Del punto A a la planificación Volumétrica: Cambiando la visión de la braquiterapia en el Cáncer de Cérvix

Gustavo Sarria Bardales, MD

Director General Departamento Radioterapia INEN AUNA

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Introduccion

Radioterapia ha empezado a sofisticarse aceleradamanete en la ultima decada , con el advenimiento y creciente rol de (**IMRT**), RT guiada por imagenes **(IGRT**), RT estereotactica ablativa (SABR), Radiocirugia (SRS**), RT Intraoperatoria**, 4D RT adaptativa, protones y **braquiterapia3D**. RT esta en continuo y acelerado desarrollo. La investigacion esta encontrando vias de refinamiento de nuevas tecnicas, combinaciones y reformulacion de aspectos radiobiologicos que afectaran la practica en esta decada pudiendo mejorar los resultados.

Vision for Radiotherapy 2014-2024.
National Health System (NHS) England & Cancer Reserach UK

Objetivos

- Reconocer los alcances y limitaciones de la braquiterapia basada en puntos para el cáncer ginecológico, paso 2D a 3D.
- Revisar las ventajas de la BATD 3D en cáncer de cérvix.
- Revisar los resultado obtenidos con IGABT en cáncer de cérvix.

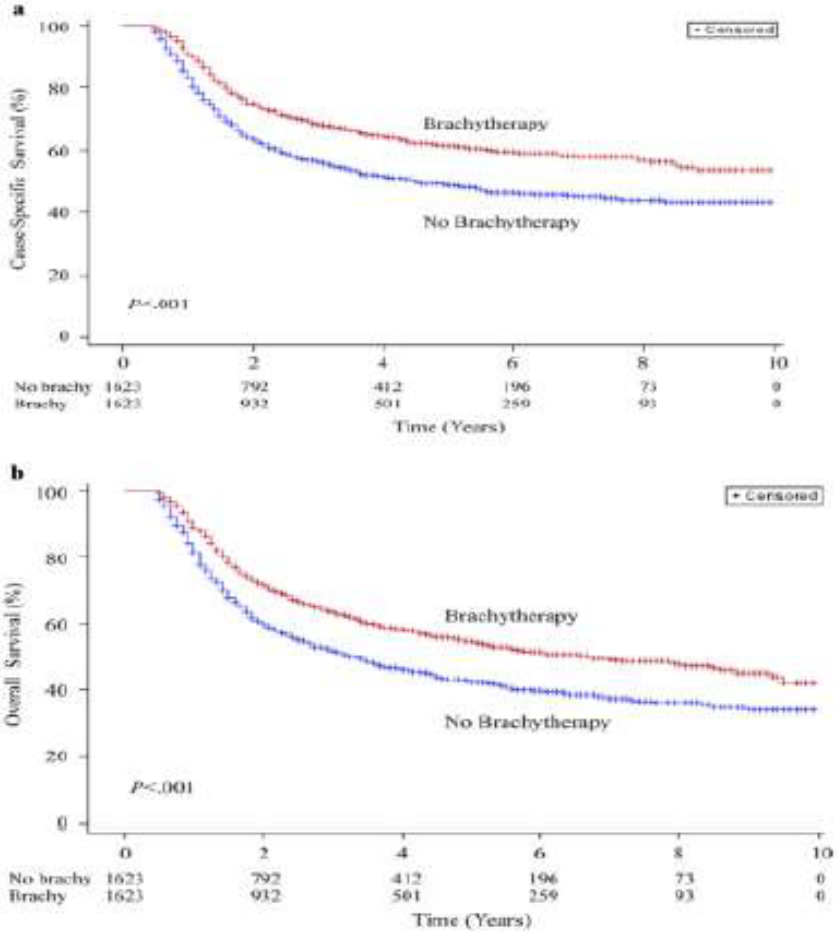
Brachytherapy in GYN cancer in USA

Decrease of Cancer specific survival

- 4-year CSS 64.3% vs 51.5%, P<.001

Decrease of Overall Survival

- 58.2% vs 46.2%, P<.001



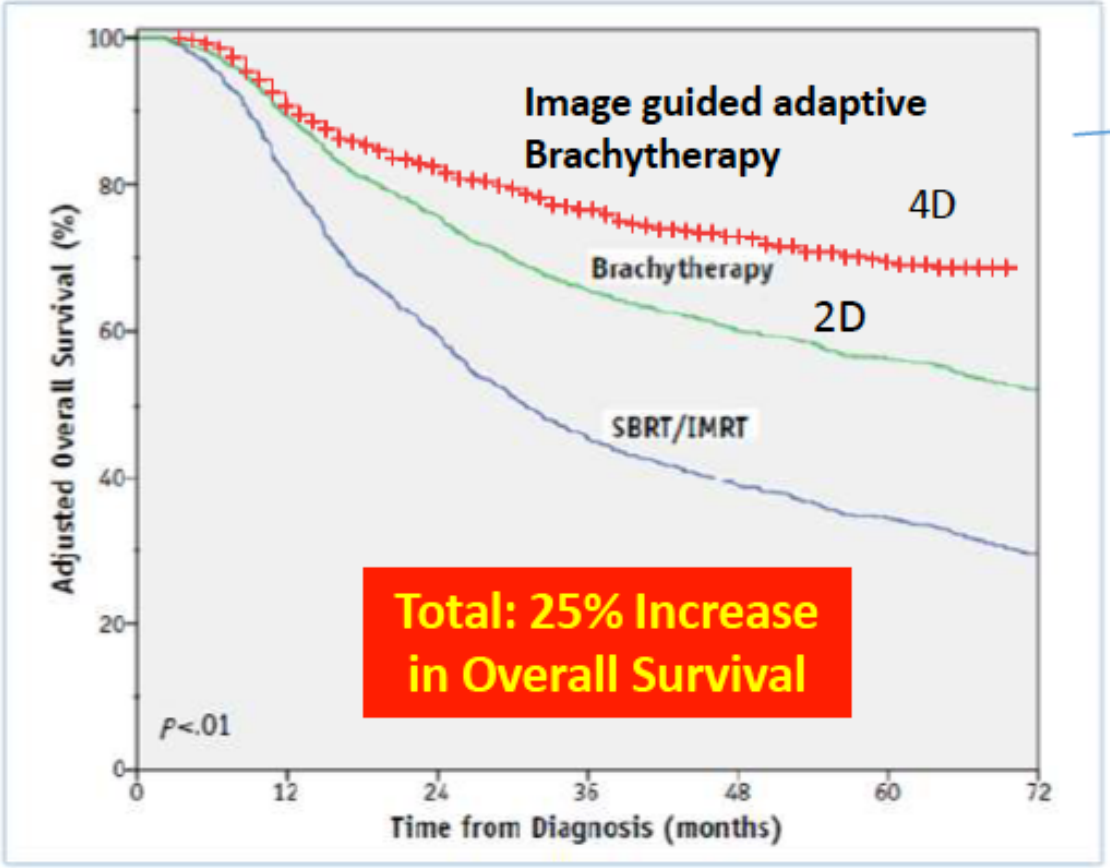
Han et al, IJROBP 87 (2013)

Fig. 2. Survival by brachytherapy use for matched cohort between 2000 and 2009. (a) Cause-specific survival; (b) overall survival, and (c) non-cancer-related survival.

Overall Survival locally advanced cervical cancer
SBRT/IMRT boost vs. 2D BT vs. 4D IGABT

Gill B et al.
IJROBP
2014;90:1083

Sturdza et al.
radiother. Oncol.
2016 (In Press)



ncepto Braquiterapia 2D 3D

Tradicionalmente la prescripción 2D referida a puntos
Habitualmente no es representaqtiva de lo que realmente sucede
En volúmenes de OAR y en el organo blanco
Los resultados han sido buenos pero esta por explicarse correlacion con las fallas de tratamiento y las toxicidades
(falta de consistencia entre las toxicidades y las dosis a puntos de referencia)

3D vs 2D?

Reflexion :

- **La aceptación y la implementación de imágenes y planeamiento para RT Externa ha estado lejos de los avances en braquiterapia**
- **La integración en braquiterapia es lenta por varias razones como disponibilidad de software, hardware, costo, tiempo y experiencia**
- **Pero vale la pena intentarlo y por que ?**

Racional

Mejorar el control local

Reducir morbilidad y toxicidad

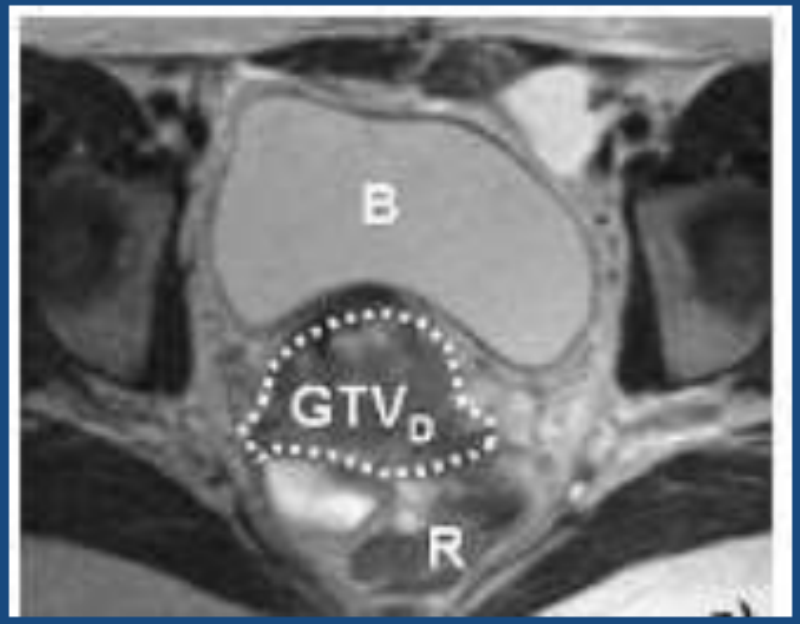
Mejorar la habilidad de predecir el pronostico

Mejorar sobrevida

Retos

Recursos y experiencia
Definir técnica optima (según realidad)
Reproductibilidad e incertidumbres de la delineación y
Planeamiento incluyendo dosimetría

Introduction



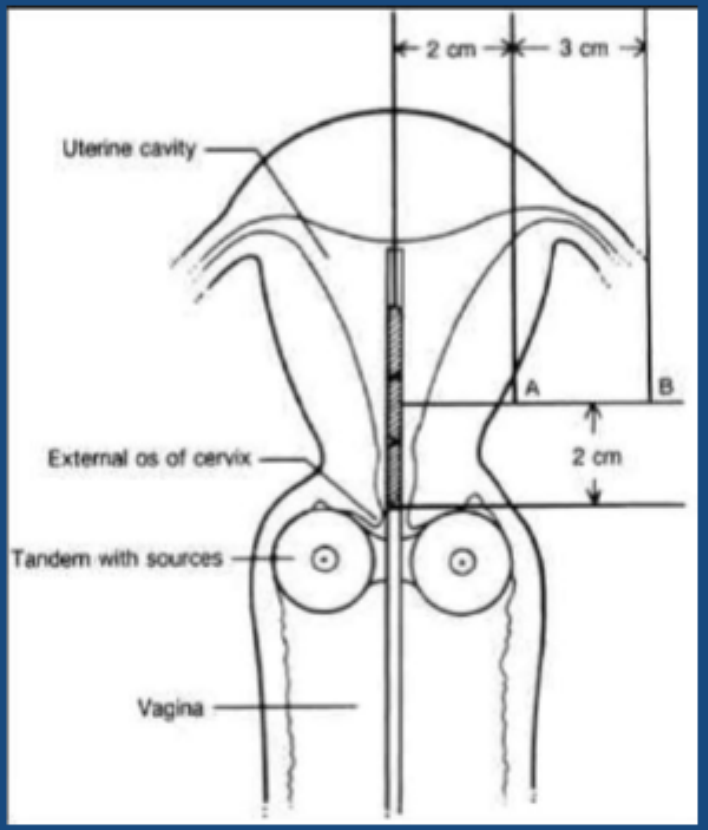
Dimopoulos Red J 2009

- Adoption of IGBT can be daunting for many practicing physicians, precluding its widespread adoption

Purpose

To de-mystify IGBT and provide a practical step-by-step approach to making a successful transition from Point A-based treatment to IGBT

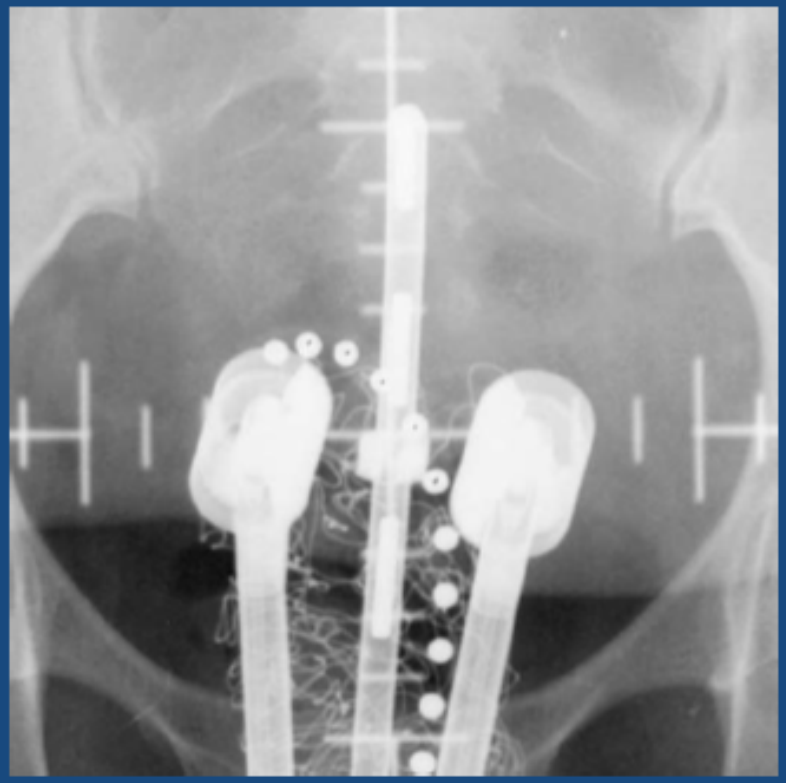
Goodbye Point A!



Goodbye Point A

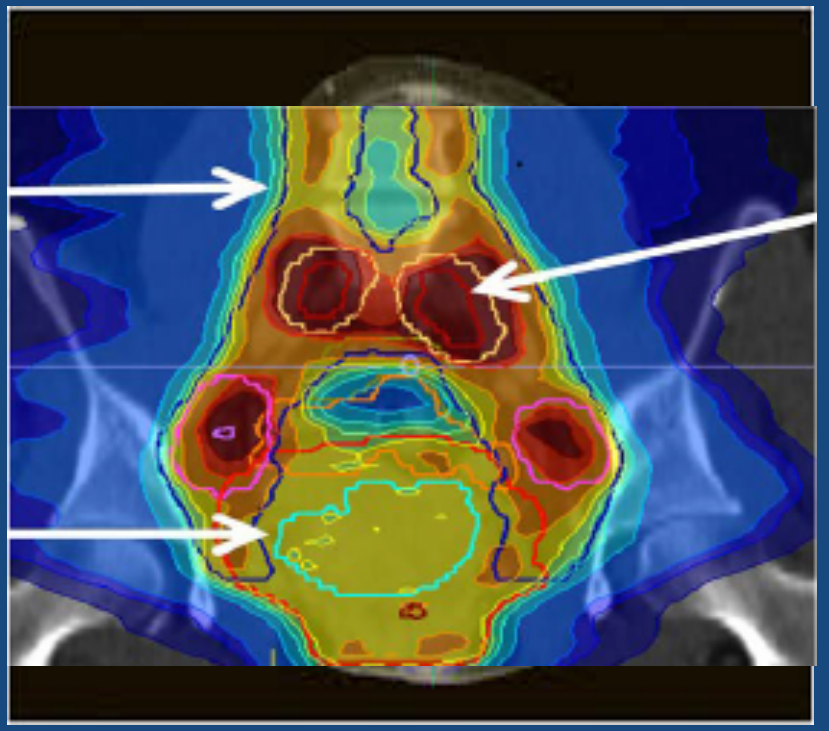
We've had our share of goodbyes in gynecologic radiation oncology

Goodbye LDR!



Hello HDR

Goodbye 4-Field Box!



Hello IMRT / VMAT

Goodbye Point A

- Each Goodbye has been hard
- We've all "grown up" with Point A and can't imagine using anything else
- But it is now time to say goodbye to Point A

Cuales son las barreras para IGBT?

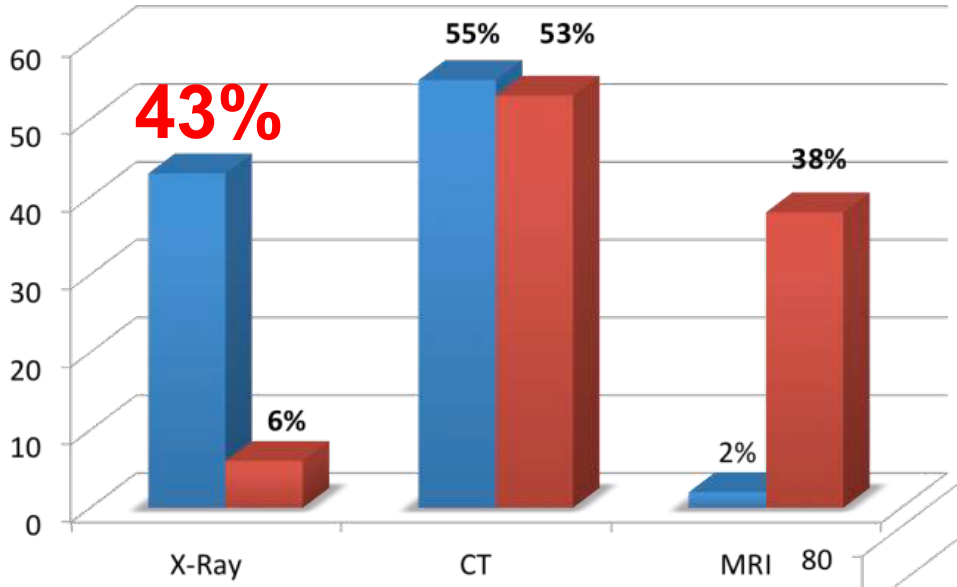
- No RM TEM en el departamento
- No se tienen los aplicadores correctos
- No se tiene el Staff
- No hay tiempo para contornear
- No experiencia en contorneo en RM
- No hay comodidad moviéndose del punto A
- No se tiene experiencia en intersticial
- No sabe por donde empezar
- La practica estándar funciona bien la mayoría del tiempo: por que cambiar?

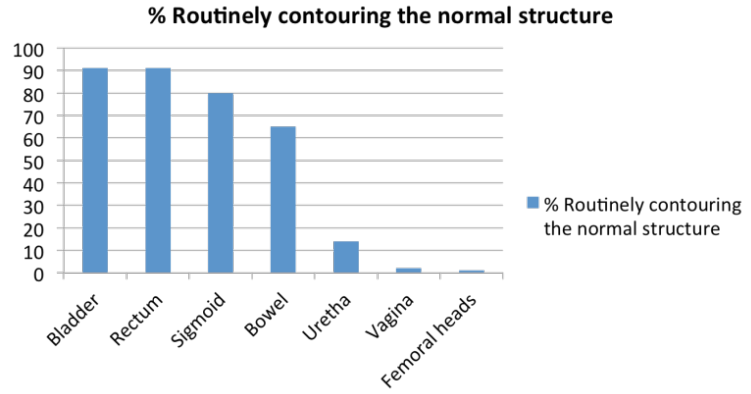
Results of Survey for 3D Brachytherapy

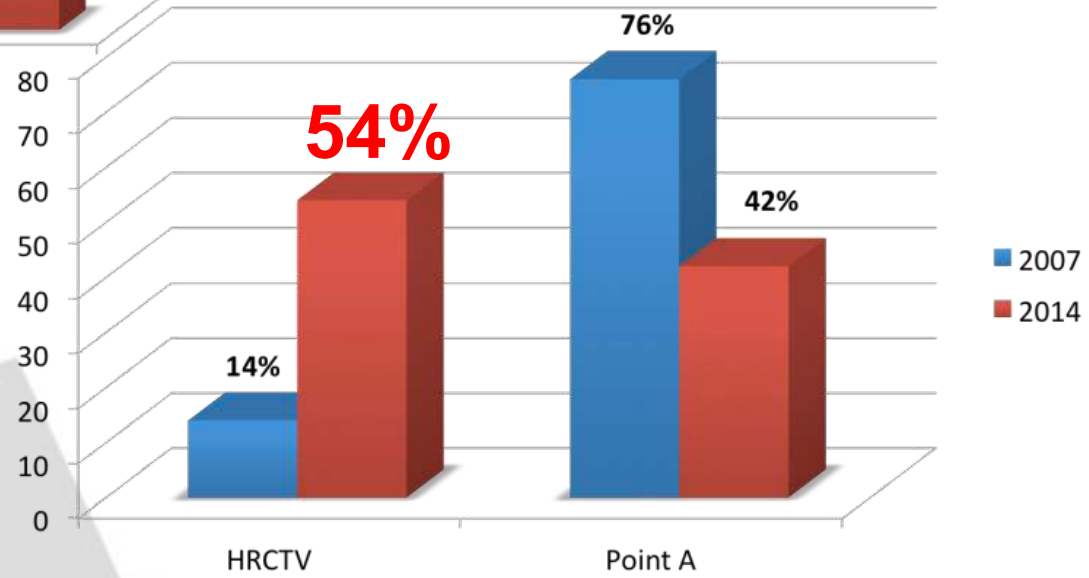
	Xray	Ct scan	MRI	2D/3D
ABS (2007)	43%	55%	2%	76%/14%
Canada	50%	45%	5%	50*%/44%
Australia NZ	30%	65%	15%	65%/35%
ABS survey (2014)	15%	95%	34%	42%/52%

The Challenge

- ABS 2014 Survey (IJROBP 2016;94:598-604)
  - Increasing use of image-based planning in US from 2007 - 2014
  - Still large gaps in the use of MR-based planning







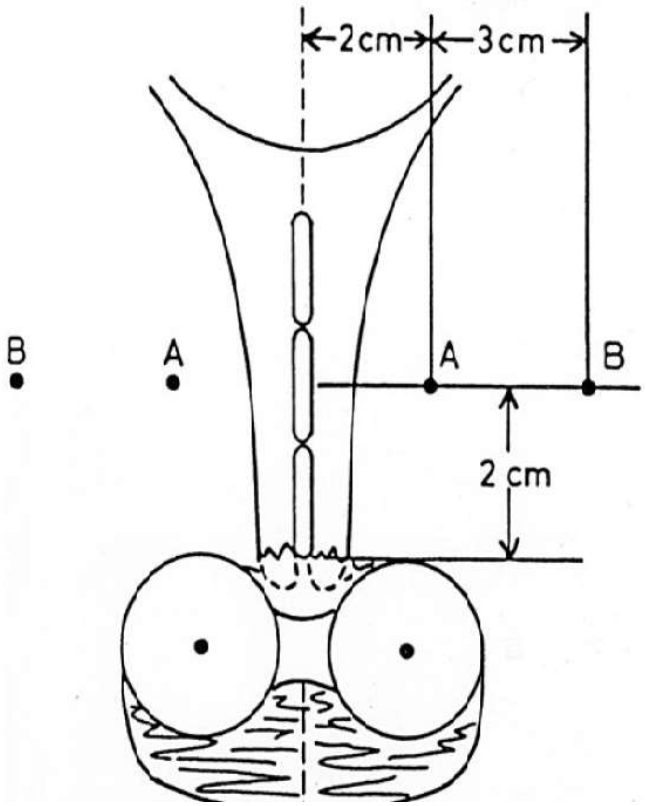
Dosimetría 2D

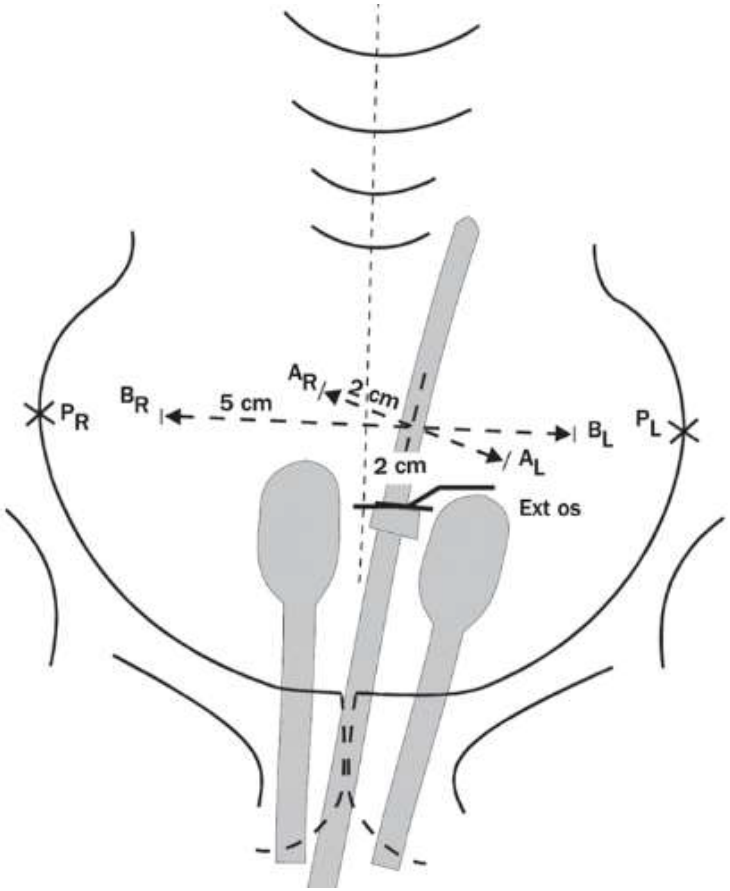
- Punto A fue seleccionado asumiendo que la dosis absorbida en el triangulo paracervical y no en el real volumen de vejiga recto o vagina determinado }por la tolerancia del volumen de tej. Normal
- Triangulo paracervical es la porción de tej.de área piramidal cuya base descansa en los fornices laterales de vagina y su ápex curvado alrededor del útero anteverso
- Esto fue considerado como la principal limitante de dosis para tratar el cérvix.

Hitos del planeamiento 2D

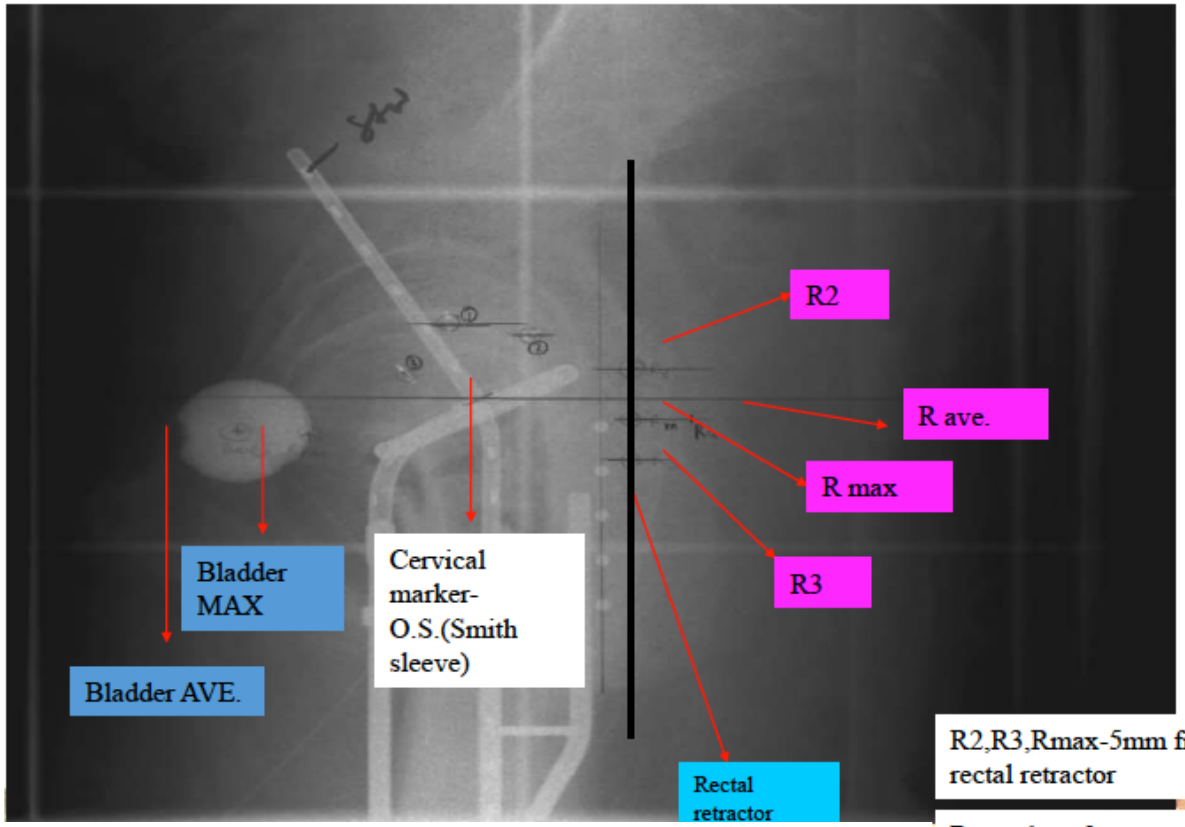
- Punto A fue modificado en 1953 como “2 cm por encima de borde inferior de la ultima fuente intra-uterina y a 2 cm lateralmente en el plano del útero, asumiendo que la os externa esta al nivel de dicha fuente y de los fornices vaginales.
- Punto A esta mas relacionado con la posición de las fuentes y el aplicador que con la anatomía.
- La variación en posición y distribución de fuentes y su relación con aplicador cambia significativamente las referencias anatómicas en la cual el punto A es definido.
- Dosimetria basada en puntos referenciales de órganos críticos no correlacionan con las máximas dosis de estos OARs

Puntos vs volumenes

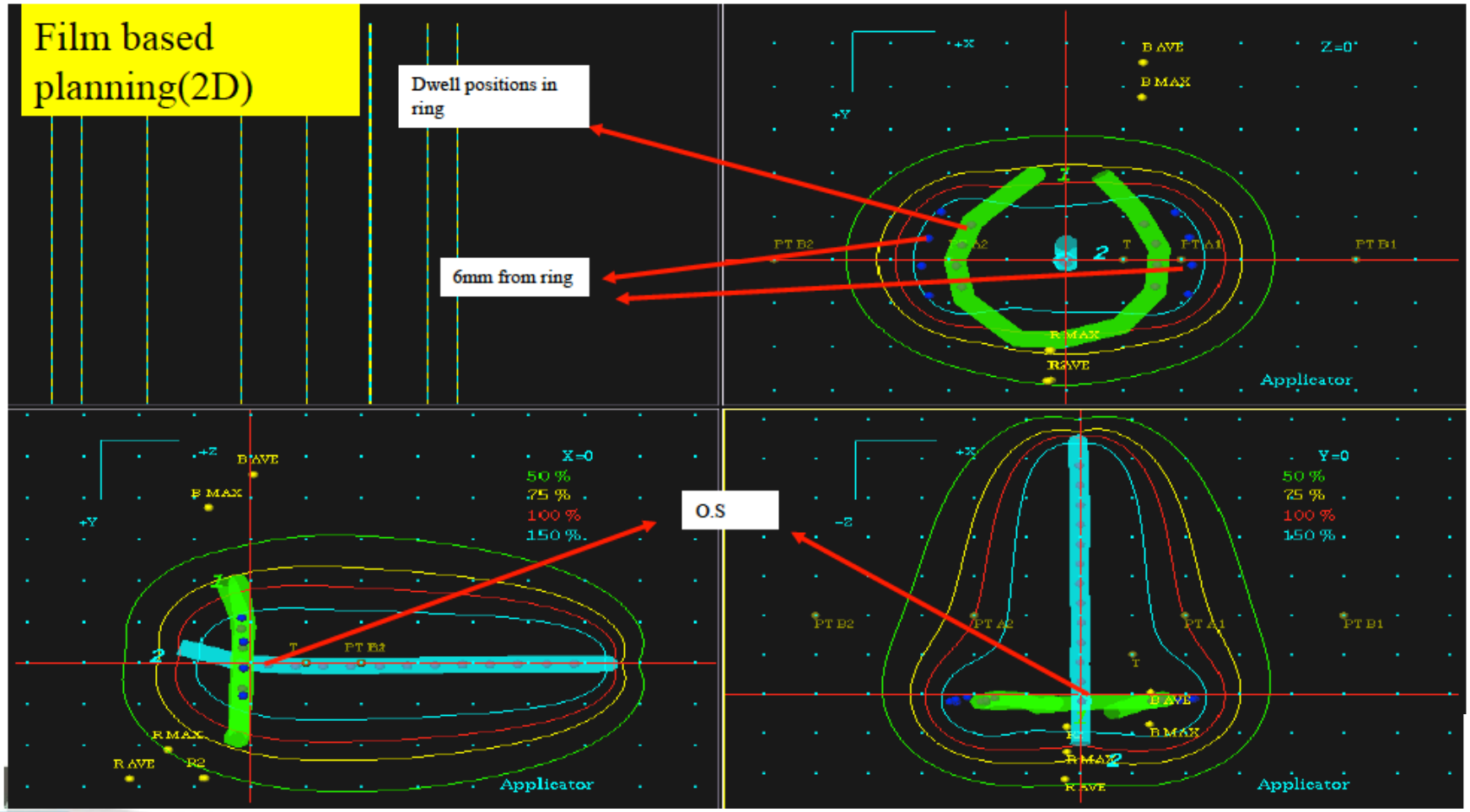




Ring and Tandem –Film Based 2D Plan Lateral



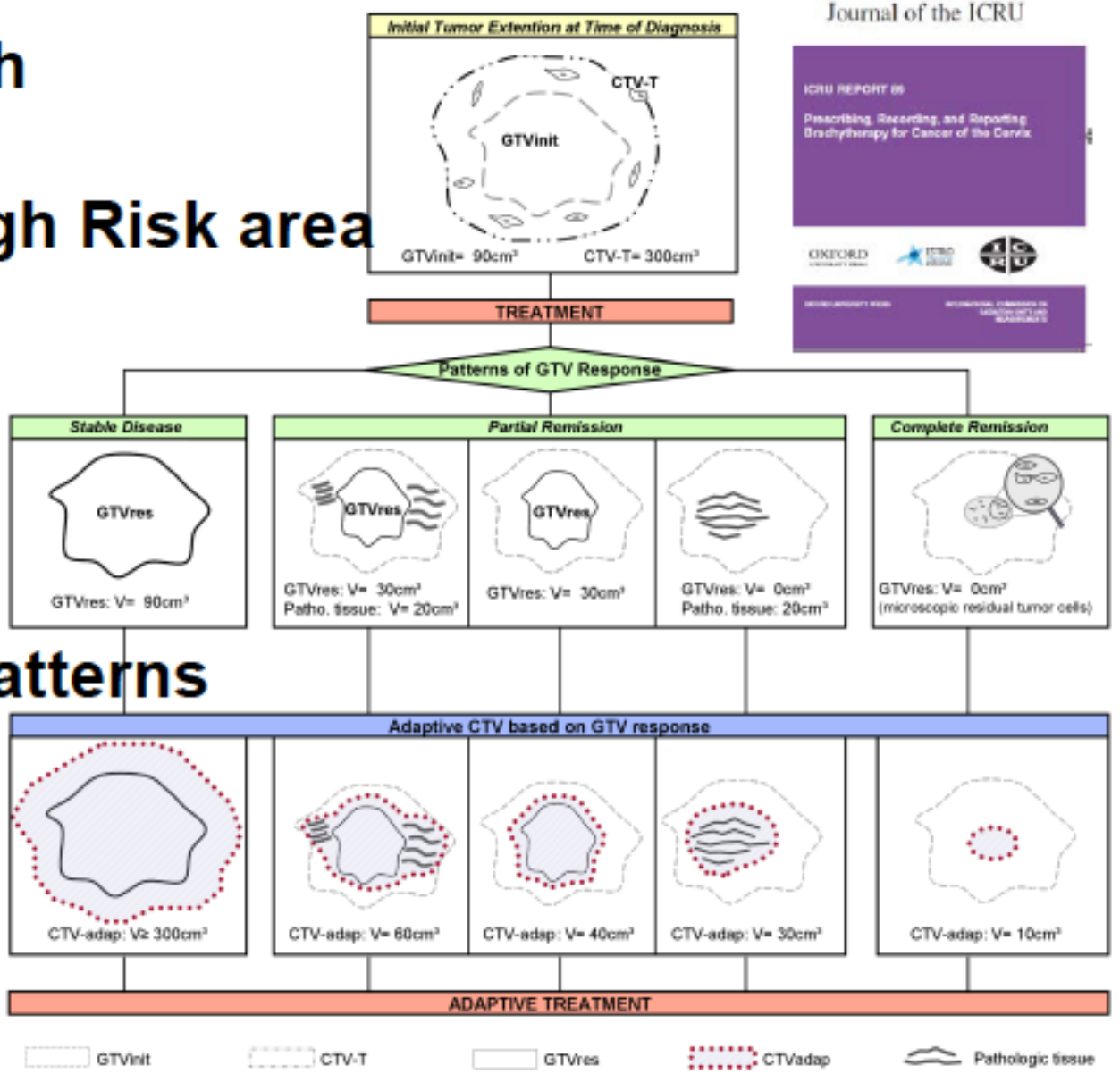
Film based planning(2D)



The two step adaptive approach for boosting Residual GTV+High Risk area

Various patterns GTV response

Corresponding patterns adaptive CTVs

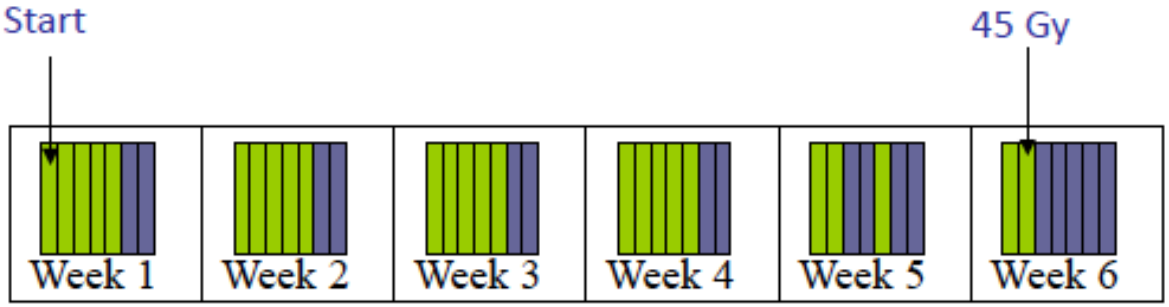


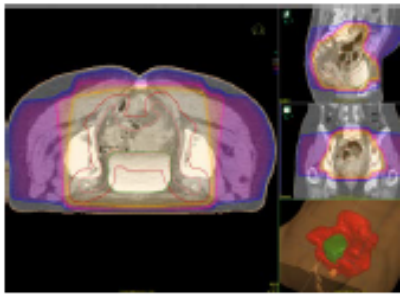
ICRU/GEC ESTRO report 89, 2016, Fig 5.3

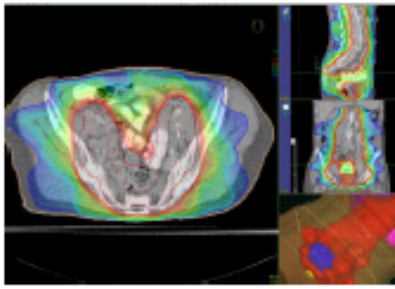
http://jicru.oxfordjournals.org/

Primary radiochemotherapy and Image guided adaptive brachytherapy (IGABT)

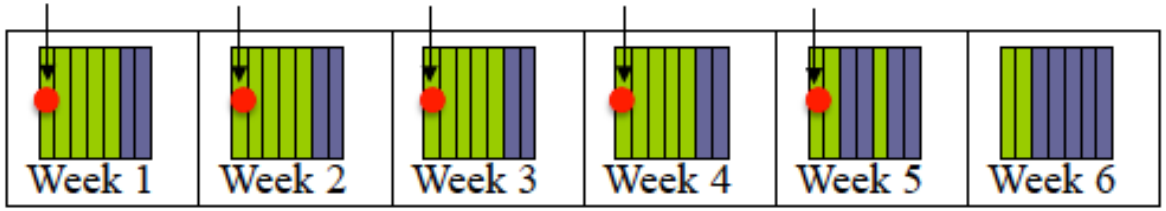
External beam radiotherapy: 3D EBRT or IMRT/VMAT





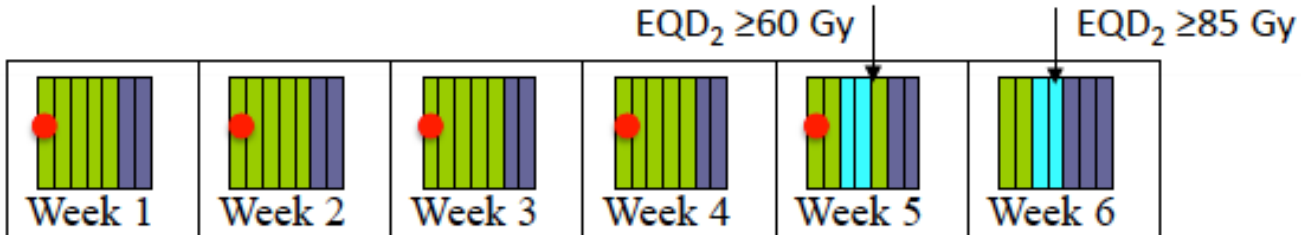


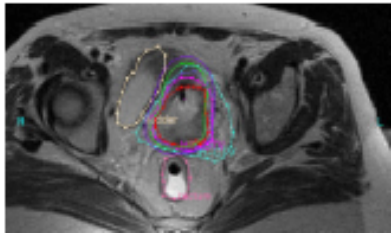
Chemotherapy



Cisplatin 40 mg/m²

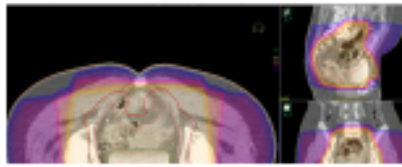
Brachytherapy: IGABT





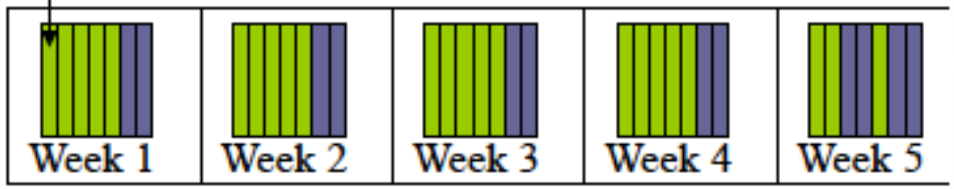
Primary radiochemotherapy and Image guided adaptive brachytherapy (IGABT)

External beam radiotherapy: 3D EBRT or IMRT/VMAT



Start

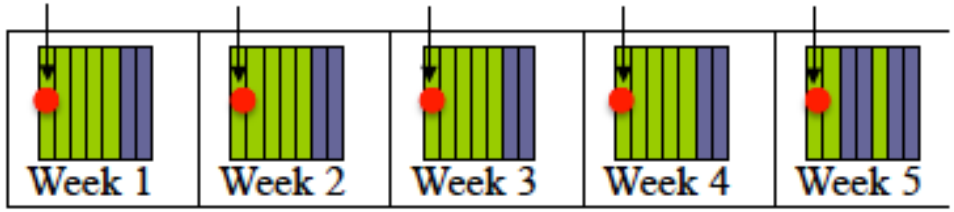
45 Gy



Chemotherapy

1. Cycle

5-6 Cycles

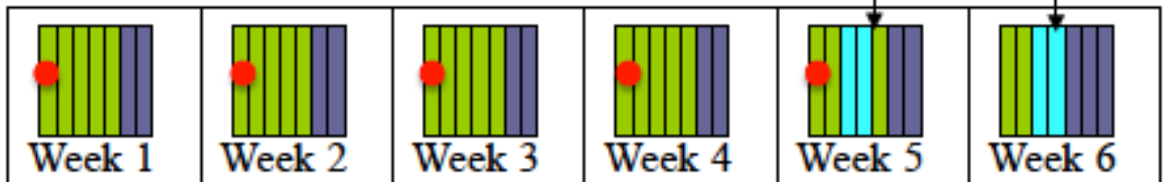


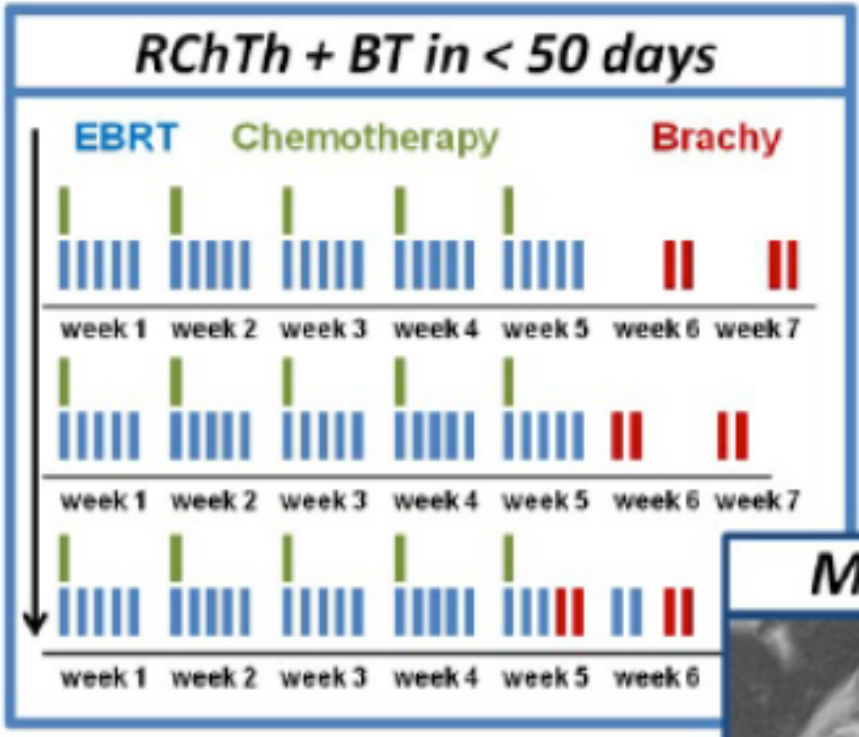
Brachytherapy: IGABT

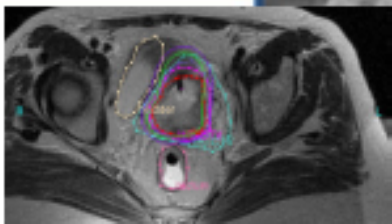
HDR or PDR

EQD_2 ≥60 Gy

EQD_2 85 Gy







Treatment Duration

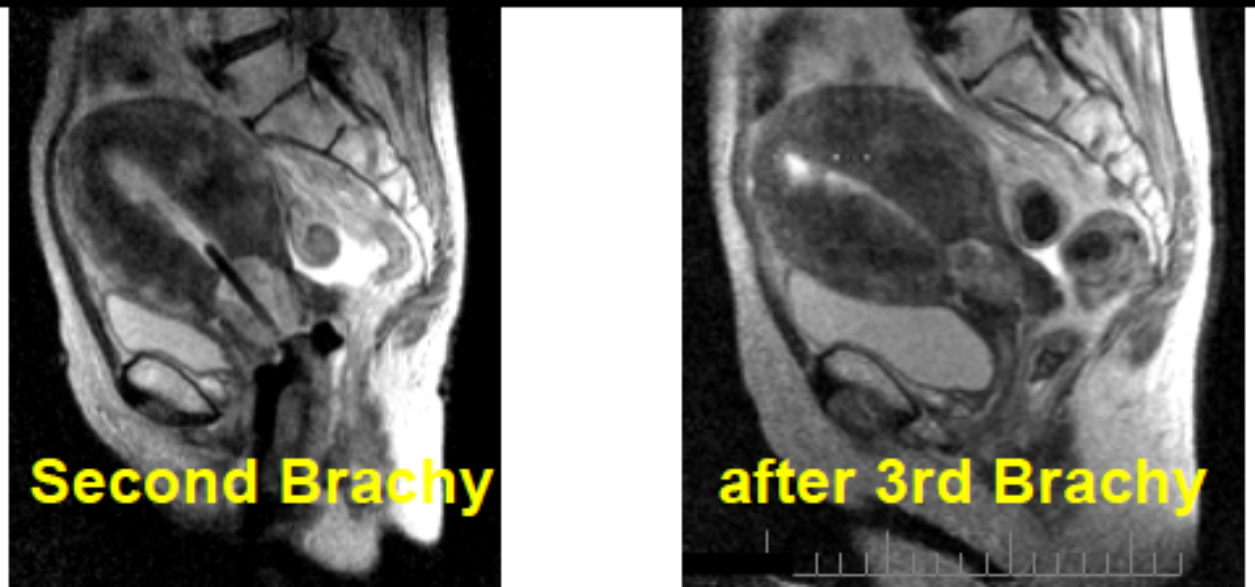
	< 6 weeks	6-7.9 weeks	8-9.9 weeks	10+ weeks
4 yr Pelvic Recurrence Rate	5%	11%	13%	20%

Lanciano et al. IJROBP 25:391, 1993

- Survival decreased @0.6% per day > 8 weeks Petereit et al. IJROBP 32:1301, 1995

The Challenge: Tumour size and topography change during treatment

The evolution of the concept of residual GTV and HR CTV



Does Image Guided Brachytherapy Make a Difference?

Prospective trial in 3D PDR brachytherapy

Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: Results of the French STIC prospective study ☆

Claire Charra-Brunaud [a,*], Valentin Harter [a], Martine Delannes [g], Christine Haie-Meder [c], Philippe Quetin [d], Christine Kerr [e], Bernard Castelain [f], Laurence Thomas [b], Didier Peiffert [a]

Radiotherapy and Oncology 2012

- 801 enrolled, 705 analyzed from 20 centers, not randomized
  - Group I: preop brachy
  - Group II: EBRT, brachy, surgery
  - Group III: EBRT, brachy
- Improved Local control at 2 yrs: 4.6%-8.3% (p=0.003)
  - Local failure: 26% and 21% for 2D and 3D, respectively in group 3
  - Point A doses: 68.5 Gy and 70.8 Gy for 2D and 3D, respectively in group 3
- HR for G3/4 toxicity was 1.9 for 2D vs 3D
- No difference in OS or DFS

STIC prospective study

	Group 1 (2D)	Group 1 (3D)	Group 2 (2D)	Group 2 (3D)	Group 3 (2D)	Group 3 (3D)
LFRS	91.9	100	84.7	93	73.9	78.5 *
RLRFS	87.9	96.1	77.2	88.6	61.2	69.6 *
DFS	86.5	89.7	73	77.1	55.2	60.3
OS	95	96	85	86	65	74

Gr. 3-4 Tox.	Group 1 (2D)	Group 1 (3D)	Group 2 (2D)	Group 2 (3D)	Group 3 (2D)	Group 3 (3D)
Urinary	5.8	1.3	7.6	5.5	9.2	1.2 *
Digestive	6.8	1.2	0.9	4.8	9	0
Global	14.6	8.9	12.5	8.8	22.7	2.6 *
Gr. 2-4 tox.						
Urinary	13.1	7.9	20.4	13.3	23.1	13.7 *
Digestive	8.3	7.4	8.3	8.8	18.7	15.2
Global	37.5	23.2	40.6	29.4	53.4	42.4

Retrospective CT data

#	Mode of treatment		Imaging During BT	Median Follow up (years)	Local control (%)	Disease specific Survival (%)	Overall Survival (%)	Grade 3-4 Toxicity
115 BWH	ChRT/HDR	IB-IIIB	CT	1.8	93+	83+	78+	---
44 UPMC	ChRT/HDR	IB-IIIB	CT+MR	0.6	88+	85+	86+	0
28 UK	ChRT/HDR	IB1-IIIB	CT	1.9	96^	81^	---	14(3GI)^

Institution (Years reported)	# Patients	Mode of treatment	Stage	Imaging During BT	Median Follow up (years)	Local control (%)	Disease specific Survival (%)	Overall Survival (%)	Late Grade 3-4 Toxicity %(#)
Vienna (1993-1997)	189	EB/HDR	IA-IVB	CT	2.8	78^	68^	58^	(3GU), (4 GI), (31 V)^
Vienna (1998-2003)	145	EB+/-Ch[¥]-HDR	IA-IVA	MR	4.3	85^	68^	58^	(3GU), (4GI), (5V)^
Vienna (2001-2008)	156	EB+/-Ch[¥]-HDR	IA-IVA	MR	3.5	95^	74^	68^	(3GU), (5GI), (2V)^
UPMC (2007-2010)	44	ChRT/HDR	IB-IIIB	CT+MR	0.6	88+	85+	86+	0
Addenbrooks (2005-2007)	28	ChRT/HDR	IB1-IIIB	CT	1.9	96^	81^	—	14(3GI)^
IGR (2000-2004)	39	Pre-op LDR	IB1-IIB	MR	4.4	91±	86±	94±	0
IGR (2000-2004)	84	ChRT/LDR	IB2-IVB	MR	4.4	89±	52±	57±	(3GU; 1GI) ±
IGR (2004-2006)	45	ChRT/PDR	IB-IVA	MR	2.2	100+	73+	78+	(1 Fi)+
BW/DFCC (2004-2011)	115	ChRT/HDR	IB-IIIB	CT	1.8	93+	83+	78+	—

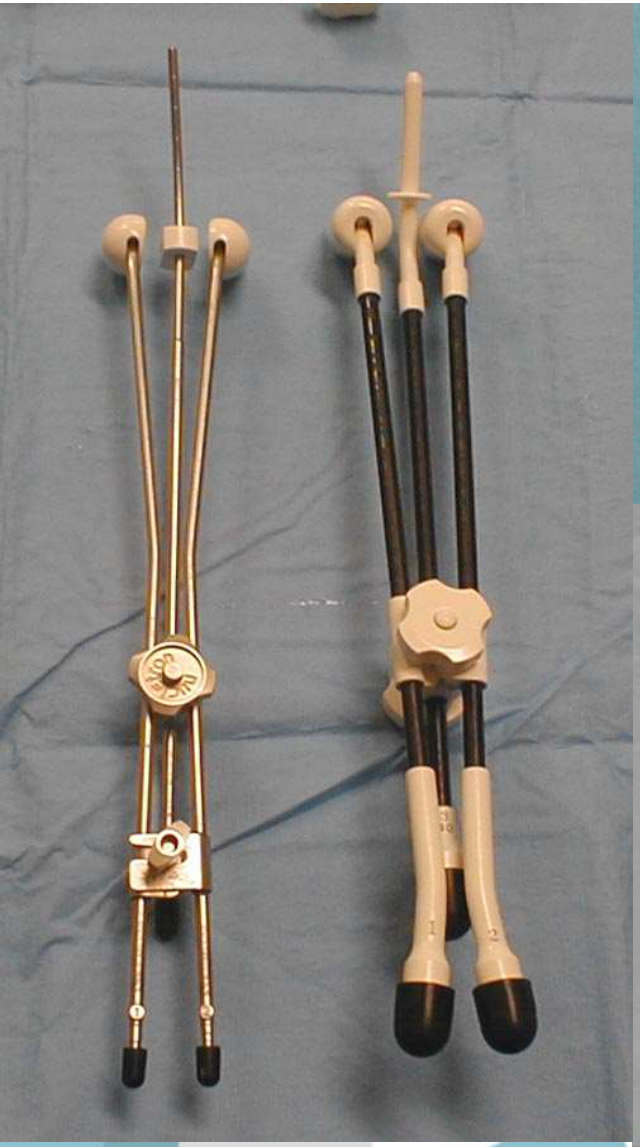
IGABT

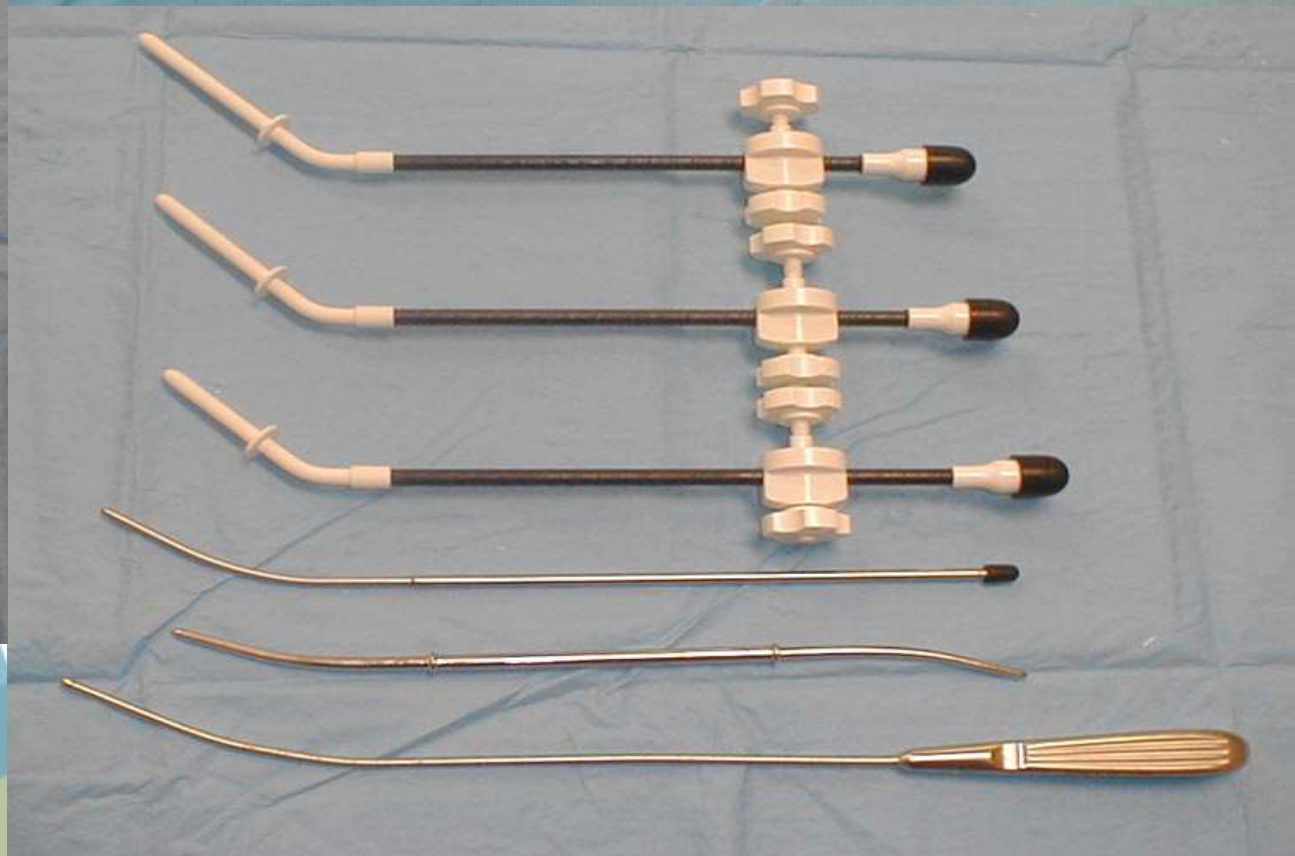
Hardware y software

Definición de blanco de y contorneo de OARs

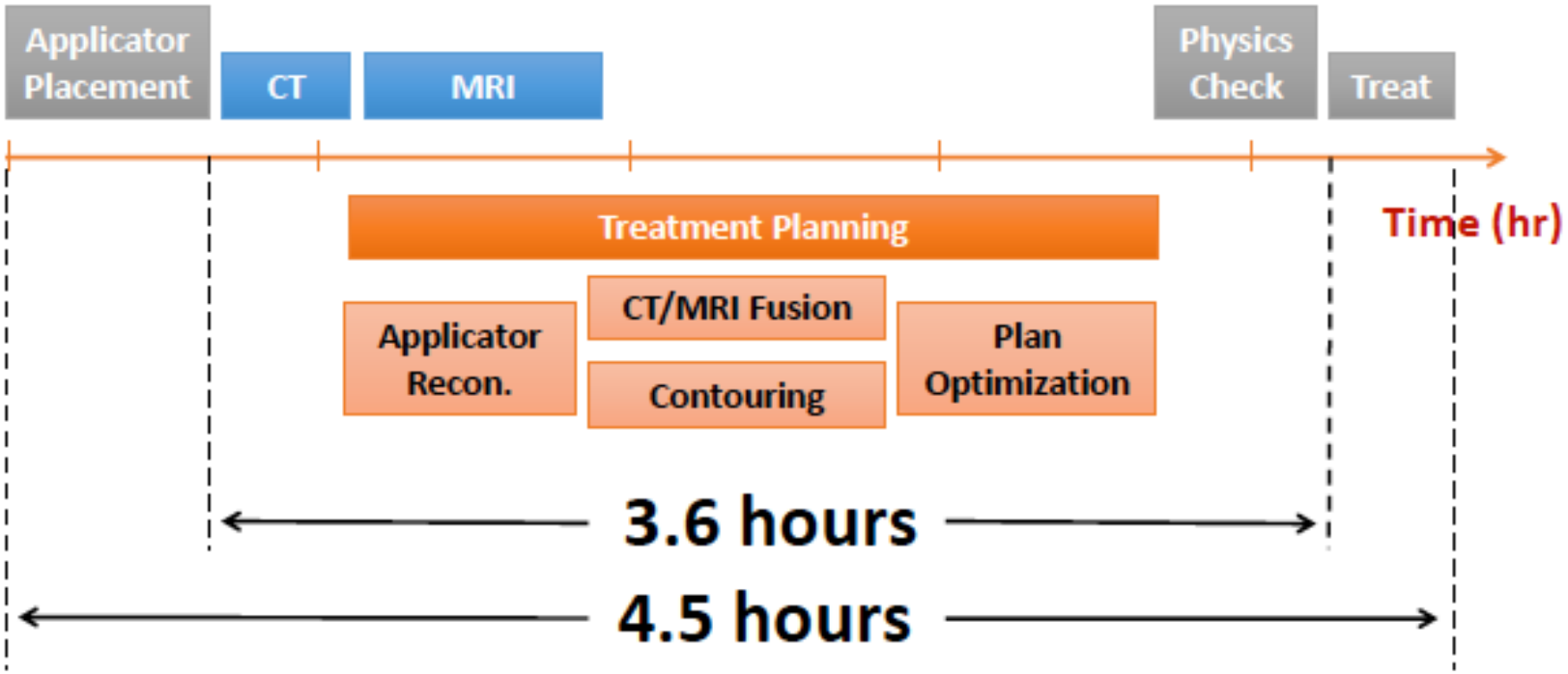
Dosis de tolerancia según volumen y no puntos

Data pronostica





Tiempo requerido



The median time from start of imaging to treatment delivery was 3.6

Comparación 2D vs 3D

Varios estudios han comparado dosis de BATD basada en imágenes de TEM
con la dosis dada basada en radiografías ofrecida al tumor cervical
Y a los OARs
Estos estudios demuestran consistentemente que la tendencia es a prescribir
Menos dosis al tumor y más dosis a los OARs

Comparación 2D vs 3D

KIM y Pareek mostraron que la BATD basada en radiografías usando Punto A
sobreestima la dosis tumor especialmente en casos avanzados
El volumen tratado a la dosis prescrita se relaciono en promedio a una aproximación real de dosis al GTV de 98.5, 89.5, 79.5 y 59.5 para EC IBI IB2 IIB y IIIB respectivamente

.

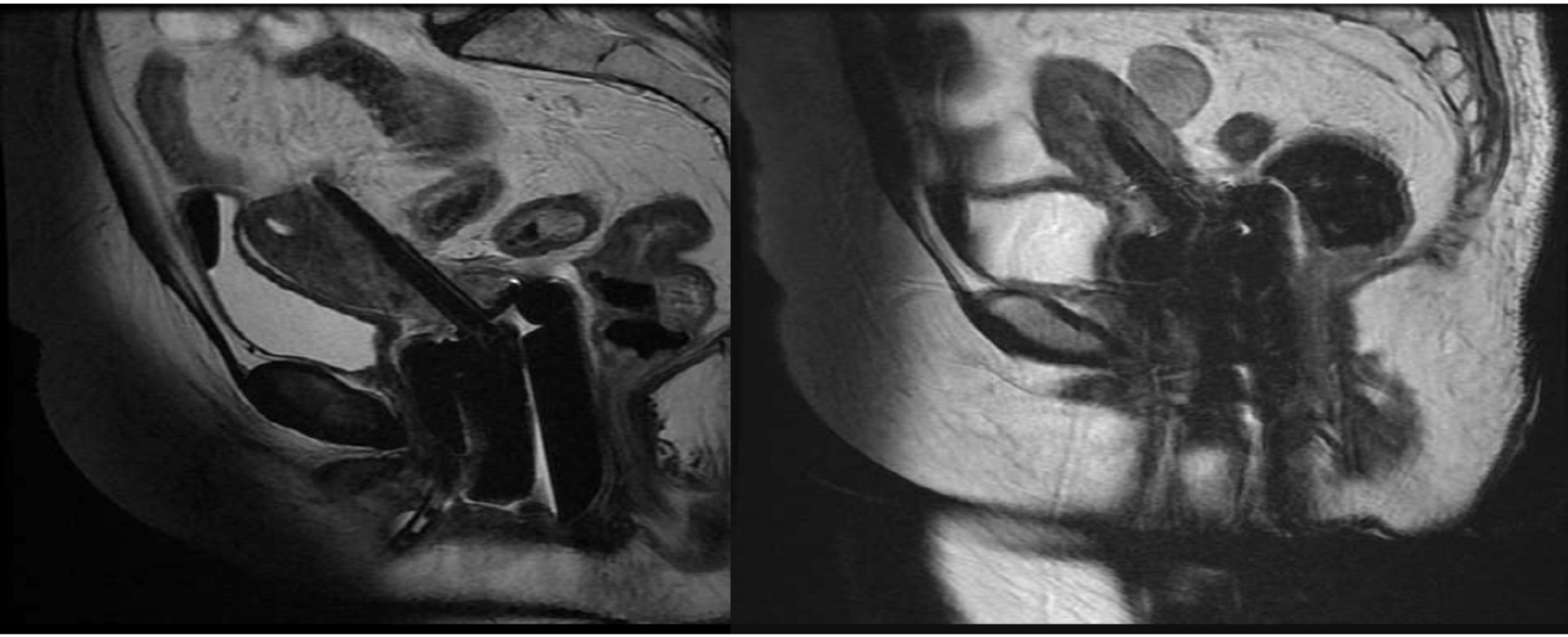
Dosimetric analysis of 3D image-guided HDR brachytherapy planning for the treatment of cervical cancer: is point A-based dose prescription still valid in image-guided brachytherapy?

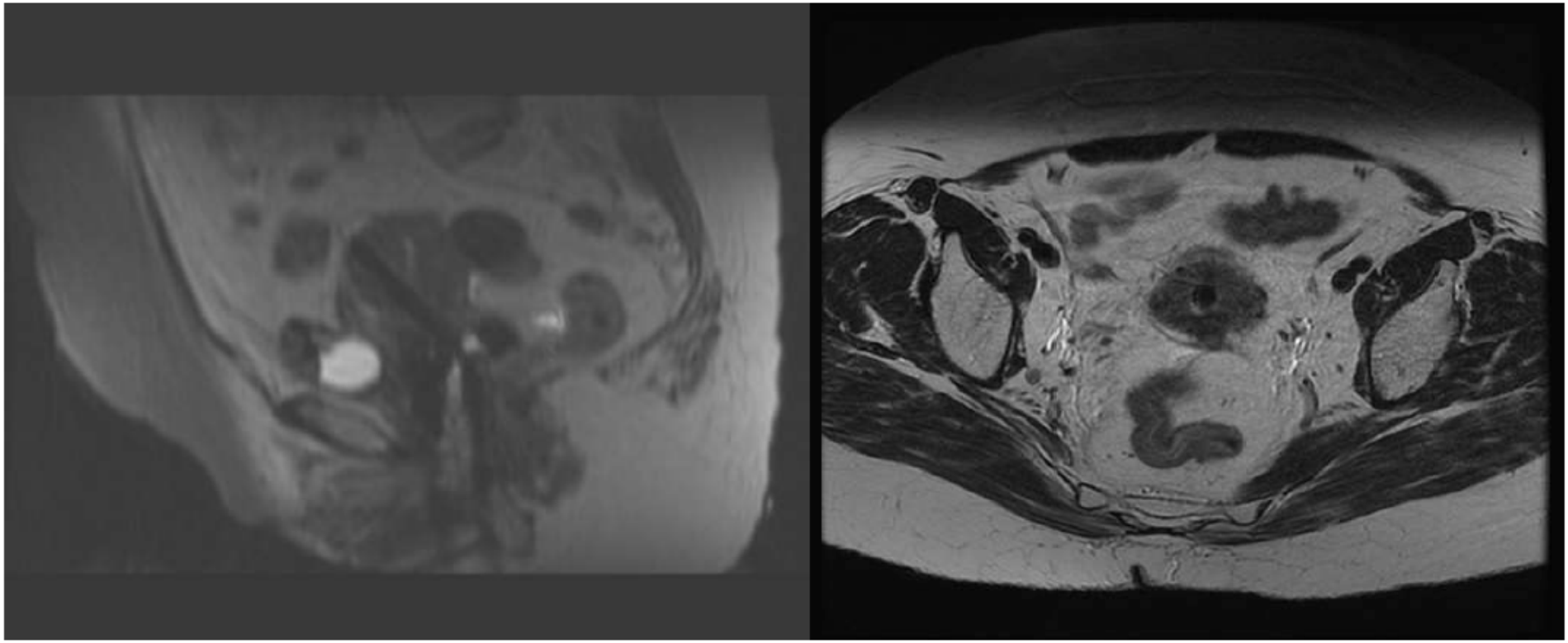
Med Dosim. 2011 Summer;36(2):166-70. 2010 May 21

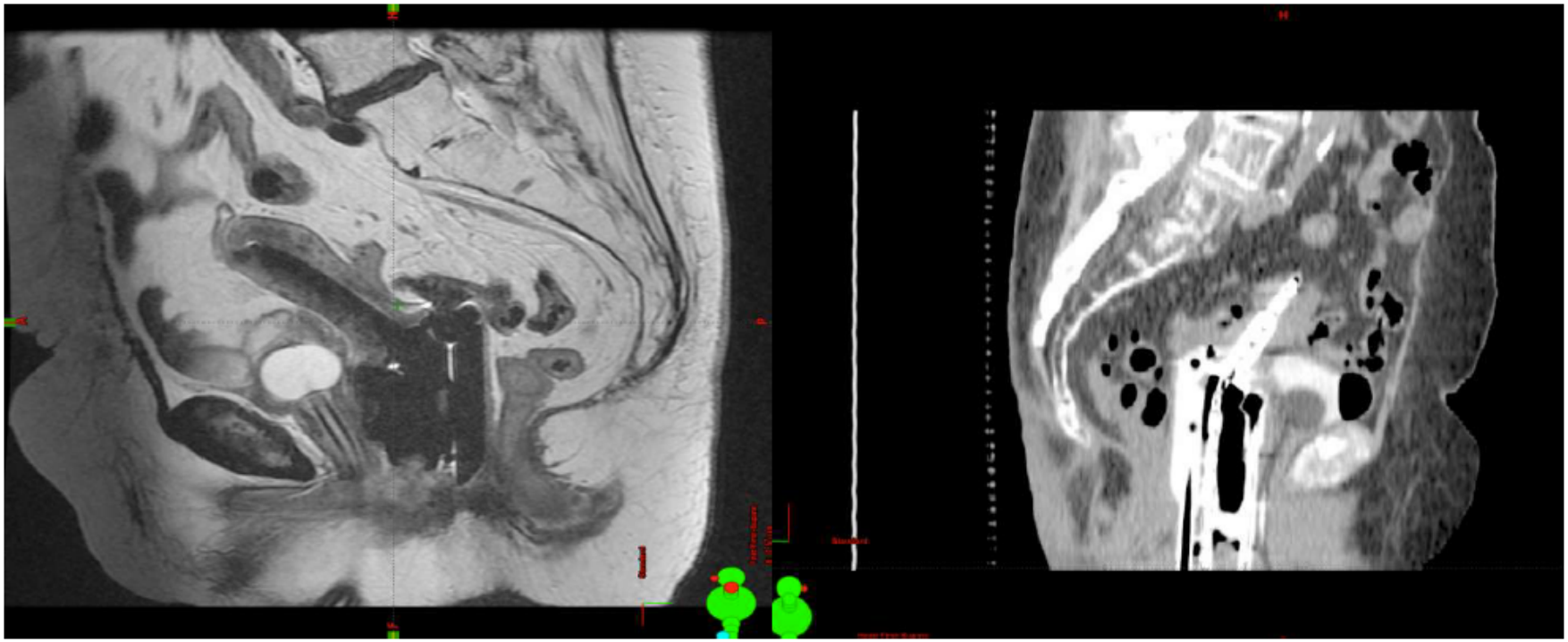
	HR CTV D90(Gy)	Point A (Gy)	p –value (for the difference between volume and point dose
Mean ±SD	83.2±4.3	78.6±4.4	<0.001

Ganancia Clínica

Verificación de posición
Evitar tratar zonas erróneas y evitar complicaciones de procedimiento
Perforaciones en segmento uerino inferior o fundus







Ganancia Clínica

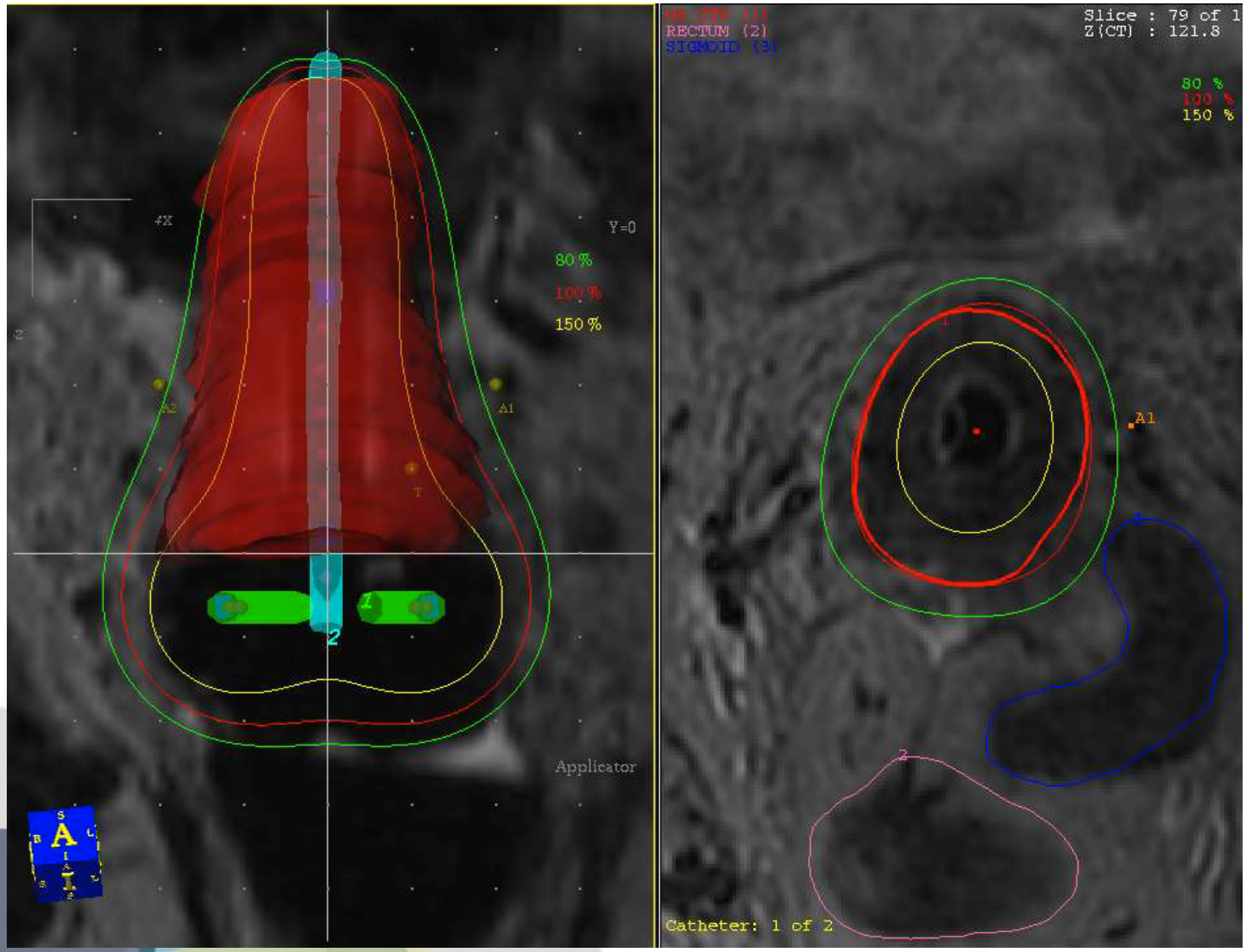
Para tumores pequeños (70 a 75%)
Reduce las dwell position y las dwell times con menor posibilidad de complicaciones inclusive escalando dosis tumoral por mejor conformalidad y homogeneidad
Menor dosis a los órganos en riesgo

2D vs 3D

HR CTV fue adecuadamente tratado (V100:::95%) 70% de pac. Tratadas Convencionalmente y 75% de las pac con planes optimizados consiguieron mejorar los indicadores

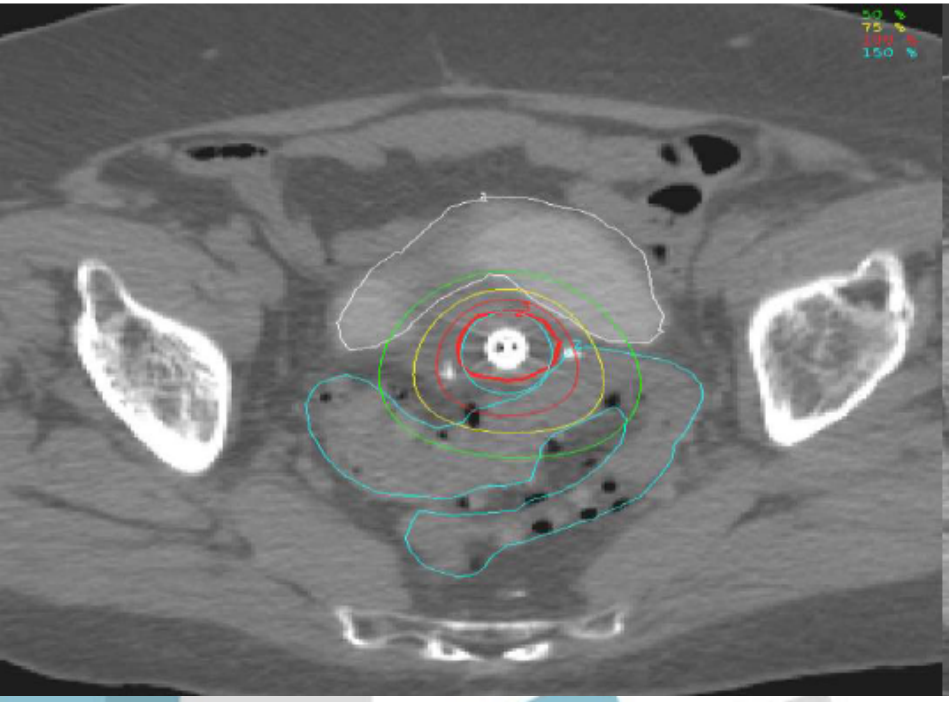
La dosis mínima a zona contigua 2cc del recto sigmoide y vejiga fue 16, 25y 9.2 Gv respectivamente .

Point A Located Outside Target/Lower Dose than Prescription Dose

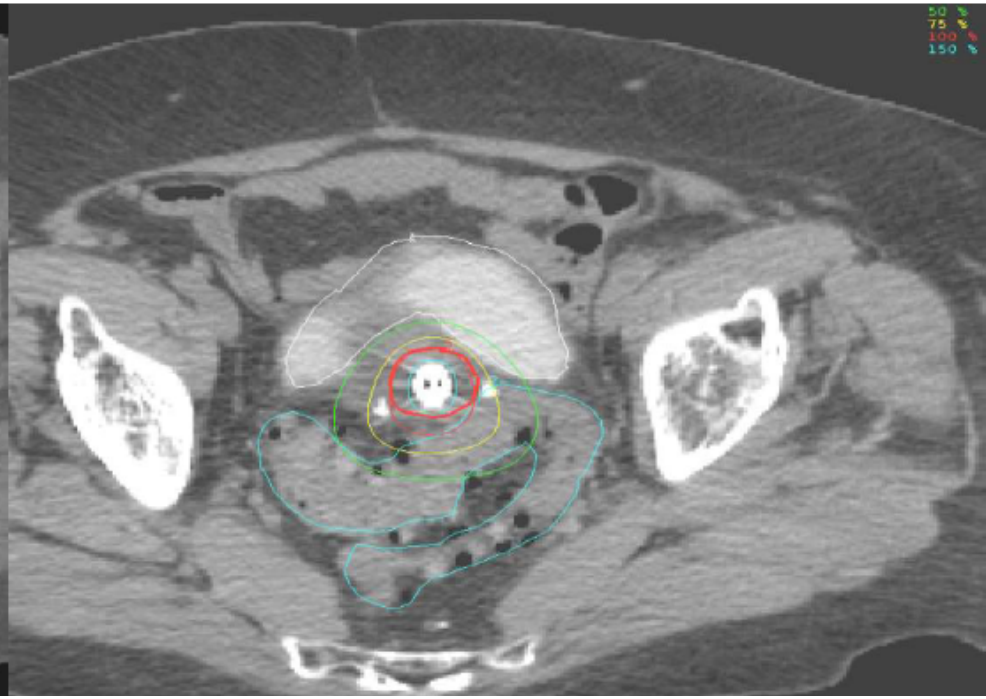


Ring and Tandem–CT Based

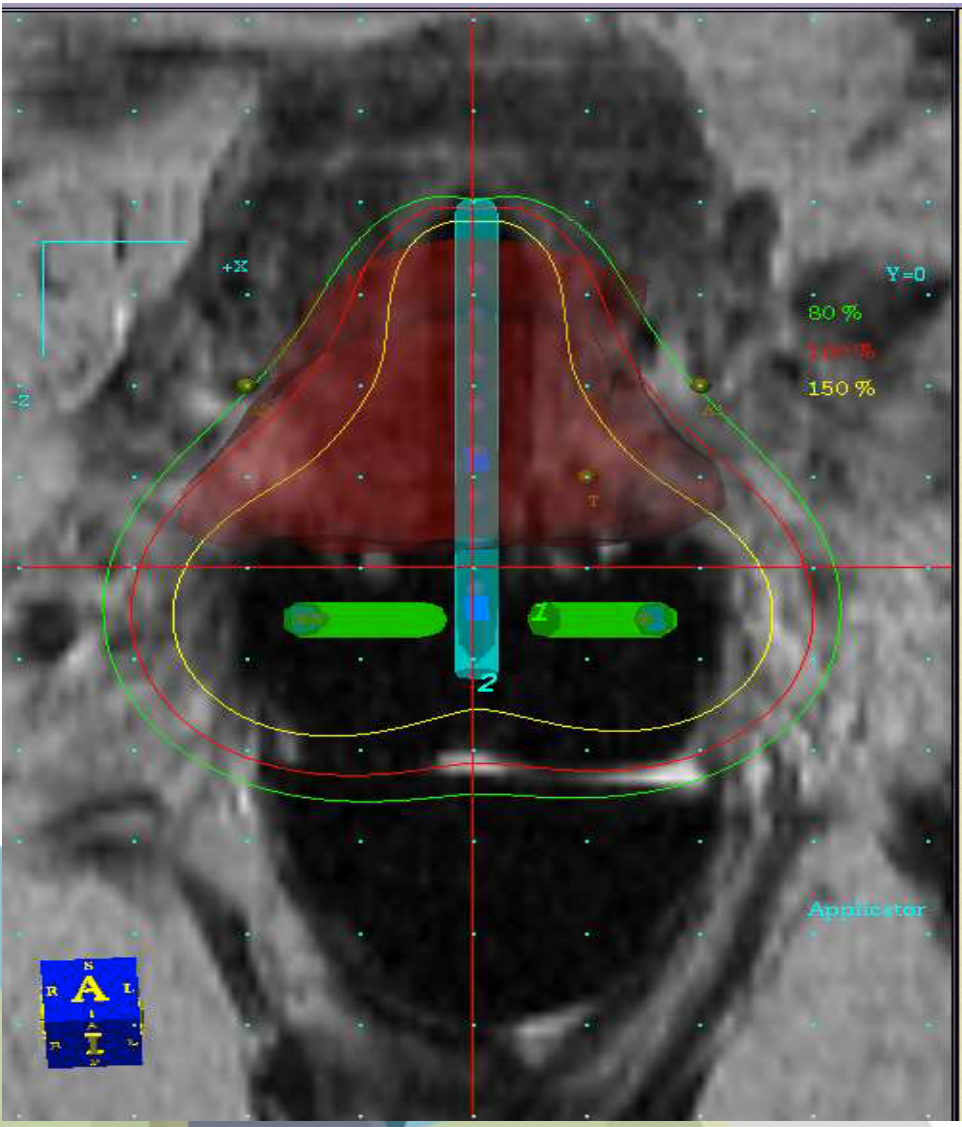
Non-optimized plan

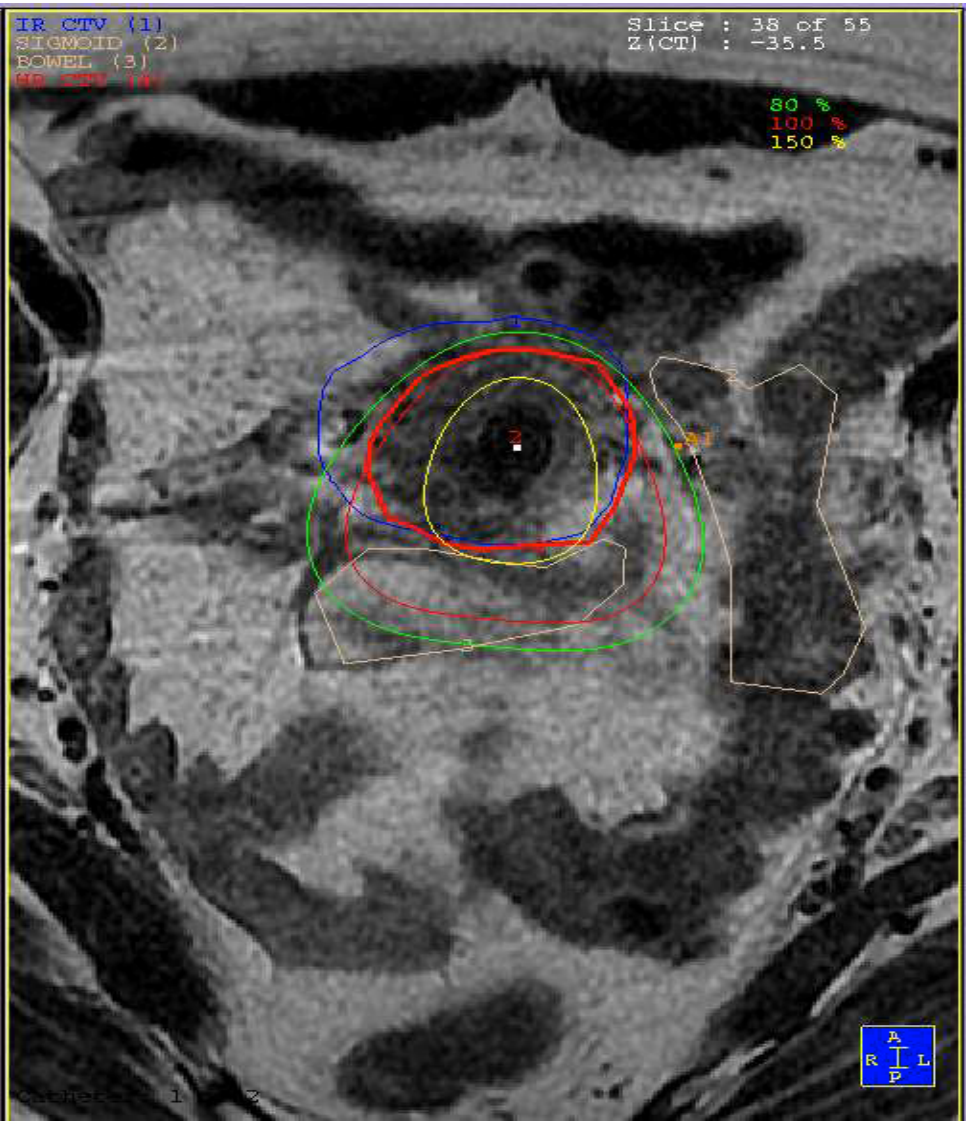


Optimized plan

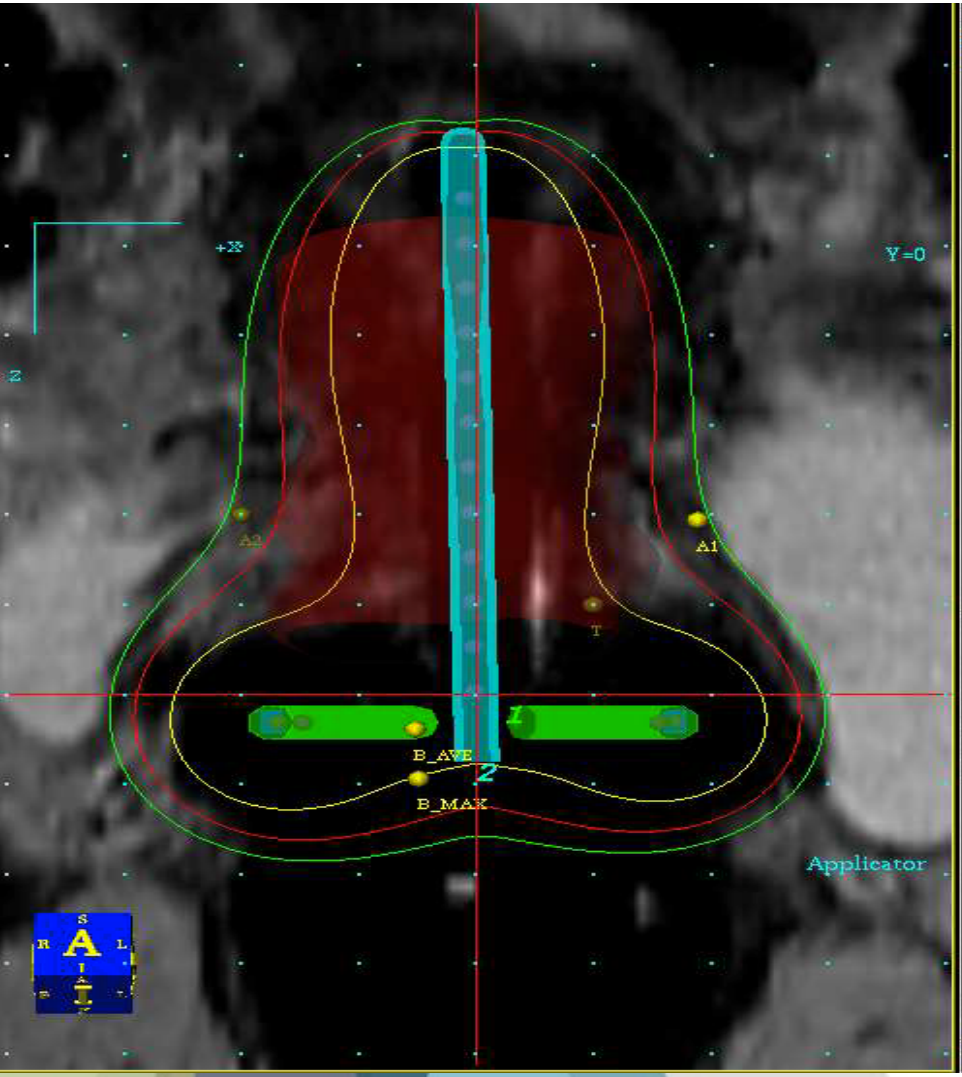


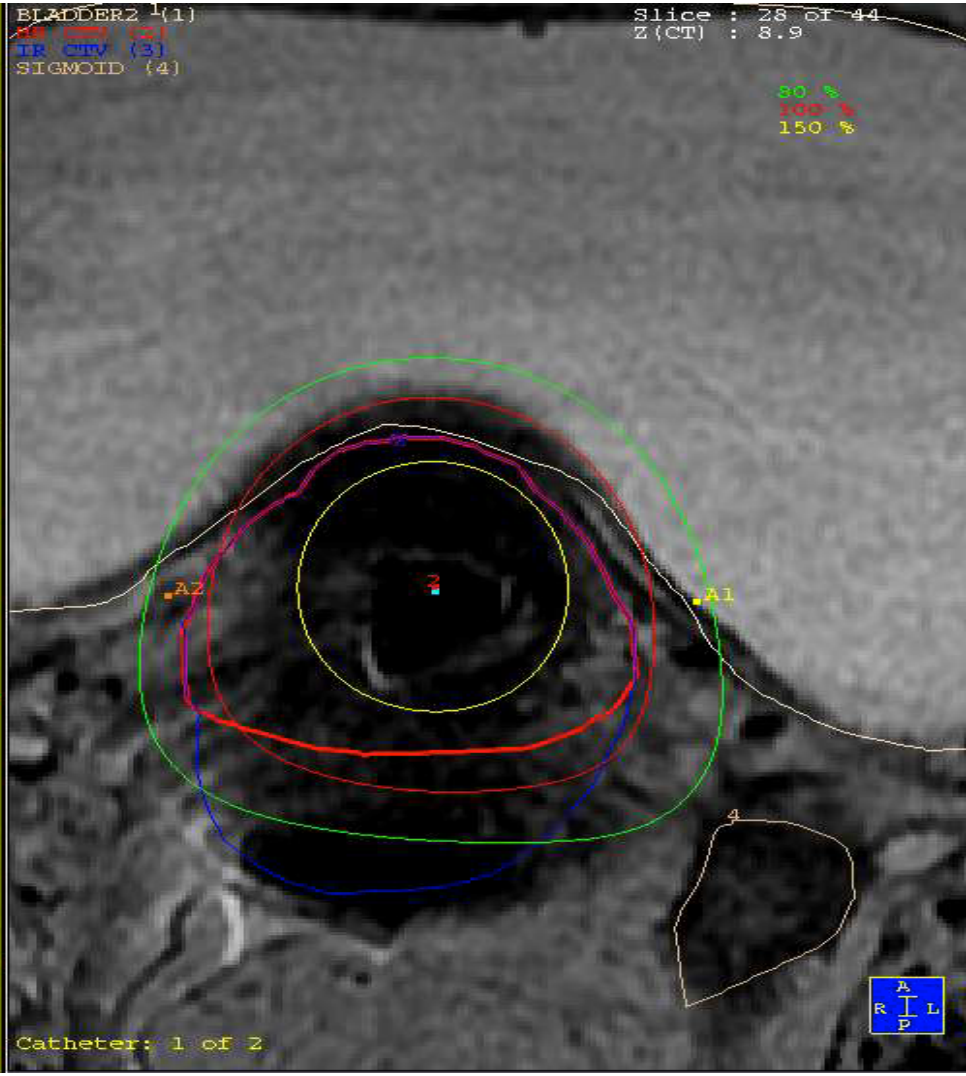
Point A Located Outside Target/Lower Dose than Prescription Dose



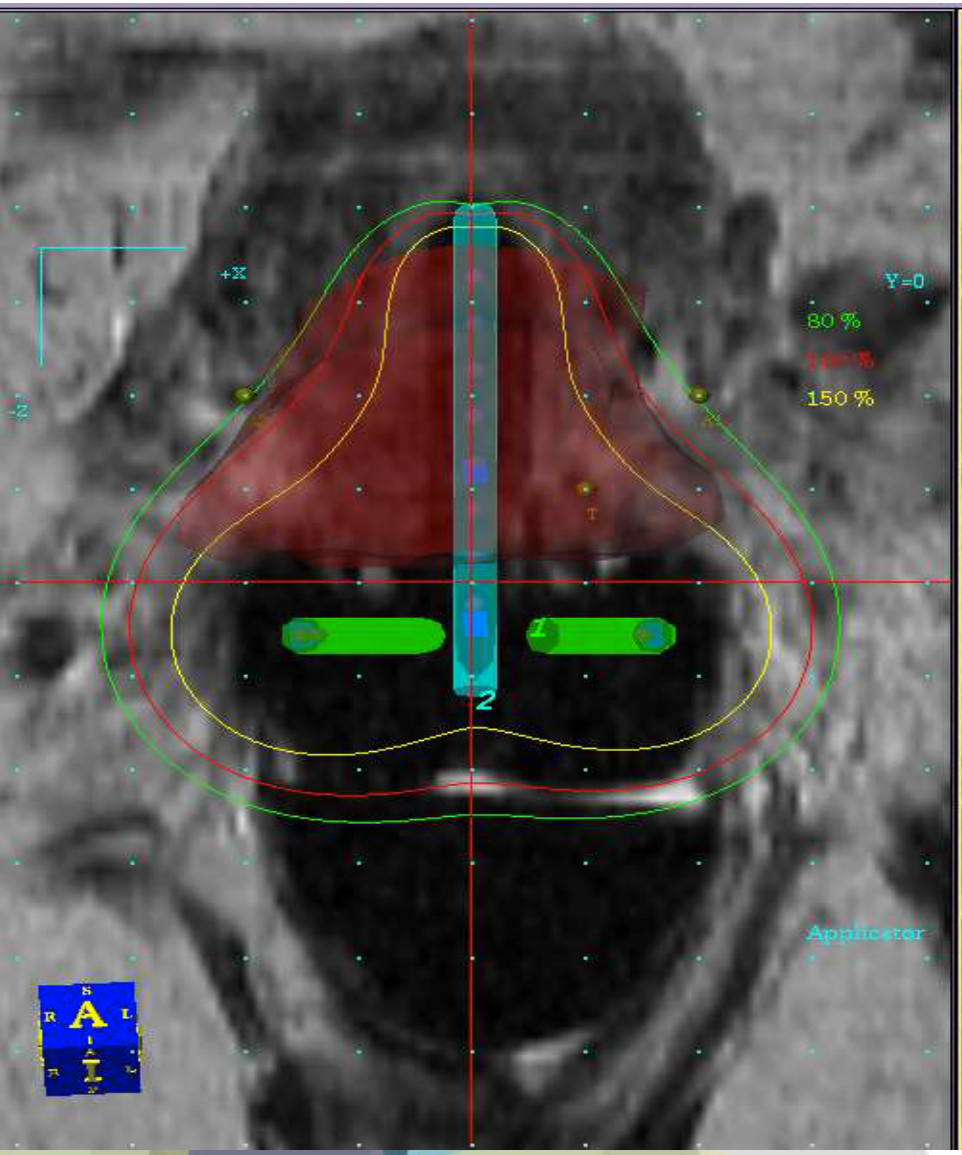


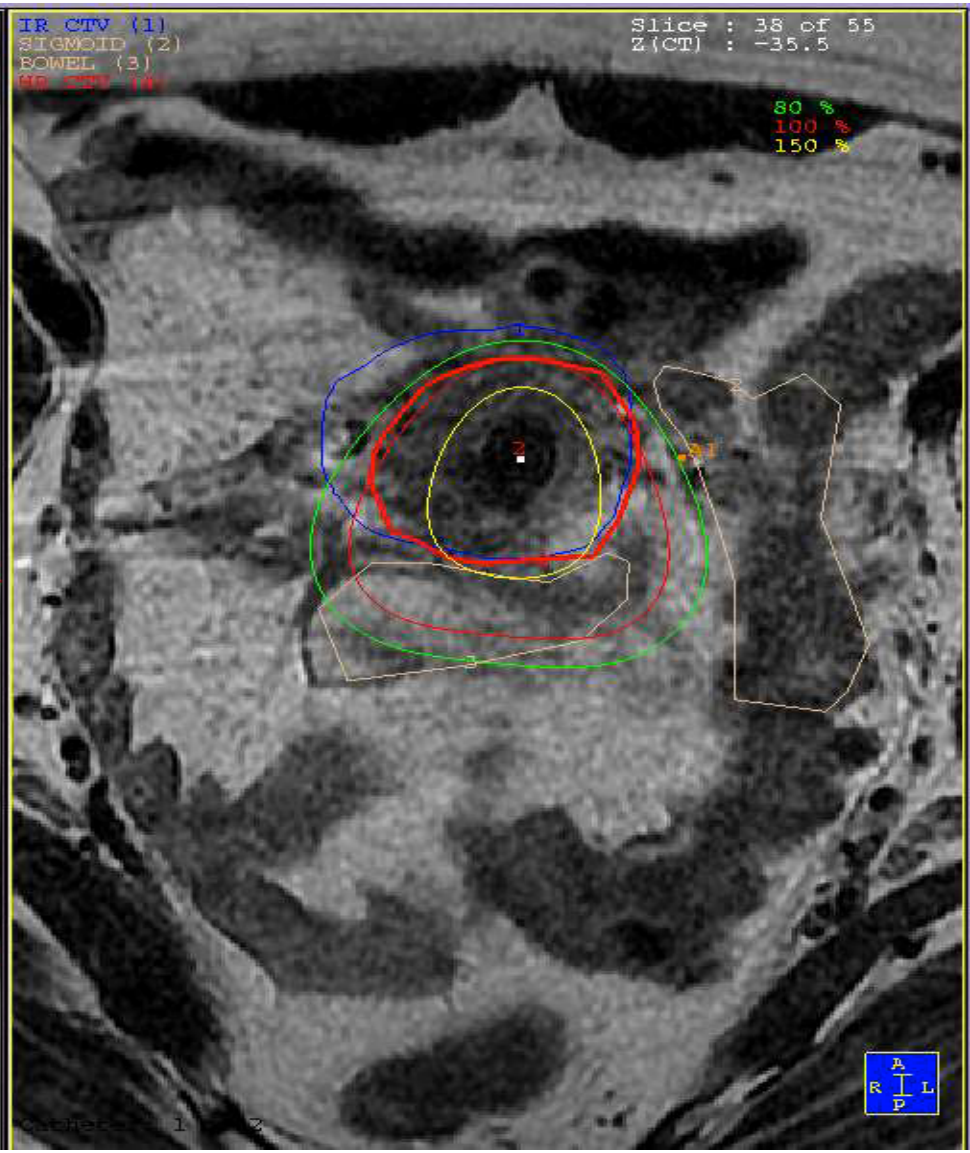
Point A Resides in Critical Organ (MR IMAGE)



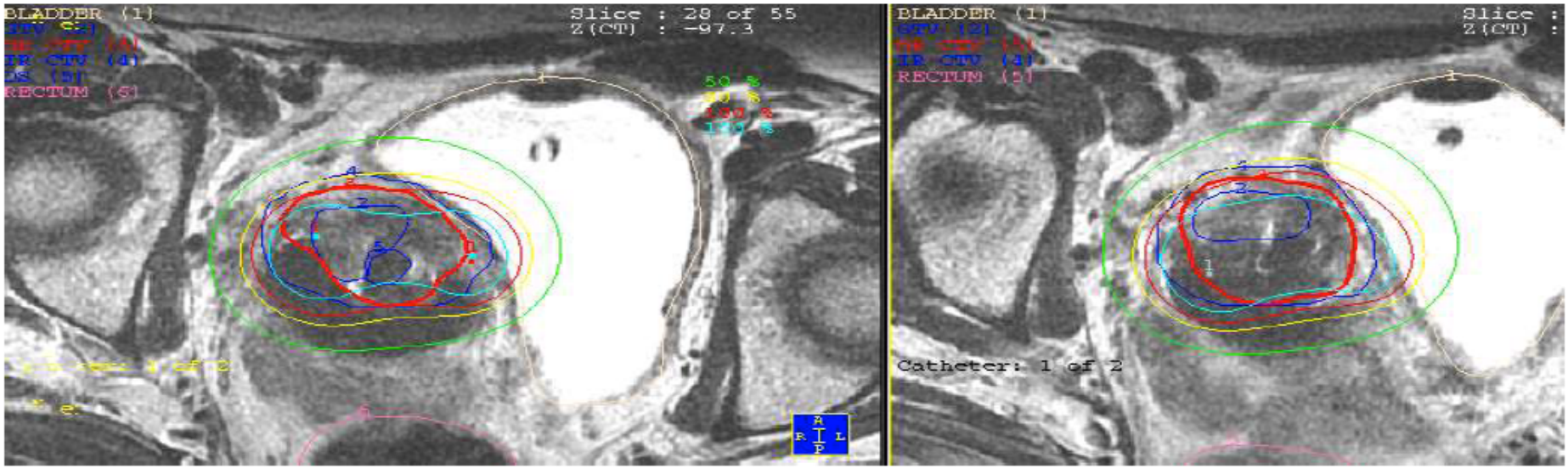


Point A Resides in Critical Organ (MR IMAGE)





Asymmetrical Dwell Positions in Ring Applicator (Axial Slices in MR Image)



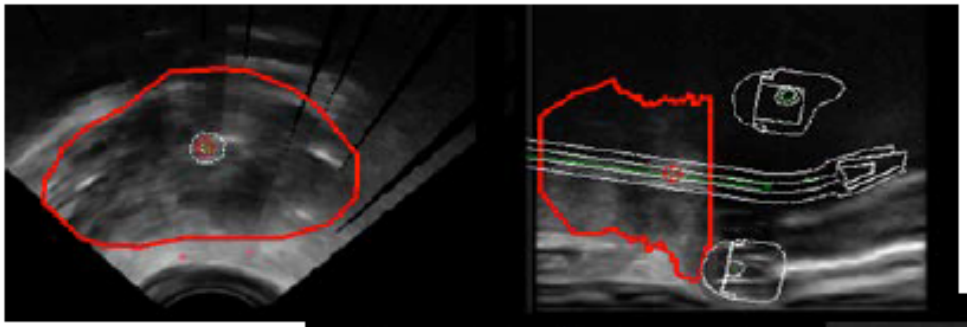
Clinical Gain

- Reduce dose to critical organs specifically sigmoid which is not accounted in 2D planning
- Help reduce risk of sigmoid stricture and ulceration

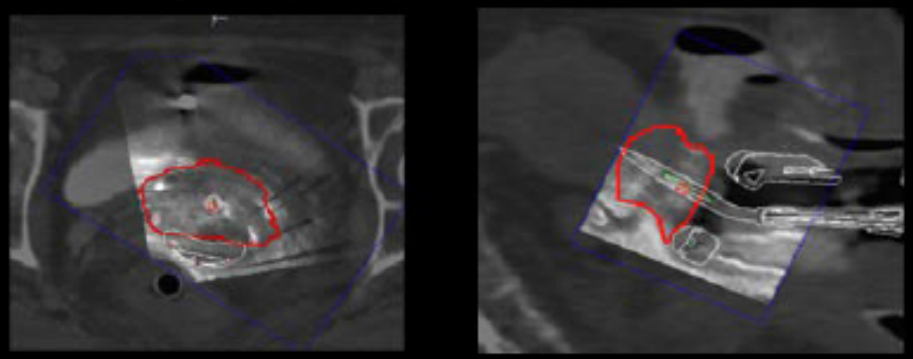
Clinical Gain

- For large tumor (20-25% of patients)
- Improve coverage of target volume by increasing weight, dwell position or extra needles
- Improve tumor control without increasing risk of toxicities

Imaging technology development integrating US, CT (and MRI) for CTV_{HR} contouring

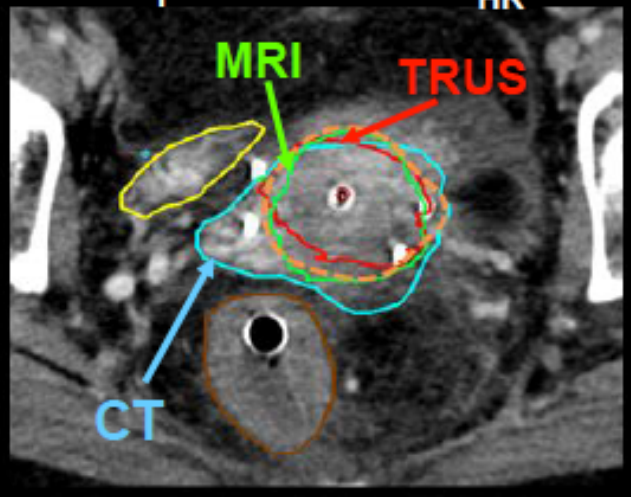


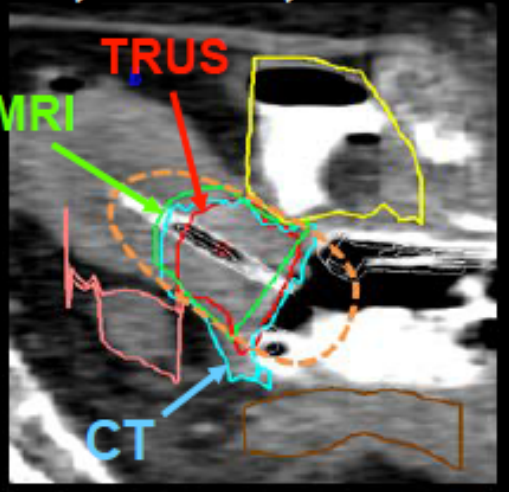
TRUS: target delineation, applicator reconstsruction



TRUS/CT
registration via applicator + target transfer to CT

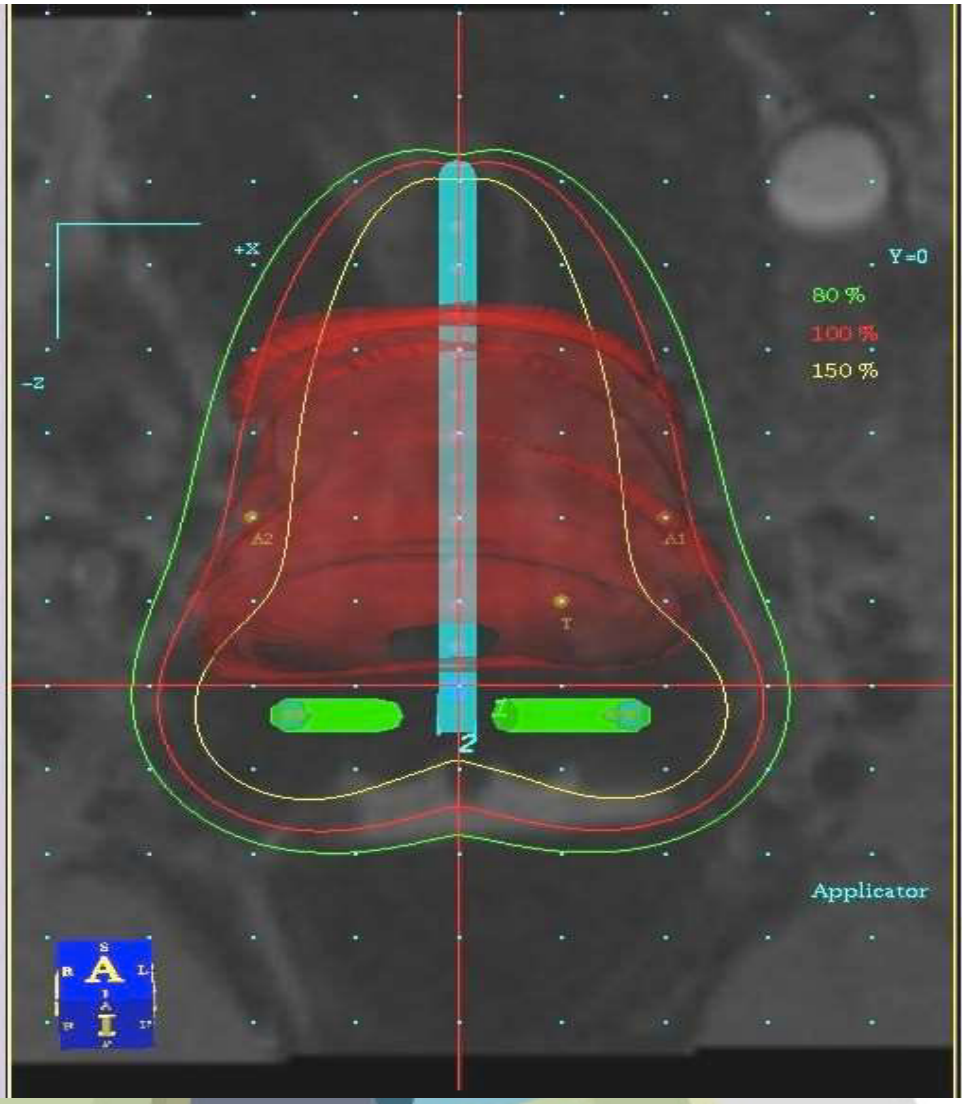
comparison of CTV_{HR} from **MRI, TRUS, CT**

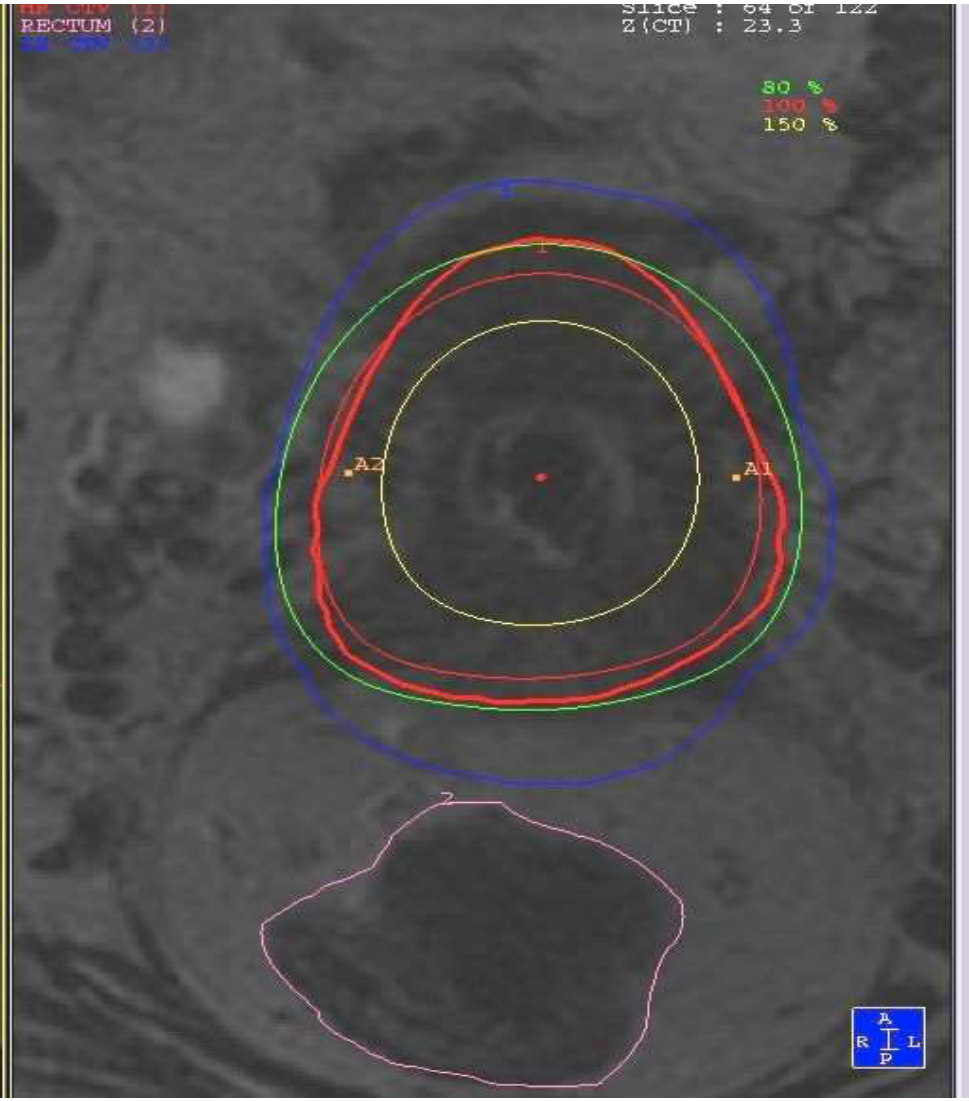


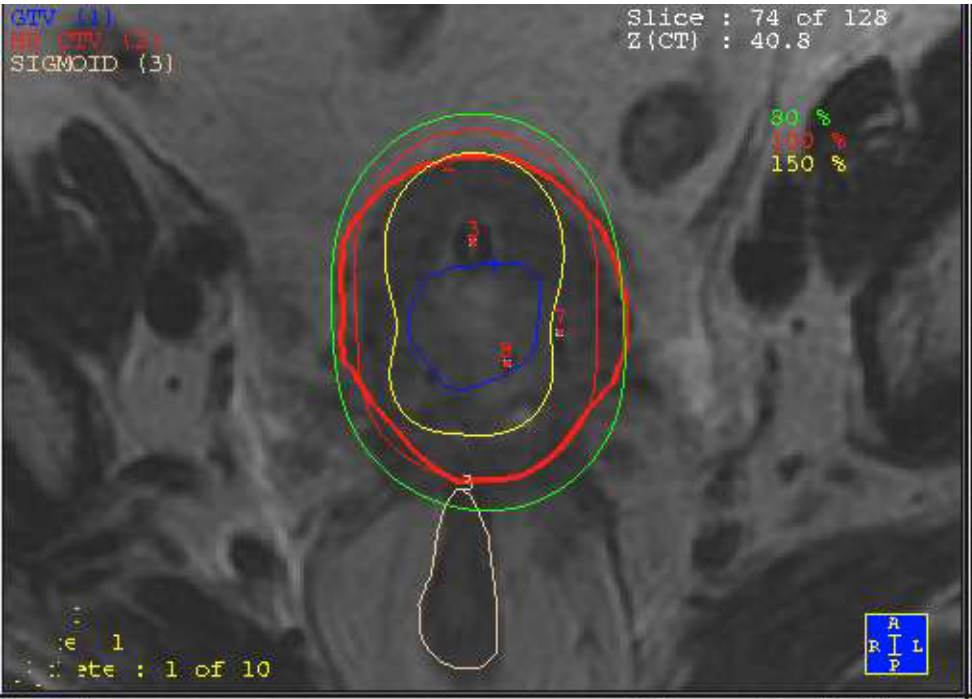


Vienna Group, work in progress:
N Nesvacil, M Schmid, C Kirisits

Point A Located Inside Target/Higher Dose than Prescription Dose



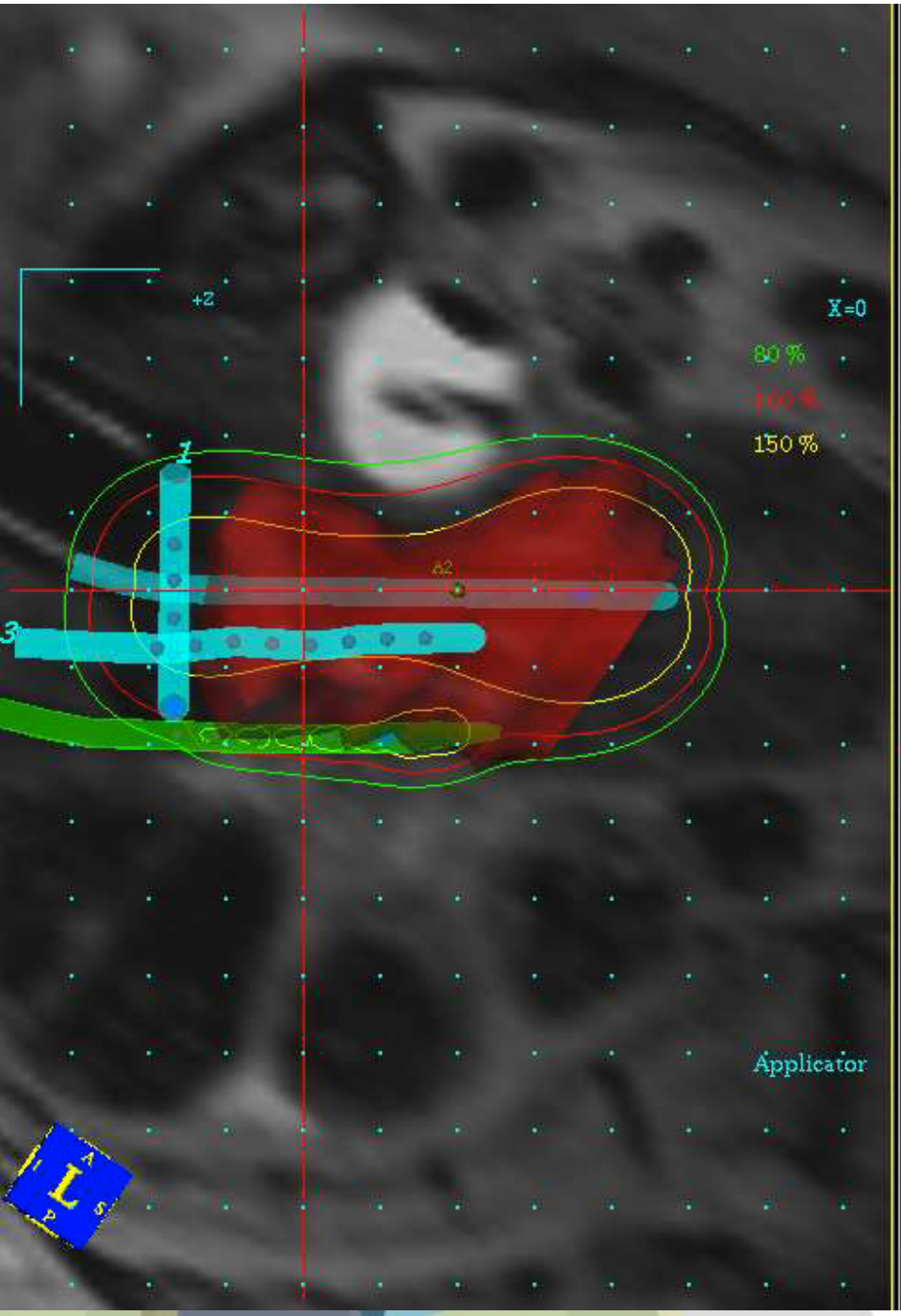


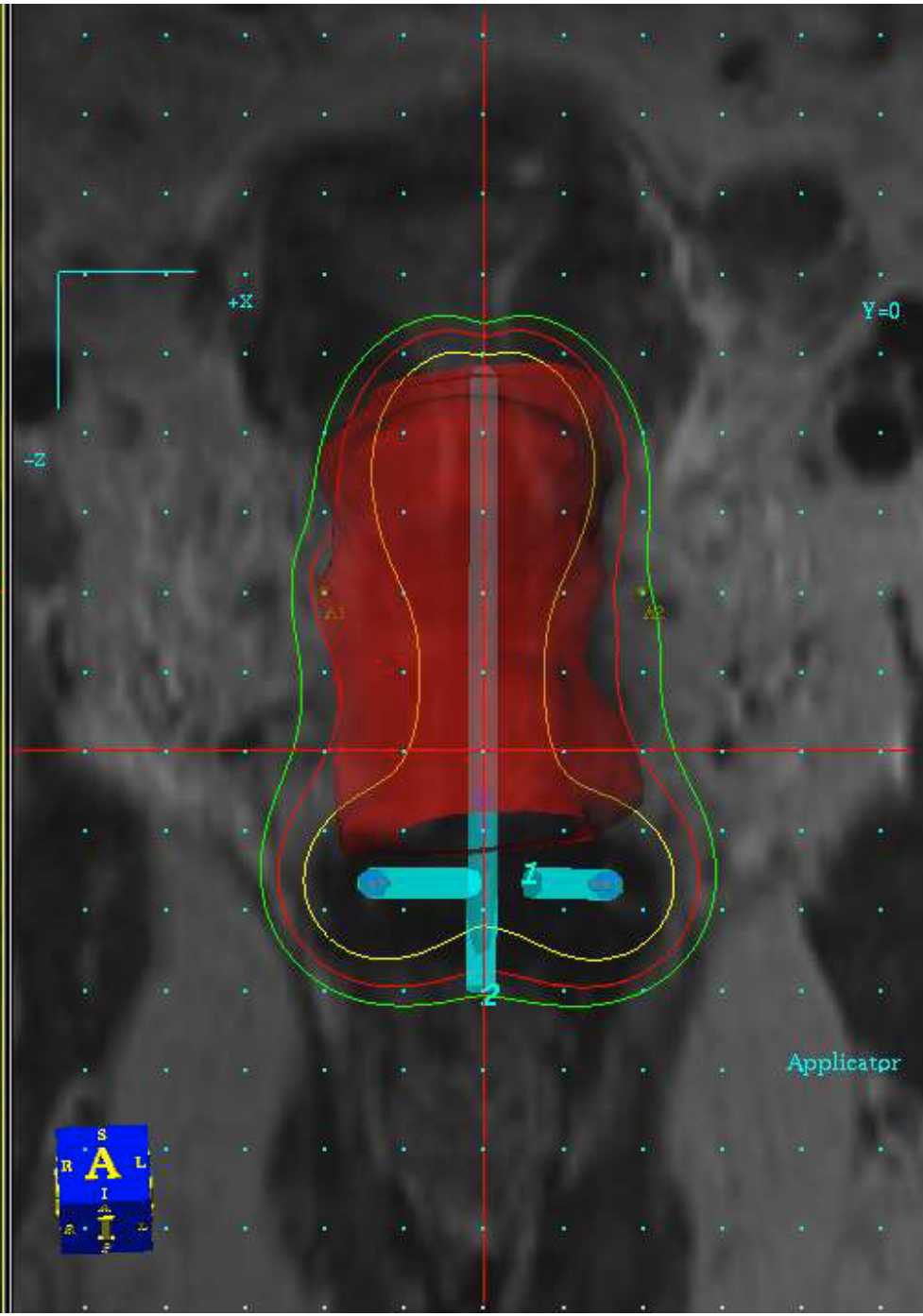

GTV (1)
HR CTV (2)
SIGMOID (3)
Slice : 74 of 128
Z(CT) : 40.8
80 %
100 %
150 %
Catheter: 1 of 10
A
R L
P


GTV (1)
HR CTV (2)
SIGMOID (3)
Slice : 71 of 128
Z(CT) : 34.8
80 %
100 %
150 %
Catheter: 1 of 10
A
R L
P

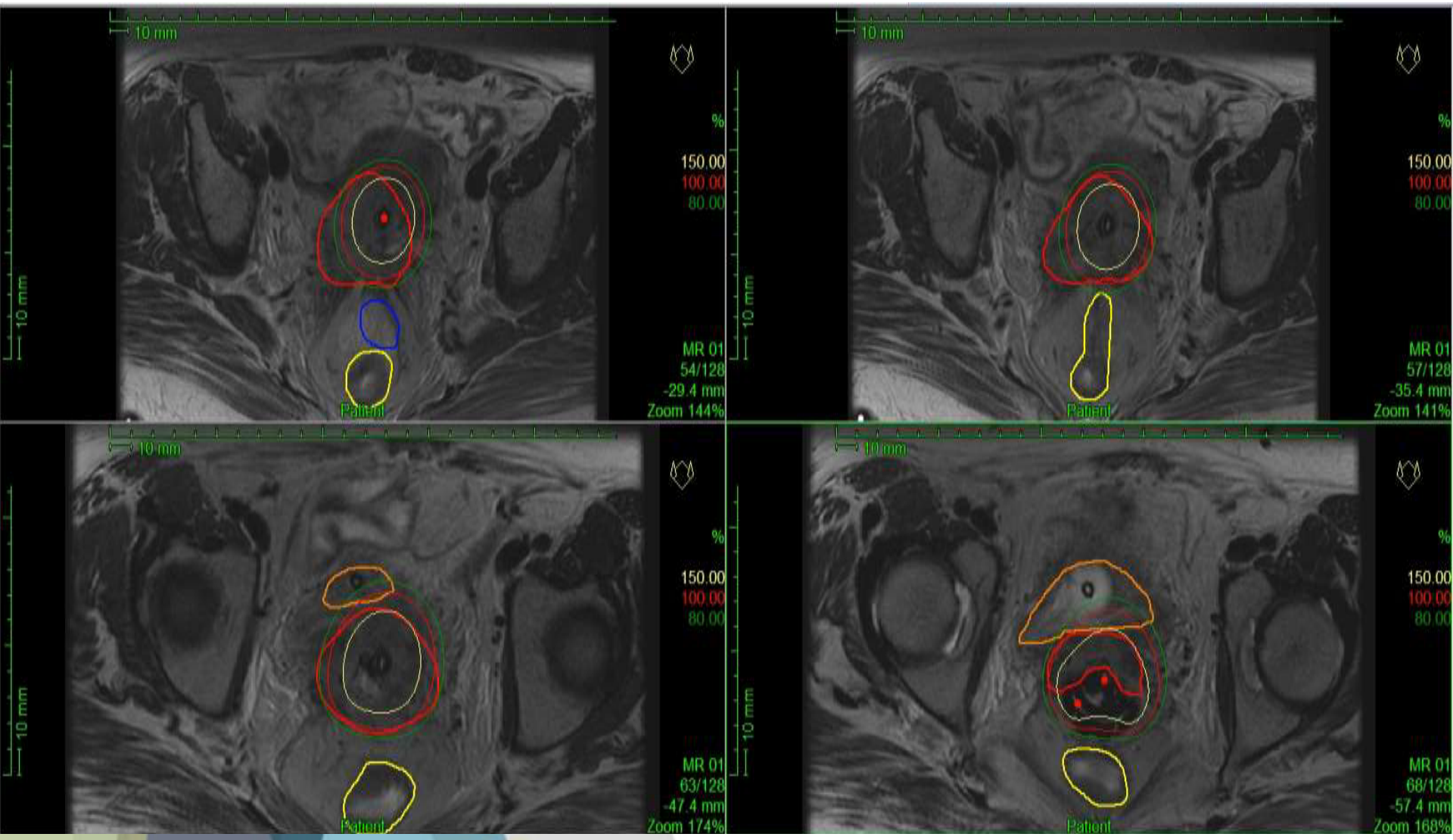

GTV (1)
HR CTV (2)
RECTUM (3)
Slice : 66 of 128
Z(CT) : 24.8
80 %
100 %
150 %
A
R L
P


BLADDER (1)
HR CTV (2)
RECTUM (3)
Slice : 55 of 128
Z(CT) : 2.8
80 %
100 %
150 %
A
R L
P

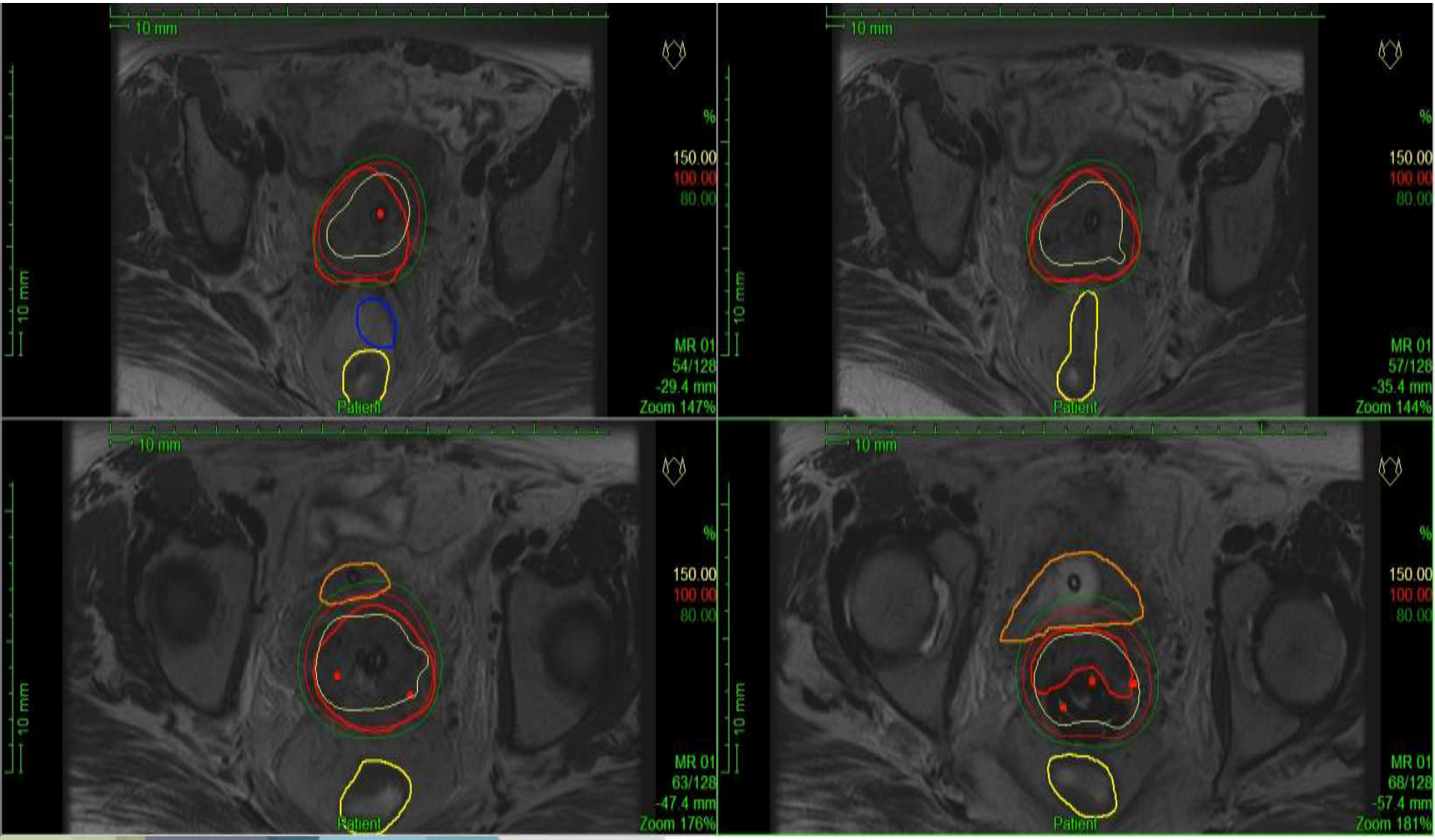

+Z
X=0
80 %
100 %
150 %
1
2
3
A1
A2
Applicator
A
P
L
S

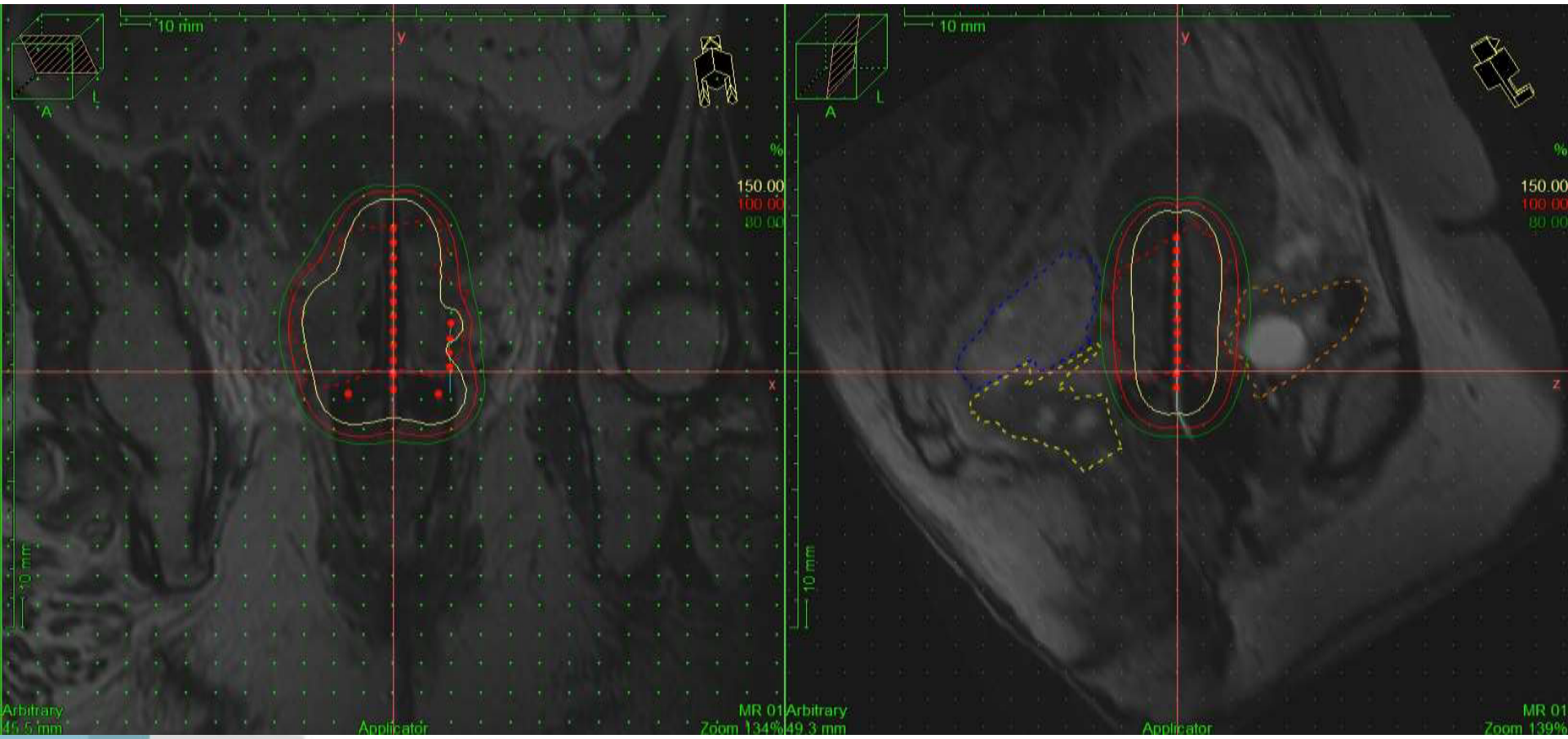

+Z
Y=0
-Z
1
2
A1
A2
Applicator
S
R
A
L
I

Without hybrid applicator



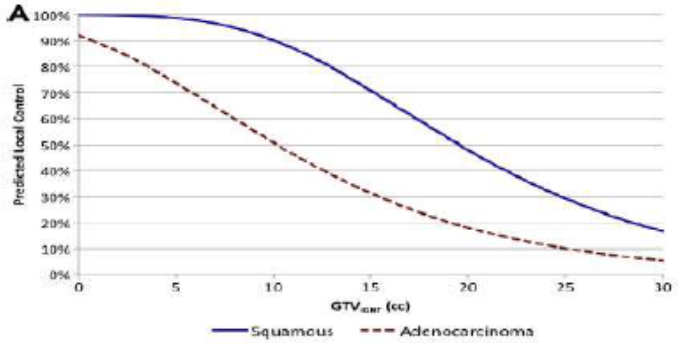
With hybrid applicator




10 mm
A
L
y
%
150.00
100.00
80.00
x
10 mm
Arbitrary
45.5 mm
Applicator
MR 01
Zoom 134%
10 mm
A
L
y
%
150.00
100.00
80.00
z
10 mm
Arbitrary
49.3 mm
Applicator
MR 01
Zoom 139%

Questions

- Does the improved coverage afforded by IC/IS in poor responders over come bad biology and improve tumor control outcomes?



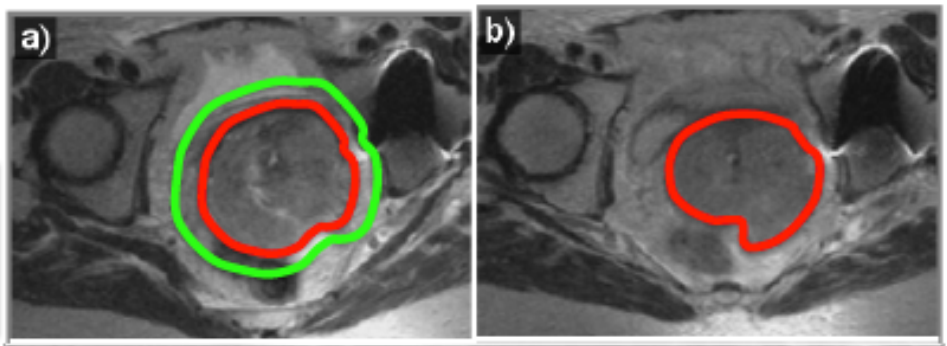
- Beriwal et al *Rad Oncol* 2015;115:78-83
  - GTV volume by MRI at the time of brachytherapy is a strong predictor of LC, DFS, and OS despite no difference in mean HRCTV D90.

Example: cervical cancer: total dose 90 Gy EQD2

EBRT dose

0 Gy

Initial GTV
Volume 75 ccm



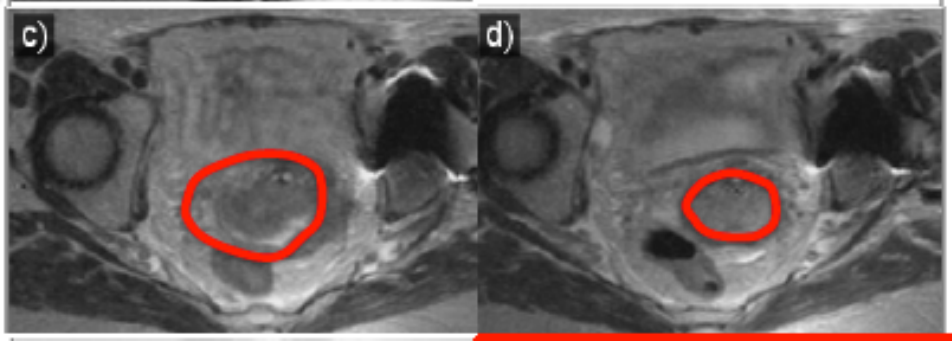
EBRT dose

9 Gy

Cisplatin (40 mg/m^2) x1

18 Gy

Cisplatin (40 mg/m^2) x2

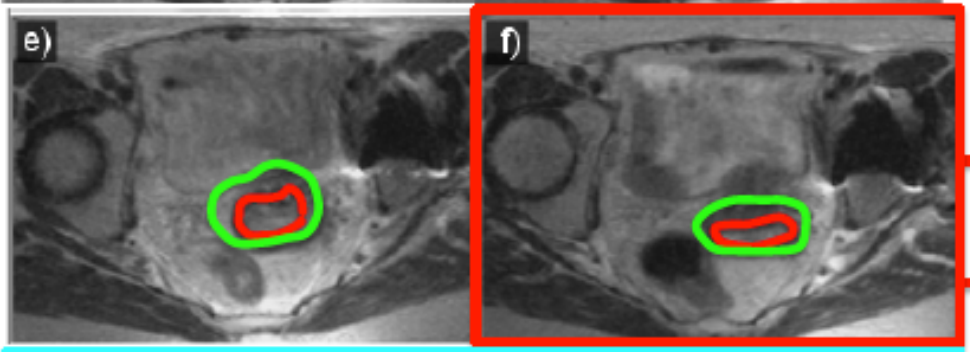


27 Gy

Cisplatin (40 mg/m^2) x3

36 Gy

Cisplatin (40 mg/m^2) x4

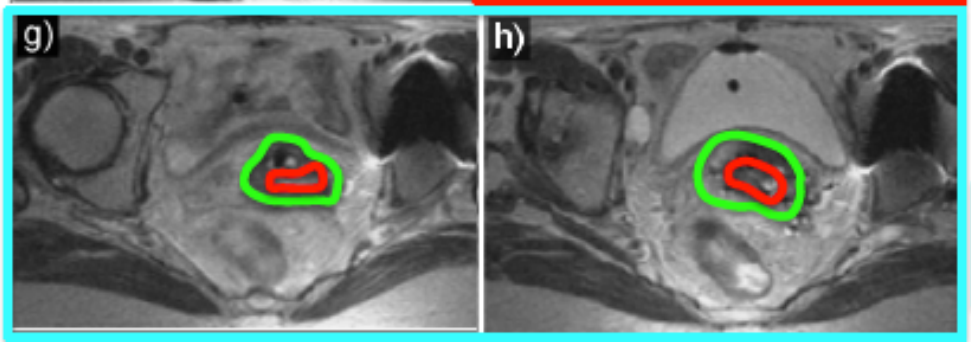


45 Gy

Pre-brachytherapy
Residual GTV: 8 ccm

EBRT45 Gy

Cisplatin (40 mg/m^2) x5



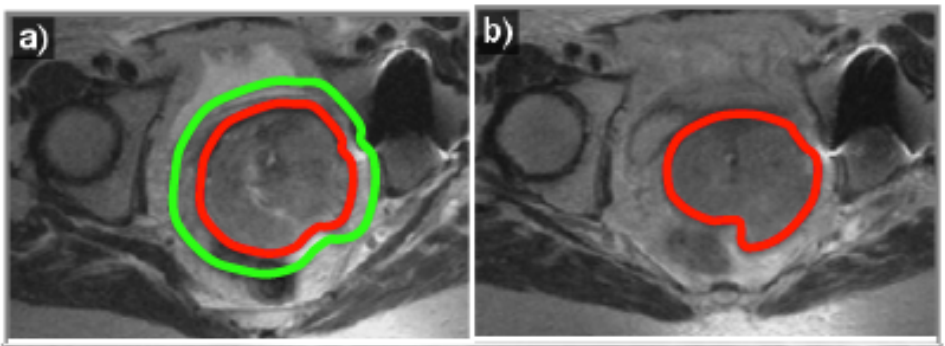
IGABT 45 Gy

Brachytherapy
HR CTV 30 ccm

GTV
CTV

modified from
ICRU 89, 2016

Example: cervical cancer, FIGO IIIB (mod. From ICRU report 89, 2016, Fig. 4.3)

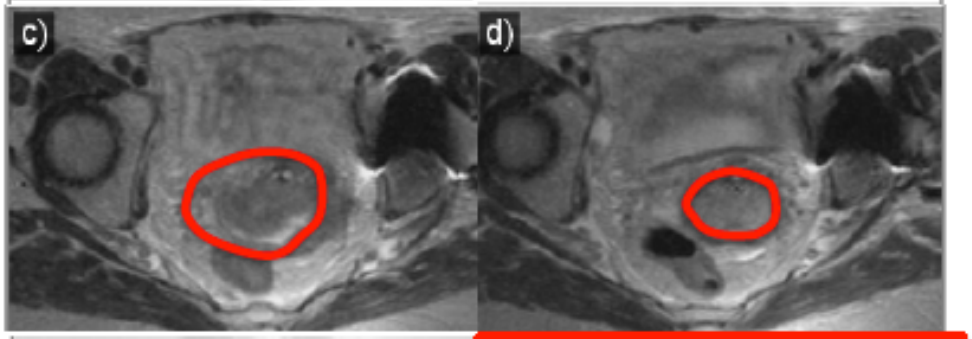


EBRT dose

0 Gy →

← 9 Gy

Cisplatin (40 mg/m^2) x1

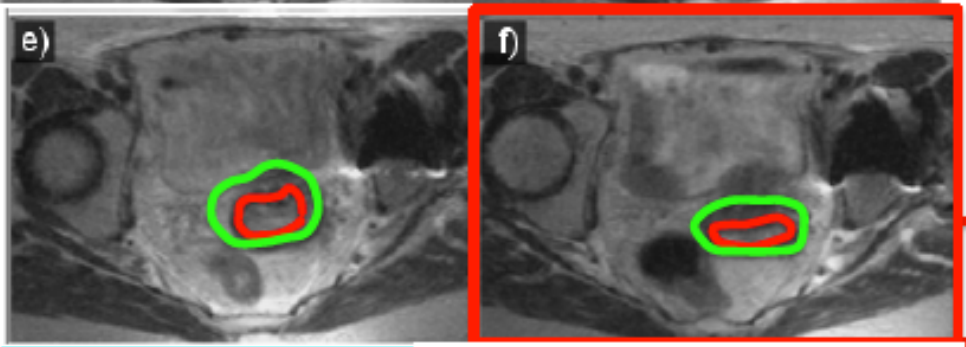


18 Gy →

Cisplatin (40 mg/m^2) x2

← 27 Gy

Cisplatin (40 mg/m^2) x3

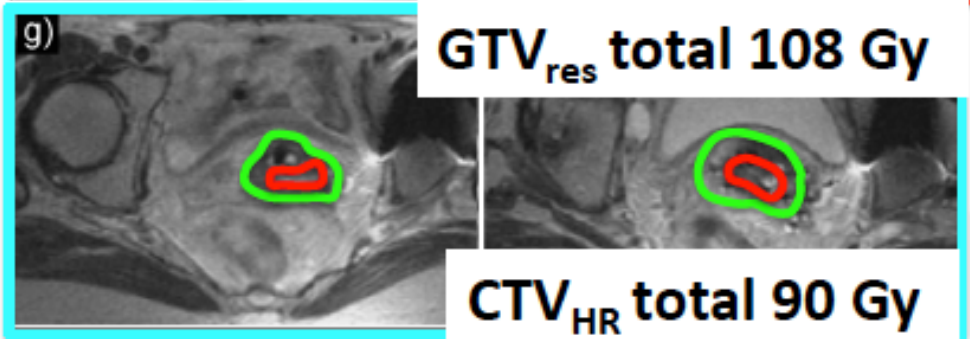


36 Gy →

Cisplatin (40 mg/m^2) x4

← 45 Gy

Pre-brachytherapy



GTV_{res} total 108 Gy

45 Gy →

Cisplatin (40 mg/m^2) x5

← + 45 Gy

CTV_{HR} total 90 Gy

Brachytherapy

GTV initial and residual

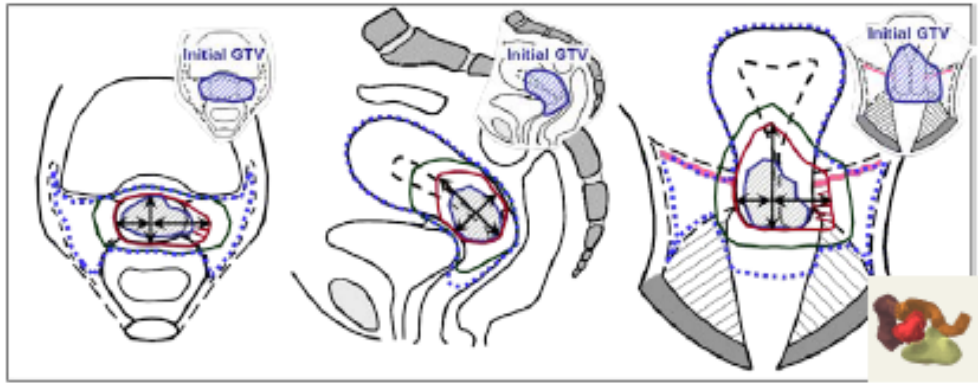
CTV initial and adaptive

Dose prescription according to risk

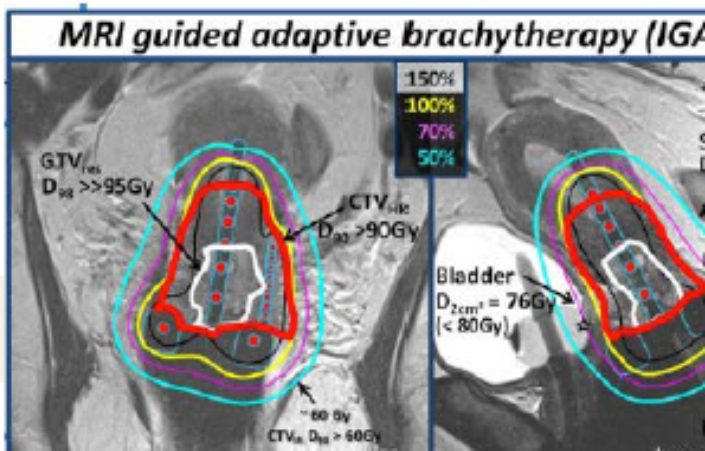
large variations in initial/adaptive volumes and doses

(EMBRACE studies (06/2017)) (n=1416 pats.)

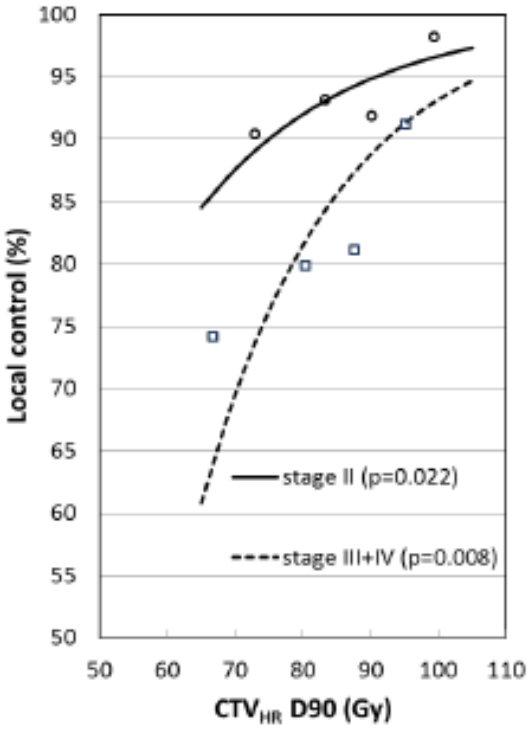
		EQD2
Initial CTV-T_{LR}	Ø 230 cm^3	≈ 50-60 Gy
Initial GTV-T	Ø 55 cm^3	≈ 70-90 Gy
Adaptive CTV-T_{IR}	Ø 78 cm^3	D90 med. 70 Gy
Adaptive CTV-T_{HR}	Ø 33 cm^3	D90 med. 89 Gy
Residual GTV	Ø 9 cm^3	D98 med. 102 Gy

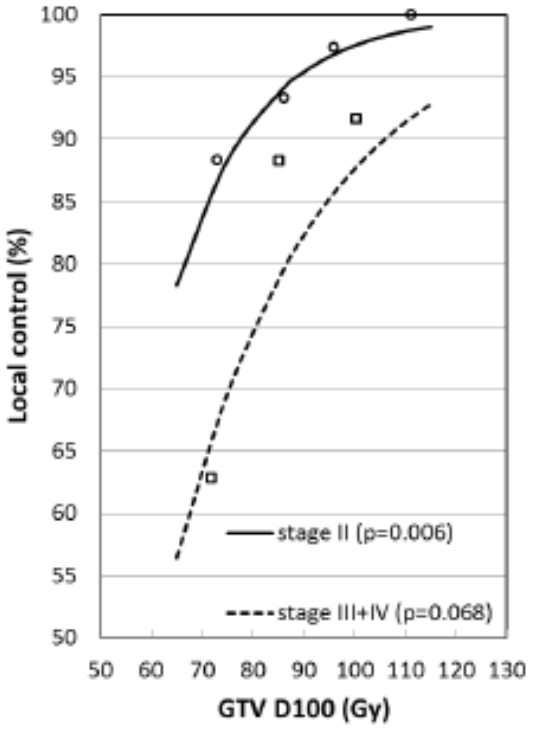


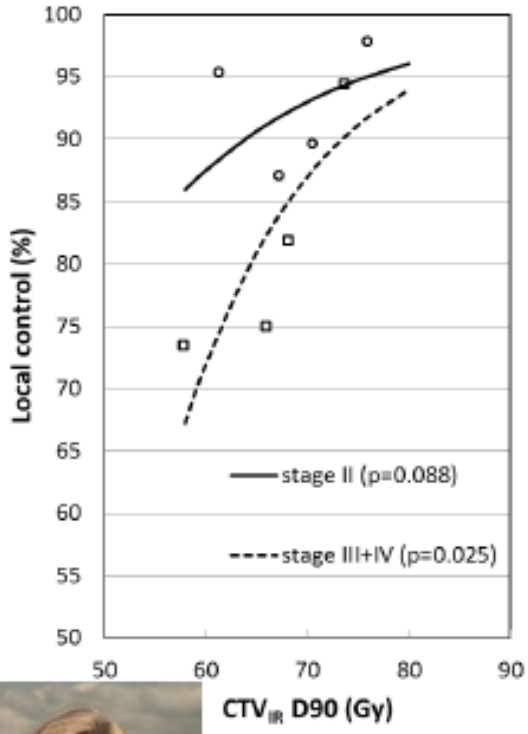
EMBRACE



Dose effect for CTV_{HR}, GTV_{res} and CTV_{IR}







RETRO EMBRACE

Tanderup et al RO, Radiother and Oncol, vol 120, 2016

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

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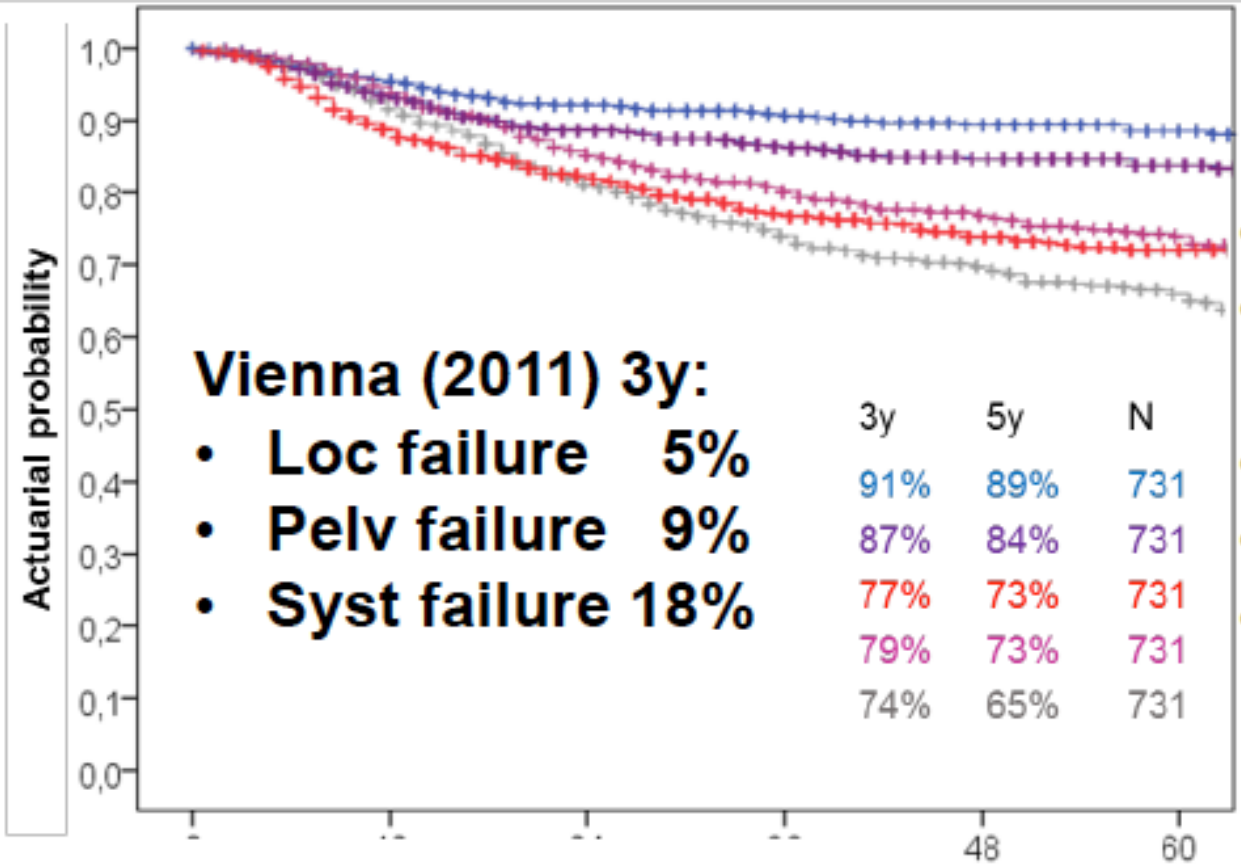
Local, pelvic and distant control, cancer specific and overall survival



Vienna (2011) 3y:

- **Loc failure 5%**
- **Pelv failure 9%**
- **Syst failure 18%**

3y	5y	N
91%	89%	731
87%	84%	731
77%	73%	731
79%	73%	731
74%	65%	731

RETRO EMBRACE

- **731 patients**
- **12 institutions**

- **Loc fail 9-11%**
- **Pelv fail 13-16%**
- **Syst fail 23-27%**

Vienna: mean D90 HR CTV 92 Gy

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

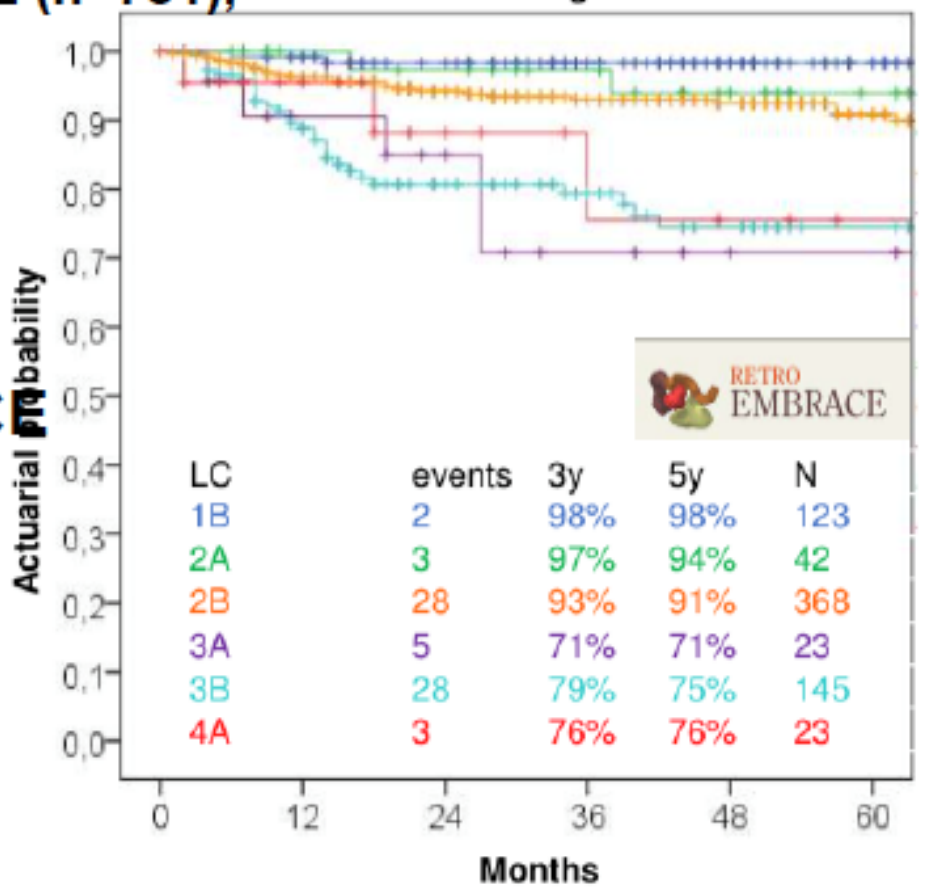
Mean D90 HR CTV 84 Gy

Sturdza et al. R&O 2016

Clinical Results for adaptive RT/BT
Local control and FIGO stage

RetroEMBRACE (n=731),

Vienna (n=158)



Local failure

RetroEMBRACE

3y

Total: 9%

IB 2%*

IIB 7%

IIIB 21%

IVA 24%

***2 events in IB2**

Local failure

Vienna (2011)

3y

Total: 5%

IB 0%

IIB 4%

IIIB 14%

IVA 2/6 (n)

Sturdza et al. R&O 2016

Pötter et al. R&O 2011

Improving Local Control

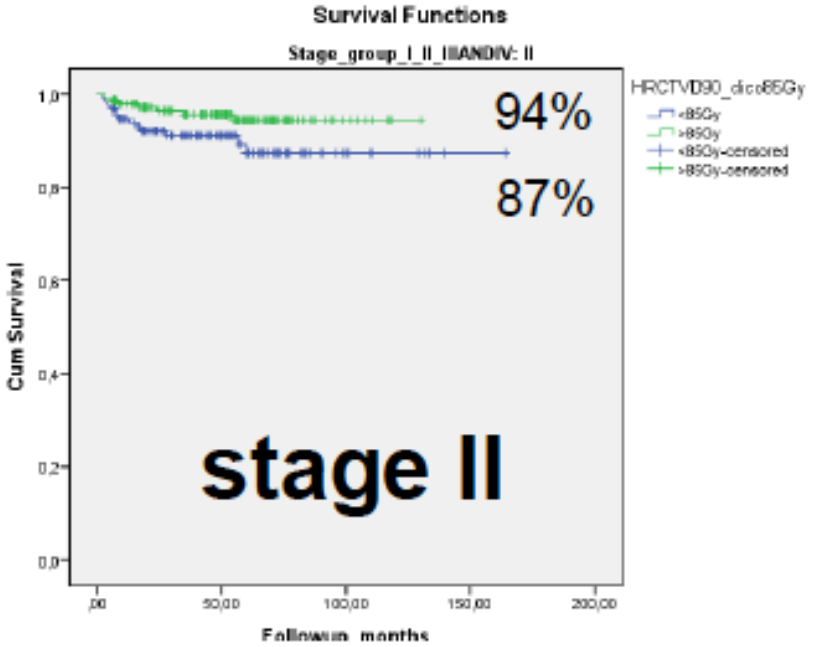
EMBRACE (as of 12/2013)

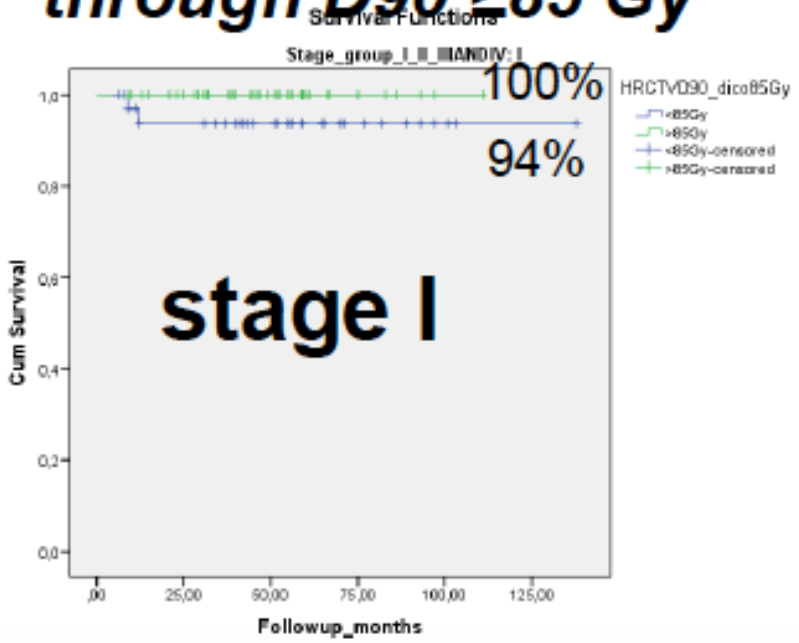
large variation in D90

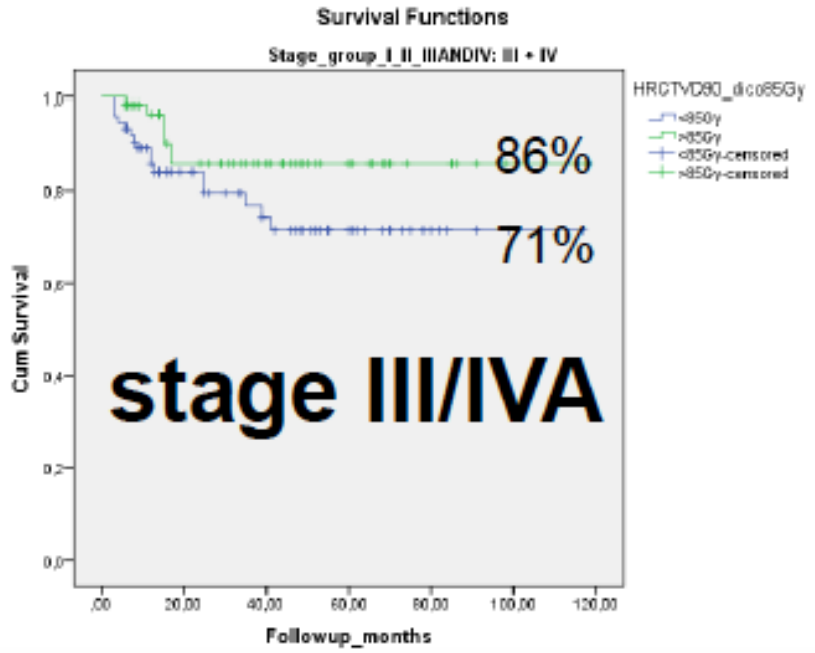
versus:

expected EMBRACE II

through D90 ≥85 Gy

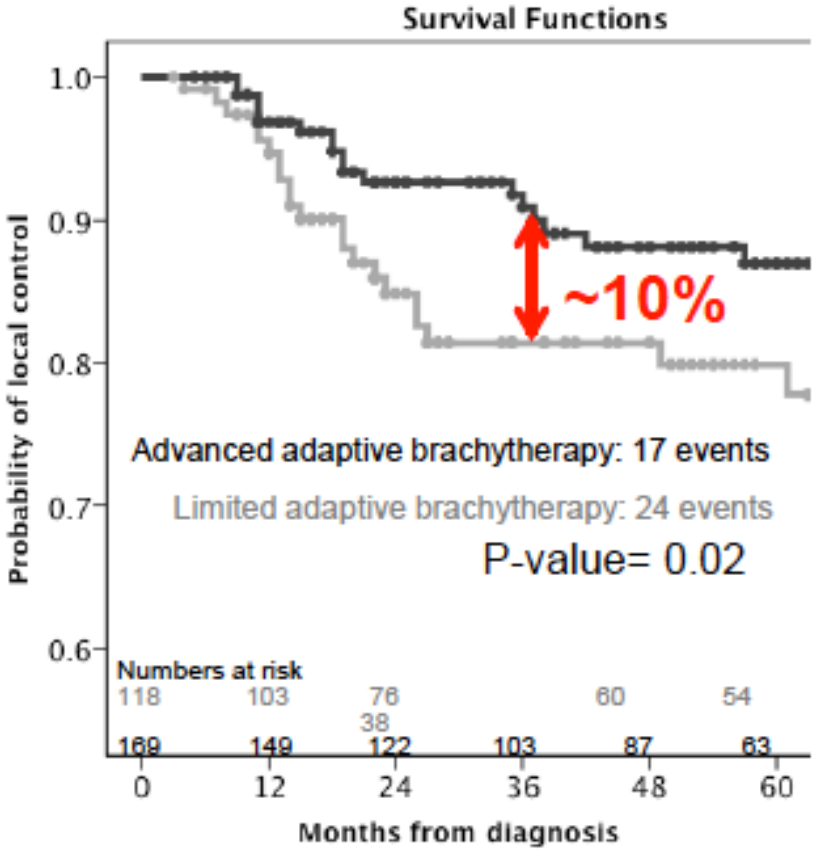




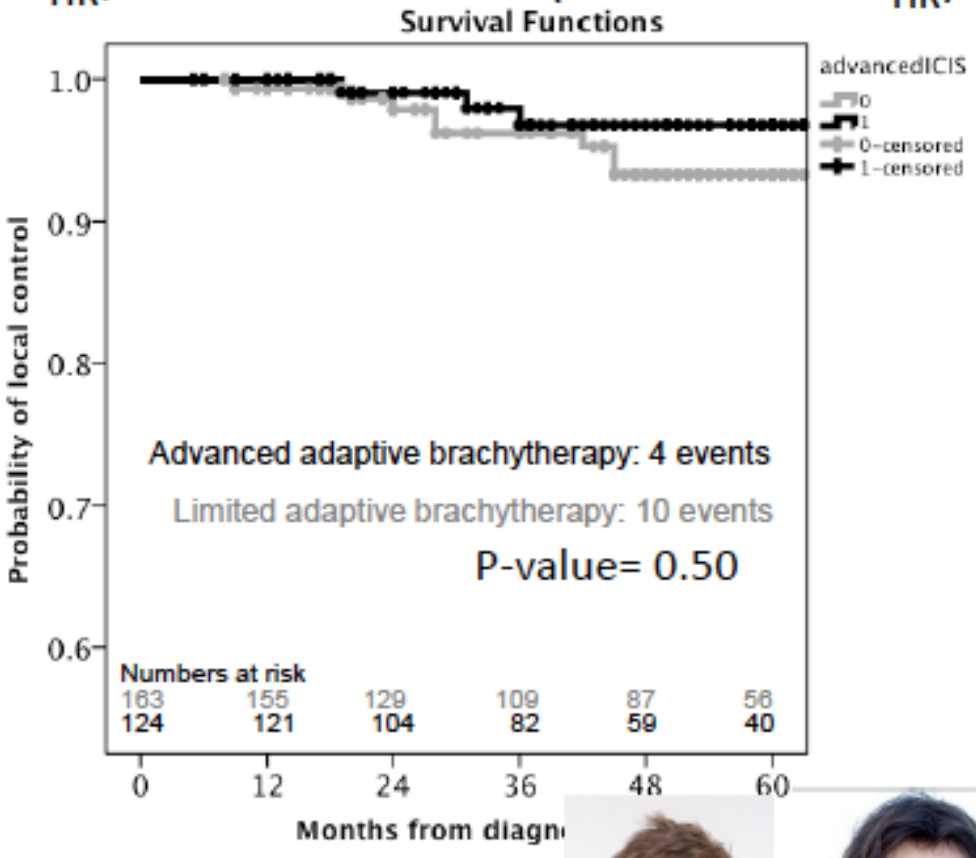


Improved local control with IC/IS in large tumours (retroEMBRACE)

Large tumours (≥30 cm^3 CTV_{HR})



Small tumours (<30 cm^3 CTV_{HR})



Fokdal et al RO, in press
Fortin et al, WCB 2016

Clinical evidence: Overall local outcome

EMBRACE cohort (n=1230)

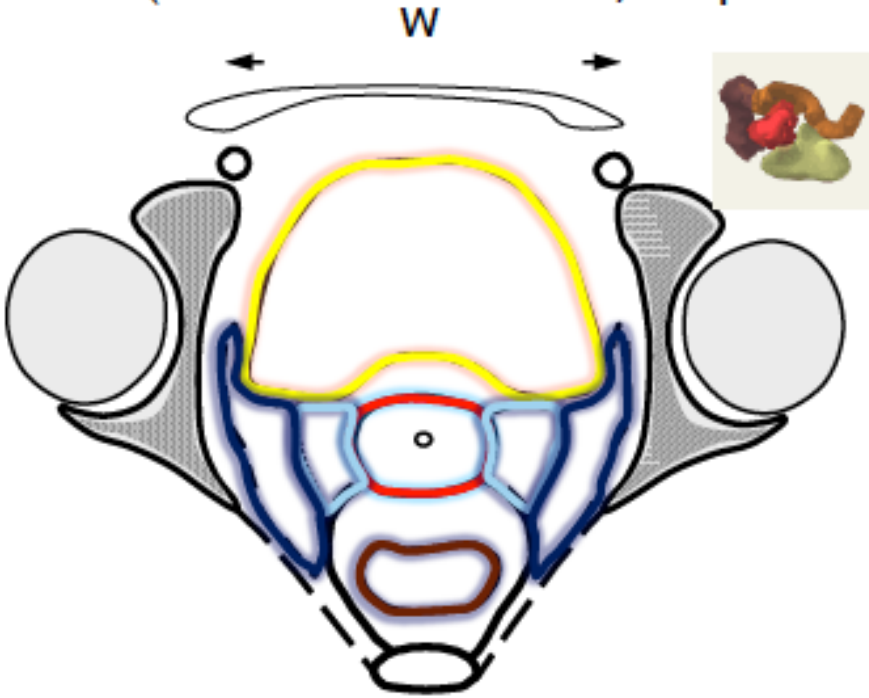
- **24 incomplete remissions (IR)** (98% complete remission rate)
  (72 incomplete remissions (IR) at 3 months, 48 resolved at 6-9 months)
- **56 local recurrences (LR)** (at median 25 months FUP)
  - Median time to local recurrence: 11.5 months
    (86% of local recurrences occured within 24months)
- **80 local failures (IR+LR) (6.5%)**
  - 42 (52%) synchronous nodal or distant failures

M. Schmid ESTRO 2017

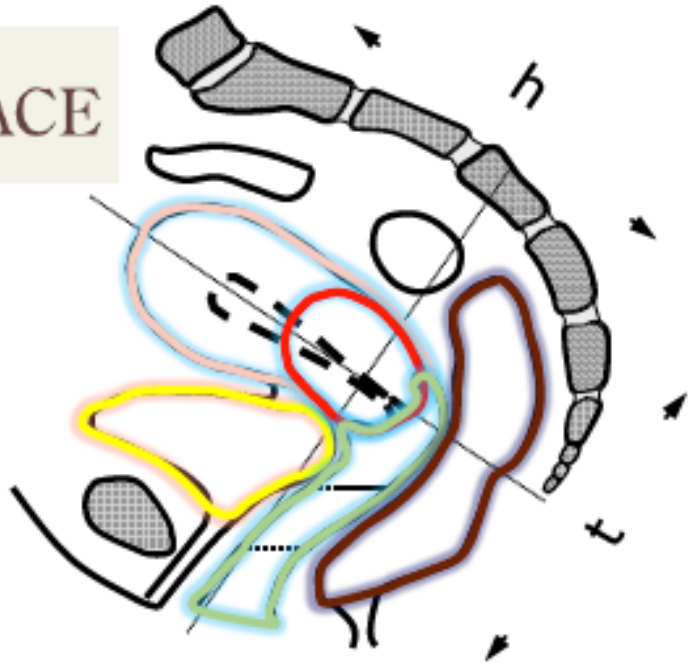
Anatomical location of local failures (n=1230)

108 locations in 63 patients with local failure

(data available in 63/80 patients (79%), multiple locations possible)



EMBRACE



Cervix and uterus: 80% (n=50)

Proximal parametria: 13% (n=8)

Distal parametria / pelvic wall: 29% (n=18)

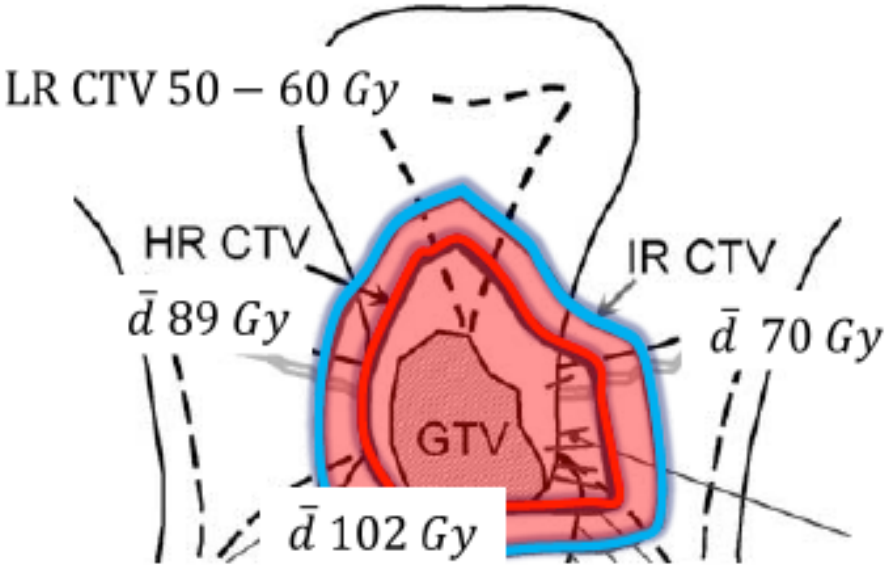
Vagina: 29% (n=18)

Urinary bladder: 19% (n=12)

Rectum: 3% (n=2)

Local failures
in regard to boost brachytherapy target volumes

data available in 53/80 patients (66%)



EMBRACE

Inside HRCTV: 51% (n=27 (+16))

Inside IRCTV: 17% (n=9)

Inside HR & IRCTV: 30% (n=16)

Not related: 2% (n=1)

Failure pattern provides
prospective clinical validation of adaptive target concept
For locally advanced cervix cancer applying BT boost
(one major aim of the EMBRACE study)

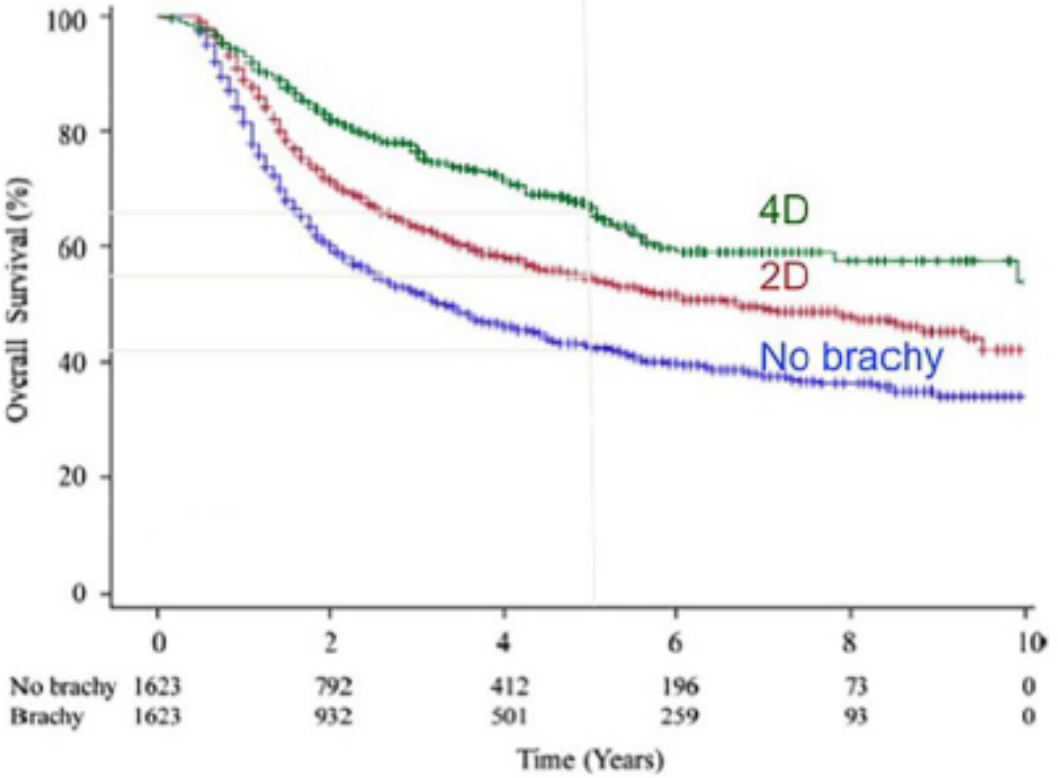
Overall Survival locally advanced cervical cancer: **the impact of brachytherapy**

Total 25% increase in Overall Survival

with „4D brachy“ (RetroEMBRACE)

compared to

„no brachy“ (Han et al)



Han et al Int J Radiation Oncol Biol Phys 2013;87:111-119

Sturdza et al. Improved local control and survival in LACC thruough Imae guided adaptive brachytherapy, submitted

Dosimetría a OARs y Resultados

Discrepancias entre las dosis a vejiga y recto

	Orthogonal film based vs	CT based
Ling et al	Bladder	1.0 - 4.1x
	Rectum	1.4 - 2.5x
Schoeppel et al	Bladder	2.1 - 2.3x
	Rectum	1.3 – 1.6x
Stuecklschweiger et al	Bladder	1.0 - 2.2x
	Rectum	1.1 - 1.6x
Kapp et al	Bladder	1.0 – 5.4x
	Rectum	1.1 – 2.7x

Correlación de hallazgos Endoscópicos y Dosimetría

	2cc	1cc	.1cc
Koom *et al* VRS ≥ 3	75Gy vs. 69 Gy	80 Gy vs. 73 Gy	90 Gy vs. 85 Gy
Georg *et al* VRS≥ 3	72Gy vs. 62 Gy	76 Gy vs. 65 Gy	88 Gy vs. 75 Gy
Georg *et al* Symptomatic	72 Gy vs. 64 Gy	76 Gy vs.67 Gy	88 Gy vs. 77 Gy

Results on morbidity, PRO, QoL
DVH based predictive dose factors

- **Rectum** proctitis, bleeding (G1-2), fistula rare
- **Bowel** diarrhea, flatulence (G1-2), anal incontinence (low), stenosis and fistula rare
- **Bladder** frequency/urgency, incontinence (G1-2), cystitis, bleeding, fistula, ureter strict. (low)
- **Vagina (G≤2)** stenosis/shorten, dryness, bleeding, mucos.

PRO shows significantly more burden from G2 symptoms for patients

- Descriptive and analytical evaluations

Work in progress, much to learn in near future (EMBRACE)

Max. incidence bladder morbidity

1176 patients with CTC-assessment

	Frequency	Incontinence	Spasm	Bladder stenosis	Ureter Stenose^	Cystitis	Bleeding	Fistula* (N=1093)
G0	470 (40.0%)	784 (66.7%)	1081 (91.9%)	1166 (99.1%)	1125 (95.7%)	958 (81.5%)	1098 (93.4%)	1083 (99.1%)
G1	470 (40.0%)	267 (22.7%)	75 (6.4%)	7 (0.6%)	15 (1.3%)	132 (11.2%)	55 (4.7%)	3 (0.3%)
G2	123 (10.4%)	106 (9.0%)	19 (1.6%)	3 (0.3%)	12 (1.0%)	75 (6.4%)	19 (1.6)	< 10%
G3	14 (1.2%)	14 (1.2%)	1 (0.1%)	0 (0%)	17 (1.4%)	10 (0.9%)	4 (0.3%)	< 5%
G4		5 (0.4%)	0 (0.1%)	0 (0%)	2 (0.2%)	1 (0.1%)	0 (0%)	3 (0.3%)

* Total of 17 fistulas were diagnosed. 7 patients had tumor involvement of the bladder at time of diagnosis and were excluded
^ 5 patients were censored due to ureter stricture G3 that persisted from baseline

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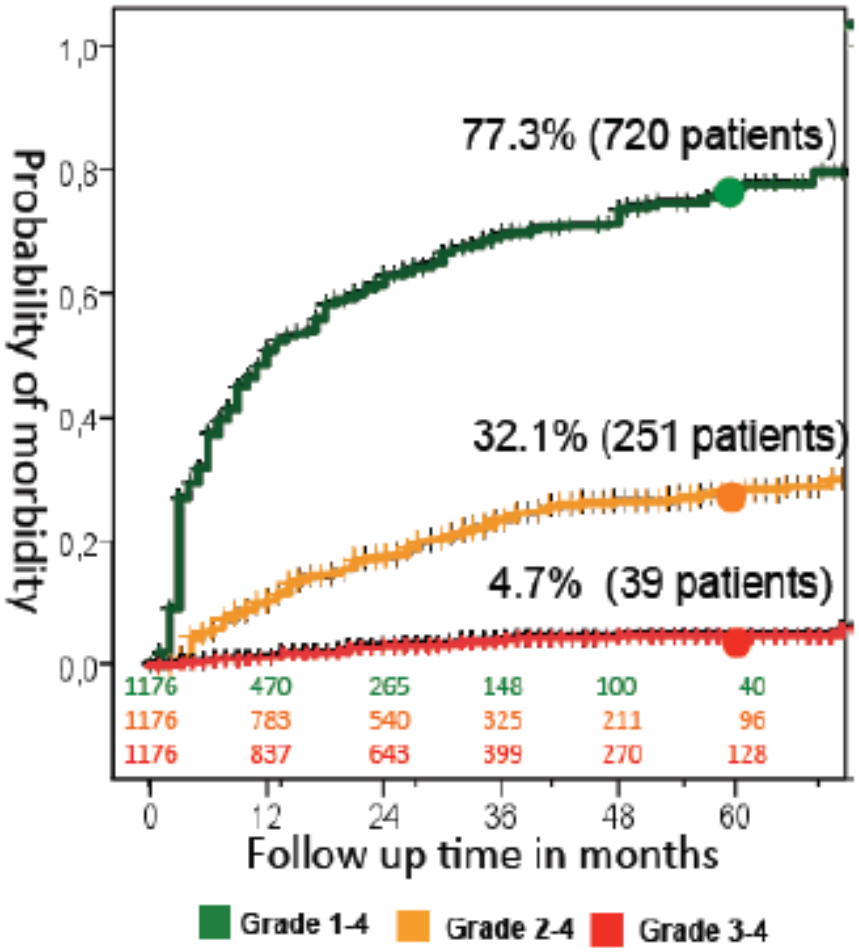
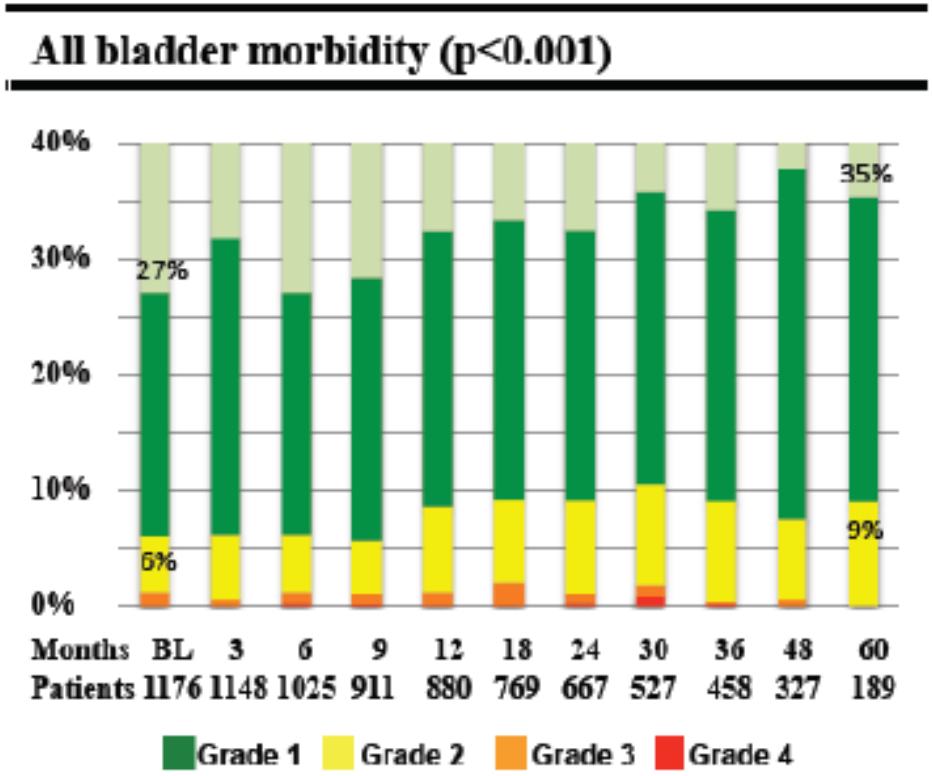
All bladder morbidity

All single CTCae endpoints grouped together

Kaplan-Meier estimates



Prevalence rates at follow up



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Conclusions

- **Low actuarial 5-year grade 3-4 morbidity**
  - All bladder symptoms 4.7%
    - Frequency/incontinence 1.9%/2.1%
    - Fistula 0.7%
    - Bleeding 0.6%
  - Ureteral stricture 3.4%
- **Maximal prevalence rates of mild and moderate physician assessed morbidity**
  - Urinary frequency G1/G2: 25.6%/4.8%
  - Incontinence G1/G2: 19.4%/5.8%
  - Cystitis G1/G2: 8.4%/4.0%
- **The burden of morbidity is weighted different by physicians and patients**
- **PRO is necessary for the evaluation of morbidity in future studies**

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Overview Rectum (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

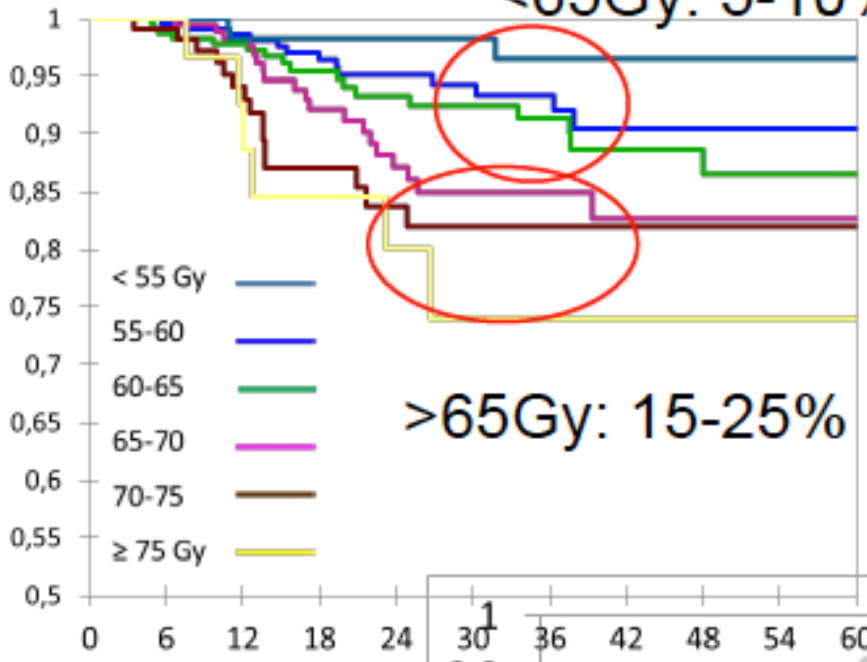
Grade 1-4	16.8+/-12.7
Grade 2-4	17.5+/-9.5
Grade 3-4	15.8+/-5.3

Mazeron et al. 2016

Rectal dose volume effects

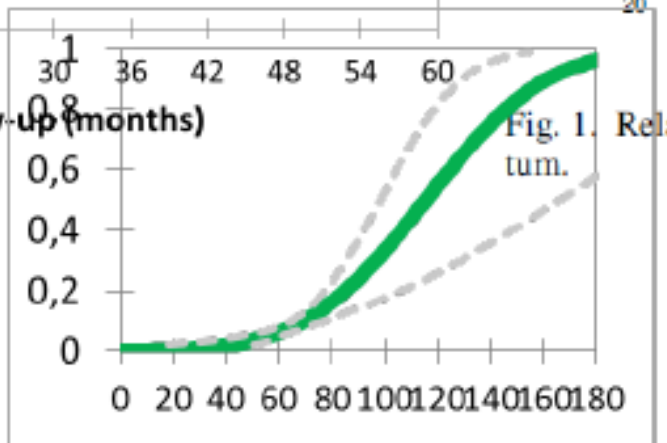
≥G2 rectal morbidity
(EMBRACE cohort, n=960)

<65Gy: 5-10%



>65Gy: 15-25%

Mazeron et al.,
RO 2016



≥G2 rectal morbidity (bleeding)
(Vienna cohort, n=145)

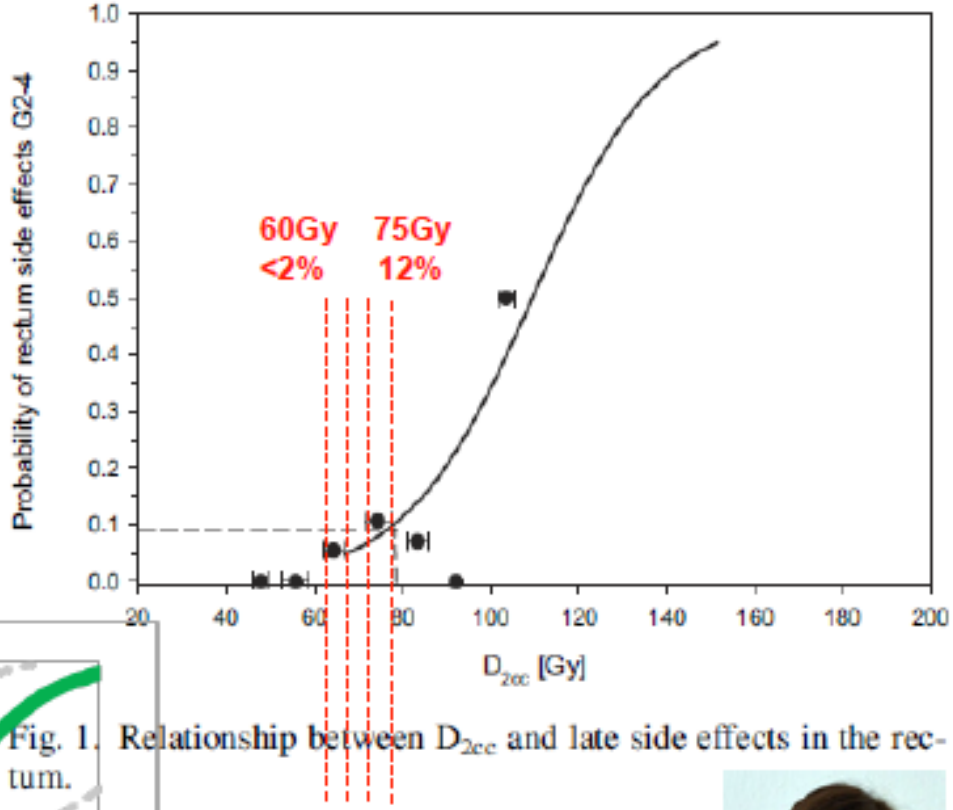


Fig. 1. Relationship between D_{2cc} and late side effects in the rectum.

P. Georg et al.,
IJROBP 2011

Summary of large studies

Institution/Country	n=	Imaging modality	Interstitial	Median follow-up (months)	Local control	Overall survival	Late grade 3+ GU/GI toxicity
Australia	292*	Ultrasound + MRI	0%	49.2	88% (crude)	5-year 65%	5.8% (crude)
Vienna	156	MRI	44%	42	3-year 95%	3-year 68%	2-4%
Pittsburgh	128	CT + MRI	7%	24	3-year 92%	3-year 77%	3.3%
French STIC Trial	117	CT or MRI	0	24	2-year 79%	2-year 74%	1.2%
Warsaw	216	CT	40%	47	5 years 90%	5 yrs 66.4%	9%
Utrecht	46	MRI	34%	41	3-year 93%	3-year 65%	9.5% (crude)
Paris	225	MRI	2.2%	39	3 years 86.4%	2-year 78%	2.2% (crude)
RetroEmbrace	455	CT + MRI	25%	20	3 yrs 91.4%	3 years 76%	

Estado de la IGABT

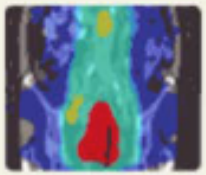
Transición de Braquiterapia de 2D a 3D adaptativa
Preferible basada en US , TEM o RMN . Repetir examen gyn.
Concepto adaptativo.
Adaptar aplicadores a la evolución clínica IC.
Alta dosis al HR CTV mayor a 85-90Gy EQD2
Tambien para GTV (mayor a 90-95 Gy)
y CTV IR 65-70 Gy
Dosis moderada a volúmenes de OARs adyacentes
Usar datos de Embrace II

Dose prescription protocol in cervix cancer

EMBRACE II (2016-2020)

prospective validation of DVH parameters for adaptive BT

	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	-	-



EMBRACE-II

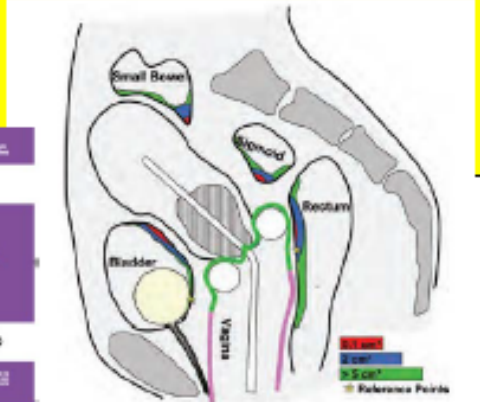
{ Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer }

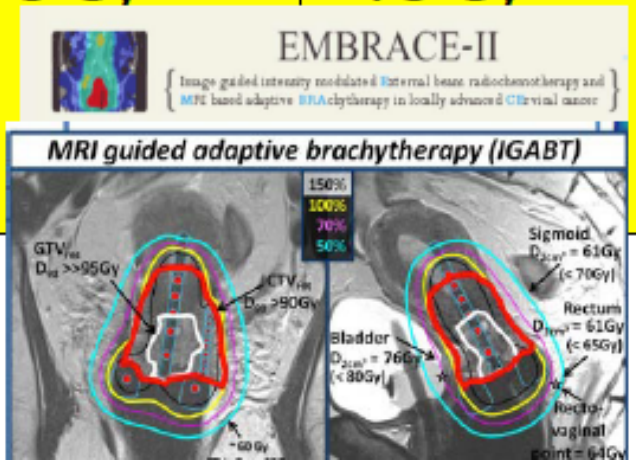
Dose prescription protocol in cervix cancer

EMBRACE II (2016-2020): OAR dose volume constraints

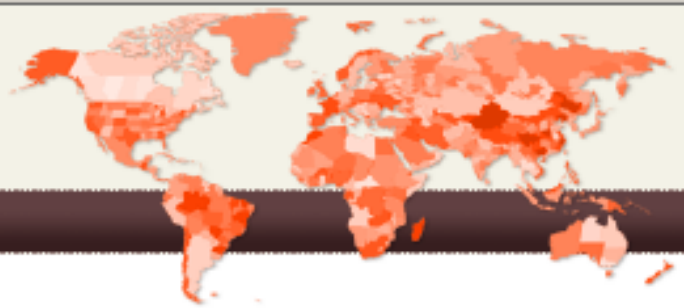
prospective validation of DVH parameters for adaptive BT

	Bladder D_{2cm^3} $EQD2_3$	Rectum D_{2cm^3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid/ Bowel D_{2cm^3} $EQD2_3$
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy*
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*





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



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Outlook

- **More evidence from EMBRACE studies (I and II)**

  volume and dose modelling

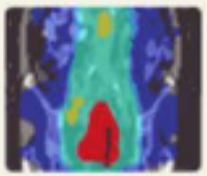
  multi-parametric prescription protocols (CTVs/OARs)

- **Spread of image guided BT and EBRT**

  using different workflows/technologies CT, US, MRI

- **Prognostic and predictive parameters (incl. translational)**

  More patient and treatment selection



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

Conclusión

Es tiempo para el cambio a 3D como ha sucedido en RT externa

Planeamiento basado en imágenes da mejor estimación de distribución volumétrica con buena correlación entre la dosis y el efecto

Permite mejor cobertura del volumen blanco y reduce dosis a órganos críticos

Data clínica actual muestra mejor control local y disminución de la morbilidad con nivel de evidencia importante

Cuales son las barreras para IGBT - Respuestas

- No RM en el departamento – Use CT/US intégrelo con RM si dispone
- No se tienen los aplicadores correctos – Razonablemente no costosos, empiece con lo que conoce.
- No se tiene el Staff – Identifique y empodere un grupo que pueda realizarlo.
- No hay tiempo para contornear – con la practica se hará mas rápido y lo vale
- No experiencia en contorneo en RM – ABS gyn Brachy / eCountouring Sessions
- No hay comodidad moviéndose del punto A – Esta bien empiece lento a su paso
- No se tiene experiencia en intersticial – tendrá las ganas de intentar luego de realizar los primeros casos
- No sabe por donde empezar – Encantado de poder ayudar
- La practica estándar funciona bien la mayoría del tiempo: por que cambiar? – porque 20 -25% se beneficiara en reducción toxicidad y mejoría control

Caso Clínico

ANTECEDENTES

- Edad: 65 años
- Personales:
    - HTA: Carvedilol 12.5mg/d, Tiazid 12.5mg/d.
    - NM mama IA: (MRMder-2001) + QT: actualidad RLR (-)
    - Tonsilectomía en la niñez
    - Hábitos nocivos: niega
    - GO: FUR: 50años, G2P2, ACOs: x 3 años, NPS: 2
- Familiares: Madre y Hermana: NM mama

RELATO DE LA Enfermedad

- TE: 4 meses
- Síntomas y Signos: ginecorragia ocasional
- Ex Físico:
  - Mama derecha: ausente por MRM, No signos de RLR.
  - TV: vulva sana, vagina: aspecto nodular en cara lateral derecha 1/3 superior, Cérvix: tumor proliferante sangrante que ocupa canal vaginal.
  - TR: parametrios infiltrados

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Cervical Cancer

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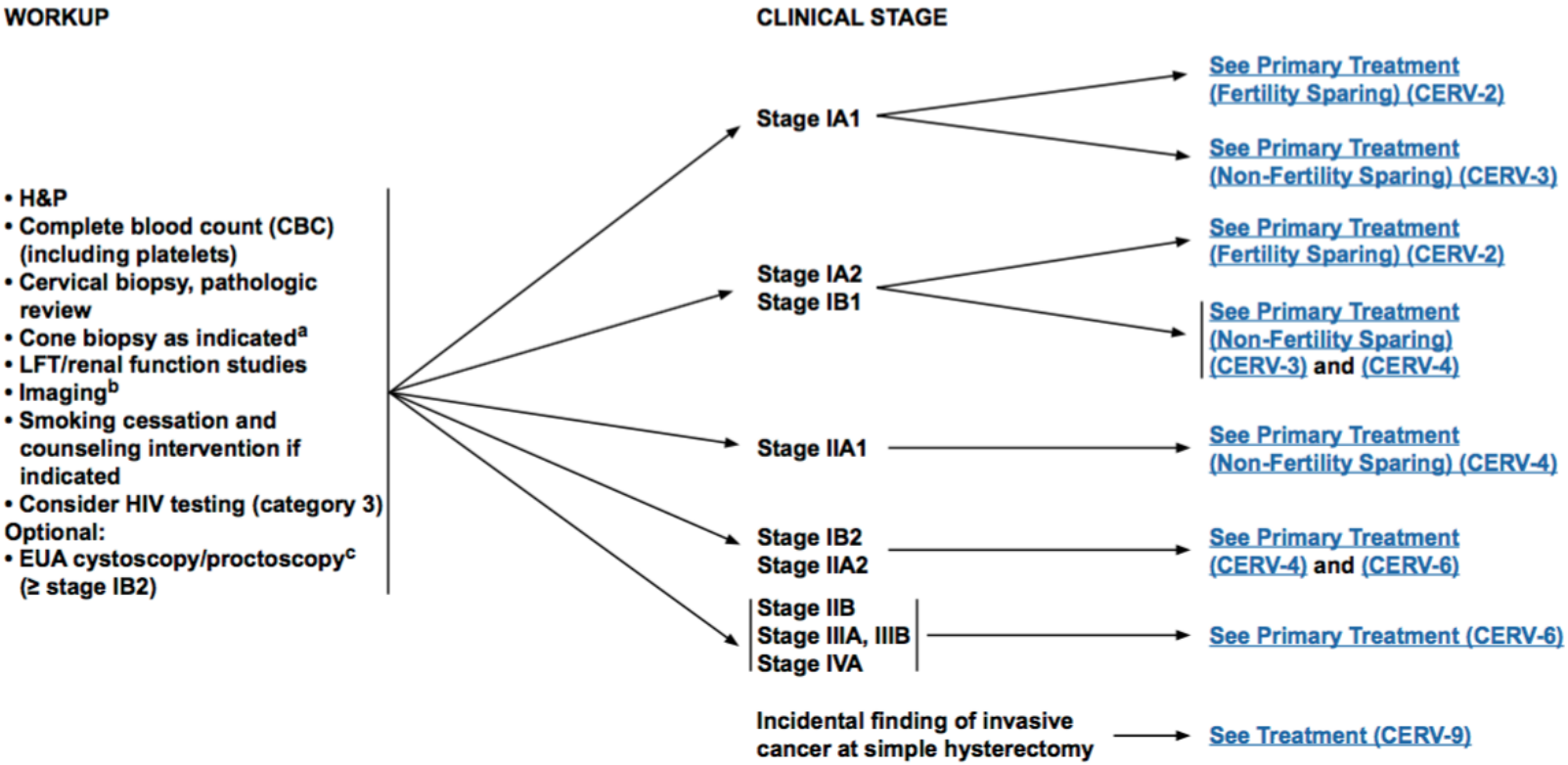

PLAN DE TRABAJO

- Biopsia Cérvix:
  Tumor 4x5cm sangrante al roce, proliferativo con vasos atípicos que deforma y protruye del cérvix.

ADENOCARCINOMA TUBULAR Y PAPILAR MODERADAMENTE DIFERENCIADO INFILTRANTE Y ULCERADO.
IHQ panel para descartar primario:
Se confirma 1rio cérvix.

- Lab: Hemograma, BQ: hb: 13.5, fn renal: N
- Imágenes:
- TEM TAP
- PET-CT: enfermedad localmente avanzada, NO metastásica

A nivel del cérvix se observa lesión sólida de aspecto neoformativo, que muestra discreta captación de la sustancia de contrase, mide aproximadamente 64 x 5 x 37 mm de diámetro longitudinal, transverso y anteroposterior, se asocia a discreta alteración de los planos grasos adyacentes y compromiso de ambos parametrios,

CONCLUSIÓN
LESIÓN SÓLIDA DE ASPECTO NEOFORMATIVO A NIVEL DEL CÉRVIX CON COMPROMISO DE AMBOS PARAMETRIOS, Y PROBABLE INFILTRACIÓN DEL ASPECTO ANTERIOR DEL TERCIO SUPERIOR DE LA VAGINA. NO HAY ADENOPATÍAS NI METASTASIS A DISTANCIA.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017 Staging Cervical Cancer

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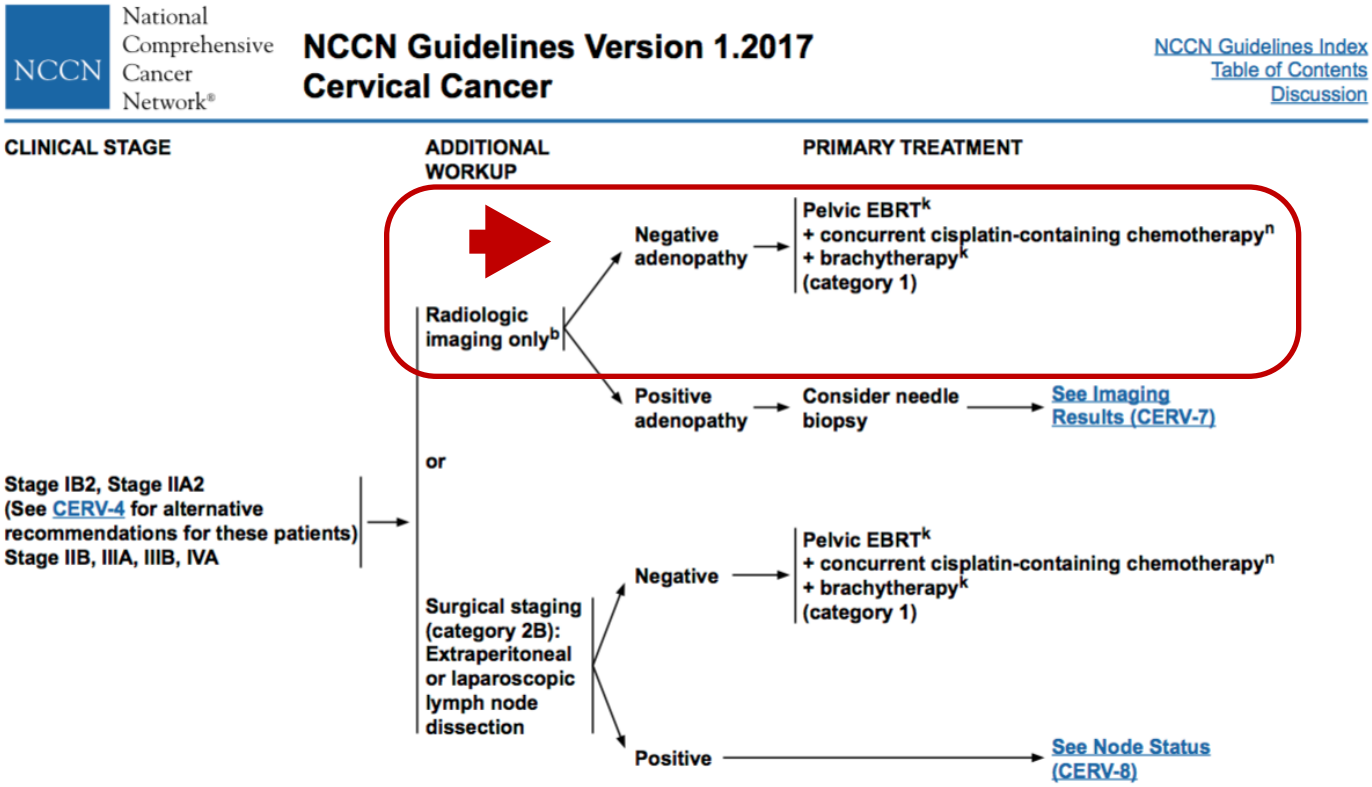
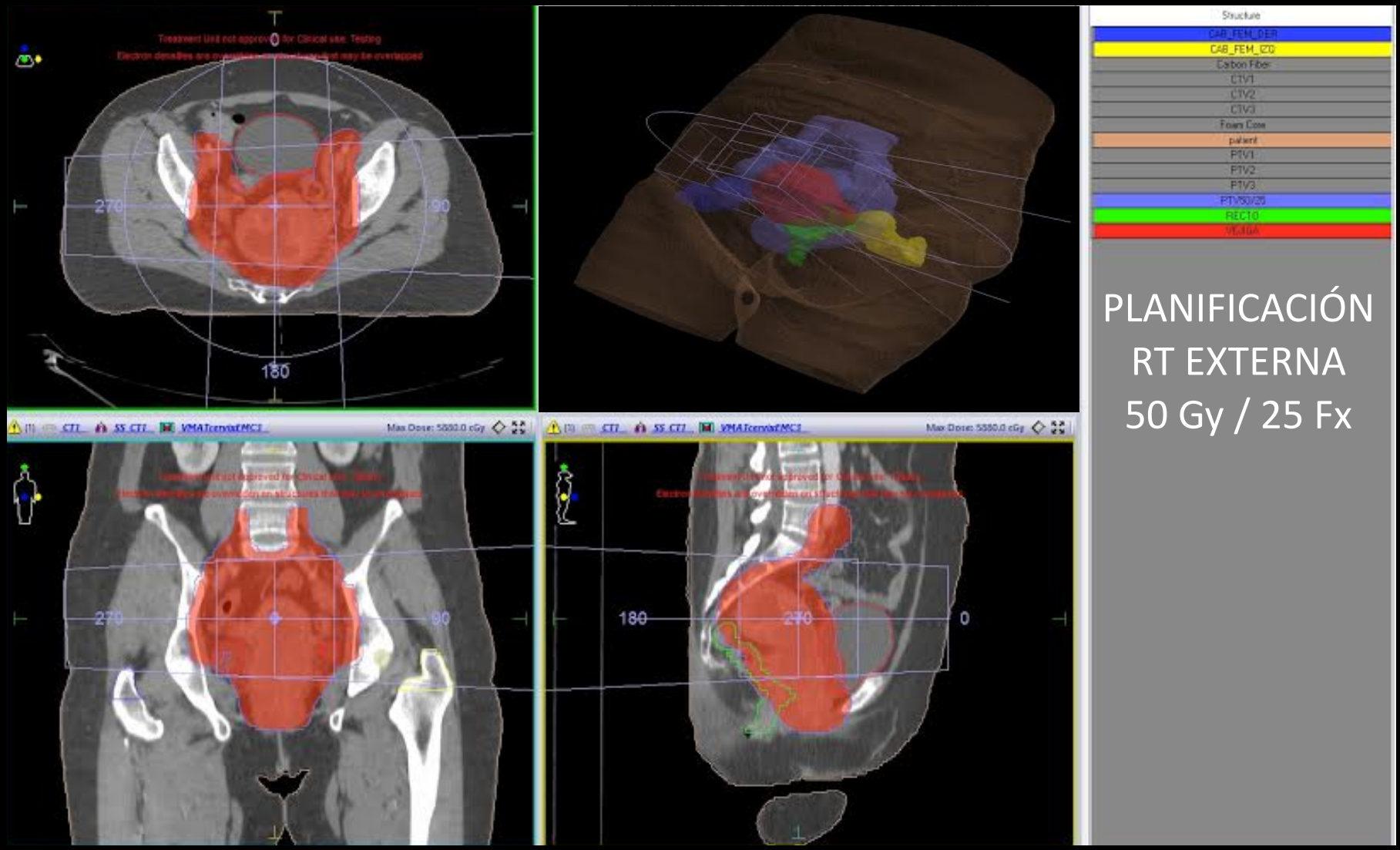
Table 1 AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Carcinoma of the Uterine Cervix

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

*Note: FIGO no longer includes Stage 0 (Tis).
**Note: All macroscopically visible lesions–even with superficial invasion–are T1b/IB.
#All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (~1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.
##On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

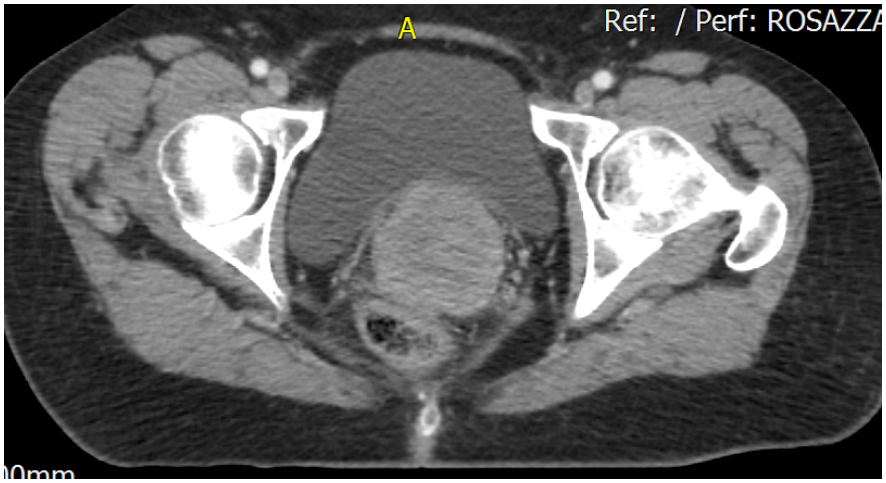
NM CERVIX IIB

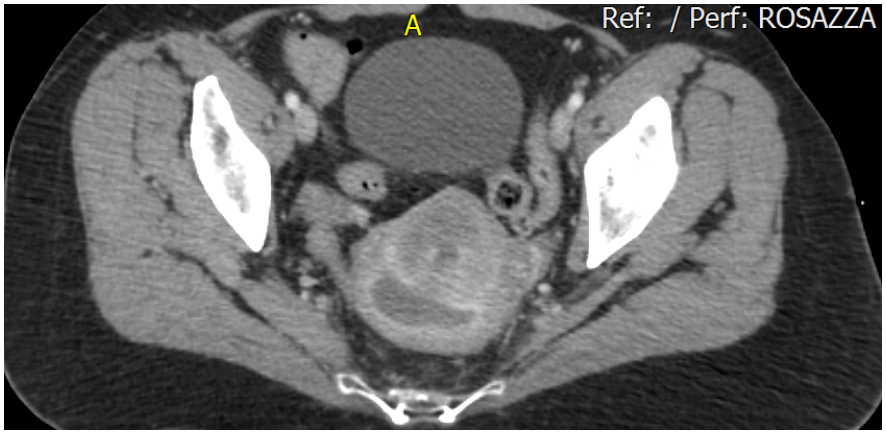



Structure
CAB_FEM_DER
CAB_FEM_IZQ
Carbon Fiber
CTV1
CTV2
CTV3
Foam Cone
patient
PTV1
PTV2
PTV3
PTV50/25
RECTO
VEJIGA
PLANIFICACIÓN
RT EXTERNA
50 Gy / 25 Fx

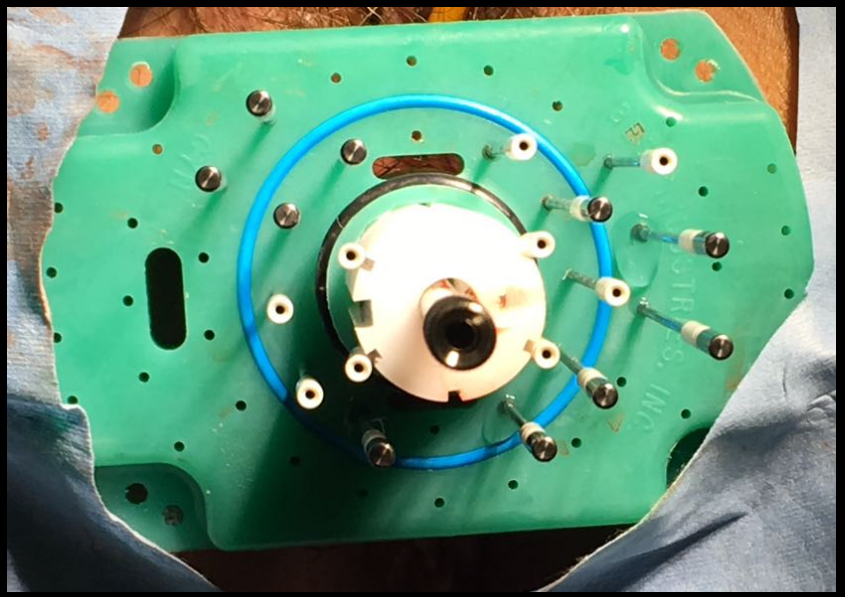
REEVALUACIÓN POST 6 CURSOS DE QT+EBRT

- dolor pélvico + ginecorragia escasa.
- EF: cérvix con extenso tumor exofítico que infiltra hasta 1/3 medio de vagina. Ambos parametrios comprometidos.
- **TEM pelvis c/c: tumor en cérvix 5.6x5.3cm (previo inicio de QT y RT: 6.4 x5cm),** adyacente a pared posterior vesical engrosada sugestivo de infiltración local. Se extiende a la vagina, tejidos blandos periuretrales. NO ADENOPATIAS.





APLICACIÓN DE BRAQUITERAPIA INTERSTICIAL 3D BAJO GUIA ECOGRAFICA

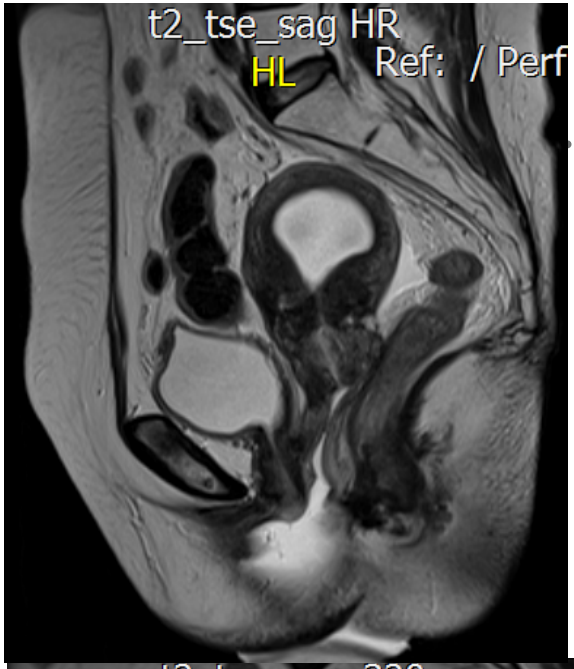


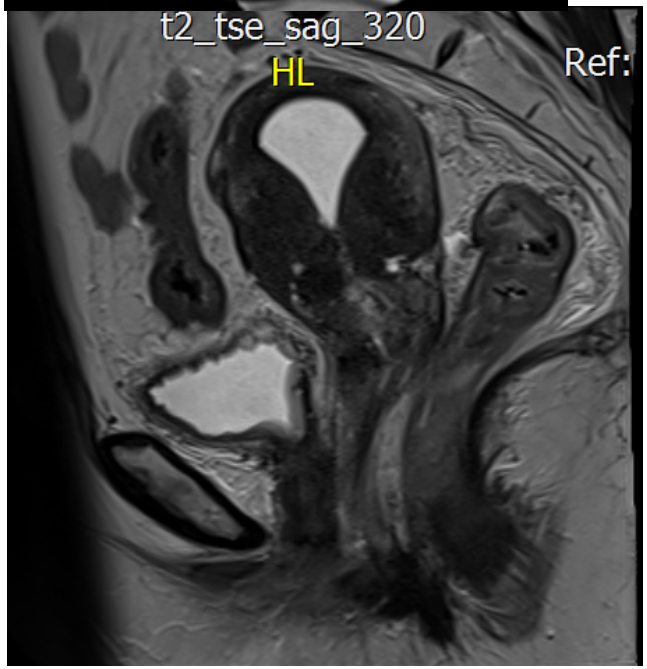
PLANIFICACIÓN DE BRAQUITERAPIA INTERSTICIAL 3D FUSIÓN TEM/RM
DOSIS 7 Gy / 5 Fx

revaluación post bt

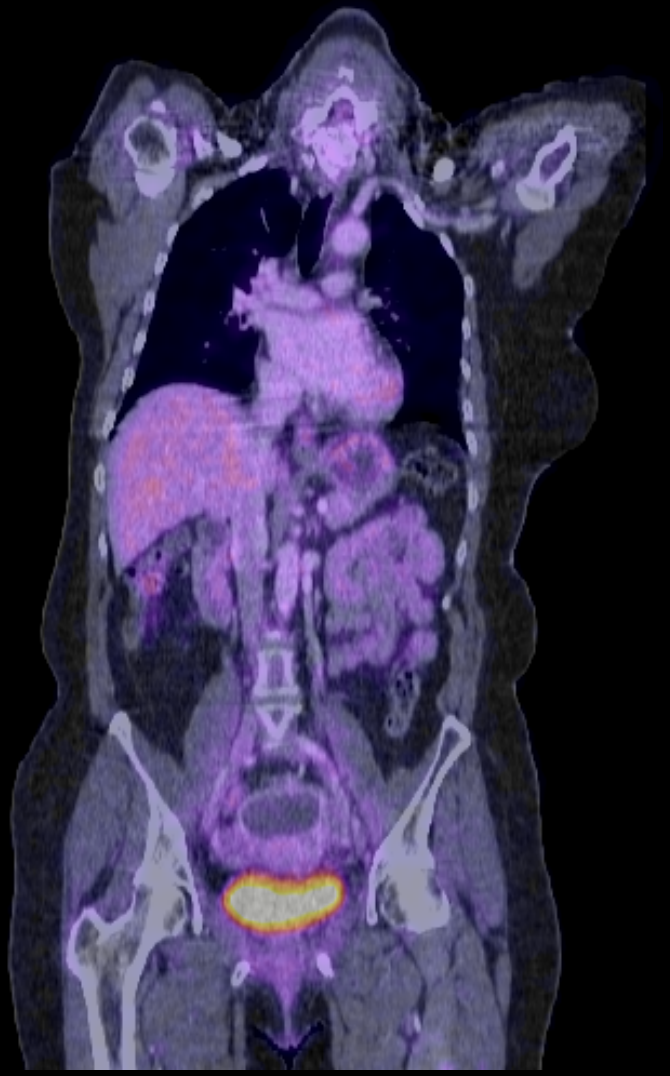
- Reevaluación: tumor cérvix 2x2 cm, fibrosis
- **RM pelvis:**

Cuello uterino mide 4.2x3.7cm, sin cambios significativos en RM previa (3meses atrás post 4/5 BT). Foco de realce y restricción de la difusión rodeando el canal cervical, sin cambios significativos, sugestivo de cambios inflamatorios post tratamiento vs enfermedad residual. Engrosamiento de la mitad superior de la pared vaginal que ha incrementado discretamente respecto al control previo, sugestivo de cambio post tratamiento.





PET 14/03/2017

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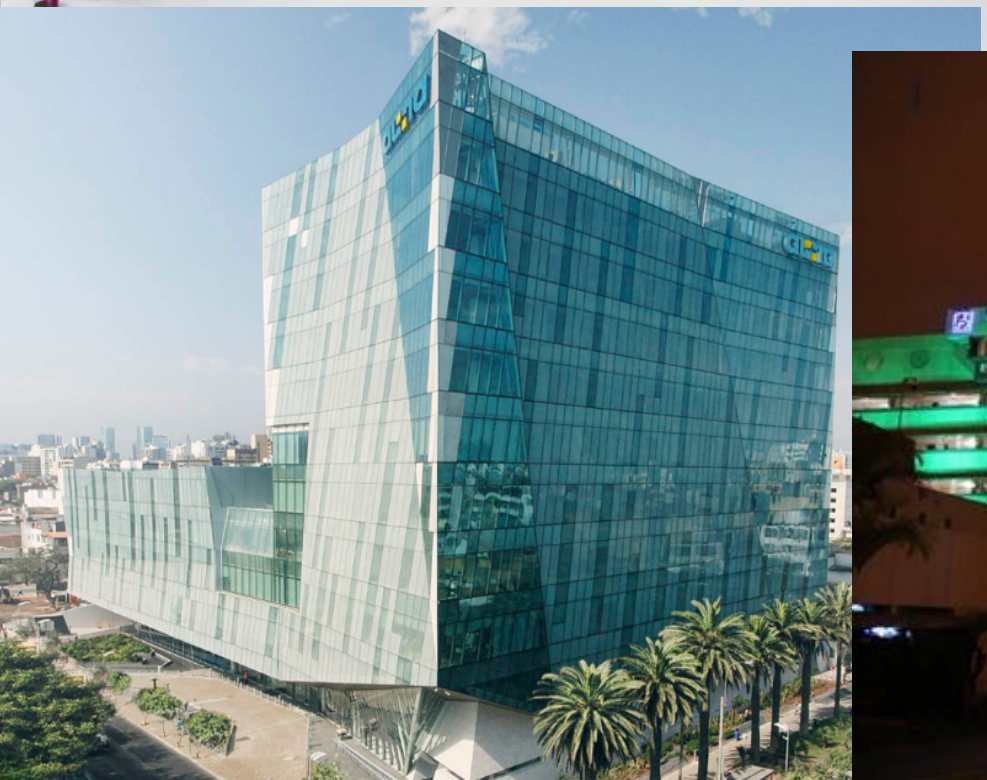
BRAQUITERAPIA



Gracias!

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