

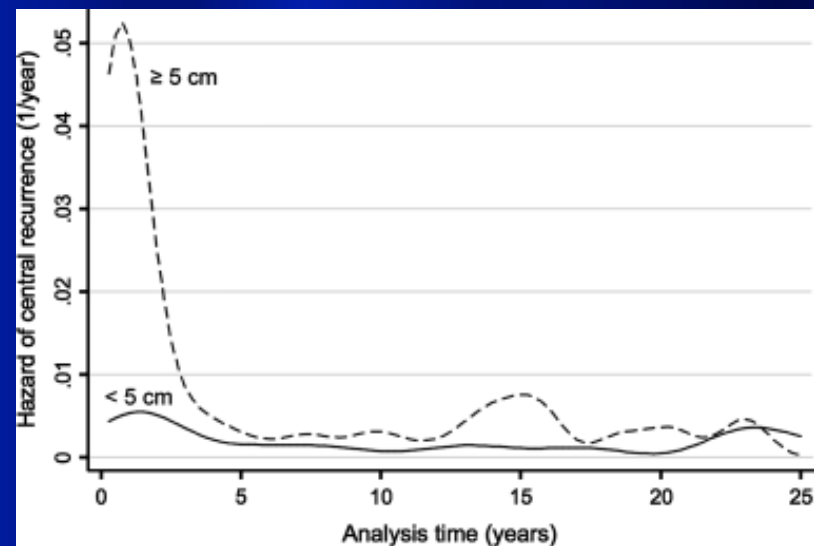
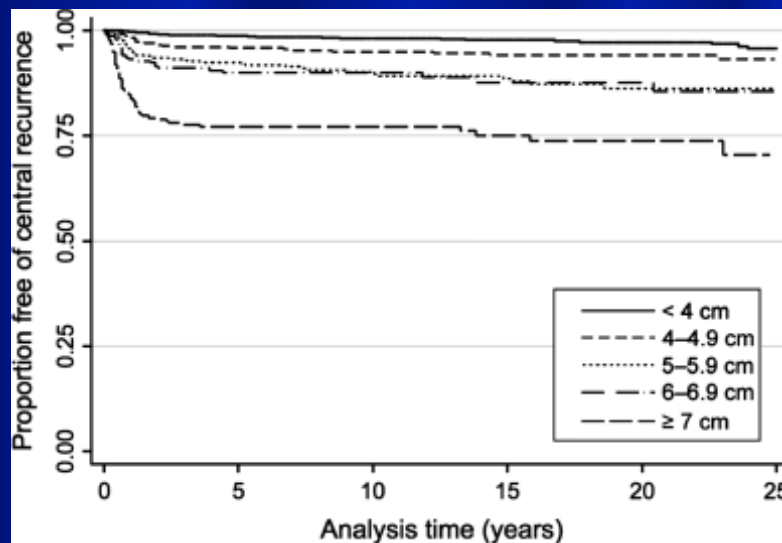
IGBT nei tumori ginecologici: applicazioni cliniche

Ines Cafaro

Istituti Ospitalieri di Cremona

Cervicocarcinoma

- La radioterapia è in grado di controllare la malattia e il risultato è correlato
 - alle dimensioni di T
 - alla **dose erogata**
 - alla durata del trattamento



Eifel PJ, *et al* Time course and outcome of central recurrence after radiation therapy for carcinoma of the cervix. *Int J Gynecol Cancer* 16, 2006

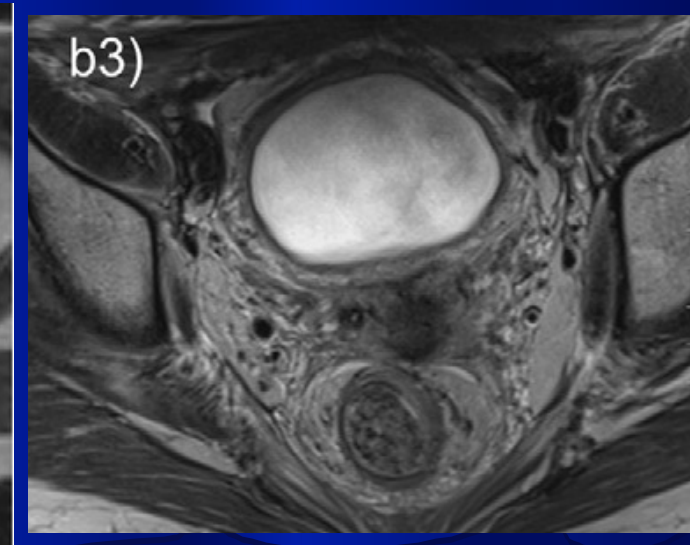
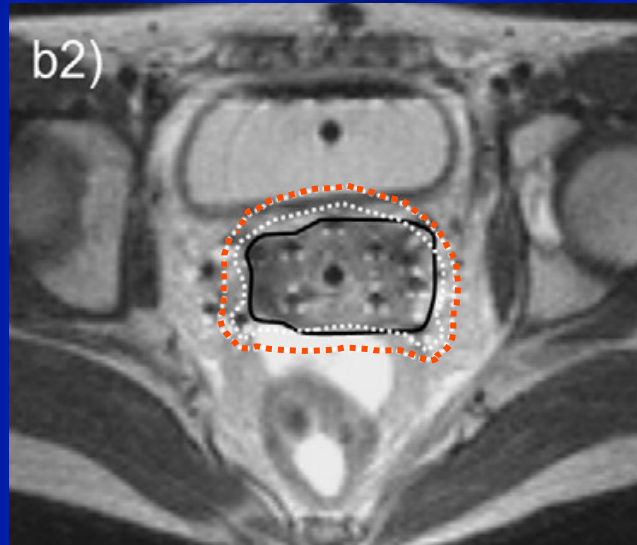
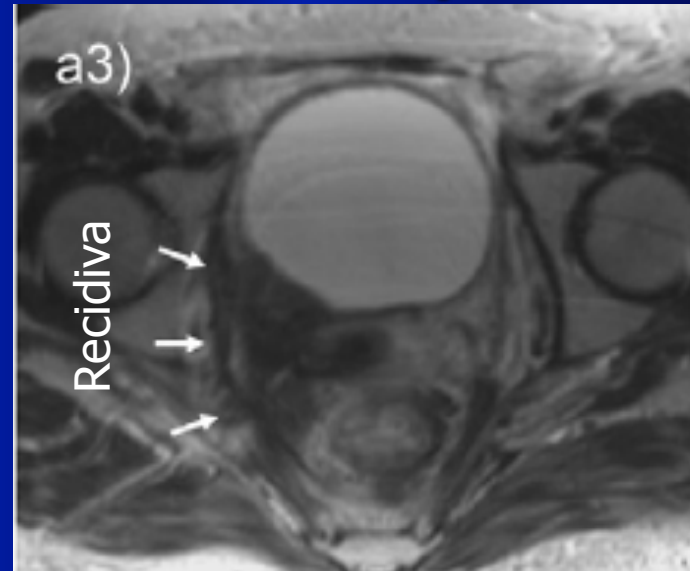
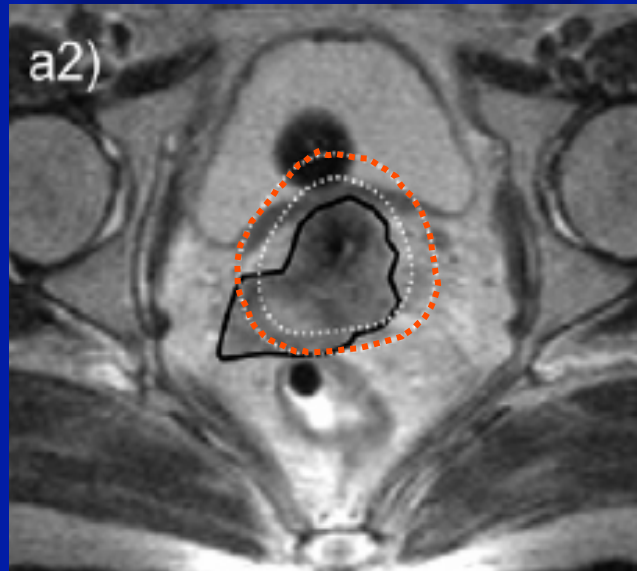
BRACHITERAPIA

Over 20 Years of Progress in Radiation Oncology: Cervical Cancer

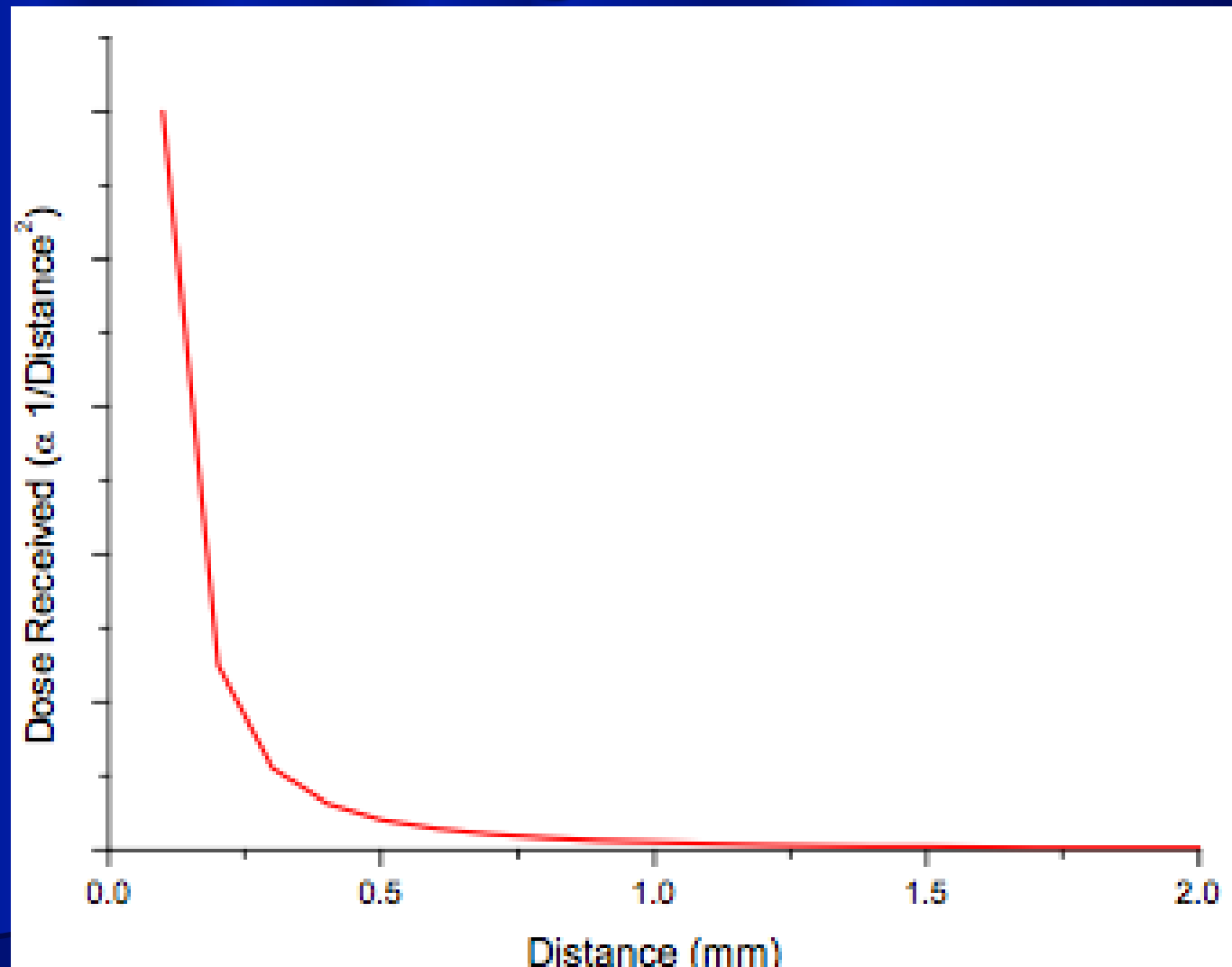
Rachelle Lanciano, Gillian Thomas, and Patricia J. Eifel

- "...mean point A dose has increased to approximately 80 Gy...
- outcome for stage I and II has remained stable... while the results have improved for stage III.
- improvement in OS and LC corresponds to an increased use of brachytherapy..."

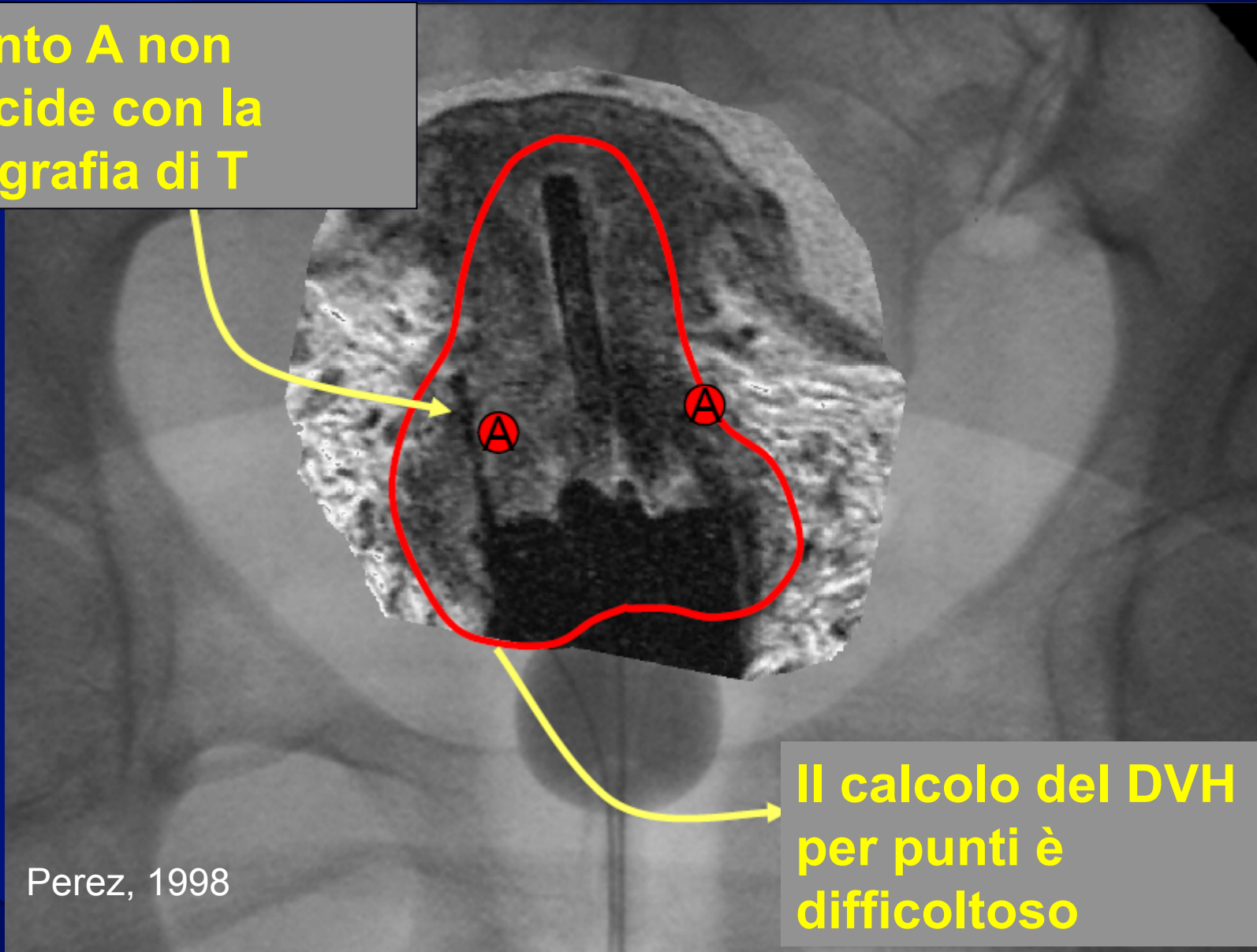
Correlazione dose e risposta



Rapporto dose/ distanza dalla sorgente



Il punto A non coincide con la topografia di T

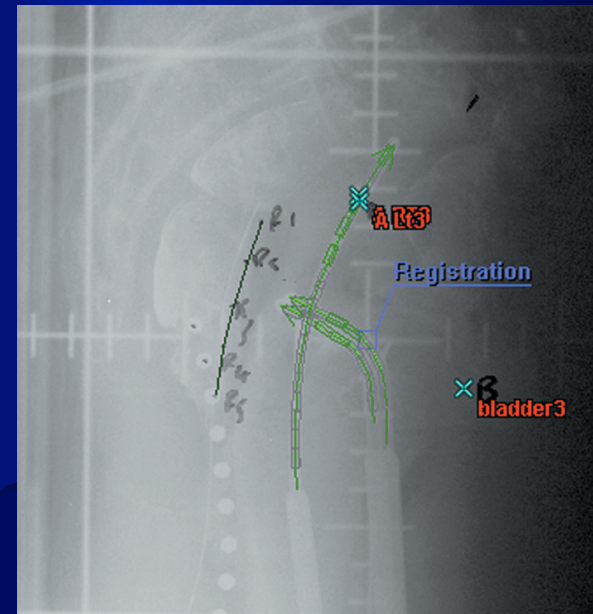
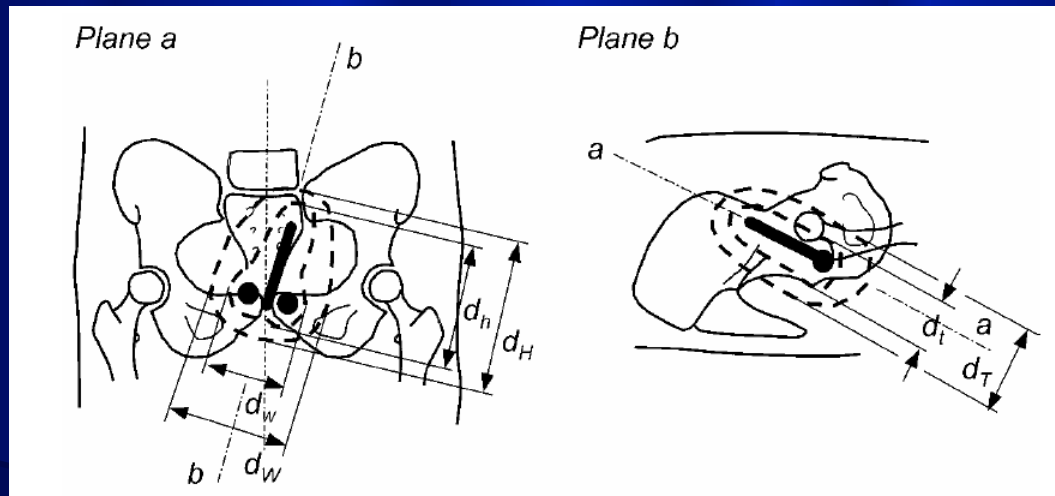
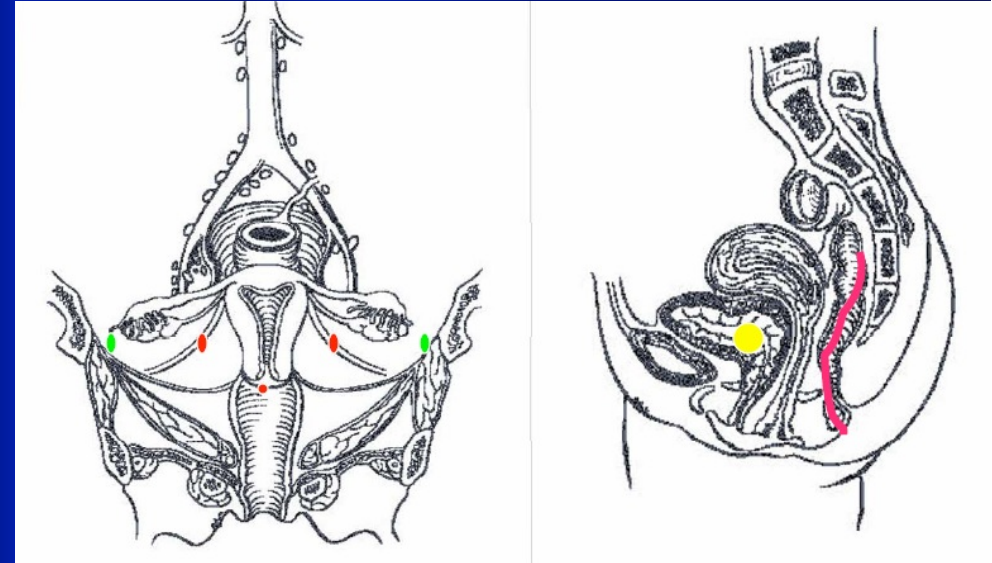


Il calcolo del DVH per punti è difficoltoso

Perez, 1998

BT 2D

- Dose in punti su radiogrammi ortogonali
- ICRU 38: Introduzione del concetto di volume

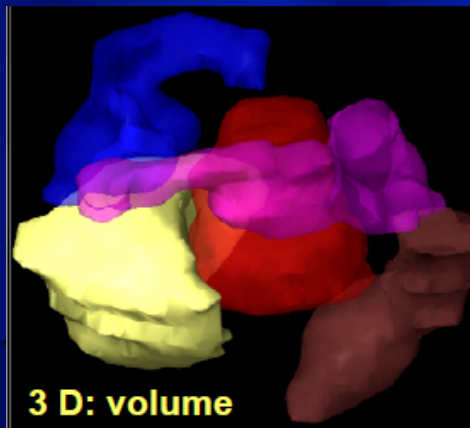


Planning 3D

- definizione dei VOI (target, retto, vescica...)
- ottimizzazione (BT conformazionale)

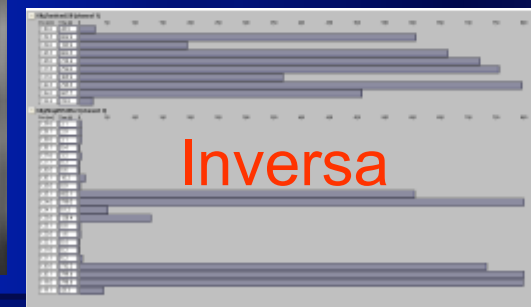
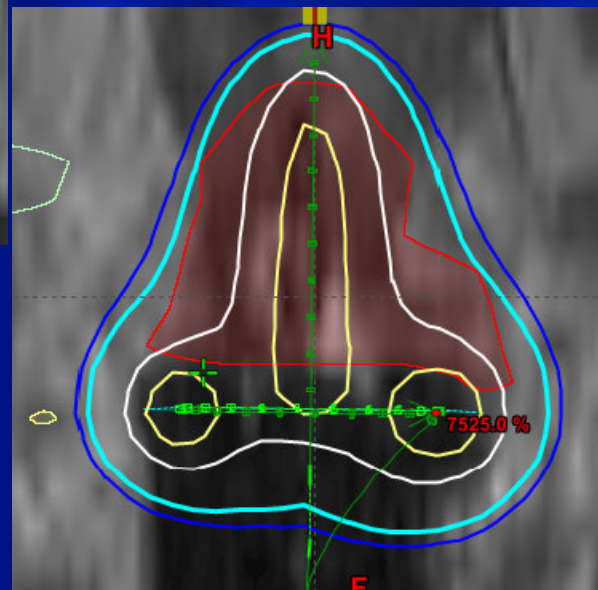
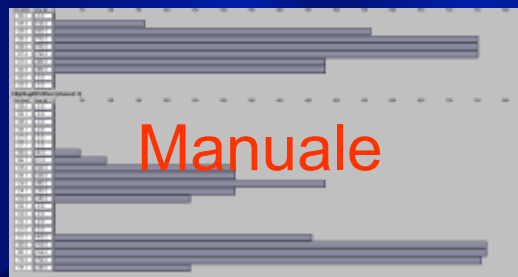
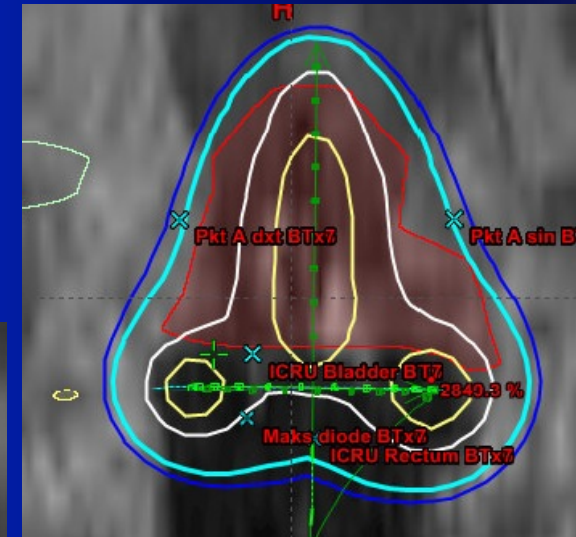
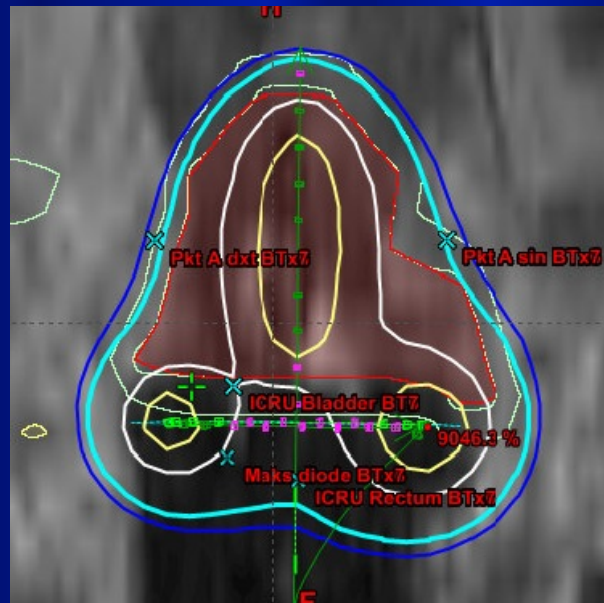


- dose escalation sul tumore (maggior controllo locale)
- dose minore ai tessuti sani (tossicità ridotta)

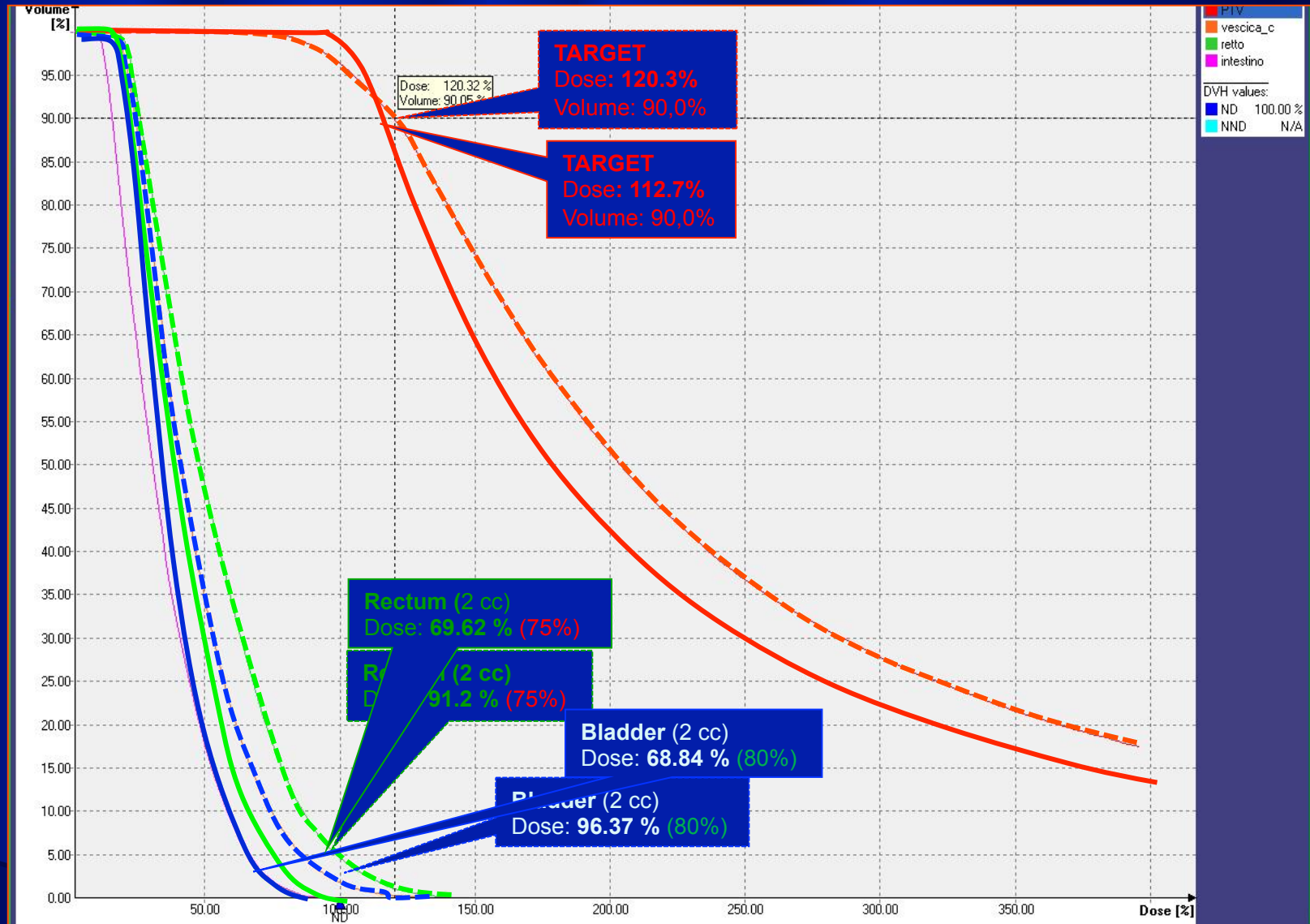


S. Nag - Radiat Oncol. 2006; 6:164

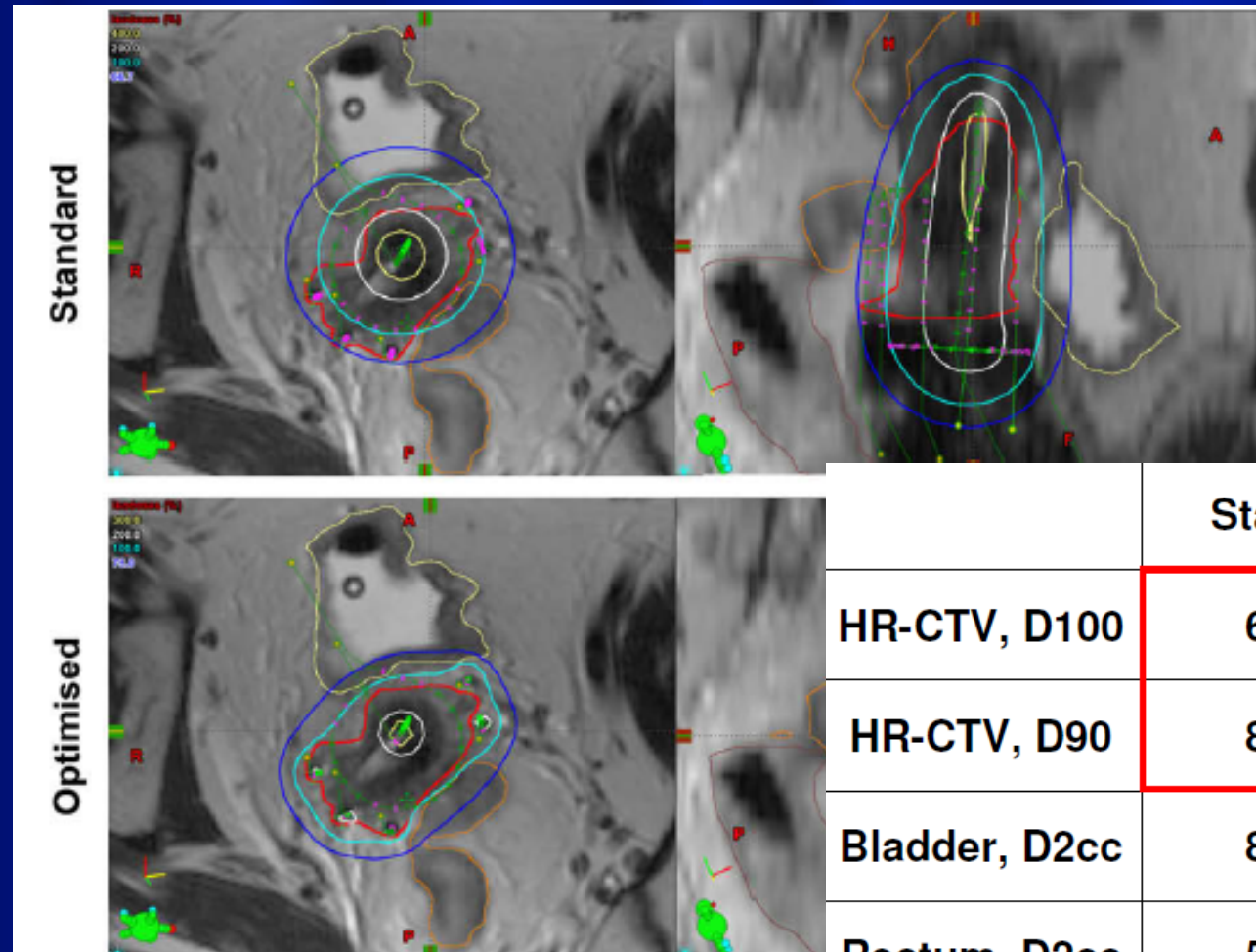
Strategie di ottimizzazione



Planning 3D: ottimizzazione



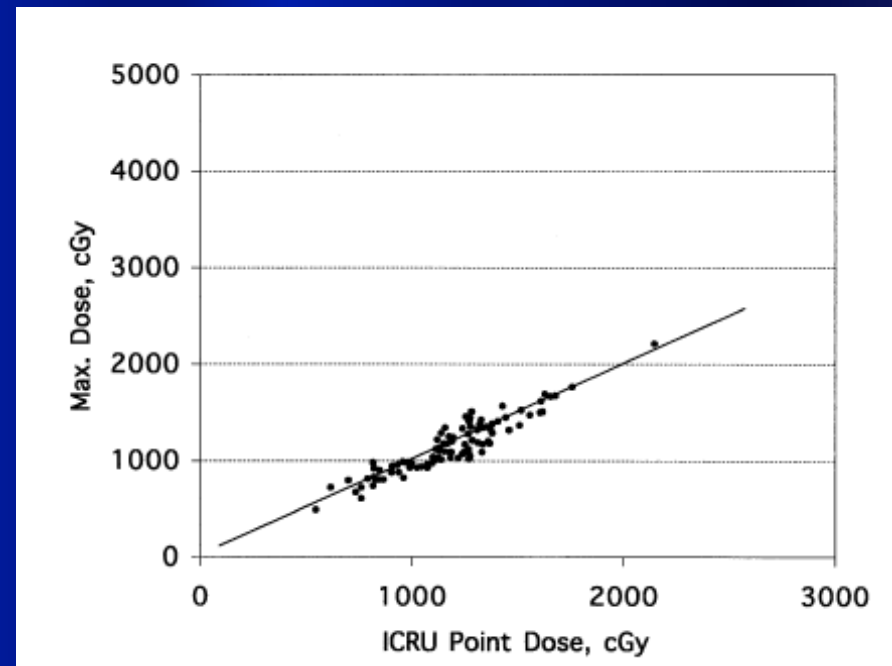
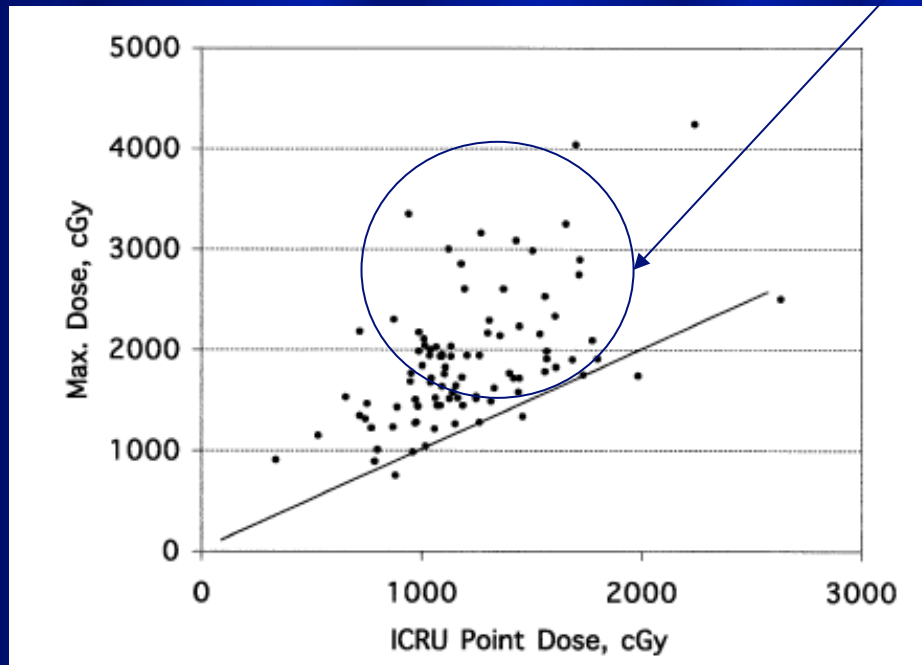
3D planning: ottimizzazione



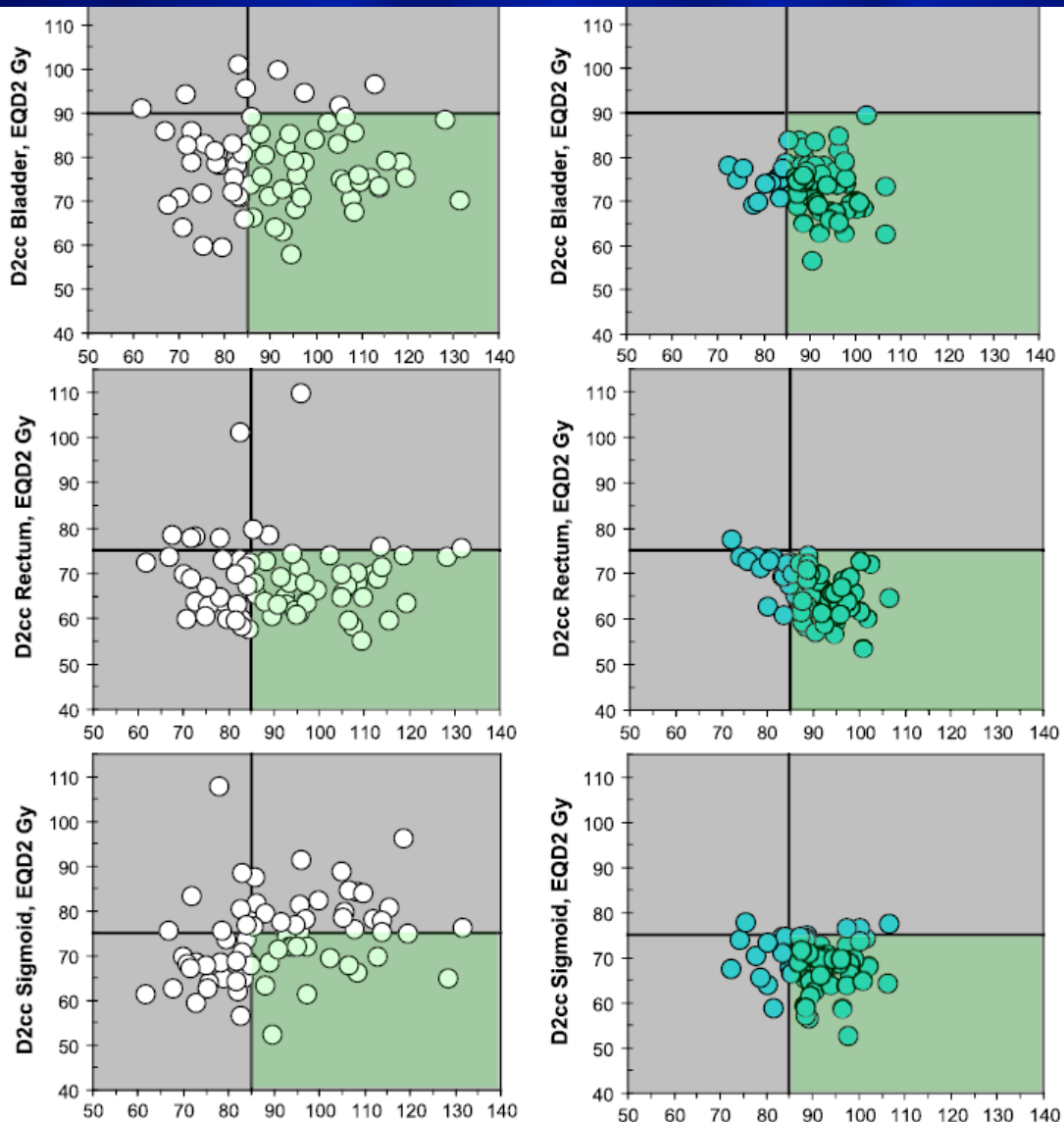
	Standard	Optimised
HR-CTV, D100	64 Gy	72 Gy
HR-CTV, D90	80 Gy	88 Gy
Bladder, D2cc	84 Gy	76 Gy
Rectum, D2cc	58 Gy	59 Gy
Sigmoid, D2cc	71 Gy	70 Gy

Confronto tra dosi al punto R e V sec ICRU 38 e su TC

Dose max alla vescica 1-8 volte maggiore rispetto al punto ICRU ref. Point Barillot 1994



Dose agli OAR con D90 HR CTV, EQD 2Gy



Le dosi per OAR sono rispettate in 14/72 pazienti con il planning standard e in 52/72 pazienti con il planning ottimizzato

K. Tanderup *Radiother Oncol* (2010)

Definizione GTV

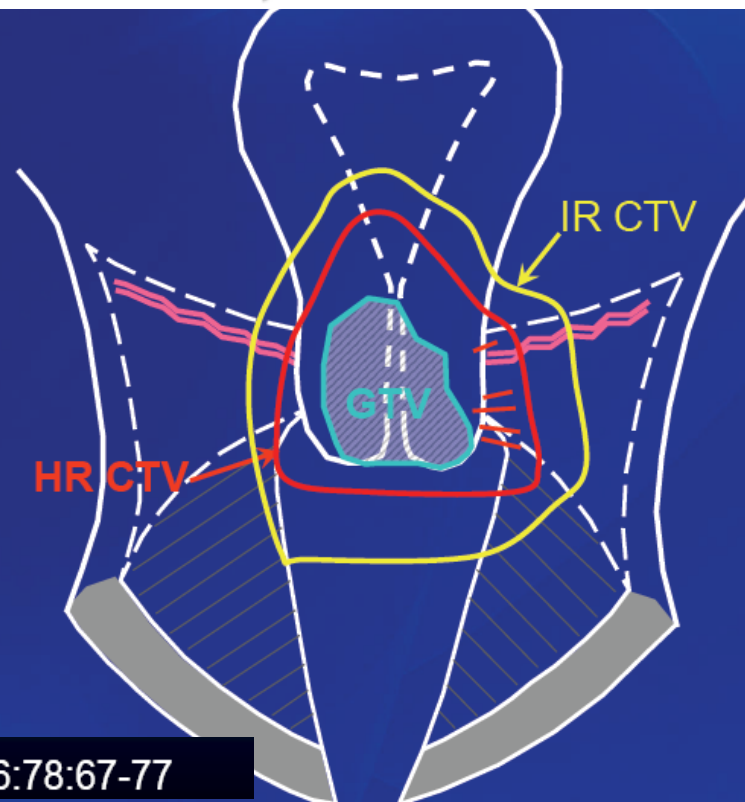
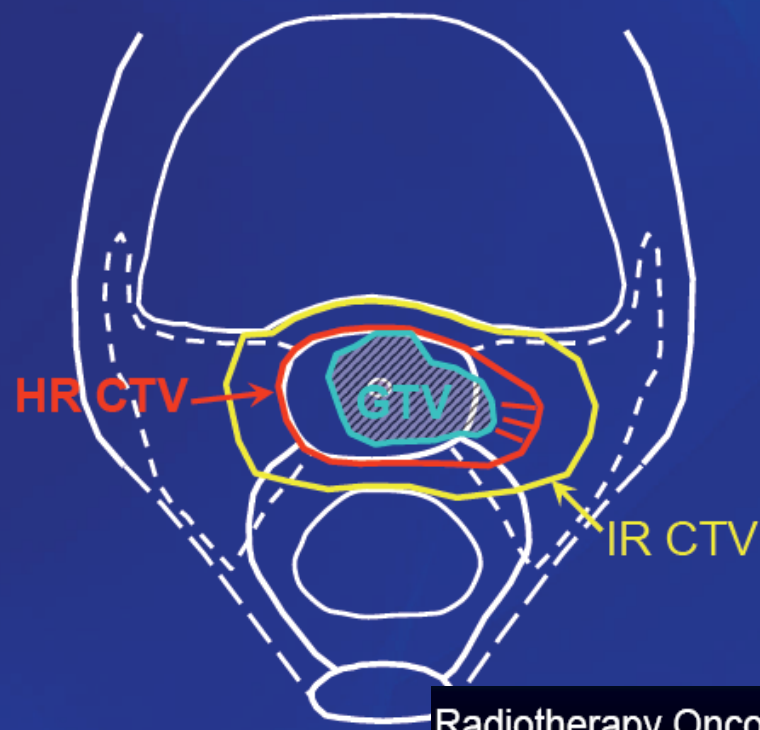
- tumore interamente determinabile
 - imaging
 - esame clinico
- GTV_D : alla diagnosi
- $GTV_{Bn (1,2..)}$: a ogni frazione BT



Introduzione CTV in BT

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

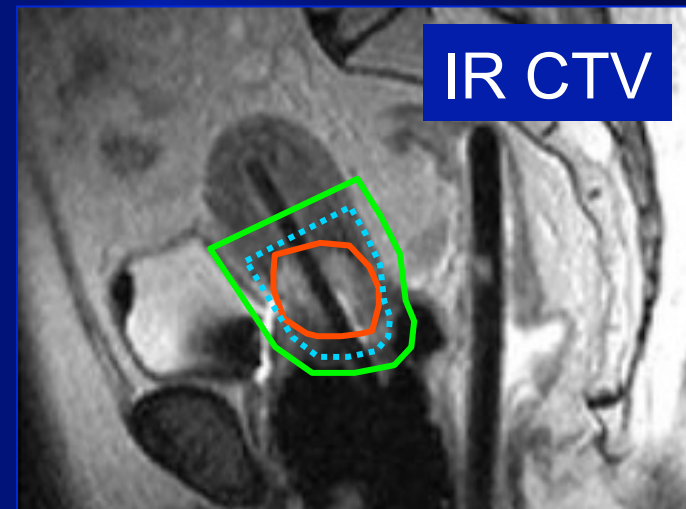
Richard Pötter^{a,*}, Christine Haie-Meder^b, Erik Van Limbergen^c, Isabelle Barillot^d, Marisol De Brabandere^c, Johannes Dimopoulos^a, Isabelle Dumas^b, Beth Erickson^e, Stefan Lang^a, An Nulens^c, Peter Petrow^f, Jason Rownd^e, Christian Kirisits^a



Definizione CTV e dosi

- High Risk CTV (HR CTV)
 - GTVBn + cervice
- dose: 80-90 Gy

- Intermediate Risk CTV (IR CTV)
 - se RP: HR CTV + 0.5-1.5 cm
 - se RC: GTV_D
- Dose \geq 60 Gy

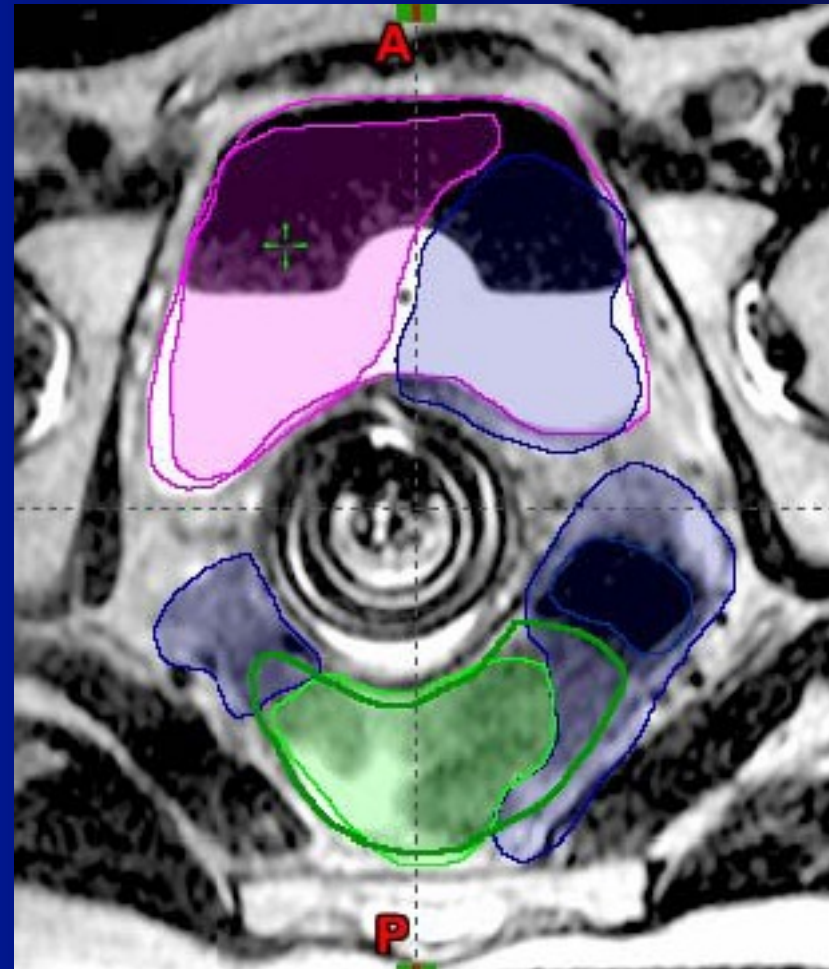


PTV

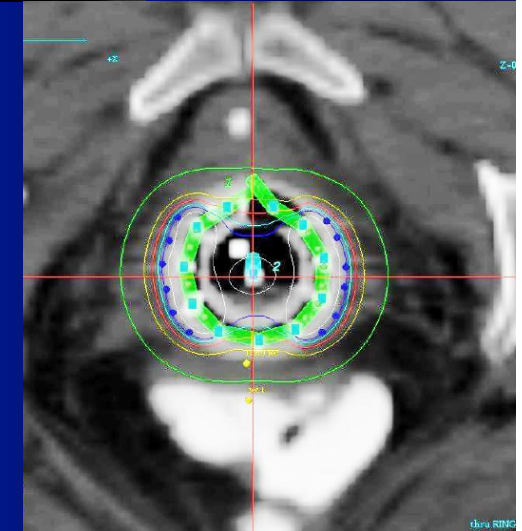
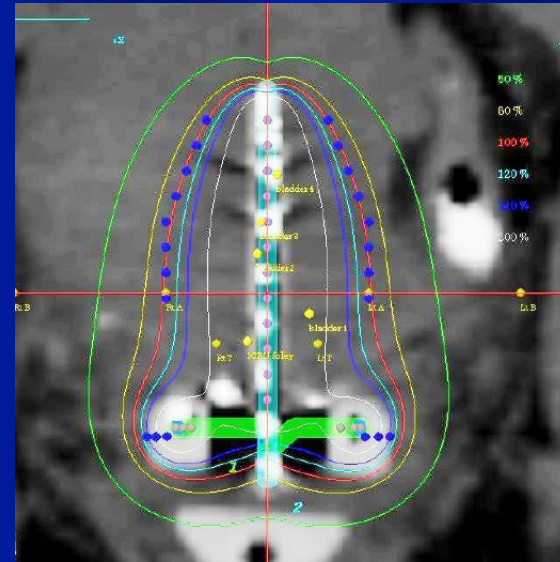
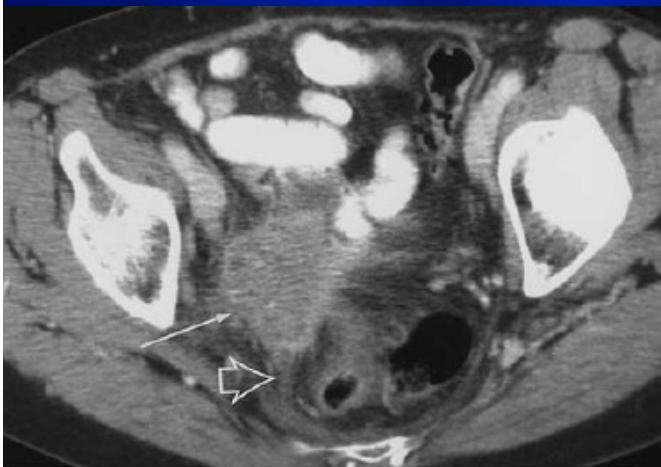
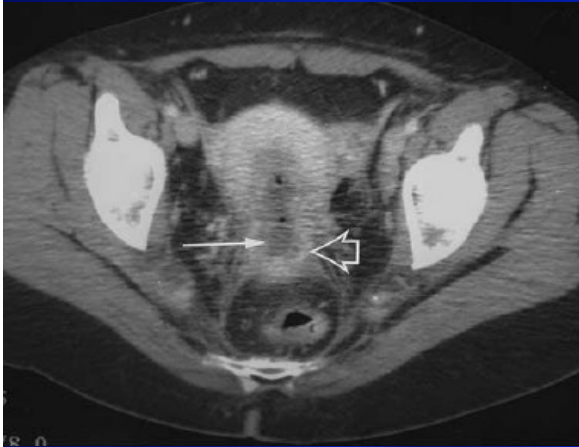
- “In brachytherapy, the PTV is defined to select appropriate source arrangement, positioning and/or movement control. The dose distribution to the PTV has to be considered as representative of the dose distribution to the CTV”.

Organ motion in BT

- Differenze misurabili ma non statisticamente significative di posizione e volume di retto, vescica e ileo nell'intervallo fra RM pre-planning e RM post-treatment



Identificazione del GTV: TC



- Definizione dei volumi (difficoltosa)
- Definizione degli organi critici (adeguata)
- Discreta visualizzazione degli applicatori

Definizione del HR CTV



In base allo stadio

In base a clinica e stadio

Su RM

Neamat Hegazy, Acta Oncologica, 2013; 52: 1345–1352

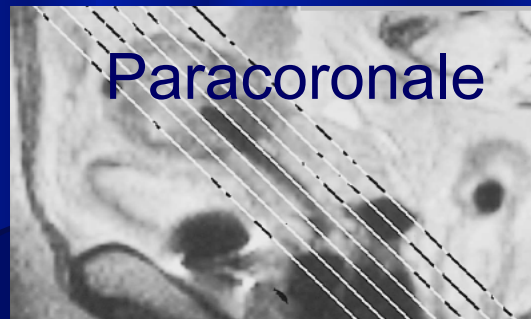
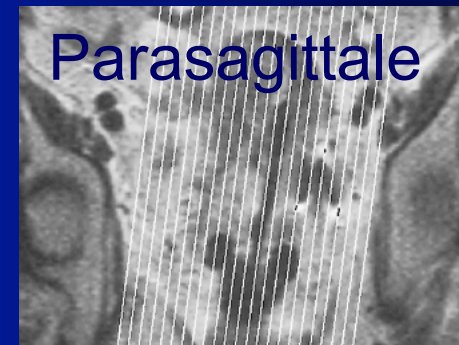
TC VS RM

- RM permette una migliore risoluzione dei tessuti molli e una più corretta visualizzazione del tumore residuo (e delle strutture critiche)



Acquisizione RM: requisiti

- Immagini T2 pesate
- Intensità di segnale elevato
- Dopo RTE: intensità di segnale intermedio (zone grigie)
- Orientamento delle immagini
 - Parallele
 - Ortogonali
 - Paratrasversali all'asse dell'applicatore
 - Paracoronali
 - Parasagittali



TC vs RM

	MRI (mean ± SD)	CT (mean ± SD)	P value
HR-CTV			
Height (mm)	45.5 ± 10.81	37.9 ± 10.01	0.001
Maximum width (mm)	44.1 ± 12.21	52.8 ± 11.41	0.009
Width Point A (mm)	32.3 ± 7.61	33.9 ± 12.24	0.571
Maximum thickness (mm)	37.9 ± 7.62	39.0 ± 5.46	0.46
Thickness Point A (mm)	27.4 ± 5.32	25.1 ± 9.52	0.1
Volume (cc)	35.2 ± 18.26	29.1 ± 19.79	0.106
IR-CTV			
Height (mm)	66.0 ± 12.36	51.7 ± 10.21	0.001
Maximum width (mm)	59.8 ± 10.80	69.2 ± 10.48	0.001
Width Point A (mm)	45.1 ± 10.42	52 ± 10.20	0.031
Maximum thickness (mm)	46.8 ± 7.14	48.4 ± 4.90	0.01
Thickness Point A (mm)	33.2 ± 5.69	33.2 ± 7.88	0.966
Volume (cc)	69.1 ± 39.64	64.5 ± 32.69	0.434

- La TC sottostima in altezza e sovrastima in larghezza HR e IR CTV

Rahul Krishnatty - Jpn J Clin Oncol 2012;42(4)309–313

Il rischio è una riduzione della dose al tumore se l'ottimizzazione tende al risparmio degli OAR o un ↑ della dose agli OAR se la dose è ottimizzata sul T

TC vs RM

TC

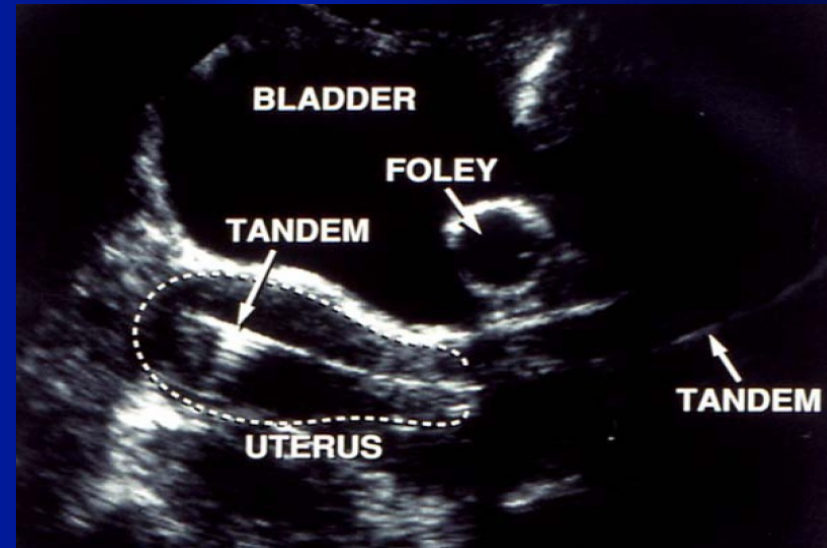
- localizzazione applicatore
- relazioni 3D tra applicatore e VOI
- dose ai VOI
- accessibilità
- applicatori standard
- no definizione di T

RM

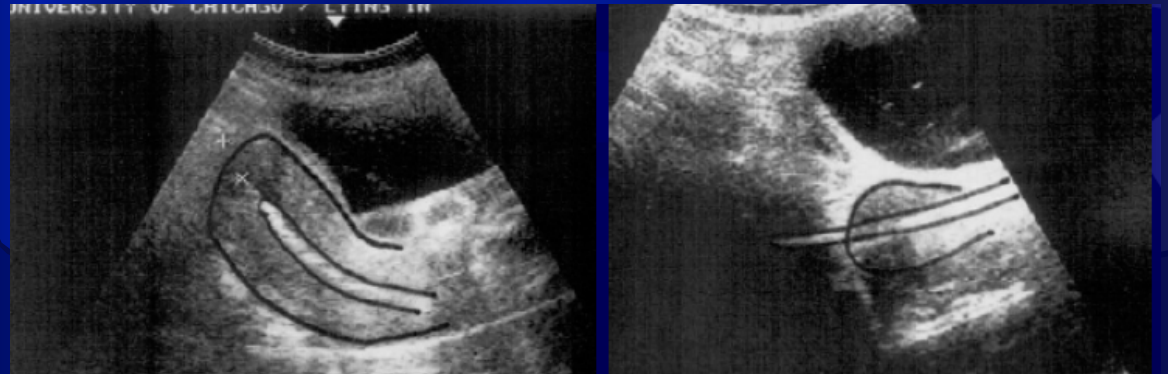
- localizzazione applicatore
- relazioni 3D tra applicatore e VOI
- dose ai VOI
- **accessibilità -costi**
- **applicatori dedicati**
- **definizione di T**

US

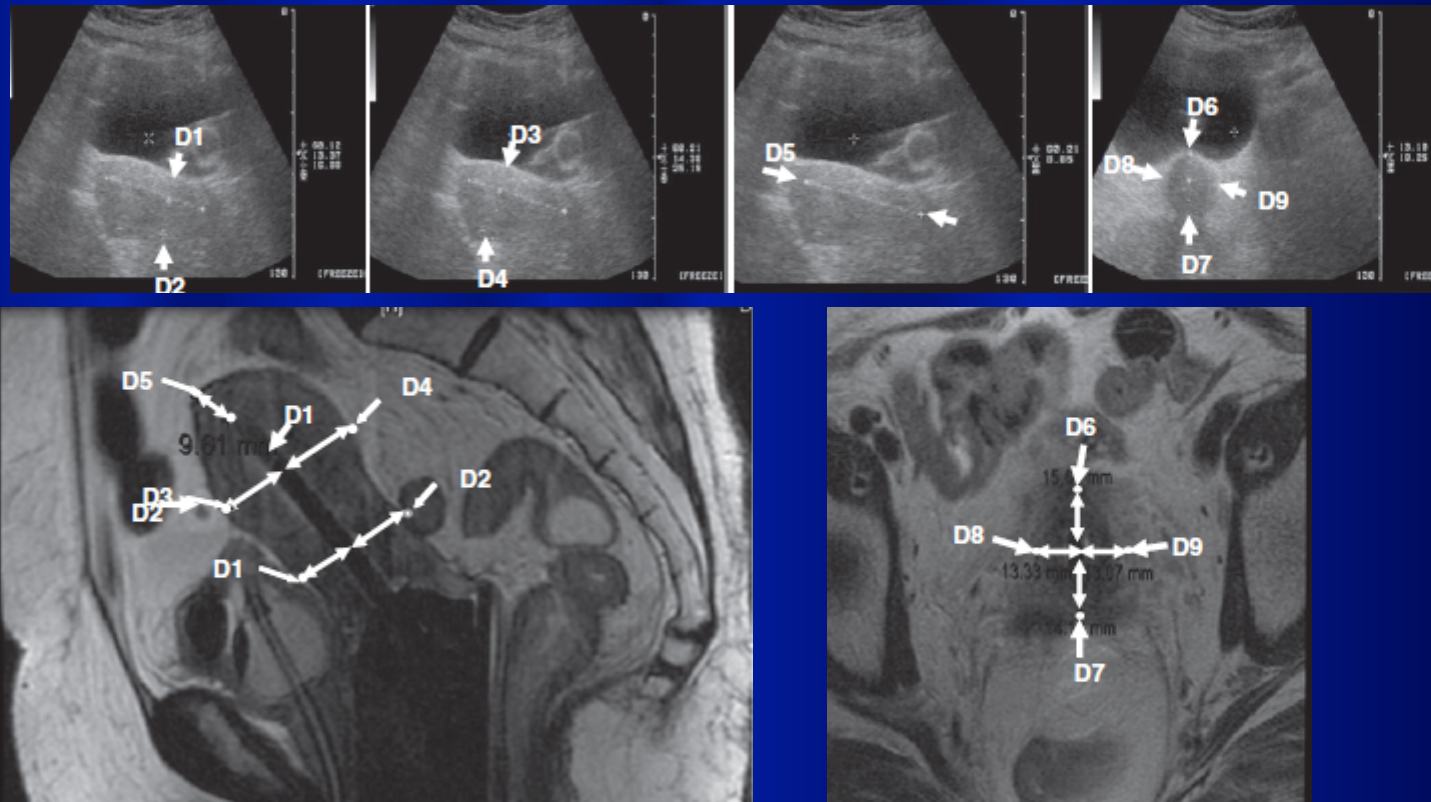
- eco transaddominale
- eco transrettale



- aiuto nel corretto posizionamento del tandem (inserzioni difficili)
- terapia interstiziale
- definizione dose vescicale (*Barillot, 1994*)



Costruzione dei volumi con US



U. Mahantshetty et al.- Radiotherapy and Oncology 2012; 102:130–134

Correlazione US e RM

Reference dimension	USG (mean) in mm	MRI (mean) in mm	Mean absolute diff. D MRI – D USG (range) in mm	Paired differences		Pearson's correlation "R"	Sig. 2-tailed
				S. D. in mm	Std. error mean		
D1 (n = 32)	11.9	12.1	0.7 (0-2.1)	0.6	0.1	0.92	<0.01
D2 (n = 32)	17.7	17.7	2 (0.1-15.9)	3.0	0.5	0.63	<0.01
D3	1	1	2 (6%)	6	1		7 (21%)
D4	3	5	8 (25%)	4	7		11 (34%)
D5	1	0	1 (3%)	3	2		5 (16%)
D6	1	1	2 (6%)	2	1		3 (9%)
D7	2	1	3 (9%)	4	1		5 (16%)
D8	0	1	1 (3%)	2	2		4 (13%)
D9	0	3	3 (9%)	1	4		5 (16%)

- Buona correlazione per la definizione della parete anteriore (0.96, p< 001)
- Moderata correlazione per la parete posteriore con una differenza di 15.9 mm (p=<001)
- Forte correlazione per cervice e neoplasia con una differenza di 6.4 mm
- Non possibile delineare i rapporti con gli OAR

3D planning

- Riduzione del sanguinamento rettale grave
 - HC Kang, Radiother Oncol 2010; 97(3): 507-513
- Aumenta la possibilità di controllo locale e la sopravvivenza (28% per la brachiterapia convenzionale vs 58% per MR-IGTB, $p=0.003$ nelle pazienti con tumori estesi)
 - R Potter, Radiother Oncol 2007; 83(2): 148-155

Tossicità

Late adverse effects (LENT SOMA) after radiotherapy ± chemotherapy and image guided adaptive brachytherapy in 156 patients (absolute numbers).

Late adverse effects	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>
Vagina	23	84	44	2	1
Bladder	121	20	12	3	0
Rectum	137	8	6	2	3
Bowel/Sigmoid	152	2	2	0	0
Total		114	64	7	4
without vagina		30	20	5	3

Esperienza Medical University di Vienna

	No. of patients n = 418	3 Year-OS (%) FIGO stage			
		IB	IIB	IIIB	IVA
Vienna: 1993–1997 ^a	189	62	70	46	40
Vienna: 1998–2000 ^b	73	80	61	12	25
Vienna: 2001–2008 ^c	156	74	79	45	33

	No. of patients n = 418	3Year-G3/G4 morbidity (%) [*] All stages		
		Bladder	Bowel/rectum	Vagina
Vienna: 1993–1997 ^a	189	3	10	31
Vienna: 1998–2000 ^b	73	3	5	7
Vienna: 2001–2008 ^c	156	2	4	1

	No. of patients n = 418	100	87	69	60
Vienna: 1993–1997 ^a	189	100	87	69	60
Vienna: 1998–2000 ^b	73	95	92	67	70
Vienna: 2001–2008 ^c	156	94	96	75	75

L'esperienza francese: STIC

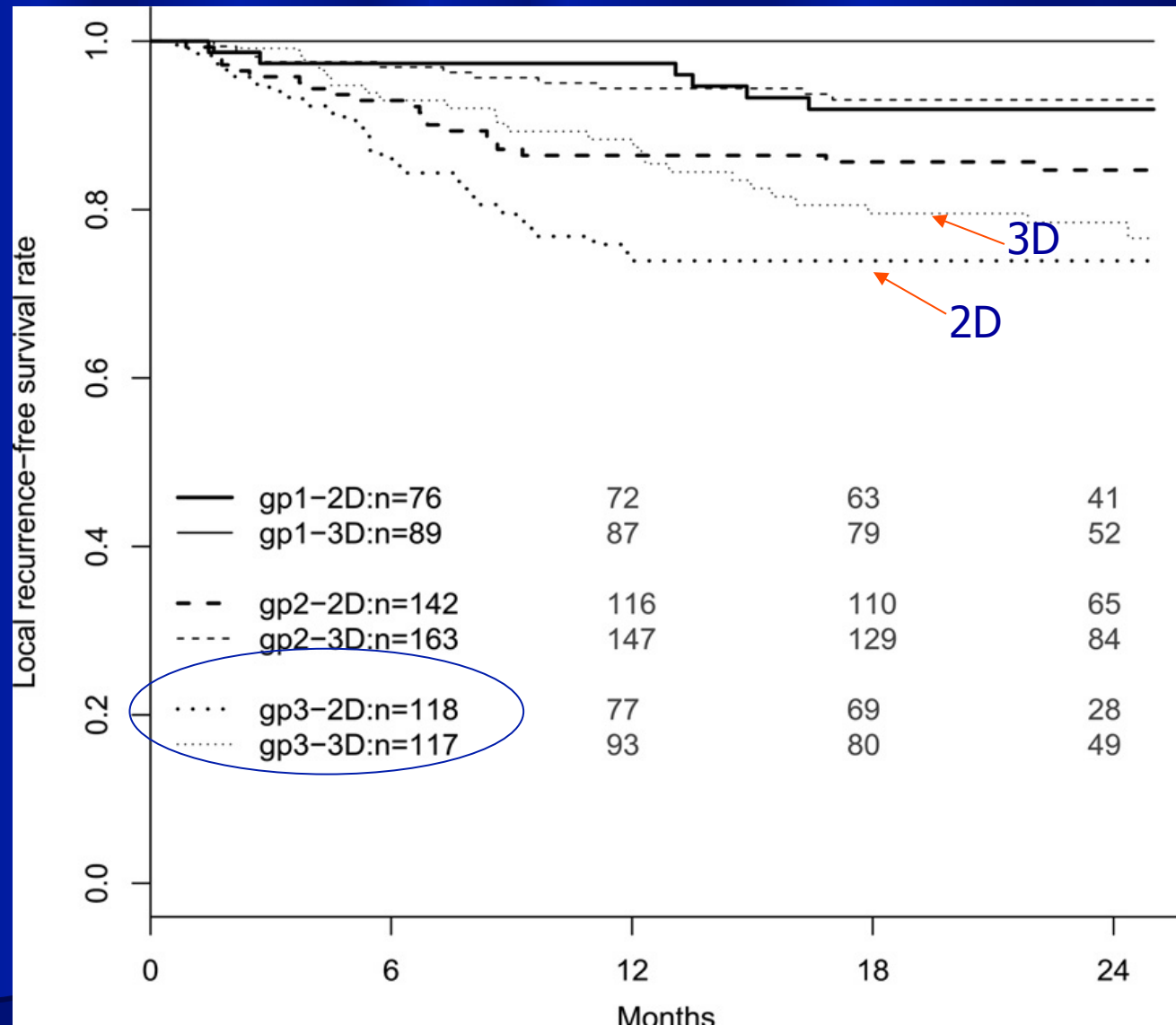
Comparison of main clinical factors between 2D and 3D arms.

	Group 1 BT followed by surgery		Group 2 EBRT BT surgery		Group 3 EBRT BT		p*
	2D	3D	2D	3D	2D	3D	
Number of patients	76	89	142	163	118	117	0.07
Mean age	47.6	46.6	49	47.6	56.1	53.4	
Histology							0.08
Squamous cell	50 (66%)	60 (67%)	120 (84%)	123 (75%)	106 (90%)	99 (85%)	
Adenocarcinoma	22 (29%)	26 (29%)	21 (15%)	38 (23%)	12 (10%)	17 (14%)	
Other	4 (5%)	3 (4%)	1 (1%)	2 (2%)	0	1 (1%)	
FIGO stage							0.27
IB1	66 (87%)	83 (93%)	13 (9%)	16 (10%)	6 (5%)	11 (9%)	
IB2 IIA IIB	10 (13%)	6 (7%)	118 (83%)	127 (78%)	70 (59%)	77 (66%)	
IIIA IIIB	0 (0%)	0 (0%)	11 (8%)	20 (12%)	42 (36%)	29 (25%)	
Mean tumor maximal size (mm)	23 ± 9	28 ± 13	46 ± 16	46 ± 14	49 ± 16	48.5 ± 16	0.44
Pelvic node ¹	3 (4%)	2 (2%)	45 (32%)	63 (39%)	52 (44%)	54 (46%)	0.34
LomboAortic node ¹	0	0	16 (11%)	16 (10%)	22 (19%)	17 (15%)	0.33

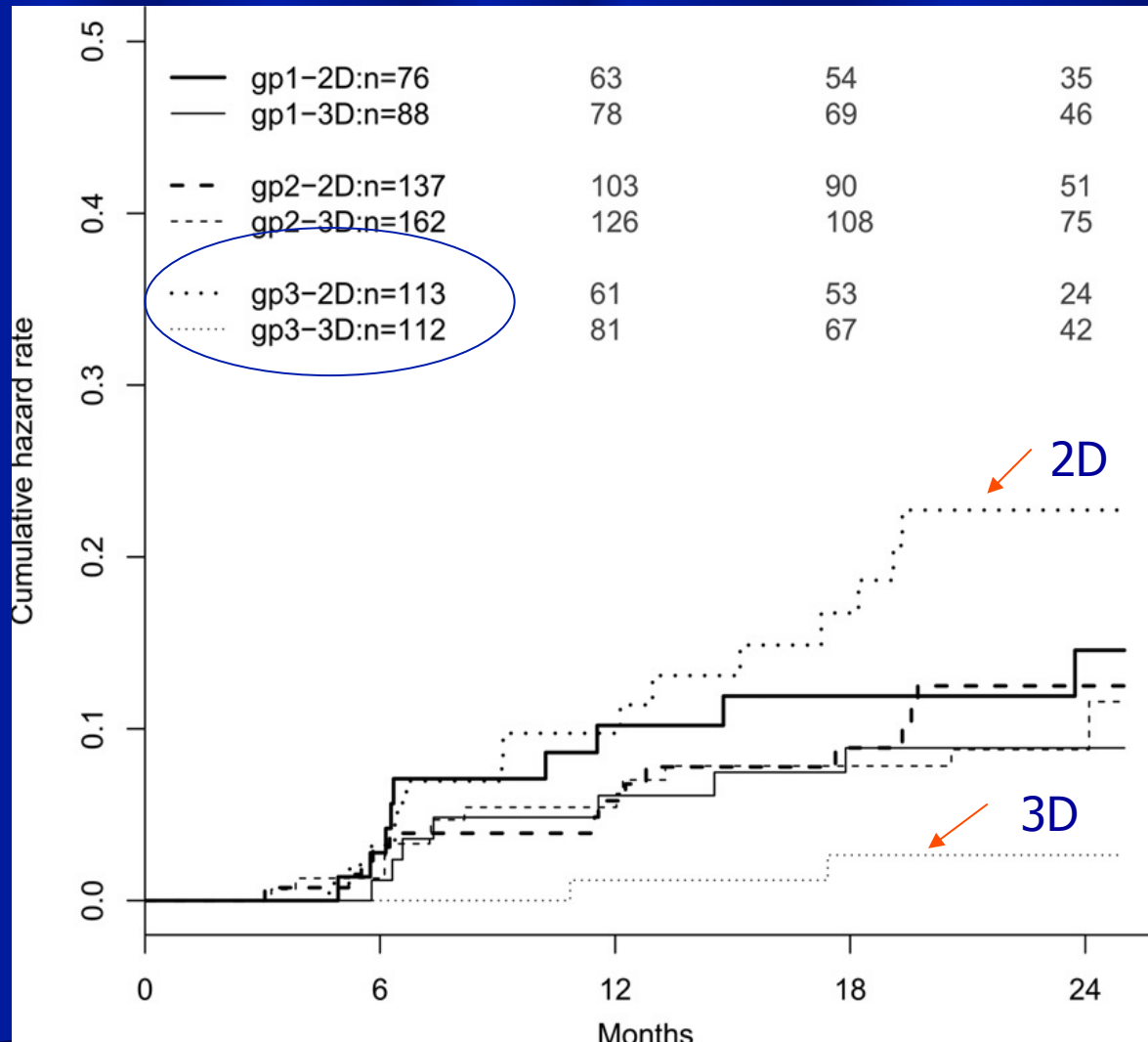
¹ nodes diagnosed on imagery (CT/MRI/ or PET CT).

* 2D–3D brachytherapy comparison: Generalized Estimated Equations adapted for nested analysis.

L'esperienza francese: LRFS

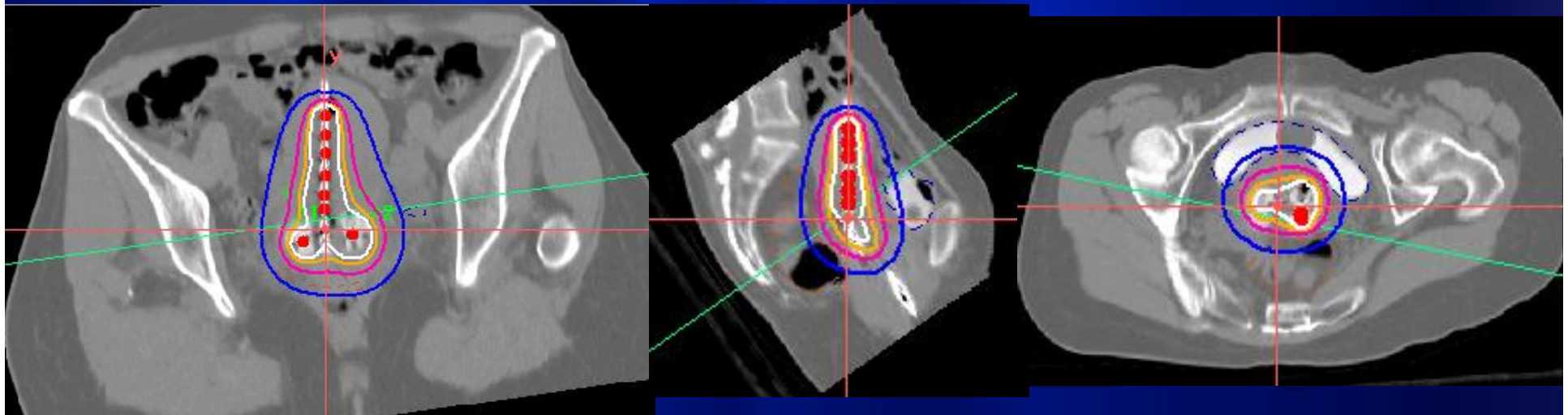


L'esperienza francese: tossicità



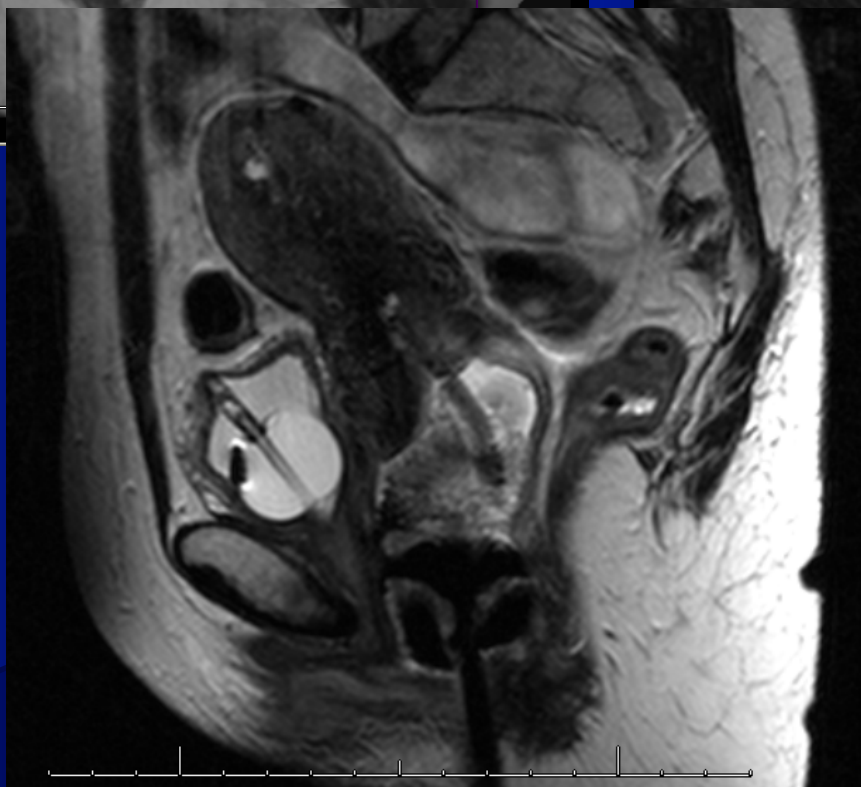
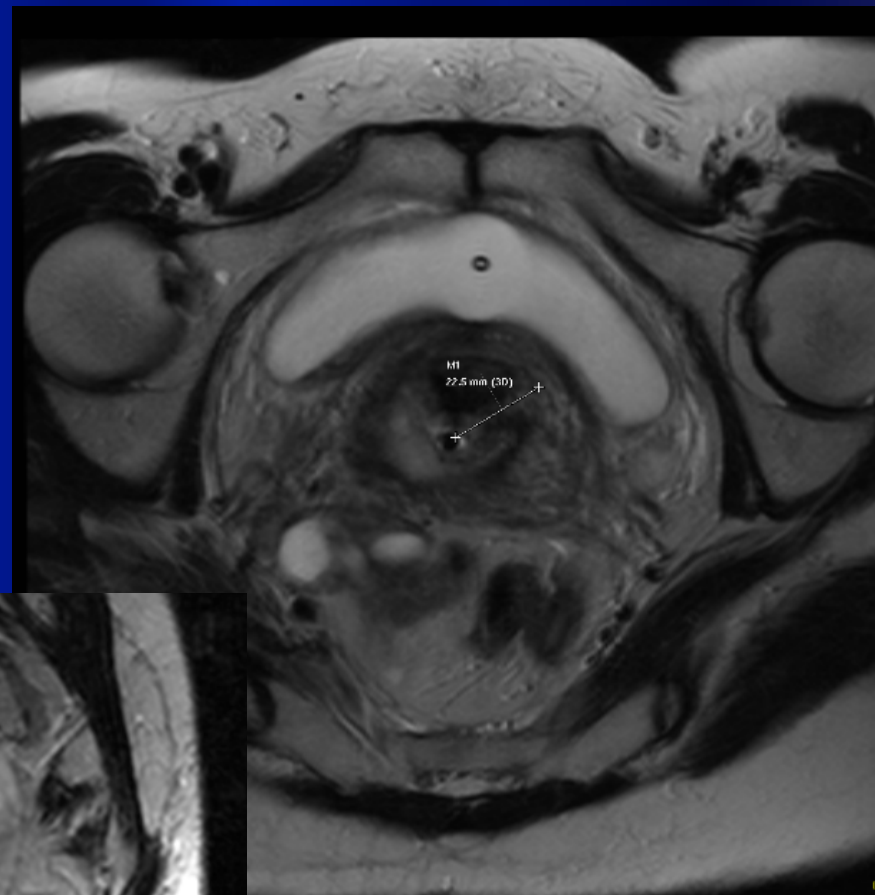
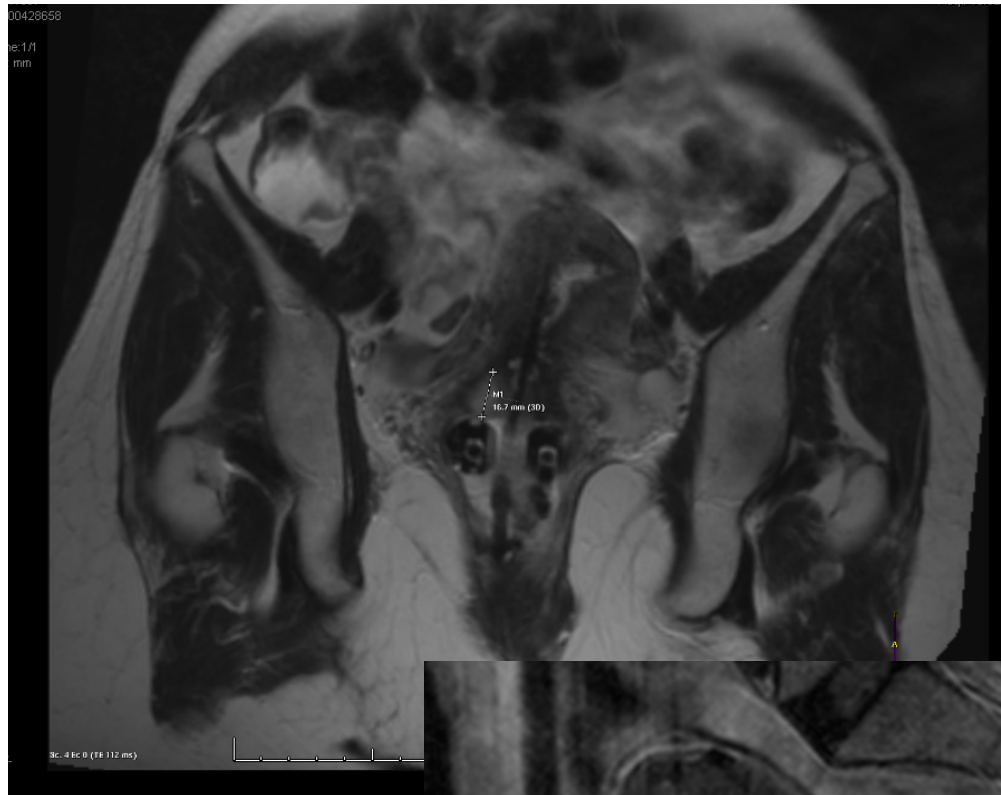
Protocollo Cremona

- Neoplasia confinata alla cervice (IB1- IB2):
 - BT endocavitaria
 - TC come base di pianificazione brachi (GTV \cong HRCTV = cervice) sempre e per ogni frazione
 - RM alla 1° seduta BT (quasi sempre)



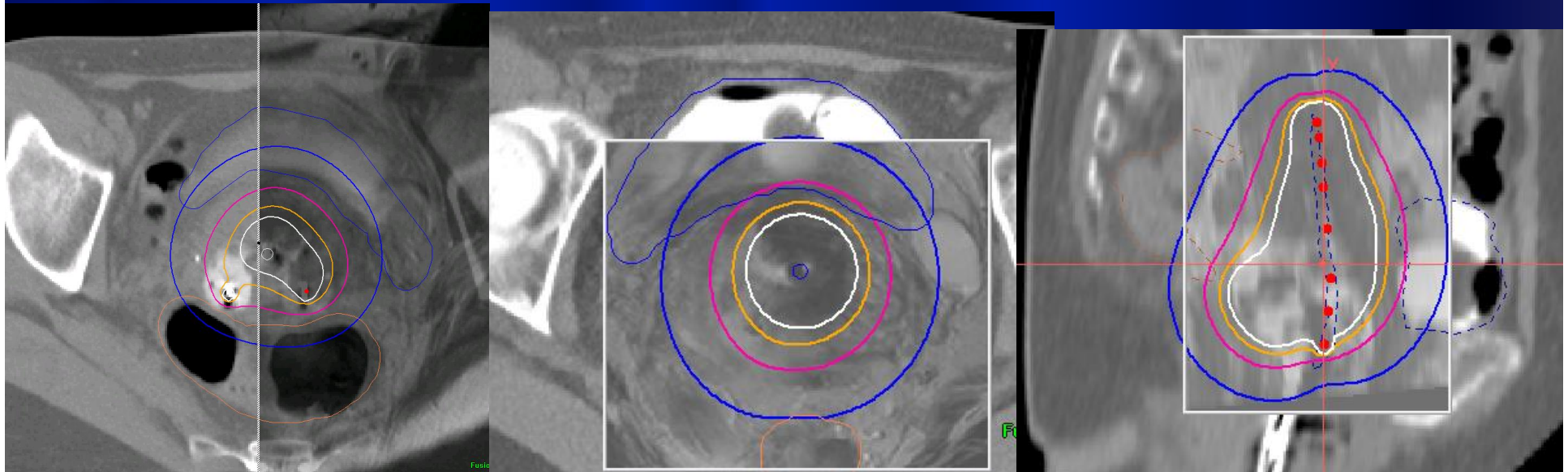
00428658

ie: T1
mm



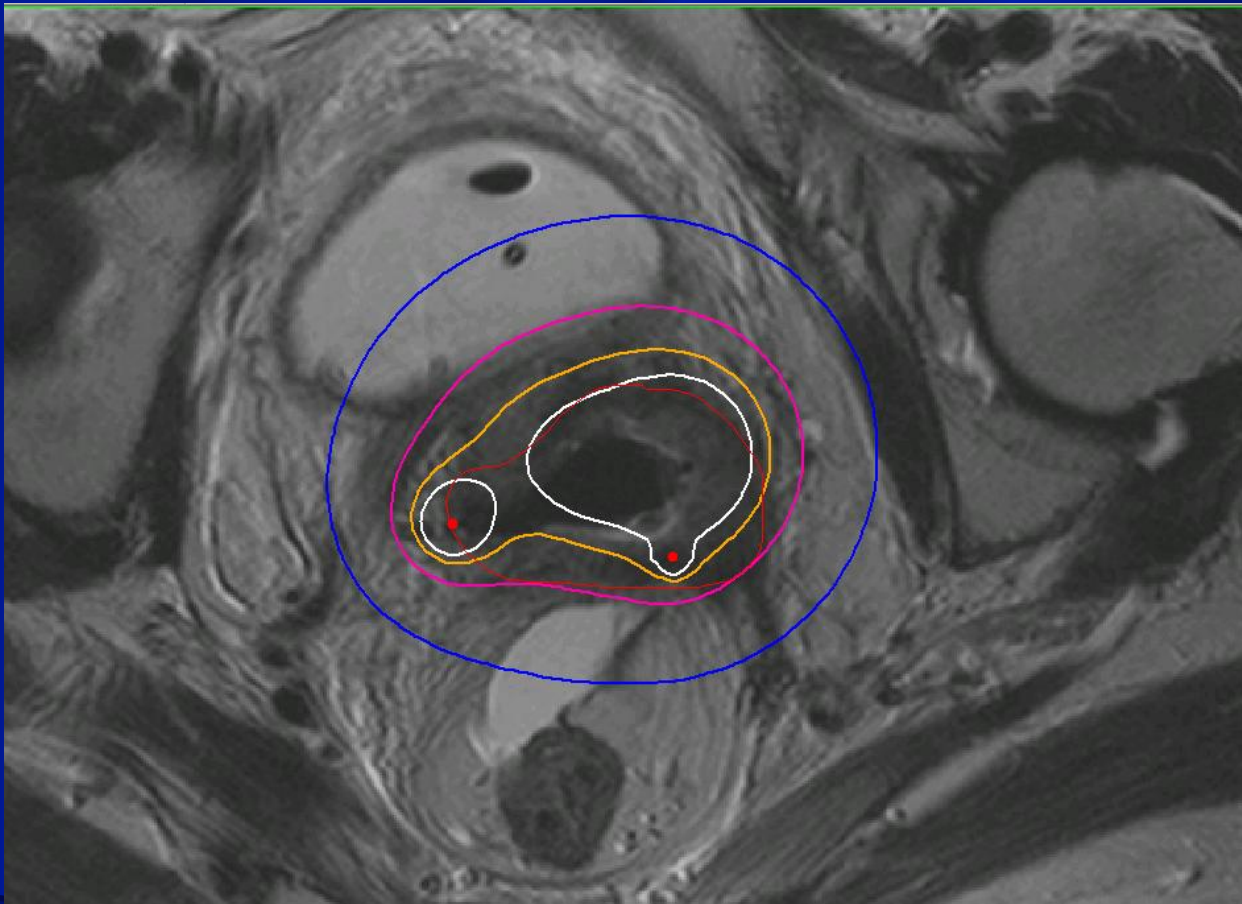
Protocollo Cremona

- Neoplasia avanzata (IIB, IIIB)
 - RM pre terapia: definizione del GTV_D
 - Se malattia intrauterina: BT endocavitaria
 - Se residuo extracervicale post RTE: BT endocavitaria + interstiziale (PDR)



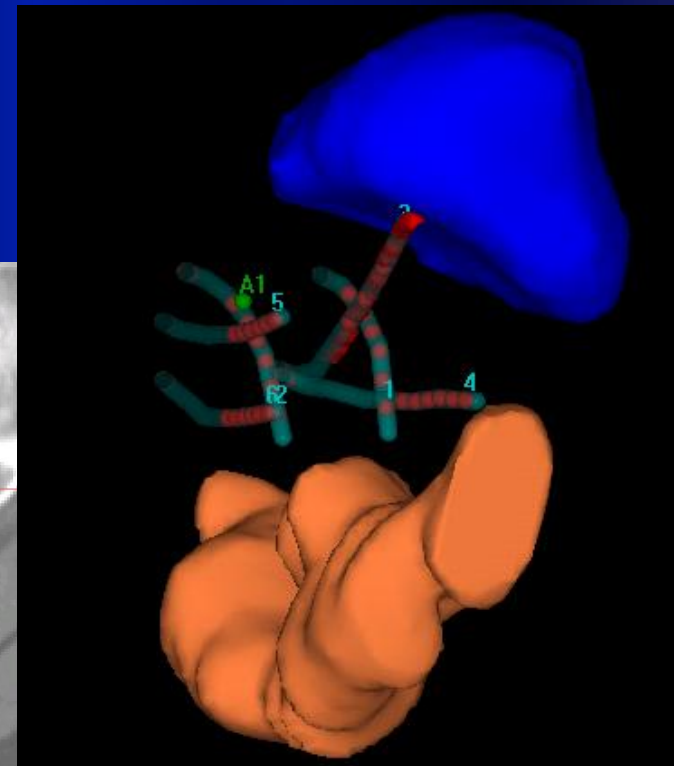
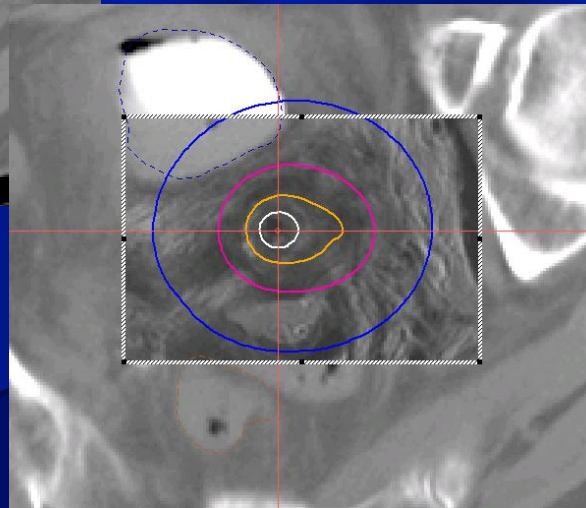
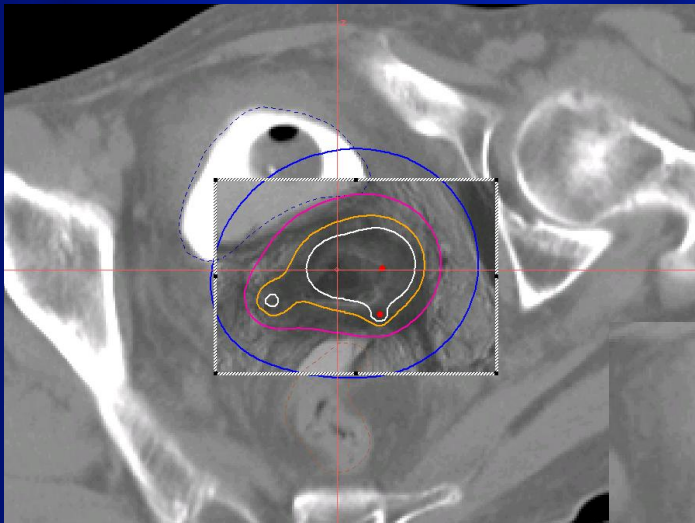
Protocollo Cremona

- Neoplasia avanzata (IIB, IIIB)
 - RM 1° frazione di brachiterapia (sempre) GTV_{BT1}

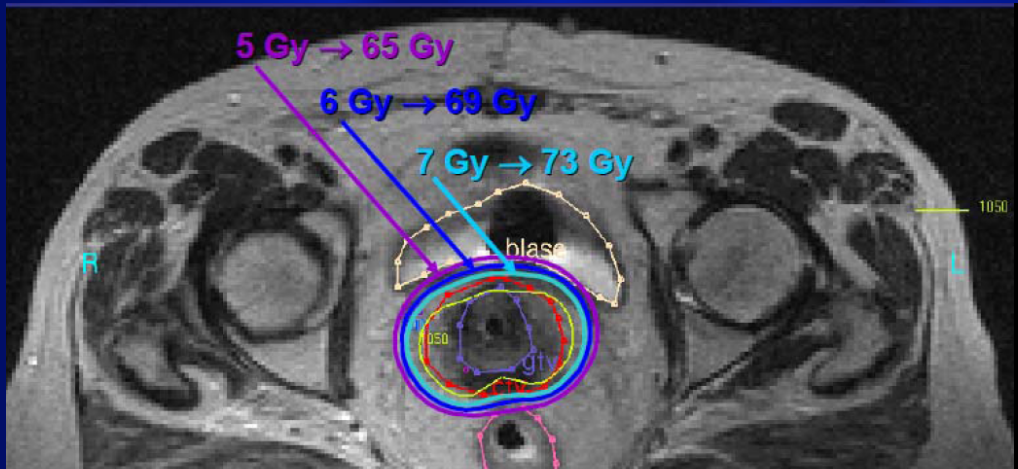


Protocollo Cremona

- Neoplasia avanzata (IIB, IIIB)
 - Fusione immagini TC/RM nelle sedute successive (applicatori come landmark)
 - Se ↓ clinica GTV in corso di BT → RM



Dose fisica



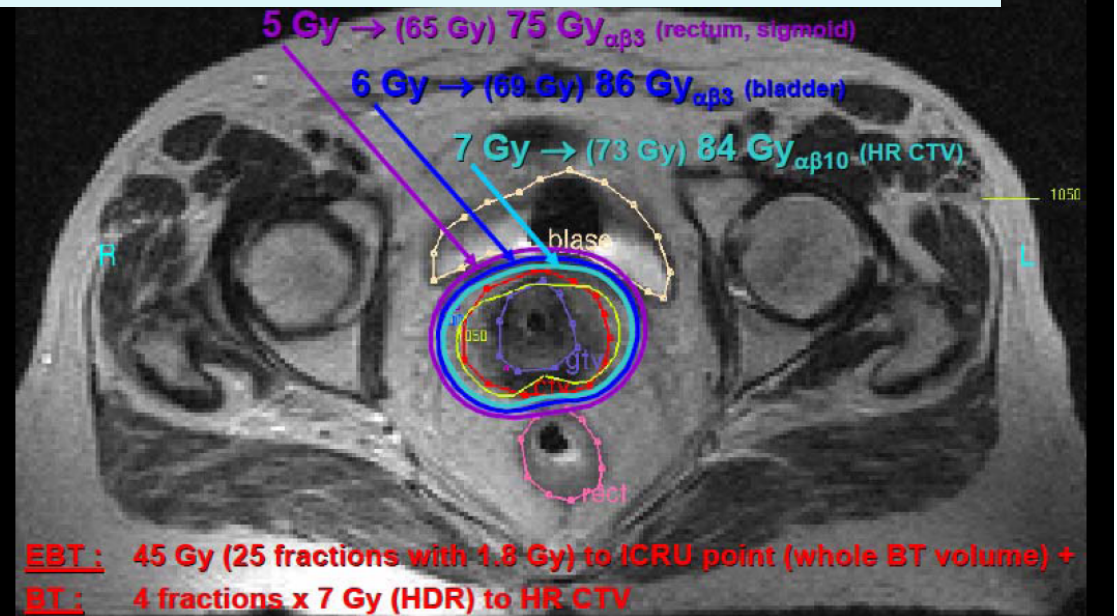
$$EQD2 = D \times \left[\frac{(d + \alpha/\beta)}{2} + \alpha/\beta \right]$$

D = dose totale

d = dose/frazione

$\alpha/\beta = 3$ per OAR

$\alpha/\beta = 10$ per il tumore



Dose biologica



ELSEVIER

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Brachytherapy

Local recurrences in cervical cancer patients in the setting of image-guided brachytherapy: A comparison of spatial dose distribution within a matched-pair analysis

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- Aumentato rischio di recidiva se EQD2 nell'HRCTV $< 87\text{Gy}$

MP Schmid et al, R & O 100:468–472, 2011

Dose biologica

- Limiti dose a OAR (2cc)
 - Retto 70 Gy EQD2
 - Vescica 90 Gy EQD2
 - Sigma 70 Gy EQD2

R Pötter et al R&O 2006; 78:67

Dose volume	Probability of EQD2 for G2–G4 side effects (Gy) for the incidence rates shown (95% CI)			
	5%	10%	20%	<i>p</i> value
Rectum				
D _{2cc}	67 (30–79)	78 (66–110)	90 (78–171)	0.0178
D _{1cc}	71 (0–89)	87 (69–209)	104 (87–443)	0.0352
D _{0.1cc}	83	132	186	0.1364
Bladder				
D _{2cc}	70 (0–95)	101 (29–137)	134 (110–371)	0.0274
D _{1cc}	71 (0–107)	116 (17–169)	164 (129–498)	0.0268
D _{0.1cc}	61*(0–155)	178 (0–368)	305 (213–2126)	0.0369

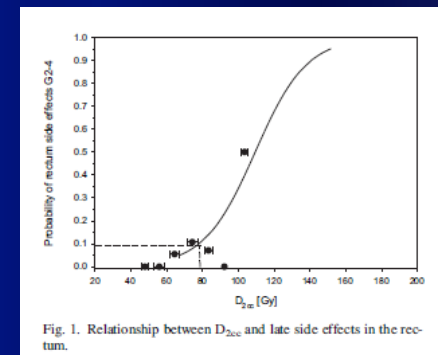


Fig. 1. Relationship between D_{2cc} and late side effects in the rectum.

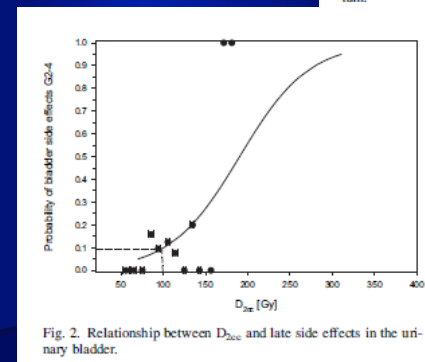
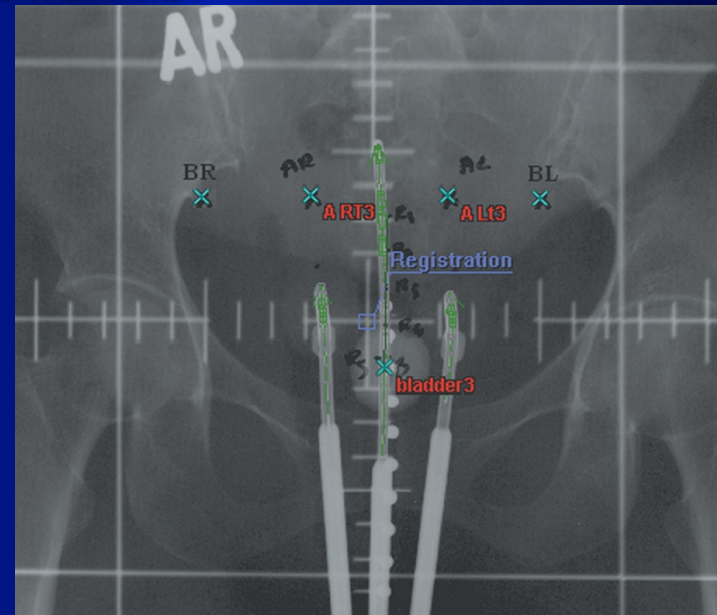


Fig. 2. Relationship between D_{2cc} and late side effects in the urinary bladder.

Evoluzione della BT

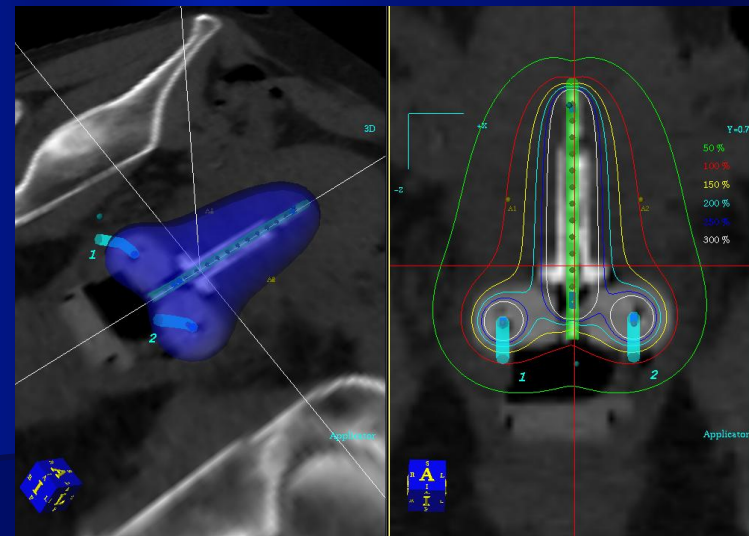
- **2D BT**

- Dose in punti su radiogrammi ortogonali



- **3D BT**

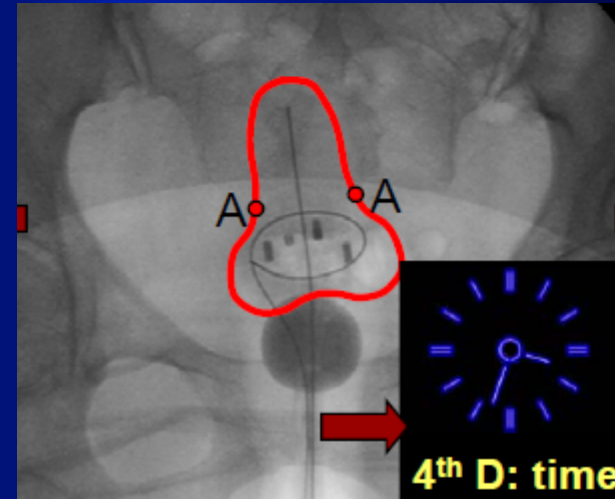
- Immagini TC e/o RM con applicatore in situ



Evoluzione della BT

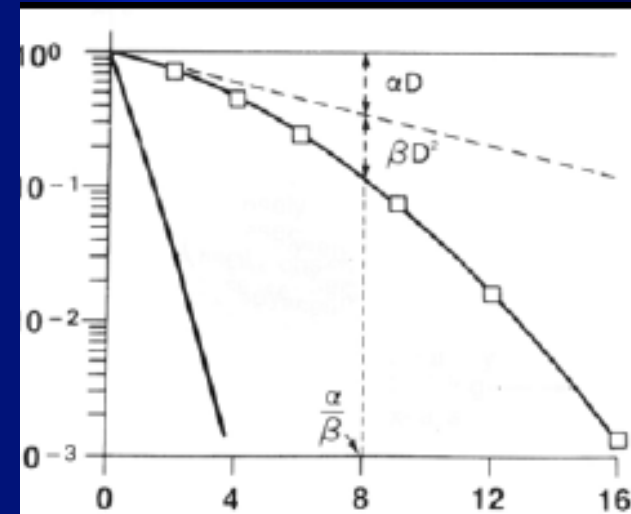
- **4D BT**

- Dose "conformata" al target nello spazio e nel tempo



- **5D BT**

- Dose pesata biologicamente



5th D: radiobiology