

WELCOME ESTRO-CARO Teaching Course

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

Toronto 4.-6. April 2016



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

In the ESTRO school for more than 10 years:

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

In total ~ 2000 participants



Discussion of Course Directors



Discussion of Course Directors

Faculty

- **ESTRO Faculty**

- Richard Pötter, Kari Tanderup *Course Directors*
- Umesh Mahantshetty, Primoz Petric *Radiation Oncologists*
- Daniel Berger *Medical Physicist*

- **CARO Faculty:**

- Israel Fortin, Kathy Han, Mike Milosevic *Radiation Oncologists*
- Kartik Jhaveri *Radiologist*
- Taymaa May *Gynaecology Oncologist*

- **ESTRO Faculty „at home“:**

- Ina Jürgenliemk-Schulz, Christine Haie-Meder, Johannes Dimopoulos *Radiation Oncologists*
- Peter Petrow *Radiologist*
- Taran Hellebust *Medical Physicist*

Clinical Evaluation

Radiograph

Diagram

Vienna 1918

Painting

MRI Since 1998

CT since 1983



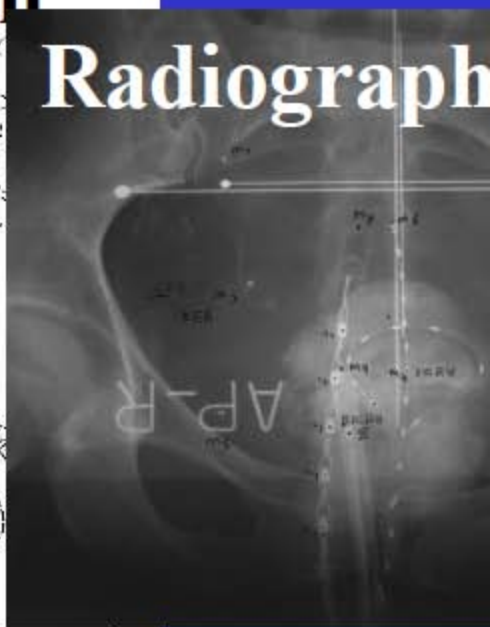
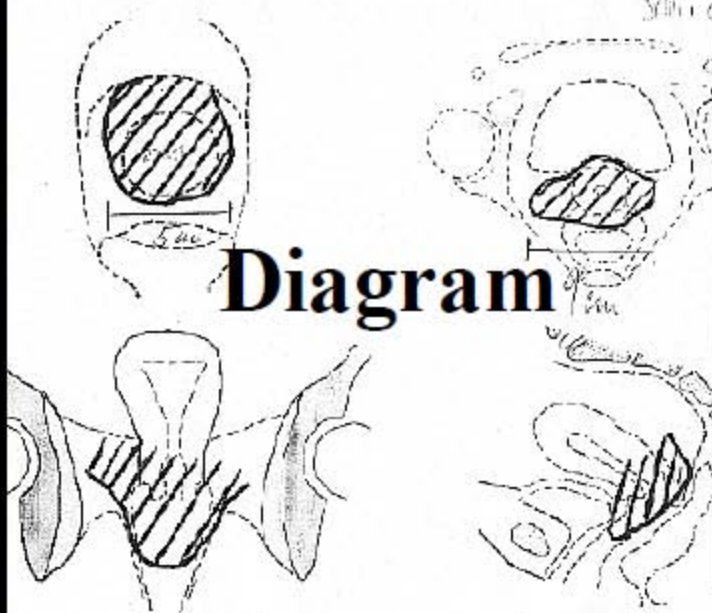
Fall 20. 1. Monate vor der Behandlung 18. X. 1918.
2. Monate nach der Behandlung 6. XII. 1918.
2 Monate später nach einer Gastrostomiefall 1917. Pat. lebt, ist gesund.



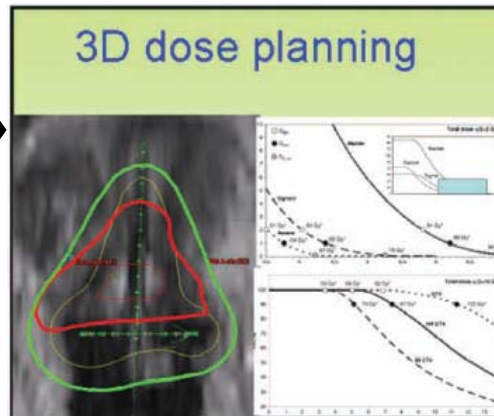
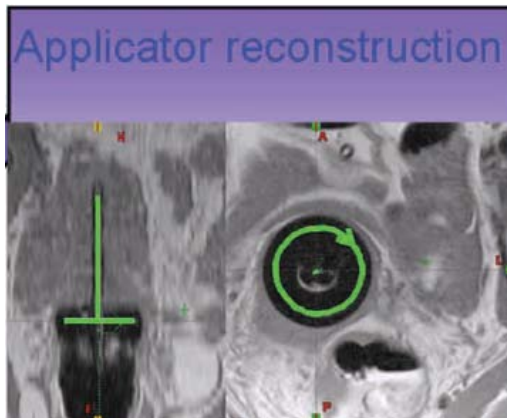
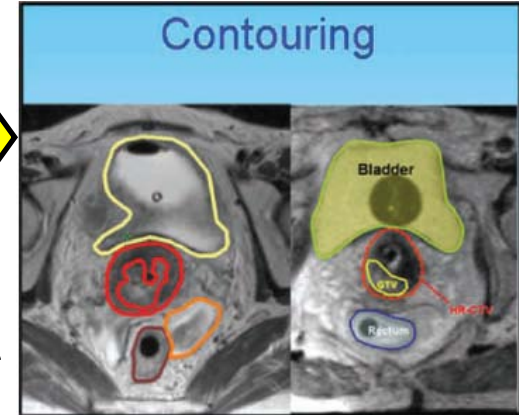
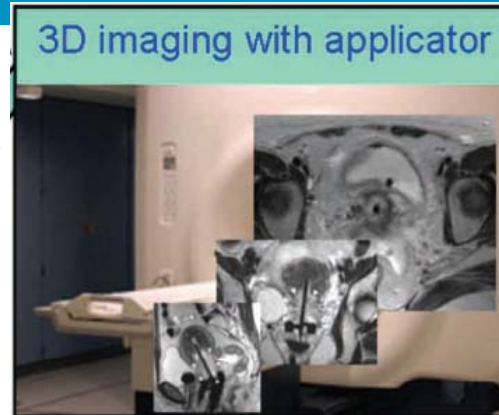
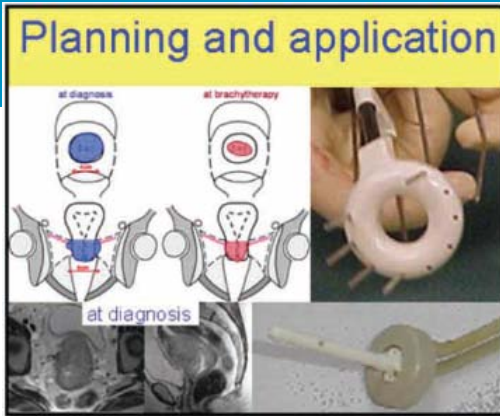
Fall 21. 1. Monate vor der Behandlung 12. X. 1918.
2. Monate nach der Behandlung 18. XII. 1918.
Perio-Substrukt 1917. Pat. lebt, ist gesund.



Adler: Strahlenth. 1918

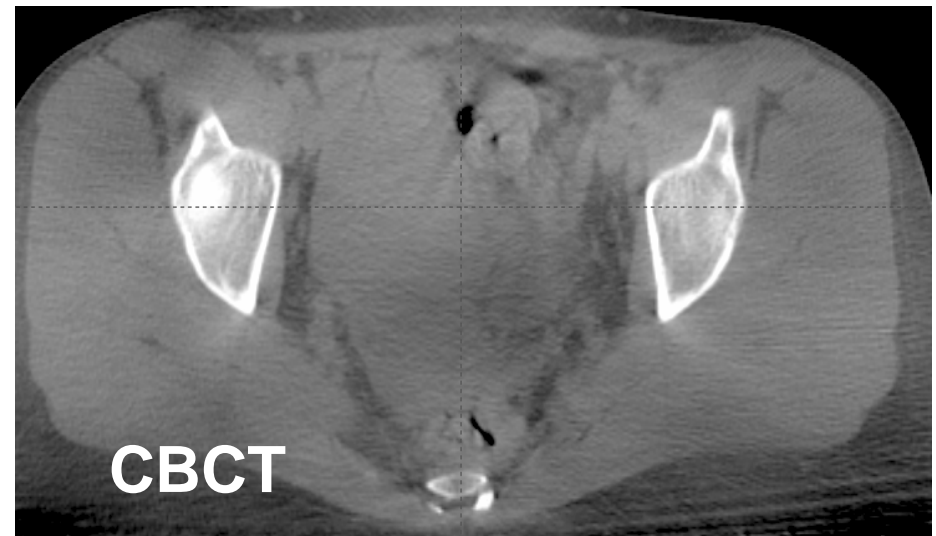
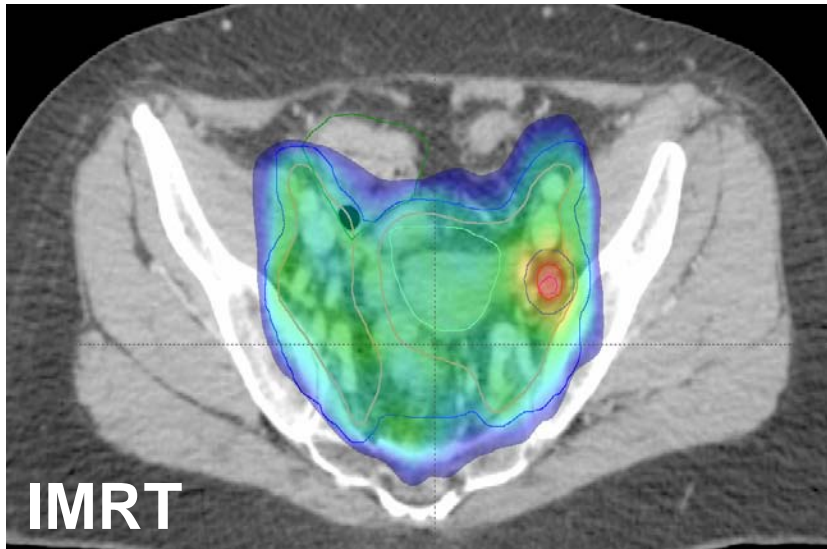


3D Image based brachytherapy



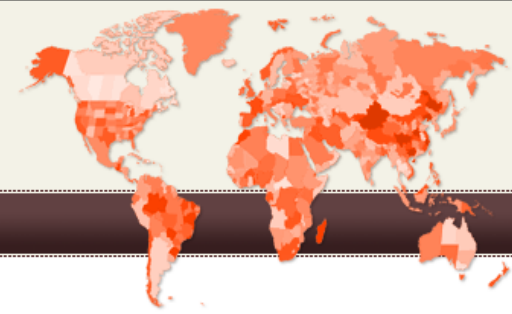
Advanced image guided EBRT

- Target concepts
- Techniques:
 - IMRT
 - IGRT



Contents of the course

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

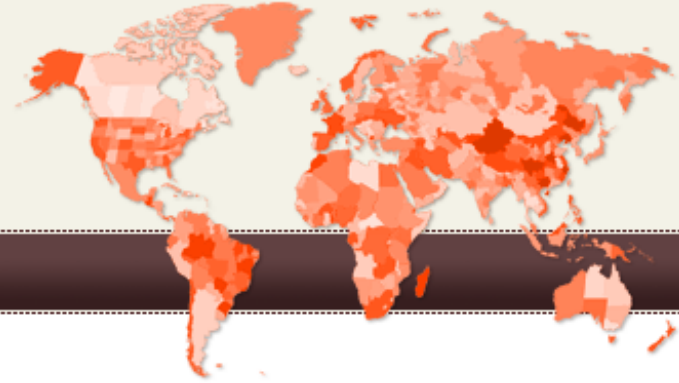


- **Web-based database with a retrospective multicentre collection of data on 3D RT plus IGABT in cervical cancer**
- **780 pts**
- **Eligibility criteria:**
 - **Diagnosis of cervical cancer and treatment with curative intent by IGABT**
 - **Reporting according to GEC ESTRO recommendations**



EMBRACE

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



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- **EMBRACE** - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer
- A prospective observational multi-centre trial
- Initiated enrollment of patients in 2008, >1200 pts accrued
- Accrual to be finalised in 2015

VARIAN
medical systems

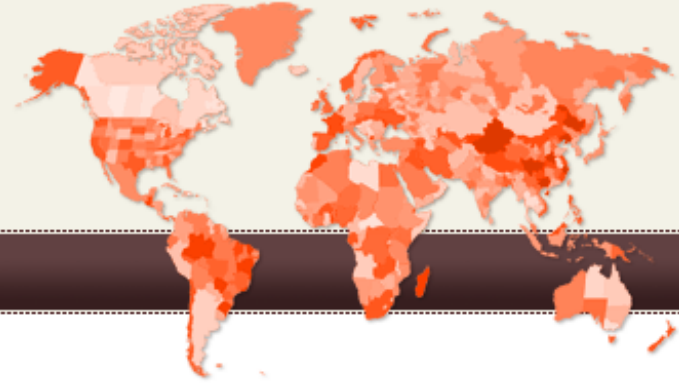
A partner for **life**

 **Nucletron**
Improving patient care

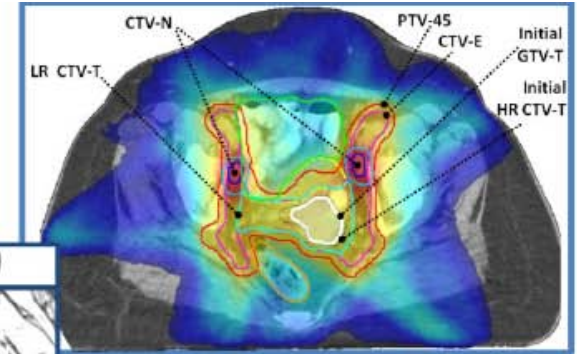
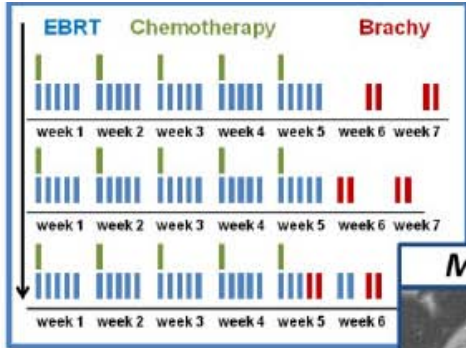


EMBRACE II

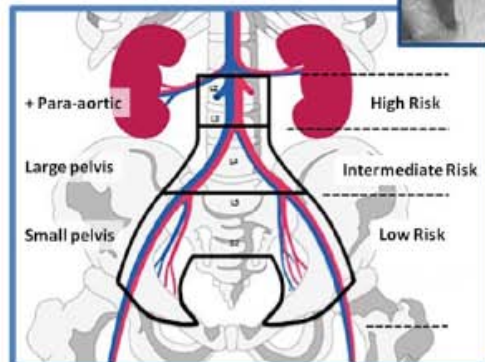
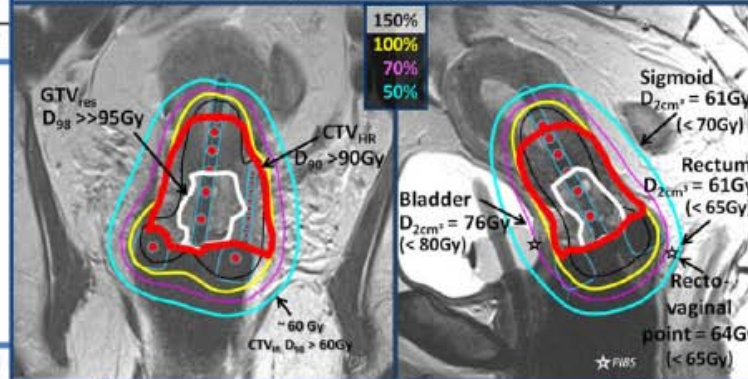
An international study
on MRI-guided BRachytherapy
in locally Advanced CErvical cancer



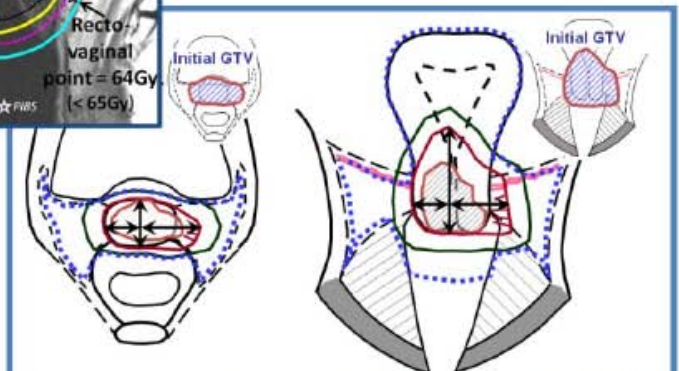
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MRI guided adaptive brachytherapy (IGABT)



Nodal CTV-E based on Risk Group

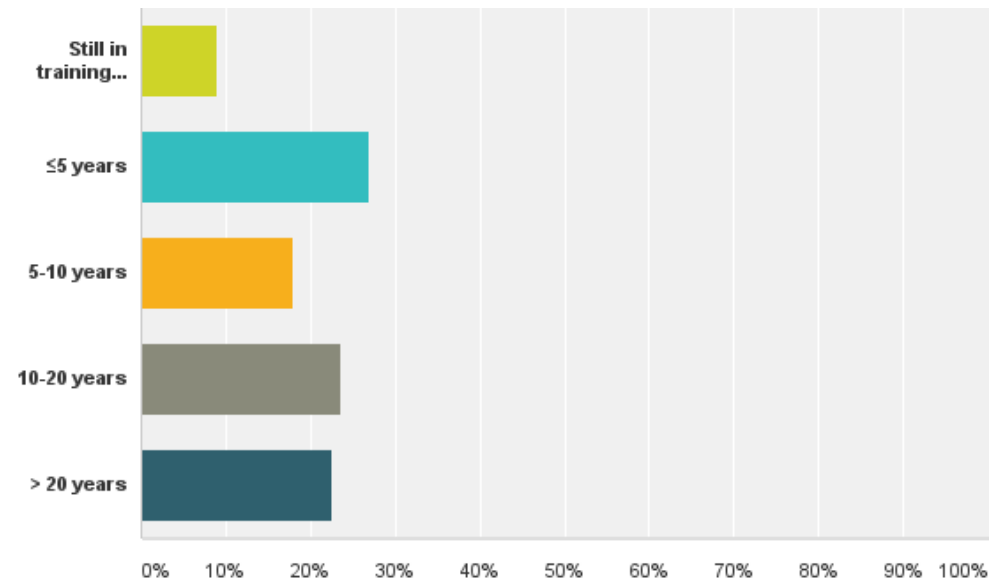
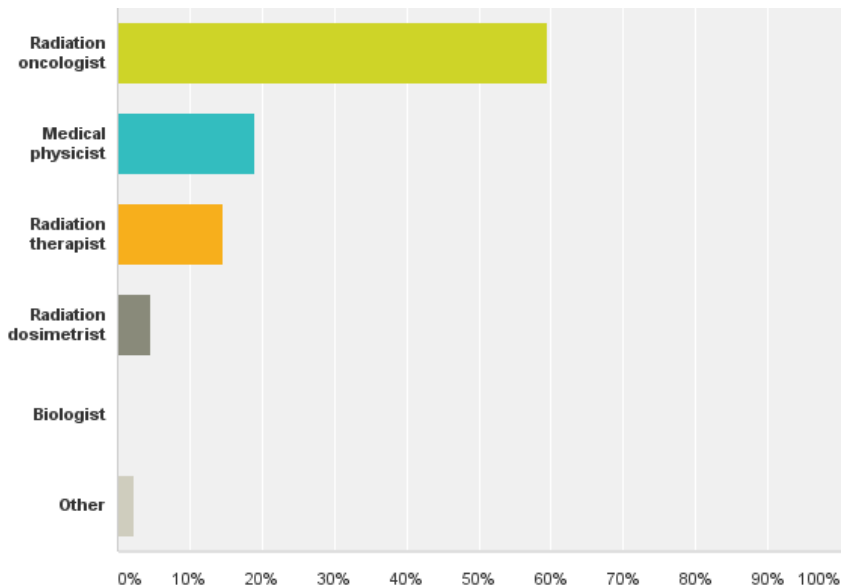


Initial GTV GTV_{res} CTV_{HR} CTV_{IR} CTV_{LR}

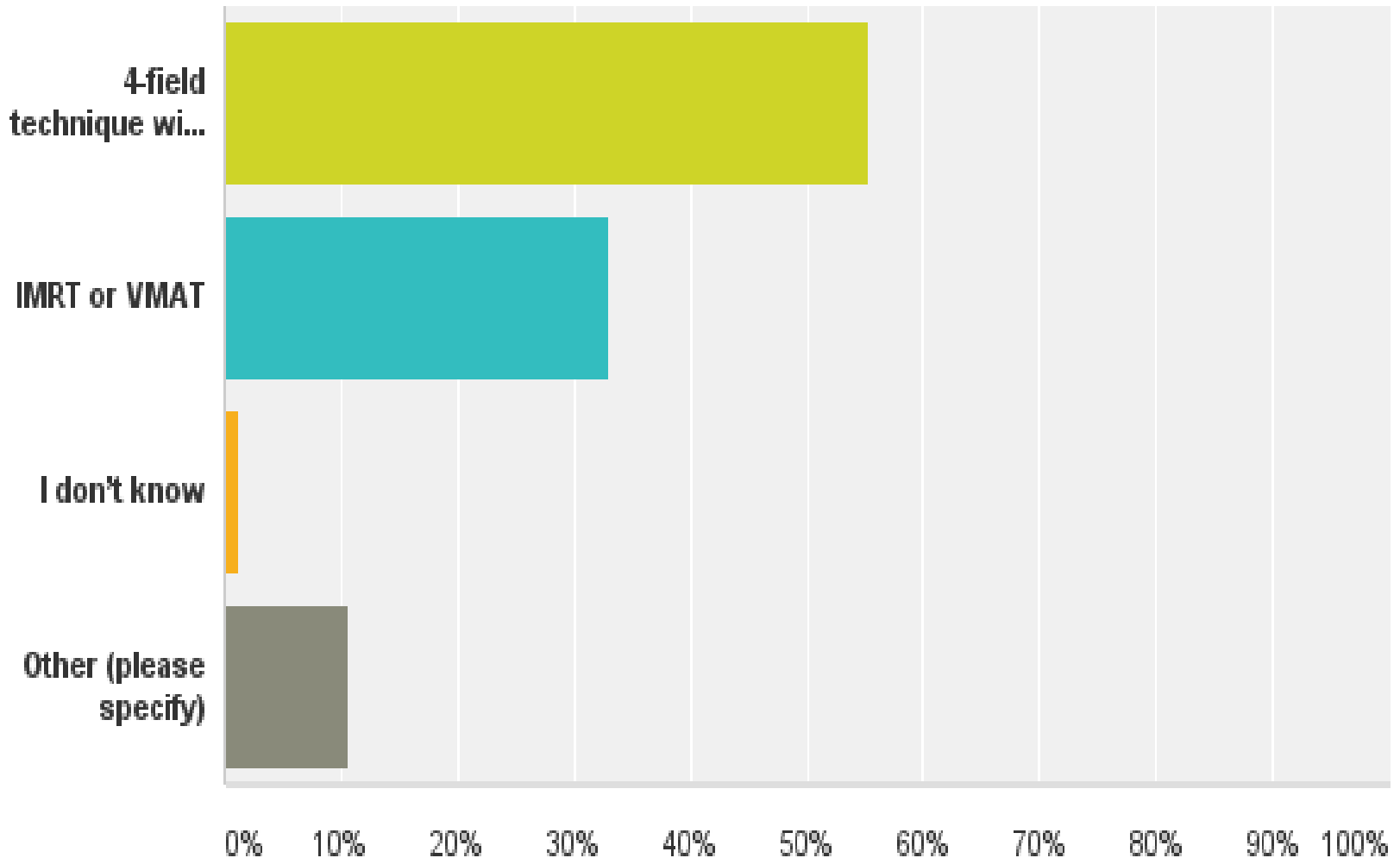
Residual GTV-T, Adaptive HR CTV-T, IR CTV-T

Who are you?

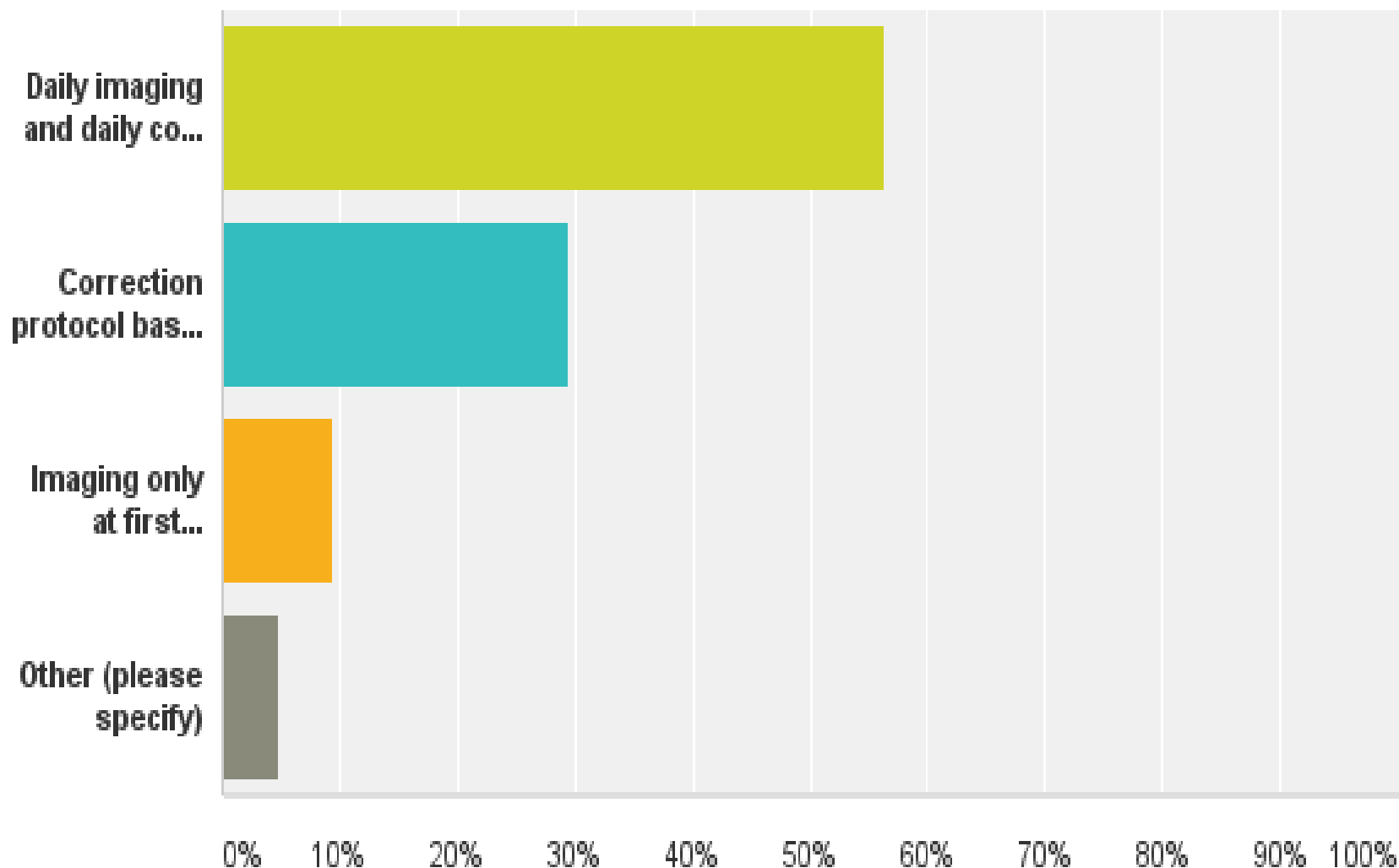
- 110 participants from 11 countries (mainly Canada)



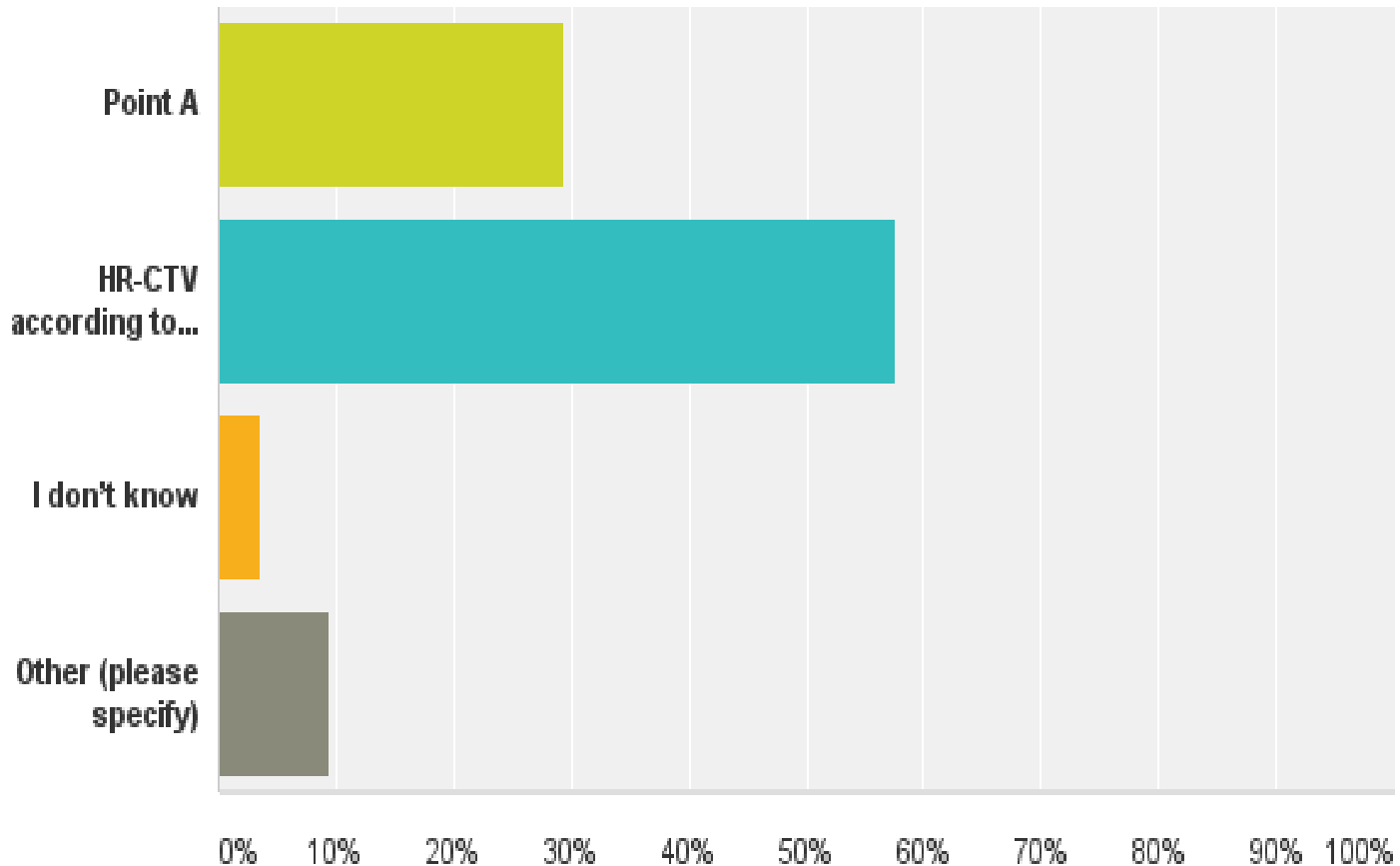
How is external beam pelvic radiotherapy typically delivered?



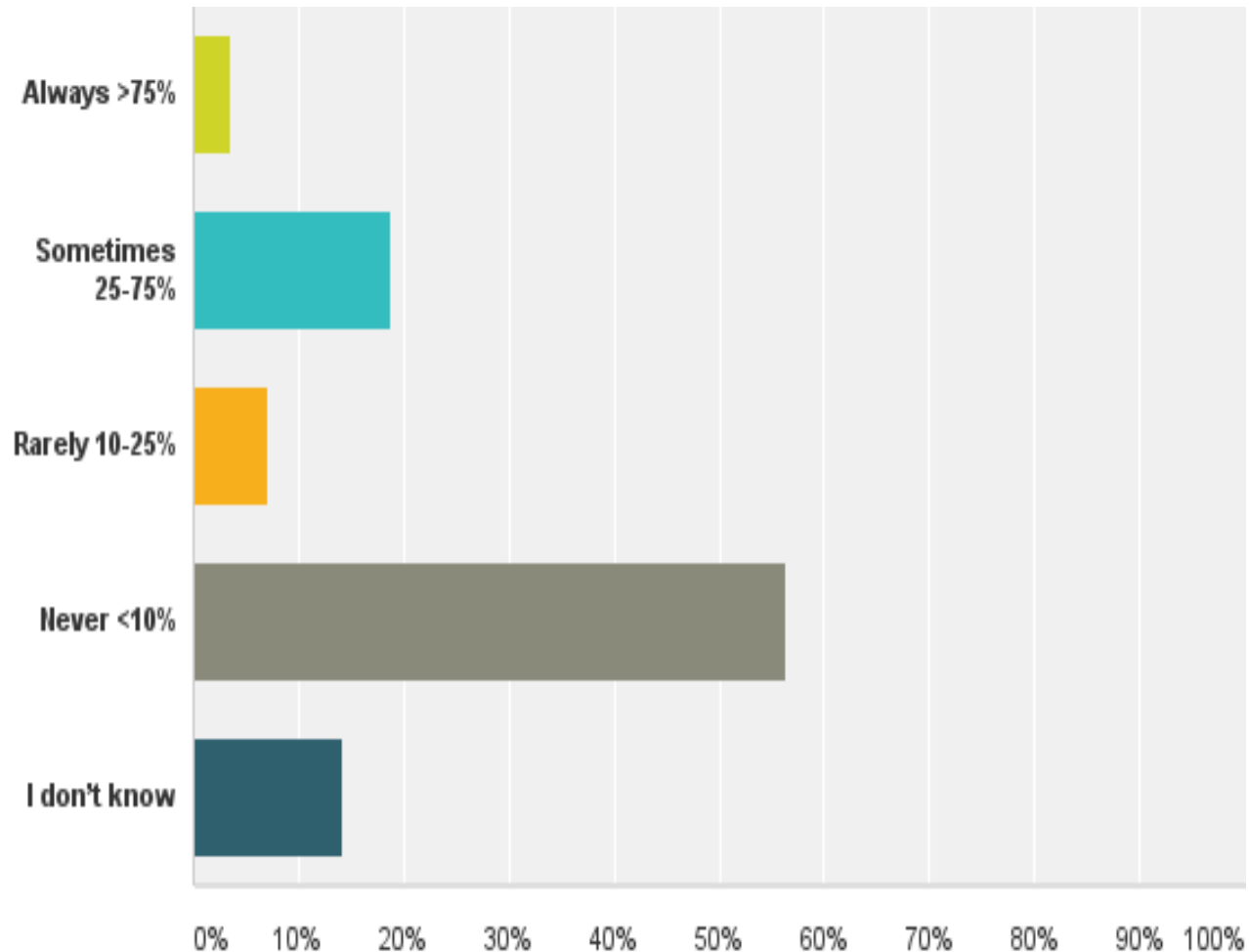
How do you perform image guidance for EBRT?



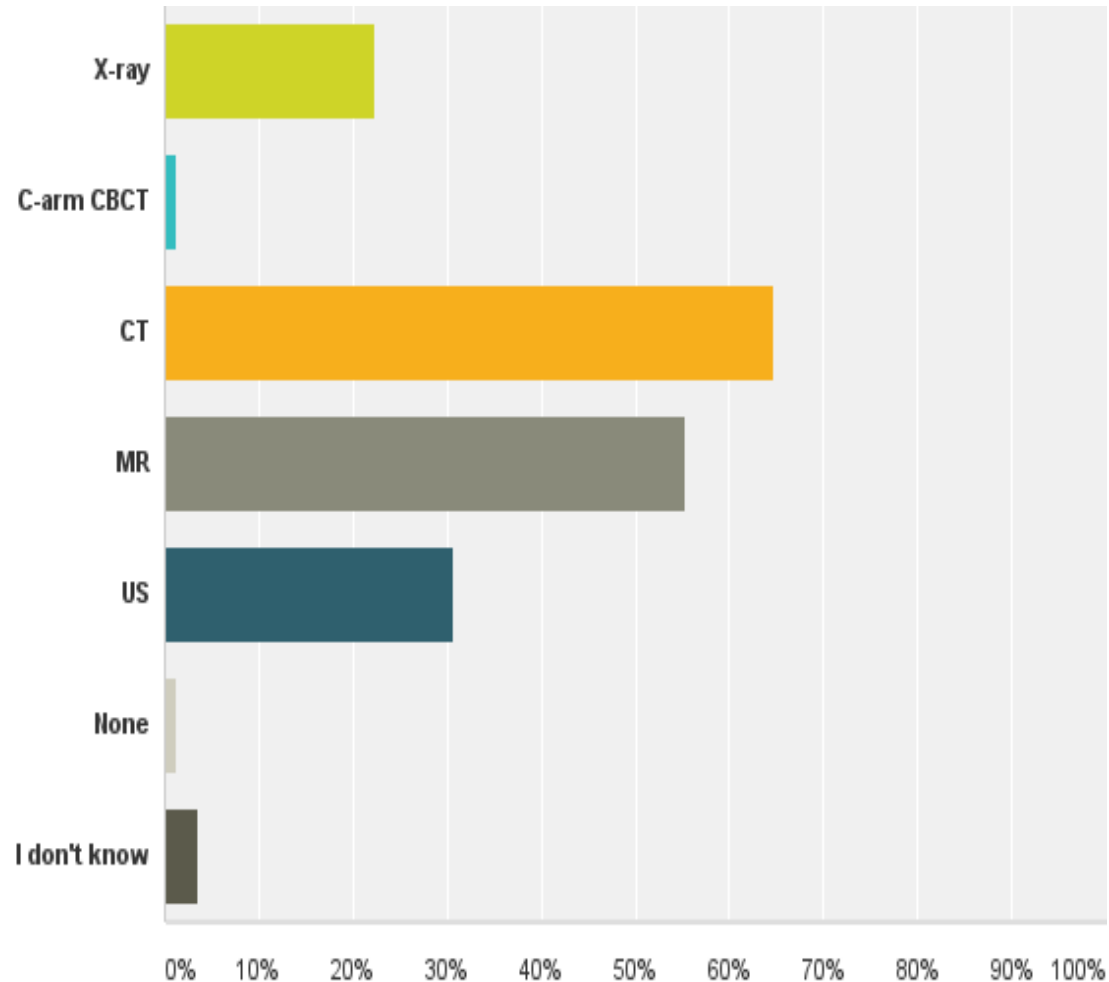
How is cervical cancer brachytherapy typically prescribed at your institution?



How often do you use a combined intracavitary-interstitial applicator for cervix cancer brachytherapy?



What imaging do you perform after applicator insertion?



Support by industry

- **Elekta**
- **Varian Medical Systems**

Organisation

- **Local Organisers:**

- *Mike Milosevic, Radiation Oncologist, PMCC, Toronto*
- *Meredith Giuilani, Radiation Oncologist, PMCC, Toronto*

- **ESTRO coordinator:**

- *Melissa Vanderijst, Project Manager, ESTRO office, Brussels*

- **Above all:**

- *The enthusiastic teaching staff*
- *The enthusiastic participants*

Anatomical considerations, clinical examination, and staging

**Taymaa May, MD MSc FRCSC
Gynecologic Oncologist
Princess Margaret Cancer Center
Assistant Professor
University of Toronto**

Disclosure

- I have No financial disclosures

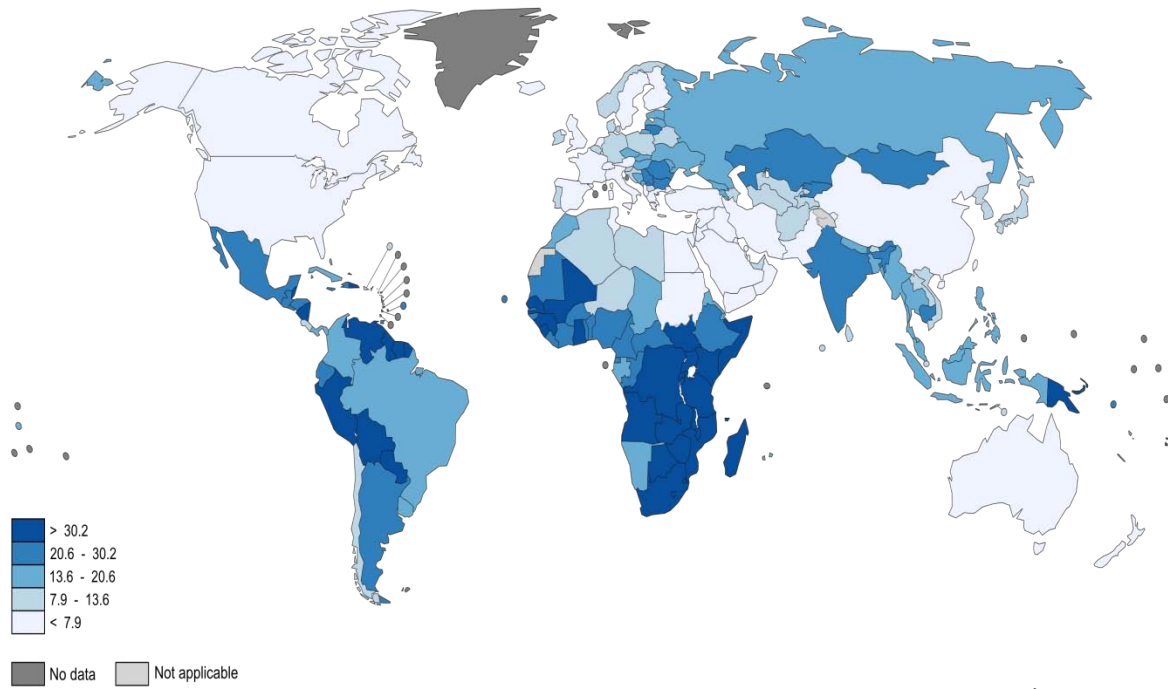
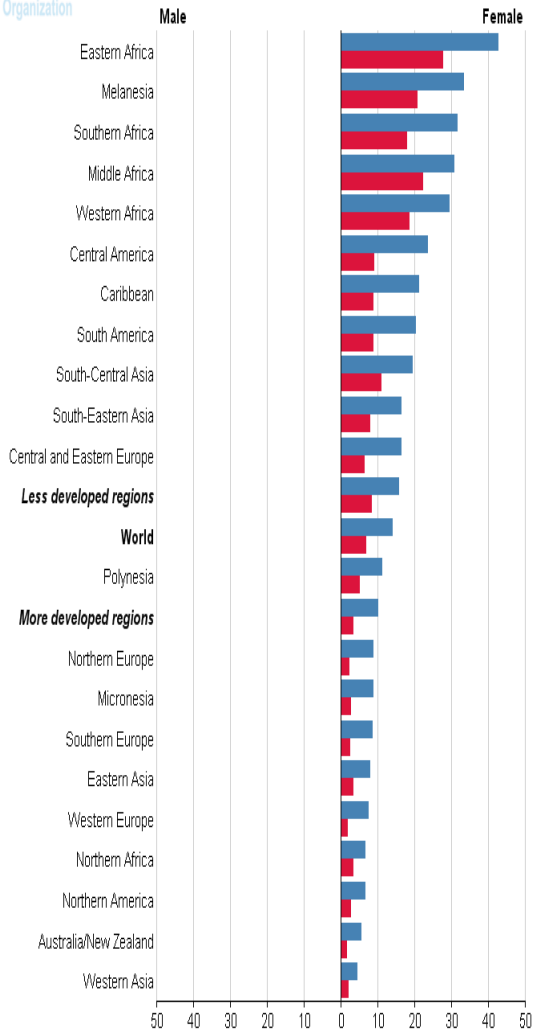


Objectives

- Clinical review of cervical carcinoma
- Review of relevant gynecologic anatomy
- Standard surgical management and surgical staging
- Advancements and new surgical techniques

Cervical Cancer Incidence

International Agency for Research on Cancer



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
 Map production: IARC
 World Health Organization

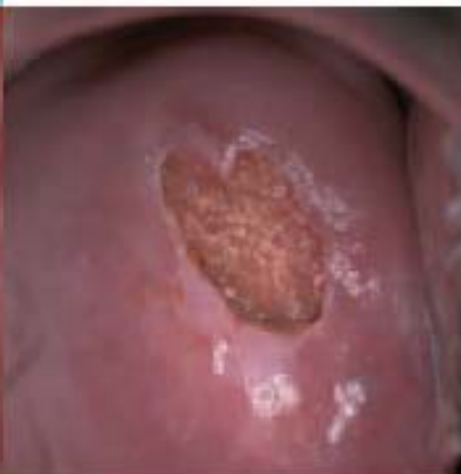
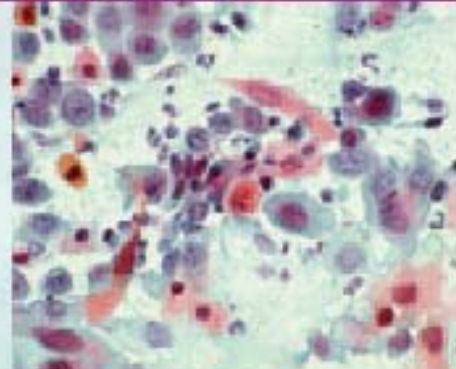
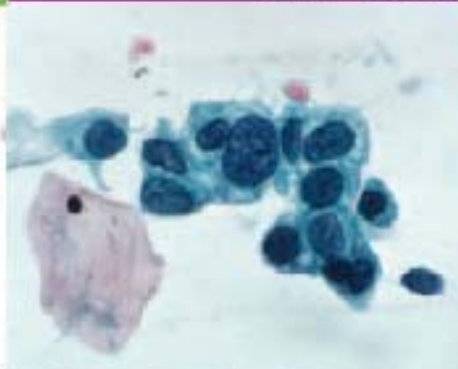
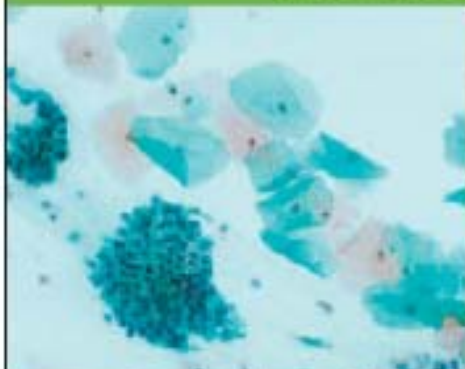


■ Incidence
■ Mortality

Cervical screening

Transient infection

HPV viral persistence



Normal cervix

Infection



Clearance

HPV-infected cervix

Progression



Regression

Precancerous lesion

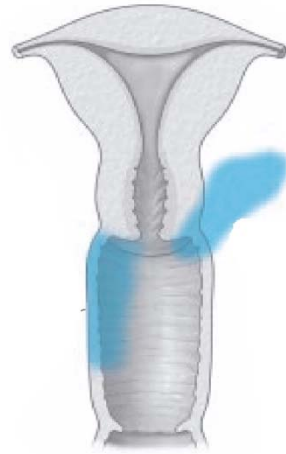
Invasion



Cancer

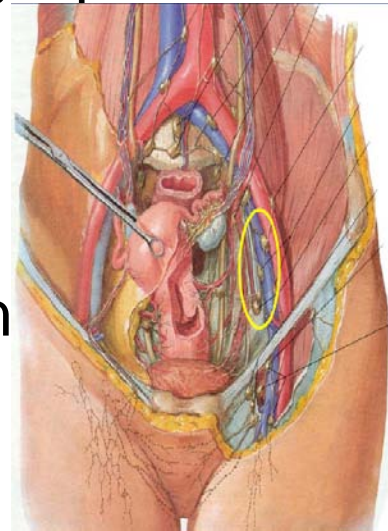
Patterns of Spread

- **Direct Invasion:** cervical stroma, vagina, parametrium

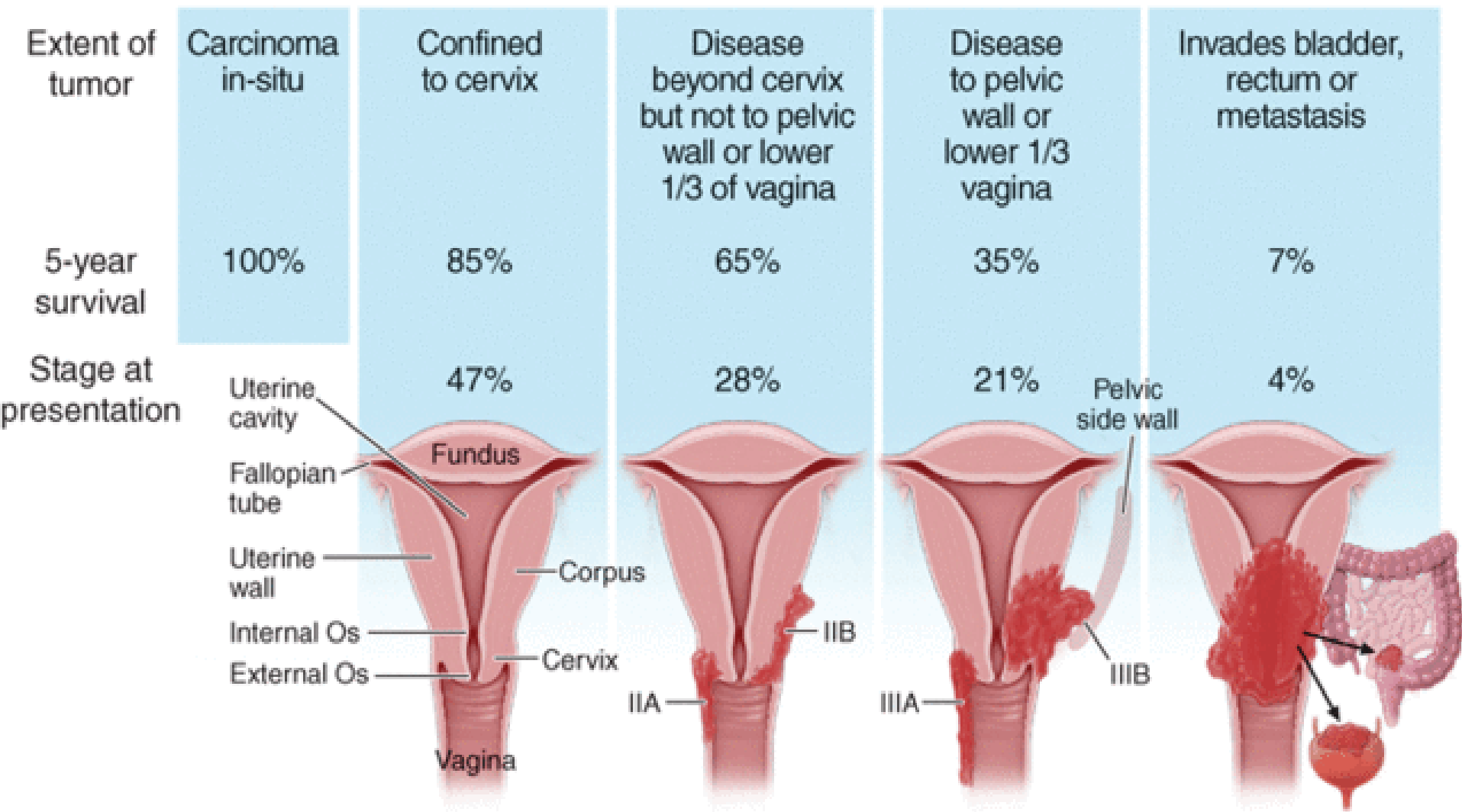


- **Lymphatic spread:** pelvic and then para-aortic lymph nodes

- **Hematogenous Spread:** lungs, liver, bone, brain

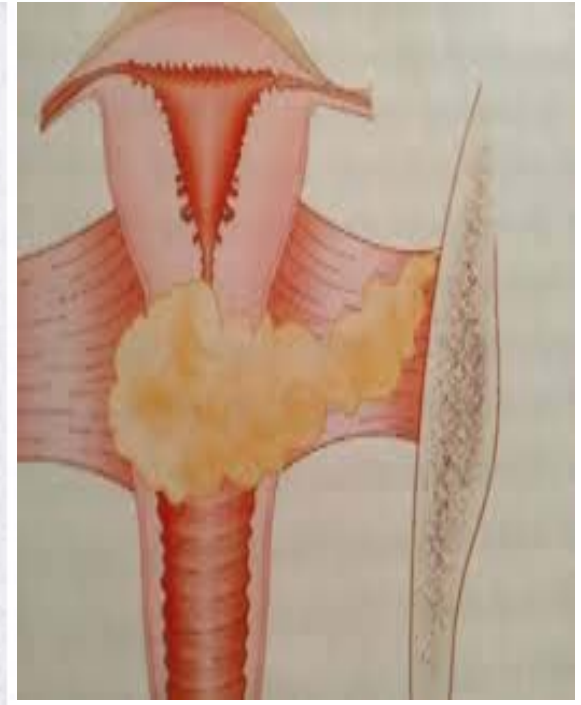
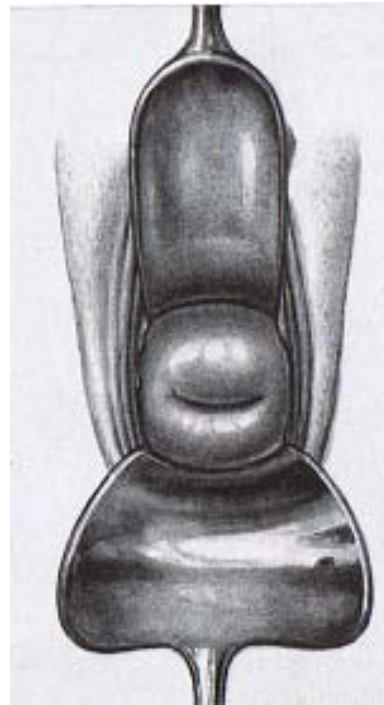
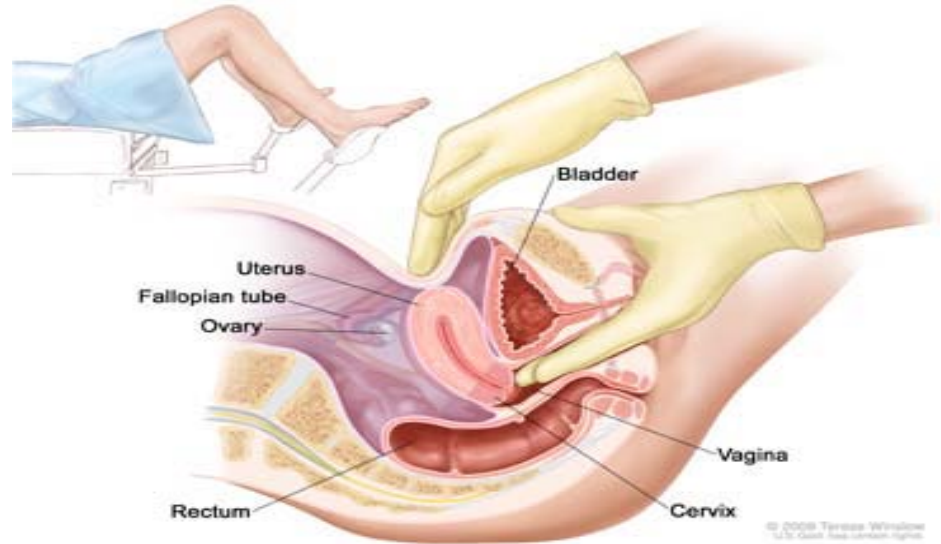


Cervical Cancer



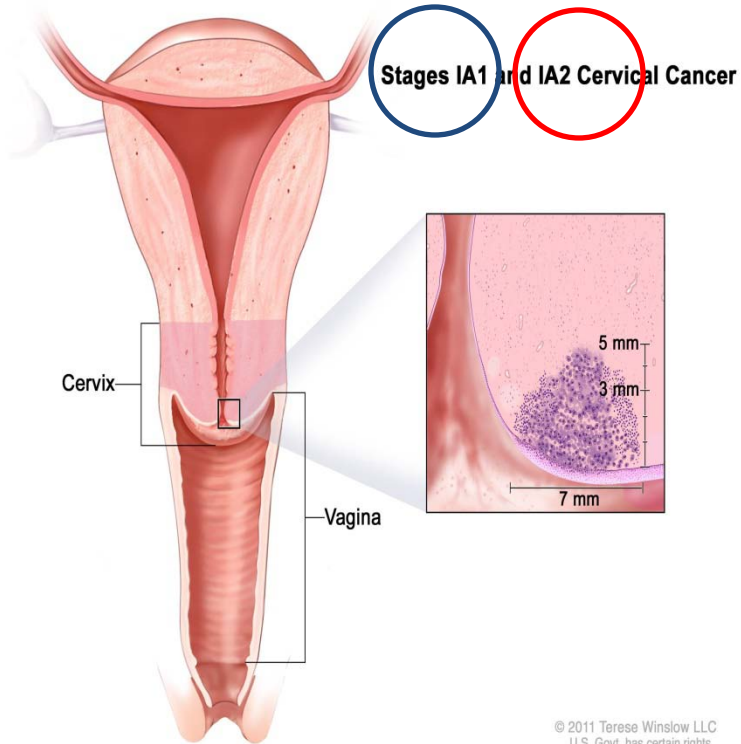
Clinical examination

- Speculum examination
 - Inspect the cervix, vagina and external genitalia
 - Cytology
 - Biopsy
- Bimanual pelvic examination
 - Assess the uterus
 - Assess the adnexa
- Pelvic/Rectal exam
 - Assess the cul de sac
 - Assess the parametrial tissue
 - Assess the pelvic side wall

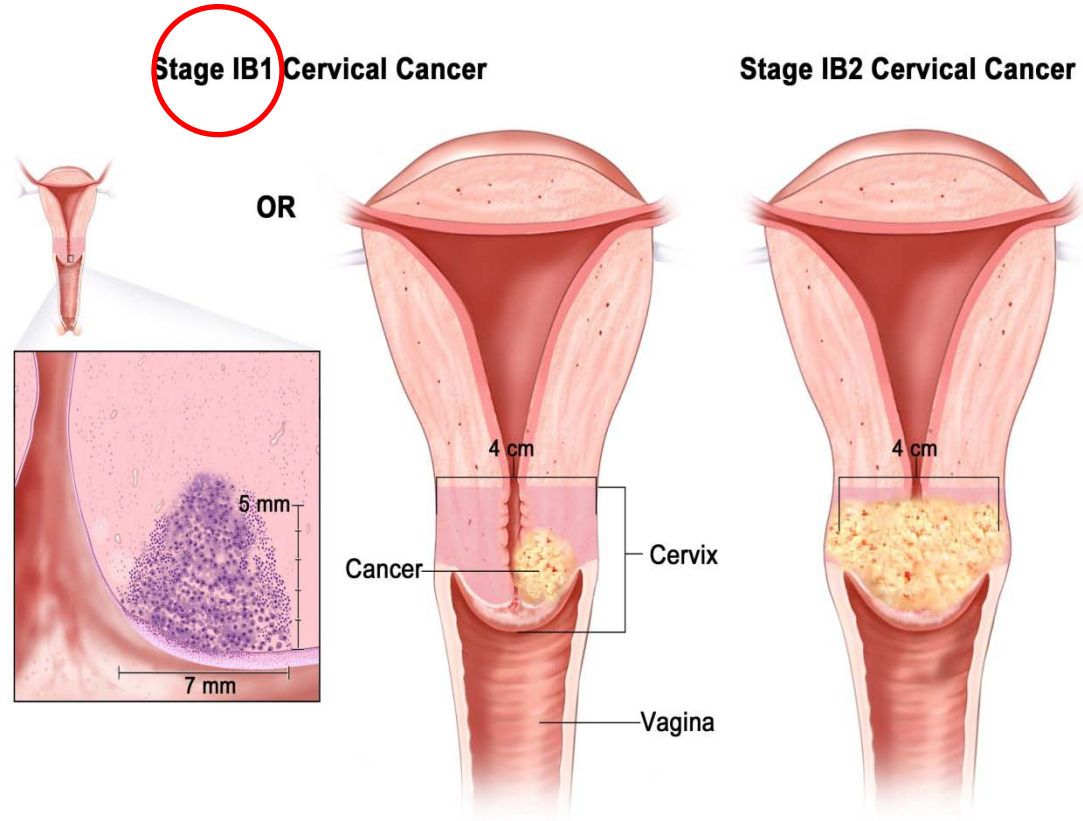


Surgical treatment options

Simple Hysterectomy



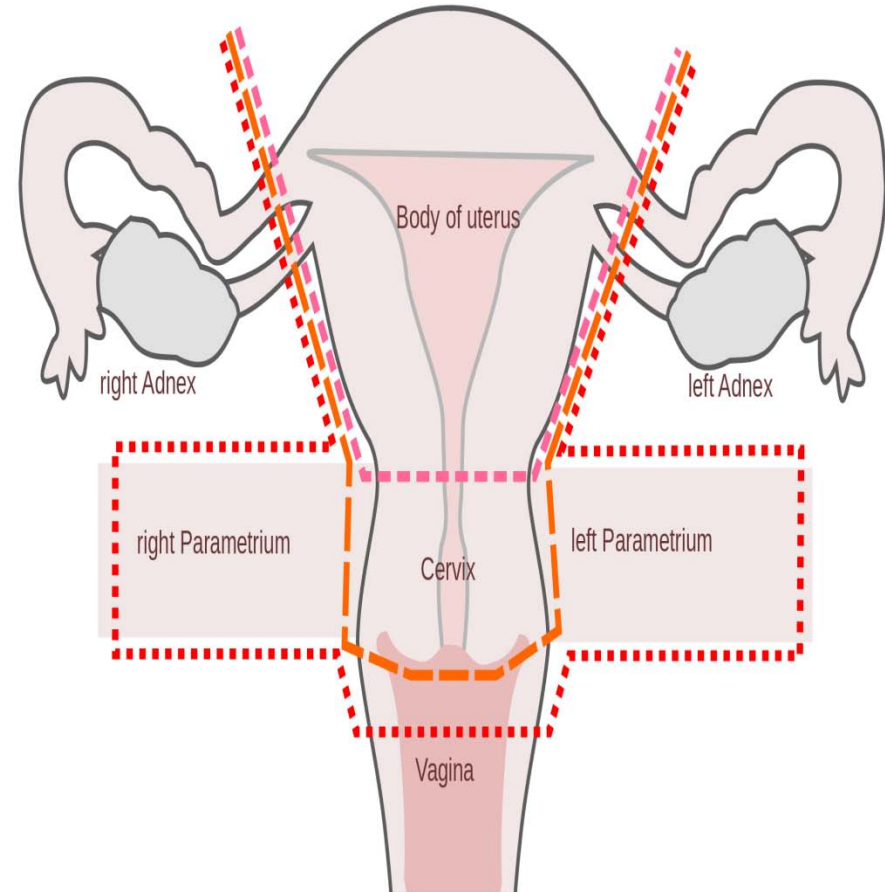
Radical Hysterectomy



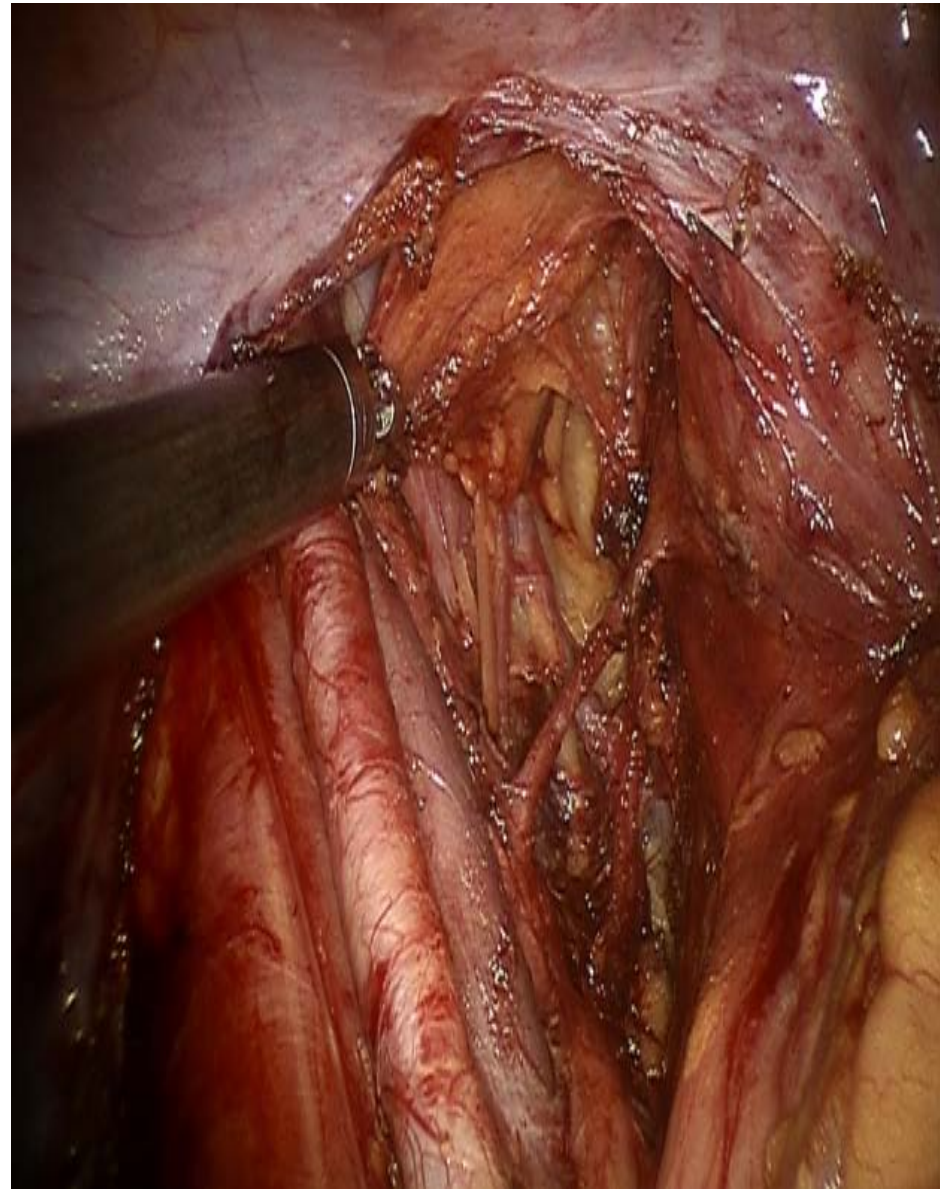
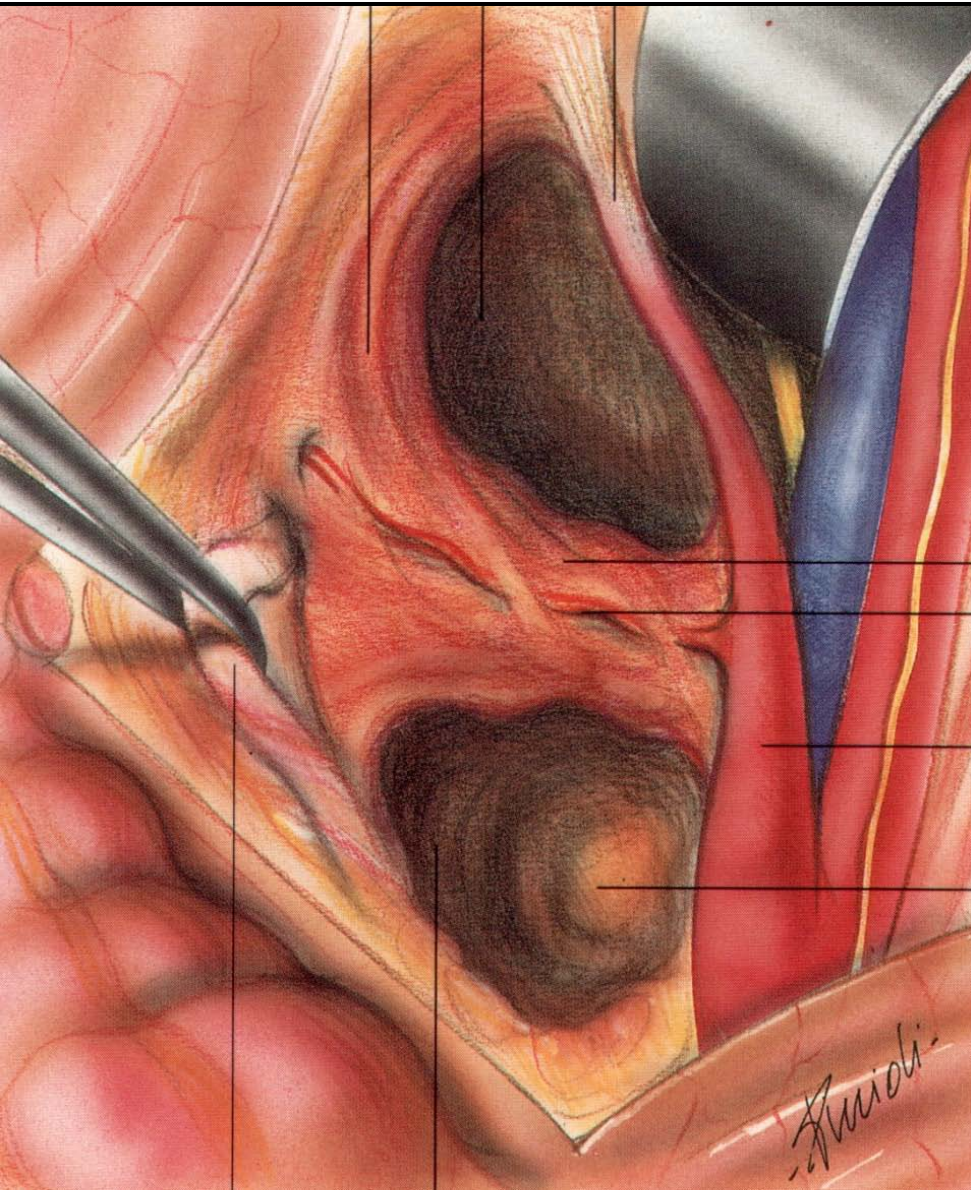
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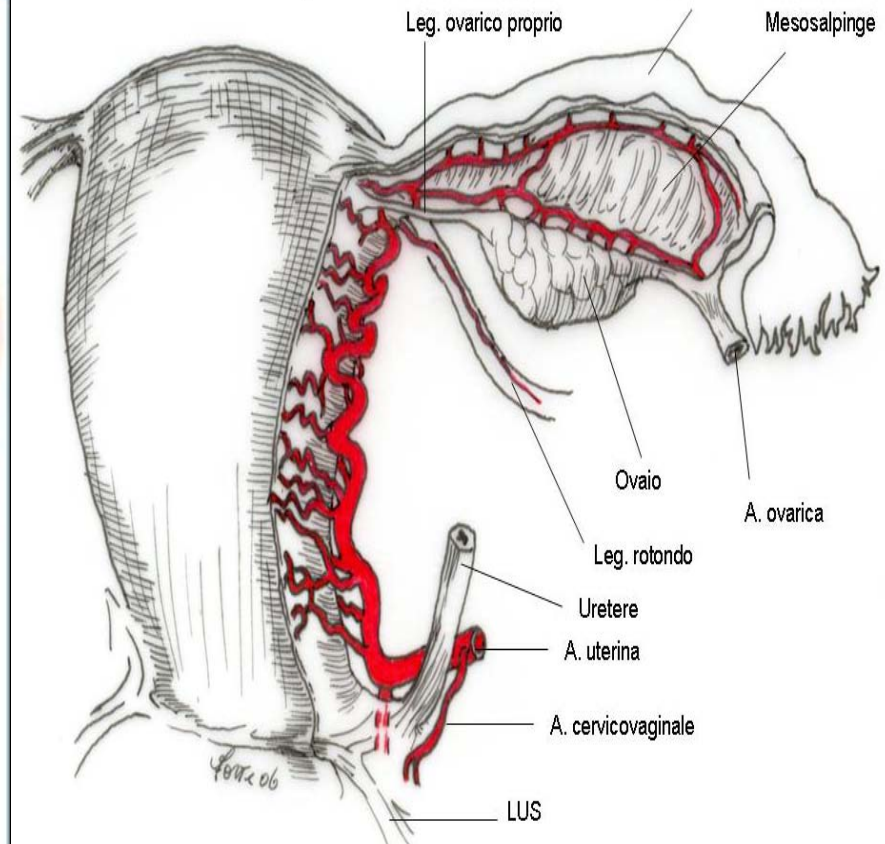
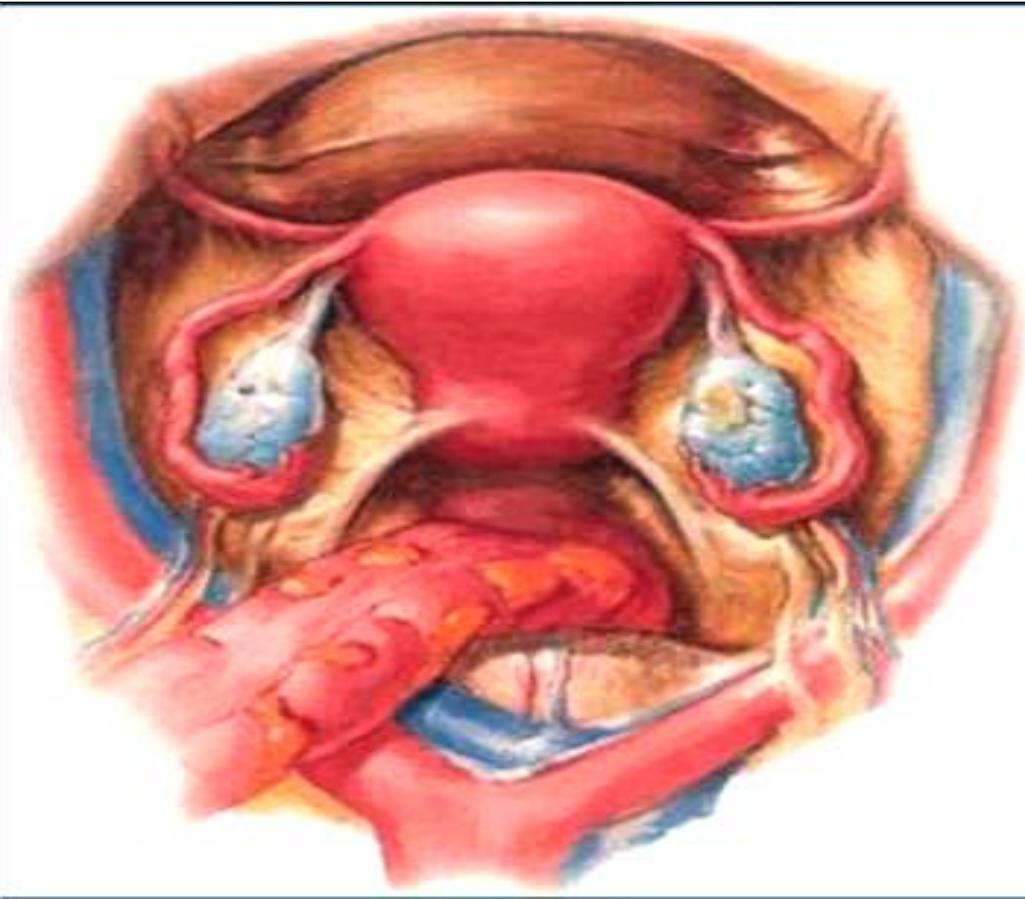
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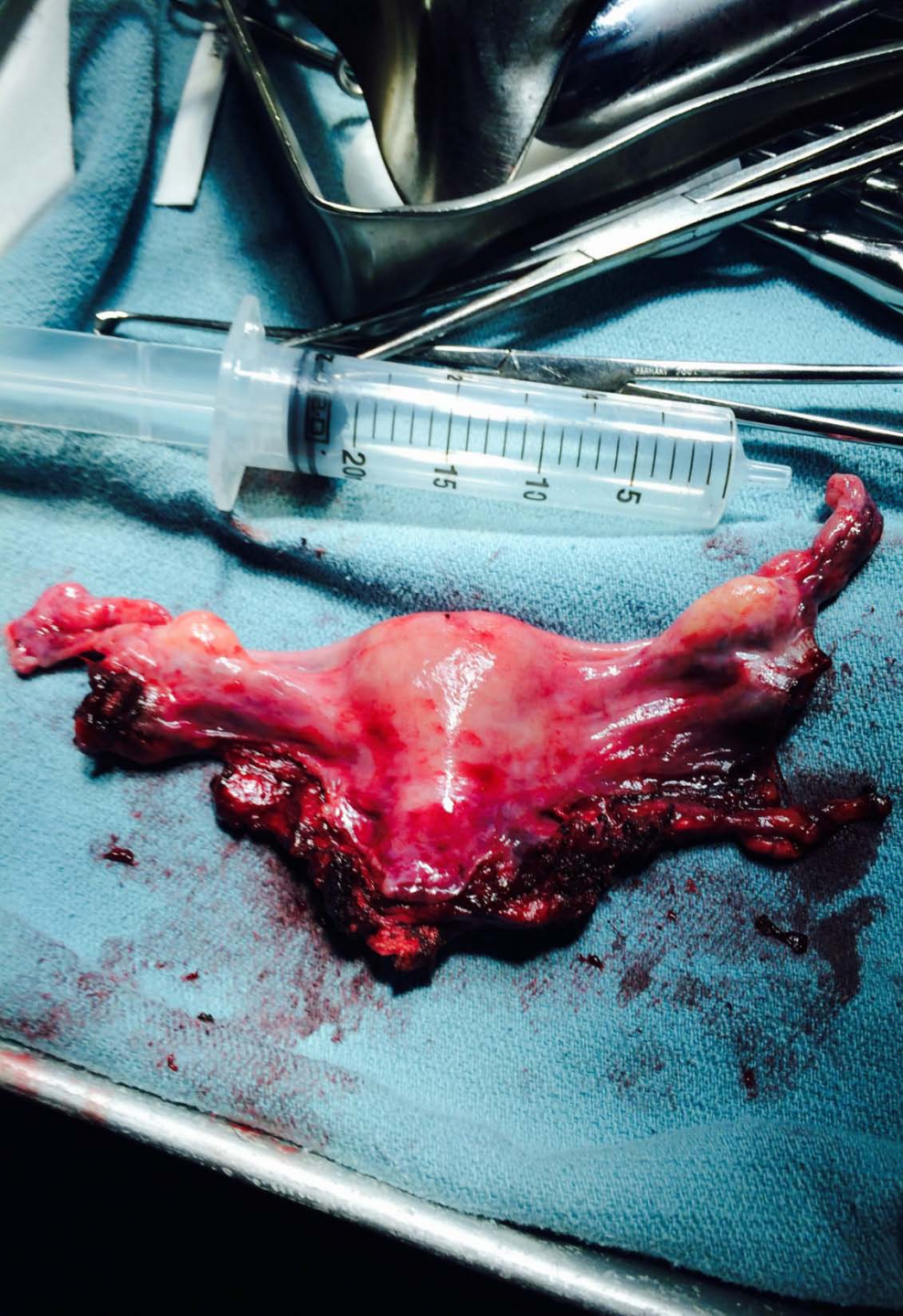
Hysterectomy



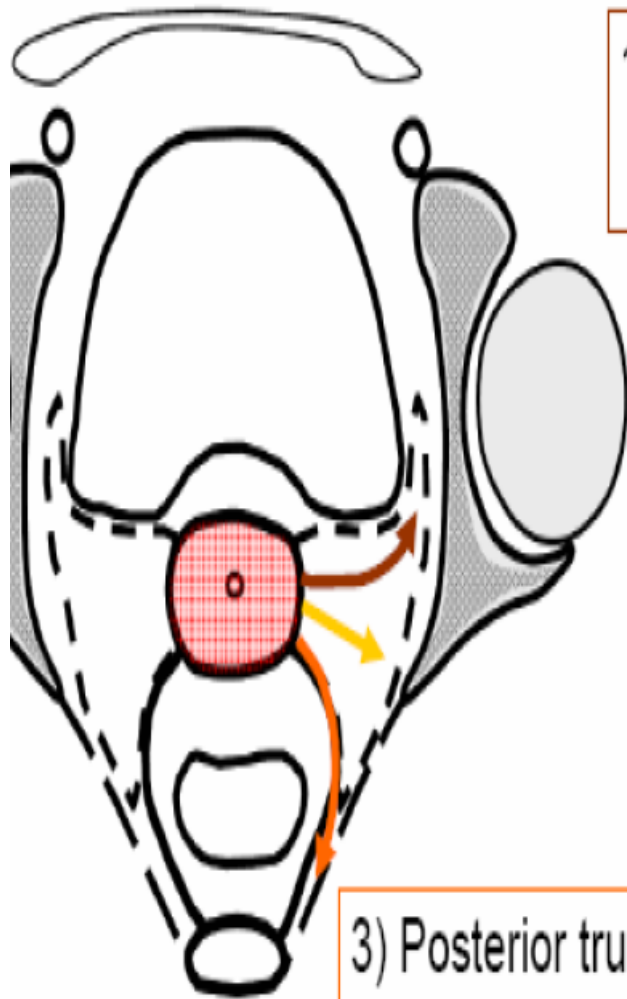
Retroperitoneal Dissection







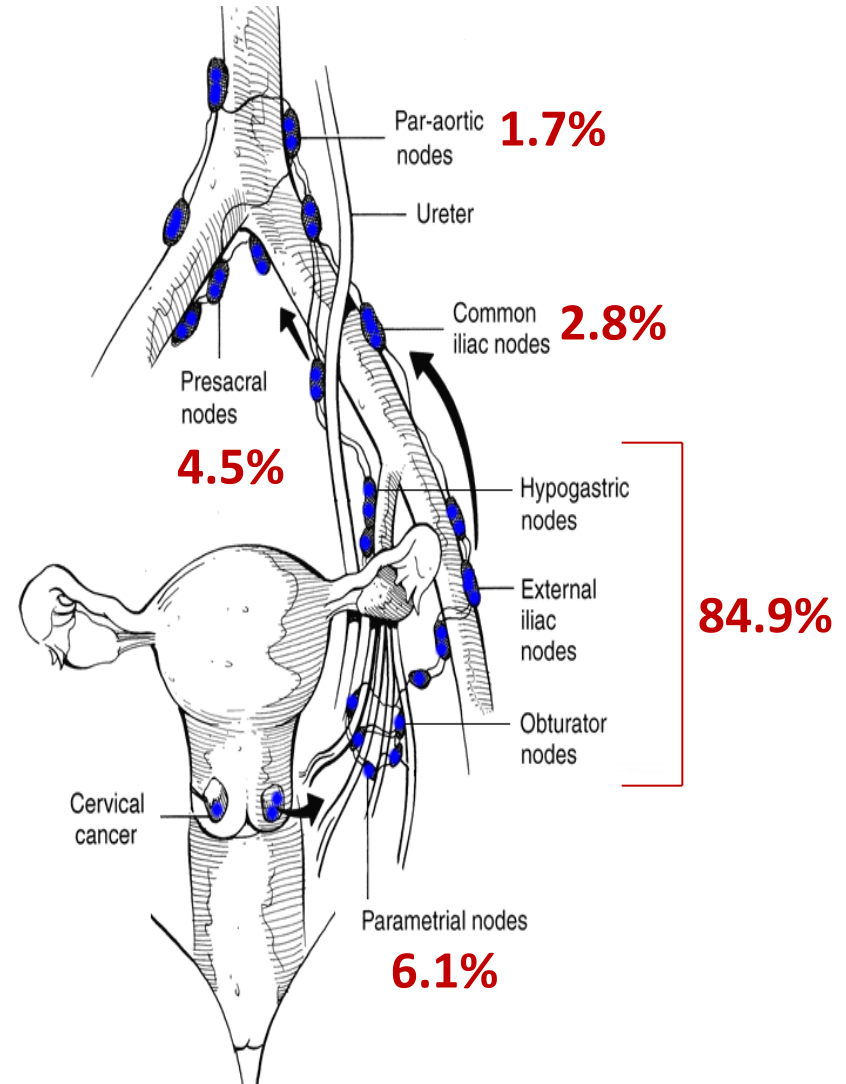
Lymphatic Spread



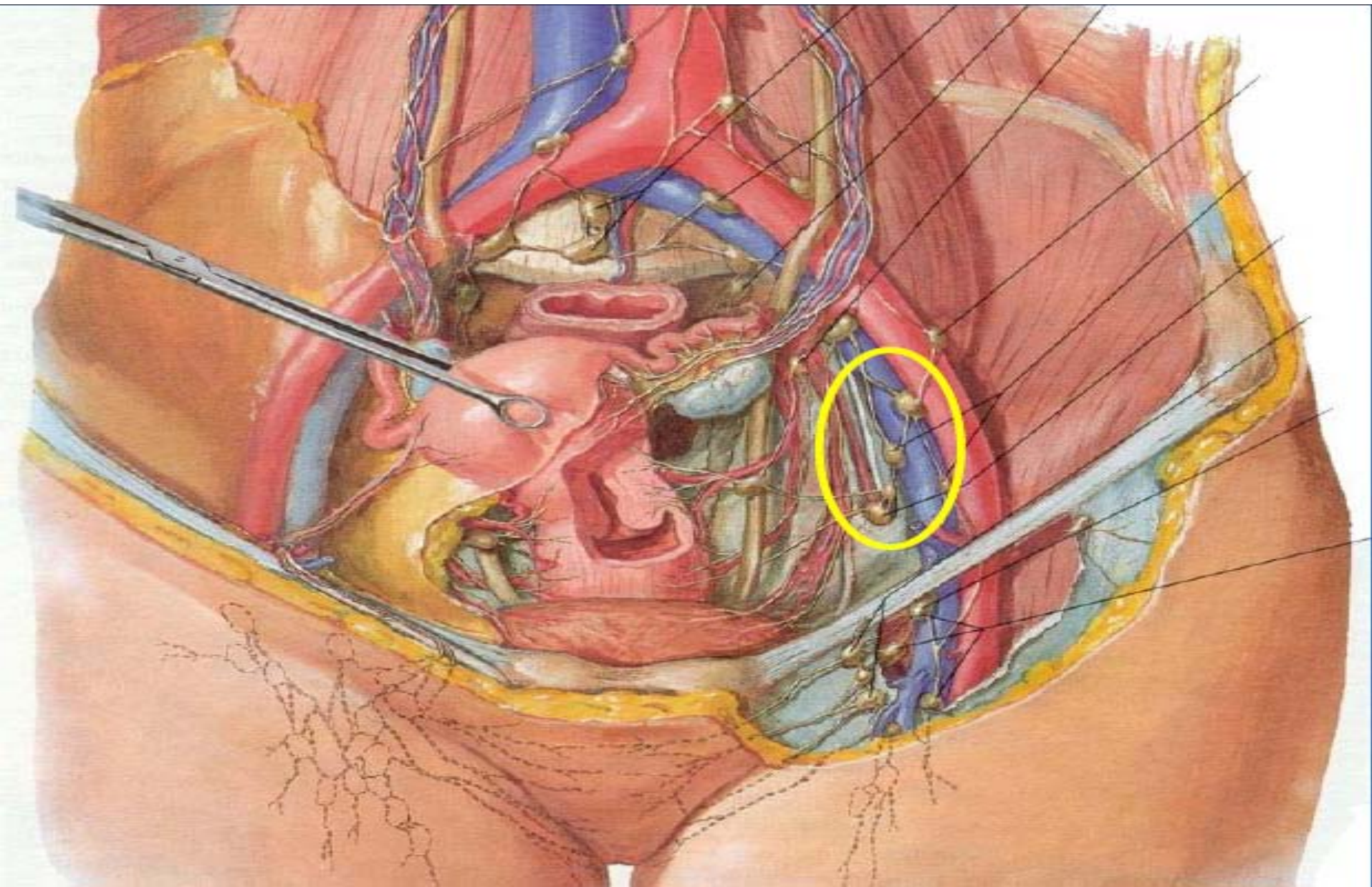
1) Anterior trunk
Ext. iliac

2) Lateral trunk
Parametrial
Obturator
Int. iliac

3) Posterior trunk
Presacral



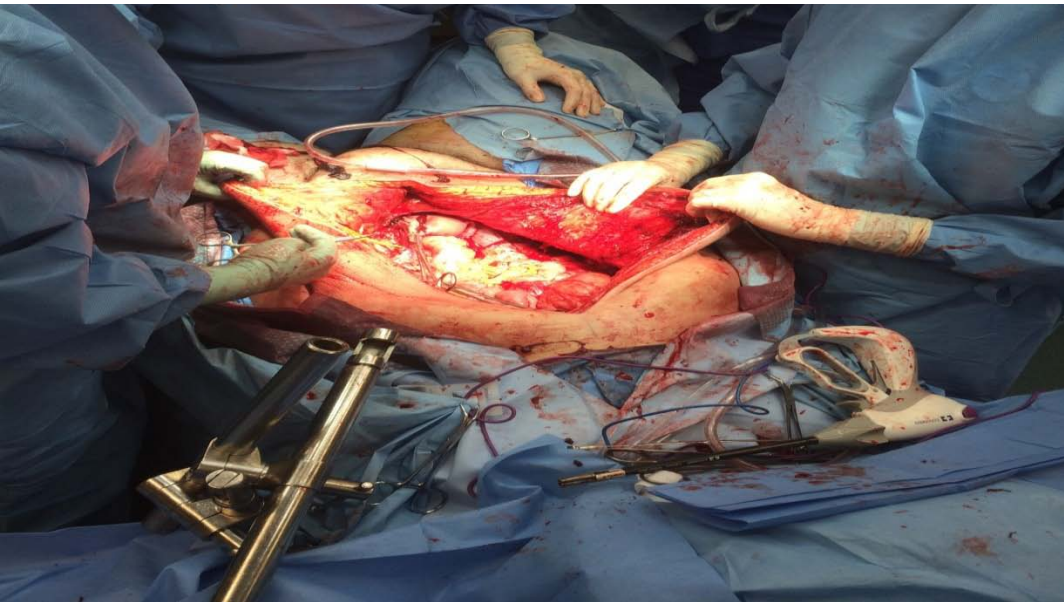
Pelvic Lymphadenectomy



Minimally Invasive Surgery vs. Laparotomy

Oncologically equivalent

Fewer short term complications in MIS



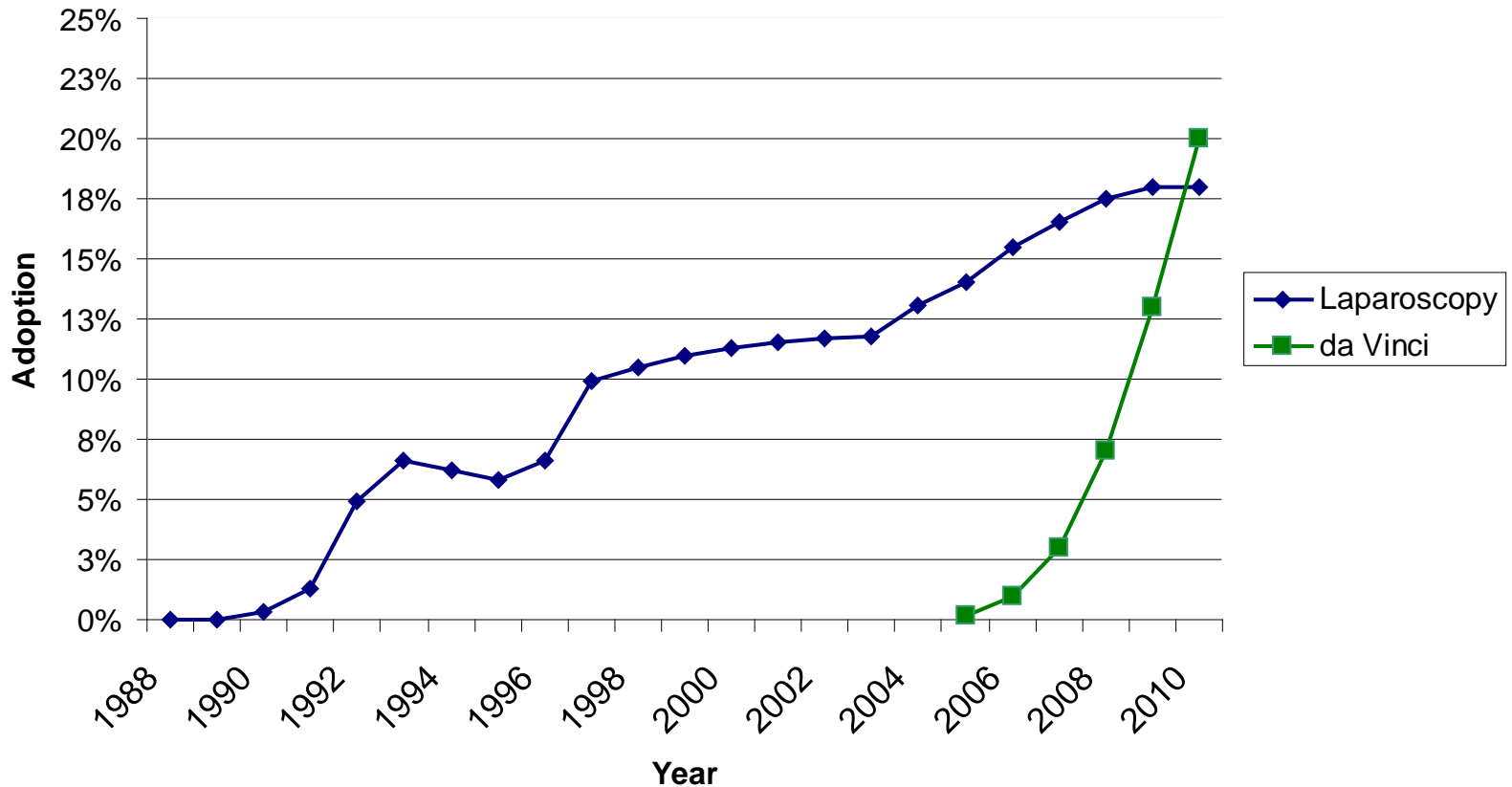
Introduction to MIS

- MIS was introduced to gynecologic oncology in 1990s
- Began to replace the traditional open surgery for cancer staging



Laparoscopy vs. Robotic

Adoption of MIS for Hysterectomy

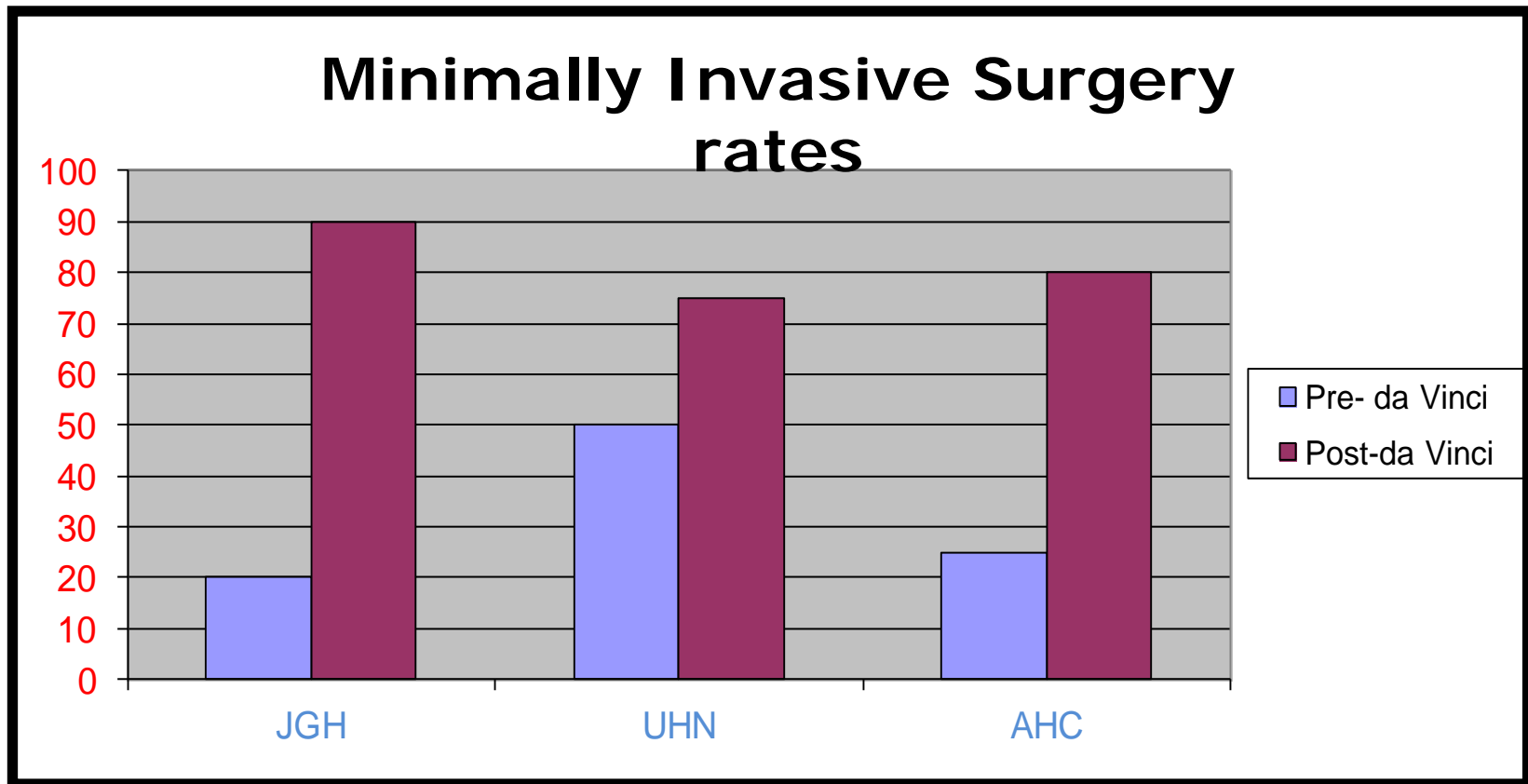


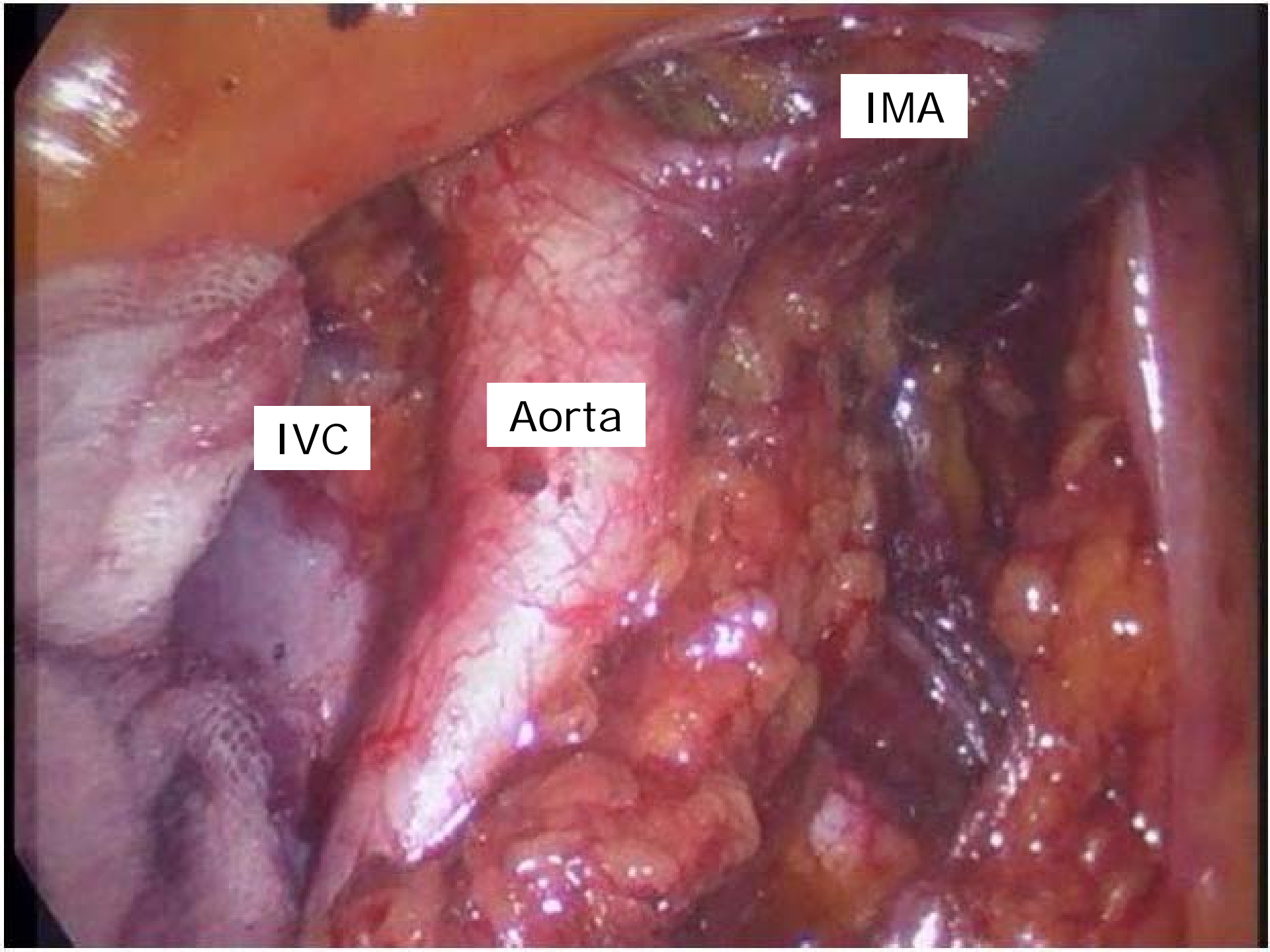
Farquhar et al. "Hysterectomy Rates in the United States: 1990–1997" *Obstet Gynecol* 2002;99:229–34

Becker et al. "Inpatient Surgical Treatment Patterns for Patients with Uterine Fibroids in the United States, 1998–2002" *Journal of the National Medical Assn.* Vol. 97 (10) October 2005

Wu et al. "Hysterectomy Rates in the United States, 2003" *Obstet & Gyn* VOL. 110, NO. 5, NOVEMBER 2007

Canadian Gyn Oncology Experience

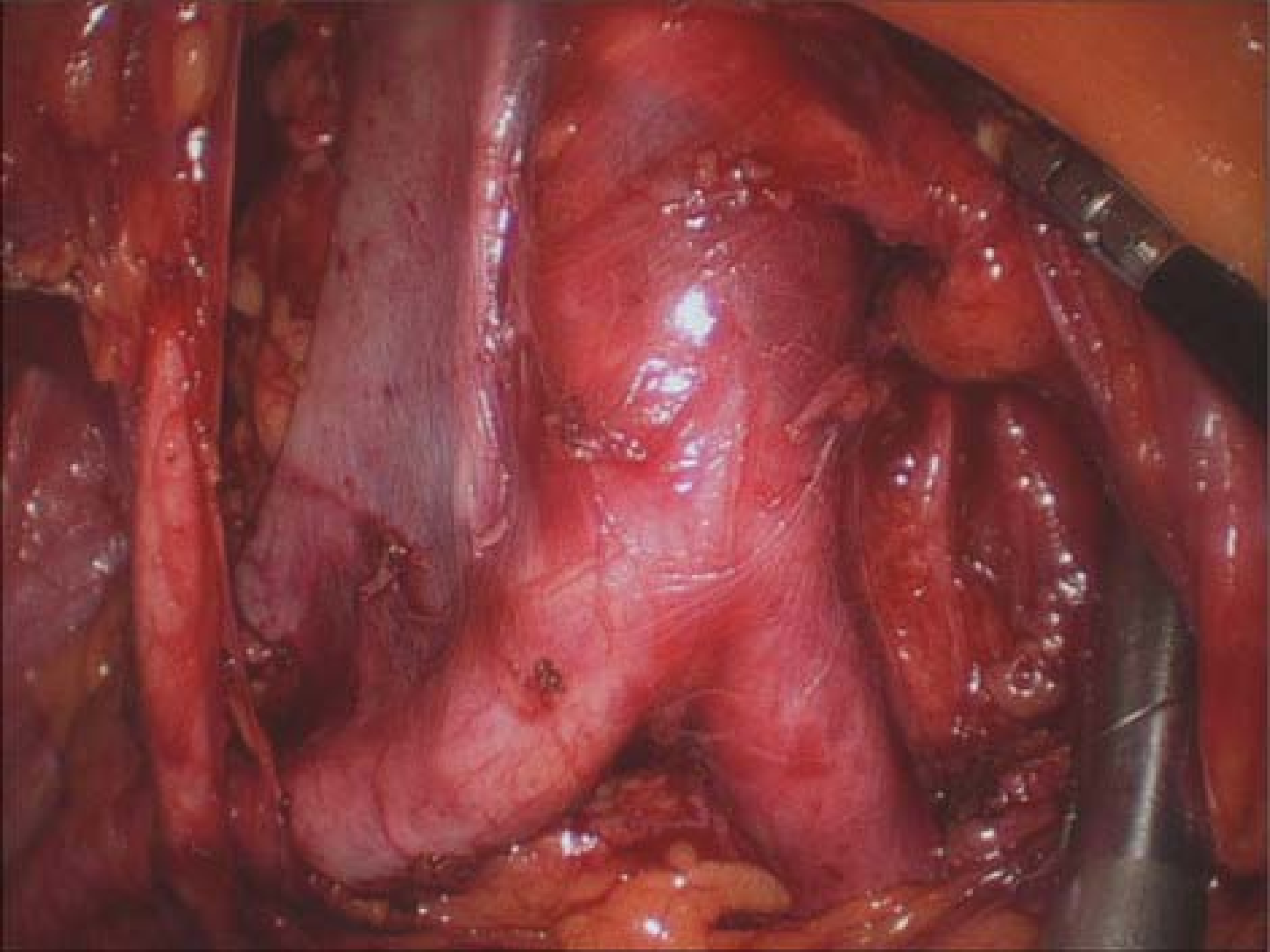


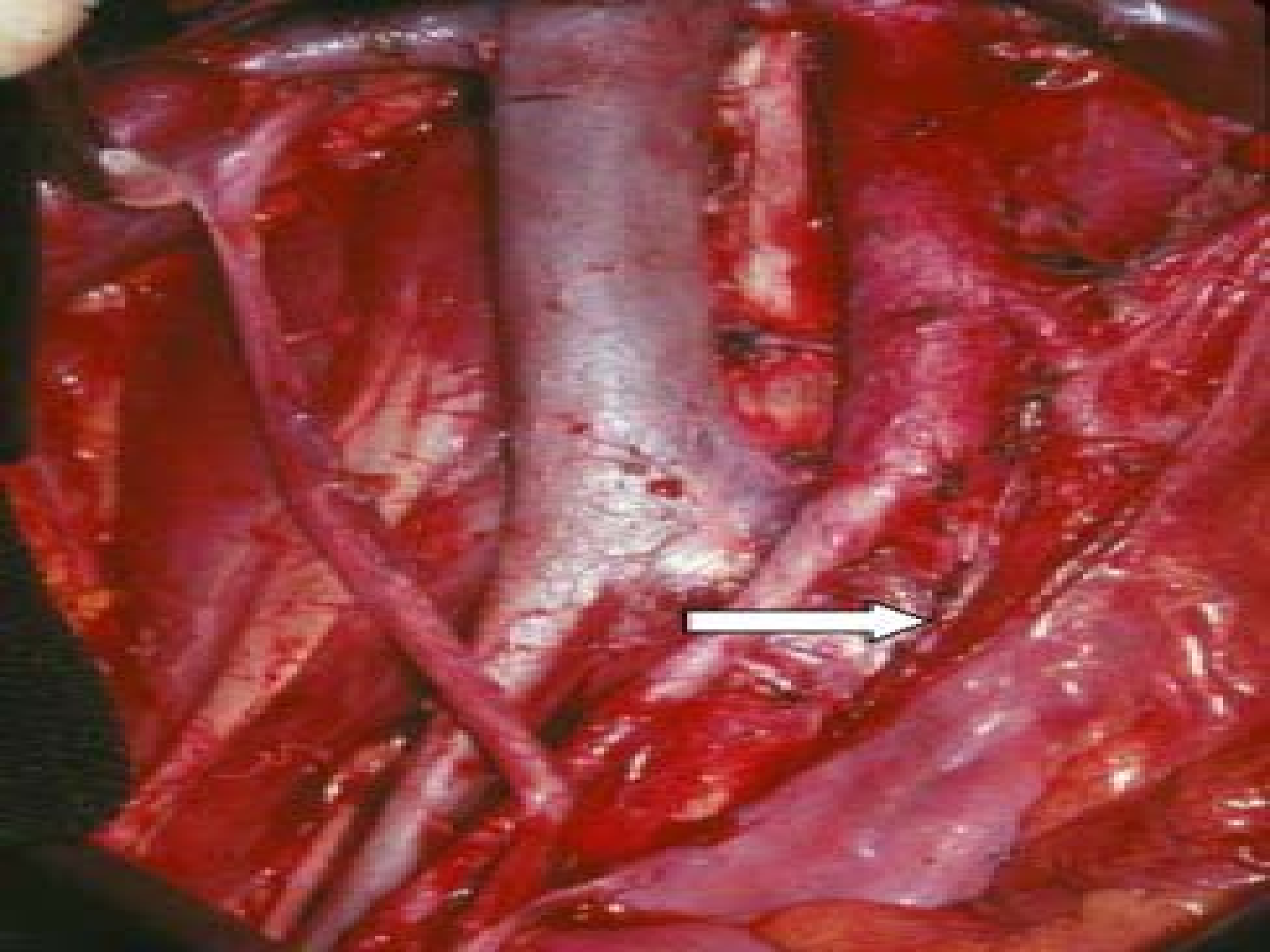


IMA

IVC

Aorta



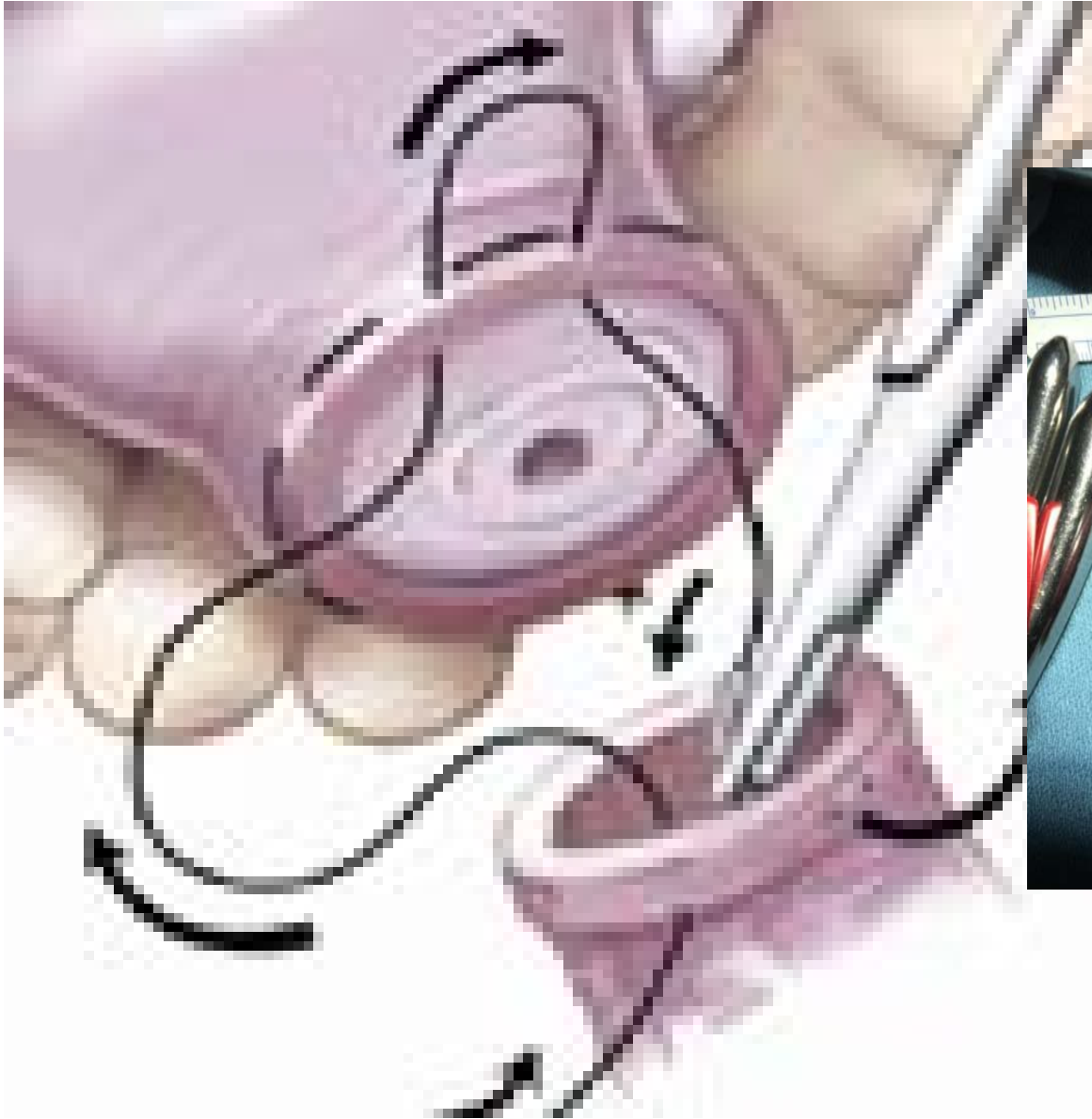


Advances in the surgical management of cervical cancer

- Expanding beyond radical Hysterectomy and Staging



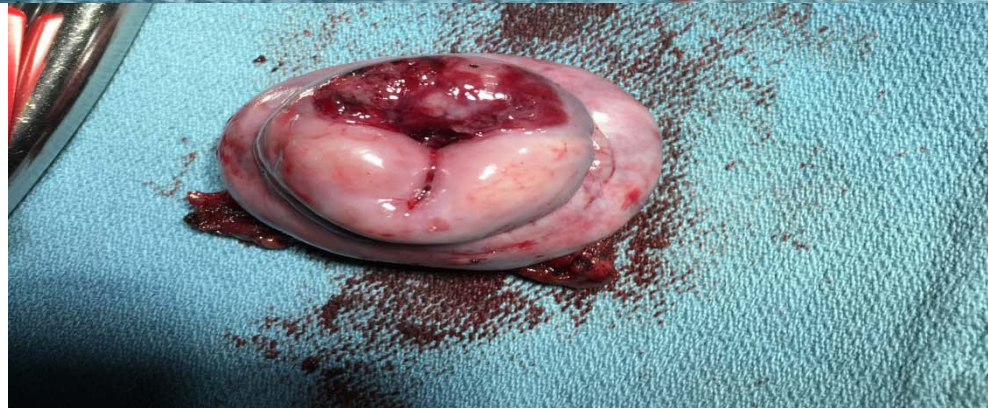
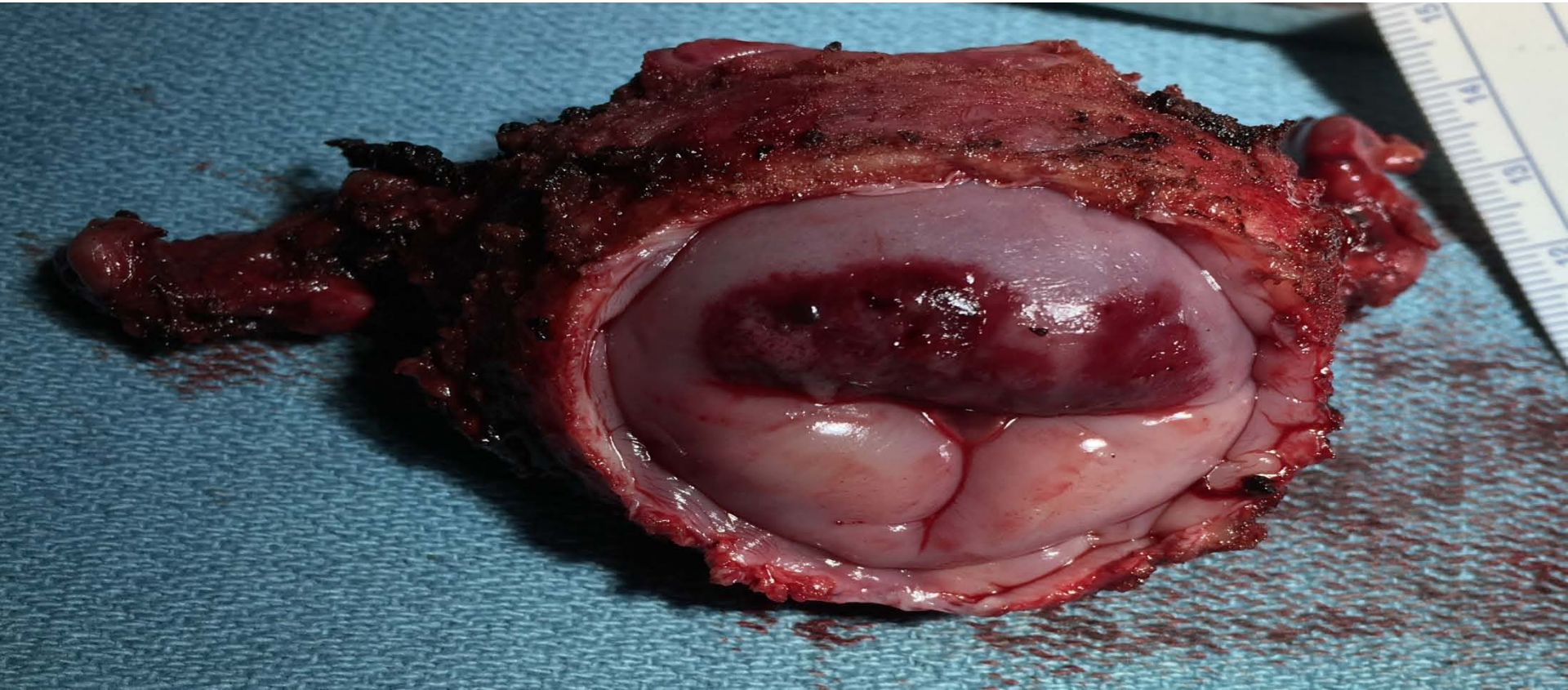
Radical Robotic Trachelectomy



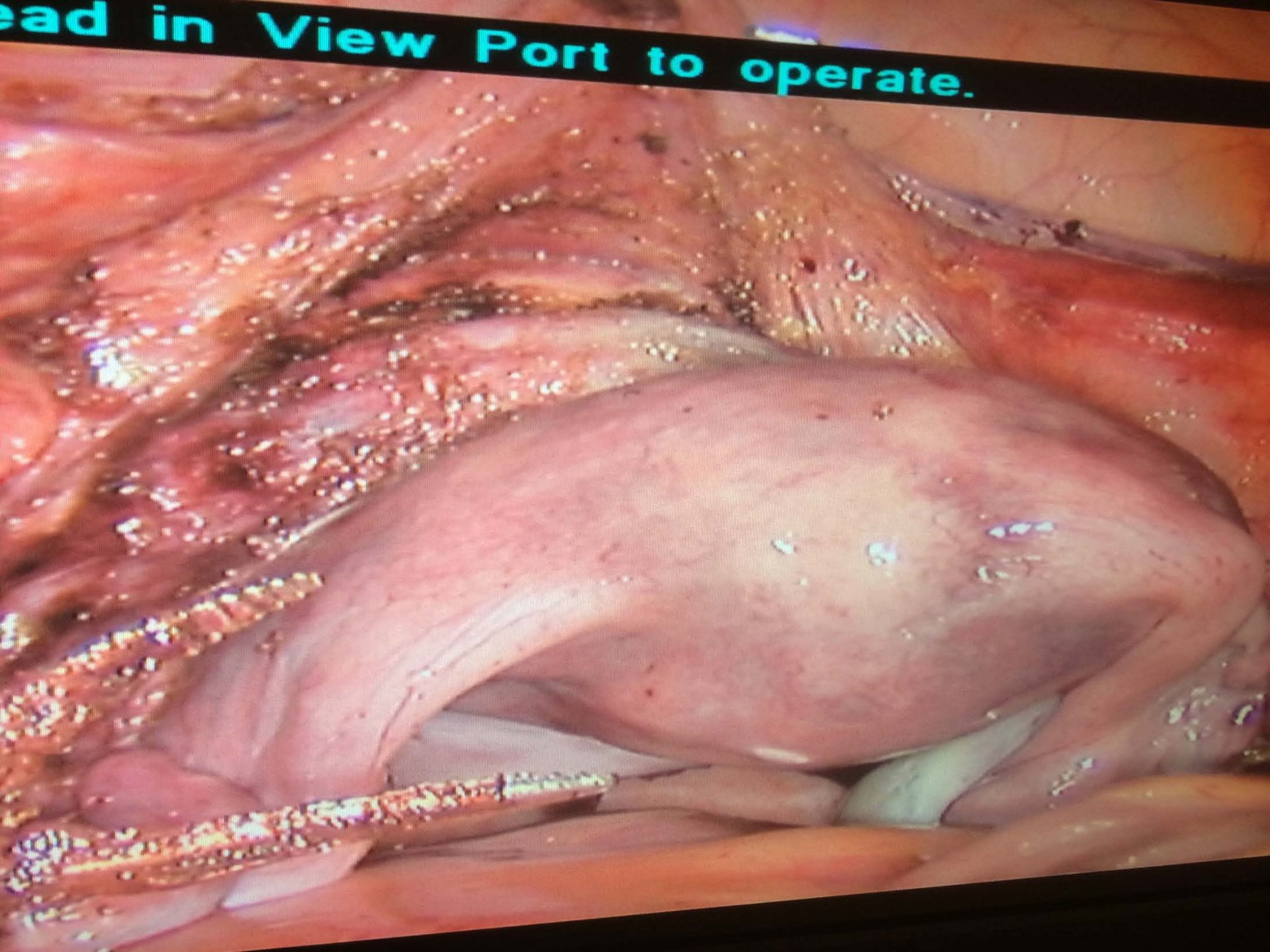
Radical Trachelectomy

- Dargent's operation
 - Described in 1994
 - Laparoscopic pelvic LND
 - Vaginal removal of cervix + parametrial tissue
- Criteria
 - Strong fertility desire
 - Age < 40
 - Stage IA1, LVSI+
 - Stage IA2 or IB1, LVSI- or +
 - Tumor size < 2 cm
 - Limited endocervical involvement
 - No evidence of LN+ or distant metastatic disease
 - Exclusion of unfavorable histology (neuroendocrine)
 - Skilled surgeon

Trachelectomy



Head in View Port to operate.



head in View Port to operate.



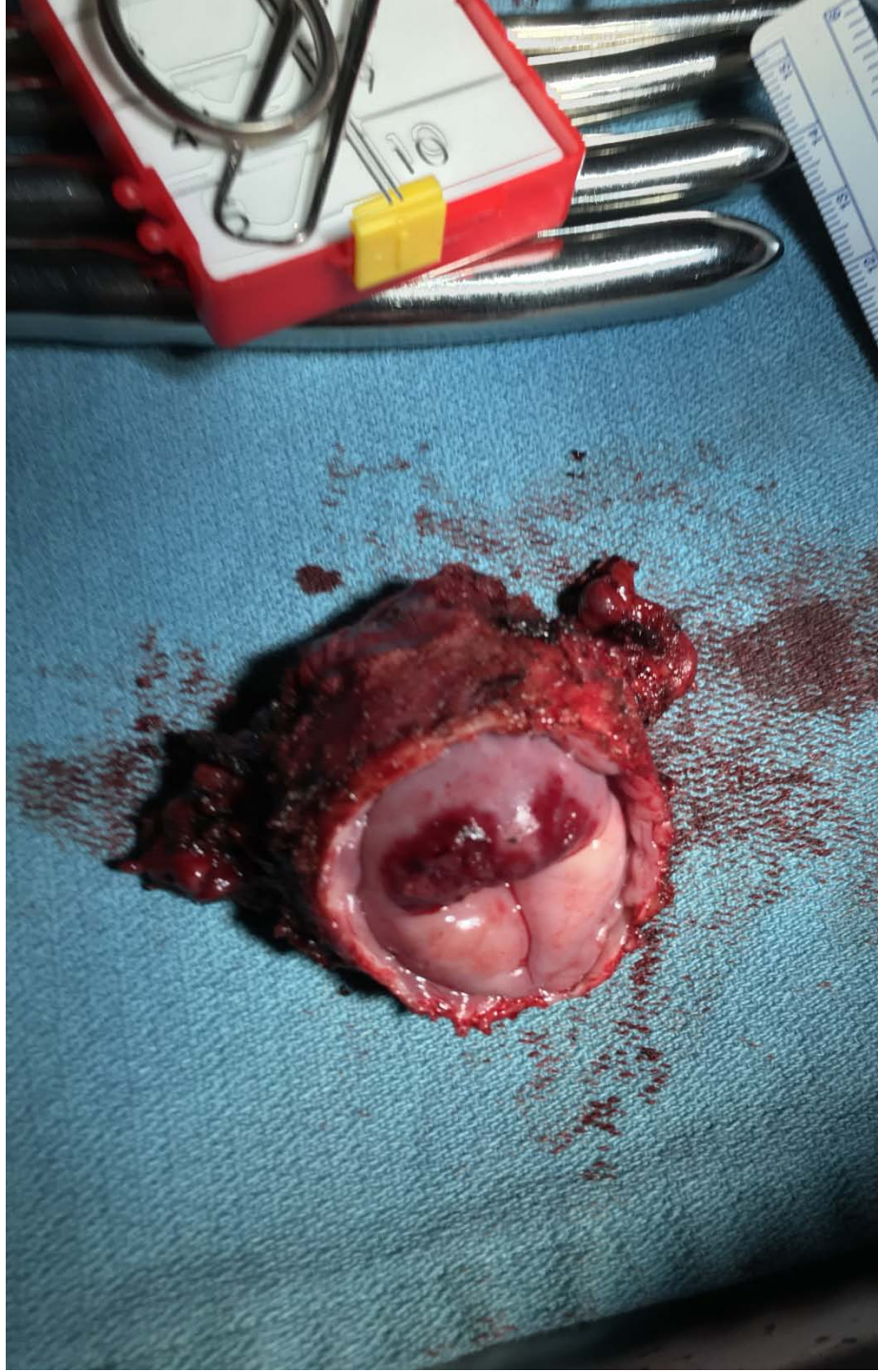


2

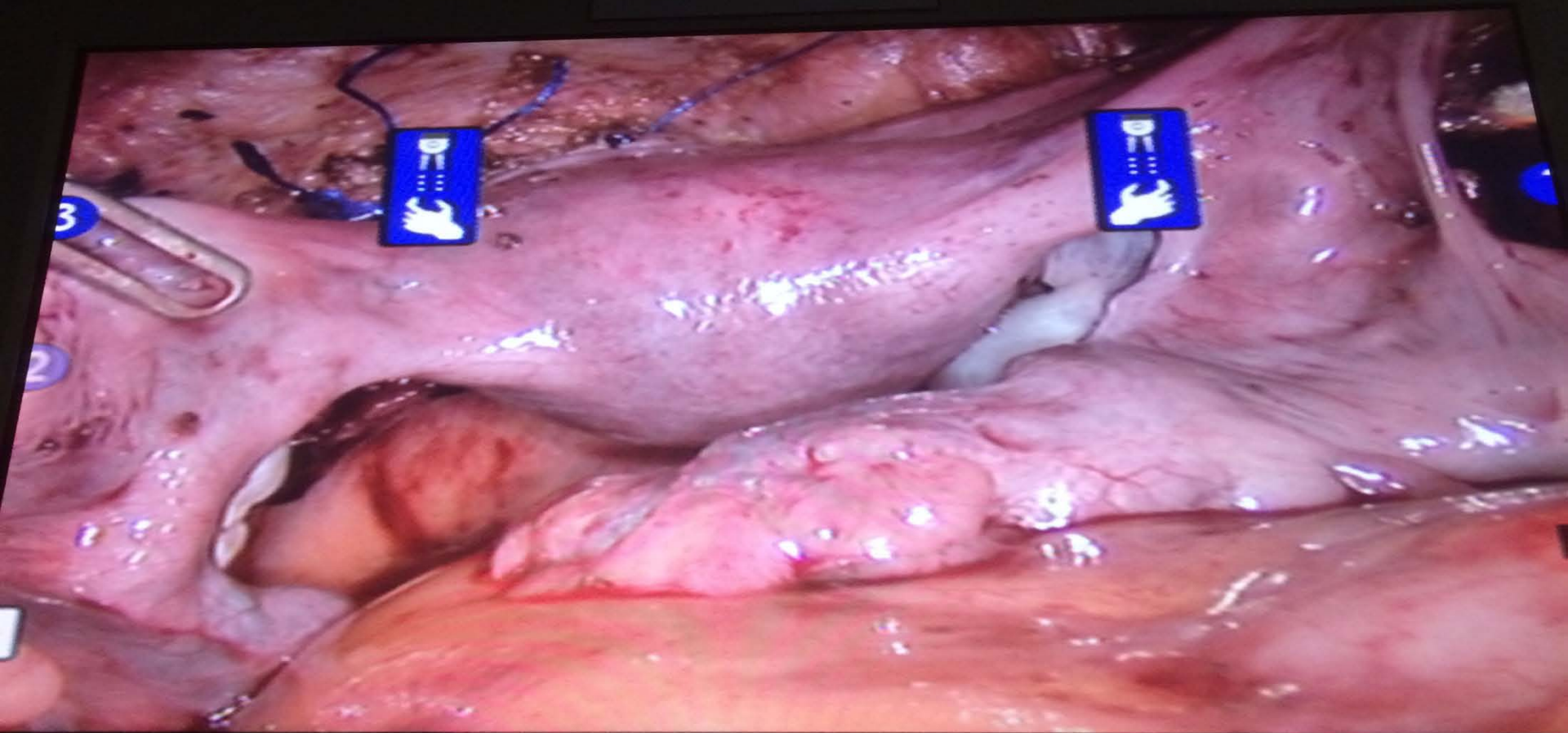
the head in View Port to operate.







2





Place head in View Port to operate.

Radical Trachelectomy Outcomes

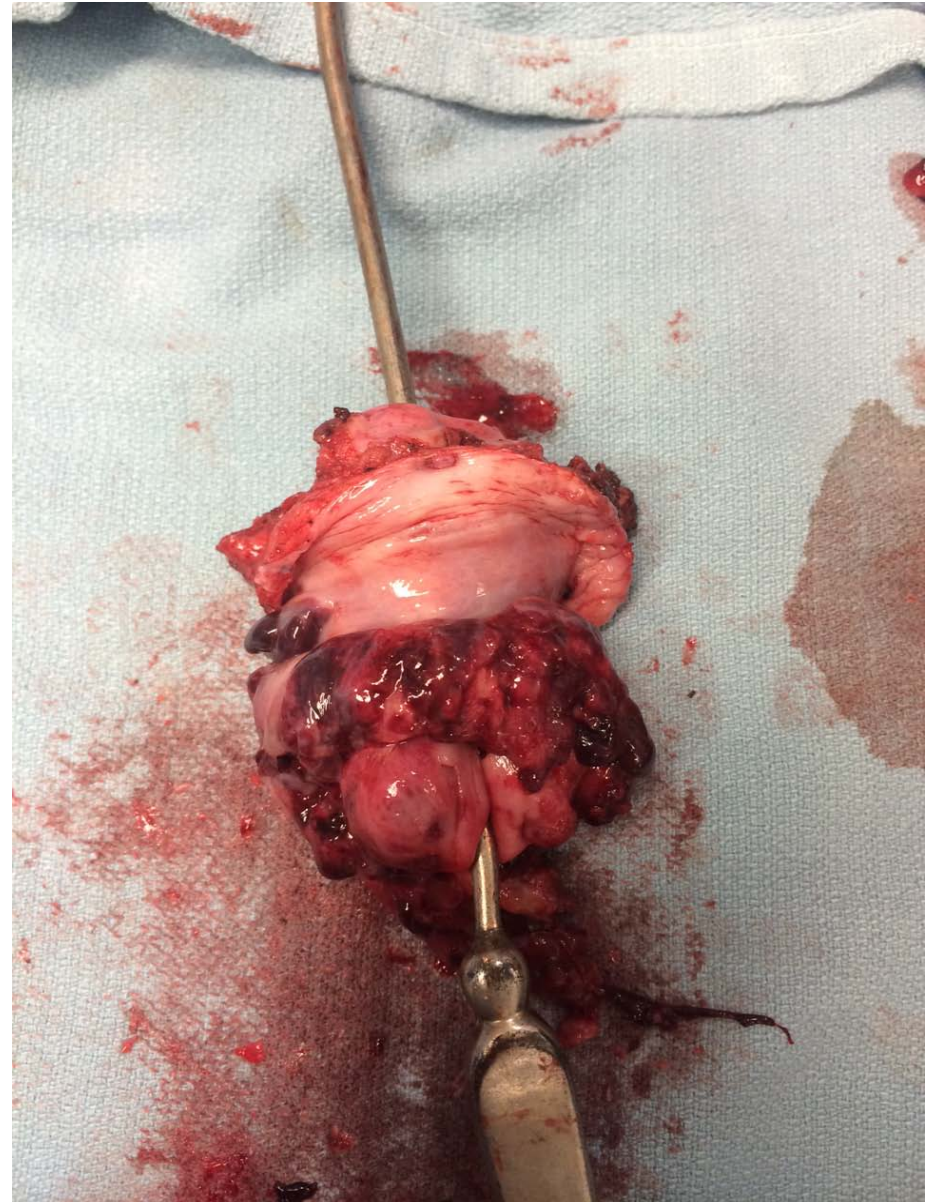
Author	No. PTs	Median F/U (Months)	Recurrence Rate (%)	Death (%)
Marchiole	118	95	7 (6%)	5 (4%)
Plante	115	74	4 (3%)	2 (2%)
Shepherd	112	45	3 (3%)	2 (2%)
Hertel	100	29	3 (3%)	2 (2%)
Covens	93	30	7 (7.5%)	4 (4%)
Sonoda	36	21	1 (3%)	0
Burnett	19	21	2 (10.5%)	--
Schlearth	10	48	0	0
TOTAL	603		27 (4.5%)	15 (2.5%)

Radical Trachelectomy

Obstetrical Outcomes

- 10-15% develop cervical stenosis
- Cumulative fertility rate 55%
- 70-79% conceive spontaneously
- 1st trimester SAB rate similar to general population (18%)
- 2nd trimester loss 2x rate of general population (8.6% vs. 4%)
- 62% reach 3rd trimester
- PTD rate (<37wks) 28%
- Overall 40% of all pregnancies culminate with healthy newborn at term

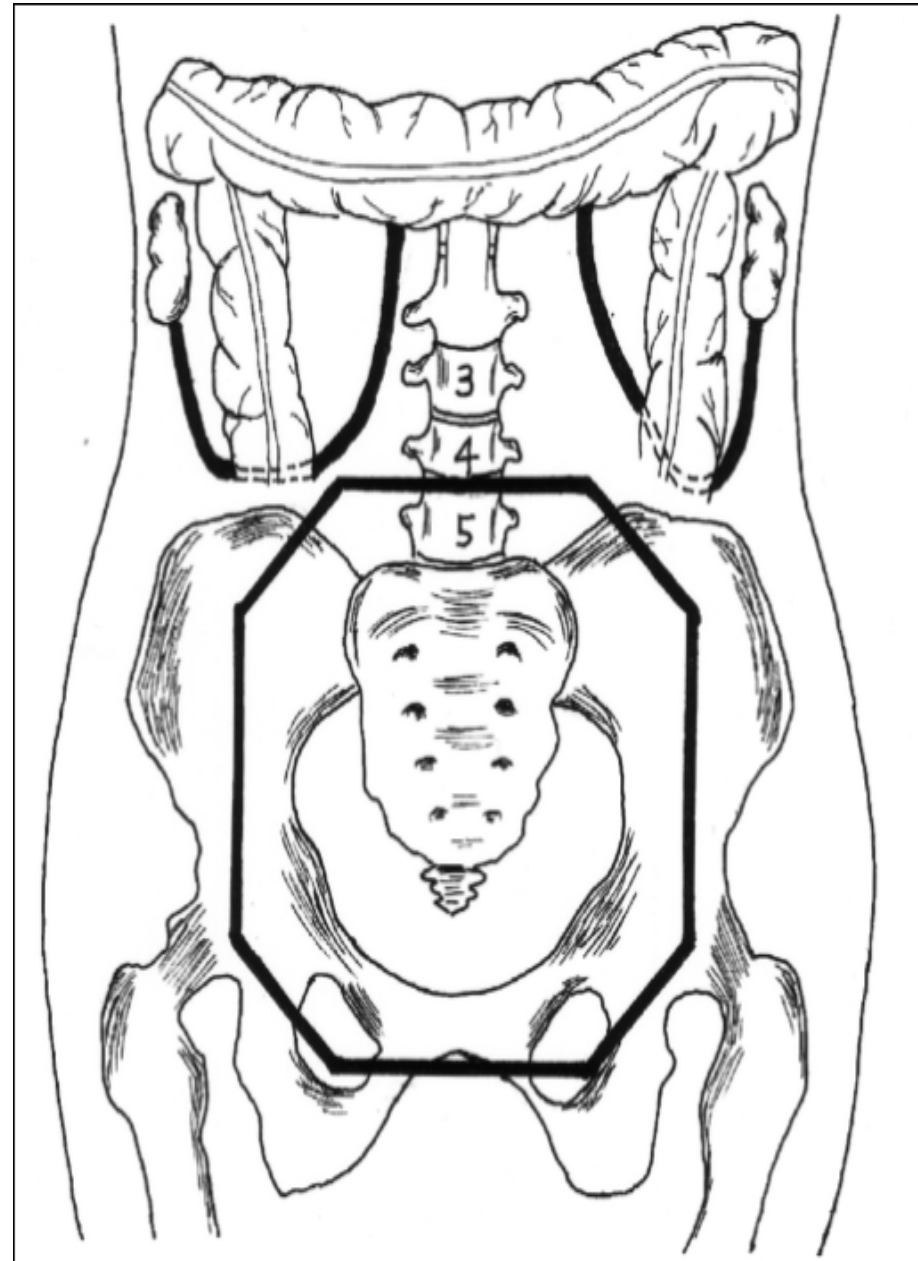
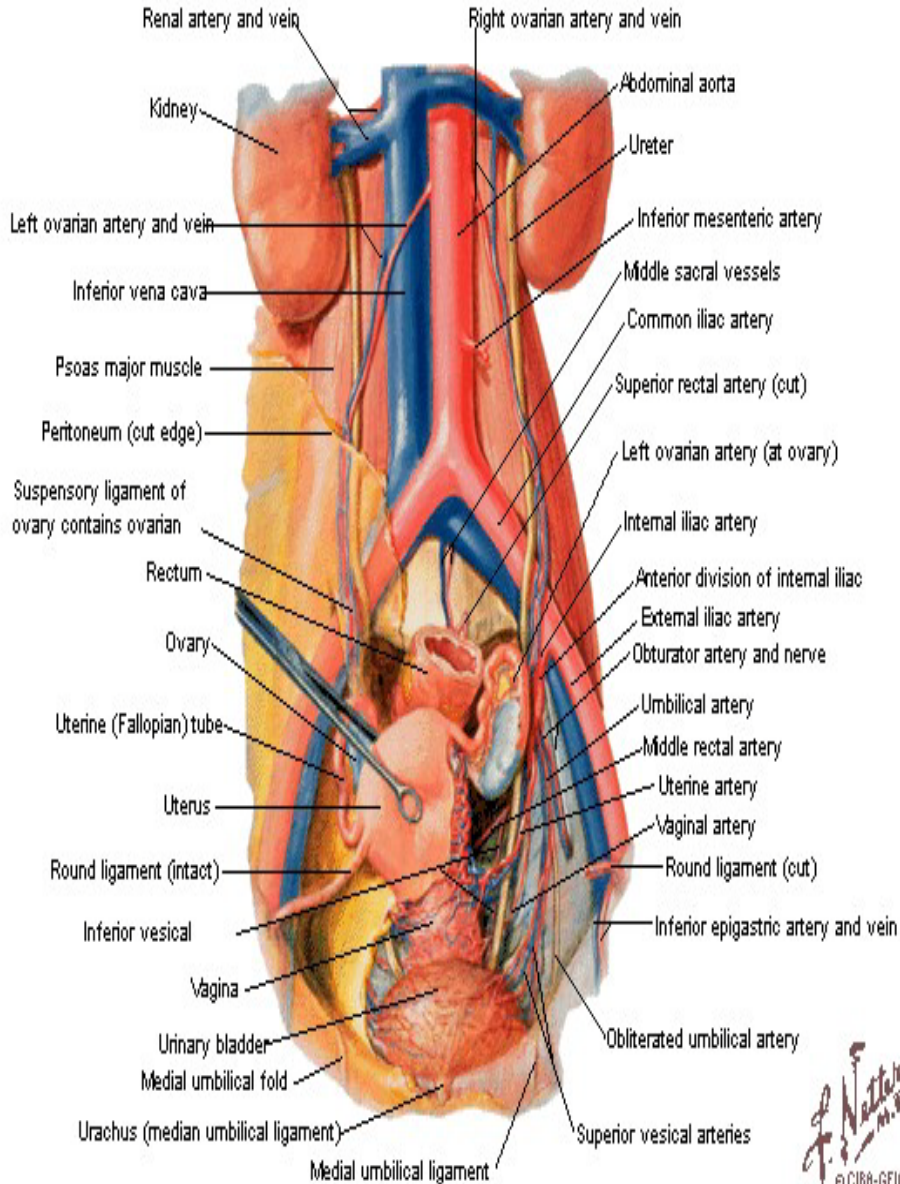
Embryonal Rhabdomyosarcoma



Ovarian Transposition

Anterior View

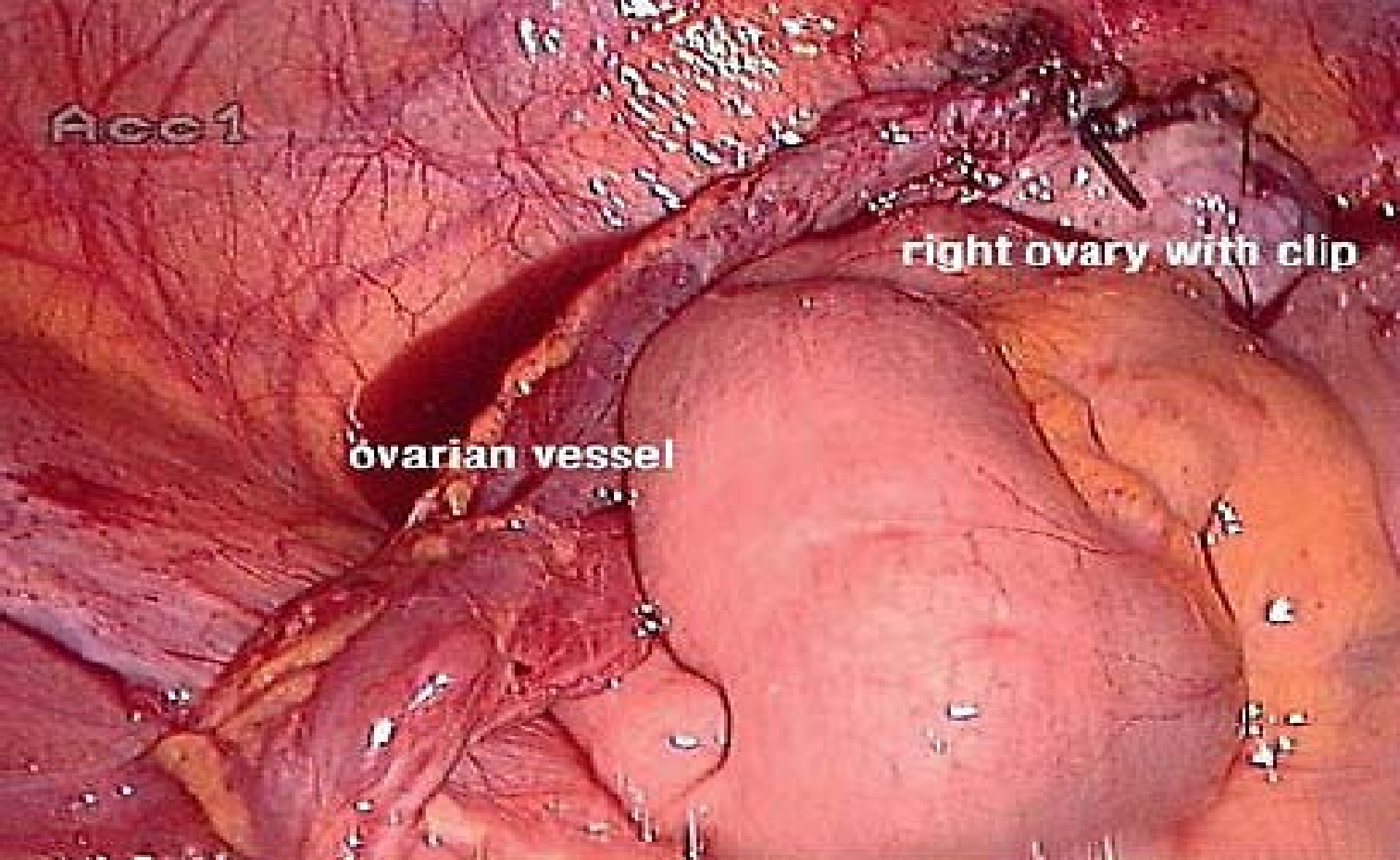
Female



Acc1

right ovary with clip

ovarian vessel



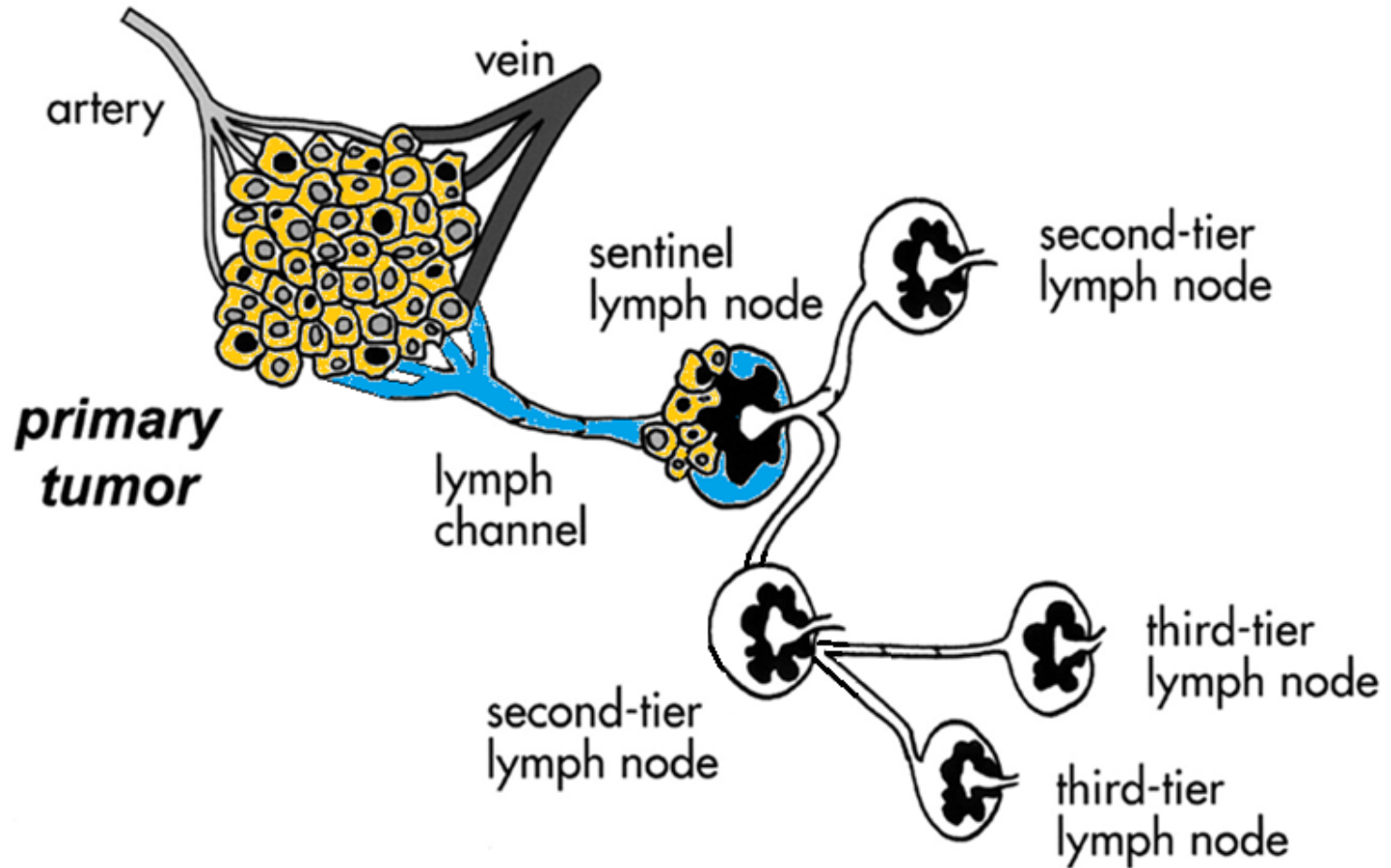


Fusion of Technology

The integration of molecular imaging with surgery

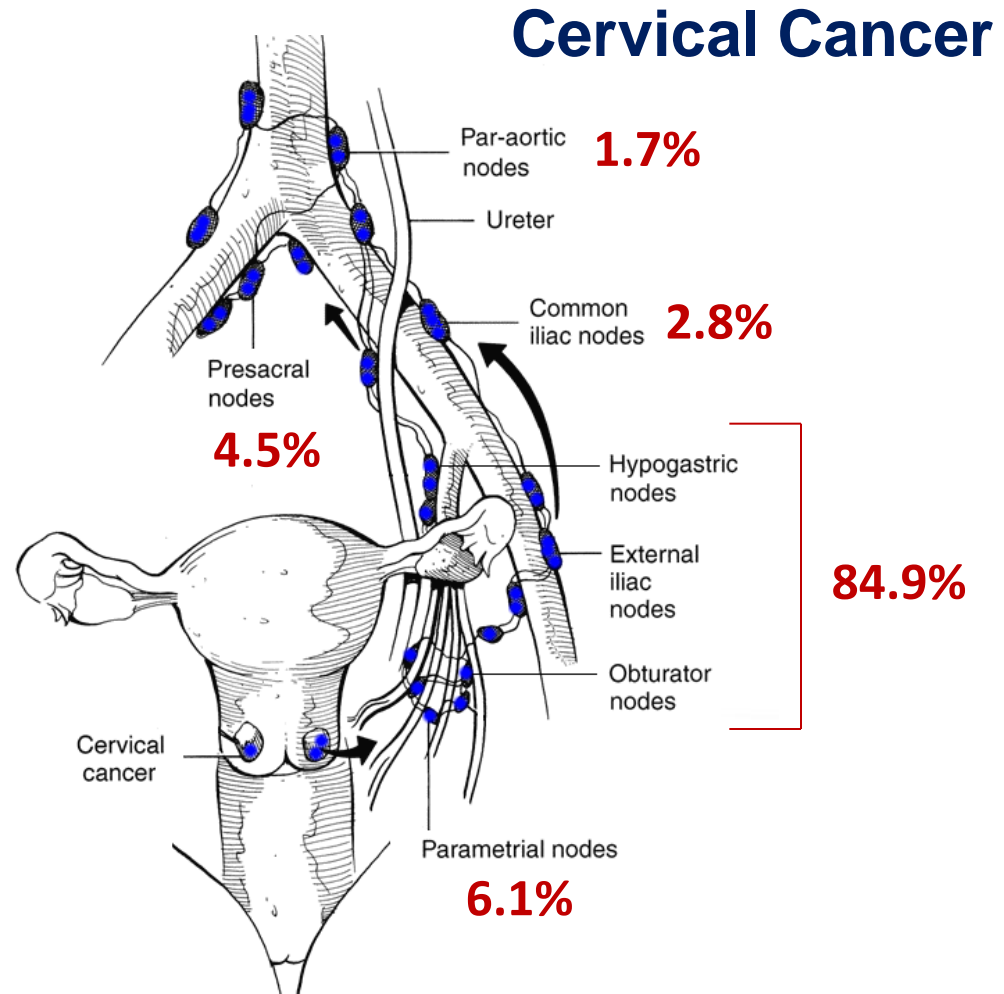


Sentinel Lymph Node Biopsy



SLNB - Multiple Advantages

- Detection of nodes in atypical localizations that may be missed on standard PLND in 9%
- Increase likelihood of finding positive LN
- Minimize morbidity associated with complete LND



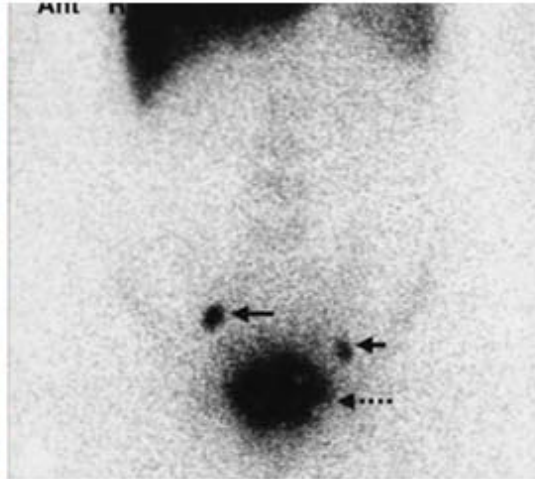
Techniques for SLN Biopsy

Blue Dye



- Start of GA
- Identify SLNs

Radioisotope

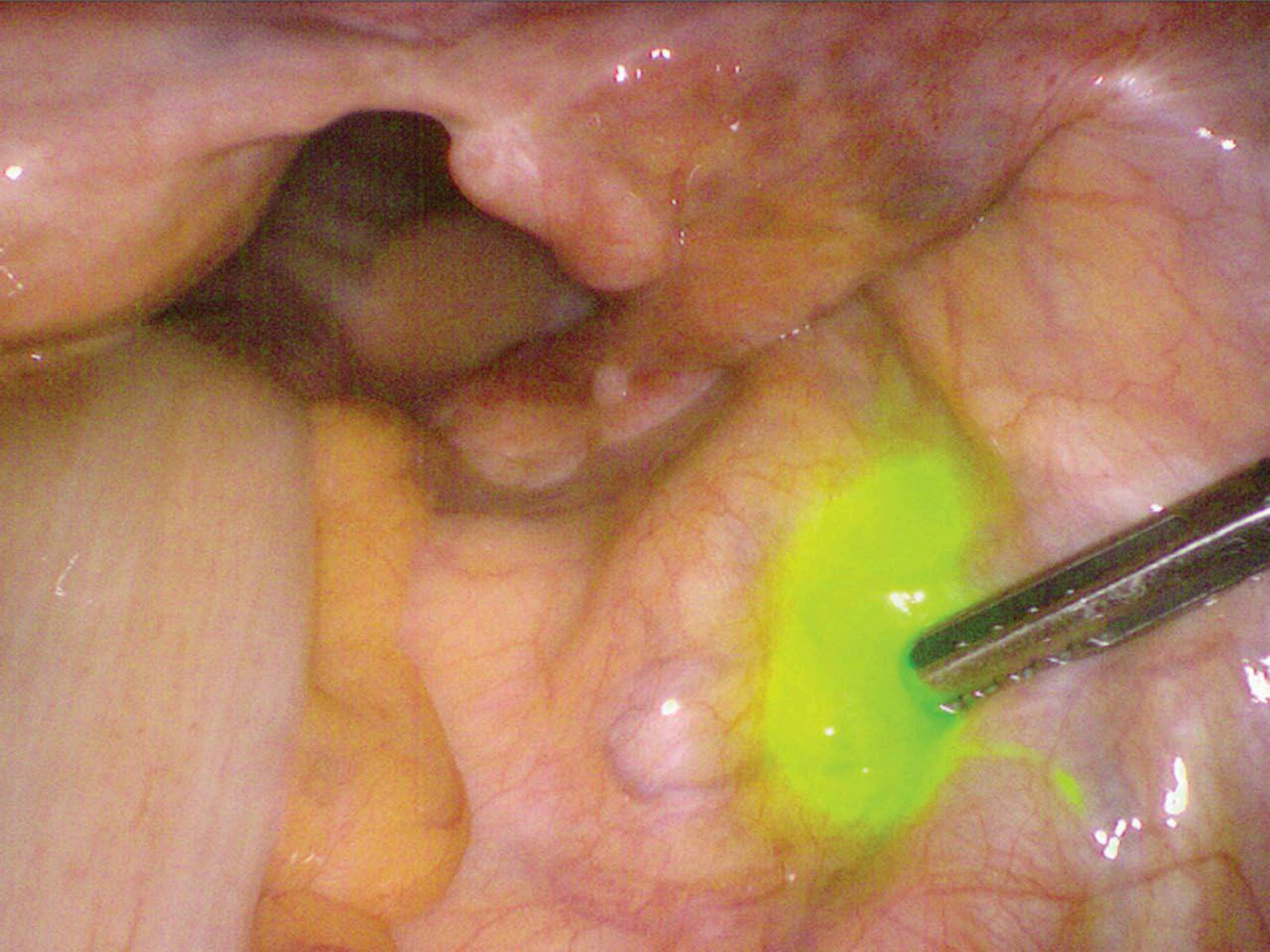


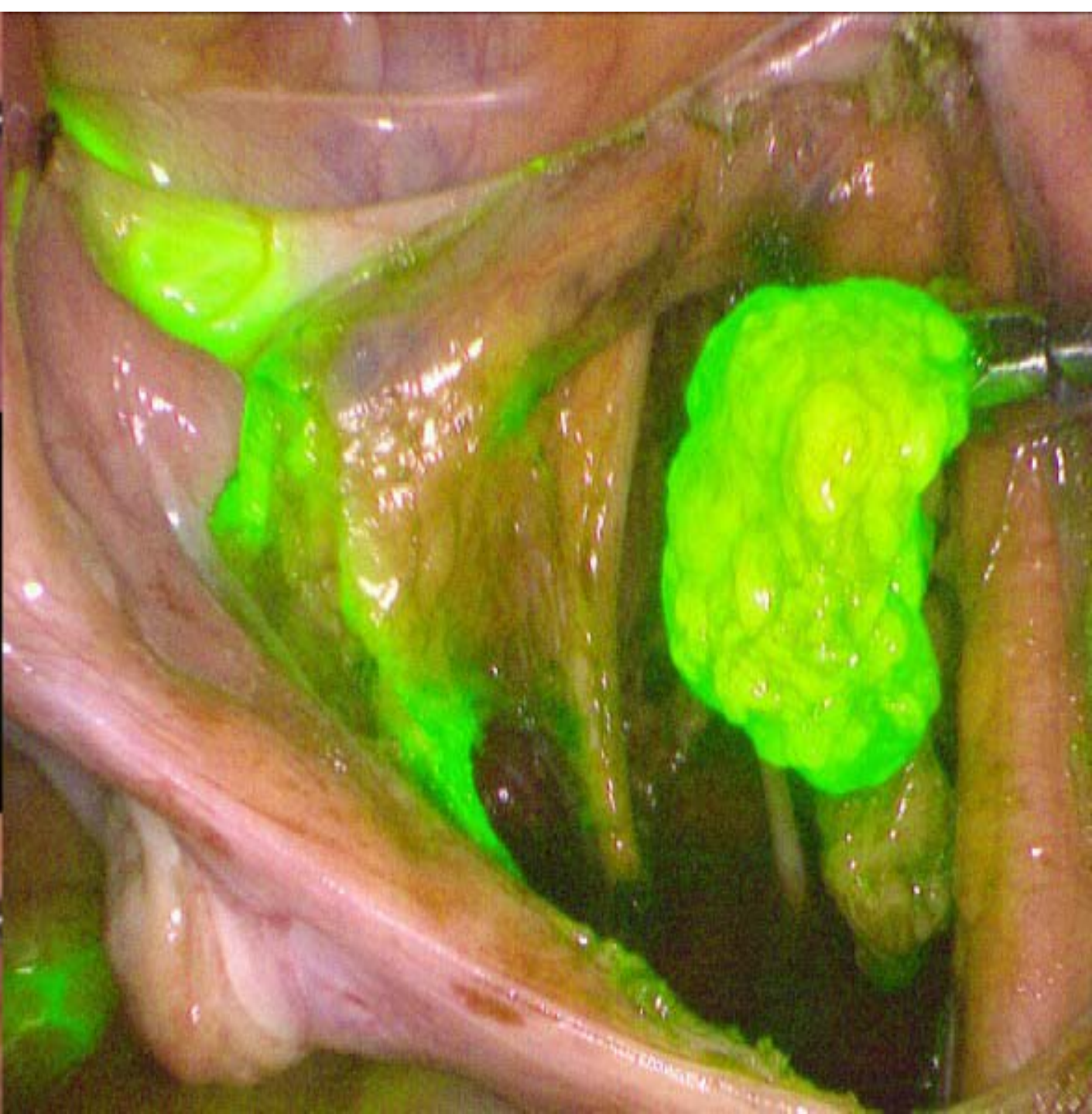
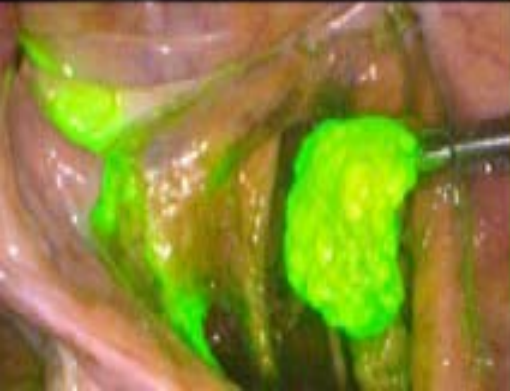
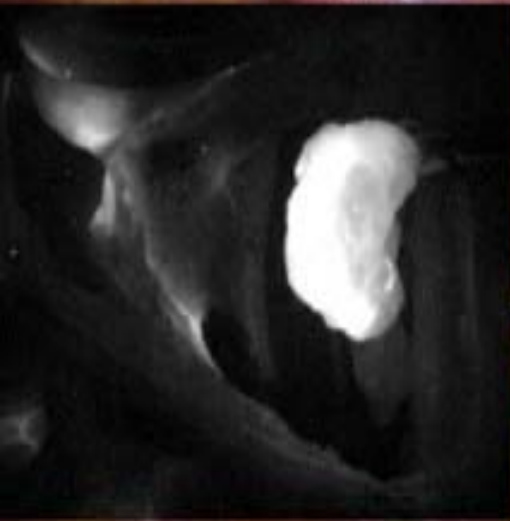
- Variable timing
 - Preoperative lymphoscintigram and intraoperative gamma probe

ICG



- Start of GA
- Near-infrared fluorescence imaging



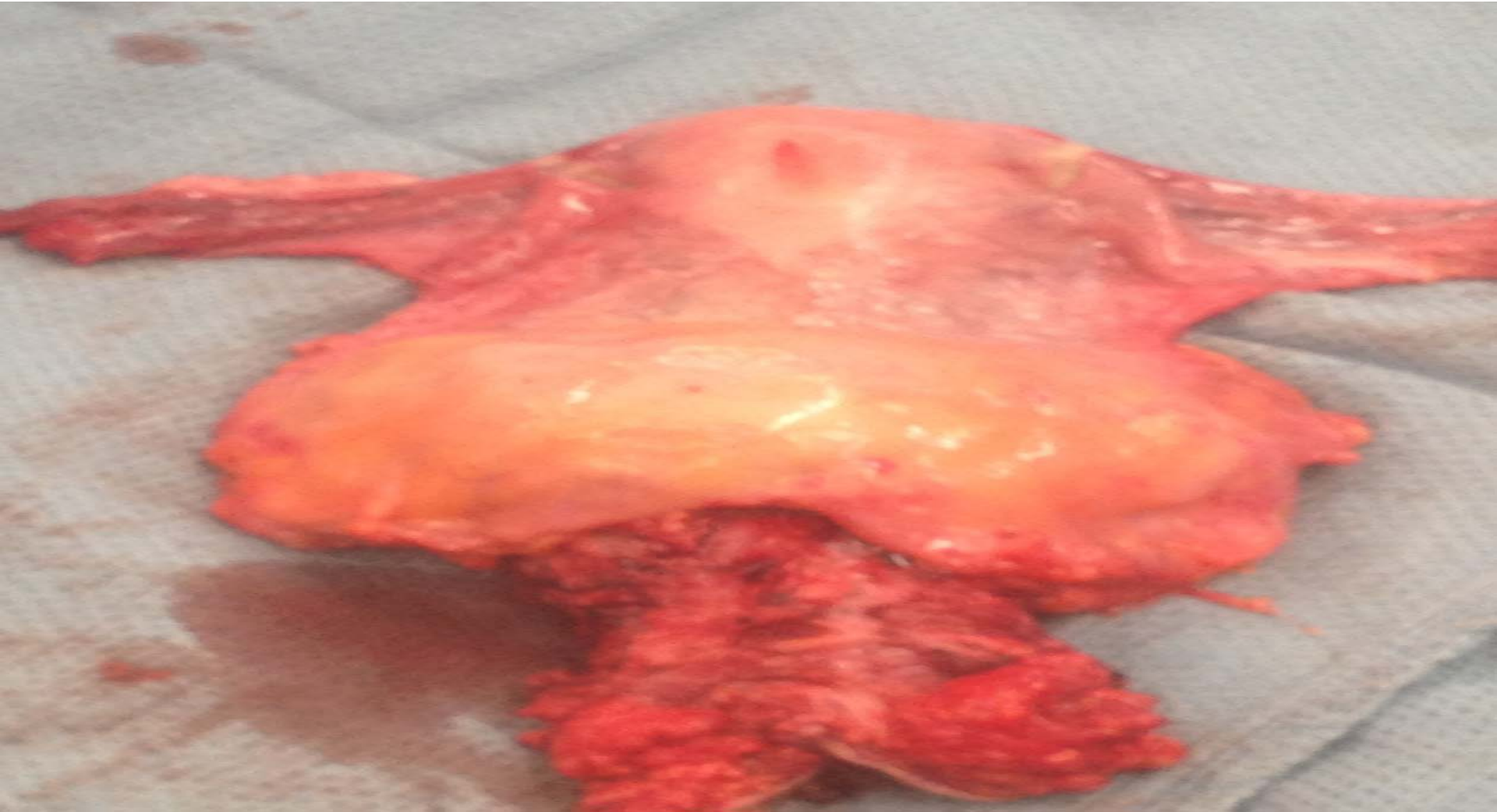


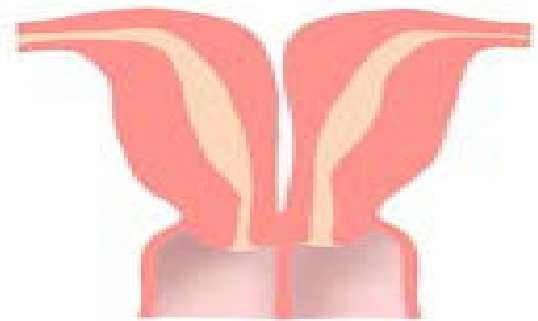
Thank You

Pushing the envelope of MIS

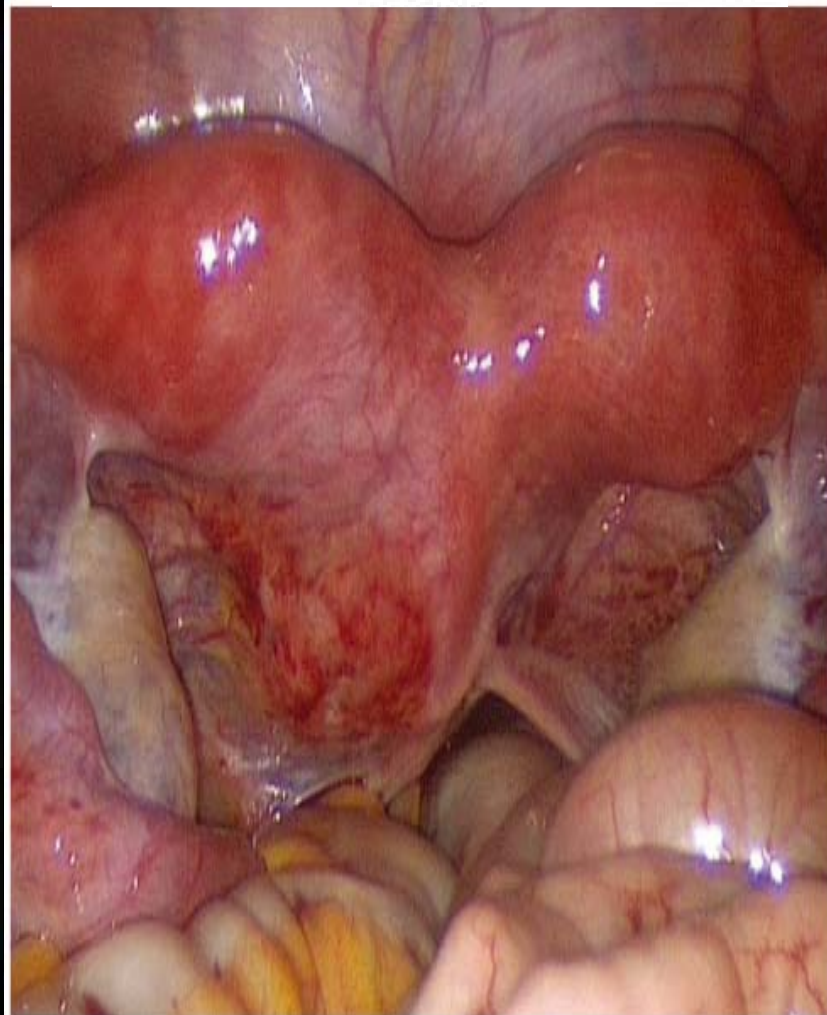
Pelvic Exenteration

First MIS case in Canada performed at UHN in 2009

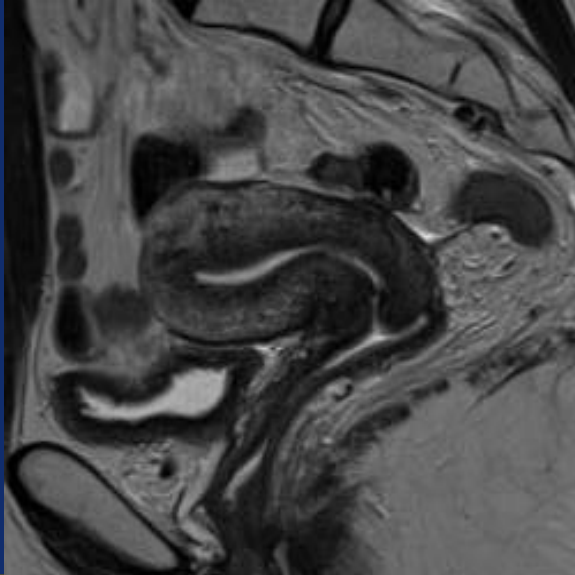




Dideliphys



MRI OF CERVIX CANCER



***KARTIK S. JHAVERI , MD FRCPC
DIRECTOR , ABDOMINAL MRI
DIRECTOR,CME PROGRAM***

**Medical Imaging • University Health Network • Mount Sinai Hospital
University of Toronto • Women's College Hospital**

OVERVIEW

MRI INDICATION

MRI PROTOCOL & PEARLS

MRI ANATOMY

CERVICAL CA STAGING

POST TREATMENT EVALUATION

SUMMARY



INDICATION

- MRI is NOT be used for cancer detection
- MRI indicated for :
 - Staging cervical carcinoma
 - Co-existent Adnexal mass evaluation
 - Post Therapy Evaluation/Recurrence
- CT : Upper Abdomen / Chest Staging



MRI PROTOCOL

- High Quality Imaging Key



MRI PROTOCOL

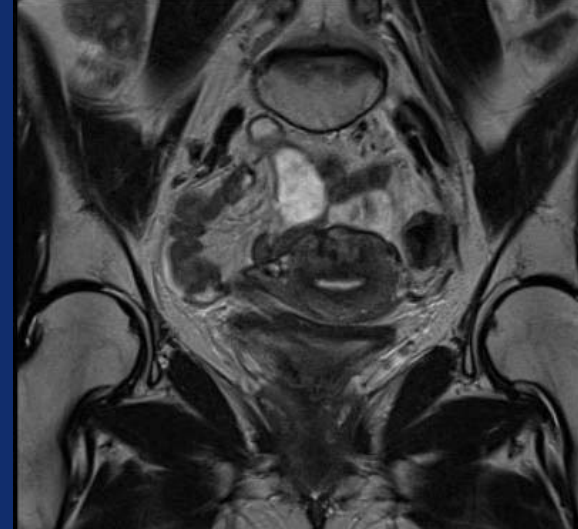
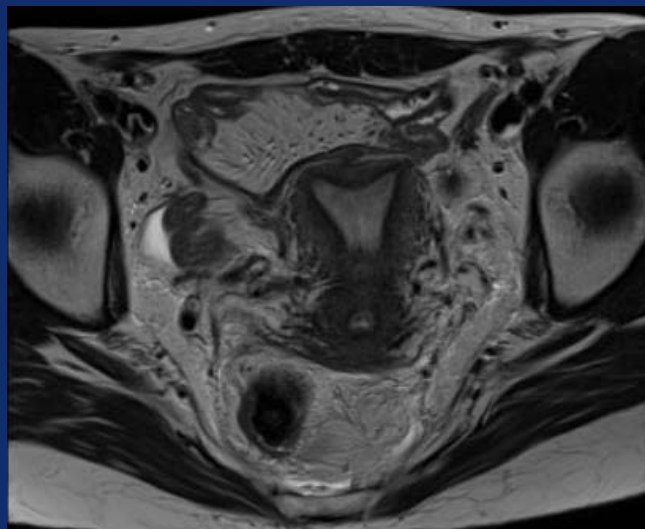
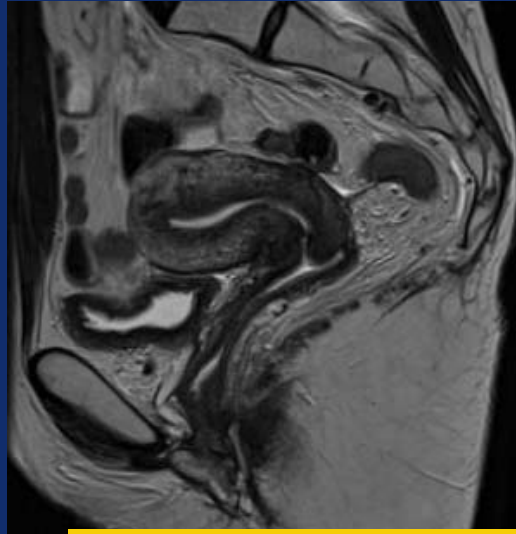
- Patient preparation
 - Fasting for 4 hours
 - Empty bladder
 - No guidelines how long post-biopsy ~6weeks
- Antiperistaltic agent
 - Butylscopolamine (Buscopan) 20-40 mg IM
 - Contraindications: glaucoma(narrow angle)
 - Glucagon 1 mg IM: second line agent



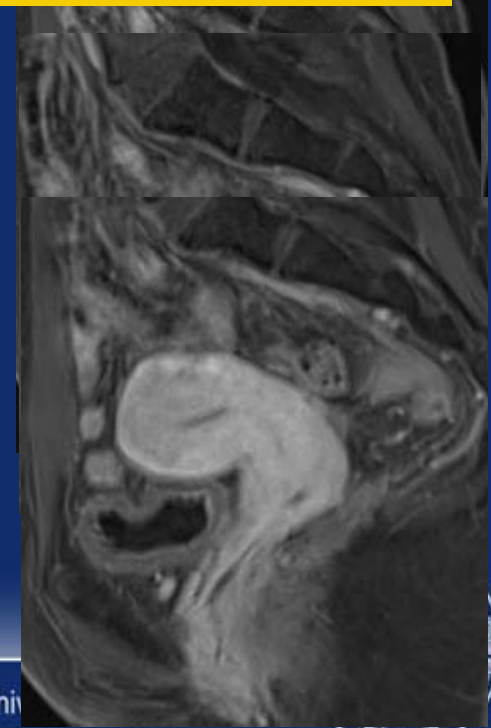
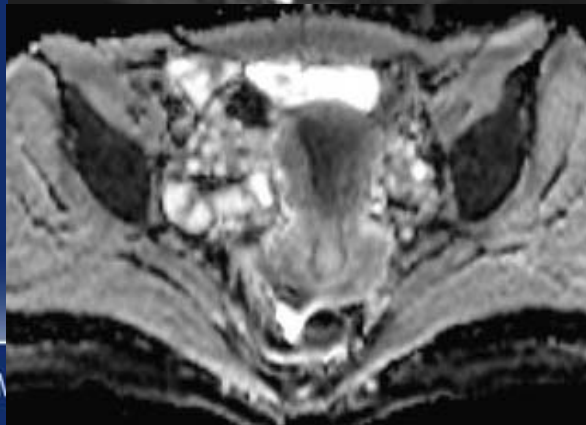
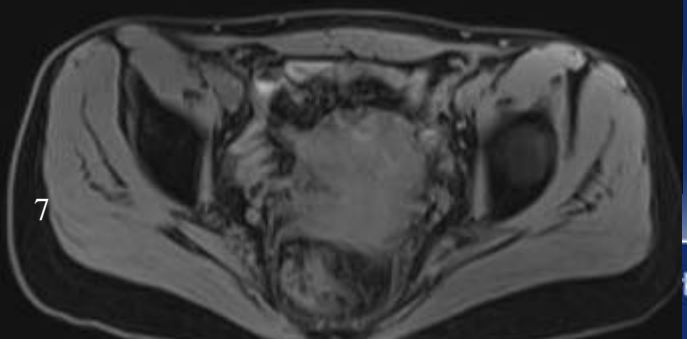
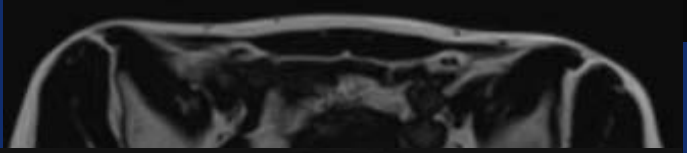
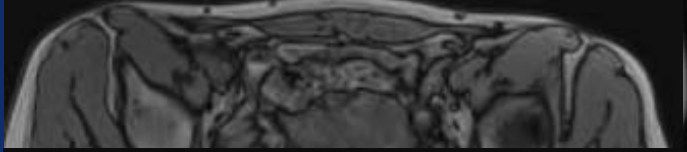
MRI PROTOCOL

- Localizers: T2 SSFSE or TrueFISP
- Sag,Axial,Coronal T2 FSE
- **Hi Res Oblique T2 TSE**
- Axial T₁ DIXON VIBE
- Axial DWI (3 b-values + ADC map)
- Sag/axial pre- and post-gad 3D T₁ Dyanmic
- Cor T₁ / HASTE Abdomen (kidneys/nodes/peritoneum)



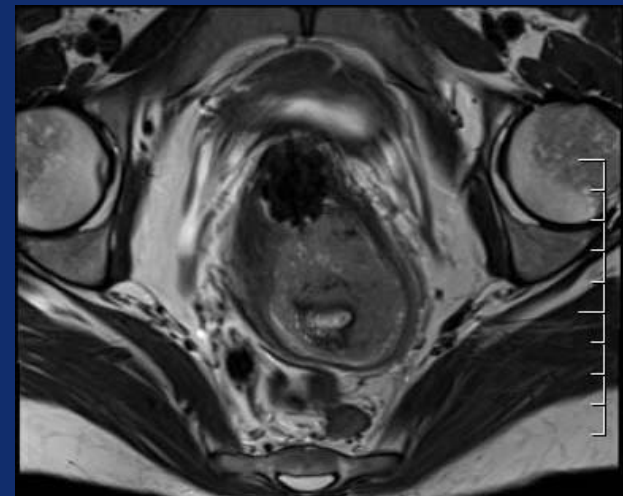
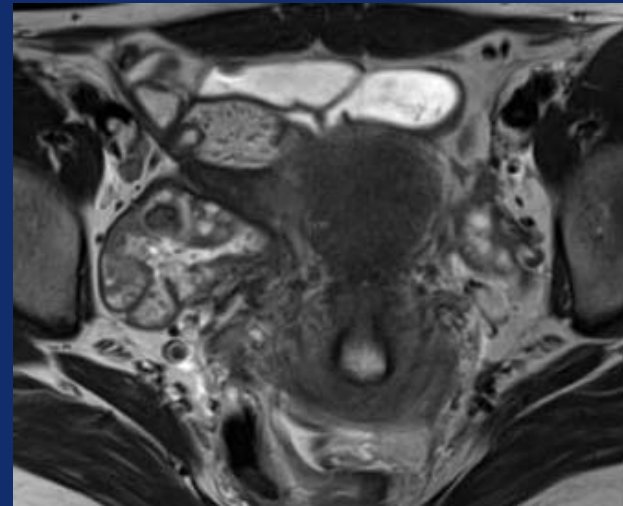
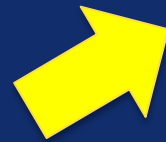
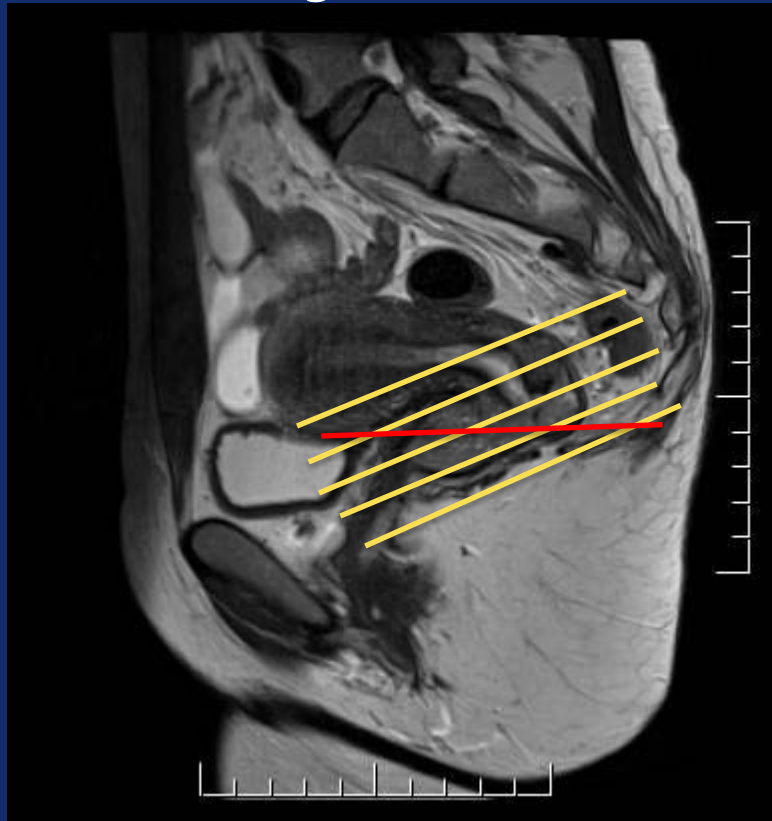


MRI PROTOCOL



HI RES OBLIQUE T2

Sag T2 TSE



Ax Obl T2 TSE

< 18 cm FOV
< 3 mm slices
> 256 x 256 matrix

DWI

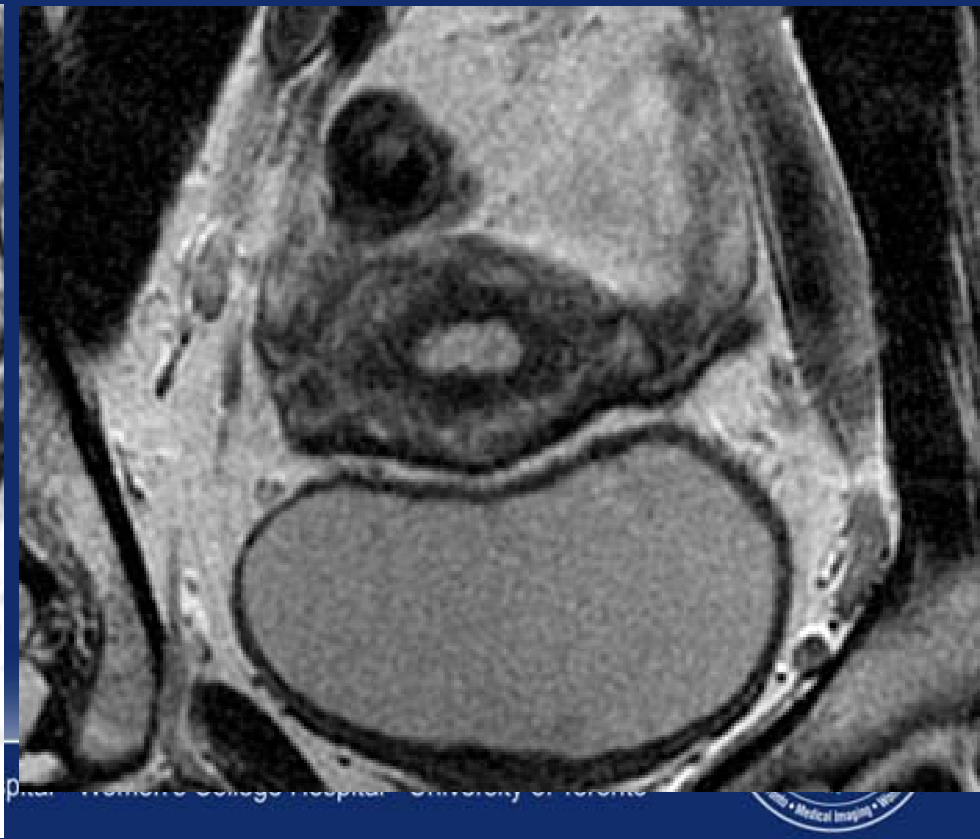
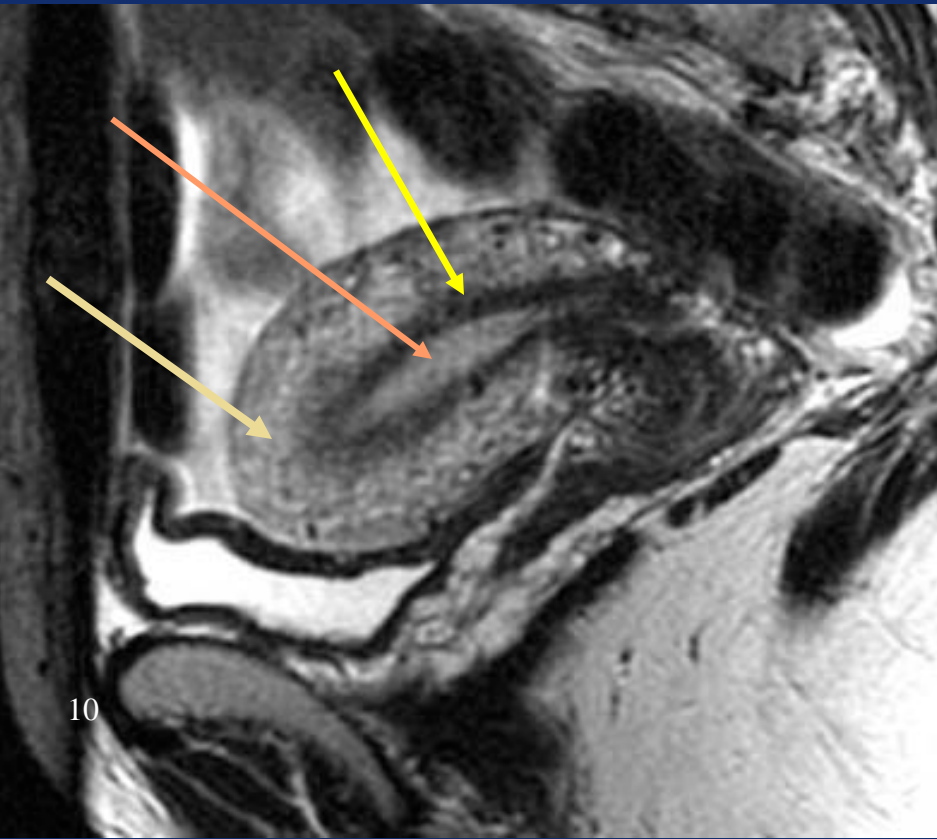
- DWI is useful adjunct to anatomical MRI:
 - Identifying lesions in challenging anatomic locations
 - Lymph node detection
 - Identifying low volume peritoneal disease
 - Distinguishing residual/recurrent disease from post treatment changes
 - Assessment of response to treatment

Kyriazi et al., Radiographics 30:1269 (2010)



Normal Anatomy

Uterus 3 zones(T2) High Signal Endometrium,
Low signal JZ
Intermediate Myometrium



Normal Anatomy

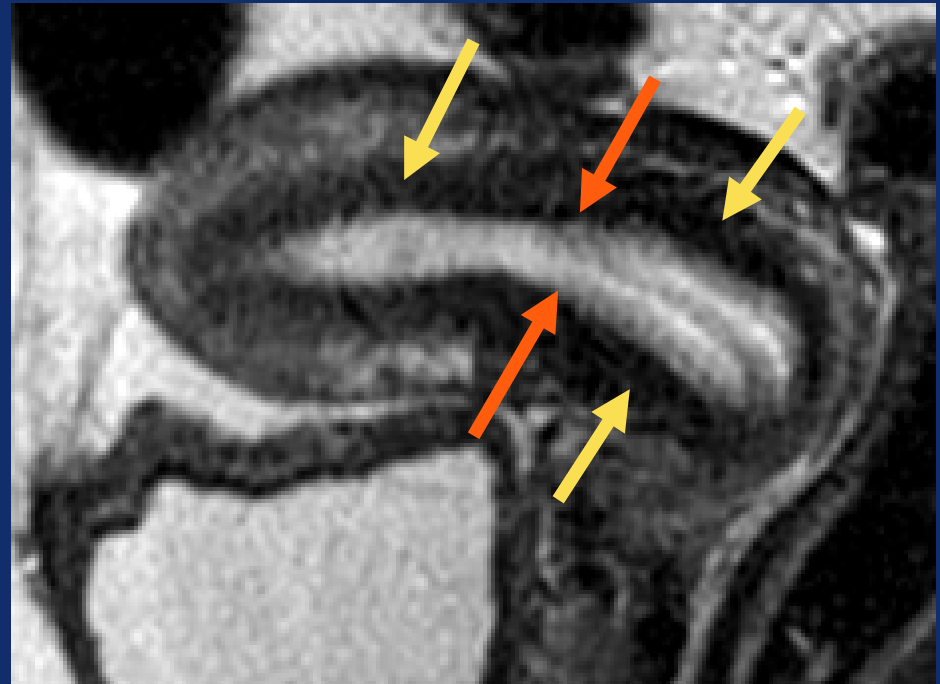
- **Junctional zone**

Dark :Compact muscle,less water,more nuclei and muscle orientation

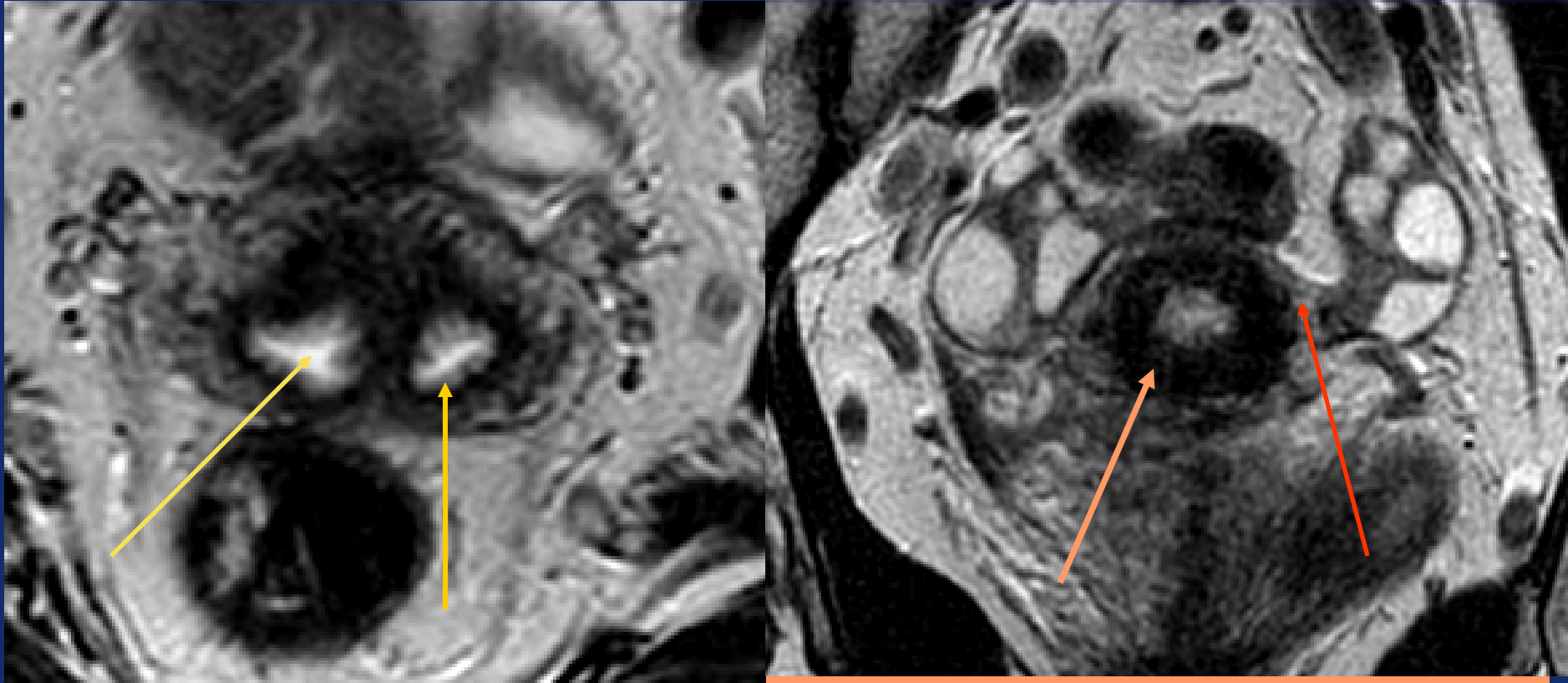
Indistinct in menopause and OCP use

- **Internal OS**

- **Cervical Stroma**



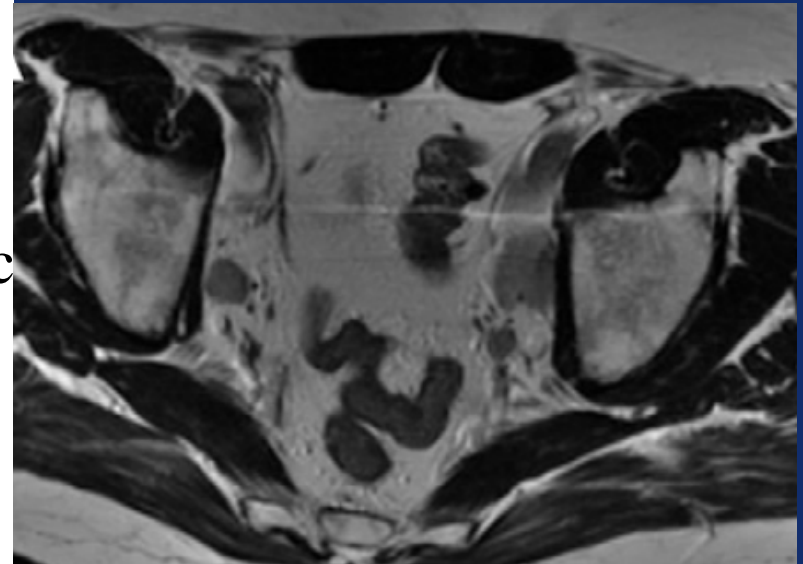
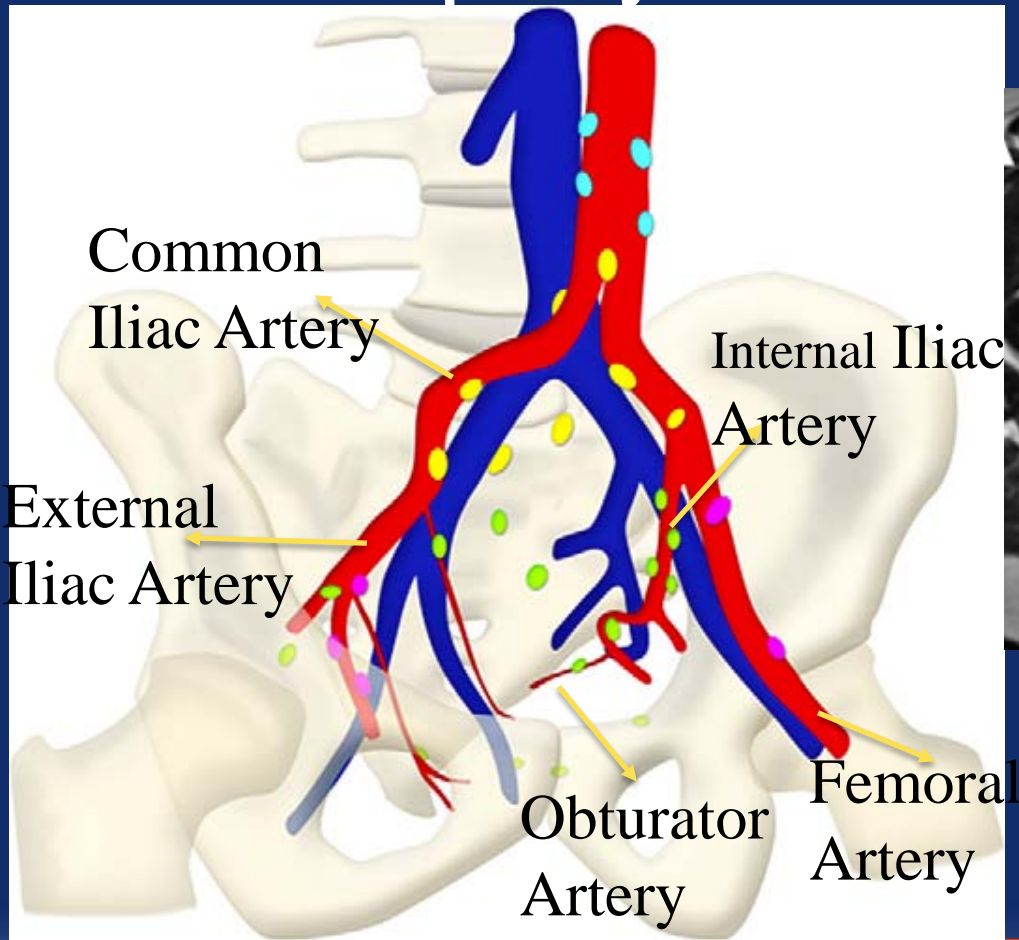
Normal Anatomy



**Cervix Stromal appearance does not change with hormonal status
However in 3rd trimester of pregnancy -High T2 signal**

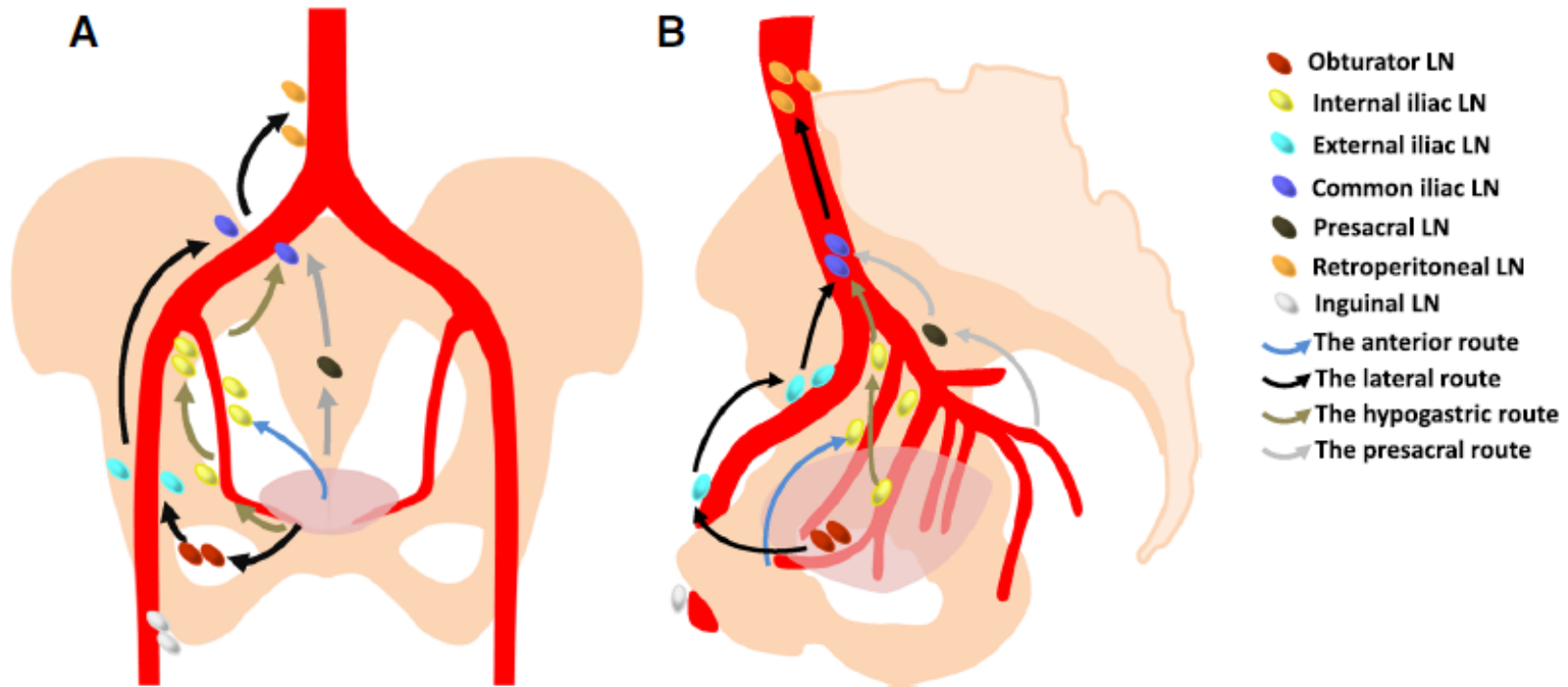
Pelvic Lymph Nodes: Anatomy

- Accompany Vessels



<http://www.cancer.org/cancer/cancerbasics/lymph-nodes-and-cancer>

Pelvic Lymph Nodes: Anatomy

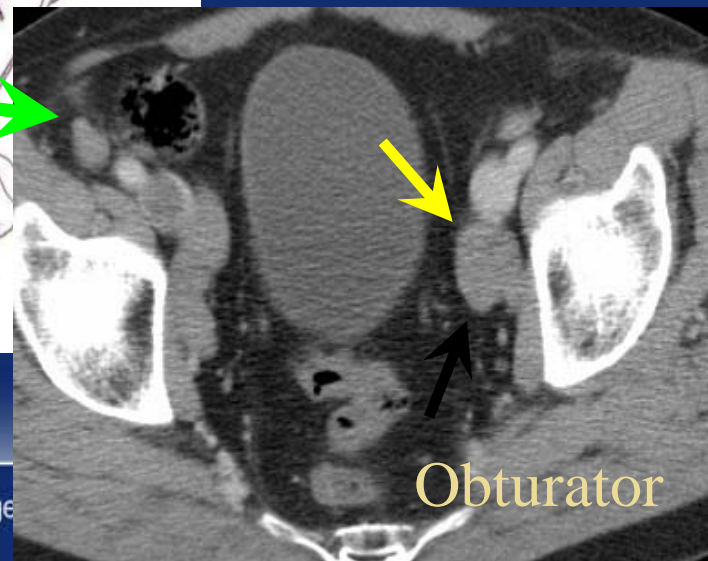
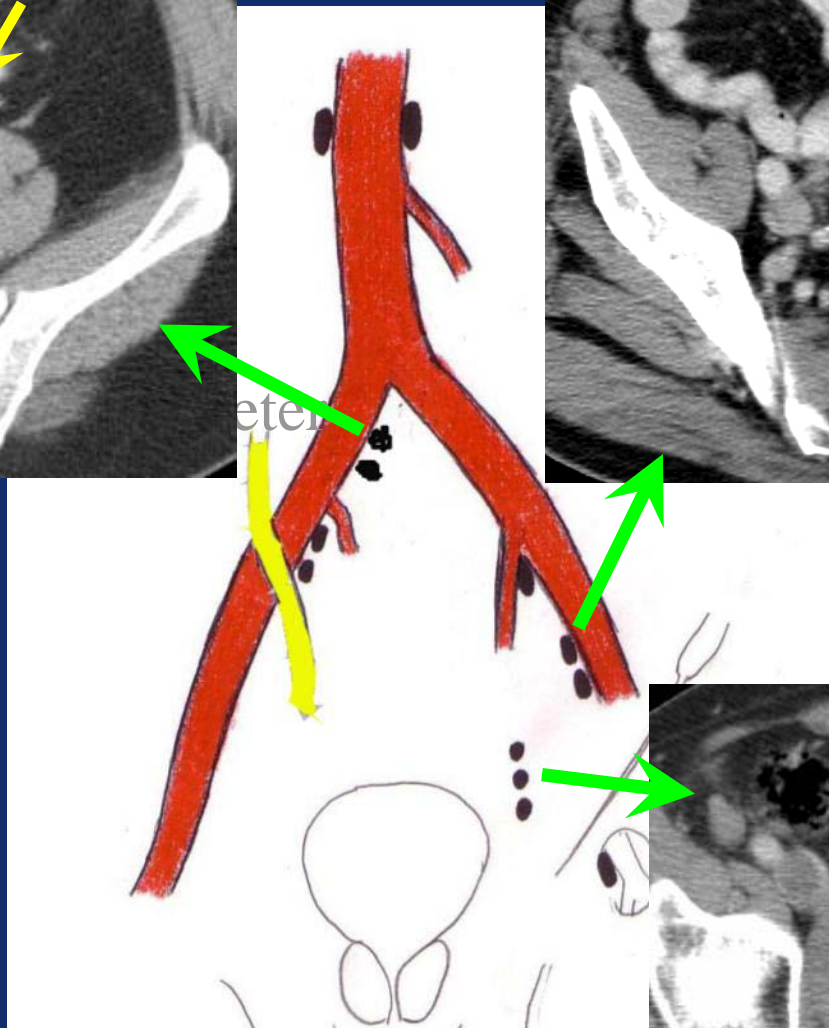
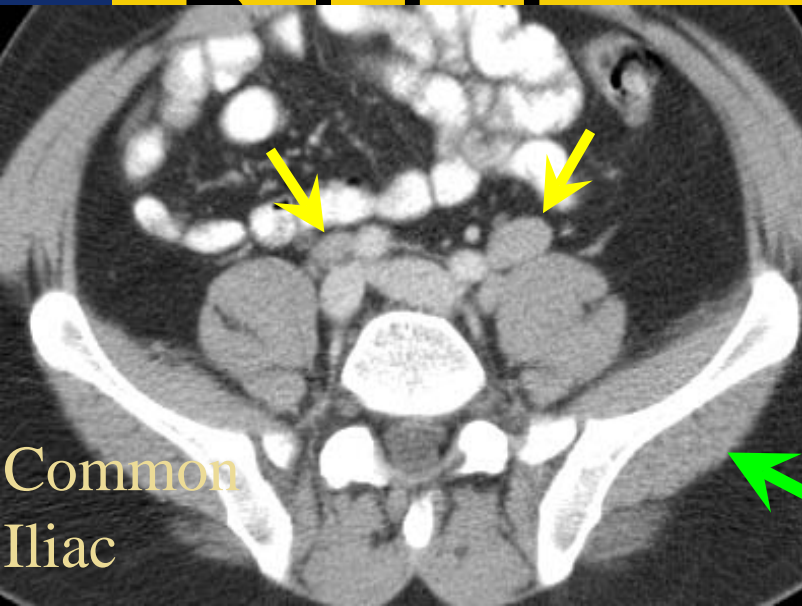


Anterior view

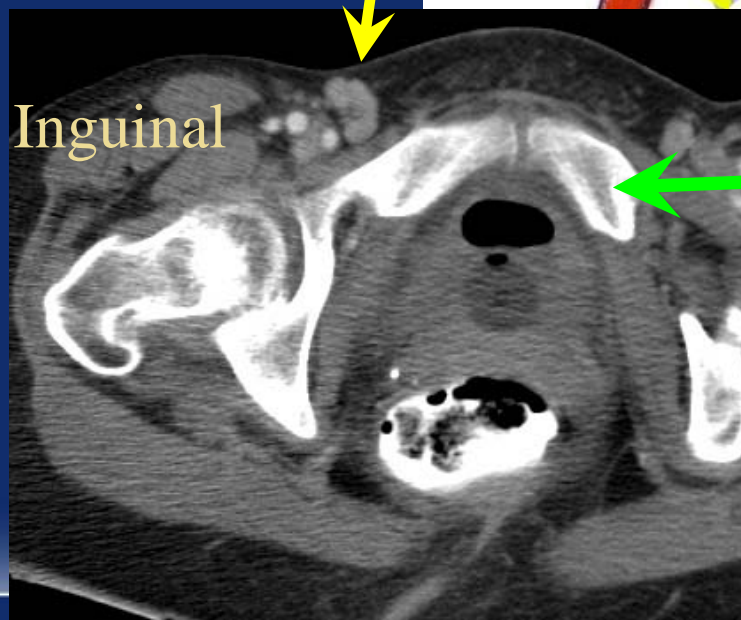
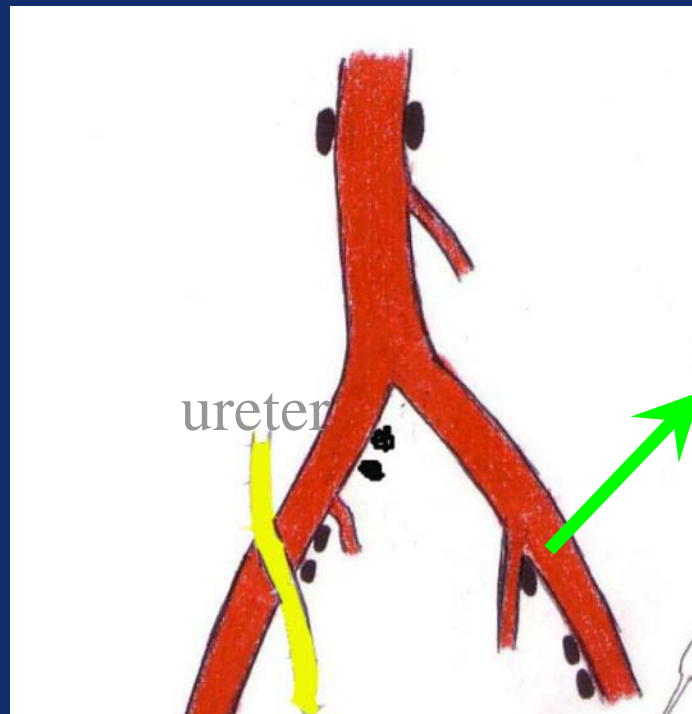
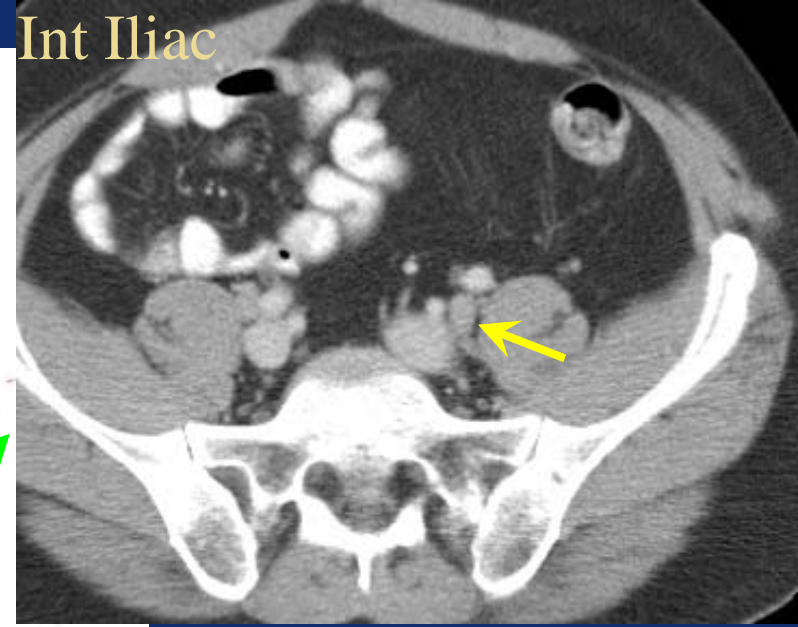
Lateral view

Magn Reson Imaging Clin N Am. 2014 May

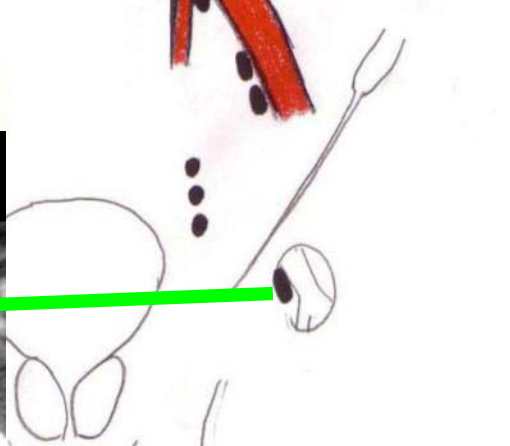
h Node



Int Iliac



Inguinal



CERVICAL CANCER



CERVICAL CANCER

- 3rd most common gynecologic malignancy
- Clinical staging can under- or over-stage disease
 - Accurate Tumor size not determined
 - Nodal status not determined
 - Parametrial assessment, Pelvic side wall ?
- Concordance between surgical and clinical FIGO staging poor (85.4, 77.4, 35.3, and 20.5% for stage IB, IB₂, IIA, and IIB)
Qin Y et al. Aust N Z J Obstet Gynaecol 49.5 (2009): 542-544



Histology

- Squamous cell carcinoma (80-90%)
 - Arising from squamocolumnar epithelium
- Adenocarcinoma (10-20%)
 - Arising from deeper columnar epithelium
 - Poorer prognosis
 - Subtypes
 - Endocervical (incl. mucinous: adenoma malignum)
 - Endometroid adenocarcinoma
- Lymphoma
- Sarcoma



Cervical Cancer : MRI



- **Moderately Hyperintense T2 signal (“Evil Grey”)**
- **Hypointense Normal Cervical Stroma**

MRI modality of choice for staging carcinoma of cervix

FIGO Staging: Clinical

- IA: Confined to cervix; stromal invasion < 7 mm
- IB: Clinically visible lesion confined to cervix
 - IB₁: < 4.0 cm
 - IB₂: > 4.0 cm
- IIA: Beyond uterus; no parametrial invasion
- IIB: Beyond uterus; parametrial invasion
- IIIA: Lower 1/3 of vagina; no pelvic wall
- IIIB: Pelvic wall or ureter (kidney affected)
- IVA: Extends outside true pelvis &/or bladder/rectum MUCOSA
- IVB(M): Distant mets



KEY ISSUES FOR TREATMENT

- **Tumor size (< 4 or > 4cm)**
- **Parametrial invasion**
- **Invasion of ureter,bladder,rectum**
- **Lymph node metastases above true pelvis**



MRI Impact

- Tumour size
 - Confirm IA stage - trachelectomy planned
 - Clinical IB₁ + stage tumours - surgery planned
 - FIGO IB₂ -chemoradiation
 - Define Clinical Target Volume(CTV)
 - Prognostic Feature

Accuracy of overall MRI local staging :85 – 96%

Okamoto Y et al. Radiographics 23.2 (2003): 425-445

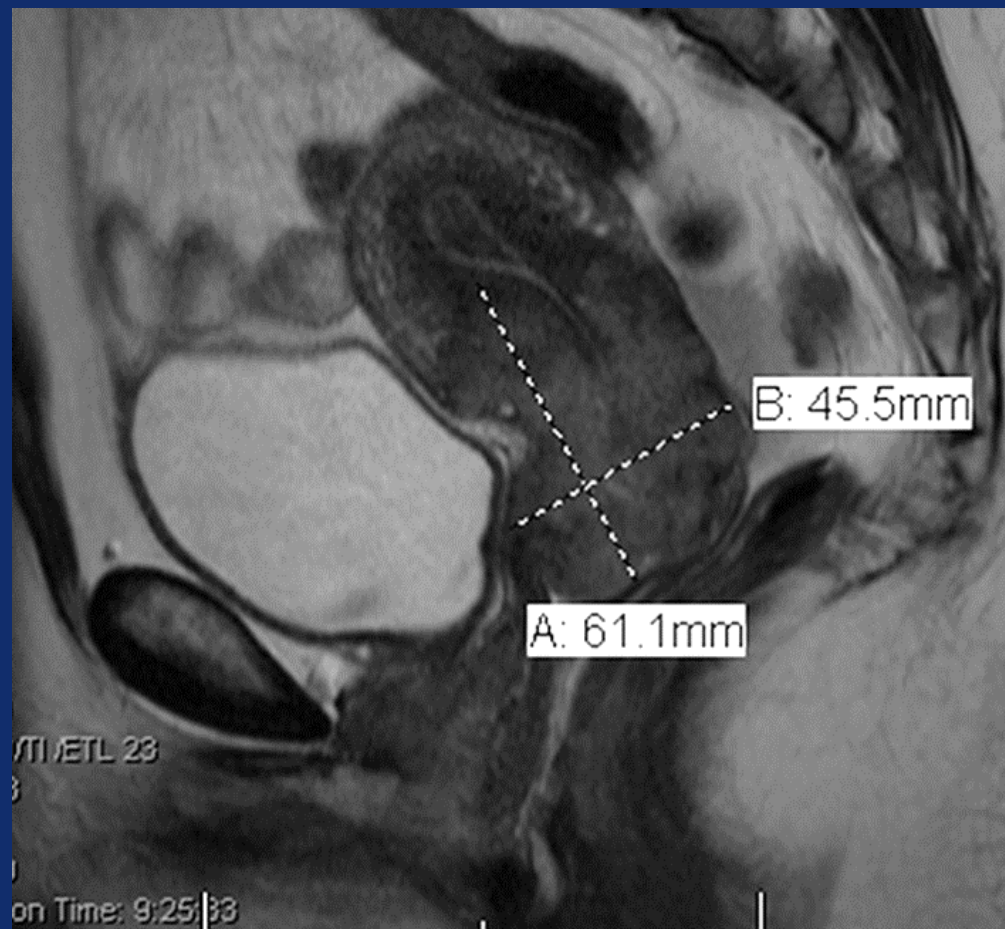
Scheidler J and Heuck AF. Radiol Clin North Am 40.3 (2002): 577-590

Ascher SM et al. Top Magn Reson Imag 12.2 (2001): 105-129



TUMOUR SIZE

- 3 dimensions
- Oblique orthogonal planes
- 4.0 cm cutoff
 - IB₁ vs. IB₂



Rauch et al., Radiographics 34:1082 (2014)

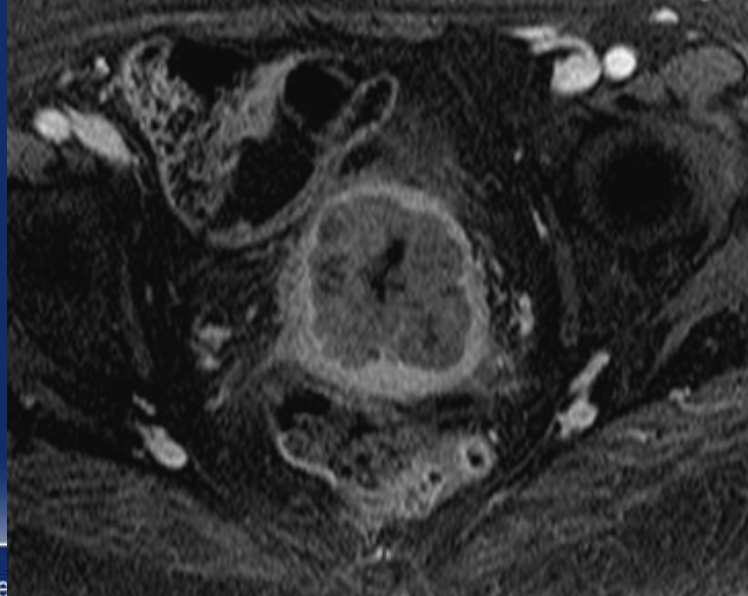
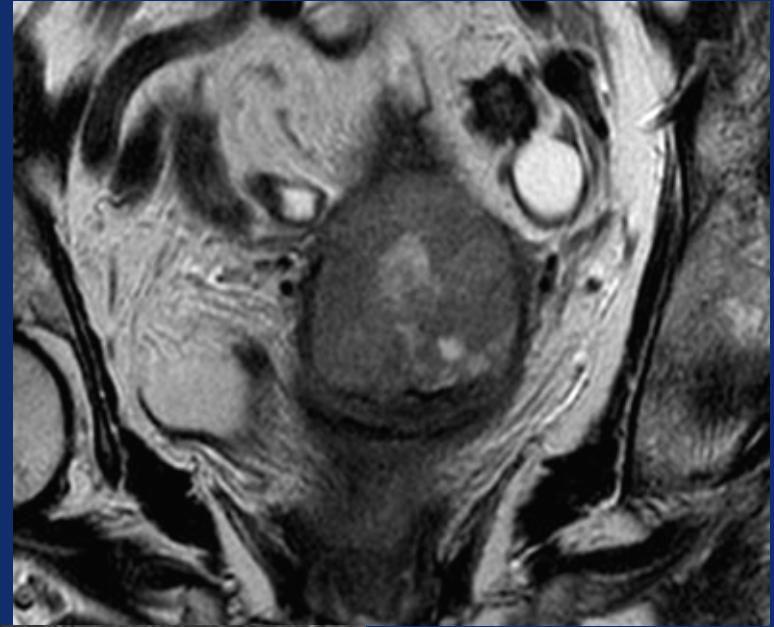
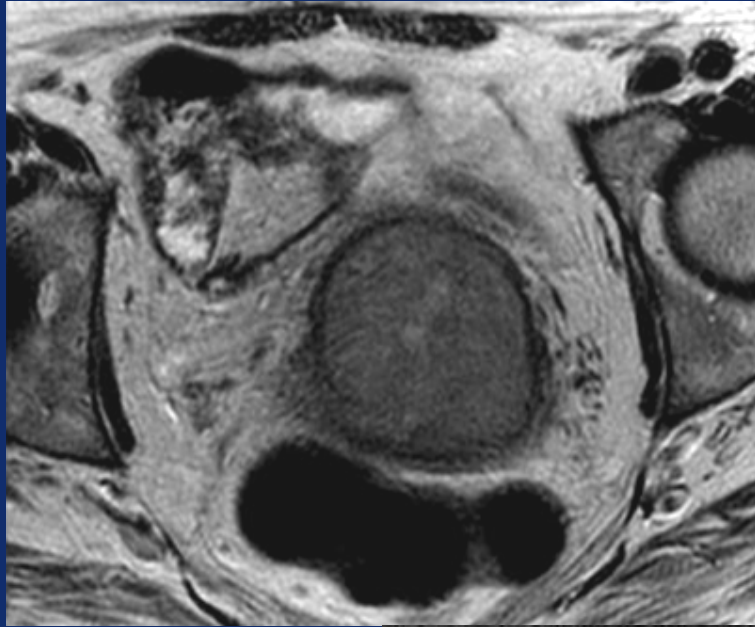
Internal Os

- Fertility-preserving Trachelectomy
 - Tumor free distance(>0.5-1cm)
 - IO Invasion / <5mm tumor/IO distance
 - Contraindication trachelectomy
 - Rad treatment planning fields
-
- MRI Very High Accuracy (95%*)



EJR 2013 Systematic Review*
Clin Radio 2016 . With Histopath correlation

IB-Cervix Stroma



MRI Impact

- Parametrial invasion

- MRI Accuracy 80 – 87%
- Specificity 93%, NPV 94 – 100% (Preserved outer stroma)
- FIGO IIB: chemoradiation

Accuracy of overall MRI local staging :85 – 96%

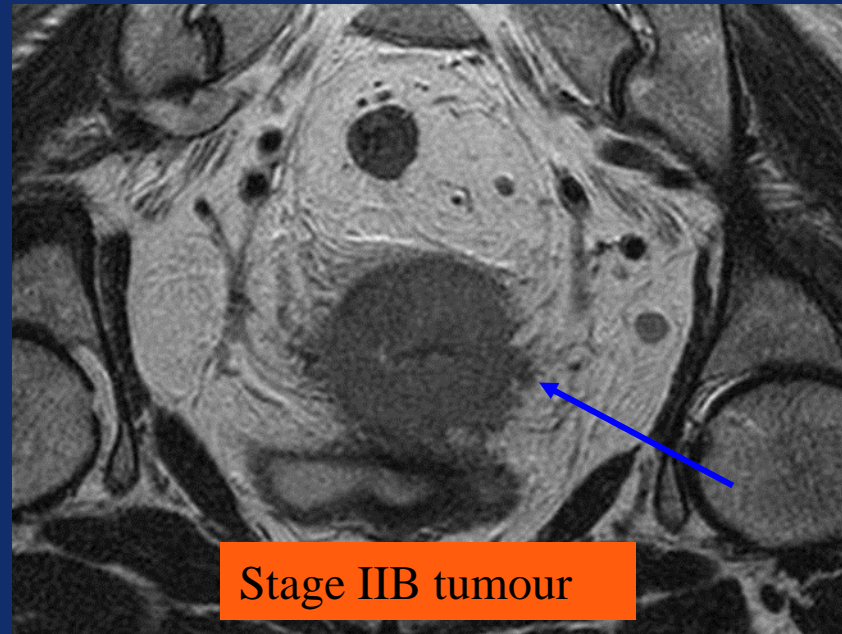
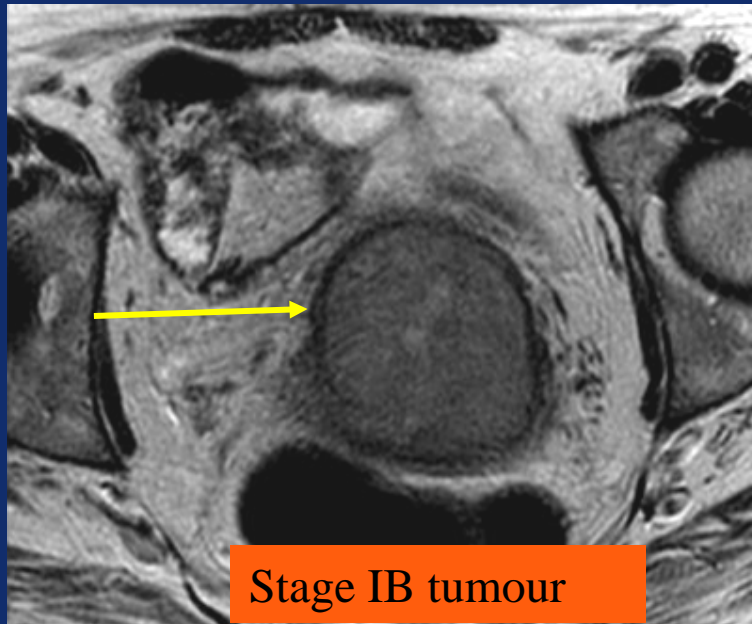
Okamoto Y et al. Radiographics 23.2 (2003): 425-445

Scheidler J and Heuck AF. Radiol Clin North Am 40.3 (2002): 577-590

Ascher SM et al. Top Magn Reson Imag 12.2 (2001): 105-129

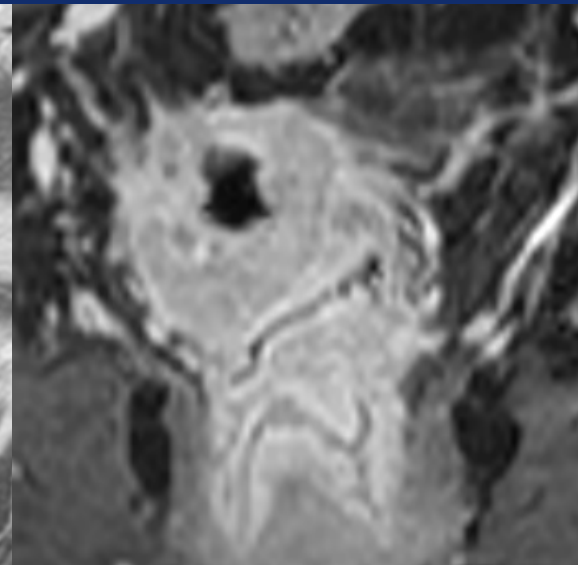
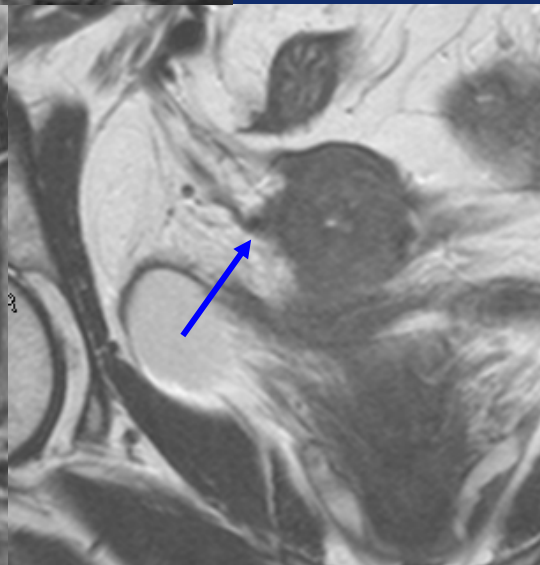
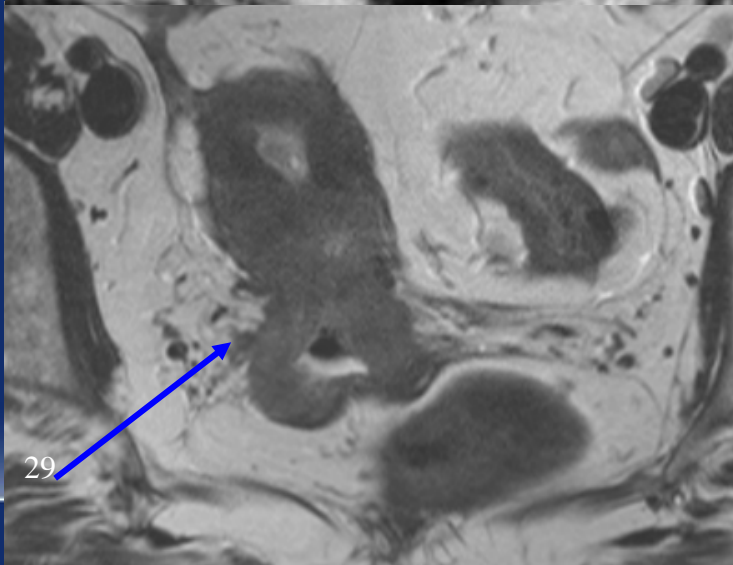
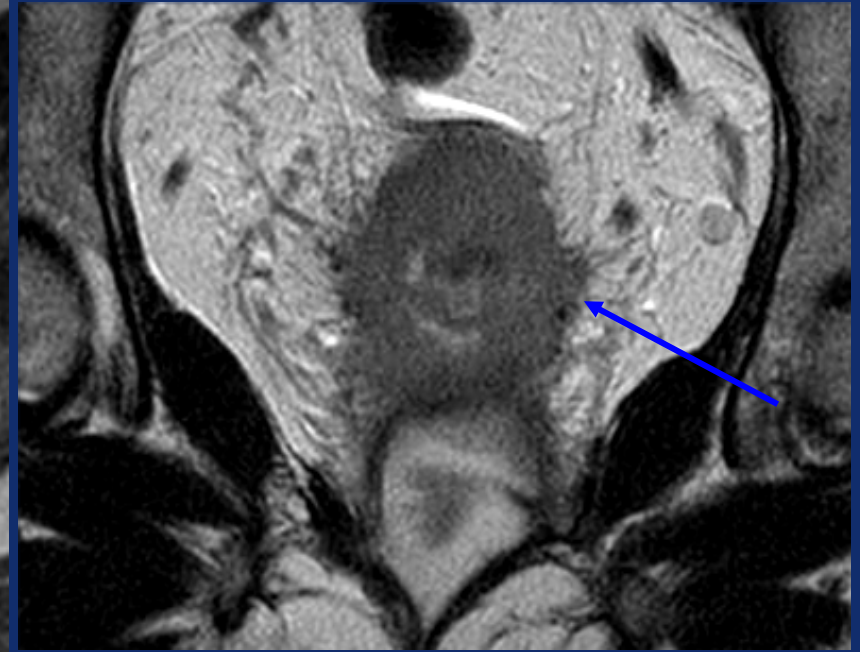
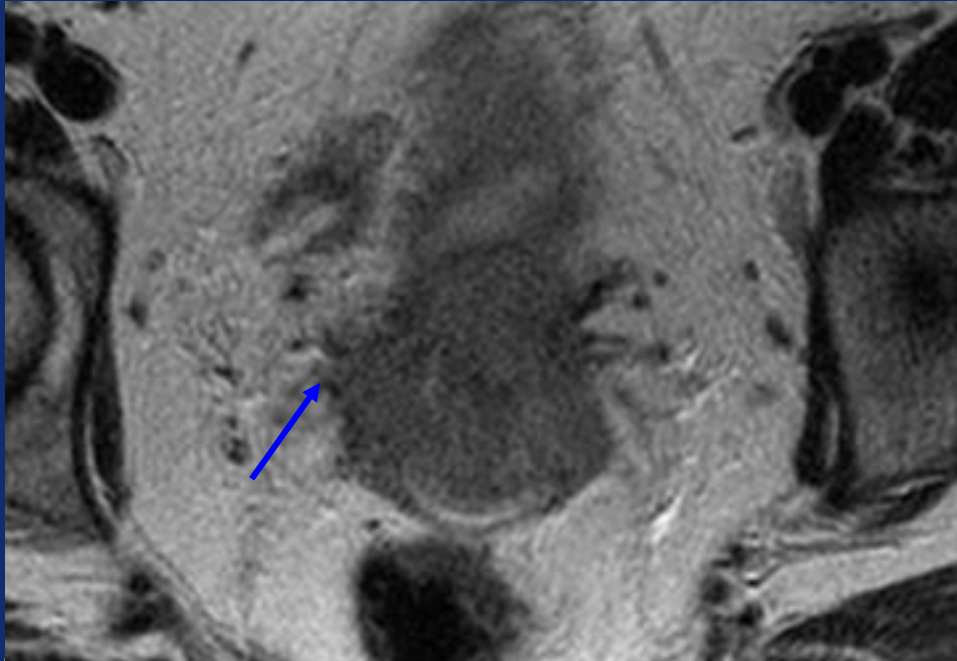


IIB- Parametrial Invasion? "To Be or Not To Be"

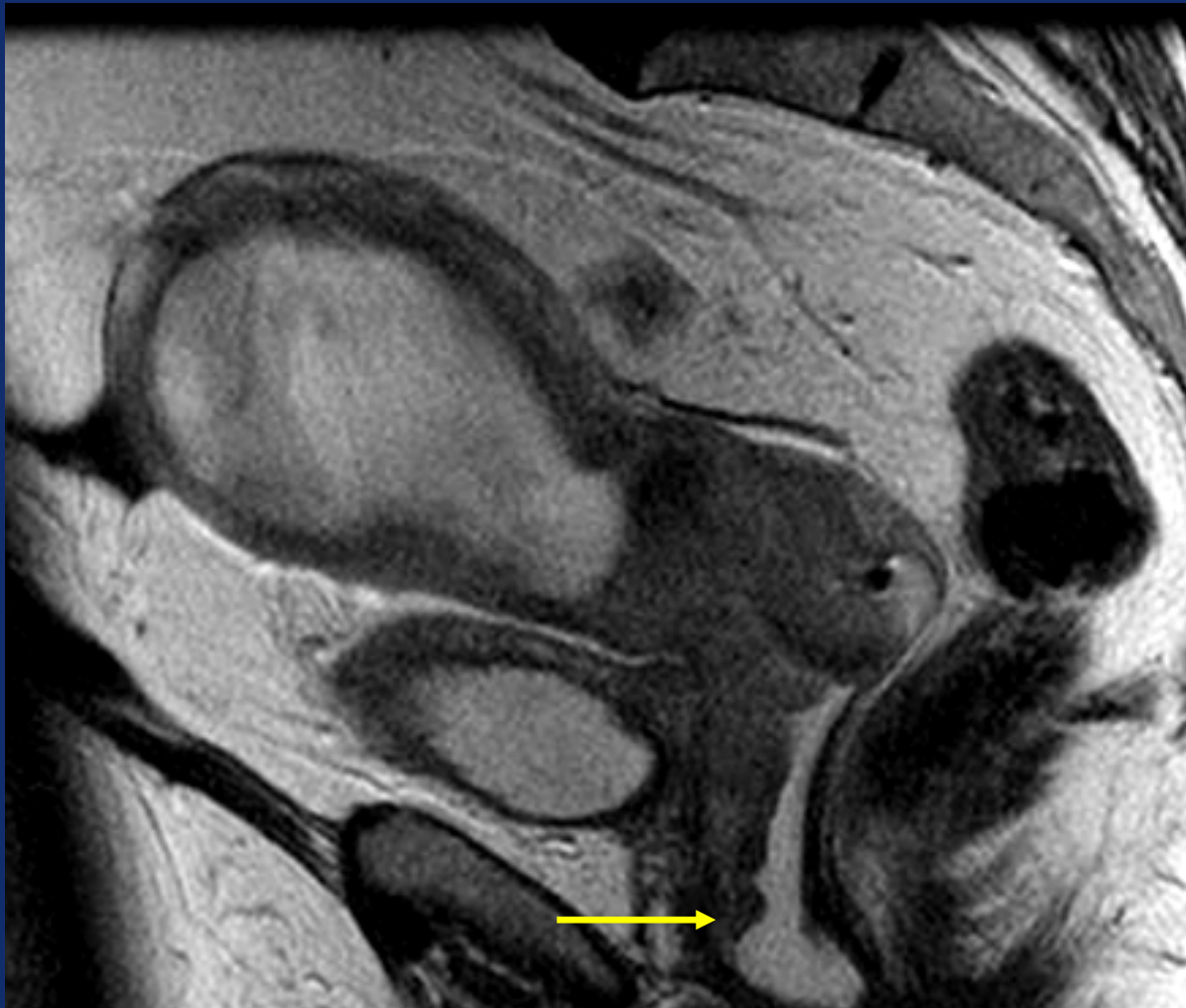


- Clear tumor signal outside cervix stroma
- Irregular/Nodular protrusions
- Not just Spiculations

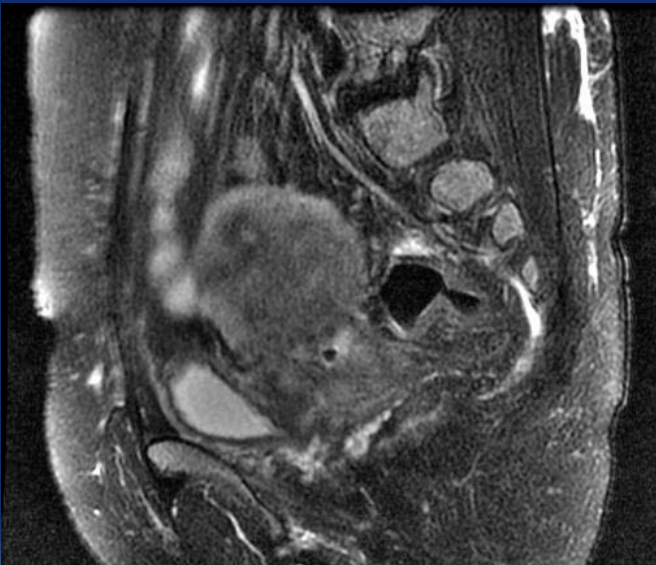
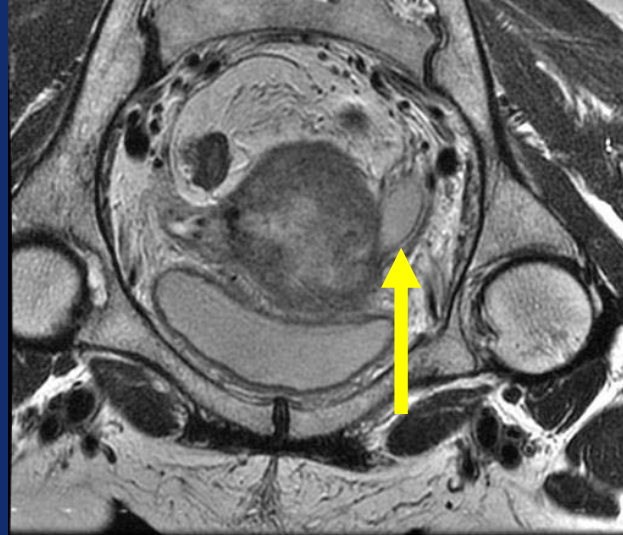
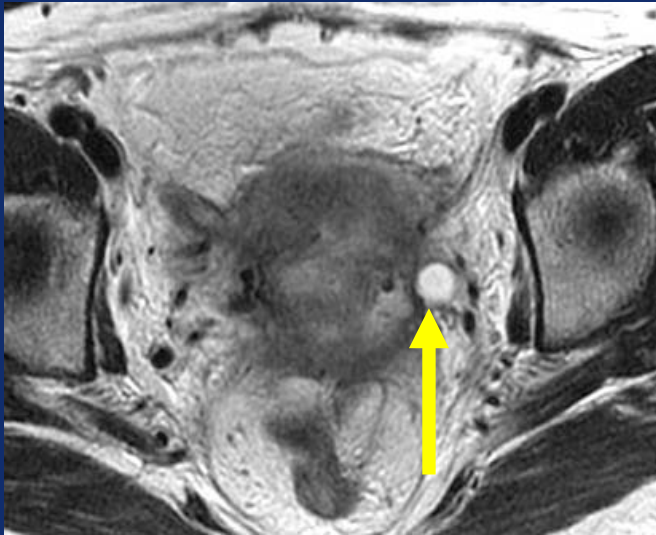
IIB-Parametrial Spread



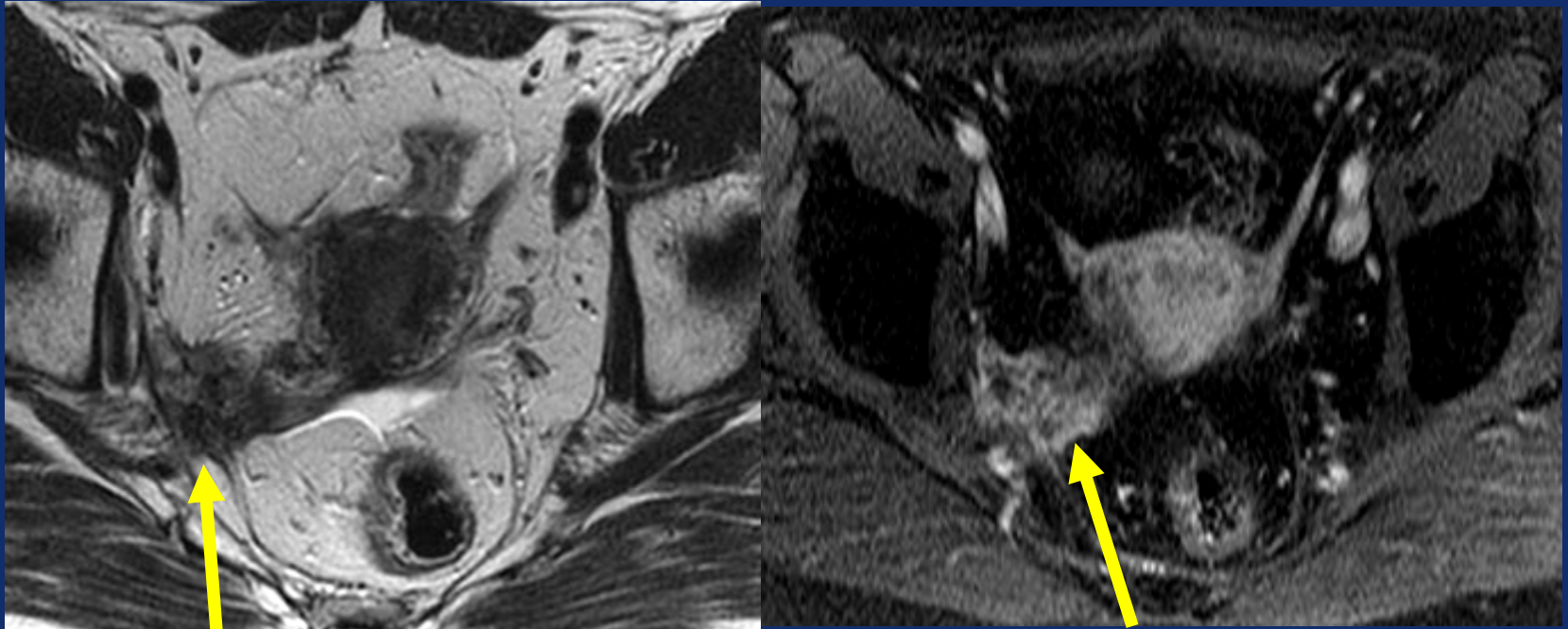
IIIA - LOWER 1/3 VAGINA



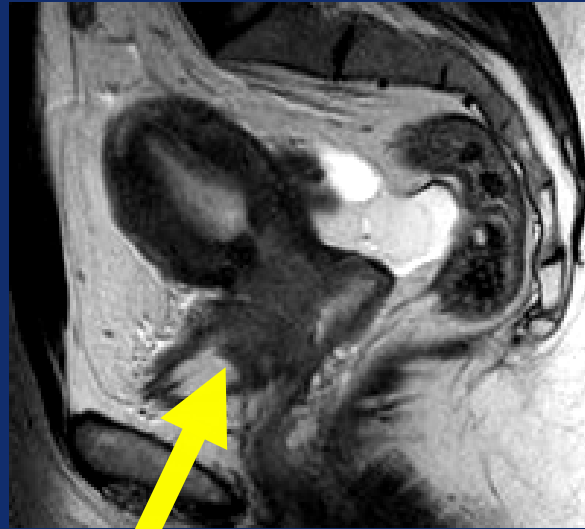
IIIB-Ureter



IIIB- Pelvic side wall

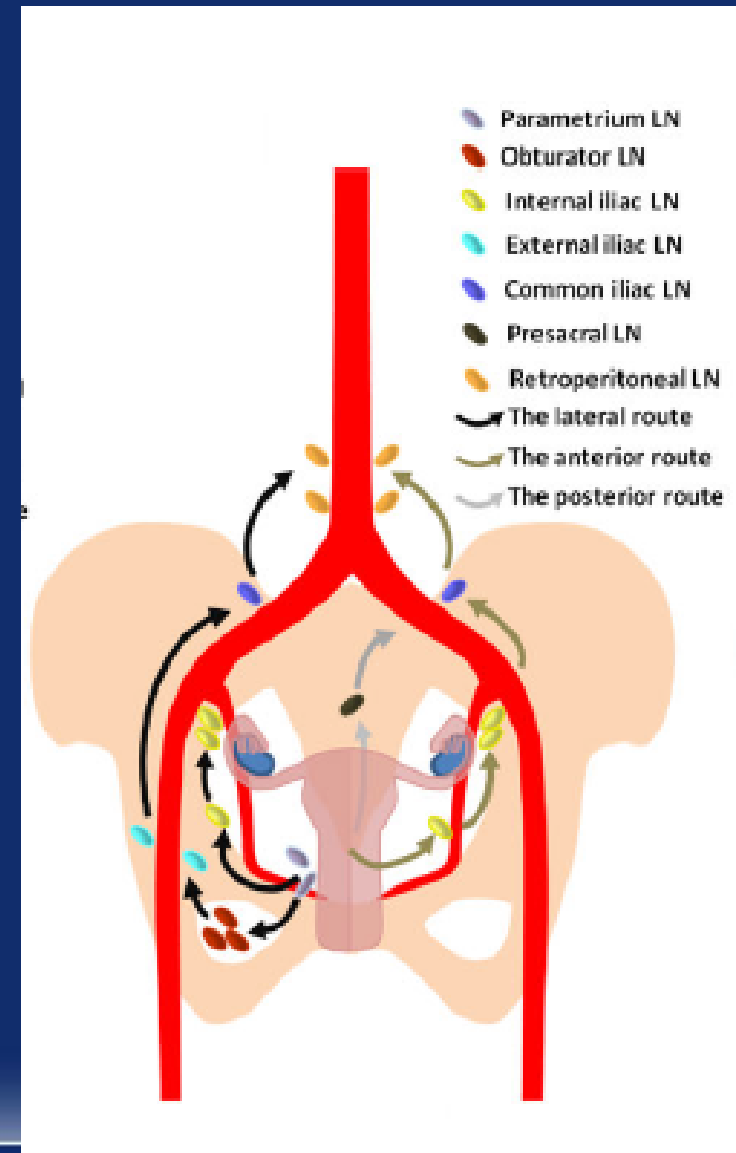


IVA-Bladder Invasion



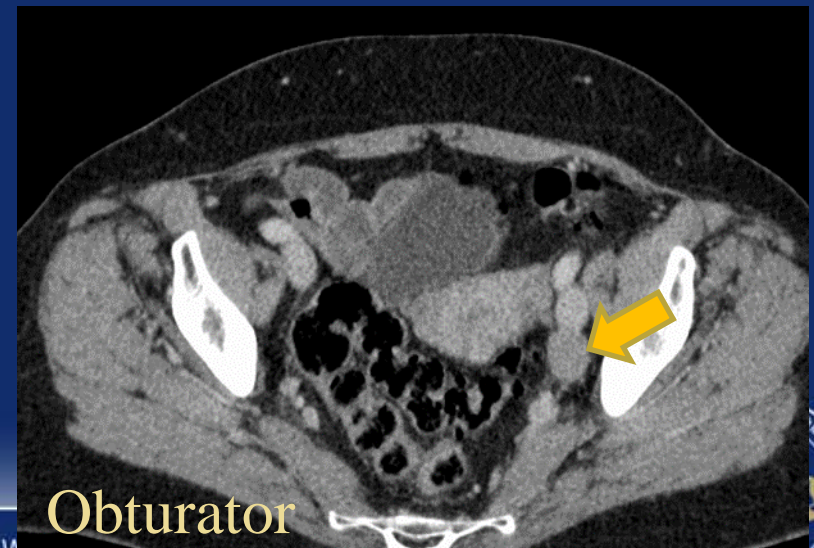
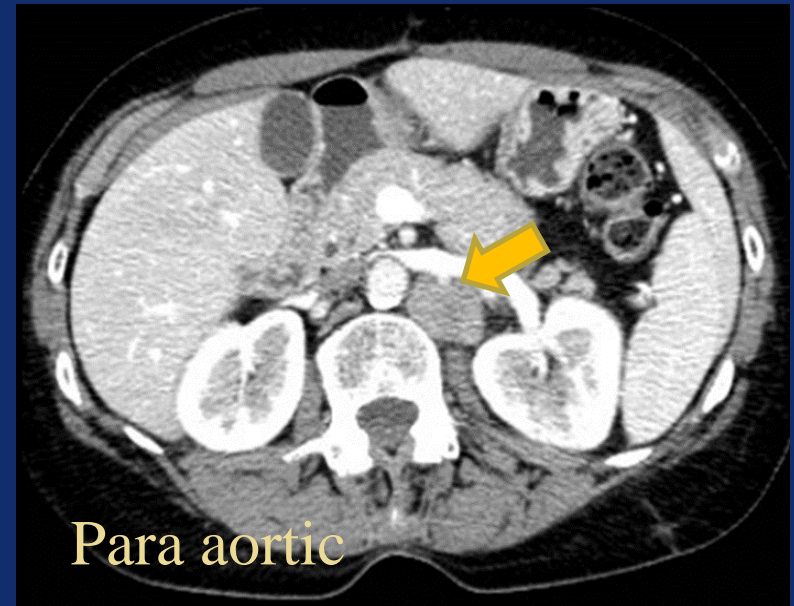
LYMPHADENOPATHY

- Nodal distribution
- Obturator
- External iliac
- Internal iliac

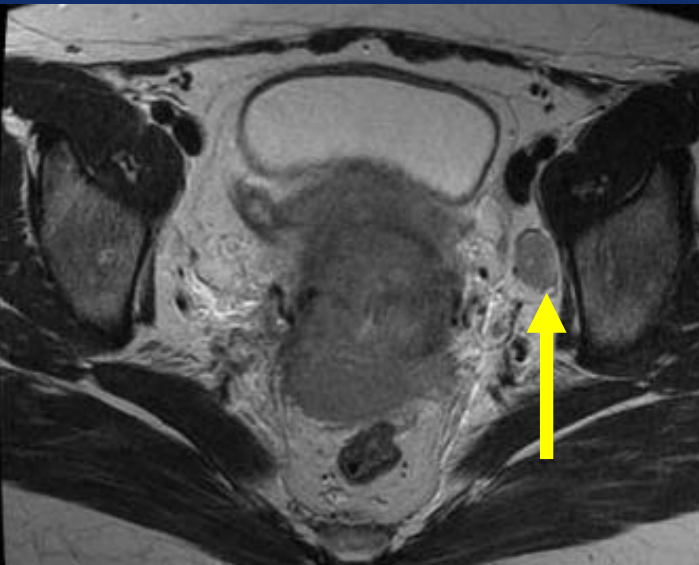
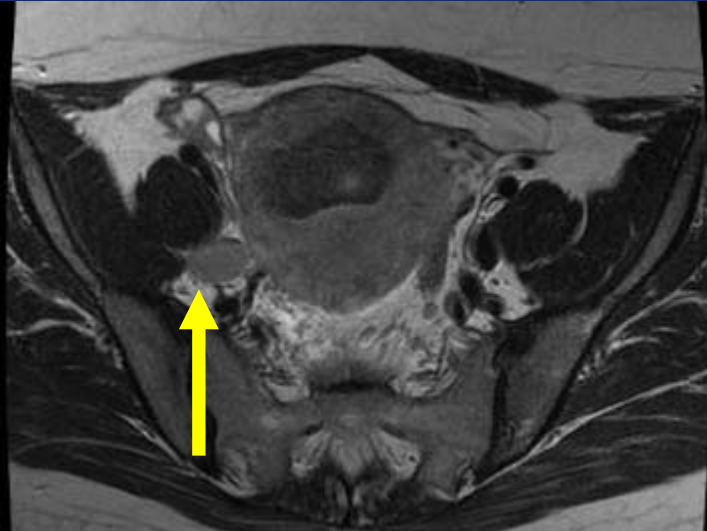


LYMPHADENOPATHY

- Correlate with parametrial extension of tumor
- higher T stage
- Para aortic nodes
- Extended surgical dissection
- Chemoradiation



LYMPHADENOPATHY



- Size >8mm or 10mm
- Round morphology
- T2 signal (hetero or matching tumour)
- Indistinct margins
- MRI Sens(70%)
Spec(44-93%)

DWI- PELVIC NODES

- DWI Increases sensitivity(86%)
- ADC Increases Specificity(84%)
- No agreed ADC cutoff (0.77-1.15)
- DWI alone cannot exclude metastases
- Heterogenous data
- Technical Variability(B-values,scanner,field st)

Shen D etal. BJR 2015 SR/Meta



PET-MRI

- Preliminary Data*
- Integrated Whole Body Imaging
- Local & Distant Staging
- Nodal Staging (91/94/93%*)
- Additional Prognostic Variables (SUV/ADC)

**Eur J Nucl Med Mol Imaging. 2015
Abdom Imaging. 2015*



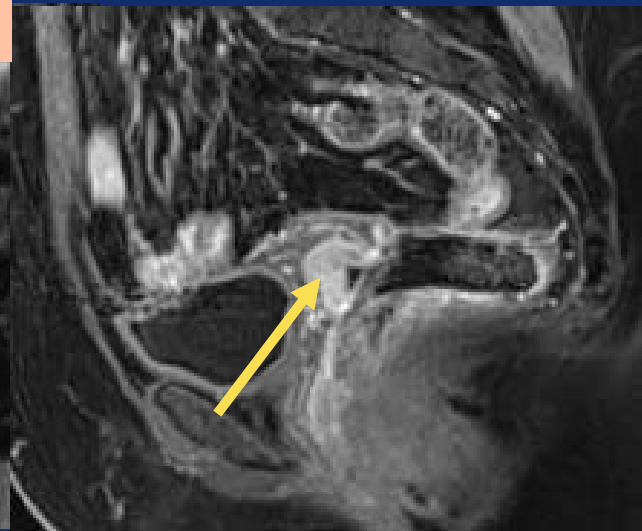
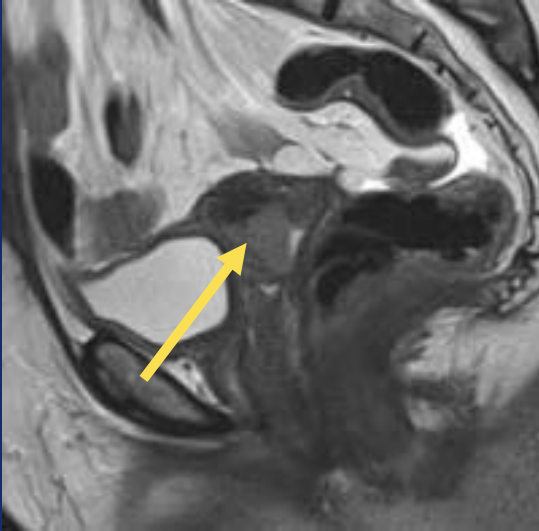
POST TREATMENT MRI

- Conventional MRI Inadequate for Post CRT effects vs Residual/Recurrent Disease
- Evolving Role -Functional Imaging
- Predicting Response
- Assess Treatment Response(Mid-Late)
- Recurrence
- Multiparametric Approach
- DWI, DCE + Conv MRI



Post Treatment Evaluation

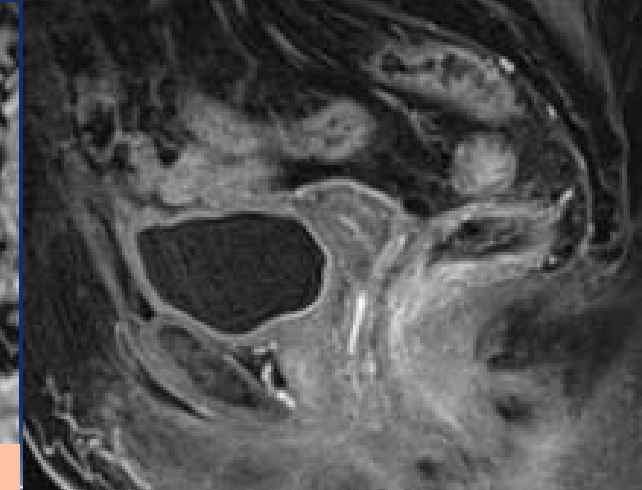
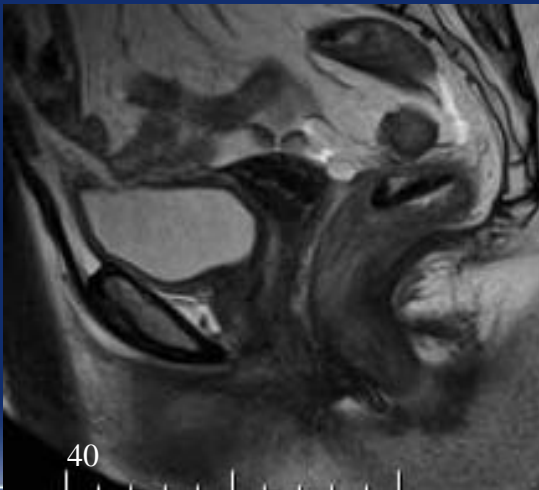
PRE RT



T2

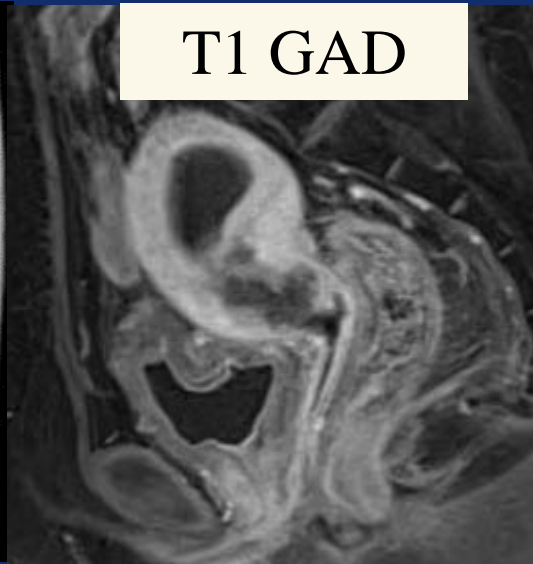
ADC

T1 GAD

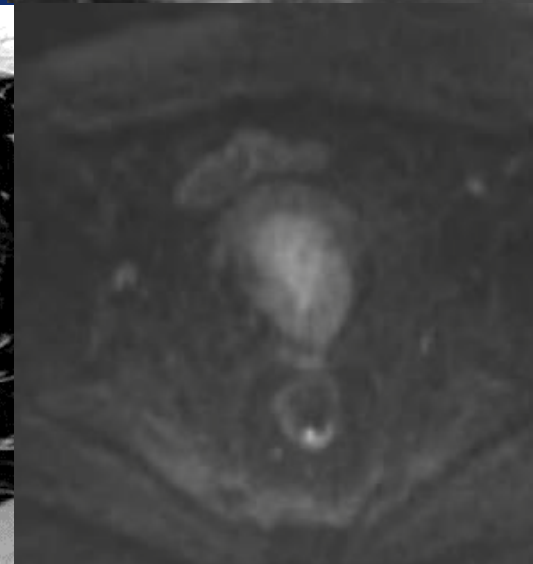
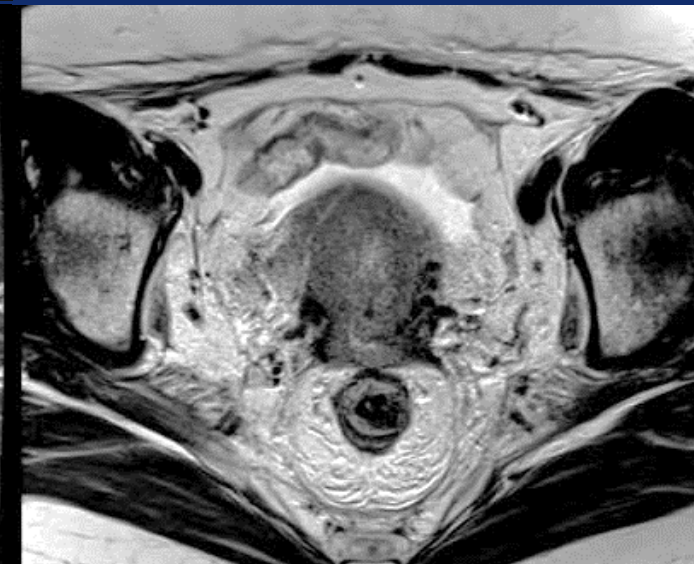


POST RT

Post Treatment Evaluation



T1 GAD

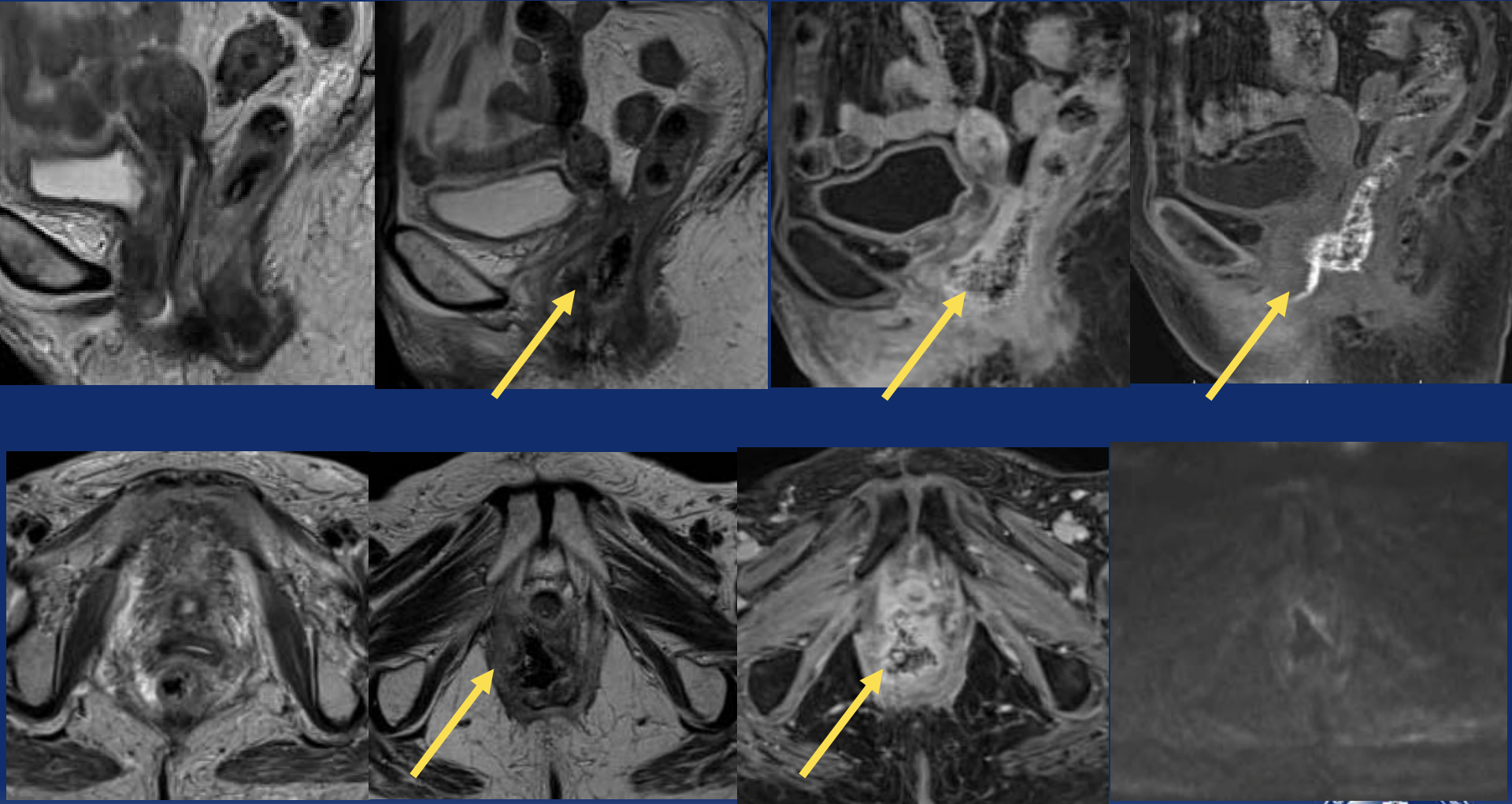


PRE T2

POST T2

DWI

FISTULA



RECURRENT DISEASE

- Cervical stump assessment
- Look for original tumour's T2 signal



SUMMARY

- MRI Technique

- High resolution (oblique) T2 imaging
- DWI
- Gad Contrast

- MRI Staging for cervical cancer

- Tumour size (< or > 4.0 cm)
- Parametrial invasion
- Lower 1/3 of vagina, ureter, pelvic side wall, Bladder

- Post Treatment Evaluation

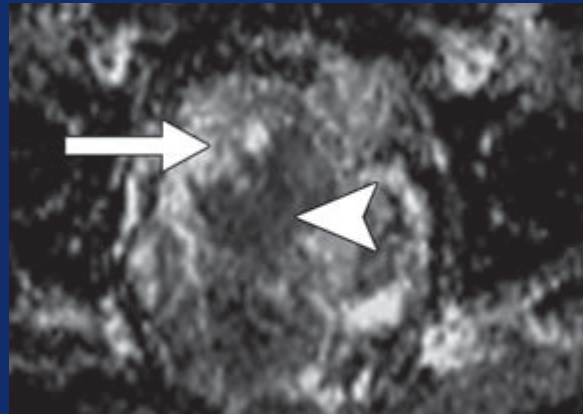
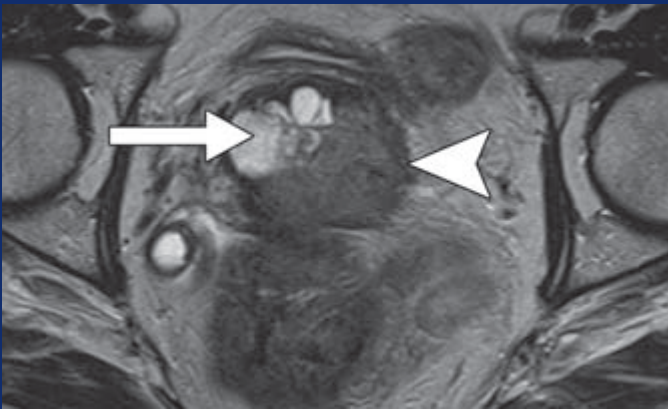
Multiparametric(T2 /DWI/Dynamic Gd)





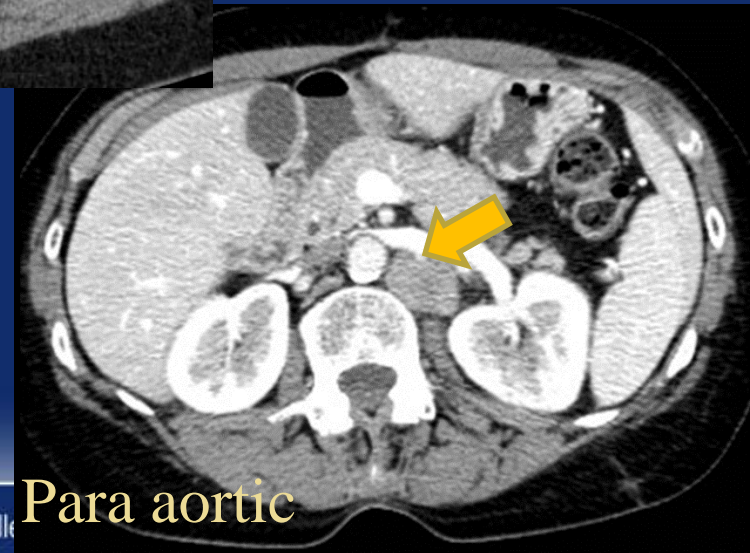
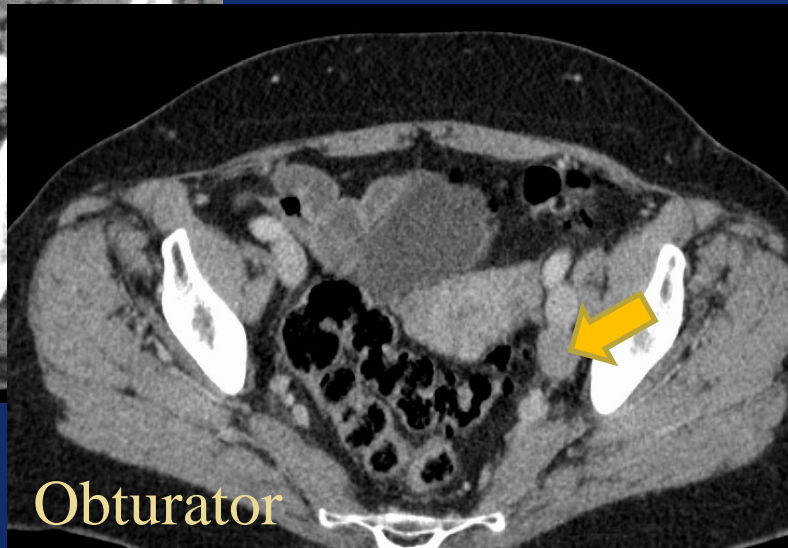
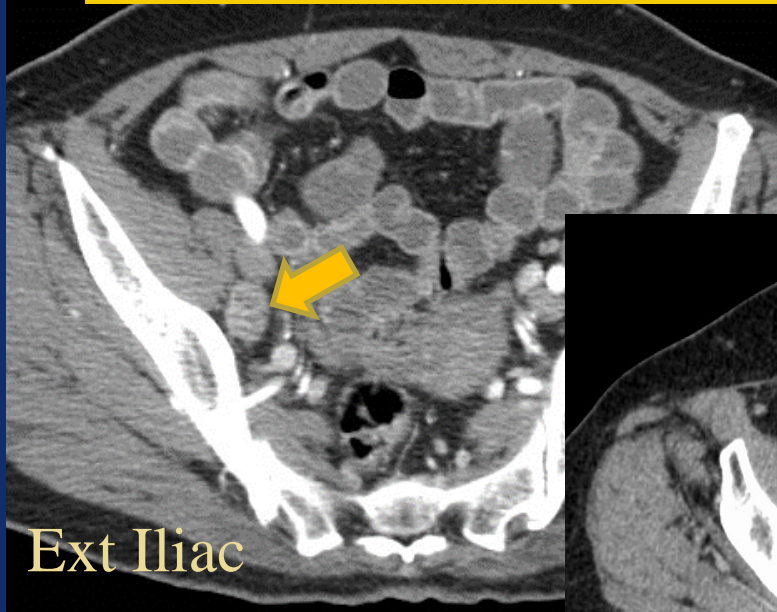
ADENOMA MALIGNUM

- Cystic malignant tumor of cervix
 - Mucinous adenocarcinoma
- Deep cervical stromal invasion
 - Contrast to tunnel clusters, nabothian cysts
- Cystic and solid components
- Poor prognosis



Reinhold et al., AJR 200:261 (2013)

LYMPHADENOPATHY



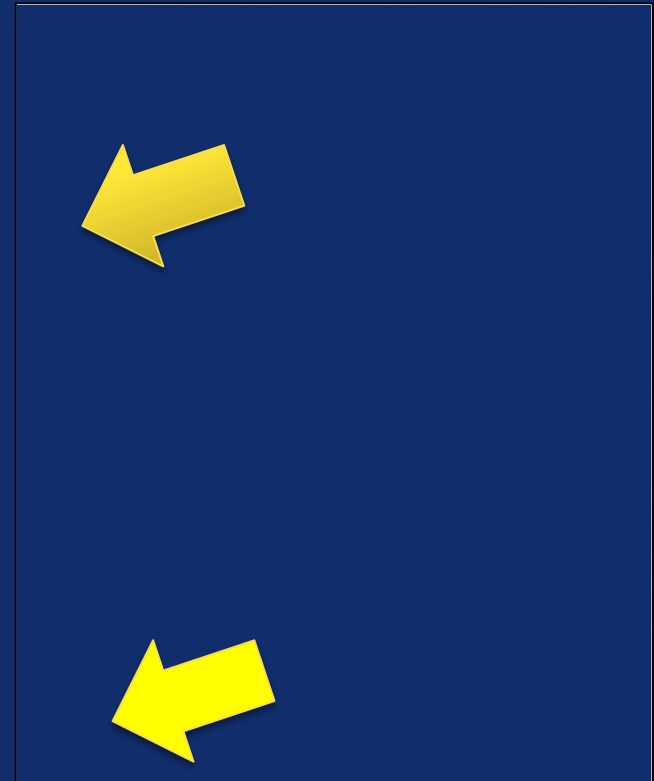
STRUCTURES THAT CAN MIMIC A LYMPH NODE ON IMAGING

- Bowel loops when not opacified with oral contrast
- Ureteric calculi can be confused with mesenteric lymph node calcification on plain radiographs
- Phleboliths mimicking lymph node on MRI
- Ovary can be mistaken for pelvic side wall lymph node: following the ovarian vein to the ovary may be useful for correct identification.



MRI Protocol: Pearls

- Anterior saturation band
 - Motion from belly breathers
- Don't respiratory trigger
 - Doesn't help much
- Adjust phase and frequency directions
 - Minimize ghosting in phase encoding direction



Correct

Radiologic (MRI) Pathology of Cervical Cancer at Brachytherapy

Radiation oncologist's perspective



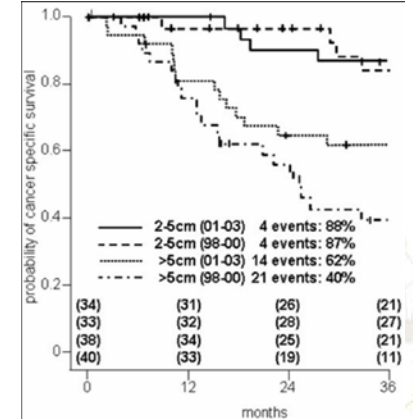
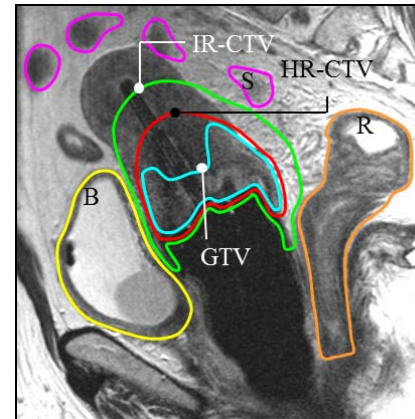
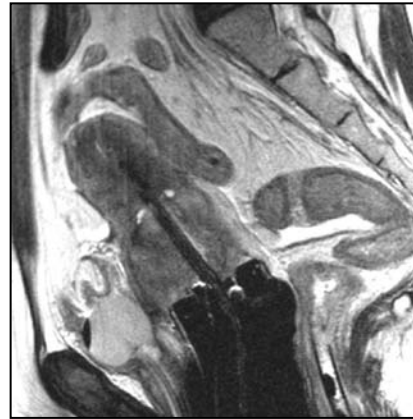
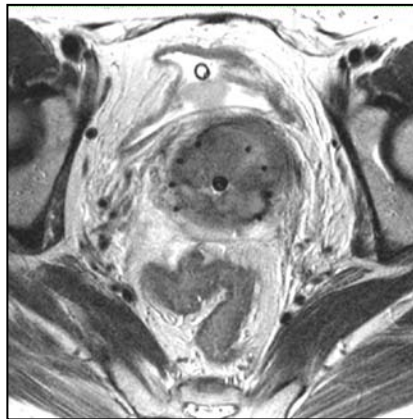
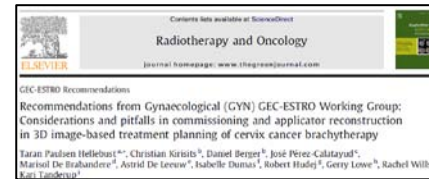
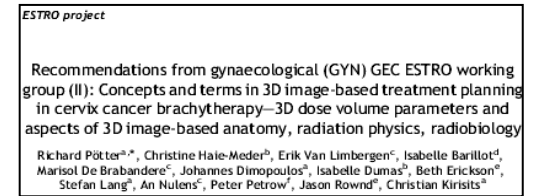
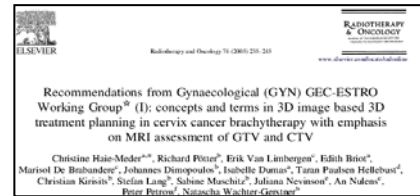
Primoz Petric, MD, Msc
Senior Consultant

Department of Radiation Oncology
NCCCR, HMC
Doha, Qatar

Gold standard: T2W MRI

Magnetic Resonance Imaging

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



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

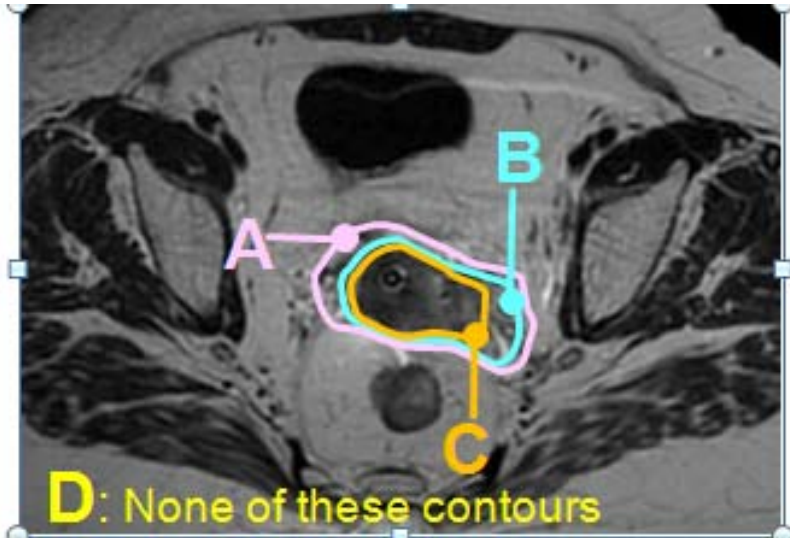
Pötter. Radiother Oncol 2011
 Pötter. Radiother Oncol 2007
 Lindegaard J. Radiother Oncol 2008
 De Brabandere M. Radiother Oncol 2008
 Jurgenliemk Shulz IM. Radiother Oncol 2009
 Cahrgari N. IJROBP 2009

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

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

Interpretation of imaging findings at BT

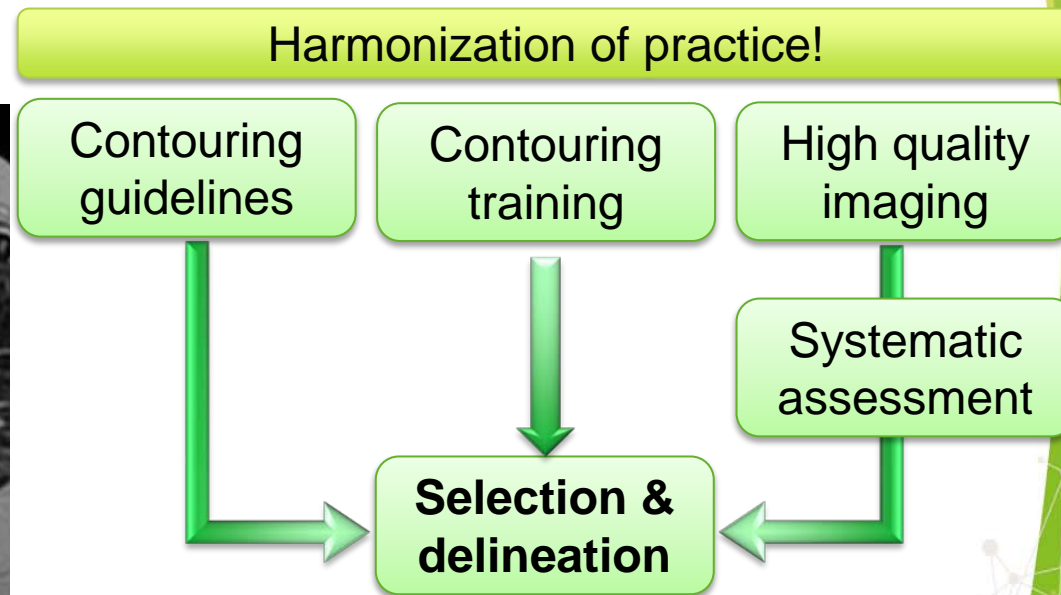
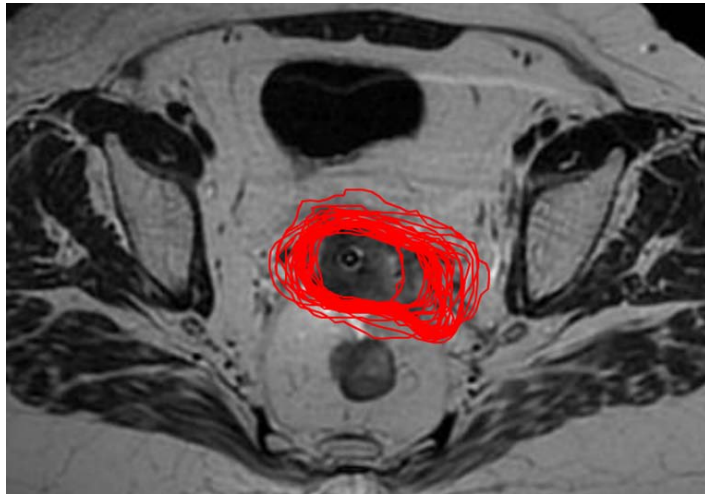
What is the High Risk CTV on this slice? (your best guess)



- A. A
- B. B
- C. C
- D. d

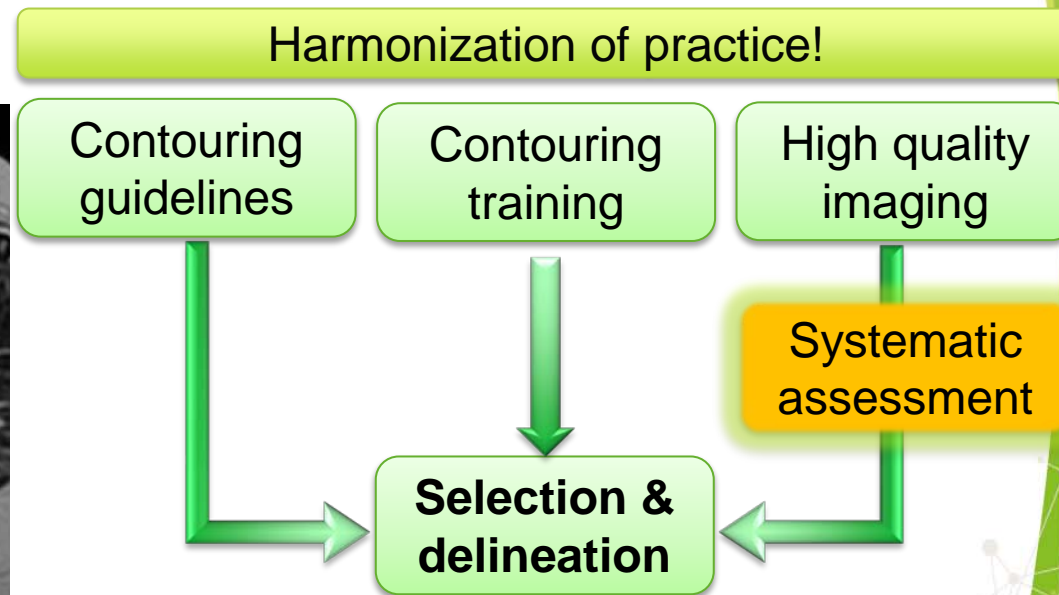
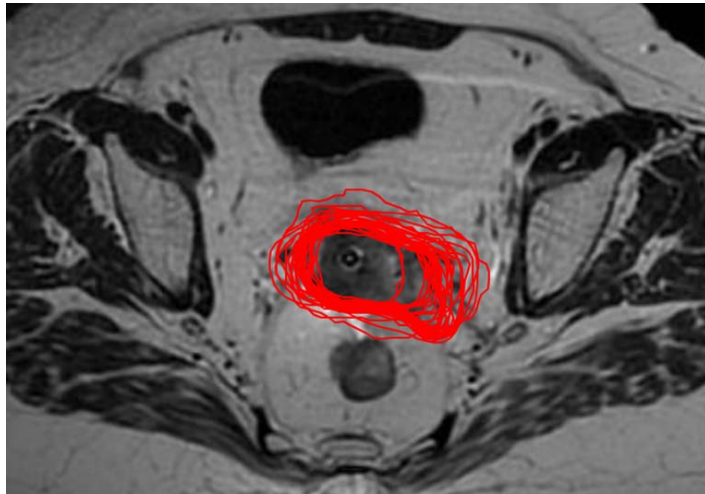
Interpretation of imaging findings at BT

Contouring uncertainties: weakest link in Image guided BT?



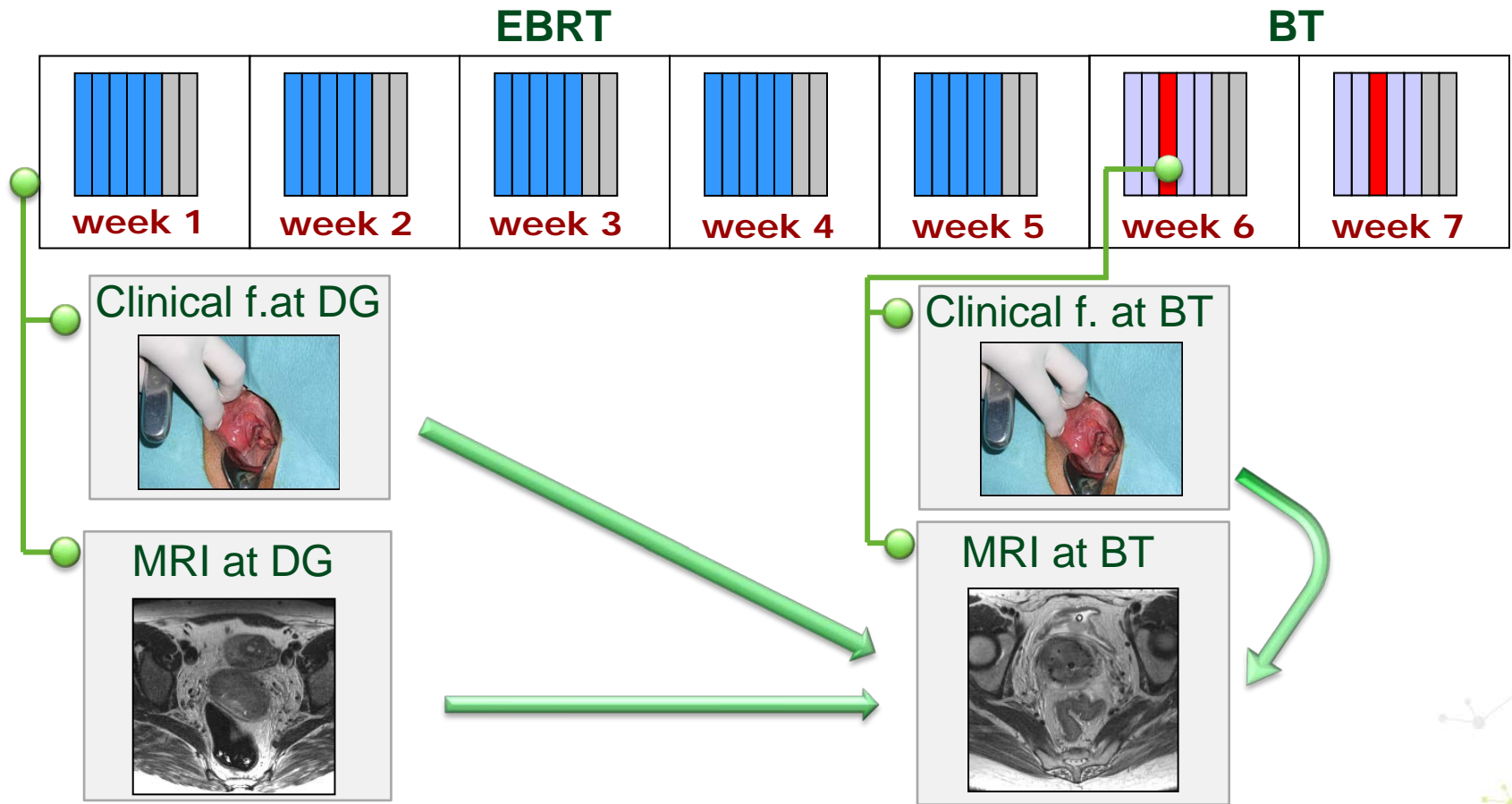
Interpretation of imaging findings at BT

Contouring uncertainties: weakest link in Image guided BT?



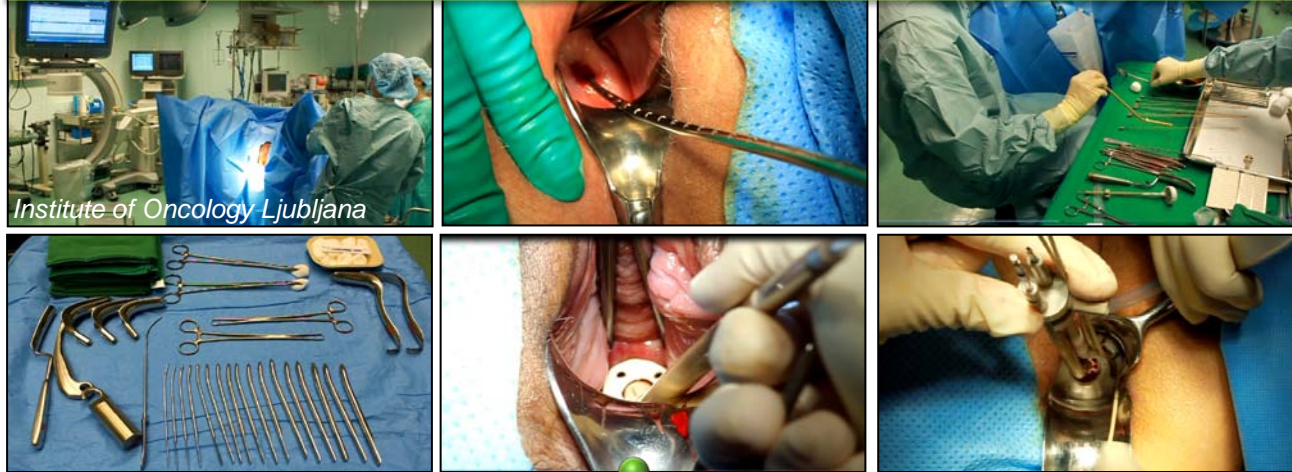
Assessment of sectional imaging at time of BT

General principles



STEPS of Assessment of MRI at BT

THEATRE



MRI SUITE

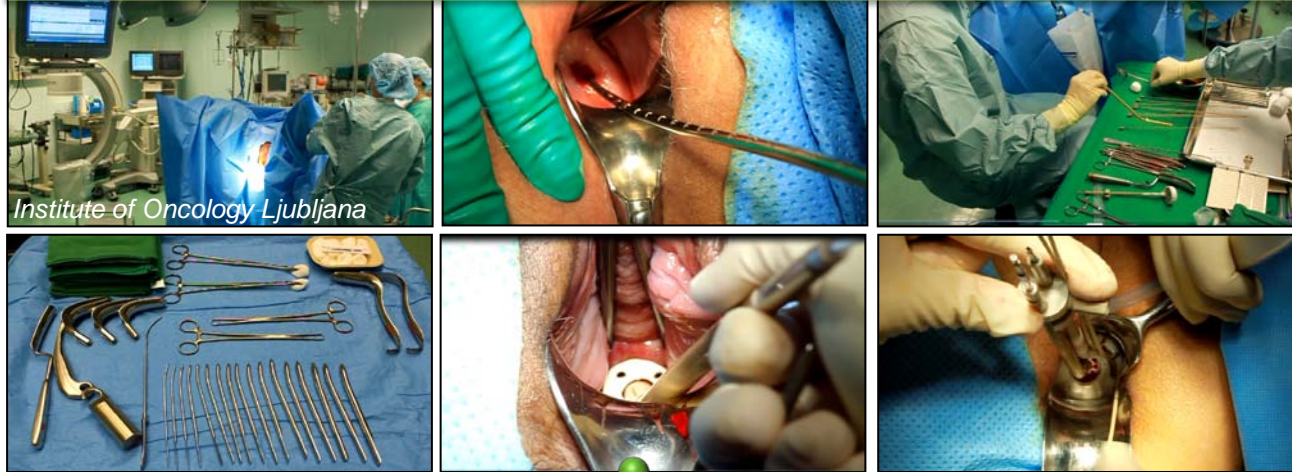


1. Rule out **FLOP**

2. Set the **STAGE** for contouring

STEPS of Assessment of MRI at BT

THEATRE



MRI SUITE



1. Rule out **FLOP**

2. Set the **STAGE** for contouring

1. Rule out **FLOP**

FL FLuid in abdomen?

OP Organ Perforation?

1. Rule out FLOP

FL FLuid in abdomen?

OP Organ Perforation?

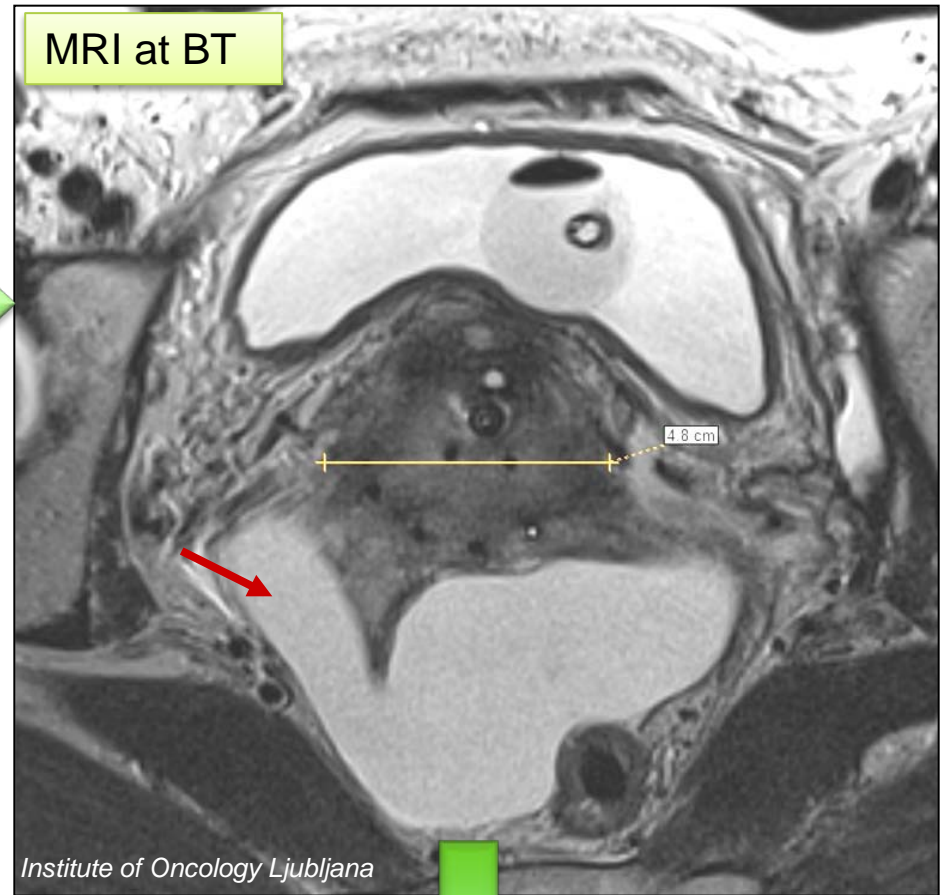
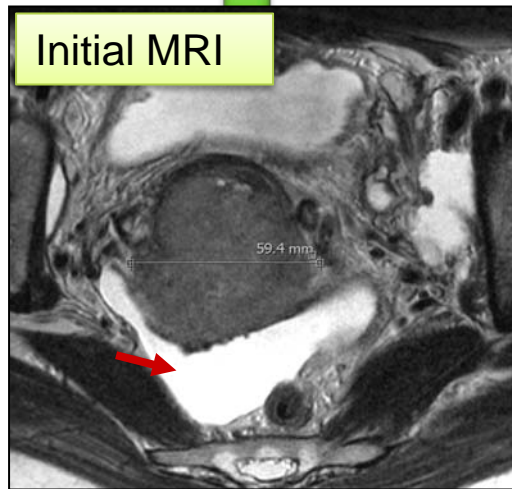
What is appearance of free blood in hyperacute bleeding?

- A. Hypointense on T2
- B. Isointense on T2
- C. Isointense or hyperintense on T2

1. Rule out FLOP

FL FLuid in abdomen?

OP Organ Perforation?

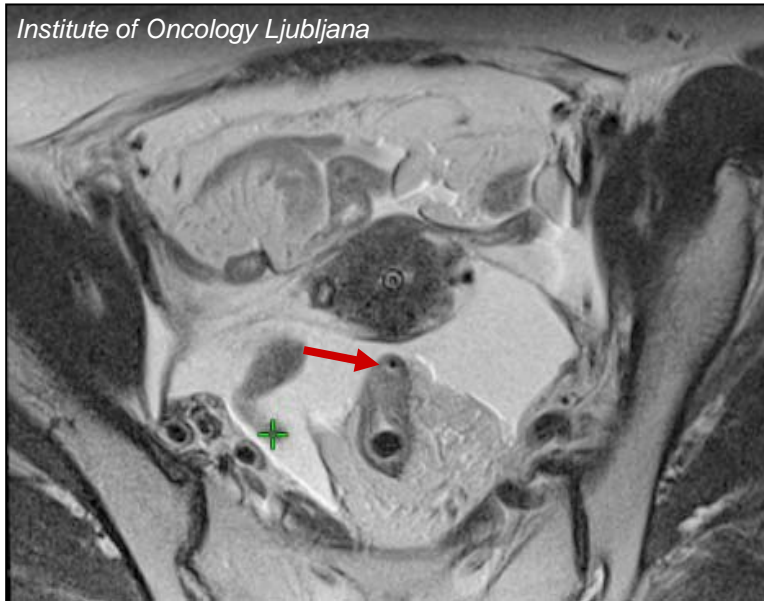


Compare with initial findings!

1. Rule out FLOP

FL FLuid in abdomen?

OP Organ Perforation?



Action?



Have institutional policies and protocols ready!

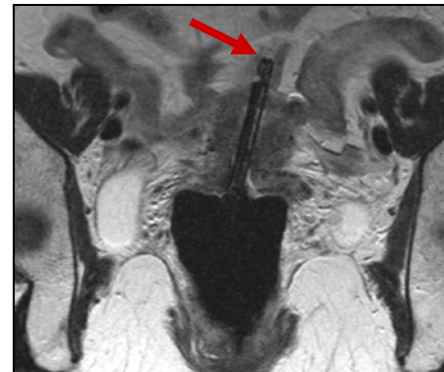
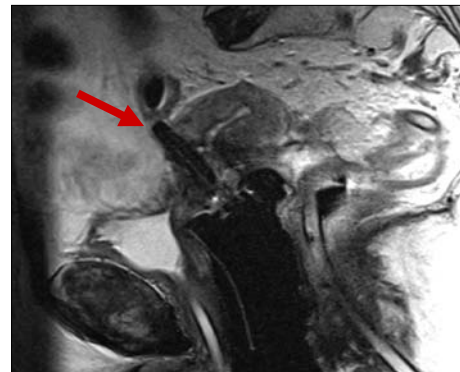
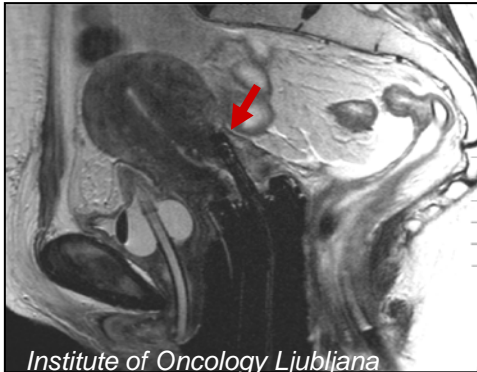
1. Rule out FLOP

FL FLuid in abdomen?

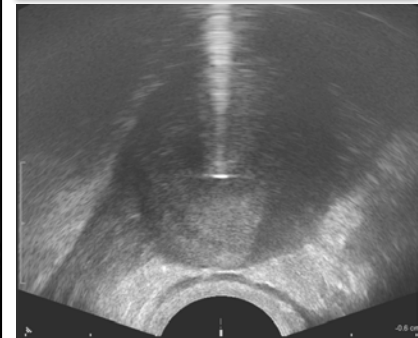
OP Organ Perforation?

Uterine perforations

Up to \approx 5-10 %!



US guidance!



Irwin W, et al. *Gynecol Oncol* 2003

Sharma DN, et al. *Gynecol Oncol* 2010

Davidson MTM, et al. *Brachytherapy* 2008

Millman RM, et al. *Clin Imaging* 1991

Jhingran A, Eifel PJ. *IJROBP* 2000

Barnes EA, et al. *Int J Gynecol Cancer* 2007

Lanciano R, et al. *IJROBP* 1994

Van Dyk S, et al. *IJROBP* 2009

Granai CO, et al. *Gyn Oncol* 1984

Segedin B, et al. *Radiol Oncol* 2013

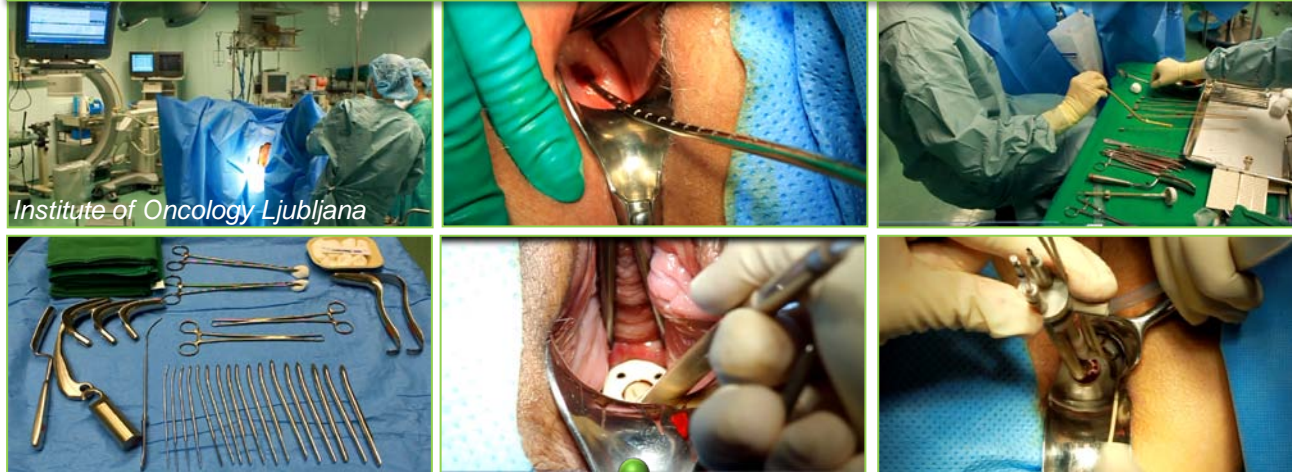
Sahinler I, et al. *IJROBP* 2004

Irwin W, et al. *Gynecol Oncol* 2003

Millman RM, et al. *Clin Imaging* 1991

Systematic Assessment of MRI at BT

THEATRE



MRI SUITE



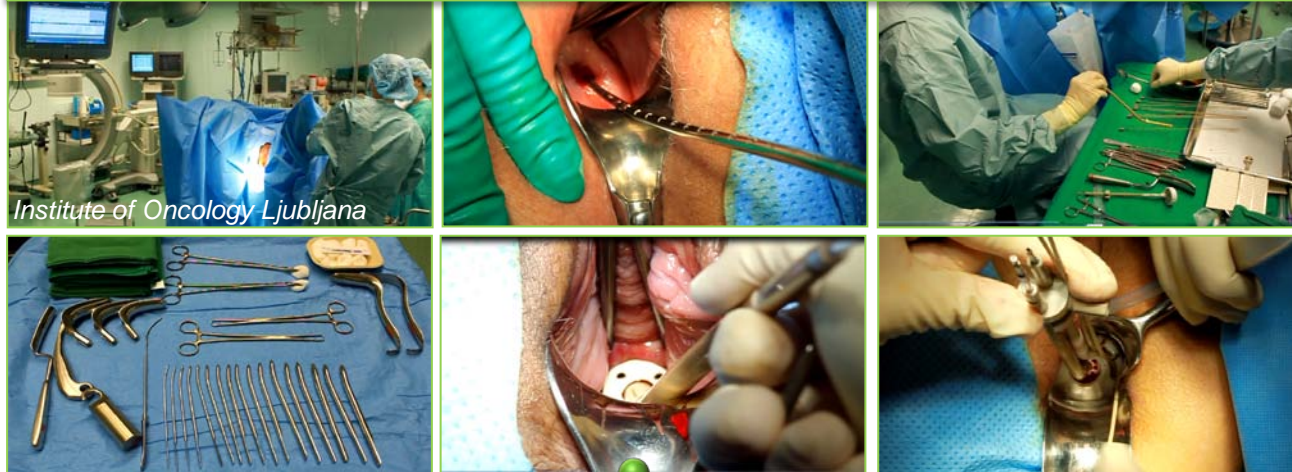
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2. Set the **STAGE** for contouring

Systematic Assessment of MRI at BT

THEATRE



MRI SUITE



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2. Set the **STAGE** for contouring

Set the **STAGE** for contouring

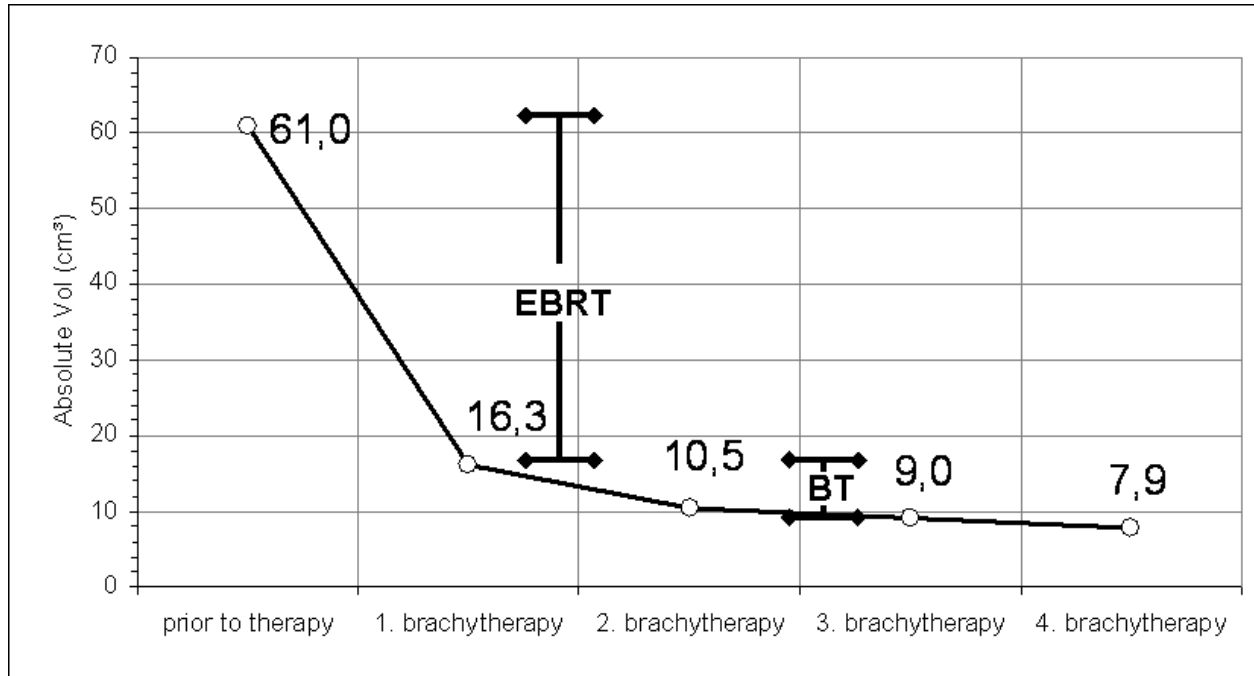
- S**ize of the residual tumor?
- T**opography of the target V?
- A**dequacy of the implant?
- G**rey zones in relation to GTV_{DG} ?
- E**xtra findings?

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

Size of the tumor at Brachytherapy

Volume change during treatment

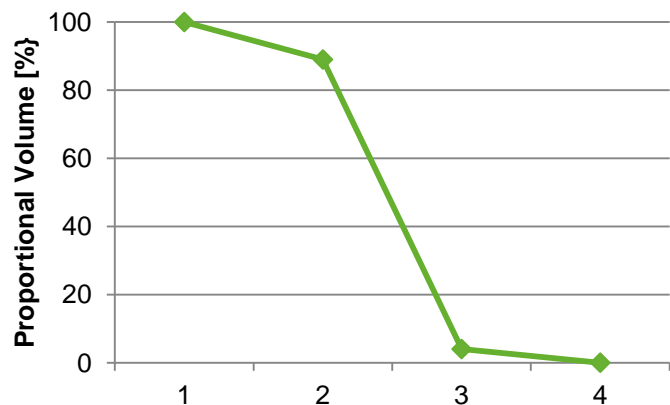
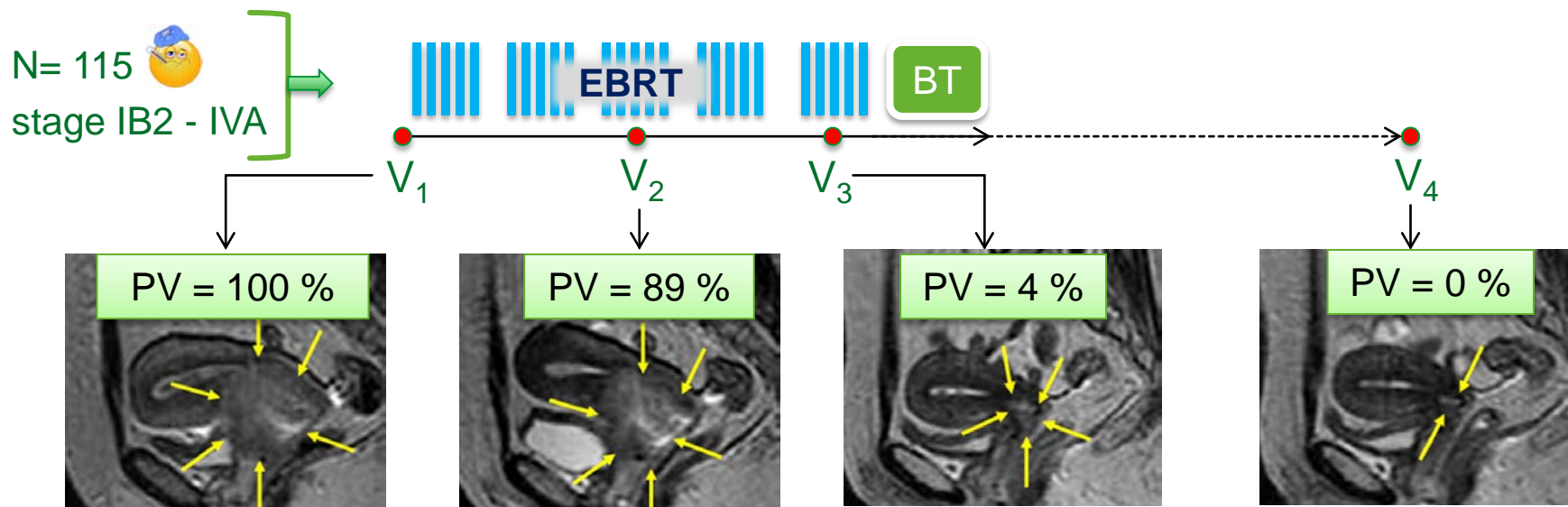


Dimopoulos J, et al. Strahlenther Onkol 2009

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

Size of the tumor at Brachytherapy

Volume change during treatment



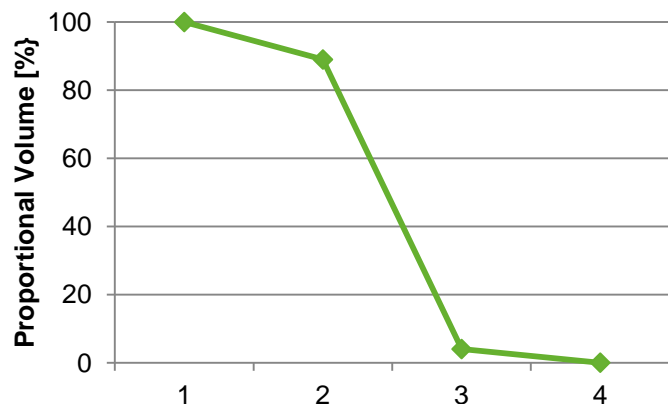
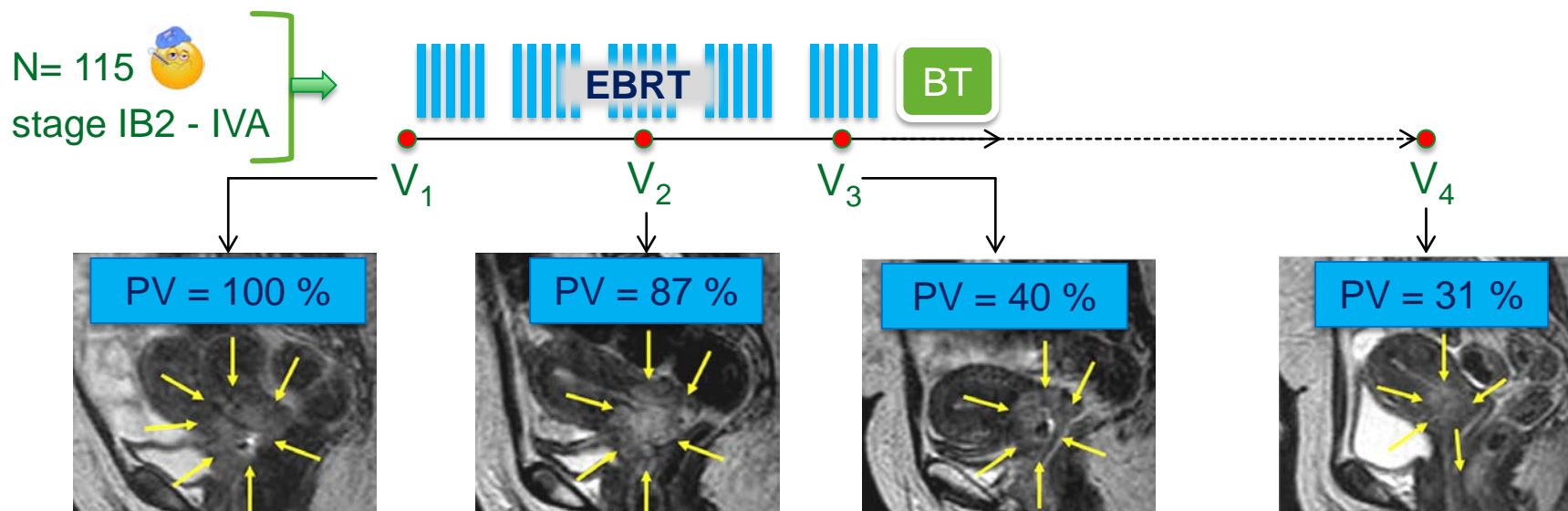
- Rapid response: 2.2% / Gy
- Steep slope
- Low AUC (24 %)

Alive & well at 7 y

Size of the tumor at Brachytherapy

Volume change during treatment

Regression to Proportional Volume: $PV = V_x / V_1$ [%]



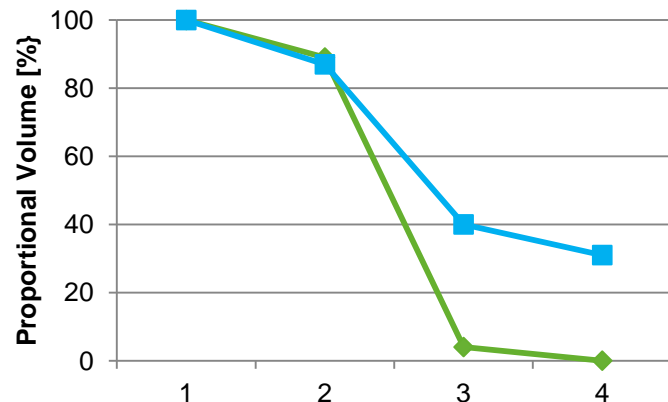
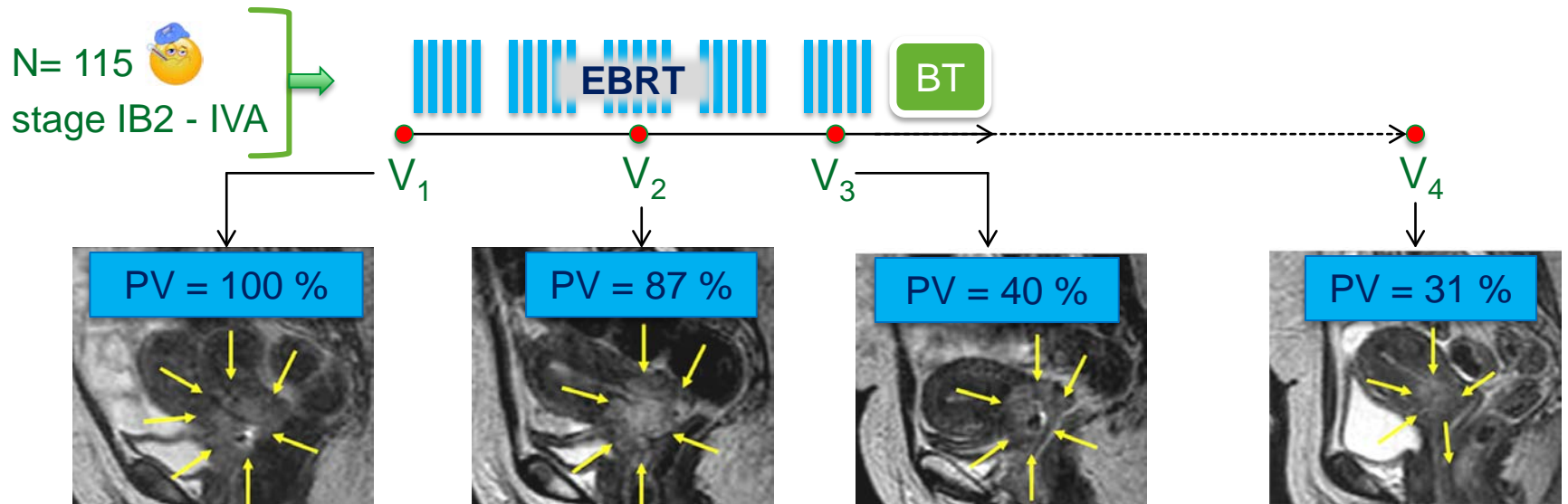
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Size of the tumor at Brachytherapy

Volume change during treatment

Regression to Proportional Volume: $PV = V_x / V_1$ [%]



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

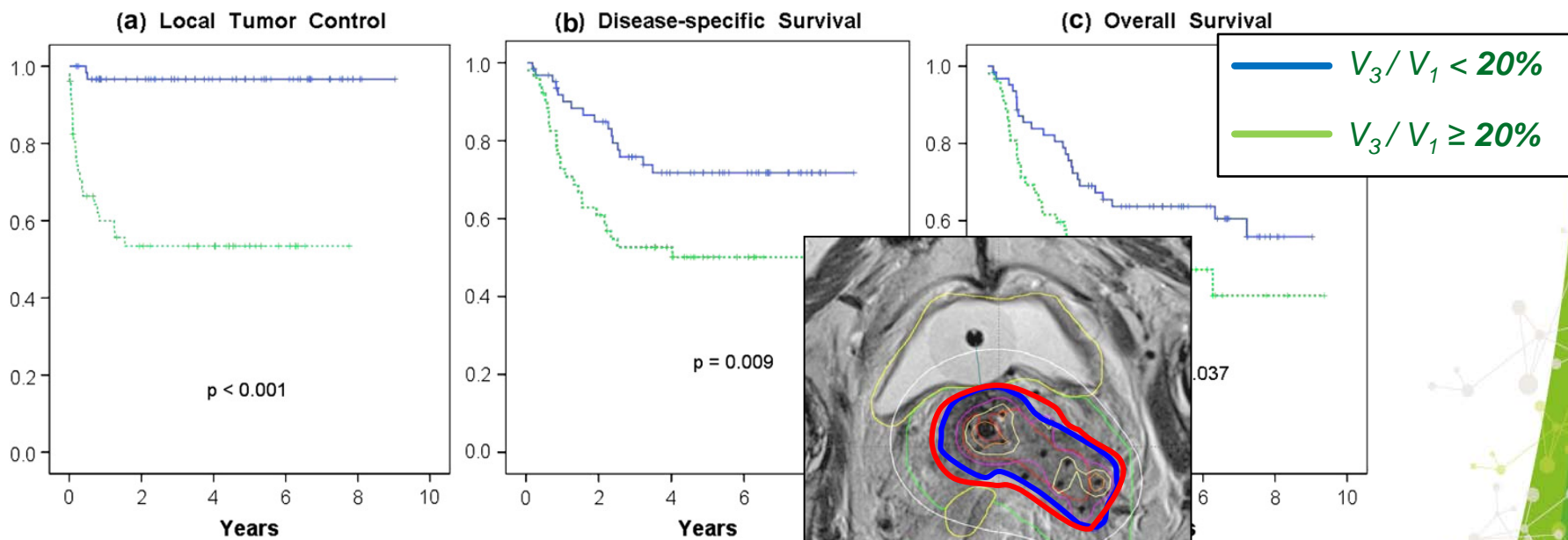
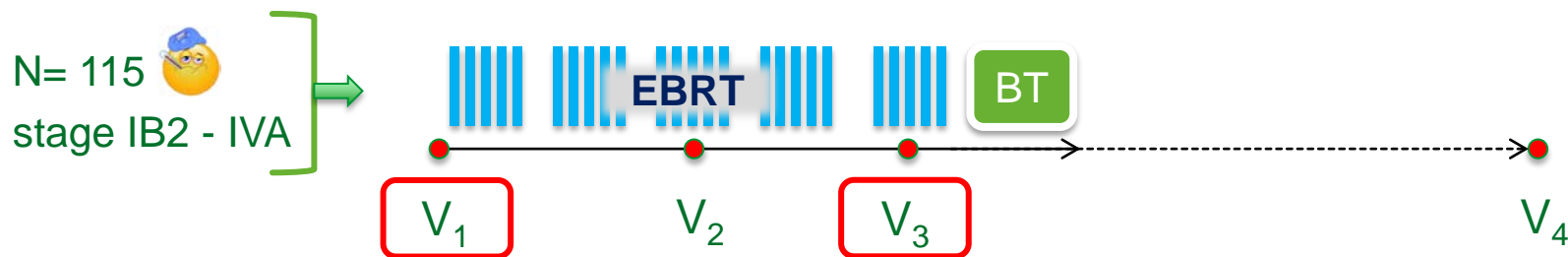
➔ Alive & well at 7 y

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

➔ LR at 1 y
Death at 2 y

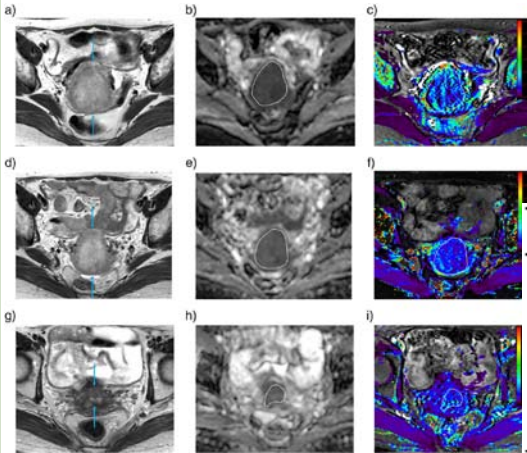
Size of the tumor at Brachytherapy

Volume change as outcome predictor



Size & functional Status of the tumor at Brachytherapy

Diffusion Weighted and Dynamic Contrast Enhanced MRI



Change in ADC & K_{trans}

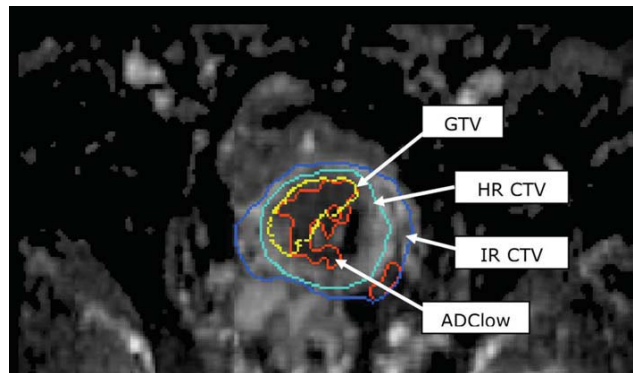


Early biomarkers, predicting response

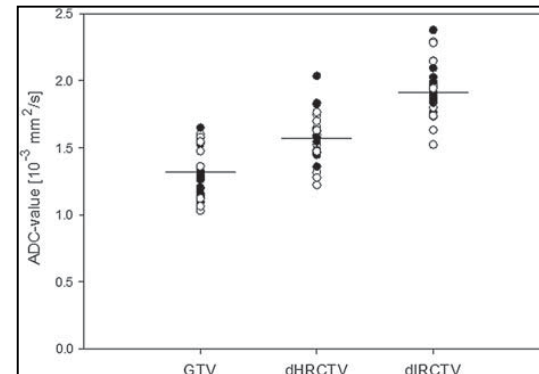
	PreTx	PostT1	PostT2	PostT3
Tumor K_{trans}	0.134 ± 0.034	0.214 ± 0.085	0.327 ± 0.123	0.265 ± 0.144
V_e	0.445 ± 0.261	0.834 ± 0.496	0.921 ± 0.318	2.125 ± 1.177
Gluteus muscle K_{trans}	0.041 ± 0.013	0.044 ± 0.016	0.044 ± 0.014	0.053 ± 0.024
V_e	0.422 ± 0.267	0.454 ± 0.312	0.424 ± 0.292	0.424 ± 0.297

	PreTx	PostT1	PostT2	PostT3
Tumor ADC ($\times 10^{-3}$ mm ² /sec)	0.89 ± 0.10 (0.84–0.94)	1.05 ± 0.10 (0.99–1.11)	1.36 ± 0.19 (1.25–1.46)	1.57 ± 0.24 (1.43–1.70)
Change in tumor ADC (%)		22.7 ± 15.0 (14.7–30.7)	53.4 ± 21.8 (41.8–65.0)	77.6 ± 33.7 (58.1–97.0)
Gluteus muscle ADC ($\times 10^{-3}$ mm ² /sec)	1.50 ± 0.08 (1.45–1.54)	1.55 ± 0.11 (1.49–1.61)	1.52 ± 0.11 (1.46–1.58)	1.50 ± 0.13 (1.42–1.57)

Park JJ, et al. Magn Res Imaging 2014



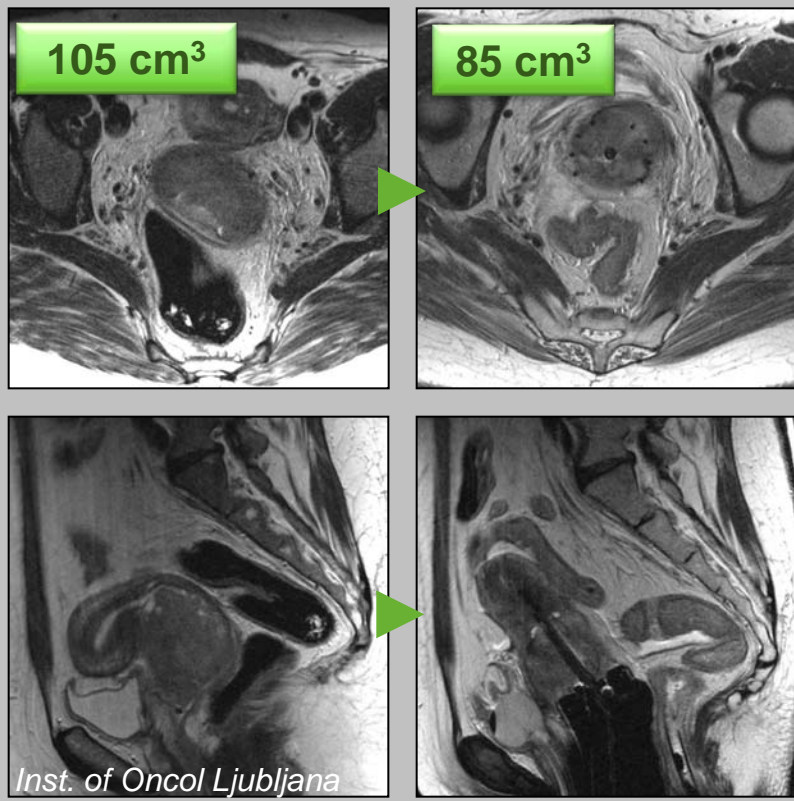
Haack S, et al. Acta Oncol 2010



Size of the tumor at Brachytherapy

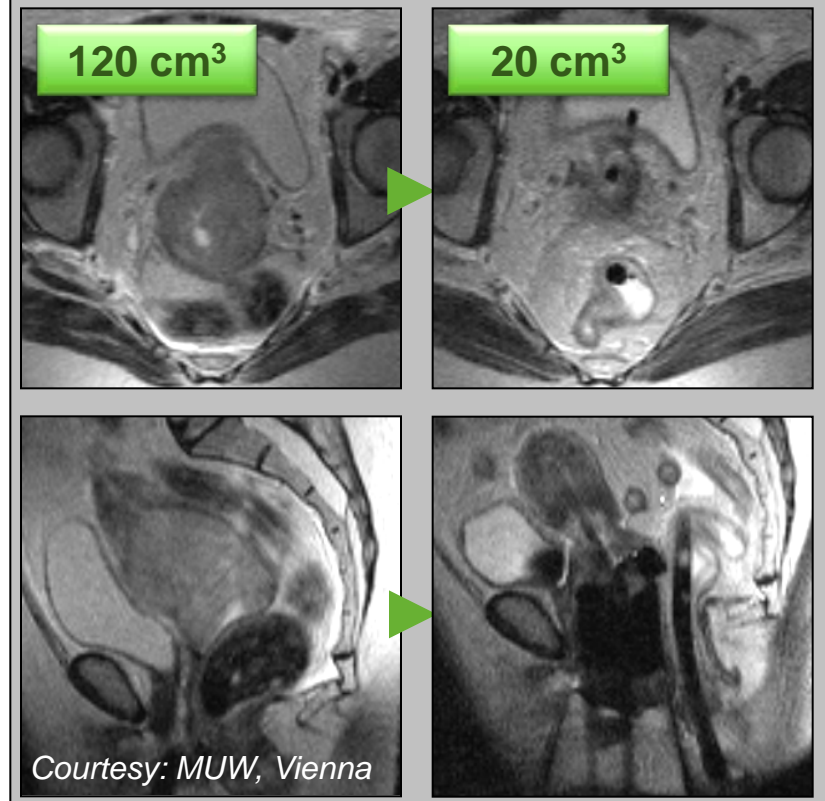
Qualitative vs. quantitative

Bad response



81 %

Good response



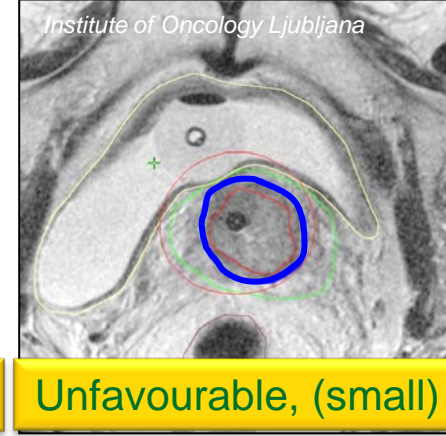
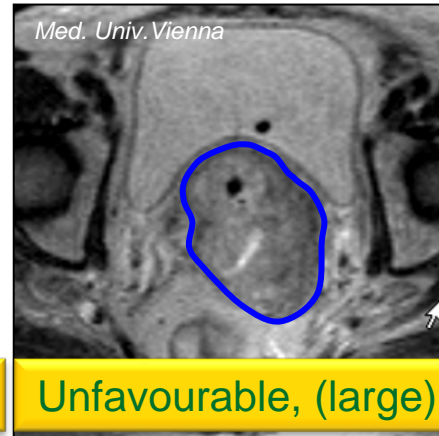
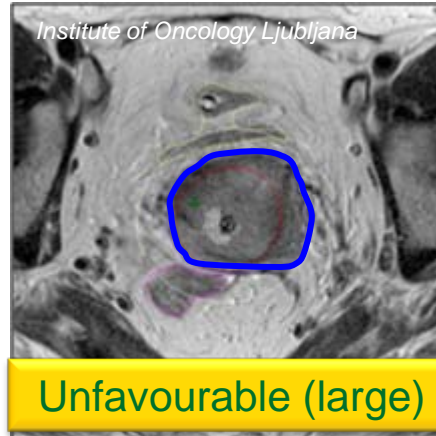
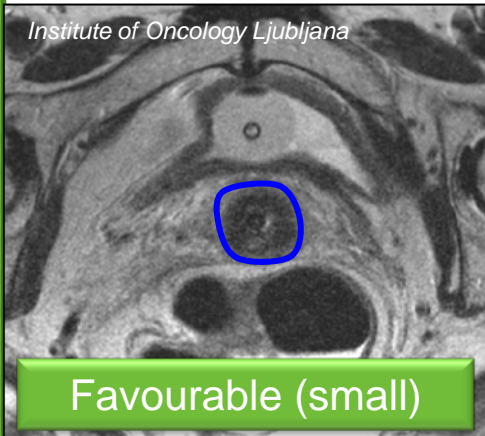
17 %

Set the **STAGE** before contouring

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

Topography of the tumour

Tumour shape and extent

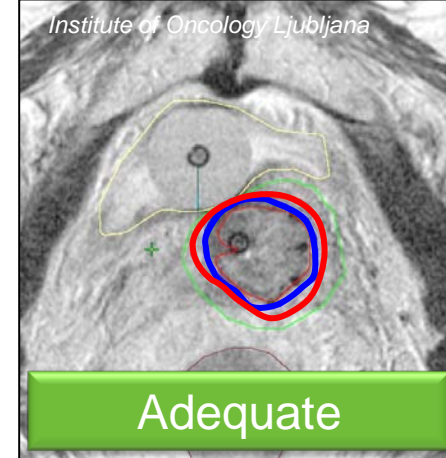
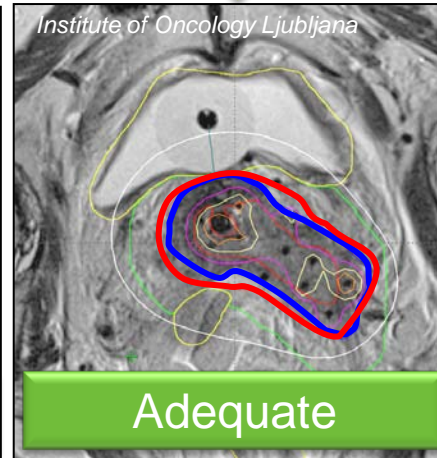
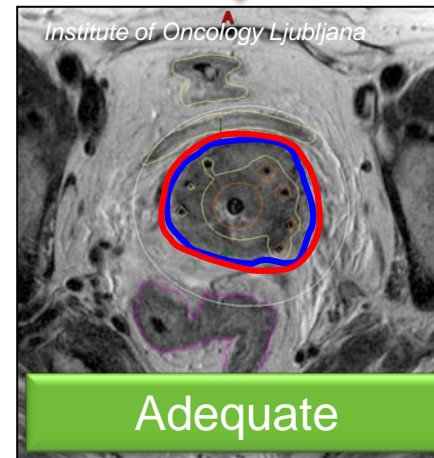
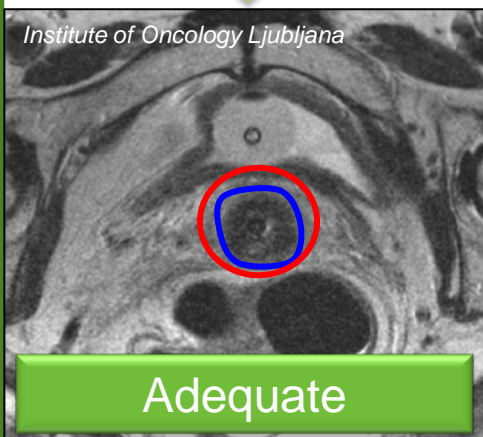
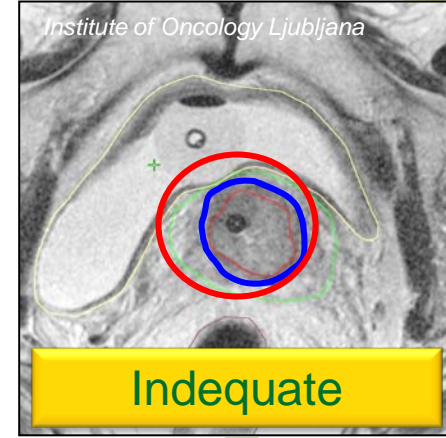
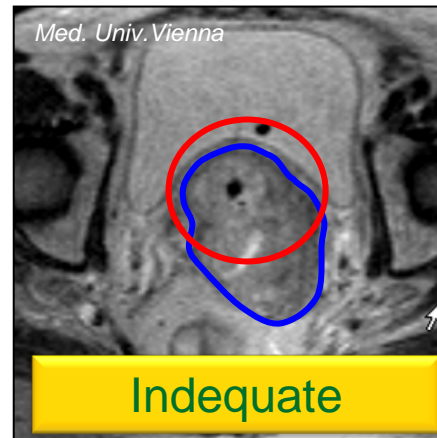
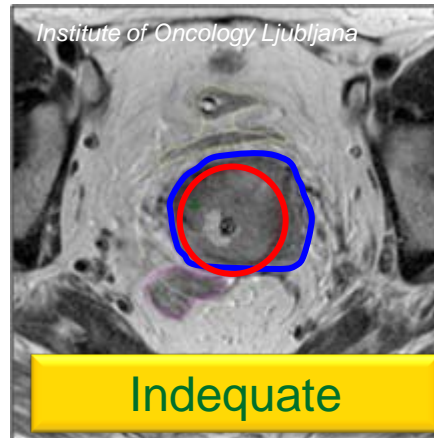
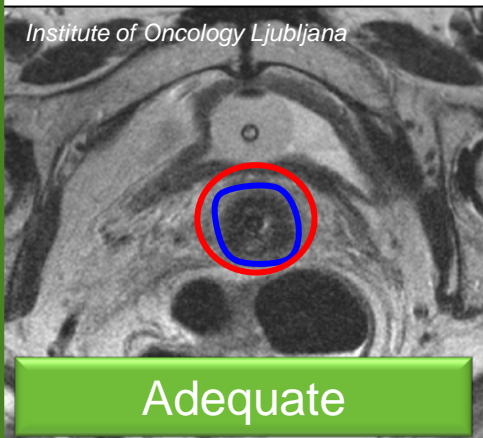


Set the **STAGE** before contouring

- 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



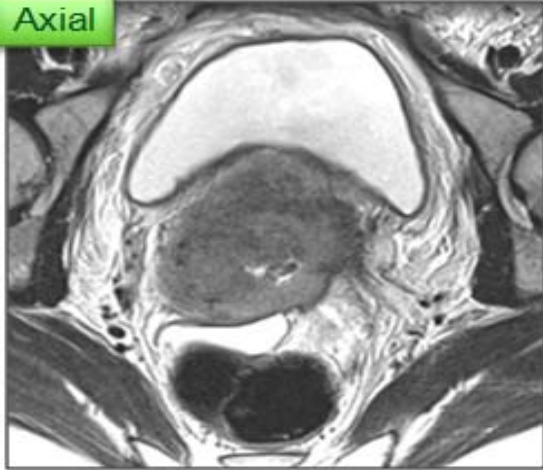
Set the **STAGE** before contouring

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Grey zones

Grey zones at BT correlate with *Initial spread*

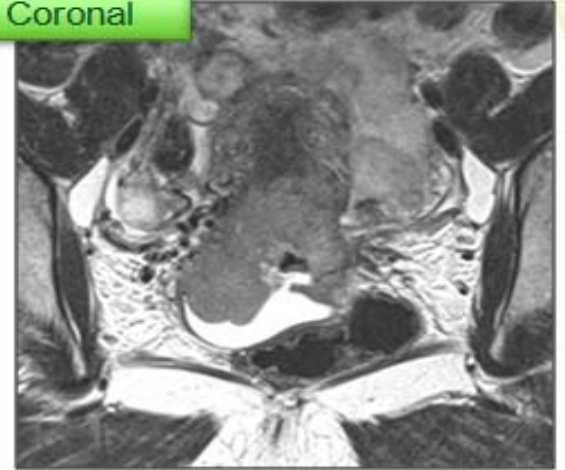
Axial



Sagittal



Coronal

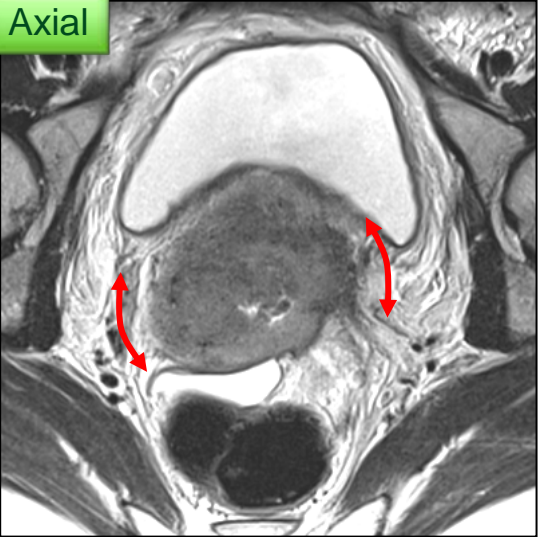


- A. < 20 %
- B. 20 – 60 %
- C. 60 – 80 %
- D. >80 %

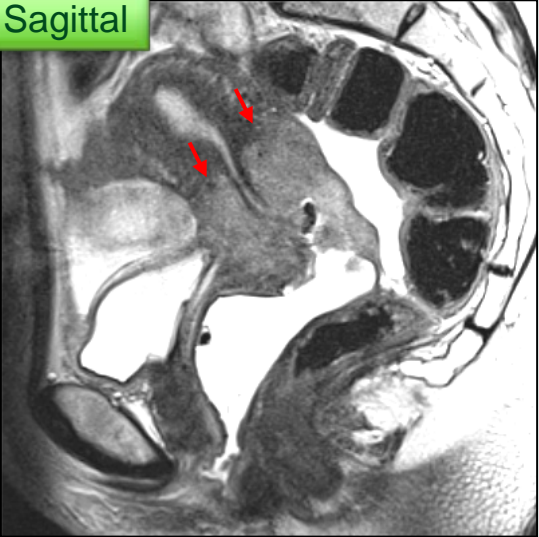
Grey zones

Grey zones at BT correlate with *Initial spread*

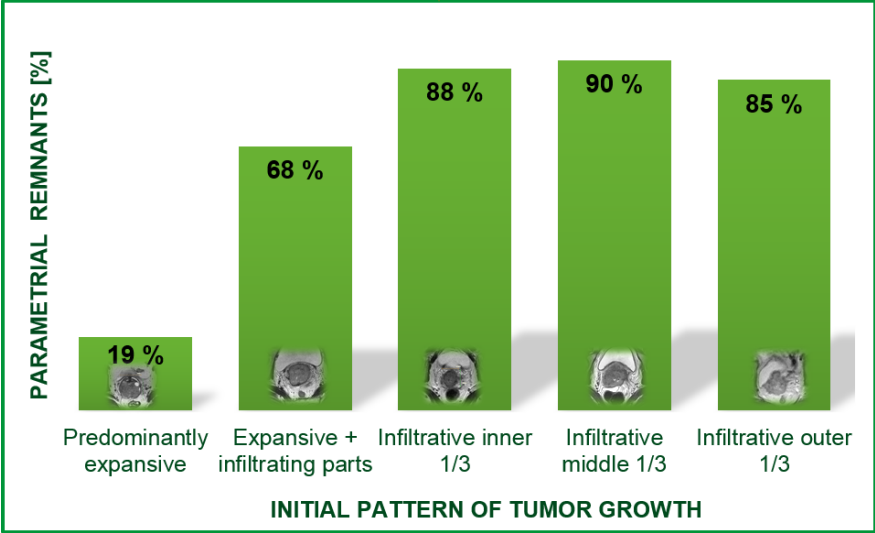
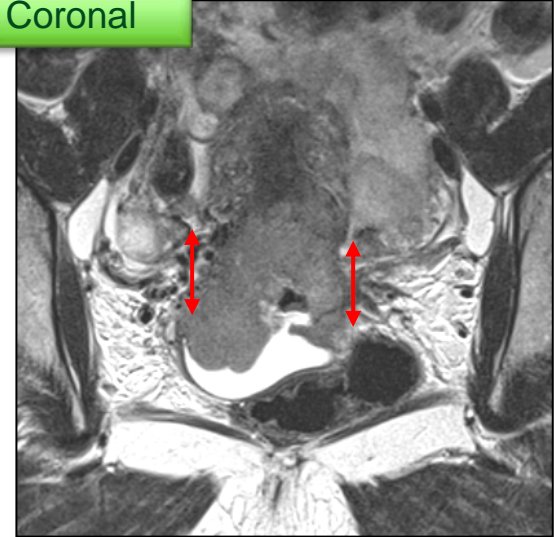
Axial



Sagittal



Coronal

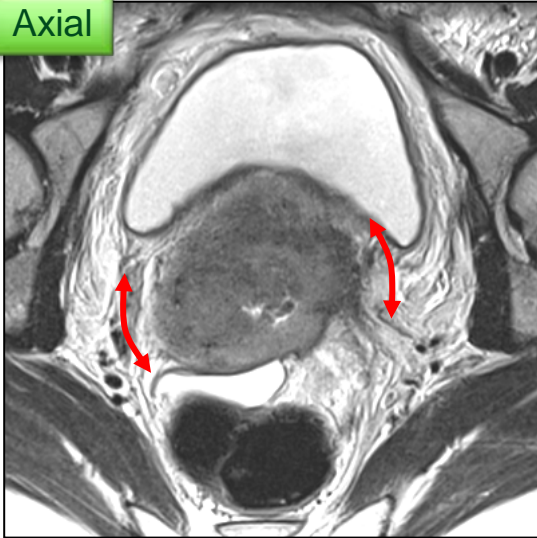


Schmid MP, et al. Acta Oncol 2013
Yoshida K, et al. IJROBP 2016

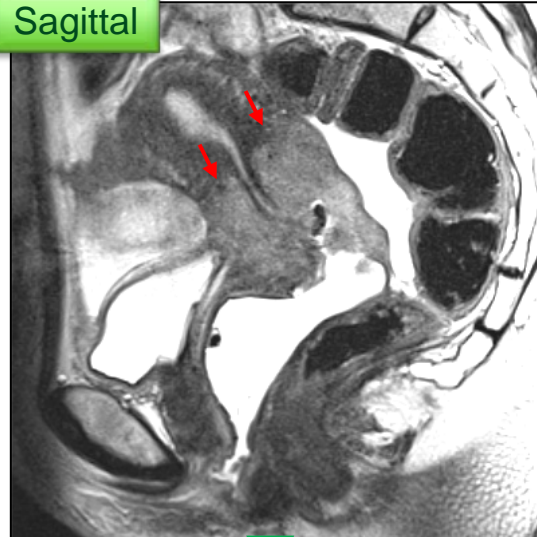
Grey zones

Grey zones at BT correlate with *Initial spread*

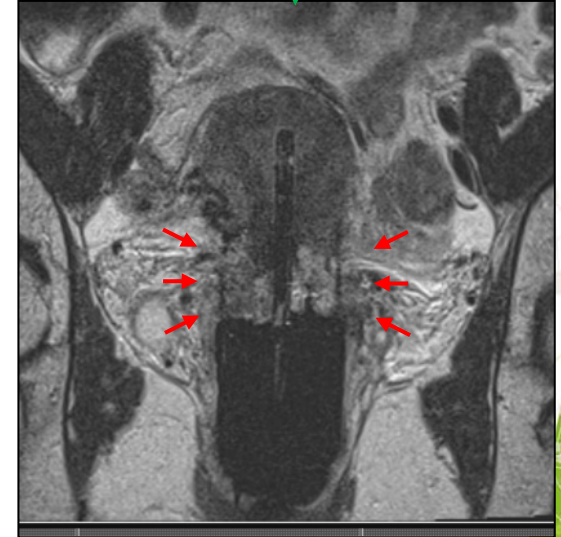
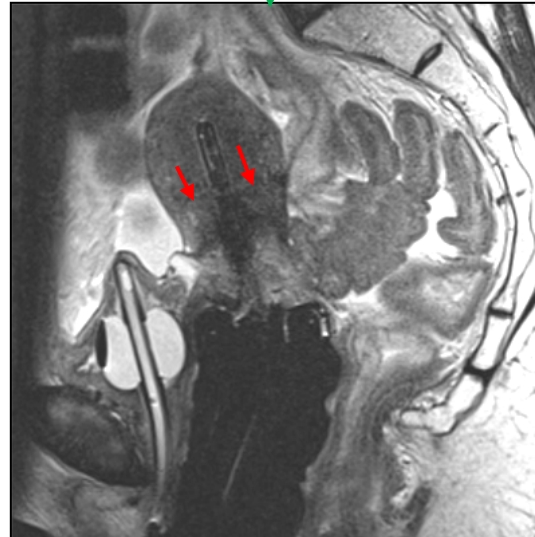
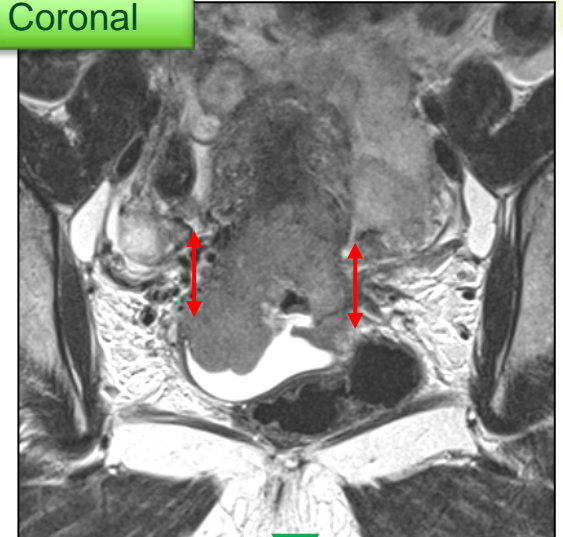
Axial



Sagittal

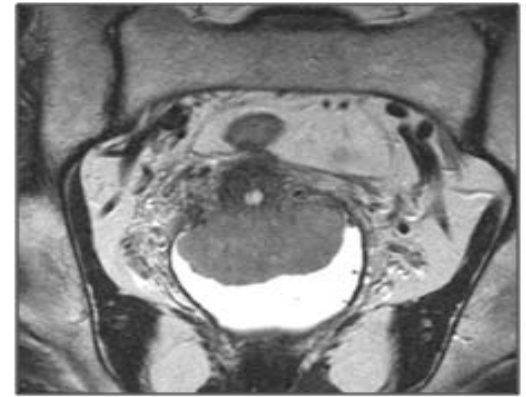
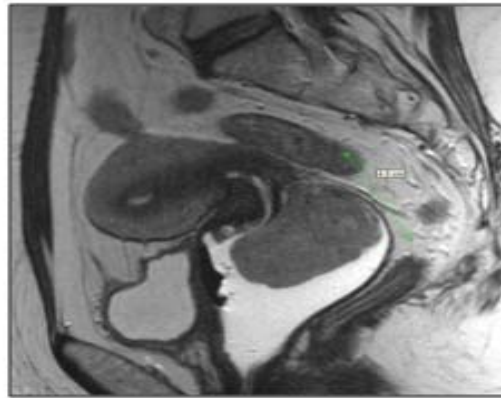
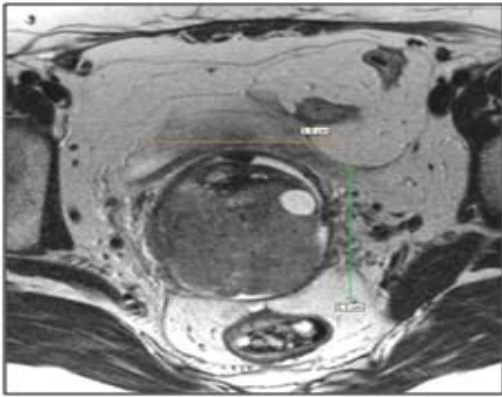


Coronal



Grey zones

Grey zones at BT correlate with *Initial spread*

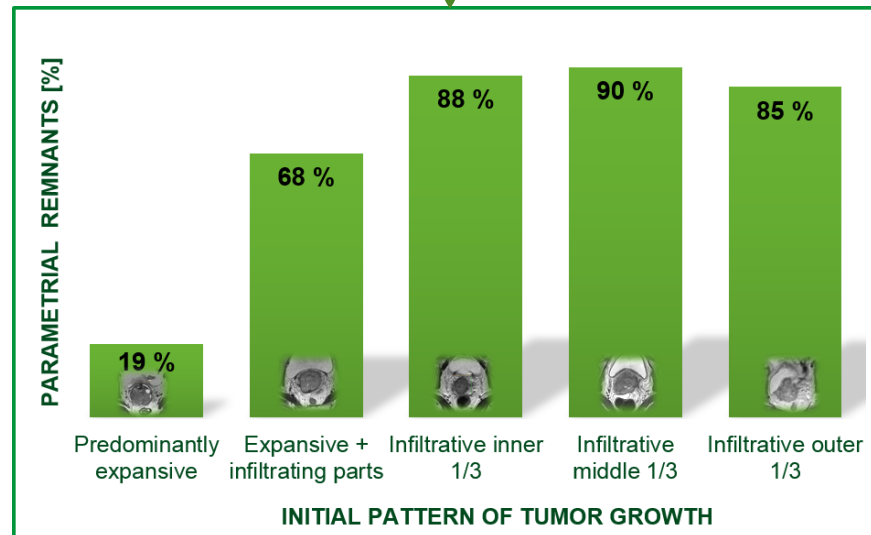
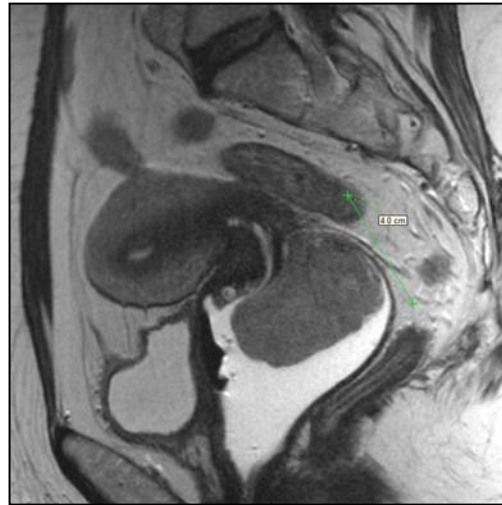
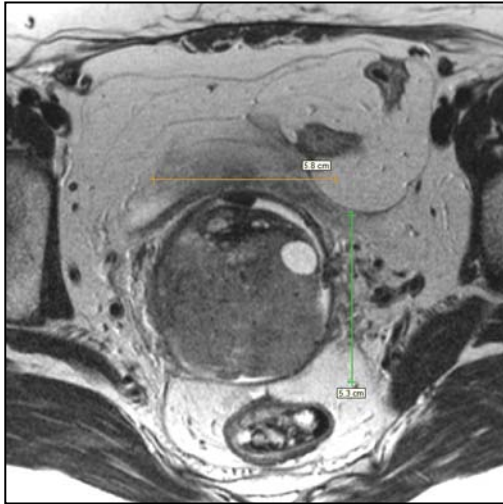


Estimate probability for residual pathological tissues in parametria after EBRT for this patient:

- A. $\approx 20\%$
- B. $20 - 60\%$
- C. $60 - 80\%$
- D. $>80\%$

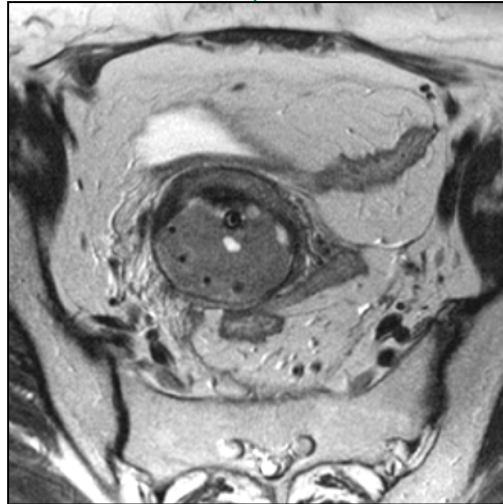
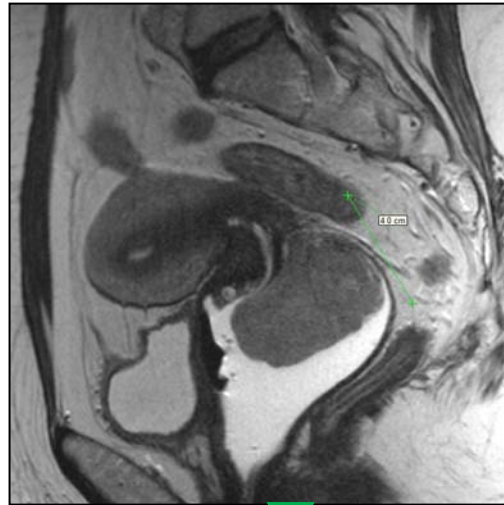
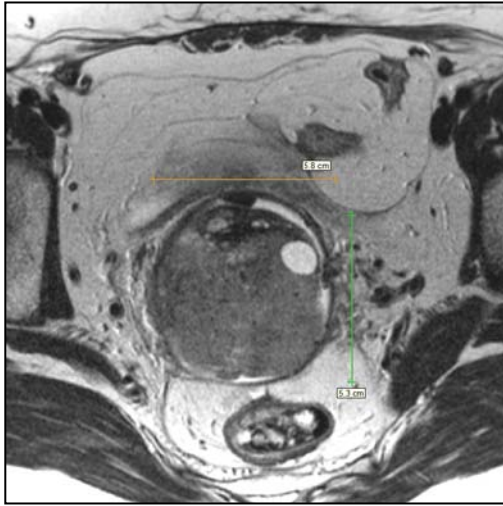
Grey zones

Grey zones at BT correlate with *Initial spread*



Grey zones

Grey zones at BT correlate with *Initial spread*



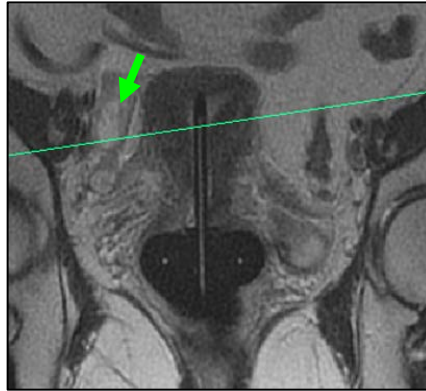
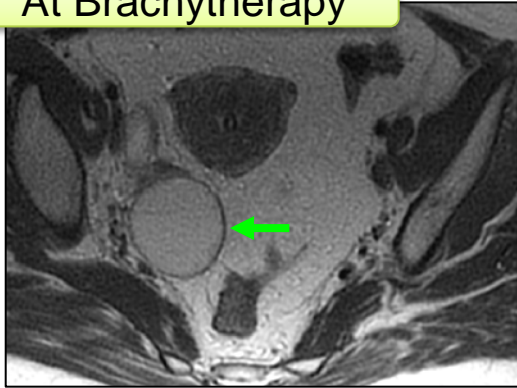
Set the **STAGE** before contouring

- 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

Rule out **FLOP**

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

1. **S**ize of the tumor:

- 8 cm³ (ellipsoid formula)
- Regression to Proportional V: PV = 20 % initial V

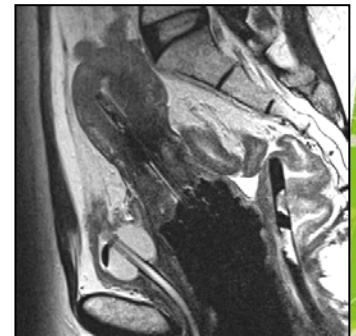
2. **T**opography: unfavourable due to right parametrial extension.

3. **A**dequate insertion geometry.

4. **G**rey zones correspond to initial infiltrative tumor: proximal third of right parametrium, dorsally.

5. “**E**xtra”:

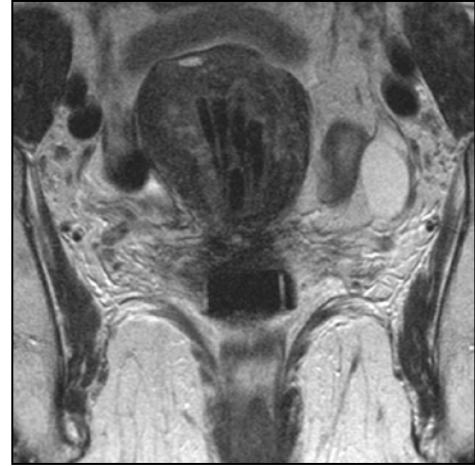
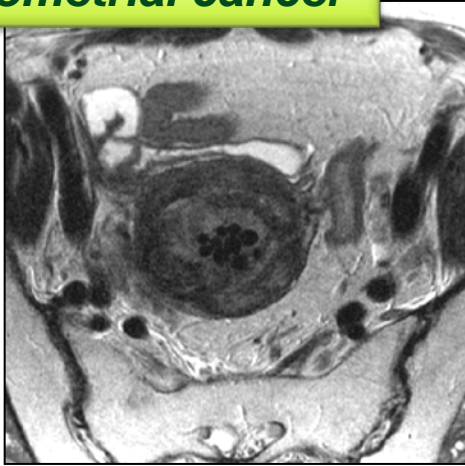
1. No necrosis.
2. *BT-related primary tumour findings reported.*
3. *Lymph nodes and other details not assessed.*



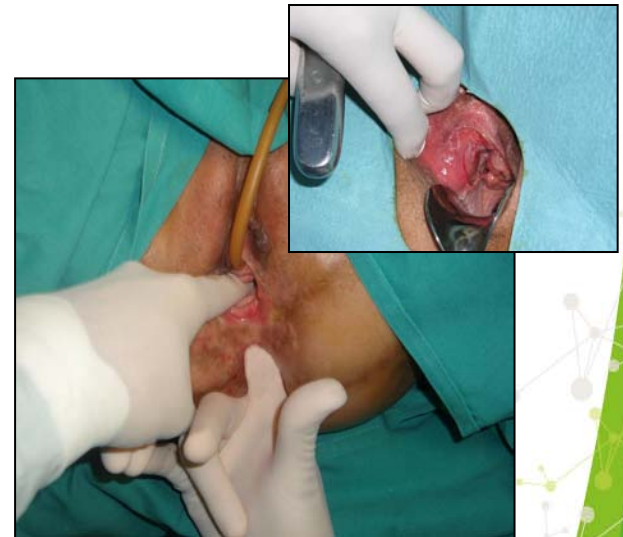
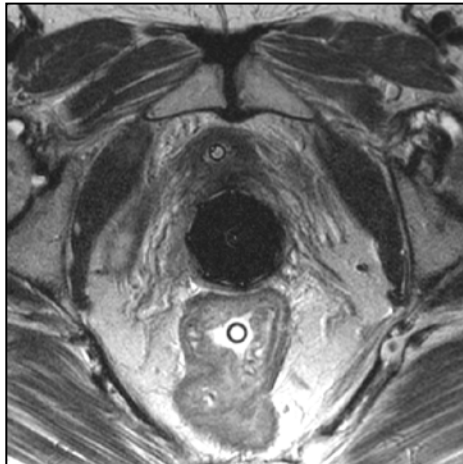
Set the **STAGE** for contouring

Other Gyn Tumor Sites!

Endometrial cancer



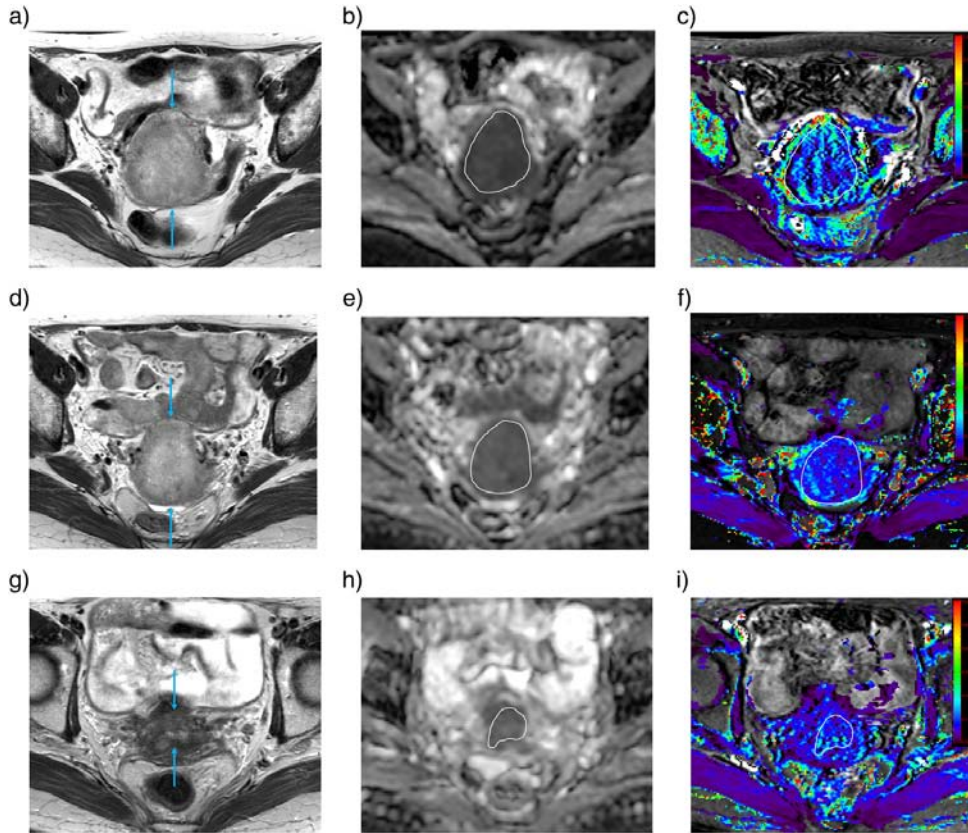
Vaginal cancer



Importance of clinical findings!

Functional MRI during therapy

Diffusion Weighted and Dynamic Contrast Enhanced MRI



Change in ADC & K_{trans}



Early biomarkers, predicting response

Tumor size and volume at each time point.

	PreTx	PostT1	PostT2	PostT3
Tumor size (cm)	5.6 ± 1.5	4.2 ± 1.4	2.3 ± 1.0	1.3 ± 0.7
Size response (%)		23.8 ± 15.8	57.7 ± 17.2	76.6 ± 9.5
Tumor volume (cm ³)	48.6 ± 37.8	28.3 ± 24.8	3.3 ± 2.6	1.4 ± 1.3
Volume response (%)		39.0 ± 24.0	89.4 ± 5.3	97.0 ± 3.2

	PreTx	PostT1	PostT2	PostT3
Tumor K_{trans}	0.134 ± 0.034	0.214 ± 0.085	0.327 ± 0.123	0.265 ± 0.144
V_e	0.445 ± 0.261	0.834 ± 0.496	0.921 ± 0.318	2.125 ± 1.177
Gluteus muscle K_{trans}	0.041 ± 0.013	0.044 ± 0.016	0.044 ± 0.014	0.053 ± 0.024
V_e	0.422 ± 0.267	0.454 ± 0.312	0.424 ± 0.292	0.424 ± 0.297

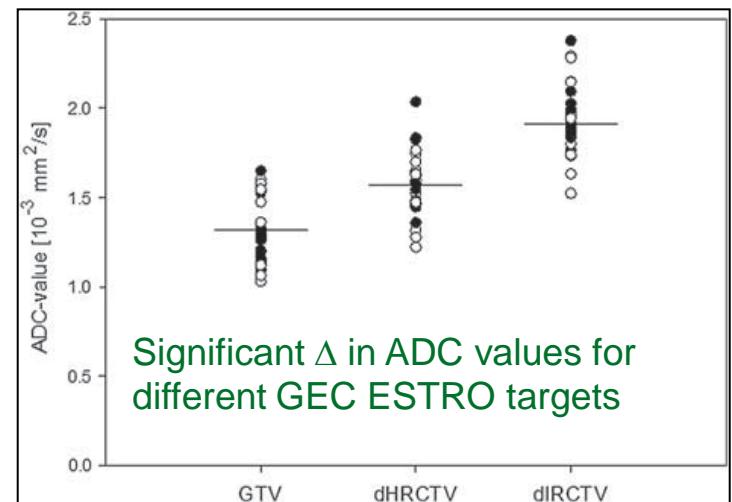
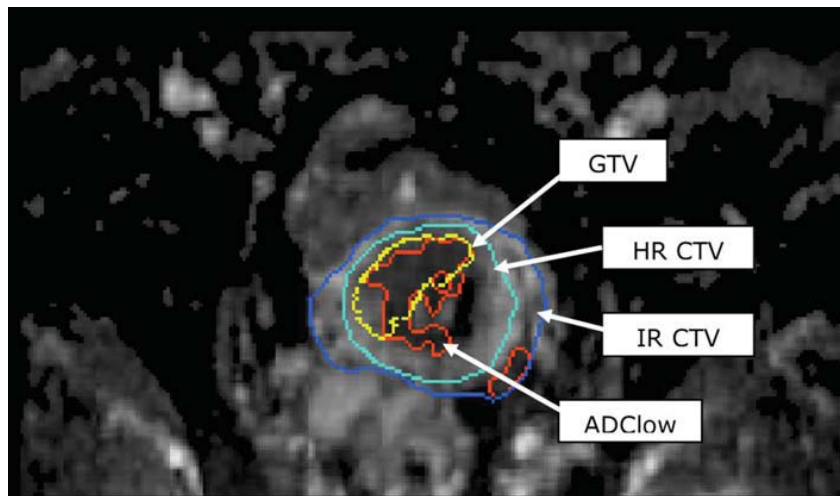
	PreTx	PostT1	PostT2	PostT3
Tumor ADC ($\times 10^{-3}$ mm ² /sec)	0.89 ± 0.10 (0.84–0.94)	1.05 ± 0.10 (0.99–1.11)	1.36 ± 0.19 (1.25–1.46)	1.57 ± 0.24 (1.43–1.70)
Change in tumor ADC (%)		22.7 ± 15.0 (14.7–30.7)	53.4 ± 21.8 (41.8–65.0)	77.6 ± 33.7 (58.1–97.0)
Gluteus muscle ADC ($\times 10^{-3}$ mm ² /sec)	1.50 ± 0.08 (1.45–1.54)	1.55 ± 0.11 (1.49–1.61)	1.52 ± 0.11 (1.46–1.58)	1.50 ± 0.13 (1.42–1.57)

Role of functional MRI at BT?

Apparent diffusion coefficients in GEC ESTRO target volumes for image guided adaptive brachytherapy of locally advanced cervical cancer

SØREN HAACK¹, ERIK MORRE PEDERSEN², SUNE N. JESPERSEN³,
JESPER F. KALLEHAUGE⁴, JACOB CHRISTIAN LINDEGAARD⁵ &
KARI TANDERUP⁵

Acta Oncologica, 2010; 49: 978–983



	ADC, BT1 Mean \pm sd [$\times 10^{-3} \text{ mm}^2/\text{s}$]	ADC, BT2 Mean \pm sd [$\times 10^{-3} \text{ mm}^2/\text{s}$]
GTV	1.33 \pm 0.20	1.36 \pm 0.19
Δ HR-CTV	1.56 \pm 0.18	1.60 \pm 0.18
Δ IR-CTV	1.83 \pm 0.17	1.86 \pm 0.16

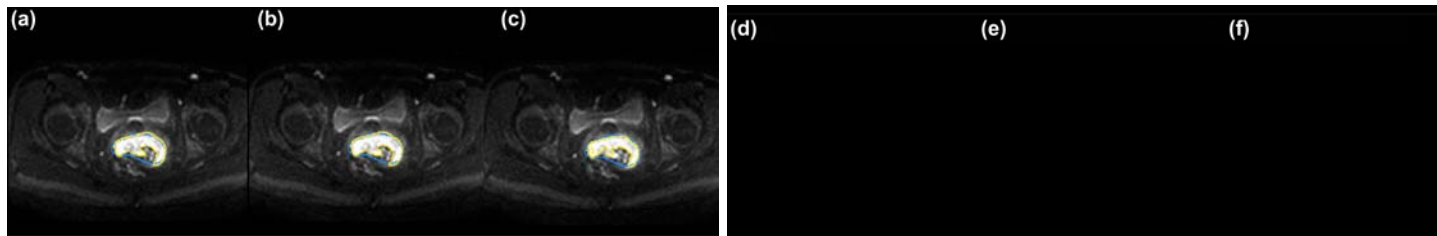
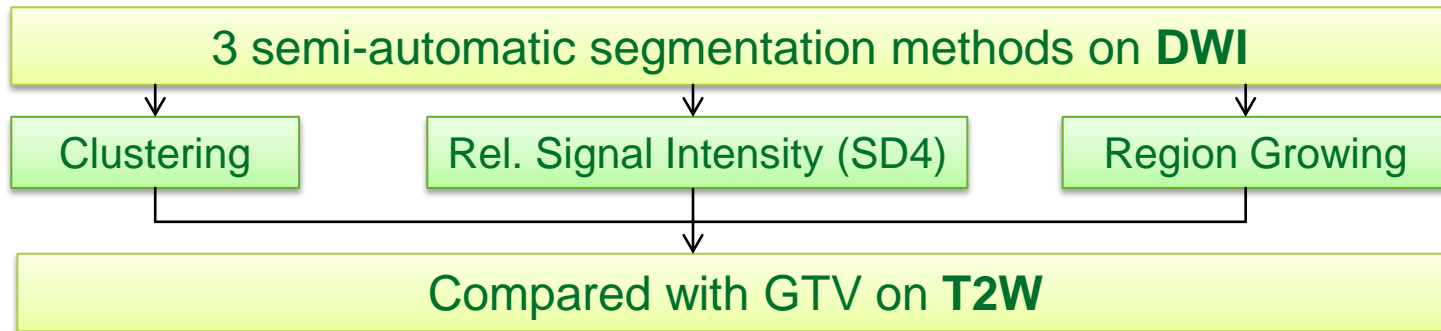
Further studies needed to evaluate role of
DWI in Cervix Cancer BT

Role of functional MRI at BT?

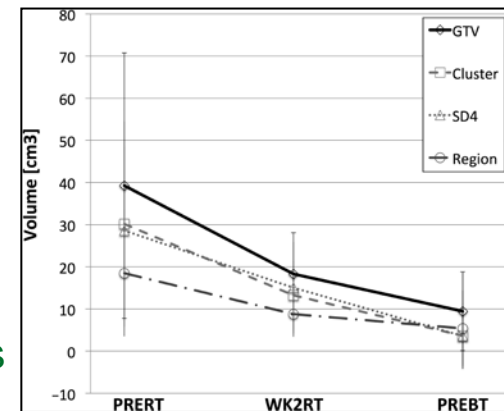
Diffusion-weighted magnetic resonance imaging during radiotherapy of locally advanced cervical cancer – treatment response assessment using different segmentation methods

SØREN HAACK^{1,2}, KARI TANDERUP², JESPER FOLSTED KALLEHAUGE³, SANDY MOHAMED ISMAIL MOHAMED^{2,4}, JACOB CHRISTIAN LINDEGAARD², ERIK MORRE PEDERSEN⁵ & SUNE NØRHØJ JESPERSEN^{6,7}

Acta Oncologica, 2015; 54: 1535–1542



- Region growing method performed poorest
- All 3 segmentation methods: $V_{DWI} < GTV_{T2W}$
- V_{DWI} is mainly located within GTV_{T2W}
- ADC value increased during treatment
- ADC values could inform the boosting strategies



Role of functional MRI at BT?

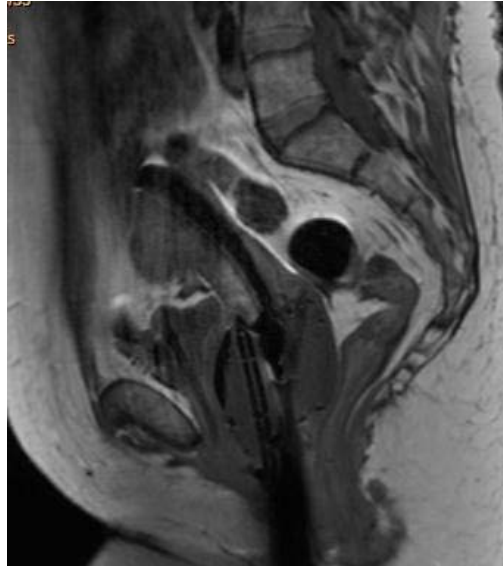
Applicator material, Field strength and Image sequence

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

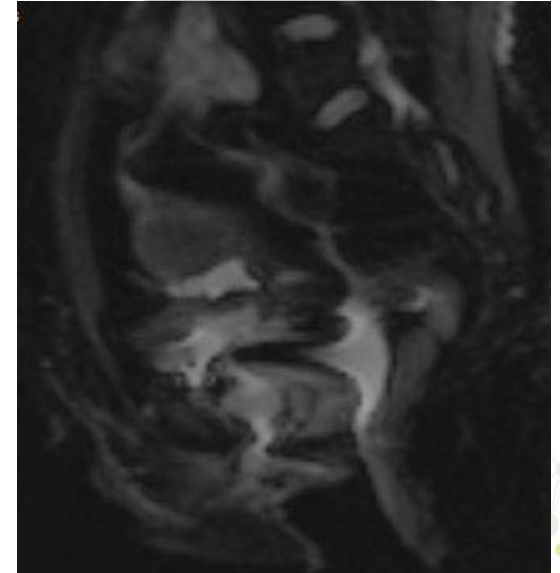
T2W, 3T



T1W, 3T



DWI, 3T



Courtesy: Kari Tanderup, AUH

Tanderup K, et al. *Seminars in Radiation Oncology* 2014;28:181-191

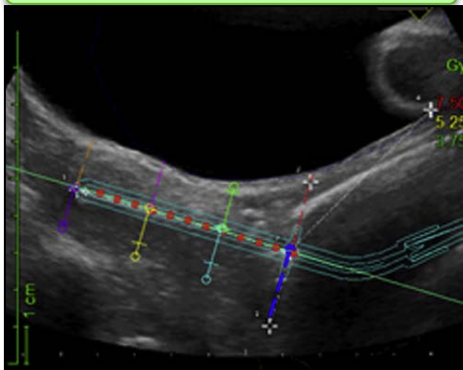
Kim Y, et al. *Int J Radiat Oncol Biol Phys* 2011; 947-955

Haack S, et al. *Radiother Oncol* 2009;187-193.

Choice of imaging modality for IGABT

ULTRASOUND

Transabdominal



Van Dyk et al. Brachytherapy 2015

Transrectal



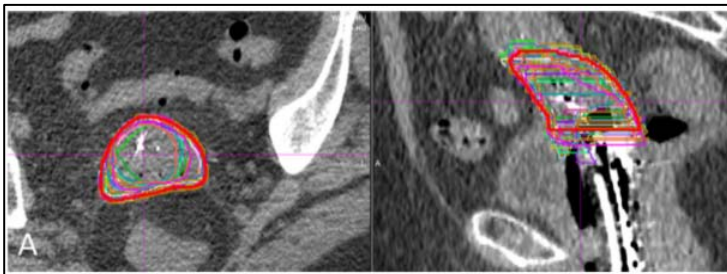
Schmid MP, et al. Radiother Oncol 2016

Rotating endocerv.?

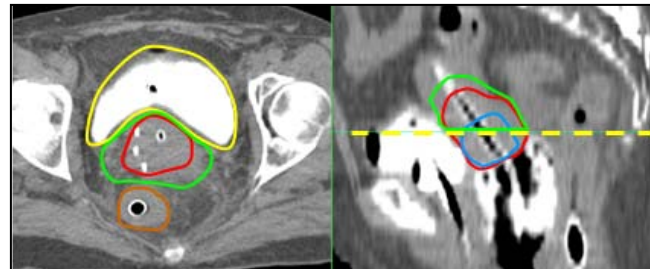


Petric P, Kirisits C. JCB 2016;Subm.

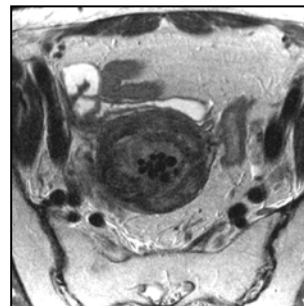
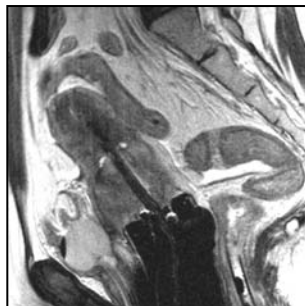
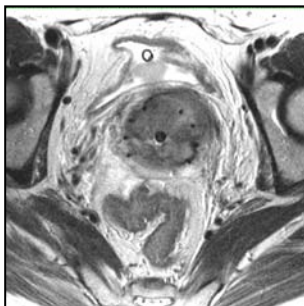
CT



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



MRI



Radiologic Pathology of Cervical Cancer at Brachytherapy



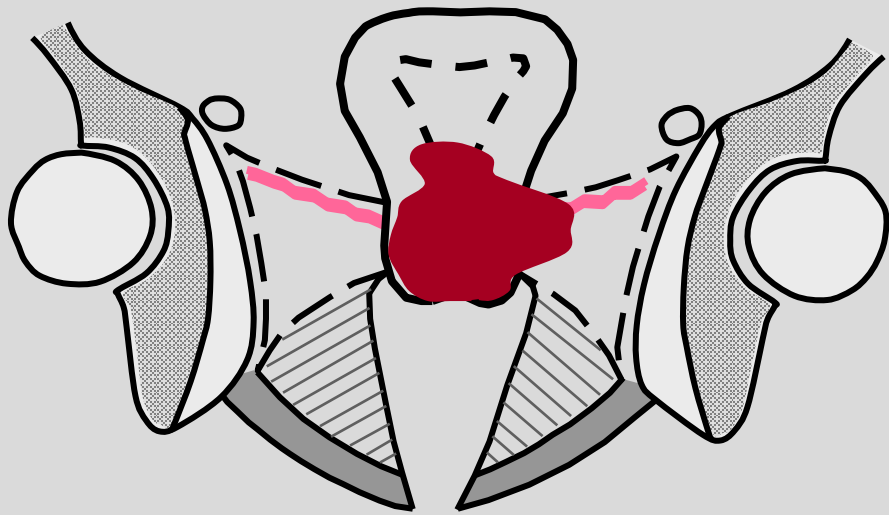
Primoz Petric, MD, Msc
Senior Consultant

Department of Radiation Oncology
NCCCR, HMC
Doha, Qatar

Combined intracavitary-interstitial technique for cervix cancer

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

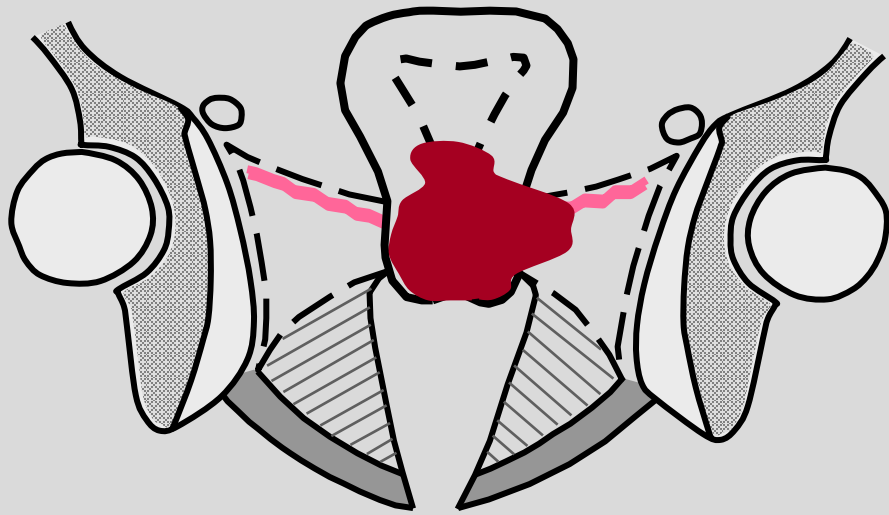
*Johannes C. Athanasios Dimopoulos, Head, Radiation Oncology
Metropolitan Hospital, Athens, Greece*



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

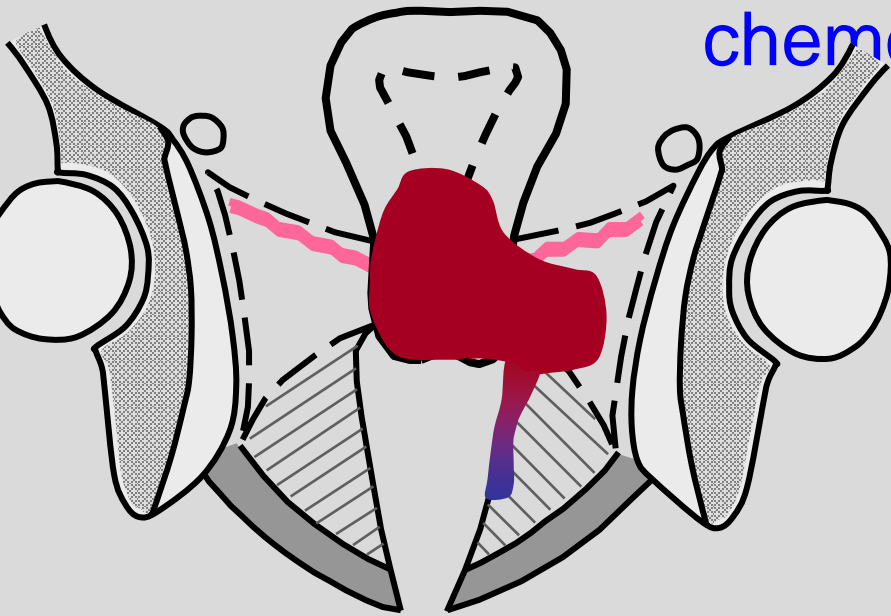
- A. Standard Intracavitary
- B. Intracavitary + interstitial
- C. EBRT boost
- D. EBRT boost + Intracavitary

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

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*

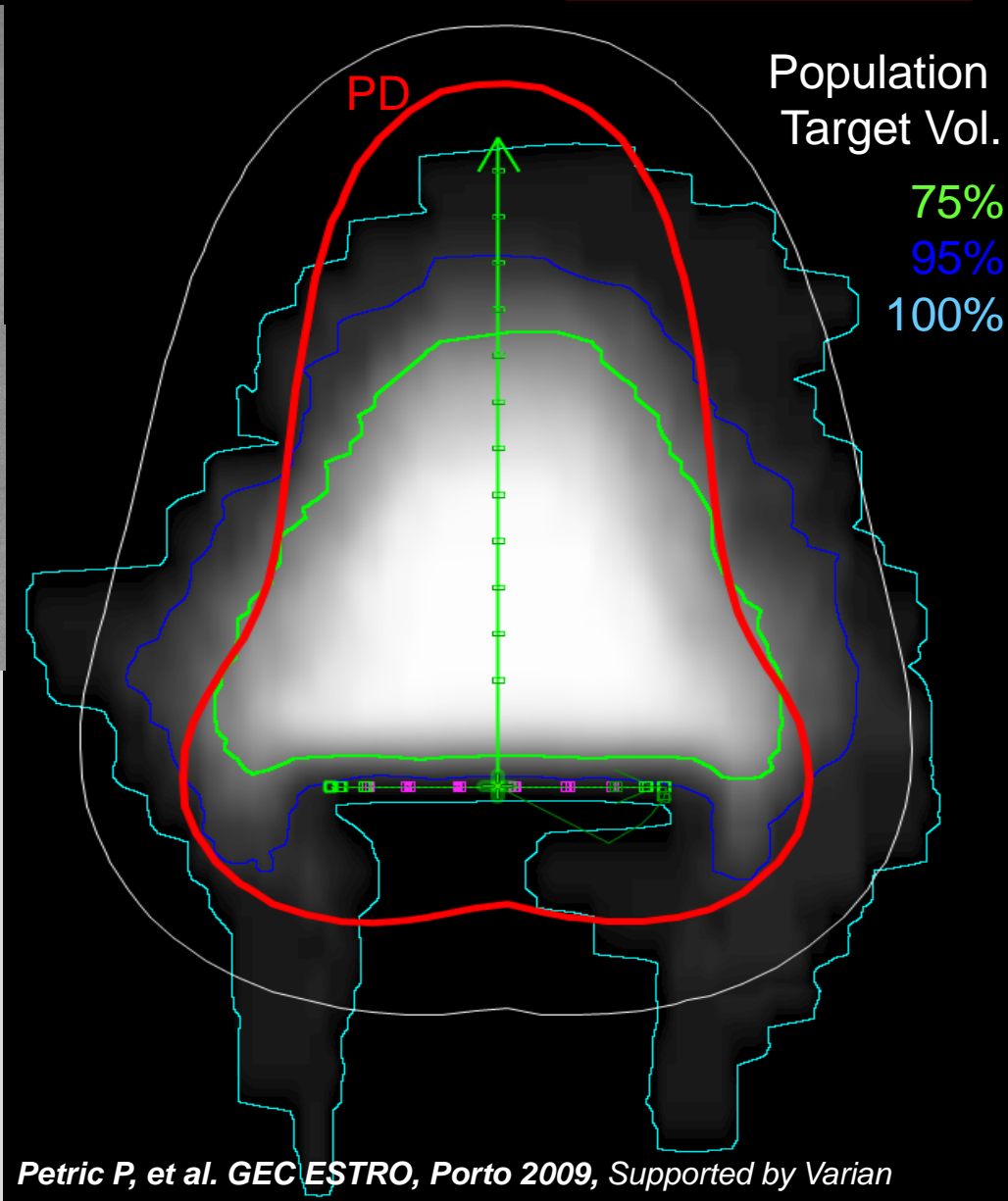
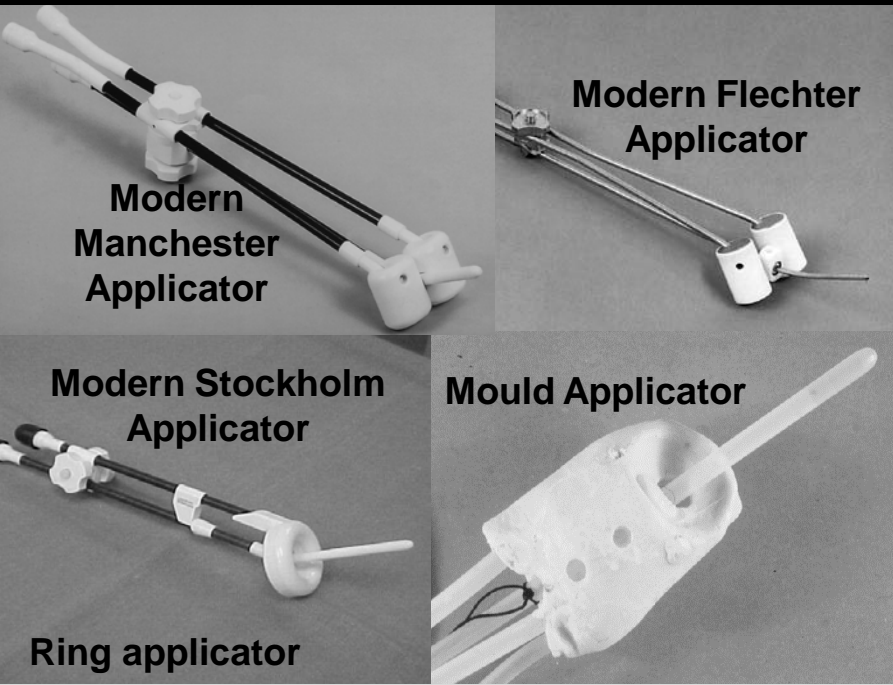
- *Optimizing Applicator placement by Image guidance*

- *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)*
- *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



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

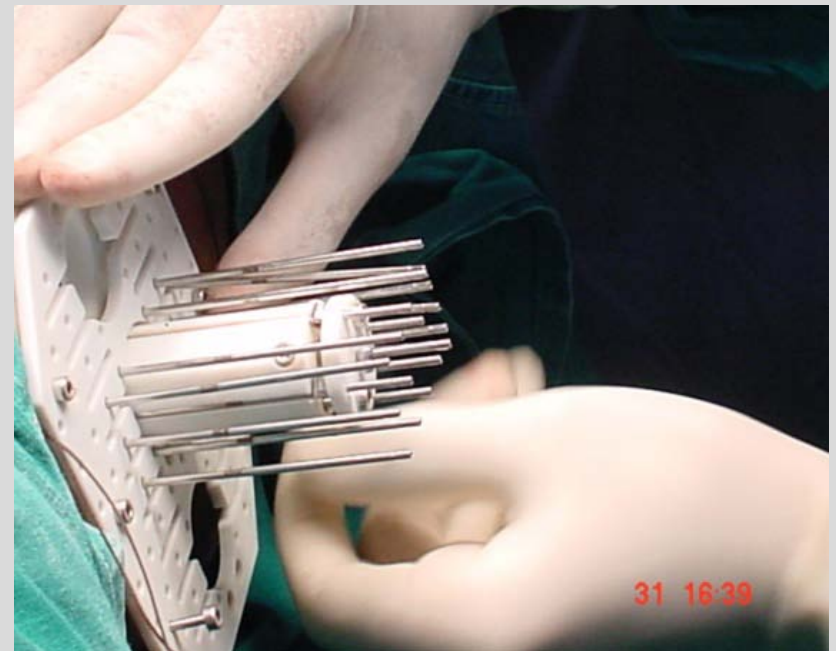
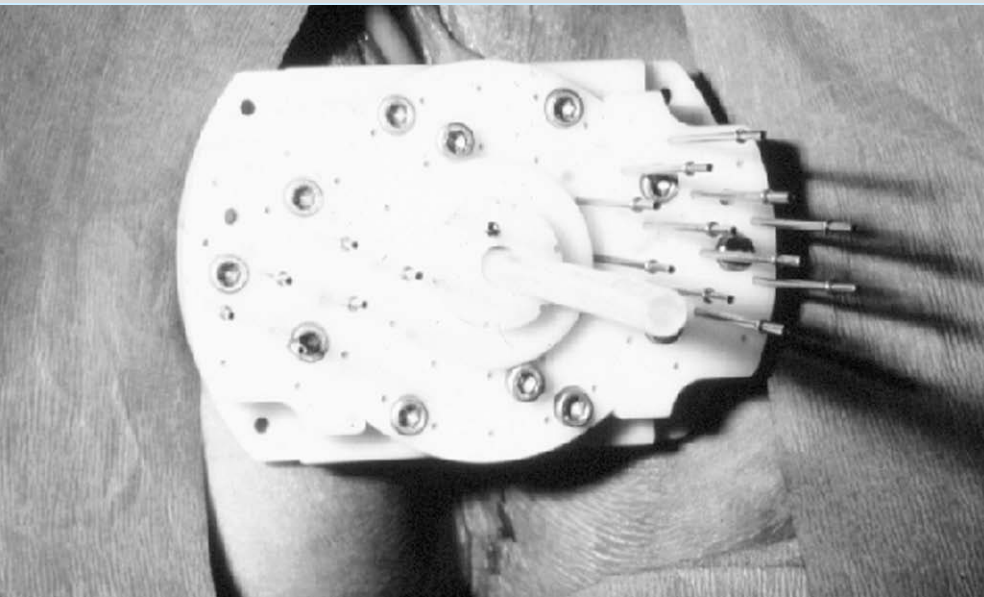


CLASSICAL INTERSTITIAL TECHNIQUES

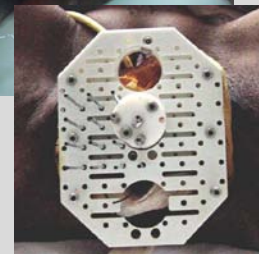
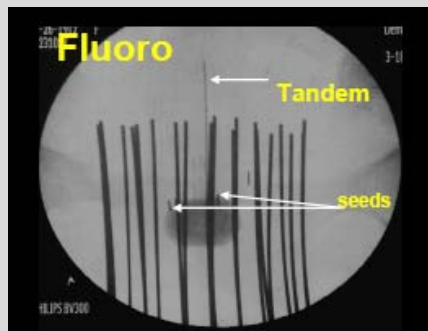
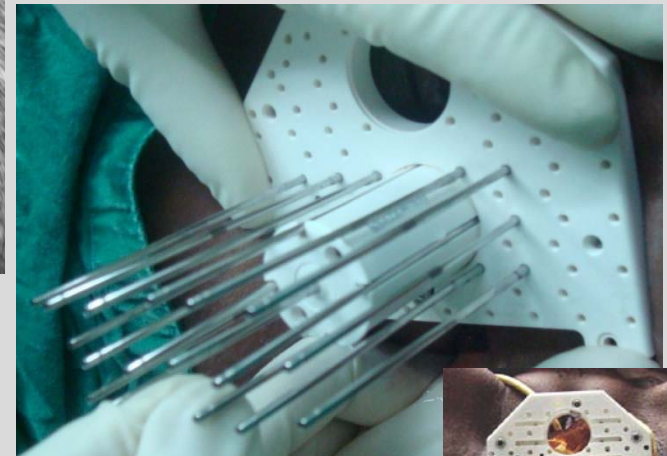
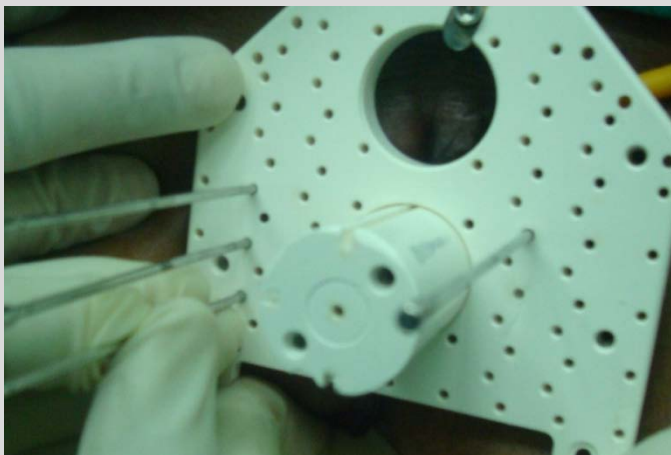
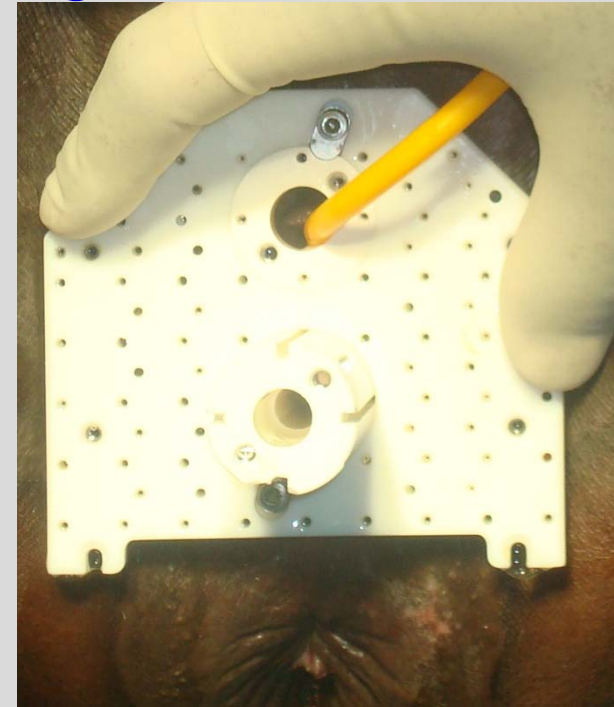
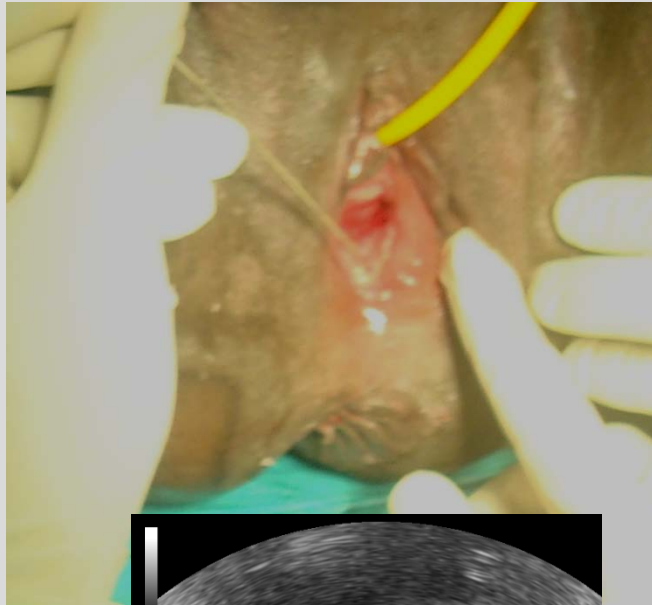
PERINEAL TEMPLATES

SYED

MUPIT

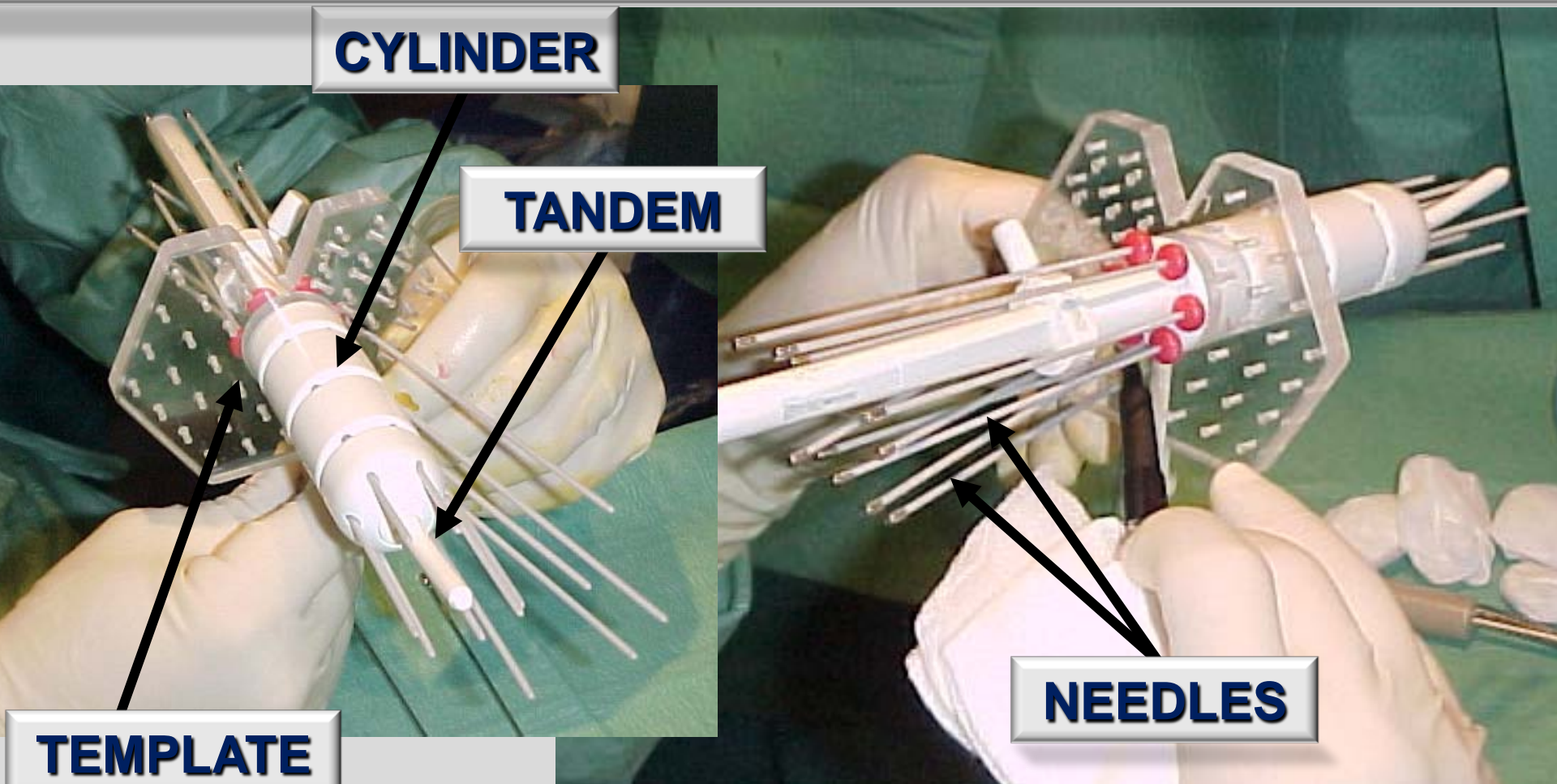


PRINICIPLES OF MUPIT PROCEDURE



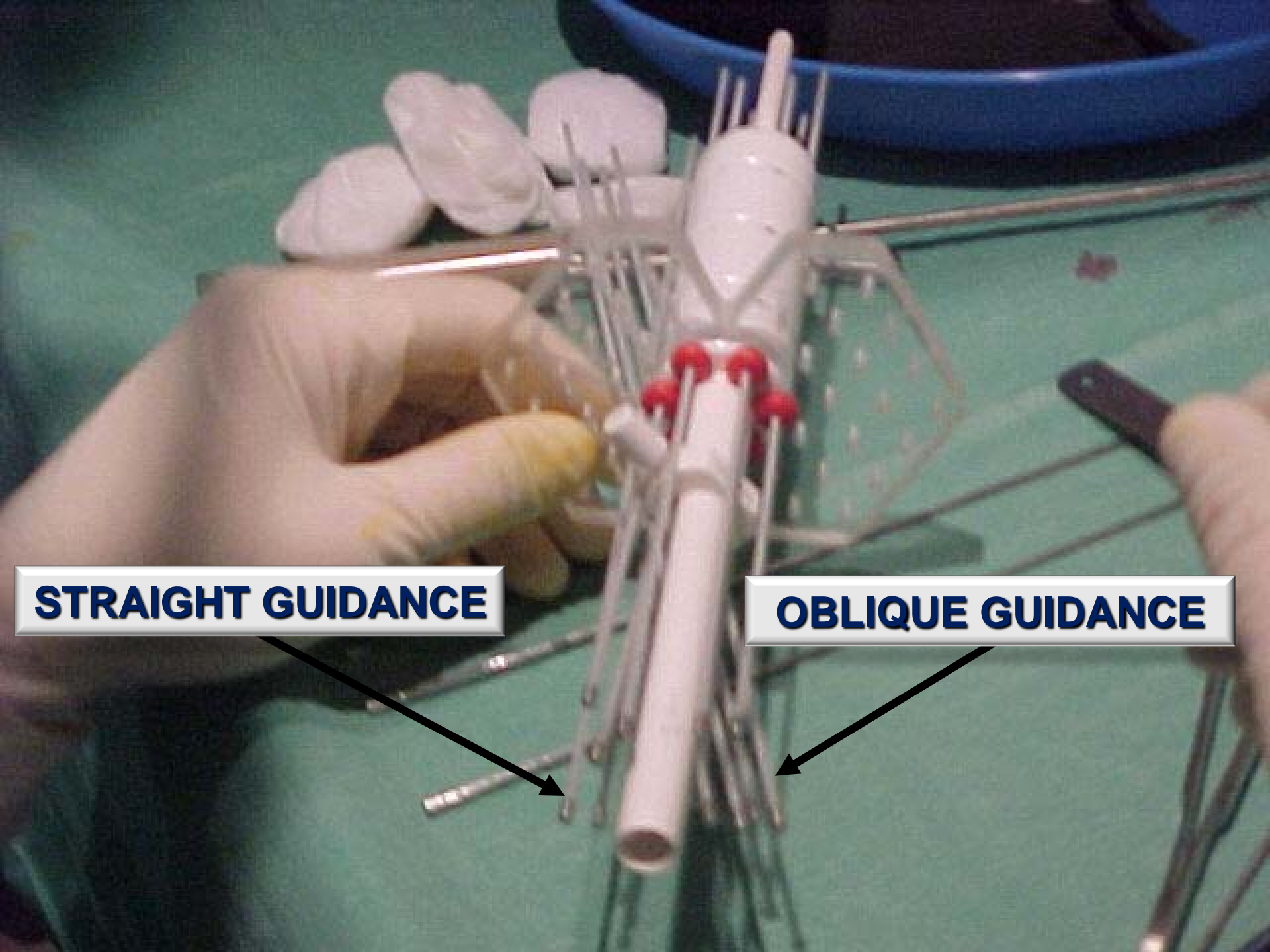
MODIFIED CLASSICAL INTERSTITIAL TECHNIQUES

MRI-compatible cylinder + tandem + template



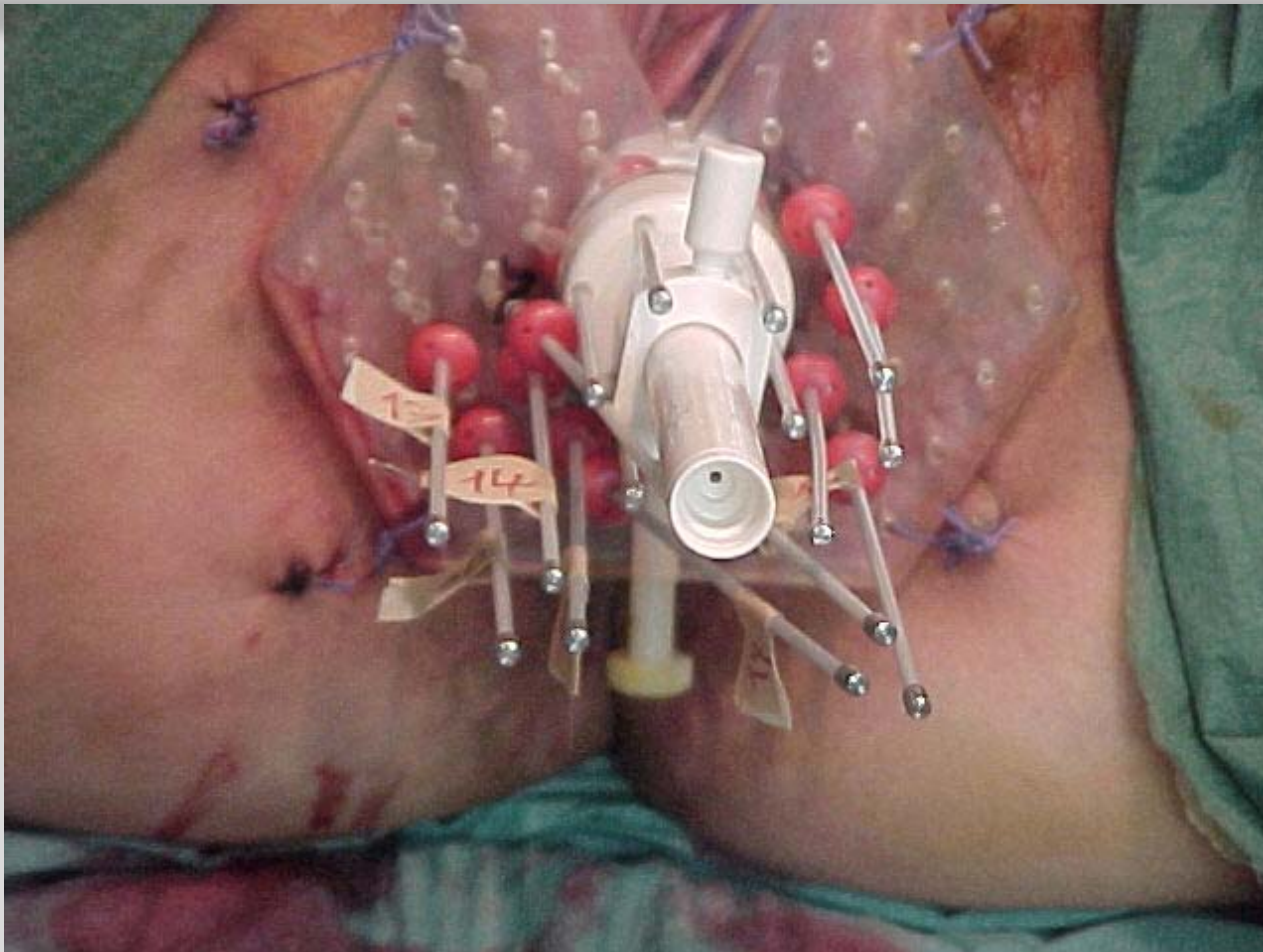
STRAIGHT GUIDANCE

OBLIQUE GUIDANCE



MODIFIED CLASSICAL INTERSTITIAL TECHNIQUES

COMPLETED IMPLANT



CLASSICAL & MODIFIED INTERSTITIAL TECHNIQUES

DRAWBACKS

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

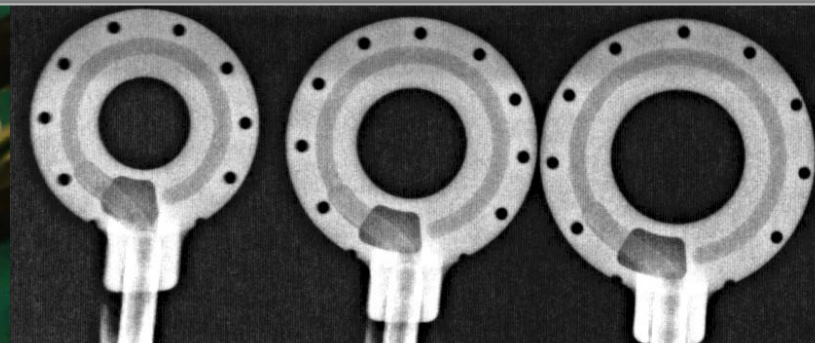
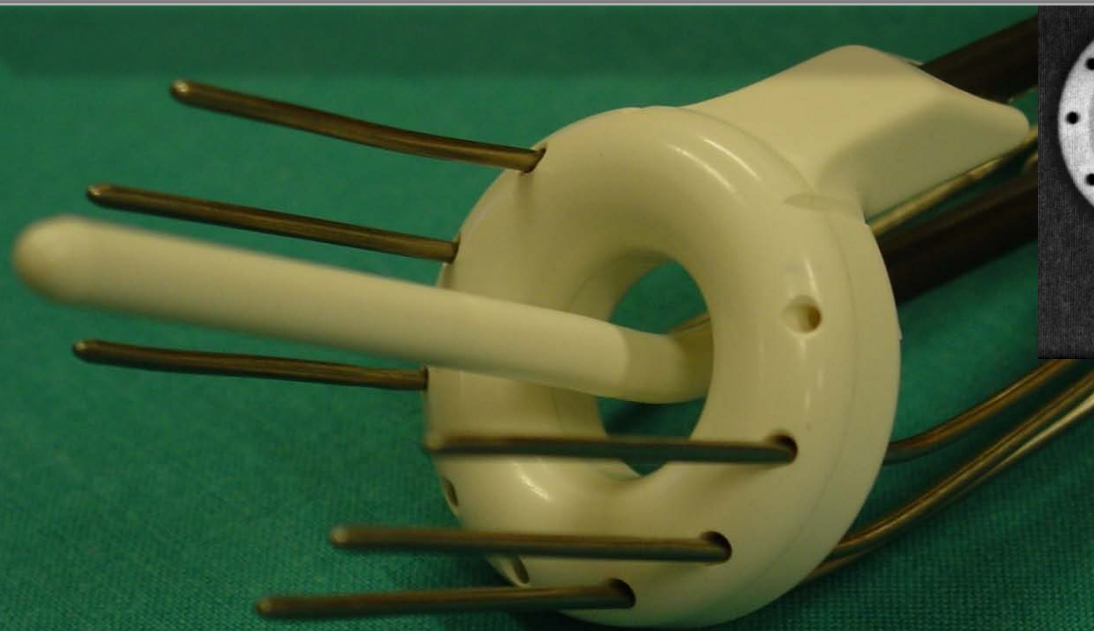
- ❑ *Perineal templates (Syed, MUPIT, others)*
 - *high number of needles used*
 - *long distances between template and target (loss of parallelism, inaccurate positioning)*
 - *impediment for general acceptance:
considerable risk of serious acute/late complications*

NOVEL INTERSTITIAL TECHNIQUES

TASKS

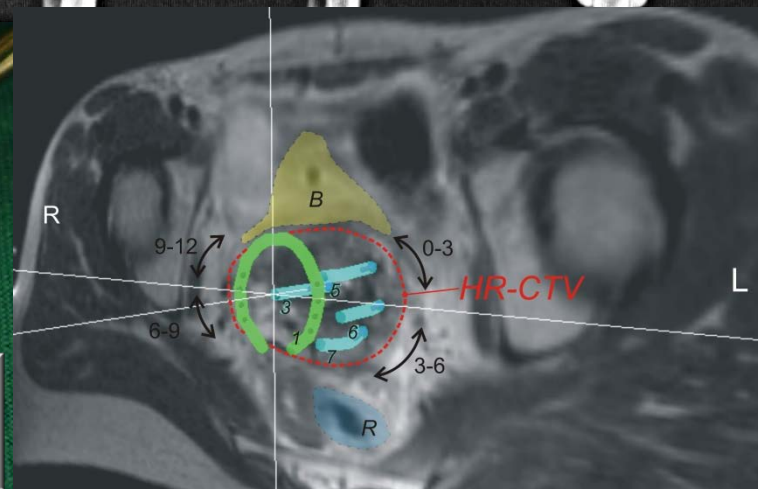
- *improve control over the placement of needles: short distance between template and the target (accurate and reproducible insertion)*
- *lesser number of needles to achieve an adequate target coverage*
- *to be combined with individualised MRI based treatment planning to tailor the dose distribution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

MODERN INTERSTITIAL TECHNIQUES



The Vienna Applicator

Intercavitory / 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)

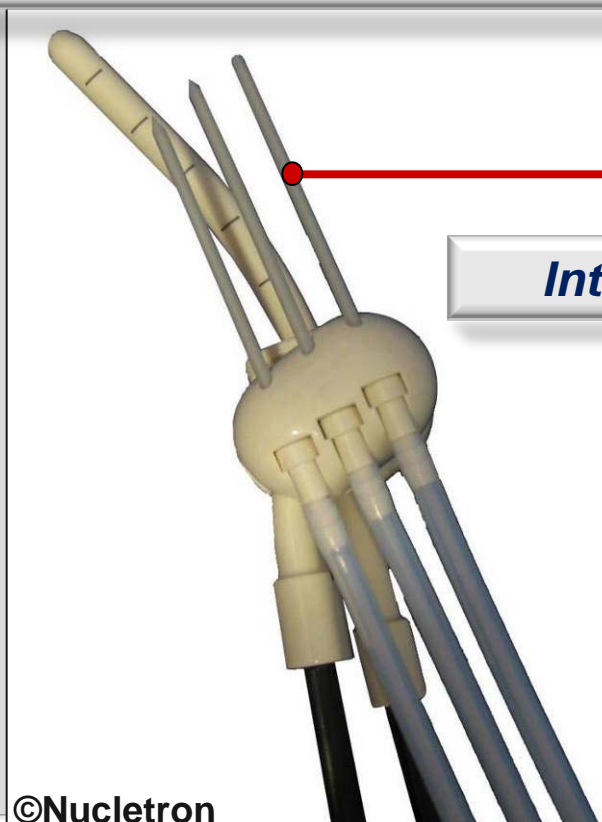
MODERN INTERSTITIAL TECHNIQUES

Applicators – special situations

Cervical cancer with moderate lateral expansion: modified principles of treatment

The Utrecht Applicator

*Intracavitary / interstitial
Fletcher Applicator*



Interstitial tubes/needles

©Nucletron

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

INTRACAVITARY + INTERSTITIAL TECHNIQUES

VIDEO PRESENTATIONS DURING LUNCH BREAK

- ***DAY 1 : VIENNA APPLICATION AT TATA***
- ***DAY 2 : VIENNA APPLICATION AT AKH VIENNA***
- ***DAY 3 : INTRACAVITARY + INTERSTITIAL UNDER LOCAL ANESTHESIA***

INTERSTITIAL TECHNIQUES

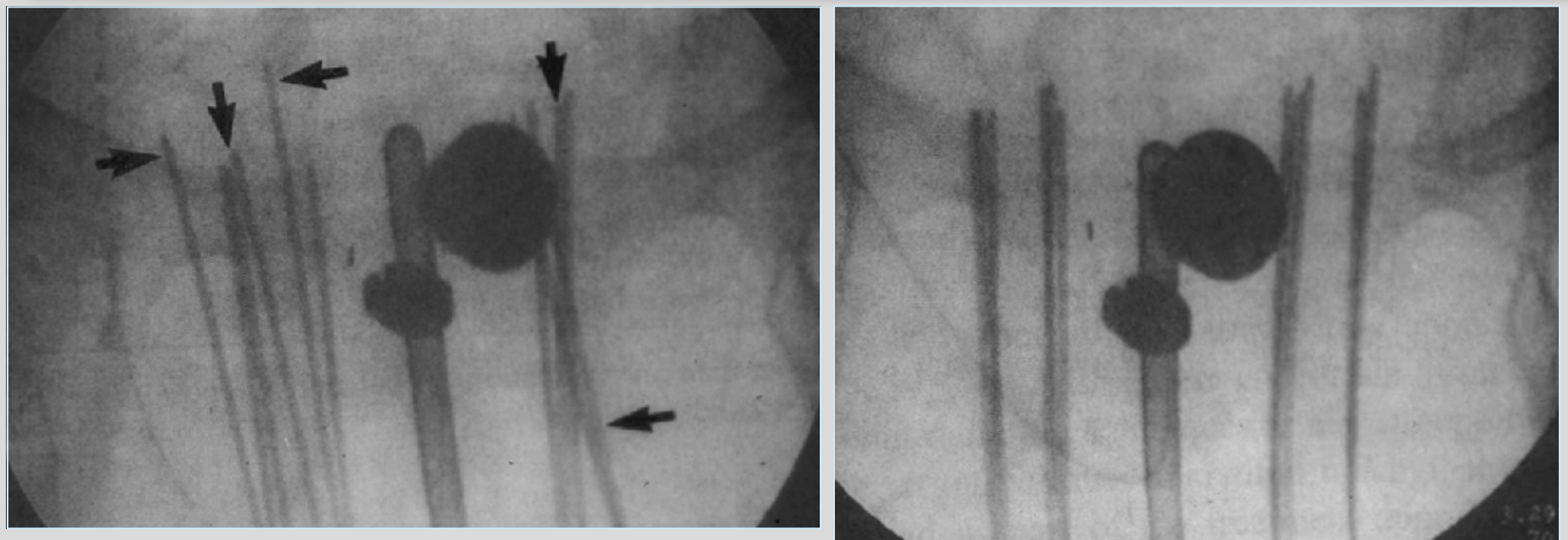
ATTEMPT TO IMPROVE PLACEMENT

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

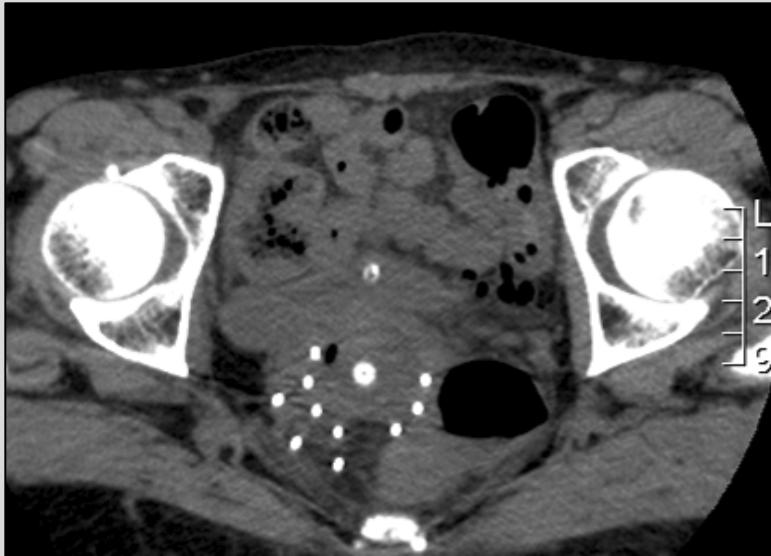
LIMITATIONS: TARGET VISUALIZATION & COVERAGE

Computed Tomography

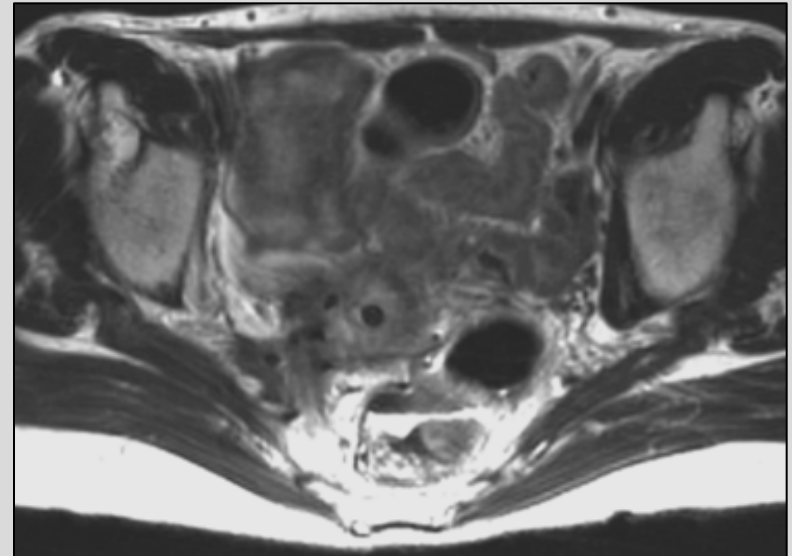
Findings at Brachytherapy

Example: cervix cancer

Assess Tumour size & Topography



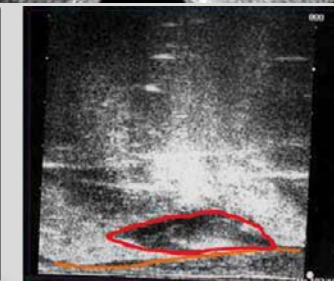
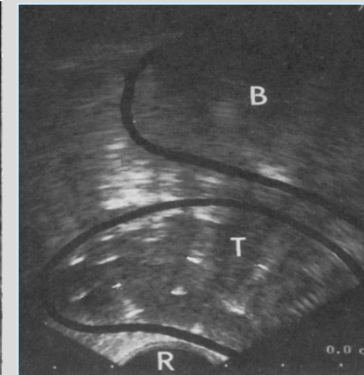
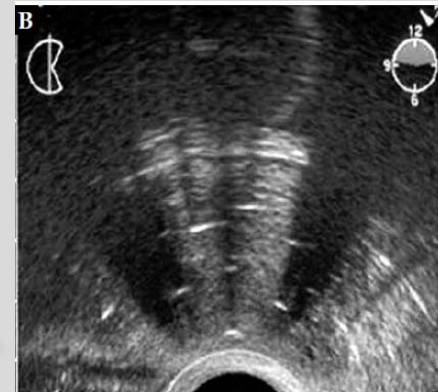
Native CT (no contrast)



T2W FSE MRI (same patient)

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

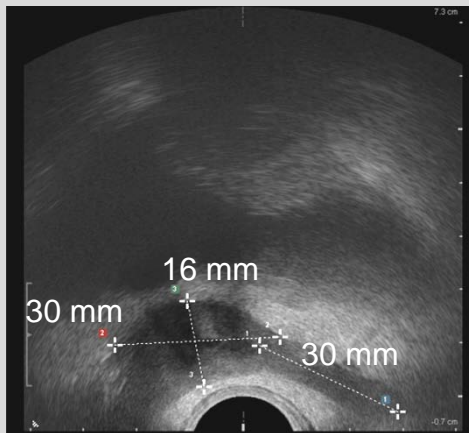
Weitmann HD et al. Strahlenther Onkol 2006; 182: 86-95.
Wenzel W. J Clin Ultrasound 1975; 3: 311-312.
Brascho DJ et al. Radiology 1978; 129: 163-167.
Stock RG et al. IJROBP 1997; 37: 819-825.
Sharma DN et al. J Gynecol Oncol 2010; 21: 12-17.

Ultrasound

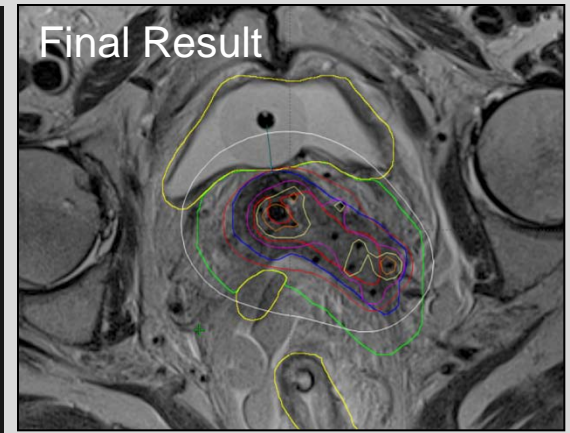
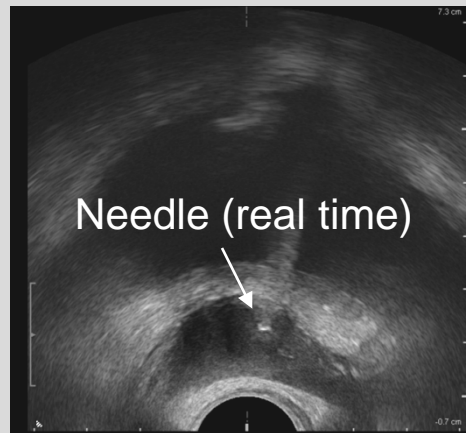
Findings at Brachytherapy

Cervix cancer

Assess Tumour size & Topography



Transrectal Ultrasound

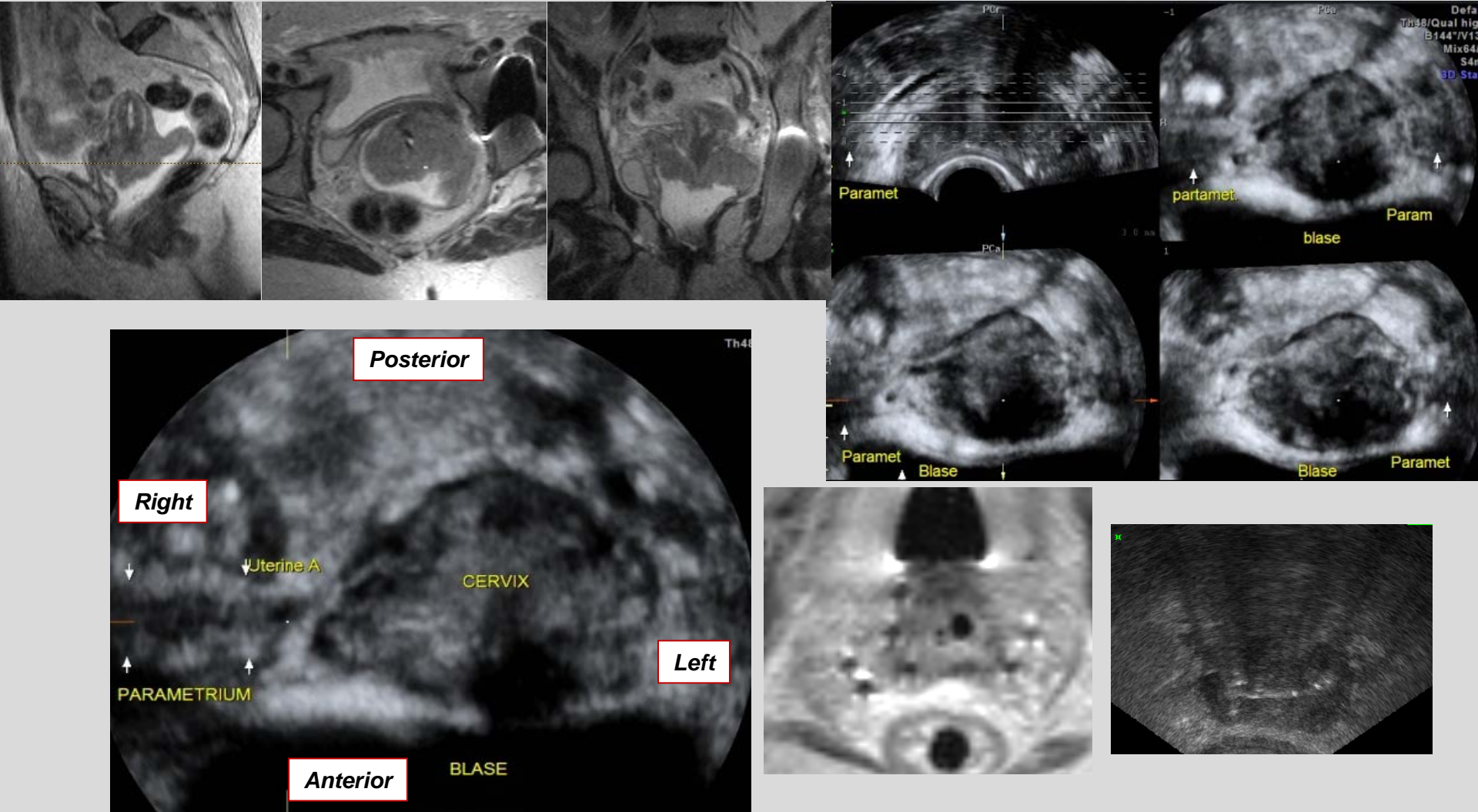


T2W FSE MRI (same patient)

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

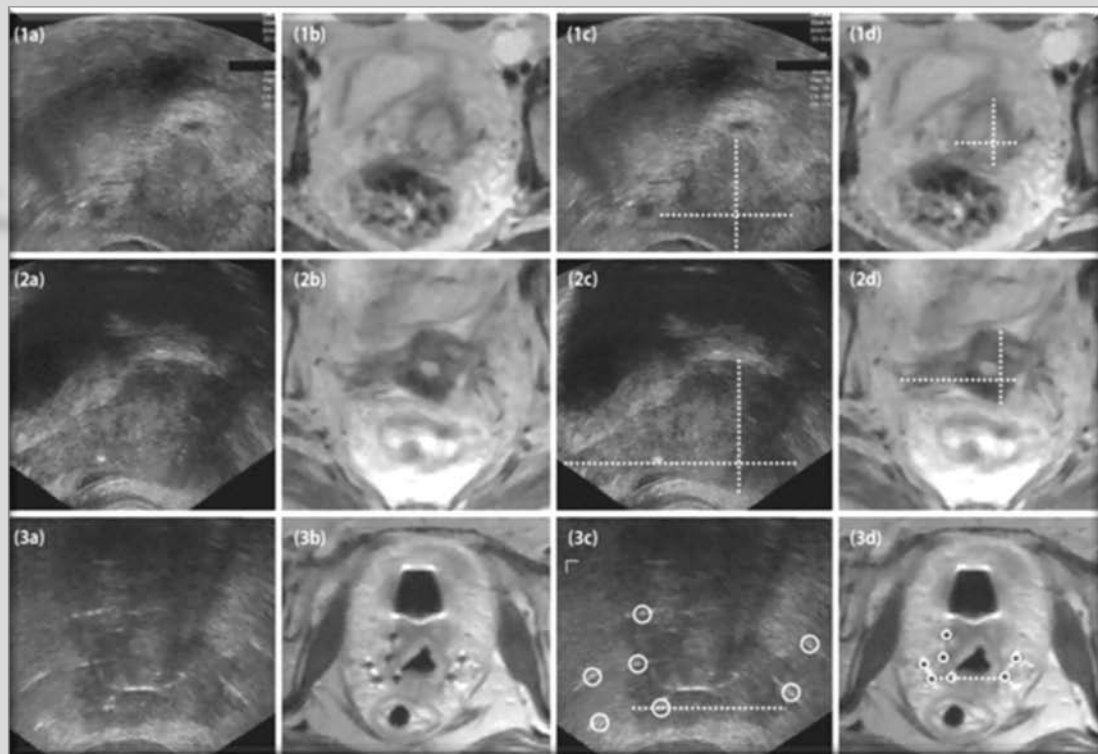
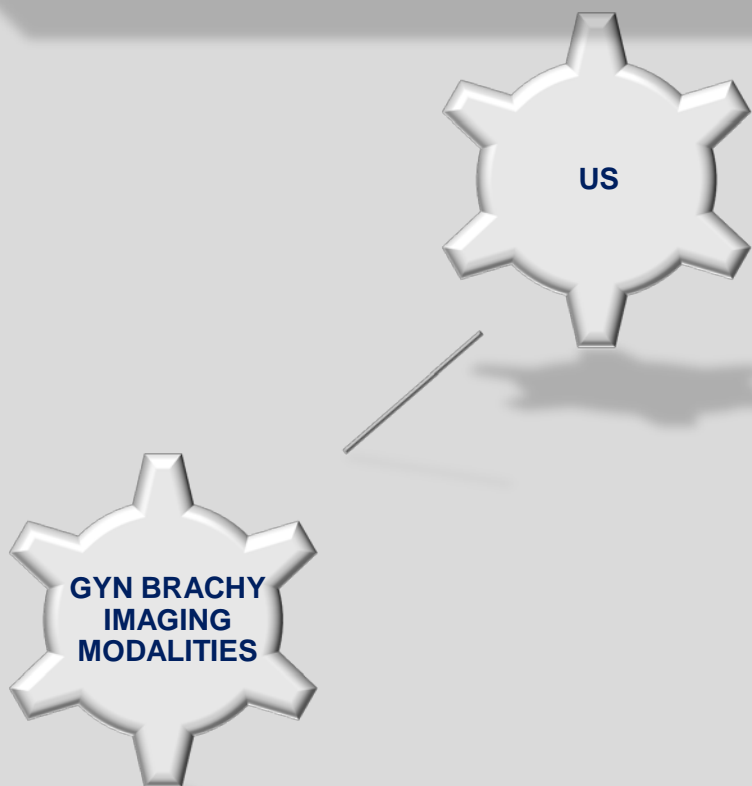
INTERSTITIAL TECHNIQUES

POTENTIAL OF MODERN US TECHNIQUES



INTERSTITIAL TECHNIQUES

POTENTIAL OF MODERN US TECHNIQUES



Good correlation between US and MRI

Schmid et al. Strahlenther Onkol 2013

*INTERSTITIAL TECHNIQUES
ATTEMPT TO IMPROVE PLACEMENT*

NEEDLE PLACEMENT ACCURACY: OPEN MRI

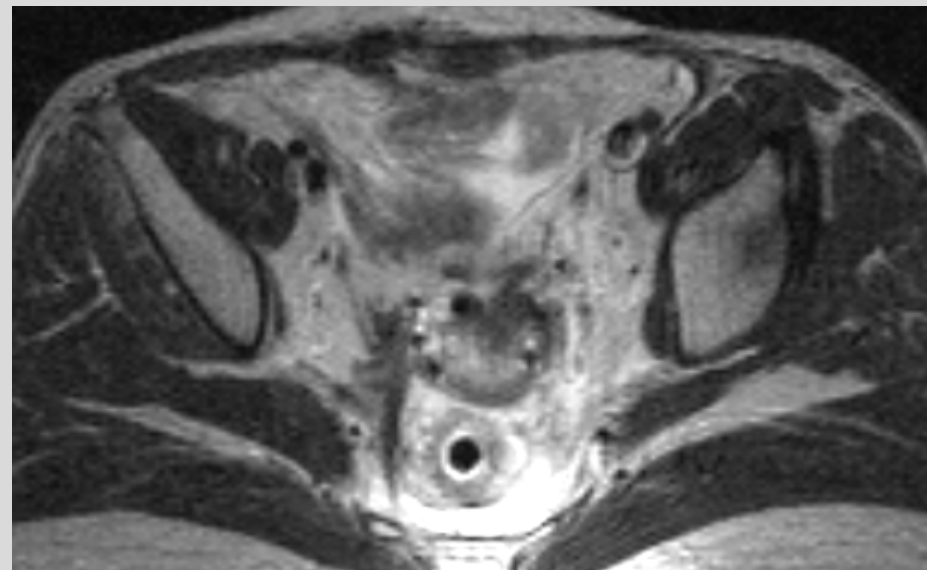
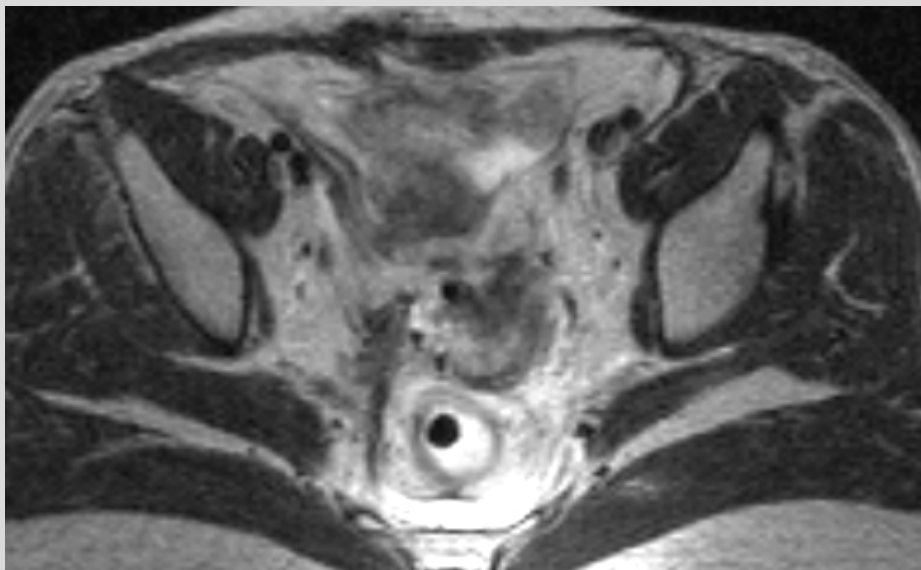
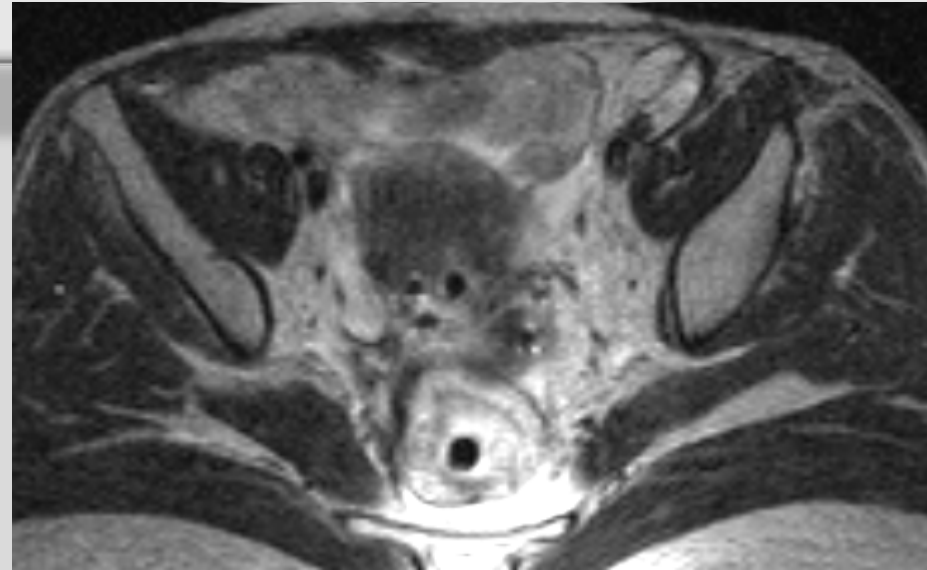
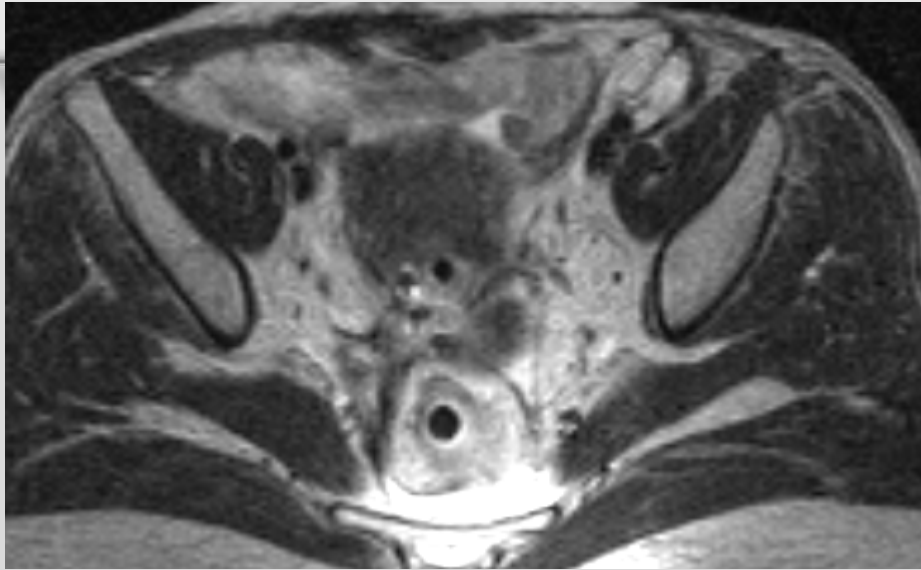
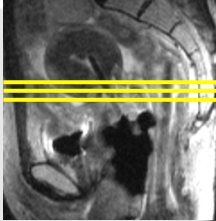
*Needle placement accuracy : open MRI with
Titanium-Zirconium needles*

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

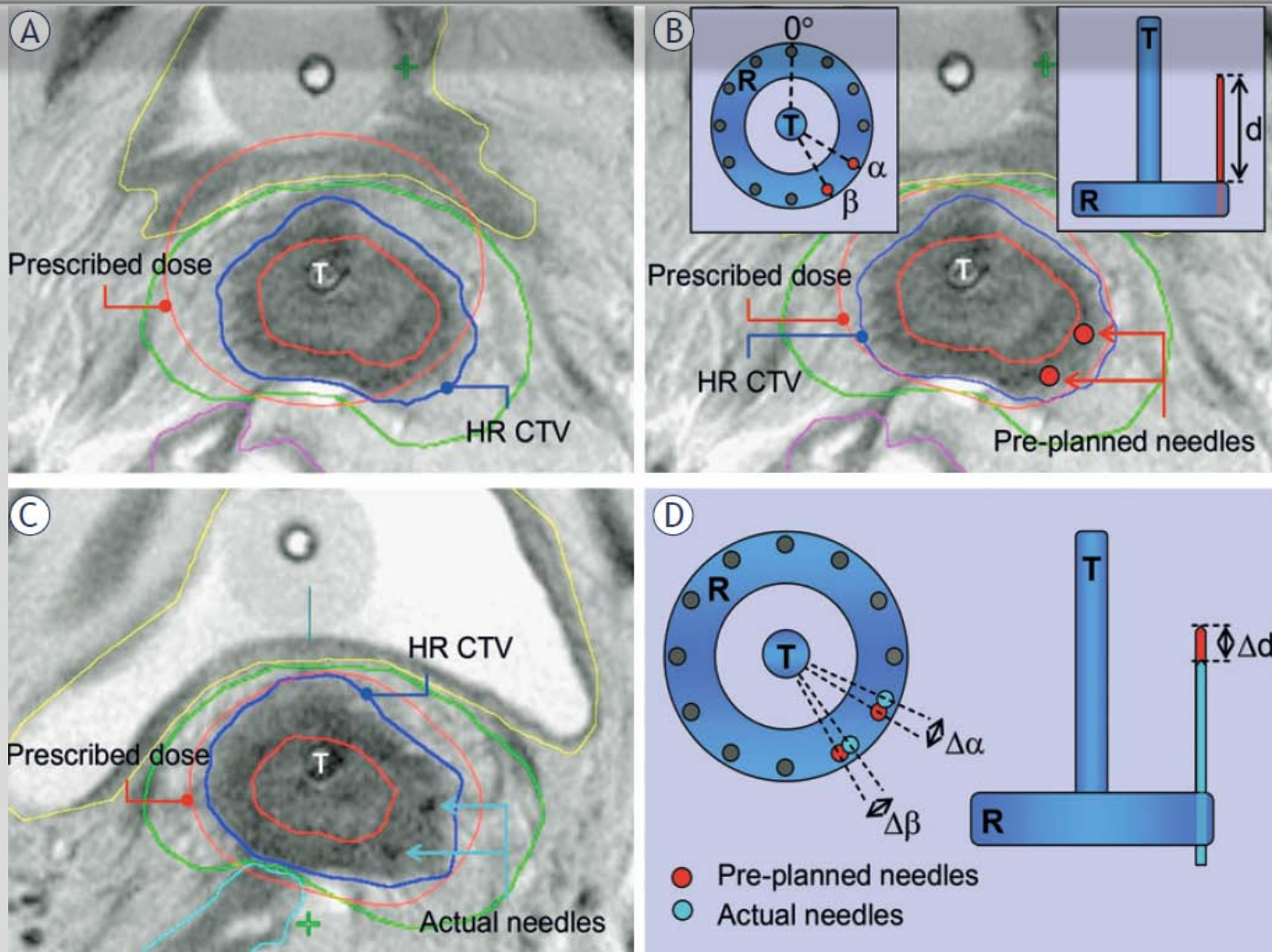
- *Improvement in the treatment quality*
- *Implantation accuracy*
- *Critical organ avoidance*

INTERSTITIAL TECHNIQUES

ATTEMPT TO IMPROVE PLACEMENT



INTERSTITIAL TECHNIQUES ATTEMPT TO IMPROVE PLACEMENT



COMBINED INTRACAVITARY & INTERSTITIAL TECHNIQUES

SELECTION OF APPLICATION TECHNIQUE

Based on clinical examination and sectional imaging:

At the time of diagnosis

- Initial tumor extension

During EBRT

- Quantitative and qualitative tumor regression

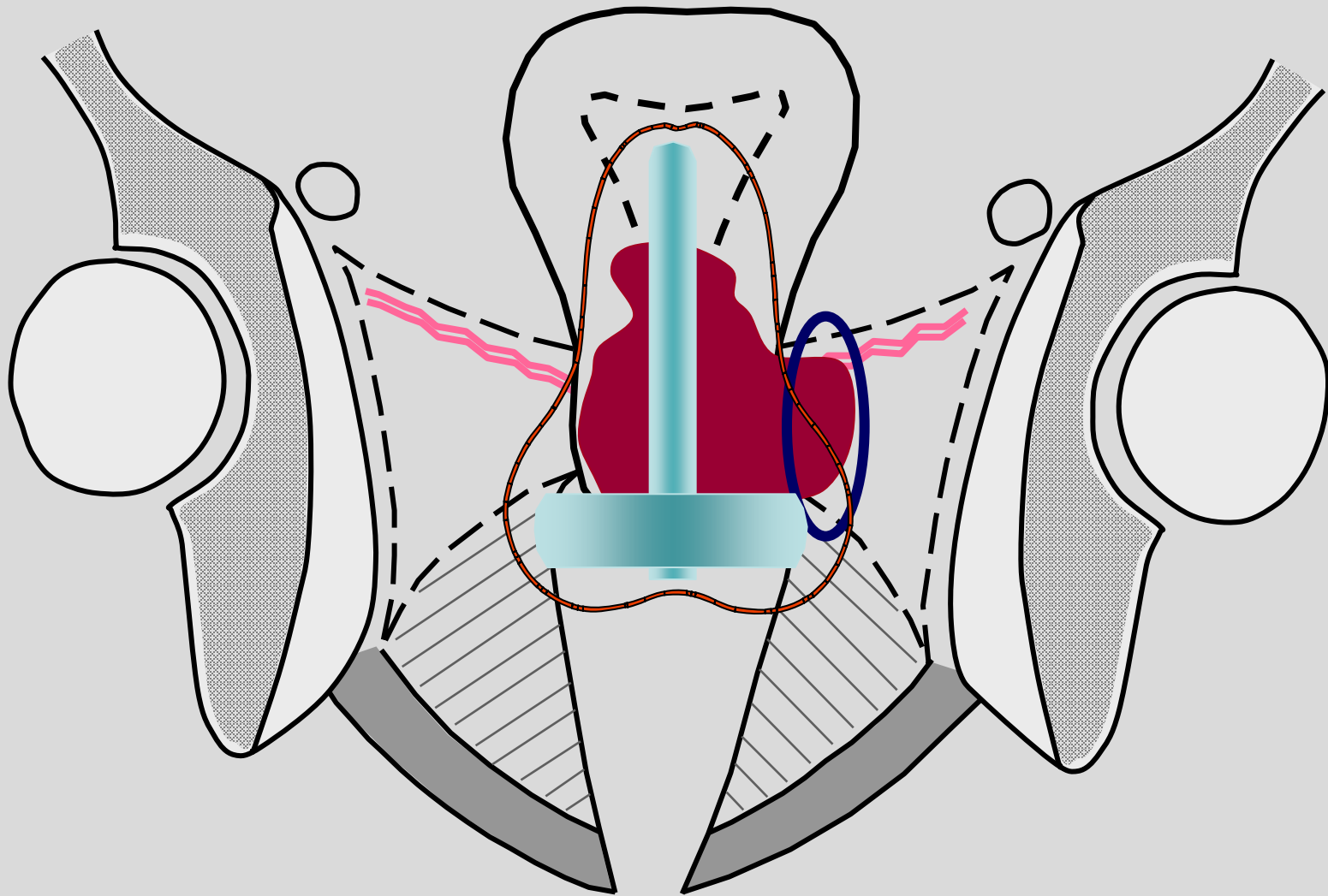
At the time of brachytherapy

- Topography of residual tumor in relation to the applicator

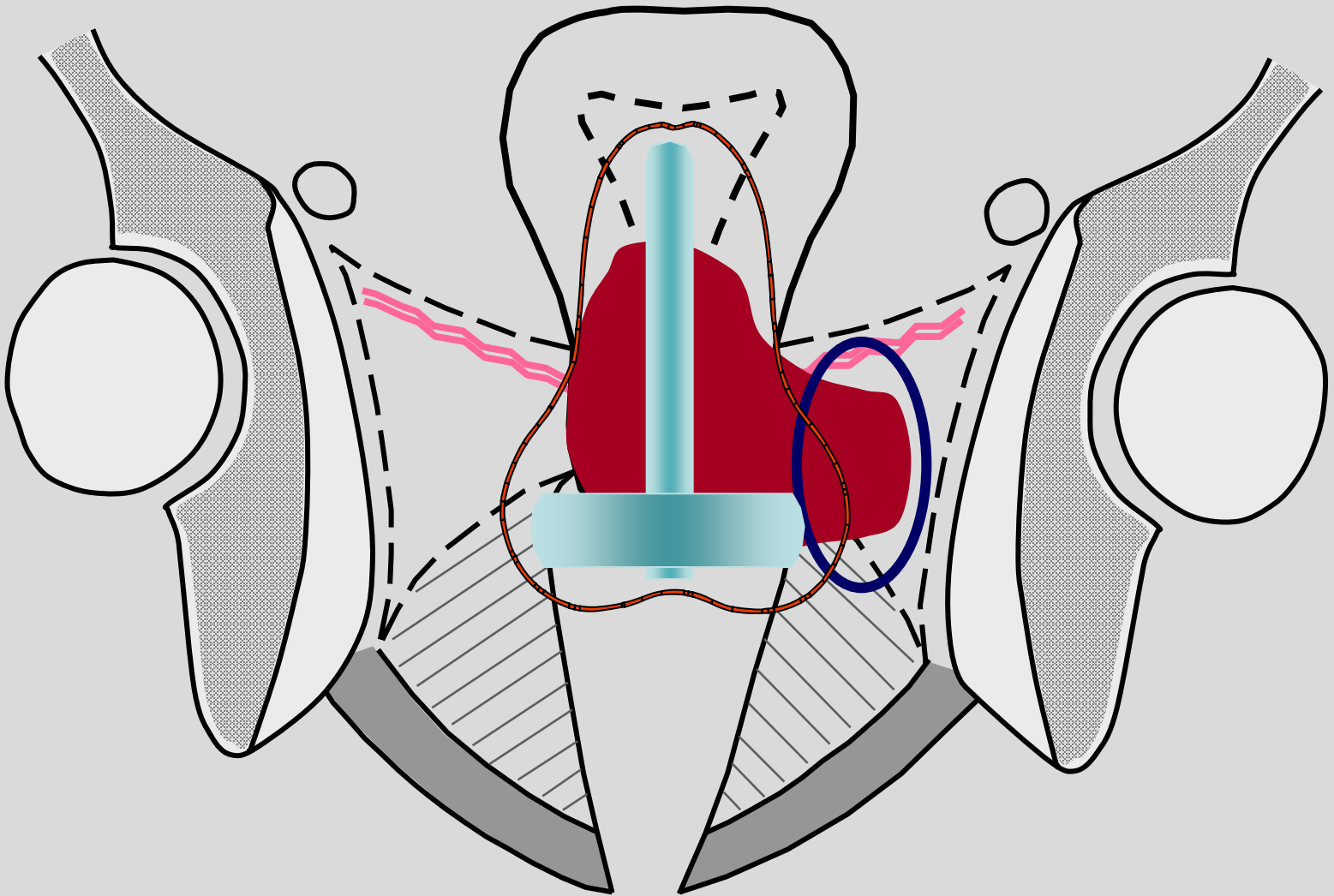
Selection of Brachytherapy Technique

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

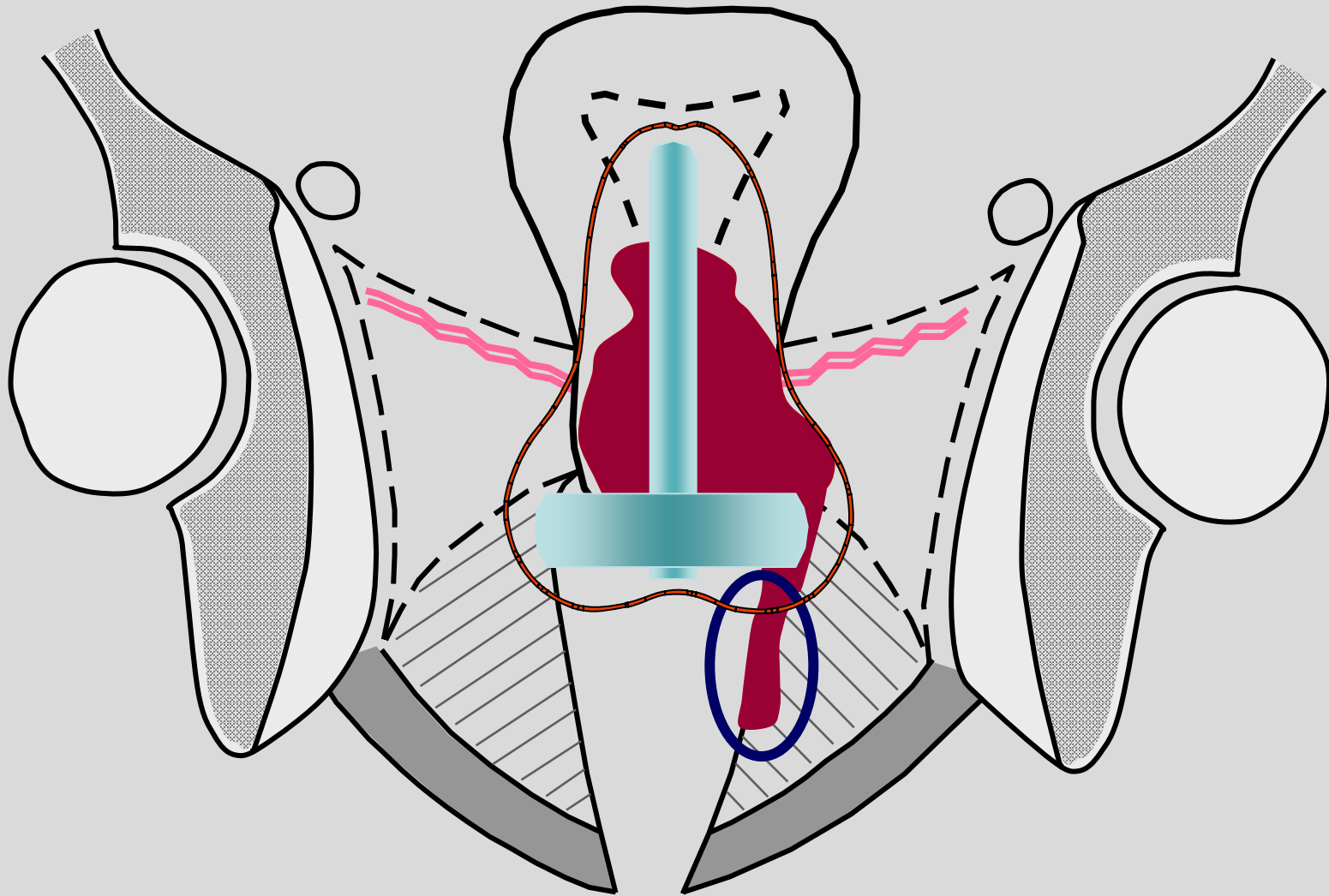
DETECTION OF INAPPROPRIATE COVERAGE: 1



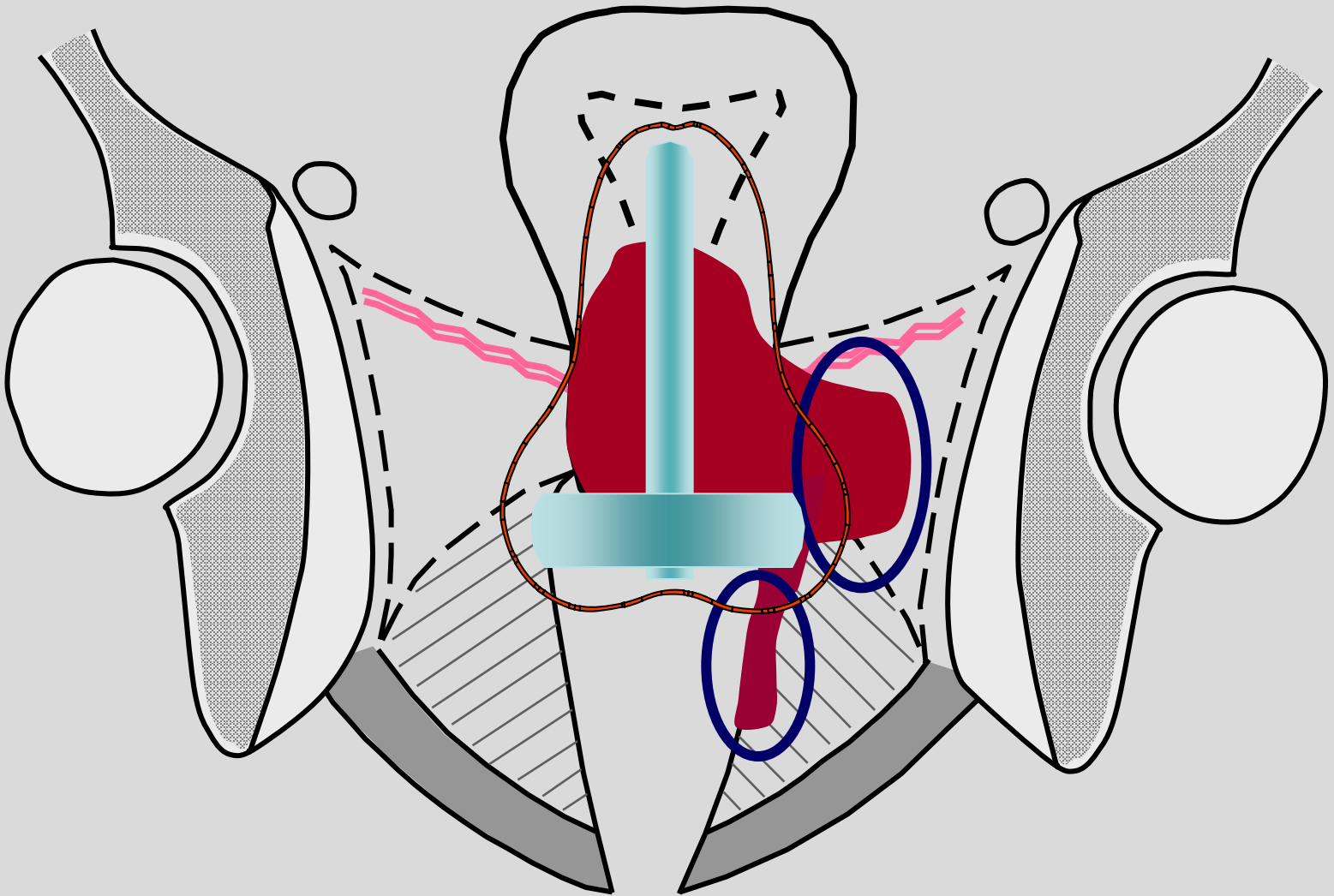
DETECTION OF INAPPROPRIATE COVERAGE: 1A



DETECTION OF INAPPROPRIATE COVERAGE: 2



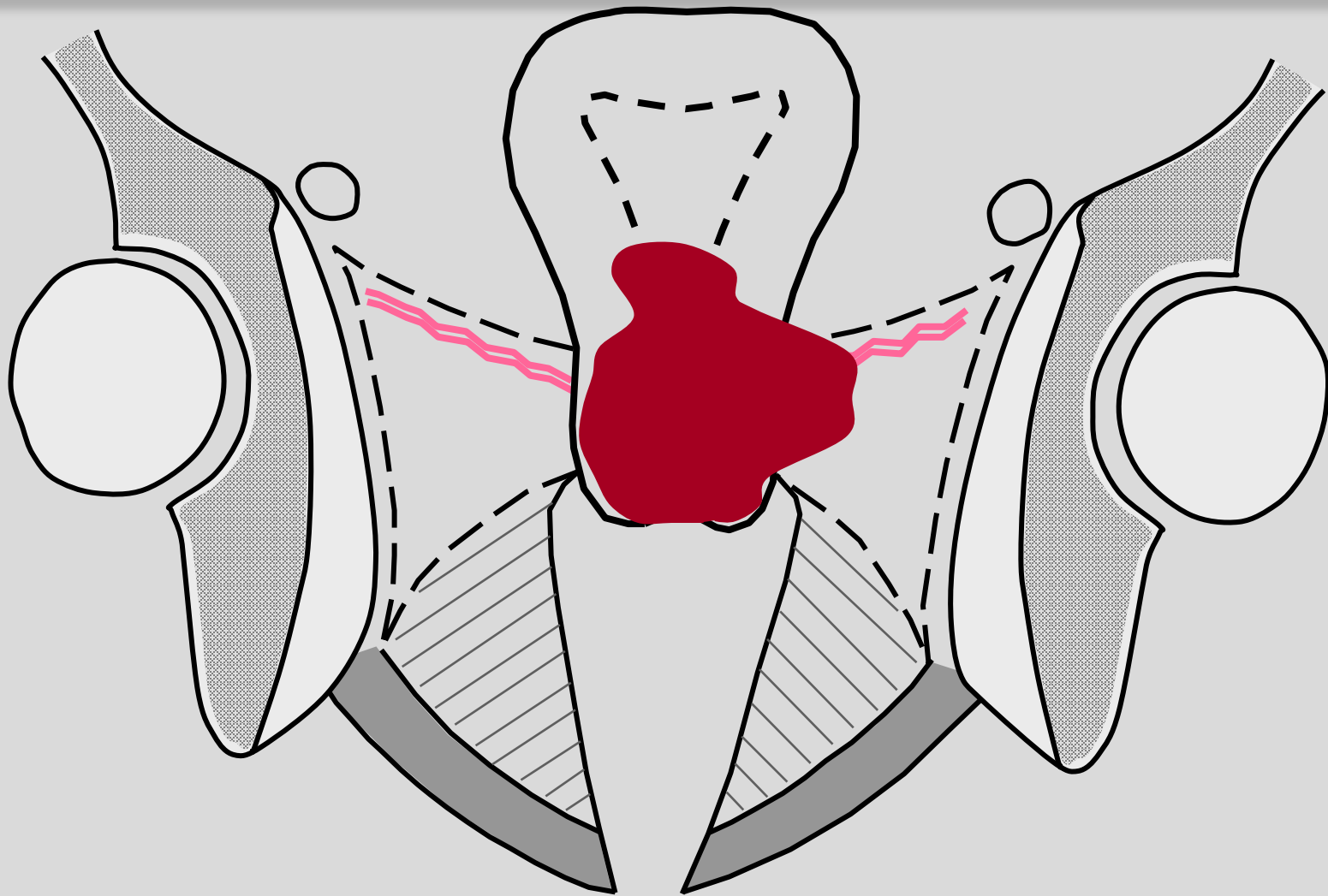
DETECTION OF INAPPROPRIATE COVERAGE: 2A



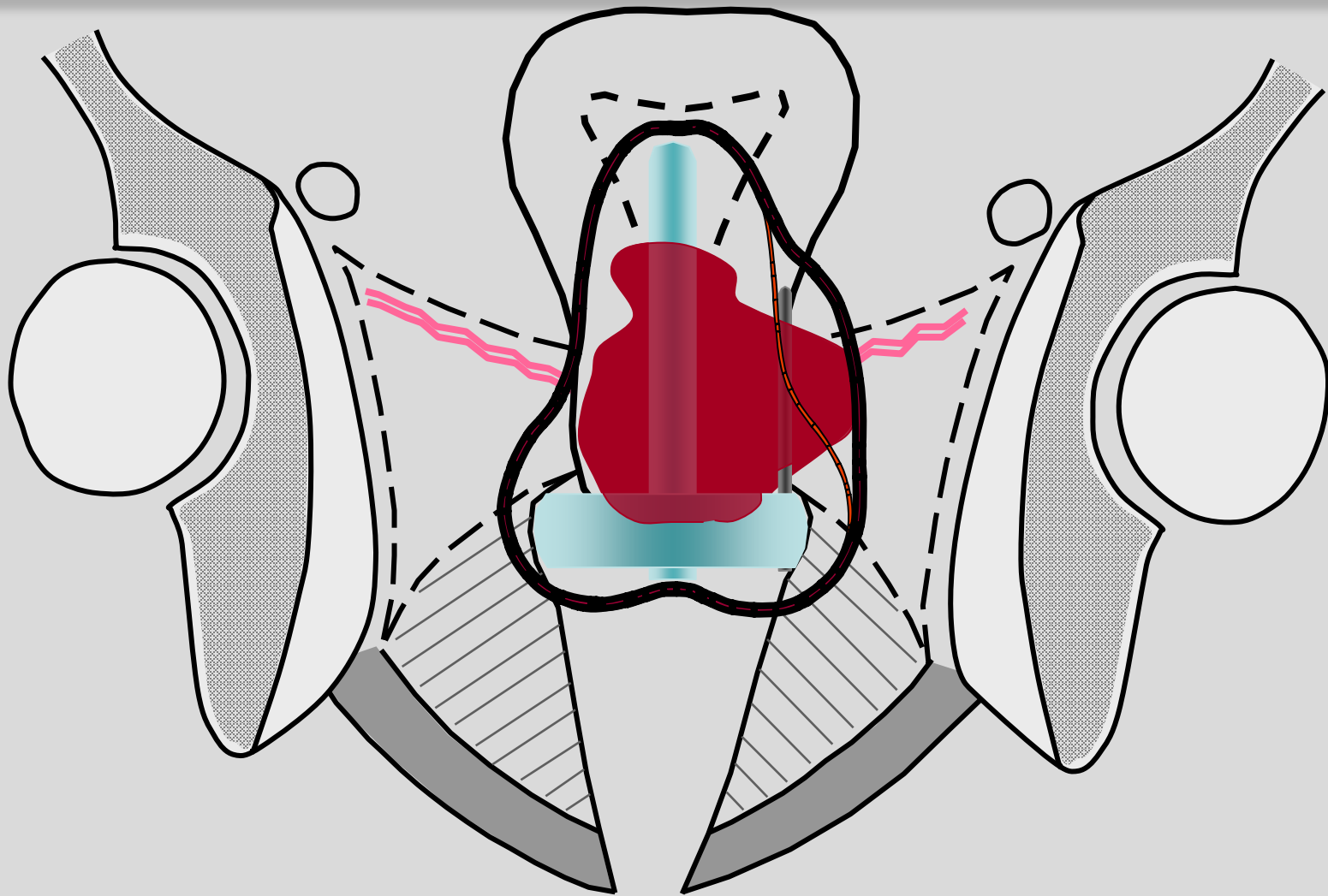
Preconditions - Management

- *Peri-operative Management (bowel preparation, measurements against thrombosis and infection, iv. hydration)*
- *Pain management - anaesthesia (spinal / epidural / general)*
- *Sectional imaging (CT / MRI)*
 - at diagnosis and before brachytherapy (alternative 1)
 - at diagnosis and at first brachytherapy (alternative 2)
 - at diagnosis and at every brachytherapy (alternative 3)
- *Equipment (appropriate set of applicators)*
- *Learning curve*

Pattern of tumor regression: 1

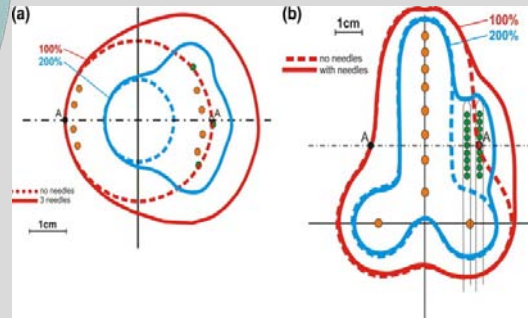
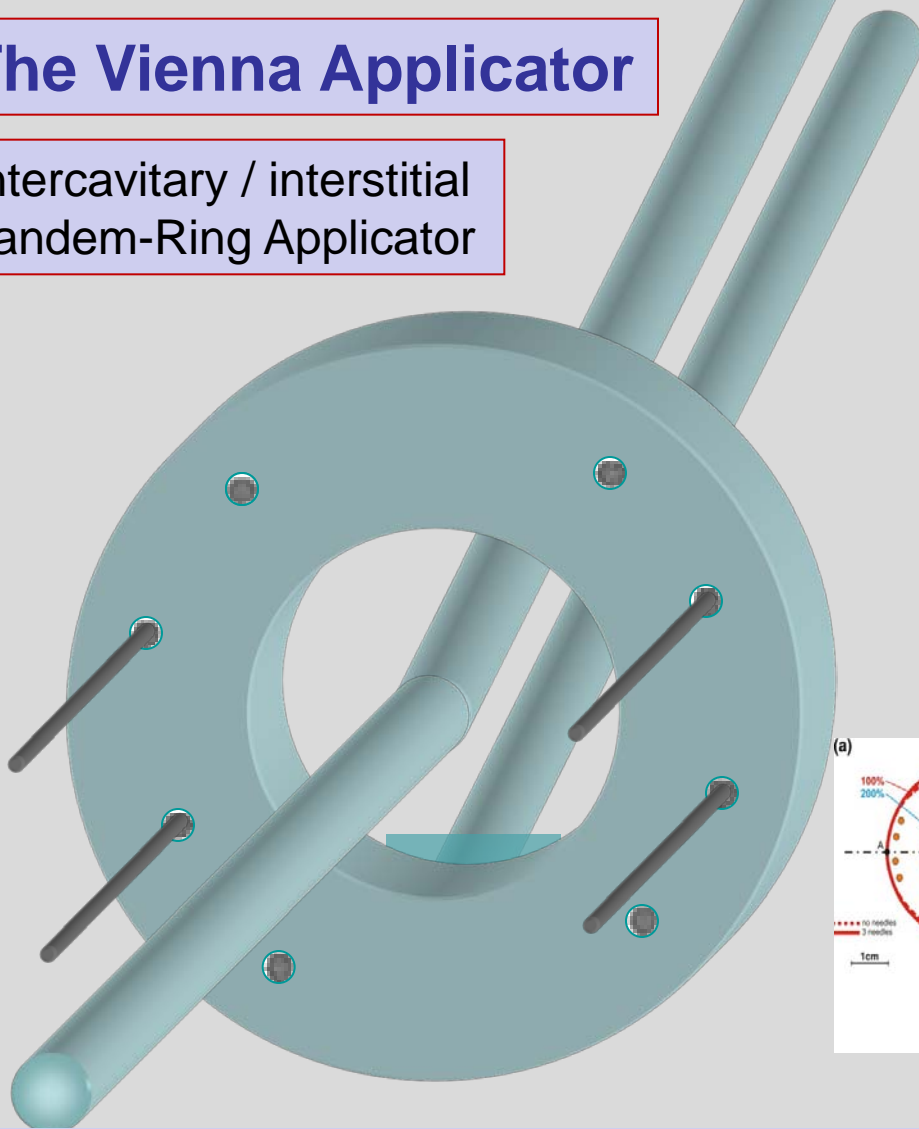


Pattern of tumor regression: 1



The Vienna Applicator

Intercavitary / interstitial
Tandem-Ring Applicator



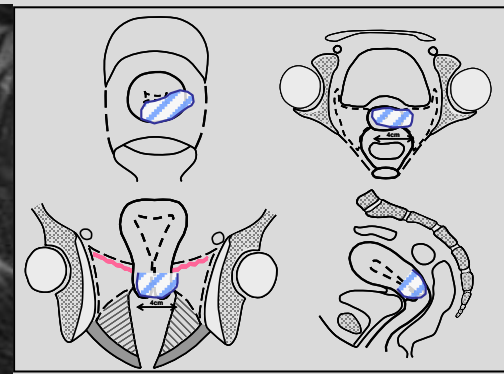
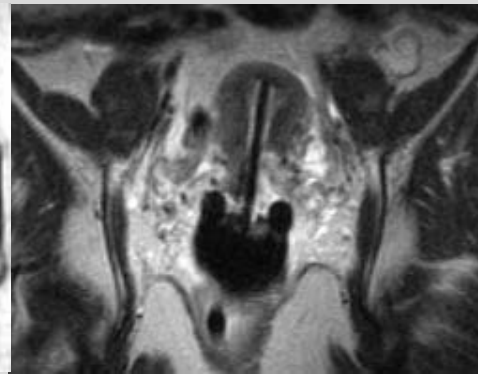
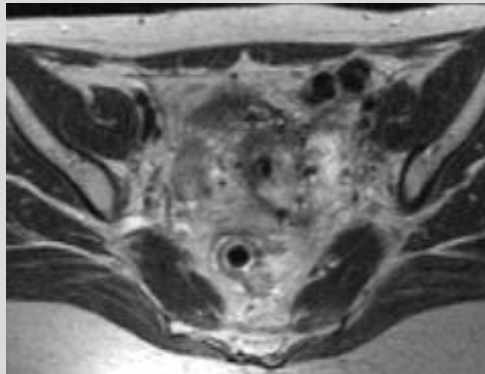
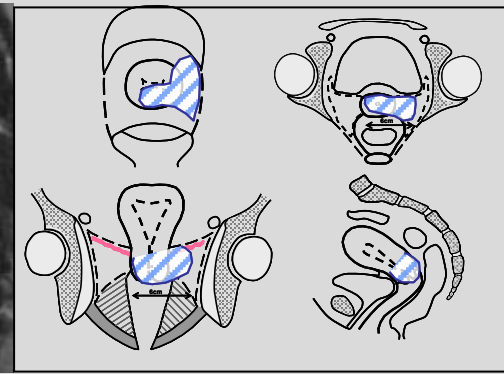
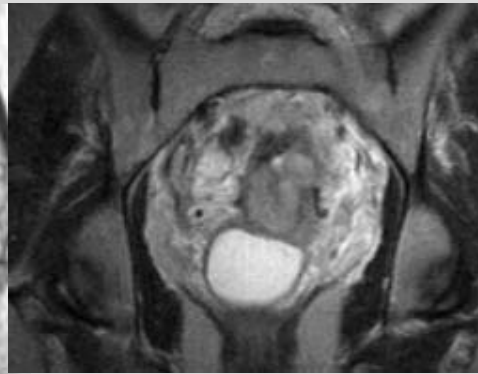
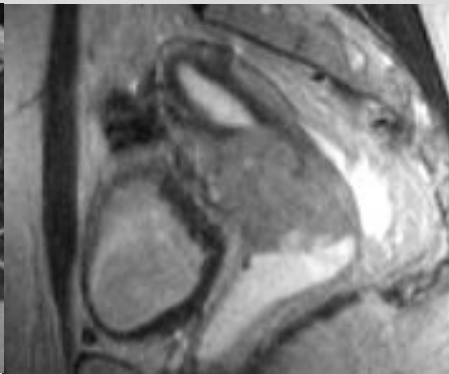
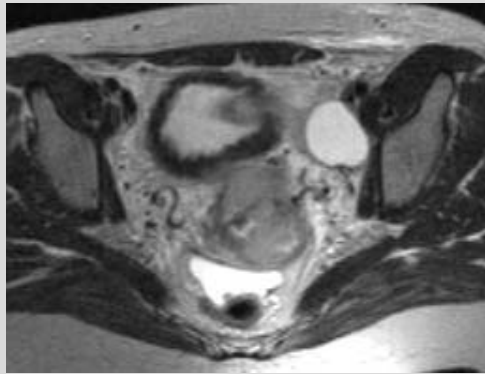
Modified Applicator: drilled holes into ring to insert needles
parallel to the Tandem

***Kirisits et al. IJROBP 2006
(technical note)***

***Dimopoulos et al. IJROBP 2006
(clinical results)***

Clinical example

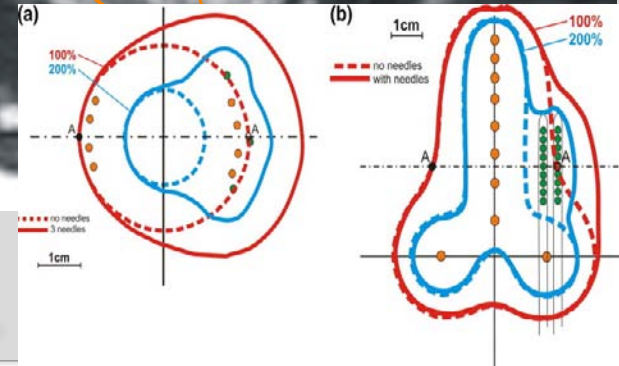
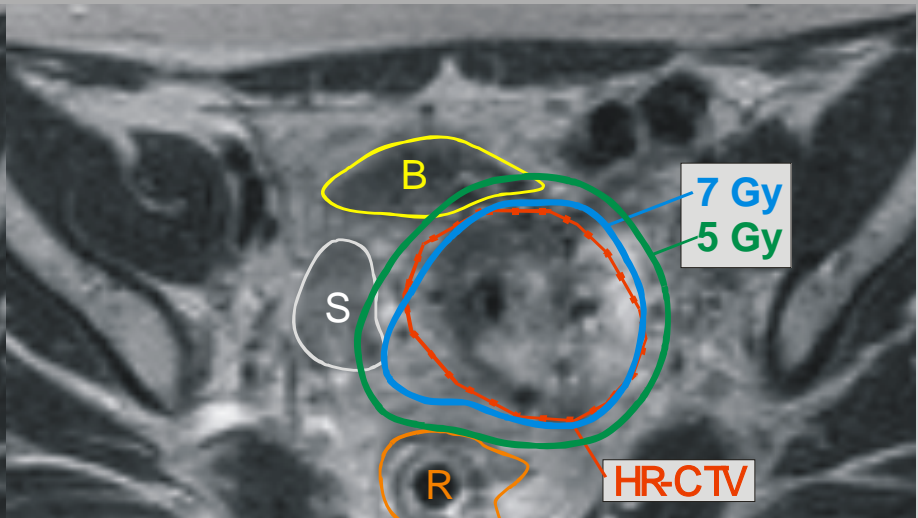
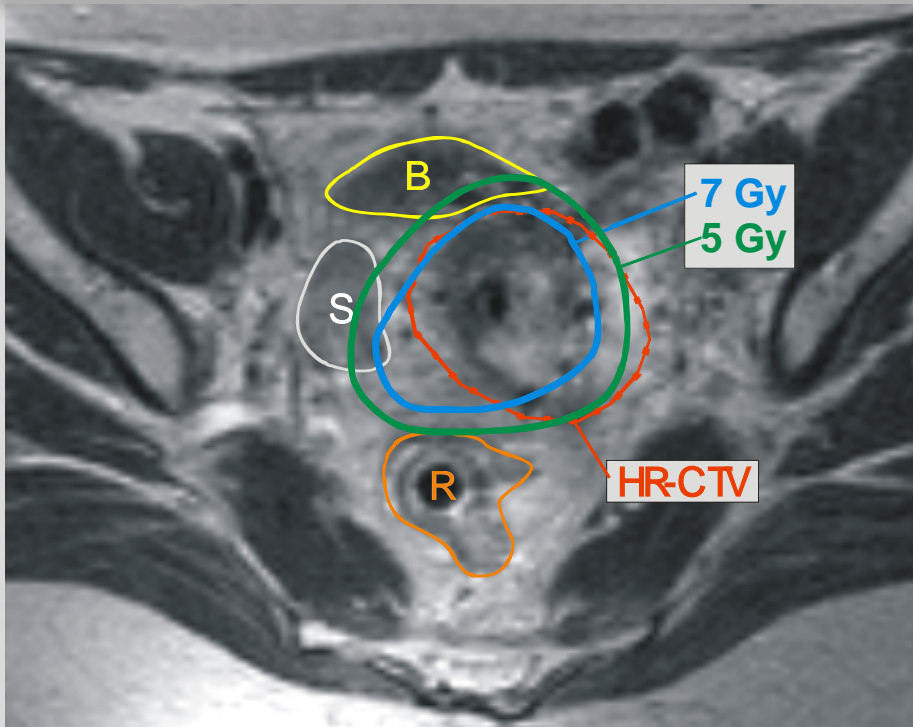
Stage IIB / distal / insufficient response



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

standard treatment plan

optimized interstitial



INTRACAVITARY PLUS NEEDLES LEFT PARAMETRIUM

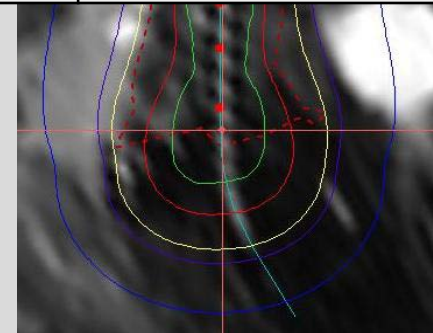
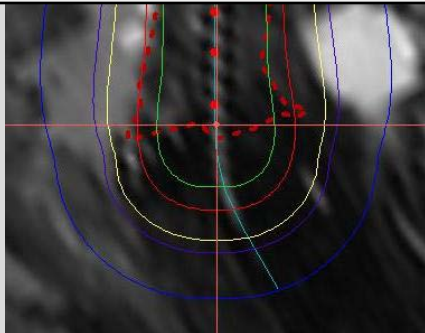
*Improved placement control - Low number of needles –
Combined with MRI based treatment planning*

UNFAVORABLE TOPOGRAPHY FOR OAR'S: 1- 2A

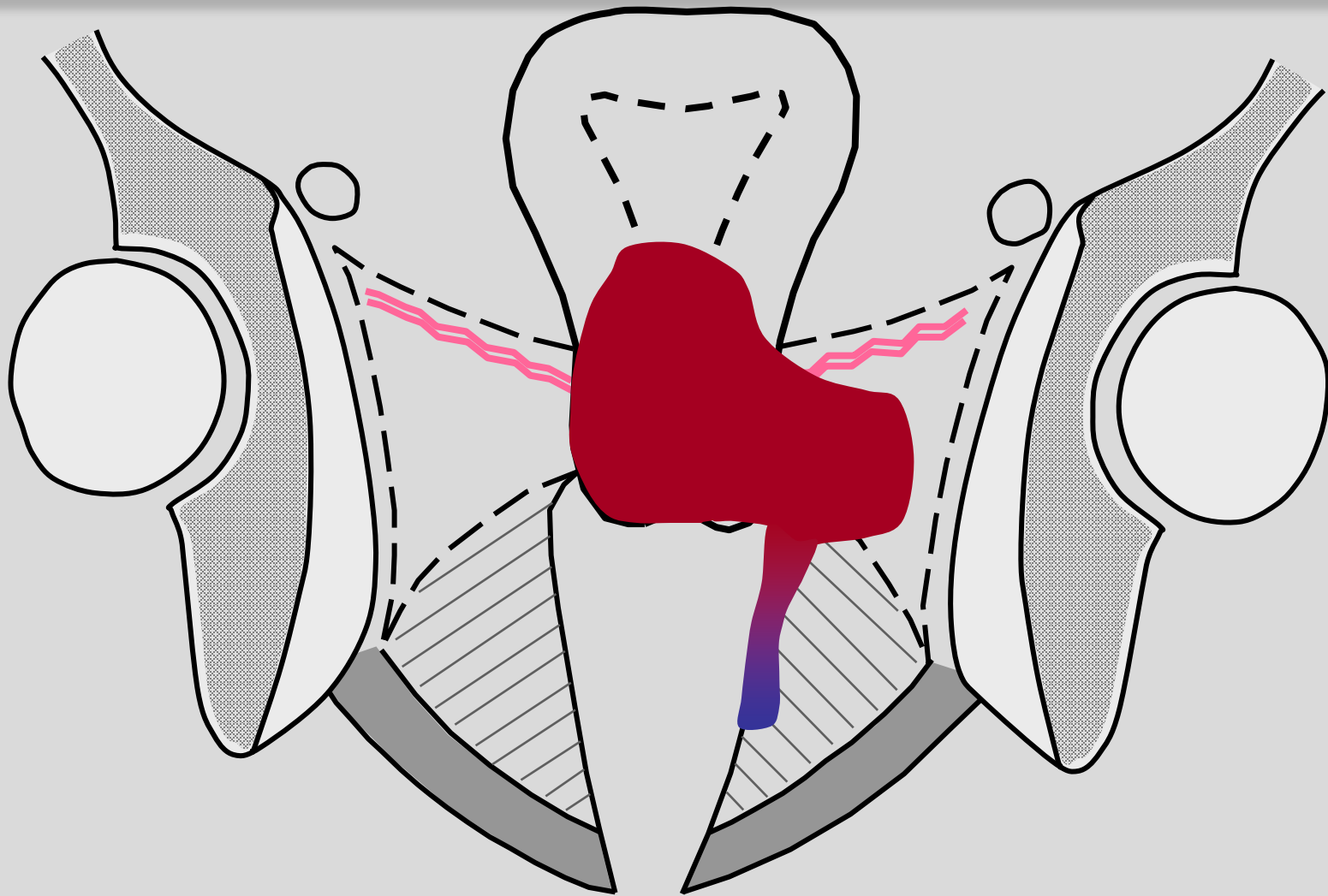
STD INTRA-CAVITARY BT

Vienna

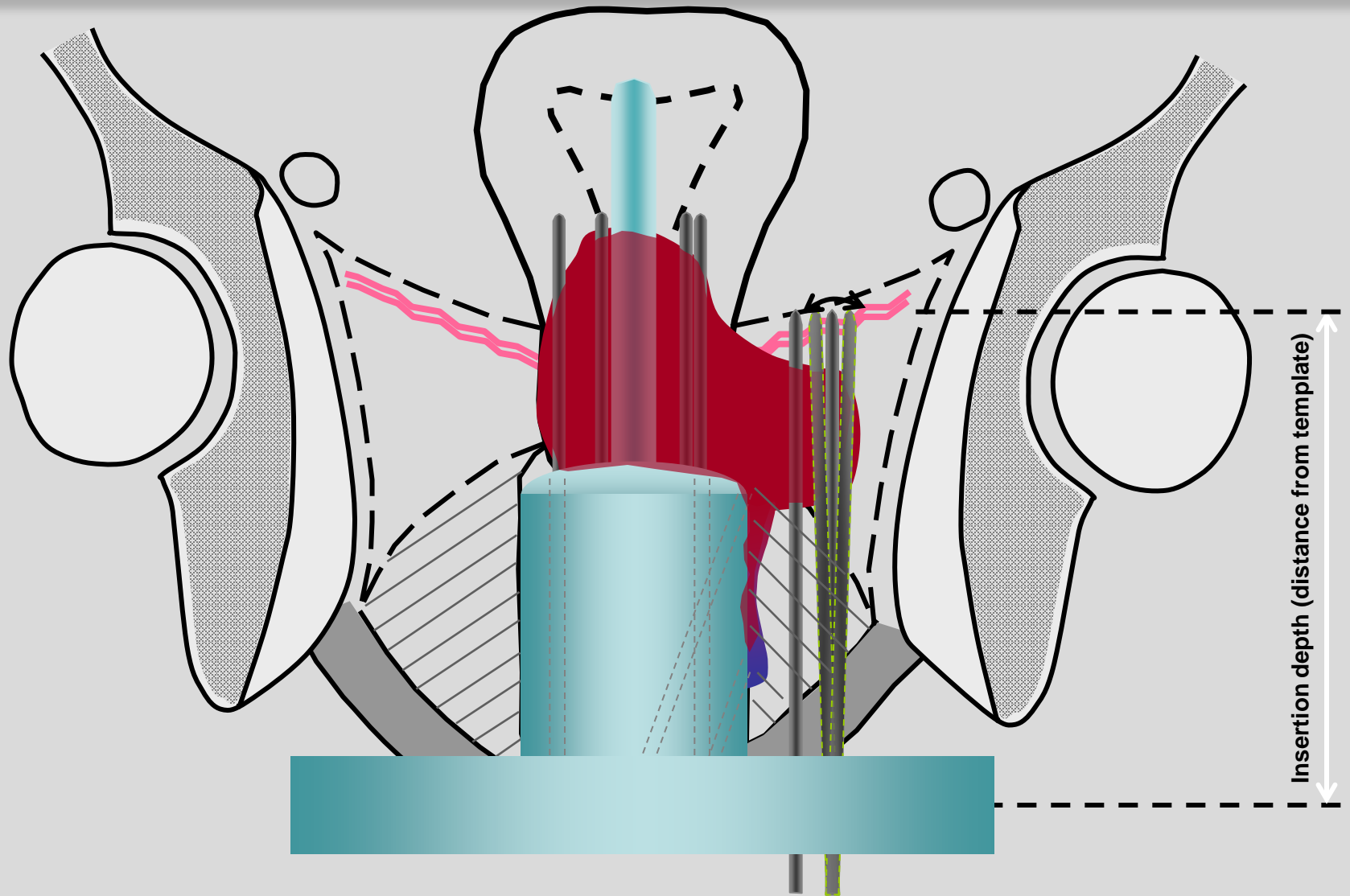
Parameters	Ring	Vienna
HRCTV D98 (Gy)	7.6	7.3
HRCTV D90 (Gy)	10.2	8.3
HRCTV V100 (%)	99	99
SIMOID 2CC-Gy	5	4
SIMOID 0.1CC-Gy	7	5.5
BLADDER 2CC-Gy	9	6.3
BLADDER 0.1CC-Gy	11.8	7.8
RECTUM 2CC-Gy	3.9	3.4
RECTUM 0.1 CC-Gy	5.2	4.5



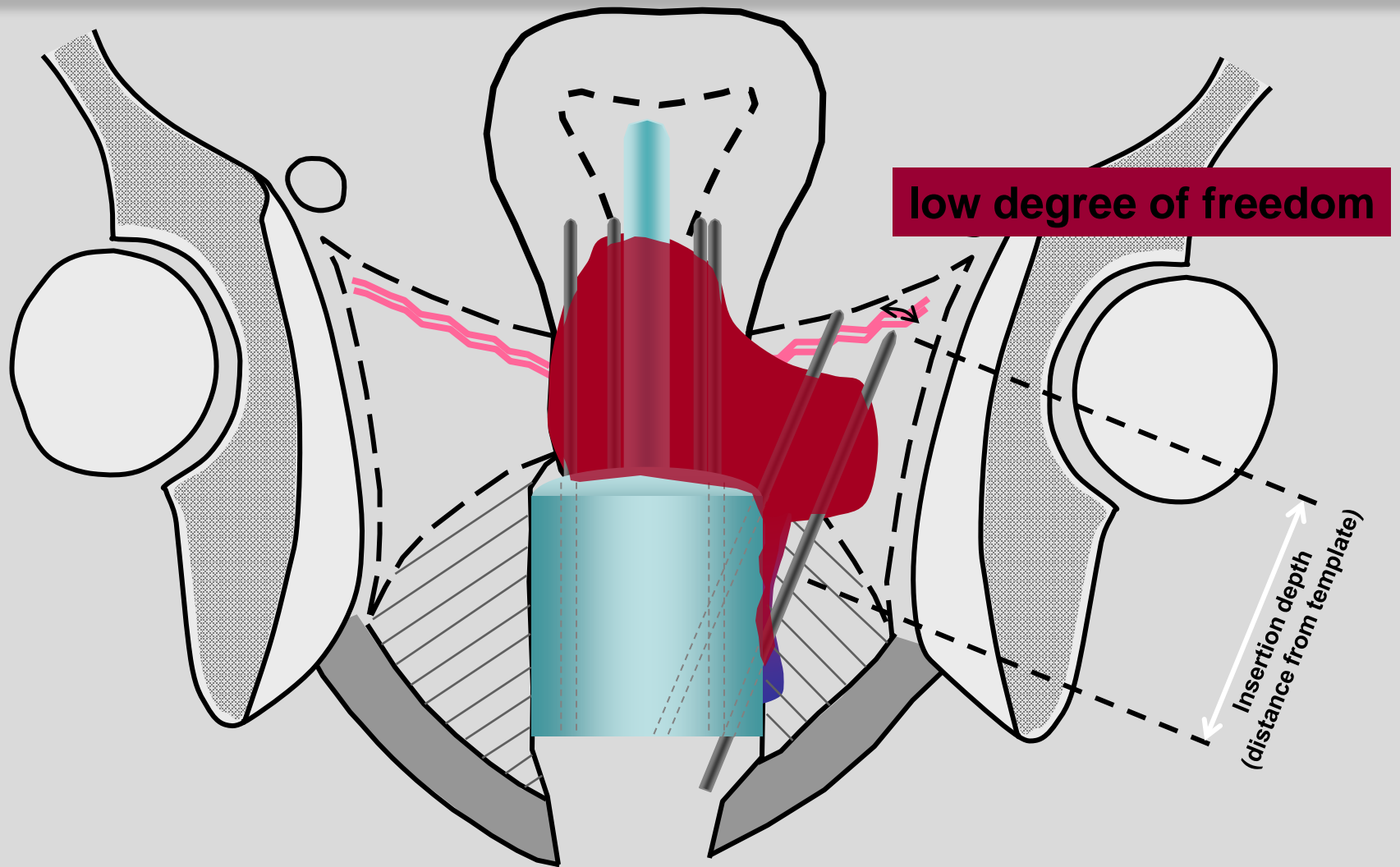
Pattern of tumor regression: 2-2A



Pattern of tumor regression

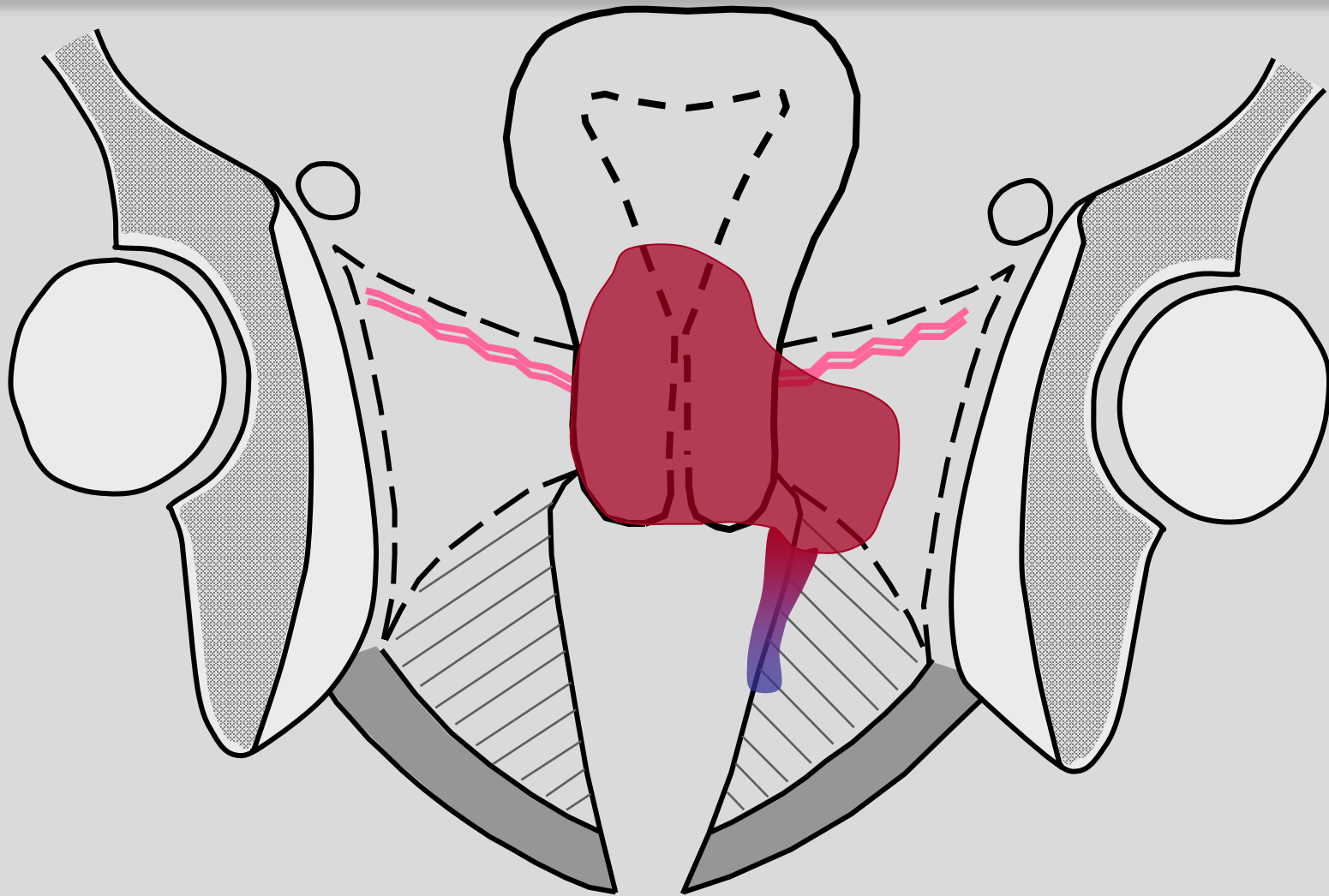


Pattern of tumor regression



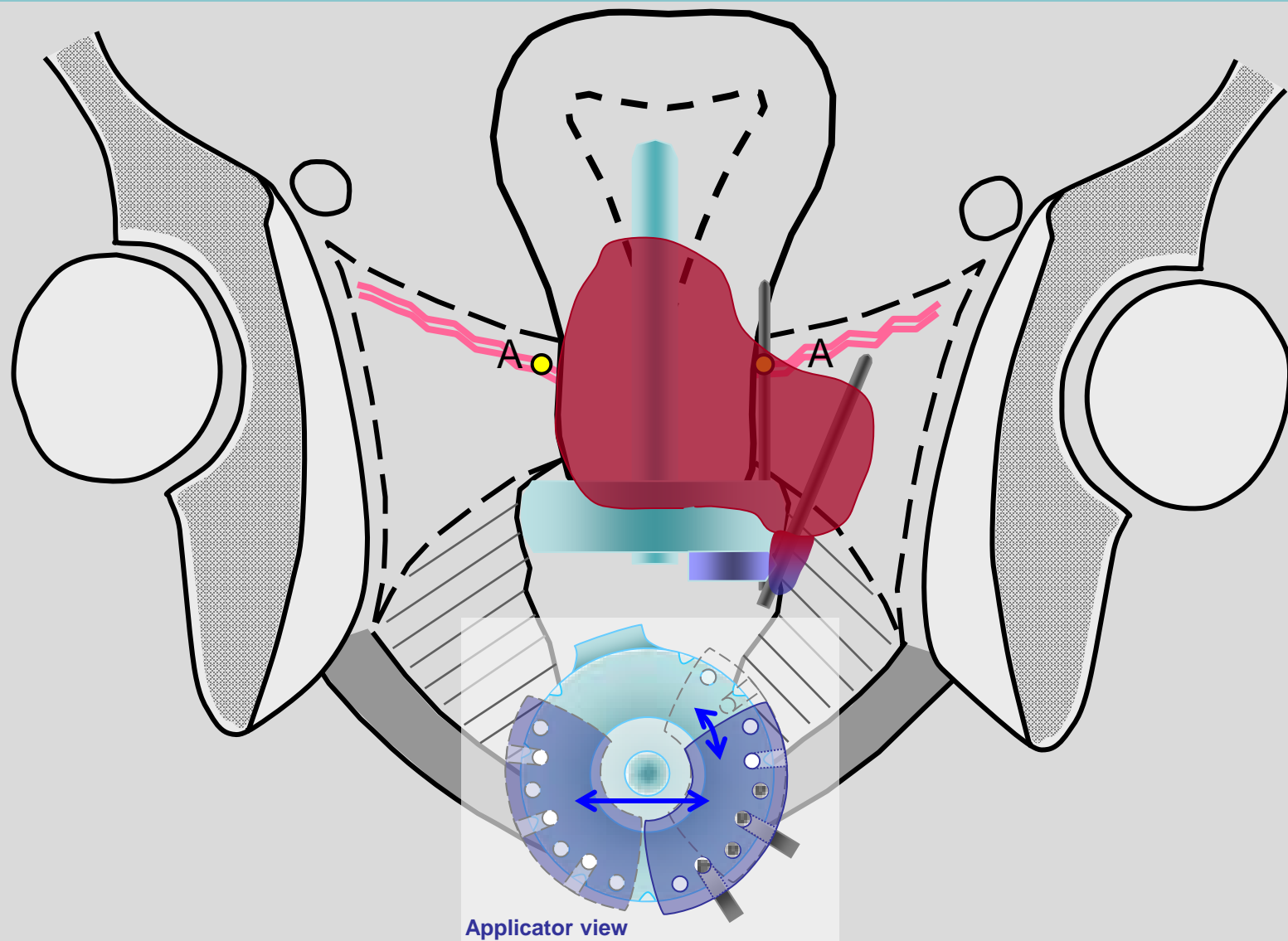
Tandem + Cylinder + Needles

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



Applicator for distal parametrial disease

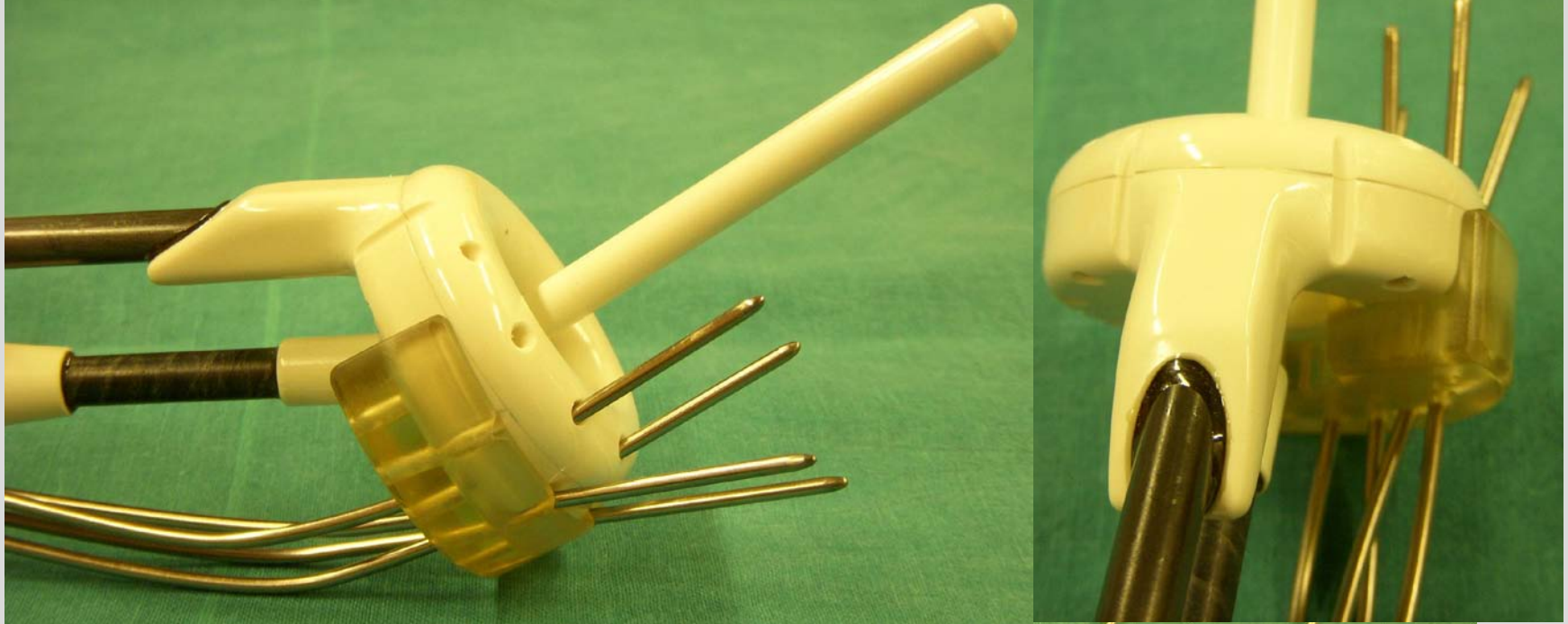
additional parallel and divergent template guided needles



Modified Vienna Ring

Pre-bended needles

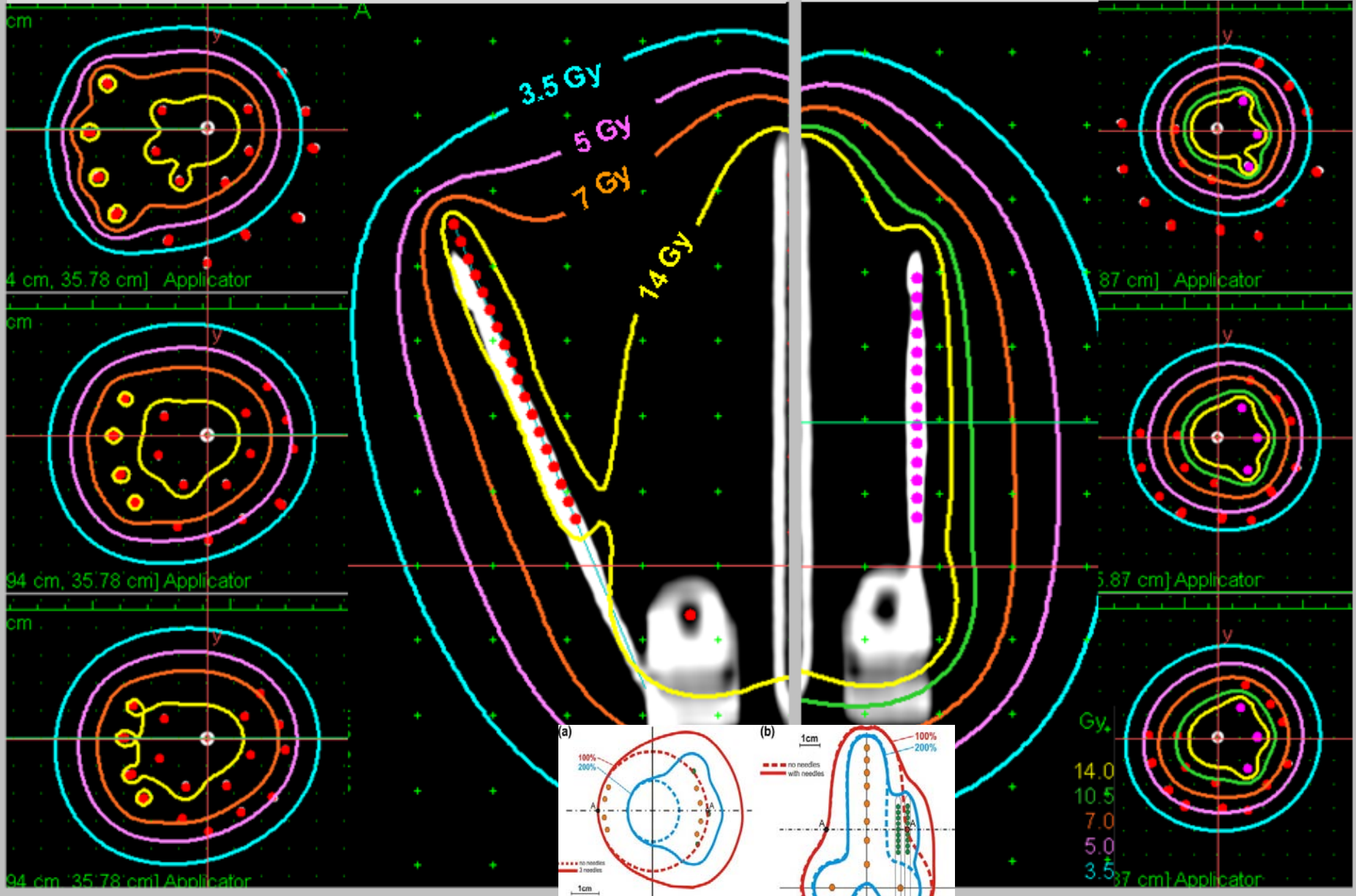
Applicator for distal parametrial disease



Approximately 60 patients experience : Vienna & Mumbai

Vienna-II

Vienna-I

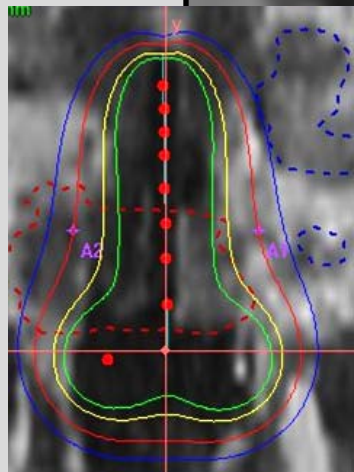
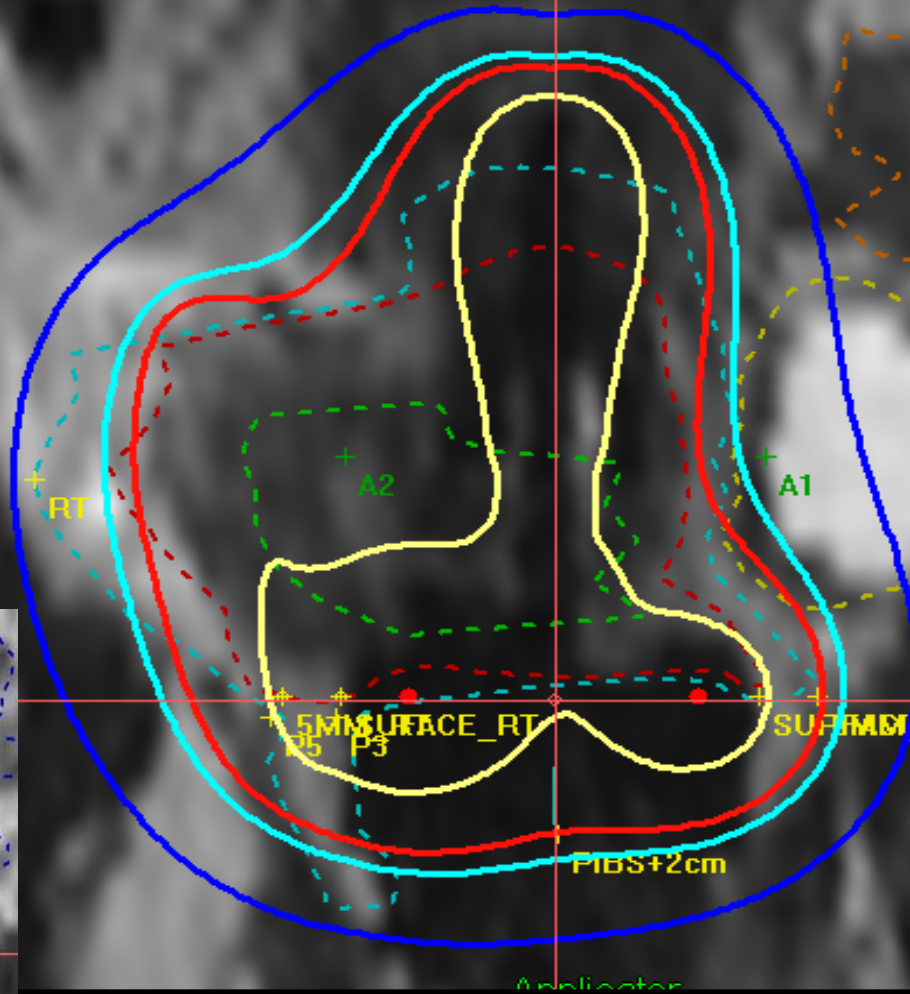


Courtesy D. Berger

PLAN EVALUATION

Coronal view

14 Gy
7 Gy
5.8 Gy
3.5 Gy



PLAN EVALUATION

Axial view

14 Gy

7 Gy

5.8 Gy

3.5 Gy

Sagittal view

14 Gy

7 Gy

5.8 Gy

3.5 Gy

Applicator

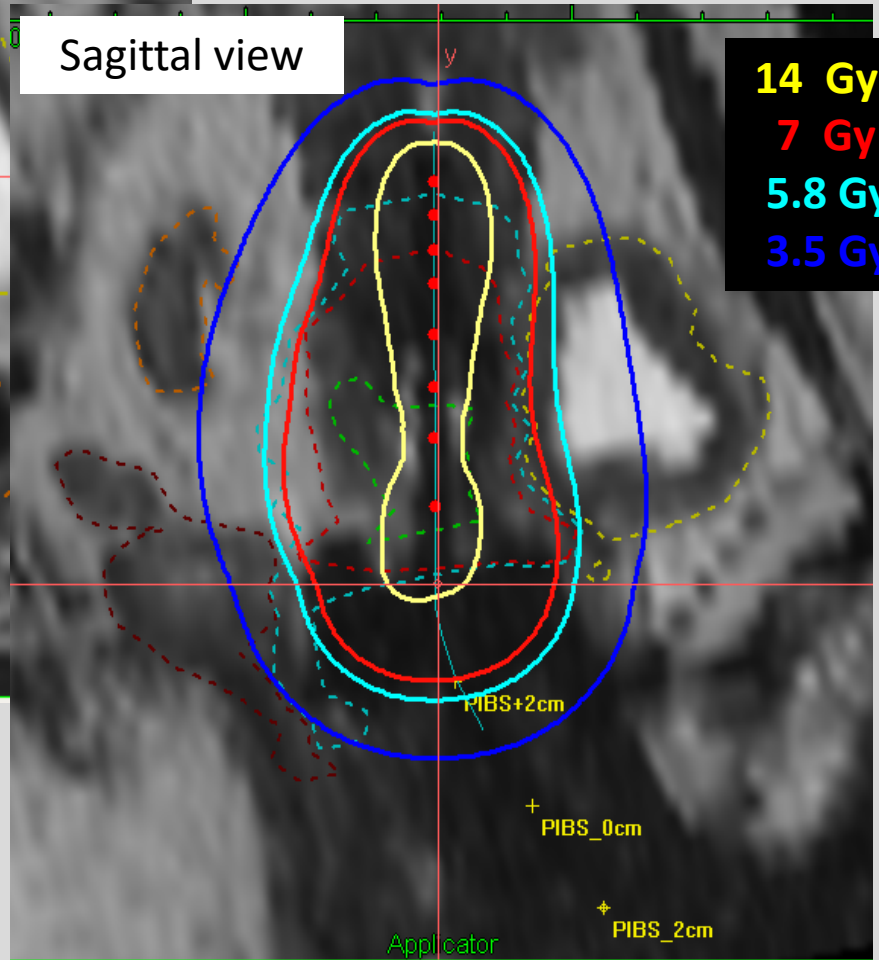
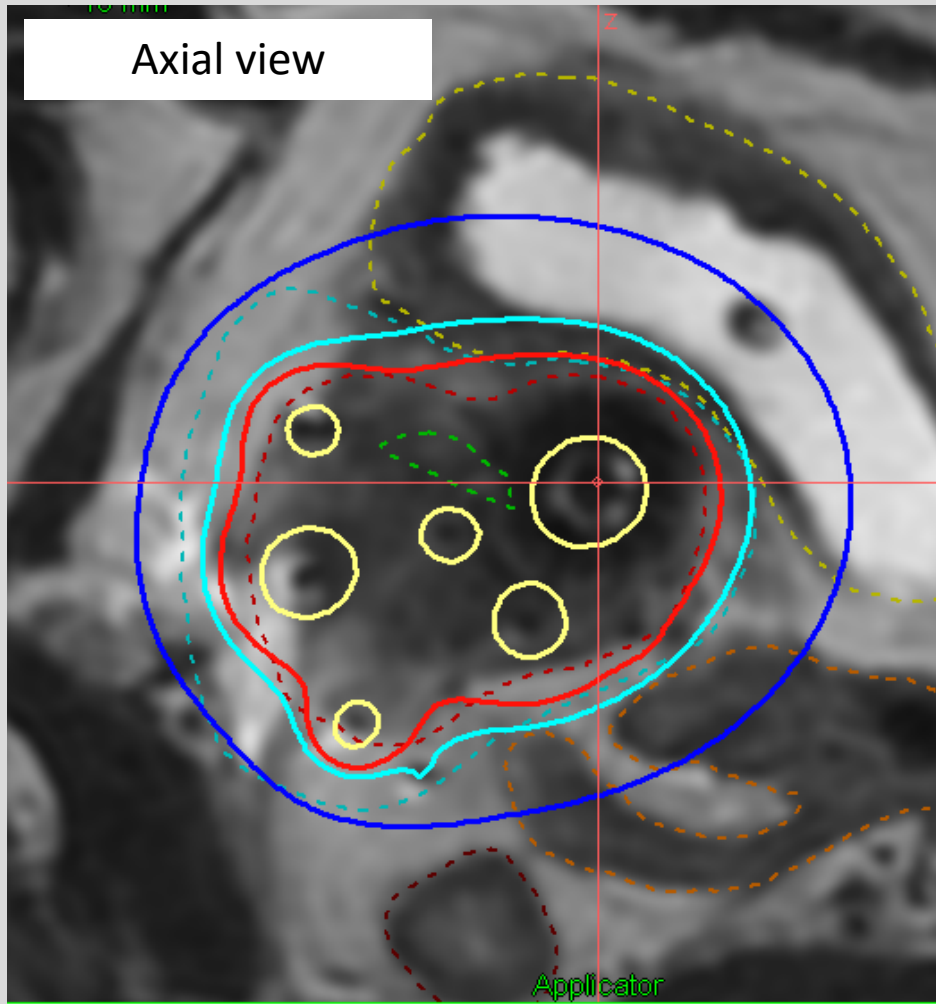
PIBS+2cm

+
PIBS_0cm

+
PIBS_2cm

Applicator

PIBS:Postero-inferior border of pubic symphysis



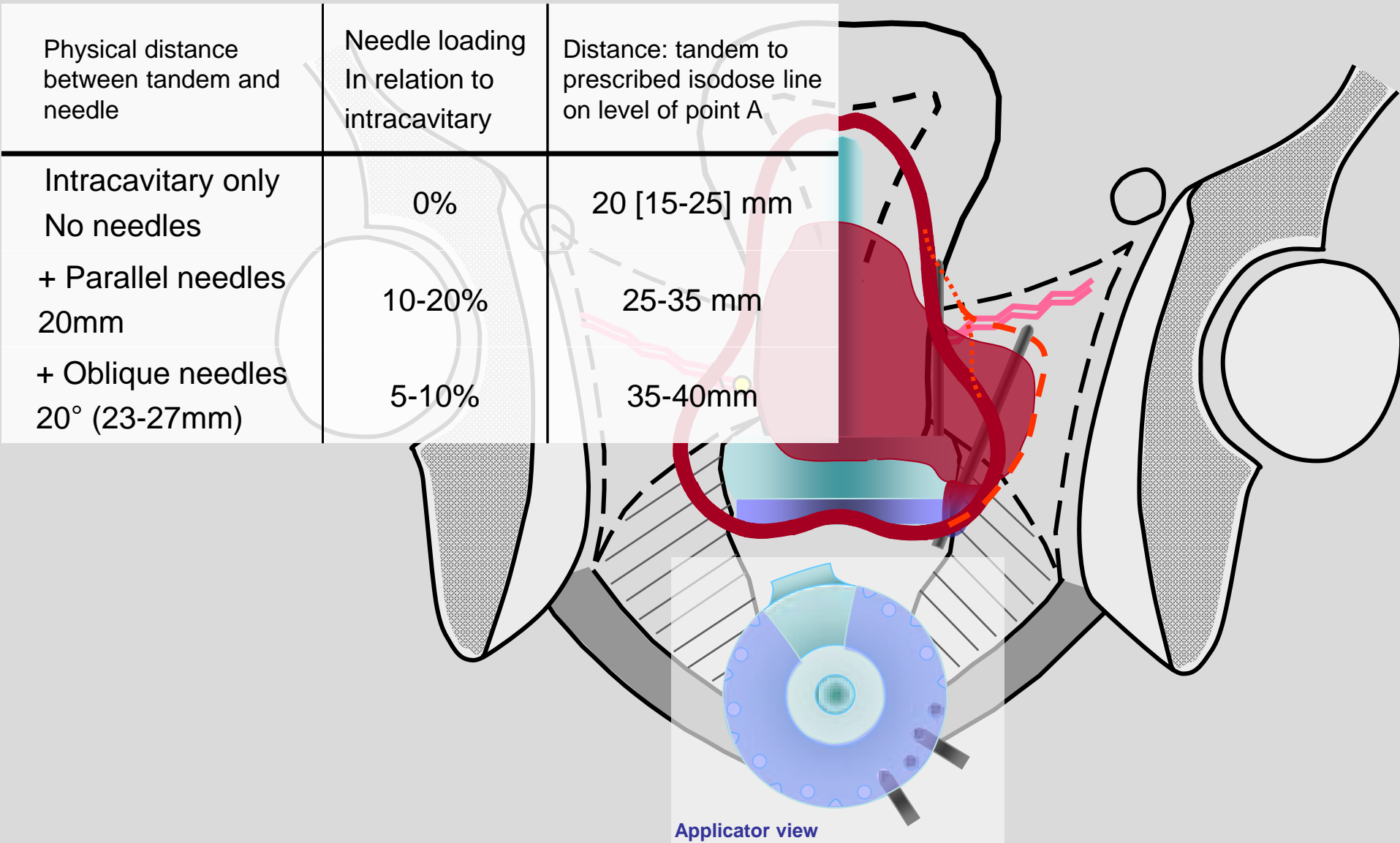
GEC –ESTRO / ICRU (89)

REPORTING OF DOSE VOLUME PARAMETERS

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

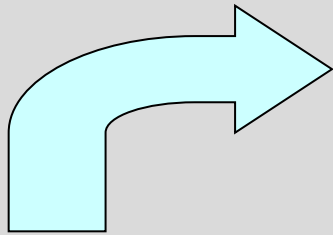
			Planning aim	Prescribed dose
CTV_{HR}	D₉₀	EQD2₁₀	≥ 85 Gy	96.2 Gy
Bladder	D_{2cm³}	EQD2₃	≤ 90 Gy	82.9 Gy
Rectum	D_{2cm³}	EQD2₃	≤ 70 Gy	68.3 Gy
Sigmoid	D_{2cm³}	EQD2₃	≤ 70 Gy	67.4 Gy

Joint Vienna-II project *Vienna and Mumbai*

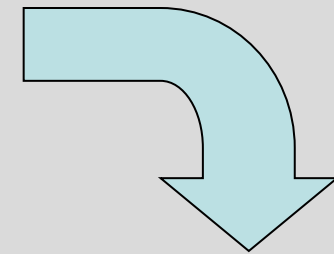
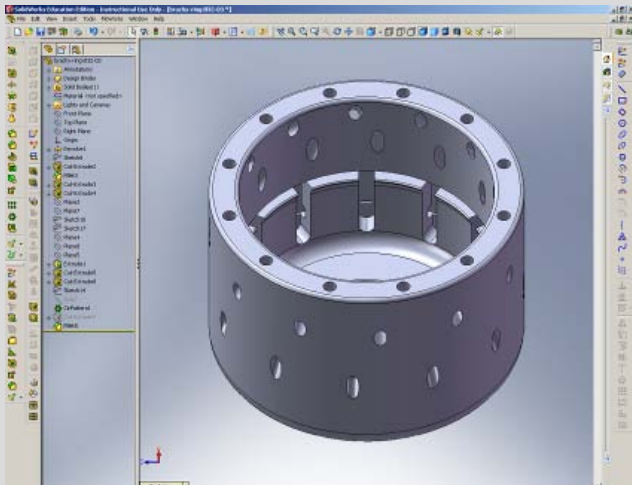


Adaptive BT applicators

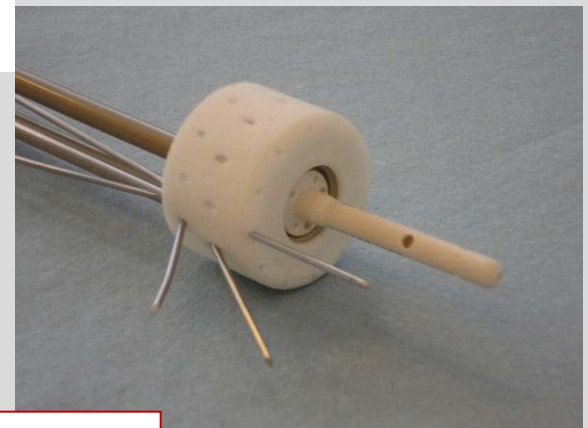
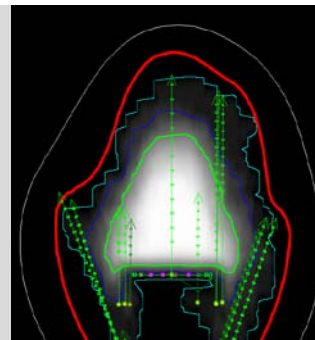
3D Printing



Virtual applicator



New applicator

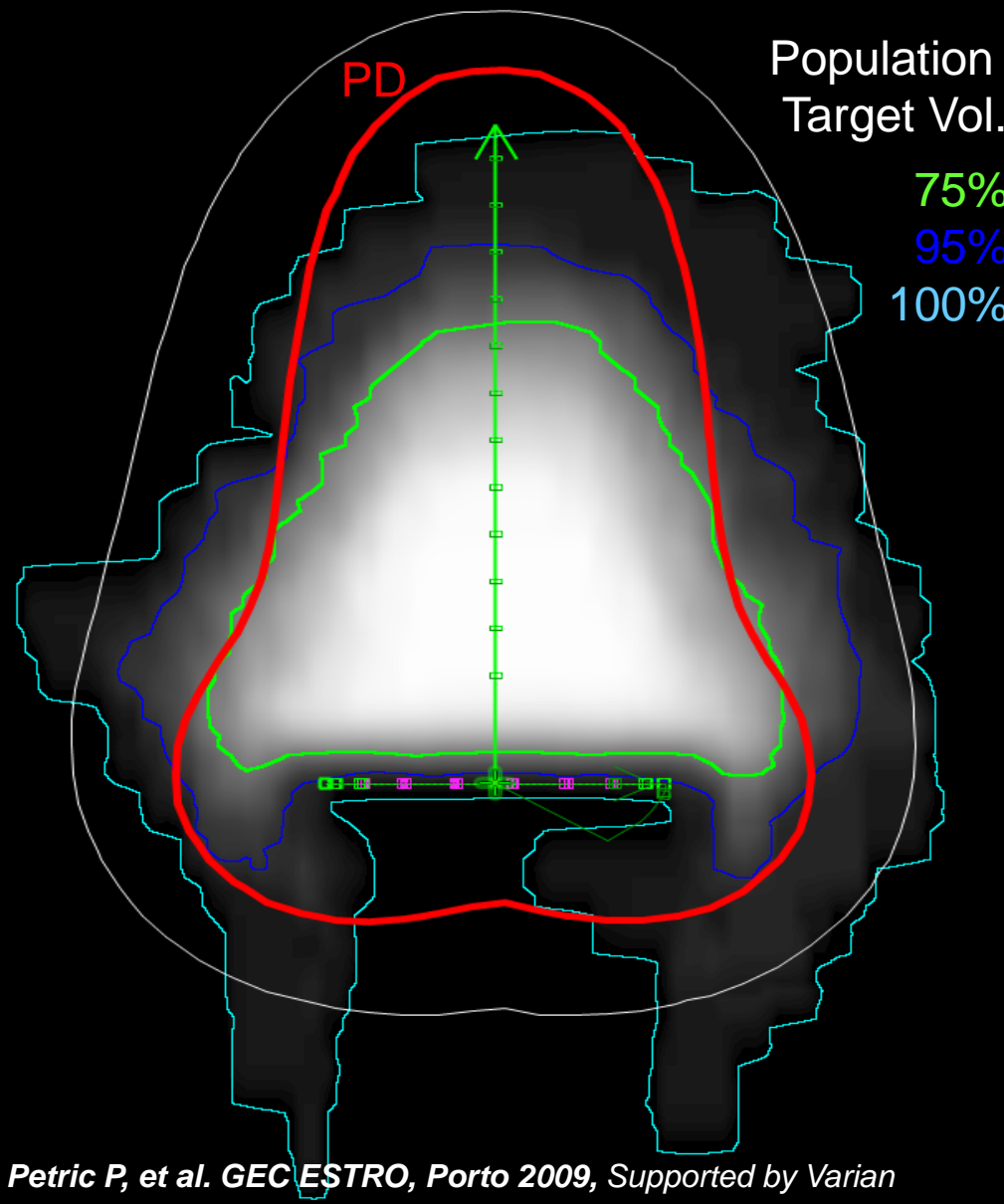
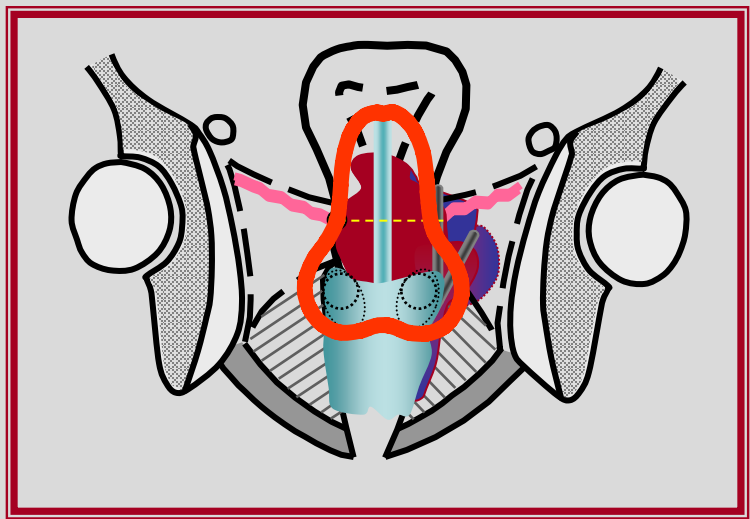
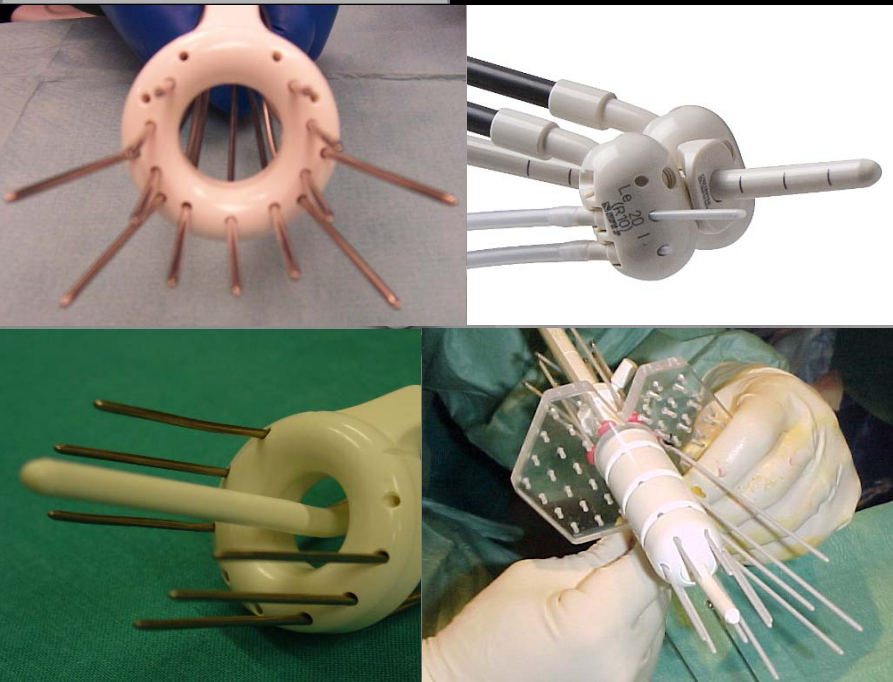


264 patients with tumour mapping Ljubljana, Vienna, Aarhus

Provided by Primoz Petric and Jacob Lindegaard Ljubljana/Aarhus

Mission

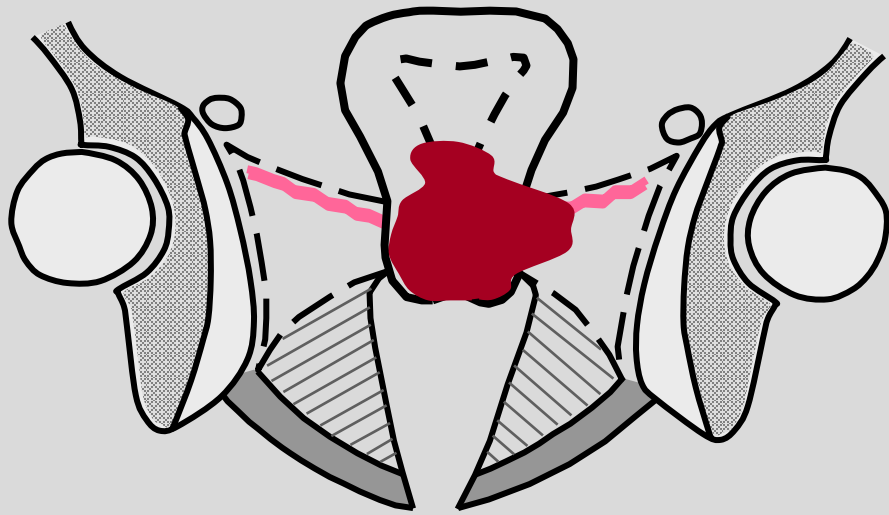
264 patients



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

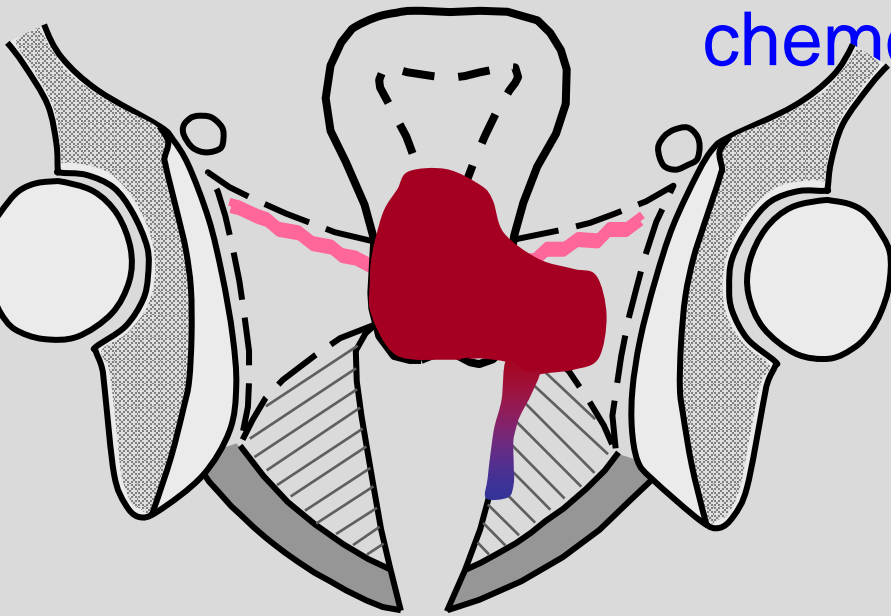
Courtesy: P. Petric, D. Berger

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

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

SUMMARY & CONCLUSIONS

- *Combined 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

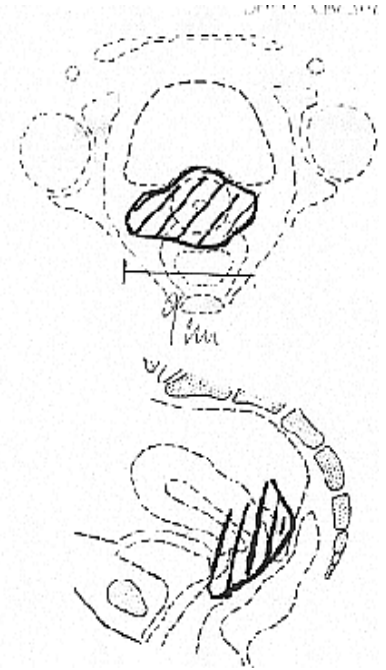
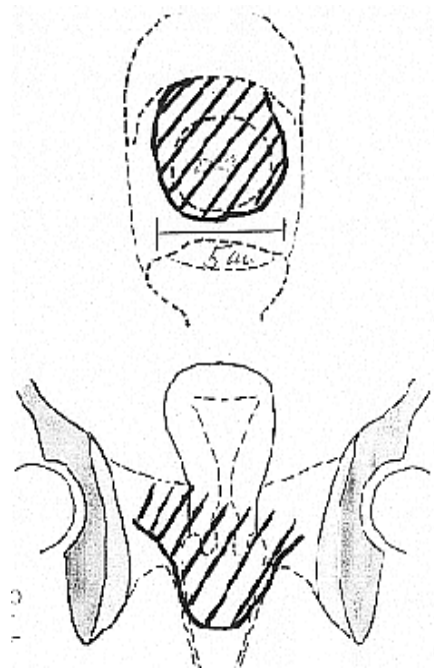
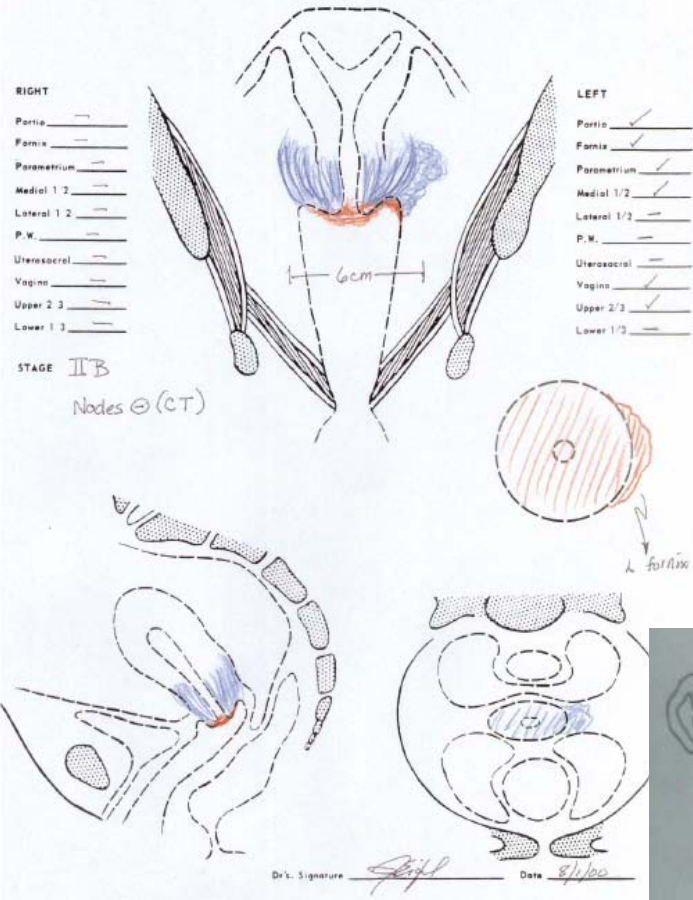
Clinical drawings aid in

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

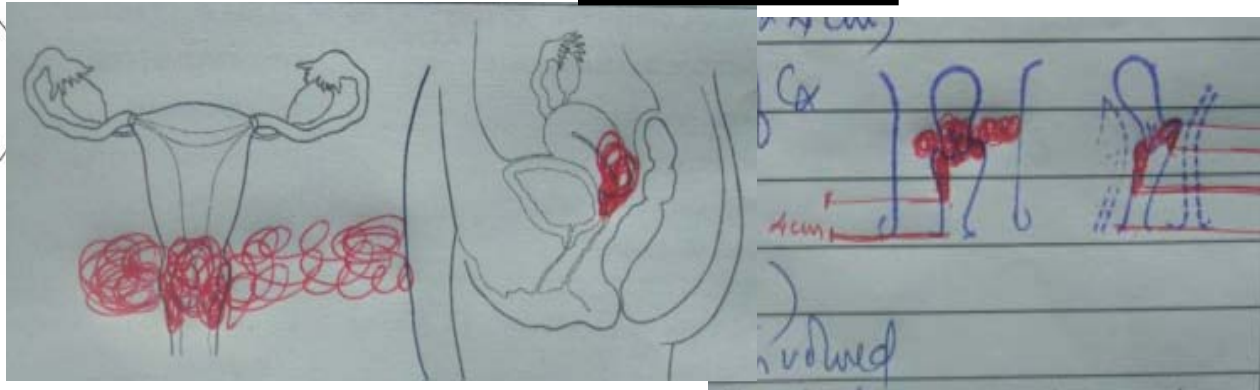
Clinical drawings

Vienna

Eifel-Levenback (ed)
Atlas of clinical oncology 2001



TMH, Mumbai

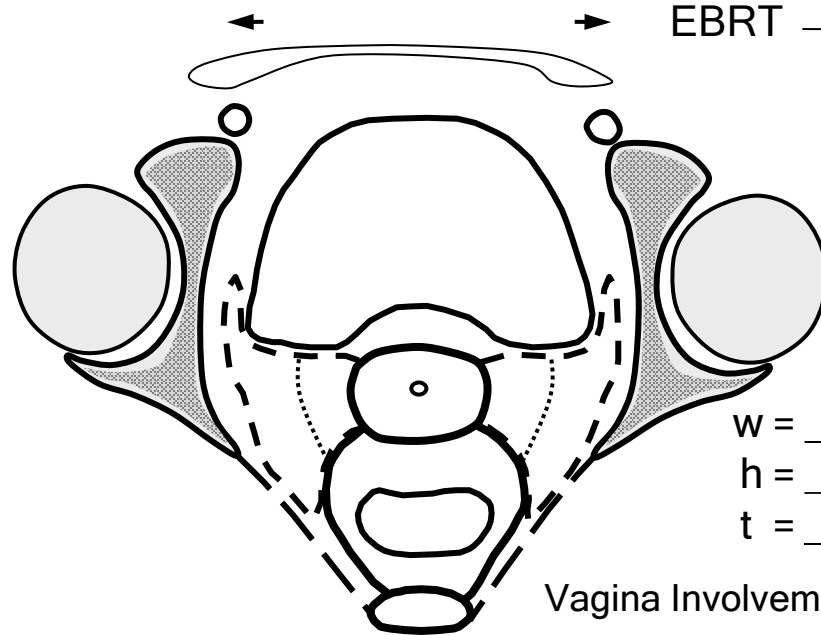
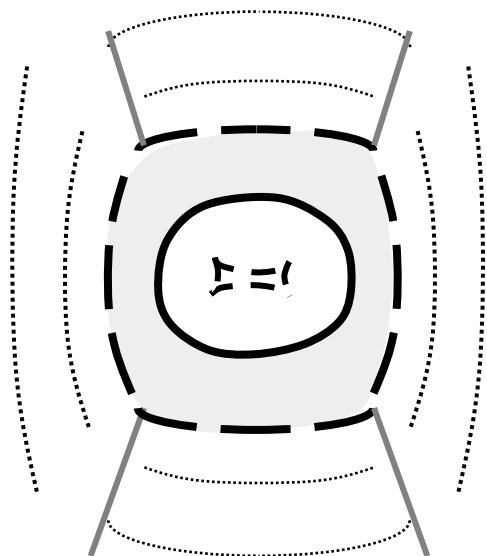


Clinical Mapping of disease extent: Critical for Image based brachytherapy practice

Patient : ABC

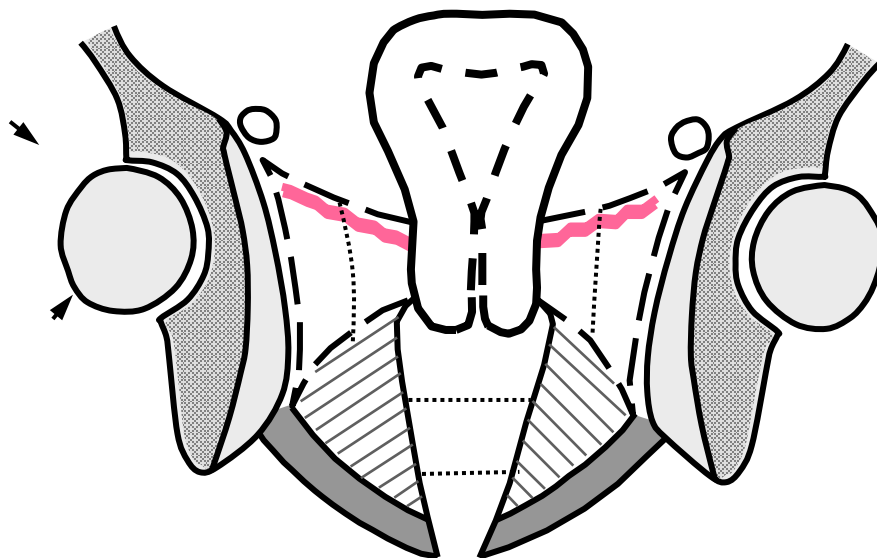
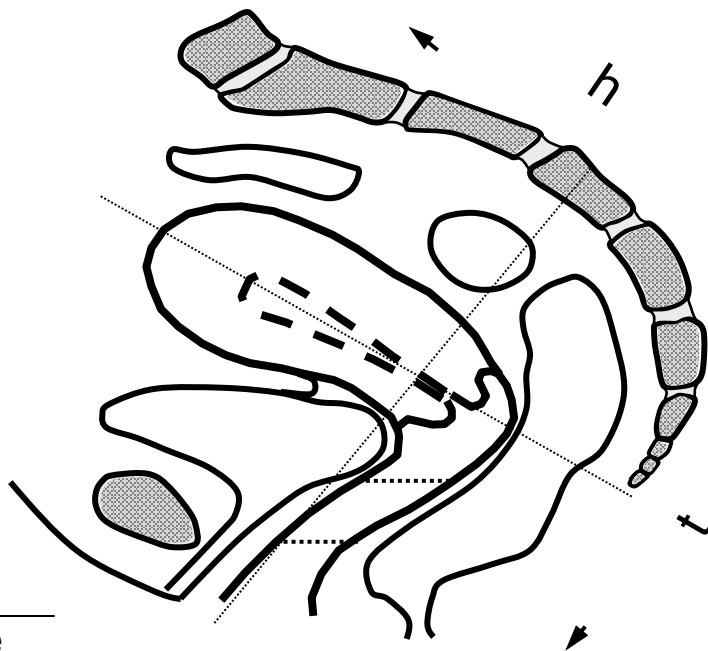
Clinical Drawing

At Diagnosis
At Brachytherapy
EBRT Gy



w = ___ cm
h = ___ cm
t = ___ cm

Vagina Involvement
= ___ cm



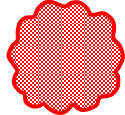
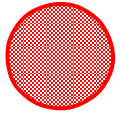
dd/mm/yy
/ /

Signature

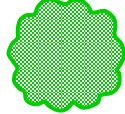
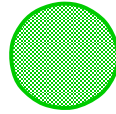
Legend: Option 1

Infiltrative Exophytic

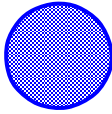
Cervix



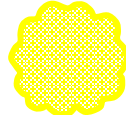
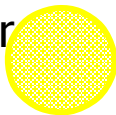
Vagina



Parametria



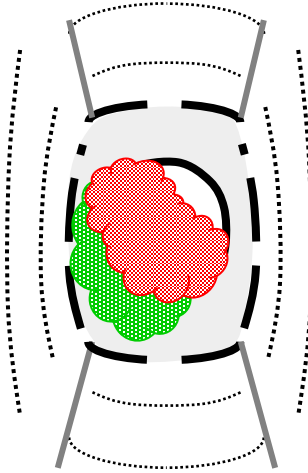
Rectum or Bladder



At Diagnosis



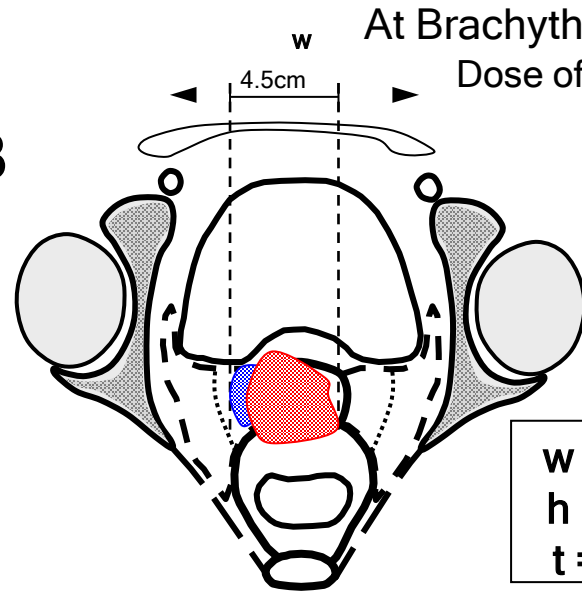
IIB



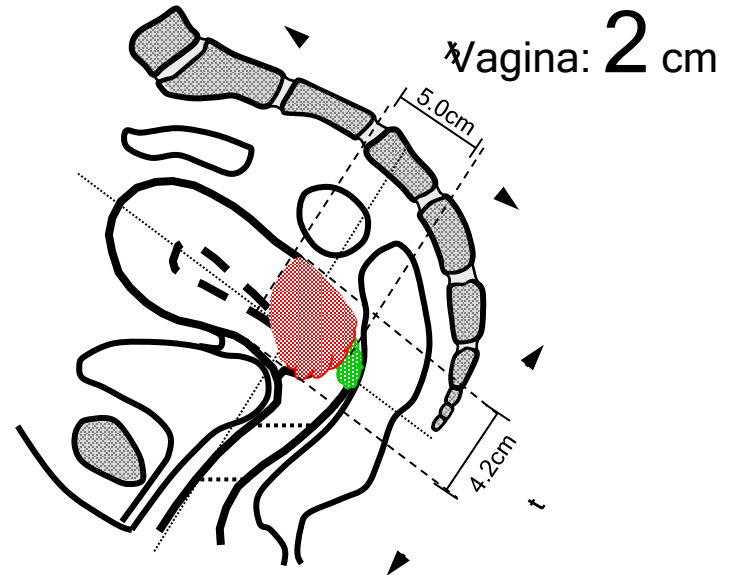
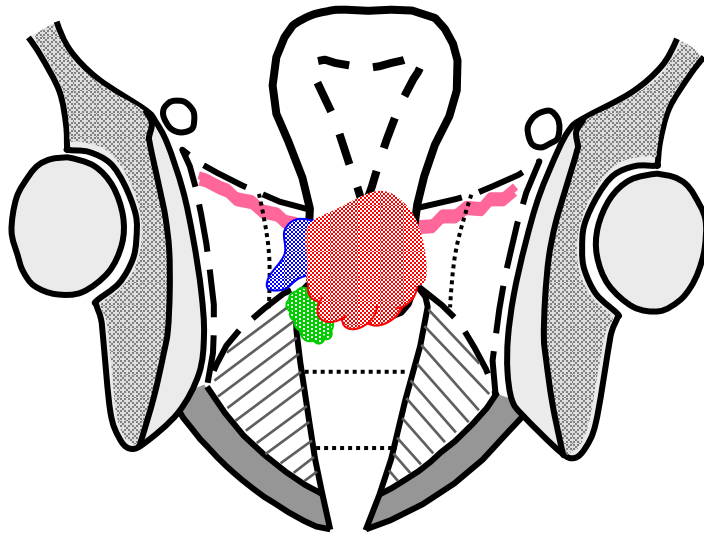
At Brachytherapy



Dose of EBRT Gy



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



dd/mm/yy

____/____/____







Signature

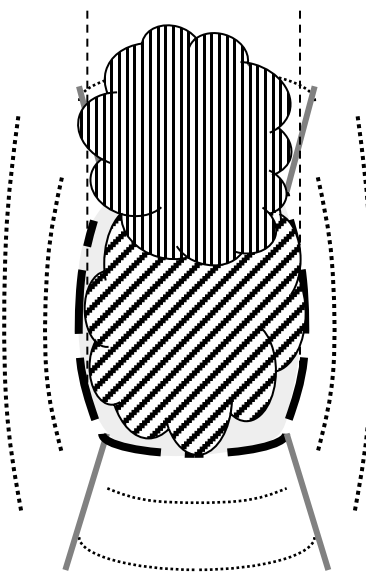
Legend: Option 2

At Diagnosis

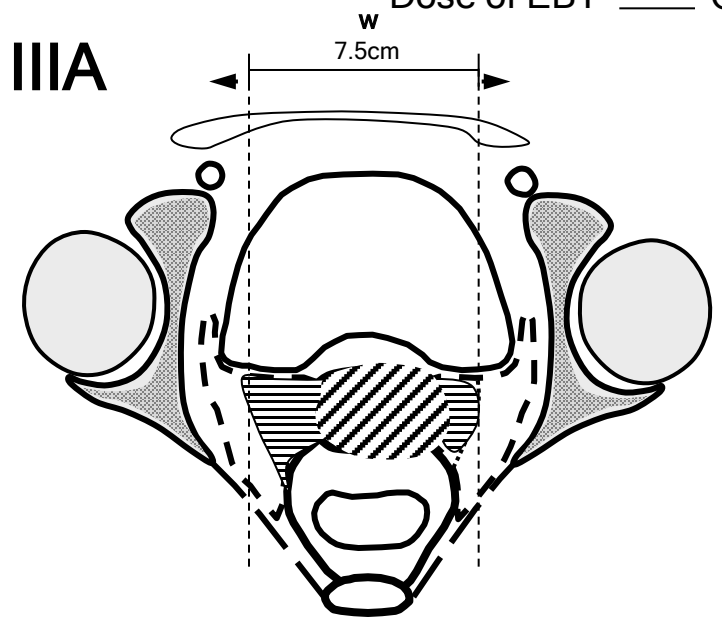
At Brachytherapy

Dose of EBT ____ Gy

-  or  Cervix
-  Vagina
-  Parametria
-  Rectum or Bladder Infiltration
-  Exophytic



IIIA

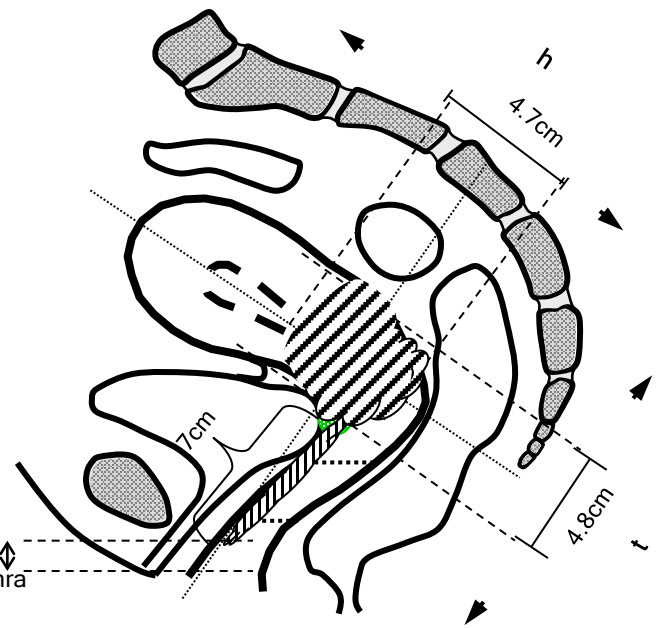
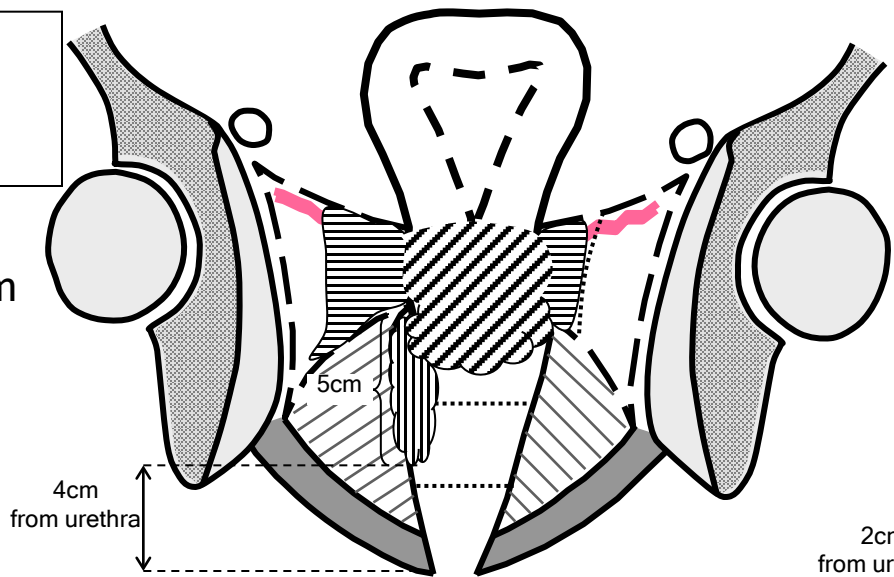


w = 7.5 cm
h = 4.7 cm
t = 4.8 cm

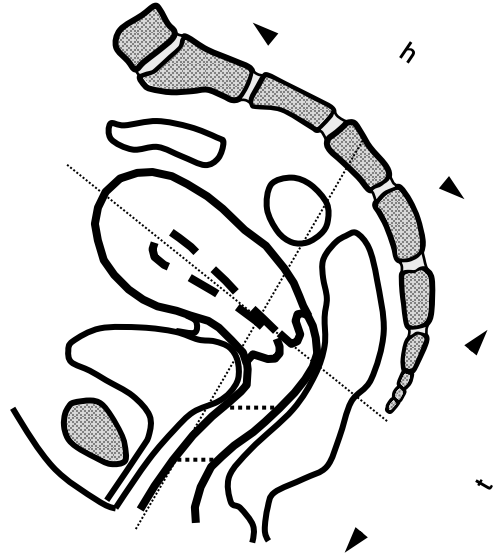
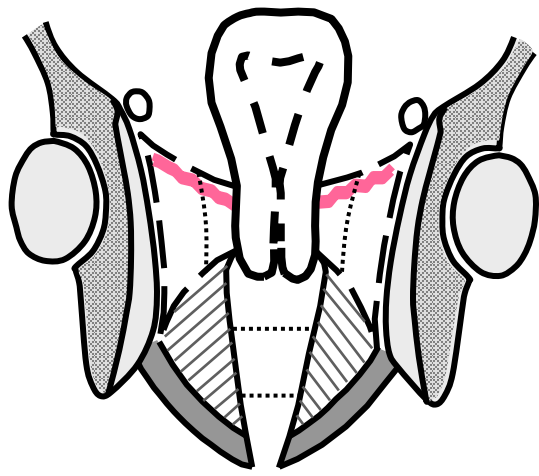
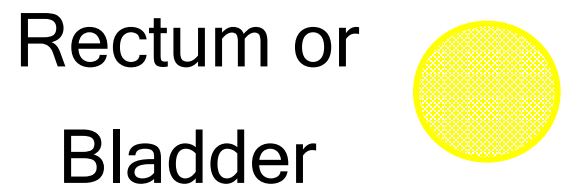
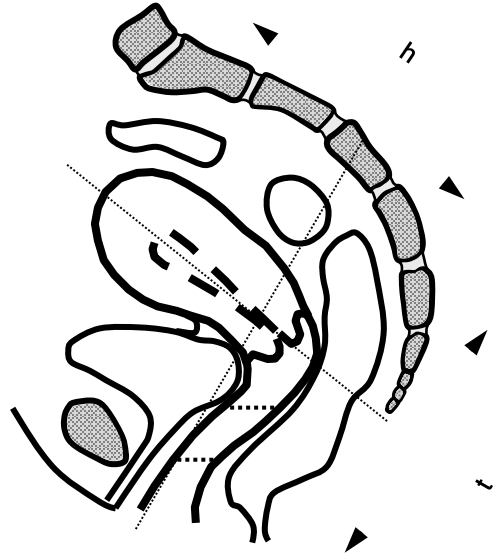
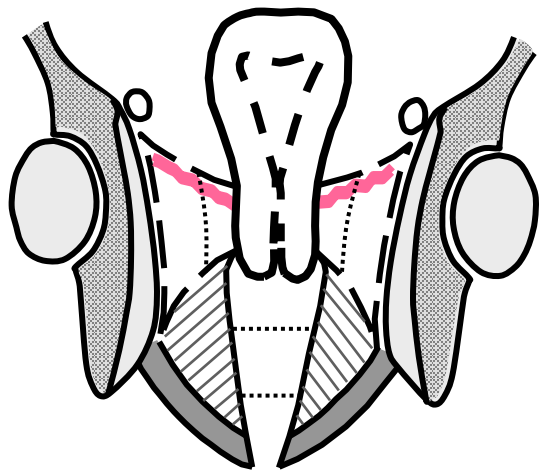
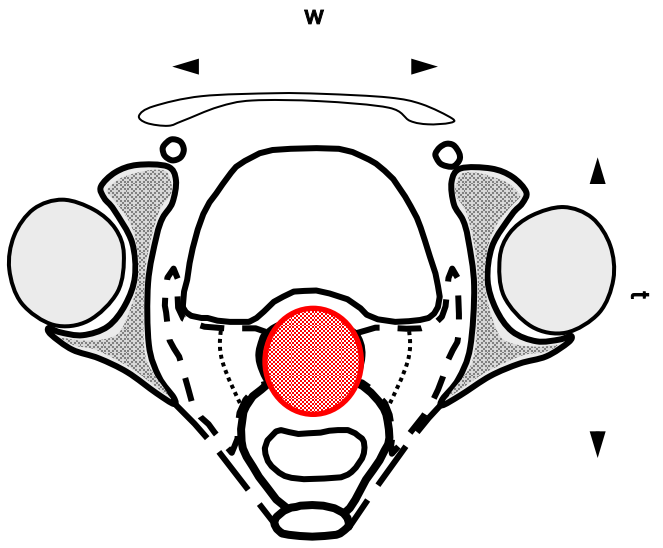
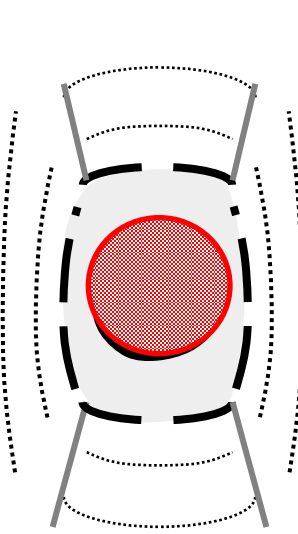
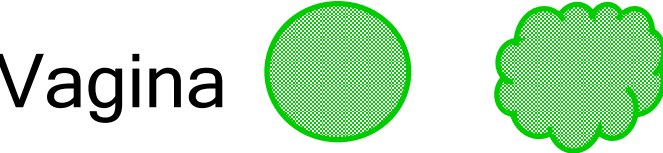
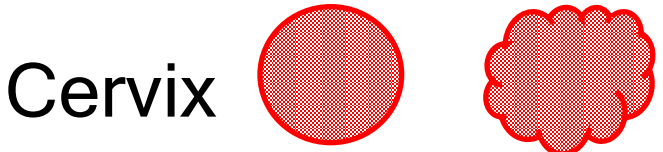
Vagina: 7 cm

dd/mm/yy
/ /

Signature



Option 3: Copy and Paste



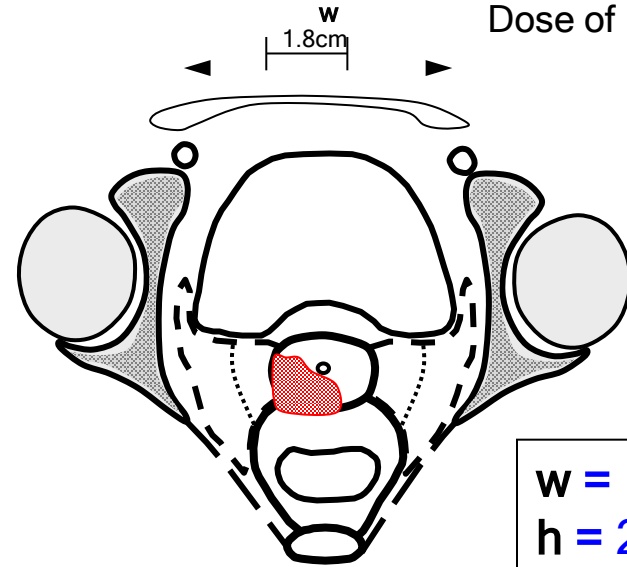
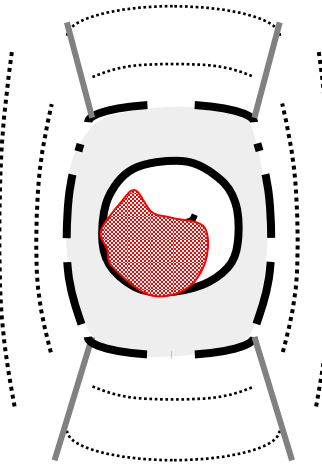
At Diagnosis

IB1

At Brachytherapy

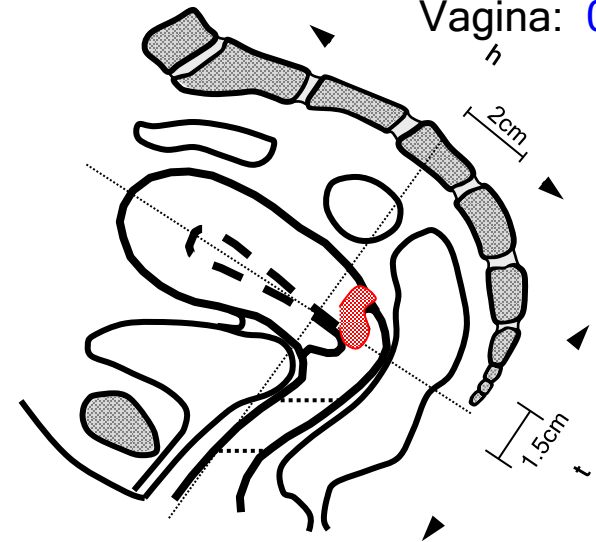
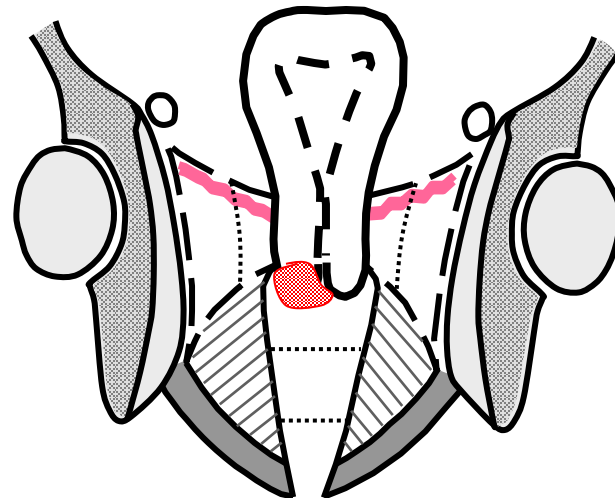
Dose of EBRT Gy

- 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
h



dd/mm/yy

/ /

Signature

At Diagnosis

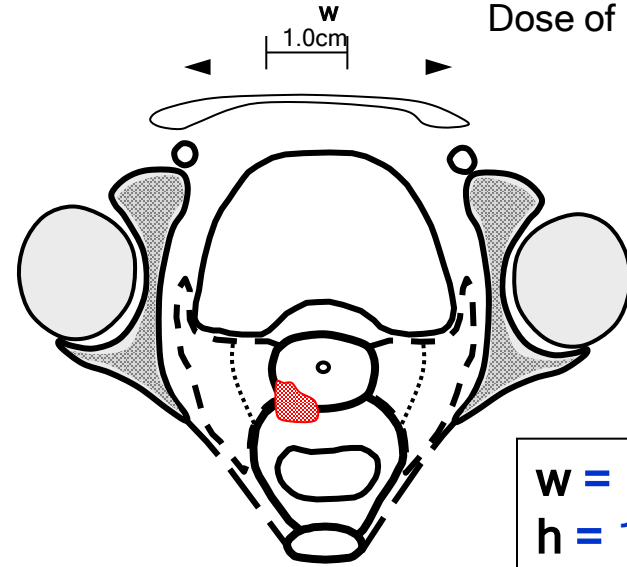
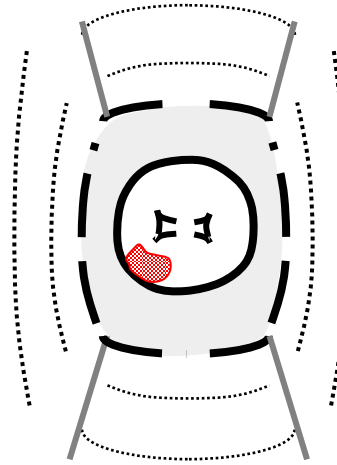
IB1

At Brachytherapy

Dose of EBRT Gy

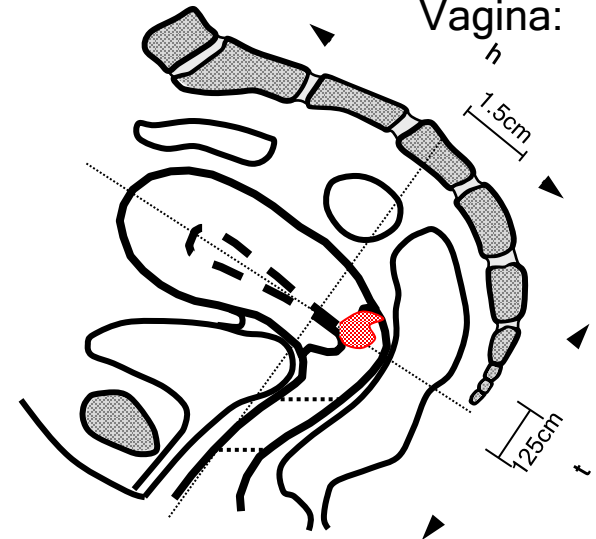
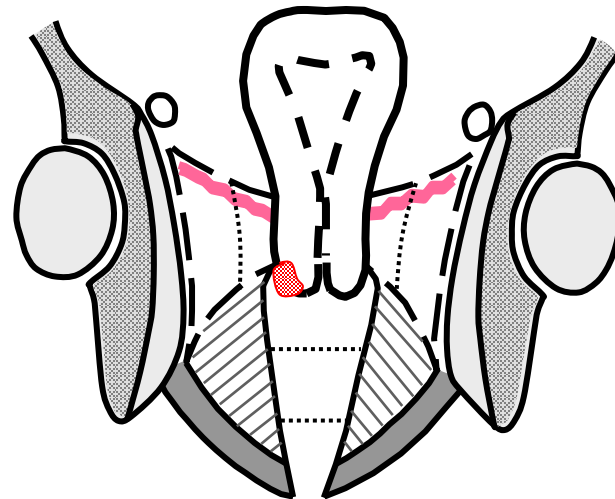
Good response

- 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

/ /

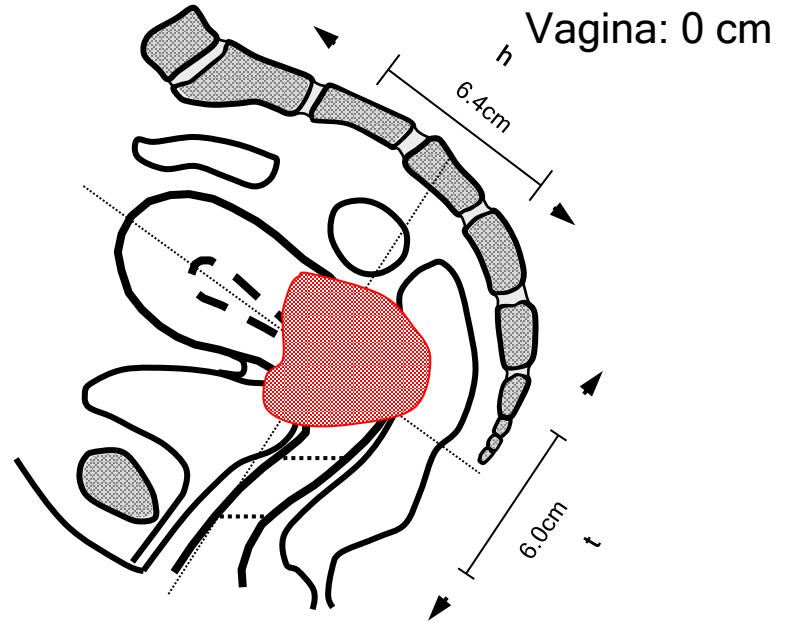
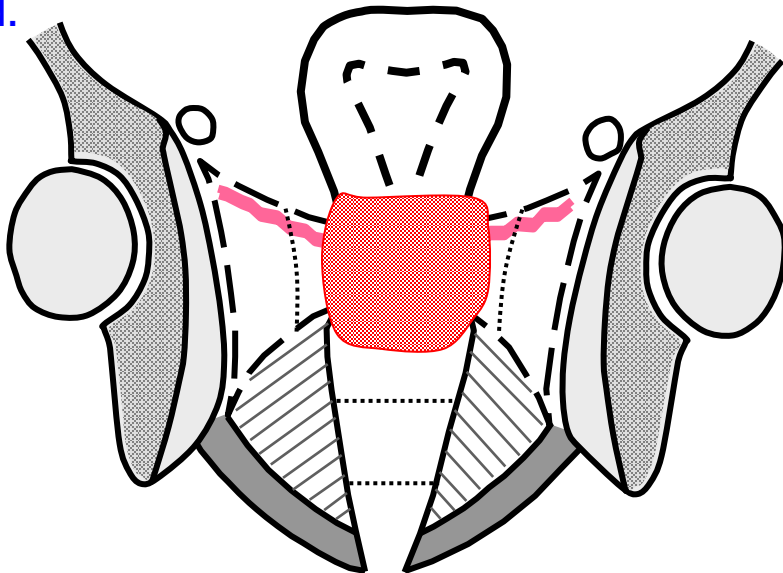
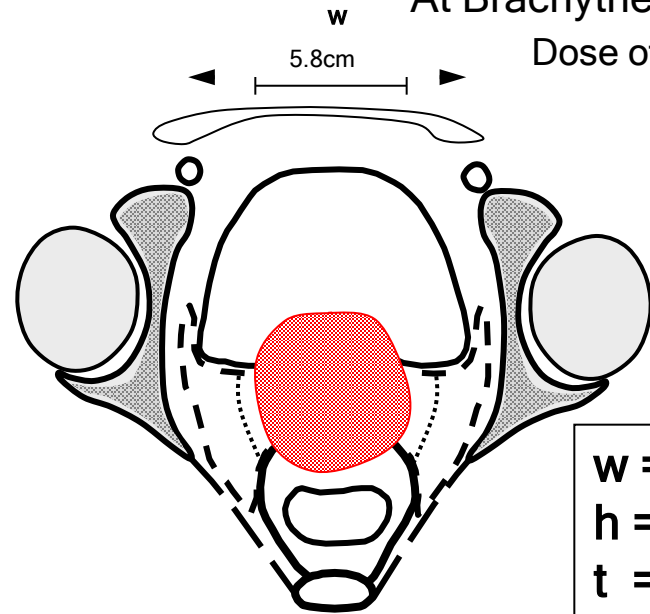
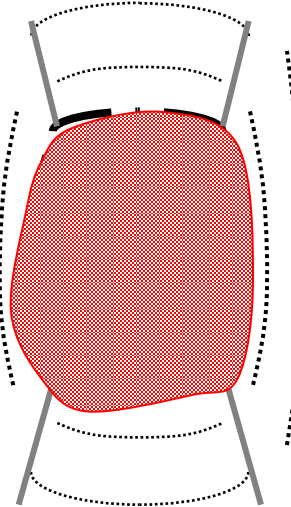
Signature

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.



dd/mm/yy

/ /

Signature

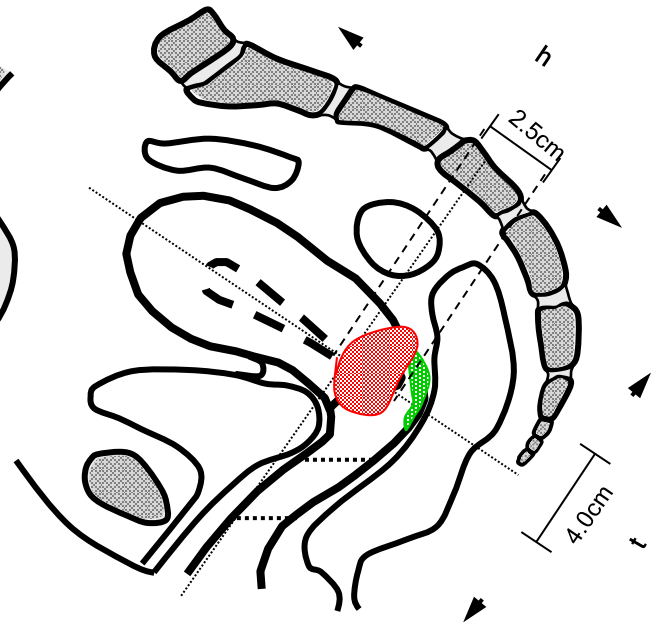
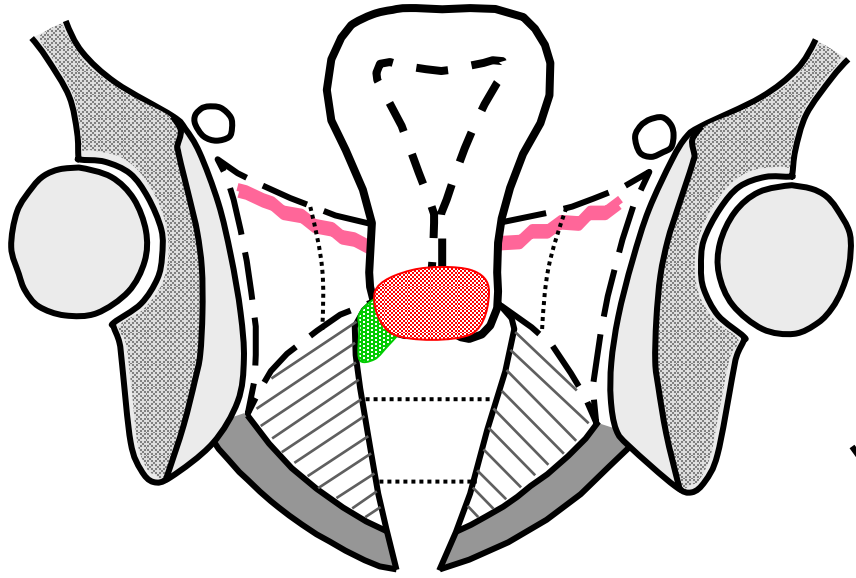
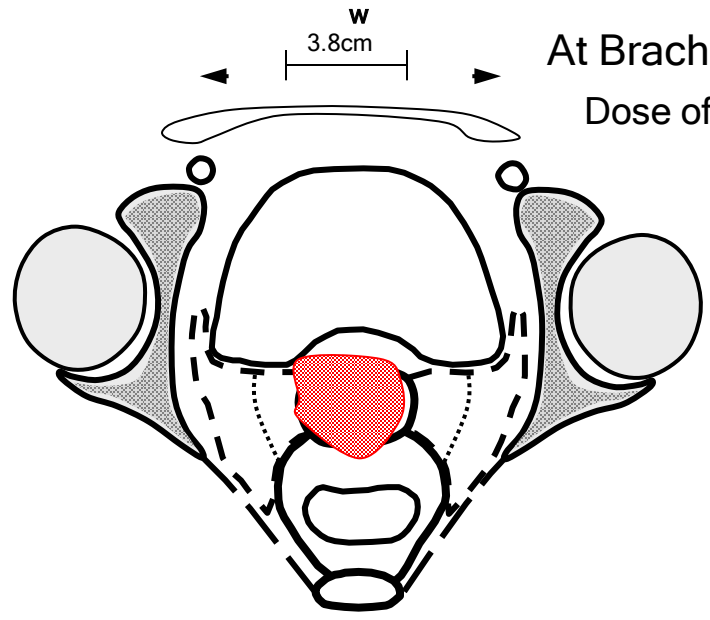
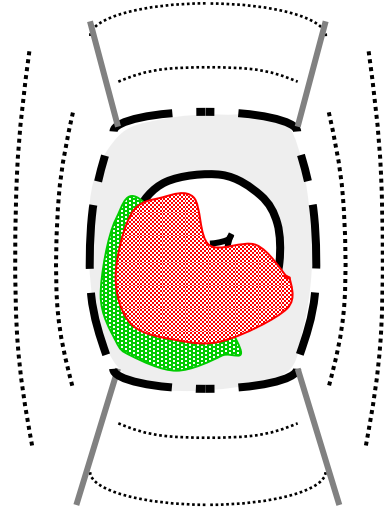
At Diagnosis

At Brachytherapy
Dose of EBRT _____ Gy

IIA

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

Vagina: 1.5 cm



dd/mm/yy
/ /

Signature

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

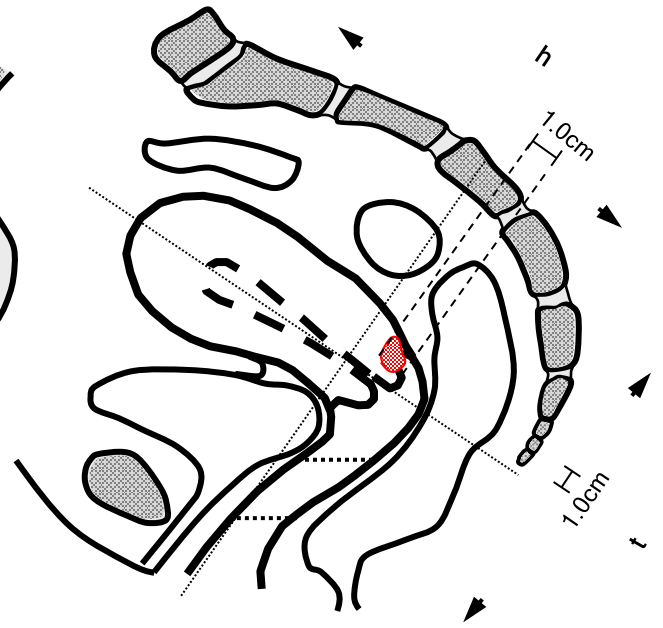
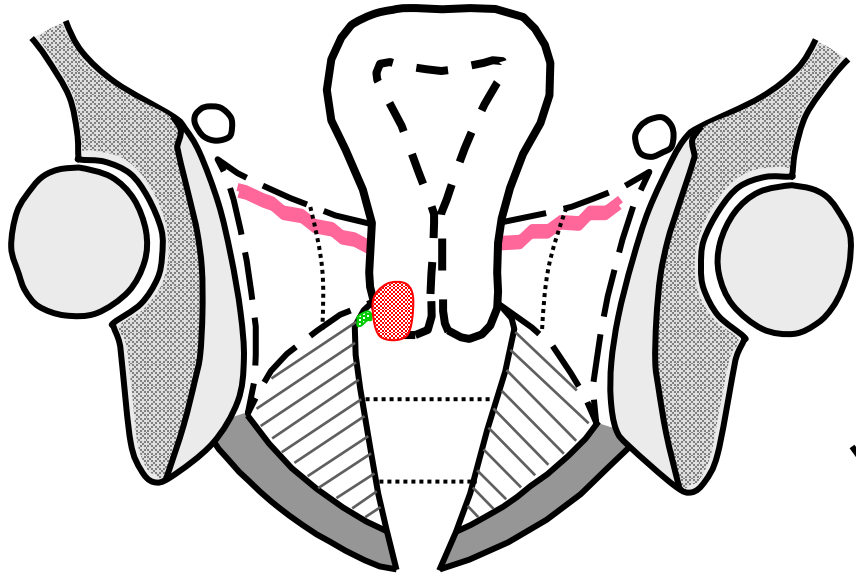
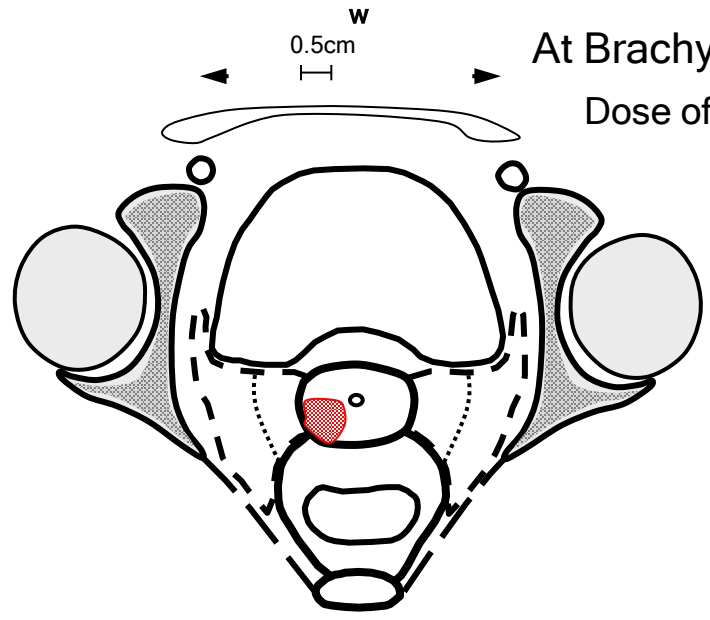
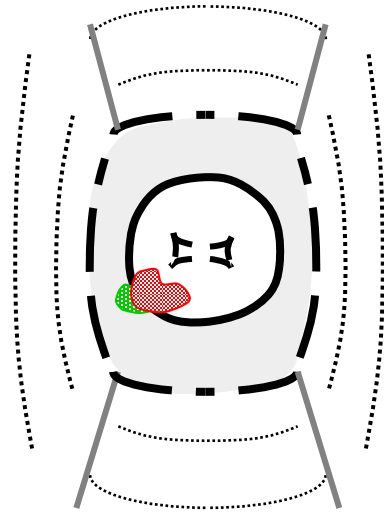
At Diagnosis

At Brachytherapy
Dose of EBRT 45 Gy

IIA

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

Vagina: 0.3 cm



dd/mm/yy
/ /

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

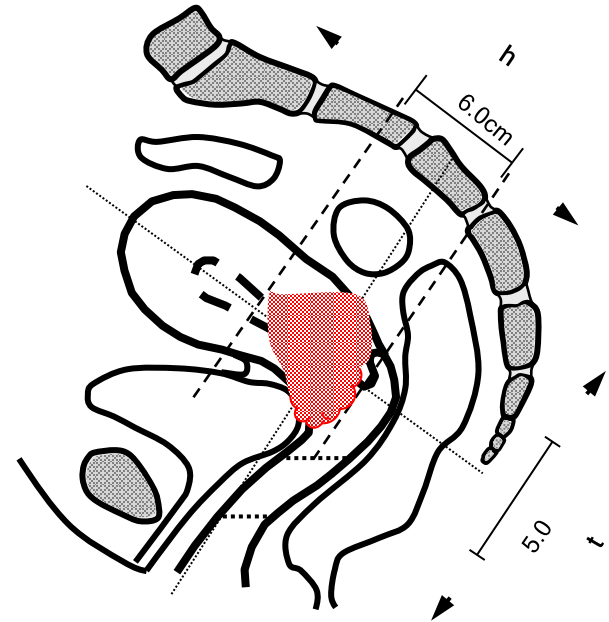
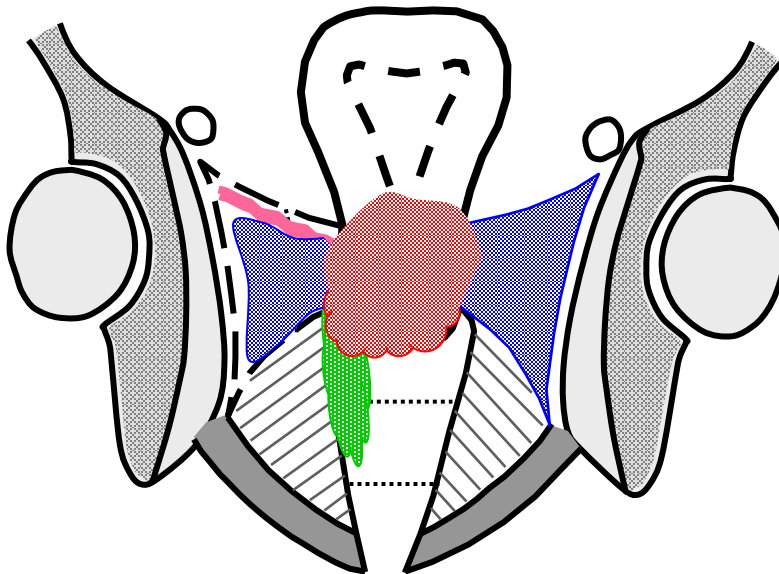
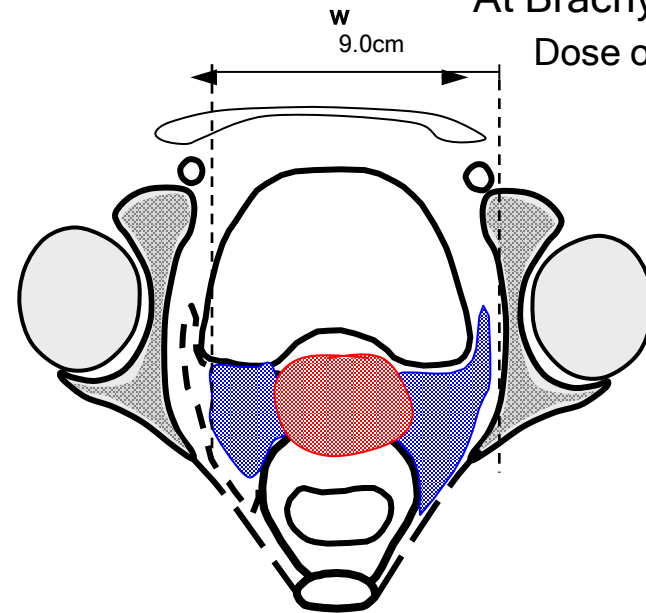
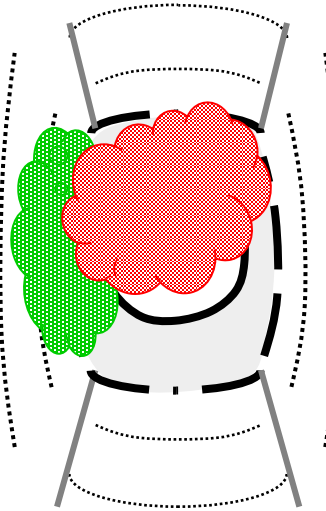
IIIB

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

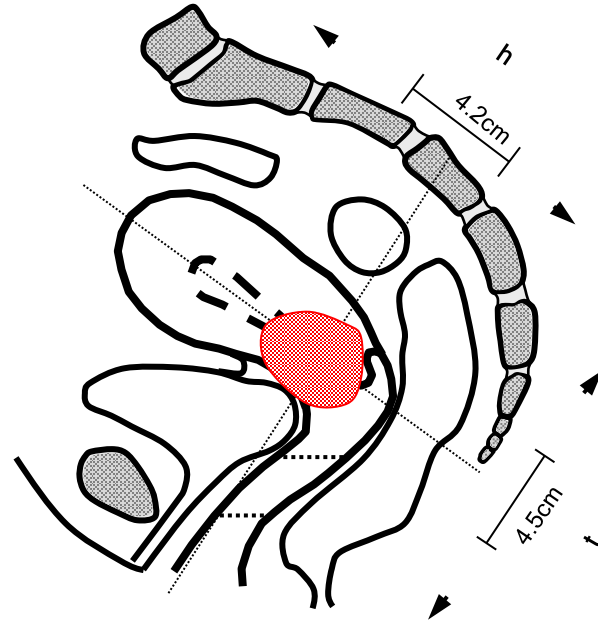
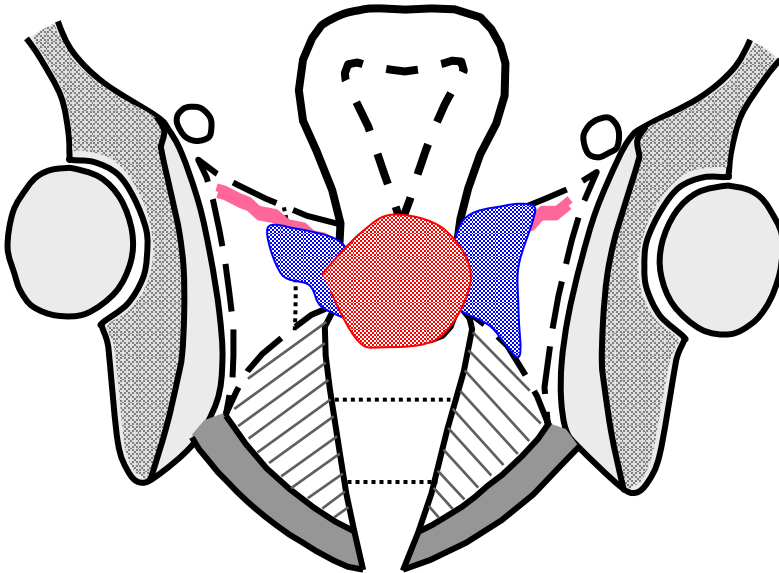
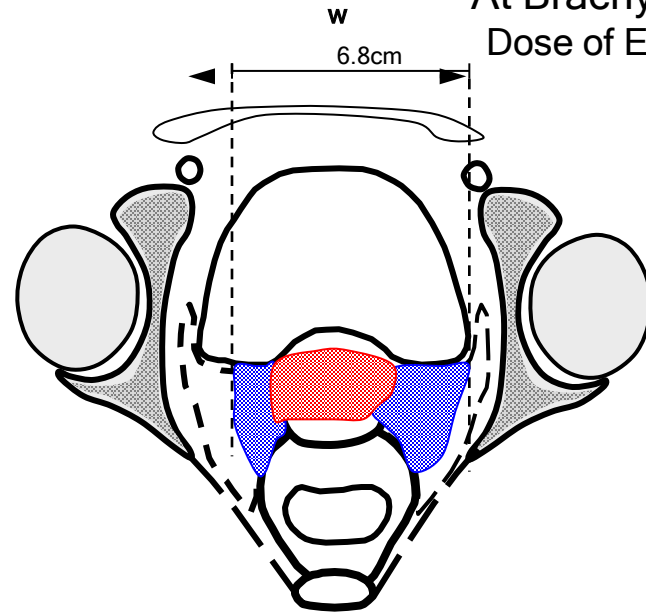
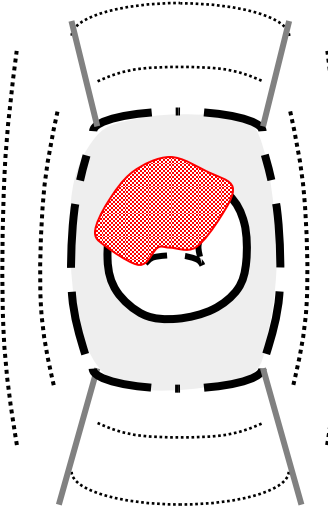
At Diagnosis

At Brachytherapy
Dose of EBRT 50.4 Gy

IIIB

$w = 6.8 \text{ cm}$
 $h = 4.2 \text{ cm}$
 $t = 4.5 \text{ cm}$

Vagina: 0 cm



dd/mm/yy

/ /

Signature

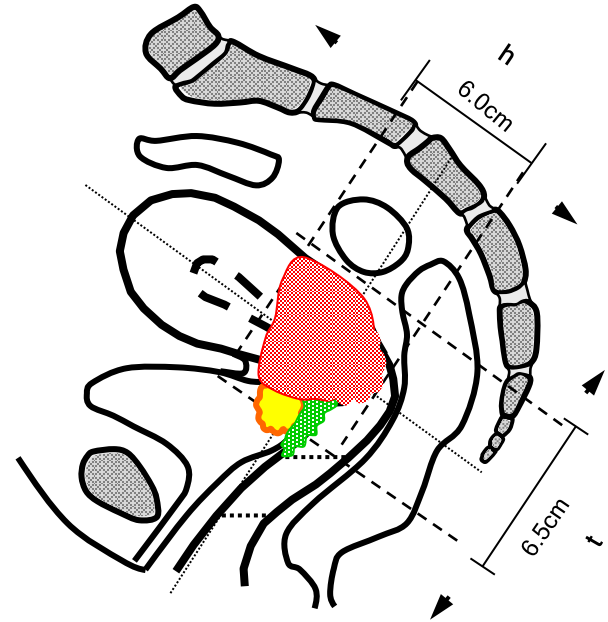
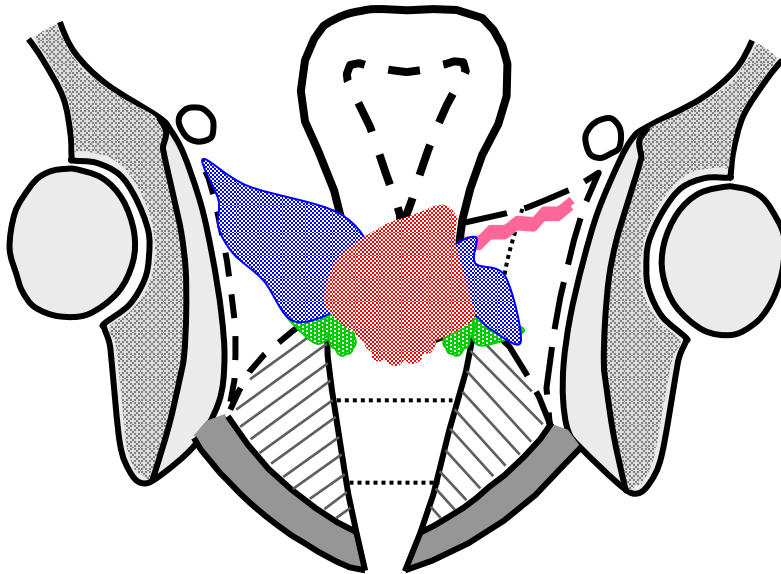
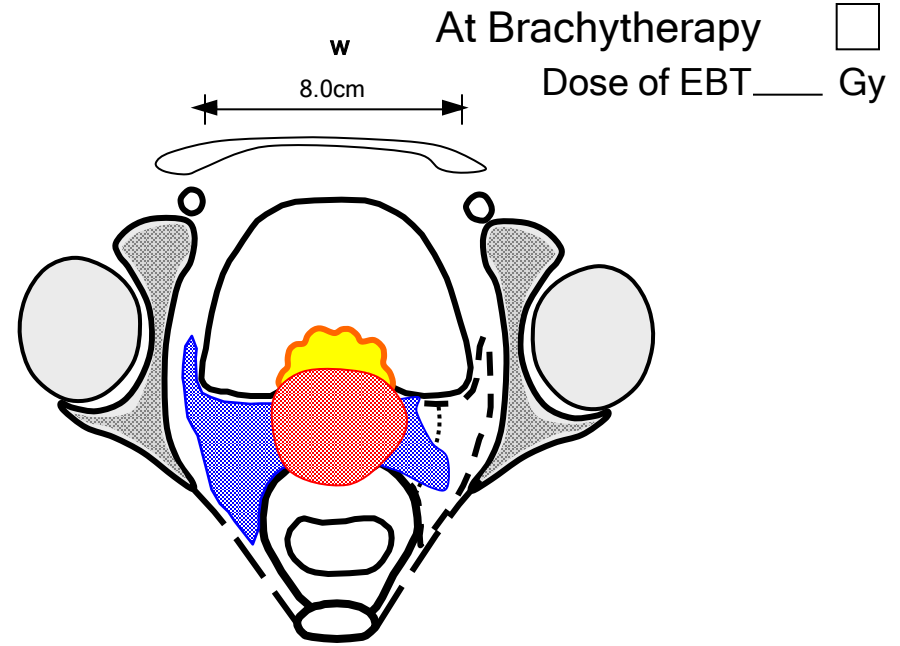
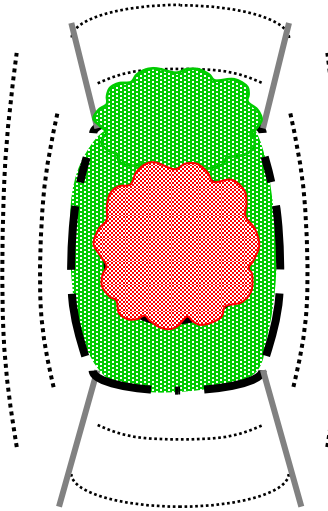
Note: parametria **not** included in h.

At Diagnosis

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

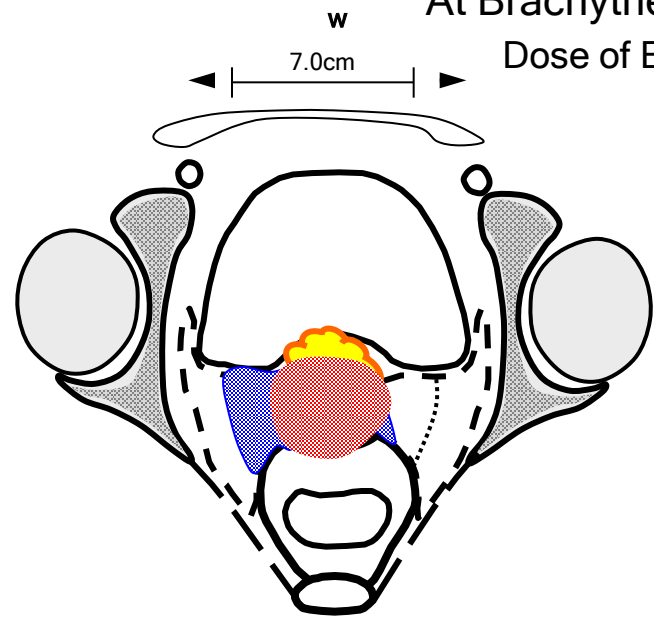
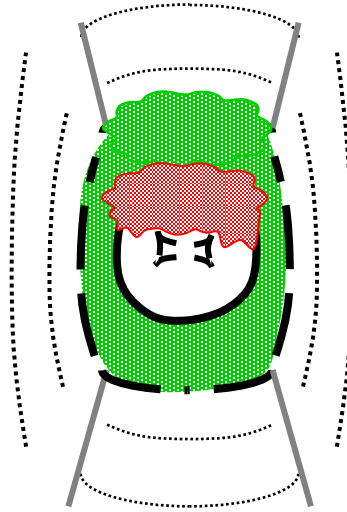
IVA - Bladder

w = 7.0 cm

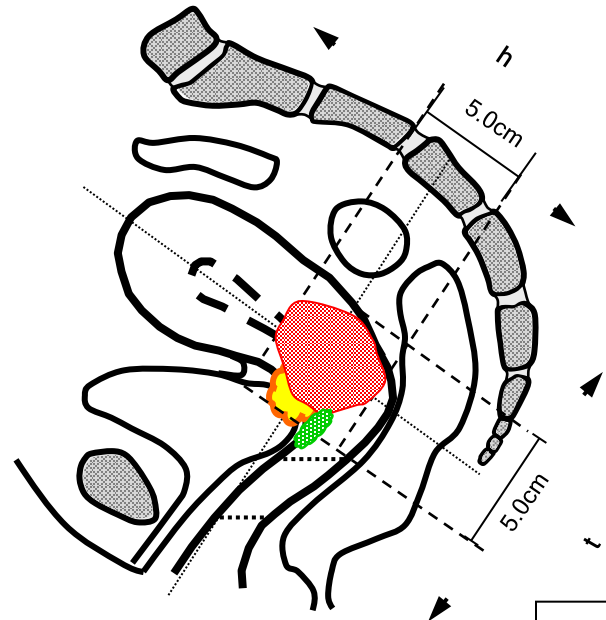
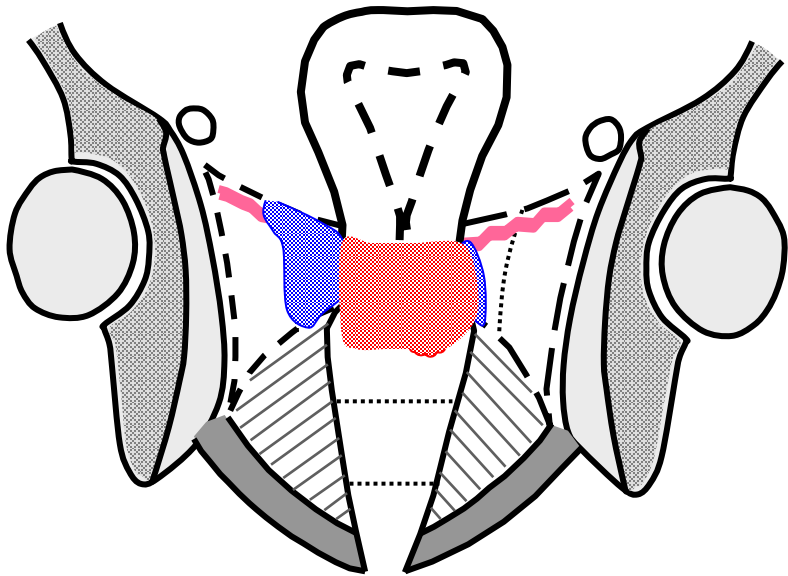
h = 5.0 cm

t = 5.0 cm

Vagina: 2.5 cm



Dose of EBRT 45 Gy



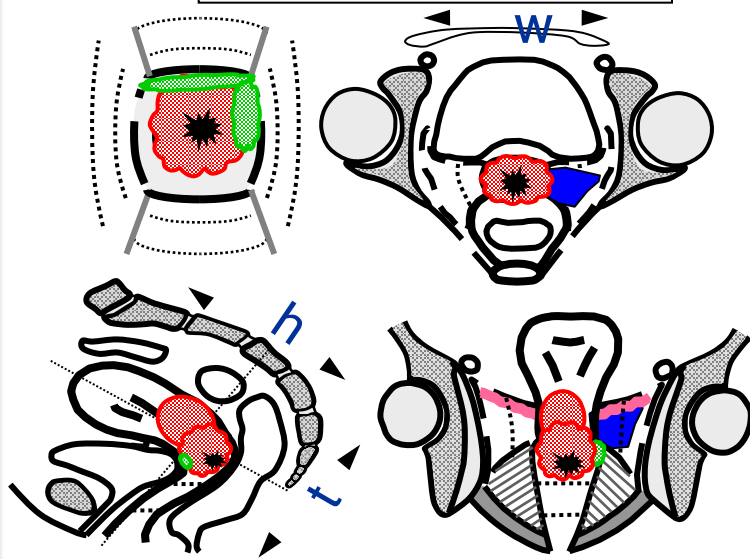
dd/mm/yy

/ /

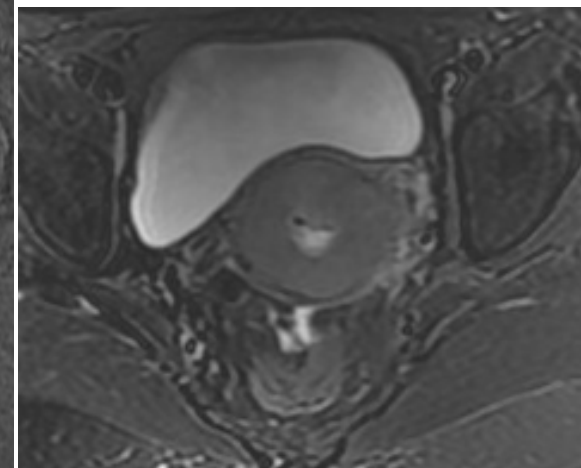
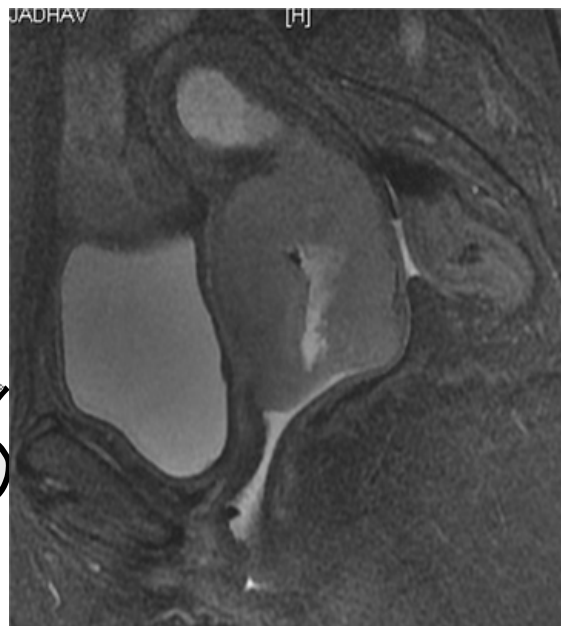
Signature

Case V

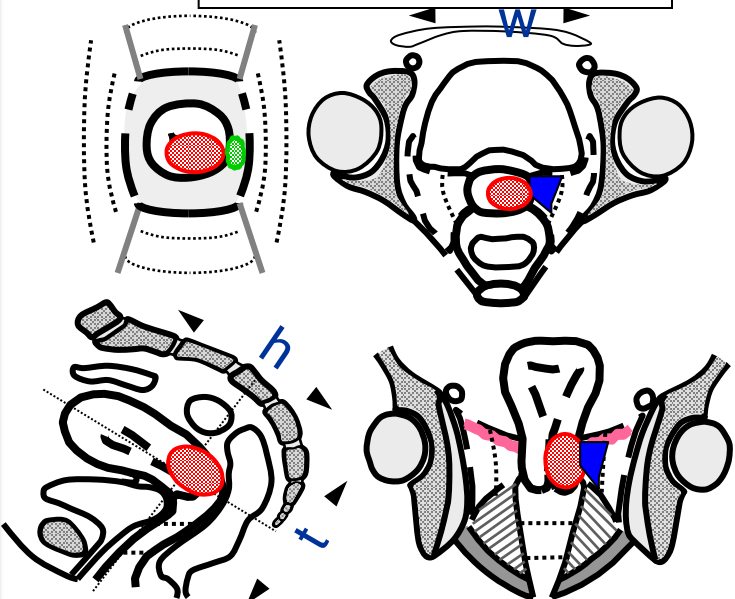
Clinical Drawing



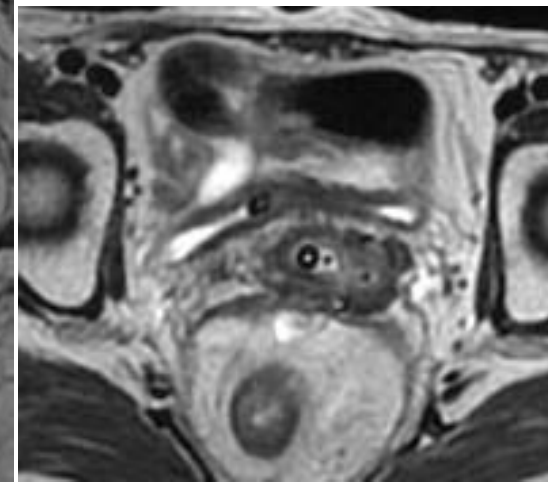
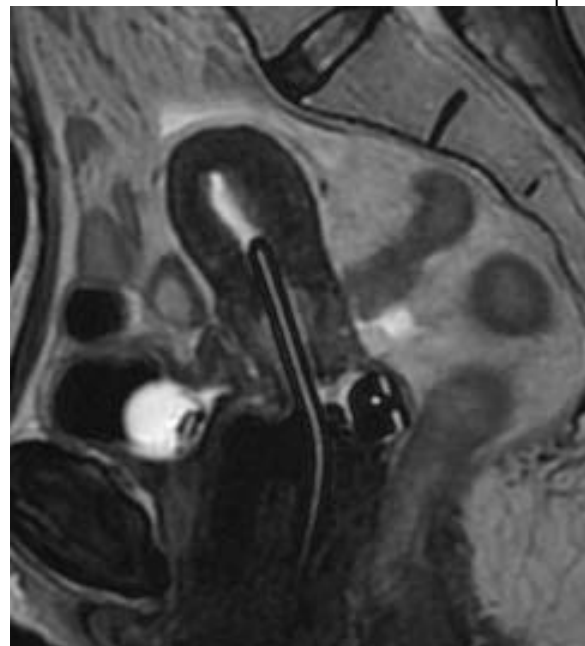
MR at Diagnosis



Clinical Drawing

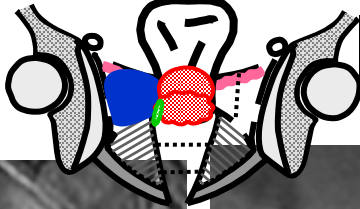


MR at Brachytherapy



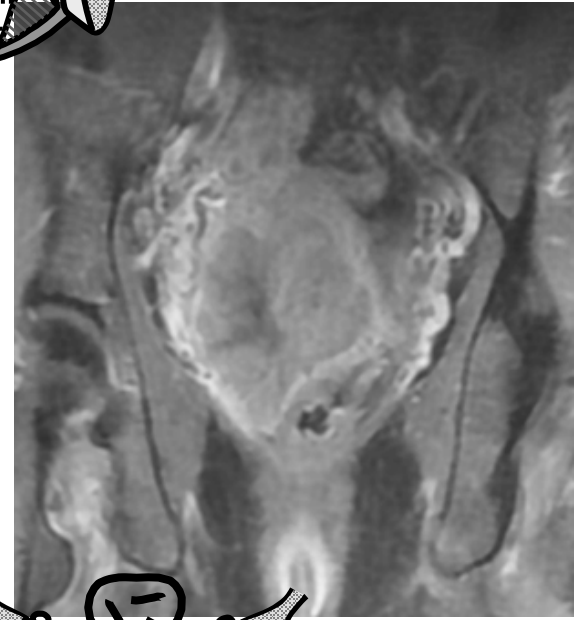
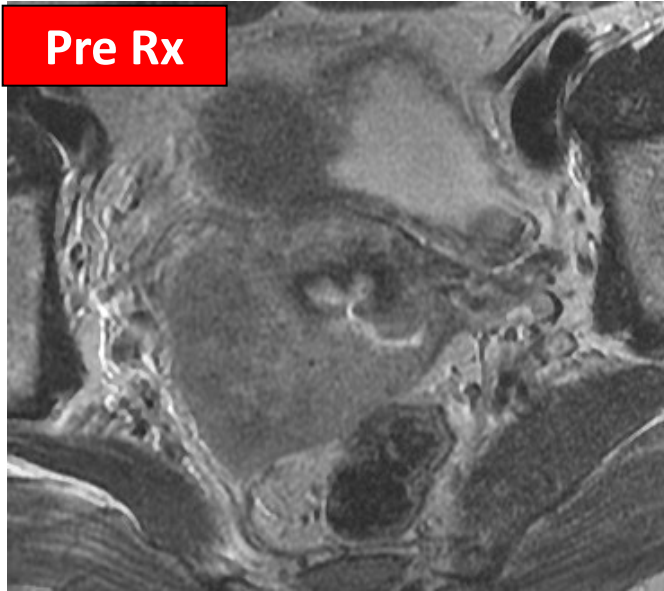
Axial

Sag

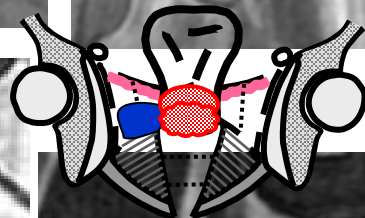
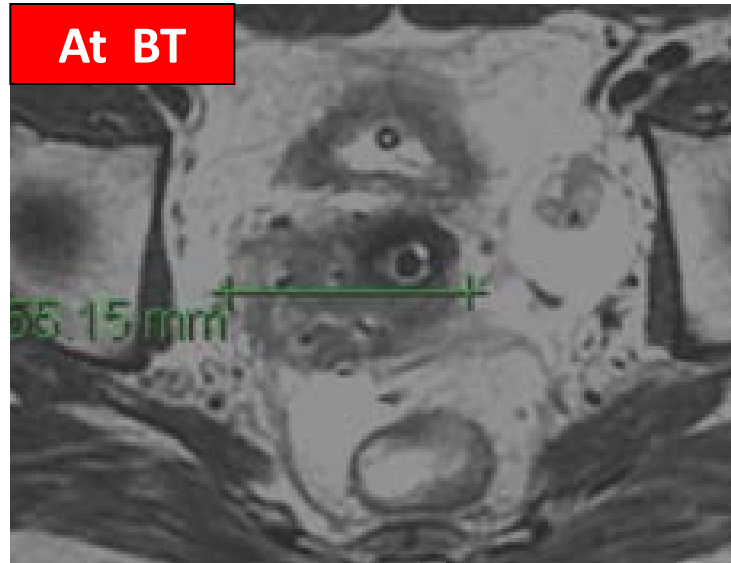


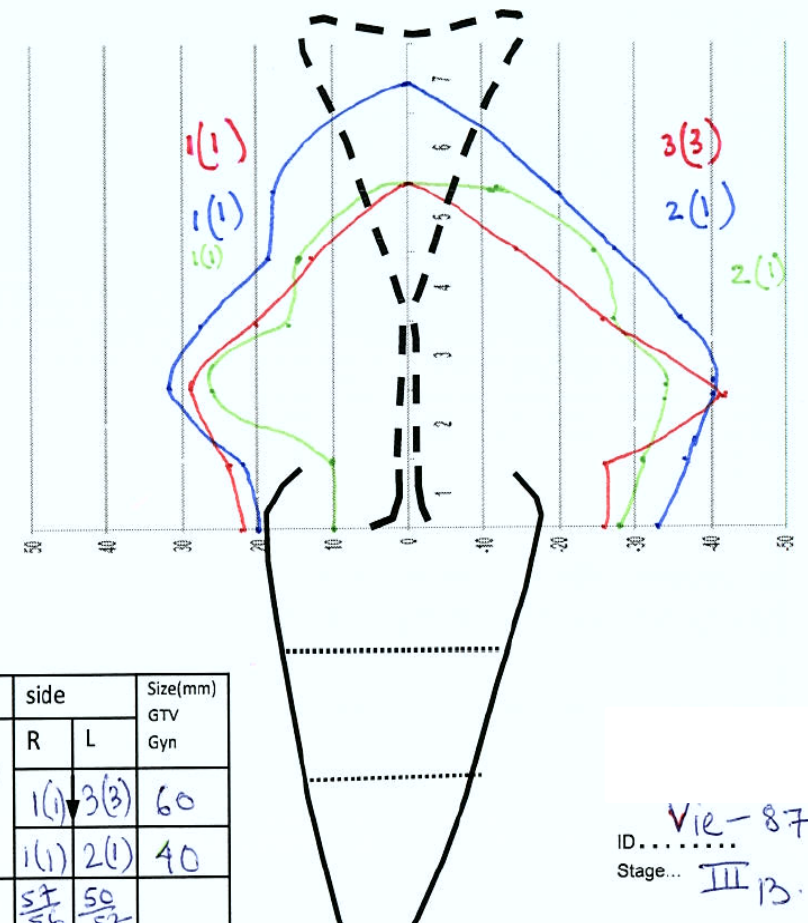
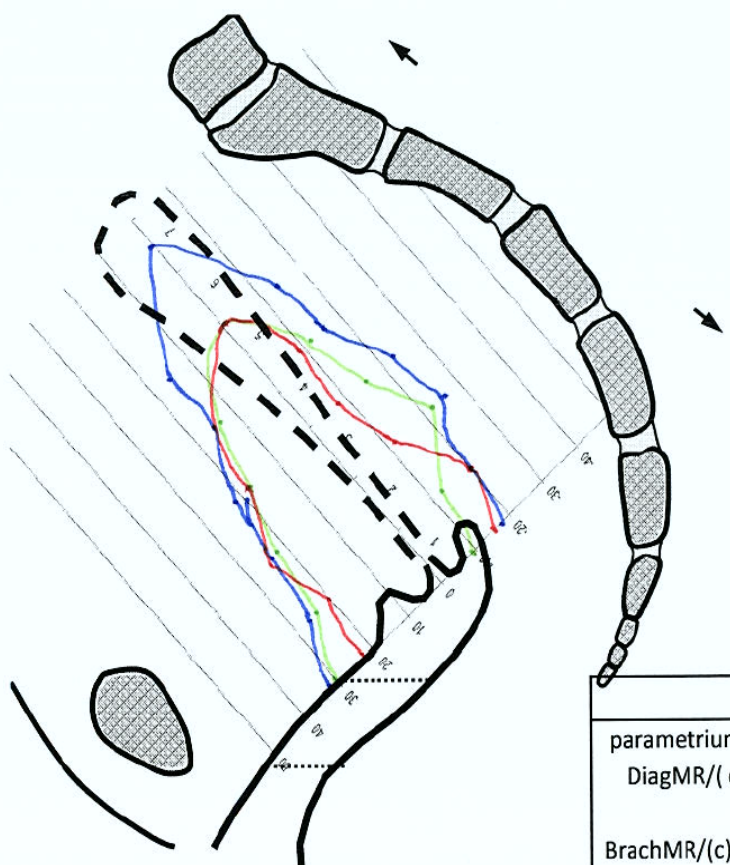
Coronal

Pre Rx



At BT





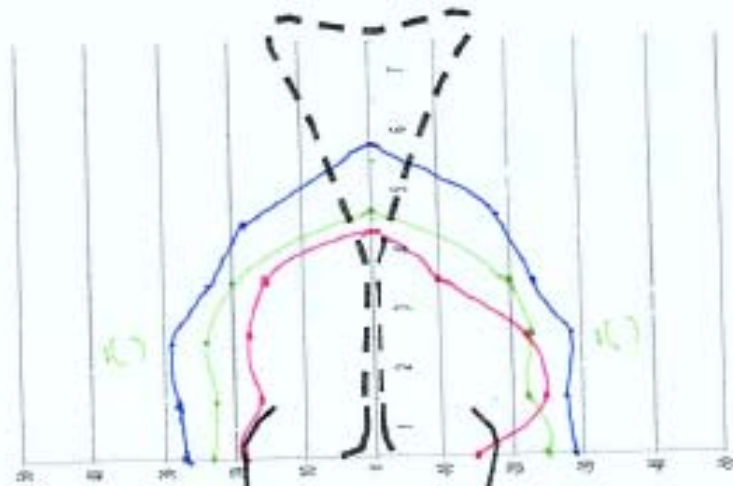
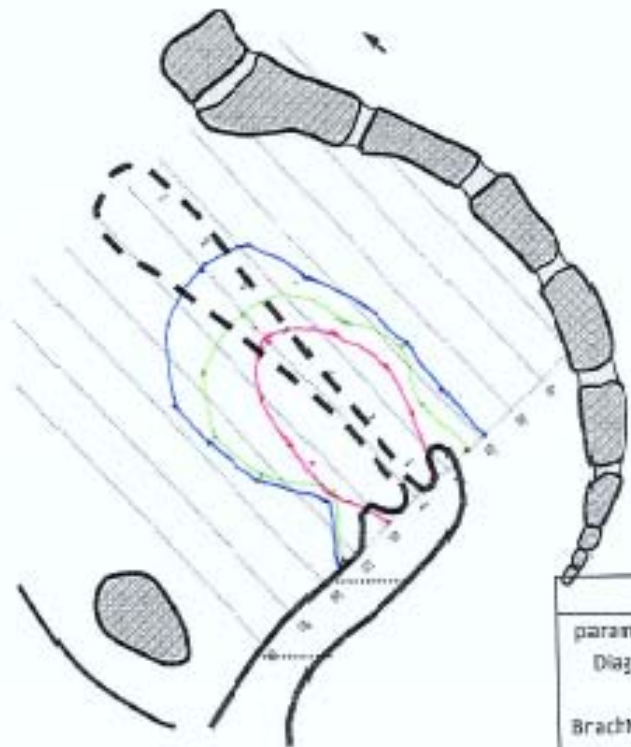
	side		Size(mm) GTV Gyn
	R	L	
parametrium DiagMR/(c)	1(1)	3(3)	60
BrachMR/(c)	1(1)	2(1)	40
Distance pelvic Wall Diag/(brachy)	57 56	50 52	

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	-	17	18		Date Brachy
LT	26	28	33	23	32	37	42	33	40	26	27	37	15	25	27	-	17	20		
ANT	22	30	30	20	24	26	24	21	23	19	18	21	16	13	15	-	17	16		
POST	15	9	18	20	12	20	11	22	26	08	15	23	08	12	16	-	17	19		

MRI Compared

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



	side		Stellen/ GTV Gyn
	R	L	
parametrium DiagMR/(c)			
BrachMR/(c)			
Distend polik Wall Dose/brachy)			

id. NUM. 751
Stage... III B

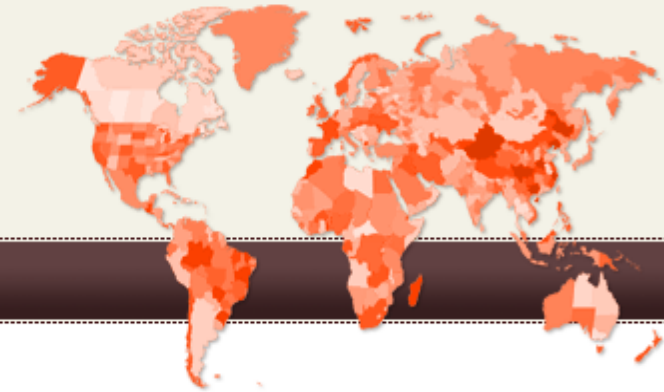
SUMMARY

- Clinical cartoons 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 }



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Appendix

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- ▶ [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

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- ▶ [Protocol PDF download](#)
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- ▶ [Quality of Life sub-study](#)
- ▶ [Embrace study committee](#)
- ▶ [Participants](#)
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www.embracestudy.dk/AboutAppendix.aspx

Applicators for intracavitary treatment of cervical cancer



Primoz Petric

National Center for Cancer Care and Research, Doha, Qatar

Historical

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester
& Fletcher

Mould

**Limitations of
IC Applicators**

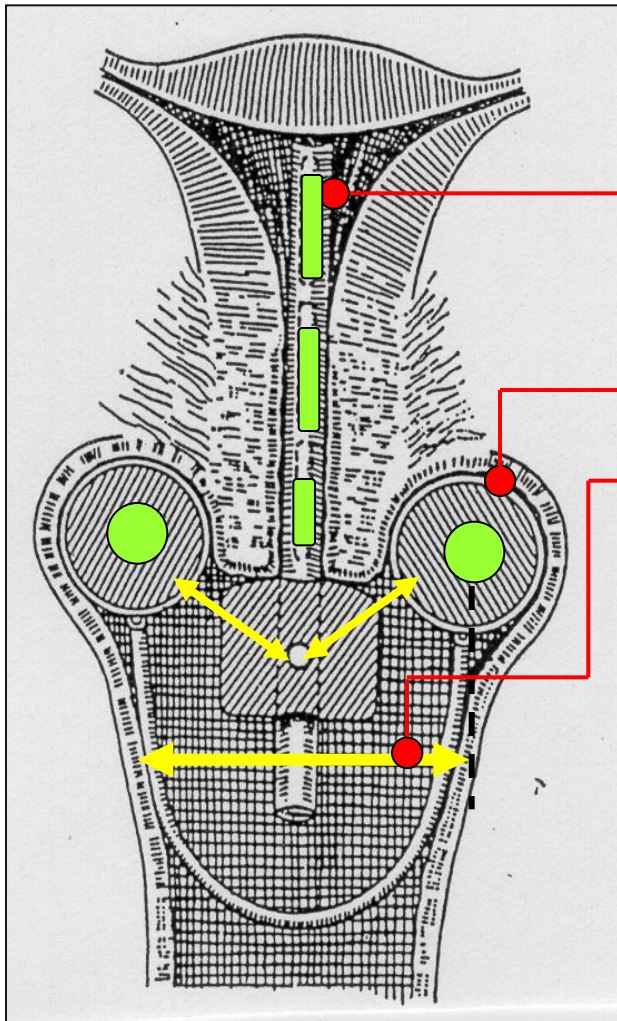
**Emerging
Technologies**

Historical Systems & Techniques



Historical Paris Technique

1910-1920: Curie Institute, Paris, France



Applicator:

Rubber tandem

Cork colpostats
(paraffin coated)

Distance – colpostats: not fixed

²²⁶Ra preloading

X mg of ²²⁶Ra for Y hours

Typical application

≈ 5 days (120 h)

7000-8000 mgh

not connected

no fixed geometry

Classical Stockholm method

1913-1914: Radiumhemmet, Stockholm, Sweden

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

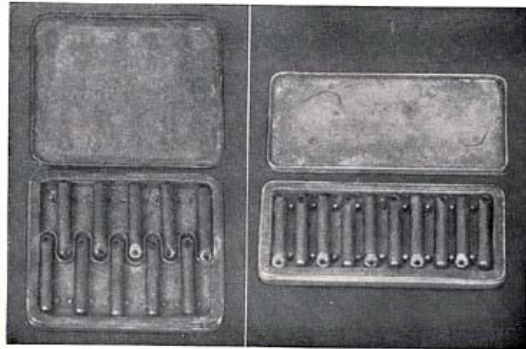
Mould

Limitations of IC Applicators

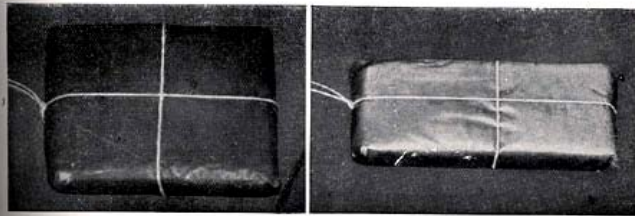
Emerging Technologies



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

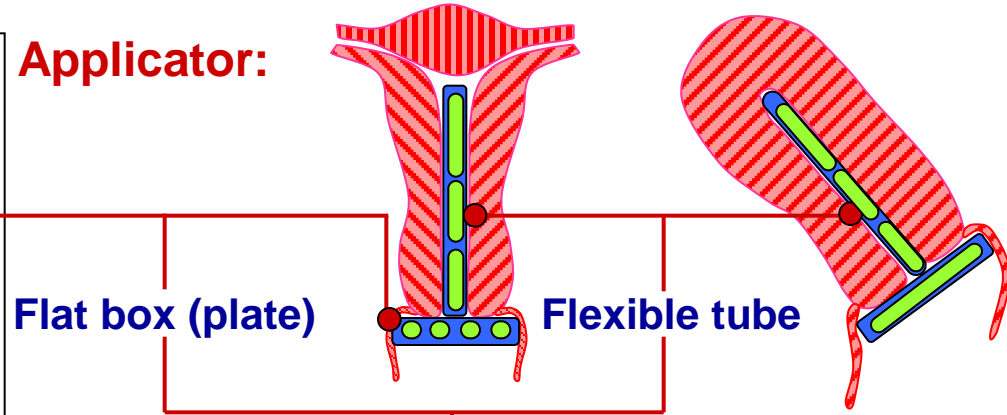


Figs. 9 and 10. The same applicators with their tubes.



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

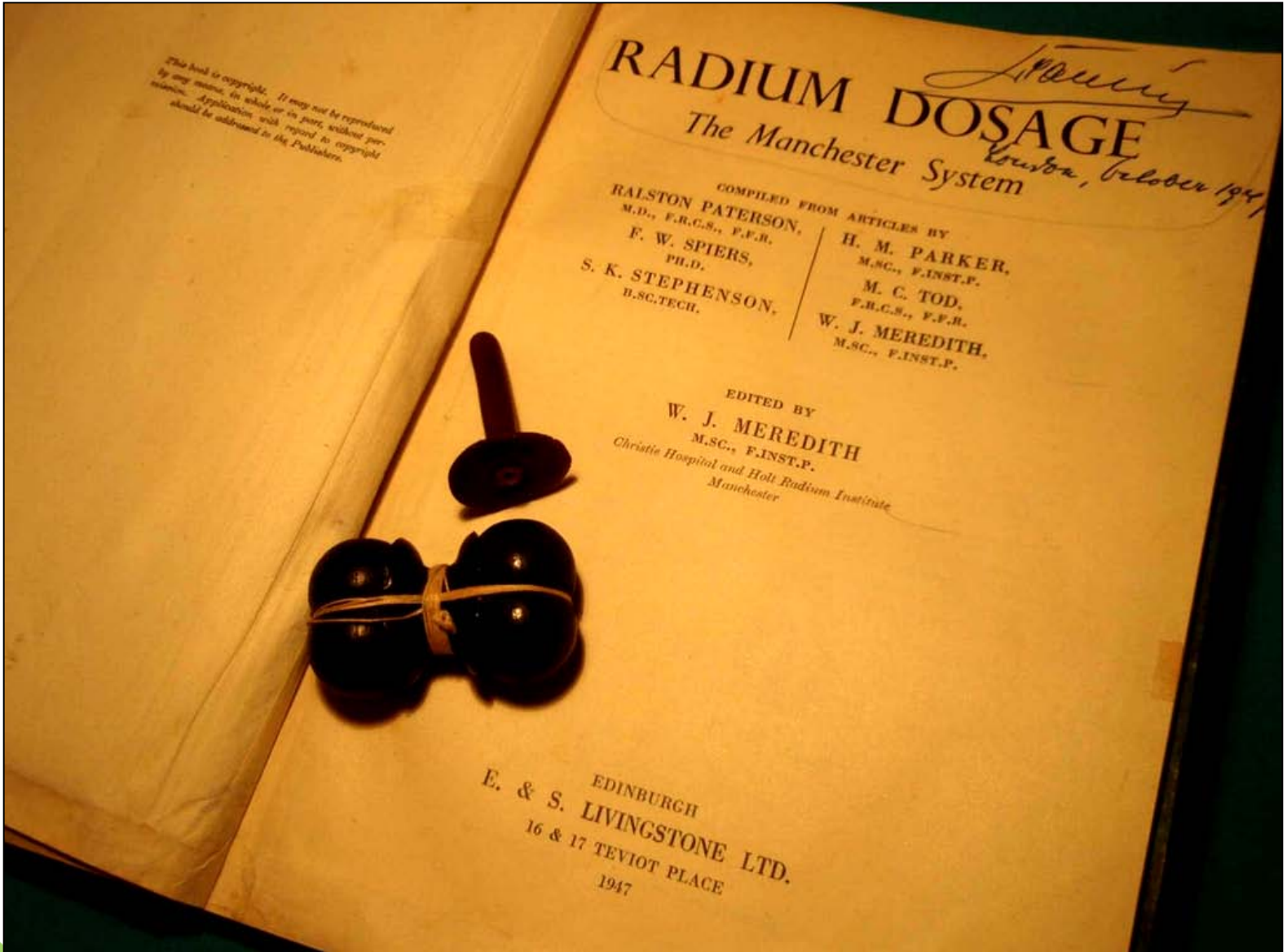
● X mg of ^{226}Ra for Y hours

Typical treatment

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

Historical Manchester System

1938: Holt Radium Institute, Manchester, England



Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

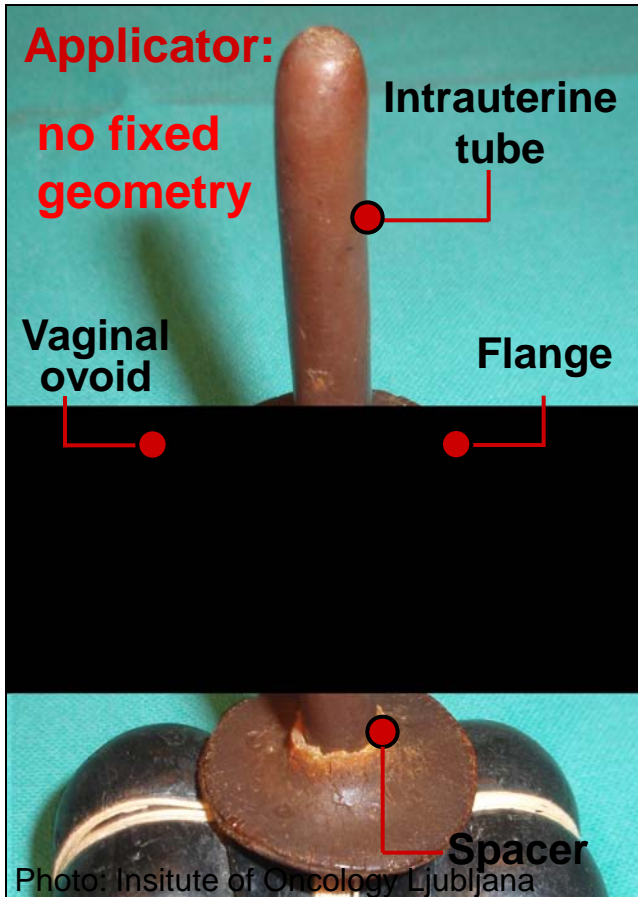
Mould

Limitations of IC Applicators

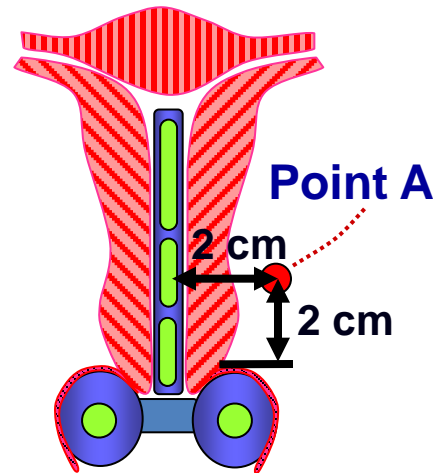
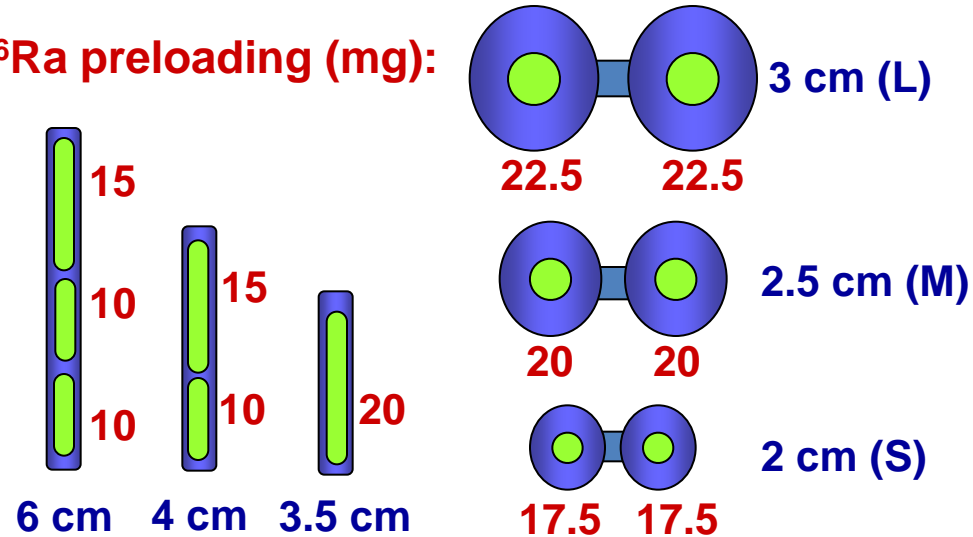
Emerging Technologies

Historical Manchester System

Related to historical Paris technique



²²⁶Ra preloading (mg):



Given tumour volume

A set of rules

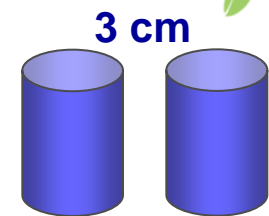
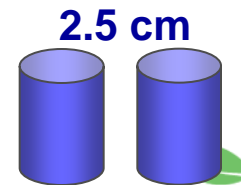
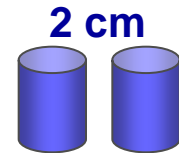
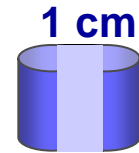
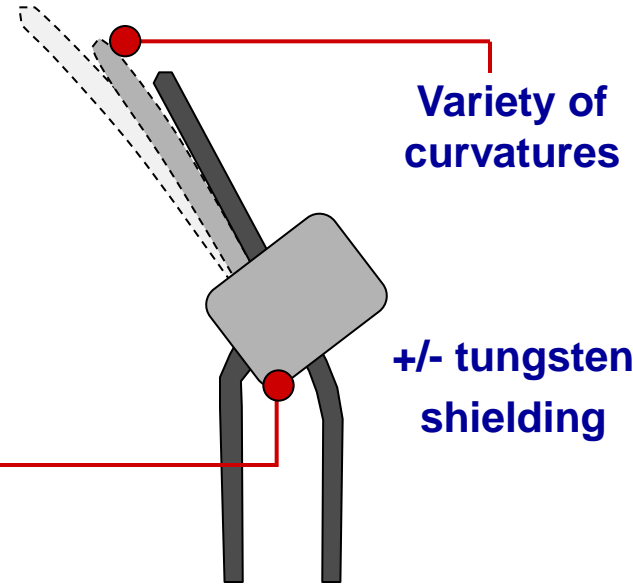
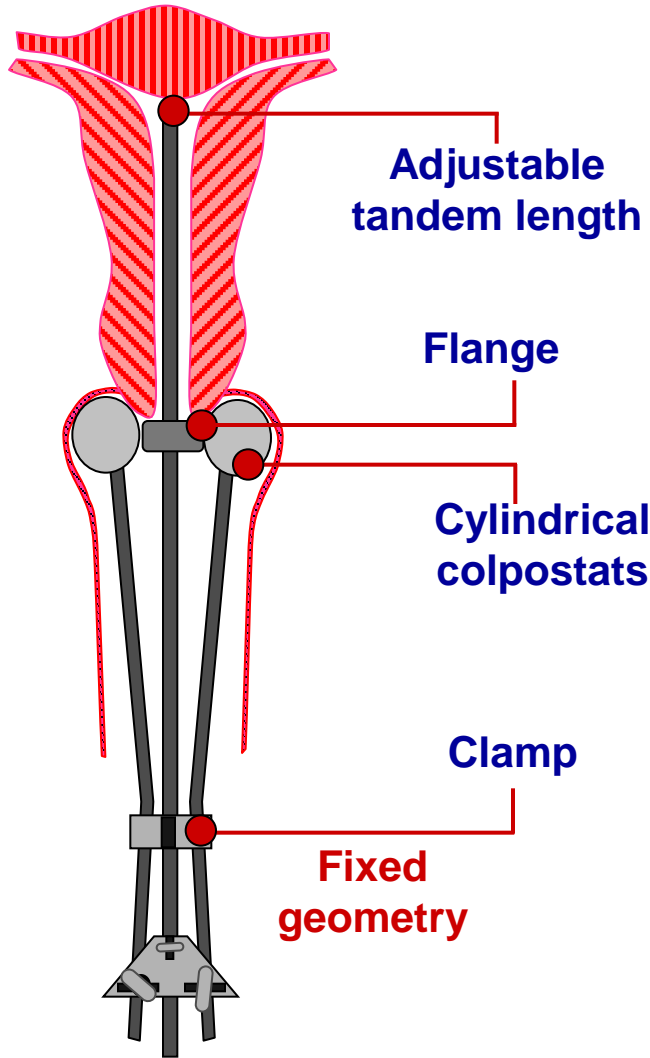
- Geometry
- mg of ²²⁶Ra
- Duration

Certain point A dose

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

Fletcher–Suit–Delclos–Horiot Technique

1950's: Fletcher



Historical

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester
& Fletcher

Mould

Limitations of
IC Applicators

Emerging
Technologies

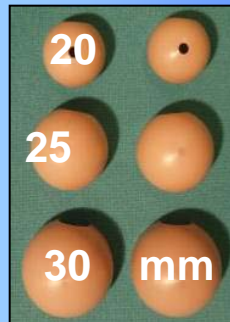
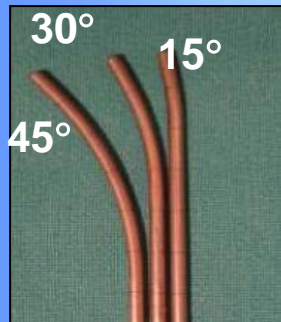
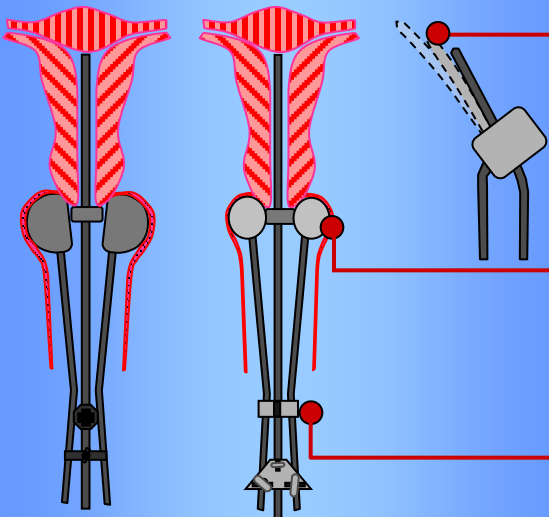
Modern Intracavitary Techniques



Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher type



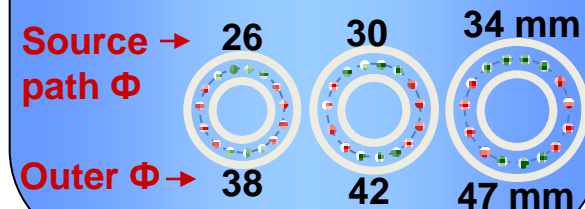
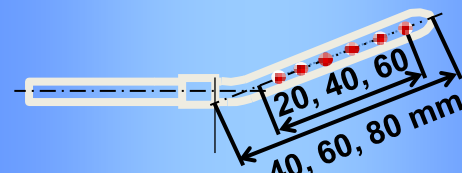
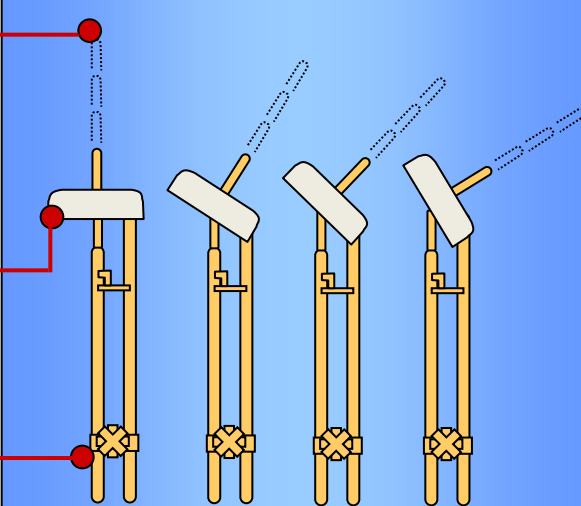
Common features:

Uterine Tandem:
various lengths,
angles or curvatures

Ovoids, cylinders, rings
various outer & source
path diameters

Clamp

Stockholm style



- Paris
- Stockholm
- Manchester
- Fletcher

- Modern
- Stockholm
- Manchester & Fletcher
- Mould

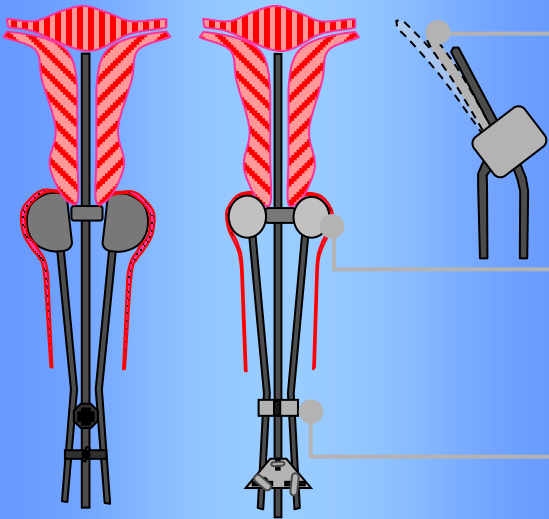
Limitations of IC Applicators

Emerging Technologies

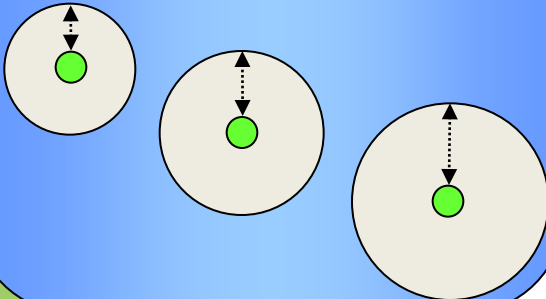
Modern Intracavitary Techniques

***Applicators:* mimicking historical geometries**

Manchester / Fletcher style



Varies with diameter



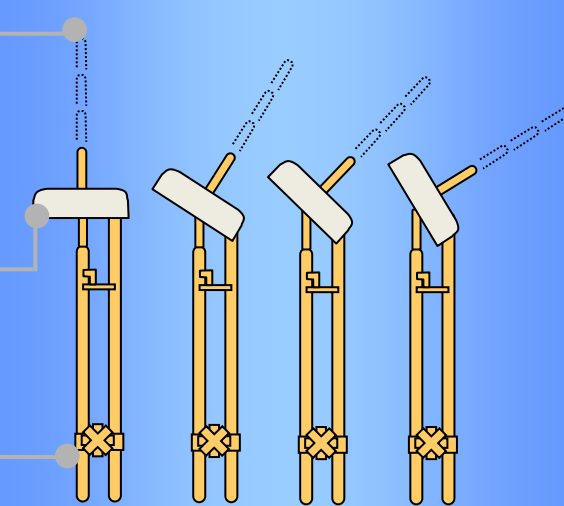
Common features:

Uterine Tandem: various lengths, angles or curvatures

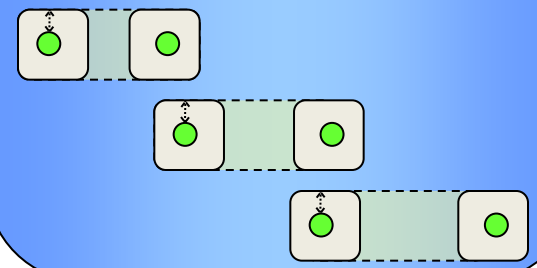
Ovoids, cylinders, rings various outer & source path diameters

Clamp

Stockholm style



Constant



Differences:

Thickness of ovoids and rings

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

Mould

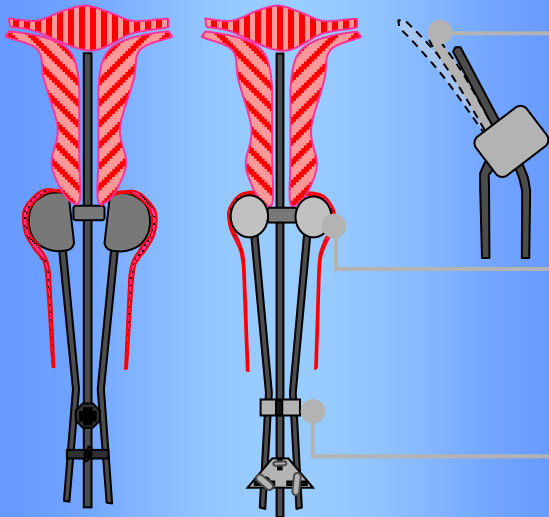
Limitations of IC Applicators

Emerging Technologies

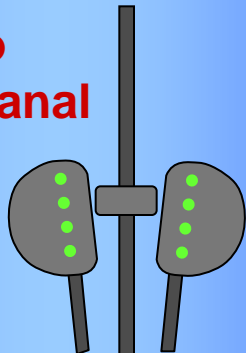
Modern Intracavitary Techniques

***Applicators:* mimicking historical geometries**

Manchester / Fletcher style



Parallel to cervical canal



Manchester style

Common features:

Uterine Tandem: various lengths, angles or curvatures

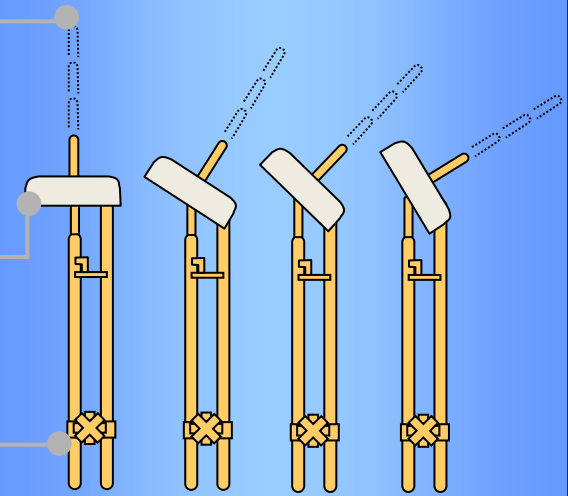
Ovoids, cylinders, rings various outer & source path diameters

Clamp

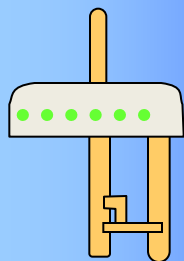
Differences:

Source path orientation

Stockholm style



Perpendicular to cervical canal



Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

Mould

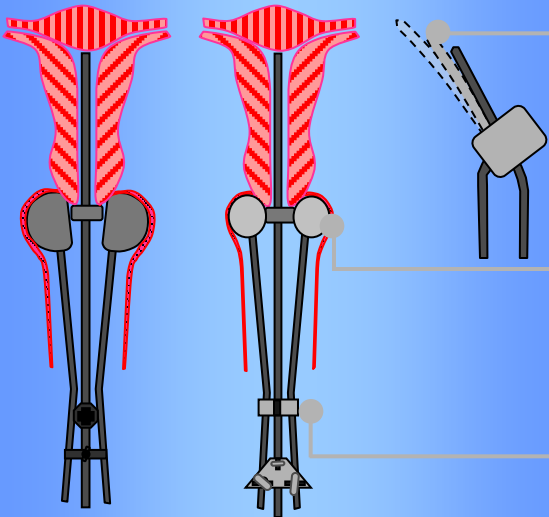
Limitations of IC Applicators

Emerging Technologies

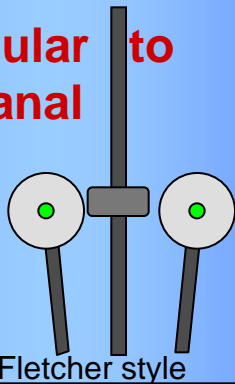
Modern Intracavitary Techniques

***Applicators:* mimicking historical geometries**

Manchester / Fletcher style



Perpendicular to cervical canal



Fletcher style

Common features:

Uterine Tandem: various lengths, angles or curvatures

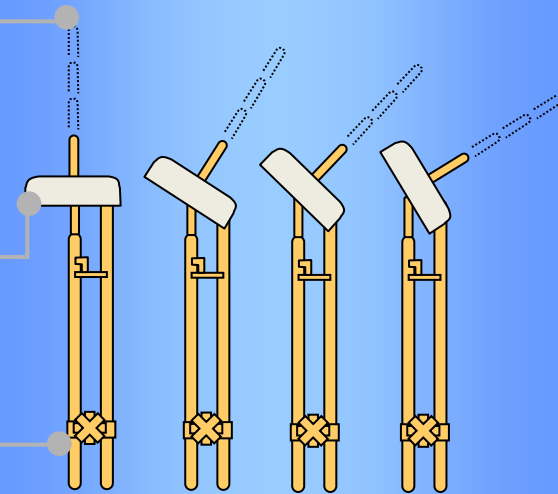
Ovoids, cylinders, rings various outer & source path diameters

Clamp

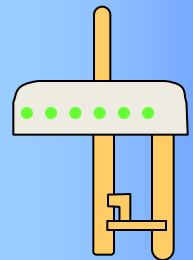
Differences:

Source path orientation

Stockholm style



Perpendicular to cervical canal



Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

Mould

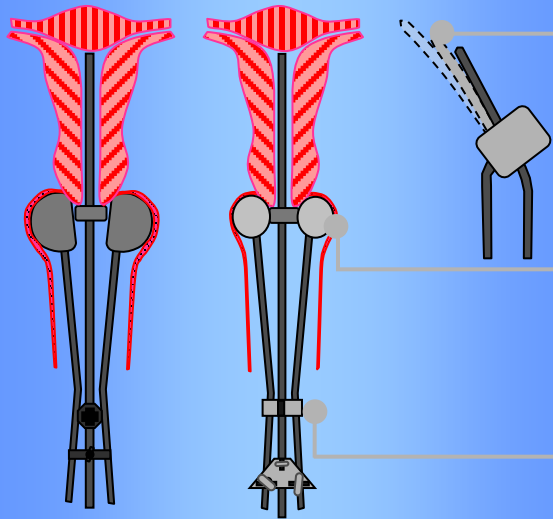
Limitations of IC Applicators

Emerging Technologies

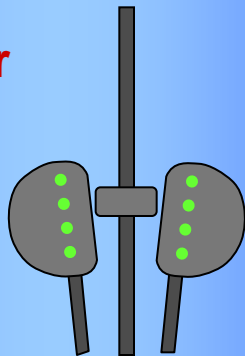
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Lower



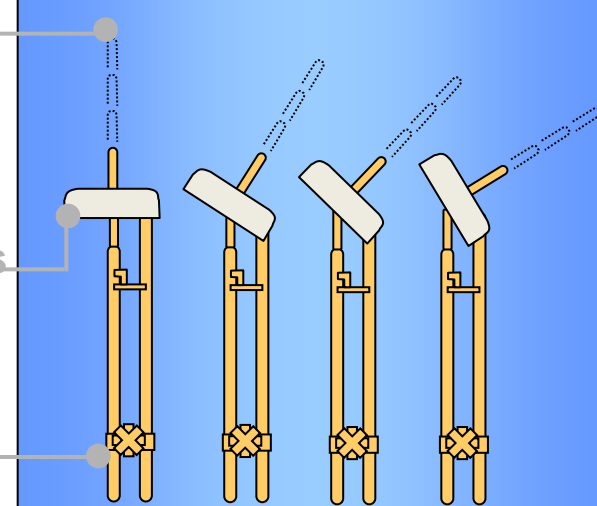
Common features:

Uterine Tandem: various lengths, angles or curvatures

Ovoids, cylinders, rings various outer & source path diameters

Clamp

Stockholm style



Higher

Differences:

Loading flexibility

- Paris
- Stockholm
- Manchester
- Fletcher

Modern

- Stockholm
- Manchester & Fletcher
- Mould

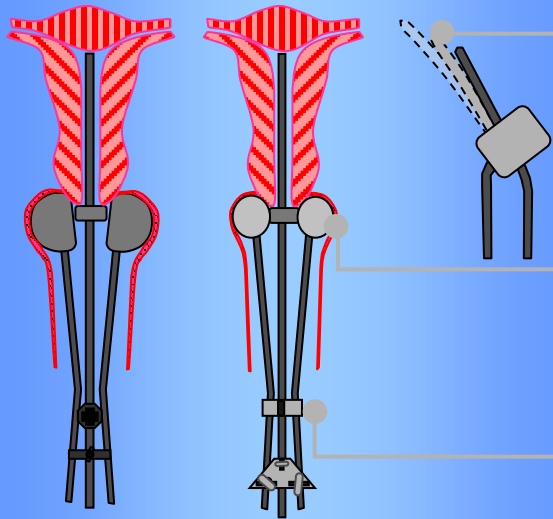
Limitations of IC Applicators

Emerging Technologies

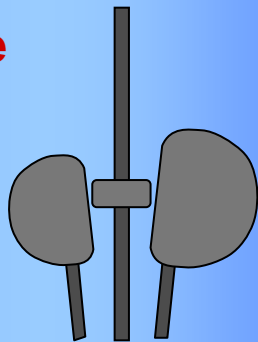
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Possible



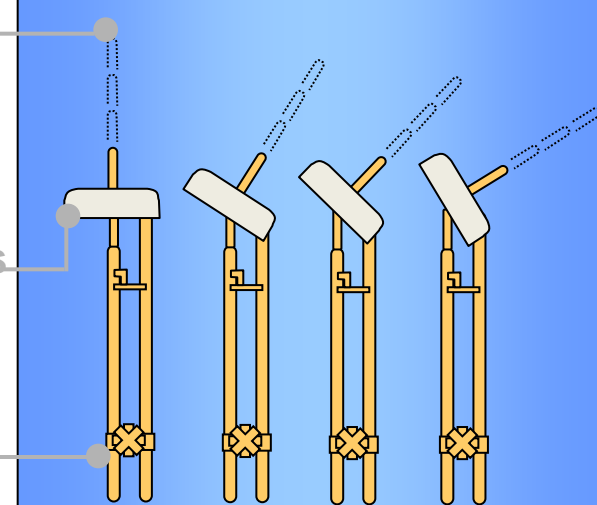
Common features:

Uterine Tandem: various lengths, angles or curvatures

Ovoids, cylinders, rings various outer & source path diameters

Clamp

Stockholm style



Not applicable

Differences:

Asymmetric insertion

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

Mould

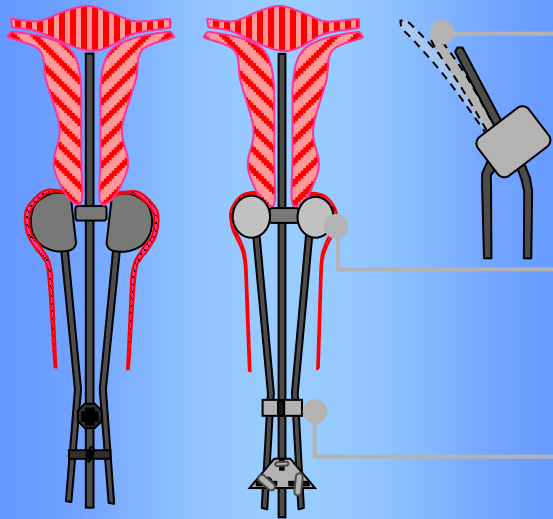
Limitations of IC Applicators

Emerging Technologies

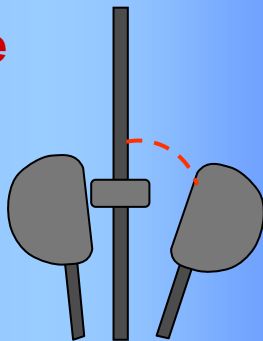
Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style



Possible



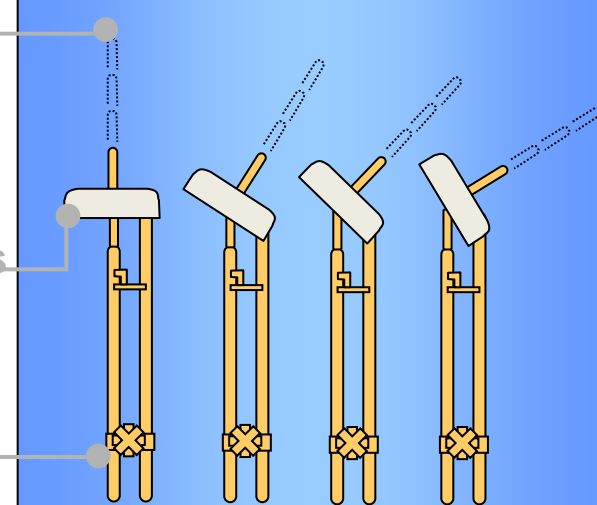
Common features:

Uterine Tandem: various lengths, angles or curvatures

Ovoids, cylinders, rings various outer & source path diameters

Clamp

Stockholm style



Not applicable

Differences:

Adjustable spacing

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

Mould

Limitations of IC Applicators

Emerging Technologies

Modern Intracavitary Techniques

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

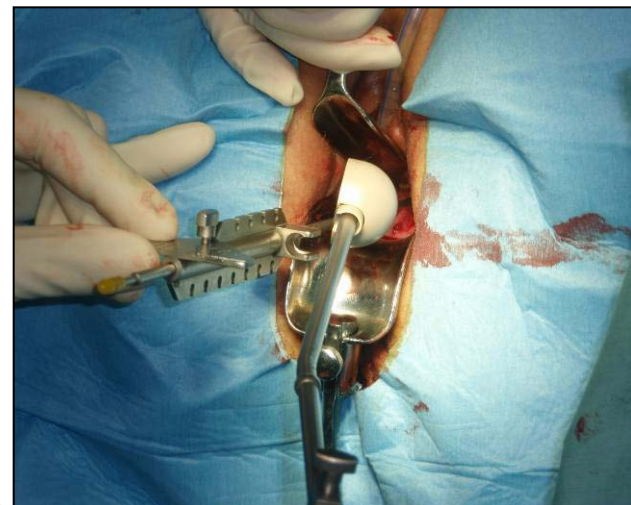
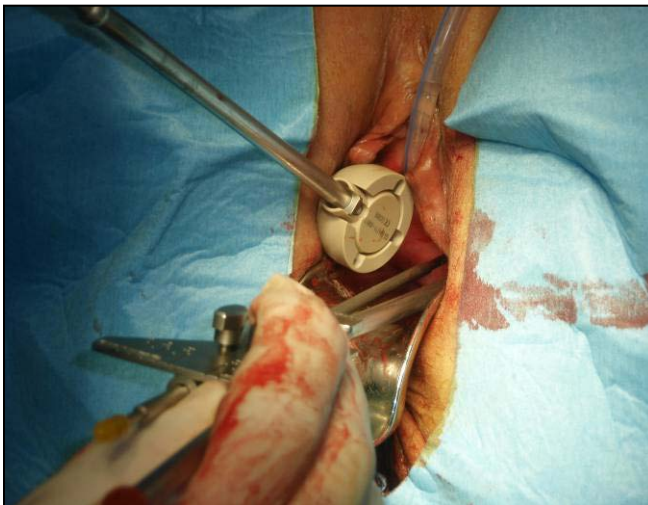
Manchester
& Fletcher

Mould

Limitations of
IC Applicators

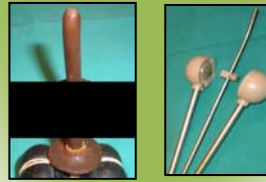
Emerging
Technologies

Applicator insertion



Modern Intracavitary Techniques

Concept: same as 100 years ago...

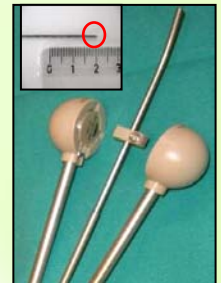


Modern IC techniques

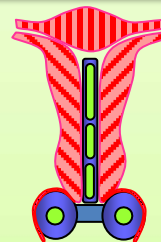
Materials:
Imaging...



Channel diameters:
Smaller



Loading patterns:
Mimicking historical



Historical

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester
& Fletcher

Mould

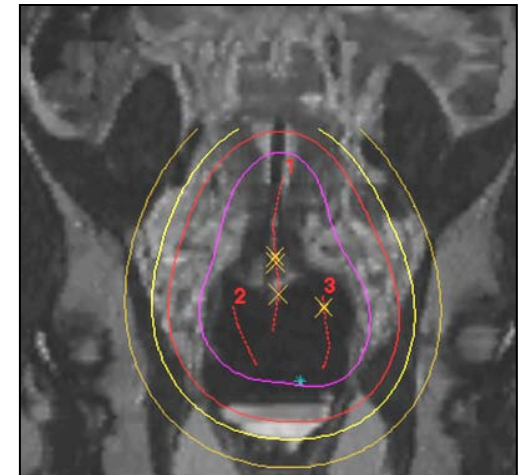
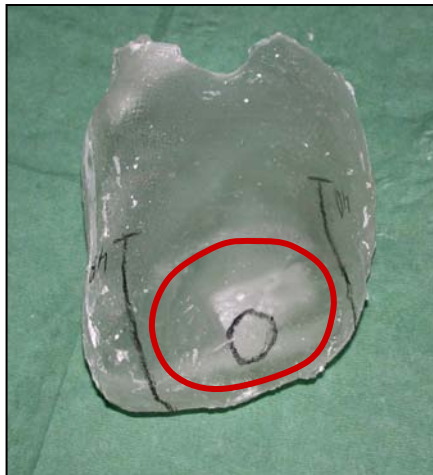
Limitations of
IC Applicators

Emerging
Technologies

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

Historical

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester
& Fletcher

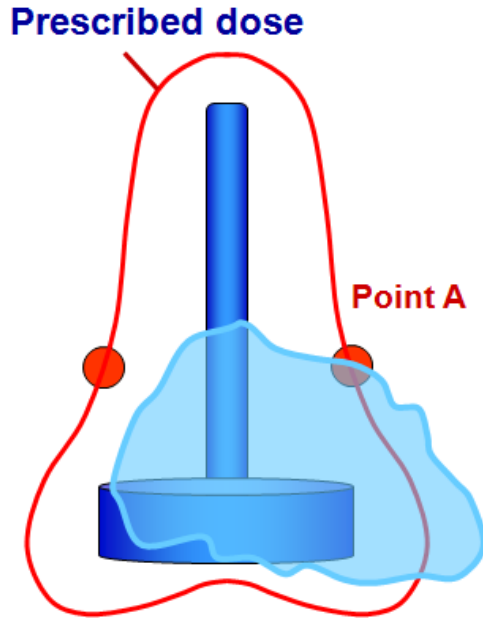
Mould

Limitations of
IC Applicators

Emerging
Technologies

Limitations of modern IC applicators

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



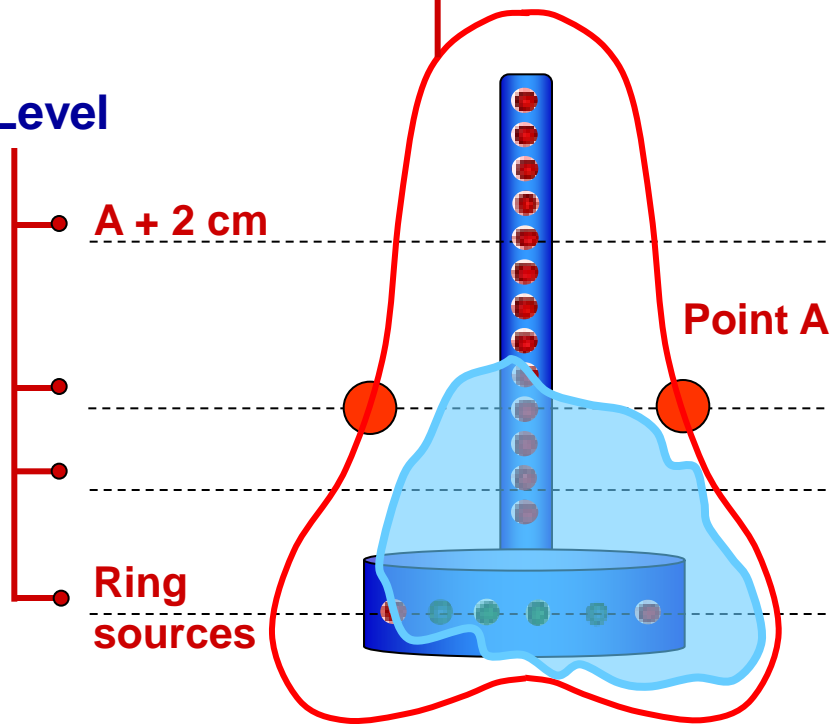
- A. Up to ~1 mm
- B. Up to ~ 4 mm
- C. Up to ~ 10 mm
- D. Up to ~ 20 mm

Dimensions of prescribed dose: different levels

Standard loading

Prescribed dose

Level



A + 2 cm

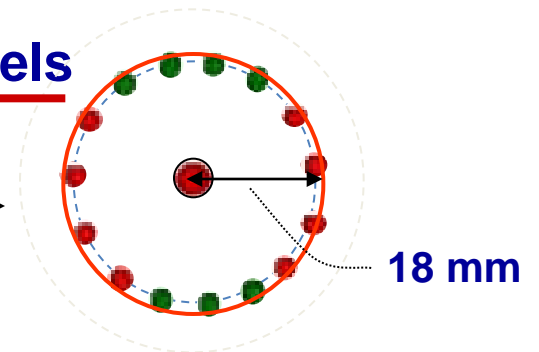
Point A

Ring sources

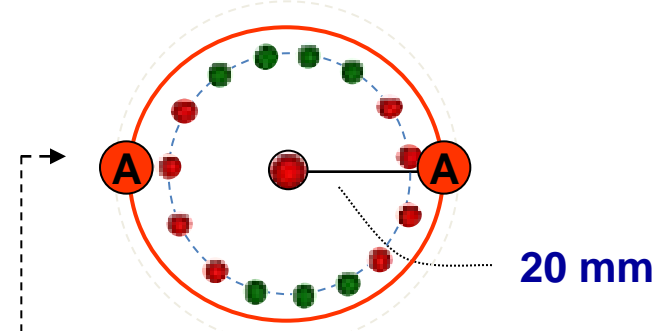
Example:

Tandem & Ring applicator:

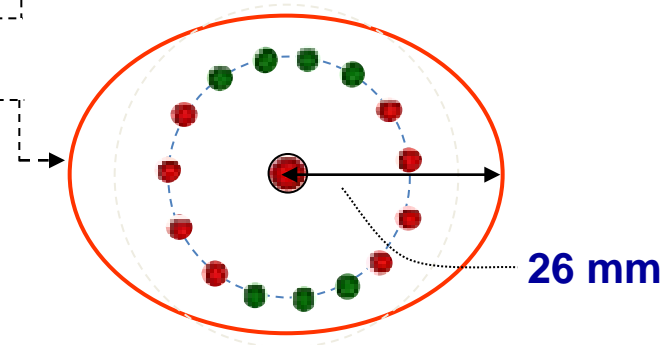
30 mm ring & 60 mm tandem



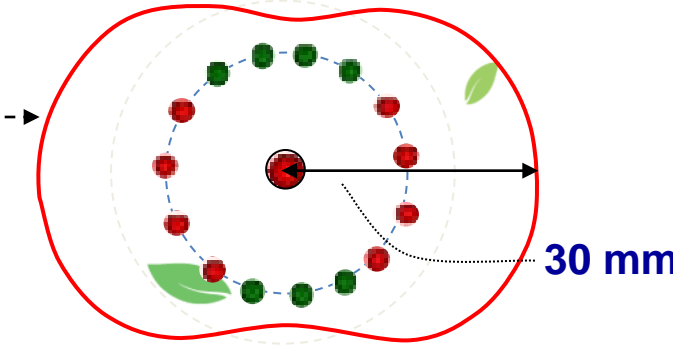
18 mm



20 mm



26 mm



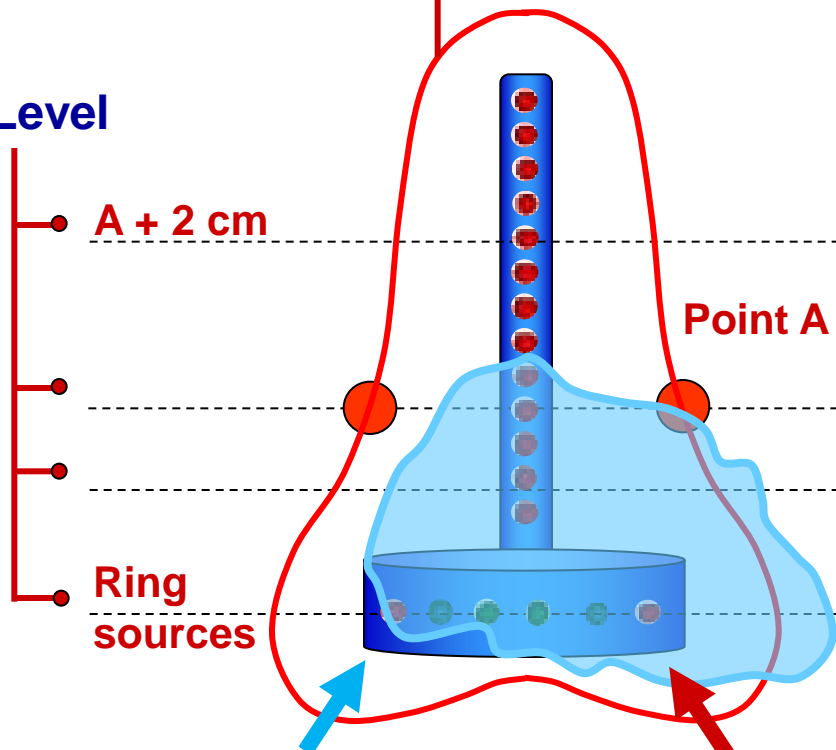
30 mm

Dimensions of prescribed dose: different levels

Standard loading

Prescribed dose

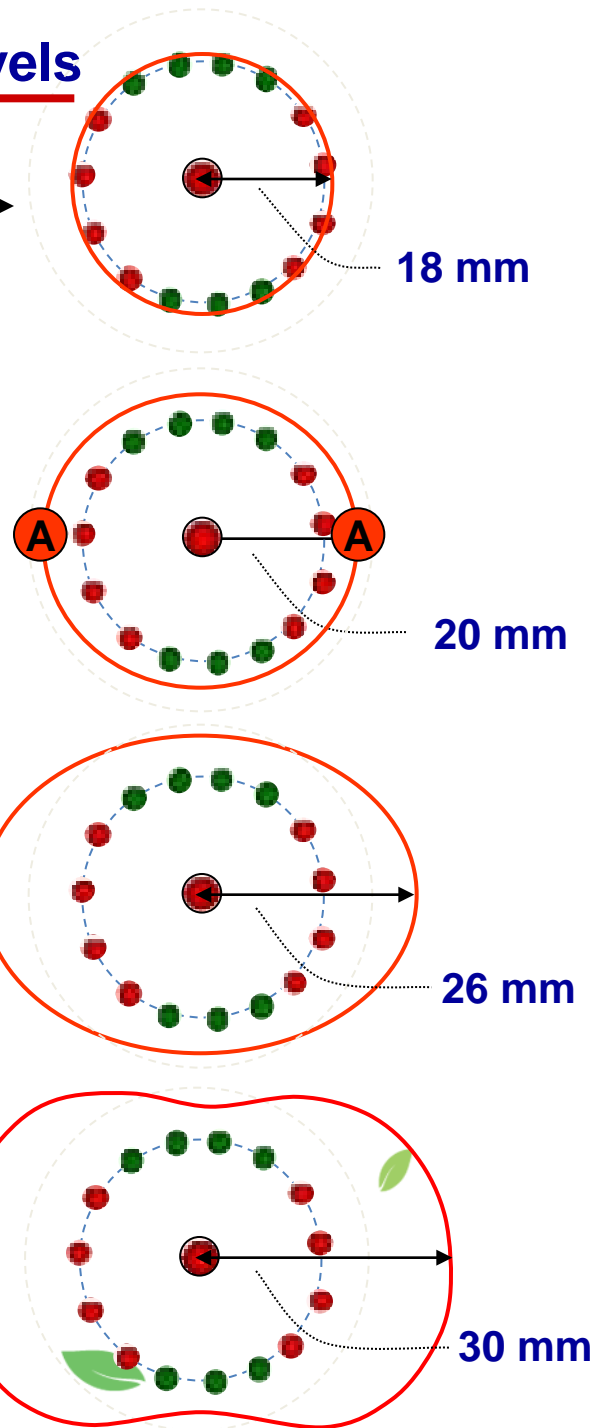
Level



Example:

Tandem & Ring applicator:

30 mm ring & 60 mm tandem



Historical

Paris

Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

Mould

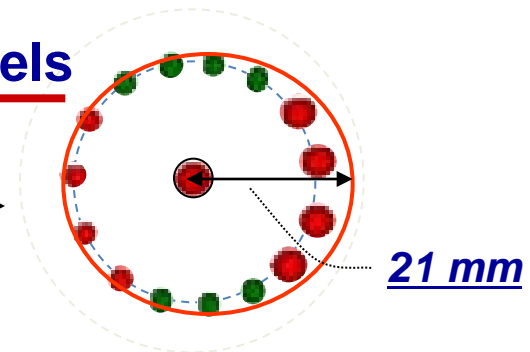
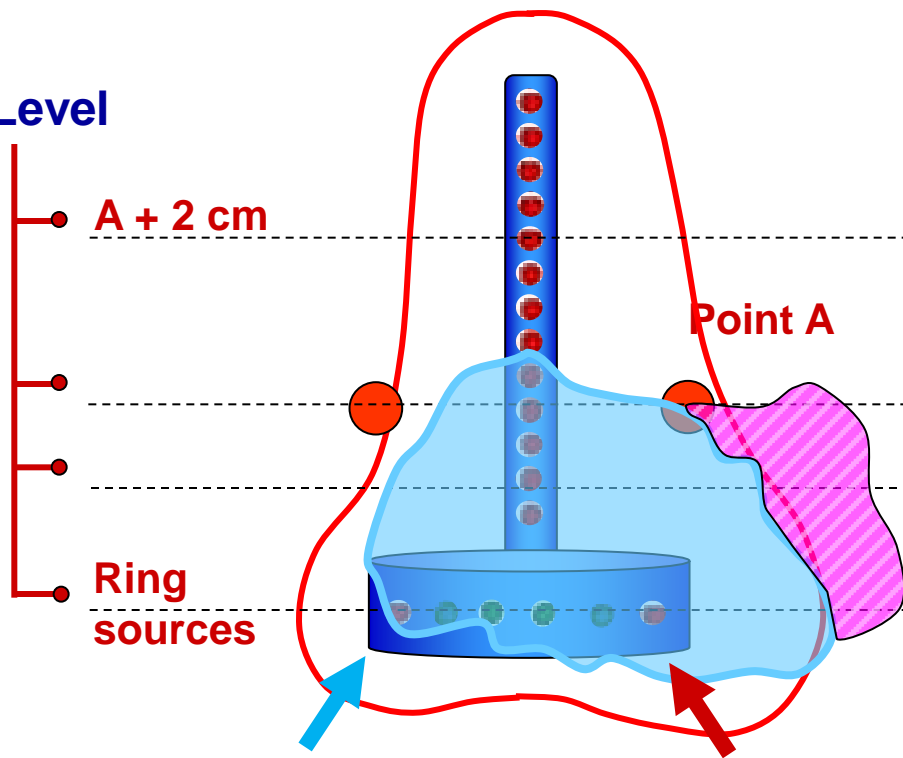
Limitations of IC Applicators

Emerging Technologies

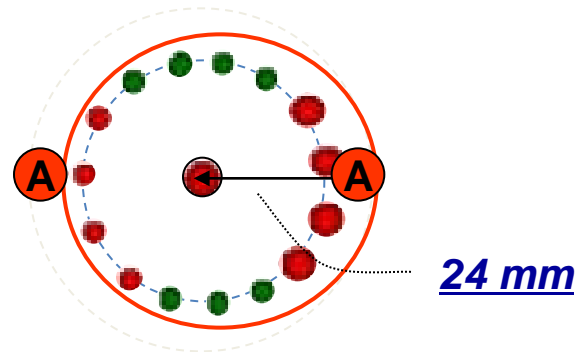
Dimensions of prescribed dose: different levels

Modified Intracavitary loading

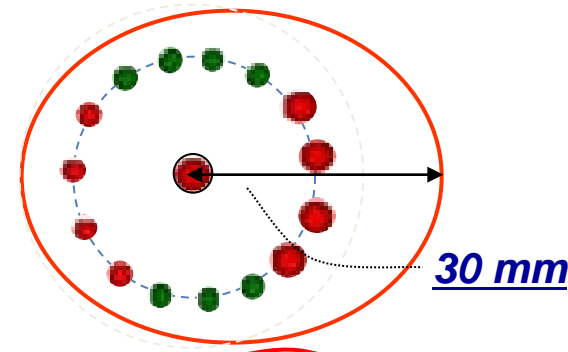
Level



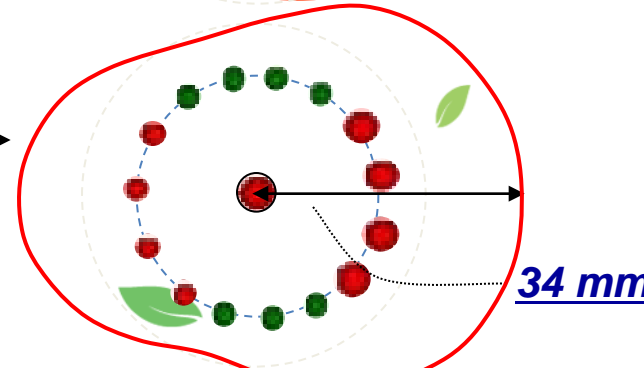
21 mm



24 mm



30 mm



34 mm

Overcoming limitations of IC applicators

Historical

Paris

Stockholm

Manchester

Fletcher

Modern

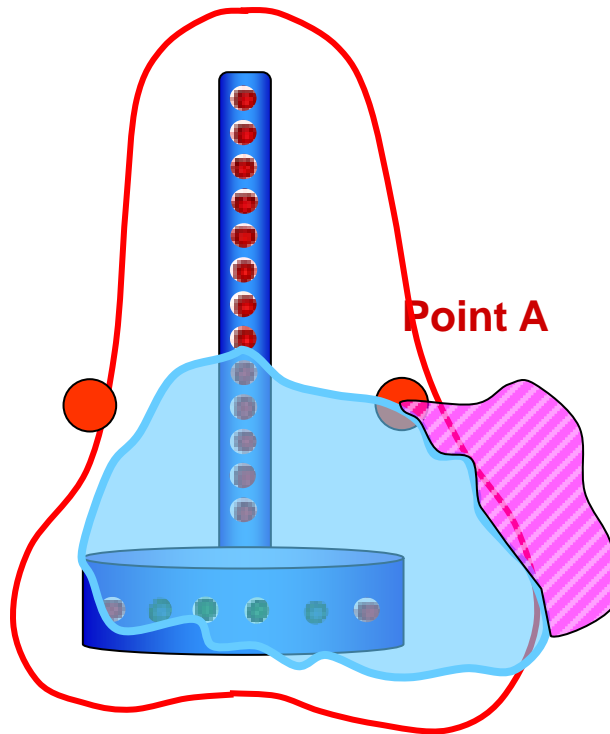
Stockholm

Manchester
& Fletcher

Mould

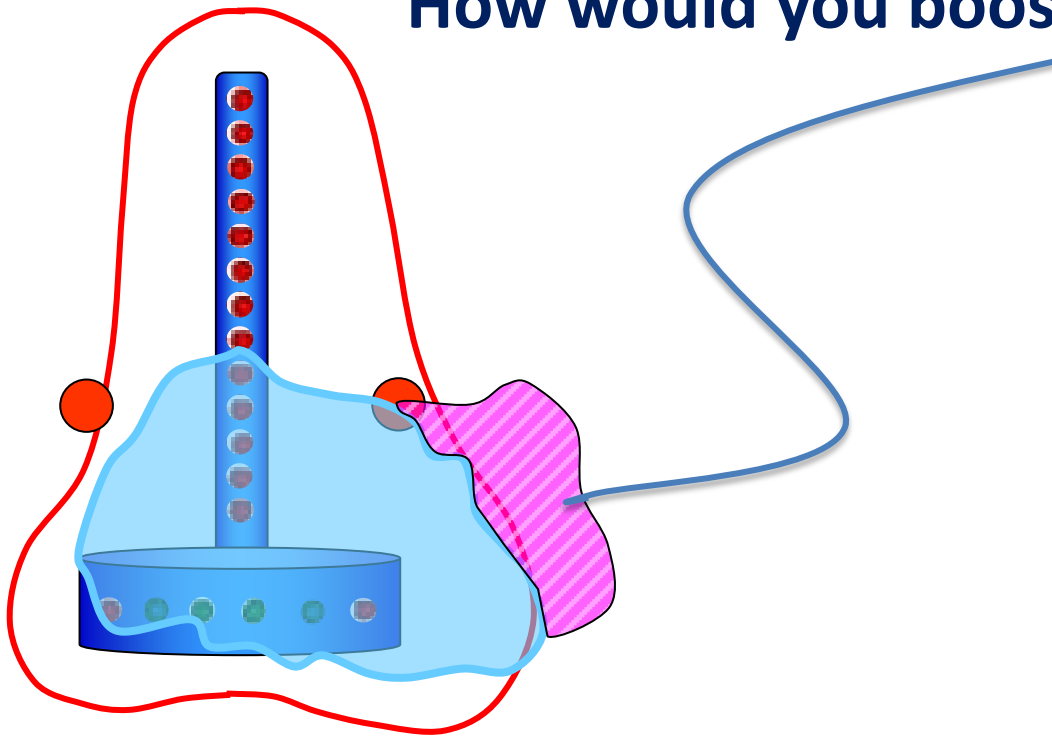
Limitations of
IC Applicators

Emerging
Technologies



Overcoming limitations of IC applicators

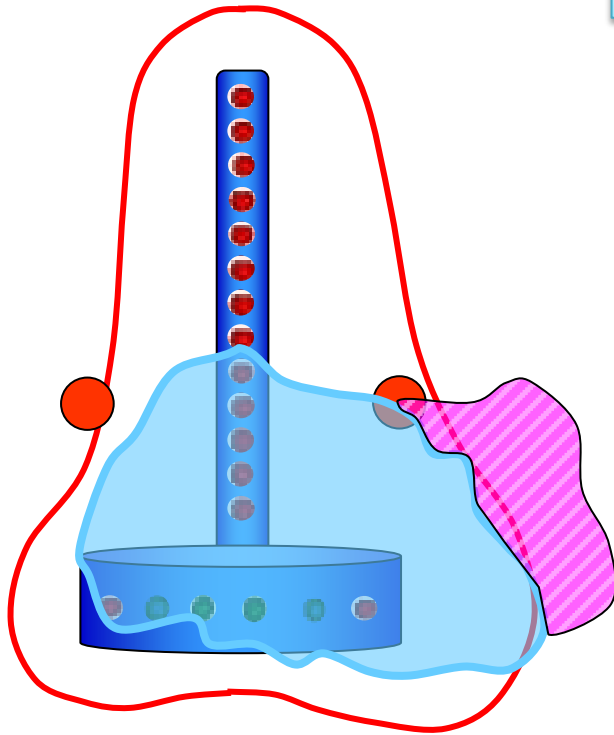
How would you boost this area?



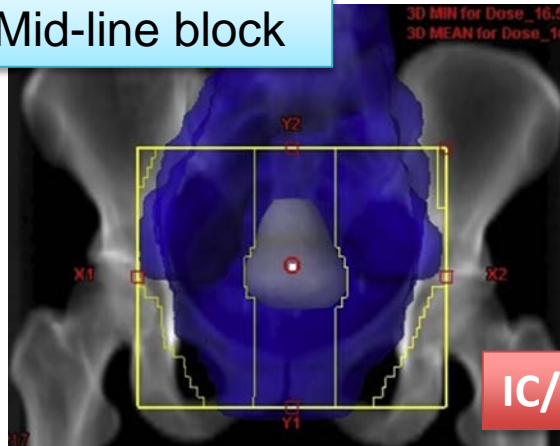
- A. By expansion of dose from IC applicator
- B. By EBRT boost with midline shielding
- C. By adding Interstitial to Intracavitary BT
- D. Other

Overcoming limitations of IC applicators

External beam boost with midline "shielding"



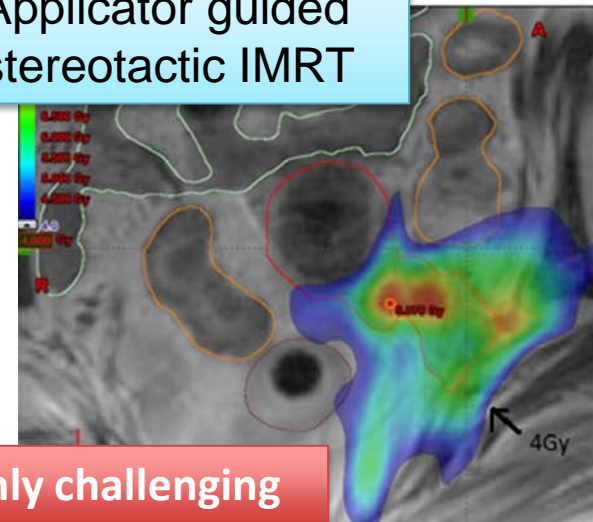
Mid-line block



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

IC/IS boost > EBRT boost

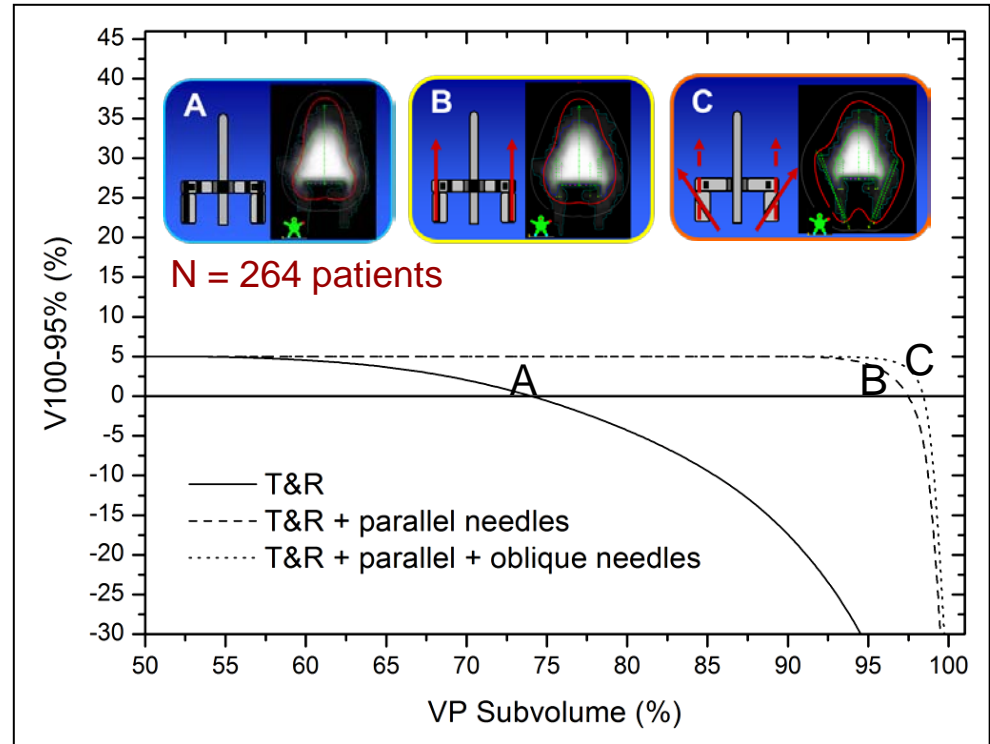
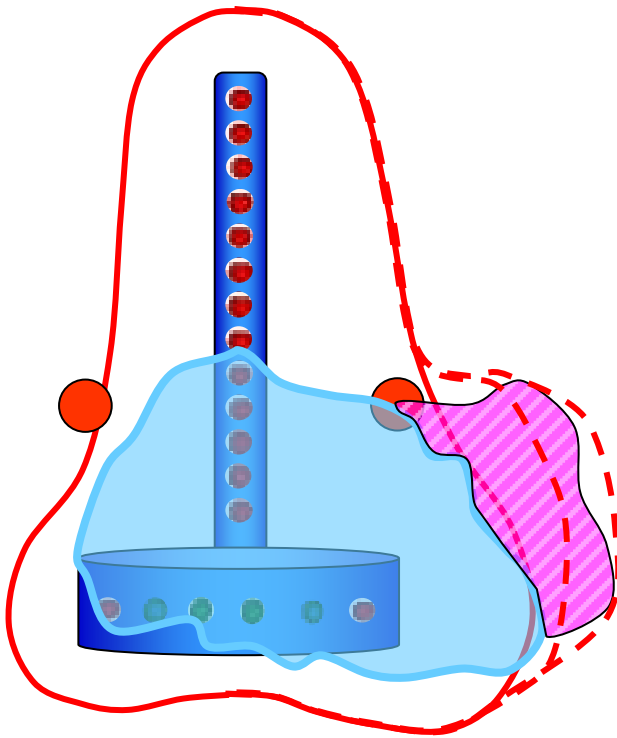
Applicator guided stereotactic IMRT



When IC/IS BT is highly challenging

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 al. IJROBP 2012
 Berger D, et al. Brachytherapy 2010 (Abstract)

Emerging technologies

Historical

Paris

Stockholm

Manchester

Fletcher

Modern

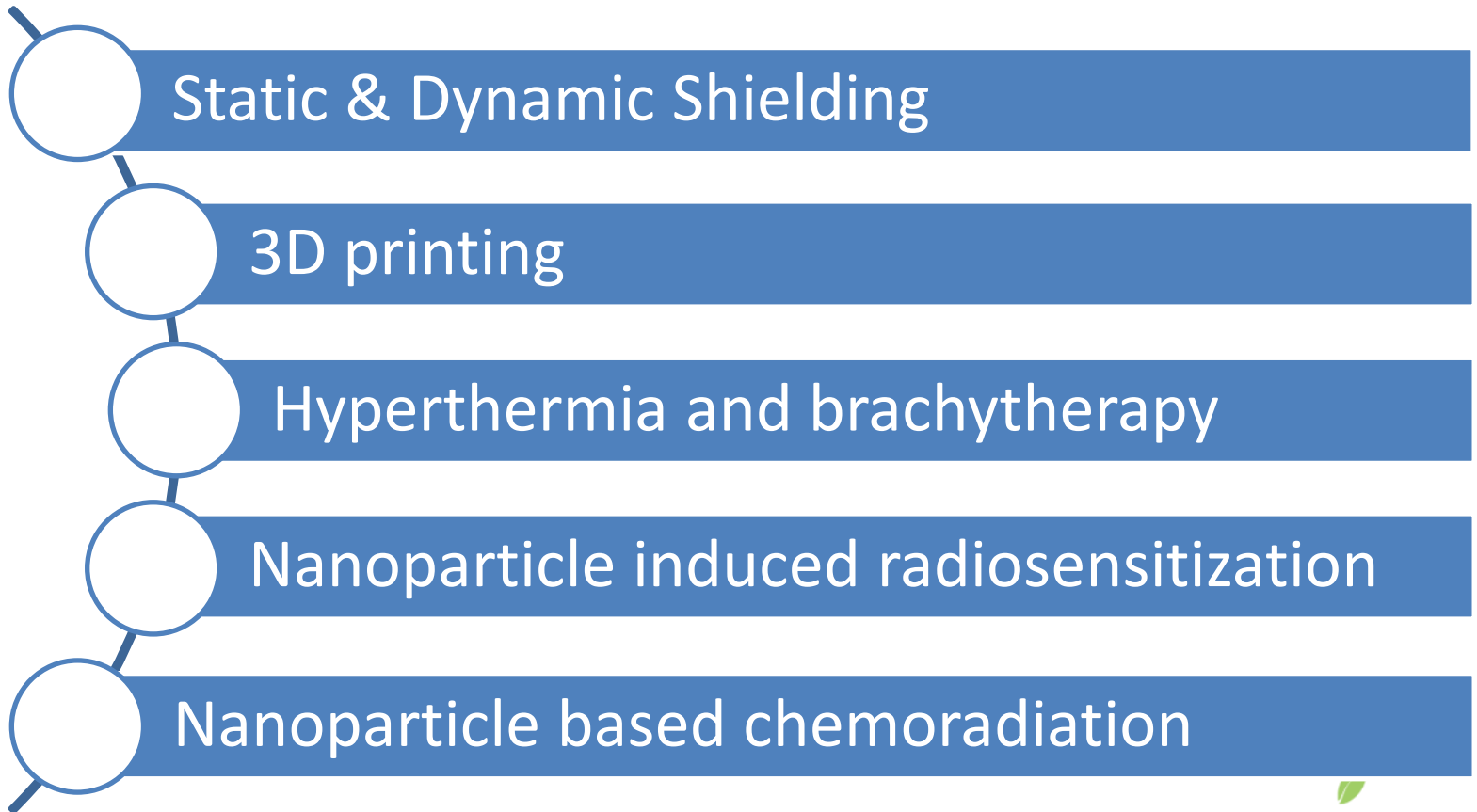
Stockholm

Manchester
& Fletcher

Mould

Limitations of
IC Applicators

Emerging
Technologies



Emerging technologies

Historical

Paris

Stockholm

Manchester

Fletcher

Modern

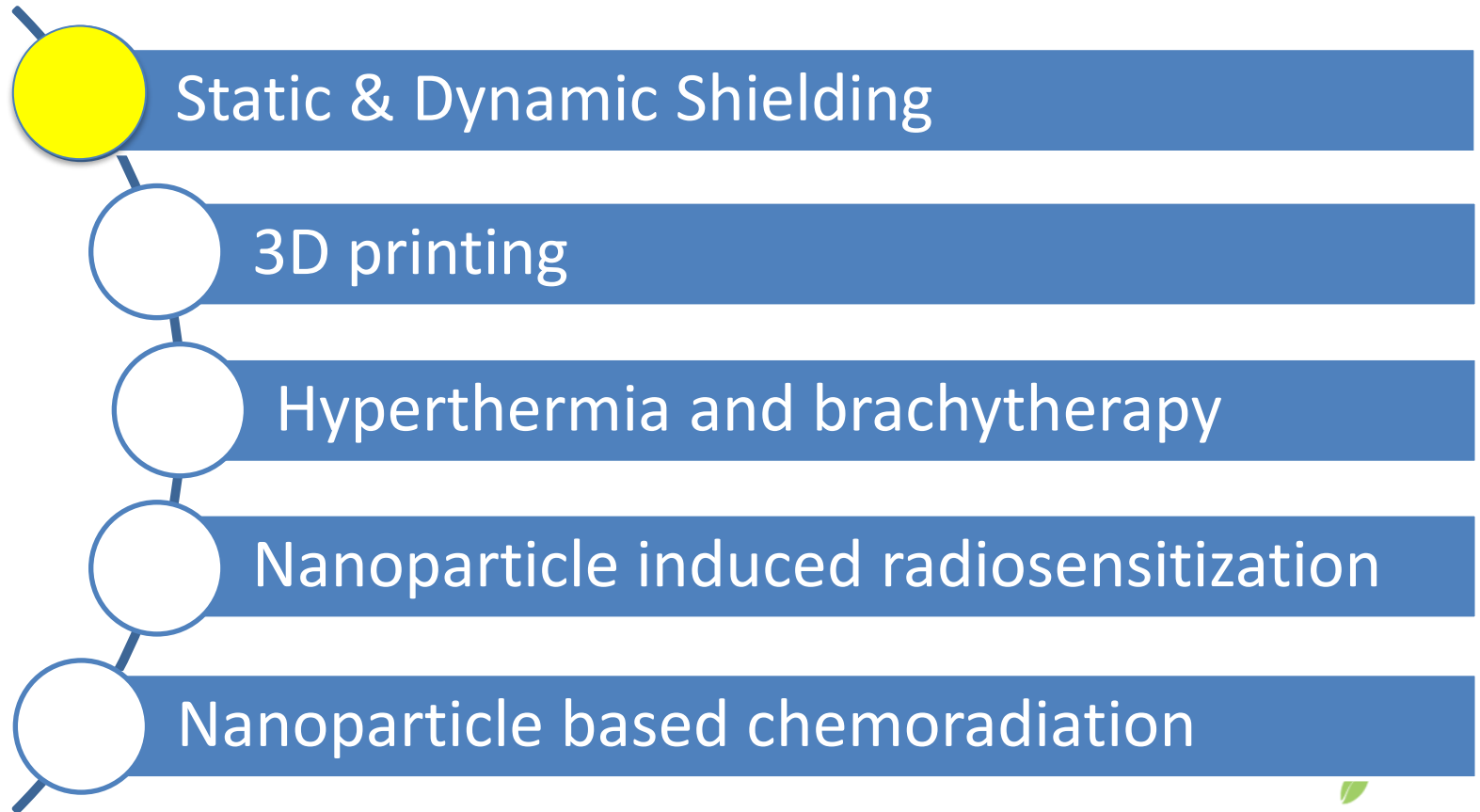
Stockholm

Manchester
& Fletcher

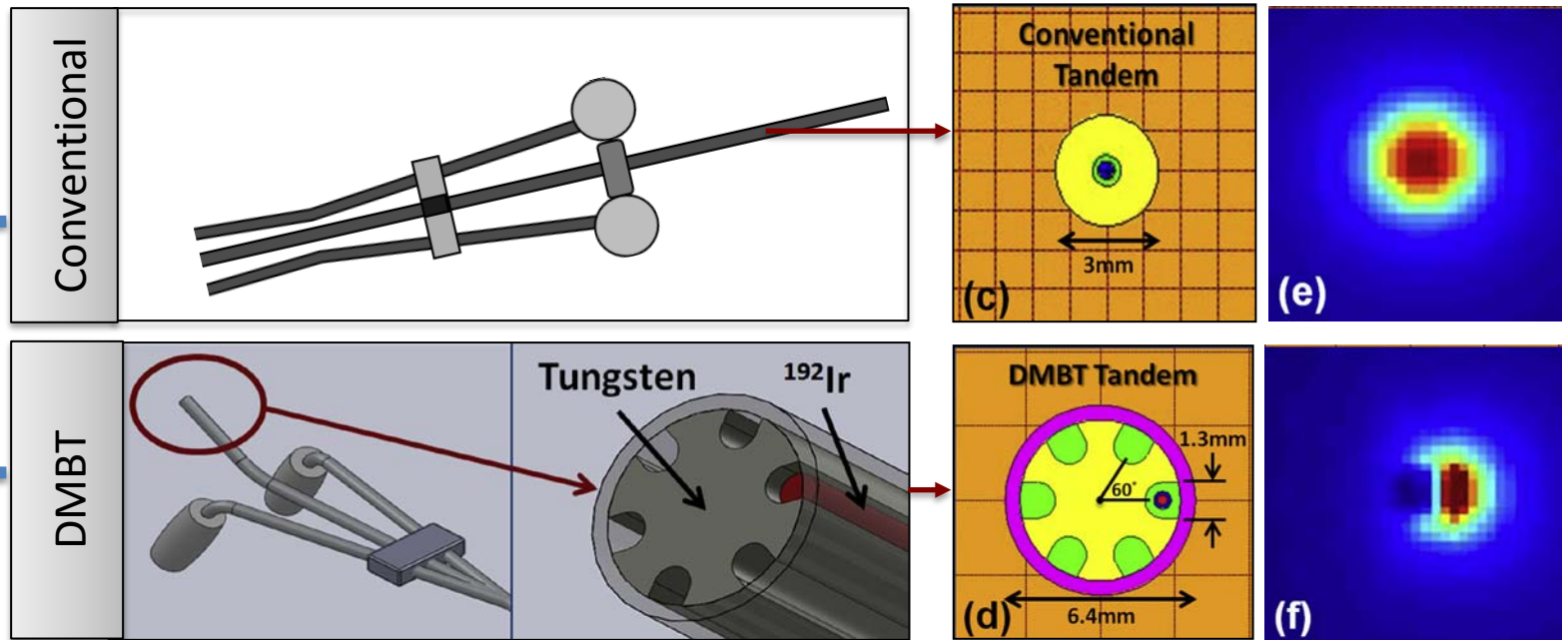
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Limitations of
IC Applicators

Emerging
Technologies



Static shielding: Direction-modulated BT (DMBT)



75 plans compared:
DMBT superior

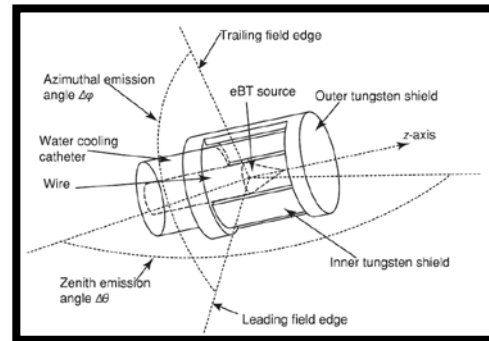
≈ D90: HR CTV
↓ D2cc: OAR

Discussion:

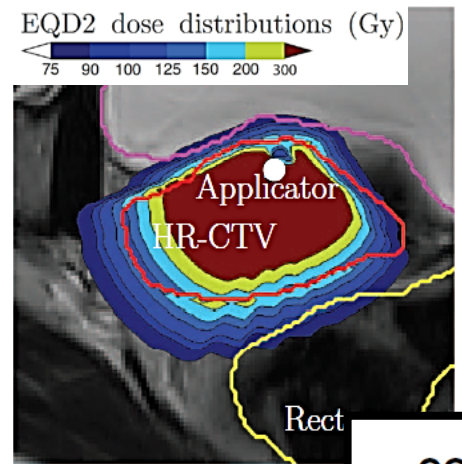
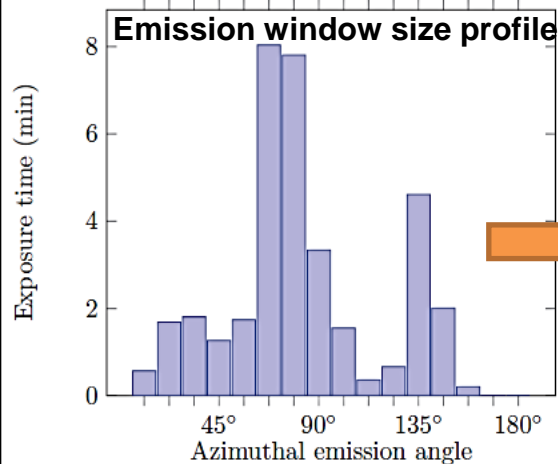
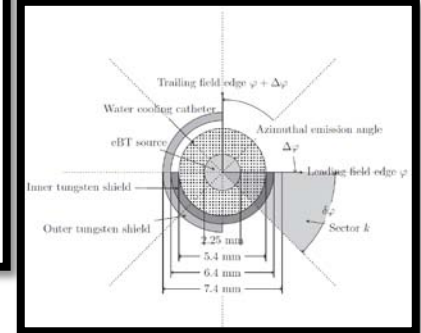
out that at least some of the advanced clinical cases in which interstitial needles are necessary (eg, parametrial or utero-sacral extensions) (15) can be replaced with the DMBT applicator. For this study, the selected patients were

Dynamic Rotating Shield Brachytherapy - D-RSBT

- Electronic brachytherapy source
- Shield: changing emission angles



Liu Y, et al. Med Phys 2013



Plans of 5 cases compared:

- D-RSBT vs. IC/IS BT
- 30 additional min. for D-RSBT:
- D90 improved for 20 Gy (EQD2)
- OAR doses +/- unchanged

CONCLUSIONS

Patients who need to be treated with HDR-BT may benefit from the D-RSBT technique. Compared to the existing interstitial BT methods such as IS + ICBT, D-RSBT can generate less invasive plans with a better dose distribution at the expense of longer delivery times. D-RSBT is also likely to yield better plans in some cases where S-RSBT may have difficulty in striking a balance between dose quality and delivery time.

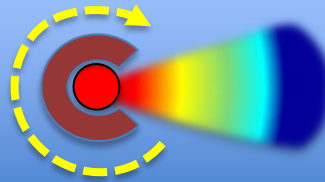
Liu Y, et al. Med Phys 2013

Adams QE, Xu J, Breitbach EK, et al. Med Phys 2014;41(5):051703
 Yang W, Kim Y, Wu X, et al. Phys Med Biol 2013;58(11):3931-41.
 Liu Y, et al. Med Phys 2013;40(5):051720
 Dadkhah H, Flynn RT, Wu X et al. Med Phys 2015; 42: 3465.
 Liu Y, Flynn RT, Kim Y, Yang W, Wu X. Med Phys 2013;40(12):12703
 Liu Y, Flynn RT, Kim Y, Wu X. Med Phys 2014;41(11):111709

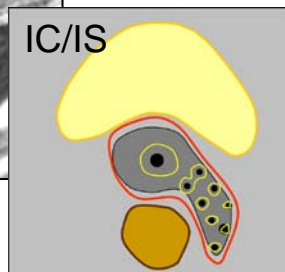
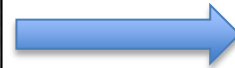
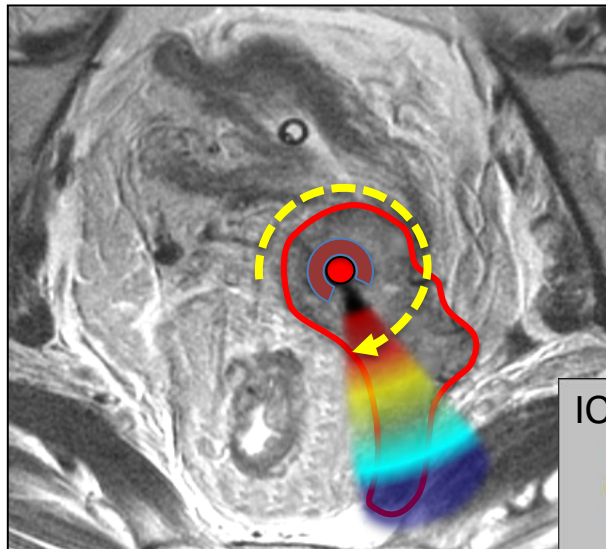
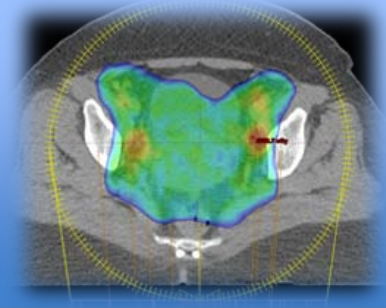
Static & Dynamic Shielding

Less invasive alternative to IC/IS BT?

CAUTION..



≠



- Fundamentally different D distribution then with IC/IS BT
 - ↑ TRAK
 - ↑ V150, V200
 - D heterogeneity
- Emission angle “Set-up” errors?
- IC / IS BT: excellent results!



Clinical impact?

Combined IC / IS & Rotational Dynamic Shielding BT?

Historical

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Fletcher

Modern

Stockholm

Manchester & Fletcher

Mould

Limitations of IC Applicators

Emerging Technologies

Emerging technologies

Historical

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Stockholm

Manchester

Fletcher

Modern

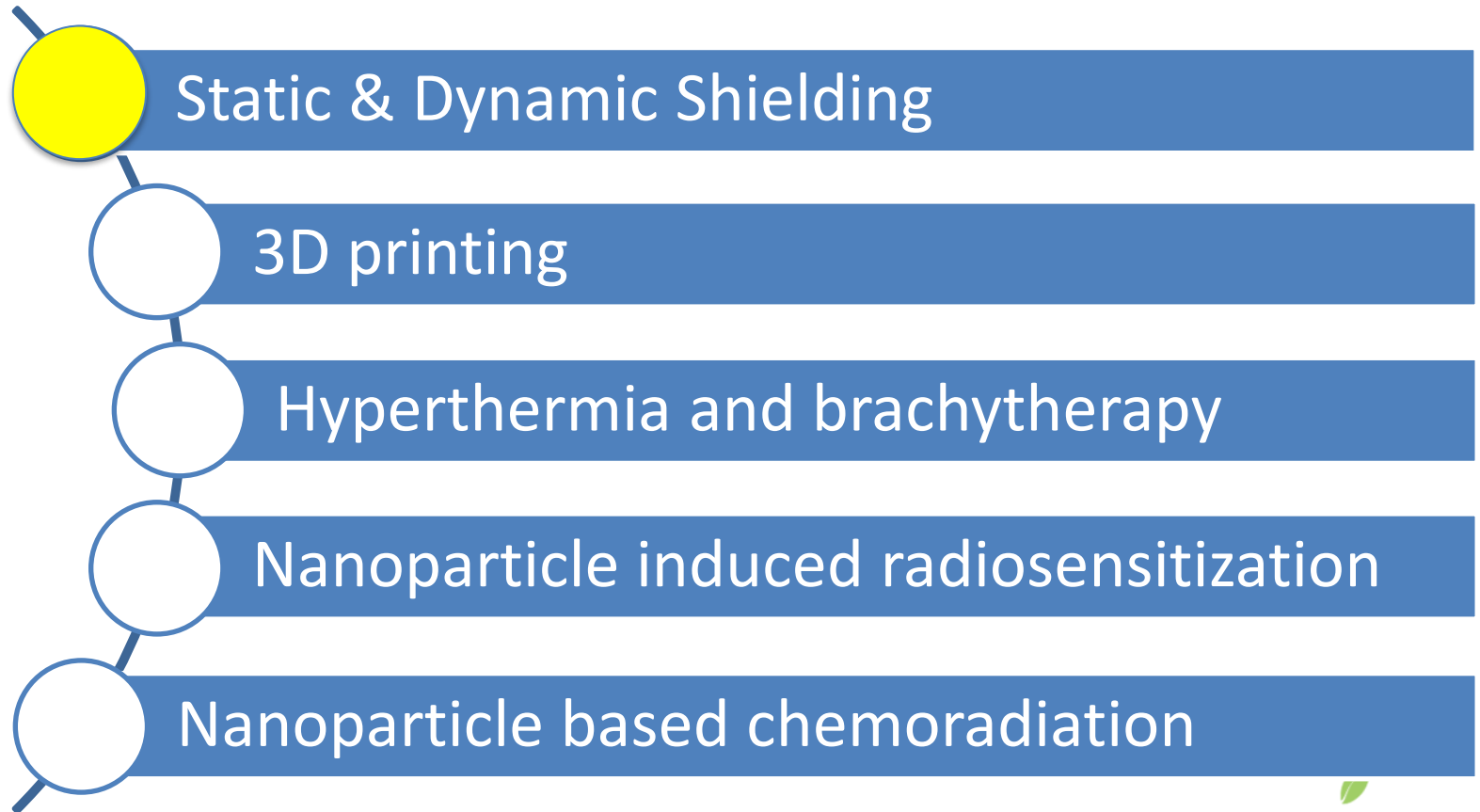
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& Fletcher

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Limitations of
IC Applicators

Emerging
Technologies



3D printing technology (IC or IC/IS)

Historical

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Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

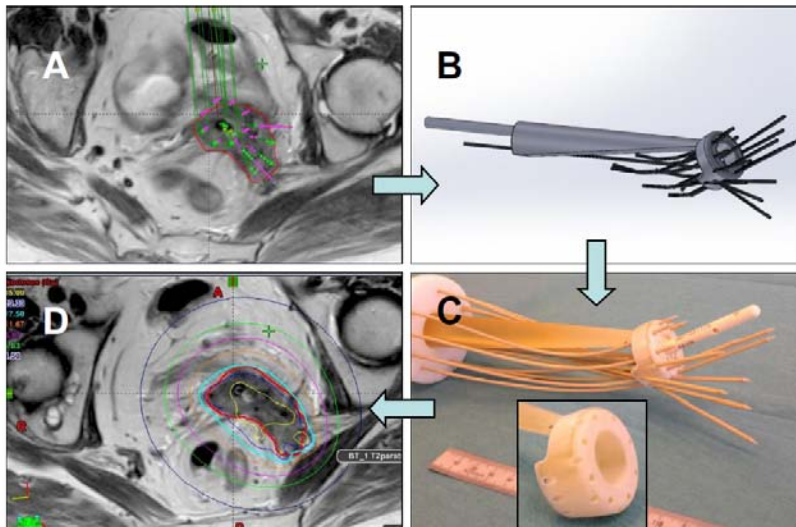
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Limitations of
IC Applicators

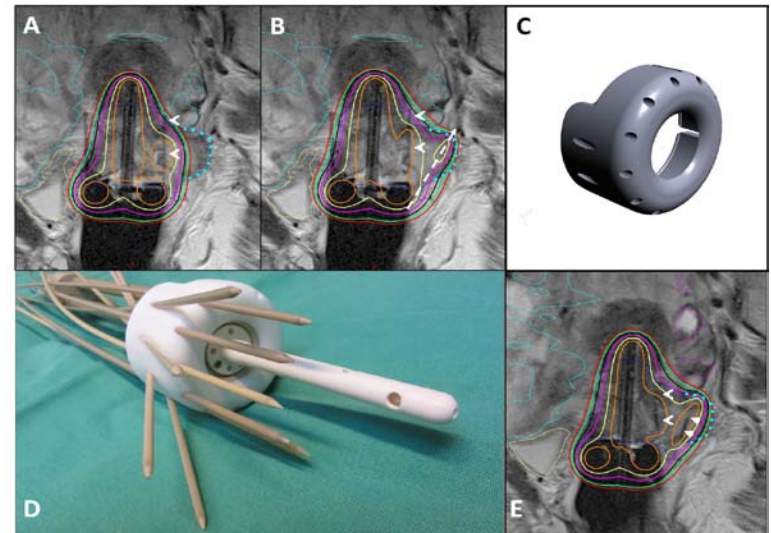
Emerging
Technologies



Classic Moulage
technique



Lindegaard J, et al. *Radiother Oncol* 2016



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

Emerging technologies

Historical

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Stockholm

Manchester

Fletcher

Modern

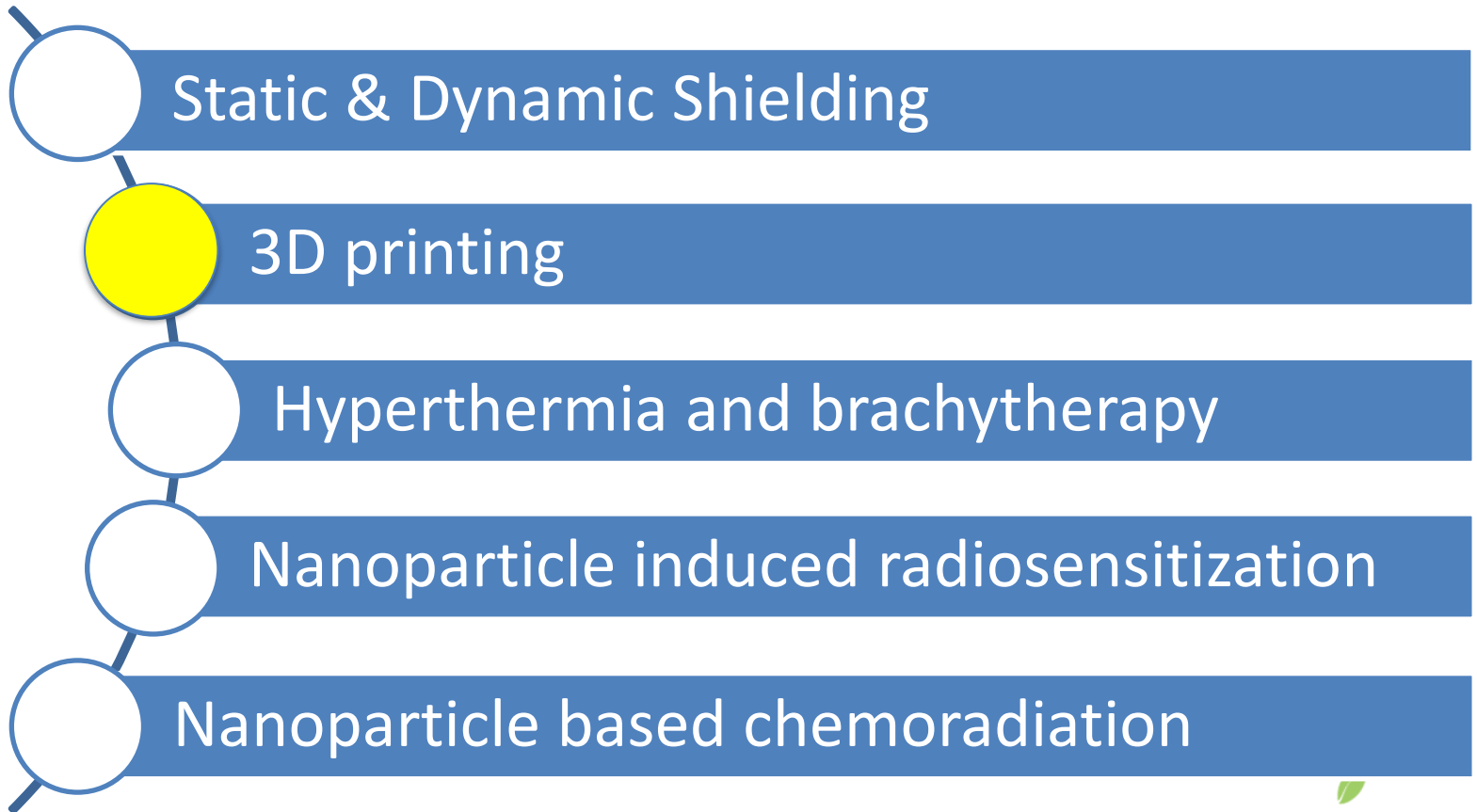
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Limitations of
IC Applicators

Emerging
Technologies



Hyperthermia & Brachytherapy

Paris

Stockholm

Manchester

Fletcher

Modern

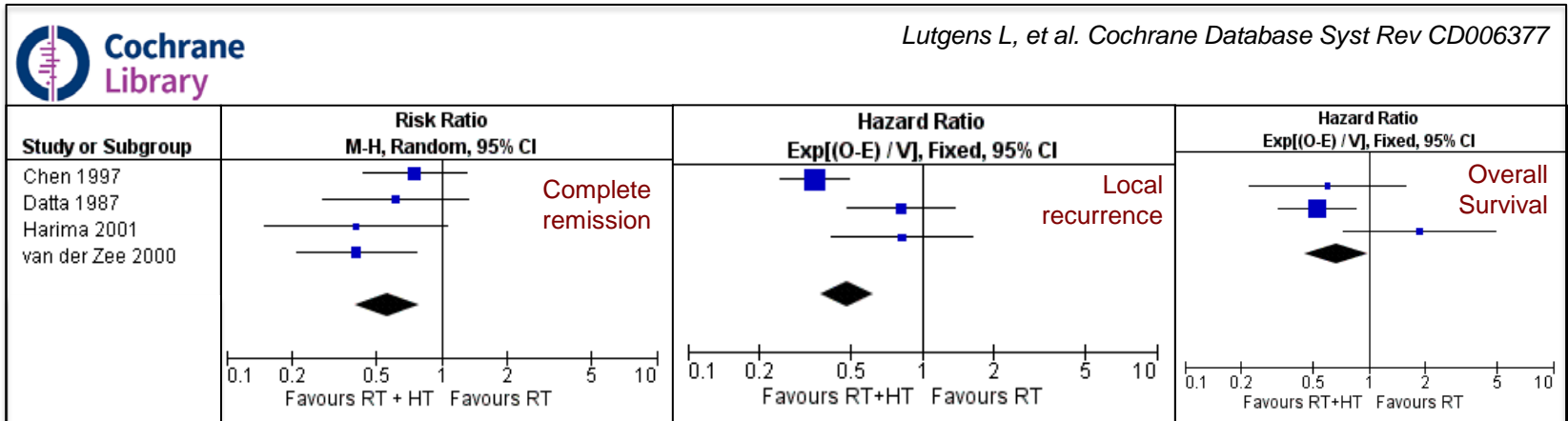
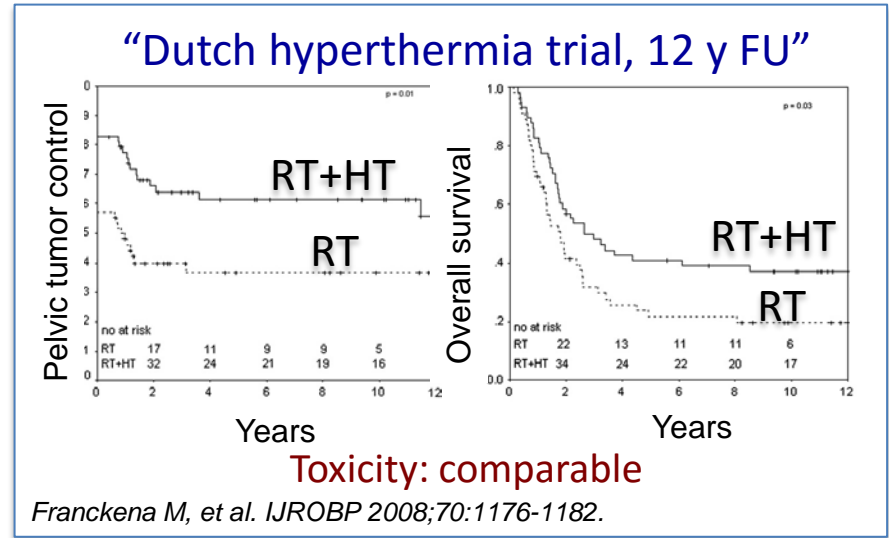
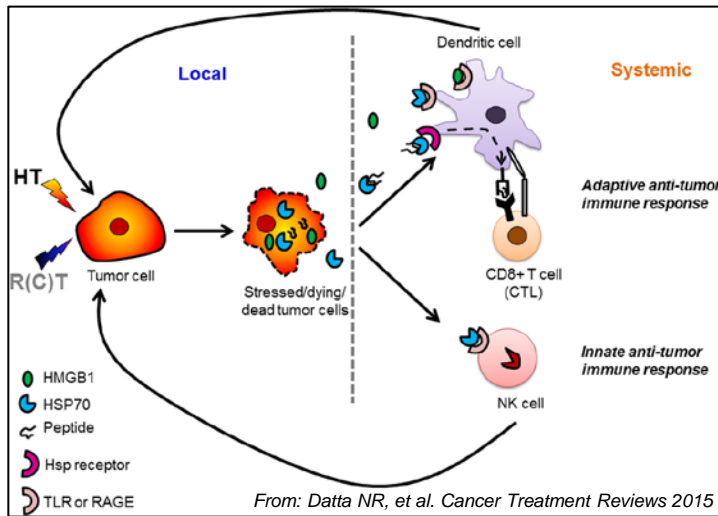
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Manchester & Fletcher

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Limitations of IC Applicators

Emerging Technologies

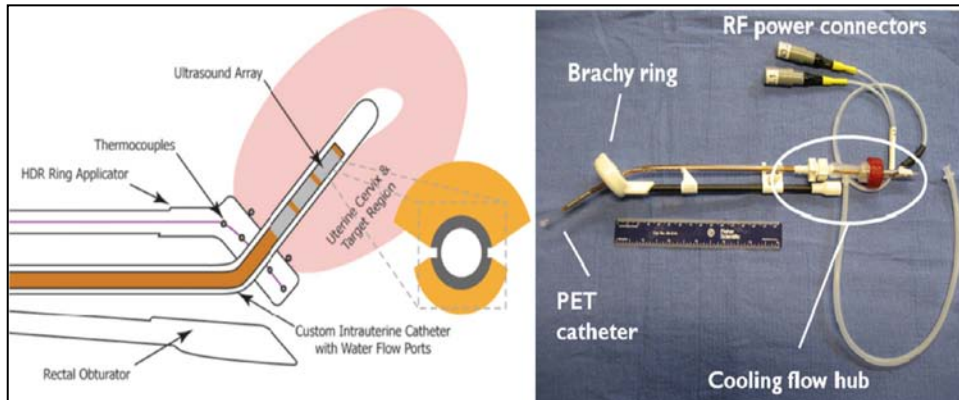


Datta NR, et al. Cancer Treatment Reviews 2015;41:742-753.
 Mallory M, et al. Critical Rev in Oncol / Hematol 2016;97:56-64.
 Warrel G, et al. Med Phys. 2015;42(6):3709.
 Chen X, et al. Int J Hyperthermia. 2010;(1):39-55.

Lutgens L, et al. Cochrane Database Syst Rev CD006377
 Franckena M, et al. IJROBP 2008;70:1176-1182.
 Franckena M, et al. IJROBP 2009;73:242-50.
 Franckena M, et al. Eur J Cancer 2009;45:1969-1978.

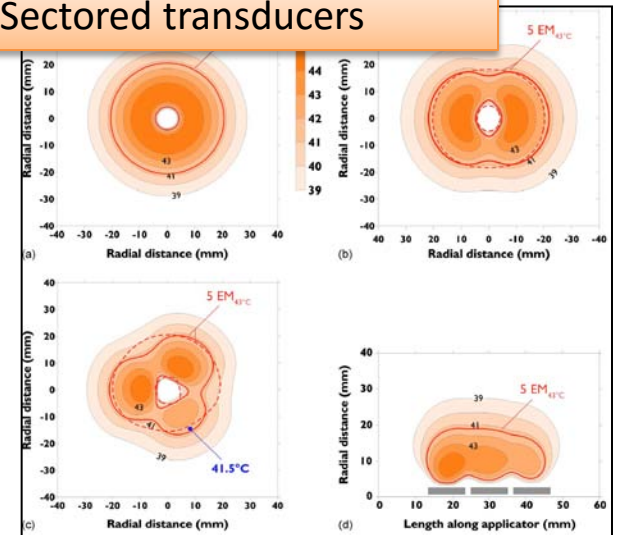
Hyperthermia & Brachytherapy

Catheter based ultrasound applicators for integrated hyperthermia

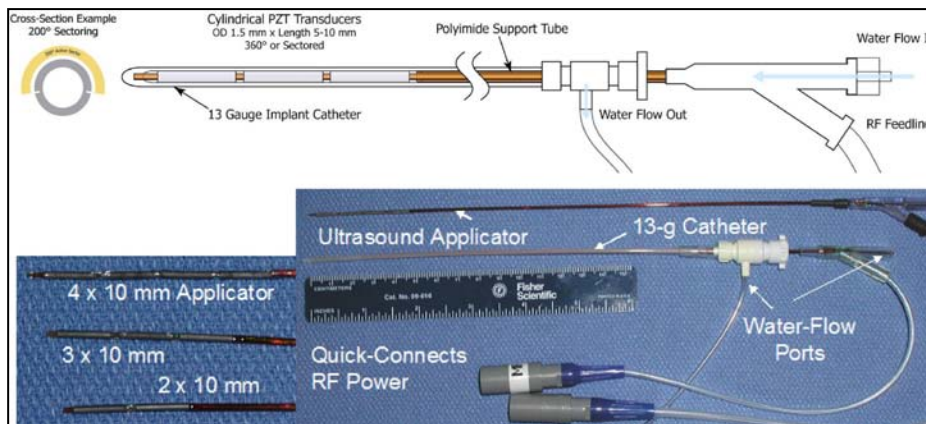


Diederich CJ, et al. Med Phys 2014

Sector transducers



Wootton JH, et al. Med Phys. 2011.



Diederich CJ, et al. Med Phys 2014

Spatial control of heating

Historical

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Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

Mould

Limitations of IC Applicators

Emerging Technologies

Hyperthermia & Brachytherapy

Catheter based ultrasound applicators for integrated hyperthermia

Historical

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Stockholm

Manchester

Fletcher

Modern

Stockholm

Manchester & Fletcher

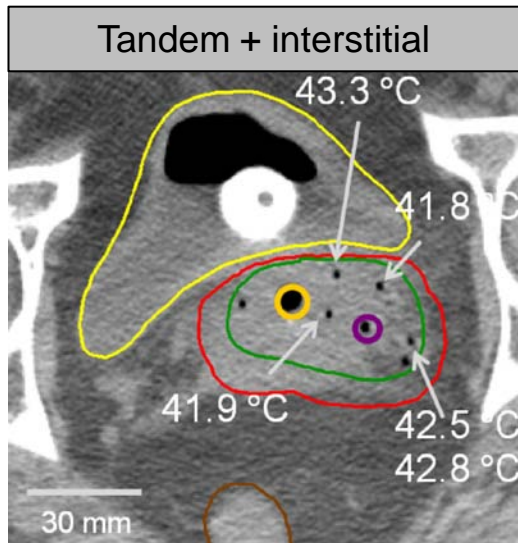
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Limitations of IC Applicators

Emerging Technologies



Wootton JH, et al. *Med Phys*. 2011;38(2):598-611



Diederich CJ, et al. *Med Phys* 2014

Spatial control of heating

Pilot studies (cervix, prostate): feasible

Further clinical studies needed...

Emerging technologies

Historical

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Manchester

Fletcher

Modern

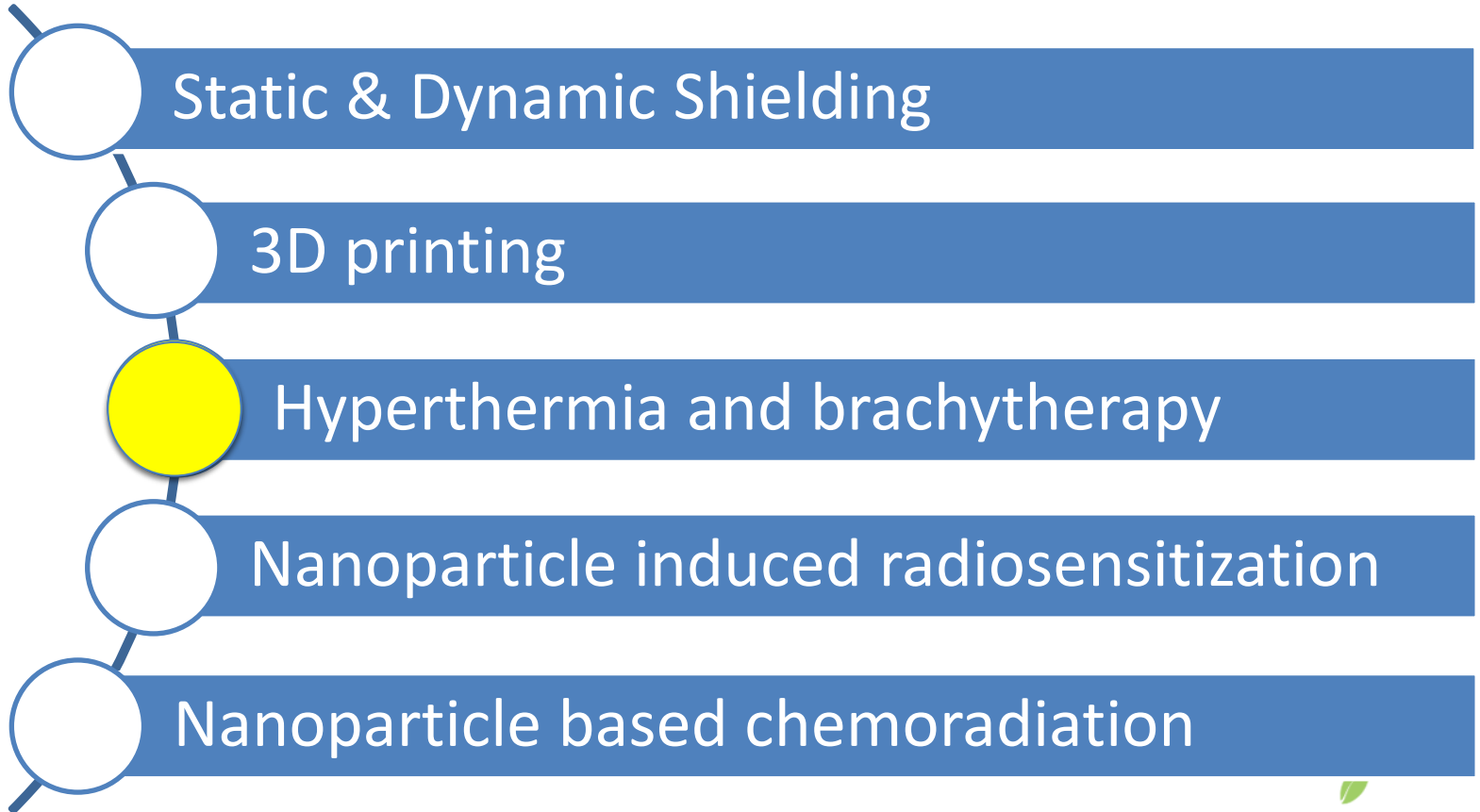
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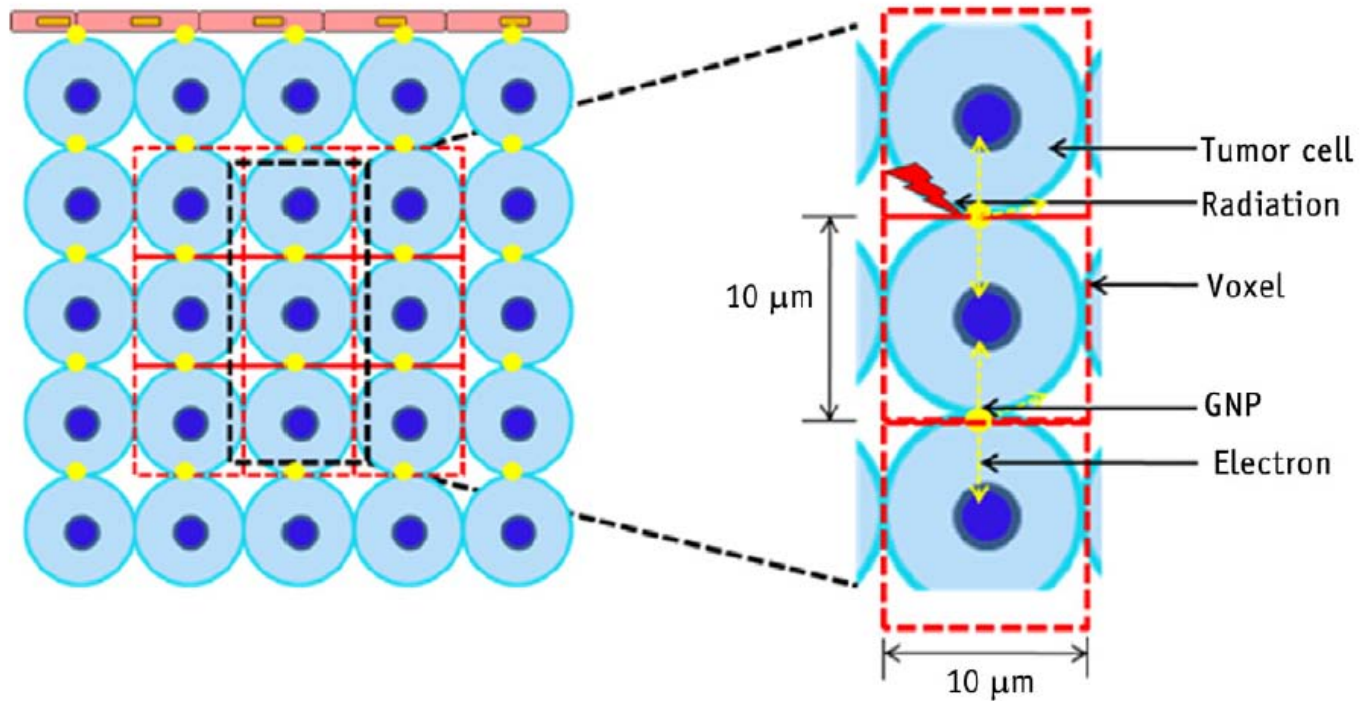
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Limitations of
IC Applicators

Emerging
Technologies



Nanoparticle – induced radiosensitization



Radiation induced photoelectrons from GNP
→ DEF of > 20% at 5 mm from BT source

Historical

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Stockholm

Manchester

Fletcher

Modern

Stockholm

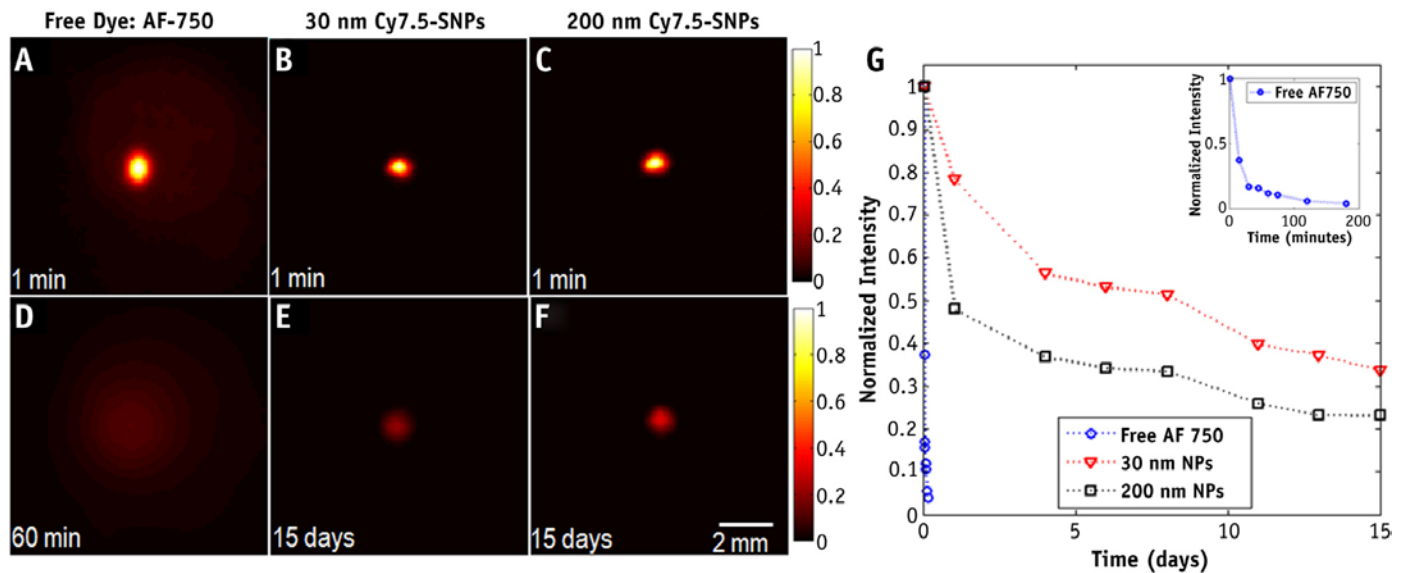
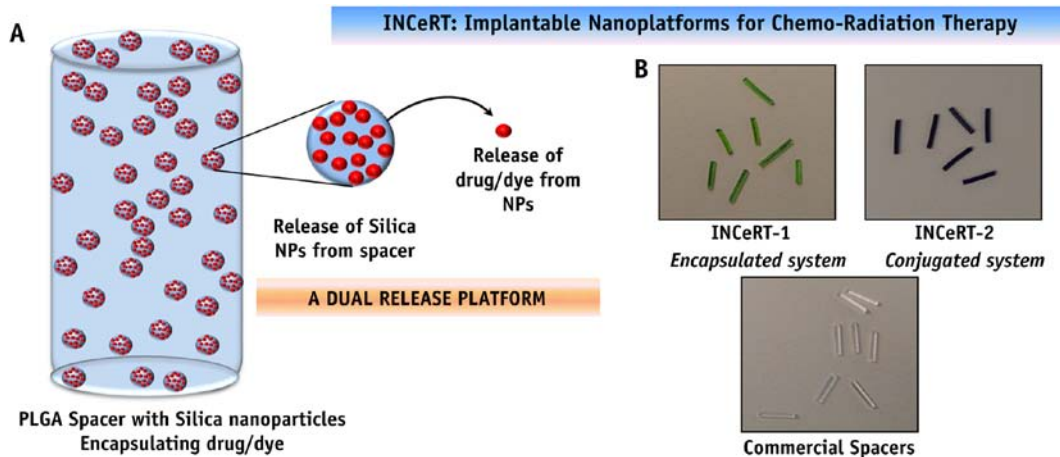
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& Fletcher

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Limitations of
IC Applicators

Emerging
Technologies

Nanoparticle - based local chemoradiation



Kumar R, Belz J, Markovic S, et al. Nanoparticle-based brachytherapy spacers for delivery of localized combined chemoradiation therapy. IJROBP 2015;91(2):393-400.
 Cormack RA, Sridhar S, Suh WW, et al. Biological in situ dose painting for image-guided radiation therapy using drug-loaded implantable devices. IJROBP 2010;76:615-623.

Summary

Historical

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Fletcher

Modern

Stockholm

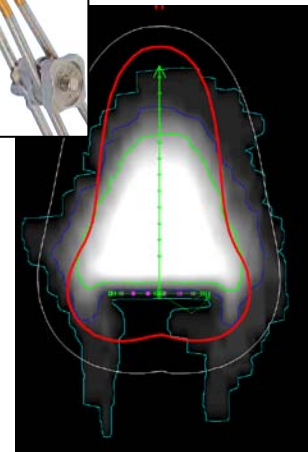
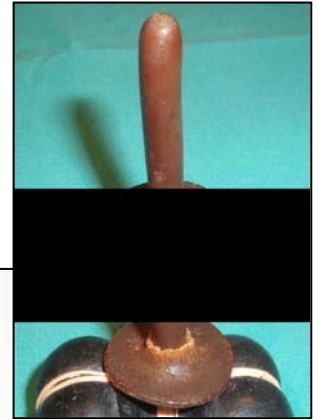
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Limitations of
IC Applicators

Emerging
Technologies

- 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, further studies needed:
 - Static and Dynamic shielding techniques
 - Applicators for catheter – based hyperthermia
 - Nanoparticle eluting



Applicators for intracavitary treatment of cervical cancer



Primoz Petric

National Center for Cancer Care and Research, Doha, Qatar



Vienna University

founded 1365



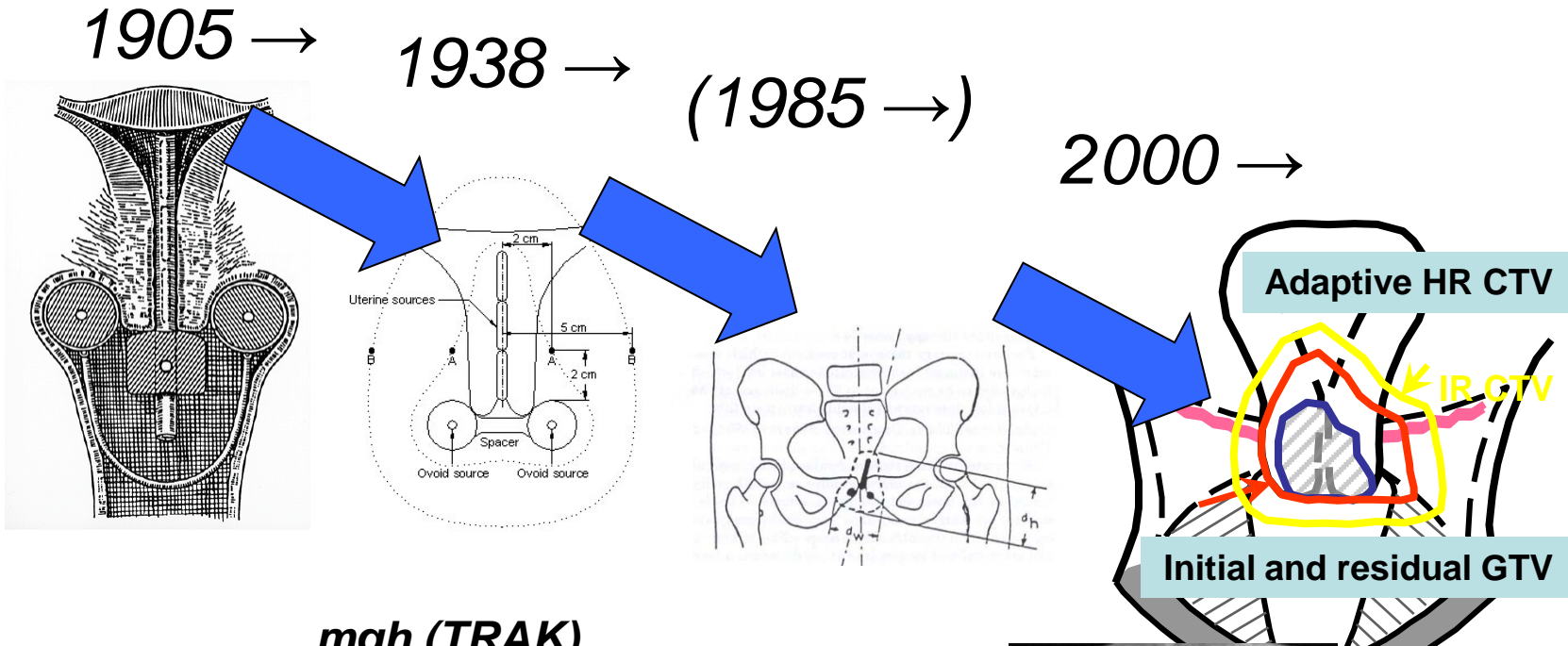
ICRU-GEC ESTRO recommendations:
GTV, CTVs at diagnosis
and at time of brachytherapy
for cervix cancer

*ESTRO-CARO Teaching Course
Image Guided Cervix Cancer Radiotherapy
Toronto, April 4-6, 2016*

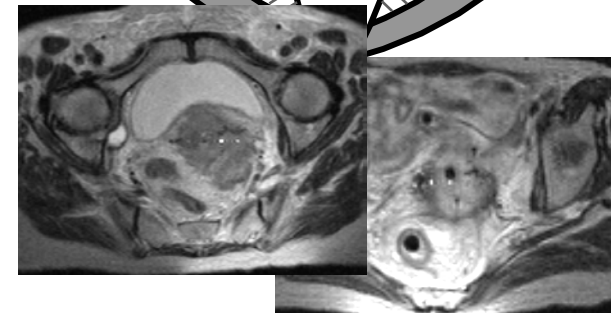


Richard Pötter, Christine Haie-Meder

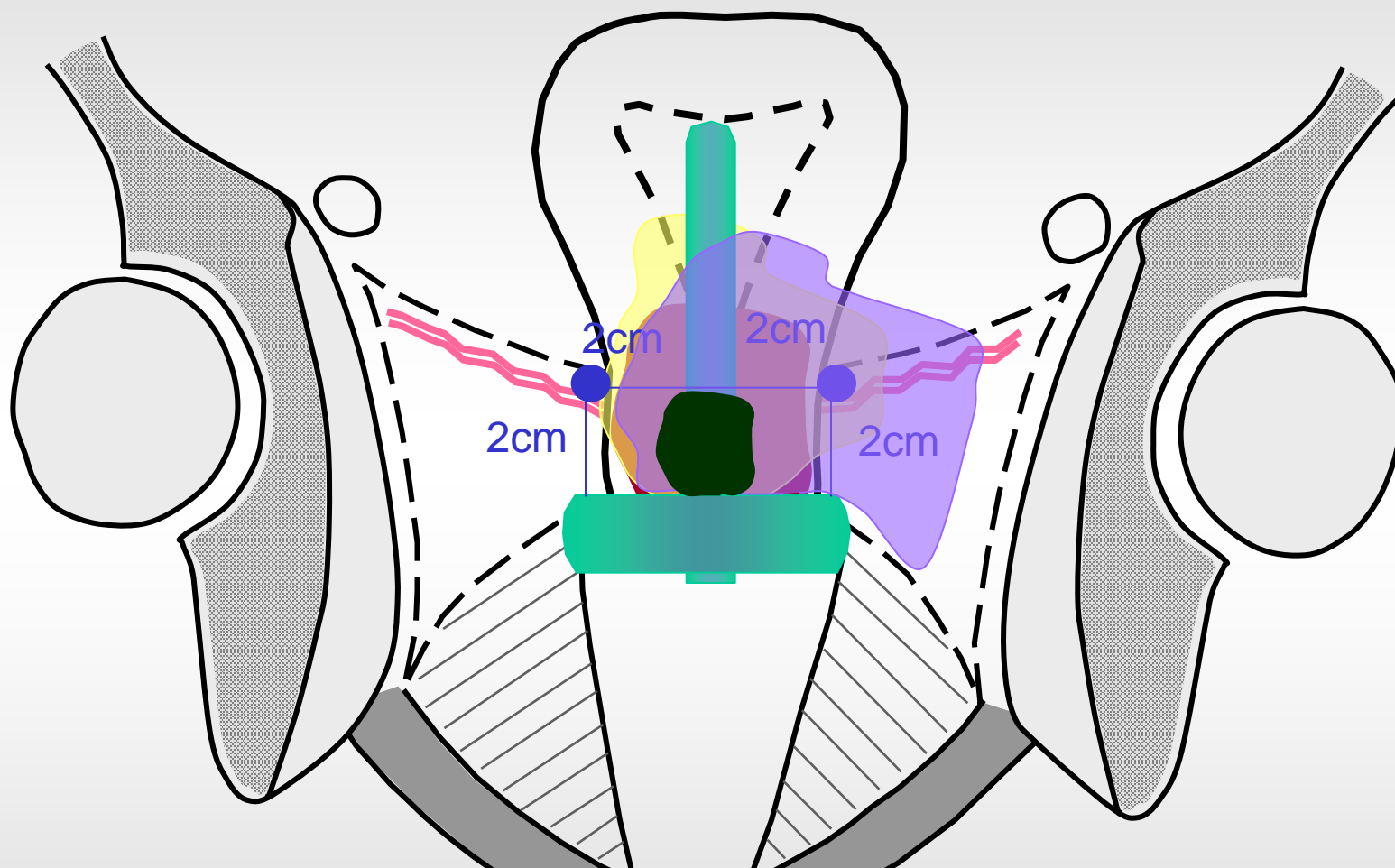
gynaecologic brachytherapy evolution



mgh (TRAK)
Dose point A (R/rad/Gy)
Ref. Dimensions/Volumes (ICRU 38, 1985)
3D image based adaptive CTVs/OARs
(GEC ESTRO Rec. 2005/ ICRU report 89, 2016)



Limitations of 2D X-ray based BT: Point A



Identical dose point specification for large variation of tumour size and configuration

GYN GEC ESTRO RECOMMENDATIONS-BACKGROUND

From 2D to 3D/4D

Historical difficulties in communicating results of cervical BT due to different traditions (point A, 60 Gy reference volume, ..., midline block)

- CTV according to GTV at diagnosis?
- CTV according to GTV at BT?

Building the tower of Babel
(confusion of languages)

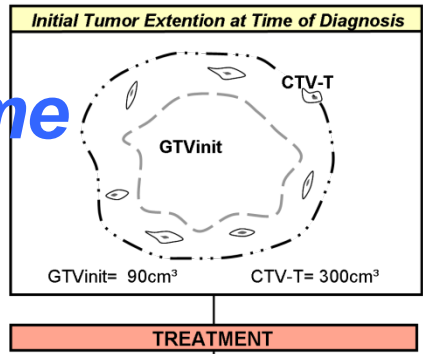
Brueghel, 16th century (1563)

Vienna, Museum of Fine Arts



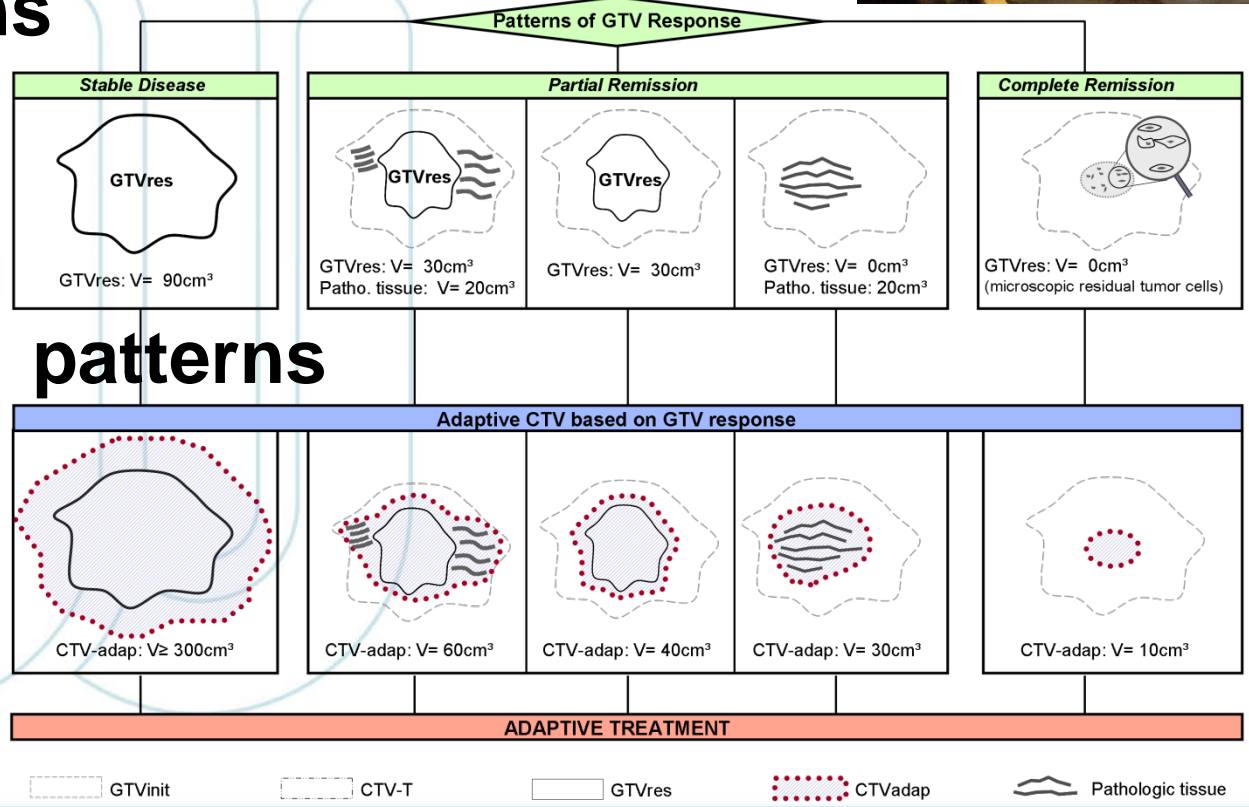
Need of a common language!

The challenge of change in tumour volume and tumour configuration during treatment



Various patterns of GTV response

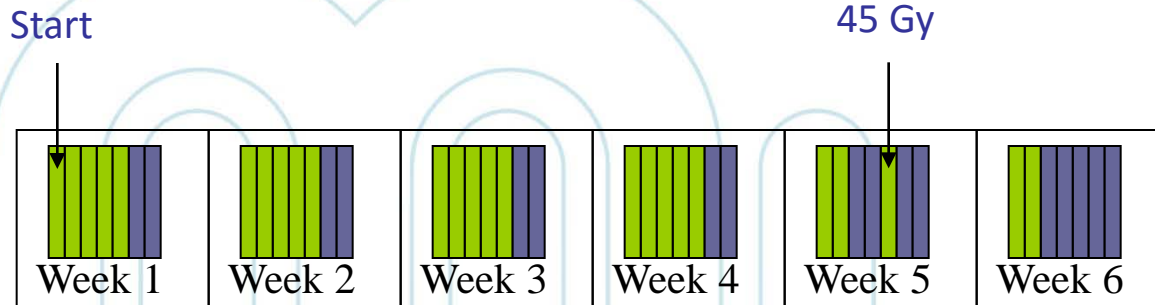
Corresponding adaptive CTVs



ICRU/GEC ESTRO
 Upcoming report 89
 Fig 5.3

Concomitant Chemoradiotherapy and boost brachytherapy (OTT < 50 days)

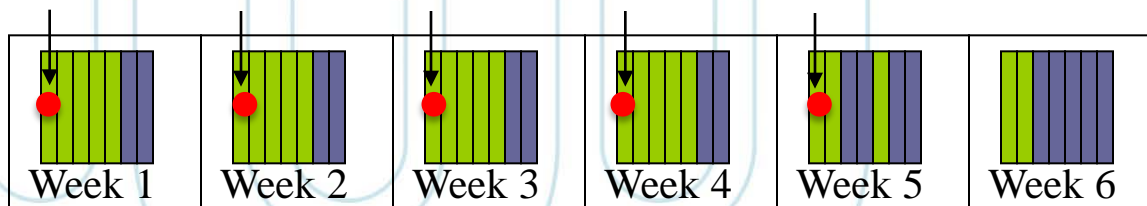
External beam radiotherapy



Chemotherapy

1. Cycle

5-6 Cycles

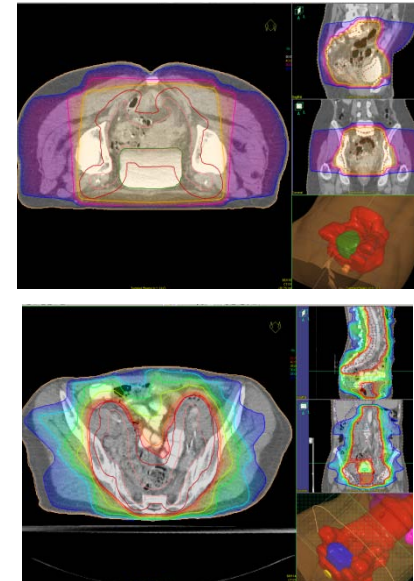
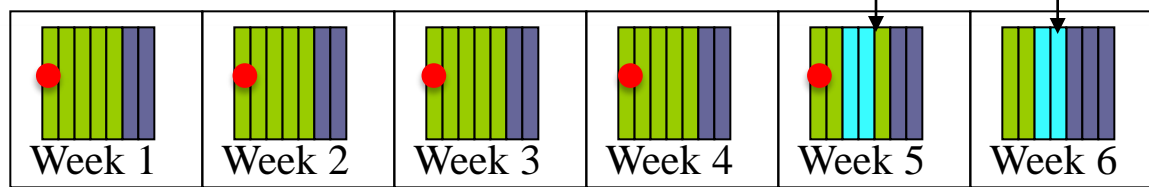


Brachytherapy

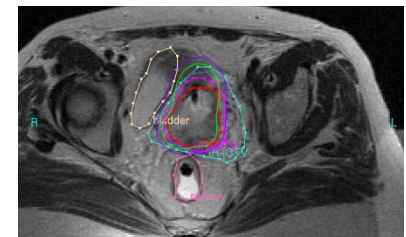
HDR or PDR

EQD₂ 65 Gy

EQD₂ 85 Gy



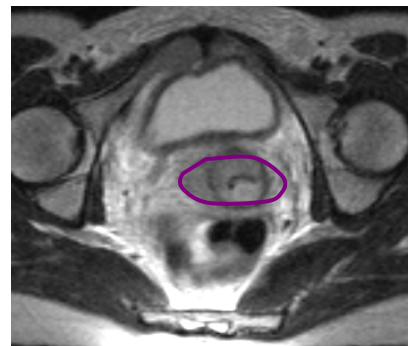
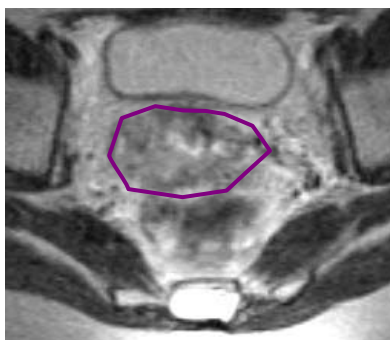
Cisplatin 40 mg/m²



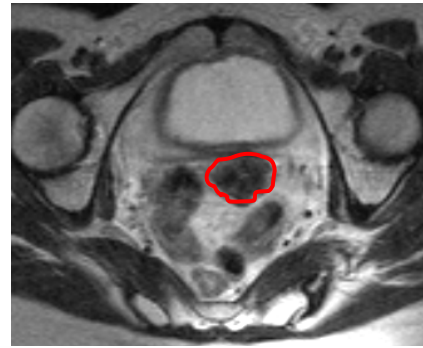
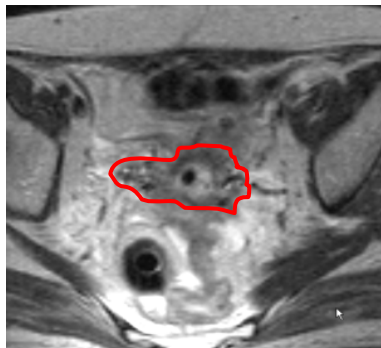
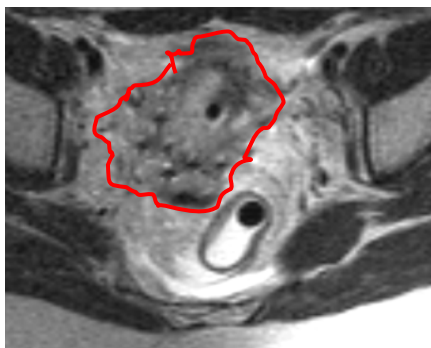
Adaptive radiotherapy: typical examples cervix cancer

Different tumour response – Adaptation of target volume

At diagnosis



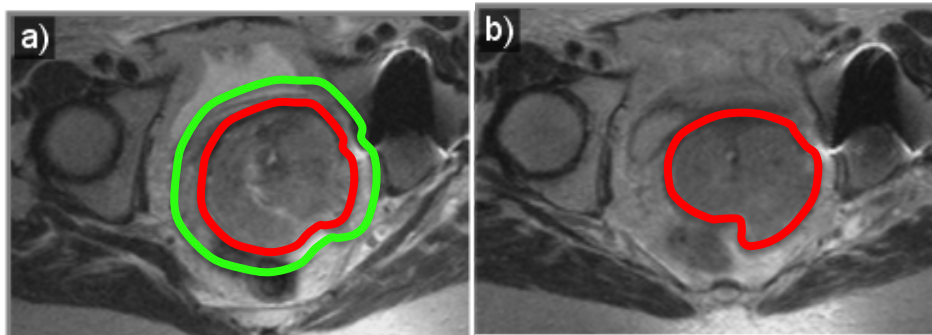
At brachytherapy (after 40-45 Gy EBRT-ChT)



Example: cervical cancer, FIGO IIIB: total dose 90 Gy EQD2

EBRT dose

0 Gy



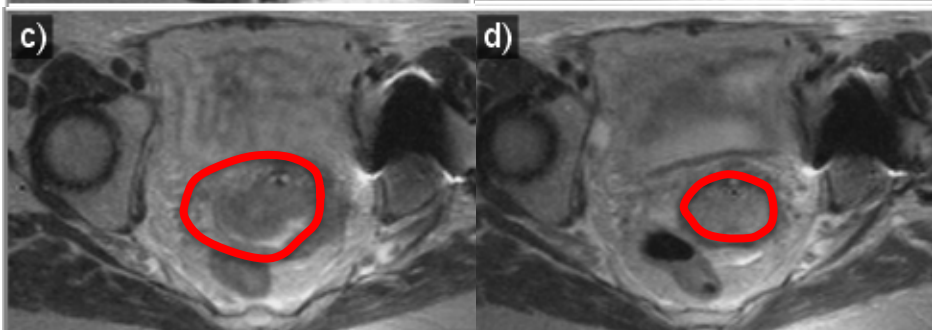
EBRT dose

9 Gy



Cisplatin (40 mg/m²) x1

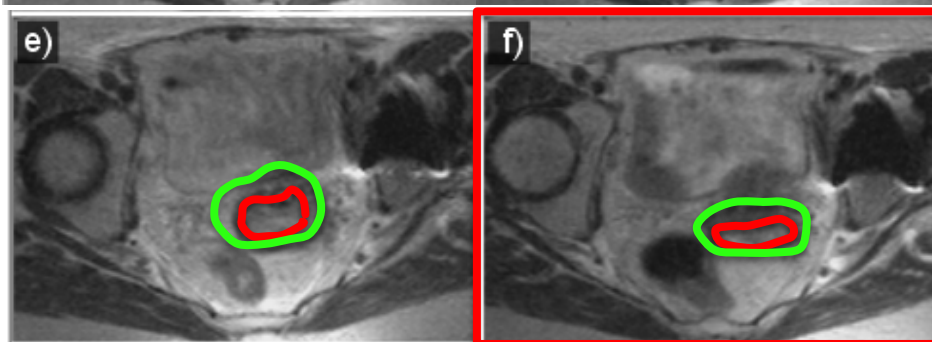
18 Gy



27 Gy

Cisplatin (40 mg/m²) x3

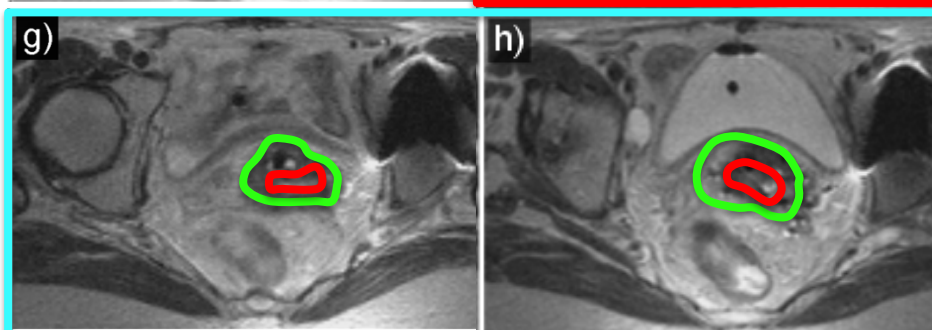
36 Gy



45 Gy

Pre-brachytherapy

EBRT45 Gy

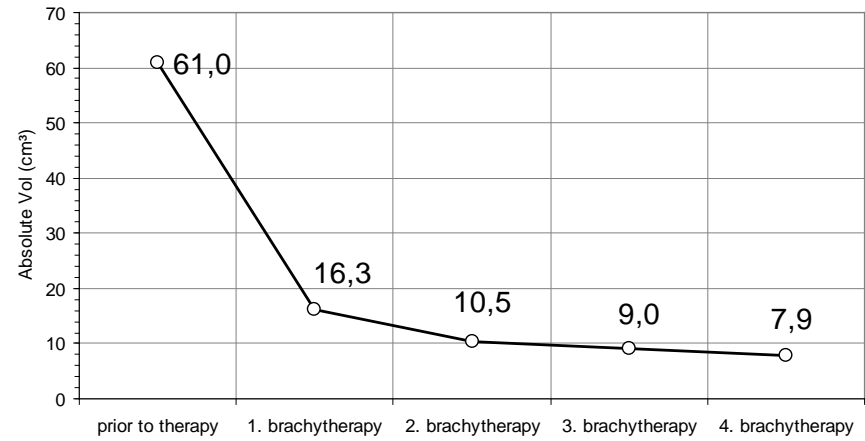
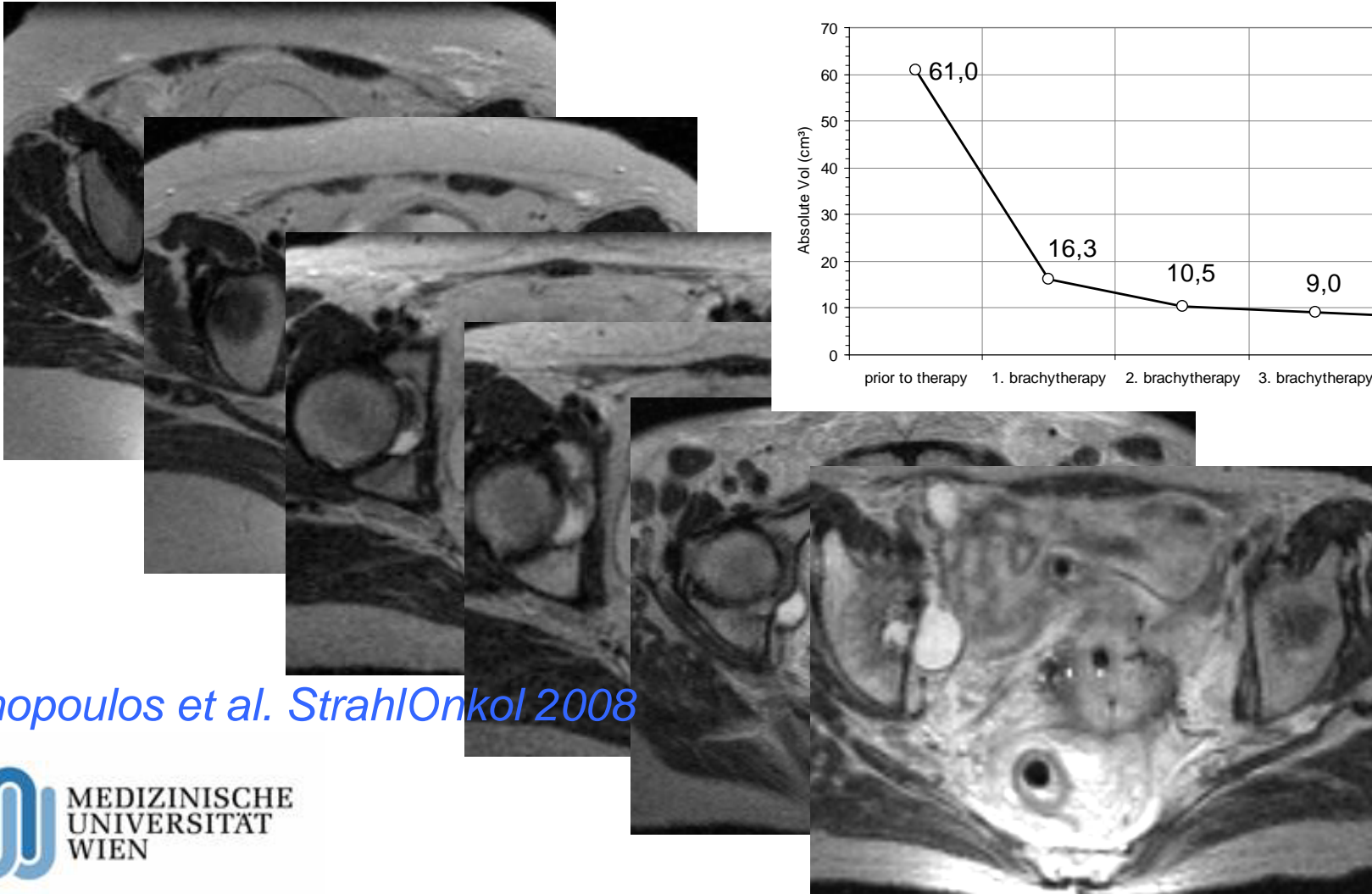


IGABT 45 Gy

Brachytherapy

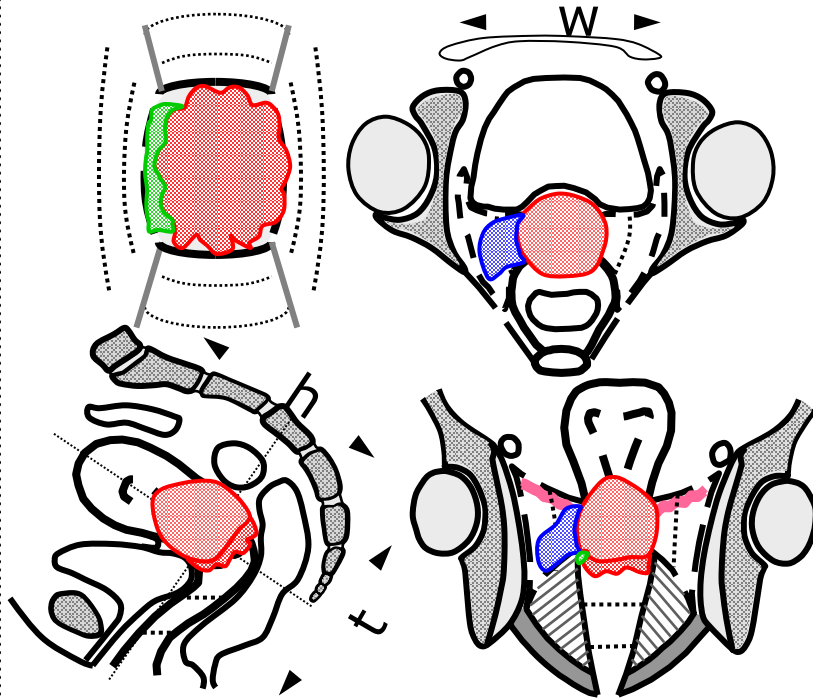
— GTV
— CTV

MRI: Initial tumour extension (3D RT) pattern of response (4D RT) for adaptive MRI based planning

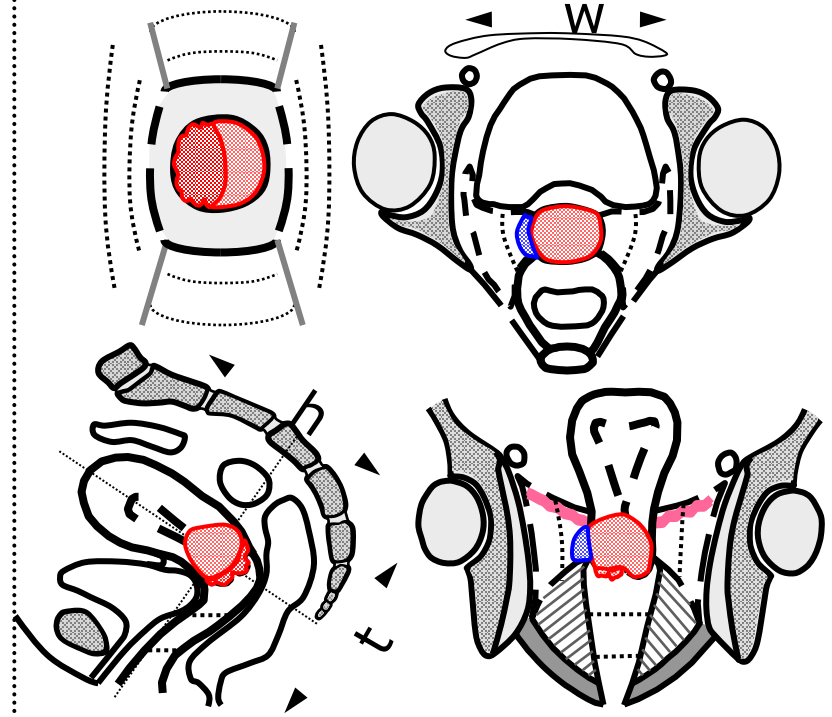


Dimopoulos et al. StrahlOnkol 2008

Findings at time of diagnosis

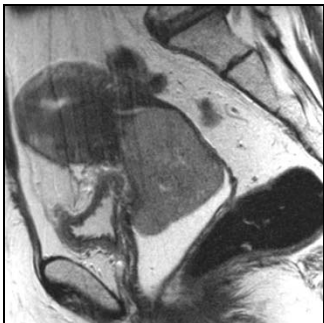
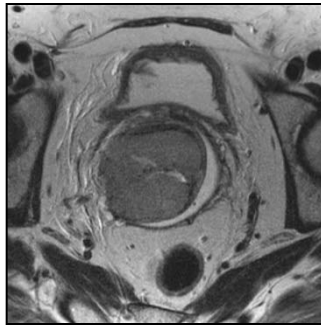


Findings at time of brachytherapy



Dimensions (cm):

Width: 7
Thickness: >5
Height: >5
Vaginal inv.: 0.5
(right fornix)



Dimensions (cm):

Width: 3.5
Thickness: 2
Height: 2
Vaginal inv.: 0

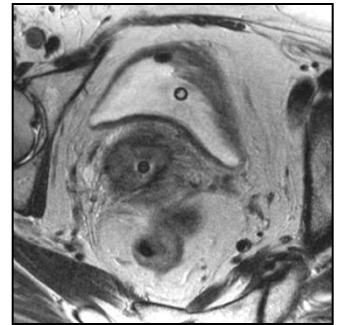


Fig.5.1

HR-CTV includes:

- A. Res GTV, res pathologic tissues, and always the whole cervix**
- B. the whole cervix + safety margins**
- C. the whole uterus + safety margins**
- D. the initial tumor extension**

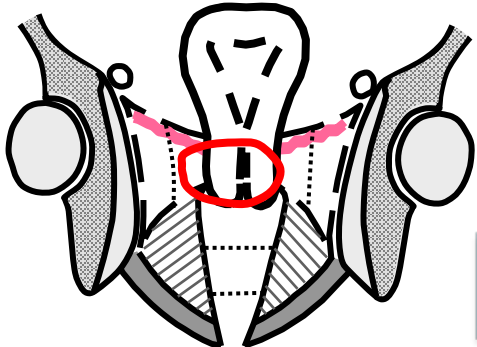
IR-CTV includes:

- A. the initial tumor extension**
without adapting to the situation at brachytherapy
- B. the whole uterus + safety margins**
- C. HR-CTV plus safety margins**
taking into account initial tumor extension

Volumetric tumour regression: FIGO stage IIB cervical cancer, large tumor at diagnosis subgroup from EMBRACE data base, N=183/345

At diagnosis

At brachytherapy

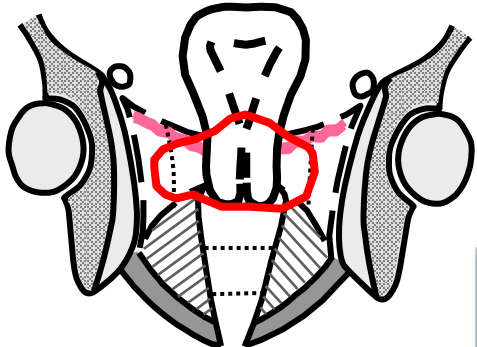
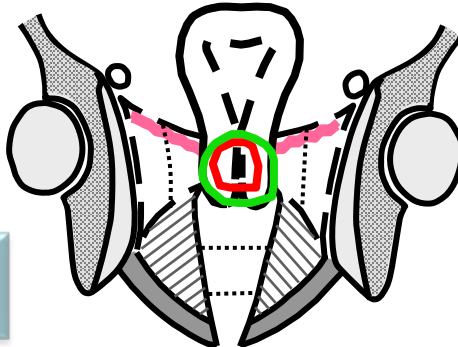


Good response

N=68

Mean GTV
45.2 cm³

Mean HR CTV
24.6 cm³

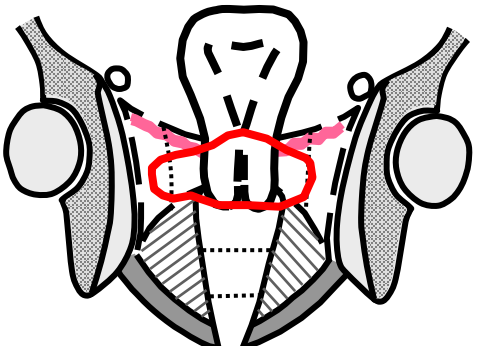
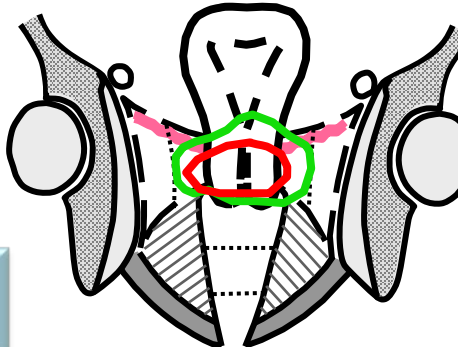


Moderate response

N=98

Mean GTV
76.7 cm³

Mean HR CTV
40.1 cm³

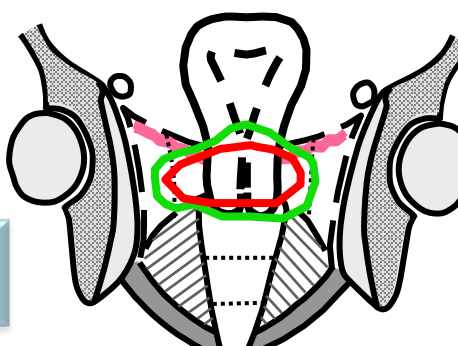


Poor response

N=17

Mean GTV
62.1 cm³

Mean HR CTV
57.8 cm³



— GTV
— HR CTV

The language challenge I

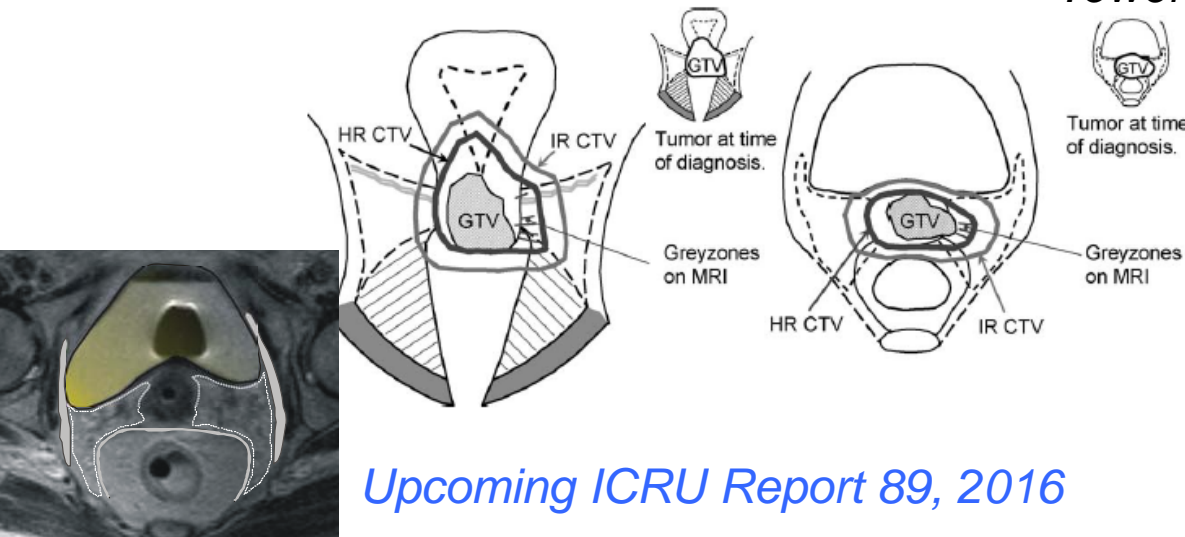
Risk orientated (“High Risk”) adaptive Target concept

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

- Assessment of initial GTV and residual GTV + pathologic residual tissue based on repetitive MRI (CT/US) + clinical exam. at diagnosis and at time of Brachytherapy (40-45 Gy)
- Introduction of an initial and adaptive target concept related to the GTV: High Risk CTV-T and Intermediate Risk CTV-T

Tower of Babel: confusion of languages

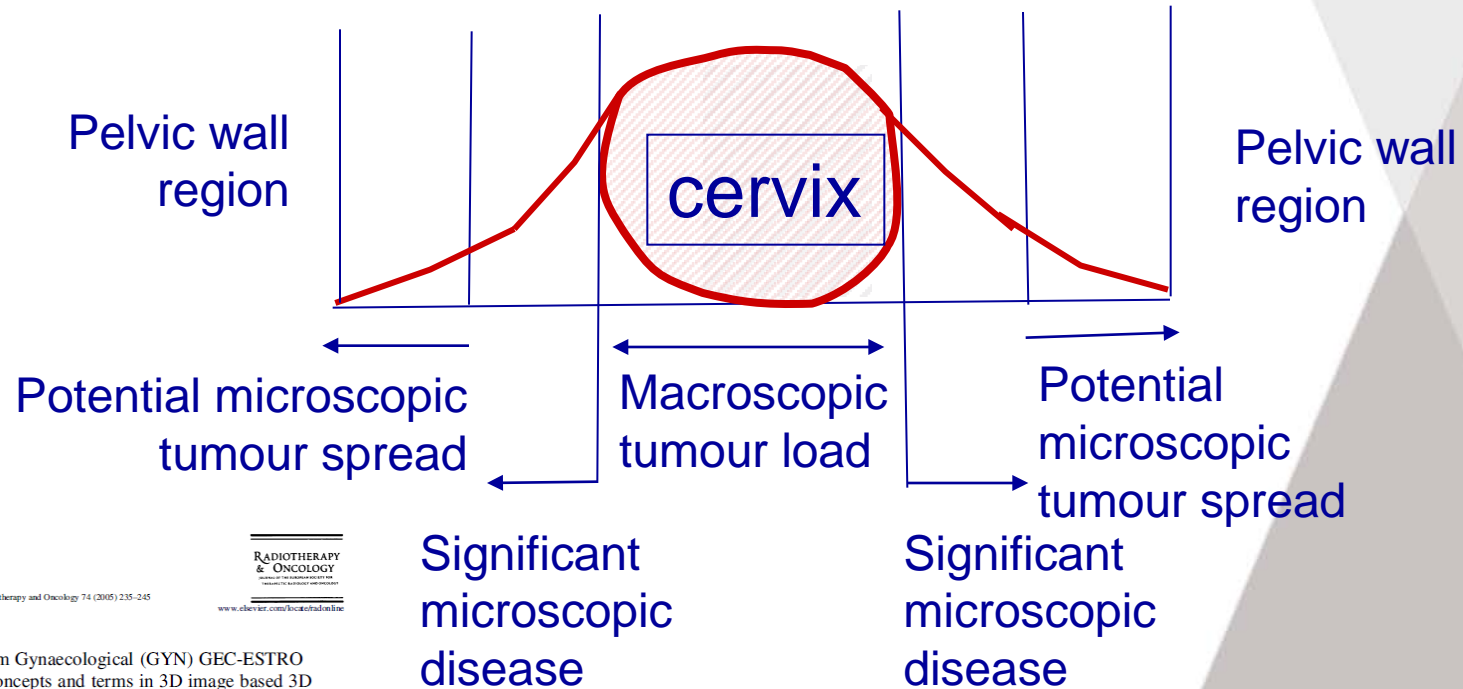


Upcoming ICRU Report 89, 2016



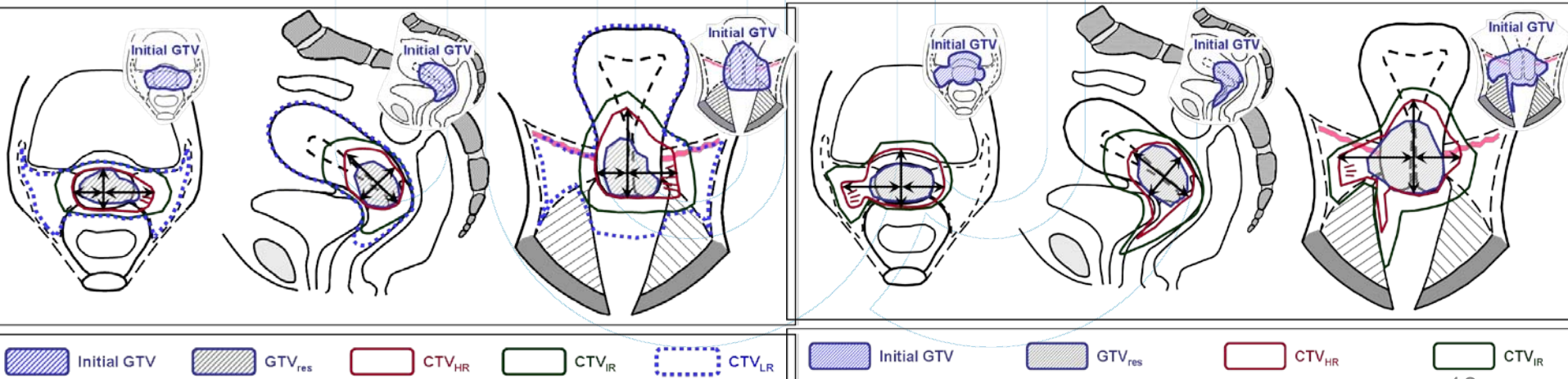
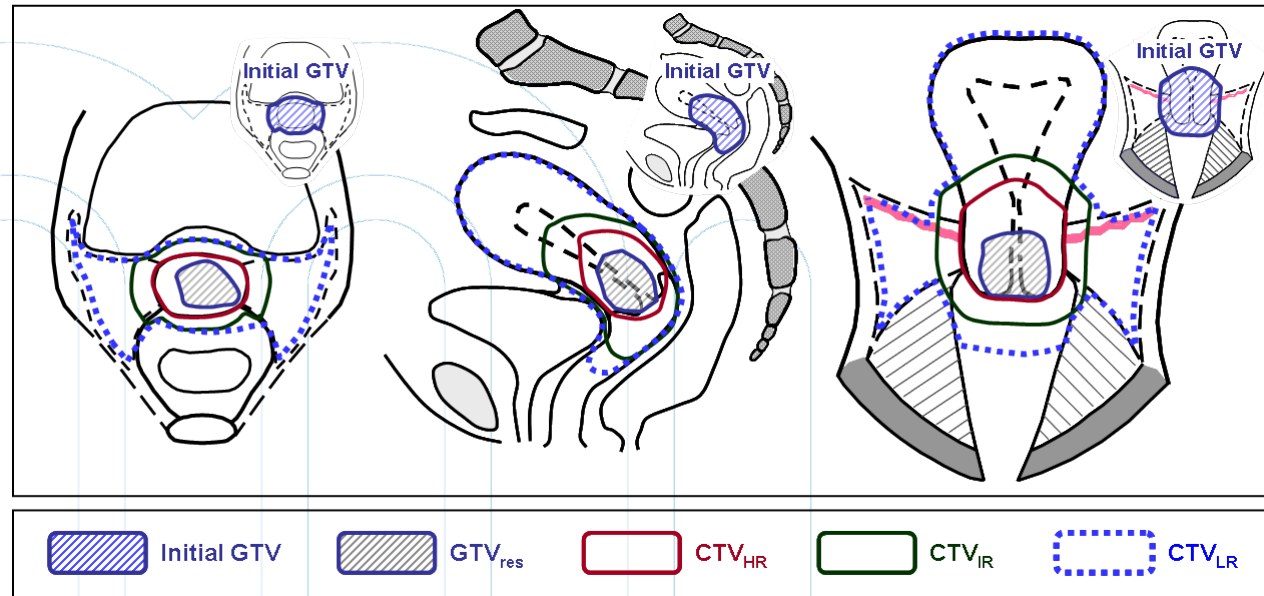
GEC ESTRO/ICRU 89 Target volume concepts

Different Cancer cell density
in 3 different target volumes: HR CTV, IR CTV, LR CTV



Overview of the adaptive target concept cervix cancer stage IB, IIB, IIB: HR+IR CTV-T

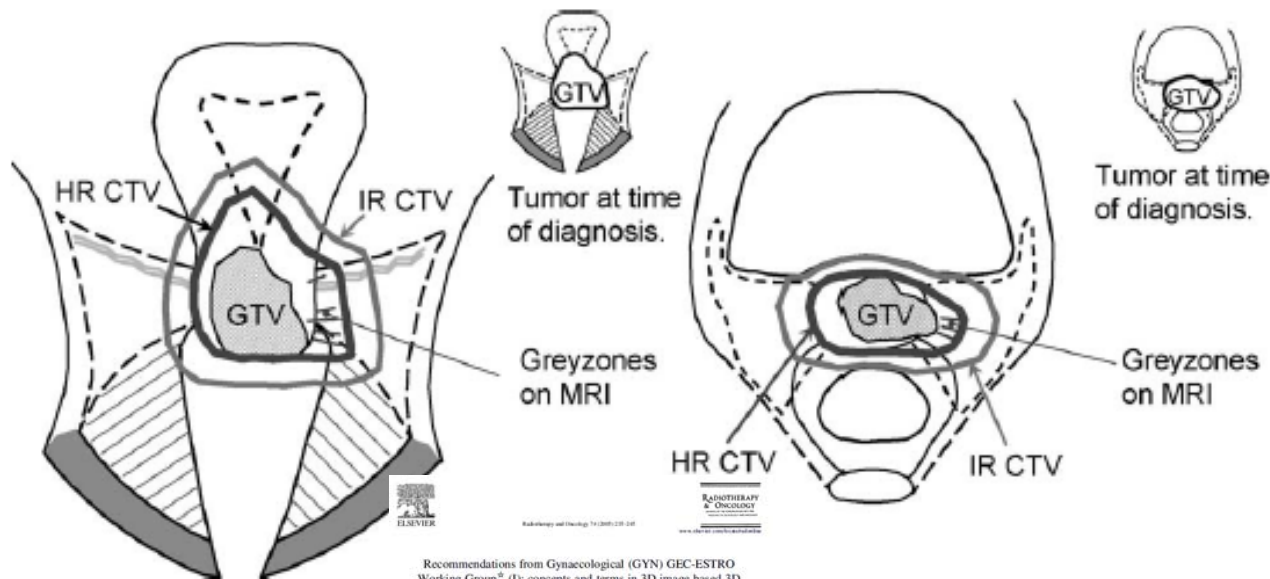
- Initial and residual GTV
- Res. patholog. tissue
- High Risk adaptive CTV
- Intermediate Risk CTV
- (Low Risk CTV)



Risk orientated adaptive Target Concept

Terms: GTV_{res} , residual pathologic tissue, CTV_{HR} ,
 CTV_{IR} , GTV_{init} ,

- CTV_{HR} : residual GTV + residual pathologic tissue + whole cervix
- CTV_{IR} : initial GTV and always CTV_{HR} + safety margin



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

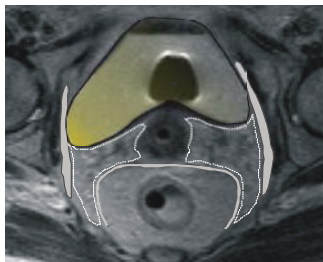
Christine Haie-Meder^{1,2*}, Richard Pötter³, Erik Van Limbergen⁴, Edith Bricot⁵, Mariëtte De Brabandere⁶, Johannes Dimech⁷, Isabelle Dumortier⁸, Taran Paulson Helleboer⁹, Christian Katsiris¹⁰, Stefan Lang¹¹, Sabine Mauch¹², Juliana Neuvonen¹³, An Noutens¹⁴, Peter Petrow¹⁵, Natascha Wachter-Gerstner¹⁶

The challenge of MRI availability

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

- **Golden standard:** *MRI at diagnosis and at brachytherapy with applicator in place* (GEC ESTRO Rec I, IV)
- **Golden standard first fraction,** *CT with appl in place next fract.* (Nesvacil et al. 2013)
- **Alternative:** *Pre brachytherapy MRI, CT with applicator in place* (Pötter et al. IJROBP 2015)
- **Complementary volumetric imaging:** **CT and US** (abdominal, vaginal, transrectal (TRUS, Schmid et al. 2015))
- **Clinical Drawing on schematic diagram always mandatory** (GEC ESTRO Rec., ICRU report 89)



Target volume concepts

HR CTV :

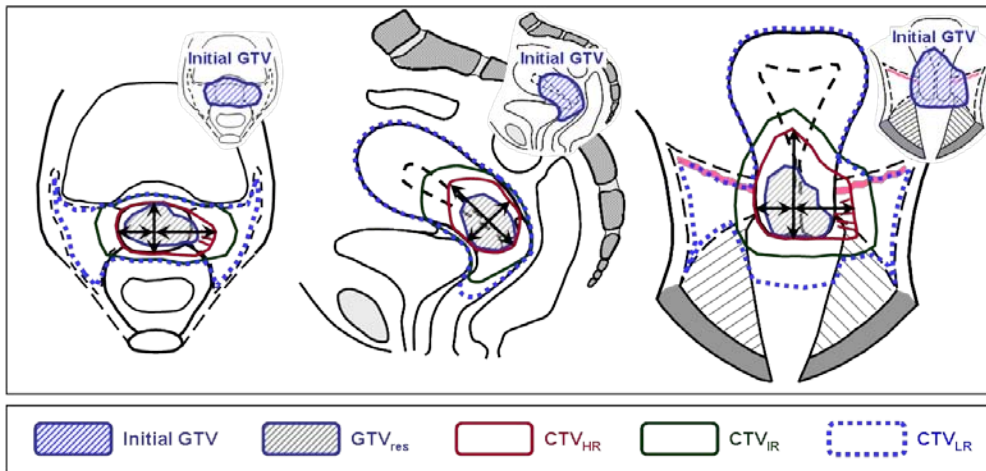
- residual GTV at the time of BT
- the whole cervix and adjacent residual pathologic tissue (with presumed residual disease in initial tumor region) assessed by both clinical examination and imaging (~20-80 cc)

Intent : 85 to 90 + Gy total dose to HR CTV in definitive radiotherapy

Target volume concepts

High Risk CTV :

- residual GTV
- presumed residual pathologic tissue
clinical assessment
residual grey zones on MRI
- always the whole cervix



Target volume concepts

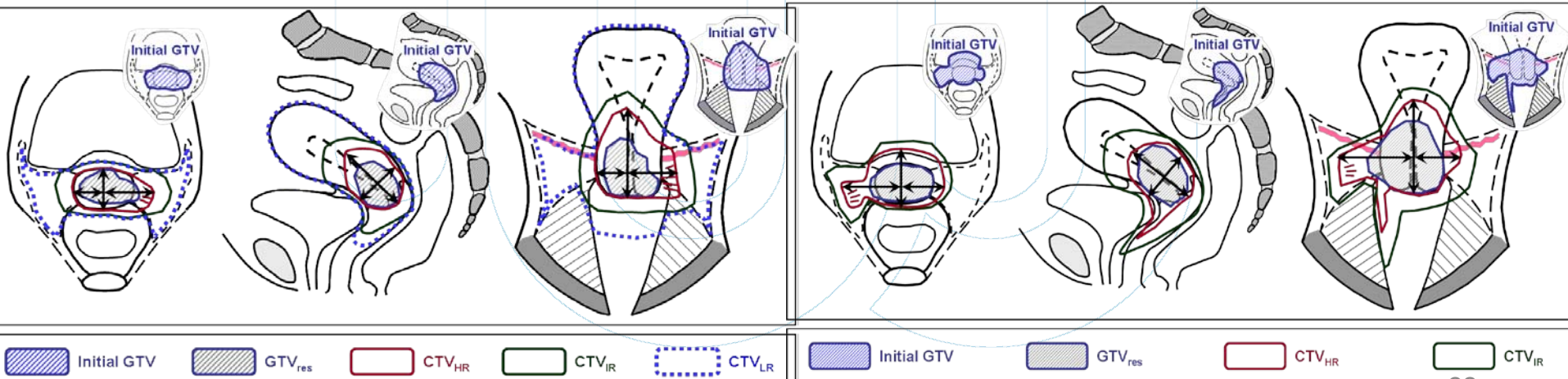
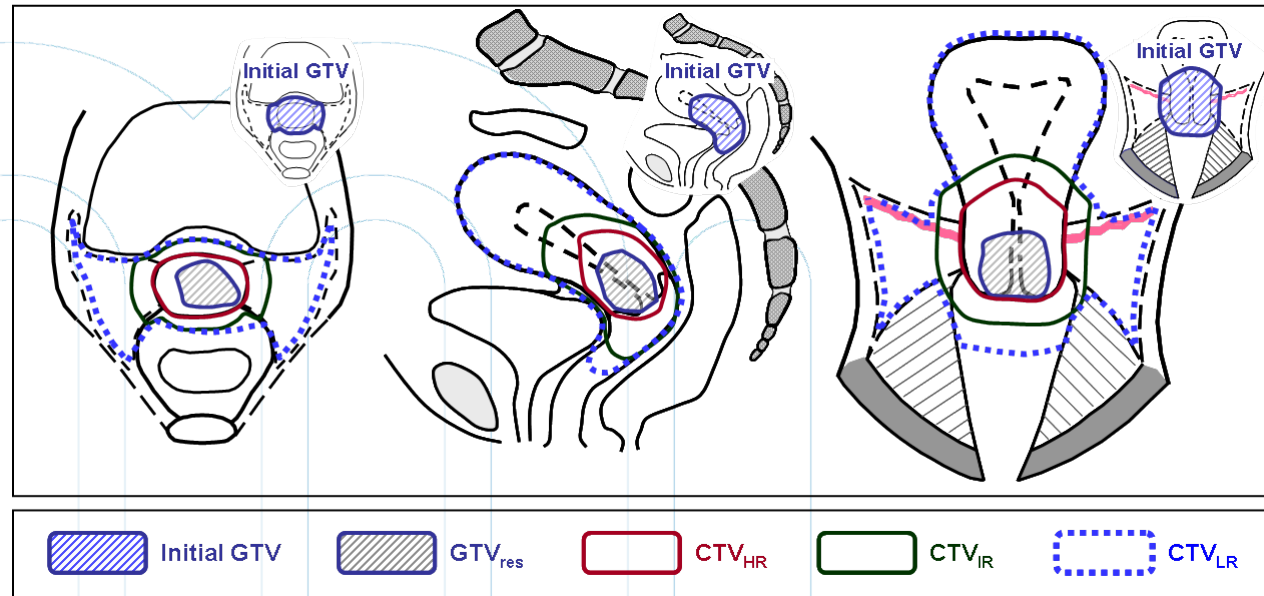
IR CTV :

- Takes into account initial GTV at the time of diagnosis
- Always includes HR-CTV
and includes safety margins to HR CTV

Intent : 60Gy+ total dose to CTV in definitive radiotherapy in advanced disease comparable with dose to the 60Gy isodose (ICRU recommendations 38, 1985)

Overview of the adaptive target concept cervix cancer stage IB, IIB, IIB: HR+IR CTV-T

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



Parametrial Disease

Variation in
GTV response

selection of HR CTV
selection of IR CTV

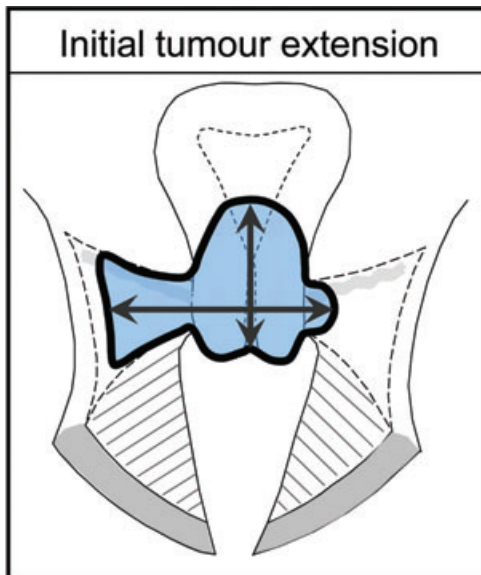
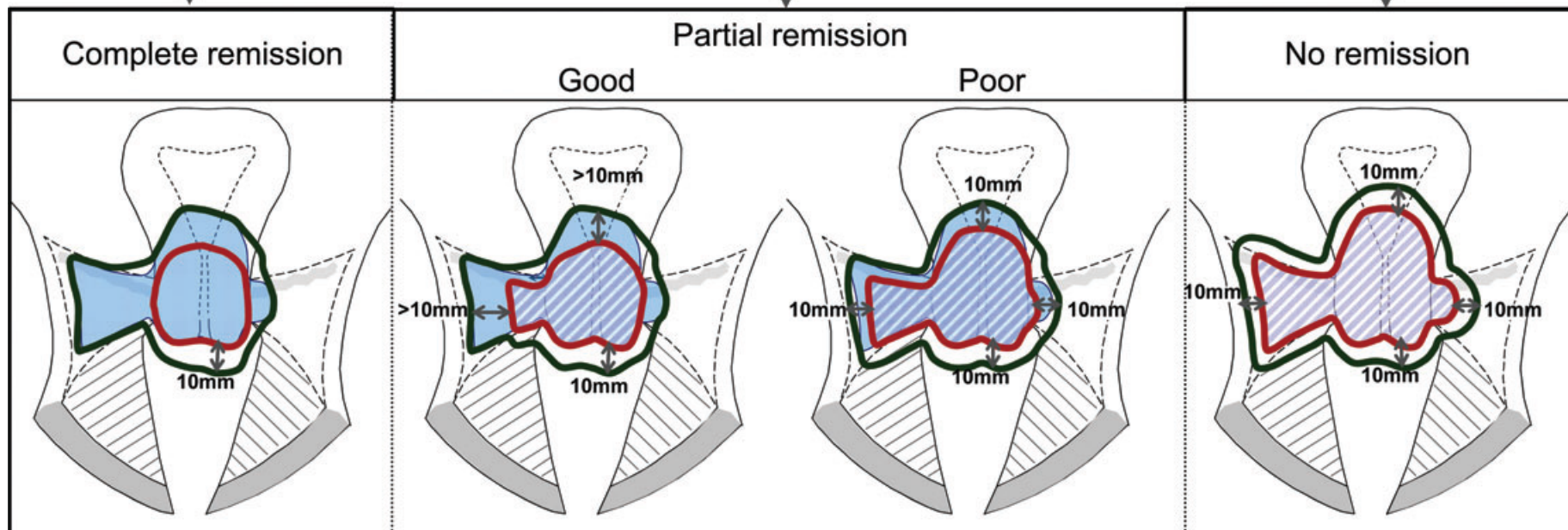



Fig. 5.13
ICRU Report 89



Initial tumour extension (at diagnosis) 

Residual disease 

CTV_{HR} 

CTV_{IR} 

Intrauterine and Vaginal Disease

Variation in GTV response

selection of HR CTV
selection of IR CTV

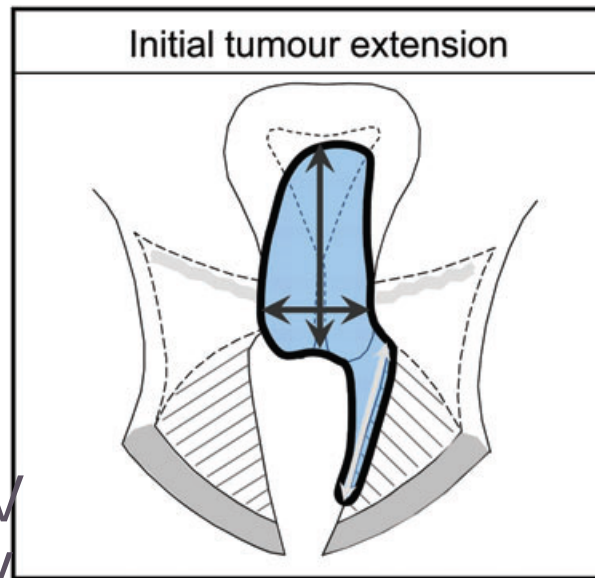
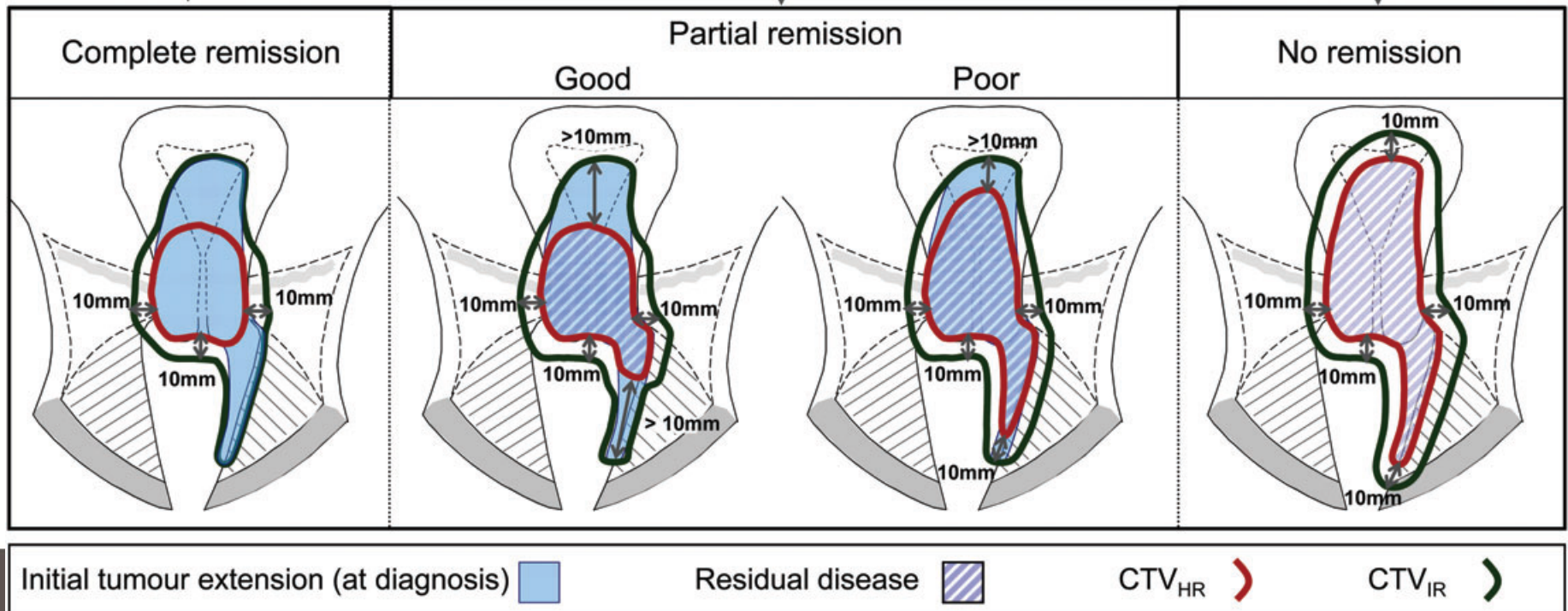


Fig. 5.14
ICRU Report 89



Cervix cancer stage IB1

initial GTV, HR CTV, IR CTV, LR CTV

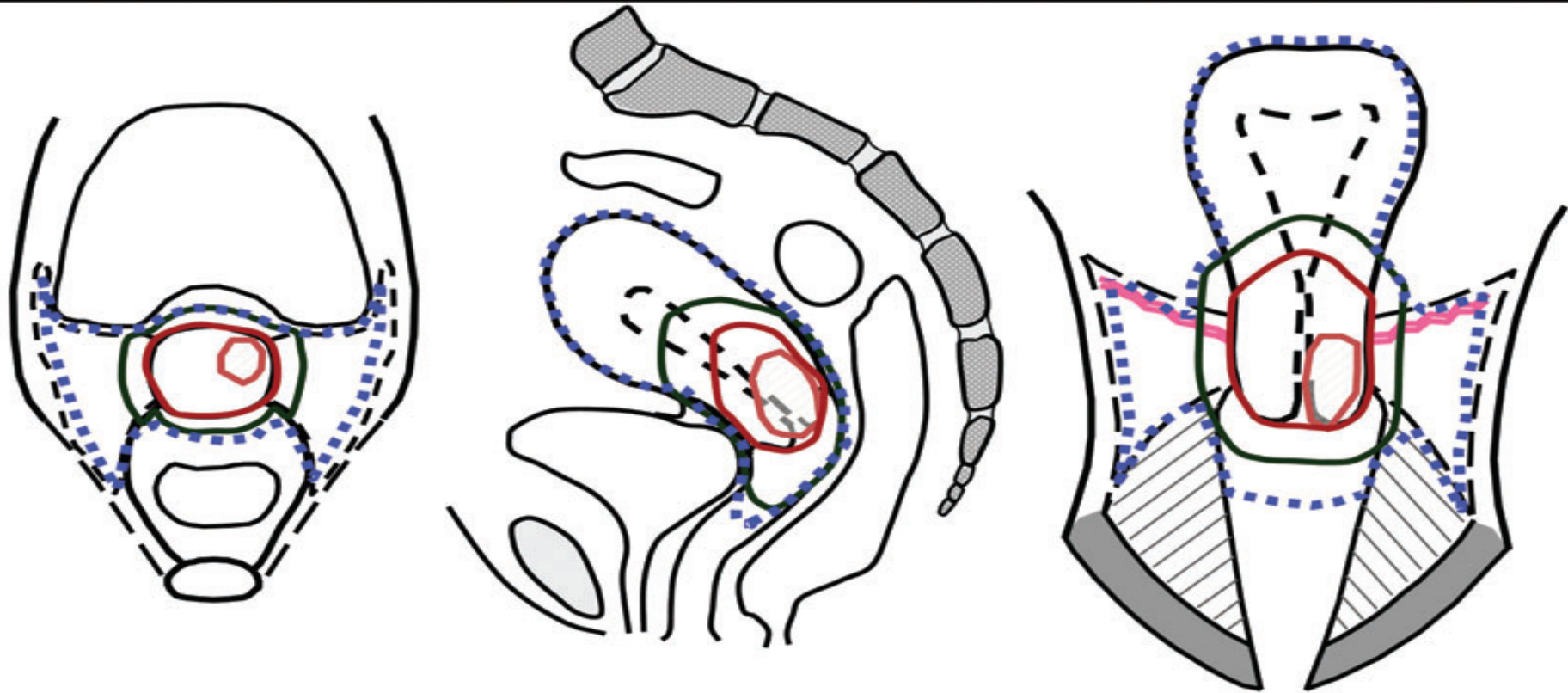
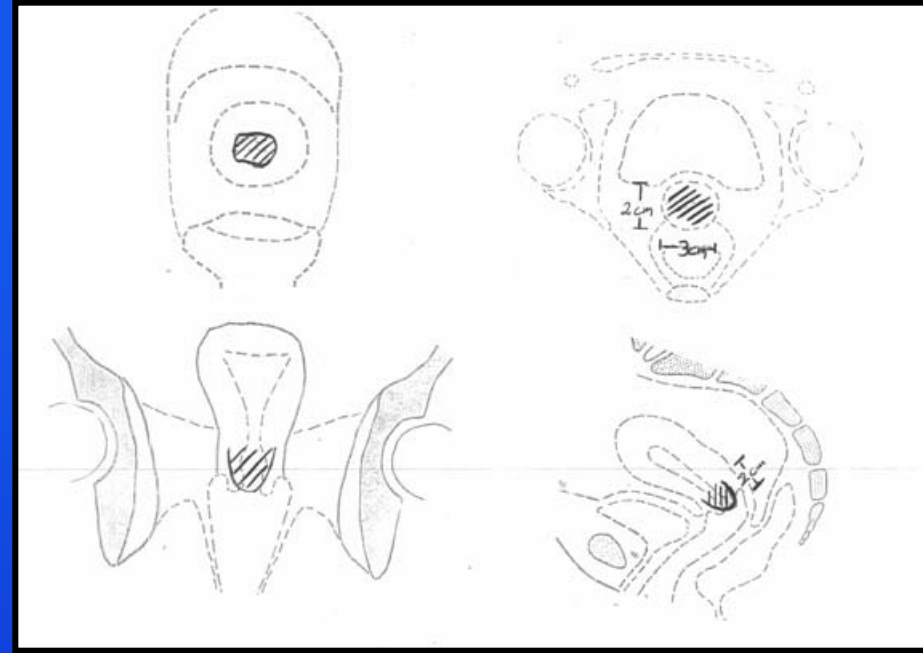


Fig. 5.8 ICRU Report 89

1. Limited disease (tumour size 2cm)

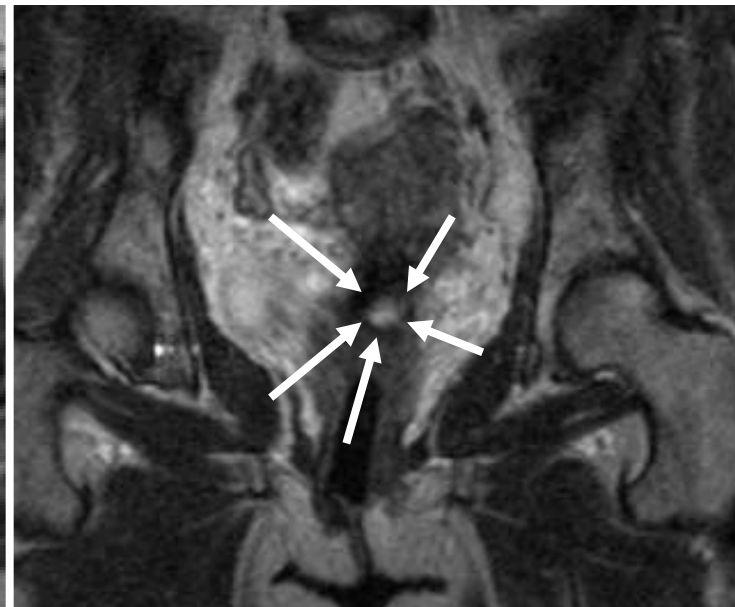
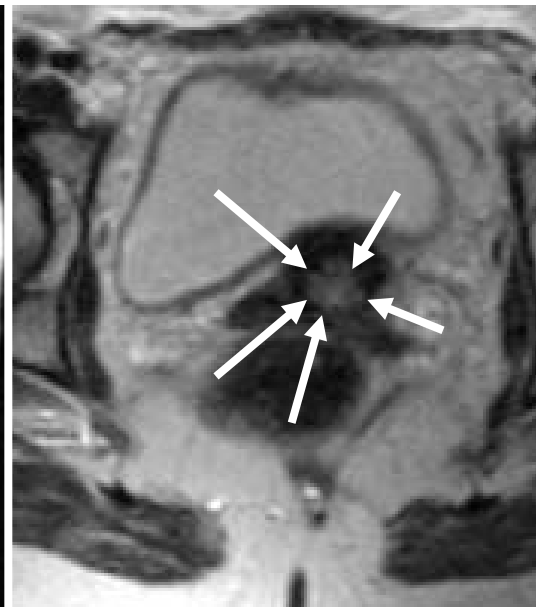
Definition of GTV

Clinical Examination:
macroscopic tumour



MRI Findings:

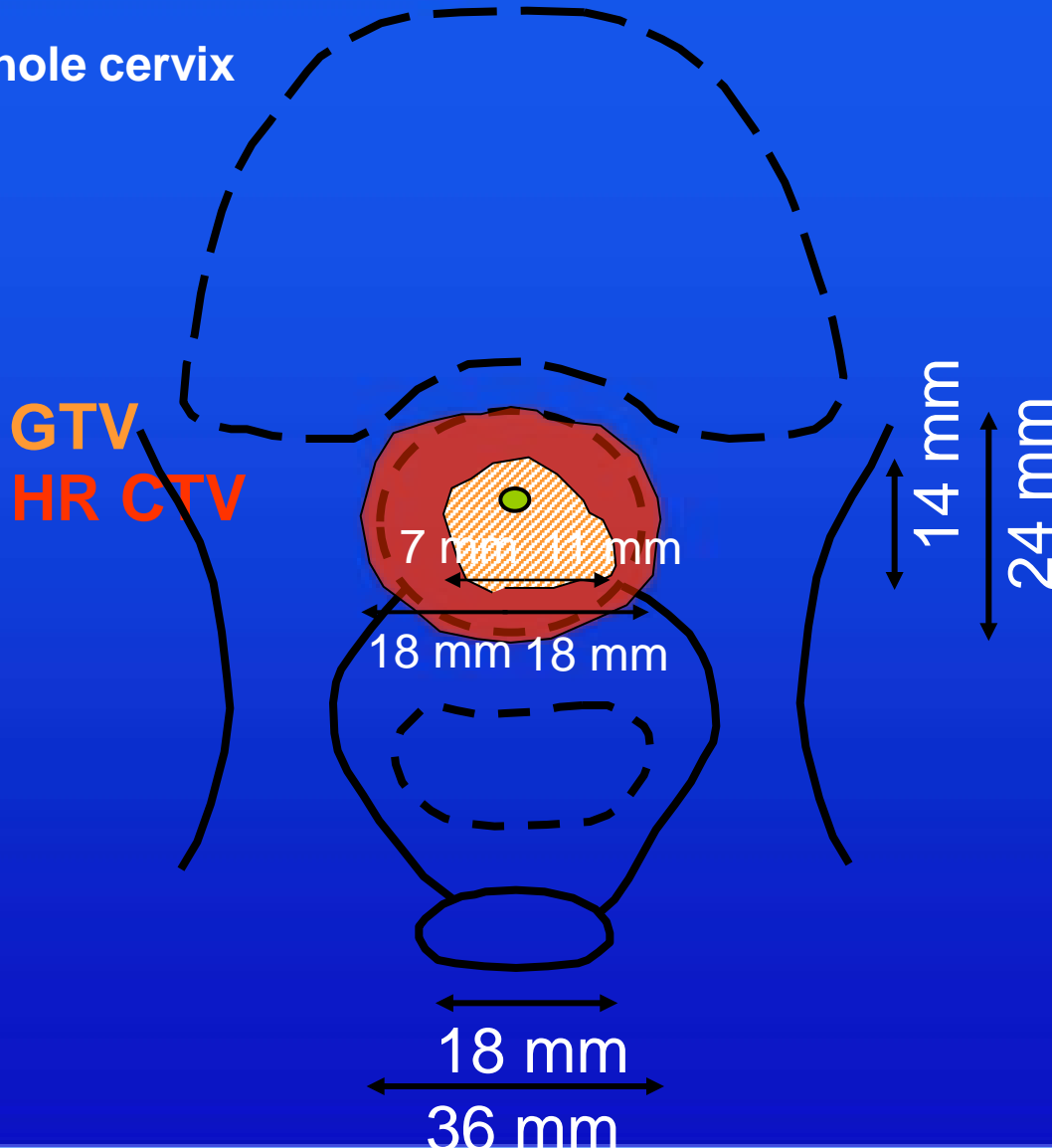
□ High signal intensity zone in cervix



1. Limited disease (tumour size 2cm)

Definition of HR-CTV:

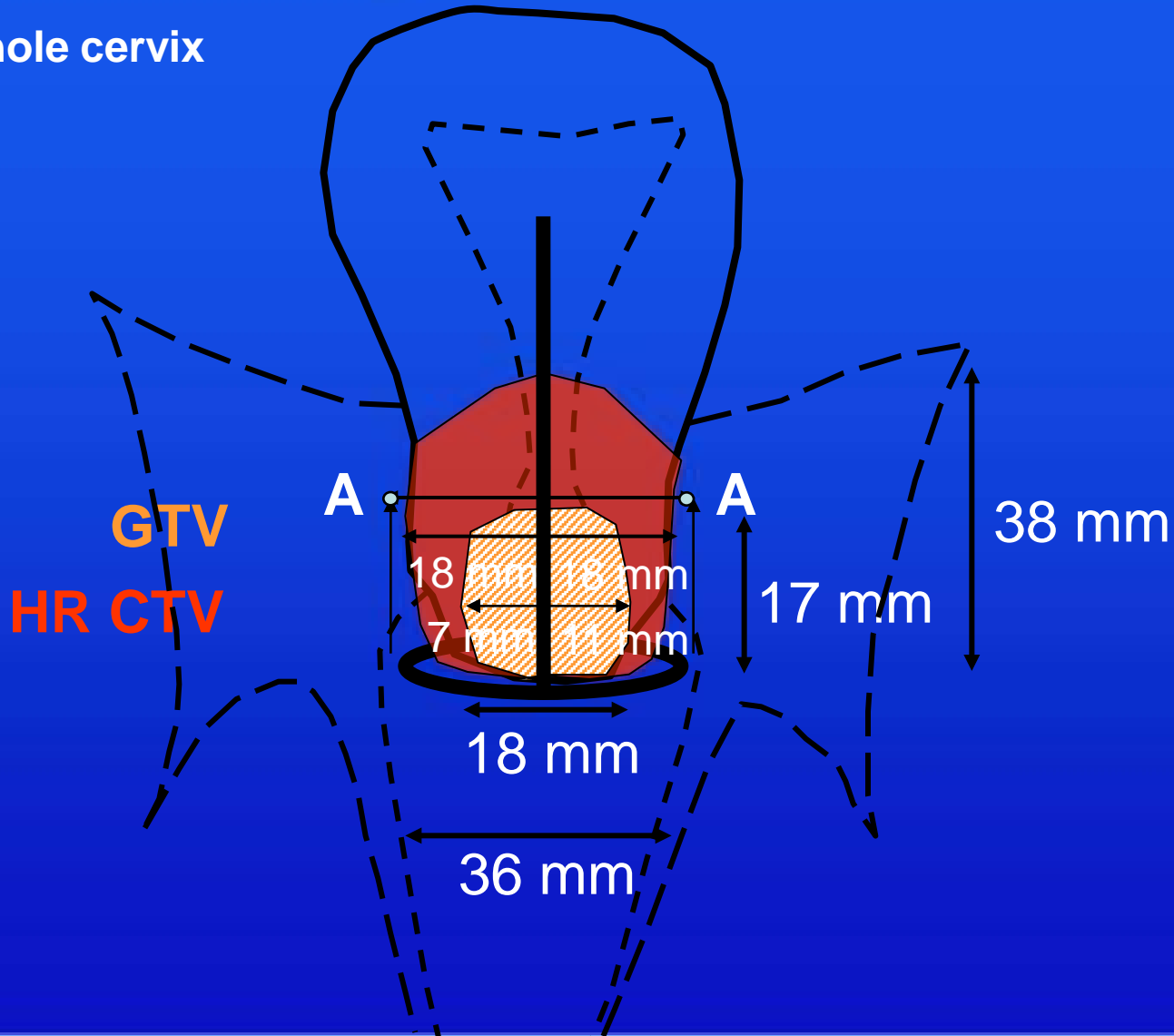
GTV + whole cervix



1. Limited disease (tumour size 2cm)

Definition of HR-CTV:

GTV + whole cervix



1. Limited disease (tumour size 2cm)

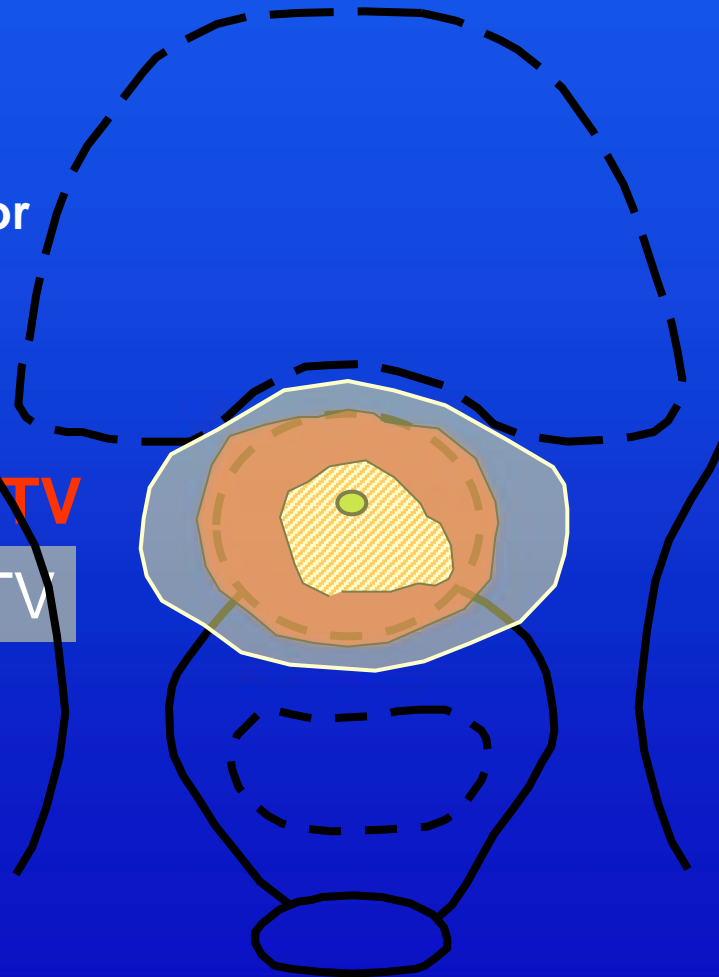
Definition of IR-CTV

HR CTV + safety margin
(area of adjacent significant microscopic tumour load)

5 mm anterior –posterior

10 mm into parametria

GTV
HR CTV
IR CTV



1. Limited disease (tumour size 2cm)

Definition of IR-CTV

HR CTV + safety margin
(area of potential adjacent significant microscopic tumour load)

5 mm anterior –posterior

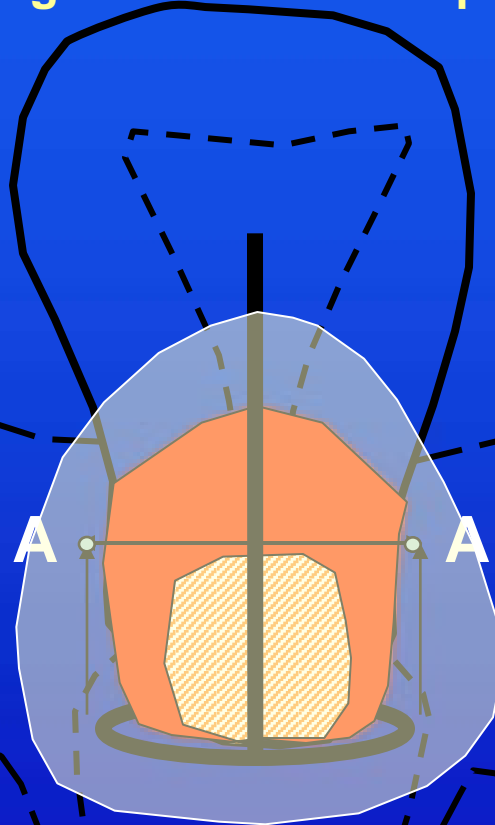
10 mm into parametria

GTV

HR CTV

IR CTV

+/- additional 5 mm



10 mm into the corpus

10 mm into the vagina

Patient n° 1: stage IB1, 3 cm

56 year-old woman
WHO=0, 70 kg, 1m69

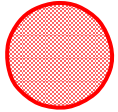
Vaginal bleeding

Biopsy: moderately differentiated squamous cell carcinoma

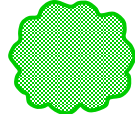
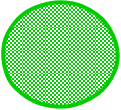
Stage IB1 : initial clinical examination

Infiltrating Exophytic

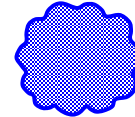
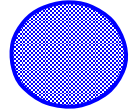
Cervix



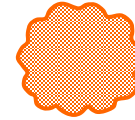
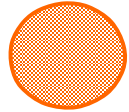
Vagina



Parametrium



Rectum or
Bladder

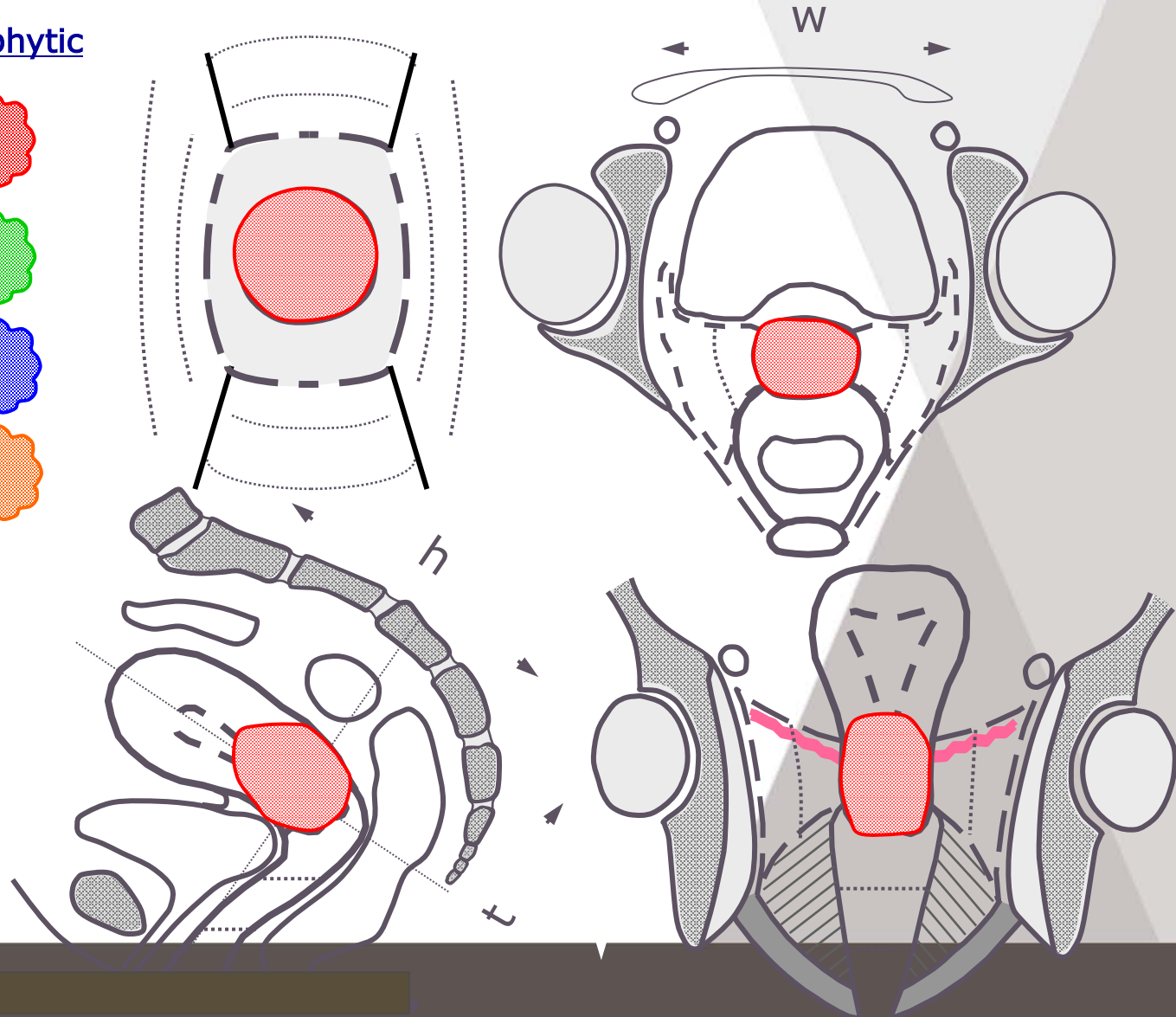


Dimensions (cm):

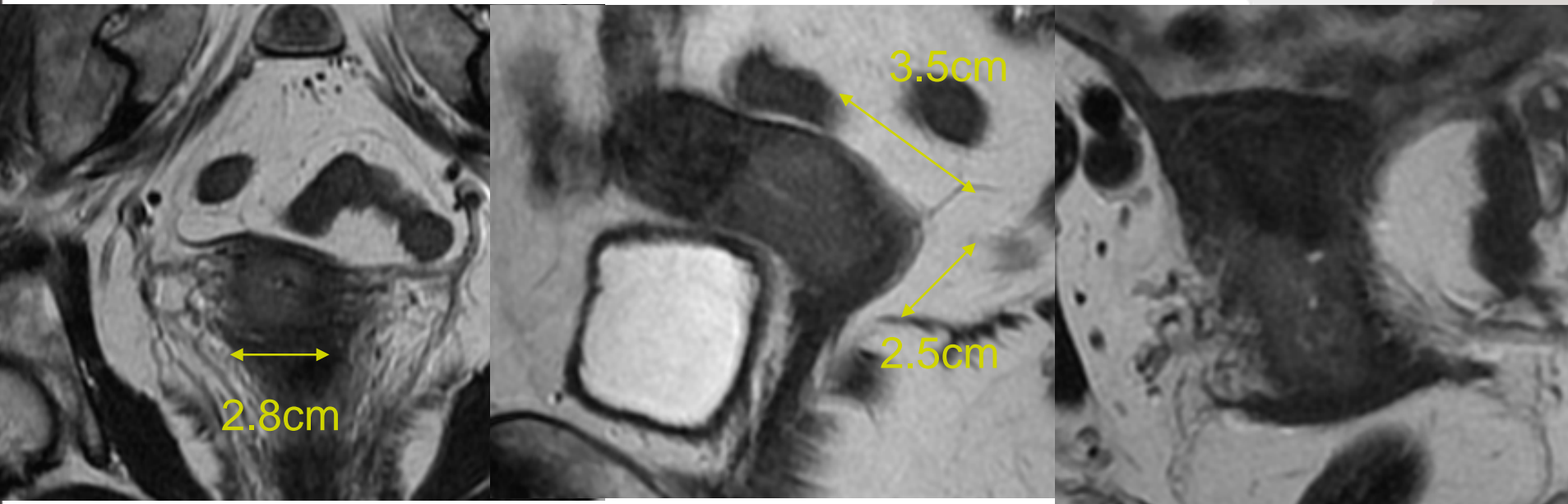
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Thickness : 2.5

Height : 3



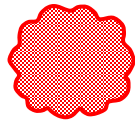
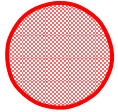
Stage IB1



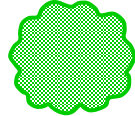
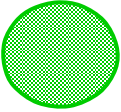
Stage IB1 : at the time of brachytherapy

Infiltrating Exophytic

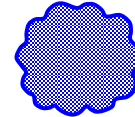
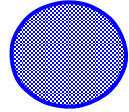
Cervix



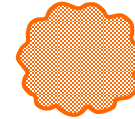
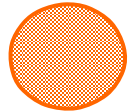
Vagina



Parametrium



Rectum or
Bladder

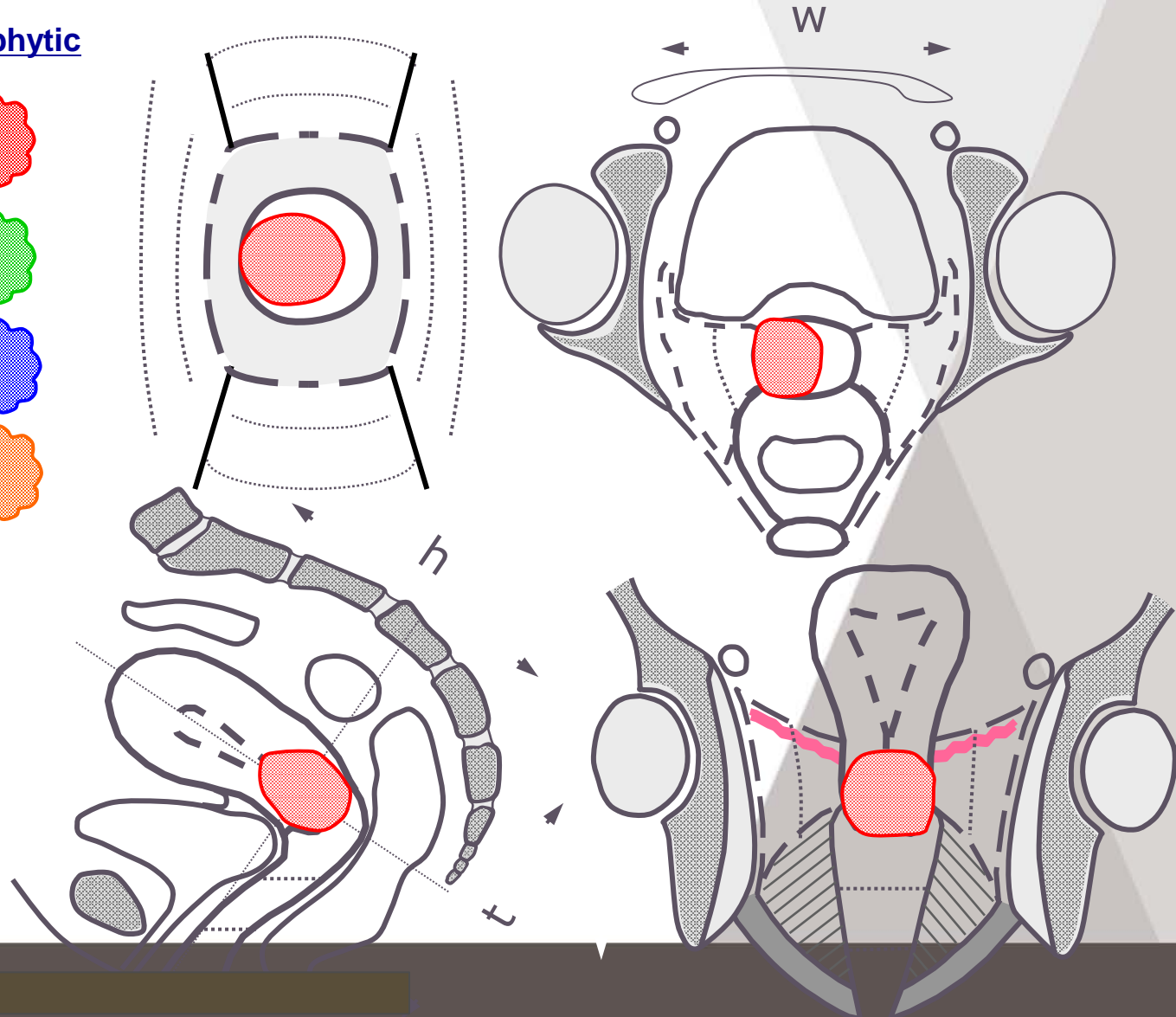


Dimensions (cm):

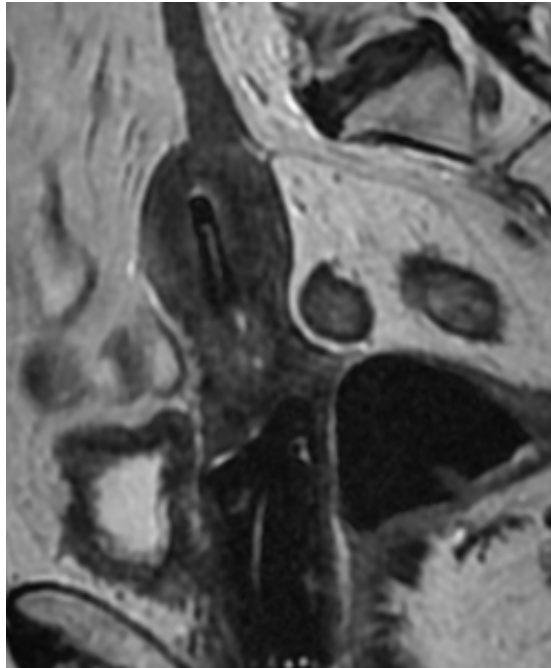
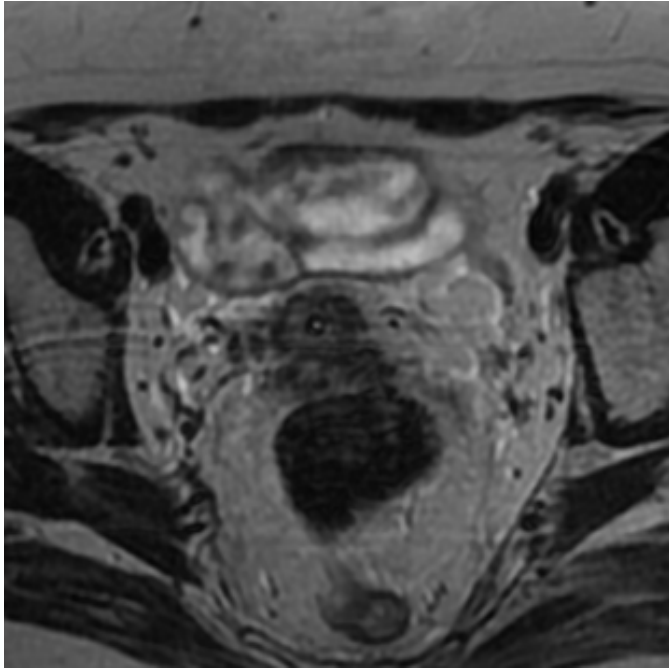
Width : 1.5

Thickness : 2

Height : 1.5



Stage IB1



Target volume concepts: stage IB

High Risk CTV :

- Residual GTV at time of brachytherapy
- Whole cervix
- Presumed extracervical tumour extension (=0)

Clinical assessment
MRI assessment

NO SAFETY MARGINS

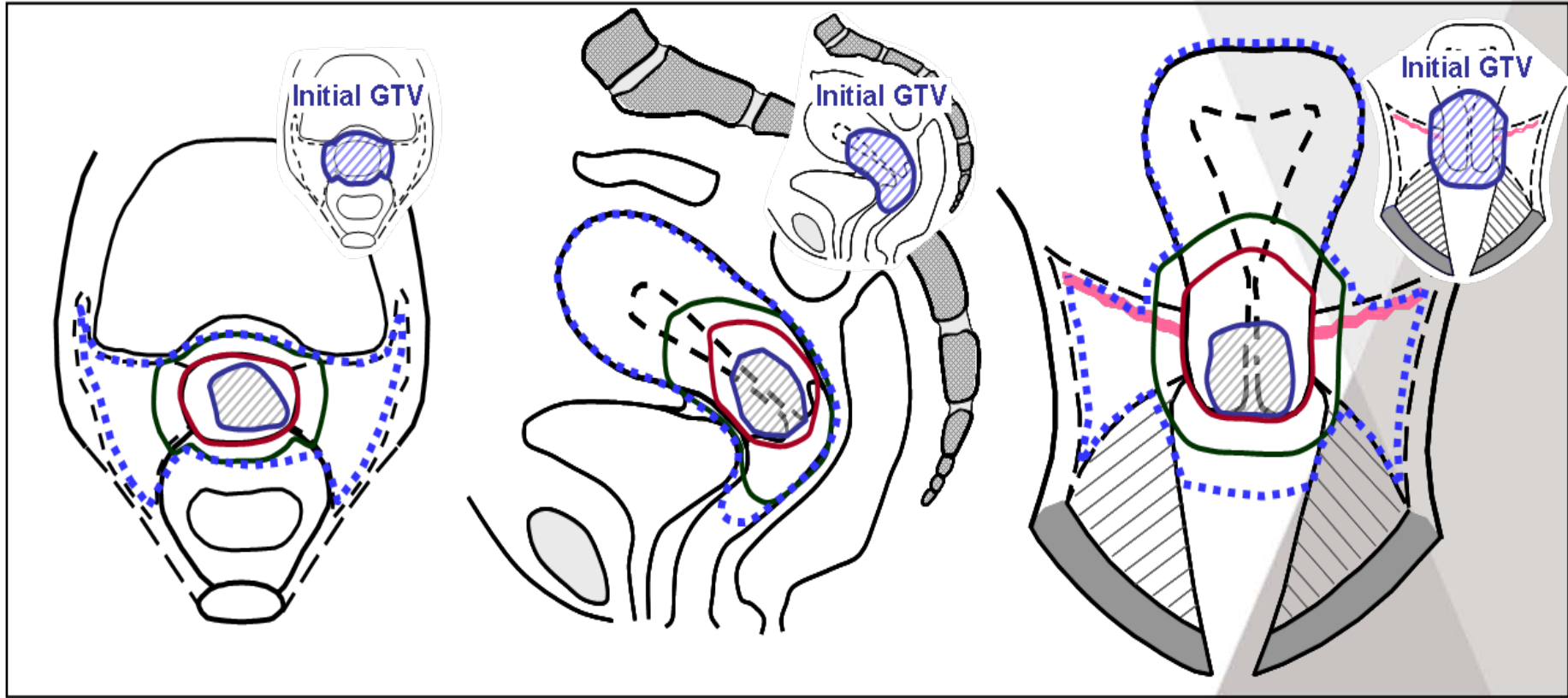
Intermediate Risk CTV :

- Initial GTV
- HR-CTV

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

Cervix cancer stage IB1

initial and residual GTV, HR CTV, IR CTV, LR CTV



Initial GTV



GTV_{res}



CTV_{HR}

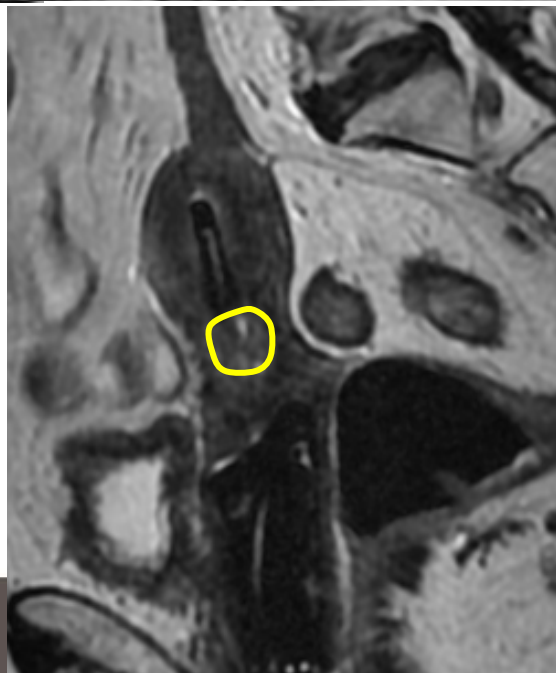
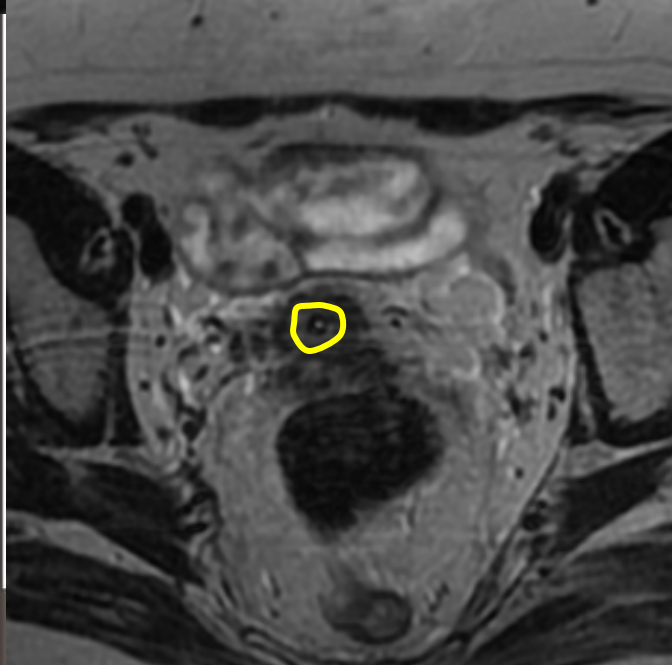
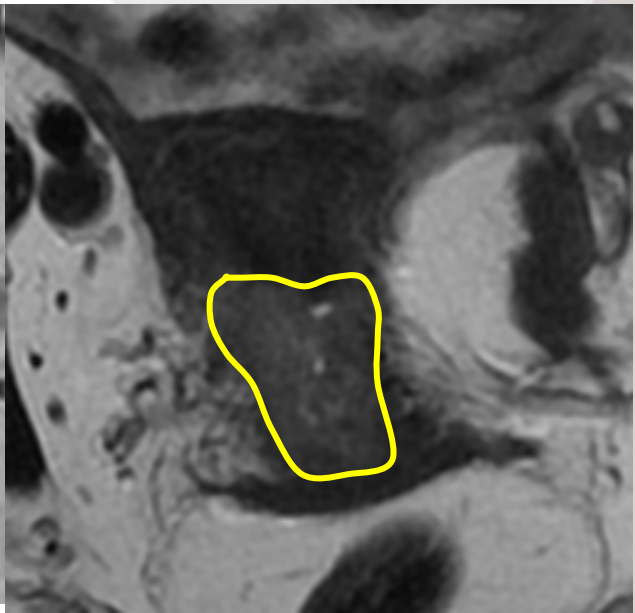
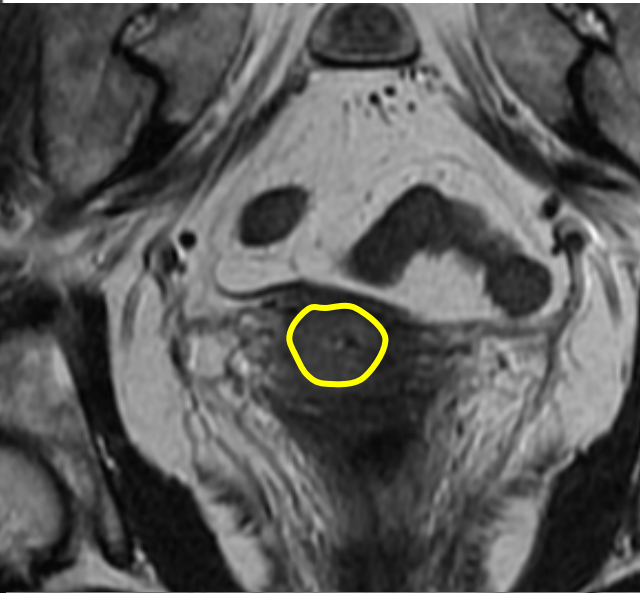


CTV_{IR}

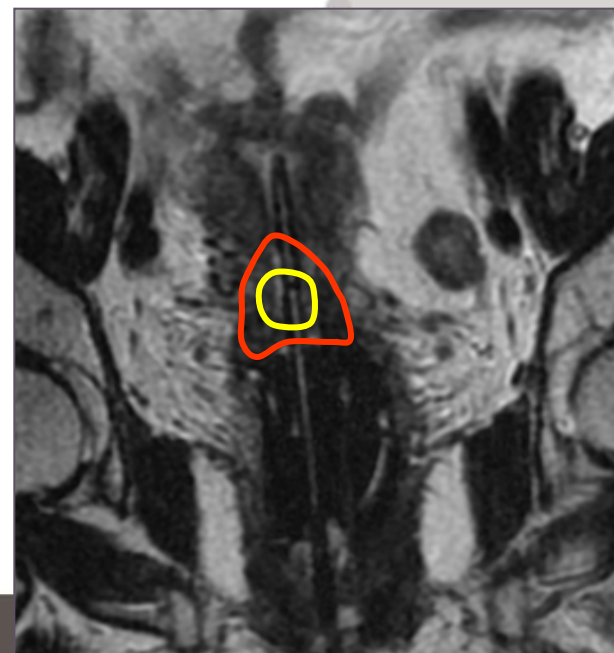
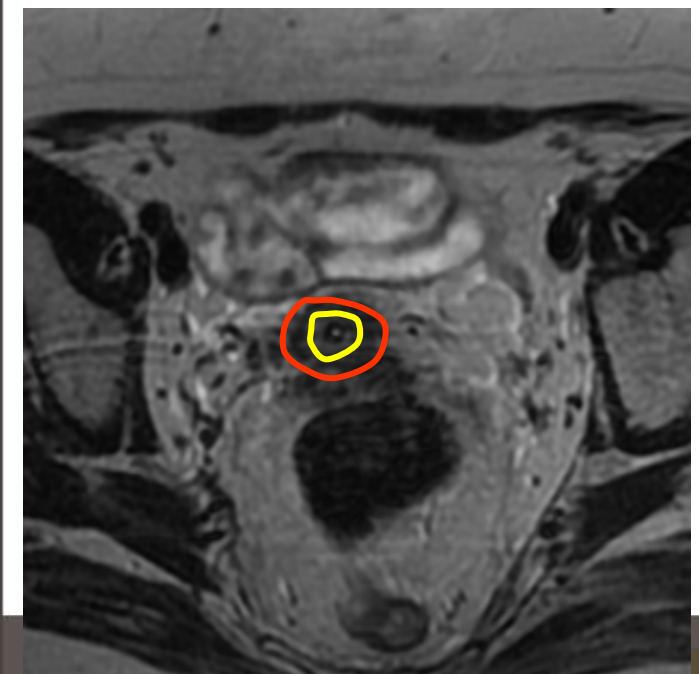
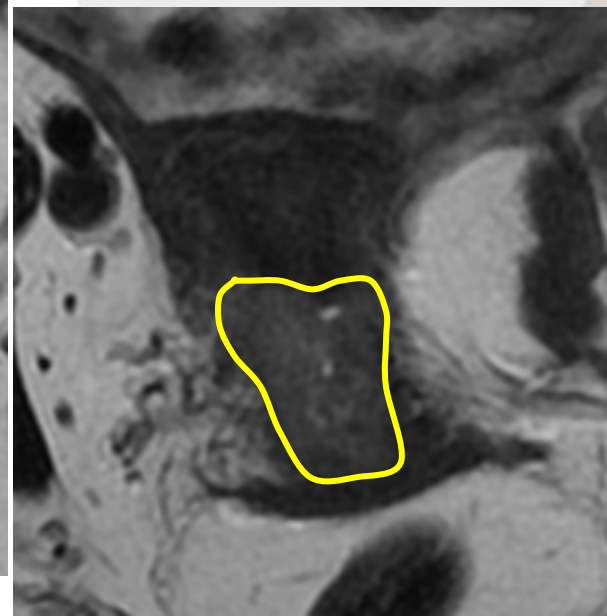
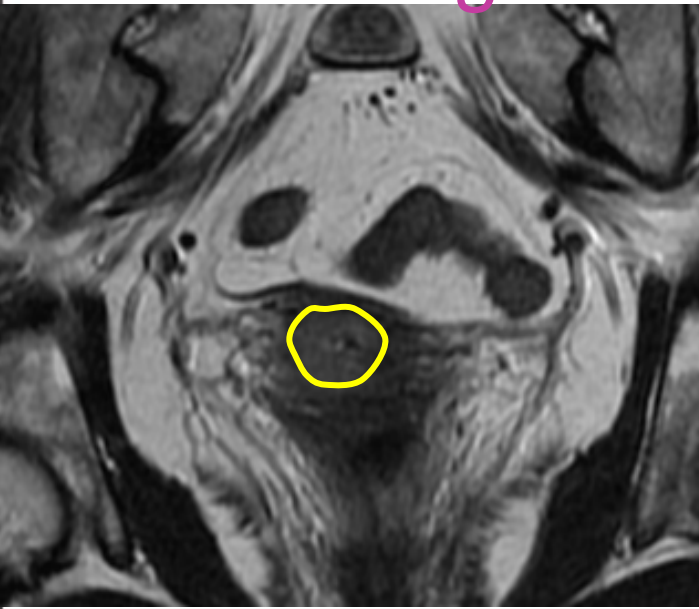


CTV_{LR}

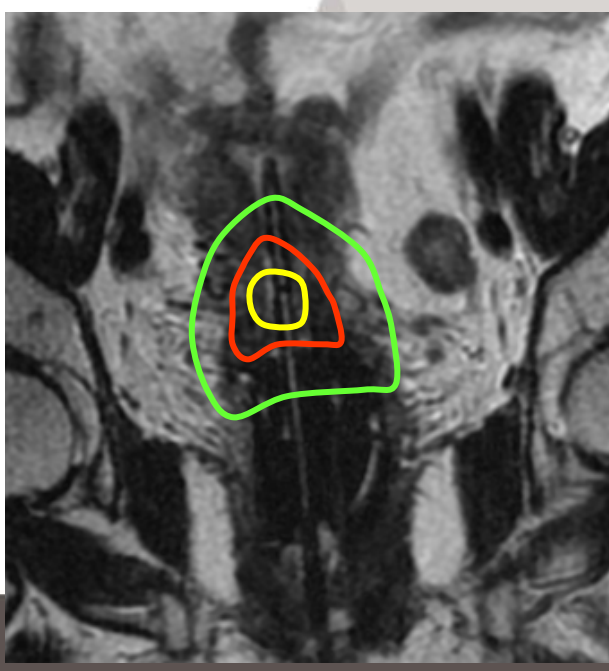
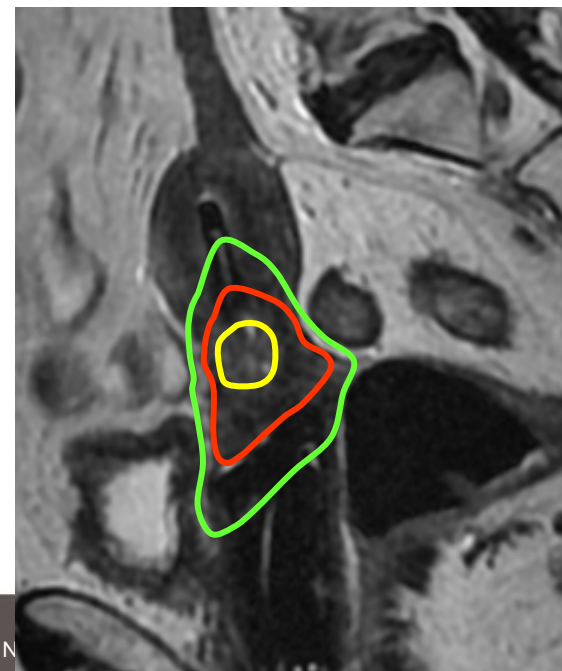
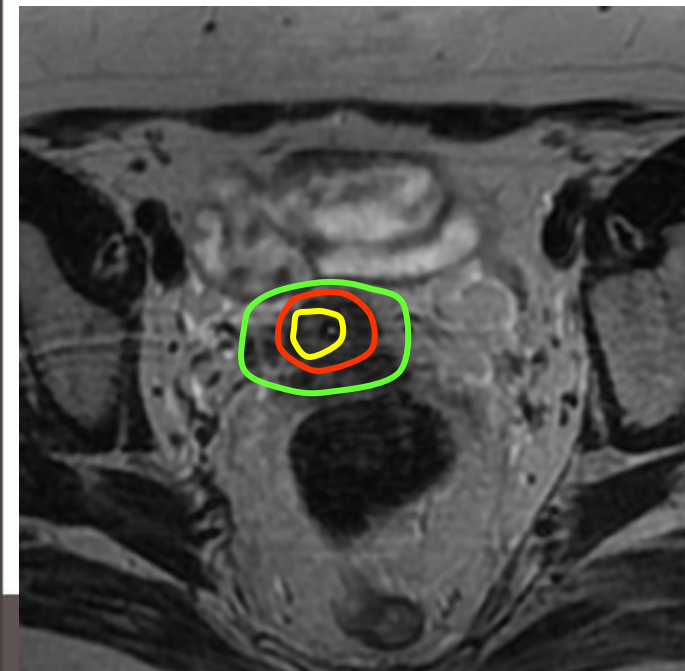
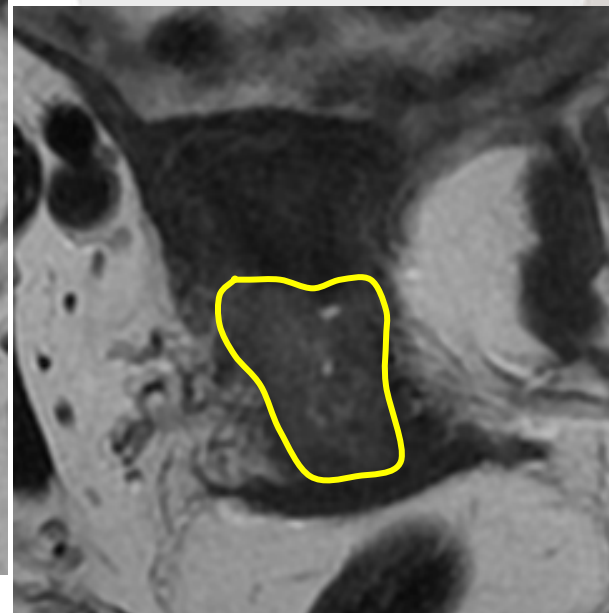
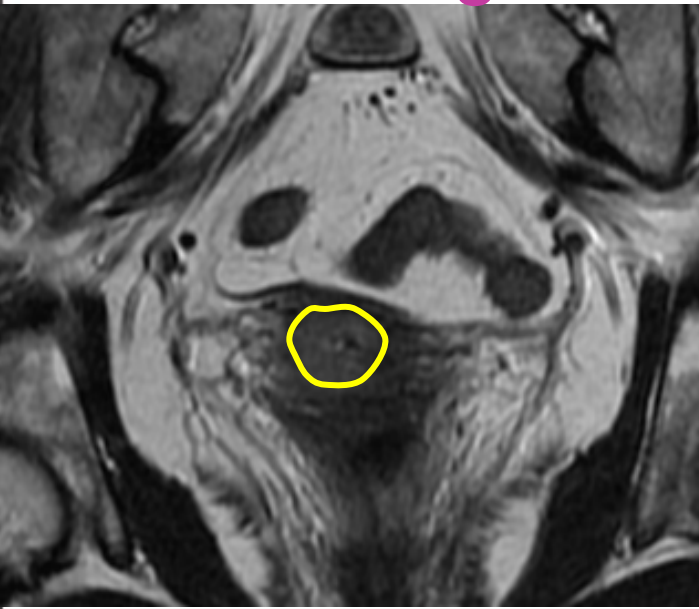
Stage IB1



Stage IB1



Stage IB1



Patient n° 2 IB2, 6 cm

Mrs V M...

33 year-old

WHO=0, 55 kg, 1m68

Vaginal bleeding

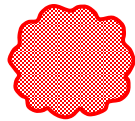
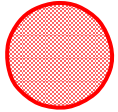
Biopsy: well differentiated squamous cell carcinoma

At clinical examination: large exophytic tumor limited to the cervix

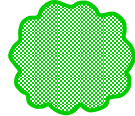
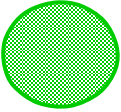
Stage IB2 : initial clinical examination

Infiltrating Exophytic

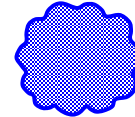
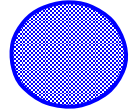
Cervix



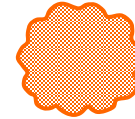
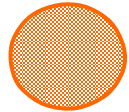
Vagina



Parametrium



Rectum or
Bladder

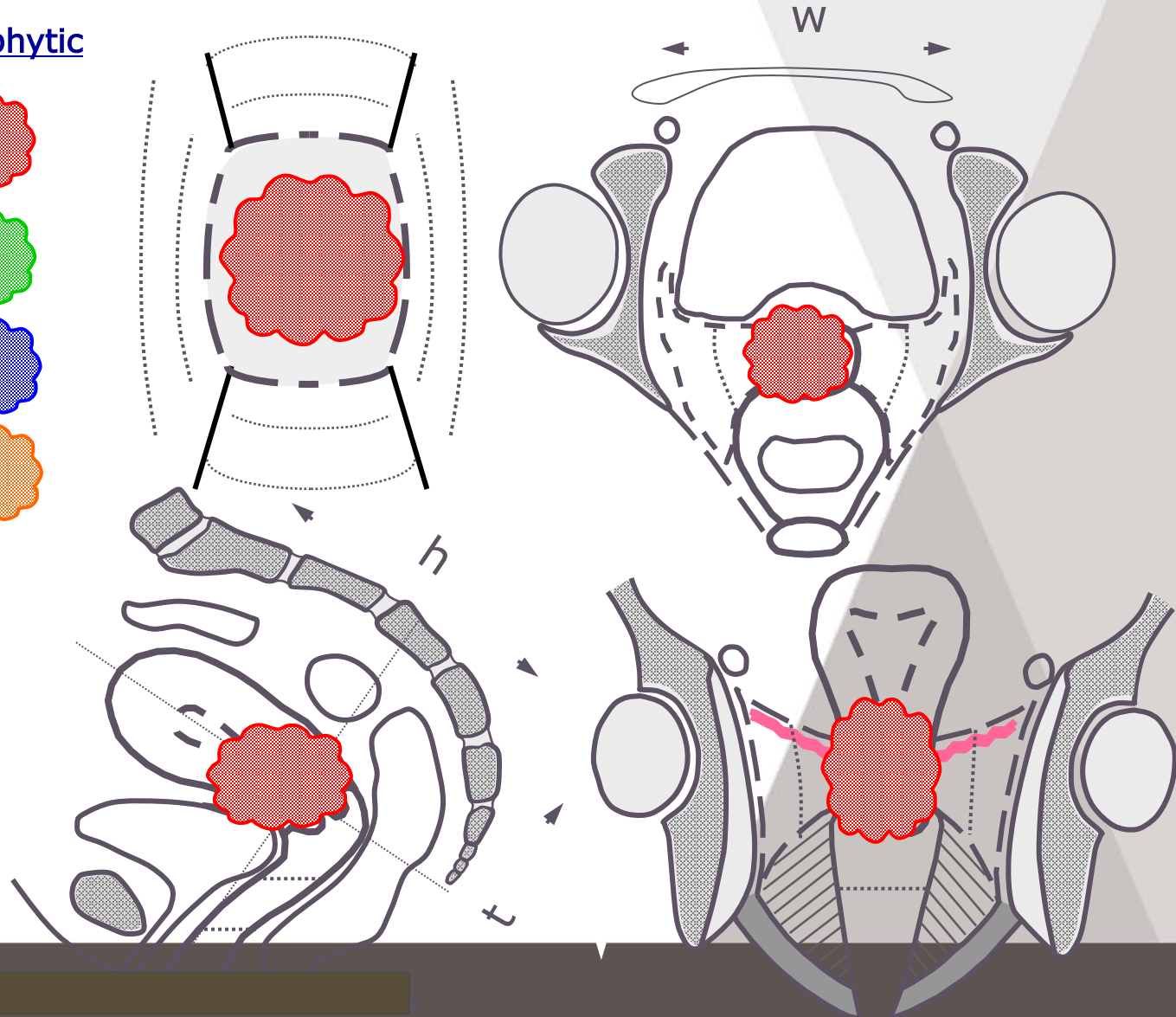


Dimensions (cm):

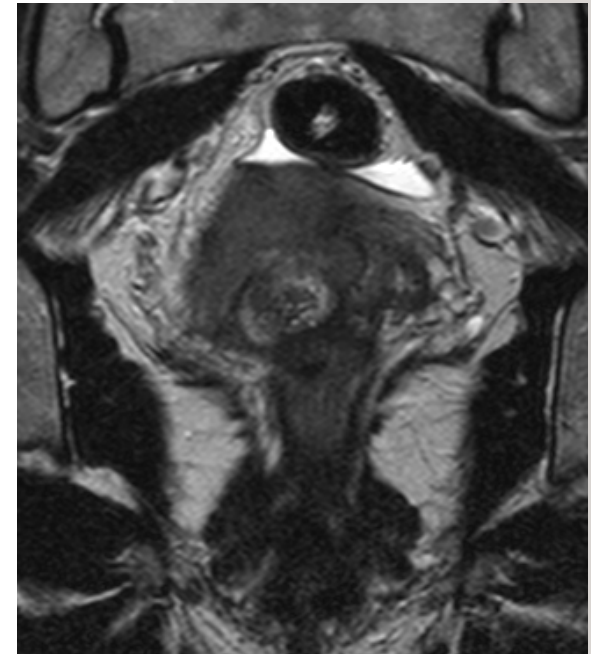
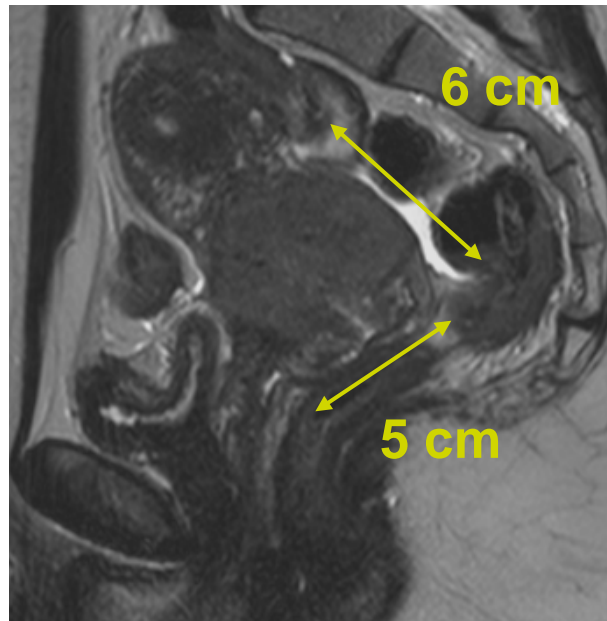
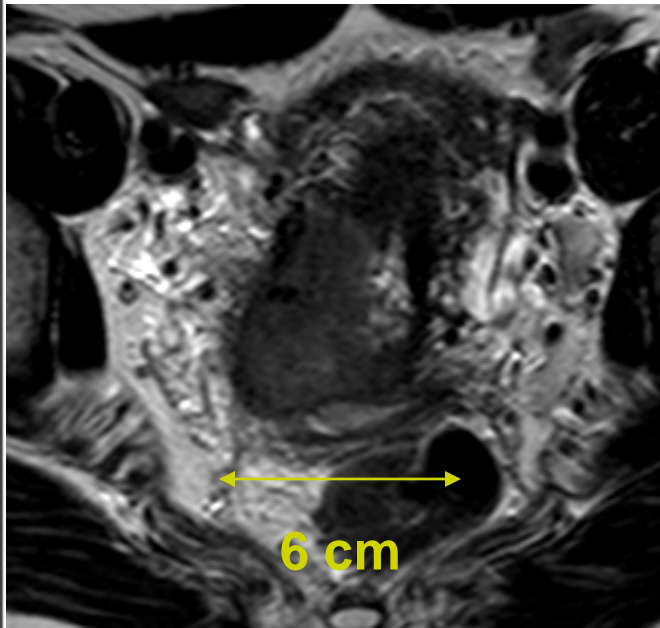
Width : 6

Thickness : 5

Height : 5



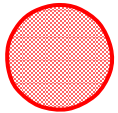
Stage IB2 : initial MRI



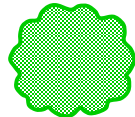
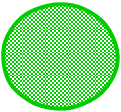
Stage IB2 : at the time of brachytherapy

Infiltrating Exophytic

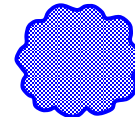
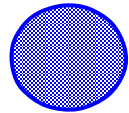
Cervix



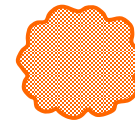
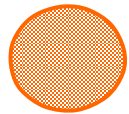
Vagina



Parametrium



Rectum or
Bladder

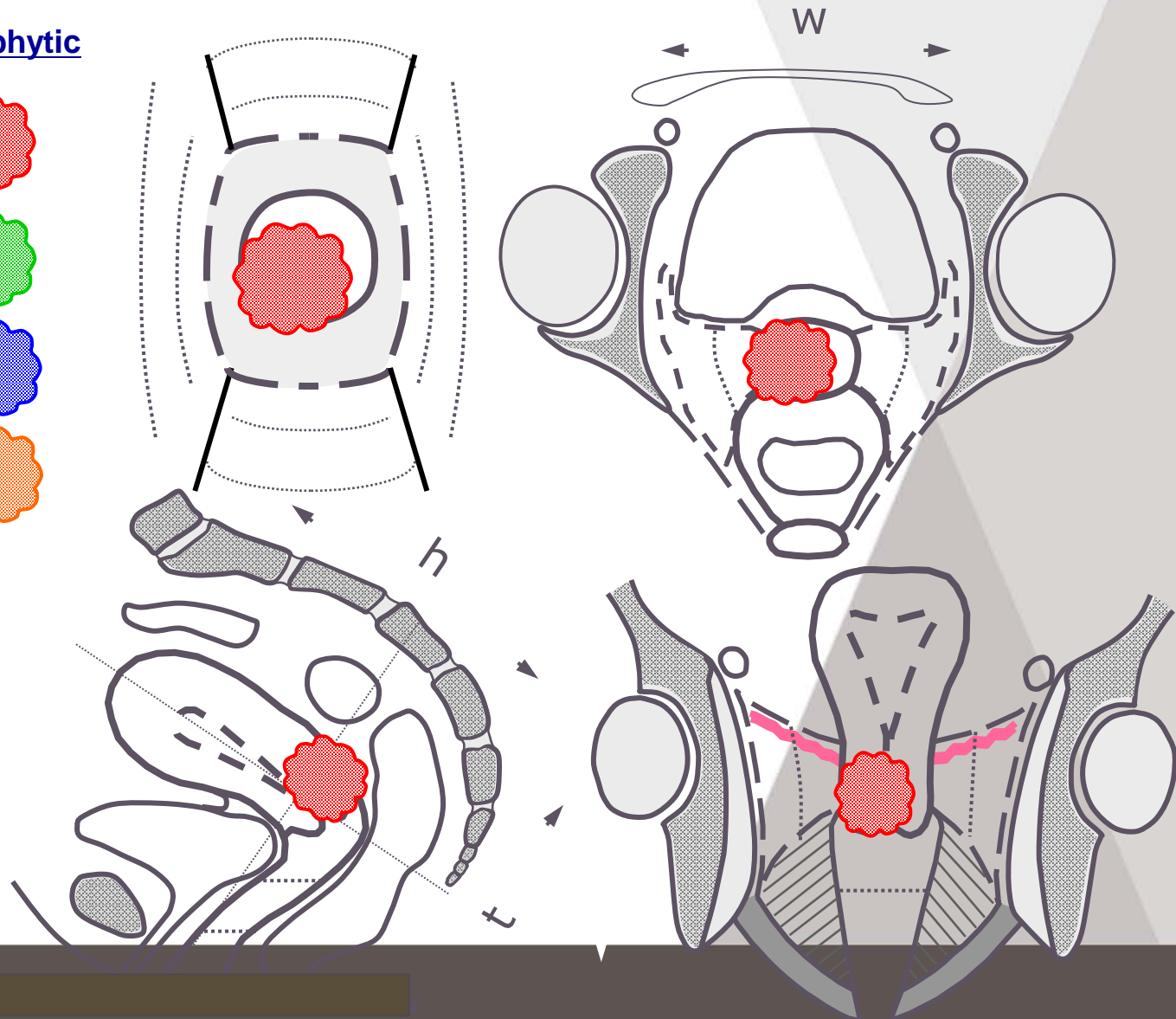


Dimensions (cm):

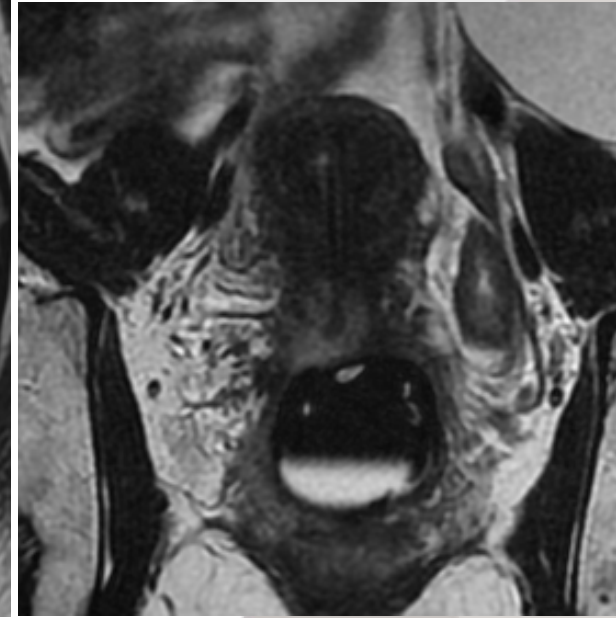
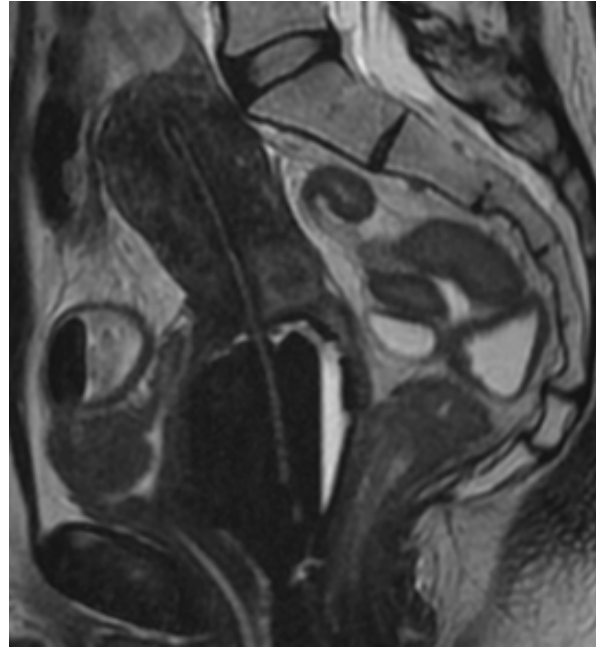
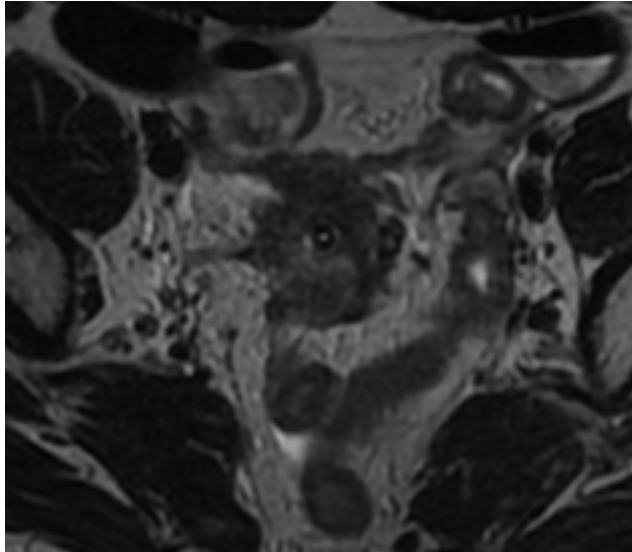
Width : 2.5

Thickness : 2

Height : 2.5



Stage IB2 : at the time of brachytherapy



HR-CTV includes:

- A. the exact initial tumor extension in cm**
- B. the whole cervix+ safety margins**
- C. the whole cervix only at BT**
- D. the whole uterus**

IR-CTV includes:

- A. the whole cervix +
initial tumor extension**
- B. the whole cervix at
BT+ safety margins**
- C. the whole cervix only**
- D. the whole uterus**

Target volume concepts: stage IB

High Risk CTV :

- Residual GTV at time of brachytherapy
- Whole cervix
- Presumed extracervical tumour extension (=0)

Clinical assessment
MRI assessment

NO SAFETY MARGINS

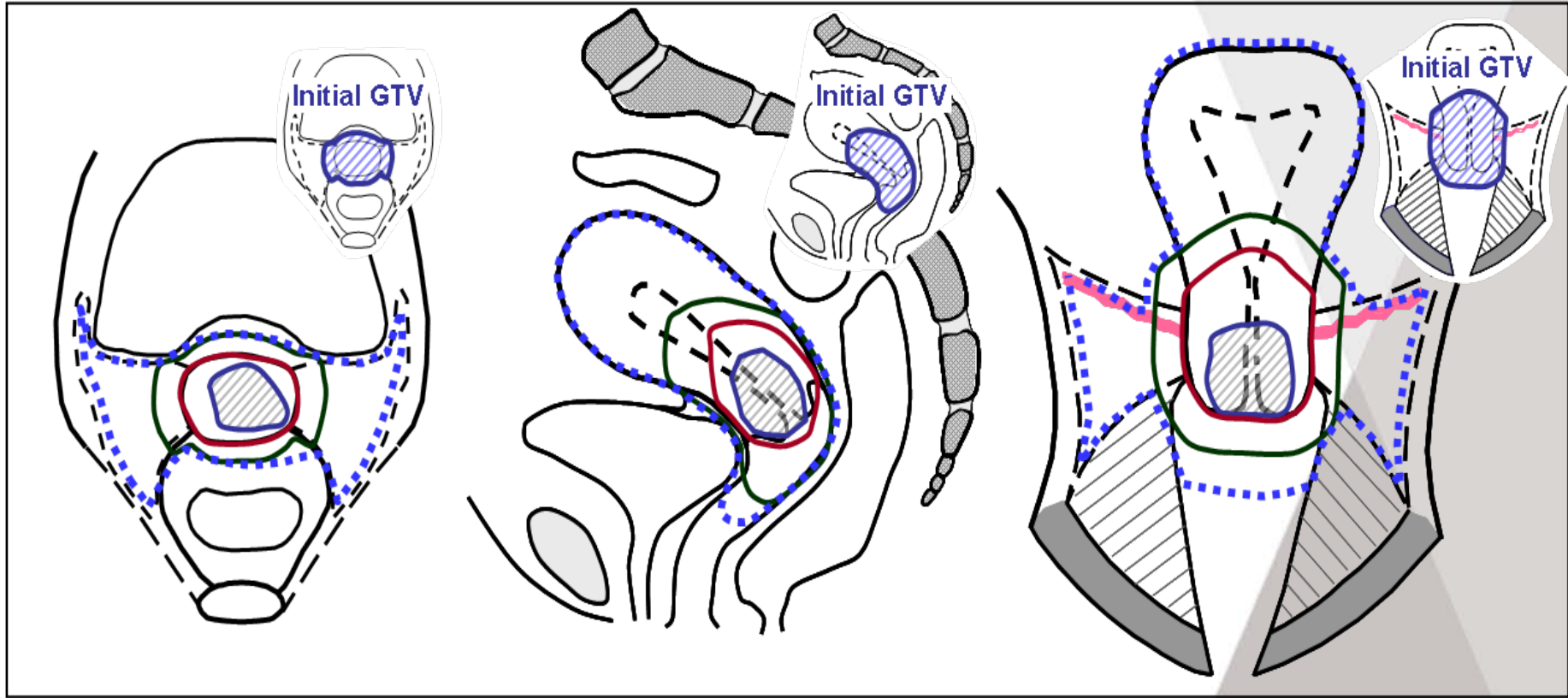
Intermediate Risk CTV :

- Initial GTV
- HR-CTV

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

Cervix cancer stage IB2

initial and residual GTV, HR CTV, IR CTV, LR CTV



Initial GTV



GTV_{res}



CTV_{HR}

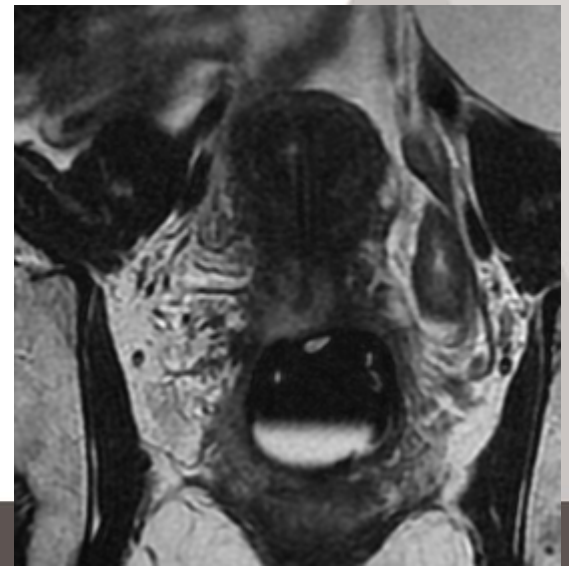
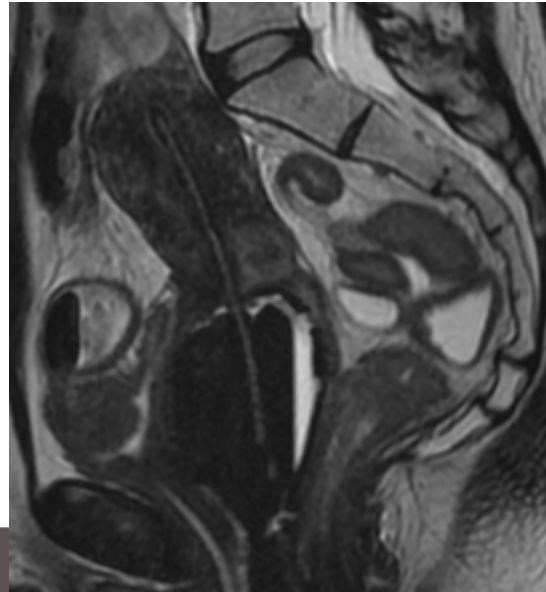
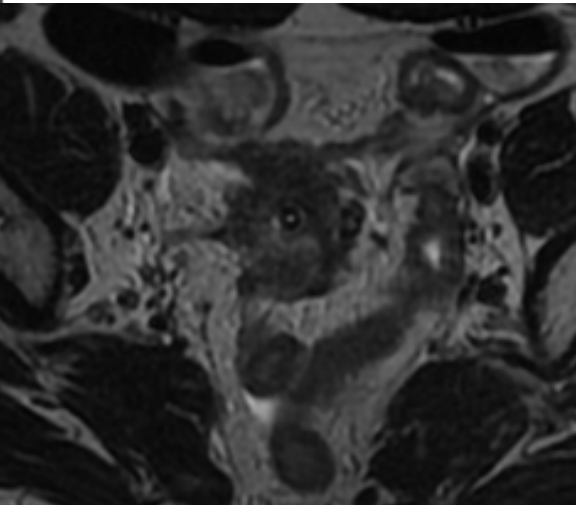
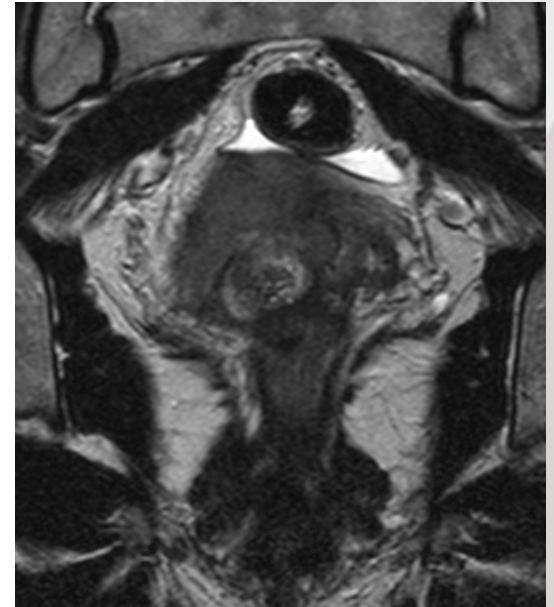
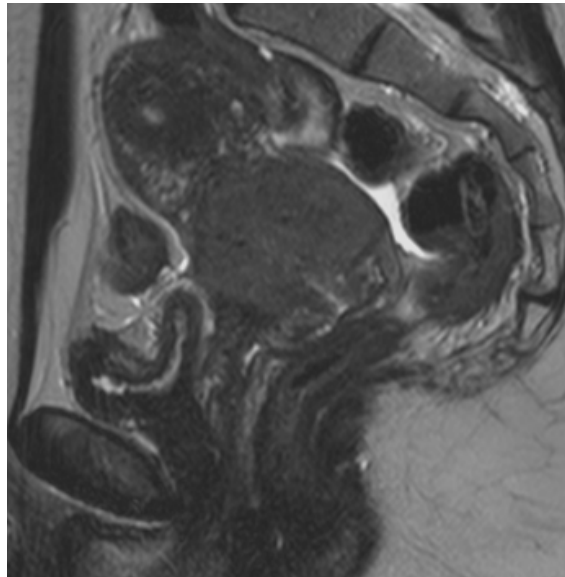
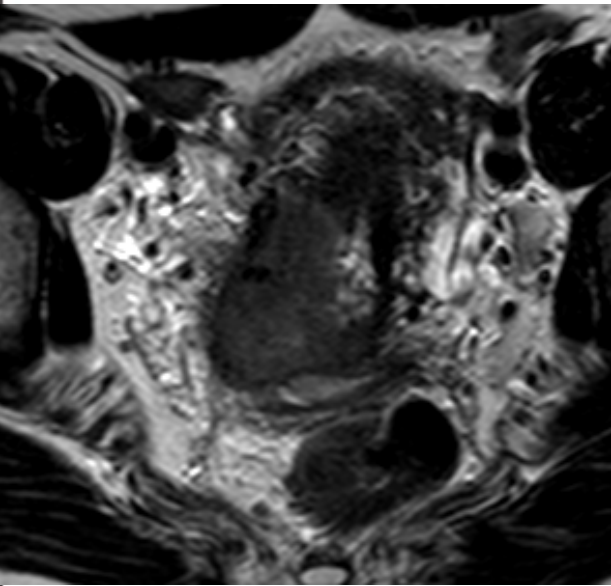


CTV_{IR}

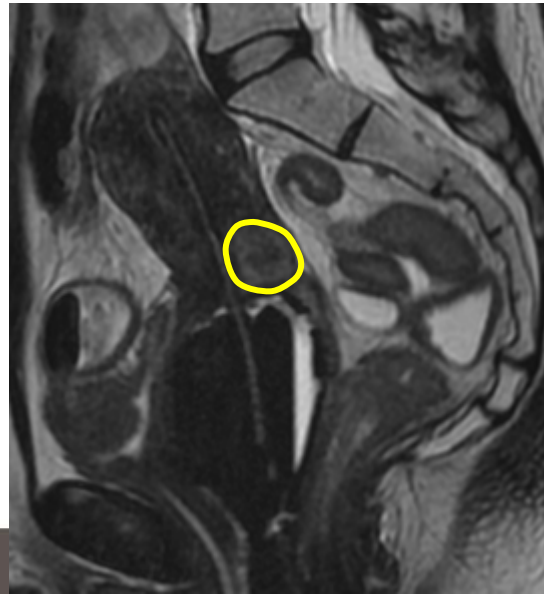
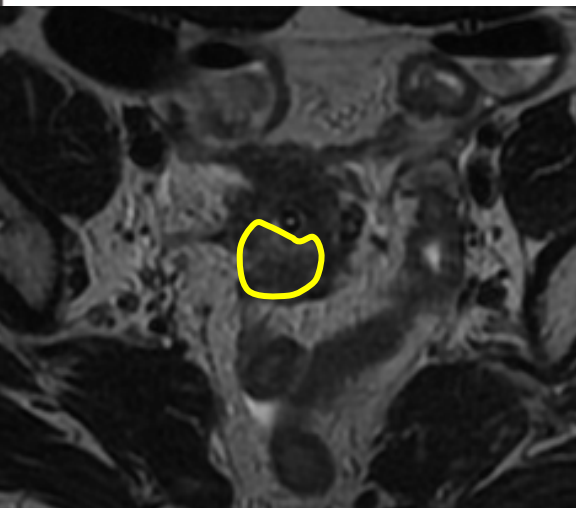
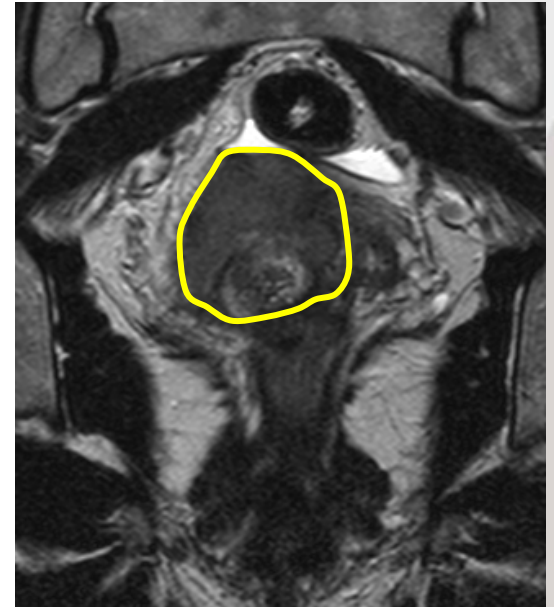
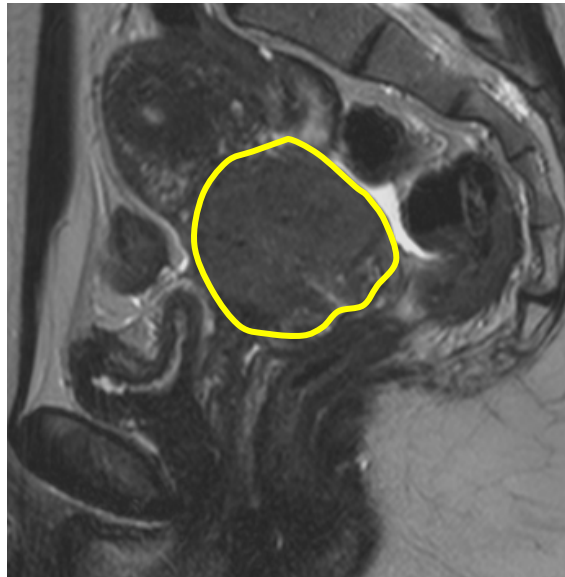
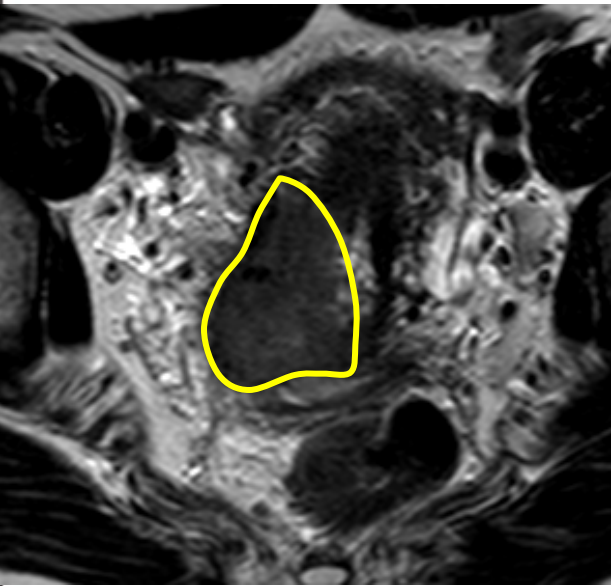


CTV_{LR}

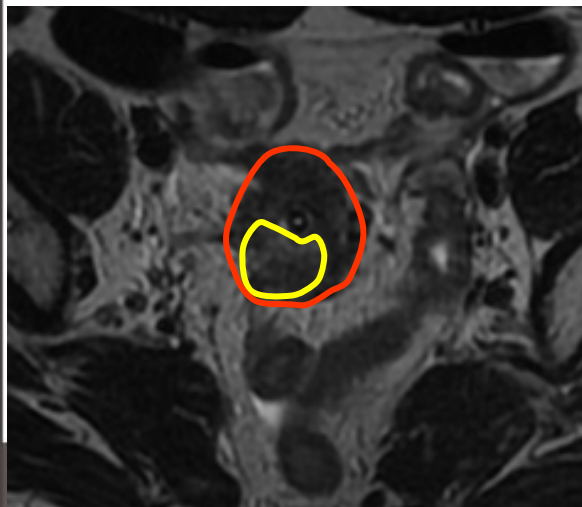
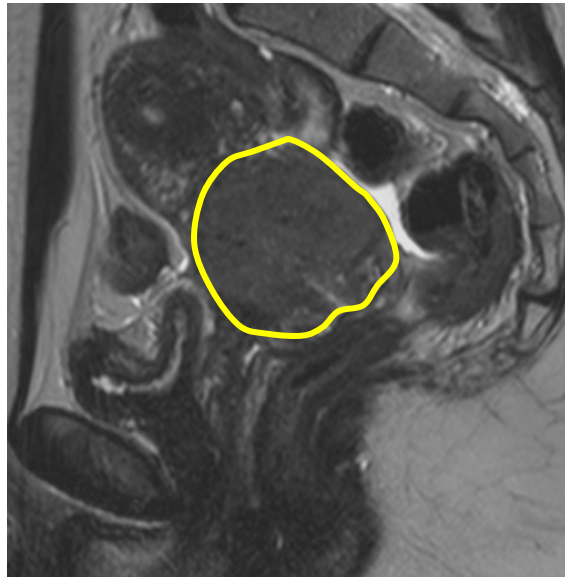
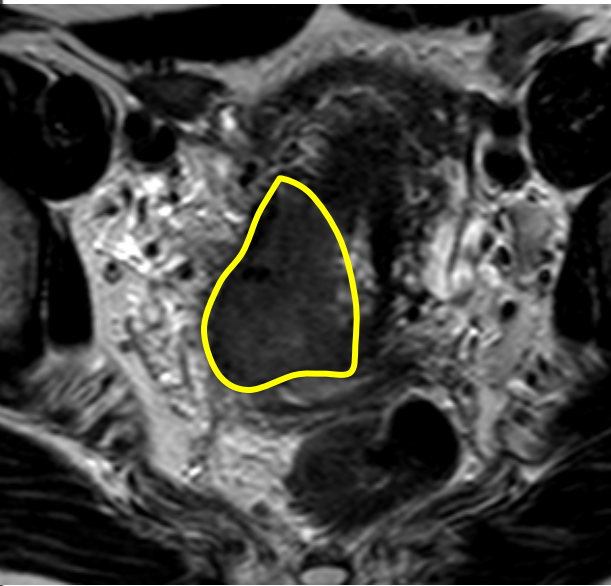
Stage IB2



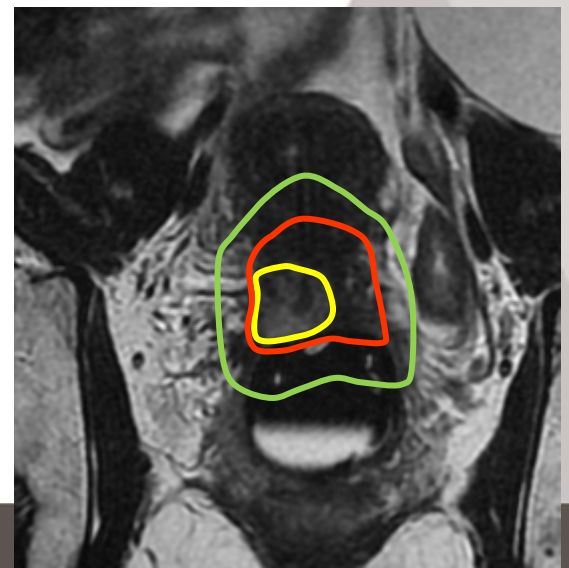
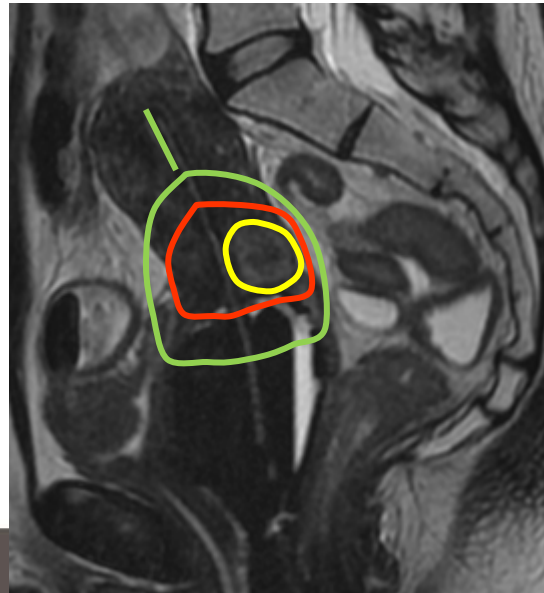
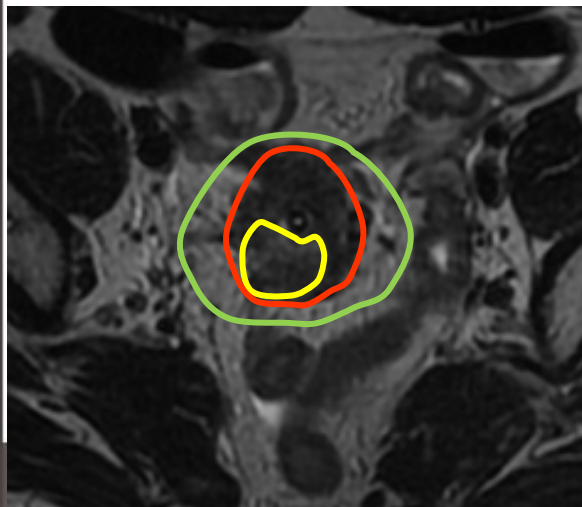
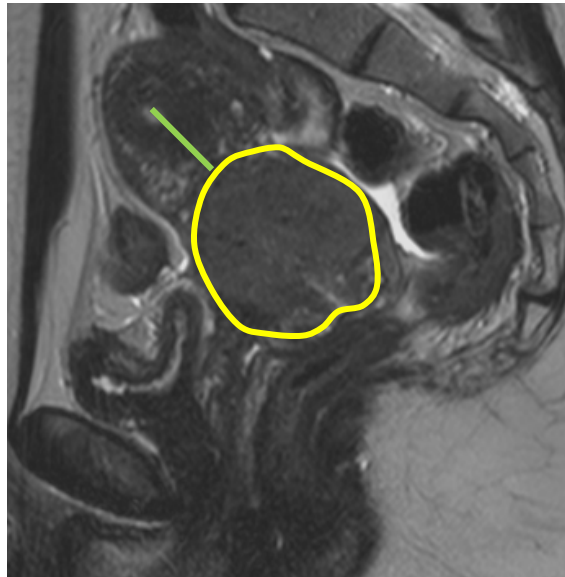
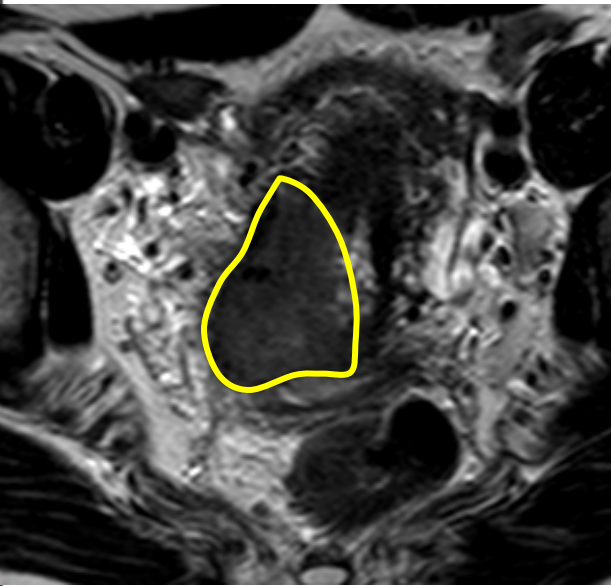
Stage IB2



Stage IB2



Stage IB2



Patient n° 3, stage IIA2, 5 cm

Mrs C P...

36 year-old

WHO=0

Vaginal bleeding

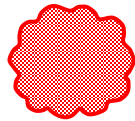
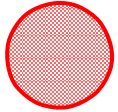
Biopsy: poorly differentiated squamous cell carcinoma

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)

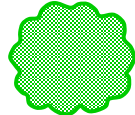
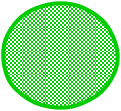
Stage IIA2 : initial clinical examination

Infiltrating Exophytic

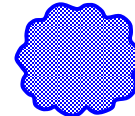
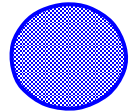
Cervix



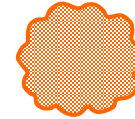
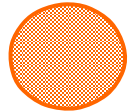
Vagina



Parametrium



Rectum or
Bladder



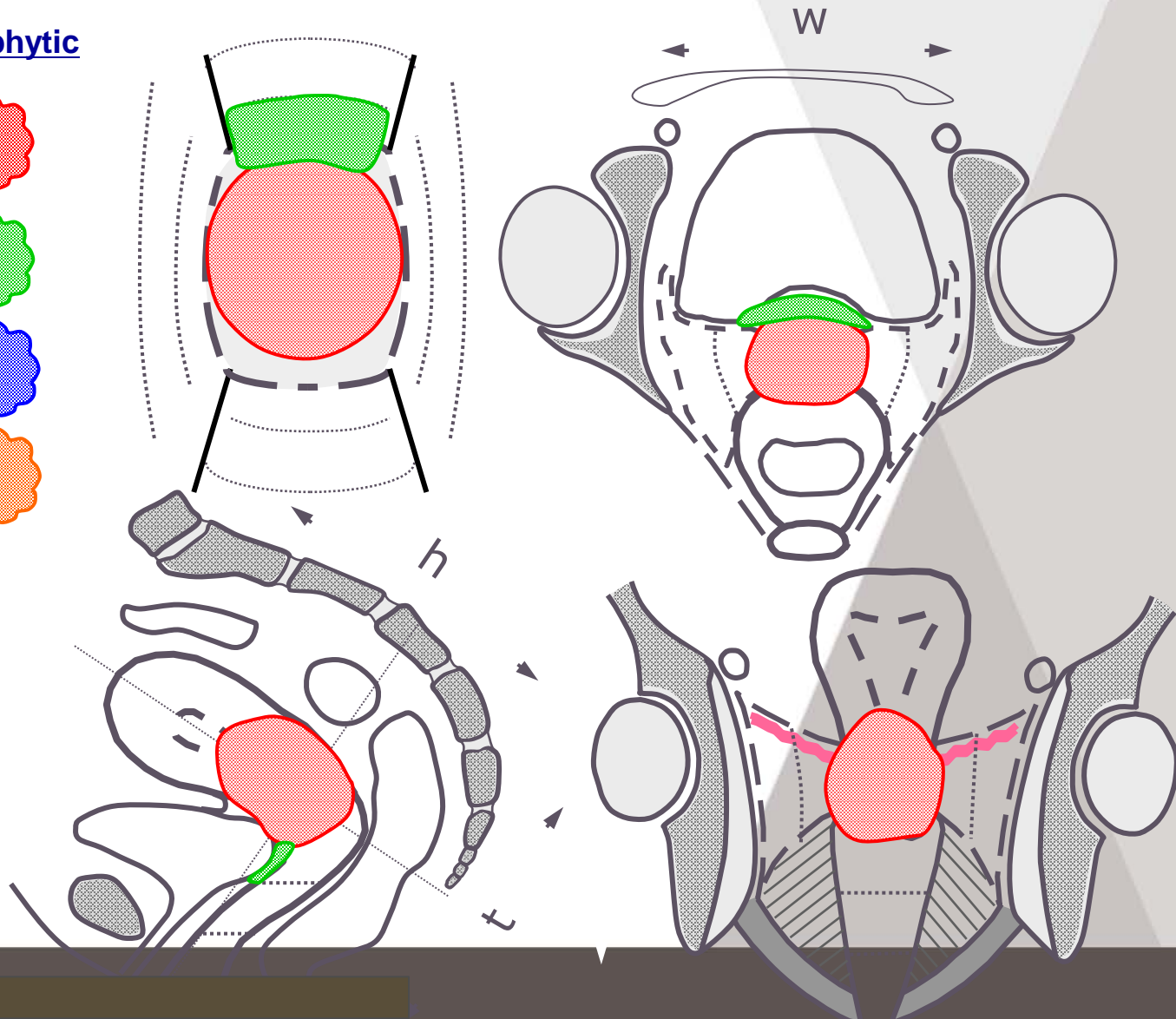
Dimensions (cm):

Width : 5

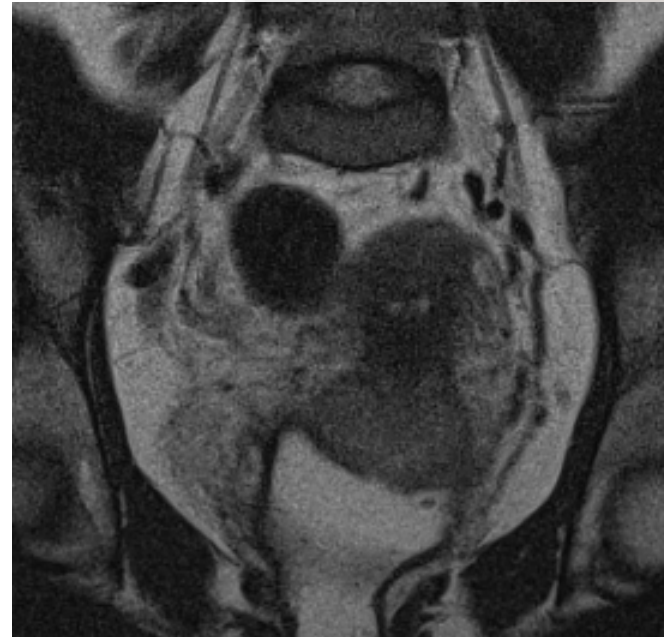
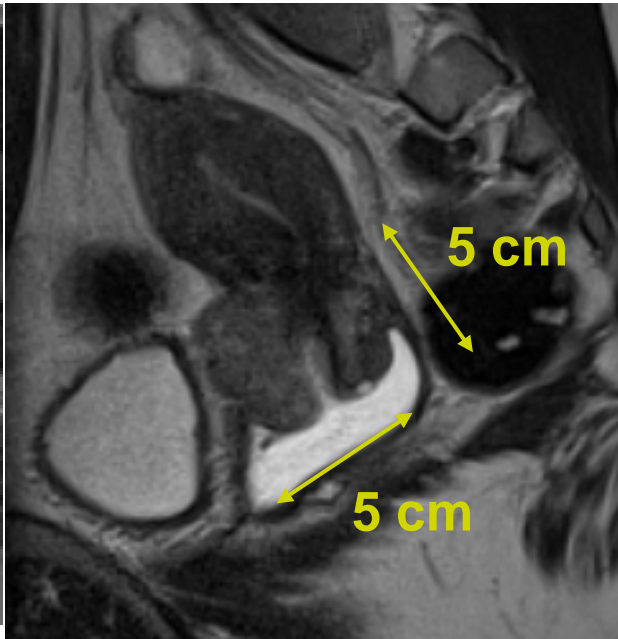
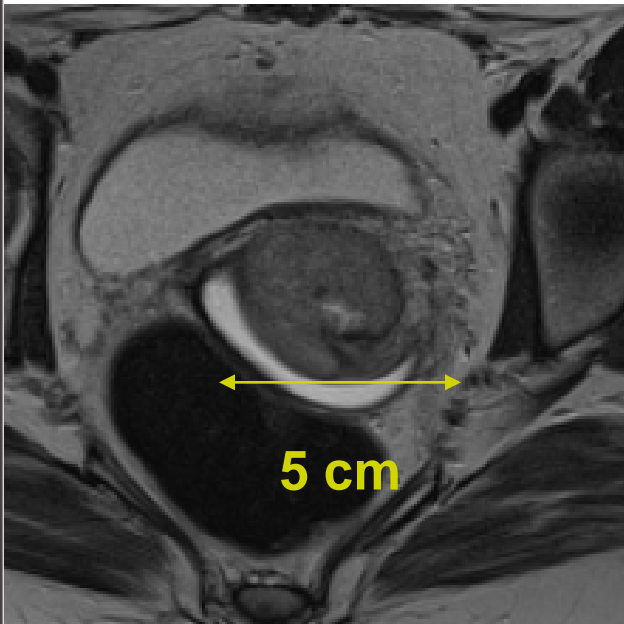
Thickness:4.5

Height : 5

Vaginal involv 1.5



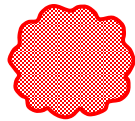
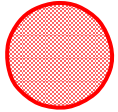
Stage IIA2 : initial MRI



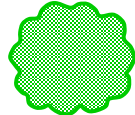
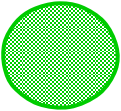
Stage IIA2 : at time of brachytherapy

Infiltrating Exophytic

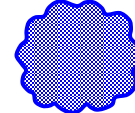
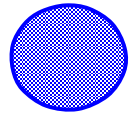
Cervix



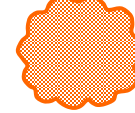
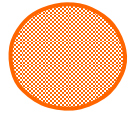
Vagina



Parametrium



Rectum or
Bladder



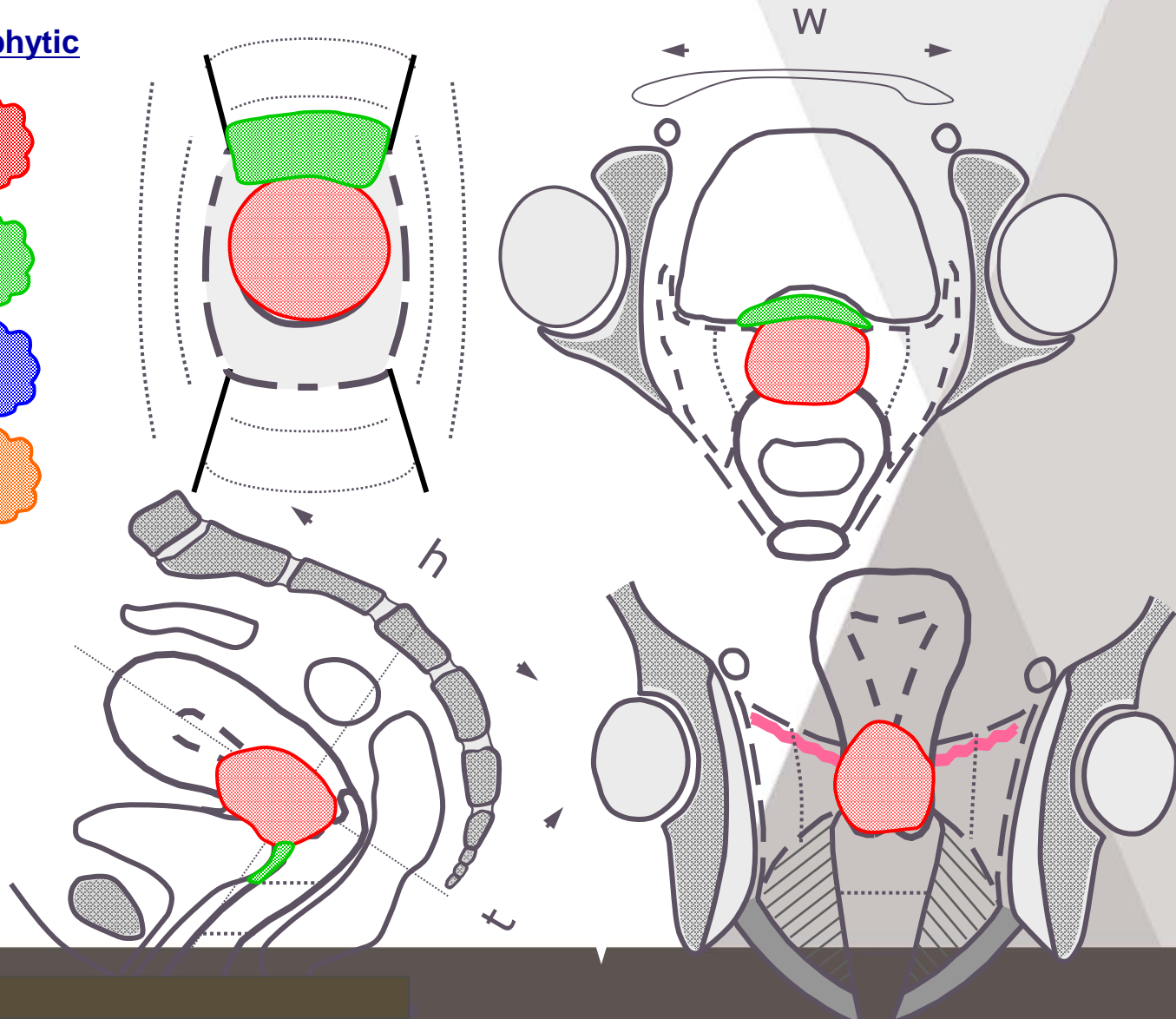
Dimensions (cm):

Width : 3.5

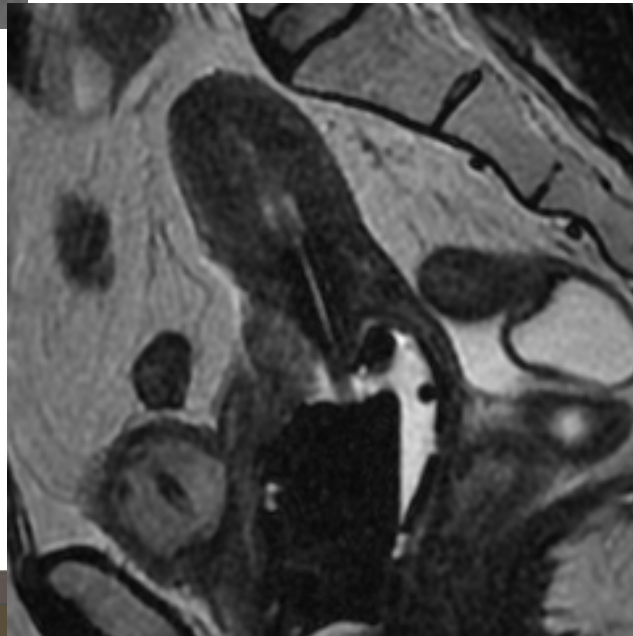
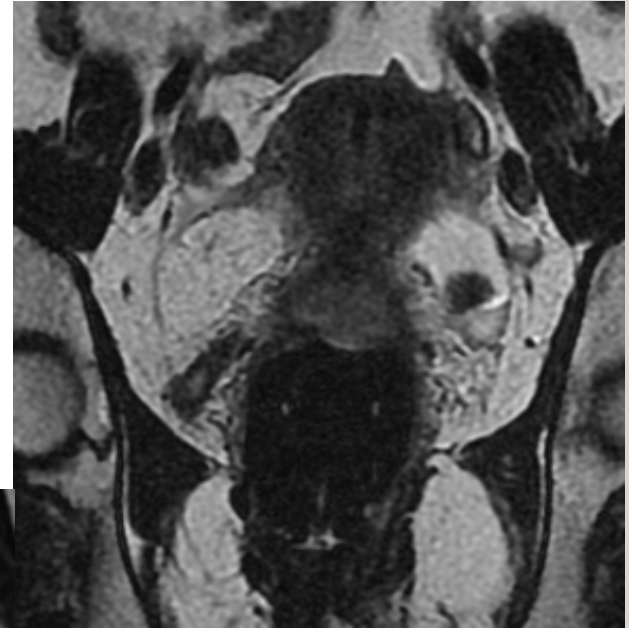
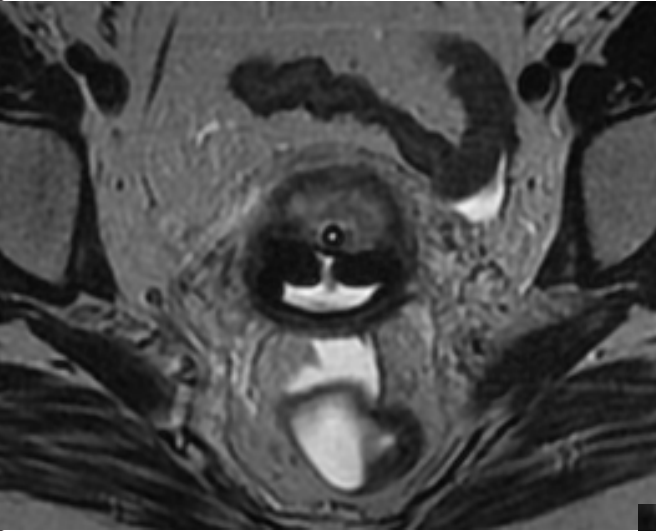
Thickness:3.5

Height : 3

Vaginal involv :1



Stage IIA2 : 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 residual GTV + whole cervix + residual vaginal involvement**

IR-CTV includes:

- A. the initial tumor extension**
- B. the residual GTV +
whole cervix +
initial vaginal
involvement
+safety margins
(HR CTV)**
- C. the whole cervix
only**
- D. the GTV + whole
cervix**

Target volume concepts: stage IB

High Risk CTV :

- Residual GTV at time of brachytherapy
- Whole cervix
- Vaginal residual tumour extension

Clinical assessment
MRI assessment

NO SAFETY MARGINS

Intermediate Risk CTV :

- Initial GTV
- Including initial vaginal involvement
- HR-CTV + safety margins

SAFETY MARGINS :

1-1.5 cm cranially
0.5cm antero-posteriorly
1cm laterally

Intrauterine and Vaginal Disease

Variation in GTV response

selection of HR CTV
selection of IR CTV

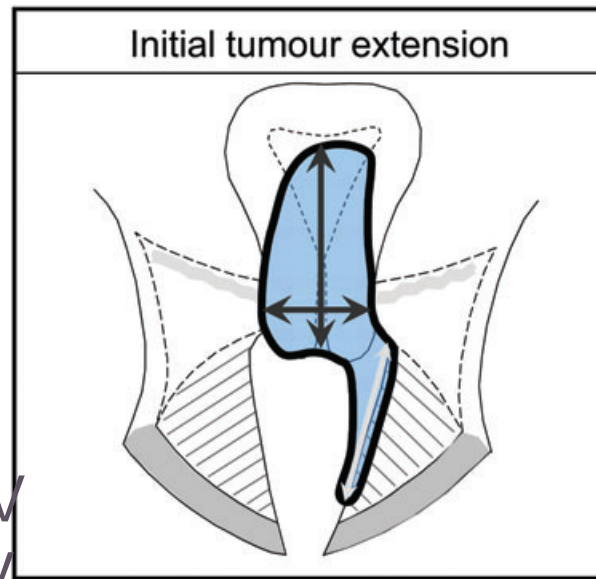
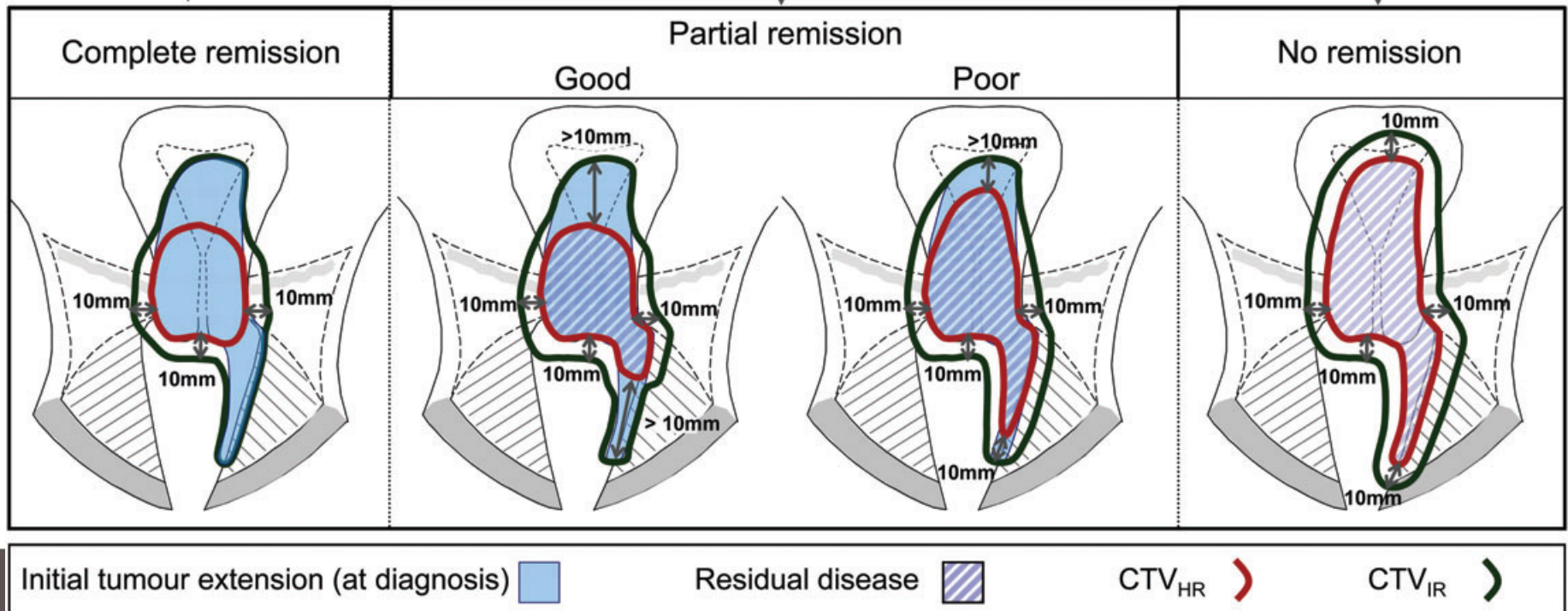
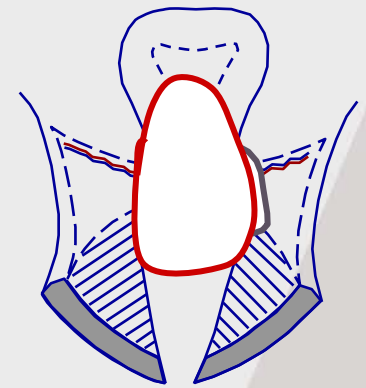
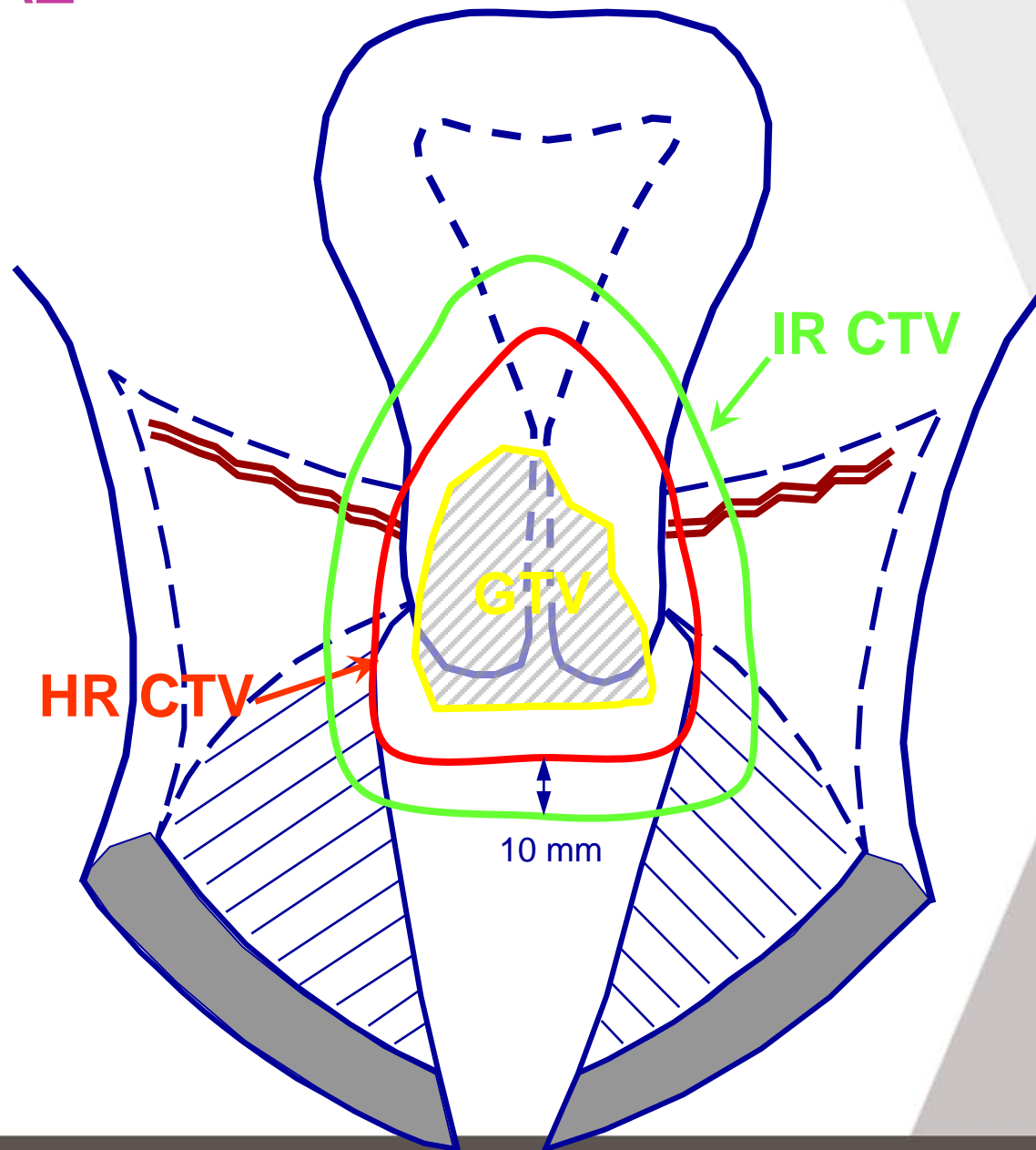


Fig. 5.14
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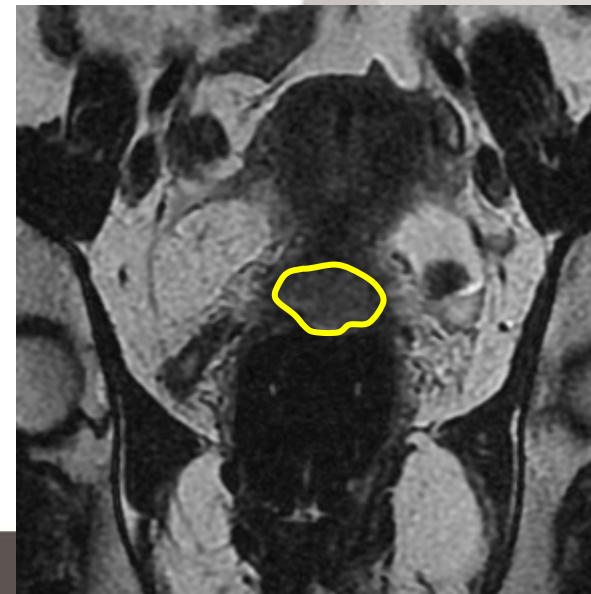
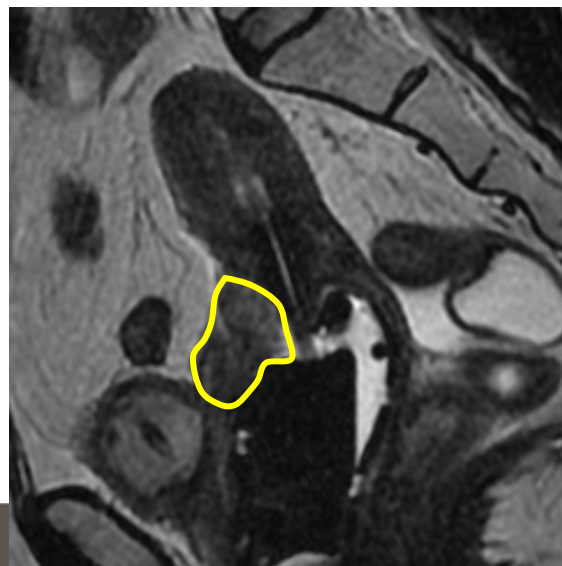
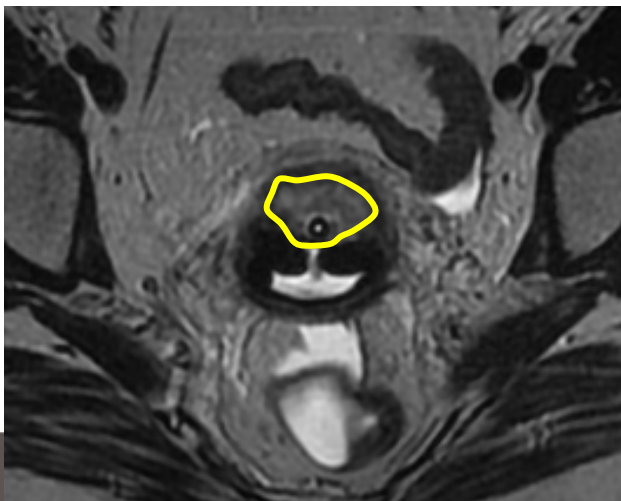
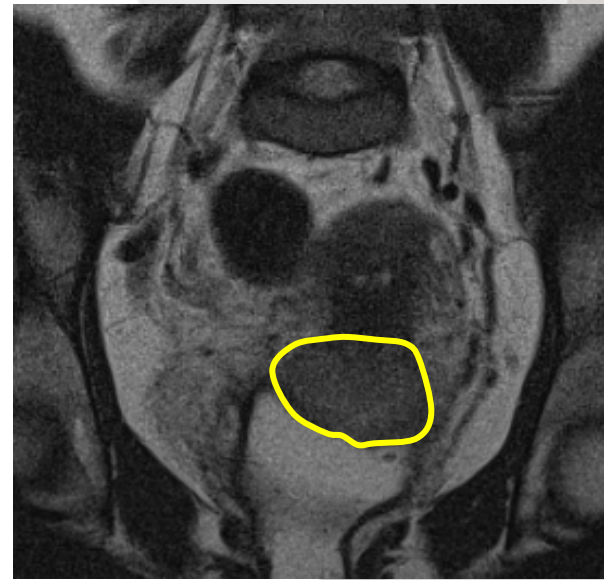
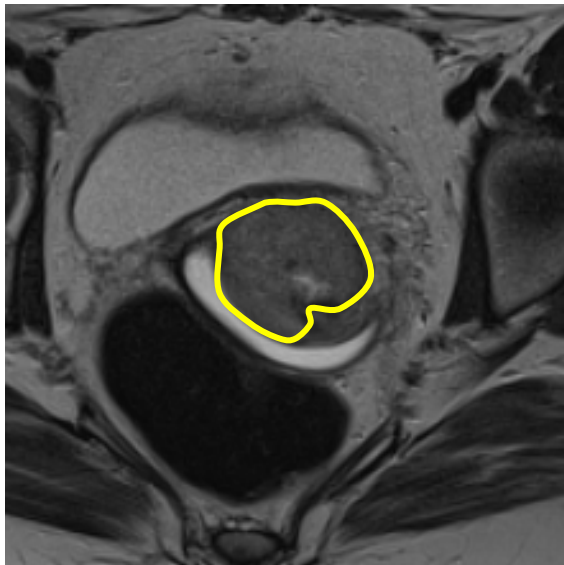


Stage IIA2

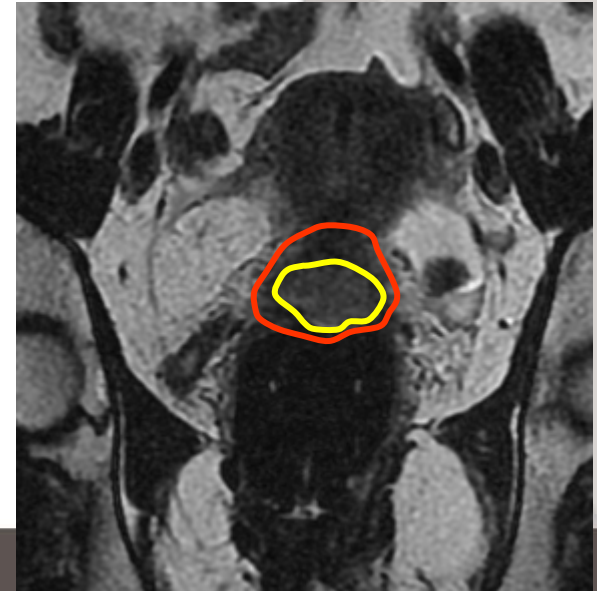
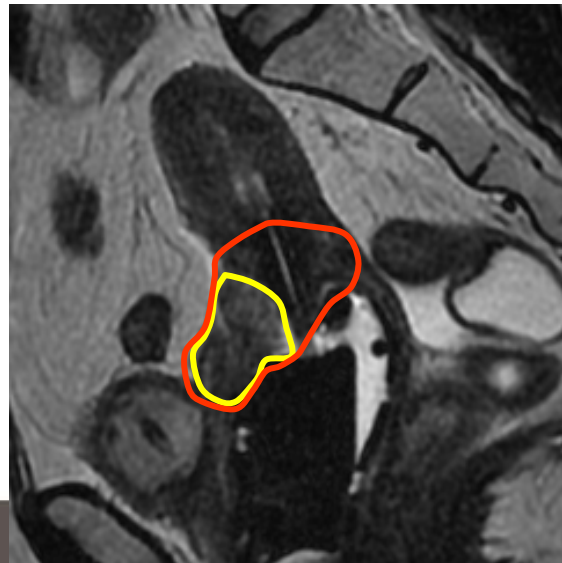
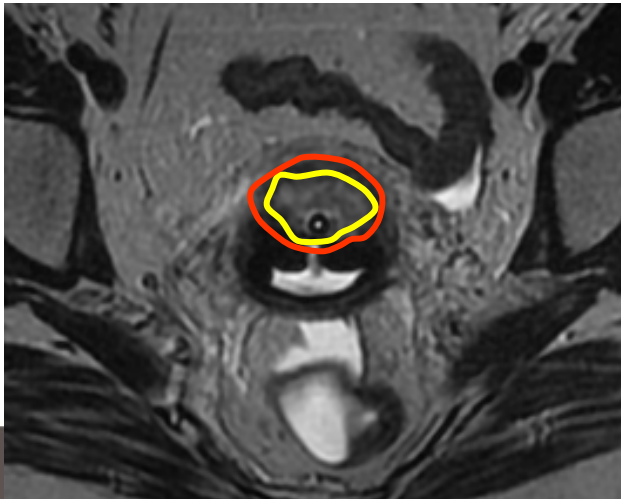
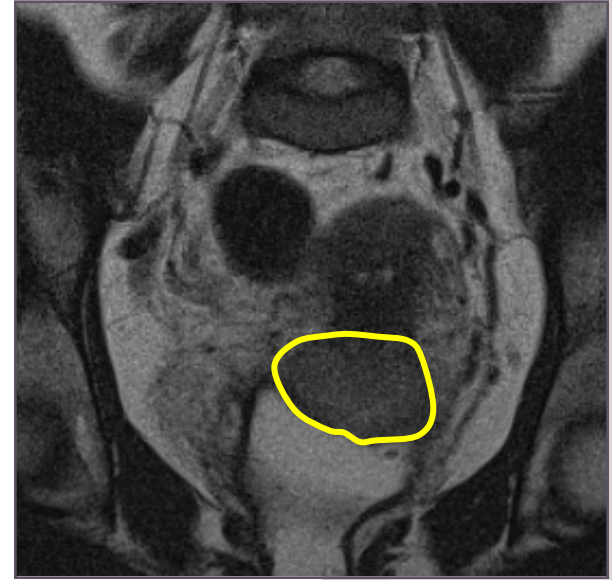
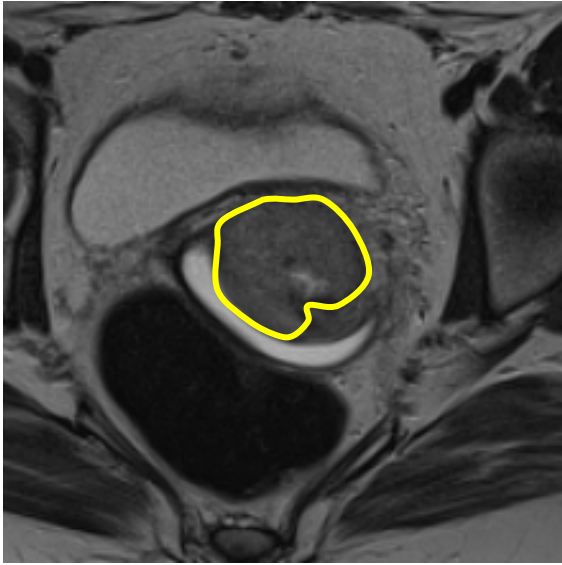


Tumor at time of diagnosis

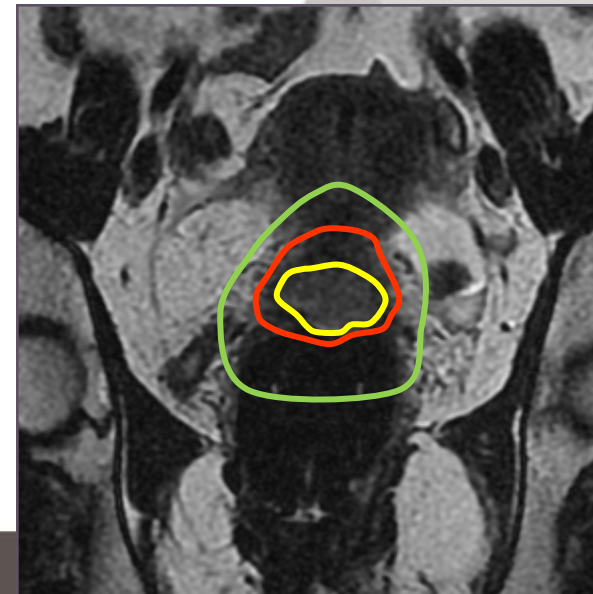
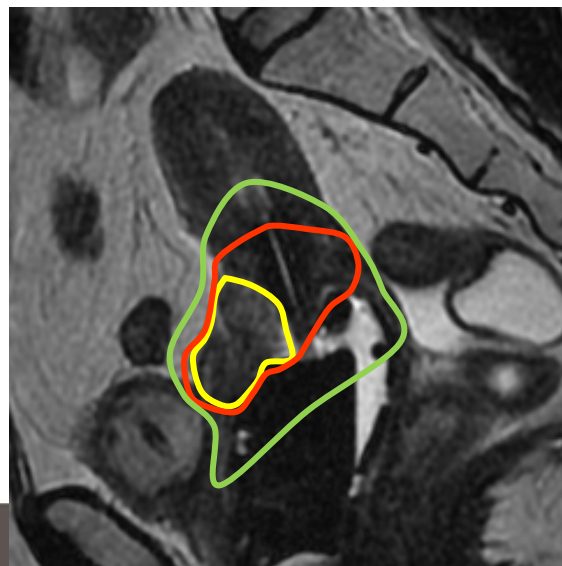
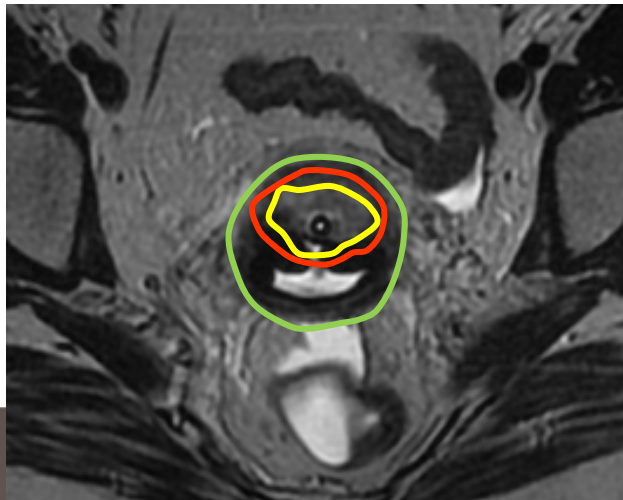
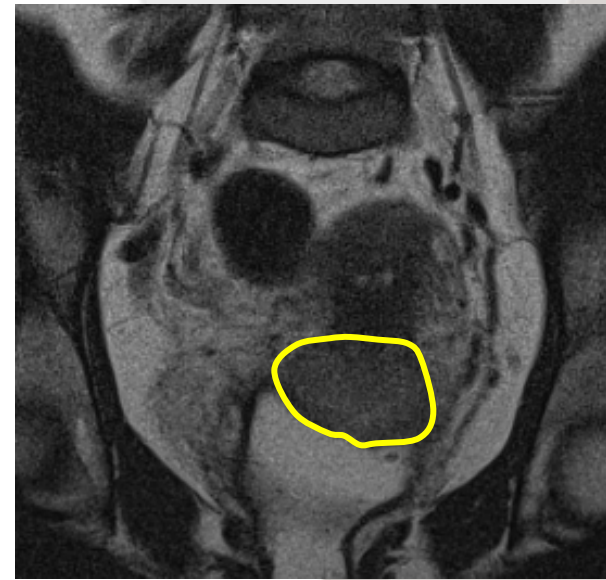
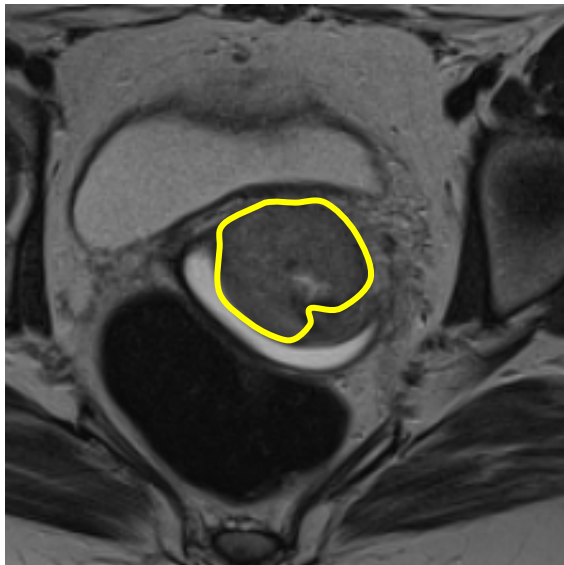
Stage IIA2



Stage IIA2



Stage IIA2



Patient n°4 stage IIB, 5 cm

Mrs E B...

46 year-old

WHO=0, 72 kg, 1m67

Vaginal bleeding

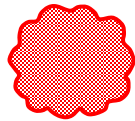
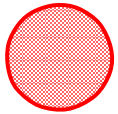
Biopsy: moderately differentiated adenocarcinoma

At clinical examination : cervical tumor +
infiltration of the anterior and posterior fornices +
infiltration of the proximal part of the left
parametrium

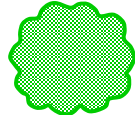
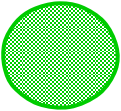
Stage IIB : initial clinical examination

Infiltrating Exophytic

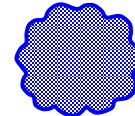
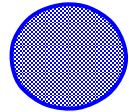
Cervix



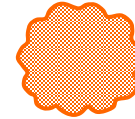
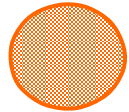
Vagina



Parametrium



Rectum or
Bladder



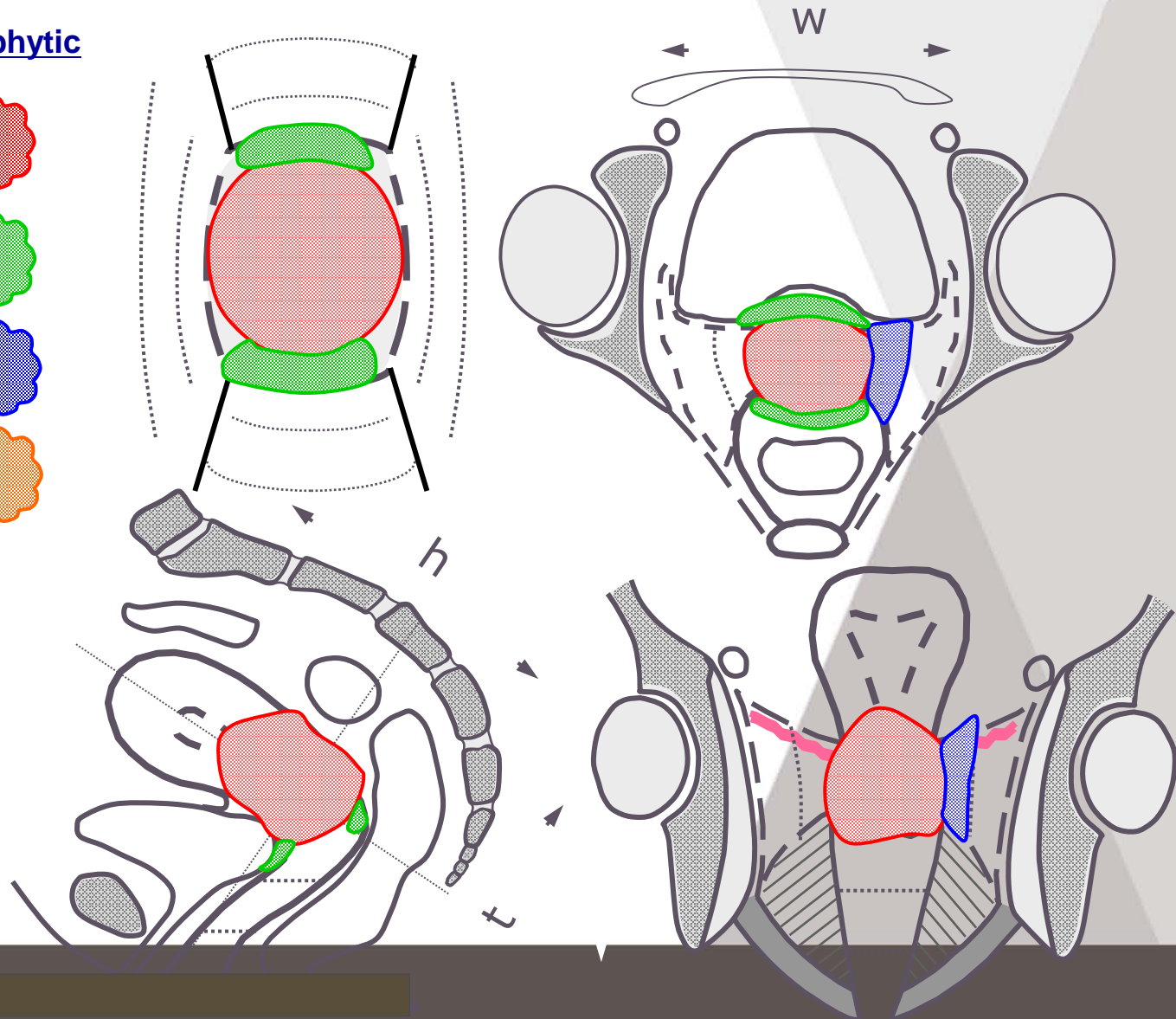
Dimensions (cm):

Width : 5

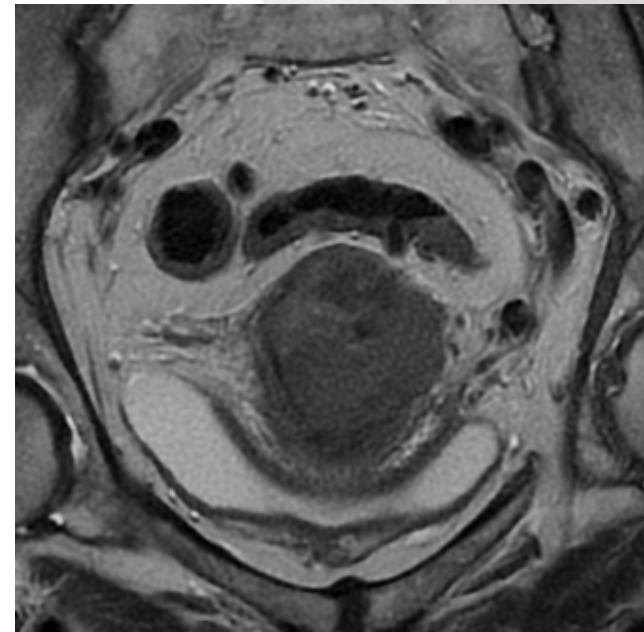
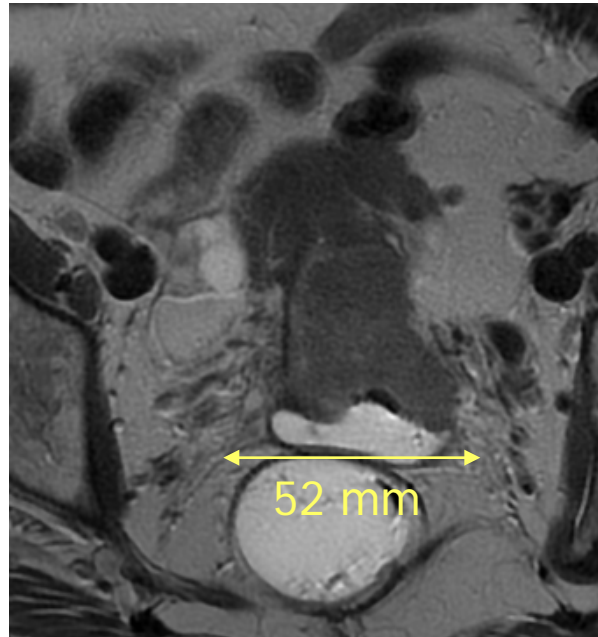
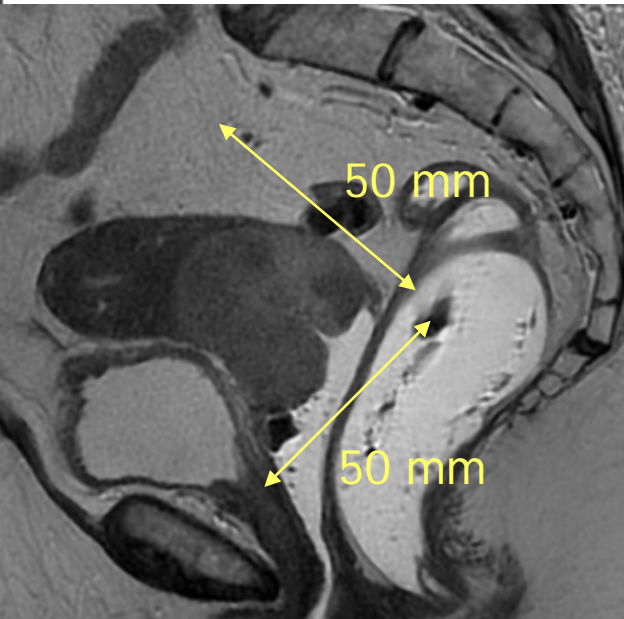
Thickness:5

Height : 5

Fornix involv 1



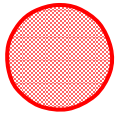
Stage IIB : initial MRI



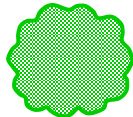
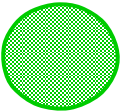
Stage IIB : at the time of brachytherapy

Infiltrating Exophytic

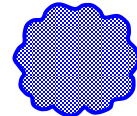
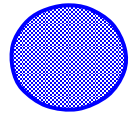
Cervix



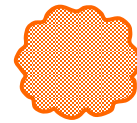
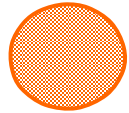
Vagina



Parametrium



Rectum or
Bladder



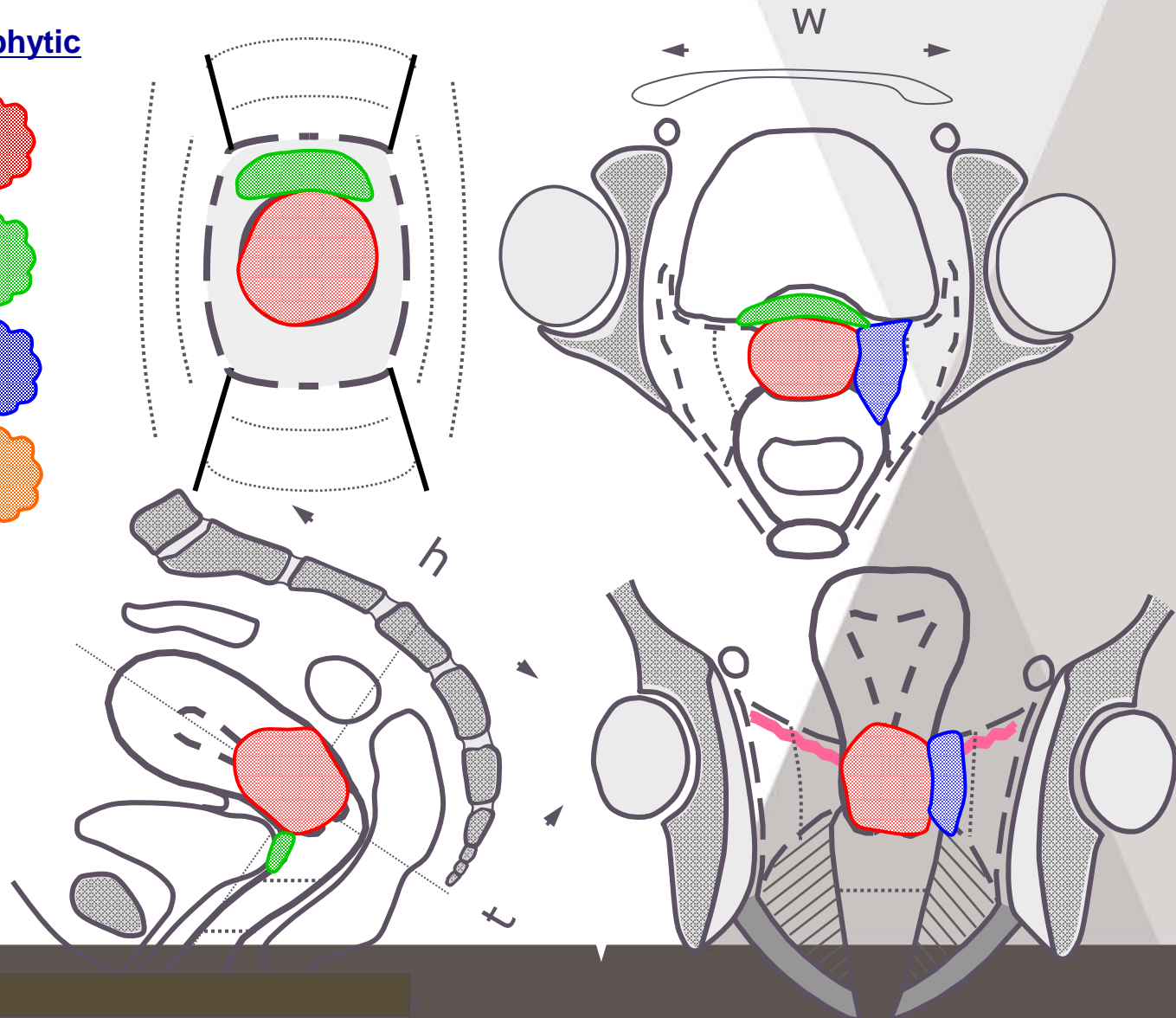
Dimensions (cm):

Largeur : 3

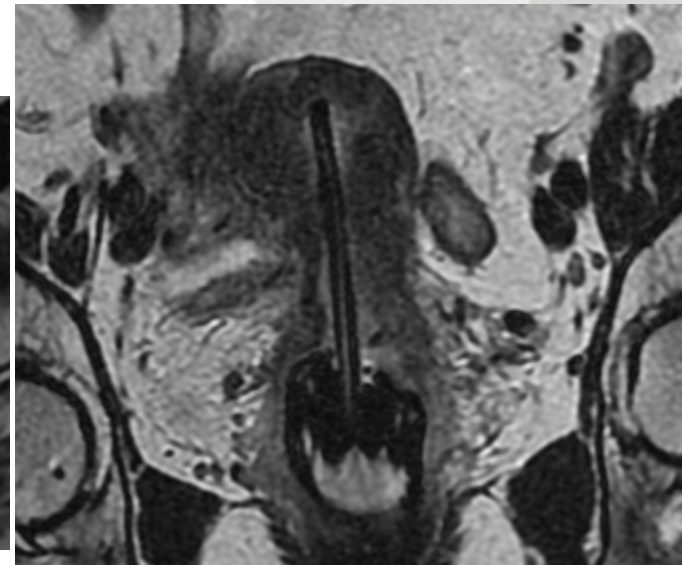
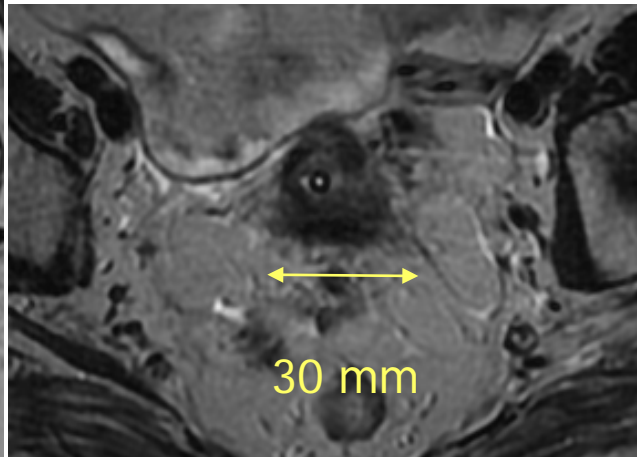
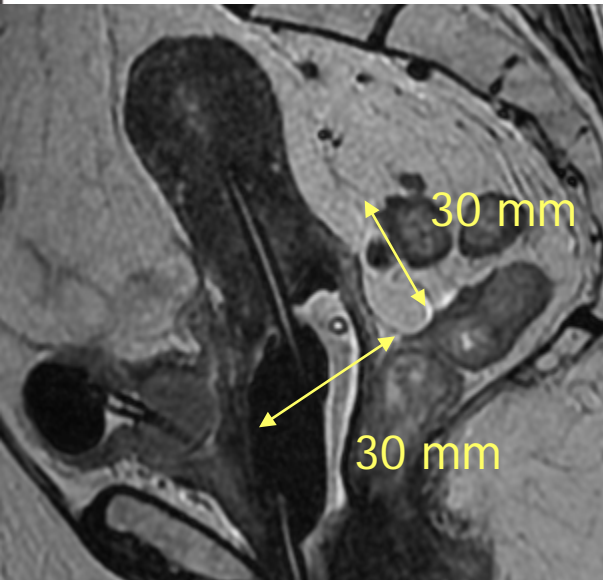
Epaisseur : 3

Hauteur : 3

Env. vaginal : 1



Stage IIB : MRI at the time of brachytherapy



Target volume concepts: stage IB

High Risk CTV :

- Residual GTV at time of brachytherapy
- Whole cervix
- Parametrial and Vaginal residual tumour extension (residual pathologic tissue)

Clinical assessment
MRI assessment

NO SAFETY MARGINS

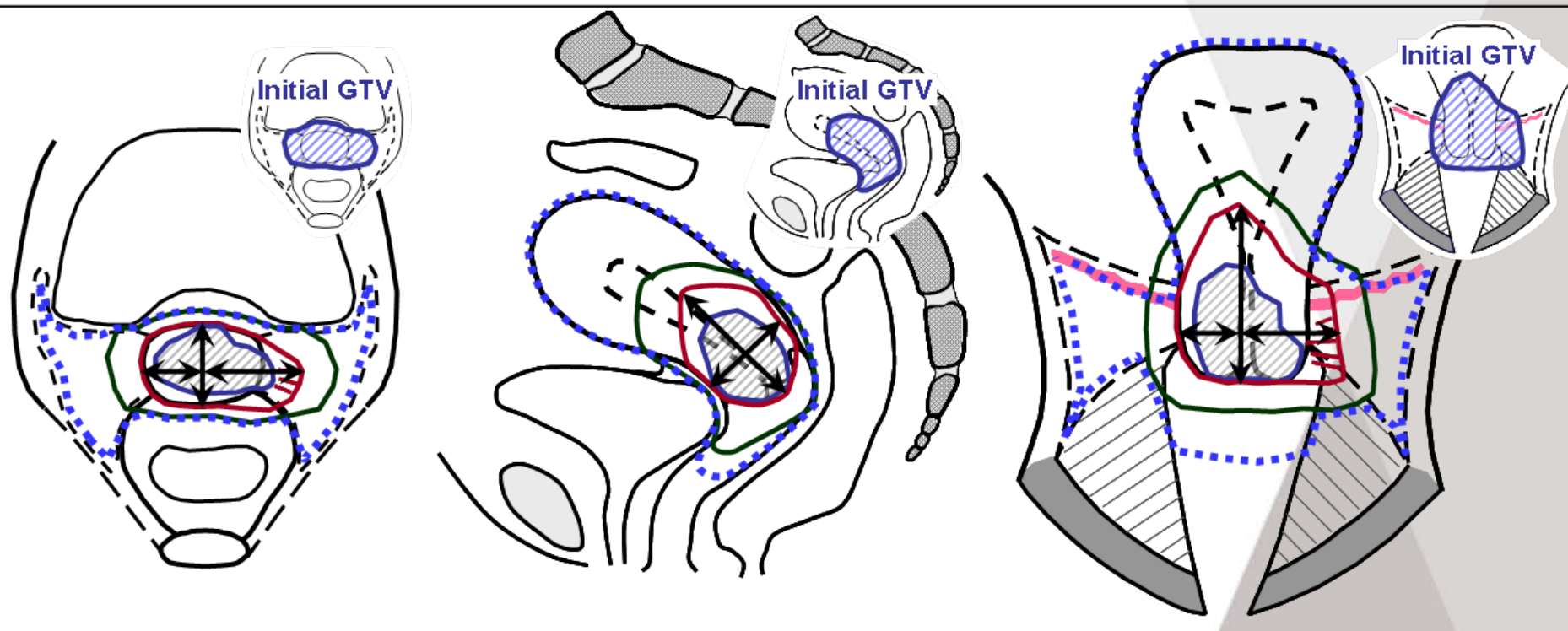
Intermediate Risk CTV :

- Initial GTV
- Including initial vaginal and parametrial involvement
- HR-CTV + safety margins

SAFETY MARGINS :

1-1.5 cm cranially
0.5cm antero-posteriorly
1cm laterally

Cervix cancer stage IIB,



Initial GTV



GTV_{res}



CTV_{HR}

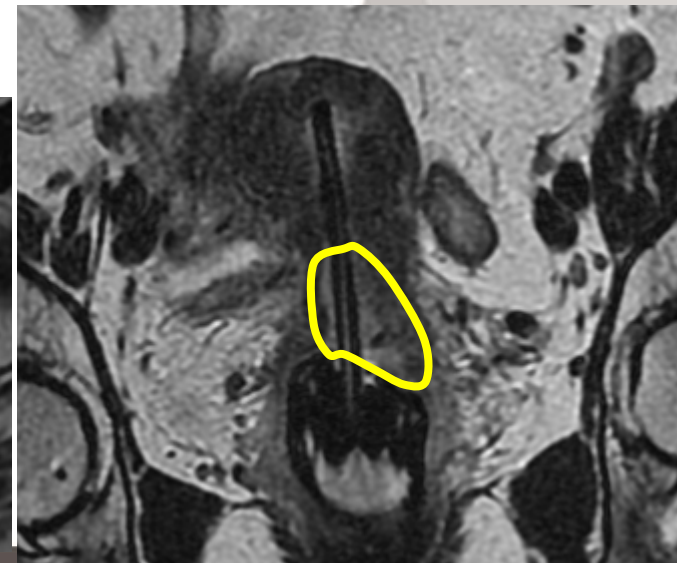
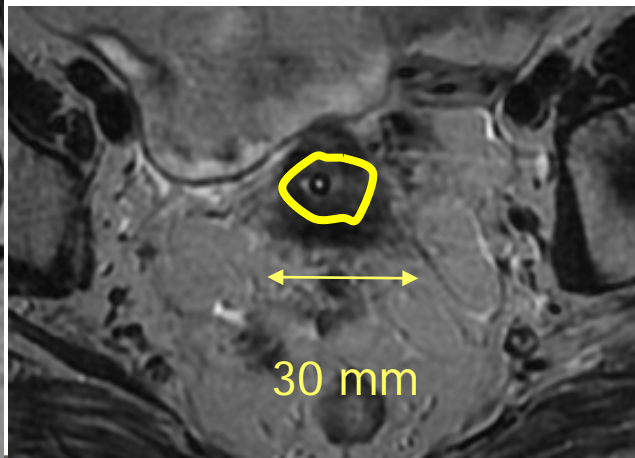
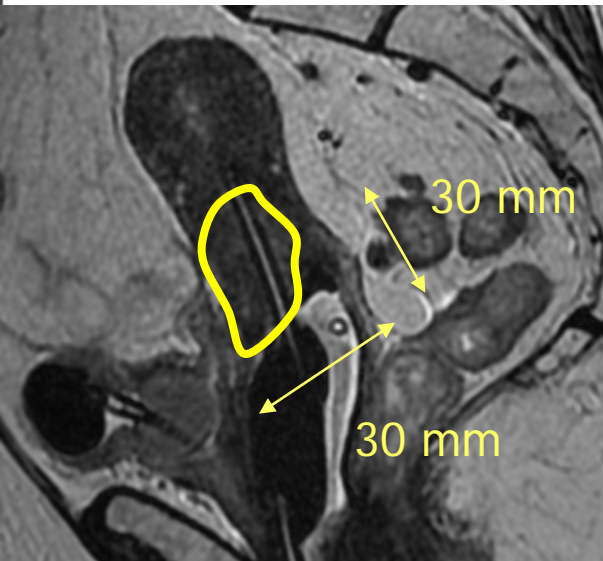
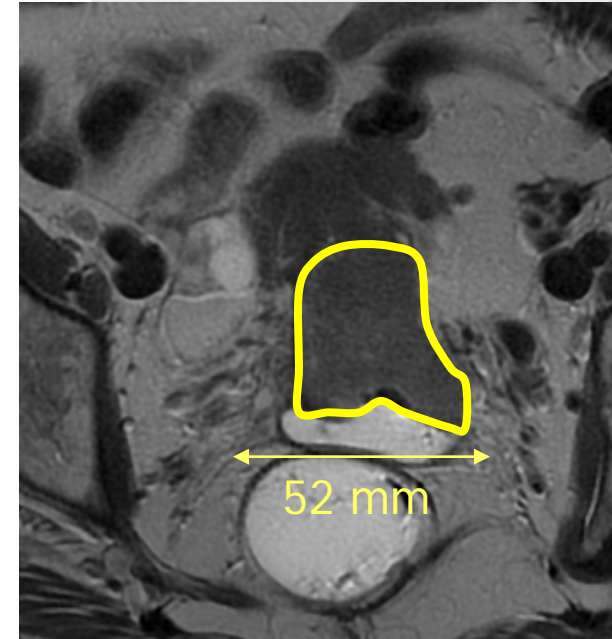
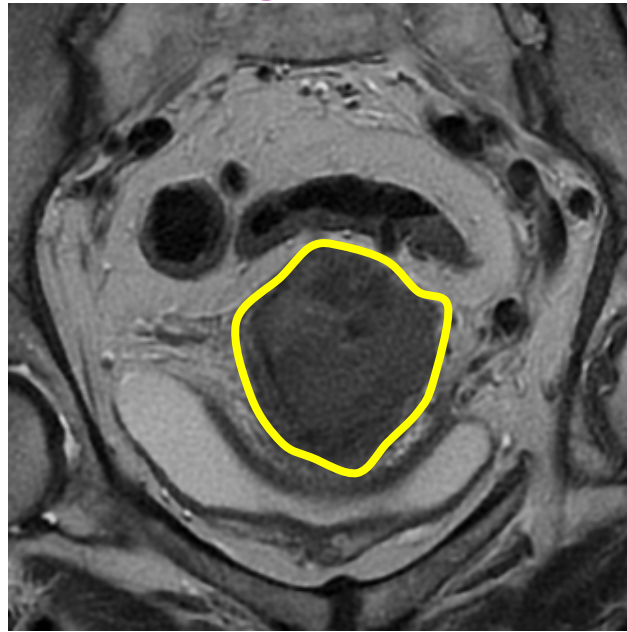
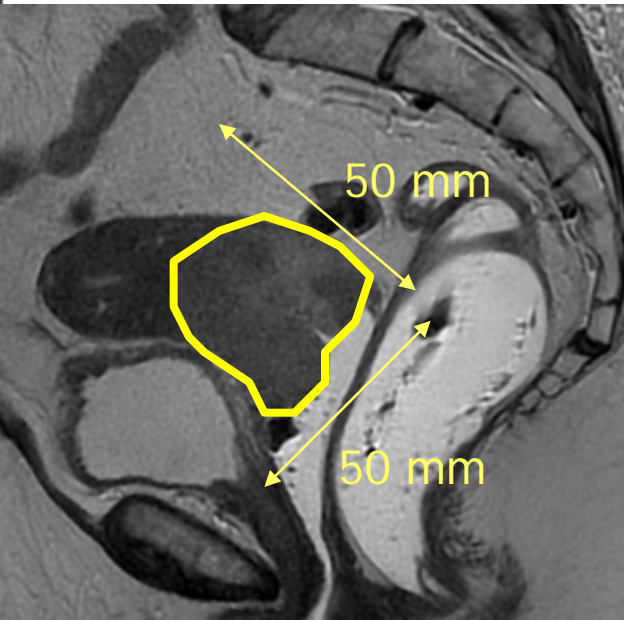


CTV_{IR}

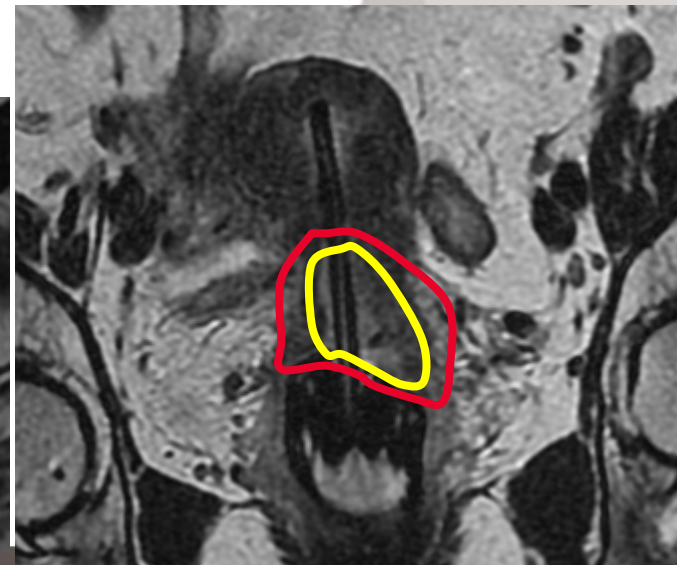
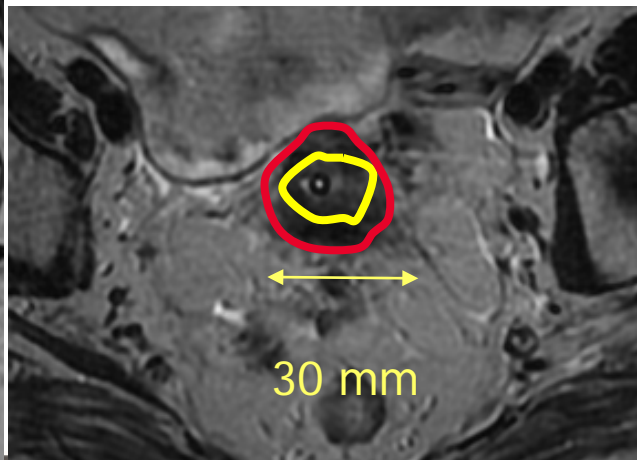
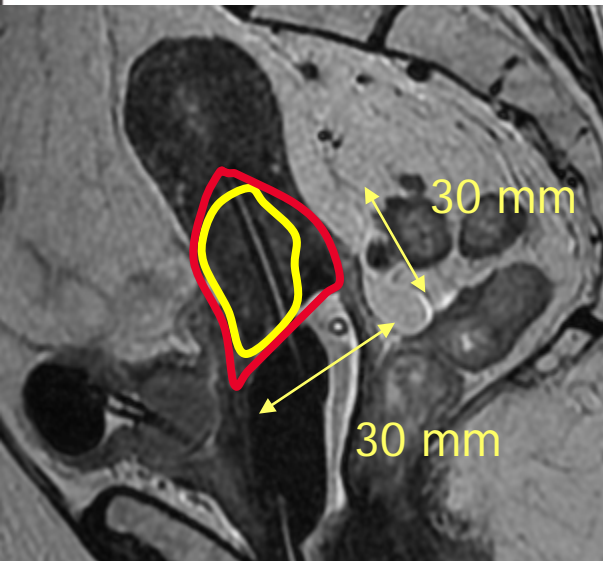
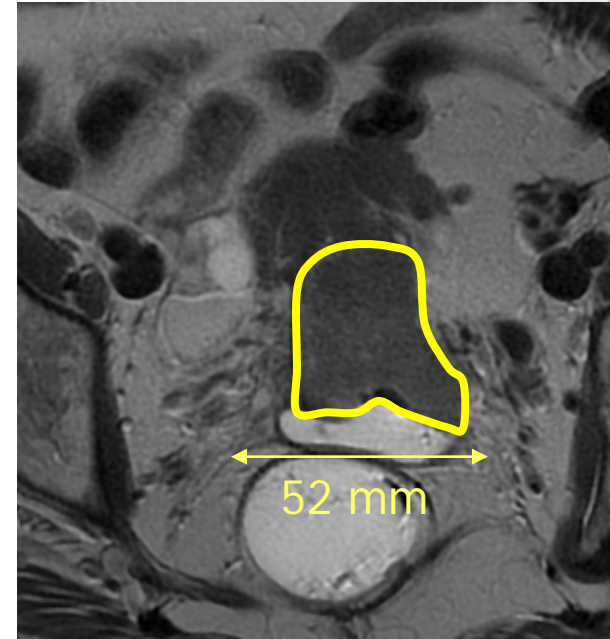
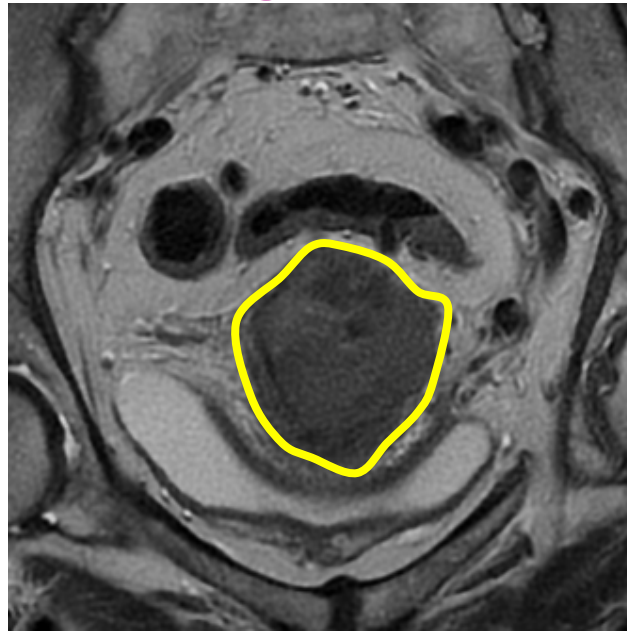
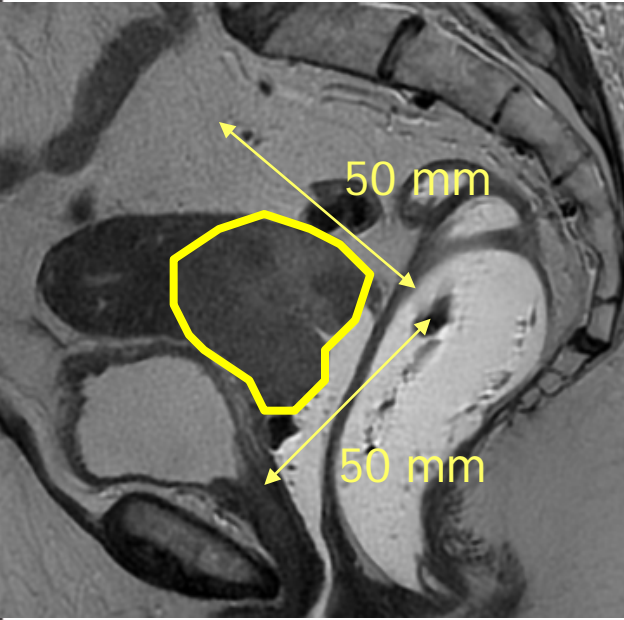


CTV_{LR}

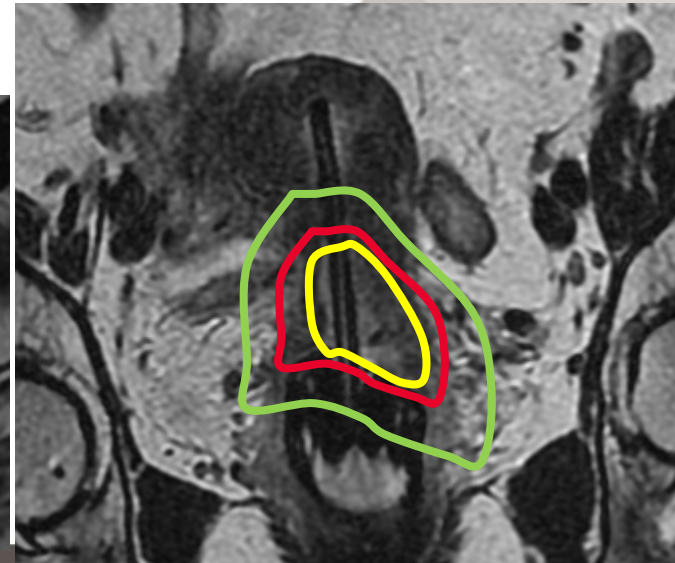
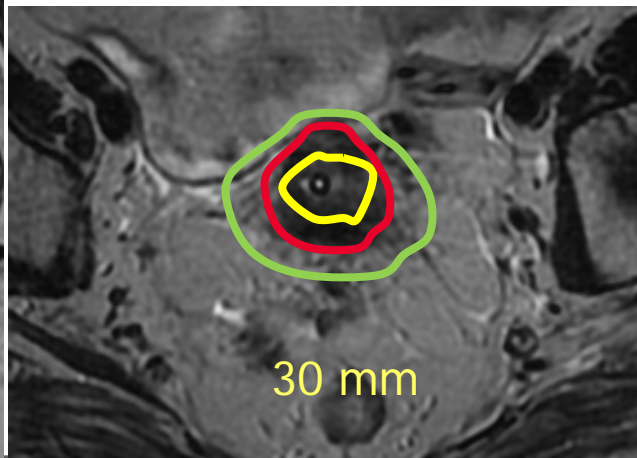
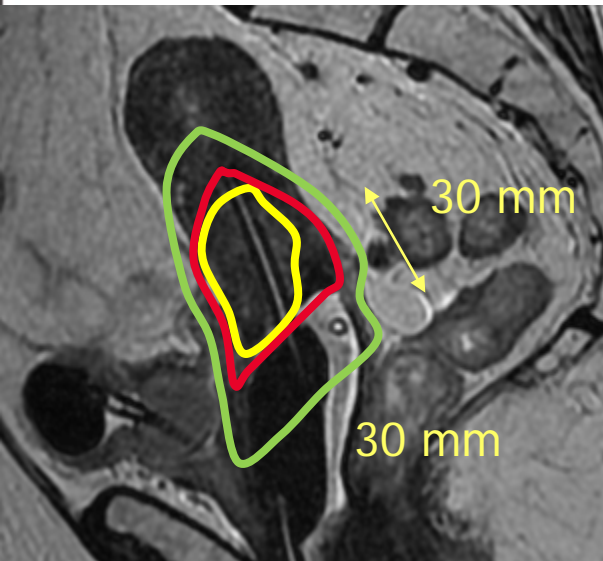
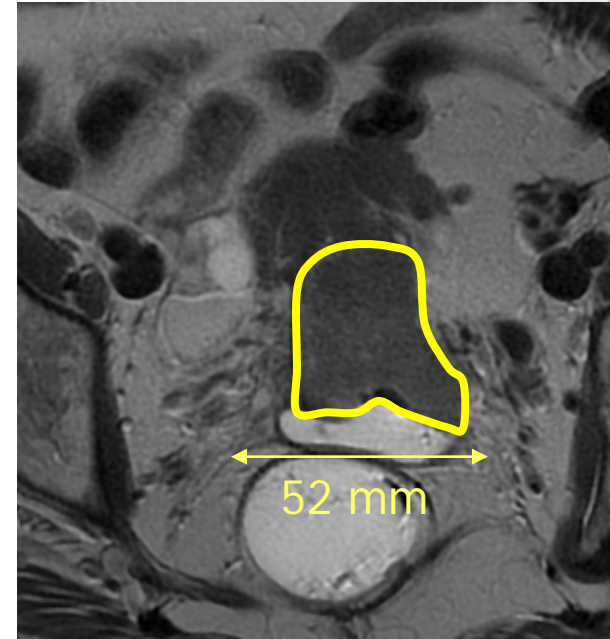
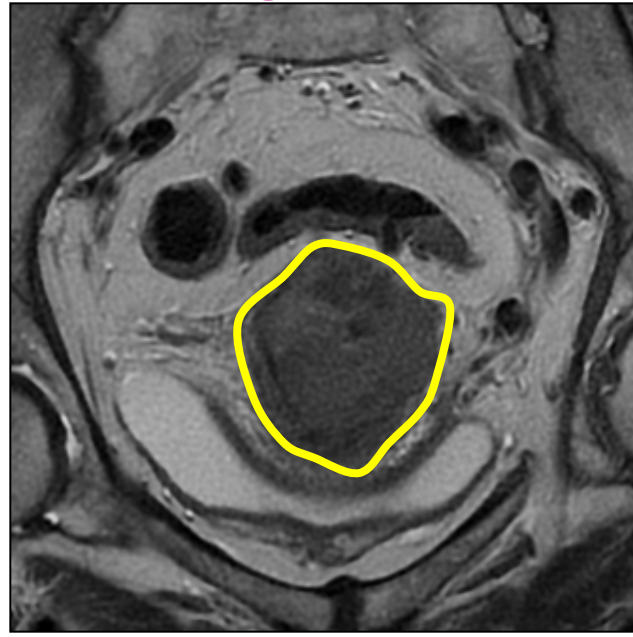
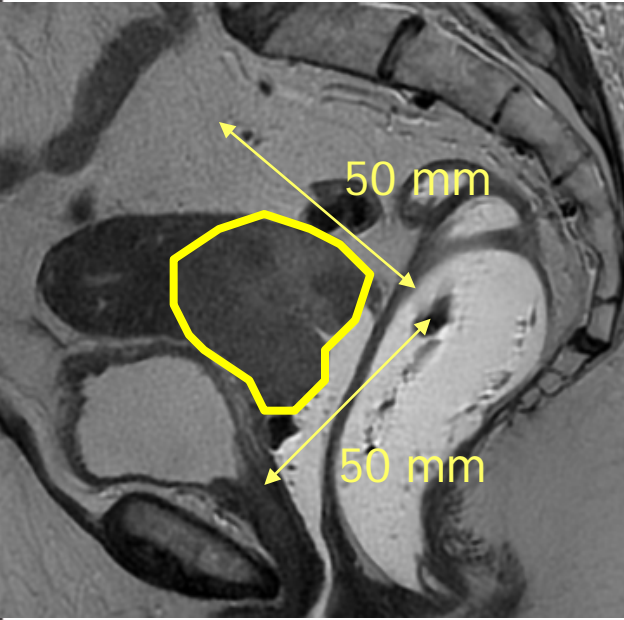
Stage IIB



Stage IIB



Stage IIB



Patient n° 5 stage IIB, 5 cm, bilateral and vaginal involvement

Mrs M S...
55 year-old

WHO=0, 60 kg, 1m53

Vaginal bleeding

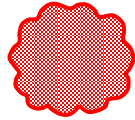
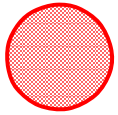
Biopsy: moderately differentiated SCC

At clinical examination : cervical tumor +
infiltration of the 1/2 upper anterior vaginal wall +
proximal infiltration of both parametria

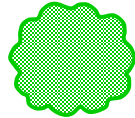
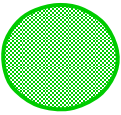
Stage IIB : initial clinical examination

Infiltrating Exophytic

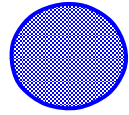
Cervix



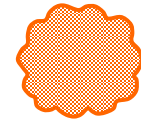
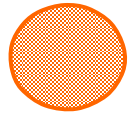
Vagina



Parametrium



Rectum or
Bladder



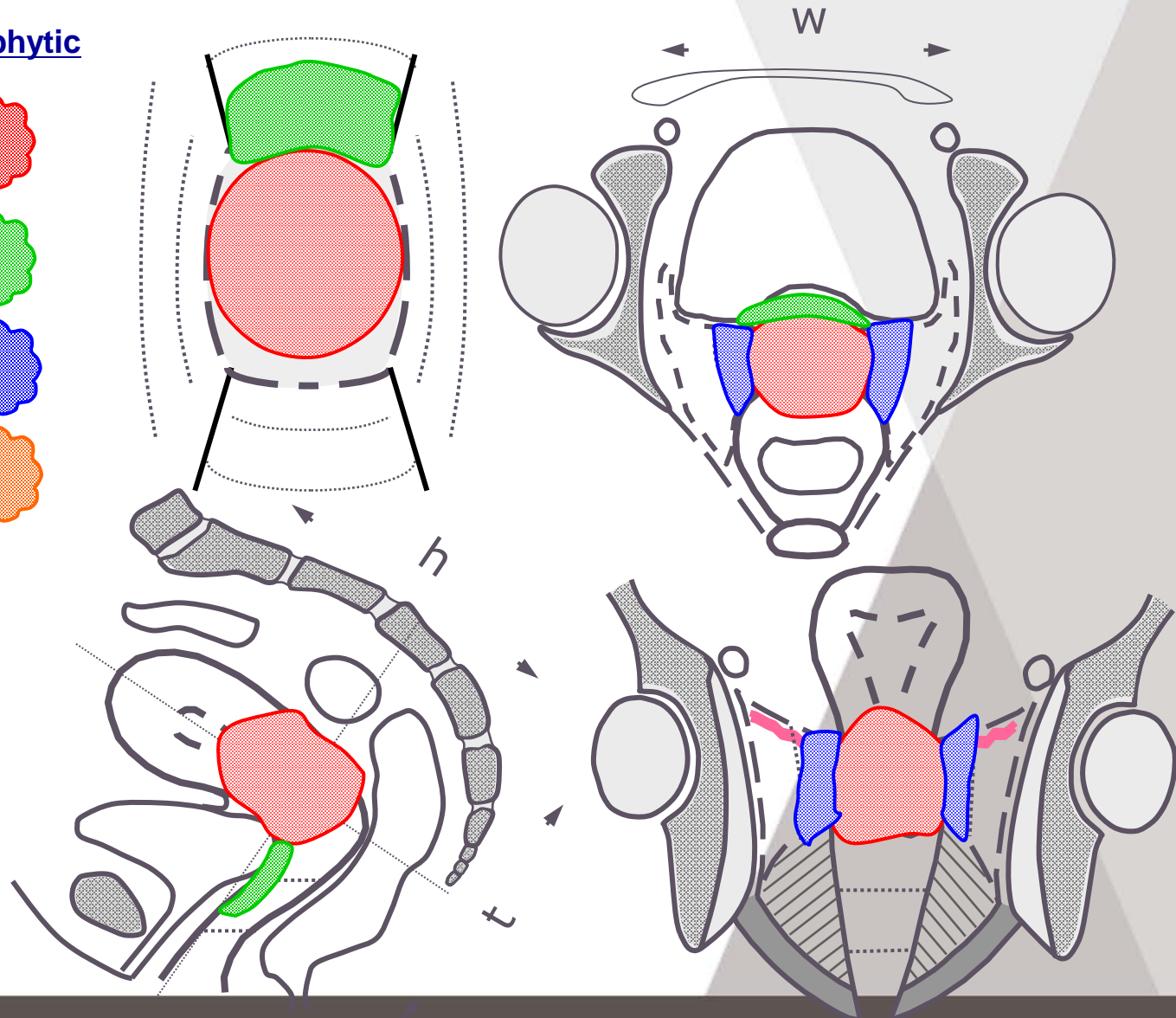
Dimensions (cm):

Width : 5

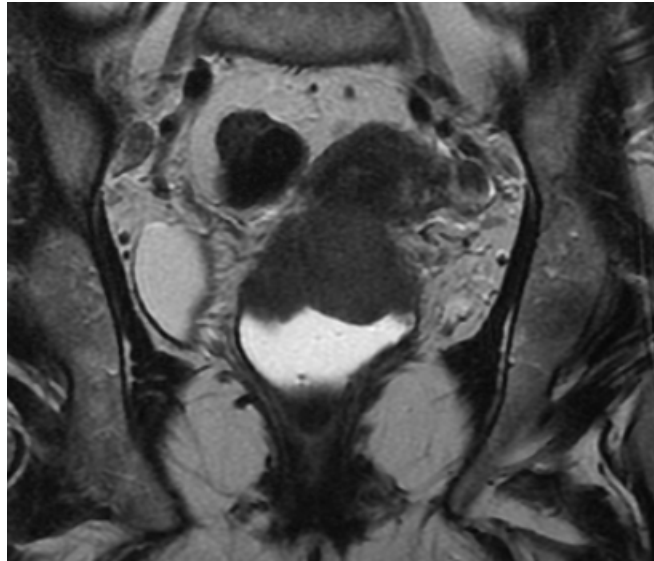
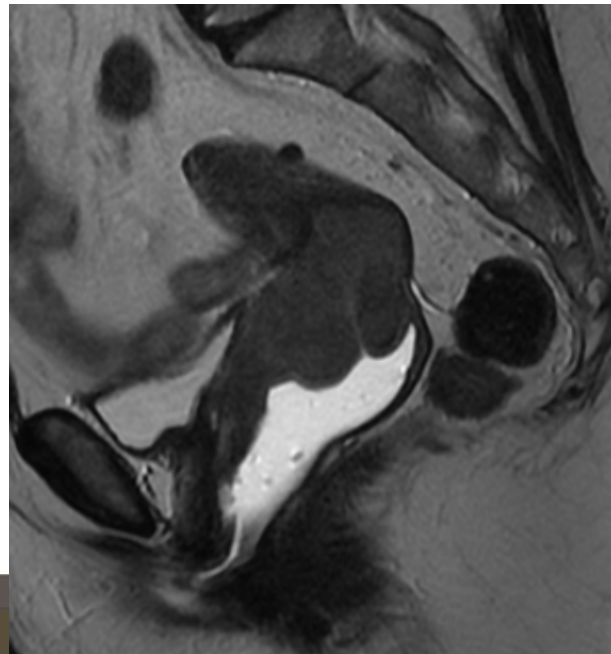
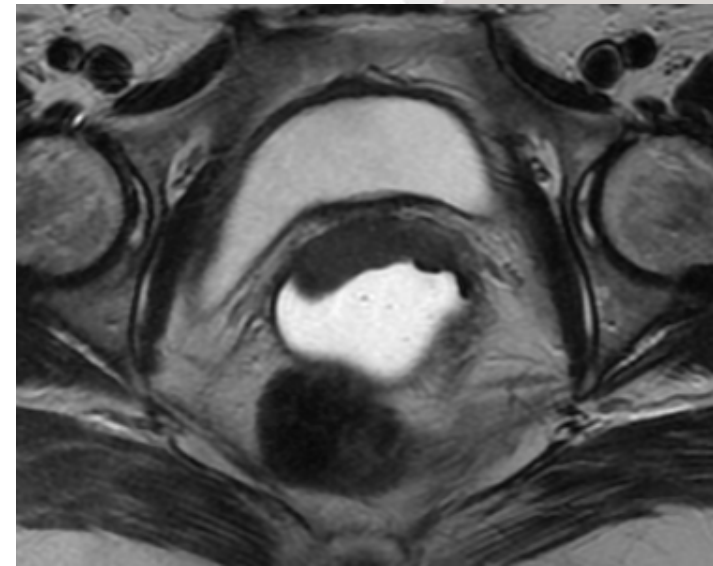
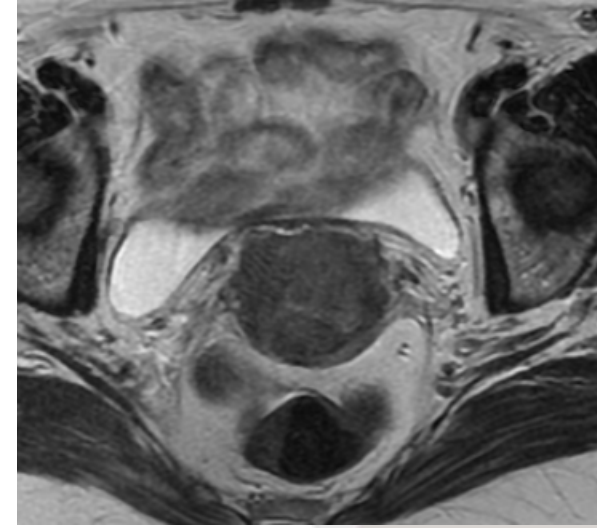
Thickness:5

Height : 5

Vag involv 3



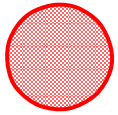
Stage IIB : initial MRI



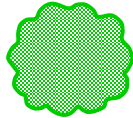
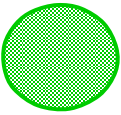
Stage IIB : clinical examination at BT

Infiltrating Exophytic

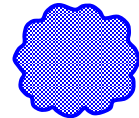
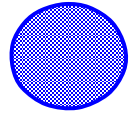
Cervix



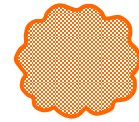
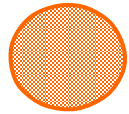
Vagina



Parametrium



Rectum or
Bladder



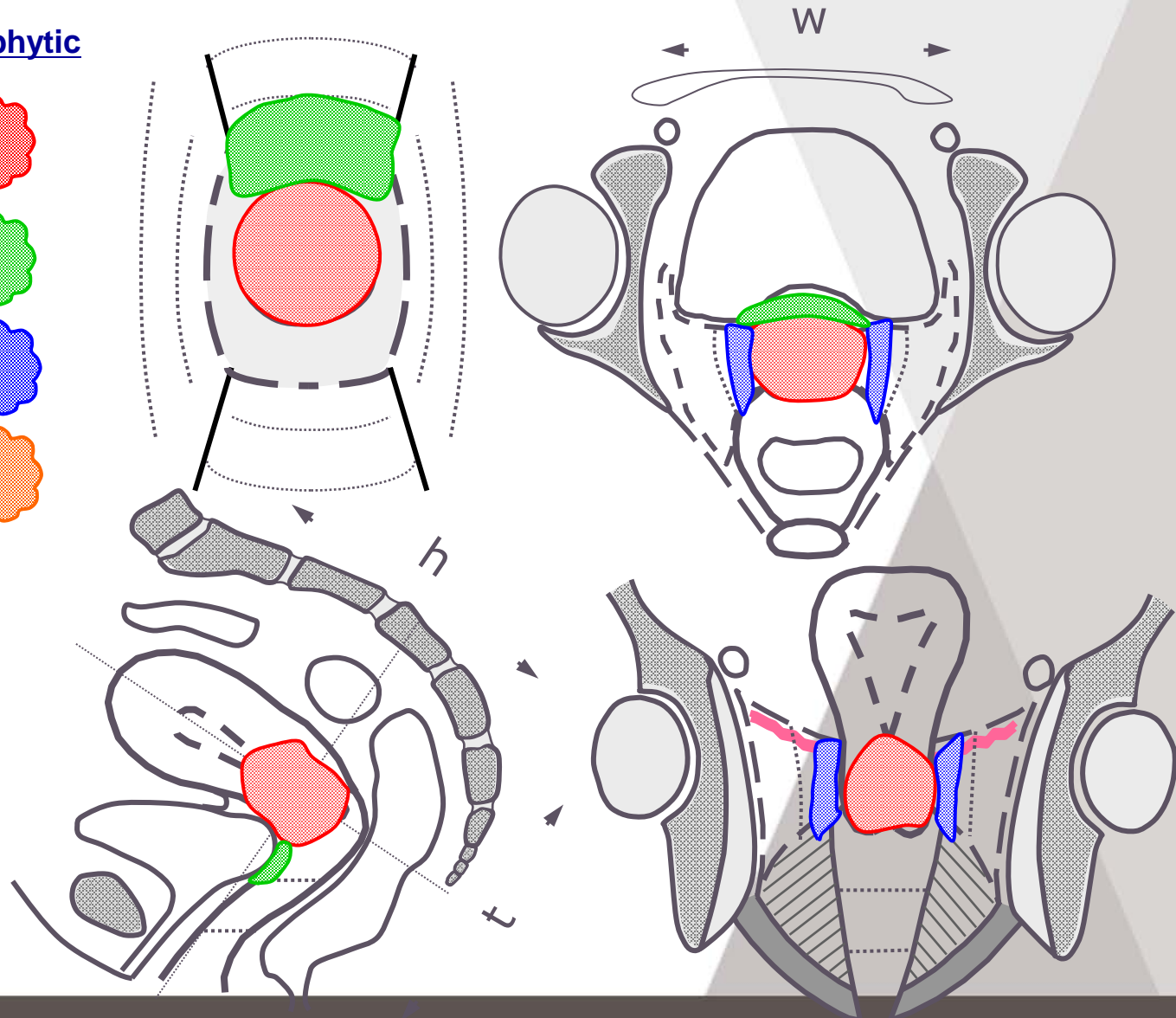
Dimensions (cm):

Width : 3.5

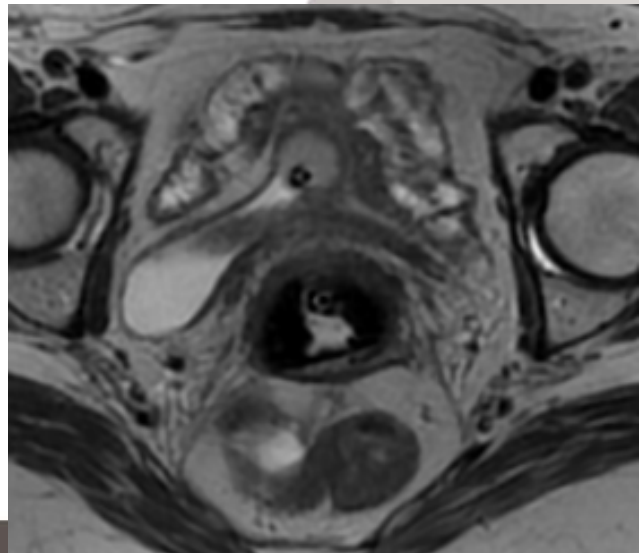
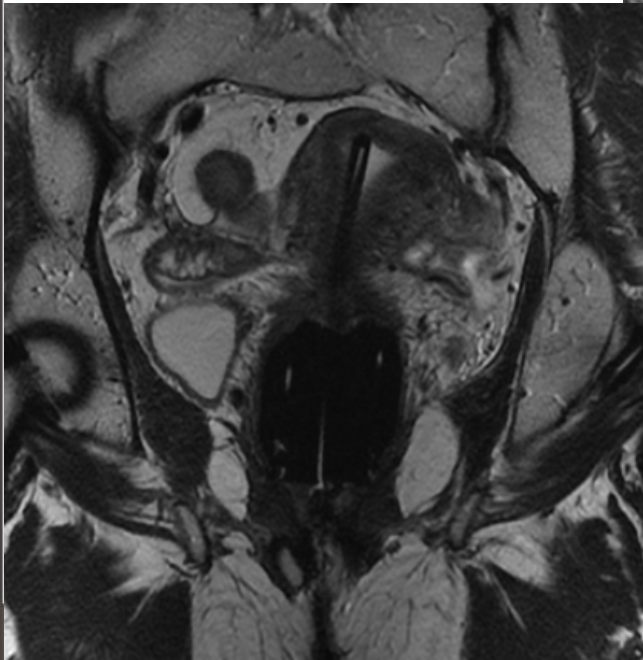
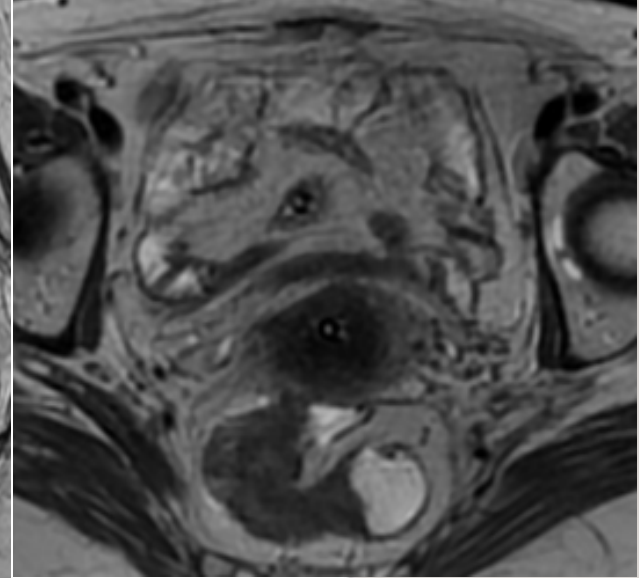
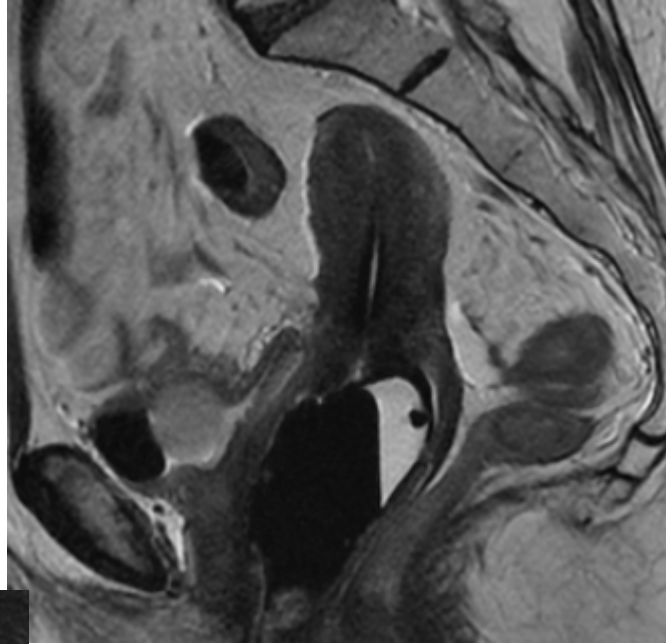
Thickness:3.5

Height : 3

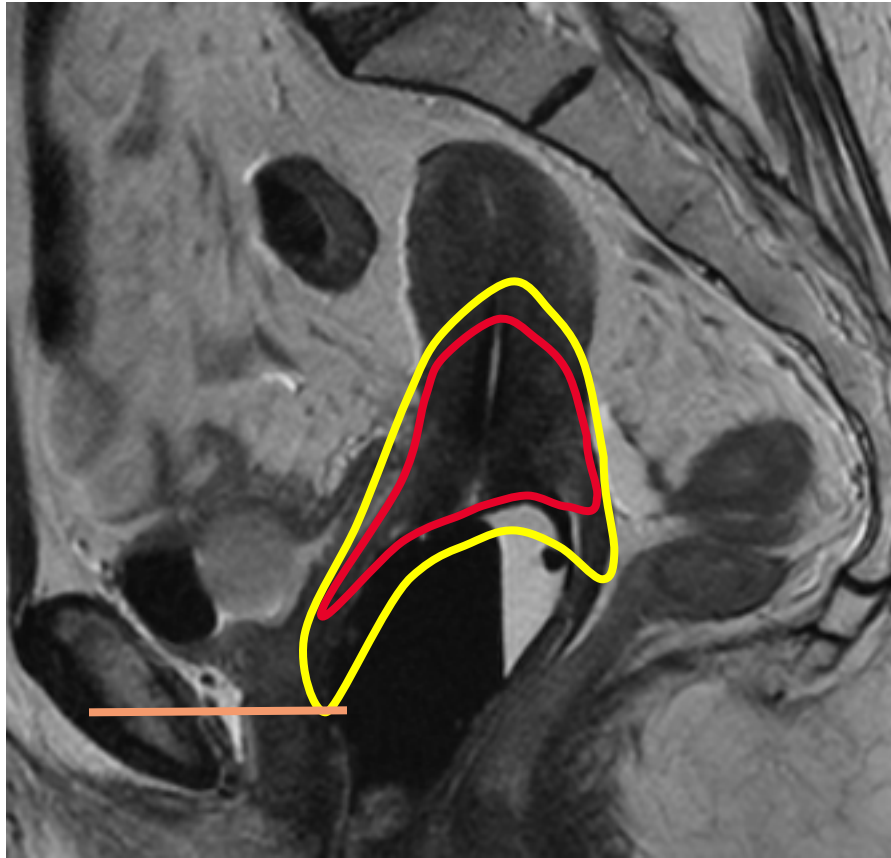
Vag involv 1.5



Stage IIB : MRI at BT



IR-CTV in the vagina



Patient n°6, IIB, 6 cm, unilateral + lateral vaginal involvement

Mrs C C...
44 year-old

WHO=0, 62 kg, 1m65

Vaginal bleeding for > 1year

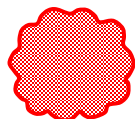
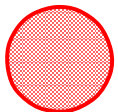
Biopsy: well differentiated carcinoma

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

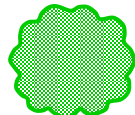
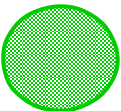
Stage IIIB : initial clinical examination

Infiltrating Exophytic

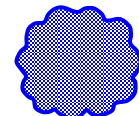
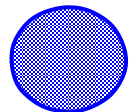
Cervix



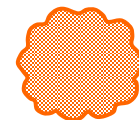
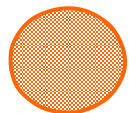
Vagina



Parametrium



Rectum or
Bladder

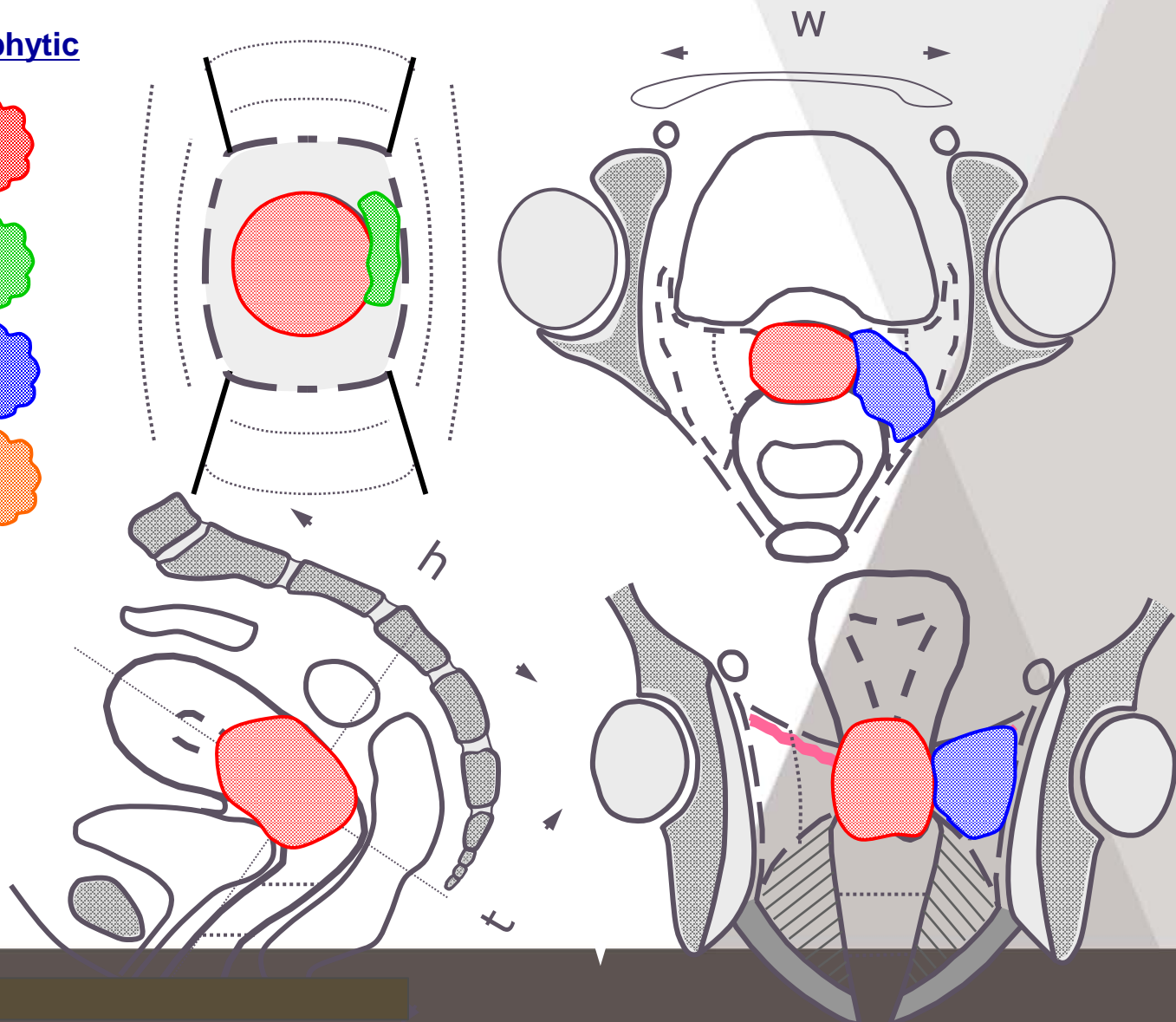


Dimensions (cm):

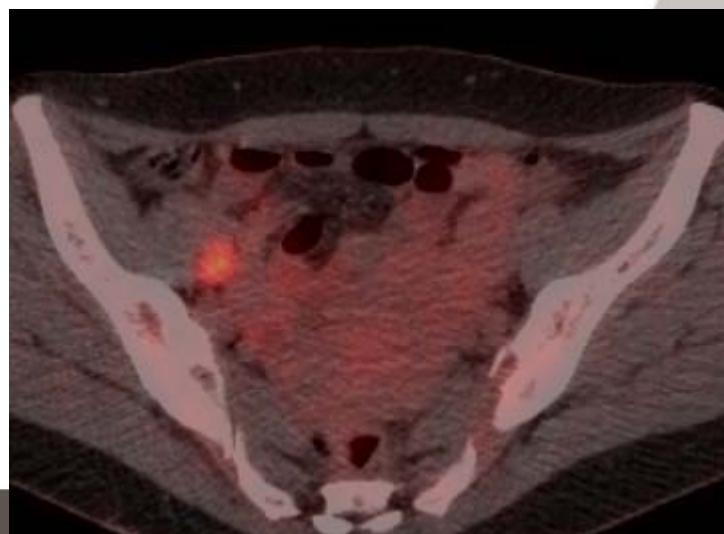
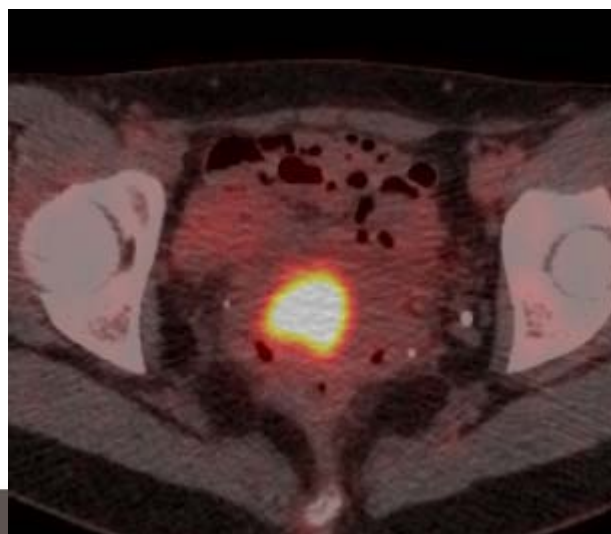
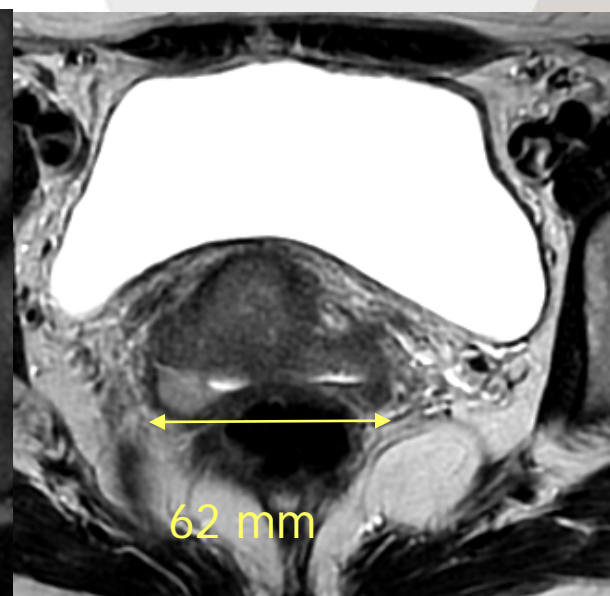
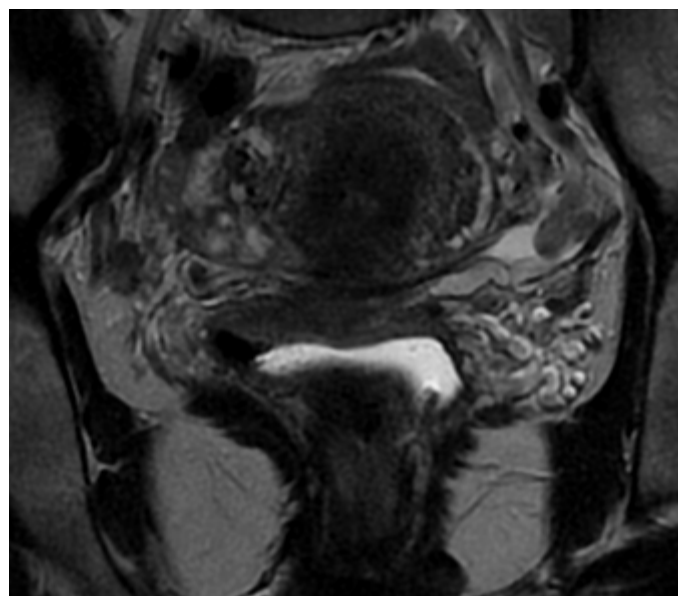
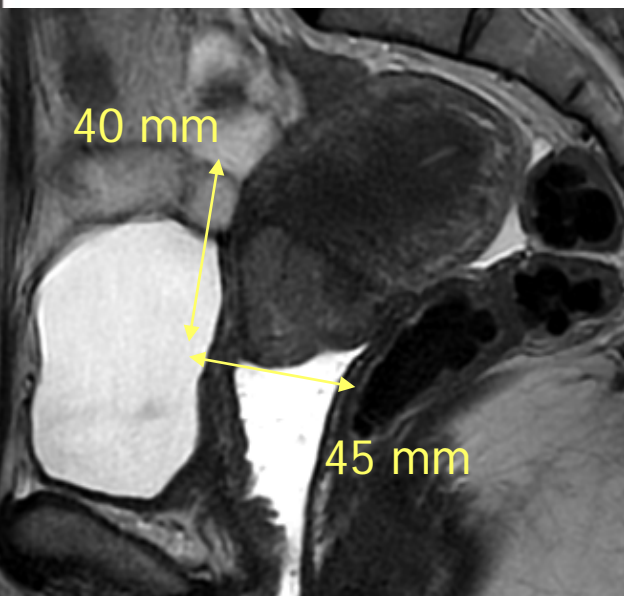
Width : 6

Thickness : 4

Height : 4



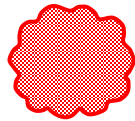
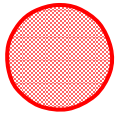
Stage IIIB : initial MRI



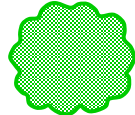
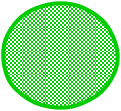
Stage IIIB : at the time of brachytherapy

Infiltrating Exophytic

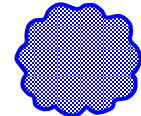
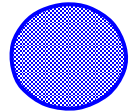
Cervix



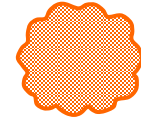
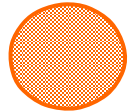
Vagina



Parametrium



Rectum or
Bladder

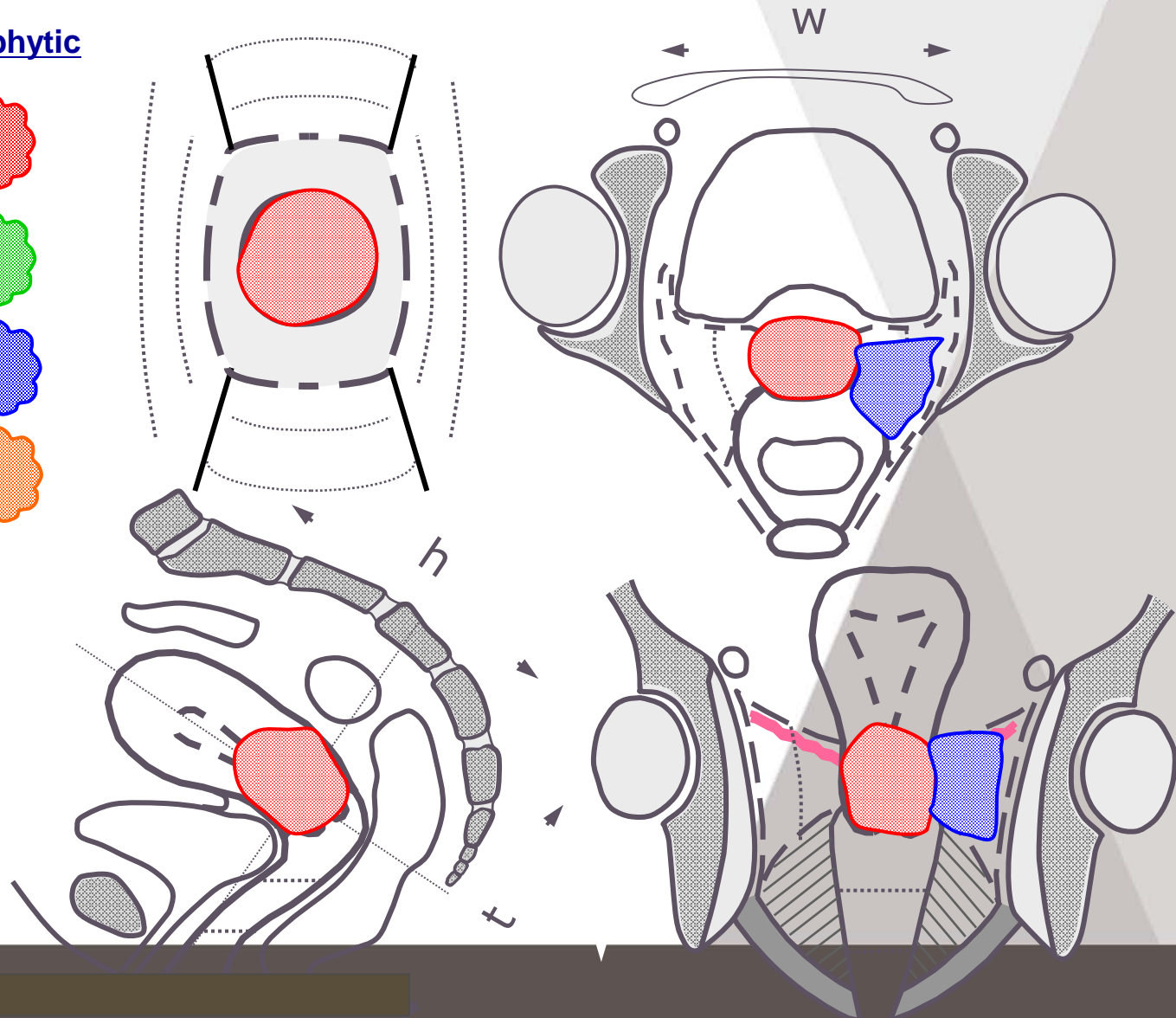


Dimensions (cm):

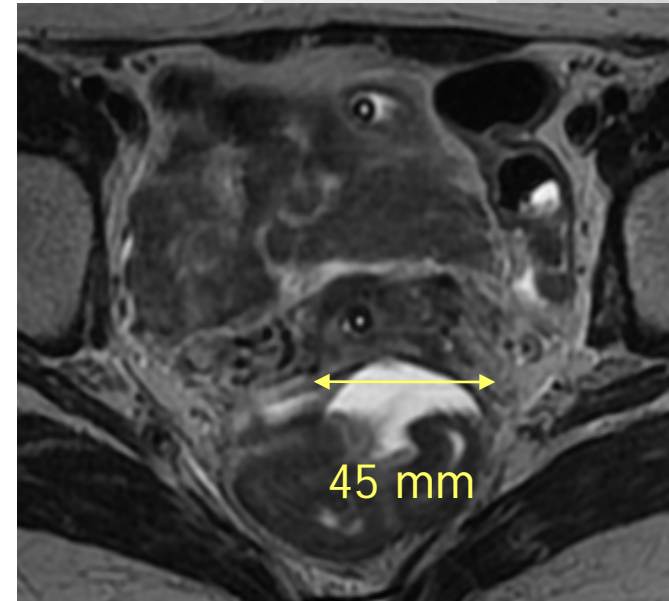
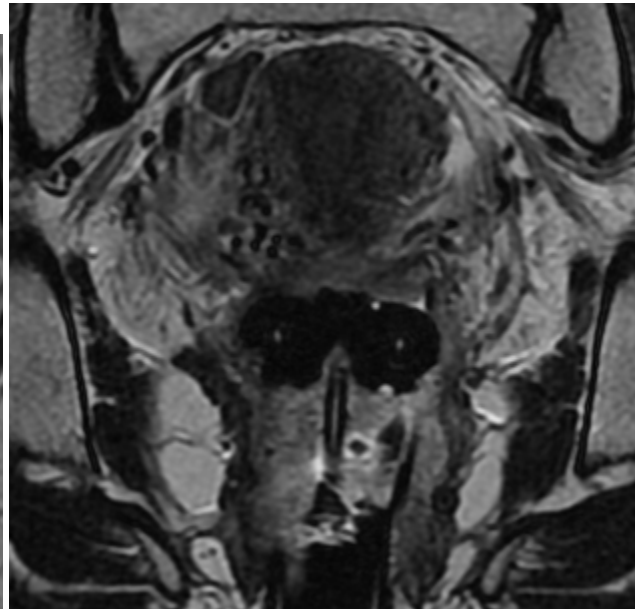
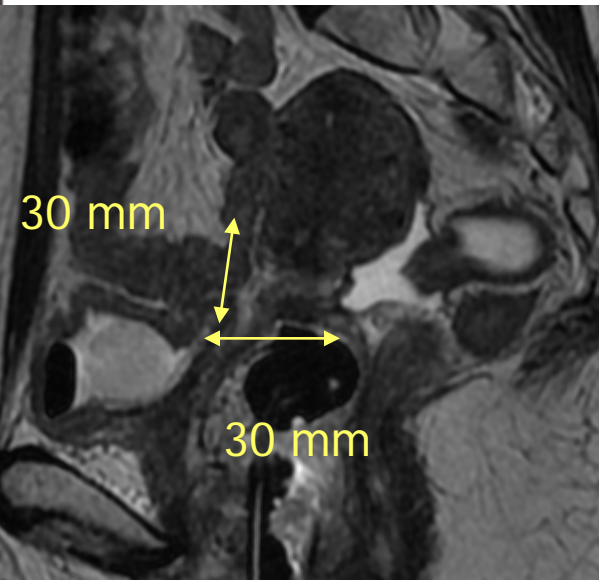
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Thickness : 3

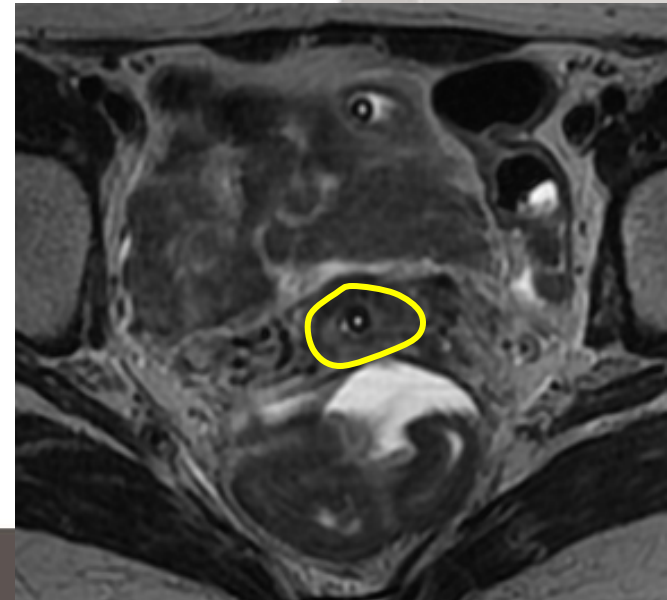
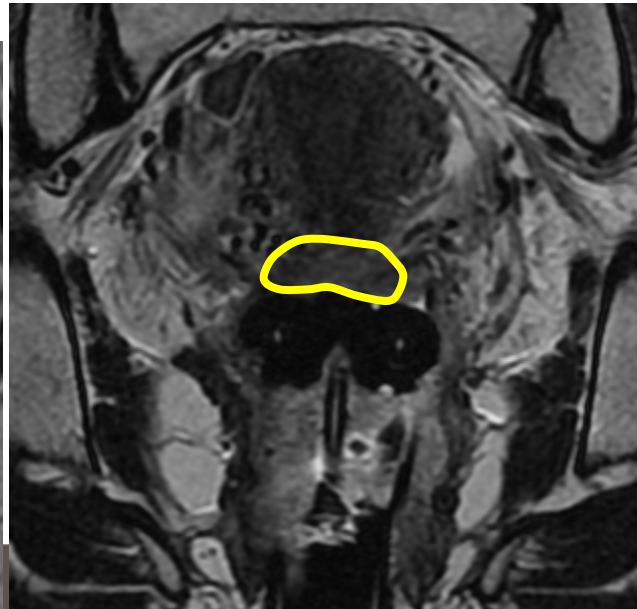
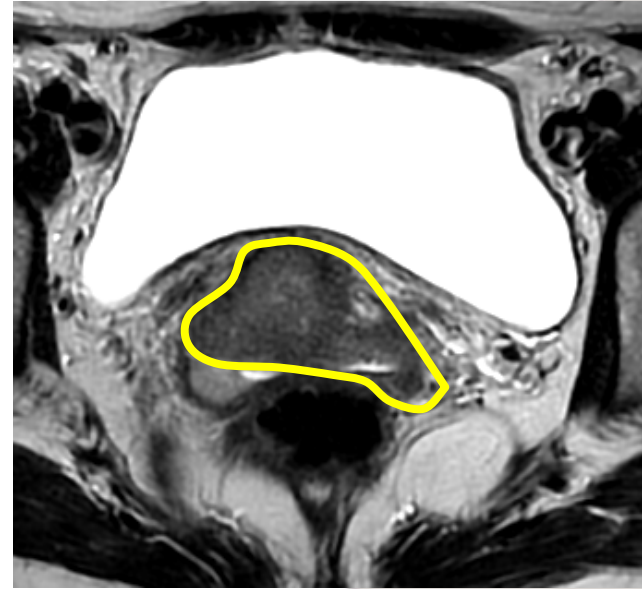
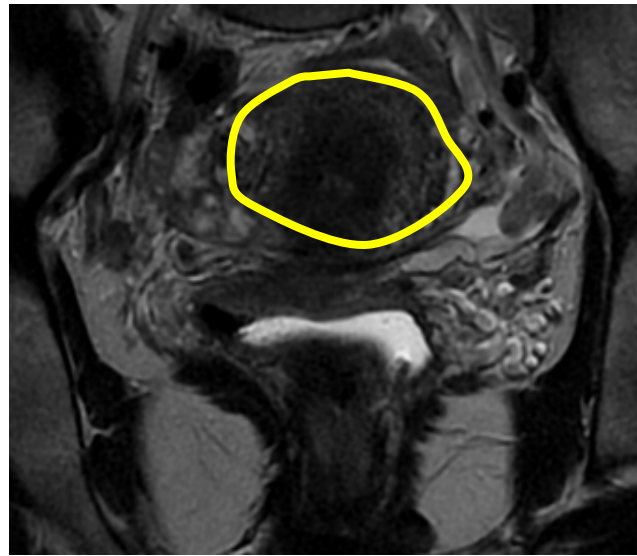
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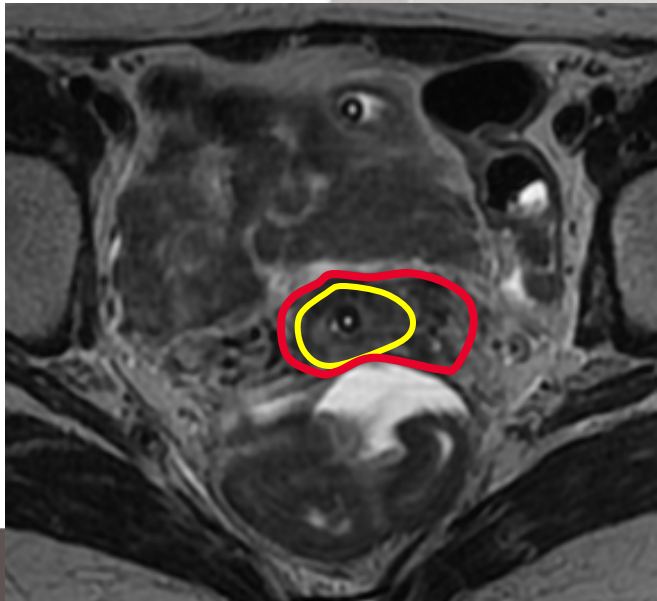
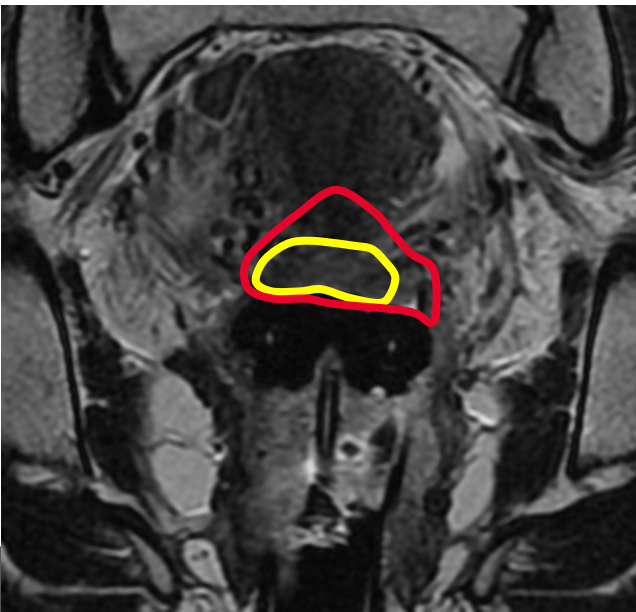
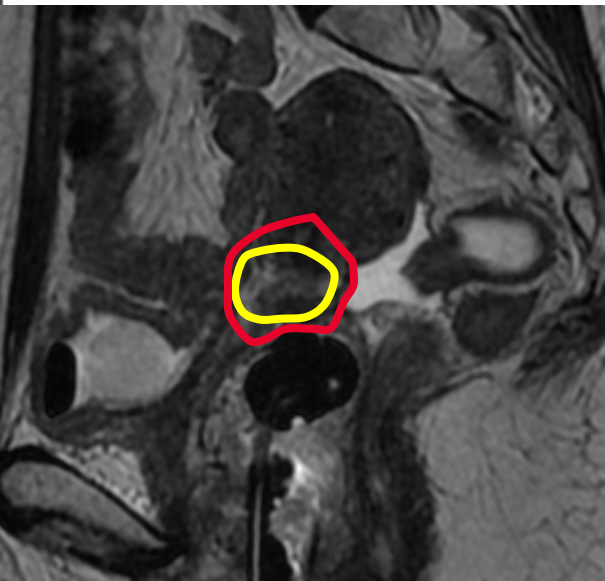
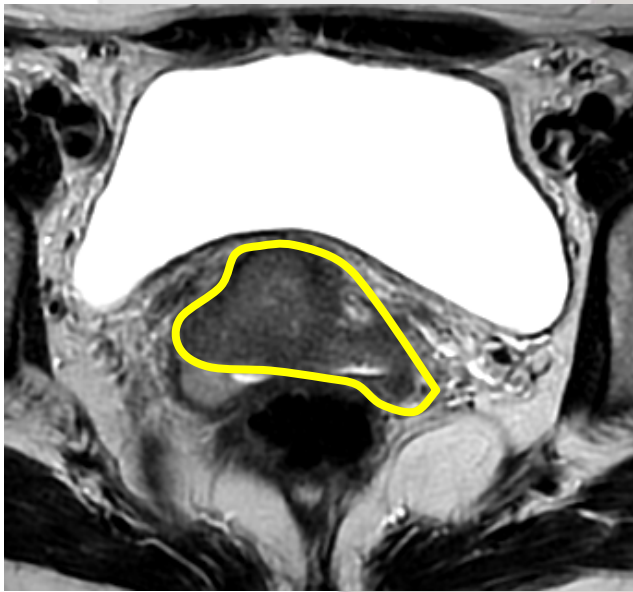
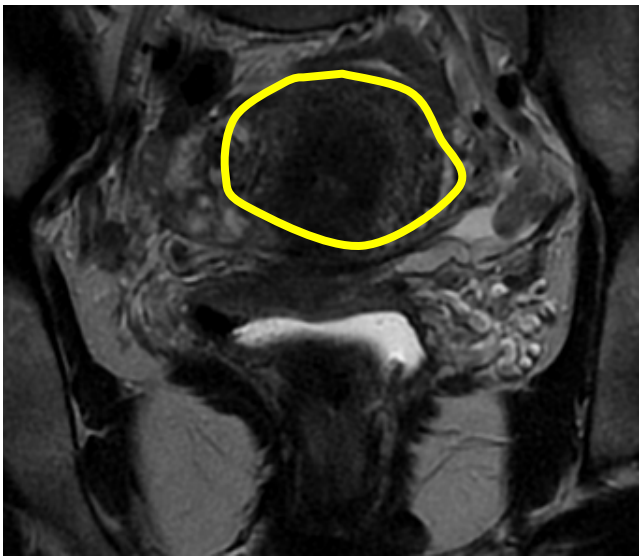
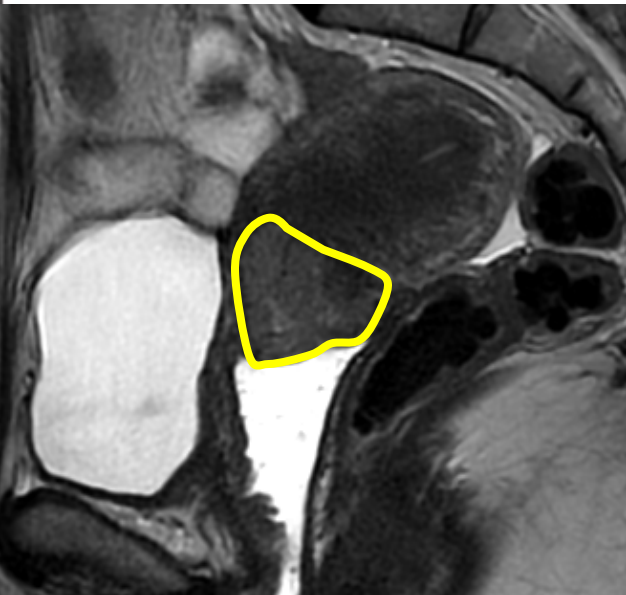
Stage IIIB : MRI at the time of brachytherapy



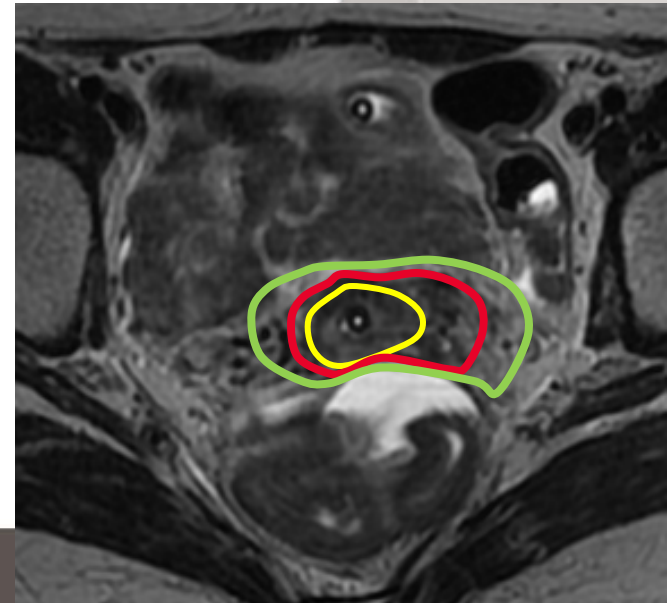
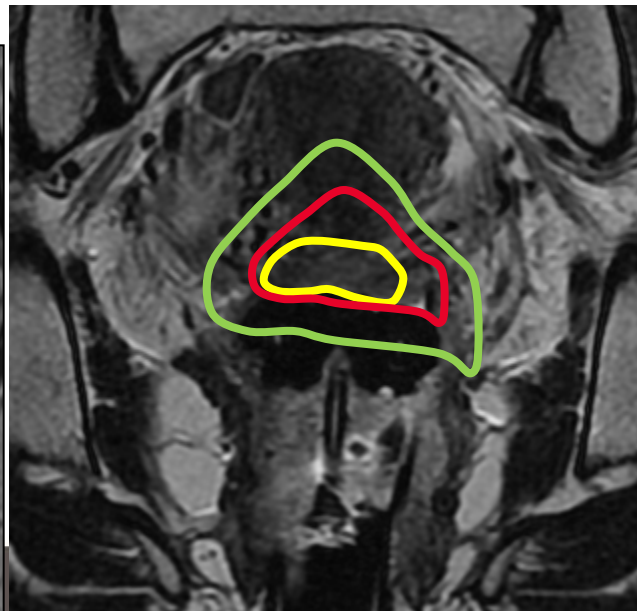
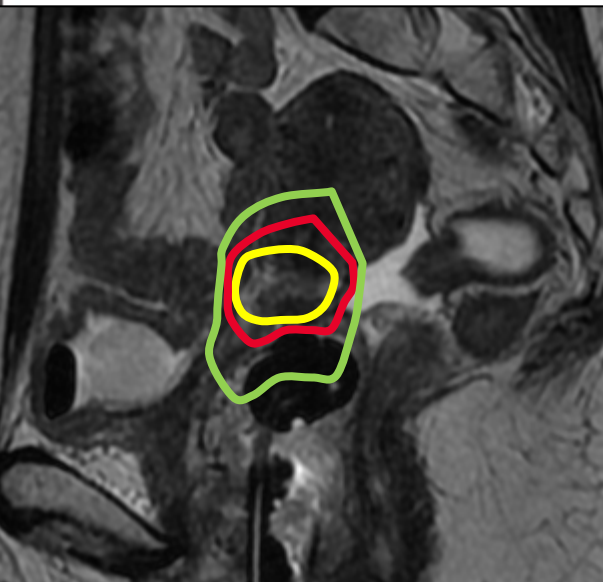
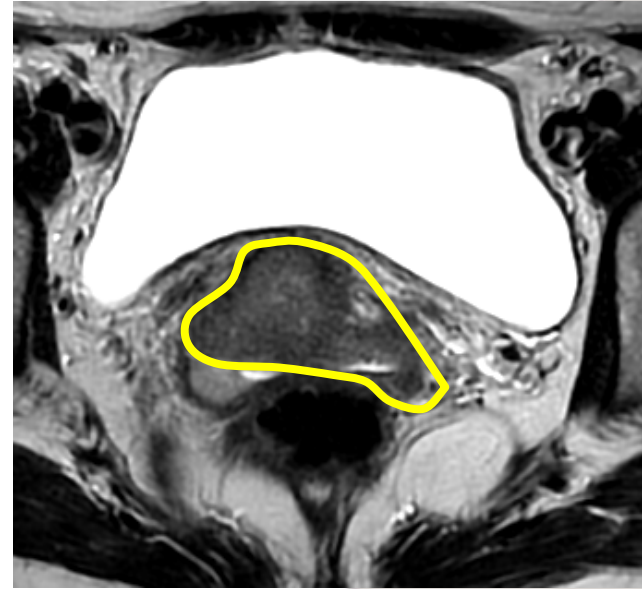
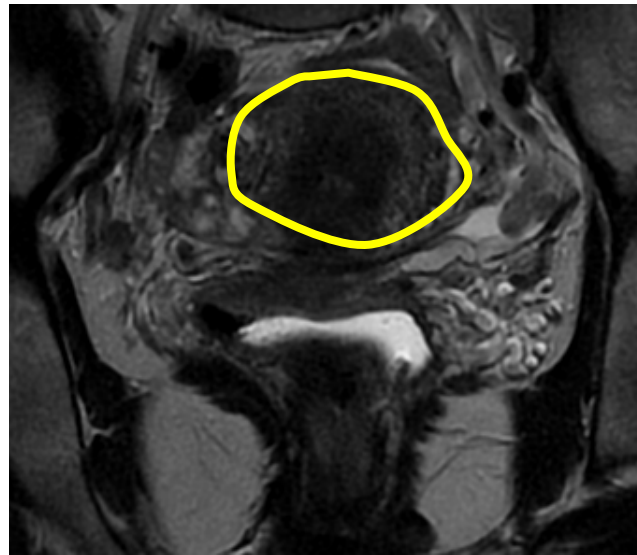
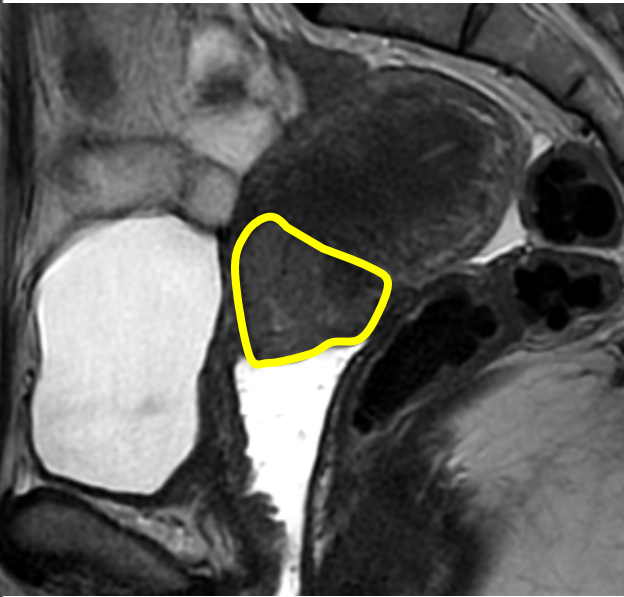
Stage IIIB



Stage IIIB

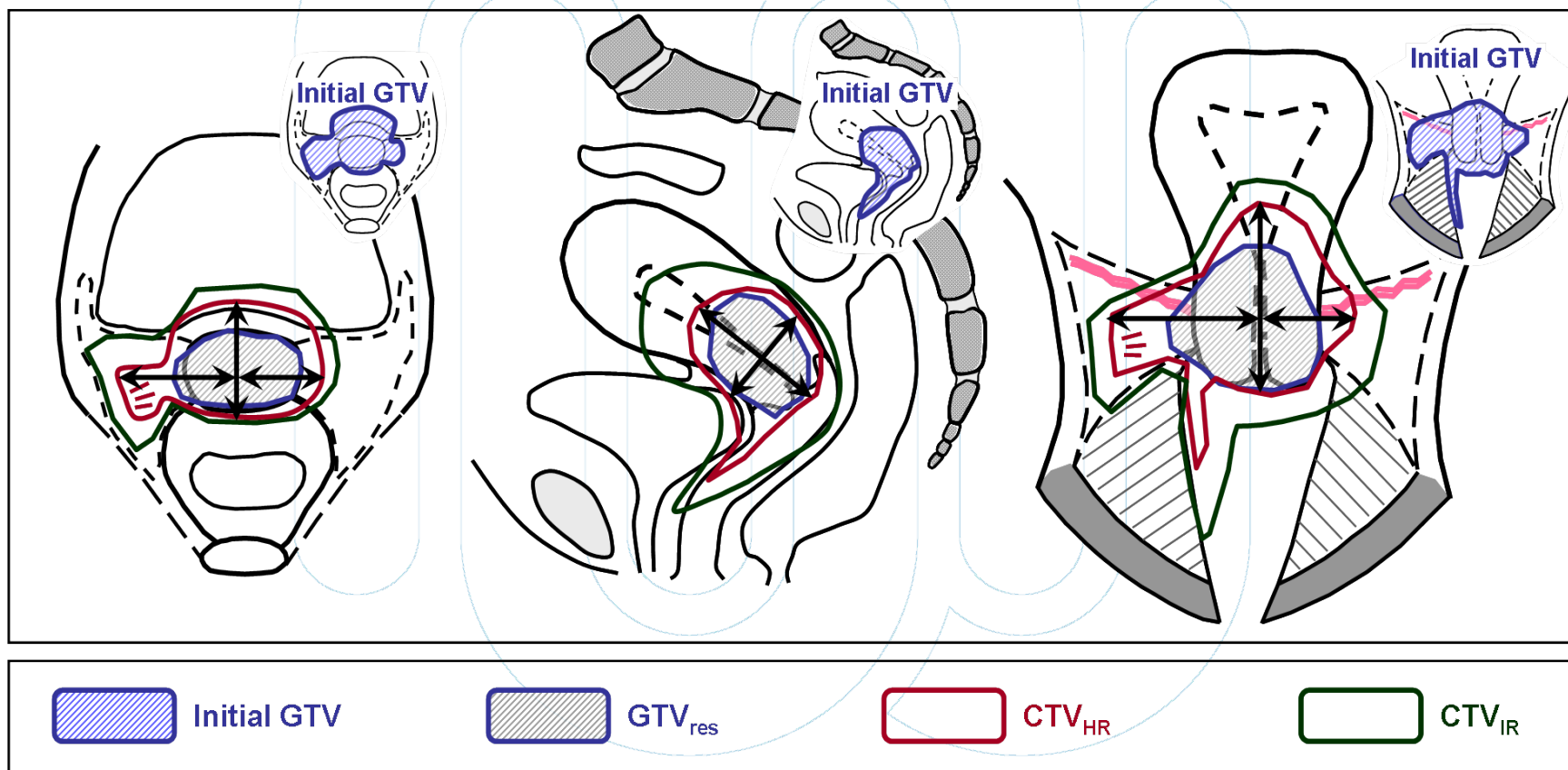


Stage IIIB

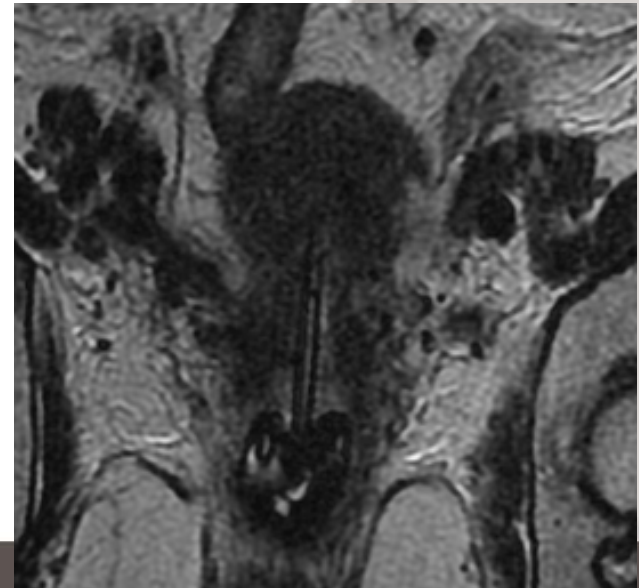
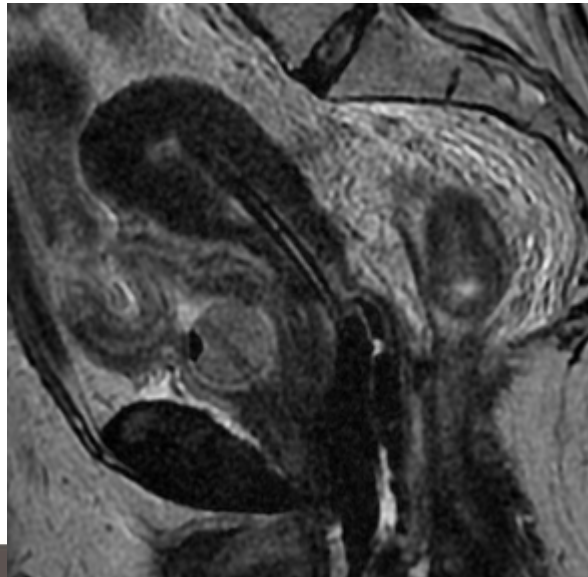
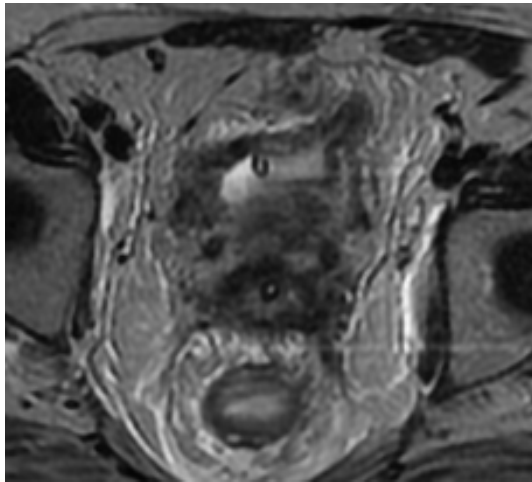
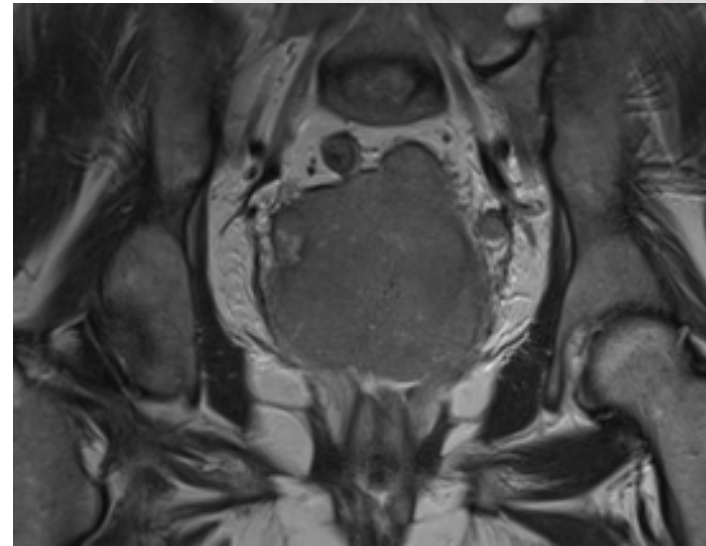
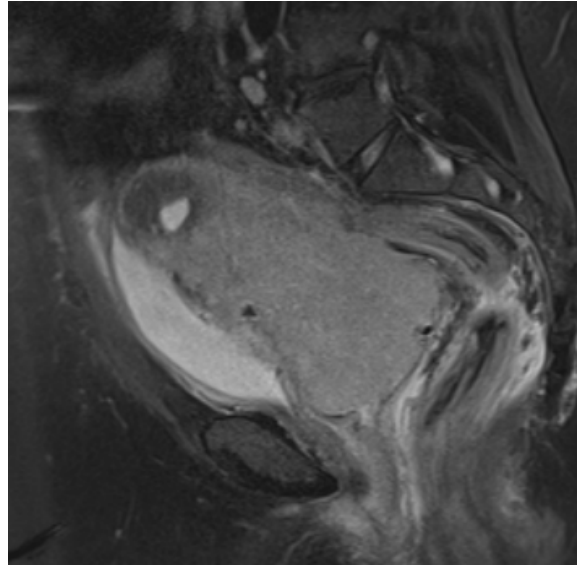
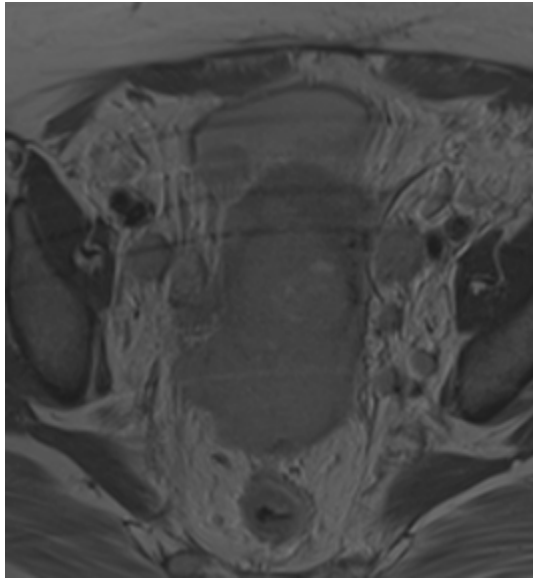


Overview of the adaptive target concept cervix cancer stage IB, IIB, IIB: HR+IR CTV-T

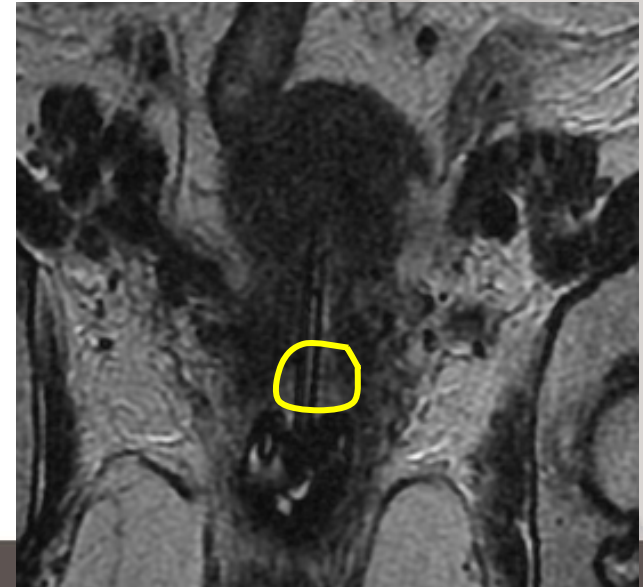
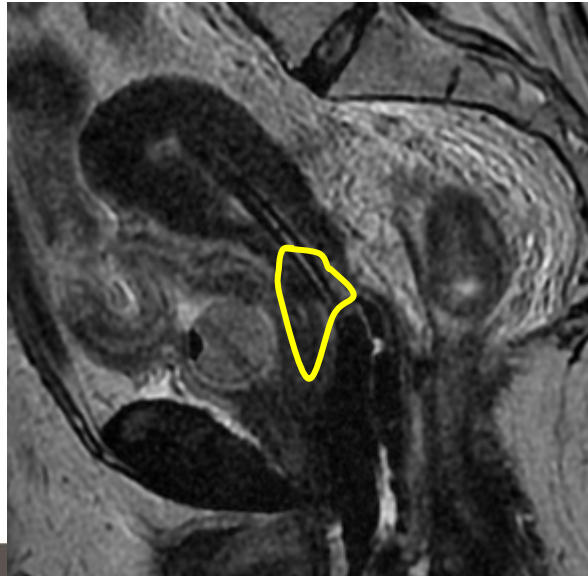
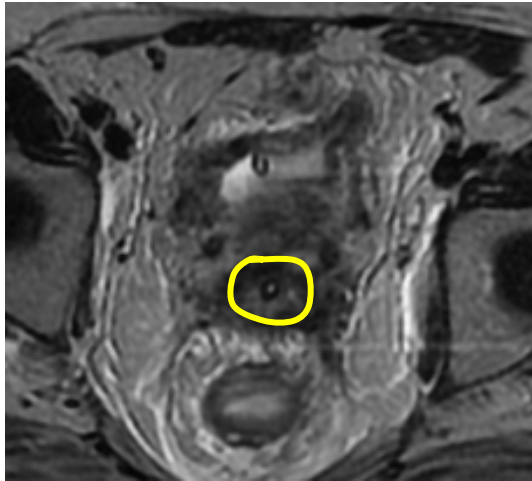
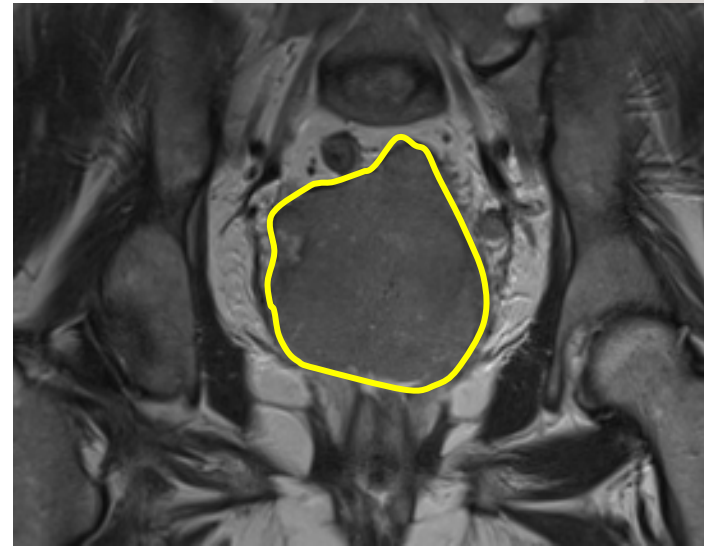
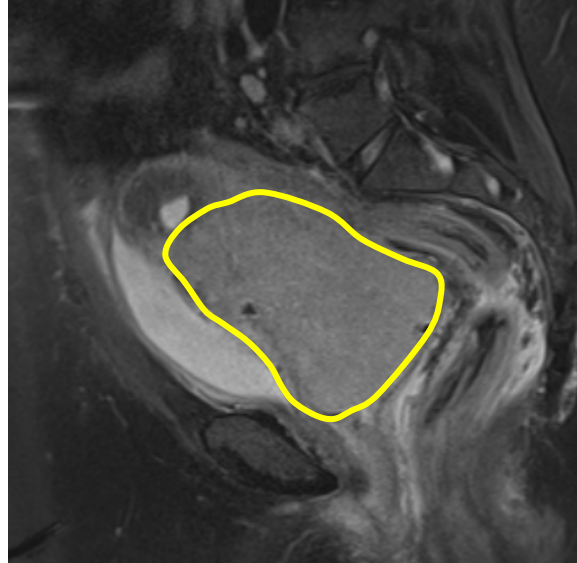
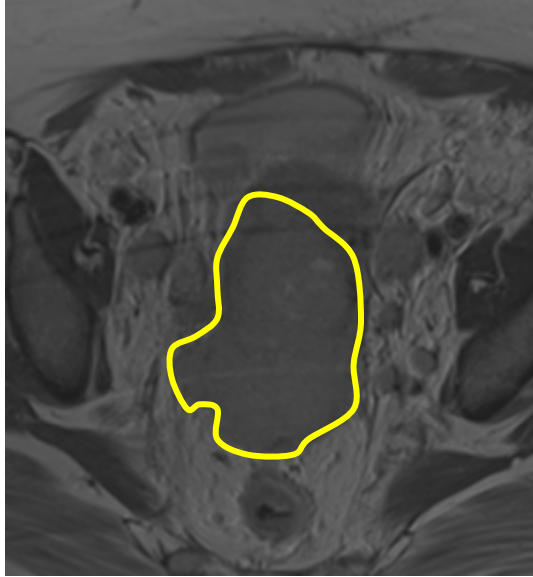
- Initial and residual GTV, Res. patholog. tissue
- High Risk adaptive CTV, Intermediate Risk CTV



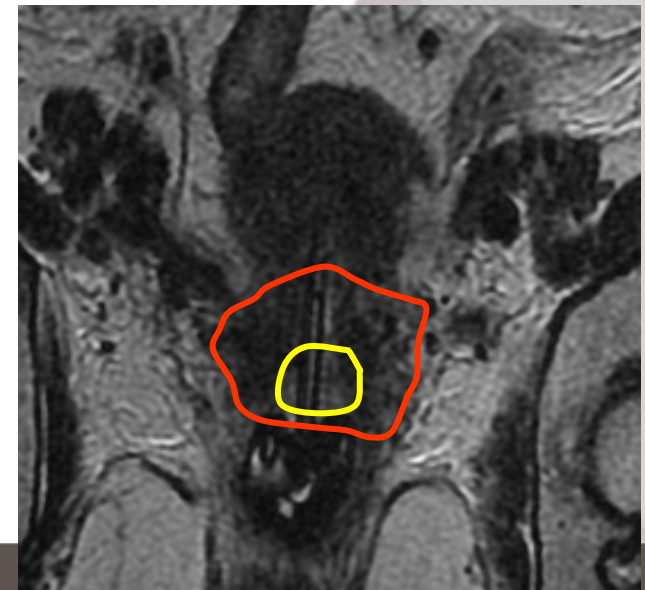
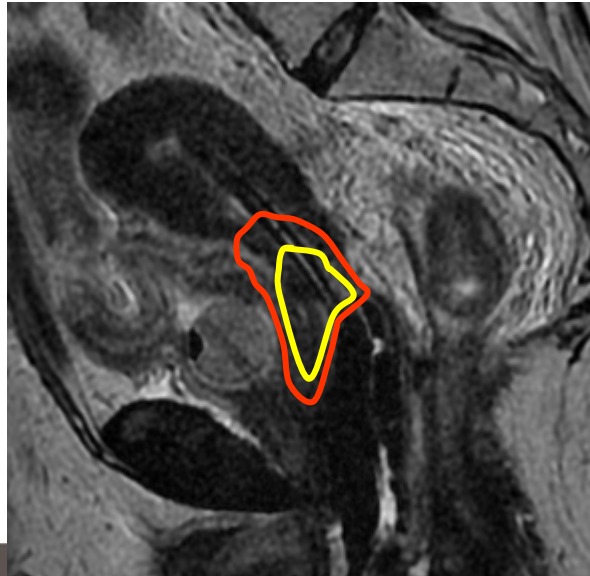
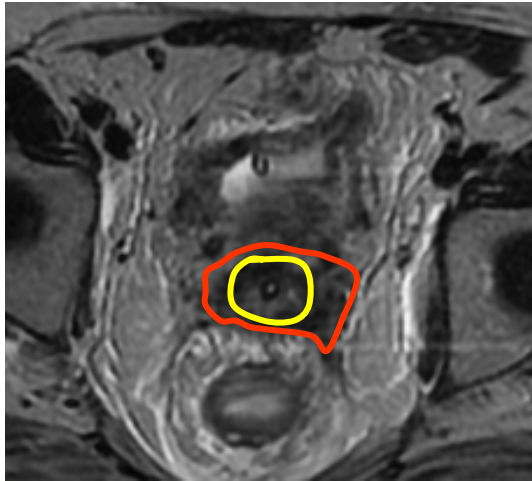
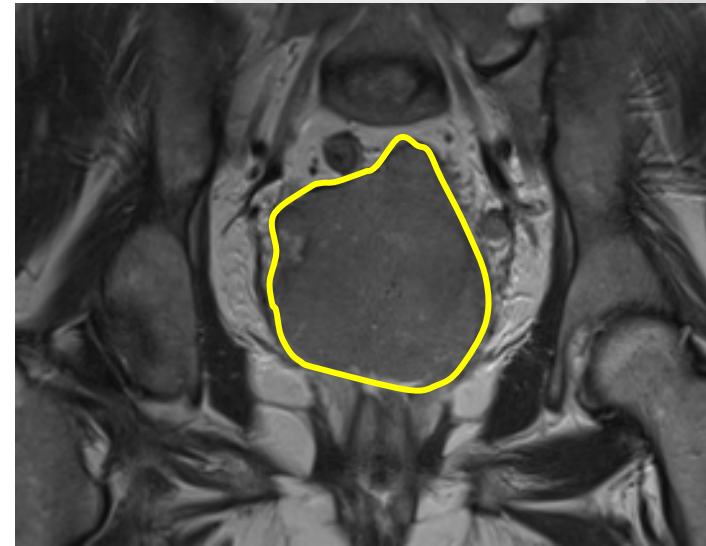
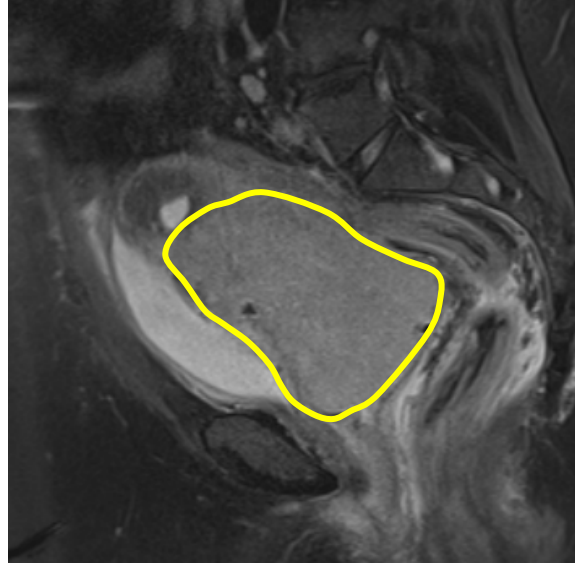
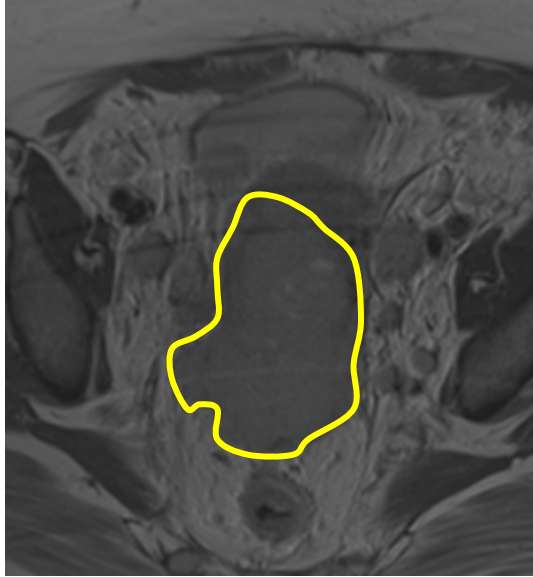
another: Stage IIIB plus uterine involvement



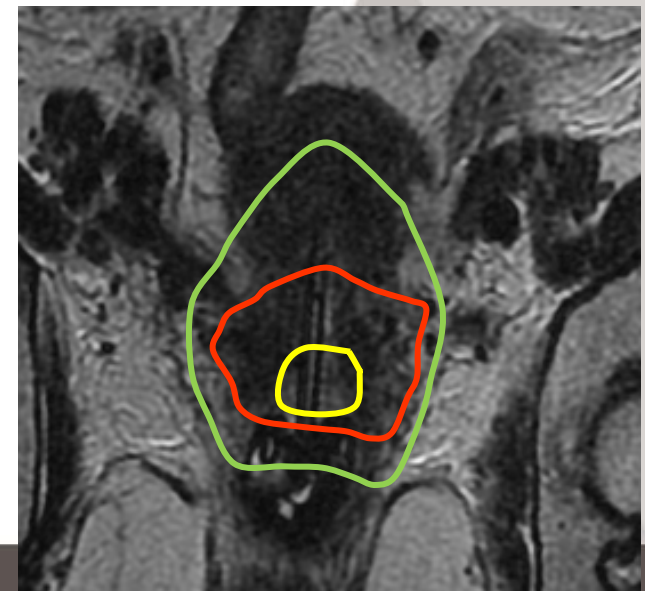
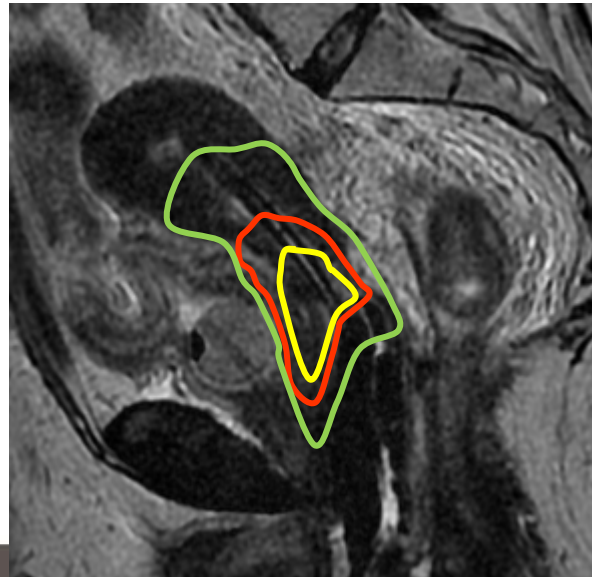
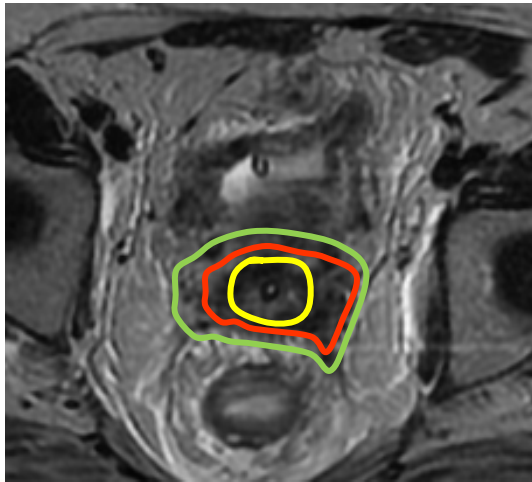
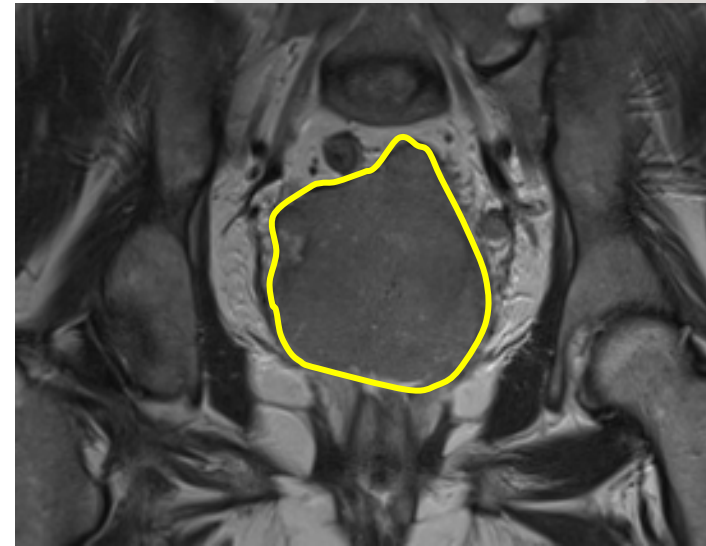
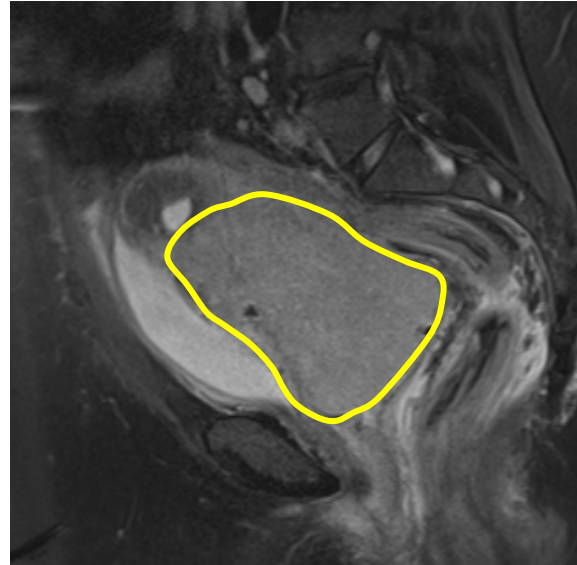
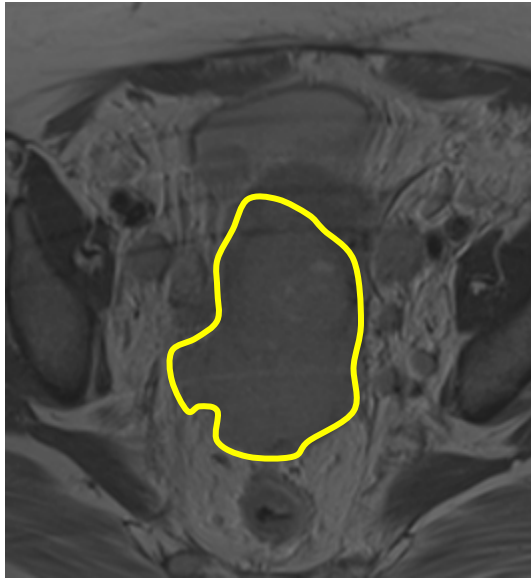
Stage IIIB plus uterine involvement



Stage IIIB plus uterine involvement



Stage IIIB plus uterine involvement



Patient n°7, IVA bladder, (IIIA+ bilateral IIIB), 8 cm

Mrs C B...

62 year-old

Vaginal bleeding for > 1 year, urinary retention

Biopsy: well differentiated squamous cell carcinoma

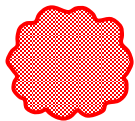
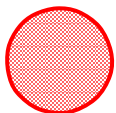
At clinical examination : cervical tumor + infiltration of the whole anterior and right vaginal wall + infiltration of the right parametrium to the pelvic wall + infiltration of the left distal parametrium

Cystoscopy : involvement of the trigonal area, + biopsy

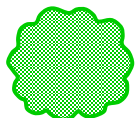
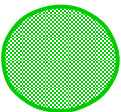
Stage IVA : initial clinical examination

Infiltrating Exophytic

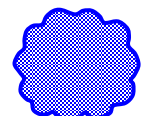
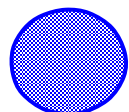
Cervix



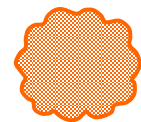
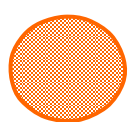
Vagina



Parametrium



Rectum or
Bladder

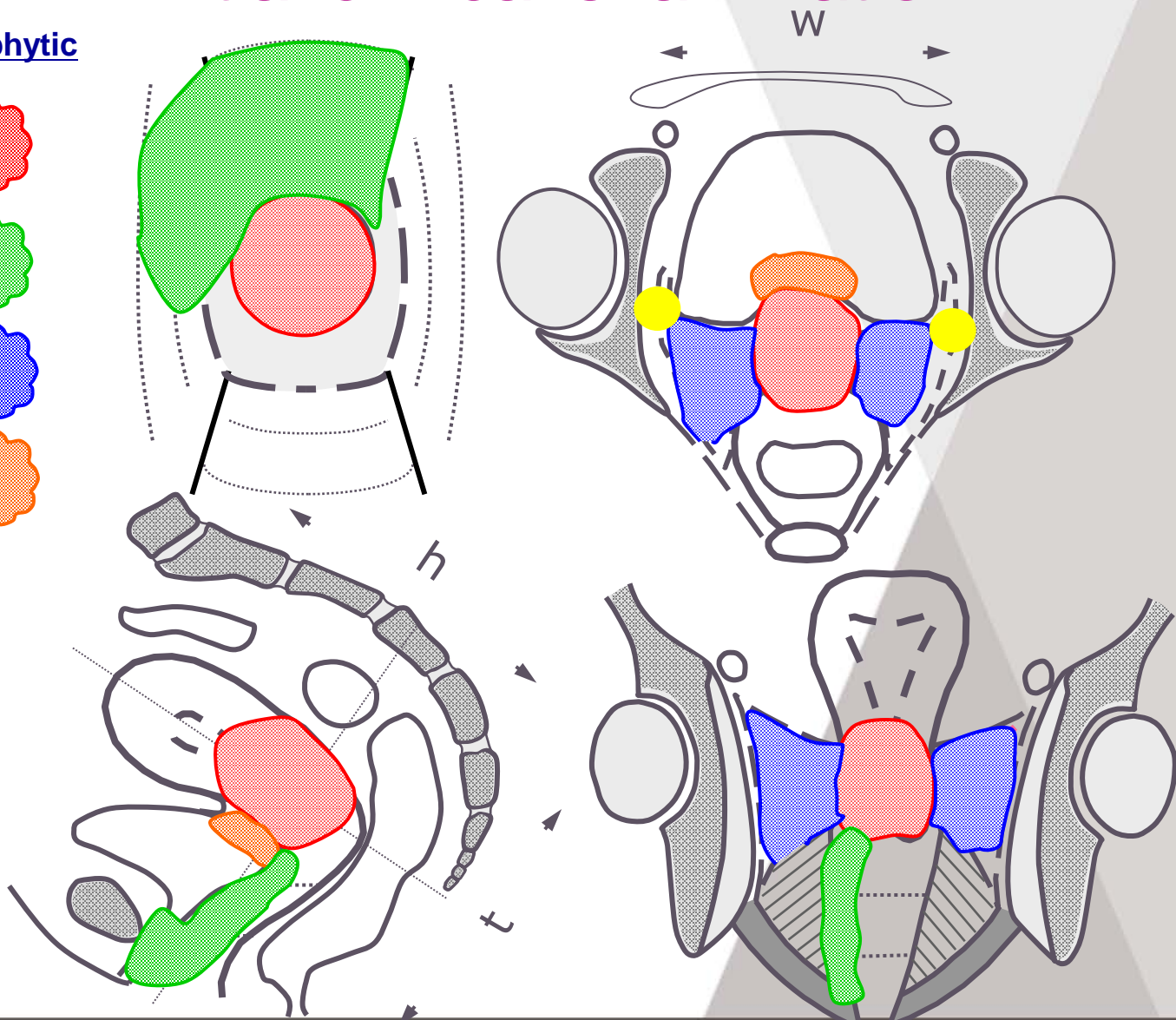


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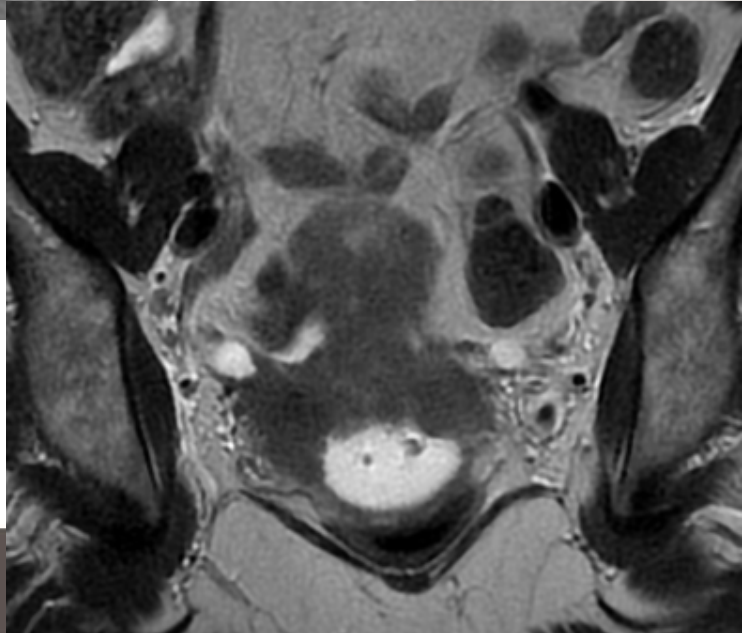
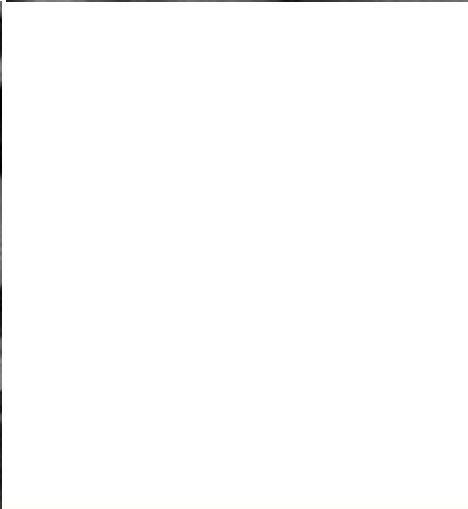
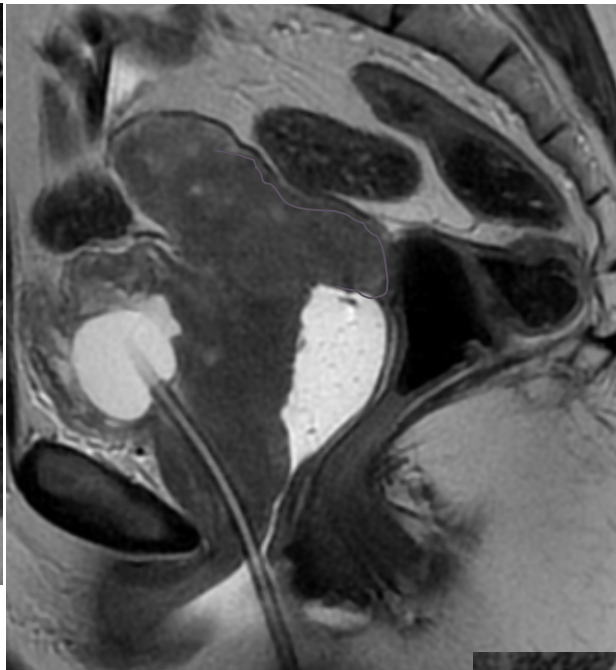
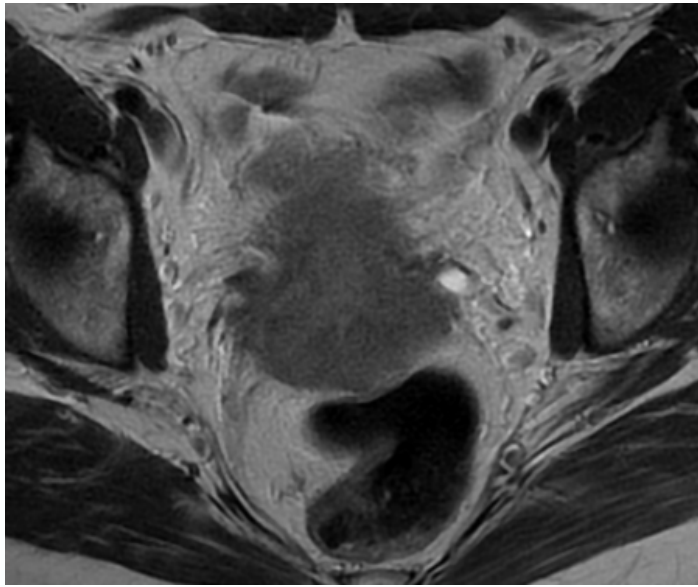
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Thickness : 6

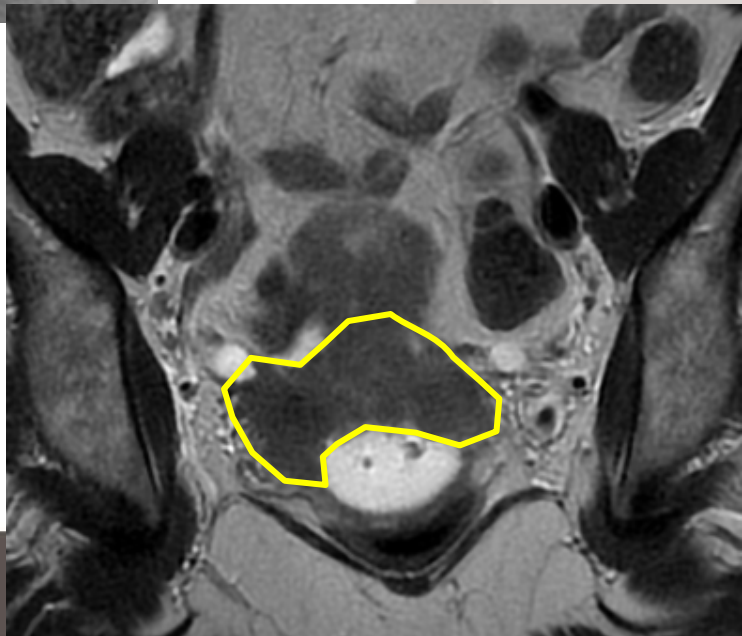
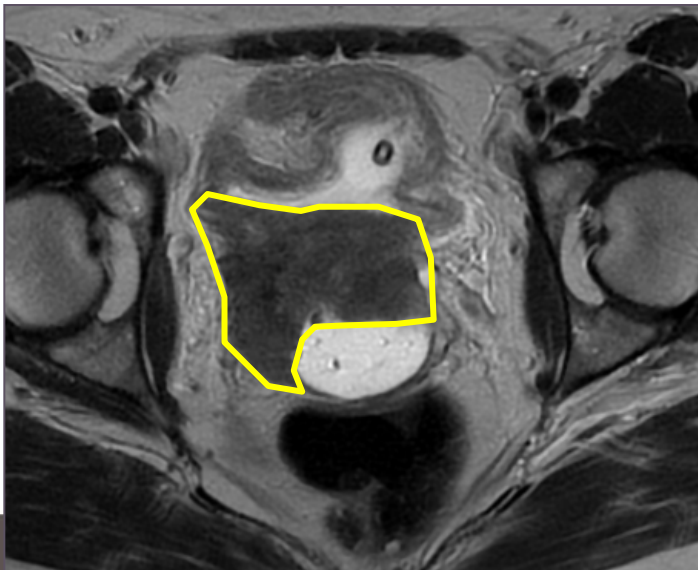
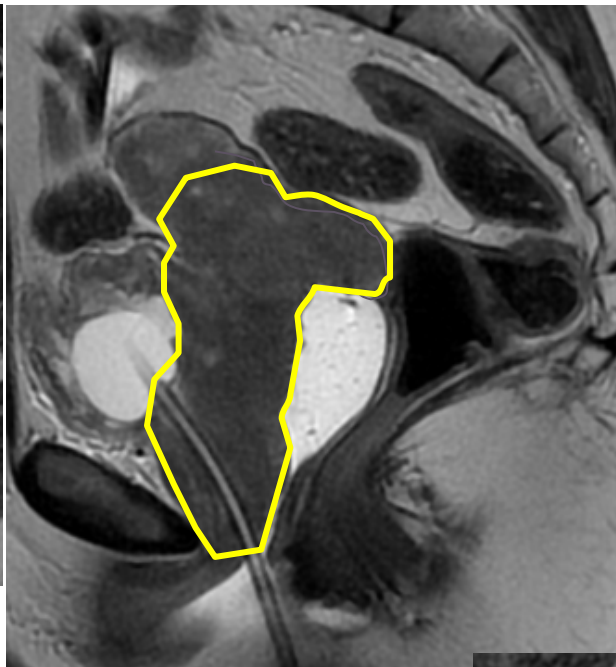
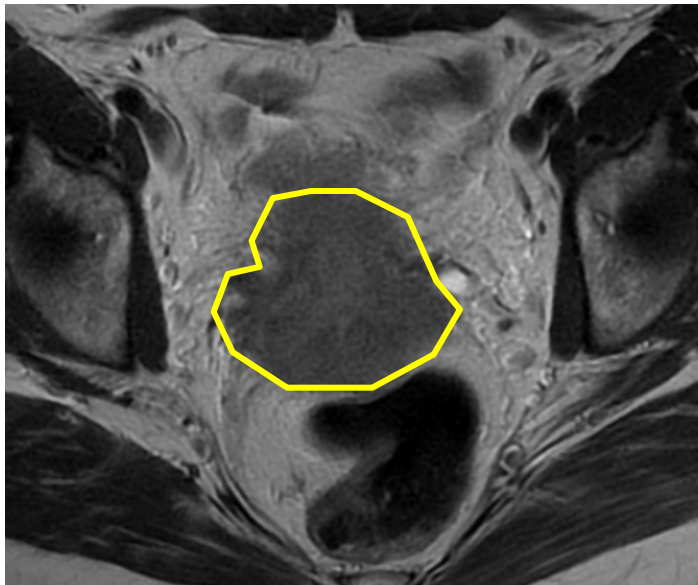
Height : 7



Stage IVA : initial MRI



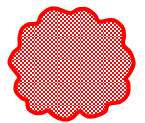
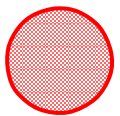
Stage IVA : initial MRI



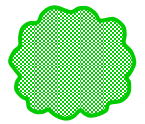
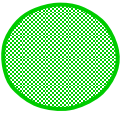
Stage IVA : at time of brachy

Infiltrating Exophytic

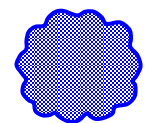
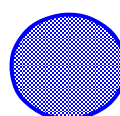
Cervix



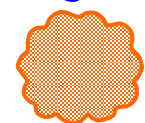
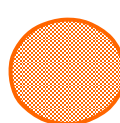
Vagina



Parametrium



Rectum or Bladder

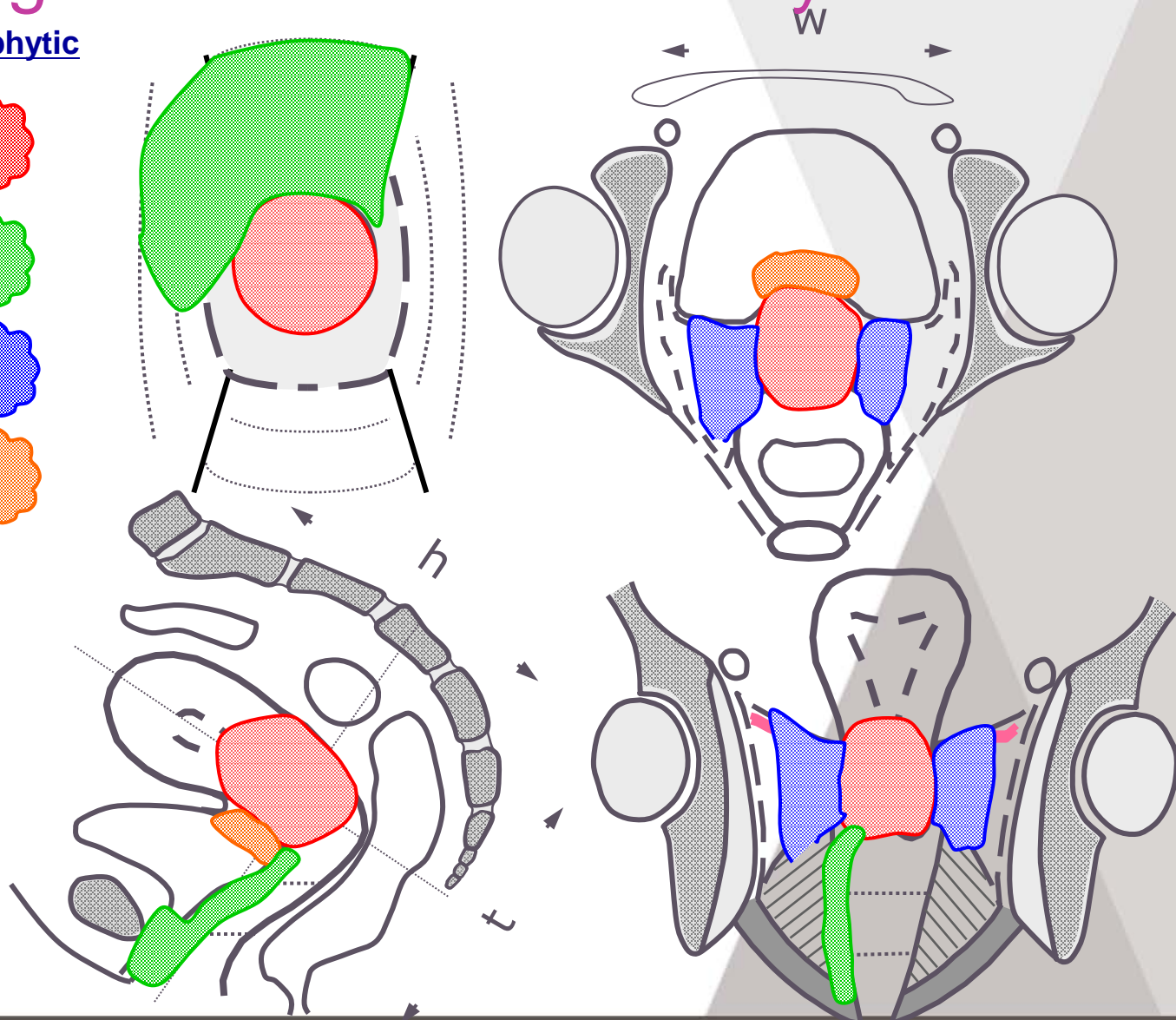


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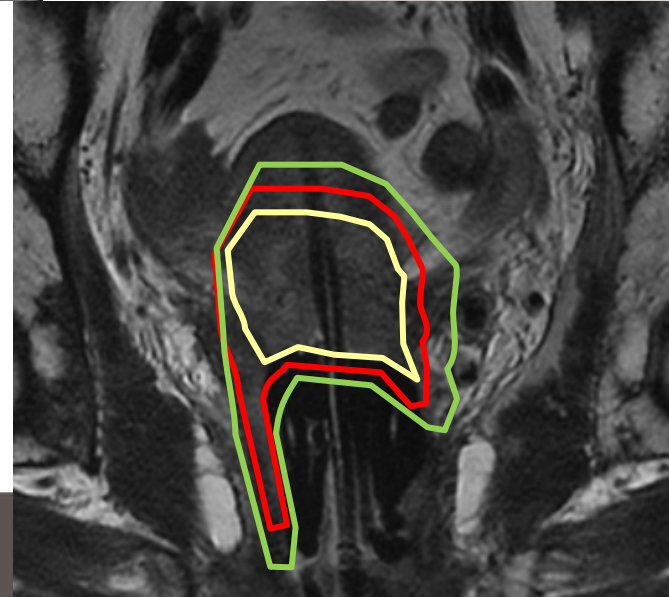
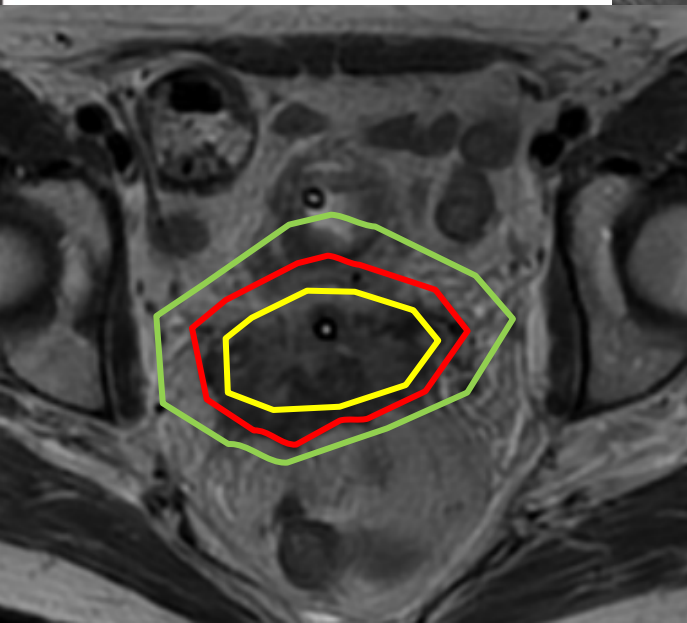
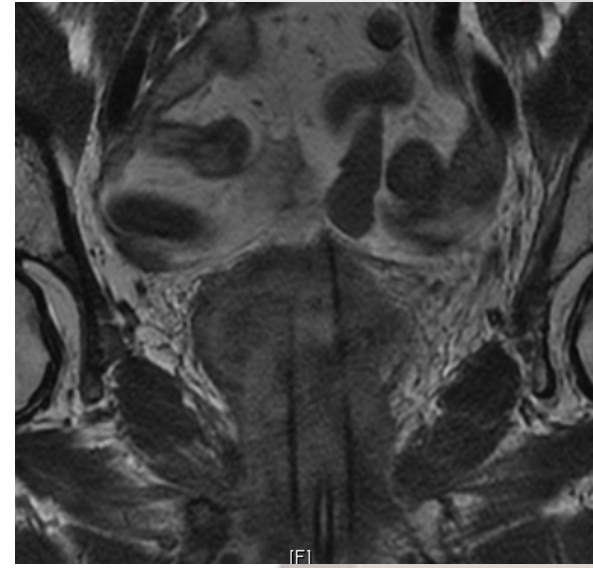
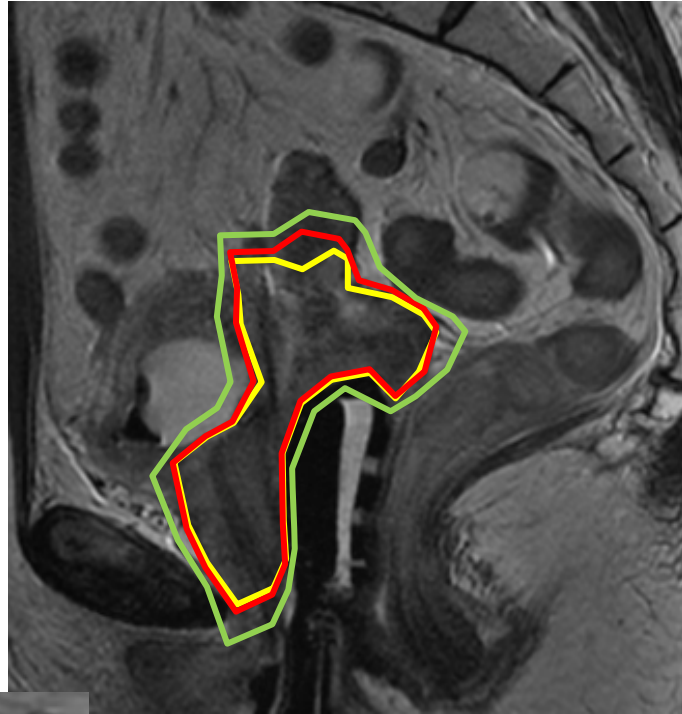
Width : 8

Thickness : 6

Height : 7



Stage IVA : at time of brachytherapy



Intrauterine and Vaginal Disease

Variation in GTV response

selection of HR CTV
selection of IR CTV

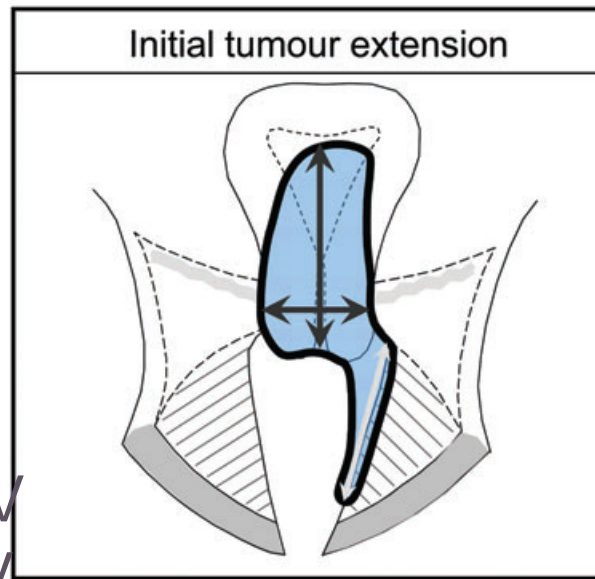
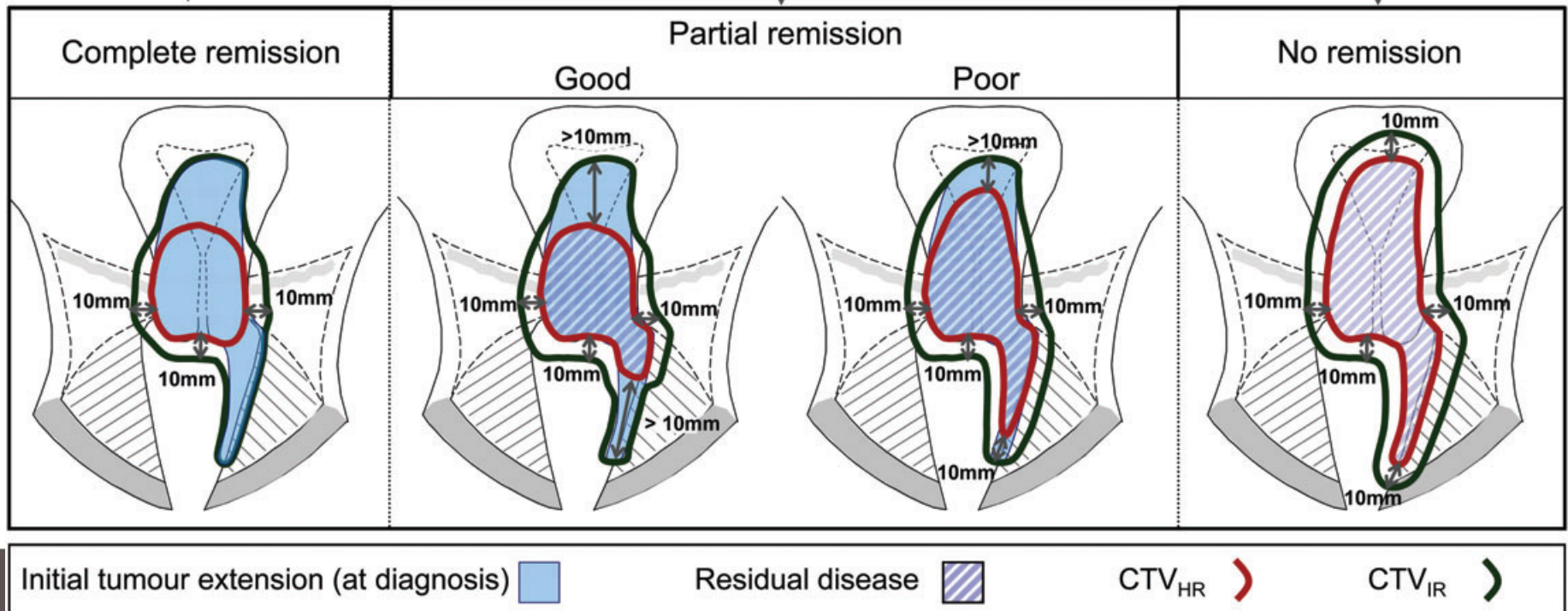
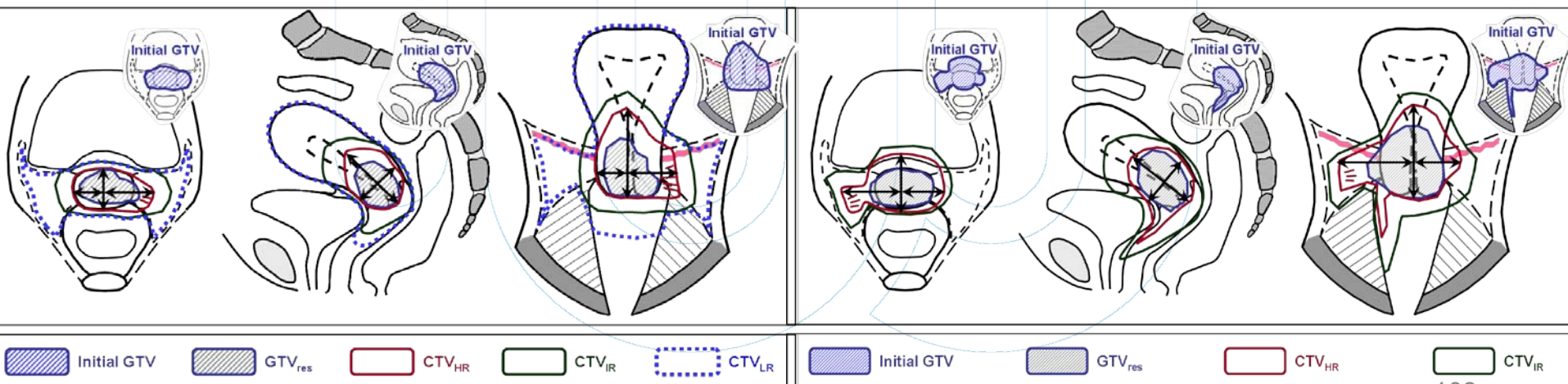
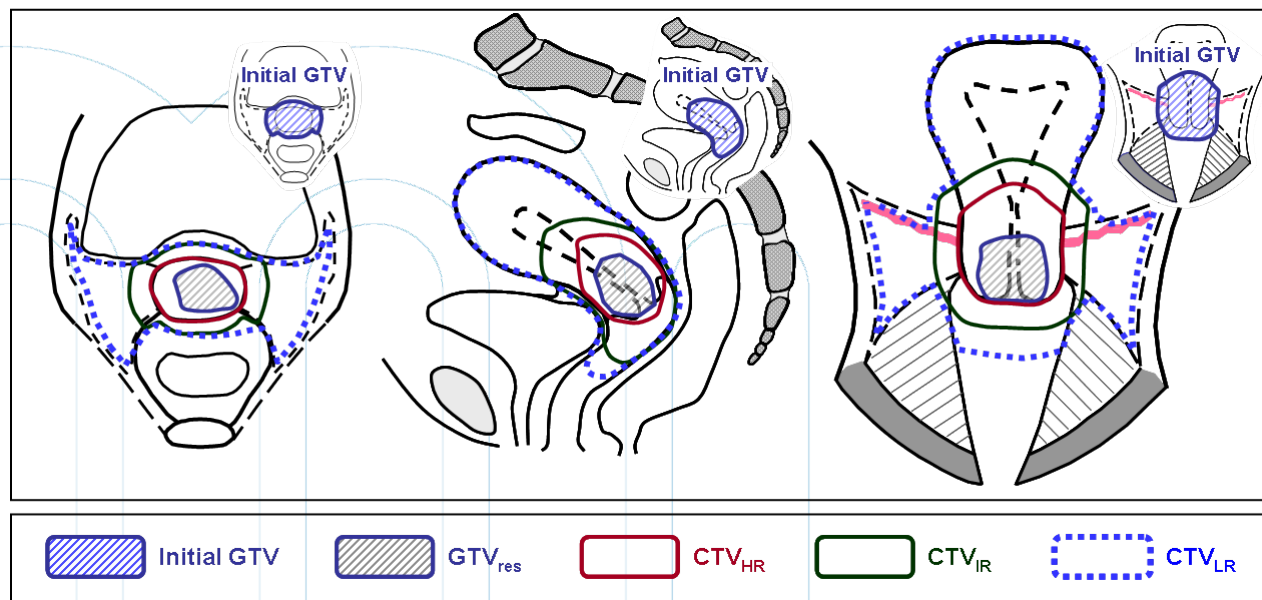


Fig. 5.14
ICRU Report 89



Overview of the adaptive target concept cervix cancer stage IB, IIB, IIIB: HR+IR CTV-T

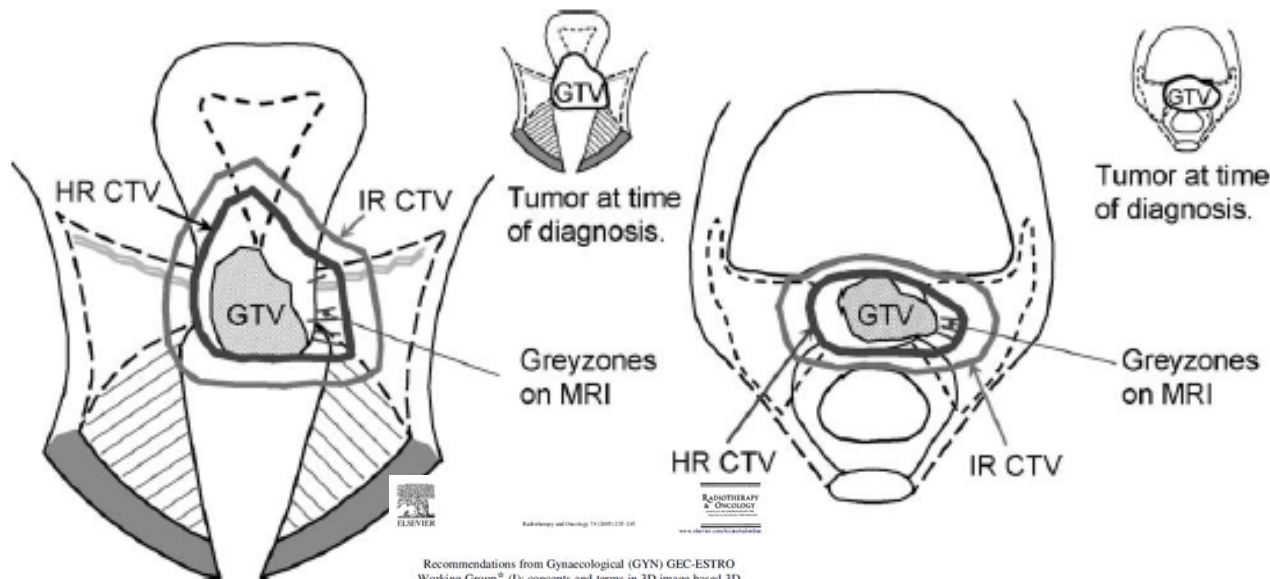
- Initial and residual GTV
- Res. patholog. tissue
- High Risk adaptive CTV
- Intermediate Risk CTV
- (Low Risk CTV)



Risk orientated adaptive Target Concept

Terms: GTV_{res} , residual pathologic tissue, CTV_{HR} ,
 CTV_{IR} , GTV_{init} ,

- CTV_{HR} : residual GTV + residual pathologic tissue + whole cervix
- CTV_{IR} : initial GTV and always CTV_{HR} + safety margin



Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group¹ (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^{1,2}, Richard Pötter³, Erik Van Limbergen⁴, Edith Bricot⁵, Mariëtte De Brabandere⁶, Johannes Dimech⁷, Isabelle Dumortier⁸, Taran Paulson Helleboer⁹, Christian Katsiris¹⁰, Stefan Lang¹¹, Sabine Mauch¹², Juliana Neuvonen¹³, An Noutens¹⁴, Peter Petrow¹⁵, Natascha Wachter-Gerstner¹⁶

HR-CTV includes:

- A. Res GTV, res pathologic tissues, and always the whole cervix**
- B. the whole cervix + safety margins**
- C. the whole uterus + safety margins**
- D. the initial tumor extension**

IR-CTV includes:

- A. the initial tumor extension**
without adapting to the situation at brachytherapy
- B. the whole uterus + safety margins**
- C. HR-CTV plus safety margins**
taking into account initial tumor extension

ICRU 88

Prescribing, Recording, and Reporting Brachytherapy (BT) for Cancer of the Cervix

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Chapter (3) – BT Techniques and Systems

Chapter (4) – BT Imaging for Treatment Planning

**Chapter (5) – Oncological Concepts and Volumes and Implications
for Adaptive Radiotherapy**

Chapter (6) – Normal Tissue Morbidity related Concepts and Volumes

Chapter (7) – Radiobiological considerations

Chapter (8) – Dose and Volume parameters for prescribing, recording, and reporting of BT alone and combined with EBRT

Chapter (9) – Physics aspects of 3D volumetric dose assessment:
applicator reconstruction, reference points, image fusion,
and inter/intra-fraction uncertainties

Chapter (10) – Radiographic Dose Assessment

Chapter (11) – Sources and dose calculation

Chapter (12) – Treatment planning

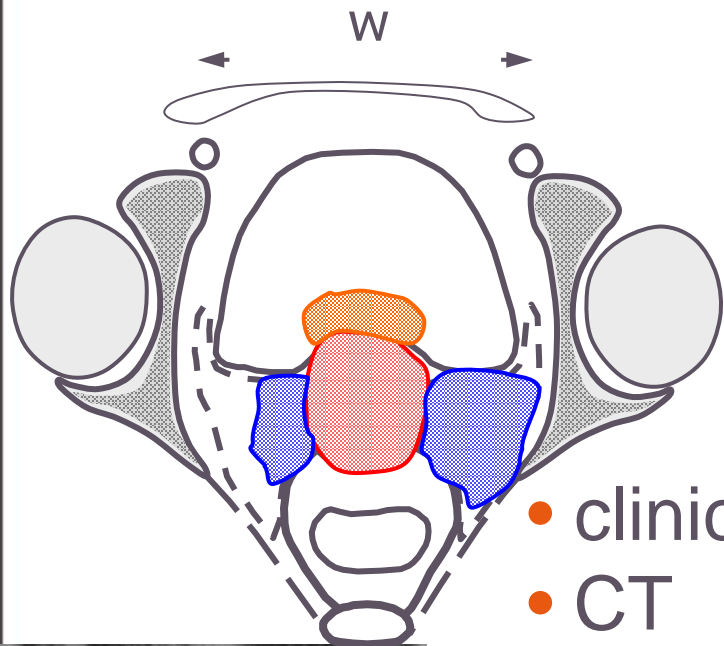
Chapter (13) – Summary of the Recommendations

ICRU 89 *(analogue to GEC ESTRO Rec I)*

Oncological volume concepts relevant to radiotherapy

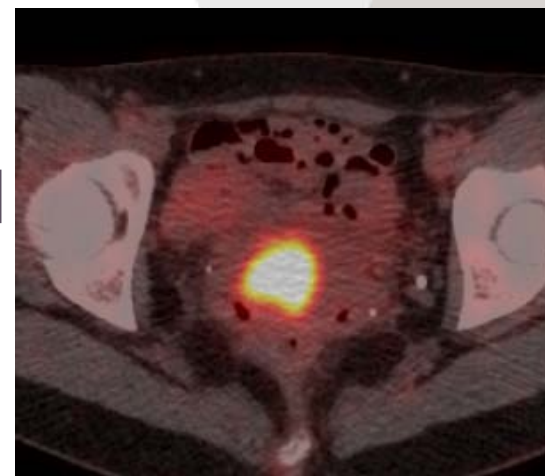
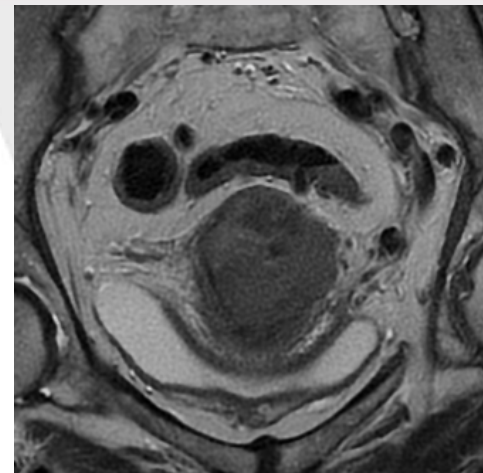
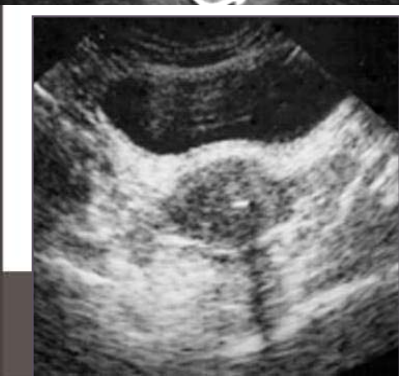
Three-dimensional imaging = selection and delineation of :

- GTV-T : composite GTV (various assessment methods)
- GTV_{res} and GTV_{init}
- CTV-T : GTV-T and potential microscopic disease
- CTV_{adapt} : GTV_{res} + residual pathologic tissue
- HR-CTV : GTV_{res} + residual pathologic tissue + whole cervix
- IR-CTV : initial GTV and always CTV_{HR} + safety margin

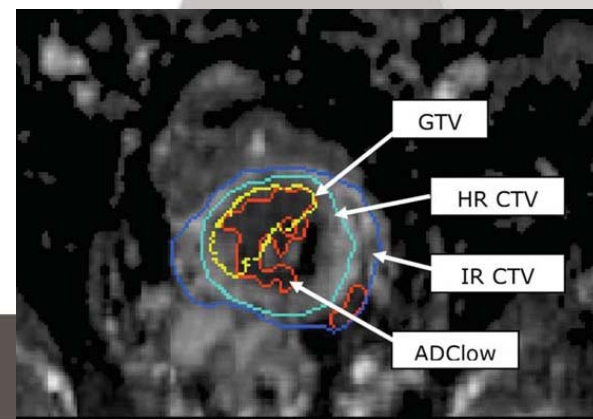


GTV_{init}

- clinical examination
- CT
- MRI (FSE) T2 weighted
- PET-CT
- MRI DWI/DCE
- US

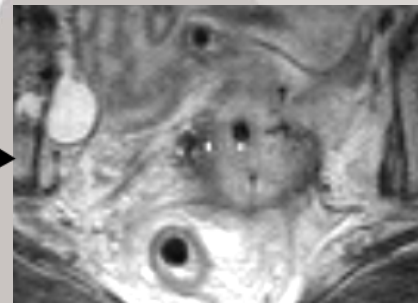
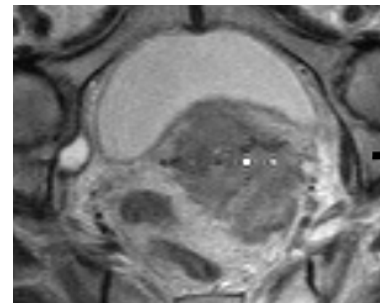
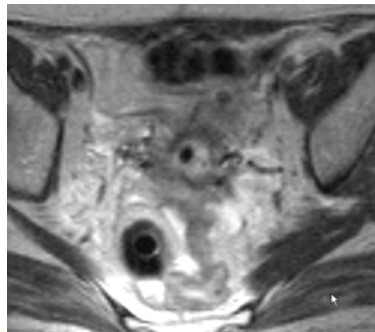
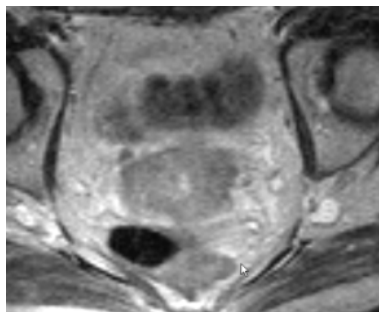


Composite GTV



GTV_{res}

- clinically detectable
- macroscopic remaining disease
- after a significant amount of treatment determined by using the same clinical or imaging investigations
- typical MR imaging: residual signal intensive zones
- Residual pathologic tissue: “grey zones”
- pathologic residual oedematous tissue

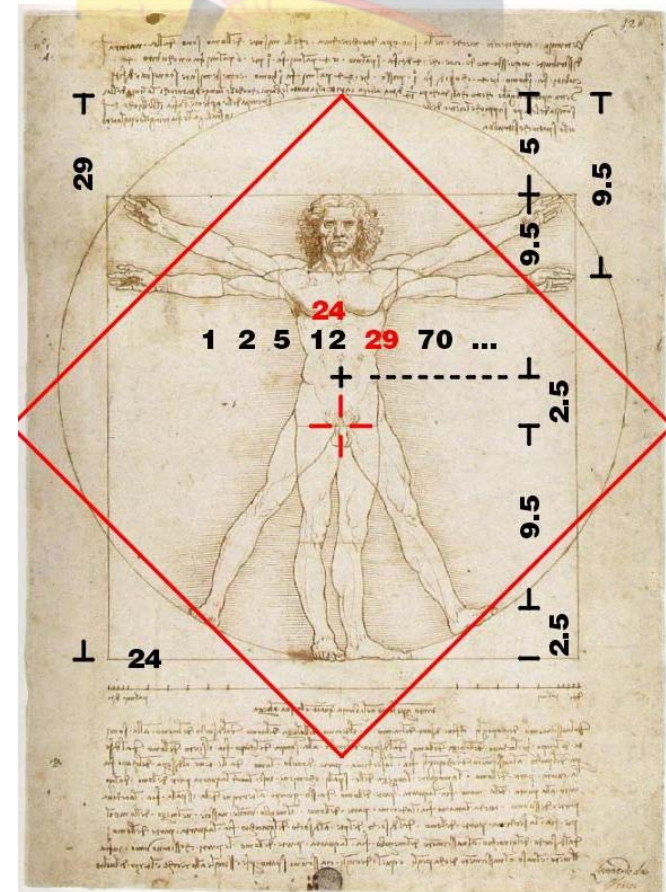
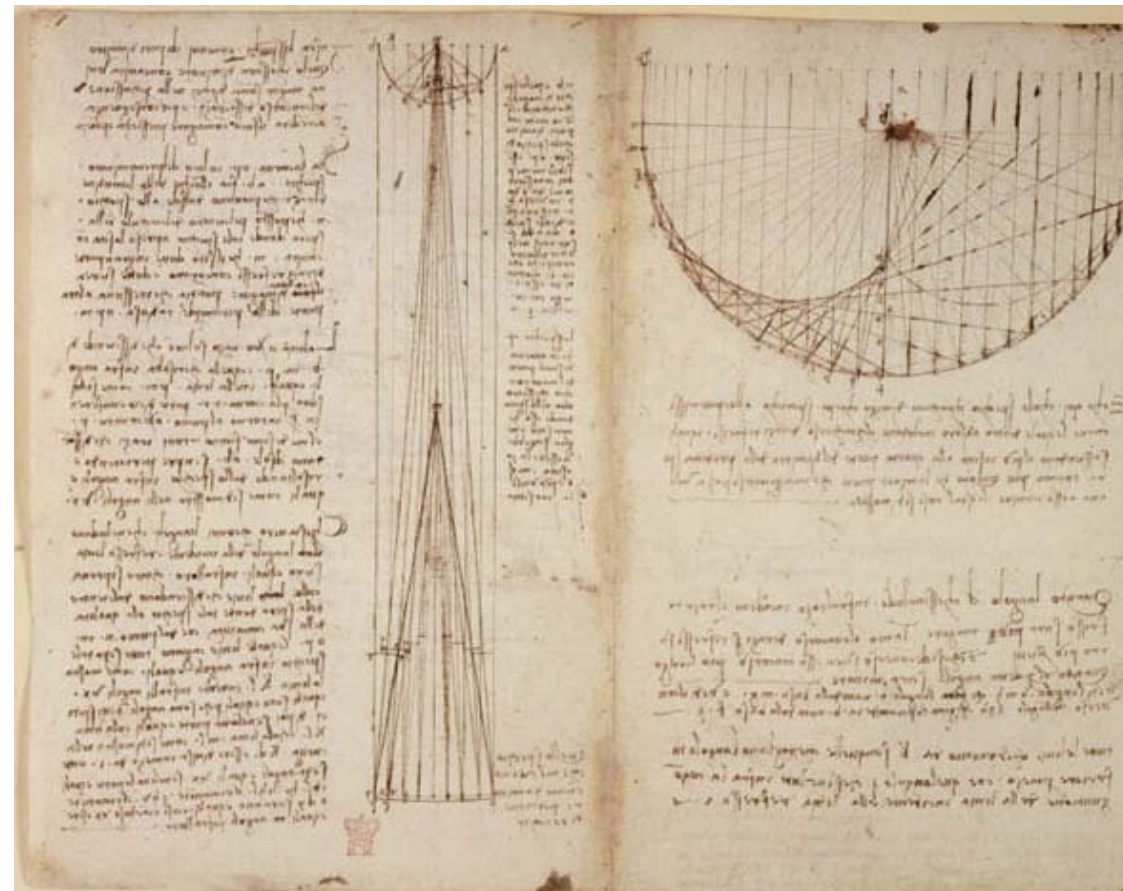


Applicator Reconstruction



Daniel Berger MSc PhD

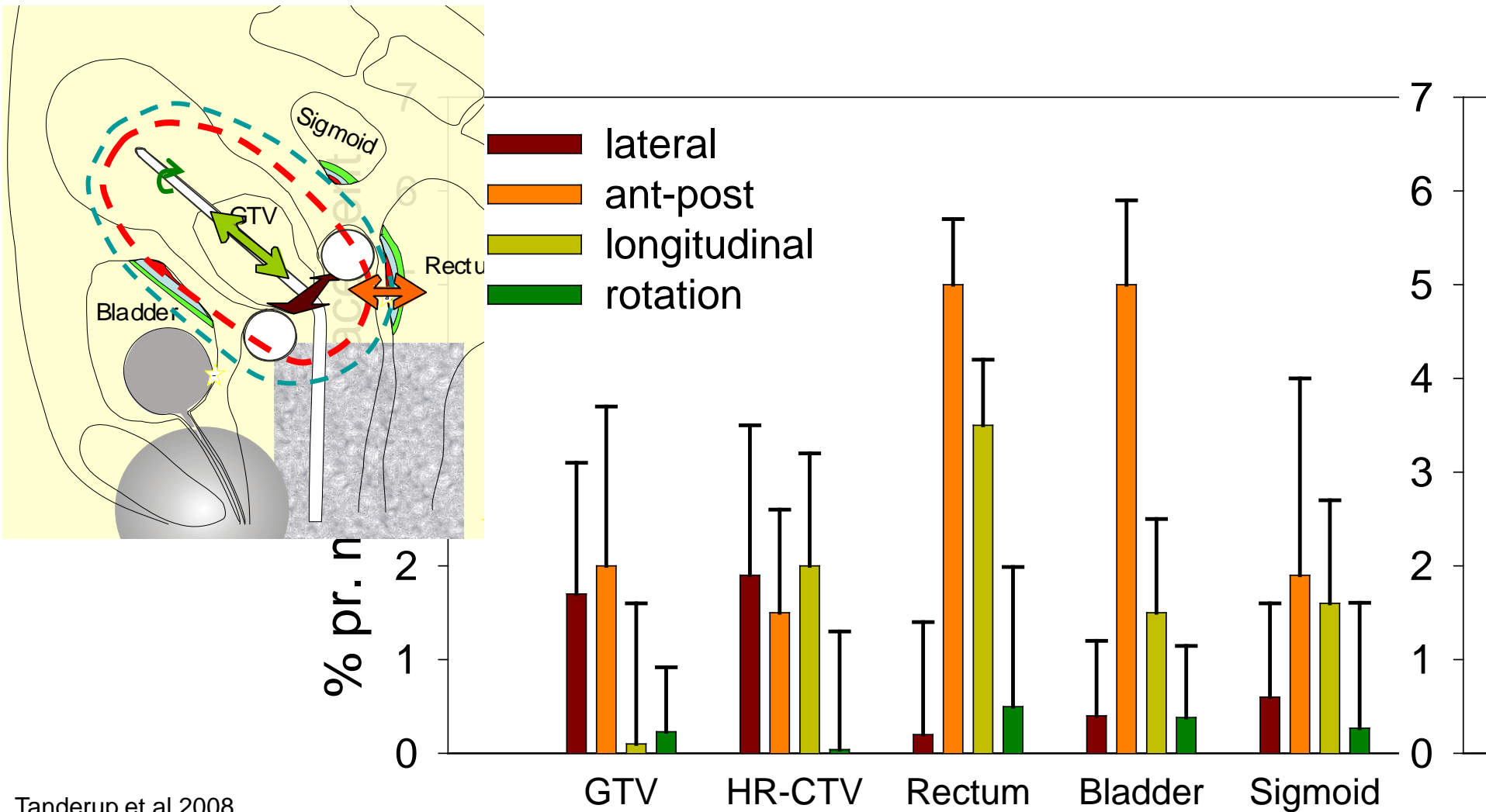
daniel.berger@akhwien.at
Senior Clinical Physicist,
Department of Radiotherapy,
General Hospital of Vienna, Austria



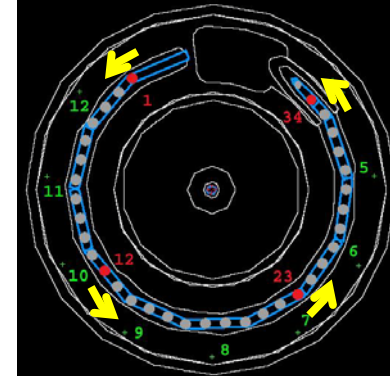
Presentation overview


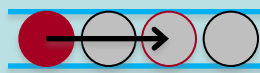
- Importance of Applicator Reconstruction
- Direct Reconstruction (of the source-path)
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- Fusion / Registration

Systematic reconstruction uncertainties in 3D based BT using a tandem ring applicator

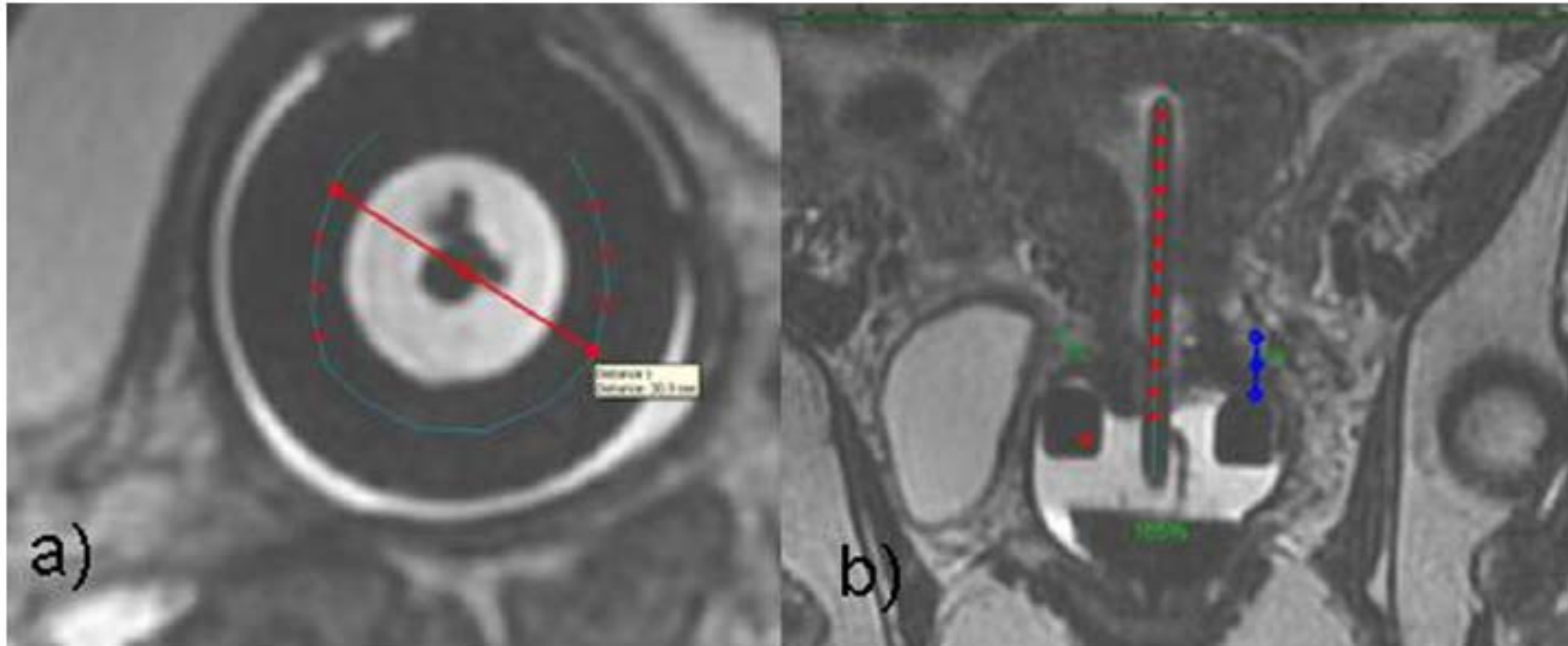


Impact of reconstruction uncertainties on DVH parameters in 3D based BT when rotating/rolling the Applicator by 1 or 2 dwell positions



DVH parameter	 ± 2.5 mm	 ± 5.0 mm
CTV D90	± 2%	-4% , +3%
CTV D100	-3% , +2%	-7% , +3%
GTV D90	± 2%	-5% , +4%
GTV D100	± 4%	-8% , +6%
Bladder D _{2cc}	± 3%	-5% , +7%
Rectum D _{2cc}	± 5%	-8% , +11%
Sigmoid D _{2cc}	-3% , +2%	± 4%

Quality assurance in MR image guided adaptive brachytherapy for cervical cancer: Final results of the EMBRACE study dummy run



(a) Incorrect reconstruction of the source path within the ring using direct digitalization not according to the true dwell positions. (b) incorrect definition of point A using wrong distance from upper ring surface plus incorrect source path with wrong offset to the tip of the tandem and wrong location of source path inside the ring.

Order of magnitude for target dose - HDR BT

Uncertainties related to

1. Source calibration	~ 1,5 %
2.a) Dose calculation in water	~ 4 %
b) Systematic effects in the clinical setting	up to 10 %
3. Accuracy of afterloader performance (time/spatial distribution)	~ 2 %
<i>Mainly site specific</i>	
4. Imaging (reconstruction, volume interpolation,...)	~ 5 %
5. Contouring	“10% Expert level”
	x %
6. Variations at patient level (inter- and intrafraction variations, organ movement/swelling)	~10 %** up to ~50%

Exclusive MRI-based tandem and colpostats reconstruction in gynaecological brachytherapy treatment planning

Perez-Calatayud J, Kuipers F, Ballester F, Granero D, Richart J, Rodriguez S, Tormo A, Santos M. *Radiother Oncol* 2009;91:181–6.

Applicator reconstruction and applicator shifts in 3D MR-based PDR brachytherapy of cervical cancer.

De Leeuw AA, Moerland MA, Nomden C, Tersteeg RH, Roesink JM and Jürgenliemk-Schulz IM. *Radiother Oncol*. 2009 Nov;93(2):341-6

Direct-reconstruction of the Vienna applicator on MR images

Berger D, Dimopoulos J, Pötter R, Kirisits C.
Radiother Oncol 2009 Nov 93(2):347-51

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.

Hellebust TP, Kirisits C, Berger D, Pérez-Calatayud J, De Brabandere M, De Leeuw A, Dumas I, Hudej R, Lowe G, Wills R, Tanderup K; **Gynaecological (GYN) GEC-ESTRO Working Group**.
Radiother Oncol. 2010 Aug;96(2):153-60

Defining the source path in relation to the patients anatomy

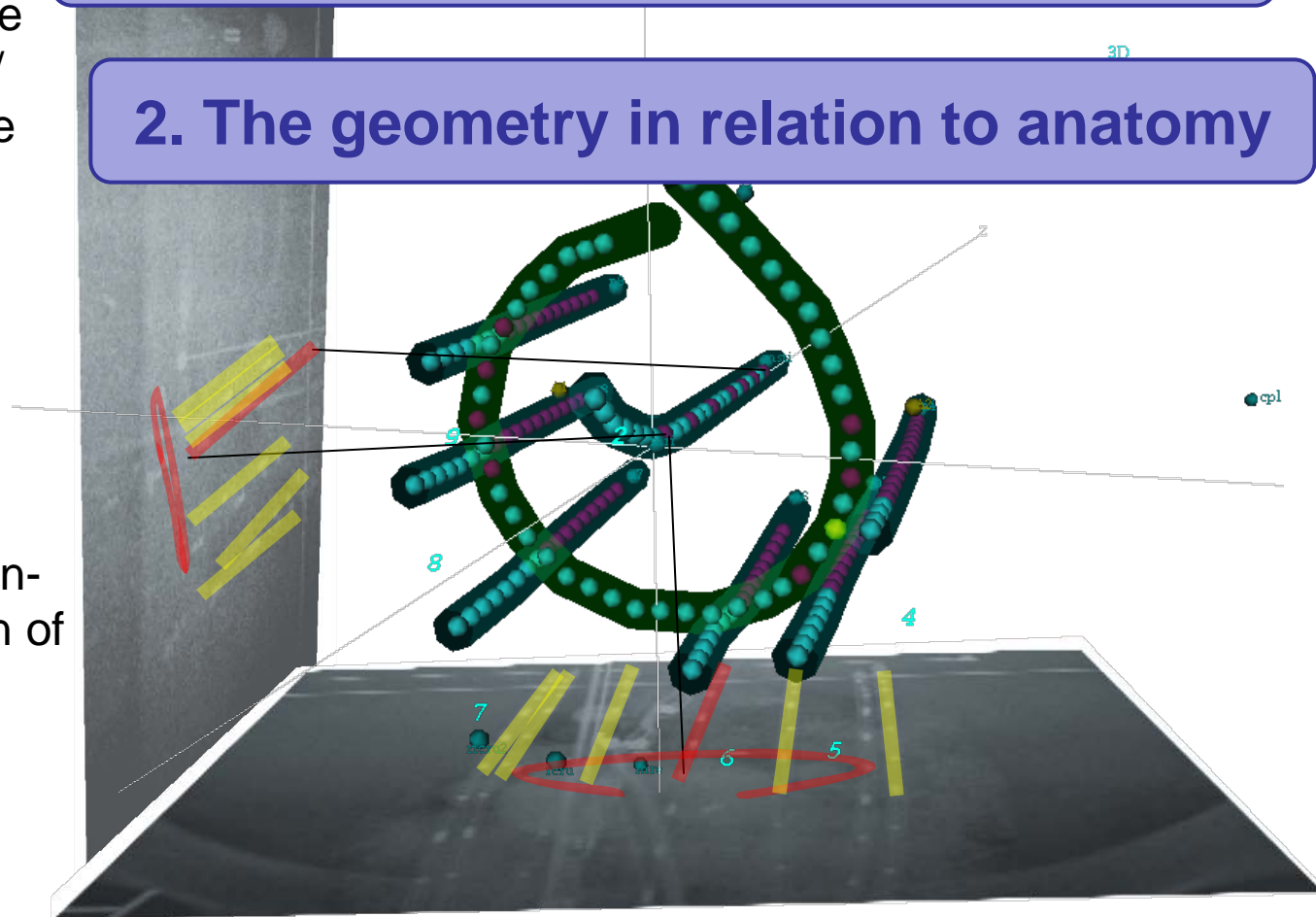
1. The geometry of the applicator itself

Depending on the image modality, the applicator/
source path needs to be defined

There are directly or in-
directly visualization
techniques

Reconstruction of the
Source path (direct, or in-
Direct) or reconstruction of
the applicator itself

2. The geometry in relation to anatomy



Localization techniques in “2D” and 3D

Depending on your equipment (2D:simulator, c-arm, ceiling mounted,3D: US,CT,MRI)

➤ Orthogonal images

➤ Semi-orthogonal

➤ Variable angle

➤ Stereo-shift

“2D”:Level 2

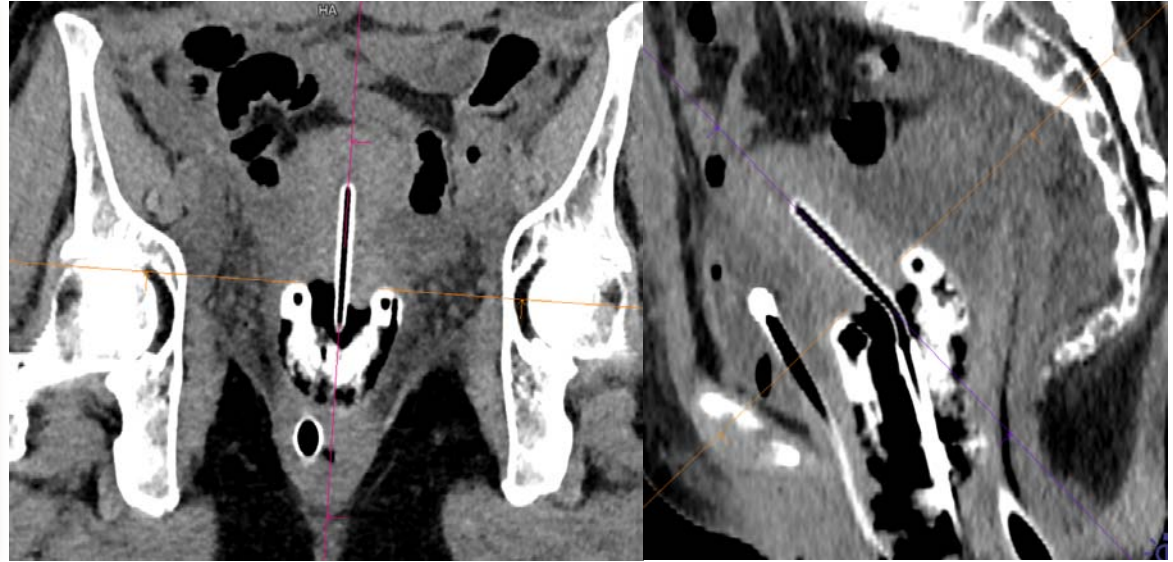
➤ Sectional Images (CT,MRI)

➤ Volumetric (US,MRI)

3D Level3

Sectional Imaging CT / MRI

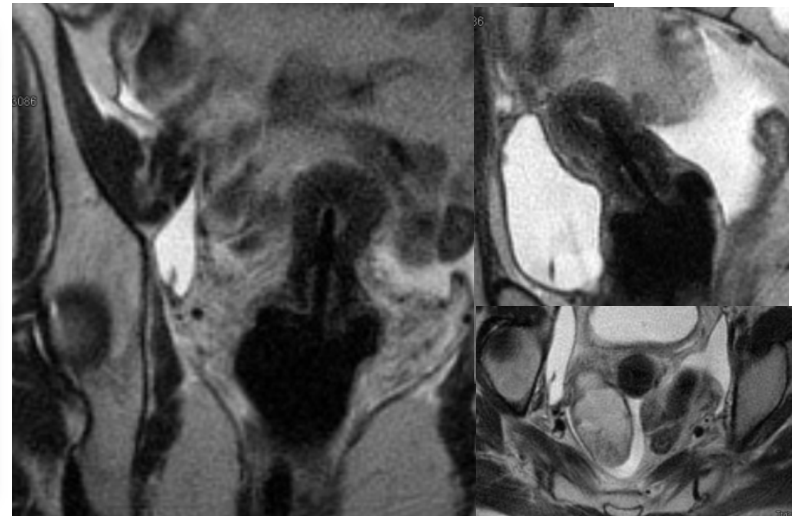
CT



high field MRI



low field MRI

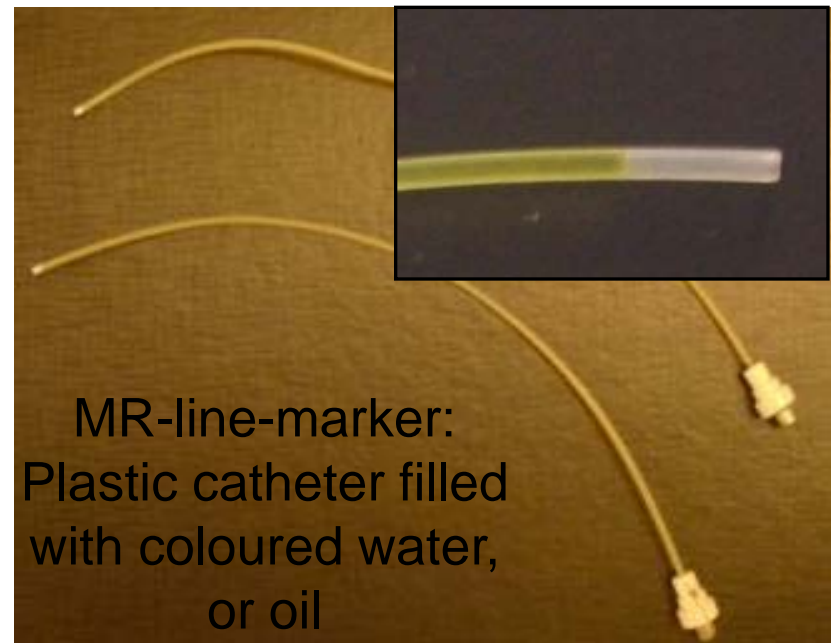
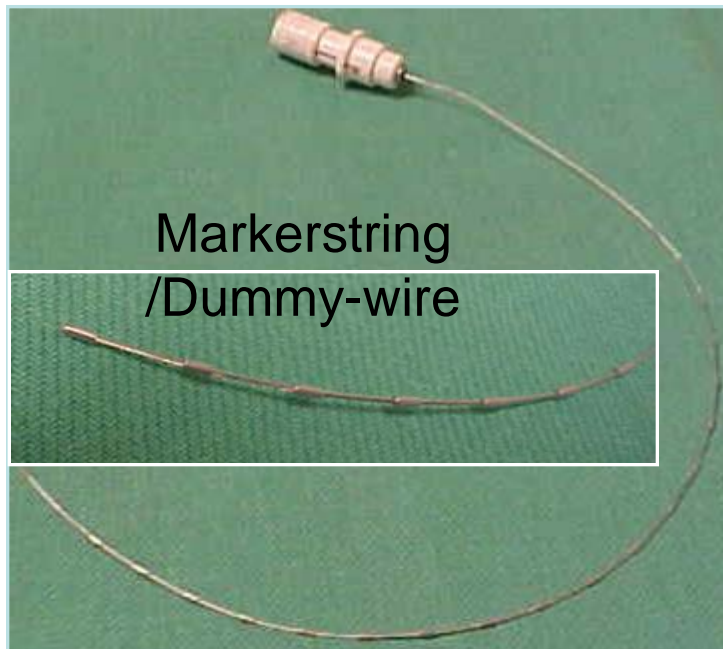


Presentation overview

- Importance of Applicator Reconstruction
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- Commissioning of Applicator and QA of the Reconstruction Process
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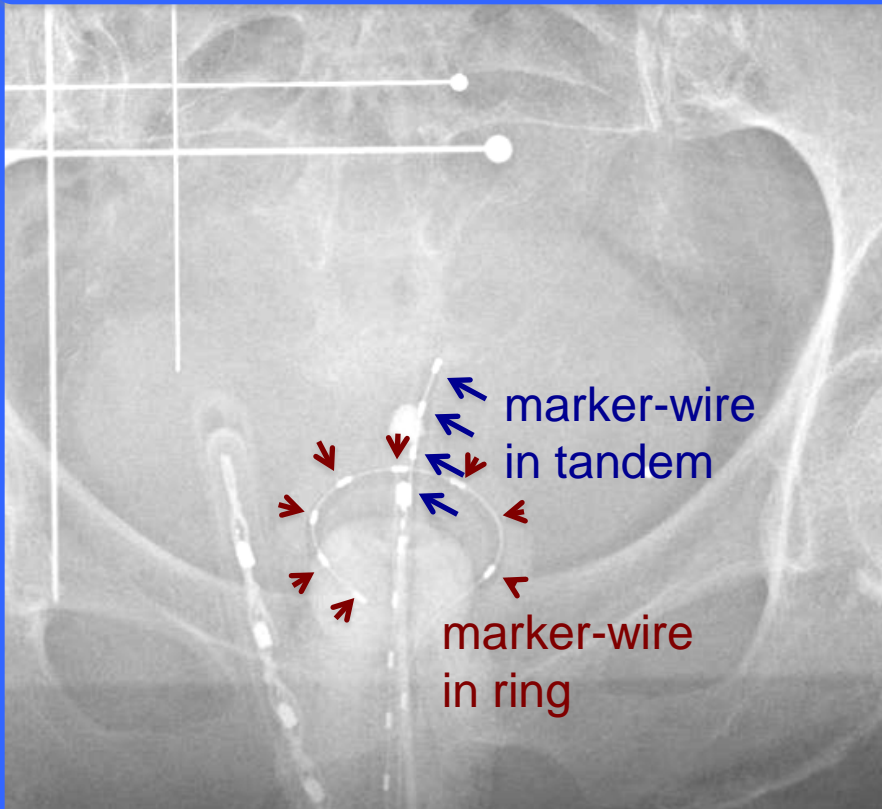
***Direct* Visualizing the Source Path**

- Find a surrogate of the the source path → inserting a “marker-string” – dummy wire or MRI (liquid filled) line marker



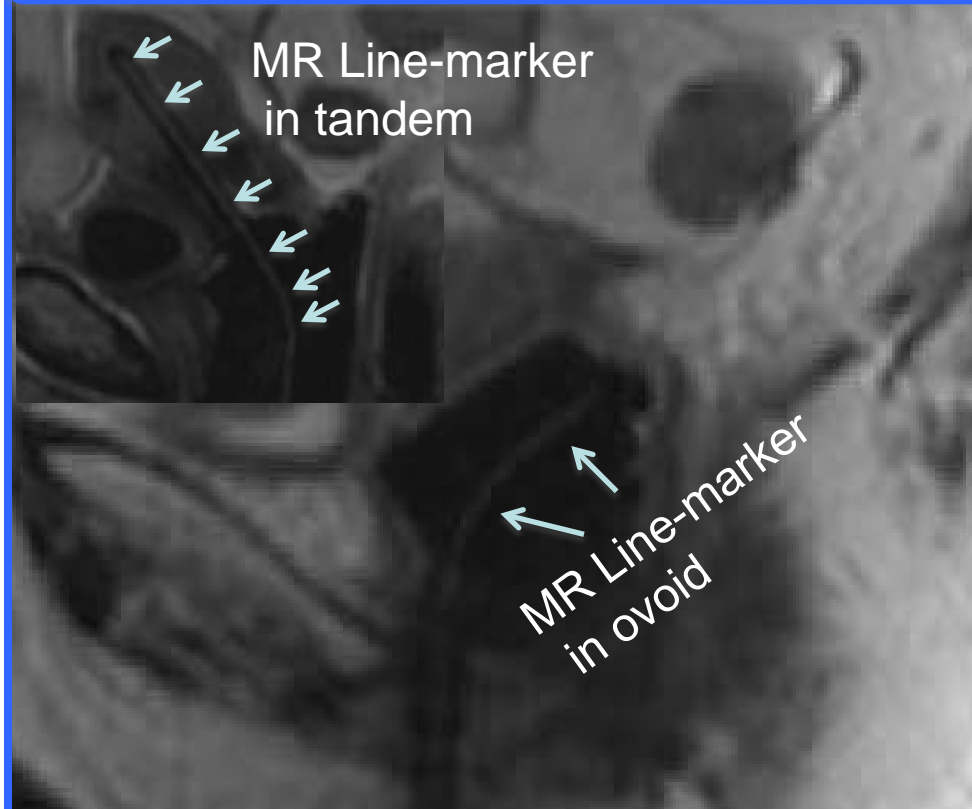
Direct Visualizing the Source Path

AP- radiograph



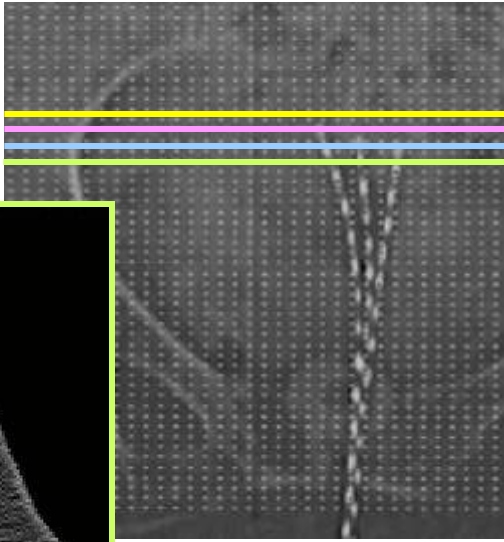
Dummy wires in TR provided by
General Hospital of Vienna, MUV

Sagittal MRI



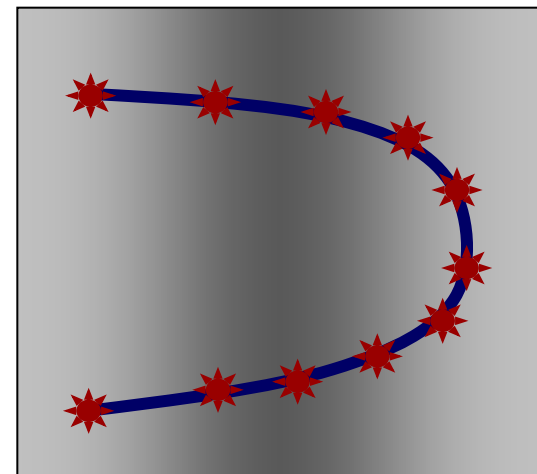
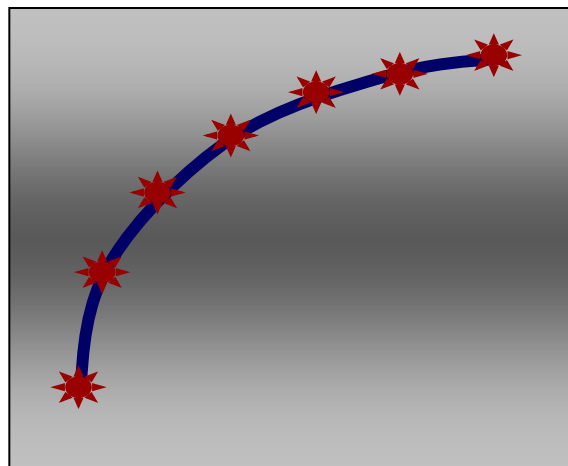
MR markers in Ovoids provided by
U. Mahantshetty, TATA, Mumbai

Direct-reconstruction on sectional images

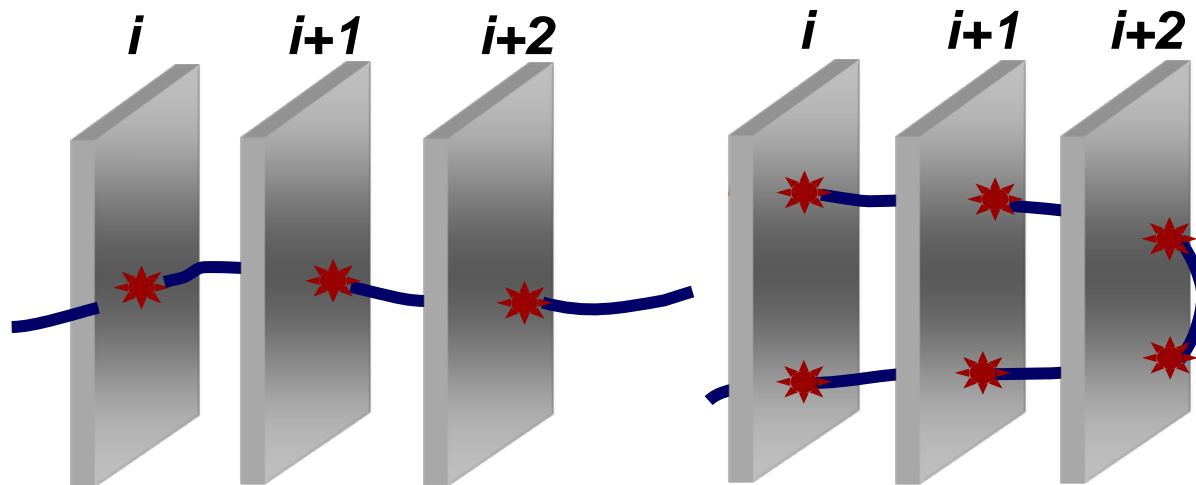


Orientation of applicator/image plane

Catheter lies completely in an acquired image

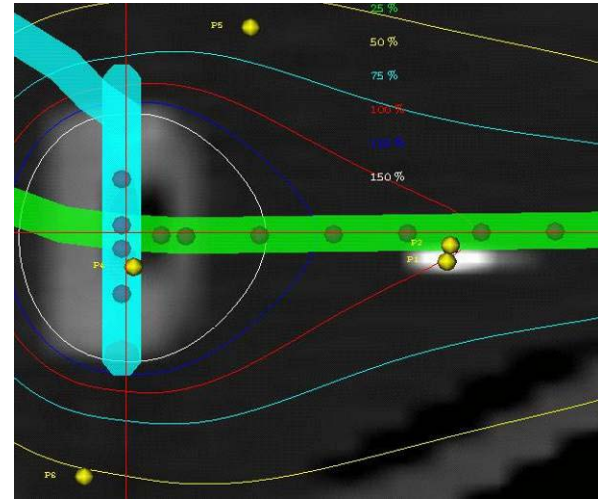
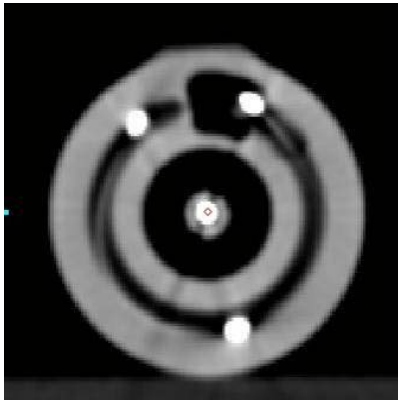


Catheter is visible in a series of images

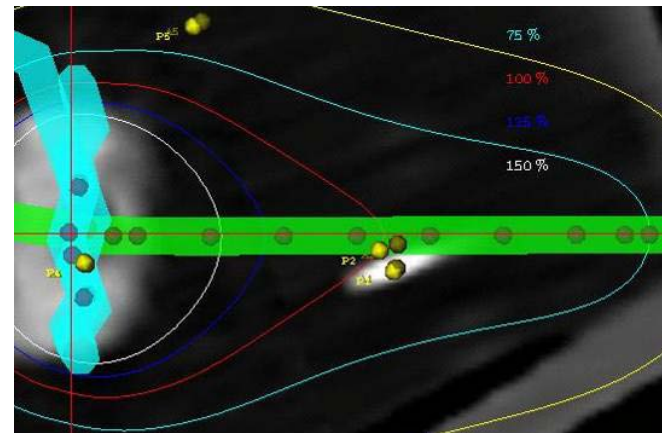
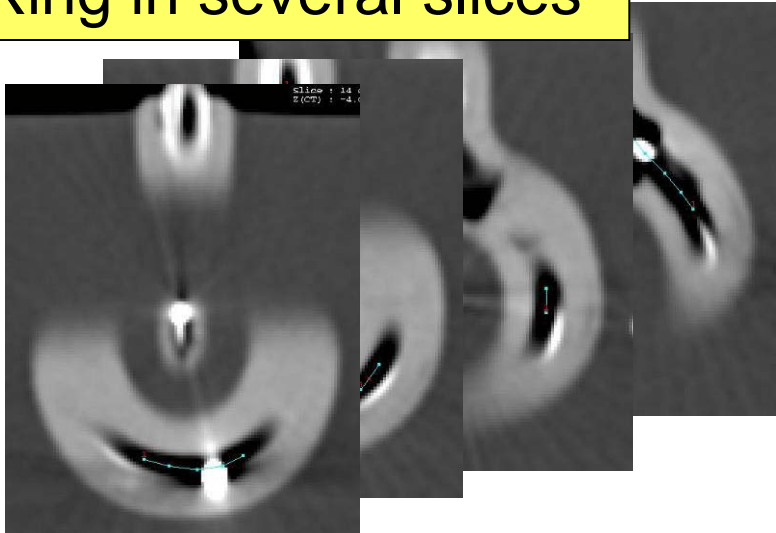


Direct reconstruction - challenge

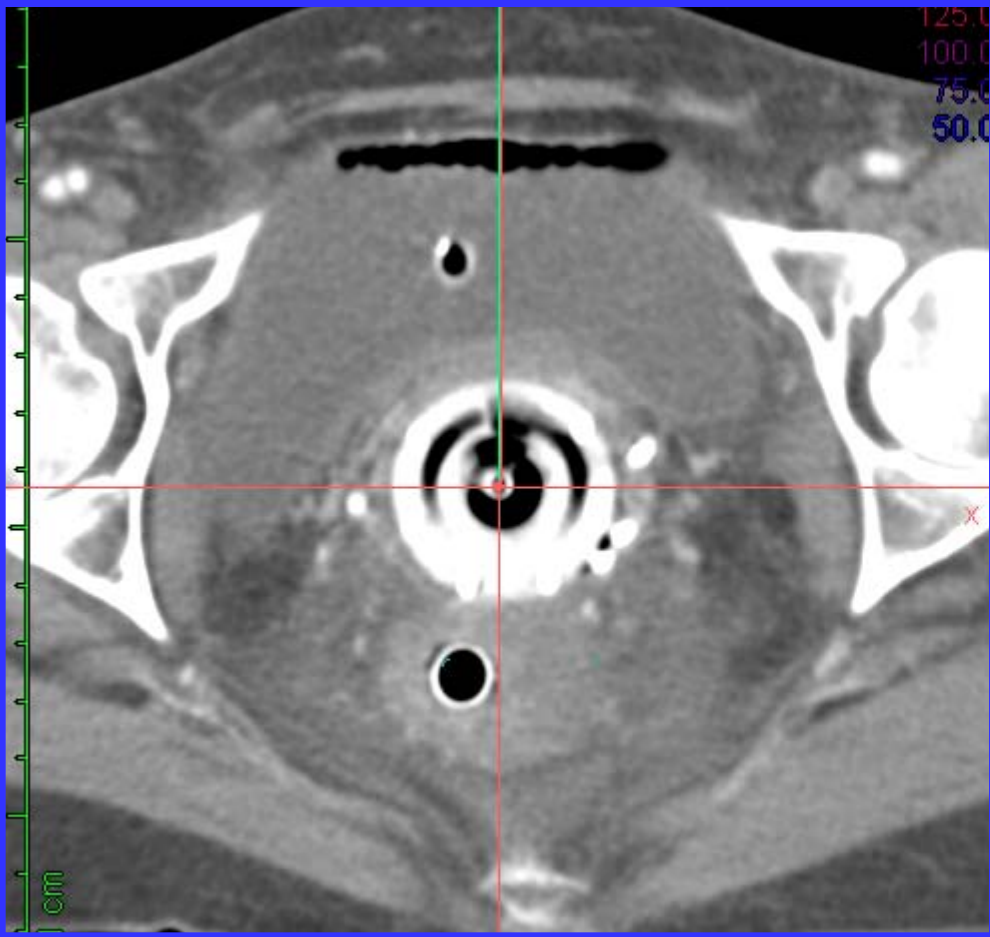
Ring in one slice



Ring in several slices



Multi Planar Reconstruction

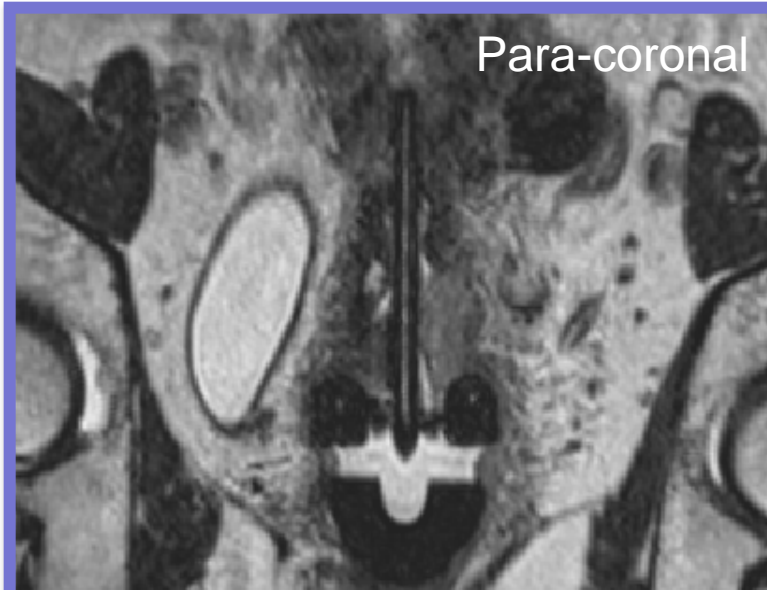


MPR CT transversal



MPR sagittal

3D (SPACE) T2 weighted MR imaging



The problem: no visible source channel

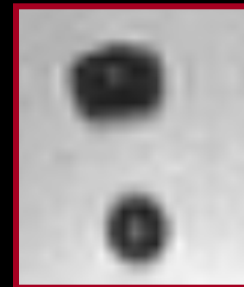
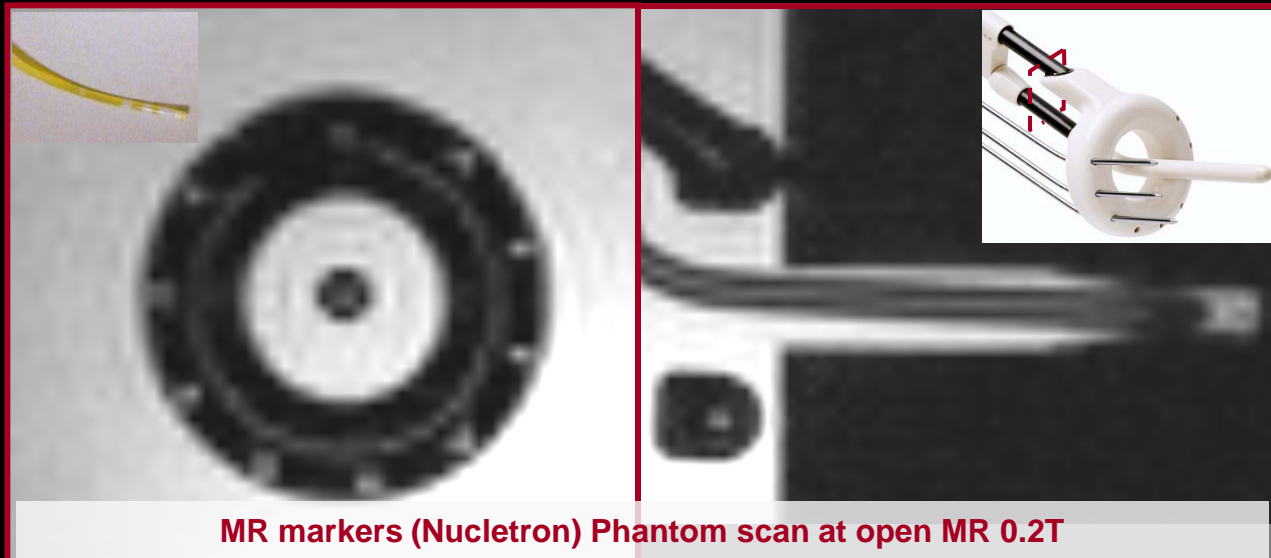


How to identify the 1st source position of the ring ?

- *Applicator geometry in relation to outer shape/dimension must be known*

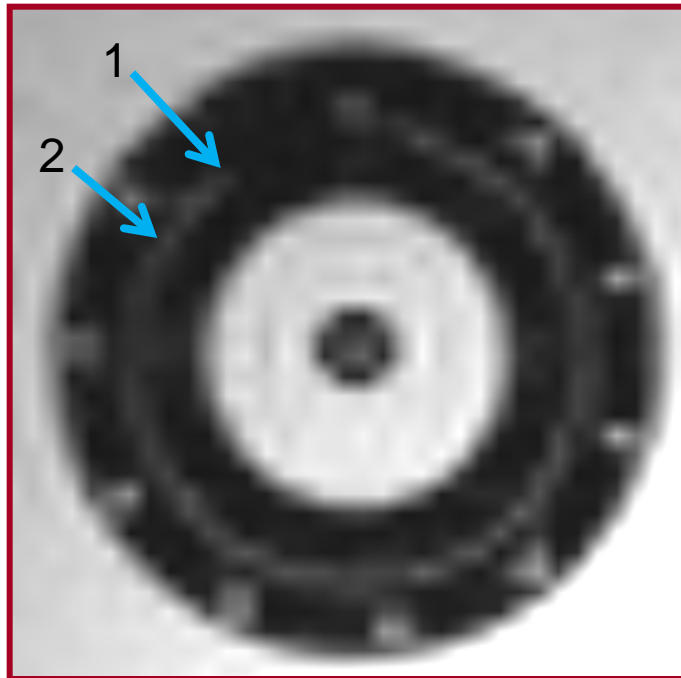
Do we need MR markers to identify the whole source channel (path) ?

- *Not necessarily when using the Vienna ring, it helps to provide additional information during the reconstruction process*



Where to start the reconstruction of the ring

1. pos. 1
2. pos.2
3. don't know, was sleeping



The problem: no visible source channel

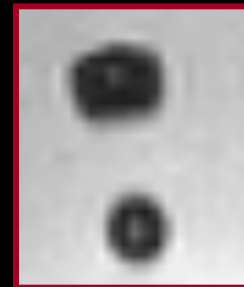
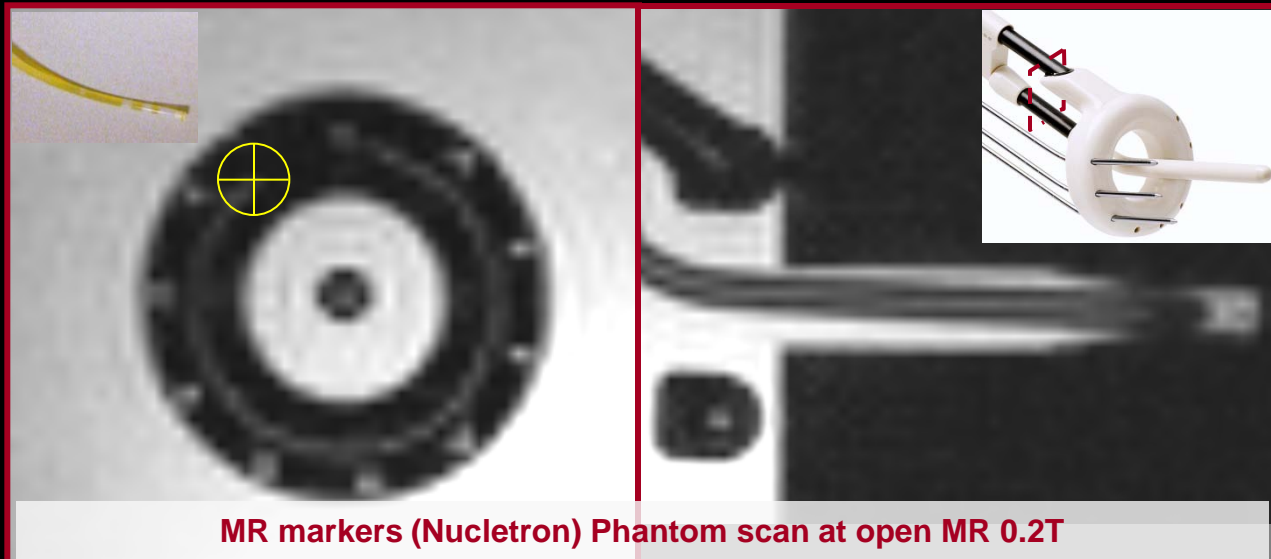


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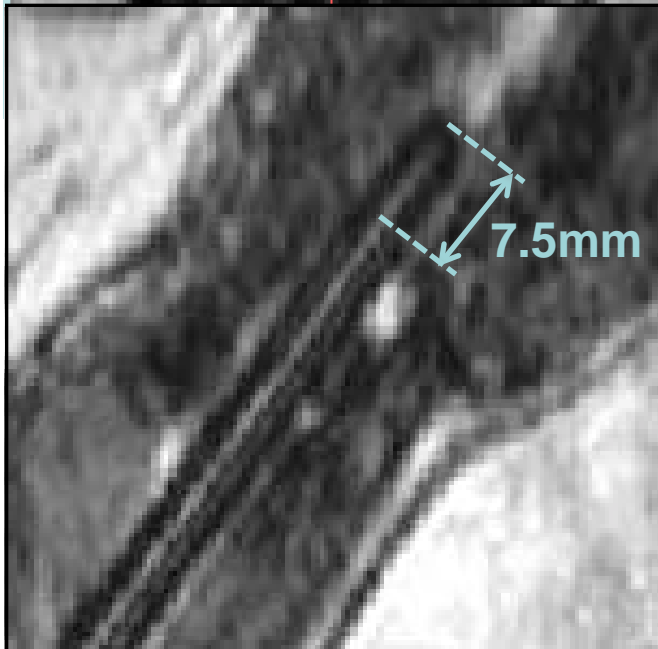
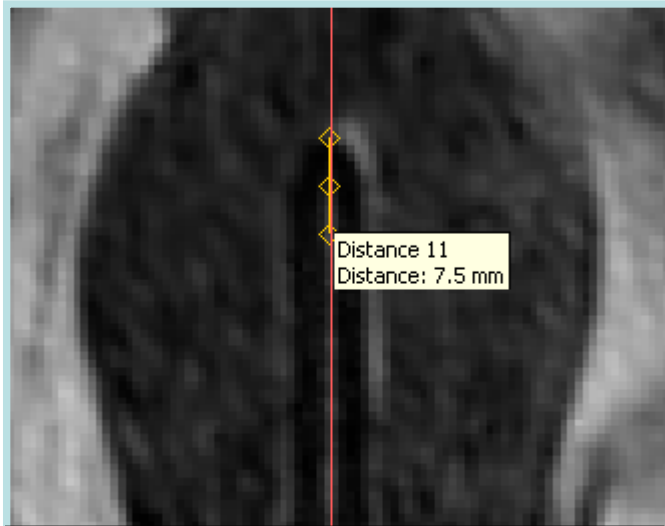
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- *Not necessarily when using the Vienna ring, it helps to provide additional information during the reconstruction process*

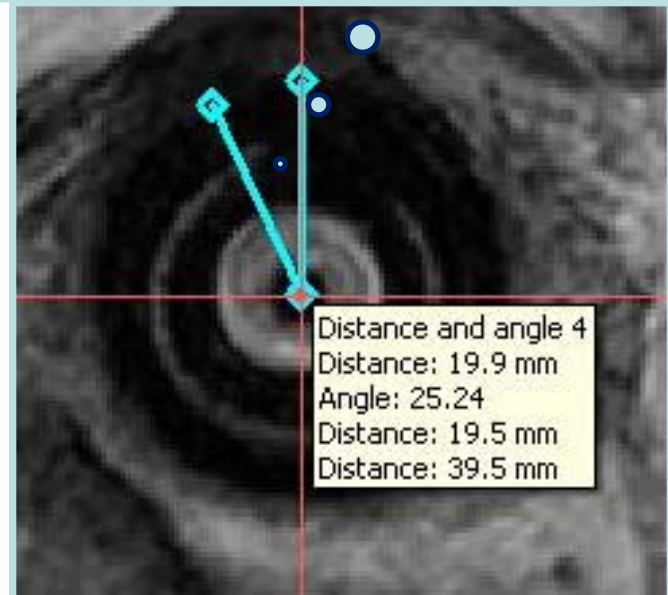
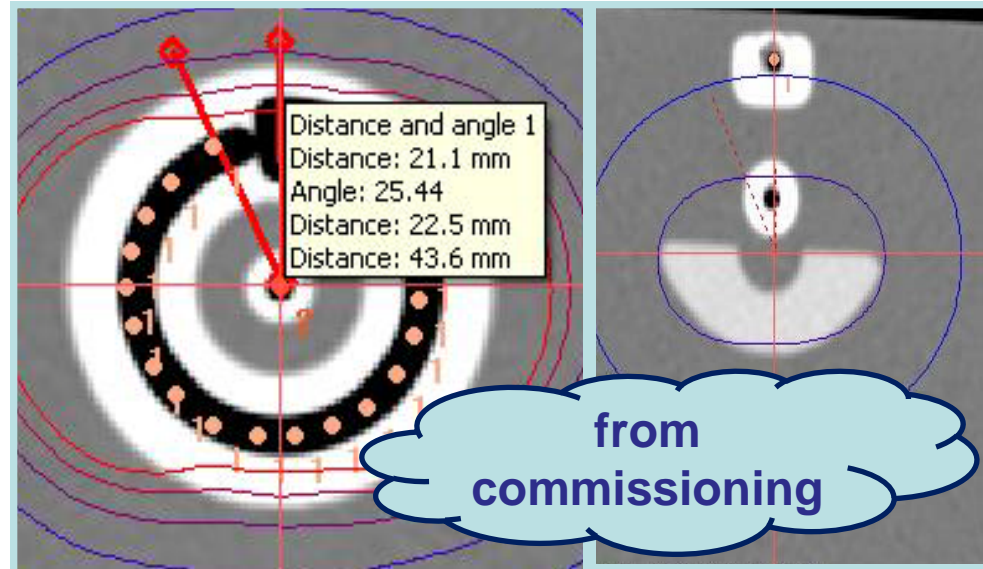


Quality Check of the reconstruction process

Tandem applicator



Ring applicator

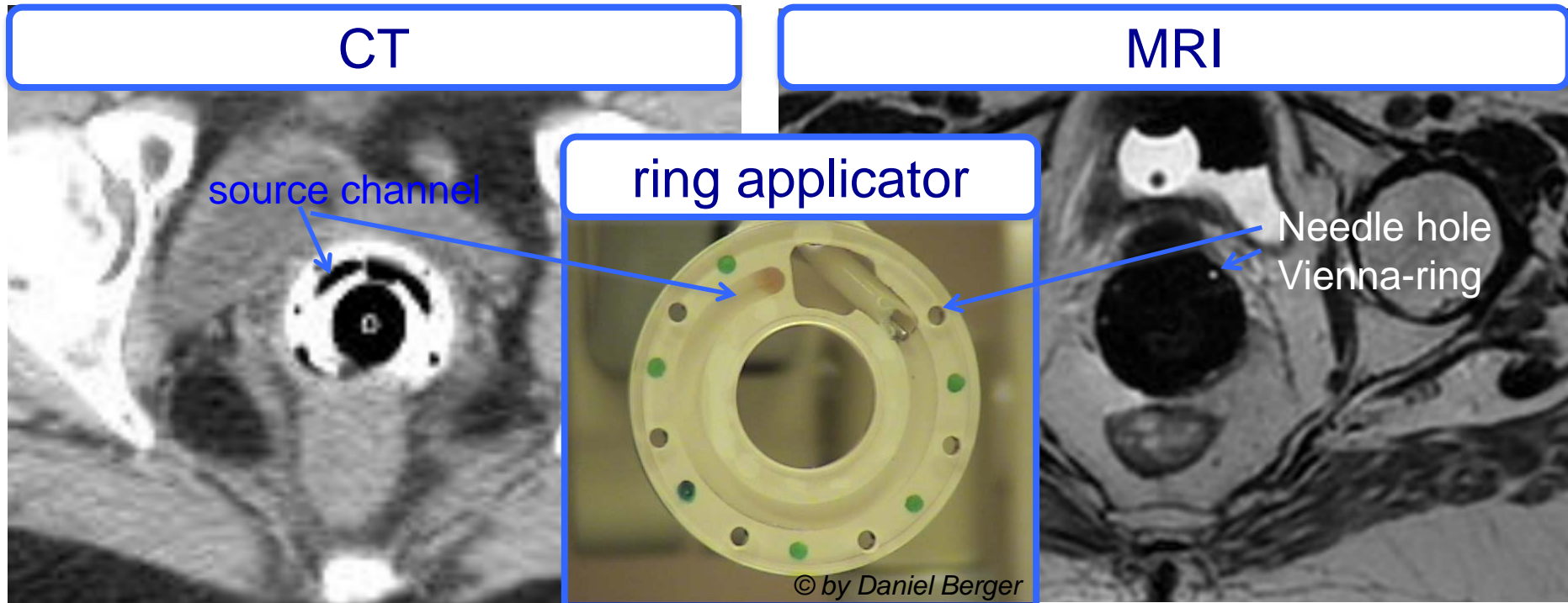


Presentation overview

- Importance of Applicator Reconstruction
- Direct Reconstruction (of the source-path)
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In-Direct Visualizing the Source Path

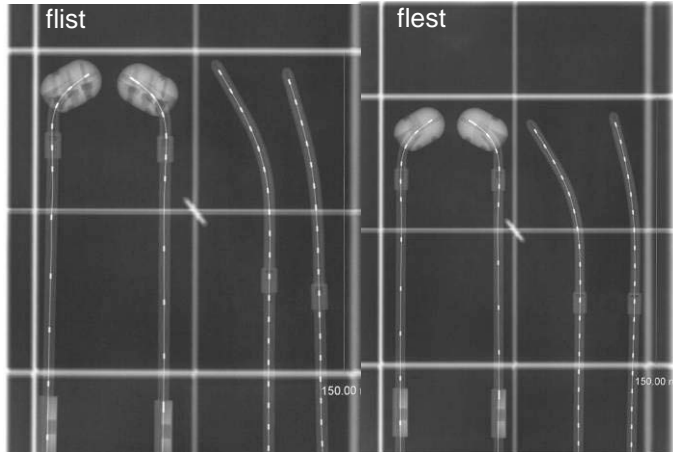
- defining the the source path by using and visible landmarks → applicator geometry



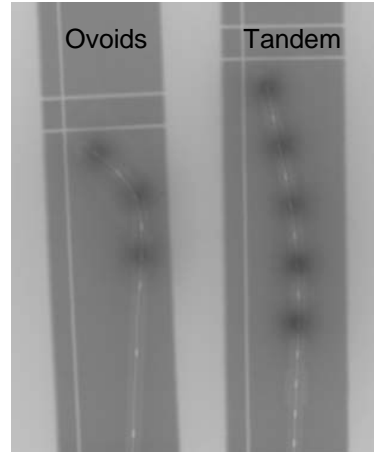
In-direct “source-path” reconstruction

Commissioning phase

1. Radiographs



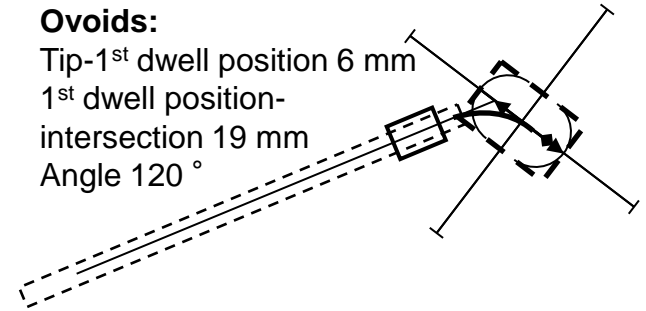
2. Auto-Radiography



3. Template for Reconstruction

Ovoids:

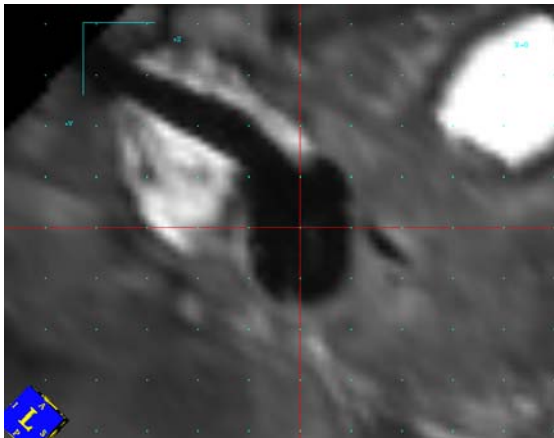
Tip-1st dwell position 6 mm
1st dwell position-
intersection 19 mm
Angle 120°



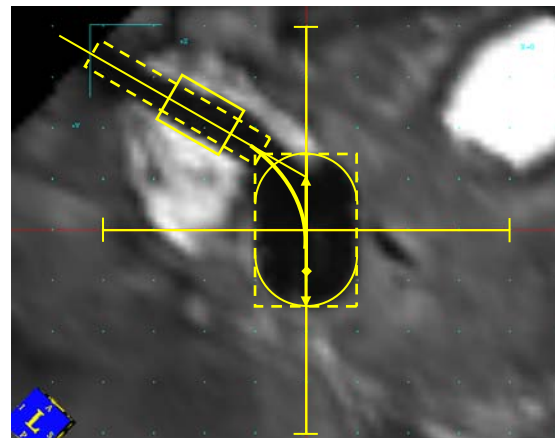
Intrauterine Tandem:
Tip-1st dwell position 7 mm

Individual patient phase

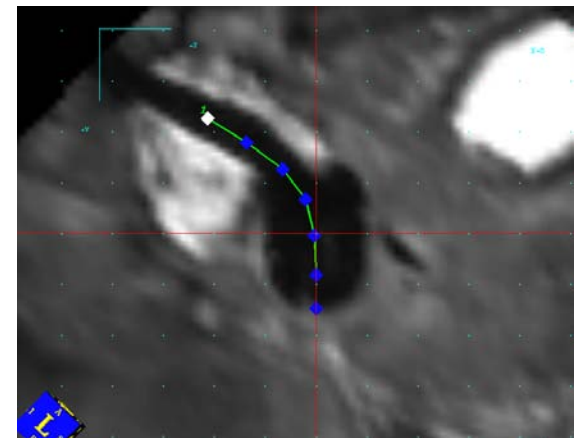
1. MR Imaging



2. Template in place

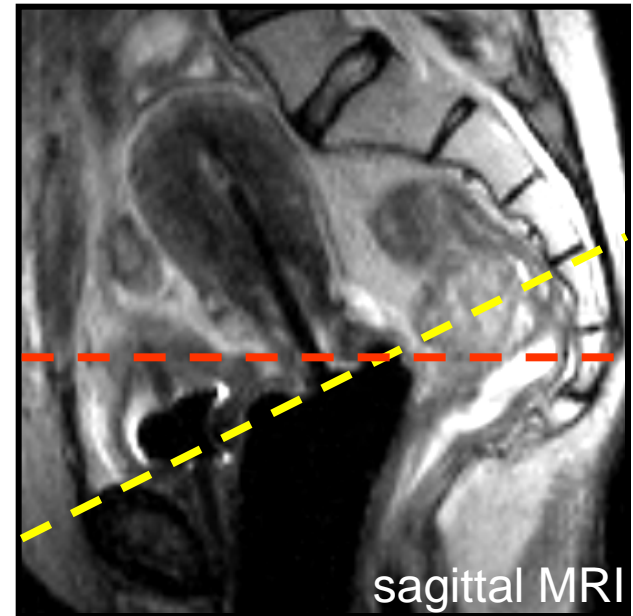
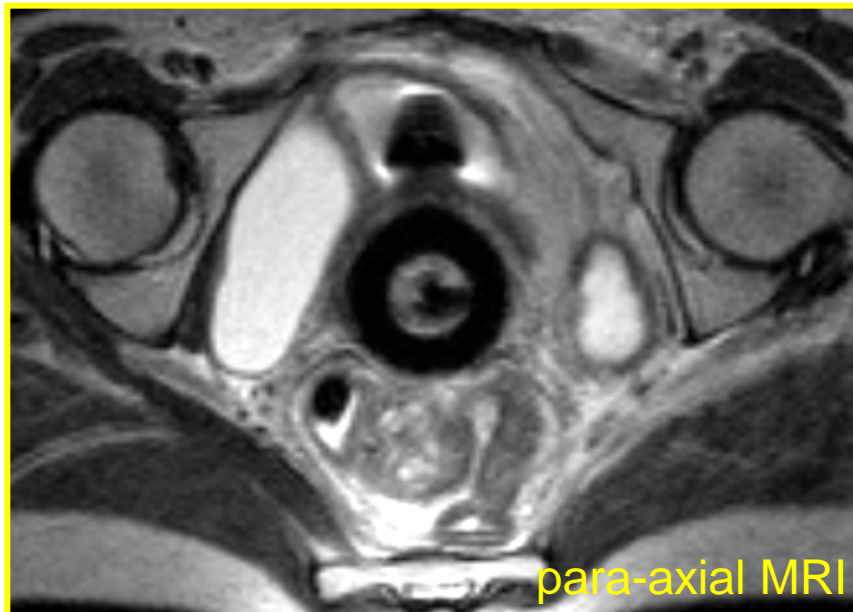
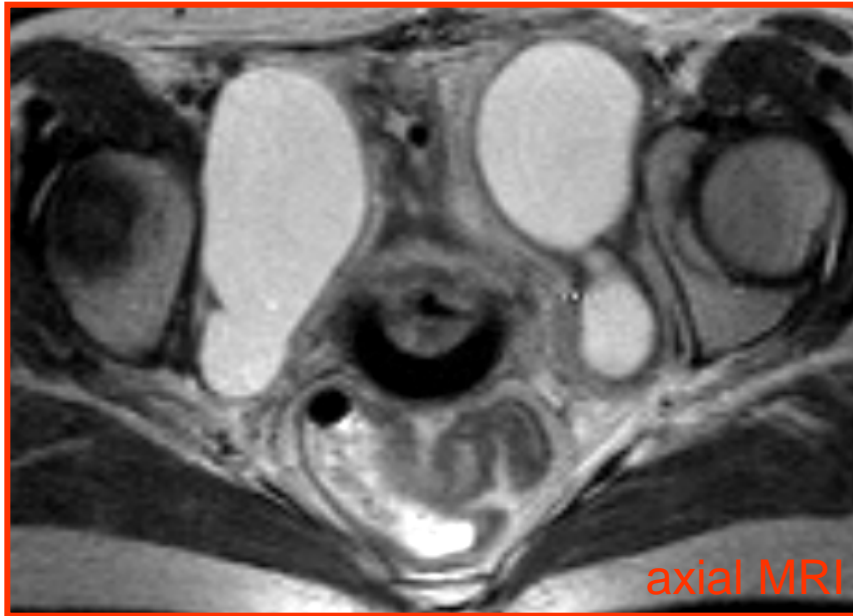


3. Reconstruction of source path



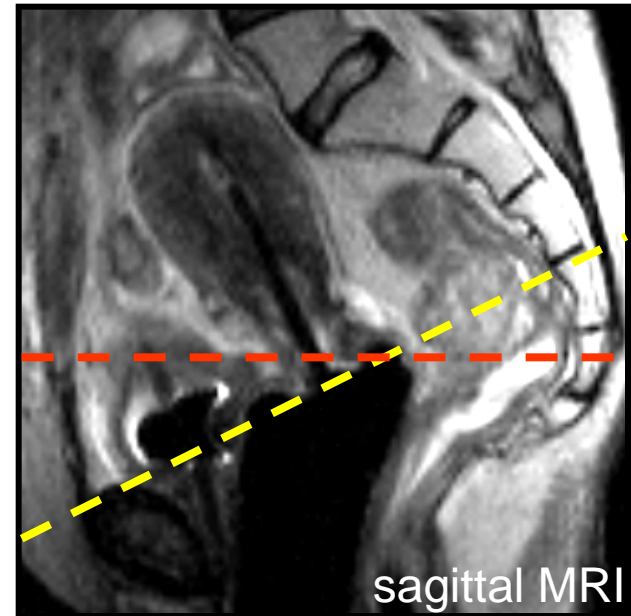
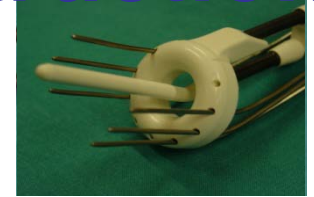
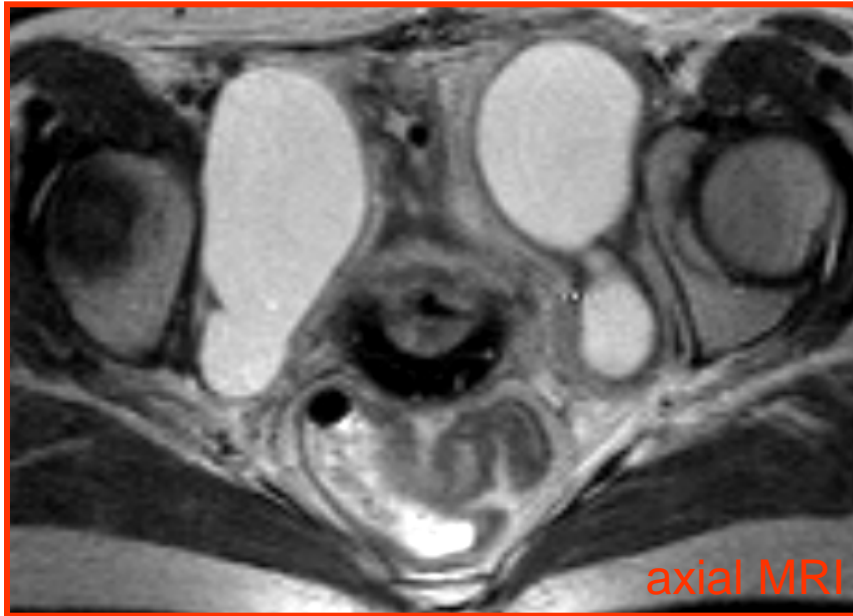
A. De Leeuw et al. Tandem- Ovoids applicator reconstruction on MRI

In-direct “source-path” reconstruction



Tandem Ring

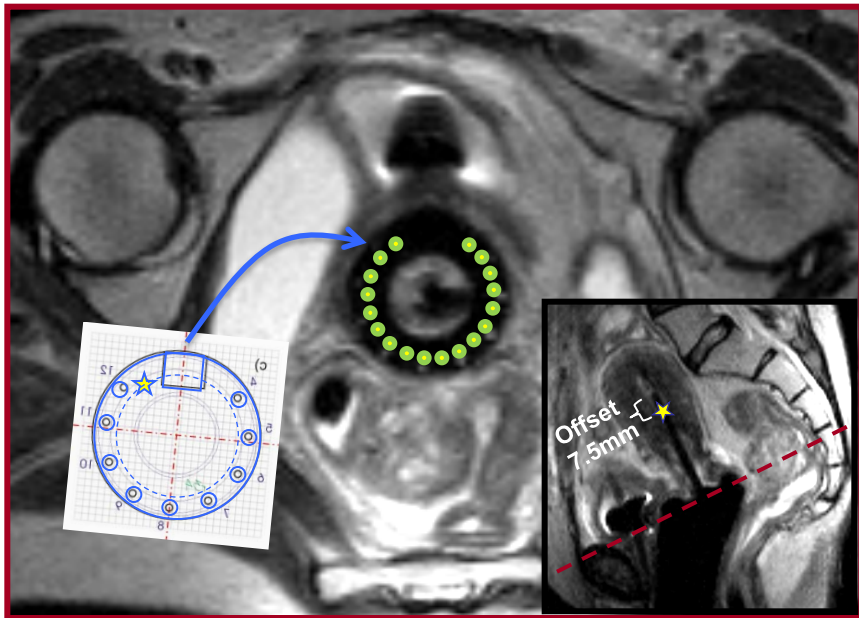
In-direct “source-path” reconstruction



Vienna Ring

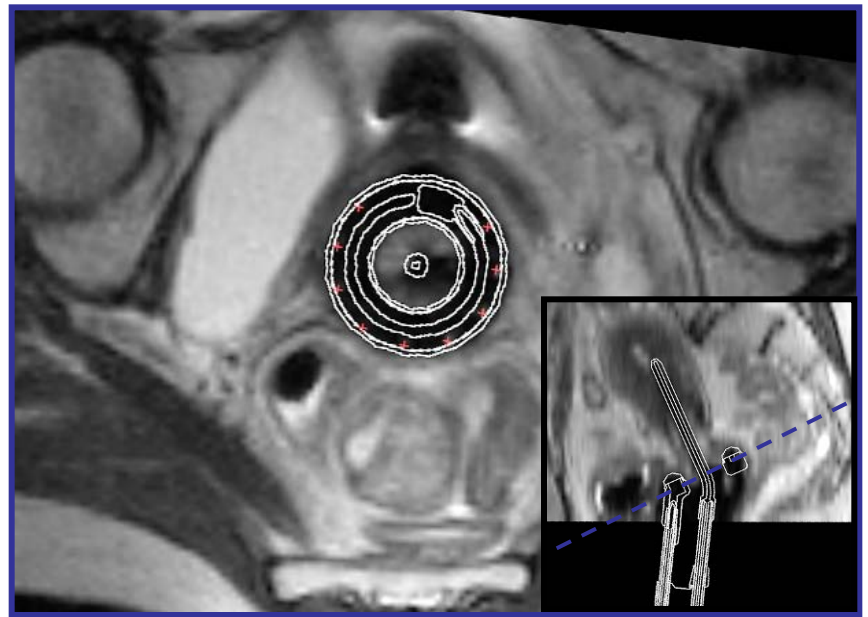
Applicator reconstruction in 3D

1. manual in-direct source path recon.



5 – 10 min

2. software integrated applicator recon.



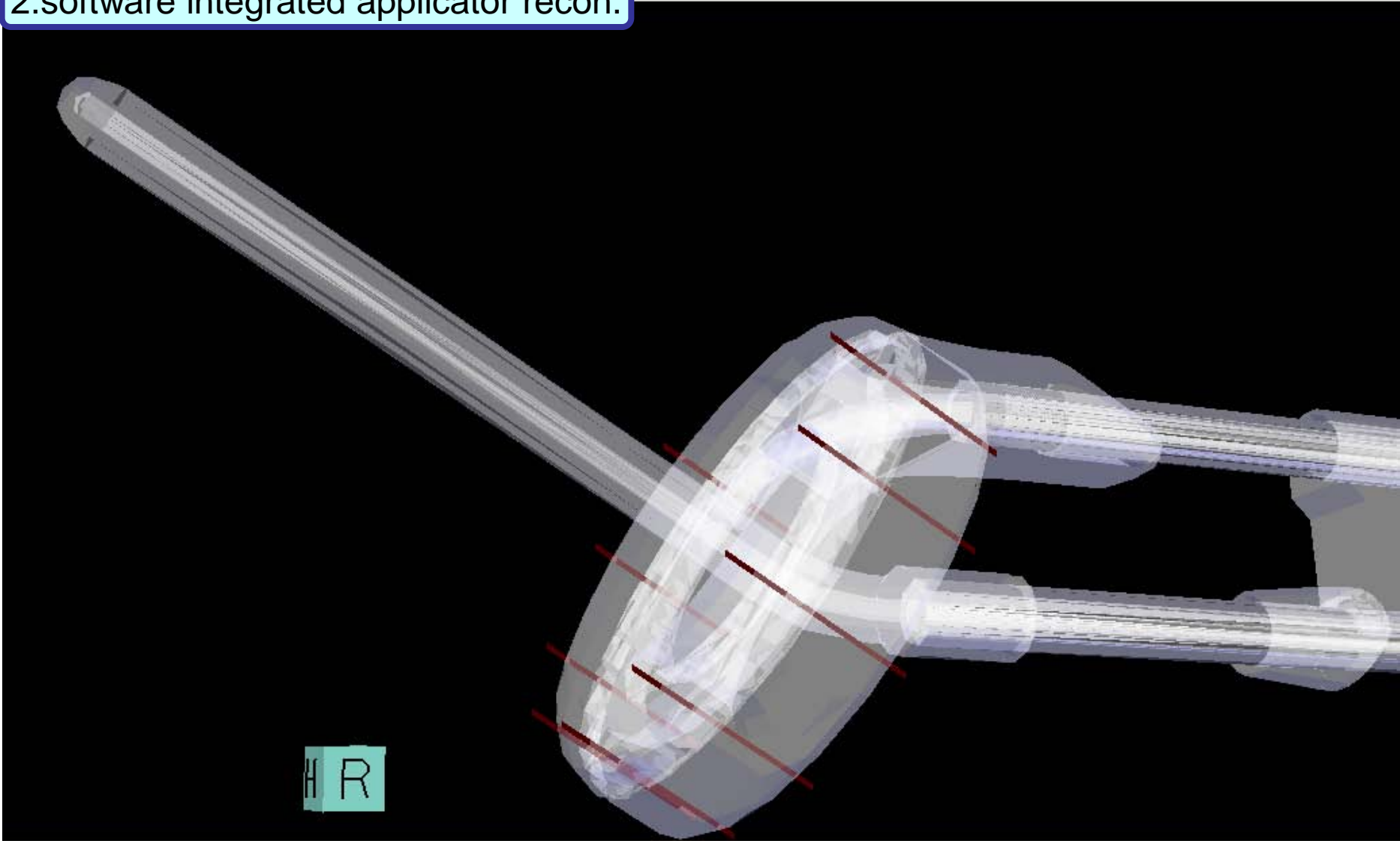
less than 5 min

If the relation between applicator shape and the source path is defined once, the reconstruction process can be performed by directly placing the applicator in the MRI dataset.

D. Berger *et al.* Direct reconstruction of the Vienna applicator on MR images

Applicator surface

2. software integrated applicator recon.



Source path

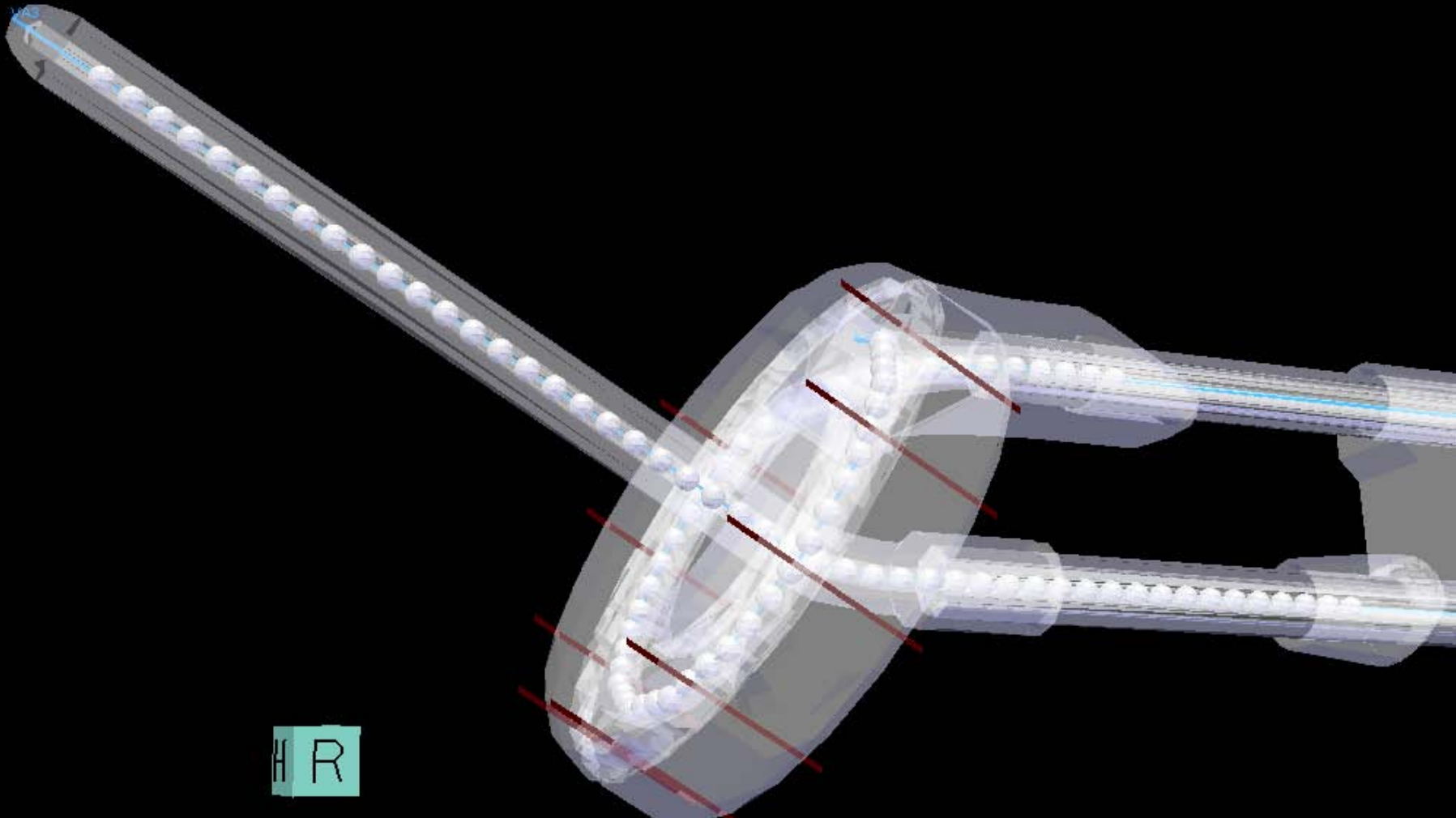
2. software integrated applicator recon.



H R

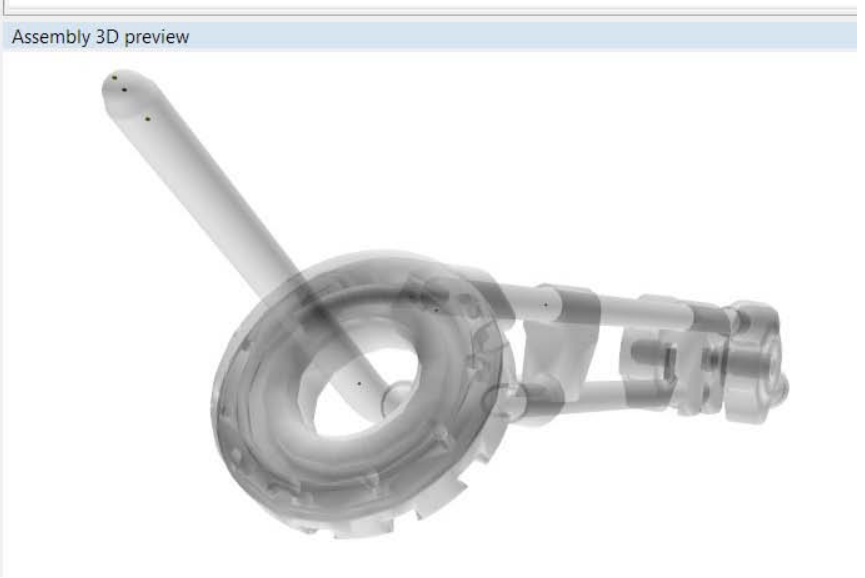
Applicator + Source path

2. software integrated applicator recon.



Predefined applicator geometry - library

Part name	Anchorpoint	Enable	Part set #	Applicator set
▶ R	Lumen tip	<input checked="" type="checkbox"/>	2011 17:33:47	110331-01
R	IU support	<input checked="" type="checkbox"/>		Interstitial Ring CT/MR
R	Center	<input checked="" type="checkbox"/>		
R	1st marker	<input checked="" type="checkbox"/>		
IU	Lumen tip	<input checked="" type="checkbox"/>		Ring CT/MR d=30mm, 60° (#110331-01)
IU	1st marker	<input checked="" type="checkbox"/>		n, 60°
IU	Tip	<input checked="" type="checkbox"/>		



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- Importance of Applicator Reconstruction
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Commissioning of Applicators

„The process in which the (clinically relevant) location of the dwell positions in relation to each other or in relation to reference points in the applicator are determined/verified and the transfer into the treatment planning system is checked”

- Characteristics of applicators

- Material (dosimetric influence, sterilisation)
- Dimensions
- Connectivity to afterloader (transfer tubes)
- Indexer length and off-set (distance of 1st or most distal dwell position to tip-end)

- Visibility of applicator in sectional imaging

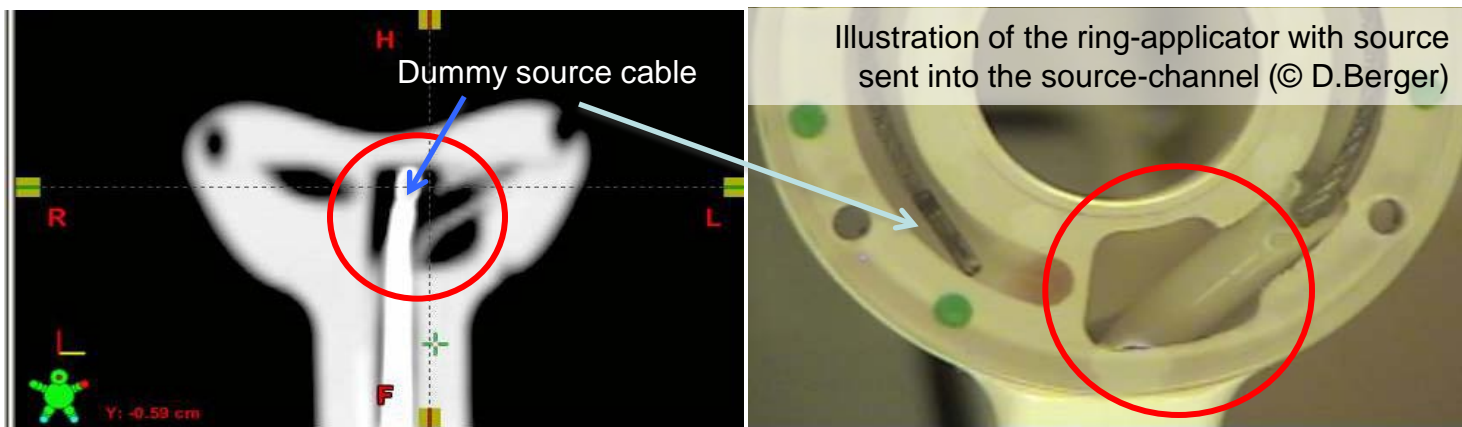
- Distortion of dimensions
- Artefacts (appearance of applicator tip-end: E.g. needle tip-end)

- Verification of the source-path

- Predefined (from vendor provided) source-path stored in Applicator library
- Direct reconstructed by the user following direct or in-direct reconstruction methods

Applicator material!

The sterilization procedure (high temperatures) and a frequent use may damage the applicator material and applicator accessories (E.g. screws)

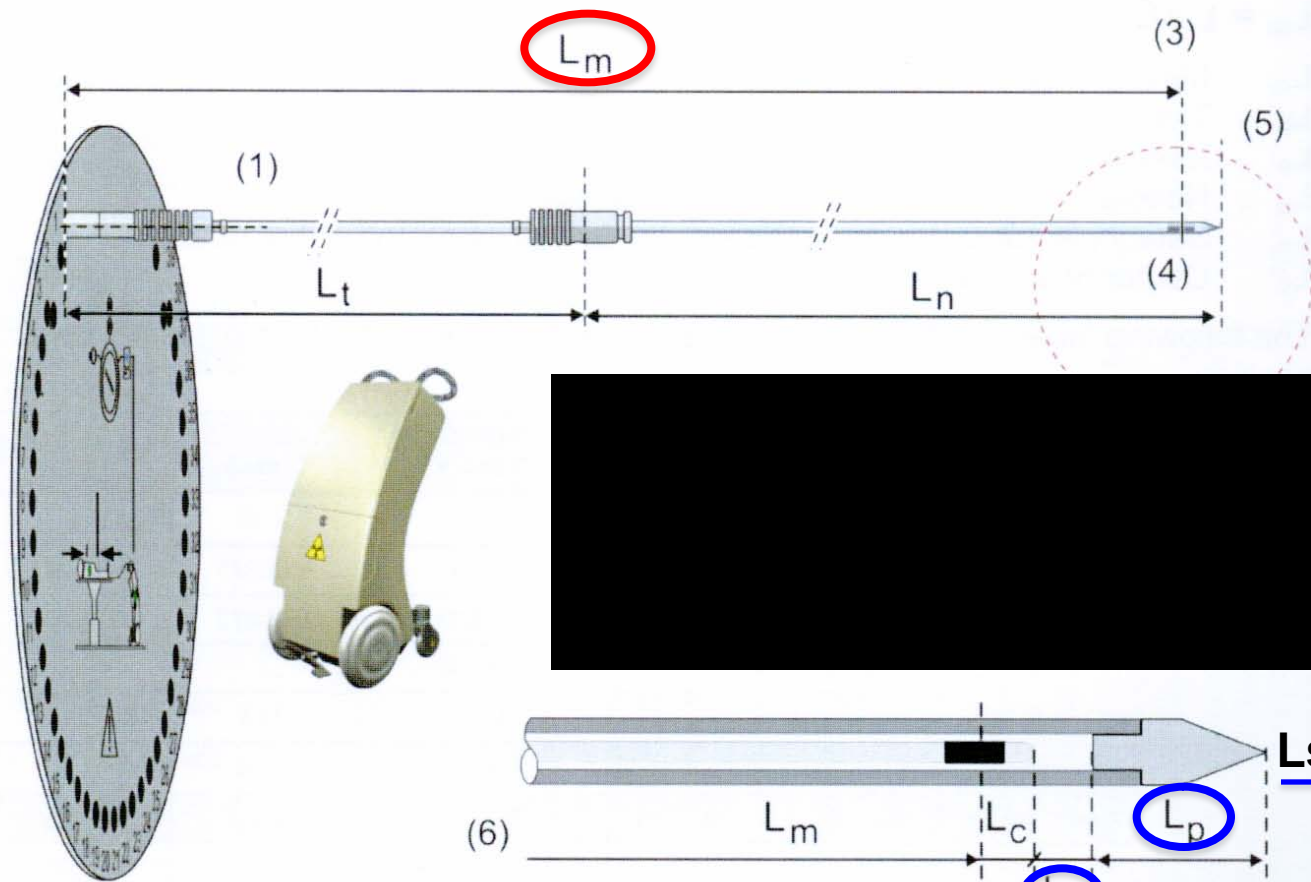


CT imaging of a damaged ring applicator provided by U. Mahanshetty

Therefore the visual inspection of applicators before clinical use is mandatory and needs to be included in the quality control procedure.

Indexer Length and Off-set

20. Flexitron; Distance to Most Distal Dwell Position \longrightarrow Indexer length



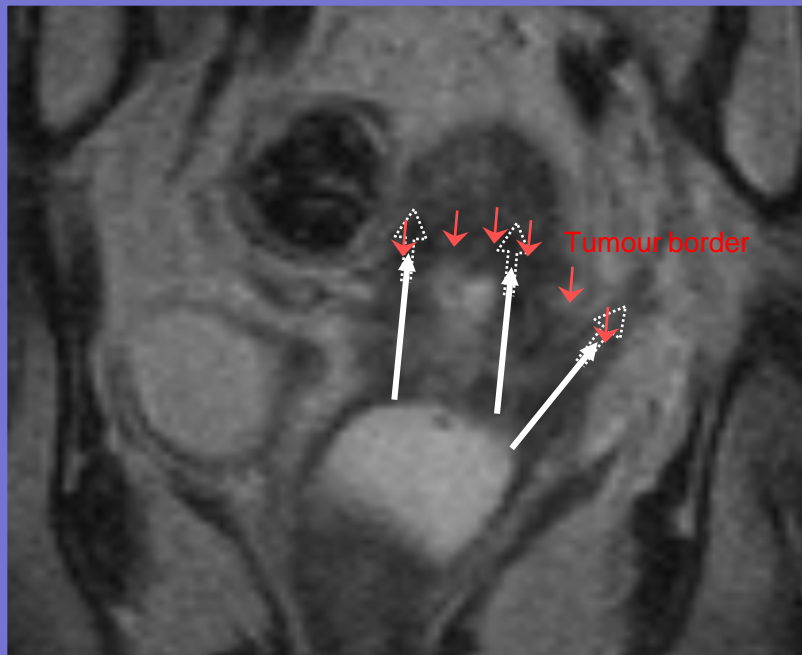
(1) Channel selector

(3) Centre of source

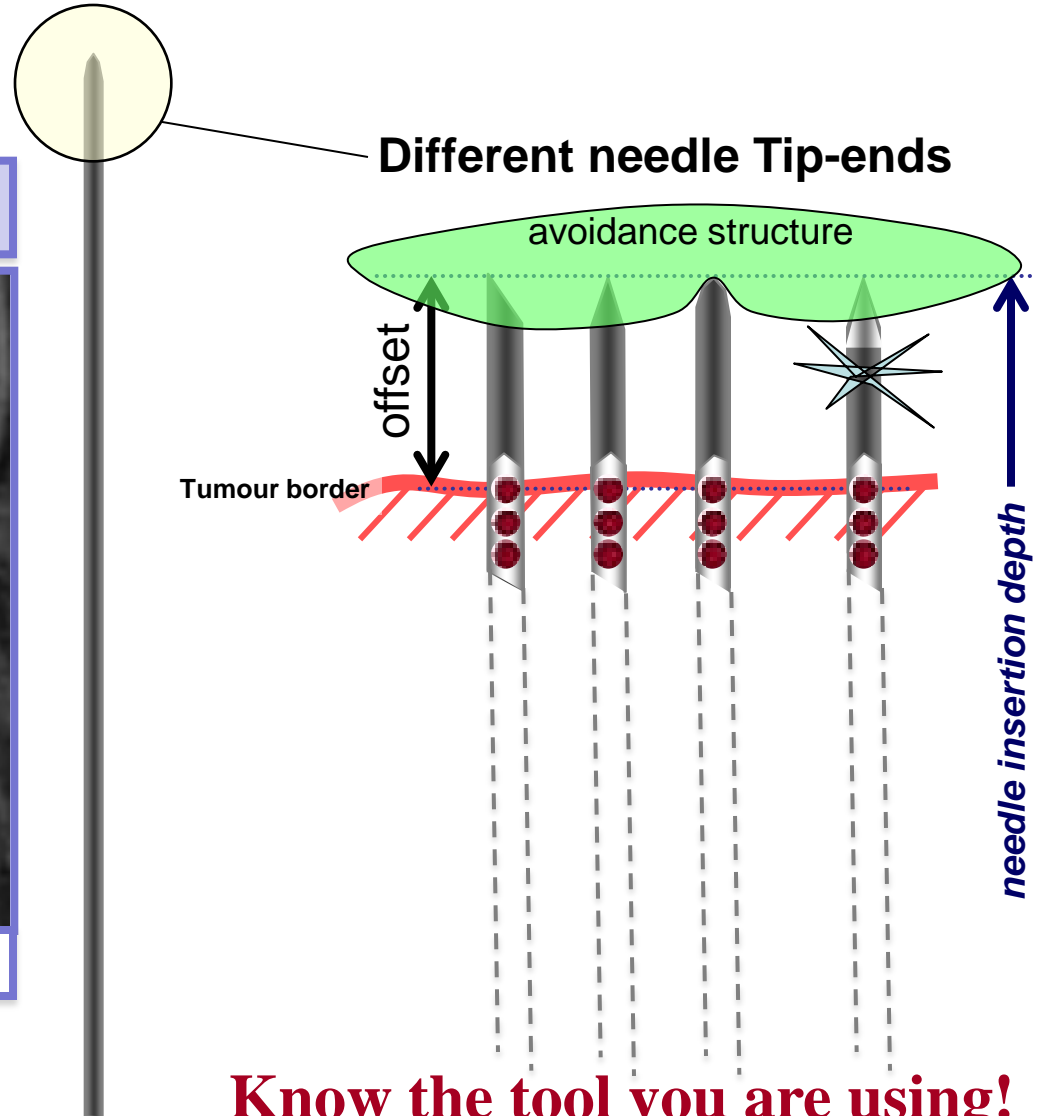
(5) See Detail A

Off-set will effect the insertion depth

Pre-planning of needle insertion




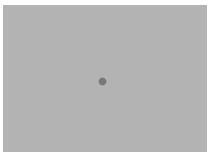




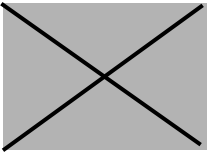
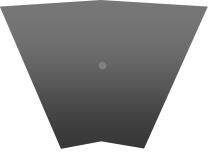
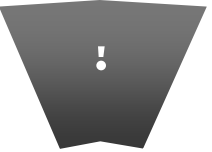



cor. MRI after 45Gy EBRT

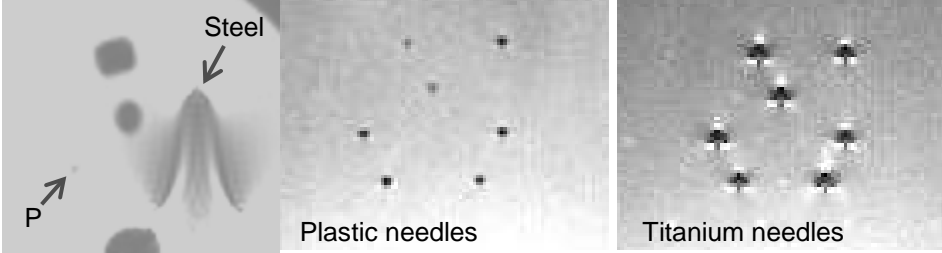


Visibility of applicator in sectional imaging

Visibility !!!

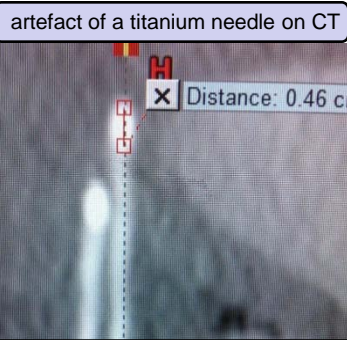
Material		
Plastic	Titanium	Steel
		
flexible	rigid	rigid
		
field strength (0.2T, 1.5T, 3T)		
		
		

Different materials scanned in 0.2 T open MRI



Steel
P
Plastic needles
Titanium needles

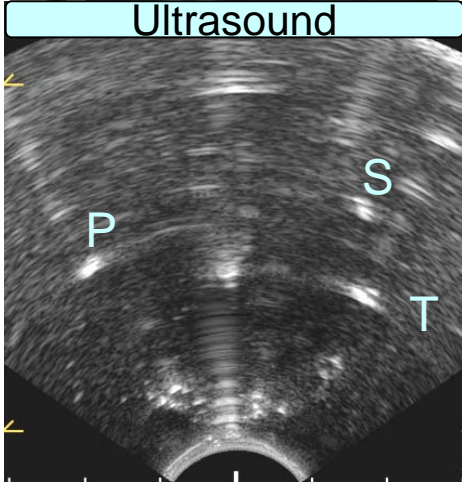
artefact of a titanium needle on CT



H
Distance: 0.46 cm

CT

Ultrasound

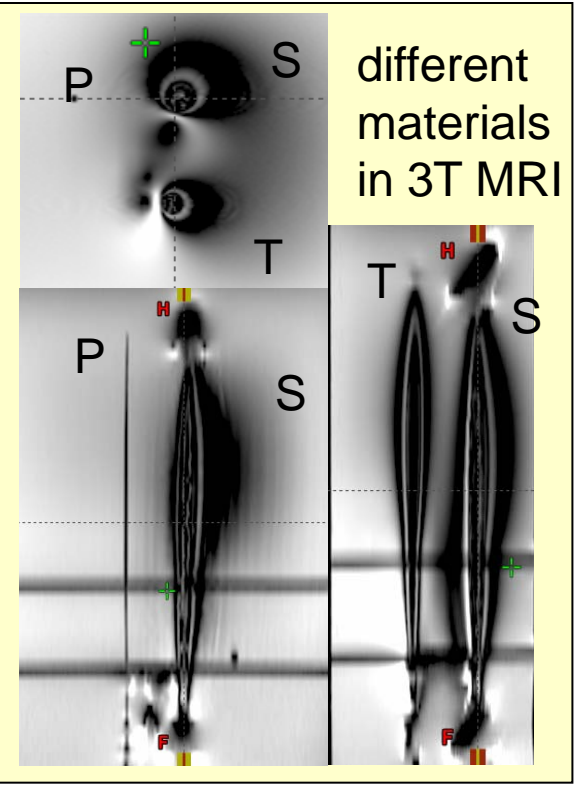


P S
T

MRI

US

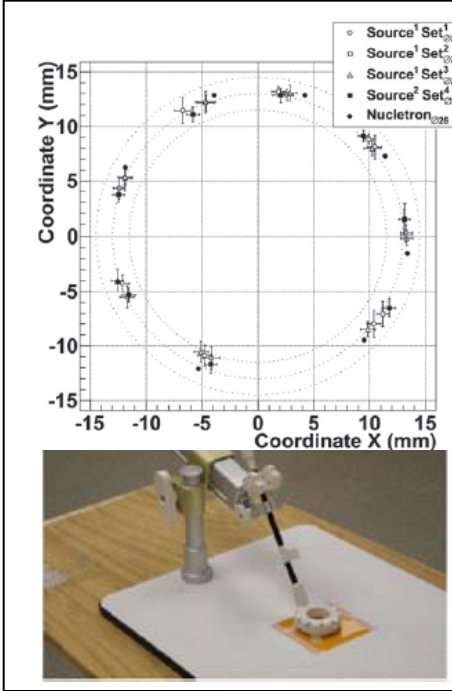
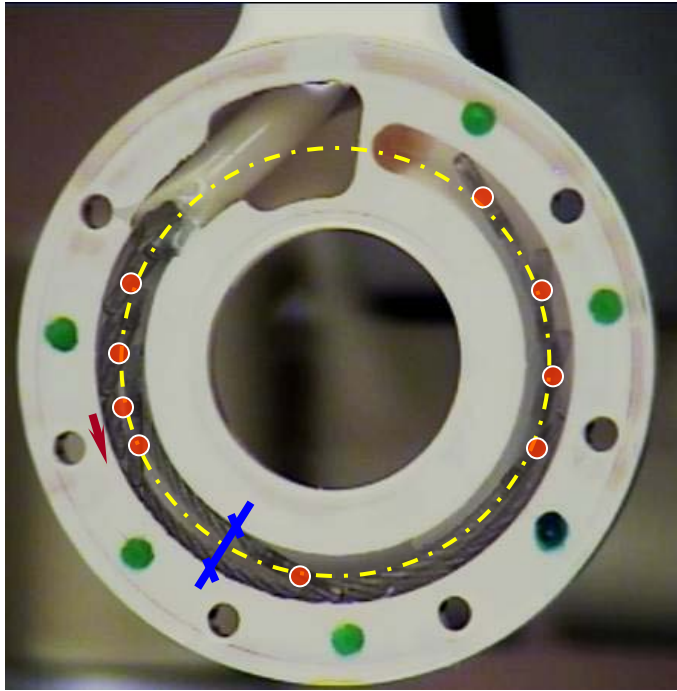
different materials in 3T MRI



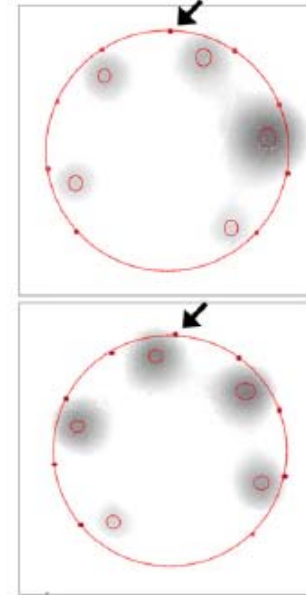
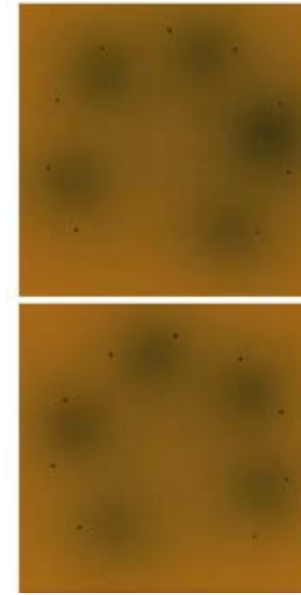
P S
T
H
S
P S
T H S
F F

Know the tool you are using!

Verify the source path using Auto-radiography



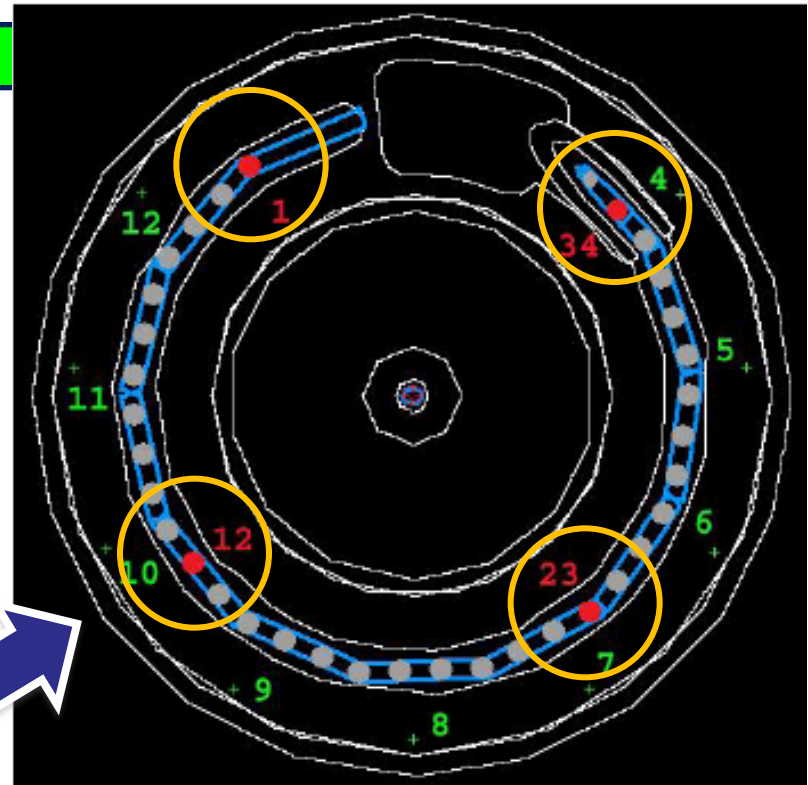
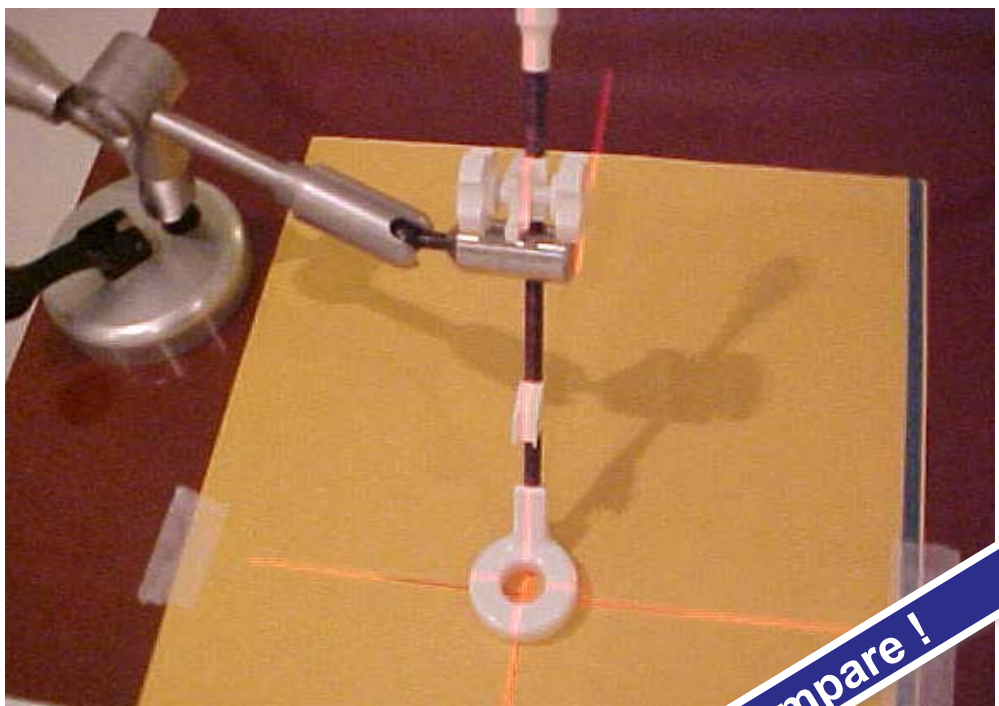
Awunor et al. 2013 PMB



The total expanded measurement uncertainty averaged over all dwell positions was observed to be 1.1 ± 0.1 mm ($\varnothing 26$ and $\varnothing 30$ mm) and 1.0 ± 0.3 mm ($\varnothing 34$ mm)

- 1) Real step-size in ring dwell positions varies depending on the location
- 2) A dummy wire dose not represent the real source path

Verification of the source-path



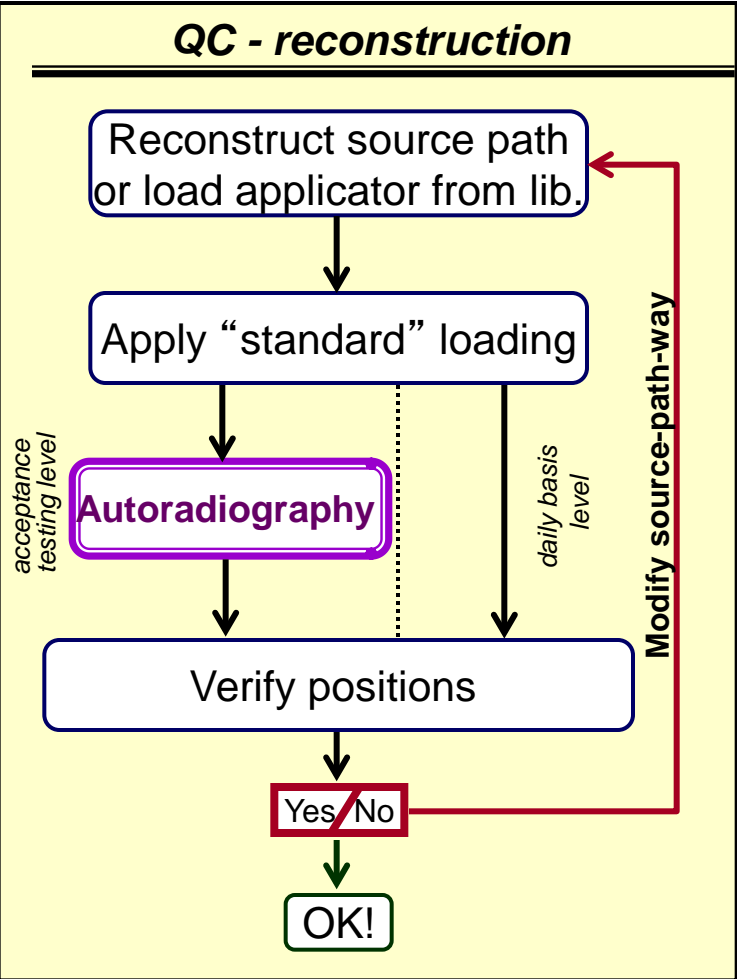
Compare !

Do acceptance tests and check

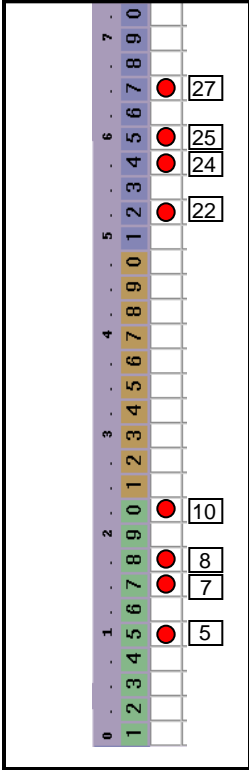


Quality Control in applicator reconstruction

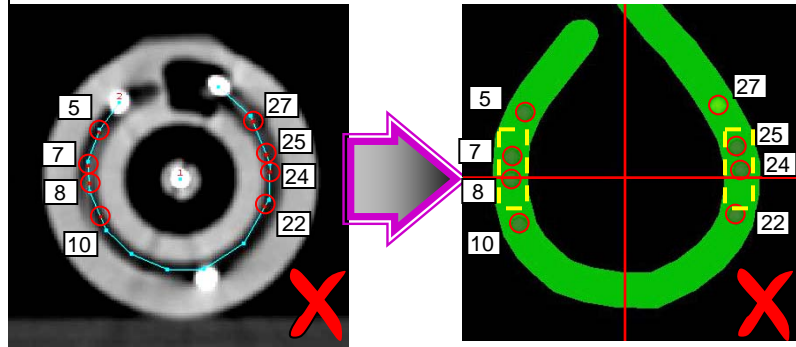
QC - reconstruction



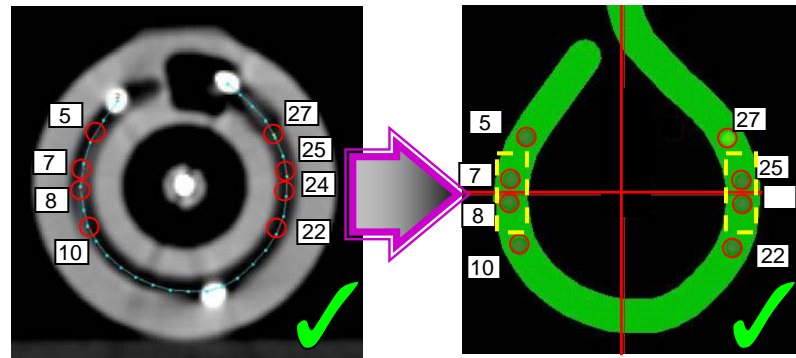
standard loading pattern



wrong source path reconstruction



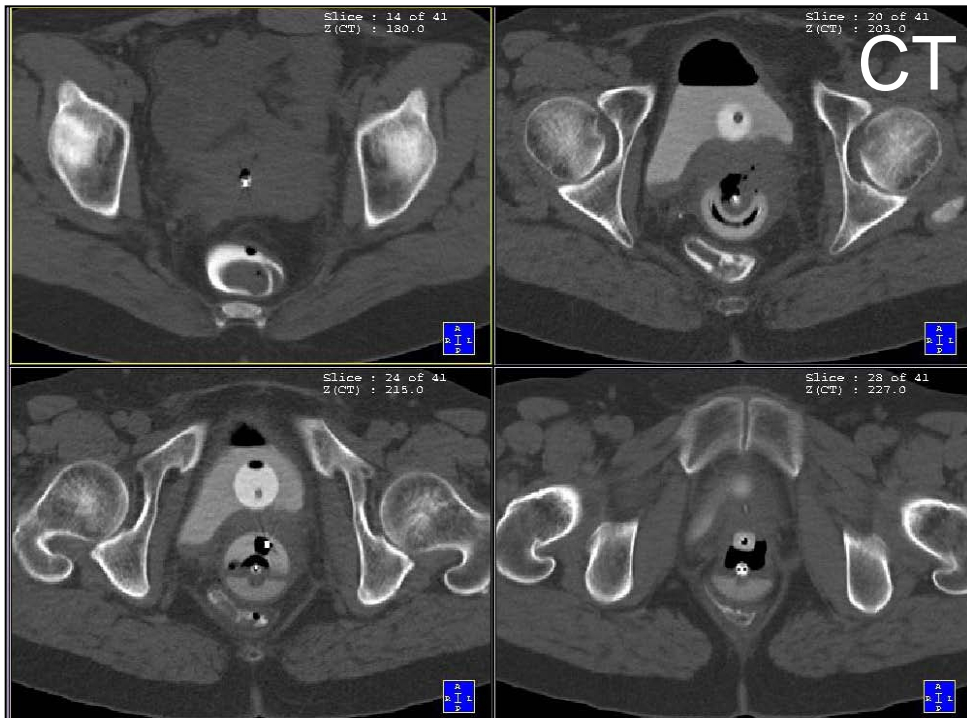
correct source path reconstruction



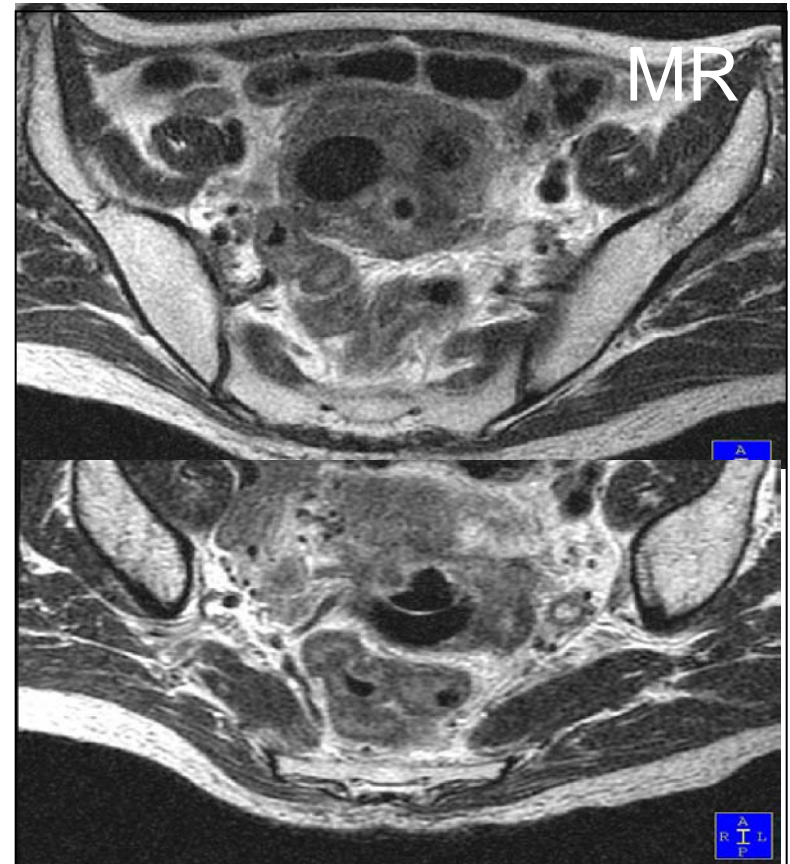
Presentation overview

- Importance of Applicator Reconstruction
- Direct Reconstruction (of the source-path)
- In-Direct Reconstruction (Applicator)
- Commissioning of Applicator and QA of the Reconstruction Process
- Fusion / Registration

Fusion / Registration



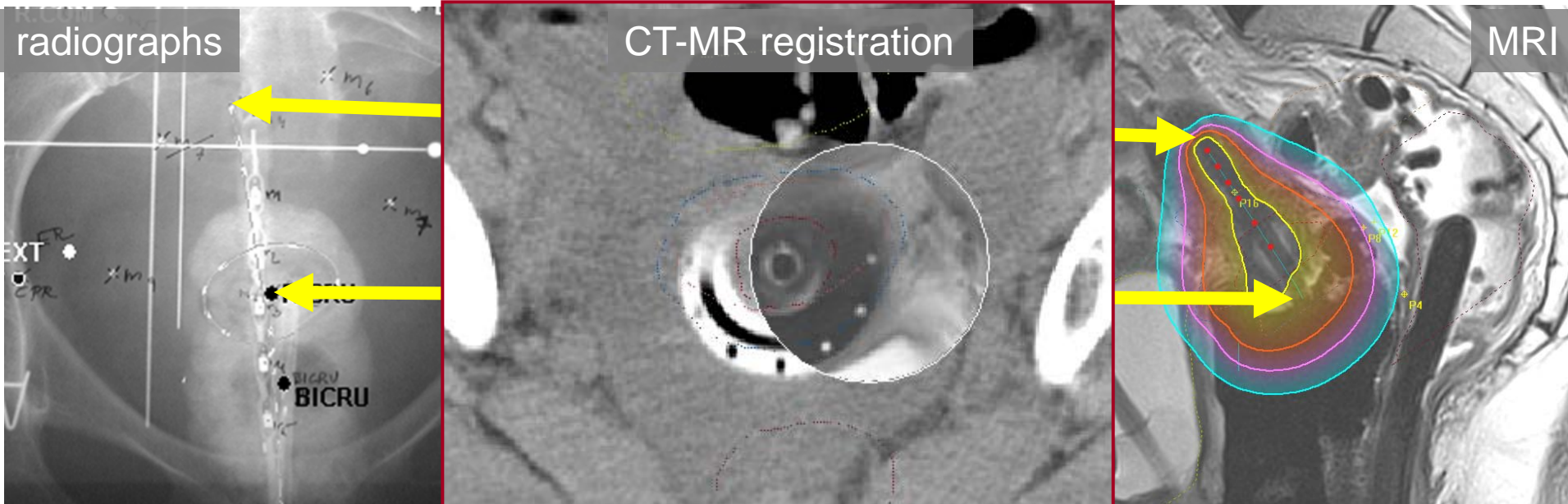
Reconstruction



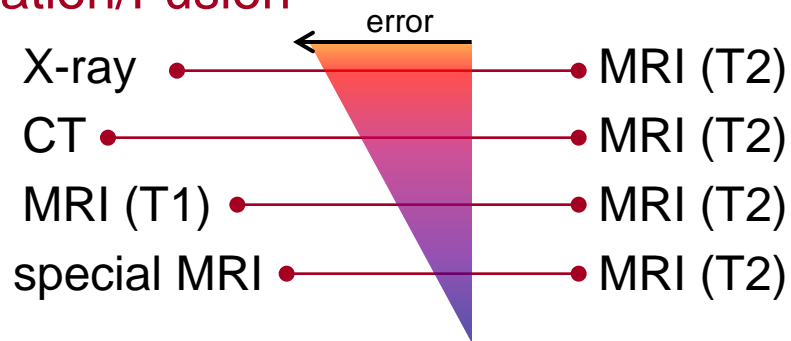
Delineation

Applicator- Reconstruction

Registration/Fusion or Direct Reconstruction



Registration/Fusion



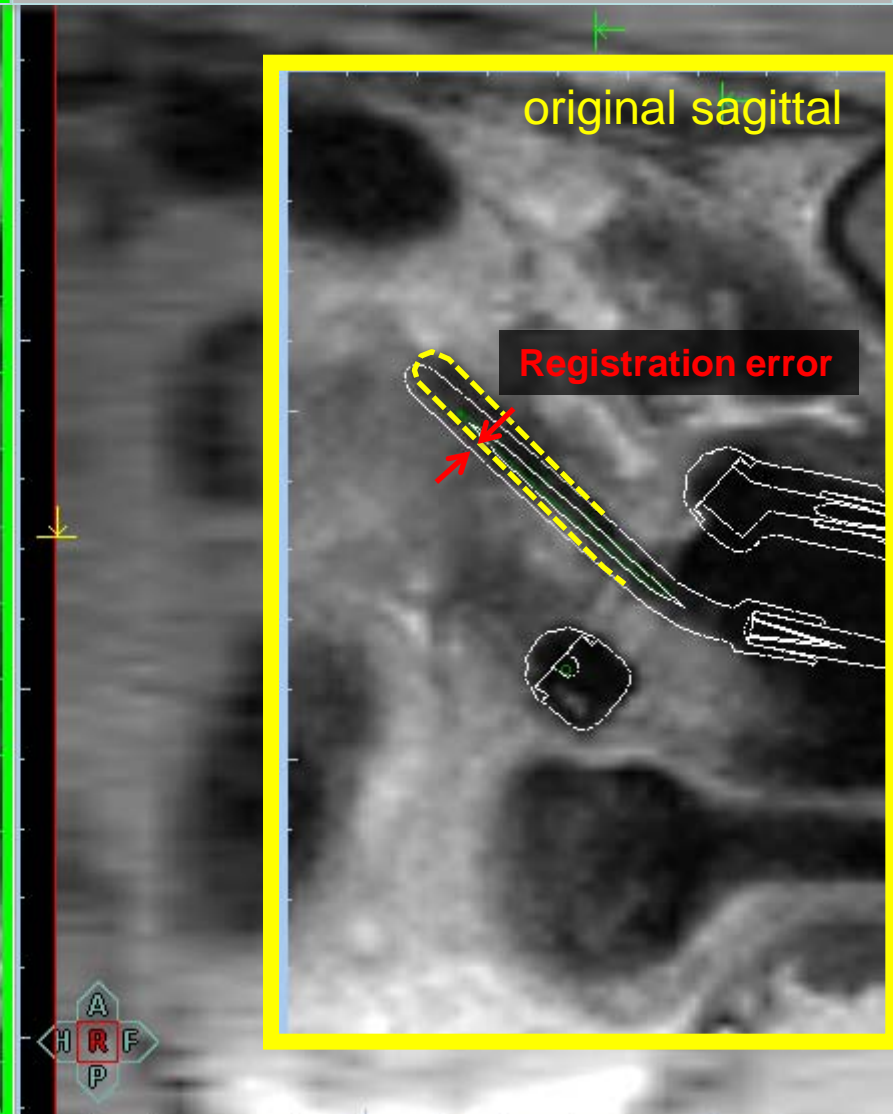
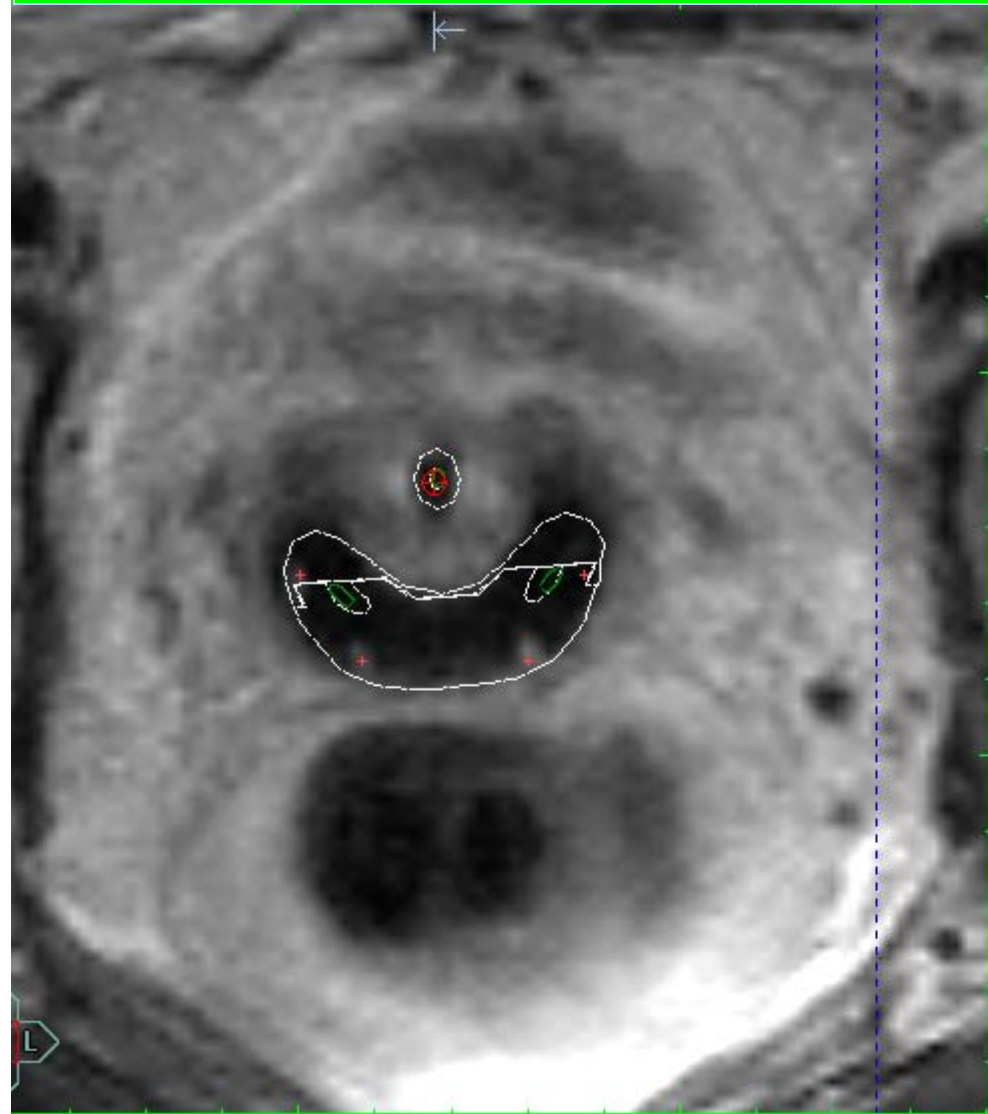
Minimized or No Registration Error
when using “direct”
MRI_(T2) applicator reconstruction

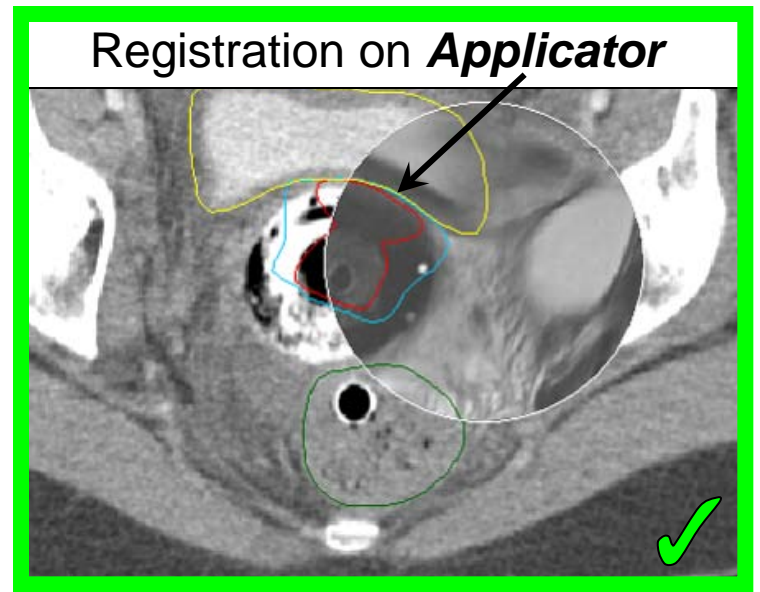
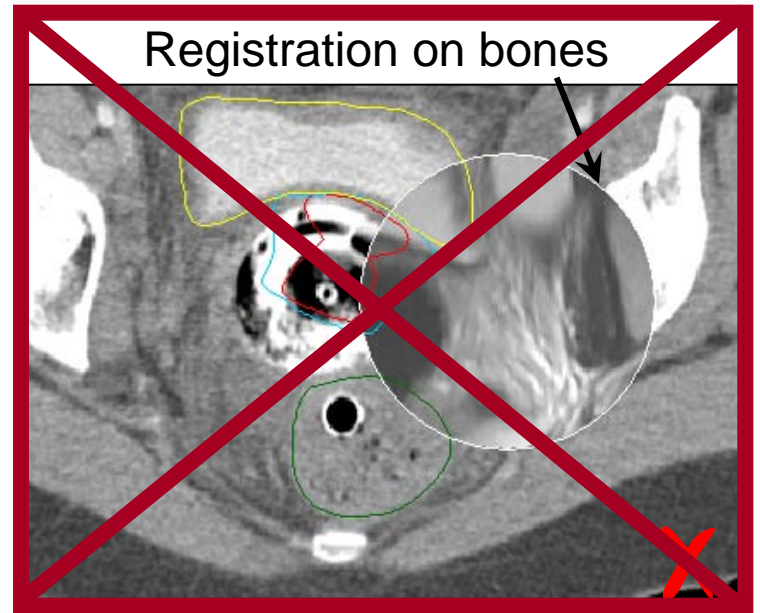
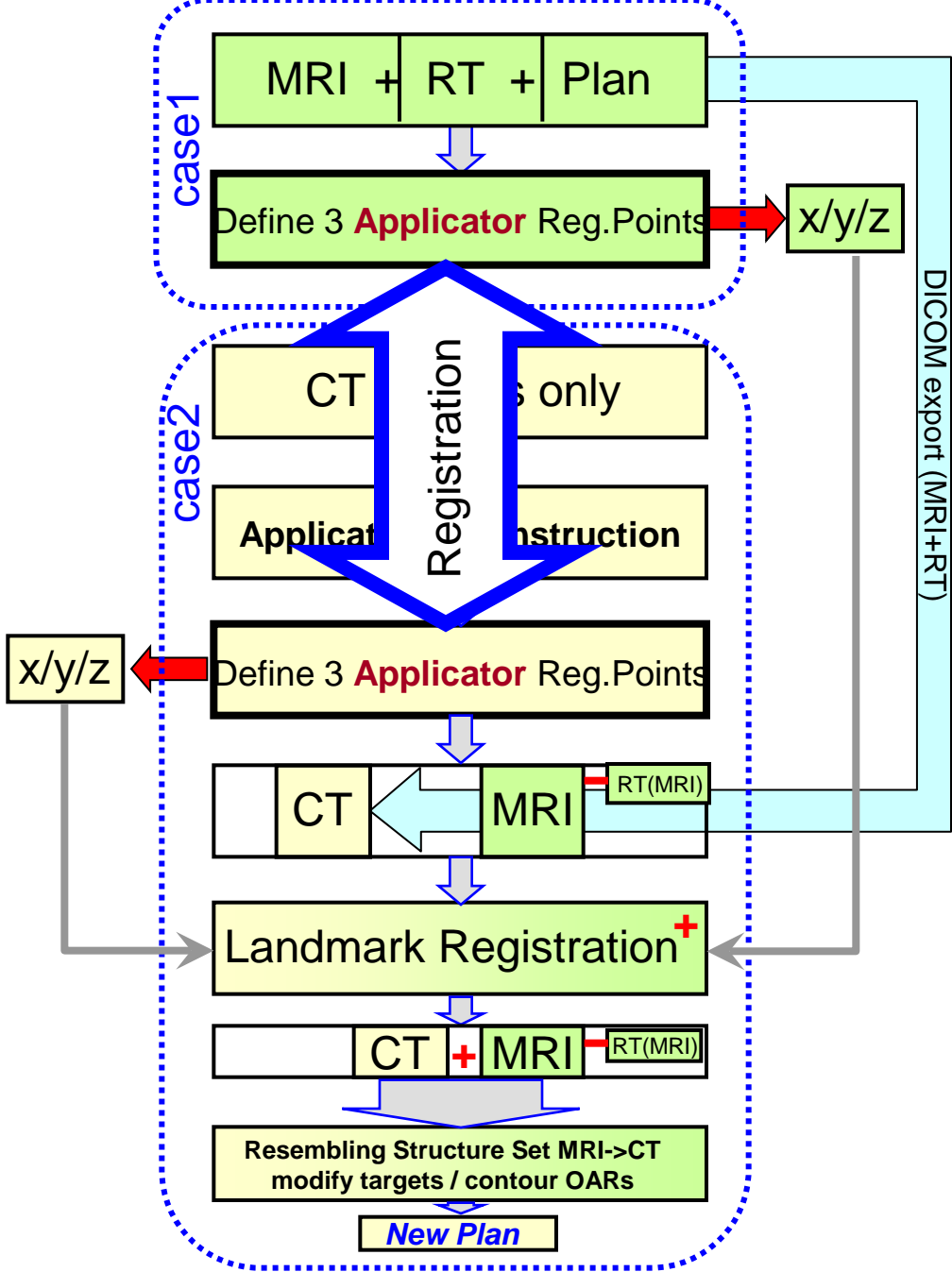
If you register different images (CT-MRI)
use “applicator based” registration

Image registration between MRIs (using DICOM coordinates)

Axial MRI

„reconstructed“ sagittal





**YOU DON'T HAVE TO BE
CRAZY TO WORK HERE...
WE'LL TRAIN YOU**



PRACTICAL EXAMPLE

TATA-2 (AD)

Large tumour, Good Response to EBRT

LARGE TUMOUR, PARTIAL RESPONSE

Overview

- Initial findings
 - Initial clinical findings
 - Initial MRI findings
 - Other
- EBRT, chemotherapy
- Findings at BRACHYTHERAPY (BT)
 - Clinical findings at BT
 - MRI findings at BT
- Delineation of GTV, CTV and Organs At Risk (OAR)

LARGE TUMOUR, PARTIAL RESPONSE

Initial findings

Patient & Tumour

Patient:

36 years old

Tumour:

Histological type: SCC

FIGO Stage: 3b

Initial clinical findings:

Portio:

Large endophytic growth

Vagina: Not involved

Fornices: Not involved

Parametria:

Right: Upto LPW

Left: Medially 1/3rd involved

Cystoscopy: Normal

CT scan Abdomen & Pelvis:

Irregular heterogeneous enhancing cervical mass. Lesion inseparable from posterior wall of bladder and anterior rectum wall. No pelvic or para-aortic lymphadenopathy. Kidneys are normal.

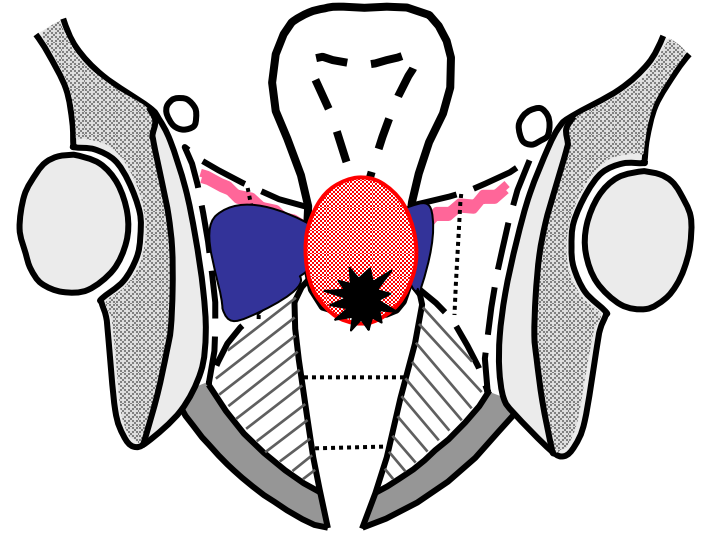
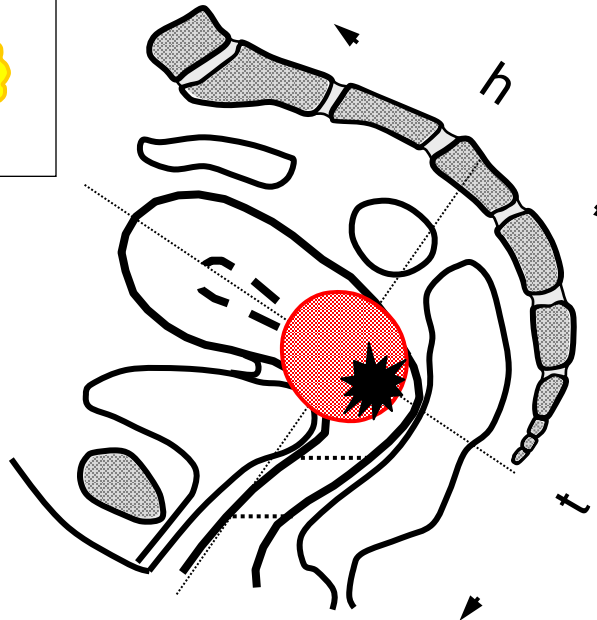
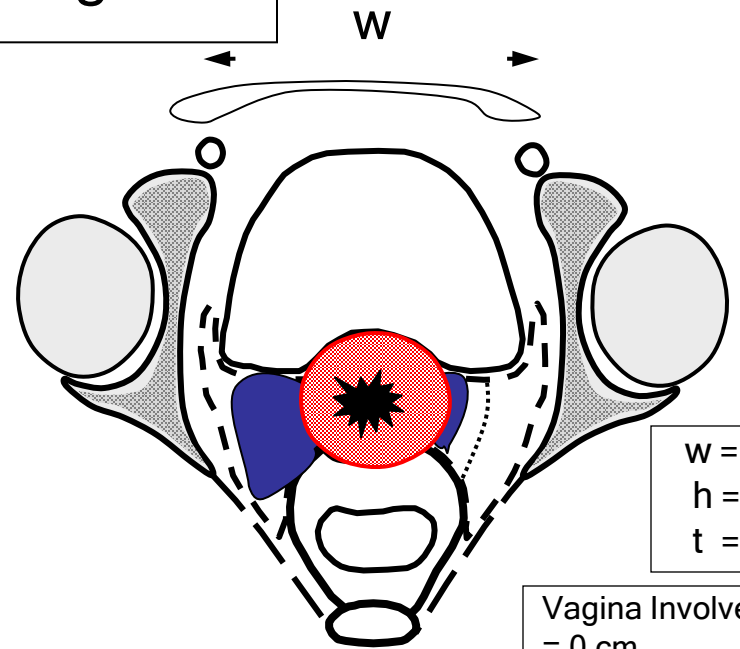
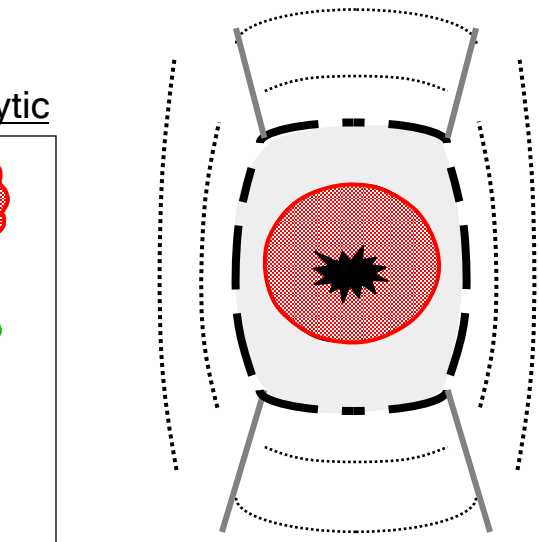
MRI Pelvis: Details

Patient ID: TATA-2 (AD)

Clinical Drawing

At Diagnosis

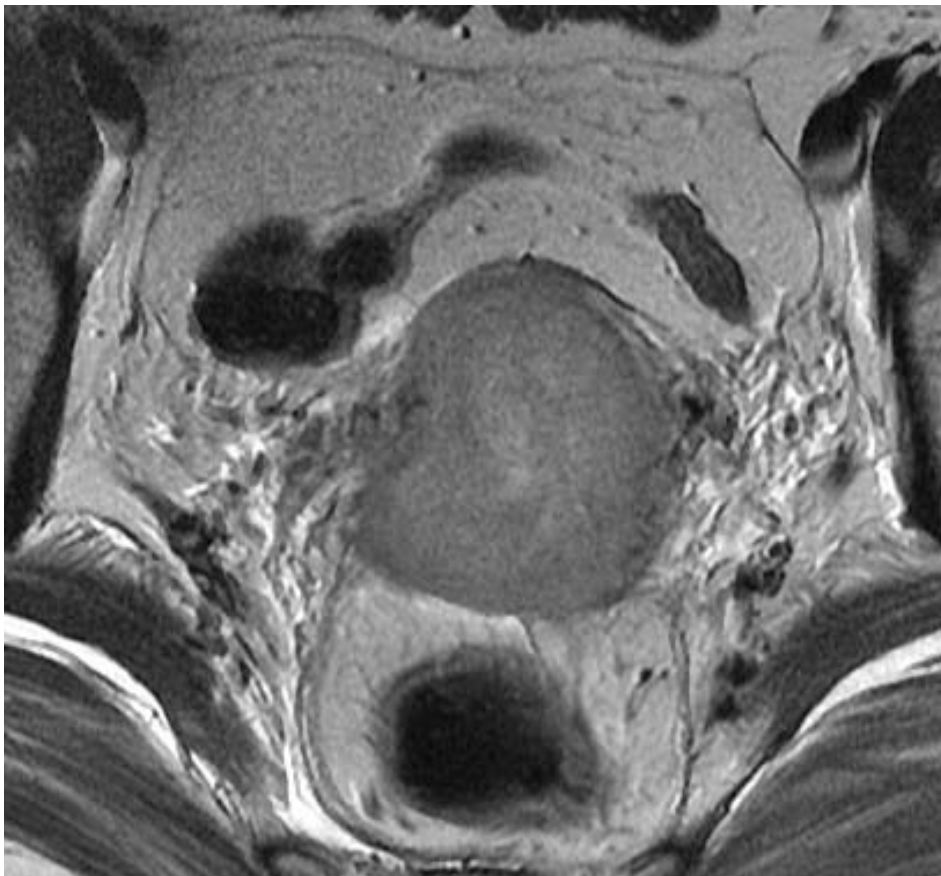
	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		



dd/mm/yy
25.04.2013

umesh
Signature

Initial



EBRT CONTOURING

- **GTV : Gross Tumor Volume**

- GTV-P: GTV at primary
- GTV-N: GTV at nodes

- **CTV : Clinical Target Volume**

- CTV-P: CTV at primary (GTV-P + bilateral parametrium upto lateral pelvic wall + Uterus + Vagina)
- CTV-N: CTV at nodes
- CTV Pelvis (CTV-P + CTV-N)

- **PTV : CTV + Margins**

Instructions to the participant:

Subsequent Slides are to assist MR Image Based Brachytherapy Contouring

LARGE TUMOUR, PARTIAL RESPONSE

EBRT, Chemotherapy

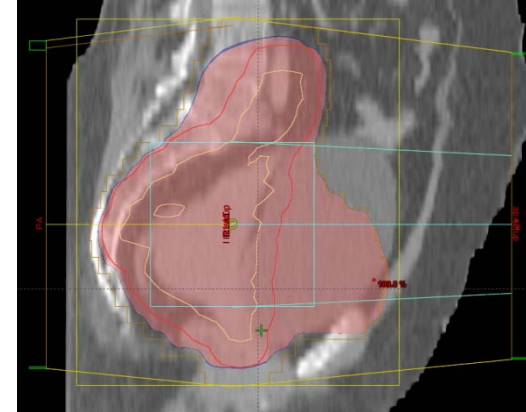
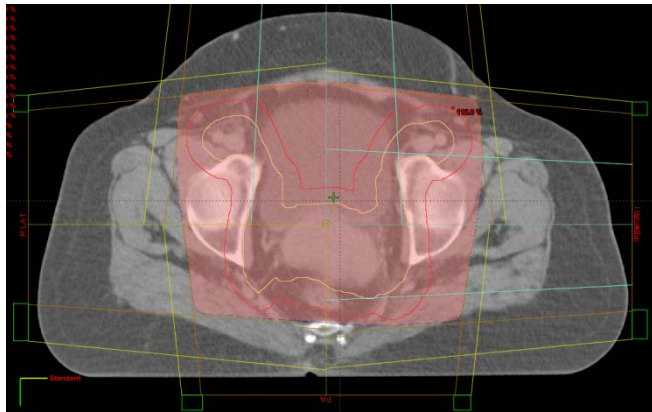
EBRT & Chemotherapy

EBRT Technique: 3D, CT based CRT; box technique

TD: 45 Gy

Dose per fraction: 1,8 Gy

Boost: no



Concomitant chemotherapy: Cisplatin 40 mg/m² weekly, 5 cycles

LARGE TUMOUR, PARTIAL RESPONSE

Findings at brachytherapy
(immediately following EBRT)

Clinical findings at BT

Portio:

Residual Disease at cervix (anterior lip more than post lip)

Vagina:

Not involved

Parametria:

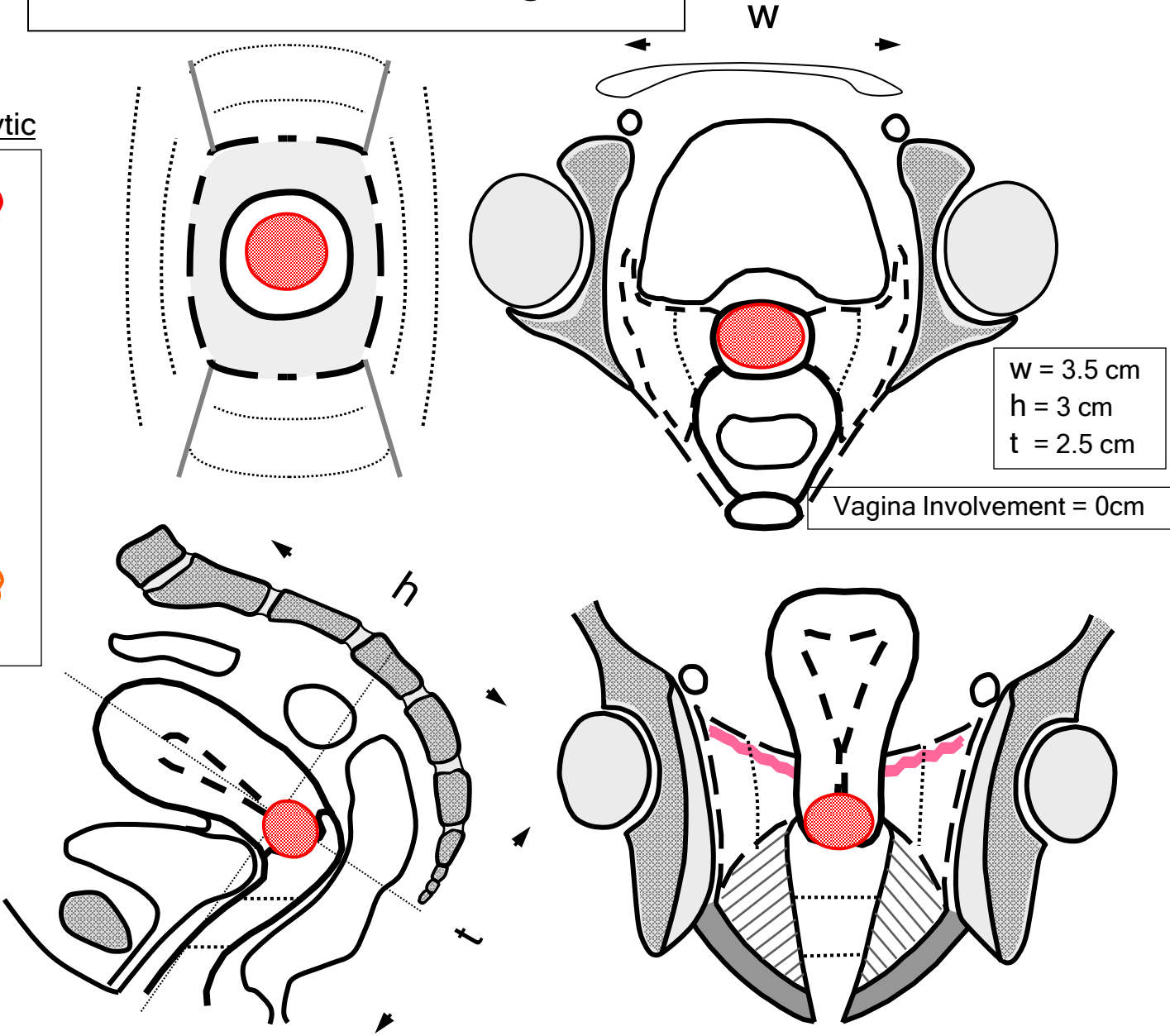
Rt para supple

Lt para Supple

Clinical Drawing

At 2nd Brachytherapy

	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		



dd/mm/yy
19.06.2013

umesh
Signature

Insertion & imaging

Anaesthesia: General

Application:

Intracavitary component:

Tandem length: 60 mm

Tandem angle: 45°

Ring diameter: 30 mm

Material: plastic

Comments: Water-filled plastic tube
inside ring & tandem.

Interstitial component:

N° of needles: 0

Insertion depth:

Material:

Vaginal packing:

Gauze impregnated with gadolinium

Imaging:

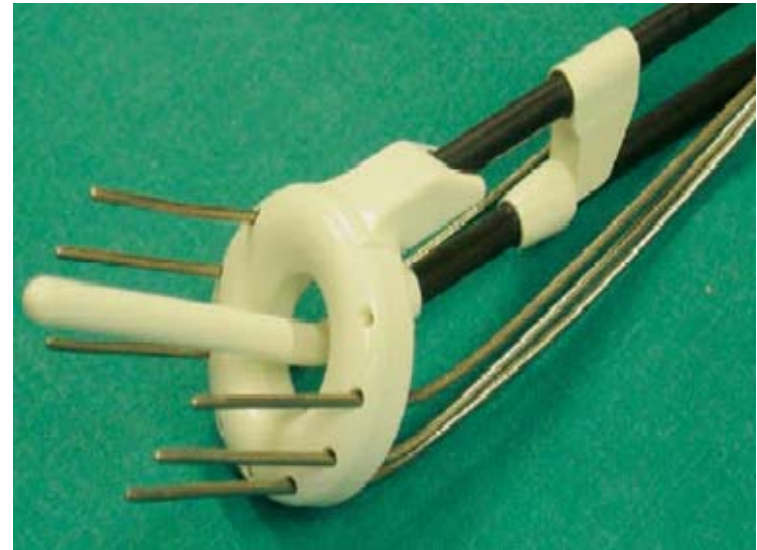
MRI field strength: 1.5 T

MRI configuration: closed

Sequence(s): T2-weighted

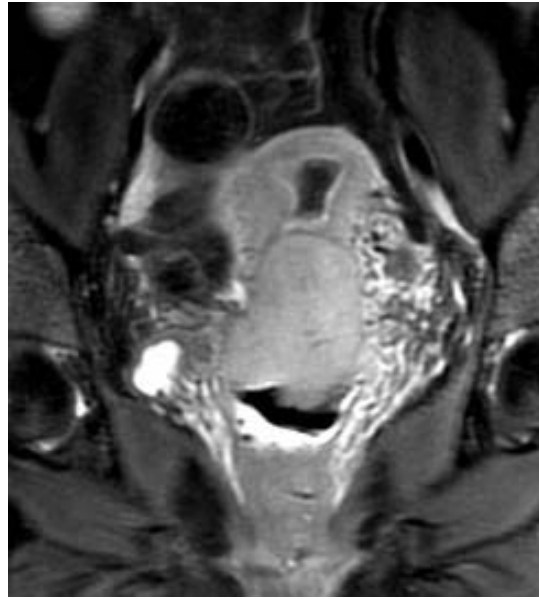
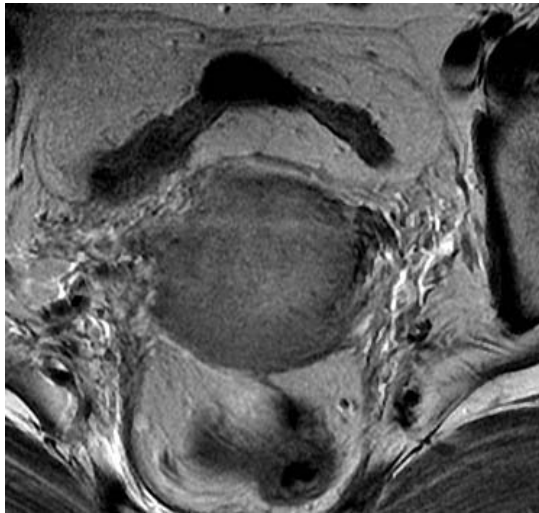
Imaging planes: transverse, sagittal, coronal

Comments regarding protocol: No contrast; Foley catheter open & empty preferable

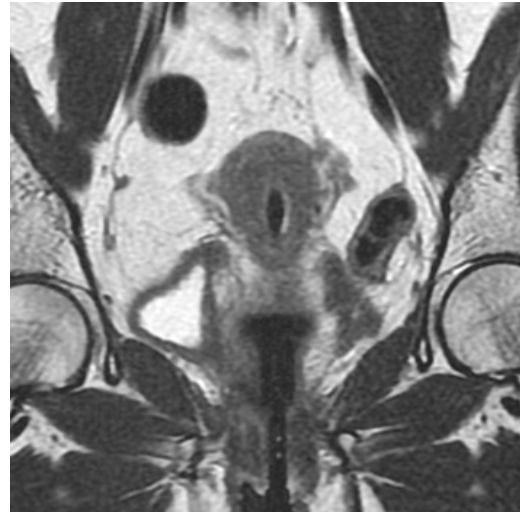
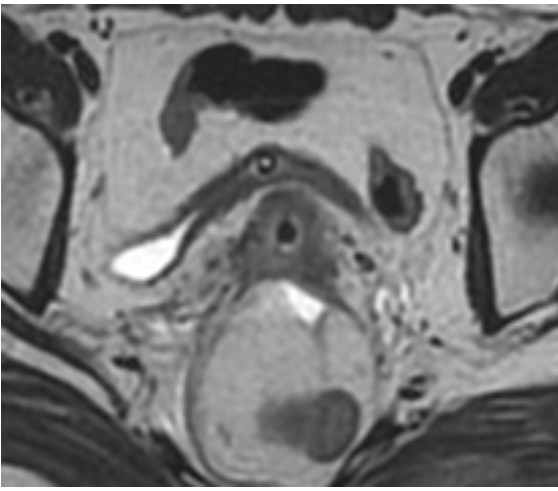
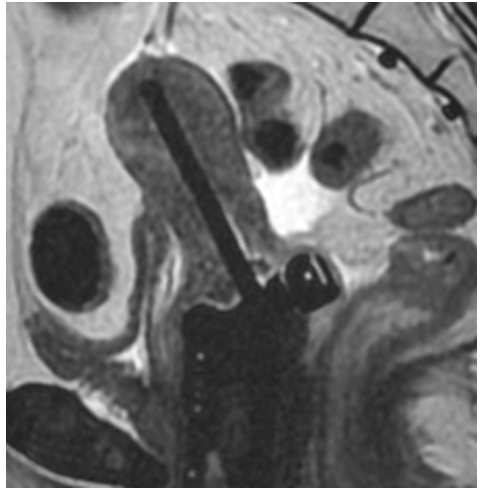


Patient ID: TATA-2 (AD)

Pre Rx



Post Rx



Workshop Instruction

Case: GYN course : TATA2-BT_MRI

TARGET: GTV-B, HR-CTV & IR-CTV

OAR: Rectum, Bladder & Sigmoid (Optional)

SAVE the contours periodically

SUBMIT only after completion of contouring

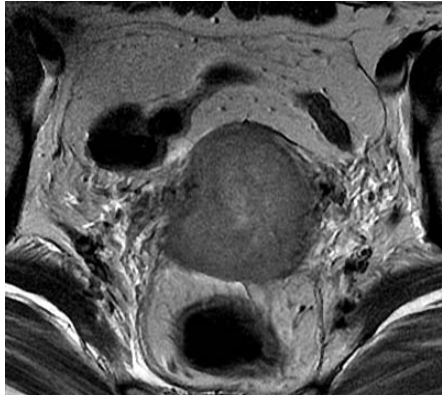
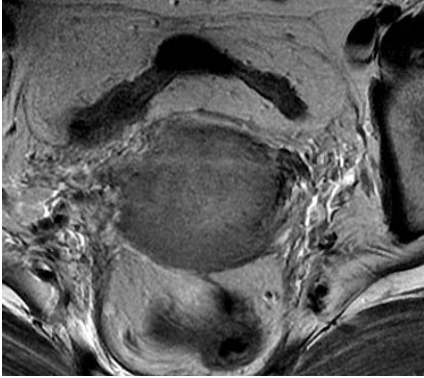
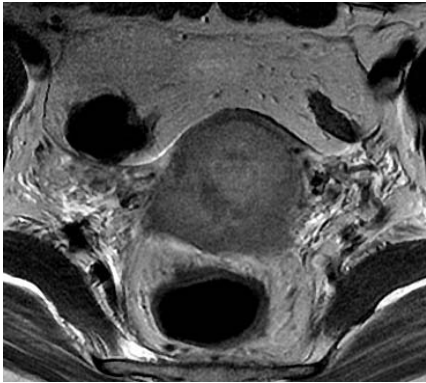
TIME: 35 minutes

Initial

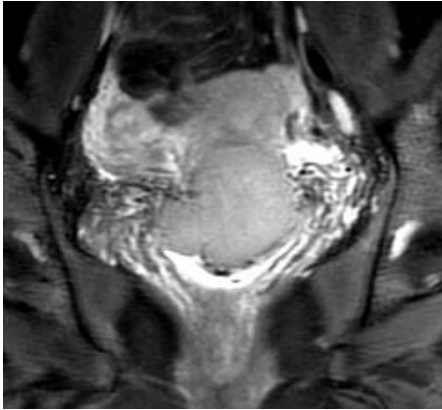
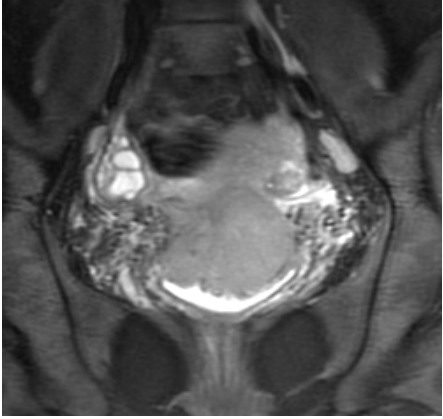
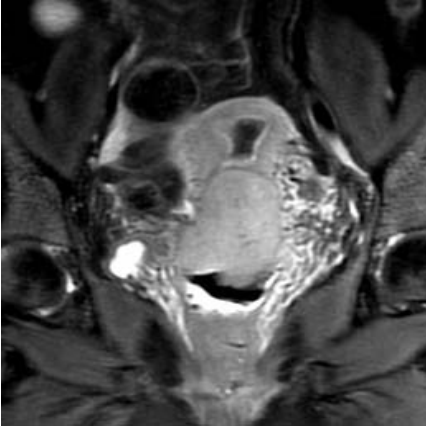
Sag



Ax

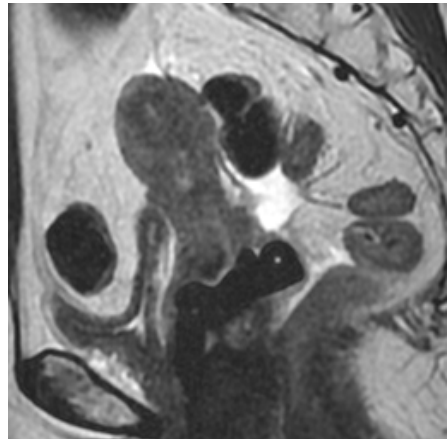
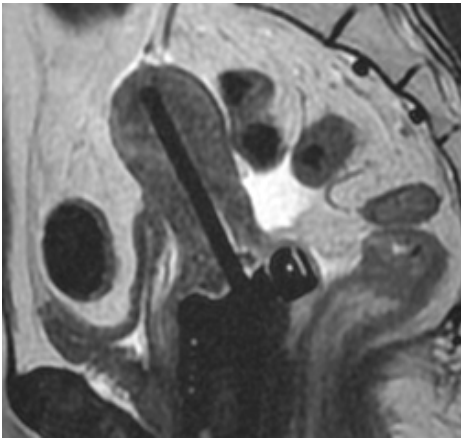
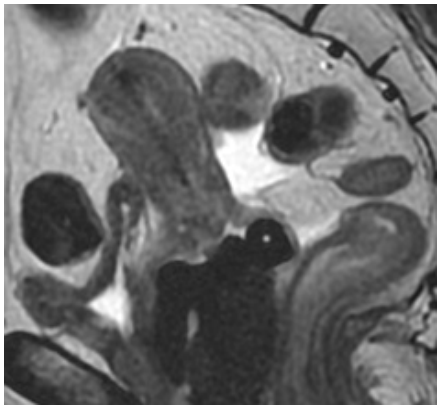


Cor

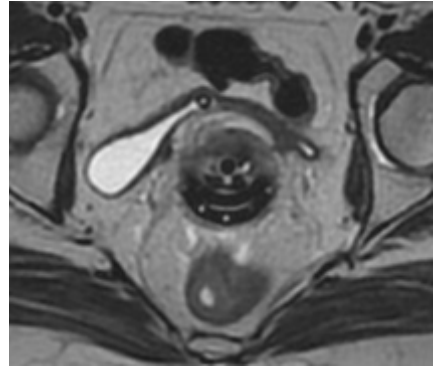


Brachytherapy

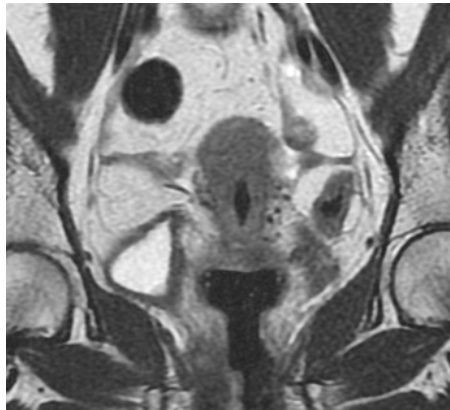
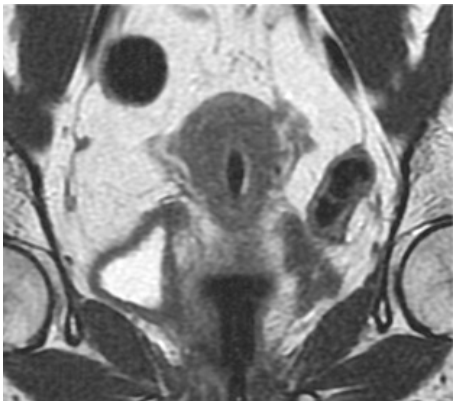
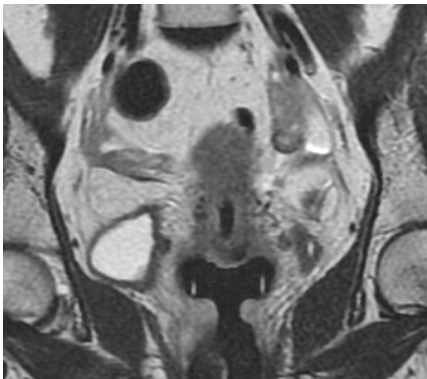
Sag



Ax



Cor



Login Educase

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estro.educase.com

with your username and password

Please use the downloaded DICOM files you should have it already!

Don't download it now – contact us

Workshop Instruction case:

GYN course VIE002-BT_MRI

GTV-B, HR-CTV & IR-CTV

OAR: Rectum, Bladder & Sigmoid

35

minutes



PRACTICAL EXAMPLE
VIE002-BT_MRI

Large tumour, good response to EBRT

LARGE TUMOUR, GOOD RESPONSE

Overview

- Initial findings
 - Initial clinical findings
 - Initial MRI findings
 - Other
- EBRT, chemotherapy
- Findings at BRACHYTHERAPY (BT)
 - Clinical findings at BT
 - MRI findings at BT
- Delineation of GTV, CTV and Organs At Risk (OAR)



LARGE TUMOUR, GOOD RESPONSE

Initial findings



Patient & Tumour

Patient:

33 years old

lap. LN-Staging: 0/9

Tumour:

Histological type: SCC

FIGO stage: 2b

Initial clinical findings:

Portio:

Exophytic tumour

Vagina:

not involved

Parametria:

Right: proximal infiltration

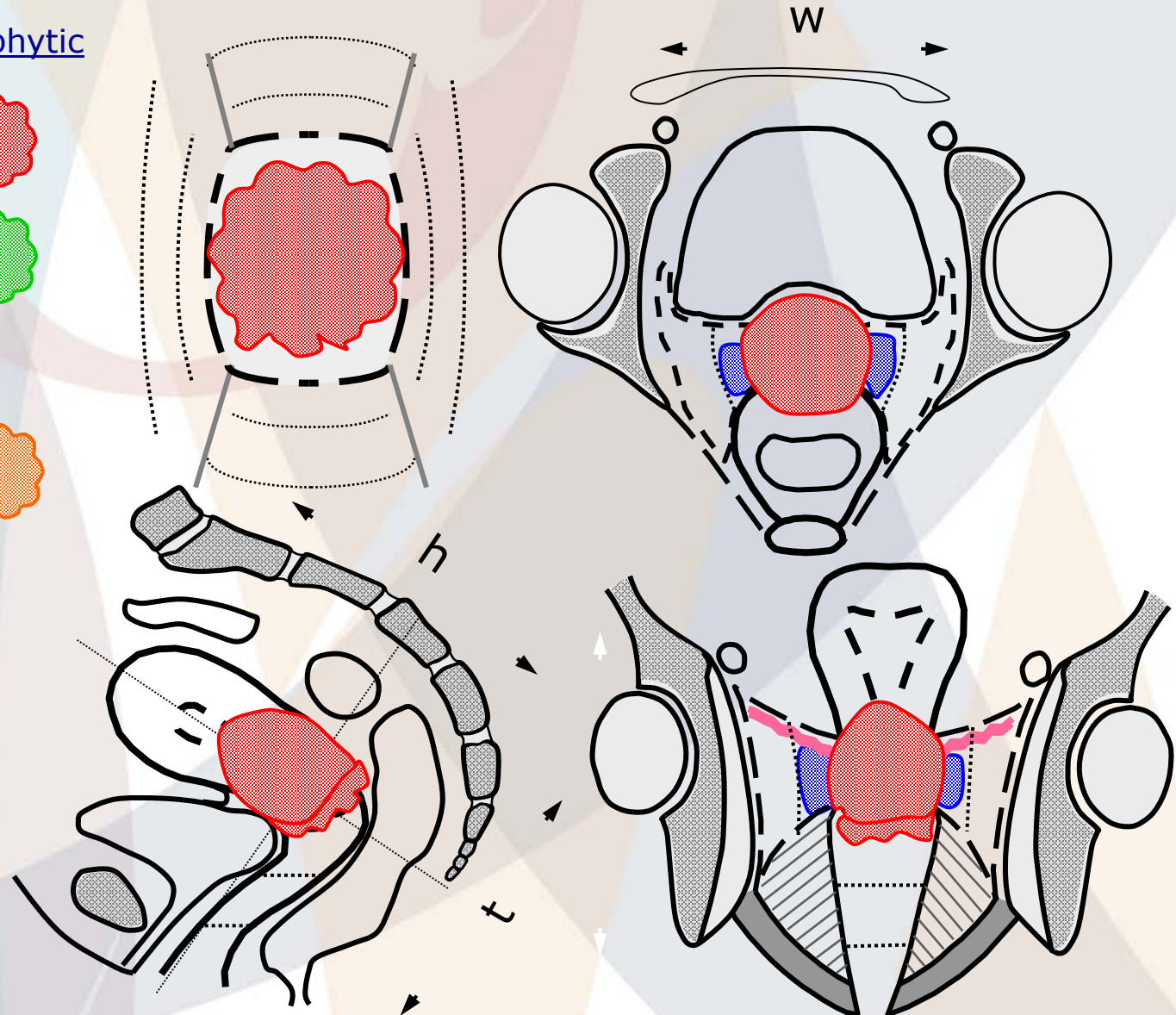
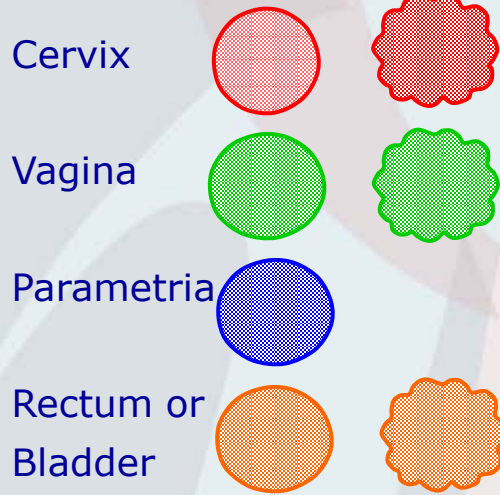
Left: proximal infiltration



Details: see *Initial Clinical Drawings* (next slide)

Initial clinical drawings

Infiltrative Exophytic



Dimensions (cm):

Width: 6

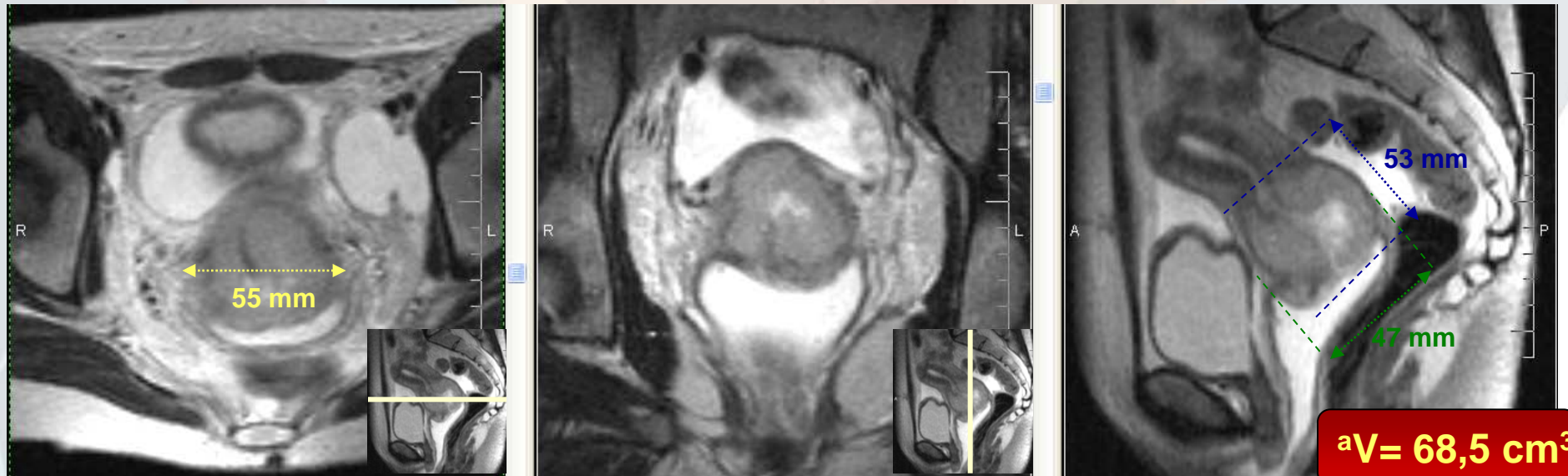
Thickness: 5

Height: 5

Vaginal inv.: 0



Initial MRI findings



Instructions to the participant:

Only representative slices are shown here.



^aEllipsoid formula applied: $V = \text{width} * \text{thickness} * \text{height} * 0.5$

LARGE TUMOUR, GOOD RESPONSE

EBRT, Chemotherapy



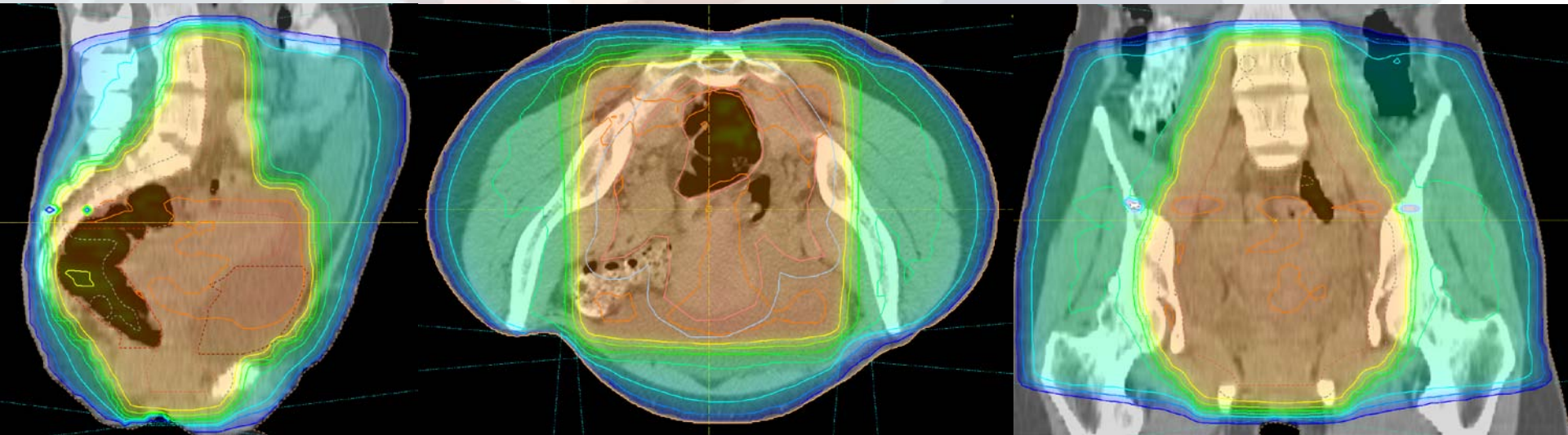
EBRT & Chemotherapy

EBRT Technique: 3D, CT based CRT; box technique

TD: 45 Gy

Dose per fraction: 1,8 Gy

Boost: no



Concomitant chemotherapy: Cisplatin 40 mg/m² weekly, 5 cycles



LARGE TUMOUR, GOOD RESPONSE

Findings at brachytherapy
(immediately following EBRT)



Clinical findings at BT

Portio:

Significant regression of exophytic part

Vagina:

≅ **diameter** (implications for selecting applicator diameter): **Large**

Involvement with tumour: No

Parametria:

Right: Proximal residuum

Left: Free

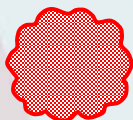
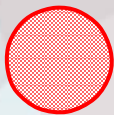


Clinical drawings at BT

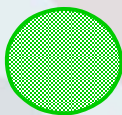
Infiltrative

Exophytic

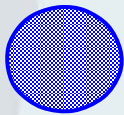
Cervix



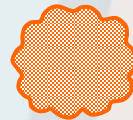
Vagina



Parametria



Rectum or Bladder



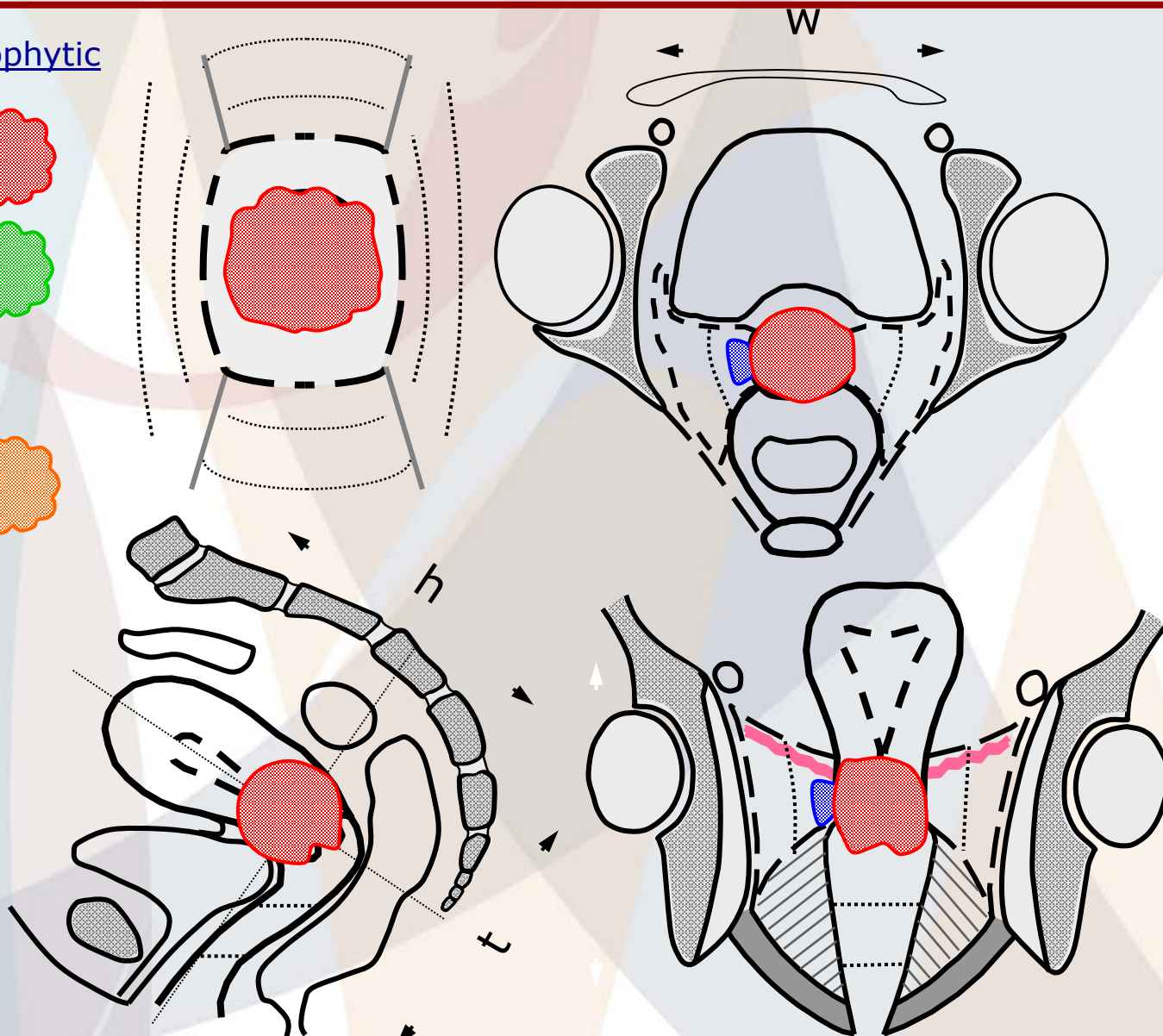
Dimensions (cm):

Width: 5

Thickness: 4

Height: 4

Vaginal inv.: 0



Insertion & imaging

Anaesthesia: epidural

Application:

Intracavitary component:

Tandem length: 60 mm

Tandem angle: 60°

Ring diameter: 34 mm

Material: plastic

Comments: Water-filled plastic tube
inside ring & tandem.

Interstitial component:

N° of needles: 2 not used

Insertion depth:

Material:

Vaginal packing:

Gauze impregnated with gadolinium

Imaging:

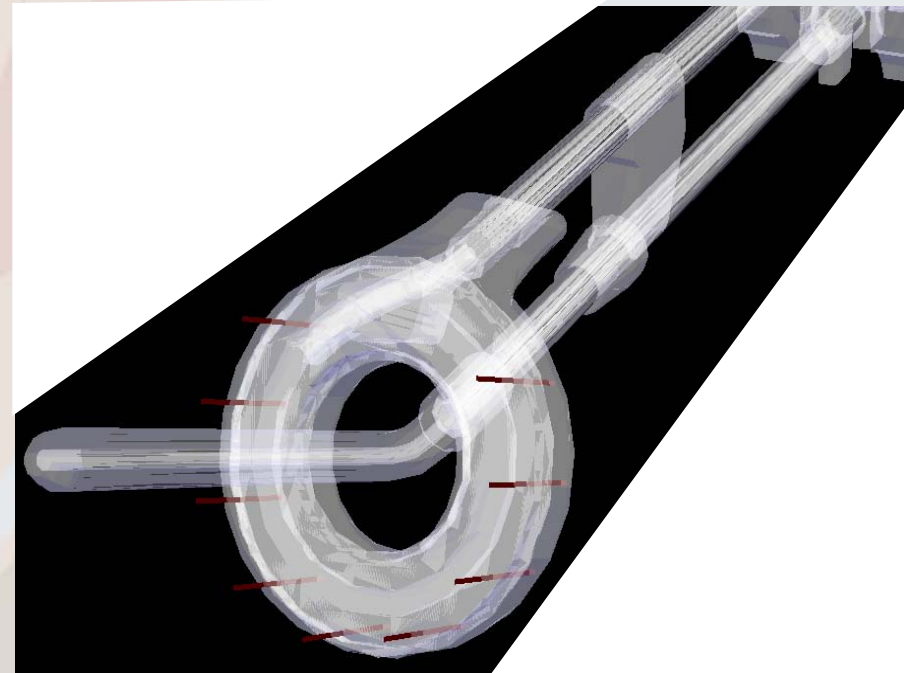
MRI field strength: 0.2 T

MRI configuration: open

Sequence(s): T2-weighted

Imaging planes: transverse, para-sagittal, para coronal

Comments regarding protocol: No contrast; Foley catheter open



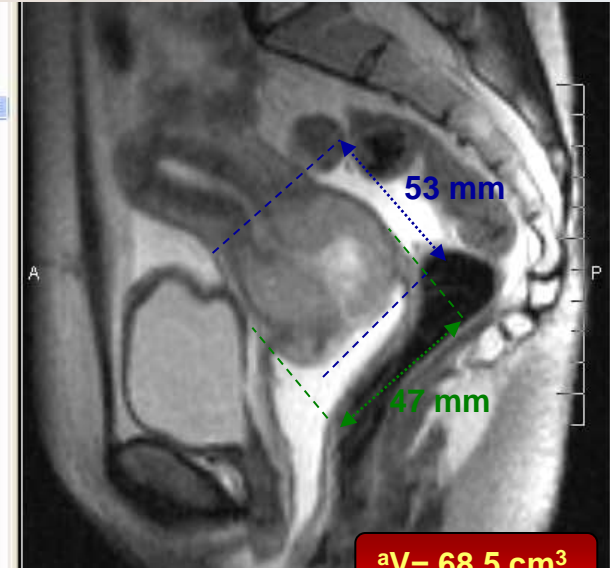
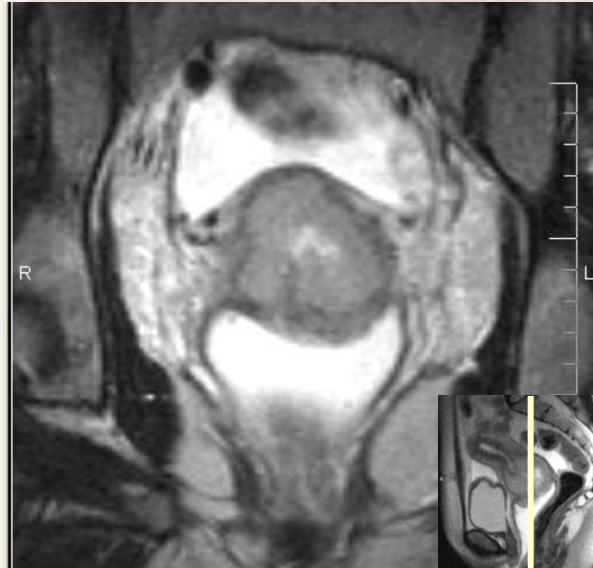
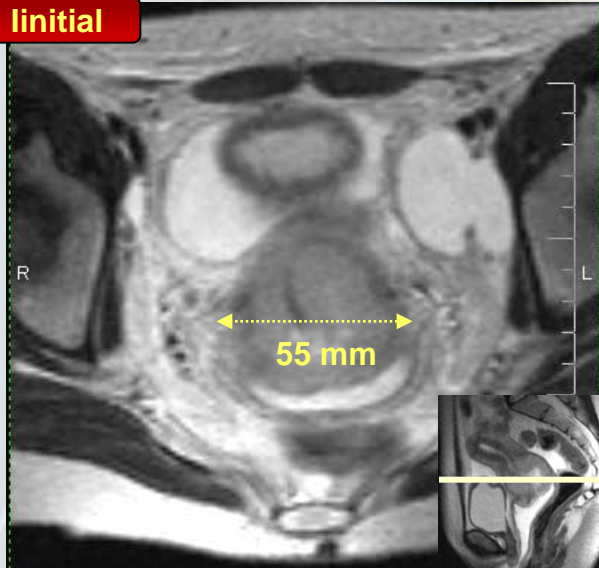
MRI findings

patient ID: VIE002CC

DICOM ID1 (initial):

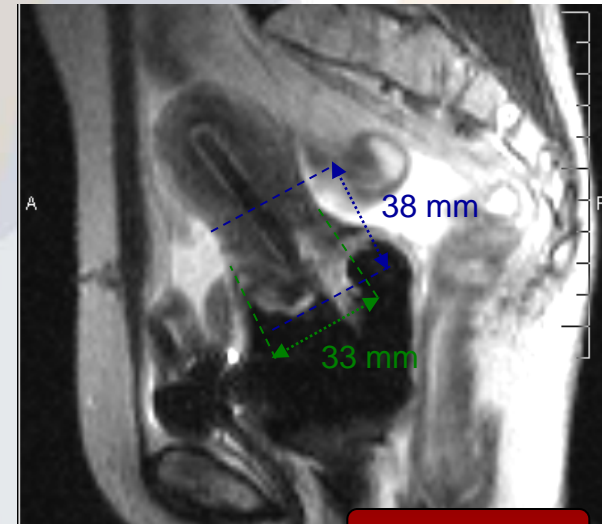
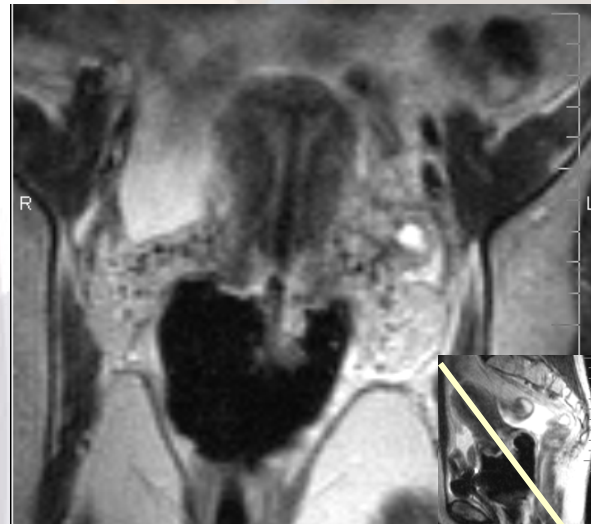
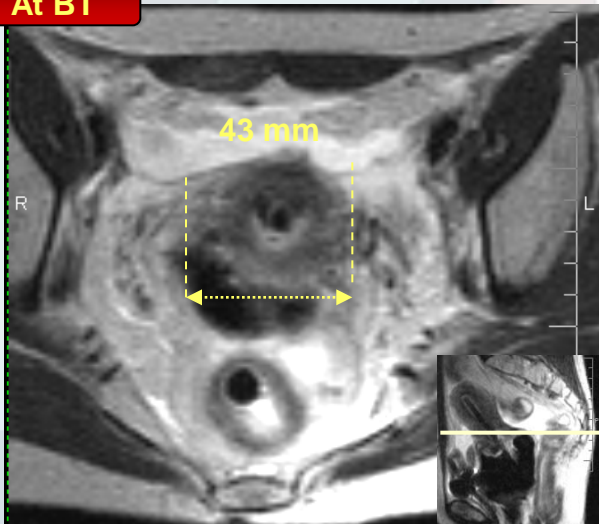
DICOM ID2: (BT):

initial



$aV = 68,5 \text{ cm}^3$

At BT



$aV = 27 \text{ cm}^3$

^aEllipsoid formula applied: $V = \text{width} * \text{thickness} * \text{height} * 0.5$

Workshop Instruction

Case: GYN course **VIE002-BT_MRI**

TARGET: GTV-B, HR-CTV & IR-CTV

OAR: Rectum, Bladder & Sigmoid (Optional)

SAVE the contours periodically

SUBMIT only after completion of contouring



TIME: 35 minutes



UMC Utrecht

CTV delineation For External Beam RadioTherapy (EBRT)



Ina Jürgenliemk-Schulz

University Medical Centre Utrecht, The Netherlands



Primoz Petric, Richard Pötter

National Center for Cancer Care and Research, Doha, Qatar

Comprehensive Cancer Center, Vienna Medical University, Austria

ESTRO teaching course

IGRT and ChT in Gyn malignancies; focus: adaptive BT

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

GTV = Gross Tumor Volume

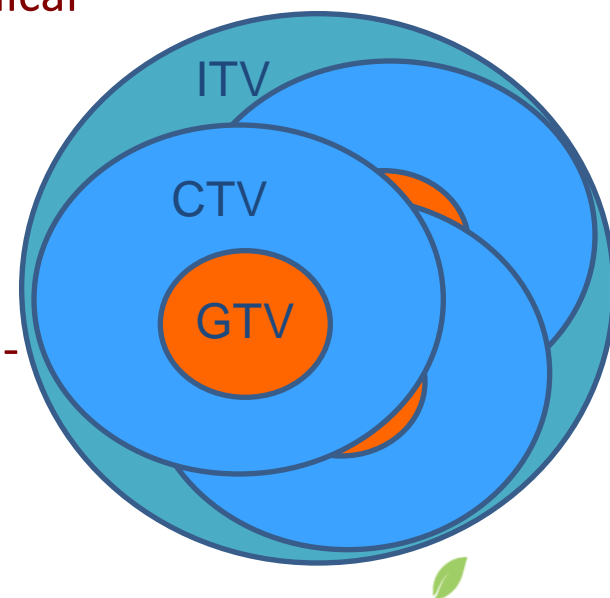
- Macroscopic tumor, visible clinically and with imaging

CTV = Clinical Target Volume

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

ITV = Internal target volume

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



ICRU reports

The CTV of the primary tumor always includes ?

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

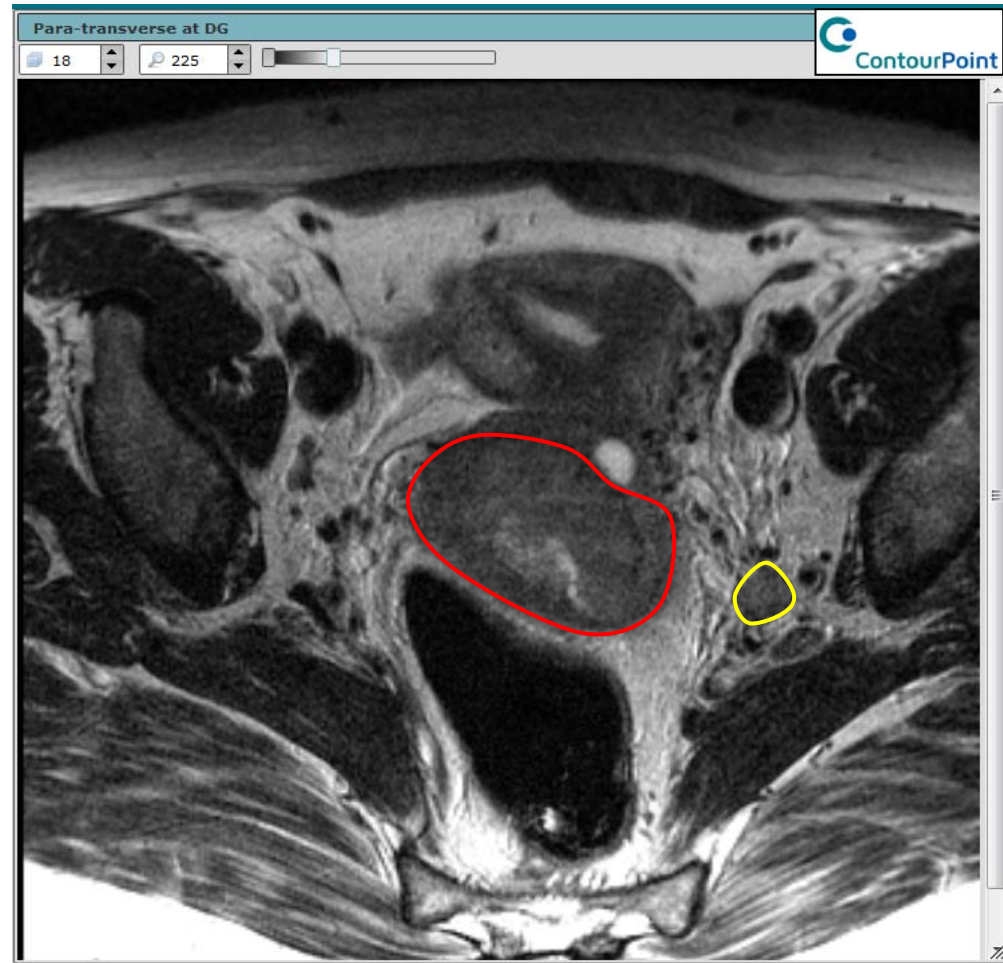


GTV (*GTV initial*)

High signal intensity on T2 weighted MRI

GTV is composed of:

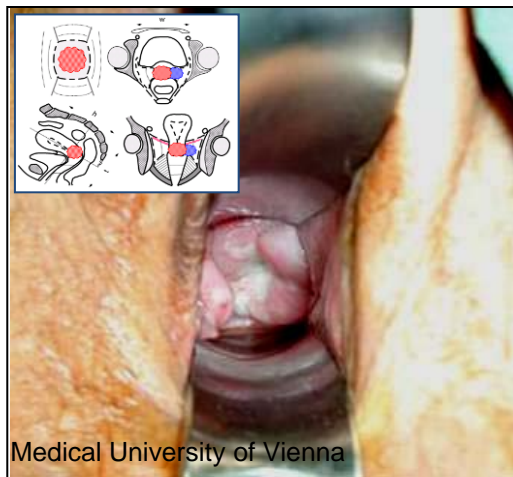
- Primary tumor
- macroscopic lymph node metastases



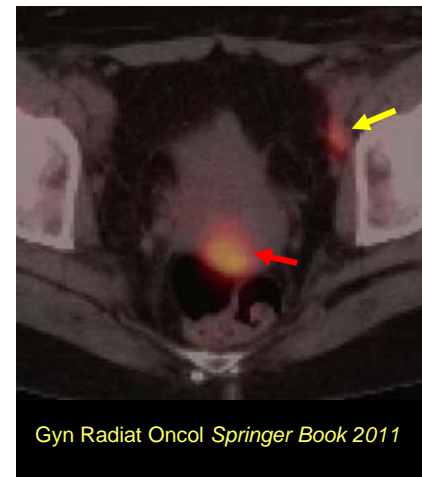
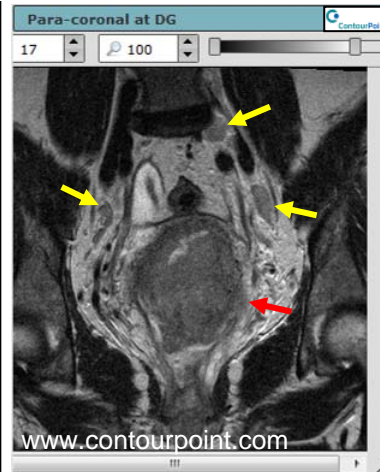
GTV

Consists of Primary Tumor and Nodal GTV (*GTV- $T_{initial}$* and *GTV- $N_{initial}$*)
Investigation modality needs to be reported

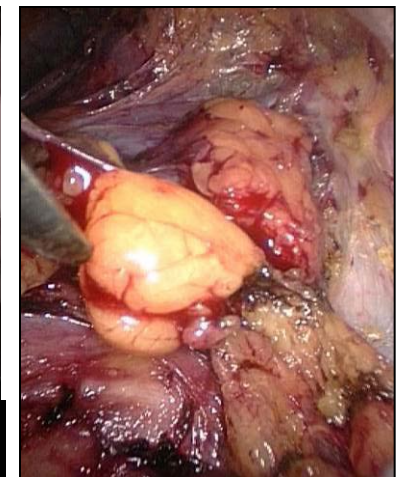
Clinical Examination



Imaging (MRI, PET CT, US)



Invasive

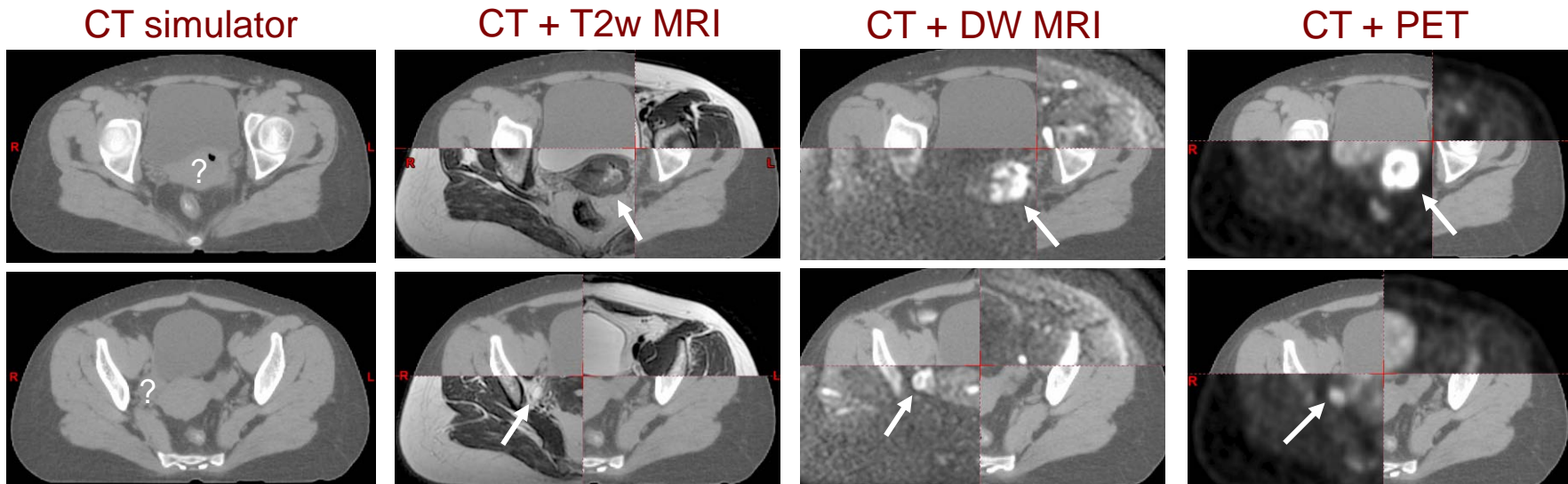


GTV contouring: combine information from different modalities

Initial GTV contouring (composite GTV)

Co-registration of different imaging modalities?

Imaging in same (treatment) position: 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)

} *HR-CTV-T initial*

} *LR-CTV-T initial*

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

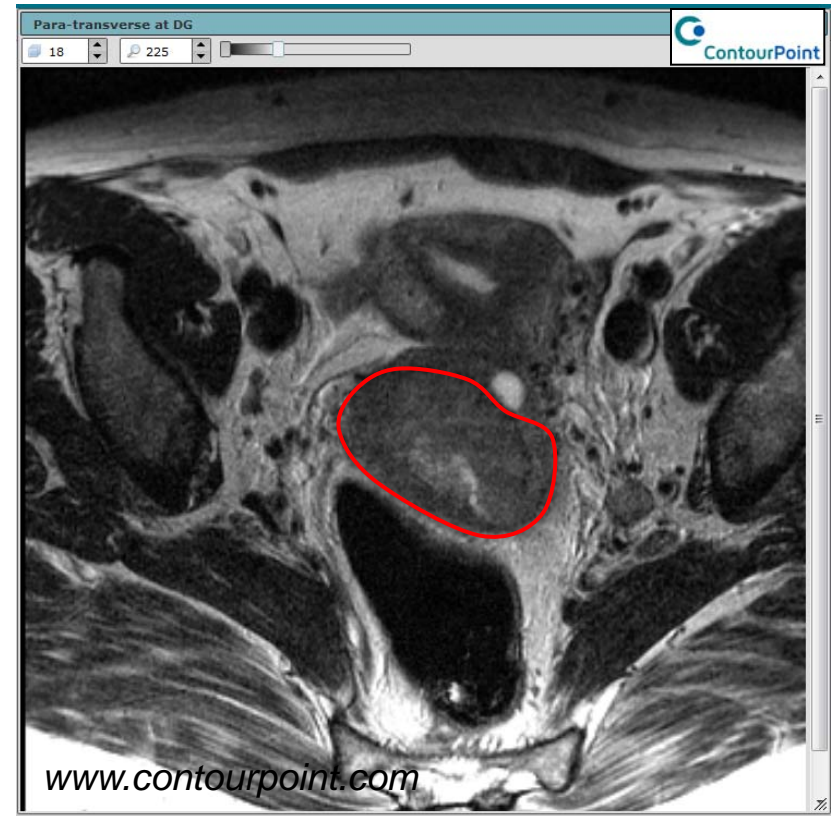
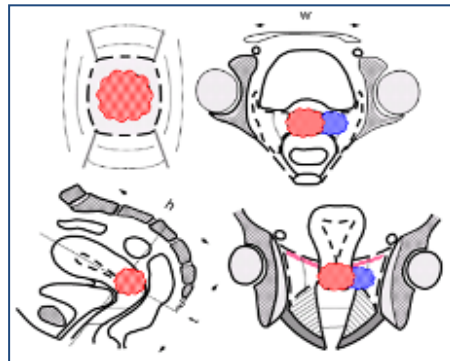
- Lymph node regions at risk (vessel orientated)
- Affected lymph-nodes: CTV-N

Initial CTV-T

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

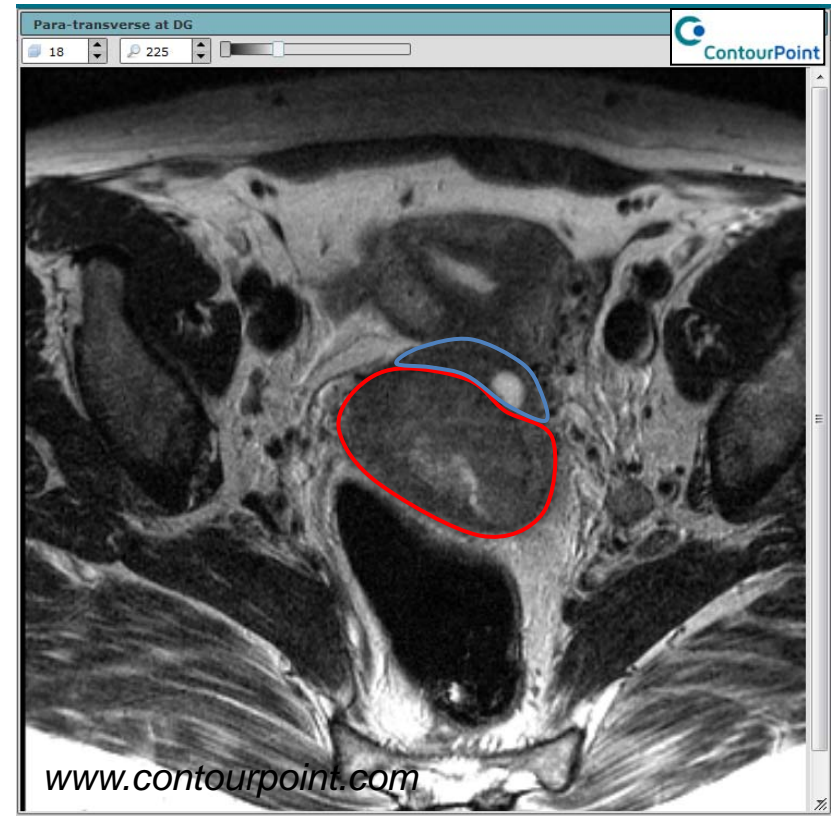
Initial CTV-T

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



Initial CTV-T: HR CTV-T_{initial}

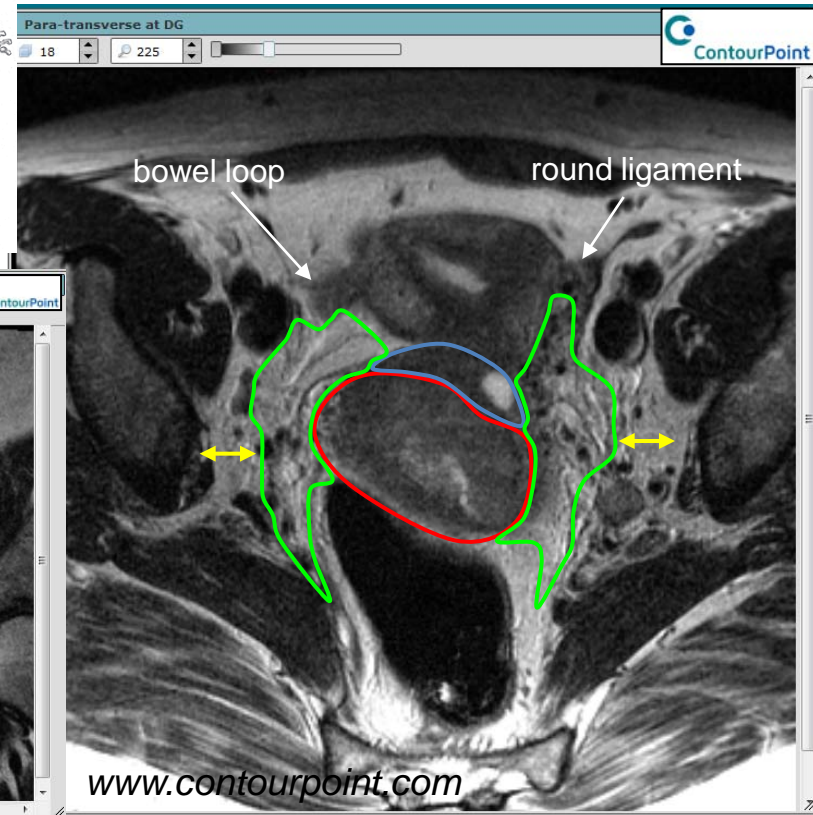
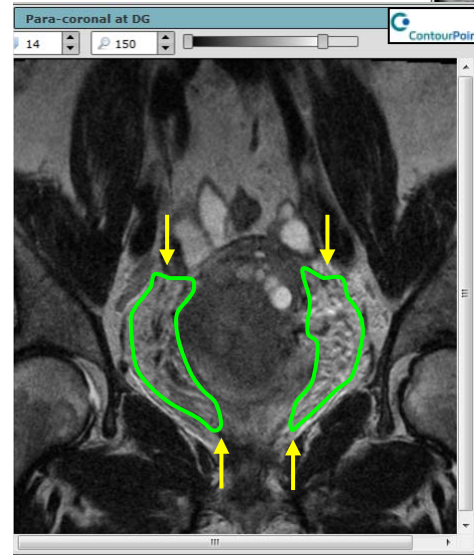
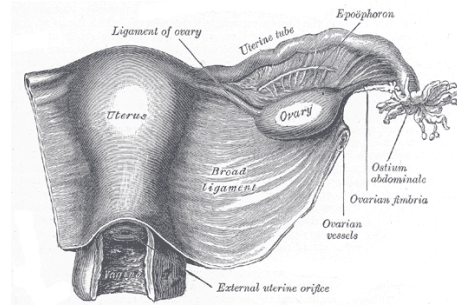
- GTV
 - Cervix
 - Parametria
 - Uterus
 - Upper Vagina
 - Involved organs (FIGO IVA)
- } *HR-CTV-T_{initial}*



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

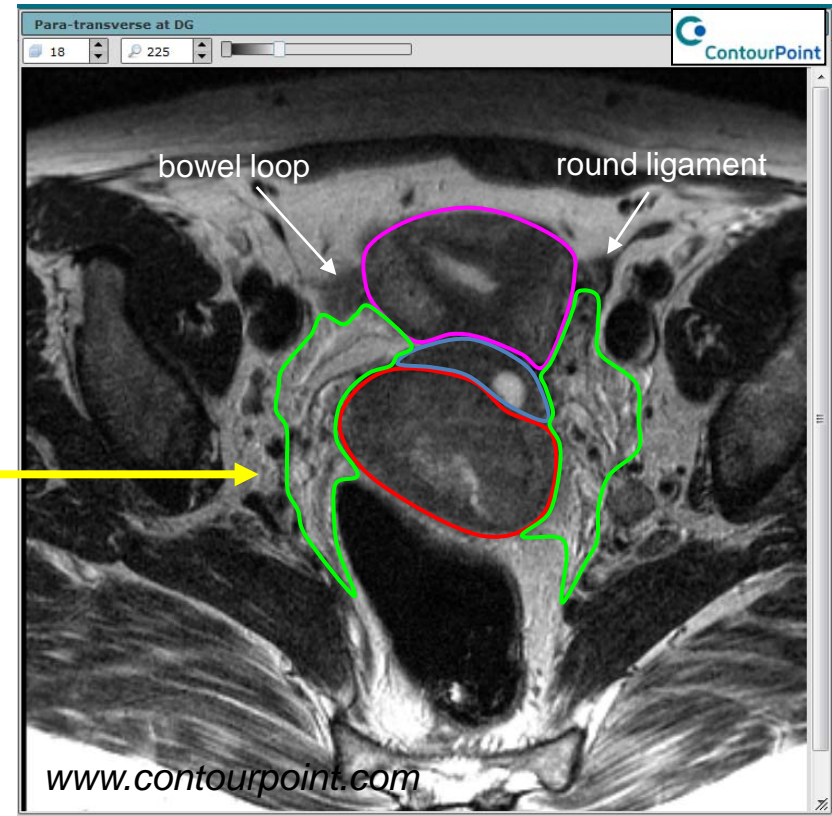
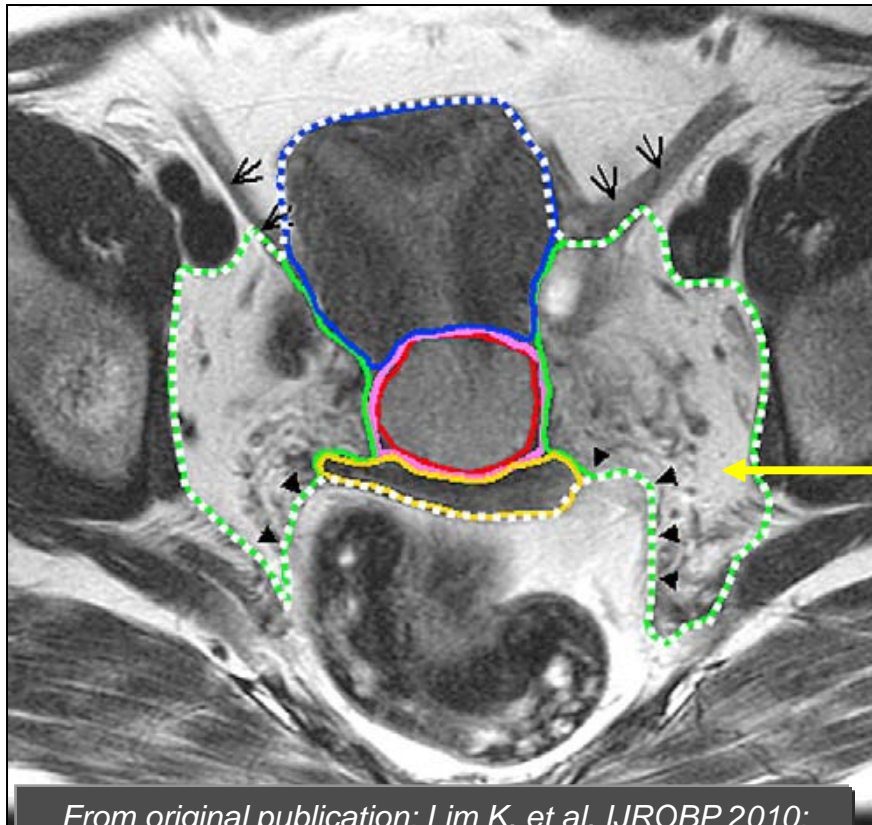


Anatomical boundaries

Anteriorly
Posteriorly
Laterally
Superiorly
Inferiorly

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

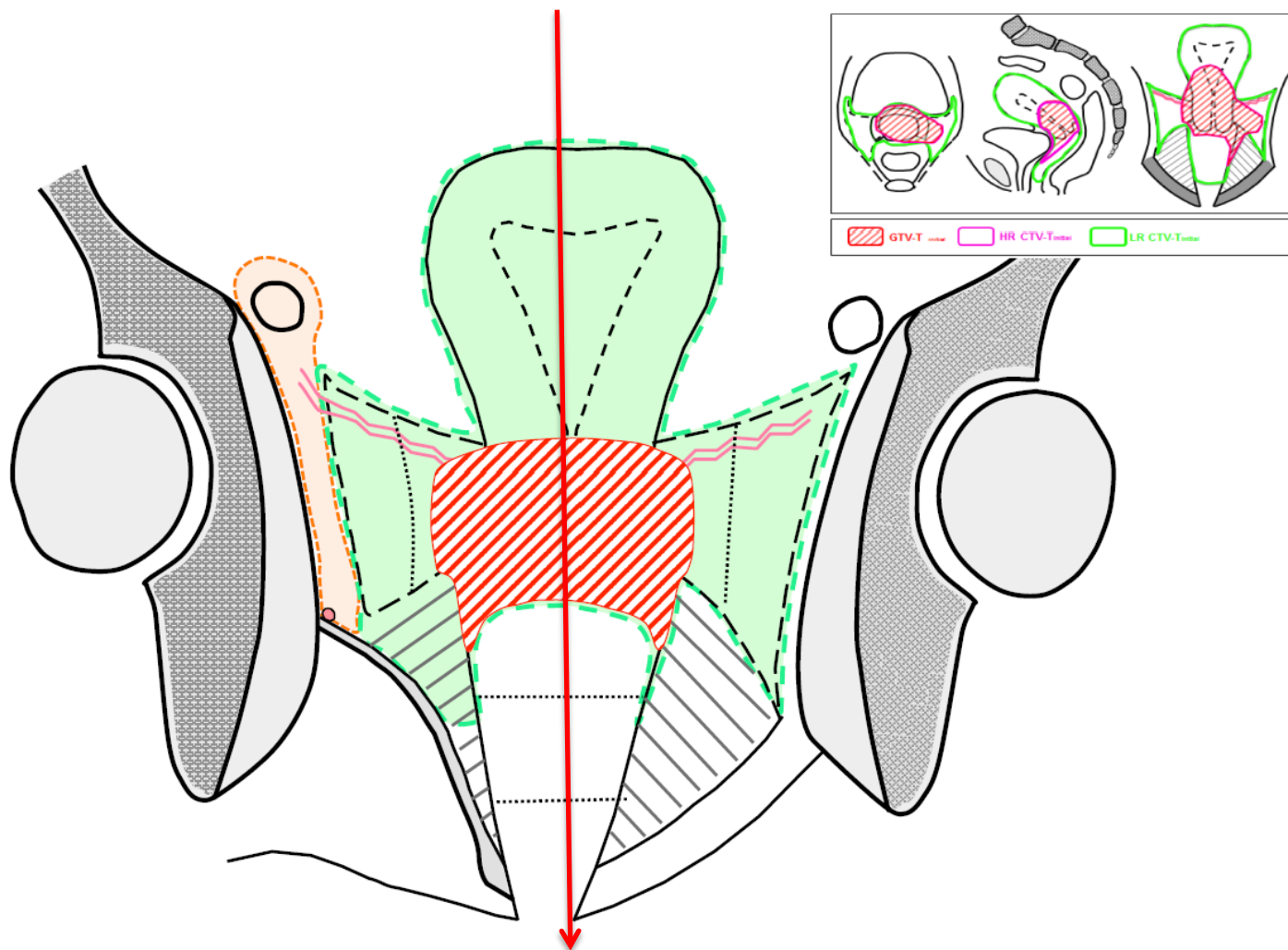
Initial CTV-T: LR CTV-T_{initial}



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

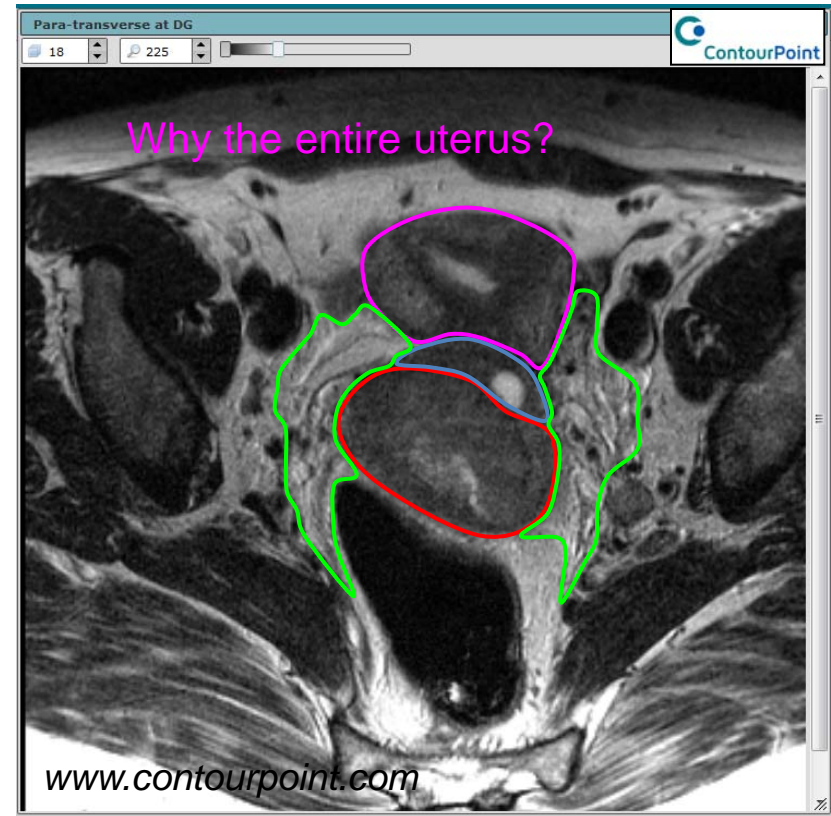
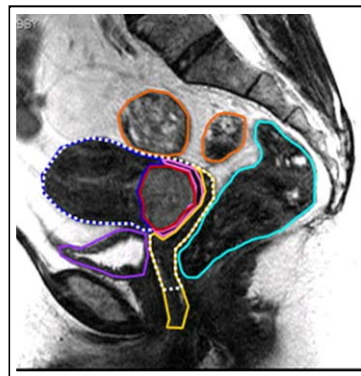
Future LR-CTV-T_{initial} and CTV-E



Courtesy Remi Nout

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

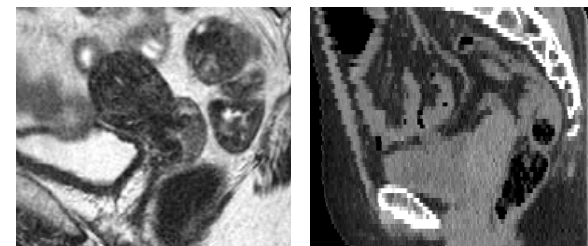
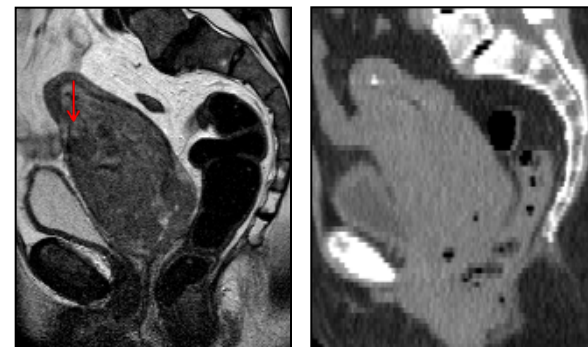
- GTV
- Cervix
- Parametria
- Uterus
- Upper Vagina
- Involved organs (FIGO IVA)



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

^aPlante M. Gynecol Oncol 2008

^bBali A, et al. Gynecol Oncol 2008

^cDiaz JP, et al. Gynecol Oncol 2008

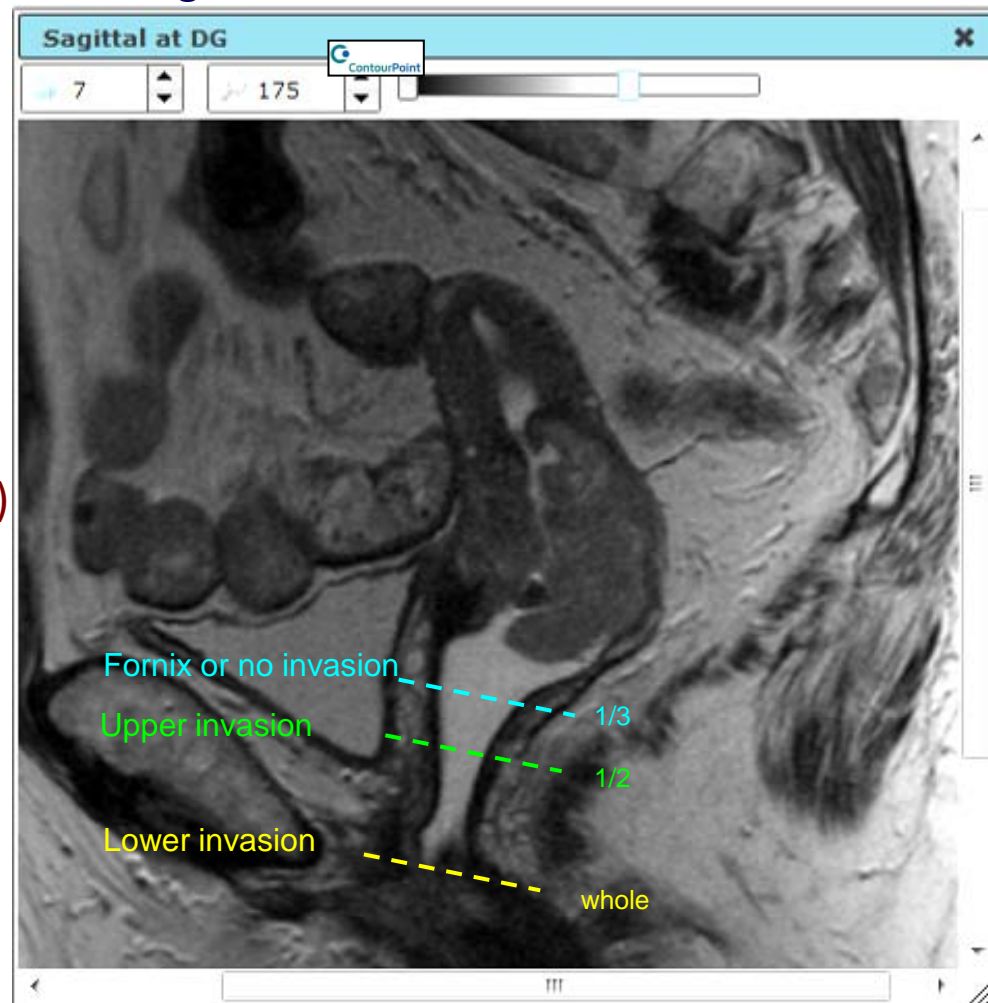
^dHertel H, et al. Gynecol Oncol 2006

^eNishio 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}

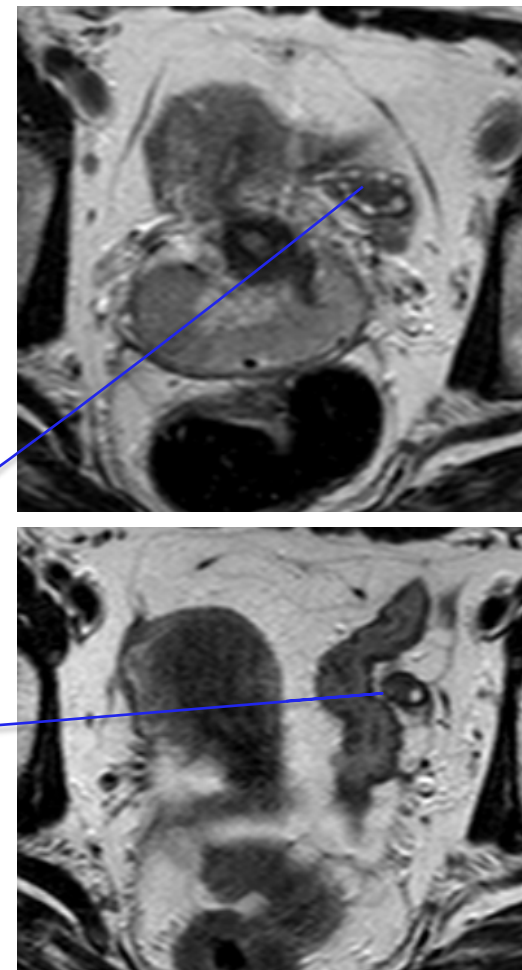
Overall risk of ovarian metastases is small, increased risk reported for:

- 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)

- Ovaries ?

LR-CTV-T_{initial}

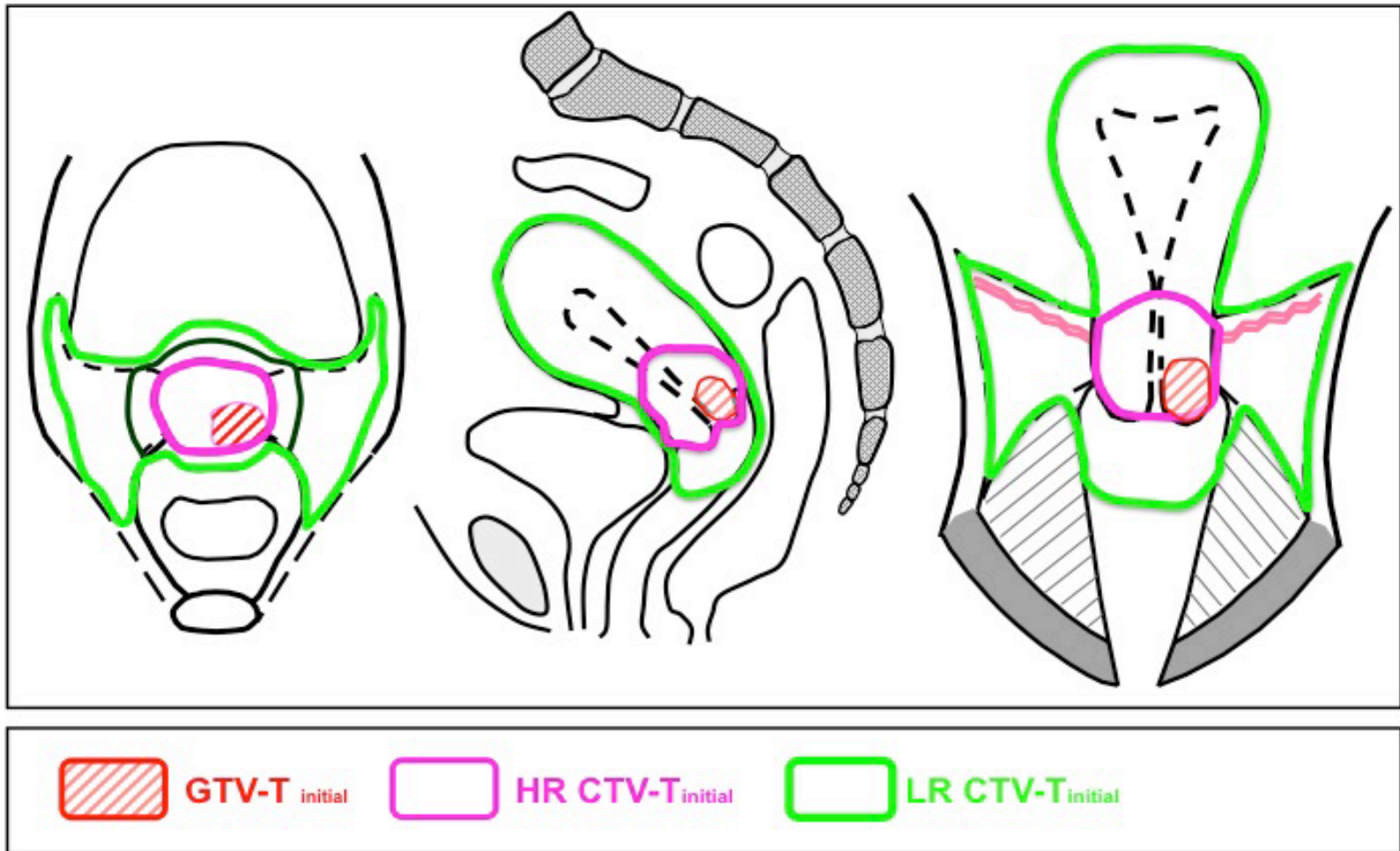


The initial LR CTV-T of the primary tumor always includes ?

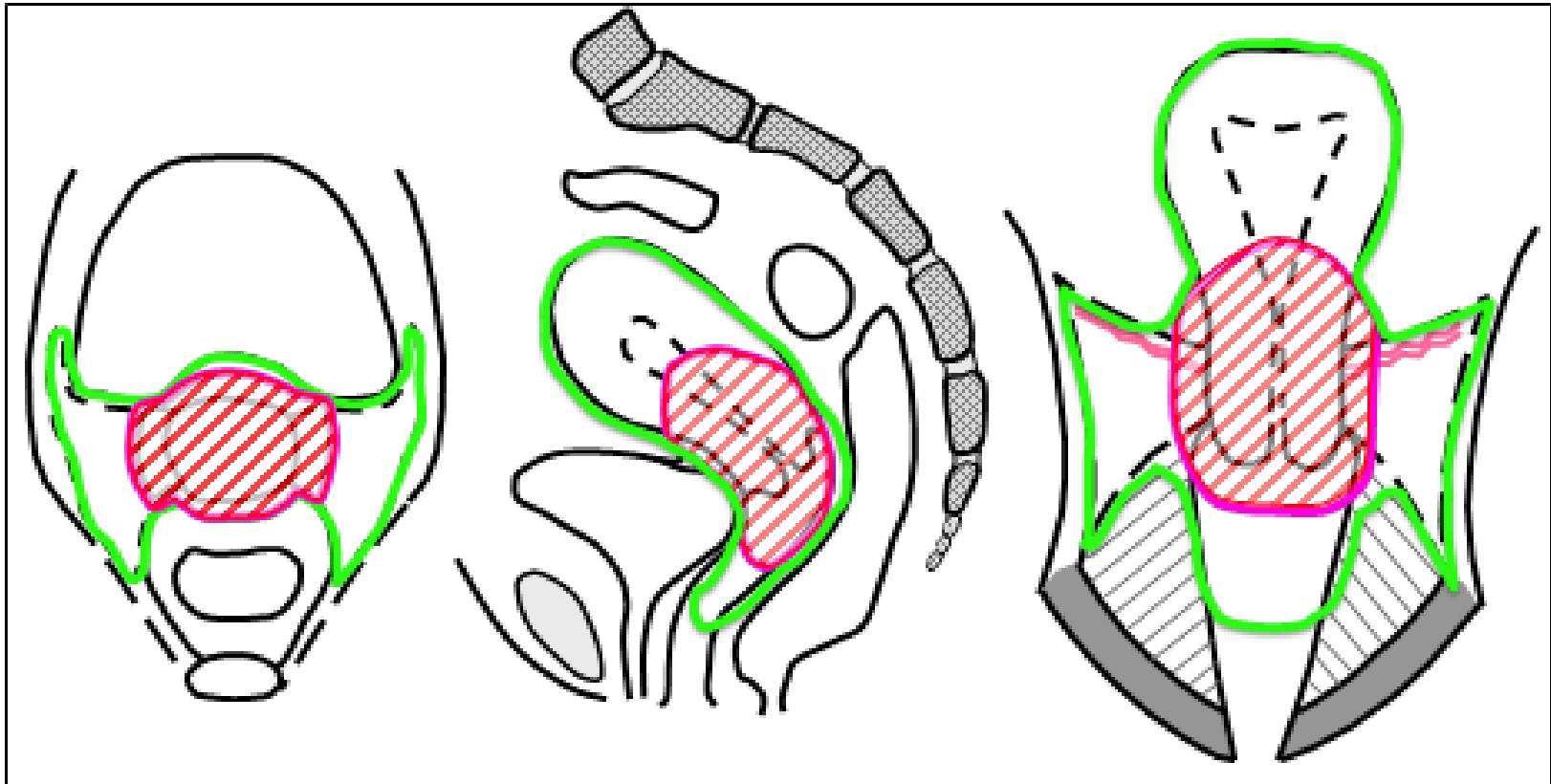
- A. GTV
- B. Remaining unaffected cervix
- C. Parametria
- D. Uterus
- E. Upper Vagina
- F. Involved organs (FIGO IVA)
- G. Ovaries



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



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



GTV-T_{initial}

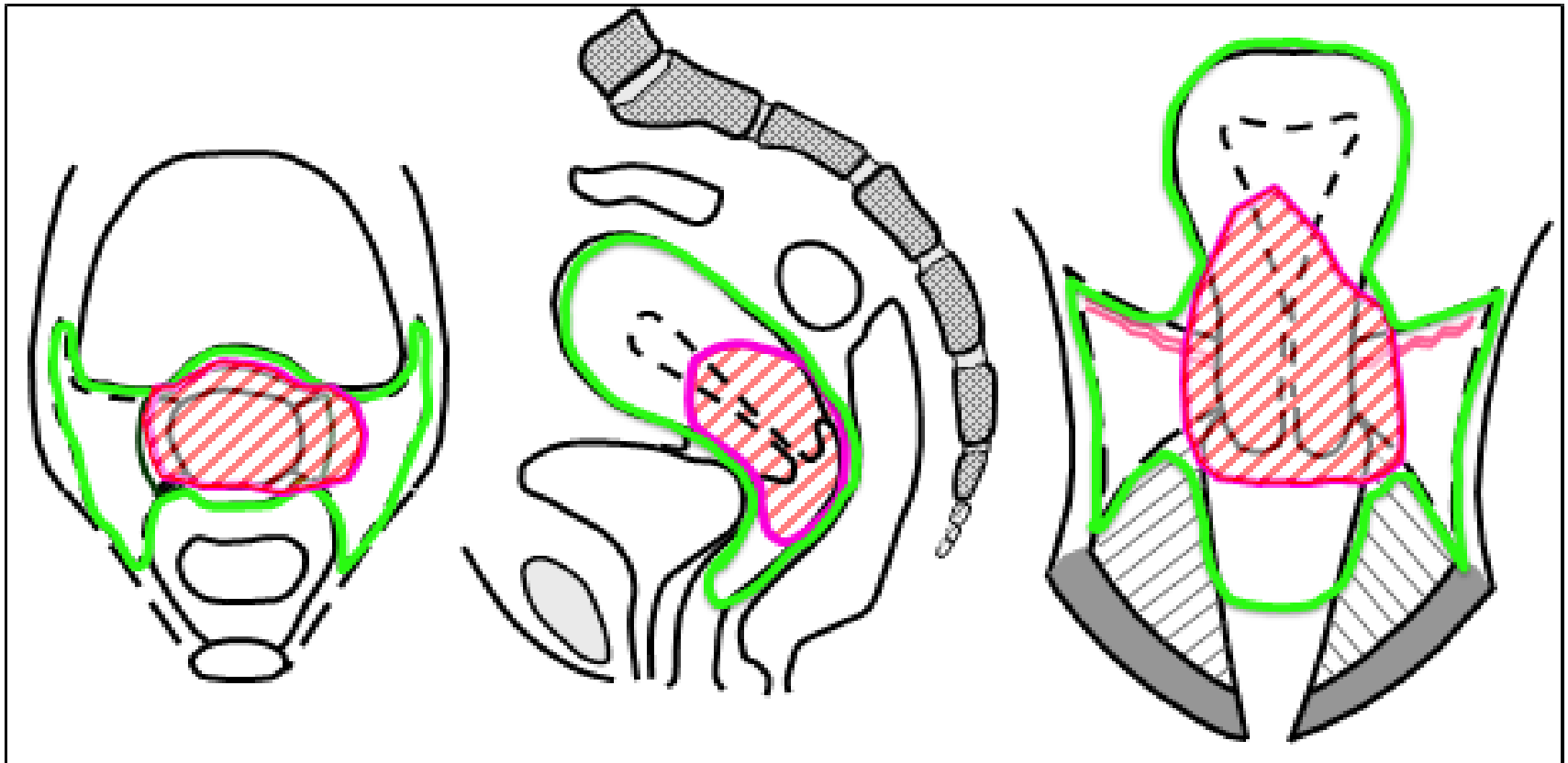


HR CTV-T_{initial}



LR CTV-T_{initial}

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



GTV-T initial

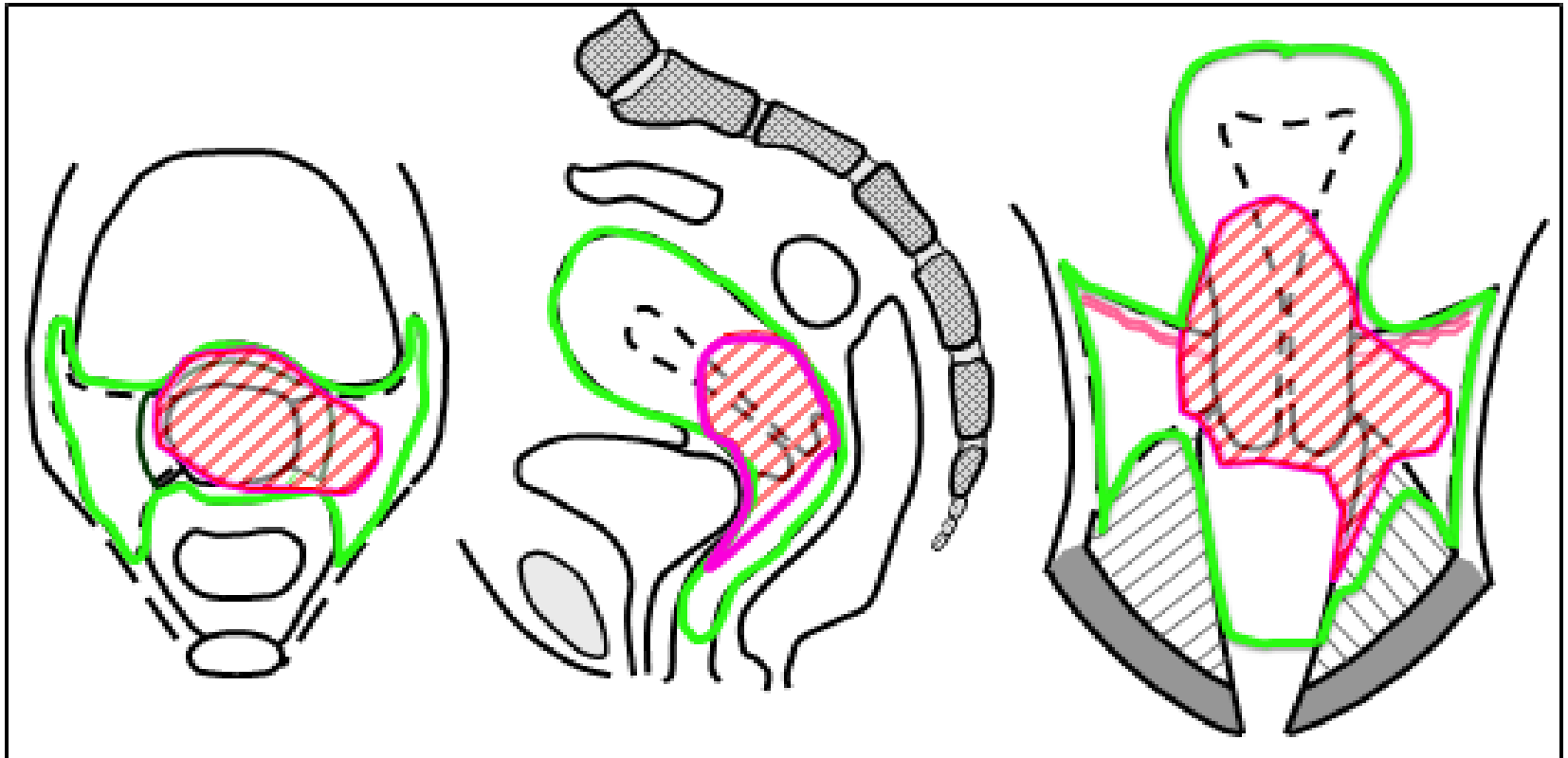


HR CTV-T initial



LR CTV-T initial

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



GTV-T_{initial}

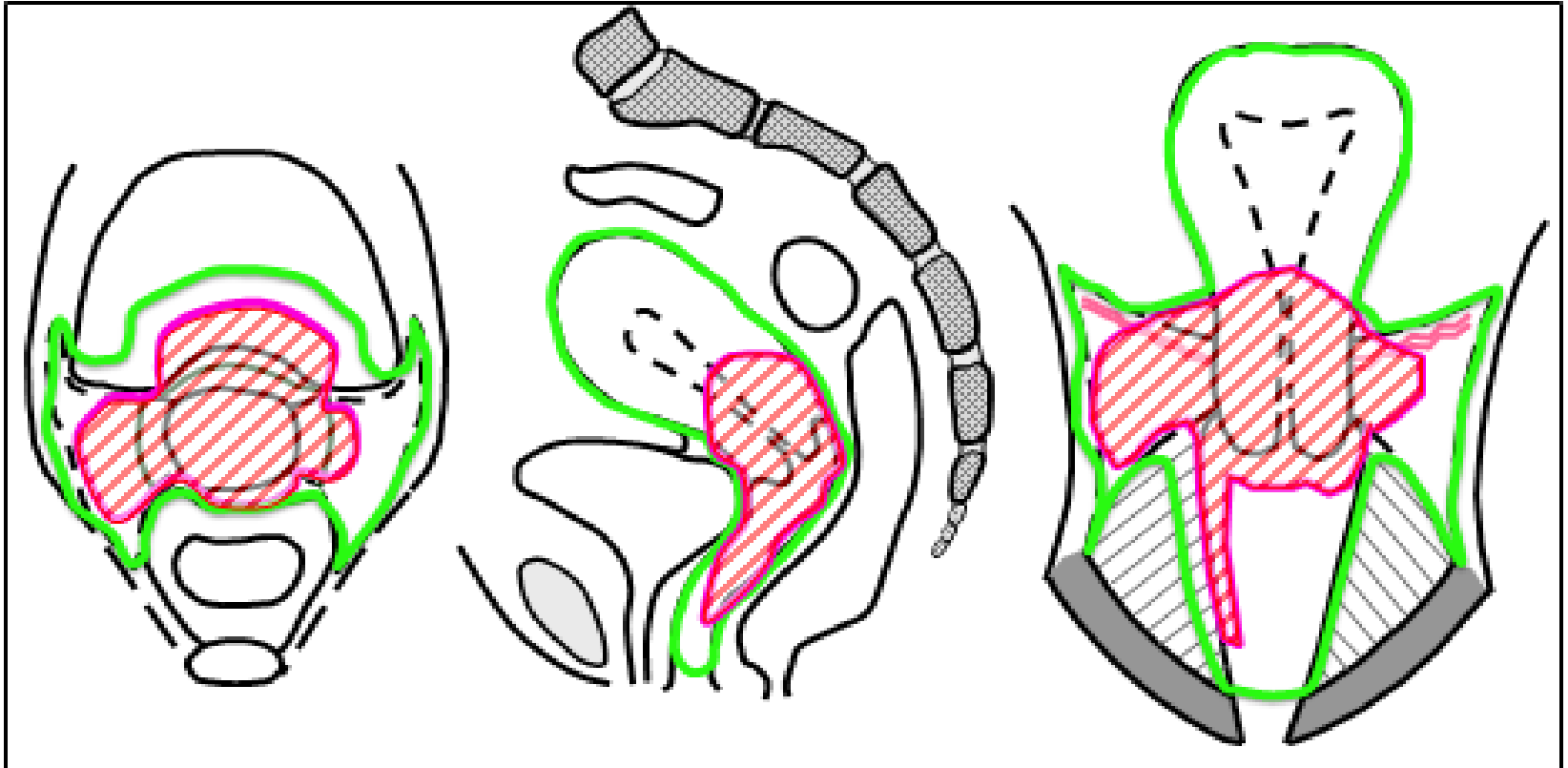


HR CTV-T_{initial}



LR CTV-T_{initial}

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



GTV-T_{initial}



HR CTV-T_{initial}

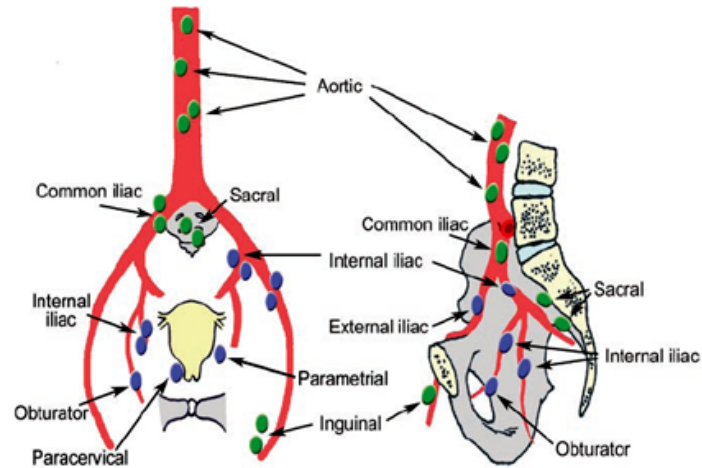


LR CTV-T_{initial}

Nodal CTV (CTV-E)

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

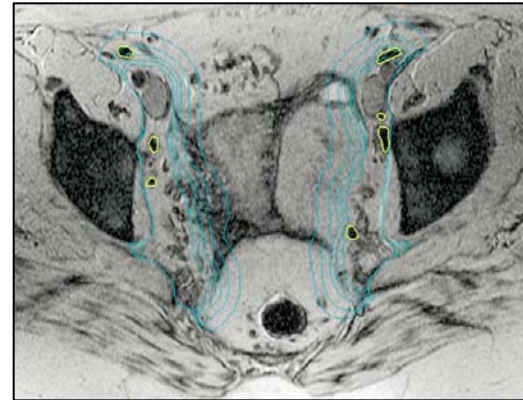


Nodal CTV

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

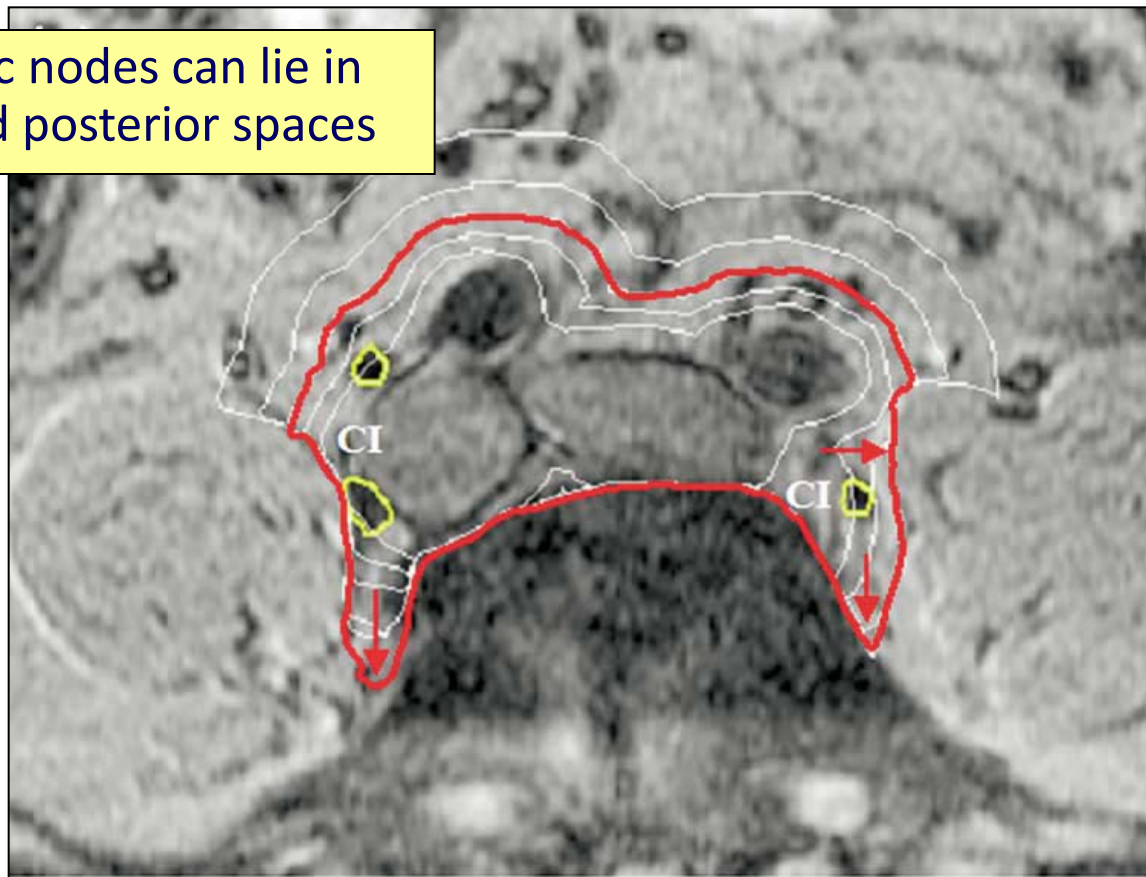
Nodal CTV

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



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



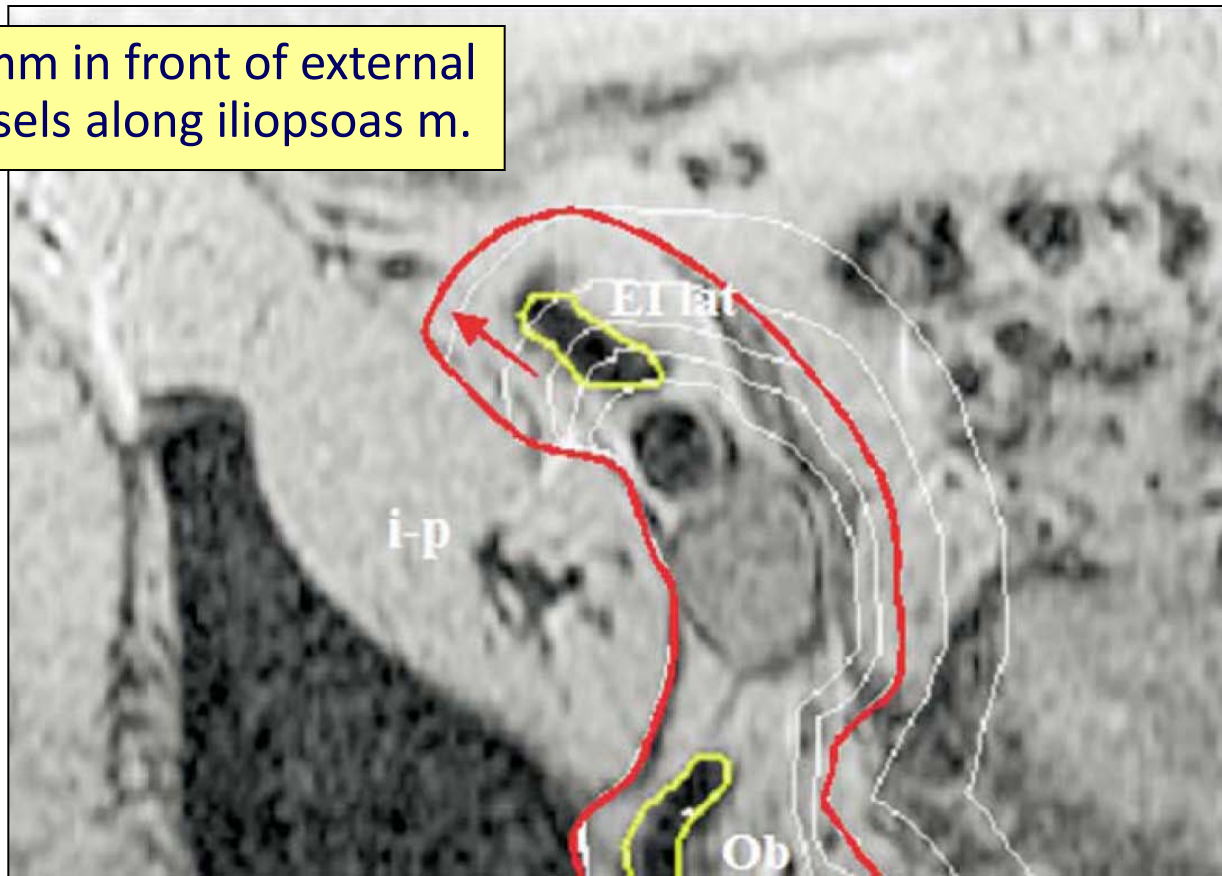
Nodal CTV

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.



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

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.

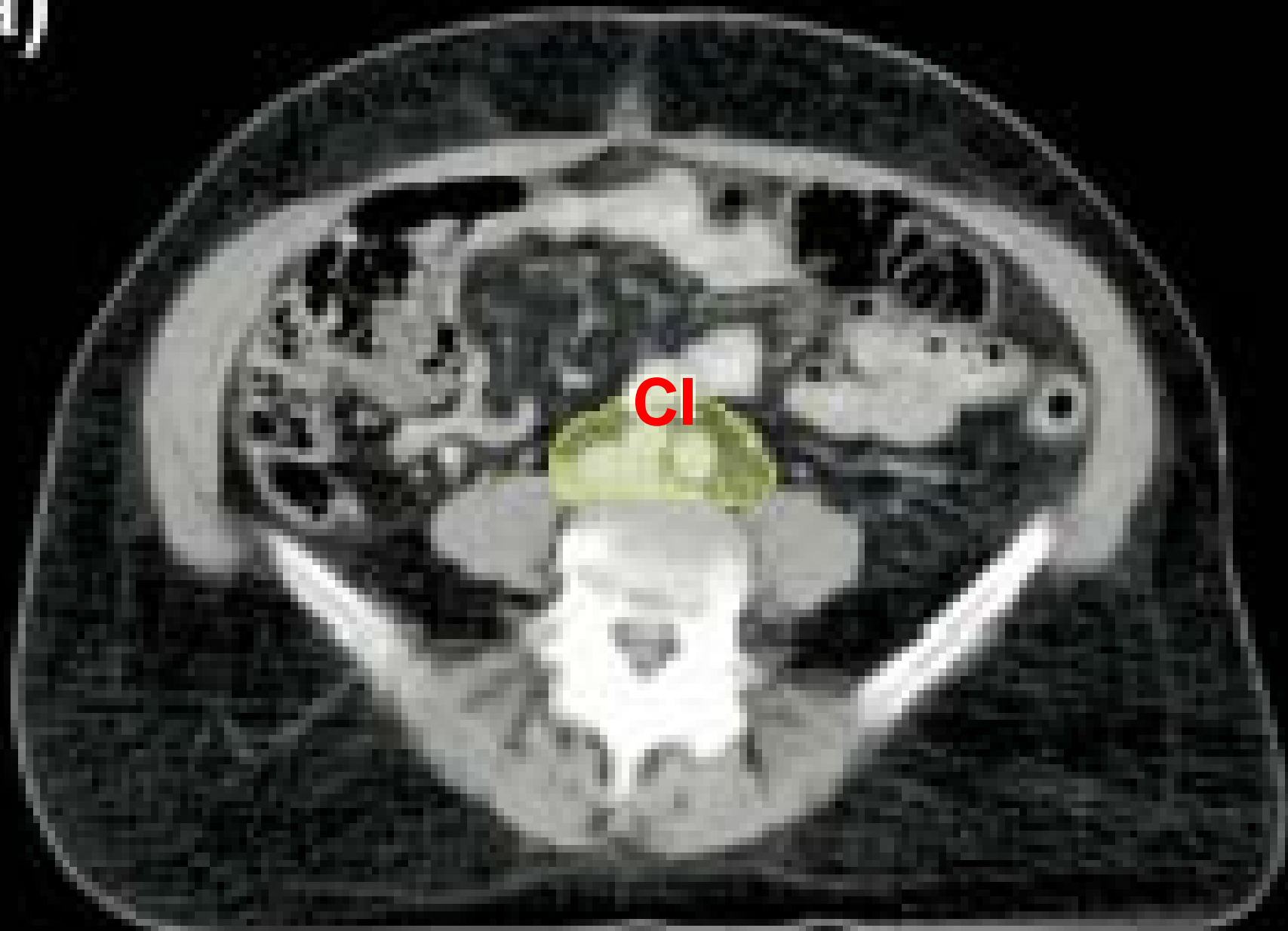
Ensure the lateral border of the volume extends to the psoas muscle and pelvic sidewall.

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.

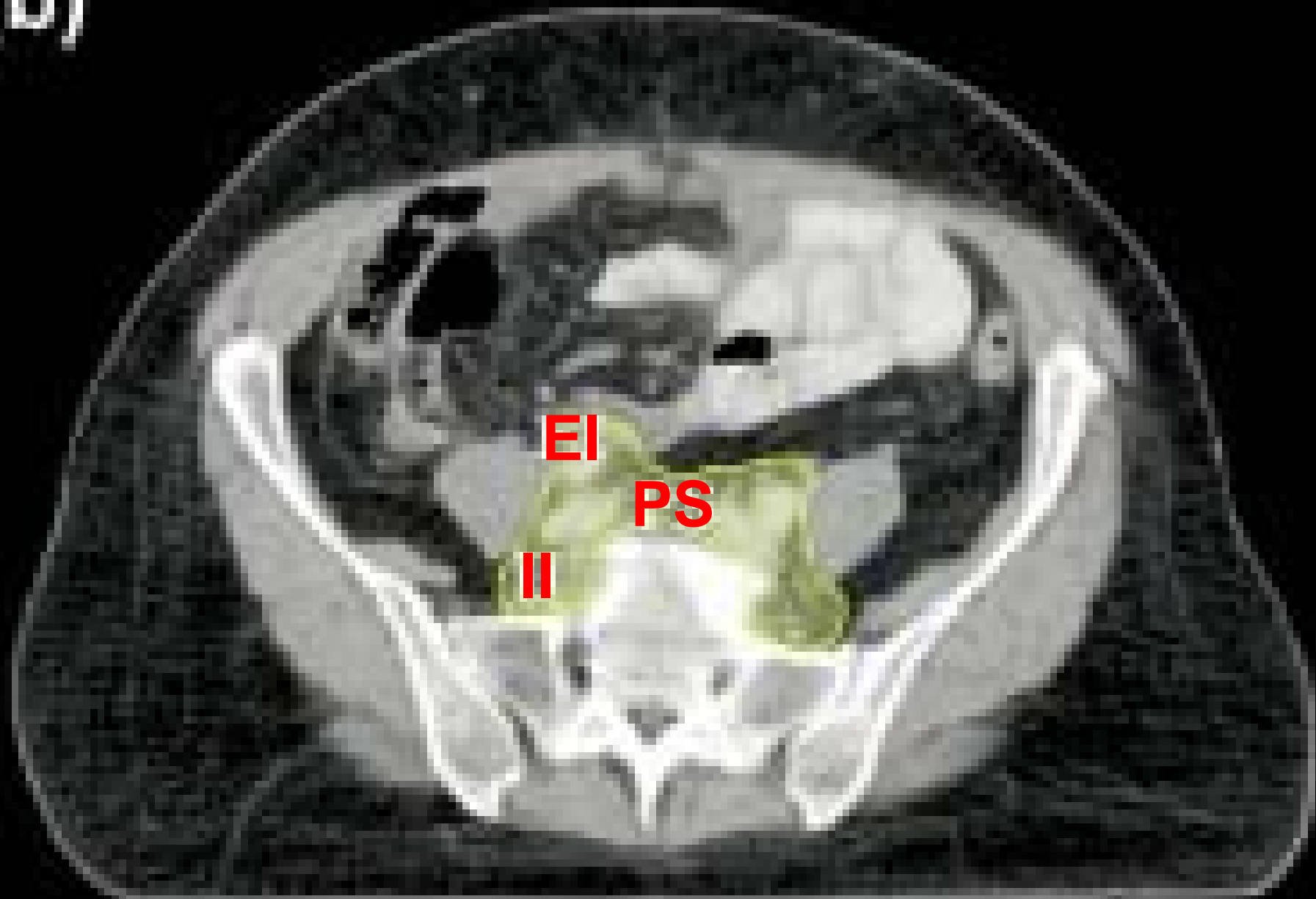
To cover the presacral region, connect the volumes on each side of the pelvis with a 10-mm strip over the anterior sacrum (S1 and S2)

(a)



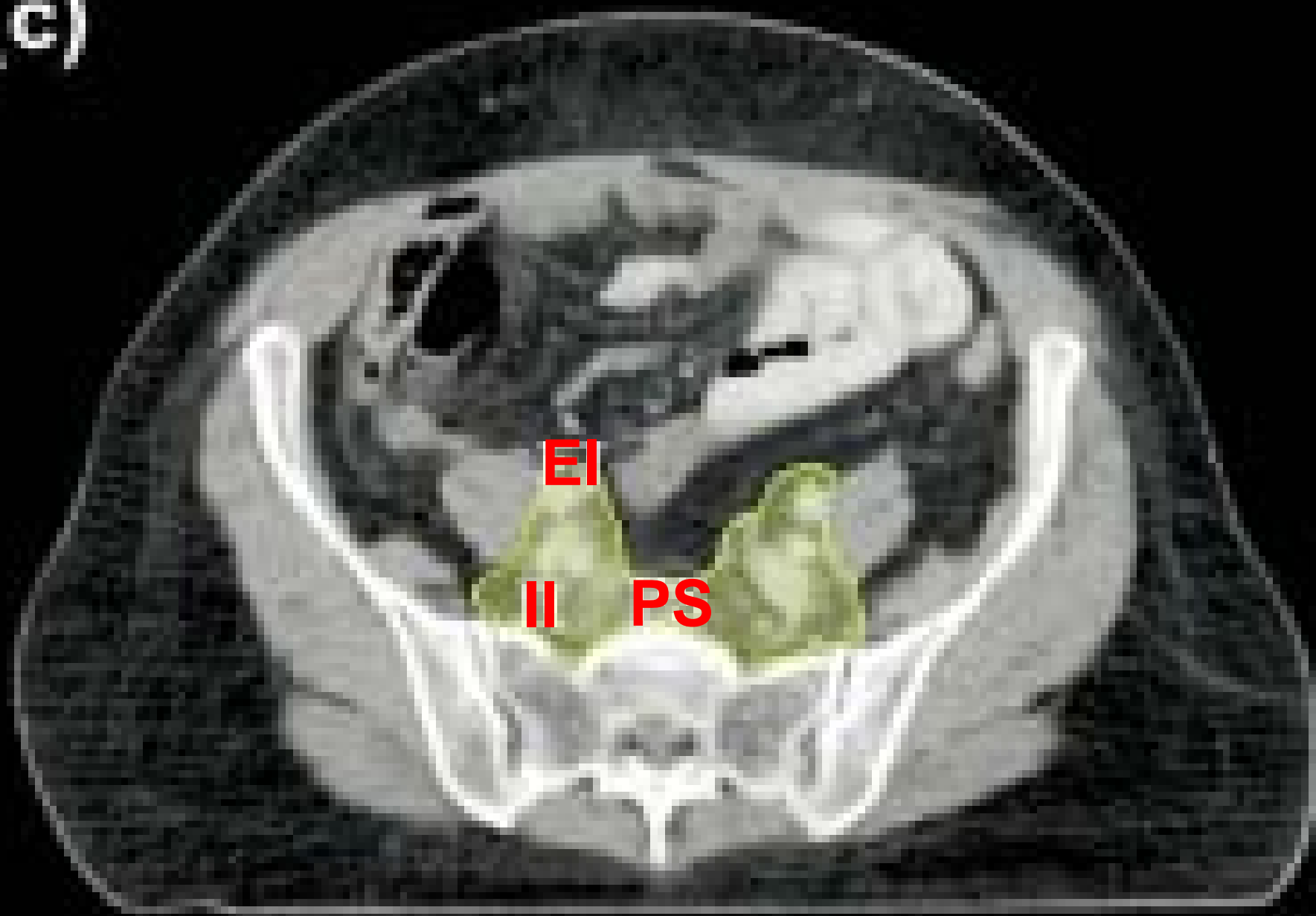
Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int. J. Radiation Oncology Biol. Phys.*, Vol 63.no.5, 1604-1612, 2005.

(b)



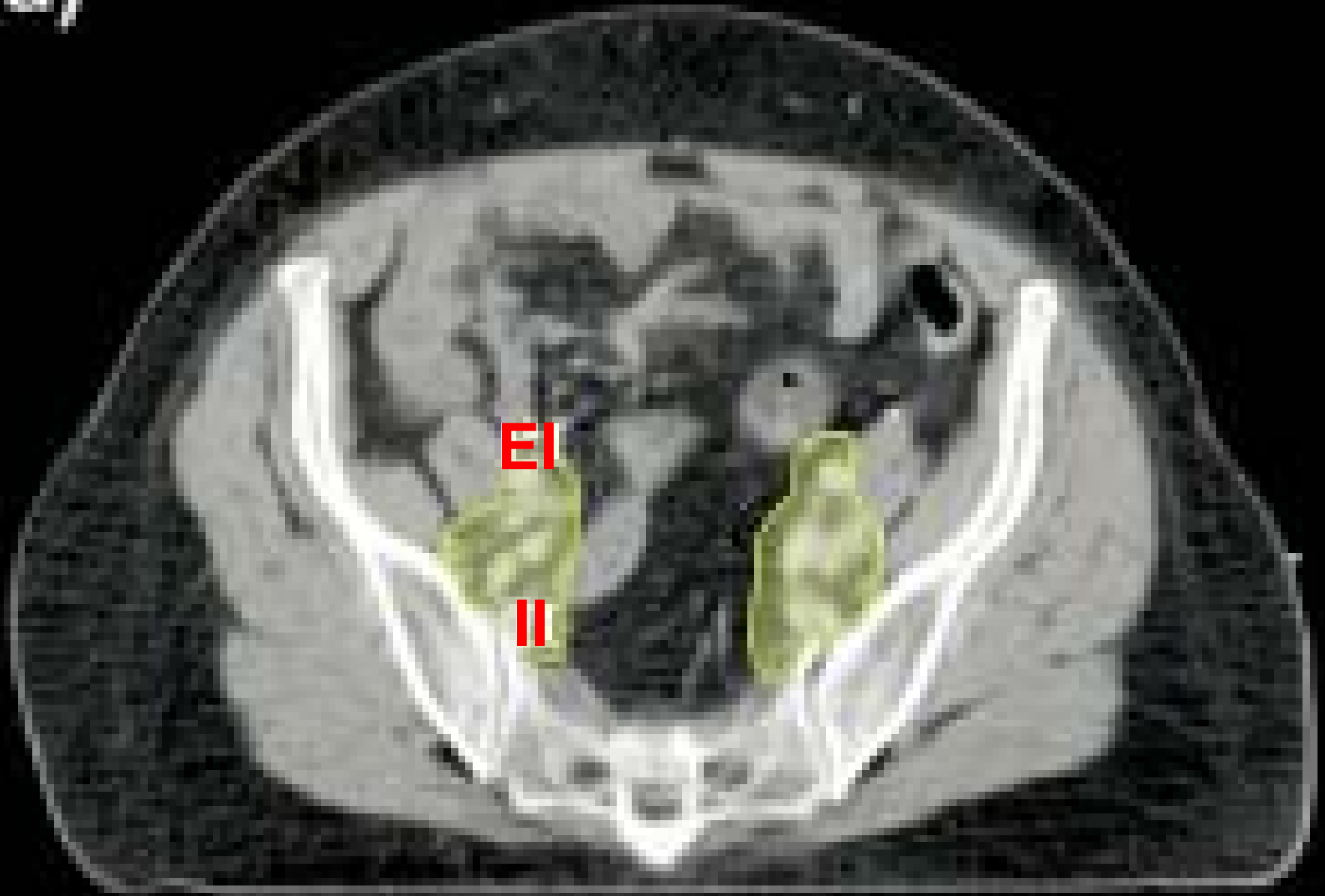
Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int. J. Radiation Oncology Biol. Phys.*, Vol 63.no.5, 1604-1612, 2005.

(c)



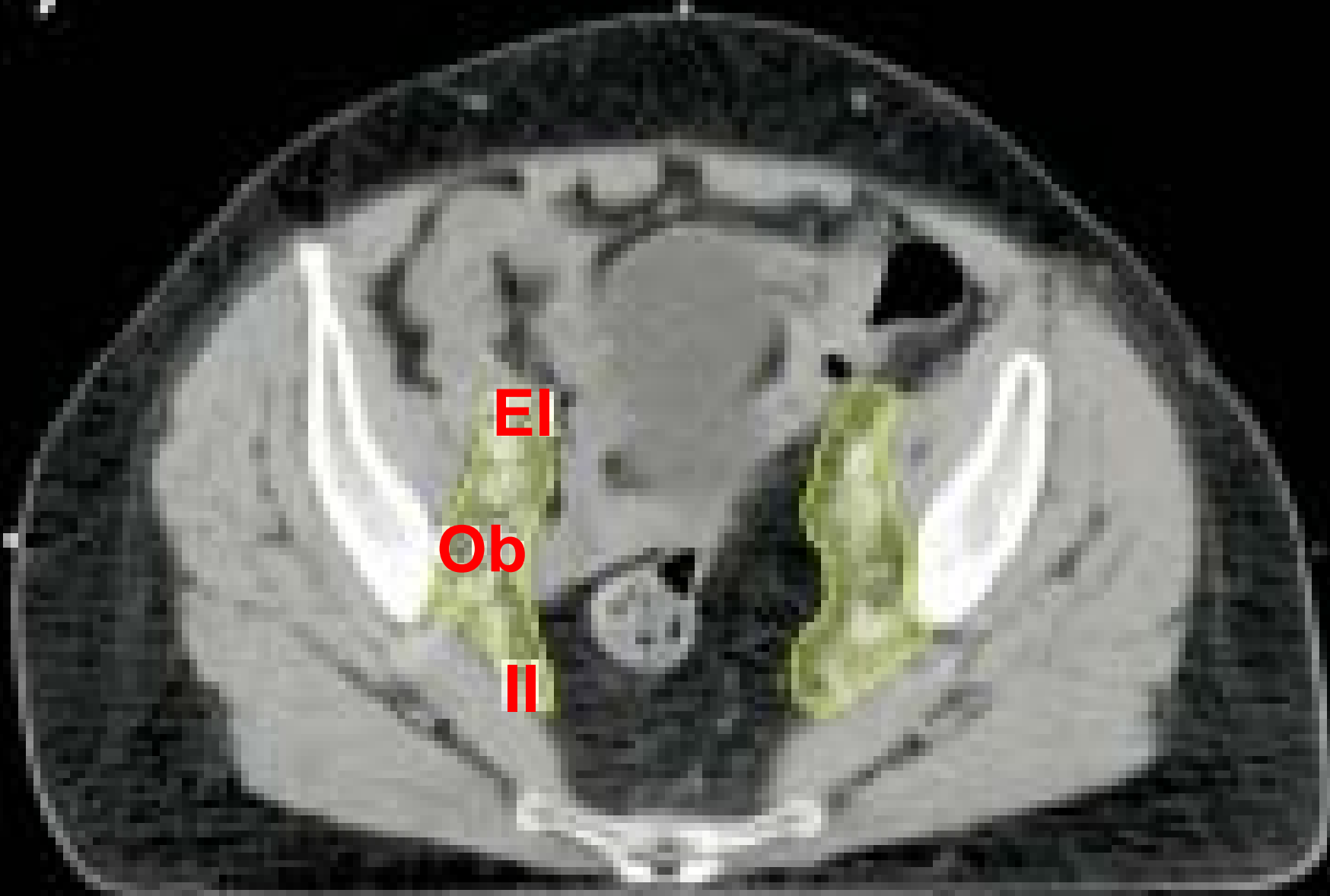
Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int. J. Radiation Oncology Biol. Phys.*, Vol 63.no.5, 1604-1612, 2005.

(d)



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.

(e)

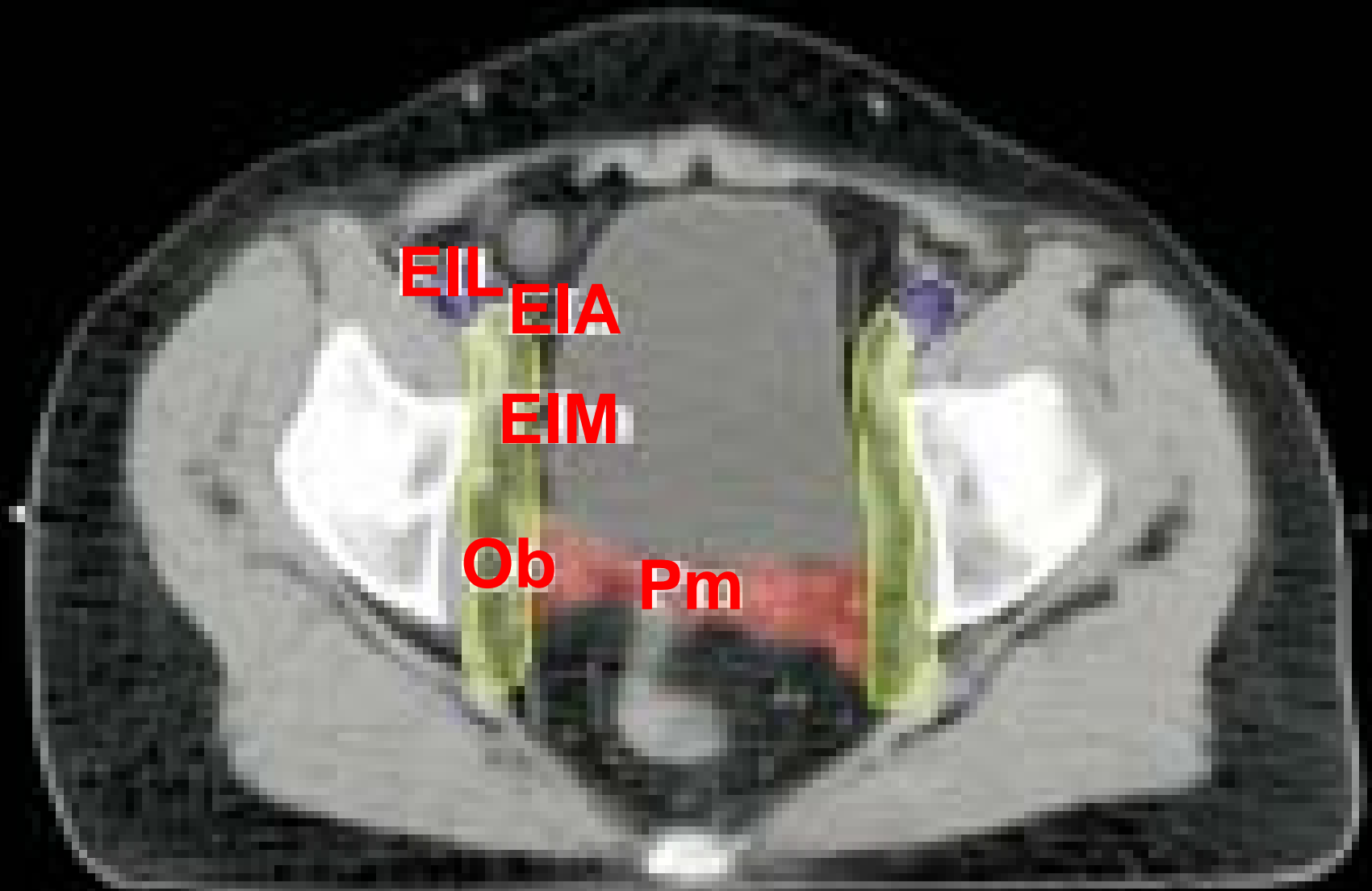


Taylor A, Rockal AG, Reznek RH et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int. J. Radiation Oncology Biol. Phys.*, Vol 63.no.5, 1604-1612, 2005.

(f)

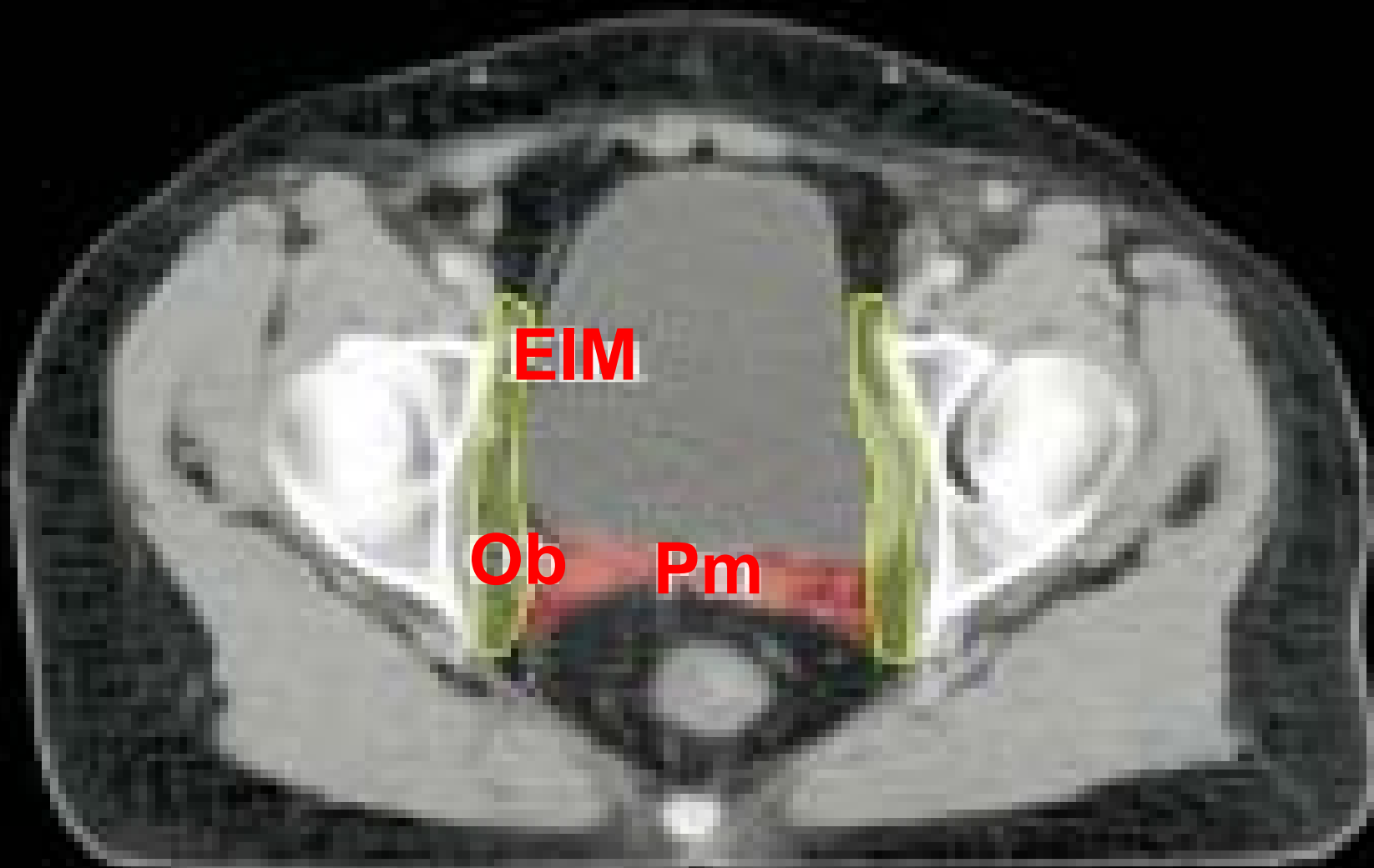


(g)



Taylor A, Rockal AG, Reznik 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.

(h)



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

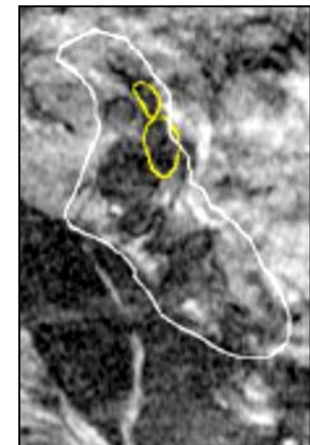
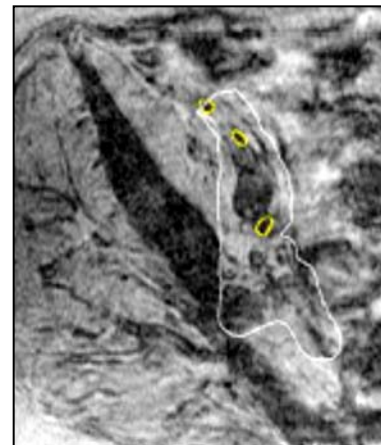
Vilarino-Varela MJ, et al. Radiother Oncol 2008

A verification study

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



99 % of nodes
were covered by
the trainee



Small W, et al. IJROBP, 2008

(postoperative setting)

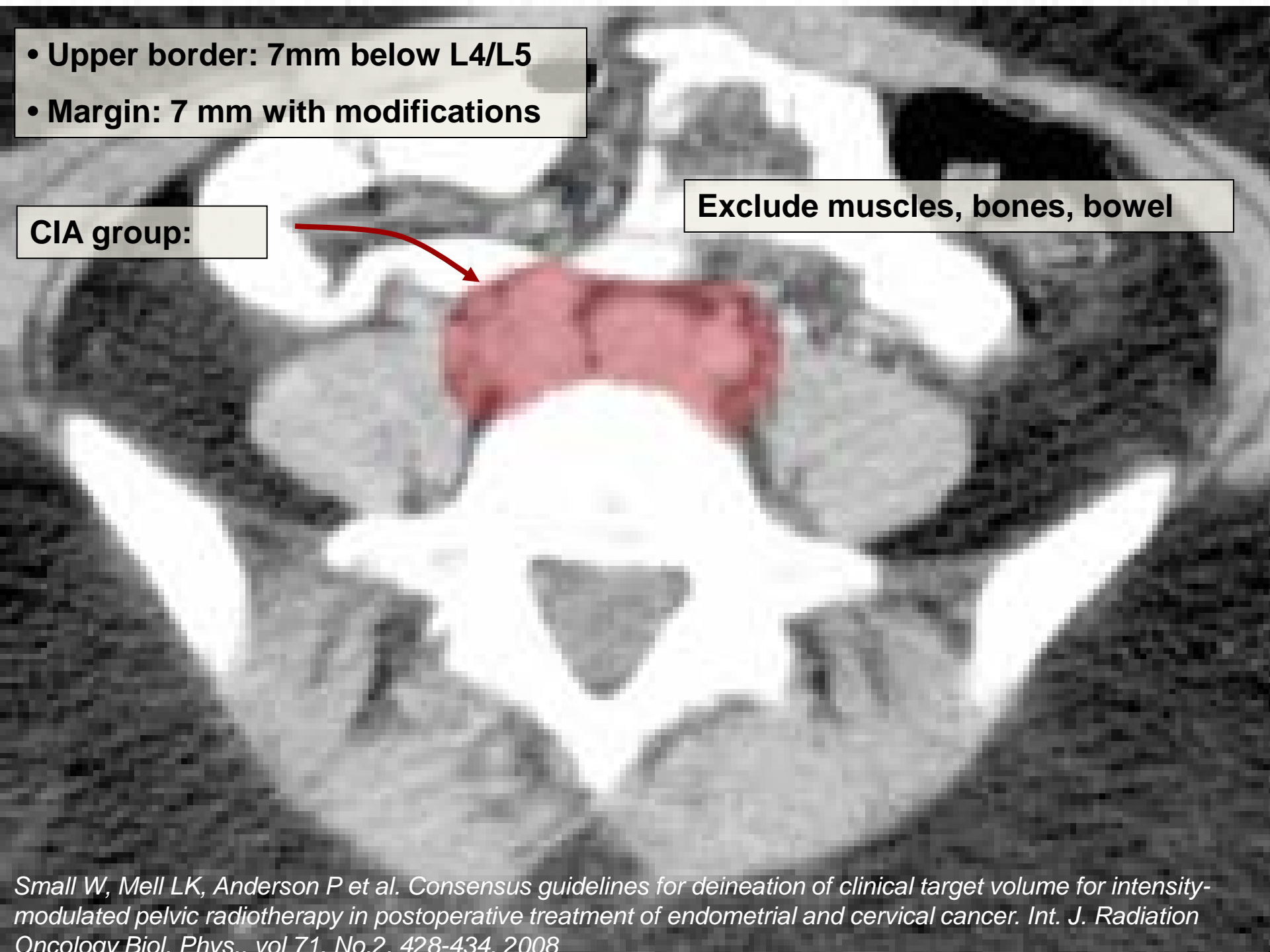
Pelvic nodal groups for cervix and endometrial cancer contouring:

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

- Upper border: 7mm below L4/L5
- Margin: 7 mm with modifications

CIA group:

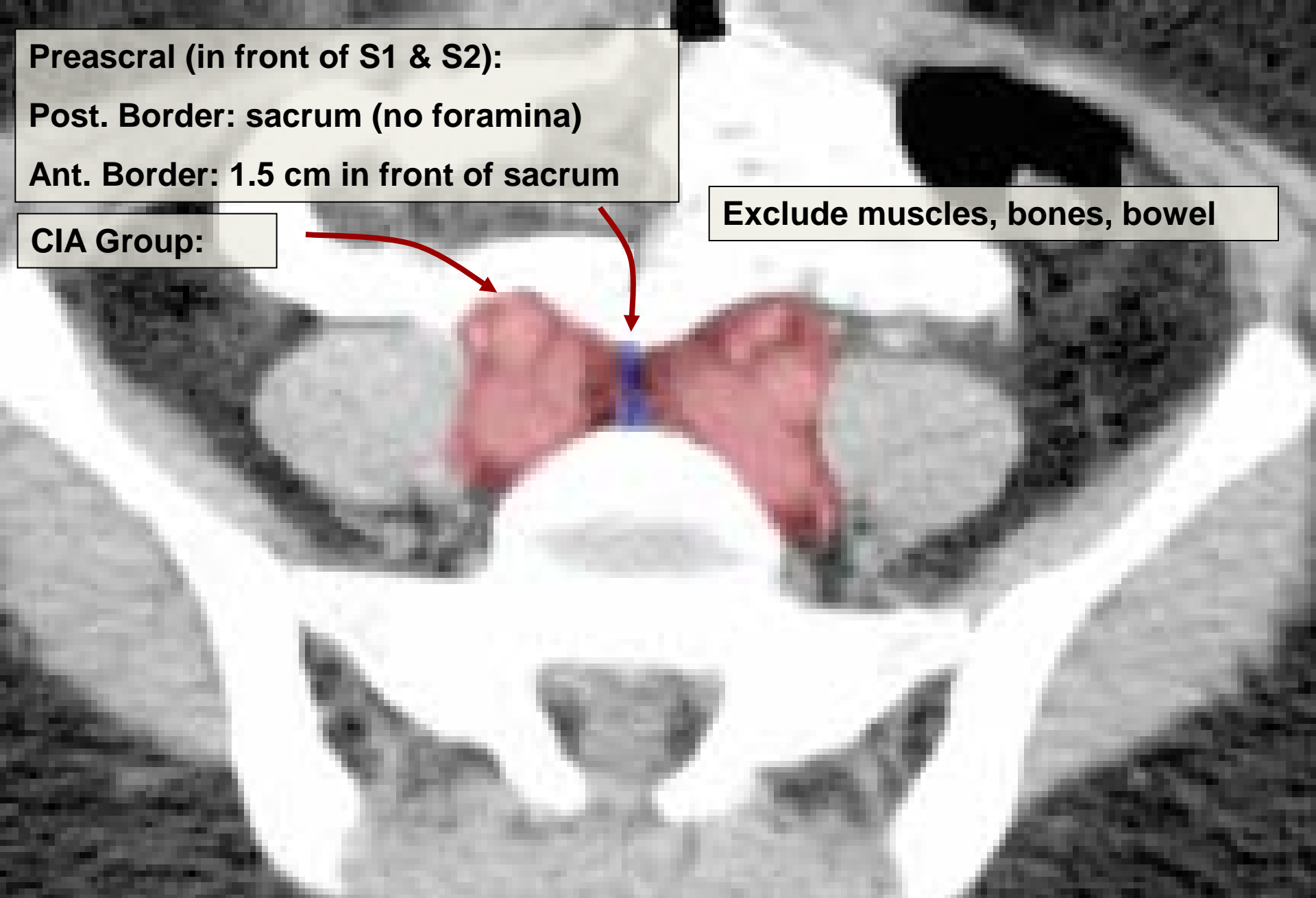
Exclude muscles, bones, bowel



Preascral (in front of S1 & S2):
Post. Border: sacrum (no foramina)
Ant. Border: 1.5 cm in front of sacrum

CIA Group:

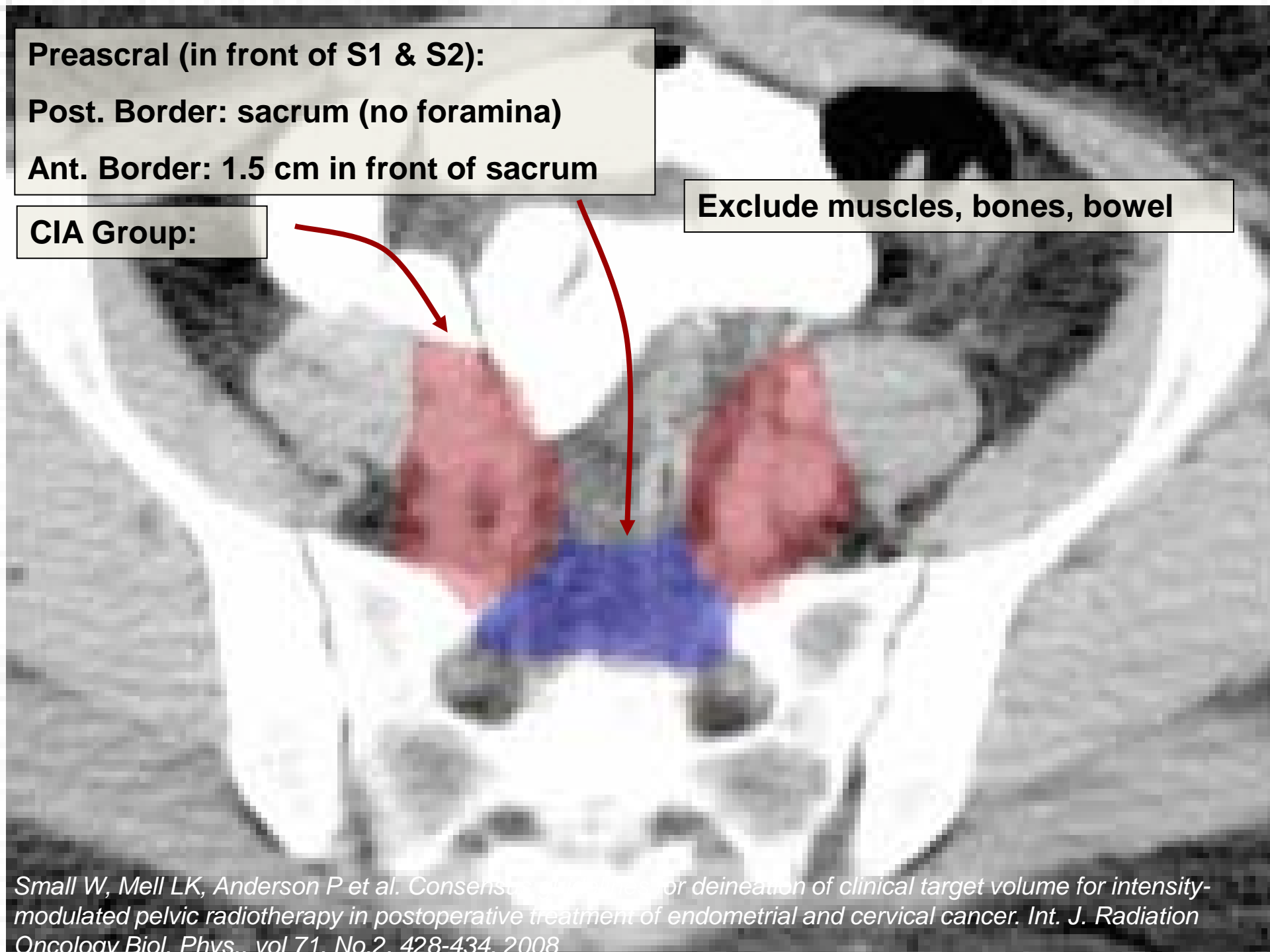
Exclude muscles, bones, bowel



Preascral (in front of S1 & S2):
Post. Border: sacrum (no foramina)
Ant. Border: 1.5 cm in front of sacrum

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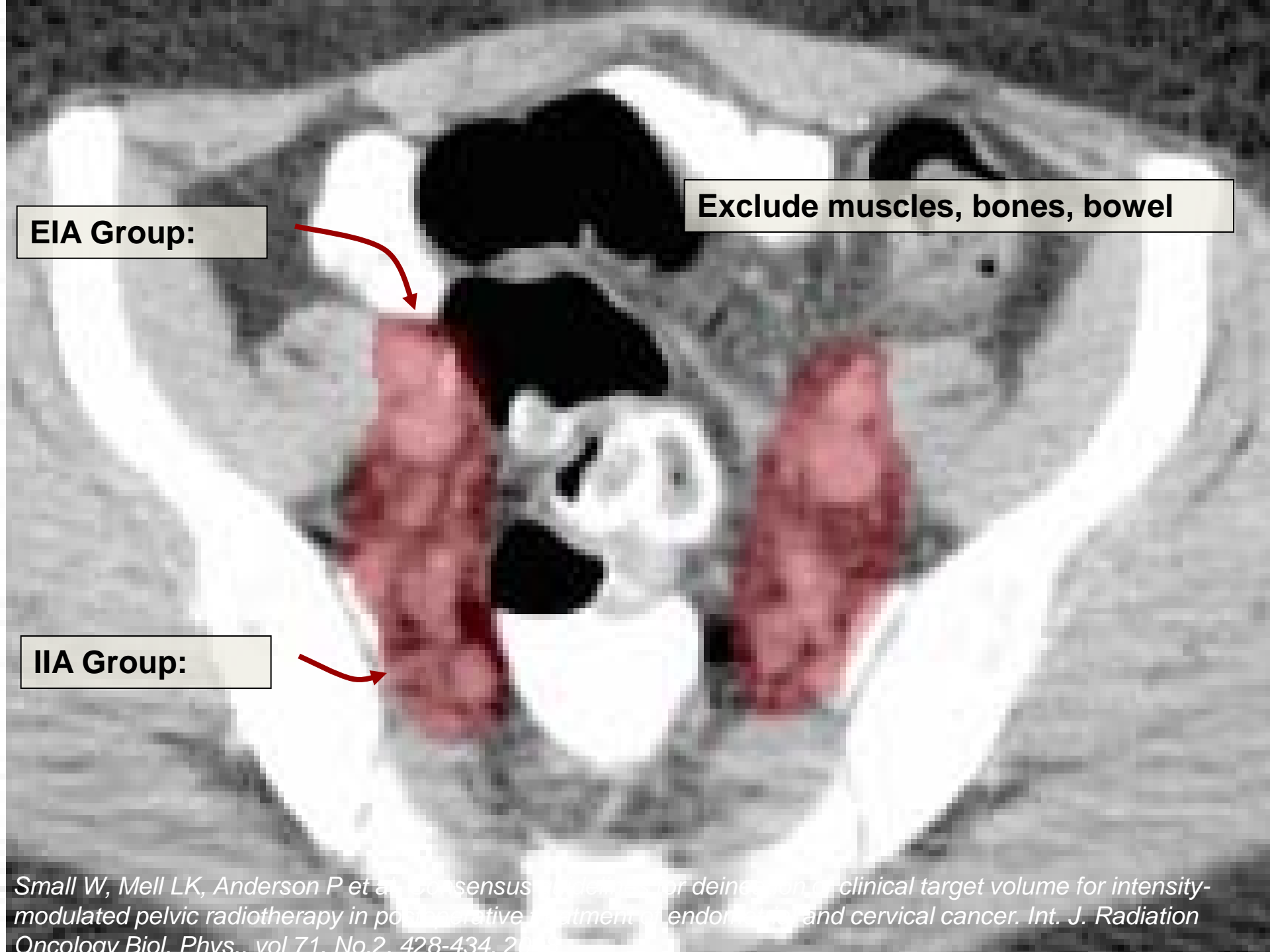
Exclude muscles, bones, bowel



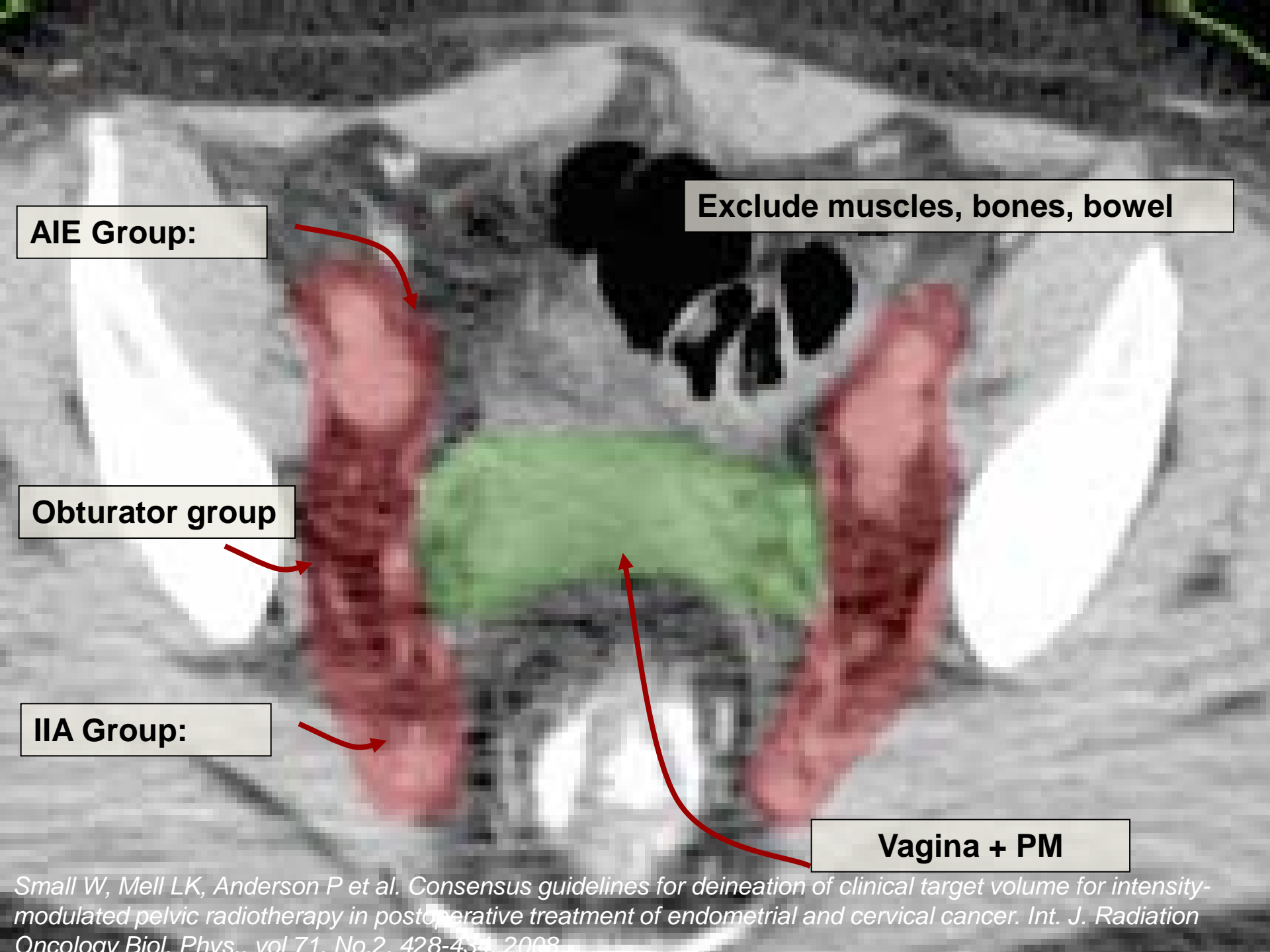
EIA Group:

Exclude muscles, bones, bowel

IIA Group:



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



AIE Group:

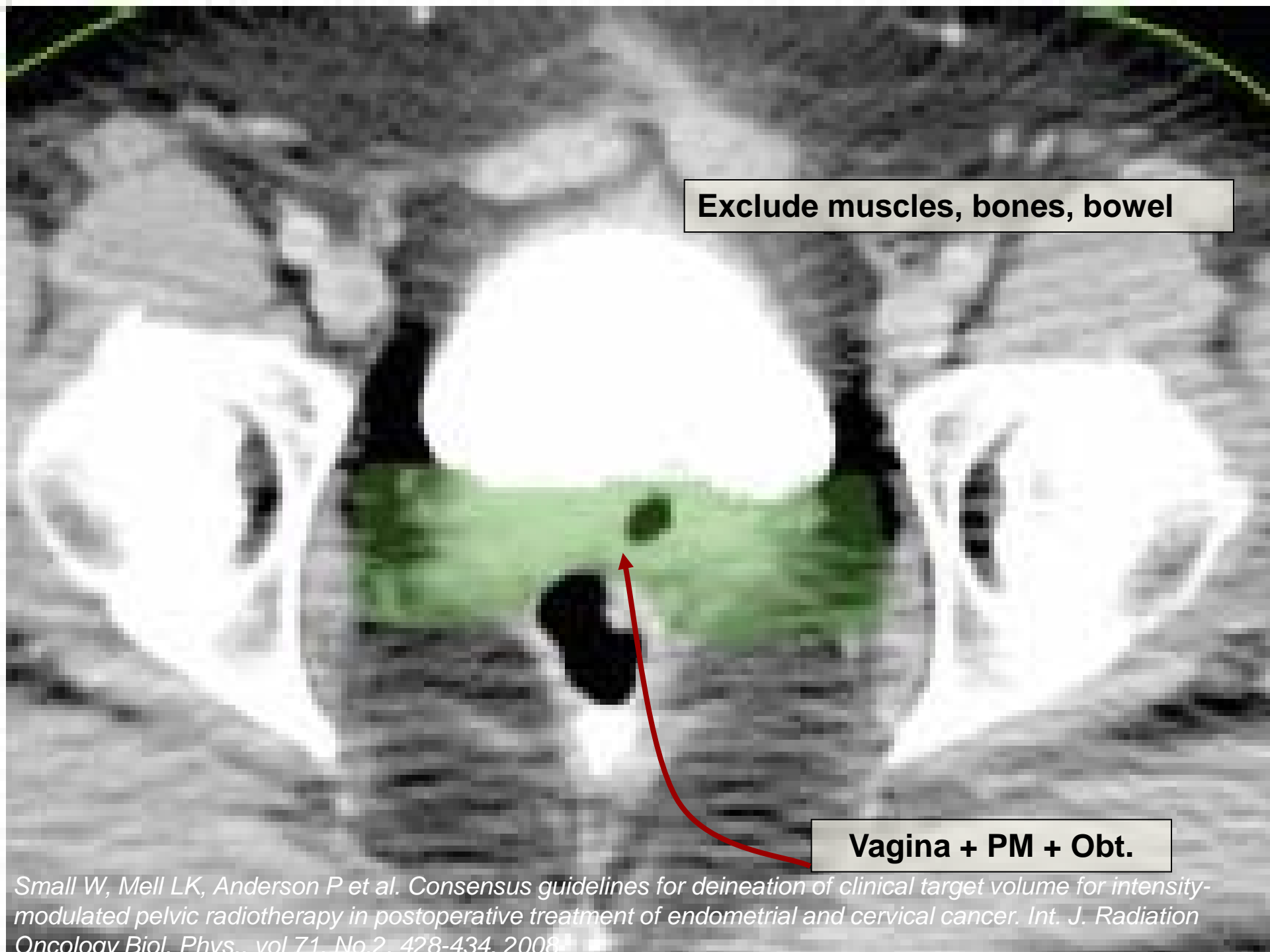
Exclude muscles, bones, bowel

Obturator group

IIA Group:

Vagina + PM

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, 2008.



Exclude muscles, bones, bowel

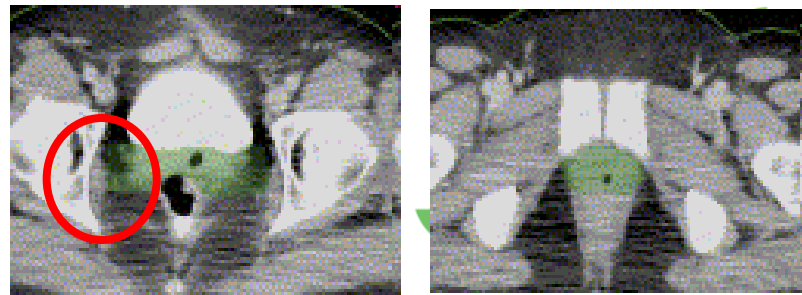
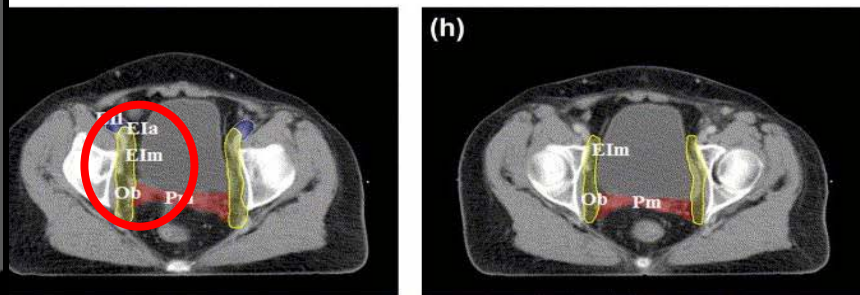
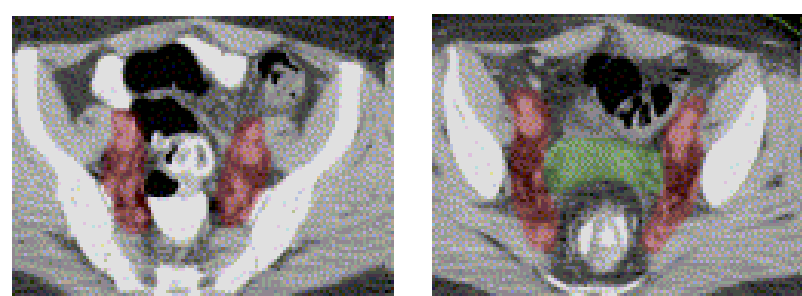
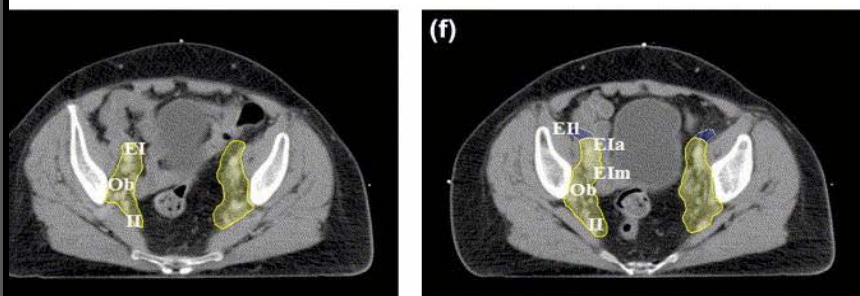
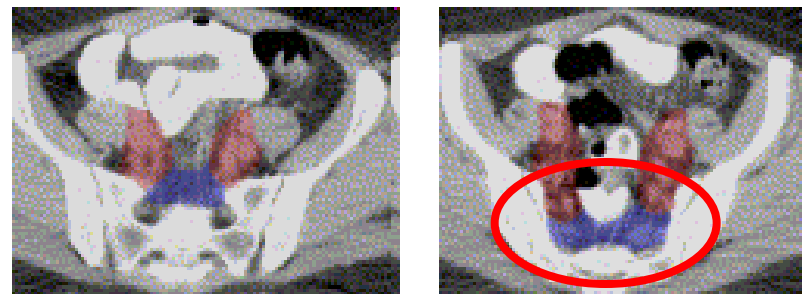
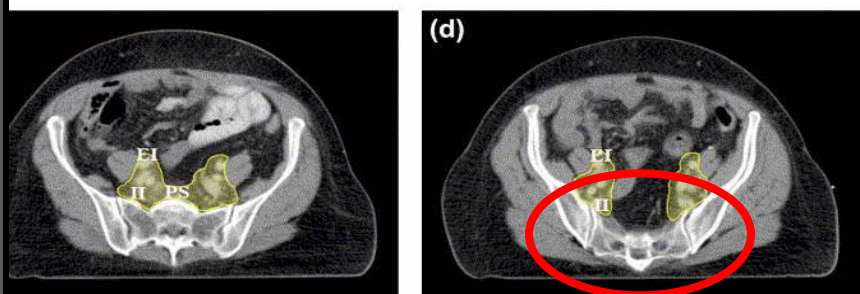
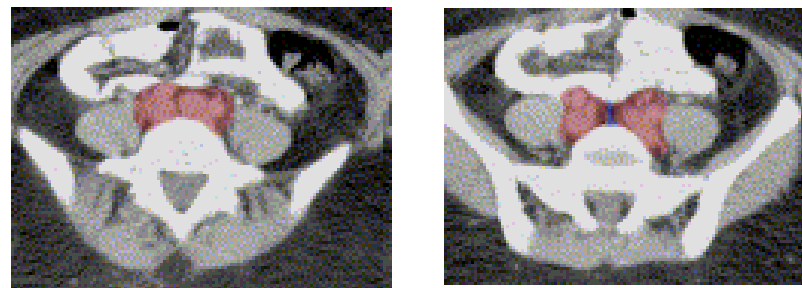
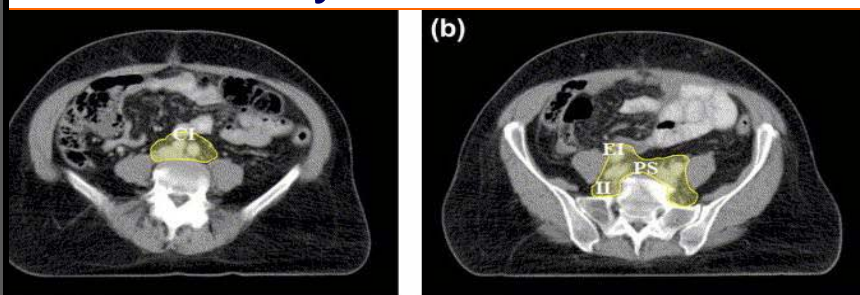
Vagina + PM + Obt.

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, 2008.

Taylor vs. Small

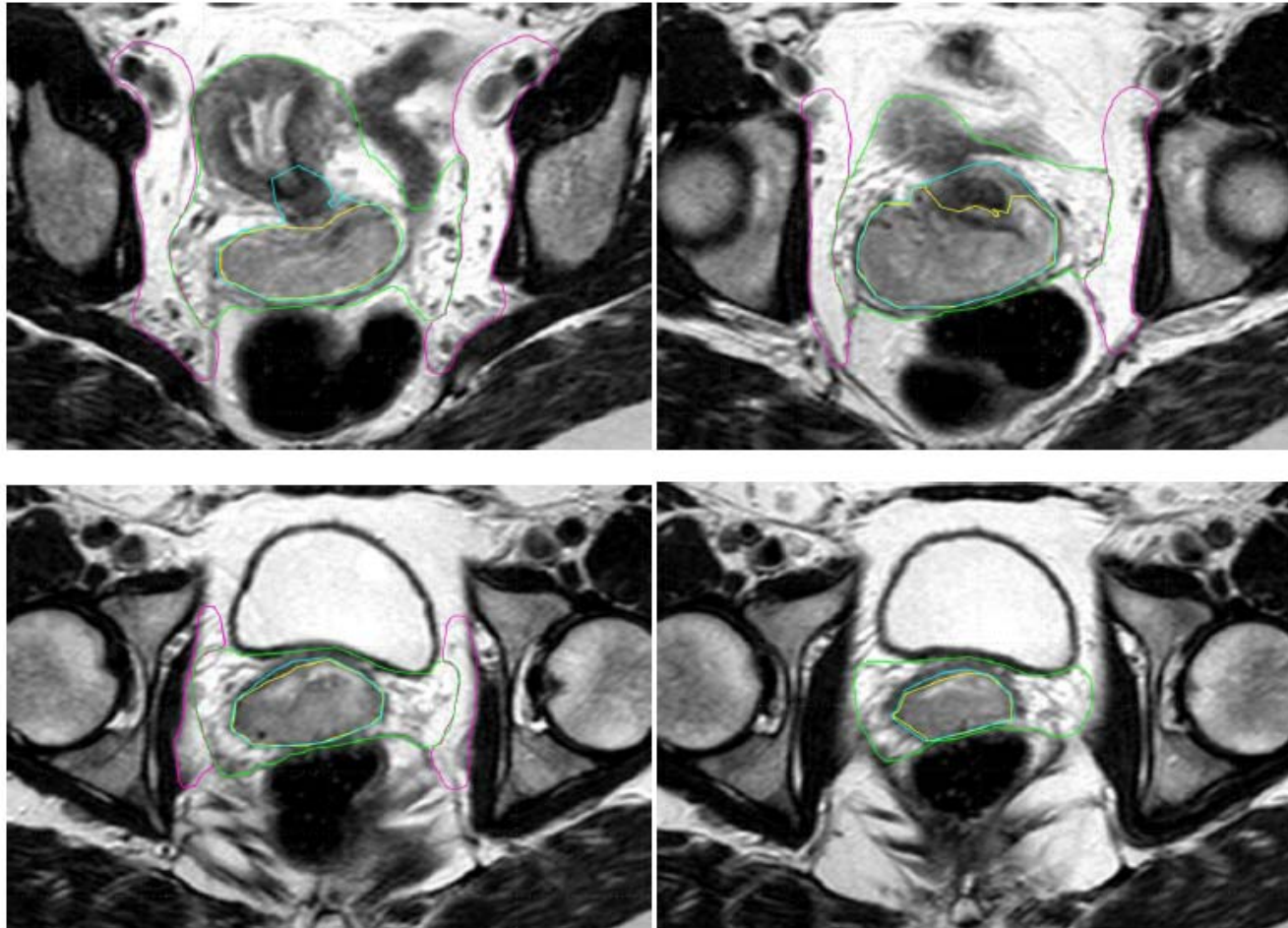
Taylor 2007

Small 2008



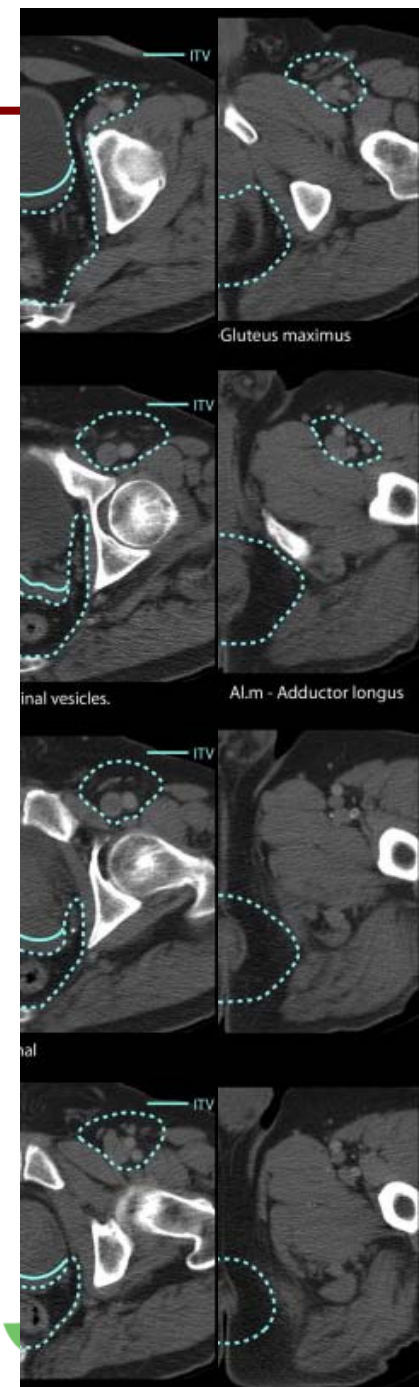
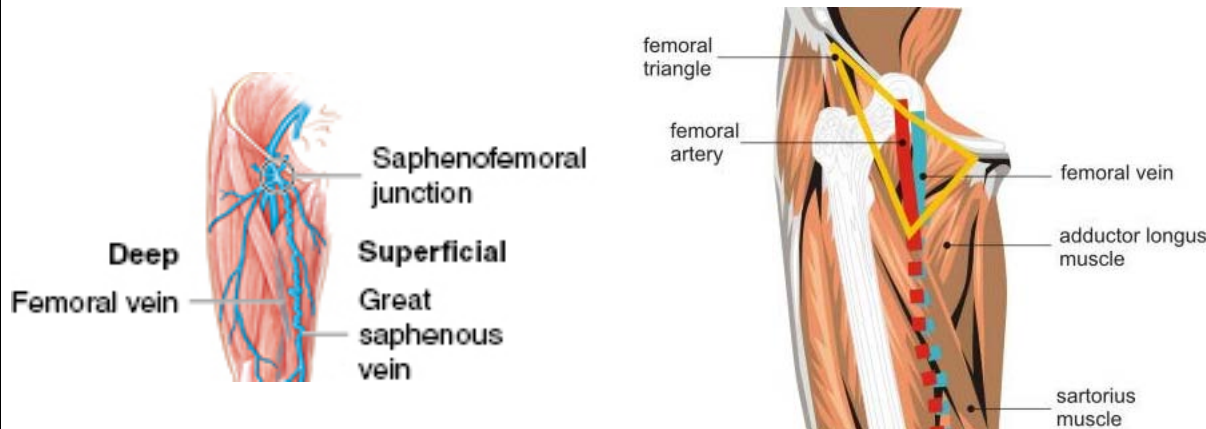
Elective nodal CTV: Caudal extension

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



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

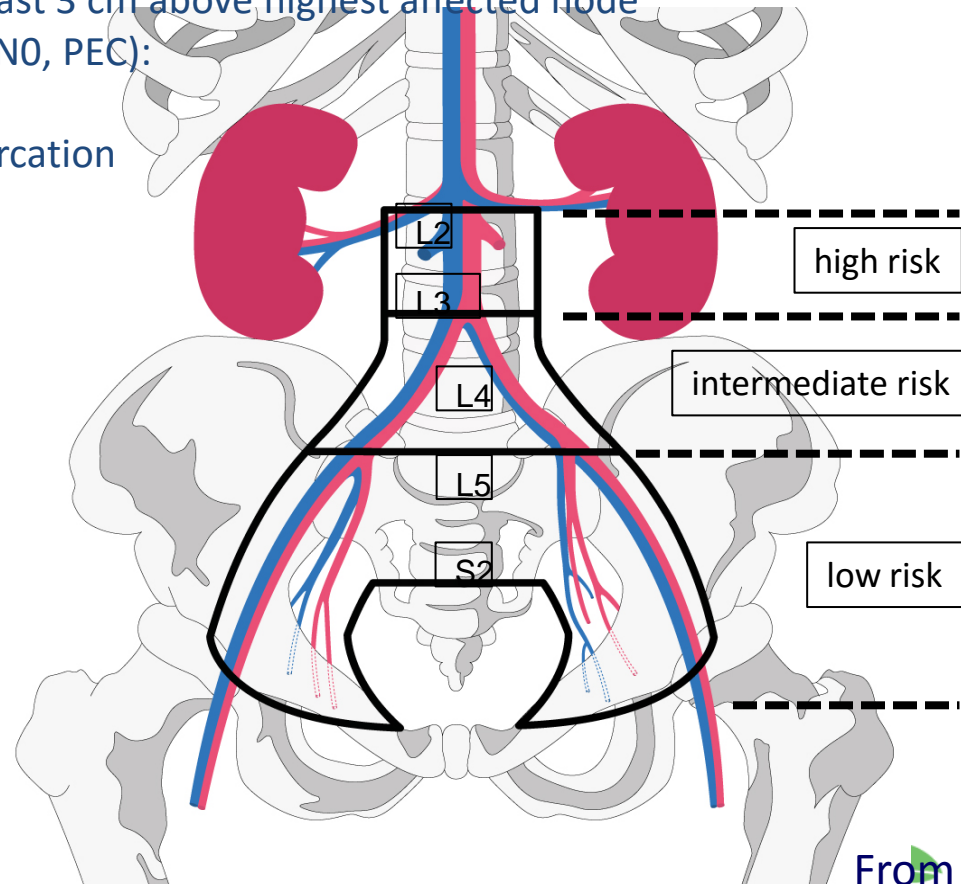


Ng et al., Australasian Gastrointestinal Trials Group (AGITG) Contouring Atlas and Planning Guidelines for Intensity-Modulated Radiotherapy in Anal Cancer, *Int. J. Radiation Oncology Biol. Phys.*, Vol 83, 1455-1462, 2005.

Elective nodal CTV: Cranial extension

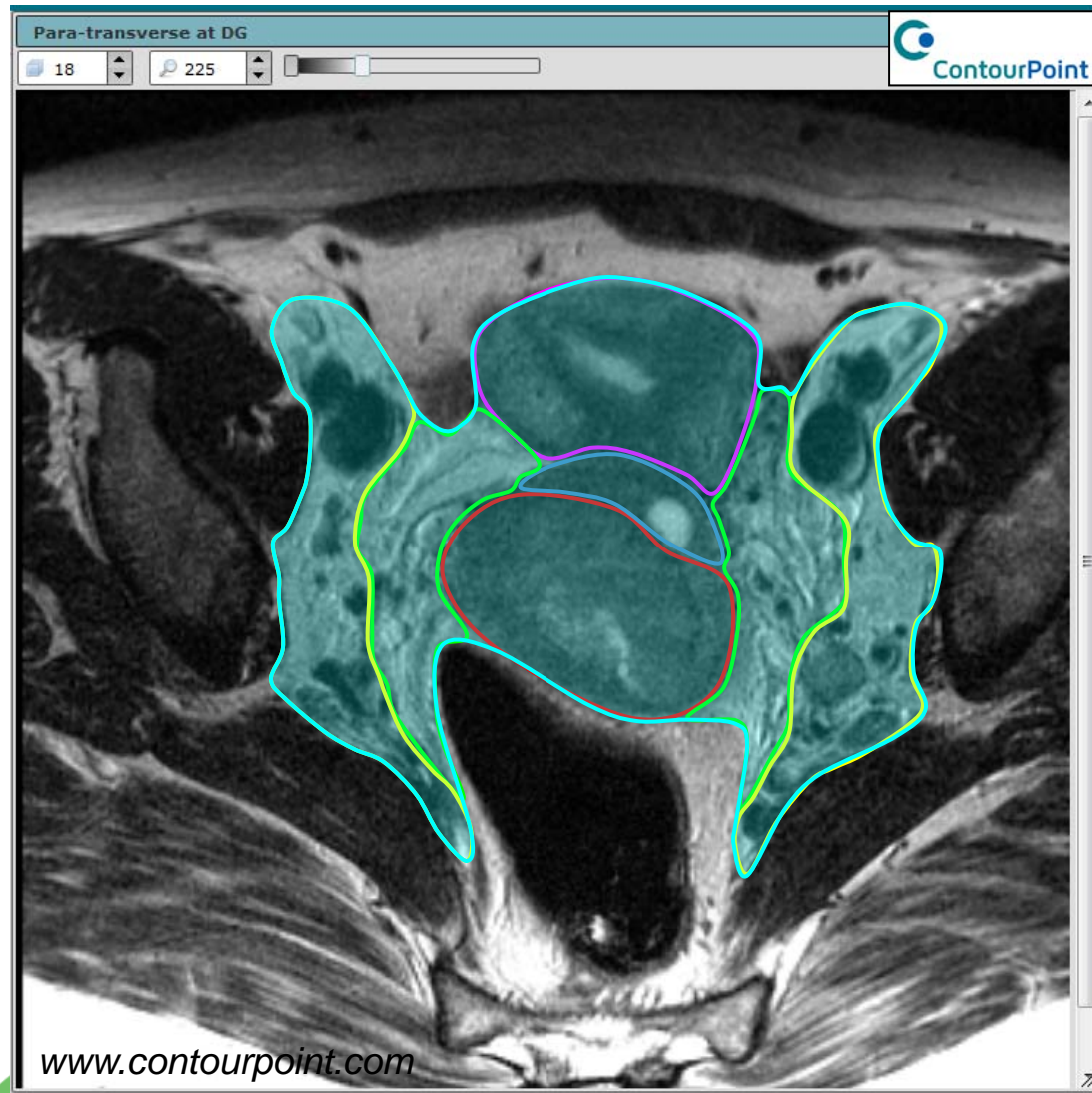
Ongoing investigations and discussion (EMBRACE II)

- 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



Total CTV for definitive cervix cancer EBRT

Initial CTV-T + Nodal CTV



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

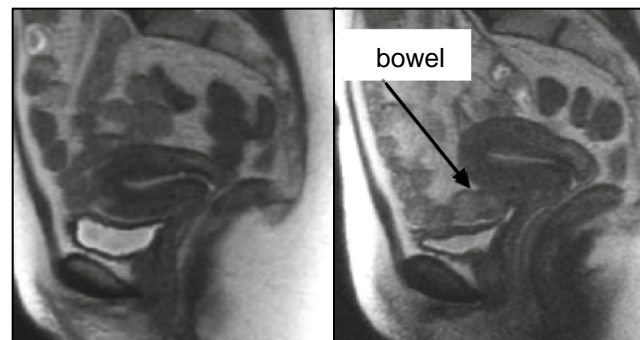
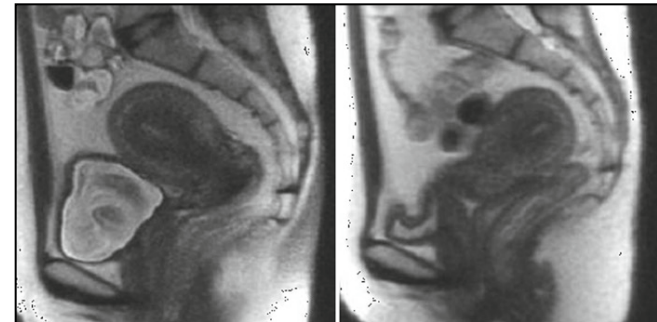
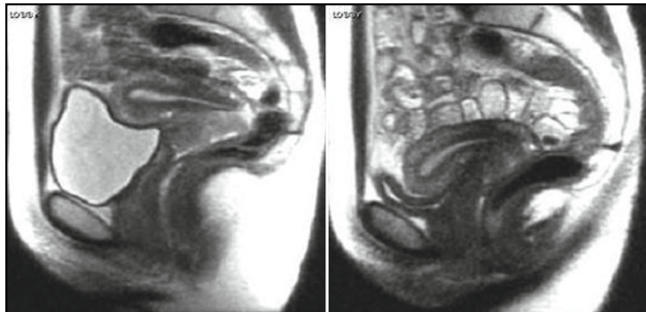
- A. 5 mm
- B. 7 mm
- C. 10 mm
- D. 5 mm with small adaptations
- E. 7 mm with small adaptations
- F. 10 mm with small adaptations



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 – Internal Target Volume

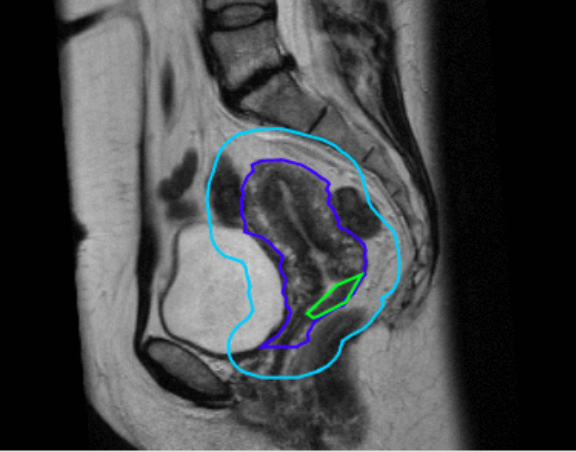
= CTV + margin for internal motion & deformation

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 MRI baseline & weekly Target motion not directly measured. Margins required to encompass GTV & CTV from week to week used as a surrogate for target shifts		Cervix cancer MRI & cine MRI – done baseline & weekly during standard EBRT Point of interest study – uterine fundus, uterine canal & cervical os		
Inter-fraction motion	GTV	CTV	Uterine fundus	Uterine canal	Cervical os
Sup/	Margin recommendations for ITV range from 10 – 24 mm				
Ant/post (mm)	Ant = 12 Post = 14	Ant = 24 Post = 17	AP = 14.5	AP = 13.1	AP = 11.2
Left/right (mm)	Rt = 12 Lt = 11	Rt = 12 Lt = 6	–	–	–
Comments	Bladder & bowel prep. not specified CTV-PTV margins recommendation: Ant = 24 mm; Post = 17 mm; Rt = 12 mm; Lt = 16 mm; Sup = 11 mm; Inf = 8 mm		Bladder & bowel prep. specified Suggested inter-fraction margins – fundus (10–40 mm); canal (10–25 mm), os (10–15 mm) Intra-fraction motion measured from 11,564 cine MRI frames Suggested intra-fraction margins- fundus (10 mm), canal (50 mm), os (5 cm)		

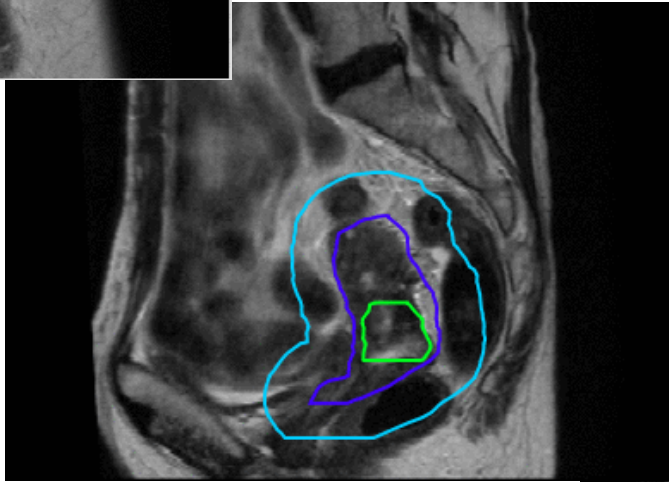
Lim K, et al. Image guidance...In: Viswanathan et al., eds. Gyn Radiat Oncol. Springer 2011

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

Target (CTV-T) motion during EBRT

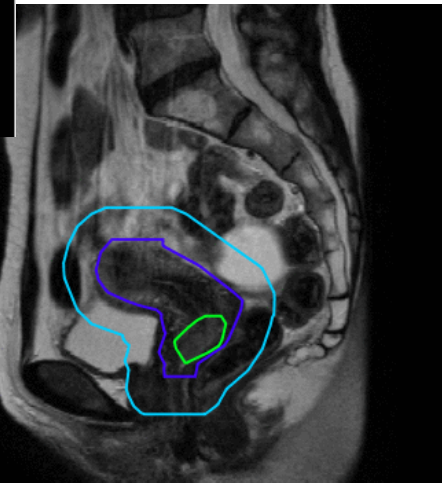


Low impact

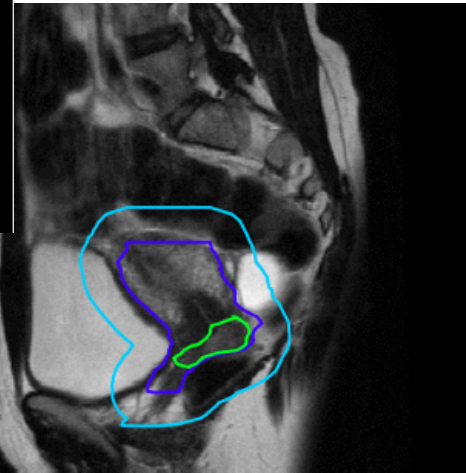


Low impact

High impact
of bladder
and bowel



High impact
of bladder



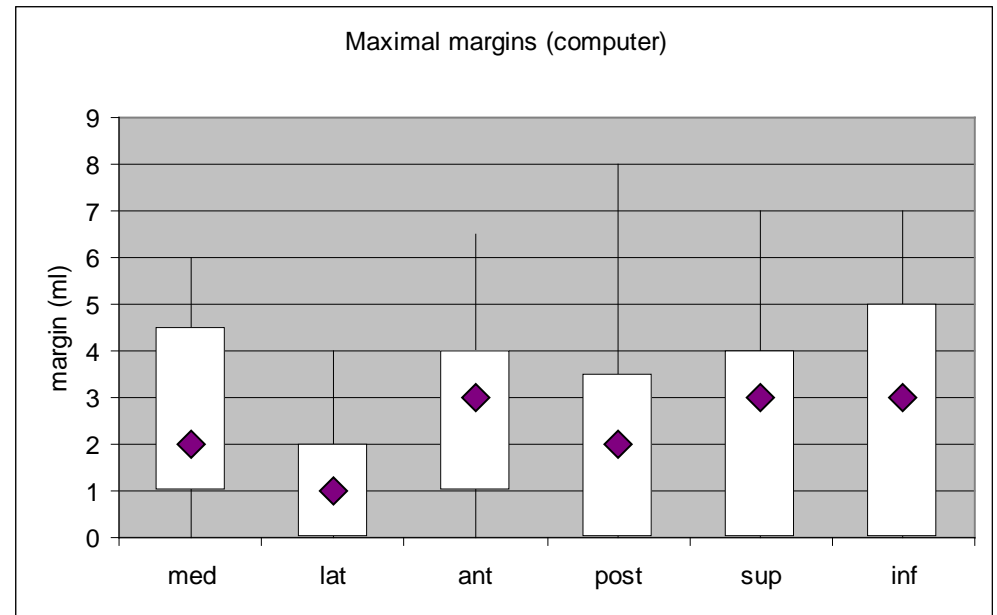
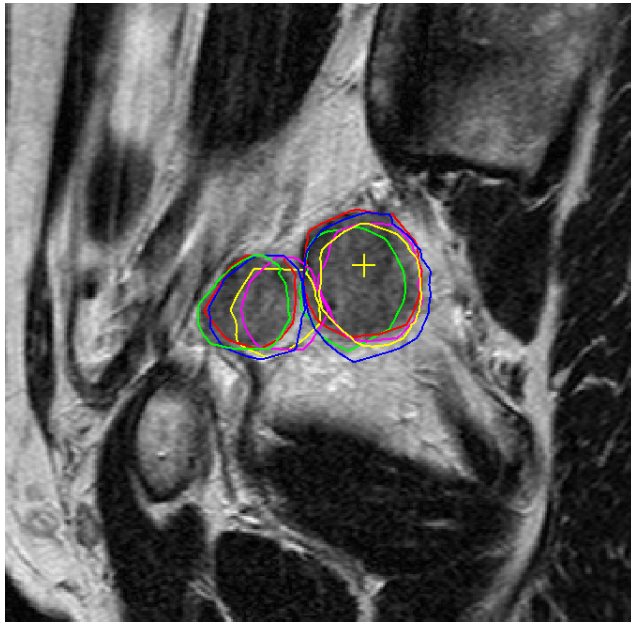
- 5 consecutive MRI's during EBRT
- Impact of changes in bladder and bowel filling on position changes of uterus
- Not only one organ is responsible

GTV
CTV
PTV

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)



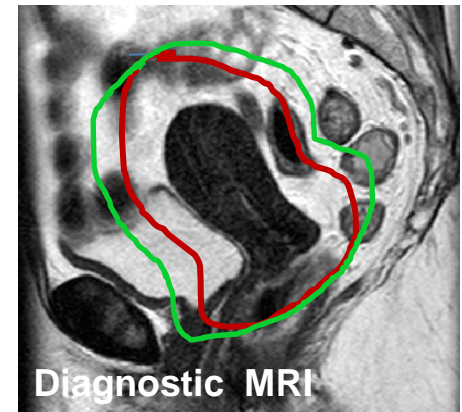
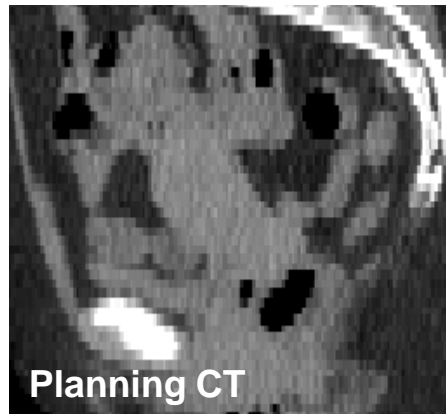
“Mover or non-mover” ?

Repeated MRI with changing bladder fillings

To detect “Movers and Non-movers”

Work in progress

Check: rectal filling!

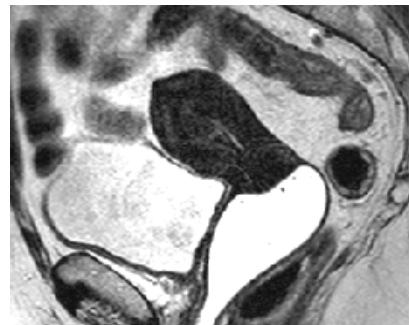
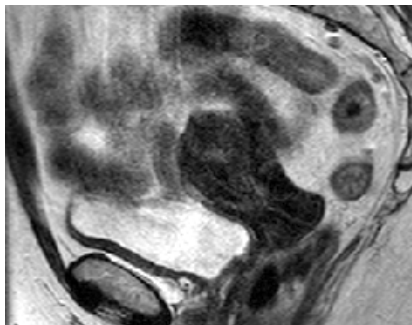
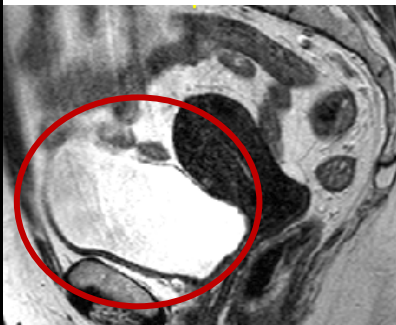


medium bladder filling intended

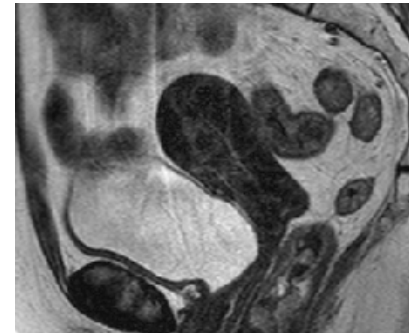
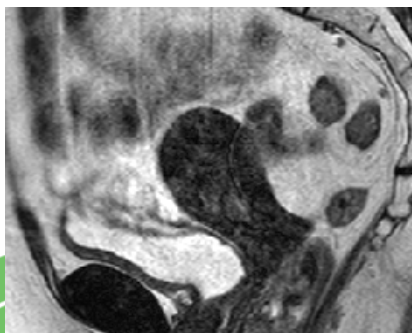
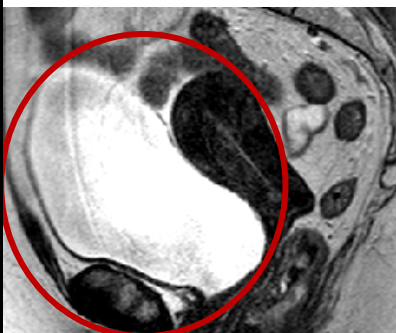
full bladder

empty bladder

medium bladder



Pre-treatment

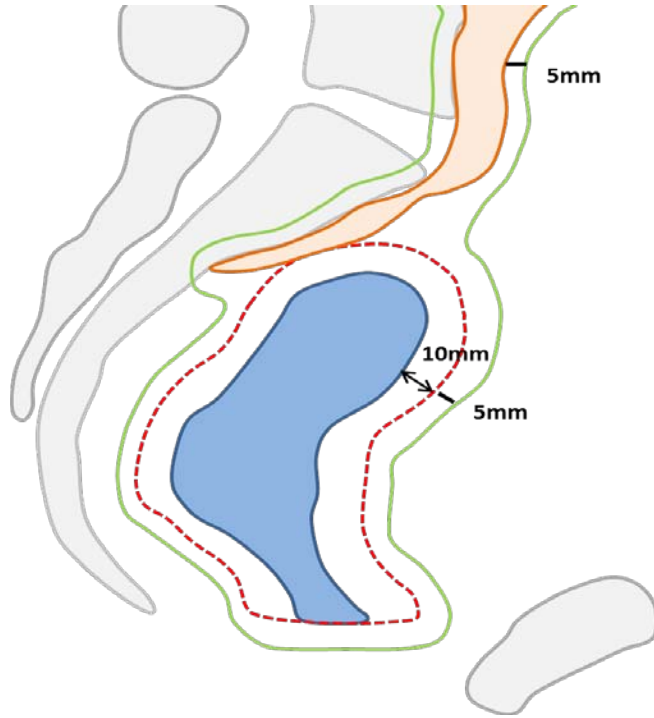


Week 1 EBRT

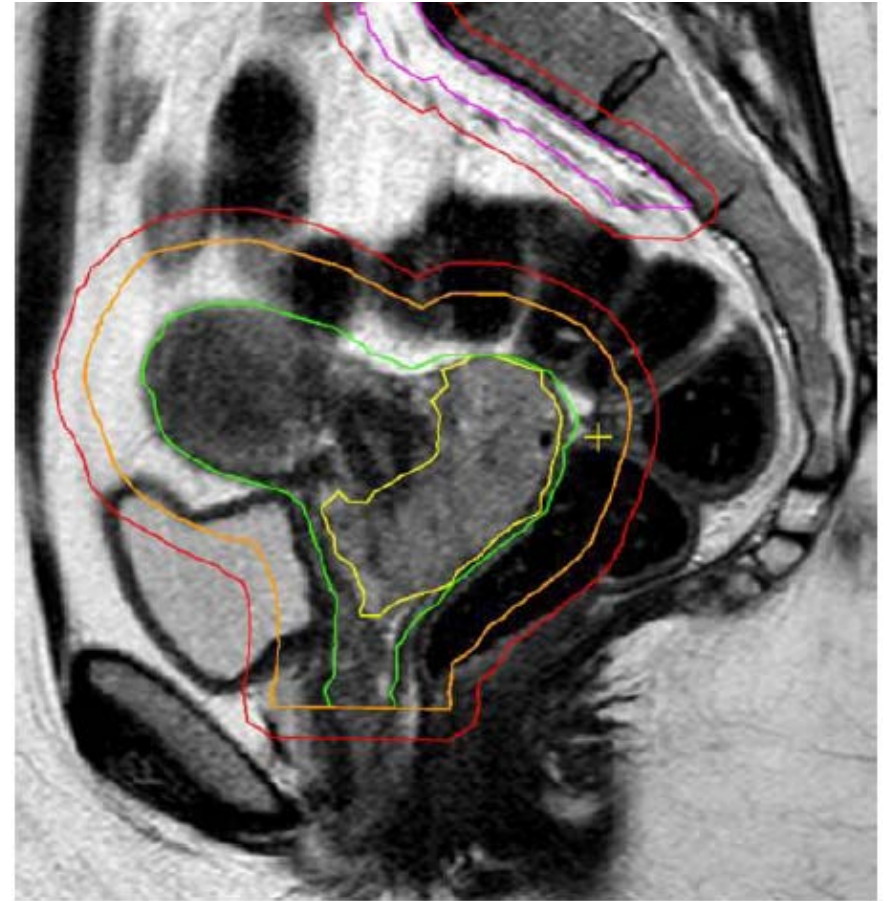


Courtesy
Petra Kroon-van Loon
Jochem Hes

ITV based on standard margin approach



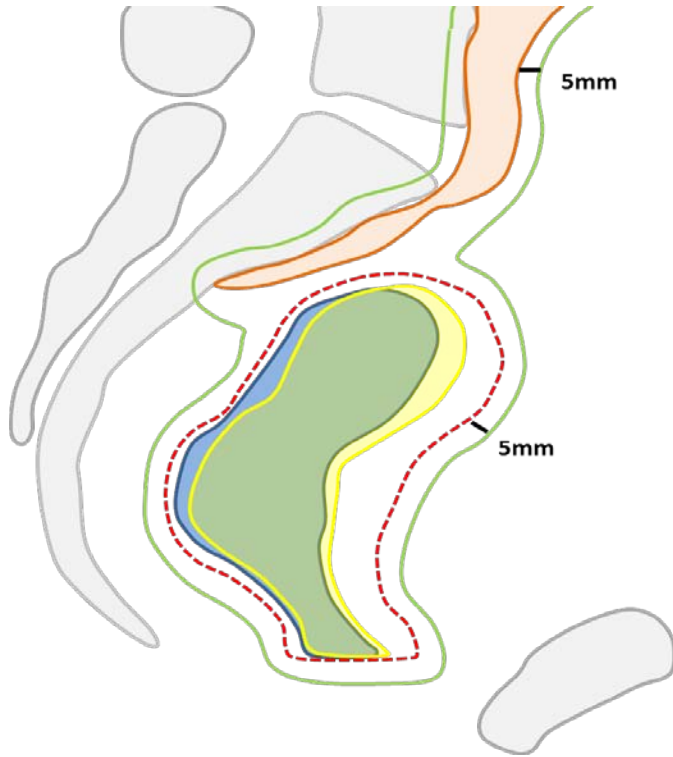
CTV-T LR (CT)
CTV-E
ITV-T LR
PTV-45



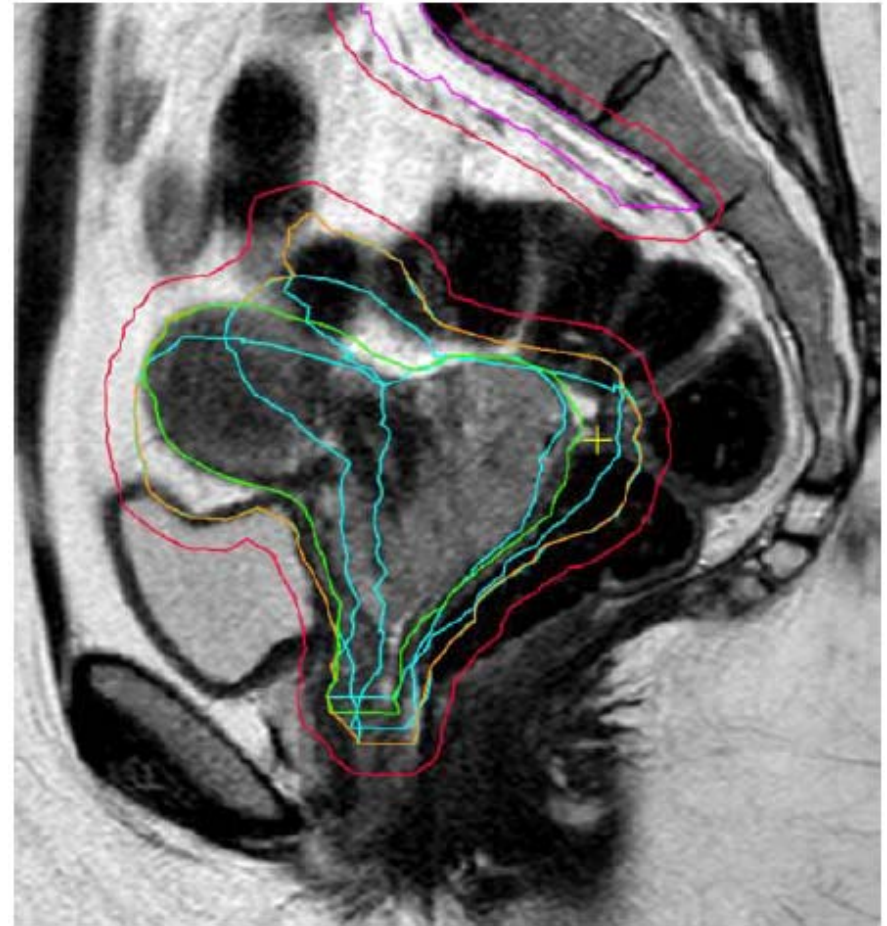
From EMBRACE II protocol



Individualized ITV



- 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 margin for internal motion & deformation
- CTV-ITV margin depends on position verification method
- No reliable recommendations for ITV margins
- Margins may differ between patients
- Nodes move a bit, too

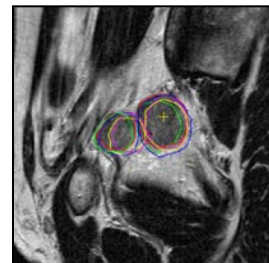
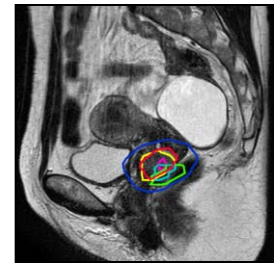
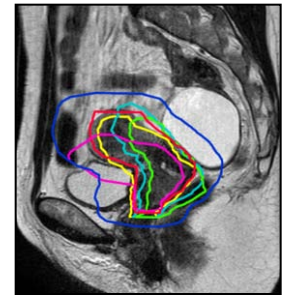
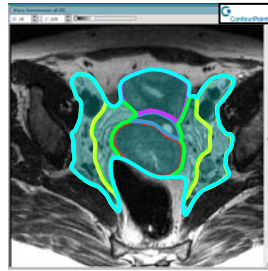


Image guidance, organ motion and ITV/PTV

ESTRO Teaching Course
Image-Guided Cervix Radiotherapy – with a special focus on adaptive
brachytherapy

Toronto 2016

Kari Tanderup, Richard Pötter

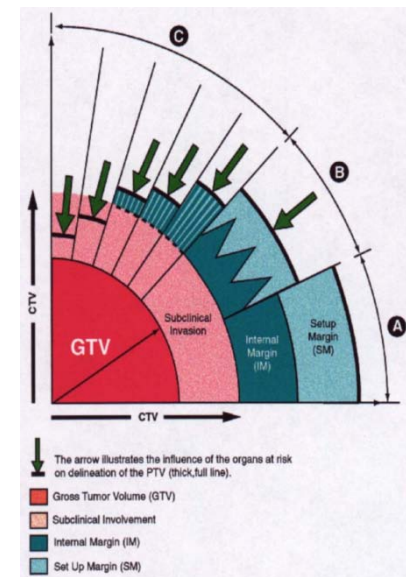
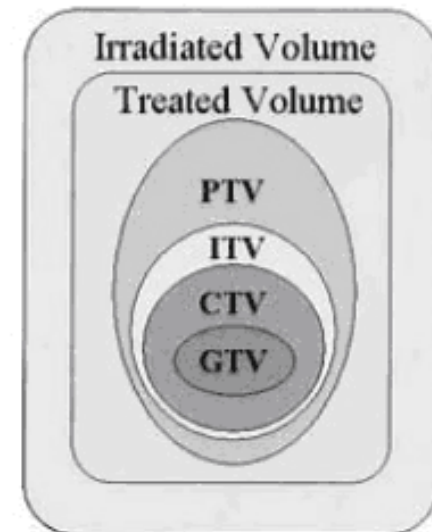


Aarhus University Hospital



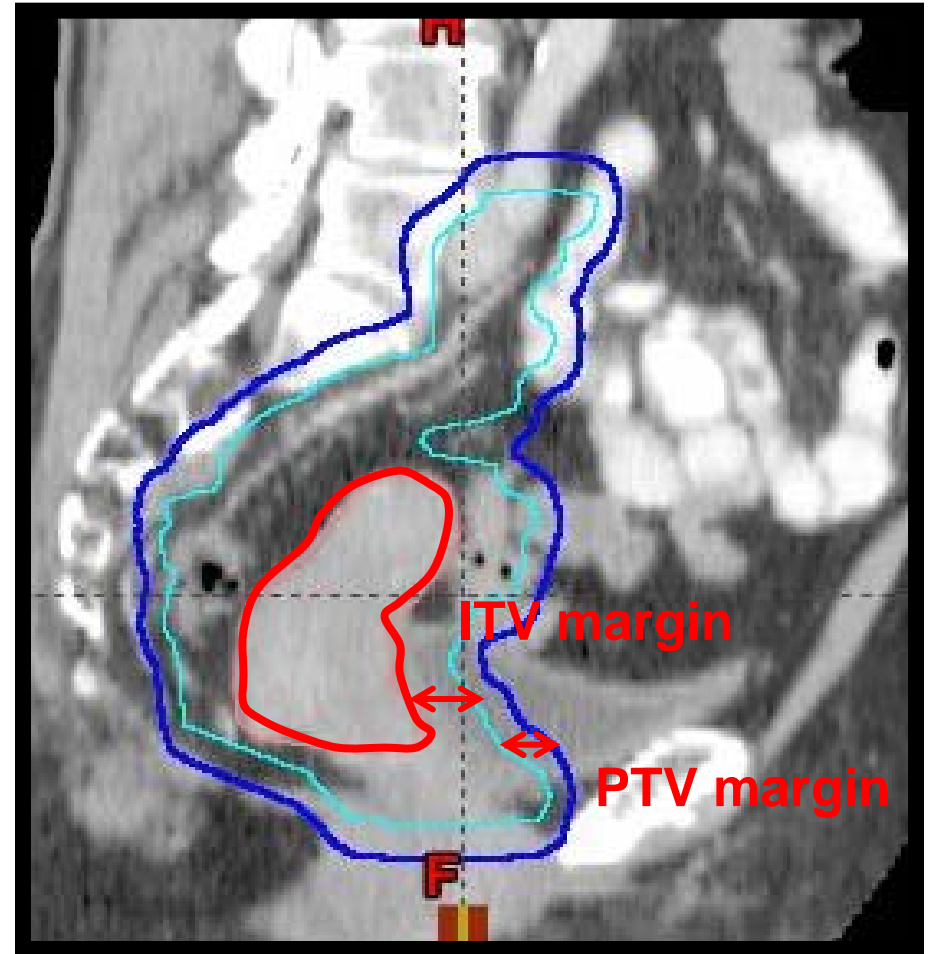
ITV and PTV

- **ITV: Internal variations**
 - **Position, size and shape of CTV**
 - Tumour shrinkage
 - Organ movement
 - Organ deformation
- **PTV: External variations**
 - **Beam positioning**
 - **Patient set-up**
- **If no considerable internal variations are present**
 - **Expansion may be performed directly from CTV to PTV**
- **ITV and PTV margins are not directly “additive”**



Margins in cervix cancer

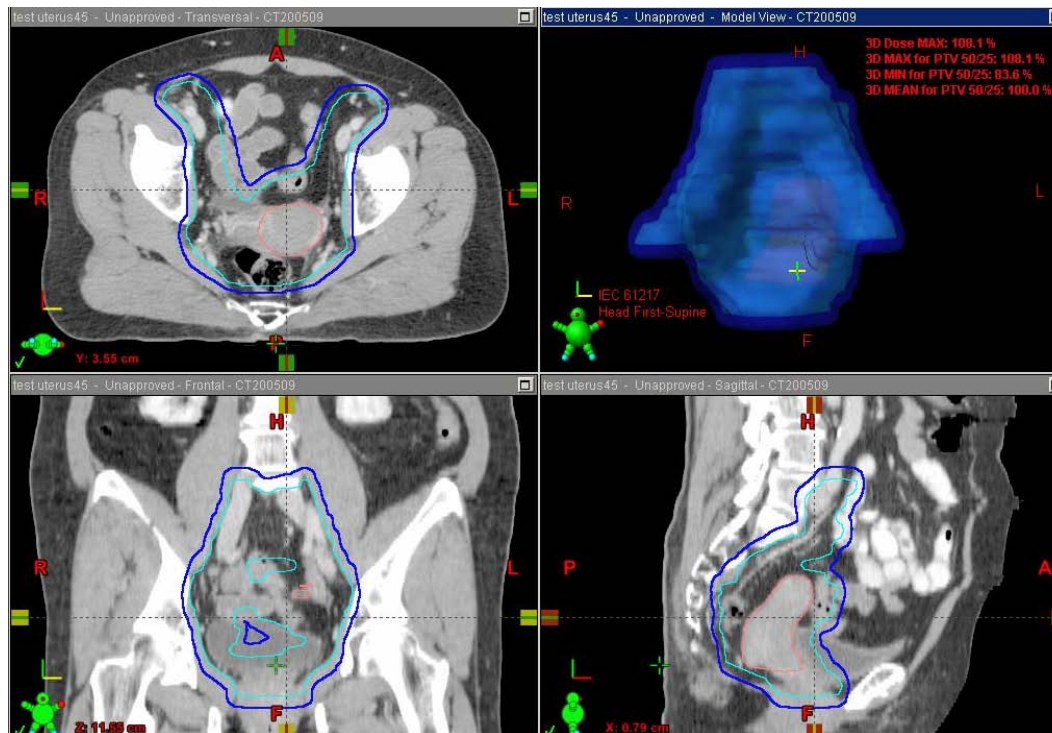
- **Primary CTV**
 - ITV margin
 - PTV margin
- **Pathologic nodes**
 - PTV margin
- **Elective CTV**
 - PTV margin



PTV elective target volume

- **Assumption:**

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

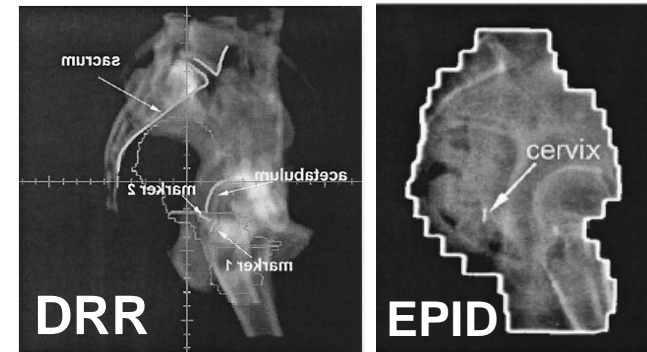


IGRT methods

● Registration on bony anatomy:

■ EPID (Electronic Portal Imaging Device)

- MV
- 2D



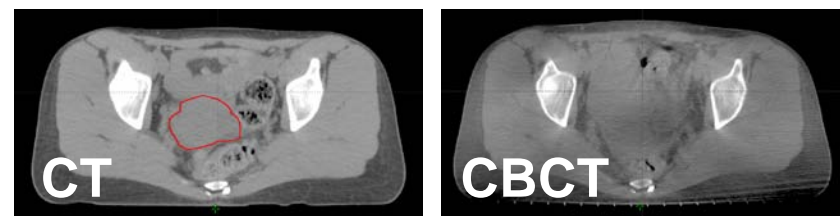
■ kV imaging (OBI – On Board Imaging)

- kV
- 2D



■ CBCT (Cone Beam CT) imaging

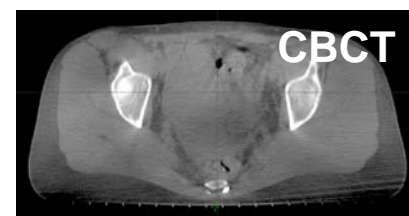
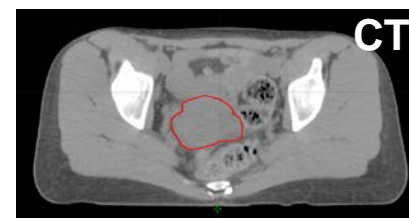
- kV
- 3D



Skin marks versus daily bony registration

● Daily image guidance with bony fusion

- Initial set-up according to skin marks
- Image fusion according to bone
- Verification of fusion
- Couch correction
- Typically 5mm PTV margin



● Set-up on skin marks (no daily image guidance):

- Imaging at first RT or e.g. weekly
- Typically 8-10mm PTV margin

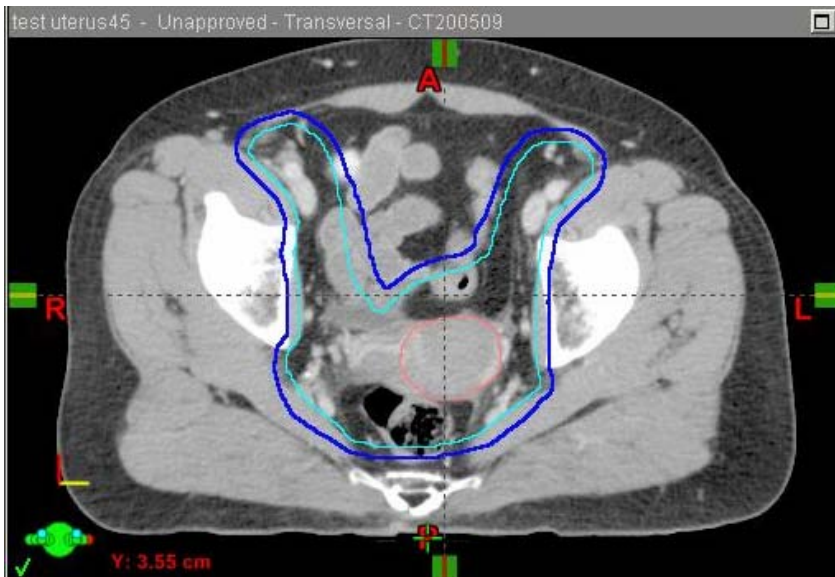
Variable	Vertical [mm]	Lateral [mm]	Longitudinal [mm]
Mean (M)	0,4	2,7	0,4
Σ	3,6	2,9	2,6
σ	3,6	3,2	2,4
Margin*	11,6	9,6	8,2

Van Herk formalism: $2,5\Sigma+0,7*\sigma$

Semin Radiat Oncol 2004; 14:52-64

Which PTV margin do you apply for CTV-E?

- A. 0-5 mm**
- B. 6-9 mm**
- C. ≥ 10 mm**



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

- 1. It is too many resources to implement daily IGRT**
- 2. It will not have impact on morbidity**
- 3. 5mm PTV margin is not safe for target coverage**
- 4. PTV margin reduction to 5mm is worthwhile**

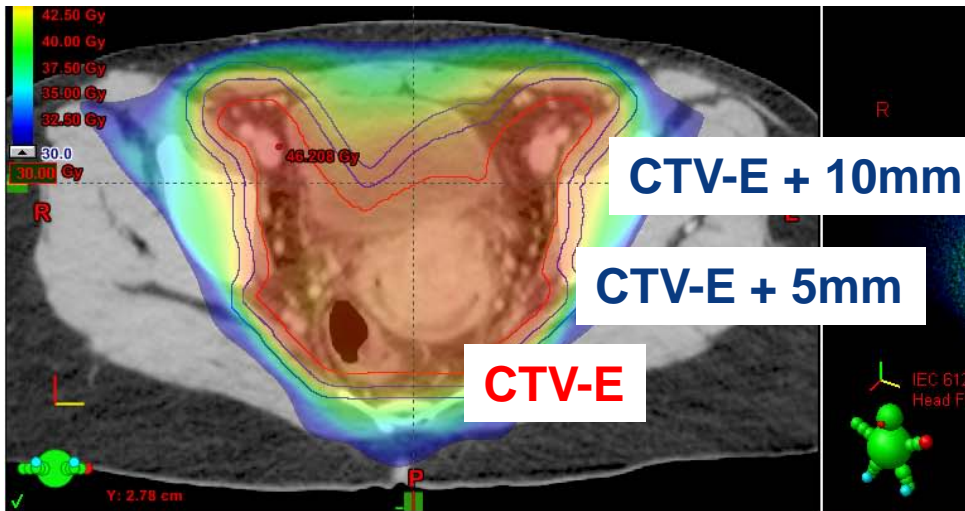
Why does the margin matter?



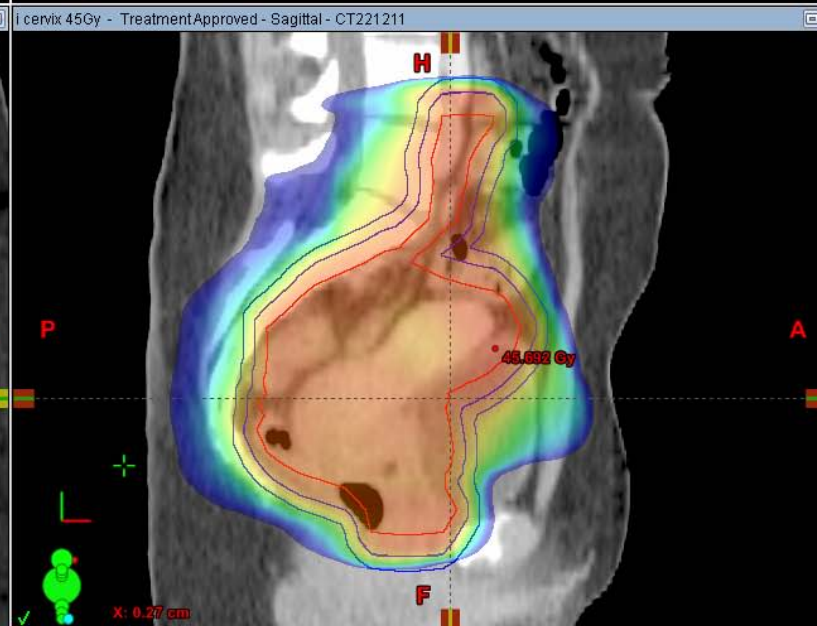
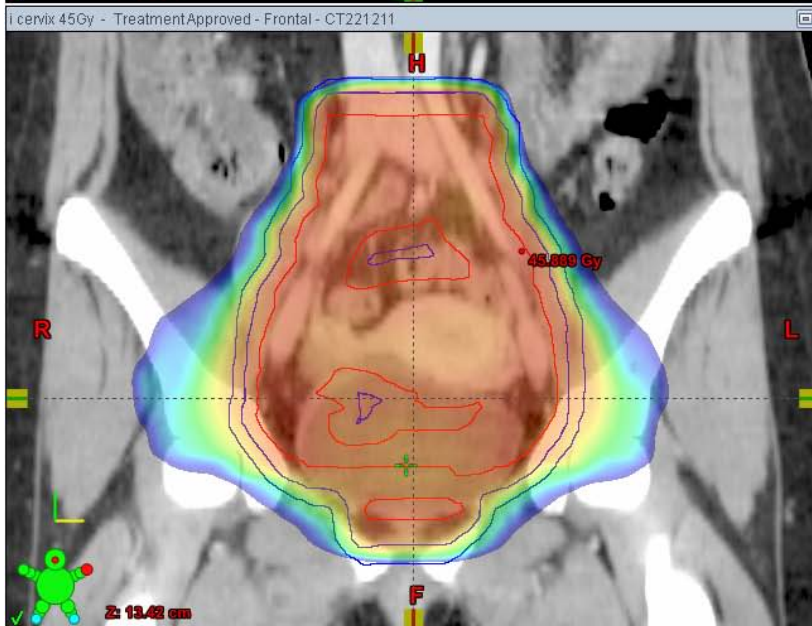
$$\begin{array}{c} r \\ \downarrow \\ \pi r^2 \\ \downarrow \\ \frac{4}{3}\pi r^3 \end{array}$$

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

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

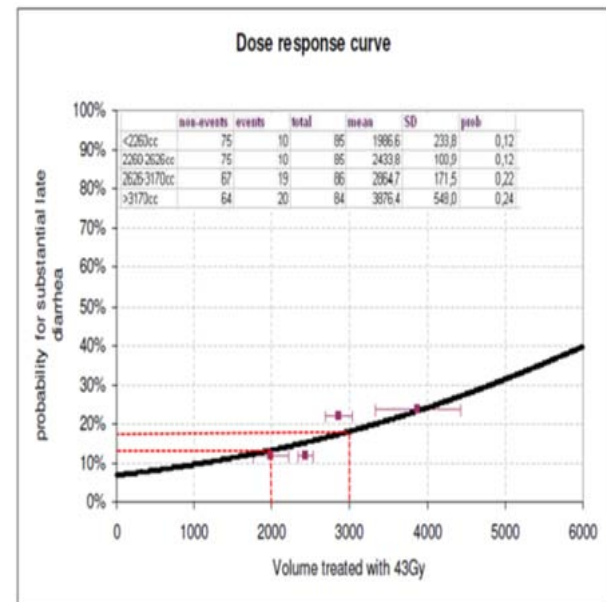
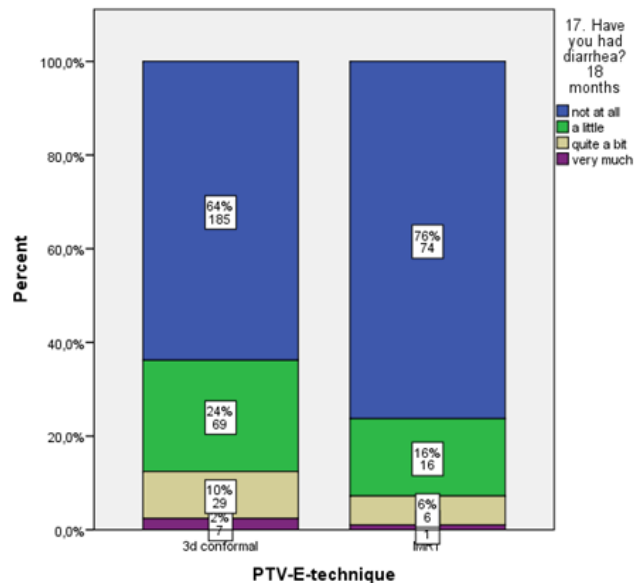


CTV-E	CTV-E + 5mm	CTV-E + 10mm
1000 cm ³	1500 cm ³	2000 cm ³
	+ 500 cm ³	+ 1000 cm ³



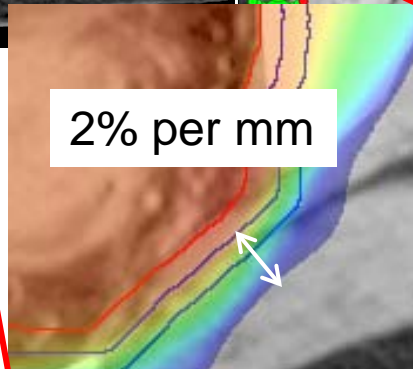
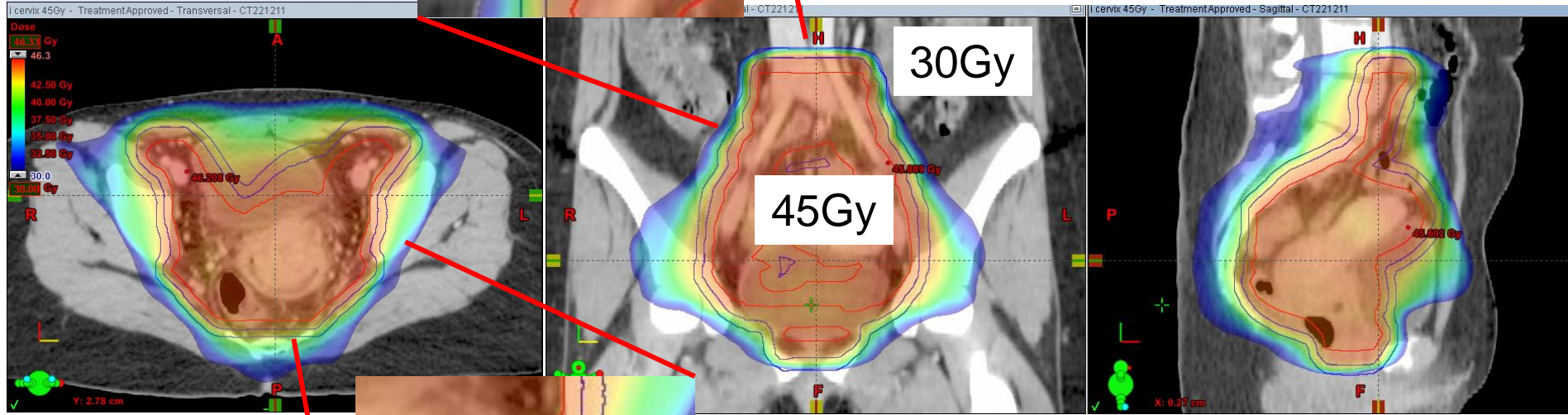
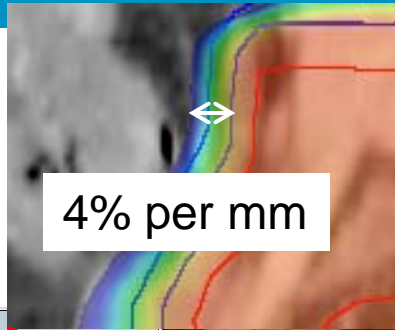
Is it important?

- Evidence that bowel irradiation is related with acute morbidity
- Upcoming evidence that bowel irradiation is related with late morbidity



Preliminary EMBRACE data

Is it risky to reduce margins? What is the dosimetric impact of margin reduction?

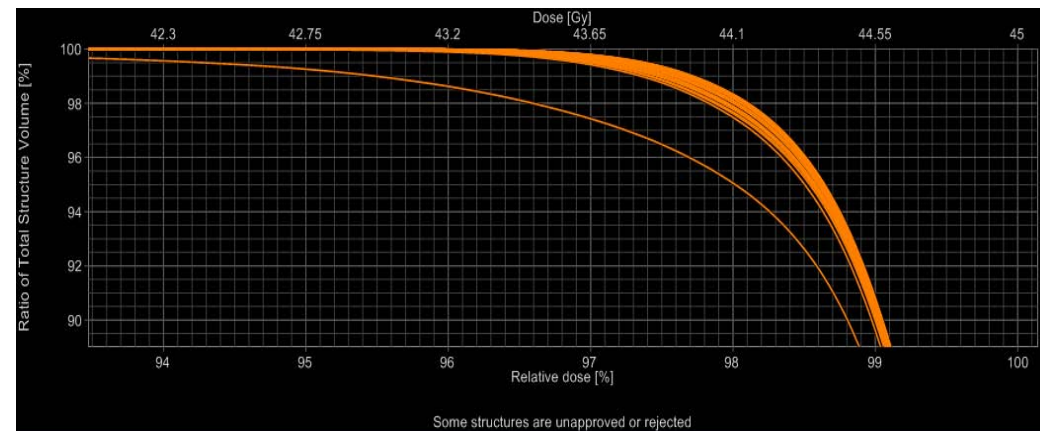


Very first results on dose accumulation for elective target: 1 patient

5mm PTV margin
PD: 45Gy



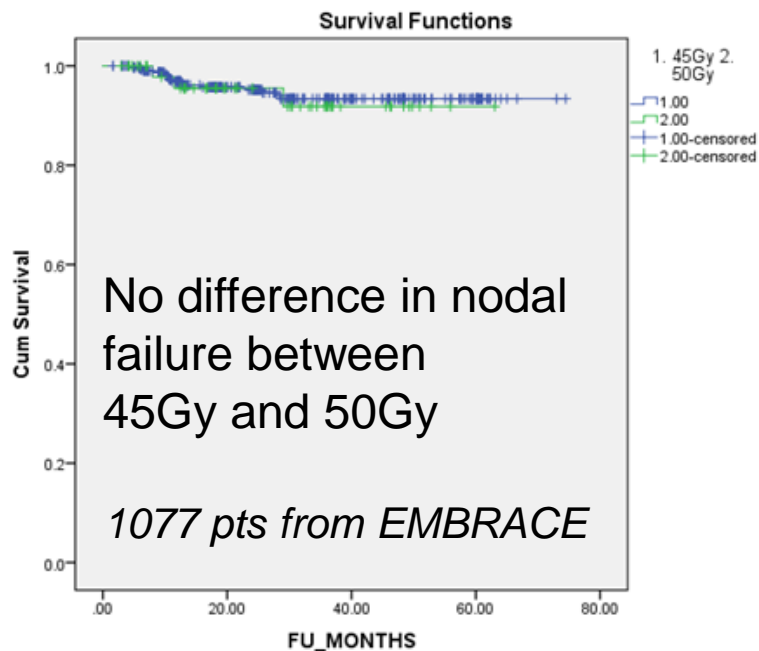
	D98	D99,9
Planned dose	44,1	43,5
Accumulated dose	44,0	43,3



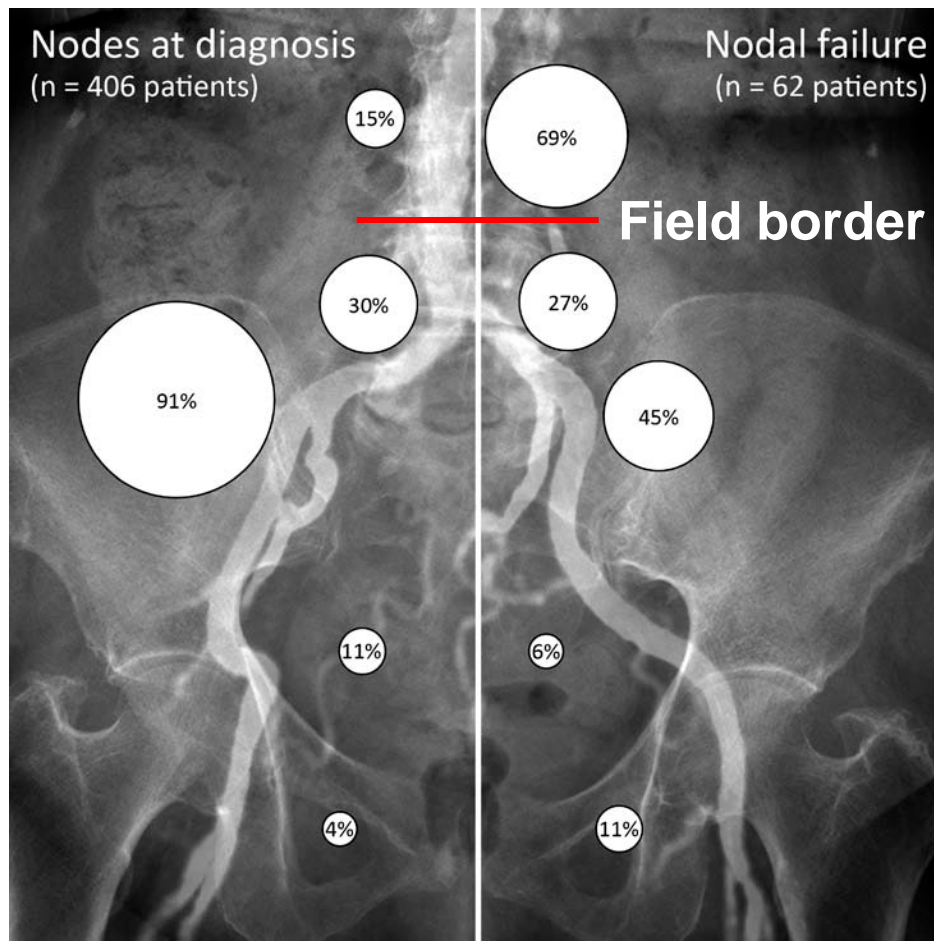
Where are the nodal failures? EMBRACE analysis

**10% of patients
have nodal failures**

Is there a dose effect???



Location of nodes (857 pts)



Thinking Gray and grey...

Not covered

Covered

Dose (Gy)

Current (EMBRACE I) and future (EMBRACE II) practice: EBRT volume



	Pelvic	Para-aortic
PTV (cc)	~ 1500 cm ³	~ 2000 cm ³
V43 (cc) EMBRACE I	~ 2500 cm ³	~ 3000 cm ³
V43Gy (cc) EMBRACE II	~ 1500 cm ³	~ 2000 cm ³

Inter-center PTV variations EMBRACE I: mean \pm 400cc (both pelvic and para-aortic)

Change of practice: EMBRACE I  EMBRACE II

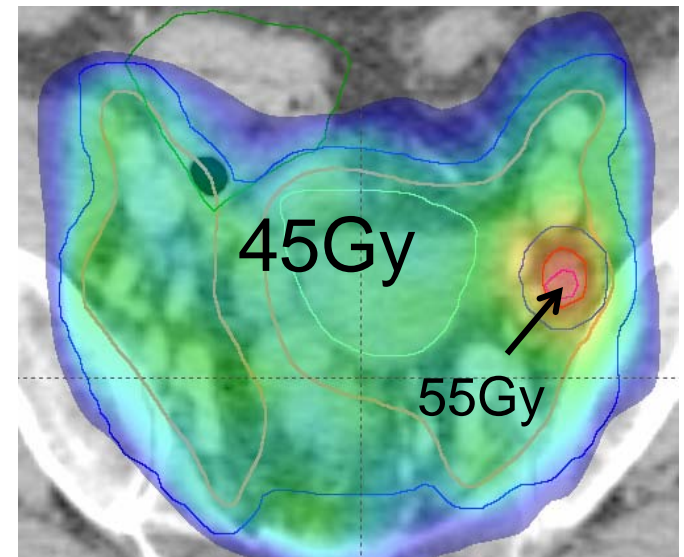
CRT  IMRT :  500cm³ (V43)

50Gy  45Gy :  400cm³ (V43)

xmm  5mm :  x cm³ (V43)

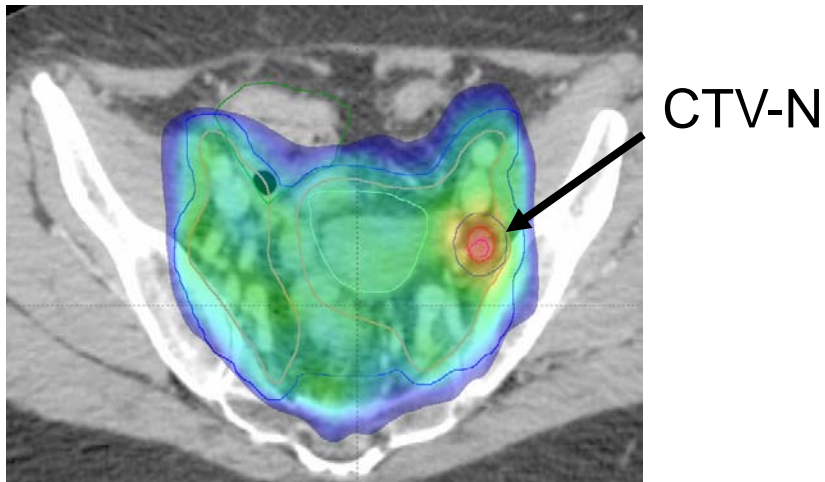
Simultaneously integrated lymph node boost (SIB)

- **Simultaneously integrated lymph node boost:**
 - Use of IMRT
 - Dose planning with two dose levels
 - Elective target
 - Pathological lymph node target
- **Recommended lymph node dose in EMBRACE II:**
 - 55Gy/25fx (within pelvis)
 - 57.5Gy/25fx (outside pelvis)



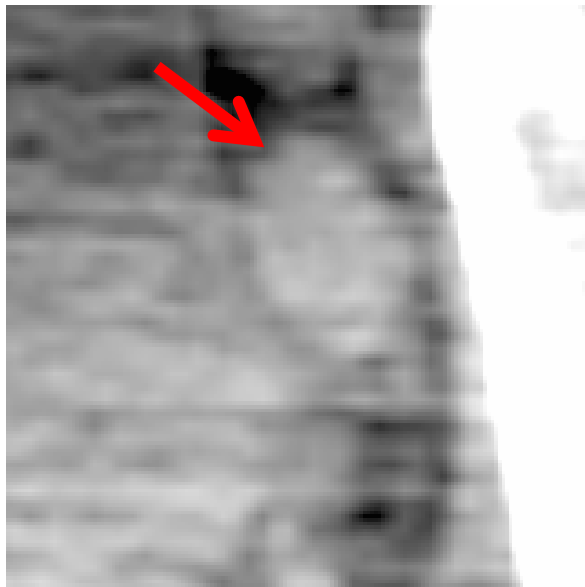
Which PTV margin do you think is necessary for the pathological CTV-N?

- A. <5 mm**
- B. 5-7 mm**
- C. 7-9 mm**
- D. ≥ 10 mm**

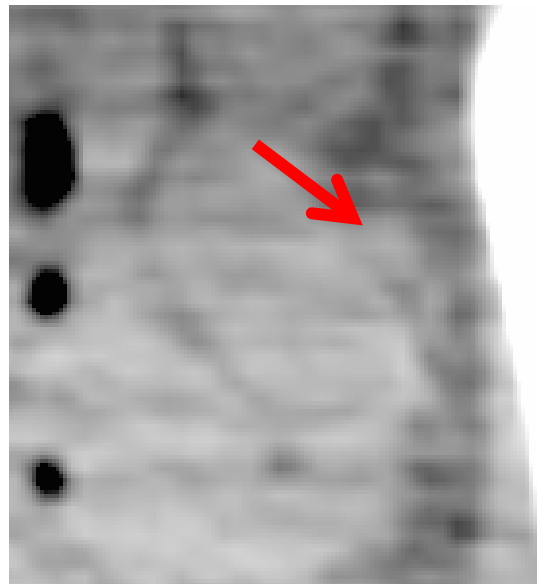


Margins for pathological lymph node boosting

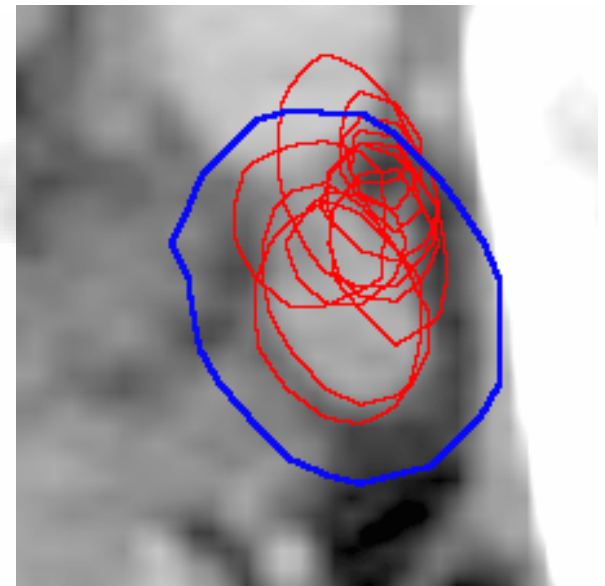
Dose was accumulated in 42 lymph nodes based on CBCT delineation



CBCT 1st treatment



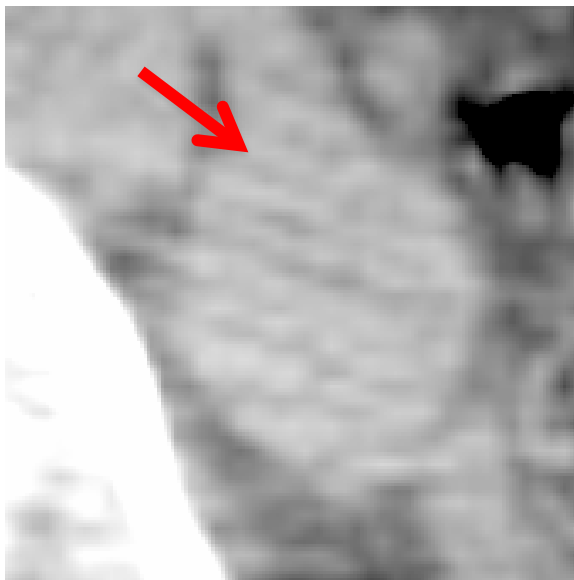
CBCT 24th treatment



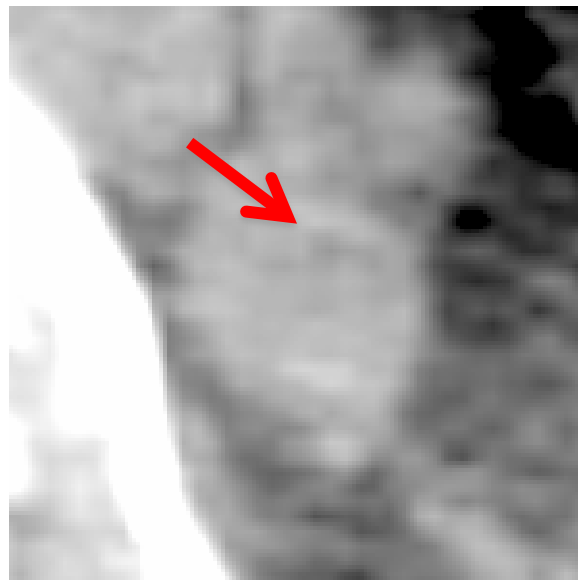
PTV (blue)
GTV on 10 CBCT (red)

Margins for pathological lymph node boosting

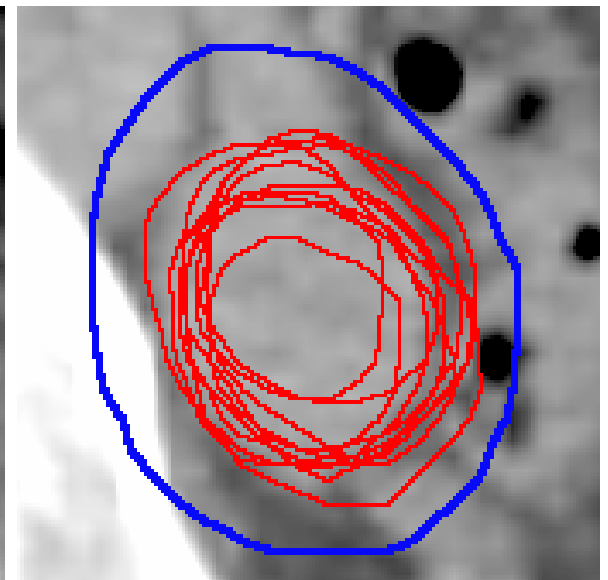
Dose was accumulated in 42 lymph nodes based on CBCT delineation



CBCT 1st treatment



CBCT 24th treatment



PTV (blue)
GTV on 10 CBCT (red)

Target and organ doses

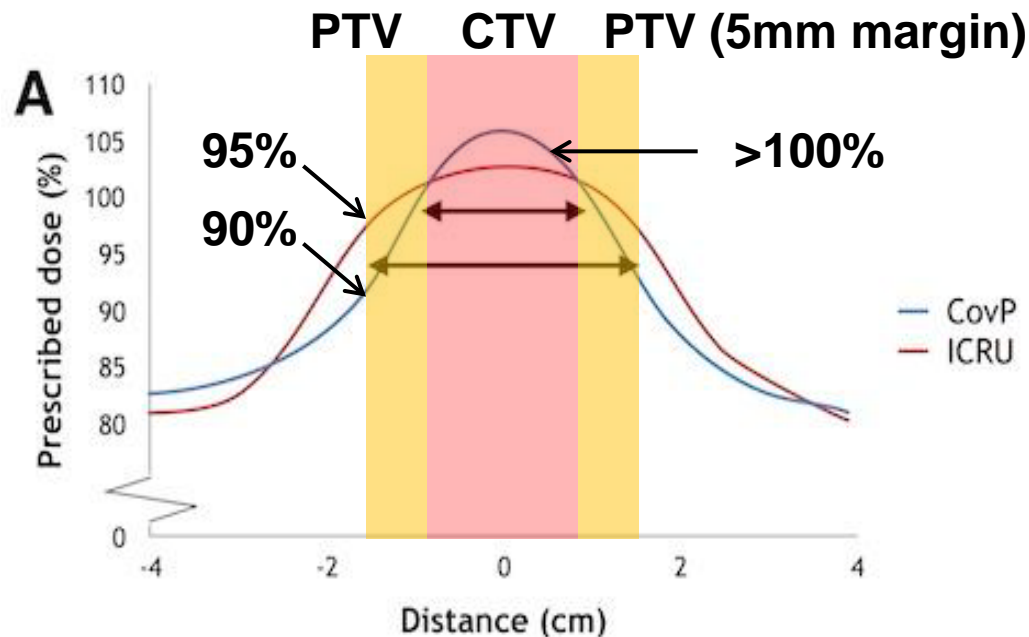
	GTV D98%
ICRU PTV _{10mm}	101 (98-102)
ICRU PTV _{5mm}	100 (99-102)
CovP	99 (93-101)

	V50Gy Body	V50 Gy Bones	V50 Gy Bowel
ICRU PTV _{10mm}	75 (32 - 315)	7 (0-50)	4 (0-106)
ICRU PTV _{5mm}	48 (16 - 209)	2 (0-25)	2 (0-68)
CovP	28 (12 - 122)	1 (0-8)	1 (0-35)

Median volumes (in cm³)

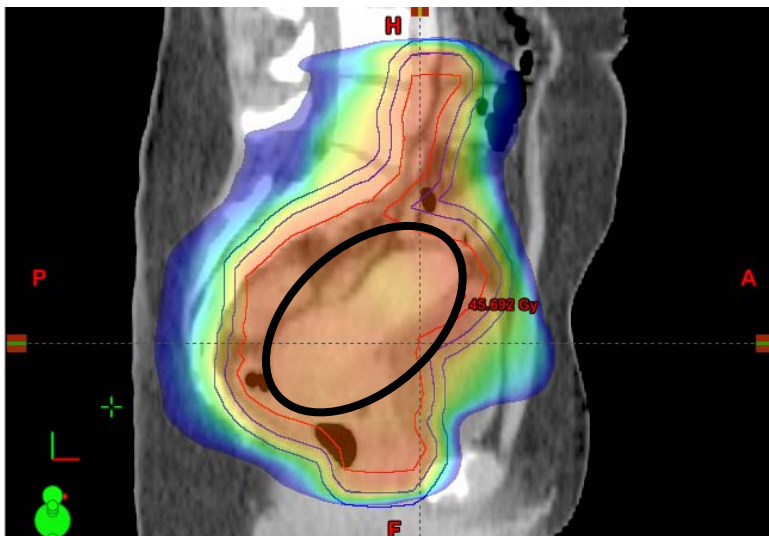
Coverage probability planning recommended in EMBRACE II

Peaks or plateaus?



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

1. 0-5 mm
2. 6-10 mm
3. 11-15 mm
4. >15mm
5. Individual margin



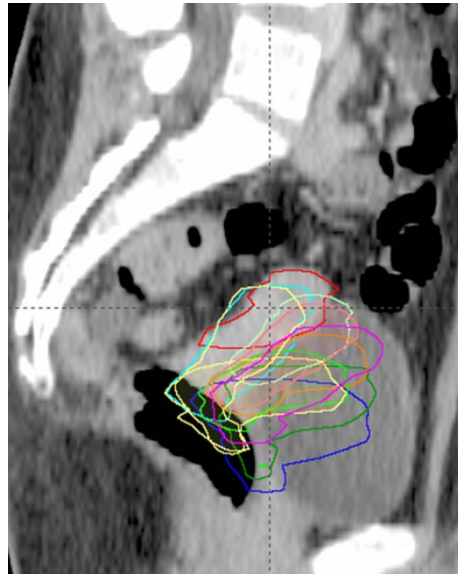
Motion and dose – primary target

- **Jadon et al. A systematic review of organ motion and image-guided strategies in external beam radiotherapy for cervical cancer. Clin Oncol (R Coll Radiol). 2014 Apr;26(4):185-96**
 - 39 relevant studies
 - Patient specific motion: 5-40mm
 - Population based margins would be large (up to 40mm)
- **Most studies evaluate geometry**
- **Few studies evaluate coverage (e.g. V95%)**
- **1 study evaluates dosimetric impact (D98)**

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

Patient case:

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

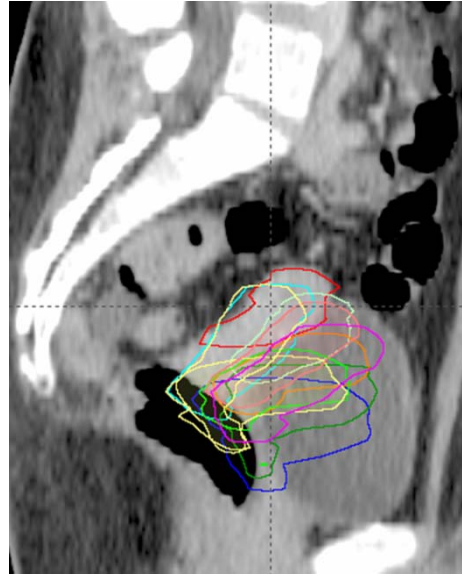


1. 20Gy
2. 30Gy
3. 35Gy
4. >45Gy

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

Patient case:

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



EBRT dose: 38Gy

BT dose: 6Gy

EBRT+BT dose: 46Gy

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

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

Which total dose is appropriate for controlling the non-involved uterus (EBRT+BT)?

1. 45Gy
2. 50Gy
3. 55Gy

EMBRACE II protocol:

- EBRT aim (delivered dose): 40Gy
- Assuming >5Gy delivered by BT

Accumulated doses

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

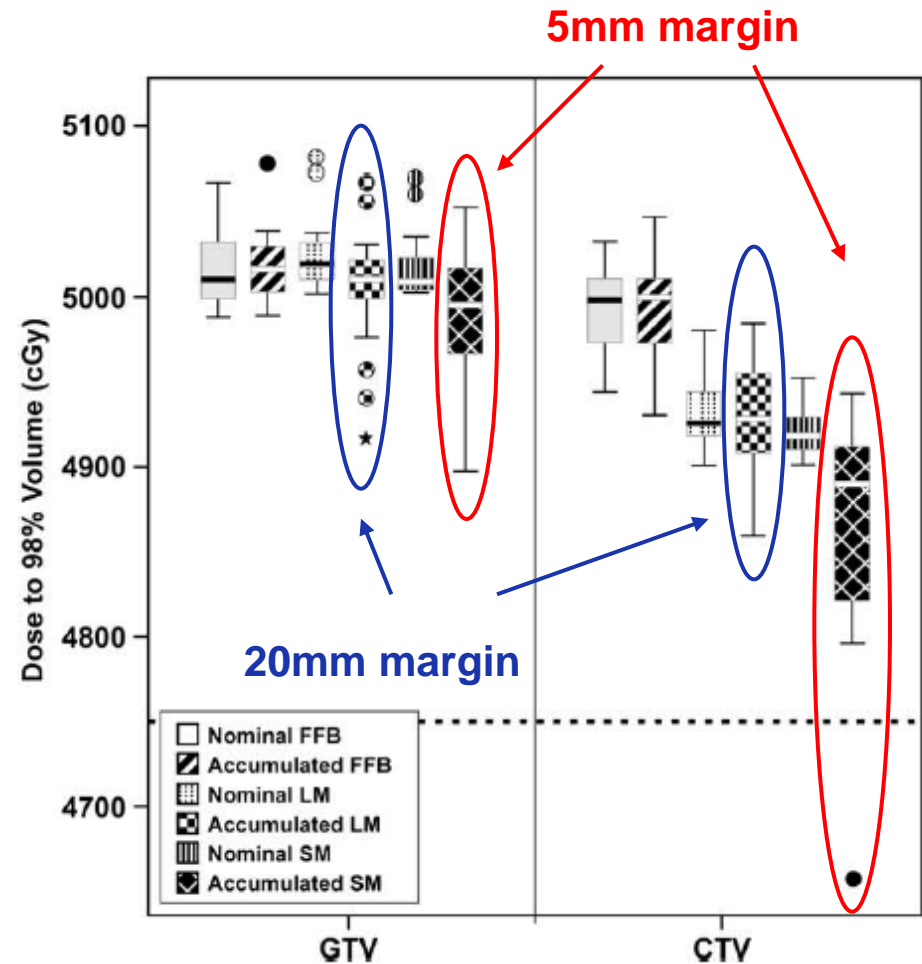


Fig. 4. Box plots of nominal and accumulated dose to 98% of gross tumor volume and primary tumor clinical target volume for four-field box (FFB), large-margin (LM), and small-margin (SM) plans.

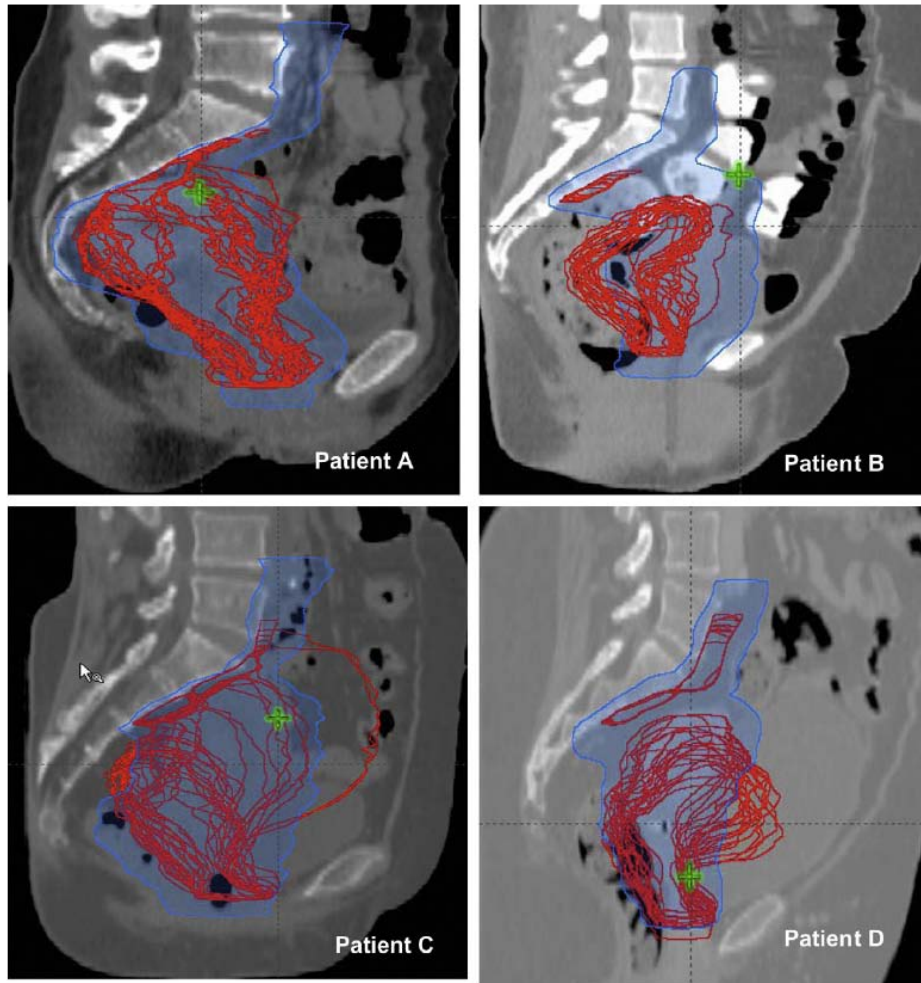
Thinking Gray and grey...

Not covered

Covered

Dose (Gy)

Which of these motion patterns are of most concern?



1. A
2. B
3. C
4. D

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

ITV-T LR recommended in EMBRACE II

Example: Full rectum

Standard:

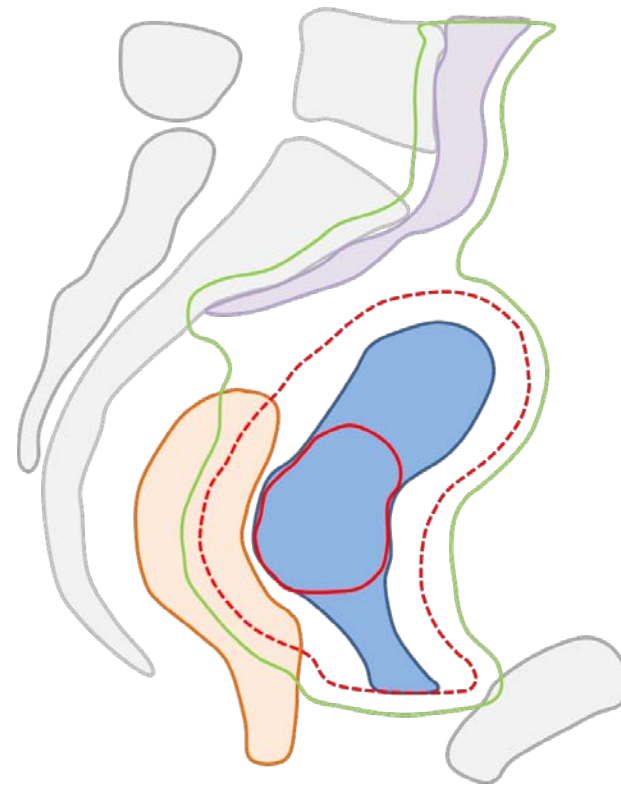
- 10mm ITV margin
- 5mm PTV margin



CTV-HR
CTV-T LR
CTV-E
ITV-T LR
PTV-45

Individualised:

- ITV expanded posteriorly
- 5mm PTV margin



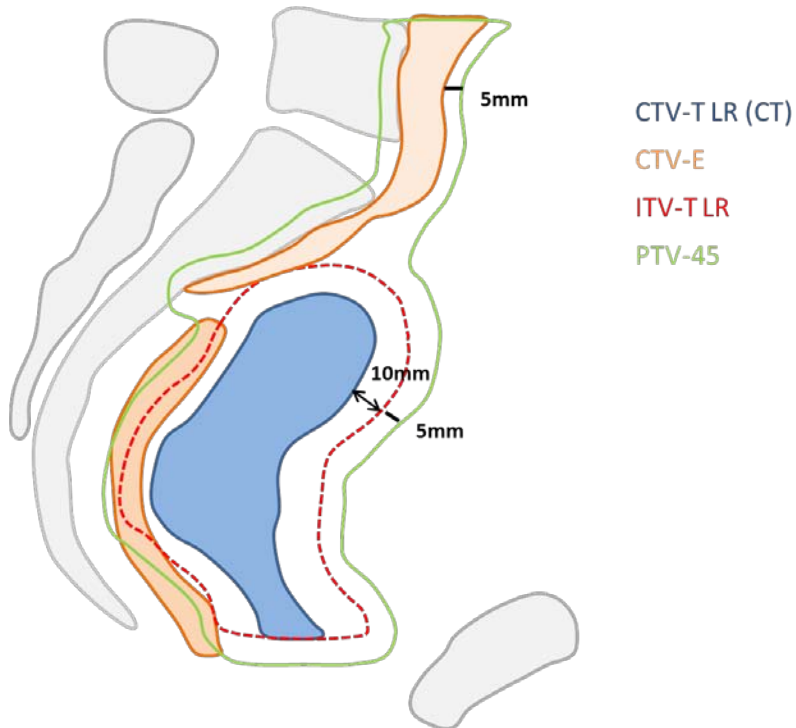
CTV-HR
CTV-T LR
CTV-E
ITV-T LR
PTV-45

ITV-T LR recommended in EMBRACE II

Example: Empty rectum + variable bladder

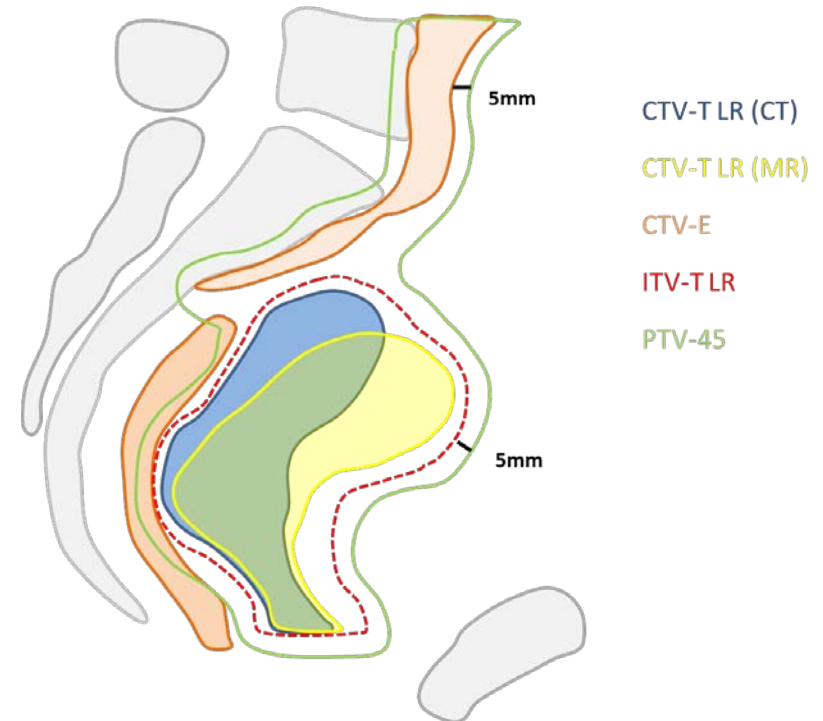
Standard:

- 10mm ITV margin
- 5mm PTV margin



Individualised (CT+MRI):

- ITV expanded anteriorly
- 5mm PTV margin

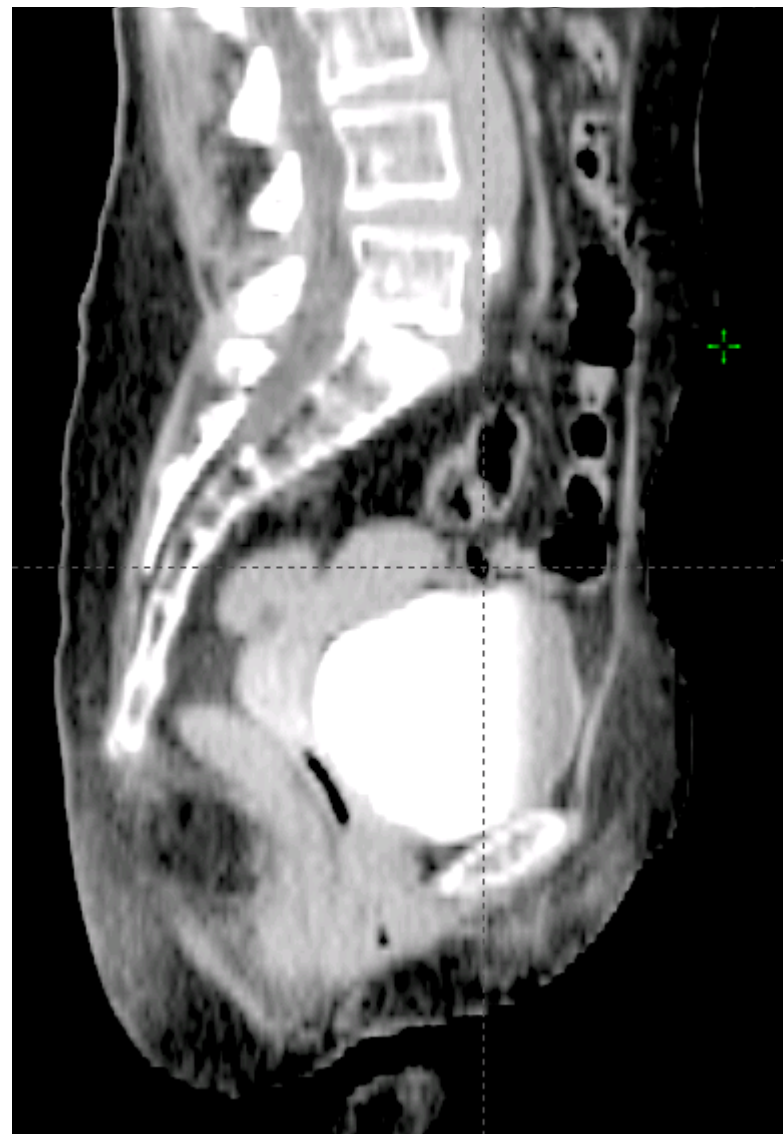


Bladder filling strategy in your department?

- 1. No bladder filling protocol**
- 2. Patient to void before each fraction for reproducible bladder filling**
- 3. Instruct patients to keep full bladder at treatment**
- 4. Specific drinking protocol**

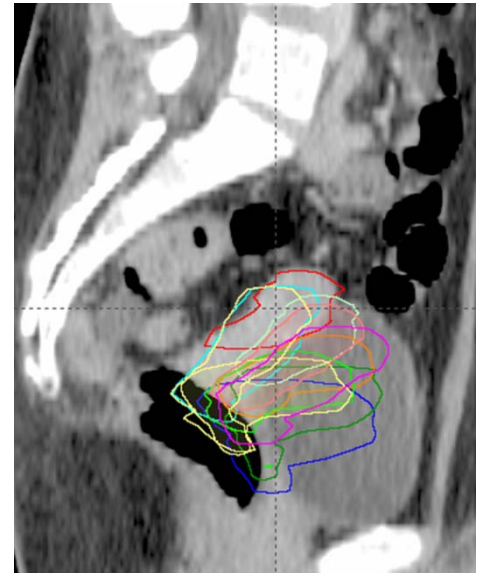
Bladder filling and bowel volume

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



Adaptive EBRT to further shrink margins/improve safety?

- **Re-planning during EBRT?**
 - Purpose: to adapt to target shrinkage
 - Strategy: new target contouring and planning during RT
- **Daily CBCT based IGART?**
 - Monitoring of uterus and/or rectal filling
 - Library of dose plans
- **Routine adaptive RT in cervix cancer is still not common**

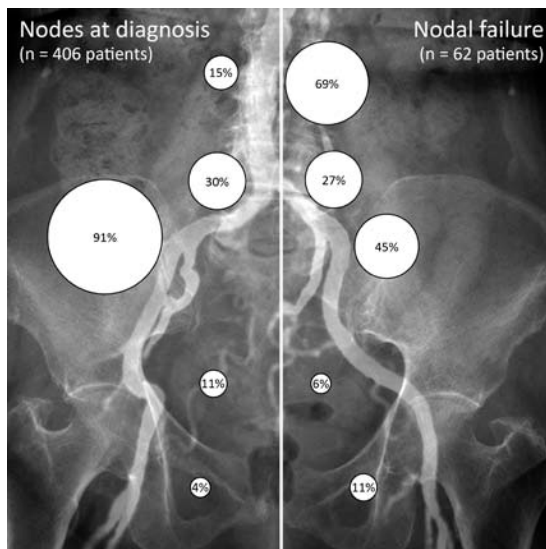


What has most impact on bowel dose?

- 1. Bladder filling protocol**
- 2. Reduction from 10 to 5mm CTV-E margin**
- 3. Re-planning during radiotherapy to address tumour shrinkage**
- 4. Implementation of daily library plans**

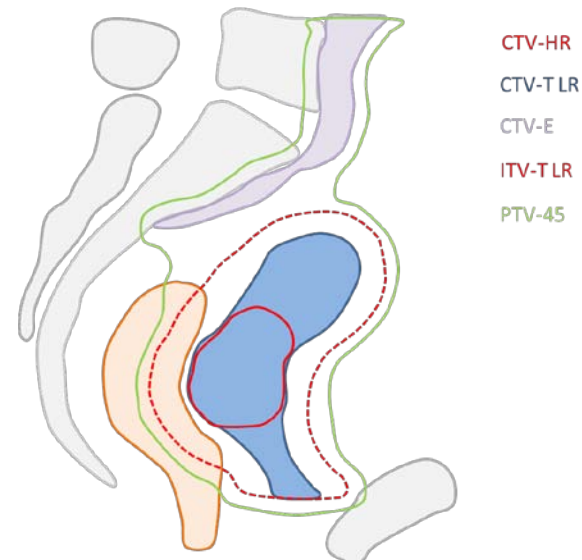
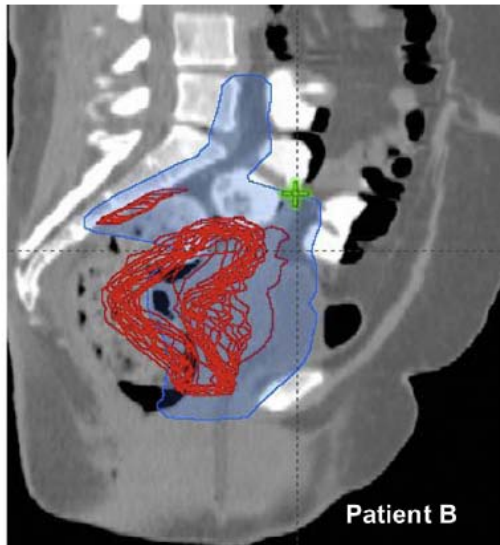
Take home message: nodal CTV

- Margins add to considerable irradiation of normal tissue
- 5mm margin is sufficient with daily image guidance and bony fusion
- Potential in pelvic elective radiotherapy to reduce irradiated volume by 40% (2500cc → 1500cc)



Take home message: primary CTV

- **Significant inter-fraction variations have been reported: 5-40mm**
- **Uninvolved uterus is not the most critical target**
- **Clinical practise and recommendation in EMBRACEII:**
 - **~10-15mm is common for CTV-T LR to PTV margin**
 - **Anatomical considerations when construction ITV**
 - **Be aware of rectal filling!**



Clinical Evidence

for

EBRT Techniques & Medical Dose Constraints including DVH parameters

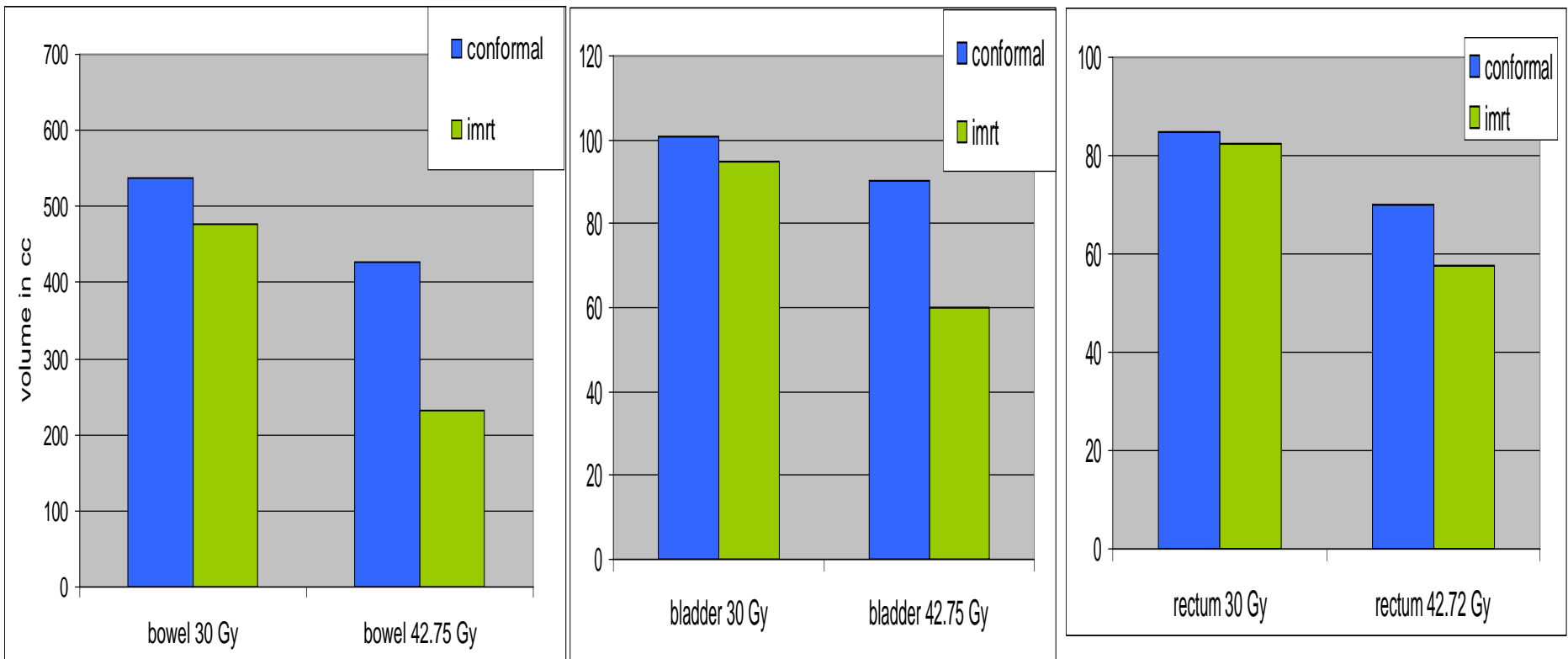
Umesh Mahantshetty

Outline

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

Dosimetric Comparison: 3D Conformal vs IMRT

Volume of OAR (Bowel , Bladder , Rectum) receiving higher doses were significantly less in IMRT than 3D-CRT plan



CLINICAL INVESTIGATION

Cervix

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

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

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

Van de Bunt et al 2006

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.

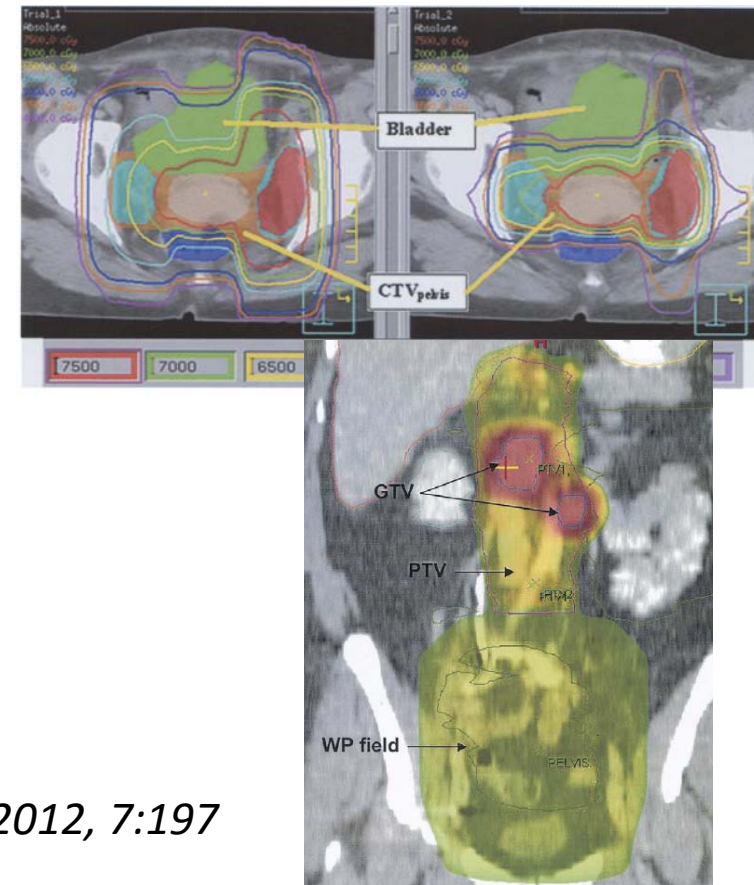
Dosimetric meta-analysis

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

Conformal to IMRT: GYN Cancers

- Numerous studies including a meta-analysis
 - Dosimetric advantage of reduction in high dose regions for OAR's
- Optimize more dose to tumor (Simultaneous boost)
 - Increase tumor control rates
- Optimize dose to normal tissue
 - Decrease the normal tissue toxicities
- Other Advantages
 - Extended field radiation



Sem Rad Oncol. 2002

Yang Radiation Oncology 2012, 7:197

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

Aaron Wagner ^a, Anuja Jhingran ^b, David Gaffney ^{a,*}

- In **postoperative cases**, IMRT use **should be considered**. To demonstrate preferred patient reported outcomes, participation on the RTOG/GOG 1203 TIME-C trial is encouraged.
- In **intact cases**, the use of IMRT should be **limited to IRB-approved protocols** secondary to additional planning concerns.
- **Consensus guidelines** exist as to contouring both postoperative and intact cases, and should be utilized. However, **changes are in progress**, secondary to concerns as noted above, and appropriate care should be taken during treatment planning, which may require patient **specific adjustments**.
- **IGRT** should be utilized when IMRT is implemented secondary to the significant inter-fraction variability that can occur.

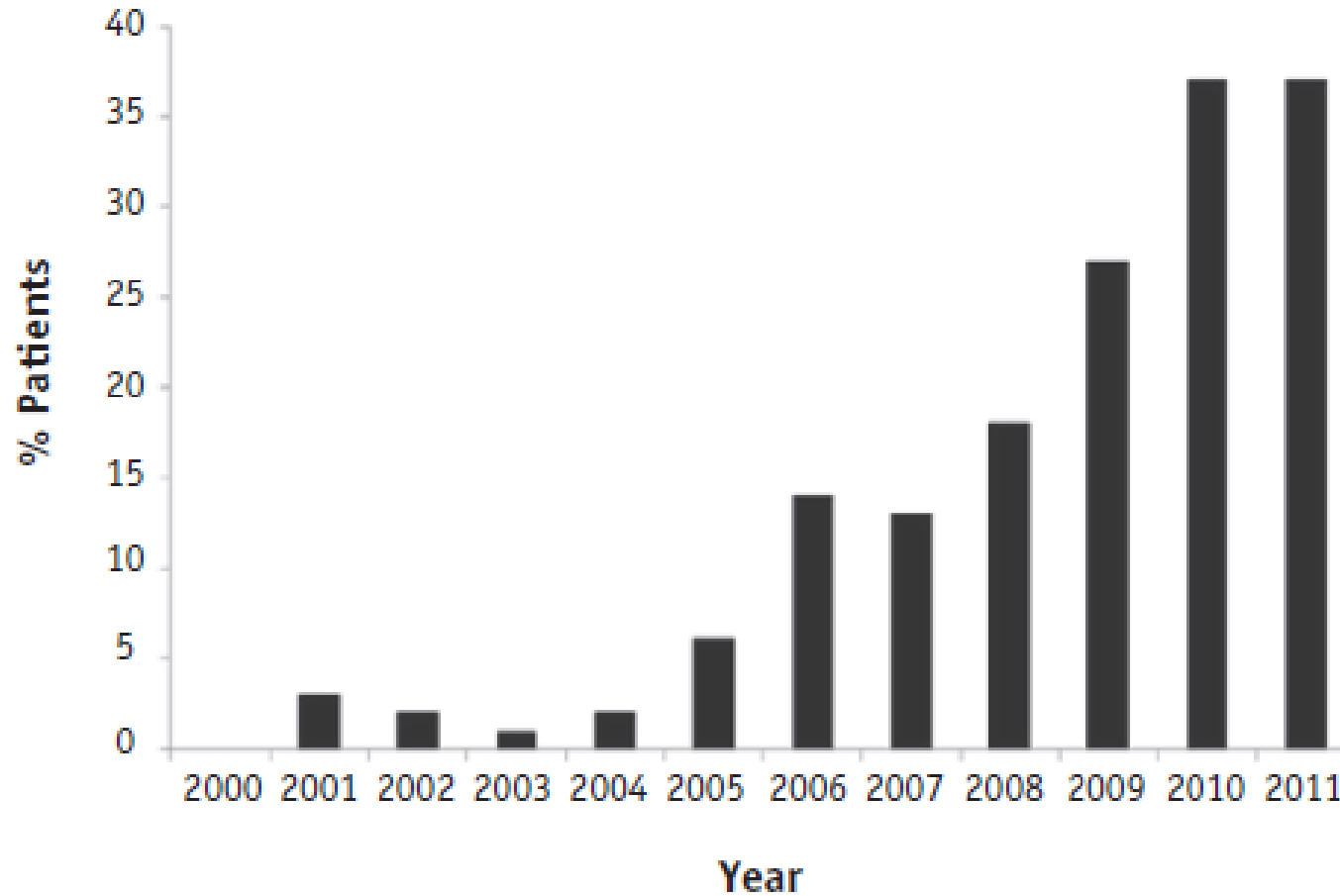
What percentage of cervical cancer patients with intact uterus undergo IMRT/VMAT treatment at your centre?

- A. 10 - 15%
- B. 25 - 30%
- C. 60 - 85% & more
- D. None

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

1999-2011

Utilization of IMRT
N = 1508 patients

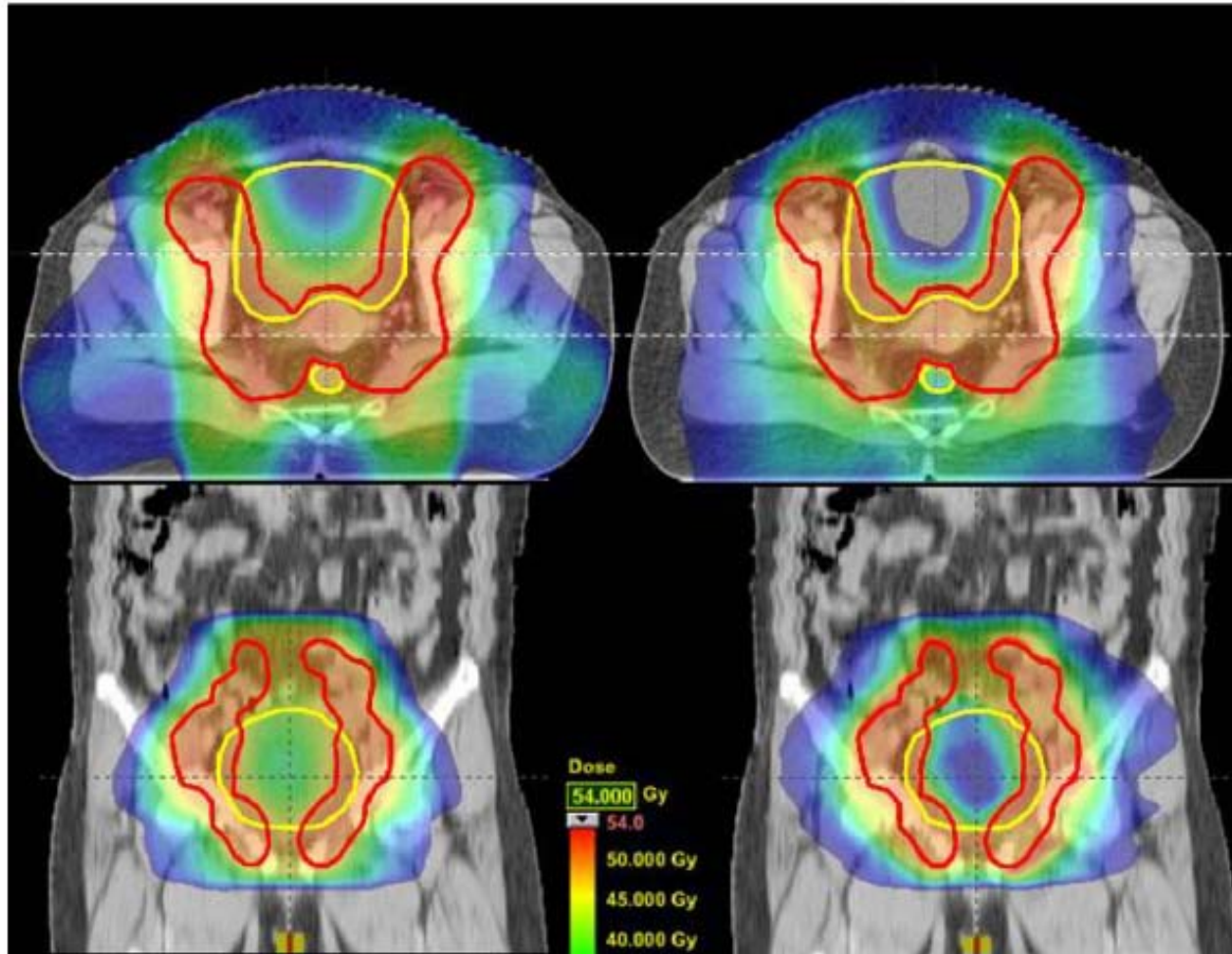


RT Techniques: IMRT Vs VMAT

8 patients with ca. cervix

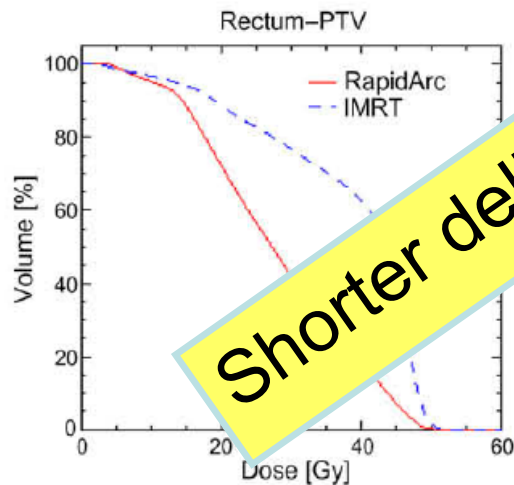
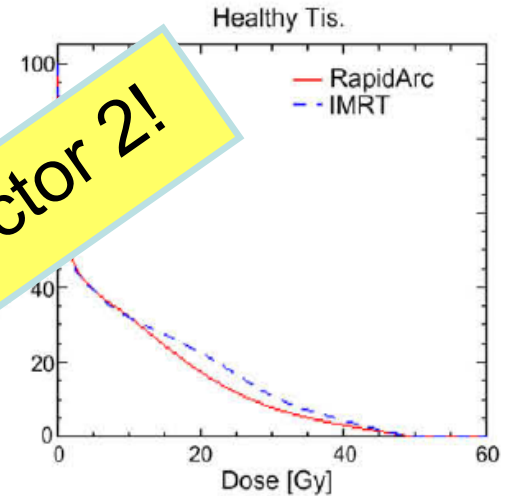
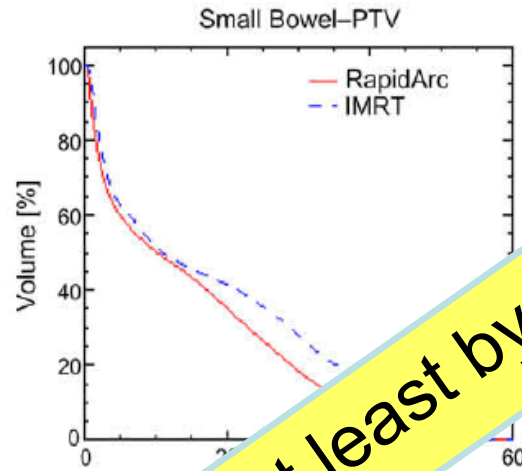
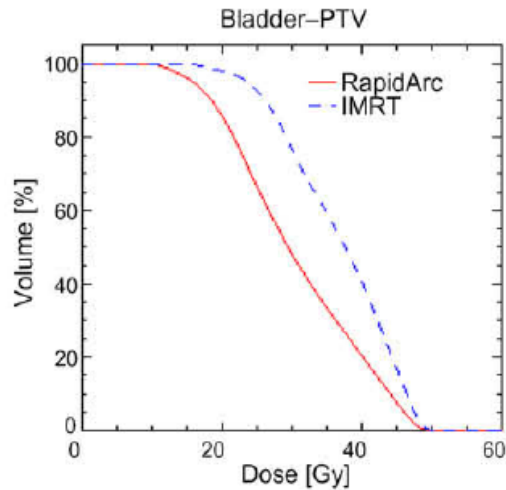
IMRT

VMAT (Rapid Arc)



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

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 Marnitz¹, Waldemar Wlodarczyk¹, Oliver Neumann¹, Christhardt Koehler², Mirko Weihrauch¹, Volker Budach¹ and Luca Cozzi^{3*}

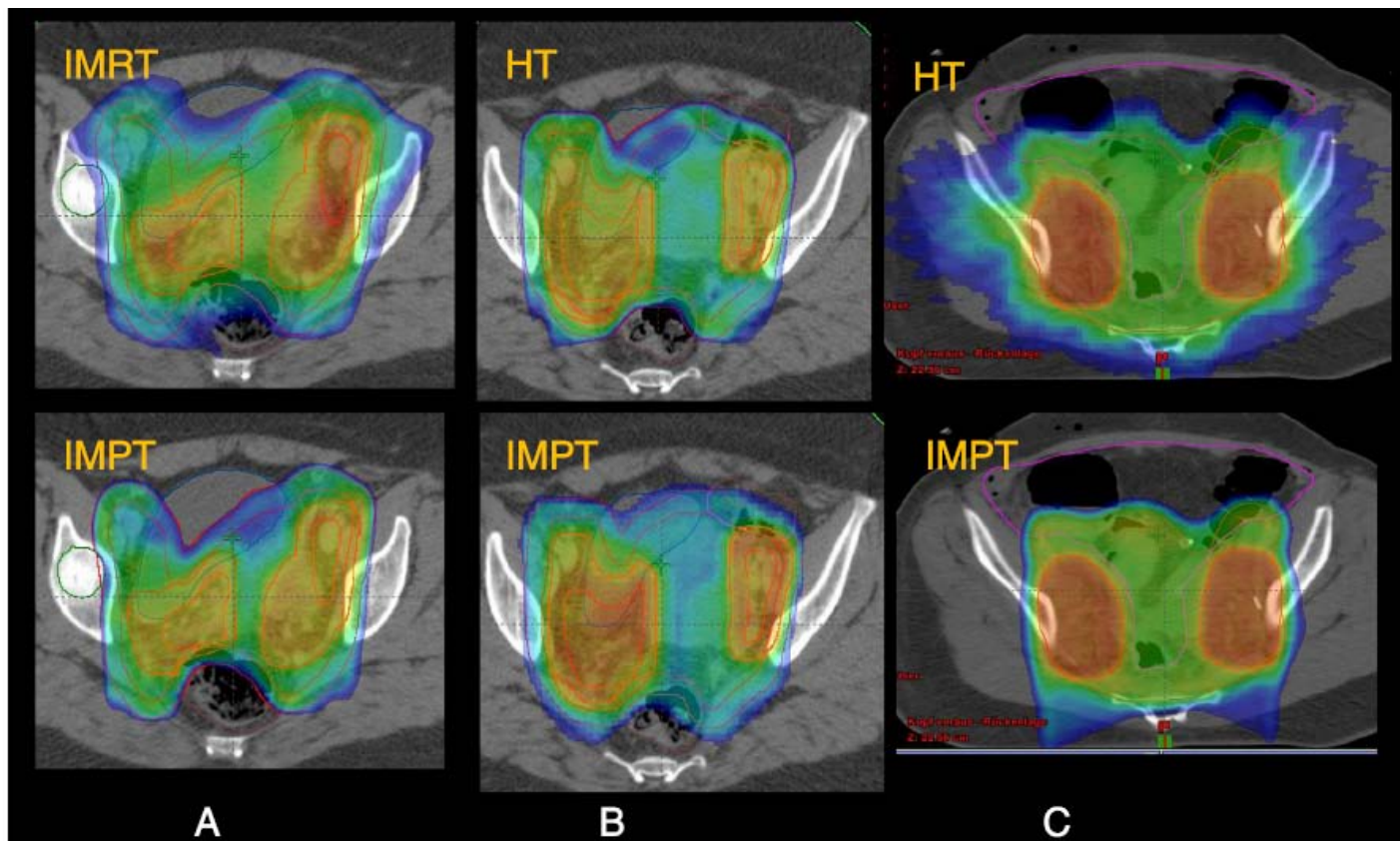


Figure 3 Examples of rectum and bowel sparing potential between techniques. **A** and **B**: rectum, colorwash is at 45 Gy; **B**: SB, colorwash is at 30 Gy.

- All techniques were proved to be **dosimetrically adequate** with regard to coverage, conformity and homogeneity
- **Intensity modulated protons** offered the best sparing of the bowels and rectum
- **IMPT** could contribute to a significant reduction of acute and late toxicity which should be proven in clinical trials

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)

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

Characteristic	WP-CRT arm	WP-IMRT arm	<i>P</i> 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

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	13.63%	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.

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

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

Carcinoma Cervix Stage IIB (SQ / Adeno CA)

100 patients

**Conventional External RT (40 Gy /20#)
+ ICA – HDR (7 Gy x 5#)
with Concomitant Chemo-radiation**

100 patients

**IMRT Pelvis (50 Gy/25#)
+ ICA – HDR (7 Gy x 5#)
with Concomitant Chemo-radiation**

HYPOTHESIS:

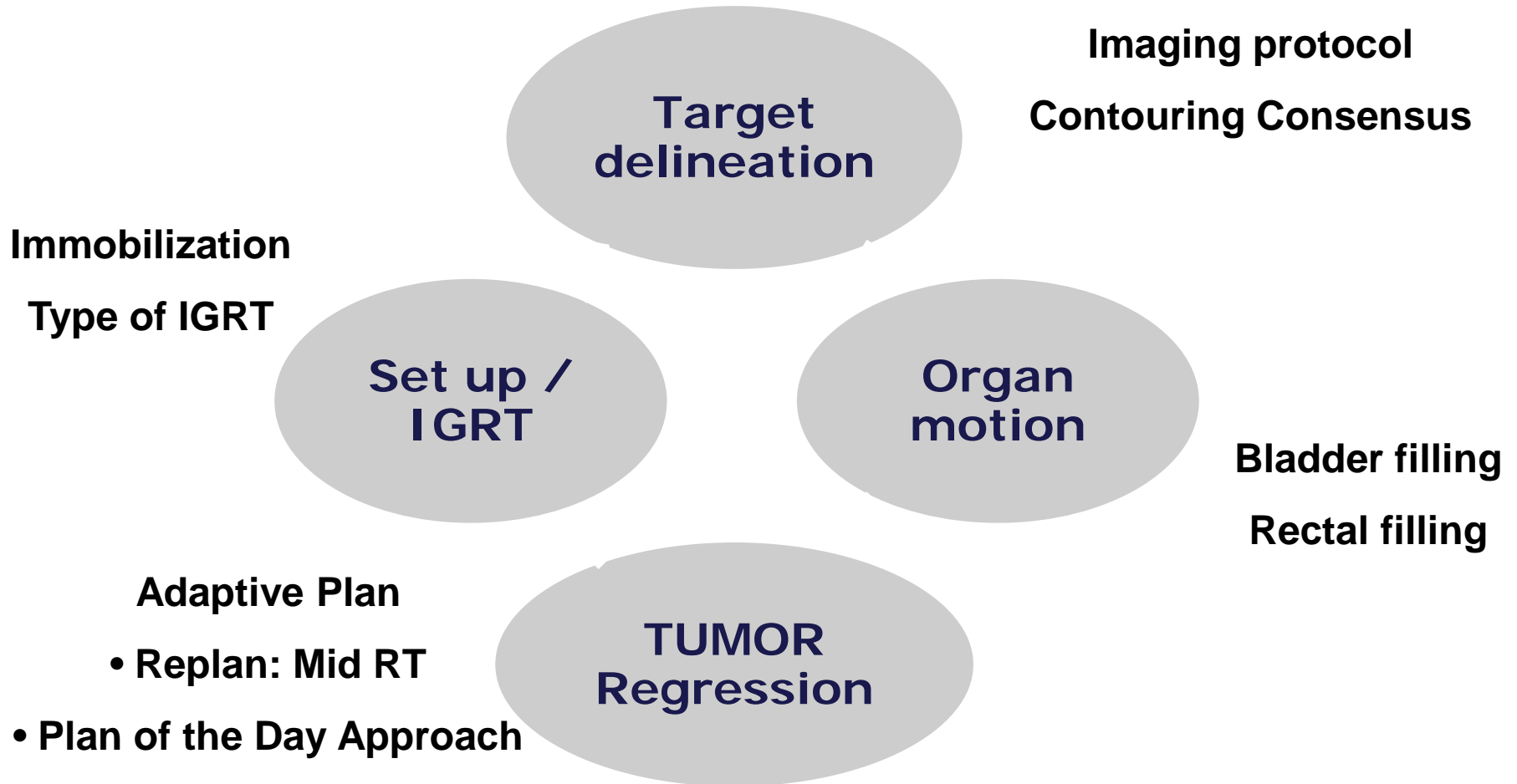
- Reduction in Acute and Late RT toxicity's by:15-25%
- Accrual Period: 5 years
- Power of detection: 80% (alpha error: 0.05)

Final Analyses: October 2016

TOXICITIES

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

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



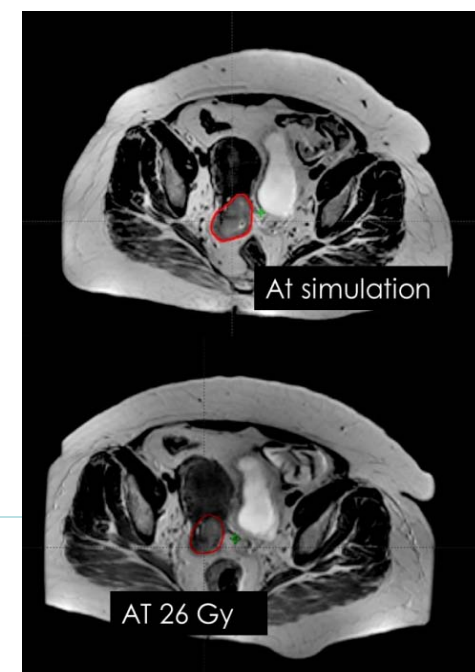
IGRT PROTOCOL : INSTITUTIONAL

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

U.M. Mahantshetty,¹ A. Nachankar,¹ Y. Ghadi,¹ S. Chaudhari,¹
 S. Jamema,¹ R. Engineer,¹ S. Chopra,² D.D. Deshpande,¹
 and S. Shrivastava³; ¹Tata Memorial Centre, Mumbai, India, ²ACTREC,

TMH Study; ASTRO 2014

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



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

Surrogate for Organ Motion : Online – Offline matching (Intrafraction)

	Mean X Lateral (mm)	Mean Y ANT-POST (mm)	Mean Z SUP-INF (mm)
Day 5	5.3	7.9	6.4
Day 10	4.9	7.8	7.6
Day 15	4.7	8.8	7.2
Day 20	6.4	7.5	8.7
Day 25	4.7	7	9.6

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

Imaging protocols MRI and CT

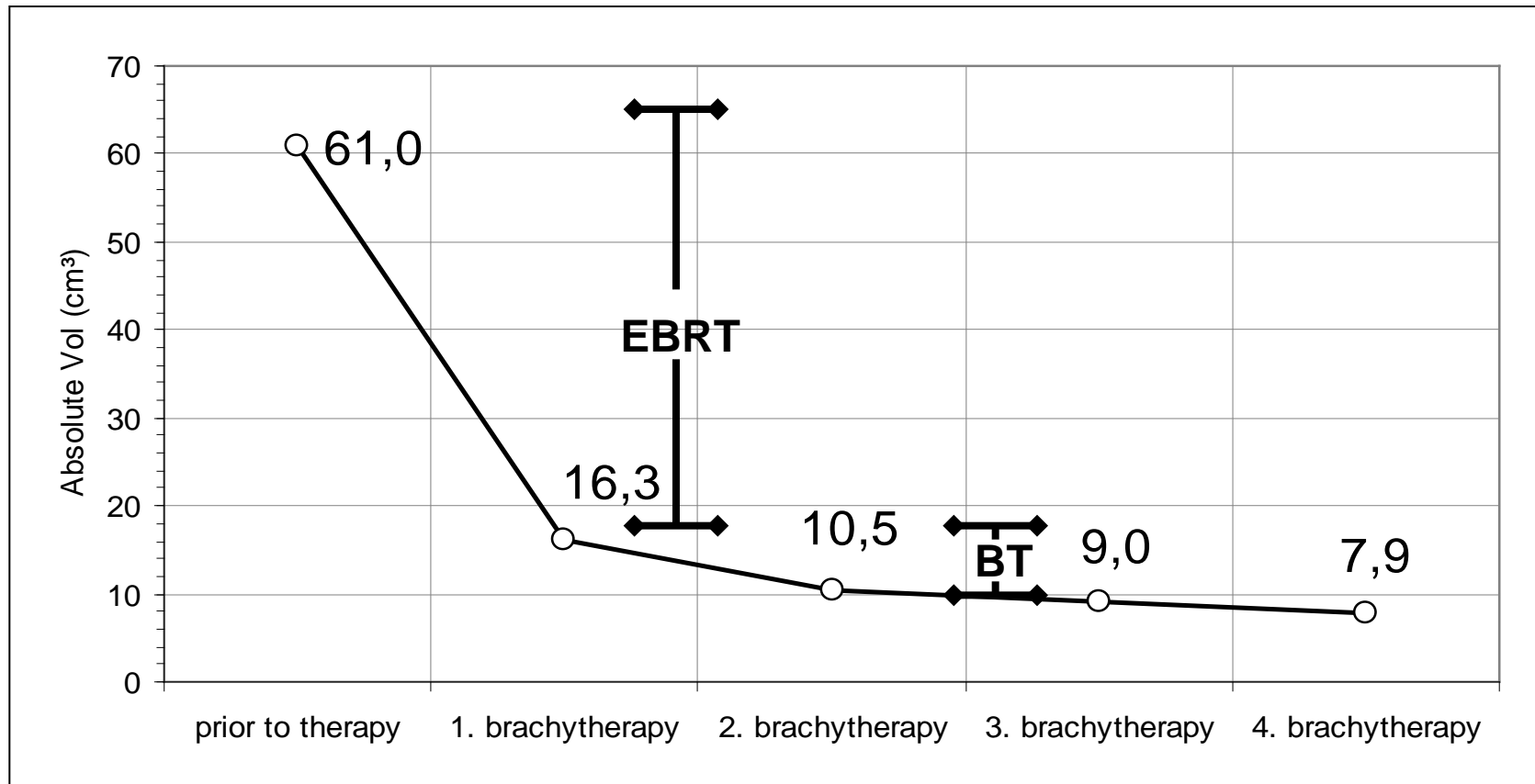
Key issues for image-guided radiotherapy

Quantitative tumor regression

Courtesy : Johannes Dimopoulos

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

easy to predict



Post Operative IMRT in GYN Cancers

I. J. Radiation Oncology • Biology • Physics

Volume 52, Number 5, 2002

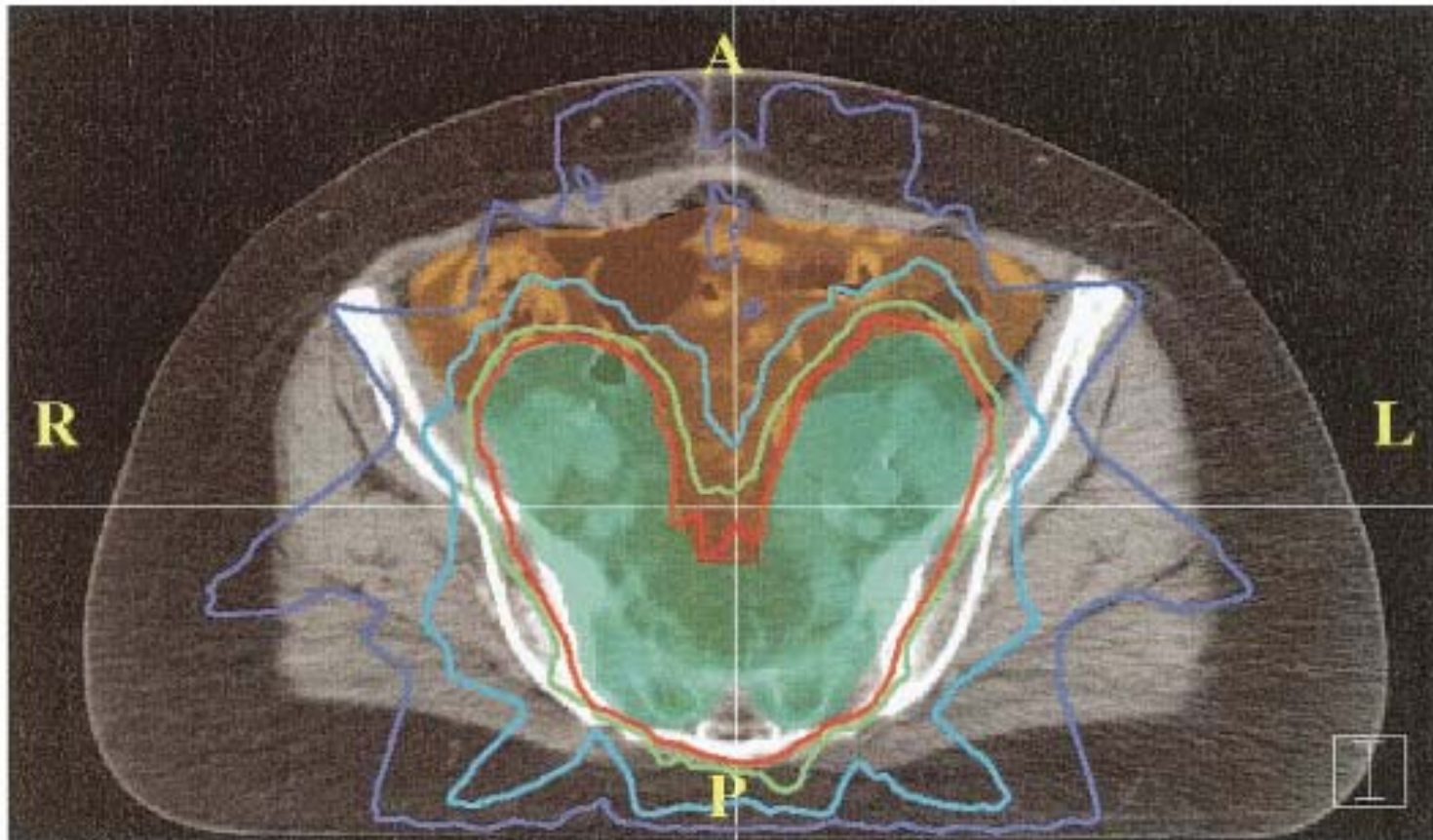


Fig. 2. Isodose curves from an IM-WPRT plan superimposed on an axial CT slice through the upper pelvis. The small bowel and PTV are shaded in orange and green, respectively. Highlighted are the 100% (red), 90% (green), 70% (light blue), and 50% (dark blue) isodose curves.

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/m²)
- 90% patients received 4 cycles of CDDP
- Pelvic IMRT with emphasis on small bowel & BM sparing technique

- 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 of bone marrow receiving 40 Gy and the median dose to bone marrow in patients receiving concurrent chemotherapy.

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 \geq II late bowel toxicity with postoperative radiation

Stratified Randomization
Type of Hysterectomy
Use of Concurrent Chemotherapy

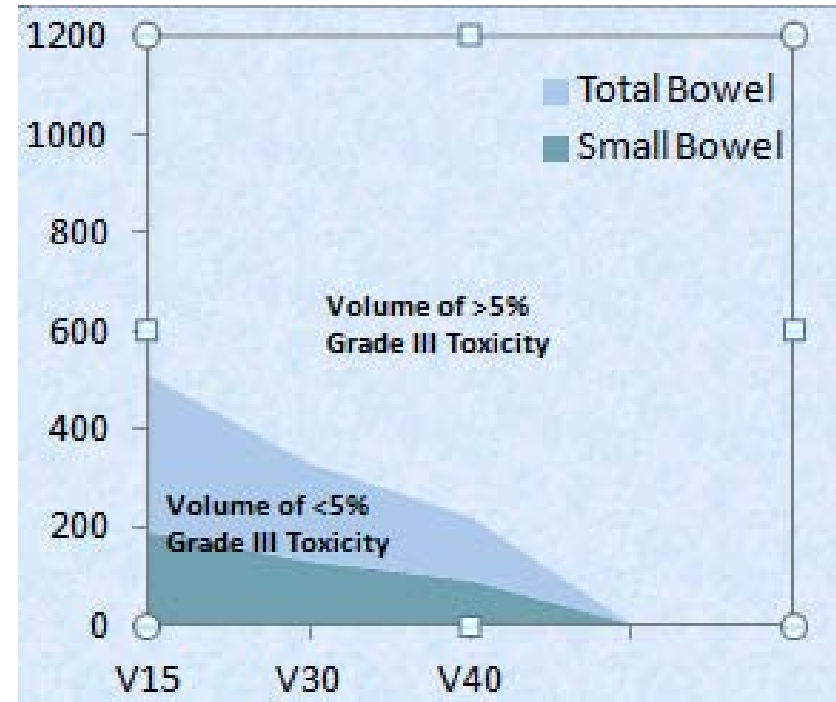
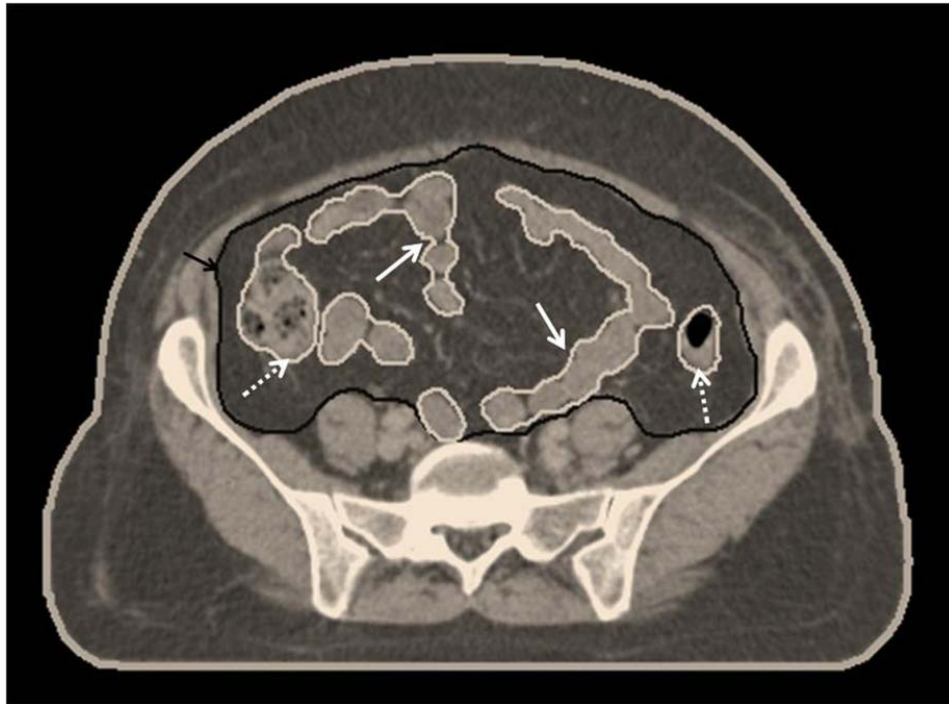
N=120
Standard RT

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.

OAR Contouring & Dose Constraints



Small & Large Bowel

Peritoneal Cavity

Rectum, Bladder

Hard Constraints:

V15 SB <190 cc, V40 SB <100 cc

Soft Constraints:

Rectum <60% vol \geq 30 Gy

<35% Bladder \geq 45 Gy

Bowel Doses : 3DCRT vs. IMRT

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

IMRT led to significant reduction in Bowel and PC doses

Primary Endpoint

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

Median Follow Up = 20 months

14% absolute difference; statistically insignificant at interim analysis

BOWEL (acute toxicity): dose-volume effect

Impact of V15 and V40

175 pts, 12% of acute Gr2-3 toxicity

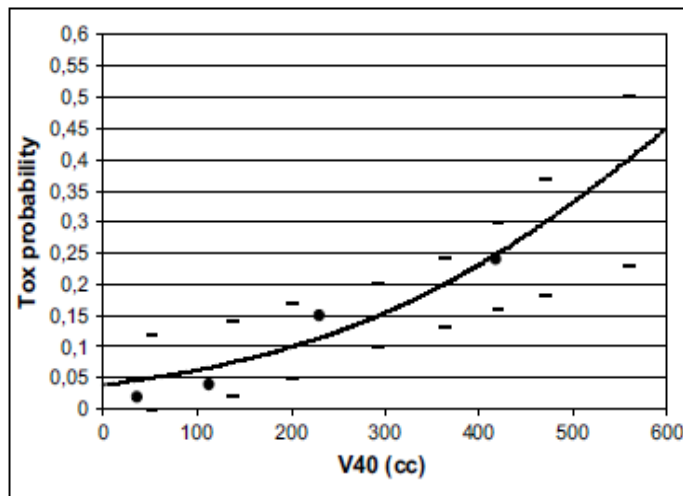


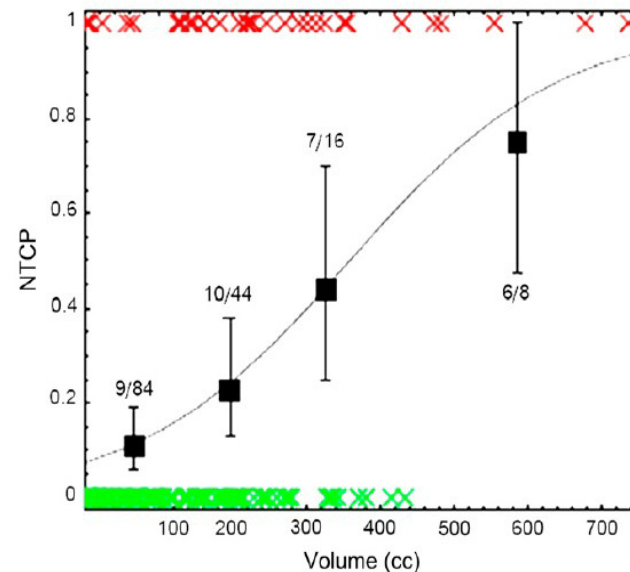
Fig. 1. The relationship between the V40 of the intestinal cavity (outside the planning target volume) and the risk of Grade 2–3 acute bowel toxicity is plotted, together with 95% confidence intervals (lo-

When: **V40** < 170 cc
V45 < 100 cc
V50 < 33 cc

the incidence of toxicity drops from 21% to 3%

*Fiorino IJROBP
2009*

Rectal cancer patients + concomitant chemotherapy ,acute G3 diarrhea



Impact of V15

AS A GEOMETRICAL SURROGATE of the HIGH DOSE (larger difference at low dose in the DVH)

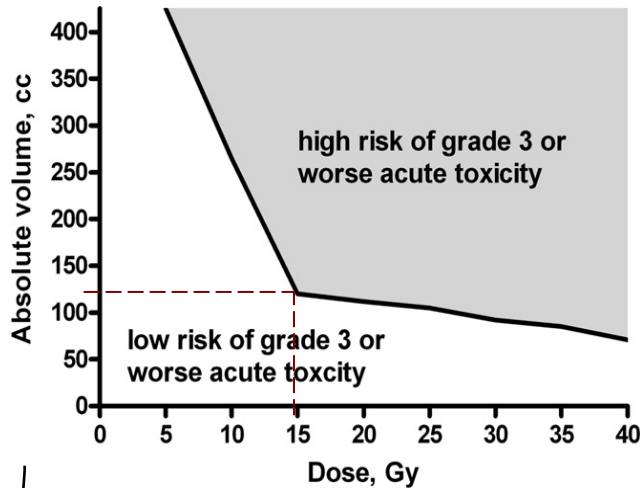
NO BIOLOGICAL MEANING - DONT USE IT ALONE FOR IMRT OPTIMIZATION

*Robertson IJROBP
2010*

Dose constraints depend on contouring approach

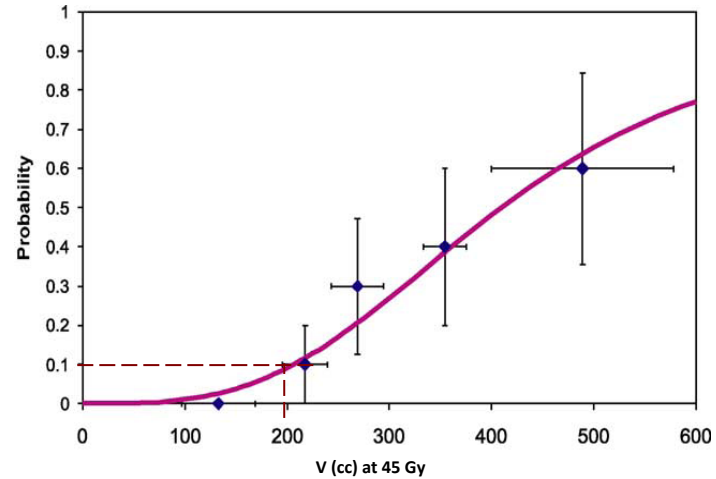
Treshold – based risk models

Baglan – Robertson, IJROBP 2002



Based on delineation of Bowel Loops

Roeske, Radiother Oncol 2003



Based on delineation of Bowel bag

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

Review: Kavanagh DB, IJROBP 2010 (QUANTEC)

Marks, IJROBP 2010 (QUANTEC)

Dose Constraints : Literature

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

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

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

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

TIME-C Trial

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

Prophylactic PA-IMRT

- Most studies
 - prospective feasibility studies
 - Mixed population of
 - locally advanced patients at high risk
 - PALN positive
- Boost dose given to positive LN
- Else 45 – 50 Gy IMRT

Duodenal toxicity in Extended field RT

- Limiting V55 to less than 15% - statistically significant differences in 3 year rate of actuarial duodenal toxicity

Verma et al; IJROBP 2014; 88: 357-362

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

Poorvu et al; IJROBP 2013; 85: 1262-8

Dose volume relationship for Gross nodes

- No clear consensus
- Escalation typically recommended upto 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.

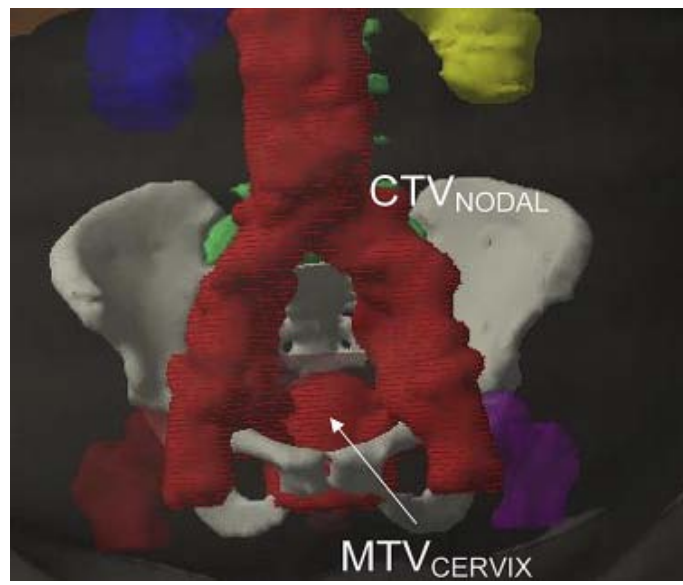
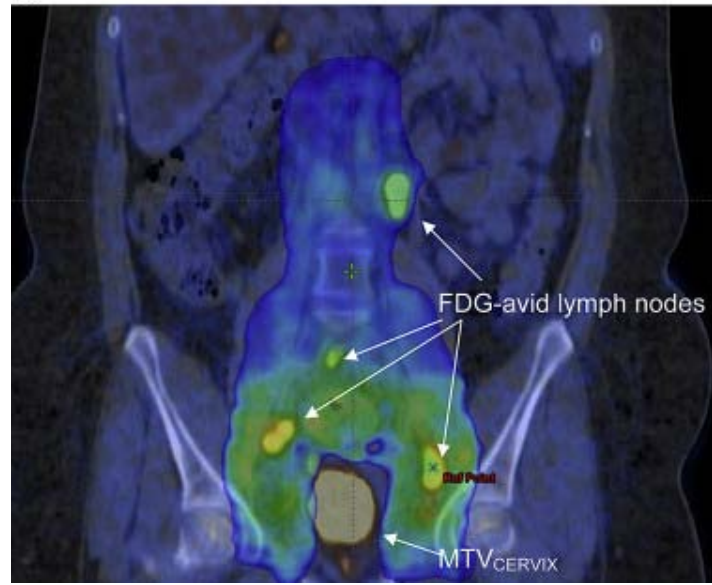
- SIB IMRT – 55Gy/25# with option of sequential boost -10Gy/5#
- FDG avid nodal disease -62Gy/31# SIB (primary tumor treated at 1.8Gy/#)

Gynecologic Oncology 135 (2014) 239–243

Cihoric et al. Radiation Oncology 2014, 9:83

CLINICAL OUTCOMES OF DEFINITIVE INTENSITY-MODULATED RADIATION THERAPY WITH FLUORODEOXYGLUCOSE-POSITRON EMISSION TOMOGRAPHY SIMULATION IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER

A.



PET- CT Based IMRT

Characteristic	IMRT	Non-IMRT	Total	<i>p</i> 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	

PET-CT Based IMRT: Outcome

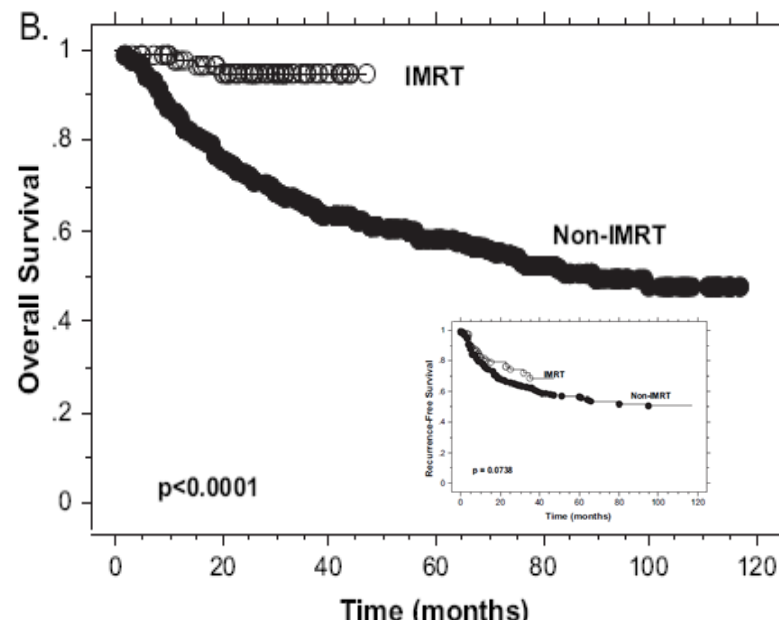
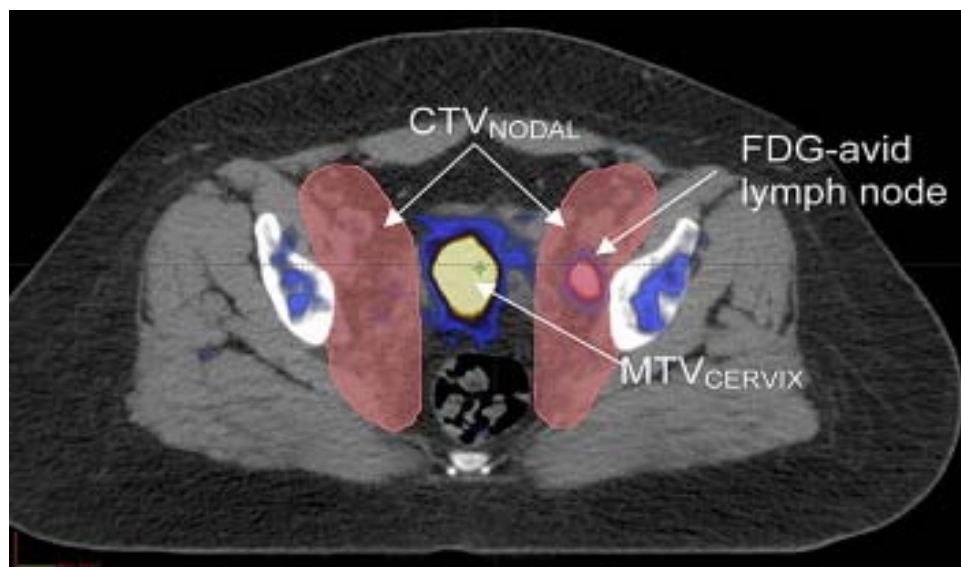


Table 2. Distribution of recurrences for the IMRT, non-IMRT, and total groups

Recurrence	IMRT	Non-IMRT	Total	<i>p</i> 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	

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

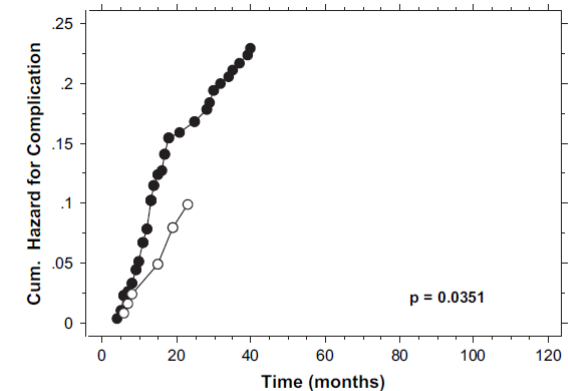


Fig. 4. Cumulative hazard function rates of bowel or bladder complication for the intensity-modulated radiation therapy (IMRT) (○) and non-IMRT (●) groups.

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

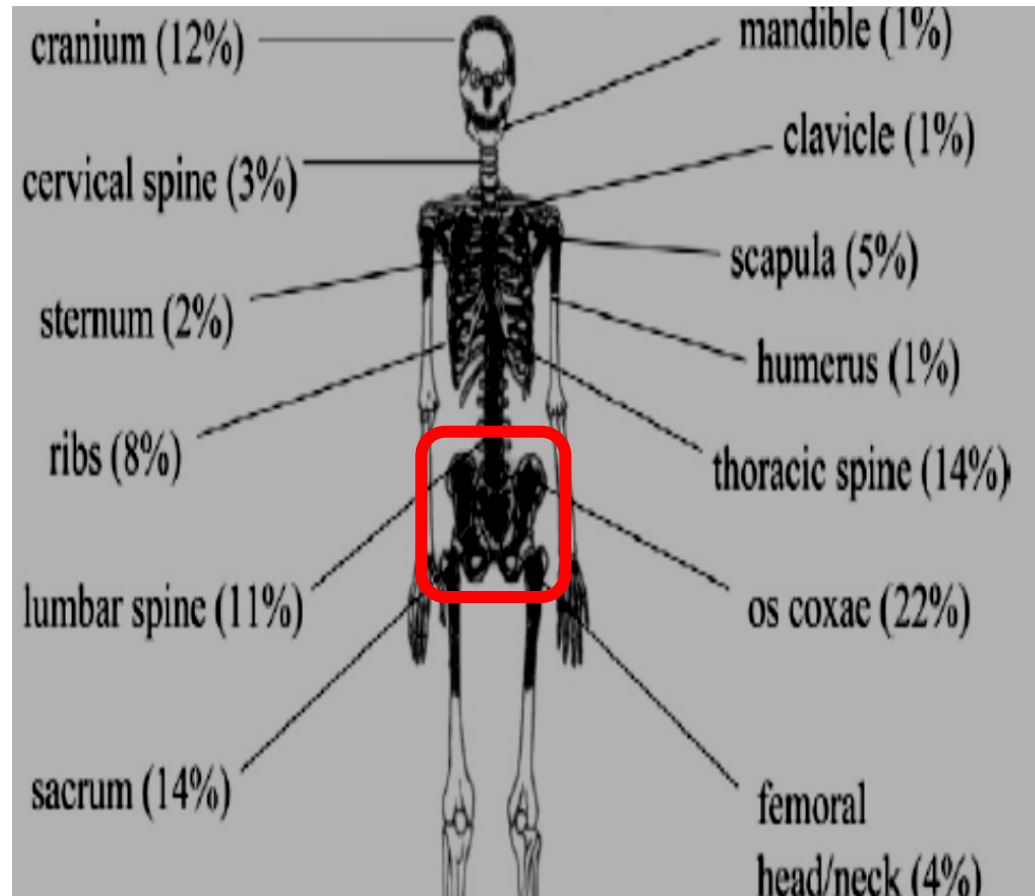
EMBRACE II Protocol CONSTRAINTS

		Hard dose constraints	Soft dose constraints
Targets	PTV45	V95% > 95% Dmax < 107%*	
	ITV45	Dmin > 95%	
	PTV-N(#)	D98% > 90% of prescribed LN dose Dmax < 107% of prescribed LN dose	
	CTV-N(#)	D98% > 100% of prescribed LN dose	D50% > 102%
Help contour	CTV-HR +10mm		Dmax < 103%
OARs	Bowel	Dmax < 105% (47.3Gy)*	When no lymph node boost: <ul style="list-style-type: none"> V40Gy < 100cm³** V30Gy < 350cm³** When lymph node boost or para-aortic irradiation: <ul style="list-style-type: none"> V40Gy < 250cm³** V30Gy < 500cm³** Dmax < 57.5Gy
	Sigmoid	Dmax < 105% (47.3Gy)*	Dmax < 57.5Gy
	Bladder	Dmax < 105% (47.3Gy)*	V40Gy < 75%** V30Gy < 85%** Dmax < 57.5Gy
	Rectum	Dmax < 105% (47.3Gy)*	V40Gy < 85%** V30Gy < 95%** Dmax < 57.5Gy
	Spinal cord	Dmax < 48Gy	
	Femoral heads	Dmax < 50Gy	
	Kidney	Dmean < 15Gy	Dmean < 10Gy
	Body	Dmax < 107%*	
	Vagina PIBS-2cm		When vagina not involved: D _{PIBS-2cm} < 5Gy
Optional	Ovaries	<5-8 Gy	
	Duodenum***	V55 < 15cm ³	

PET-CT Based Active Bone Marrow as a potential OAR

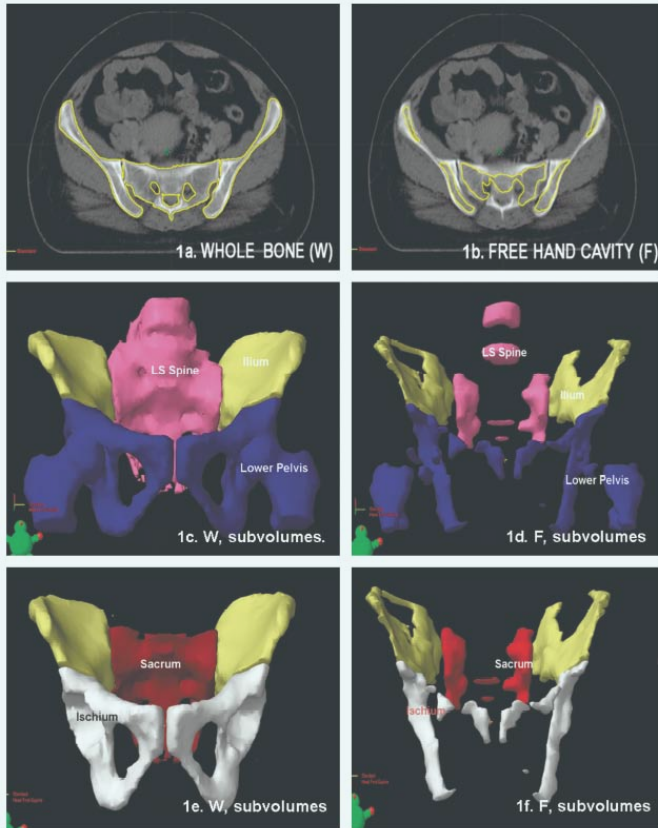
Bone marrow : Organ at risk for haematological toxicities

Adult: Haematopoietic Tissue Distribution

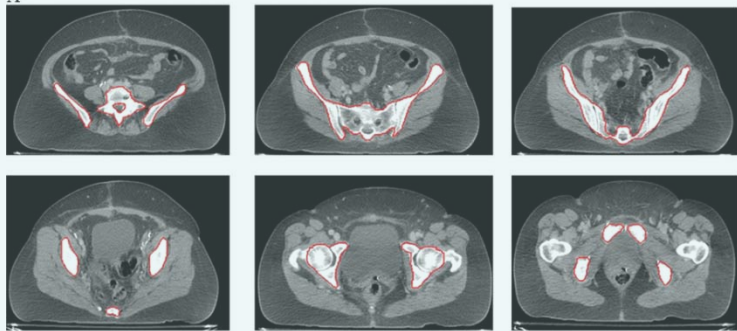


- **Approx. 45-50% of active marrow in pelvic field**
- **Constitutes critical mass for toxicities**

CT Based

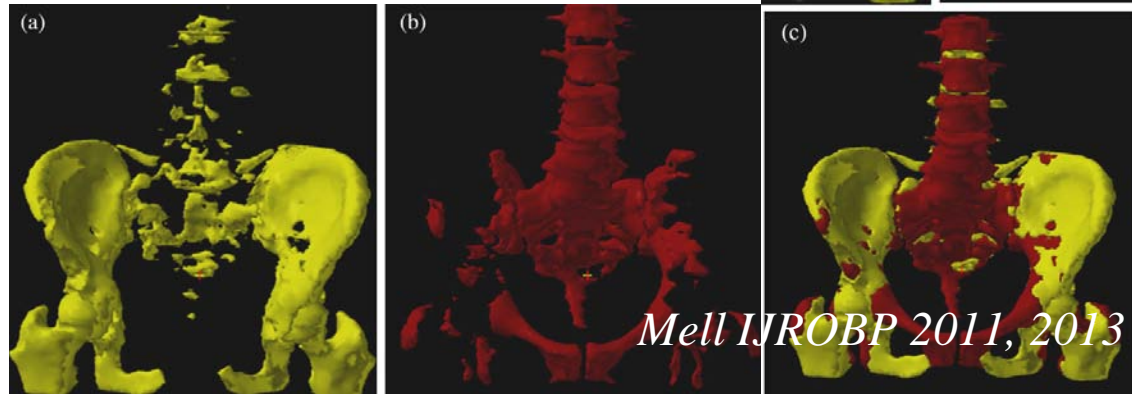


Umesh IJGC Oct. 2012

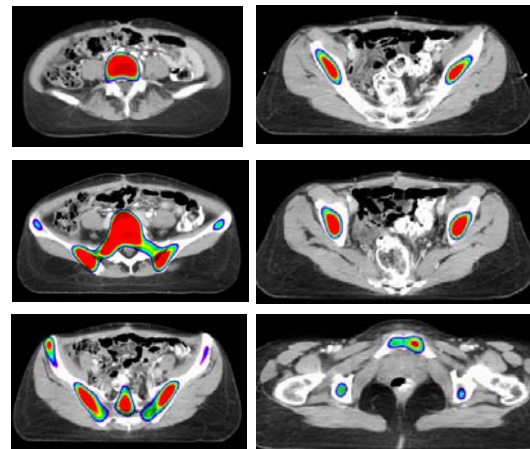


IJROBP 2013

FDG PET: $SUV > \text{Mean corrected for body weight}$

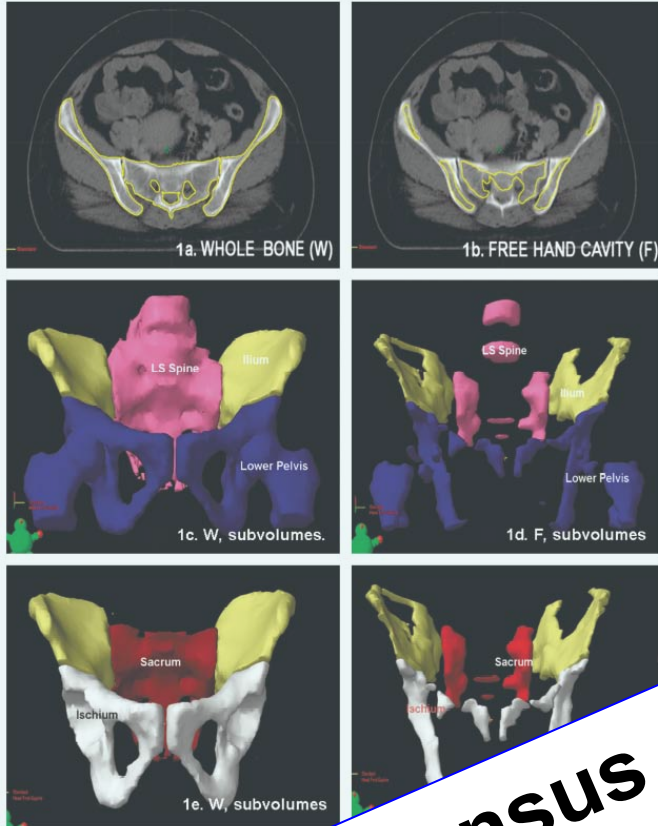


SPECT-CT: Tc 99m sulphur colloid defined hot-spots

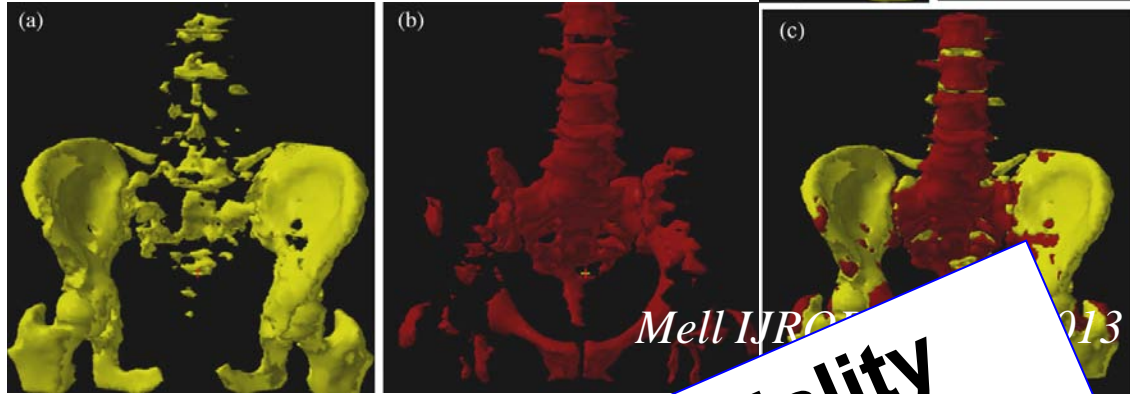


Roeske et al; Rad. Oncol 2005

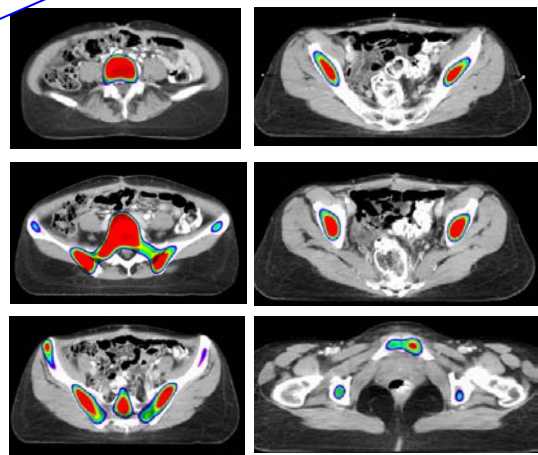
CT Based



FDG PET: $SUV > \text{Mean corrected for body weight}$



Tc 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	<u>100</u>	<u>85(15)</u>	<u>91(3.6)</u>	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**

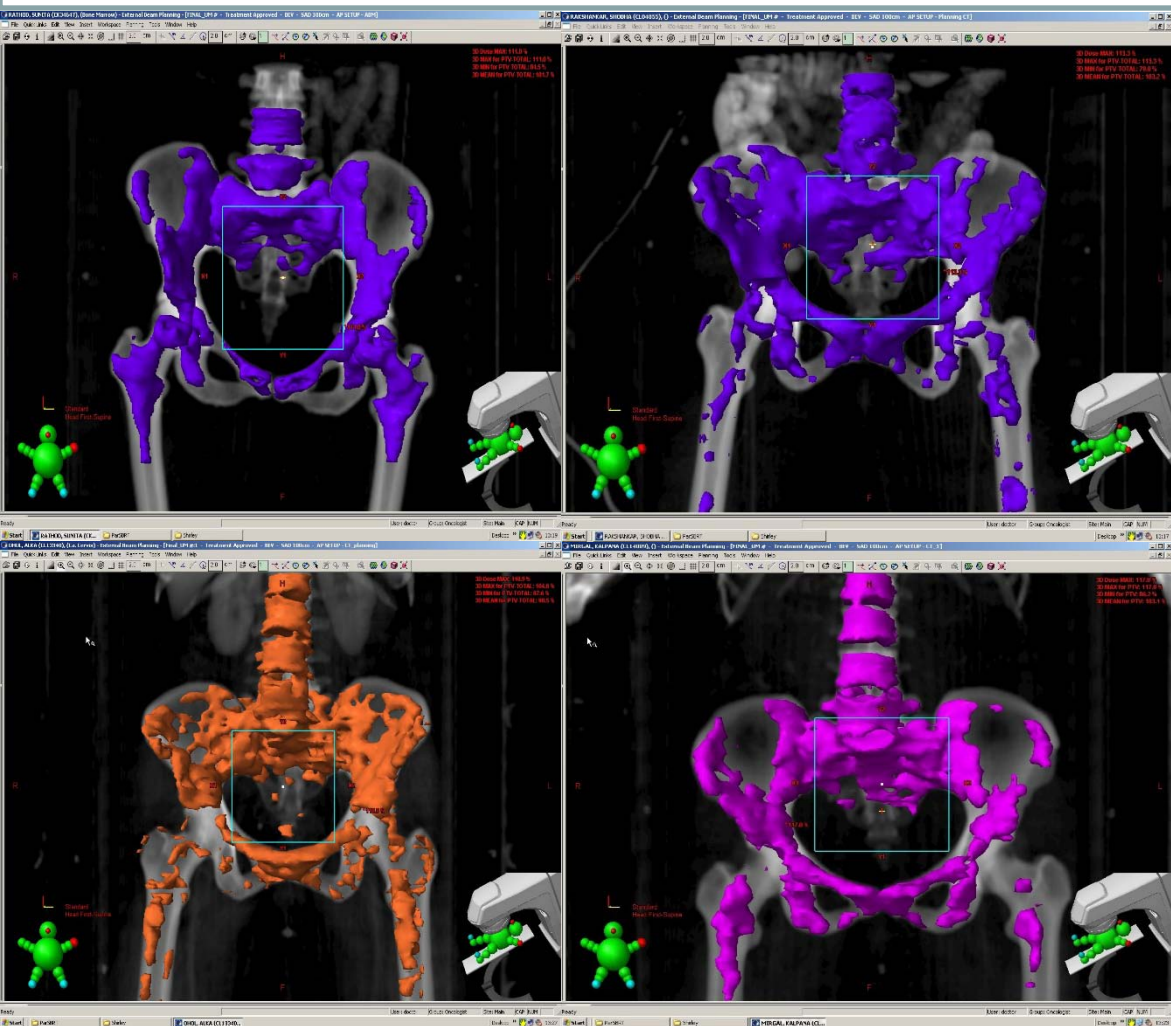
UC San Diego

RADIATION ONCOLOGY

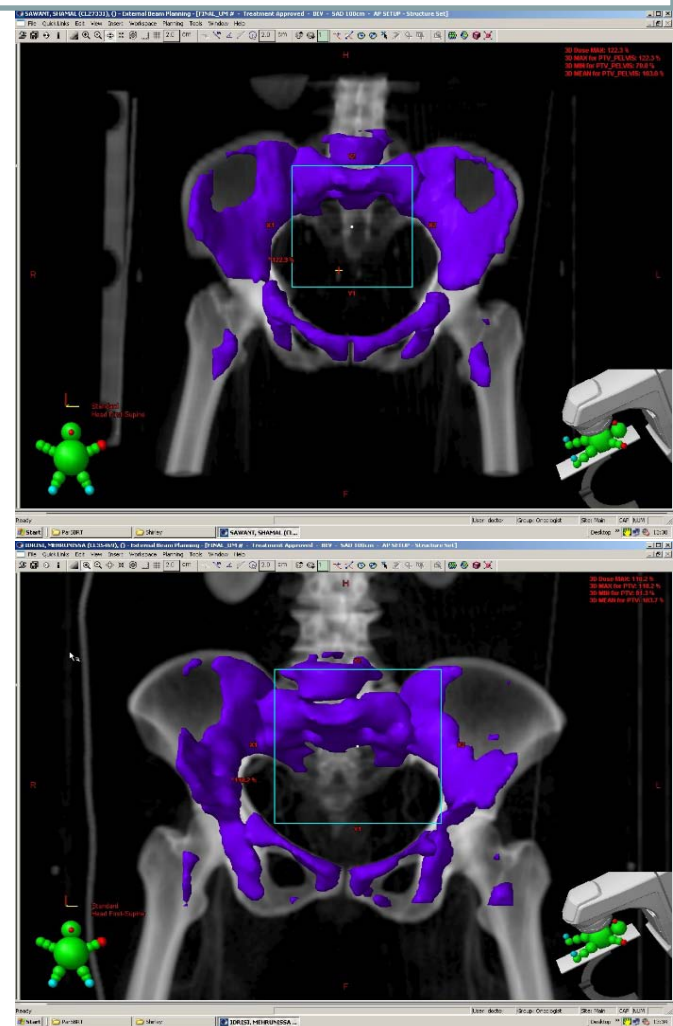
CART CENTER FOR
ADVANCED
RADIOTHERAPY
TECHNOLOGIES
UCSD

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

EVIDENCE

Can High Tech XRT replace BT?

High Tech XRT

Vs

BT (Conventional)

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



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

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

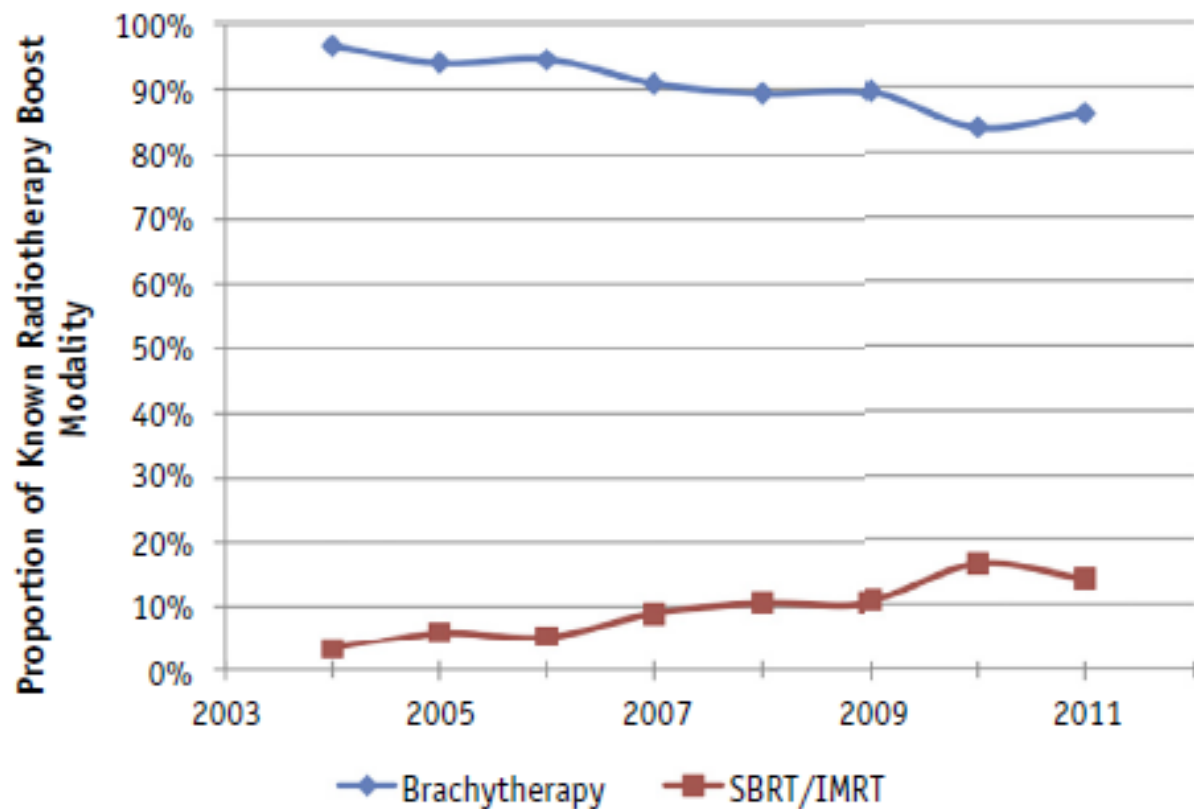


Fig. 1. Changes in radiation therapy boost modality utilization over time from 2004 to 2011. IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation therapy.

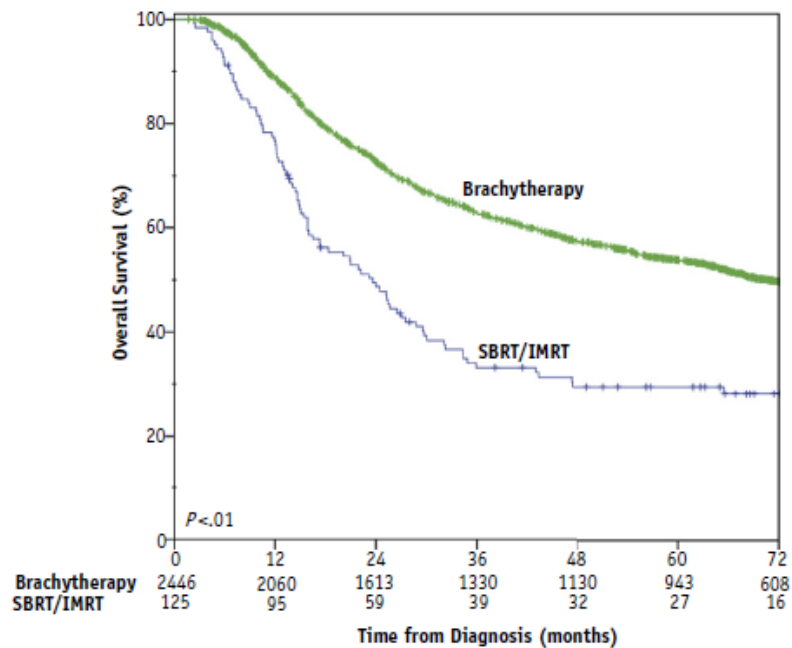


Fig. 2. Kaplan-Meier overall survival estimate stratified by boost modality. IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation therapy.

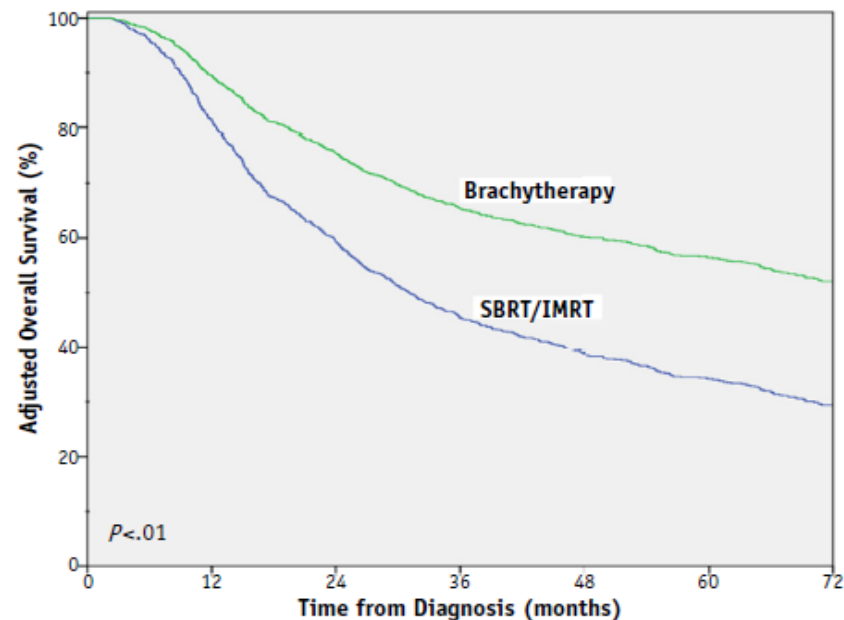


Fig. 3. Adjusted overall survival estimate, stratified by boost modality and corrected for significant variables on multivariable Cox proportional hazard model analysis (age, Charlson/Deyo score, stage, and chemotherapy utilization). IMRT = intensity modulated radiation therapy; SBRT = stereotactic body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

SUMMARY

- **Pelvic IMRT**
 - IMRT /IGRT reduces toxicities especially in post op pelvic settings
 - Ongoing studies : BM sparing potential for further interventions
- **PA Region IMRT**
 - Potential to reduce toxicities
 - Dose Escalation protocols with PET : promising
- **SBRT – IMRT Vs BT**
 - Use of SBRT results in inferior outcome as compared to 2D BT



ESTRO Gyn Teaching Course
Image Guided Radiotherapy & Chemotherapy in gynaecologic cancer-
with a special focus on adaptive brachytherapy



ICRU-GEC-ESTRO recommendations on dose volume reporting

Richard Pötter

Recommendations, DVH parameters

Radiotherapy and Oncology 78 (2006) 67-77
www.thegreenjournal.com

ESTRO project

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

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

^aDepartment of Radiotherapy and Radiobiology, Medical University of Vienna, Austria, ^bDepartment of Radiotherapy, Brachytherapy Unit, Institut Gustave Roussy, Villejuif, France, ^cDepartment of Radiotherapy, University Hospital Gasthuisberg, Leuven, Belgium, ^dDepartment of Radiation Oncology, Centre George-Francois Leclerc, Dijon, France, ^eDepartment of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, USA, ^fService de Radiodiagnostic, Institut Curie, Paris, France

PRESCRIBING, RECORDING, AND REPORTING BRACHYTHERAPY FOR CANCER OF THE CERVIX (ICRU GEC ESTRO REPORT 88)

Report Committee:

R. Pötter (Co-Chairman), Medical University of Vienna, Vienna, Austria

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Commission Sponsors:

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To be added

Consultants to the Report Committee:

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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 gynecological 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 ASSESSMENT
- 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 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 safety margin if used for prescription)**

At Diagnosis

At Brachytherapy

Dose of EBRT ___ Gy

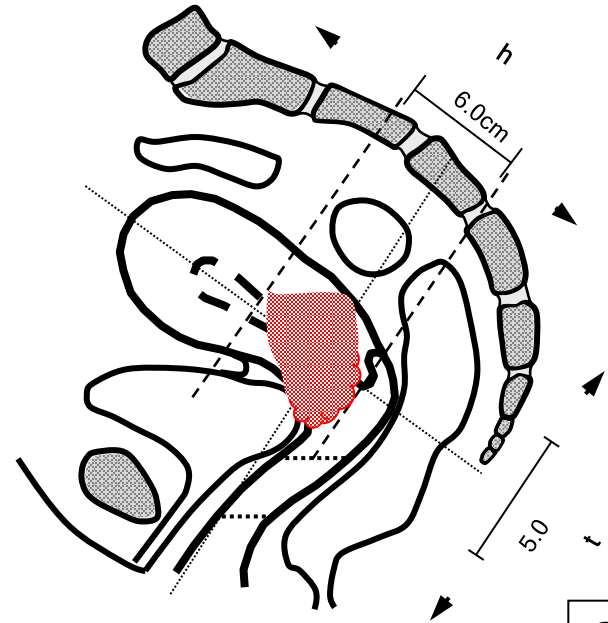
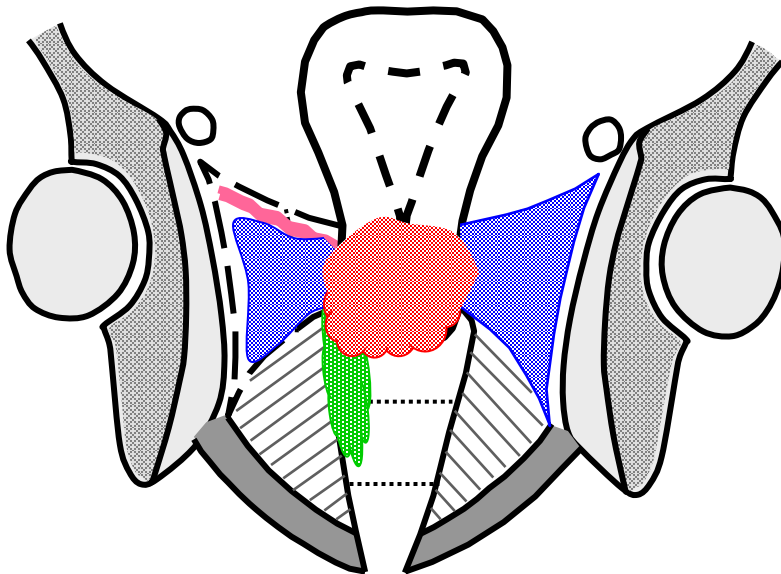
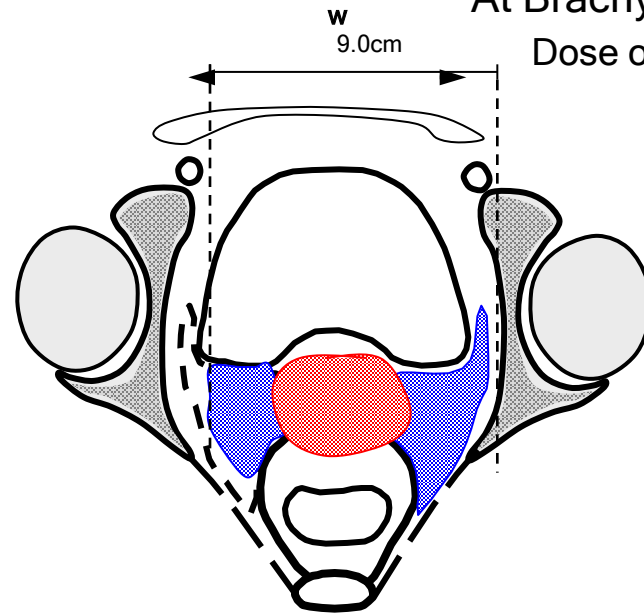
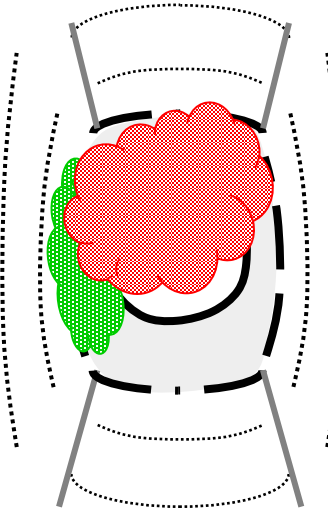
IIIB

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

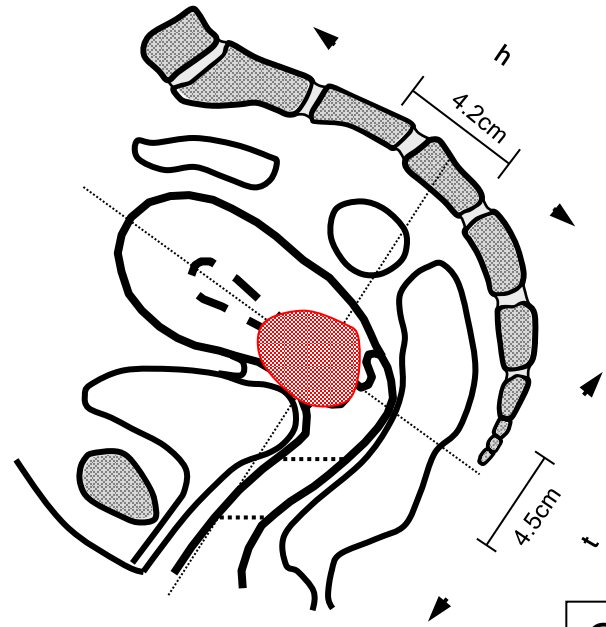
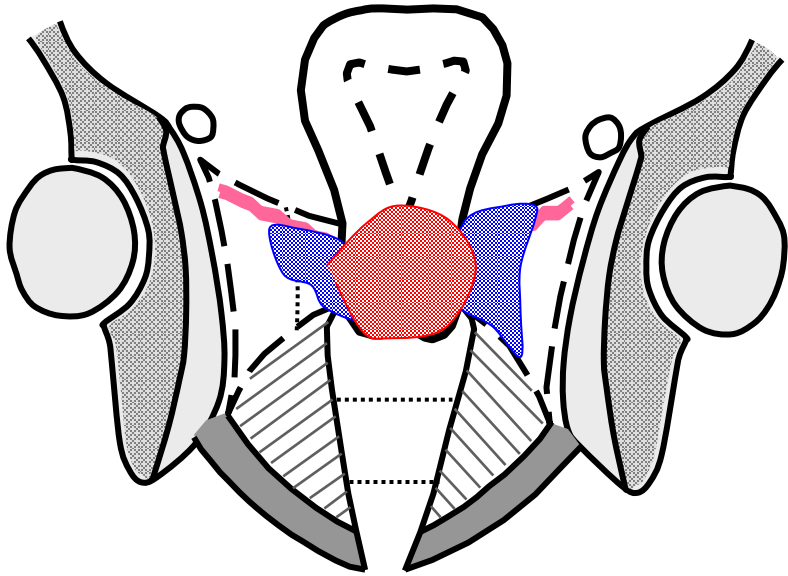
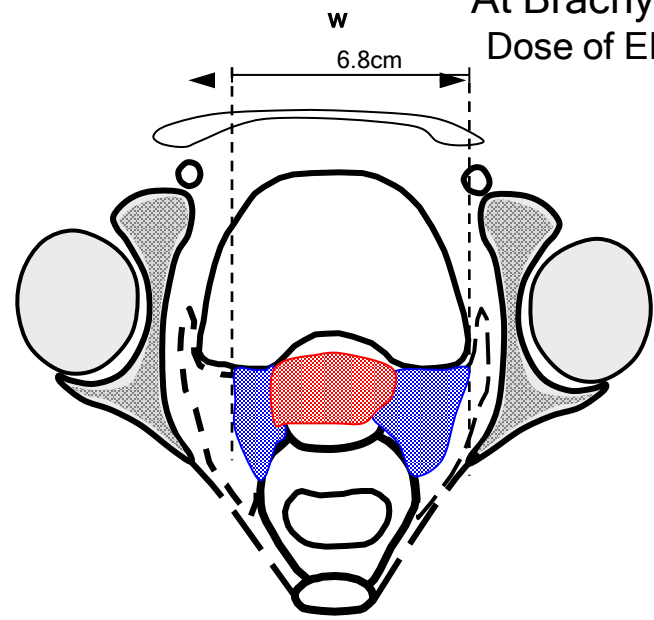
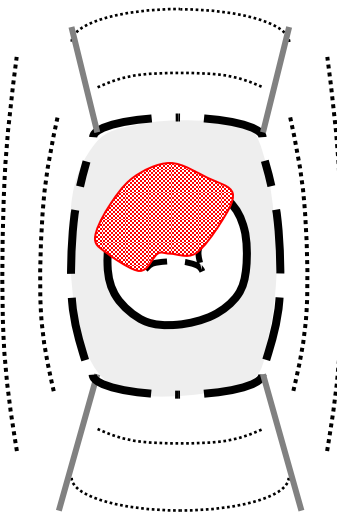
At Diagnosis

At Brachytherapy
Dose of EBRT 50.4 Gy

IIIB

$w = 6.8 \text{ cm}$
 $h = 4.2 \text{ cm}$
 $t = 4.5 \text{ cm}$

Vagina: 0 cm



dd/mm/yy
/ /

Signature

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

Case IV

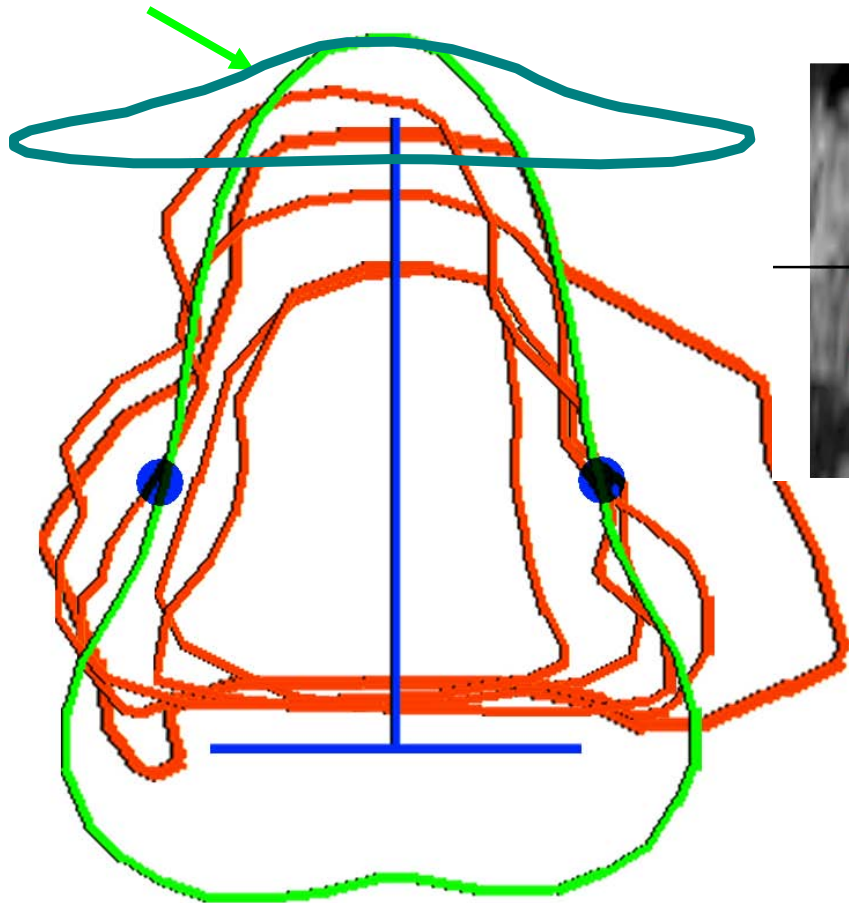
Level 1 – *minimum standard for reporting*

Dose reporting:

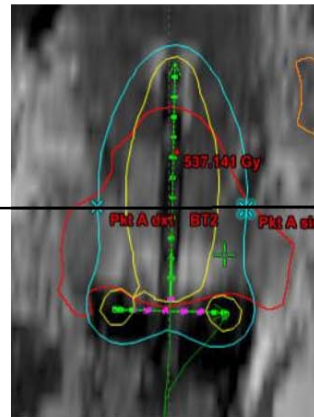
- TRAK
- Point A dose
- Recto-vaginal reference point dose (prior: ICRU rectum point)
- Bladder reference point for radiographs (if 2D imaging)
- $D_{0.1\text{cm}^3}$, $D_{2\text{cm}^3}$ for bladder, rectum (if 3D imaging)
- Overall treatment time

Point-A based brachytherapy

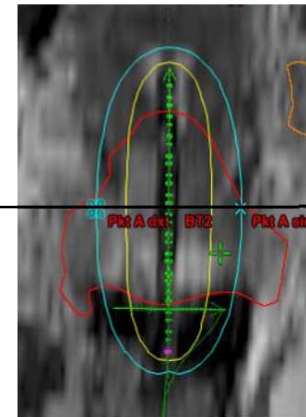
Point A isodose



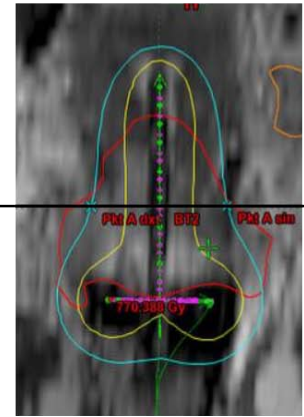
Milwaukee



Toronto



Vienna



Dose Delivery Pattern ICRU 89

Absorbed dose rate/dose per fraction

Number of fractions

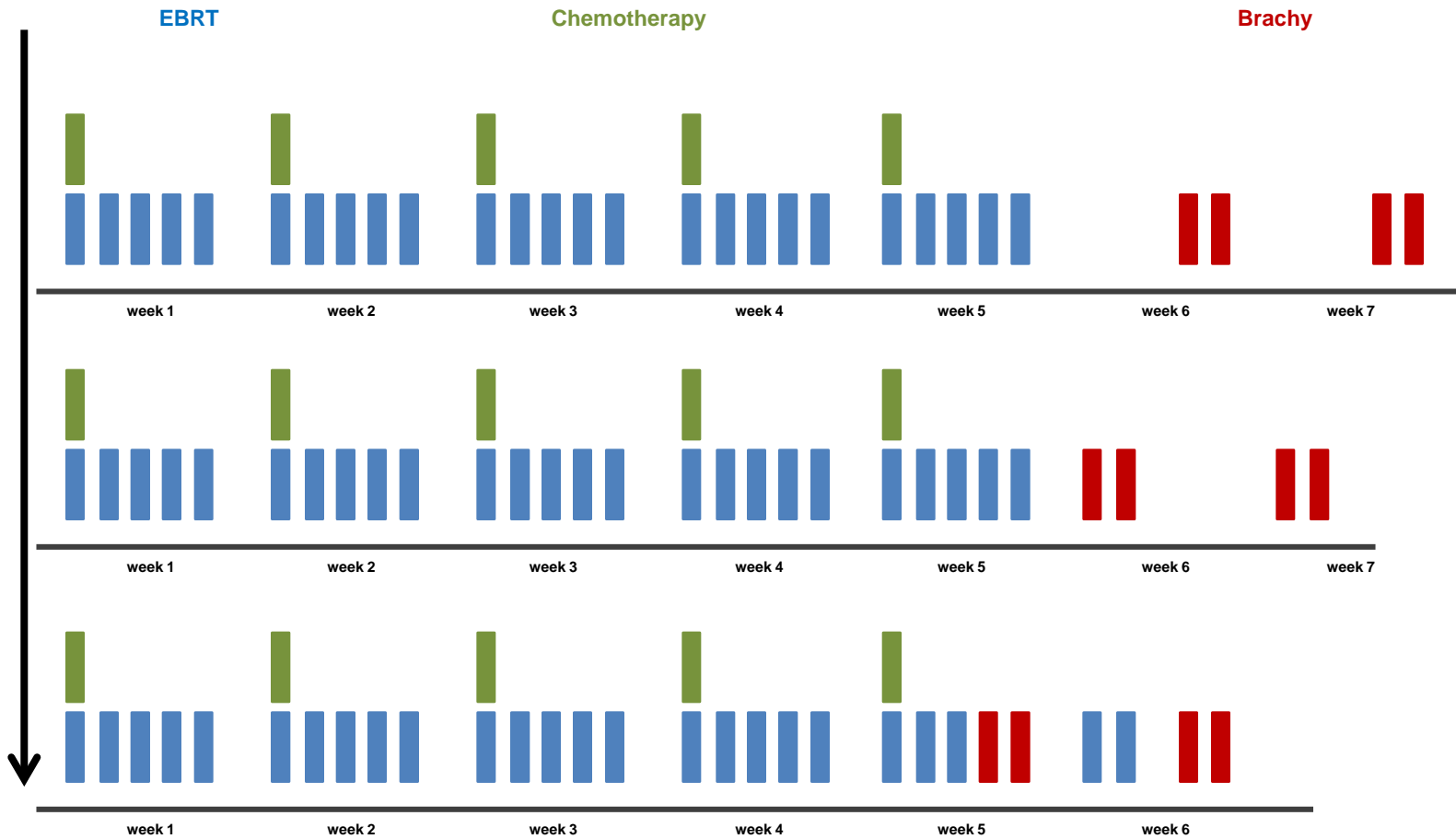
Time between fractions

(Pulse number, size, time, if PDR)

Overall treatment time

Total EQD2

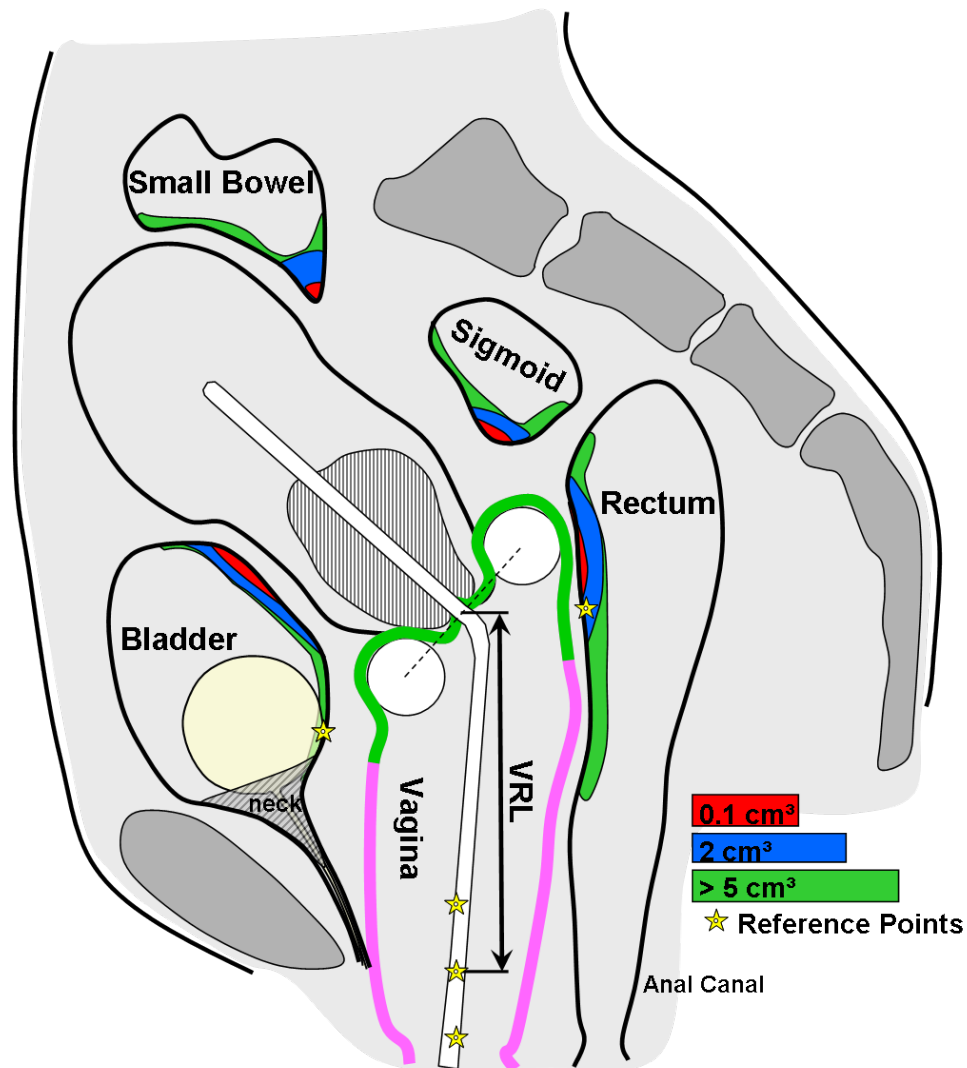
Overall Treatment Time (BT, EBRT, total)



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

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

DVH Parameters and Reference Points,

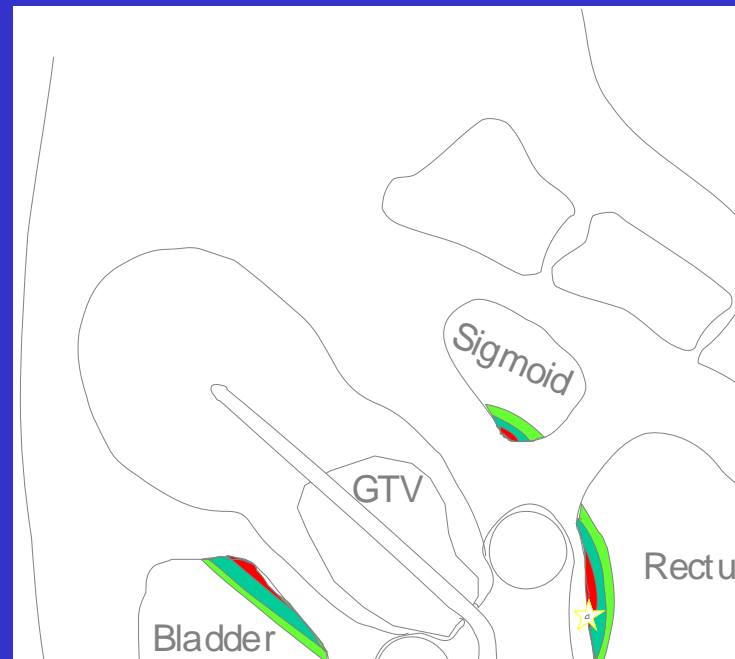


ICRU/GEC ESTRO
report 89
under publication
Fig. 6.4, Fig. 8.8

3D-based Dose Volume Parameters for OAR

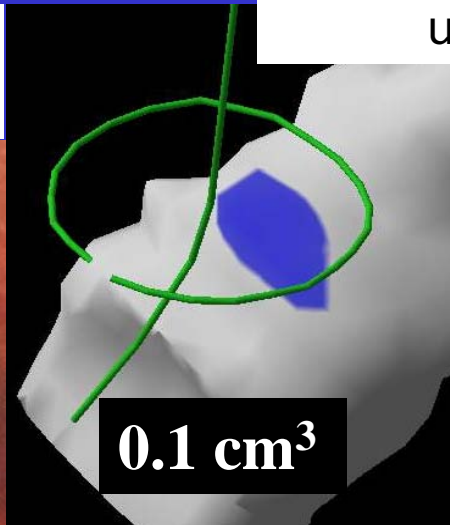
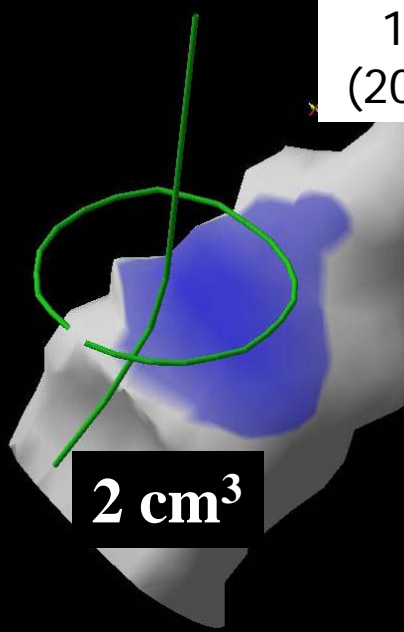
CLASSICAL MAX DOSE in 2D:
in 3D a voxel is no clinical relevant endpoint

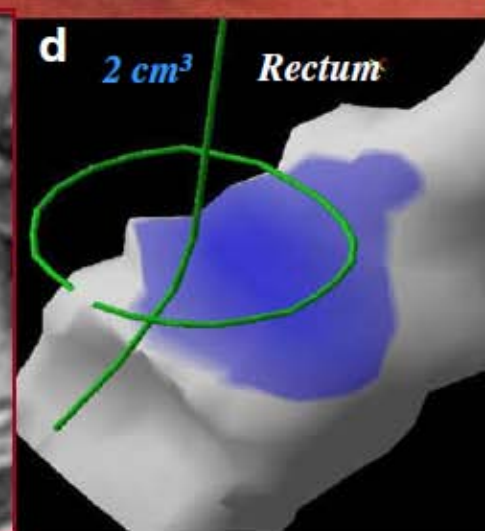
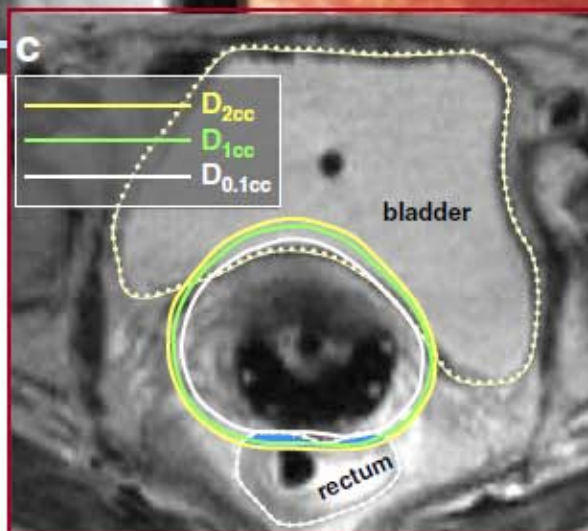
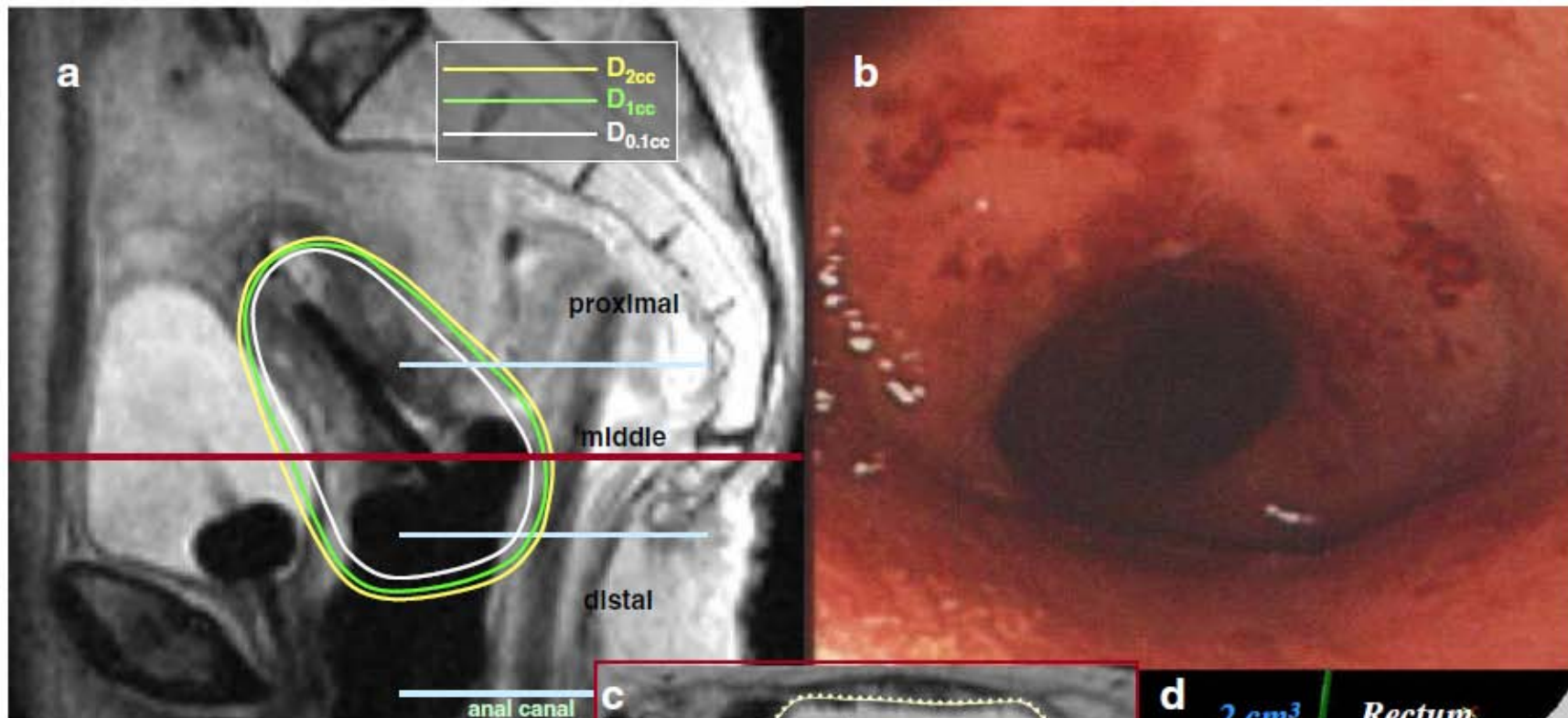
FIXED VOLUME: tolerance dose (total dose)-
"minimum dose to the most exposed tissue"*



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

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



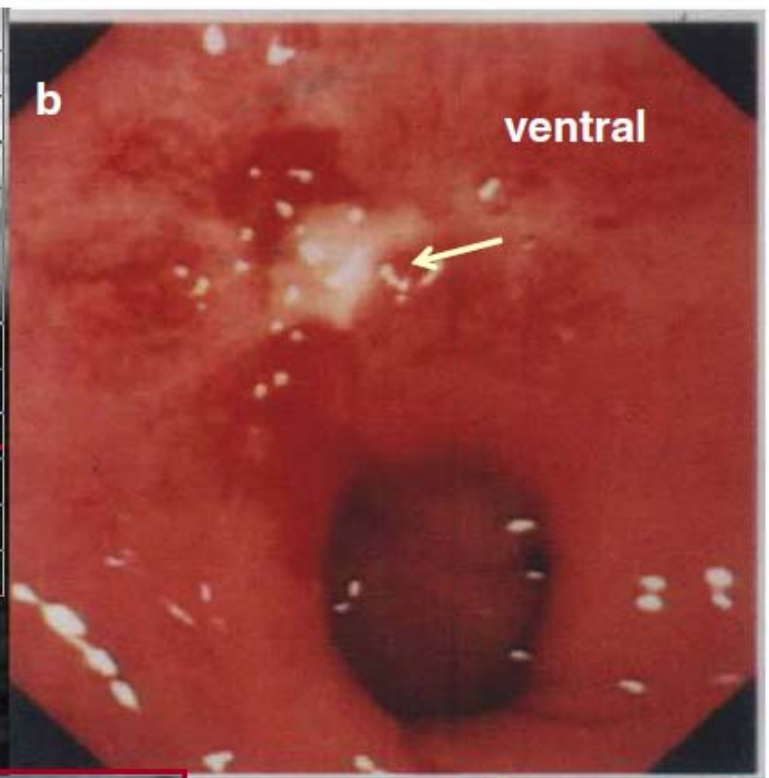
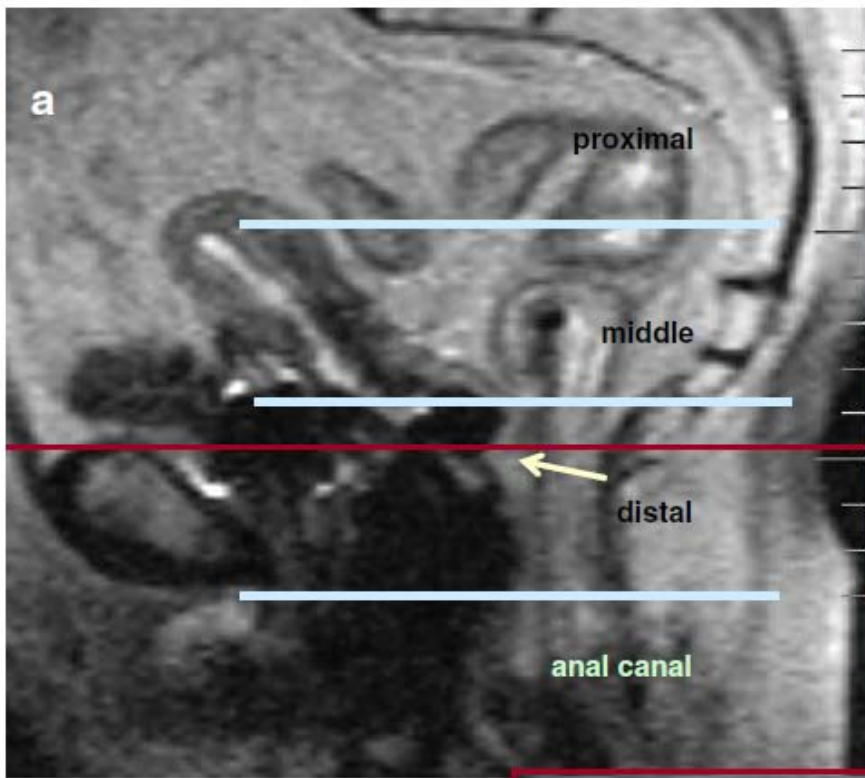


Total DVH parameters
(calculated taking into account all 4 fractions)

$D_{2cc} = 75$ Gy EQD2

$D_{1cc} = 82$ Gy EQD2

$D_{0.1cc} = 103$ Gy EQD2

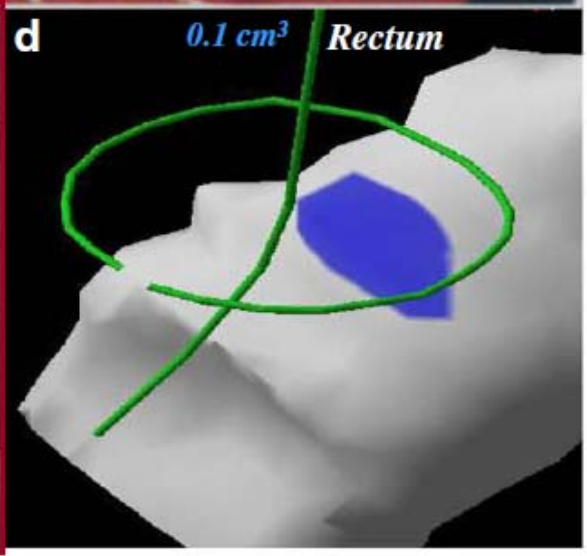
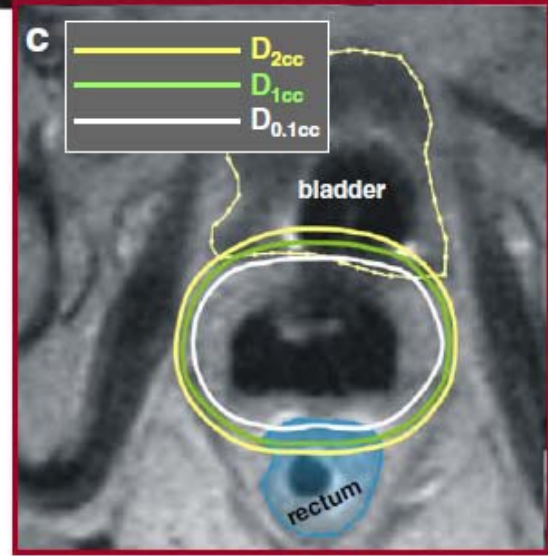


Total DVH parameters
(calculated taking into account all 4 fractions)

$D_{2cc} = 81 \text{ Gy EQD2}$

$D_{1cc} = 90 \text{ Gy EQD2}$

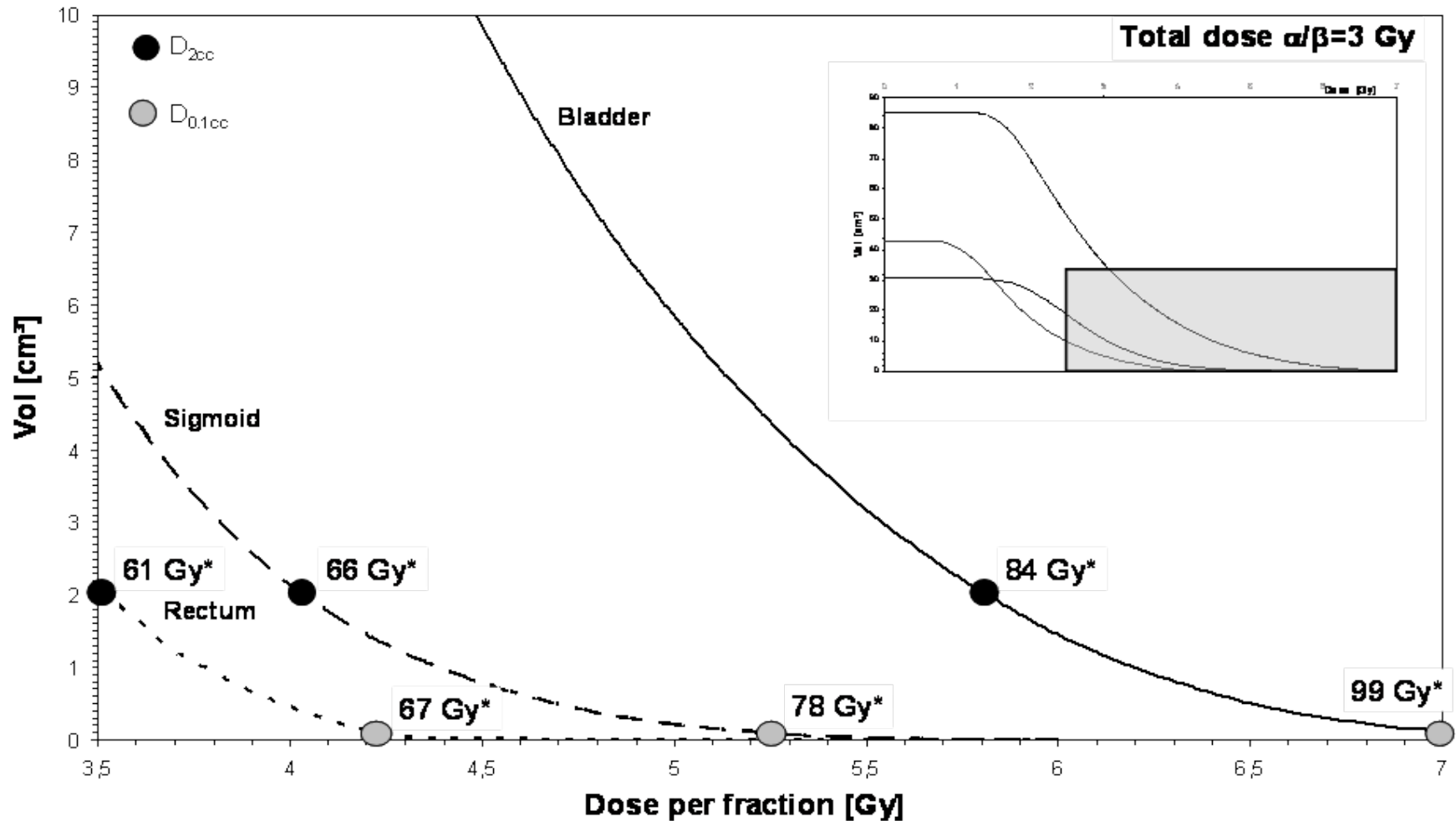
$D_{0.1cc} = 108 \text{ Gy EQD2}$



D_{2cm3} for rectum is endpoint for

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

DVH Parameters for organs at risk (ICRU 89)

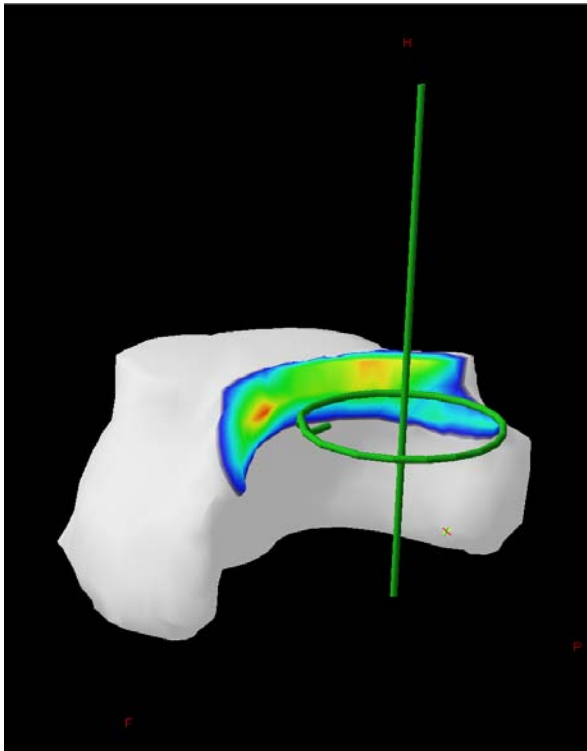


Bladder

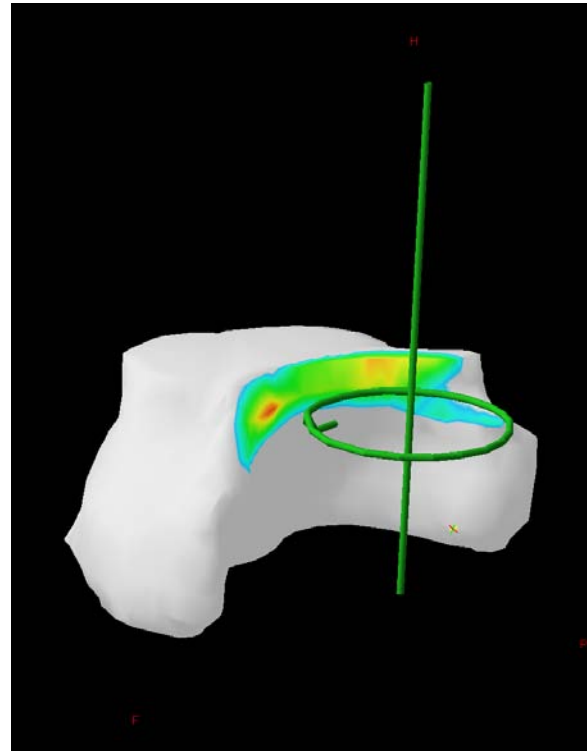
D_{2cc}

w x h:

40mm x 20mm

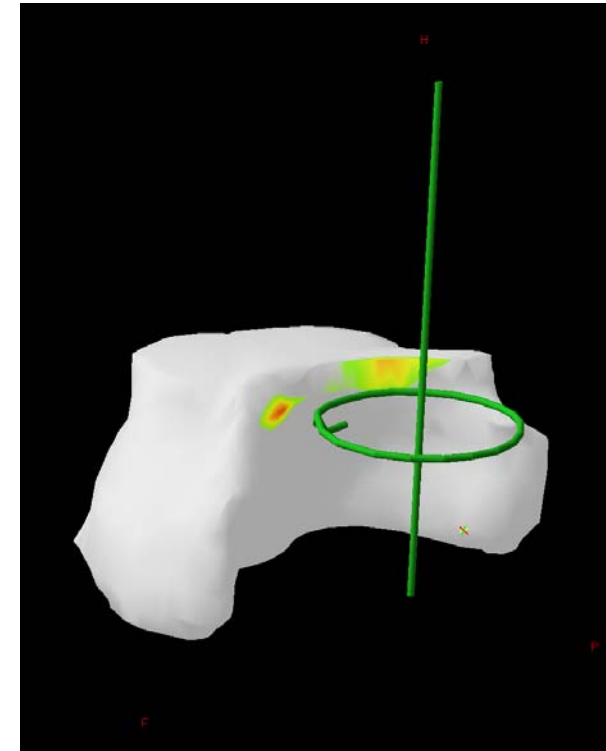


D_{1cc}



$D_{0.1cc}$

20mm x 10mm

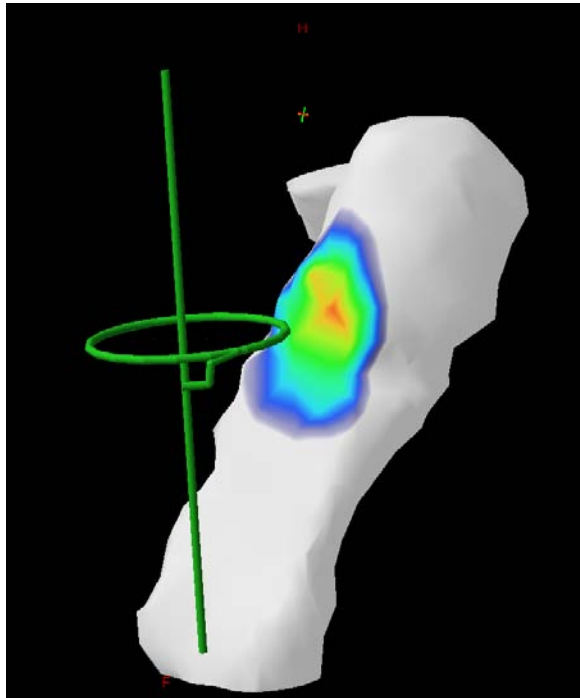


Rectum

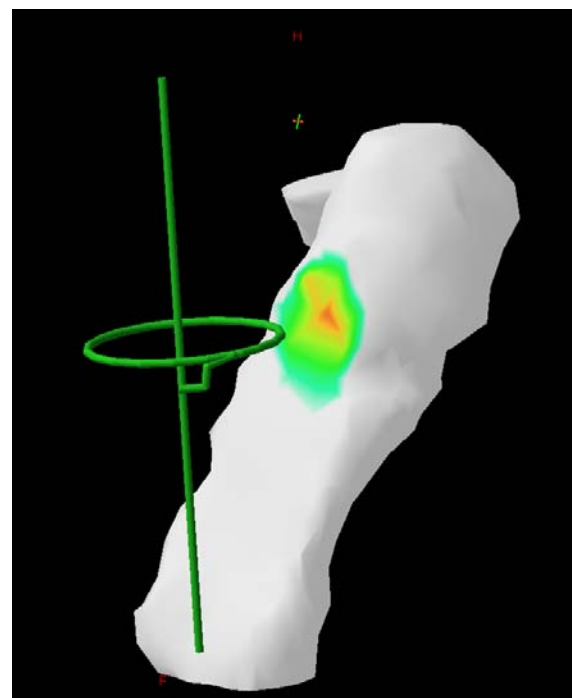
D_{2cc}

w x h:

30mm x 30mm

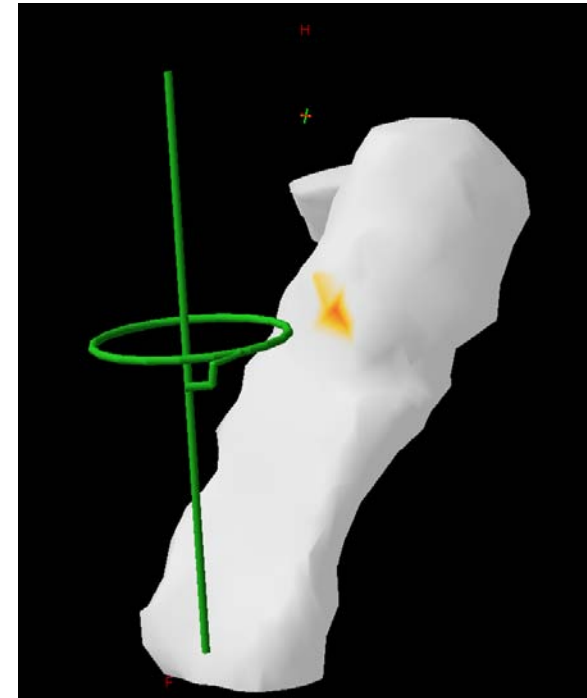


D_{1cc}



$D_{0.1cc}$

10mm x 10mm

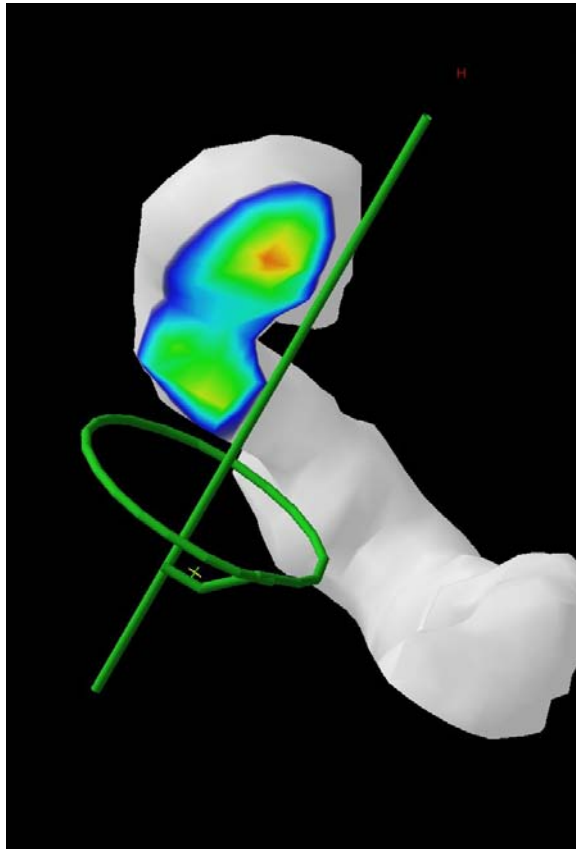


Sigmoid

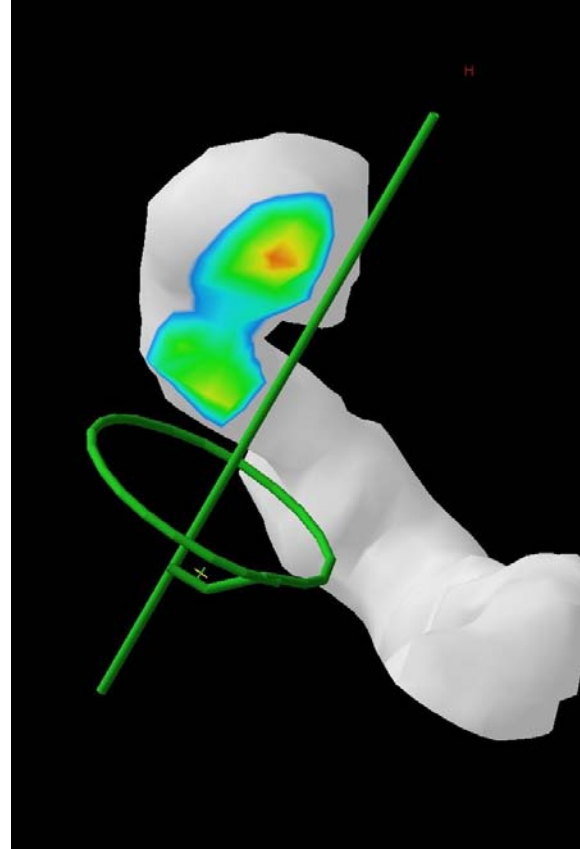
D_{2cc}

w x h:

25mm x 20mm

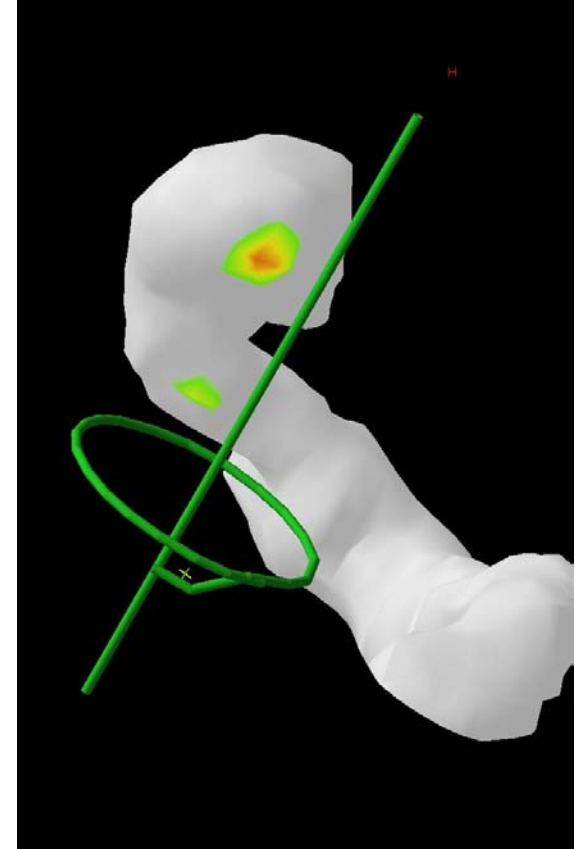


D_{1cc}

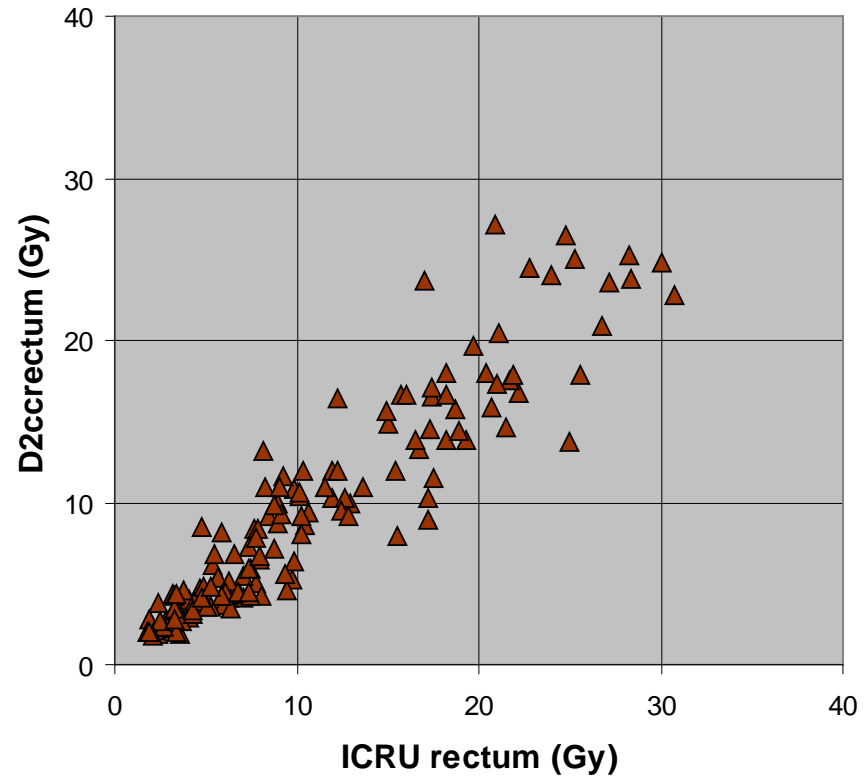
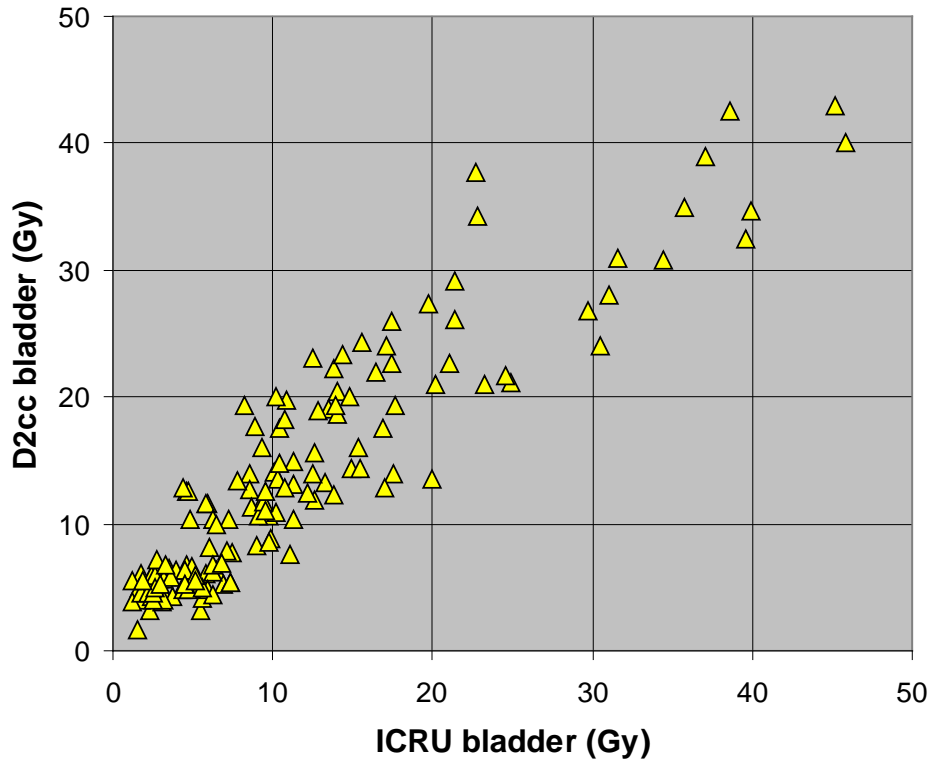


$D_{0.1cc}$

10mm x 10mm



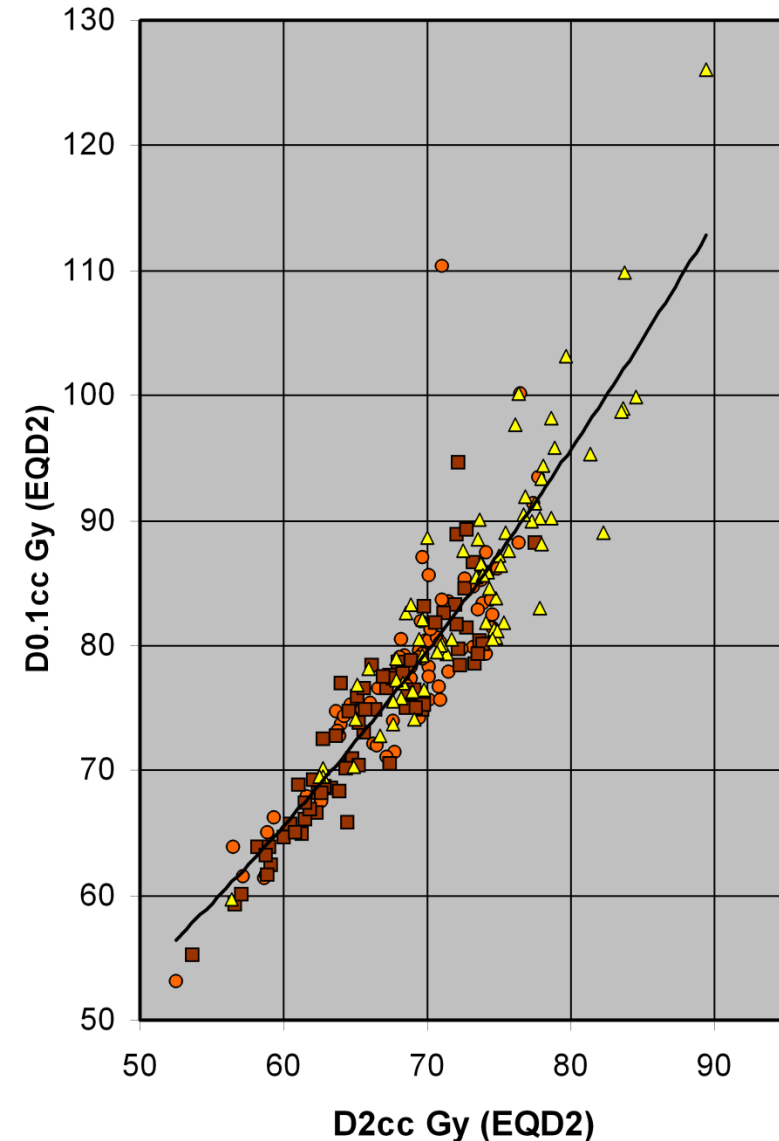
ICRU point dose and D2cc doses



EMBRACE data, Tanderup et al.

D2cc and D0.1cc

	D2cc Gy EQD2	D0.1cc Gy EQD2
Bladder	71 ± 7	81 ± 13
Rectum	65 ± 6	72 ± 8
Sigmoid	67 ± 6	74 ± 12



$D_{0.1cc} / D_{2cc} : 134\% \pm 9\%$
(Physical doses)

$D_{2\text{cm}^3}$ and $D_{0.1\text{cm}^3}$ for OAR

- A. $D_{2\text{cm}^3}$ is identical to $D_{0.1\text{cm}^3}$
- B. $D_{2\text{cm}^3}$ is larger than $D_{0.1\text{cm}^3}$
- C. $D_{2\text{cm}^3}$ is smaller than $D_{0.1\text{cm}^3}$

Level 2 - *Advanced standard for reporting*

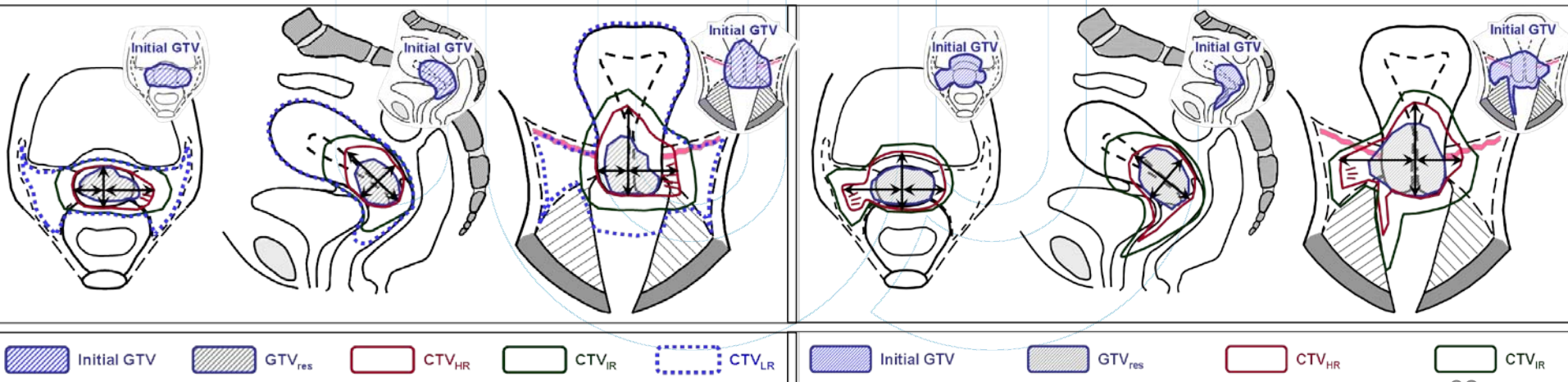
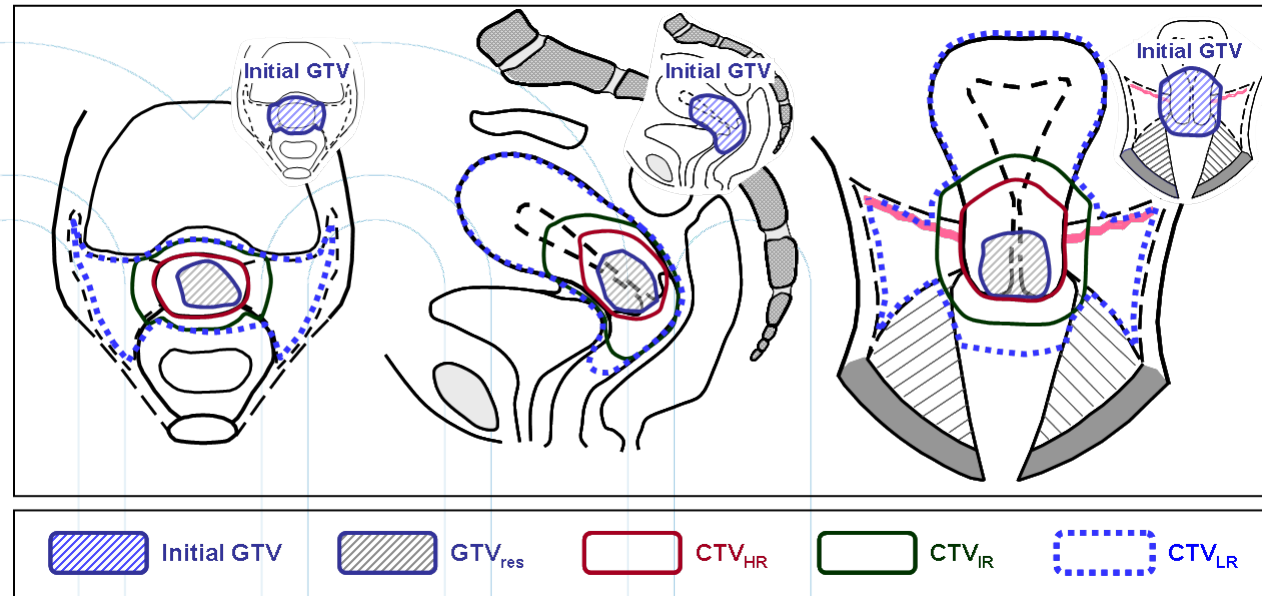
All that is reported in level 1 plus (ICRU 89):

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)



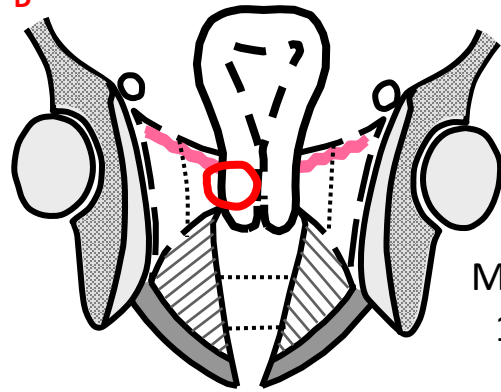
At diagnosis

GTV_D

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

At brachytherapy

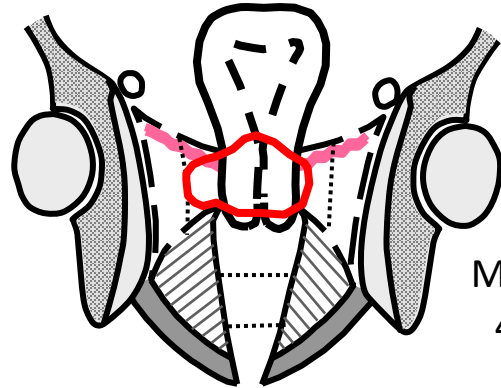
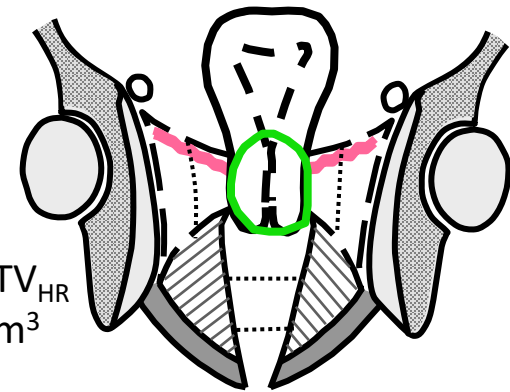
HR-CTV



Group 1
"Stage IB₁-like"
N=55 (11%)

Mean GTV_D
12.6 cm³

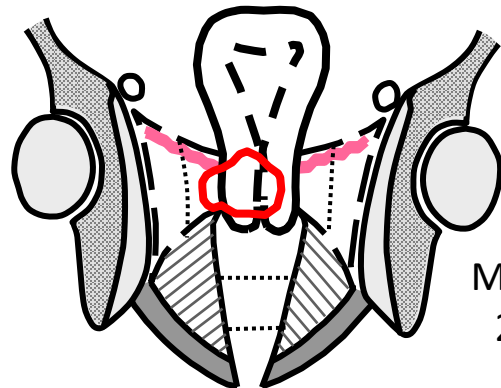
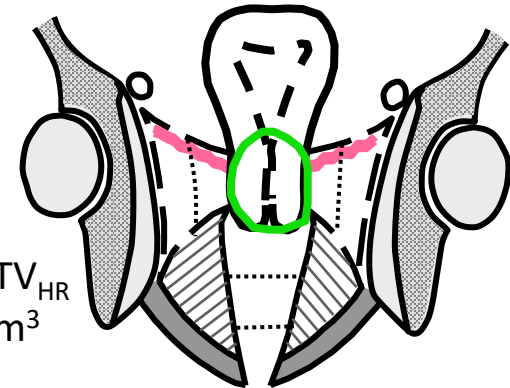
Mean CTV_{HR}
23.7 cm³



Group 2
Good response
N=78 (16%)

Mean GTV_D
47.5 cm³

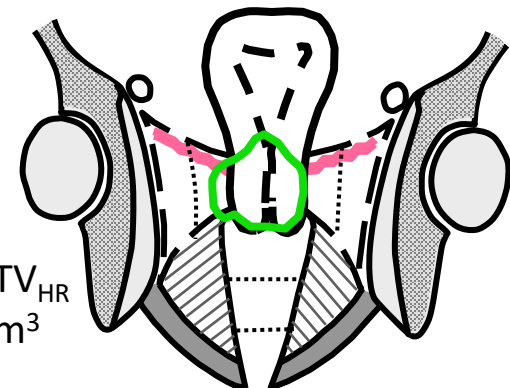
Mean CTV_{HR}
25.3 cm³



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

Mean GTV_D
23.9 cm³

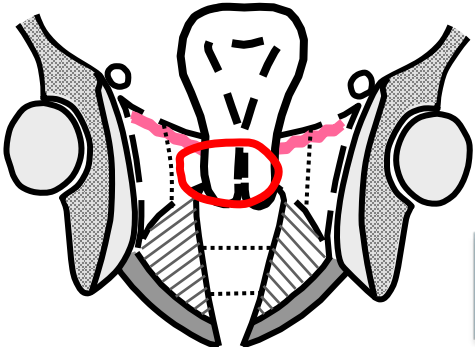
Mean CTV_{HR}
29.9 cm³



Volumetric tumour regression: FIGO stage IIB/IIIB cervical cancer, large tumor at diagnosis subgroup from EMBRACE data base, N=183/345

At diagnosis

At brachytherapy

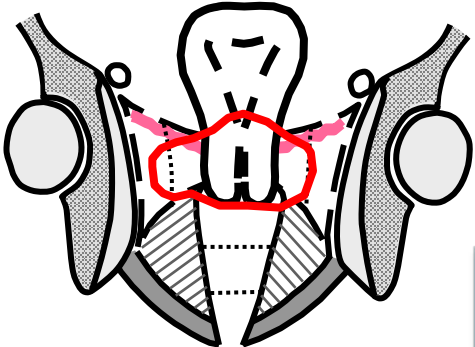
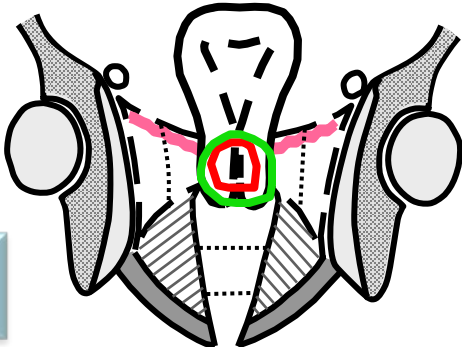


Good response

N=68

Mean GTV
45.2 cm³

Mean HR CTV
24.6 cm³

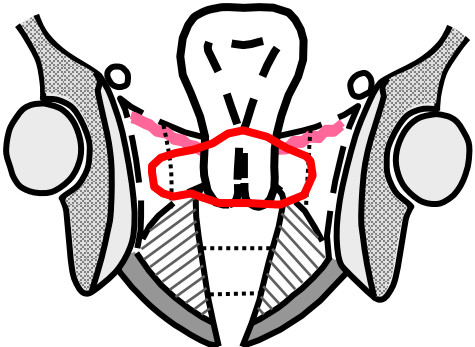
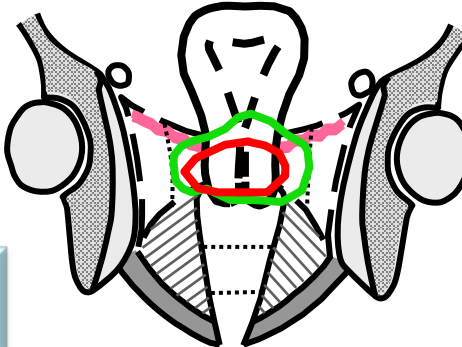


Moderate response

N=98

Mean GTV
76.7 cm³

Mean HR CTV
40.1 cm³

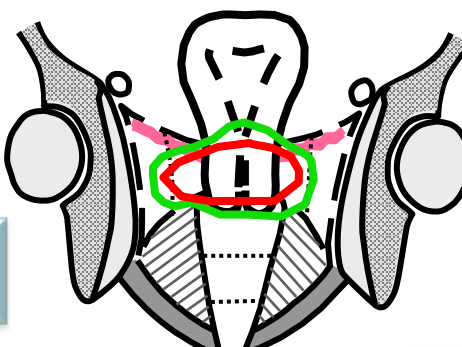


Poor response

N=17

Mean GTV
62.1 cm³

Mean HR CTV
57.8 cm³



— GTV
— HR CTV

Level 2 - *Advanced standard for reporting*

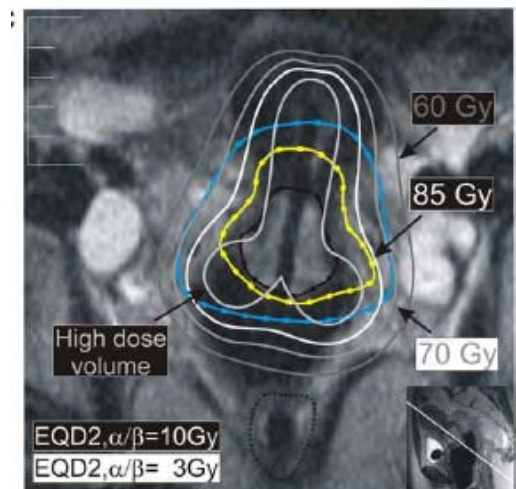
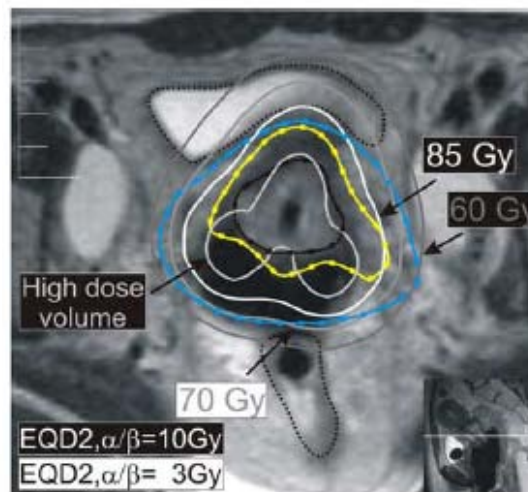
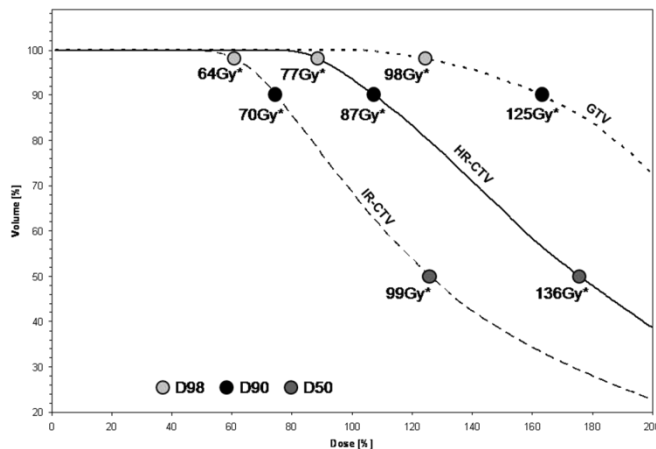
All that is reported in level 1 plus (ICRU 89):

Dose reporting for defined volumes based on volumetric imaging:

- D_{98} , D_{90} , D_{50} for CTV_{HR}
- (D_{98} , D_{90} , D_{50} for CTV_{IR} if used for prescription)
- D_{98} for GTV_{res}
- D_{98} for pathological lymph nodes

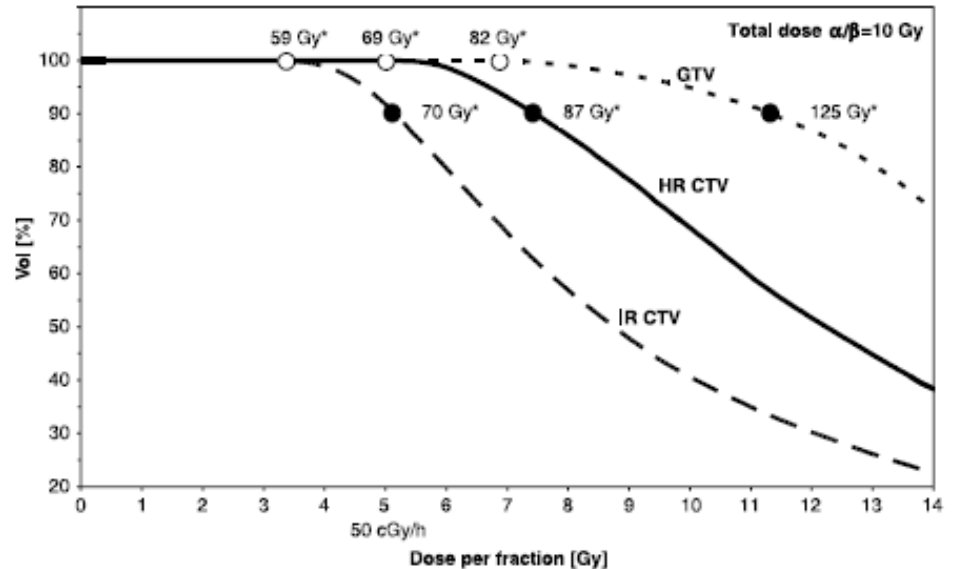
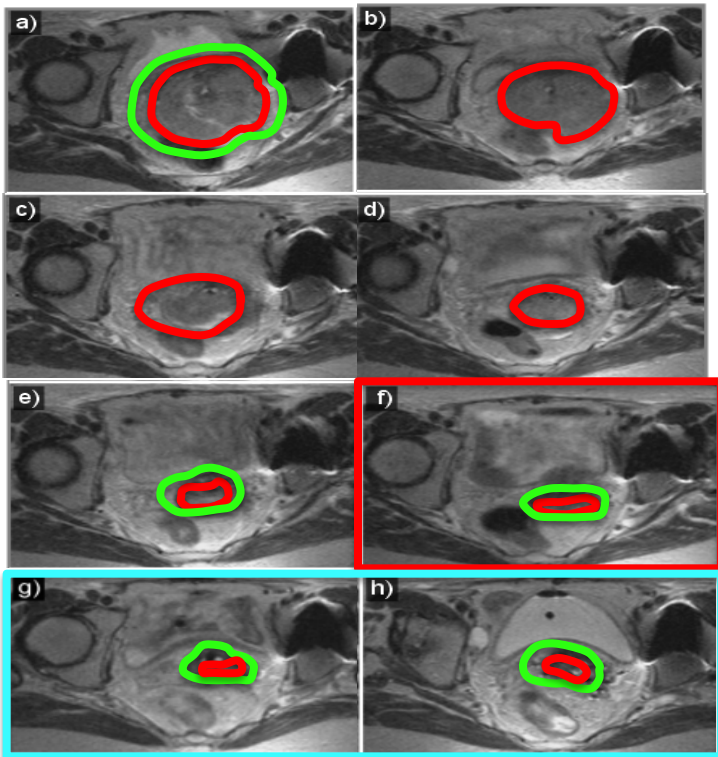
DVH-parameters CTV-T_{HR} (ICRU 89)

- **D90: Minimum dose within most exposed 90% of volume of interest**
- reliable and reproducible, but 10% „neglected“ (clin relevance)
- **D 98: Minimum dose within most exposed 98% of volume of interest**
- reliable and reproducible, 2% not included
- **[V100: Volume receiving 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**



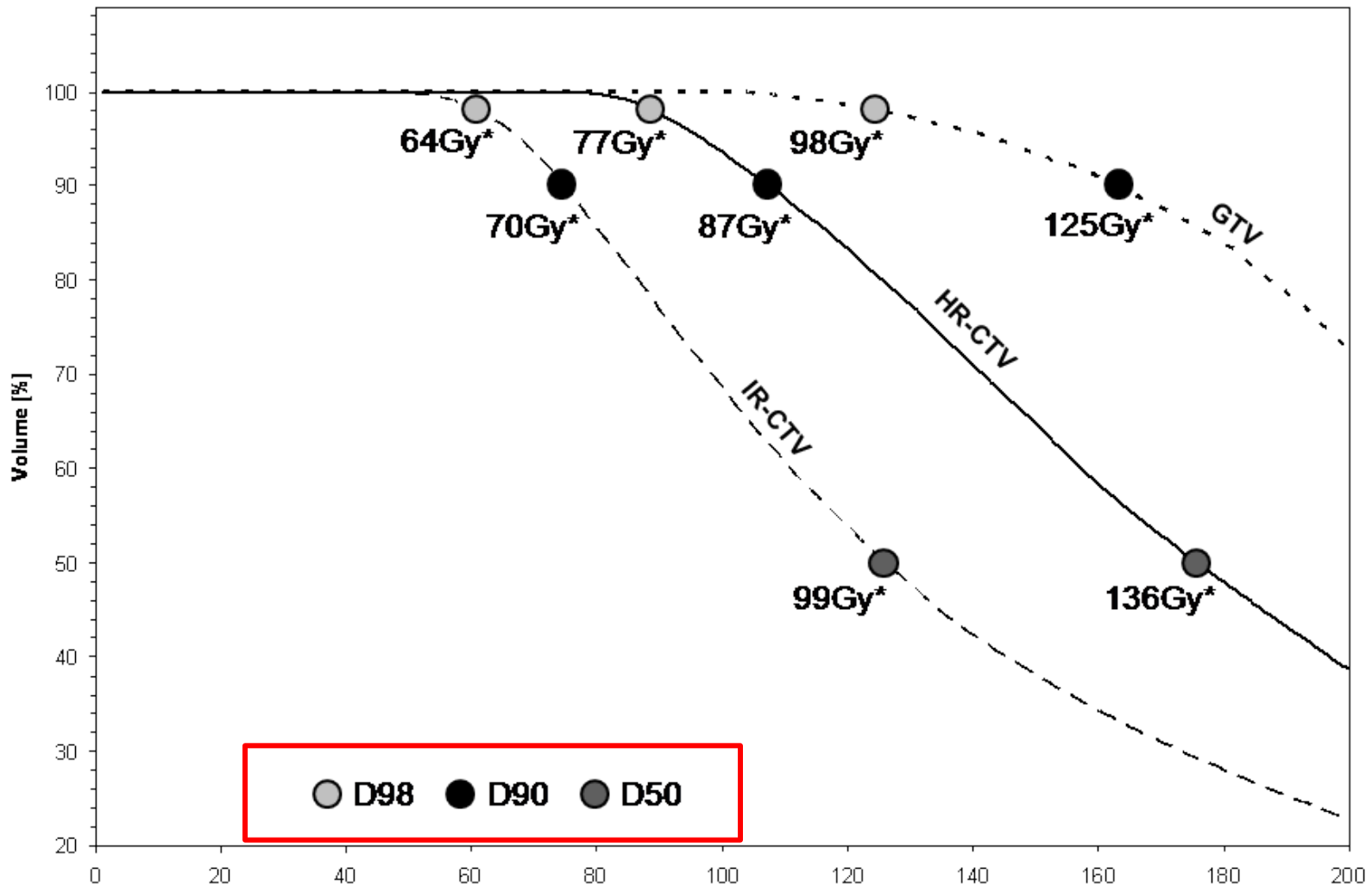
Dose and Volume Parameters (Vienna data 1998-2008)

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

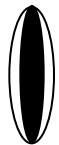
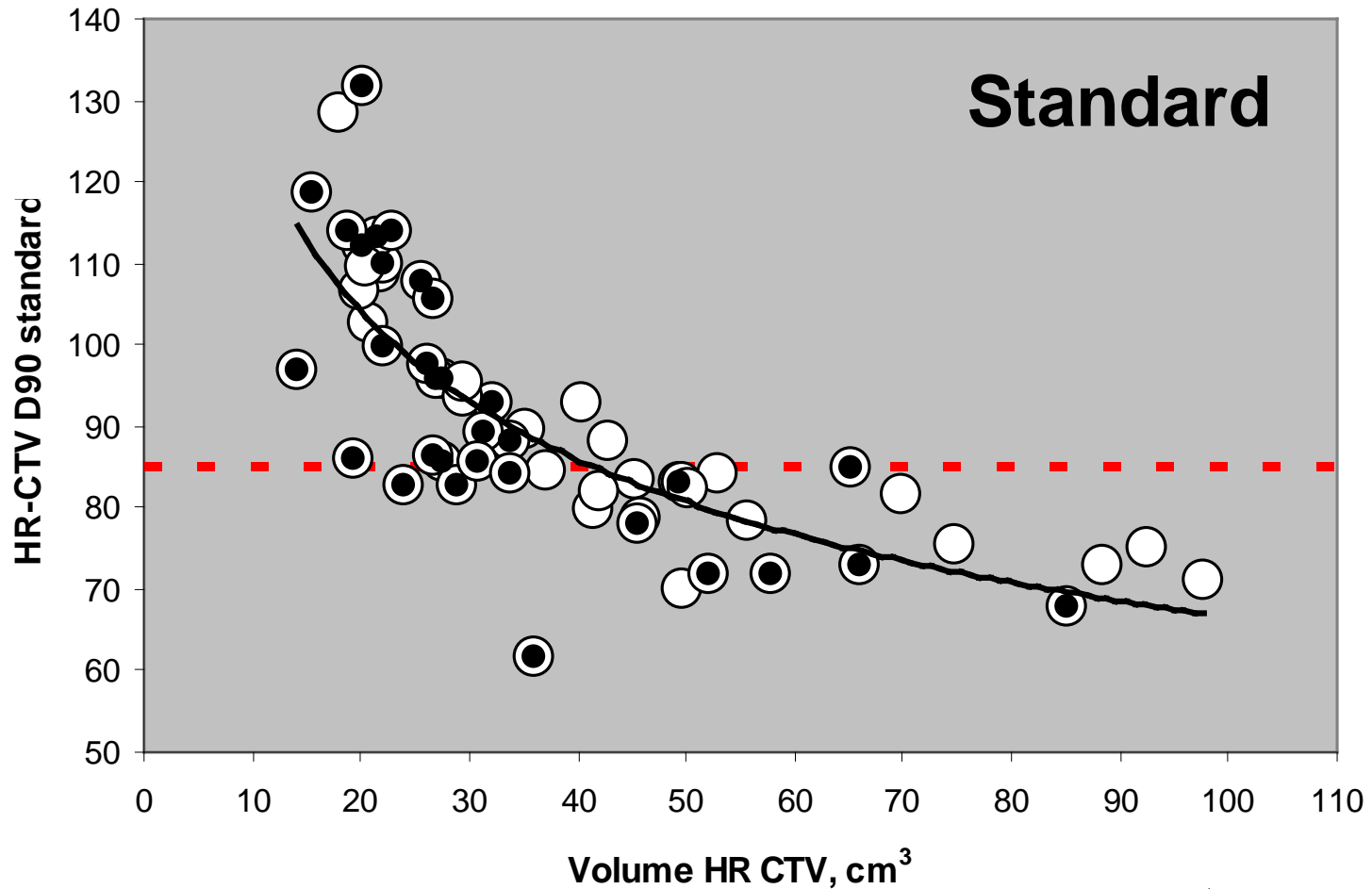
DVH parameters targets: GTV, CTV-HR, CTV-IR



Dose in D90 and HR CTV for point A prescription

High Target Doses in small tumours

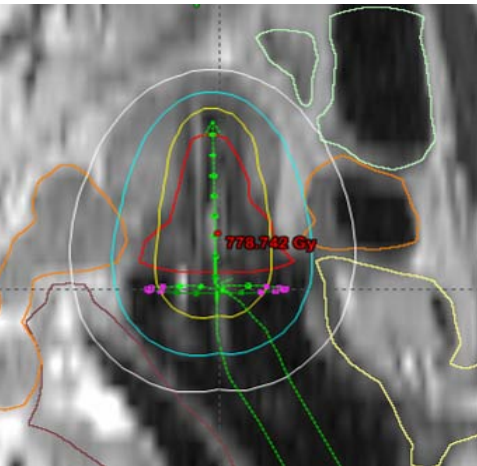
Low Target Doses in large tumours



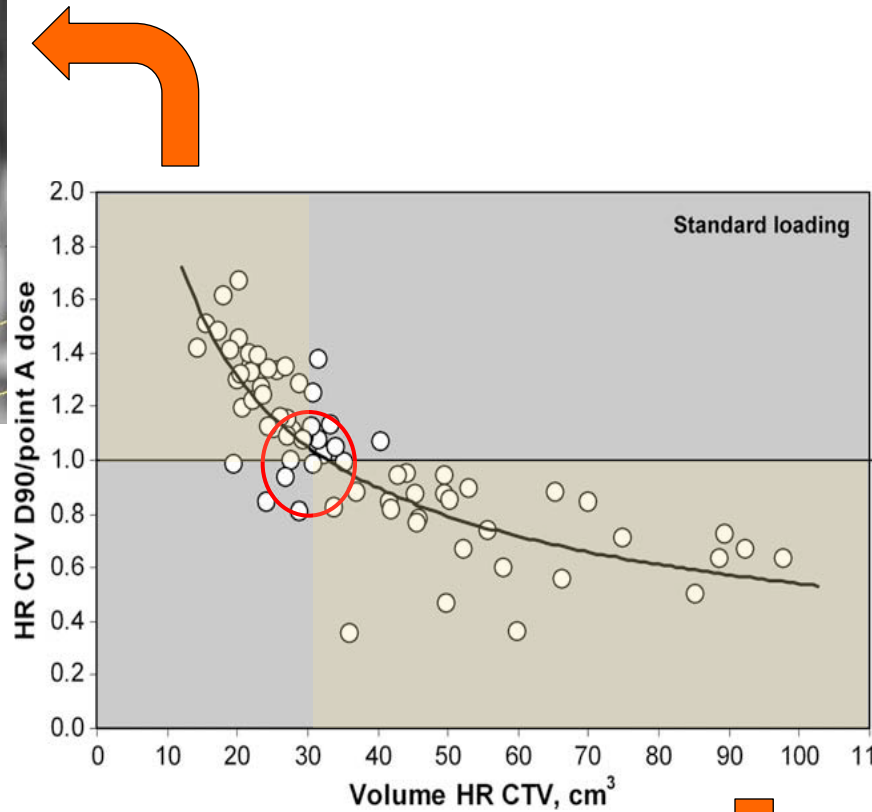
Violation of OAR constraint

Tanderup et al.

Consequences of prescribing to Point-A

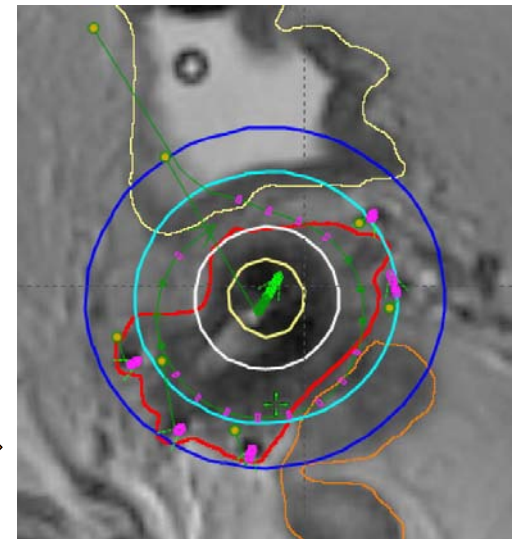


Overdosing
organs at
risk



Tanderup et al, Radiotherapy Oncol 2010

Underdosing
the tumour



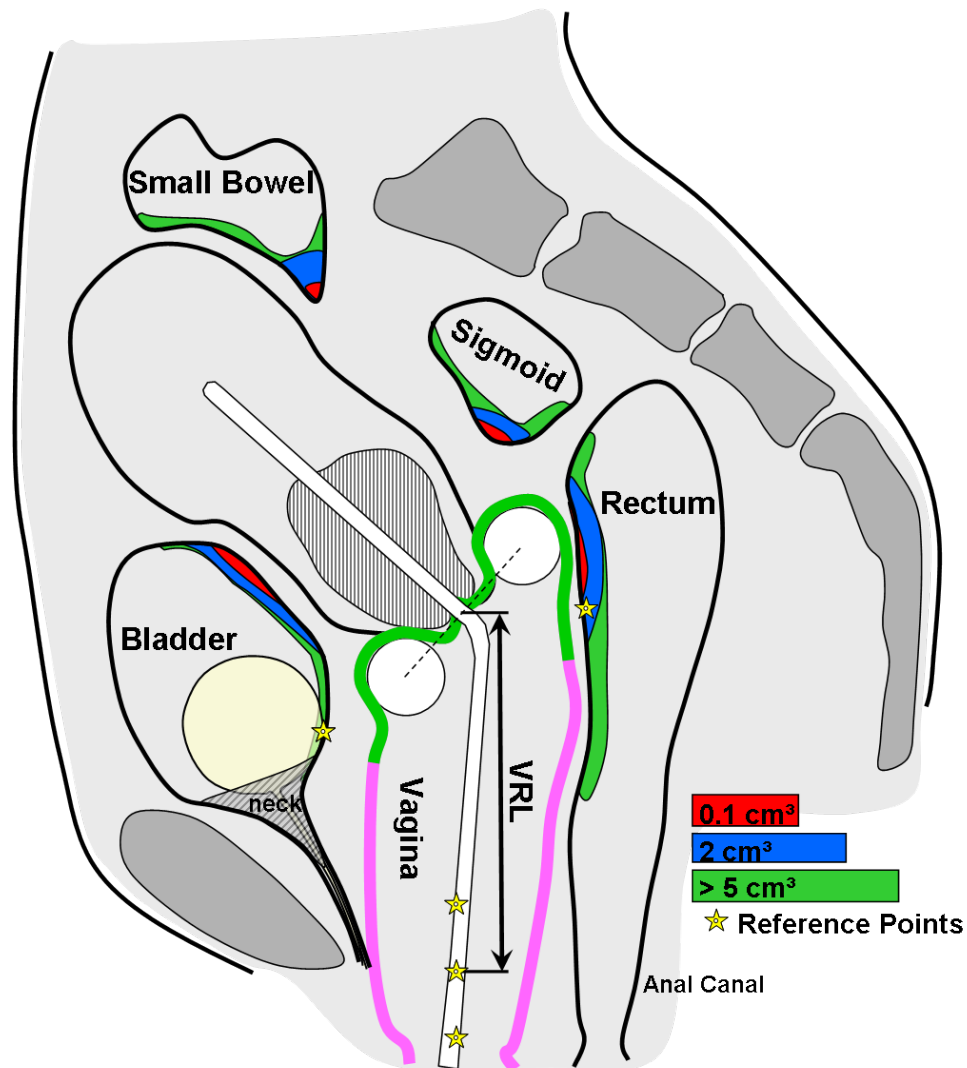
Level 2 - *Advanced standard for reporting*

All that is reported in level 1 plus (ICRU 89):

Dose reporting based on volumetric imaging for OARs:

- Bladder reference point dose
- $D_{0.1\text{cm}^3}$, $D_{2\text{cm}^3}$ for sigmoid
- $D_{2\text{cm}^3}$ bowel
- Intermediate and low dose parameters in bladder, rectum, sigmoid, bowel (e.g. $V_{15\text{Gy}}$, $V_{25\text{Gy}}$, $V_{35\text{Gy}}$, $V_{45\text{Gy}}$ 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 $\pm 2\text{cm}$)

DVH Parameters and Reference Points,

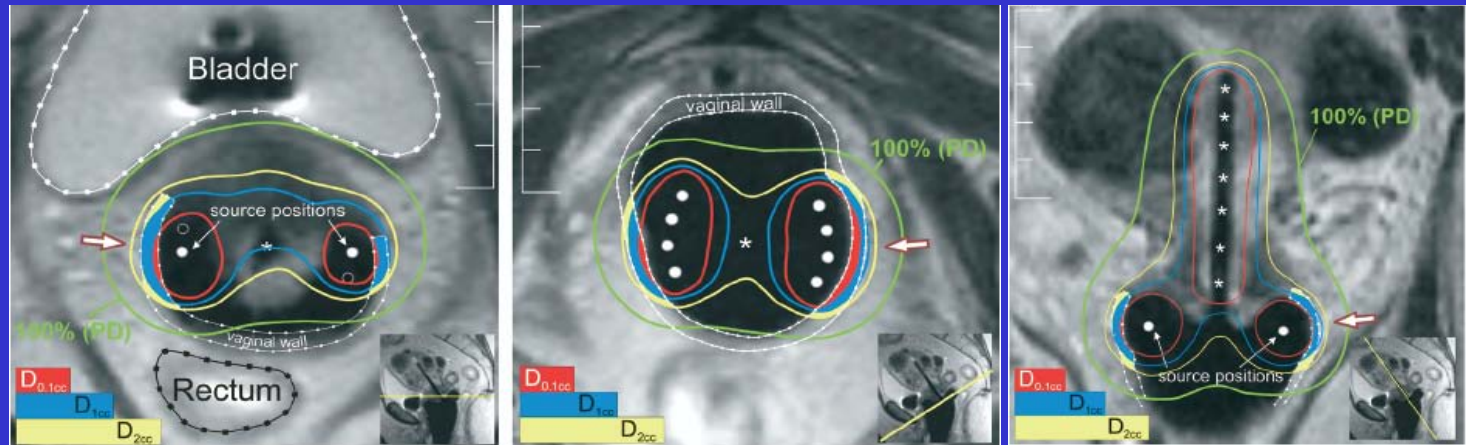


ICRU/GEC ESTRO
report 89
under publication
Fig. 6.4, Fig. 8.8

Vaginal dose assessment and reporting

UNCERTAINTIES IN ASSESMENT OF THE VAGINAL DOSE FOR INTRACAVITARY BRACHYTHERAPY OF CERVICAL CANCER USING A TANDEM-RING APPLICATOR

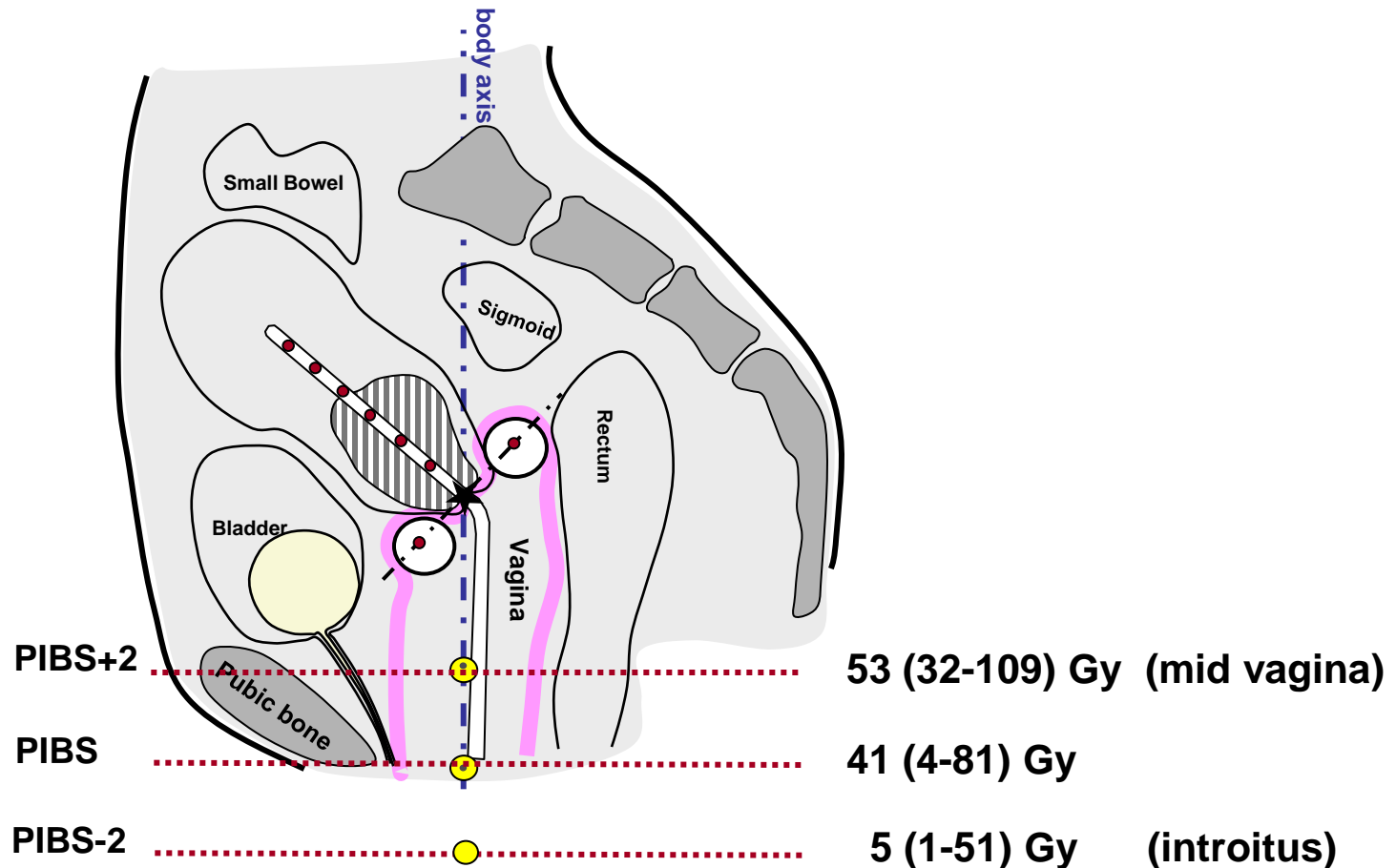
DANIEL BERGER, M.Sc., JOHANNES DIMOPOULOS, M.D., PETRA GEORG, M.D., DIETMAR GEORG, Ph.D.,
RICHARD PÖTTER, M.D., AND CHRISTIAN KIRISITS, Sc.D.



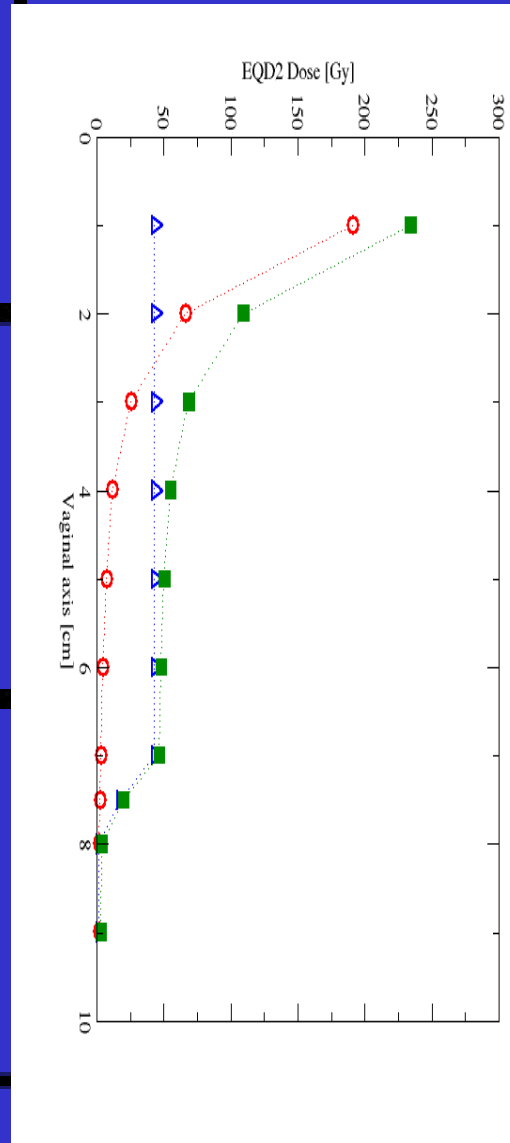
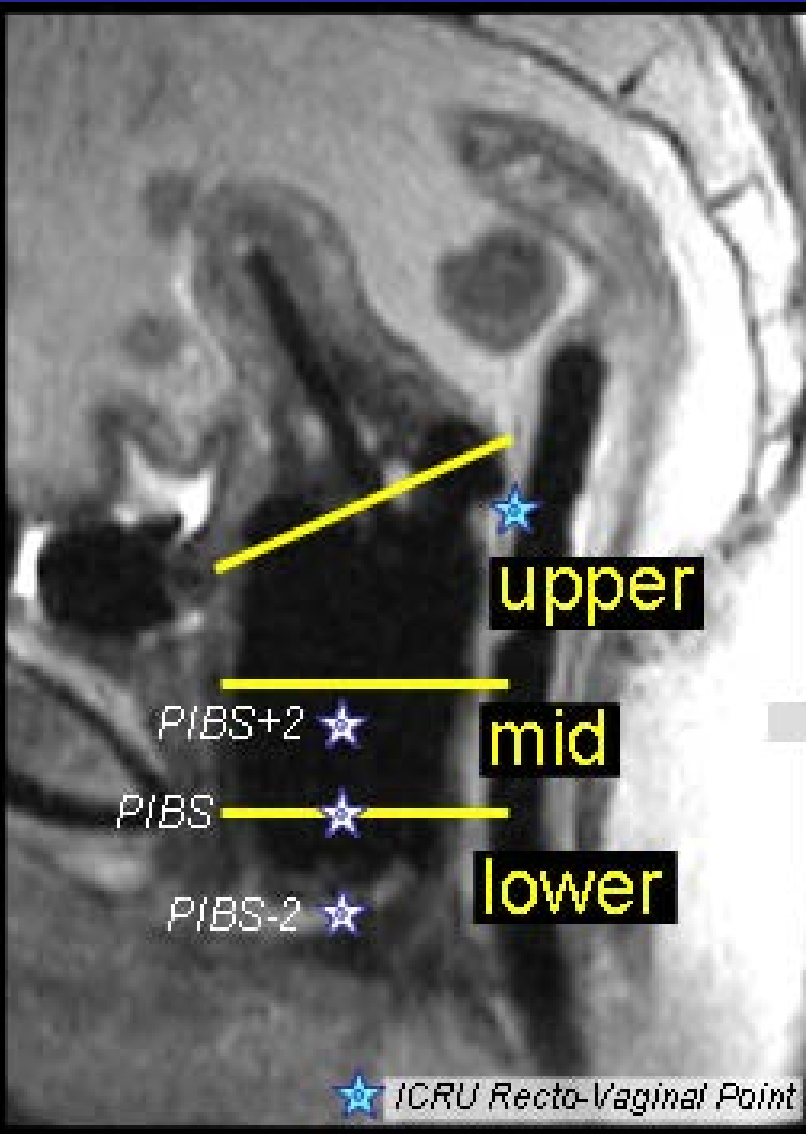
DVH parameters have HIGH uncertainty for representative vaginal dose estimation

They are influenced by the resolution of sectional imaging, contouring accuracy and applicator reconstruction

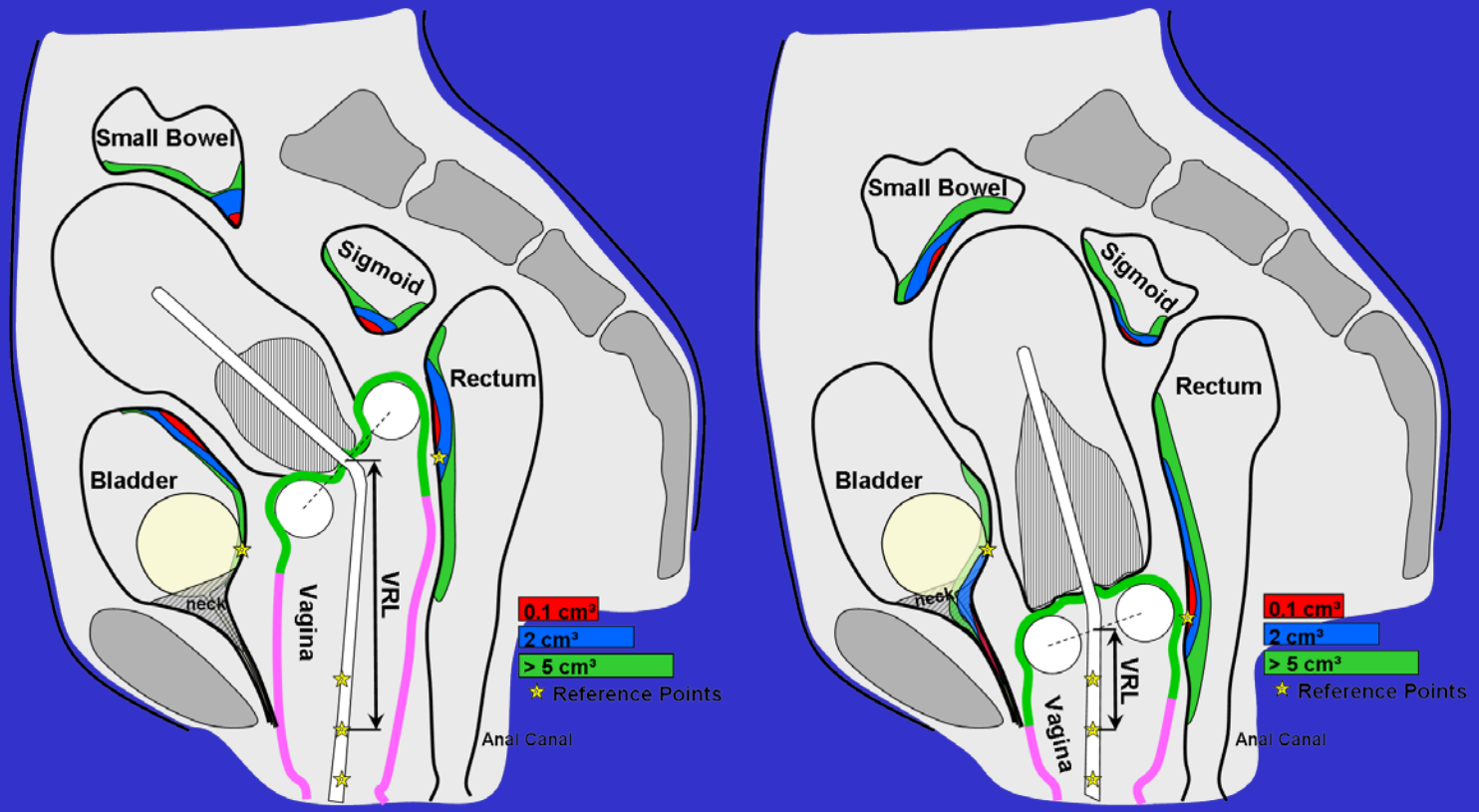
Vaginal reference points



Vaginal morbidity and radiation doses



DVH Parameters and Reference Points, Vaginal point: *variations in application*



ICRU/GEC ESTRO
report 89
Fig. 6.4, Fig. 8.8

$D_{2\text{cm}^3}$ and $D_{0.1\text{cm}^3}$ 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: $\alpha/\beta=3$ Gy for late effects in OAR and 10 Gy for tumour, and $T_{1/2}=1.5$ h

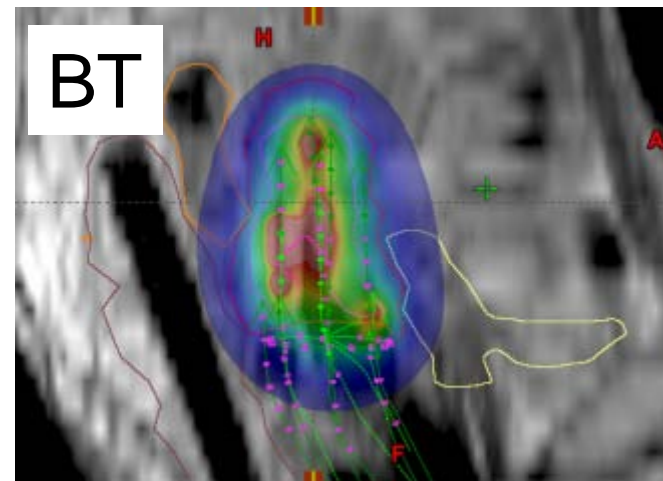
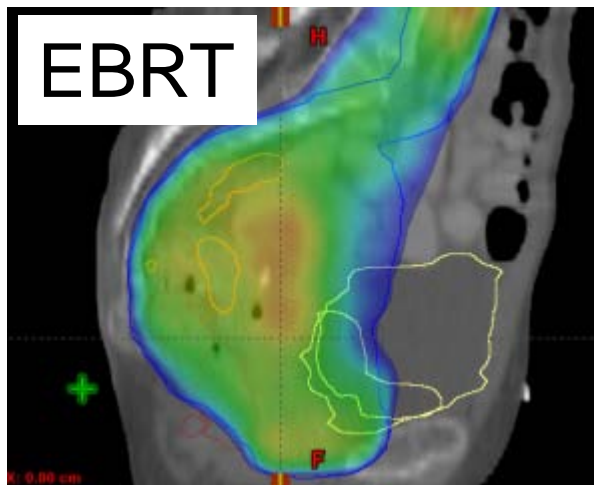
Pelvic EBRT (elective) + BT

- Elective target volume and CTV-T:
 - Normally homogeneous dose within 95%-107% of PD

Recommended assessment of total EQD2 dose:

Target (HR CTV-T): $D_{90_{EQD2}}(\text{total}) = PD_{EQD2}(\text{EBRT}) + D_{90_{EQD2}}(\text{BT})$

OAR: $D_{2\text{cm}^3, EQD2}(\text{total}) = PD_{EQD2}(\text{EBRT}) + D_{2\text{cm}^3, EQD2}(\text{BT})$



Calculation of EQD2 in spreadsheet

● EBRT+BT

● EQD₂ calculations

- Tumor: $\alpha/\beta = 10 \text{ Gy}$
- OAR: $\alpha/\beta = 3 \text{ Gy}$
- $T_{1/2} = 1.5 \text{ h}$

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
T _{1/2} (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
<i>Point-A</i>		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
<i>Clinical tumor size</i>		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
<i>GTV</i>		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%
<i>HR CTV</i>		Volume of HR CTV	cm ³	29,5	29,1	24,5	27,7	2,3
		D100 =MTD	Gy	9,4	9,6	9,3		
		D100 _{iso}	Gy	10,4	10,6	10,2	31,3	81,3
		D90	Gy	13,7	14,9	13,3		
		D90 _{iso}	Gy	16,7	18,7	16,2	51,7	101,7
		V100	%	99,9%	100,0%	100,0%	100,0%	0,1%

When adding doses from EBRT and BT You assume for the HR CTV for BT that

- A. 50% of the ICRU point dose of EBRT has been applied (or of median EBRT dose)
- B. 90% of the dose of the ICRU point dose of EBRT has been applied (or of median EBRT dose)
- C. 100% of the dose of the ICRU point dose of EBRT has been applied (or of median EBRT dose)

When adding doses from EBRT and BT You assume for the 2 cm³ for OAR that

- A. 50% of the EBRT ICRU point dose has been applied (or of median EBRT dose)
- B. 90% of the EBRT ICRU point dose has been applied (or of median EBRT dose)
- C. 100% of the EBRT ICRU point dose EBRT has been applied (or of median EBRT dose)

Limitations of adding doses according to „ICRU point-3D model“ both for CTV and OAR

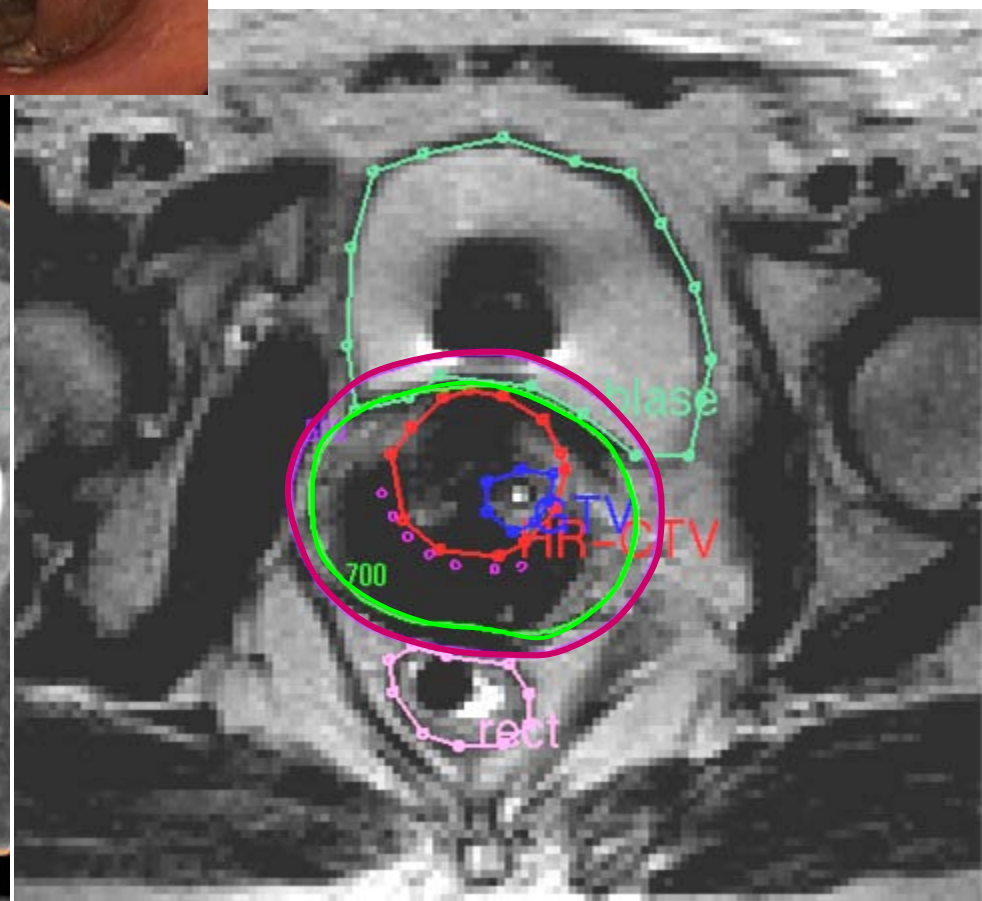
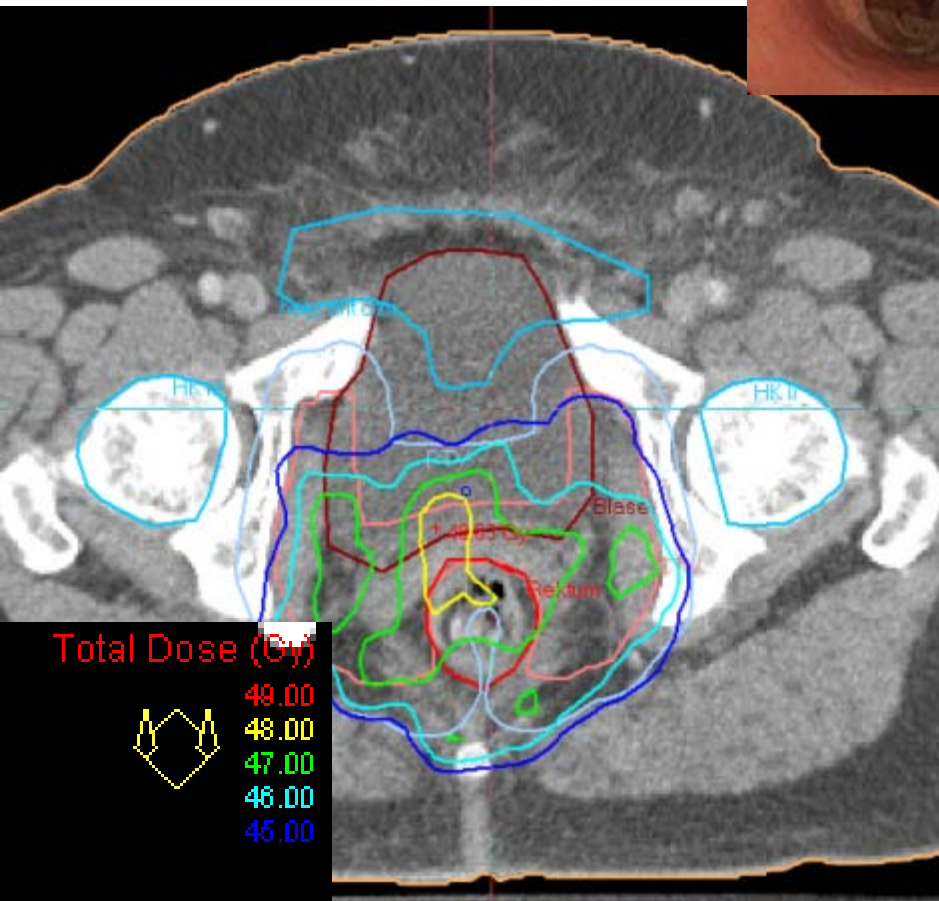
- **Non-homogenous dose distribution EBRT
e.g. IMRT, VMAT...**
- **Parametrial boost**
- **Lymph node boost**
- **Limitations of the linear-quadratic model**
- **Future solution for complex adding doses....**

How could this happen?

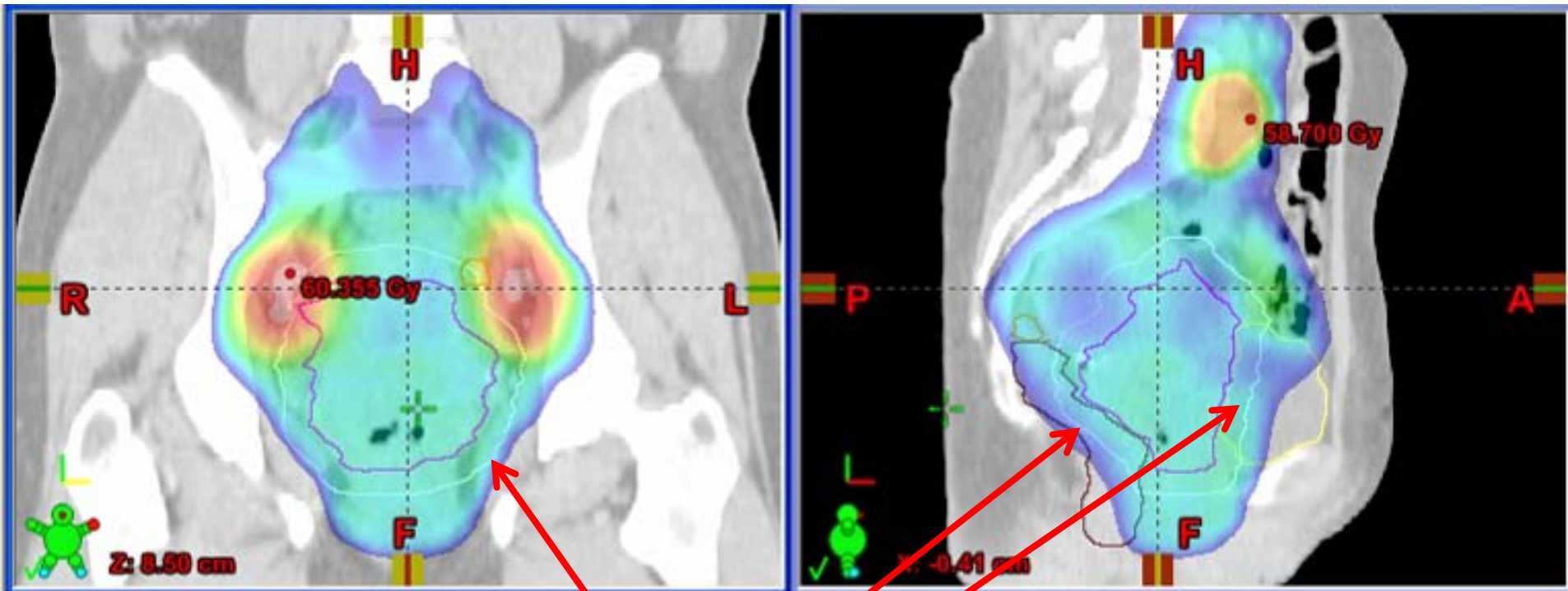
$D_{2cc} = 65.7 \text{ Gy EQD2}_{(\alpha/\beta=3)}$



$D_{2cc} = 79.2 \text{ Gy EQD2}_{(\alpha/\beta=3)}$

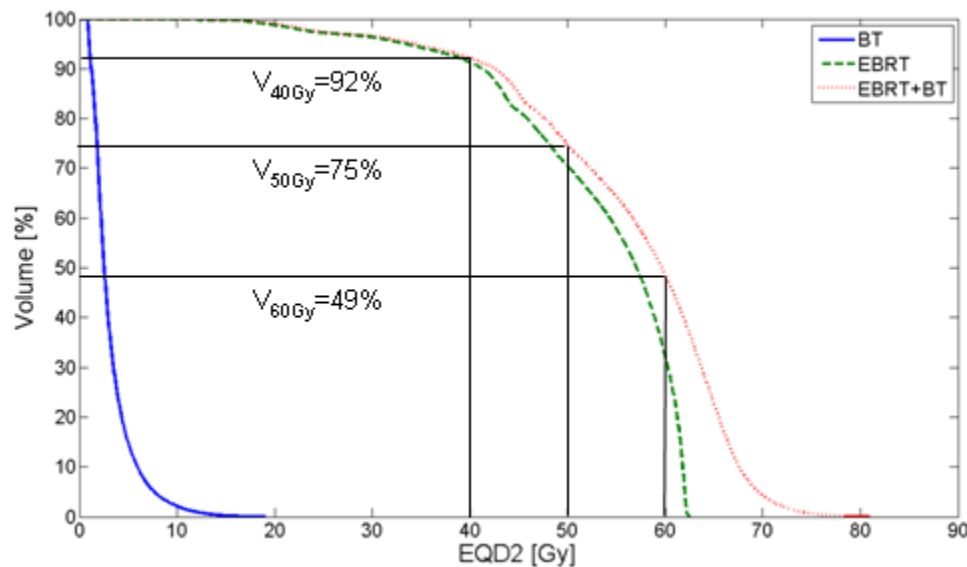
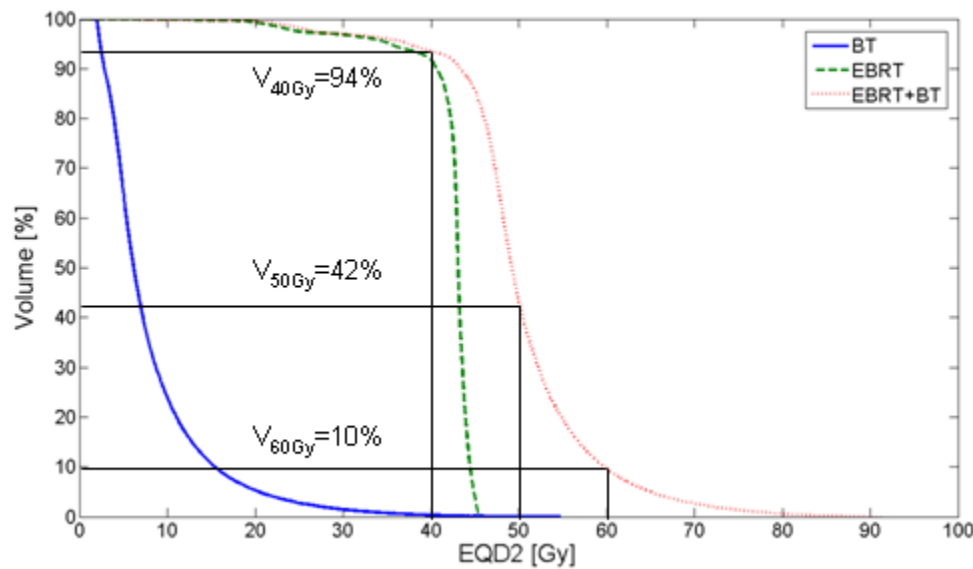


Be aware of IMRT hot spots in the BT region!



Homogenous volume for inverse dose planning

DVHs for different contributions of EBRT and BT *and* specific morbidity endpoints



**ICRU/GEC ESTRO
report 88
Fig. 8.8**

FROM PLANNING AIMS TO PRESCRIPTION

Traditional concepts:

“when prescribing to a target, the prescription dose is the planned dose to cover this target as completely as possible.”

or

prescription to a 100% isodose which is “to cover” the target volume”

Need for common terminology according to ICRU reports on proton treatment and IMRT

- **Planning aim dose**

- Set of dose and dose/volume constraints for a treatment

- **Prescribed dose**

- Finally accepted treatment plan (which is assumed to be delivered to an individual patient)

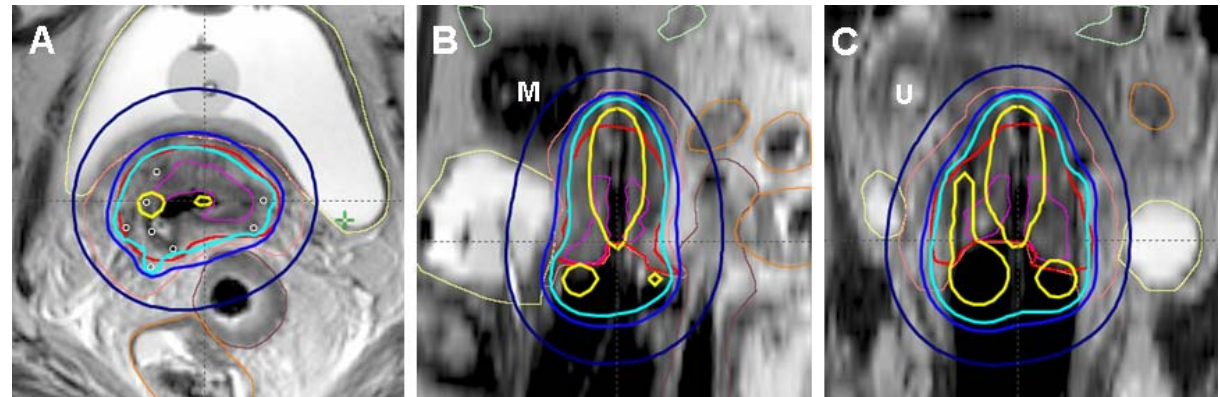
- **Delivered dose**

- Actually delivered dose to the individual patient

Planning aim and prescription dose

- Planning aim: what you want to obtain
- Prescribed dose: what you decide to treat

Case 6
Appendix,
ICRU 89

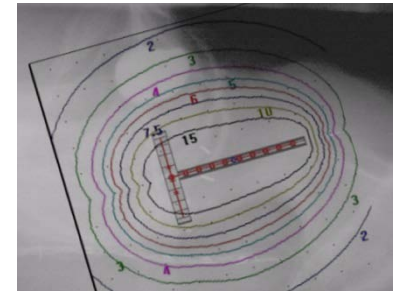


Structure	Dose-volume parameter	Planning aim, Gy	Prescribed dose Gy
CTV _{HR}	EQD2 ₁₀ D ₉₀	≥ 85	88.9
Bladder	EQD2 ₃ D _{2cm} ³	≤ 90	71.1
Rectum	EQD2 ₃ D _{2cm} ³	≤ 70	65.6
Sigmoid	EQD2 ₃ D _{2cm} ³	≤ 70	57.4
Bowel	EQD2 ₃ D _{2cm} ³	≤ 70	53.3

Planning aim and prescription dose

- **Planning aim: what you want to obtain**
- **Prescribed dose: what you decide to treat**

Example 2



Structure	Dose parameter	Planning aim, Gy	Prescribed dose Gy
Target	Point A	7Gy	6.5Gy
Bladder	ICRU point	$\leq 7\text{Gy}$	6.8 Gy
Rectum	ICRU point	$\leq 75\%$ of 7Gy	5.3 Gy

Example

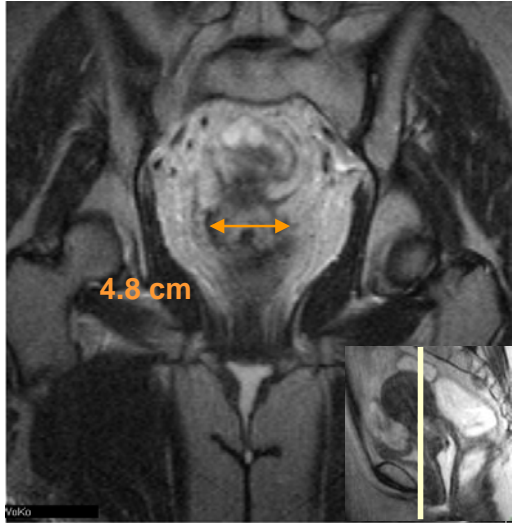
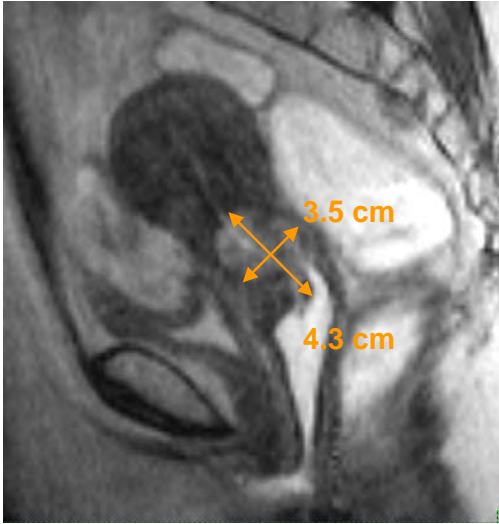
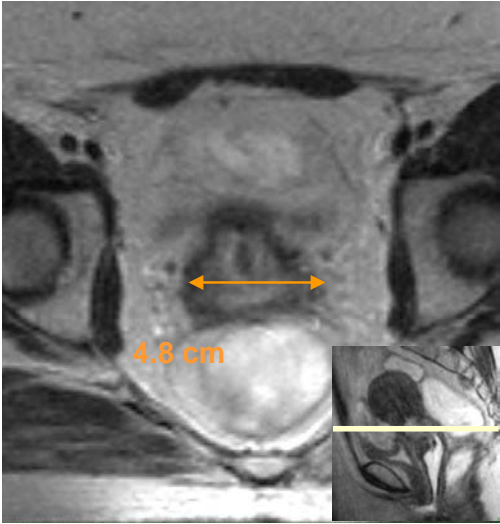
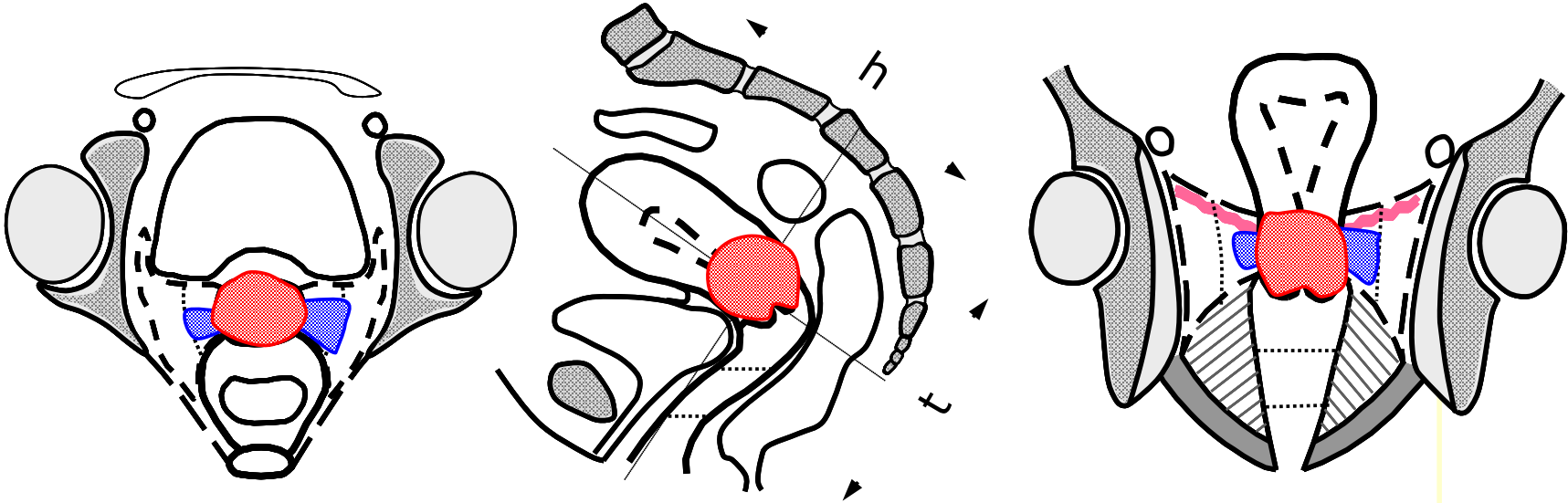
(Appendix case 5, ICRU 89)

Table A.5.3. Treatment planning aim and prescribed doses.

				Planning aim (Gy)	Prescribed dose (Gy)
CTV _{HR}	D_{90}	EQD2 ₁₀	≥ 85		92.3
Bladder	$D_{2\text{cm}^3}$	EQD2 ₃	≤ 90		80.6
Rectum	$D_{2\text{cm}^3}$	EQD2 ₃	≤ 70		64.3
Sigmoid	$D_{2\text{cm}^3}$	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 EQD2₁₀ isodose surface volumes

	1 st application	2 nd application
Nominal tandem length	60 mm	60 mm
Nominal ring diameter	30 mm	30 mm
Number of active needles	3	3
TRAK	2 x 4.3 mGy	2 x 4.2 mGy
<i>60 Gy volume</i>	<i>262 cm³</i>	<i>250 cm³</i>
<i>75 Gy volume</i>	<i>181 cm³</i>	<i>168 cm³</i>
<i>85 Gy volume</i>	<i>85 cm³</i>	<i>83 cm³</i>

Example (dose points)

(Appendix case 5, ICRU 89)

			1 st application		2 nd 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)

		1 st application		2 nd 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 _{0.1cm³}	7.2	7.2	7.2	7.2	102.0
	D _{2cm³}	5.6	5.6	5.4	5.4	80.6
Rectum	D _{0.1cm³}	4.8	4.8	5.0	5.0	74.2
	D _{2cm³}	3.8	3.8	3.9	3.9	64.3
Sigmoid	D _{0.1cm³}	1.9	1.9	4.4	4.4	59.9
	D _{2cm³}	1.5	1.5	2.6	2.6	51.7

Clinical evidence for dose-effects for disease and morbidity/QoL outcome: Dose prescription, dose constraints and planning aims in brachytherapy

ESTRO Teaching Course
Image-Guided Cervix Radiotherapy – with a special focus on adaptive brachytherapy

Toronto 2016

Kari Tanderup
Richard Pötter

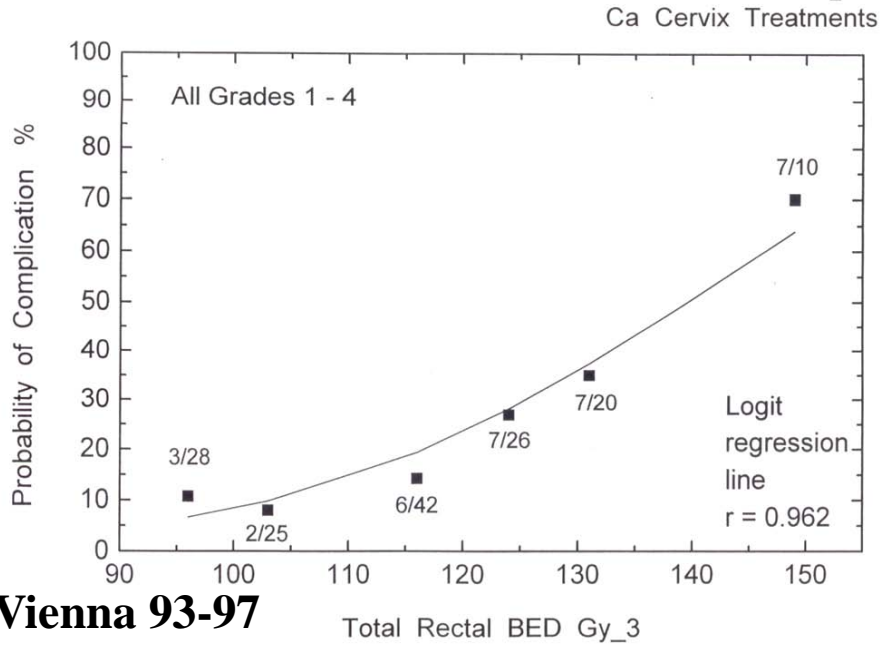


DOSE EFFECT RELATIONSHIP POINT A

	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%

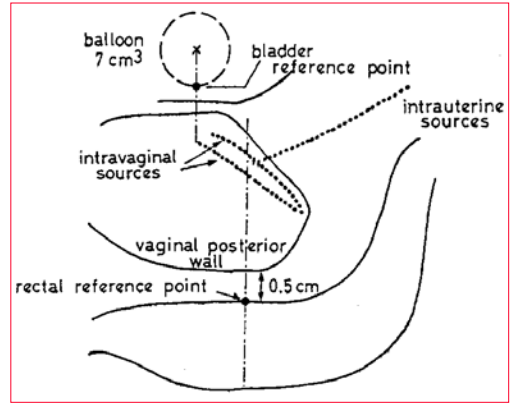
„Refinements in brachytherapy techniques are necessary to improve the present results“ (Perez et al IJROBP 1998)

Dose Effect relationship for late rectum side effects based on points (ICRU reference points)



Vienna 93-97

32 „events“ in 151 patients
Actuarial rate 3y: 24%



BED ~120-130 Gy₃ „cut-off level“ in recent experience

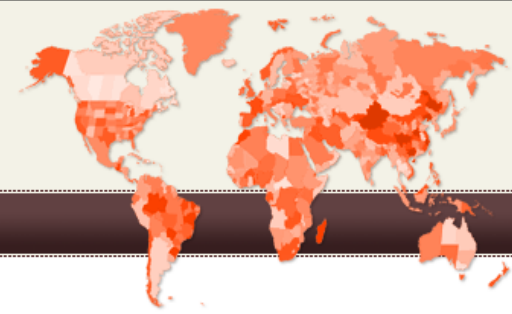
**Iso-effective dose in 2Gy/fr
~ 70-80 Gy_{αβ3,2Gyfr}**

**no clear dose effect relations
bladder, sigmoid, vagina**

Clinical Evidence in IGABT Cervix Cancer

Upcoming Evidence

- Mono-institutional cohorts (ongoing, publicat. since 2007)
- Multi-center cohorts with retrospective evaluation
 - RetroEMBRACE (publications in press)
- Prospective Trials
 - STIC: comparative 2D vs. 3D (published 2012)
 - EMBRACE I: observational, 08/2008 - 12/2015
 - EMBRACE II: interventional, from 03/2016

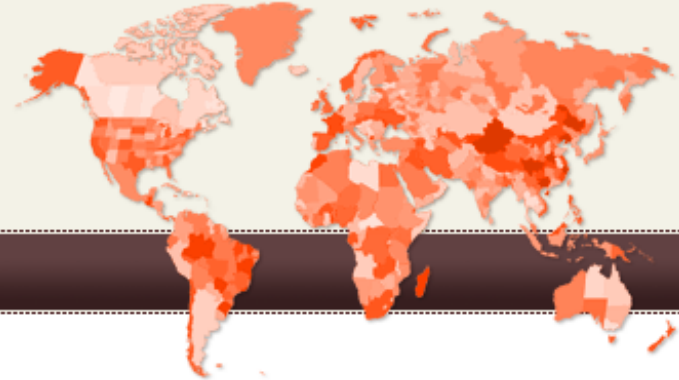


- **Web-based database with a retrospective multicentre collection of data on 3D RT plus IGABT in cervical cancer**
- **780 pts**
- **Eligibility criteria:**
 - **Diagnosis of cervical cancer and treatment with curative intent by IGABT**
 - **Reporting according to GEC ESTRO recommendations**



EMBRACE

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



[About Embrace](#)

[Contacts](#)

[Participation](#)

[Login](#)

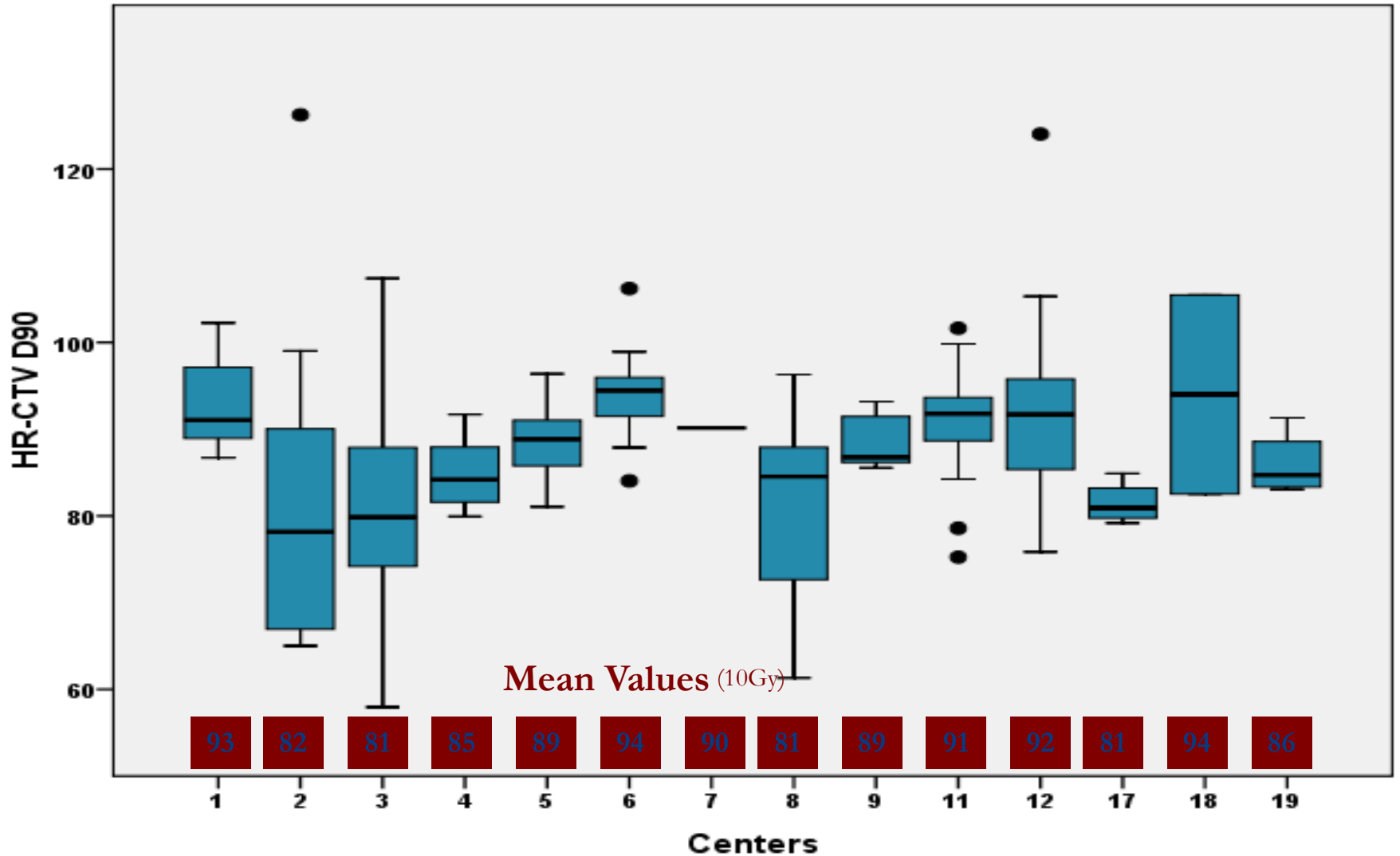
- **EMBRACE - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer**
- **A prospective observational multi-centre trial**
- **Initiated enrollment of patients in 2008, >1200 pts accrued**
- **Accrual to be finalised in 2015**

VARIAN
medical systems

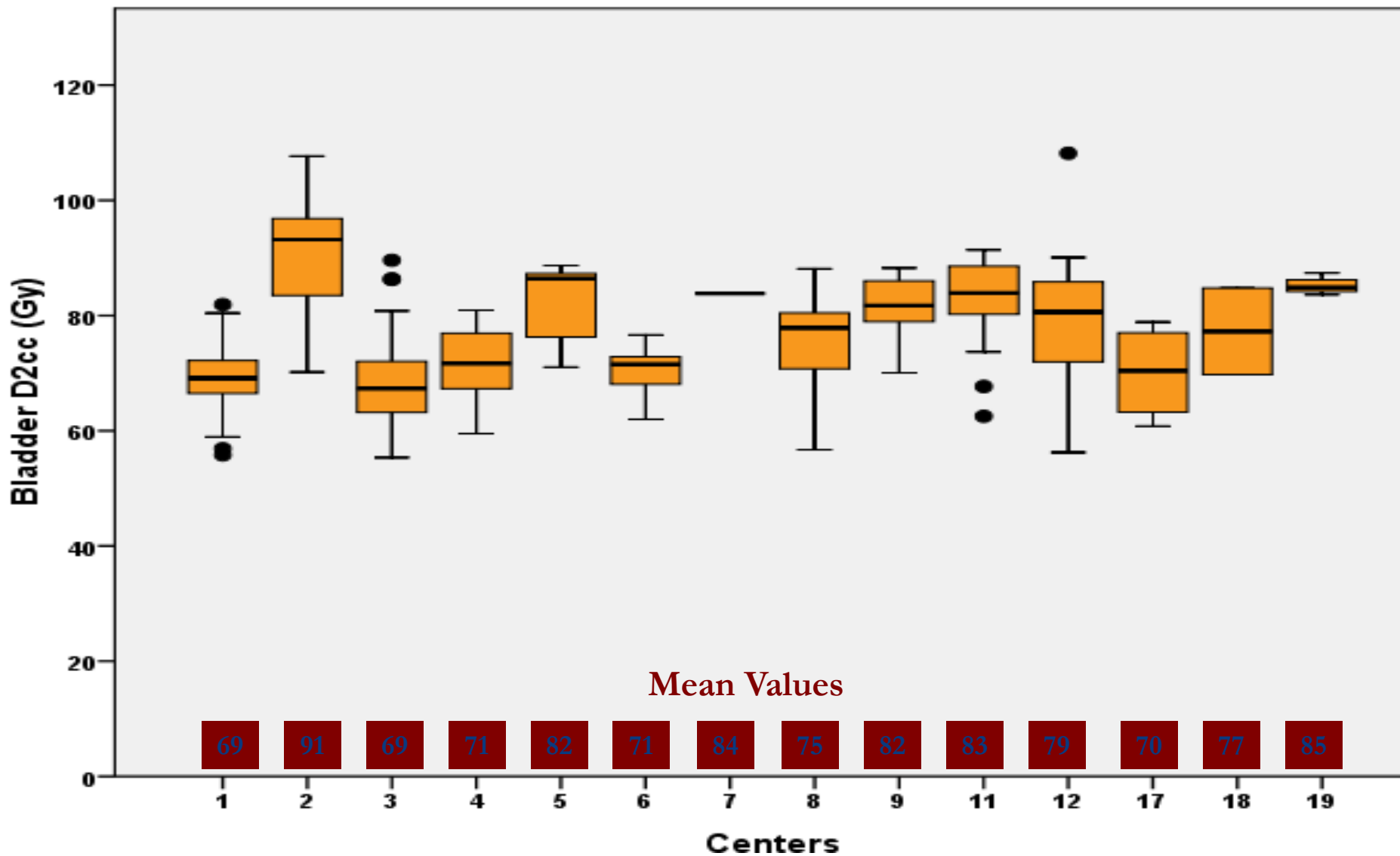
A partner for **life**

 **Nucletron**
Improving patient care

Heterogeneity of dose prescription: HRCTV D90

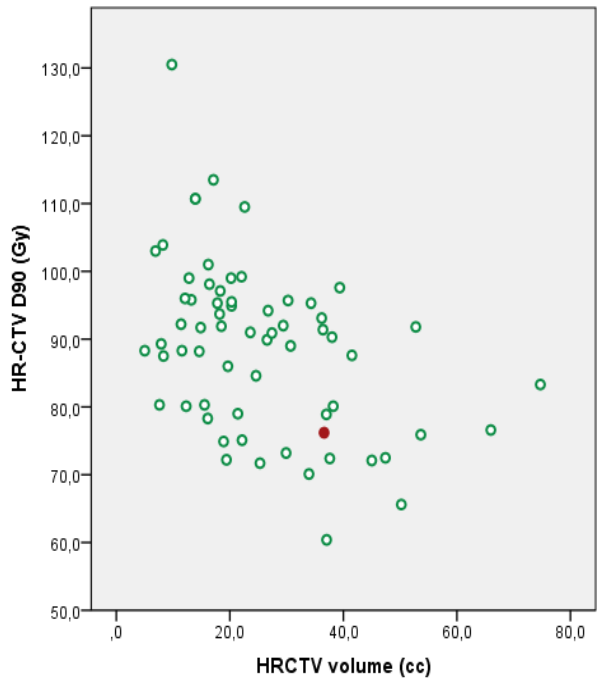


Heterogeneity of dose prescription: Bladder D2cc

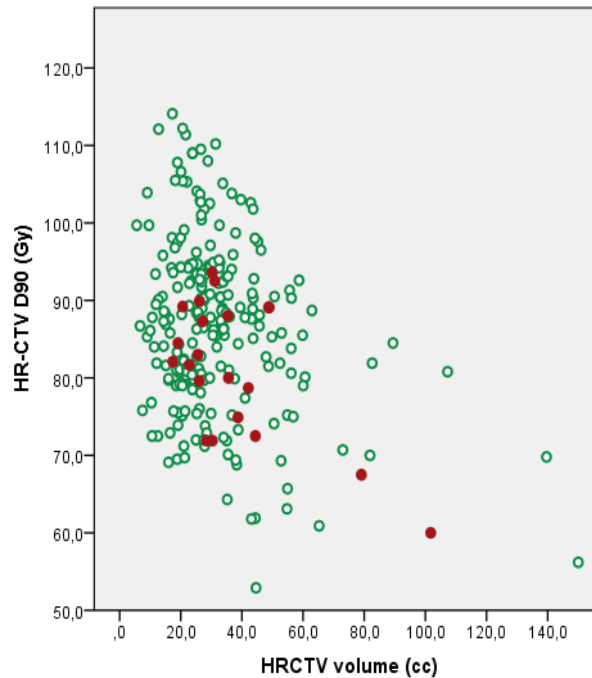


Recurrences according to dose and volume

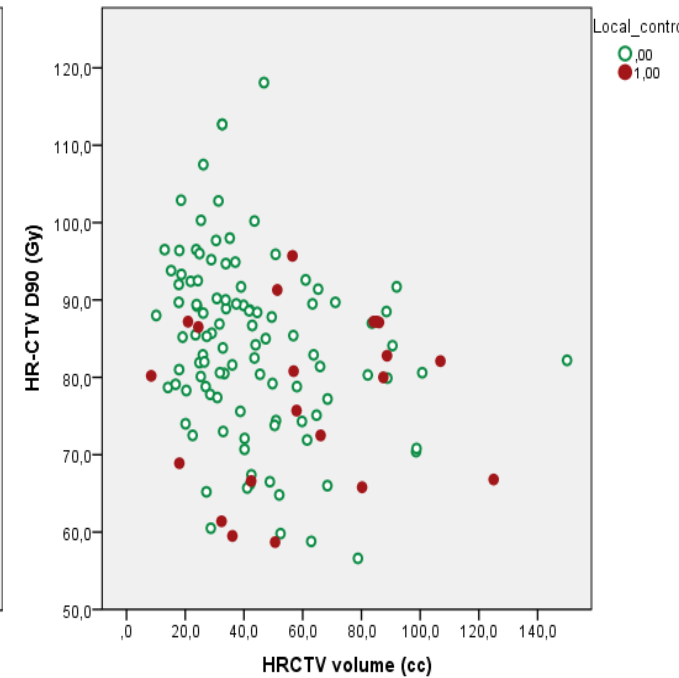
Stage I



Stage II

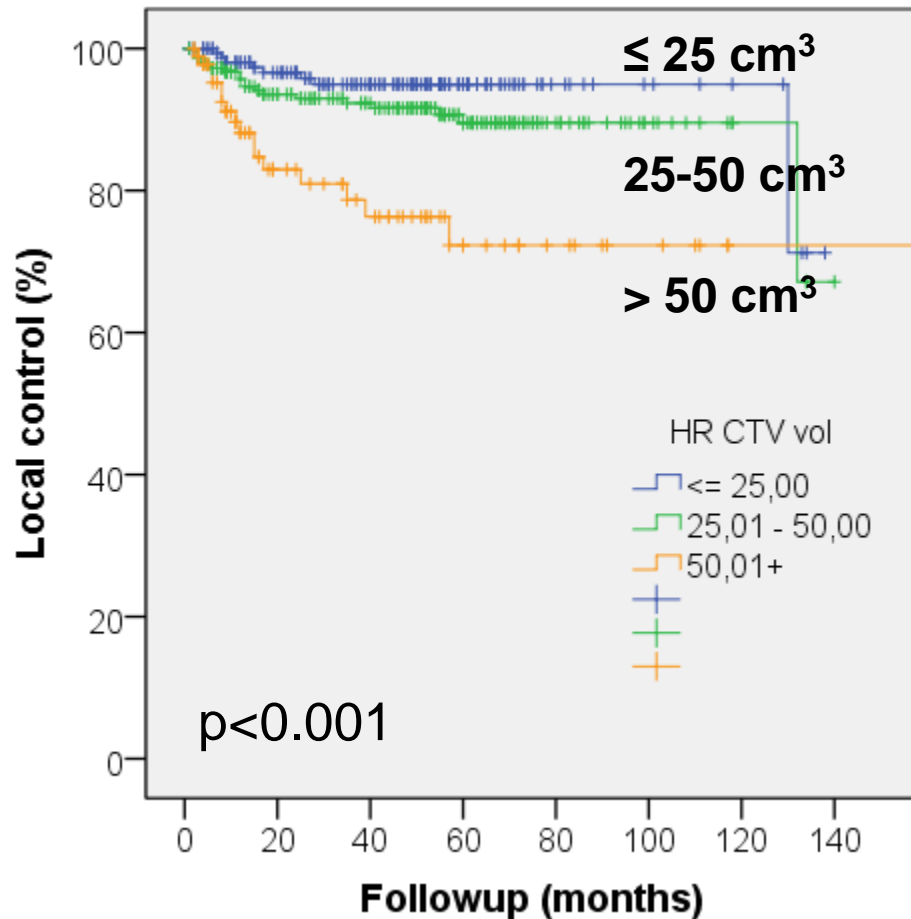


Stage III+IV

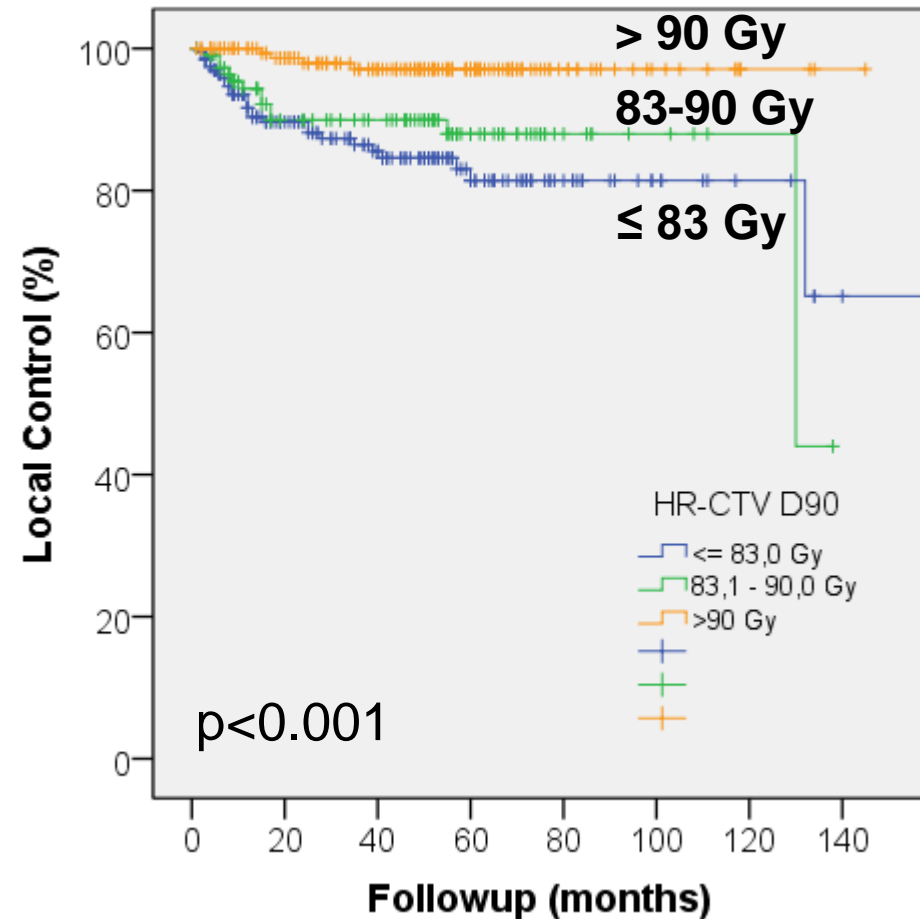


Actuarial local control HR CTV dose and volume

CTV_{HR} volume



CTV_{HR} dose



Dose, volume, and time effect

Effect of dose, volume and time:

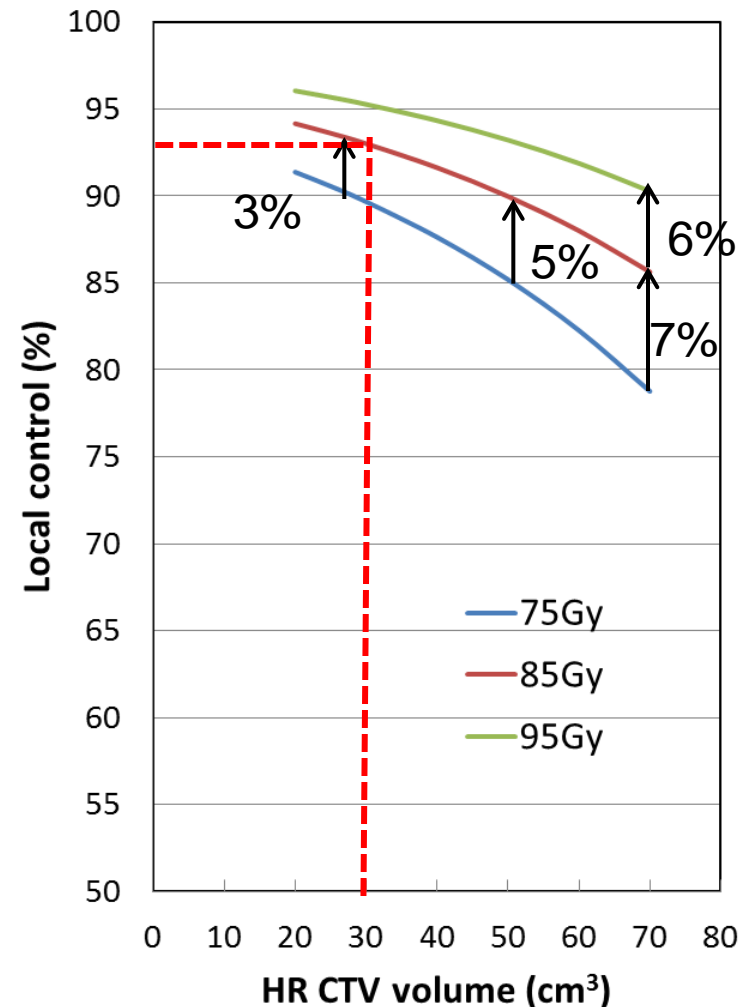
Dose: 10Gy → 5% LC

Time: 7 days ~ 5Gy

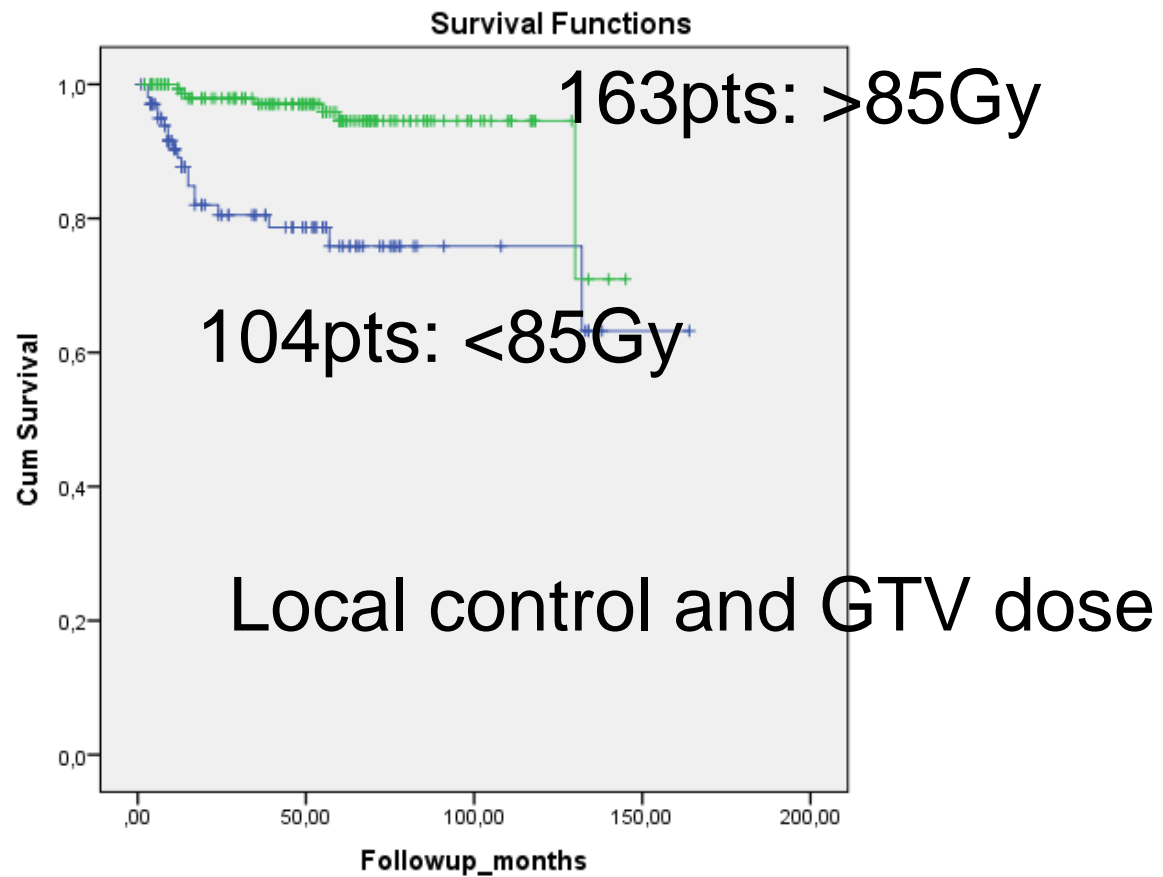
Volume 10cm³ ~ 5Gy

85Gy for 30cm³ CTV_{HR}: 93% LC

Local control at 3 years

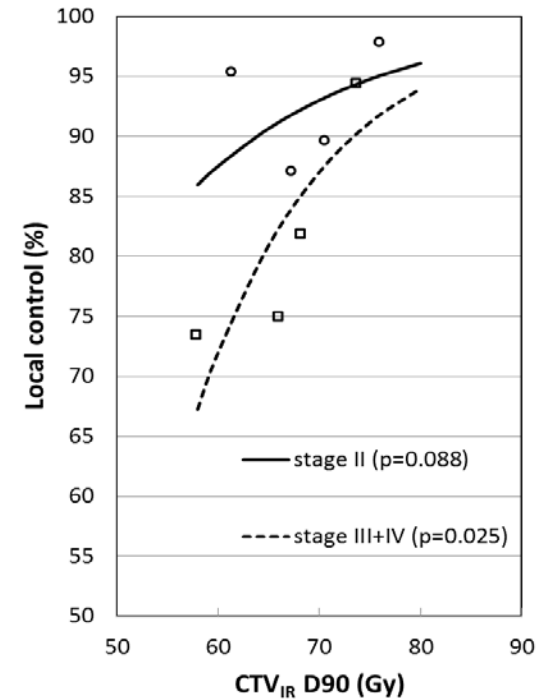
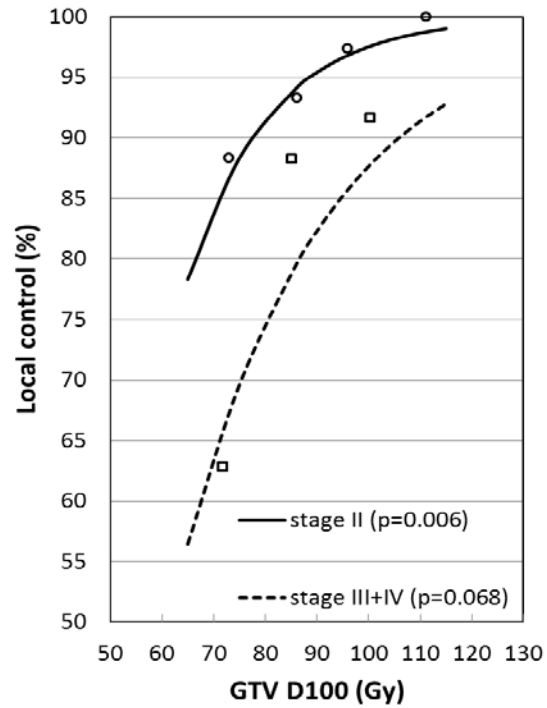
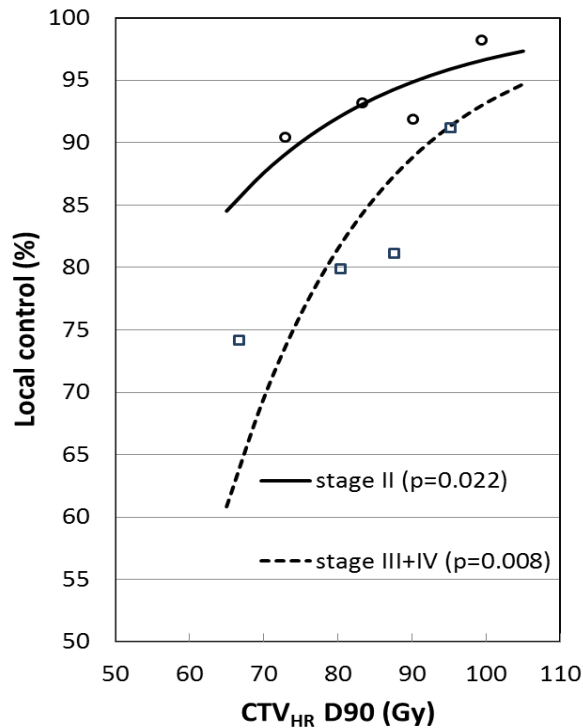


Dose volume response for GTV

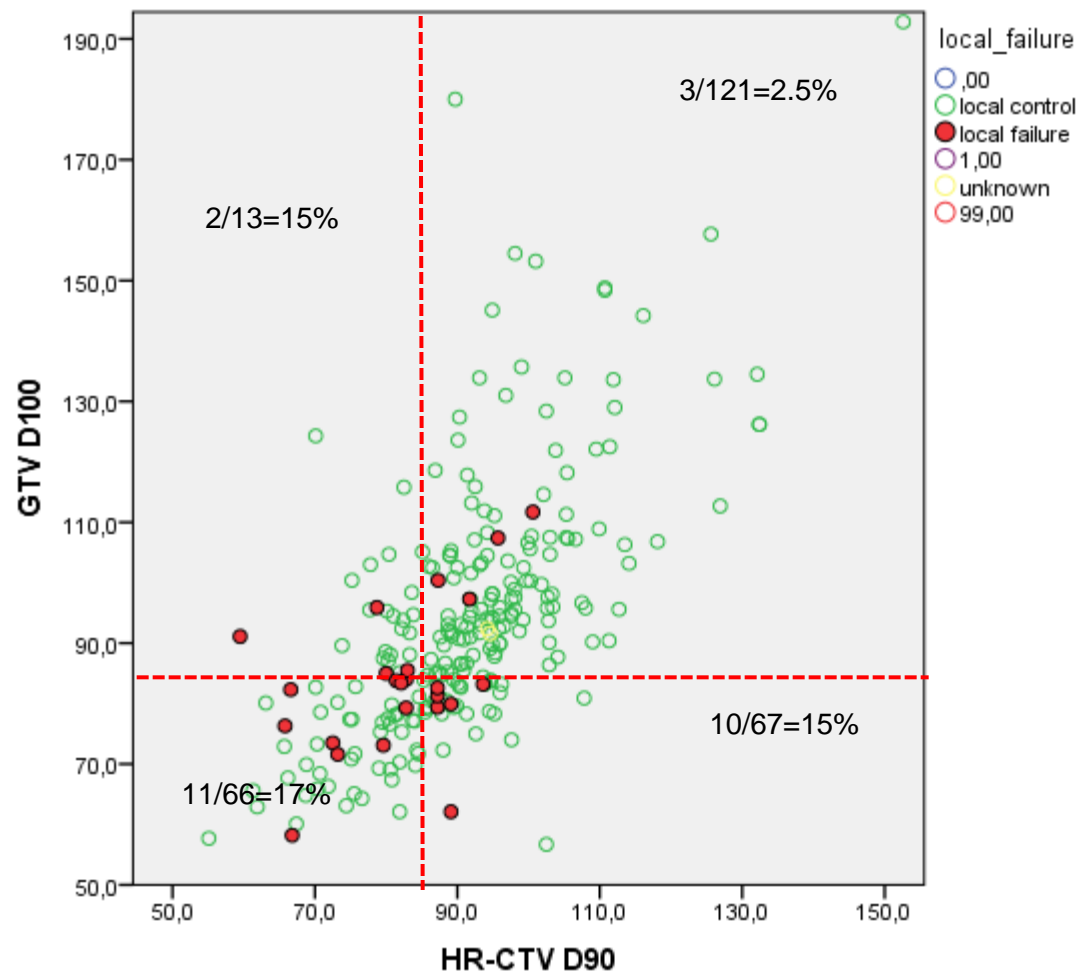


Dose effect GTV, CTV_{HR} and CTV_{IR}

Stage-wise analysis

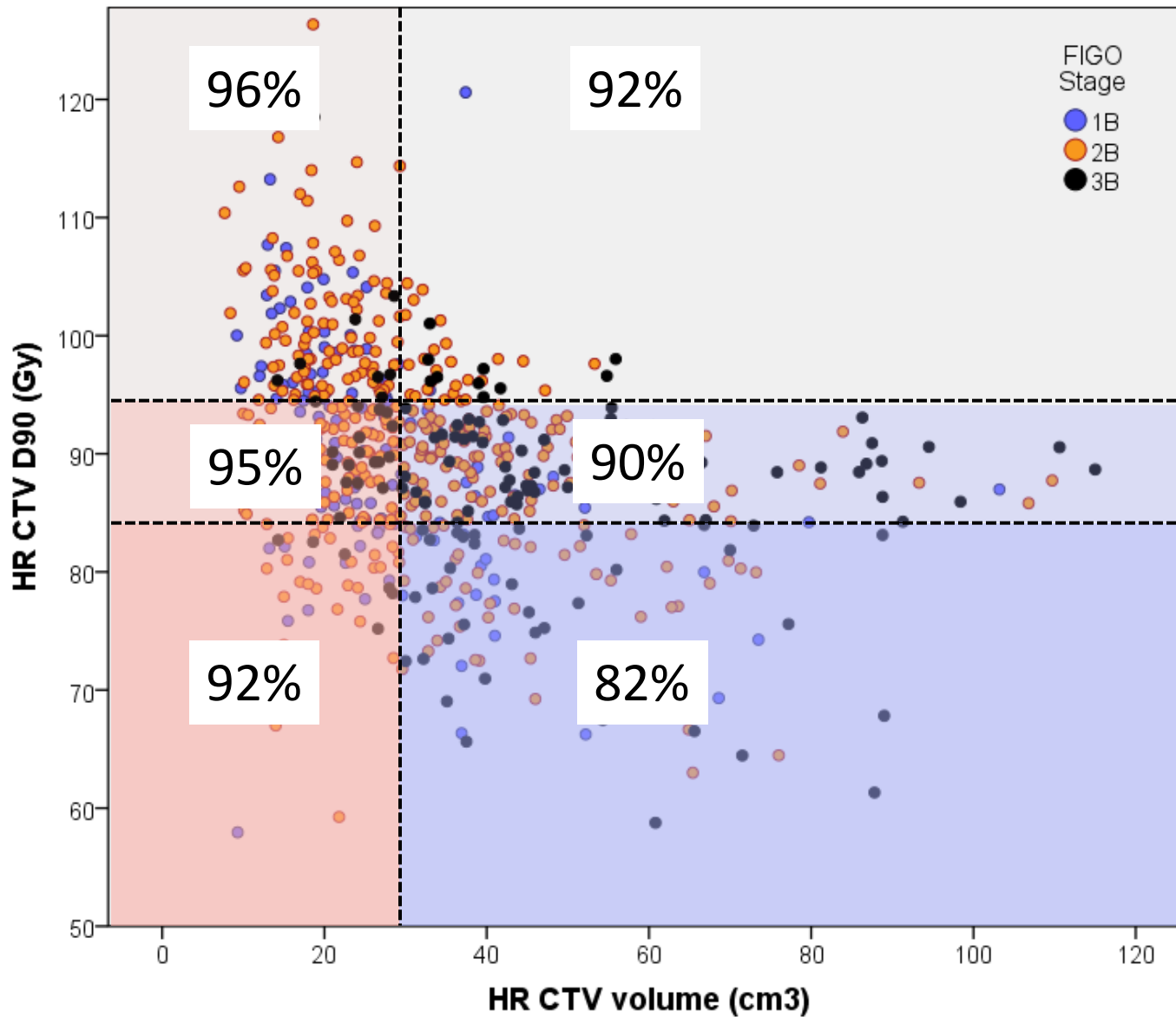


Combined constraints for GTV and CTV_{HR}

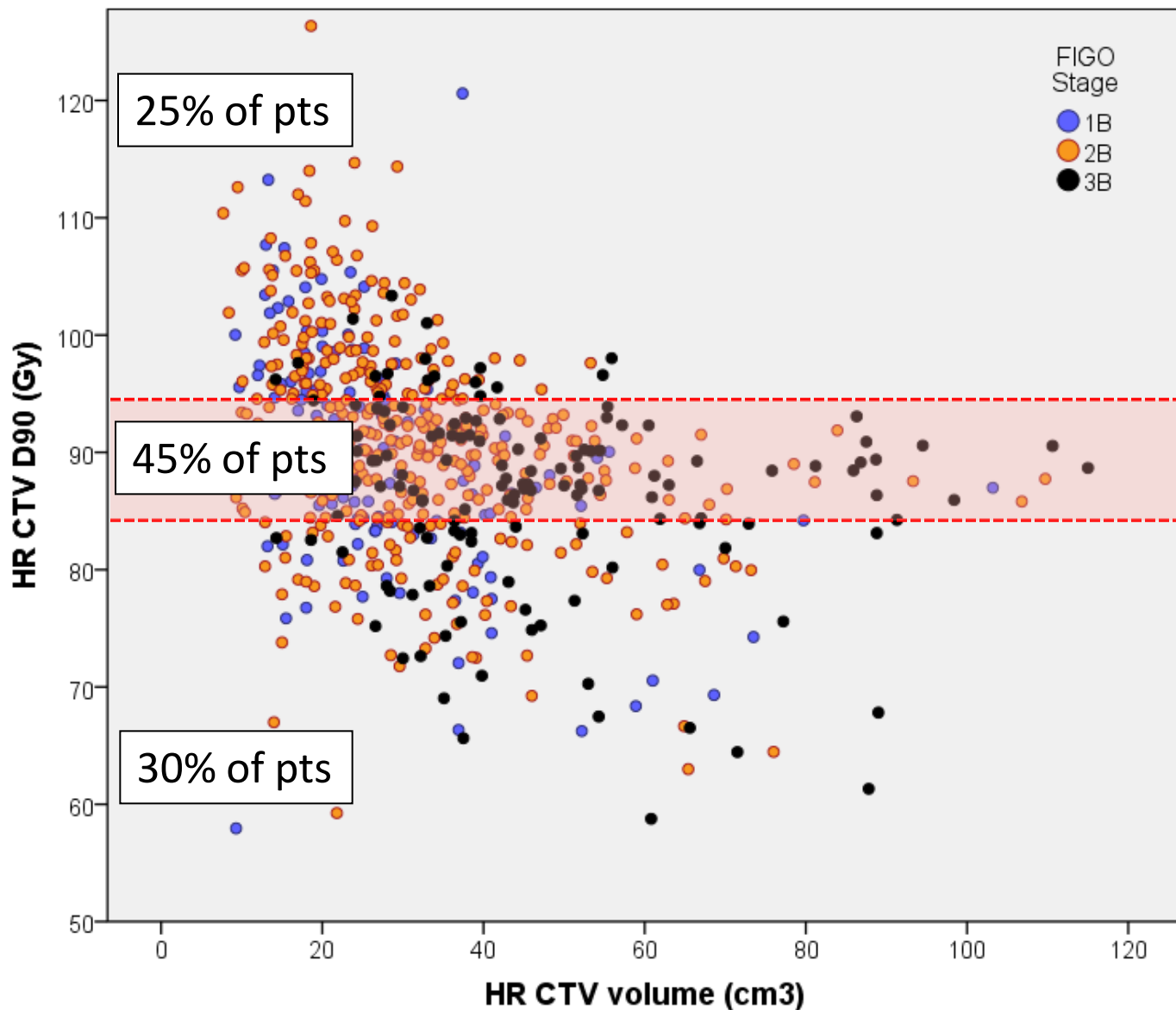


Practice in EMBRACE I

769 pts EMBRACE



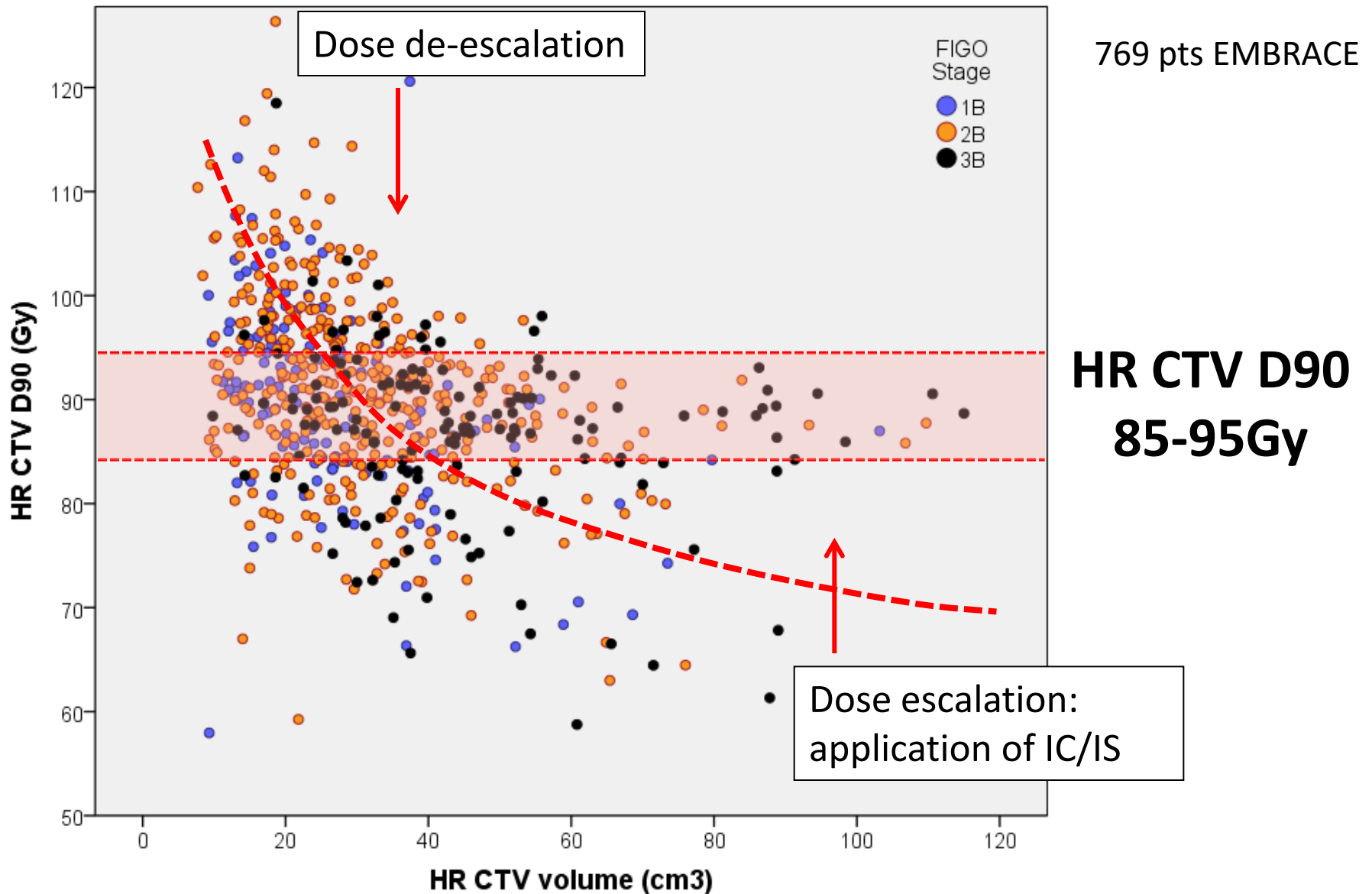
EMBRACE practice



769 pts EMBRACE

**HR CTV D90
85-95Gy**

EMBRACE II dose prescription



Beach boy approach – Barcelona 2013

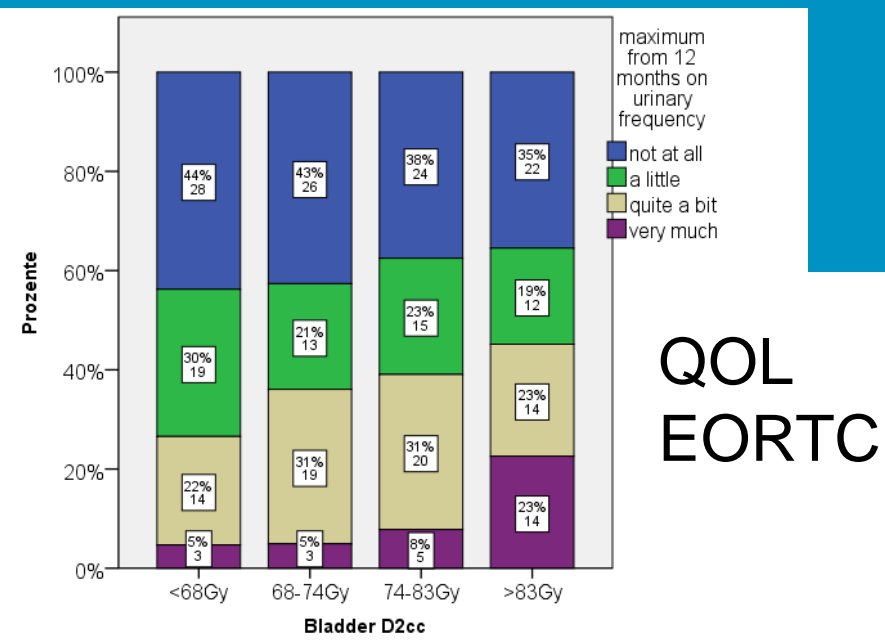


Dose de-escalation

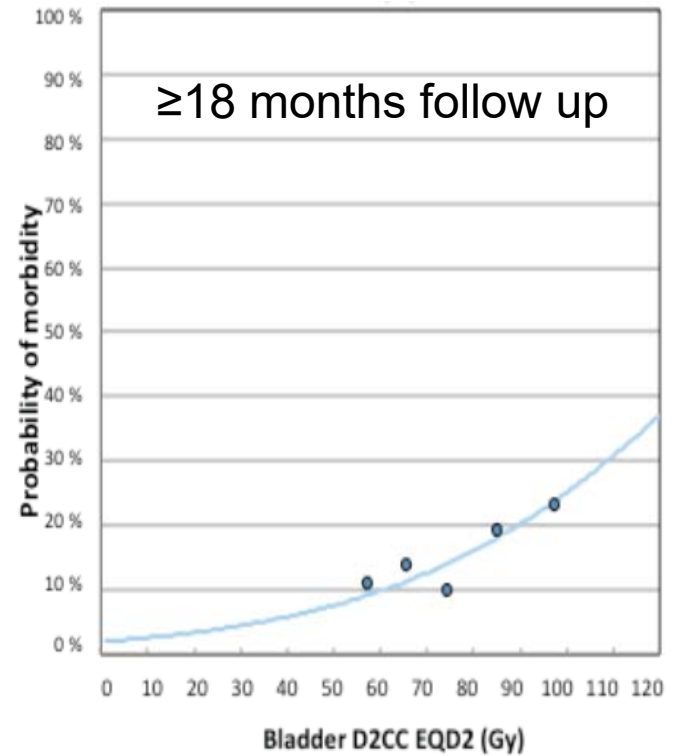
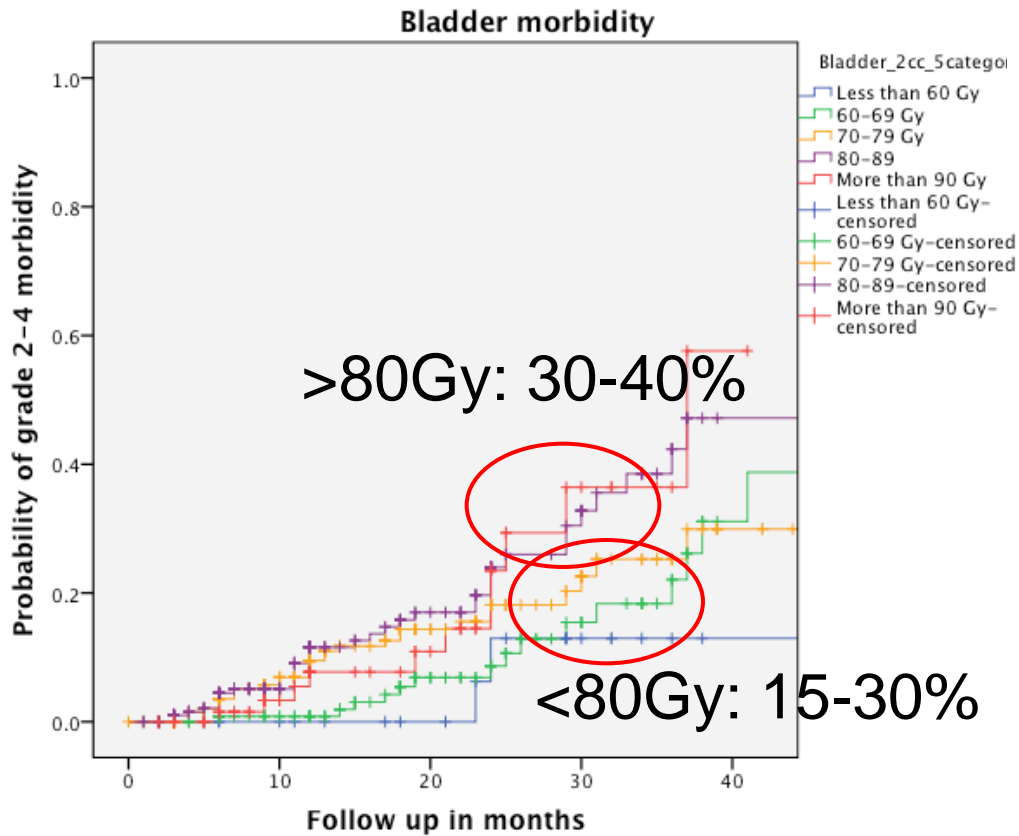
Dose escalation:
application of IC/IS

Bladder D_{2cm3}

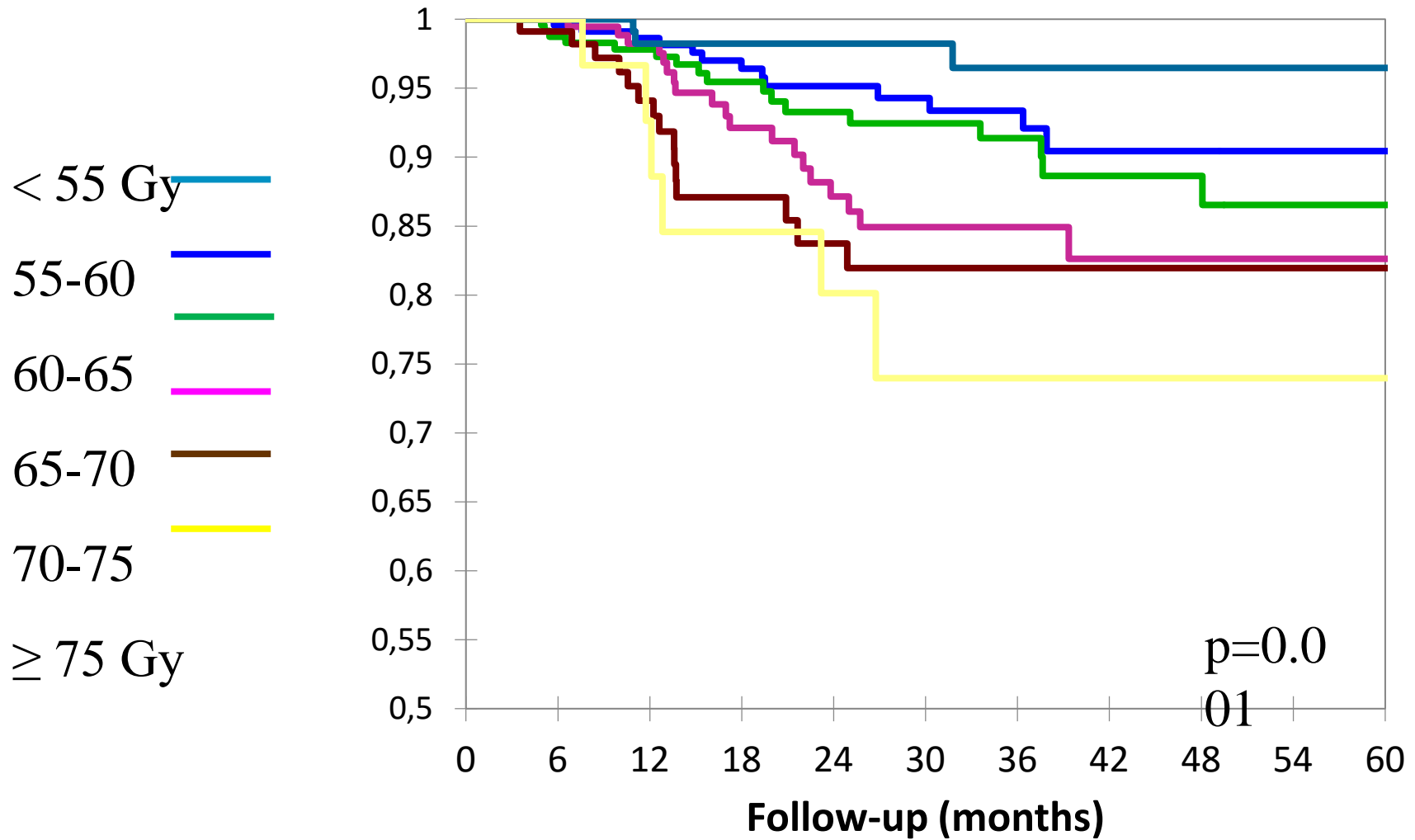
- EMBRACE CTCAE
- All endpoints except ureter stenosis G_{≥2}



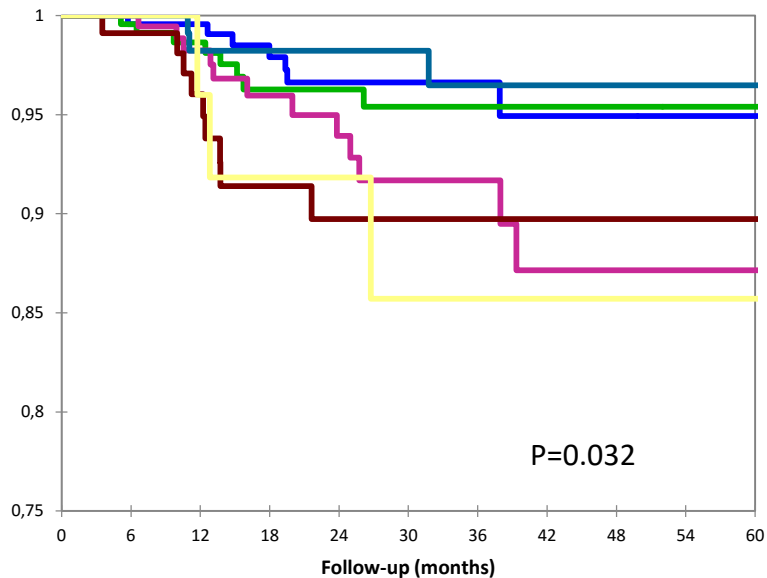
QOL
EORTC



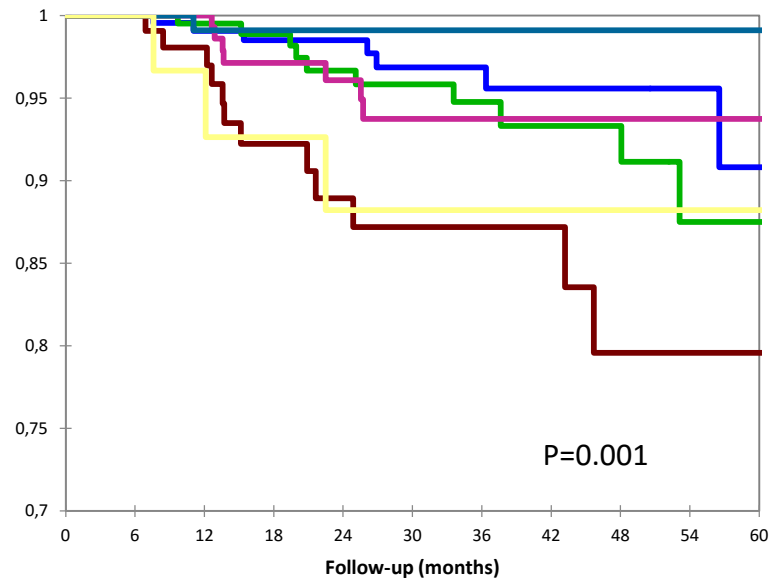
Rectum D_{2cm3}



Proctitis

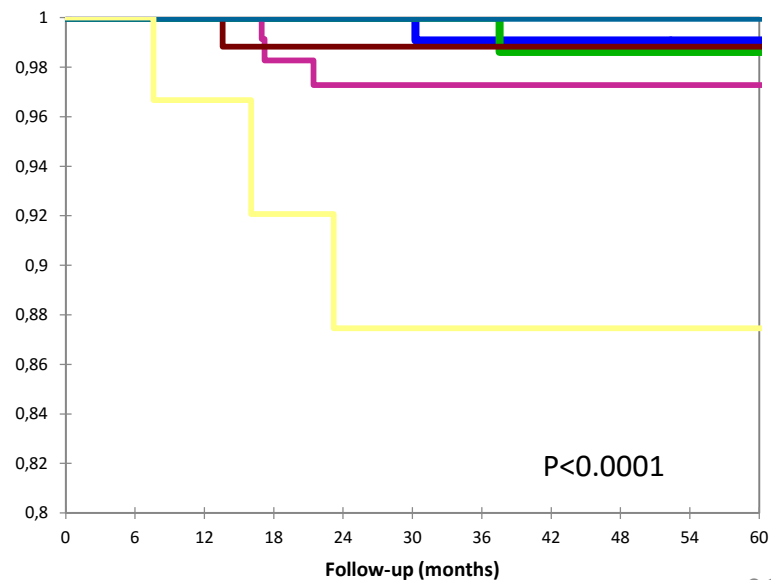


Bleeding



- < 55 Gy —
- 55-60 —
- 60-65 —
- 65-70 —
- 70-75 —
- ≥ 75 Gy —

Fistula

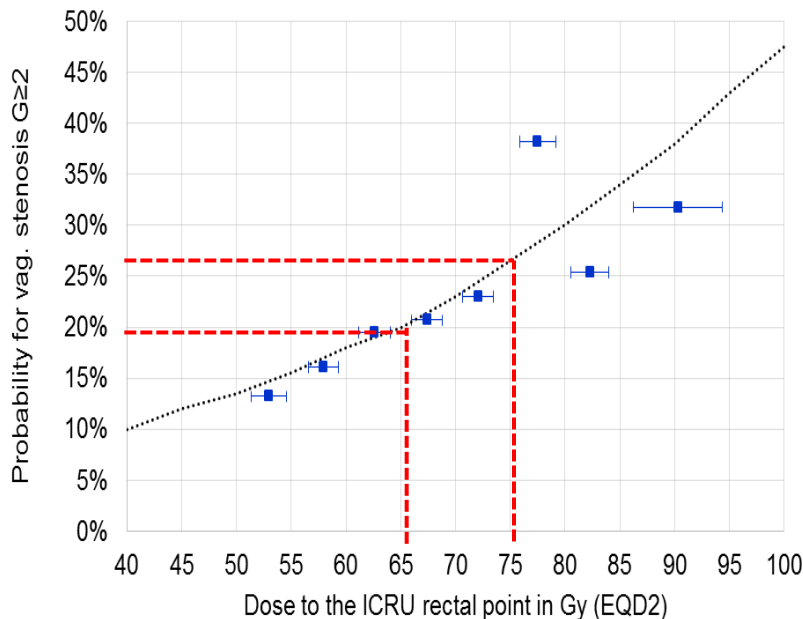


Vaginal stenosis

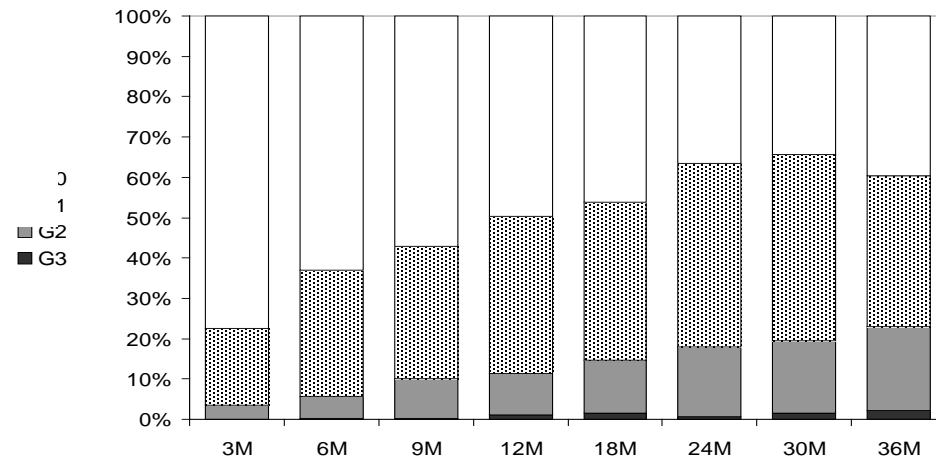
ICRU recto-vaginal point (630 pts)

Cox-regression, 2 year actuarial risk of \geq G2 stenosis

- Significant impact of EBRT dose (45Gy versus 50Gy)
- Significant impact of BT ICRU recto-vaginal dose



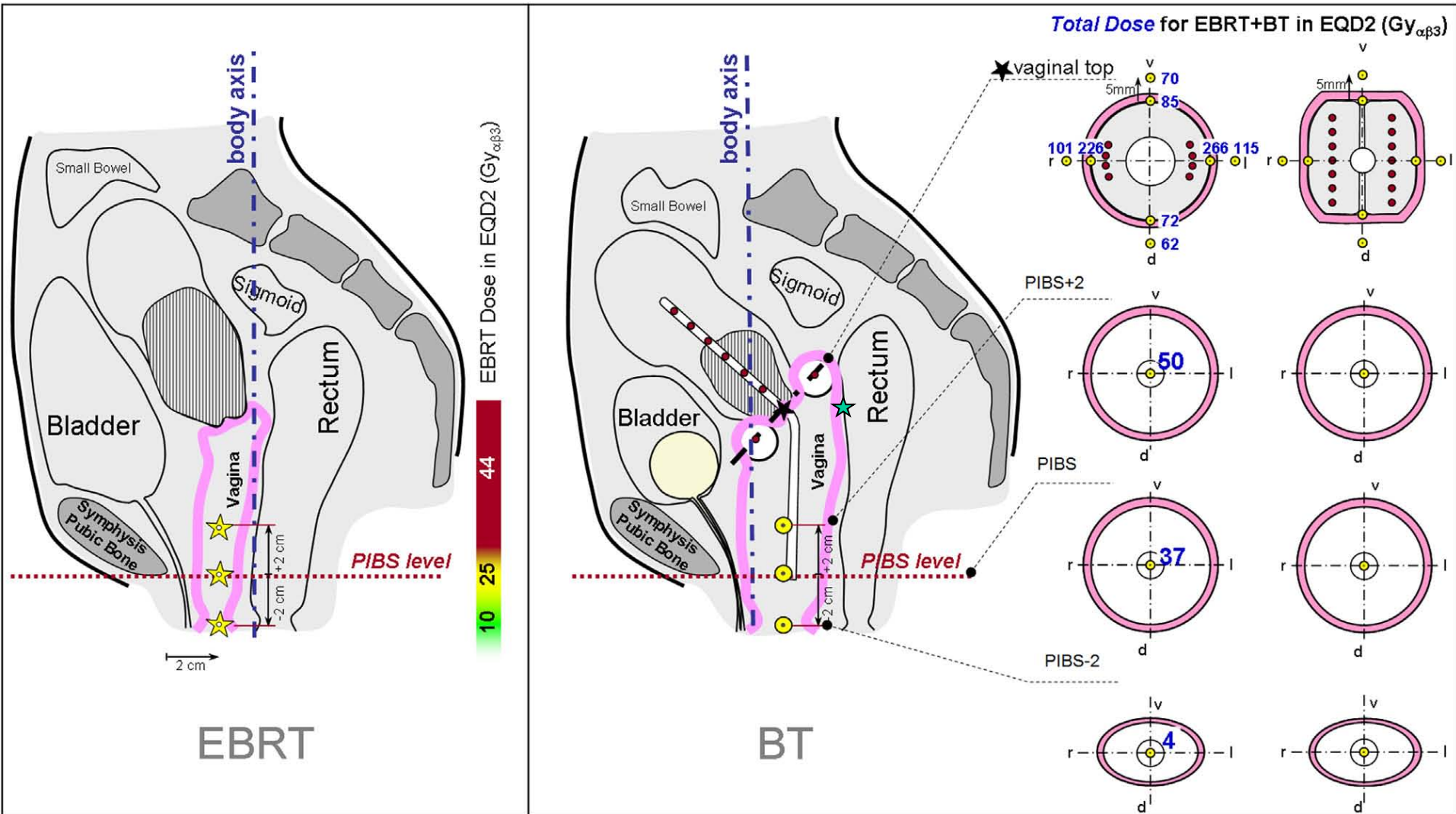
Prevalence vaginal stenosis



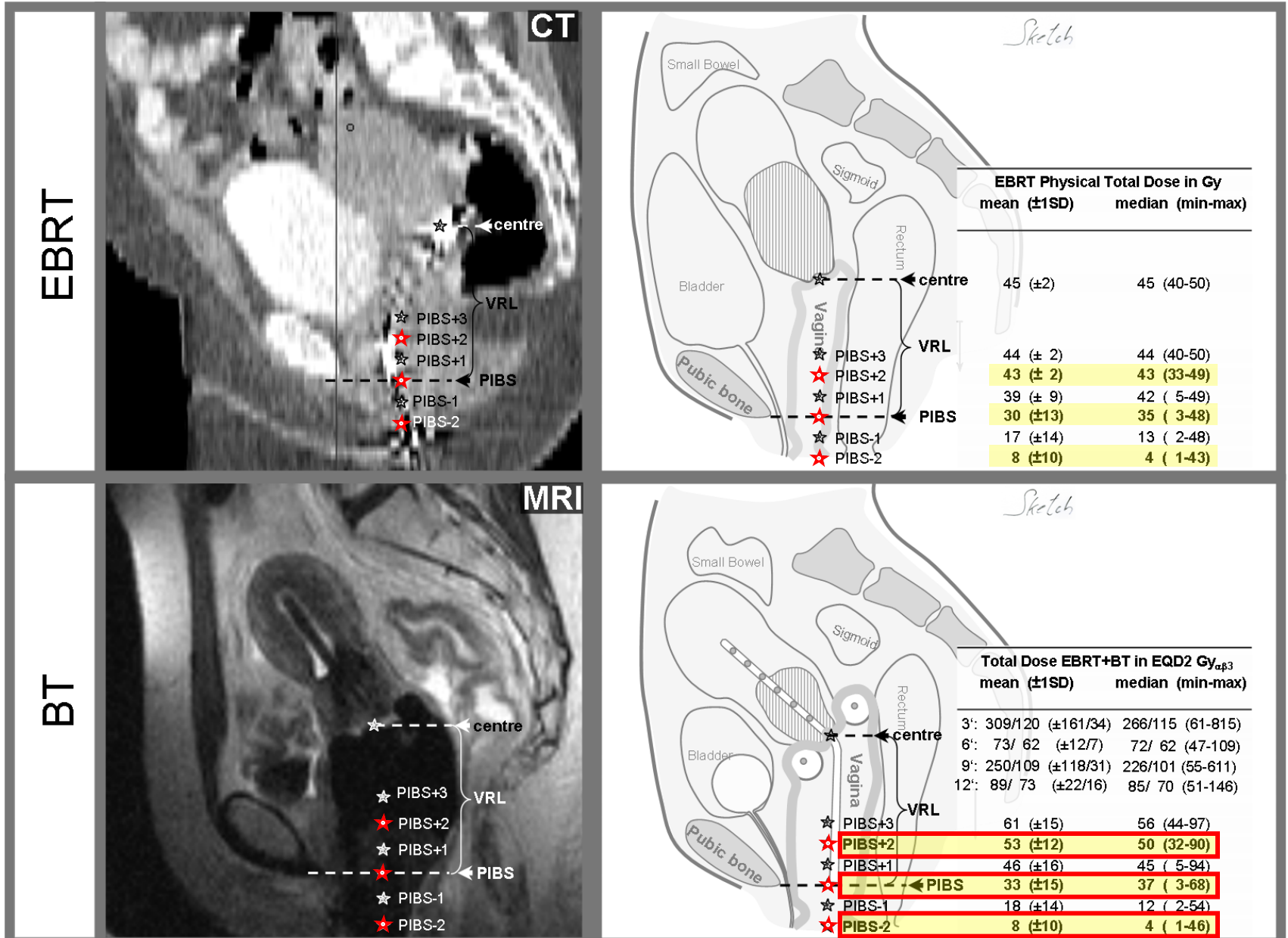
Kirchheiner K et al. Manifestation pattern of early-late vaginal morbidity. IJROBP 2014 May 1;89(1):88-95

**K Kirchheiner et al, MUW/AUH
2015, Submitted RO**

Vaginal Dose Points: PIBS, PIBS+2, PIBS-2



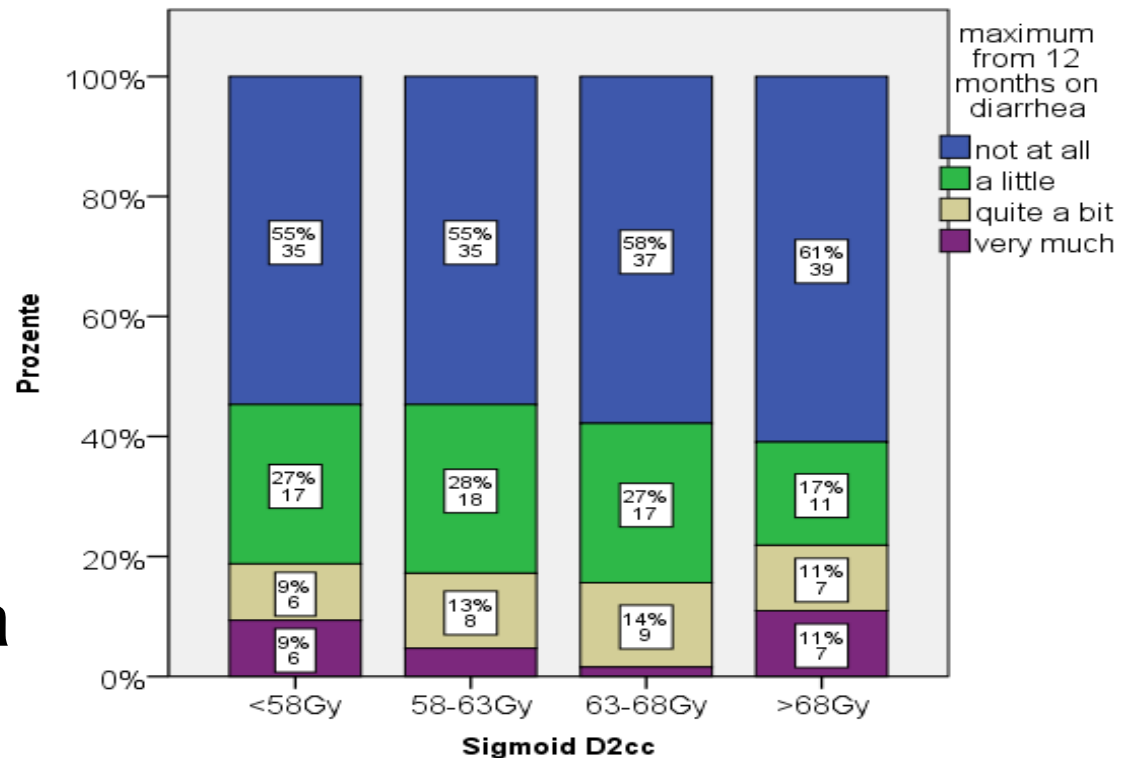
Vaginal Dose Points



Sigmoid D_{2cm3} , preliminary data

- No dose effect established – so far

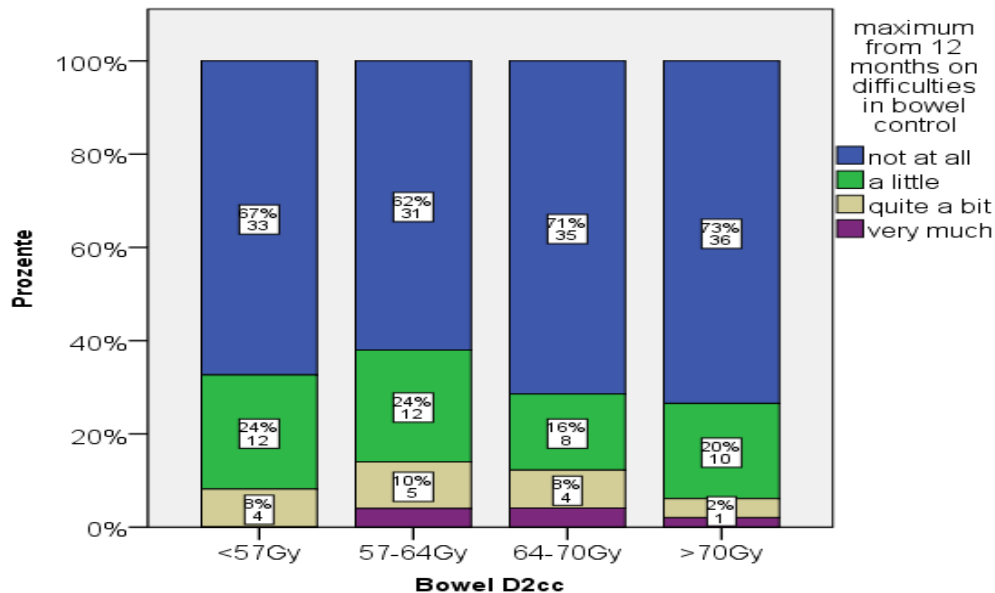
Diarrhea



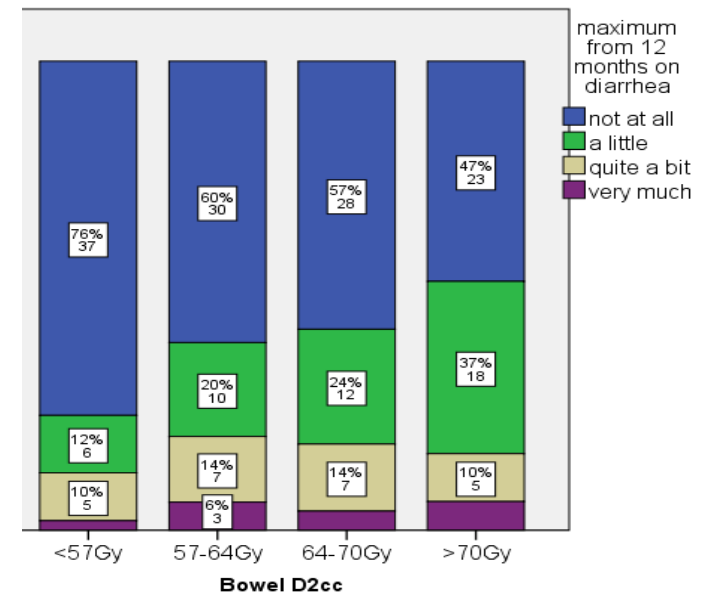
Bowel D_{2cm3}, preliminary data

- No dose effect established – so far

Bowel control



Diarrhea



Dose prescription protocol in cervix cancer

	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	-	-

Dose prescription protocol

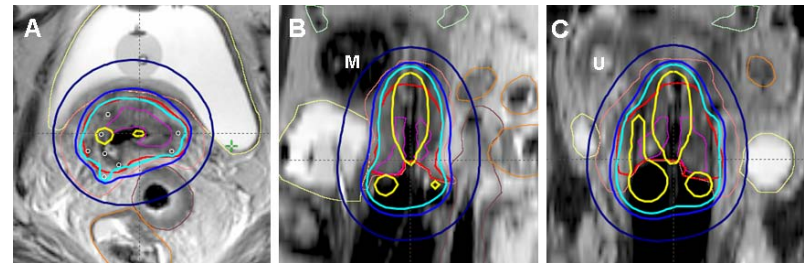
	Bladder $D_{2\text{cm}^3}$ EQD2 ₃	Rectum $D_{2\text{cm}^3}$ EQD2 ₃	Recto- vaginal point EQD2 ₃	Sigmoid/ Bowel $D_{2\text{cm}^3}$ EQD2 ₃
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy*
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*

* for the sigmoid/bowel structures these dose constraints are valid in case of non-mobile bowel loops resulting in the situation that the most exposed volume is located at a similar part of the organ

Planning aim and prescription dose

- **Planning aim: what you want to obtain**
- **Prescribed dose: what you decide to treat**

Example 1

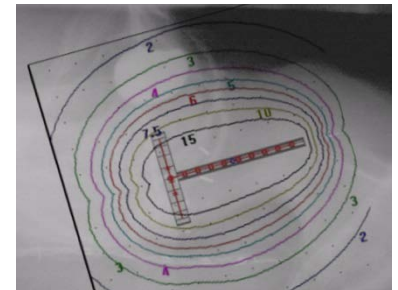


Structure	Dose-volume parameter	Planning aim, Gy	Prescribed dose Gy
CTV _{HR}	EQD2 ₁₀ D ₉₀	≥ 85	88.9
Bladder	EQD2 ₃ D _{2cm} ³	≤ 90	71.1
Rectum	EQD2 ₃ D _{2cm} ³	≤ 70	65.6
Sigmoid	EQD2 ₃ D _{2cm} ³	≤ 70	57.4
Bowel	EQD2 ₃ D _{2cm} ³	≤ 70	53.3

Planning aim and prescription dose

- **Planning aim: what you want to obtain**
- **Prescribed dose: what you decide to treat**

Example 2



Structure	Dose parameter	Planning aim, Gy	Prescribed dose Gy
Target	Point A	7Gy	6.5Gy
Bladder	ICRU point	$\leq 7\text{Gy}$	6.8 Gy
Rectum	ICRU point	$\leq 75\%$ of 7Gy	5.3 Gy

Conclusion (I)

- **Dose effect demonstrated for:**
 - Residual GTV D100, adaptive CTV_{HR} D90, and CTV_{IR} D90
 - Bladder D 2cm³
 - Rectum D 2cm³
 - Vagina (recto-vaginal point)

- **Dose effect not demonstrated for**
 - Sigmoid and bowel
 - Dose to adhesive bowel loops may be important!

- **Perspective: prospective dose prescription protocol taking into account multiple parameters:**
 - Target dose, volume and overall treatment time
 - OARs

What is the proposed planning aim for CTV_{HR} – indicate all correct answers

- A. Planning aim: 90-95Gy**
- B. Hard constraint: >85Gy**
- C. Hard constraint: >90Gy**
- D. Hard constraint: <95Gy**

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**
- B. HR-CTV D90=90Gy,
Bladder D2cm3=85Gy**
- C. I cannot decide without
more clinical
information**

Physics aspects of treatment planning intracavitary +/- interstitial techniques in cervix cancer

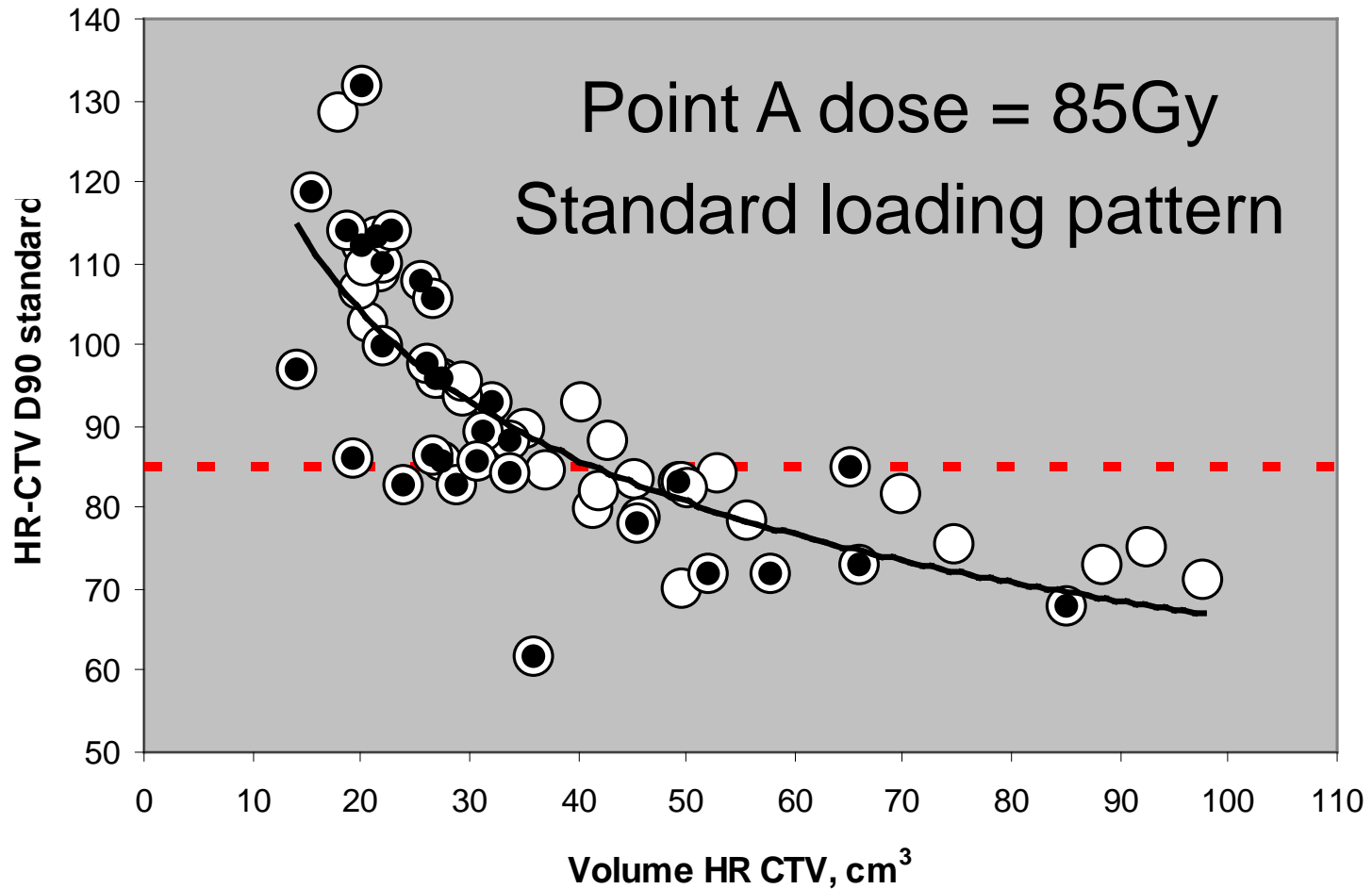
ESTRO Teaching Course
Image-Guided Cervix Radiotherapy – with a special focus on adaptive
brachytherapy

Toronto 2016

Kari Tanderup



Limitation of standard loading pattern with dose prescription to point A



● Violation of OAR constraint

With dose optimisation in a small tumour...

- 1. Point A dose becomes typically higher**
- 2. HR CTV D90 becomes typically higher**
- 3. OAR dose becomes typically lower**

Tools for dose optimisation

- **Manual dose optimisation**
- **Graphical optimization / Dose shaper**
- **Inverse planning**

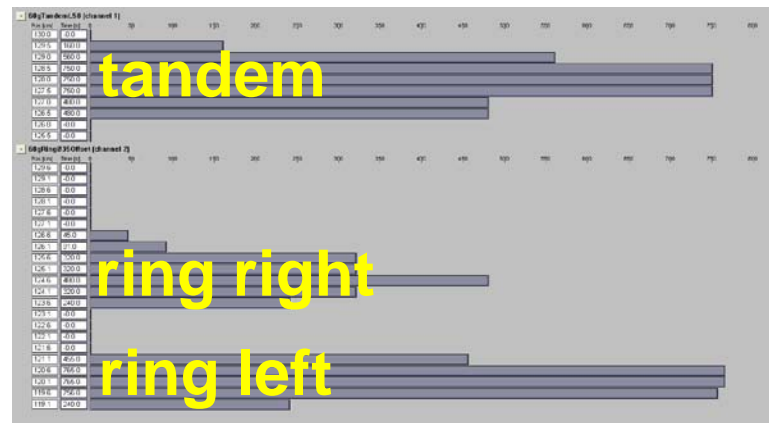
Manual optimisation

Dwell times

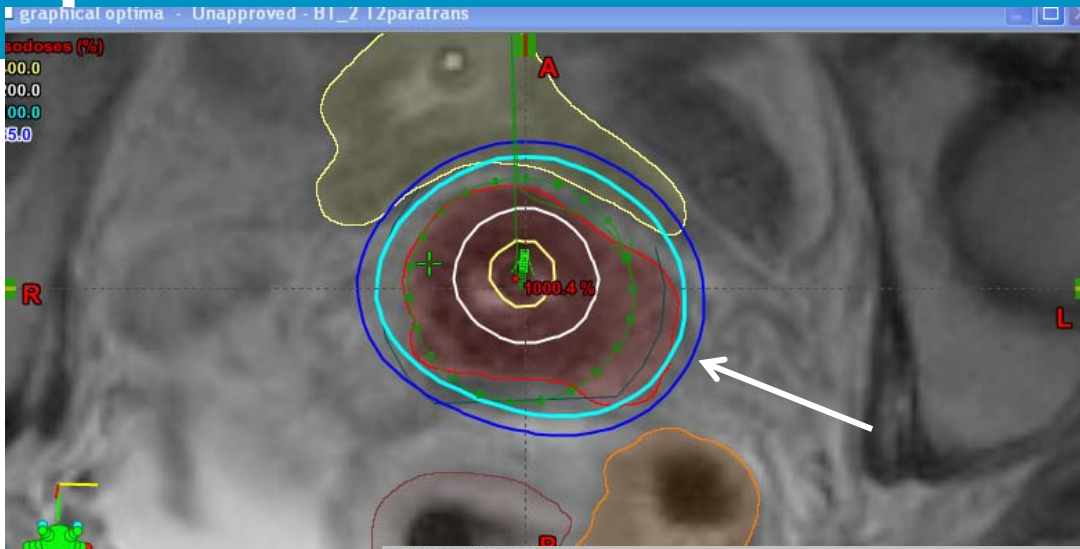
Standard



Manually optimised



Graphical dose optimisation – “drag and drop”



Dose Shaper

Dose shaping effect

Global Local

OK Cancel

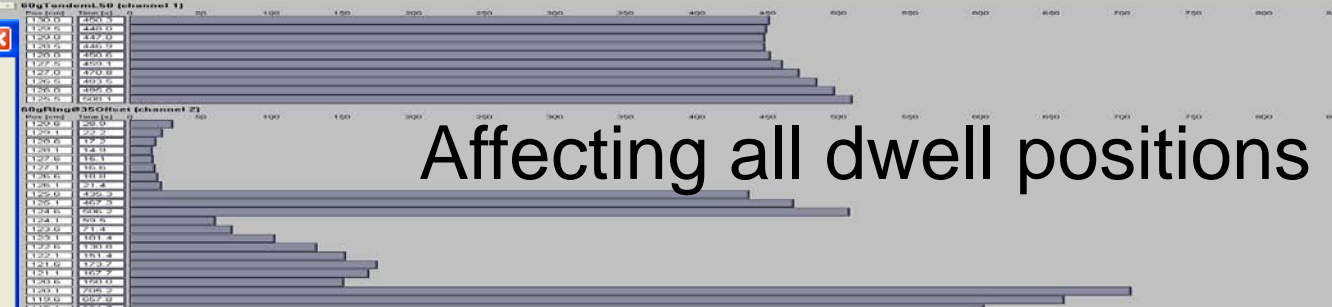


Dose Shaper

Dose shaping effect

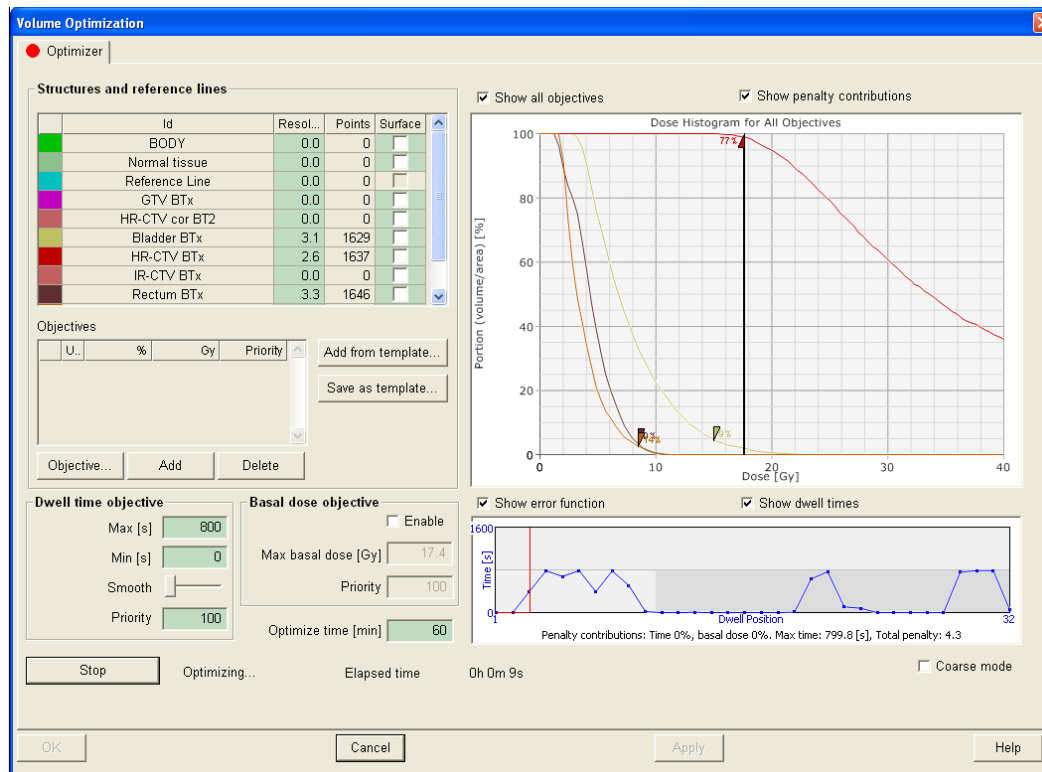
Global Local

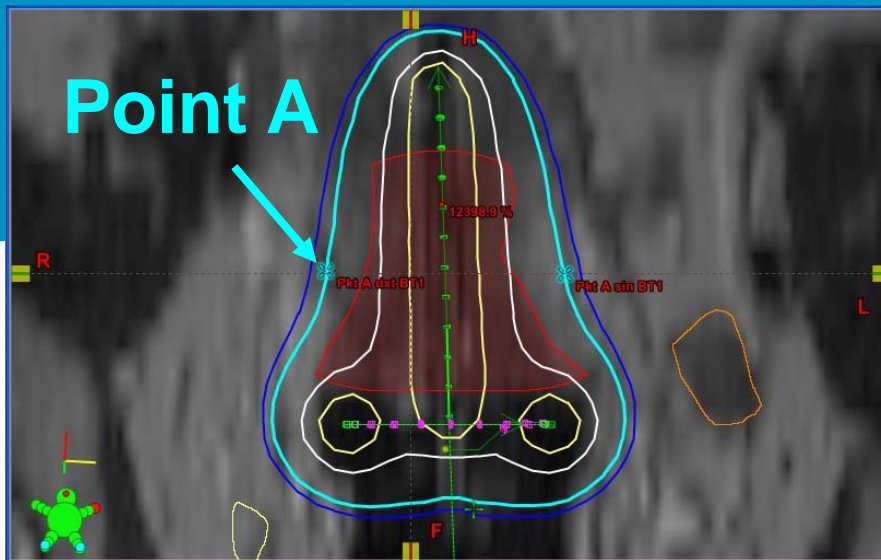
OK Cancel



Inverse dose optimisation

- Controlled by DVH constraints
- Weighting factors for different structures

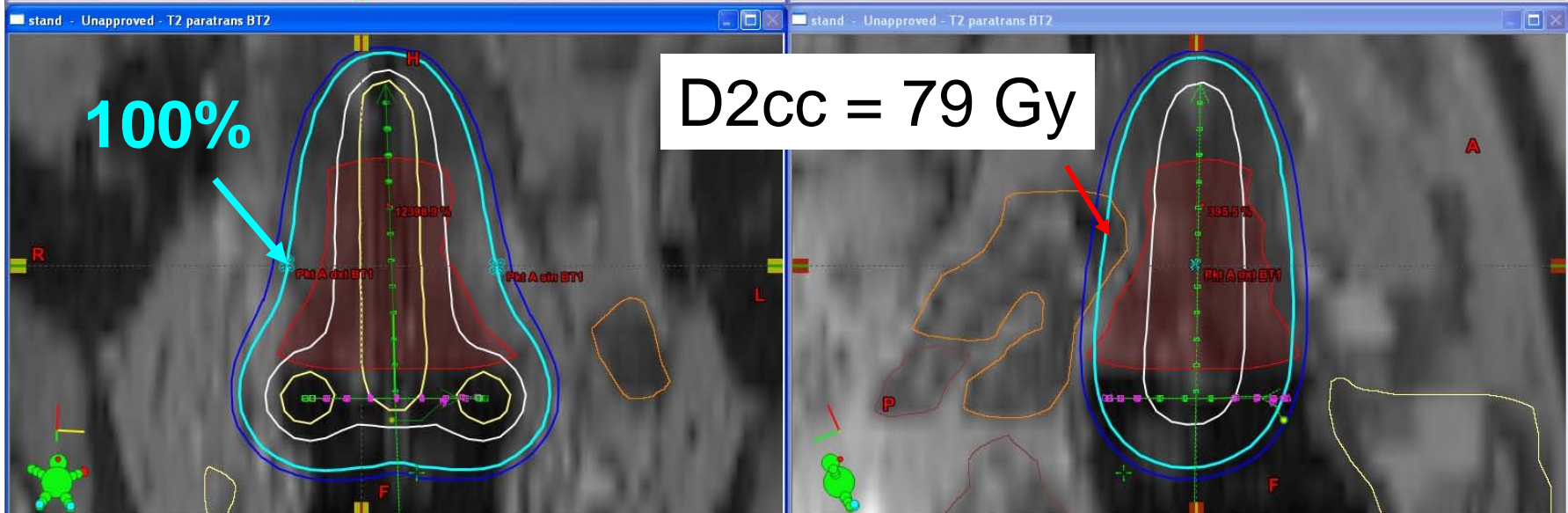
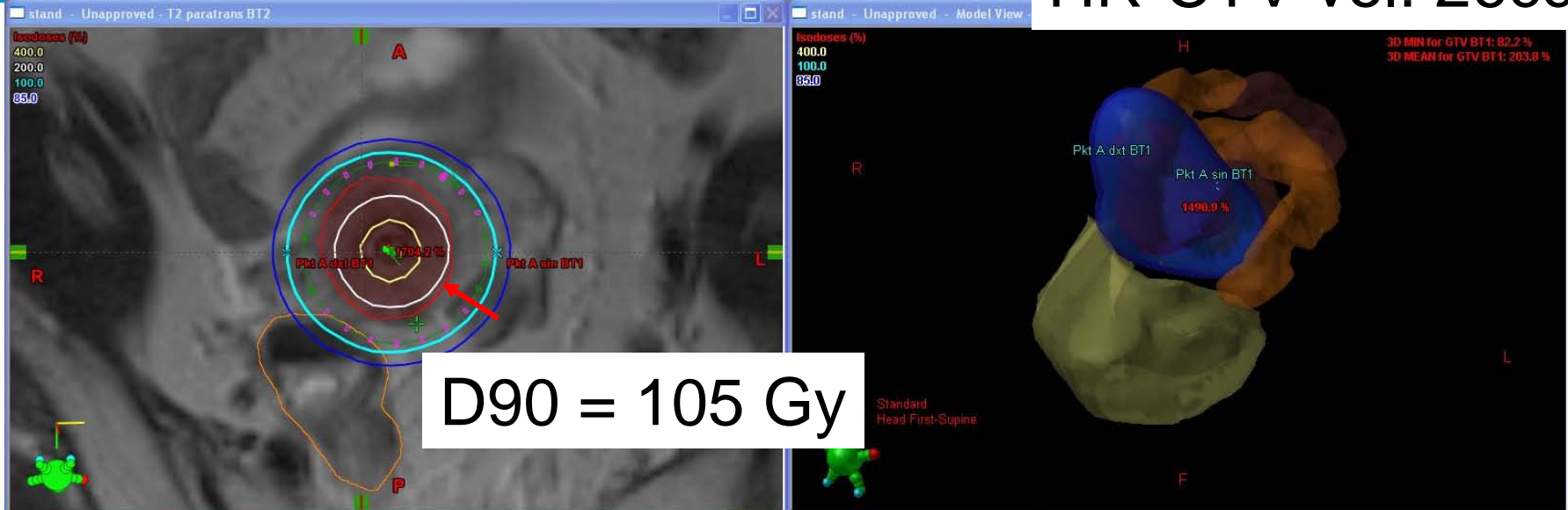




Always start optimisation
with
Standard loading pattern
Standard prescription

Example 1: good response stage IB2 Standard plan

HR-CTV vol: 26cc



Example 1

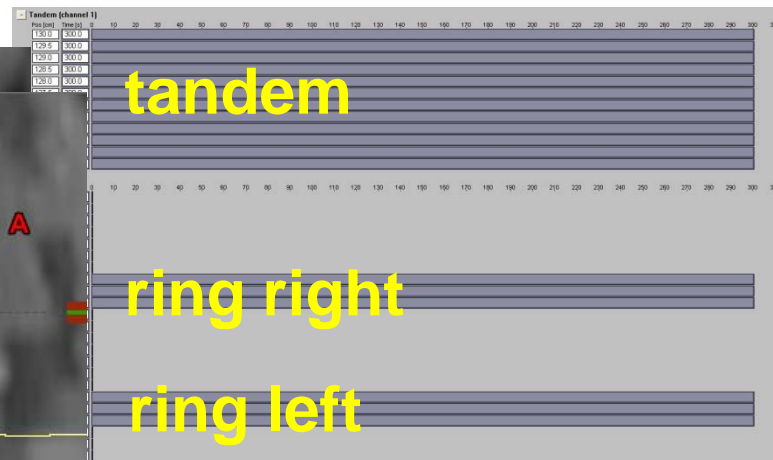
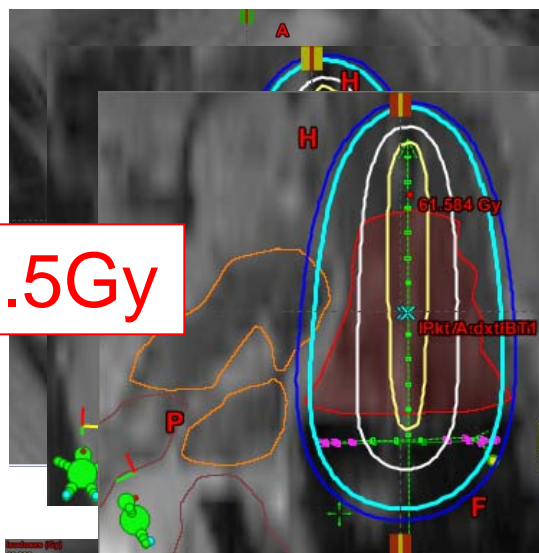
Manual dose optimisation

Dose

Dwell times

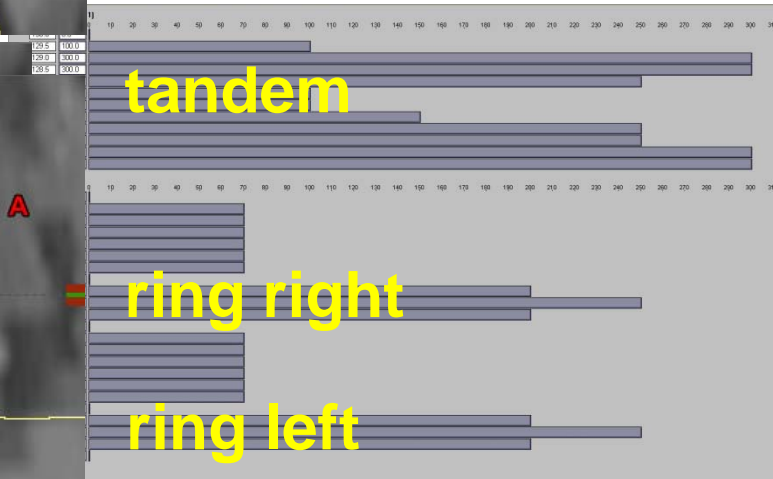
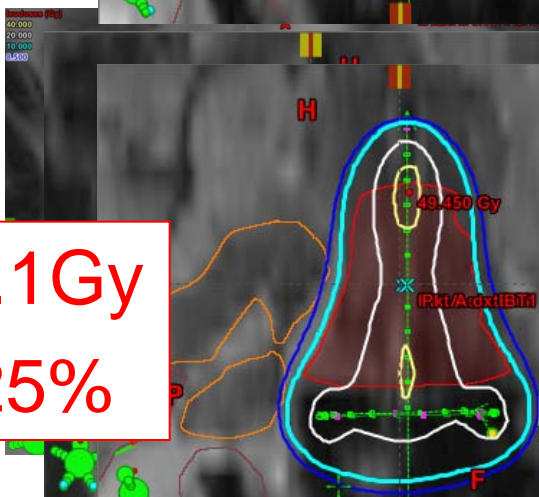
Standard

Point A = 17.5Gy

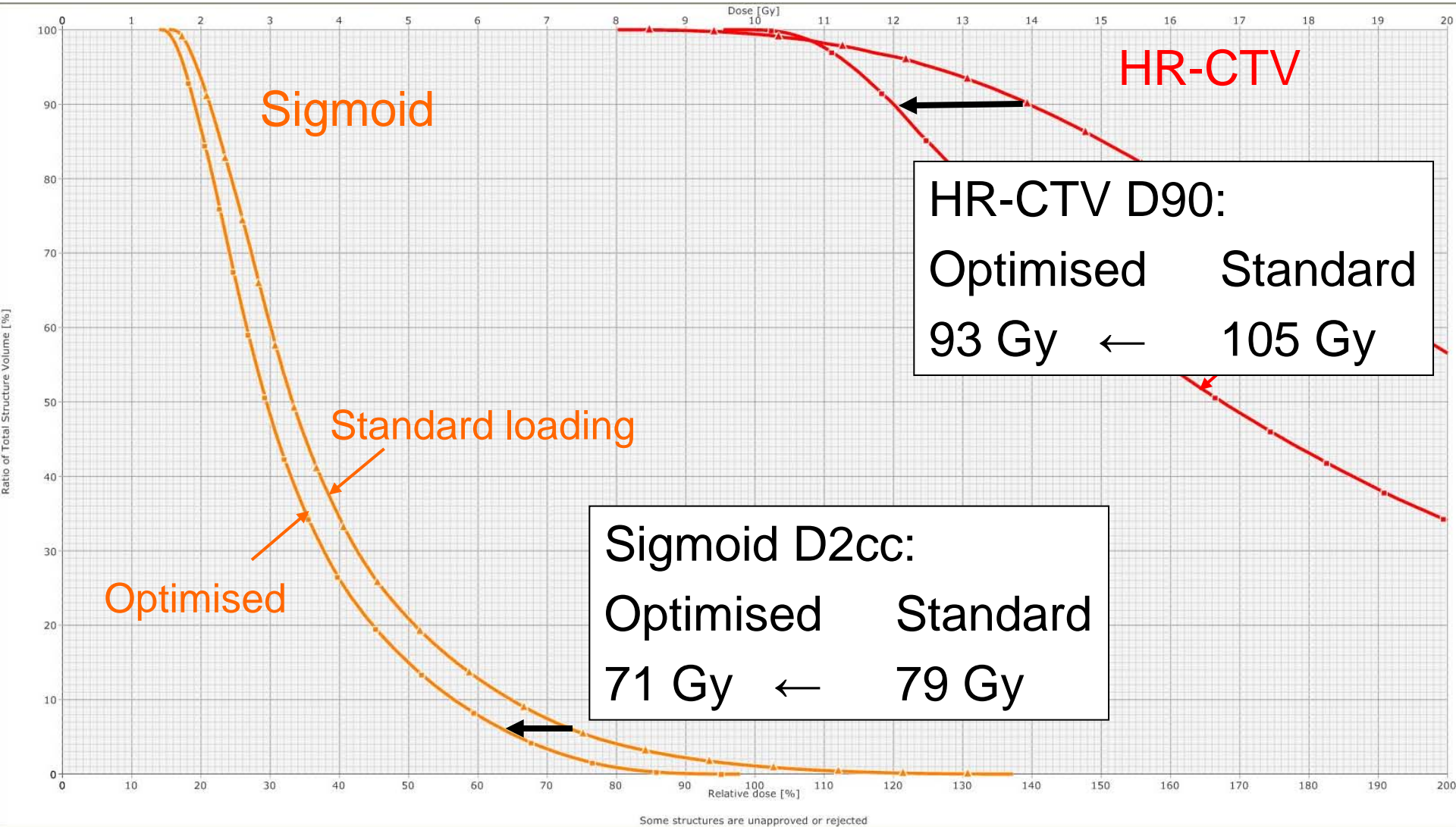


Manual optimisation

Point A = 13.1Gy
Reduction: 25%



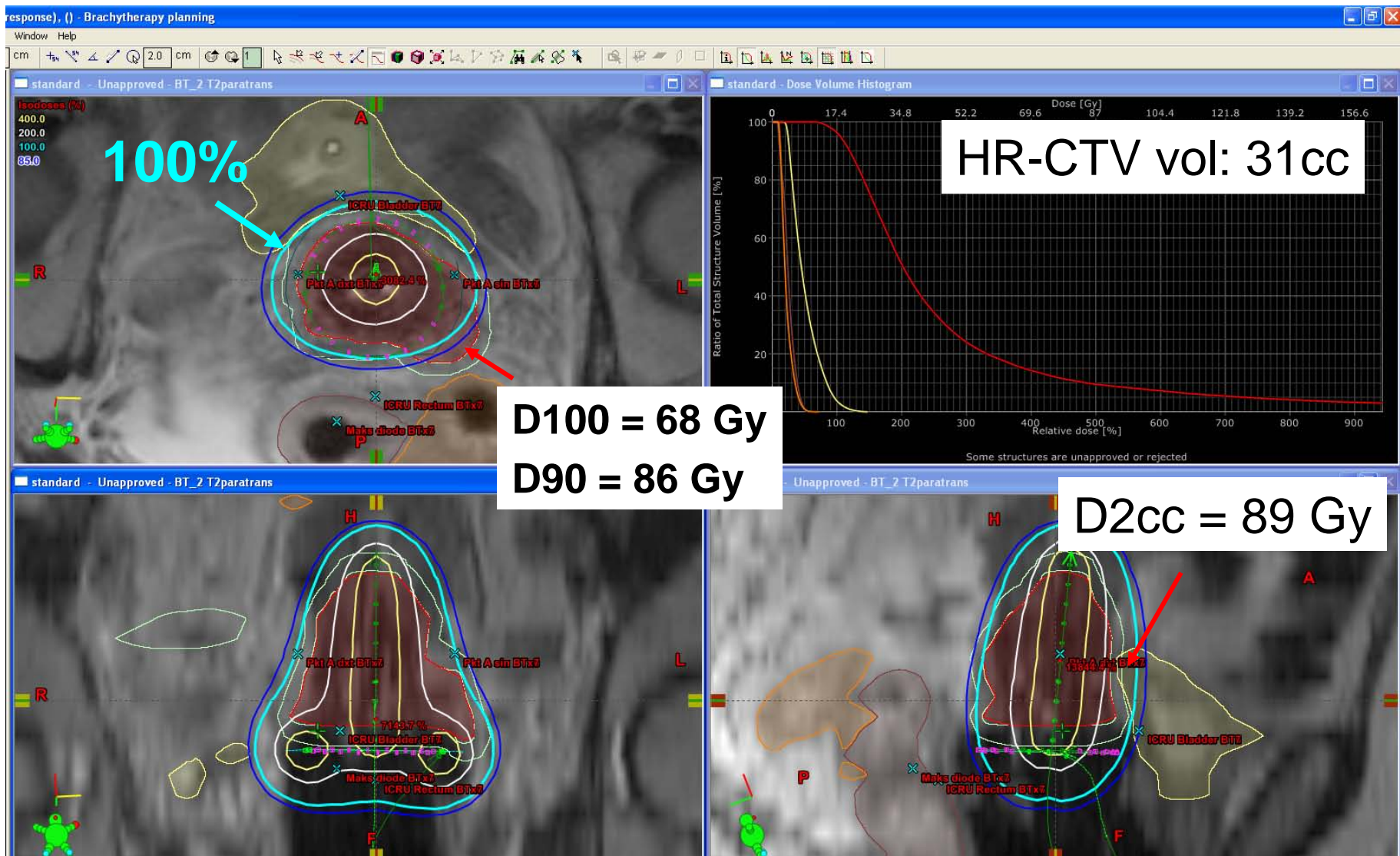
Example 1, DVH



Example 1, summary

- **Small tumour (HR-CTV vol 26cc)**
- **Decrease of pear (and point A dose)**
- **OAR dose decreased**
- **Planning aim: >85Gy**
- **Prescribed dose HR CTV D90: 93Gy**
- **100% isodose adjusted by ~5mm**

Example 2, Stage IIB Standard plan



Example 2

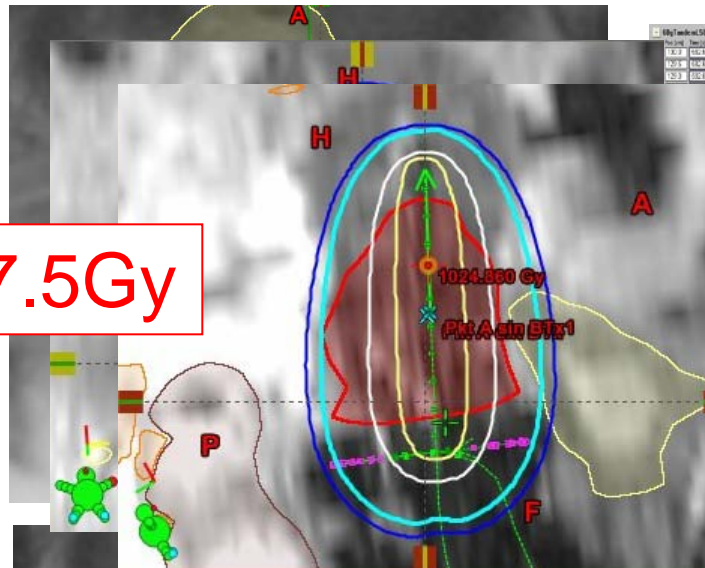
Manual dose optimisation

Dose

Dwell times

Standard

Point A = 17.5Gy



tandem

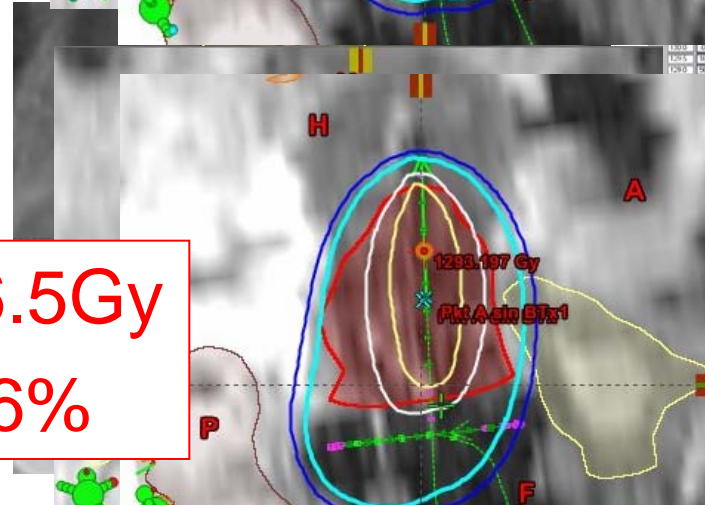
ring right

ring left



Manual optimisation

Point A = 16.5Gy
Reduction: 6%



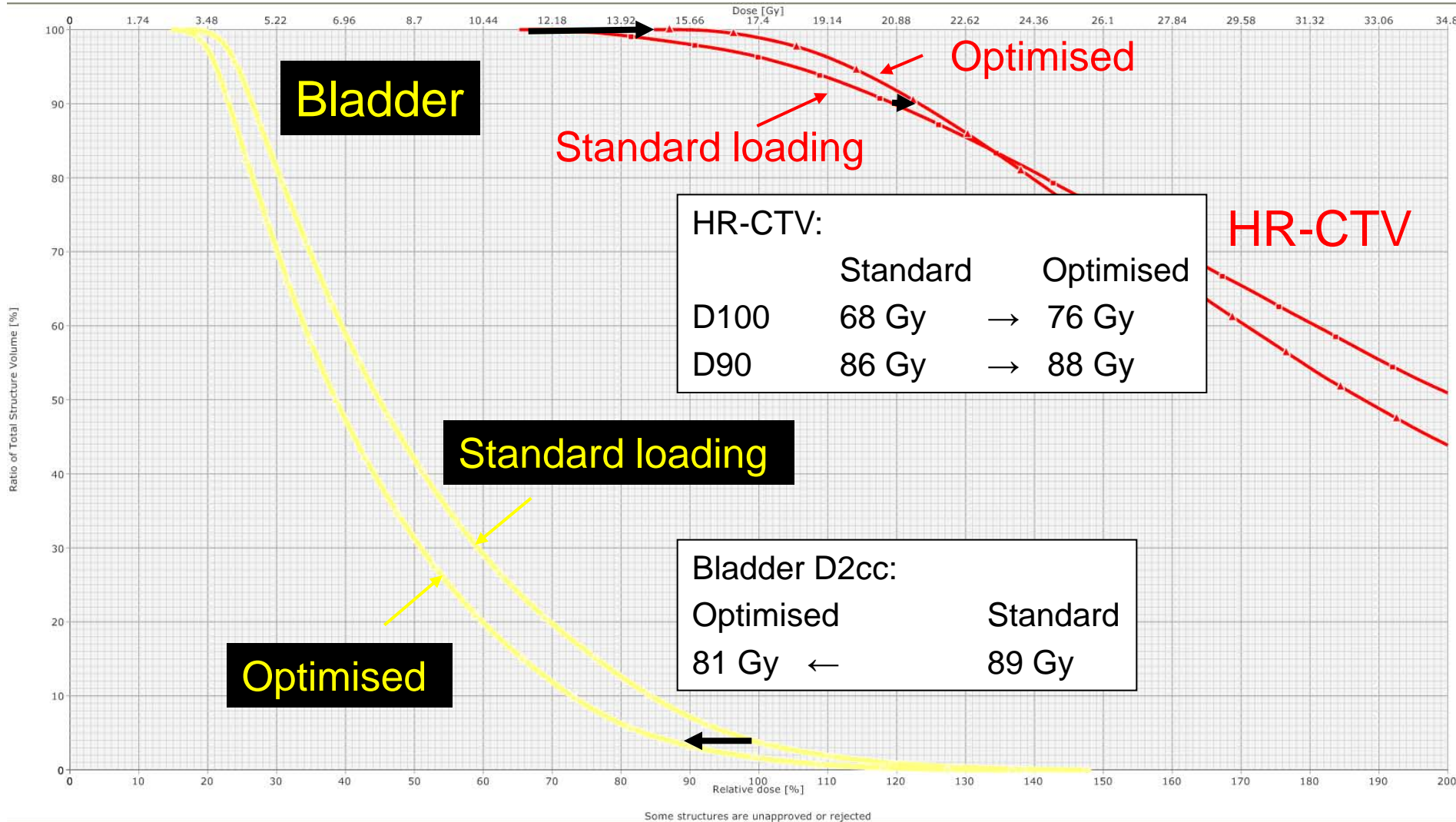
tandem

ring right

ring left



Example 2, DVH

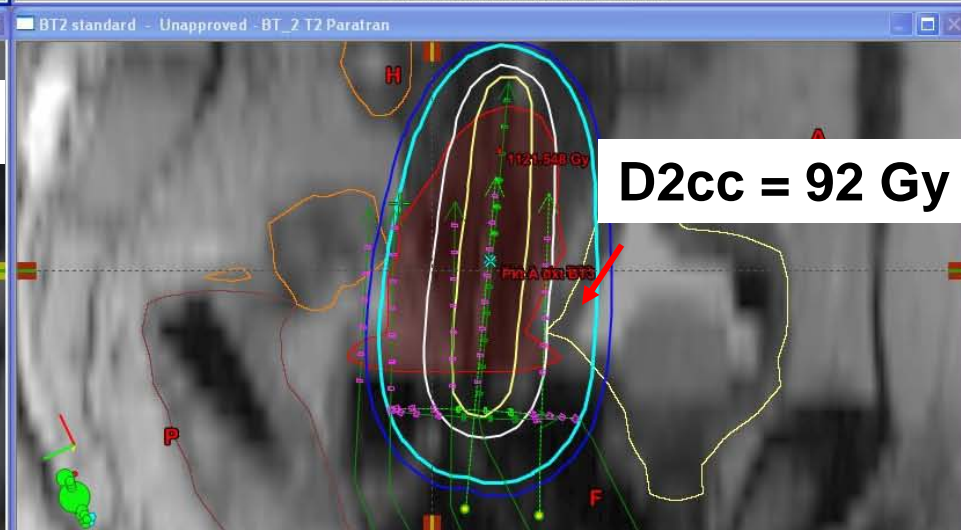
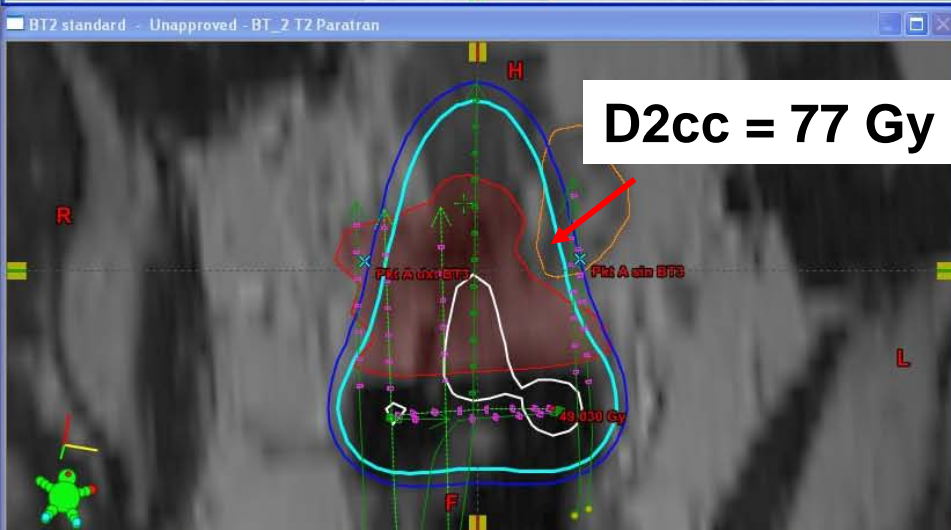
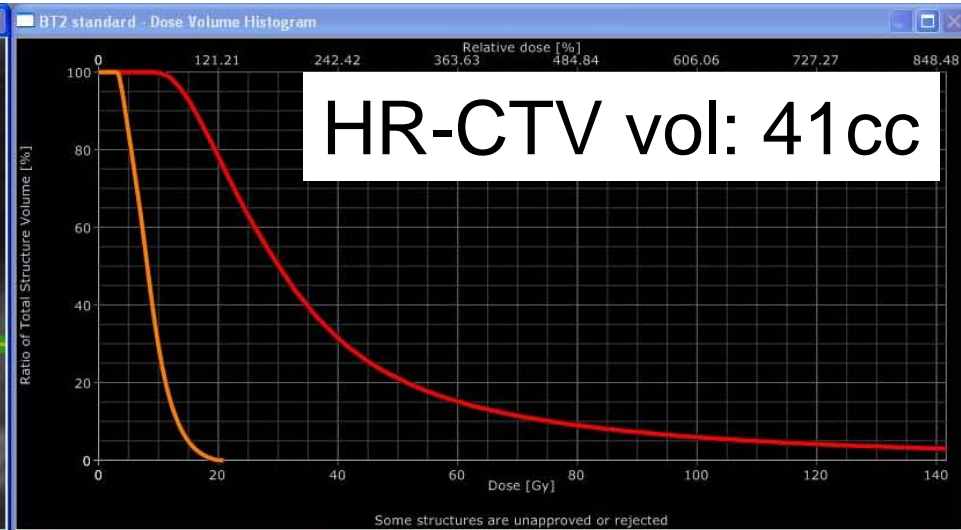
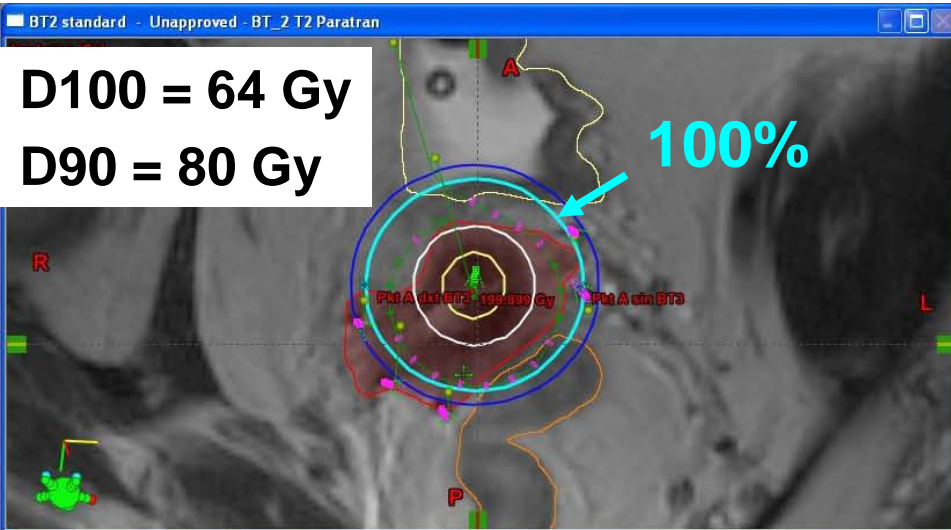


Some structures are unapproved or rejected

Example 2, summary

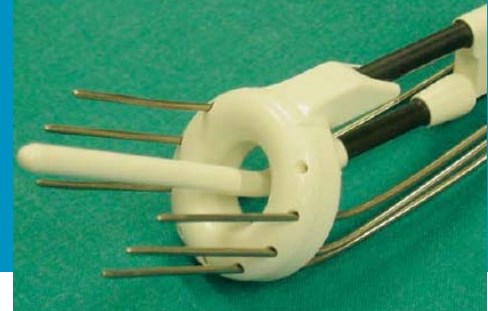
- **Small tumour (HR-CTV vol 31cc)**
- **Relatively small adaptations of the standard pear shaped isodose**
- **Target coverage increased – OAR dose decreased**
- **Planning aim: >85Gy**
- **Prescribed dose HR CTV D90: 88Gy**
- **100% isodose adjusted by ~5mm**

Example 3, Stage IIIB Standard dose plan



Example 3

Manually optimised plan



Dose

Dwell times

Standard

TRAK = 2.1 cGy



Manual optimisation

TRAK = 2.2 cGy

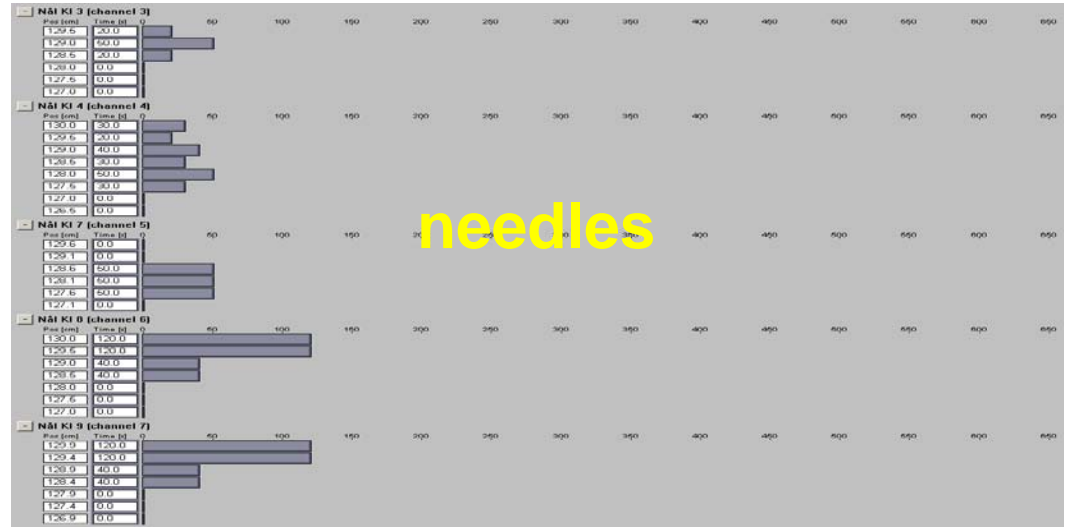
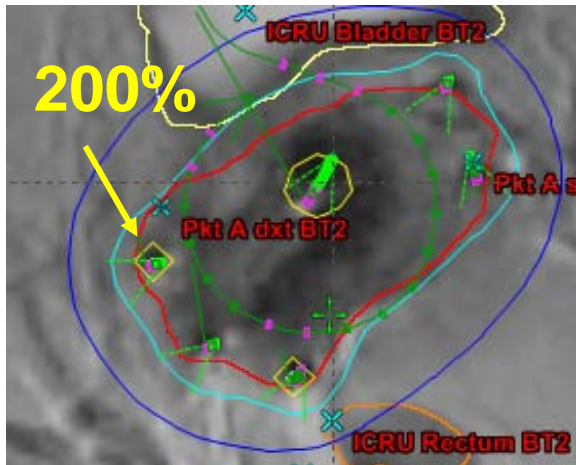
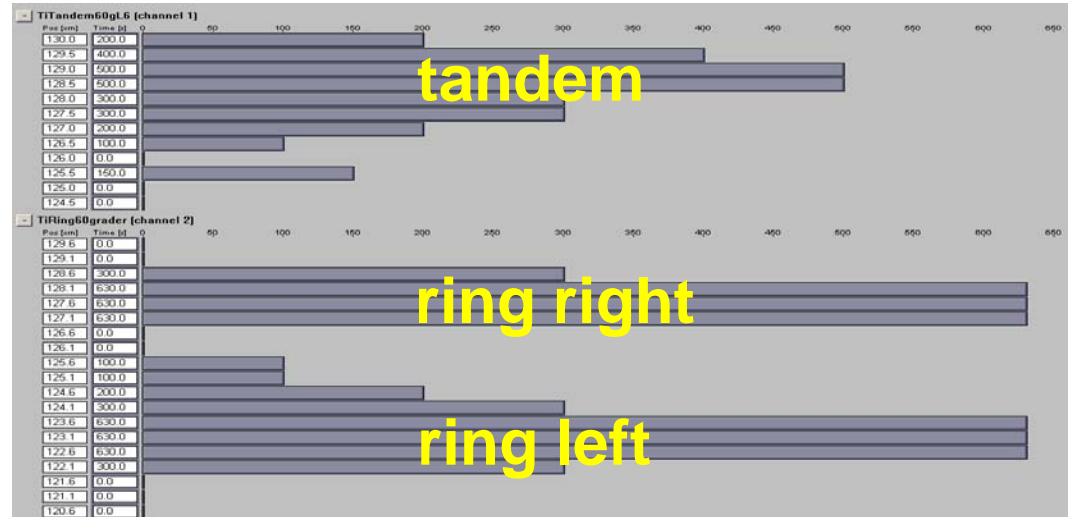
Increase: 7%



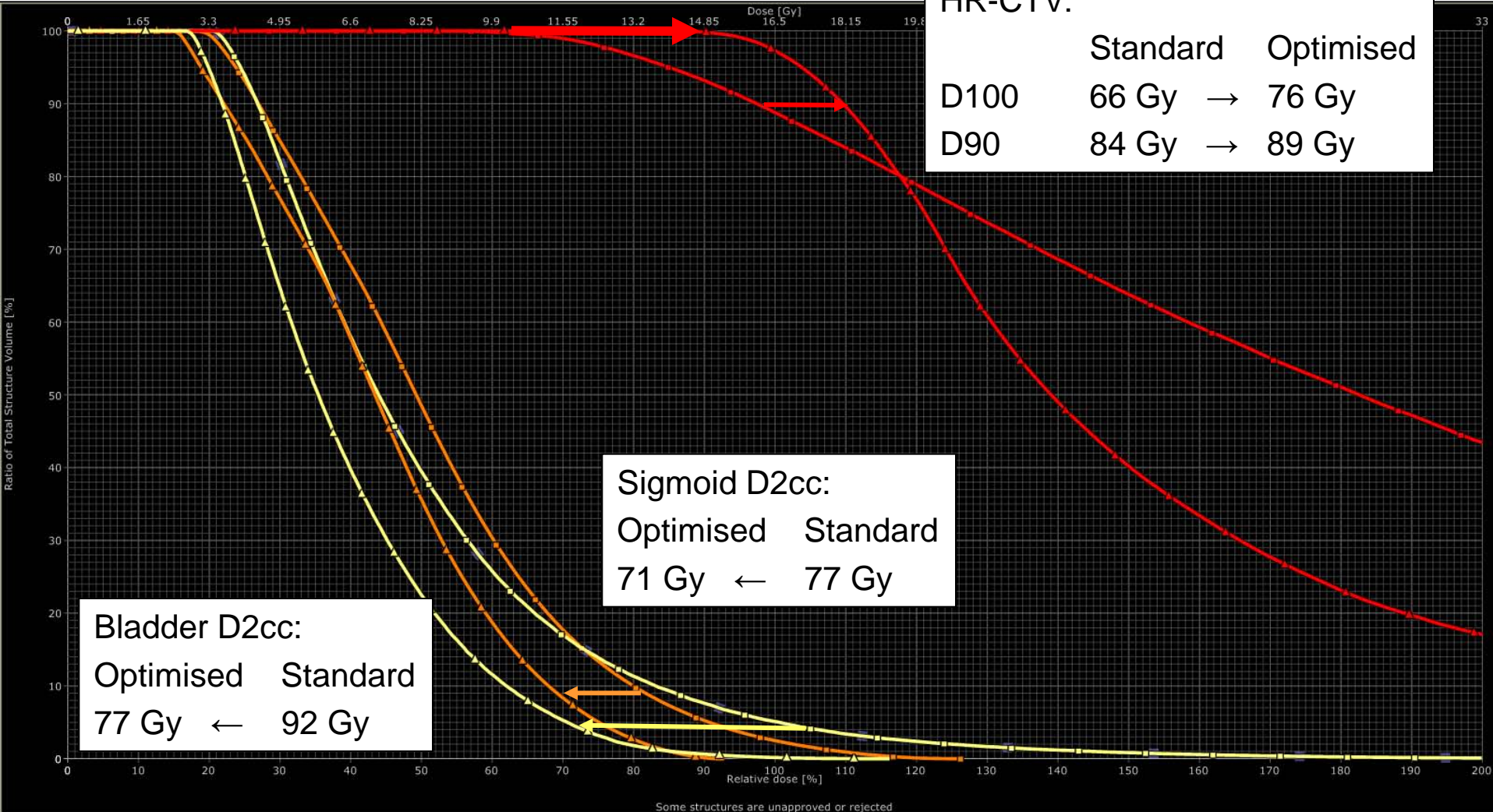
Loading of needles: dwell times and isodoses

Dwell times needles:
10-20% of dwell time in
tandem/ring

May be >10-20% if
needle is placed
directly in the GTV



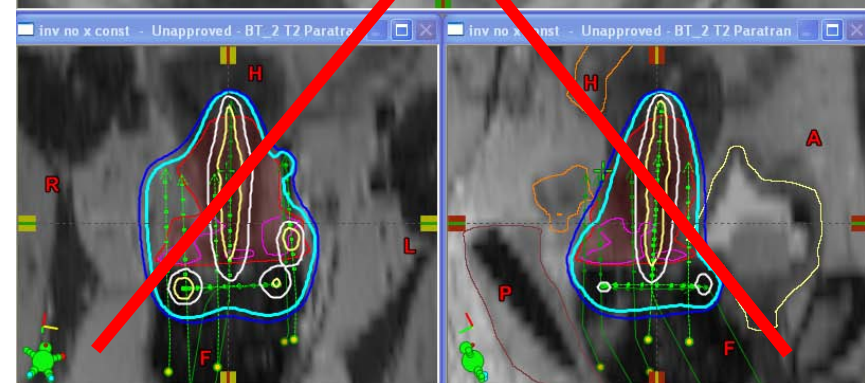
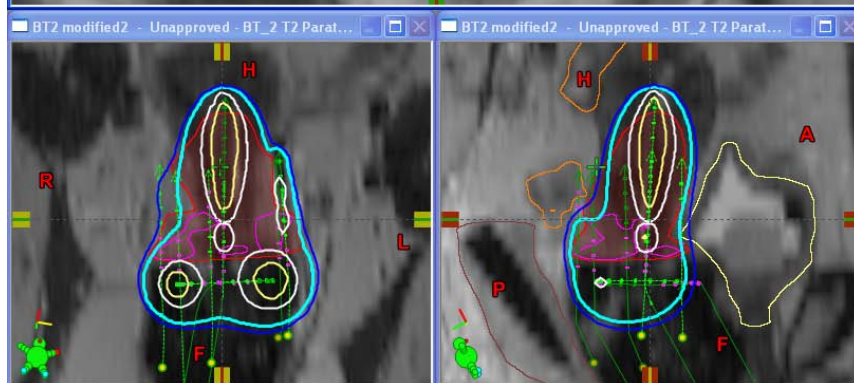
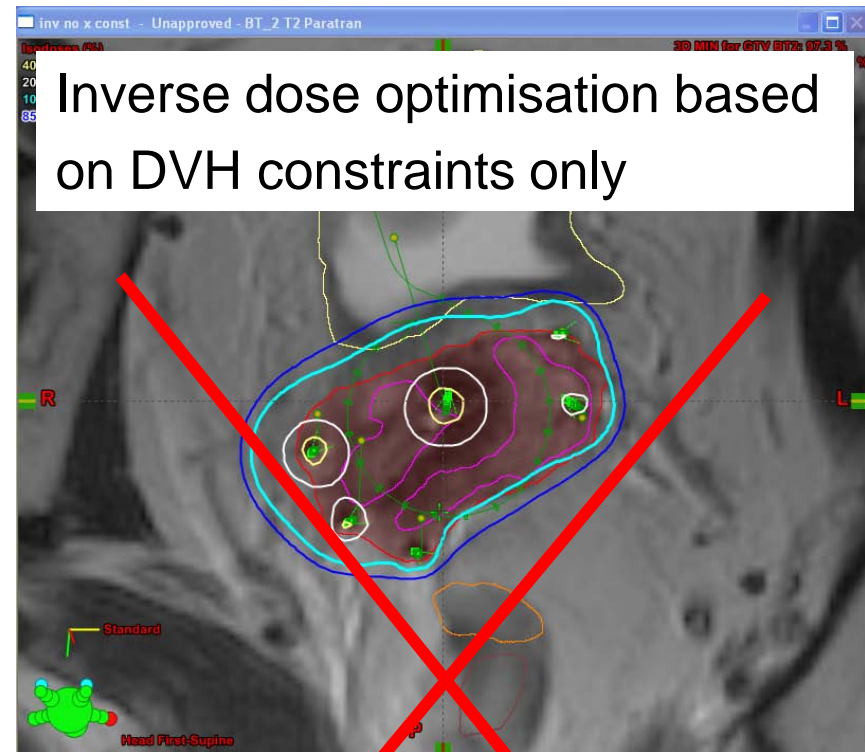
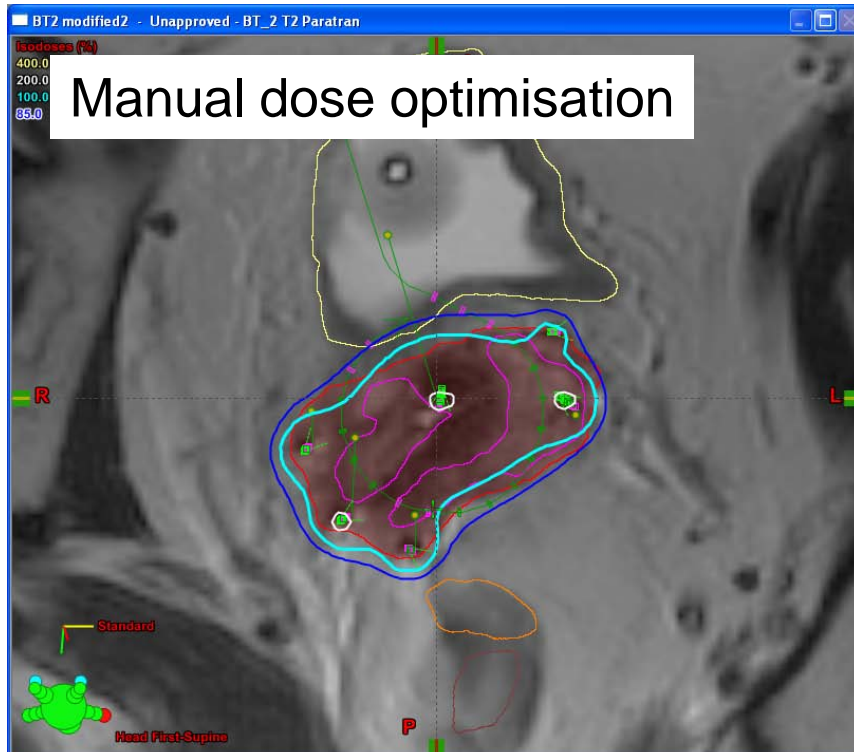
Example 3, DVH



Example 3, summary

- **Bad response (HR-CTV vol 41cc)**
- **Need of modified applicator (ring+needles)**
- **Needle loading: <20%**
- **Target coverage significantly increased – OAR dose significantly decreased**
- **Planning aim: >85Gy**
- **Prescribed dose HR CTV D90: 89Gy**
- **100% isodose adjusted by ~ 10 mm**

Example 3, inverse planning



When to use graphical dose optimisation (dose shaper)?

Standard plan



Manual optimisation



Graphical dose optimisation



Visual inspection of dwell times + adaptation

70%

90%

98%

100%

When to use graphical dose optimisation (dose shaper)?

Standard plan



Graphical dose optimisation



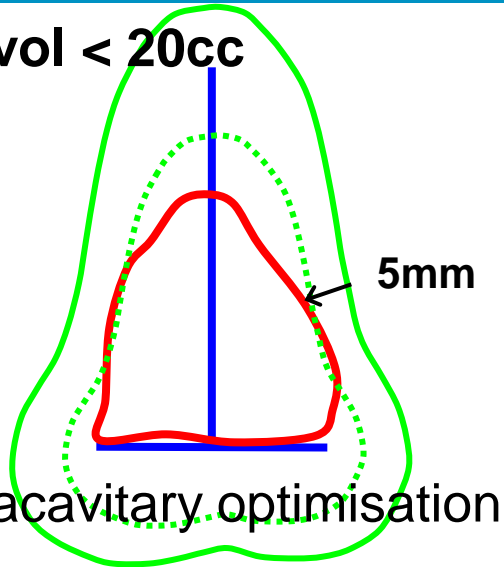
Visual inspection of dwell times + adaptation

Risk:

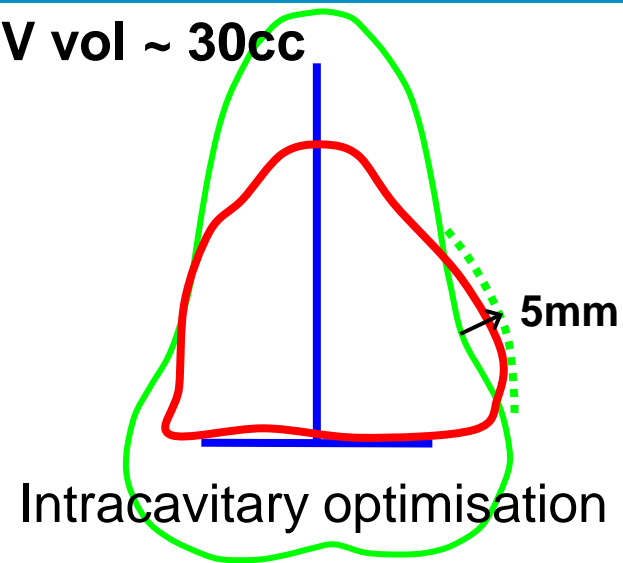
- Blowing up needle loading
- Loosing intuition of acceptable dwell times

Typical scenarios of dose optimisation

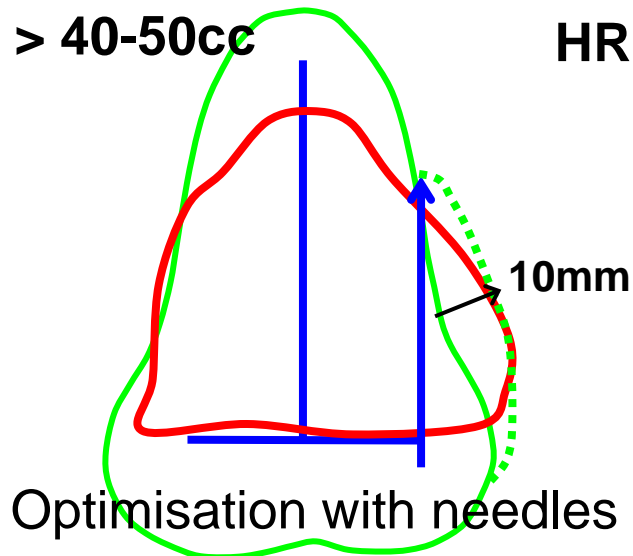
HR-CTV vol < 20cc



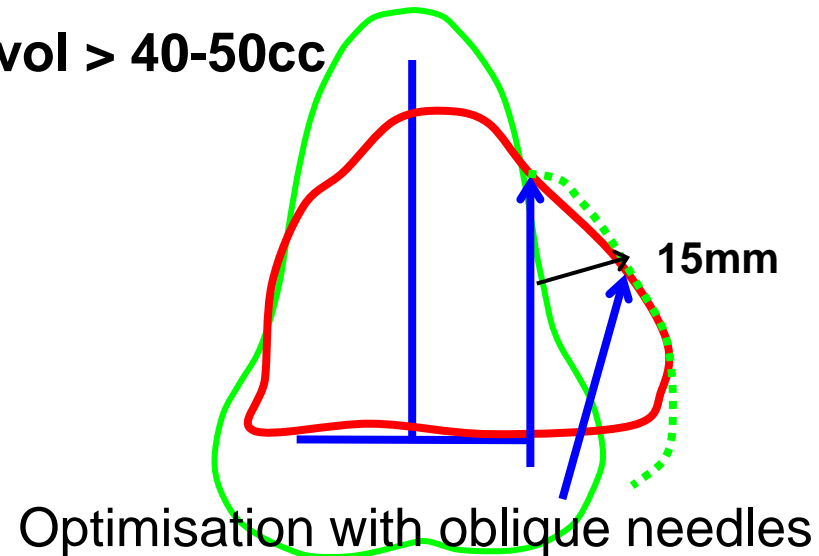
HR-CTV vol ~ 30cc



HR-CTV vol > 40-50cc



HR-CTV vol > 40-50cc

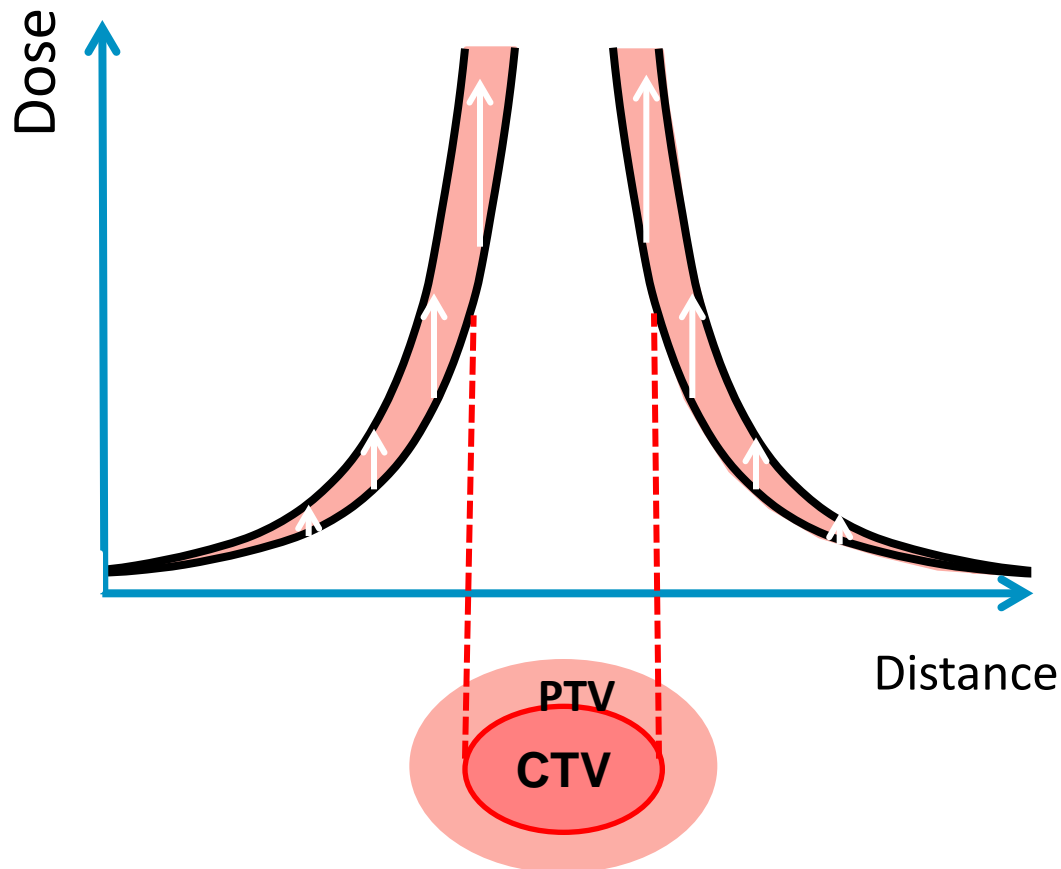


Conclusion – optimisation techniques

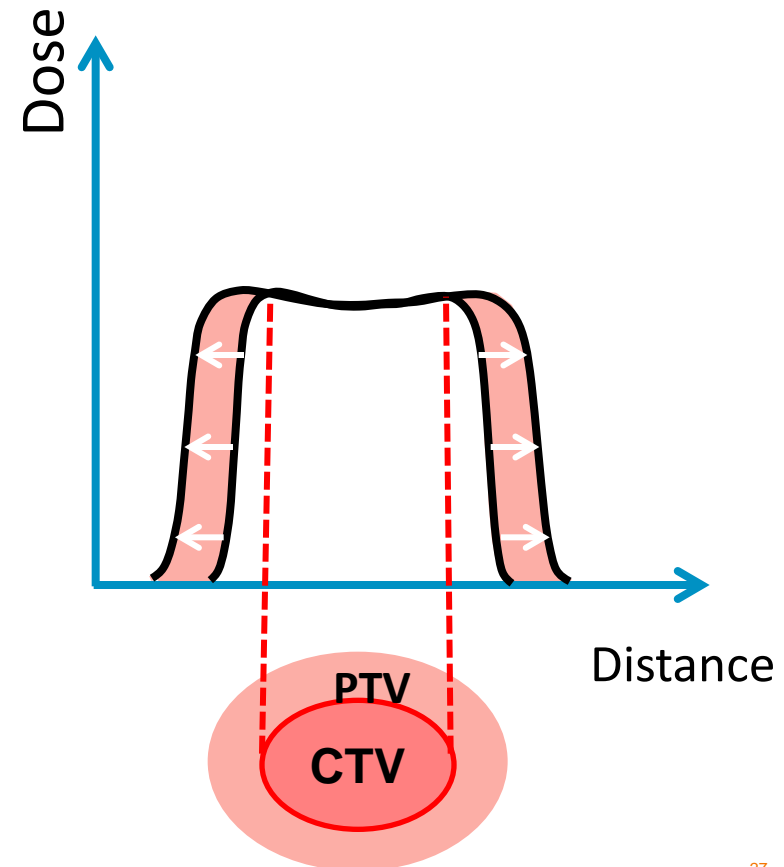
Manual	Conservative and “safe” Iterative procedure Dependent on experience of dose planner
Graphical	Fast for small adaptations and fine tuning after manual opt Beware of: -dwell times -deviations from standard loading
Inverse	Fast Requires extra contouring + manual adaptations Beware of: -dwell times -high dose regions -dose to non-contoured tissue -deviations from standard loading

PTV margins

BT

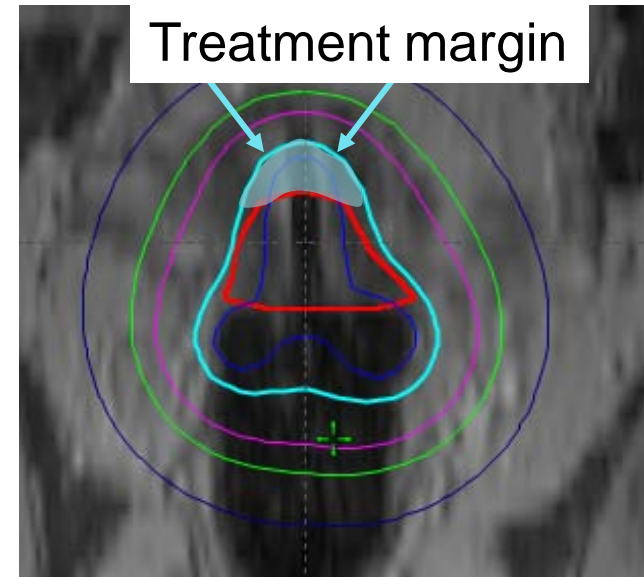
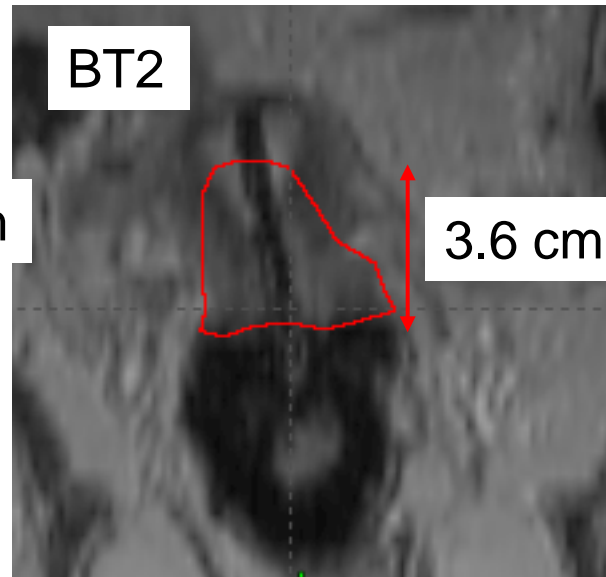
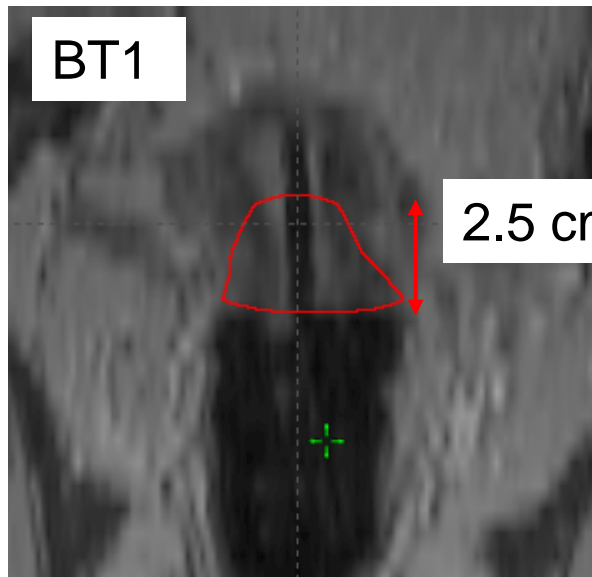


EBRT



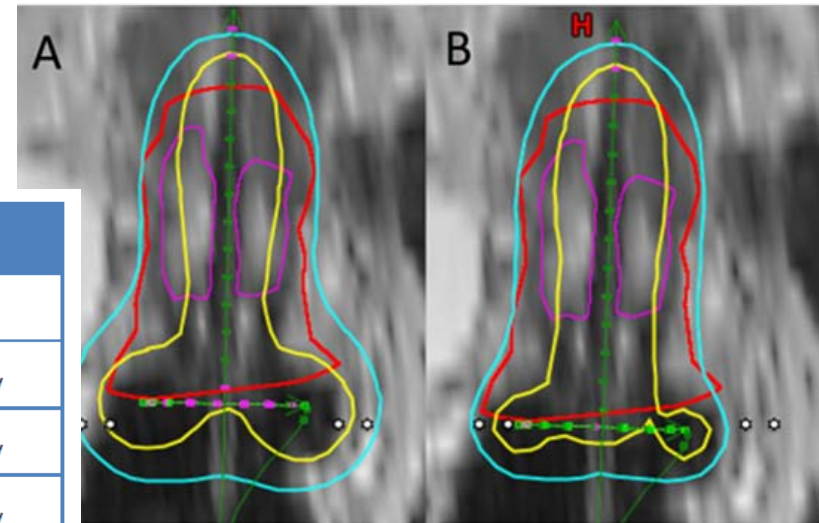
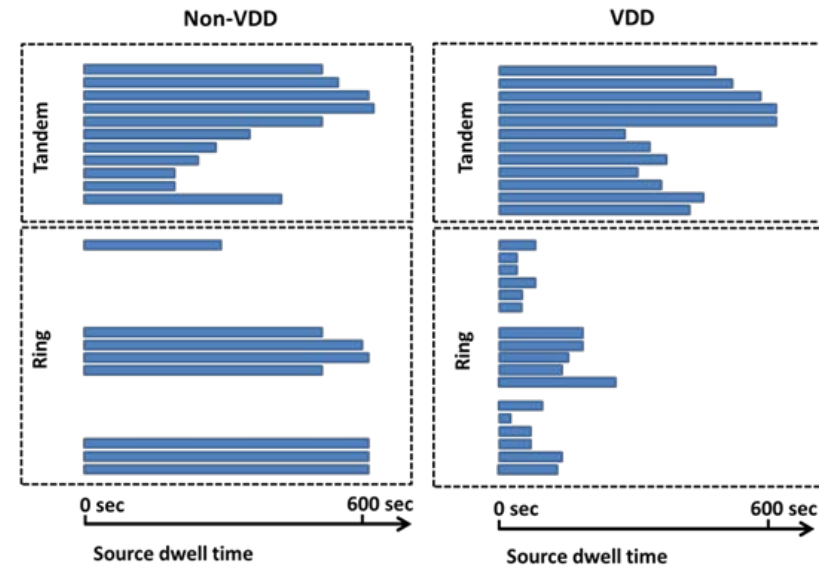
Example contouring uncertainty

- Variation in cranial border of HR-CTV
- Intra-observer variation!



Vaginal dose de-escalation

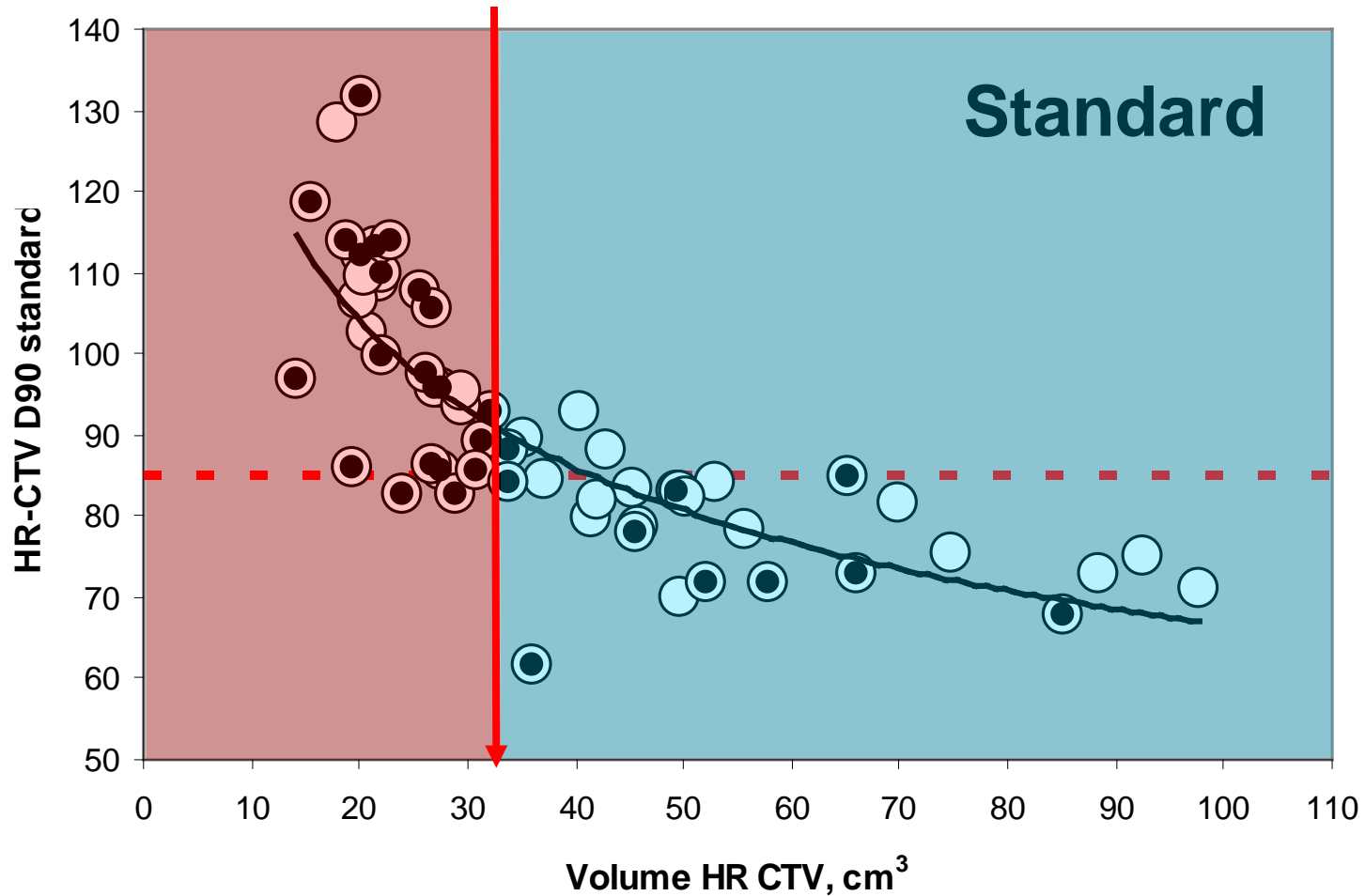
- **Change of loading pattern:**
 - **Shift of dwell time from vaginal sources to tandm/needles**
 - **E.g. 140% isodose out of vaginal mucosa**
 - **Aim for <30-40% loading in ring/ovoids**



	Aim	Priority
ICRU recto-vaginal point dose	<65Gy EQD2 (EBRT+BT)	Primary
The ratio of vaginal TRAK and total TRAK	<30-40%	Secondary
Vaginal lateral dose points at 5mm	<85Gy EQD2 (EBRT+BT)	Secondary
Visual inspection of the 140% isodose	Intruding as little as possible into vaginal tissue, and preferentially located within the applicator	Secondary

Volume is important!

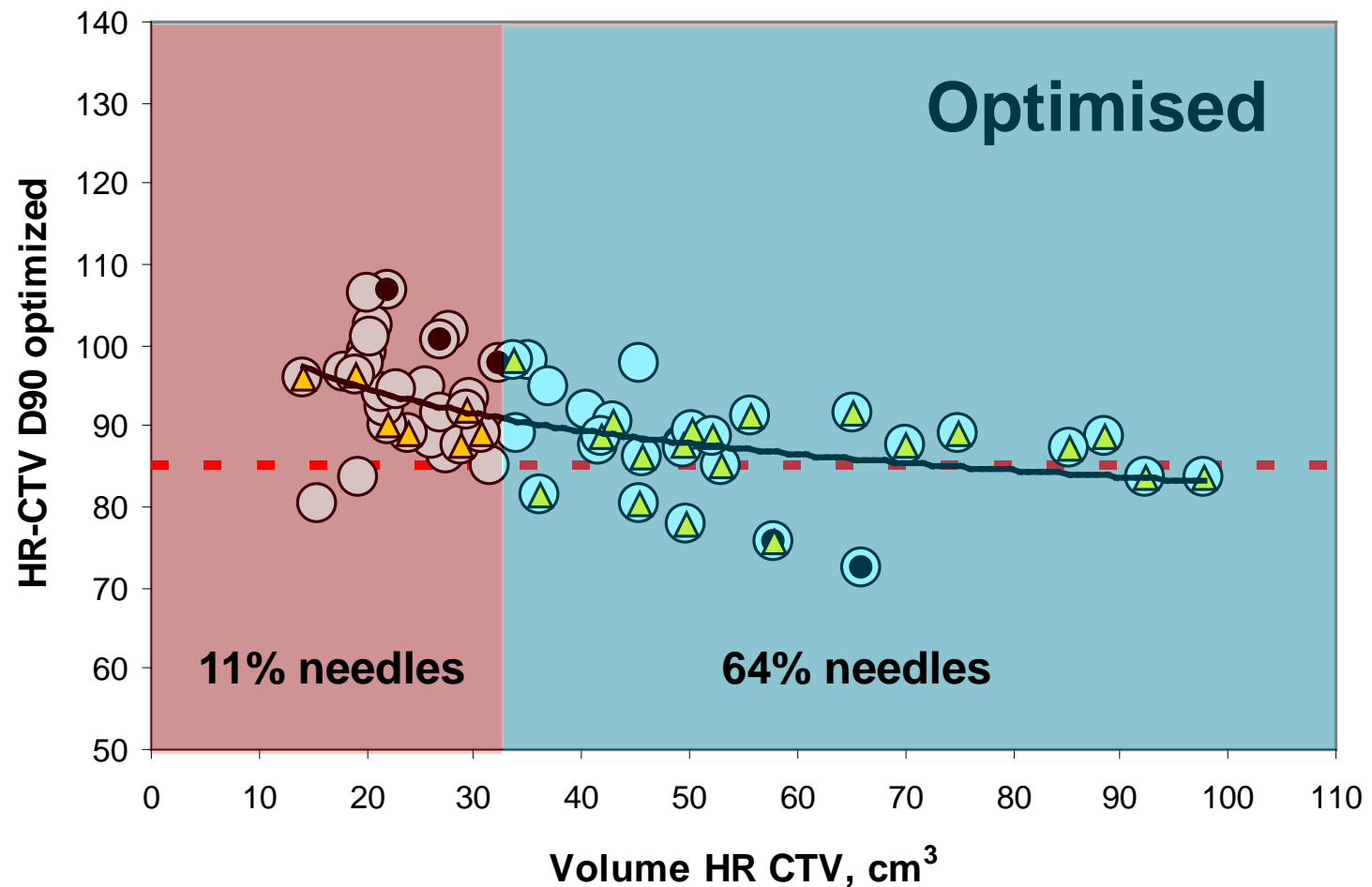
Median volume: 32cc



● Violation of OAR constraint

Volume is important!

K Tanderup et al, Radiother Oncol 2010



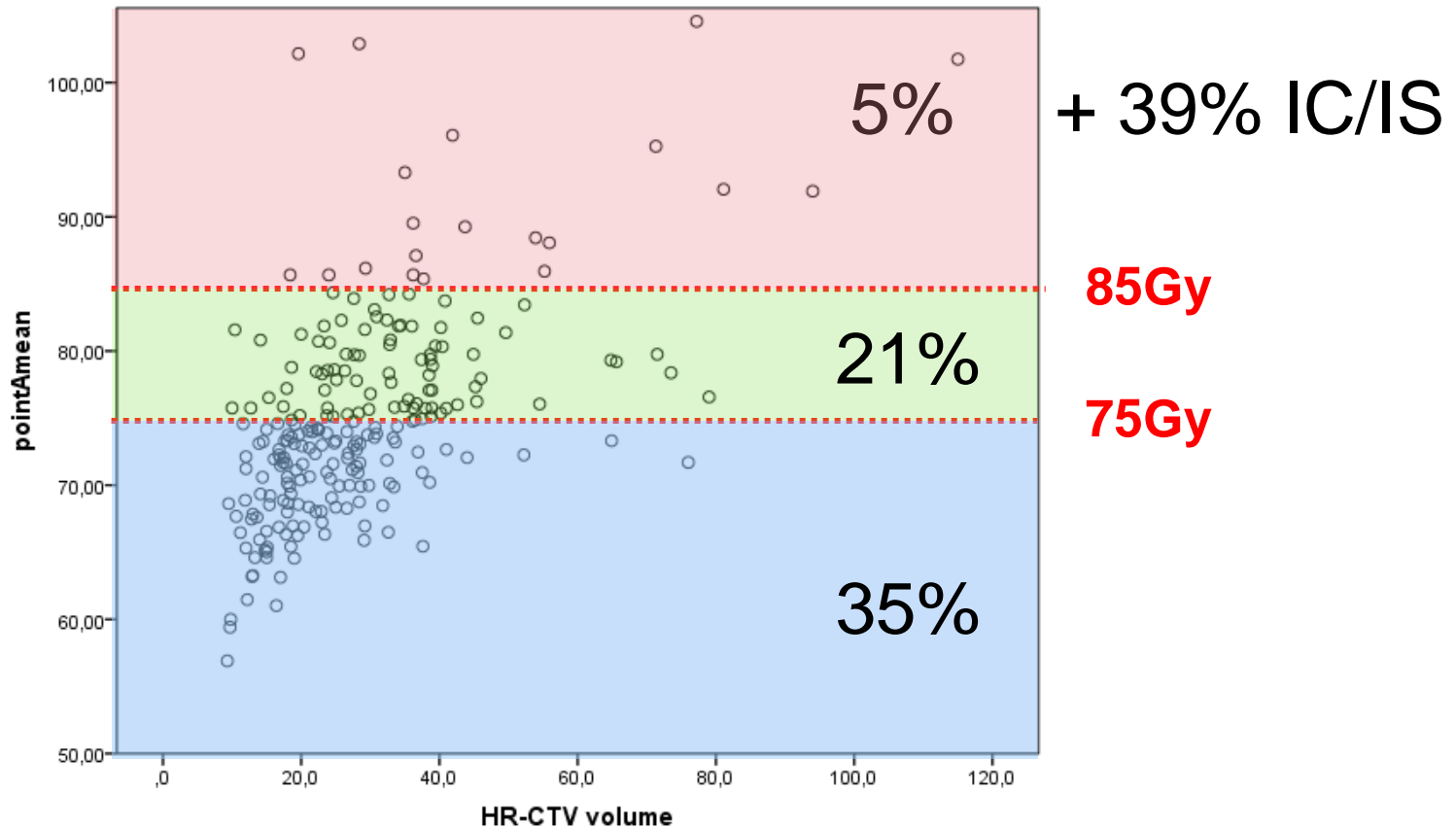
● Violation of OAR constraint

▲ Application of needles

Point A dose and HR CTV volume

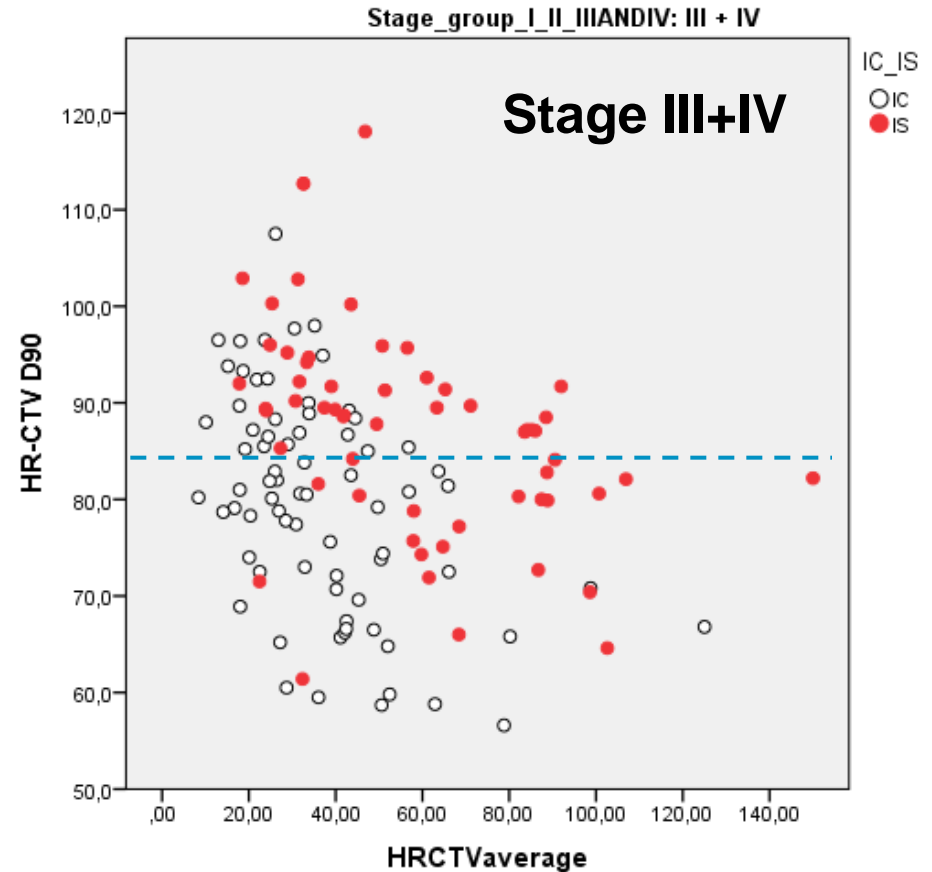
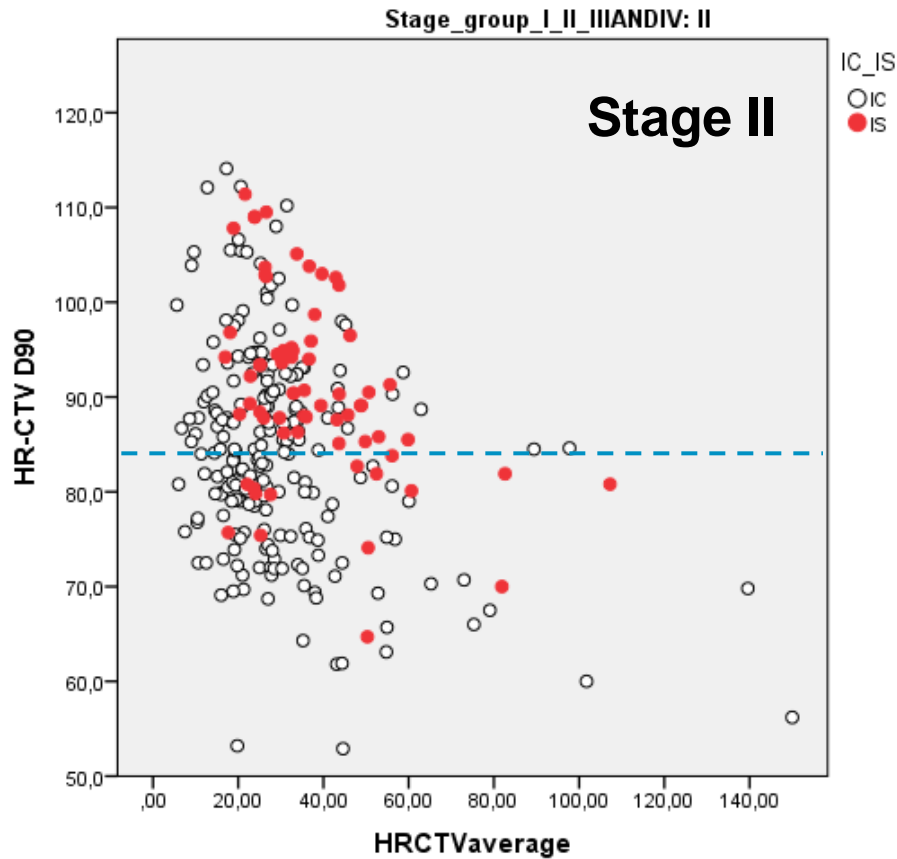
EMBRACE - Intracavitary applications

- There is a significant variation of point A dose as compared to traditional levels like 75Gy and 85Gy
 - 35% < 75Gy
 - 44% either >85Gy or IC/IS



Importance of needles

IC/IS increases therapeutic window by ~10Gy (Fokdal L et al. *Radiother Oncol* 2013 April;107(1):63-8)



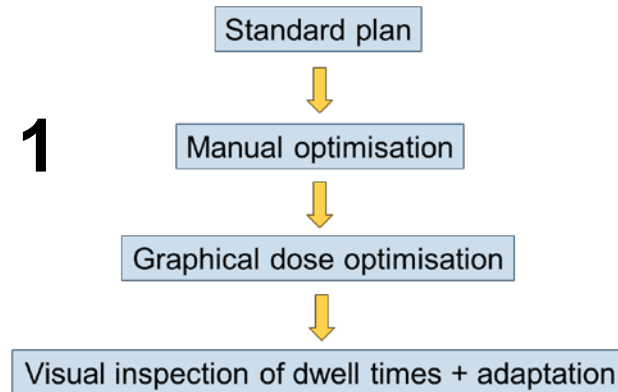
Take home message – dose optimisation

- **Always start dose optimisation with standard loading pattern**
- **Use manual dose optimisation for major changes**
- **Use graphical optimisation for minor adaptation**
- **Needle loading: start with 10-20%**

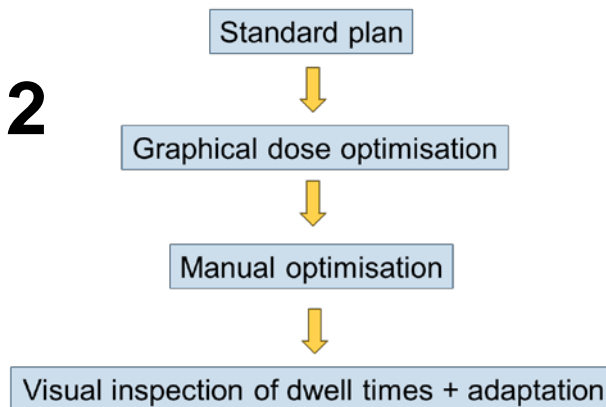
- **Application of combined intracavitary-interstitial applicator: increased therapeutic window by ~10Gy**

I prefer to do optimisation

1. Flow 1



2. Flow 2



With dose optimisation in a small tumour...

- 1. Point A dose becomes typically higher**
- 2. HR CTV D90 becomes typically higher**
- 3. OAR dose becomes typically lower**

***Radiobiological models to combine dose from
external beam radiotherapy
and
brachytherapy (HDR, MDR, LDR, PDR)***

Daniel Berger

**Teaching Course on
Image-guided cervix radiotherapy
- with a special focus on adaptive BRACHYTHERAPY**

Which dose rates are you mainly using at your department for GYN ?

1. HDR
2. MDR
3. LDR
4. PDR

Are you correcting for the radiobiological effect ?

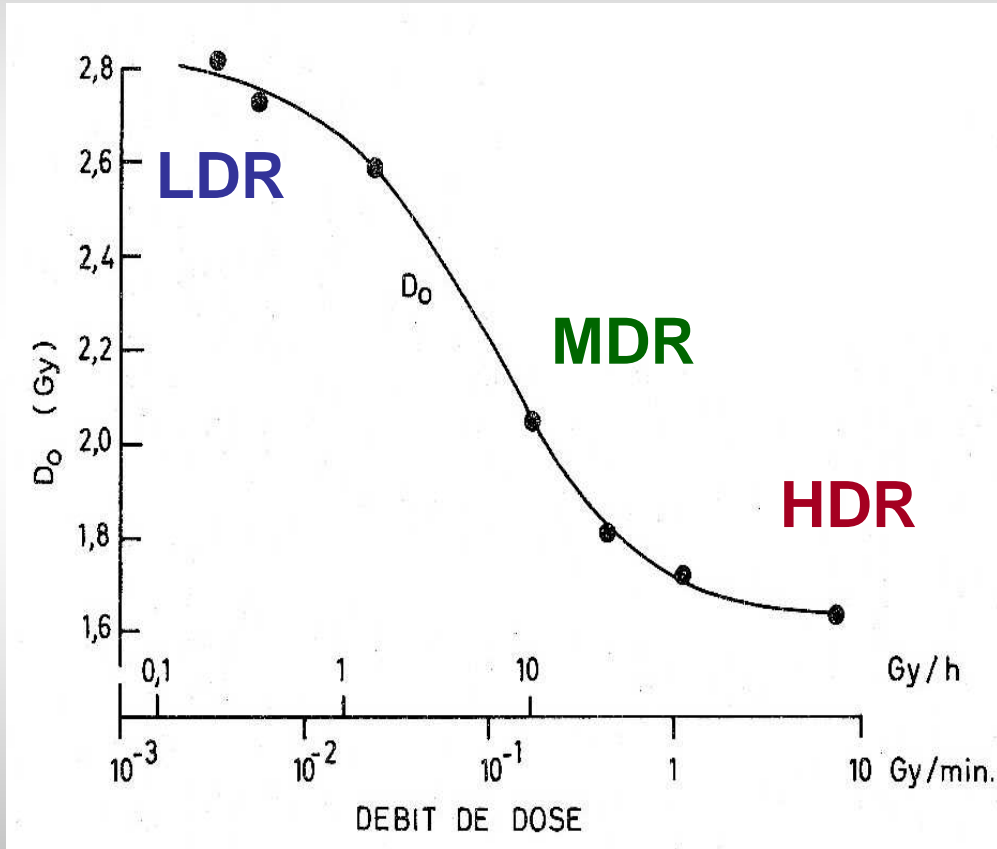
1. NO – the physical dose values will sum-up to a total dose
2. YES

Which of the following radiobiological effect(s) is(are) taken into account in the EQD2 calculation when using the LQ-model?

1. Recovery or Repair
2. Redistribution
3. Repopulation
4. Reoxygenation
5. all

Dose Rates in Brachytherapy

Doses are only comparable for a specified dose rate



ICRU Report 38 dose rate definitions

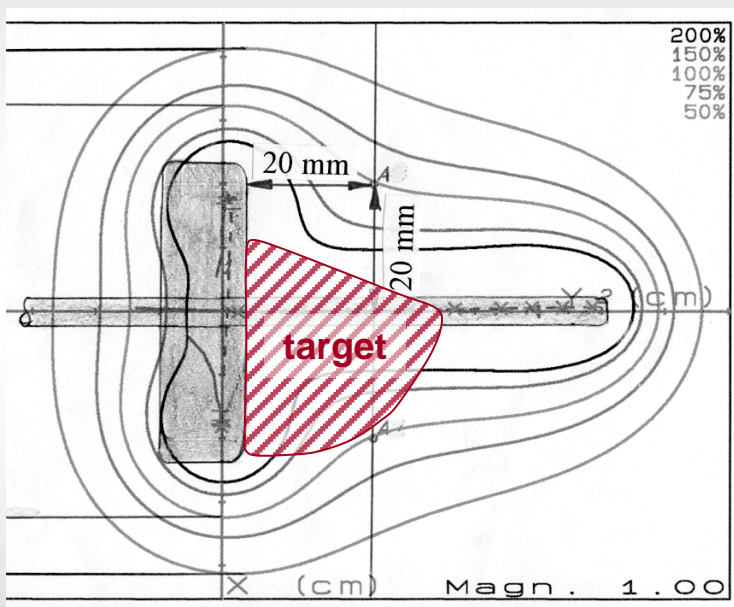
LDR 0.4 - 2 Gy/h

MDR 2 Gy - 12 Gy/h

HDR ≥ 12 Gy/h
 ≥ 0.2 Gy/min

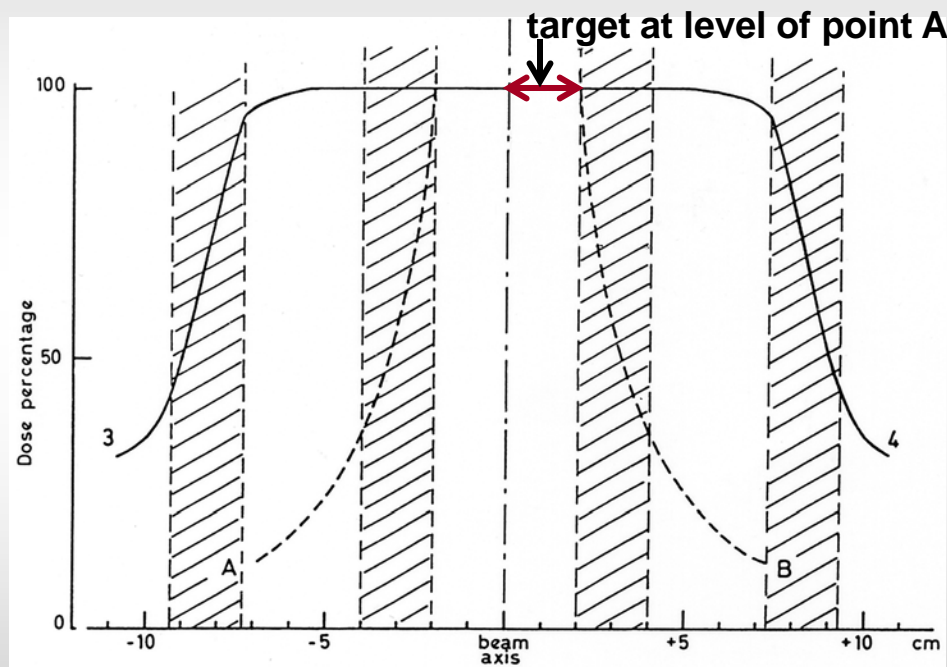
Volume Effect of Intracavitary Brachytherapy

- With intracavitary brachytherapy a very heterogenous dose is applied to target and organs at risk (steep dose gradient)
- significant change in dose within a few millimeters



taken from GEC ESTRO Handbook of Brachytherapy

Standard dose distribution with a tandem-ring applicator



taken from ICRU Report 38

Variation of dose along the lateral axis of EBRT (full line) vs. intracavitary BT (dotted line)

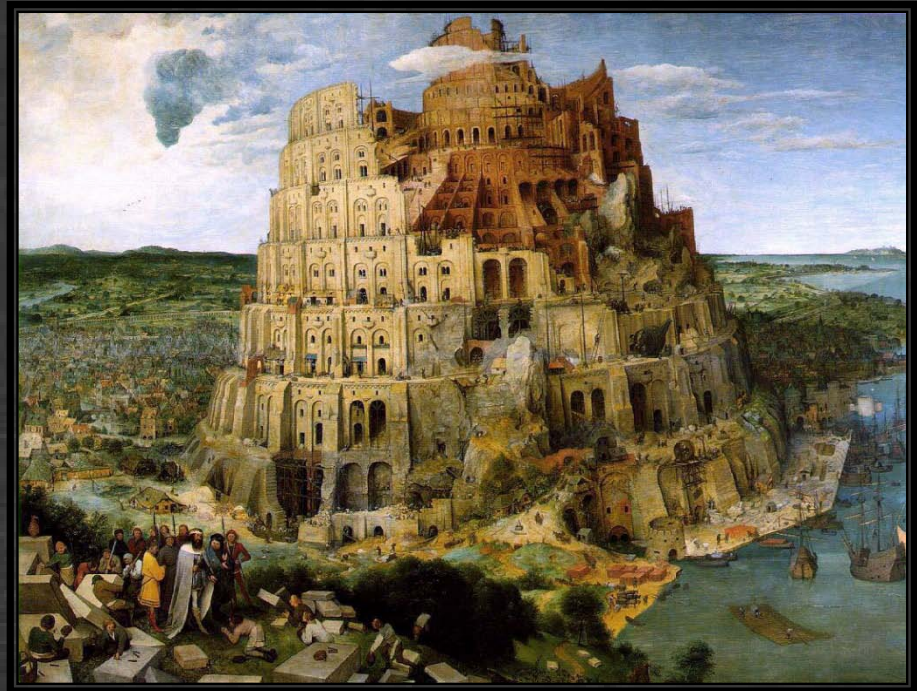
Different Fractionation Schedules (examples HDR)

Point A

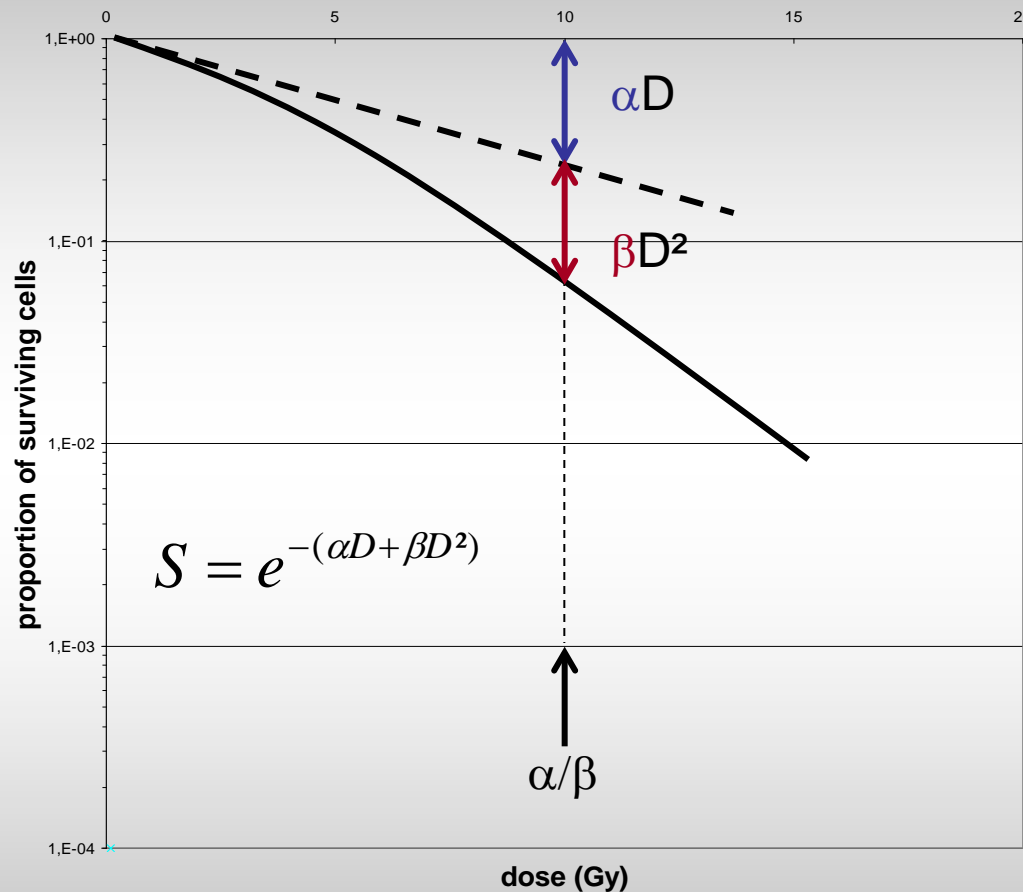
- 45 Gy EBT + 4x 7 Gy
- 45 Gy EBT + 4x 6 Gy
- 50 Gy EBT + 2x 8.5 Gy

Organs at Risk (ICRU point)

- 45 Gy EBT + 4x 5 Gy Rectum
6 Gy Bladder
- 45 Gy EBT + 4x 4.5 Gy Rectum
5 Gy Bladder
- 50 Gy EBT + 2x 6 Gy Rectum
7 Gy Bladder



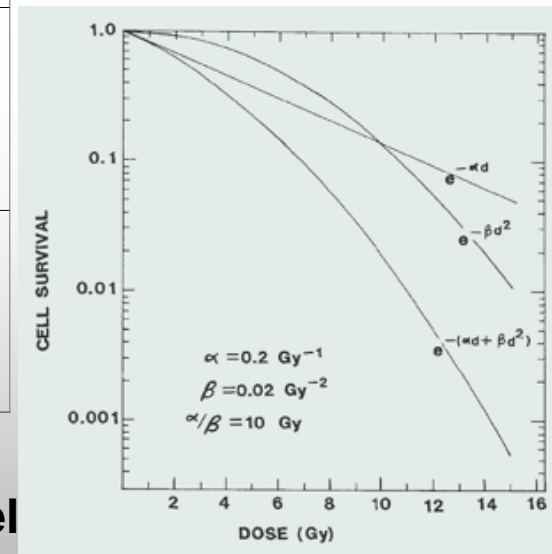
Linear-Quadratic Model



Survival curve according to the LQ-model

-> Lethal damage

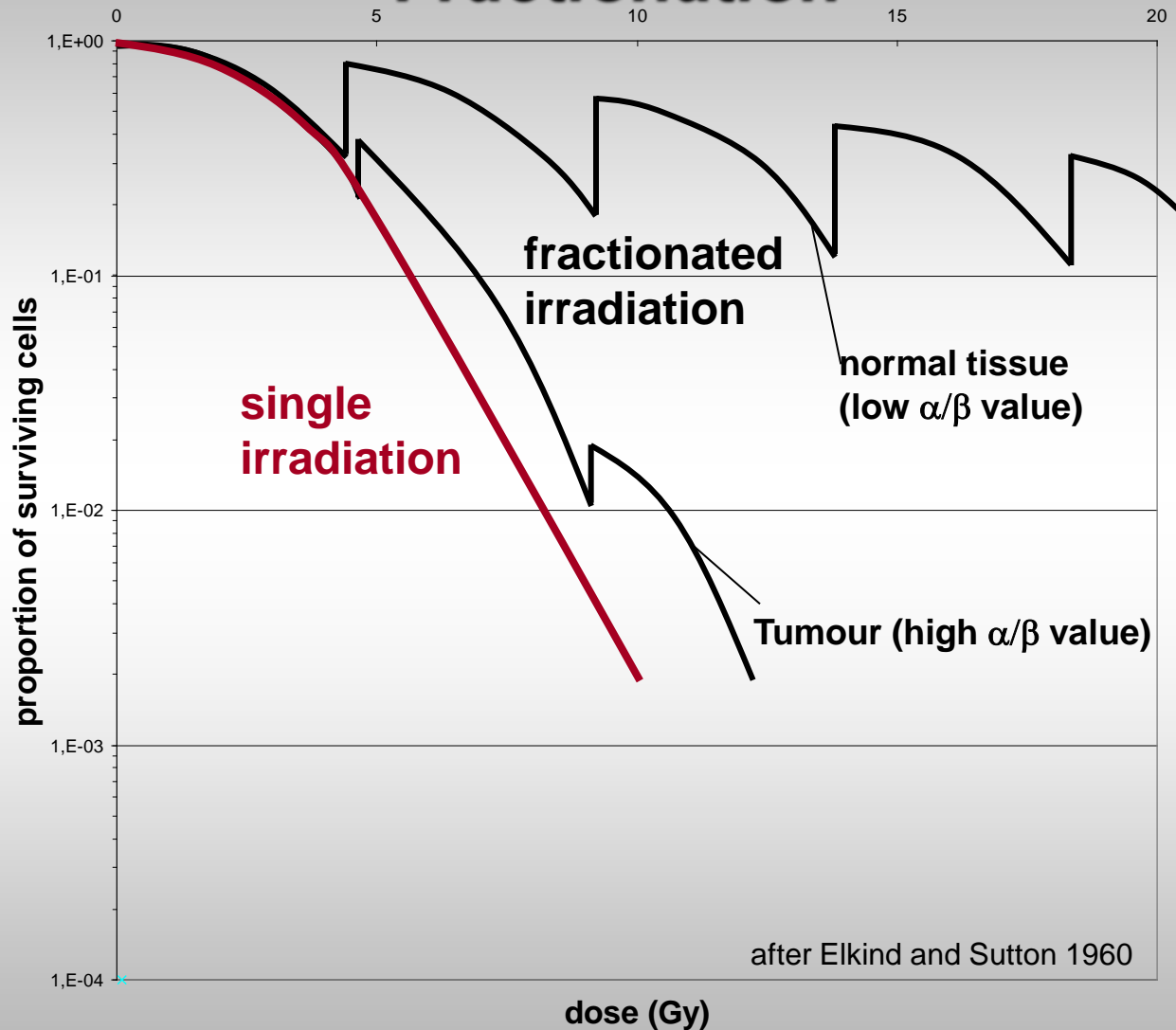
-> Sublethal damage



This can be used to fit a continuously bending curve to cell survival data

remember survival curve by Puck and Marcus

Fractionation



Limitation

4 Rs of Radiobiology

- Recovery or Repair (half-time ~1hour)

• ~~Redistribution~~

• ~~Repopulation (< 1 day)~~

• ~~Reoxygenation~~

Considered in the mathematical description (“equation”)

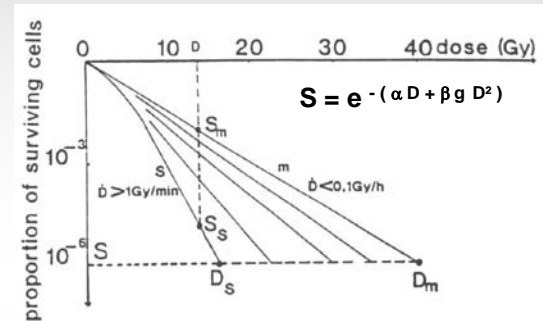
Radiobiological Considerations

Linear - Quadratic model for incomplete monoexponential sublethal (DNA) damage repair

- Biologically Effective Dose:

1

$$\text{BED} = nd \left[1 + g d / (\alpha/\beta) \right]$$



The Role of Dose Rate in Brachytherapy (J. Dutreix) In: A Practical Manual of Brachytherapy (Pierquin / Marinello, Medical Physics Publishing)

- BED ... virtual dose value that produces the same biological effect as the physical dose with an infinite low dose rate

n ... number of equal fractions

d ... dose per fraction

tissue dependent parameters :

α/β ... parameter describing lethal / sublethal lesions

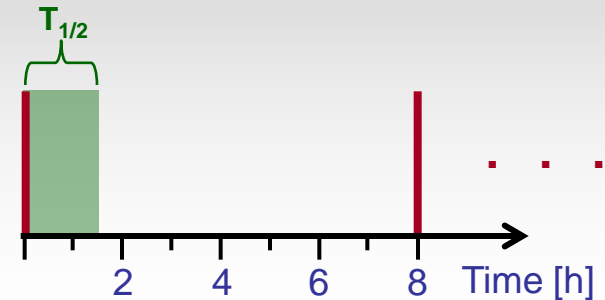
g ... repair function depending on

- half time for cell repair $T_{1/2}$
- fractionation

Mathematical Description / Repair Function

➤ External beam radiotherapy and HDR brachytherapy :

no repair during irradiation (min)
 repair function $g = 1$



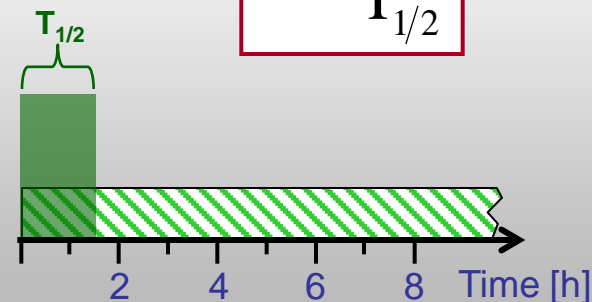
➤ LDR, MDR brachytherapy :

repair during irradiation (hours - days) is significant

$$g(LDR, MDR) = \frac{2}{\mu t} \left[1 - \frac{1 - e^{-\mu t}}{\mu t} \right]$$

$$\mu = \frac{\ln 2}{T_{1/2}}$$

μ ... repair rate
 $T_{1/2}$... half time for repair
 t ... irradiation time



Mathematical Description / Repair Function

- PDR brachytherapy :
- repair between successive pulses (hours) and during the whole fraction (hours - days) is significant

$$g(PDR) = \frac{2}{\mu t} \left[1 - \frac{ny - sy^2}{n\mu t} \right]$$

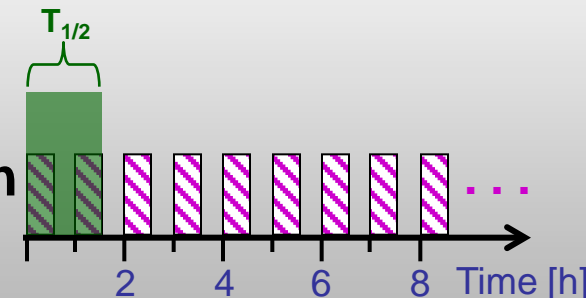
$$s = \frac{nk - k - nk^2 e^{-\mu t} + k^{n+1} e^{-\mu n t}}{(1 - ke^{-\mu t})^2}$$

$$y = 1 - e^{-\mu t}$$

$$\mu = \frac{\ln 2}{T_{1/2}}$$

$$k = e^{-\mu x}$$

- μ ... **repair rate**
- $T_{1/2}$... **half time for repair**
- t ... **irradiation time for each pulse**
- x ... **time between pulses without irradiation**
- n ... **number of equal pulses**

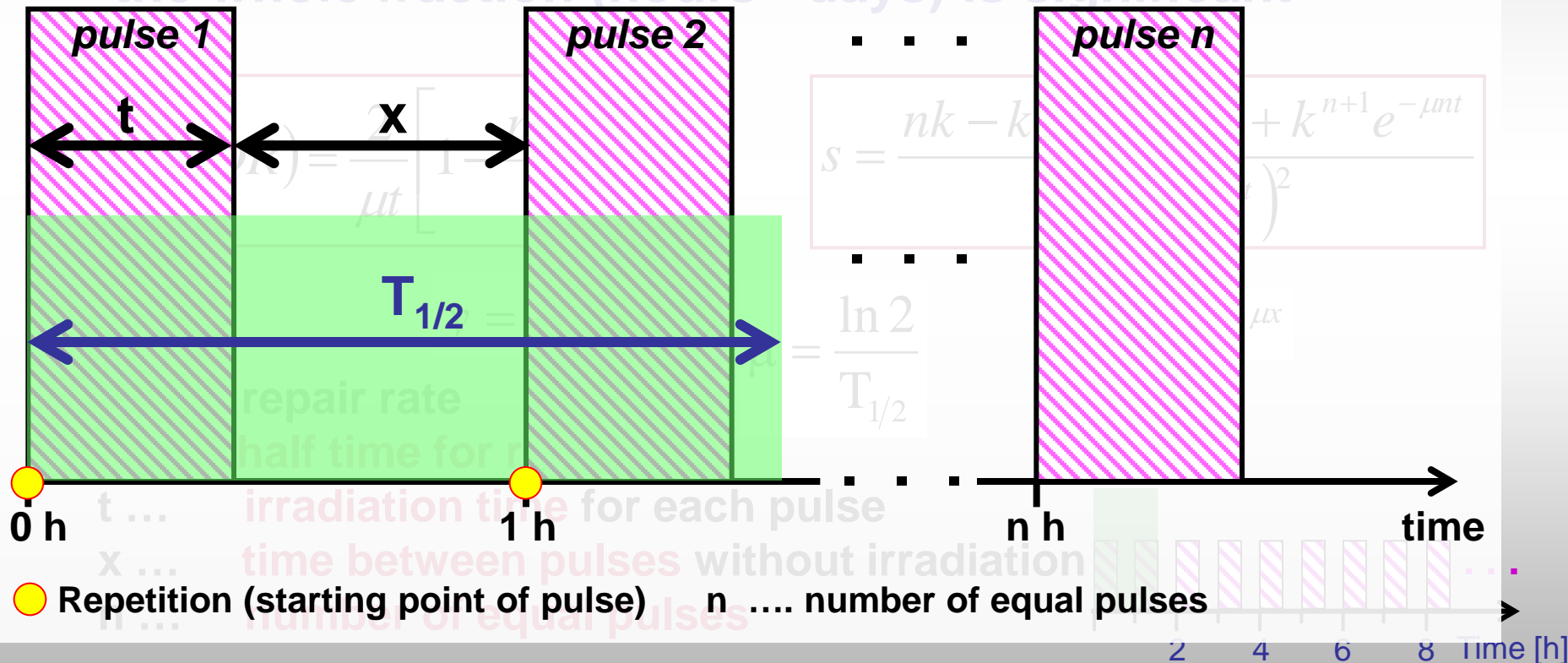


Mathematical Description / Repair Function

t Irradiation time of each pulse

x Time between pulses without irradiation

$T_{1/2}$ Half time for repair



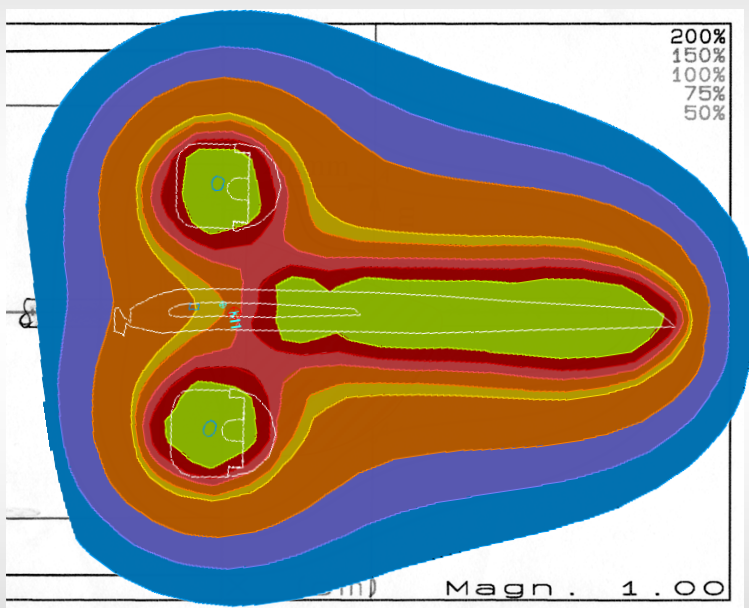
Application of this Biological Model to the Clinical Situation

➤ Assumptions:

- Time between fractions is long enough to enable full sublethal damage repair (min. ~ 8 - 12 hours)
- All investigated points and volumes from BT receive full EBRT dose
- In fractionated treatments the investigated points or volumes represent the same anatomical position throughout the whole treatment (worst case assumption)
- The same absorbed dose and time dose pattern of EBRT and BT produces the same biological effect
- **ATTENTION: dose and dose rate inhomogeneity within BT volume**

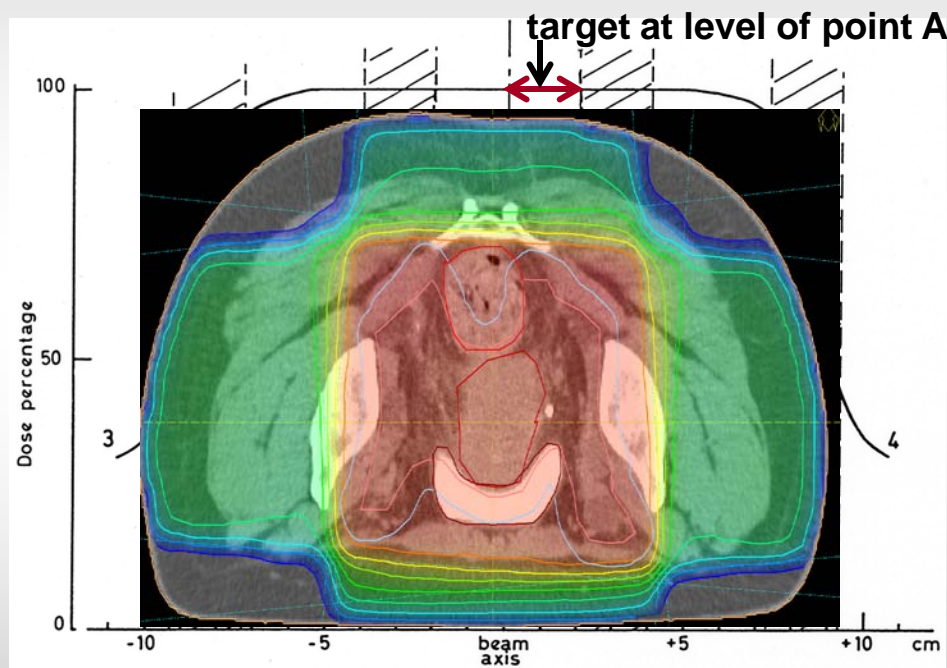
Volume Effect of Intracavitary Brachytherapy

- With intracavitary brachytherapy a very heterogenous dose is applied to target and organs at risk (steep dose gradient)
- significant change in dose within a few millimeters



taken from GEC ESTRO Handbook of Brachytherapy

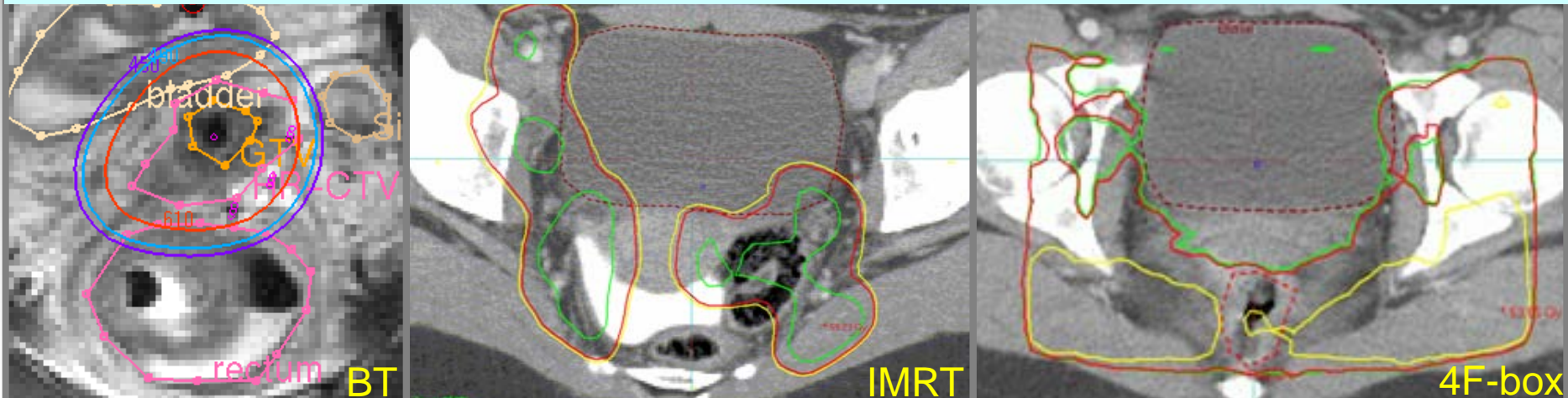
Standard dose distribution with a tandem-ring applicator



taken from ICRU Report 38

Variation of dose along the lateral axis of EBRT (full line) vs. intracavitary BT (dotted line)

Compare the **Position** of the Most Exposed $D_{x_{CC}}$ Areas in **EBRT** and **BT**



So it is deserving to compute for OARs in BT dose planning in this way: they had received approximately the PD of the external beam treatment.

- **bladder**: not the same volume receives the highest dose in IMRT than in 4F-box treatments
- **rectum**: sometimes the close same division
- **sigmoid**: always the close same

OAR	IMRT	4F	p
bladder	-1.6	1.4	0.03
rectum	2.9	2.6	>0.05
sigmoid	5.2	0.0	0.0001

The dose of **BT** in the most exposed 2 ccm in **IMRT** and **4F** plans
 $[D_{EBRT-BT} (\% - PD)]$

Provided by G. Fröhlich, Budapest, Hungary

Application of Biological Model to Clinical Situation

- **Assumptions:**
- Time between fractions is long enough to enable full sublethal damage repair (min. ~ 8 - 12 hours)
- All investigated points and volumes from BT receive full EBRT dose

➤ In fractionated treatments the investigated points or volumes represent the same anatomical position throughout the whole treatment (*worst case assumption*)

➤ The same absorbed dose and time dose pattern of EBRT and BT produces the same biological effect

➤ **ATTENTION: dose and dose rate inhomogeneity within BT volume**

Mathematical Description /Normalization - EQD2

➤ LQ model gives biological equivalence for

1. classical LDR brachytherapy (50 cGy/h) and
2. conventional external beam therapy (2 Gy / fraction) with $T_{1/2} = 1.5$ hours (clinical experience, ICRU 38)

1

➤ Calculated BED values are normalized to conventional EBRT with 2 Gy / fraction (reference schedule) :

$$BED = D_{\text{IsoE}} \left[1 + 2 / (\alpha/\beta) \right]$$

$$D_{\text{IsoE}} = BED / \left[1 + 2 / (\alpha/\beta) \right] = EQD_2$$

2

“isoeffective dose” = “equivalent dose in 2 Gy fractions”

➤ To calculate the total isoeffective dose D_{IsoE} of a combined treatment, all isoeffective doses D_{IsoE} are added up :

$$D_{\text{IsoE},\text{TOTAL}} = D_{\text{IsoE},\text{EXTERNAL}} + D_{\text{IsoE},\text{BRACHY}}$$

$$D_{\text{isoE}} = \frac{nd \cdot \left(1 + \frac{d}{(\alpha/\beta)}\right)}{1 + \frac{2}{(\alpha/\beta)}}$$

Values of biological parameters

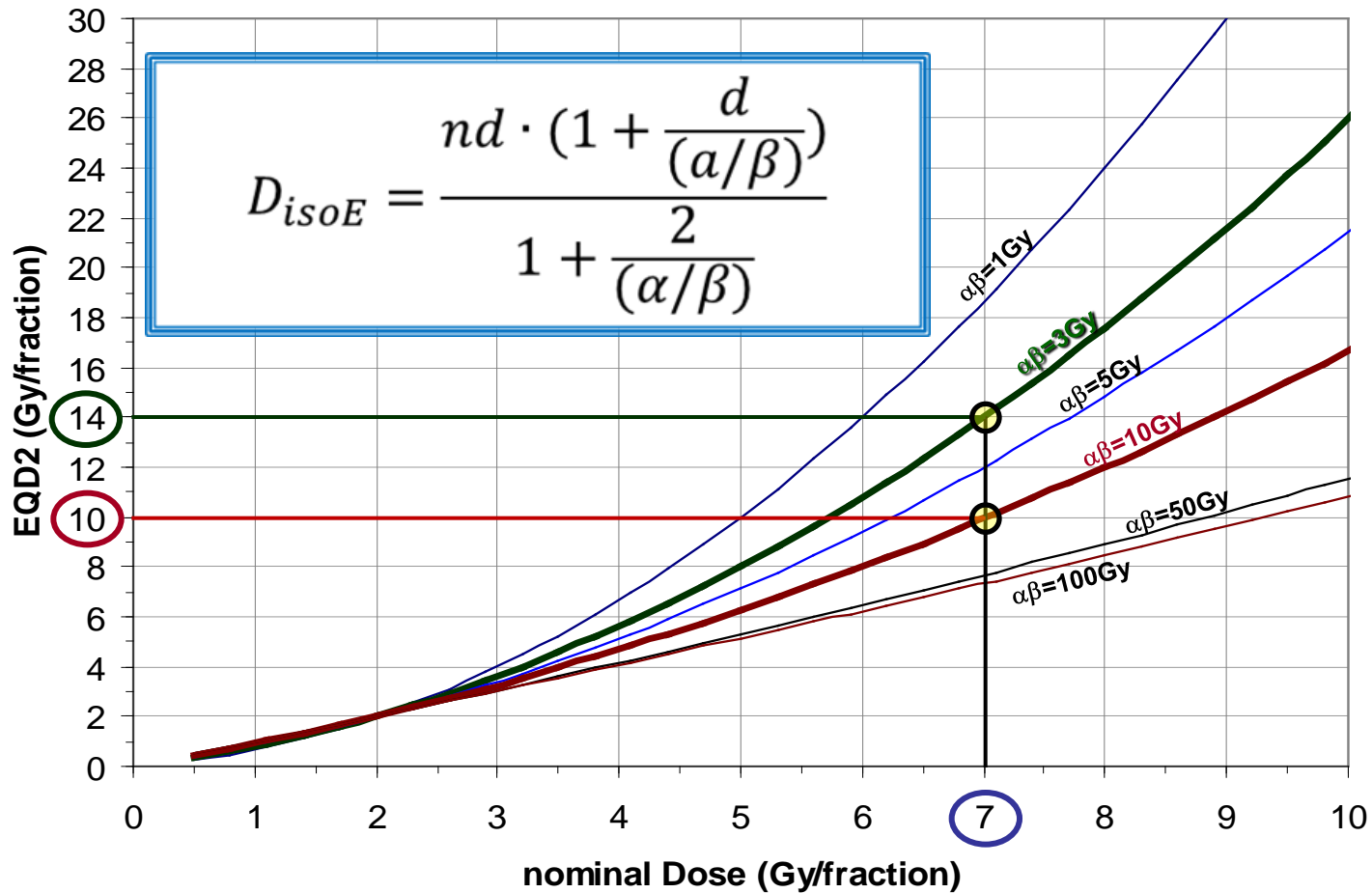
- Tumour and early reacting normal tissue:

$\alpha/\beta \sim 10 \text{ Gy}$	7 – 20 Gy for most tumours 9 – 10 Gy for cervix carcinoma
$T_{1/2} \sim 1.5 \text{ hours}$	0.5 – 1.5 hours

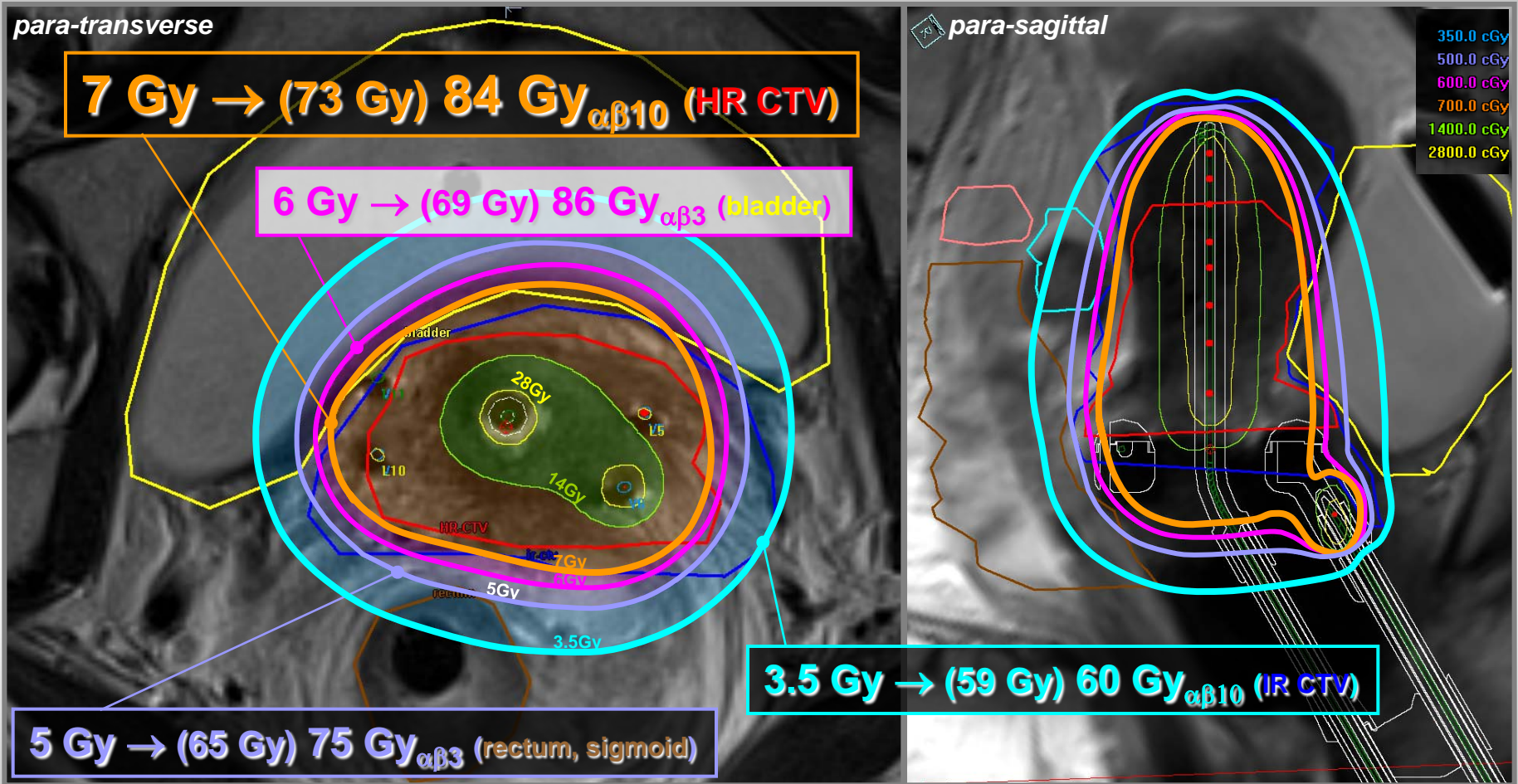
- Late reacting normal tissue:

$\alpha/\beta \sim 3 \text{ Gy}$	0.5 – 6 Gy 3 – 4 Gy for bladder, rectum, sigmoid
$T_{1/2} \sim 1.5 \text{ hours}$	1 – 2 hours

Clinical and experimental experience



Physical - biological treatment planning for HDR BT of cervical cancer



EBRT : 45 Gy (25 fractions with 1.8 Gy) to ICRU point (whole BT volume) +

BT : 4 fractions x 7 Gy (HDR) to HR CTV → Planning Aim

A single fraction HDR dose of 7Gy
to the tumour corresponds to a
EQD2 of

1. 5Gy
2. 7Gy
3. 10Gy

Limitation

4 Rs of Radiobiology

- Recovery or Repair (half-time ~1hour)

- ~~• Redistribution~~

- Repopulation (< 1 day)

- ~~• Reoxygenation~~



Repopulation

– changing the overall treatment time -
Influencing the local control rate

$$EQD_{2,T} = EQD_{2,t} - (T - t)D_{prolif}$$

- Increasing OTT by one week is equivalent to a loss of 5 Gy in CTV_{HR} D90

Table 13.3

Tanderup, retroEMBRACE, 2016, submitted

Early reactions

Skin (erythema)

Mucosa (mucositis)

Lung (pneumonitis)

Tumours

Head and neck

Larynx

Tonsils

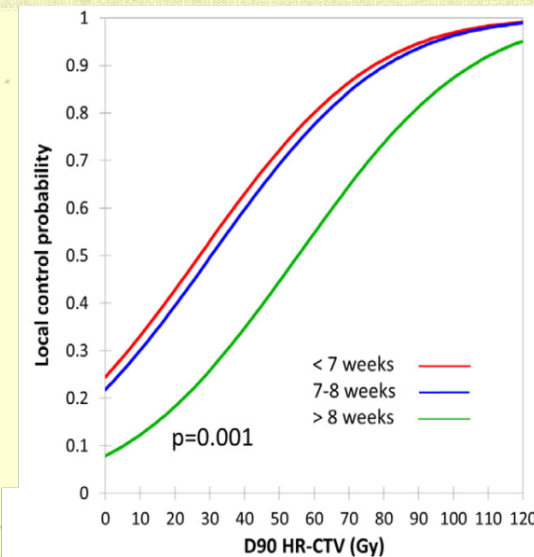
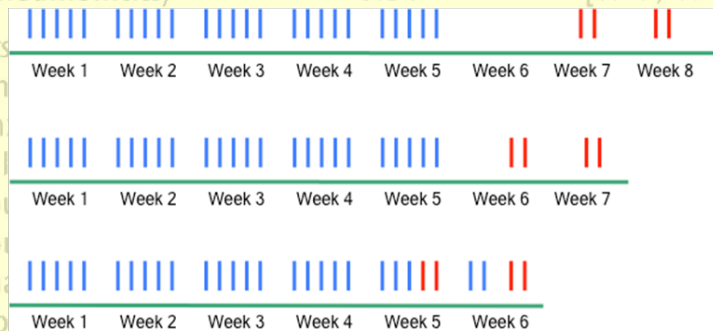
Variety

Variety

Non-small cell lung cancer

Medullary thyroid cancer

- Timing of the BT boost?



* Pooled estimate from EBRT studies in the literature ** T_k is the asynchrony parameter
Reference details are in Michael Baumann.



Mazon et al, Radiother Oncol 2015

„Per day delay in overall treatment time results in loss of ~ 0.3 – 0.8 Gy/day“

Which of the following radiobiological effect(s) is(are) taken into account in the EQD2 calculation when using the LQ-model?

1. Recovery or Repair
2. Redistribution
3. Repopulation
4. Reoxygenation
5. all

Limitations of the EQD2 model for BT

- **Chemotherapy is not taken into account**
- **Uncertainty increases for single fraction dose values >10Gy**
- **Only cell repair is considered**
- **α/β values and $T_{1/2}$ are under discussion (E.g. tumour type prostate, OAR etc.)**
- **dose and dose rate inhomogeneity within BT volume is not considered**
- **Overall uncertainty of the biological dose calculation (values) in the range of ~10% -> Reasonable rounding of values**

Clinical radiobiology

All models are wrong, but some are useful
(David R. Wigg)

LQ-model has proven to be a useful tool for radiobiological calculations in brachytherapy:

- Fowler JF. Dose response for carcinoma of the cervix. Radiother Oncol 1983;1:1-6
- Dale RG et al. Carcinoma of the cervix. Int J Radiat Oncol Biol Phys 1997;38:633-642
- Nag S, et al. A simplified LQ model for brachytherapy. Int J Radiat Oncol Biol Phys 2000;48:1-6
- Lang S, et al. Treatment of carcinoma of the cervix with brachytherapy: dose constraints and the effect of alternative values in the treatment planning system. Int J Radiat Oncol Biol Phys 2001;50:1-6
- Determining DVH parameters for adding for patients with carcinoma of the cervix. Int J Radiat Oncol Biol Phys 2001;50:1-6

3. Find x .

Here it is

SIMPLICITY

of carcinoma of the
cervix. Radiother Oncol
1983;1:1-6
Int J Radiat Oncol
Biol Phys
1997;38:633-642
Int J Radiat Oncol
Biol Phys
2000;48:1-6
Int J Radiat Oncol
Biol Phys
2001;50:1-6
Int J Radiat Oncol
Biol Phys
2001;50:1-6
Int J Radiat Oncol
Biol Phys
2001;50:1-6

Despite all limitations
for treatment planning

can be used

Thank You

Merci

Danke

Gracias



Dept. of Radiotherapy
Medical University of Vienna



Inter- and intra-fraction uncertainties and imaging strategies (MRI/CT) in brachytherapy

ESTRO Teaching Course
Image-Guided Cervix Radiotherapy – with a special focus on adaptive brachytherapy

Toronto 2016

Kari Tanderup



Largest dose uncertainty for target?

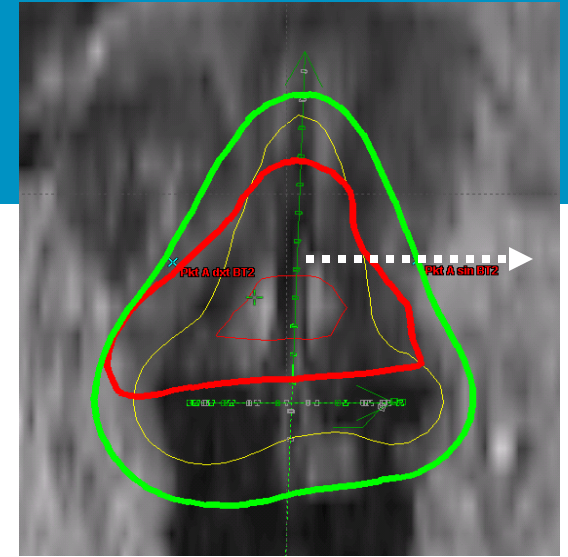
- 1. Dose calculation**
- 2. Applicator reconstruction**
- 3. Target contouring**
- 4. Target motion**

Largest dose uncertainty OARs?

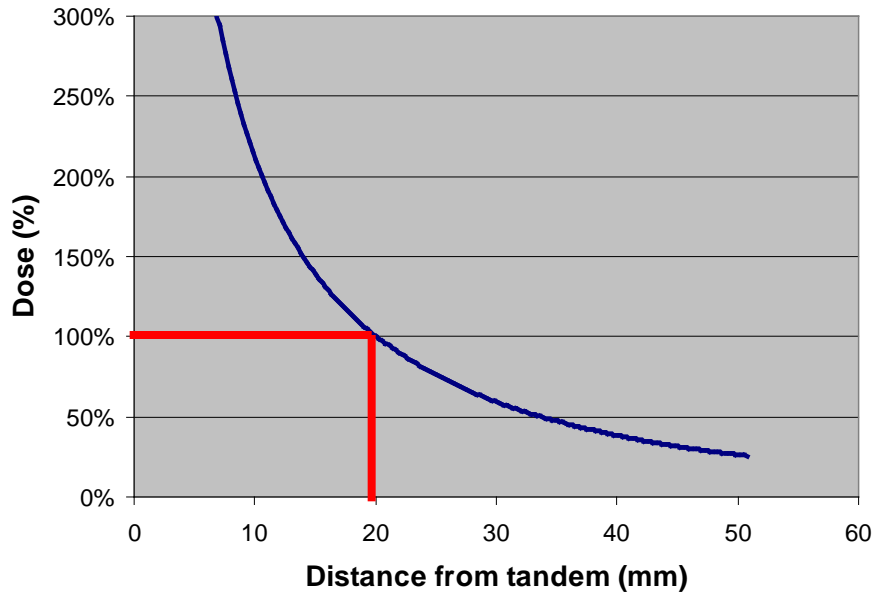
- 1. Dose calculation**
- 2. Applicator reconstruction**
- 3. OAR contouring**
- 4. OAR motion**

Uncertainties in the high gradient BT dose distribution

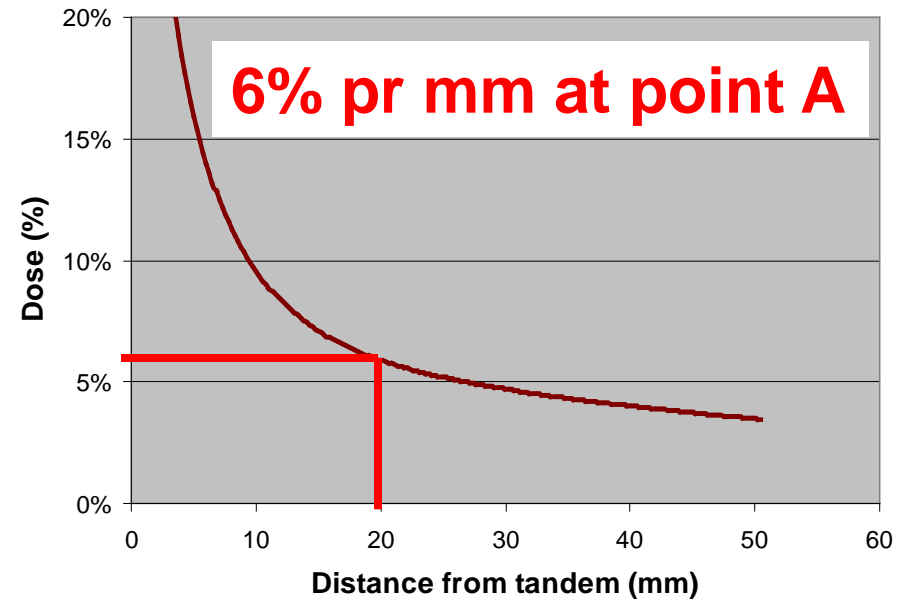
Radial dose profile



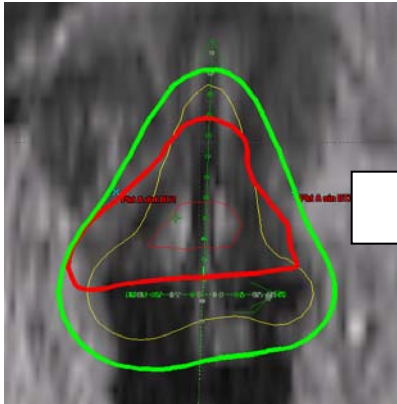
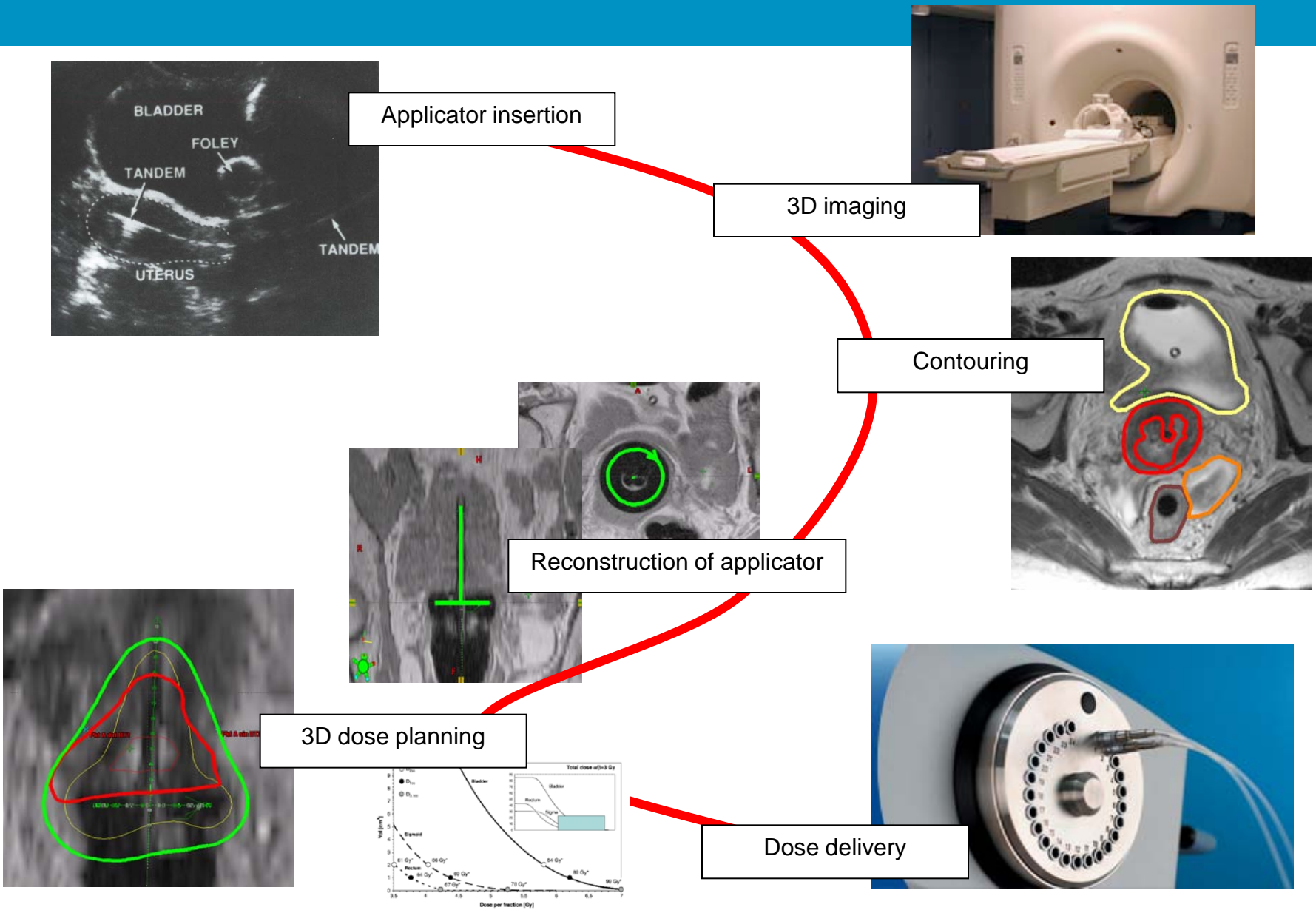
Dose profile at level of point A



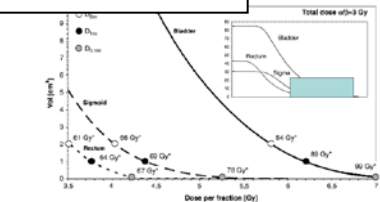
Dose gradient per mm



The 6 steps of IGABT



3D dose planning

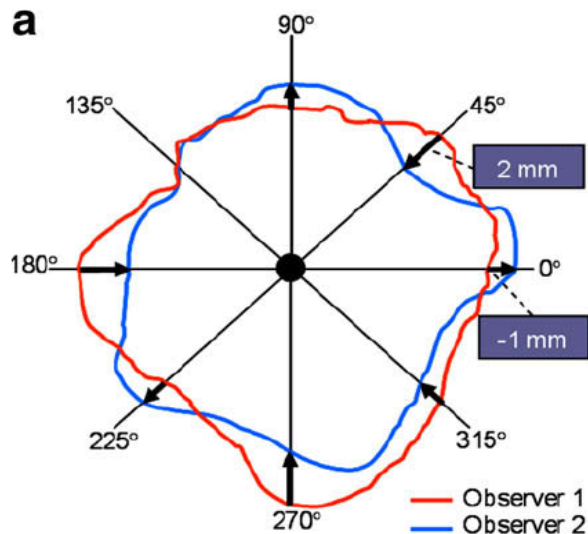


Dose delivery

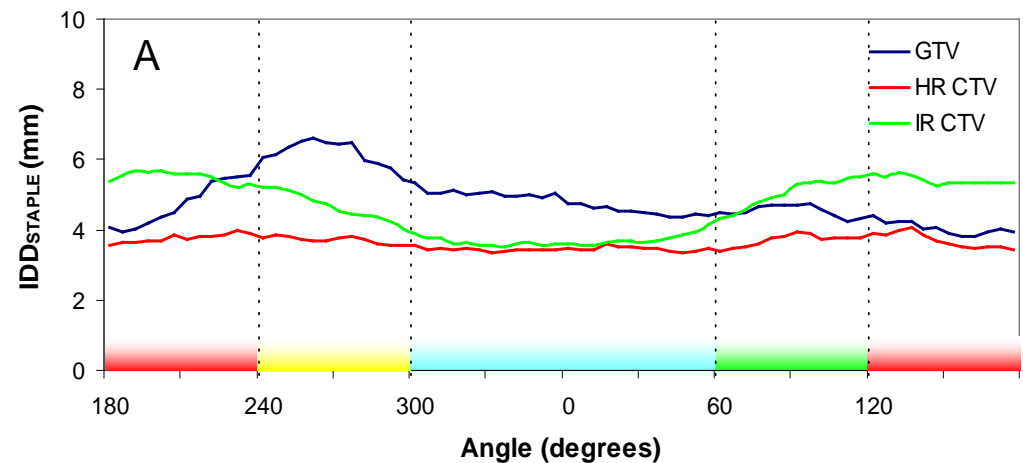
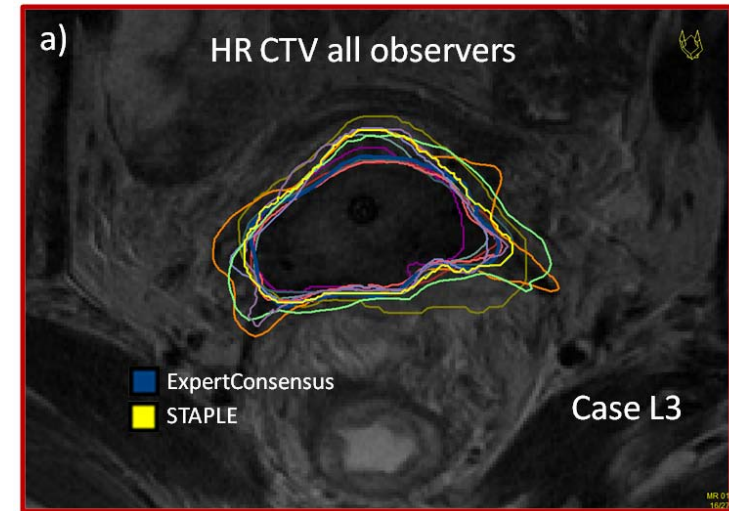


Contouring uncertainties HR-CTV on MRI

- **HR CTV:**
 - Mean deviation <4mm
- **GTV, IR CTV:**
 - Mean deviation <6-7mm

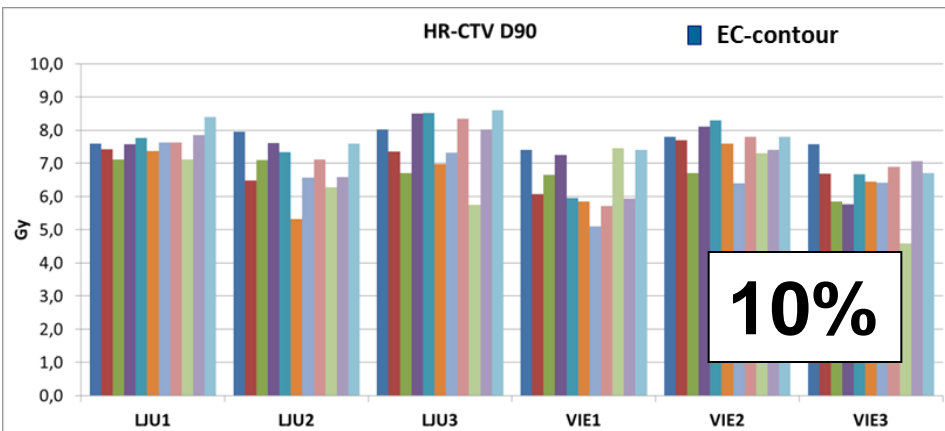


Petric et al, R&O 2008

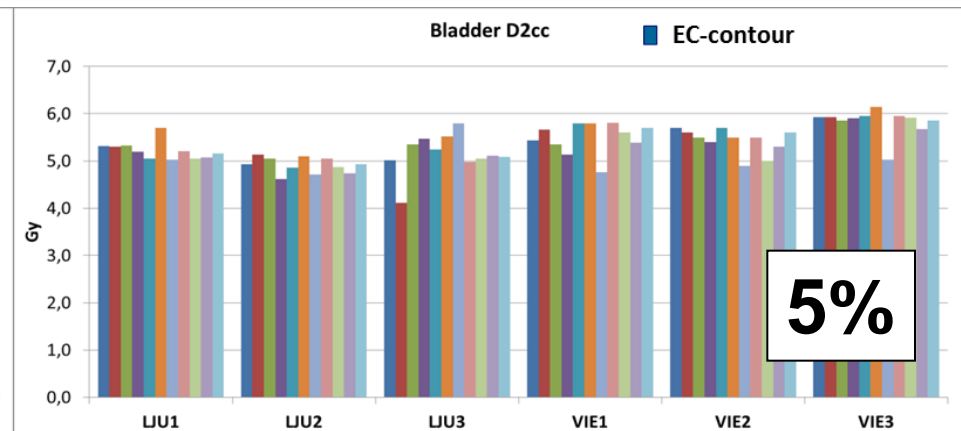


Petric et al, RO 2013

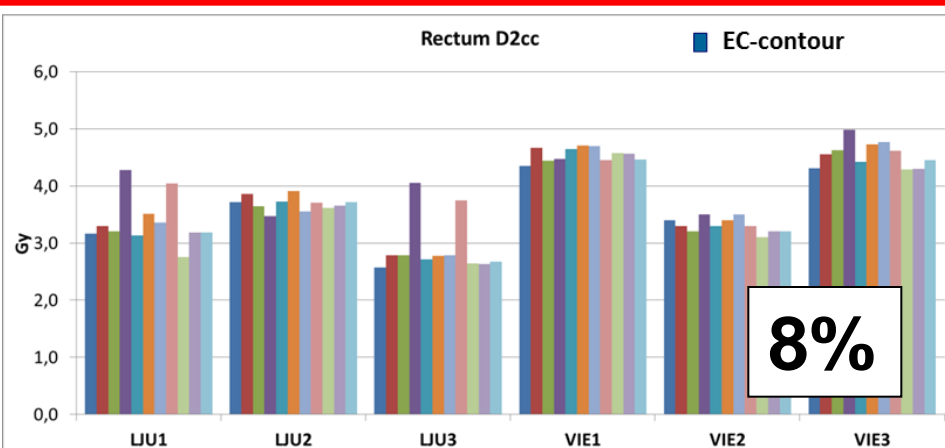
Impact of contouring uncertainties on dose



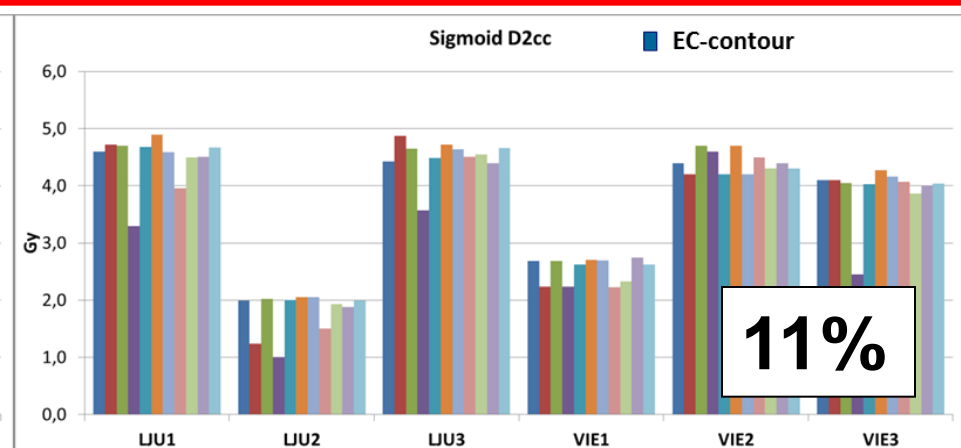
	LUJ1	LUJ2	LUJ3	VIE1	VIE2	VIE3
Mean (Gy)	7,59	6,80	7,61	6,34	7,51	6,31
SD (Gy)	0,38	0,70	0,95	0,81	0,59	0,74
Rel.SD (%)	5,0	10,3	12,5	12,7	7,9	11,7



	LUJ1	LUJ2	LUJ3	VIE1	VIE2	VIE3
Mean (Gy)	5,21	4,91	5,17	5,5	5,4	5,82
SD (Gy)	0,20	0,18	0,45	0,34	0,26	0,30
Rel.SD (%)	3,9	3,6	8,7	6,2	4,9	5,2



	LUJ1	LUJ2	LUJ3	VIE1	VIE2	VIE3
Mean (Gy)	3,39	3,68	2,96	4,57	3,30	4,57
SD (Gy)	0,45	0,13	0,51	0,11	0,13	0,22
Rel.SD (%)	13,3	3,6	17,1	2,4	4,0	4,8



	LUJ1	LUJ2	LUJ3	VIE1	VIE2	VIE3
Mean (Gy)	4,45	1,77	4,51	2,51	4,41	3,91
SD (Gy)	0,47	0,38	0,35	0,22	0,20	0,52
Rel.SD (%)	10,6	21,6	7,9	8,9	4,6	13,4

Applicator reconstruction uncertainties

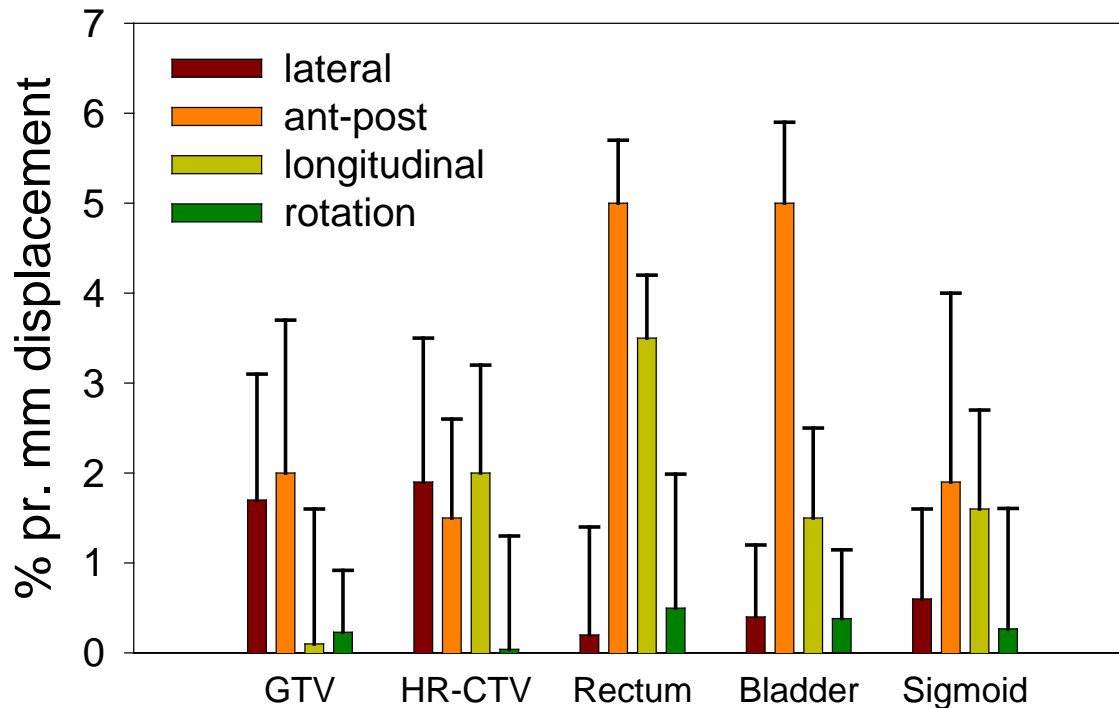
MRI based intracavitary/interstitial brachytherapy

Reconstruction uncertainties in mm (SD):
~ 0.5mm in lateral and ant-post directions
~ 1-2mm in longitudinal directions

	Longitudinal SD (mm)	Lateral SD (mm)	Ant-posterior SD (mm)	Rotation SD (mm)
Ring	1.4	0.6	0.4	1.2
Tandem	1.7	0.6	0.5	-
Titanium Needle	2.2	0.4	0.3	-
EBRT comparison	4-5	4-5	4-5	

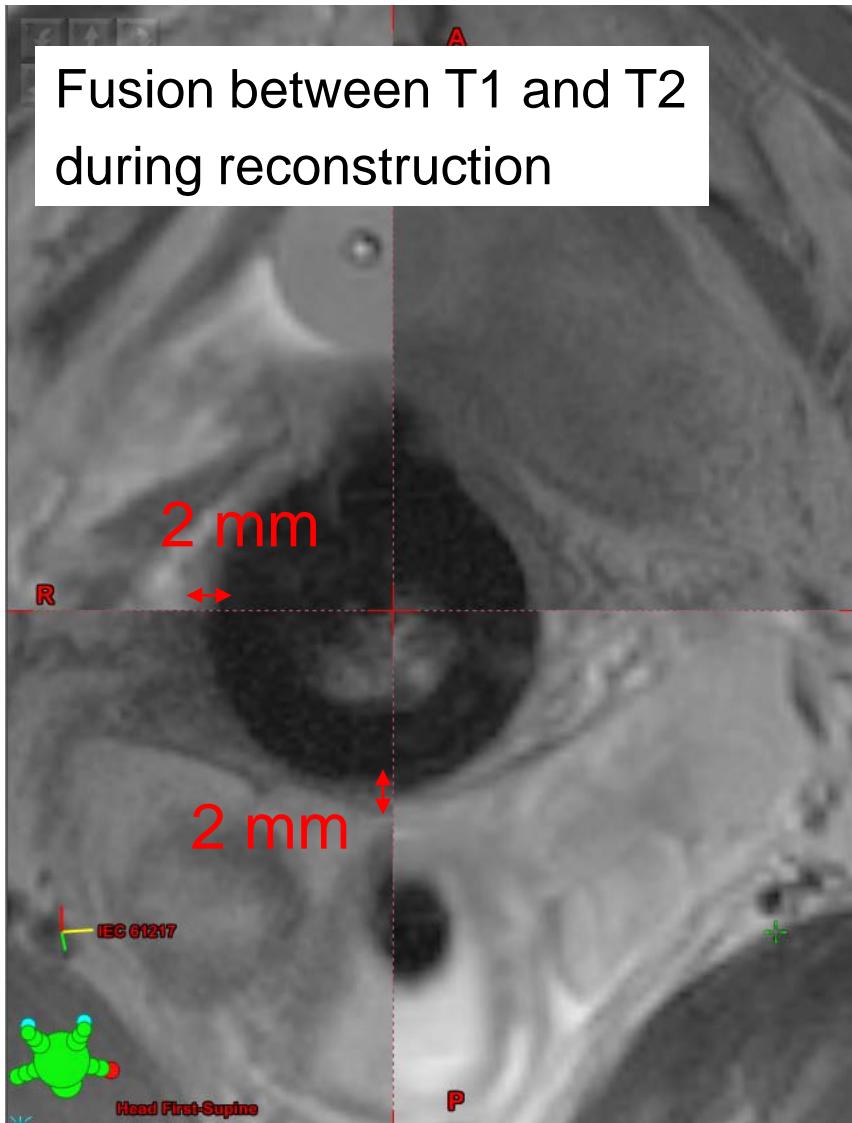
Reconstruction uncertainties

- Evaluation of the impact of reconstruction uncertainties on DVH parameters (mean and standard deviation)



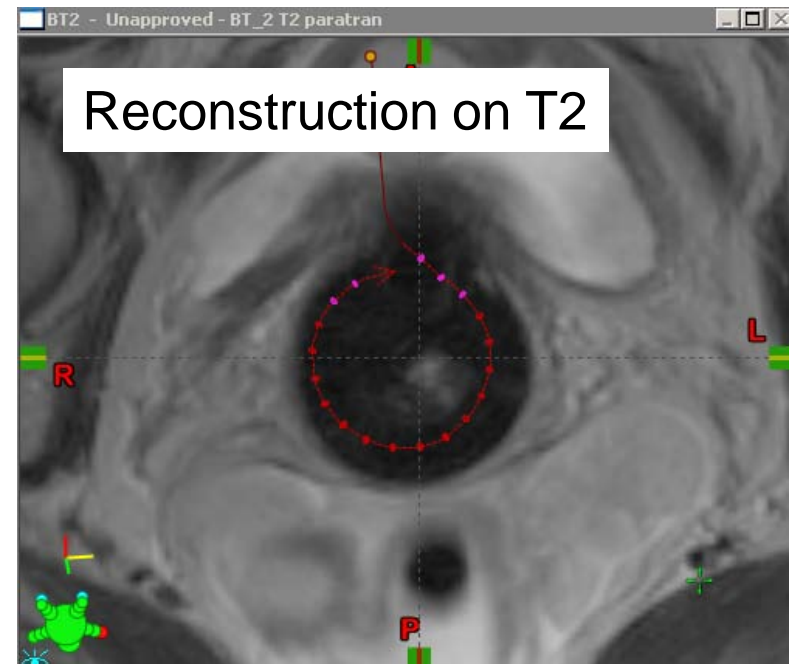
Fusion uncertainties

Fusion between T1 and T2 during reconstruction

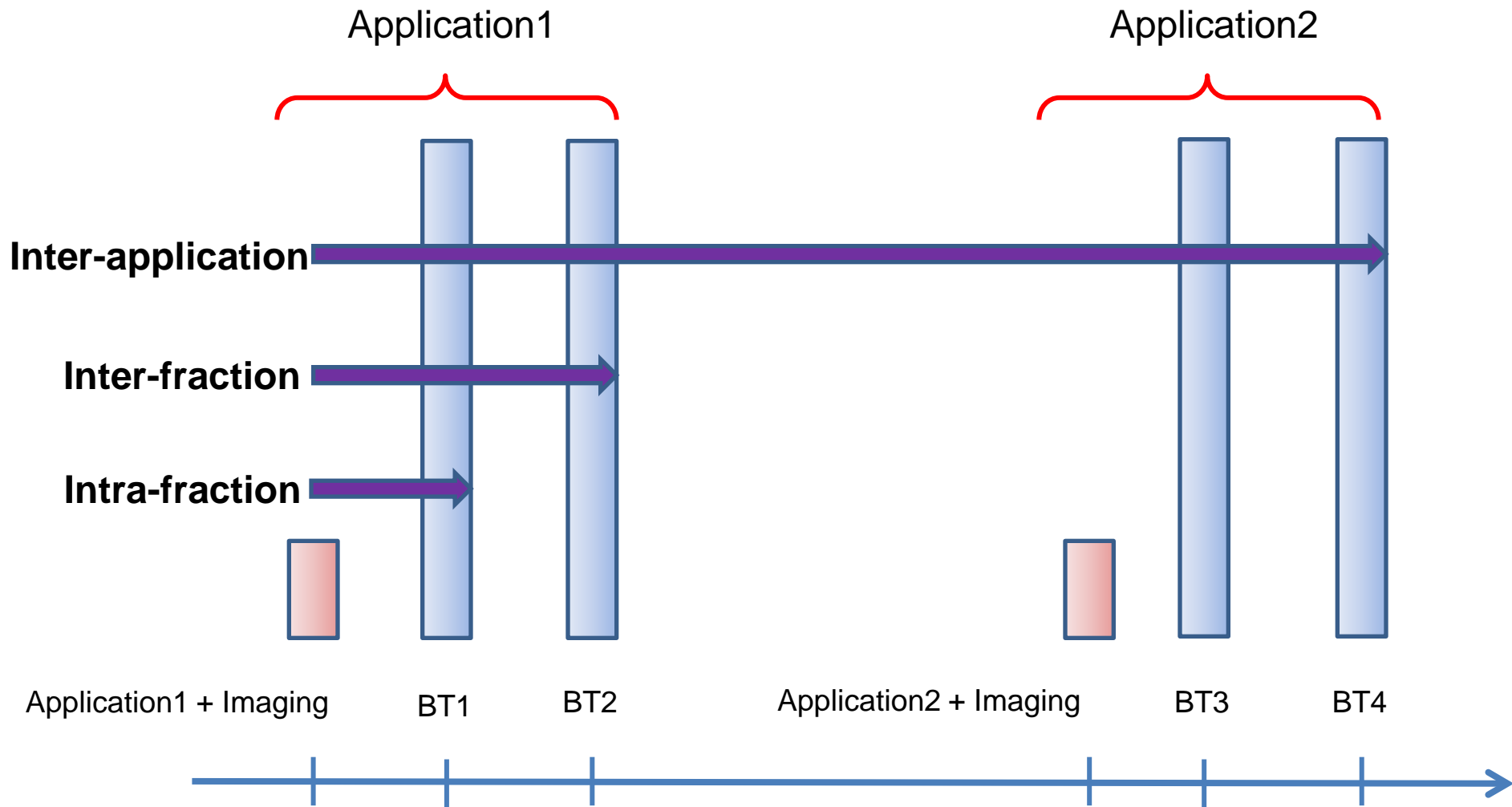


Impact on DVH parameters:
HR CTV: 7% (underestimation)
Bladder: 10% (overestimation)
Rectum: 13% (underestimation)

Reconstruction on T2



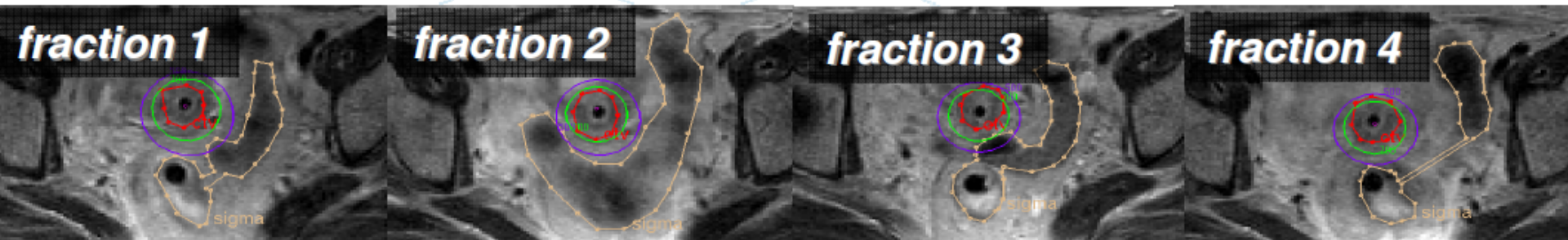
Definition of inter-intra fraction/application uncertainties



Random dosimetric variations during Brachtherapy

Same plan used for 4 fractions, anatomical changes between irradiations may lead to large random dosimetric uncertainties

Lang et al. 2013, Radiother Oncol



Results of a multicentre study between 6 centres with different treatment/application techniques (Nesvacil et al. 2013, Radiother Oncol 107 and references therein) :



De Leeuw et al.; Hellebust et al.; Anderson et al.; Mohamed et al.; Lang et al.; Jamema et al.

Bladder
SD D2cc

Rectum
SD D2cc

Sigmoid
SD D2cc

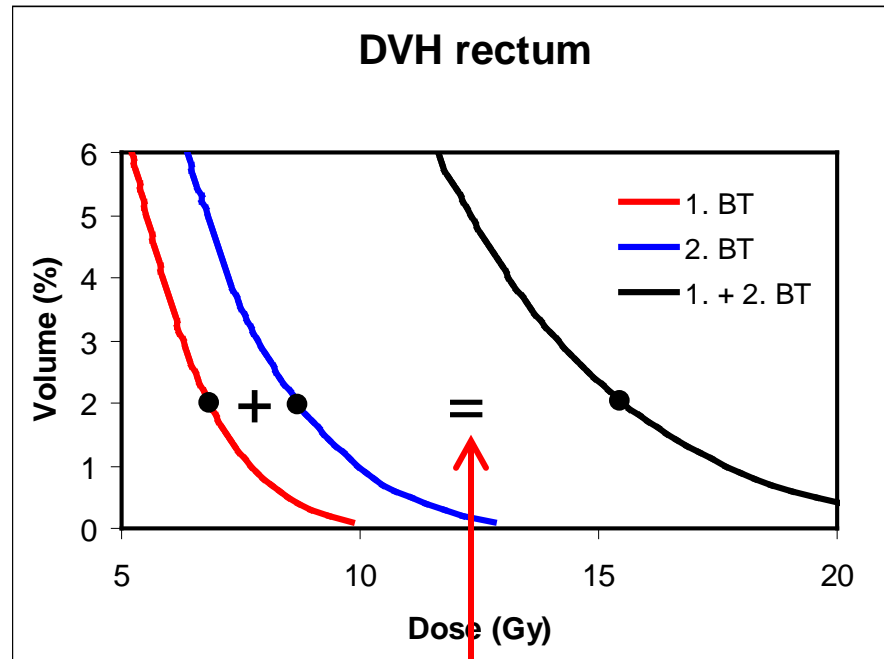
HR CTV
SD D90

	Bladder		Rectum		Sigmoid		HR CTV					
	SD	D2cc	SD	D2cc	SD	D2cc	SD	D90				
total	2.7	1.5	20.3%	4.5	4.1	22.0%	1.6	-0.9	26.8%	-1.1	-1.7	13.1%
Intraapplication	1.3	1.5	17.7	3.8	2.3	20.5	-2.3	-3.7	23.5	-2.5	-4.3	10.8
interapplication	3.9	0.0	22.3	5.8	5.2	23.2	6.8	3.7	30.2	0.4	-0.8	15.1

Note: Changes correspond to physical dose change between 2 time points during course of BT. Effect on total EQD2 (EBRT+BT) depends on fractionation schedule (PDR, HDR, ...)

“Worst case assumption”

Calculation of DVH for several fractions

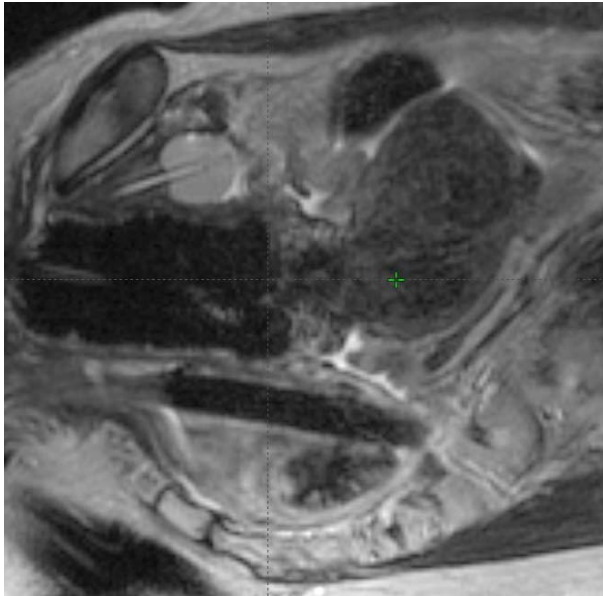


Approximation

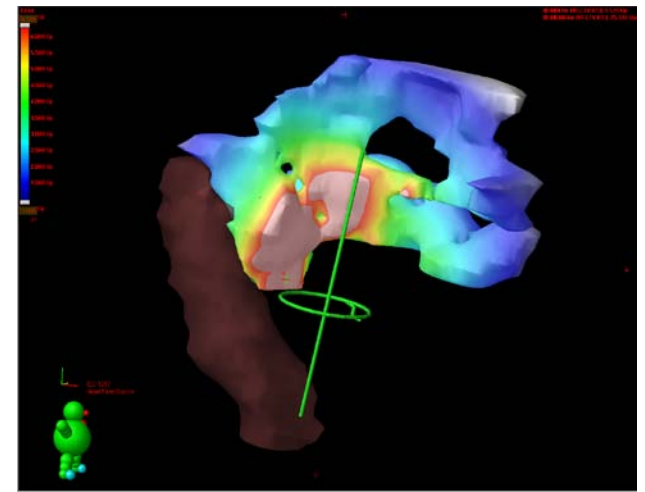
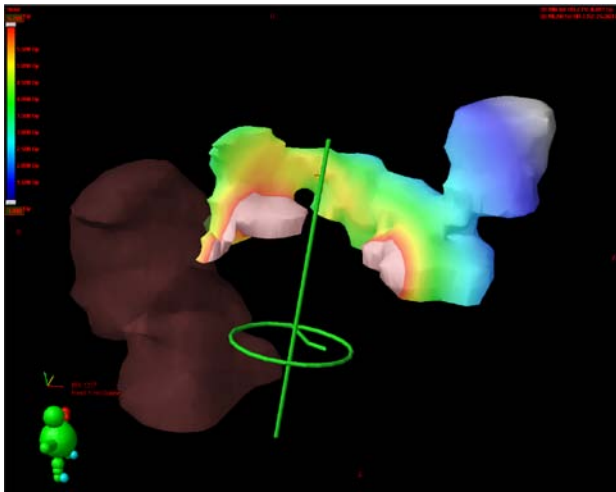
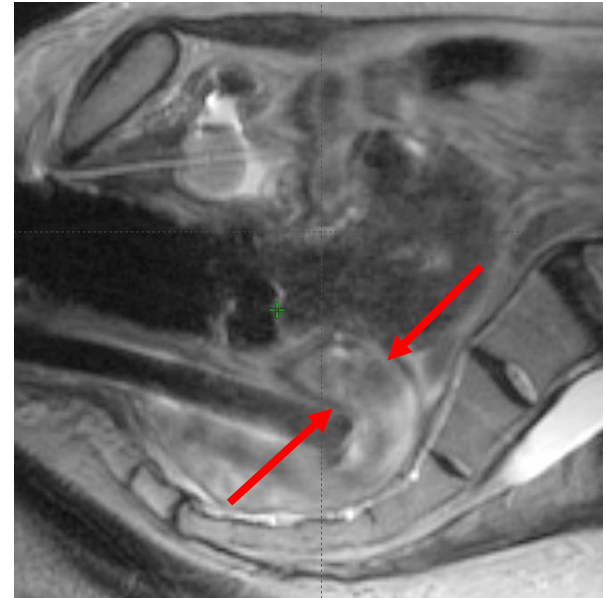
“Worst case assumption” or DVH addition

Different location of hotspots

1. BT



2. BT



Influence of organ deformation

- **Sigmoid**
 - Highly mobile
 - DVH calculation conservative
- **Rectum and bladder**
 - Less mobile
 - Addition of DVH accurate

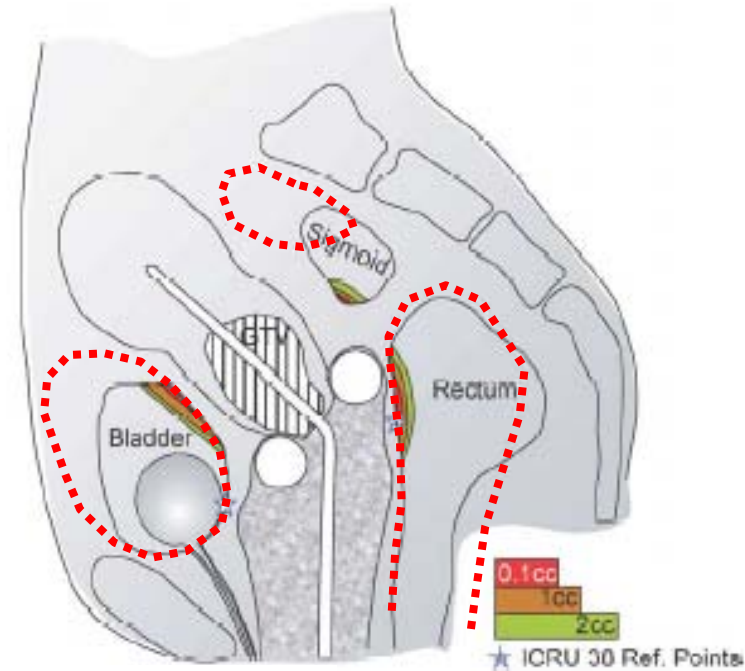


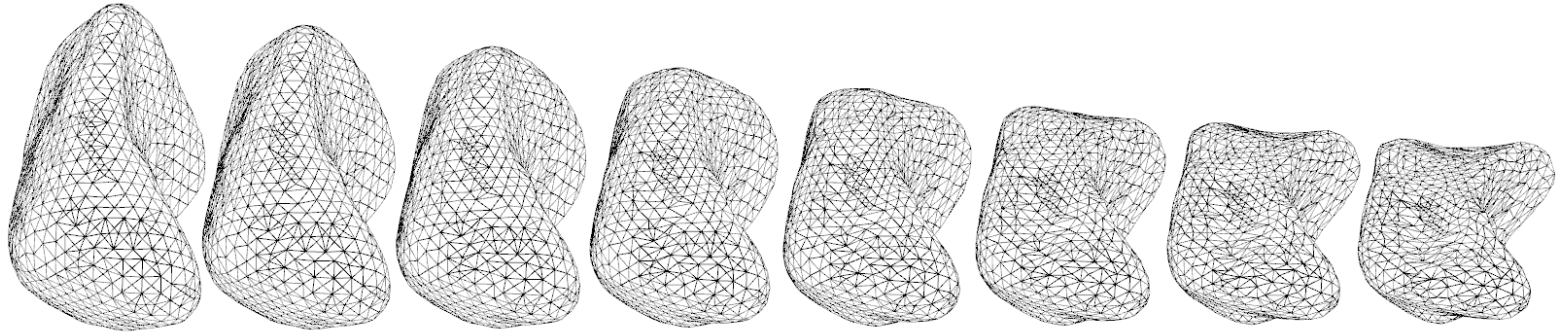
Table 2

Summary of results of spatial location of $D_{2\text{cm}^3}$ hot spot region for each of the OAR.

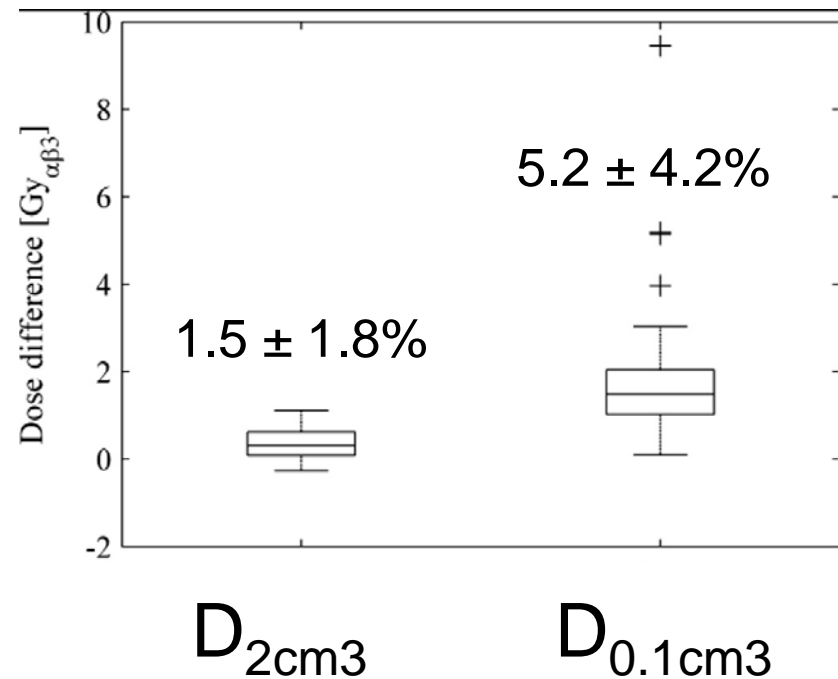
Categories	Rectum ($n = 27$)	Bladder ($n = 27$)	Sigmoid ($n = 27$)
1. Overlapping region >50%	16	8	3
2. Overlapping region 10–50%	7	14	9
3. Overlapping region <10%/no overlap	4	5	15

Jamema S et al,
vol 107, RO 2013

Bladder dose accumulation with deformable registration (biomechanical)



Difference between DVH addition and 3D dose accumulation:



DVH addition

- **Bladder and rectum dose:**

$$\mathbf{BT_{total} = BT1 + BT2 + BT3 + BT4}$$

- **Sigmoid dose potential over-estimation of dose:**

$$\mathbf{BT_{total} < BT1 + BT2 + BT3 + BT4}$$

Largest dose uncertainty for target?

- 1. Dose calculation**
- 2. Applicator reconstruction**
- 3. Target contouring**
- 4. Target motion**

Largest dose uncertainty OARs?

- 1. Dose calculation**
- 2. Applicator reconstruction**
- 3. OAR contouring**
- 4. OAR motion**

Total uncertainties

- Radiotherapy and Oncology vol 107(1), 2013
- 19 papers on brachytherapy and mainly on uncertainties

Table 1

Uncertainty budget (SD) for one intracavitary brachytherapy fraction. The overall uncertainty for the entire treatment course is depending on the fractionation schedule and level of verification.

	Target (HR CTV D90)	OARs (D _{2cm³})
Source strength	2%	2%
Dose and DVH calculation	3%	3%
Dwell position uncertainty (reconstruction and source positioning)	4%	4%
DVH addition across fractions (previously called “worst case assumption”)	NA	1% ^a -7%
Contouring (inter-observer)	9%	5-11%
Intra- and inter-fraction (intra-application) uncertainties ^b (5)	11%	20-25%
Total ^c	12%	21-26%

^a For the bladder and likely rectum, whereas it has not been evaluated for sigmoid.

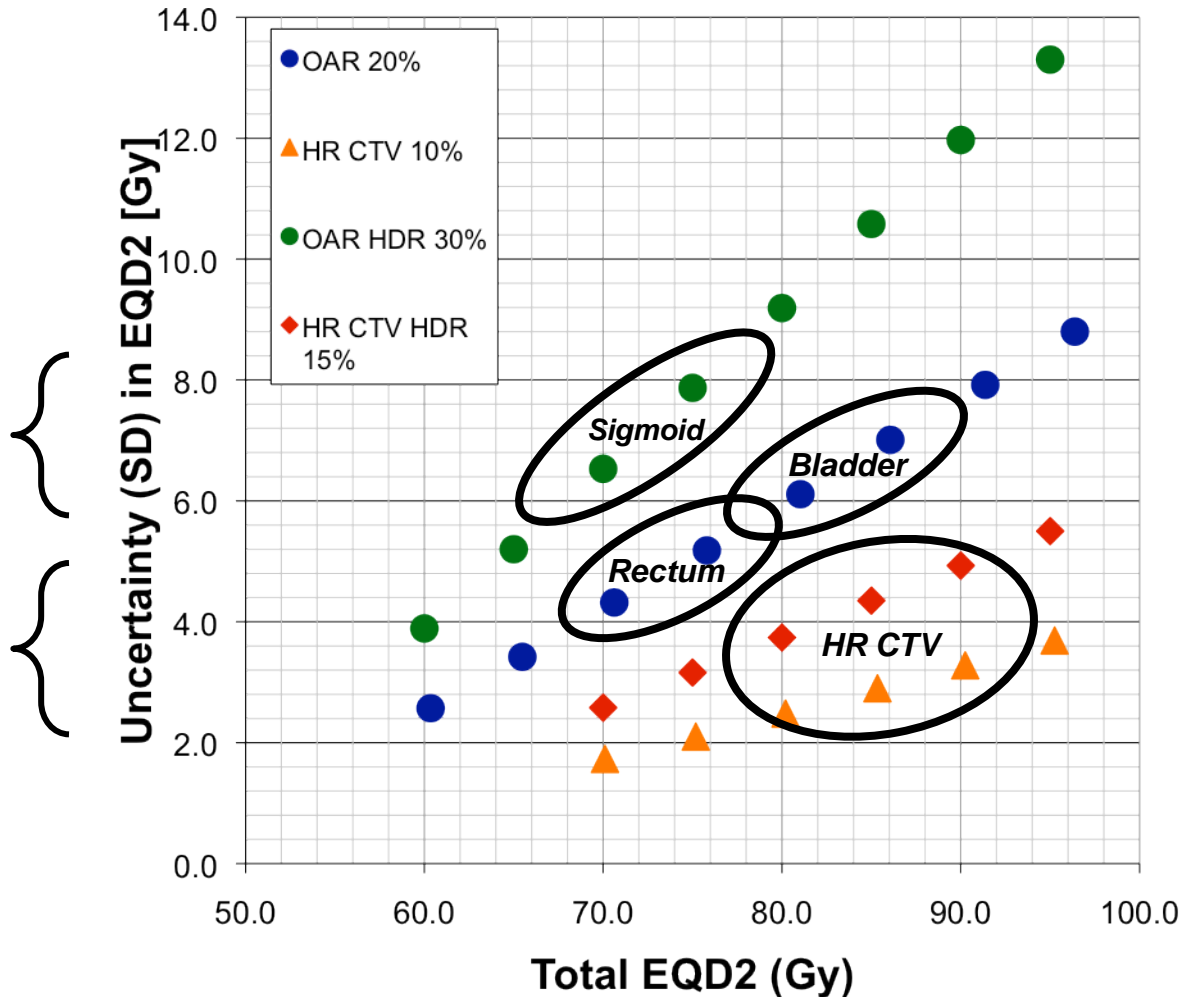
^b Per se including intra-and inter-observer contouring variations.

^c Contouring uncertainties included through intra- and inter-fraction uncertainties.

Impact of uncertainties on total dose

OAR
6-8 Gy (SD)

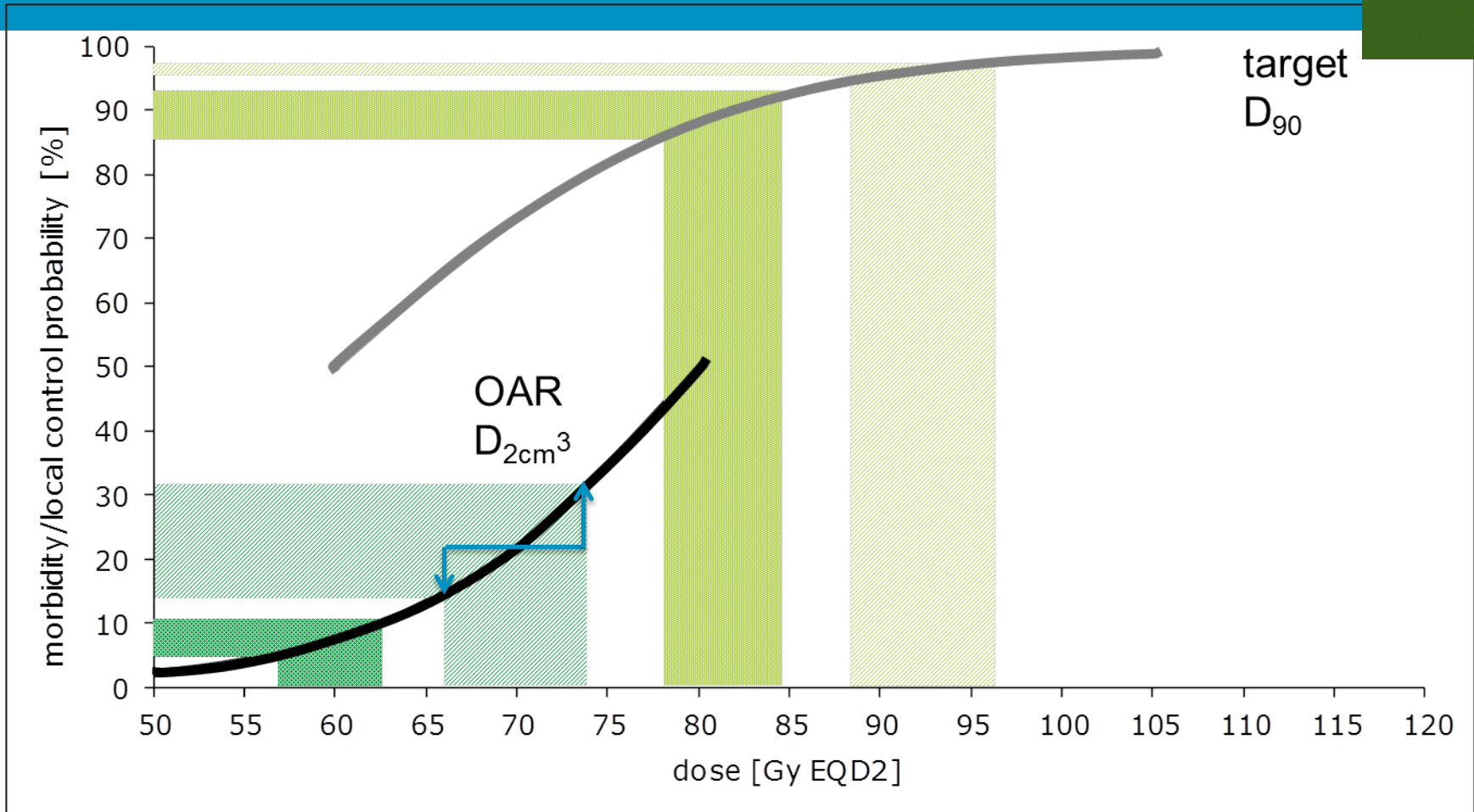
HR CTV
2-5 Gy (SD)



Examples total dose and uncertainty

- **HR CTV:** **$D_{90} = 90 \pm 4\text{Gy}$**
- **Bladder:** **$D_{2\text{cm}^3} = 85 \pm 7\text{Gy}$**
- **Rectum:** **$D_{2\text{cm}^3} = 70 \pm 4\text{Gy}$**
- **Sigmoid:** **$D_{2\text{cm}^3} = 70 \pm 7\text{Gy}$**

Dosimetric uncertainties and dose-response relationships



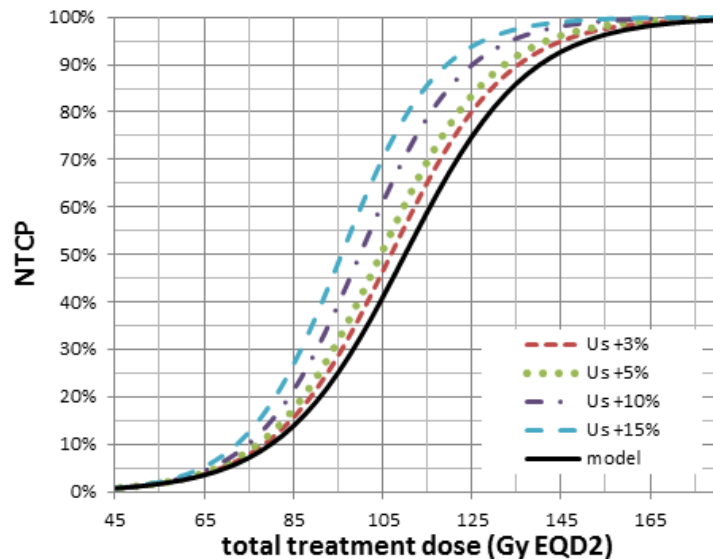
Schematic illustration of the effect of dosimetric uncertainties of prescribed vs. delivered dose on response probabilities.

Effect of uncertainties on observed dose response relationships

Comparison of model dose response curve (based on published curves, see previous slides), and simulated „observed“ dose response curves assuming different systematic and random uncertainties.

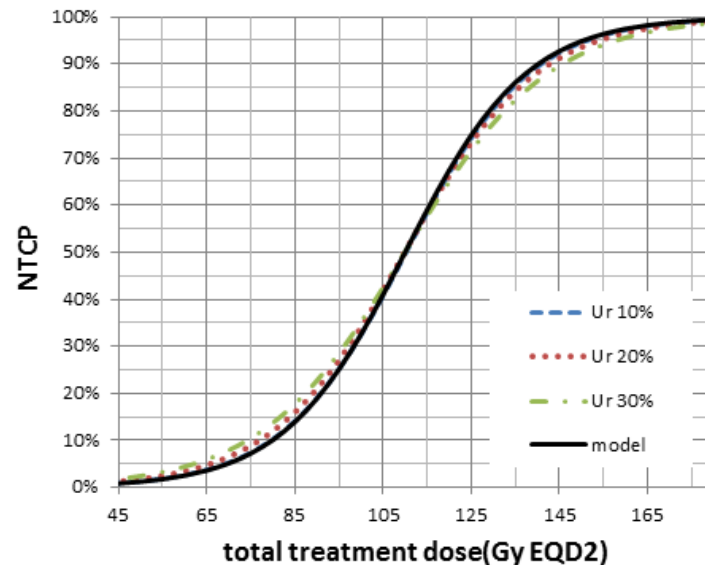
systematic dosimetric uncertainty

e.g. rectum $D_{2\text{cm}^3}$ (+3,+5,+10,+15 % / fx)



random dosimetric uncertainty

e.g. rectum $D_{2\text{cm}^3}$ ($\pm 10, \pm 20, \pm 30$ % / fx)

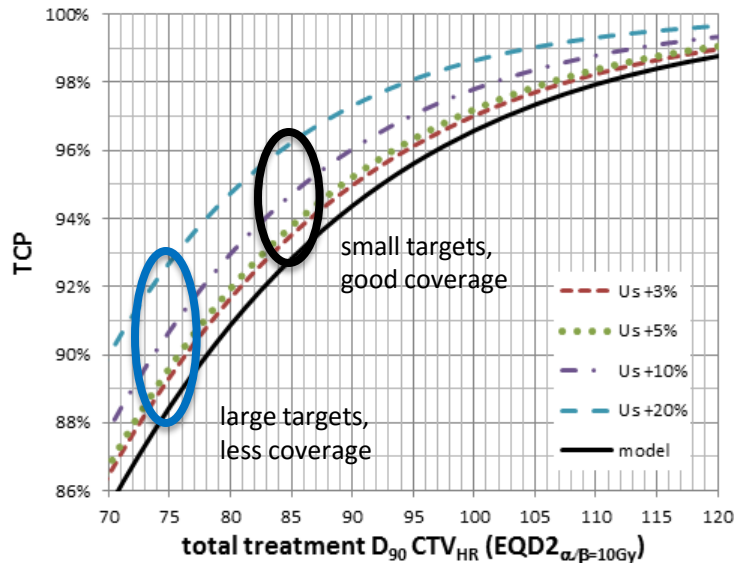


Simulations of patient cohort with total dose = 45Gy EBRT + 4 fx BT (equal PD for each fx), model based on *Georg et al. 2012, IJROBP*

Systematic dosimetric uncertainties

Systematic inter-/intra fraction variations for MRI-based cervix BT (Nesvacil et al. 2013, R&O 107):

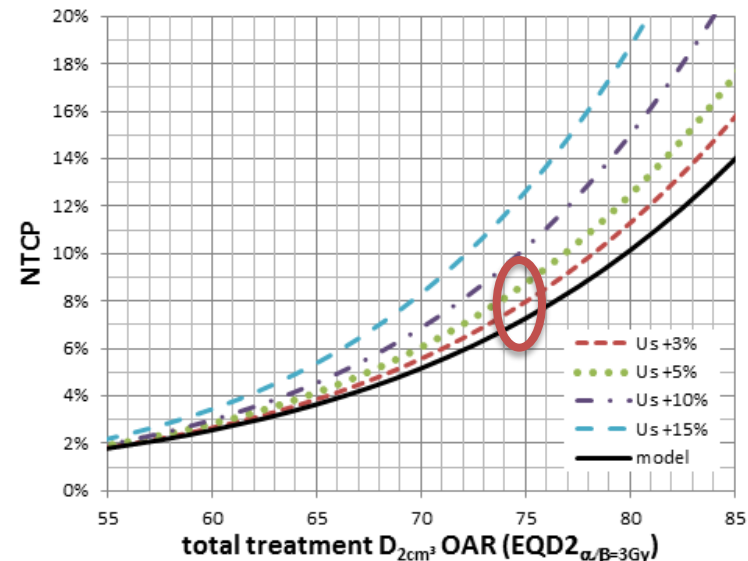
e.g. $\Delta D_{90} < +3\%/fx \Rightarrow$ „observed“ local control @85 Gy 1% higher than model prediction



Systematically larger contours on CT vs. MRI \Rightarrow underestimation of D_{90} by CT contours (e.g. Viswanathan et al. 2007, IJROBP 68):

- e.g. i) $\Delta D_{90} = +10\%/fx \Rightarrow$ 2% overestimation of local control @ 85 Gy
- ii) $\Delta D_{90} = +20\%/fx \Rightarrow$ 3.5% overestimation of local control @ 85 Gy

systematic underestimation of rectum D_{2cm^3} : rectum probe (iv. dosimetry) stays inside - rectum always fills with gas in between image acquisition and treatment $\rightarrow D_{2cm^3}$ is systematically higher for each fraction

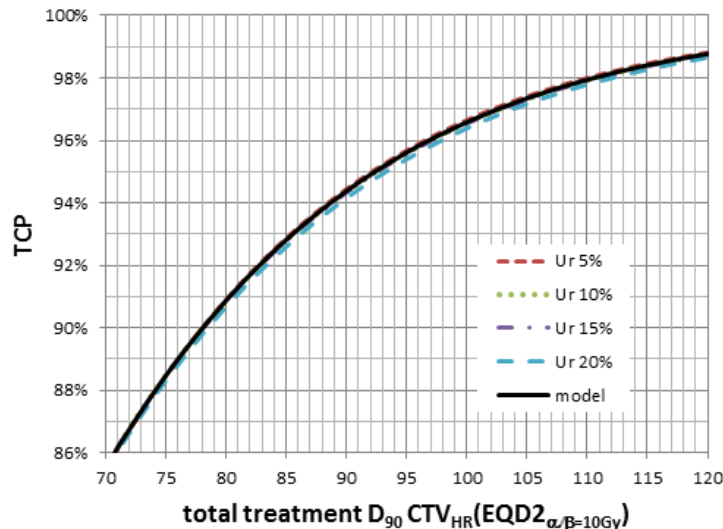


- e.g. i) $\Delta D_{2cm^3} = +3\%/fx \Rightarrow$ observed morbidity @75Gy 1% higher than model prediction
- ii) $\Delta D_{2cm^3} = +5\%/fx \Rightarrow$ observed morbidity @75 Gy is 2% higher than model prediction

“Can reduction of uncertainties in cervix cancer brachytherapy potentially improve clinical outcome?” Nesvacil et al. 2016, submitted to R&O

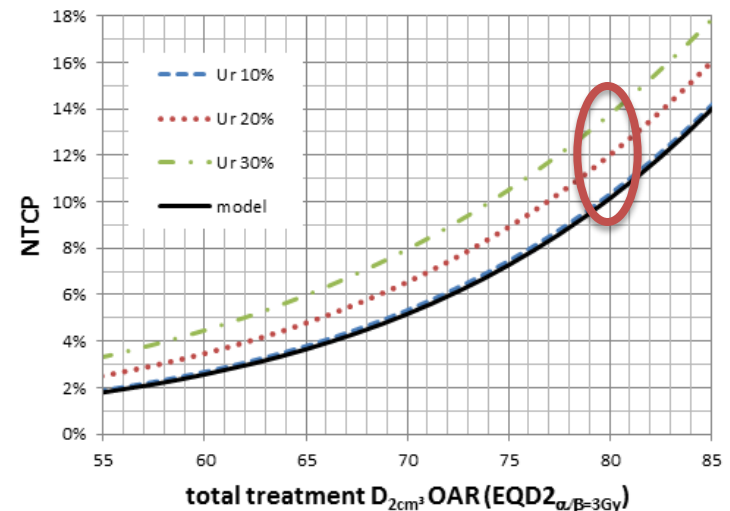
Example: random uncertainties for target OAR

Random variation of target D_{90} ,
e.g. random inter-observer variation



For target – differences in TCP < 0.5%

Random variation of rectum D_{2cm^3}
e.g. random intra-/inter-fraction variation of
organ position or shape



- $\Delta D_{2cm^3} = \pm 10\%/fx$ -> observed morbidity 7.5 %
(vs 7.3% model prediction)
- $\Delta D_{2cm^3} = \pm 20\%/fx$ -> observed morbidity 8.9 %
- $\Delta D_{2cm^3} = \pm 30\%/fx$ -> observed morbidity 10.5 %
- Model prediction: 10.5% NTCP@ 80Gy EQD2

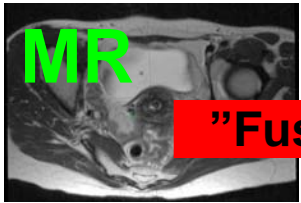
Image modality?

Pre-BT

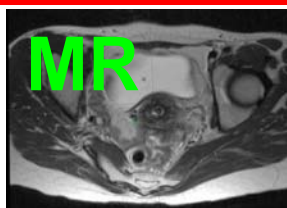
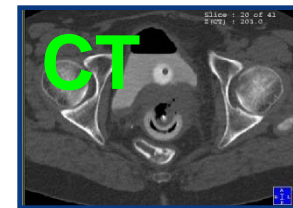
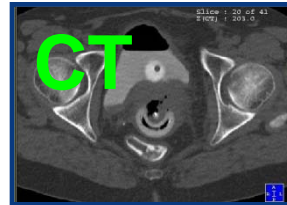
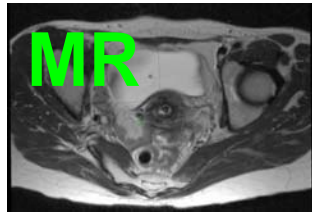
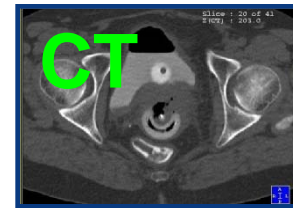
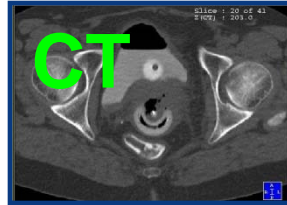
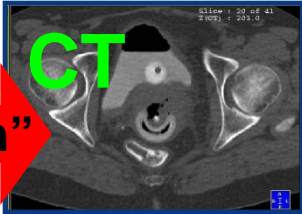
BT1

BT2

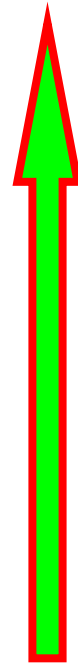
BT3



"Fusion"



Golden standard



Increasing uncertainty

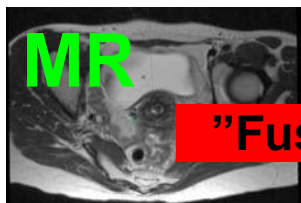
Pre-BT MRI + CT

Pre-BT

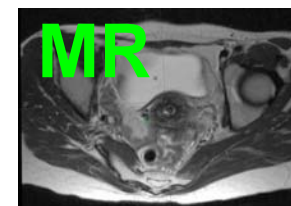
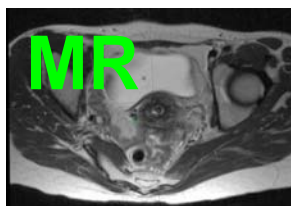
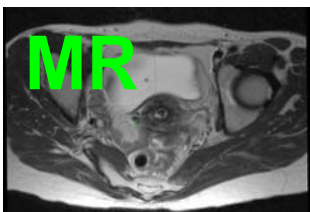
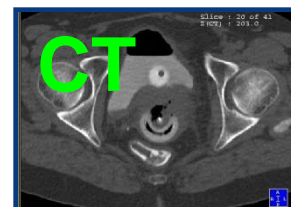
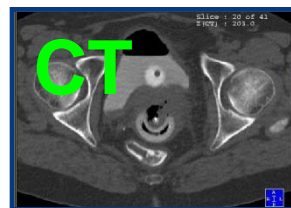
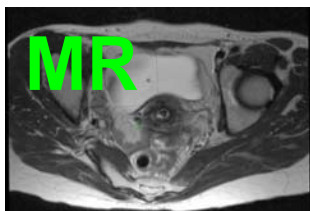
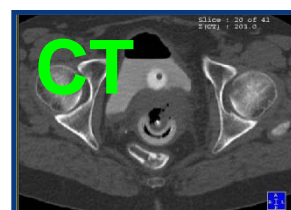
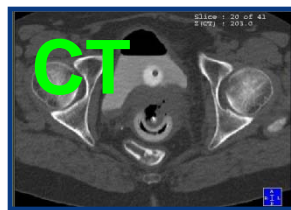
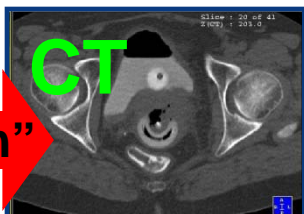
BT1

BT2

BT3

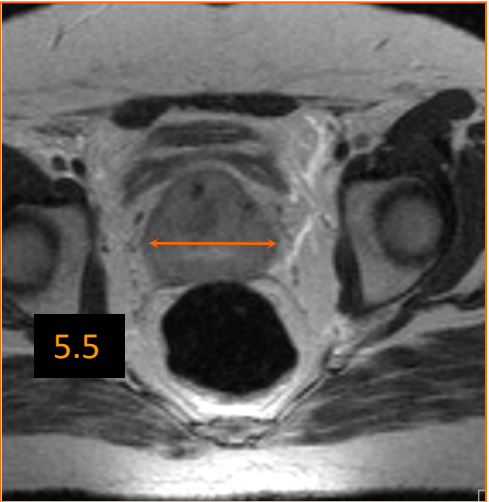
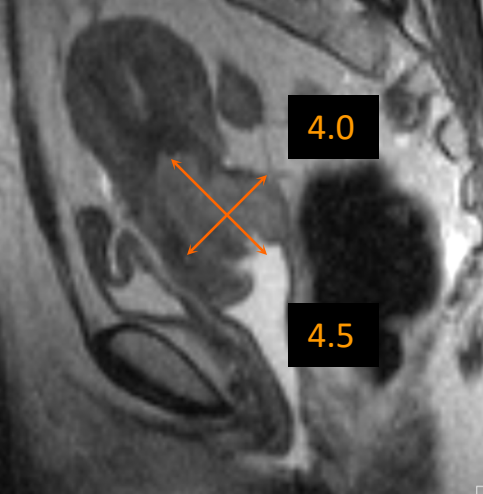


"Fusion"

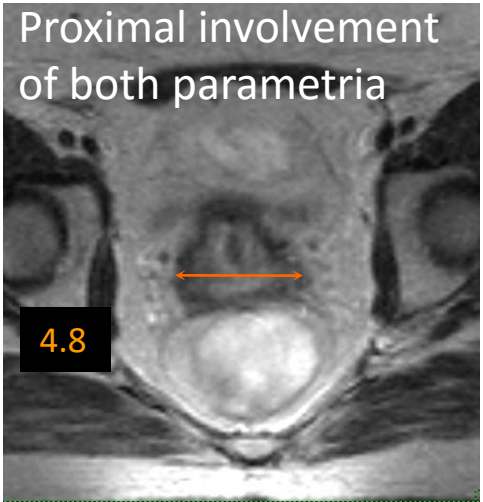
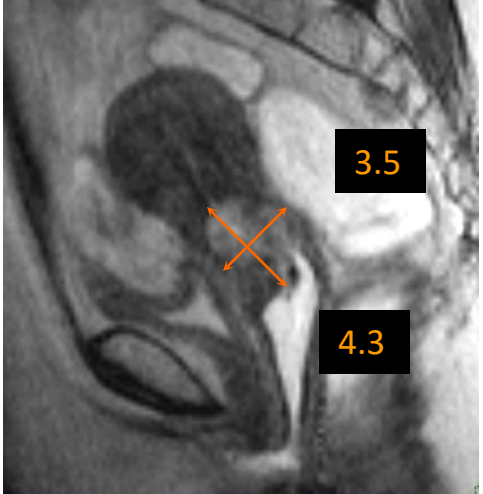


Example: HR CTV „pre-BT MRI“ (HR CTV 3)

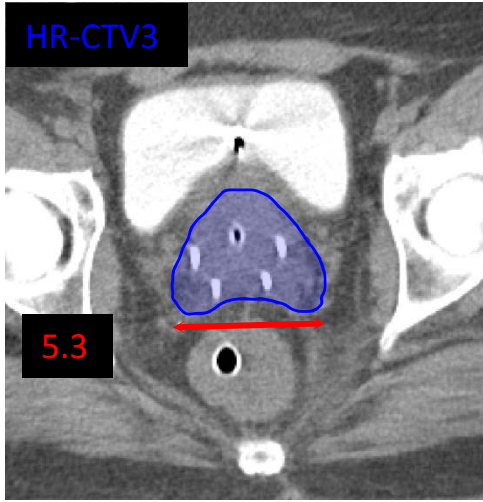
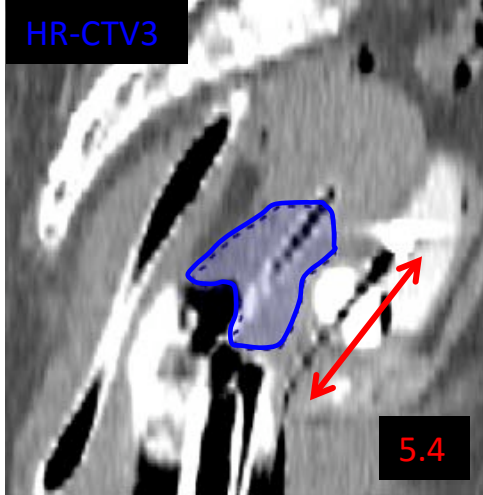
Diagnosis



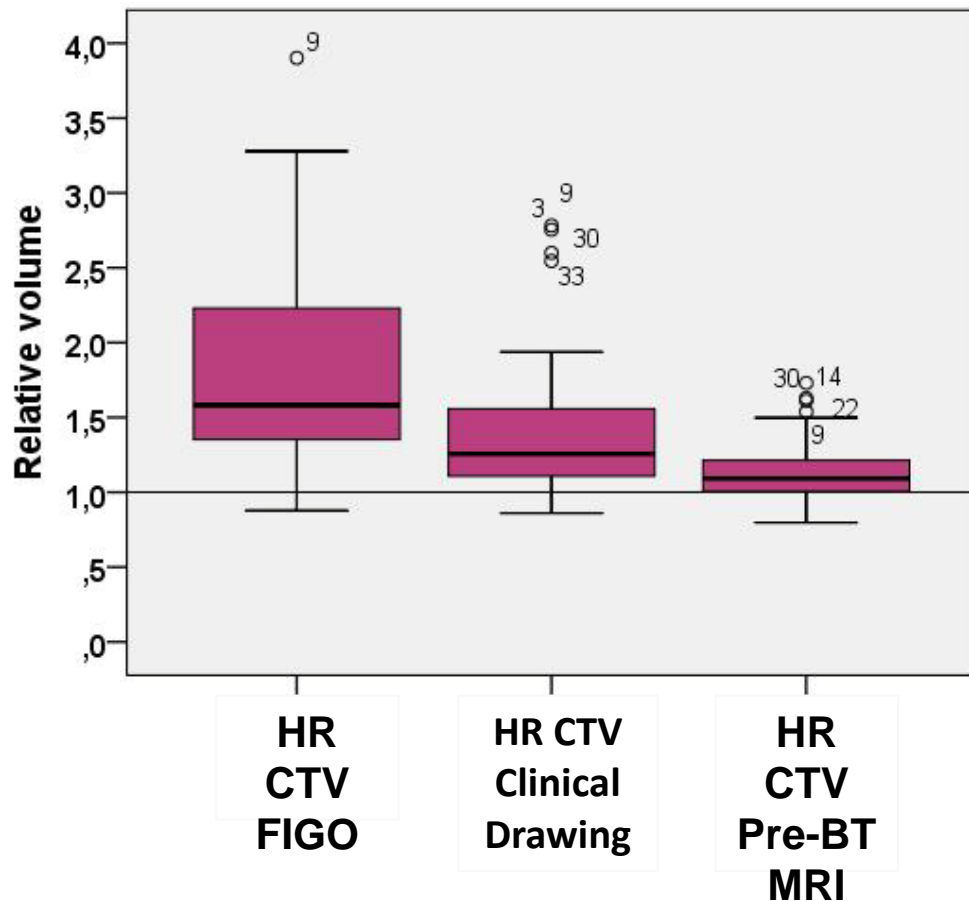
1st Brachytherapy



Proximal involvement of both parametria

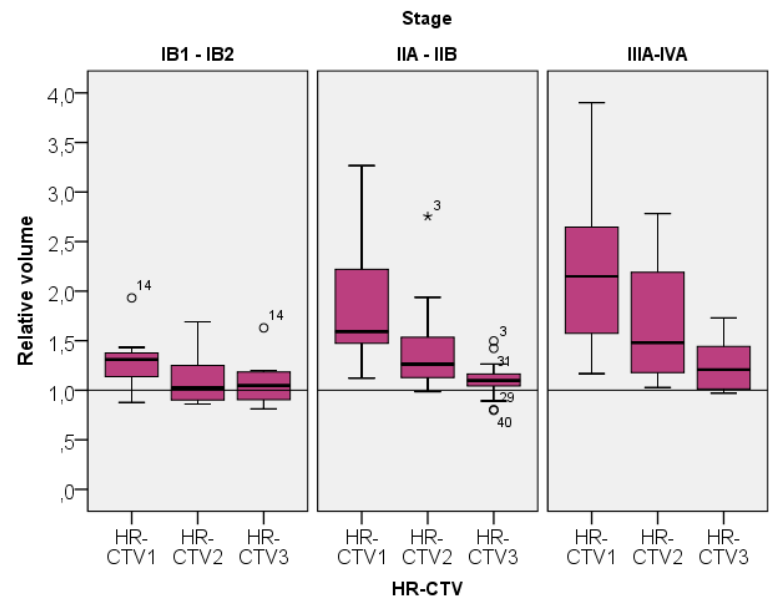


Delineation on CT according to three principles



Three increasingly comprehensive principles for delineation on CT:

- FIGO only
- FIGO + clinical drawing
- FIGO + clinical drawing + pre-BT MRI



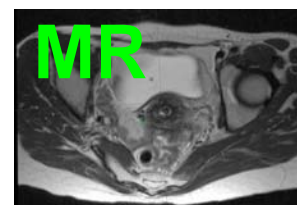
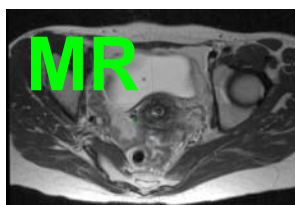
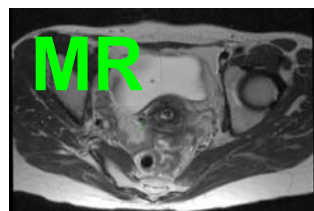
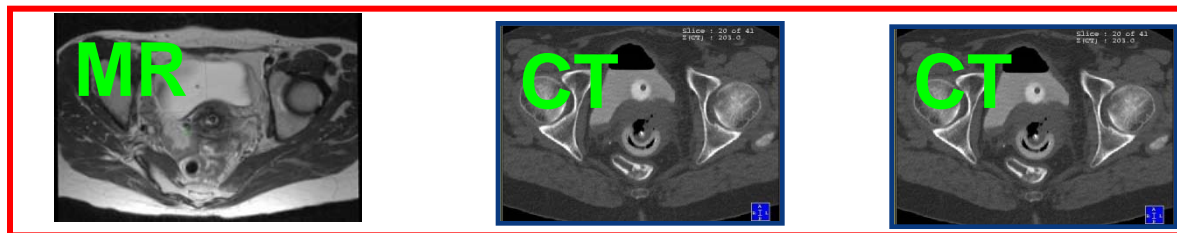
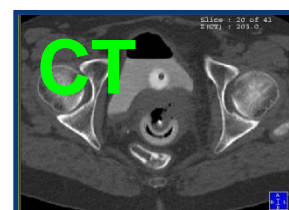
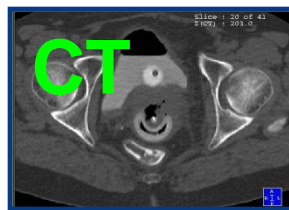
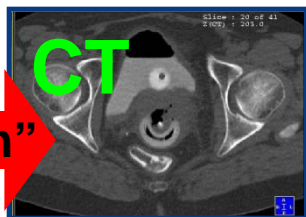
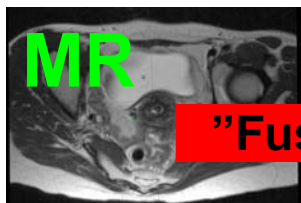
Pre-BT MRI + CT

Pre-BT

BT1

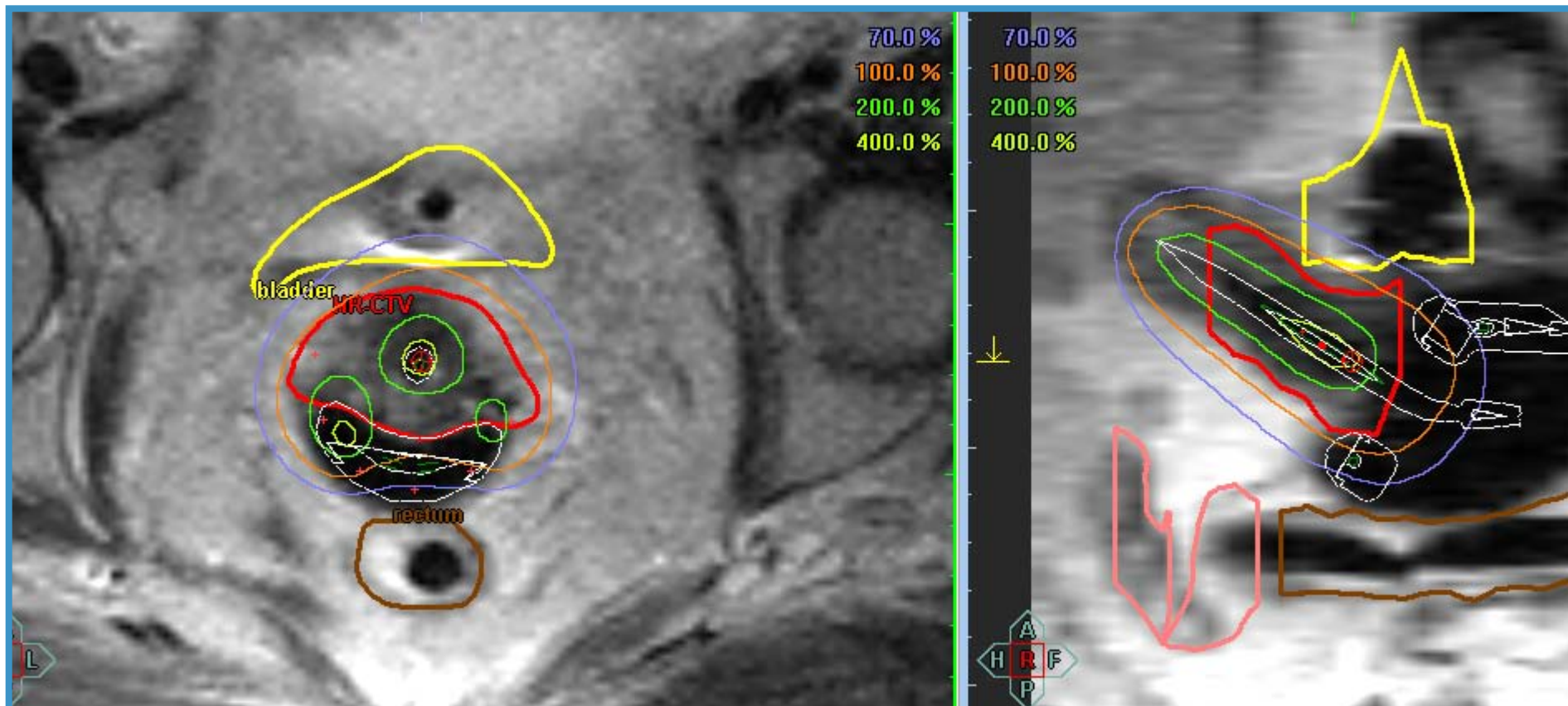
BT2

BT3



1st application: MRI

Applicator, target (HR CTV), OAR (rectum, bladder, sigmoid)
Dose planning and optimization on target+organ contours



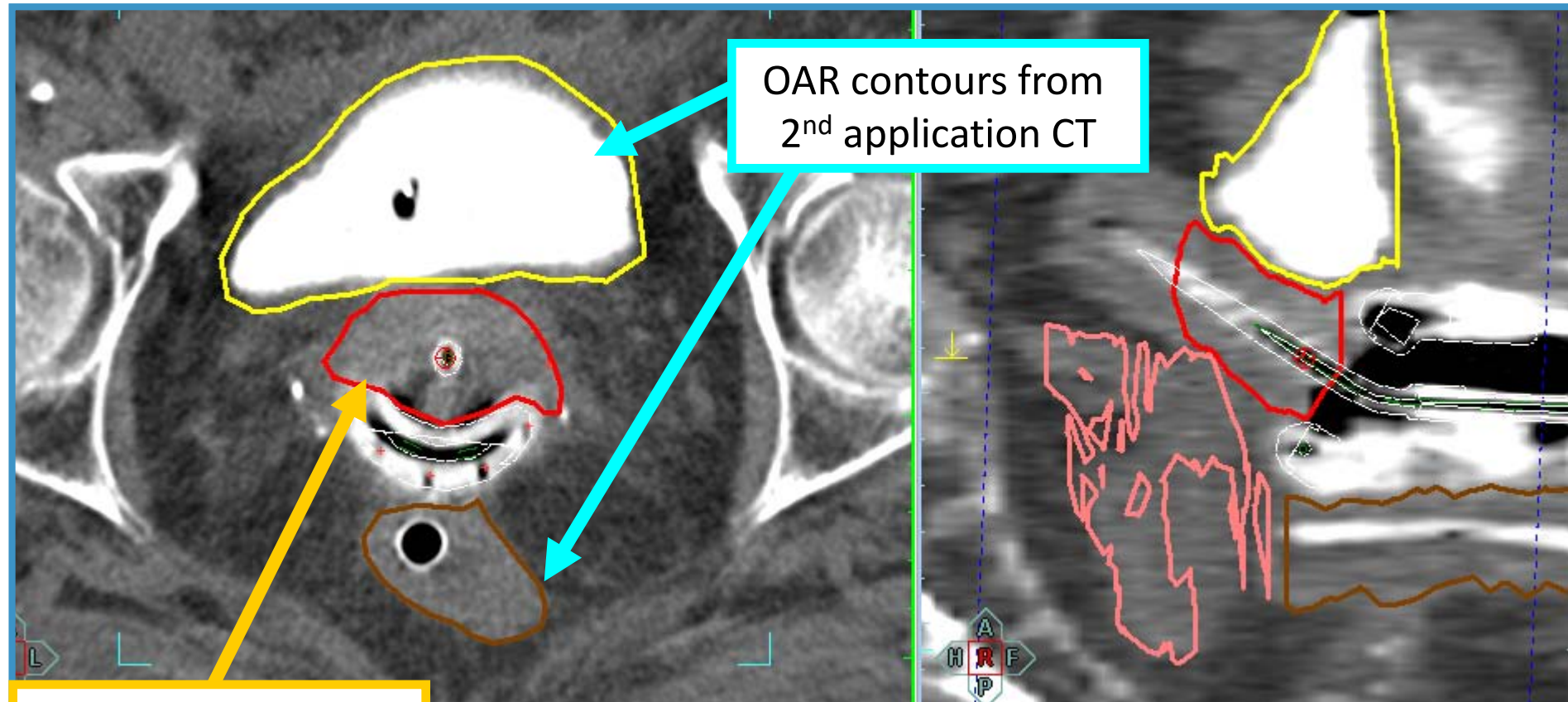
2nd application: CT

3D applicator reconstruction
Target transfer



2nd application: CT

Contouring OAR on CT



Target contour from 1st application MRI

Courtesy of Nicole Nesvacil, General Hospital of Vienna

MR imaging and treatment planning for every fraction?

- **Depends on local infrastructure**
- **Important considerations regarding imaging:**
 - **MRI is more important in large tumors as compared to tumours without parametrial infiltration**
 - **BT after major tumour shrinkage: 1st fraction MRI (or pre-BT MRI), succeeding fractions can be done with CT**
 - **Complex BT applications (IC combined with IS) and/or expected target shrinkage: repeated MRI and plan adaptation are recommended**

What is possible in your department?

1. X-ray
2. CT each fraction
3. MRI each fraction
4. CT combined with MRI
5. Other

Canadian Experience with Implementation of MRI-Guided Brachytherapy

Kathy Han, MD, MSc, FRCPC
Princess Margaret Cancer Centre
ESTRO-CARO Course
April 5th, 2016

Outline

- Importance of brachytherapy
- Canadian patterns of practice
- Canadian quality indicators
- The Princess Margaret experience

Canadian community practise CARO

Introduction	Mike Milosevic
BCCA Experience	Francois Bachand, Juanita Crook
Edmonton Experience	Ericka Wiebe
London experience	Vikram Velker
Quebec City experience	William Foster, Eric Vigneault

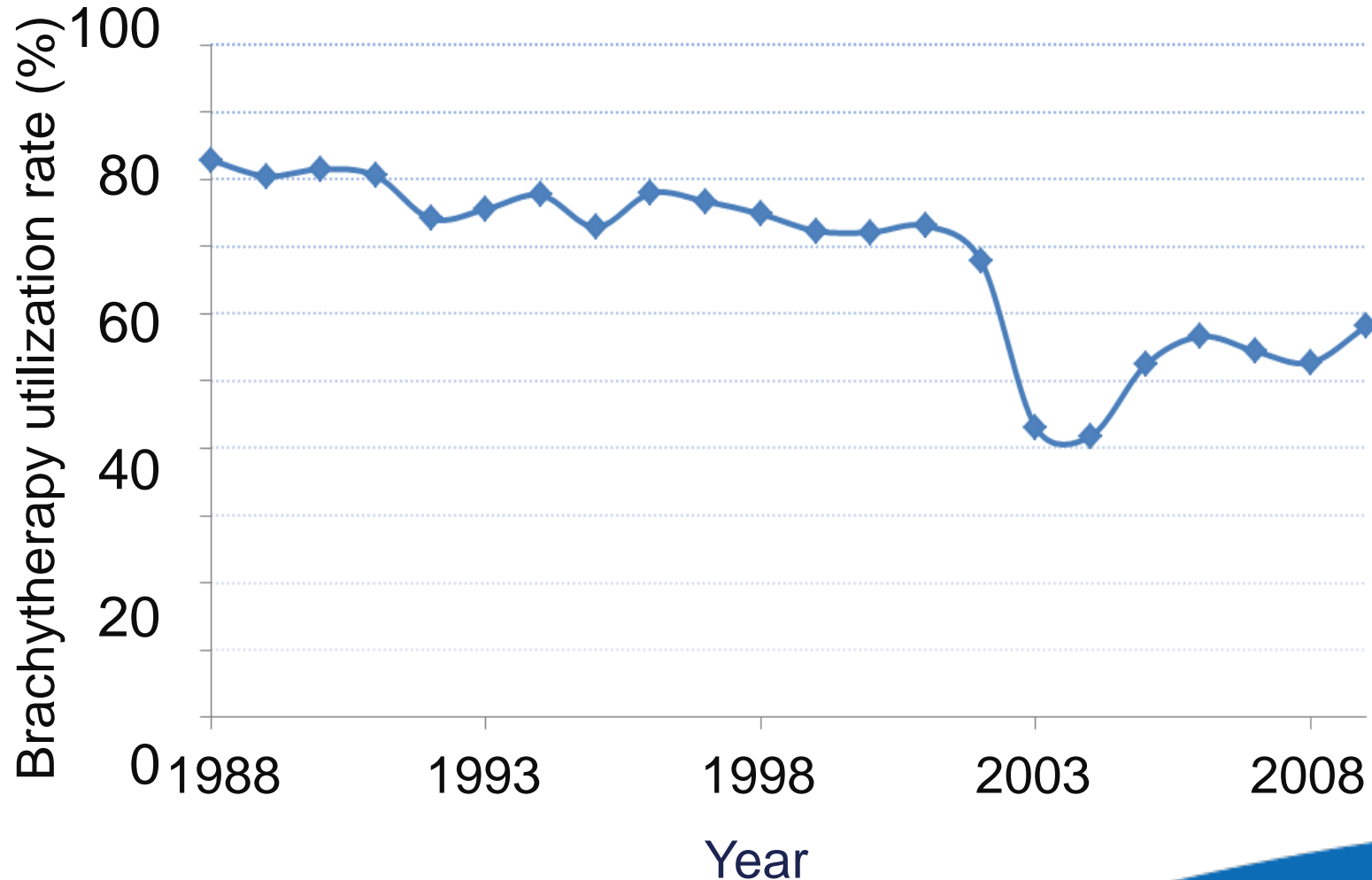
13.35 - 15.05 (90min)

Why Brachytherapy?

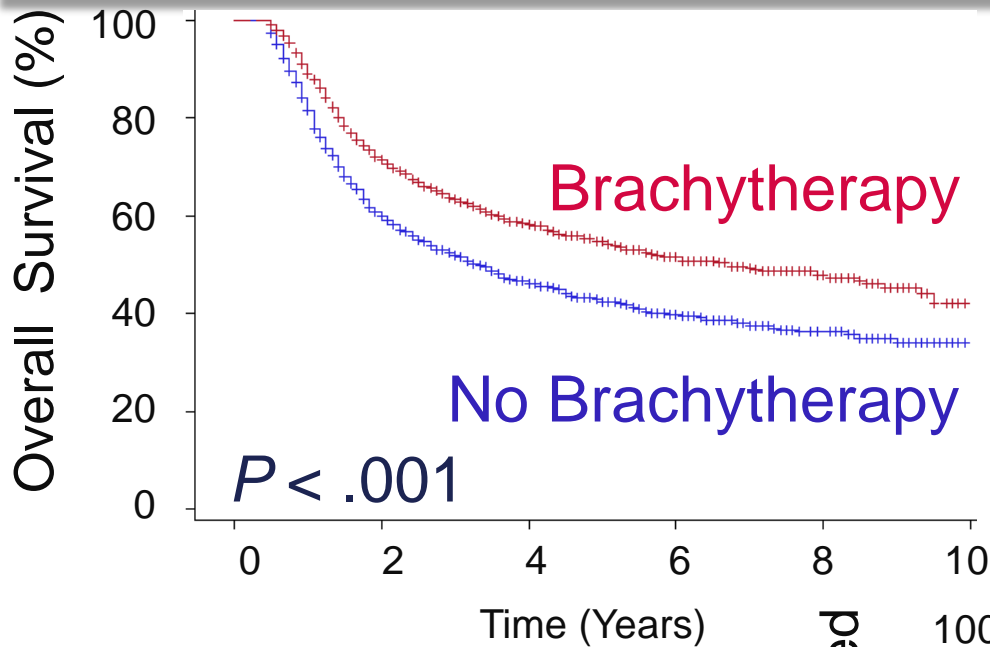
- Escalates dose to the tumor
- ↑ local control and survival

	EBRT only	EBRT + brachytherapy
Montana <i>et al</i> (n=203)		
Local Control	40%	52%
5yr survival	29%	36%
Patterns of Care (n=271)		
4yr local control	45%	67%
4yr survival	19%	46%

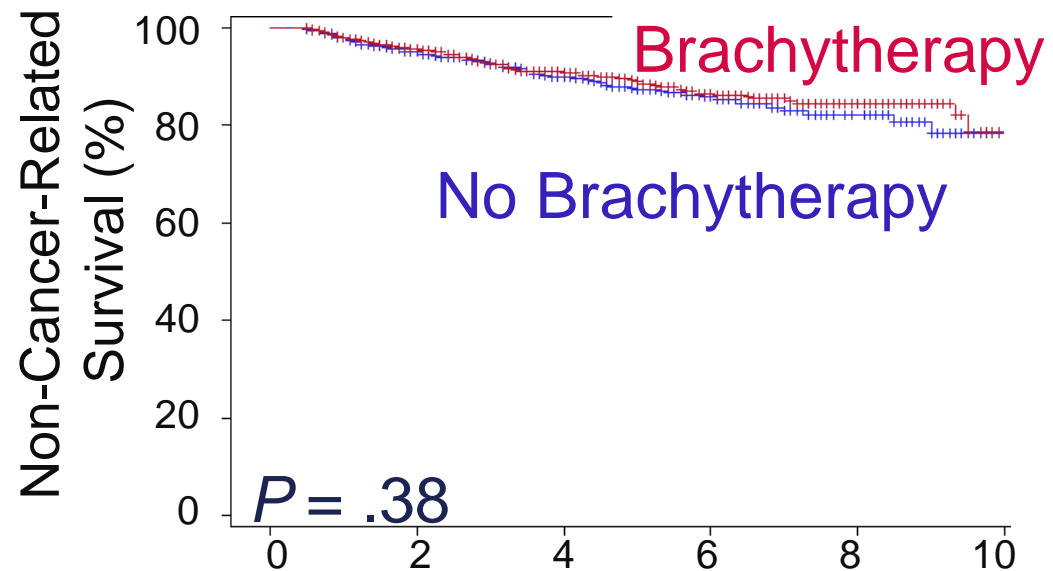
Brachytherapy utilization rate in 18 SEER registries



Survival by brachytherapy use

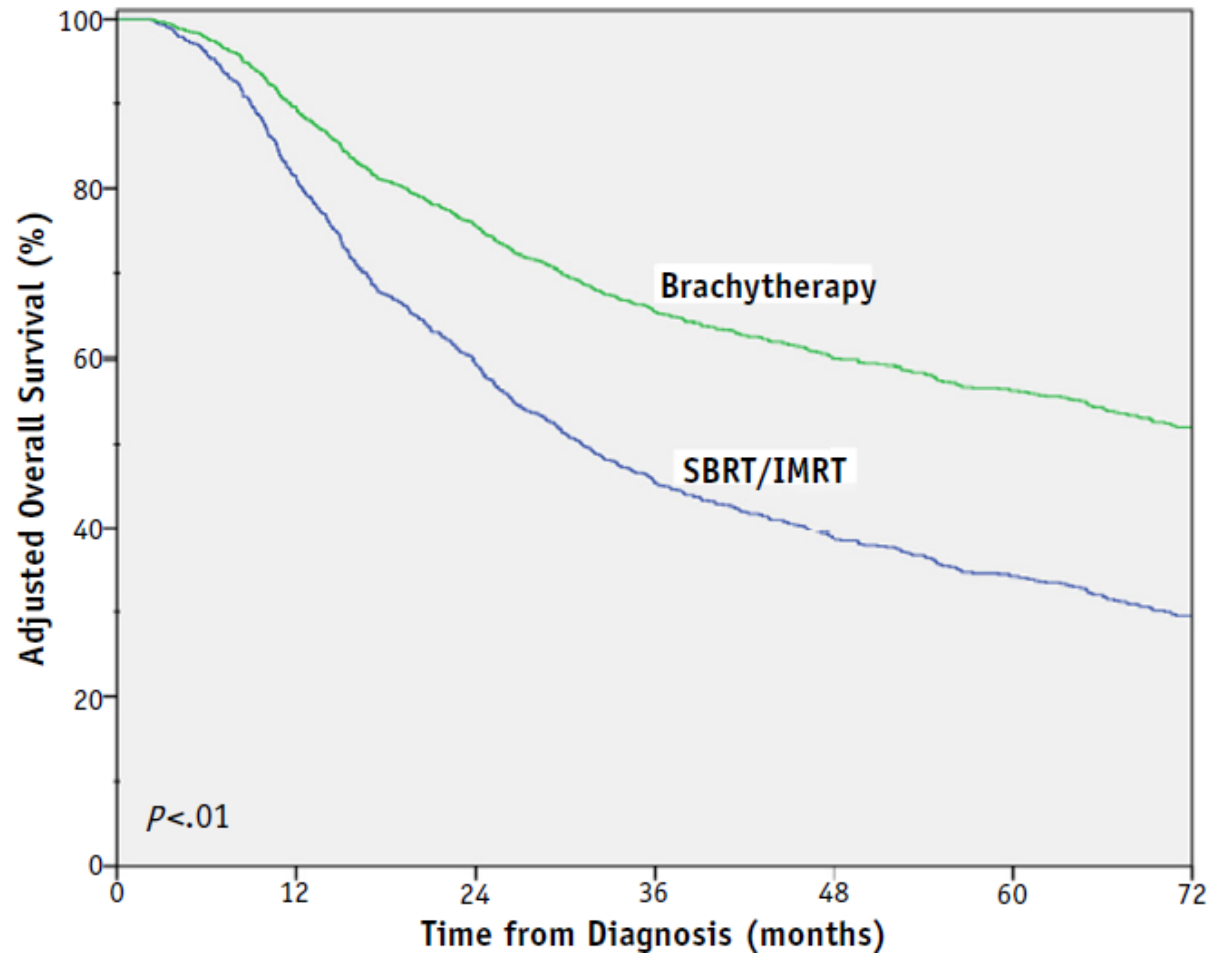


Propensity-score matched
n = 3246



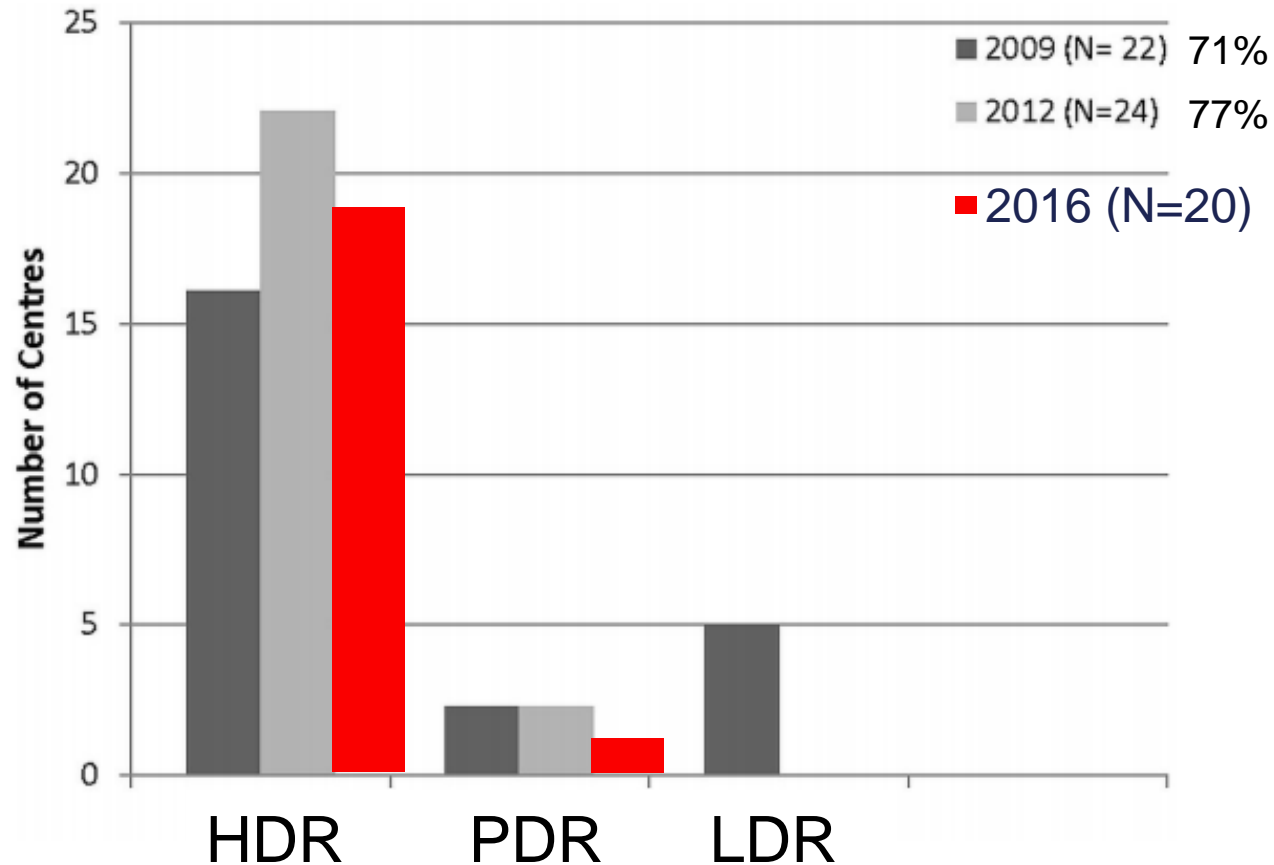
Han et al, *IJROBP* 87:111-9, 2013

The Impact of New Technological Advancements

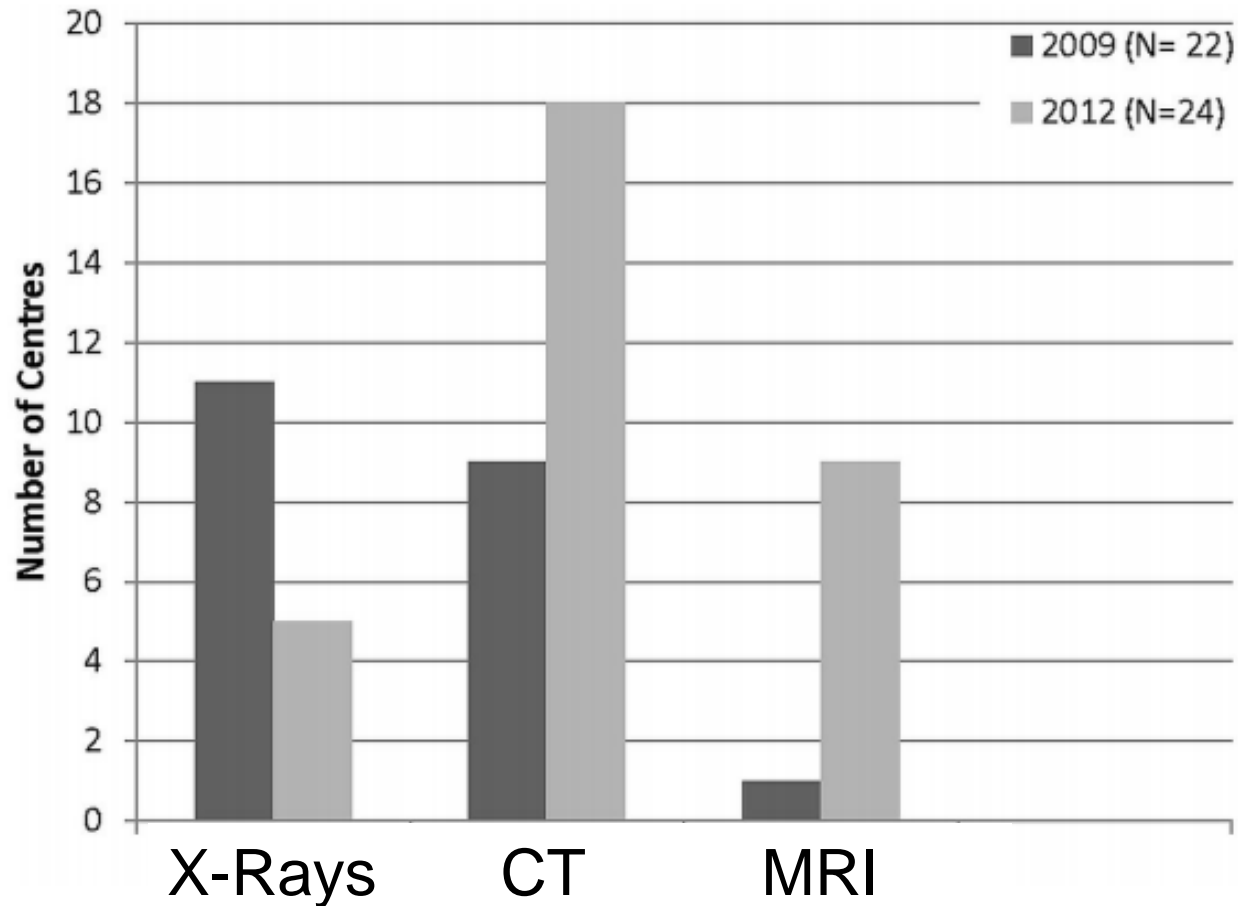


Canadian Patterns of Practice

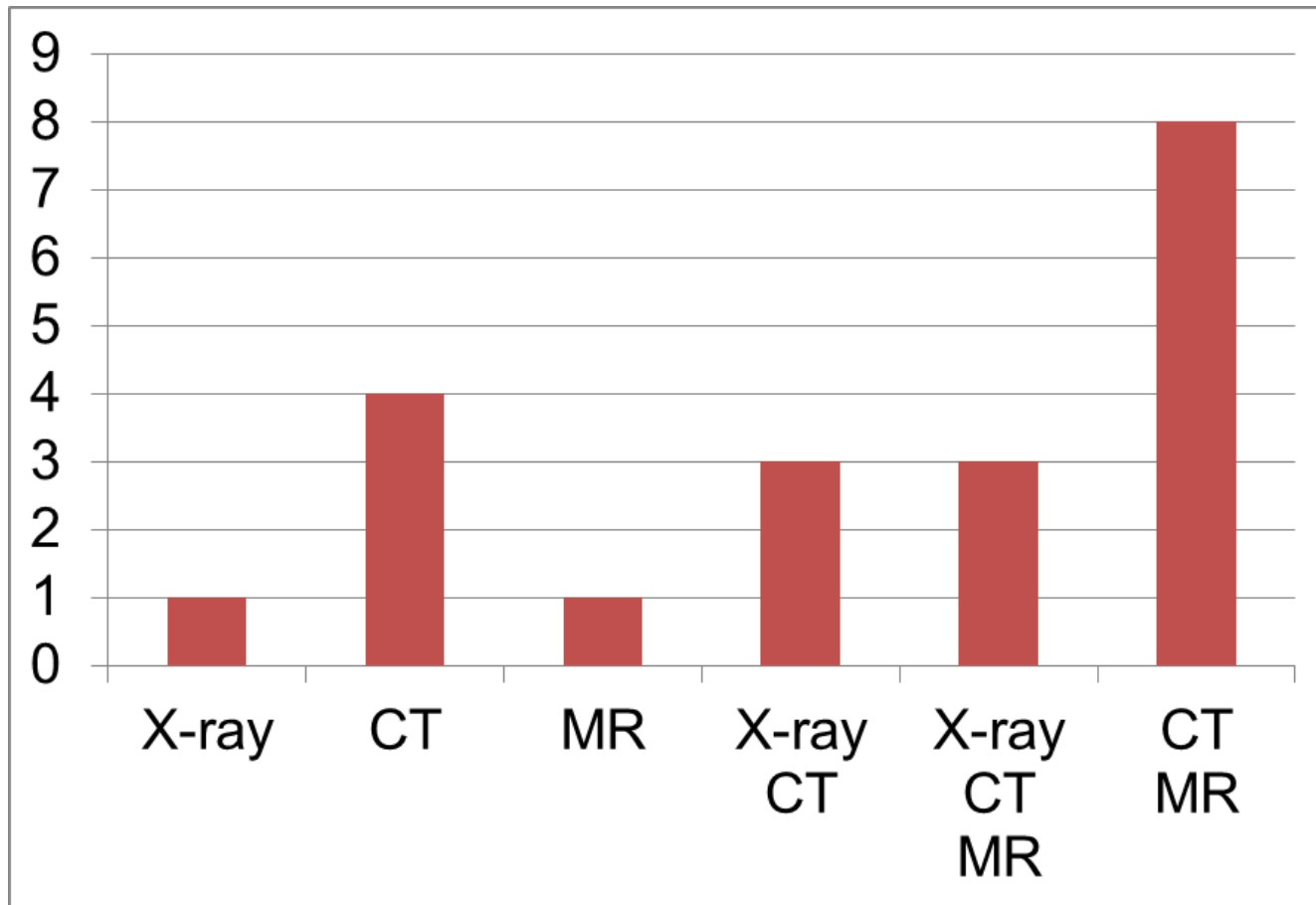
Canadian Practice Survey



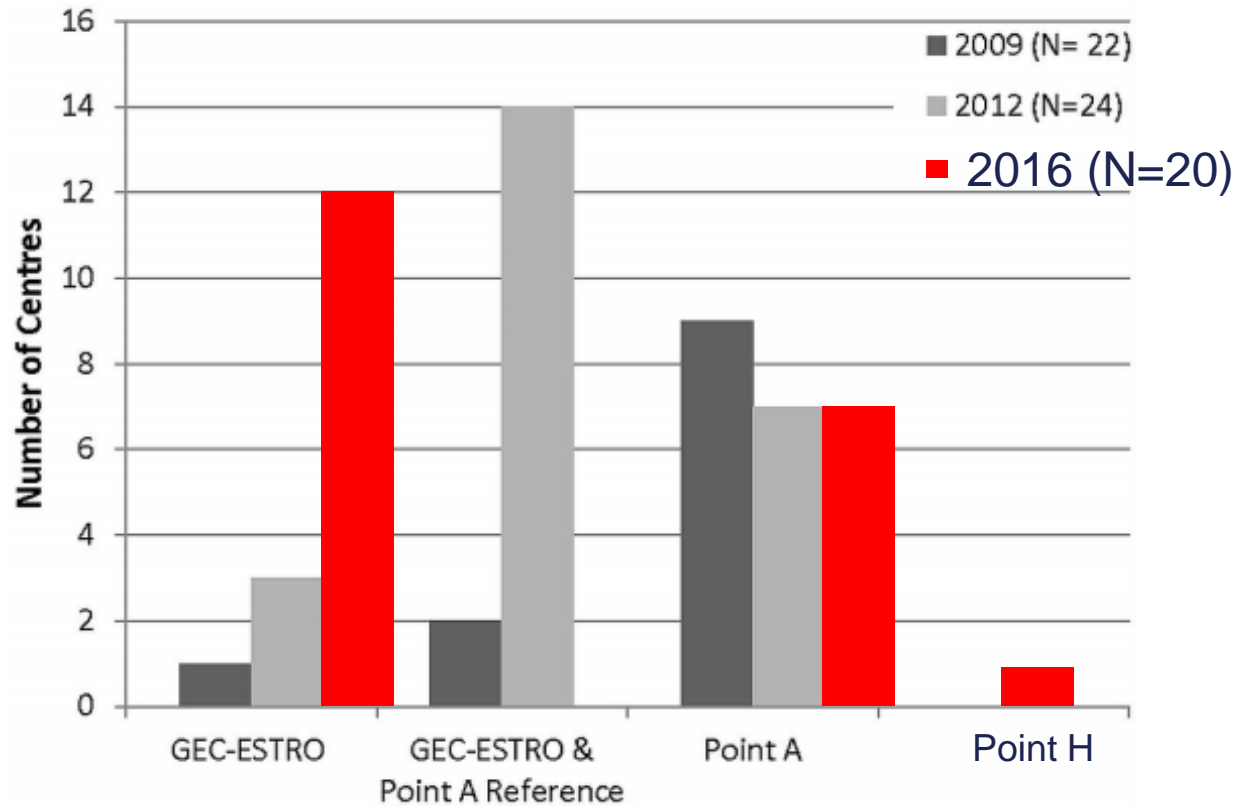
Imaging modalities for brachytherapy planning



What imaging do you perform after applicator insertion for applicator position verification and/or treatment planning?



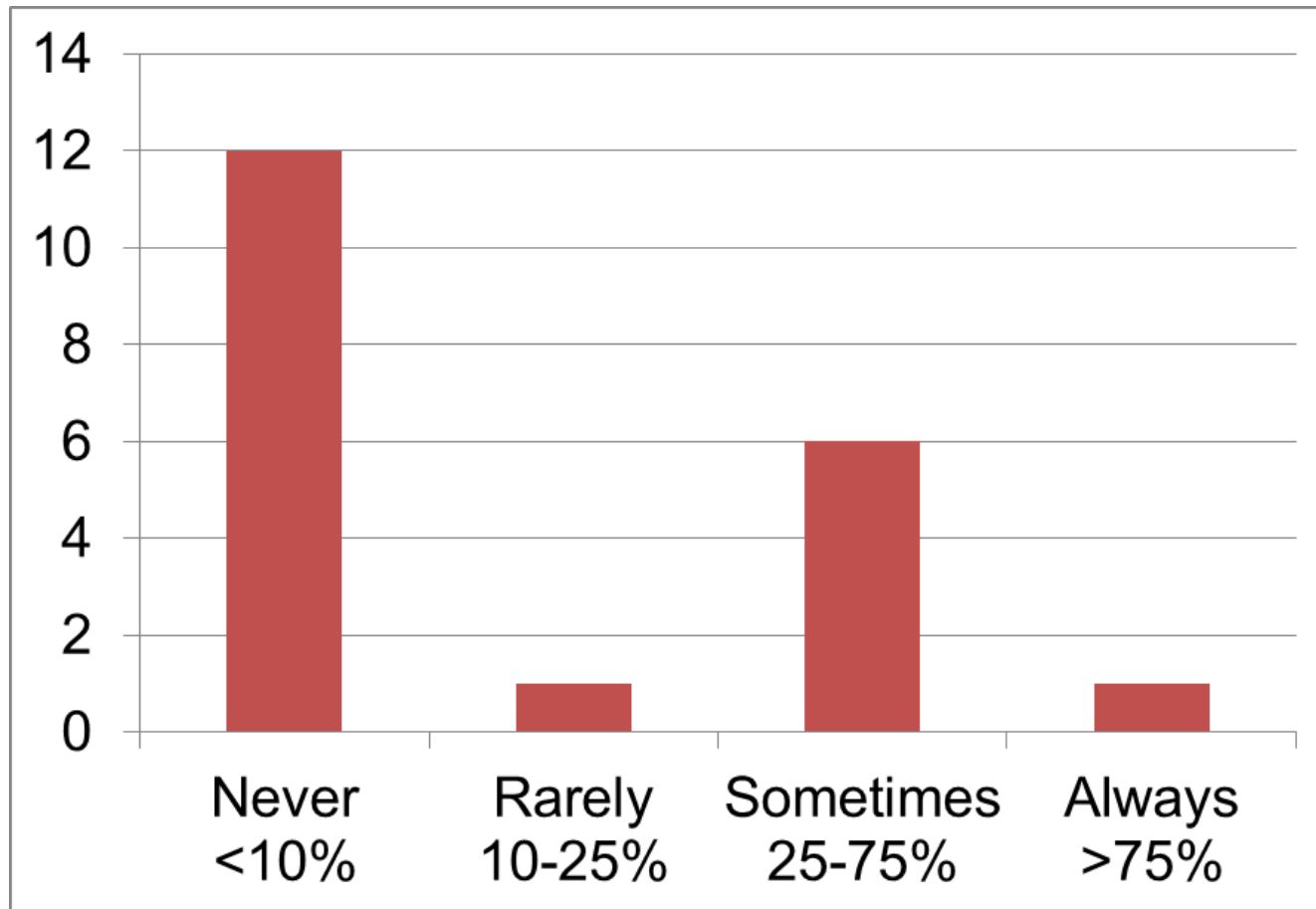
Dose prescription



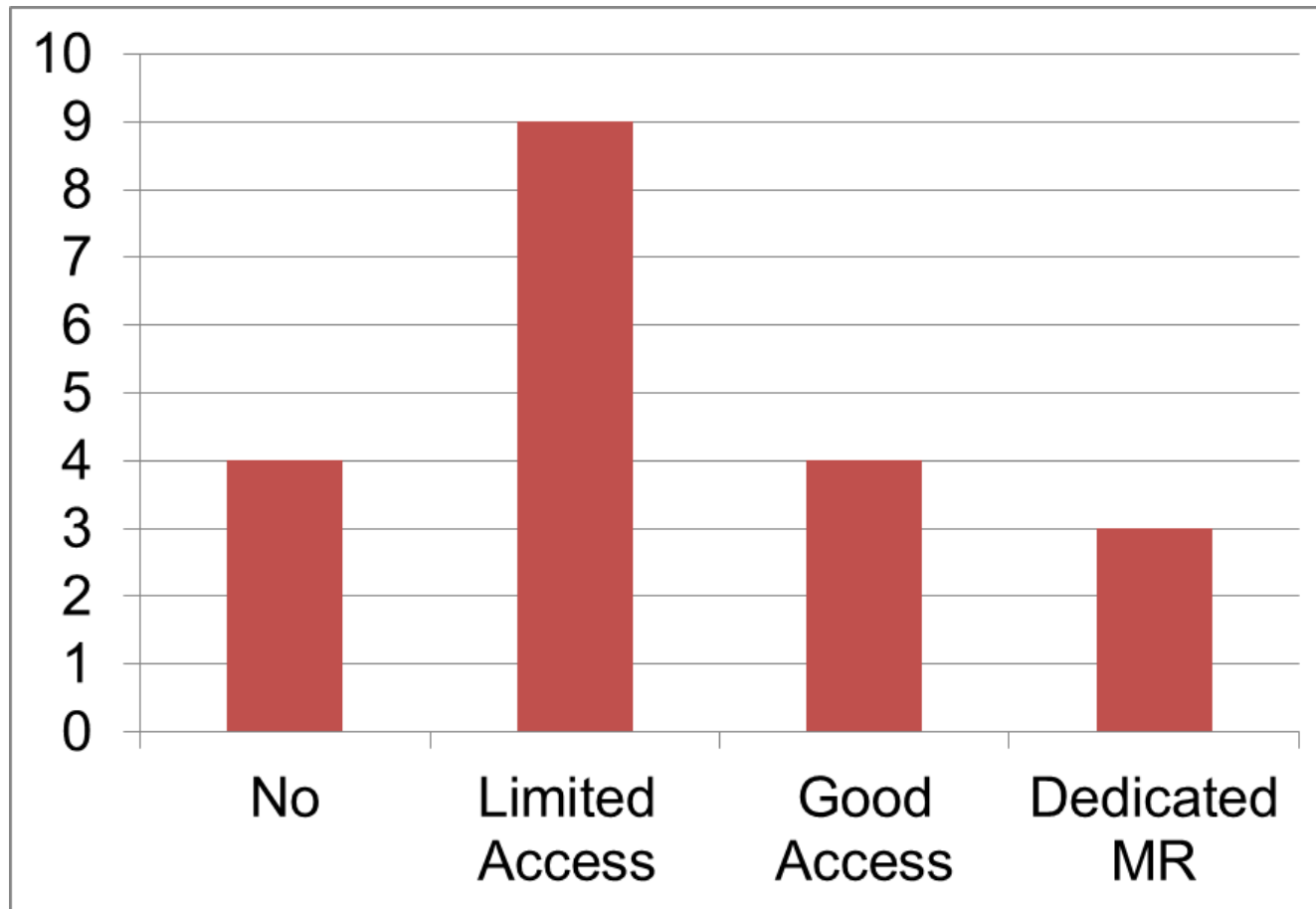
Brachytherapy Dose-Fractionation

Dose	Fractions	EQD2	Centres using (<i>n</i>)	<u>2016</u>
6 Gy	5	40 Gy	6	4
8 Gy	3	36 Gy	5	4
7 Gy	4	39.7 Gy	3	7
5.5 Gy	5	35.5 Gy	3	2
6.5 Gy	4	35.8 Gy	2	0
6 Gy	3	24 Gy	1	0
6 Gy	4	32 Gy	1	0
6.75	4	37.7 Gy	1	1
35 Gy ^a	—	35 Gy	2	1
4.6 Gy	6	33.6 Gy		1

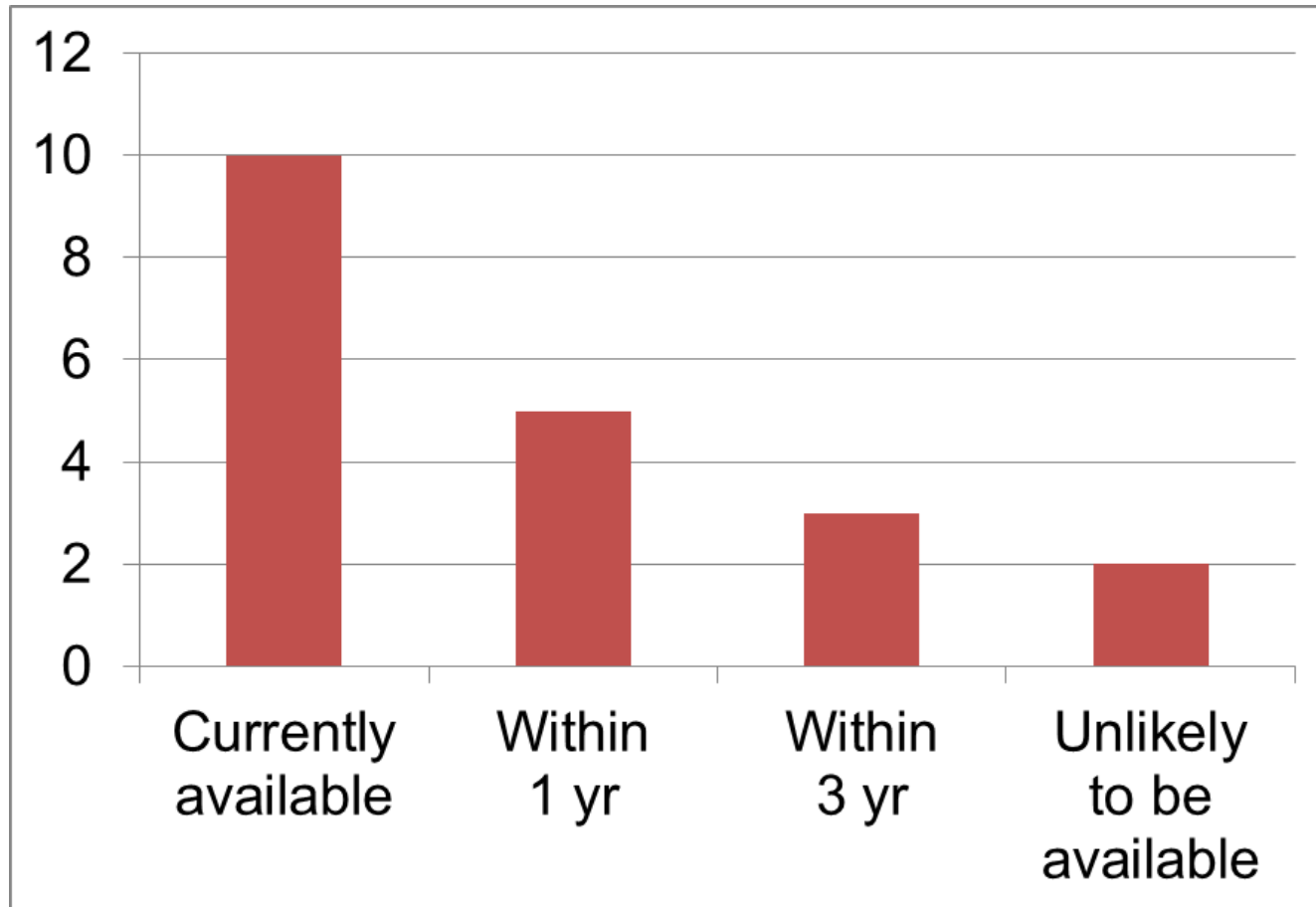
How often do you use interstitial needles?



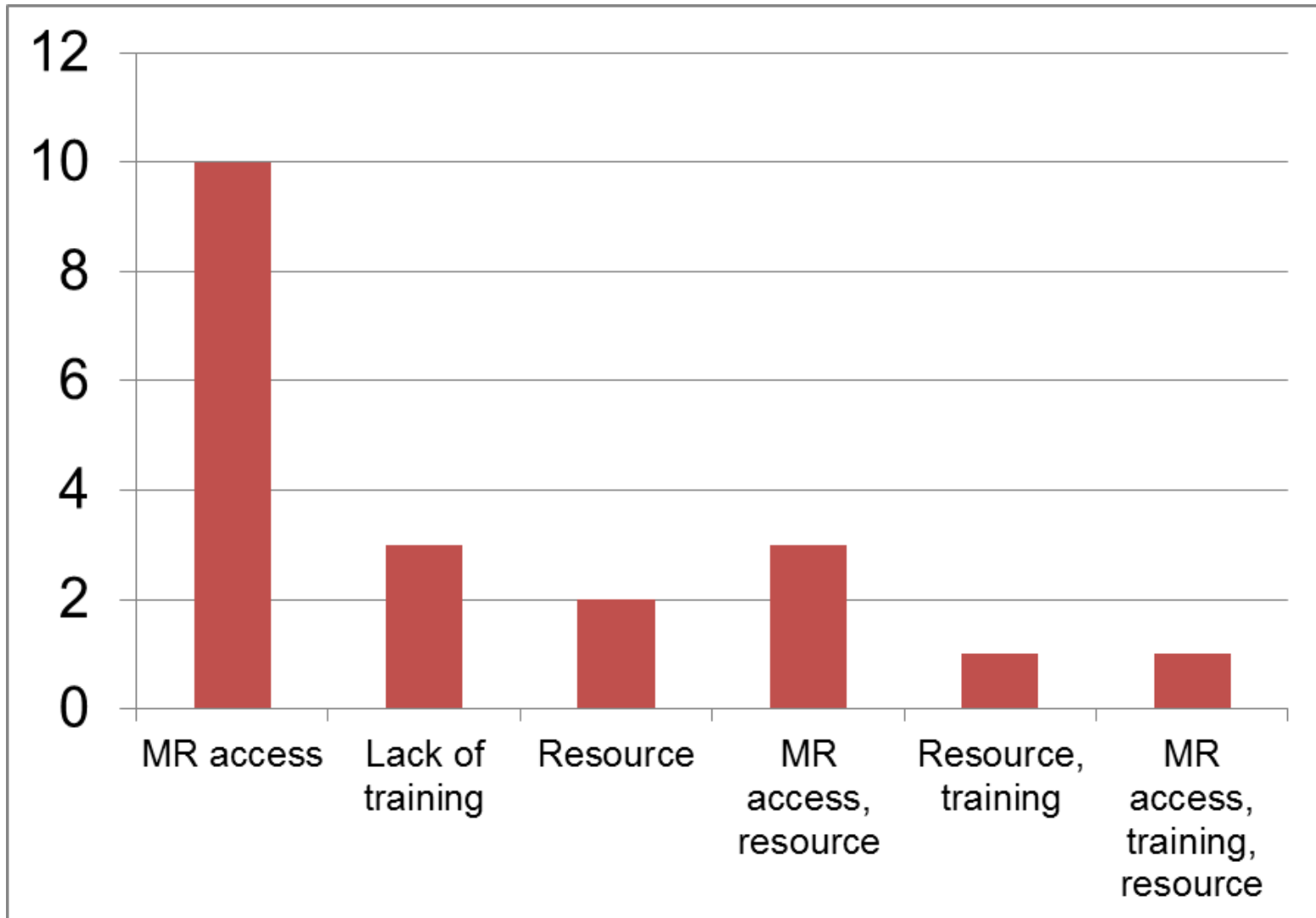
Is MR simulation available?



What is the current status of MR-guided brachytherapy (full 3D planning) at your centre?



What are/were the barriers to implementing MR-guided brachytherapy?



Cervical Cancer Key Quality-of-Care Indicators

Key Quality-of-Care Indicators

- Best practice Key Quality Indicators (KQIs) for the treatment of locally advanced cervical cancer in Canada
- Reflective of current (2014) and future (2019) practice
- Delphi method:
 - Phase 1: Survey of all Canadian GYN ROs
 - Phase 2: Face-to-face meeting of experts from across Canada

Endorsed Brachytherapy KQIs

1. Intracavitary brachytherapy is incorporated into treatment of locally advanced cervix cancer
2. Total external beam plus brachytherapy (Point A or HRCTV EQD2) is ≥ 80 Gy
3. CT or MR imaging is used after the first applicator insertion for brachytherapy planning
4. Doses to the OARs are documented in the medical record
5. Applicator stability is assured over the course of treatment
6. Dose to point A is documented in the medical record

Aspirational Brachytherapy KQIs

Future practice (2019)

1. MR-guided intracavitary brachytherapy is incorporated into treatment of locally advanced cervix cancer
2. Interstitial brachytherapy is available when indicated
3. MRI is used after each insertion for target and OAR delineation and treatment planning

The Princess Margaret Experience

PM Brachytherapy Technique

PDR

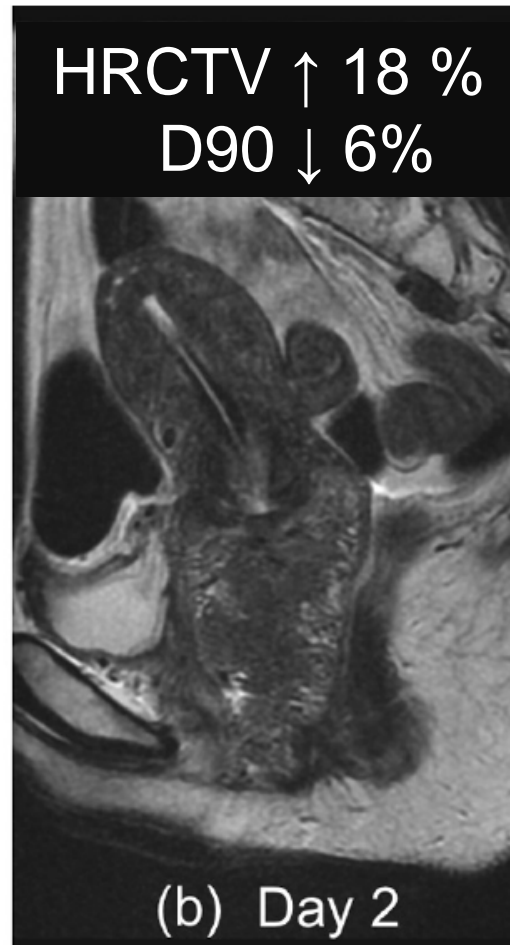
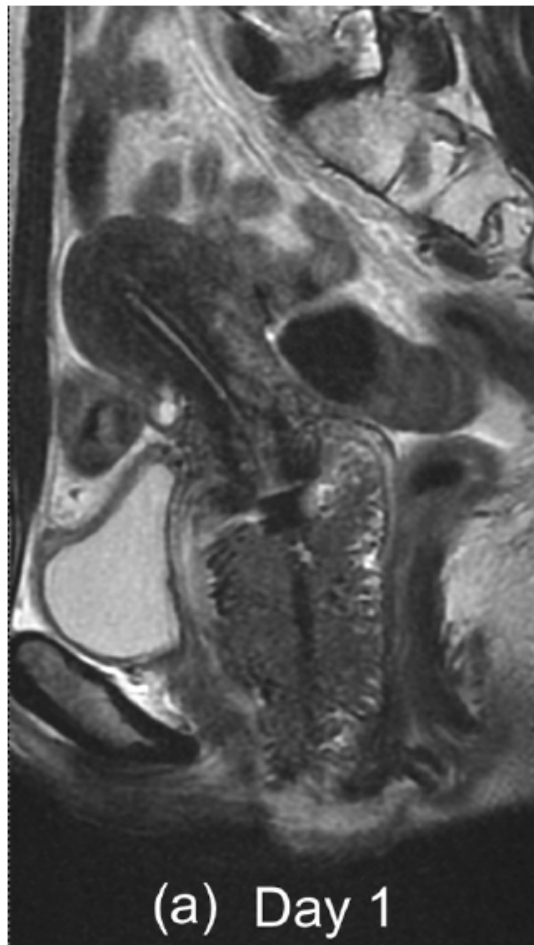
2008

Feb
2014

July
2014

Oct
2014

Increase in uterine volume & HRCTV during PDR brachytherapy



PM Brachytherapy Technique

PDR

2008

HDR

Feb
2014

July
2014

Oct
2014



PM HDR Brachytherapy Process

Pre-Brachy MRI

Fraction 1

Insert
Applicator

MRI

Contour
& Plan

Treat: 7 Gy

Fraction 2

MRI

Contour
& Plan

Treat: 7 Gy

Fraction 3

Insert
Applicator

MRI

Contour
& Plan

Treat: 7 Gy

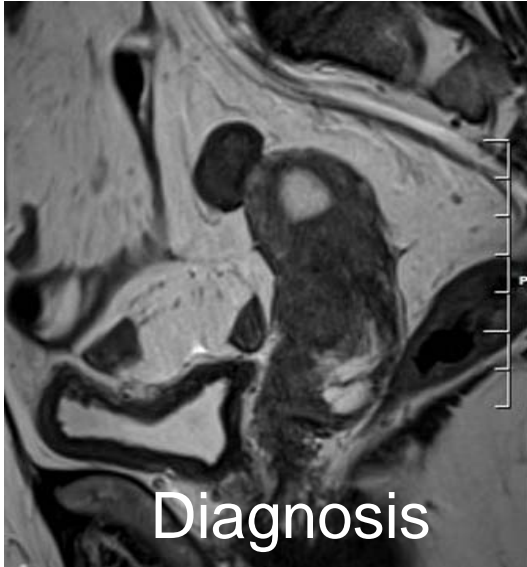
Fraction 4

MRI

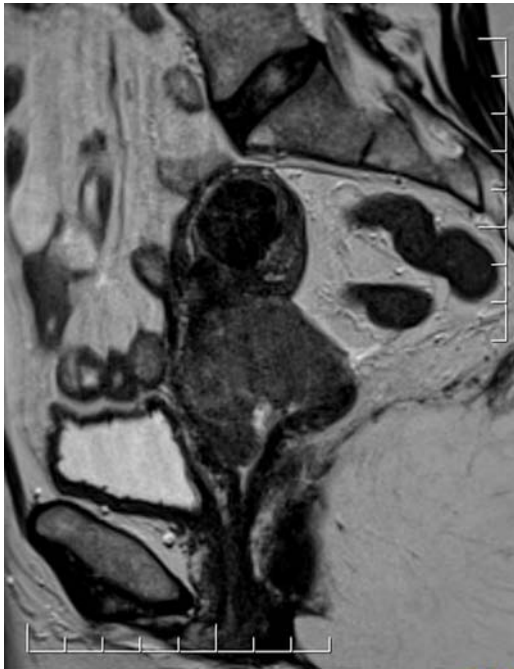
Contour
& Plan

Treat: 7 Gy

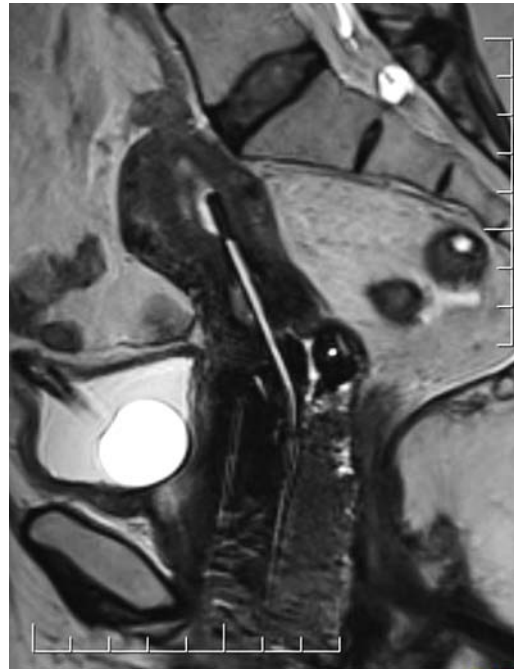
Changes during HDR Brachytherapy



Changes during HDR Brachytherapy



Diagnosis



Fraction 1



Fraction 2

PM Brachytherapy Technique

PDR

2008

HDR

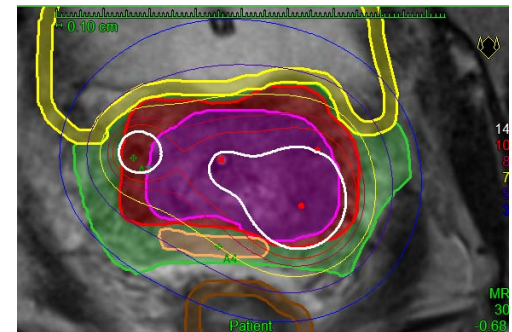
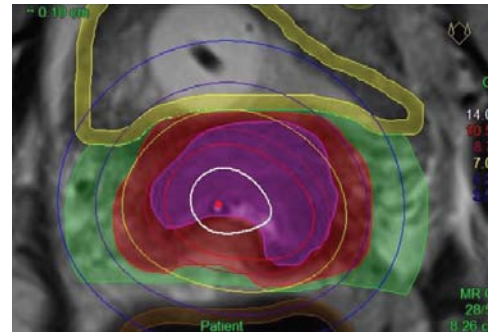
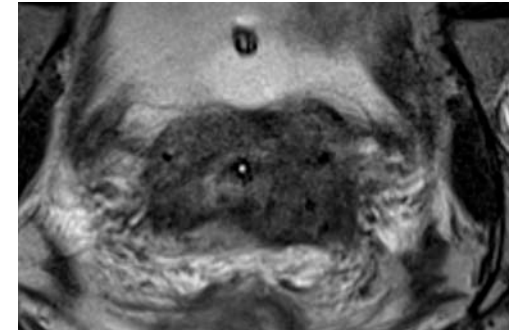
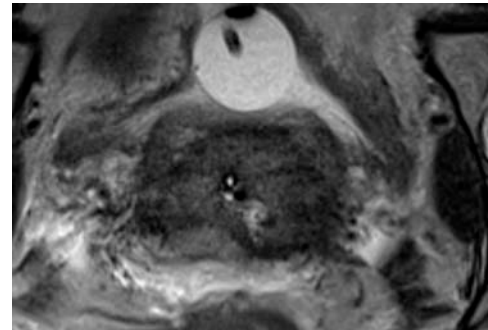
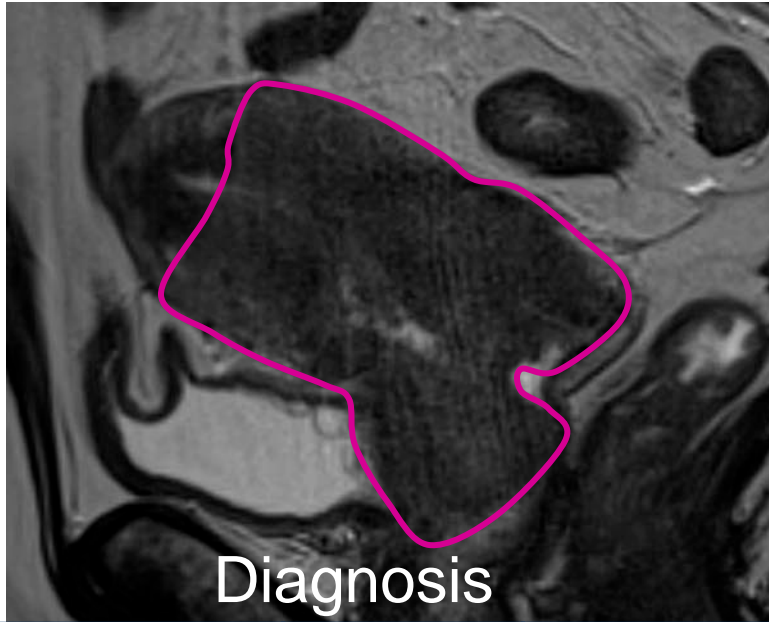
Feb
2014

July
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Oct
2014



Stage IVA Cervical SCC

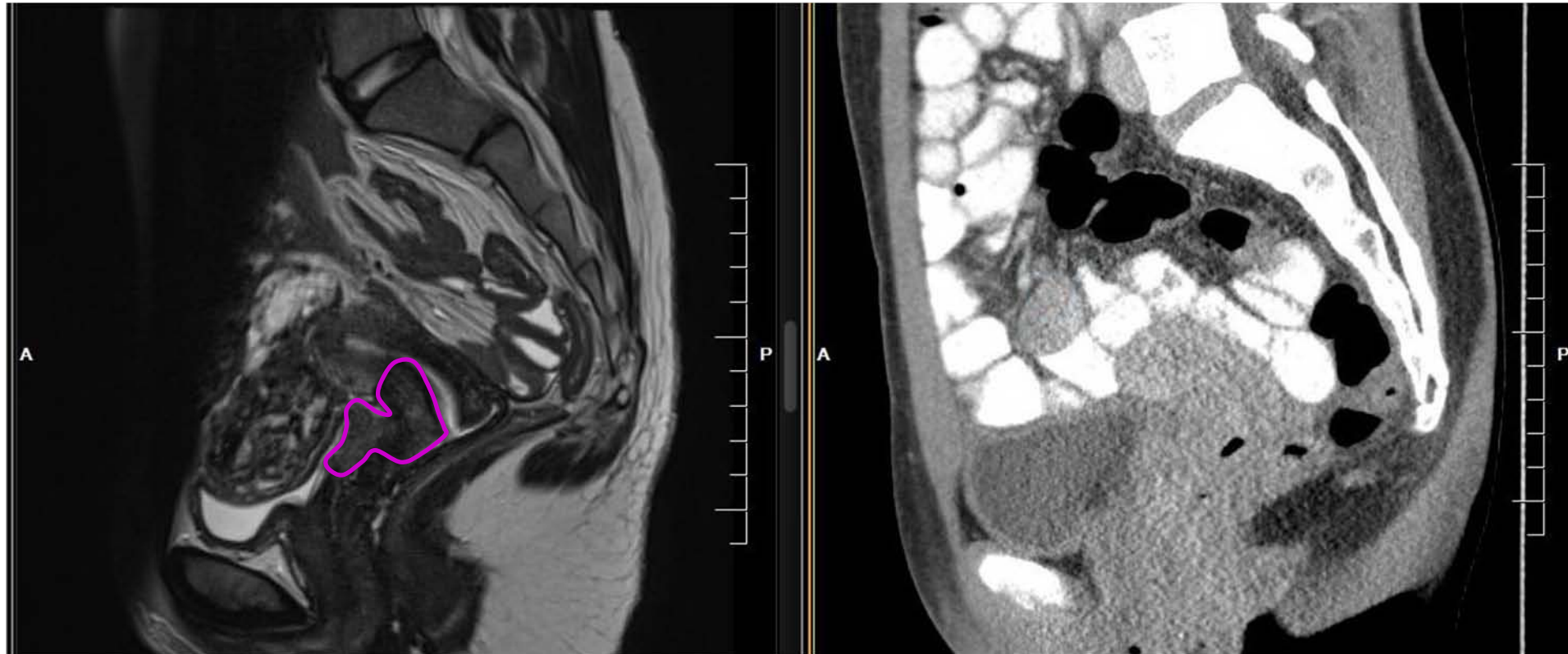


Fraction 1

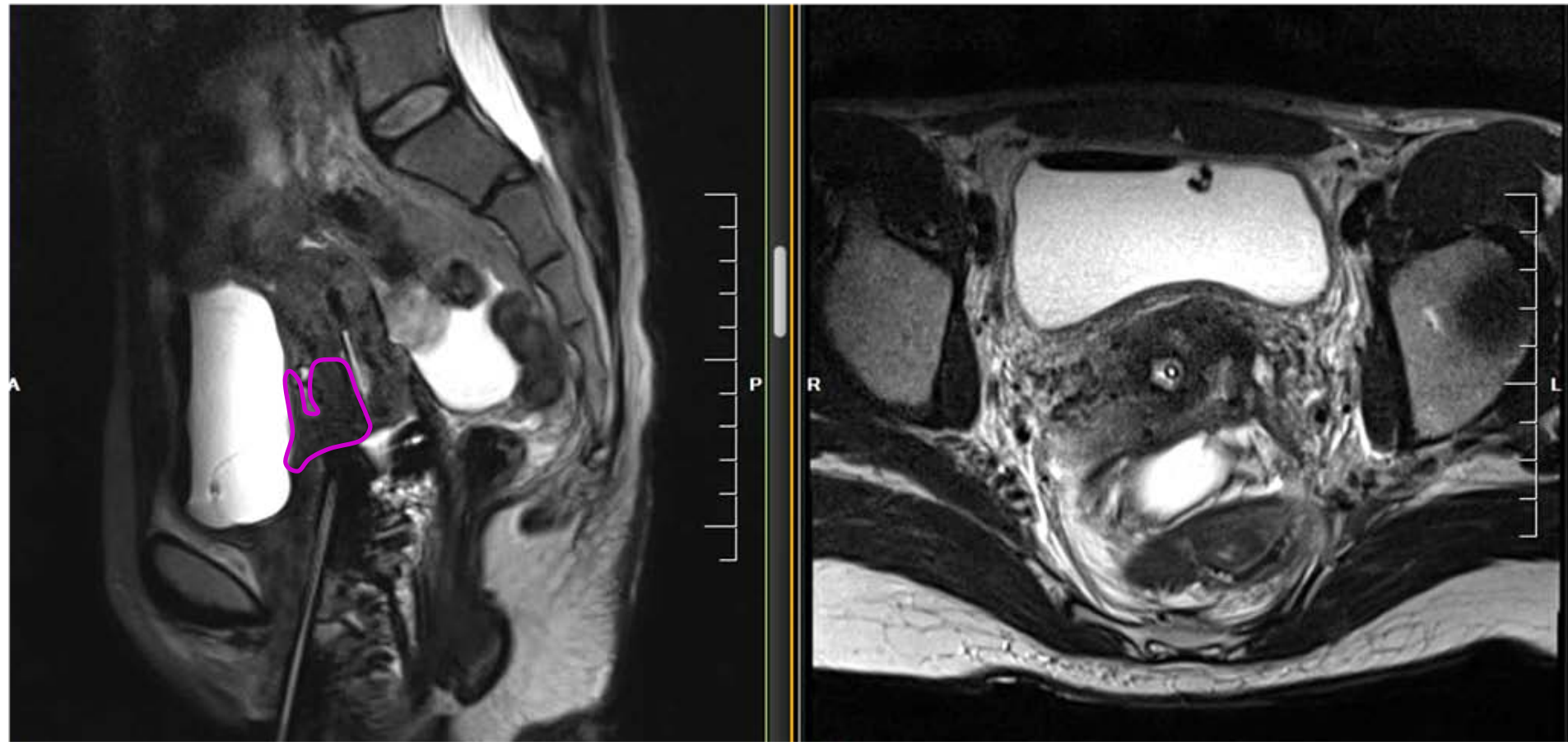
Fraction 3

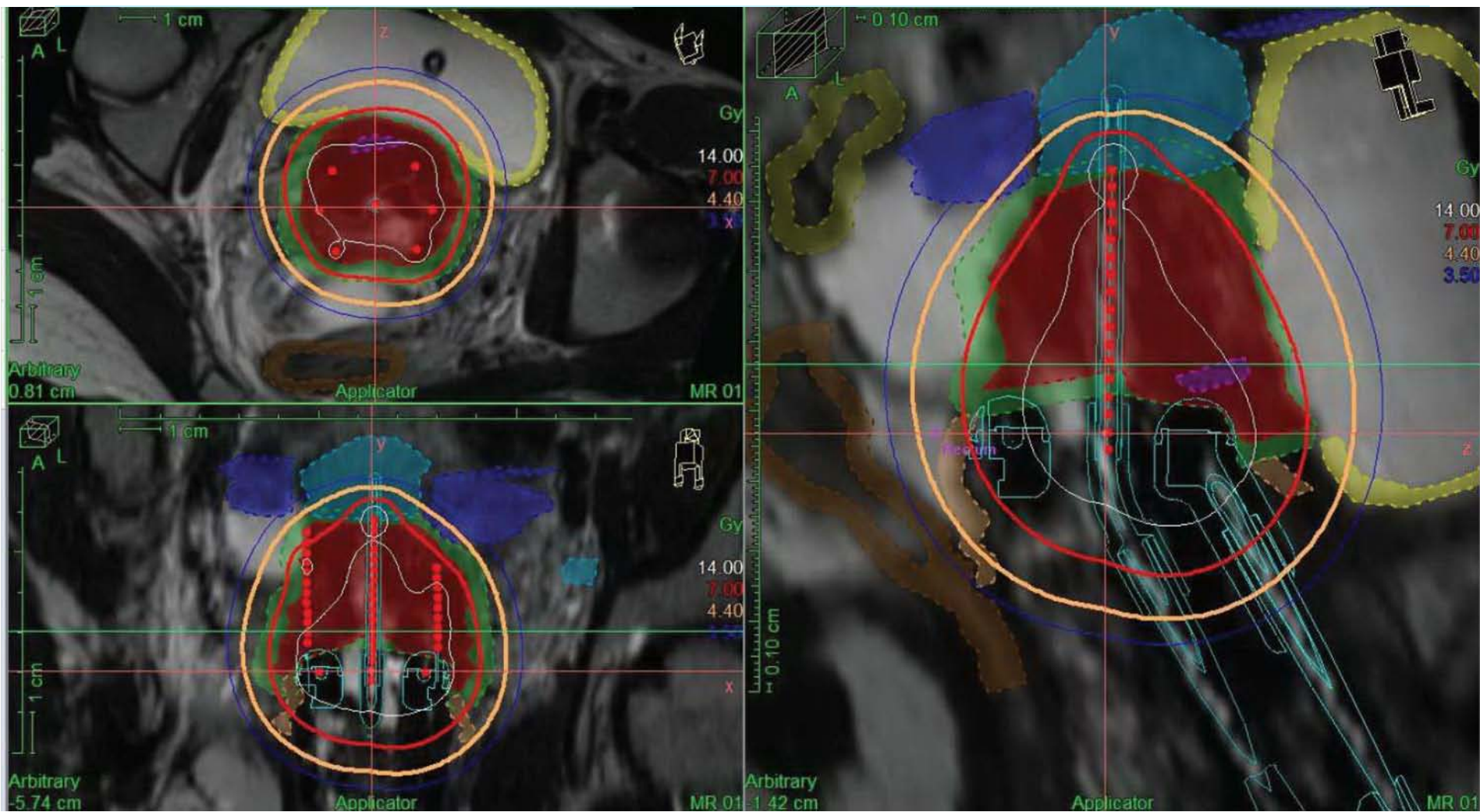
	TR Only F1, F2	Needles F3, F4
HR CTV D ₉₀	79 Gy ₁₀	85 Gy ₁₀
Rectum D _{2cc}	75 Gy ₃	71 Gy ₃
Sigmoid D _{2cc}	78 Gy ₃	74 Gy ₃
Bladder D _{2cc}	105 Gy ₃	95 Gy ₃

Stage IVA Cervical SCC



Stage IVA Cervical SCC





HRCTV D90 93 Gy
D_{2cc} bladder 85 Gy

D_{2cc} sigmoid 55 Gy
D_{2cc} rectum 55 Gy
D_{2cc} small bowel 67 Gy

PM Brachytherapy Technique

PDR

2008

HDR

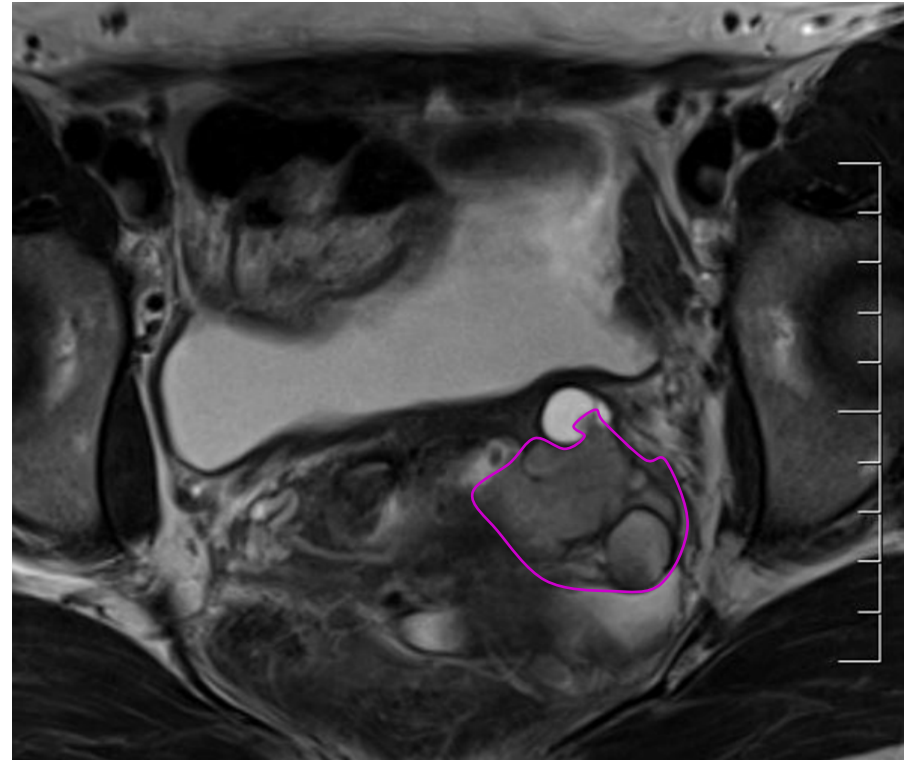
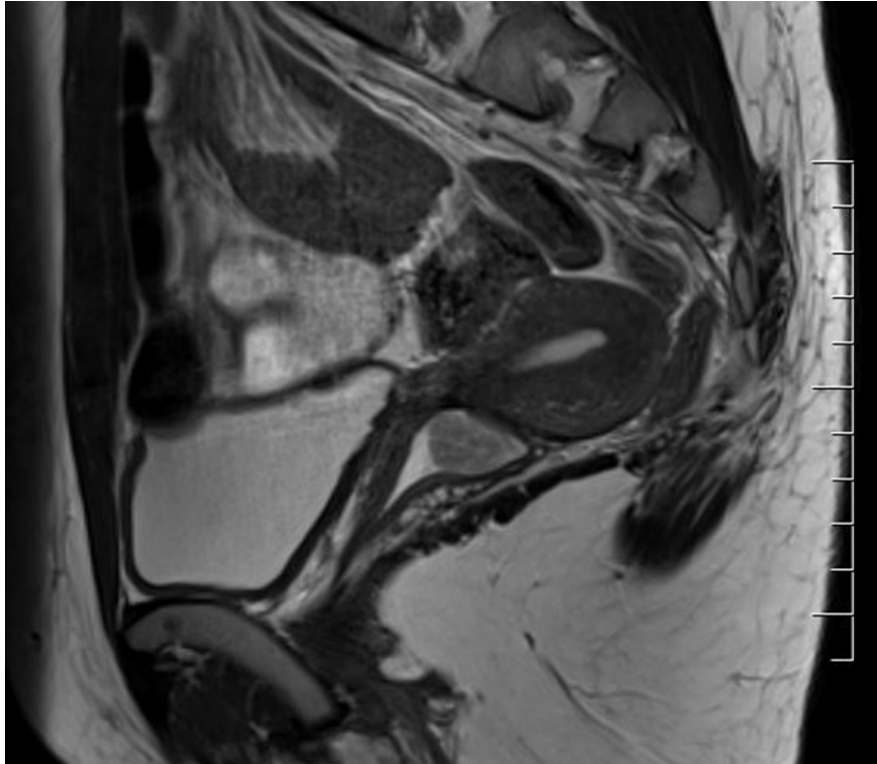
Feb
2014

July
2014

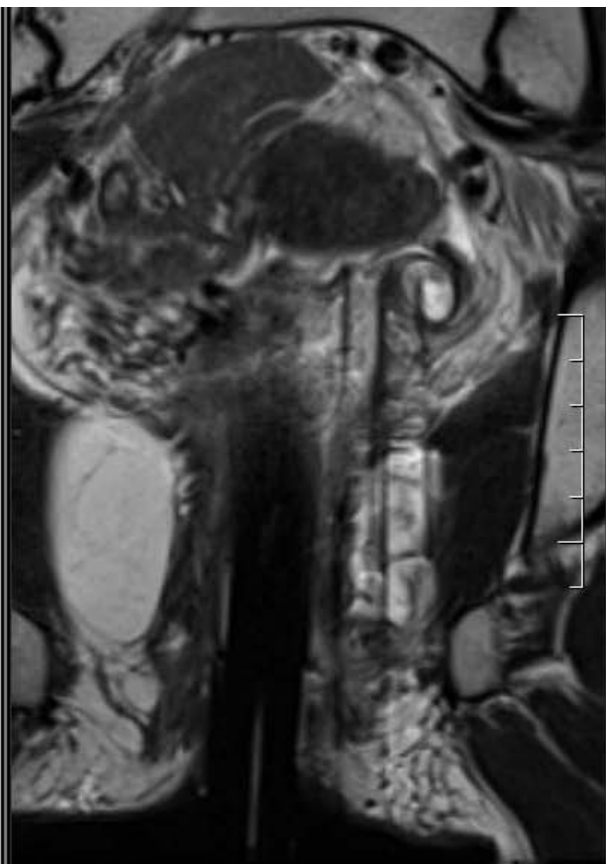
Oct
2014



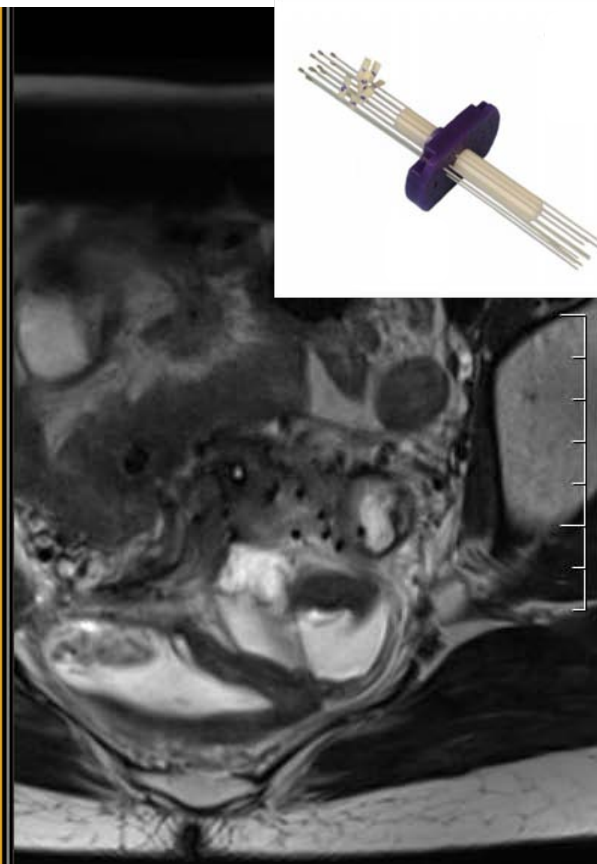
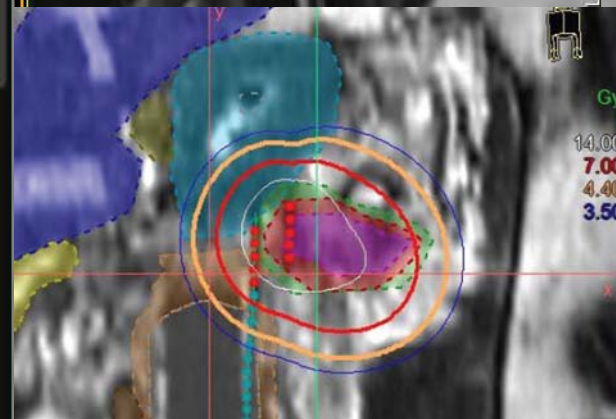
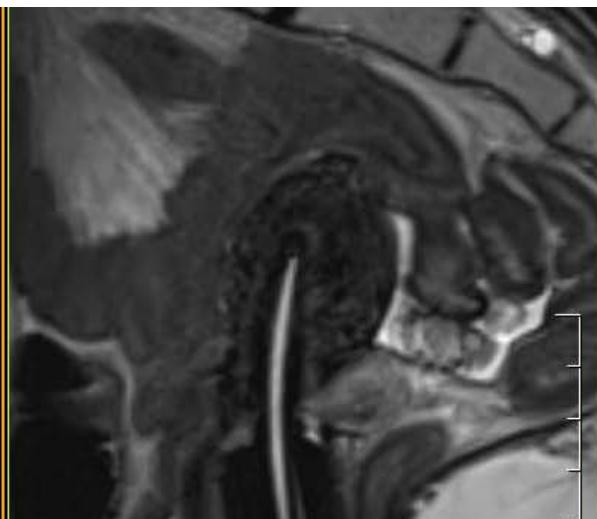
Vaginal recurrence of cervical adenocarcinoma after trachelectomy



Vaginal recurrence of cervical adenocarcinoma after trachelectomy



HRCTV D90 97 Gy



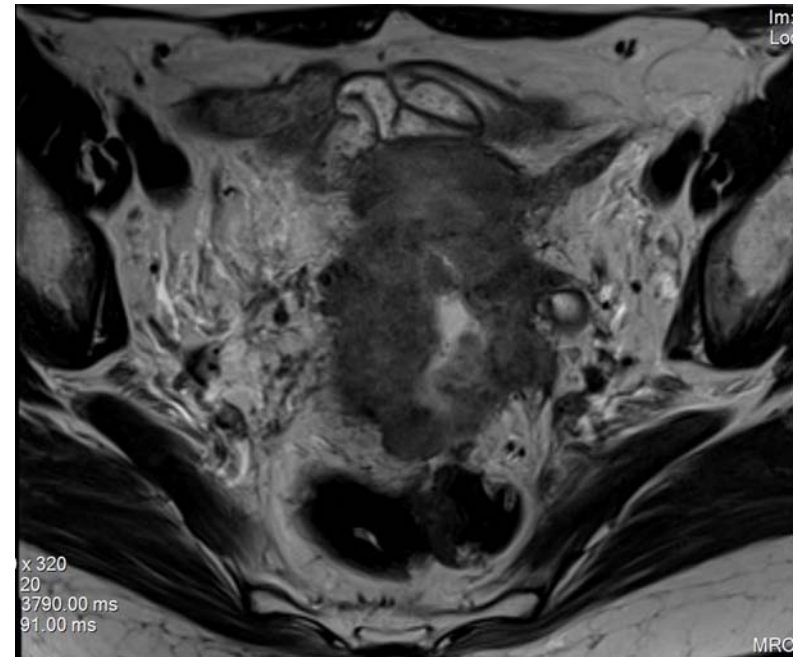
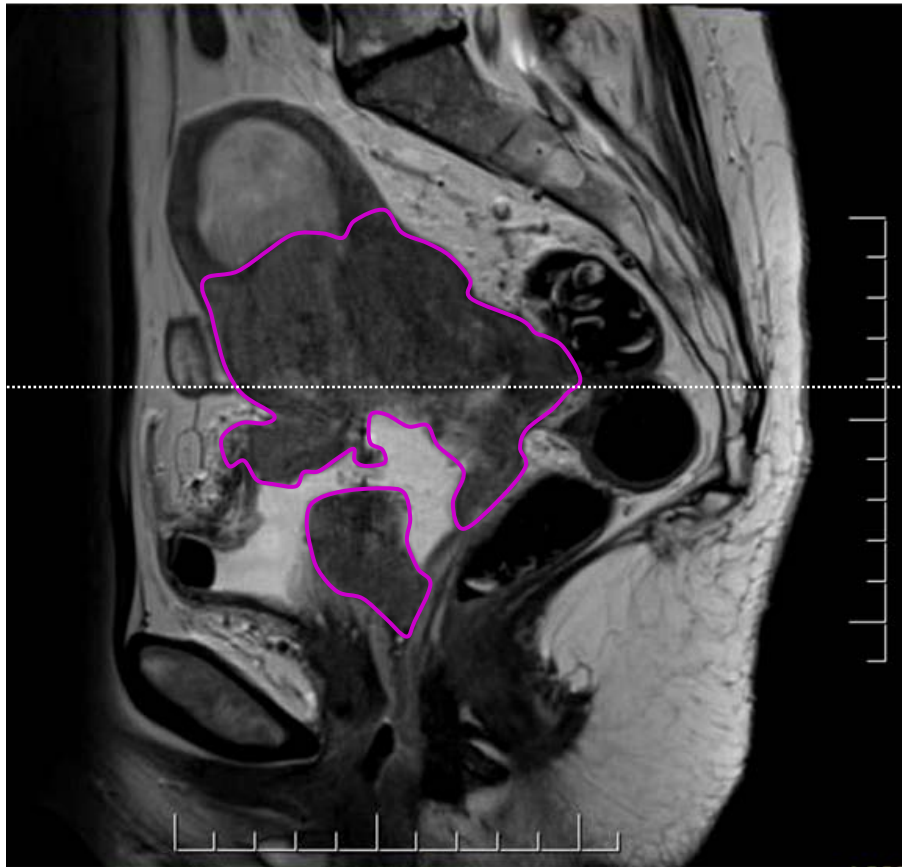
D_{2cc} bladder 67 Gy

D_{2cc} rectum 59 Gy

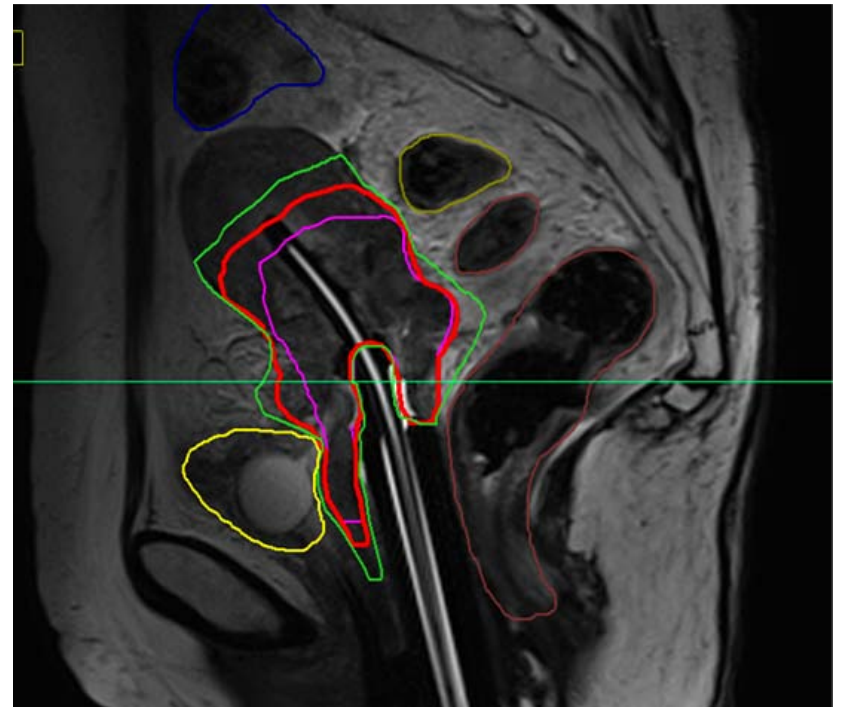
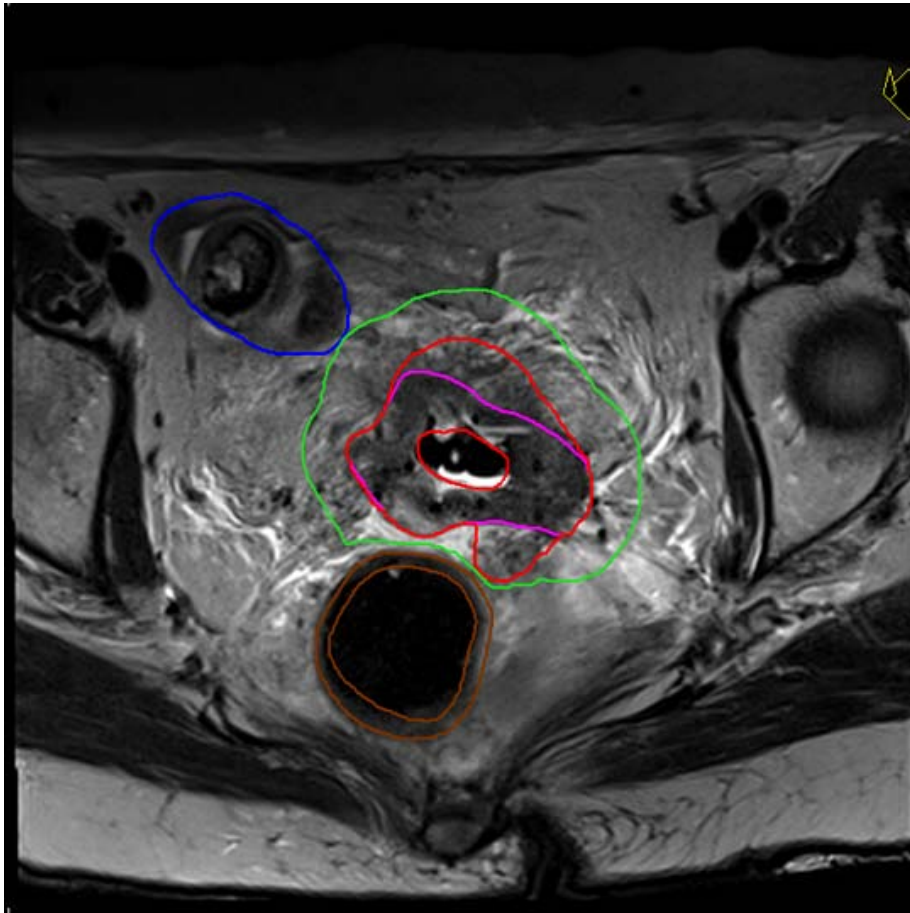
D_{2cc} small bowel 53 Gy

D_{2cc} sigmoid 52 Gy

Stage IVA Cervical SCC



Stage IVA Cervical SCC

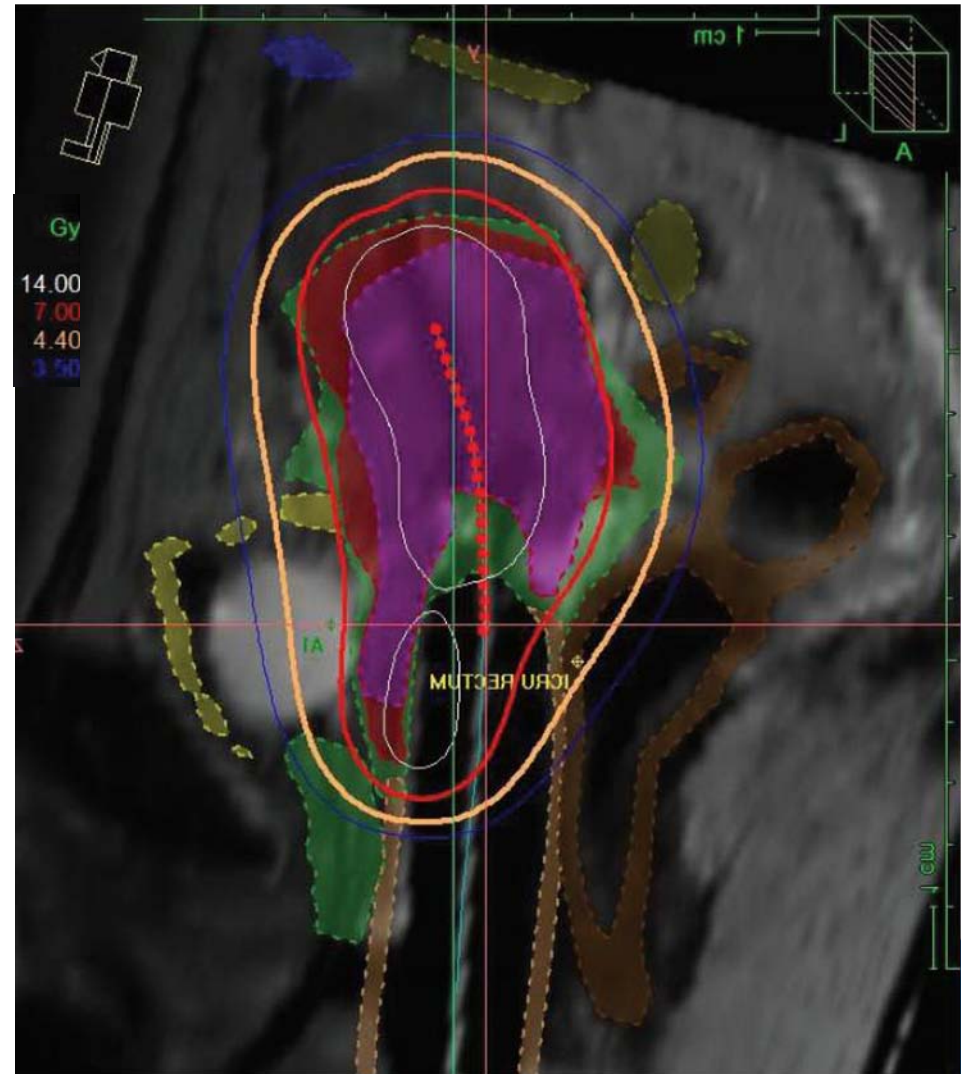
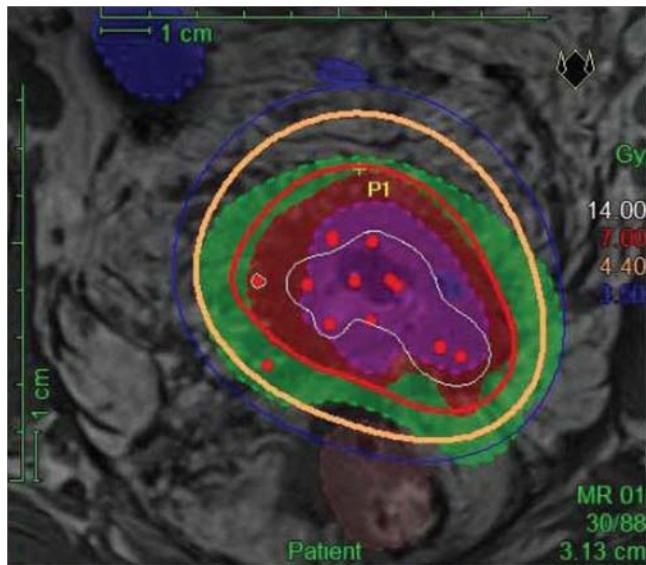


GTV

HRCTV

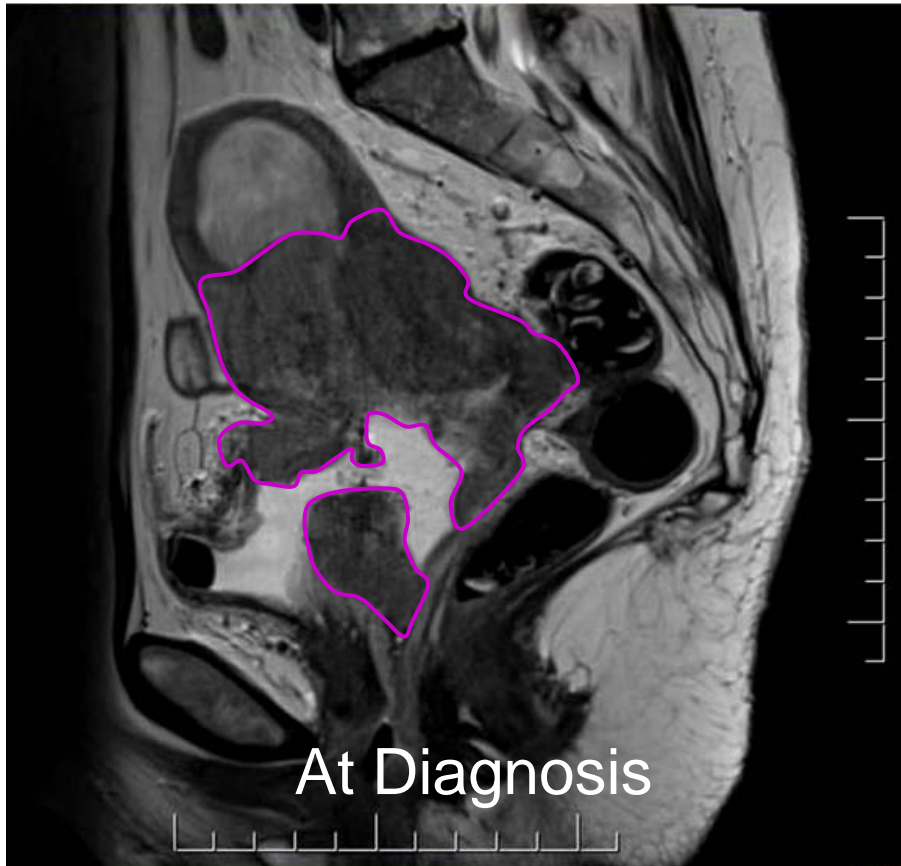
IRCTV

Stage IVA Cervical SCC



HRCTV D90	92 Gy
D_{2cc} bladder	72 Gy
D_{2cc} rectum	72 Gy
D_{2cc} sigmoid	64 Gy

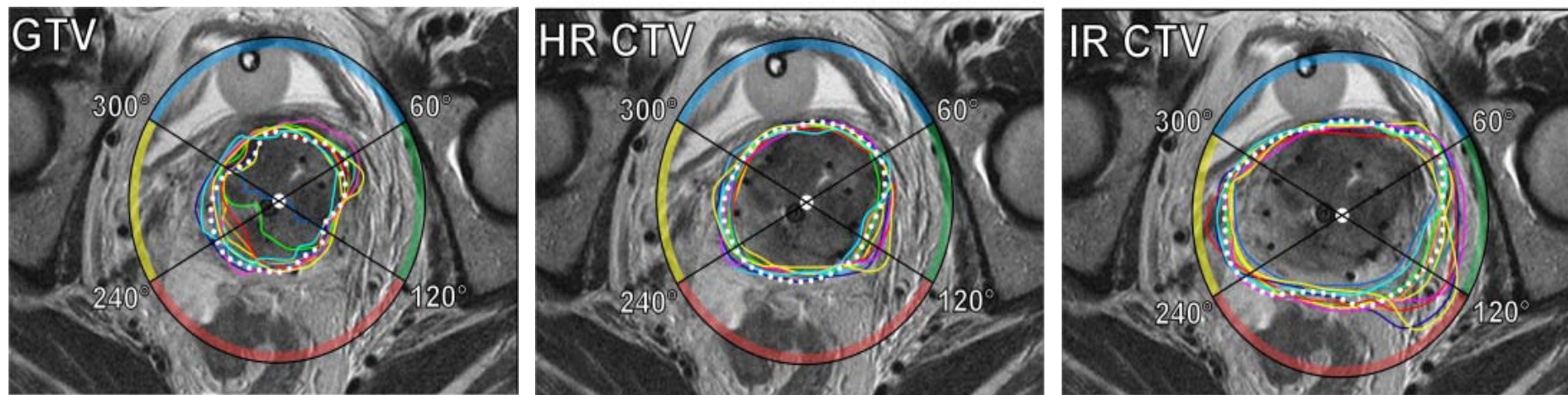
Stage IVA Cervical SCC



Planning Aims

Structure	Aims (EQD2)	
	Previous	Current/ EMBRACE II
GTV D98	--	> 95 Gy
HRCTV D90	> 85 Gy	> 90 - < 95 Gy
Rectum D _{2cc}	< 75 Gy	< 65 Gy
Sigmoid D _{2cc}	< 75 Gy	< 70 Gy
Bladder D _{2cc}	< 90 Gy	< 80 Gy

Inter-Observer Variability Among Experts



“In the future, functional MRI and scanners with high field strength may further improve the accuracy of target (sub) volume delineation...”

Prospective Study of DCE-MRI, DWI and ¹⁸F-FDG-PET Imaging for Target Delineation in Brachytherapy for Cervix Cancer

Brachytherapy applicator insertion

Standard 3T T2w MRI simulation + *DWI & DCE-MRI*

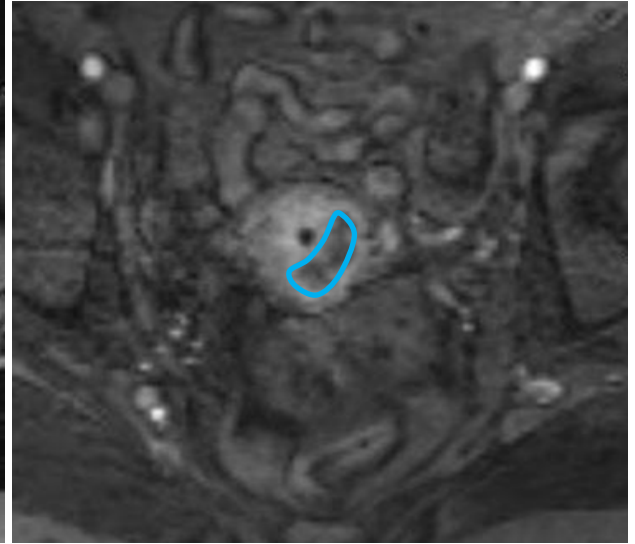
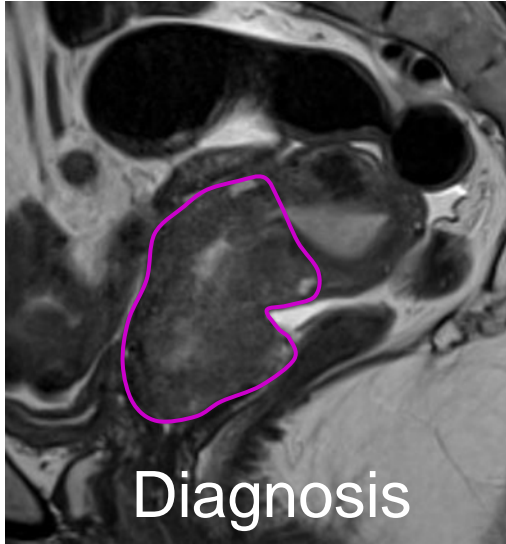
FDG PET-CT

Optimised Brachytherapy

*MRI (T2w, DWI & DCE-MRI) every 3 months x 2 years
& FDG PET-CT 3 months after finishing Rx*

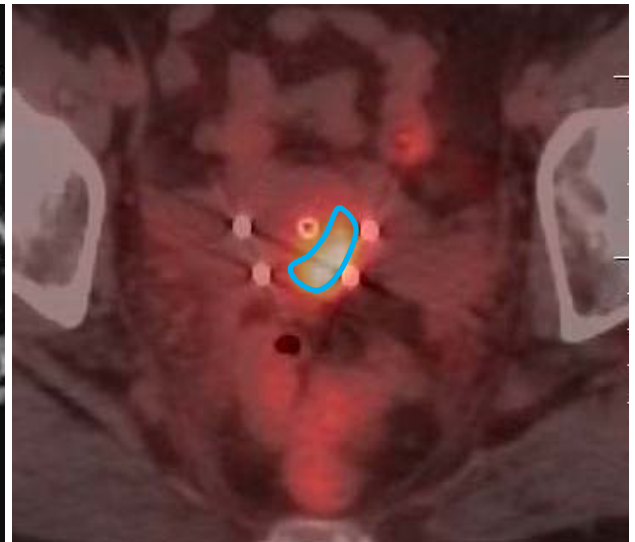
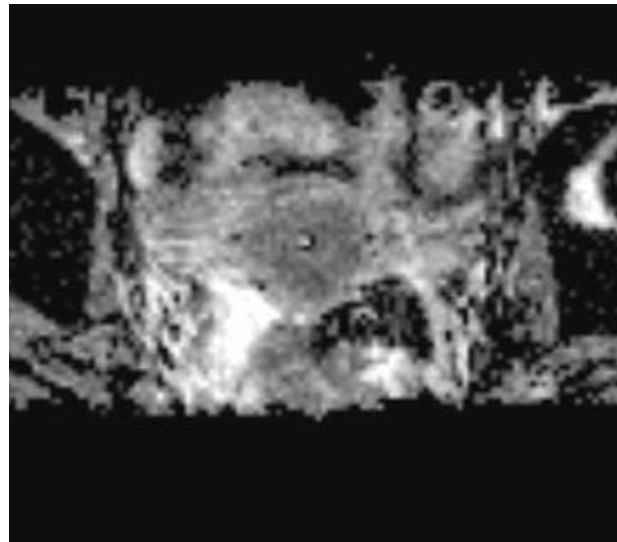
T2

DCE

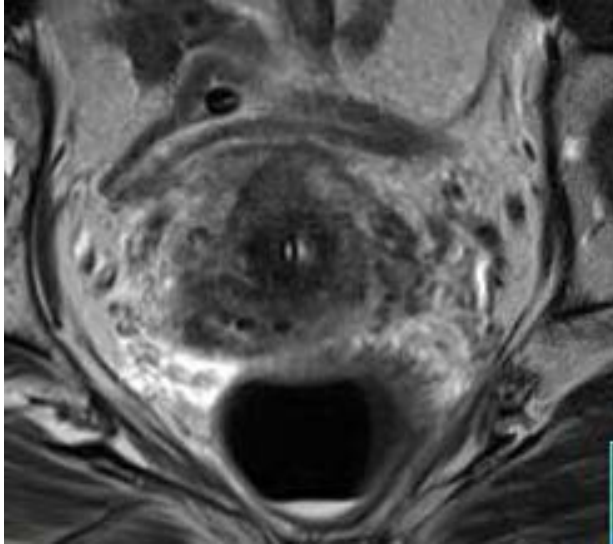


ADC (DWI)

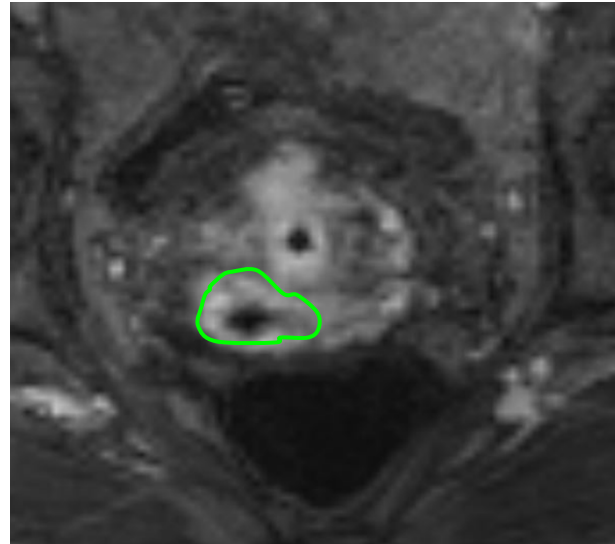
FDG PET



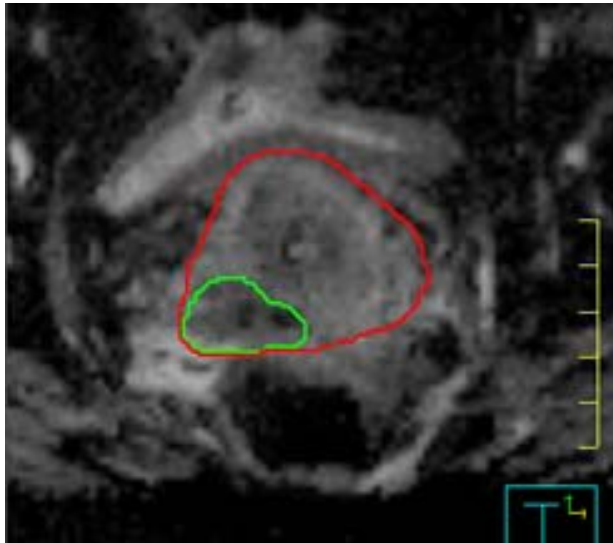
T2



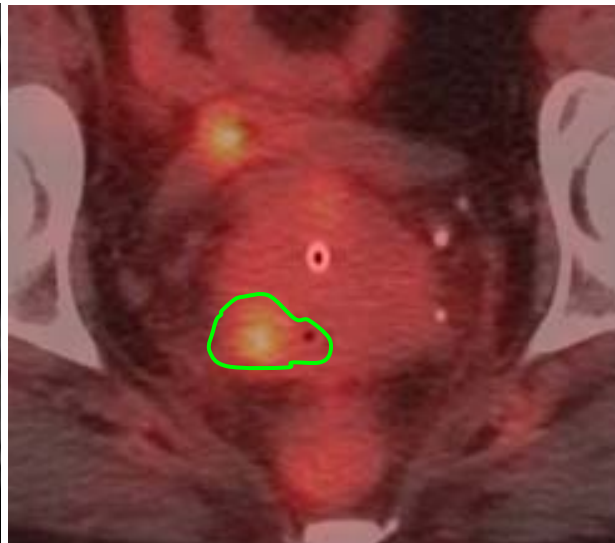
DCE



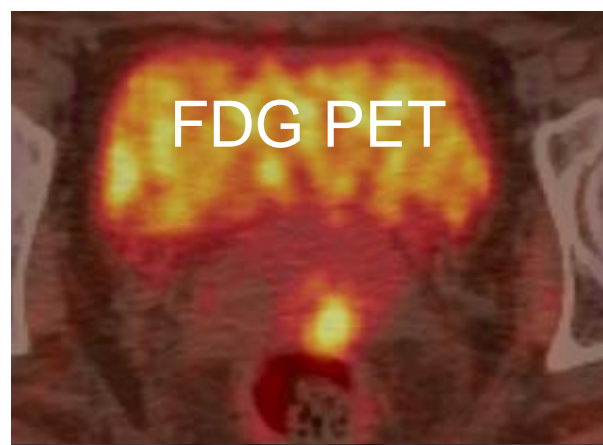
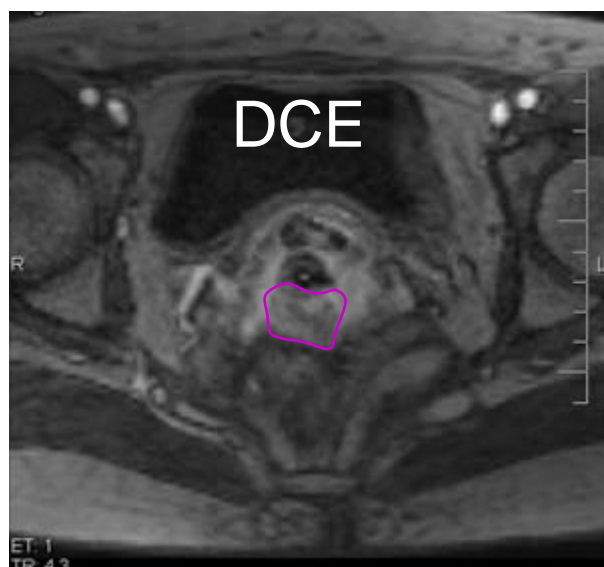
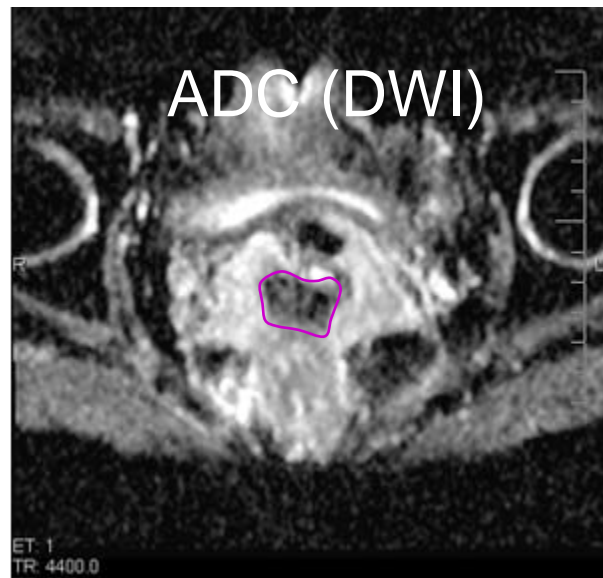
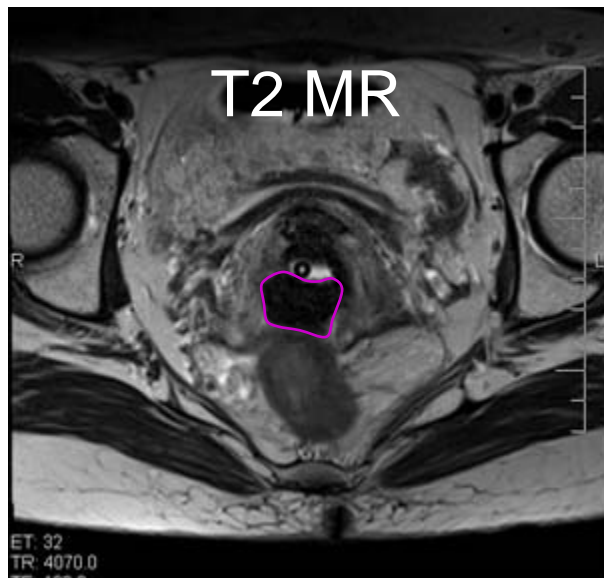
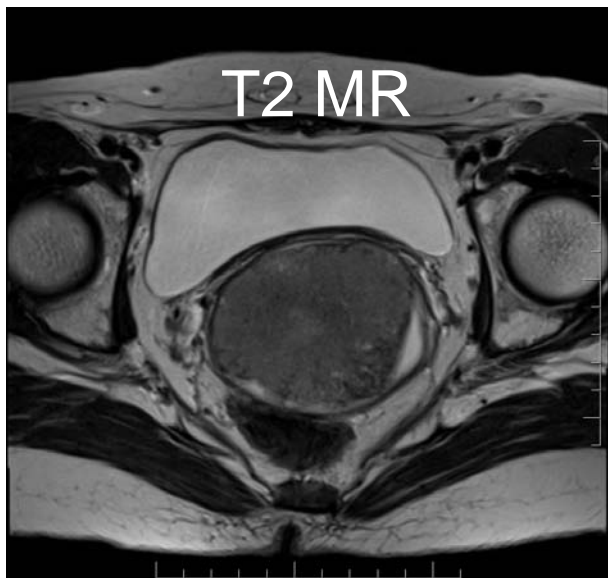
ADC (DWI)



FDG PET



Diagnosis



HRCTV D90 = 98Gy

MR-Guided Radiotherapy Suite



MR-Guided Brachytherapy Suite



MR-Guided Brachytherapy Suite



Summary

- Brachytherapy is crucial for the cure of cervix cancer with RT
- MR-guided brachytherapy has been implemented by many centres in Canada
- The main barrier remains access to MRI
- The goal is to use MR for planning after each insertion and interstitial needles when indicated

Acknowledgements

Radiation Oncology: A. Fyles, M. Milosevic, J. Croke, W. Levin, E. Leung, C. Menard, A. Viswanathan
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Biostatistics: M. Pintilie

CARO-Elekta
RSNA
EIRR21
TFRI

ESTRO-CARO Course Directors, Coordinators & Participants



The Terry Fox Research Institute
L'Institut de recherche Terry Fox



ELEKTA



**PRACTICAL EXAMPLE
VIE003JR**

Large tumour, bad response to EBRT

LARGE TUMOUR, BAD RESPONSE

Overview

- Initial findings
 - Initial clinical findings
 - Initial MRI findings
 - Other
- EBRT, chemotherapy
- Findings at BRACHYTHERAPY (BT)
 - Clinical findings at BT
 - MRI findings at BT
- Delineation of GTV, CTV and Organs At Risk (OAR)

LARGE TUMOUR, BAD RESPONSE

Initial findings

Patient & Tumour

Patient:

41 years old

lap. LN-Staging:pN0

Tumour:

Histological type: SCC

FIGO stage: 2b

Initial clinical findings:

Portio:

Exo-/Endophytic tumour

Vagina:

Involvement of left fornix

Parametria:

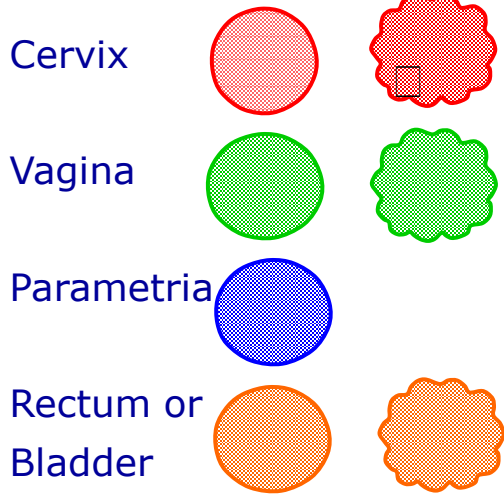
Right: proximal infiltration

Left: distal infiltration

Details: see *Initial Clinical Drawings* (next slide)

Clinical drawings at diagnosis

Infiltrative Exophytic



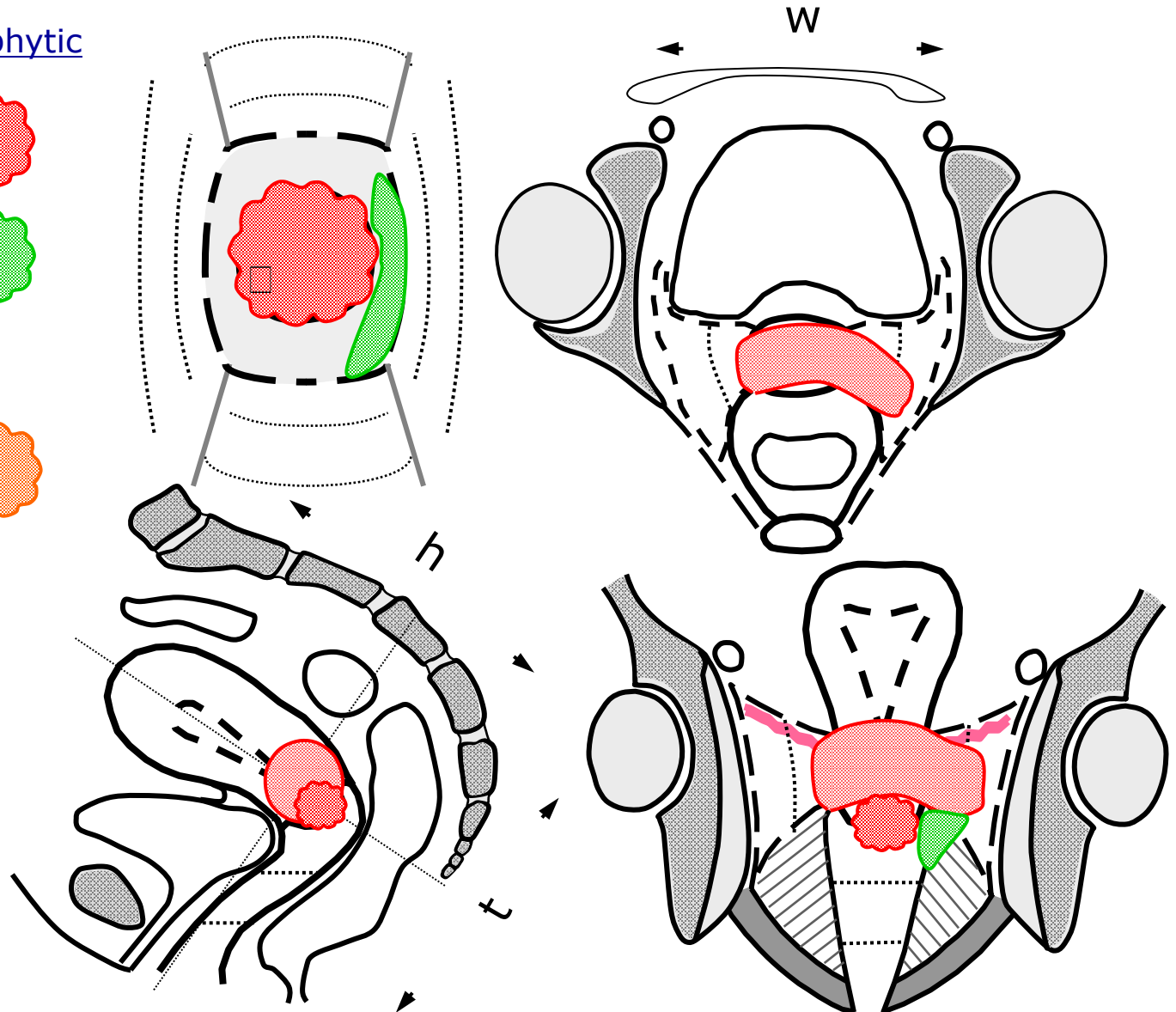
Tumour size:

Width: 6 cm

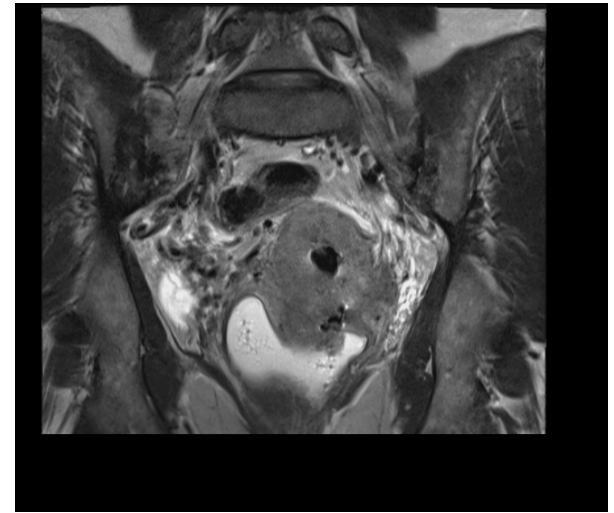
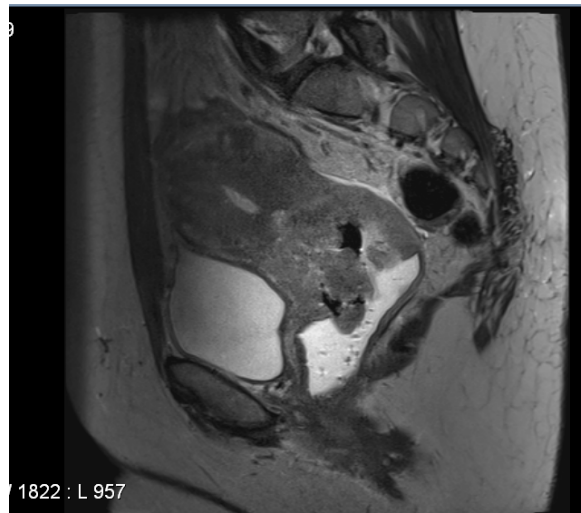
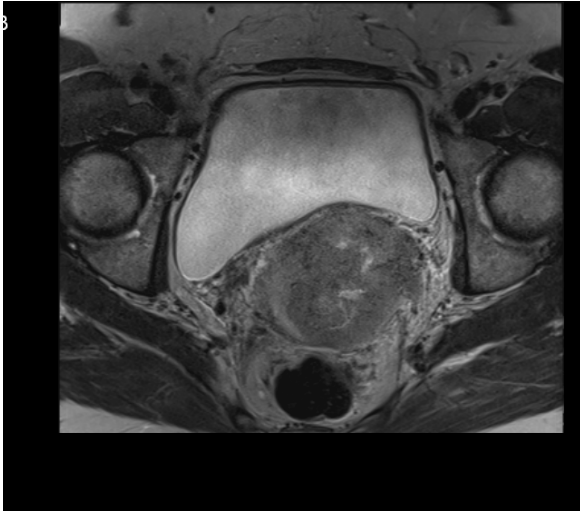
Thickness: 6 cm

Height: 5 cm

Vaginal inv.: 1 cm



MRI findings at diagnosis



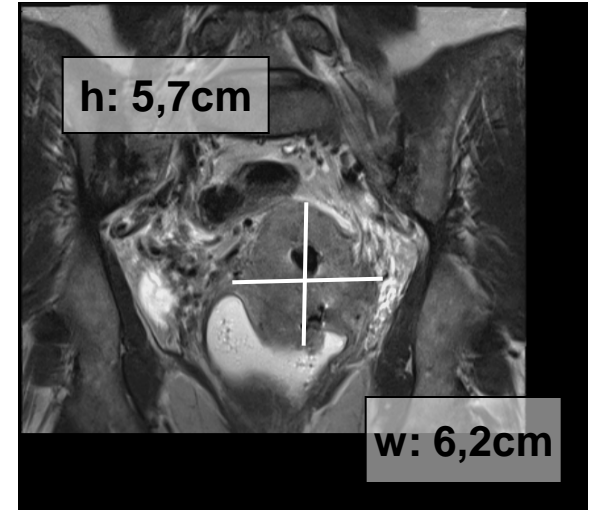
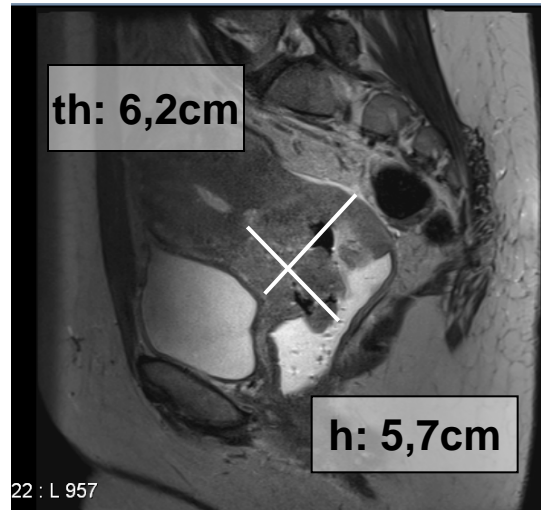
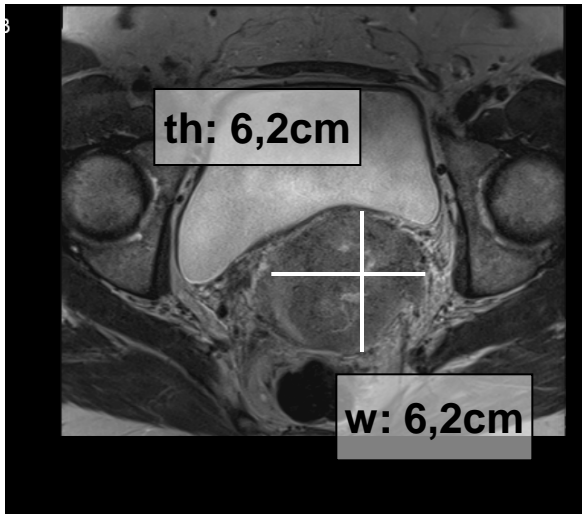
EBRT Treatment

EBRT: IMRT; pelvis

TD: 45 Gy

Concurrent cisplatin 40 mg/m², 5 cycles

MRI findings at diagnosis



$$V=110\text{cm}^3$$

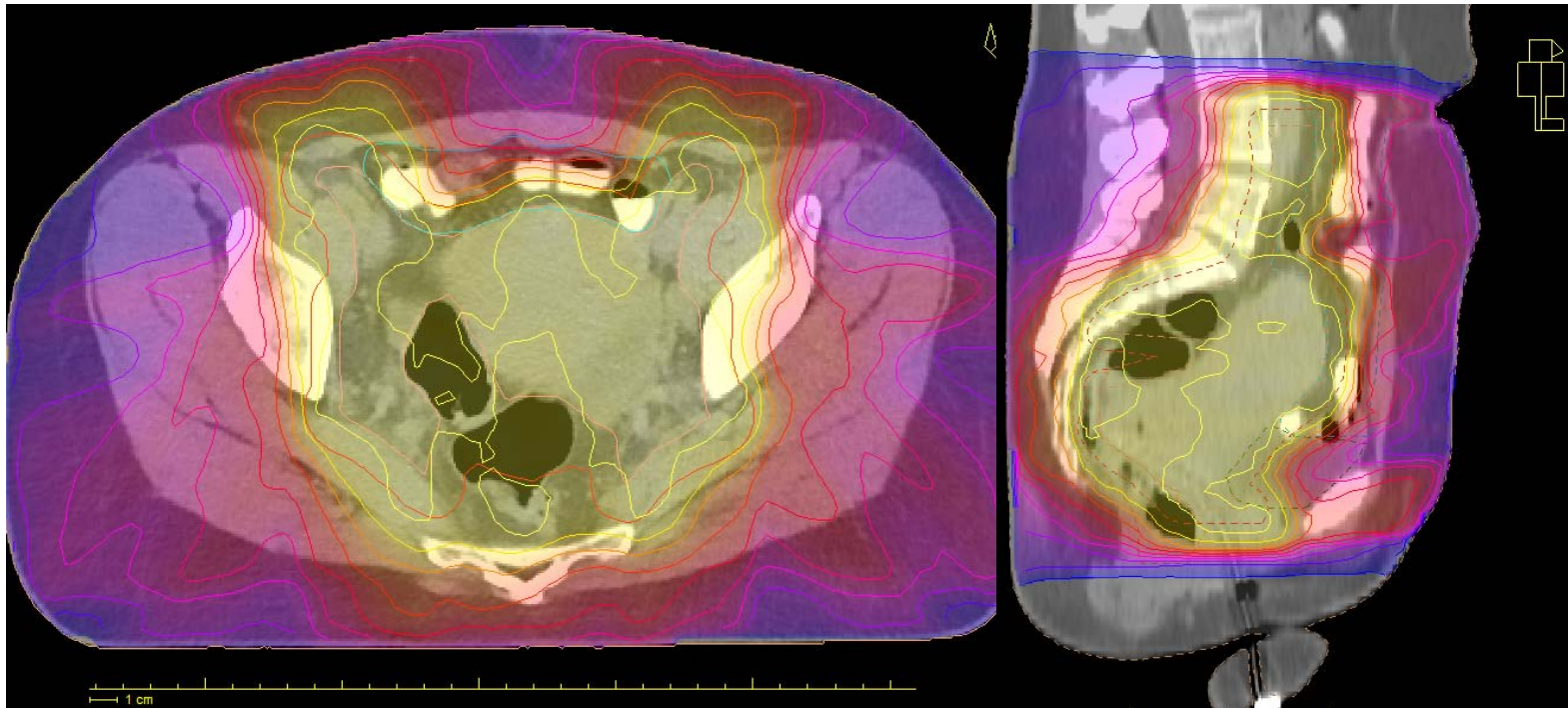
Treatment

EBRT: IMRT; pelvis

TD: 45 Gy; 1.8Gy per fraction

Concurrent cisplatin 40 mg/m², 5 cycles

MRI-based adaptive BT: 7 Gy x 4 fractions – EQD2 > 85 Gy



LARGE TUMOUR, BAD RESPONSE

Findings at brachytherapy
(immediately following EBRT)

Clinical findings at BT

Portio:

minimal regression of exophytic part

Vagina:

≅ diameter (implications for selecting applicator diameter): **Large**

Involvement with tumour: **Minimal residual disease**

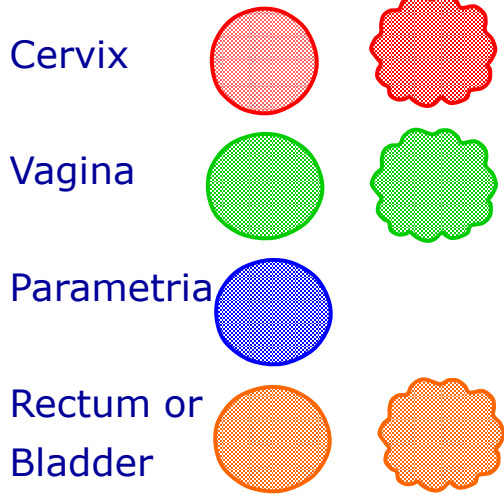
Parametria:

Right: **Proximal residual disease**

Left: **Distal residual disease**

Clinical drawings at BT

Infiltrative Exophytic



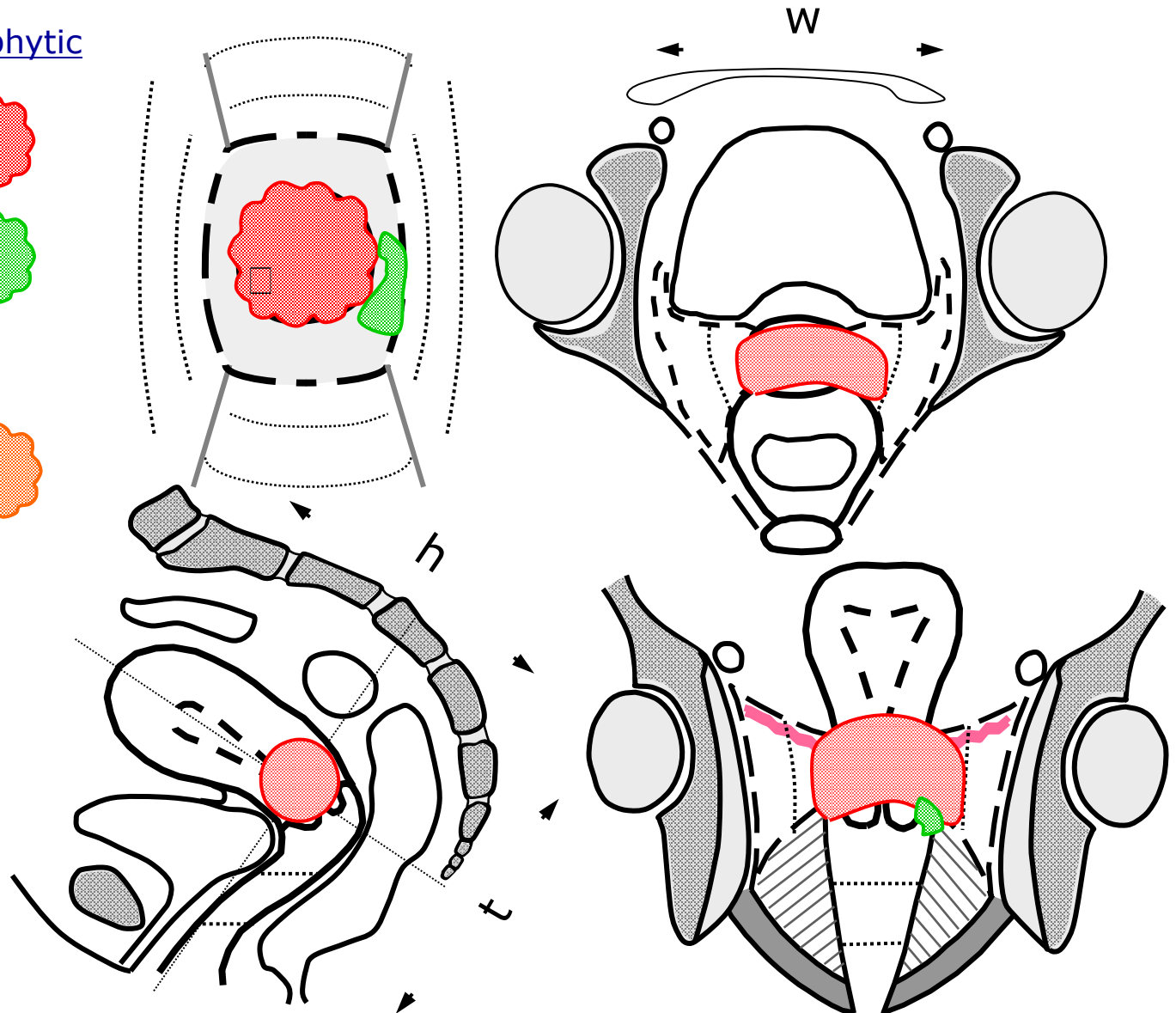
Tumour size:

Width: 5 cm

Thickness: 4 cm

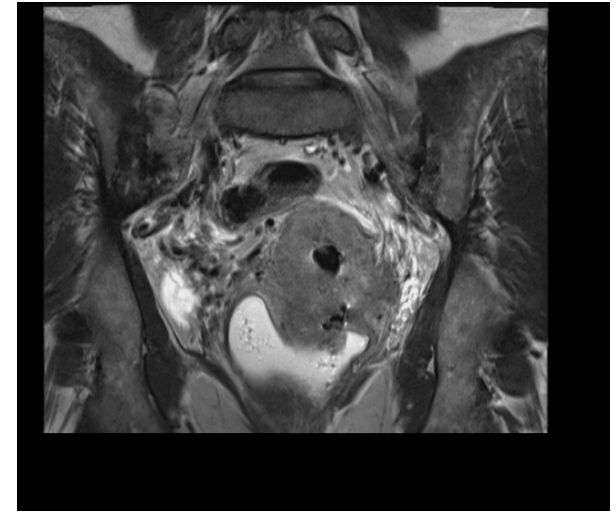
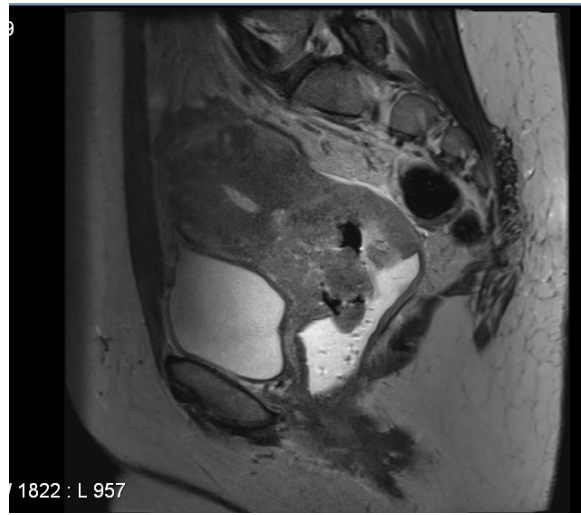
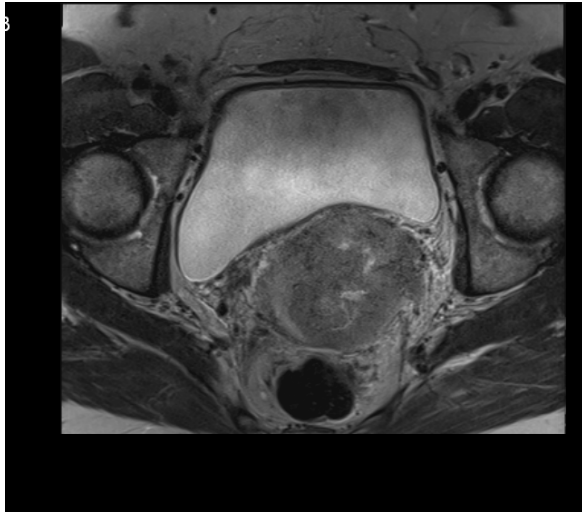
Height: 5 cm

Vaginal inv.: 1 cm

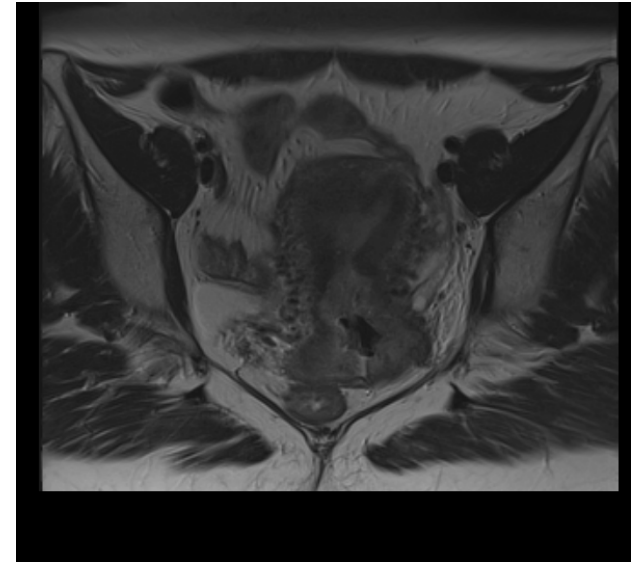
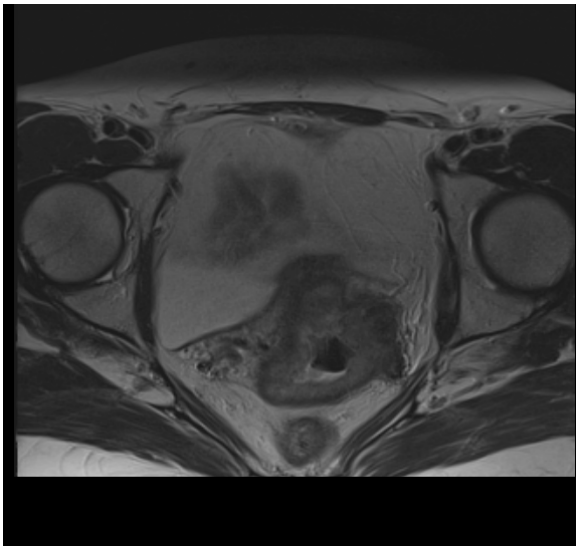


MRI findings

Diagnosis

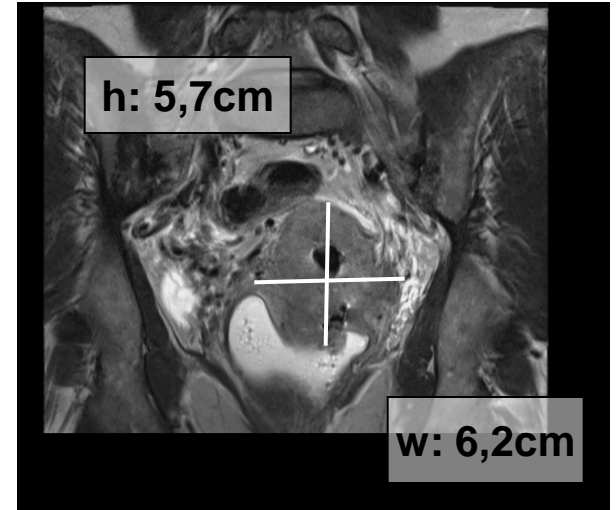
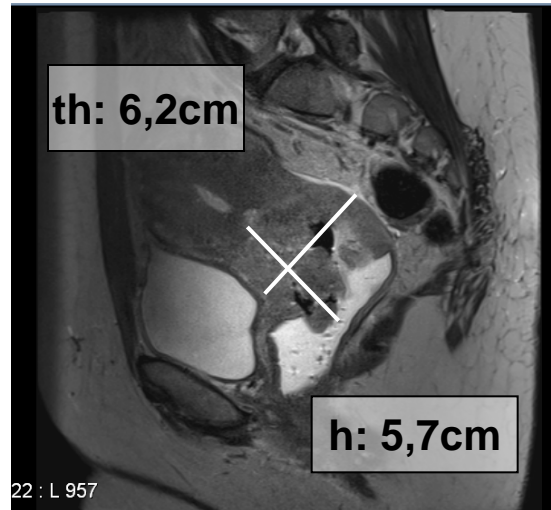
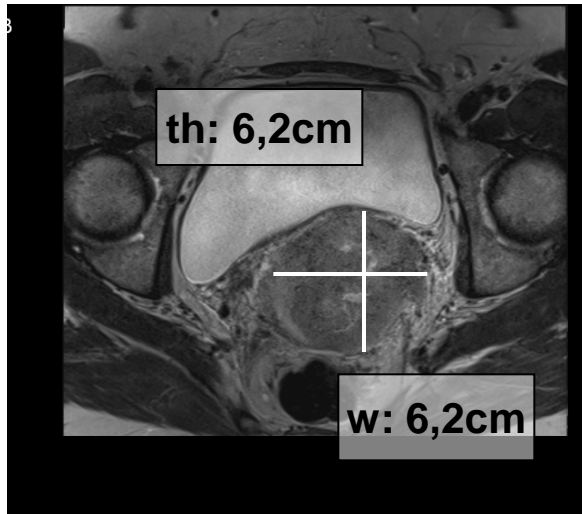


Before BT EBRT Dose 34.2Gy

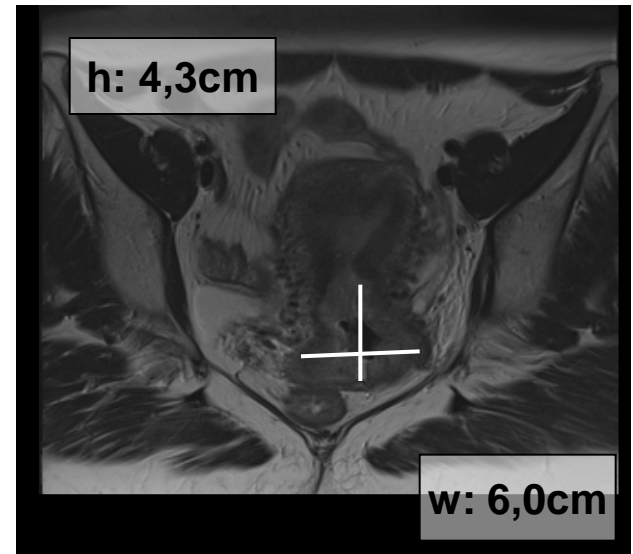
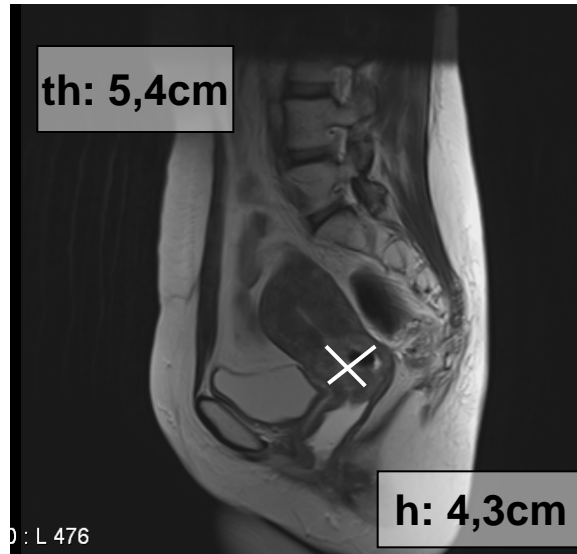
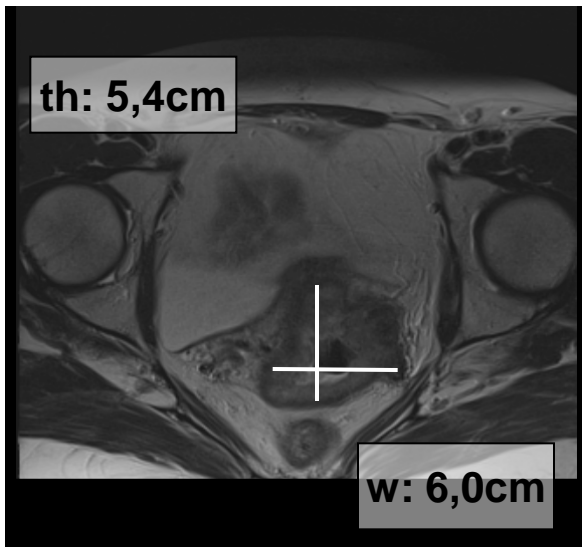


MRI findings

Diagnosis $V=110\text{cm}^3$



Before BT $V=70\text{cm}^3$



Insertion & imaging

Anaesthesia: epidural

Application:

Intracavitary component:

Tandem length: 60 mm

Tandem angle: 60°

Ring diameter: 34 mm

Material: plastic

Comments: Vienna II.

Interstitial component:

N° of needles: 7+5

Insertion depth:

Material: Titanium

Vaginal packing:

Gauze impregnated with gadolinium

Imaging:

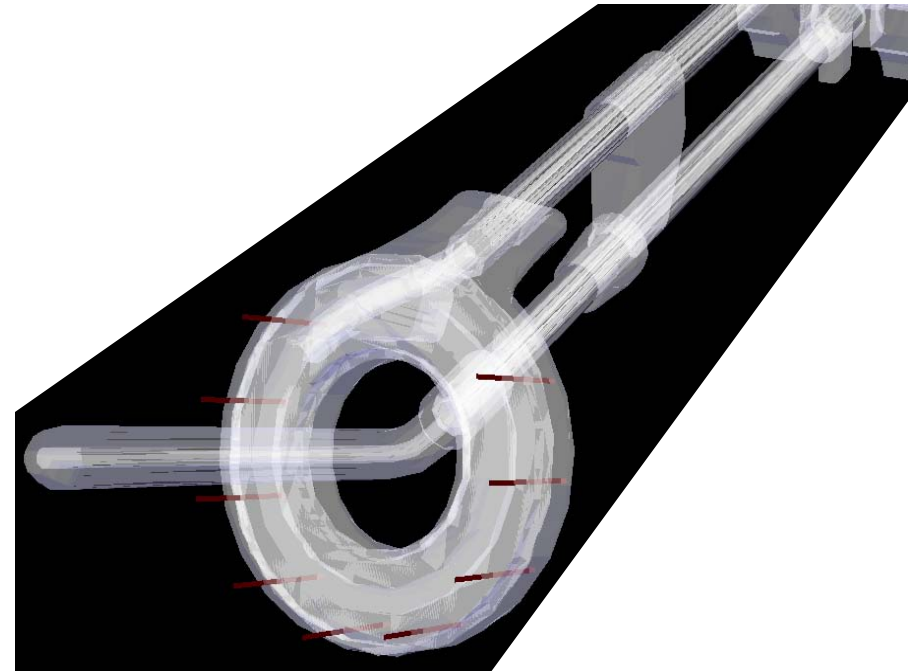
MRI field strength: 1.5 T

MRI configuration:

Sequence(s): T2-weighted

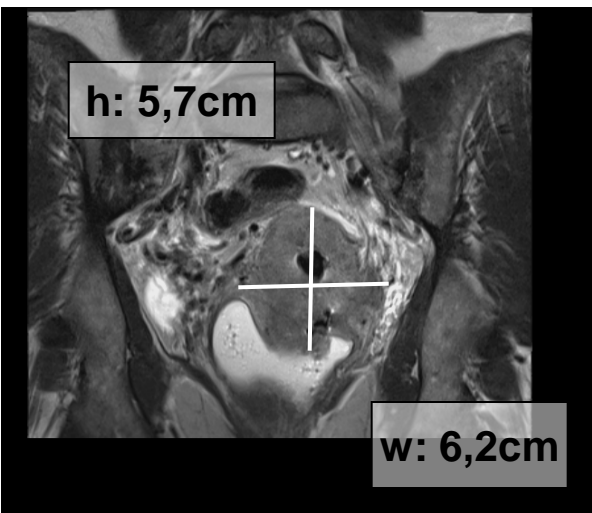
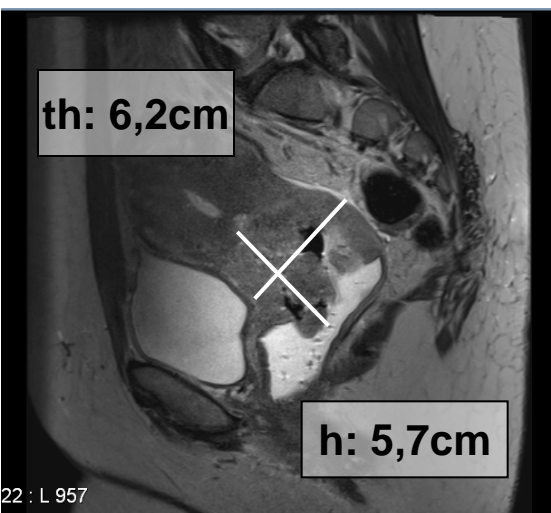
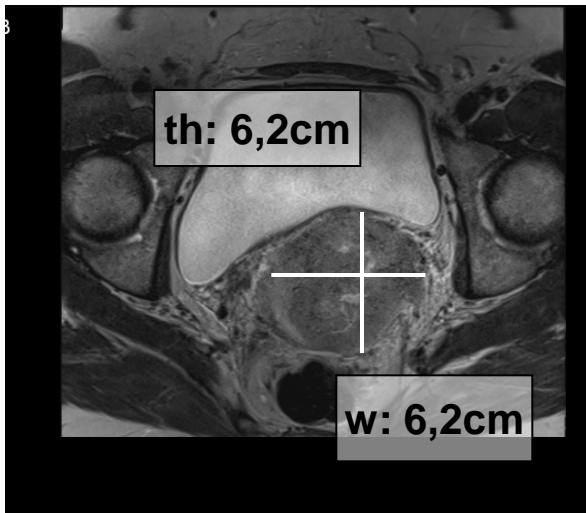
Imaging planes: para-transverse, para-sagittal, para coronal

Comments regarding protocol: No contrast; Foley catheter open



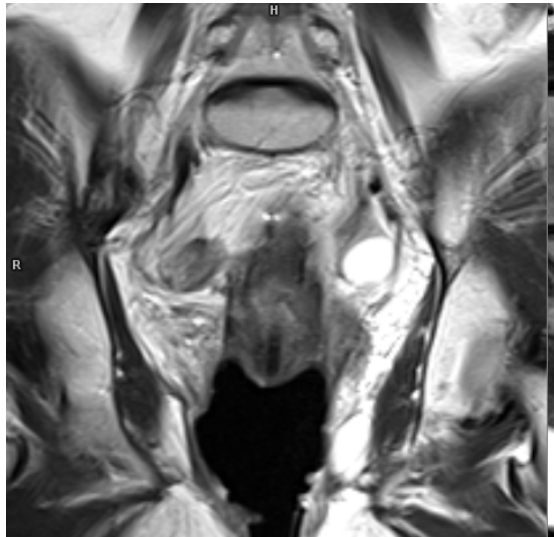
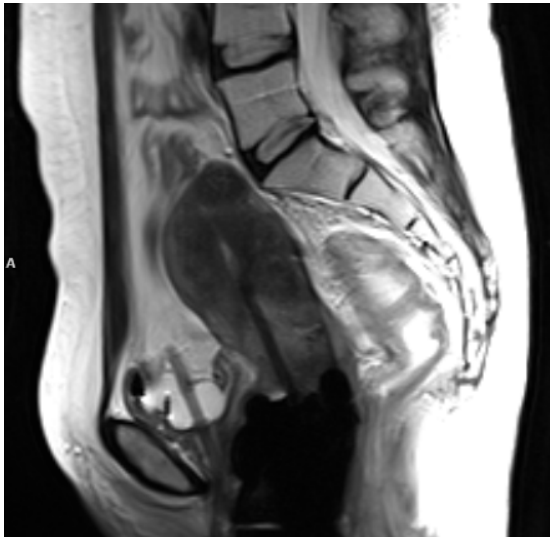
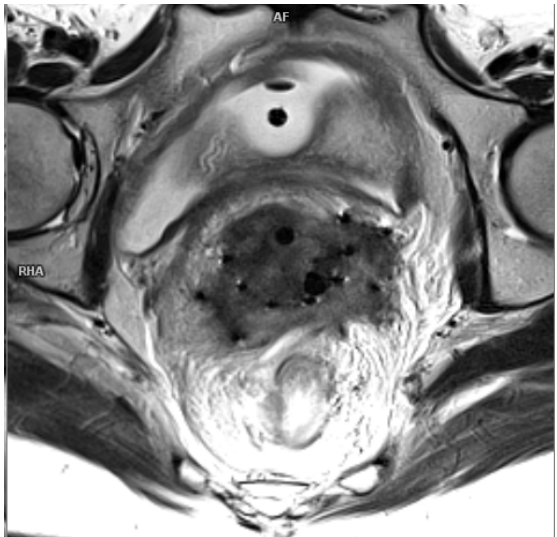
MRI findings

Diagnosis $V=110\text{cm}^3$

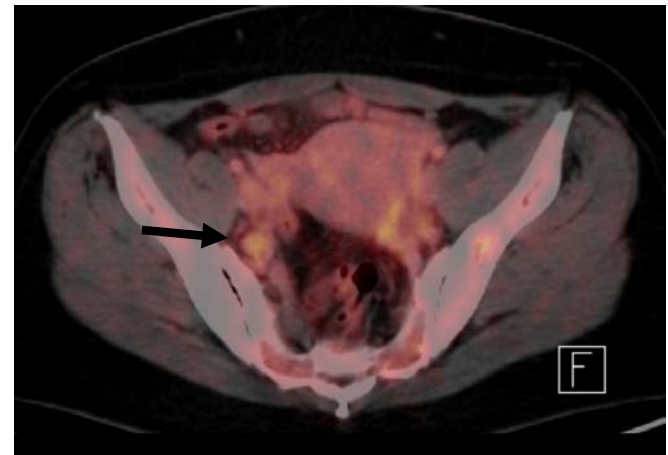
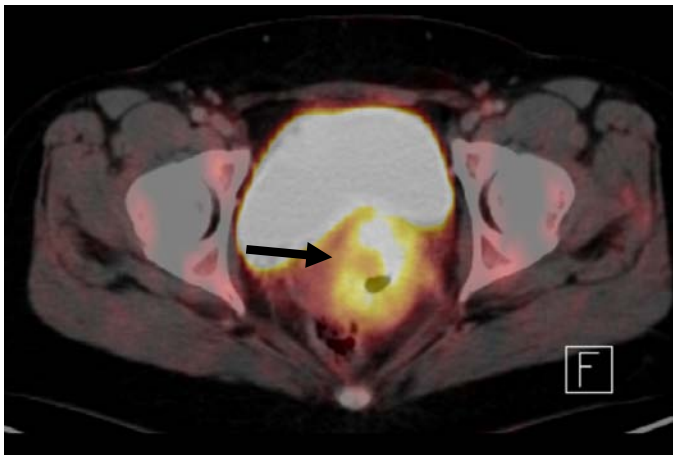


At BT (last week of EBRT dose 39.6Gy)

$V=30\text{cm}^3$



PET-CT findings at diagnosis



lap. Lymph node staging: 0/22 pos lymph nodes

Practical exercise for dose reporting

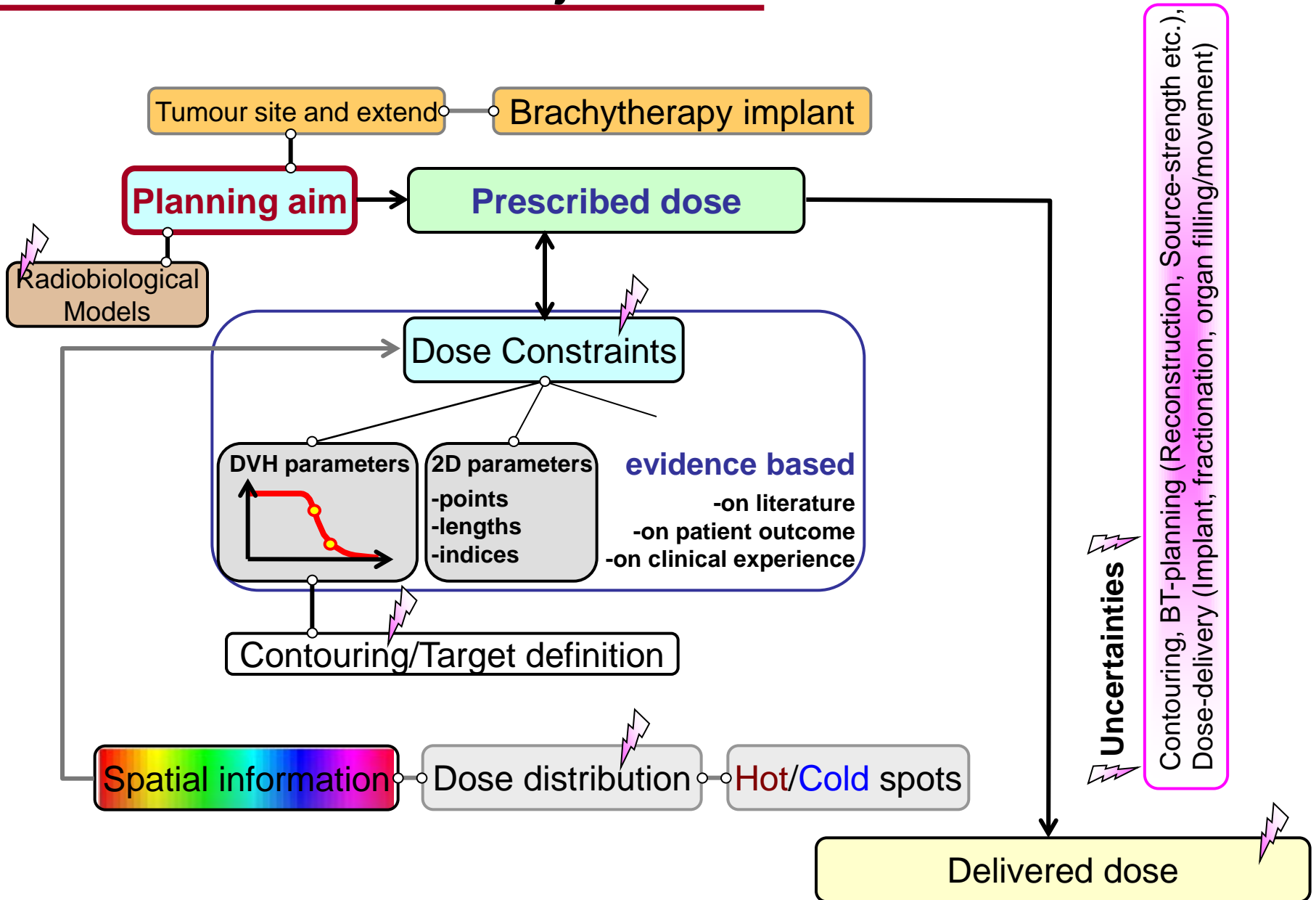
***Daniel Berger
and all participants***

A treatment plan can only be judged by how well the **planning aim** is achieved

The evaluation is related to individual **treatment objectives** including **limitations and uncertainties** as well as **risk-benefit assessment**



Individual Treatment Objectives



Evaluation / Reporting



Clinical GYN examination, Radiographic imaging (w/o add. 3D Imaging at time of diagnosis)



Clinical GYN examination, Volumetric imaging (MRI,CT,US,PET,CT) at time of Diagn. and BT

Level 1 Minimum standard for reporting



TRAK, Point A,
Bladder ref.point, Rectum ref.point

Additional (Quality) parameter: VDref (V7Gy)
V2Dref(V14Gy)



TRAK, Point A,
D_{0.1cm³}, D_{2cm³} for bladder, recum and sigmoid (bowel)

Additional (Quality) parameter: VDref (V7Gy)
V2Dref(V14Gy)

Level 2 Advanced standard for reporting



Target: near minimum dose to vol. def. as CTV_{HR}
according to estimated Width and Thickness

Vagina: dose points at level of sources (lat. 0mm,5mm)
Low and mid vagina as an astemiate for the applied
Contribution from EBRT and BT (PIBS,PIBS±2cm)



Target: CTV_{HR} D98, D90, D50 or CTV_{IR} D98, D90
GTV at time of BT D98, patholo. Lymph nodes D98

Vagina: dose points at level of sources (lat. 0mm,5mm)
Low and mid vagina as an astemiate for the applied
Contribution from EBRT and BT (PIBS,PIBS±2cm)

Level 3 Research oriented reporting



Pelvic wall points
Lymphatic trapezoid

Length of treated vagina (85Gy/60Gy-EQD2)
Sigmoid point?, additional OAR points (e.g. anus)



Target: CTV_{IR} D98, D90 GTV at time of BT D90
DVH parameters for the PTV
Pathological lymph nodes D50

OAR: Baldder and rectum reference (ICRU) points
Dose to OAR subvolumes and spatial distribution within
OAR -> Dose-Vol. and Dose-Surface Histograms
Bladder trigonum or neck point; Anal dose point
Intermediate and low dose assessment (DV and VD)
Dose profiles

Evaluation / Reporting

Level 1 Minimum standard for reporting

Dose delivery pattern

HDR

LDR

PDR

Absorbed Dose (Gy)
Fraction size (Gy)
Number of Fractions
Interval between fr. (h)

Absorbed Dose (Gy)
Dose Rate (Gy/h)
Number of Fractions
and Treatment-time

Absorbed Dose (Gy)
Pulse size (Gy)
Number of pulses, and
interval between pulses
Number of fractions and
interval between fr.

Total treatment-time (TT) in hours or days of EBRT, BT and overall TT

Source and Dose calculation (Radionuclide, Source model, Source Strength, Dose calculation algorithm)

Level 2 Advanced standard for reporting

Biological dose reporting

EQD2 values for target and OAR (endpoints)
Respective α/β values* for the target and OAR
Respective T1/2 of recovery*
Applied recovery model, mono- or bi-exponential

Level 3 Research oriented reporting

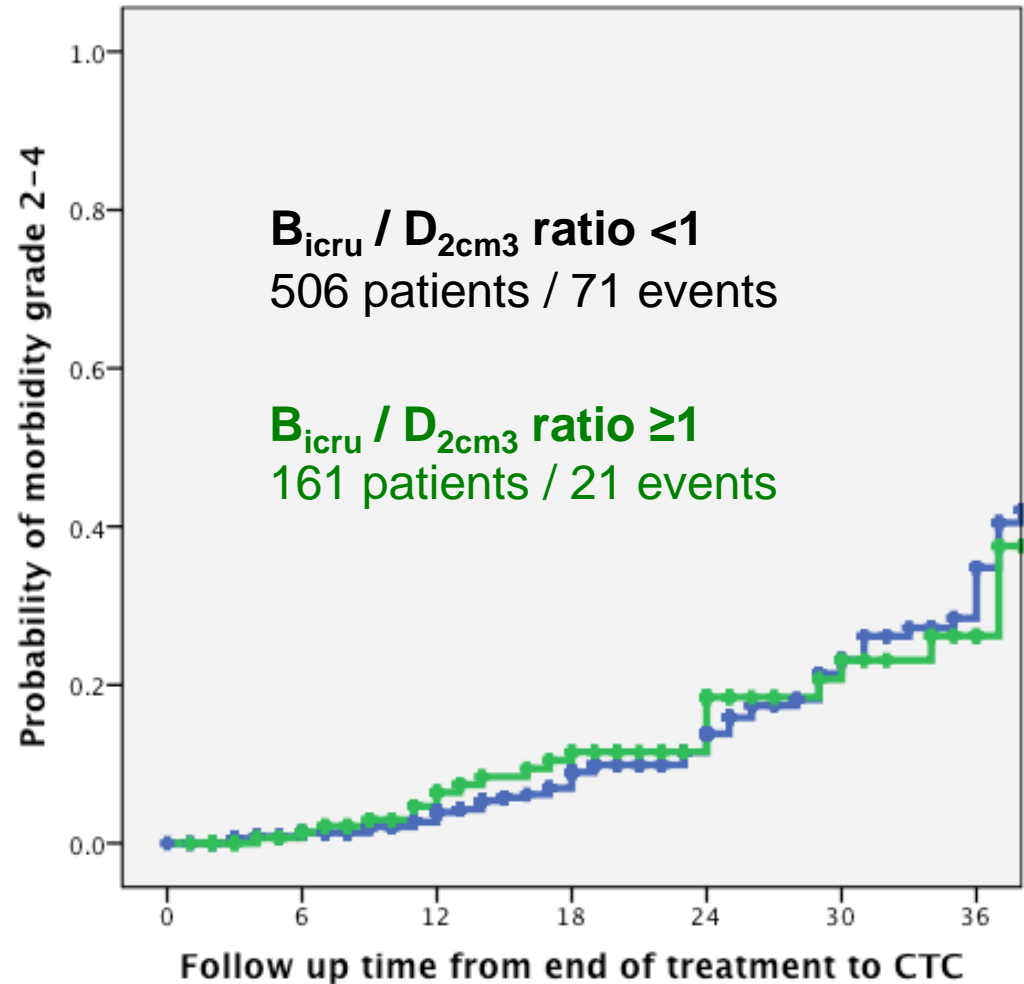
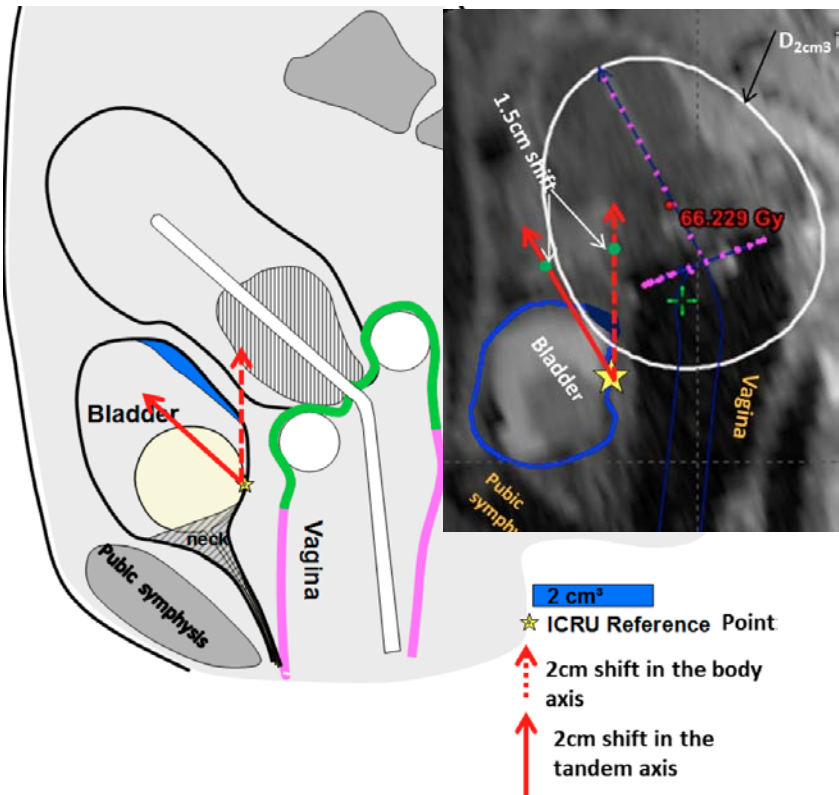
EUD or other biologically effective dose model calc. for target and OAR endpoints

TCP or NTCP calculation, with the model explicitly stated

*For the moment - advise to follow GEC-ESTRO recommendations $\alpha/\beta=3\text{Gy}$ for late Effects in OAR and 10 Gy for tumour response, and $T_{1/2}$ of 1.5h for both.

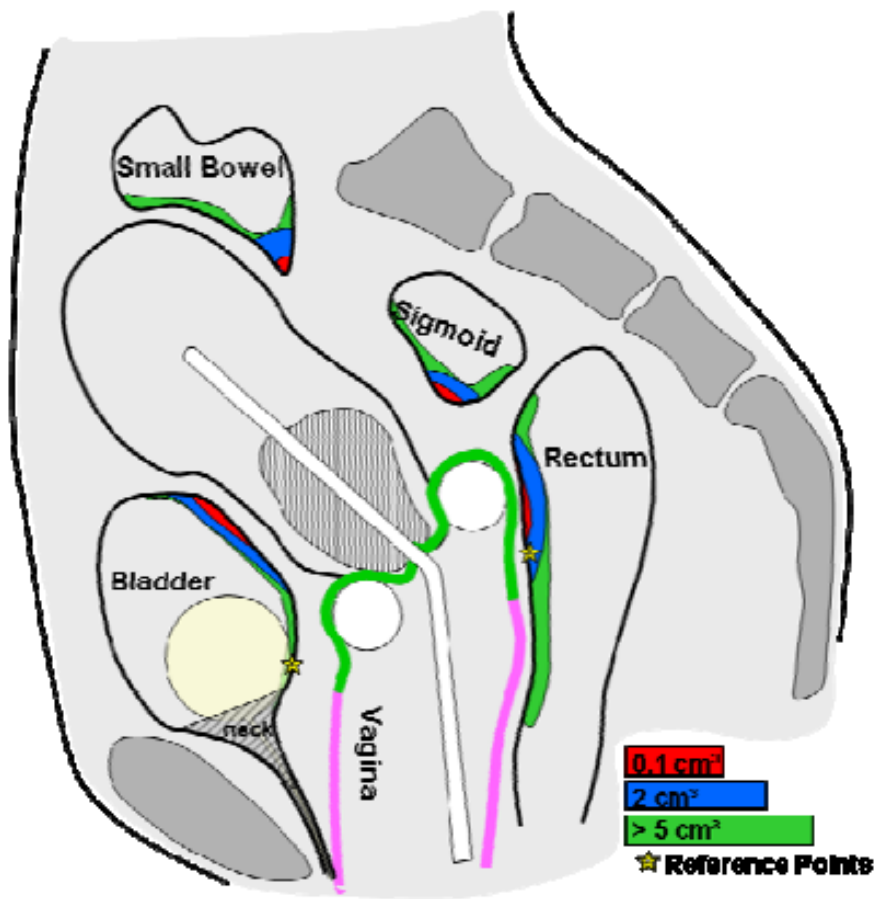
Bladder B_{icru} / D_{2cm^3} ratio

Bladder sub-volumes and different morbidity profiles?

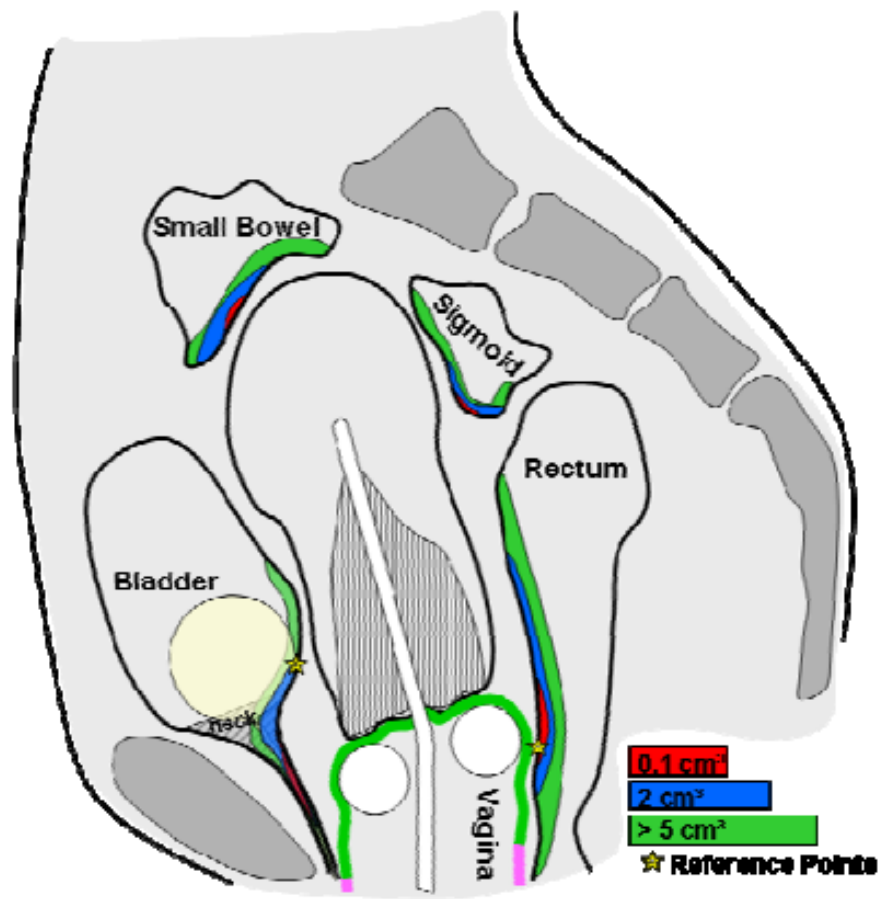


B_{icru} / D_{2cm^3} ratio ≥ 1 indicating D_{2cm^3} at the bladder base

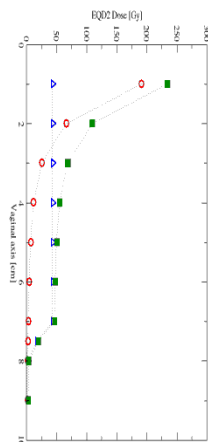
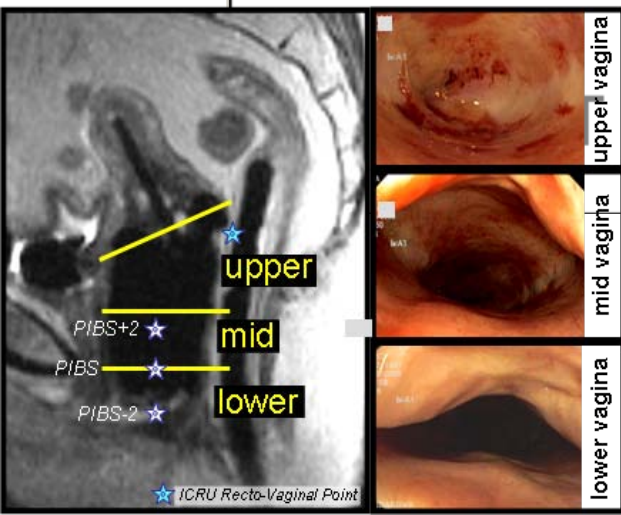
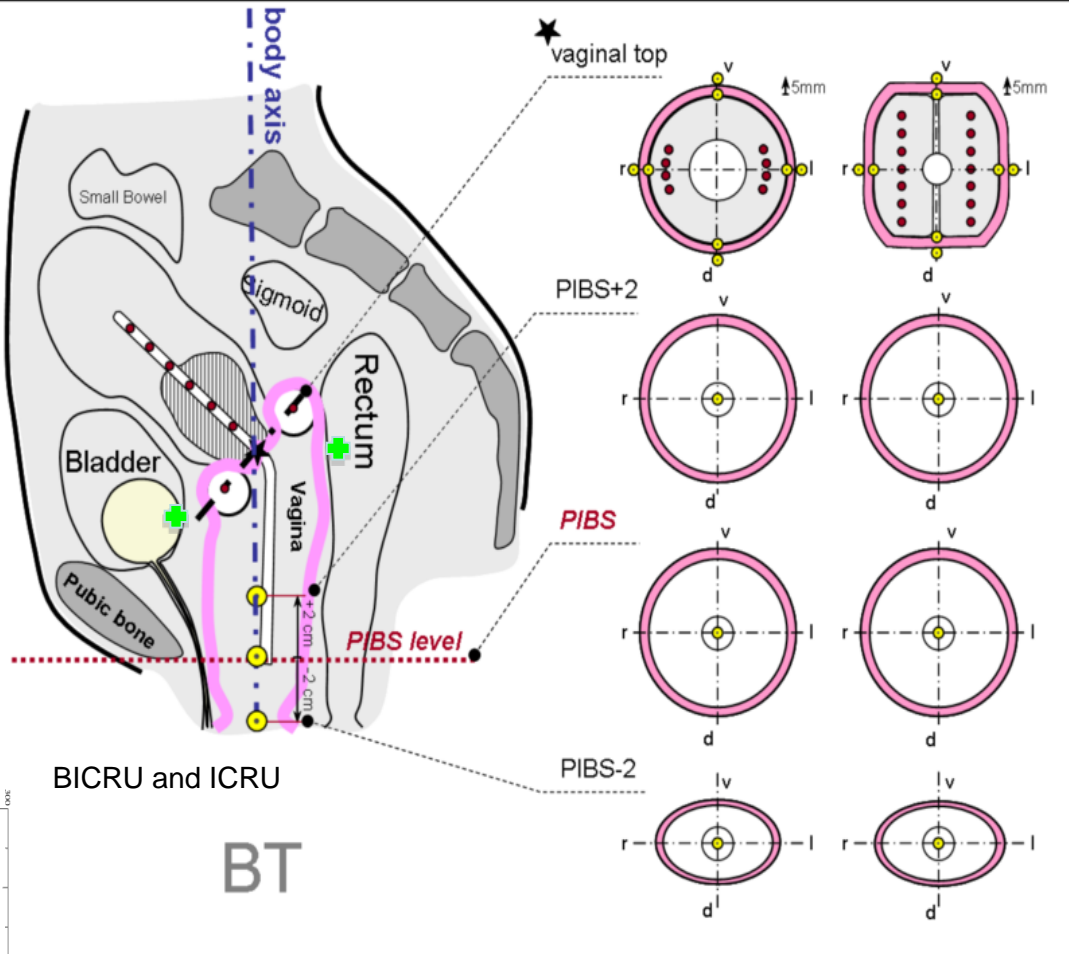
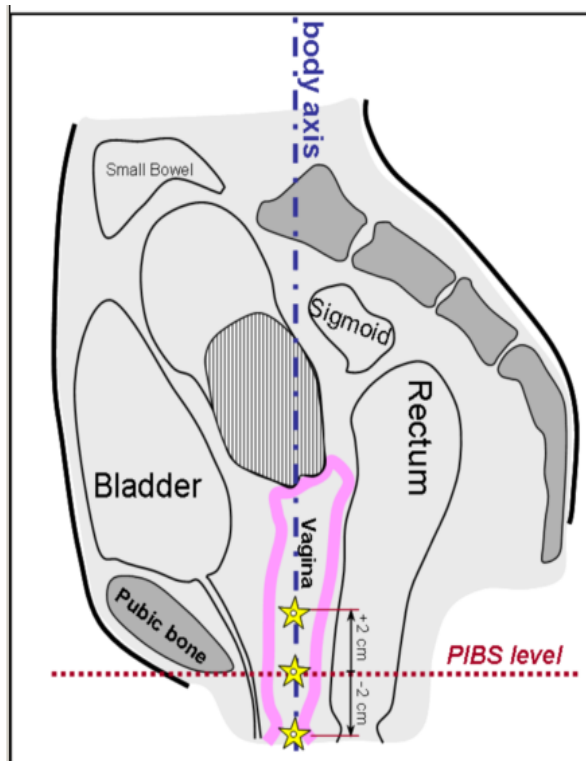
B_{icru} / D_{2cm3} ratio < 1



B_{icru} / D_{2cm3} ratio ≥ 1



„ICRU 89“ Reference Points



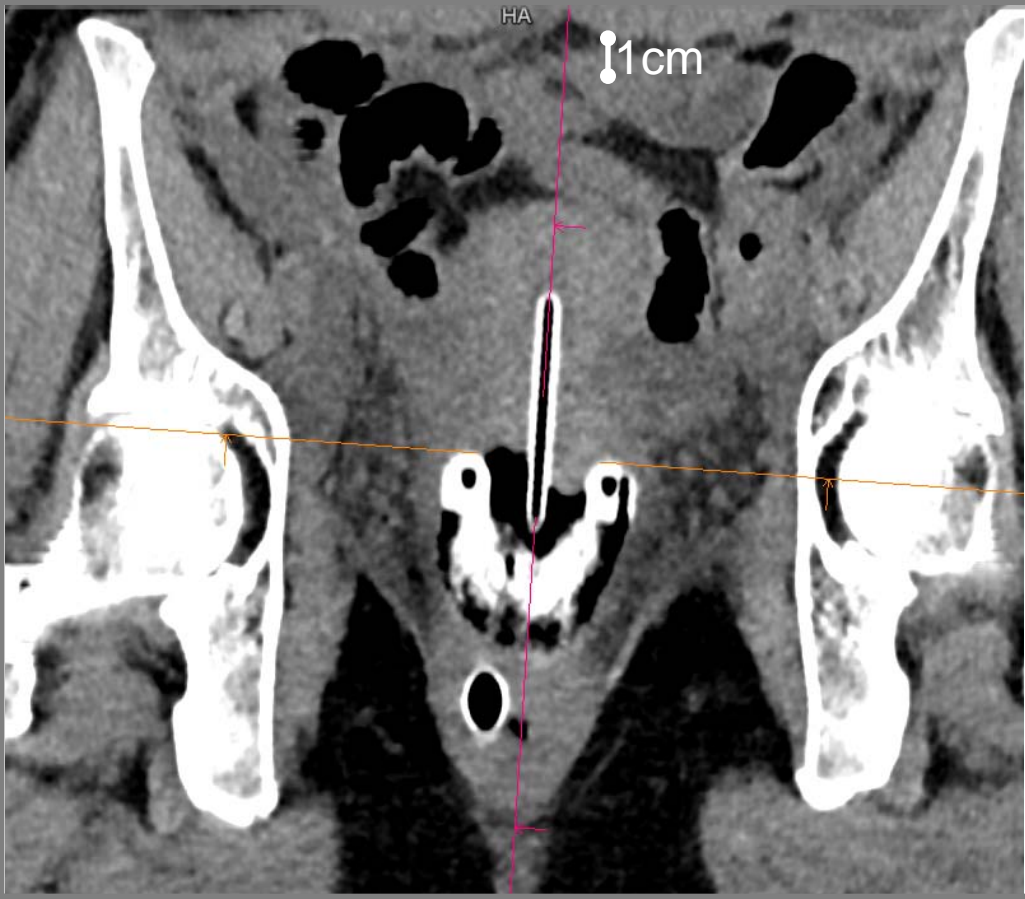
BICRU and ICRU

BT

ICRU/GEC ESTRO Report 89
under publication Fig. 6.1/Fig. 8.11

Please Define Point A and ICRU reference points

Para-coronal CT

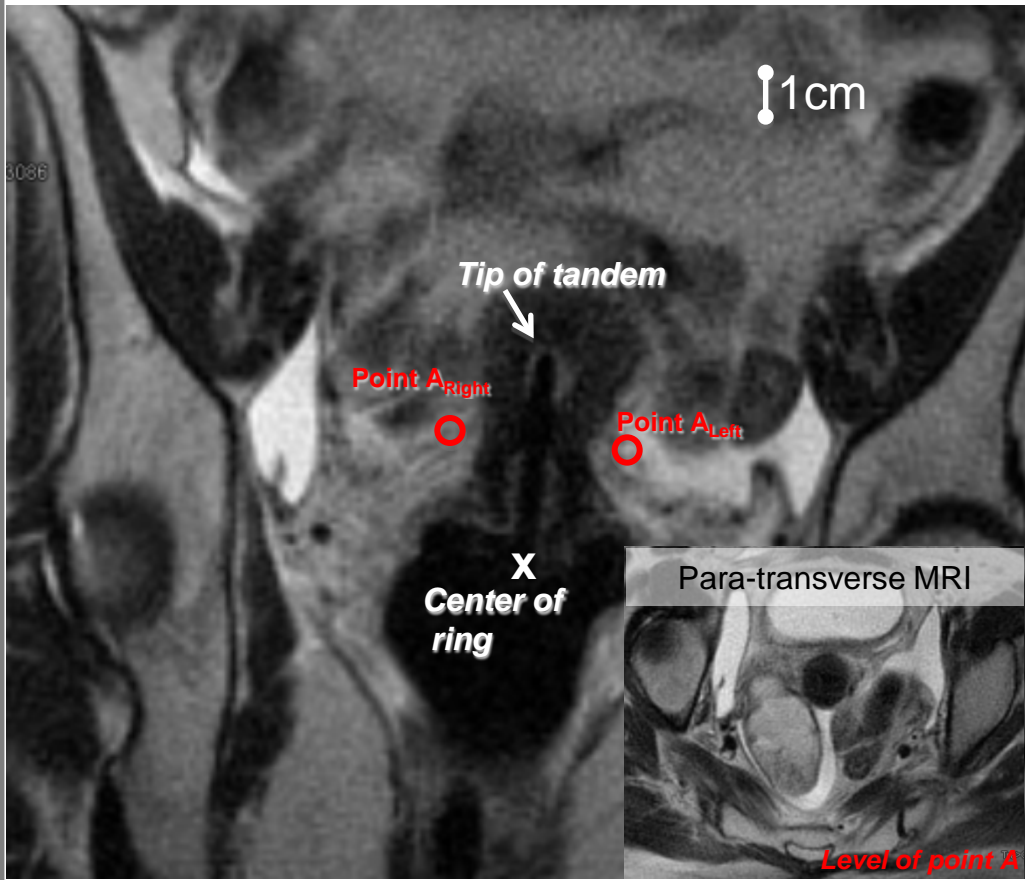


Para-sagittal CT

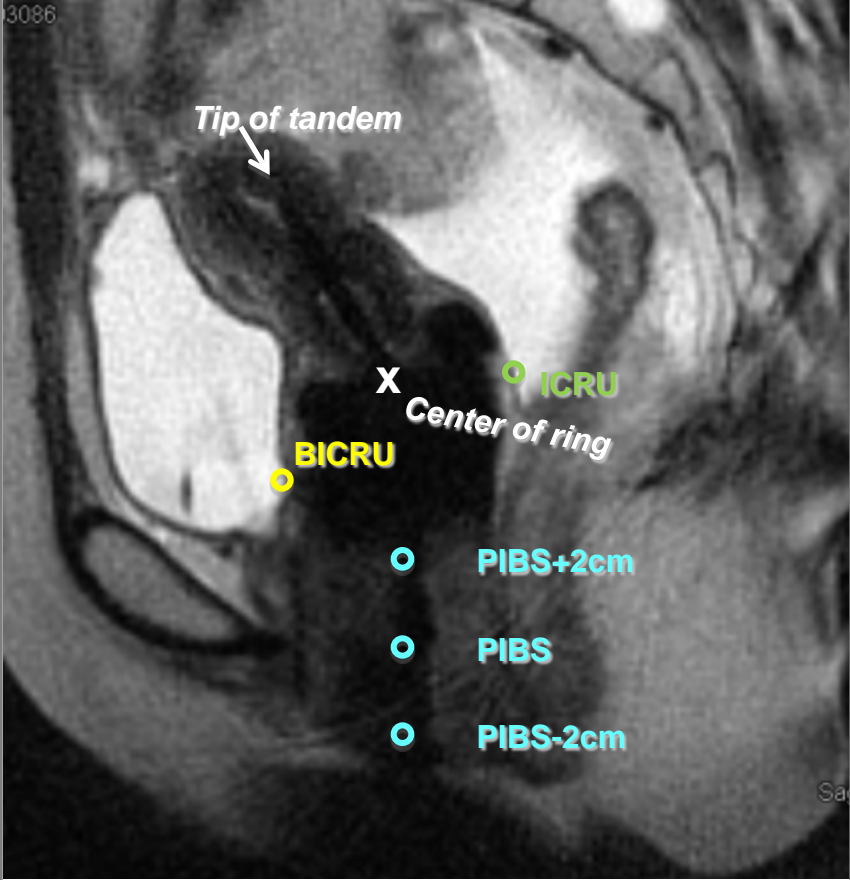


Please Define Point A and ICRU reference points

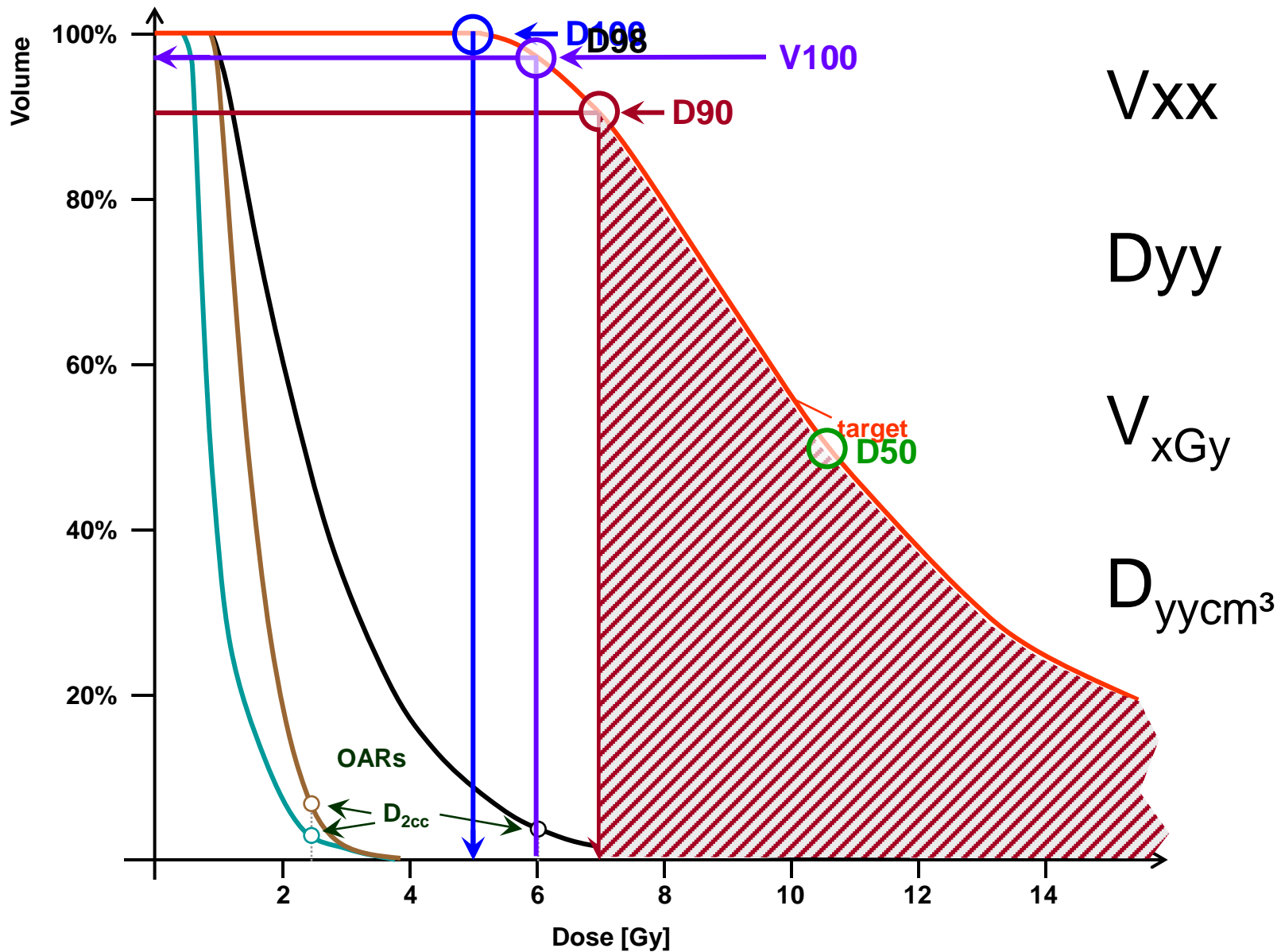
Para-coronal MRI



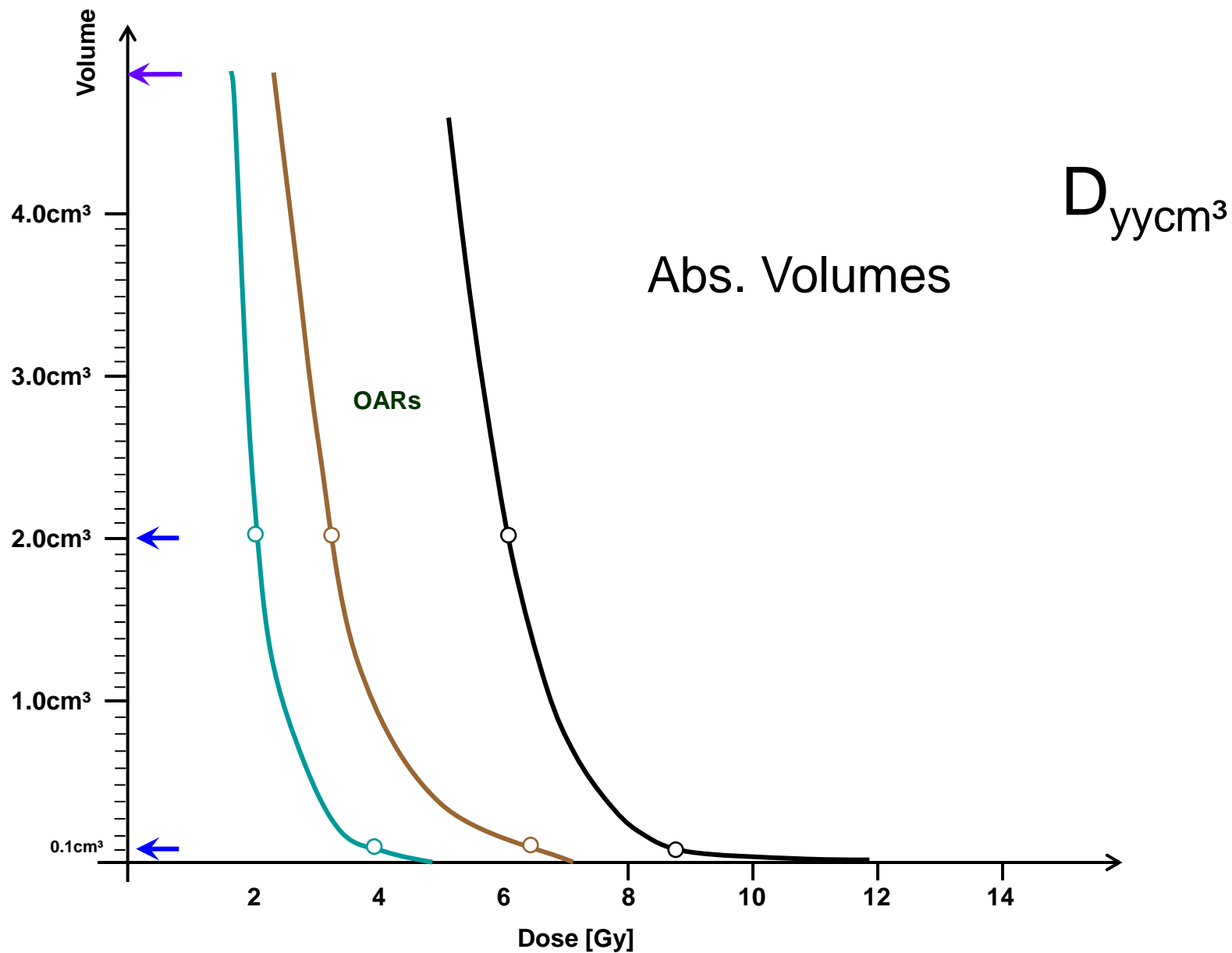
Para-sagittal MRI



DVH-Parameters



DVH-Parameters

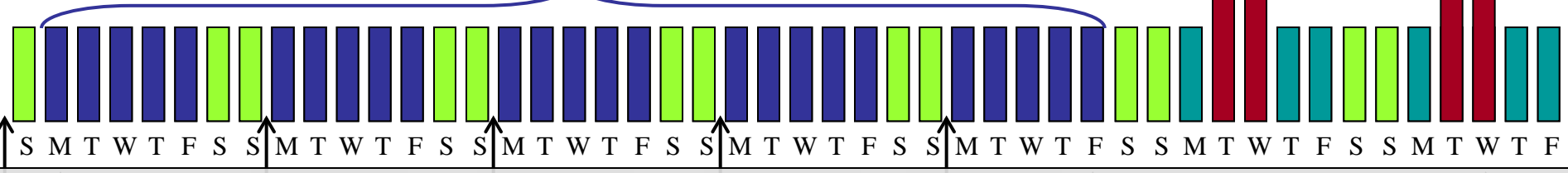


MUV standard treatment concept for cervical cancer

tumours [Aim: dose 85 Gy_{EQD2}]

BrachyTherapy (4x 7Gy)

EBRT 1.8Gy
BT 7Gy
External Beam RadioTherapy (25x 1.8Gy = 45Gy)



Let us get values !

Documentation of gynaecological HDR BT

PHYSICAL - BIOLOGICAL DOCUMENTATION OF GYNAECOLOGICAL HDR BT

PATIENT , ID-number

tumour entity cervix ca

EXTERNAL BEAM THERAPY	TUMOUR	OAR
dose per fraction	$D_{iso} [\alpha/\beta=10Gy]$	$D_{iso} [\alpha/\beta=3Gy]$
fractions without central shield	44,3	43,2
fractions with central shield	0,0	0,0
total dose	44,3	43,2

FIGO, TNM IIB
cT2b pN0

GTV at diag. 88 cm³

chemoth. cisplatin

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
<i>mean</i>	<i>stddev</i>

Documentation of gynaecological HDR BT

fraction number:	F 1	F 2	F 3	F 4	F 5	F 6	TOTAL BT	TOTAL BT+EBT
TRAK [cGy at 1m]	0,54	0,49	0,47	0,44			1,94	
prescribed dose PD	7	7	7	7				
PD _{iso} [$\alpha/\beta=10\text{Gy}$]	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} [$\alpha/\beta=10\text{Gy}$]	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			mean volume	stagev
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} [$\alpha/\beta=10\text{Gy}$]	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} [$\alpha/\beta=10\text{Gy}$]	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} [$\alpha/\beta=10\text{Gy}$]	11,4	9,9	9,9	9,1	0,0	0,0	40,3	84,6
GTV [cm³]	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} [$\alpha/\beta=10\text{Gy}$]	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} [$\alpha/\beta=10\text{Gy}$]	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 [cm³]	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} [$\alpha/\beta=10\text{Gy}$]	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} [$\alpha/\beta=10\text{Gy}$]	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%

This XLS- sheet will be distributed by ESTRO for your personal use

Documentation of gynaecological HDR BT

fraction number:	F 1	F 2	F 3	F 4	F 5	F 6	TOTAL BT	TOTAL BT+EBT
BLADDER [cm³]	98,5	76,1	86,9	101,4			90,7	10,0
ICRU - dose	7,2	8,1	5,5	6,3				
ICRU - D _{iso} [α/β=3Gy]	14,7	18,0	9,4	11,7	0,0	0,0	53,7	96,9
ICRUcr1,5cm - dose	8,3	10,6	5,4	7,0				
ICRUcr1,5cm - D _{iso} [α/β=3Gy]	18,8	28,8	9,1	14,0	0,0	0,0	70,7	113,9
ICRUcr2,0cm - dose	8,6	12,2	5,4	7,1				
ICRUcr2,0cm - D _{iso} [α/β=3Gy]	20,0	37,1	9,1	14,3	0,0	0,0	80,5	123,7
0,1cm³ - dose	8,0	8,0	9,5	7,5				
0,1cm ³ - D _{iso} [α/β=3Gy]	17,6	17,6	23,8	15,8	0,0	0,0	74,7	117,9
1cm³ - dose	6,4	6,5	7,2	6,3				
1cm ³ - D _{iso} [α/β=3Gy]	12,0	12,4	14,7	11,7	0,0	0,0	50,8	94,0
2cm³ - dose	6,0	6,0	6,4	5,9				
2cm ³ - D _{iso} [α/β=3Gy]	10,8	10,8	12,0	10,5	0,0	0,0	44,1	87,3
RECTUM [cm³]	45,1	33,1	34,8	38,5			37,9	4,6
ICRU - dose	4,2	5,0	3,4	3,0				
ICRU - D _{iso} [α/β=3Gy]	6,0	8,0	4,4	3,6	0,0	0,0	22,0	65,2
ICRUprobe - dose	4,0	4,9	3,4	3,0				
ICRUprobe - D _{iso} [α/β=3Gy]	5,6	7,7	4,4	3,6	0,0	0,0	21,3	64,5
0,1cm³ - dose	5,9	4,9	4,6	4,3				
0,1cm ³ - D _{iso} [α/β=3Gy]	10,5	7,7	7,0	6,3	0,0	0,0	31,5	74,7
1cm³ - dose	4,8	4,2	3,7	3,6				
1cm ³ - D _{iso} [α/β=3Gy]	7,5	6,0	5,0	4,8	0,0	0,0	23,2	66,4
2cm³ - dose	4,3	3,9	3,4	3,3				
2cm ³ - D _{iso} [α/β=3Gy]	6,3	5,4	4,4	4,2	0,0	0,0	20,2	63,4
SIGMOID [cm³]	17,4	21,1	24,6	26,3			22,4	3,4
0,1cm³ - dose	6,6	5,7	4,7	5,2				
0,1cm ³ - D _{iso} [α/β=3Gy]	12,7	9,9	7,2	8,5	0,0	0,0	38,4	81,6
1cm³ - dose	5,4	4,7	3,8	4,2				
1cm ³ - D _{iso} [α/β=3Gy]	9,1	7,2	5,2	6,0	0,0	0,0	27,5	70,7
2cm³ - dose	4,7	4,2	3,4	3,8				
2cm ³ - D _{iso} [α/β=3Gy]	7,2	6,0	4,4	5,2	0,0	0,0	22,8	66,0



*Dept. of Radiation Oncology
Comprehensive Cancer Center
Medical University of Vienna*



Morbidity and QoL after IGABT in Cervix Cancer

Rectum, Sigmoid, Bladder, Vagina

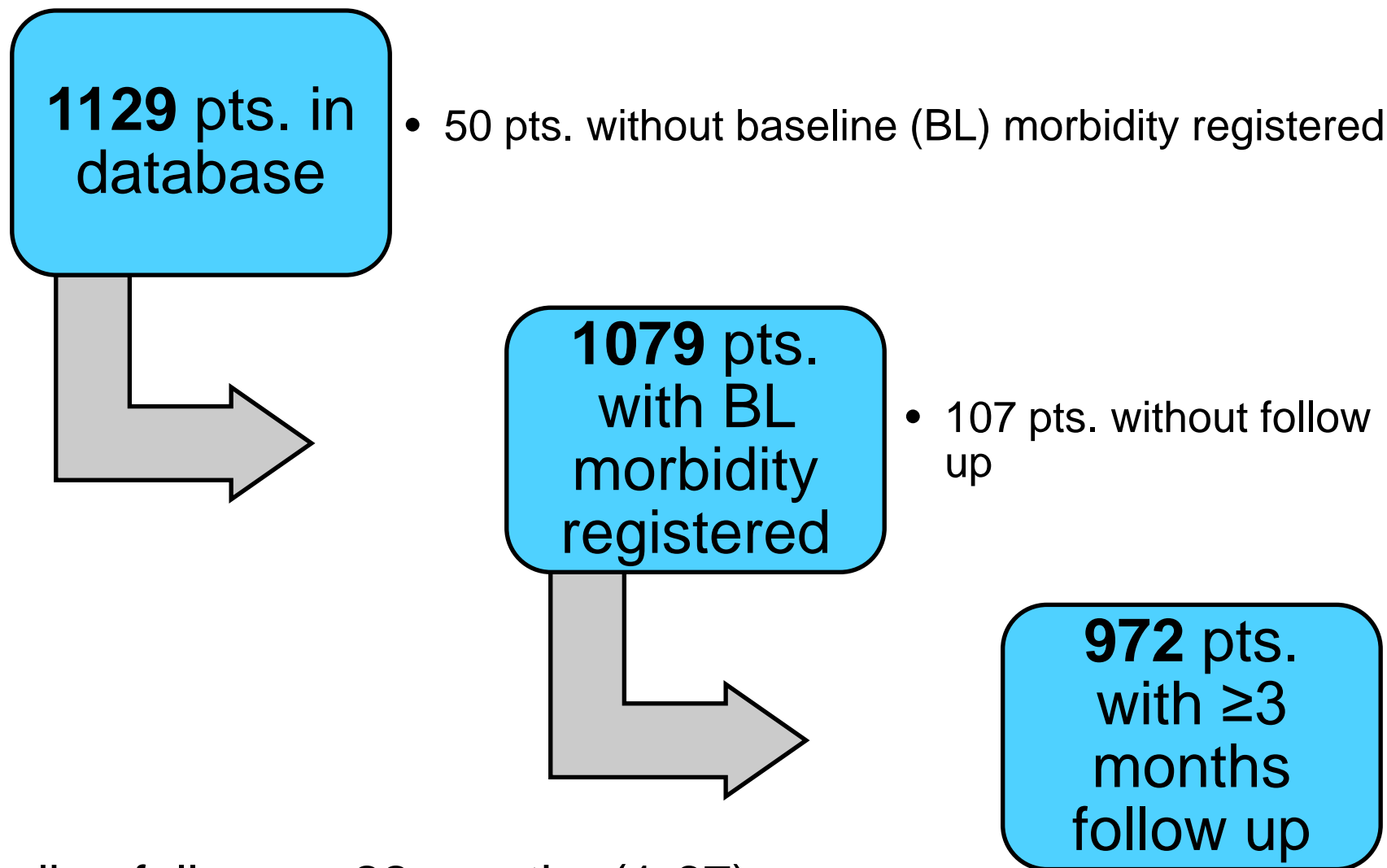
Richard Pötter

**ESTRO-CARO Teaching Course
Image Guided Cervix Cancer Radiotherapy –
With a special focus on adaptive brachytherapy
April, 4-6, Toronto, Canada**

Learning Objectives I

- Know about typical late morbidity patterns for rectum, bladder, bowel and vagina after IGABT for cervix cancer combined with radio-chemotherapy;
- Know about typical mid and long term impairments in quality of life (functional aspects in daily life and patient reported symptoms) after IGABT for cervix cancer combined with radio-chemotherapy;

Patients with baseline and follow up information bladder, bowel, rectum



Median follow up 22 months (1-67)

Late Morbidity: Bladder

EMBRACE I. CTCAE v3
Urinary frequency/urgency
Incontinence, urinary
Cystitis
Bladder spasm
Bleeding (Hemorrhage GU) – bladder, ureter, urethra
Stenosis/stricture – bladder, ureter, urethra
Fistula – bladder, ureter, urethra
Bladder other

Descriptive

crude incidence

actuarial incidence

prevalence

(Analytical

mono-factor-

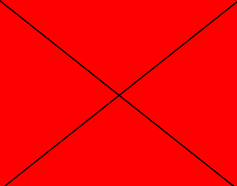
dose-effect-

multi-factor-)

Fokdal and Kirchheiner

Maximum incidence of single bladder symptoms

Number of patients 970

	Frequency	Incontinence	Spasm	Bladder contracture	Ureter stenosis	Cystitis	Bleeding	Fistula
G0	482 (47.7%)	643 (66.3%)	898 (97.9%)	964 (92.6%)	930 (95.9%)	797 (82.2%)	916 (94.4%)	957 (98.7%)
G1	378 (30.0%)	225 (23.2%)	58 (6.0%)	58 (6.0%)	10 (1.0%)	109 (11.2%)	41 (4.2%)	3 (0.3%)
G2	96 (9.9%)	86 (8.9%)	13 (1.3%)	13 (1.3%)	9 (0.9%)	57 (5.9%)	11 (1.1%)	2 (0.2%)
G3	14 (1.4%)	12 (1.2%)	1 (0.1%)	1 (0.1%)	18 (1.9%)	5 (0.6%)	2 (0.2%)	5 (0.5%)
G4		4 (0.4%)	0 (0%)	0 (0%)	3 (0.3%)	1 (0.1%)	0 (0%)	3 (0.3%)

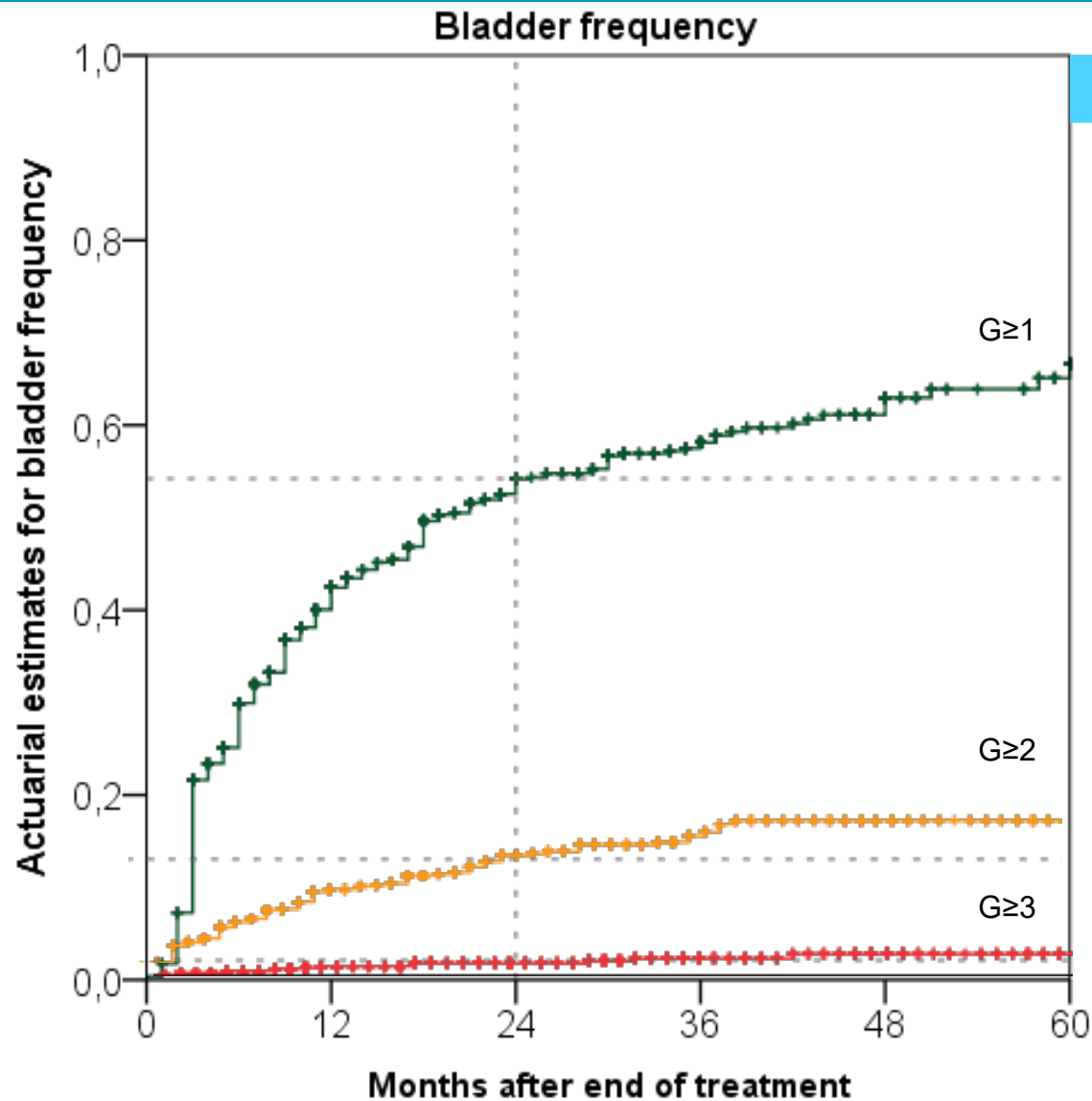
* 7 patients had tumor involvement of the bladder at time of diagnosis

Maximum incidence PROM

Number of patients 852

N= 852	frequency	Incontinence	Bladder emptying	Pain
Not at all	259 (30.4%)	442 (51.9%)	570 (66.9%)	534 (62.5%)
A little	262 (30.8%)	265 (31.1%)	182 (21.4%)	214 (25.1%)
Quite a bit	223 (26.2%)	102 (12.0%)	69 (8.1%)	64 (7.5%)
Very much	107 (12.6%)	43 (5.0%)	31 (3.6%)	42 (4.9%)

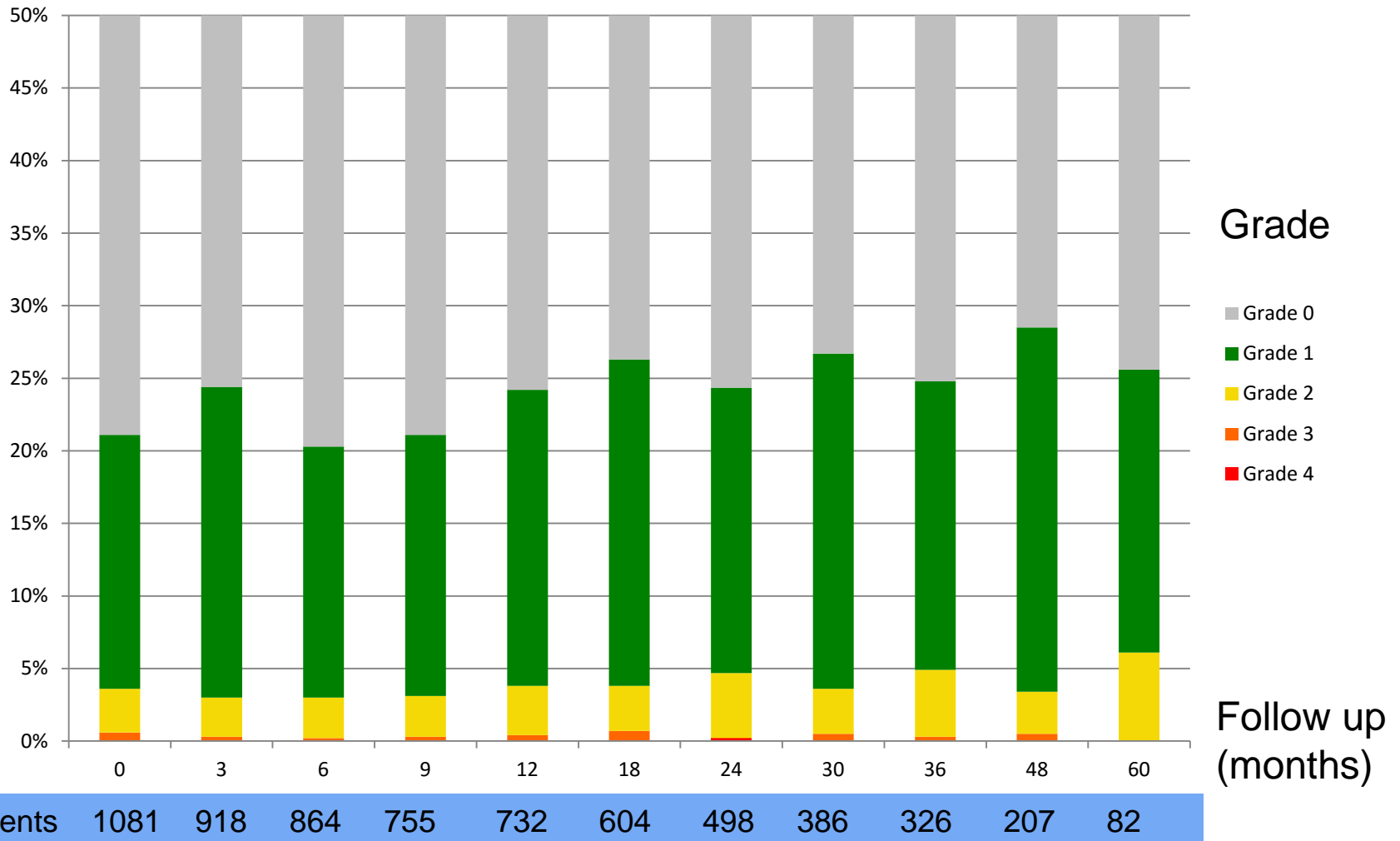
Bladder frequency



Bladder frequency

Annual prevalence rates

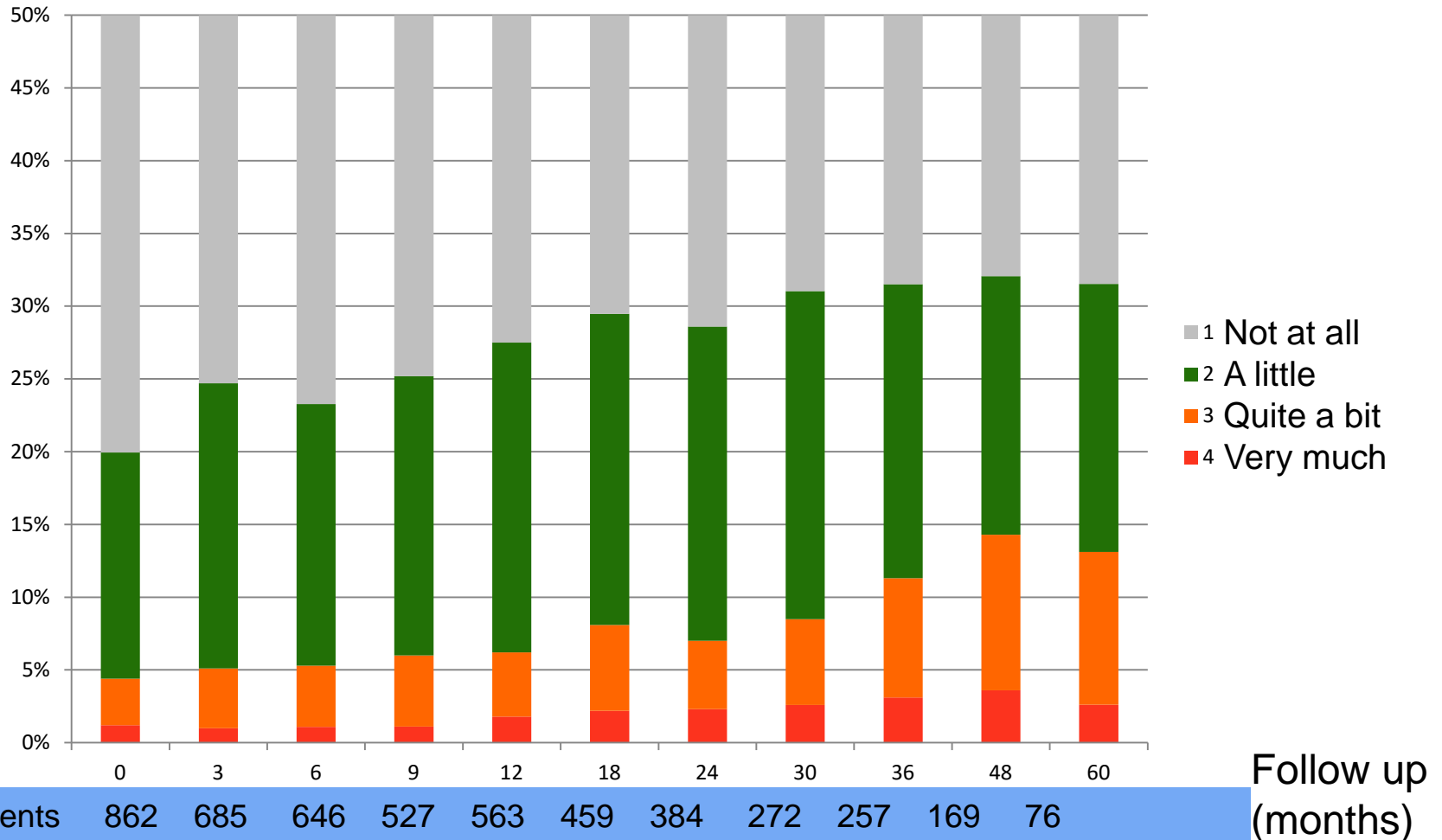
Percentage



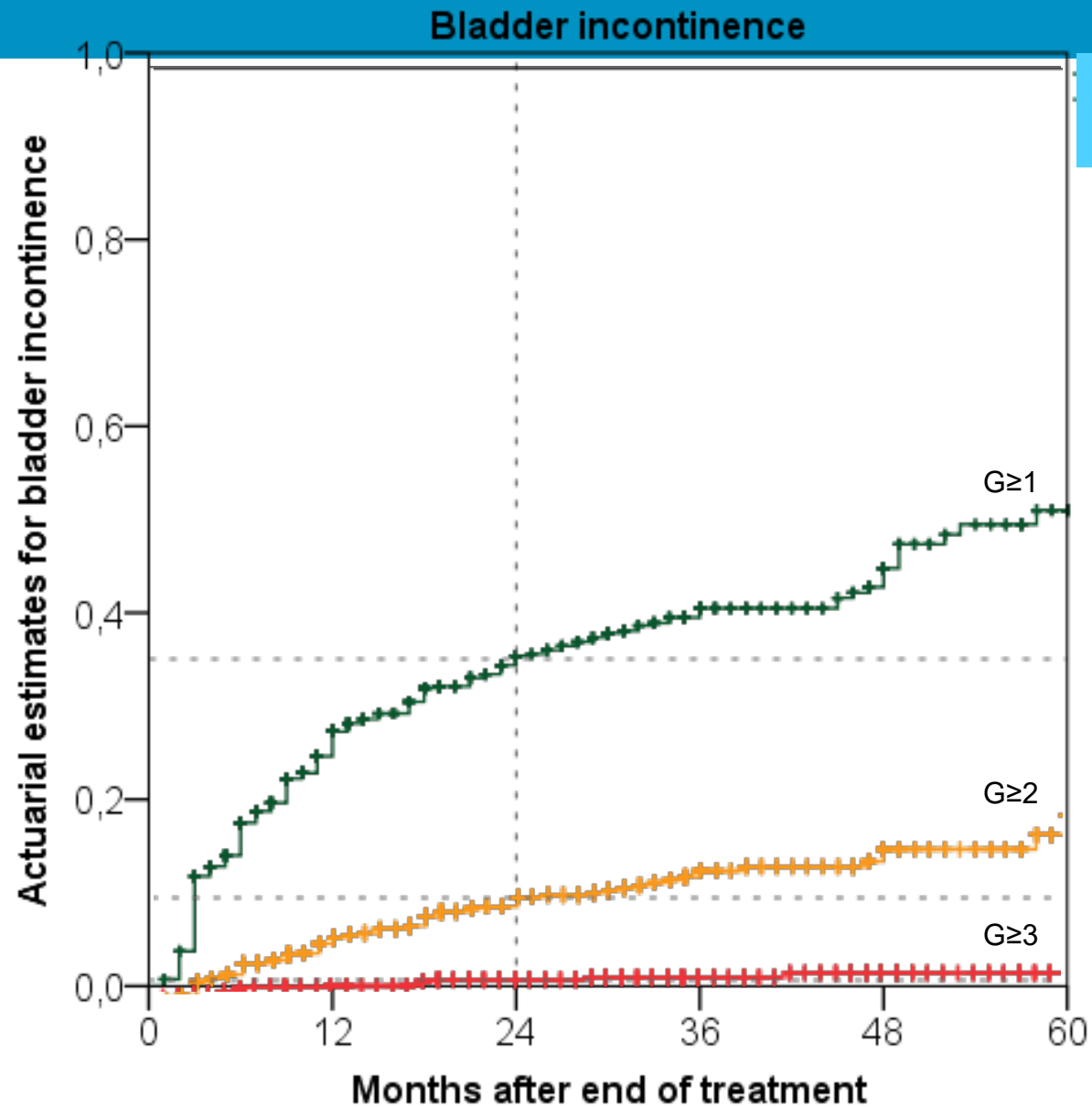
PROM bladder frequency

Annual prevalence rates

Percentage



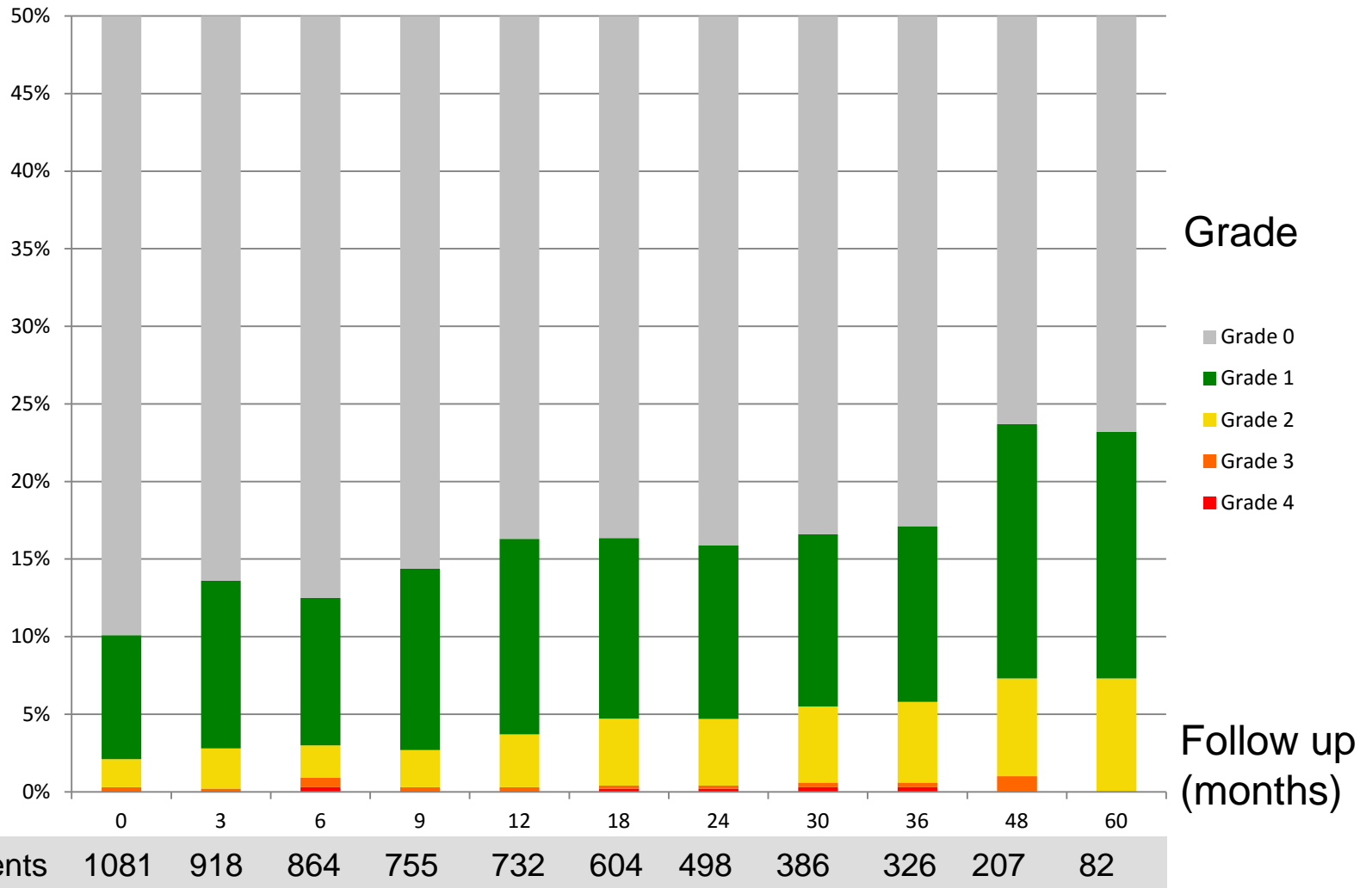
Bladder Incontinence



Bladder incontinence

Annual prevalence rates

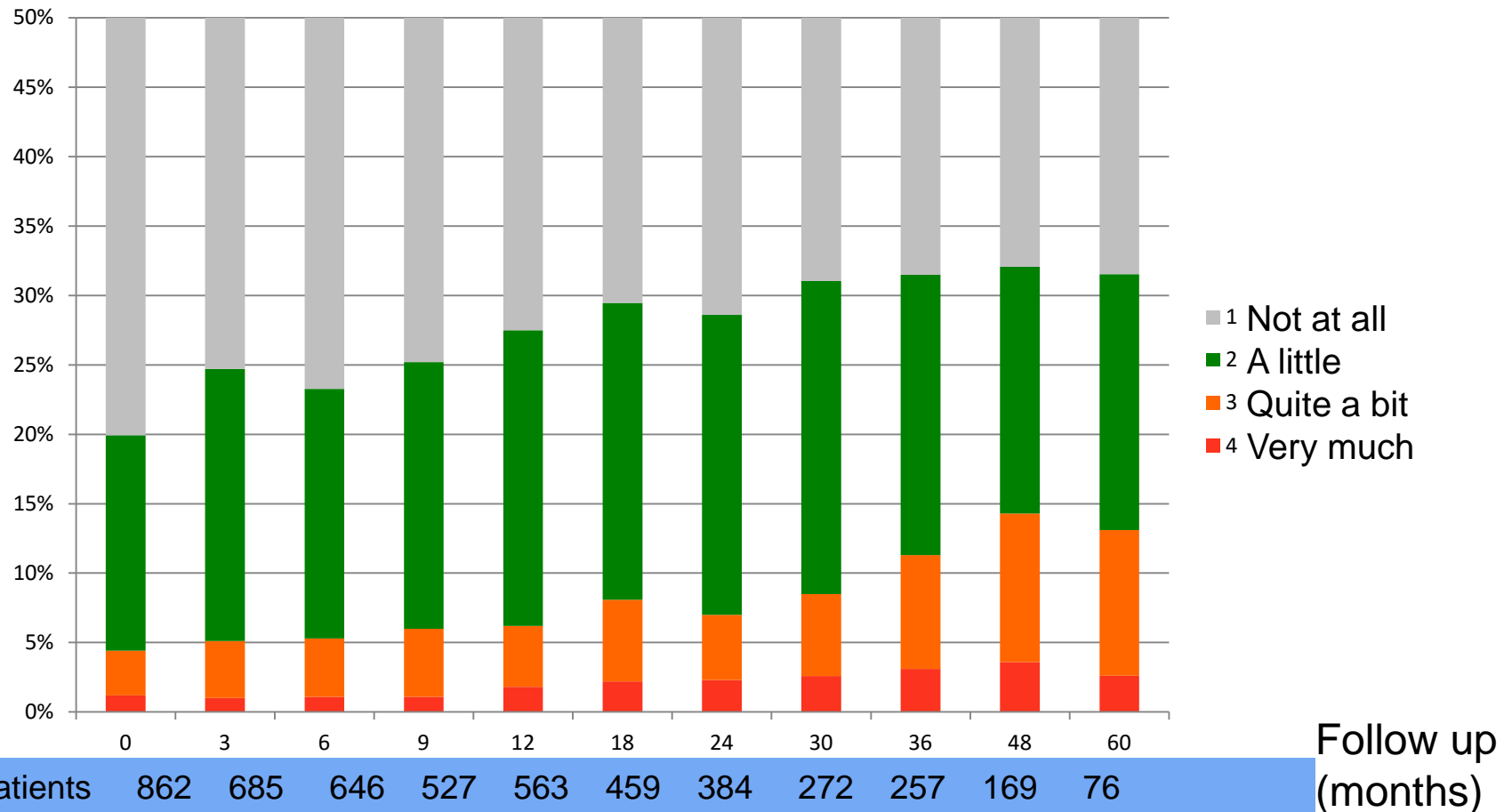
Percentage



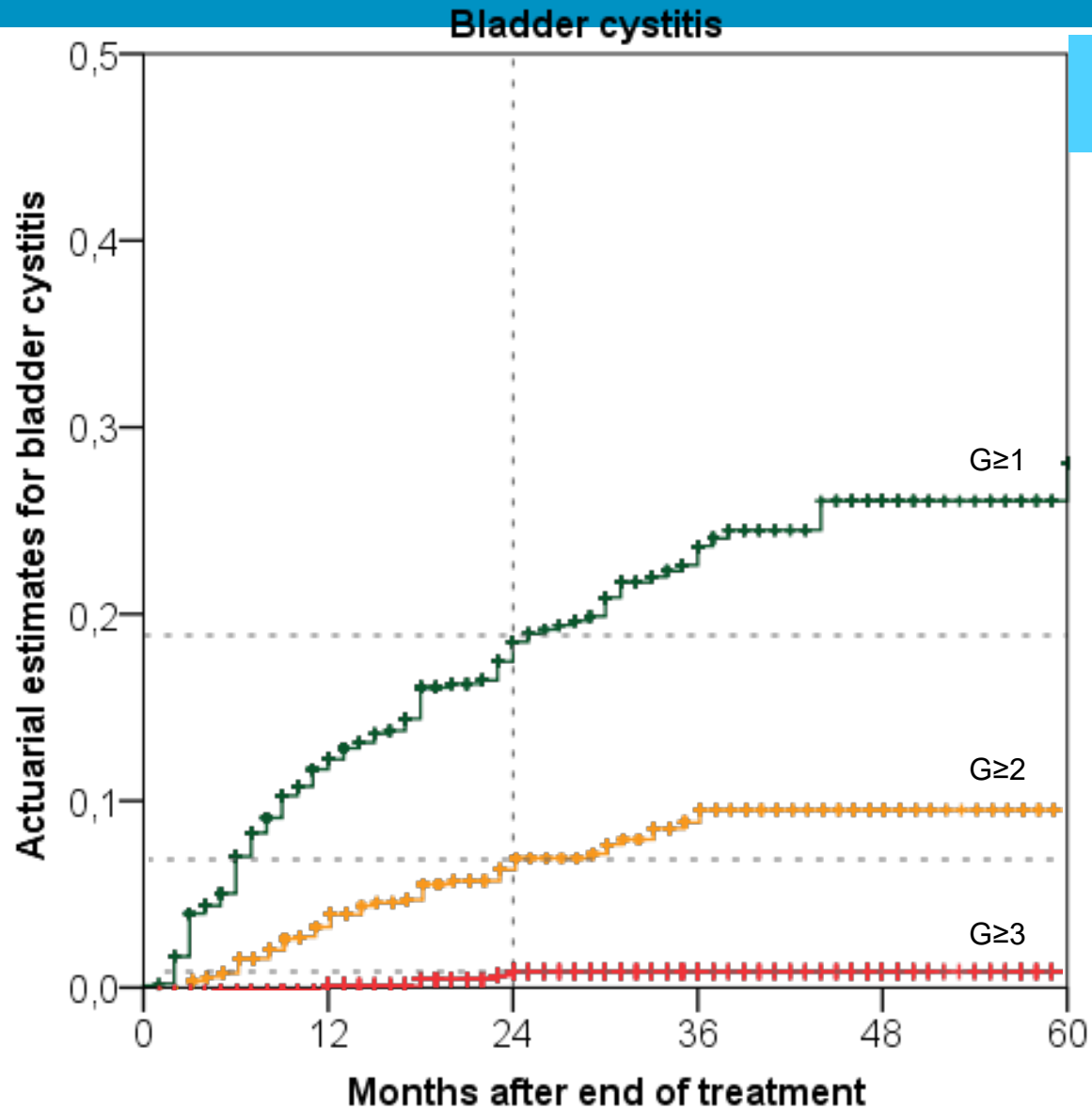
PROM bladder incontinence

Annual prevalence rates

Percentage



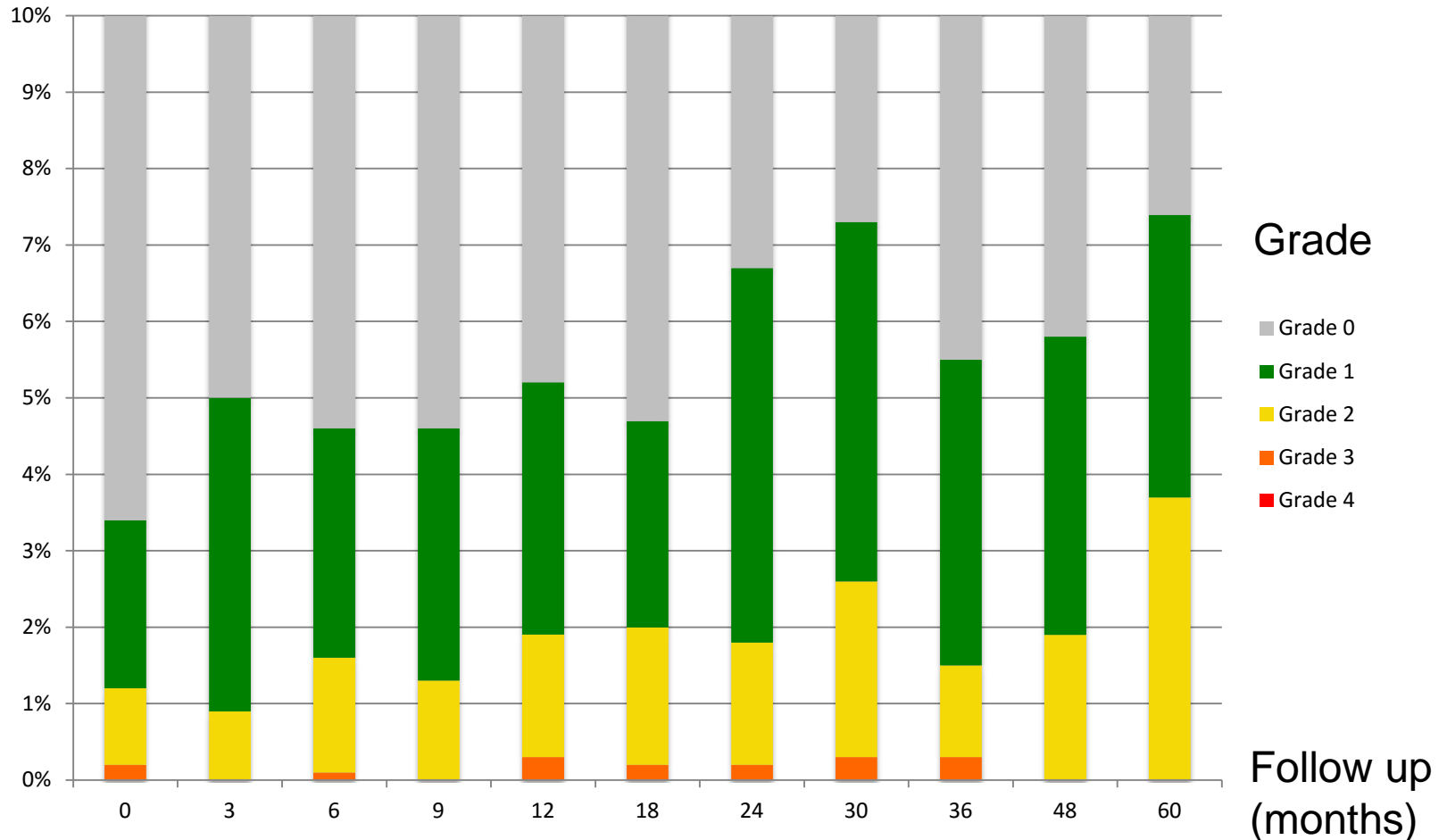
Bladder cystitis



Bladder cystitis

Annual prevalence rates

Percentage

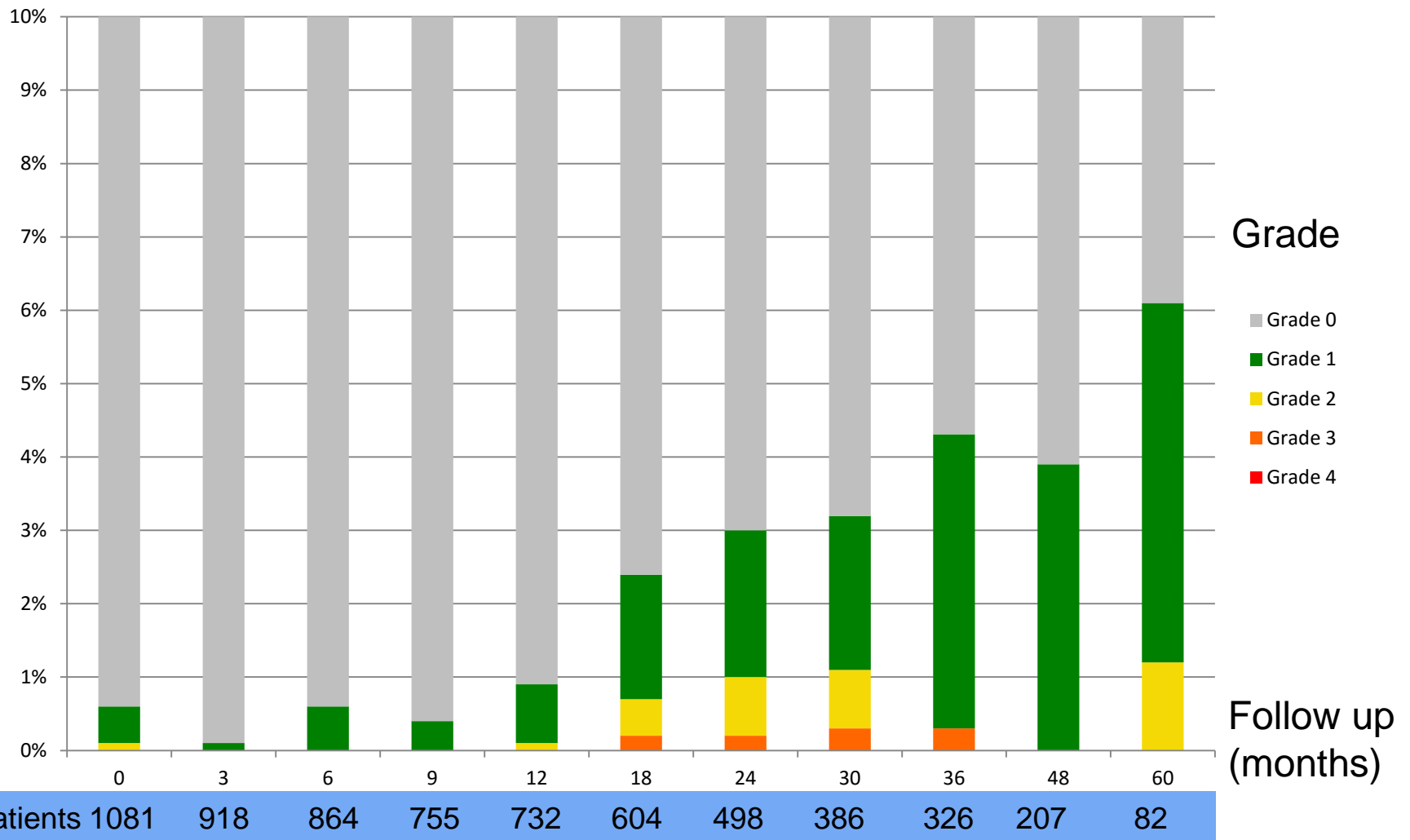


# patients	1081	918	864	755	732	604	498	386	326	207	82
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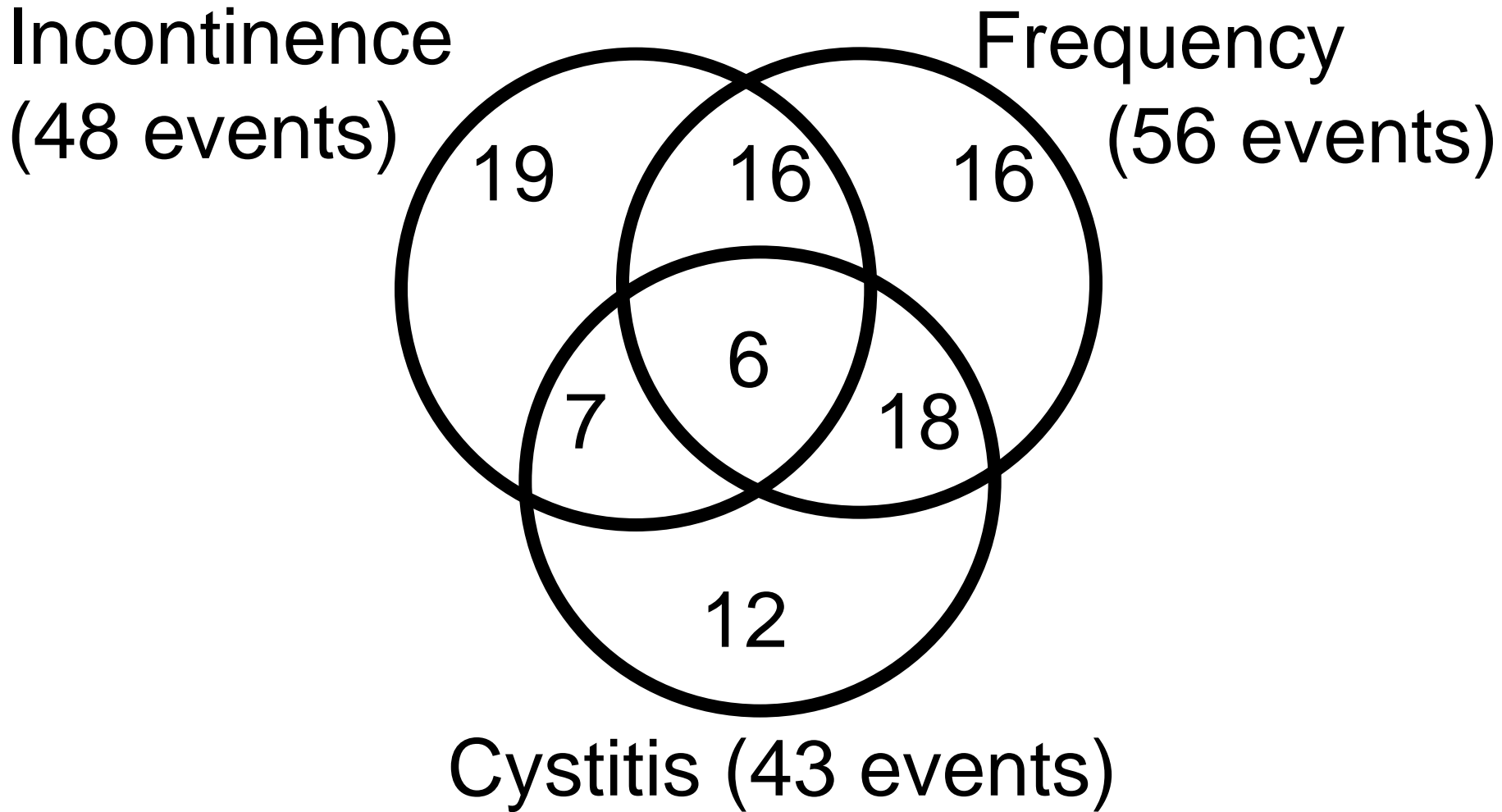
Bladder bleeding

Annual prevalence rates

Percentage



Analysis of single- or groups of symptoms?



Late Morbidity: GI, Rectum, Bowel

EMBRACE I. CTCAE v3
Diarrhea
Flatulence
Incontinence (anal)
Proctitis
Bleeding (hemorrhage GI, anus, rectum, sigmoid, colon, small bowel)
Stricture / stenosis (anus, rectum, sigmoid, colon, small bowel)
Fistula (anus, rectum, sigmoid, colon, small bowel)
Gastro-intestinal other

Descriptive

crude incidence

actuarial incidence

prevalence

(Analytical

mono-factor-

dose-effect-

multi-factor-)

Overview (CTCAE)

	Proctitis		Bleeding		Stenosis		Fistula		ALL	
	N	%	N	%	N	%	N	%	N	%
Grade 0	782	81.5	805	83.8	949	98.9	951	99.1	694	72.3
Grade 1	135	14.1	114	12.0	5	0.5	0	0	193	20.1
Grade 2	39	4.1	31	3.2	6	0.6	5	0.5	58	6.0
Grade 3	4	0.4	10	1.0	0	0	3	0.3	14	1.6
Grade 4	0	0	0	0	0	0	1	0.1	1	0.1

Median Follow-up: 25.4 months

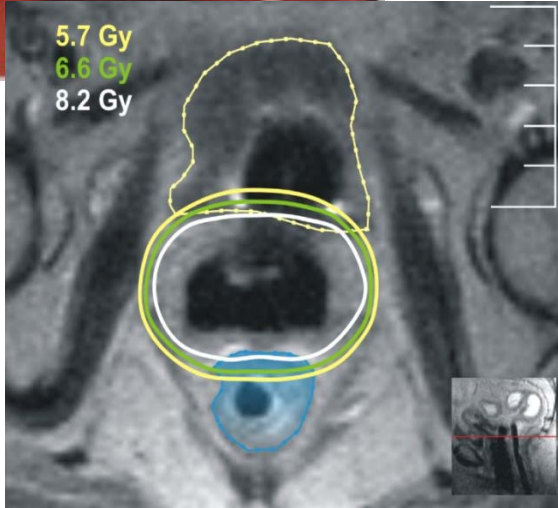
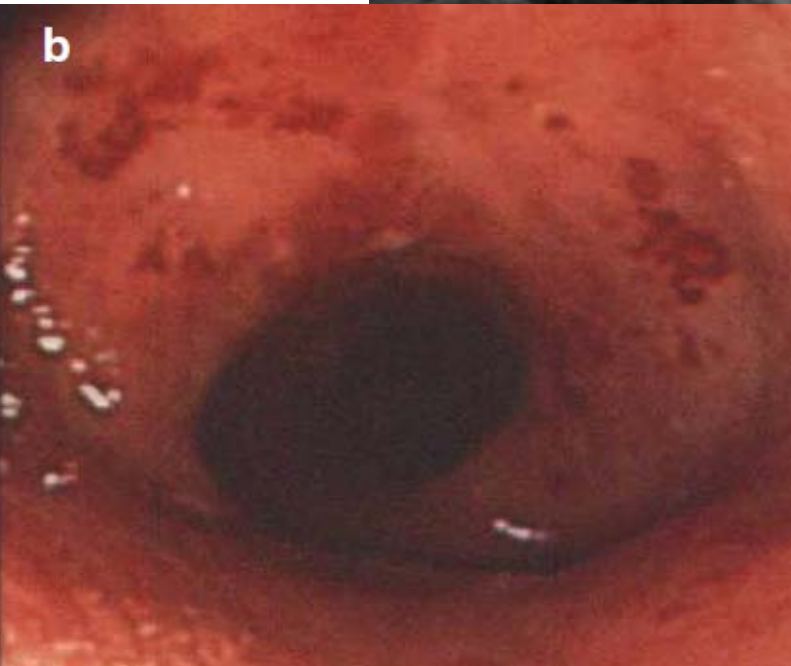
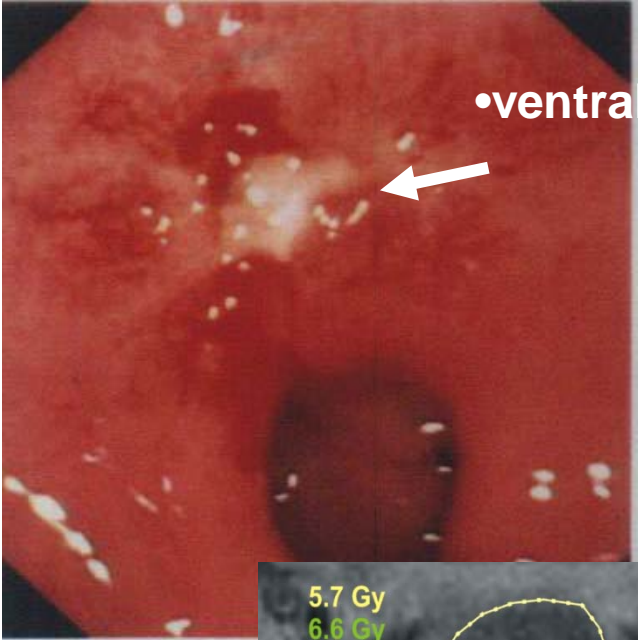
Times to onset
From 1st fraction

Grade 1-4	16.8+/-12.7
Grade 2-4	17.5+/-9.5
Grade 3-4	15.8+/-5.3

Rectum: Late telangiectasia and micro-ulceration

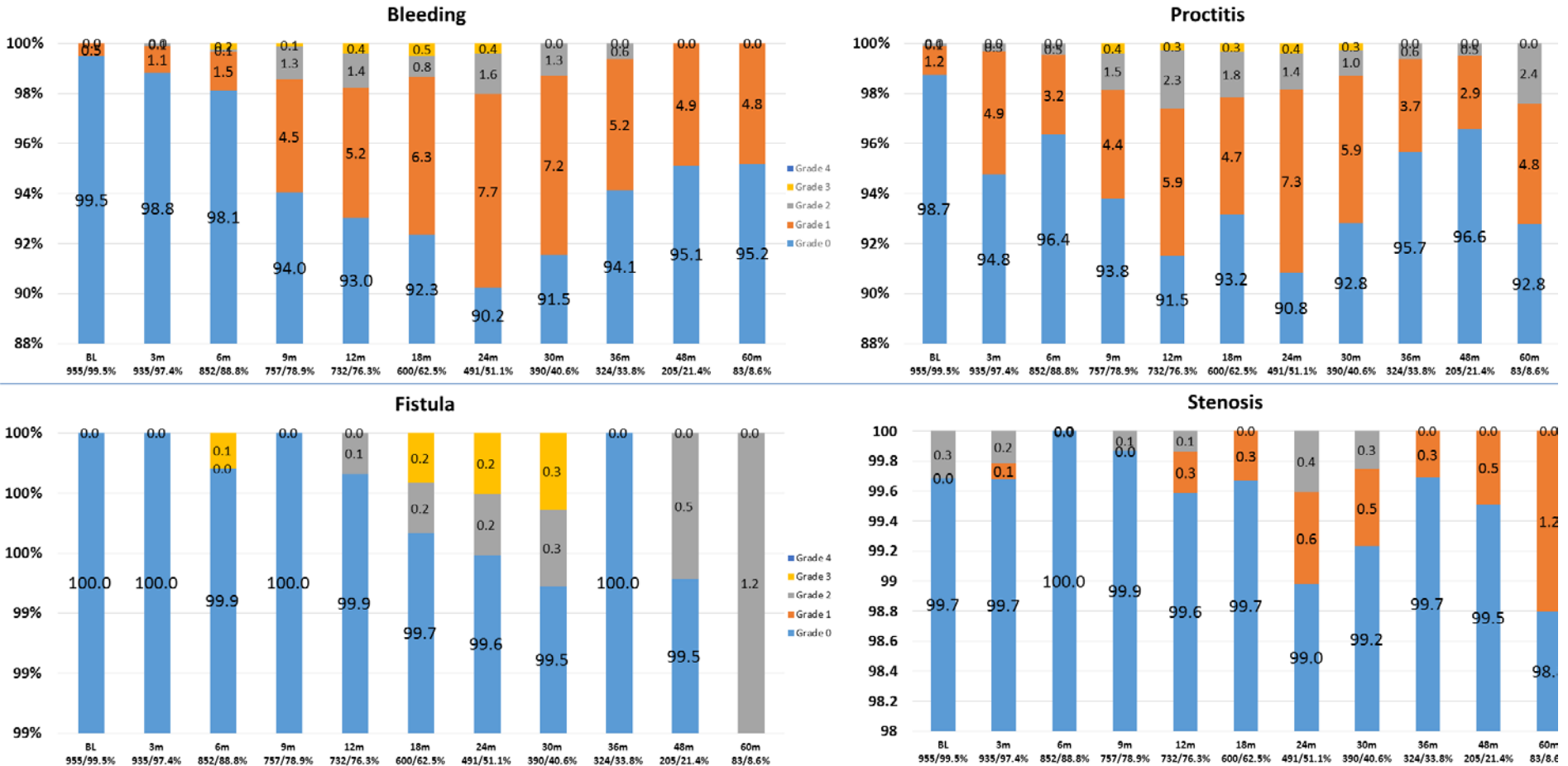


Endoscopy

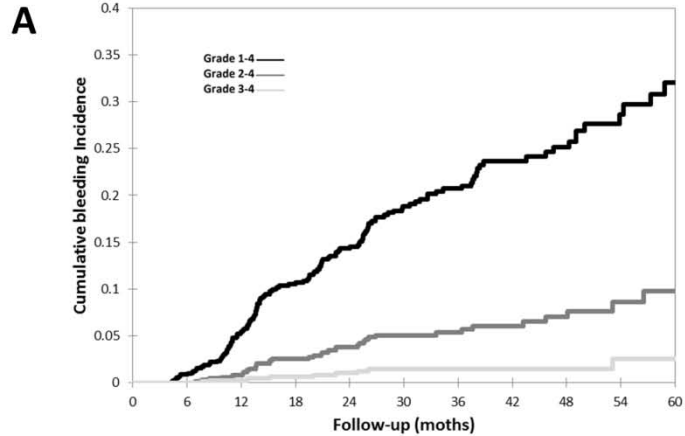


•Georg P et al. R&O 2009

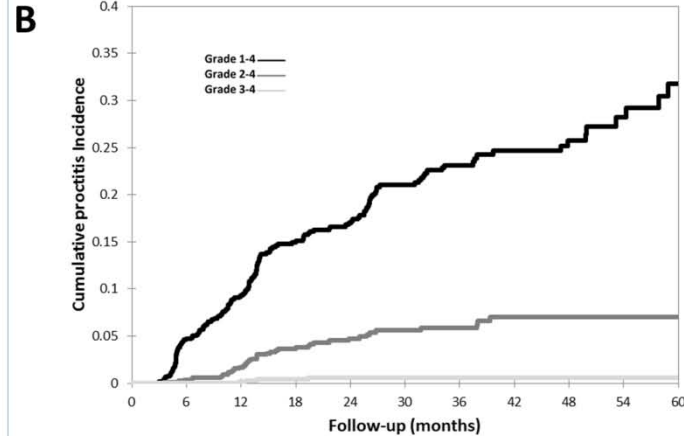
Prevalence for bleeding, proctitis, fistula, stenosis (rectum)



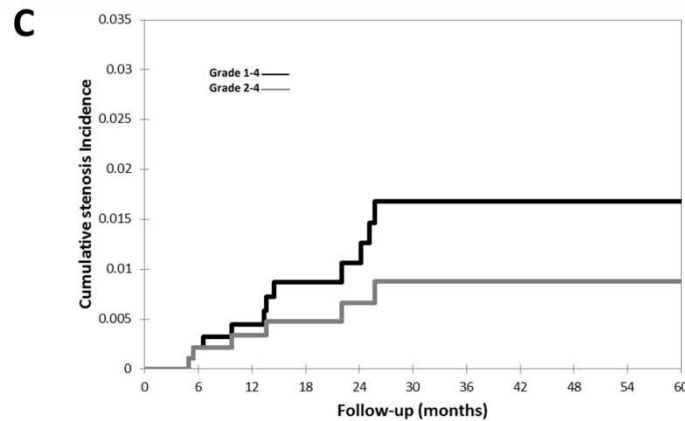
Actuarial estimate of bleeding, proctitis, fistula, stenosis



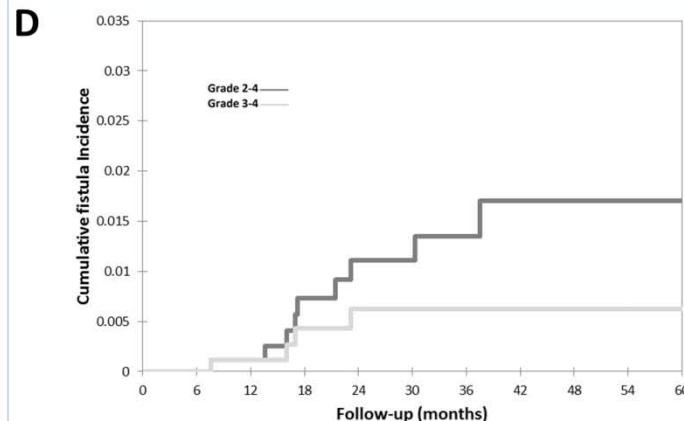
Number at risk						N events		Inc. at 3-y	
	6	12	18	24	30				
Grade 1-4	960	722	436	260	137	155	20.7%		
Grade 2-4	960	755	489	311	169	41	5.4%		
Grade 3-4	960	759	501	319	175	10	0.6%		



Number at risk						N events		Inc. at 3-y	
	6	12	18	24	30				
Grade 1-4	960	695	426	257	136	175	23.1%		
Grade 2-4	960	747	482	305	163	43	5.8%		
Grade 3-4	960	760	504	322	177	4	0.6%		



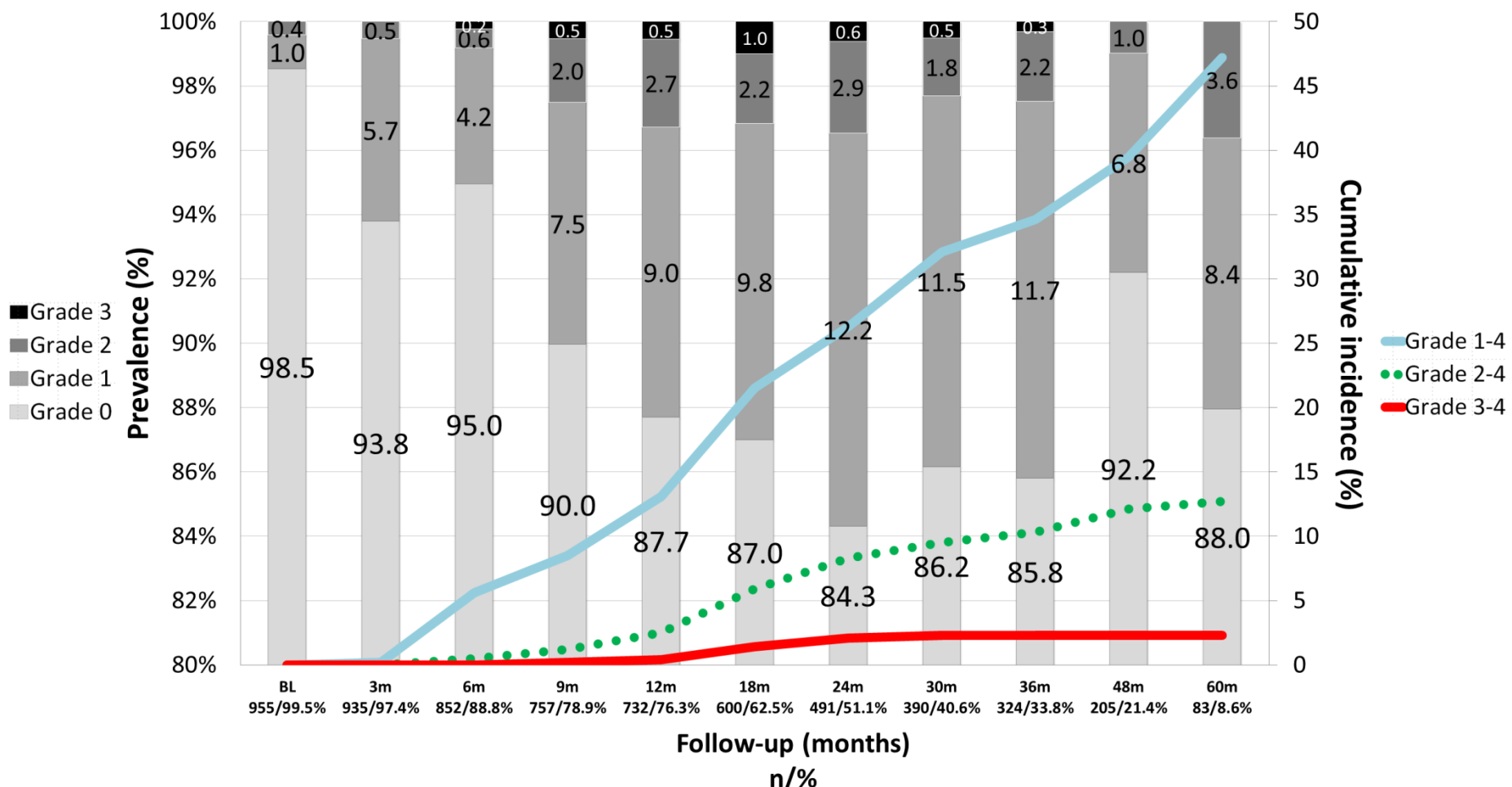
Number at risk						N events		Inc. at 3-y	
	6	12	18	24	30				
Grade 1-4	960	760	503	319	174	11	1.7%		
Grade 2-4	960	760	504	321	176	6	0.9%		
Grade 3-4	960	761	507	324	179	0	0%		



Number at risk						N events		Inc. at 3-y	
	6	12	18	24	30				
Grade 1-4	960	760	503	322	178	9	1.4%		
Grade 2-4	960	760	503	322	178	9	1.4%		
Grade 3-4	960	760	504	322	178	4	0.6%		

**EMBRACE,
Mazeron et al.
Submitted to
green journal**

Prevalence and actuarial cumulative incidence: rectal morbidity



Late Morbidity: GI, Rectum, Bowel

EMBRACE I. CTCAE v3

Diarrhea

Flatulence

Incontinence (anal)

Proctitis

Bleeding (hemorrhage GI, anus, rectum, sigmoid, colon, small bowel)

Stricture / stenosis (anus, rectum, sigmoid, colon, small bowel)

Fistula (anus, rectum, sigmoid, colon, small bowel)

Gastro-intestinal other

Descriptive

crude incidence

actuarial incidence

prevalence

Analytical

mono-factor-

dose-effect-

multi-factor-

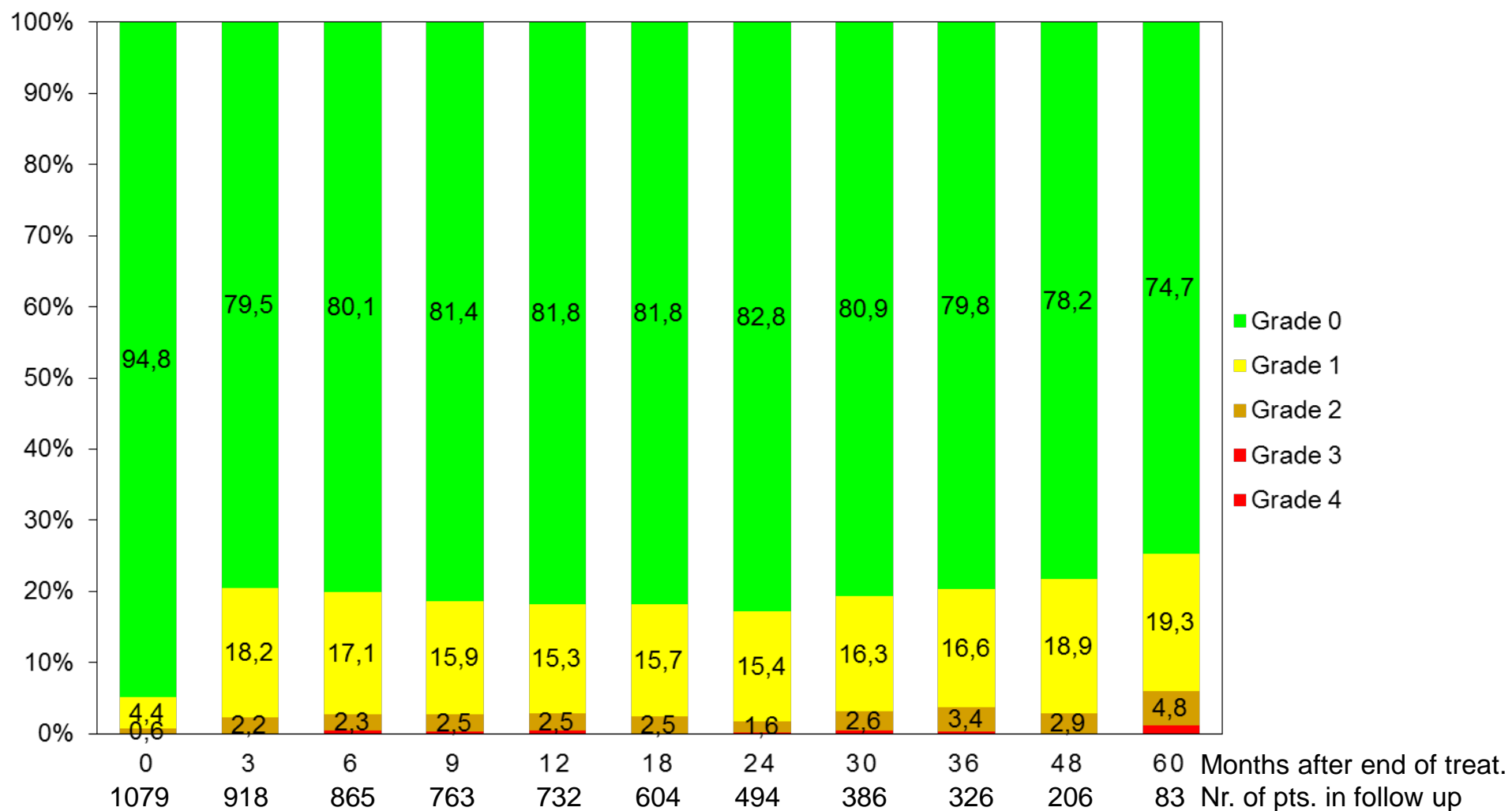
Nina Jensen

Maximum incidence of single bowel symptoms, CTCAE during all follow up

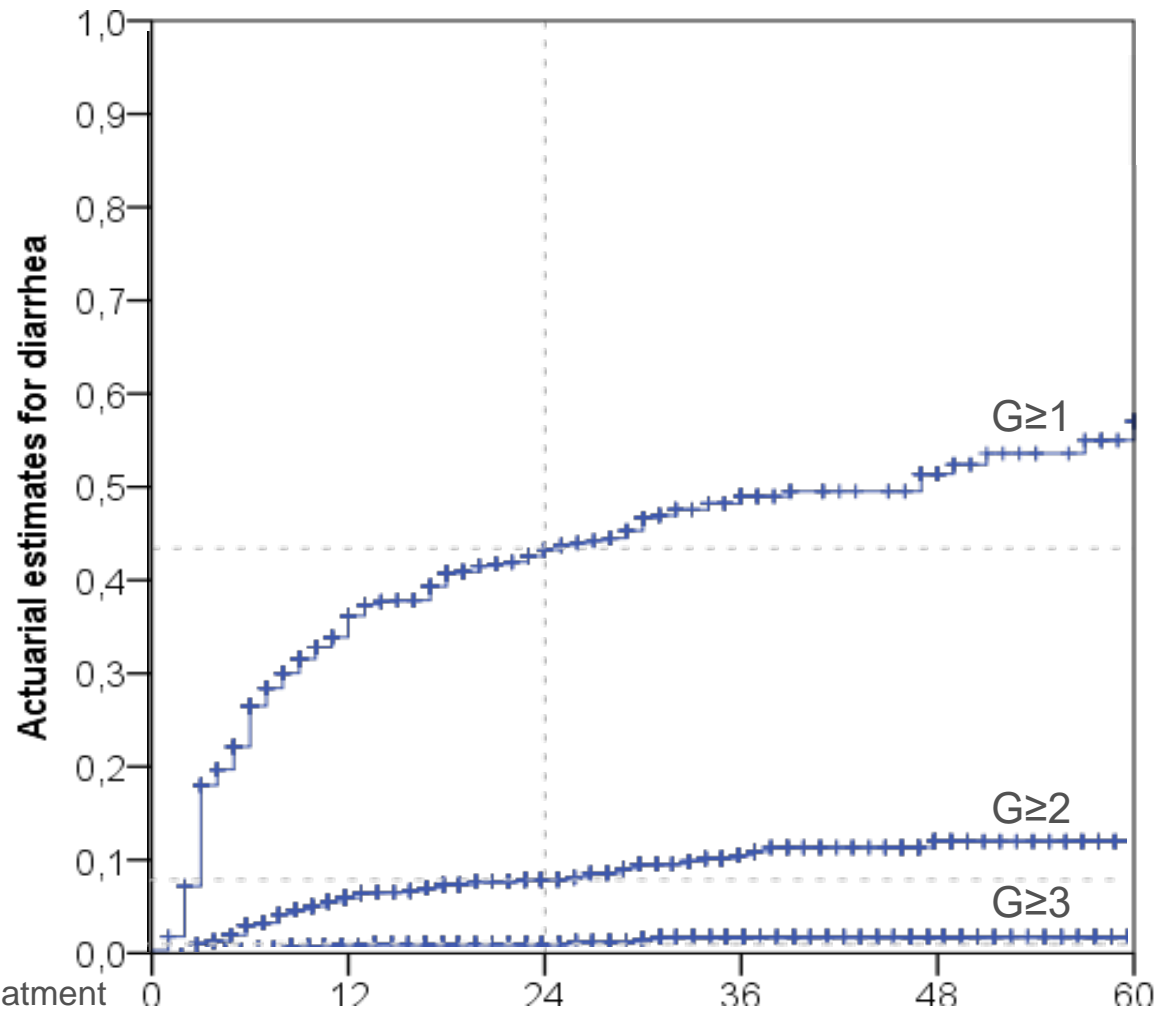
Number of patients 972 (missing 157)

	Diarrhea	Flatulence	Incontinence (anal)
G0	569 (58.5%)	593 (61.0%)	839 (86.3%)
G1	317 (32.6%)	298 (30.7%)	109 (11.2%)
G2	72 (7.4%)	81 (8.3%)	20 (2.1%)
G3	13 (1.3%)		2 (0.2%)
G4	1 (0.1%)		2 (0.2%)

Prevalence rates for all gradings of diarrhea, CTCAE



Actuarial estimates for diarrhea, CTCAE

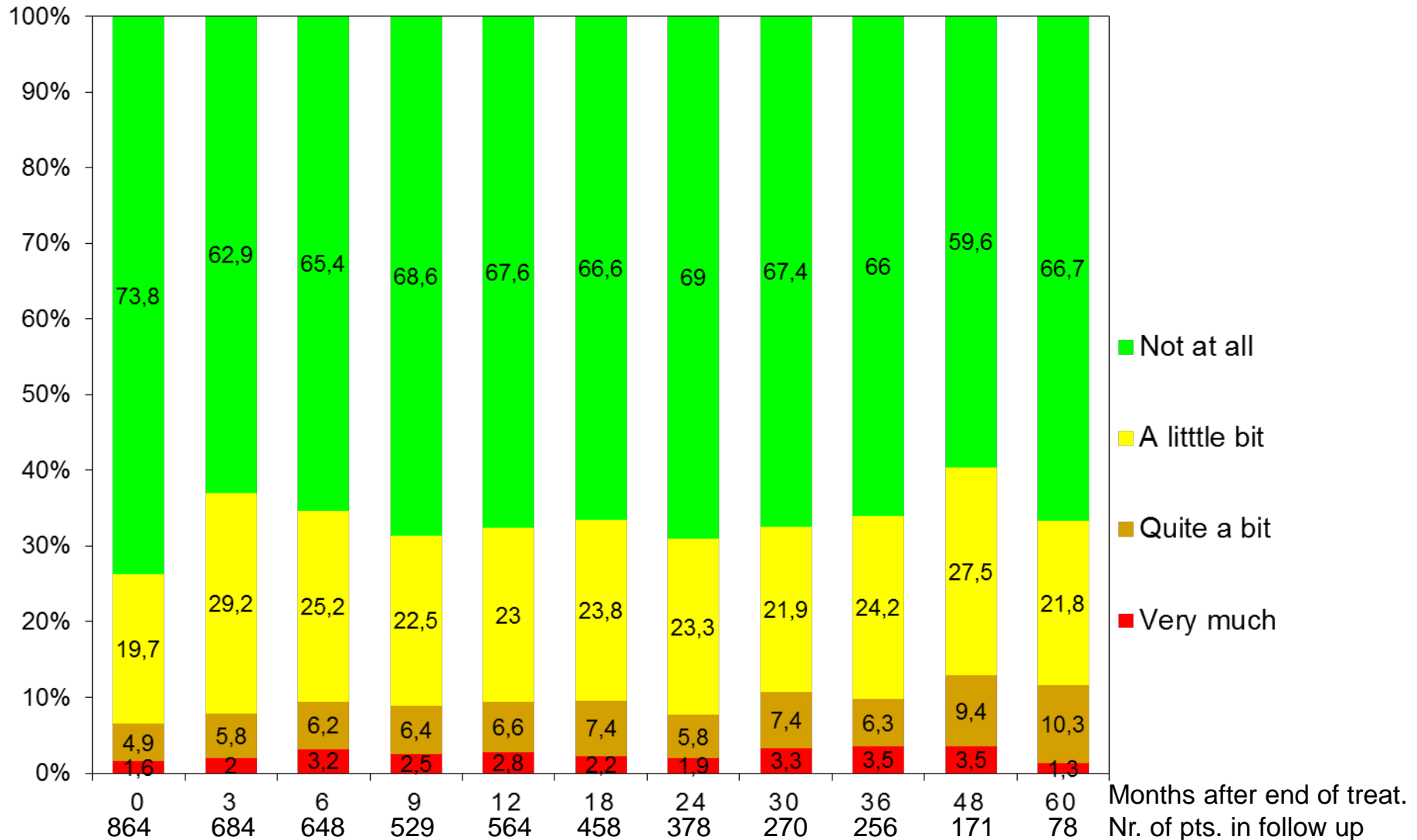


Months after end of treatment	0	12	24	36	48	60
Pts. at risk for any $G \geq 1$	968	487	252	138	66	21
Pts. at risk for any $G \geq 2$	968	700	446	260	132	38
Pts. at risk for any $G \geq 3$	968	738	478	289	148	44

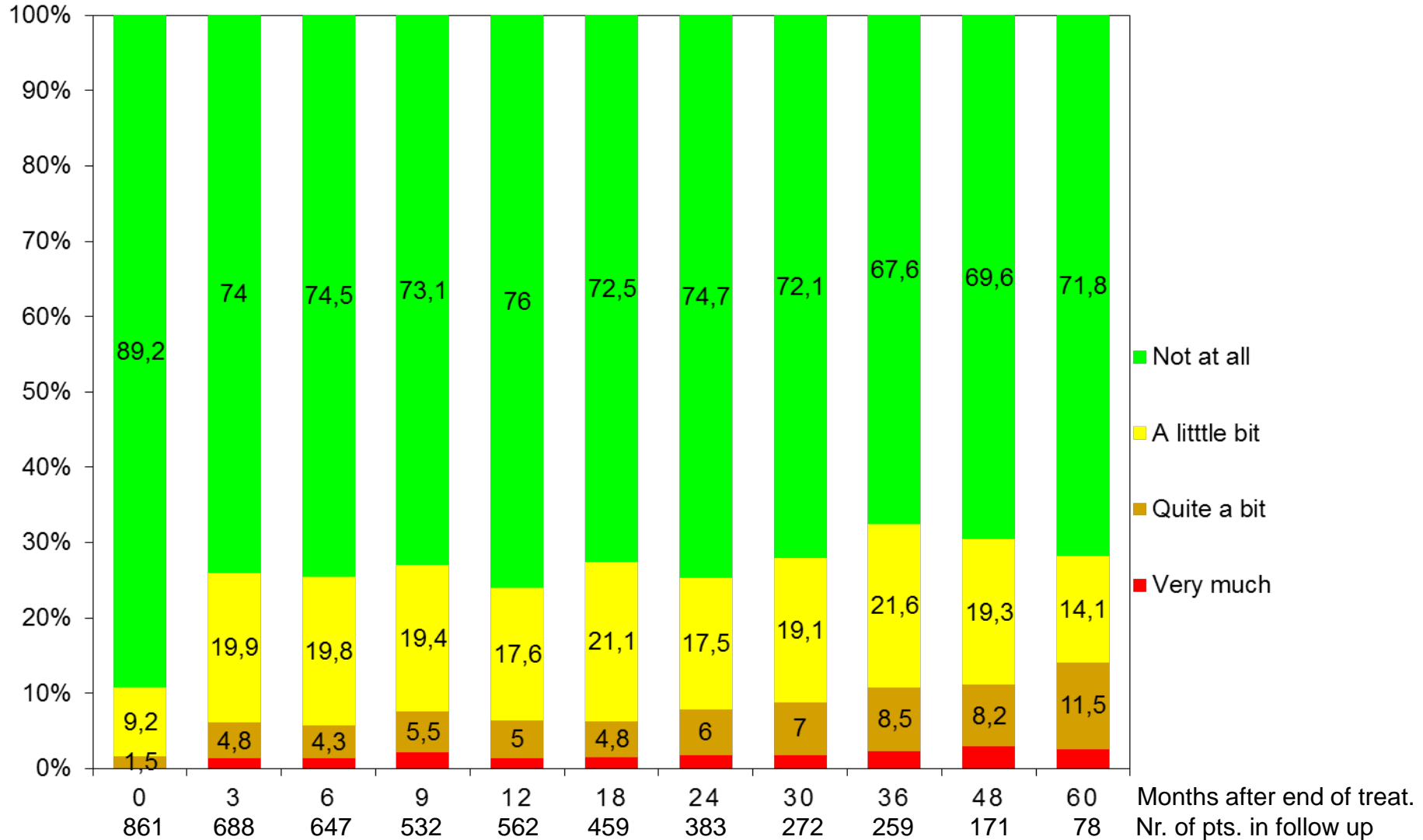
Maximum incidence of single bowel symptoms, EORTC C30+CX24

	Have you had diarrhea	Have you been constipated	Have you had cramps in your abdomen	Have you had difficulty in controlling your bowels
1="Not at all"	336 (39,3%)	484 (56,6%)	329 (38,5%)	433 (50,7%)
2="A little"	318 (37,2%)	249 (29,1%)	316 (37,0%)	276 (32,3%)
3="Quite a bit"	140 (16,4%)	91 (10,6%)	143 (16,7%)	102 (11,9%)
4="Very much"	61 (7,1%)	31 (3,6%)	66 (7,7%)	43 (5,0%)
Number of patients (Missing)	855 (274)	855 (274)	854 (275)	854 (275)

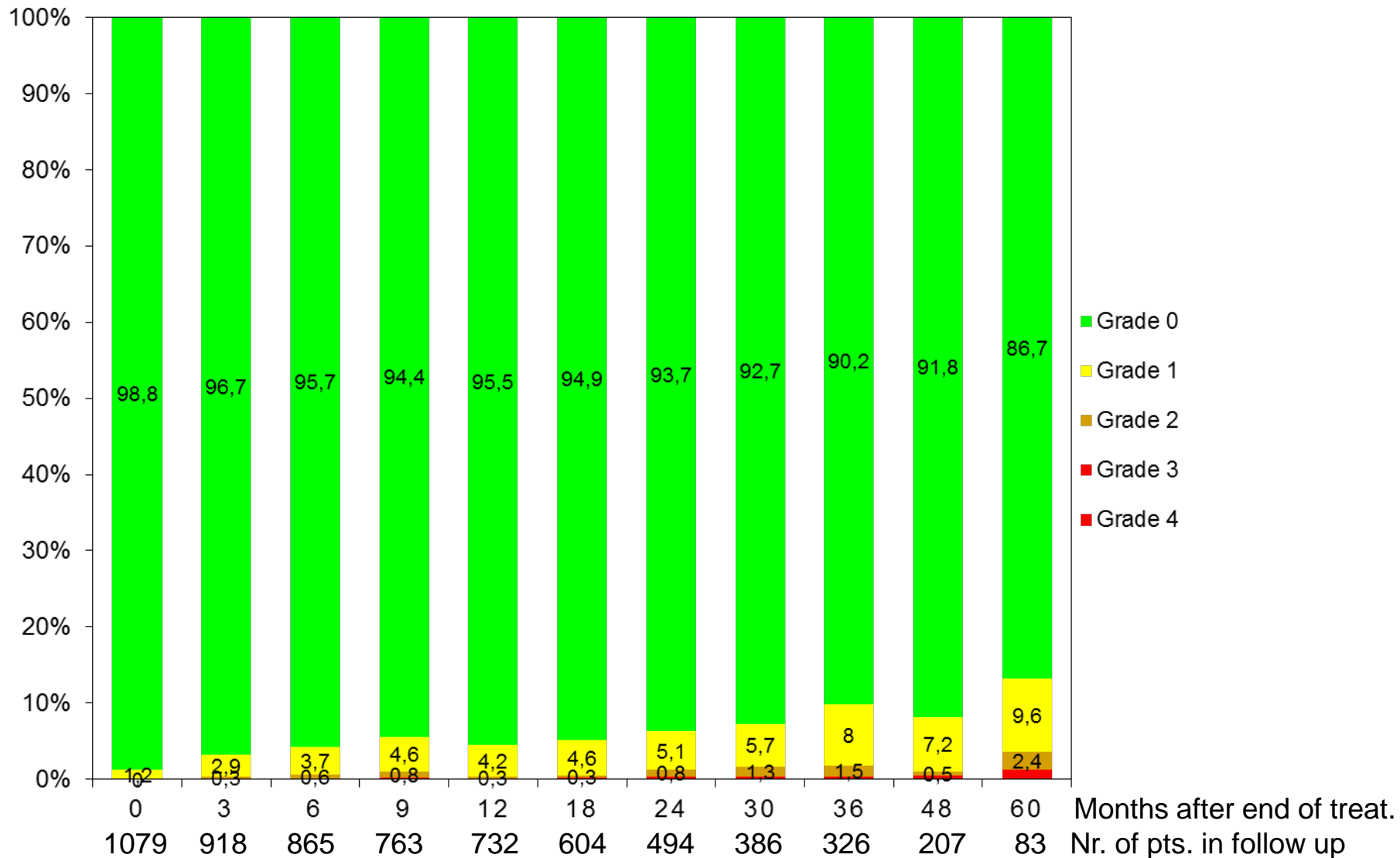
Prevalence rates for all gradings of diarrhea, EORTC



Prevalence rates for all gradings of difficulty controlling bowel, EORTC



Prevalence rates for all gradings of incontinence, CTCAE



Development of sigmoid, colon and small bowel stenosis/strictures grade ≥ 2

	3 month	6 month	9 month	12 month	18 month	24 month	30 month	36 month	48 month	60 month	*Bowel+ sigmoid D2CC	**Prev abd. surg.	57 Gy vol.	Nodal vol.
Pt. 1	0	0	3	67.78	No	1212	165
Pt. 2	0	0	0	0	0	2	3	0	0	.	.	Yes	156	394
Pt. 2	0	0	0	2	0	1	0	0	0	.	60.86	Yes	156	394
Pt. 3	0	4	3	3	Yes	0	.
Pt. 4	0	0	.	2	2	0	0	4	.	.	73.57	No	356	58
Pt. 5	0	0	4	0	0	0	61.06	No	0	.
Pt. 6	0	0	0	0	3	3	.	0	0	0	73.82	No	0	.
Pt. 7	0	0	3	3	0	0	0	0	.	.	77.73	No	0	.
Pt. 8	0	0	.	0	0	3	2	2	1	0	85.38	No	0	.
Pt. 9	0	0	.	3	0	0	0	0	.	.	75.53	No	592	116
Pt. 10	0	0	0	0	0	0	0	3	0	0	62.18	No	0	.
Pt. 11	0	0	2	0	0	0	0	0	.	.	65.33	No	0	.
Pt. 12	0	0	0	2	0	0	0	0	0	.	66.99	No	0	105
Pt. 13	0	0	0	0	0	2	2	.	.	.	70.37	No	370	85
Pt. 14	0	0	0	2	64.85	No	0	50
Pt. 15	0	2	0	0	0	0	0	0	.	.	59.99	No	0	.

Bowel D2CC median 62.51 (43.2-104.52). Sigmoid D2CC median 64.30 (43.2-106.30). **Previous major pelvic/abd. surgery.

Development of sigmoid and small bowel fistulas grade ≥ 2

	3 month	6 month	9 month	12 month	18 month	24 month	30 month	36 month	48 month	60 month	*Bowel+ Sigmoid D2CC	**Prev. abd. surg.	57 Gy vol.
Pt. 1	0	0	0	0	0	5	No	0
Pt. 2	0	0	3	0	73.57	No	356
Pt. 3	0	0	.	0	0	3	0	0	0	.	82.73	No	0
Pt. 4	0	0	0	0	2	2	No	0
Pt. 5	0	0	4	0	0	0	0	.	.	.	70.37	No	370
Pt. 6	0	0	0	0	0	3	3	2	0	0	70.10	No	0
Pt. 7	0	0	2	2	0	68.84	No	748

*Bowel D2CC median 62.51 (43.2-104.52). Sigmoid D2CC median 64.30 (43.20-106.30)

**Previous major pelvic/abdominal surgery.

Late Morbidity: Vagina

EMBRACE I. CTCAE v3
Vaginal dryness
Vaginal stenosis/length
Vaginal mucositis
Bleeding (hemorrhage GU)
Fistula (Vagina cont.)
Vaginal other
Hormonal therapy
Regular vaginal dilatation

Descriptive

crude incidence

actuarial incidence

prevalence

(Analytical

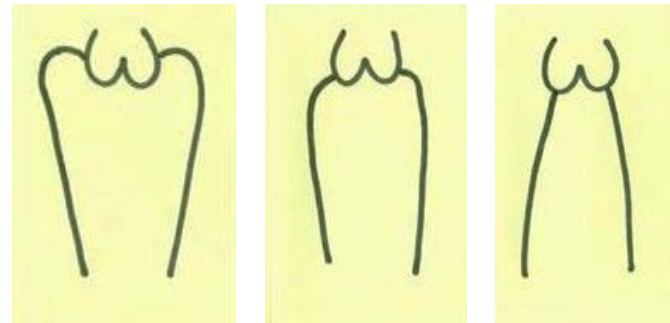
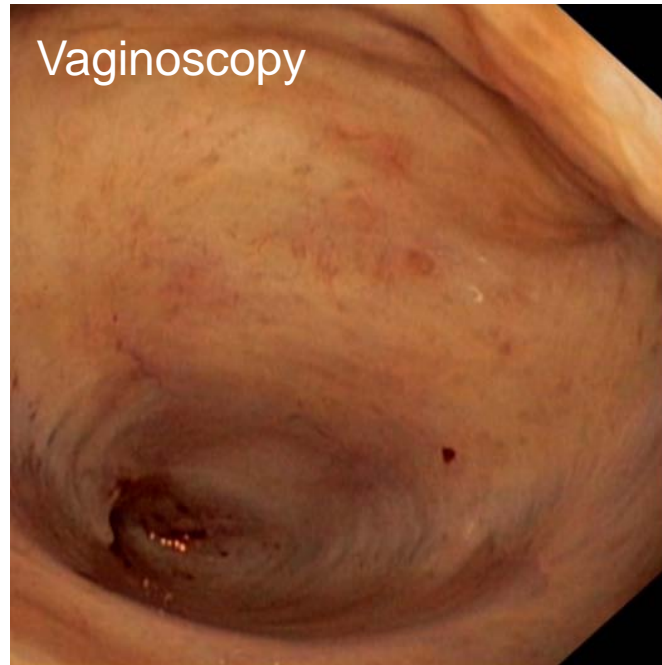
mono-factor-

dose-effect-

multi-factor-)

Vaginal stenosis

Flattening of the fornices → „conical appearance“



Impact on sexuality:

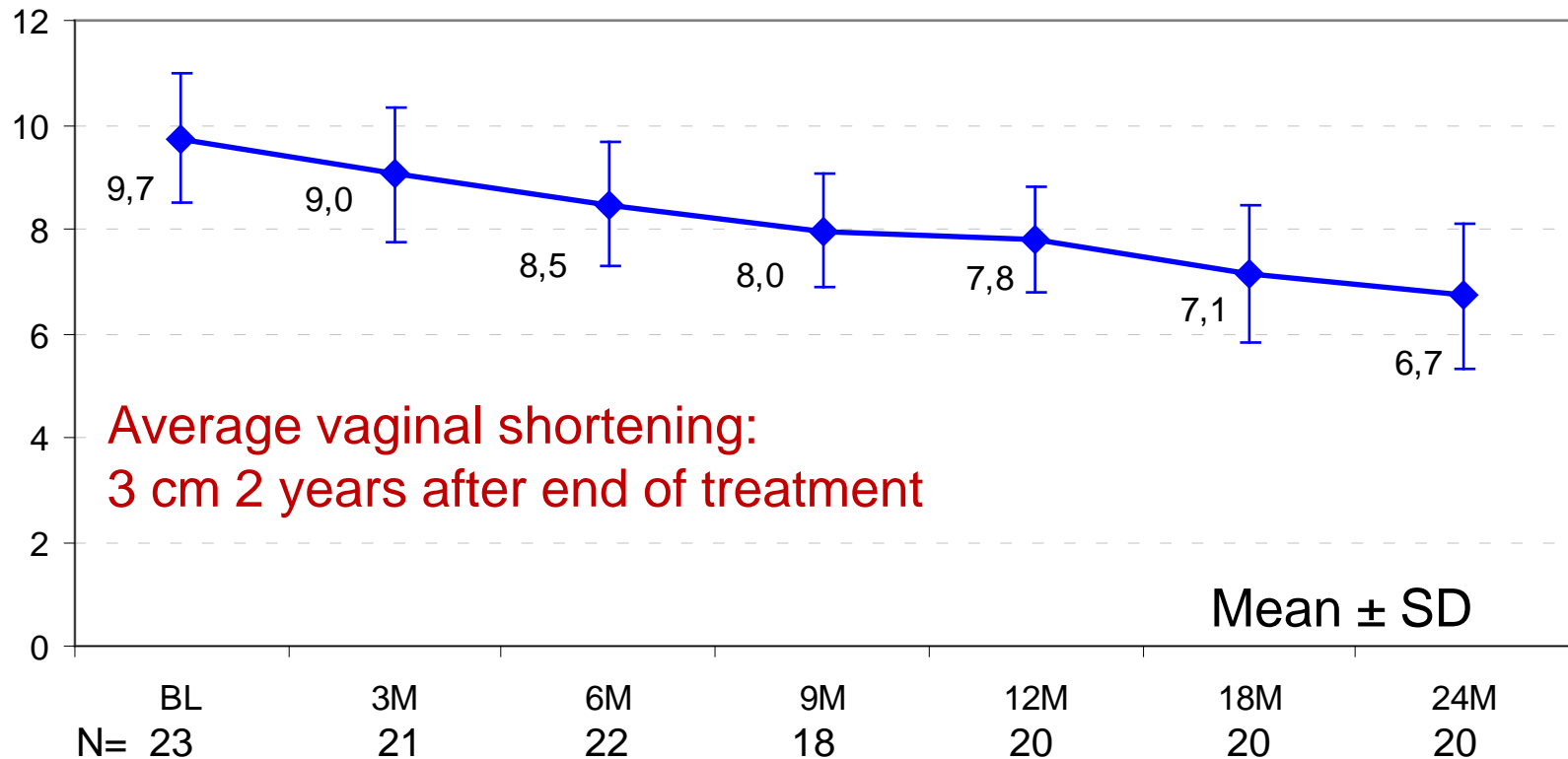
Feeling of vaginal shortening

Feeling of vaginal tightening, esp. at the introitus

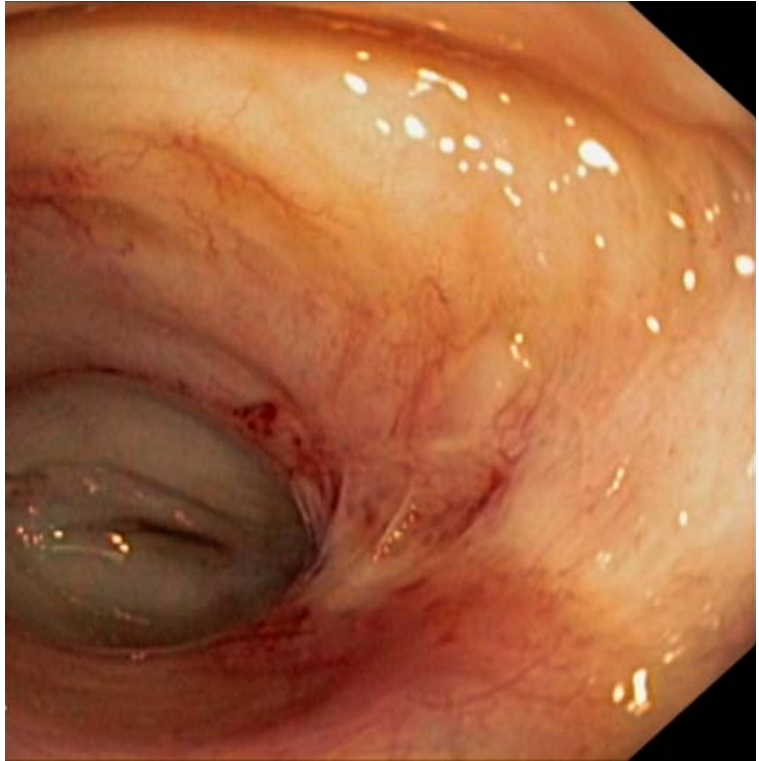
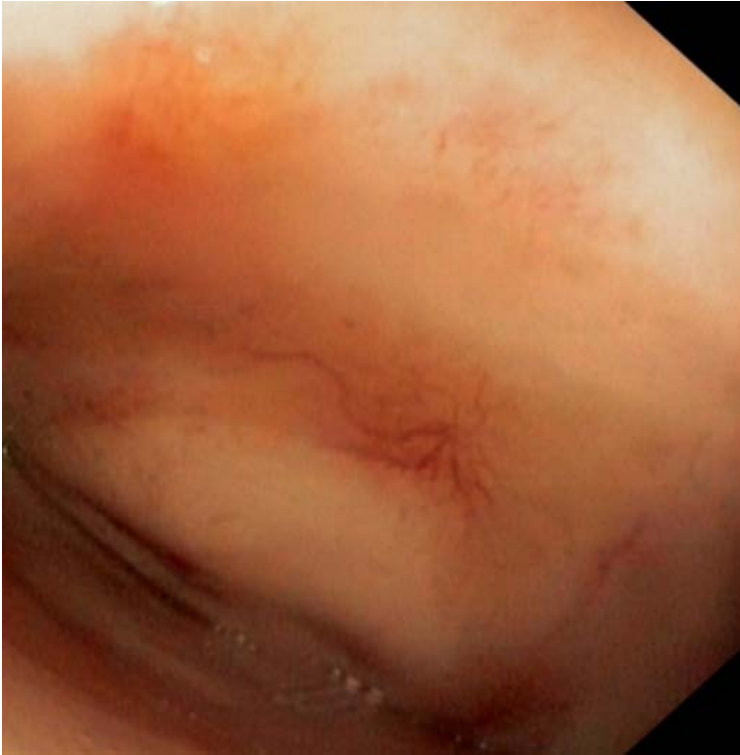
→ Pain during intercourse (dyspareunia)

Vaginal length reduction

Fibrosis, loss of elasticity



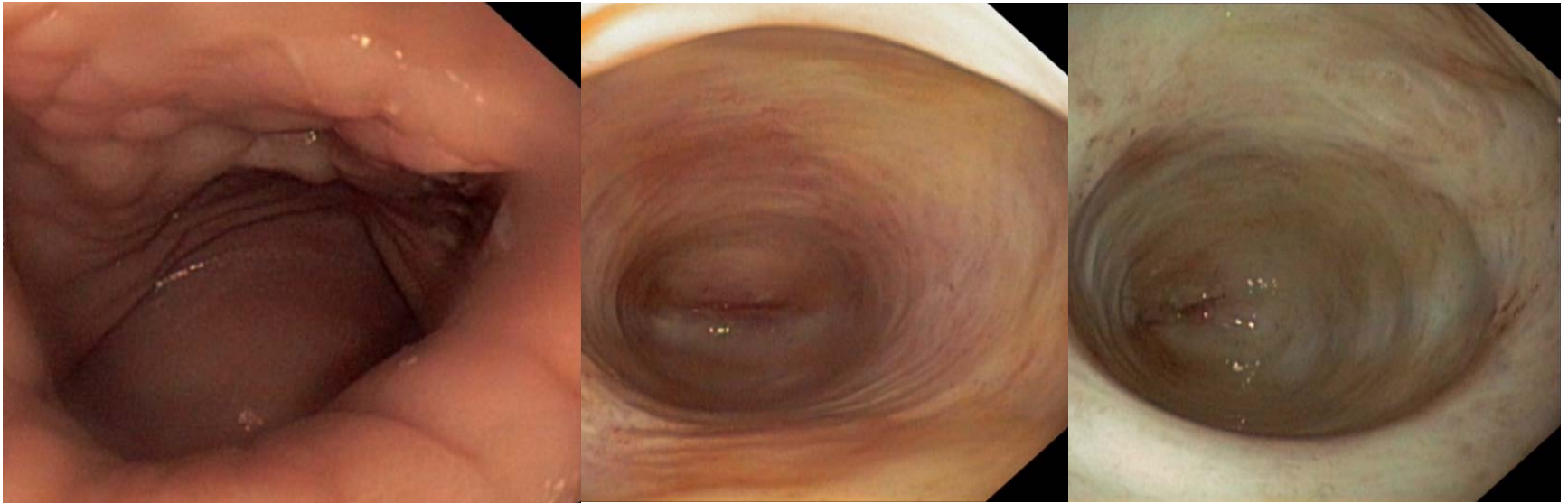
Telangiectasia



Impact on sexuality:

Contact bleeding during or after intercourse
(causes fear of recurrence)

Atrophy of the mucosa

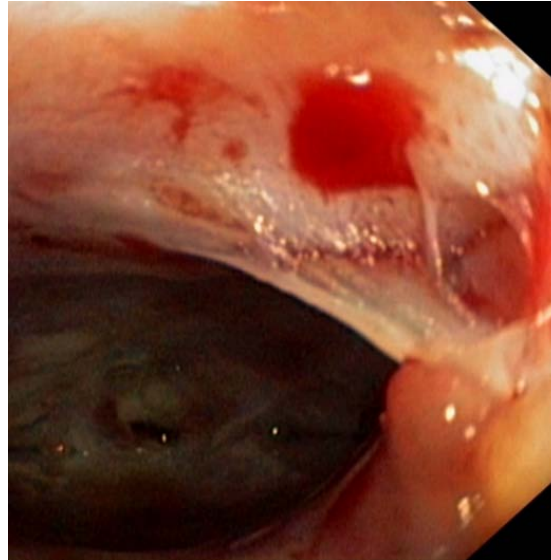
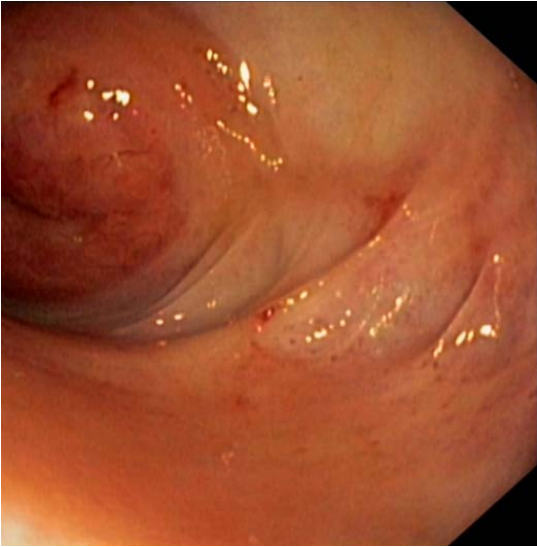


Impact on sexuality

Reduced lubrication despite sexual arousal
→ painful friction and irritation of the mucosa,

Feeling of soreness, itching, burning

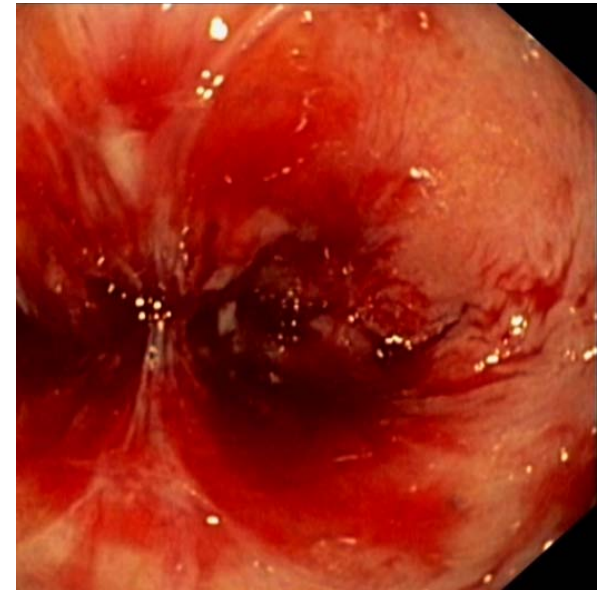
Adhesions



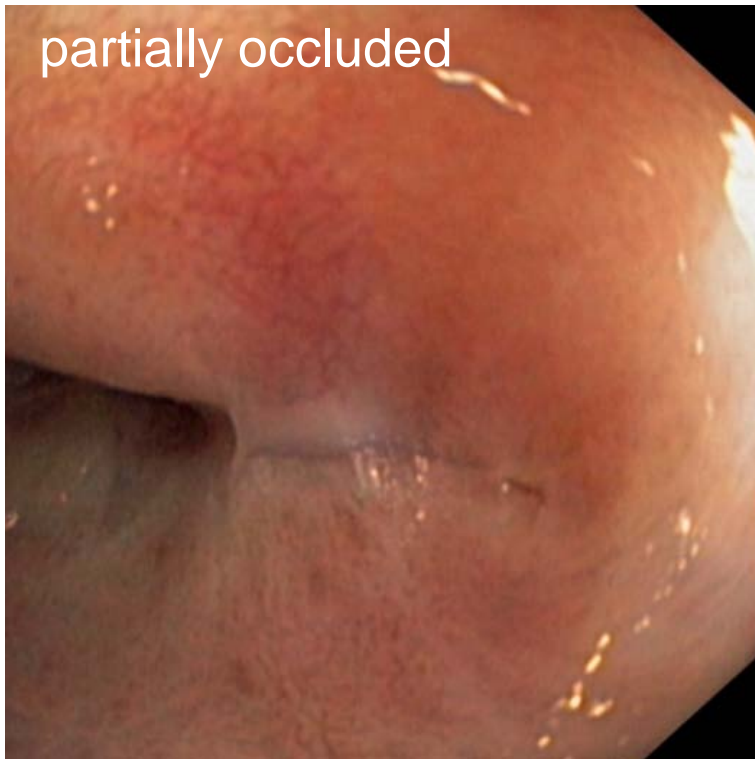
Resolvment during examination often painful

Impact on sexuality:

Rupture of adhesion during intercourse causes pain and bleeding



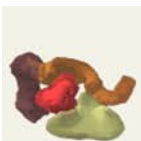
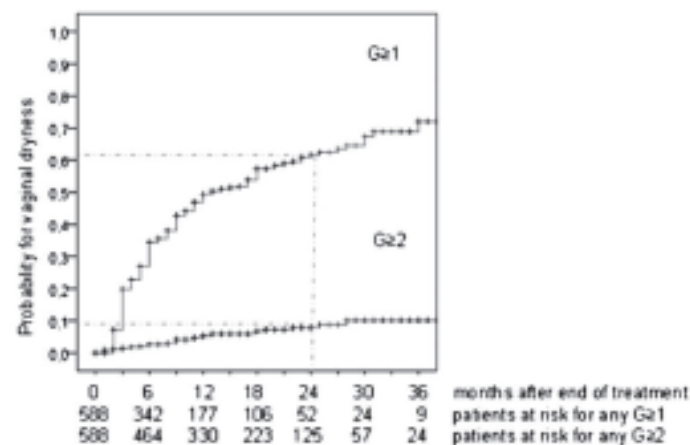
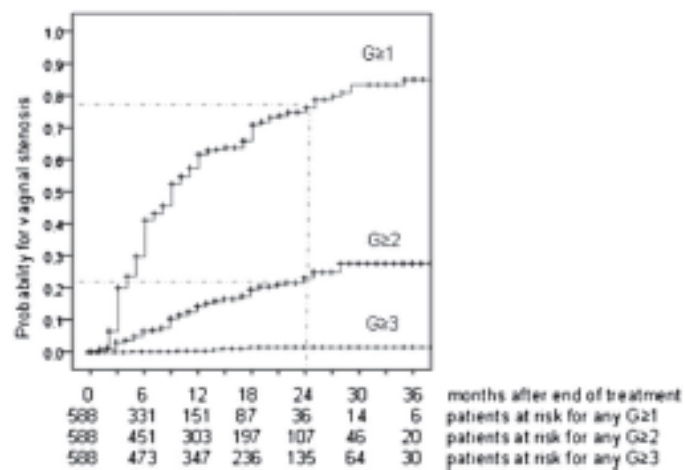
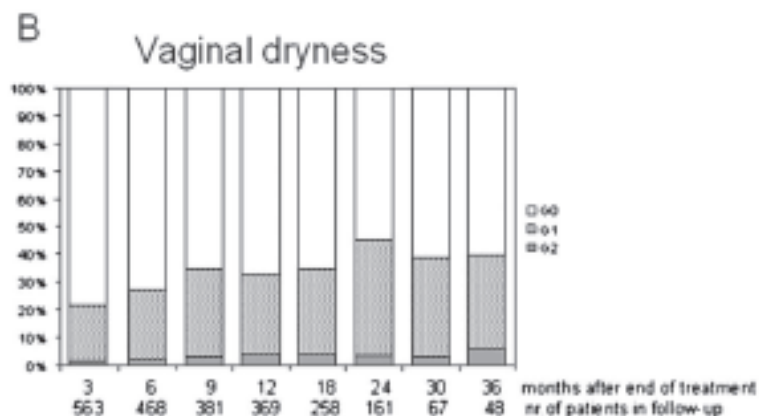
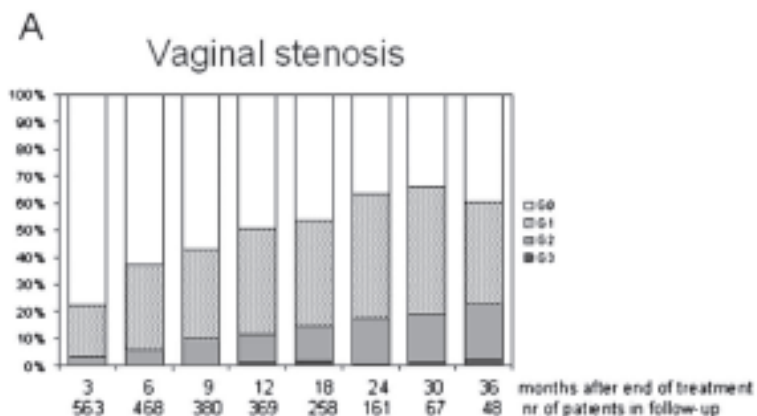
Vaginal occlusion



Prevention:
Regular dilation
and / or intercourse



Patterns of manifestation: Prevalence rates and Actuarial estimates



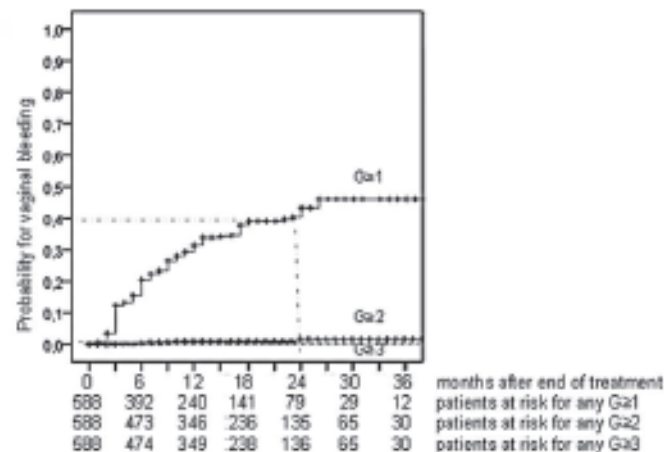
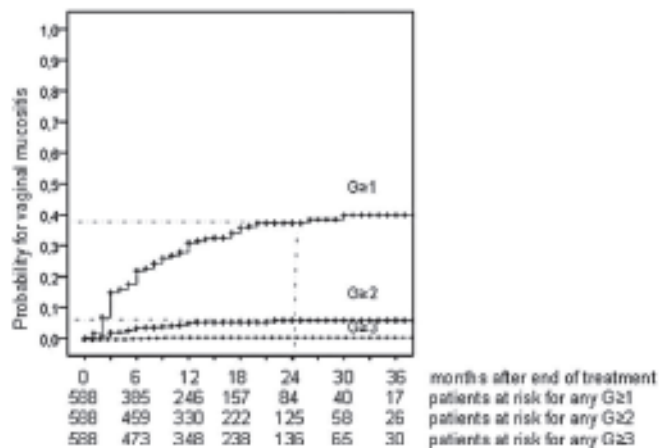
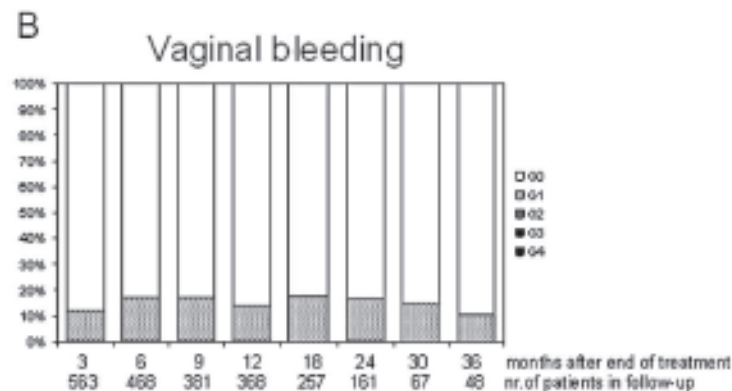
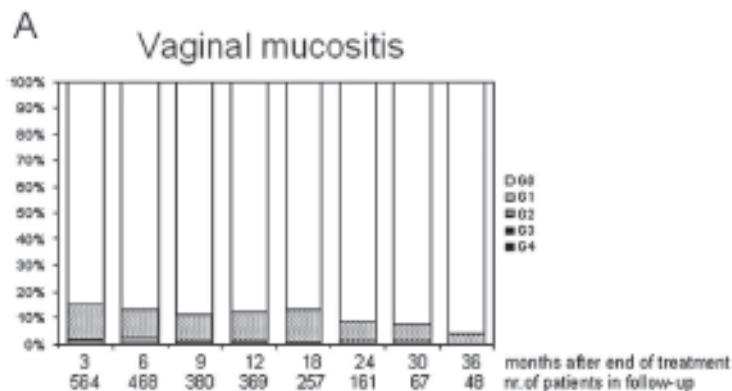
EMBRACE

{ An international study
on MRI-guided Brachytherapy
in locally Advanced Cervical cancer }



Kirchheiner et al.
IJROBP 2014

Patterns of manifestation: Prevalence rates and Actuarial estimates



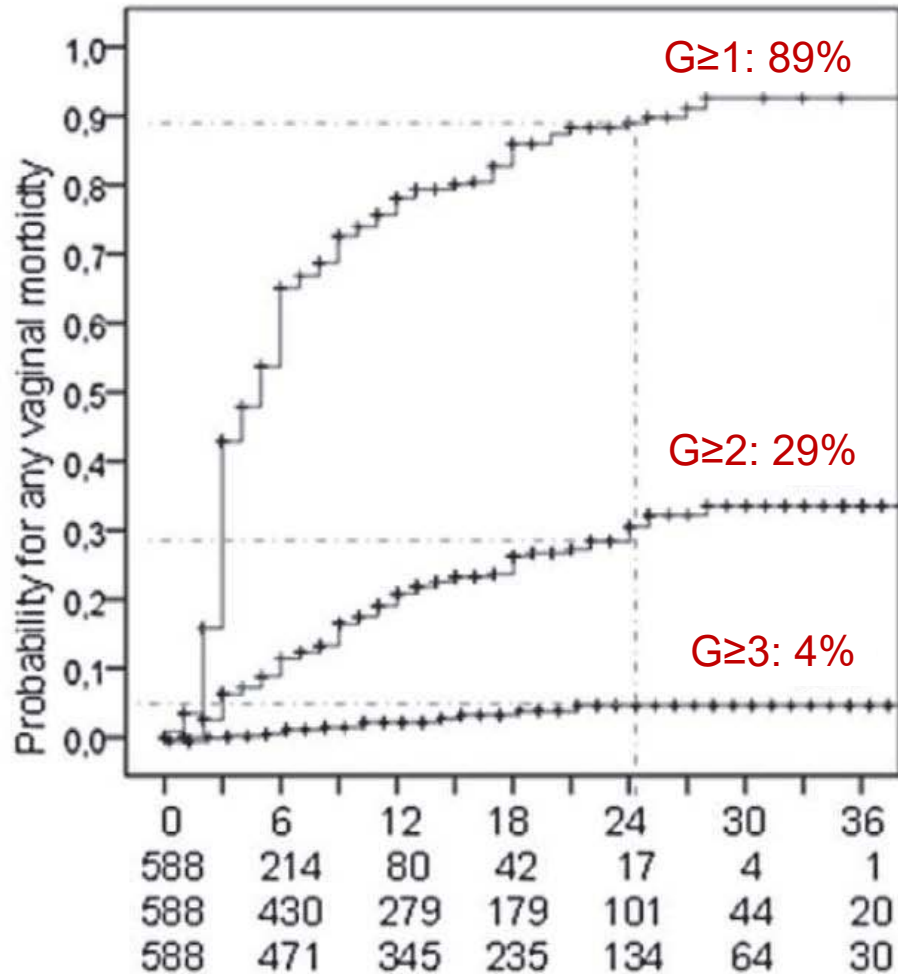
EMBRACE

{ An international study
on MRI-guided Brachytherapy
in locally Advanced Cervical cancer }



Kirchheiner et al.
IJROBP 2014

Vaginal morbidity after definitive radiochemotherapy + IGABT in LACC



- N=588 LACC within EMBRACE study
- Prospective assessment of morbidity (CTCAE 3) at baseline and regular follow-ups (median 15 months)
- Endpoints: vaginal stenosis, dryness, mucositis, bleeding, fistula

Table 3 Crude incidences of treatment-related individual vaginal symptoms and overall vaginal morbidity in 588 patients with a median follow-up time of 15 months

Grade	Vaginal stenosis	Vaginal dryness	Vaginal mucositis	Vaginal bleeding	Vaginal fistula	Other vaginal symptoms	Overall vaginal morbidity
G0	241 (41%)	312 (53%)	415 (71%)	407 (69%)	582 (99%)	523 (89%)	155 (26%)
G1	256 (43%)	244 (42%)	146 (25%)	175 (30%)	2	47 (8%)	309 (53%)
G2	86 (15%)	32 (5%)	23 (4%)	5 (1%)	0	14 (2%)	111 (19%)
G3	5 (1%)	N.A.	3	1	4 (1%)	4 (1%)	12 (2%)
G4	N.A.	N.A.	1	0	0	0	1
G5	N.A.	N.A.	0	0	0	0	0

Abbreviation: N.A. = not applicable.

Summary

Crude incidence, rates for single vaginal endpoints

At two years, actuarial probability of severe vaginal morbidity ($G \geq 3$) was 3.6%.

However, mild and moderate vaginal symptoms were still pronounced ($G \geq 1$: 89%, $G \geq 2$: 29%), of which the majority developed within 6 months.

Stenosis was most frequently observed, followed by vaginal dryness. Vaginal bleeding and mucositis was mainly mild and infrequently reported.

Summary & Conclusion

With increasing dose to the recto-vaginal reference point, the probability of vaginal stenosis $G \geq 2$ increases significantly ($p=0.003$).

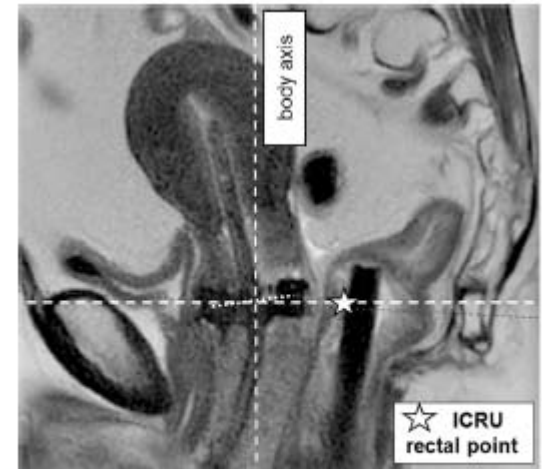


Fig. 1. ICRU rectal point depicted on sagittal T2 MRI, positioned at the intersection level between tandem and the source positions in the ring and 5 mm dorsal of the posterior vaginal wall on the axis perpendicular to the body axis.

Based on the model curve, the risk was 20% at 65Gy, 27% at 75Gy and 34% at 85Gy (recto-vaginal reference point dose).

Keeping the EBRT dose at 45Gy/25fractions and decreasing the dose contribution of brachytherapy to the vagina decrease the risk of stenosis.

A planning aim of ≤ 65 Gy EQD2 (EBRT+brachytherapy dose) to the recto-vaginal reference point is therefore proposed.

Late Morbidity: others

EMBRACE I. CTCAE v3
Fibrosis – deep connective tissue (pelvis right / left)
Fracture – insufficiency (Pelvic ring / Femoral head)
Muscle/soft tissue/bone other
Edema: limb
Edema: trunk/genital
Fatigue
Insomnia
Hot flashes
Other, specify category and grade

Descriptive

crude incidence
actuarial incidence
prevalence

Analytical

mono-factor-
dose-effect-
multi-factor-

QUALITY OF LIFE DURING AND EARLY AFTER TREATMENT

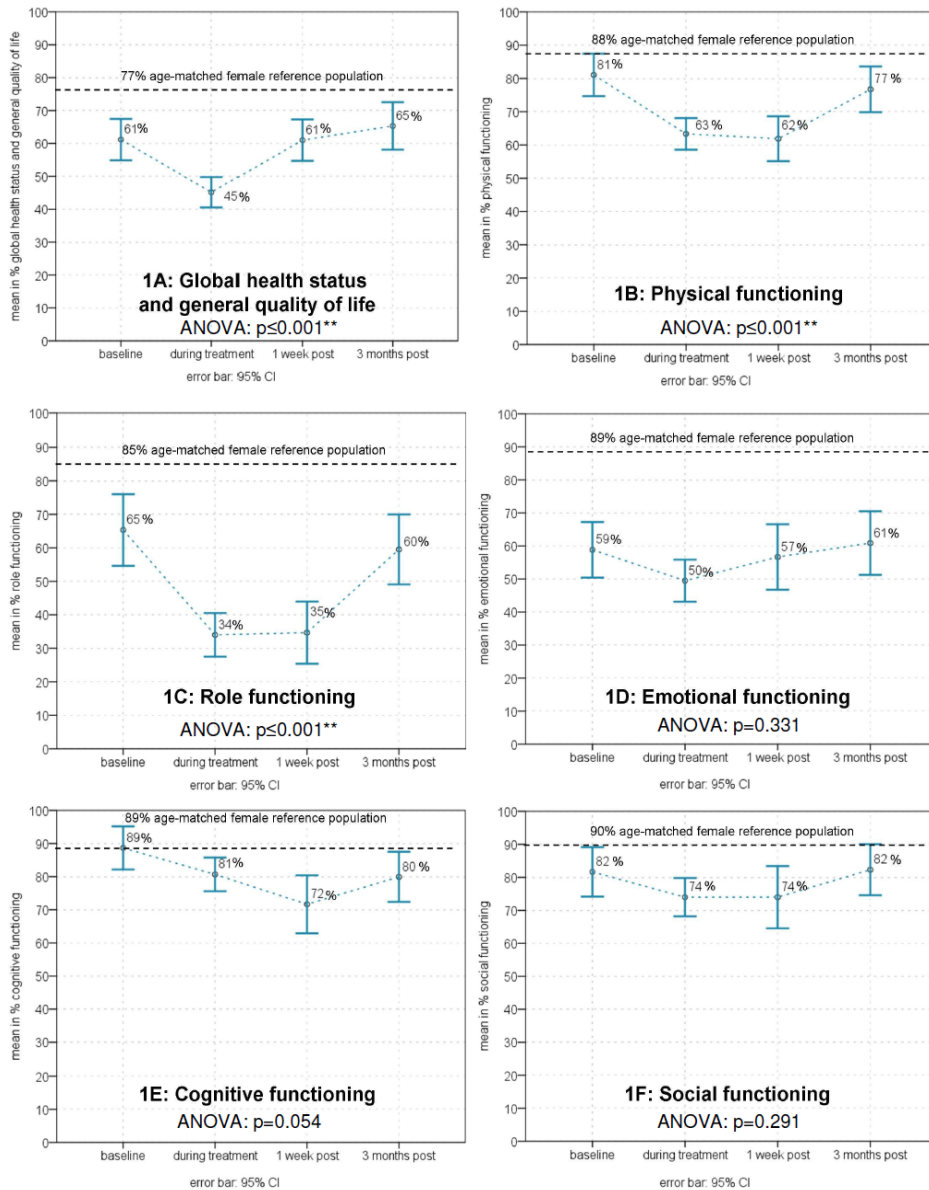
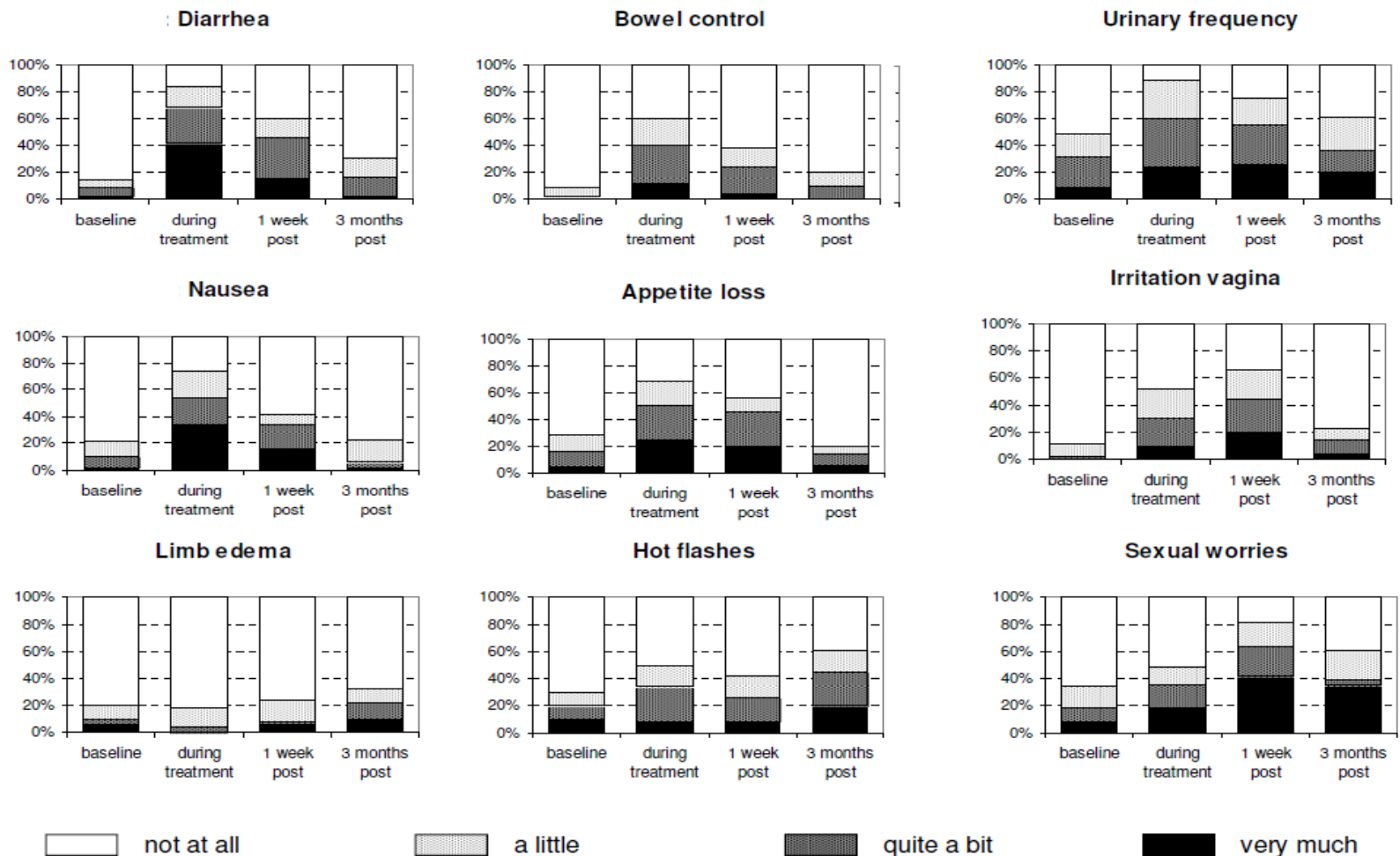


Figure 1: HR-QoL functioning scales over time, mean \pm 95% confidence intervals are shown. The dotted line represents reference values of an age-matched healthy female reference population. P-values are derived from one-way repeated measures analyses of variance (ANOVA), after Bonferroni-Holm correction for multiple tests. Higher percentages represent better functioning and QoL.

- 50 consecutive, mono-institutional LACC patients
- Prospective QoL assessment with EORTC-QLQ-C30+CX24
- Prior to and during treatment, one week after IGABT and three months thereafter.
- Higher score represent better functioning and QoL
- Comparison with age-matched, female normative reference population (dotted line).

PATIENT REPORTED SYMPTOMS DURING AND EARLY AFTER TREATMENT

Figure: Patient reported symptoms on single item level over time: diarrhea, bowel control, abdominal cramps, appetite loss, nausea, vomiting, urinary frequency, urinary pain / burning and leaking of urine. The proportion of patients is shown in percentages with the answer categories “not at all”, “a little”, “quite a bit” and “very much”.



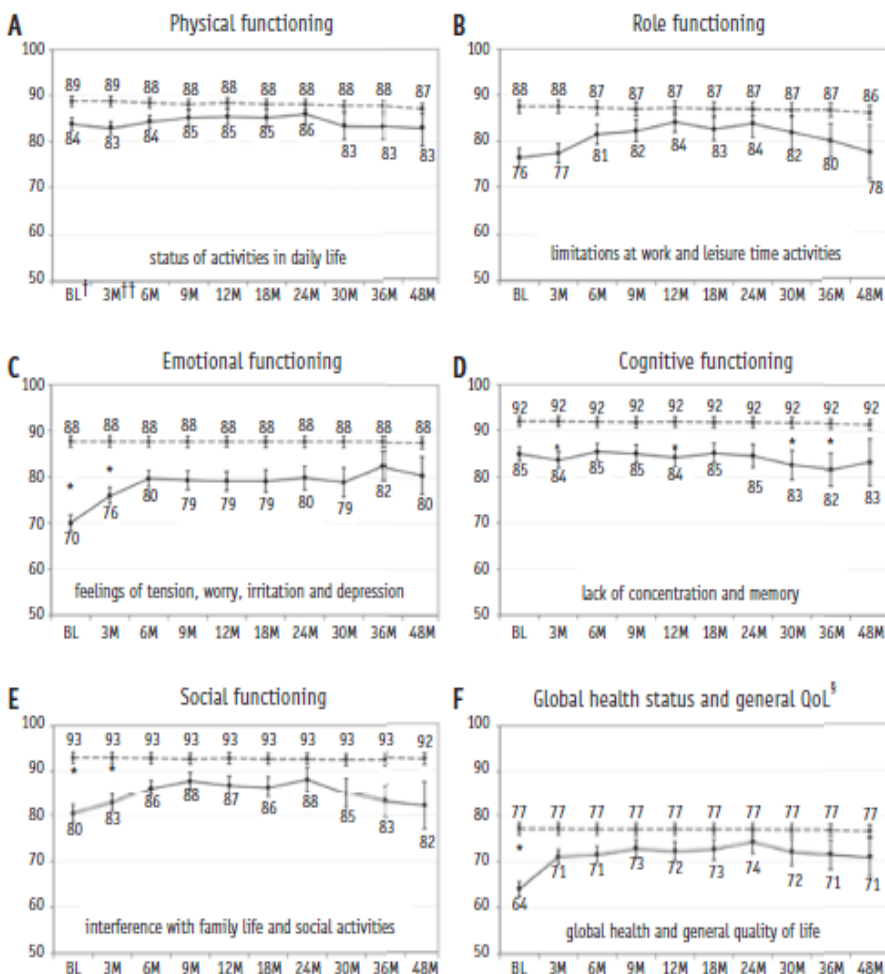
SUMMARY

DURING AND EARLY AFTER TREATMENT

During definitive radio(chemo)therapy with IGABT, the global health status / general QoL, physical and role functioning is substantially impaired.

Although the functioning returns to patients' baseline levels three months after treatment, it remains markedly lower compared to an age matched reference population.

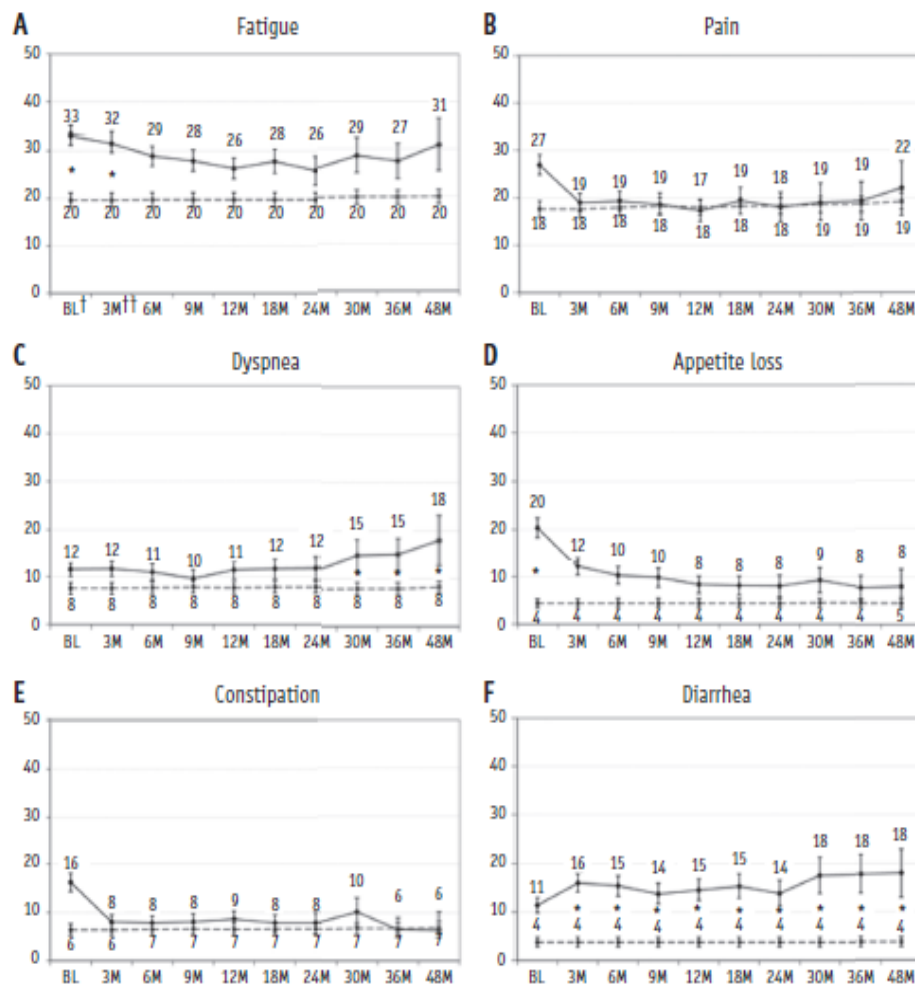
The transient decrease in functioning is paralleled by a transient increase in patient reported treatment-related symptoms, notably fatigue syndrome, diarrhea, urinary frequency and nausea.



LONG-TERM QUALITY OF LIFE

- 744, multi-institutional LACC patients (EMBRACE study)
- Prospective QoL assessment with EORTC-QLQ-C30+CX24
- Median follow-up 21 months
- Higher score represent better functioning and QoL
- Comparison with age-matched, female normative reference population (dotted line).

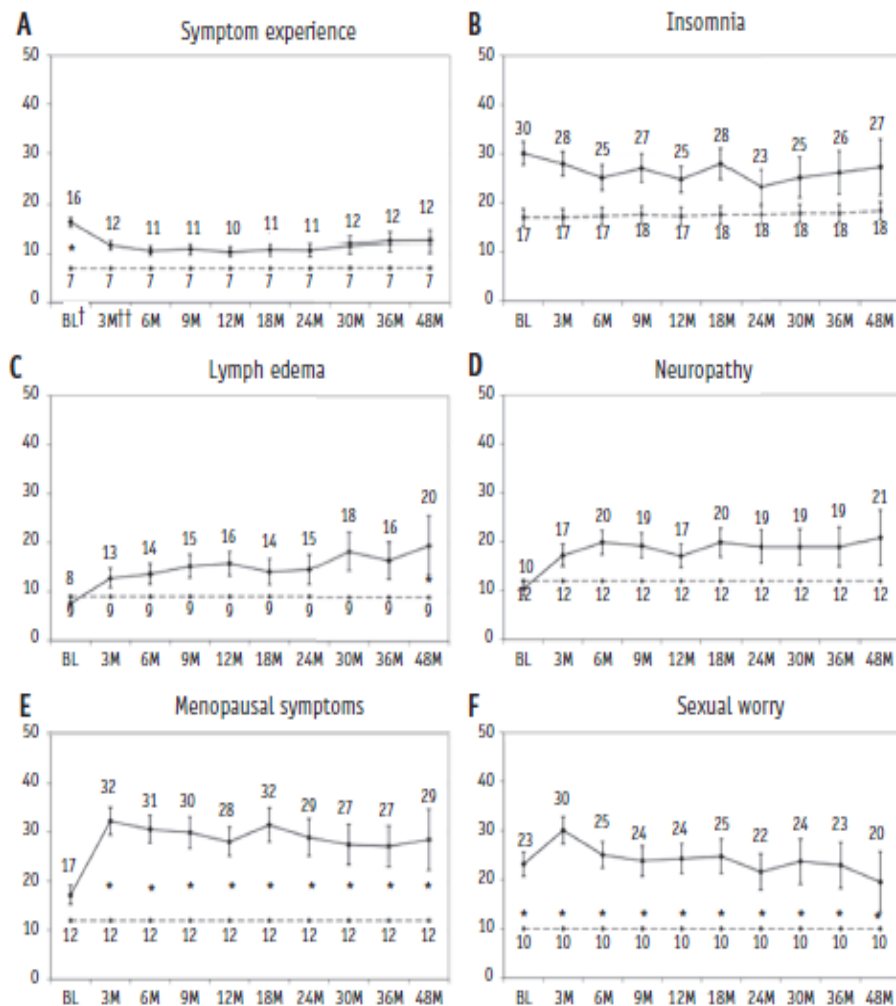
Fig. 1. (A-F) EORTC QLQ-C30 functioning scales over time; mean \pm 95% confidence interval scores between 50 and 100 are shown. Higher scores represent better functioning and QoL. Dotted line indicates reference values from an age-matched general female population (18). *Clinically relevant differences between the patient cohort and reference population (medium to large effect sizes (19)). *Abbreviations:* BL = baseline; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer module 30; M = months of follow-up; QoL = quality



LONG-TERM PATIENT REPORTED SYMPTOMS

- Higher score represent higher symptom burden
- Comparison with age-matched, female normative reference population (dotted line).

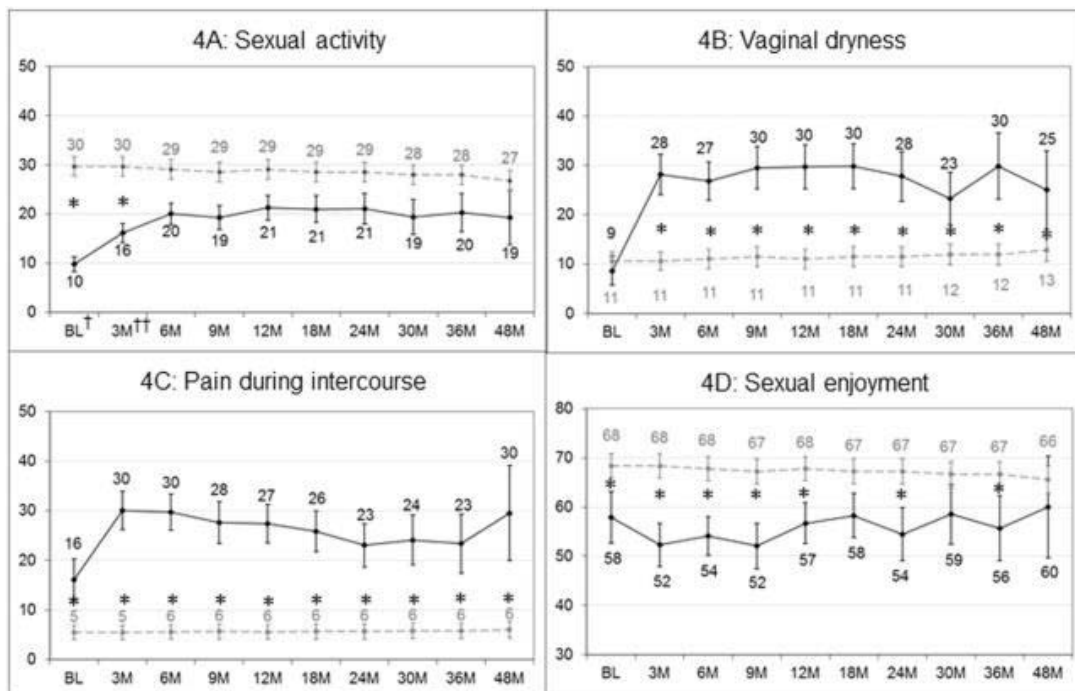
Fig. 2. (A-F) EORTC QLQ-C30 symptom scales over time; mean \pm 95% confidence interval scores between 0 and 50 are shown. Higher scores represent higher symptom burden. Dotted line indicates reference values from an age-matched general female population (18). *Clinically relevant differences between the patients cohort and reference population with medium to large effect sizes (19). *Abbreviations:* BL = baseline; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer module 30; M = months of follow-up.



LONG-TERM PATIENT REPORTED SYMPTOMS

- Higher score represent higher symptom burden
- Comparison with age-matched, female normative reference population (dotted line).

Fig. 3. (A-F) EORTC QLQ-CX24 symptom scales over time; mean \pm 95% confidence interval scores between 0 and 50 are shown. Higher scores represent higher symptom burden. Dotted line indicates reference values from a female general population (20). *Clinically relevant differences (≥ 10) between the patient cohort and reference population. *Abbreviations:* BL = baseline; EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer module 24; M = months of follow-up.



LONG-TERM IMPACT ON SEXUALITY

- Higher score represent higher symptom burden
- Comparison with age-matched, female normative reference population (dotted line).

SUMMARY

General QoL, emotional and social functioning are impaired at baseline, but improve during the first 6 months after treatment to reach a level comparable to the reference population, while cognitive functioning remains impaired.

Both social and role functioning show lowest scores at baseline, that increase after treatment to reach a plateau at 6 months, but declines slightly at 3 and 4 years.

The overall symptom experience is elevated at baseline and decreases to a level within the range of the reference population.

Similarly, tumor-related symptoms (e.g. pain, appetite loss and constipation), which are present before treatment, decrease substantially at the first follow-up after treatment.

Several treatment-related symptoms develop either immediately and persist over time (diarrhea, menopausal symptoms, peripheral neuropathy and sexual functioning problems) or develop gradually after treatment (lymph edema and dyspnea).

Learning Objectives II

- Be able to discuss the differential value of physician assessed morbidity and patient reported symptoms after IGABT combined with radio-chemotherapy.

Morbidity assessment in clinical trials (Kirchheiner)

objective



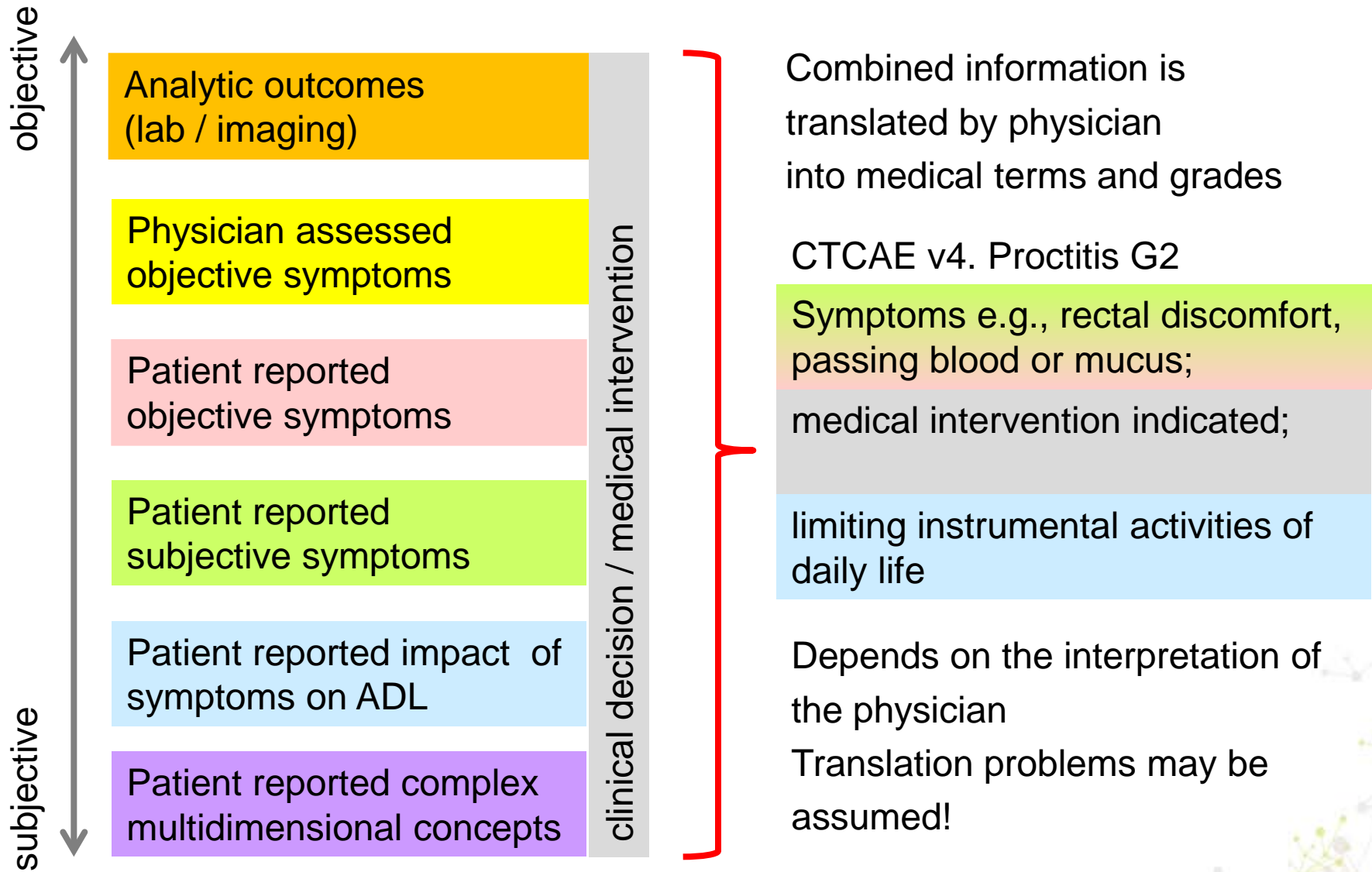
Analytic outcomes (lab / imaging)	Anemia defined as reduction in the amount of hemoglobin in 100 ml of blood.
Physician assessed objective symptoms	Atrophy of the vaginal mucosa, ulceration, necrosis, fistula
Patient reported objective symptoms	Number of stools / day, consistency of stool
Patient reported subjective symptoms	Fatigue, pain, sexual functioning problems
Patient reported impact of symptoms on ADL	Impact of difficulties controlling bowel on activities of daily life / quality of life
Patient reported complex multidimensional concepts	Health-related quality of life, functioning aspects in daily life, psychological status

clinical decision / medical intervention

subjective

Physician assessed morbidity

Common Toxicity Criteria of AE



Inter-rater reliability of CTCAE morbidity assessment

Atkinson et al. Qual Life Res 2012

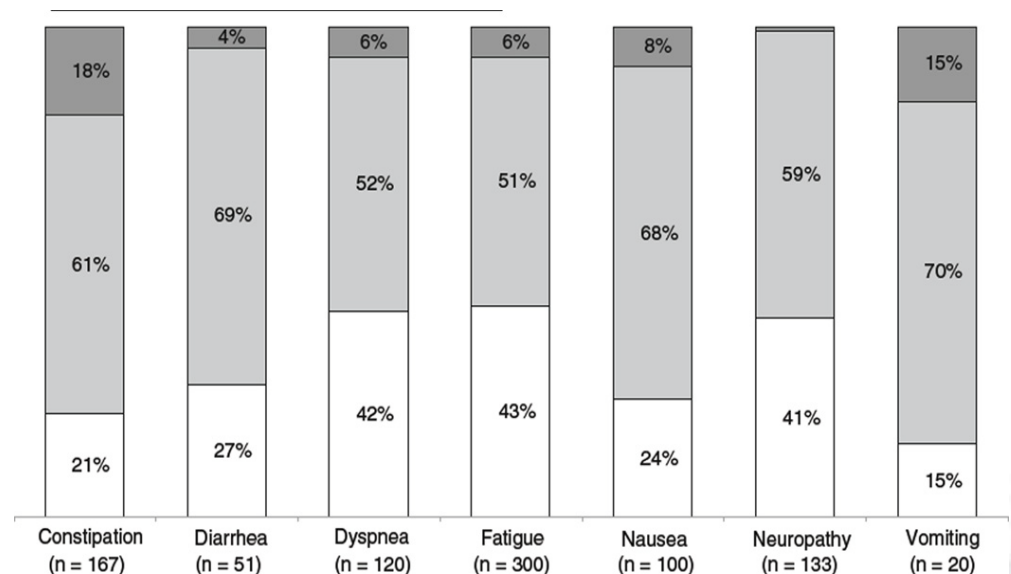
N=393 patients, mixed cancer type

CTCAE assessed by 2 independent physicians within ~1h

Results in symptomatic patients

- 15-43% agreement
- 51-70% 1 grade differences
- 1-18% 2 grades differences

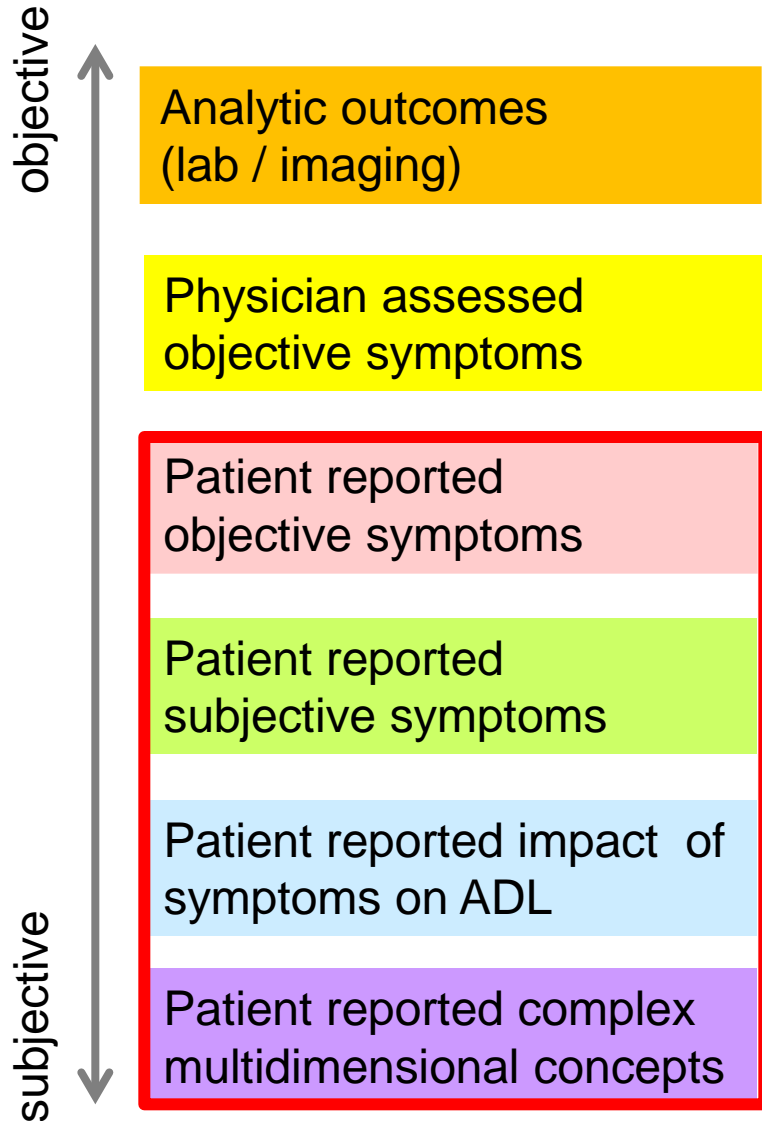
CTCAE agreement between
2 physicians is moderate at best!



The lower the CTCAE grading, the more variation between physicians is observed.
Disagreement mainly between G0/G1/G2.

Chinnachamy et al. Jpn J Clin Oncol 2013

Patient reported outcomes (PRO)



PRO considered as Gold standard

“...any report of the status of a patient’s health condition that comes **directly from the patient, without interpretation** of the patient’s response by a clinician or anyone else.”

Final FDA PRO Guidance, Dec 2009

Objectifying the subjective experience by questionnaires with predefined response categories and robust psychometric properties

Health-related quality of life assessment

EORTC QLQ C30
European Organization of
Research and Treatment of Cancer
Quality of Life Questionnaires
(Aaronson et al.) *Europe*

FACT-G
Functional Assessment of Cancer
Therapy
(Cella et al.) *US*

SF 36
Short Form Health Survey 36
(Ware et al.) *beyond oncology*

Basic module and different disease-
and treatment related modules
available

Assessment

1. Overall quality of life
2. Aspects of functioning in daily life
physical, social, emotional,
role, cognitive
functioning
3. Patient reported symptoms

EORTC / FACT QoL

Answer categories

- not at all
- a little
- (somewhat)
- quite a bit
- very much

Widely used for PRO symptom assessment

Answer categories not precise

No linear association with CTCAE grading

PRO-CTCAE

PRO assessment tool of the future

Compatible with CTCAE v4, covers 78 symptoms

Currently under development and validation

Frequency

- never
- rarely
- occasionally
- frequently
- almost constantly

Severity of symptoms

- none
- mild
- moderate
- severe
- very severe

Interference with usual activities

- not at all
- a little
- somewhat
- quite a bit
- very much

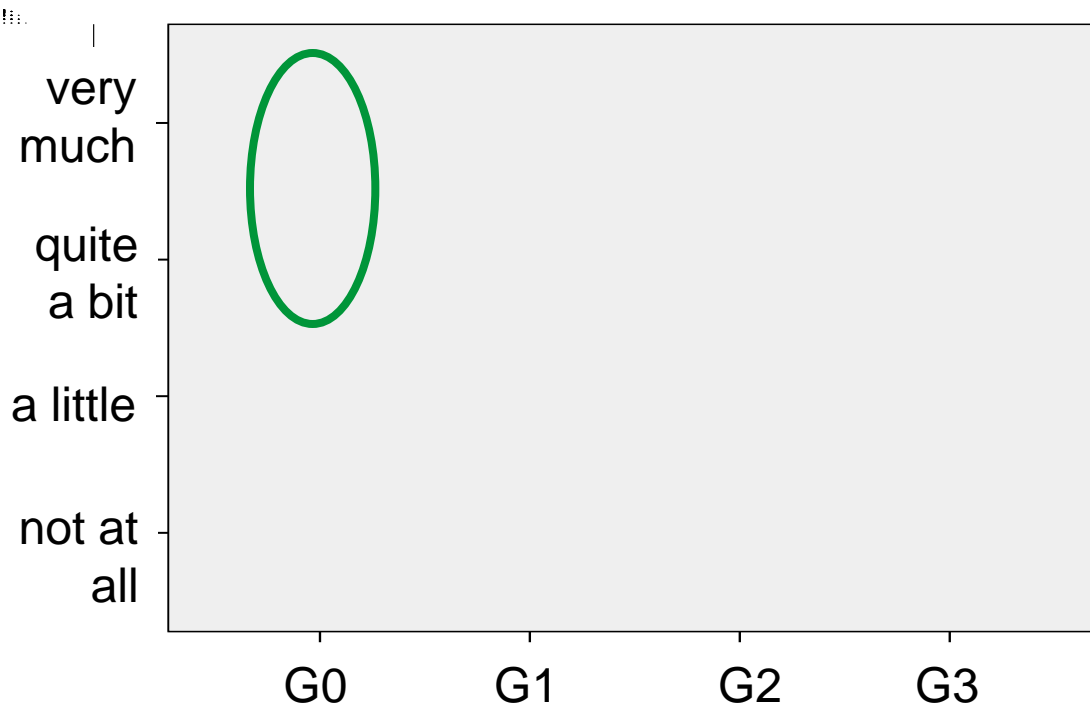
Agreement physician assessed vs. Patient reported symptoms

Kirchheiner et al. SUON 2012

N=223 cervical cancer, CTCAE v3 vs. EORTC C30 + CX24

3 months after end of definitive radiochemotherapy

EORTC : Did you pass water / urine frequently?



Discrepancy:

Patient reported symptom
“quite a bit” to “very much”
in EORTC QLQ
→ CTCAE grading 0

CTCAE Urinary frequency

12 overlapping symptoms CTCAE & EORTC QLQ	nr.of “quite a bit” or “very much” problems reported	nr.of discrepancies (CTCAE G0)
diarrhea	27	13
anal incontinence	17	15
bleeding hemorrhage GI	1	1
urinary frequency	52	23
urinary incontinence	15	7
bleeding hemorrhage GU	2	1
limb edema	21	10
fatigue	53	22
insomnia	53	26
hot flashes	73	19
vaginal dryness*	22	11
vaginal stenosis*	24	11
N=223 patients at 3 months FUP	In total 360 substantial problems reported	159 (44%) of substantial problems not recognized by physician assessed CTCAE

Possible explanations

Patients

- tendency to “please the doctor”, based on gratitude
- certain symptoms too embarrassing to report
- level of distress caused by the symptoms is rated (highly subjective)
- psychological coping strategies (dissimulating / aggravating symptoms)

Physicians

- more emphasis on identifying severe G3/G4 morbidity than milder morbidity
- limited time to fully explore symptoms (general questions about any symptoms vs. systematical assessment of each symptom)
- continuum of severity along which a patient is put into context

Summary & Conclusion

- Technical developments in RT → less severe G3/G4 morbidity
Focus to milder and moderate G1/G2 morbidity and impact on QoL, PRO are especially sensitive
- Physician assessed CTCAE morbidity has a wide range of interpretation and therefore a low inter-rater reliability
(especially in mild to moderate morbidity)
- Low associations between physician assessed and patient reported morbidity are consistently described in literature
- Both provide valuable information → combined reports or a collaborative approach provide a more accurate understanding of morbidity



ESTRO-CARO Teaching Course
Image Guided Radiotherapy in cervix cancer
- with a special focus on adaptive brachytherapy -

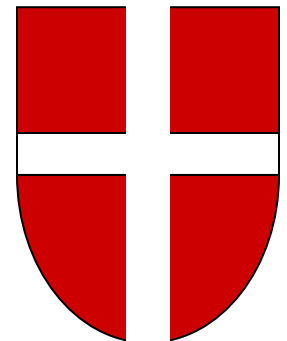


Disease Outcome IGRT/IGABT

Cervix cancer



Richard Pötter



RESULTS OF DEFINITIVE RADIOTHERAPY IN LIMITED DISEASE

Authors		N° pts	Stage	5-yr survival (%)	Local control (%)
Manchester 80-88	LDR	294	I/IIA	90-94 (DFS)	
Hunter 1993		45	IB	71 (OS)	
	1993 (62)	70	IIB	52 (OS)	
Perez (87)	LDR	384	IB	85	90
		128	IIA	70	81
		353	IIB	72	77
Fletcher (35)	LDR	494	IB IIA MDAH	84	93
		207	IIB MDAH	70	82
French cooperative group		229	I MDAH	89 (89)	93 (95)
LDR		315	IIA MDAH	81 (85)	83 (88)
Horiot (53)		314	IIB MDAH	76 (76)	80 (78)
Kim (66)	LDR	169	IB	82	89
		83	IIA	78	91
Lowrey (74)	LDR	130	IB	81	88
		64	IIA	74	84
Pernot (92)	LDR	173	IIA-B prox.	74	79
Coia (18)		203	IB	80	90
Joslin (64, 65)	HDR	95	I	94	97
		170	II	62	74
Petereit (93)	HDR	59	IB	86	85
		64	II	65	80
Vienna	HDR	42	IB/IIA	85 (DSS)	97
Pötter (96)		124	IIB	69 (DSS)	82

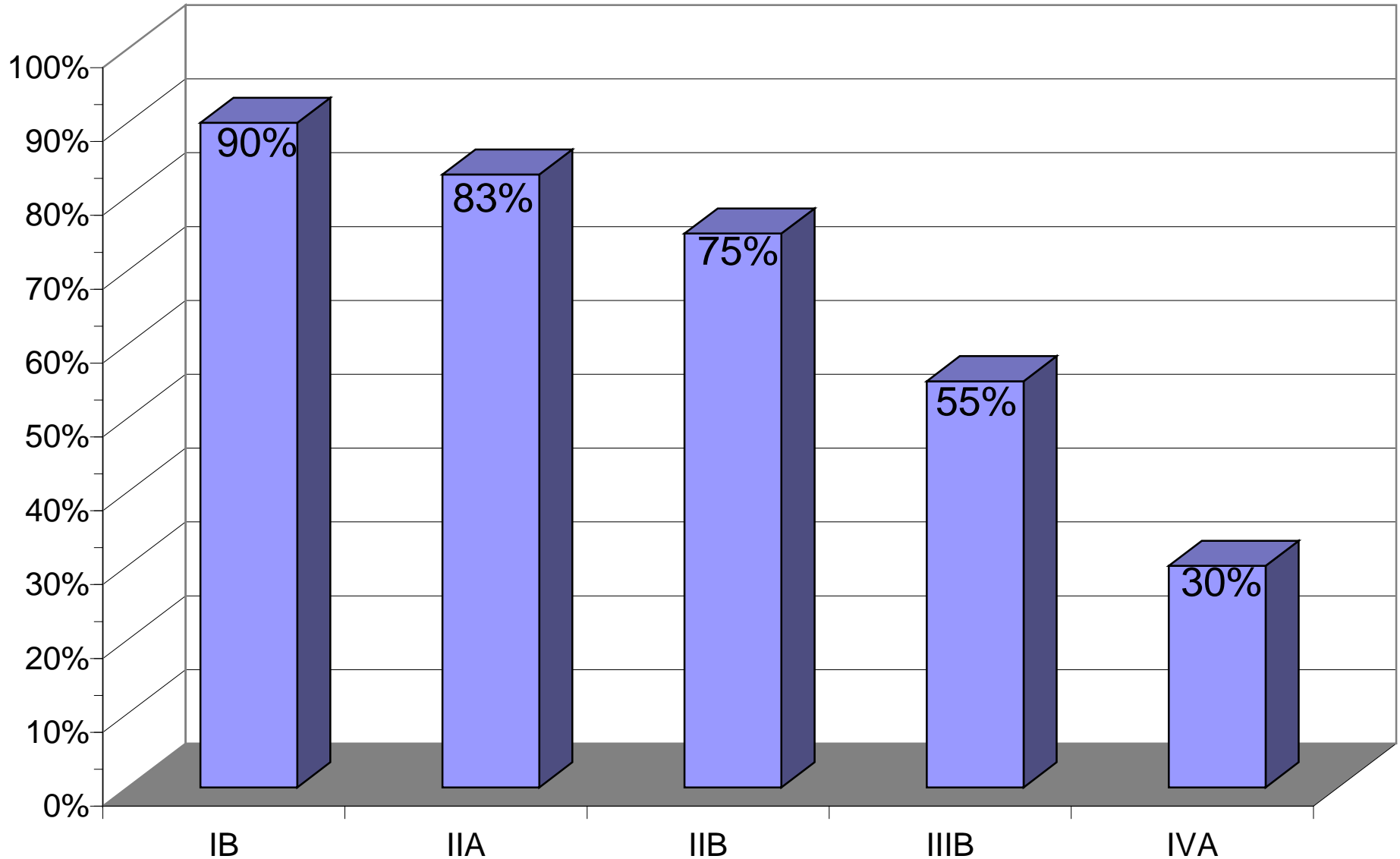
*Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma.
In: Gerbaulet A, Pötter R, Mazon JJ, Meertens H, Van Limbergen E, eds. (2002)
The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO*

RESULTS OF DEFINITIVE RADIOTHERAPY IN EXTENDED DISEASE

Authors	N° pts	Stage	5-yr survival (%)	5-y Local control (%)
Manchester 1993 LDR Hunter 2001 (62)	50	III	34 OS	
Perez (86) LDR	293 20	III IV	52 DFS 0	59 25
Houston MDAH (26, 28) Fletcher LDR (73)	73 a* 25 b* 983	IB ₂ IIB (bulk) IIIB (UICC)	44 OS 60 OS 36 DSS	67 84 78
French cooperative group LDR (53)	266 216 32	IIIA MDAH IIIB MDAH IV	61 OS (62) 39 OS (50) 20 OS	68 (63) 45 (57) 18
Paris IGR (42) LDR	58 416	Distal II IIIA-B, IV	65 OS 42 OS	78 66
Pernot (92) LDR	60 107	Distal IIB III	70 OS 42 OS	77 54
Joslin (64, 65) HDR	106	III	38 OS	56
Petereit (93) HDR	50	IIIB	33 OS	44
Vienna HDR Pötter (96)	78 12	IIIB IVA	48 DSS 19 DSS	65 48

*Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma.
In: Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Van Limbergen E, eds. (2002)
The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO*

TREATMENT RESULTS DEFINITIVE RADIOTHERAPY 2D X-RAY BASED PLANNING/POINT A



*Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma.
In: Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Van Limbergen E, eds. (2002)
The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO*

BENEFIT FROM CONCOMITANT RADIOCHEMOTHERAPY

SURVIVAL AND RECURRENCE AFTER CONCOMITANT CHEMOTHERAPY AND RADIOTHERAPY FOR CANCER OF UTERINE CERVIX: A SYSTEMATIC REVIEW AND META-ANALYSIS

3656 patients (19 studies)

LOCAL RECURRENCE RATE WAS SIGNIFICANTLY REDUCED BY CHEMORADIATION
OR 0.61, 95% CI 0.51-0.73, p < 0.0001

	RCHT	RT
OS	52%	40%
PFS	63%	47%
Toxicity Grade 3-4		
Haematological	16%	8%
Gastrointestinal	9%	4%

Green et al. Lancet 2001;358:781-86

J Clin Oncol. 2002

RT

66%

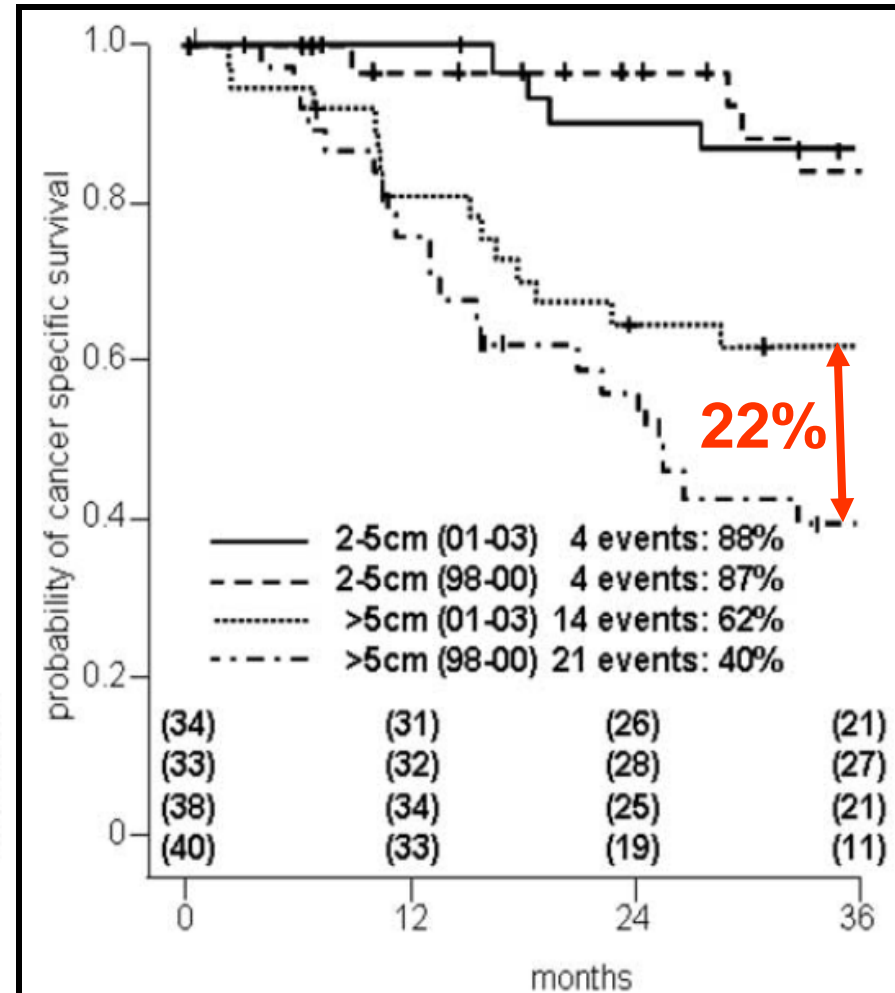
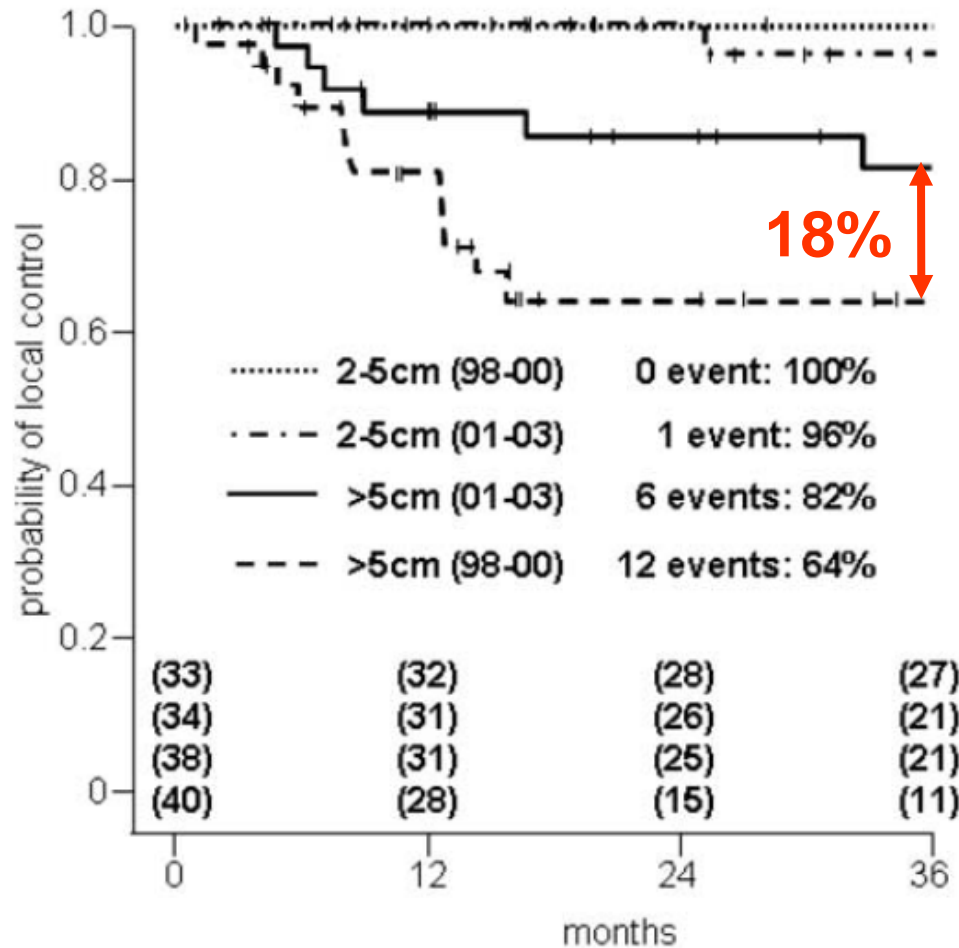
(p=0.42)

Clinical Evidence in IGABT Cervix Cancer

Upcoming Evidence

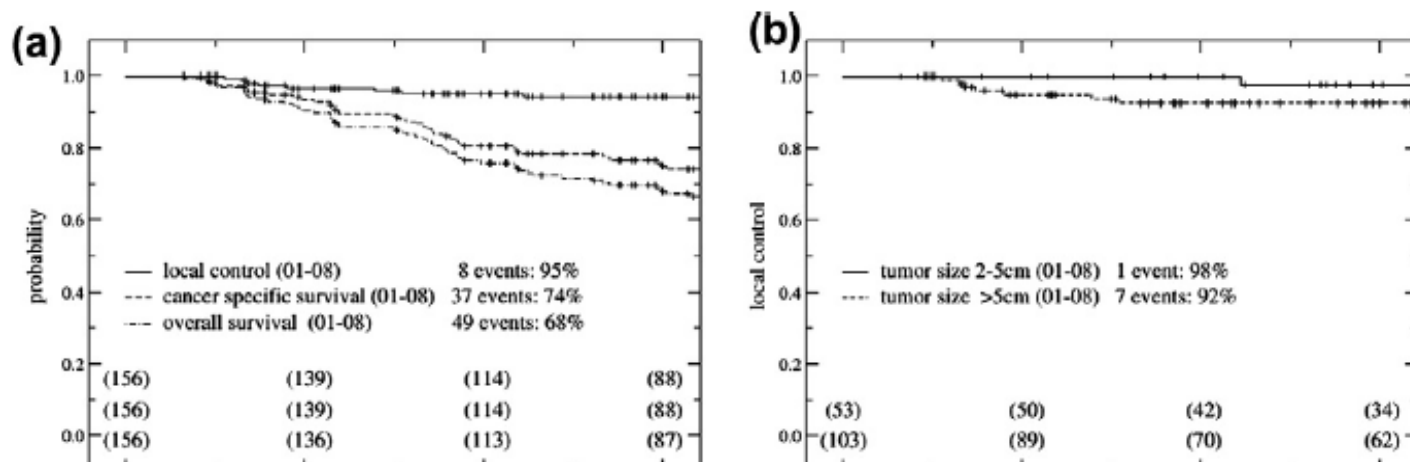
- Mono-institutional cohorts (ongoing, publicat. since 2007)
- Multi-center cohorts with retrospective evaluation
 - RetroEMBRACE (publications expected for 2015+)
- Prospective Trials
 - STIC: comparative 2D vs. 3D (published 2012)
 - EMBRACE I: observational, 08/2008 - 12/2015
 - EMBRACE II: interventional, start 01/2016

Image guided adaptive brachytherapy (IGBT) cervix cancer Local Control and Cancer Specific Survival (1998-2003) TREATMENT PERIOD (-/+ IGBT) AND TUMOUR SIZE



mean 81 Gy vs. 90 Gy in HR CTV

OUTCOME AFTER 3D BASED CERVICAL CANCER BT: Local Control, Cancer Specific Survival, Overall Survival



156 patients MRI guided BT, Vienna 2001-2008, mean D90 to HR CTV 92 Gy
7/156 with G3 and 4/156 G4 toxicity (LENT SOMA)

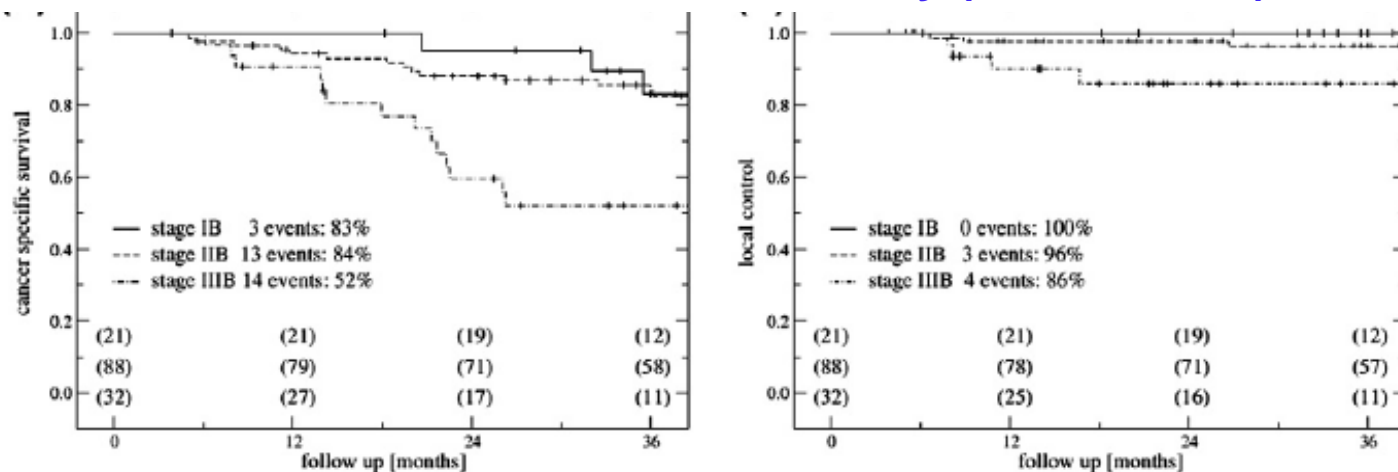


Fig. 1. Outcome after radiotherapy ± chemotherapy and image-guided adaptive brachytherapy. (a) Local control, cancer specific survival and overall survival for all 156 patients. (b) Local control and tumour size. (c) Cancer specific survival for FIGO stages IB, IIB, IIIB. (d) Local control for FIGO stages IB, IIB, IIIB.

CONTINUOUS COMPLETE REMISSION 3 YEARS*

VIENNA 1993-2003: 335 patients

TREATMENT PERIOD	CCR	
	2-5cm (REC.)	>5cm (REC.)
2001-2003**	96% (1/34)	90% (3/34)
1998-2000**	96% (1/33)	71% (9/37)
1993-1997***	90% (5/65)	67% (27/124)

** Pötter et al. 2007 *Radioth Oncol*

*** Pötter et al. *Cancer Radioth* 2000

* Actuarial data (Kaplan Meier)



Universitätsklinik für Strahlentherapie
und Strahlenbiologie Wien

CONCLUSIONS

(Vienna experience 1998-2008)

**MRI assisted treatment planning
in definitive intracavitary cervical cancer brachytherapy
Plus risk adapted interstitial brachytherapy
plus 3D CRT +/- cis-PLATINUM (n=228)**



■ Local control

tumours < 5 cm: ~95-100+%

D90: 90-95 Gy

tumours \geq 5 cm: ~90%

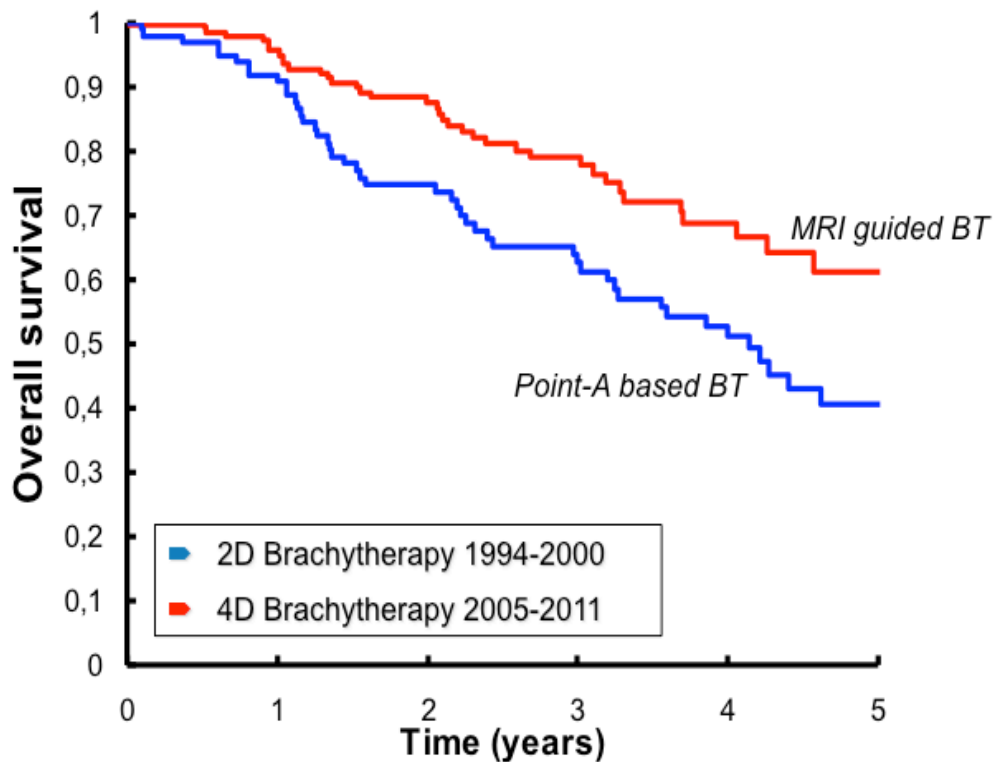
D90: 90+ Gy

■ Low rate of late side effects

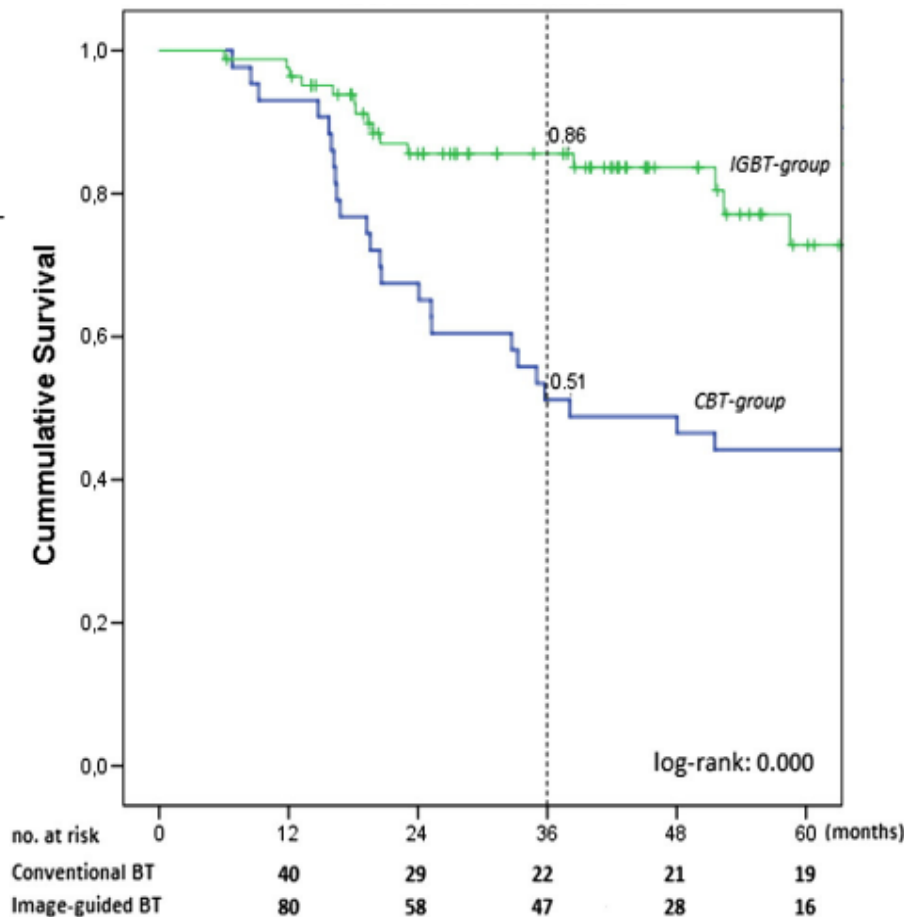
Grade 3 and 4: <5% per organ site

Better local control = improved survival

Aarhus Experience



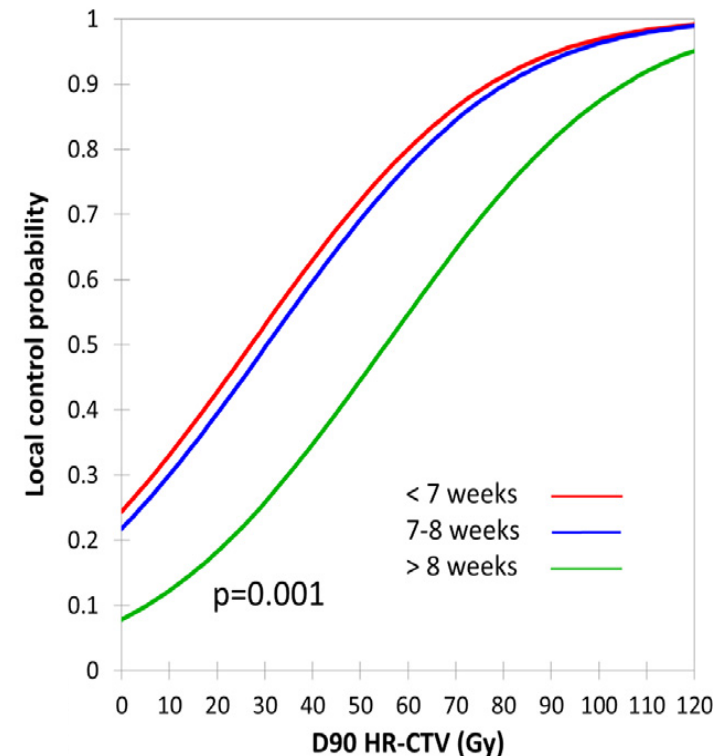
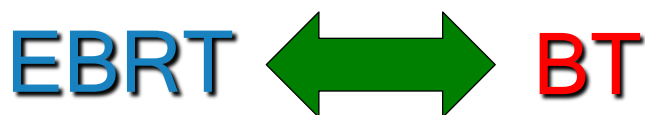
Leiden Experience

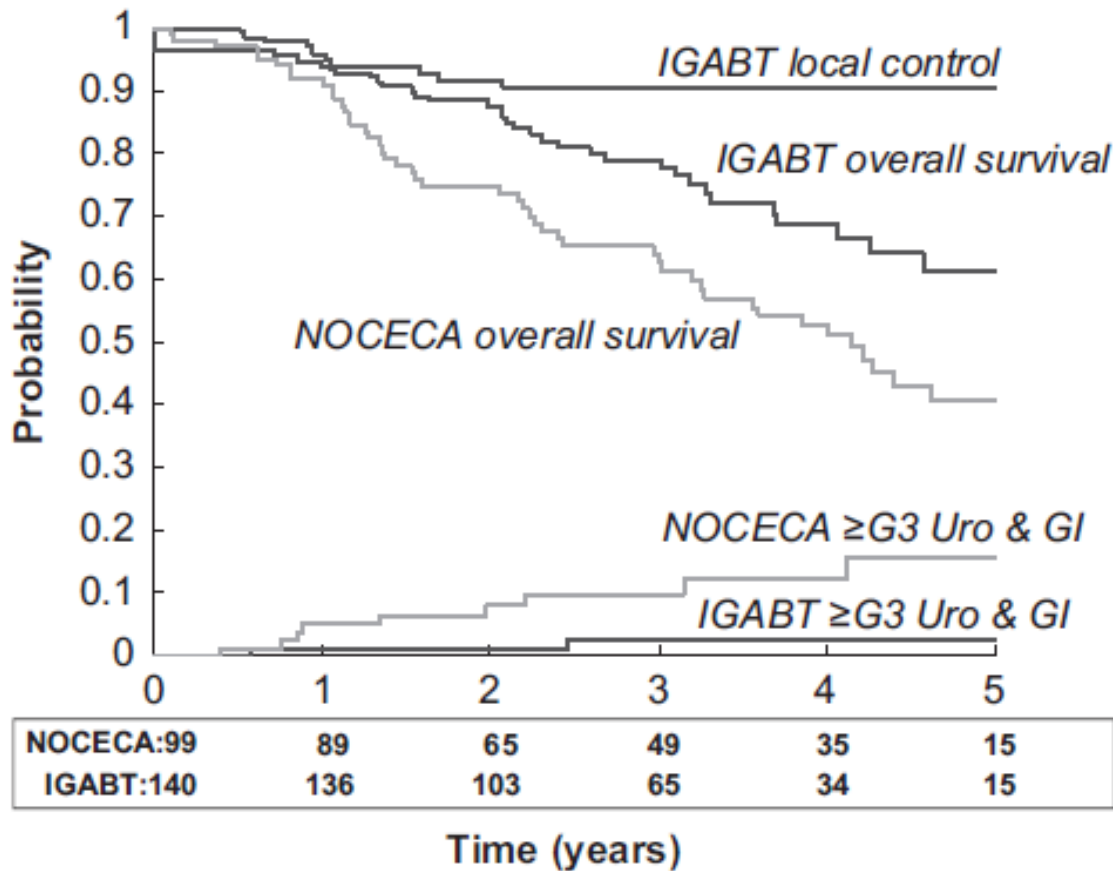


Overall treatment time (OTT)

- Increasing OTT by one week is equivalent to a loss of 5 Gy in $CTV_{HR} D_{90}$ Janderup, retroEMBRACE, 2015, submitted

- Timing of the BT boost?





LC 3 y: 90%

OS 3 y:

IGABT/ChTh: 79%

NOCECA: 63%

morbidity 3y ≥G3:

10%

3%

Figure 3. Actuarial local control, overall survival and \geq 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.

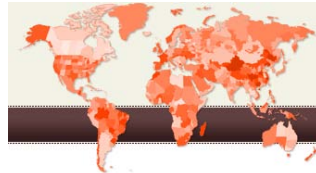
Multicenter studies with IGABT in cervix ca.

STIC



- Prospective
- 2D vs. 3D (CT)
 - **Non random.**
 - **Availability**
- Completed
- 2005-2008
- 20 centers
- 705 pts
- **Def. EBRT+BT**
- **Preop BT**
- **Preop. EBRT+BT**

Embrace

- Prospective
- Phase IV (MRI)
- 
- Accruing
- 2008-2012
- 20 centers
- 415/600 pts
- **Def. EBRT+BT**

Retro Embrace

- Retrospective
- Before Embrace
- Collecting
- 2011-2012
- 9 centers
- 183/600 pts
- **Def. EBRT+BT**

From 2D – 3D X Ray vs CT/MRI (STIC trial)

At 24 months	Group 1 BT followed by surgery		Group 2 EBRT BT surgery		Group 3 EBRT BT		P*
	2D	3D	2D	3D	2D	3D	
LRFS	91.9%	100%	84.7%	93%	73.9%	78.5%	0.003
RLRFS	87.9%	96.1%	77.2%	88.6%	61.2%	69.6%	0.001
DFS	86.5%	89.7%	73%	77.1%	55.2%	60.3%	0.086

LRFS: local free relapse survival; RLRFS: loco regional relapse free survival; DFS: disease free survival

* 2D-3D brachytherapy comparison : Cox proportional hazard model adjusted for regimens.

Table 6: 24-month Relapse Survivals

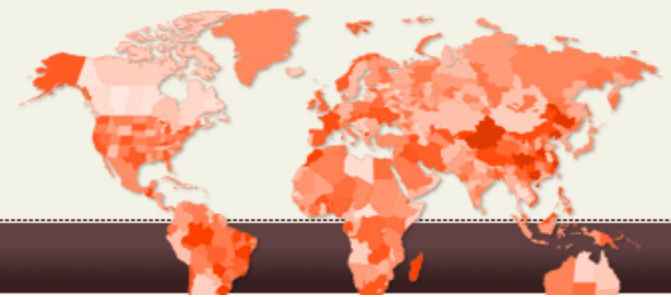
705 Pts available for analysis

Charra-Brunaud

Group 1: BT followed by surgery; 165 patients (2D arm: 76; 3D arm: 89);

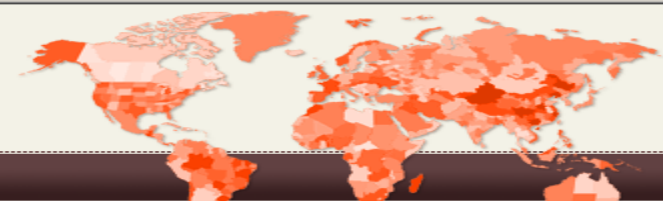
Group 2: EBRT (+/- chemotherapy), BT, then surgery; 305 patients (2D arm: 142; 3D arm: 163);

Group 3: definitive radiotherapy: EBRT (+/- chemotherapy), then BT; 235 patients, (2D arm: 118; 3D arm: 117).



Results:

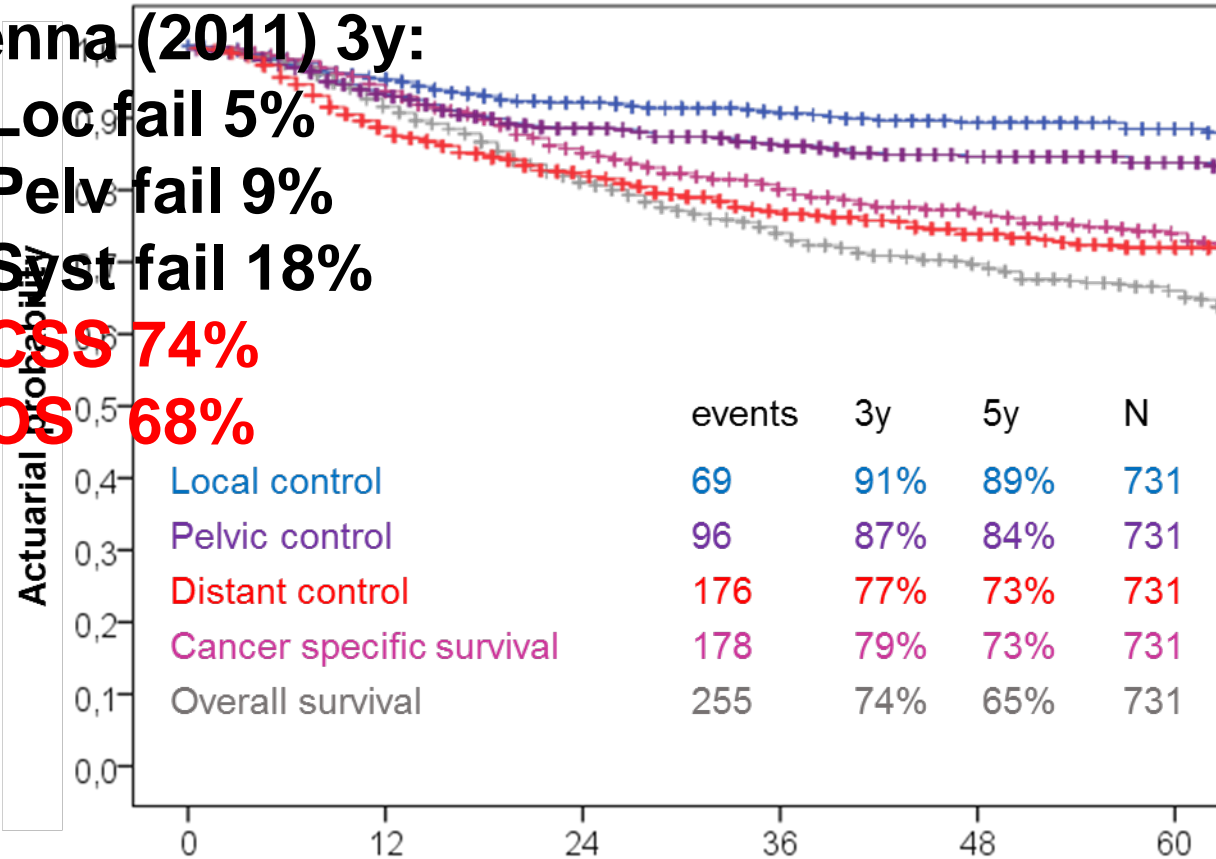
Variable		No of patients
Median Age (years)	53 (23 – 91)	731
FIGO Stage	1A	2 (0.3 %)
	1B	123 (16.8%)
	2A	42 (5.7 %)
	2B	368 (50.3 %)
	3A	23 (3.1 %)
	3B	145 (19.8 %)
	4A	23 (3.1 %)
	4B	5 (0.7 %)
Histology	Squamous cell Ca	620 (84.8%)
	Adenocarcinoma	71 (9.7%)
	Adenosquamous	29 (4%)
	Others	11 (1.5%)
Median tumour width	Clinically: 50 mm	MRT @ diagnosis: 47 mm
Nodal status	N+	296 (40%)
	N-	436 (60%)
CHT	Yes: 566 (76.5%)	No: 165 (22.5%)
	47 months	



Local, pelvic and distant control, cancer specific and overall survival

Vienna (2011) 3y:

- **Loc fail 5%**
- **Pelv fail 9%**
- **Syst fail 18%**
- **CSS 74%**
- **OS 68%**



- **731 patients**
- **12 institutions**
- **Loc fail 9-11%**
- **Pelv fail 13-16%**
- **Syst fail 23-27%**
- **CSS 79-73%**
- **OS 74-65%**

Vienna: mean 92 Gy HR CTV Months

LC	731	603	491	384	294	187
PC	731	603	491	384	294	187
DC	731	603	491	384	294	187
CSS	731	651	537	429	332	220
OS	731	651	537	429	332	220

**Mean D90
In HR CTV
84 Gy**

Local control and FIGO stage (RetroEMBRACE)

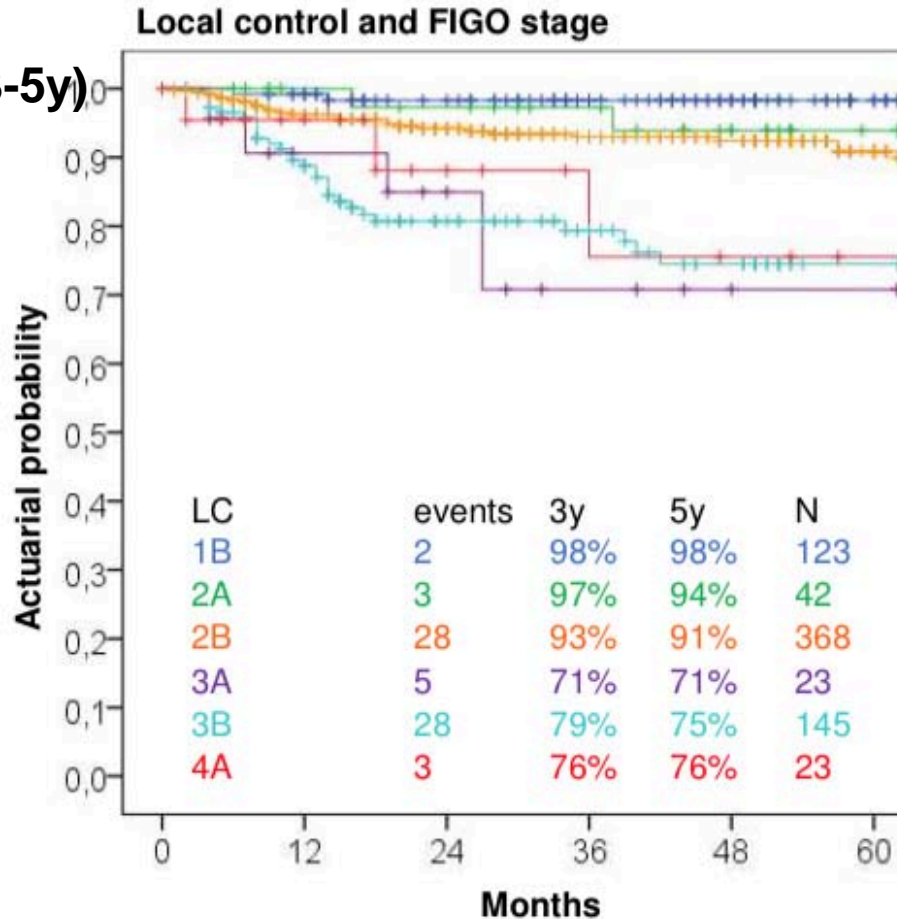
Loc failure (Retro 3-5y)

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%

Local control – advanced treatment adaptation including interstitial brachytherapy (RetroEMBRACE)

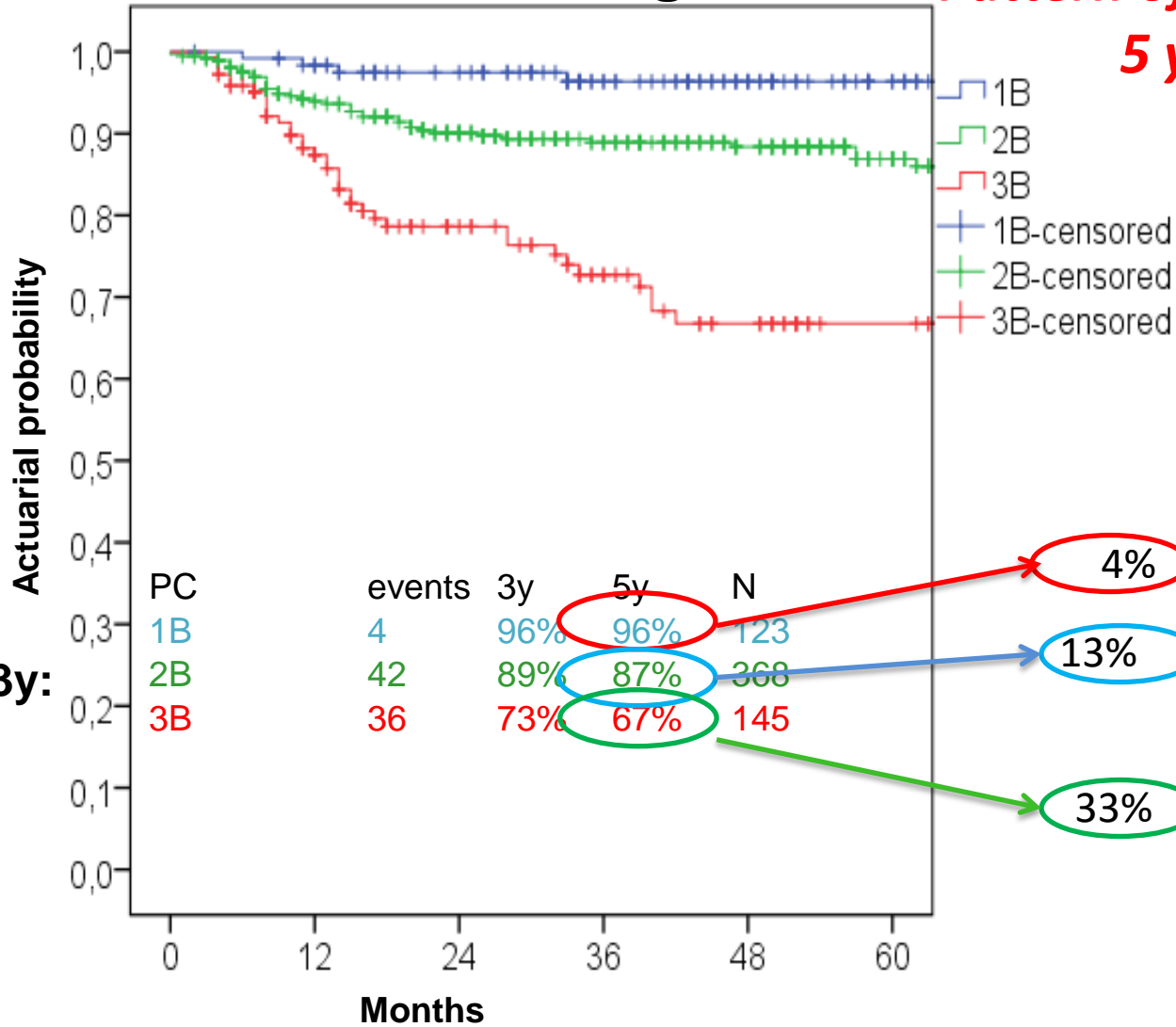
Width in MRI at diagnosis	Local control at 5 year (%)	
	Limited adaptation	Advanced adaptation
Tumor <5cm	95%	94%
Tumor ≥5cm	77%	86%

The use of advanced adaptation including interstitial BT improves local control in large tumors



Pelvic control and FIGO stage

*Pattern of Relapse
5 years*



RetroEMBRACE 3y:
overall 87%

Vienna (2011) 3y:
overall 91%

4%

13%

33%



123	116	100	75	53	30
368	303	256	205	164	107
145	108	72	53	40	26

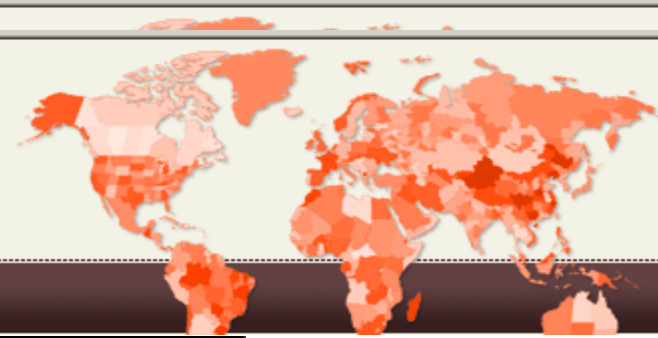
RetroEMBRACE Outcome Sturdza et al. 2015





RETRO EMBRACE

{ An international study
on MRI-guided BRachytherapy
in locally Advanced CERvical cancer }

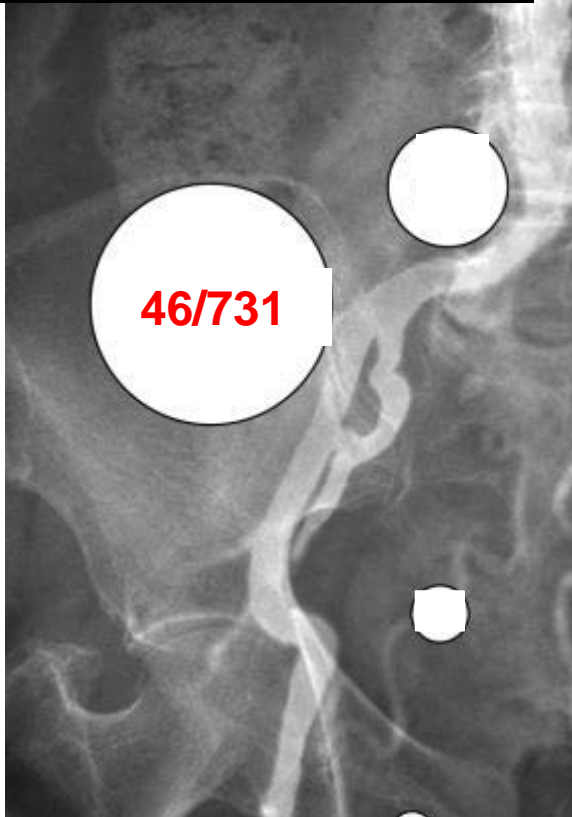


[About Retro-Embrace](#)

[Contacts](#)

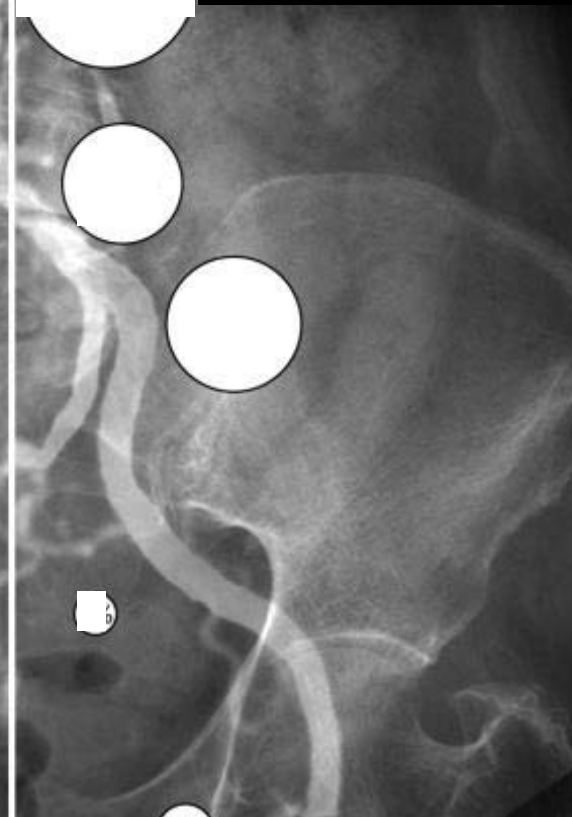
[Login](#)

296/731 N+ at diagnosis



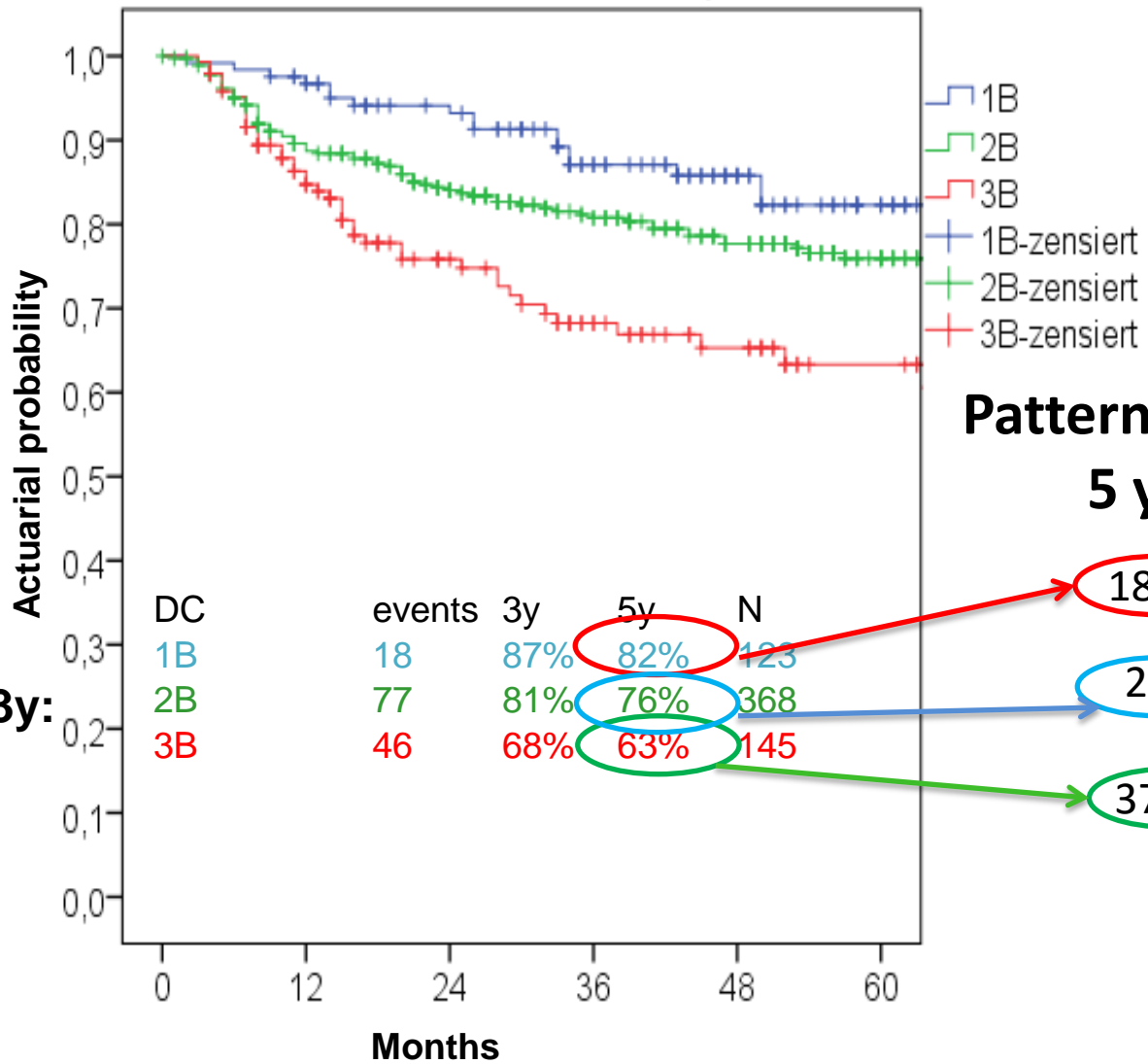
63/731

*Pattern of Nodal
Relapse*



Nodal boost through IMRT/VMAT may result in improved nodal control

Distant control and FIGO stage



**Pattern of Relapse
5 years**

18%
24%
37%

**RetroEMBRACE 3y:
overall 77%**

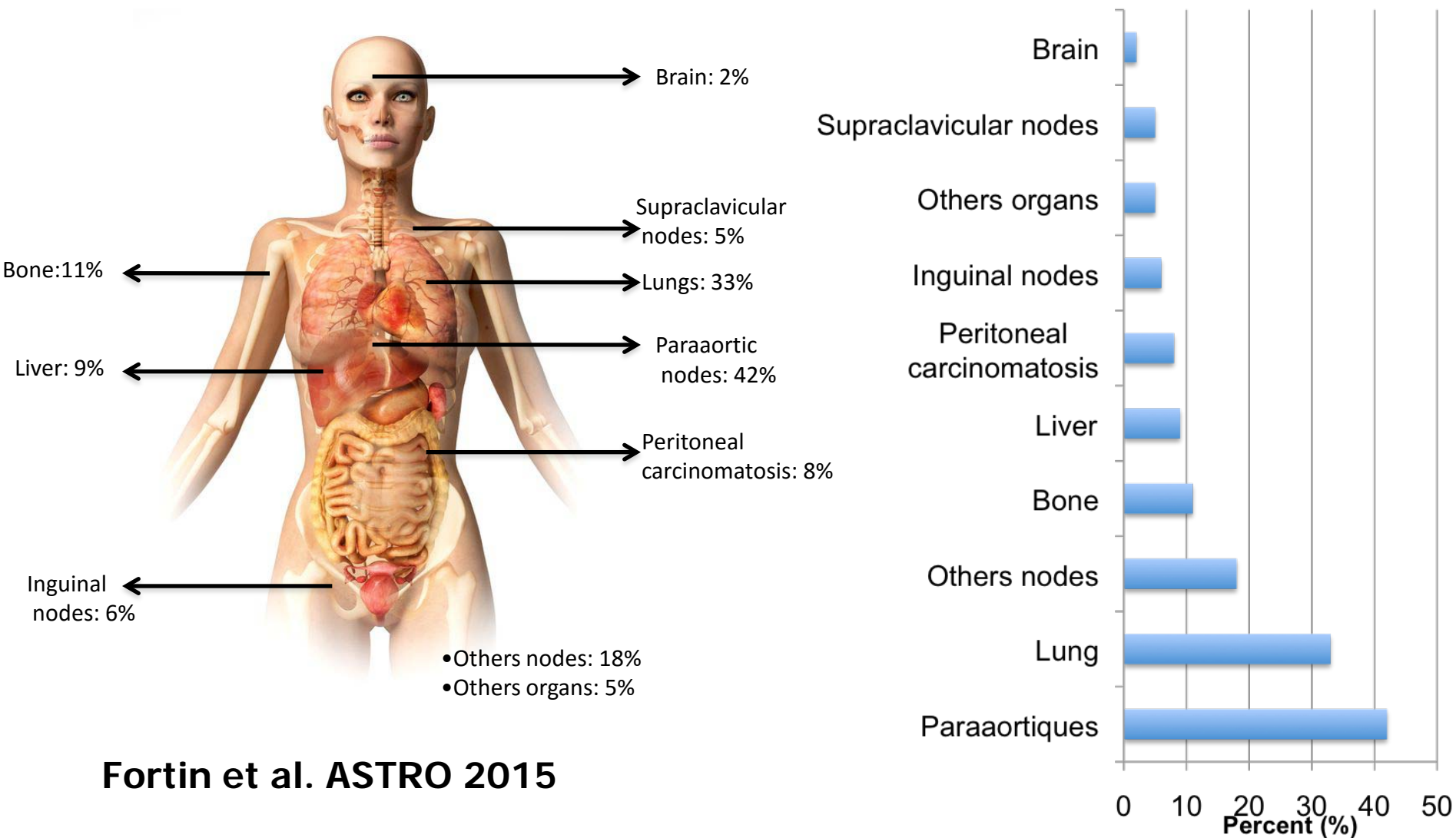
**Vienna (2011) 3y:
overall 82%**

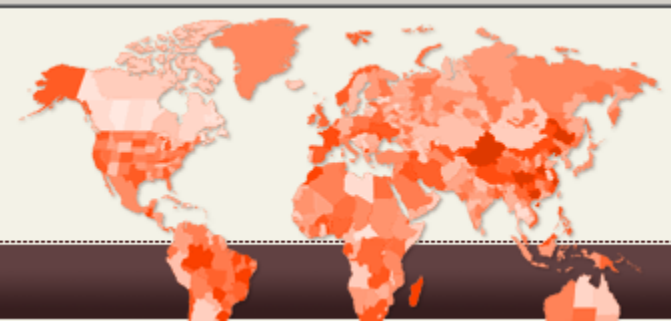
123	116	100	75	53	30
368	303	256	205	164	107
145	108	72	53	40	26



Systemic (distant) recurrence analysis (EMBRACE data, 133 events in 753 patients)

Systemic recurrences at first event

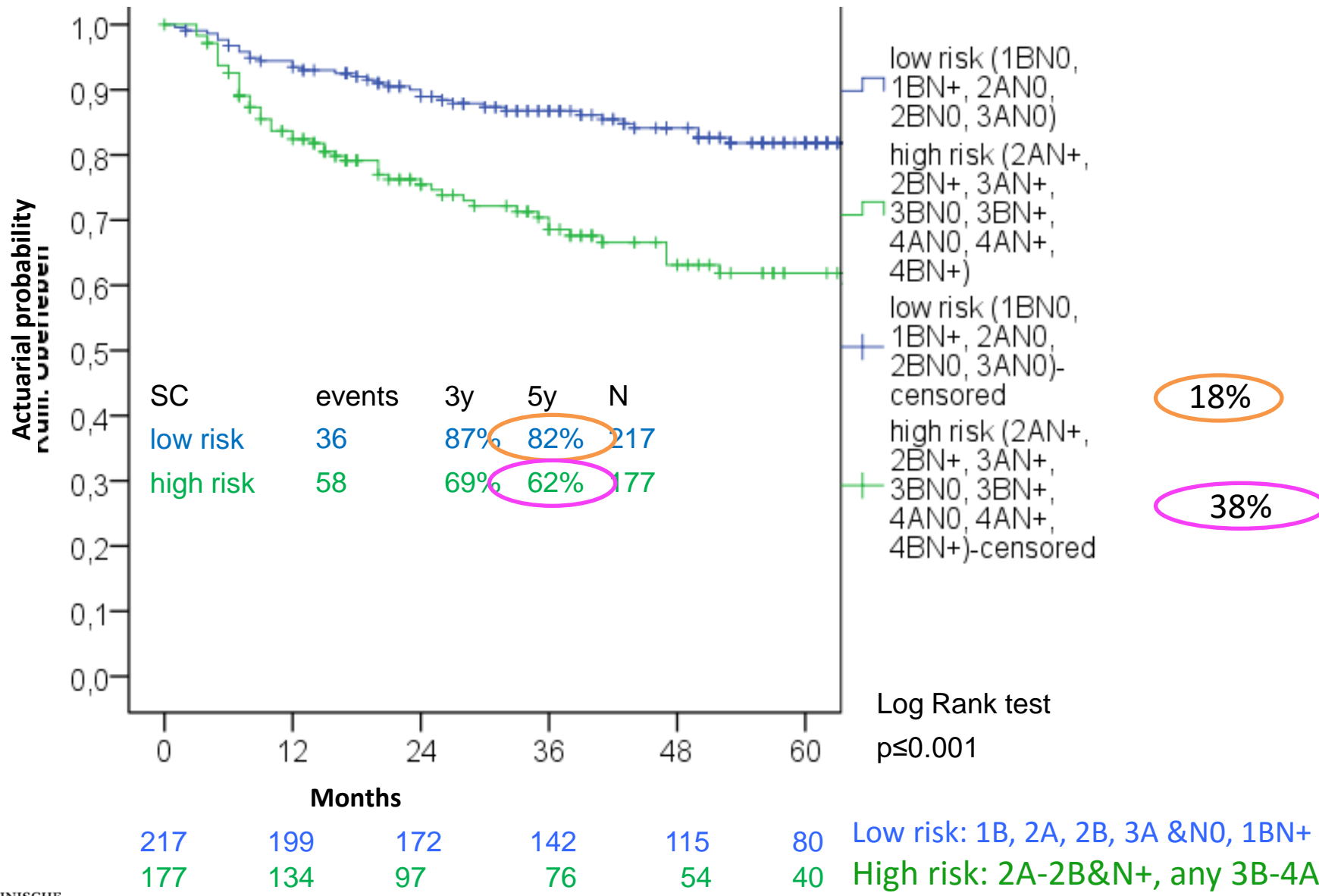




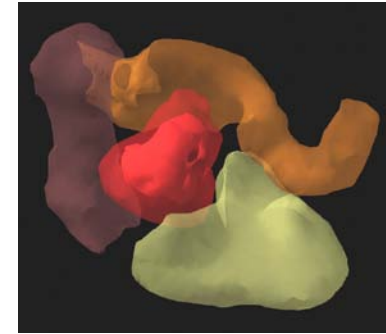
Subgroup analysis (distant control)

- 394 consecutive patients from 7 centres treated with RCHT and IGBT
(5 centers enrolled selected patients)
- Two groups based on univariate analysis
Low risk: 1B, 2A, 2B, 3A & N0, 1BN+
High risk: 2A-2B & N+, any 3B-4A

Distant control in consecutive patients treated with radiochemotherapy



Provisional comparison DVH parameters & local control based on multi-centre experience



Study	<i>HR CTV</i> D90 (Gy)	<i>Bladder</i> D2cc (Gy)	<i>Rectum</i> D2cc (Gy)	<i>Sigmoid</i> D2cc (Gy)	<i>2y Local Control</i>	<i>2y G3-G4 BL + GI</i>
STIC 3 Def EBRT+BT n=201	73	70	61	58	79%(74)	1% (14)
EMBRACE n=850	89	76	64	62	>90%	?
Retro EMBRACE n=698	89	79	65	65	>91%	~10%

Interpretation of RetroEMBRACE results (IGABT compared to large population based cohorts 2D BT)

Pelvic failure (crude)	Concomitant chemo	IB	IIB	IIIB	total
retroEMBRACE (n=731)	77%	4%	11%	25%	13%
Perez 1998	0%	12%	21%	41%	
Barillot 1997	0%	13%	24%	49%	23%
Improvement		Δ8-9%	Δ10-13%	Δ16-24%	Δ10%

Overall Survival Radio-chemo	retroEMBRACE Consecutive 3D/4D IGABT	UK Survey Vale 2010 2D BT	US SEER 2000-2009 2D BT	US NCDDBA 2004-2011 2D BT
No of pts	394	471	3246	2571
5y OS	67%	55%	55%	54%
Improvement	Reference	Δ12%	Δ12%	Δ13%

BENEFIT FROM CONCOMITANT RADIOCHEMOTHERAPY

AUTHOR	RANDOMISATION ARMS	STAGE	LOCOREGIONAL RECURRENCE	3 YEAR OVERALL SURVIVAL
Keys et al <i>N Engl J Med.</i> 1999	RT + Cisplatin + HE RT+ HE	Bulky IB	9% 21% RR 0.51 (95% CI)	83% 74% (p=0.008)
Whitney et al <i>J Clin Oncol.</i> 1999	RT + Cis/5-FU RT + HU	IIB,III, IVA	24.9% 30.4% RR 0.79 (90% CI)	67% 57% (p=0.018)
Rose et al <i>N Engl J Med.</i> 1999	RT + Cisplatin RT + Cis/5-FU+HU RT + HU	IIB,III, IVA	Not reported	65% 65% 47% (p=0.004)
Morris et al <i>N Engl J Med.</i> 1999	RT + Cis/5-FU RT (pelvis + paraaortal)	IB-IVA (~70% IB-IIB in each group)	19% 35% RR 0.47 (95% CI)	75% 63% (p=0.004)
Peters et al <i>J Clin Oncol.</i> 2000	HE + RT + Cis/5-FU HE + RT	IA2,IB, IIA	5.5% 17%	81% 71% (p=0.007)
Pearcey et al <i>J Clin Oncol.</i> 2002	RT+Cisplatin RT	IB-IVA	Not reported	69% 66% (p=0.42)

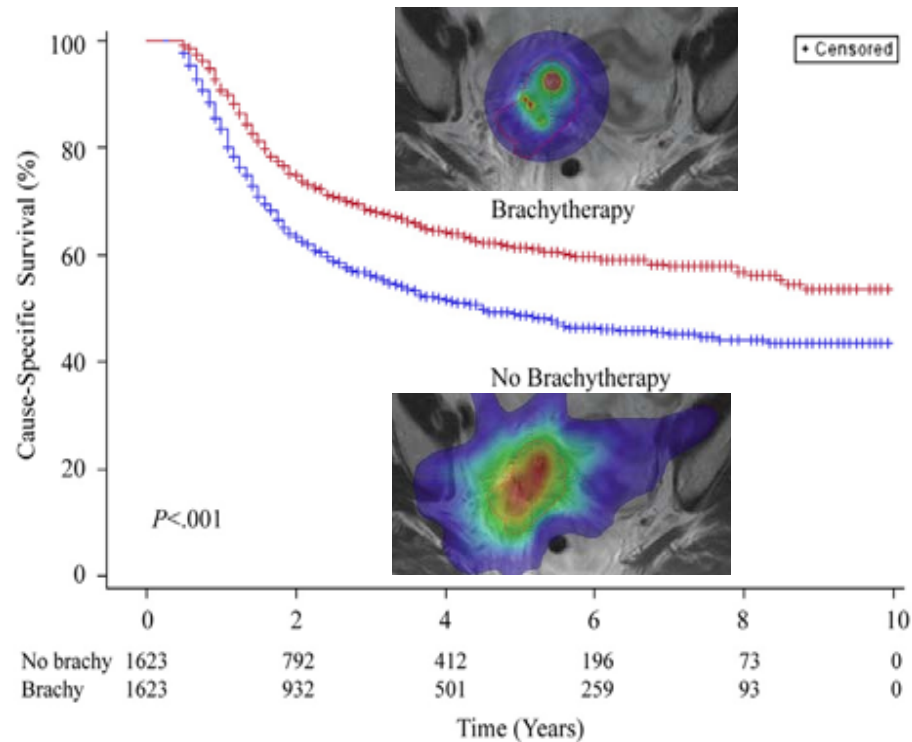
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Improvement	Reference	Δ12%	Δ12%	Δ13%

Paradoxon!

- Advances in brachytherapy are (more) important
- Understanding the limitations of EBRT: volume and dose





LOCAL CONTROL - CLINICAL DATA/AIMS

DOSE at POINT A vs. as D90 IN IMAGE GUIDED ADAPTIVE BT

	DOSE Pt A / D90 HR	BEST STANDARDS*	AIM
EARLY DISEASE	75 Gy / 85-95+ Gy	90-95%	~100%

**Expected Improvement through Image Guided Adaptive BT
local control by 5-40%; overall survival by 2-20% (?)**

IIB<5cm	80 Gy / 85-90 Gy	70-85%	95-100%
IIB/IIIB>5cm	85 Gy / 90+ Gy	50-65%	85-90%

*** Including a gain through chemoradiation of 5-10%**

Next generation of clinical trials based on IGABT + IGRT as RCT

- Hypothesis driven -

- Comparative Trials on IGABT vs. 2D (randomized)
- Dose escalation for advanced disease HR CTV (LC, OS)
- Dose de-escalation for limited and favourable advanced disease (good response,...) (Morb/QoL)
- Para-aortic RT, Lymphnode Boost (NC, OS)
- Systematic concomitant radiochemotherapy min. 5 cycl. for subgroups with high risk of distant metastases (OS)
- Testing Dose/Volume constraints for Target and OARs
- Biomarker investigation (Hypoxia, HPV, EGFR, VEGF..)



Acknowledgements

Gyn GEC ESTRO network EMBRACE study and research group, ICRU report committee



Sponsored by:



Support:



Facilitated through



4th Annual EMBRACE meeting Vienna 12/2012

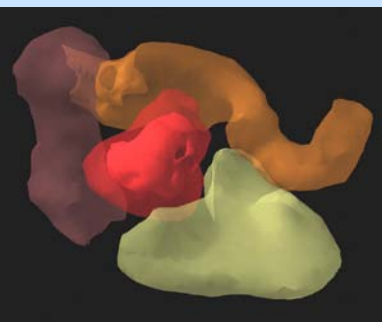


ESTRO Teaching Course Utrecht (2015)
Image Guided Radiotherapy & Chemotherapy in gynaecologic cancer-
with a special focus on adaptive brachytherapy

GEC-ESTRO gyn network

and EMBRACE I and II

EMBRACE



R. PÖTTER
K. TANDERUP



Gyn GEC ESTRO NETWORK R&D, Educ.

since 5/2005, coordinator Medical Uni.Vienna and Aarhus Uni.Hosp.



Aarhus



Athens



Leeds



Leuven



Ljubljana



Milwaukee



Mount
Vernon



Mumbai



Oslo



Paris
IGR



Utrecht



Vienna

ESTRO

N

E

T

W

O

R

K

3D based
contouring of
CTV and OAR

WP1

Appliator
reconstruction

WP2

Treatment planning

WP3

Appliator
development

WP4

W O R K P A C K A G E S

EMBRACE Study (since 2008)

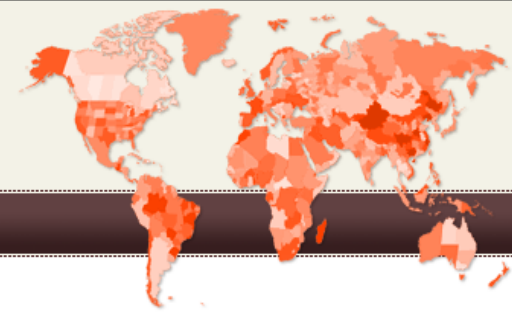
supported by Elekta/Varian/Bebig

A C T I V I T I E S

P U B L I C A T I O N S O N :

- WORKSHOPS FOR CONTOURING Dublin, Washington, Milwaukee, Utrecht
- WORKSHOP FOR IMAGE GUIDED GYN BT UTRECHT 2006
- WORKSHOP FOR TREATMENT PLANNING Ljubljana 2007
- EMBRACE KICK OFF MEETING Brussels 2008
- WORKSHOP FOR APPLIATOR DEVELOPMENT Leuven 2009
- WORKSHOP FOR OUTCOME ASSESSMENT IN IGABT Paris 2010
- WORKSHOP ON UNCERTAINTIES IN IGABT AARHUS 2011
- WORKSHOP ON MORBIDITY AND DISEASE OUTCOME ATHENS 2012
- WORKSHOP on EMBRACE and retroEMBRACE research 2011, 2012, 2013, 2014, 2015

- CONTOURING
- DOSE REPORTING
- 3D IMAGING
- INTER-OBSERVER VARIATIONS
- APPLICATOR RECONSTRUCTION
- TREATMENT PLANNING
- UNCERTAINTIES

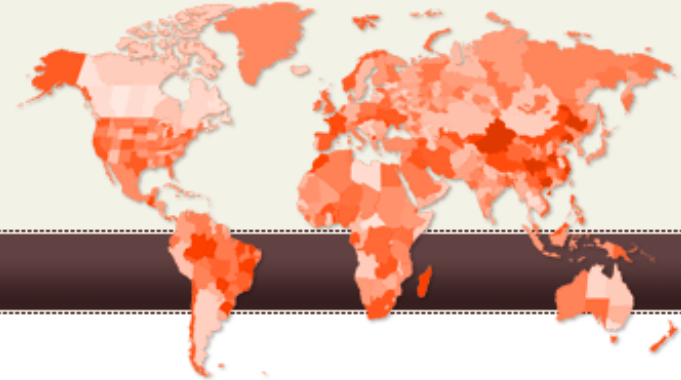


- **Web-based database with a retrospective multicentre collection of data on 3D RT plus IGABT in cervical cancer**
- **780 pts**
- **Eligibility criteria:**
 - **Diagnosis of cervical cancer and treatment with curative intent by IGABT**
 - **Reporting according to GEC ESTRO recommendations**



EMBRACE

{ An international study
on MRI-guided Brachytherapy
in locally Advanced Cervical cancer }



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- **EMBRACE** - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer
- A prospective observational multi-centre trial
- Initiated enrollment of patients in 2008, >1200 pts accrued
- Accrual to be finalised in 2015

VARIAN
medical systems

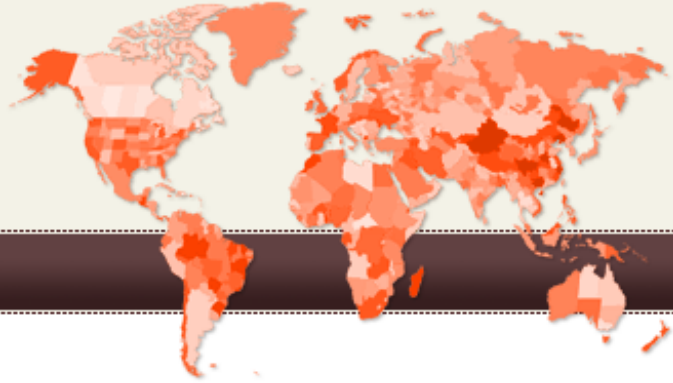
A partner for **life**

 **Nucletron**
Improving patient care

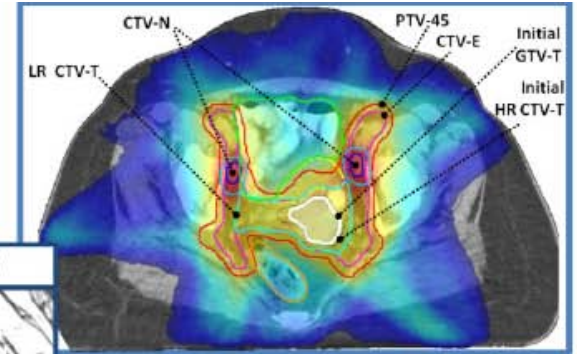
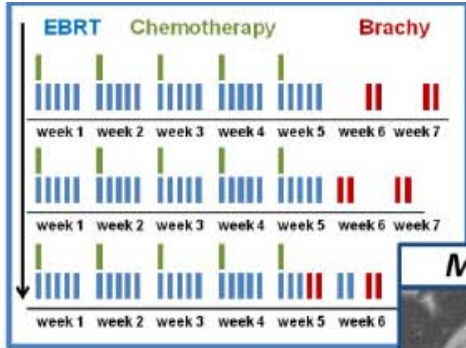


EMBRACE II

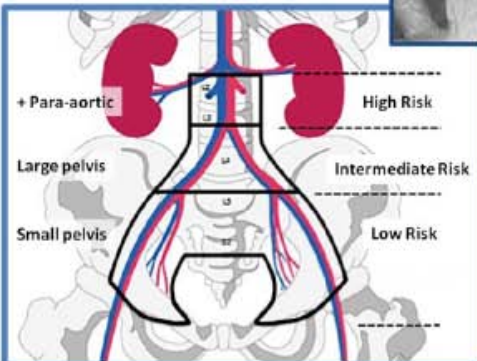
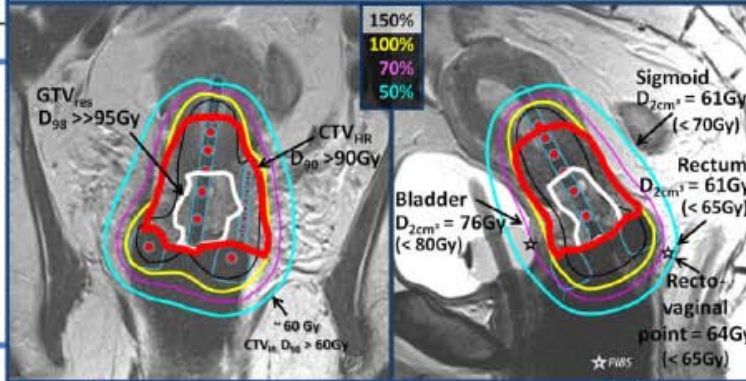
An international study
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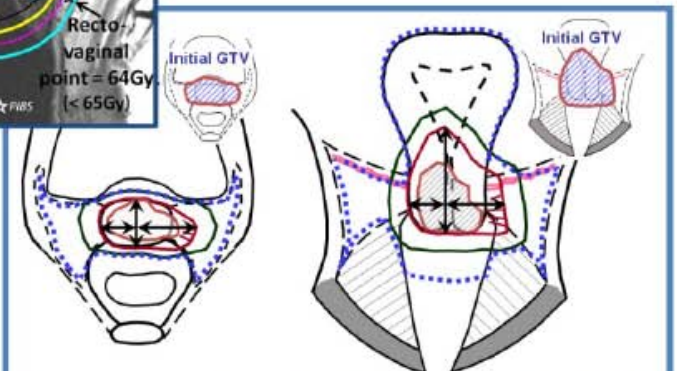
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MRI guided adaptive brachytherapy (IGABT)



Nodal CTV-E based on Risk Group



Initial GTV GTV_{res} CTV_{HR} CTV_{IR} CTV_{LR}

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

EMBRACE II design

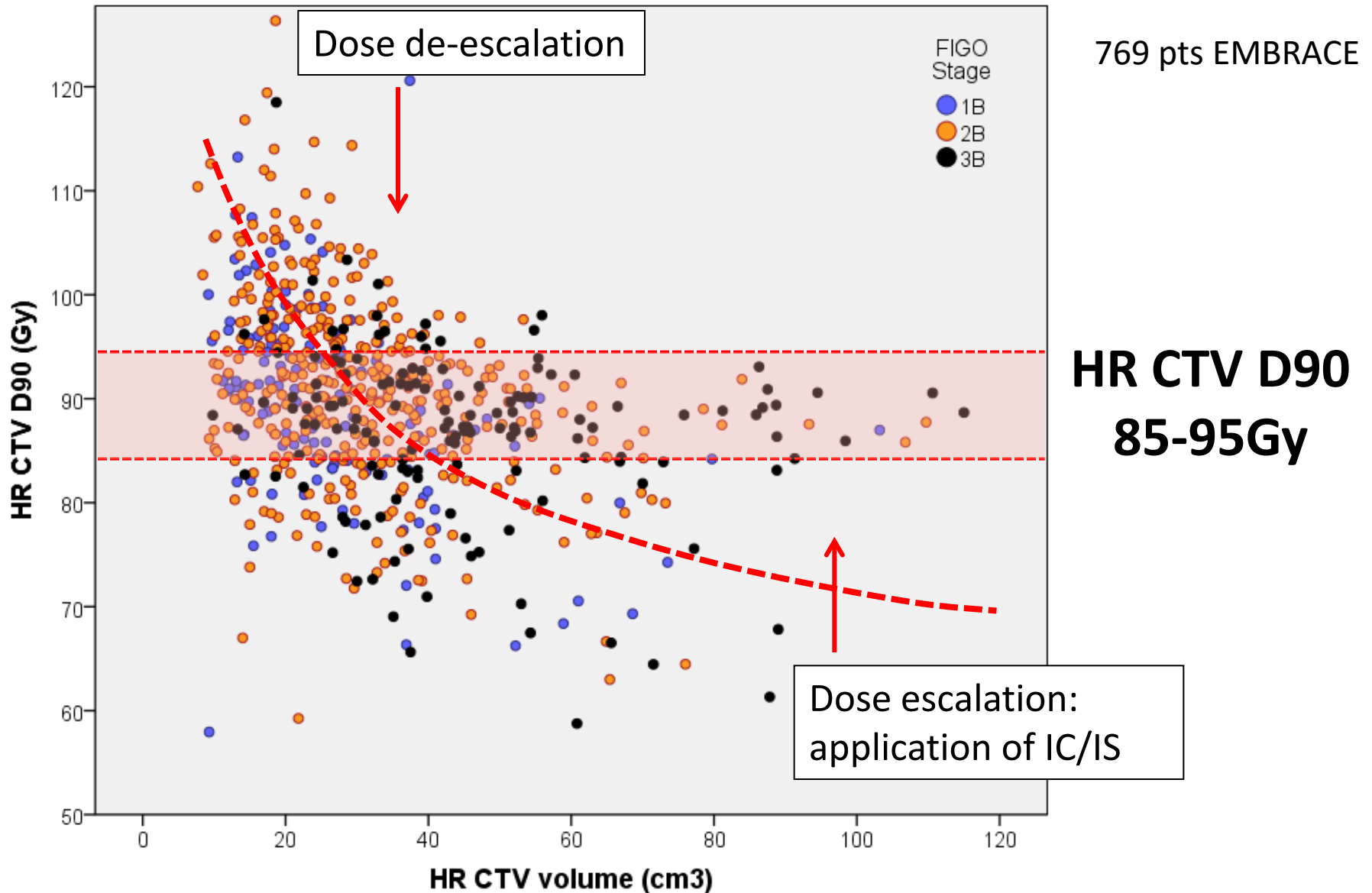
- **Prospective interventional and observational study**
- **Multiple endpoints**
- **Multicenter: >25 centers**
 - 25 current EMBRACE centers and >10 new centers
- **1000 patients in 4 years and follow up for 5 years**

- **Substudies on**
 - Adaptive EBRT
 - Vaginal morbidity
 - Functional imaging
 - Translational research

EMBRACE II interventions

- **Increased use of IC/IS technique in BT**
- **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

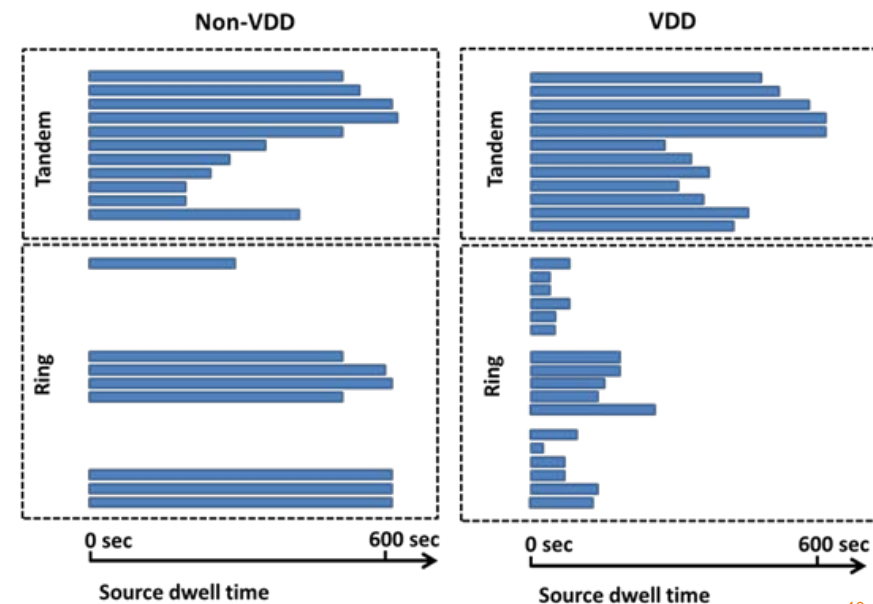
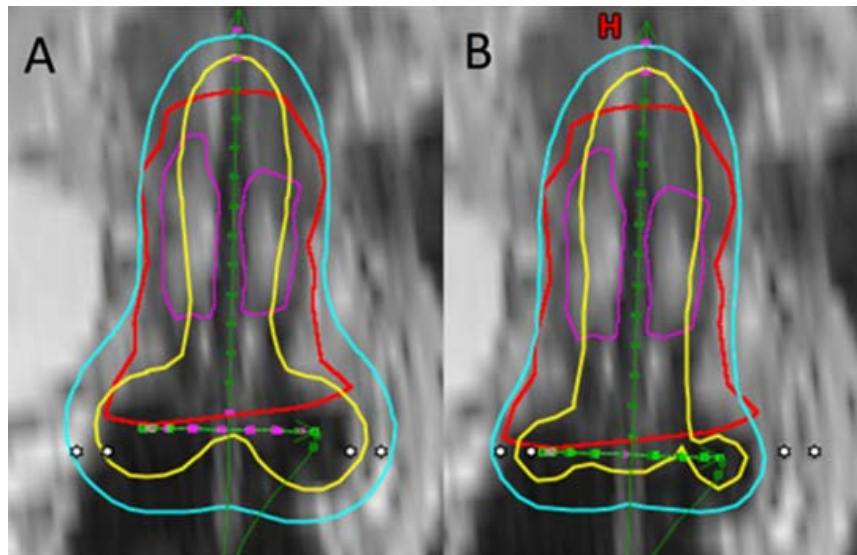


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Vaginal dose de-escalation

	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

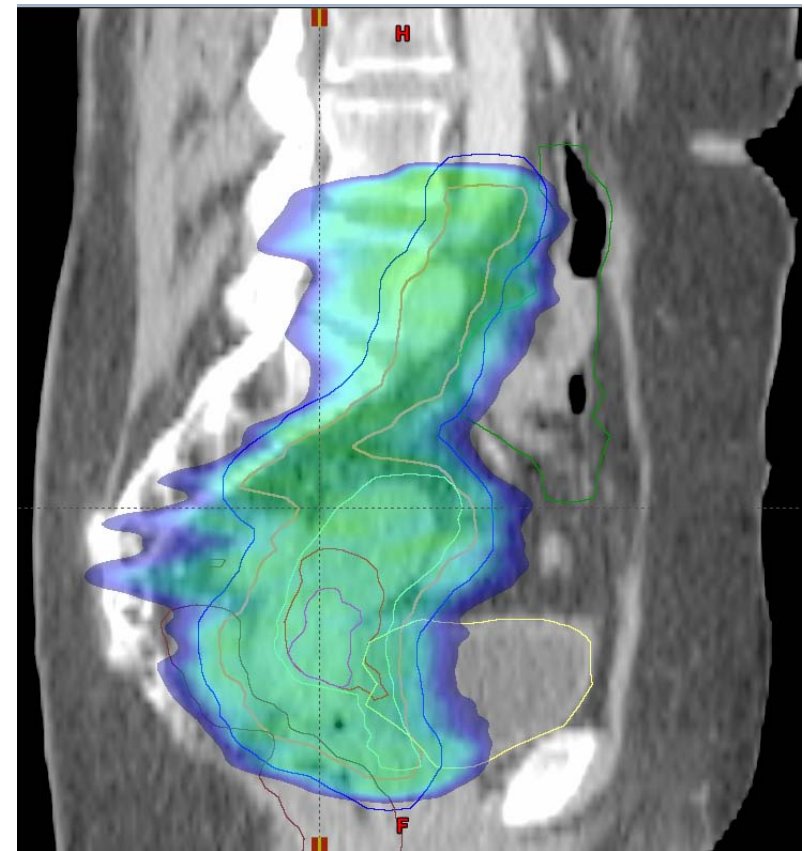
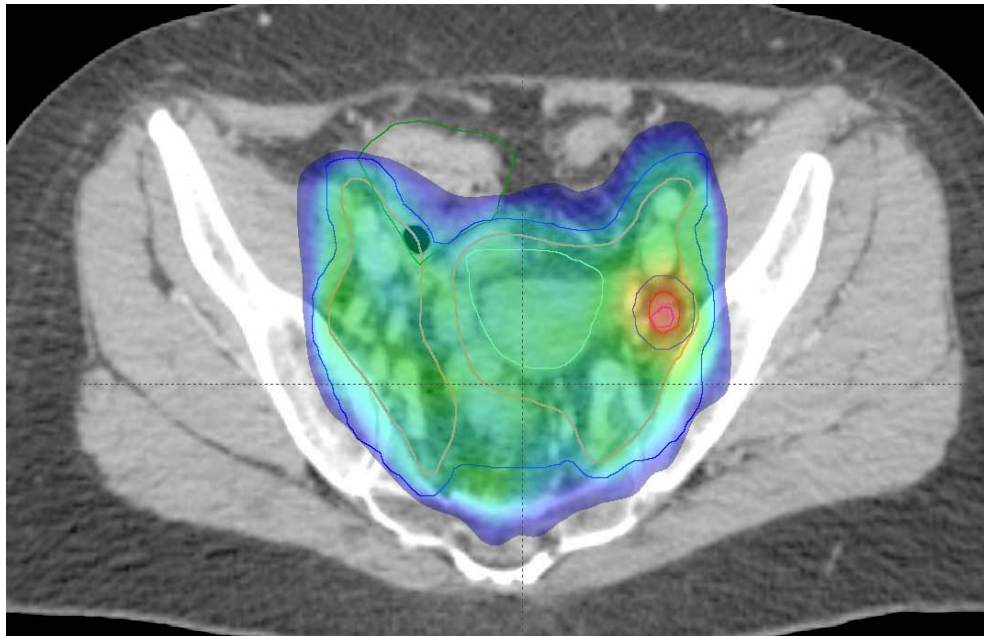


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IMRT + daily IGRT

- 5mm PTV margin
- SIB LN boosting

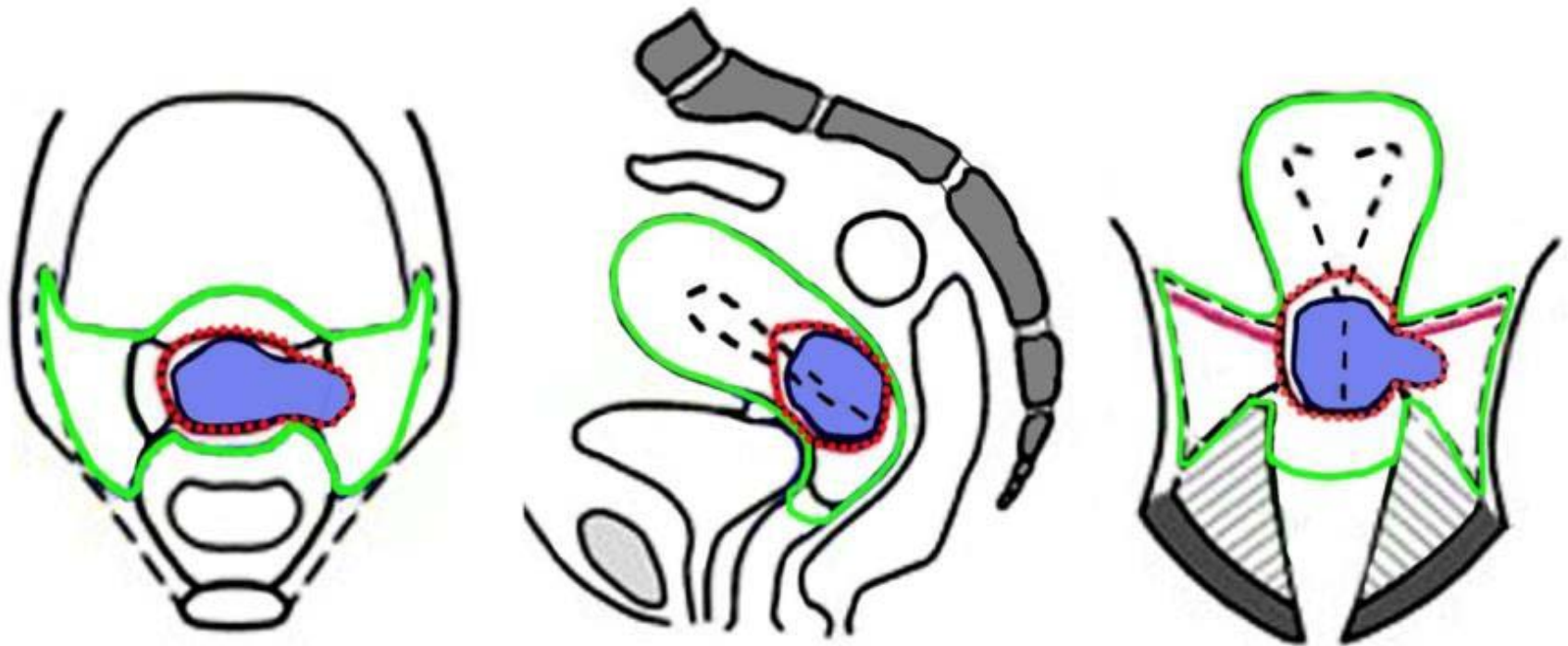


EMBRACE II interventions

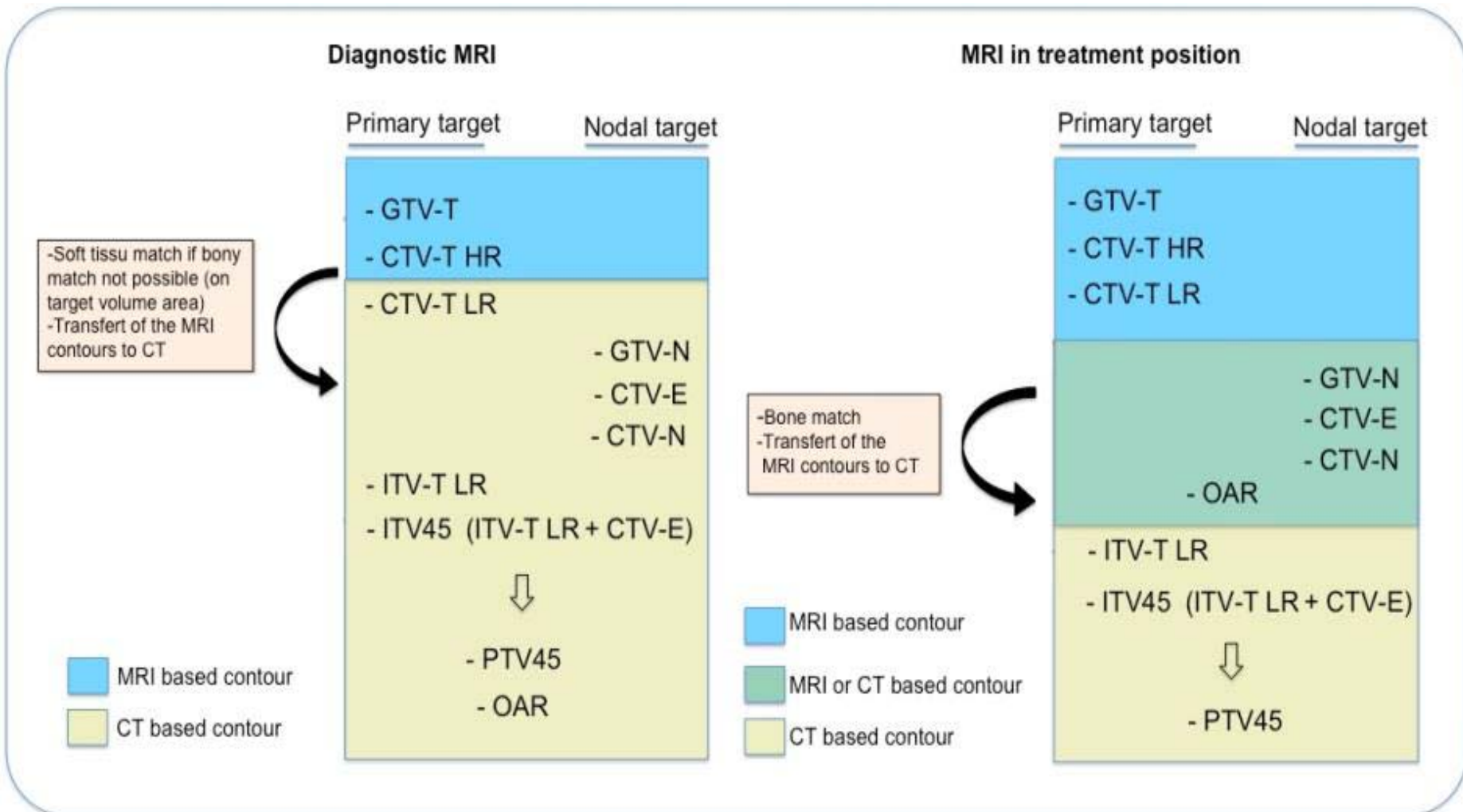
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Target concept related to primary tumour

- Initial GTV (blue)
- Initial HR CTV-T (red): GTV+cervix
- LR CTV-T (green): HR CTV + uterus + parametria + vagina

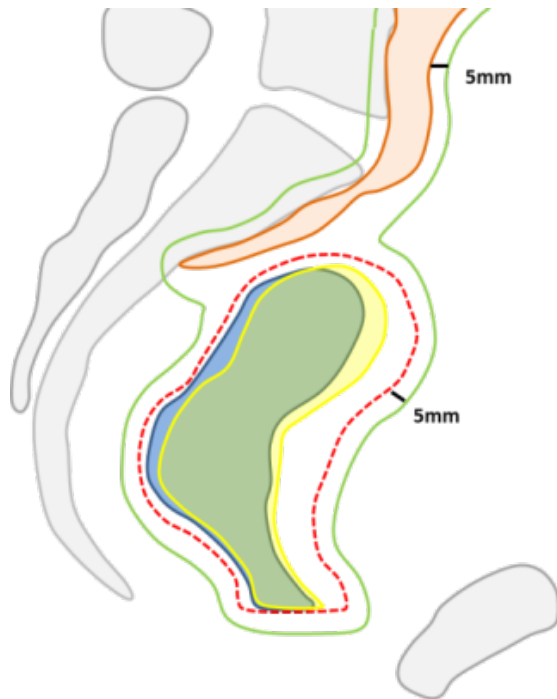


Workflow target contouring



Internal target volume

- Combined appearance on CT and MRI
- Anatomical knowledge of organ motion



CTV-TLR (CT)
CTV-TLR (MR)
CTV-E
ITV-TLR
PTV-45



CTV-TLR (CT)
CTV-TLR (MR)
CTV-E
ITV-TLR
PTV-45

EMBRACE II interventions

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- Reduction of vaginal source loading
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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**

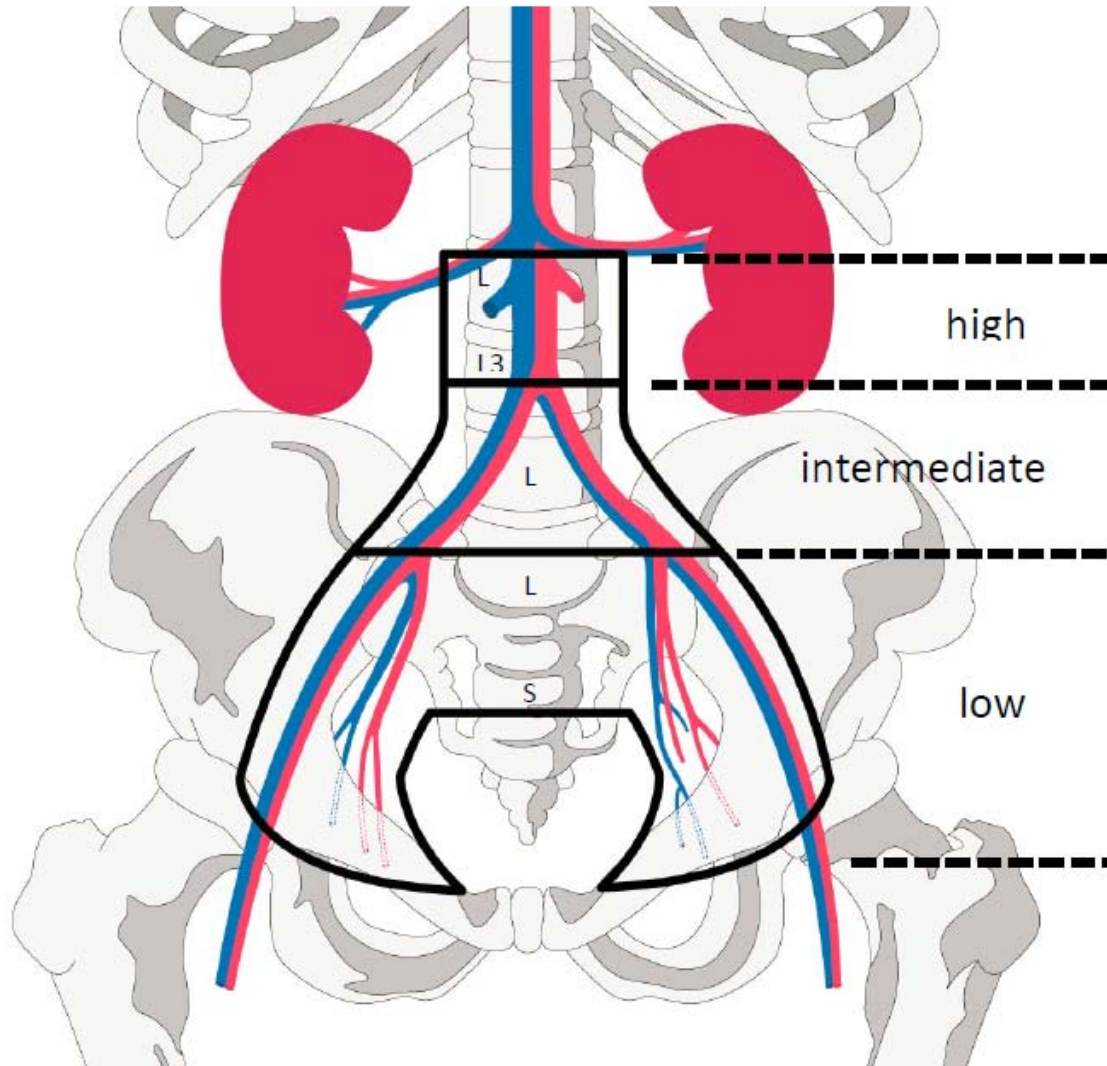
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Target concept related to elective lymph nodes

Risk Group LN	Definition	EBRT lymph node regions
Low Risk (LR LN)	Tumour size ≤ 4 cm 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: <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • ≥ 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].

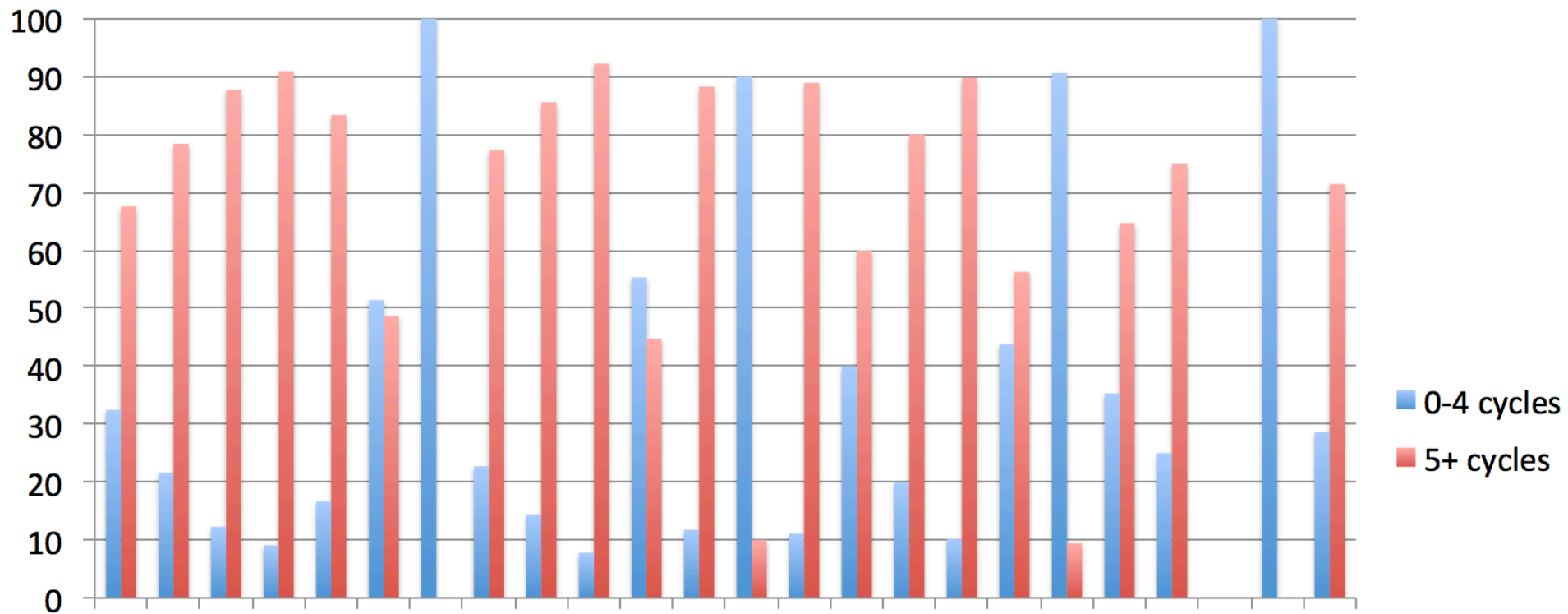
Target concept related to elective lymph nodes



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**
- Reduction of overall treatment time

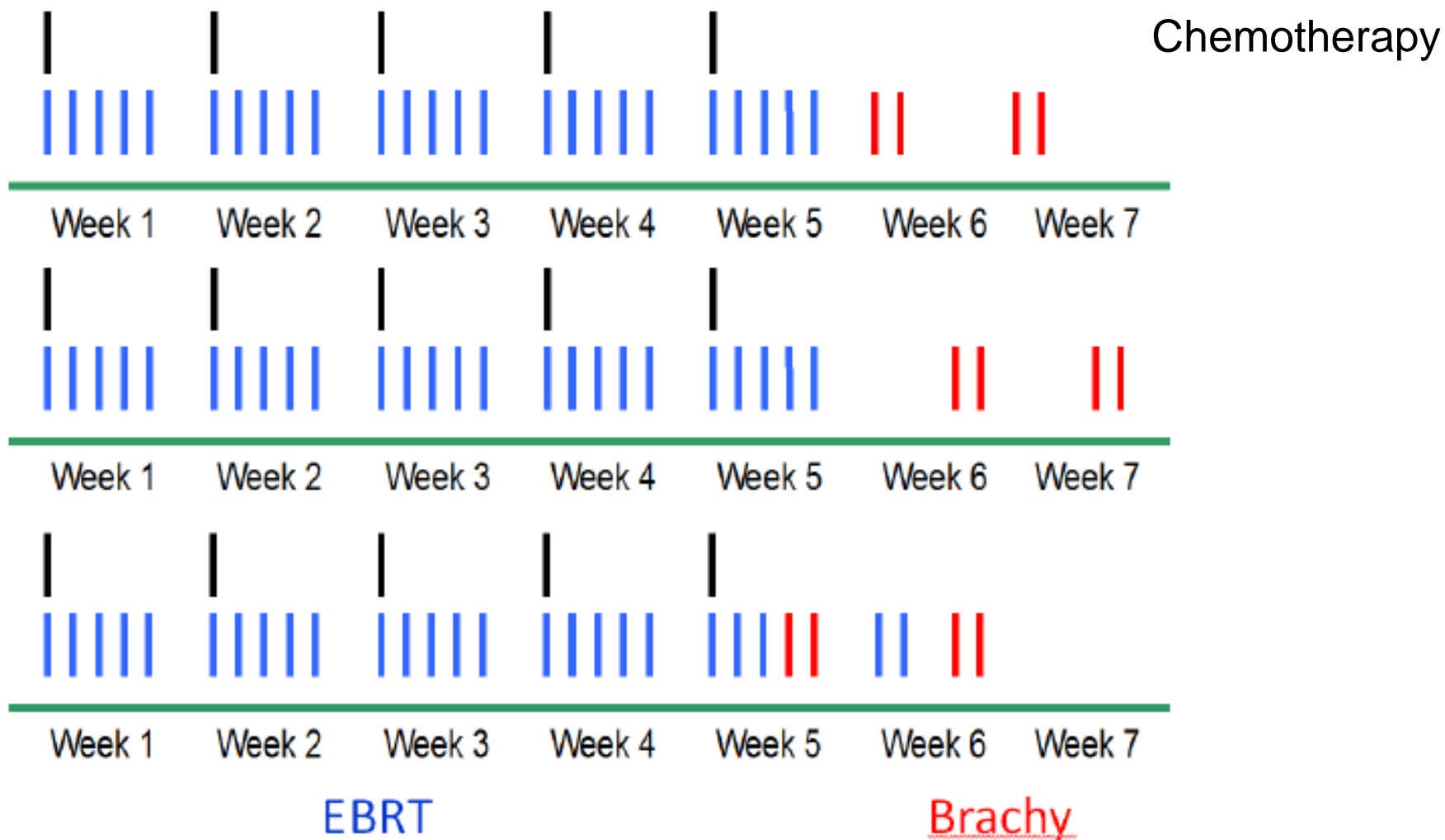
Administration of chemotherapy in EMBRACE I



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**

Control of OTT: 3 examples of schedules



Accreditation and dummy run for new centers

- **Documentation of compliance (web based)**
 - **Treatment of >10 pts per year qualifying for accrual to EMBRACE II**
 - **Both EBRT and BT performed in the center**
 - **Routine use of IMRT or VMAT**
 - **Routine use of daily IGRT with bony fusion**
 - **Routine use of MRI guided IGABT**
 - **Routine use of combined IC/IS (>20-50% of pts)**

Accreditation and dummy run for new centers

● Dummy run

- **Contouring training for EBRT and BT (self-assessment)**
- **EBRT planning exercise (self assessment)**
- **Registration of 5 patient in registration database**
- **Submission of EBRT and BT contours**
- **Submission of EBRT and BT treatment plan**

Roadmap EMBRACE II

- **Oct 2015:** **Protocol distributed to EMBRACE centers**
- **Nov 2015:** **Protocol distribution to interested centers**
- **Spring 2016:** **Dummy run EMBRACE centers**
- **March 2016:** **Start of accrual**
- **Autumn 2016:** **Dummy run new centers**

Contact to EMBRACE office for interested centers:

ian.dilworth@akhwien.at

Richard.poetter@akhwien.at

Karitand@rm.dk

Information about EMBRACE, retro-EMBRACE and 3D Gyn GEC ESTRO network

- www.embracestudy.dk
- www.retroembrace.com
- www.estro.org



**ESTRO Teaching Course on
Image-guided radiotherapy & Chemotherapy in
Gynaecological Cancer
- with a special focus on adaptive BT-**

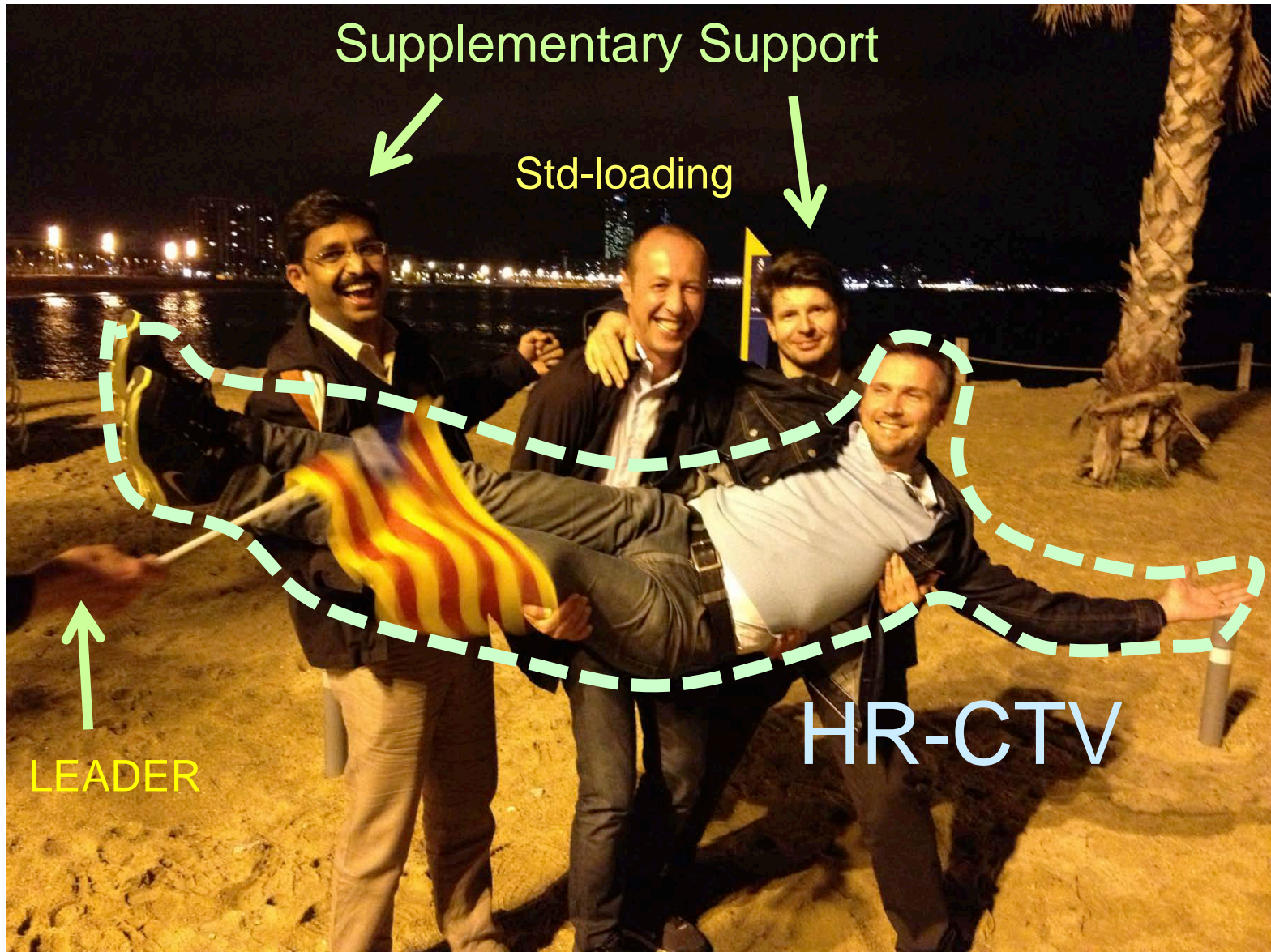


Tips and Tricks

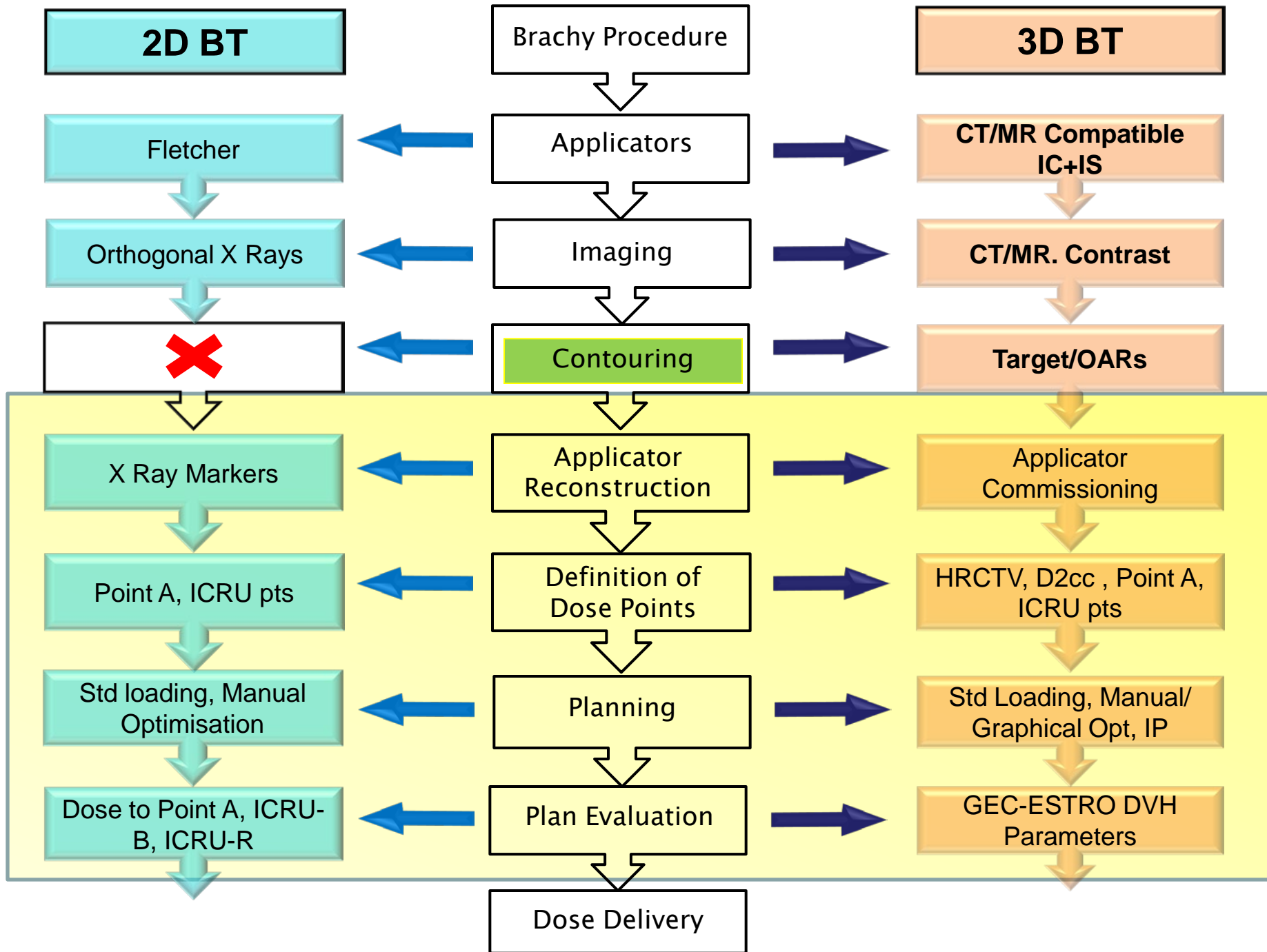
D Berger, U. Mahantshetty and R Pötter



Team work at TC Barcelona 2013

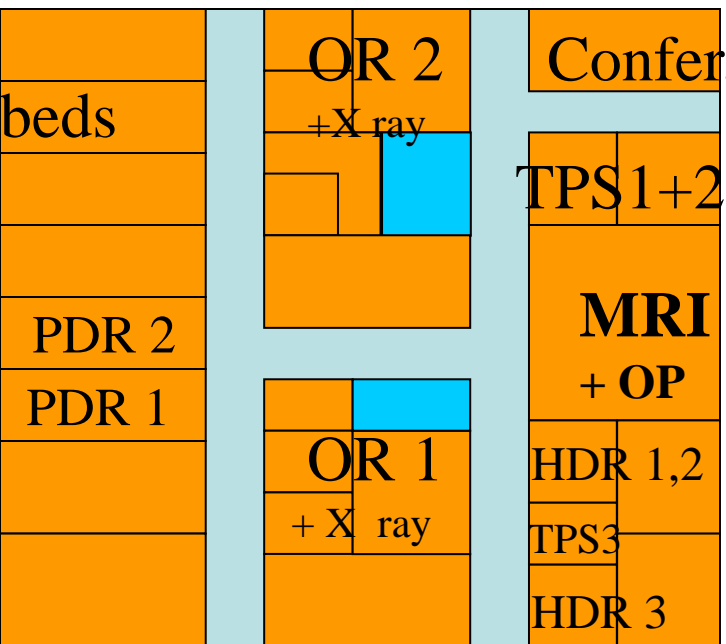


With permission





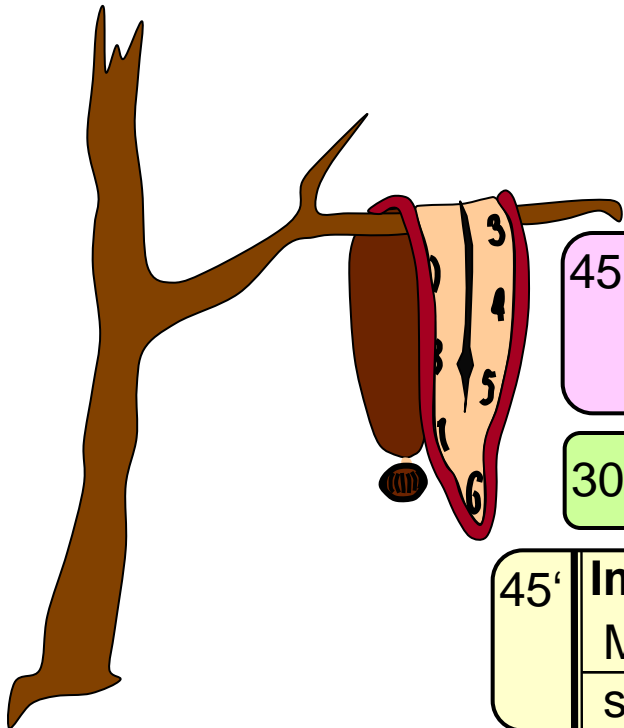
New open 0.35T MRI since July 2014



Brachytherapy Vienna

Costs for open MRI: ~500.000 €

Working Schedule Brachytherapy of Cervix Cancer



15'	Preparation Patient med.tech. Documents DVH pre-planning	Surgical-nurse /Physician Technician Physician and Physicist
-----	--	--

45'	Anaesthesia Spinal/Epidural or General	Anaesthetist / Anaesthesia-nurse
-----	---	-------------------------------------

30'	Application	Physician / surgical-nurse
-----	--------------------	----------------------------

45'	Imaging MR / CT	Technician
	supervision + discussion	Physician and Physicist

30'	Contouring Organs at Risk Target Volume	Technician / Physician 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**
- **Treatment planning principles**
- **Analgesics**
- **Removal of application**
- **Manage the bleeding after removal**
- **Do not use sharp needles**
- **Optimization tools**
- **Learning Curve**

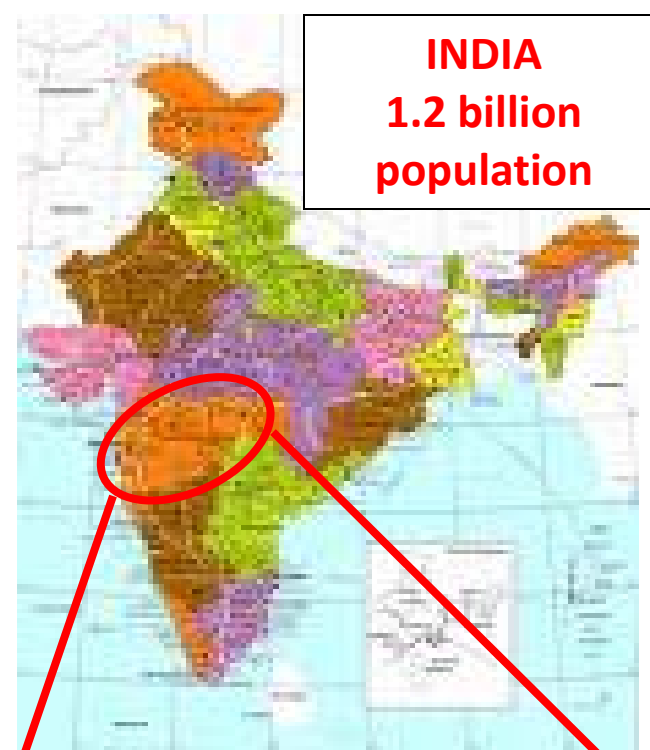


Tata Memorial Hospital

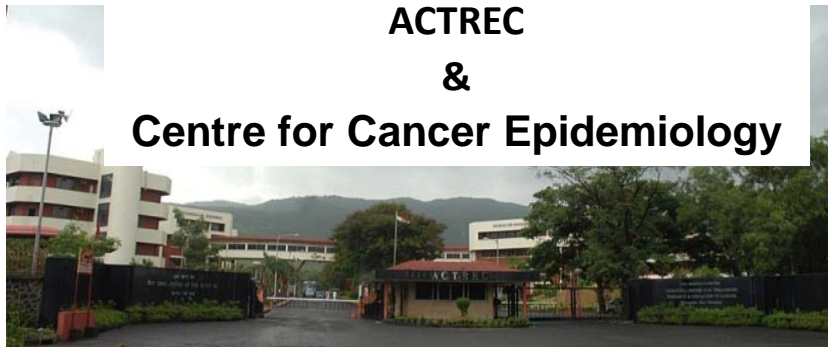


MISSION
Service
Research
Education

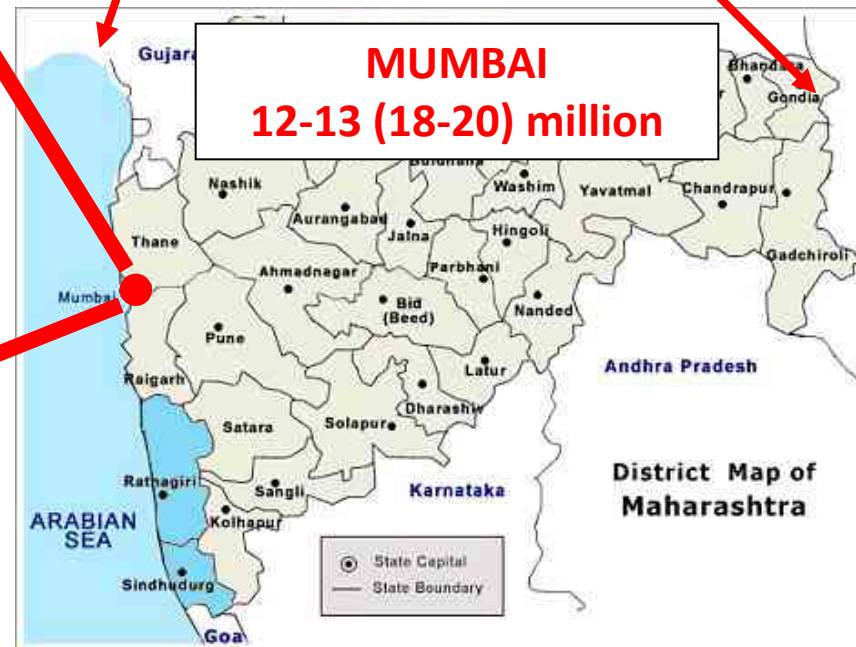
INDIA
1.2 billion
population



**ACTREC
&
Centre for Cancer Epidemiology**

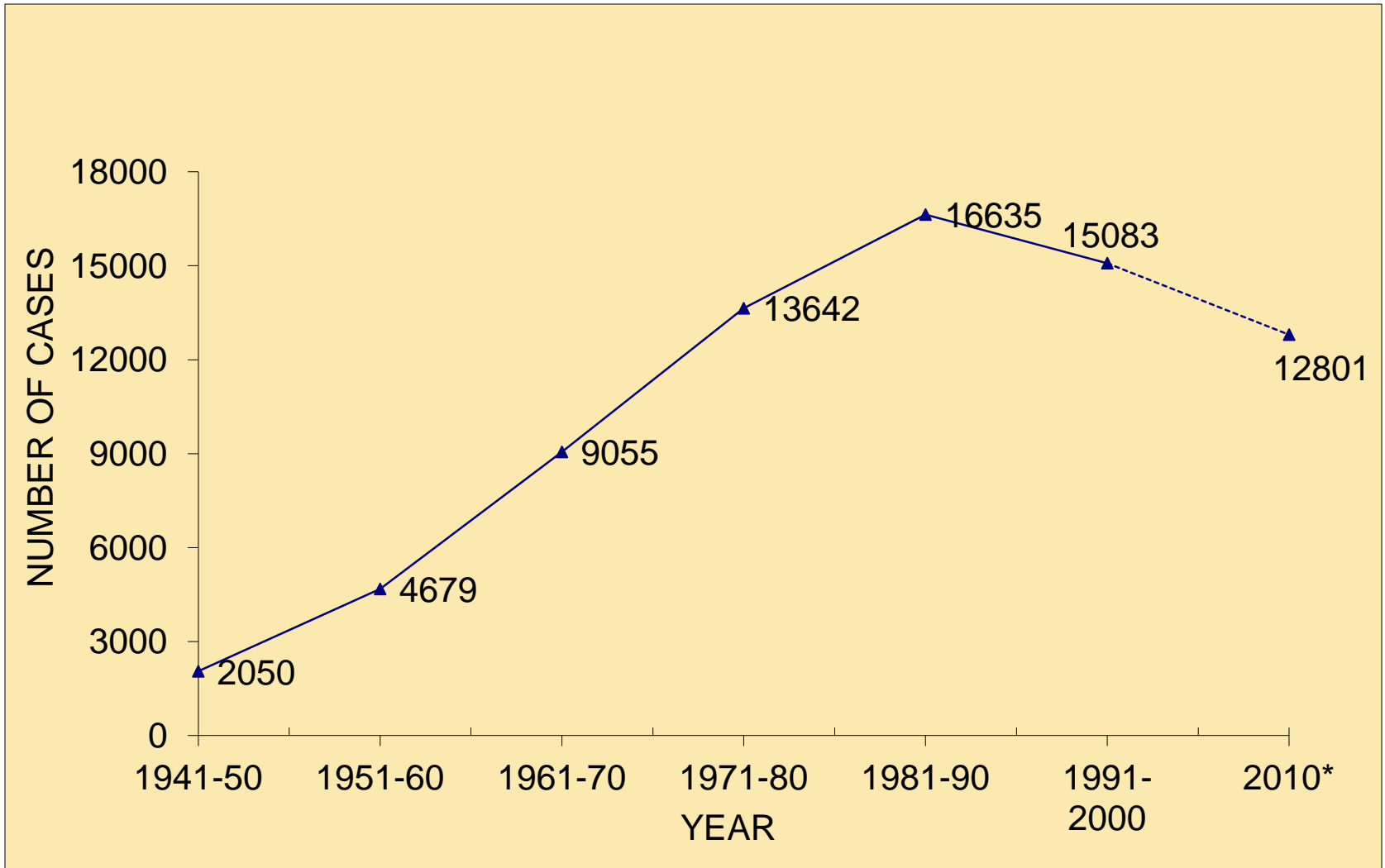


MUMBAI
12-13 (18-20) million



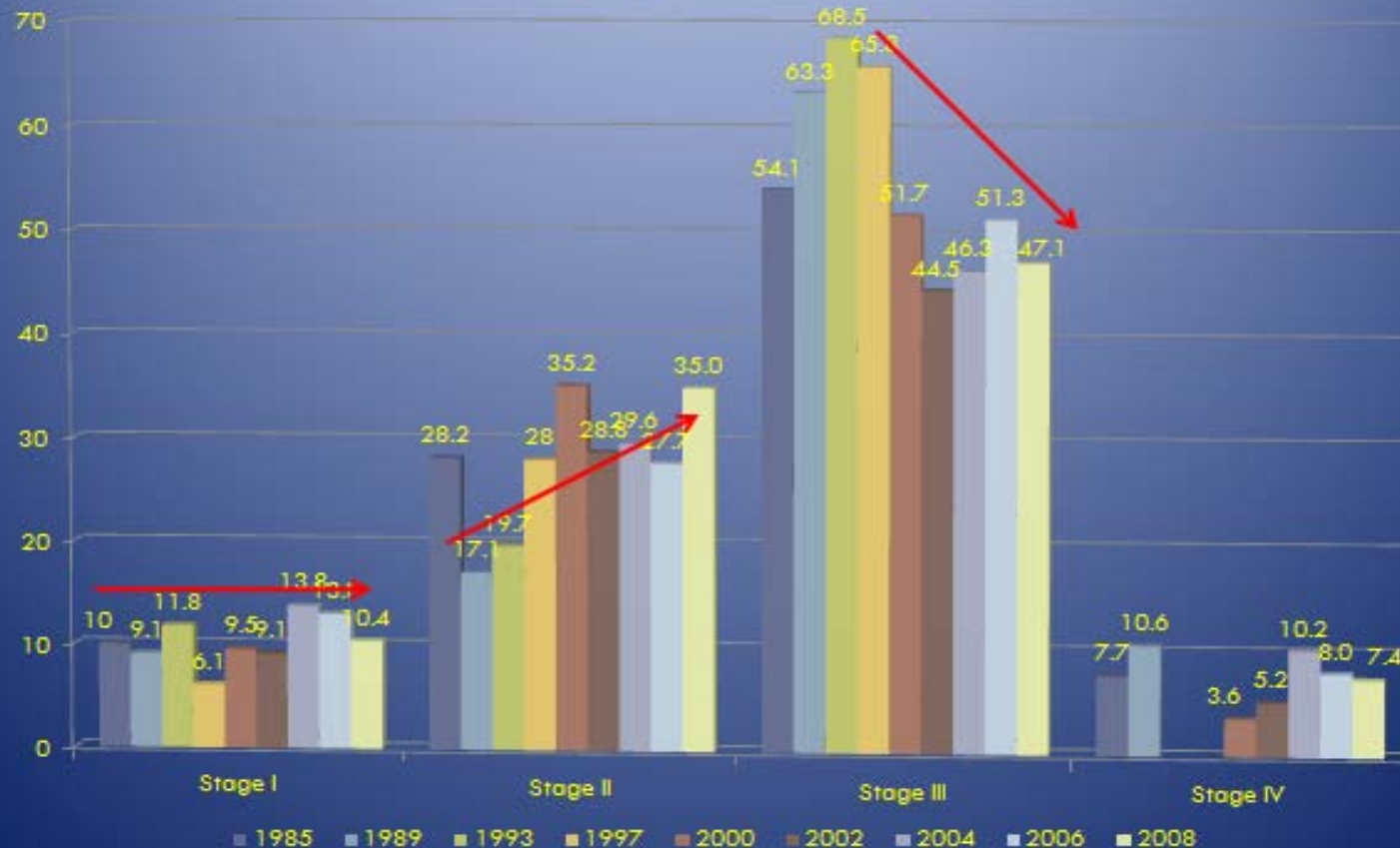
DOWN THE DECADES

CANCER CERVIX : TATA MEMORIAL HOSPITAL 1941-2010



TATA MEMORIAL HOSPITAL CANCER REGISTRY (1985 – 2008)

Down Staging of Carcinoma Cervix



- 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

TRANSITION FROM 2D TO 3D

SECRET TO A SUCCESSFUL JOURNEY!

- Attended the GYN Teaching Course: **Understand the Concepts**
- Hands on Workshop including procedures : **Atleast 1 – 2**
- Learning Curve & Standardization of processes : **10 - 15 pts**
- Retrospective Analyses and Introspection
- Transition to 3 D: MR / CT
- Prospective Collaborative Studies & Research
- Teaching / Hands on Workshops

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 Europeen 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	<p style="text-align: center;">LESSONS LEARNT</p> <p style="text-align: center;">Retrospective Data: 24 patients</p> <p style="text-align: center;">Tumor Volumes larger: Advanced Stages</p> <p style="text-align: center;">Bladder and Sigmoid Doses Higher</p>					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					

CLINICAL OUTCOME

TMH Retrospective Data (Dec 2006 - May 2008) (N = 24)

Median Follow-up : 18 (12 - 40) months

	Stage			
	I B2 / IIA N=2	IIB N=10	IIIB N=12	Total N=24
Local	--	2*	1#	3
Pelvic Node	--	--	1	1
Dist. metastasis	--	--	1	1
Total	--	2	3	5

* Point A: 79 Gy and HR-CTV D90 doses : 56.5, 67 Gy;

Point A: 70 Gy and HR-CTV D90 doses : 65Gy;

Late sequelae: 1 pt with protco-sigmoiditis

(0.1 and 2cc : R 46 & 64; S: 260 & 140 Gy)

**TMH - AKH Collaboration: 2008-2009
Bilateral Exchange Program**

Pranayama

Pratyahara

Asana

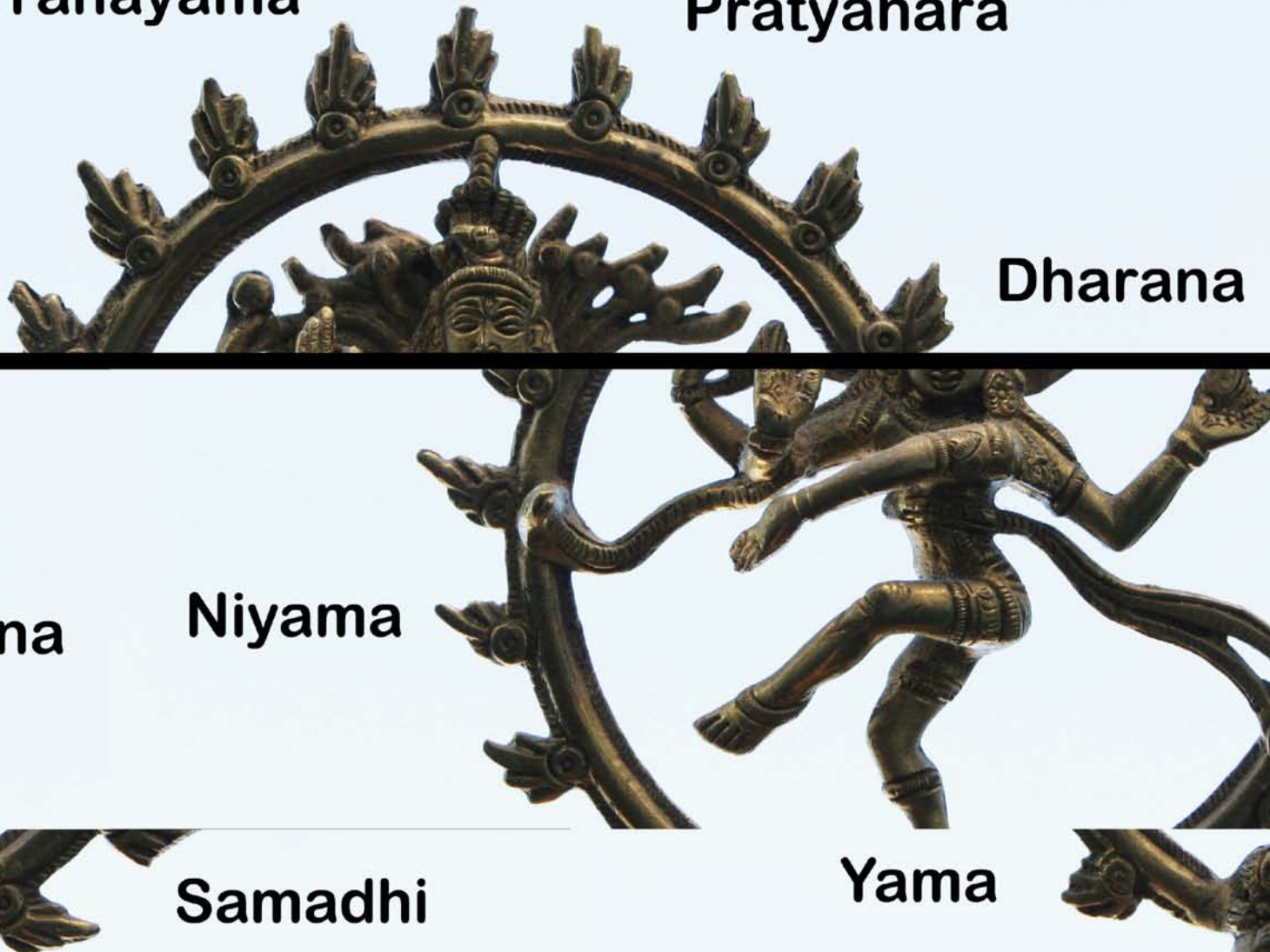
Dharana

Dhyana

Niyama

Samadhi

Yama



TMH - AKH Vienna Collaboration: 2008 – 2009

Bilateral Exchange Program



Tata Memorial Hospital Participation in International Multicentric Studies

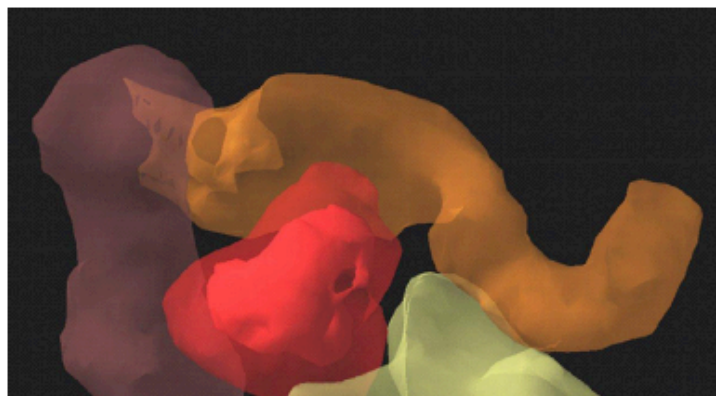
- Refine treatment standards

- GYN GEC-ESTRO Research Network

A European study on MRI-guided brachytherapy
in locally advanced cervical cancer

EMBRACE

(ENDORSED BY GEC ESTRO)



2009 ONWARDS

TATA HOSPITAL CONTRIBUTION TO EMBRACE

100 patients (IIB-IVA)

TMH EMBRACE Data
Prospective MR Based Brachytherapy
Dec 2009 – March 2014
N = 100 patients

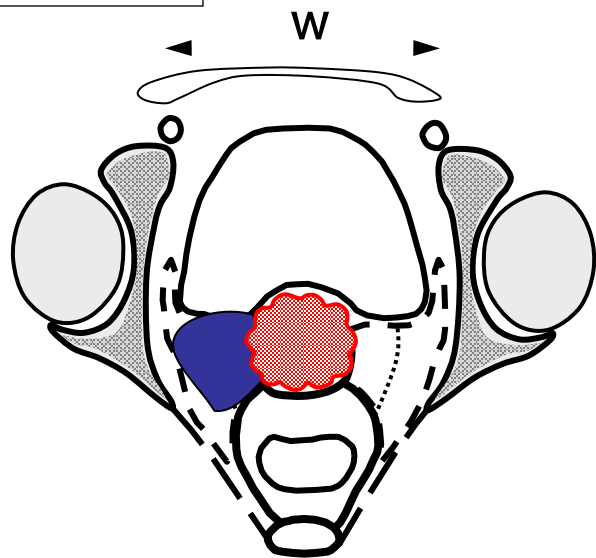
Total no of patients	47/100 patients
Median Age (range)	51 \pm 8 (28-65) years
Histology	
Squamous Carcinoma	40
Adenocarcinoma	05
AdenoSquamous	02
FIGO Stage (n)	47
IIB	18
IIIB	25
IVA	04
Intracavitary Brachytherapy (HDR)	4 fractions of 7 Gy to HRCTV
Median follow-Up (Range)	16 \pm 8.3 (7-36) months

w = 60 mm
h = 50 mm
t = 50 mm

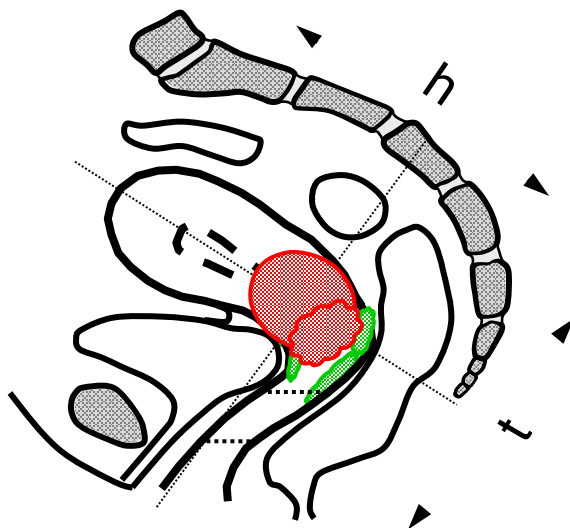
Vagina
Involvement
= 4 cm (Post)

A Clinical Example

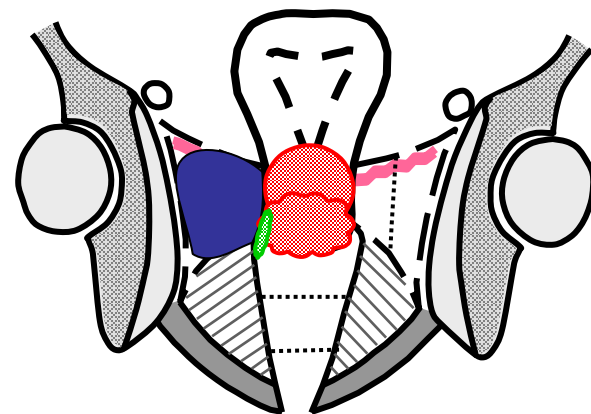
At Diagnosis



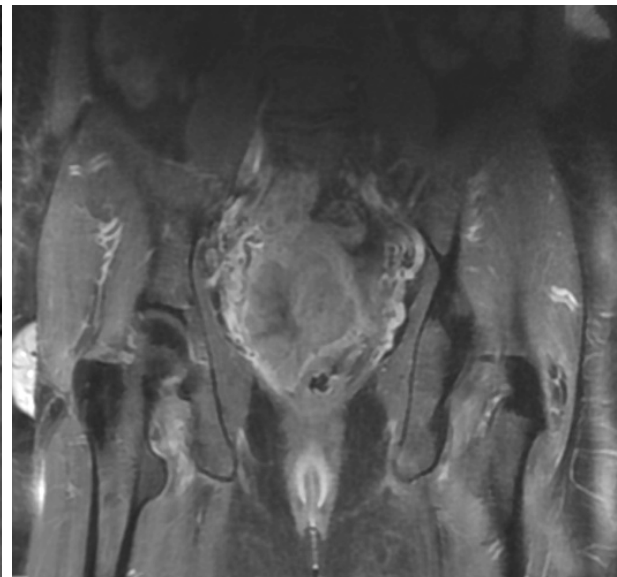
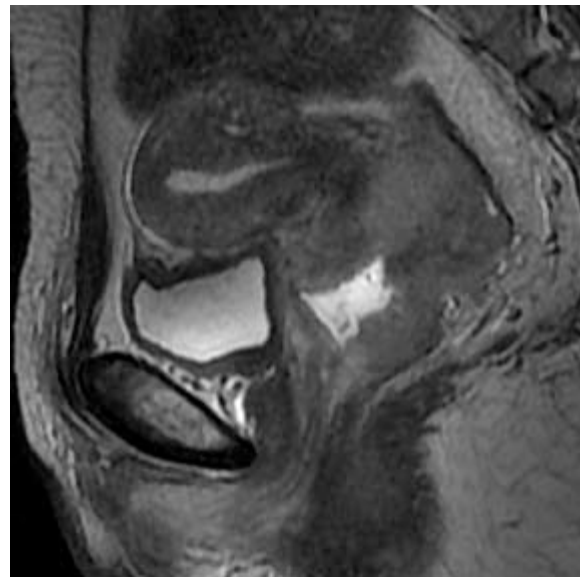
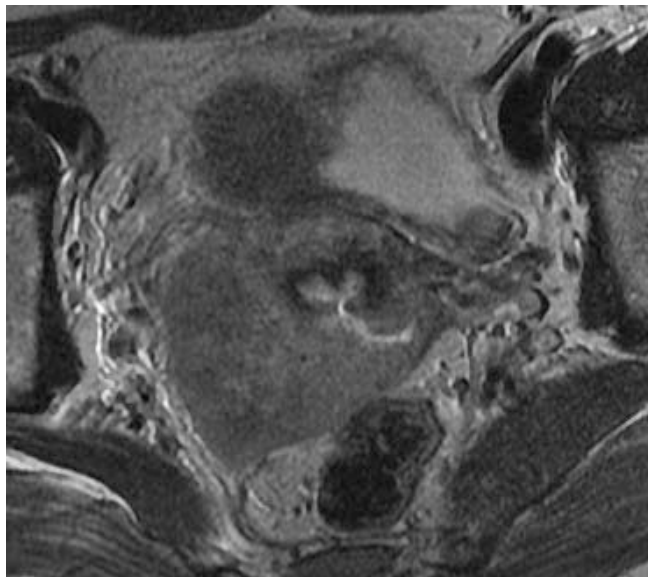
Axial



Sag



Coronal

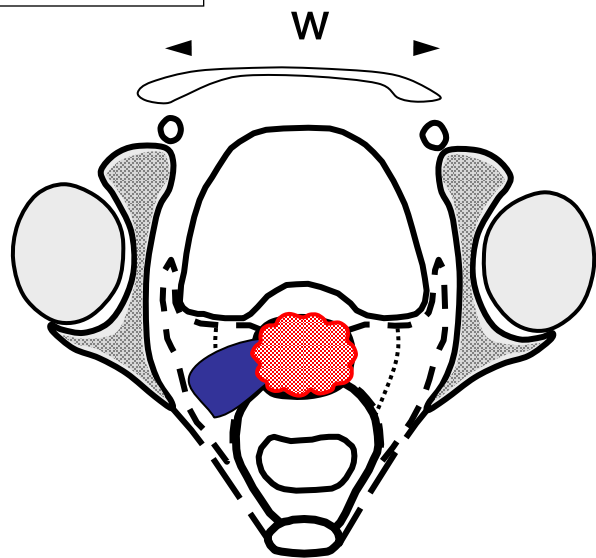


w = 60 mm
h = 40 mm
t = 30 mm

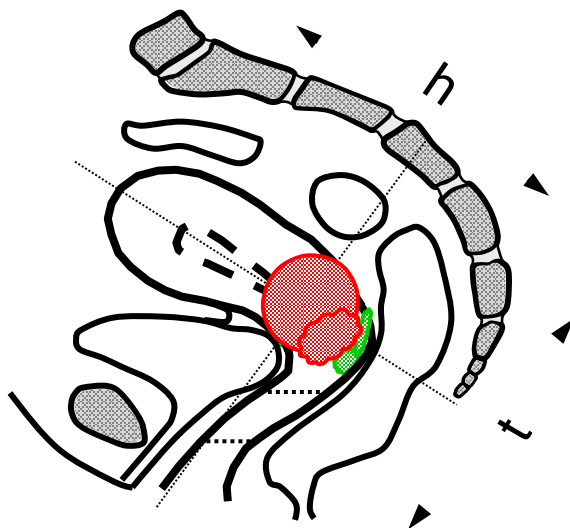
Vagina
Involvement
= 20mm (Post)

Clinical Drawing

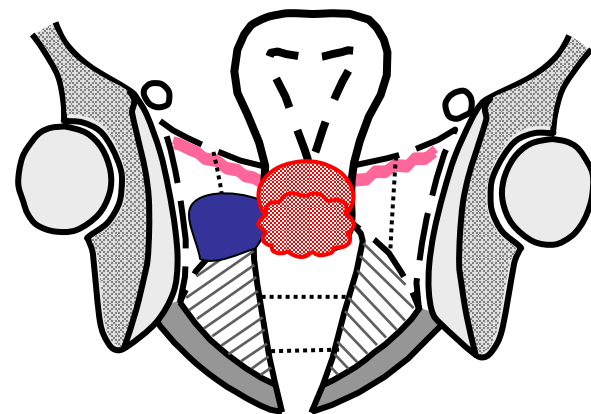
At Brachytherapy



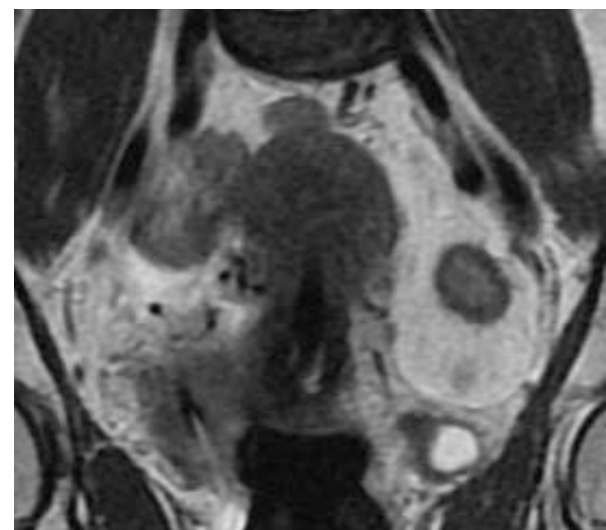
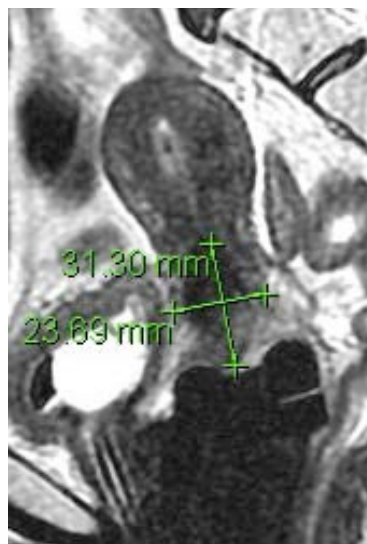
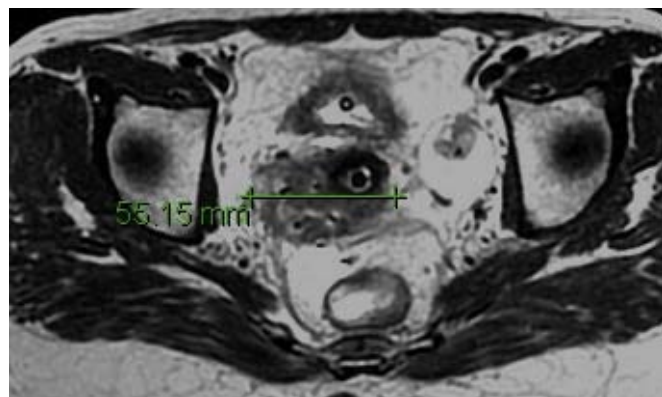
Axial



Sag



Coronal

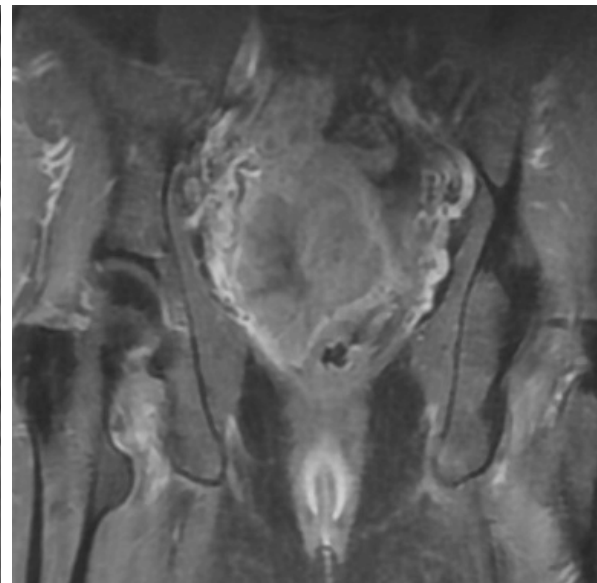
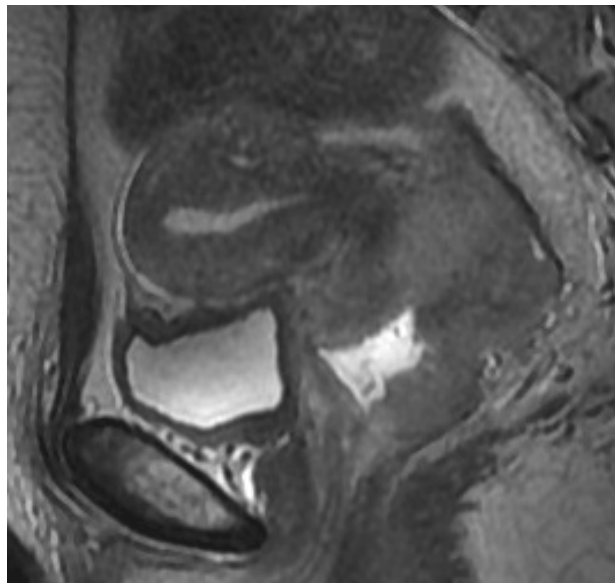
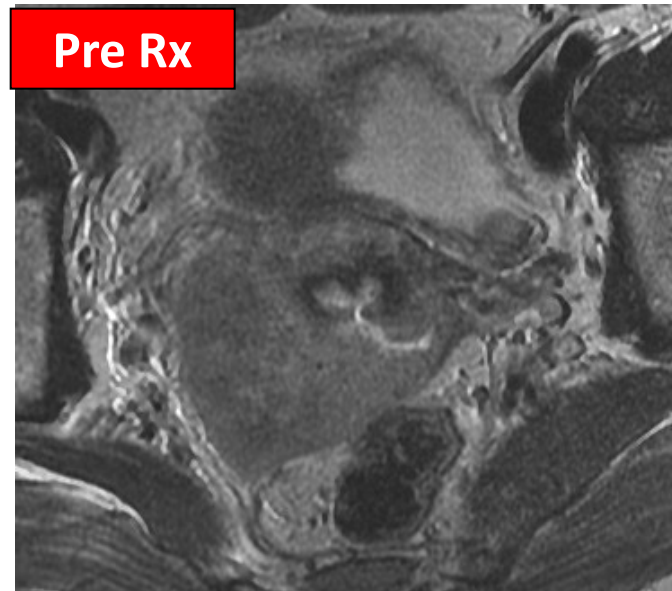


Axial

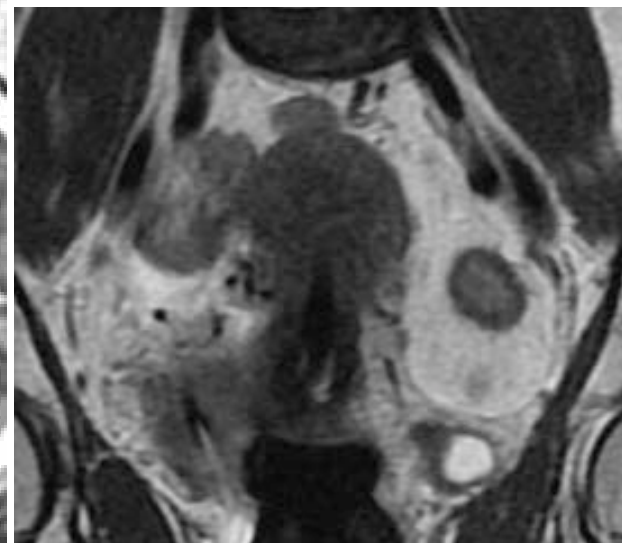
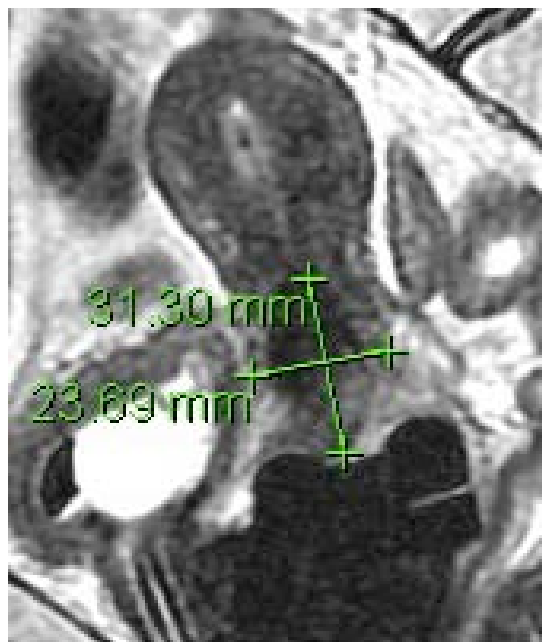
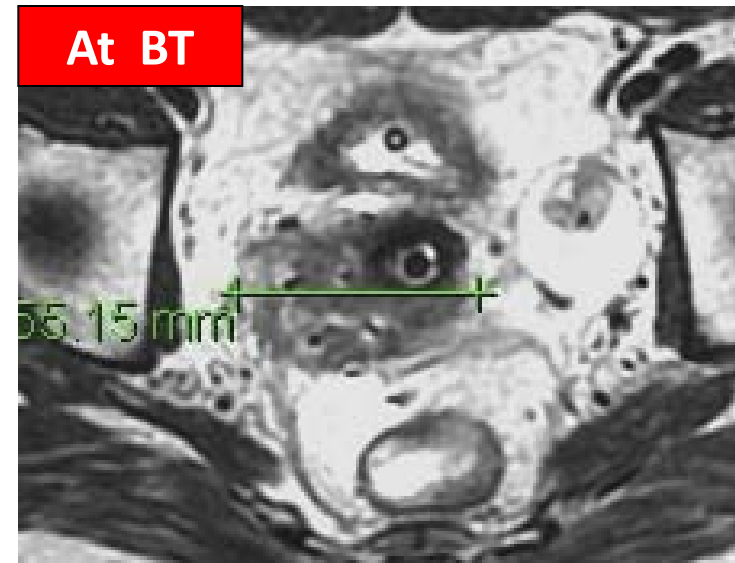
Sag

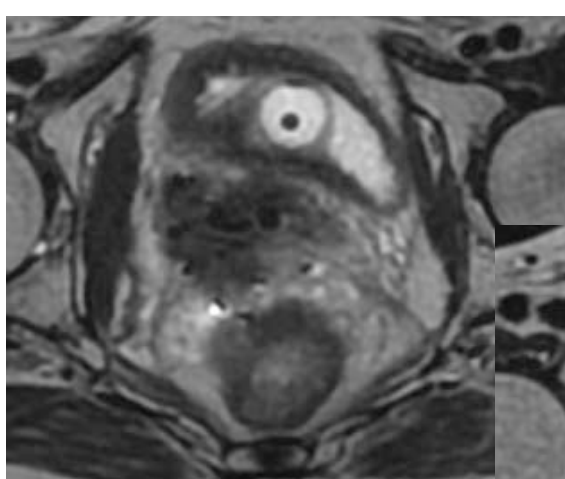
Coronal

Pre Rx

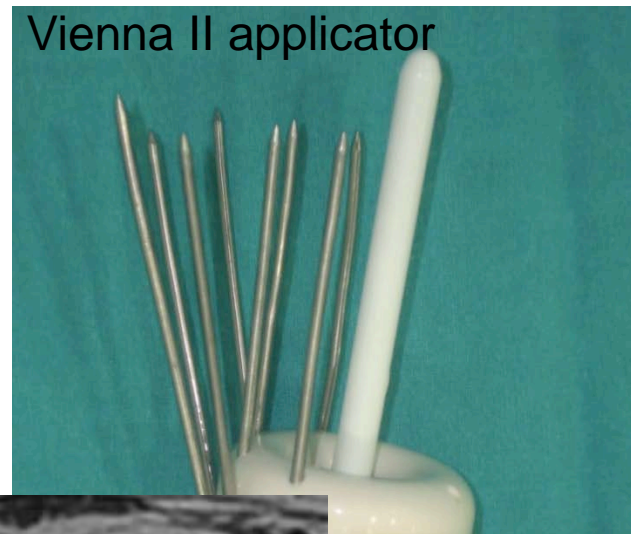
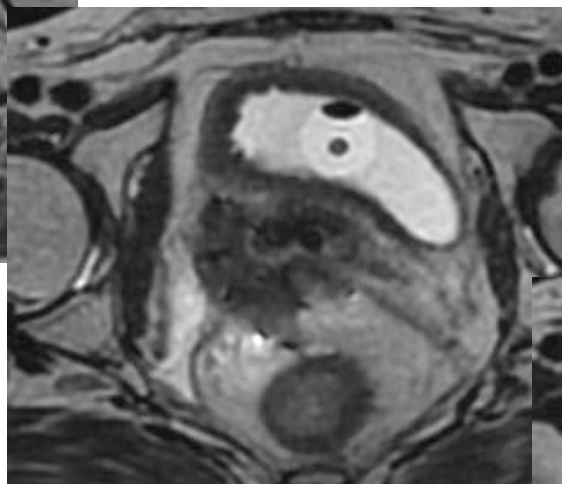


At BT





Serial Axial

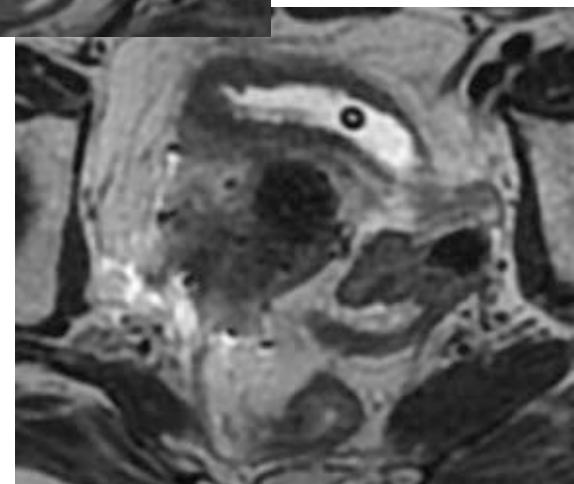
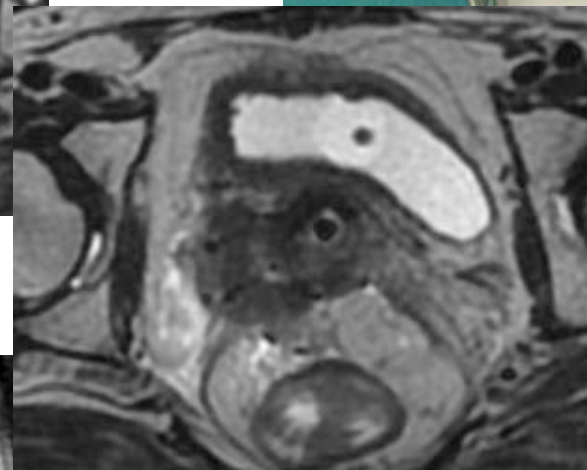


Vienna II applicator

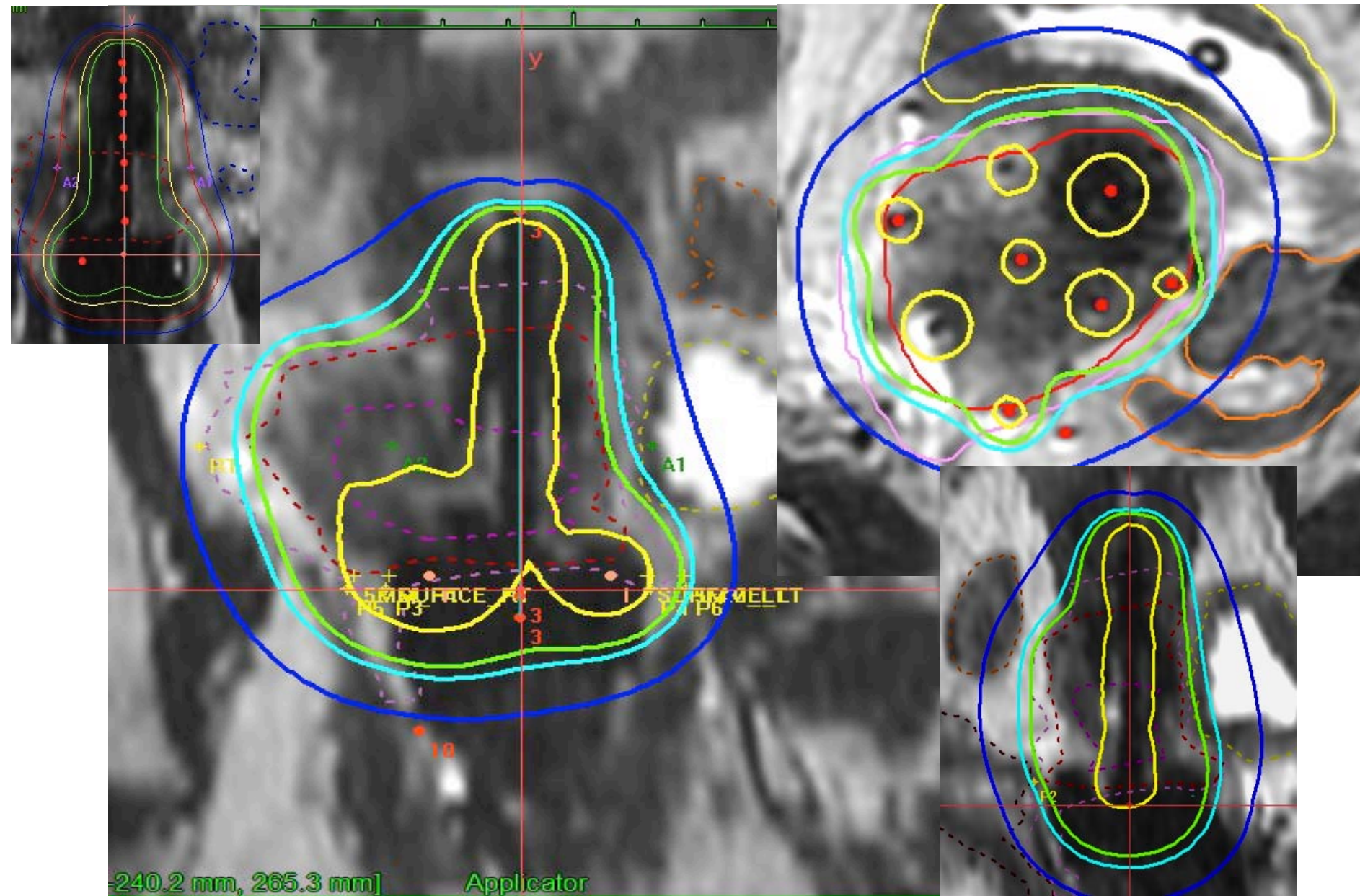
Sagittal



Coronal



Treatment planning / optimization



Dosimetric Comparison (1# BT)

Parameters	Ring STD ICA Only	Vienna with one set of needles	Vienna (with additional needles)
HRCTV D90 (Gy)	4.38	6.2	8.3
HRCTV D98 (Gy)	3.45	4.5	7.0
SIGMOID 2CC	4.6	4.5	4.1
SIGMOID 0.1CC	6.1	5.8	5.2
BLADDER 2CC	7.9	6.5	5.5
BLADDER 0.1CC	10.2	8.5	6.5
RECTUM 2CC	3.9	3.8	4.2
RECTUM 0.1 CC	5.4	5.3	5.6

PLAN EVALUATION

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

			Planning aim	Prescribed dose
CTV_{HR}	D₉₀	EQD2 ₁₀	≥ 85 Gy	96.2 Gy
Bladder	D_{2cm³}	EQD2 ₃	≤ 90 Gy	82.9 Gy
Rectum	D_{2cm³}	EQD2 ₃	≤ 70 Gy	68.3 Gy
Sigmoid	D_{2cm³}	EQD2 ₃	≤ 70 Gy	67.4 Gy

Post treatment 3months follow-up

Clinical and MR findings

- **Portio:** Cervix flush with vagina;
- **Vagina:** Vaginal wall Normal
- **Parametria:** Right parametrium : fibrosed

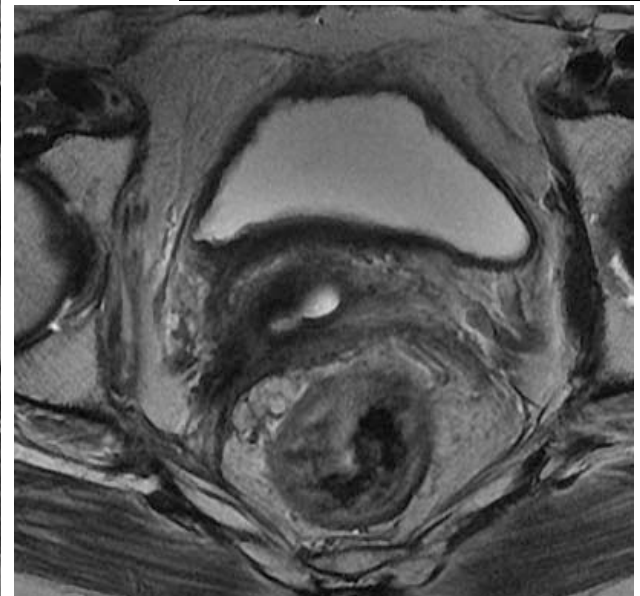
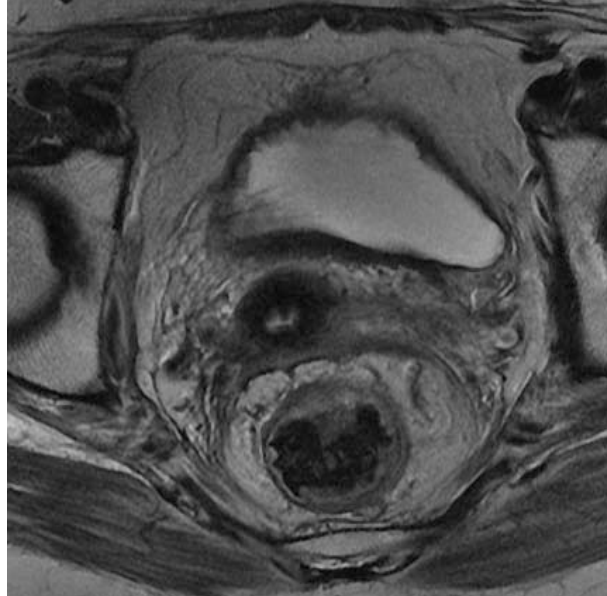
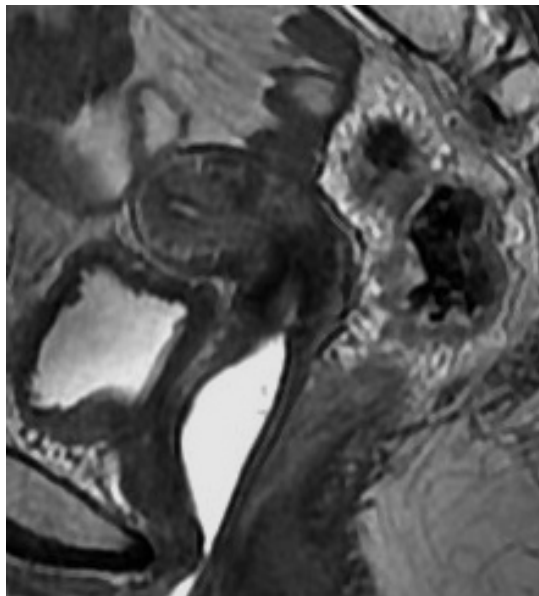


Clinico - Radiologically: Complete Response

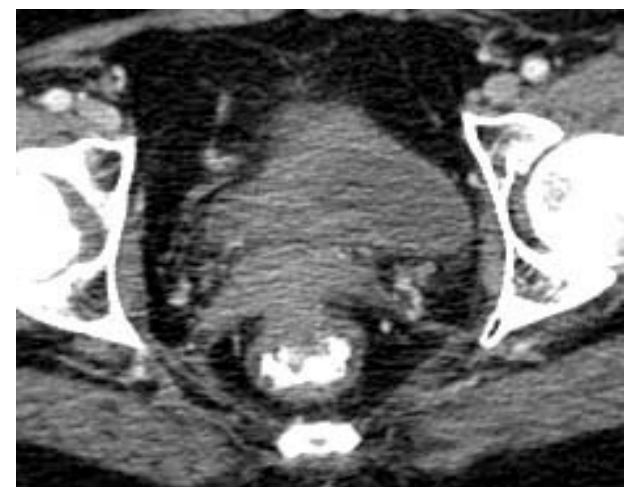
Post treatment 12 months follow-up

Clinical and MR findings

- **Portio:** Cervix flushed with vagina; No growth Palpable / seen
- **Vagina:** Normal
- **Parametria:** Rt para fibrosed ; Lt para supple
- **Sexual Activity :** Normal
- **CBC & renal function tests:** normal



Post RT 36 months
follow-up CT Images



DOSIMETRIC COMPARISON: Retrospective Vs Prospective Data Vs Literature

	Vienna (IC)	VIE (IC/IS)	Brabandere	TMH: RD	TMH: PD
HRCTV					
Vol in cc	34 +/- 17	44 +/- 27	48+/-19	45.2 ± 15.8	46.9+24.6
D100	66 +/- 7	70 +/- 6	64+/-6	54.1 ± 6.5	65.7+4.6
D90	87 +/-10	96 +/- 12	79+/-7	70.9 ± 10.6	88.3+4.4
Avg. Pt A	82 +/- 9	--	79+/-5	73.4 ± 4.5	93.1 ±24.8
Bladder					

LESSONS LEARNT

Prospective Data: 94 patients

HR-CTV Volumes larger: Advanced Stages

Higher doses to HR-CTV

Bladder and Sigmoid Doses Better

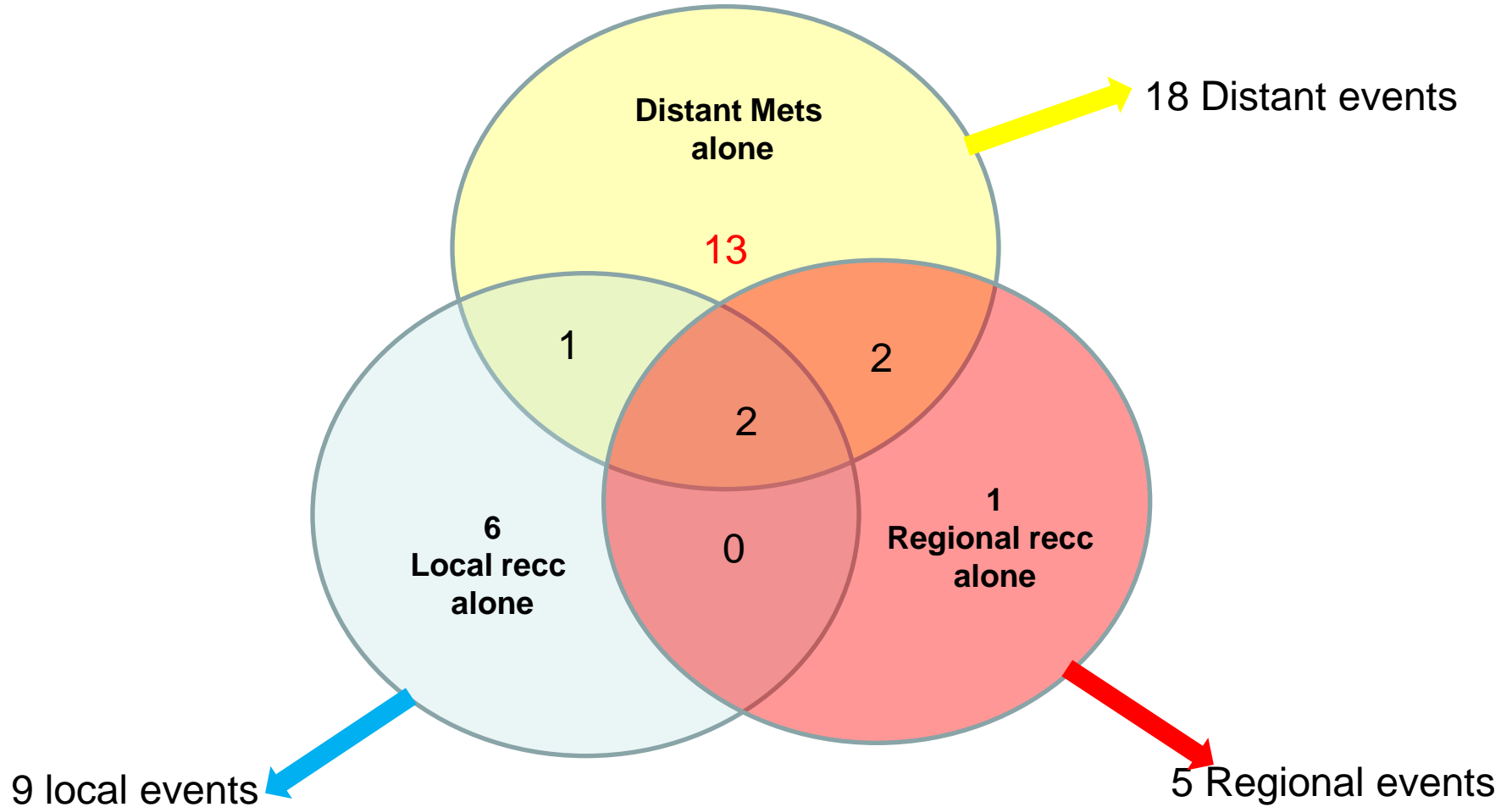
				80.4 ± 34.4	76.4 ±15.5
				139.1 ± 54.7	109.6 ±19.7
				93.4 ± 24.6	85.7+9.8
				63.5 ± 8.1	68 ±7.9
				66 ± 9.9	71.5 ±7.5
				57.8 ± 7.7	65.5+7.2
D0.1cc	79 +/- 12	85 +/- 14	82+/-13	109.4 ± 45.2	74 ±8.6
D2cc	63 +/- 7	67 +/- 7	68+/-7	74.6 ± 19.6	67+8.8

TMH – Embrace Outcomes

Total 94 patients : stage IIB-IV A

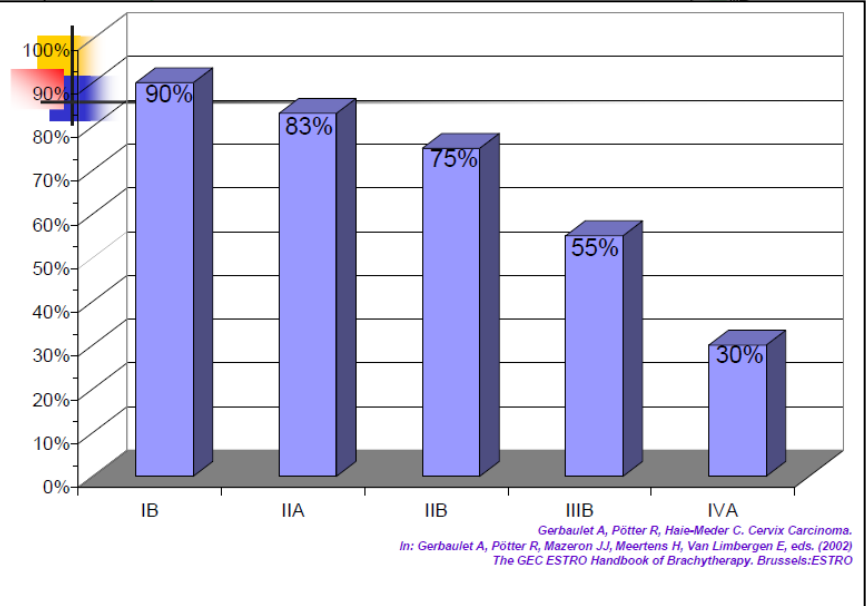
Median Follow up 39 months

Overall Relapses : 25 pts (26.6%)



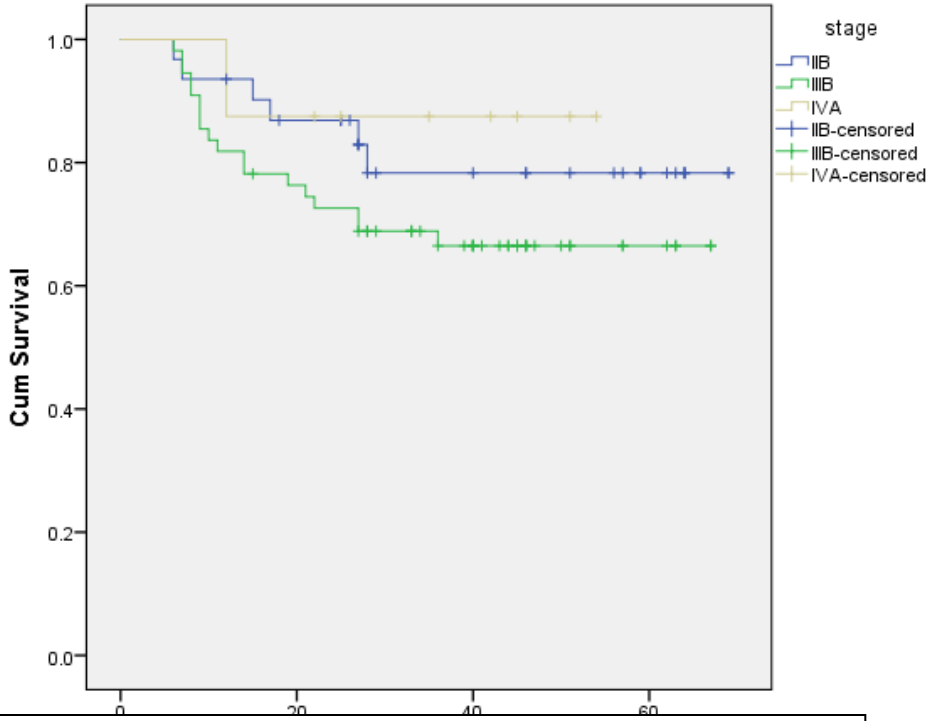
Actuarial local control

Survival Functions



Progression free survival

Survival Functions

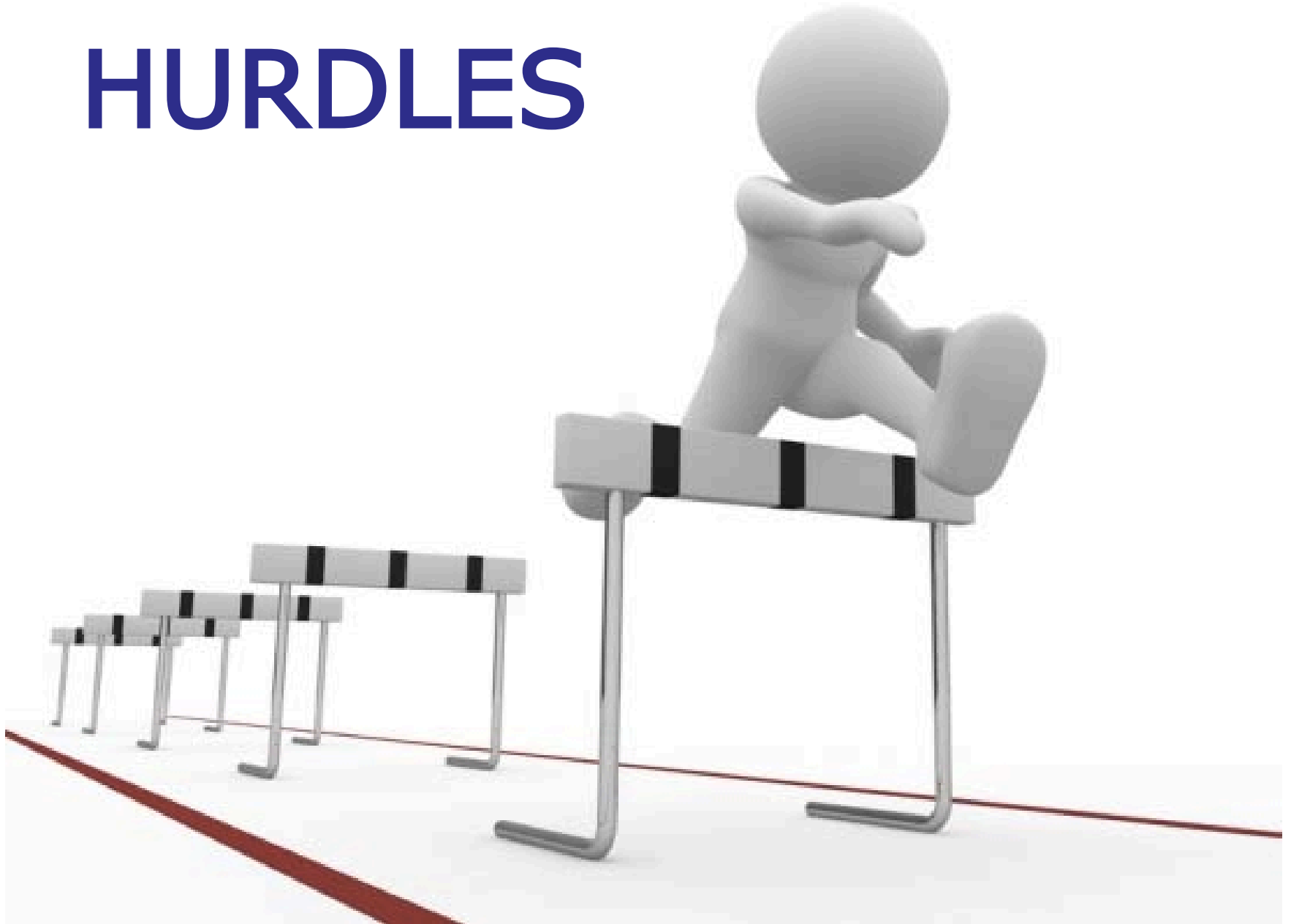


	2D	2D + CT	3D + CT	
IIB	75%	85%	96-100%	~ 11%
IIIB	55%	65%	84-86%	~ 20%

IIIB	55	9	46	83.6%
IVA	8	0	8	100.0%
Overall	94	9	85	90.4%

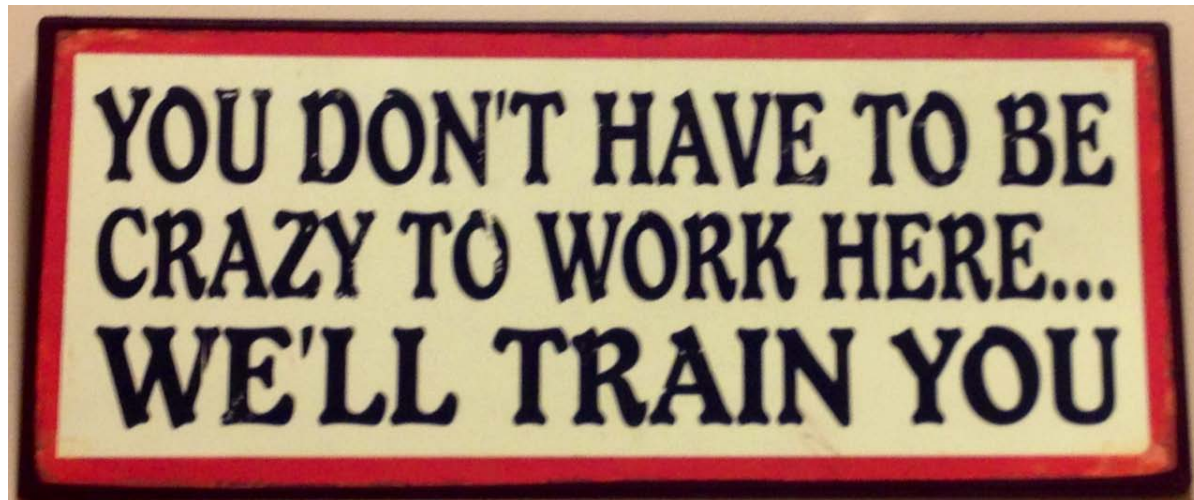
IIB	94	9	25	26.4%
IIIB	55	18	37	67.3%
IVA	8	1	7	87.5%
Overall	94	25	69	73.4%

HURDLES



Brachytherapy Skills

*Work hard to Strengthen your skills
like laparoscopic and Robotic Surgeons!!*



COMMITMENT!

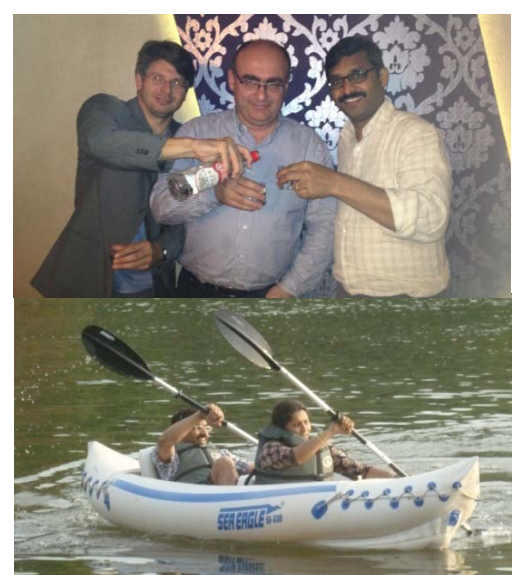
BE OPTIMISTIC!



Communication, Co-ordination and Leadership

*Co-ordination with Radiologist , Anesthetist,
Physicist, Technologist and others*

Discussion
Interaction
Teaching
PARTY!



Train Your Contouring and pass your knowledge to your friends ;)

ABOUT THE SCHOOL
LIVE COURSES
E-LEARNING
FALCON
Online Delineation Workshop - Gynaecological Cancer
Online Delineation Workshop - Head and Neck Cancer
EAGLE
DOVE
EUROPEAN TRAINING
PUBLICATIONS
GRANTS
FAQ

FALCON

Fellowship in Anatomic deLineation & CONtouring

ONLINE DELINEATION WORKSHOP ON GYNAECOLOGICAL CANCER

10-24 October, 2014

Faculty
Workshop Director
Umesh Mahantshetty, Radiation Oncologist, Tata Memorial Hospital, Mumbai, India

Gynaecological Cancer Specialist
Ina Jurgenliemk-Schulz, Radiation Oncologist, University Medical Centre, Utrecht, The Netherlands

Aims
The workshop will be conducted through three interactive web conference sessions that offer the opportunity to compare delineations from participants and experts and discuss inter-observer variability and the available guidelines.

Target Group
This online delineation workshop is aimed at junior clinical or radiation oncologists who wish to improve their contouring skills or at more senior specialists who want to refresh and validate their knowledge and skills in this field.
This workshop is mainly directed for participants coming from Asia and Australia. Participants from those regions will be given priority. RANZCR, JASTRO and AROI all have an allocation of 25 participants. Additionally places will be given on "first come first serve" basis.

Educational Programme
All sessions will start at 18.00 AEDT (Sydney time)

1st session, 10 October:
-presentation of the programme of the workshop and the methodology
-presentation of the workshop and how to communicate during the session

12 years of "GYN" ESTRO Teaching Course: around 2000 participants

Merci - Thank you

Sleeping and freeeeezing faculty



17th Edition of TC, Toronto 2016

MR-based Brachytherapy for Cervical Cancer

Cross Cancer Institute Experience

E Wiebe, F Huang, G Menon, W Read, B Rose,
M Dickey, L Kellogg, J Zimmer, R Pearcey

CARO-ESTRO
Canadian Community of Practice
April 6, 2016

Cross Cancer Institute

- Edmonton, AB
- Tertiary cancer centre (one of 2 in AB)
- Urban/rural catchment ~1.5 million
 - also northern AB, +/- central AB, NWT
 - historically also NE BC, YK, NW SK
- In-house facilities
 - Operating room (no ICU)
 - Oncology-focused Diagnostic Imaging
 - Ultrasound to OR
 - 1.5T MRI
 - PET/CT
 - 53 inpatient beds: 2 dedicated to PDR



MR-BT at CCI

Pilot Study

2008-2010



EMBRACE I

2010-2015



MR-BT standard

Nov 2011



Combined IC-IS

Since 2013

~20 patients

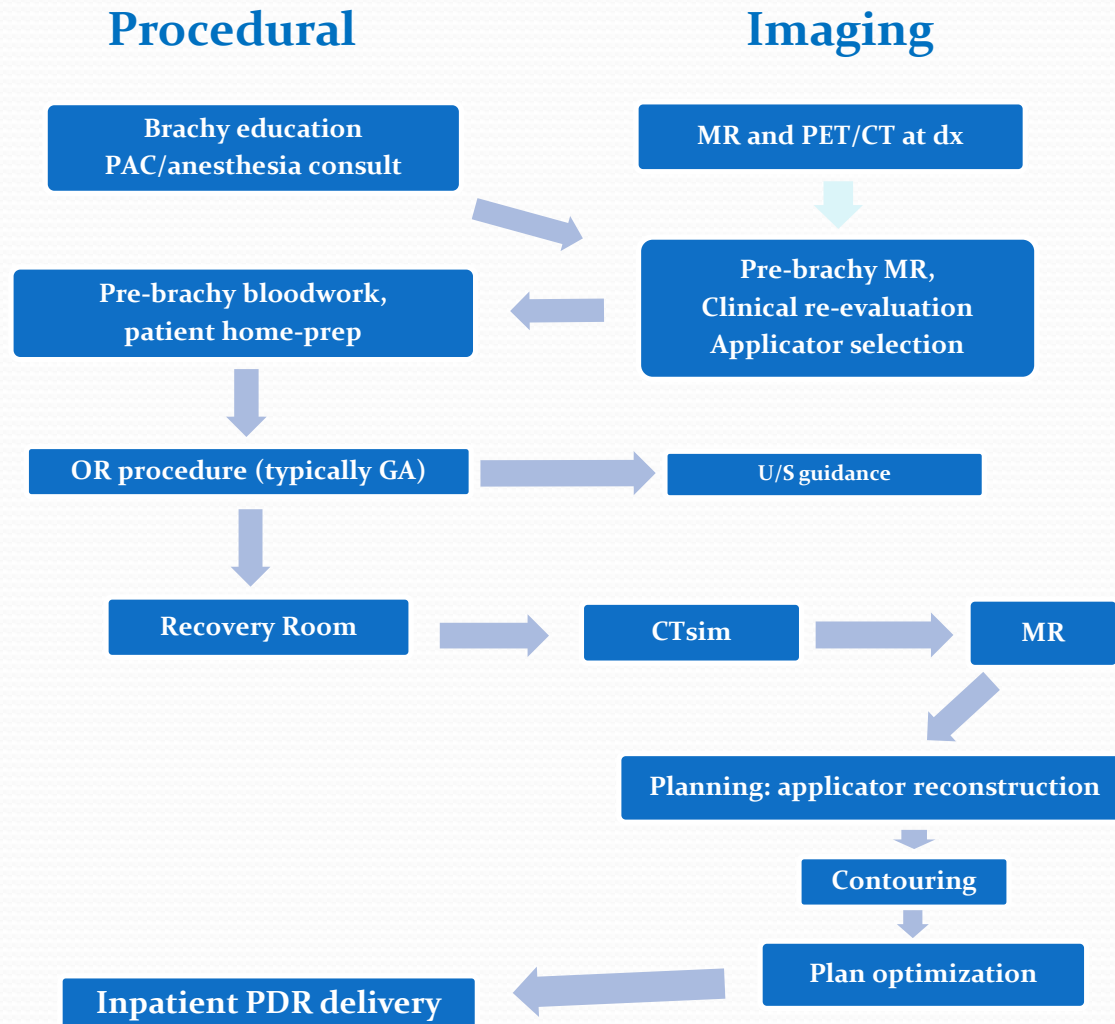
63 patients

Total experience 155+ cases MR-BT

Currently ~50% with IS; 25+ IC-IS cases



Current workflow for MR-BT



The Team (2007 – present)

- Radiation Oncology
 - Robert Pearcey
 - Fleur Huang
 - Ericka Wiebe
 - George Dundas
 - Julie Cuartero
 - Jim Rose
- Brachytherapy
 - Wendy Read
 - Kim Gadbois
 - Janet Zimmer
 - Rebecca Petit
 - Kitta Thavone
 - Sherry Riddell
 - Brenda Rose
- Physics
 - Ron Sloboda
 - Geetha Menon
 - Don Robinson
- Extra-departmental
 - OR: anesthetists, nurses
 - Ward: hospitalists, nurses
 - DI: radiologists, ultrasonographers, MRI techs
- CT Simulator
 - Rotating
- Planning/dosimetry
 - Leanne Kellogg
 - Mike Dickey
 - Brenda Rose
 - Lori Underwood
 - Doreen Anderson
 - Lee-Anne Polkosnik

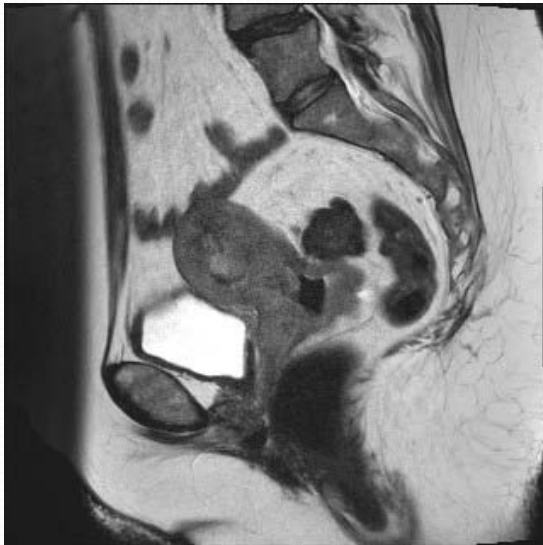
Radiotherapy for Cervix Ca

- Simulation
 - 2 CTsim
- External beam radiotherapy
 - 7 linacs (5 VMAT-capable), 1 tomo
- Brachytherapy
 - 1 HDR (Ir-192: 10 Ci nominal activity)
 - 2 PDR (Ir-192: 0.5 Ci nominal activity)
 - range of commercial applicators in clinical use
 - tandem+ring (with interstitial option)
 - tandem+ovoids (with interstitial option)
 - tandem+cylinder (with multichannel option)

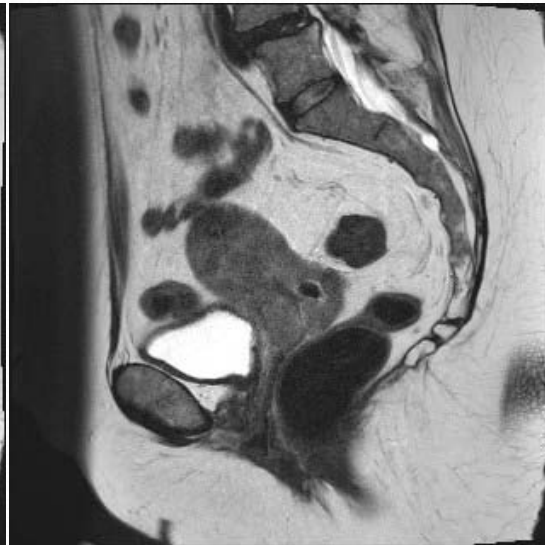


FIGO IIIB Squamous Cell Ca

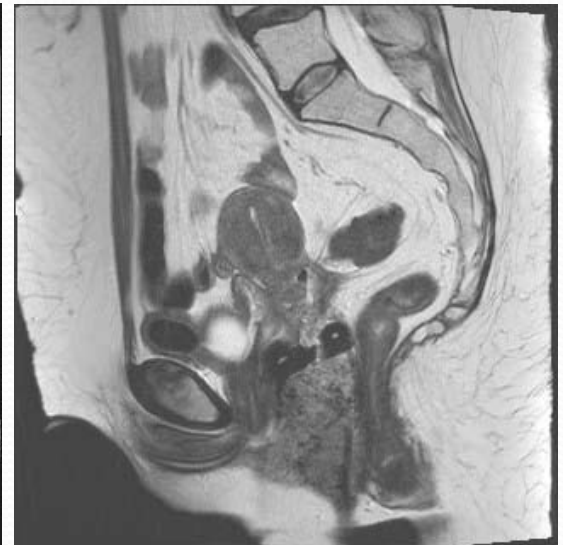
L hydronephrosis, bilateral parametria +, 8 cm cervix centrally necrotic and eroded, anterior vaginal involvement; pelvic & PA-N+



At Diagnosis



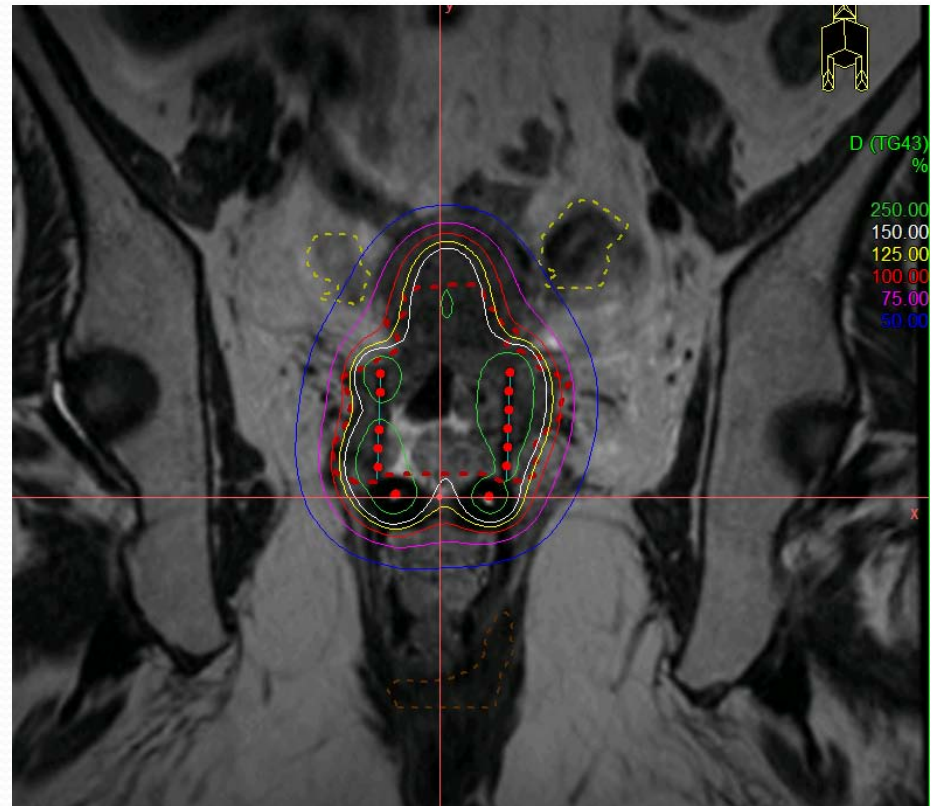
**After 45 Gy EBRT + SIBT:
partial response**



At Brachytherapy

Bulky Tumour, Partial Response

	EQD ₂
HR-CTV D ₉₀	88.4 Gy ₁₀
HR-CTV D ₉₈	75.7 Gy ₁₀
Rectum D _{2cc}	58.9 Gy ₃
Sigmoid D _{2cc}	70.1 Gy ₃
Bladder D _{2cc}	89.3 Gy ₃



HR-CTV = 60.6 cc

Implementation of MR-BT

- Exploration & Installation
 - Structures (e.g. second PDR room in 2010)
 - Processes (e.g. MR booking)
- Initial Implementation
 - Transitioning (e.g. From LDR to PDR in tandem with MR-BT)
 - Resource allocation (e.g. research-use 3T MR)
- Full Implementation
 - Interdepartmental support (e.g. access to clinical-use 1.5T MR)
- Sustaining & Building
 - Dynamic: adapt processes (e.g. workflow modifications)

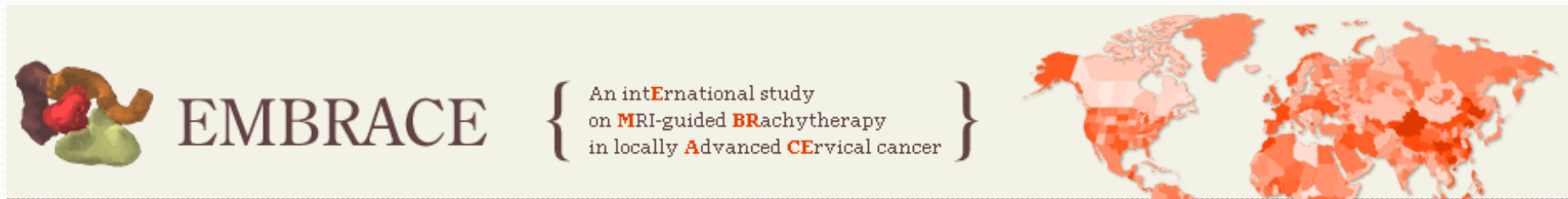
What helped

- People
 - MR-BT trained radiation oncologists
 - Dedicated brachytherapy dosimetrists & brachytherapists
 - Cross-training: brachytherapist transitioned to planning
- Communication
 - Extra-departmental partners (e.g. Diagnostic Imaging)
 - Open culture for discussion
- Training & Improvement
 - External meetings and courses
 - Team meetings: sharing learnings, MR-BT plan QA
 - Optimize clinical and operational processes

What helped

- EMBRACE framework
 - Participation 2010 – 2015 (n=63 enrolled on EMBRACE₁)
 - protocol as foundation for consistent practice
 - rationalize MR-BT endeavors
 - within and outside department
 - network for learning/sharing

... implementation was faster, easier, and of better quality



Current Topics of Interest

- Pre-planning
 - Current pre-brachy MR: ~4 days prior to brachy, without applicator in situ
- Routine U/S-guidance intra-operatively
 - U/S technician (DI) vs brachytherapist
 - Optimize U/S findings and guidance, ?role for trans-rectal
- Combined interstitial-intracavitary
 - Case selection, needle positioning

Future opportunities?

- Practicalities and patient-centered care
 - Efficiencies in workflow
 - Further optimization of planning strategies
 - PDR vs. HDR (outpatient?)
- Technical innovation
 - MR-linac (real-time guidance)
 - PET/MR
- Data driving
 - Synoptic reporting

Installing SPRING in Canada

Loading... Please Wait



Installation failed.
Error 404: SPRING not found.
SPRING is not available in your area.

Milestones

- 2007: PDR licensing
- 2008: first case with MRI (post-brachy)
- 2008: first case with ad hoc U/S guidance
- 2009: routine MRI pre-brachy
- 2009: moved from 3T MRI to 1.5T MRI
- 2010: full capacity for MR-BT (2 rooms)
- 2012: expanding applicator set (range of treatable geometries)
- 2013: first hybrid intracavitary/interstitial case
- 2013: stopped using Gado in packing
- 2013: routine intra-op U/S via DI
- 2015: routine practice of “ruling out” interstitial component
- 2015: routine SIB instead of sequential nodal boost

MR Guided Cervix Brachytherapy: London Experience

Vikram Velker

Radiation Oncologist , London Regional Cancer Program
Assistant Professor, Western University

London...Ontario

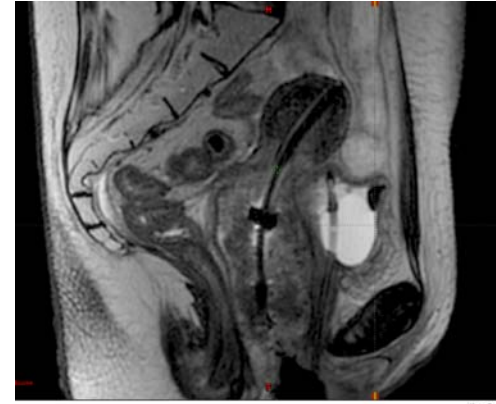


London Ontario Brachytherapy Program

- Radical cervix cases seen per year (~30-40)
 - Cervix HDR brachytherapy implants performed
 - Tandem and Ring
 - Tandem and Ovoids
 - Hybrid Interstitial (tandem, cylinder + needles)
 - Collaboration with regional cancer centres
 - EBRT at home centre, Brachytherapy in London
 - Active interstitial implant program since 2004
 - In last year, referrals from multiple Ontario centres for implants

Dose and fractionation

- Most patients:
 - 28 Gy in 4 fractions (700 cGy/fx)
 - 2 insertions one week apart
 - Start during last week of external beam treatment
 - 2 fractions with each insertion (at least 6 hours apart)
 - 900 cGy x 2 (single implant) has been used in select cases (*Patil, Brachytherapy 2011*)



Brachytherapy Work flow (Implant #1)

Day 0

Admitted in afternoon to inpatient ward

- Blood work
- NPO at midnight

Day 1

EUA and Insertion under anaesthesia (1 hr)

- Intraop U/S verification

CT simulation

MR simulation

Planning, Contouring, QA

1st fraction delivered

Day 2

2nd fraction delivered

Applicators removed

- Awake, midazolam offered

Brachytherapy Work flow (Implant #2)

Day 0

Admitted in afternoon to inpatient ward

- Blood work
- NPO at midnight

Day 1

Insertion under anaesthesia (1 hr)

- Intraop U/S verification

CT simulation

MR simulation

Planning, Contouring, QA

3rd fraction delivered

Day 2

4th fraction delivered

Applicators removed

- Awake, midazolam offered

MR utilization

- MR guidance for contouring implemented since: November 2011 (>150 cases completed)
- MR is shared resource with hospital
- MR-CT Hybrid Planning
 - MR performed following week 1 insertion
 - Fuse for week 2, import previous contours and modify
 - If interstitial implant to be used for 1st insertion -> MR sim with cylinder week prior to brachy -> then fused

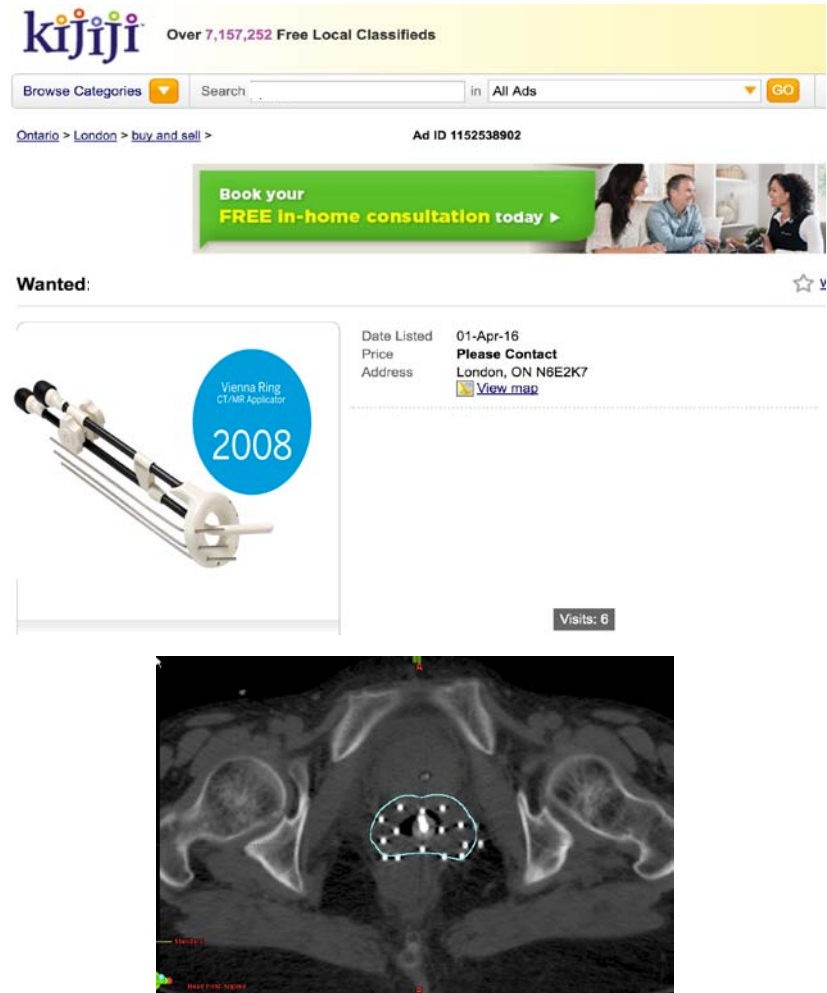
MR guided planning

- GEC-ESTRO volumes
 - Delineate HR-CTV, IR-CTV, OARs
 - Incorporate EUA findings
- Manual optimization
 - Start with pear shaped distribution
 - Modify to ensure coverage of the HR-CTV
 - Reduce/optimize OAR doses
 - We report dose coverage of volumes and Pt A dose



“Hybrid” Interstitial

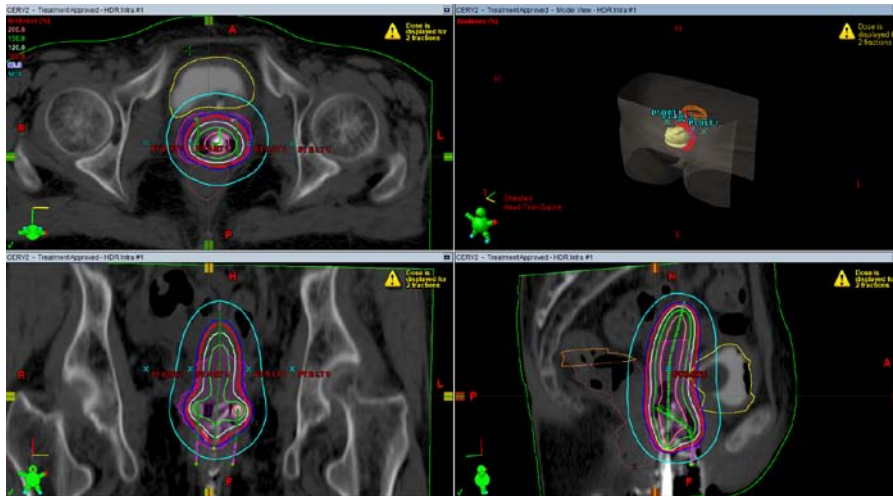
- Vienna applicator not yet available
- We use a perineal template with titanium needles
- If week 1 dose coverage conventional implant (ie. tandem and ring) suboptimal
 - Will treat 1 or 2 fractions
 - Week 2 will proceed with tandem, cylinder, and interstitial needles



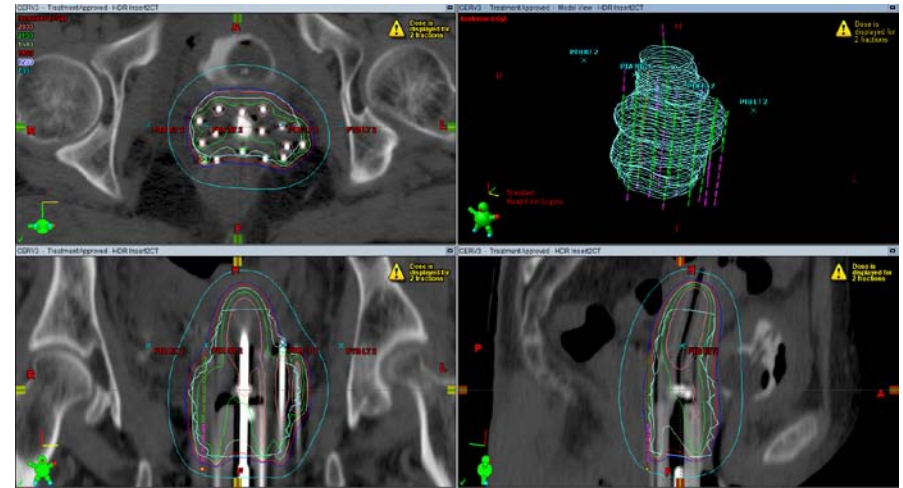
The image shows a screenshot of a Kijiji classified advertisement. At the top, the Kijiji logo is displayed with the text "Over 7,157,252 Free Local Classifieds". Below the logo is a search bar with "Browse Categories" and "GO" buttons. The ad is located in "Ontario > London > buy and sell" and has an "Ad ID 1152538902". A green banner at the top of the ad says "Book your FREE in-home consultation today". The ad is titled "Wanted:" and features a photograph of a "Vienna Ring CT/MR Applicator" with a blue circular badge that says "2008". To the right of the photo, the listing details are: "Date Listed: 01-Apr-16", "Price: Please Contact", and "Address: London, ON N6E2K7" with a "View map" link. A "Visits: 6" badge is located at the bottom right of the ad. Below the ad is a CT scan image of a pelvis with a blue outline of the applicator and several small white dots representing needles.

“Hybrid” Interstitial

Week 1: Tandem and Ovoids



Week 2: Hybrid Interstitial



Challenges

- Resource intense
 - Anesthesia time
 - Inpatient beds
- MRI not in RT department
- Patient transferred off stretcher for scans
- Interstitial template not MRI compatible
- Radiology collaboration for MR reporting
 - *“presence of brachytherapy applicators limits interpretation”*

Current refinements in progress

- Real time QA
 - 2 physicist
 - **2 physician** (one contours, one verifies)
- Dose prescription and planning standards
- Cervix physical exam reporting
 - documentation (3 dimensions) at consult/brachy



www.shutterstock.com · 305115008

Thank you

London Gyne Brachytherapy Team

– Radiation Oncologists

- David D'Souza
- Alex Hammond
- Eric Leung (Sunnybrook)
- Vikram Velker
- Brian Yaremko

– OR nurses

- Leanne Derrah
- Tammie Murray



– Medical Physics

- **Kathleen Surry**
- George Hajdok
- Doug Hoover
- **Hatim Fakir**

– Radiation Therapists

- **Quinn Benwell**
- Kathlin Crewdson
- Jason Jamieson
- Wendy Wells

MR Guided Cervix Brachytherapy: London Experience

Vikram Velker

Radiation Oncologist , London Regional Cancer Program
Assistant Professor, Western University

Canadian Interstitial Brachytherapy Contouring Study: Vaginal Tumours

Eric Leung, Odette Cancer Centre, Sunnybrook, Toronto

David D'Souza, London Regional Cancer Program

Ananth Ravi, Odette Cancer Centre, Sunnybrook, Toronto



Radiation Oncology
UNIVERSITY OF TORONTO



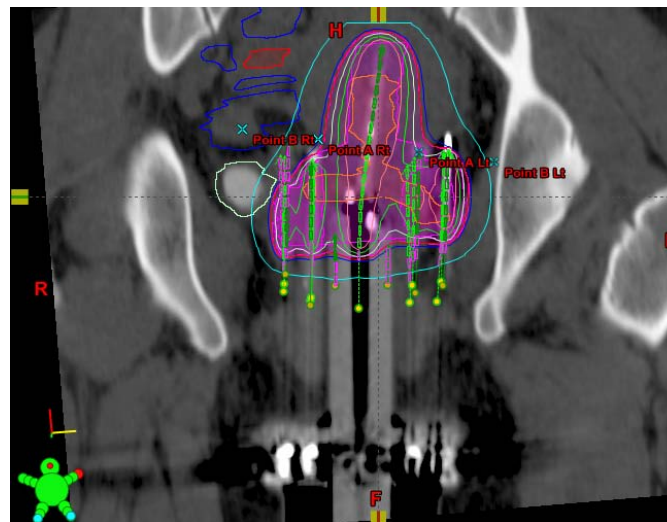
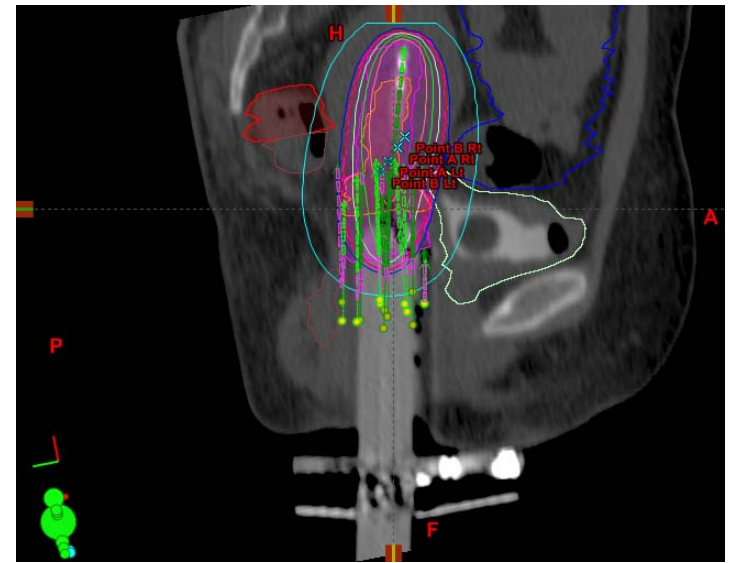
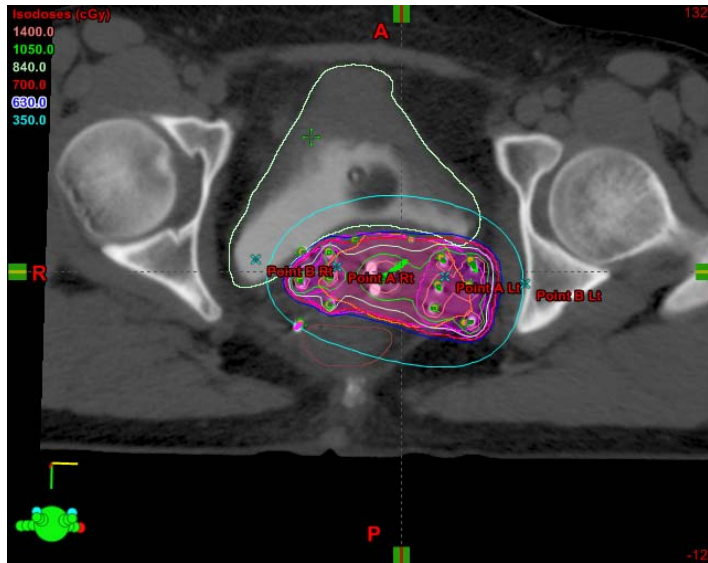
London Health Sciences Centre
London Regional Cancer Program



Sunnybrook
ODETTE CANCER CENTRE

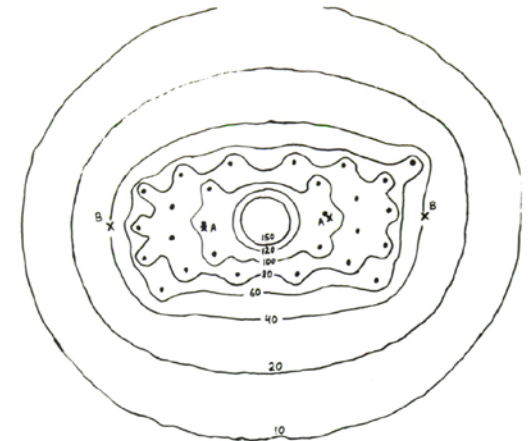
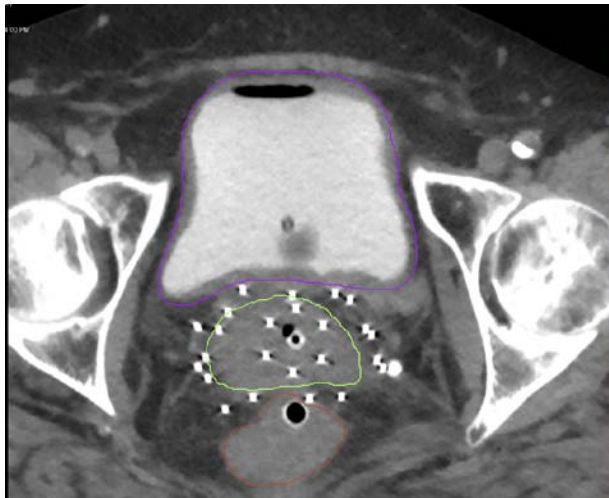
A Cancer Care Ontario Partner

Sunnybrook GYN Interstitial Brachytherapy



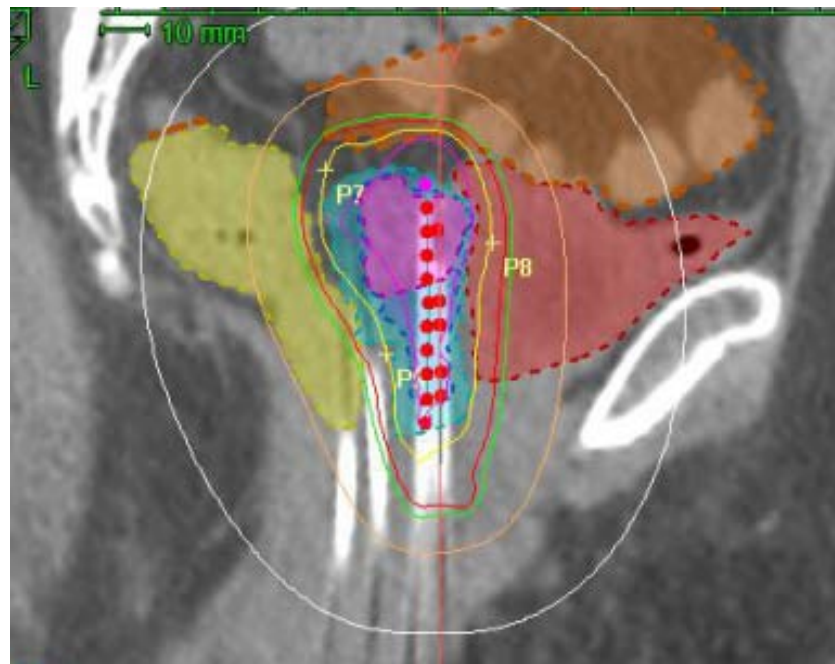
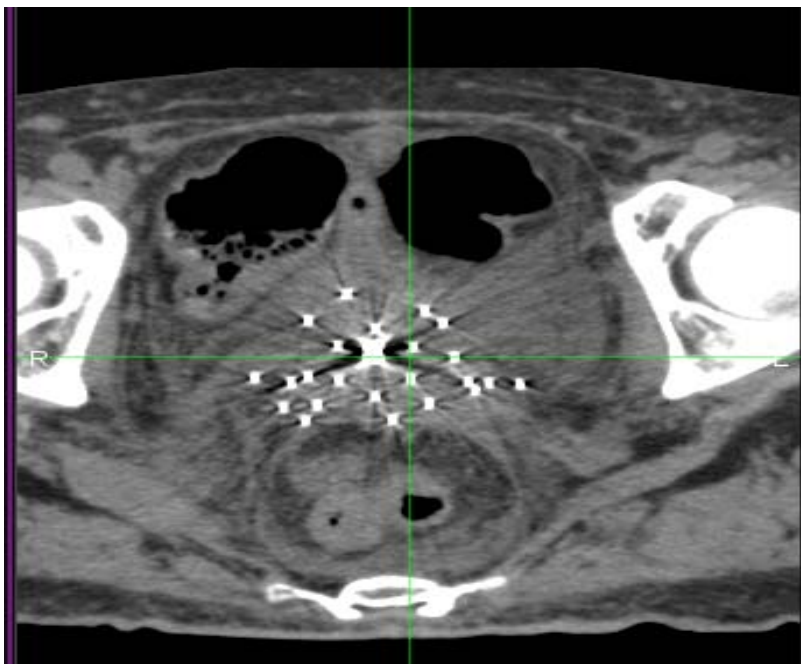
Interstitial Brachytherapy

- Interstitial Brachytherapy
- 2D => 3D
- Increasing experience in Canada

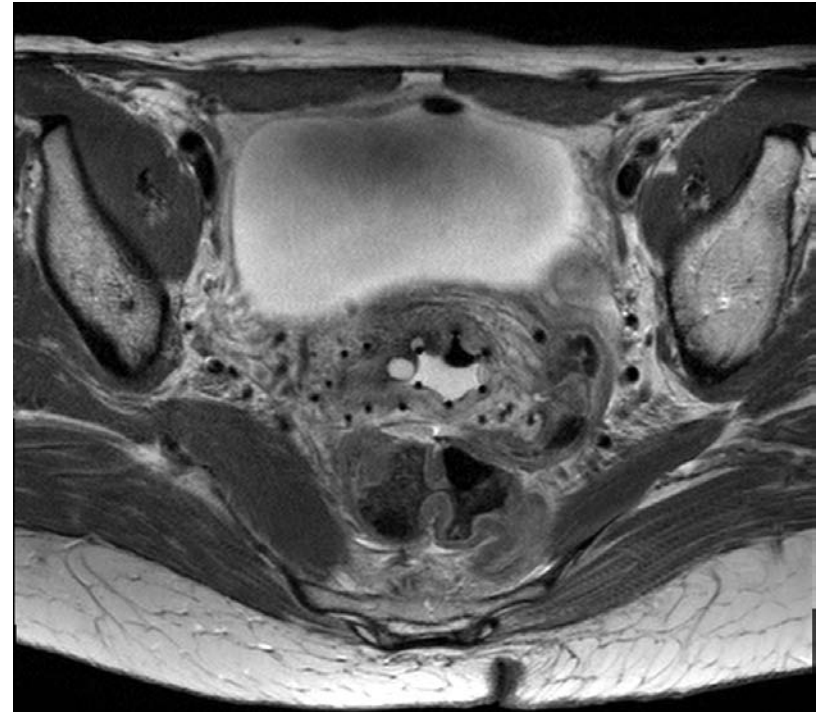


Aristizabel et al, 1983

3D Imaging

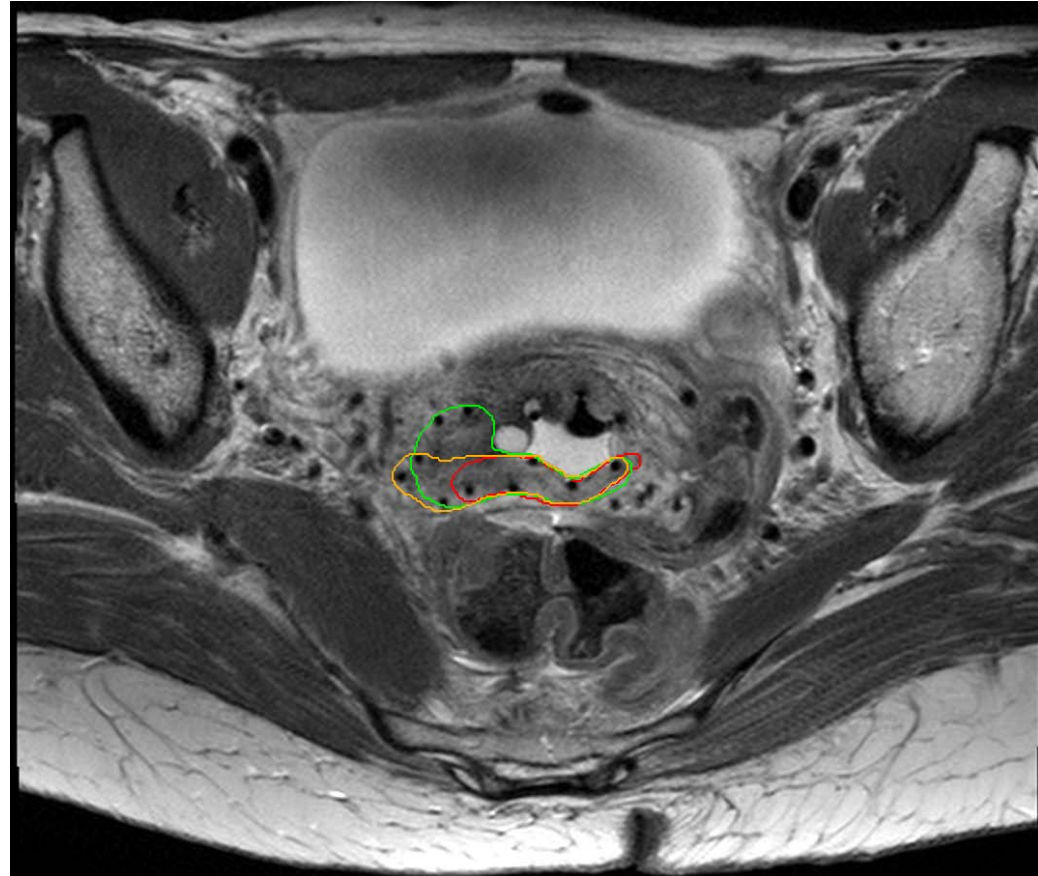


Contouring Variability



Contouring Study

- **Canadian Study**
- **Collaboration of interstitial brachy centres**
- **Vaginal tumours**



Methods

- **3 cases**
- **Provided material:**
 - **Clinical case**
 - **Clinical drawings at the time of diagnosis and brachy**
 - **MRI at diagnosis**
 - **MRI after external beam (pre-plan)**
- **Contour**
 - **CT with applicator**
 - **MRI with applicator**
- **Planning**



Collaboration

- Kelowna
- Edmonton
- Calgary
- Toronto
- Mississauga
- London
- Quebec
- Montreal
- Halifax
- additional centres?



eric.leung@sunnybrook.ca

Definitions

Fokdal

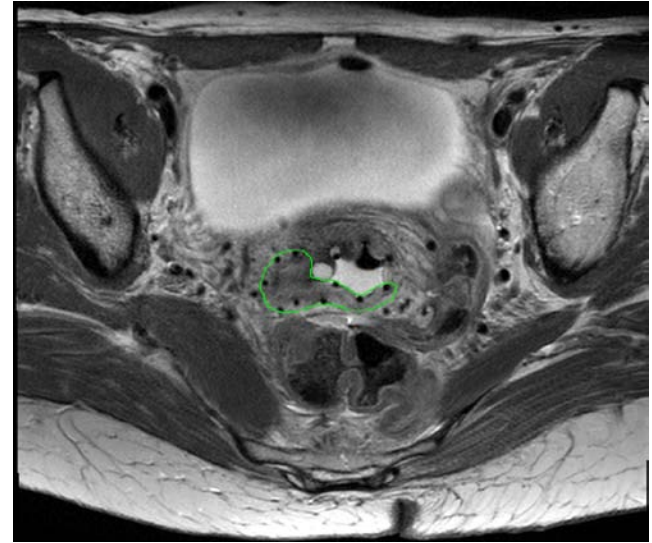
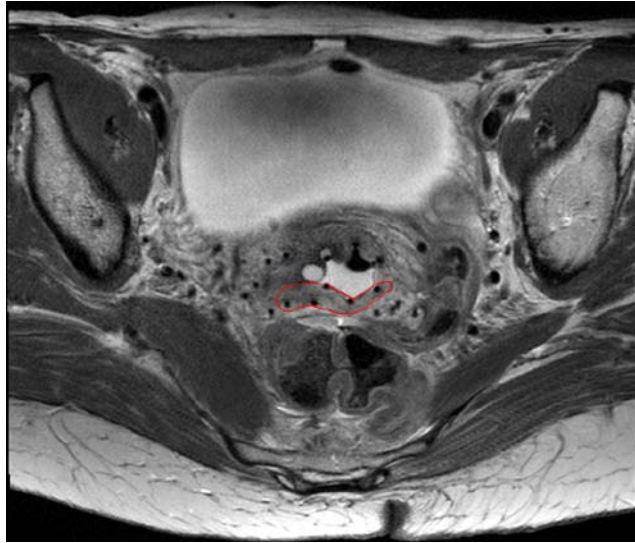
- GTVBT : high signal intensity
- HRCTV : **GTVBT + grey zones in parametrial, vagina and para-vagina**
- IRCTV : **10 mm margin to HRCTV, crop out OAR and applicator, add margin based on clinical exam and MRI at diagnosis to ensure full coverage to initial tumour volume**

Dimopoulos

- GTVBT : macroscopic tumour extension at the time of BT as detected by clinical exam and MRI (high signal intensity)
- HRCTV : **clinically palpable disease, residual disease as seen on MRI and grey zones plus circumference of entire vagina at level of residual tumour**
- IRCTV : carries microscopic tumour load and includes region of initial tumour extension plus remaining vagina due to possible submuscoel multifocal tumour spread



Contouring Variability



- Haussedorff tells the millimeter difference between 2 contours sets (1 millimeter boundary)
- **Collected doses on what was acceptable,**
 - Coverage of volumes
 - Heterogeneity
 - Dose to OAR
- **Take dose grid on consensus plan.**
 - Is this true concern in target coverage.
 - Is plan good enough.... Or contours good enough..

- **Data set**
- **Per voxel , look at all contours if in 95% of contours.**
- **Weight contouring on experience level.**

- **Contour Analysis Methods**
 - **STAPLE**
 - **Conformity index**
- **Consensus contour**
- **Planning**

- **Sunnybrook**
 - E, L, L, T
- **PMH**
 - M, K, A, J
- **Quebec**
 - E
- **Montreal**
 - M
- **L**
 - D, V
- **Edmonton**
 - E, F
- **Kelowna**
 - J, F

