Controversie sull'utilizzo della brachiterapia in ginecologia oncologica

Dosi e frazionamenti

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Dose and fractionation in Gynecological Brachytherapy

- **Dose specification and prescription**
- 2D versus 3D
- Dose rate and fractionation (LDR and HDR)
- EBRT and BRT
- Treatment duration

Dosimetric Systems

- Dosimetric systems are set of rules, specific to a radioisotope and its spatial distribution in the applicator to deliver a defined dose to a designated region

- Within any system, specification of treatment in terms of dose, timing, and administration is necessary so as to implement prescription in a reproducible manner.

Manchester System

- Standardized system: Predetermined doses and dose-rates directed to fixed points in the pelvis
- Specified intracavitary treatment in absorbed dose or roentgens, rather than mg-hrs
- Points A and B: Theory that dose in the paracervical triangle reflected normal tissue tolerance

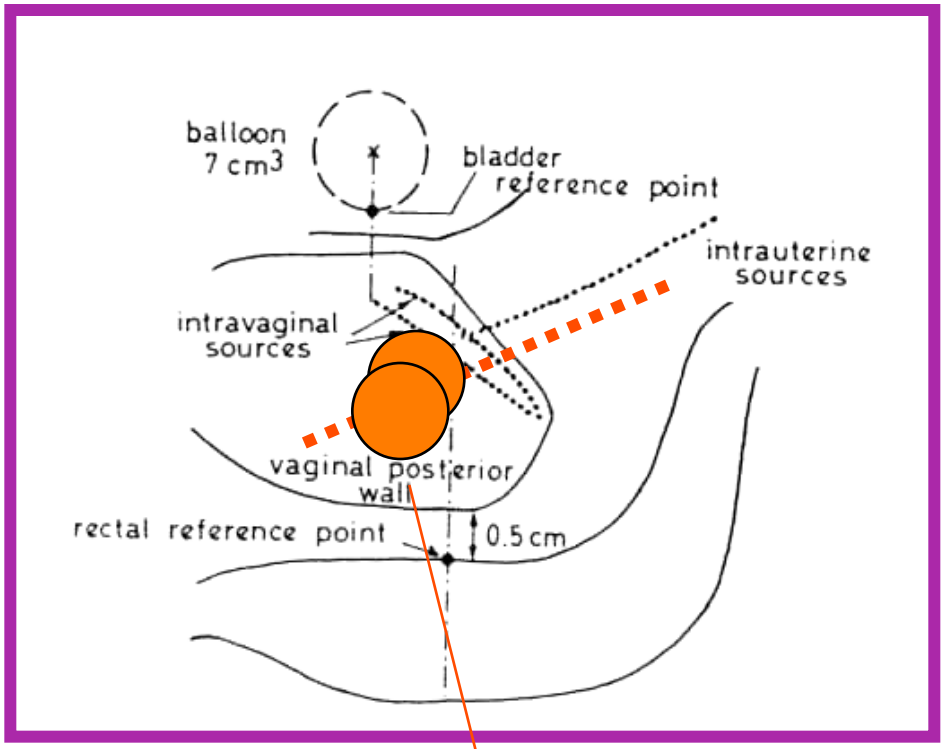
Fletcher System

Current Approach

- 40 – 45 Gy external beam; 6000-6500 Mg-RA eq Cs 137
- Implant loadings and duration retrospectively analyzed:

Point A – 57 cGy/hr	Total dose: 87 Gy
Vag surface – 100cGy/hr	Total dose: 120-140 Gy
Point B – 28% Point A	
Rectum – 54% Point A	Total dose: 68 Gy
Bladder – 60% Point A	Total dose: 70 Gy

ICRU 38: rules on critical organ dose consideration



Space visible on X Ray due to radio-opaque packing material - the packing increases the distance between vagina and rectum to reduce dose to the rectum

- There is general agreement that correlation of radiation point doses and dose volume effects is inferior to correlation of dose volume relations and dose volume effects in any given organ.
- However, for gynaecologic brachytherapy, this correlation could hardly be investigated until now.

Linee guida AIRO

Calcolo della distribuzione di dose 2 D con radiografie ortogonali

Punti dose

Vanno definiti i seguenti punti secondo l'**ICRU Report n. 38**, rispetto ai quali sarà calcolata la dose.

- punti parete pelvica dx e sn
- punto dose di riferimento rettale
- punto dose di riferimento vescicale
- Anche se non richiesti dall'ICRU Report n° 38 vanno definiti:
- punti A dx e sn
- punti B dx e sn

Volumi

Vanno definiti i seguenti volumi (altezza x larghezza x profondità in mm, per la dose complessiva di radioterapia transcutanea + brachiterapia):

- trattamento (specificando la dose di trattamento)
- riferimento (all'isodose 60 Gy)

Dose specification and prescription

- milligram per hour of radium

- TRAK
- specific well-defined points (e.g. point A)
- reference volume

ICRU 38

- target volume

3D BRT

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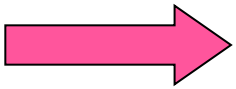
Different treatment strategies for cervical cancer

Traditional

- point A
- 60 Gy reference volume



3D image based

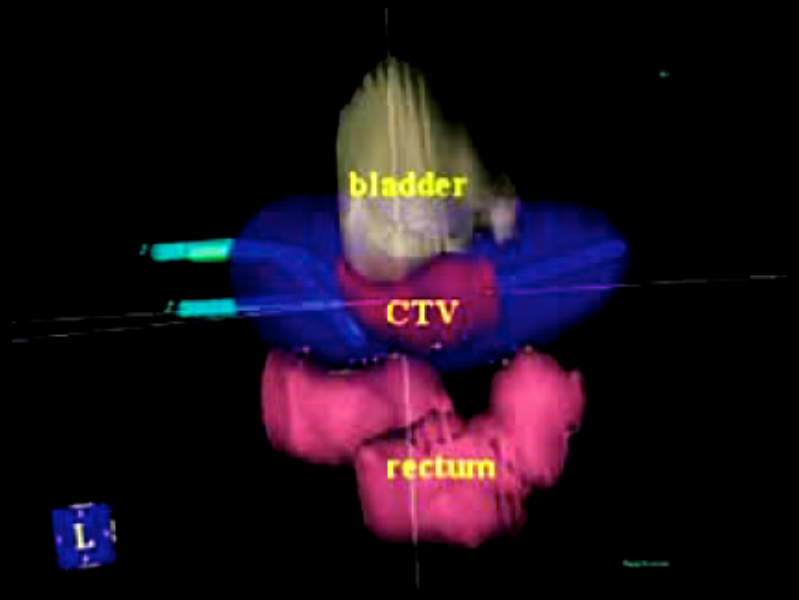
- GTV
- CTV
- Dose/volume relations

Comparison of point A plan with 3D plan

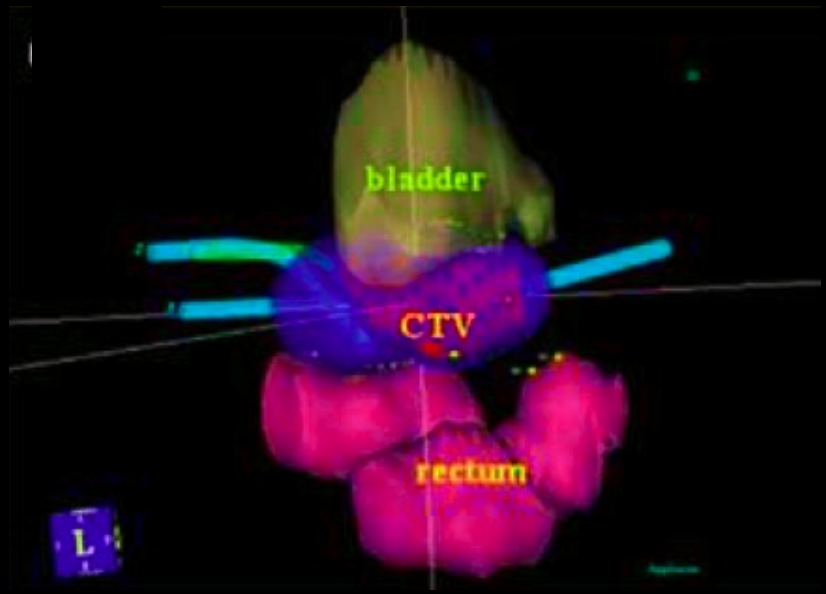
Small CTV

(CTV) fully encompassed by 100% isodose line prescribed to point A

Conventional plan



3D plan



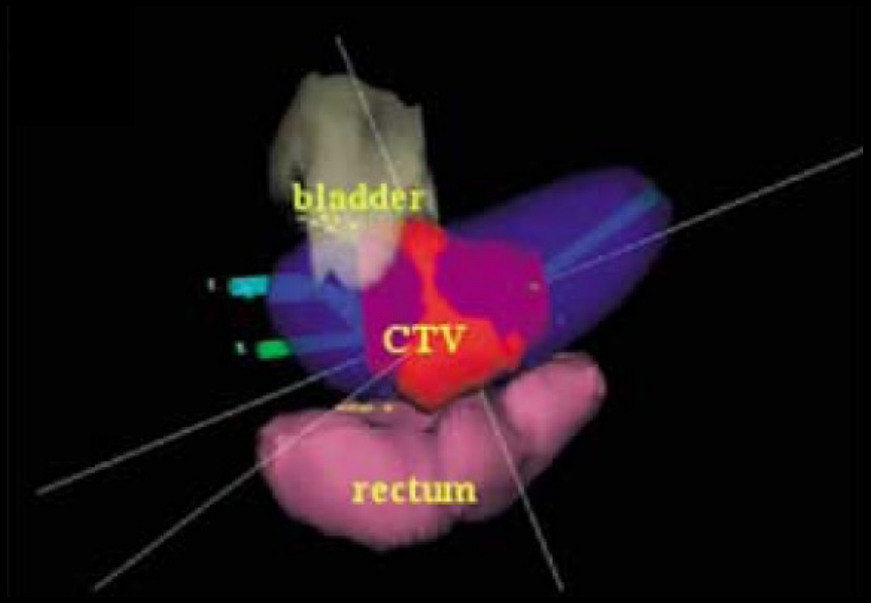
Kyung Wan Shin.. et al. Int. J. Radiation Oncology Biol. Phys., 64, 197–204, 2006

Comparison of point A plan with 3D plan

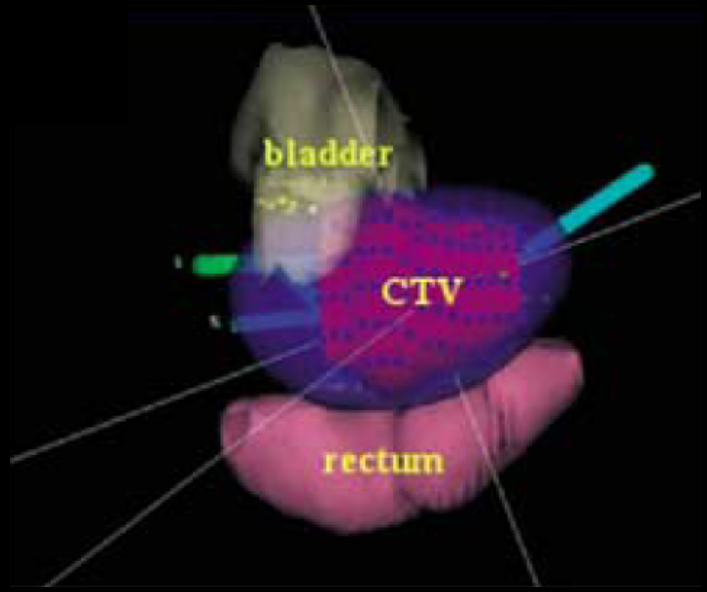
Large CTV

(CTV) not fully encompassed by 100% isodose line prescribed to point A

Conventional plan

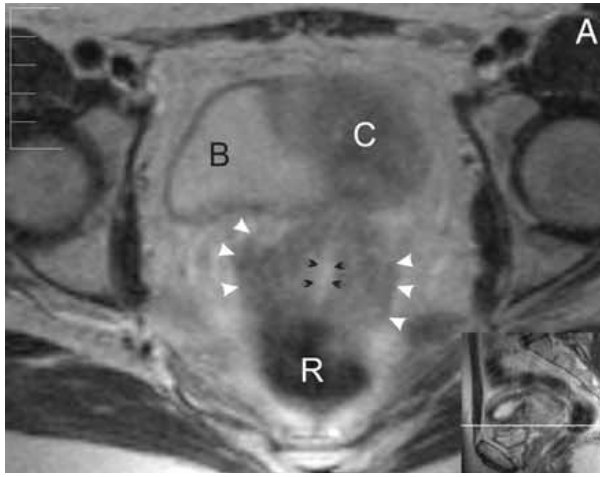


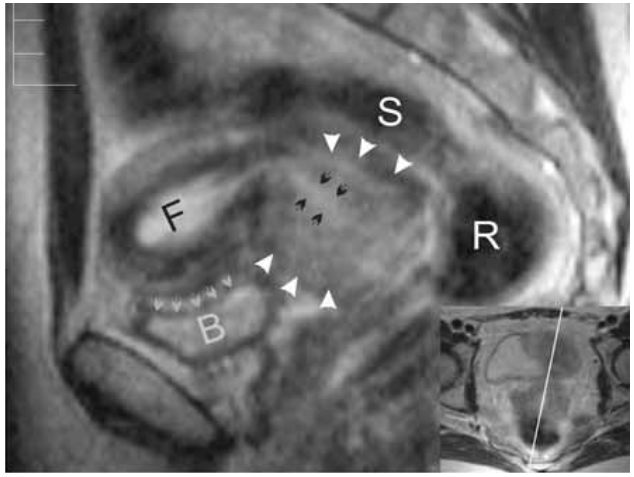
3D plan

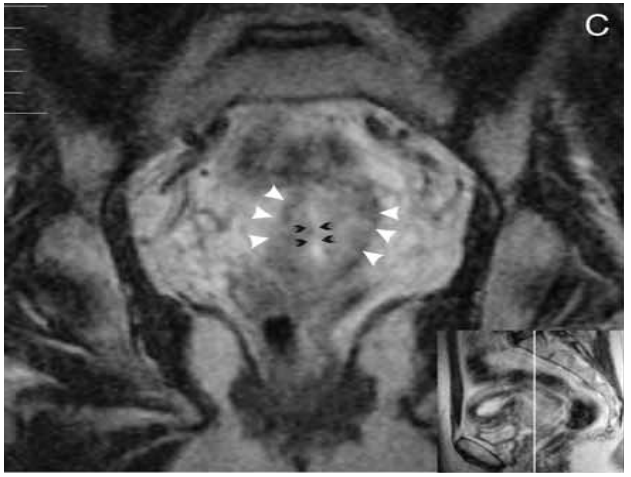


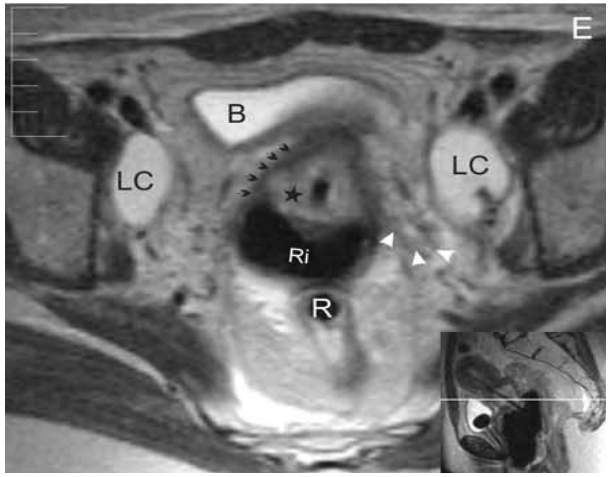
Kyung Wan Shin.. et al. Int. J. Radiation Oncology Biol. Phys., 64, 197–204, 2006

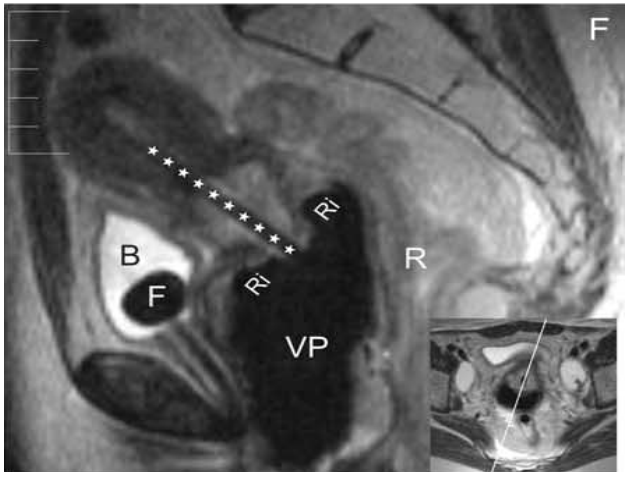
Axial, sagittal and coronal images at diagnosis and at time of brachytherapy

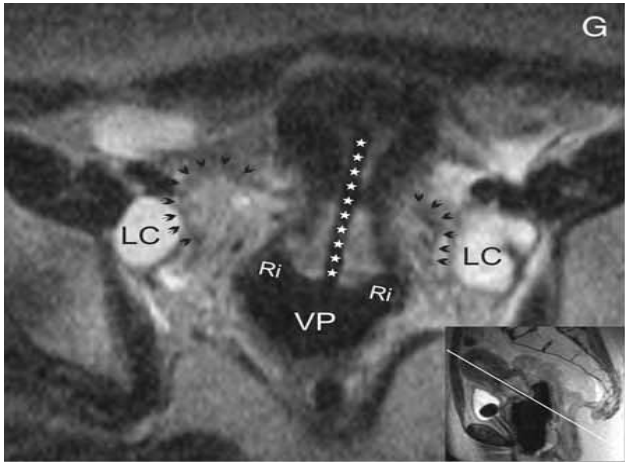




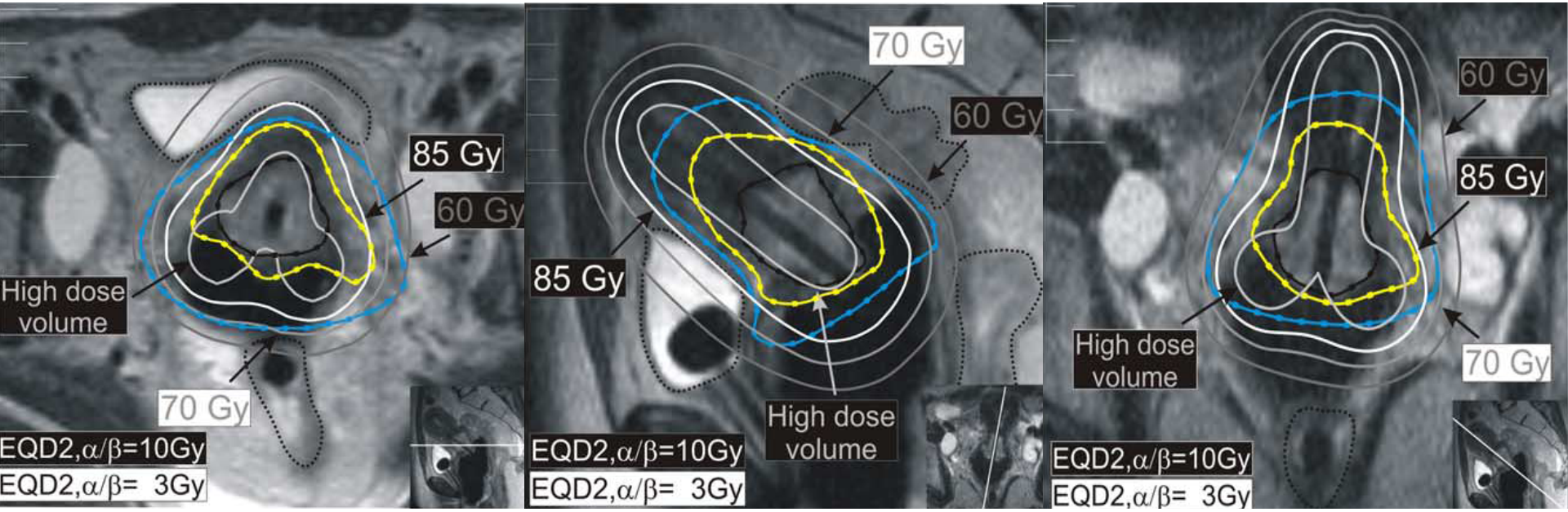








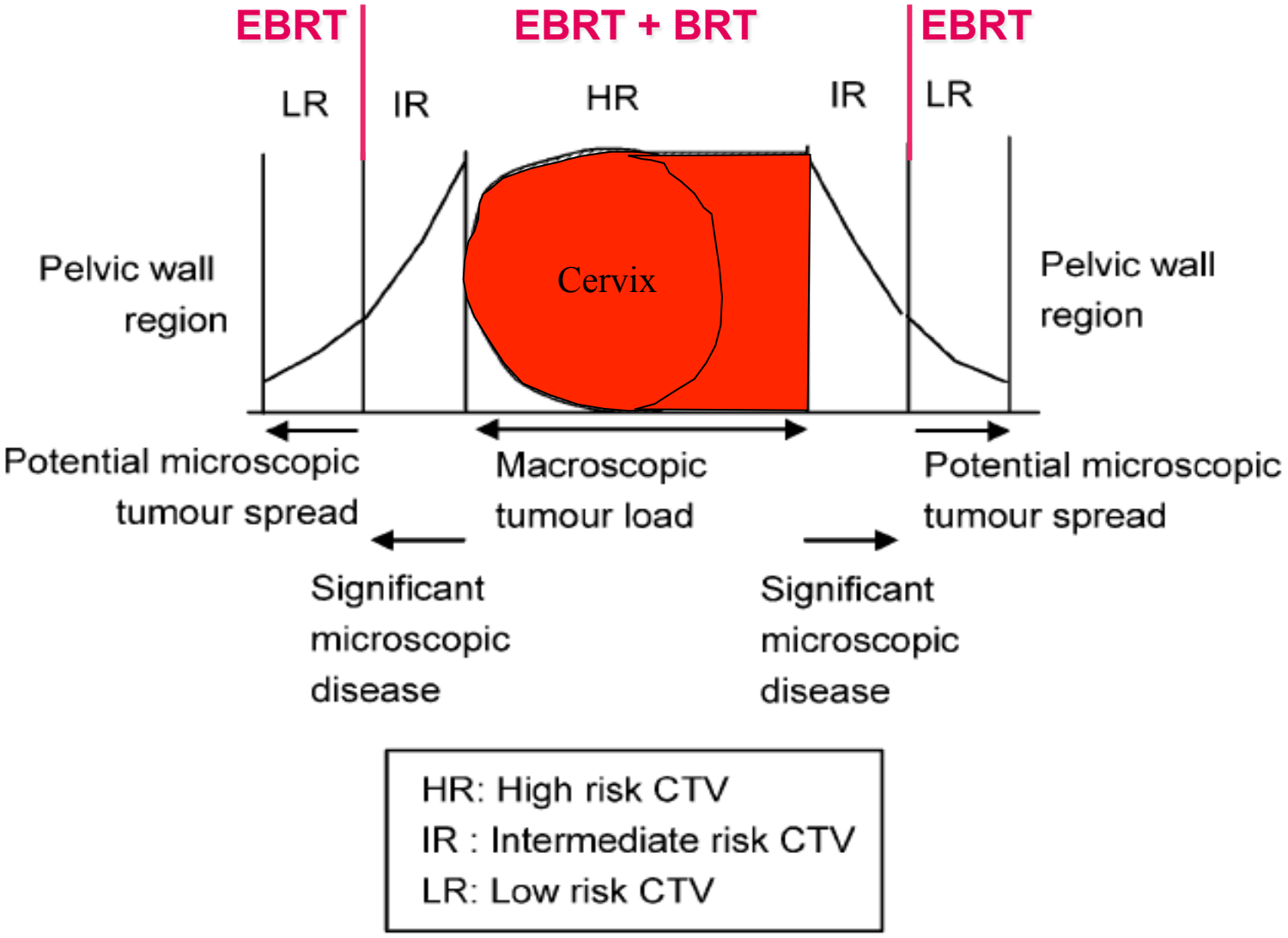
MRI based 3D treatment plan with relevant dose volume parameters for GTV, HR/IR CTV and OAR



Two CTVs

- A **'high risk' CTV (HR CTV)** with a major risk of local recurrence because of residual macroscopic disease. The intent is to deliver a **total dose** as high as possible and **appropriate to eradicate all residual macroscopic tumour.**
- An **'intermediate risk' CTV (IR CTV)** with a major risk of local recurrence in areas that correspond to initial macroscopic extent of disease with at most residual microscopic disease at time of BT. The intent is to deliver a **total radiation dose appropriate to cure significant microscopic disease** in cervix cancer, which corresponds to a dose of at least 60 Gy.

Three different target volumes according to cancer cell density



Two approaches in volume delineation and dose prescription

point A as a reference point

- GTV as it presents at time of BT
- CTV for BT limited to cervix and adjacent structures with presumed residual disease (w30–60 cc)
- Dose: 80-90 Gy
- Dose comparable with dose to point A

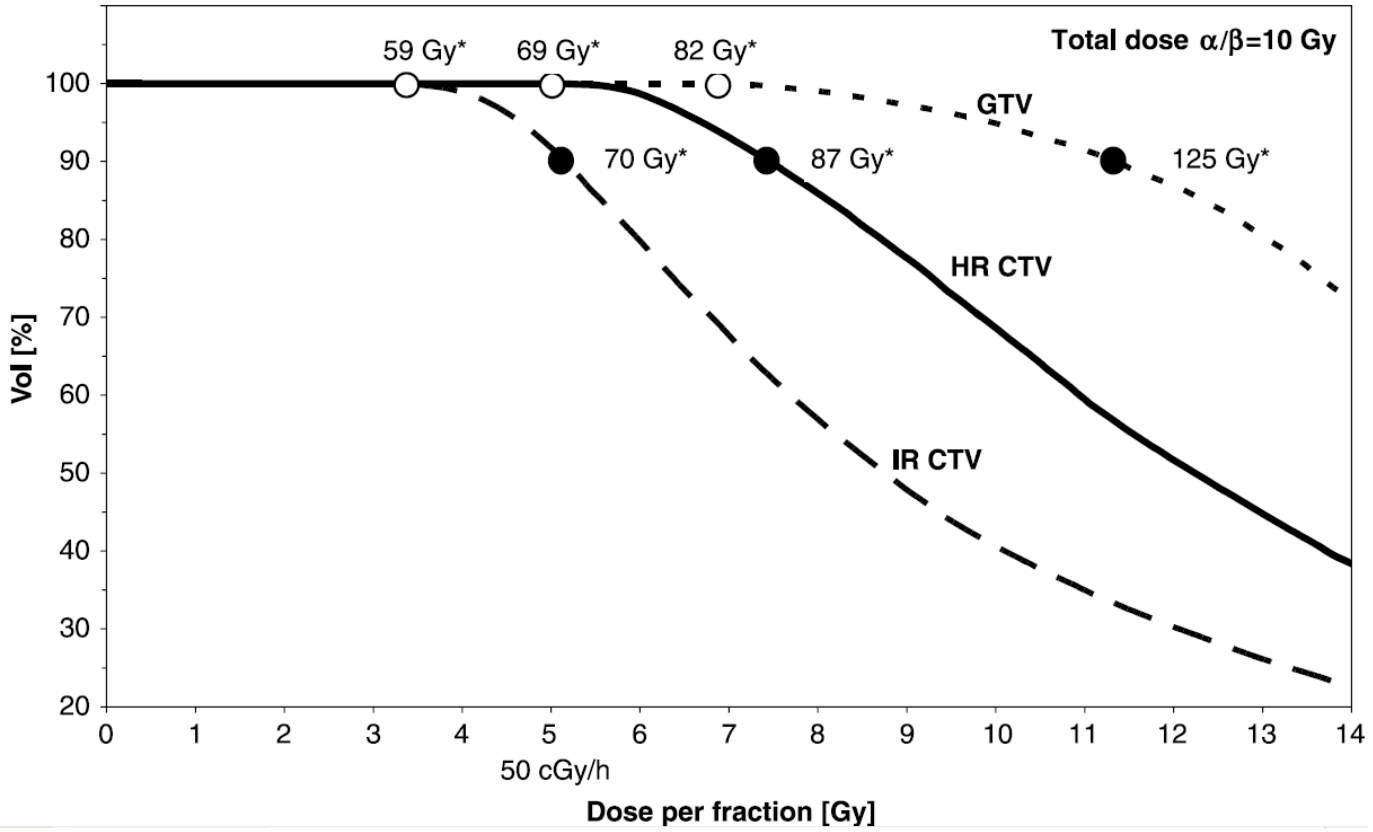
Reference volume in ICRU 38 recommendations

- GTV at diagnosis
- CTV including anatomically targeted safety margins with regard to dimensions of GTV at diagnosis (w150–300 cc)
- Dose: 60 Gy at a dose-rate of 50 cGy per hour
- Not comparable with dose and dose rate to point A

Intercomparison of treatment concepts for 3D image guided brachytherapy of cervical carcinoma based on a GEC-ESTRO study protocol

	IGR Paris	University of Leuven	University of Vienna
Point A	91 Gy	85 Gy	85 Gy
CTV HR D90	86 Gy	87 Gy	84 Gy
CTV HR D100	74 Gy	64 Gy	65 Gy
CTV IR D90	69 Gy	73 Gy	73 Gy
CTV IR D100	55 Gy	58 Gy	58 Gy
2 cm^3 bladder wall	70 Gy	81 Gy	85 Gy
2 cm^3 rectum wall	53 Gy	62 Gy	64 Gy
2 cm^3 sigma wall	60 Gy	67 Gy	63 Gy
Isodose through point A max dimensions (HxVxT)	8,6x4,8x3,7 cm	8,4x6,9x4,5 cm	8,5x6,5x4,1 cm
At point A level (WxT)	3,8x2,9 cm	3,7x4,0 cm	4,0x3,7 cm

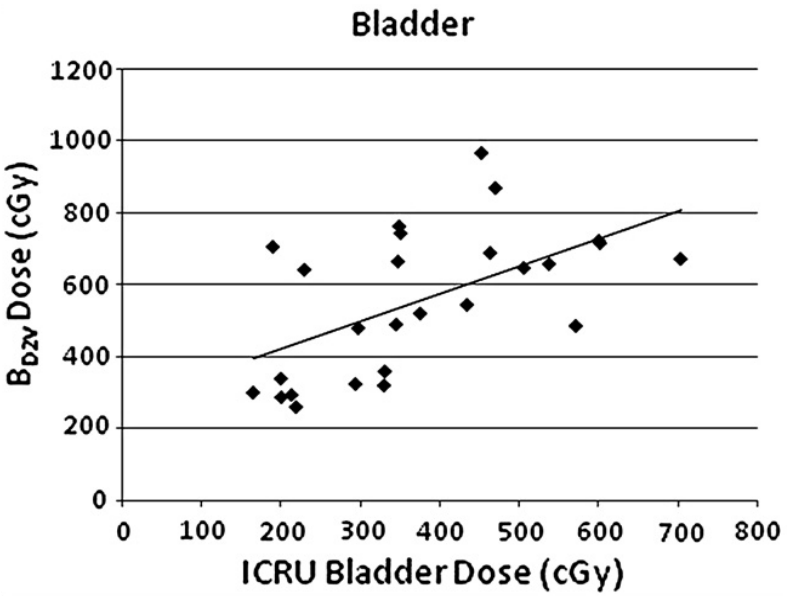
Dose volume histograms of GTV, HR CTV, and IR CTV for one fraction of HDR intracavitary brachytherapy

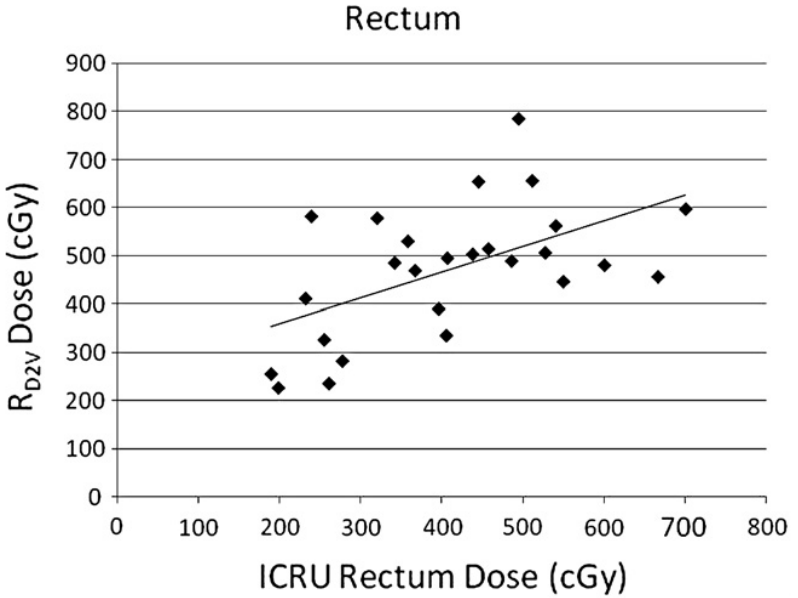


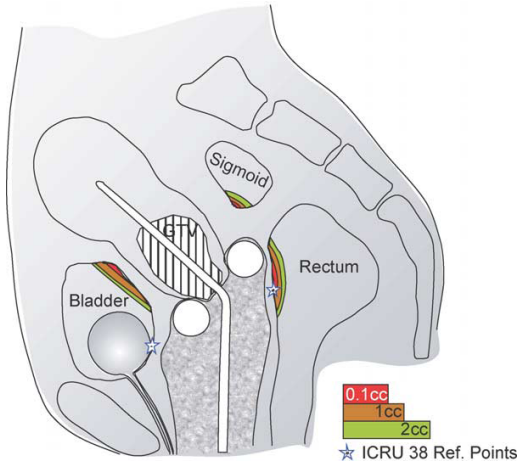
Dose reporting

- D_{100} **minimum dose** delivered to 100% of the volume of interest
- D_{90} **minimum dose** delivered to 90% of the volume of interest
- V_{100} **volume** (with regard to the GTV or CTV) receiving 100% of prescribed equivalent dose EQD2
- $V_{60\ GyEQD2}$ **volume** (with regard to the GTV or CTV) receiving 60 Gy equivalent dose EQD2
- $V_{85\ GyEQD2}$ **volume** (with regard to the GTV or CTV) receiving 85 Gy equivalent dose EQD2

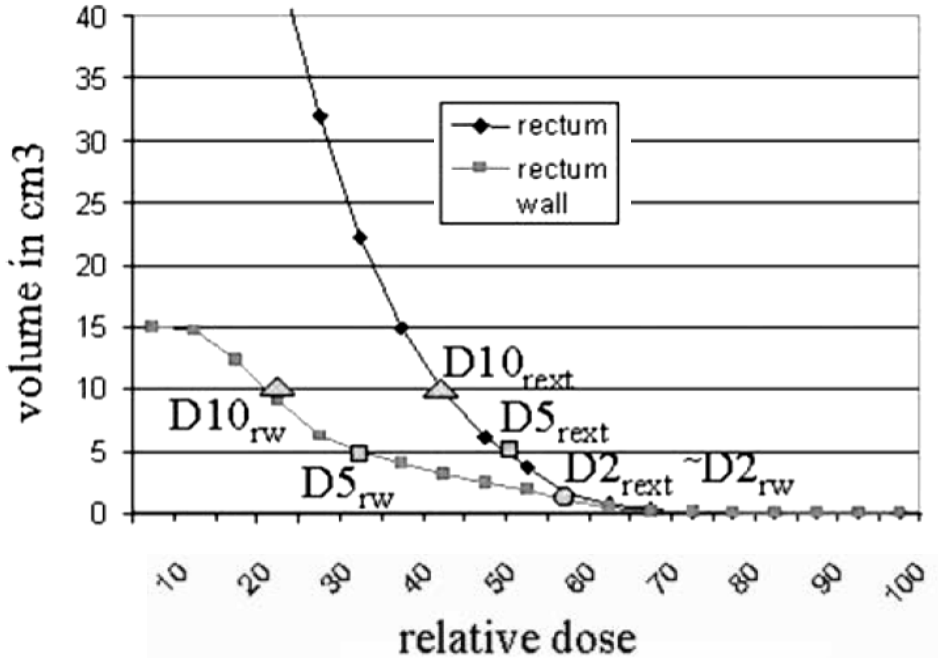
Comparison of the bladder and rectum dose calculated at the ICRU reference point and BD2V.

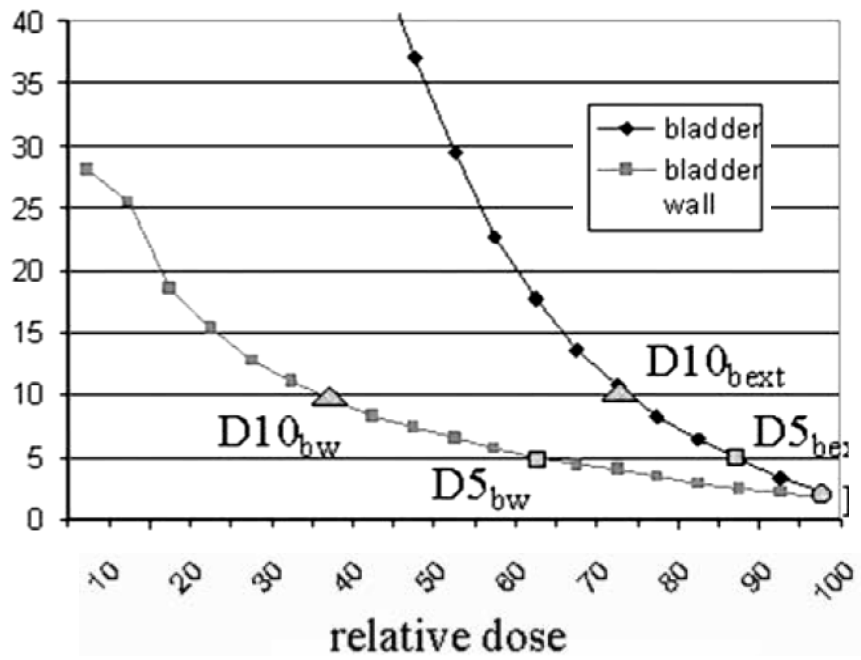






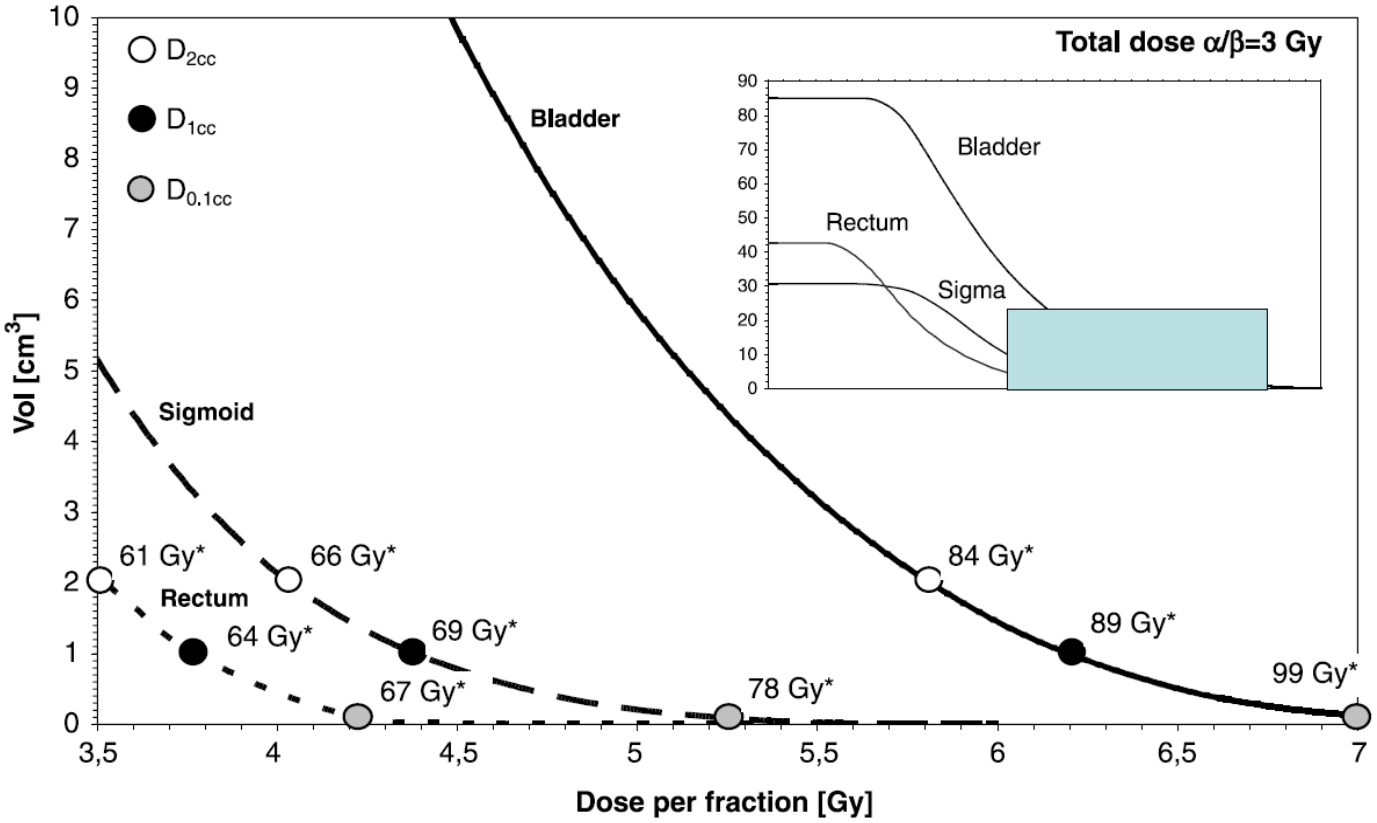
Relationship between dose at 2cm^3 bladder volume and dose at 2cm^3 rectum and bladder wall





Wachter-Gerstner N. et al. Radiotherapy and Oncology 68 (2003) 269–276

Cumulative dose volume histograms of bladder, rectum and sigmoid



Treatment Reporting

ICRU 38

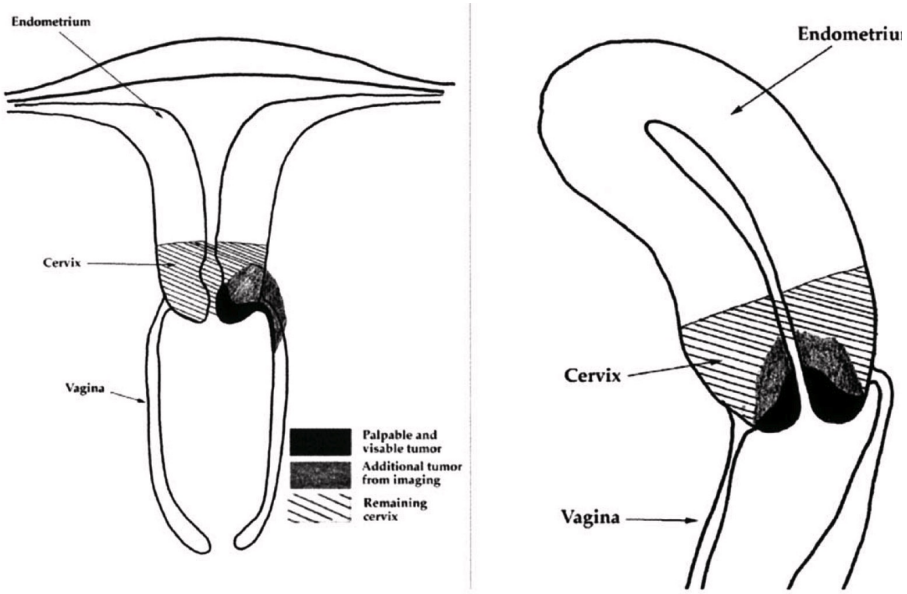
- Description of the technique used
- Total reference air kerma (cGy @ 1m)
- Reference volume
  - Usually at isodose with D_{total} of 60Gy, must specify otherwise
    - $D_{total} = D_{EBRT} + D_{BT}$
  - Shape (pear) and dimensions
- Absorbed dose at reference point
  - Bladder
  - Rectum
  - Lymphatic trapezoid
  - Pelvic wall reference point
- Time dose pattern

GYN GEC ESTRO – 3D

- Source localization
  - MRI (preferred over CT)
- Volume delineation
  - GTV, HR CTV, IR CTV
  - Organ at Risk – bladder, rectum, sigmoid, vagina
- Computer dose calculation
- Dose
  - Point A
- ICRU 38 – only bladder and rectum
  - D100, D90 for GTV, HR CTV, IR CTV
  - $D_{0.1cc}$, D_{1cc}, D_{2cc} for OARs if volumes are delineated
  - D_{5cc}, D_{10cc} for OAR if walls are contoured
- Optimization
  - Dose points
  - Dose volume
    - Shape
    - DVH

PROPOSED GUIDELINES FOR IMAGE-BASED INTRACAVITARY BRACHYTHERAPY FOR CERVICAL CARCINOMA

- GTV(I) is defined as the gross tumor volume as defined through imaging
- GTV is defined as the GTV(I) plus any clinically visualized or palpable tumor extensions
- GTV cx is defined as the GTV plus the entire cervix



- The Group recommended **T2-weighted MRI** using a pelvic surface coil with MRI-compatible brachytherapy applicators in place for image-based intracavitary brachytherapy for cervical cancer
- The Group thought that the current **dose prescription method in use for cervical cancer brachytherapy (i.e., to prescribe to Point A in most institutions) should not be changed as yet**, because image-based dosimetry is not ready for routine practice

Nag S. et al. Int. J. Radiation Oncology Biol. Phys., 60,1160–1172, 2004

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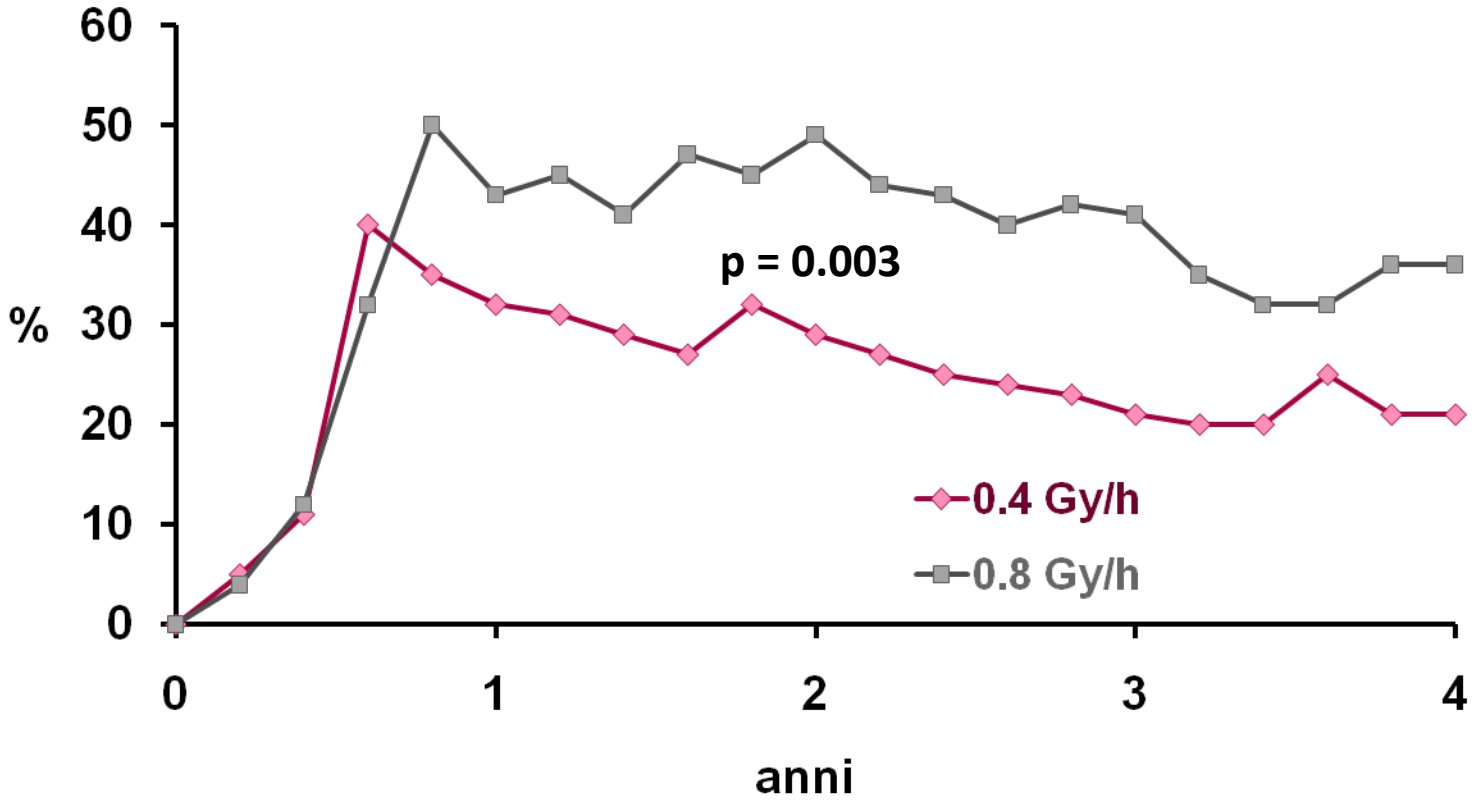
EFFETTI DEL DOSE RATE SULLA PREVALENZA DELLE COMPLICAZIONI



(Haie-Meder, IJROBP, 1994)

Biological Equivalent Dose

HDR treatments

$$BED = n\,d\,(1 + d / \alpha/\beta)$$

n = number of fractions
d = dose per fraction

LDR treatments

$$BED = NRT\,(1 + G \times d/\alpha/\beta) - k$$

N= number of insertions
R= dose rate (Gy/hr)
T= total treatment duration (hr)
α/β= LQ constant
G= $2/\mu t\,(1- (1-(\exp-\mu t/\mu t)$
μ = repair constant
k= repopulation constant

O.I.R.M. S.ANNA

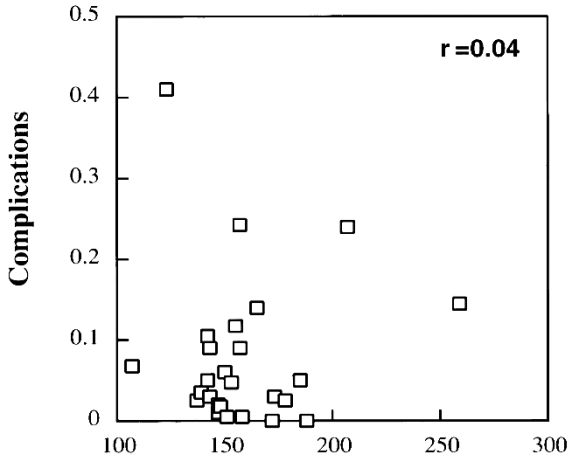
L iological Q uadratic E quivalent D ose 2

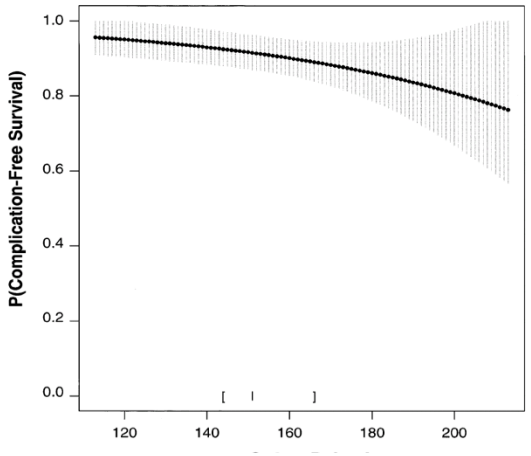
LQED 2 = BED/ (1 + **2** / α/β)

- α/β 10 Gy for GTV and CTV
- α/β 3 for OAR
- $T_{1/2}$ 1.5 hours for GTV, CTV and OAR

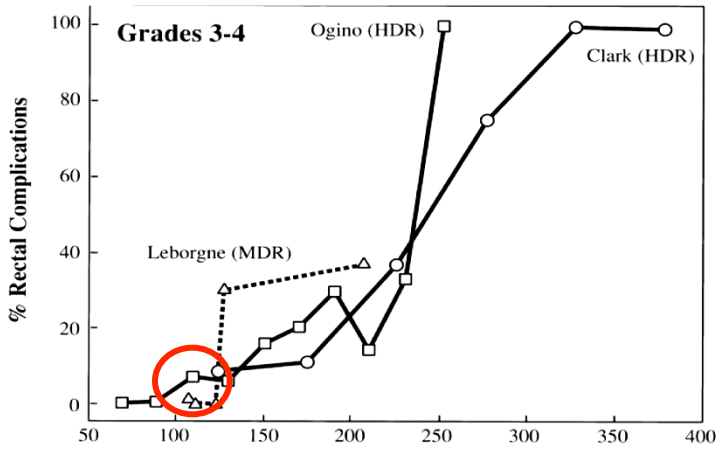
N. fraz. HDR	Gy/fraz. HDR	LQED (α/β 10)	LQED (α/β 3)
6	4.5	32.6	40.5
5	5	31.2	40
4	6	32	43.2
3	7	29.7	42

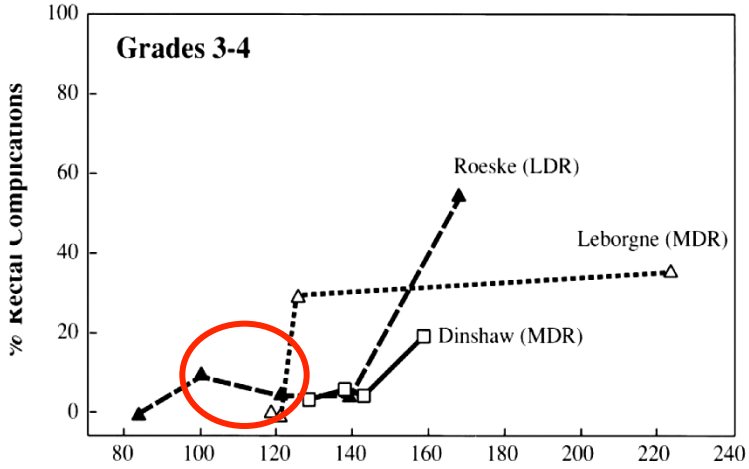
Relationship between BED (Gy3) and complications





Point A





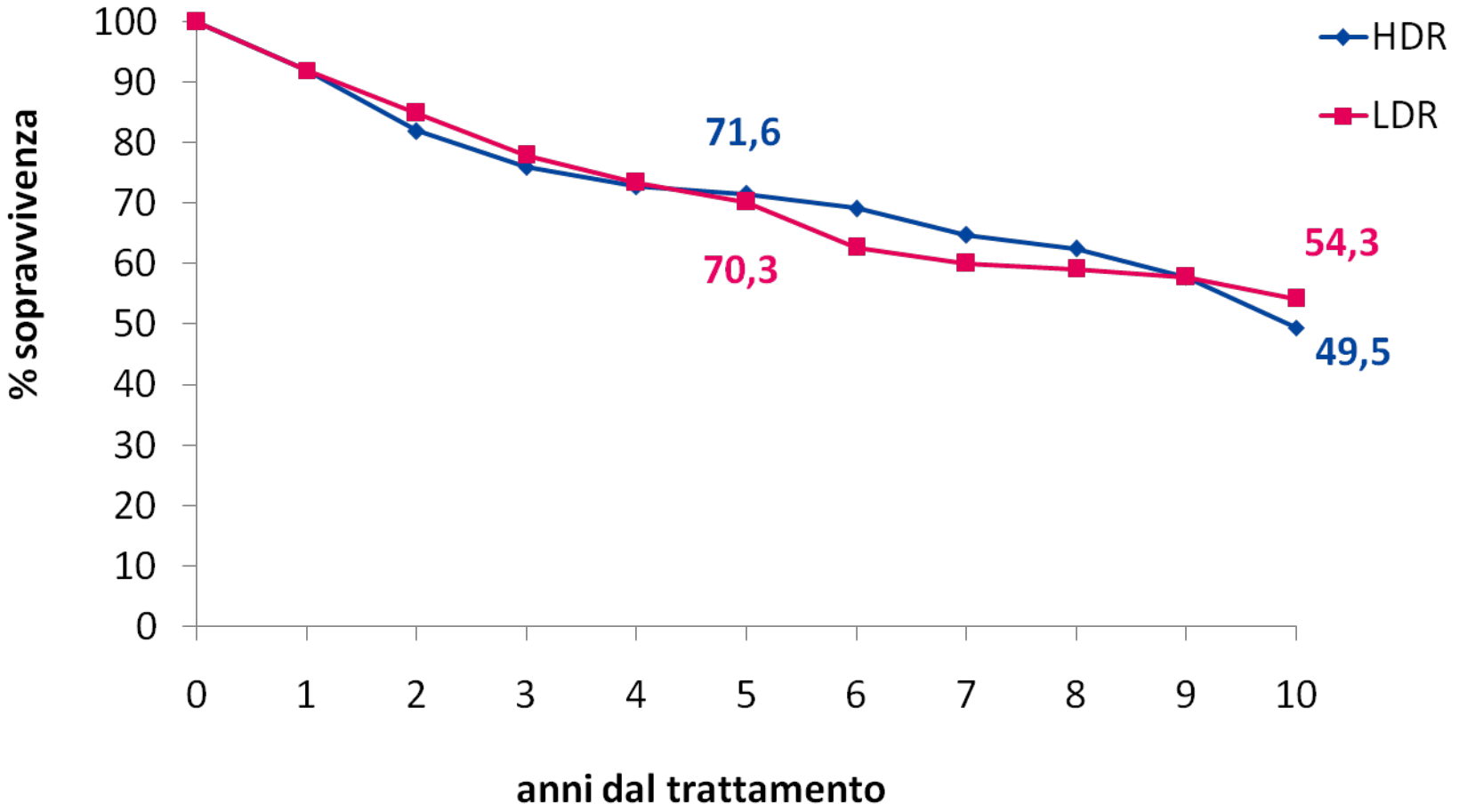
ICRU Point R

(Petereit D., IJROBP, 1999)

Carcinoma della cervice stadi I-III

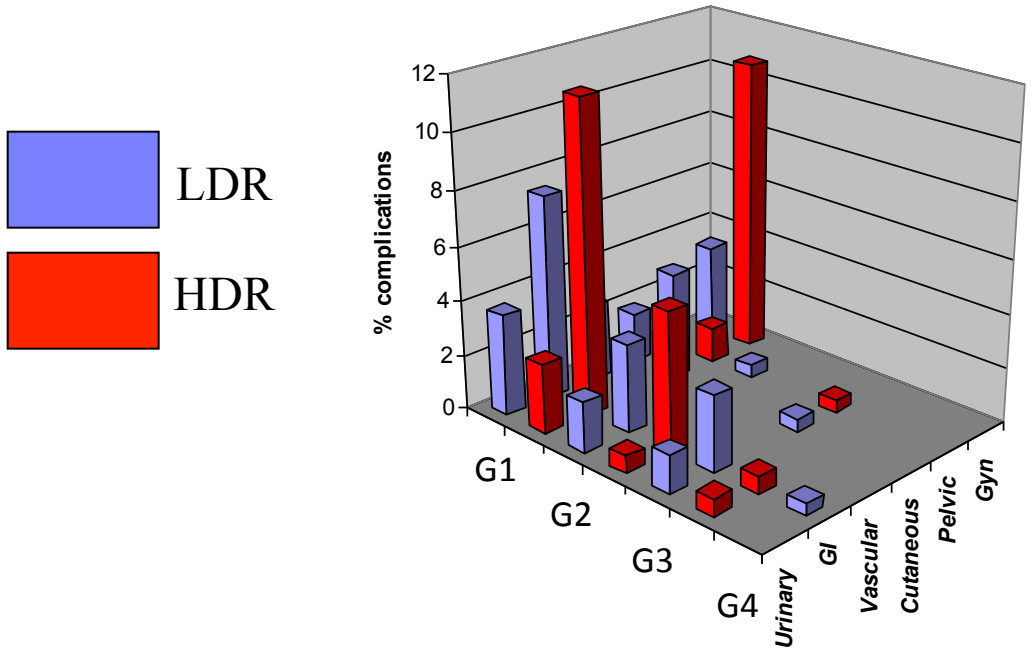
confronto fra HDR e LDR

survey condotto in 13 istituzioni giapponesi (circa 550 pts)



(da Okawa et al., 1994)

Complications of treatment of carcinoma of the cervix
LDR versus HDR



Actuarial Complications (Grade ≥ 3) by Organ Site at 5 Years

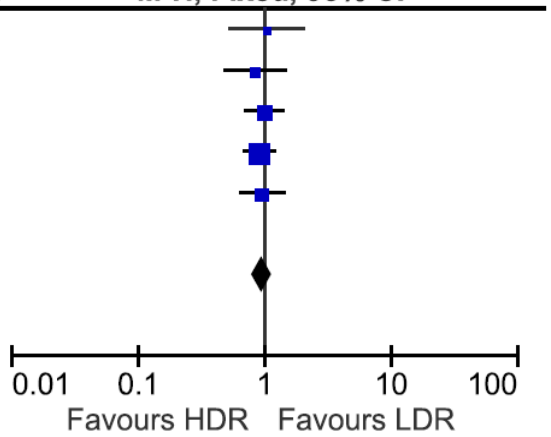
Rate	Patient no.	Overall (%)	Rectum (%)	Small bowel (%)	Bladder (%)
HDR	61	10	3.5	2.4	4.0
LDR	71	13	8.7	1.6	7.5

Overall mortality in cervix cancer

Study or Subgroup	Weight	Odds Ratio M-H, Fixed, 95% CI
Hareyama 2002	6.7%	1.04 [0.52, 2.08]
Lertsanguansinchai 2004	10.8%	0.84 [0.47, 1.49]
Pattel 1993	24.9%	1.00 [0.69, 1.43]
Shrivastava 2006	38.0%	0.91 [0.67, 1.23]
Teshima 1993	19.7%	0.95 [0.63, 1.44]
Total (95% CI)	**100.0%**	**0.94 [0.78, 1.13]**
Total events		

Heterogeneity: Chi² = 0.39, df = 4 (P = 0.98); I² = 0%

Test for overall effect: Z = 0.64 (P = 0.52)



Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Low dose rate brachytherapy	Corresponding risk High dose rate brachytherapy	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Overall mortality for all clinical stage cervix cancer (follow-up: median 5 years)	Medium risk population		OR 0.96 (0.85 to 1.08)	2065 (5)	⊖⊖⊖O moderate[1]
	332 per 1000	323 per 1000 (297 to 349)			
Overall mortality for clinical stage I cervix cancer (follow-up: median 5 years)	Medium risk population		OR 0.68 (0.36 to 1.29)	134 (2)	⊖⊖OO low[2]
	286 per 1000	214 per 1000 (126 to 341)			
Overall mortality for clinical stage II cervix cancer (follow-up: mean 5 years)	Medium risk population		OR 0.84 (0.56 to 1.24)	500 (4)	⊖⊖⊖O moderate[1]
	263 per 1000	231 per 1000 (167 to 307)			
Overall mortality for clinical stage III cervix cancer	Medium risk population		OR 1.22 (0.95 to 1.56)	1079 (5)	⊖⊖⊖O moderate[1]
	430 per 1000	479 per 1000 (417 to 541)			

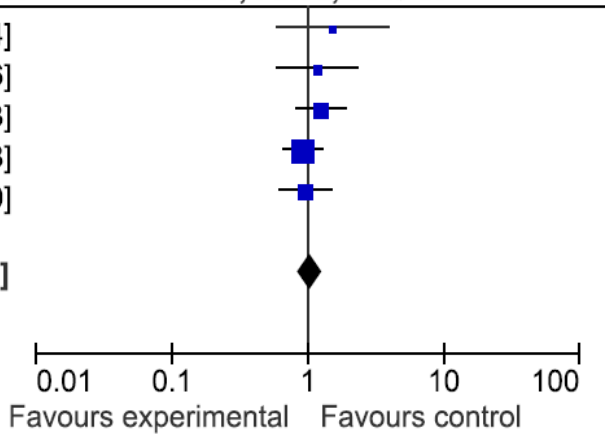
Local recurrence in cervix cancer

Study or Subgroup	Weight	Odds Ratio M-H, Fixed, 95% CI
Hareyama 2002	4.0%	1.52 [0.58, 3.94]
Lertsanguansinchai 2004	8.7%	1.18 [0.59, 2.36]
Pattel 1993	21.7%	1.25 [0.81, 1.93]
Shrivastava 2006	42.2%	0.92 [0.65, 1.28]
Teshima 1993	23.3%	0.96 [0.61, 1.50]
Total (95% CI)	**100.0%**	**1.05 [0.85, 1.29]**

Total events

Heterogeneity: Chi² = 2.10, df = 4 (P = 0.72); I² = 0%

Test for overall effect: Z = 0.41 (P = 0.68)



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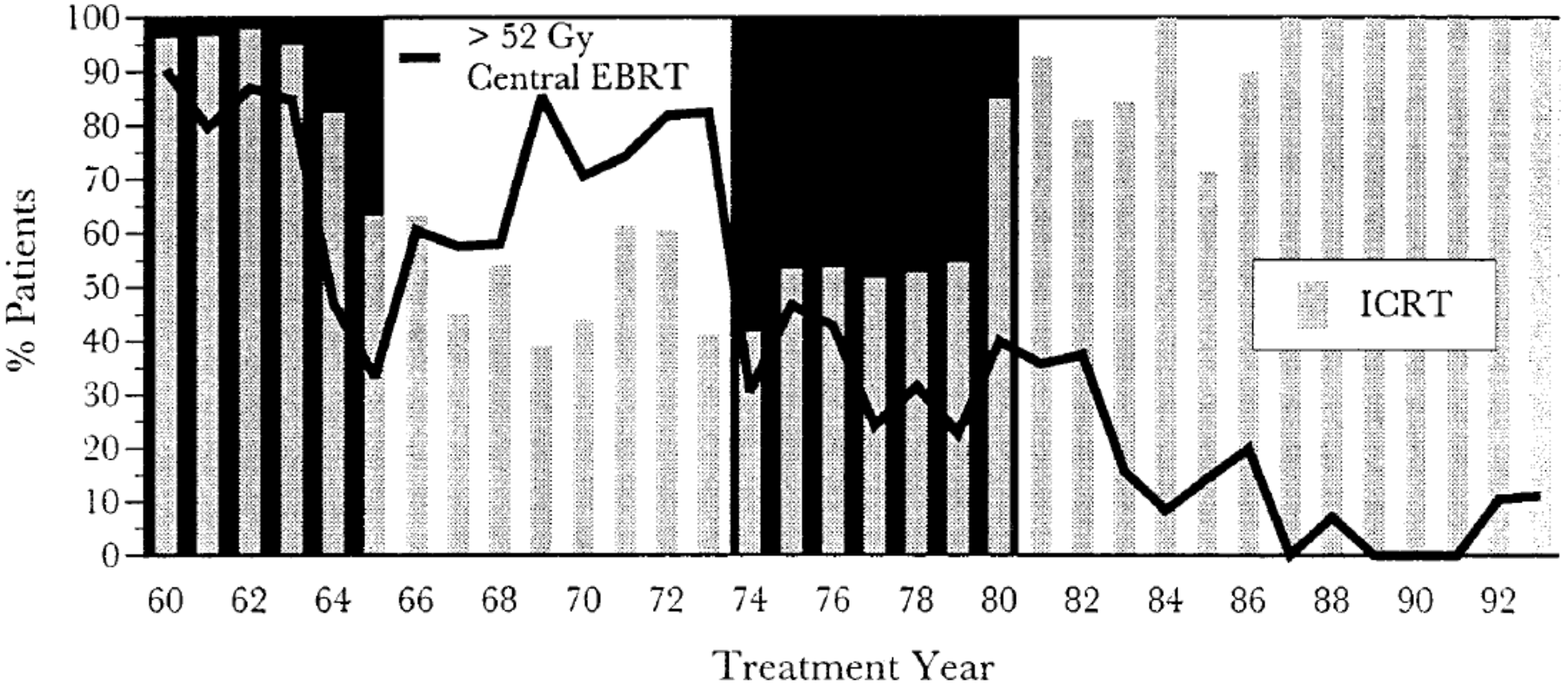
Overall mortality for all clinical stage cervix cancer (follow-up: median 5 years)	Medium risk population		OR 0.96 (0.85 to 1.08)	2065 (5)	⊖⊖⊖O moderate[1]
	332 per 1000	323 per 1000 (297 to 349)			
Overall mortality for clinical stage I cervix cancer (follow-up: median 5 years)	Medium risk population		OR 0.68 (0.36 to 1.29)	134 (2)	⊖⊖OO low[2]
	286 per 1000	214 per 1000 (126 to 341)			
Overall mortality for clinical stage II cervix cancer (follow-up: mean 5 years)	Medium risk population		OR 0.84 (0.56 to 1.24)	500 (4)	⊖⊖⊖O moderate[1]
	263 per 1000	231 per 1000 (167 to 307)			
Overall mortality for clinical stage III cervix cancer	Medium risk population		OR 1.22 (0.95 to 1.56)	1079 (5)	⊖⊖⊖O moderate[1]
	430 per 1000	479 per 1000 (417 to 541)			

Dose and fractionation in Gynecological Brachytherapy

- Dose specification and prescription
- 2D versus 3D
- Dose rate and fractionation (LDR and HDR)
- **EBRT and BRT**
- Treatment duration

Changes in the approach to treatment of patients with Stage IIIB cervical cancer at M. D. Anderson Cancer Center between 1960 and 1993



FIGO IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy

Table 4. Correlation of treatment parameters and DSS in 907 patients who completed treatment with curative intent

Treatment	No. patients	Patients receiving ICRT (%)	DSS at 5 years	*p*
Received ICRT				< 0.0001
Yes	641		45	
No	266		24	
Central pelvic EBRT dose*				< 0.0001
34–47 Gy	166	162 (97)†	53	
48–52 Gy	182	166 (92)†	53	
53–57 Gy	49	47 (94)†	29	
58–62 Gy	234	204 (87)	34	
> 62 Gy	207	38 (18)	27	
Investigational treatments**				
Hyperbaric oxygen	64	35 (55)	36	
Concomitant IA 5-FU	22	4 (18)	41	
Neutrons††	66	21 (32)	23	
Neoadjuvant IA CT††	38	36 (95)	46	

DSS = disease-specific survival rate at 5 years; ICRT = intracavitary therapy; EBRT = external beam radiation therapy; IA 5-FU = intraarterial 5-flourouracil; IA CT = intraarterial chemotherapy.

* Sixty-nine patients treated with neutrons are excluded.

† Twenty-one patients who received < 58 Gy of EBRT and completed treatment with curative intent had no ICRT. Of these, 4 had adjuvant surgery, 4 underwent a boost to the cervix with transvaginal irradiation, and 14 were included in investigational protocols of concurrent intraarterial chemotherapy and EBRT.

** Only studies that included more than 20 patients are listed.

†† Two patients received both IA CT and neutron treatments.

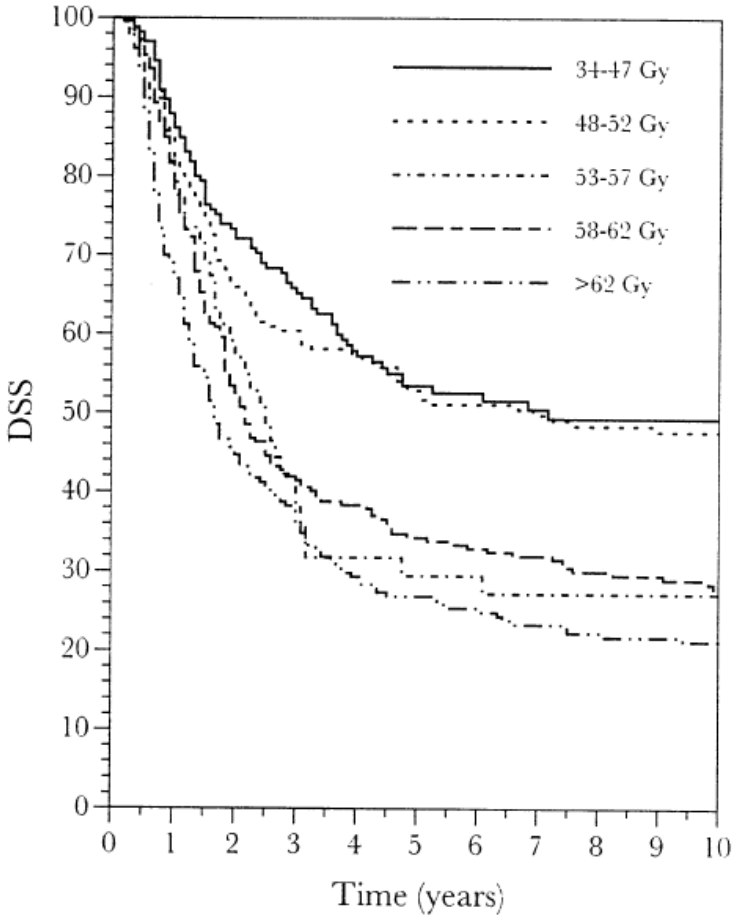


Fig. 2. The disease-specific survival (DSS) rate for patients who completed treatment that was given with curative intent according to the does of EBRT given to the central pelvis. Patients who were treated with neutrons are excluded.

Linee guida AIRO

RADIOTERAPIA ESCLUSIVA

- La radioterapia esclusiva **deve necessariamente prevedere un tempo di brachiradioterapia**. C'è evidenza in letteratura che la brachiterapia sia determinante nella prognosi.
- Nei rari casi in cui non sia possibile effettuare una brachiterapia per motivi anatomici (2-5%) è prevista una sovradose centrale con radioterapia transcutanea.

Linee guida AIRO

Dosi complessive (EBR + BRT LDR)

- **Stadio IB1 – IIA < 4 cm**
  Punto A: 70 - 75 Gy
  Punto B: 45 Gy
- **Stadio IB2 – IIA > 4 cm**
  Punto A: 80 - 85 Gy
  Punto B: 50 Gy
- **Stadio IIB**
  Punto A: 85 – 90 Gy
  Punto B: 60 Gy
- **Stadio III**
  Punto A: 85 – 95 Gy
  Punto B: 60 – 65 Gy
- **Stadio IV**
  Punto A: 85 – 95 Gy
  Punto B: 60 – 65 Gy

Le dosi maggiori sono previste per le neoplasie voluminose.
Per le neoplasie allo stadio IIIA è consigliabile una personalizzazione del piano di trattamento in funzione dell'estensione cervicale e vaginale della neoplasia.
E' ammesso il trattamento con sola brachiterapia endocavitaria in casi particolari (neoplasia < 2 cm, paziente anziana, con basso PS o patologie concomitanti).

Suggested doses of EBRT and LDR intracavitary brachytherapy

AMERICAN BRACHYTHERAPY SOCIETY RECOMMENDATIONS

Stage	T. extent	Whole pelvis	Pelvic wall	Parametrial boost	Dose to point A	Total dose to point A
IA 1		0	0	0	50-60	50-60
IA 2		0	0	0	60-70	60-70
Select IB 1	Superficial ulceration less than 1 cm in diameter or involving fewer than two quadrants	0	0	0	60-70	60-70
IB 2, IIA		45	45	0	40	85
IIB		45	45	9-15	40	85
III		45-50	45-50	9-15	40	85-90
IIB, IIIB, IV	Poor pelvic anatomy, patient not readily treated with intracavitary insertions (barrel-shaped cervix not regressing, inability to locate external os)	50	50	9-15	40	90
	Or interstitial	39.6-45	39.6-45	0-15	35-40	75-85

Suggested doses of EBRT and HDR brachytherapy to be used in treating early cervical cancer

AMERICAN BRACHYTHERAPY SOCIETY RECOMMENDATIONS

EBRT (Gy) @ 1.8 Gy/fraction	No. of HDR fractions	HDR dose/ fraction
20	6	7.5
20	7	6.5
20	8	6.0
45	5	6.0
45	6	5.3

Suggested doses of EBRT and HDR brachytherapy to be used in treating advanced cervical cancer

AMERICAN BRACHYTHERAPY SOCIETY RECOMMENDATIONS

EBRT (Gy) @ 1.8 Gy/fraction	No. of HDR fractions	HDR dose/ fraction
45	5	6.5
45	6	5.8
50.4	4	7.0
50.4	5	6.0
50.4	6	5.3

Dose and fractionation in Gynecological Brachytherapy

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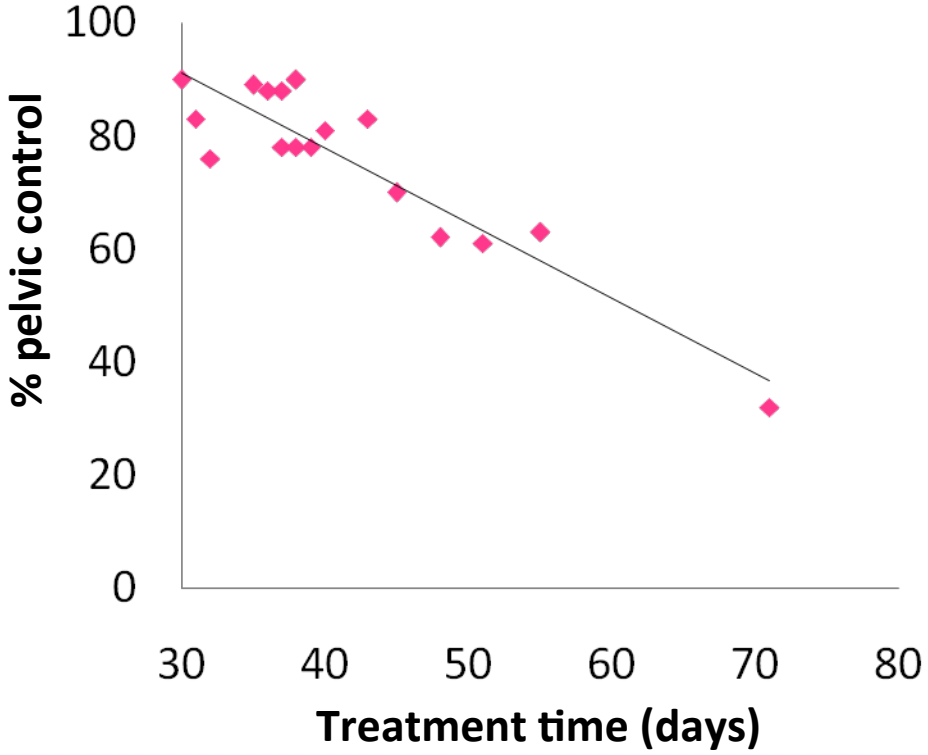
Treatment duration



- Survival and Local Control may decrease 0.6-1.2% per day beyond the optimum duration
- Total duration must be carefully considered when planning the integration and timing of implants with external beam
- Treatment breaks between external beam and implants must be carefully considered

Fyles, Radiother Oncol, 1992

Patterns of care studies

The patterns of care studies recommend that:

- **the total paracervical tumor dose (sum of external-beam radiotherapy and brachytherapy) be between 85 and 90 Gy (low-dose-rate [LDR] equivalent),**
- **that total pelvic sidewall dose be between 55 and 65 Gy**
- **that overall treatment time not exceed 8 weeks. Prolonged treatment time, beyond 50 to 56 days, is associated with a 1% loss of local control for every additional day of treatment.**
- **Brachytherapy is an integral part of radiotherapy for cervical cancer and is critical for obtaining cure. It allows for high cervical and para-cervical doses that would be impossible to give with external beam alone.**