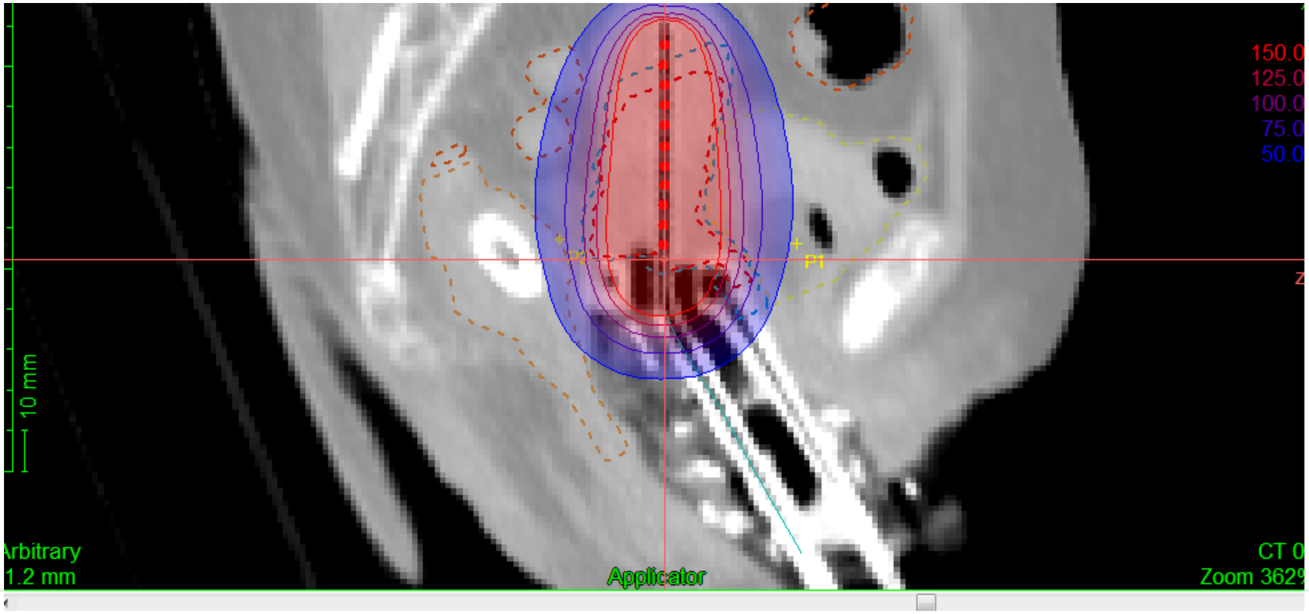


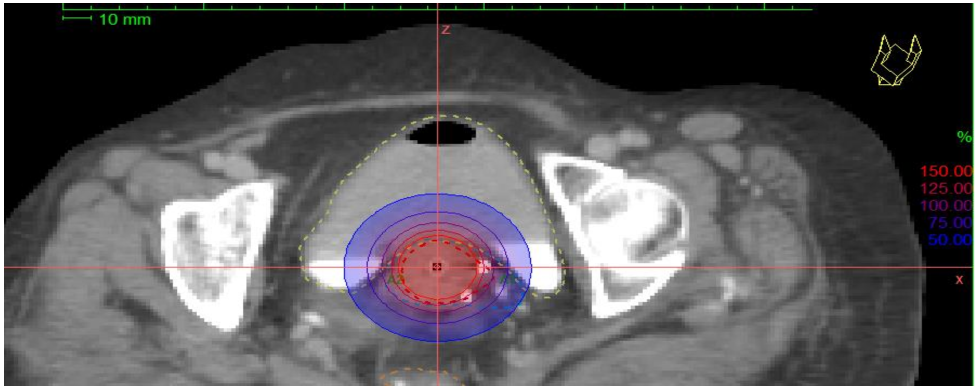
10 mm
A
L
y
D (TG43)
%
200.00
150.00
100.00
50.00
25.00
z
PIBS+2
PIBS0
PIBS-2
10 mm
Arbitrary
-4.4 mm
Applicator
CT 01

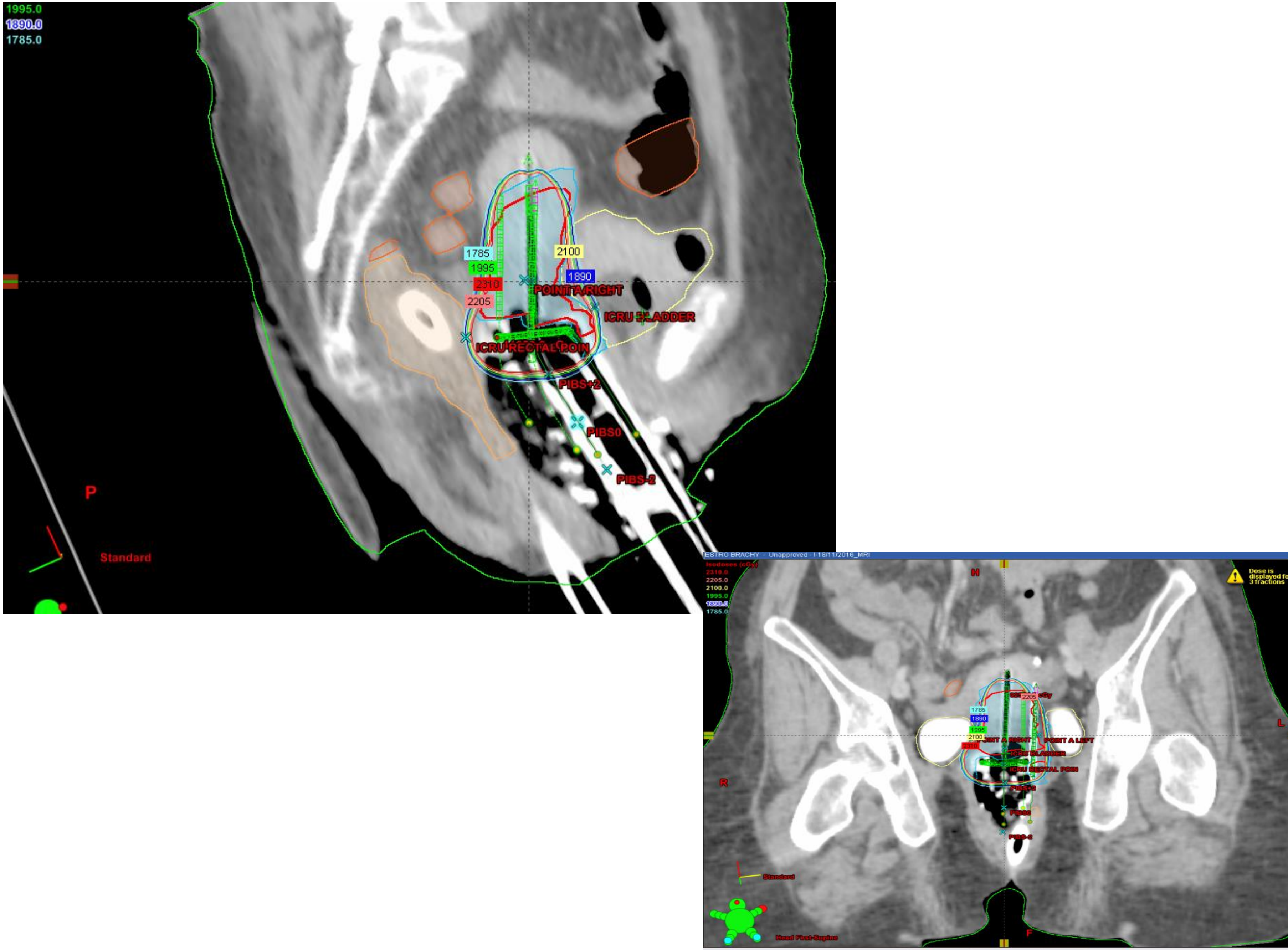

A
L
cGy
700
IPSA
1 cm
Arbitrary


1 cm
A
L
cGy
700
1 cm
Sagittal
Patient


R3
R2


150.0
125.0
100.0
75.0
50.0
10 mm
P1
Arbitrary
1.2 mm
Applicator
CT 0
Zoom 362


10 mm
%
150.00
125.00
100.00
75.00
50.00



1995.0
1890.0
1785.0
1785
1995
2310
2205
2100
1890
POINT A RIGHT
ICRU BLADDER
ICRU RECTAL POIN
PIBS+2
PIBS0
PIBS-2
P
Standard
ESTRO BRACHY - Unapproved - F18/11/2016_MRI
Isodoses (cGy)
2310.0
2205.0
2100.0
1995.0
1890.0
1785.0
H
Dose is displayed for 3 fractions
L
R
POINT A LEFT
F
Standard
Head First-Supine

Points for discussion

- Reconstruction – offset
- Reference points(ICRU B, ICRU RV, PIBS, Pt A)
- Optimization

Home work - Brachytherapy - Tata 03	Tata _Ref	GGS	BHU	Kasirajan	Malaysia
Source (Ir 192 / Co 60)	Ir 192	Ir-192	Ir-192	Ir-192	**Cobalt-60**
Treatment planning system	Oncentra	Oncentra 4.3	Oncentra	Oncentra	**Onsentra Brachy**
Reconstruction		**Manual**	**Manual**	**Manual/auto**	**Manual**
If manual offset applied		-6.5	yes	no	
Tandem (mm)	-7	50	-6	-	**12mm**
Ring (mm)	-7	8 + 8 (Left+Right of ring)	-6	-	**5mm**
Needles (mm)	-10		-6	-	**4mm**
Loading Pattern					
Tandem positions	8	11 active positions	(3) 3-21	Manual	**55 to 295 (5mm gap)**
Ring positions	8	tions, 4 Left side of ring & 4 Righ	(1) 1-11,19-	Manual	**37, 282, 277, 240, 235, 230**
Needles positions	10		(2) 8-15, 20	Manual	**275, 270, 255, 250, 245**
Dwell time	**368.1**				**270, 265, 260, 255**
Tandem mm	189.5	204.8	199.5	412.6	
Ring mm	138	204.8	246.3	447.9	
Needles	40.6		116.5	476	
Optimization (Manual/Graphical/inverse..)	**M+Gr**	No optimization	Manual/Gr	Graphical	

Medical aspects of brachytherapy treatment planning and dose constraints

Clinical evidence for dose point and dose volume effects

2nd AROI ESTRO Gyn Teaching Course

3D Radiotherapy with a Special Emphasis on Implementation of MRI/CT based Brachytherapy in Cervical Cancer

Lucknow, March 2017

Richard Pötter

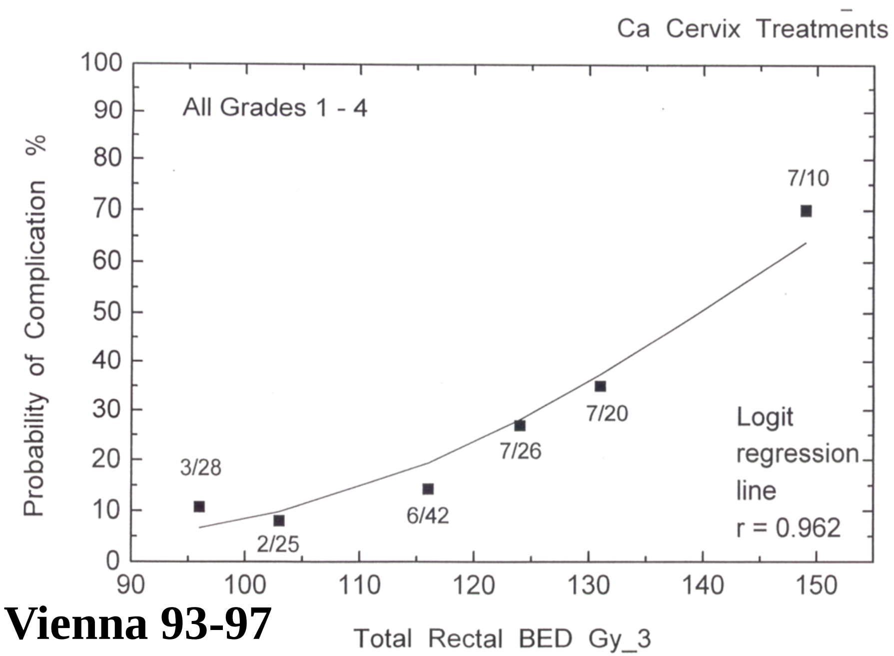
Kari Tanderup

DOSE EFFECT RELATIONSHIP POINT A

N=1499		Dose pt A	Pelvic failure
Stage IB and IIA	(<2 cm)	70-80 Gy	<10%
	(>2 cm)	up to 85-90 Gy	25-37%
Stage IIB		70 Gy	50%
	nonbulky	>80 Gy	20%
	bulky	>80 Gy	30%
Stage III unilateral		up to 70 Gy	50%
		>70 Gy	35%
Stage III bilateral/bulky		< 70 Gy	60%
		>70 Gy	50%
		>85 Gy	35%

„Refinements in brachytherapy techniques are necessary to improve the present results“ (Perez et al IJROBP 1998)

Dose Effect relationship for late rectum side effects based on points (ICRU reference points)

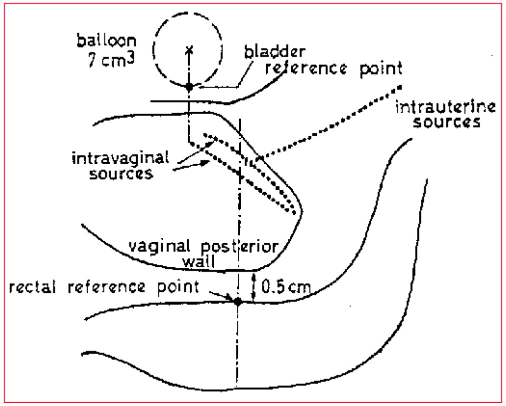


Vienna 93-97

J. Fowler, Knocke, Pötter 1998 unpublished

32 „events" in 151 patients

Actuarial rate 3y: 24%



BED ~120-130 Gy_3 „cut-off level" in recent experience

Iso-effective dose in 2Gy/fr ~ 70-80 Gy $_{\alpha\beta3,2Gyfr}$

no clear dose effect relations bladder, sigmoid, vagina

Clinical Evidence in IGABT Cervix Cancer dose point and 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)

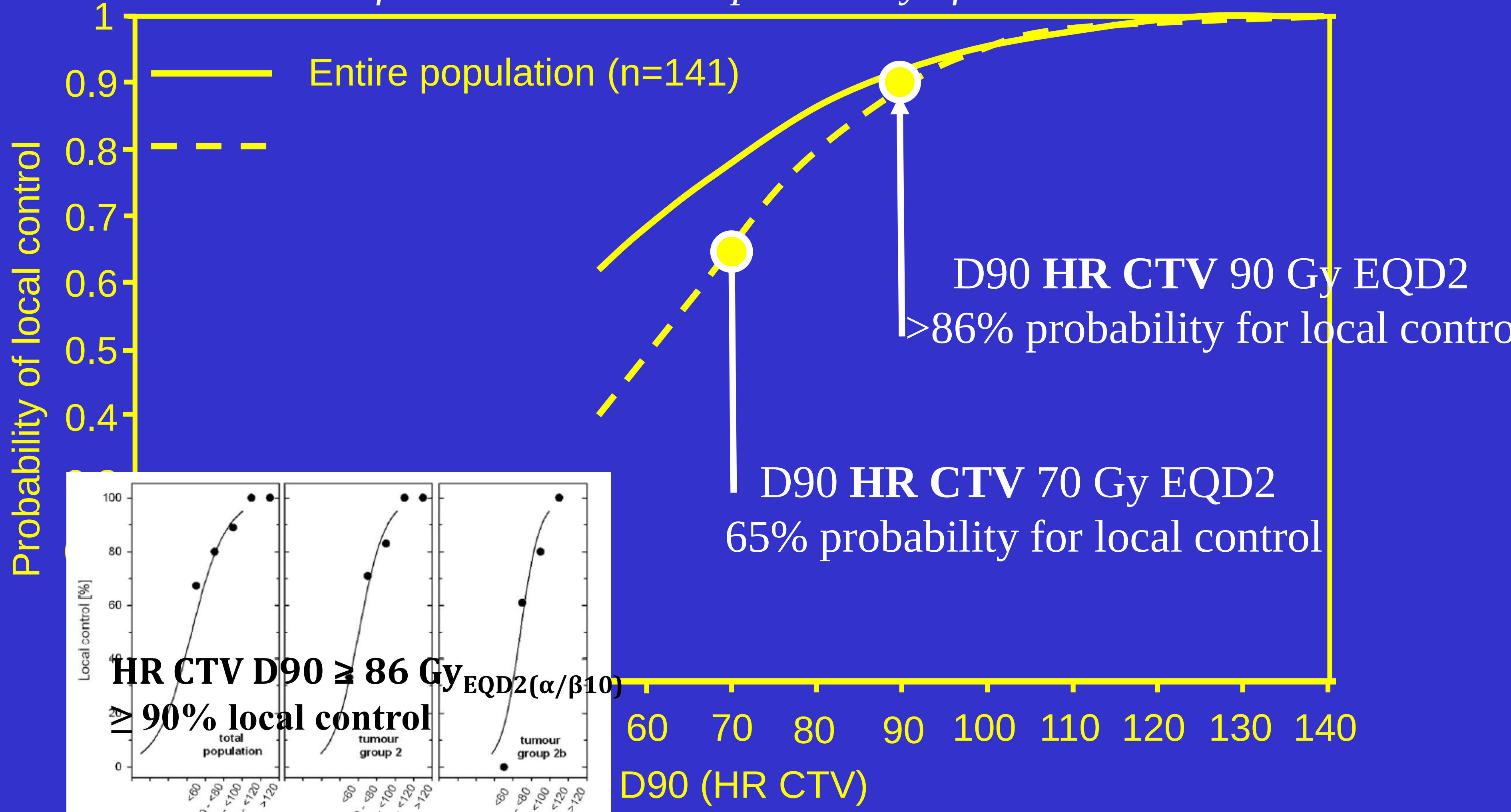
- **Vienna** (Dimopoulos 2008, 2010, Georg 2009,2011(Pötter 2007, 2011))
- **Seoul** (Kim et al. 2008)
- **Paris** (Mazeron 2014, 2015 (Castelnaud-Marchand 2015, Haie-Meder))
- **Aarhus** (Lindegaard, Tanderup 2014)
- **Leuven** (Ribeiro, Limbergen 2016)

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

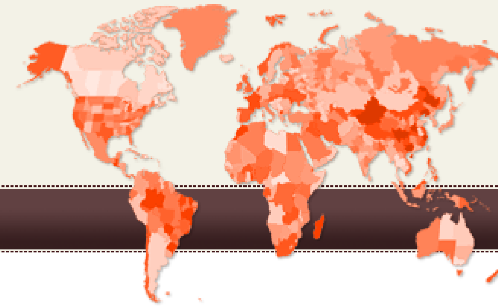


Dimopoulos et al., R&O 2010 *Dimopoulos et al. IJROBP 2008*

RETRO
EMBRACE

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

About Retro-Embrace | Contacts | Login



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

- 780 pts

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

Overall outcome published by Sturdza et al. Radioth Oncol 2016

VARIAN medical systems | A partner for life

Nucletron Improving patient care

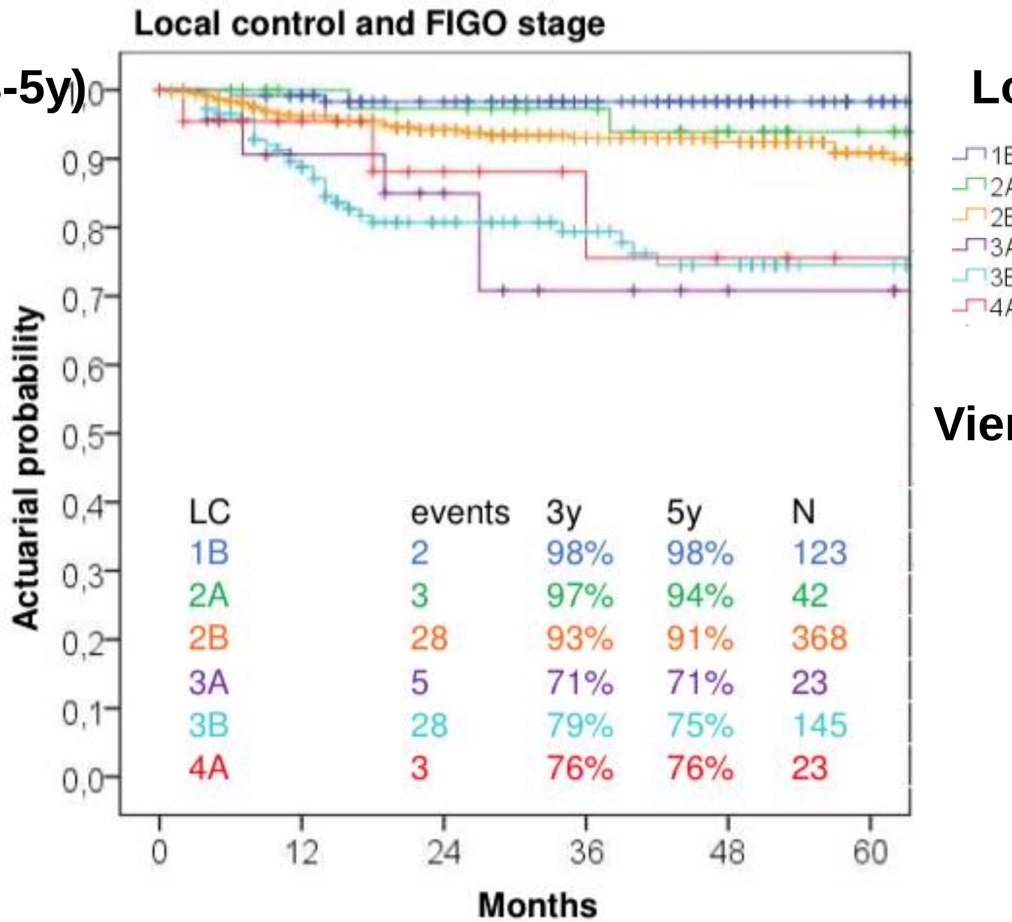
Local control and FIGO stage (RetroEMBRACE)

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:

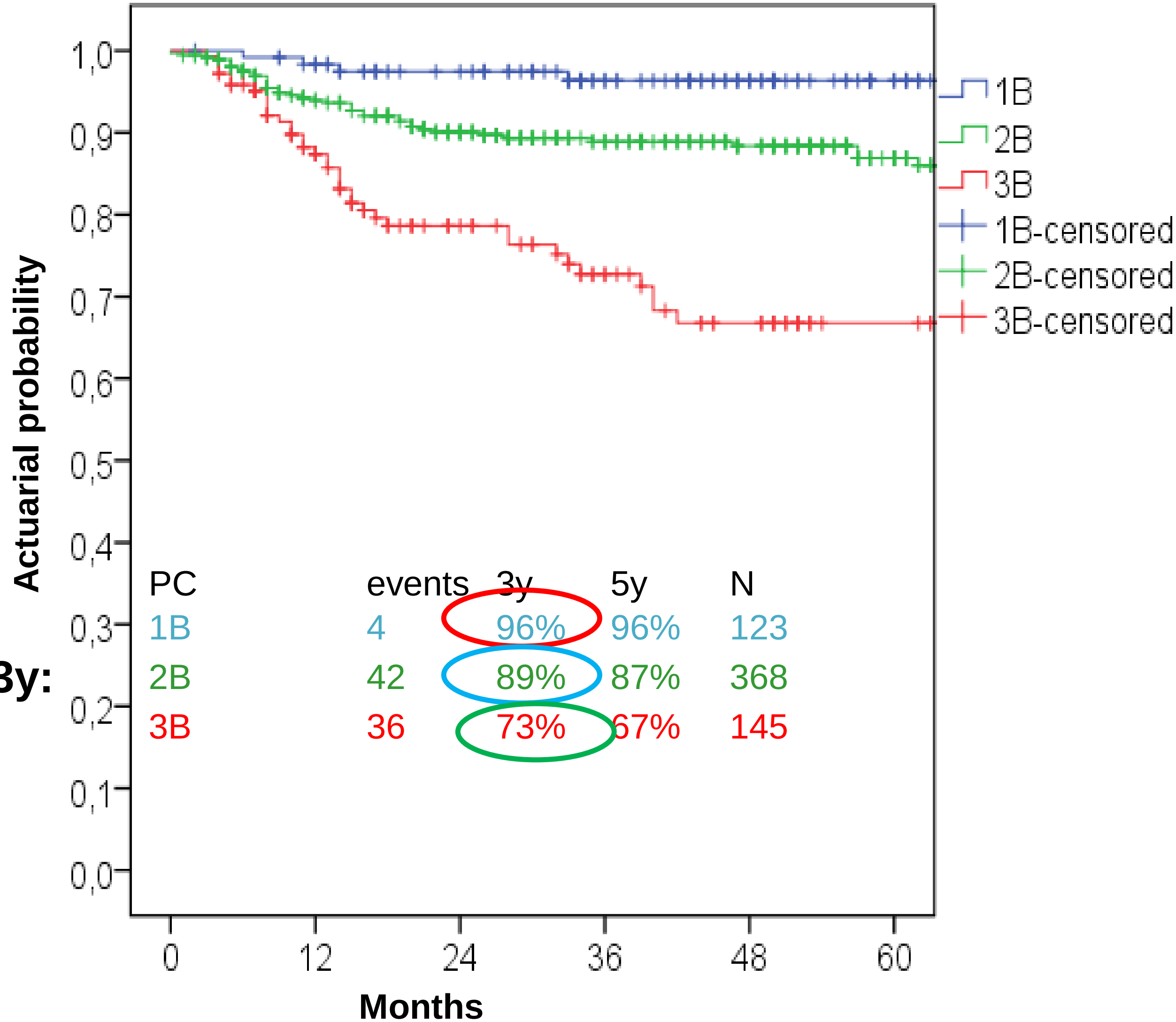
IB: 100%
IIB 96%
IIIB 86%

RetroEMBRACE (2016) 3y:
Overall local control 91%

Vienna (2011) 3y:
Overall local control 95%

Sturdza et al. 2016

Pelvic control and FIGO stage



PC	events	3y	5y	N
1B	4	96%	96%	123
2B	42	89%	87%	368
3B	36	73%	67%	145

RetroEMBRACE 3y: overall 87%

Vienna (2011) 3y: overall 91%

123	116	100	75	53	30
368	303	256	205	164	107
145	108	72	53	40	26

MEDIZINISCHE UNIVERSITÄT WIEN

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**
CTV_{HR} **<30cm³**	95%	94%
CTV_{HR} **≥ 30cm³**	77%	86%

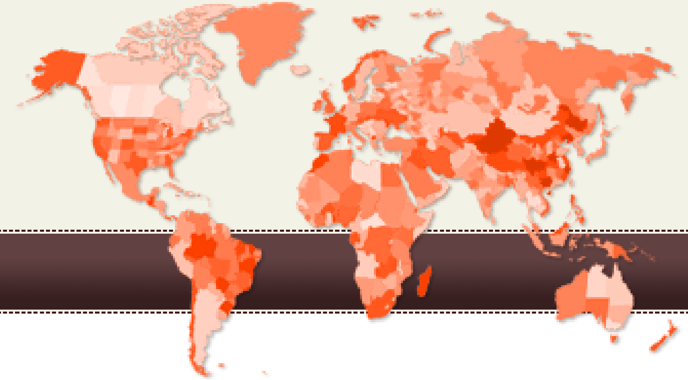
The use of advanced adaption including interstitial BT improves local control in tumors with CTV_{HR} ≥ 30cm³ and does not increase late morbidity

Fokdal et al. 2016. Fortin et al.to be submitted

EMBRACE

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

About Embrace | Contacts | Participation | Login

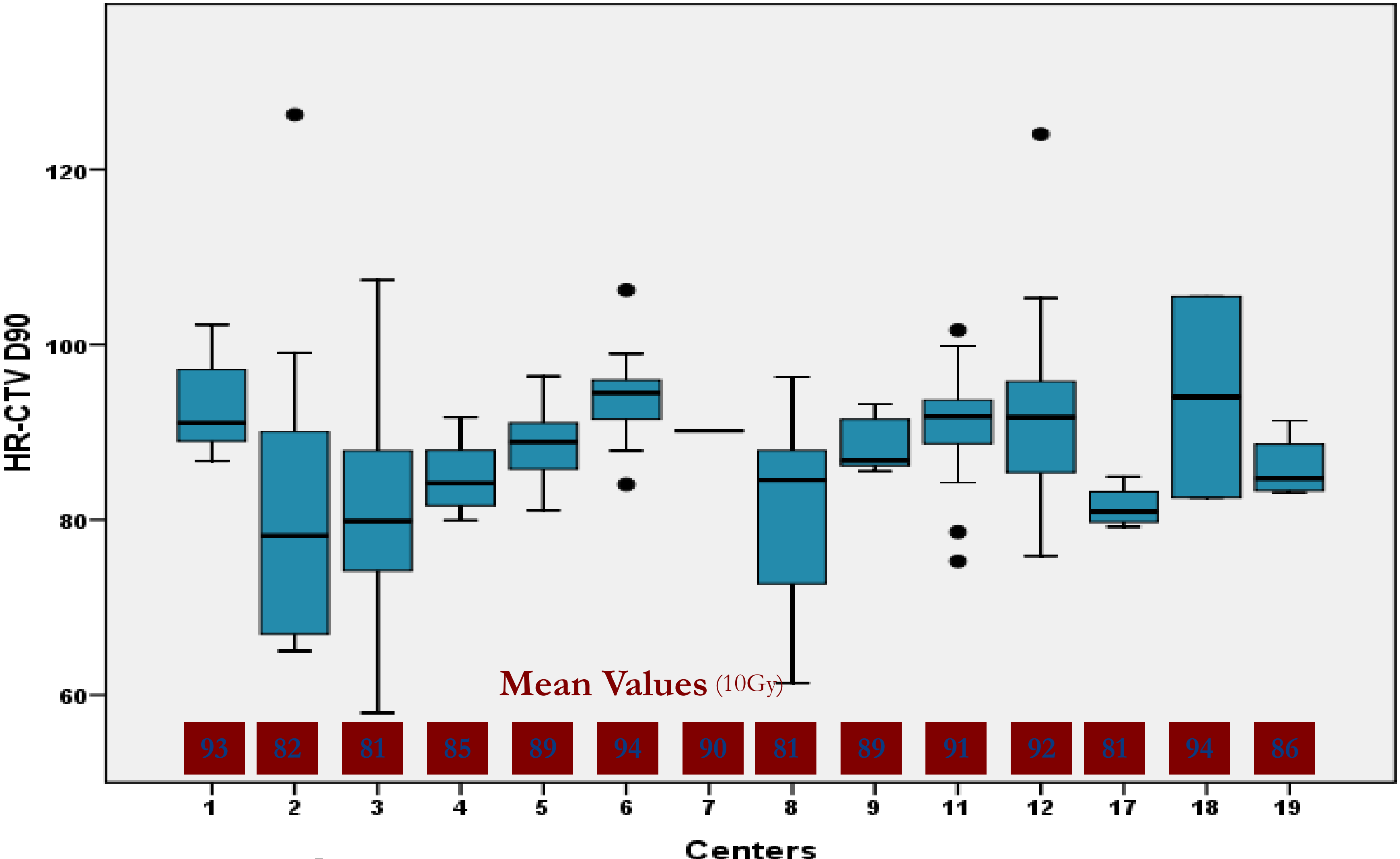


- **EMBRACE - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer**
- **A prospective observational multi-centre trial**
- **Major endpoint: local control; multiple other endpoints**
- **multiple hypthese on dose volume effects**
- **Enrollment of patients 7/2008-12/2015, 1416 pts accrued**

VARIAN medical systems | A partner for life

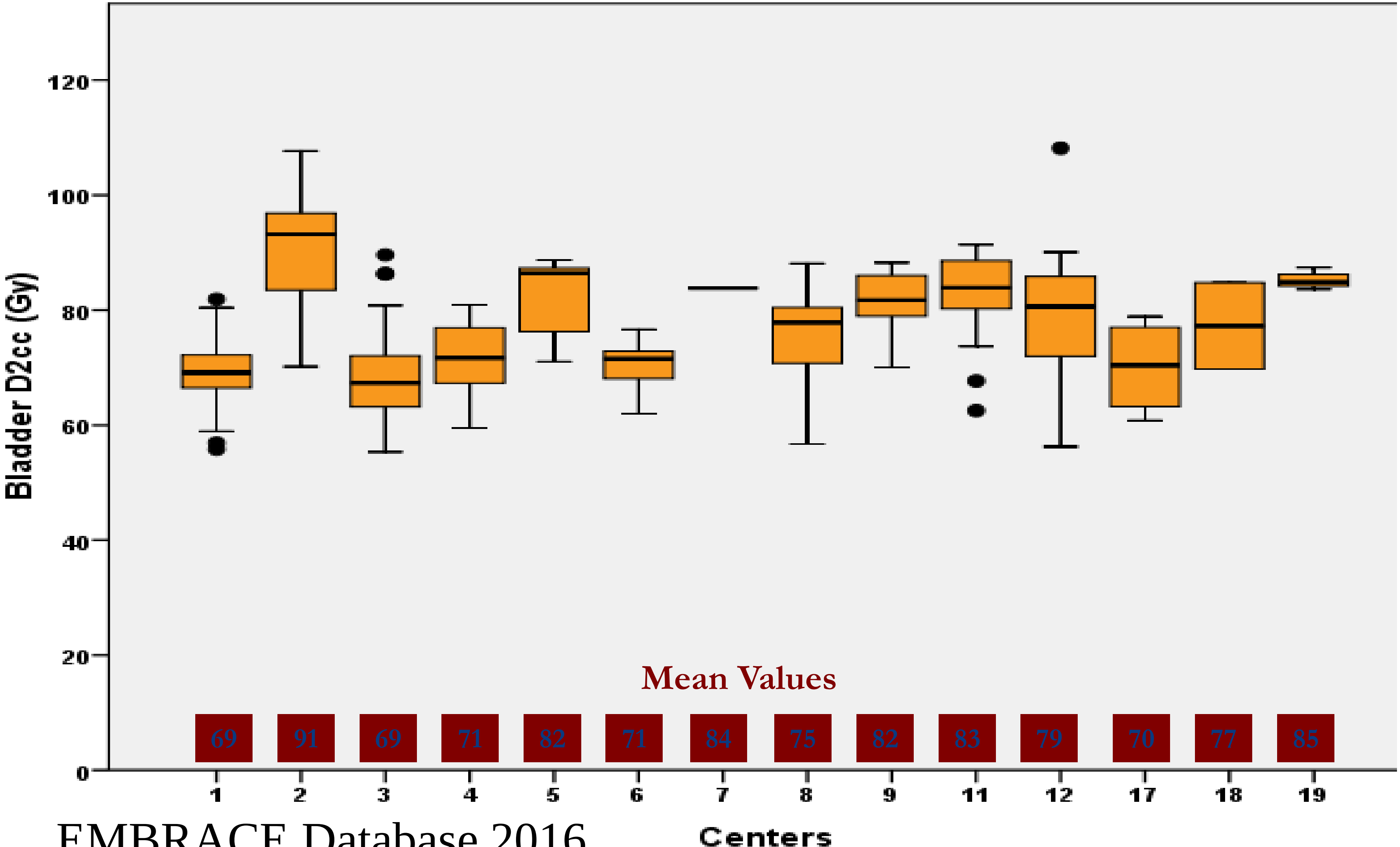
Nucletron Improving patient care

Heterogeneity of dose prescription: HRCTV D90



EMBRACE Database 2016

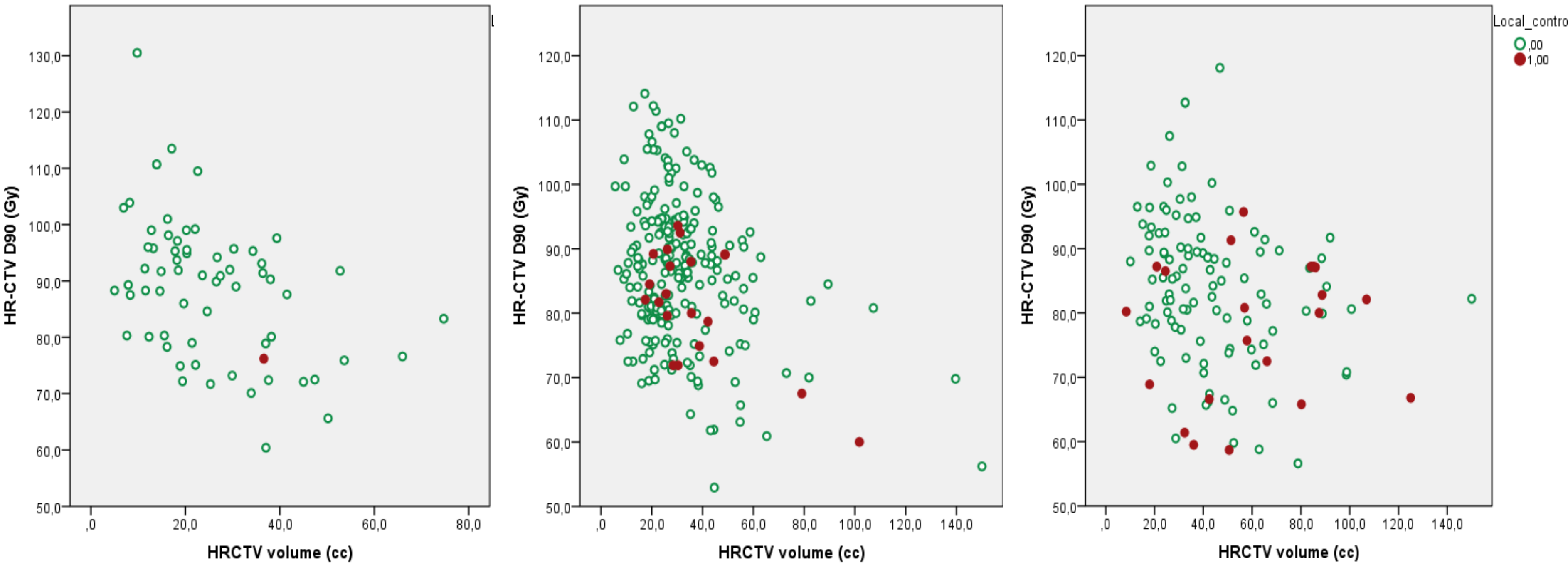
Heterogeneity of dose prescription: Bladder D2cc



EMBRACE Database 2016

Recurrences according to dose and volume

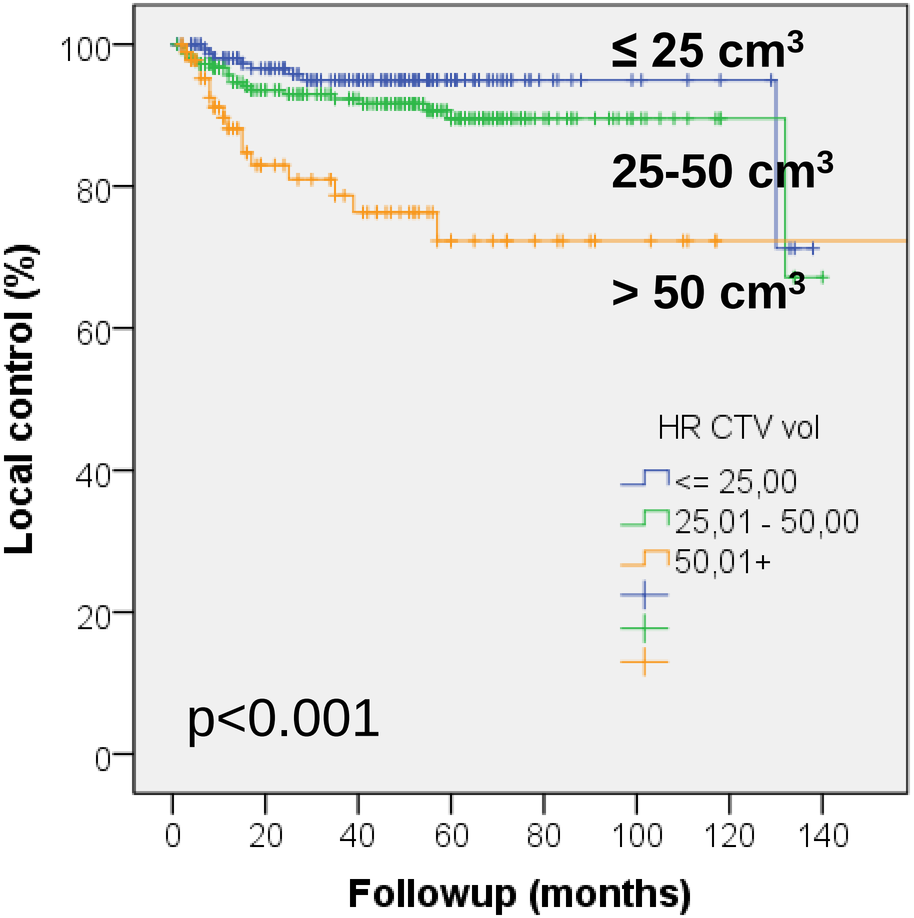
Stage I **Stage II** **Stage III+IV**



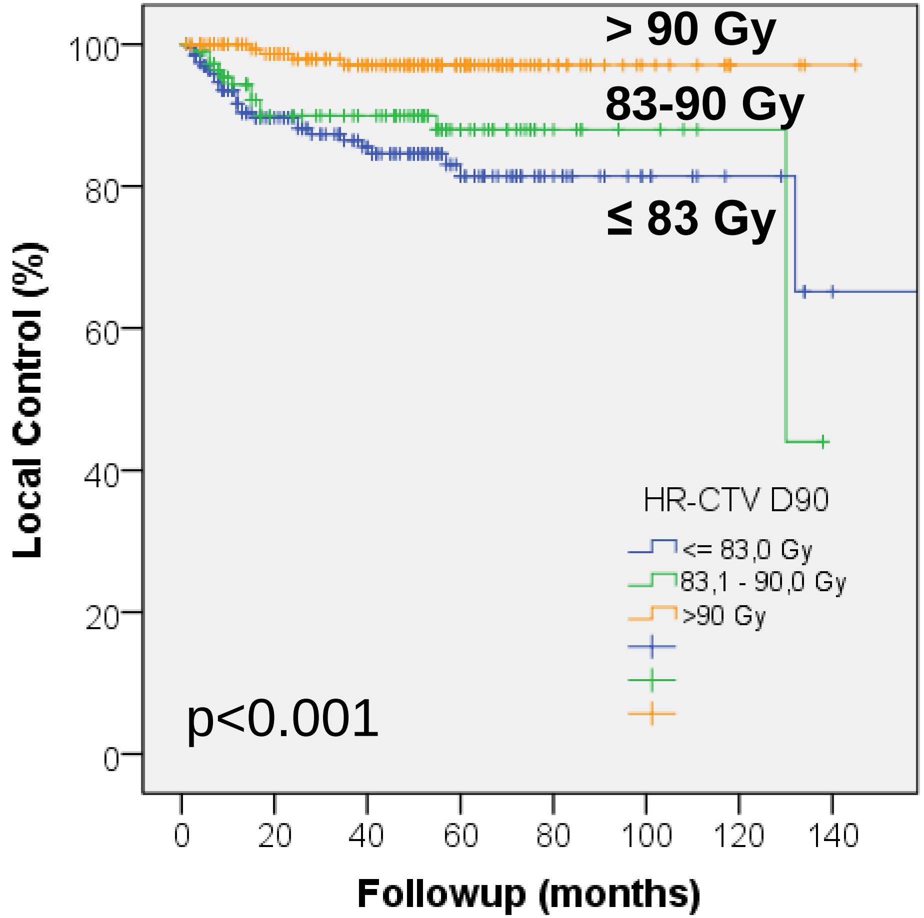
Tanderup et al. Radiotherapy and Oncology 2016

Actuarial local control: univariate analysis separate for HR CTV volume and dose

CTV_{HR} volume



CTV_{HR} dose



Tanderup et al 2015

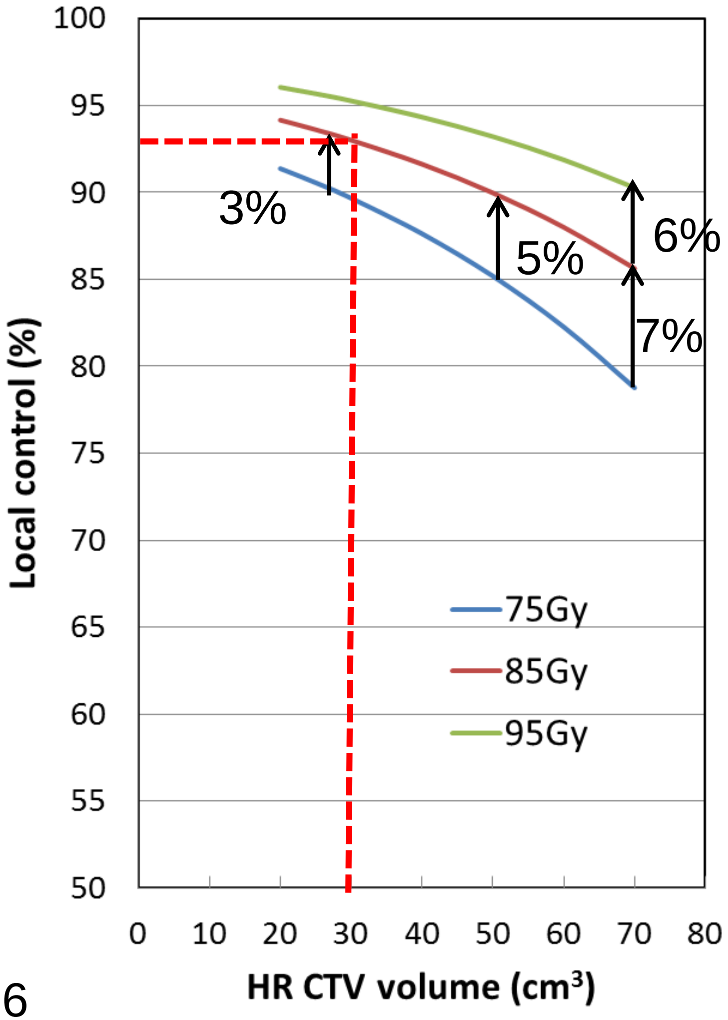
Dose, volume, and time effect

Effect of dose, volume and time:

Dose: 10Gy → 5% LC
Time: 7 days ~ 5Gy
Volume $10cm^3$ ~ 5Gy

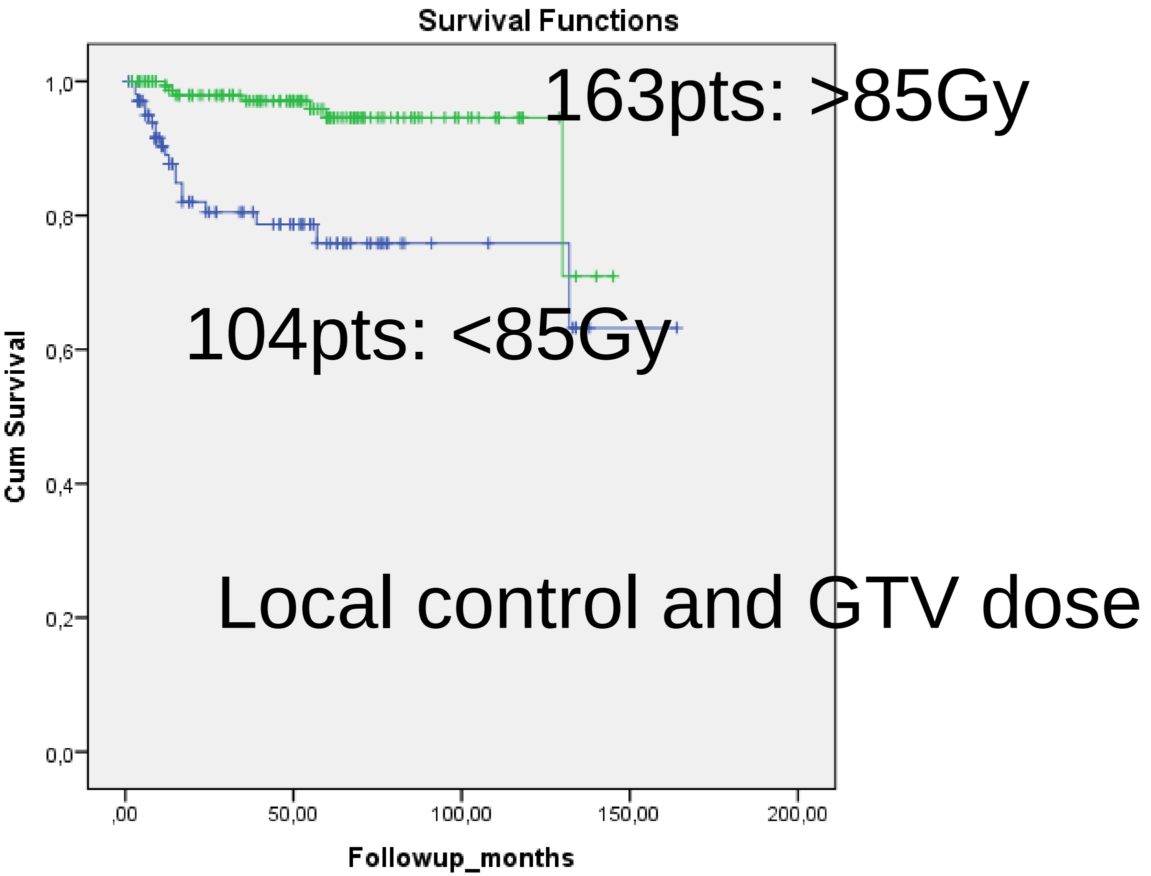
85Gy for $30cm^3$ CTV_{HR}: 93% LC
85Gy for $20cm^3$ CTV_{HR}: 94% LC
85Gy for $70cm^3$ CTV_{HR}: 86% LC

Local control at 3 years



Tanderup et al, Radiotherapy and Oncology 2016

Dose volume response for GTV

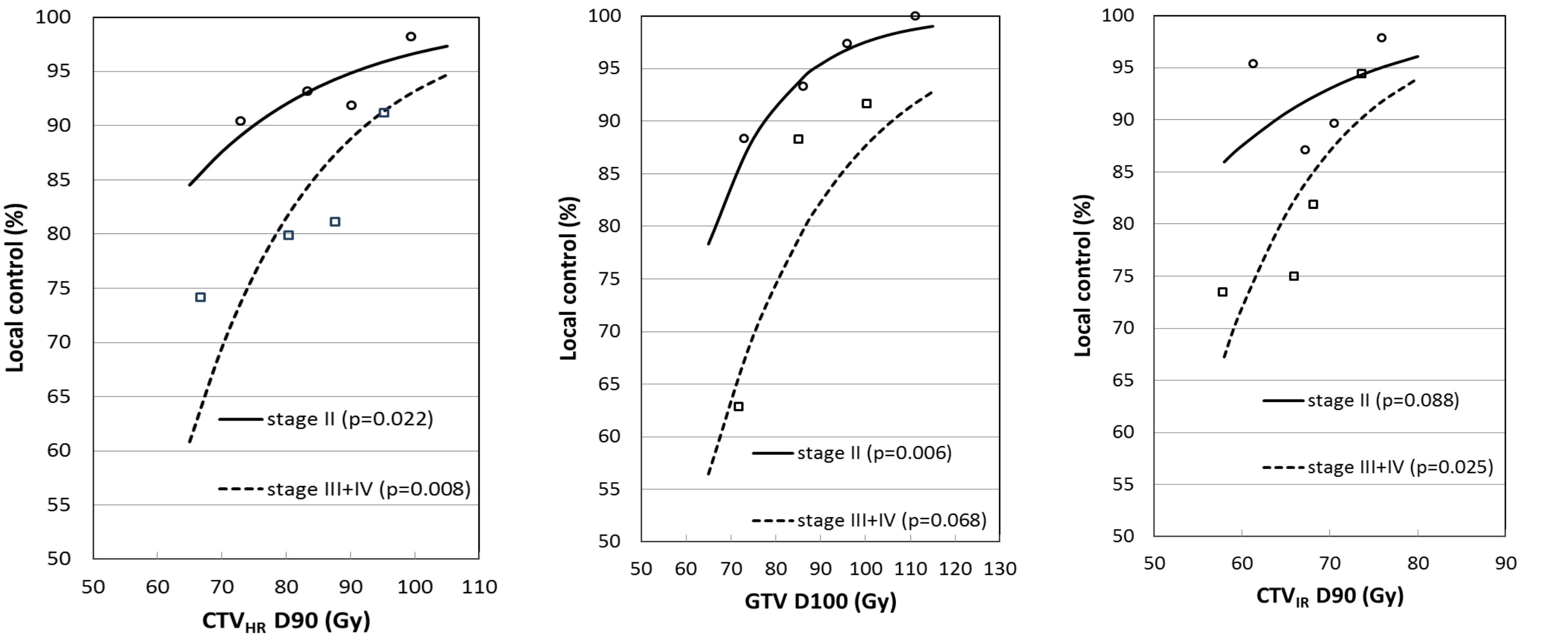


Tanderup 2015

Preparation for EMBRACE II

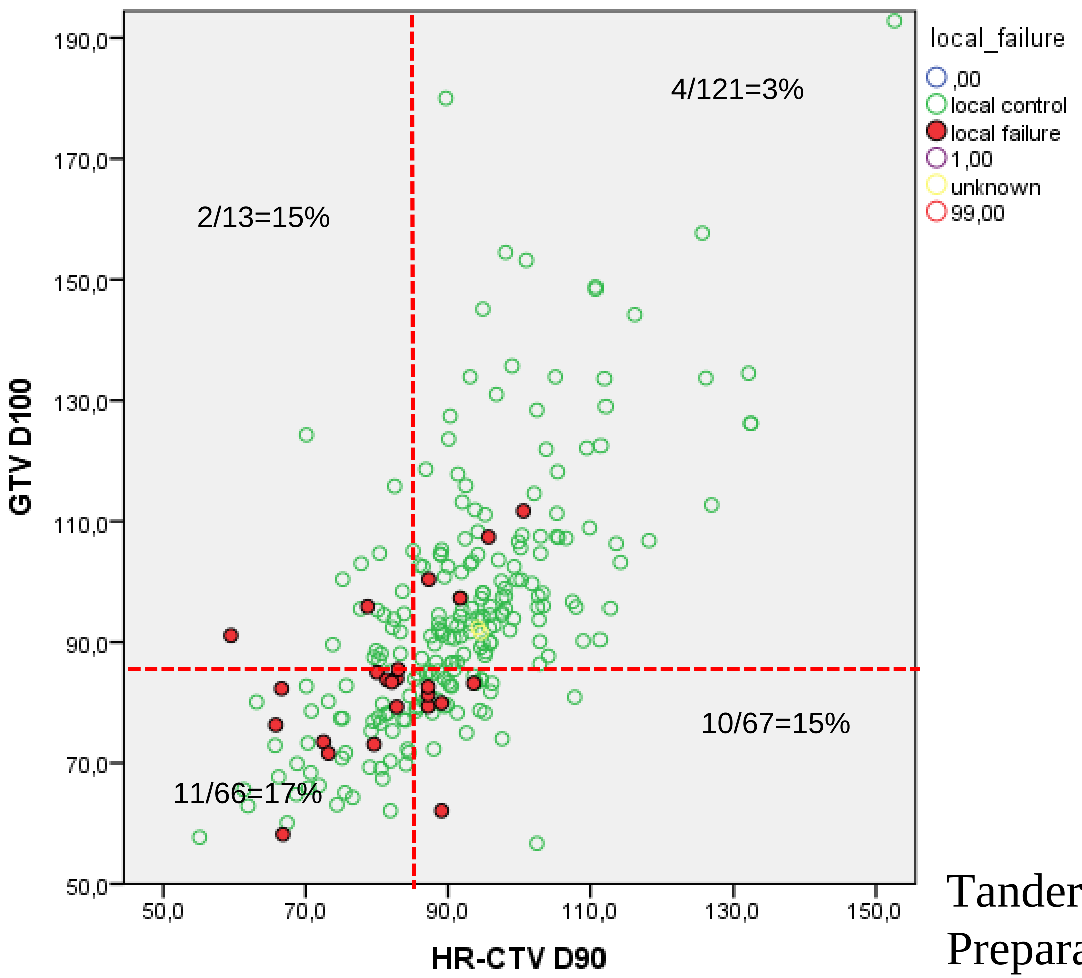
Dose effect GTV, CTV_{HR} and CTV_{IR}

Stage-related analysis



Tanderup et al. Radiotherapy and Oncology 2016

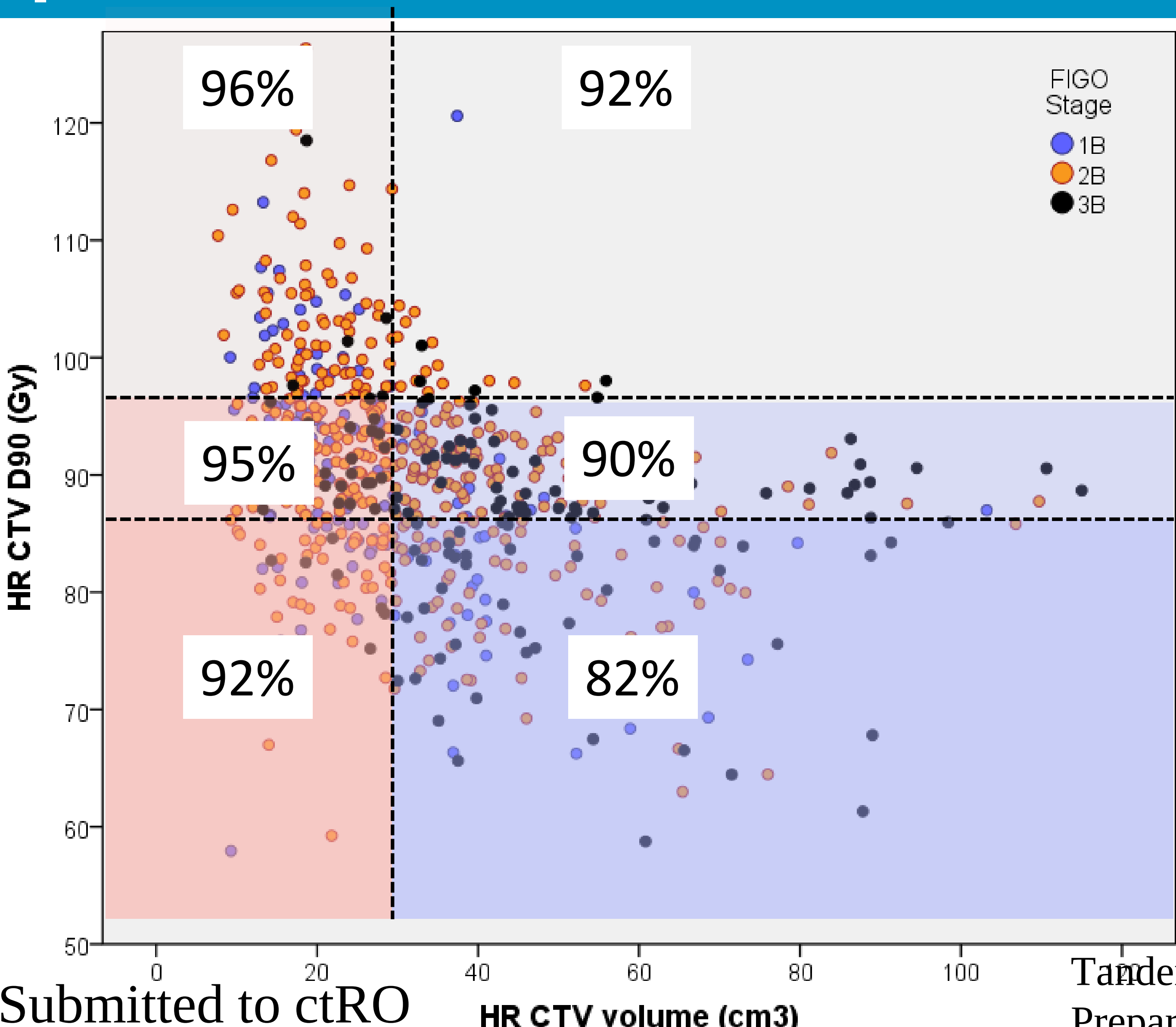
Combined constraints for GTV and CTV_{HR}



Tanderup 2015
Preparation for EMBRACE II

Practice in EMBRACE I and predicted local control from RetroEMBRACE

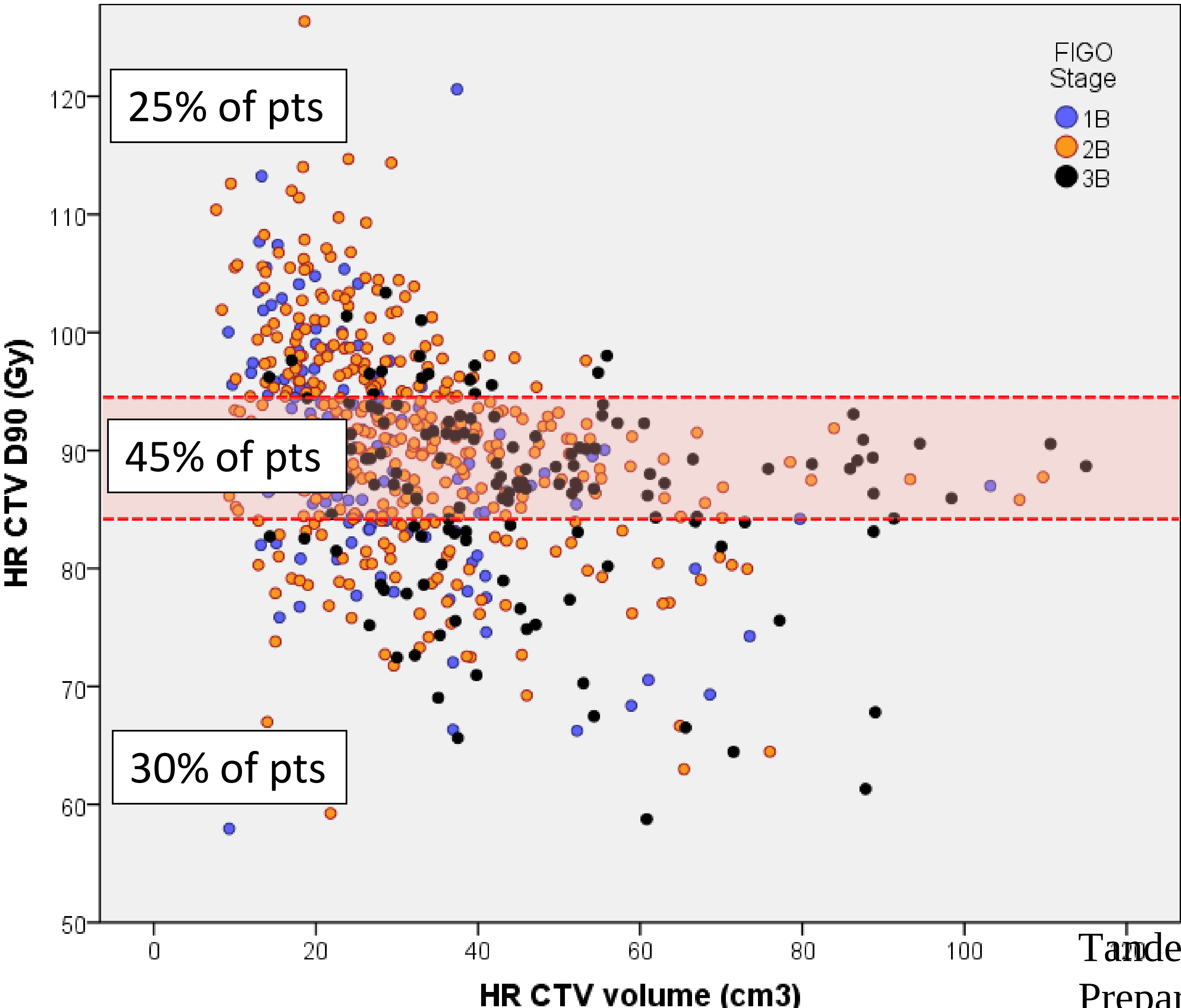
769 pts EMBRACE



Submitted to ctRO

Tanderup 2015
Preparation for EMBRACE II

EMBRACE I practice

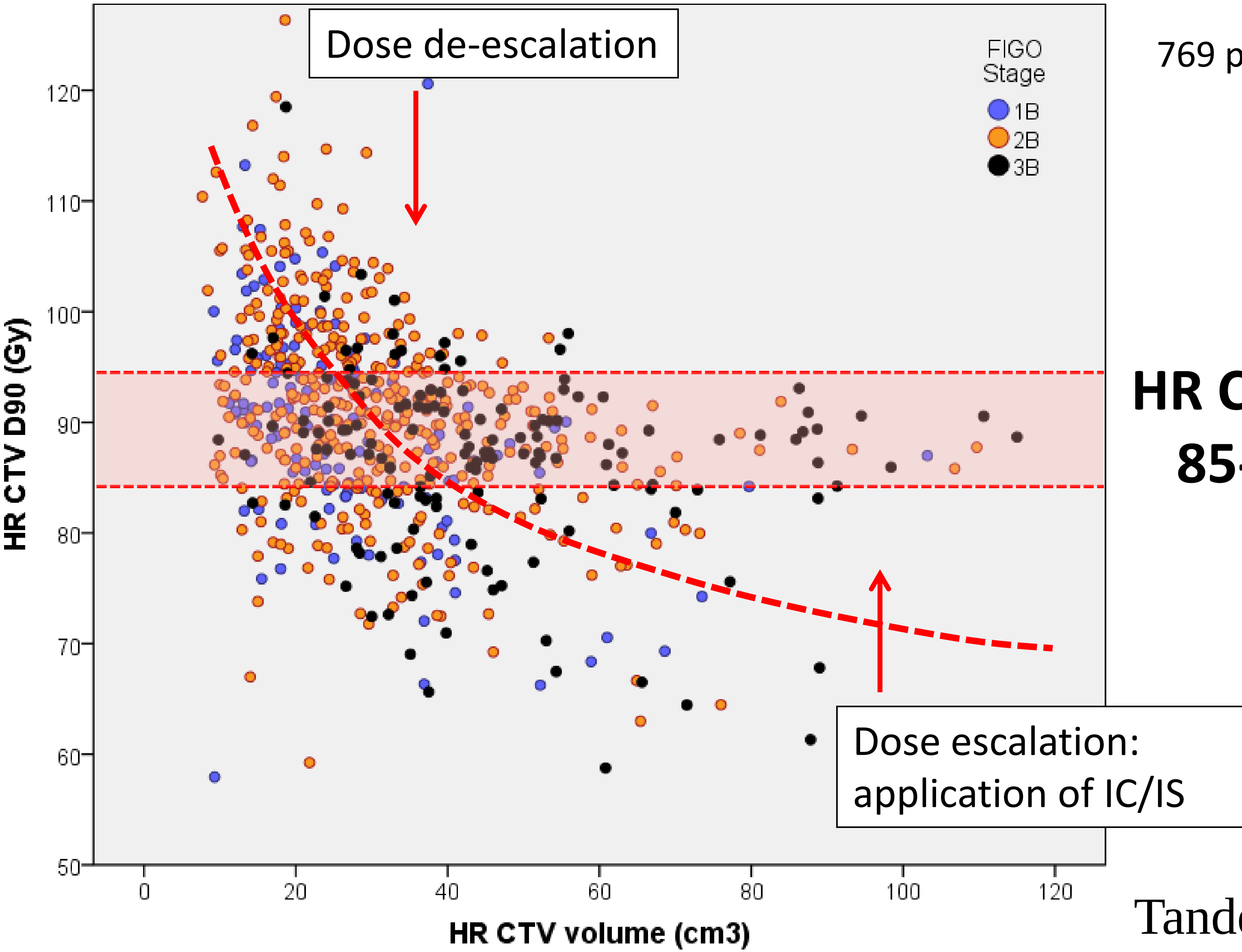


769 pts EMBRACE

HR CTV D90 85-95Gy

Tanderup 2015
Preparation for EMBRACE II

EMBRACE II dose prescription

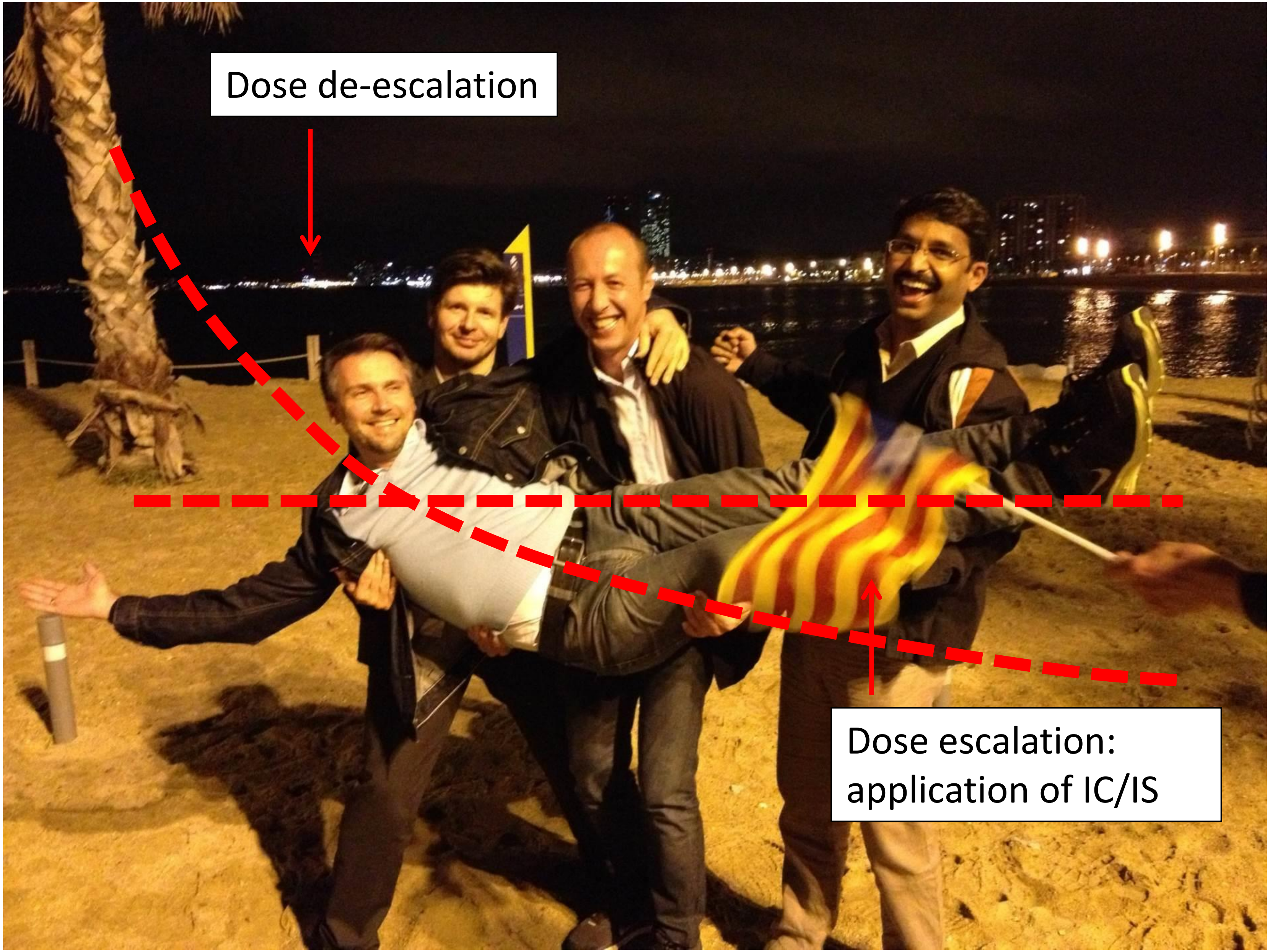


769 pts EMBRACE

HR CTV D90 85-95Gy

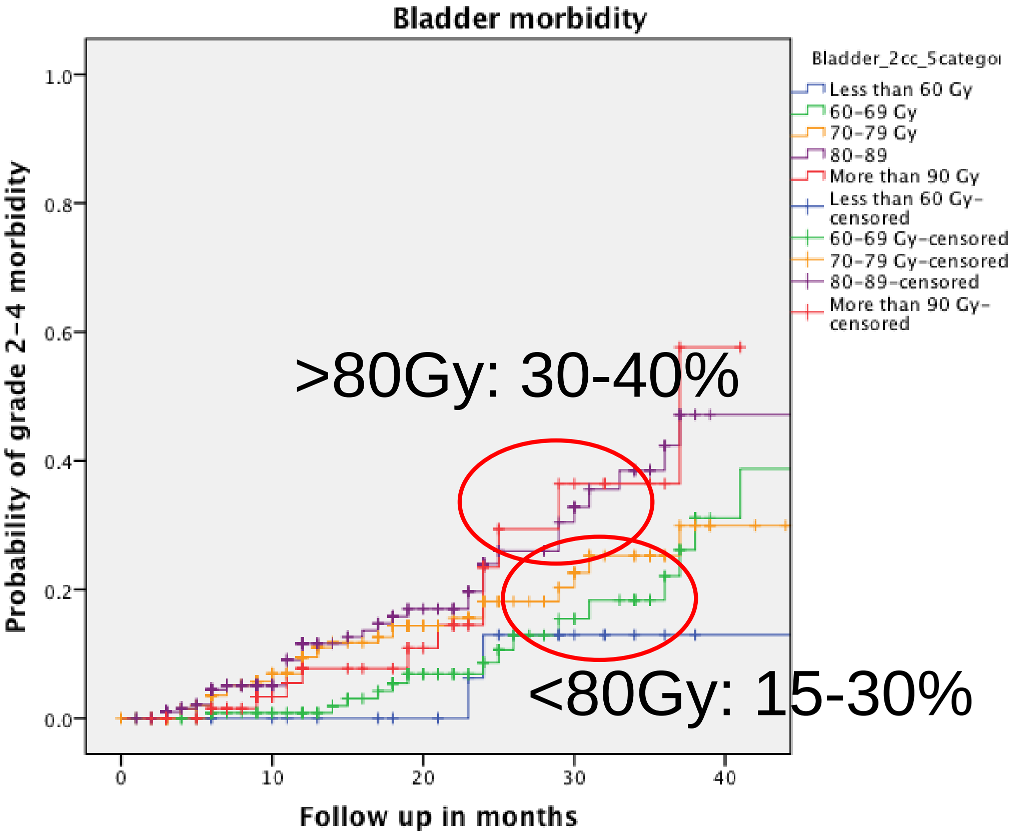
Tanderup 2015

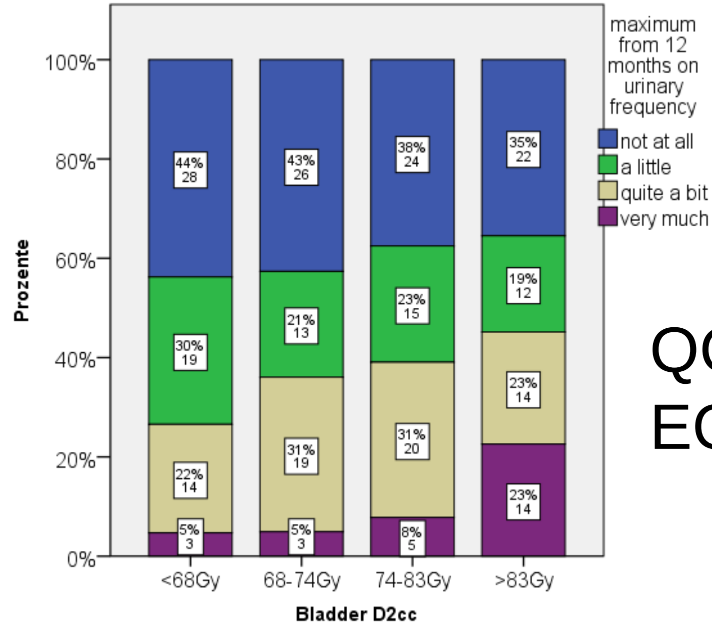
Beach boy approach – Barcelona 2013



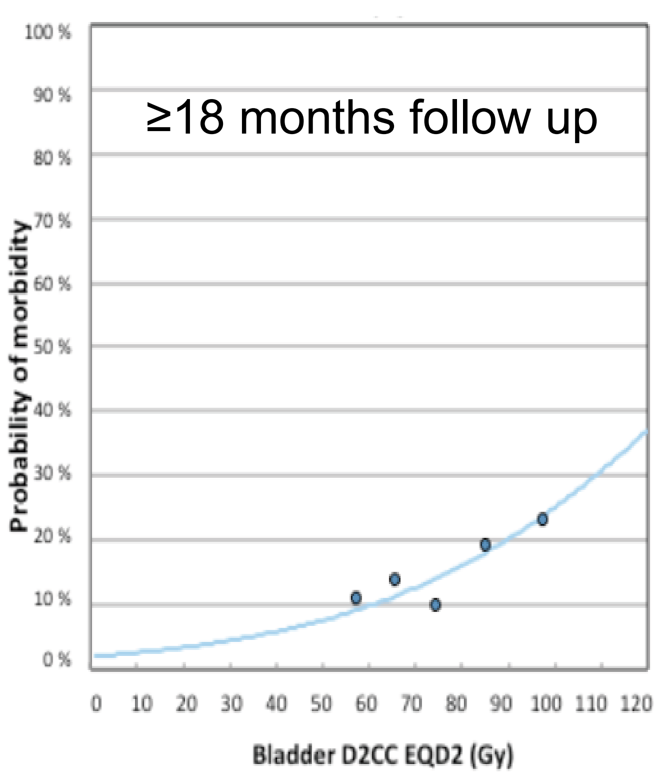
Bladder D_{2cm3}

- **EMBRACE CTCAE**
- **All endpoints except ureter stenosis G≥2**



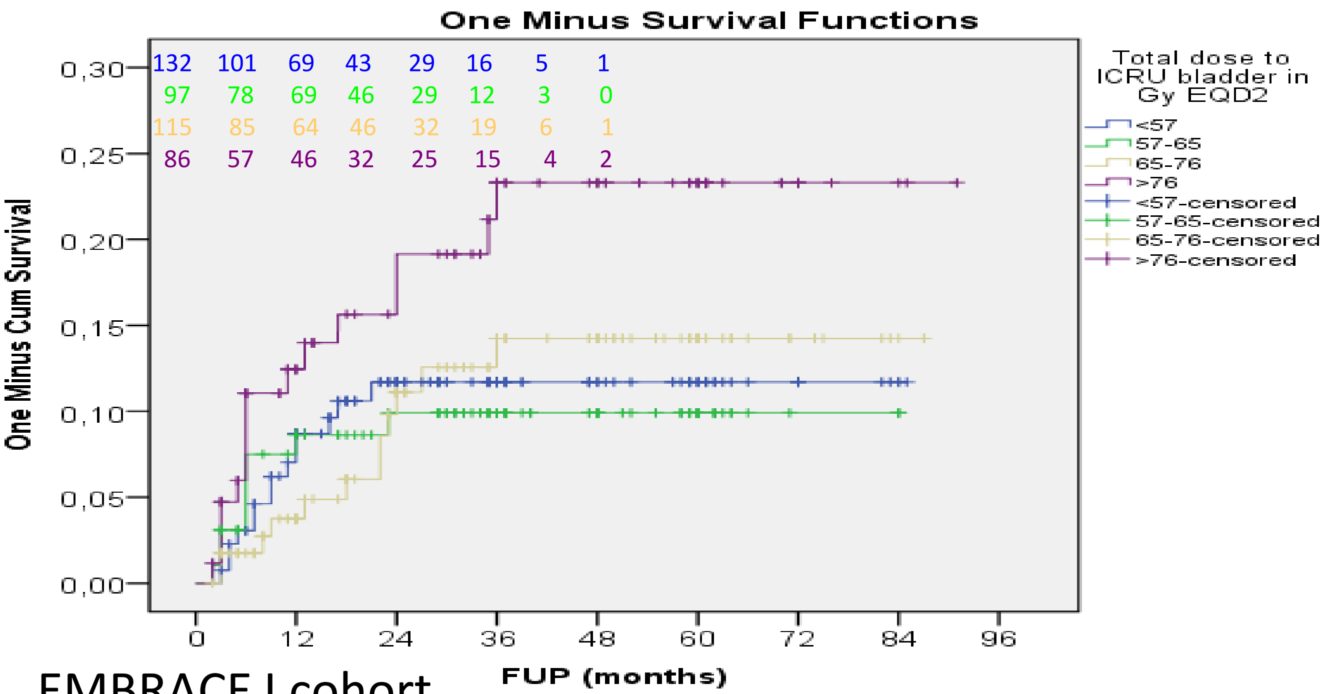


QOL EORTC



Fokdal et al 2015

Frequency G≥2 and **ICRU bladder point dose** representing bladder trigonum dose



Work in progress:

Dose constraint:

<76 Gy

Up to 12% G≥2

EMBRACE I cohort

5 centers included

Patients with Bladder wall infiltration excluded

Patients with Baseline morbidity assessment

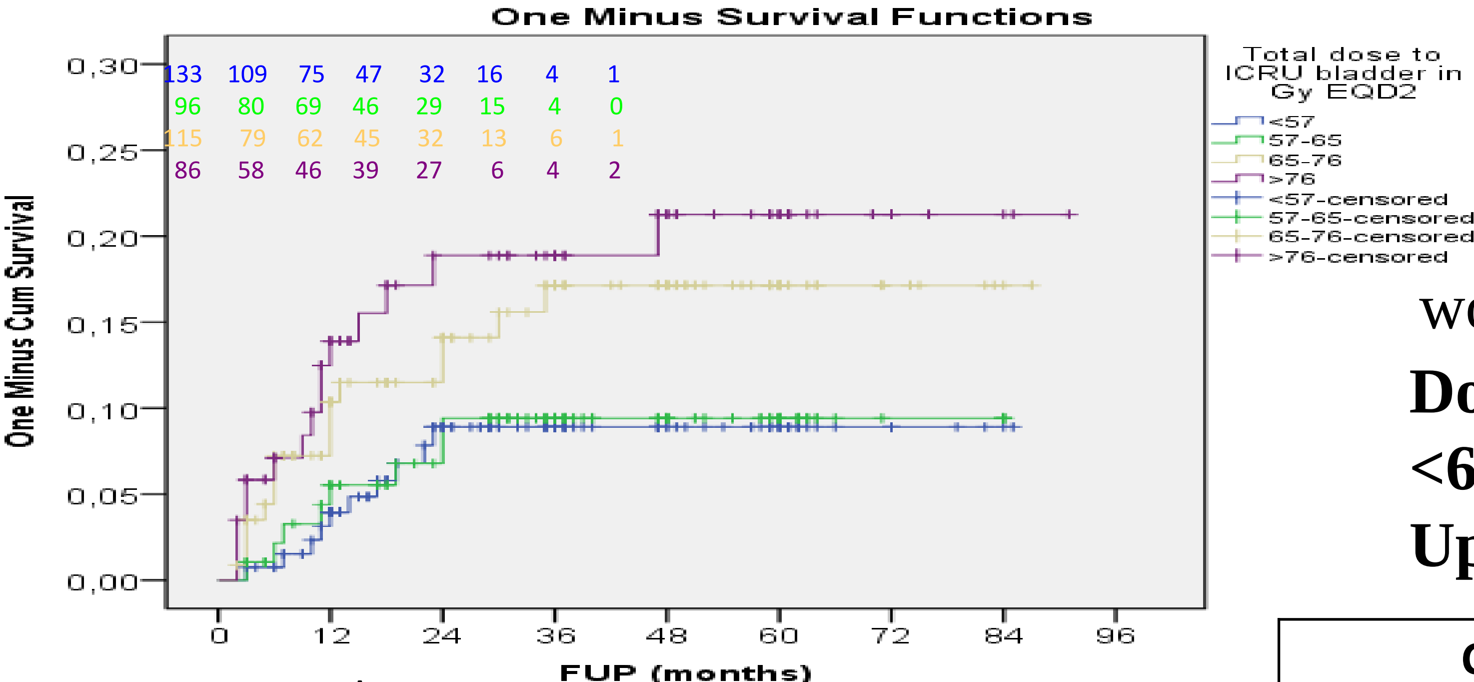
and at least one Follow Up included

451 patients

CTC Grade	
0	172
1	213
2	50
3	4

Spampinato, Tanderup et al. Work in progress

Incontinence G≥2 and **ICRU bladder point dose** representing bladder trigonum dose



work in progress:

Dose constraint:

<65 Gy

Up to 9% G≥2

EMBRACE I cohort

5 centers included

Patients with Bladder wall infiltration excluded

Patients with Baseline morbidity assessment

and at least one Follow Up included

451 patients

CTC Grade	
0	258
1	128
2	48
3	4
4	1

Spampinato, Tanderup et al. Work in progress

Bladder D_{2cm3} and ICRU point (trigonum)

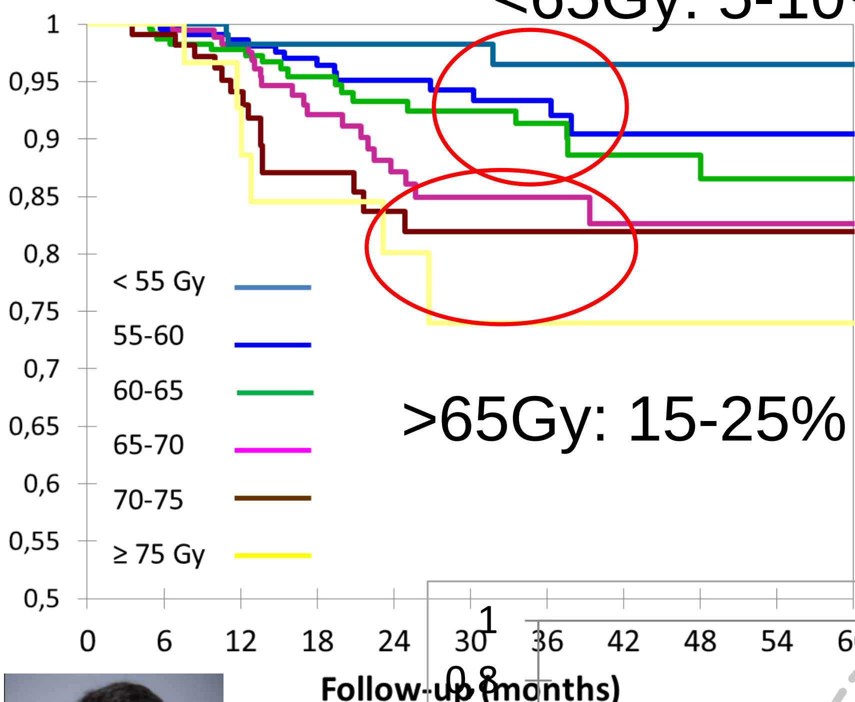
- **EMBRACE CTCAE**

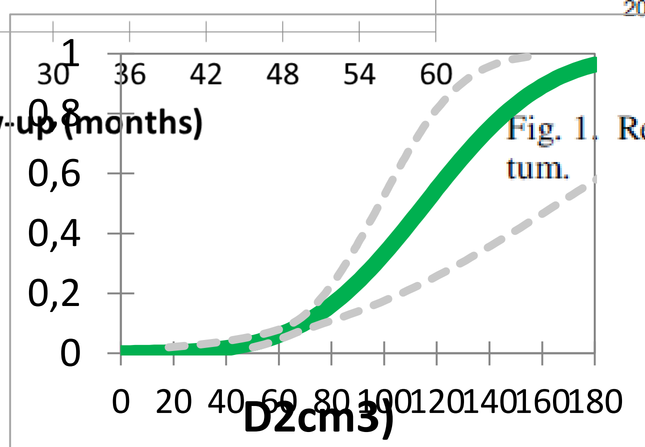
- **Bladder 2 cm3**
  - **bleeding**
  - **ulceration**
  - **fistula**
  - **cystitis**

- **ICRU bladder Point (representing bladder trigonum dose)**
  - **frequency**
  - **urgency**
  - **incontinence**

Rectal dose volume effects (2cm^3)

≥G2 rectal morbidity
(EMBRACE cohort, n=960)





Mazeron et al.,
RadOnc 2016

≥G2 rectal morbidity (bleeding)
(Vienna cohort, n=145)

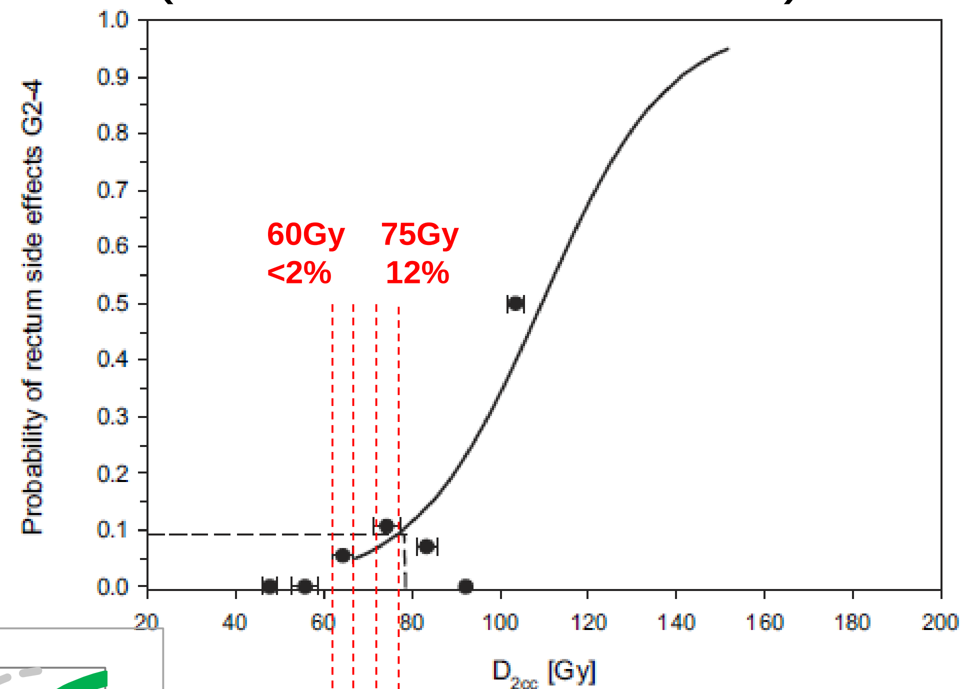
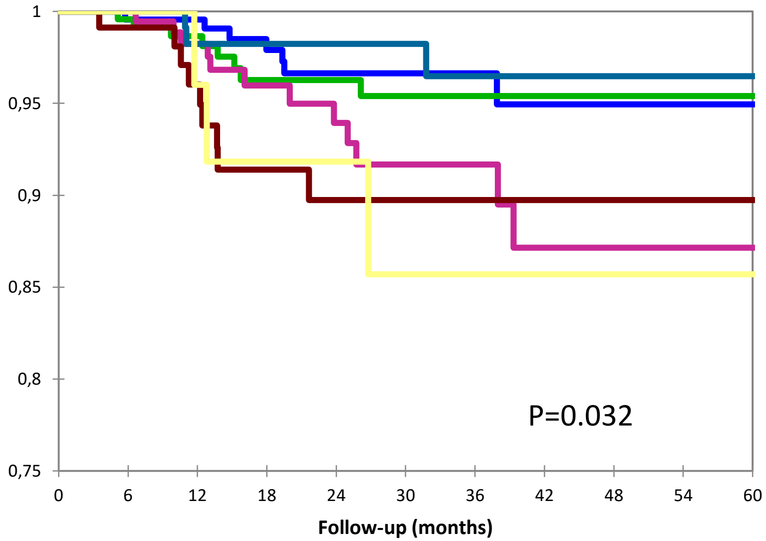


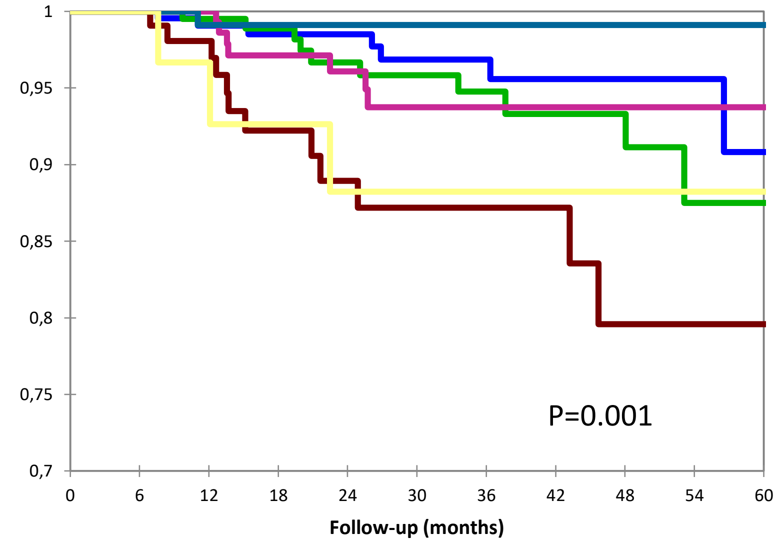
Fig. 1. Relationship between D_{2cc} and late side effects in the rectum.

P. Georg et al.,
IJROBP 2011

Proctitis



Bleeding



dose effects for different endpoints for rectal morbidity EMBRACE (n=960)

< 55 Gy

55-60

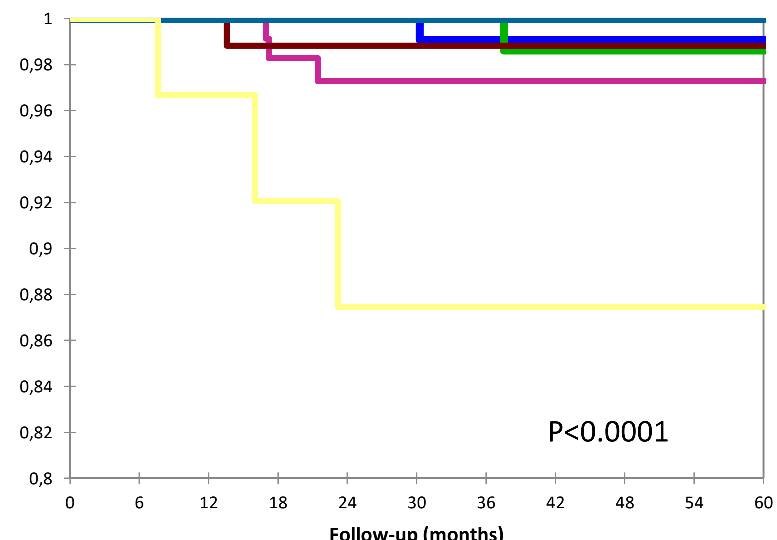
60-65

65-70

70-75

≥ 75 Gy

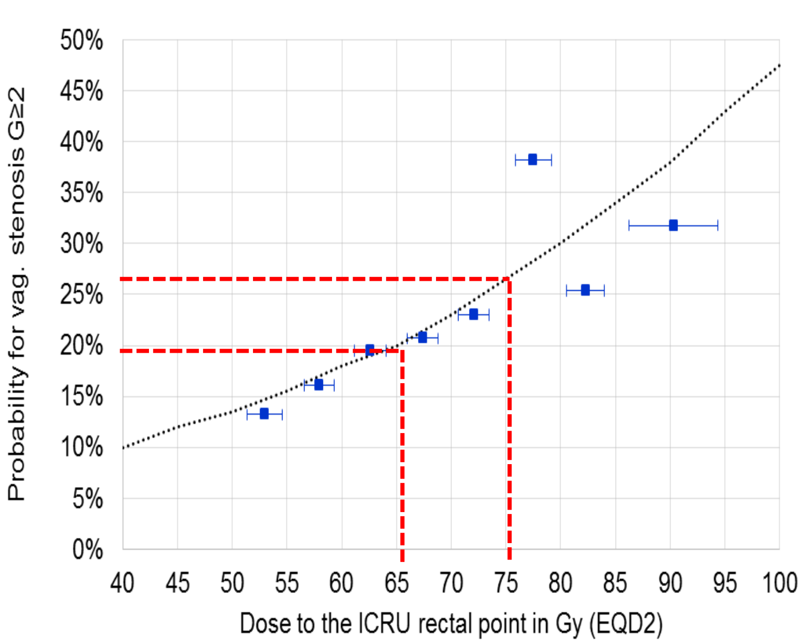
Fistula



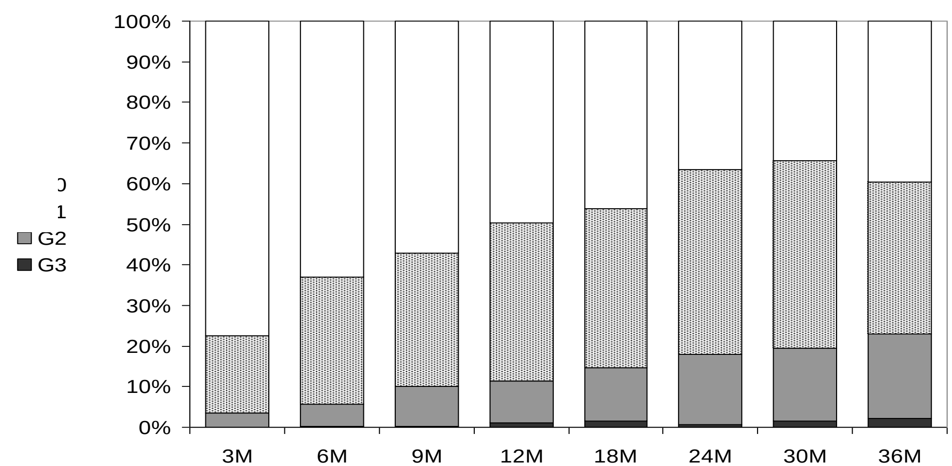
Mazeron et al, RadiothOncol 2016

Vaginal stenosis and ICRU recto-vaginal point (630 pts)

Cox-regression, 2 year actuarial risk of ≥G2 stenosis
- Significant impact of EBRT dose (45Gy versus 50Gy)
- Significant impact of BT ICRU recto-vaginal dose



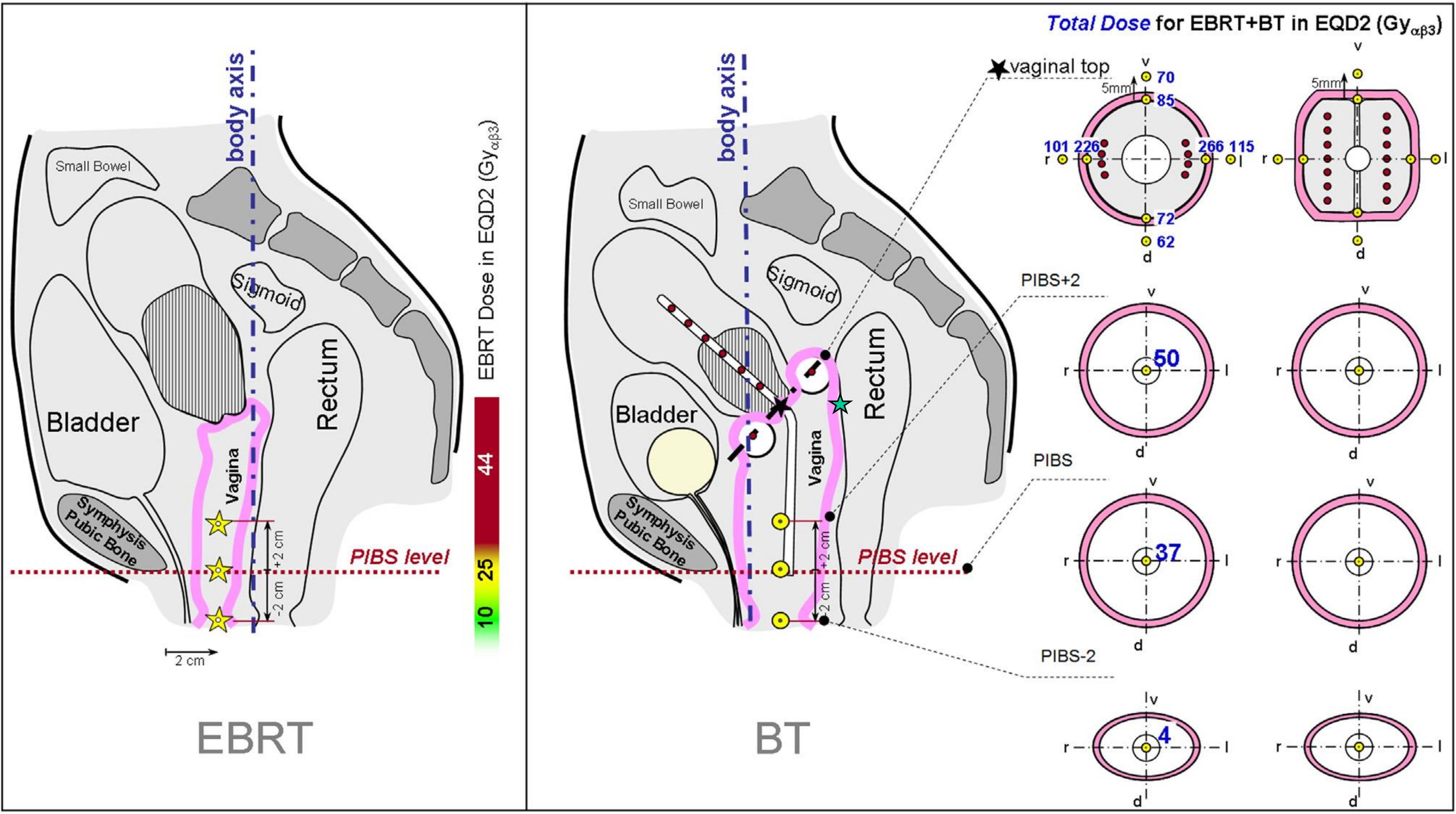
Prevalence vaginal stenosis



Kirchheiner K et al.Manifestation pattern of early-late vaginal morbidity. IJROBP 2014 May 1;89(1):88-95

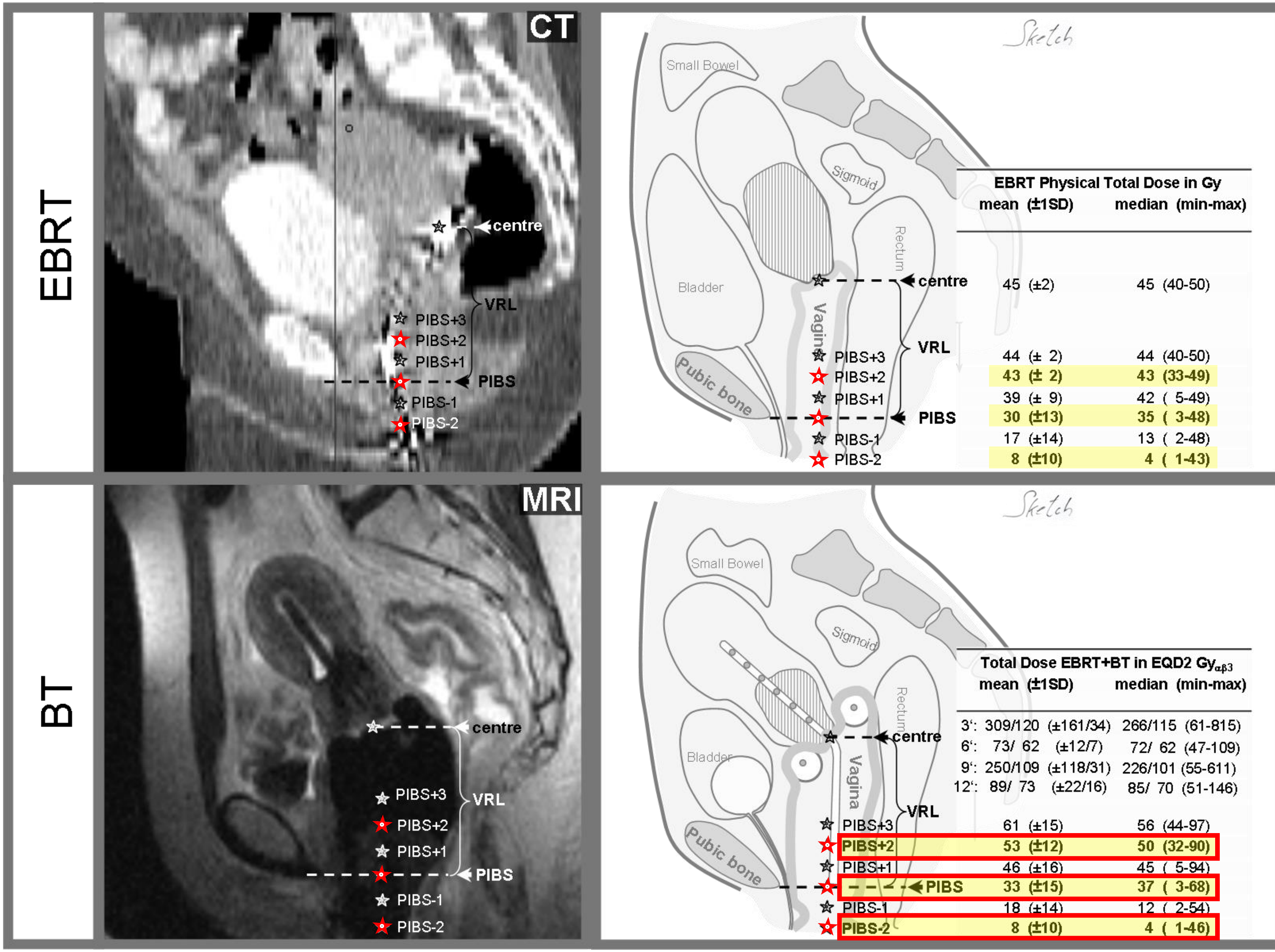
K Kirchheiner et al, EMBRACE data MUW/AUH, RadiothOncol 2016

Vaginal Dose Points: PIBS, PIBS+2, PIBS-2:
no clinical evidence (too early): contribution from BT and EBRT



Westerveld et al. RadiothOncol 2013

Vaginal Dose Points (dose values based on Vienna cohort, n=59)



Westerveld et al. Radiotherapy and Oncology 2013

Image guided brachytherapy in cervical cancer

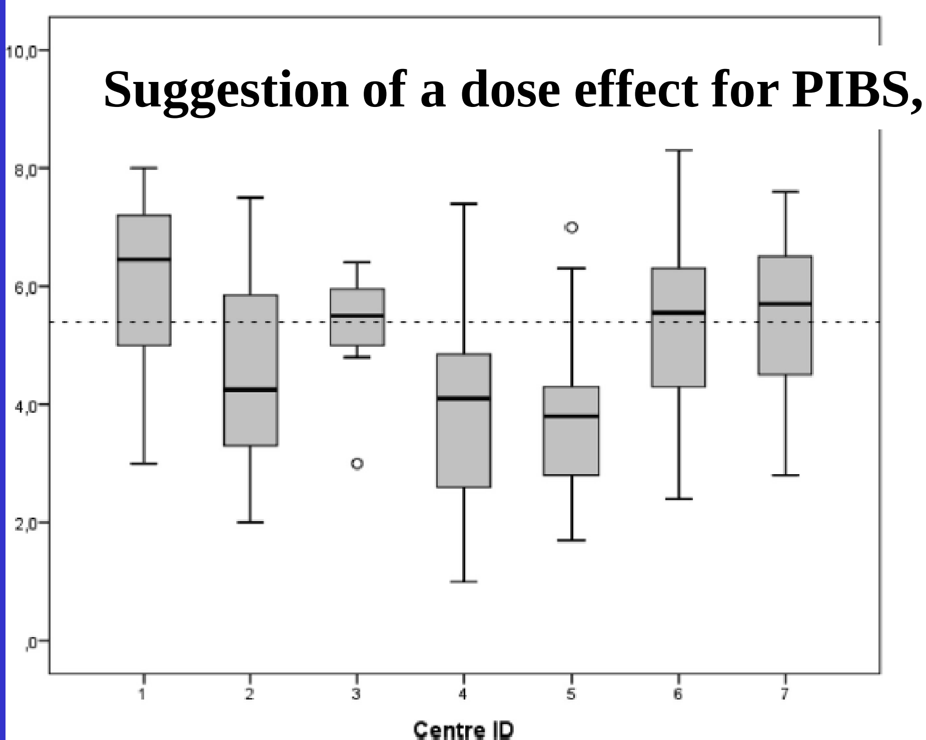
Multicentre evaluation of a novel vaginal dose reporting method in 153 cervical cancer patients

Henrike Westerveld [a,b,*], Astrid de Leeuw [c], Kathrin Kirchheiner [b], Pittaya Dankulchai [d], Bernard Oosterveld [e], Arun Oinam [f], Robert Hudej [g], Jamema Swamidas [h], Jacob Lindegaard [i], Kari Tanderup [i], Richard Pötter [b,j], Christian Kirisits [b,j], the EMBRACE Collaborative Group

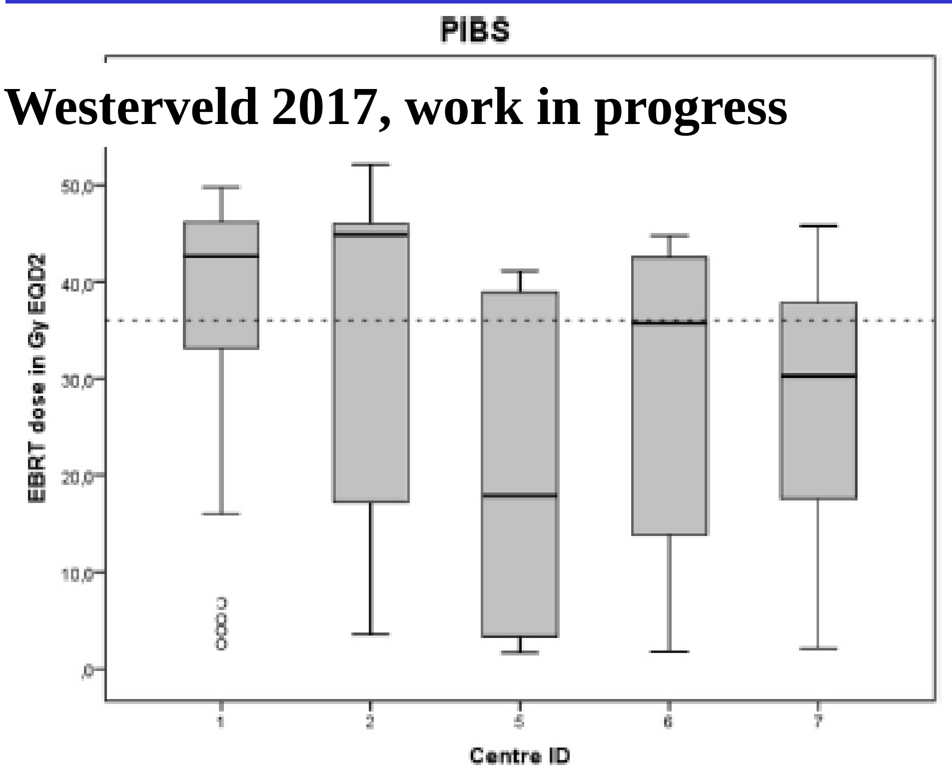
[a] Department of Radiotherapy, Academic Medical Centre, University of Amsterdam, The Netherlands; [b] Department of Radiation Oncology, Comprehensive Cancer Centre, Medical University of Vienna, Austria; [c] Department of Radiation Oncology, University Medical Centre Utrecht, The Netherlands; [d] Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [e] Department of Radiation Oncology, Radiotherapiegroep, Arnhem, The Netherlands; [f] Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [g] Department of Radiotherapy, Institute of Oncology Ljubljana, Slovenia; [h] Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India; [i] Department of Oncology, Aarhus University Hospital, Denmark; and [j] Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Austria

Radioth and Oncol 2016

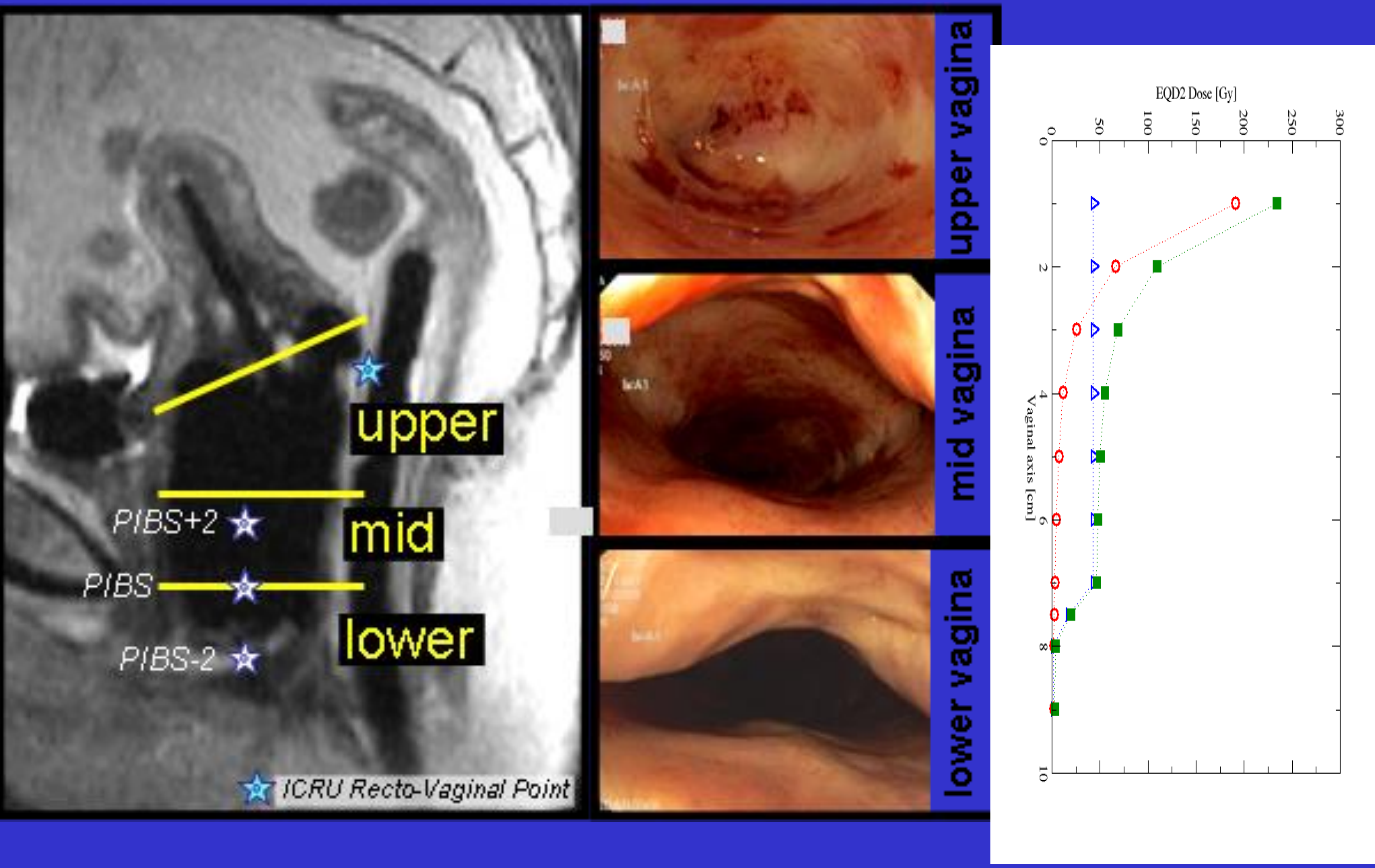
Suggestion of a dose effect for PIBS, Westerveld 2017, work in progress



ginal reference length (VRL) in cm per centre. The dotted line represents the median length of the entire cohort.



Vaginal morbidity and radiation doses

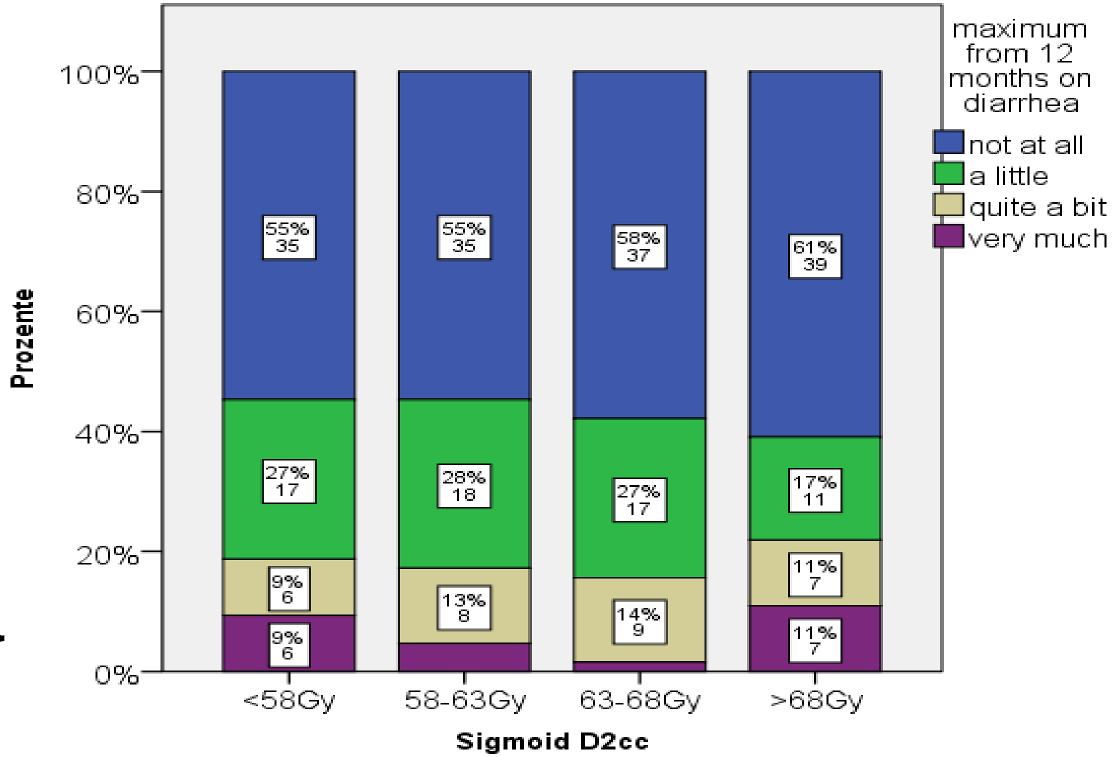


ICRU/GEC ESTRO Report 89 Fig. 6.1/Fig. 8.11

Sigmoid D_{2cm3}, preliminary data (2015)

- No dose effect established – (so far)
- Uncertainties for D 2 cm^3
- Clinical endpoint critical, e.g. Bleeding, ulceration

Diarrhea

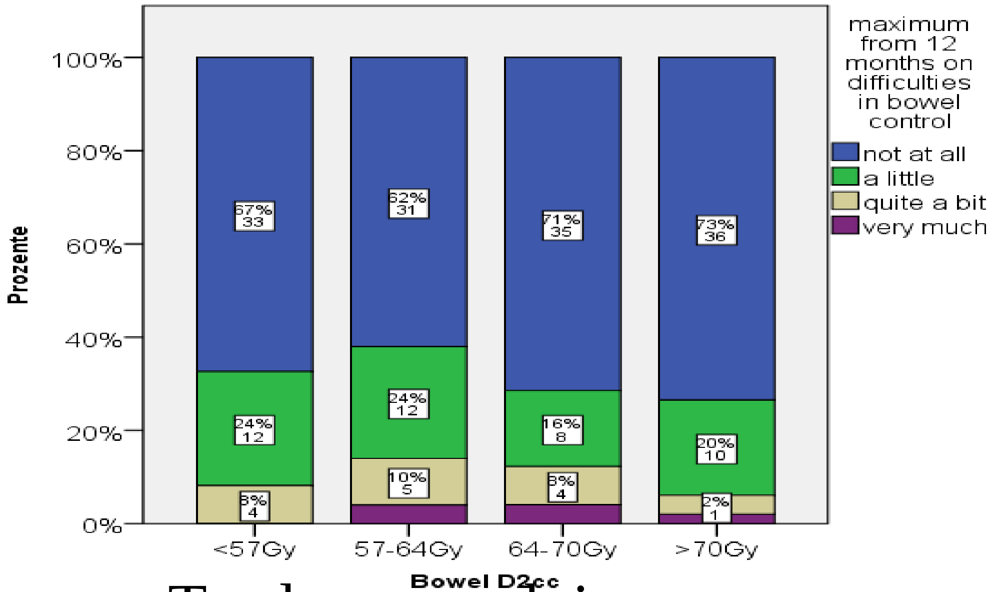


Bowel D_{2cm3}, and EBRT preliminary data

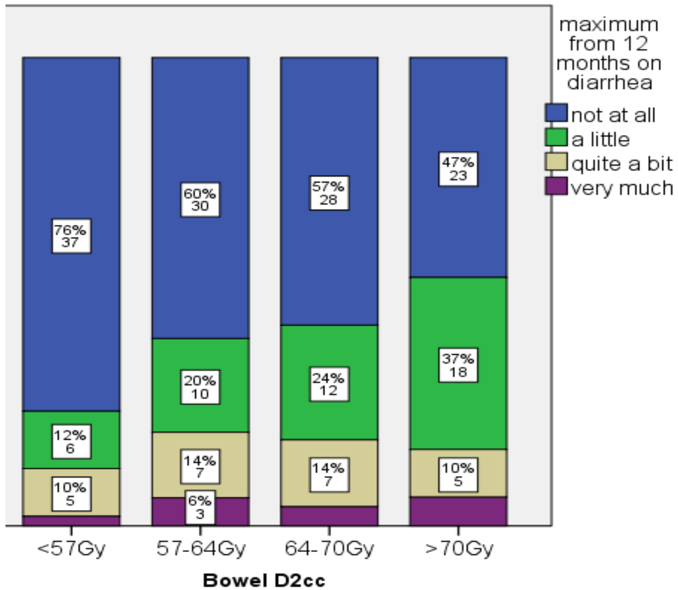
- **dose effect likely to become established for diarrhea**

2 cm³ (BT) and EBRT: dose (45/50Gy), boost, PA RT

Bowel control



Diarrhea



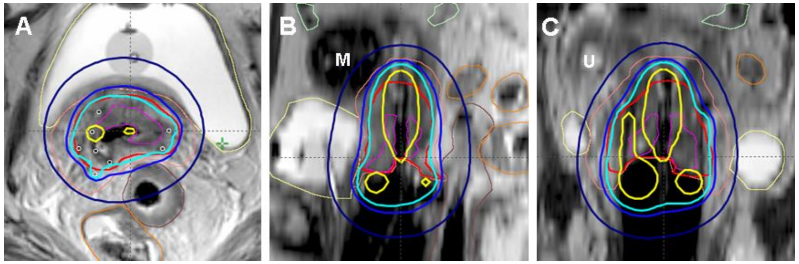
Jensen, Tanderup work in progress

Planning aim and prescription dose

- **Planning aim: what you want to obtain, e.g. 4x7 Gy**
- **Prescribed dose: what you decide to treat**

Case 6, IIIB, IC/IS BT

Appendix, ICRU 89, PP201-207



Structure	Dose-volume parameter	Planning aim, Gy	Prescribed dose Gy
CTV_{HR}	$EQD2_{10}\ D_{90}$	≥ 85	88.9
Bladder	$EQD2_3\ D_{2cm^3}$	≤ 90	71.1
Rectum	$EQD2_3\ D_{2cm^3}$	≤ 70	65.6
Sigmoid	$EQD2_3\ D_{2cm^3}$	≤ 70	57.4
Bowel	$EQD2_3\ D_{2cm^3}$	≤ 70	53.3

Conclusion dose effect BT (I)

- **Dose effect demonstrated for:**
  - **Residual GTV D100, 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 + clinical endpoint specific**
- **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 (EMBRACE II) 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 (since 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 Doses	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*

*D_{2cm3} most exposed volumes should be located at a similar organ part

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

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Review Article

The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies

Clinical and Translational Radiation Oncology 9 (2018) 48–60

Richard Pötter[a,1], Kari Tanderup[b,1,*], Christian Kirisits[a], Astrid de Leeuw[c], Kathrin Kirchheiner[a], Remi Nout[d], Li Tee Tan[e], Christine Haie-Meder[f], Umesh Mahantshetty[g], Barbara Segedin[h], Peter Hoskin[i], Kjersti Bruheim[j], Bhavana Rai[k], Fleur Huang[l], Erik Van Limbergen[m], Max Schmid[a], Nicole Nesvacil[a], Alina Sturdza[a], Lars Fokdal[b], Nina Boje Kibsgaard Jensen[b], Dietmar Georg[a], Marianne Assenholt[b], Yvette Seppenwoolde[a], Christel Nomden[c], Israel Fortin[a,o], Supriya Chopra[g], Uulke van der Heide[n], Tamara Rumpold[a], Jacob Christian Lindegaard[b], Ina Jürgenliemk-Schulz[c], the EMBRACE Collaborative Group[2]

A B S T R A C T

The publication of the GEC-ESTRO recommendations one decade ago was a significant step forward for reaching international consensus on adaptive target definition and dose reporting in image guided adaptive brachytherapy (IGABT) in locally advanced cervical cancer. Since then, IGABT has been spreading, particularly in Europe, North America and Asia, and the guidelines have proved their broad acceptance and applicability in clinical practice. However, a unified approach to volume contouring and reporting does not imply a unified administration of treatment, and currently both external beam radiotherapy (EBRT) and IGABT are delivered using a large variety of techniques and prescription/fractionation schedules.

With IGABT, local control is excellent in limited and well-responding tumours. The major challenges are currently loco-regional control in advanced tumours, treatment-related morbidity, and distant metastatic disease. Emerging evidence from the RetroEMBRACE and EMBRACE I studies has demonstrated that clinical outcome is related to dose prescription and technique. The next logical step is to demonstrate excellent clinical outcome with the most advanced EBRT and brachytherapy techniques based on an evidence-based prospective dose and volume prescription protocol.

The EMBRACE II study is an interventional and observational multicentre study which aims to benchmark a high level of local, nodal and systemic control while limiting morbidity, using state of the art treatment including an advanced target volume selection and contouring protocol for EBRT and brachytherapy, a multi-parametric brachytherapy dose prescription protocol (clinical validation of dose constraints), and

Acknowledgements
Gyn GEC ESTRO network
EMBRACE study and research group

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Facilitated through

ESTRO

EMBRACE kick-off meeting Brussels 04/2008

Support:

Nucletron
Improving patient care

Now, an ELEKTA company

VARIAN medical systems

6th Gyn GEC ESTRO network meeting Paris 06/2010

9th Annual EMBRACE meeting: March 23/24, 2018 Vienna

4th Annual EMBRACE meeting Vienna 12/2012

Time dose fractionation for EBRT + HDR BT

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

Lucknow 2018

Prof Kari Tanderup, PhD

Prof Richard Pötter

Aarhus University Hospital

Combination of EBRT and BT

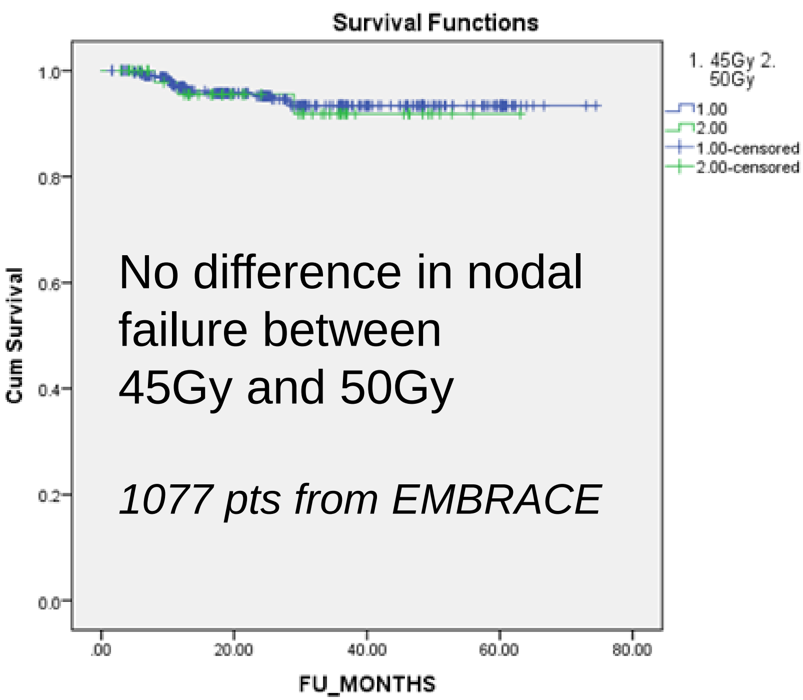
- **EBRT dose and fractionation**
- **BT dose and fractionation**
- **Timing of BT boost**
- **Overall treatment time**

Which dose do you deliver to the elective lymph node target?

A. 45-46Gy whole pelvis
B. 50Gy whole pelvis
C. 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?**



No difference in nodal failure between 45Gy and 50Gy

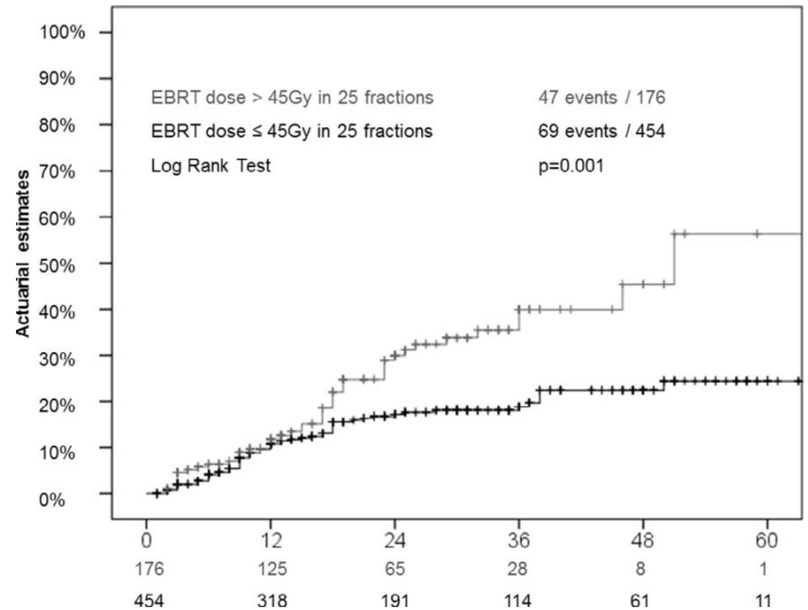
1077 pts from EMBRACE

C Nomden, A de Leeuw, IM Jürgenliemk- Schultz, UMCU

- **Difference in morbidity between 45Gy and 50Gy?**

Vaginal stenosis

630 pts from EMBRACE



Kirchheiner et al, RO 118 160–166, 2016

Which total EBRT dose do you deliver to pathologic lymph nodes?

A. No boost
B. ~ 55Gy
C. ~ 60Gy
D. >60Gy

What do we know about dose to pathological nodes?

Nodal recurrence in pathological nodes after boost

Pittsburgh, IJROBP 2015:

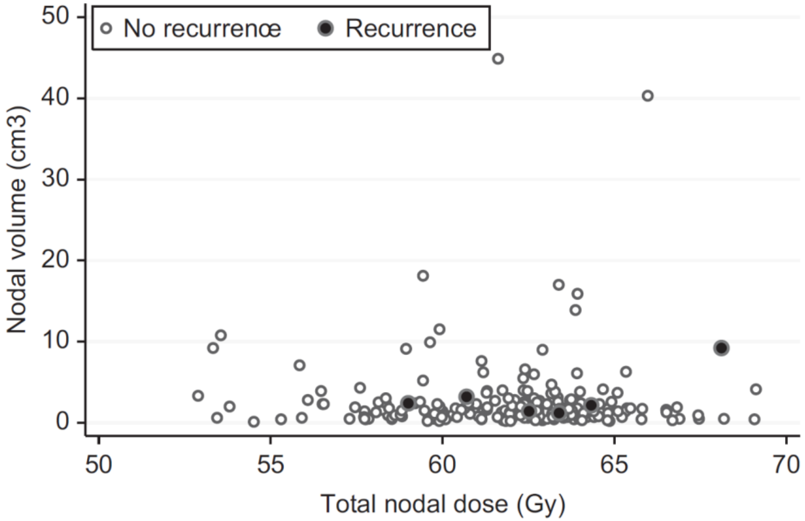
0% after boost dose of 55Gy

EMBRACE I:

12% failures within nodes boosted to a median dose of 59Gy

Ramlov et al, Acta Oncol, 2015:

limited dose effect for pathological nodes (~55-65Gy boosts)

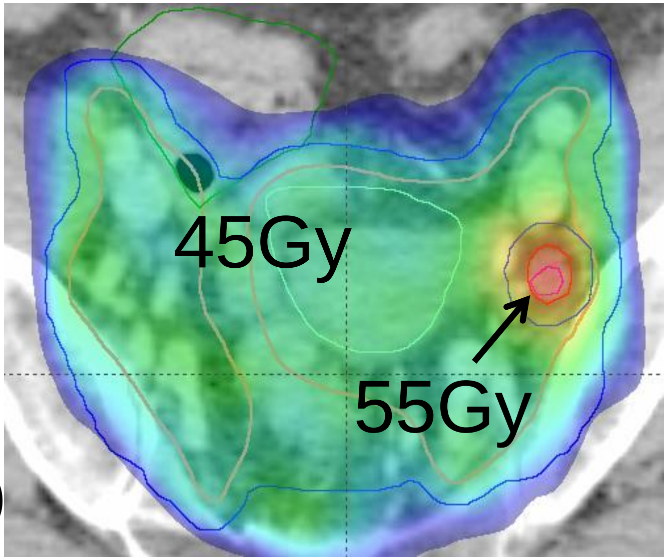


Post-boost with CRT

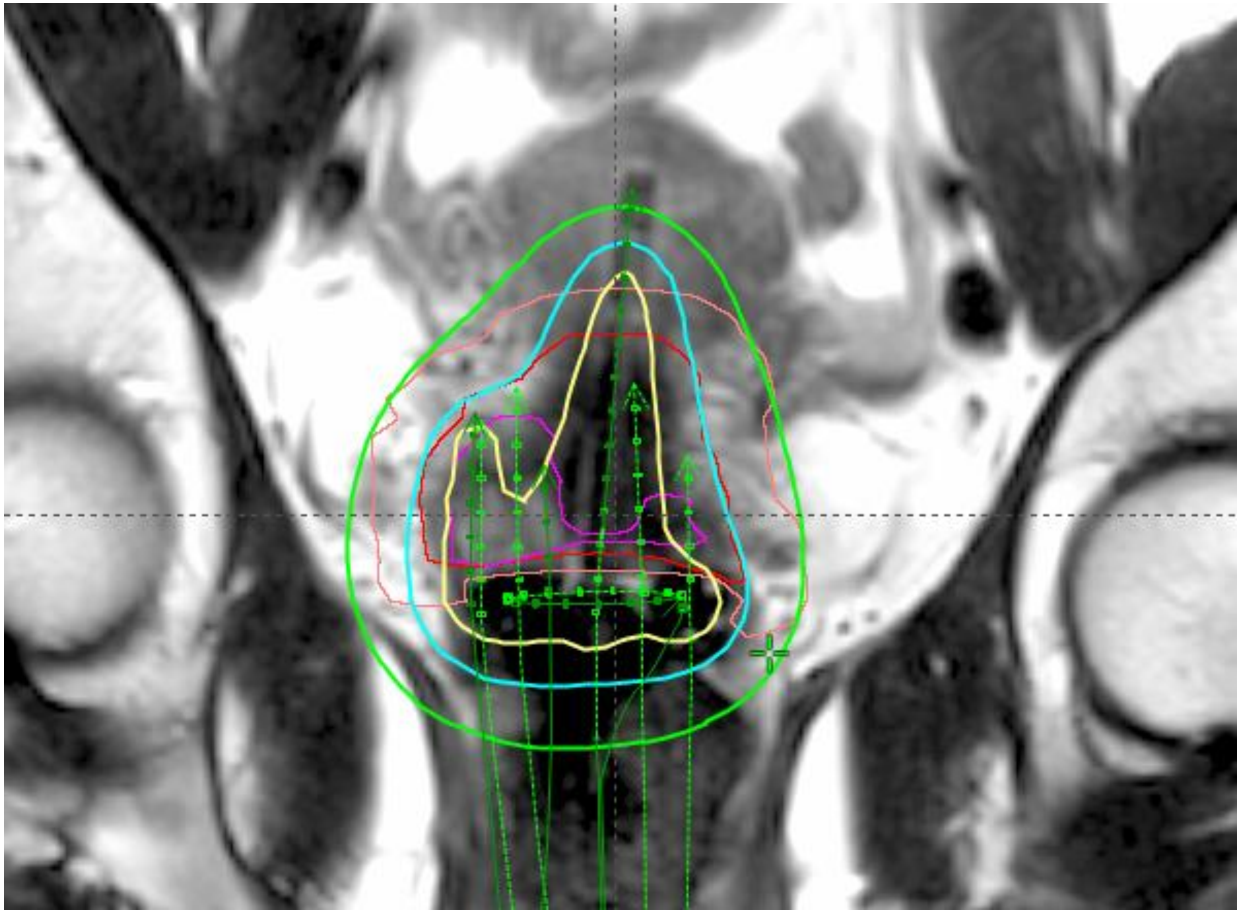
- AP-PA or 4 Field Box
- Avoid central pelvis irradiation
- Assessment of BT contribution (~0-6Gy)
- Examples of dose and fractionation:
  - Aim for total EBRT+BT dose of 55-60Gy
  - E.g. 50Gy whole pelvis + 5Gy
  - E.g. 45Gy whole pelvis + 10Gy

Recommendation of EMBRACE II:
Simultaneously integrated lymph node boost (SIB)

- **Simultaneously integrated lymph node boost:**
  - **IMRT**
  - **Dose planning with two dose levels**
    - **Elective target**
    - **Pathological lymph node target**
  - **In case of very big nodes: to consider a replan after 20-25Gy**
- **Recommended lymph node dose in EMBRACE II**
  - **Total 60Gy EQD2**
  - **45Gy/25fx to elective CTV**
  - **55Gy/25fx (within pelvis: 3-4Gy BT)**
  - **57.5Gy/25fx (outside pelvis: 0Gy BT)**



Time, dose and fractionation primary tumour

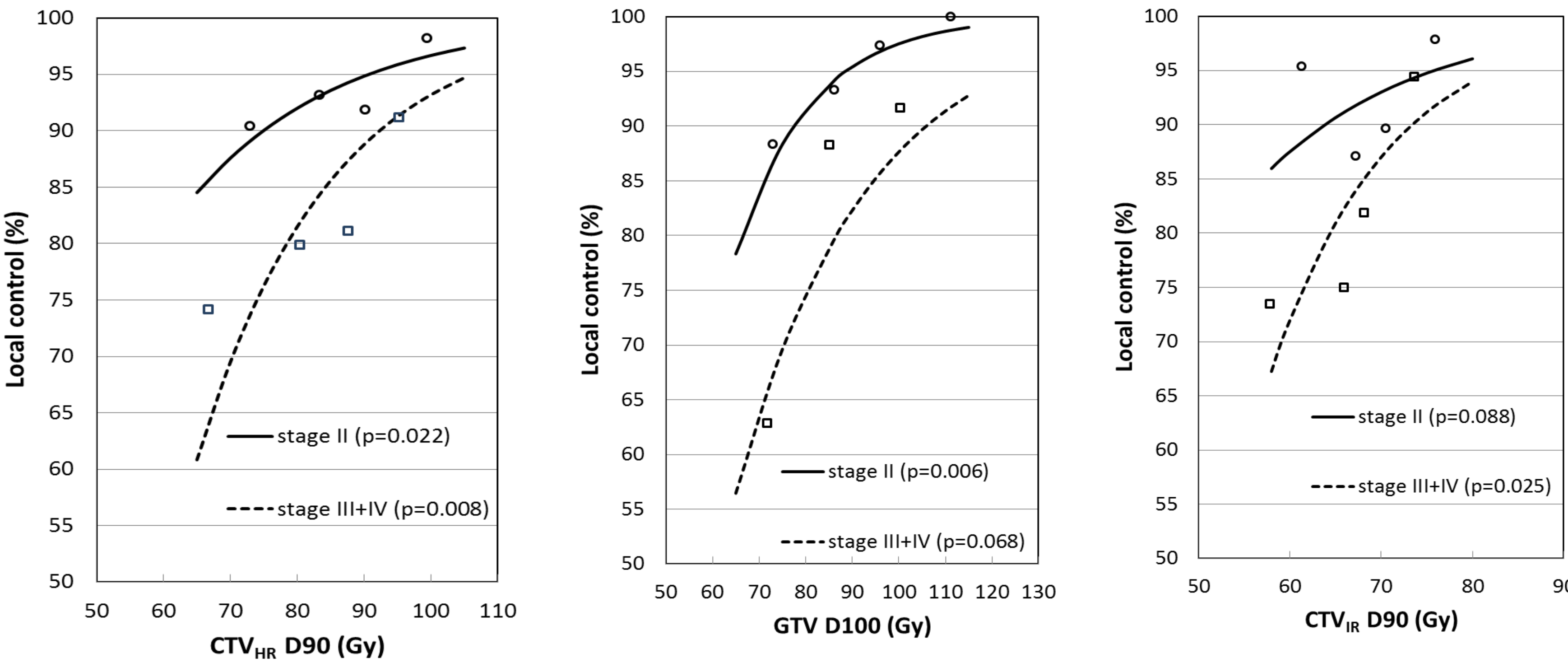


EQD2 for some common schedules

EBRT dose	EBRT #fx	BT fraction dose	BT fractions	Total EQD2
50Gy	25 fx	7Gy	3 fx	80Gy
50Gy	25 fx	8Gy	3 fx	86Gy
50Gy	25 fx	9Gy	2 fx	79Gy
45Gy	25 fx	7Gy	4 fx	85Gy

Dose effect GTV, CTV_{HR} and CTV_{IR}

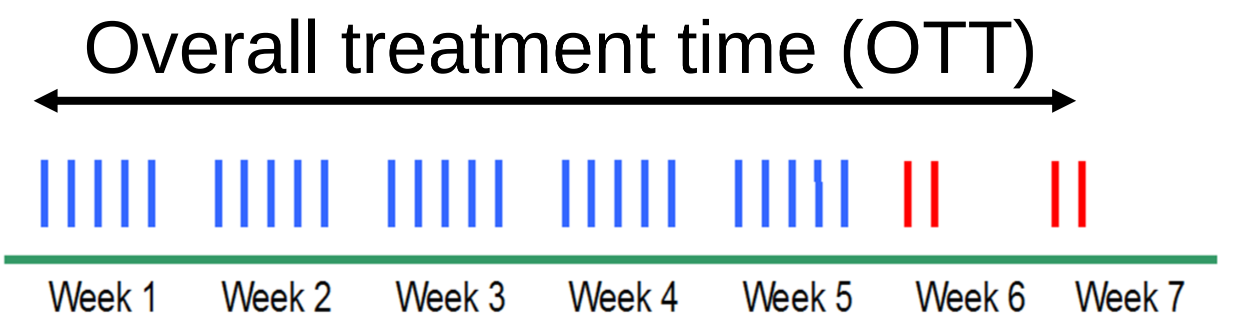
Analysis according to stage



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/m²) x1

18 Gy

Cisplatin (40 mg/m²) x2

27 Gy

Cisplatin (40 mg/m²) x3

36 Gy

Cisplatin (40 mg/m²) x4

45 Gy

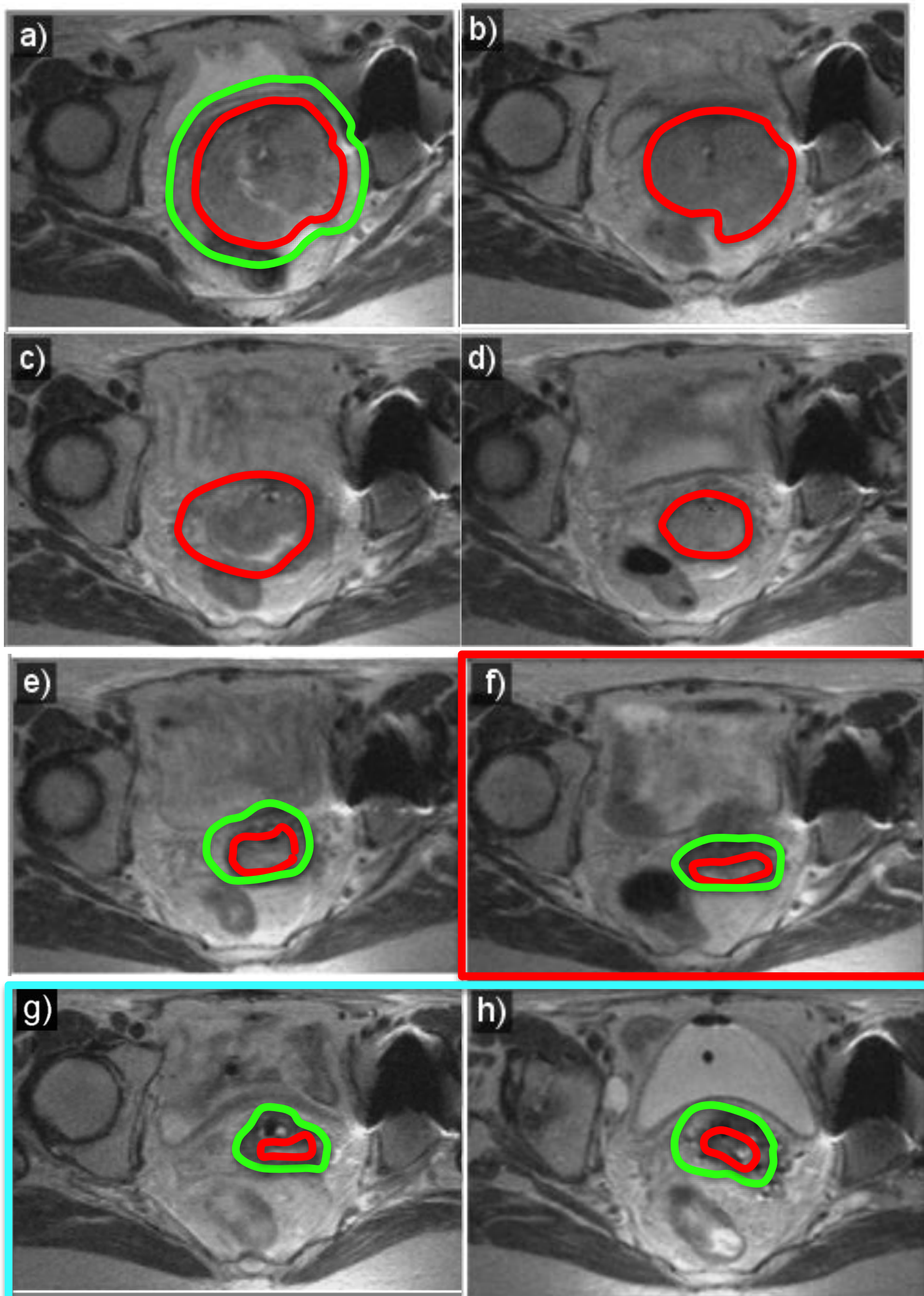
Pre-brachytherapy

EBRT45 Gy

Cisplatin (40 mg/m²) x5

IGABT 45 Gy

Brachytherapy



GTV

CTV

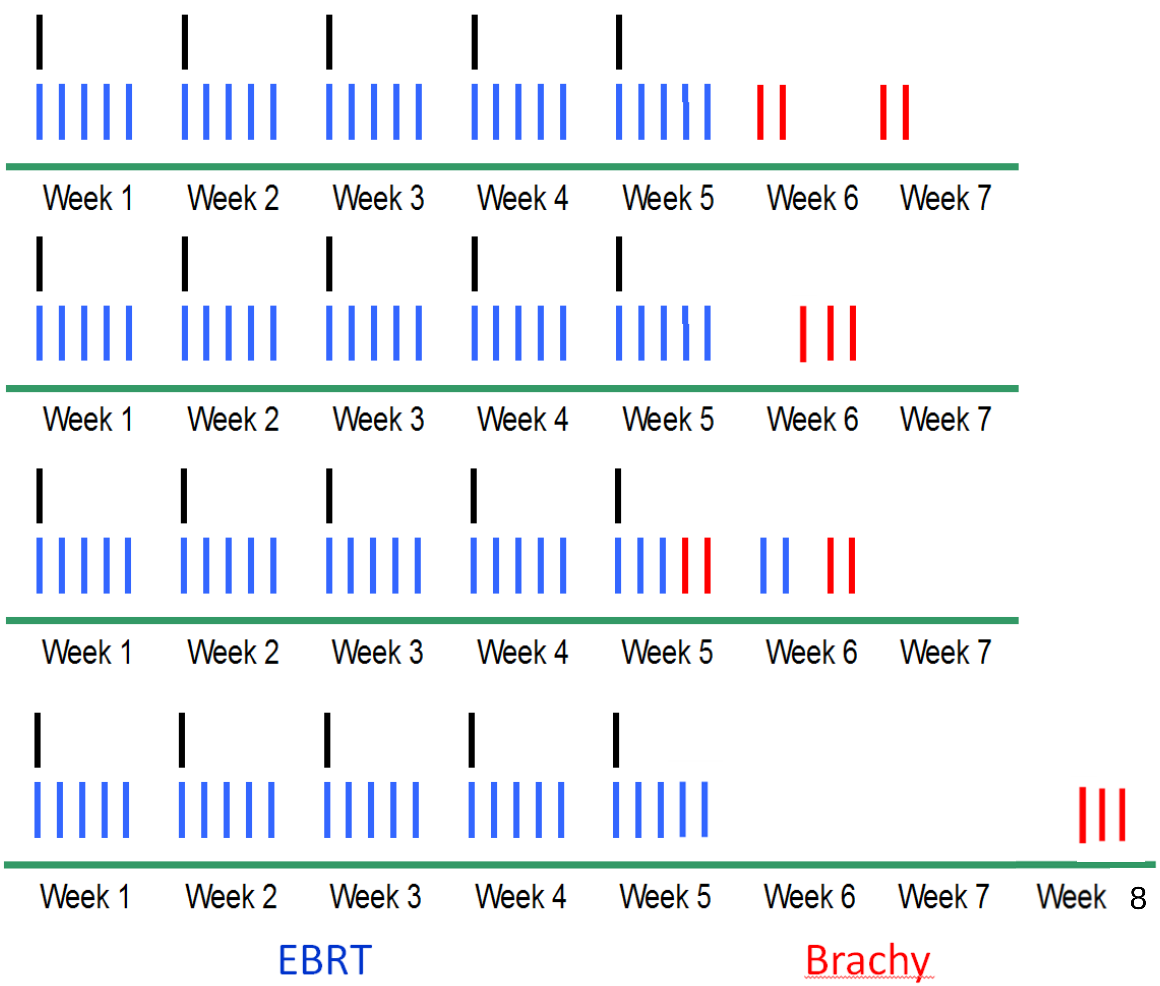
Impact of overall treatment time

1 week extra OTT ~ 5Gy less to CTV_{HR}

1 week extra OTT ~ loss of 2.5% local control

- **How to keep overall treatment time limited?**
- **Primary tumour:**
  - **Start BT towards the end of EBRT or immediately after end of EBRT**
  - **With the help of IC/IS it is not necessary to wait further for tumour shrinkage**
- **Pathological lymph nodes**
  - **Simultaneously integrated boost**

Equieffective dose and impact of overall treatment time



	EQD2	OTT correction
45Gy/25 fx EBRT 7Gy x 4 fx HDR BT	85Gy	+2Gy
50Gy/25 fx EBRT 7Gy x 3 fx HDR BT	80Gy	+5Gy
45Gy/25 fx EBRT 7Gy x 4 fx HDR BT	85Gy	+5Gy
50Gy/25 fx EBRT 7Gy x 3 fx HDR BT	80Gy	-5Gy

Common dose planning aims for target structures

	EBRT dose	BT dose EQD2	Total EQD2 EBRT+BT
Elective lymph node target: CTV-E	45-50Gy	-	45-50Gy
Pathological lymph nodes	55-60Gy	0-4Gy	60Gy
Intermediate Risk CTV: CTV_{IR}	45-50Gy	15-20Gy	60-70Gy
High Risk CTV: CTV_{HR}	45-50Gy	35-45Gy	85-90Gy
GTV	45-50Gy	50-55Gy	95-100Gy
Point A	45-50Gy	25-40Gy	70-85Gy

EMBRACE

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

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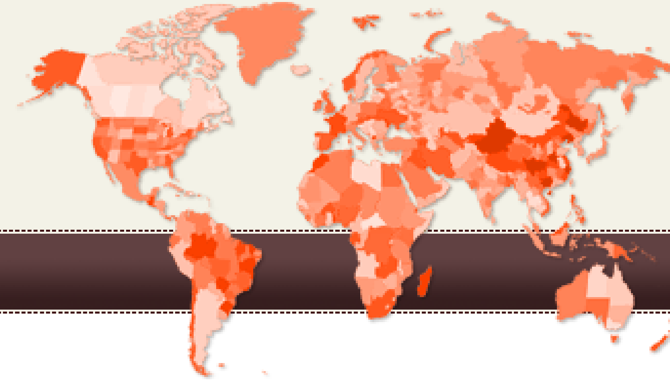
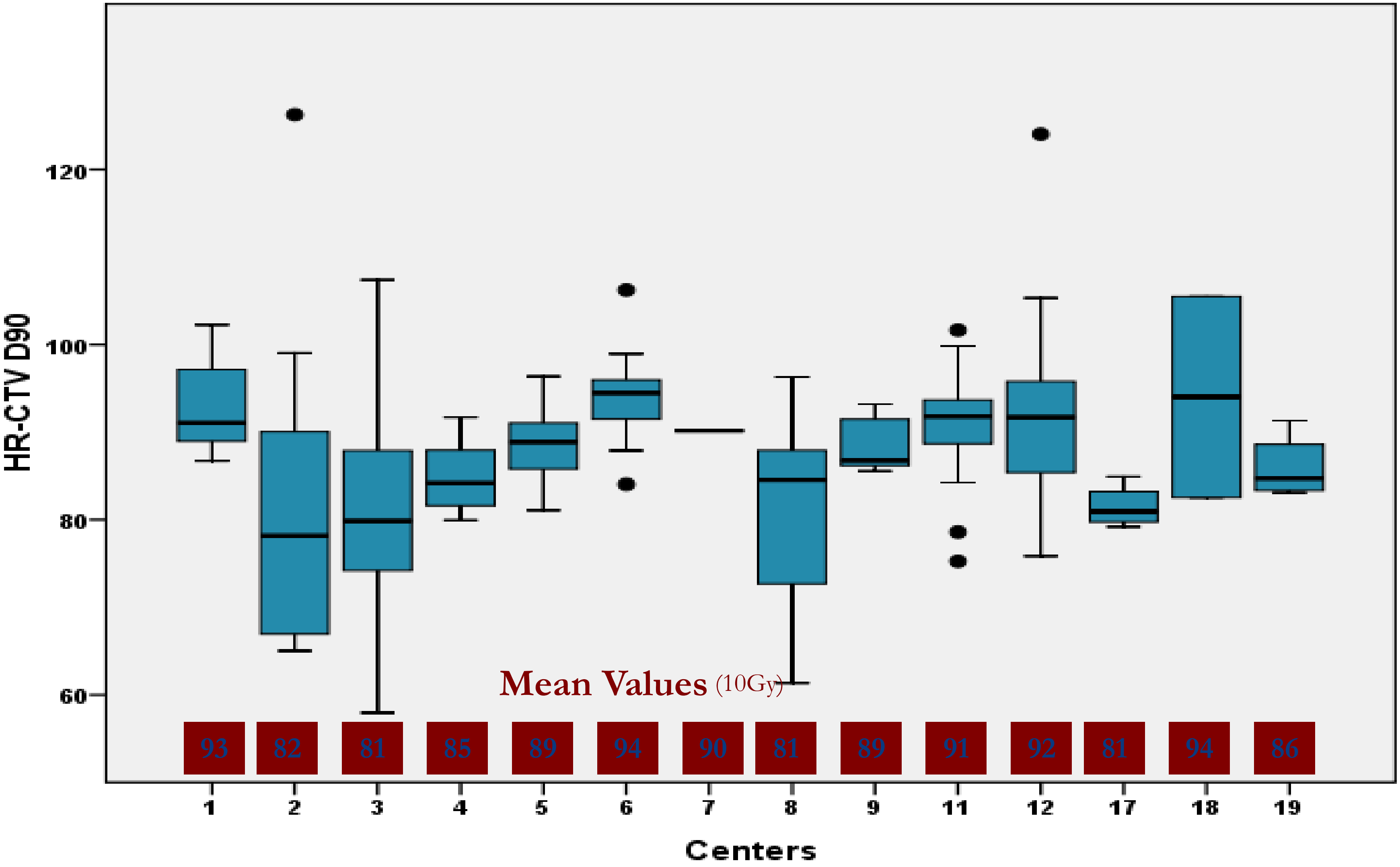


- **EMBRACE - Int<u>e</u>rnational study on <u>M</u>RI-based 3D <u>bra</u>chytherapy in locally advanced <u>ce</u>rvical cancer**
- **A prospective observational multi-centre trial**
- **Contouring and reporting according to GEC ESTRO recommendations**
- **Fractionation, planning and prescription according to institutional practice**
- **Enrollment of patients in 2008-2015, 1419 pts accrued**

VARIAN medical systems | A partner for life

Nucletron Improving patient care

Heterogeneity of dose prescription: HRCTV D90



RETRO EMBRACE

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

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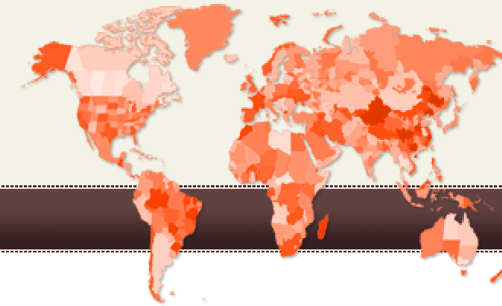


- Web-based database with a retrospective multicentre collection of data on 3D RT plus IGABT in cervical cancer

- 780 pts

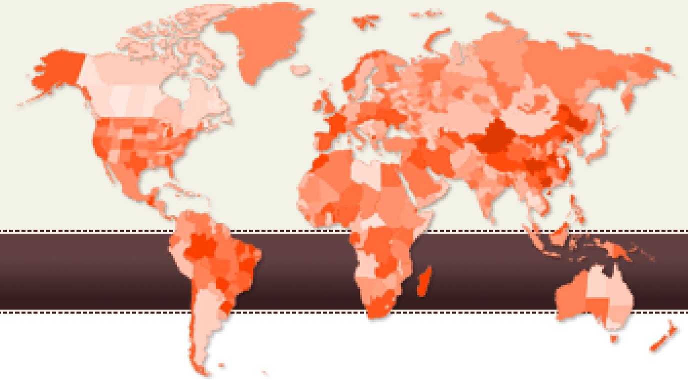
- Eligibility criteria:
  - Diagnosis of cervical cancer and treatment with curative intent by IGABT
  - Reporting according to GEC ESTRO recommendations

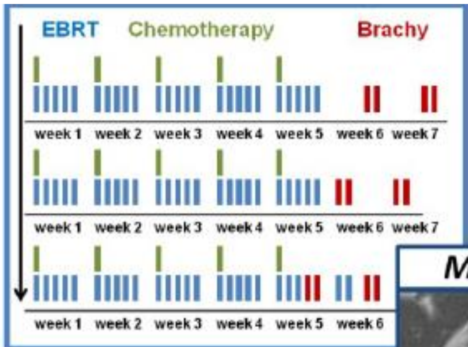
VARIAN medical systems | A partner for life

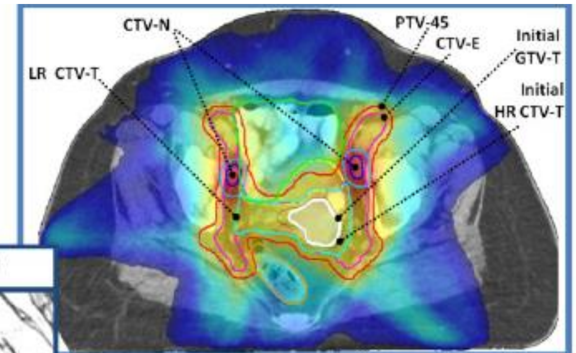
Nucletron Improving patient care

EMBRACE II

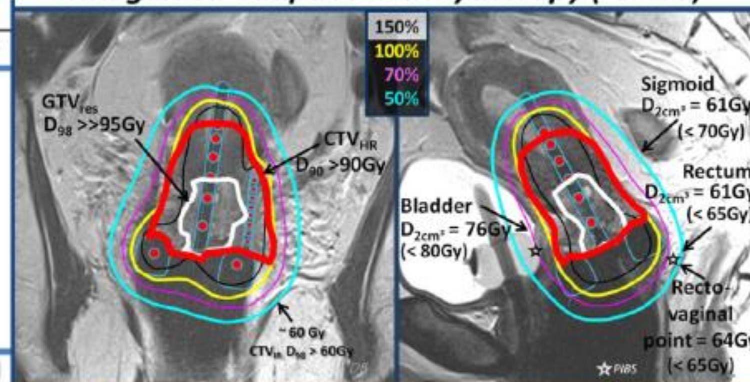
An intErnational study
on MRI-guided BRachytherapy
in locally Advanced CErvical cancer

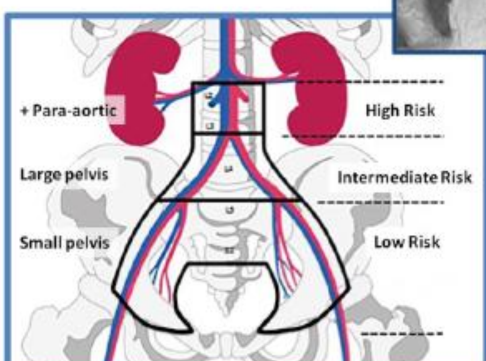




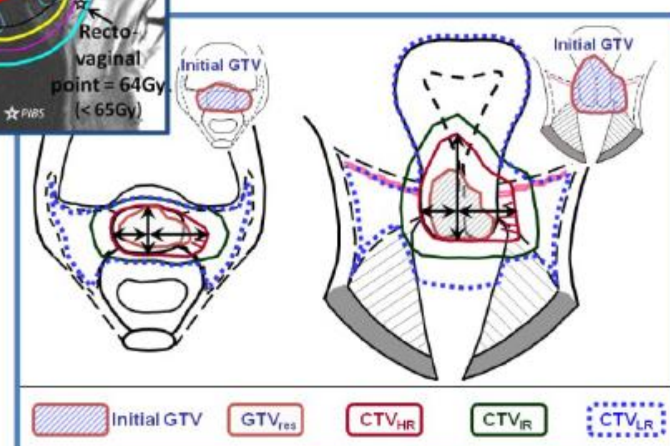


MRI guided adaptive brachytherapy (IGABT)





Nodal CTV-E based on Risk Group



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

EMBRACE II design

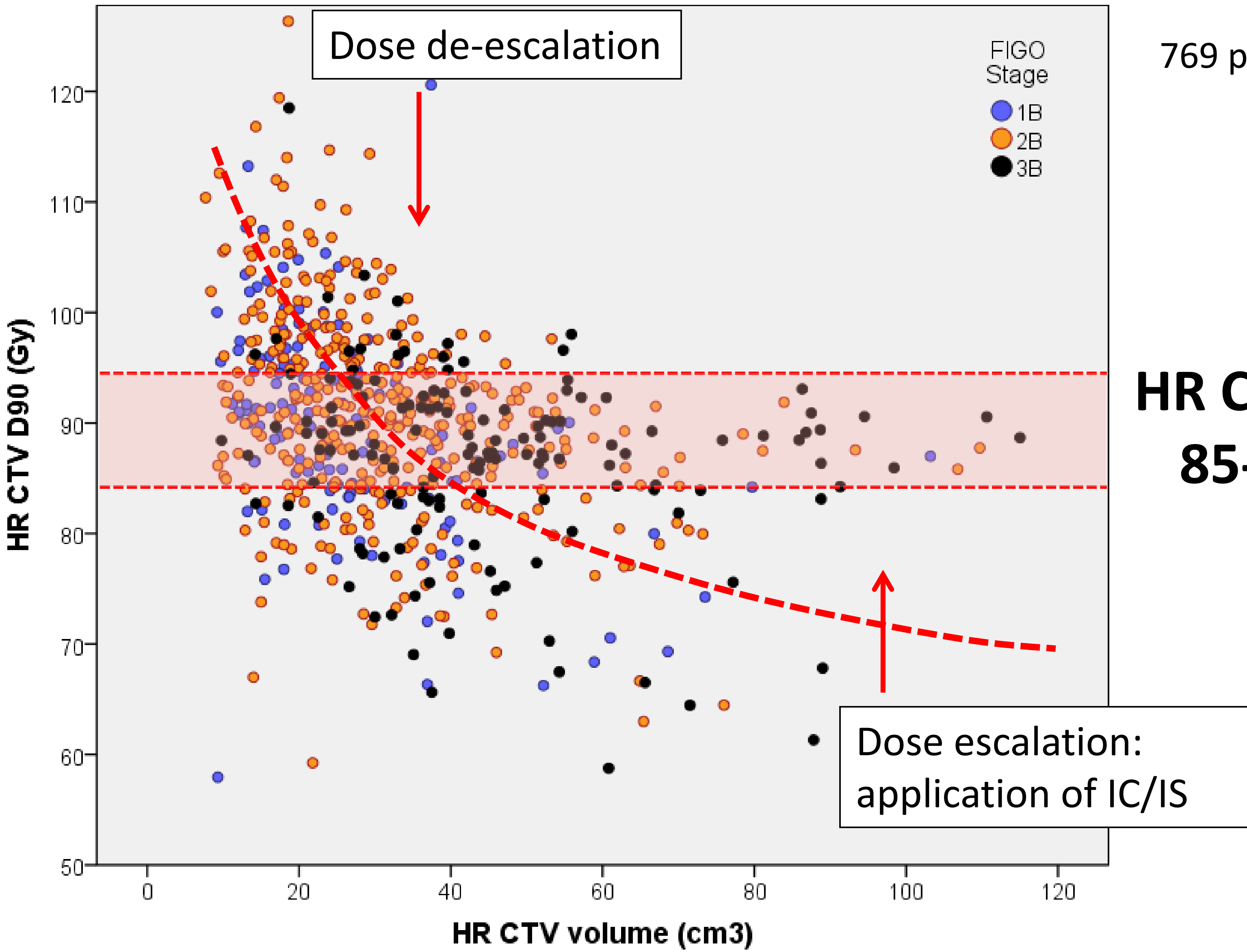
- Prospective interventional and observational study
- Multiple endpoints
- Multicenter: >25 centers
  - 25 current EMBRACE centers and >10 new centers
- 1000 patients in 4 years and follow up for 5 years

- Substudies on
  - Adaptive EBRT
  - Vaginal morbidity
  - Functional imaging
  - Translational research

EMBRACE II interventions

- Increased use of IC/IS technique in BT:
  - HR CTV >30cm3: utilisation of IC/IS of >70% in patients and CTV_{HR}>85Gy in 80% of patients (63% in EMBRACE I))
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

EMBRACE II dose prescription



769 pts EMBRACE

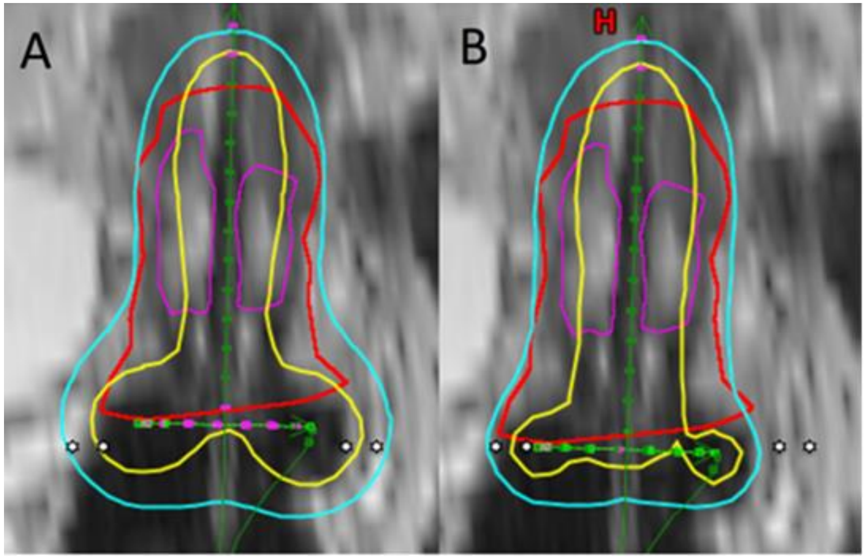
HR CTV D90 85-95Gy

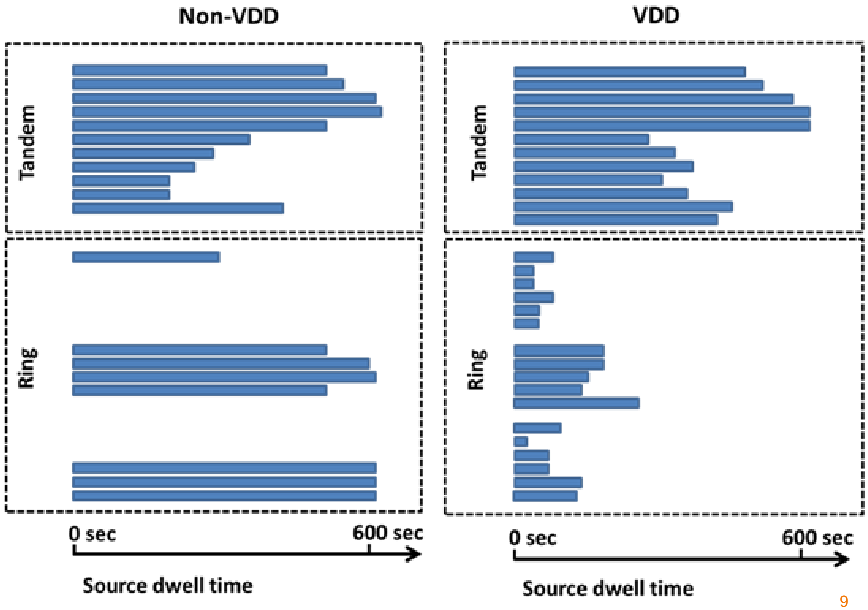
EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading (<33% of total loading (51% in EMBRACE I)
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

Vaginal dose de-escalation

	Aim	Priority
ICRU recto-vaginal point dose	<65Gy EQD2 (EBRT+BT)	Primary
The ratio of vaginal TRAK and total TRAK	<30-40%	Secondary
Vaginal lateral dose points at 5mm	<85Gy EQD2 (EBRT+BT)	Secondary
Visual inspection of the 140% isodose	Intruding as little as possible into vaginal tissue, and preferentially located within the applicator	Secondary



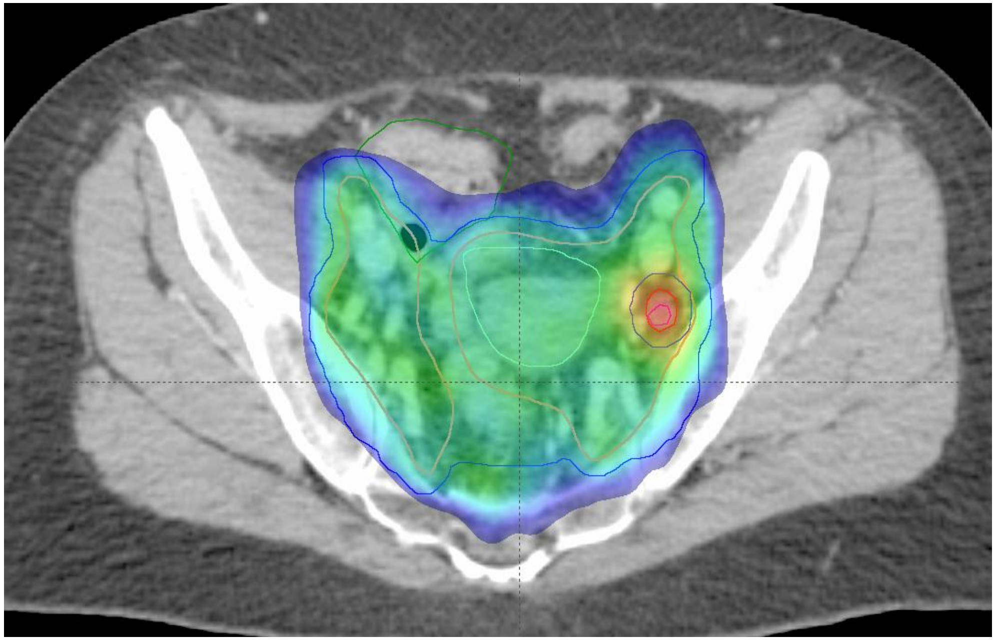


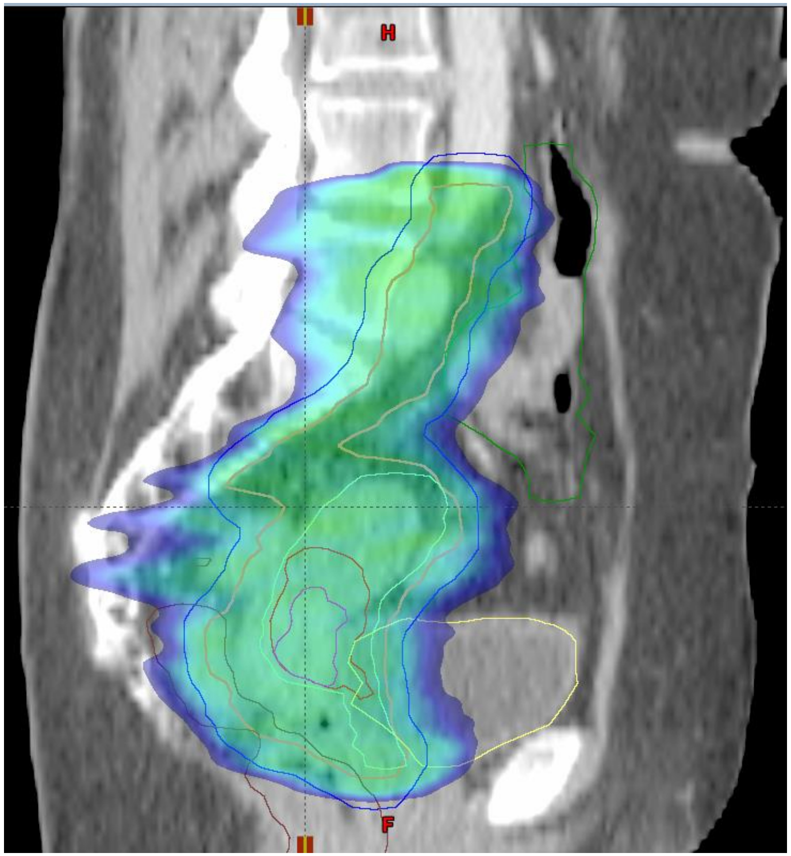
EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT + Utilisation of daily IGRT (reduction of V43Gy by 1000cm3 (from 2500cm3 to 1500cm3 pelvis)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

IMRT + daily IGRT

- 5mm PTV margin
- SIB LN boosting



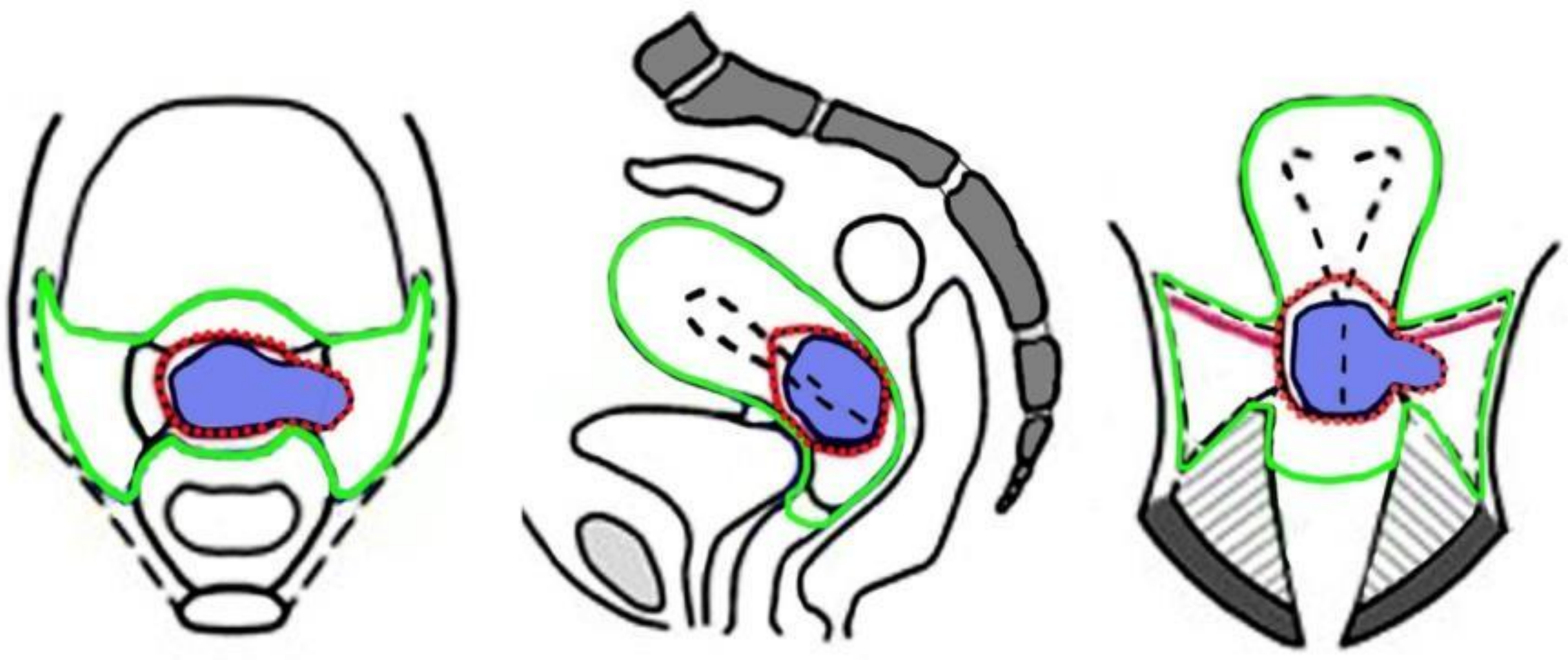


EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

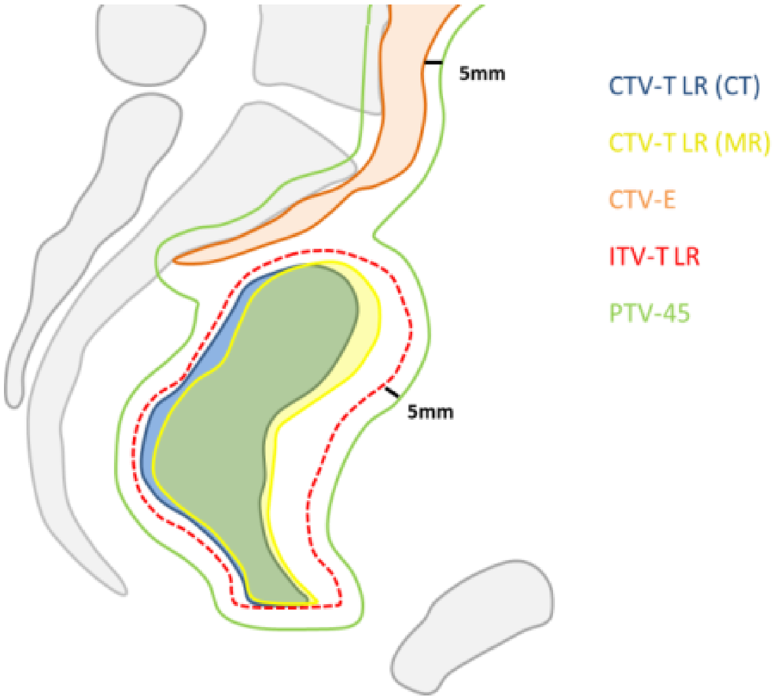
Target concept related to primary tumour

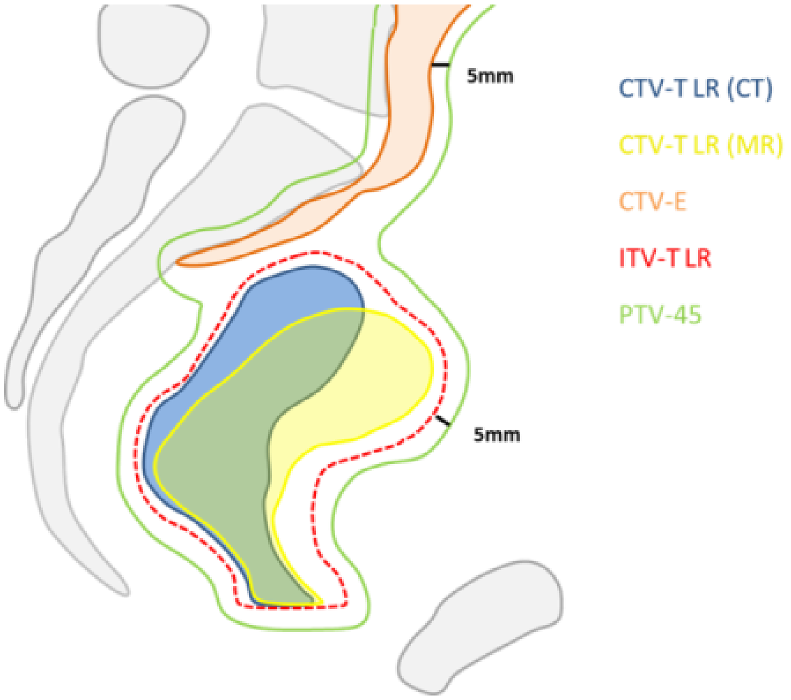
- **Initial GTV (blue)**
- **Initial HR CTV-T (red): GTV+cervix**
- **LR CTV-T (green): HR CTV + uterus + parametria + vagina**



Internal target volume

- **Combined appearance on CT and MRI**
- **Taking organ motion into account**





EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription and reporting (45Gy/25 fx in all fractions (30% patients with >45Gy in EMBRACE I)
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

EBRT dose prescription

- **CTV-E:**
  - **45Gy/25fx**

- **CTV-N**
  - **Delivered as SIB**
  - **Suggested dose and fractionation**
    - **55Gy/25 fx inside pelvis (assuming 3-4Gy BT contribution)**
    - **57.5Gy/25fx outside pelvis**
    - **Equivalent to a total of 60Gy EQD2**

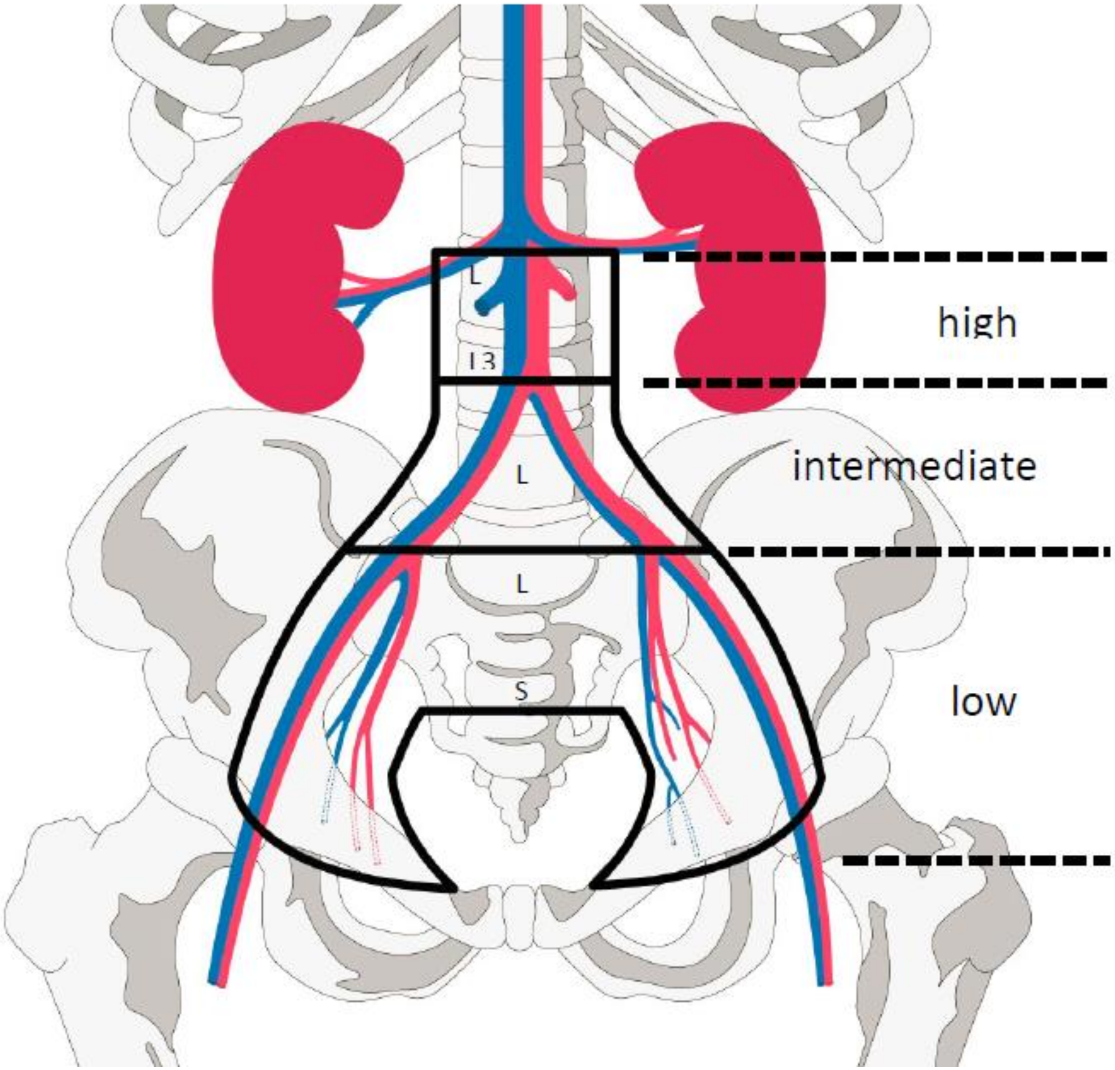
EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence (application of PAN irradiation in 55% of N+ patients (25% in EMBRACE I))
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time

Target concept related to elective lymph nodes

Risk Group LN	Definition	EBRT lymph node regions
Low Risk (LR LN)	Tumour size ≤4cm AND stage IA/IB1/IIA1 AND N0 AND squamous cell carcinoma AND no uterine invasion	**"Small Pelvis"** internal iliac external iliac obturator presacral
Intermediate Risk (IR LN)	Not low risk No high risk features	**"Large Pelvis"** Nodes included in "Small Pelvis" and common iliac region (including the aortic bifurcation). In addition: • inguinal in case of distal vaginal involvement. • Mesorectal space in case of mesorectal nodes and advanced local disease
High Risk (HR LN)	Based on nodal pathology • ≥ 1 pathologic node at common iliac or above • OR ≥ 3 pathologic nodes	**"Large Pelvis + Para-aortic"** Nodes included in "Large Pelvis" and para-aortic region with the upper border of CTV minimum at the level of renal veins (usually incl. L2), and at least 3 cm cranial of the highest pathological node in case of para-aortic nodes].

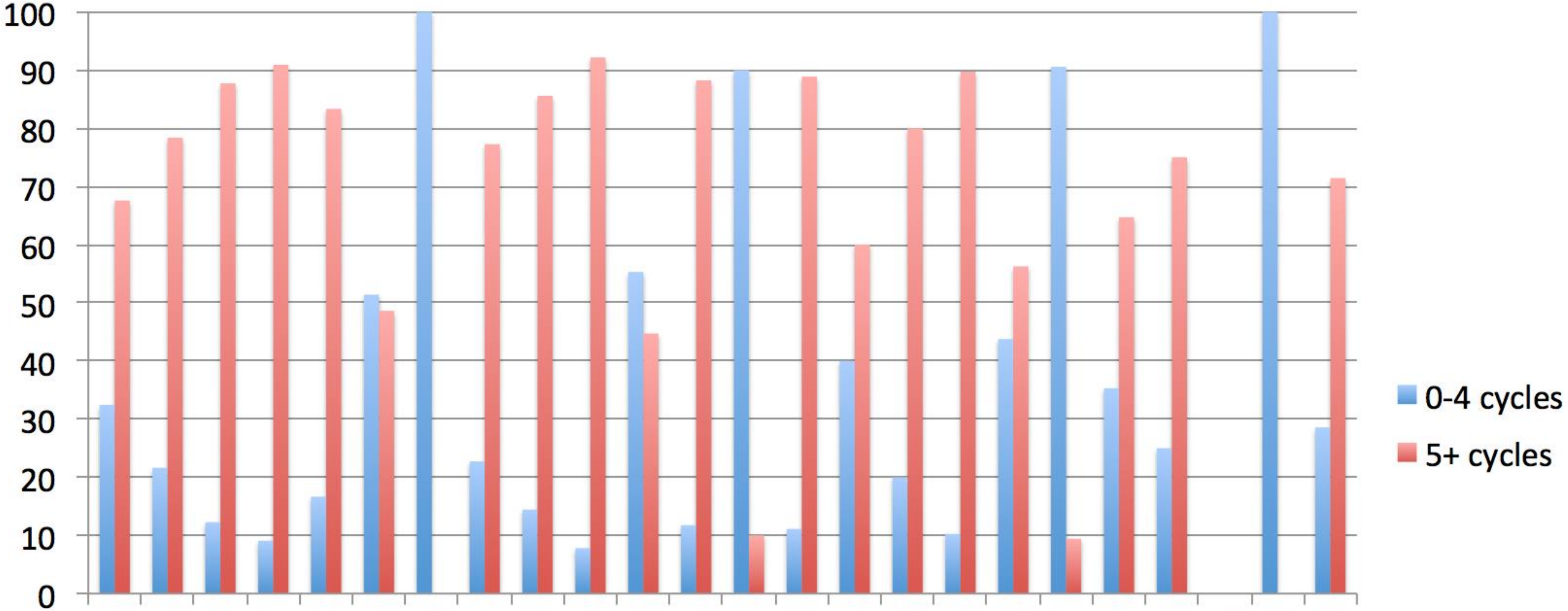
Target concept related to elective lymph nodes



EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy (administration of 5 cycles in 80% of patients (69% in EMBRACE I)
- Reduction of overall treatment time

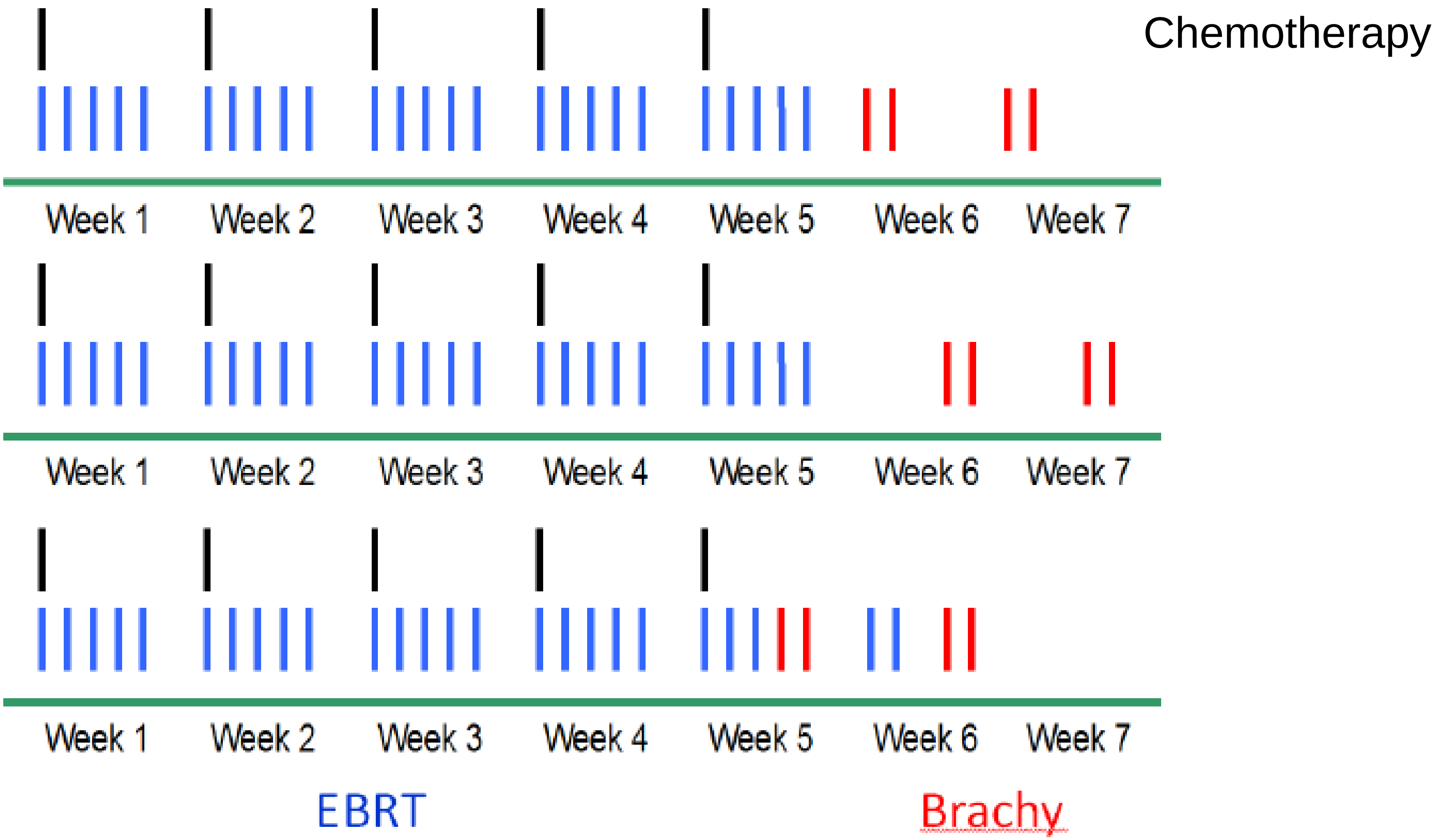
Administration of chemotherapy in EMBRACE I



EMBRACE II interventions

- Increased use of IC/IS technique in BT
- Reduction of vaginal source loading
- Systematic utilisation of IMRT
- Utilisation of daily IGRT (set-up according to bony structures)
- EBRT target concept related to the primary tumour; concepts for OAR contouring
- EBRT dose prescription (45Gy/25fx) and reporting
- Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
- Systematic application of simultaneous chemotherapy
- Reduction of overall treatment time (OTT<50 days in 80% of patients

Control of OTT: 3 examples of schedules



Accreditation and dummy run for new centers

- Documentation of compliance (web based)
  - Treatment of >10 pts per year qualifying for accrual to EMBRACE II
  - Both EBRT and BT performed in the center
  - Routine use of IMRT or VMAT
  - Routine use of daily IGRT with bony fusion
  - Routine use of MRI guided IGABT
  - Routine use of combined IC/IS (>20-50% of pts)

Accreditation and dummy run for new centers

- Dummy run
  - Contouring training for EBRT and BT (self-assessment)
  - EBRT planning exercise (self assessment)
  - Registration of 5 patient in registration database
  - Submission of EBRT and BT contours
  - Submission of EBRT and BT treatment plan

Roadmap EMBRACE II

- **Spring 2016:** **Dummy run EMBRACE centers**
- **April 2016:** **Start of accrual**
- **Autumn 2016 →** **Dummy run new centers**
- **March 2018** **150 patients enrolled from 9 centers, 10 centers ready to include**
  16 centers under accreditation

Contact to EMBRACE office for interested centers:

Tamara.rumpold@akhwien.at

Richard.poetter@akhwien.at

Karitand@rm.dk

Clinical Outcome : Disease and Toxicities

Christine Haie Meder

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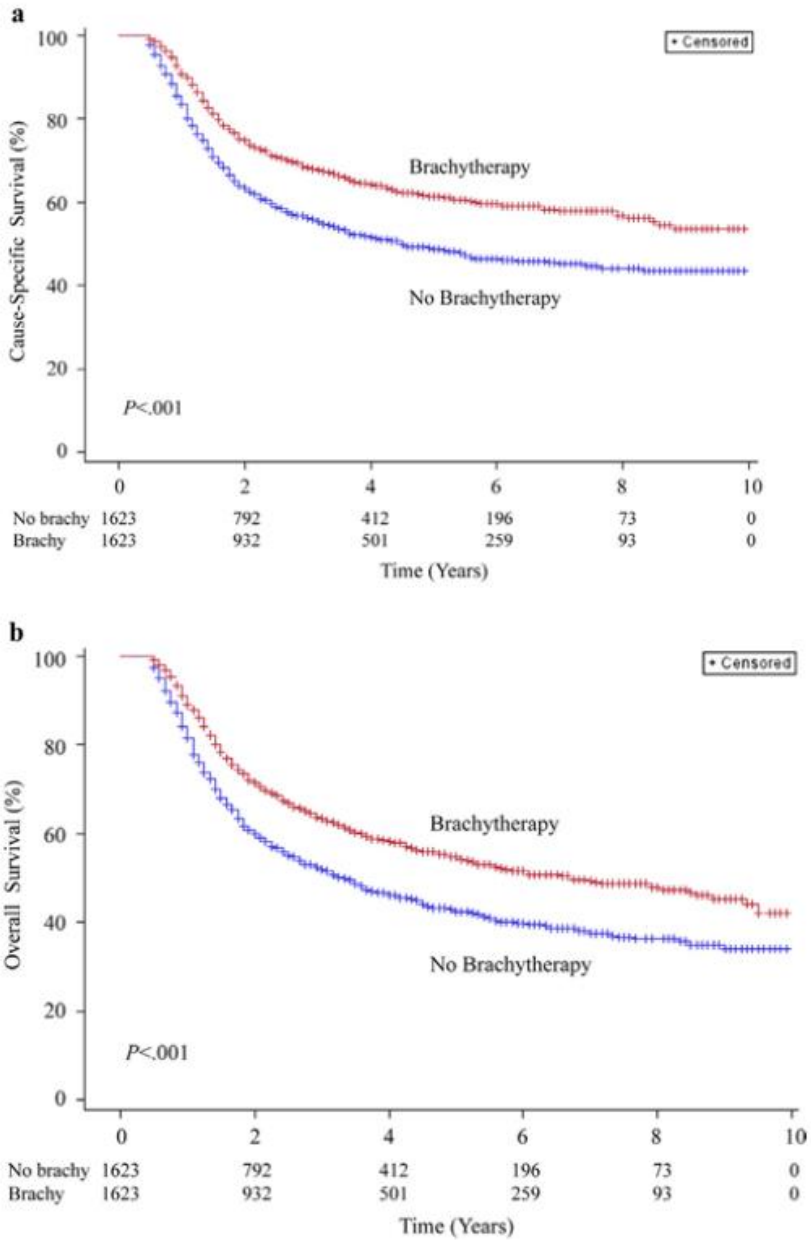
EDITORIAL

Curative Radiation Therapy for Locally Advanced Cervical Cancer: Brachytherapy Is NOT Optional

Kari Tanderup, PhD,[*,†] Patricia J. Eifel, MD,[‡] Catheryn M. Yashar, MD,[§]
Richard Pötter, MD,[||] and Perry W. Grigsby, MD[*]

Int J Radiation Oncol Biol Phys 88:537-9;2014

Importance of brachytherapy +++



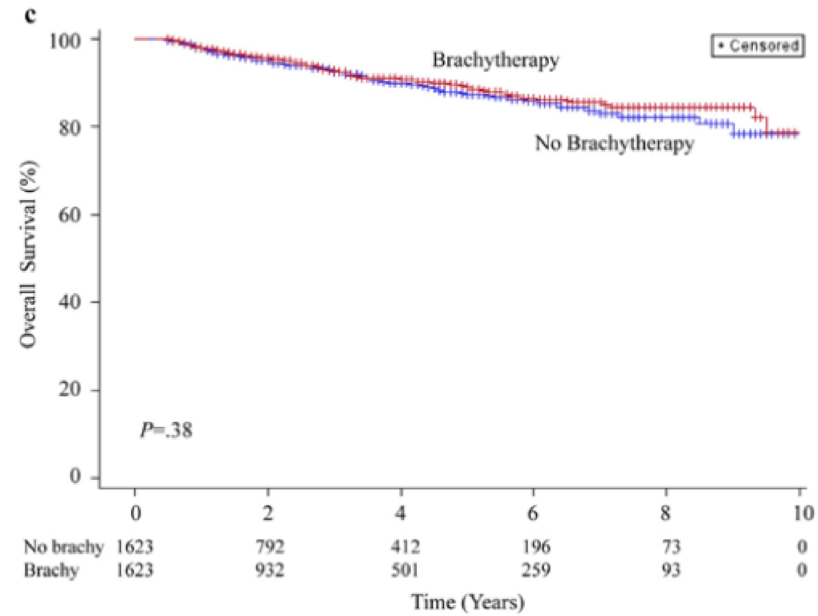


Fig. 2. Survival by brachytherapy use for matched cohort between 2000 and 2009. (a) Cause-specific survival; (b) overall survival, and (c) non-cancer-related survival.

Clinical Investigation: Gynecologic Cancer

Trends in the Utilization of Brachytherapy in Cervical Cancer in the United States

Kathy Han, MD,* Michael Milosevic, MD,* Anthony Fyles, MD,* Melania Pintilie, MSc,[†] and Akila N. Viswanathan, MD, MPH[‡]

*Radiation Medicine Program, Princess Margaret Hospital, University Health Network, Toronto, Ontario, Canada; [†]Department of Biostatistics, Princess Margaret Hospital, Toronto, Ontario, Canada; and [‡]Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, Massachusetts

Received Mar 24, 2013, and in revised form Apr 30, 2013. Accepted for publication May 20, 2013

Results of radiotherapy in early-stage disease (before the era of concomitant chemo-radiotherapy and IGABT)

Authors	N° pts	Stage	5-yr survival (%)	Local control (%)
Manchester 80-88 LDR Hunter 1993 1993 (62)	294 45 70	I/IIA IB IIB	90-94 (DFS) 71 (OS) 52 (OS)	
Perez (87) LDR	384 128 353	IB IIA IIB	85 70 72	90 81 77
Fletcher (35) LDR	494 207	IB IIA MDAH IIB MDAH	84 70	93 82
French cooperative group LDR Horiot (53)	229 315 314	I MDAH IIA MDAH IIB MDAH	89 (89) 81 (85) 76 (76)	93 (95) 83 (88) 80 (78)
Kim (66) LDR	169 83	IB IIA	82 78	89 91
Lowrey (74 LDR	130 64	IB IIA	81 74	88 84
Pernot (92) LDR	173	IIA-B prox.	74	79
Coia (18)	203	IB	80	90
Joslin (64, 65) HDR	95 170	I II	94 62	97 74
Petereit (93) HDR	59 64	IB II	86 65	85 80
Vienna HDR Pötter (96)	42 124	IB/IIA IIB	85 (DSS) 69 (DSS)	97 82

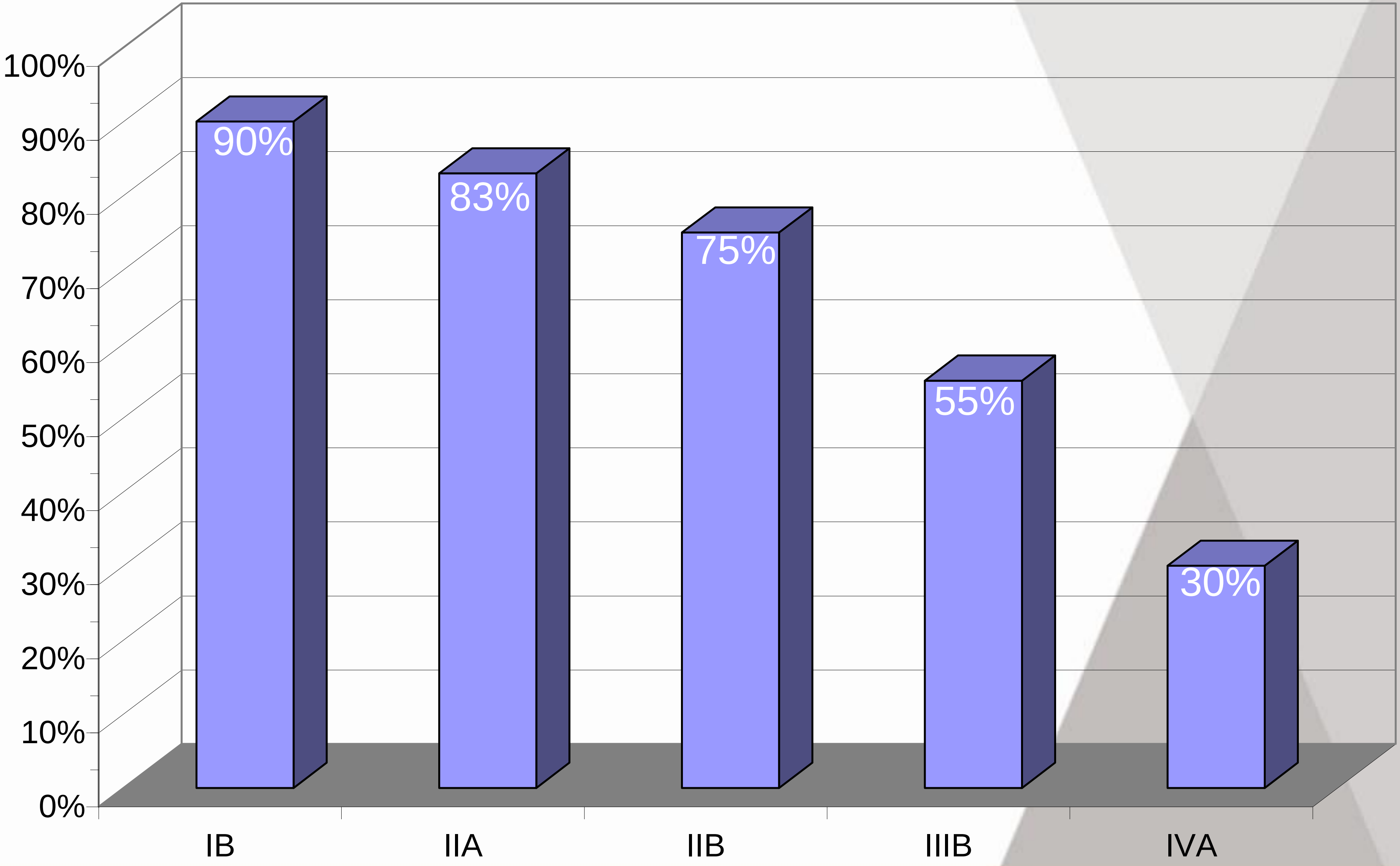
Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma.
In: Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Van Limbergen E, eds. (2002) The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO

Results of radiotherapy in advanced disease (before the era of concomitant chemo-radiotherapy and IGABT)

Authors	N° pts	Stage	5-yr survival (%)	5-y Local control (%)
Manchester 1993 LDR Hunter 2001 (62)	50	III	34 OS	
Perez (86) LDR	293 20	III IV	52 DFS 0	59 25
Houston MDAH (26, 28) Fletcher LDR (73)	73 a* 25 b* 983	IB_2 IIB (bulk) IIIB (UICC)	44 OS 60 OS 36 DSS	67 84 78
French cooperative group LDR (53)	266 216 32	IIIA MDAH IIIB MDAH IV	61 OS (62) 39 OS (50) 20 OS	68 (63) 45 (57) 18
Paris IGR (42) LDR	58 416	Distal II IIIA-B, IV	65 OS 42 OS	78 66
Pernot (92) LDR	60 107	Distal IIB III	70 OS 42 OS	77 54
Joslin (64, 65) HDR	106	III	38 OS	56
Petereit (93) HDR	50	IIIB	33 OS	44
Vienna HDR Pötter (96)	78 12	IIIB IVA	48 DSS 19 DSS	65 48

Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma.
In: Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Van Limbergen E, eds. (2002)
The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO

Results of definitive radiotherapy 2D X-ray based point A prescription



Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma. In: Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Van Limbergen E, eds. (2002) The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO

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

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration

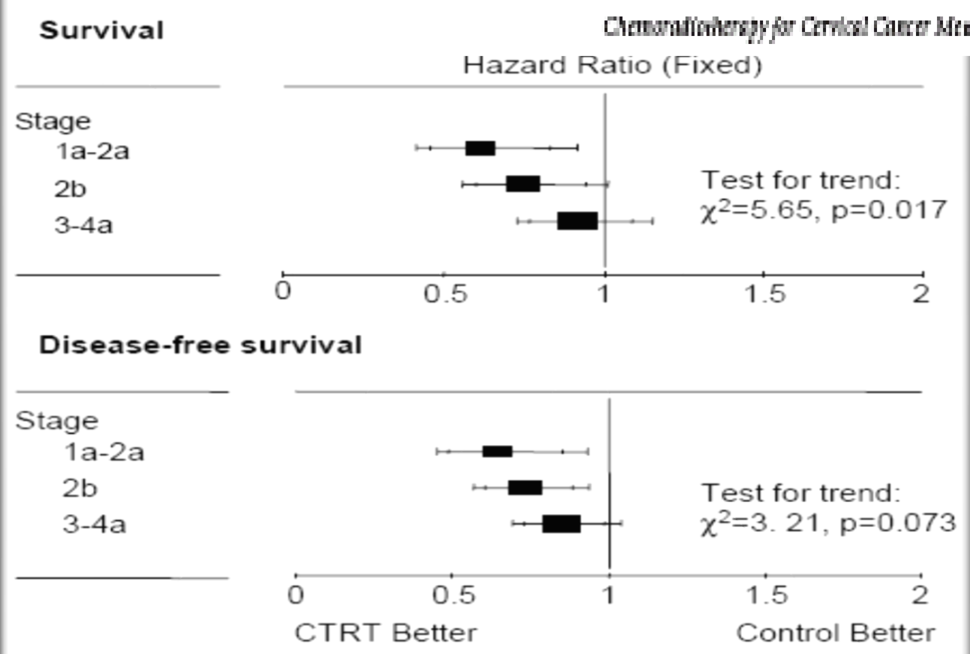
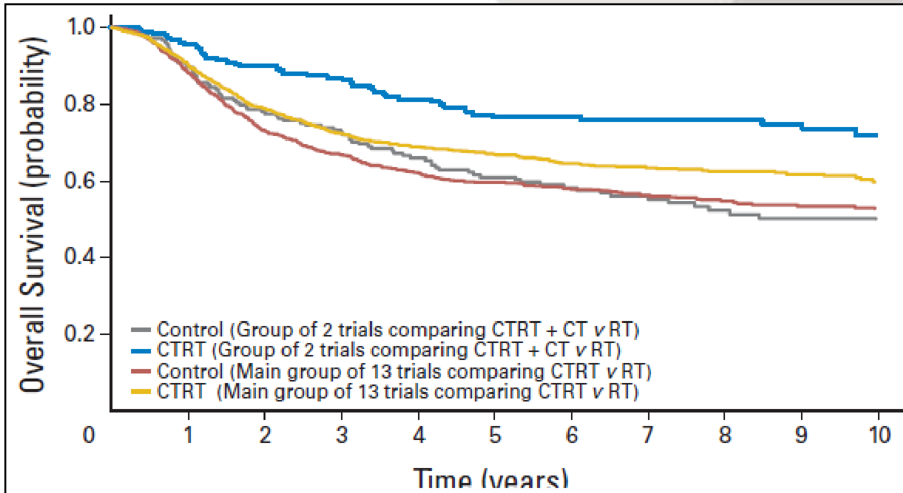


Figure 3. Survival and disease-free survival by tumour sta
of 13 trials only)



Adjuvant CT after CRT needs to be further explored

There was however the suggestion of a decreasing relative effect of chemo-radiation on survival with increasing tumor stage, with estimated absolute survival benefits of **10% (stage Ib-IIa), 7% (stage IIb) and 3% (stage III-IVa) at 5-years**

Results of definitive radiotherapy with IGABT

- **New paradigms**

  - 3D representation of GTV / CTV / OAR

  - DVH parameters based on individualised 3D treatment planning (D90 CTV: HR and IR CTV)

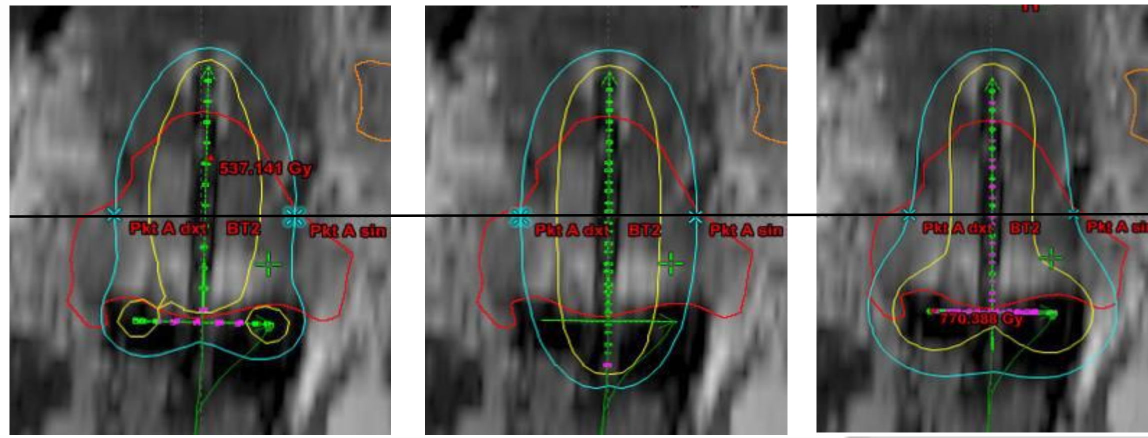
- **Did we improve the practice heterogeneity in prescription?**

- **Clinical results**

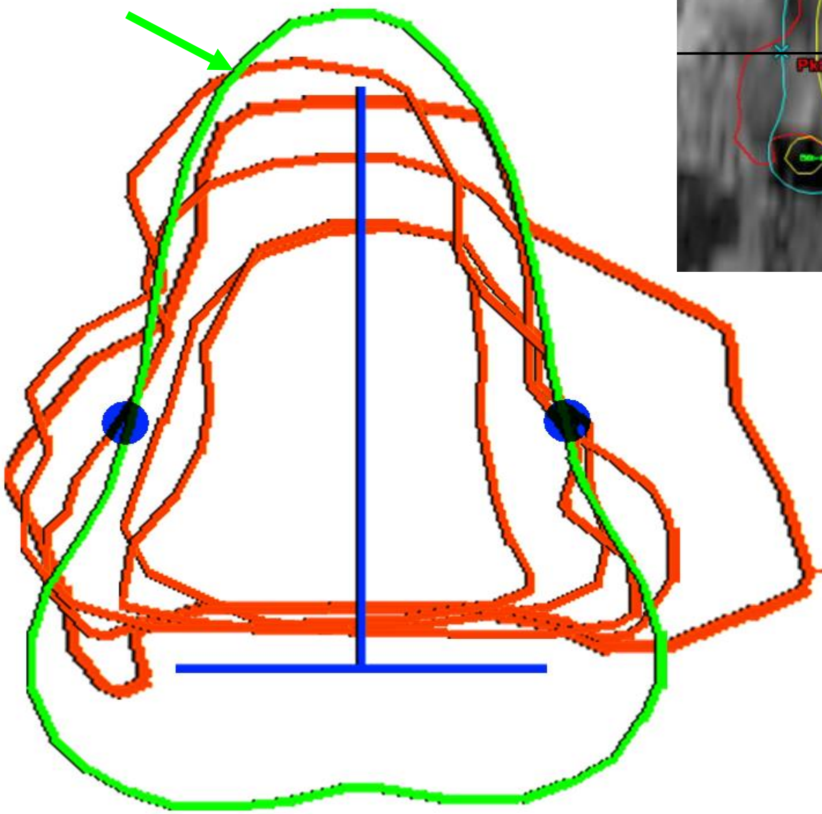
  - Local control related to 3D dose volume parameters

Prescription to point A

Milwaukee Toronto Vienna



Point A isodose



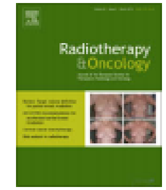
IGABT cervix cancer
Practice homogeneity

Radiotherapy and Oncology 94 (2010) 339–345

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Cervix cancer brachytherapy

Variation of treatment planning parameters (D90 HR-CTV, D_{2cc} for OAR) for cervical cancer tandem ring brachytherapy in a multicentre setting: Comparison of standard planning and 3D image guided optimisation based on a joint protocol for dose–volume constraints

Ina M. Jürgenliemk-Schulz [a,1], Stefan Lang [b,*,1], Kari Tanderup [c], Astrid de Leeuw [a], Christian Kirisits [b], Jacob Lindegaard [c], Primoz Petric [d], Robert Hudej [d], Richard Pötter [b], On behalf of the Gyn GEC ESTRO network

Table 1
Treatment concepts of the different ring centres (R1–R6): EBRT dose, BT dose rate and fractionation schedule, additional interstitial sources.

Centre	R1	R2	R3	R4	R5	R6
EBRT						
Physical dose (Gy)	45	45	45	45	45	45
Fractionation	25 × 1.8	25 × 1.8	25 × 1.8	25 × 1.8	25 × 1.8	25 × 1.8
Brachytherapy						
Dose rate	PDR	PDR	HDR	HDR	HDR	HDR
Number of fractions	3	2	6	5	4	3
Prescribed physical dose/fraction (Gy)	12	20	4.7	5.5	7	7
Interstitial needles	Yes	Yes	No	No	Yes	No

IGABT cervix cancer
Practice homogeneity

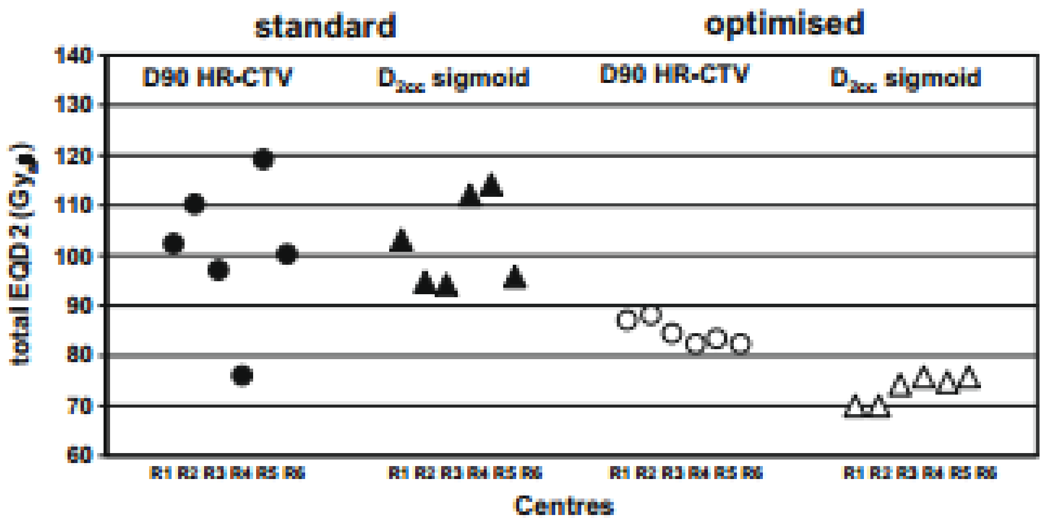


Fig. 2. Dose level variations (D90 HR-CTV and D_{2cc} sigmoid) in standard and optimised plans from the different centres for the limited volume case. The radiobiological effect of dose rate (PDR: R1/R2, HDR: R3/R4/R5/R6) and fractionation is indicated for the different treatment schedules (3rd and 4th column). Number of fractions is decreasing and dose per fraction is increasing for R3–R6 (compare Table 1).

Jürgenliemk-Schulz Radiother Oncol 2010;94:339-45

Clinical Evidence in IGABT Cervix Cancer

- Mono-institutional cohorts (publications since 2007)
- Multi-center cohorts with retrospective evaluation
  RetroEMBRACE (Sturdza, Fokdal 2016 …)
- Prospective Trials
  STIC: comparative 2D vs. 3D (Charra-Brunaud 2012)
  EMBRACE I: observational, 08/2008 - 12/2015
  EMBRACE II: interventional, start 01/2016

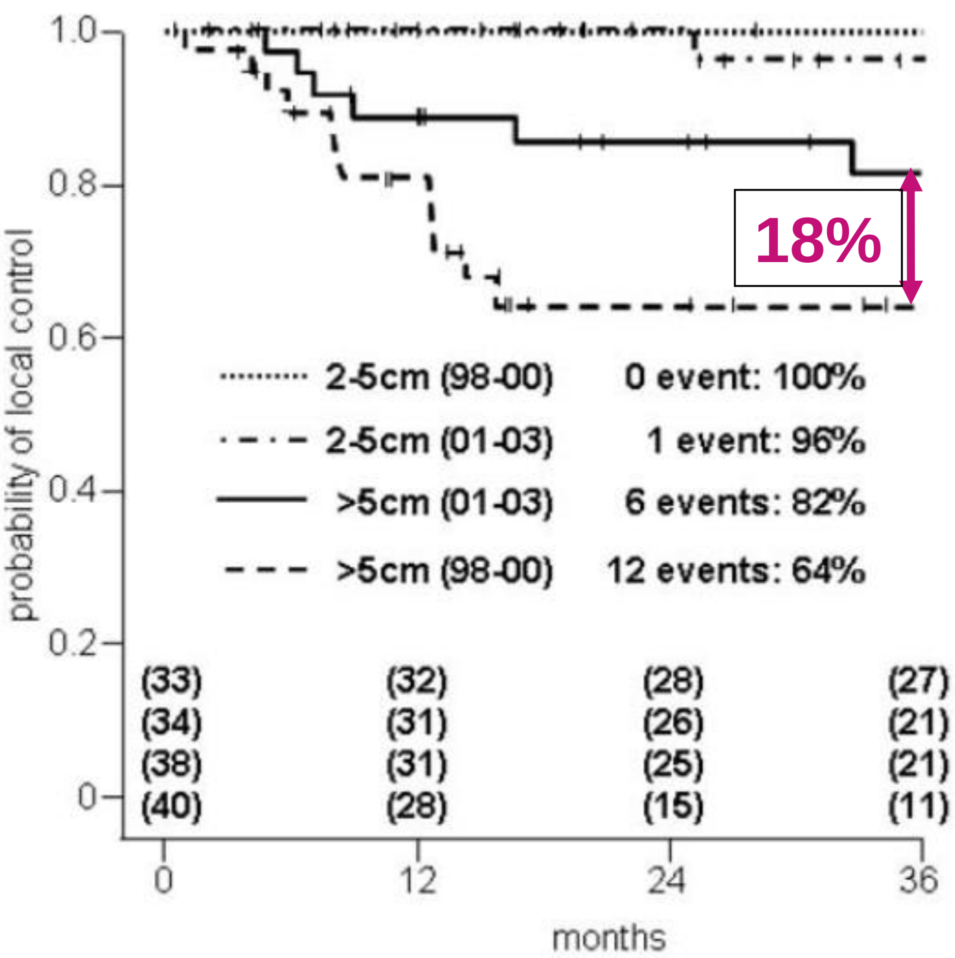
IGABT cervix cancer
Mono-institutional results

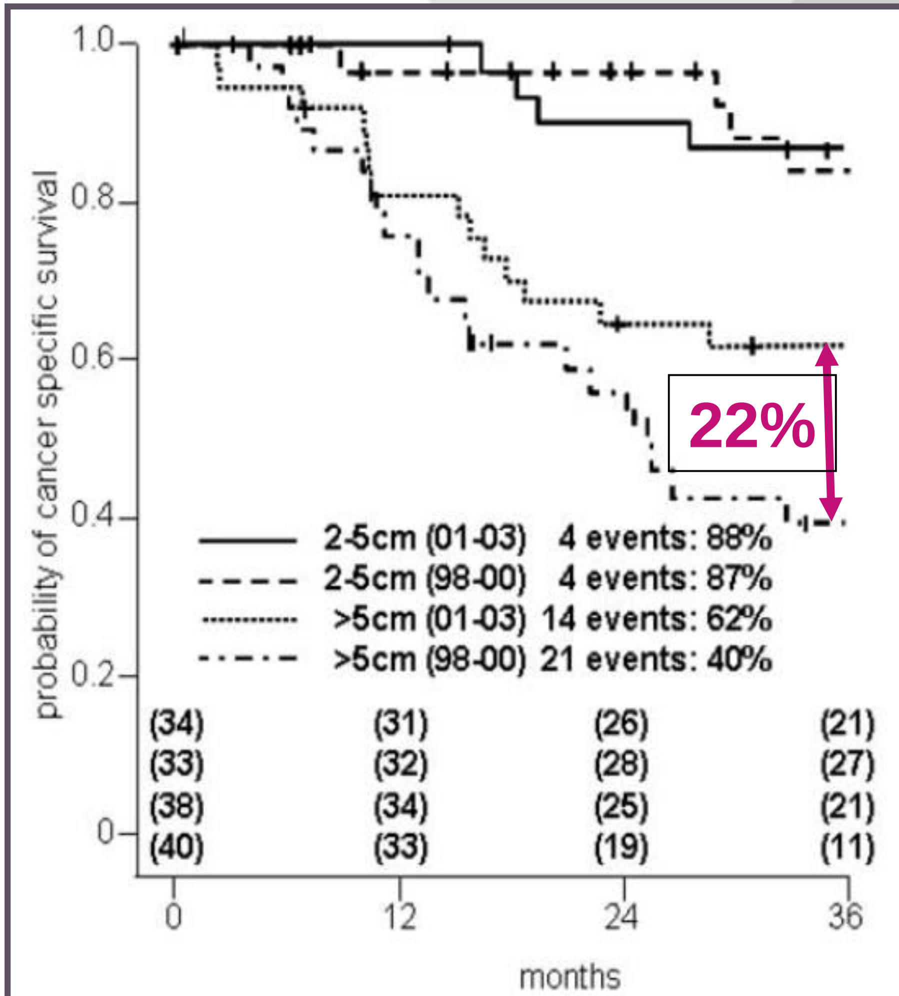
Author	Pt nb	image modal.	BT modal.	Total EQD2 D90 HR-CTV	Local control
Haie-Meder 2010	84	MRI	LDR	79	90%
Beriwal 2011	44	Hybrid	HDR	83	88%
Potter 2011	156	MRI	HDR	93	97%
Mahantshetty 2012	24	MRI	HDR	71	21/24
Lindegaard 2013	140	MRI	PDR	91	90%
Mazeron 2013	163	MRI	PDR	78	95%
Nomden 2013	46	MRI	PDR/HDR	84	93%
Refaat 2013	40	MRI/CT	PDR	±80	90%
Tharavichitkul 2013	47	MRI	HDR	93	98%
Rikjmans 2014	83	MRI	HDR	81	93%
Castelnau 2015	225	MRI	PDR	80	86%
Ribeiro 2016	170	MRI	PDR	85	96%

IGABT cervix

Local control and cancer specific survival (1998-2003)

Treatment period (-/+ IGABT) and tumor size





mean 81 Gy vs. 90 Gy in HR CTV

Pötter R. et al Radiother Oncol 2007

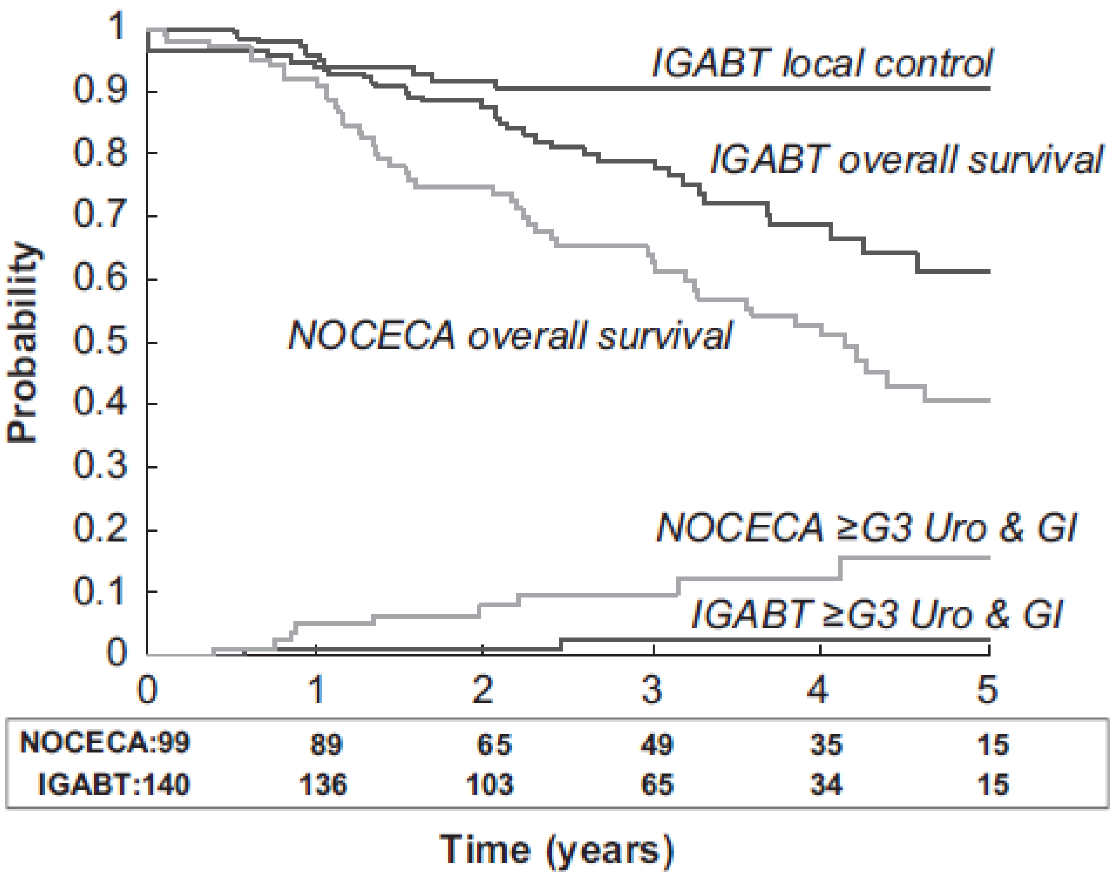


Figure 3. Actuarial local control, overall survival and ≥ grade 3 combined urological-gastrointestinal morbidity in 140 patients treated with IGABT (black lines). For comparison the curves for overall survival and morbidity in 99 patients treated with 2D x-ray-based brachytherapy (NOCECA) are indicated (grey lines). Patient number at risk for overall survival is indicated below the x-axis.

3 y-LC : 90%

3 y-OS :
IGABT/ChTh : 79%
NOCECA : 63%

3 y-morbidity ≥G3 :
10%
3%

Lindegaard et al. Acta Oncologica 2013

Leiden

126 patients:
43 conventional BT
83 IGABT

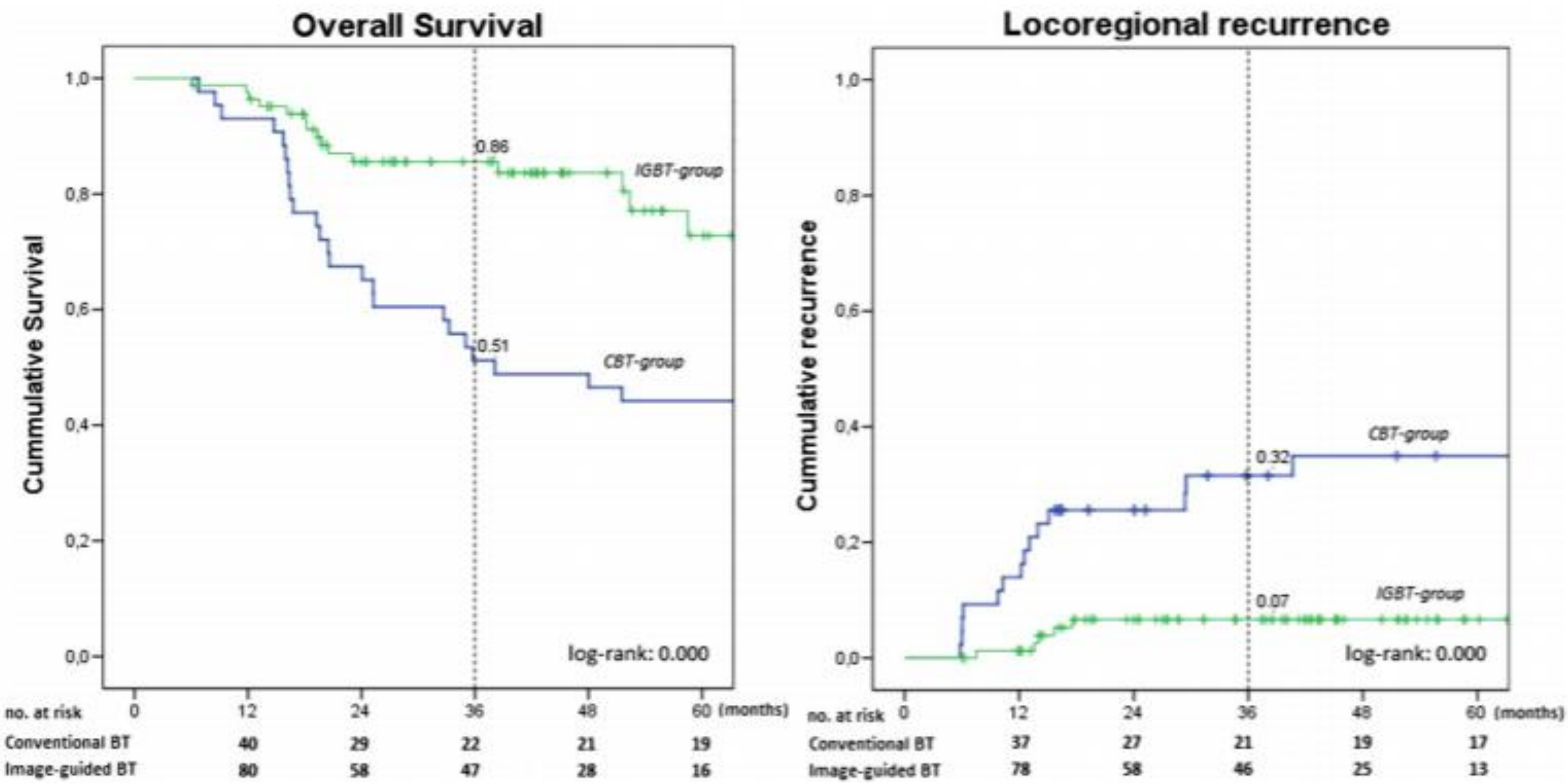


Fig. 1. Overall survival and pelvic recurrence rates by treatment group (CBT vs. IGBT).

Rikjmans et al. Gynecol Oncol 2014

Cervical cancer brachytherapy

Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy

Renaud Mazeron [a,b,*], Pauline Castelnau-Marchand [a], Isabelle Dumas [c], Eleonor Rivin del Campo [a], Léopold Kamsu Kom [a], Florent Martinetti [c], George Farha [a], Anne Tailleur [a], Philippe Morice [d], Cyrus Chargari [a], Dimitri Lefkopoulos [b,c], Christine Haie-Meder [a]

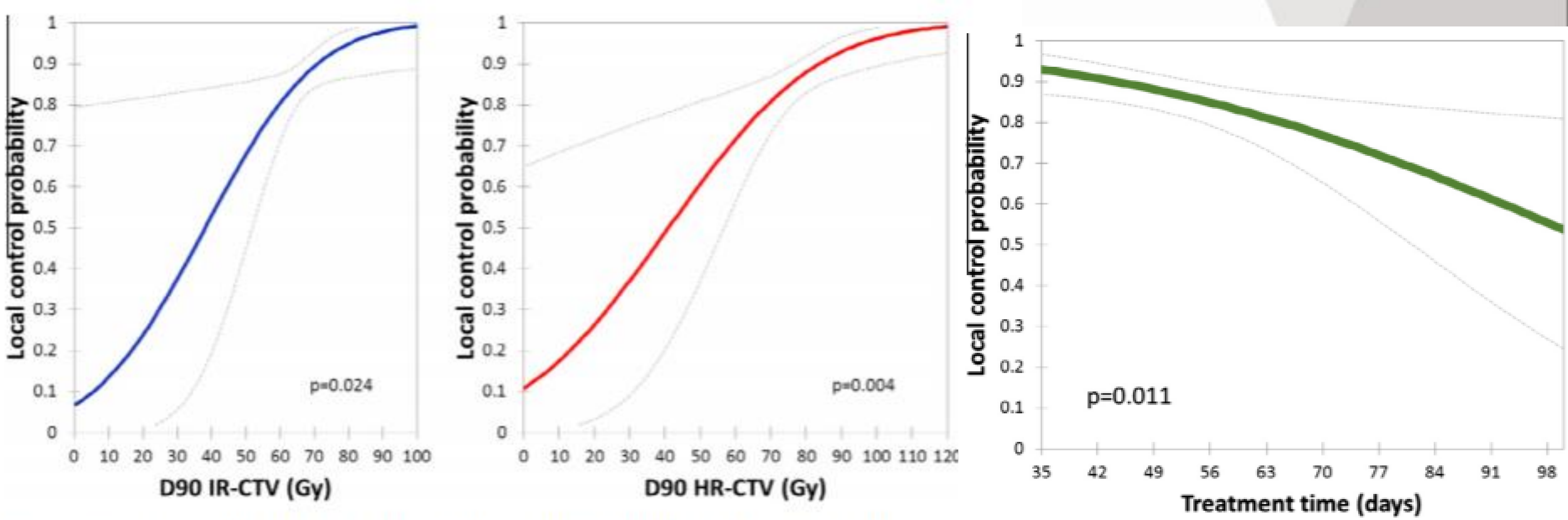


Fig. 2. Dose–response relationships for local control: D90% HR-CTV and D90% IR-CTV Greay dashes: 95% confidence interval.

Cervical cancer brachytherapy

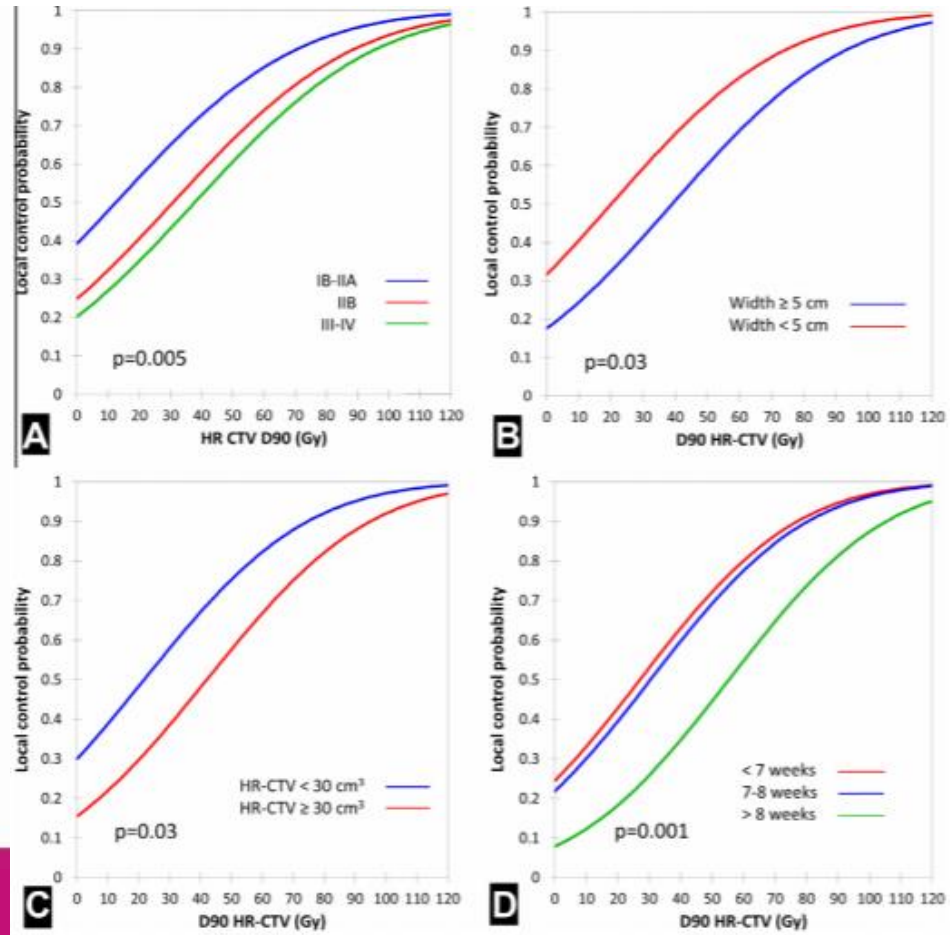
Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy

Renaud Mazeron [a,b,*], Pauline Castelnau-Marchand [a], Isabelle Dumas [c], Eleonor Rivin del Campo [a], Léopold Kamsu Kom [a], Florent Martinetti [c], George Farha [a], Anne Tailleur [a], Philippe Morice [d], Cyrus Chargari [a], Dimitri Lefkopoulos [b,c], Christine Haie-Meder [a]

To achieve a 90% LC probability D90 to HR-CTV should be :

- 71.5 Gy in tumor stage IB–IIA
- 89.7 Gy in IIB
- 97 Gy in III–IV

Based on the HR-CTV volume
92 Gy if volumes ≥ 30 cm3
73.9 Gy if volumes < 30 cm3



Radiother Oncol 2015;114:257–63

Multicenter studies with IGABT in cervix carcinoma

STIC

- Prospective
- 2D vs. 3D (CT)
  - Non random.
  - Availability
- Completed
- 2005-2008
- 20 centers
- 705 pts

- **Def. EBRT+BT**
- Preop BT
- Preop. EBRT+BT

Retro Embrace

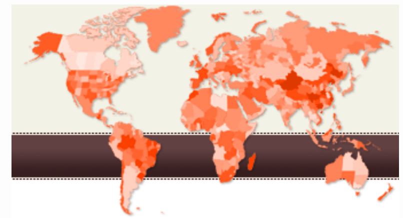
- Retrospective
- Before Embrace

- Completed
- 1998-2012
- 12 centers
- 731 pts

- **Def. EBRT+BT**

Embrace

- Prospective
- Phase IV (MRI)



- Completed
- 2008-2012
- 24 centers
- 1419 pts

- **Def. EBRT+BT**

Radiotherapy and Oncology 103 (2012) 305–313

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journal homepage: www.thegreenjournal.com

Prospective trial in 3D PDR brachytherapy

Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: Results of the French STIC prospective study ☆

Claire Charra-Brunaud [a,*], Valentin Harter [a], Martine Delannes [g], Christine Haie-Meder [c], Philippe Quetin [d], Christine Kerr [e], Bernard Castelain [f], Laurence Thomas [b], Didier Peiffert [a]

Table 1
Comparison of main clinical factors between 2D and 3D arms.

	Group 1 BT followed by surgery		Group 2 EBRT BT surgery		Group 3 EBRT BT		p^*
	2D	3D	2D	3D	2D	3D	
Number of patients	76	89	142	163	118	117	
Mean age	47.6	46.6	49	47.6	56.1	53.4	0.07
Histology							0.08
Squamous cell	50 (66%)	60 (67%)	120 (84%)	123 (75%)	106 (90%)	99 (85%)	
Adenocarcinoma	22 (29%)	26 (29%)	21 (15%)	38 (23%)	12 (10%)	17 (14%)	
Other	4 (5%)	3 (4%)	1 (1%)	2 (2%)	0	1 (1%)	
FIGO stage							0.27
IB1	66 (87%)	83 (93%)	13 (9%)	16 (10%)	6 (5%)	11 (9%)	
IB2 IIA IIB	10 (13%)	6 (7%)	118 (83%)	127 (78%)	70 (59%)	77 (66%)	
IIIA IIIB	0 (0%)	0 (0%)	11 (8%)	20 (12%)	42 (36%)	29 (25%)	
Mean tumor maximal size (mm)	23 ± 9	28 ± 13	46 ± 16	46 ± 14	49 ± 16	48.5 ± 16	0.44
Pelvic node[1]	3 (4%)	2 (2%)	45 (32%)	63 (39%)	52 (44%)	54 (46%)	0.34
LomboAortic node[1]	0	0	16 (11%)	16 (10%)	22 (19%)	17 (15%)	0.33

[1] nodes diagnosed on imagery (CT/MRI/ or PET CT).
[*] 2D–3D brachytherapy comparison: Generalized Estimated Equations adapted for nested analysis.

Prospective trial in 3D PDR brachytherapy

Charra-Brunaud Radiother Oncol 2012;103:305-13

Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: Results of the French STIC prospective study ☆

Claire Charra-Brunaud [a,*], Valentin Harter [a], Martine Delannes [g], Christine Haie-Meder [c], Philippe Quetin [d], Christine Kerr [e], Bernard Castelain [f], Laurence Thomas [b], Didier Peiffert [a]

Clinical results at 2 years

At 24 months	Group 1 (%)		Group 2 (%)		Group 3 (%)		P^*
	2D	3D	2D	3D	2D	3D	
LFRS	91.9	100	84.7	93	73.9	78.5	0.003
RLRFS	87.9	96.1	77.2	88.6	61.2	69.6	0.001
DFS	86.5	89.7	73	77.1	55.2	60.3	0.086
OS	95	96	85	86	65	74	0.27
Grade 3–4 toxicity							
Urinary	5.8	1.3	7.6	5.5	9.2	1.2	0.02
Digestive	6.8	1.2	0.9	4.8	9	0	0.17
Urinary + digestive	9.9	2.5	7.8	9	13.8	1.2	0.027
Gynecologic	5.7	7.5	6.4	2.8	15.4	1.4	0.01
Global	14.6	8.9	12.5	8.8	22.7	2.6	0.002
Grade 2–4 toxicity							
Urinary	13.1	7.9	20.4	13.3	23.1	13.7	0.03
Digestive	8.3	7.4	8.3	8.8	18.7	15.2	0.45
Gynecologic	18.7	12.9	17.9	14.7	35.7	19.4	0.125
Global	37.5	23.2	40.6	29.4	53.4	42.4	0.028

LRFS: local free relapse survival; RLRFS: loco regional relapse free survival; DFS: disease free survival; OS: Overall Survival.

* 2D-3D brachytherapy comparison: Cox proportional hazard model adjusted for regimens.

Original article

Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study

Radiother Oncol 2016;120:428-33

Alina Sturdza [a], Richard Pötter [a,*], Lars Ulrik Fokdal [b], Christine Haie-Meder [c], Li Tee Tan [d], Renaud Mazeron [c], Primoz Petric [e], Barbara Šegedin [e], Ina Maria Jurgenliemk-Schulz [f], Christel Nomden [f], Charles Gillham [g], Orla McArdle [g], Erik Van Limbergen [h], Hilde Janssen [h], Peter Hoskin [i], Gerry Lowe [i], Ekkasit Tharavichitkul [j], Elena Villafranca [k], Umesh Mahantshetty [l], Petra Georg [a], Kathrin Kirchheiner [a], Christian Kirisits [a], Kari Tanderup [b], Jacob Christian Lindegaard [b]

Image guided brachytherapy in cervical cancer

Radiother Oncol 2016;120:434–40

Image guided adaptive brachytherapy with combined intracavitary and interstitial technique improves the therapeutic ratio in locally advanced cervical cancer: Analysis from the retroEMBRACE study

CrossMark

Lars Fokdal [a,*], Alina Sturdza [b], Renaud Mazeron [c], Christine Haie-Meder [c], Li Tee Tan [d], Charles Gillham [e], Barbara Šegedin [f], Ina Jürgenliemk-Schultz [g], Christian Kirisits [b], Peter Hoskin [h], Richard Pötter [b], Jacob C. Lindegaard [a], Kari Tanderup [a]

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

Radiother Oncol 2016;120:441–46

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

RetroEMBRACE outcome data

- **Primary Objective: Local control in IGABT within multi-institutional frame prior to EMBRACE study**

- **12 institutions participating January 1998 - August 2012**
  - 852 patients included, 49 excluded for unknown disease status and 72 excluded due to adjuvant therapy, **731** analyzed

- **2 IA (0.3%), 123 IB (16.8%), 42 IIA (5.7%), 368 IIB (50.3%), 23 IIIA (3.1%), 145 IIIB (19.8%), 23 stage IVA (3.1%), 5 IVB (0.7%)**

- **Median width at diagnosis: 50 mm clinical, 46 mm at MRI examination**

- **Nodal status : N+ 40%, N- 60%**

RetroEMBRACE outcome data

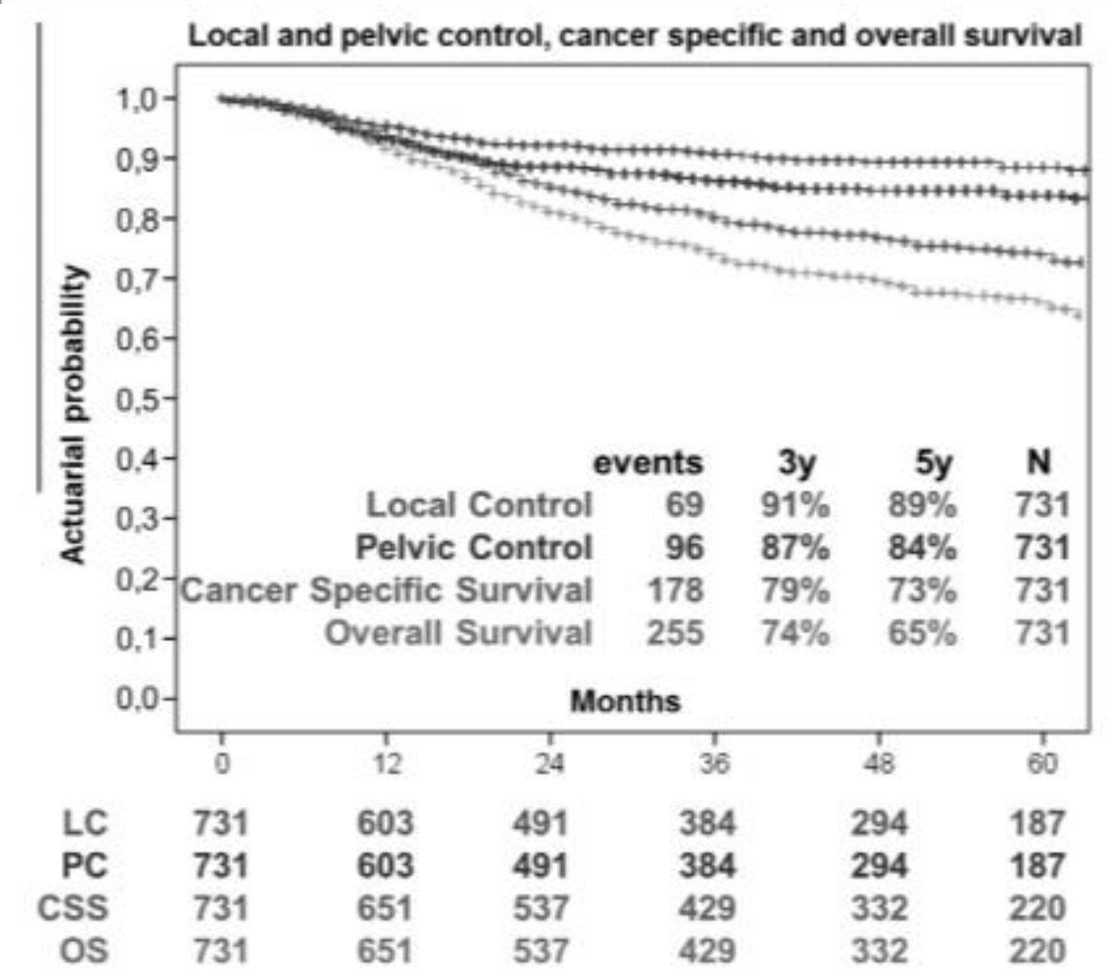


Fig. 1. Actuarial Kaplan–Meyer estimates for local control (LC), pelvic control (PC), cancer specific survival (CSS) and overall survival (OS) in 731 patients. Absolute number of events and actuarial estimates for outcome at 3 and 5 years are indicated.

Mean HR-CTV volume : 37 ± 24 cm3

Mean D90 (EQD210) :
HR-CTV 87 ± 15 Gy
IR-CTV 69 ± 8 Gy

Mean D90 HR-CTV
Stage I 93 ± 17 Gy
Stage IIB 88 ± 14 Gy
Stage IIIB 83 ± 13 Gy

Sturdza Radiother Oncol 2016;120:428-33

RetroEMBRACE outcome data

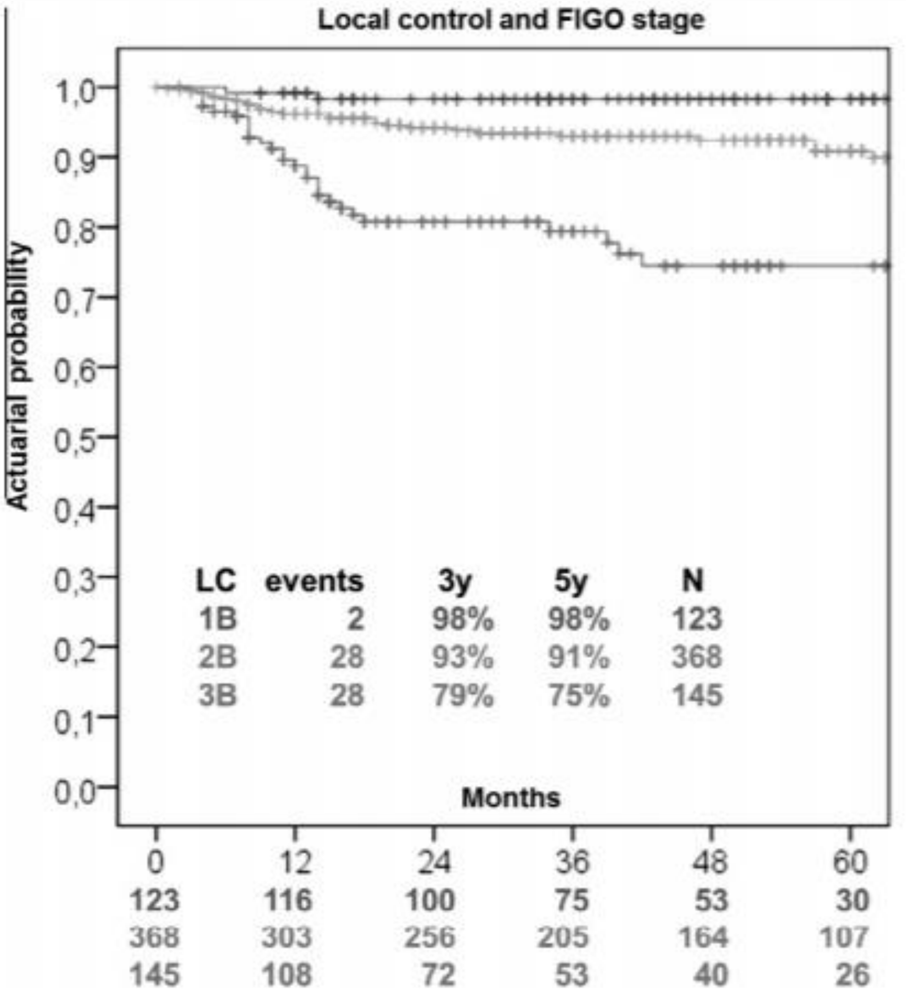


Fig. 2. Actuarial Kaplan–Meier estimates for stage related local control (LC) in patients with stage IB, IIB, IIIB disease (*n* = 636). Absolute number of events and actuarial estimates for outcome at 3 and 5 years are indicated.

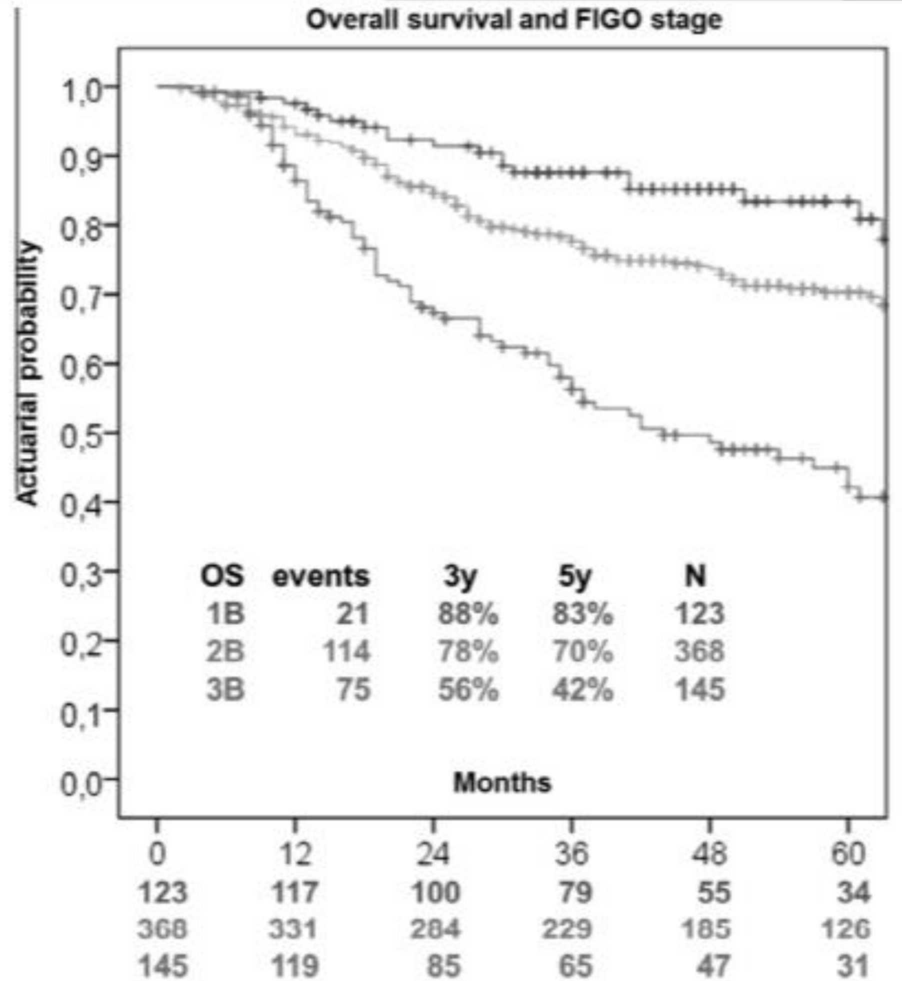


Fig. 4. Actuarial Kaplan–Meier estimates for stage related overall survival (OS) in patients with stage IB, IIB, IIIB disease (*n* = 636). Absolute number of events and actuarial estimates for outcome at 3 and 5 years are indicated.

RetroEMBRACE outcome data

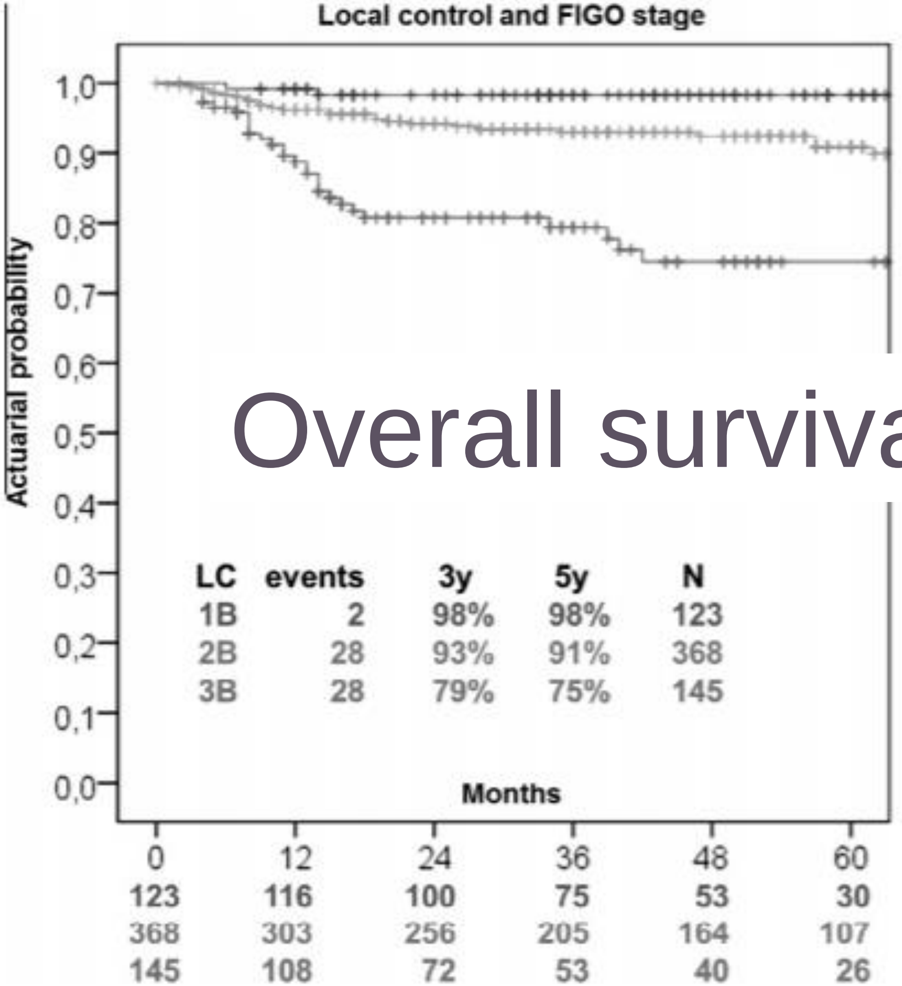


Fig. 2. Actuarial Kaplan–Meier estimates for stage related local control (LC) in patients with stage IB, IIB, IIIB disease ($n = 636$). Absolute number of events and actuarial estimates for outcome at 3 and 5 years are indicated.

Overall survival benefit of 10%

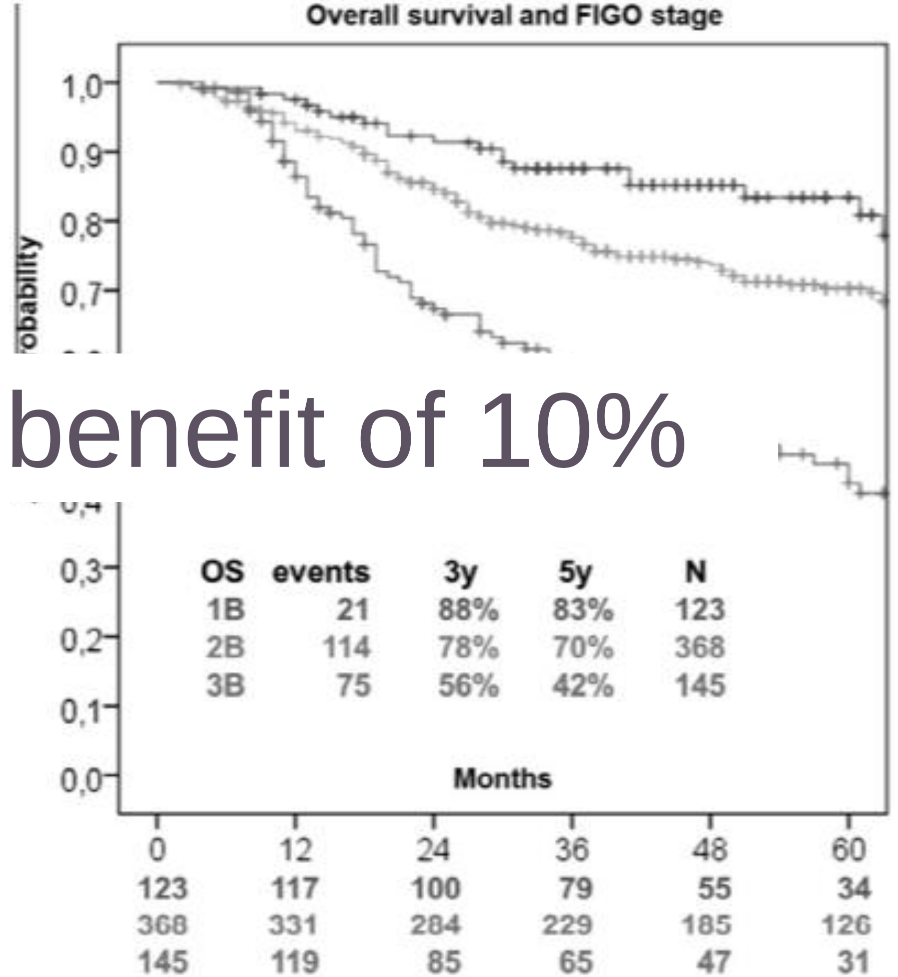


Fig. 4. Actuarial Kaplan–Meier estimates for stage related overall survival (OS) in patients with stage IB, IIB, IIIB disease ($n = 636$). Absolute number of events and actuarial estimates for outcome at 3 and 5 years are indicated.

RetroEMBRACE role of interstitial BT

610 patients with LACC retroEMBRACE study :
IC group N = 310
IC/IS group N = 300

Table 1
Patient characteristics.

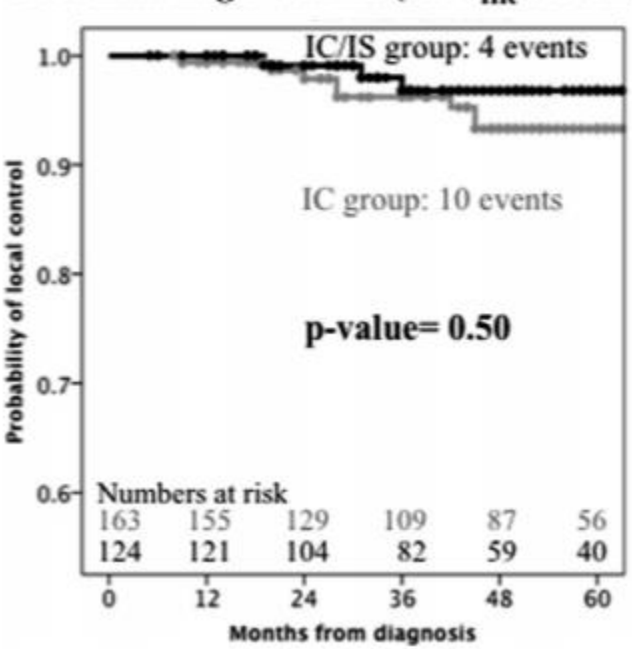
Variable		IC/IS group ($N = 300$)	IC group ($N = 310$)	*P*-value
Median age (years)		56 (23–89)	53 (24–91)	0.01
FIGO stage	IB	18%	19%	0.40
	2A	6%	7%	
	2B	48%	49%	
	3A	3%	4%	
	3B	21%	17%	
	4A + 4B	4%	4%	
Tumour width	Clinical	51 (20–100)	49 (10–100)	0.11
Staging with laparoscopy		28%	24%	0.25
Lymph nodes	Pelvic	42%	42%	0.36
	PAN	4%	10%	0.02
	Groin	2%	3%	0.60
Histology	SQCC	86%	83%	0.39
	AC + other	14%	17%	
Follow up (Months)		40 (3–163)	41 (3–138)	0.80

RetroEMBRACE role of interstitial BT

Table 3
Dose volume parameters in all patients and in the intracavitary/interstitial group or intracavitary group.

Variable doses in Gy	All patients (*N* = 610)	IC/IS group (*N* = 300)	IC group (*N* = 310)	*p*-Value
Volume HR CTV	36 ± 24	39 ± 25	33 ± 24	<0.01
HR CTV D90	88 ± 14	92 ± 13	83 ± 14	<0.01
D2CC Bladder	81 ± 22	79 ± 12	83 ± 29	0.07
D2CC Rectum	64 ± 8	65 ± 7	64 ± 10	0.12
ICRU Rectum	69 ± 13	69 ± 9	69 ± 15	0.84
D2CC Sigmoid	65 ± 10	65 ± 7	66 ± 12	0.38

2C. Small target volume (CTV_{HR}<30 cm^3)



Fokdal
Radiother Oncol
2016;120:434-40

2B. Large target volume (CTV_{HR}≥30 cm^3)

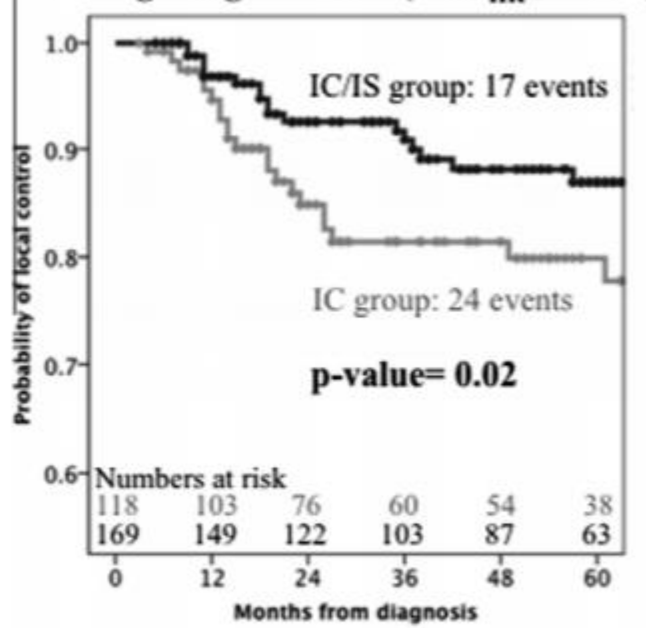


Table 2
Local failures (crude percentage) are listed according to stage, as well as CTV_{HR} volume and total $EQD2_{10}$ (EBRT + BT) doses for CTV_{HR}, GTV and CTV_{IR} (mean and standard deviation).

Stage	# local failures/# pts	% local failures	CTV_{HR} volume 488 pts	CTV_{HR} D90 488 pts	GTV D100 267 pts	CTV_{IR} D90 353 pts
All stages	43/488	8.8%	36 ± 22 cm³	86 ± 12 Gy	92 ± 19 Gy	68 ± 7 Gy
IB	1/67	1.5%	25 ± 15 cm³	89 ± 13 Gy	101 ± 27 Gy	71 ± 7 Gy
IIA + IIB	21/280	7.5%	33 ± 19 cm³	87 ± 11 Gy	93 ± 18 Gy	69 ± 6 Gy
IIIA + IIIB + IV	21/141	14.9%	47 ± 27 cm³	83 ± 12 Gy	88 ± 18 Gy	66 ± 7 Gy

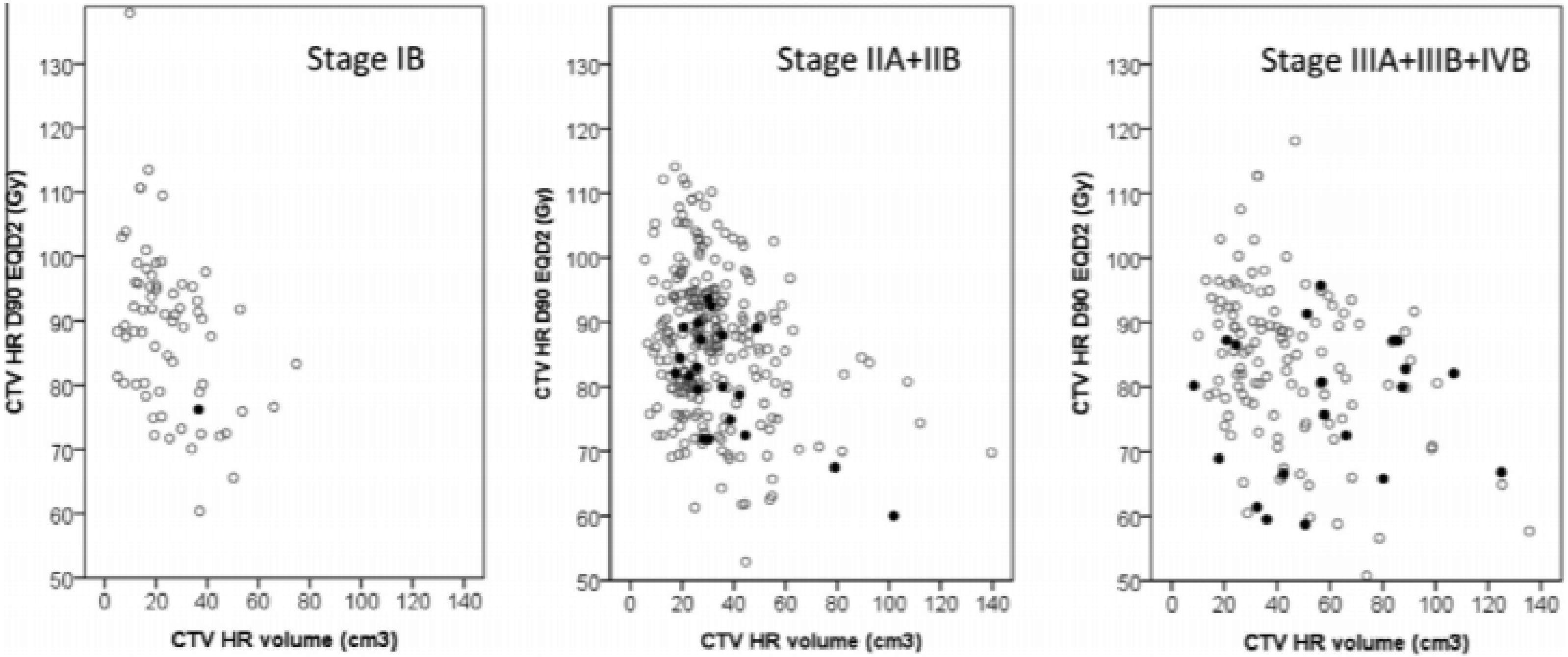


Fig. 1. Distribution of local failures according to stage as a function of CTV_{HR} volume and dose (D90). Patients with local control are indicated with open circles. Patients with local failure are indicated with filled circles.

Demonstration of clinical evidence for dose effect for CTVHR

3-year local control rates D90 CTVHR dose ≥85 Gy in 7 weeks:

- >94% in limited size CTVHR (20 cm3)
- >93% in intermediate size CTV HR (30 cm3)
- >86% in large size CTVHR (70 cm3)

Doses of 90–95 Gy add 1–4% to local control

An increase of OTT by one week is equivalent to de-escalating CTVHR dose by 5 Gy

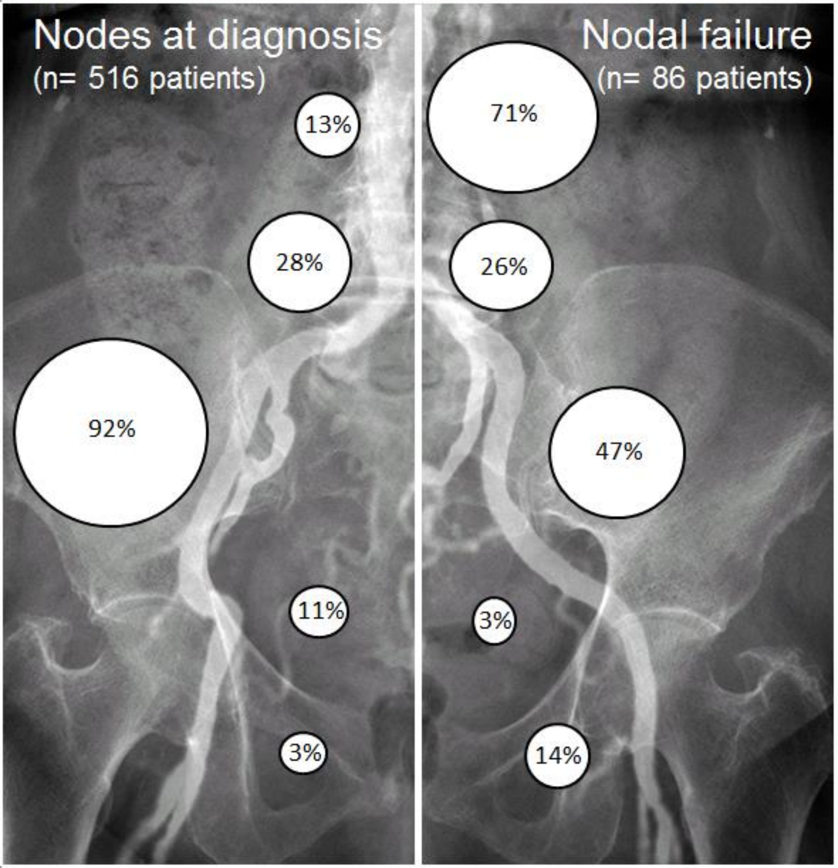
An increased CTVHR volume by 10 cm3 requires an additional 5 Gy for equivalent local control.

Tanderup Radiother Oncol 2016;120:441–46

Nodal Recurrence

EMBRACE and RetroEMBRACE

EMBRACE cohort 1077 patients:



RetroEMBRACE cohort

296/731 N+ at diagnosis (40%)

nodal recurrence: overall 86/1077 (8%)

Nomden et al. under submission

IGABT: main carcinologic event : metastasis

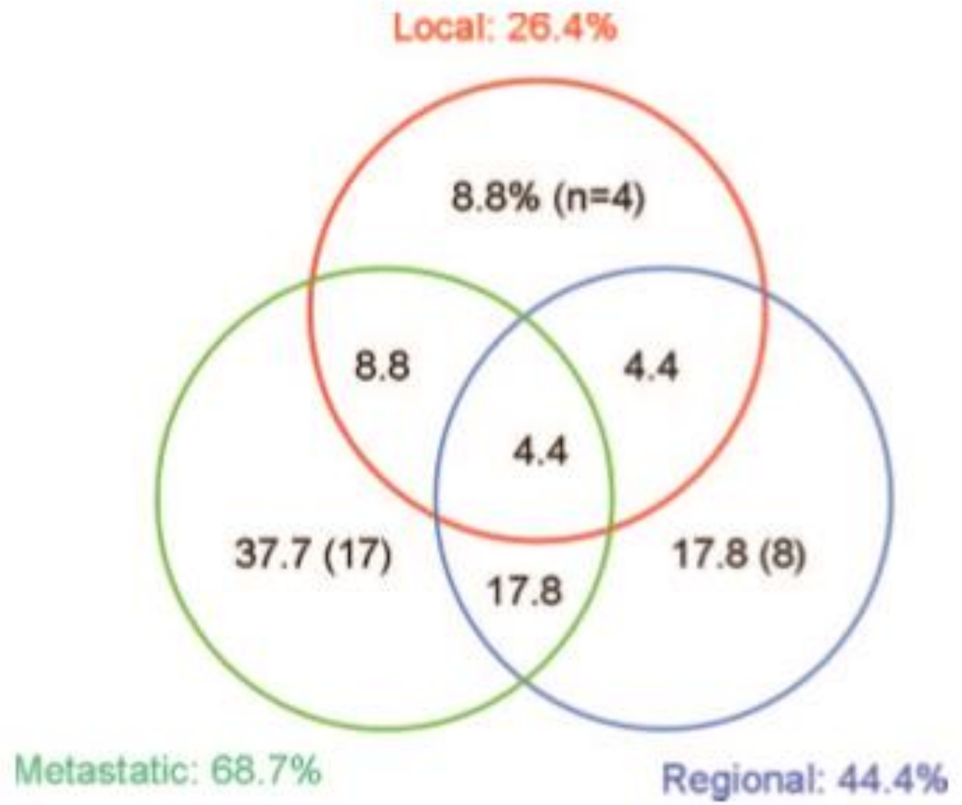


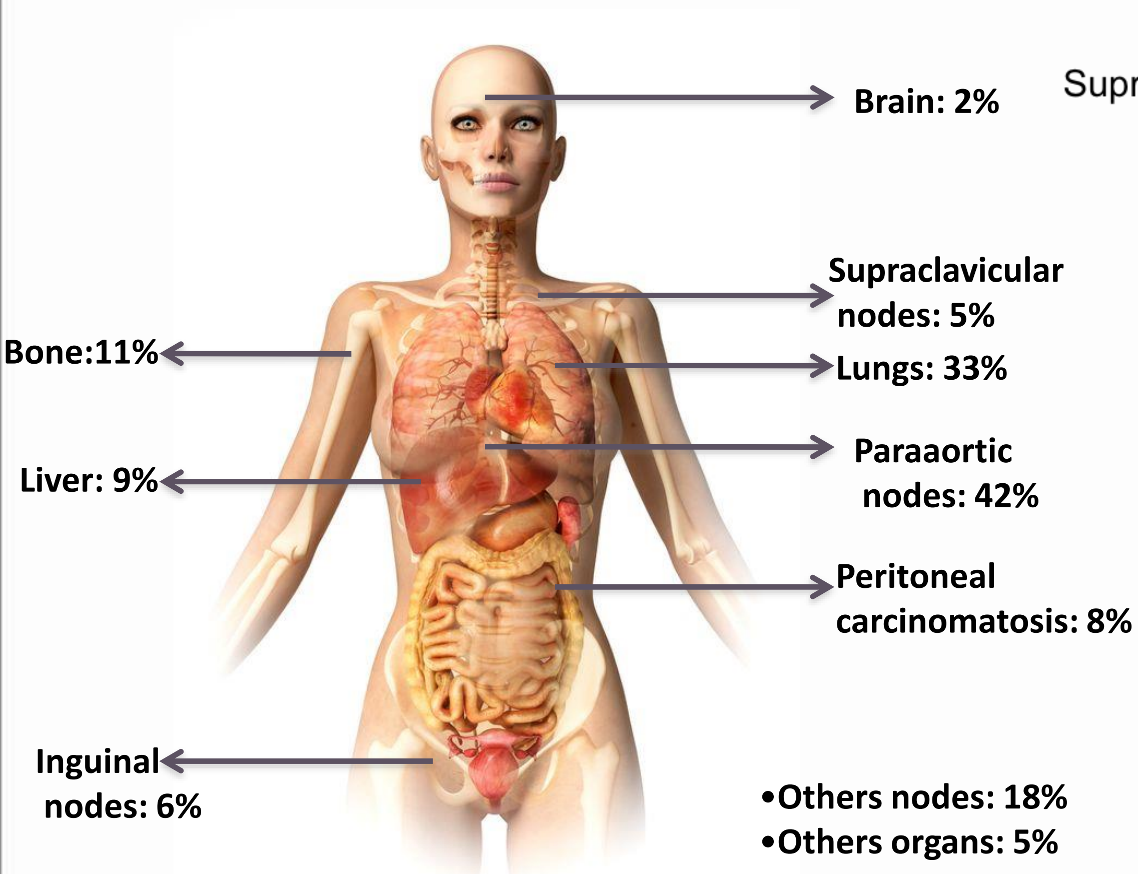
Figure 1. Pattern of relapses.

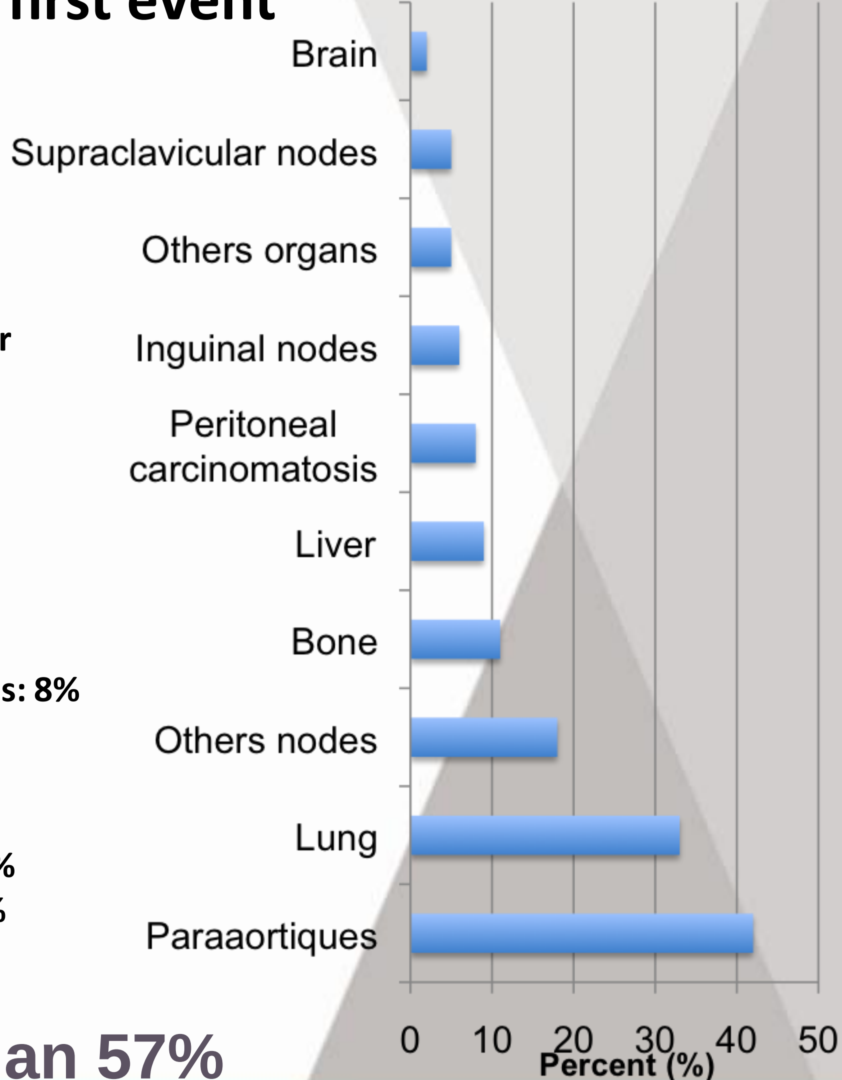
Mazeron et al. The Oncologist 2013

Systemic (distant) recurrence analysis (EMBRACE data, 133 events in 753 patients)

EMBRACE

Systemic recurrences at first event





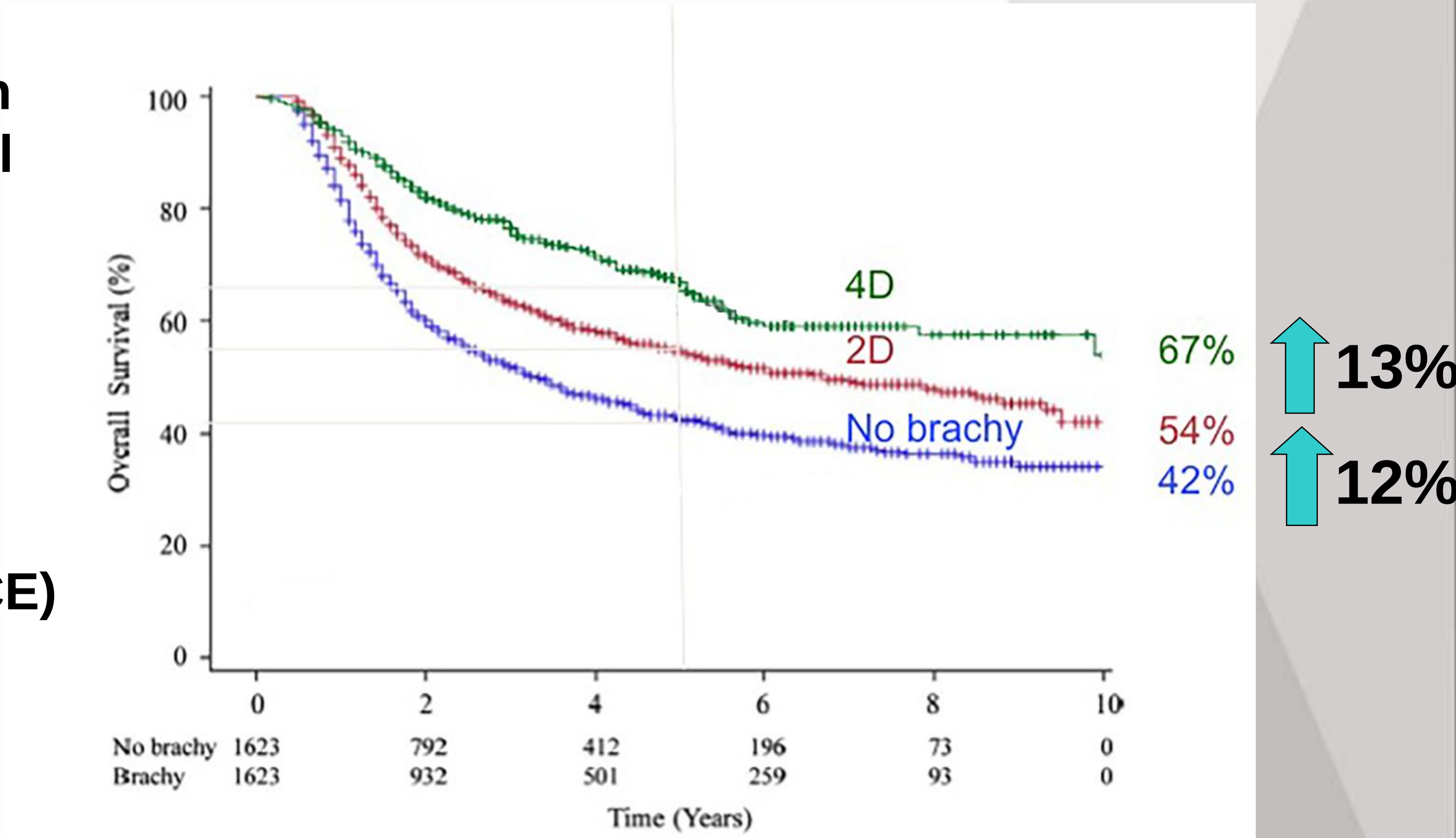
Major lymph node component in distant recurrence: LN 64%, organ 57%

Fortin et al. ASTRO 2015

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 Oncology 2016mitted

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 46

2016 Research Paper

Neutrophilia in locally advanced cervical cancer: A novel biomarker for image-guided adaptive brachytherapy?

Alexandre Escande[1], Christine Haie-Meder[1], Pierre Maroun[1,2], Sébastien Gouy[3], Renaud Mazeron[1], Thomas Leroy[4], Enrica Bentivegna[3], Philippe Morice[2,3,5], Eric Deutsch[1,2,5], Cyrus Chargari[1,2,5,6,7]

113 patients advanced cervical cancer treated with chemoradiotherapy and IGABT

Prognostic factors for local failure-free survival :

Univariate analysis :

- pre-treatment neutrophilia ($p < 0.001$) & leukocytosis ($p = 0.002$)
- tumor size ($p = 0.003$)
- HR-CTV volume ($p = 0.003$)
- anemia ($p = 0.036$)

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 46

2016 Research Paper

Neutrophilia in locally advanced cervical cancer: A novel biomarker for image-guided adaptive brachytherapy?

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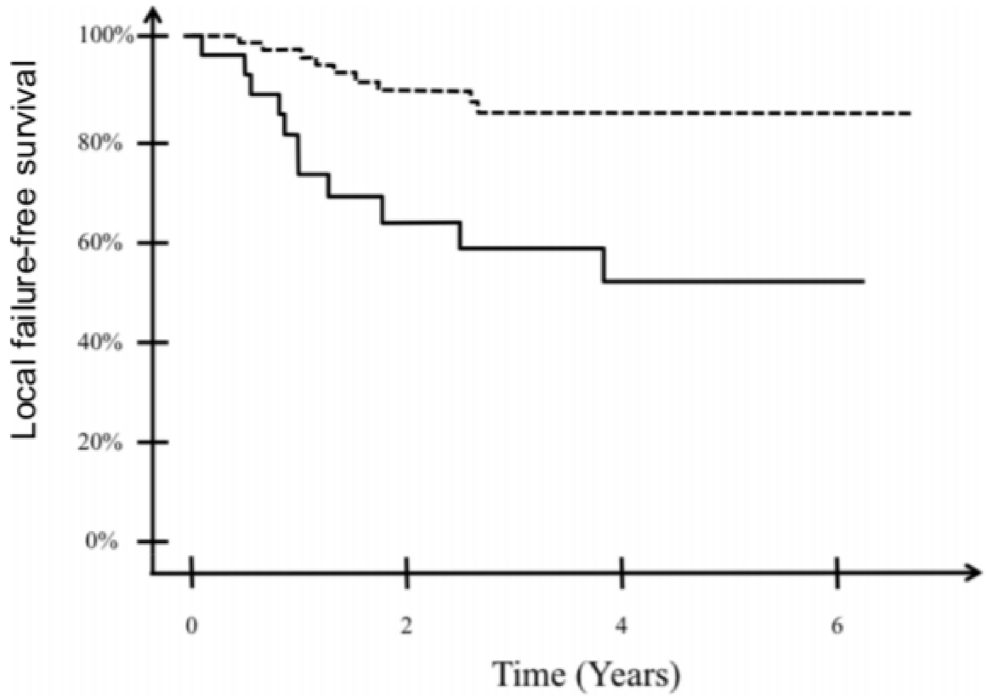

Dotted line for patients with PNN < 7,500/µl

Full line for patients with PNN ≥ 7,500/µl

Figure 1: Estimated survival without local failure in patients with or without neutrophilia.

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 46

2016 Research Paper

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Multivariate analysis

Variable	Local Failure-Free Survival	
	Log-rank	Cox model (HR)
FIGO III-IV	0.669	--
Tumor > 5 cm	0.003	0.383
Pelvic LN	0.914	--
HR-CTV > 25 cc	0.003	**0.026 (3.1)**
Neutrophilia[a] > 7,500/µl	0.000	**0.018 (3.1)**
Leucocytosis[a]	0.002	0.287
Anemia	0.036	0.177

Clinical Outcome IGABT : Toxicities

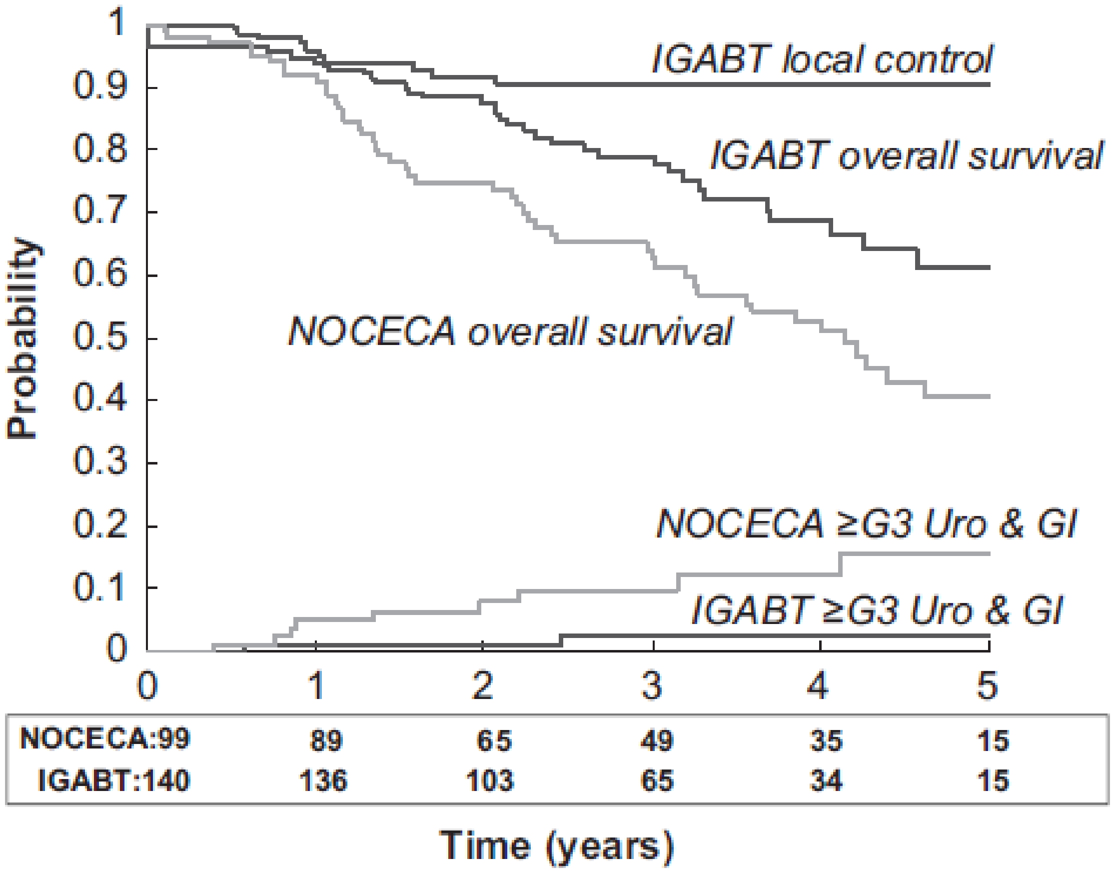


Figure 3. Actuarial local control, overall survival and ≥ grade 3 combined urological-gastrointestinal morbidity in 140 patients treated with IGABT (black lines). For comparison the curves for overall survival and morbidity in 99 patients treated with 2D x-ray-based brachytherapy (NOCECA) are indicated (grey lines). Patient number at risk for overall survival is indicated below the x-axis.

3 y-LC : 90%

3 y-OS :
IGABT/ChTh : 79%
NOCECA : 63%

3 y-Morbidity ≥G3 :
10%
3%

Lindegaard et al. Acta Oncologica 2013

Cervical brachytherapy

Pulsed-dose rate image-guided adaptive brachytherapy in cervical cancer: Dose–volume effect relationships for the rectum and bladder

Renaud Mazeron [a,b,*], Pierre Maroun [a], Pauline Castelnau-Marchand [a], Isabelle Dumas [c], Eleonor Rivin del Campo [a], Kim Cao [a], Andrea Slocker-Escarpa [a], Rodrigue M'Bagui [a], Florent Martinetti [c], Anne Tailleur [a], Alain Guemnie-Tafo [c], Philippe Morice [d], Cyrus Chargari [a,b], Dimitri Lefkopoulos [b,c], Christine Haie-Meder [a]

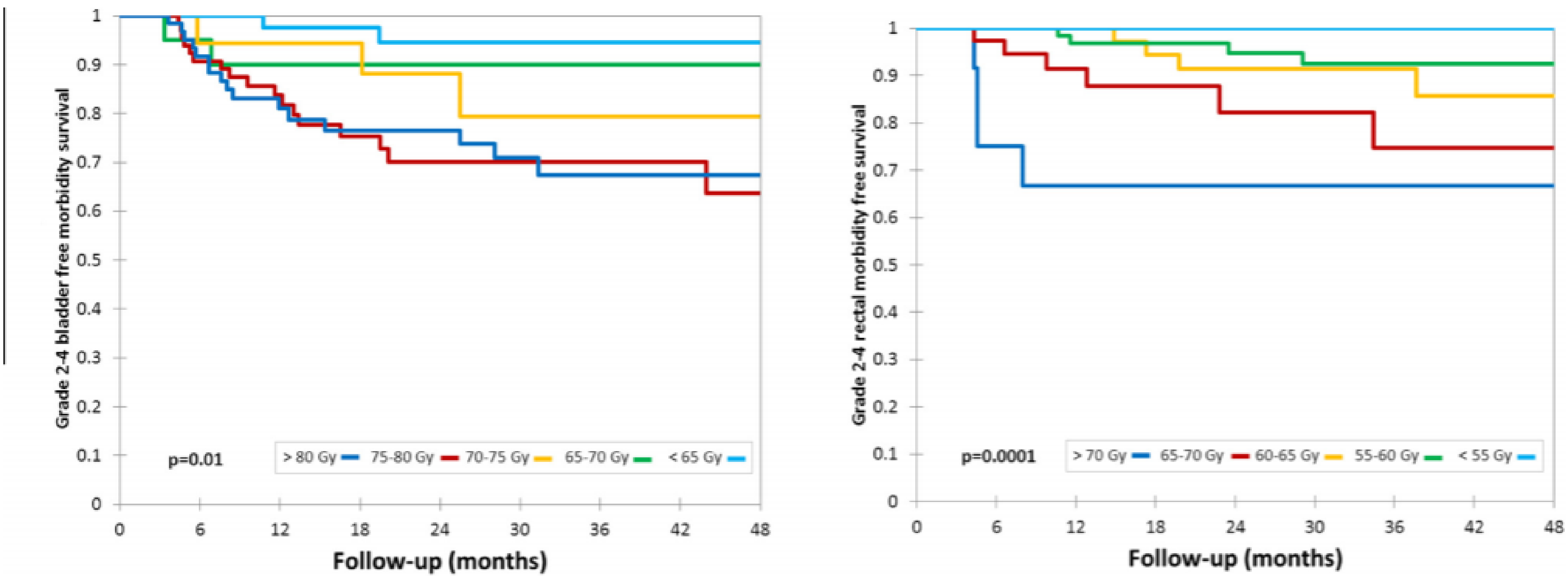
Table 2
Dosimetric parameters according to grade.

		N (%)	D0.1 cm^3 (Gy)		D2 cm^3 (Gy)	
			Mean ± SD	p^*	Mean ± SD	p^*
Bladder	Grade 0	119 (54.8)	83.9 ± 18.3	0.009	68.3 ± 8.7	0.006
	Grade 1	56 (25.8)	84.0 ± 17.1		67.3 ± 7.9	
	Grade 2	34 (15.7)	90.6 ± 18.7		71.1 ± 8.6	
	Grade 3	8 (3.7)	99.8 ± 23.3		76.3 ± 9.1	
Rectum	Grade 0	166 (76.5)	68.0 ± 11.0	0.360	59.3 ± 6.3	0.072
	Grade 1	36 (16.6)	69.5 ± 12.3		60.5 ± 6.9	
	Grade 2	13 (6.0)	74.2 ± 17.4		63.9 ± 7.4	
	Grade 3	2 (0.9)	84.8 ± 21.5		70.0 ± 10.9	

N: number of patients, SD: standard deviation.
* Kruskal–Wallis test.

225 patients treated with PDR IGABT

Consistent improvements of morbidity outcomes for D2 cm3 <75 Gy for the bladder and <65 Gy for the rectum



> 80 Gy	21	14	11	4	2
75-80 Gy	18	17	13	6	3
70-75 Gy	43	36	26	16	4
65-70 Gy	69	63	48	33	21
< 65 Gy	66	61	49	31	26

> 70 Gy	13	13	11	6	3
65-70 Gy	36	28	22	11	10
60-65 Gy	42	37	24	16	11
55-60 Gy	70	63	51	34	20
< 55 Gy	56	50	39	28	14

Fig. 3. Grade 2–4 morbidity free survivals according to D2 cm^3 levels.

Mazeron et al. Radiother Oncol 2015

Prospective trial in 3D PDR brachytherapy

Charra-Brunaud Radiother Oncol 2012;103:305-13

Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: Results of the French STIC prospective study ☆

Claire Charra-Brunaud [a,*], Valentin Harter [a], Martine Delannes [g], Christine Haie-Meder [c], Philippe Quetin [d], Christine Kerr [e], Bernard Castelain [f], Laurence Thomas [b], Didier Peiffert [a]

Clinical results at 2 years

50% reduction of grade 3-4 morbidity with IGABT

At 24 months	Group 1 (%)		Group 2 (%)		Group 3 (%)		P*
LFRS							0.003
RLRFS							0.001
DFS							0.086
OS							0.27
Grade 3–4 to							
Urinary	5.8	1.3	7.6	5.5	9.2	1.2	0.02
Digestive	6.8	1.2	0.9	4.8	9	0	0.17
Urinary + digestive	9.9	2.5	7.8	9	13.8	1.2	0.027
Gynecologic	5.7	7.5	6.4	2.8	15.4	1.4	0.01
Global	14.6	8.9	12.5	8.8	22.7	2.6	0.002
Grade 2–4 toxicity							
Urinary	13.1	7.9	20.4	13.3	23.1	13.7	0.03
Digestive	8.3	7.4	8.3	8.8	18.7	15.2	0.45
Gynecologic	18.7	12.9	17.9	14.7	35.7	19.4	0.125
Global	37.5	23.2	40.6	29.4	53.4	42.4	0.028

LRFS: local free relapse survival; RLRFS: loco regional relapse free survival; DFS: disease free survival; OS: Overall Survival.

* 2D-3D brachytherapy comparison: Cox proportional hazard model adjusted for regimens.

No significant difference in late actuarial grade 2–5 or grade 3–5 bladder or GI
Trend of higher actuarial grade 3–5 vaginal morbidity in the IC/IS group (p = 0.08)

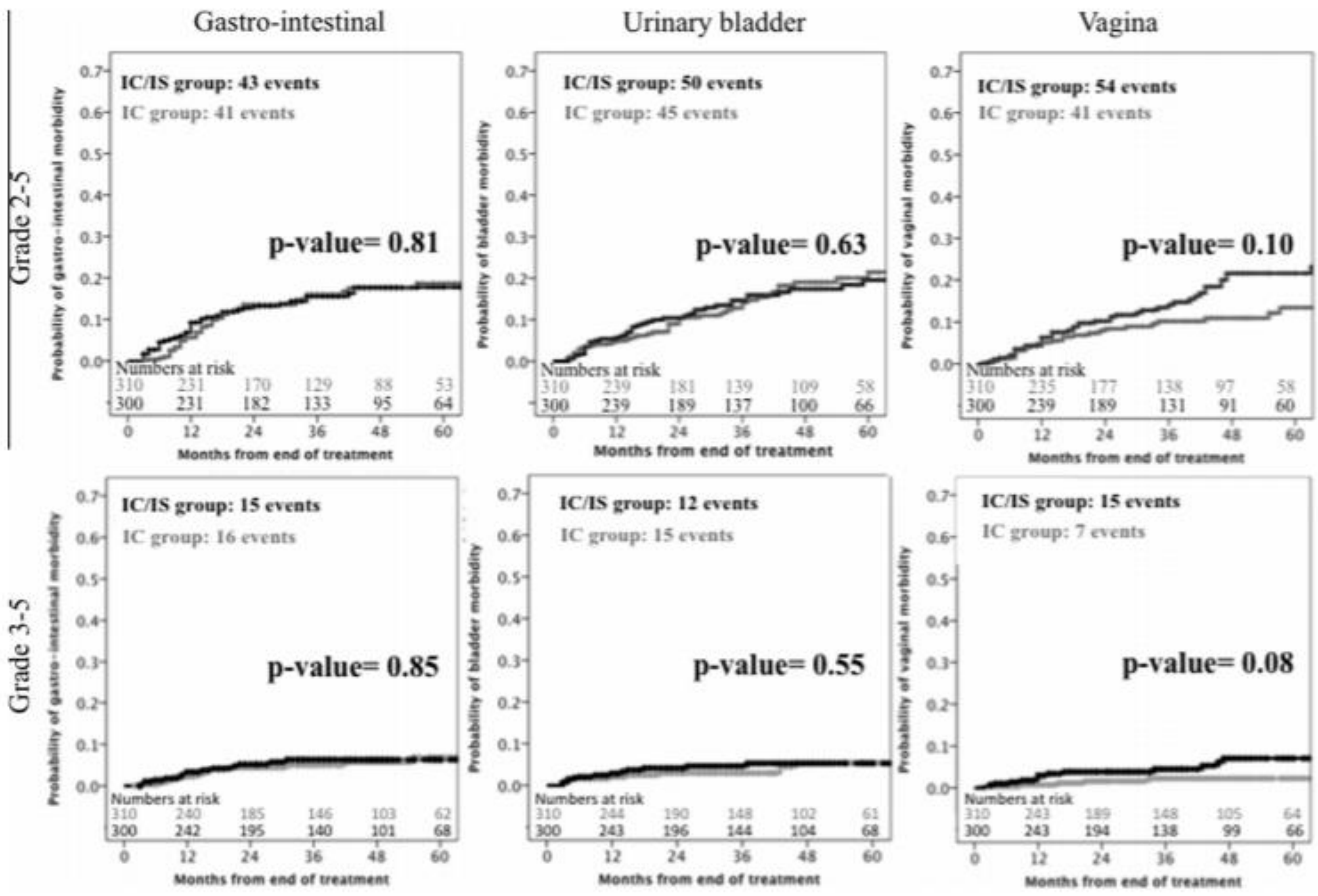


Fig. 3. Late morbidity in the intracavitary group in dark grey and combined intracavitary/interstitial group in black.

Fokdal Radiother Oncol 2016;120:434-40

Dose–volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study ☆

Renaud Mazeron [a,*], Lars U. Fokdal [b], Kathrin Kirchheiner [c], Petra Georg [c], Noha Jastaniyah [c], Barbara Šegedin [d], Umesh Mahantshetty [e], Peter Hoskin [f], Ina Jürgenliemk-Schulz [g], Christian Kirisits [c], Jacob C. Lindegaard [b], Wolfgang Dörr [c], Christine Haie-Meder [a], Kari Tanderup [b], Richard Pötter [c], on behalf of the EMBRACE collaborative group[1]

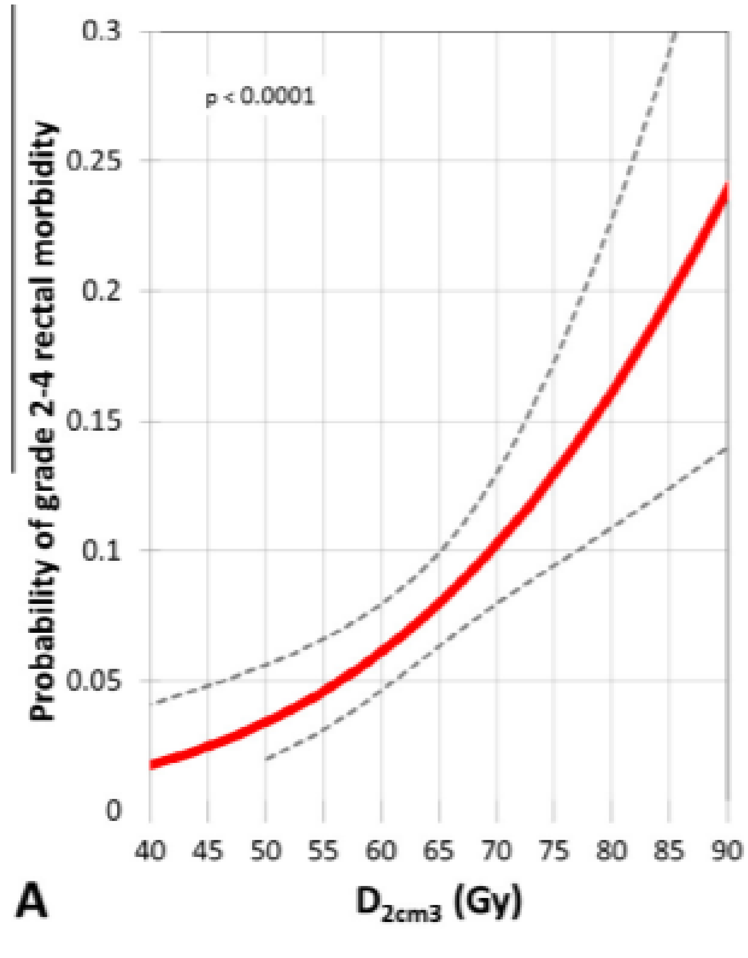
960 patients Median FU : 25,4 months

Depiction of rectal morbidity.

	Proctitis		Bleeding		Stenosis		Fistula		All	
	N	%	N	%	N	%	N	%	N	%
Grade 0	782	81.5	805	83.8	949	98.9	951	99.1	694	72.3
Grade 1	135	14.1	114	12.0	5	0.5	0	0	193	20.1
Grade2	39	4.1	31	3.2	6	0.6	5	0.5	58	6.0
Grade 3	4	0.4	10	1.0	0	0	3	0.3	14	1.6
Grade 4	0	0	0	0	0	0	1	0.1	1	0.1

N: number, %: percentage of the series.

Actuarial estimate evaluation of overall rectal morbidity at 3 years
D2cm3 ≥75Gy risk of 30% of grade 2–4
D2cm3 ≤65 Gy risk of <10% of grade 2-4



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

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

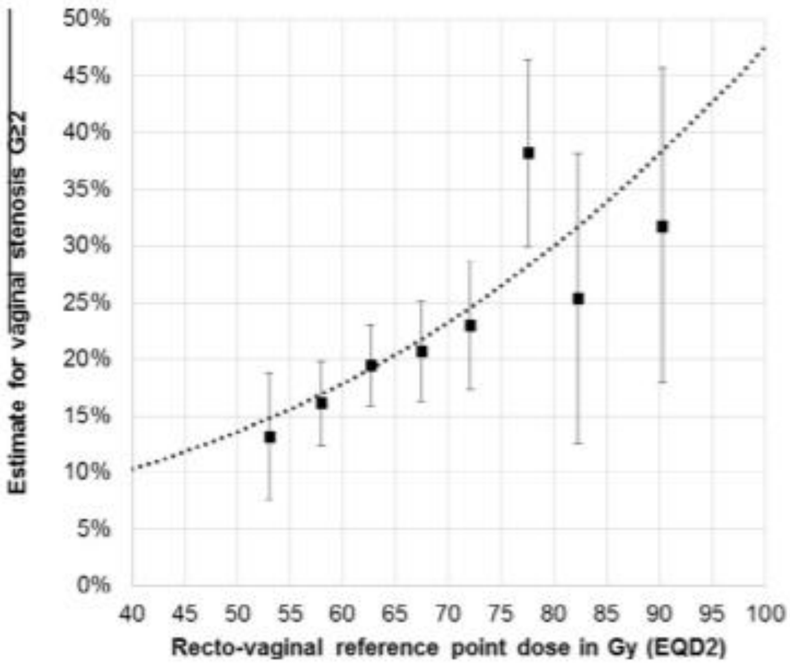


Fig. 4. Dose–effect relationship of the combined EBRT and brachytherapy dose to recto-vaginal reference point in EQD2 and vaginal stenosis $G \geq 2$ in $N = 630$ patients.

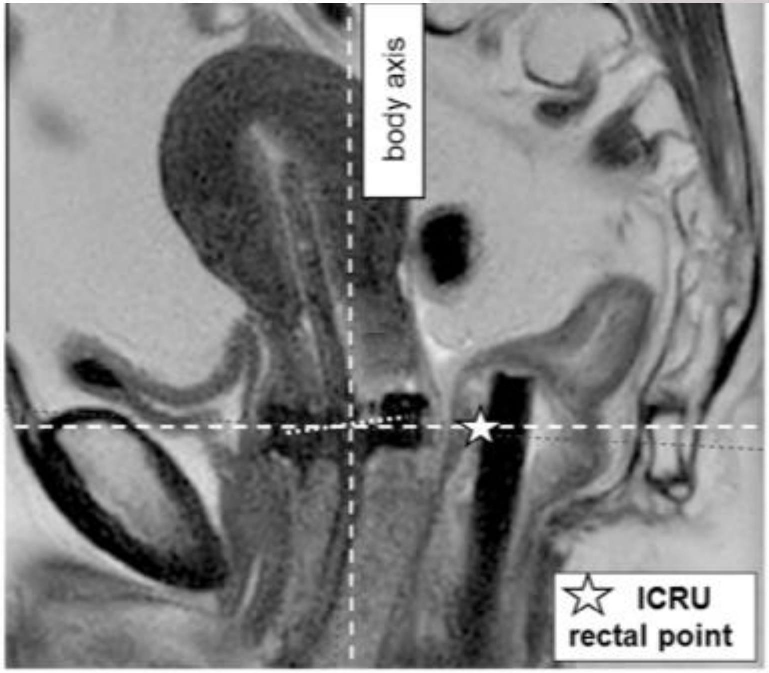


Fig. 1. ICRU rectal point depicted on sagittal T2 MRI, positioned at the intersection level between tandem and the source positions in the ring and 5 mm dorsal of the posterior vaginal wall on the axis perpendicular to the body axis.

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

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Recommendations:

- ERT dose not exceeding 45Gy
- Planning aim ≤65 Gy EQD2 ICRU recto-vaginal point

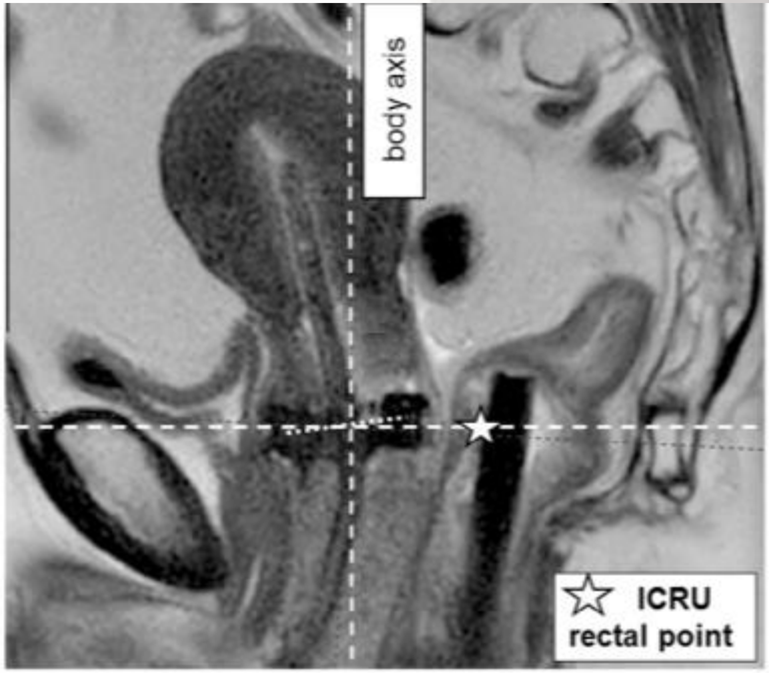


Fig. 1. ICRU rectal point depicted on sagittal T2 MRI, positioned at the intersection level between tandem and the source positions in the ring and 5 mm dorsal of the posterior vaginal wall on the axis perpendicular to the body axis.

Kircheiner et al. Radiother Oncol 2016

Summary

Improvement of results with IGABT
Overall treatment time <50 days

Dose escalation for advanced disease HR CTV (LC, OS)

Para-aortic lymph node issue

Systematic concomitant radiochemotherapy min. 5 cycles

Testing Dose/Volume constraints for Target and OARs

Biological investigations (radiomics, immunotherapy)

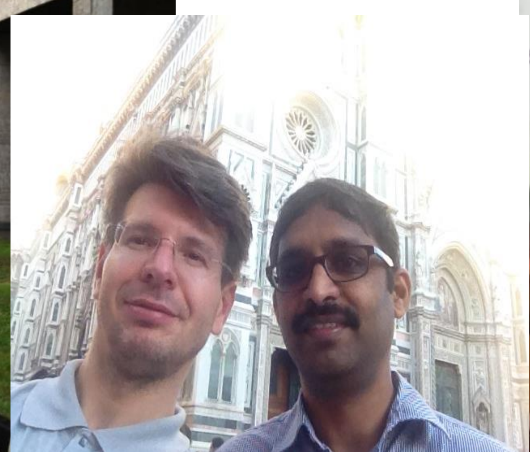
2ND AROI - ESTRO GYN Teaching Course -2018

Tips,Tricks &

Roadmap

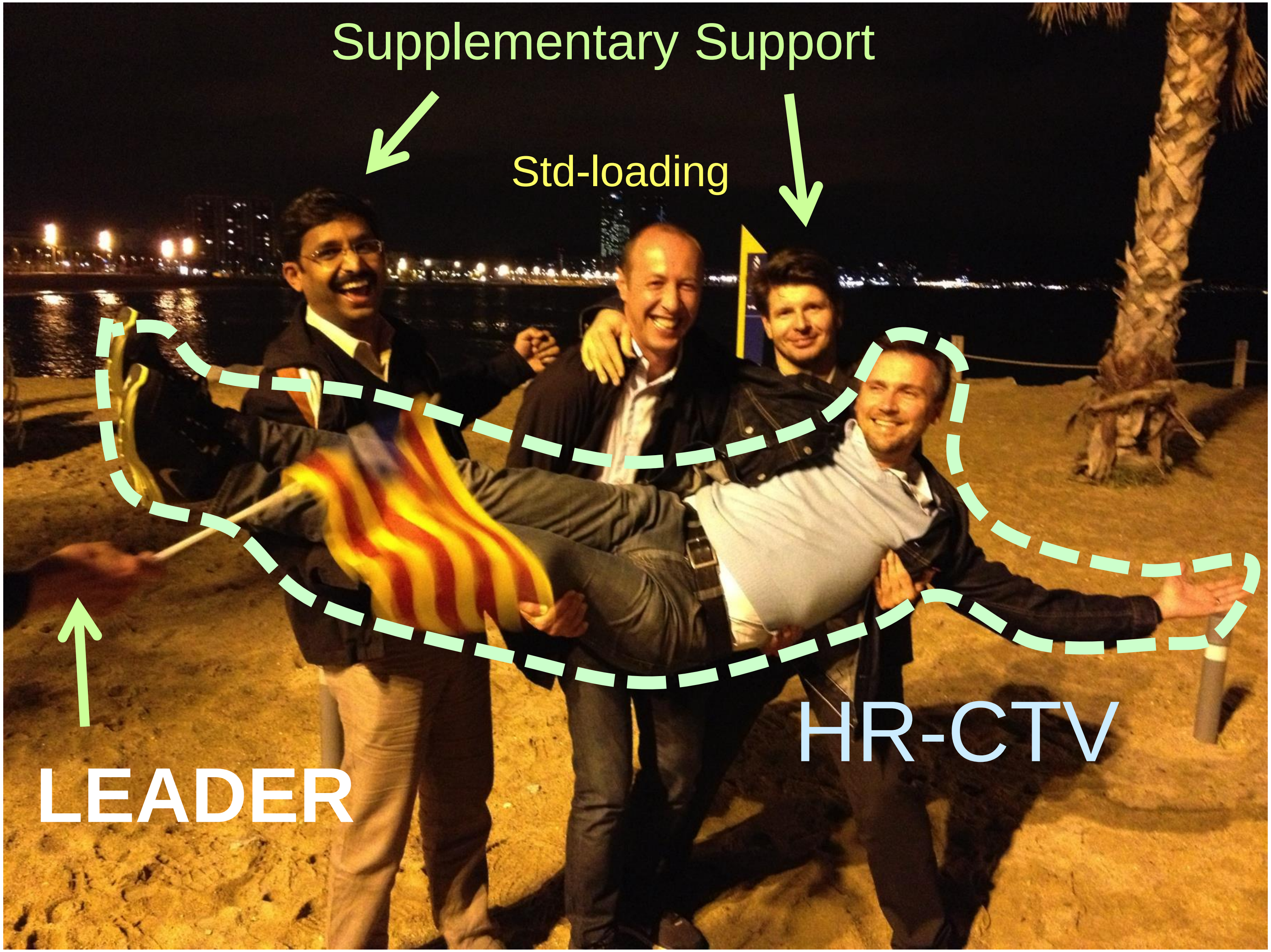
U. Mahantshetty, D Berger and R Pötter


Moscow2013

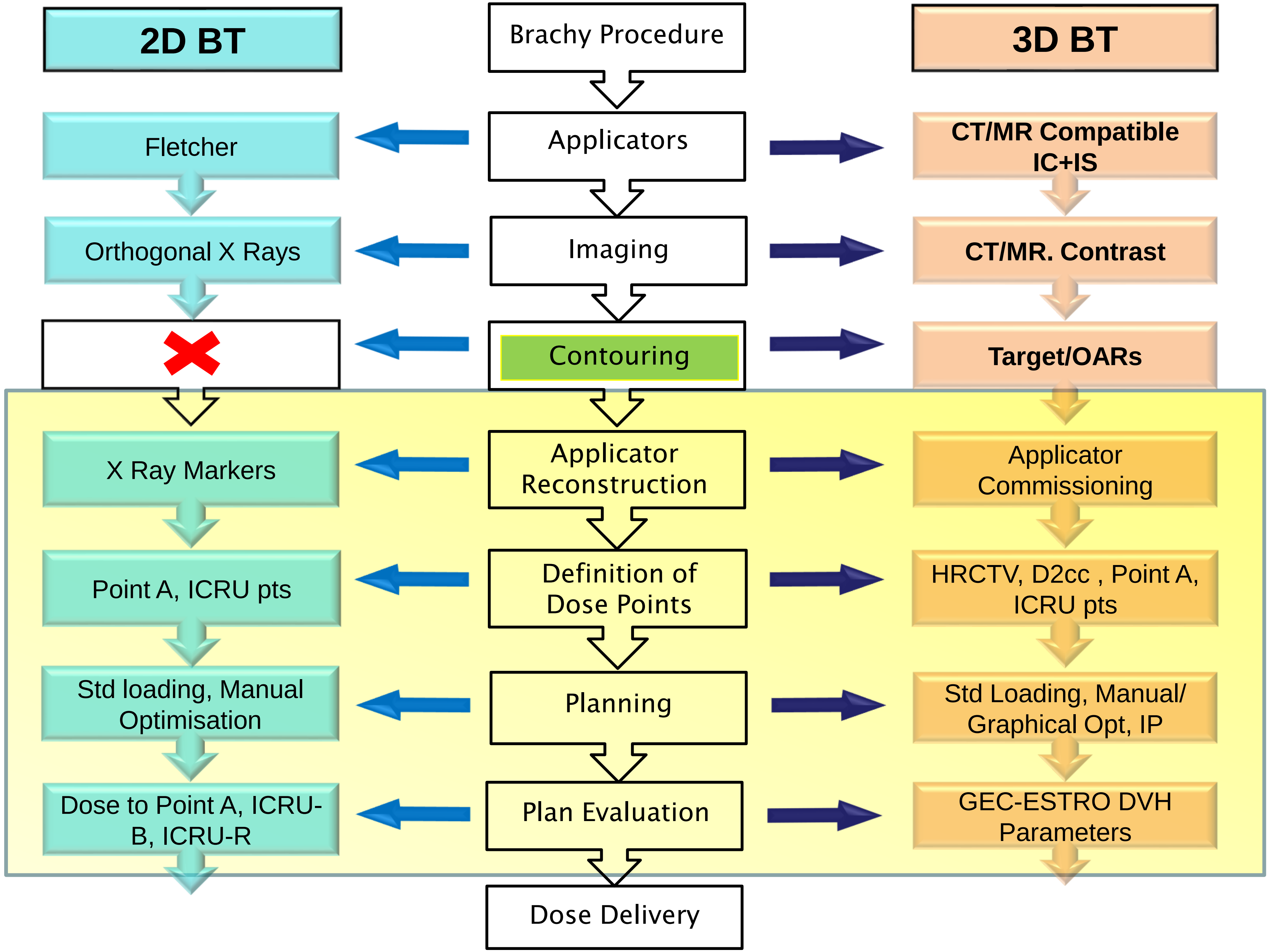


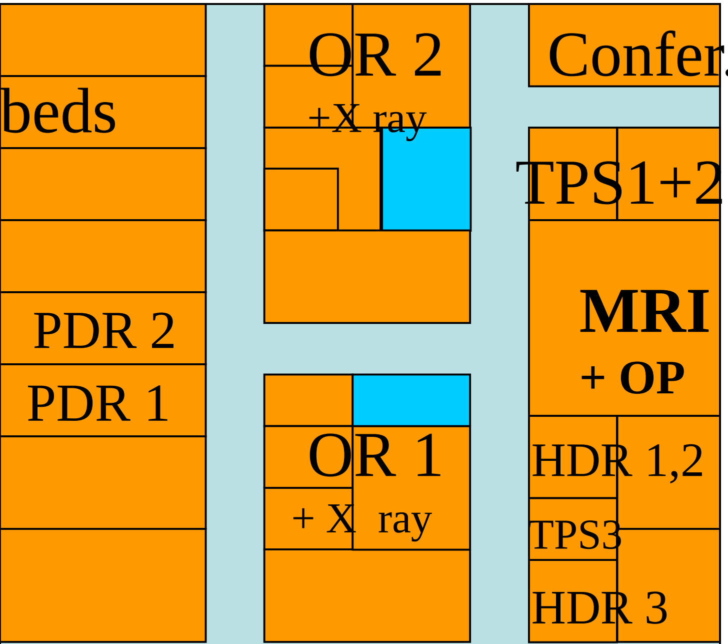

Chandigarh 2011

Team work at TC Barcelona 2013

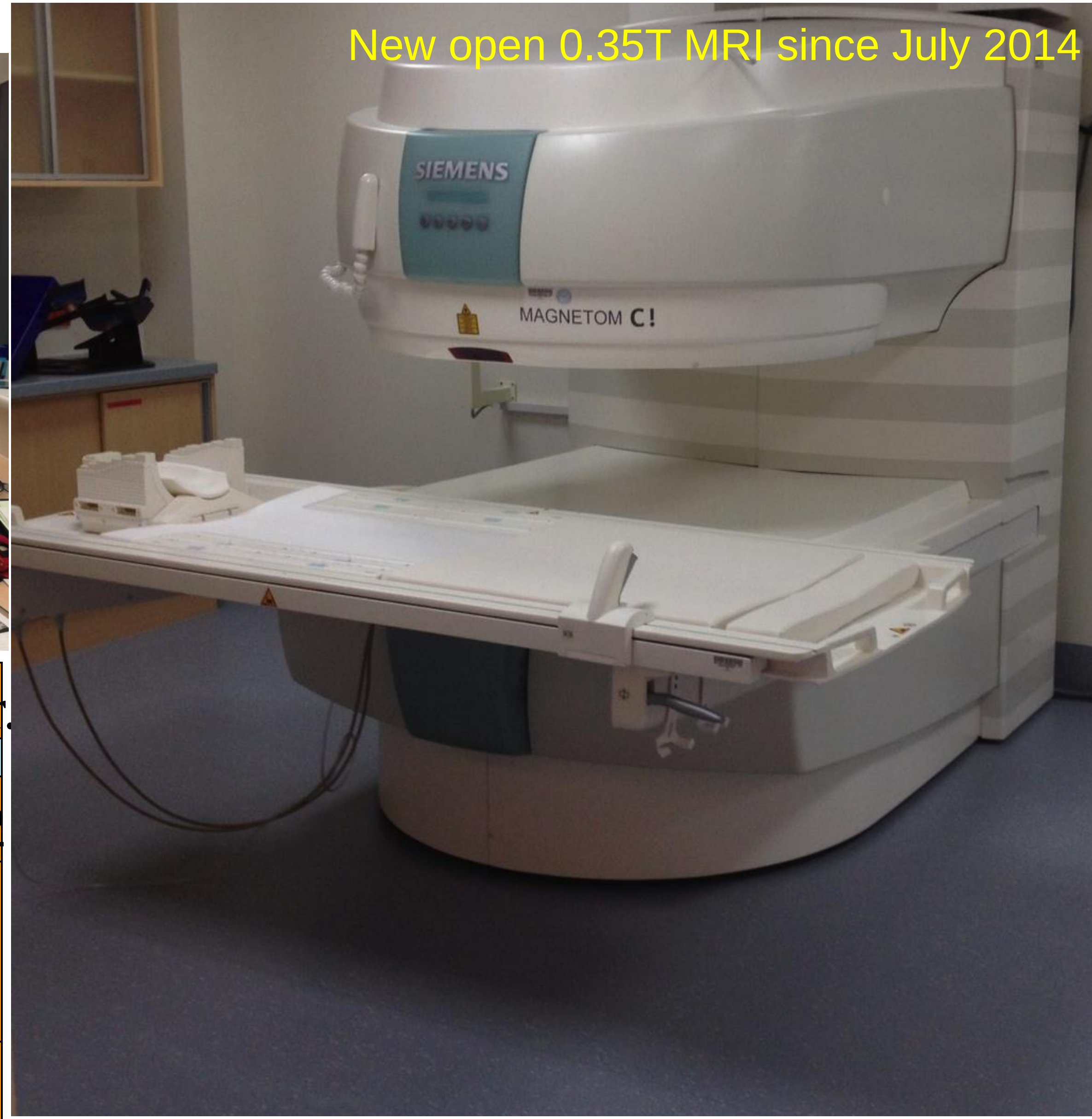


With permission


2D BT
Brachy Procedure
3D BT
Fletcher
Applicators
CT/MR Compatible IC+IS
Orthogonal X Rays
Imaging
CT/MR. Contrast
Contouring
Target/OARs
X Ray Markers
Applicator Reconstruction
Applicator Commissioning
Point A, ICRU pts
Definition of Dose Points
HRCTV, D2cc , Point A, ICRU pts
Std loading, Manual Optimisation
Planning
Std Loading, Manual/ Graphical Opt, IP
Dose to Point A, ICRU-B, ICRU-R
Plan Evaluation
GEC-ESTRO DVH Parameters
Dose Delivery

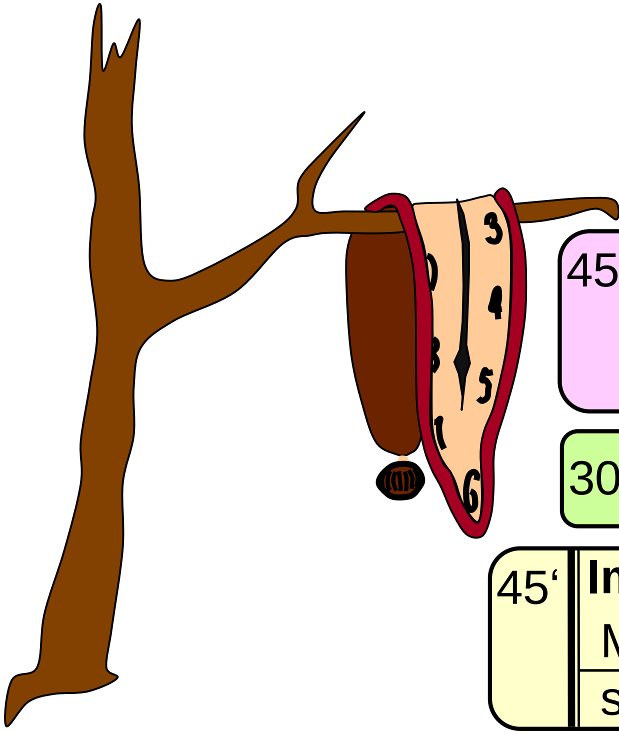


Brachytherapy Vienna



Costs for open MRI: ~500.000 €

Working Schedule Brachytherapy of Cervix Cancer

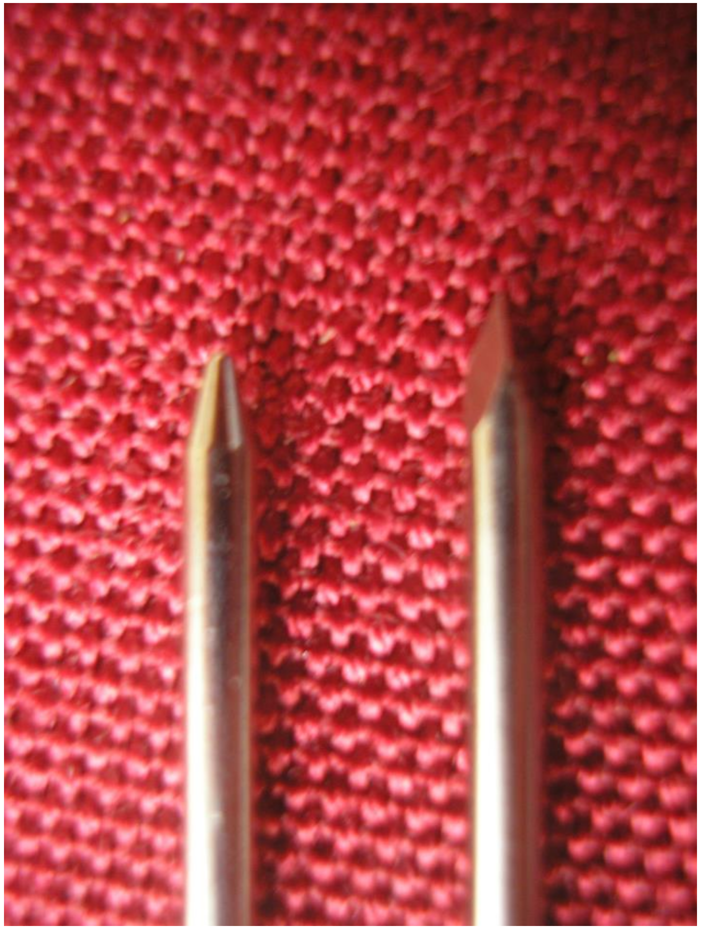


15‘	**Preparation**	
	Patient	Surgical-nurse /Physician
	med.tech. Documents	Technician
	DVH pre-planning	Physician and Physicist
45‘	**Anaesthesia**	
	Spinal/Epidural or General	Anaesthetist / Anaesthesia-nurse
30‘	**Application**	Physician / surgical-nurse
45‘	**Imaging**	
	MR / CT	Technician
	supervision + discussion	Physician and Physicist
30‘	**Contouring**	
	Organs at Risk	Technician / Physician
	Target Volume	Physician
45‘	**Treatment Planning**	
	Reconstruction / Constraints	Technician / Physicist
	Discussion and Validation	Physicist and Physician
15‘	**Radiation Treatment**	Technician

Total
Time
3h 45min

PRE-REQUISITES

- Check list
- Dummy run
- Workflow and various processes
- Applicators : Commissioning and QA
- Treatment planning principles
- Analgesics
- Removal of application
- Manage the bleeding after removal
- Do not use sharp needles
- Optimization tools
- Learning Curve

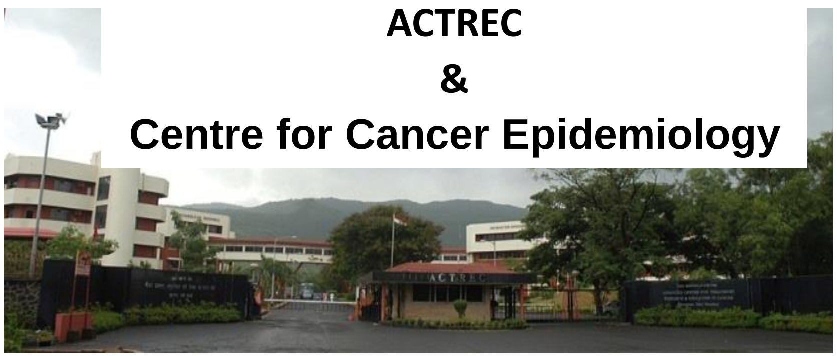


Tata Memorial Hospital

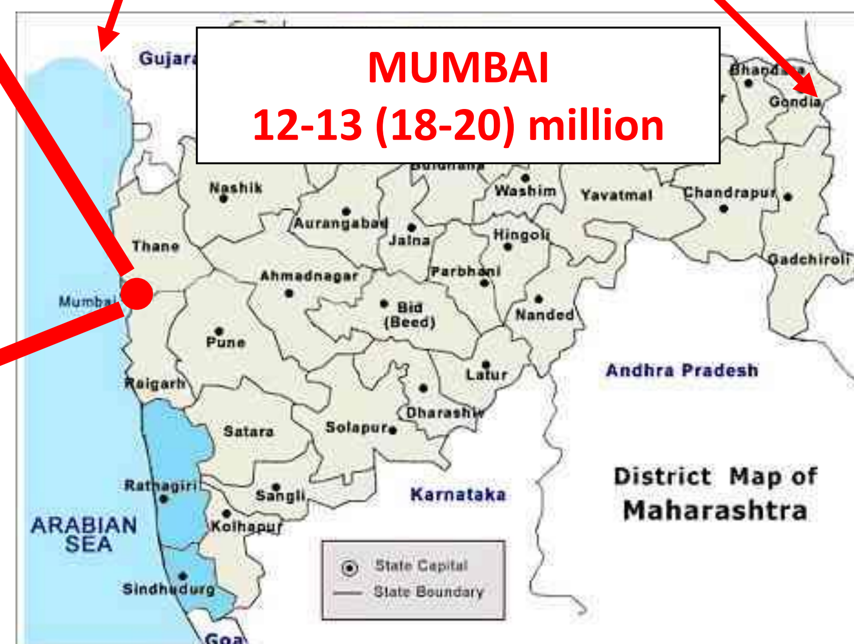
MISSION
Service
Research
Education

INDIA
1.2 billion
population

ACTREC
&
Centre for Cancer Epidemiology

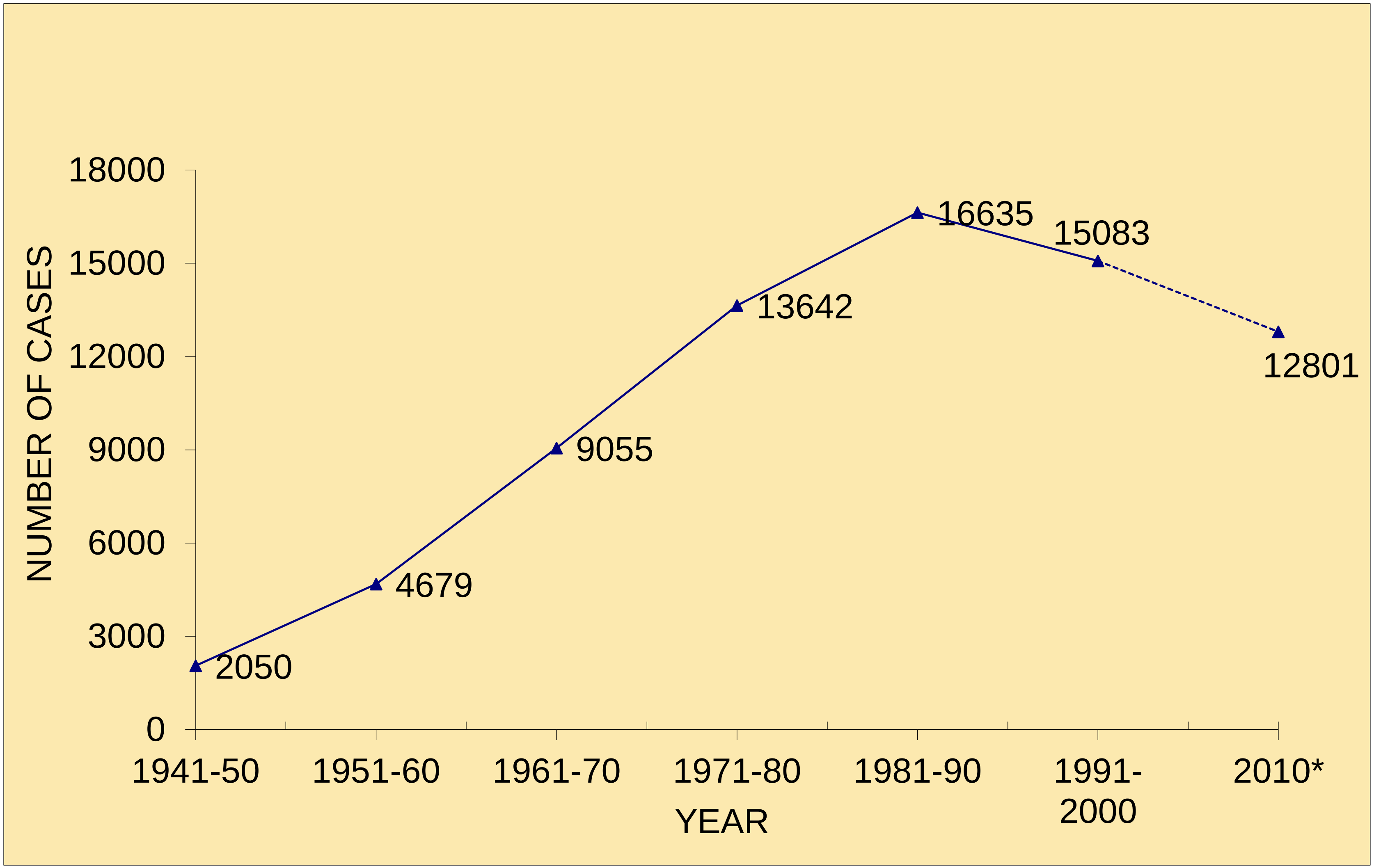


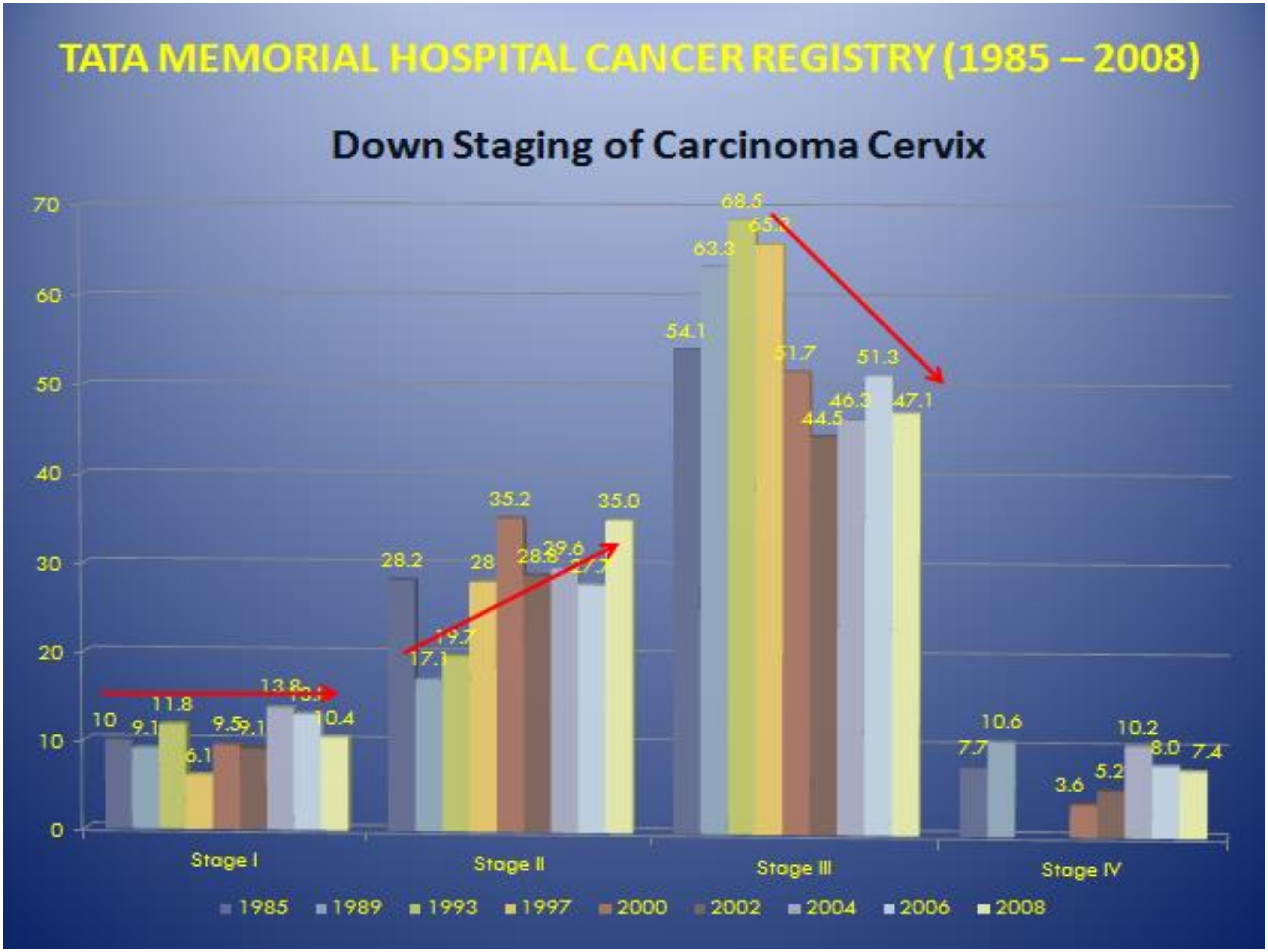
MUMBAI
12-13 (18-20) million



DOWN THE DECADES

CANCER CERVIX : TATA MEMORIAL HOSPITAL 1941-2010





- Routine Practice: Radical Rx : 550 – 600 patients annually
  - Average 6 (4 - 10) Cx brachy per day + 1-2 Interstitial /wk
  - 3-4 X-ray; 2-3 CT; 1 MR Based Planning
  - All procedures done under general anesthesia

Retrospective and feasibility study : Dec 2006 - May 2008 (N = 24)

Conventional Treatment Planning

Prescription to Point 'A'

MR Protocol Standardization and Understand the Volume Concepts

Retrospective contouring and evaluation of DVH parameters

International Journal of Gynecological Cancer:
August 2011 - Volume 21 - Issue 6 - pp 1110-1116
doi: 10.1097/IGC.0b013e31821caa55
Radiation Therapy

Reporting and Validation of Gynaecological Groupe Euopeen de Curietherapie European Society for Therapeutic Radiology and Oncology (ESTRO) Brachytherapy Recommendations for MR Image-Based Dose Volume Parameters and Clinical Outcome With High Dose-Rate Brachytherapy in Cervical Cancers: A Single-Institution Initial Experience

Mahantshetty, Umesh MD, DNBR, DMRT*; Swamidas, Jamema MSc, DRP*; Khanna, Nehal MD*; Engineer, Reena DNBR*; Merchant, Nikhil H. MD†; Deshpande, Deepak D. DRP, PhD*; Shrivastava, Shyamkishore MD, DNBR*

	Vienna IC IJROBP2005	Vienna IC/IS IJROBP2005	Brabandere RO 2008	Lindegaard IJROBP2008	Chargari IJROBP 2008	TMH study IJGC 2011
HRCTV						
Vol in cc	34 +/- 17	44 +/- 27	48+/-19	34+/- 12	36.3±35	**45.2 ± 15.8**
D100	66 +/- 7	70 +/- 6	64+/-6	76 +/- 7	61.66±7	**53.9 ± 6.5**
D90	87 +/-10	96 +/- 12	79+/-7	91 +/- 10	74.85±10	**70.3 ± 10.6**
Avg. Pt A	89 +/- 8	93 +/- 9	79+/-5	92 +/- 9	71.4±6	**73.4 ± 4.5**
Bladder						
Vol in cc	--	--		--		**80.3 (20.3-235)**
ICRU Bmax	75 +/-16	73 +/- 19	74+/-15	67 +/- 31	63.7±9	**80.4 ± 34.4**
D0.1cc						**136.0 ± 54.7**
D2cc						**91.4 ± 24.6**
Rectum						
Vol cc						**33.4 (11-64.6)**
ICRU Rmax						**63.5 ± 8.1**
D0.1cc						**67.2 ± 9.9**
D2cc						**57.9 ± 7.7**
Sigmoid						
Vol cc	--	--		--		**49.0 (14.5-97.5)**
D0.1cc	79 +/- 12	84 +/- 14	82+/-13	79 +/- 13	72.7±18	**101.9 ± 45.2**
D2cc	63 +/- 7	67 +/- 7	68+/-7	69 +/- 9	60.6±6	**74.4 ± 19.6**

LESSONS LEARNT

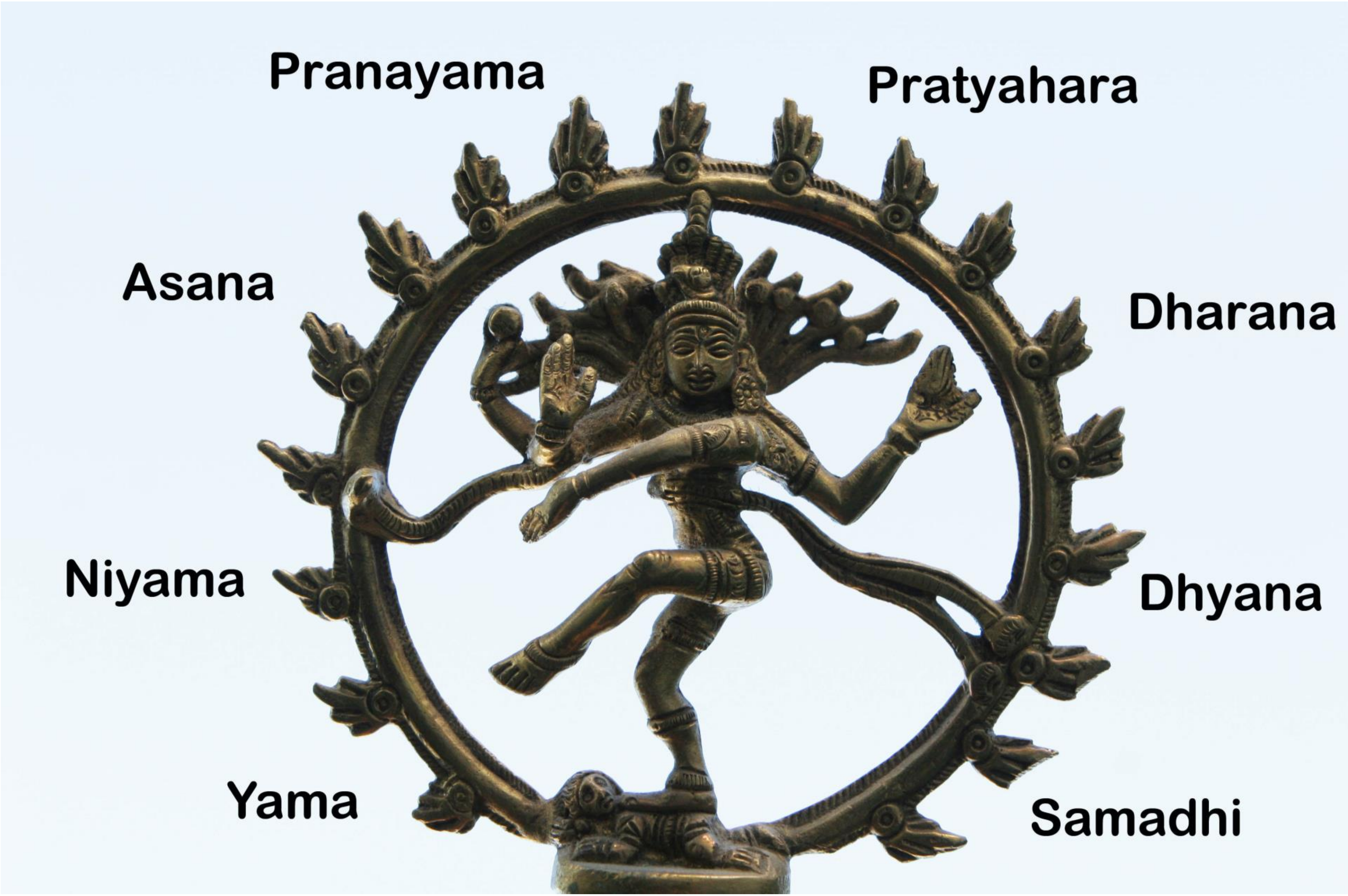
Retrospective Data: 24 patients

Tumor Volumes larger: Advanced Stages

Bladder and Sigmoid Doses Higher

Mahantshetty et al, IJGC Aug. 2011

TMH - AKH Collaboration: 2008-2009
Bilateral Exchange Program



TMH - AKH Vienna Collaboration: 2008 – 2009

Bilateral Exchange Program

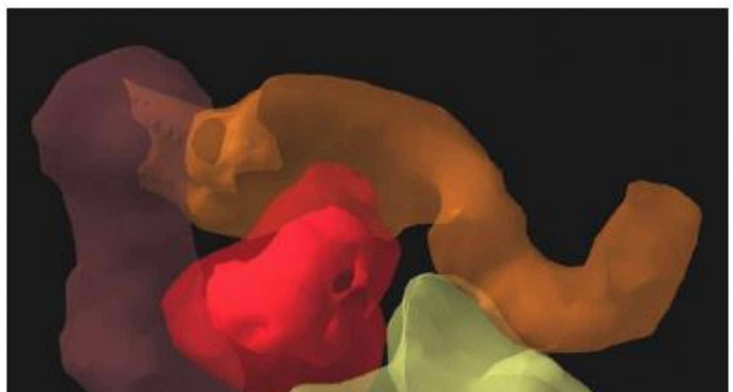
Tata Memorial Hospital Participation in International Multicentric Studies

- Refine treatment standards
- GYN GEC-ESTRO Research Network

A European study on MRI-guided brachytherapy in locally advanced cervical cancer

EMBRACE

(ENDORSED BY GEC ESTRO)



2009 ONWARDS

TATA HOSPITAL CONTRIBUTION TO EMBRACE

100 patients (IIB-IVA)

TMH EMBRACE Data
Prospective MR Based Brachytherapy (N = 94 patients)
Dec 2009 – March 2014

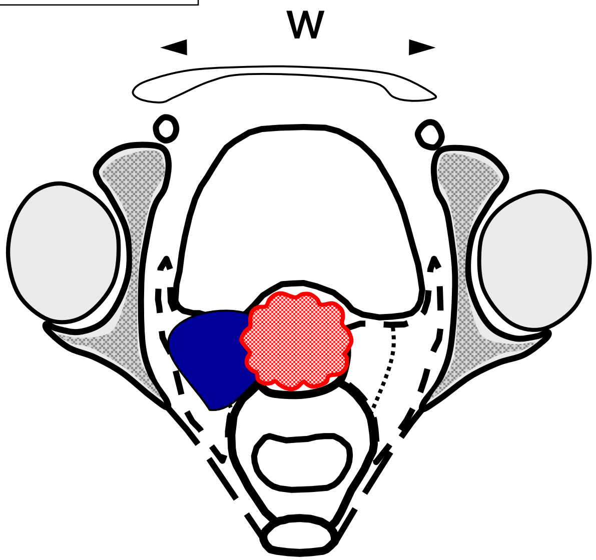
Total no of patients	**47/100 patients**
Median Age (range)	**49(42 - 65) years**
Histology	
Squamous Carcinoma	**81**
Adenocarcinoma	**09**
AdenoSquamous	**04**
FIGO Stage (n)	**94**
IIB	**31**
IIIB	**55**
IVA (Bladder mucosa invasion)	**08**
Intracavitary Brachytherapy (HDR)	**4 fractions of 7 Gy to HRCTV**
Median follow-Up (IQR)	**39 (26-50) months**

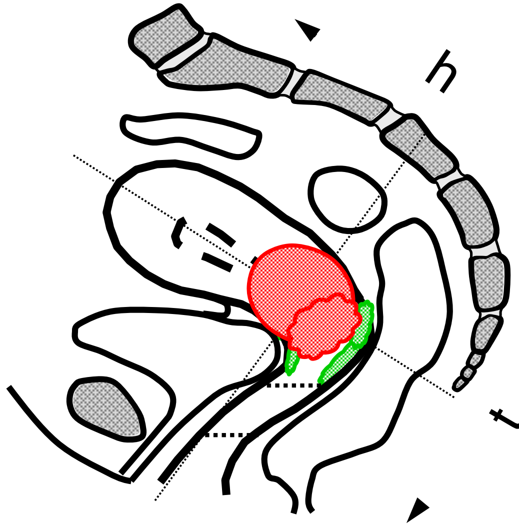
A Clinical Example

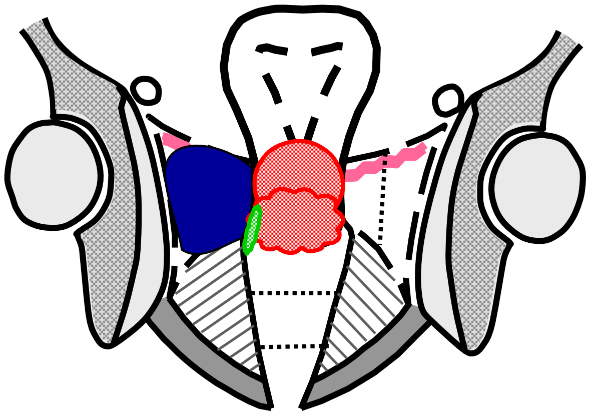
w = 60 mm
h = 50 mm
t = 50 mm

Vagina Involvement
= 4 cm (Post)

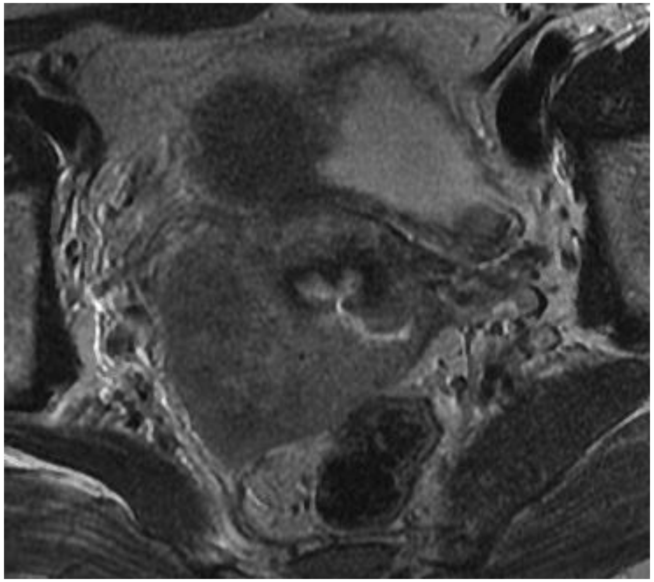
At Diagnosis

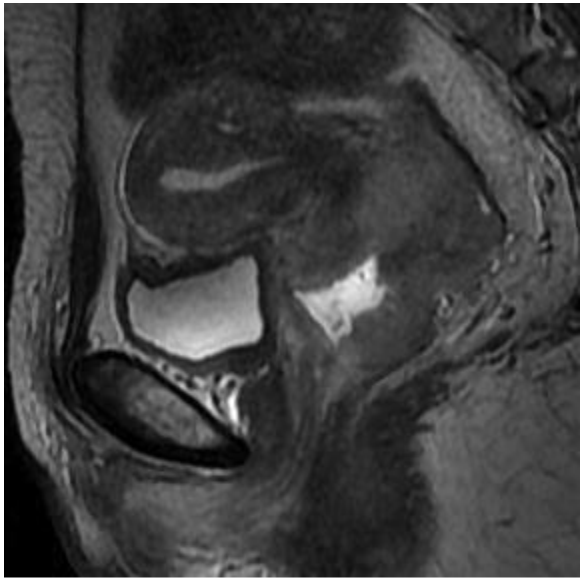


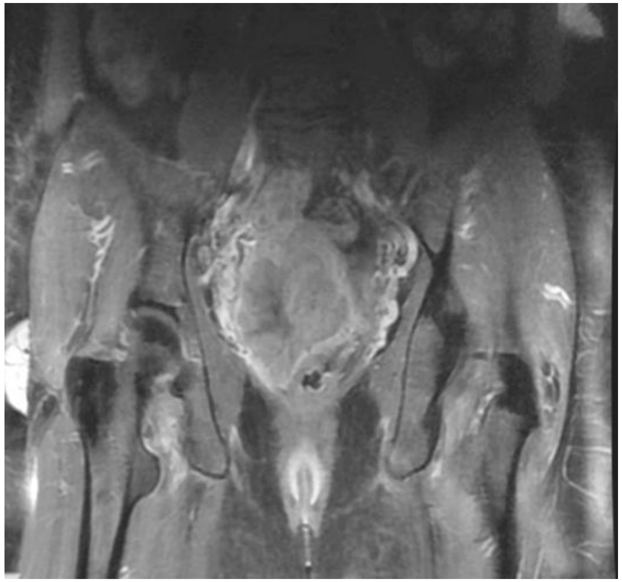




Axial | Sag | Coronal





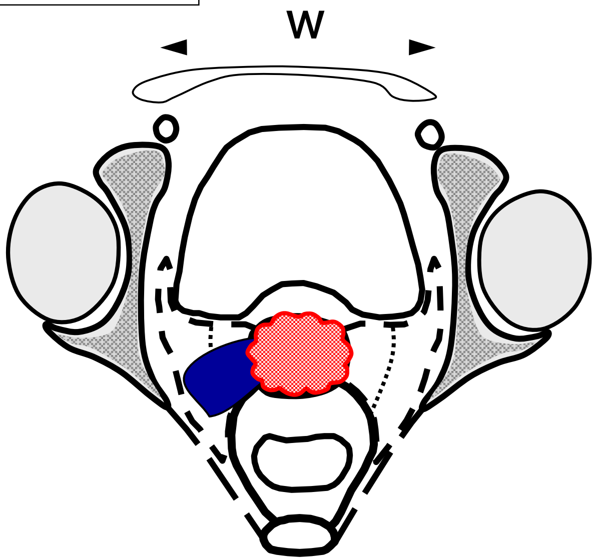


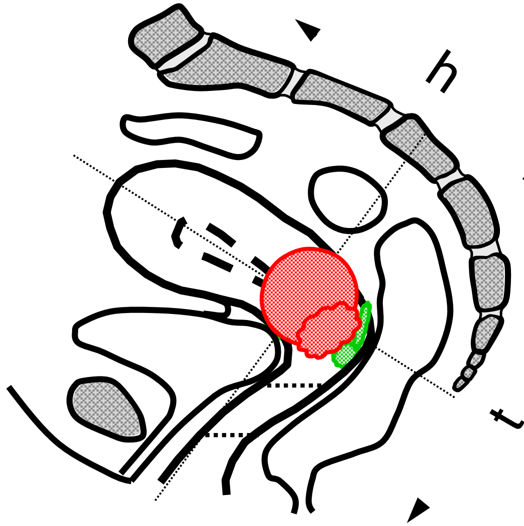
w = 60 mm
h = 40 mm
t = 30 mm

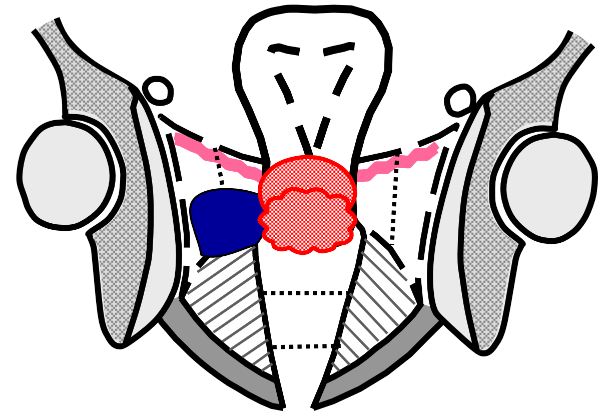
Vagina Involvement = 20mm (Post)

Clinical Drawing

At Brachytherapy



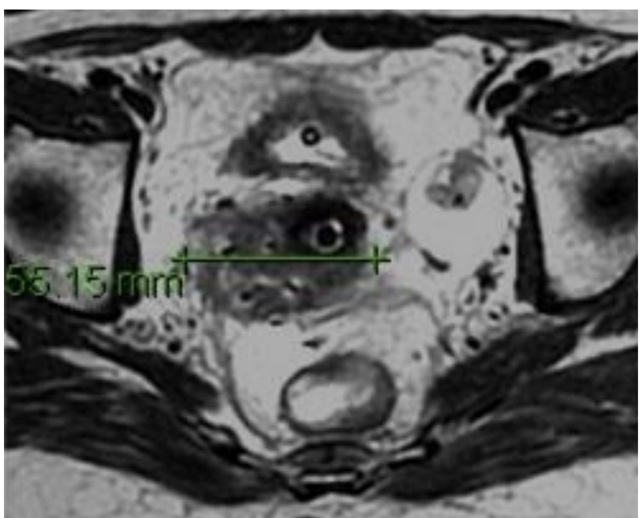


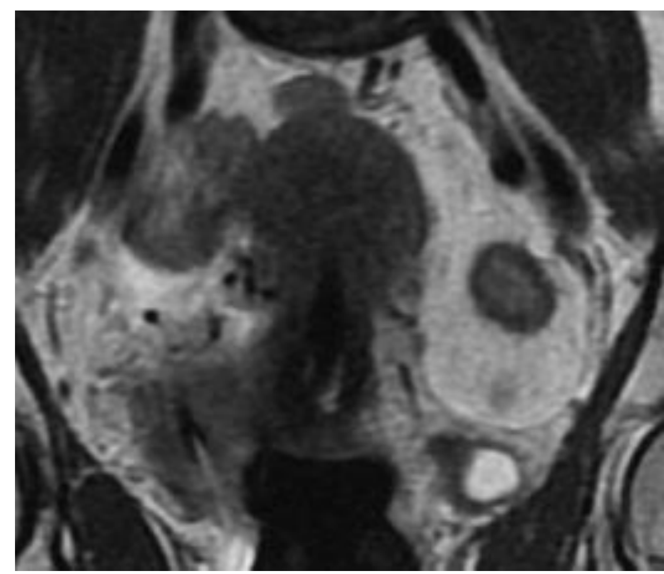


Axial

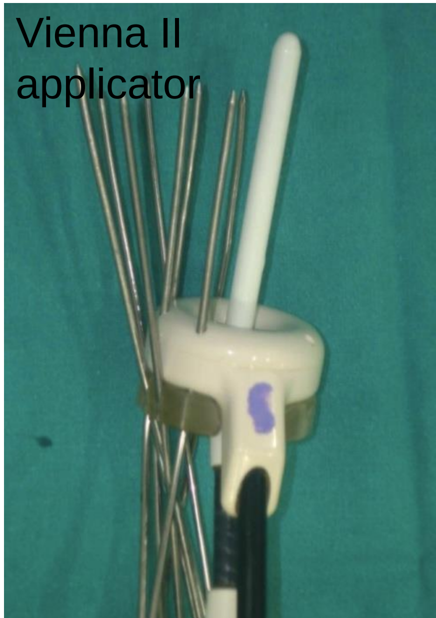
Sag

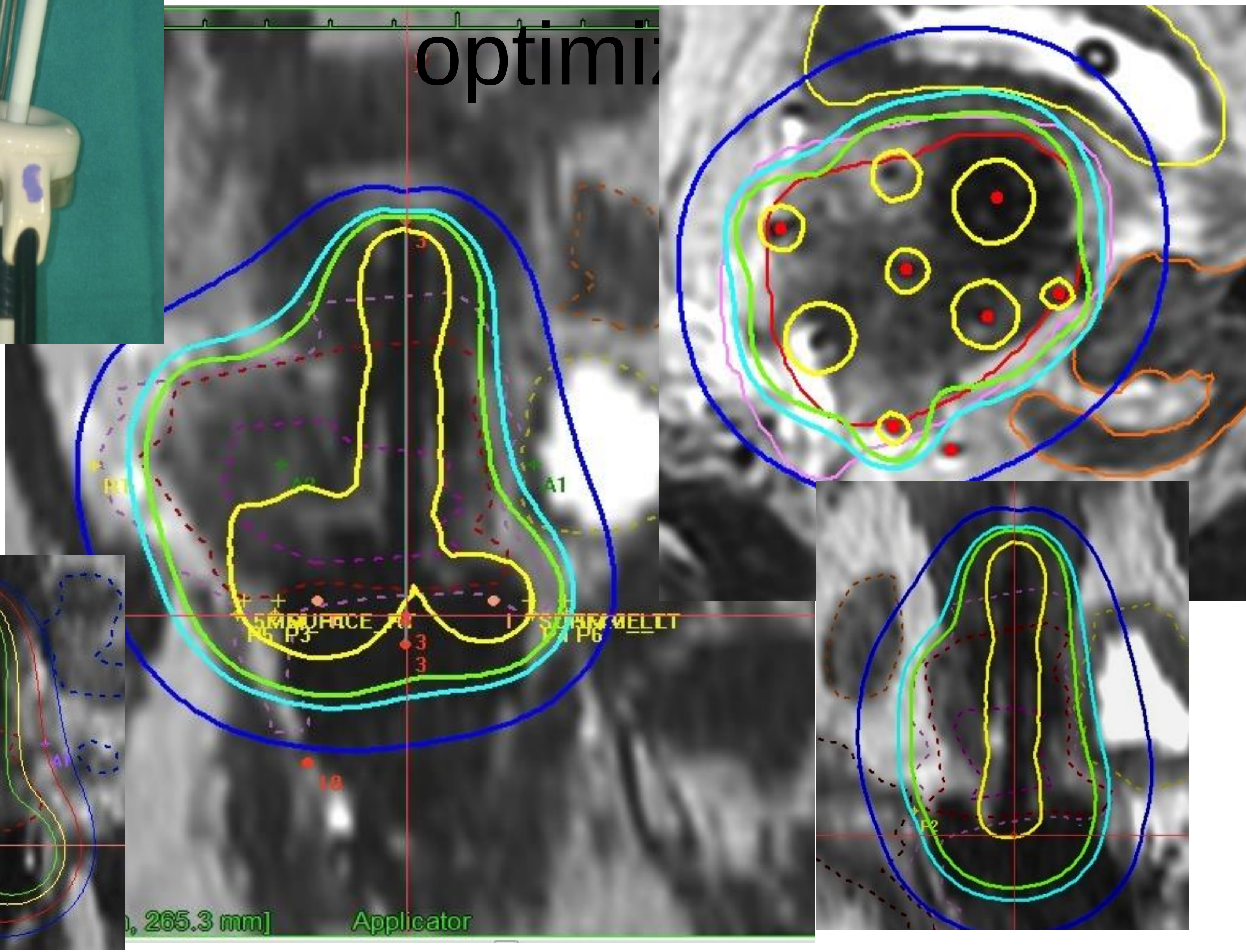
Coronal





Treatment planning / optimiz



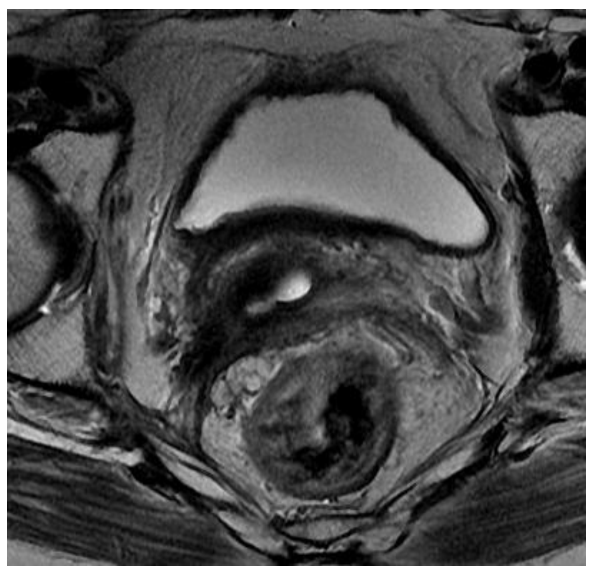


	Dosimetric comparison for 1 #			Cumulative RT Doses (4# of BT)	
DVH Parameters	Ring STD ICA Only	Vienna with one set of needles	Vienna with additional needles	Planning aim	Prescribed dose
HRCTV D90 (Gy)	4.38	6.2	8.3	≥ 85 Gy	96.2 Gy
HRCTV D98 (Gy)	3.45	4.5	7.0		
SIGMOID 2 CC	4.6	4.5	4.1	≤ 70 Gy	67.4 Gy
SIGMOID 0.1 CC	6.1	5.8	5.2		
BLADDER 2 CC	7.9	6.5	5.5	≤ 90 Gy	82.9 Gy
BLADDER 0.1 CC	10.2	8.5	6.5		
RECTUM 2 CC	3.9	3.8	4.2	≤ 70 Gy	68.3 Gy
RECTUM 0.1 CC	5.4	5.3	5.6		

Post Rx 3months follow-up
Clinico - MR Complete Response
with RT para fibrosis

Post Rx 12 months follow-up
Clinico - MR Controlled
with RT para fibrosis

Post Rx 4 years follow-up
Clinico – radiologically Controlled
with RT para fibrosis



Cancer Cervix FIGO IV A (Bladder Mucosa Involved)
MRI and Cystoscopy shows bladder invasion at Diagnosis

Cystoscopy positive

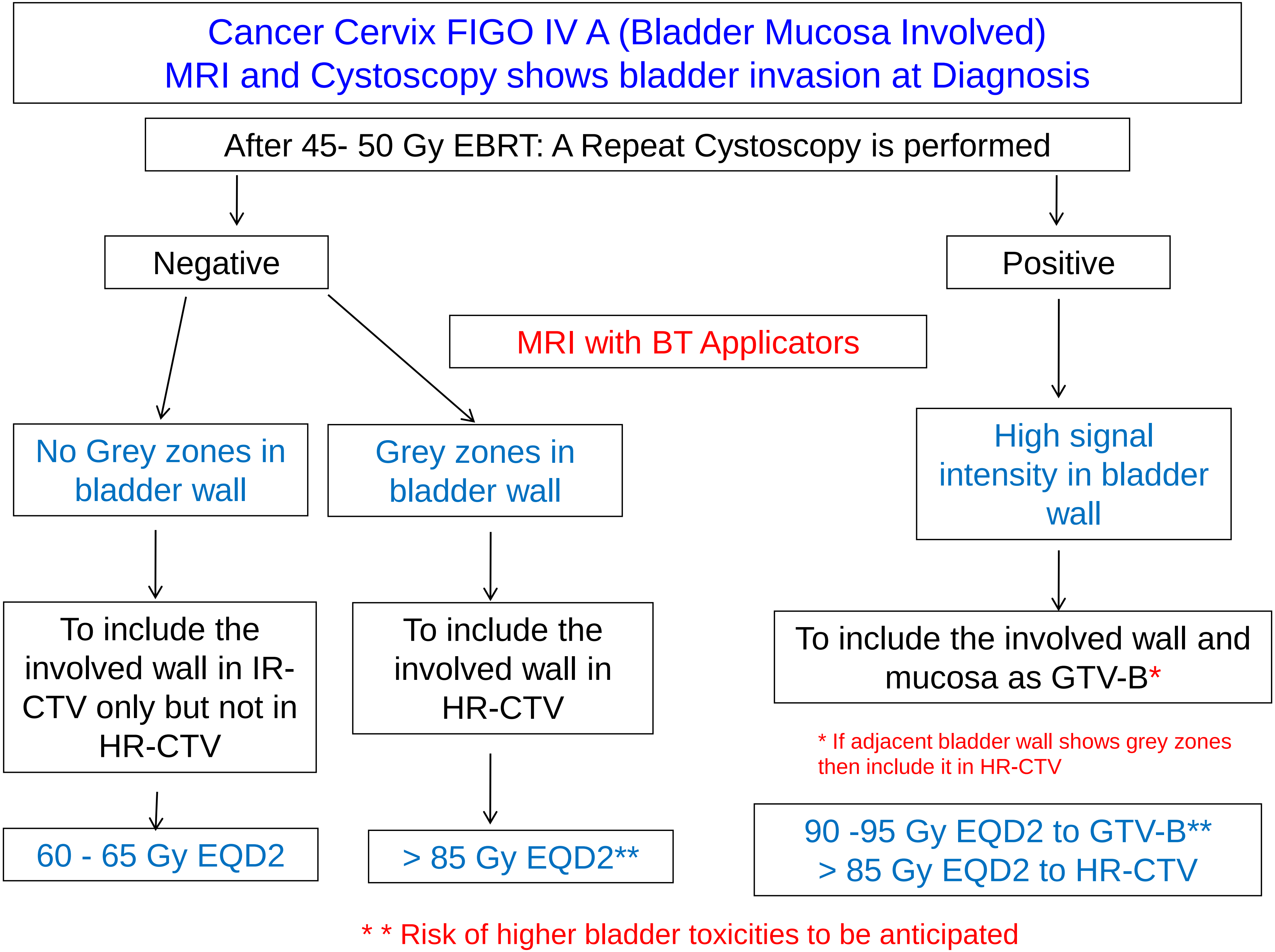
Focal Invasion
<2 cm *

Extensive Invasion

Radical
Chemoradiation

Chemotherapy and
assess after 3-4 cycles
with cystoscopy

** Arbitrary and not based on any evidence-*


Cancer Cervix FIGO IV A (Bladder Mucosa Involved)
MRI and Cystoscopy shows bladder invasion at Diagnosis
After 45- 50 Gy EBRT: A Repeat Cystoscopy is performed
Negative
Positive
MRI with BT Applicators
No Grey zones in bladder wall
Grey zones in bladder wall
High signal intensity in bladder wall
To include the involved wall in IR-CTV only but not in HR-CTV
To include the involved wall in HR-CTV
To include the involved wall and mucosa as GTV-B*
* If adjacent bladder wall shows grey zones then include it in HR-CTV
60 - 65 Gy EQD2
> 85 Gy EQD2**
90 -95 Gy EQD2 to GTV-B**
> 85 Gy EQD2 to HR-CTV
* * Risk of higher bladder toxicities to be anticipated

DOSIMETRIC COMPARISON: Retrospective Vs Prospective Data Vs Literature

	Vienna (IC)	VIE (IC/IS)	Brabandere	TMH: RD (24 pts)	TMH: Embrace data (94 pts)
HRCTV					
Vol in cc	34 +/- 17	44 +/- 27	48+/-19	45.2 ± 15.8	46.9+24.6
D100	66 +/- 7	70 +/- 6	64+/-6	54.1 ± 6.5	65.7±4.6
D90	87 +/-10	96 +/- 12	79+/-7	70.9 ± 10.6	88.3+4.4
Avg. Pt A	82 +/- 9	--	79+/-5	73.4 ± 4.5	93.1 ±24.8
I				34.4	76.4 ±15.5
				54.7	109.6 ±19.7
				24.6	85.7+9.8
I				8.1	68 ±7.9
				9.9	71.5 ±7.5
				7.7	65.5+7.2
Sigmoid					
D0.1cc	79 +/- 12	85 +/- 14	82+/-13	109.4 ± 45.2	74 ±8.6
D2cc	63 +/- 7	67 +/- 7	68+/-7	74.6 ± 19.6	67+8.8

LESSONS LEARNT

Prospective Data: 94 patients

HR-CTV Volumes larger: Advanced Stages

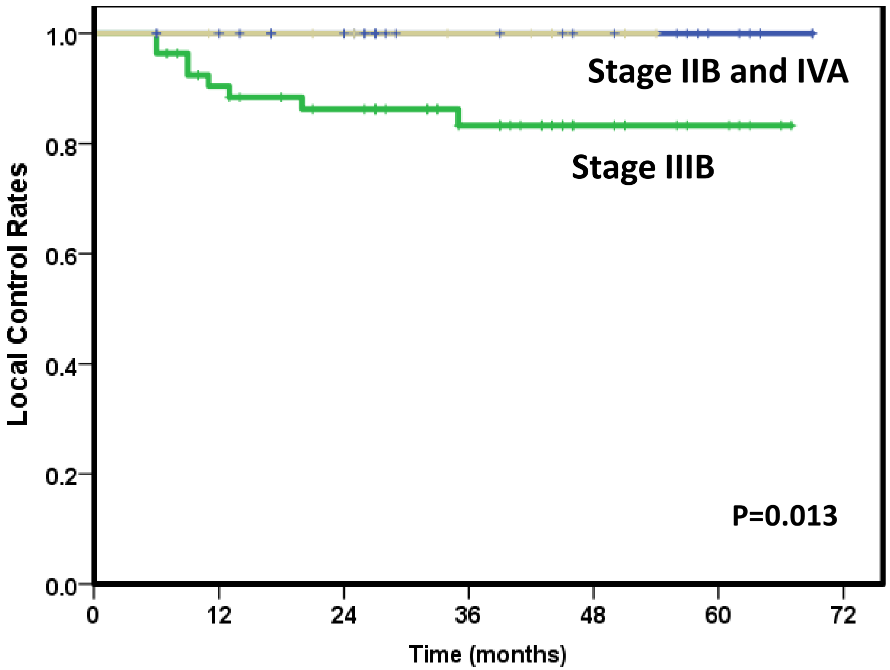
Higher doses to HR-CTV

Bladder and Sigmoid Doses Better

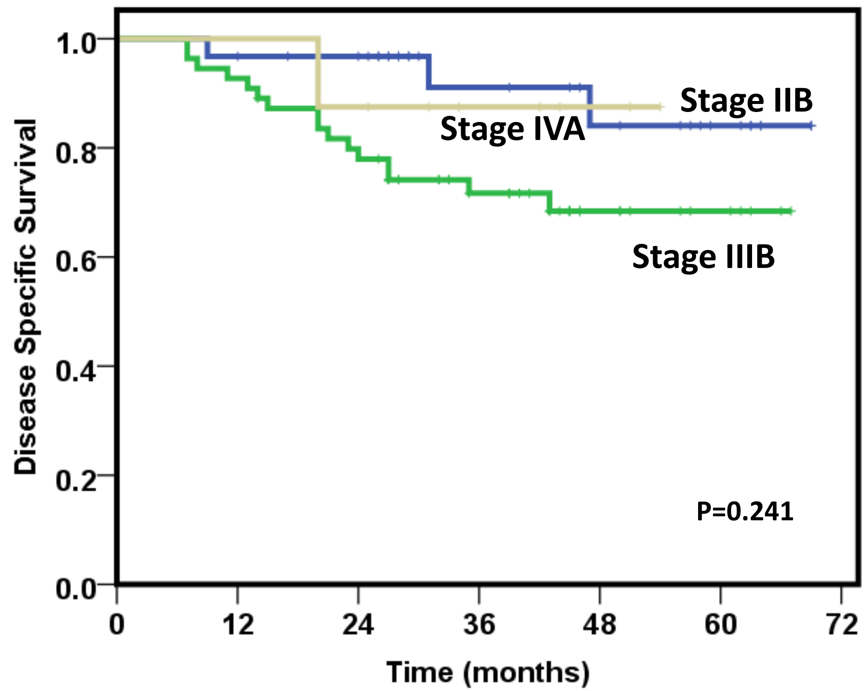
MR IMAGE BASED BRACHYTHERAPY

EMBRACE STUDY : 1400 PATIENTS

TMH ACCRUAL: 94 PATIENTS



IIB	31	28	24	15	12	07	01
IIIB	55	45	39	27	10	05	01
IVA	08	07	06	04	02	00	00

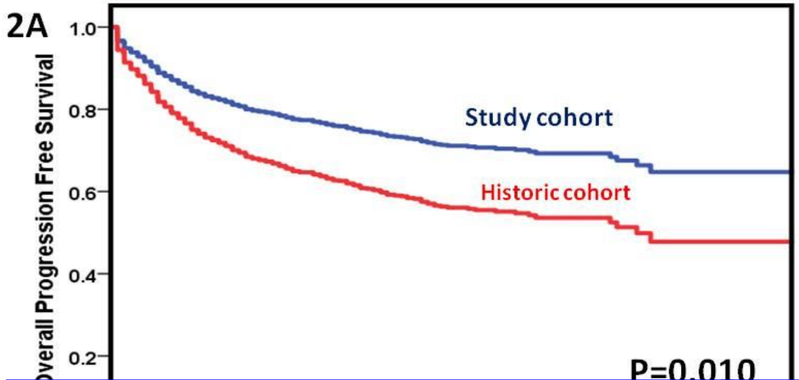


IIB	31	29	26	16	12	07	01
IIIB	55	51	43	28	10	05	01
IVA	08	08	07	04	02	00	00

EXCELLENT LOCAL CONTROL RATES FOR ALL STAGES

Mahantshetty et al, IJROBP 2017

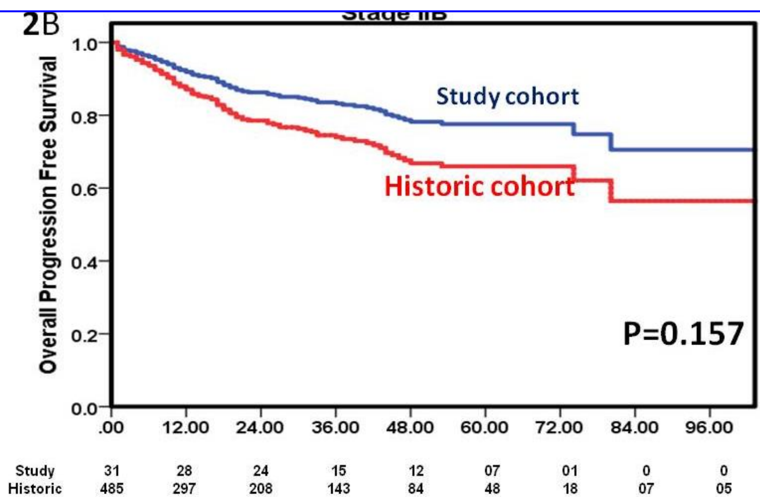
COMAPRISON OF HISTORICAL CONTROLS Vs MR BT EXPERIENCE: TMH



HISTORIC COHORT B: CONVENTIONAL BT SERIES (1979-94)

STUDY COHORT : MR IGABT APPROACH

MR IMAGE BASED BRACHYTHERAPY BENEFICIAL
LOGISTICS : Availability, Cost & Implementation Issues



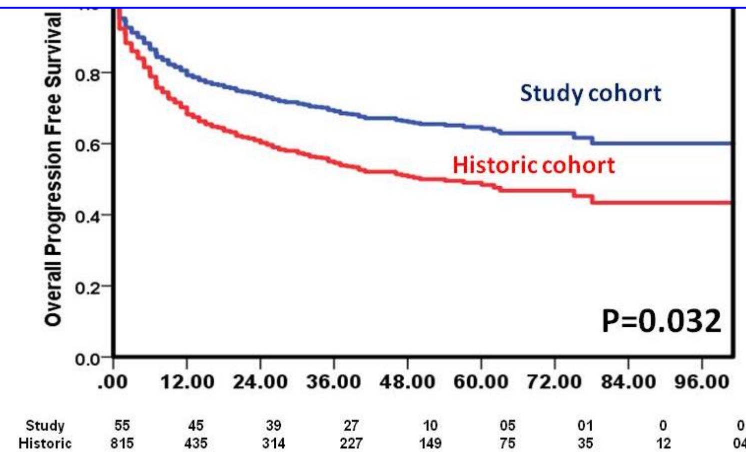


Figure 2: Comparison of overall progression free survival using log rank test for study cohort and historic cohort [21] for, all patients (A), stage IIB (B), and stage IIIB (C).

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COST BENEFIT ANALYSIS MR IGABT Approach

ELSEVIER

BRACHYTHERAPY

Brachytherapy ■ (2017) ■

Income generated by women treated with magnetic resonance imaging-based brachytherapy: A simulation study evaluating the macroeconomic benefits of implementing a high-end technology in a public sector healthcare setting

Santam Chakraborty*, Umesh Mahantshetty, Supriya Chopra, Shirley Lewis, Vinod Hande, Shivakumar Gudi, Rahul Krishnatry, Reena Engineer, Shyam Kishore Shrivastava

Department of Radiation Oncology, Tata Memorial Hospital, Parel, Mumbai, India

Is it Economically Feasible to Have a MRI In the RT Department for Image Guided Brachytherapy in India

Expenditure for 5 Years
MR Compatible Applicators and MRI in RT Dept.

3 New Applicator Costs	15000000
MRI+ 1 Year Warranty	50000000
CAMC Year 2	2500000
CAMC Year 3	2750000
CAMC Year 4	3025000
CAMC Year 5	3327500
Salary for 2 Technicians	1200000
Total	77802500

INR 7.8 Crores (~ USD 1.2 Million)

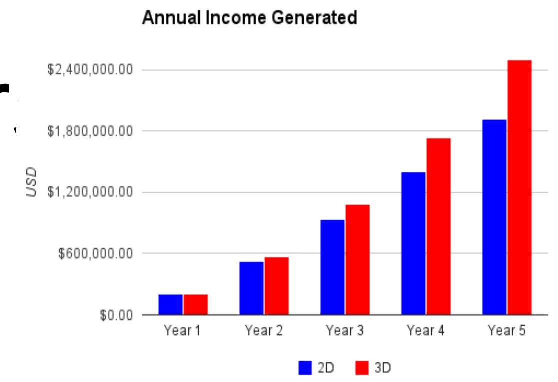
Note as useful life of MRI is at least 10 years, cost of acquisition is divided by 2 for the 5 year projection.

Outcome Assumptions from Our Historical Datasets

	Year 1	Year 2	Year 3	Year 4	Year 5
Proportion Alive 2D	100.00%	70.00%	65.00%	60.00%	55.00%
Patients Alive 2D	1318	2240.6	3097.3	3888.1	4613
Proportion Alive 3D	100.00%	85.00%	75.00%	79.00%	65.00%
Patients Alive 3D	1318	2438.3	3426.8	4349.4	5206.1
Proportion with Toxicity 2D	0.00%	10.00%	20.00%	30.00%	30.00%
Patients with Toxicity 2D	0	131.8	395.4	790.8	1186.2
Proportion with Toxicity 3D	0.00%	1.00%	2.00%	3.00%	3.00%
Patients with Toxicity 3D	0	13.18	39.54	79.08	118.62
Working Patients 2D	**1318**	**2108.8**	**2701.9**	**3097.3**	**3426.8**
Working Patients 3D	**1318**	**2425.12**	**3387.26**	**4270.32**	**5087.48**

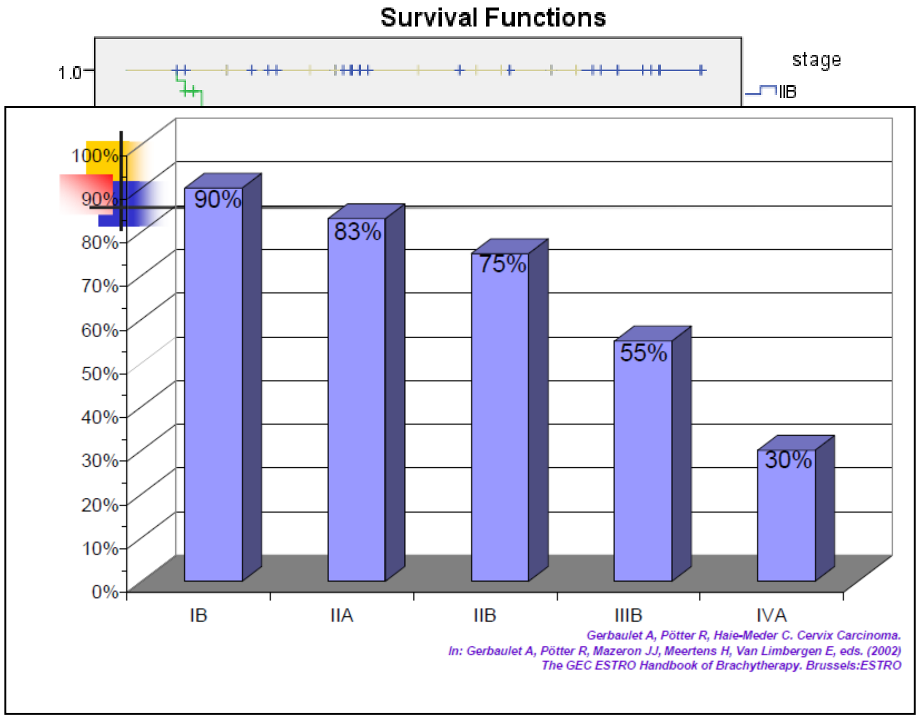
**** Grade ≥ 3 toxicity : precludes normal work***

Income Model for 5 Year

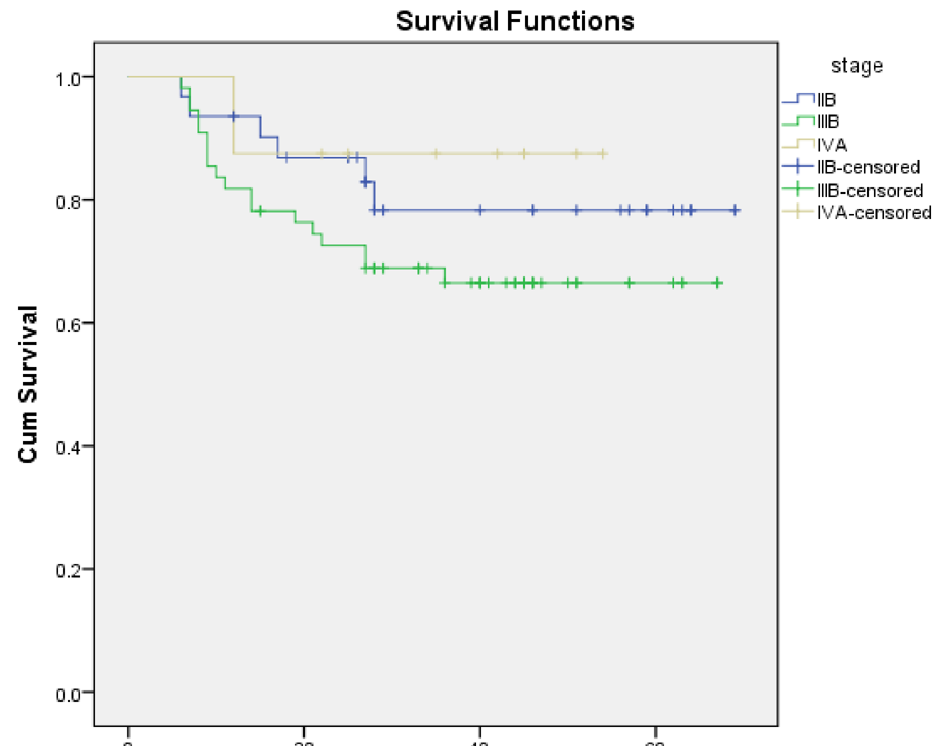


1. Total patients treated annually : 1318 ***(assuming only 25% working)***
2. After 5 years the patients alive and without toxicity would have contributed:
   a. 2D Brachy: Rs 322,894,160.83 (USD 4.9 million)
   b. 3D Brachy: Rs 395,139,293.00 (USD 6.1 million)
   c. **Gain: INR 7.2 Crores (USD 1.1 million)**
3. Within 5 years these patients would have contributed back almost the entire investment made

Actuarial local control



Progression free survival



	2D	2D + CT	3D + CT	
IIB	75%	85%	96-100%	~ 11%
IIIB	55%	65%	84-86%	~ 20%

IIB	31	0	31	100.0%
IIIB	55	9	46	83.6%
IVA	8	0	8	100.0%
Overall	94	9	85	90.4%

IIB	31	6	25	80.6%
IIIB	55	18	37	67.3%
IVA	8	1	7	87.5%
Overall	94	25	69	73.4%

HURDLES

TRANSITION FROM 2D TO 3D

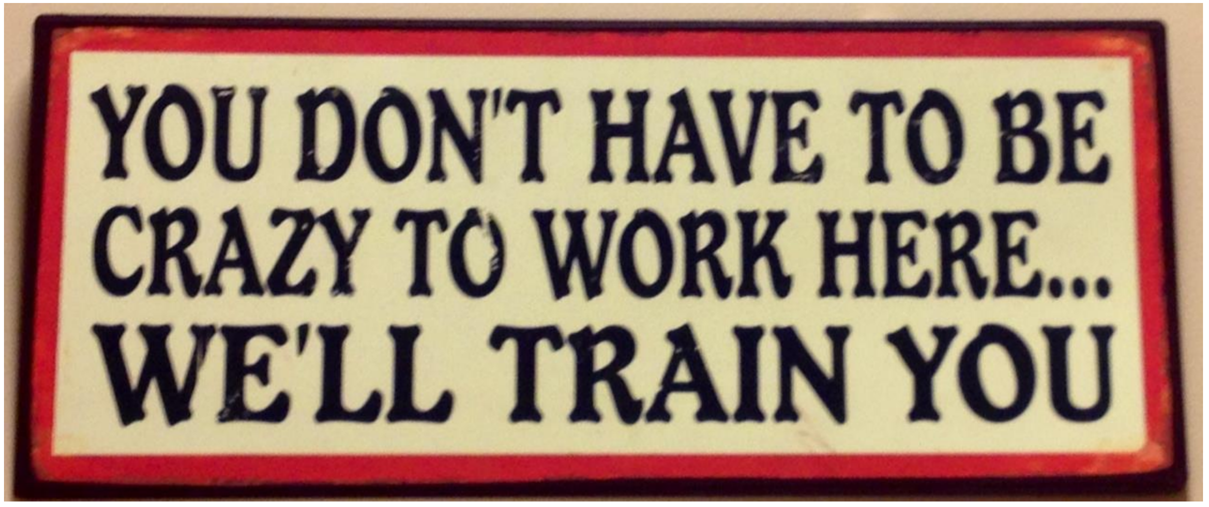
SECRET TO A SUCCESSFUL JOURNEY!

- Attended the GYN Teaching Course: Understand the Concepts
- Hands on Workshop including procedures : Atleast 1 – 2
- Learning Curve & Standardization of processes : 15 - 25 pts
- Retrospective Analyses and Introspection
- Transition to 3D: MR / CT
- Prospective Collaborative Studies & Research
- Teaching / Hands on Workshops

Brachytherapy Skills

Work hard to Strengthen your skills

like laparoscopic and Robotic Surgeons!!



Teaching Courses!

Hands on

Workshops!

Cadeveric

workshops!

COMMITMENT!

BE OPTIMISTIC!

1st AROI ESTRO GYN TC at MS Ramaiah Medical College March 2017

ESTRO
School

Theme: 3D Radiotherapy with a Special Emphasis on Implementation of MRI/CT Based Brachytherapy in Cervical Cancer

8th to 11th March, 2018

Department of Radiation Oncology
Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow (U.P) INDIA

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

17^{th} Edition of TC, Toronto 2016

Working for success
will make you a Master;

But

Working for satisfaction
will make you a Legend.

Motivated young generation
There is no third choice!