Gynecologic Cancer InterGroup
Cervix Cancer Research Network

Basics of Cervix Brachytherapy

William Small, Jr., MD
Professor and Chairman
Loyola University Chicago

Cervix Cancer Education Symposium, January 2017, Mexico

OBJECTIVES

1. Review the history of Brachytherapy in Cervical Cancer.
2. Review the need for Brachytherapy in modern radiation.
3. Discuss HDR Co-60 vs. Ir-192
4. Review Modern Image Guided Brachytherapy

Marie and Pierre Curie
Antoine Henri Becquerel

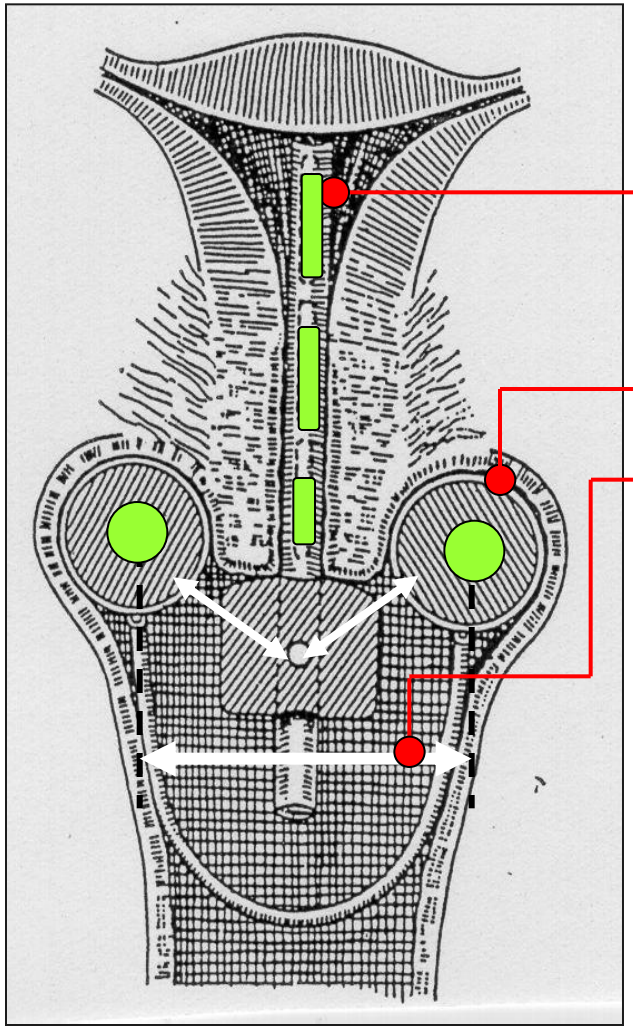
The discovery of radioactivity, 1896 - 1898

Applicators for intracavitary treatments

Manchester / Fletcher: Tandem & Ovoids
Stockholm: Tandem & Ring
Institute Gustave Roussy: Mould technique

Historical Paris Technique

1910-1920: Curie Institute, Paris, France



GEC ESTRO Handbook of Brachytherapy

Applicator:

- Rubber tandem
- Cork colpostats (paraffin coated)

→ not connected → no fixed geometry

- Distance – colpostats: not fixed

^{226}Ra preloading

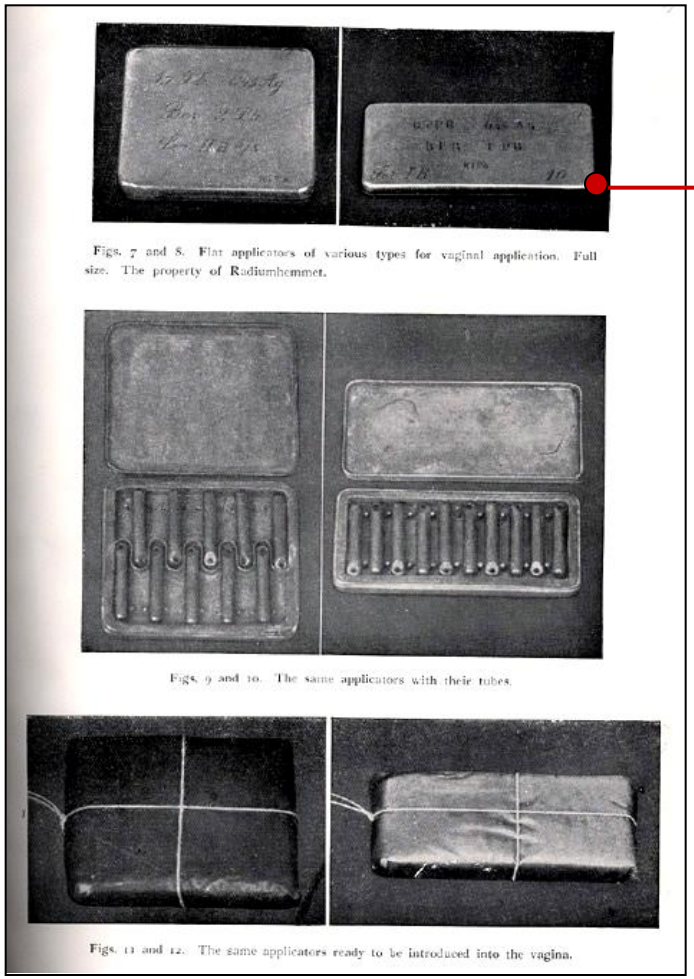
- X mg of ^{226}Ra for Y hours

Typical application

- ≈ 5 days (*120 h*)
- 7000-8000 mgh

Classical Stockholm method

1913-1914: Radiumhemmet, Stockholm, Sweden

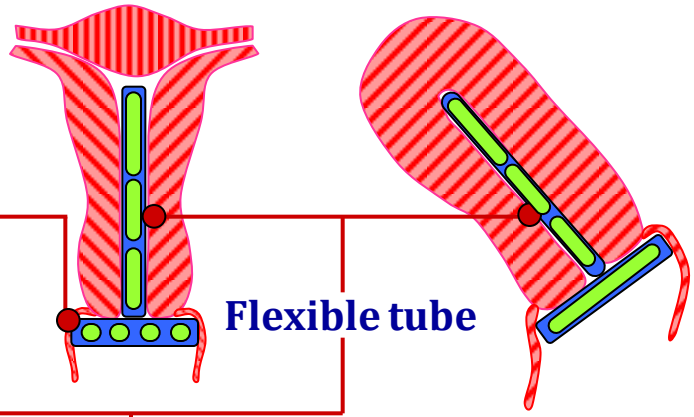


Figs. 7 and 8. Flat applicators of various types for vaginal application. Full size. The property of Radiumhemmet.

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

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

Applicator:



- Flat box (plate)
- Flexible tube
- not connected → No fixed geometry

^{226}Ra preloading

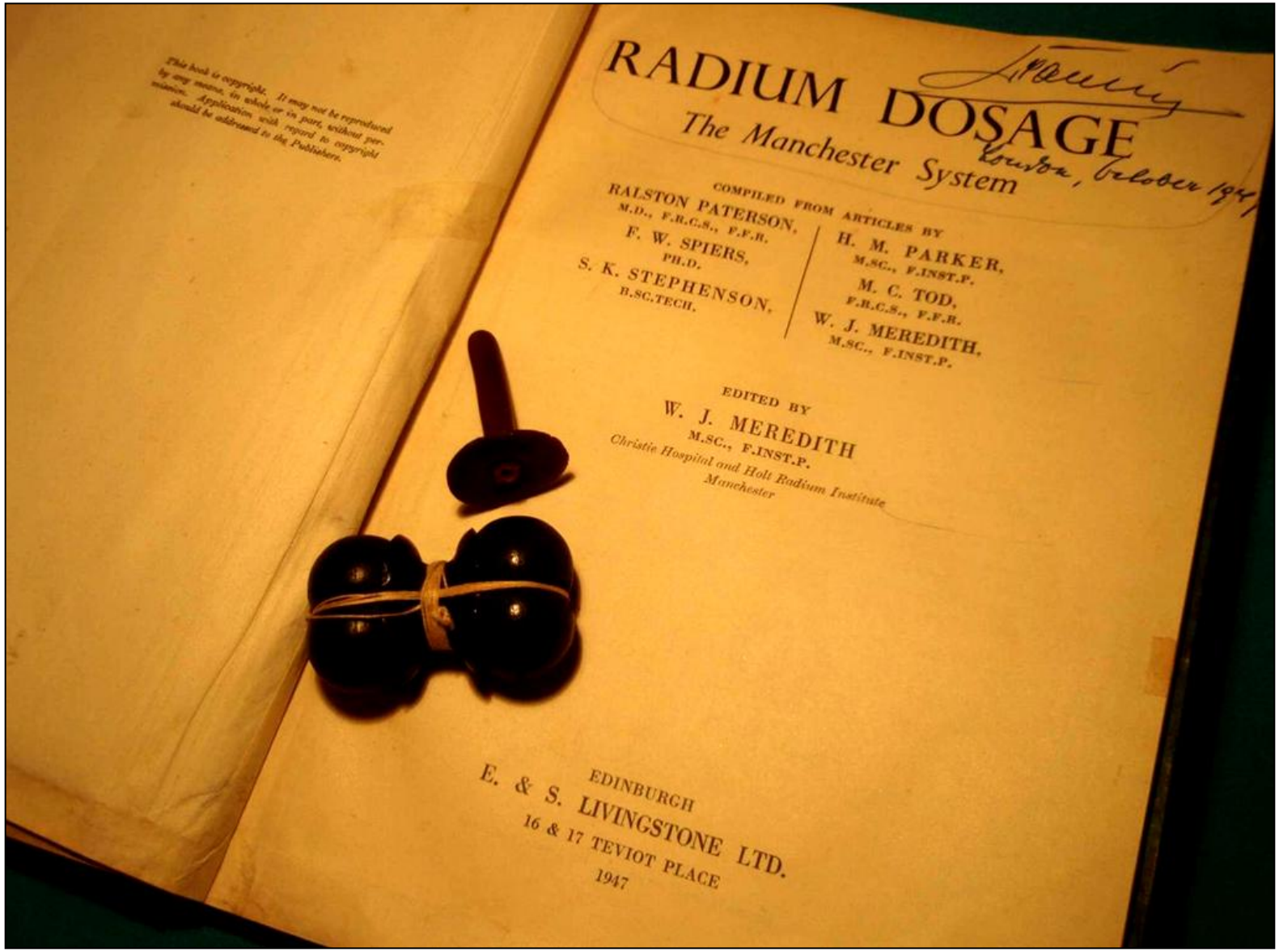
- Intrauterine tube: 30-90 mg
- Vaginal plate: 60-80 mg
- Unequal loading of uterine / vaginal ^{226}Ra

Typical treatment

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

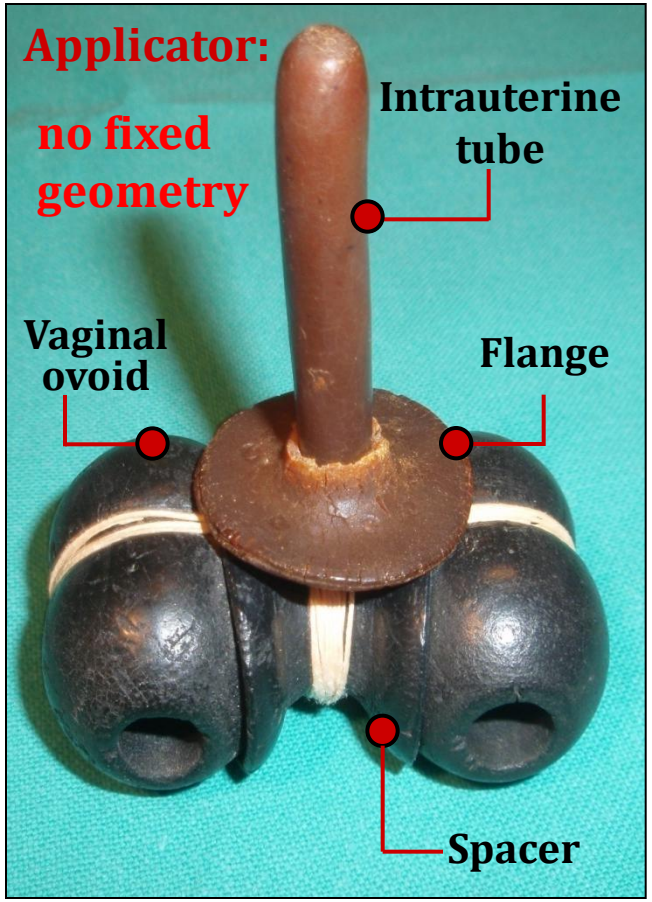
Historical Manchester System

1938: Holt Radium Institute, Manchester, England



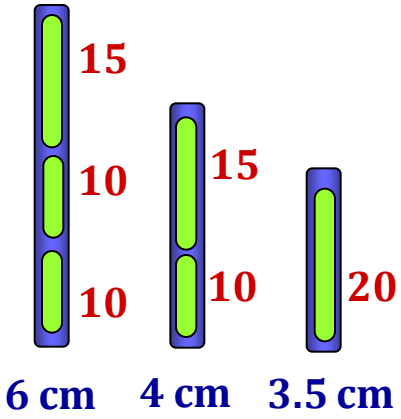
Historical Manchester System

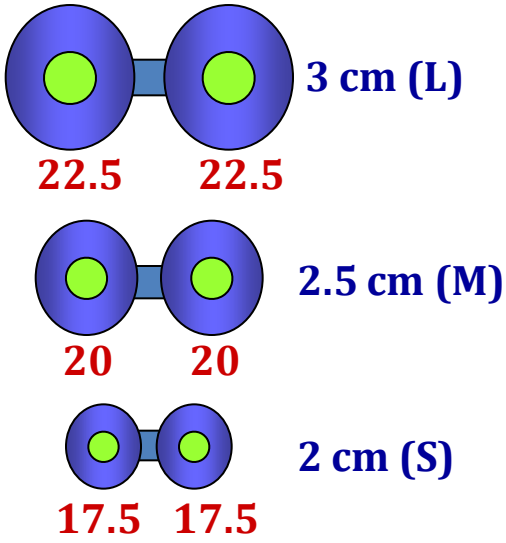
Related to historical Paris technique

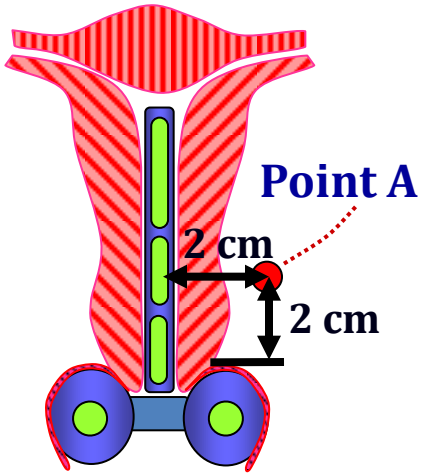


TYPICAL TREATMENT:
140 hours for 7500 R at point A
(dose rate 53 R/h)

^{226}Ra preloading (mg):







Given tumour volume

↓

A set of rules

- Geometry
- mg of ^{226}Ra
- Duration

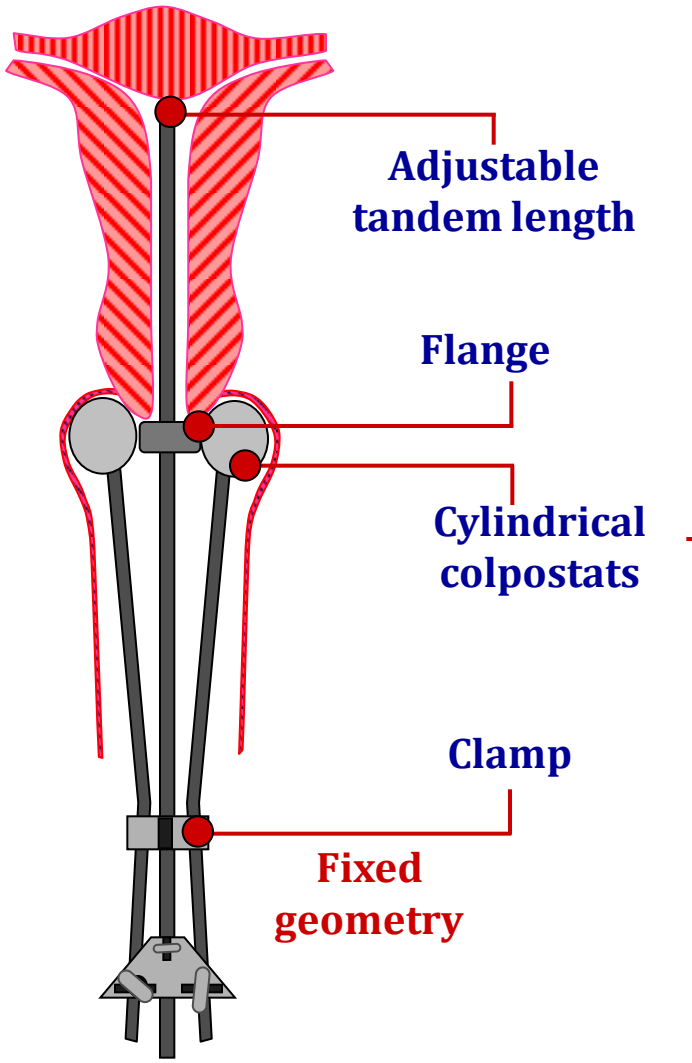
↓

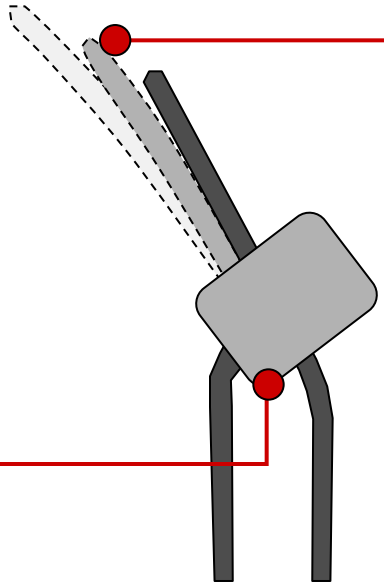
Certain point A dose

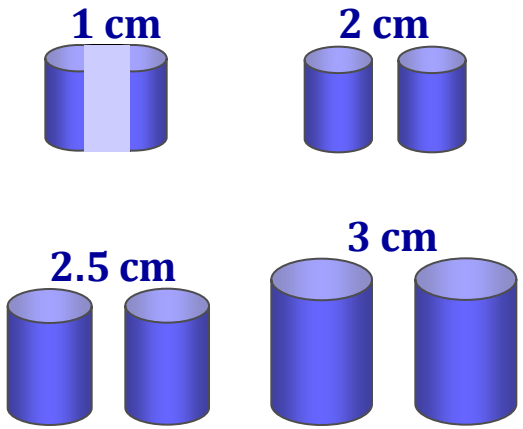
Meredith WJ, ed.. Radium dosage. The Manchester system. Edinburgh;1947.

Fletcher–Suit–Delclos–Horiot Technique

1950's: Fletcher



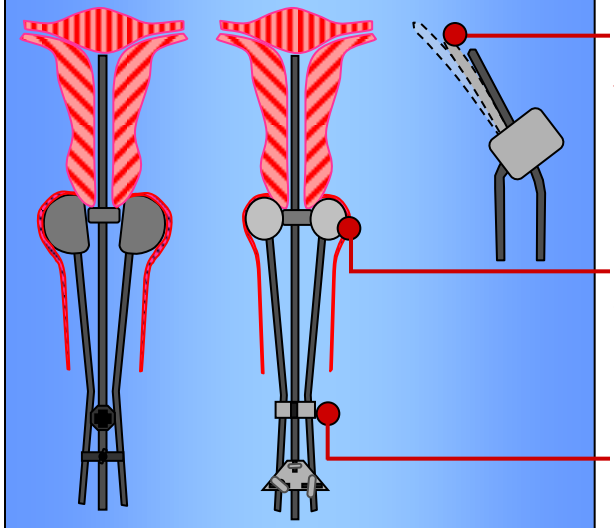


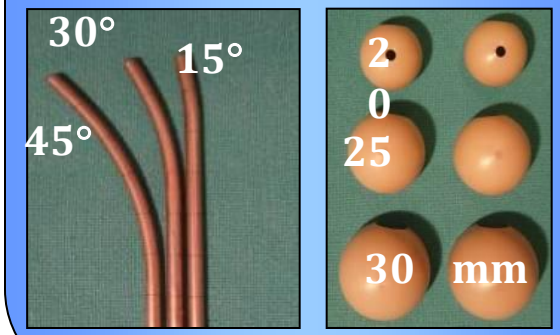


Modern Intracavitary Techniques

Applicators: mimicking historical geometries

Manchester / Fletcher style

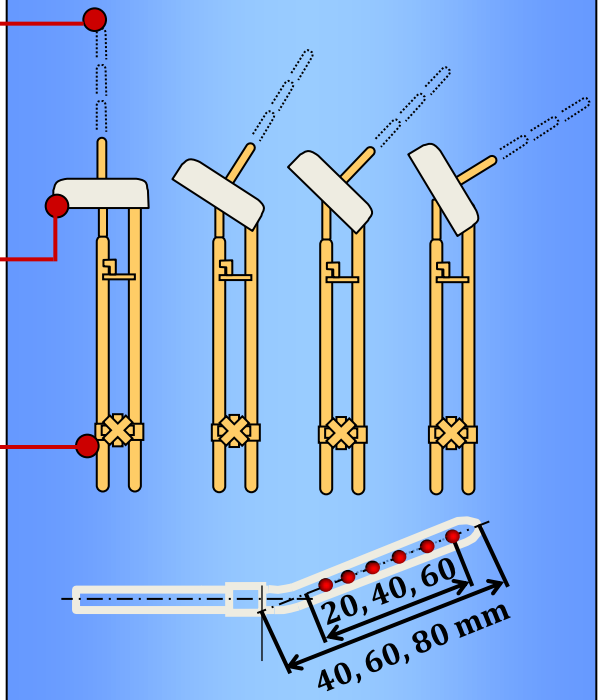


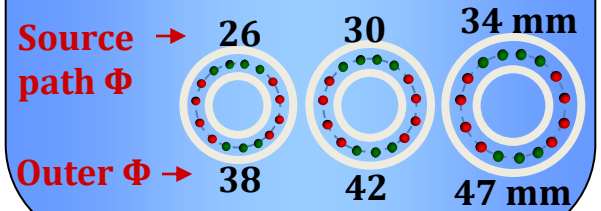


Common features:

- Uterine Tandem: various lengths, angles or curvatures
- Ovoids, cylinders, rings various outer & source path diameters
- Clamp

Stockholm style





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An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Is There a Need for Brachytherapy with Modern External Beam Radiation?

Cervix Cancer Education Symposium, January 2017, Mexico

Methods

- Population-based, retrospective cohort study of 18 SEER registries
- **Inclusion Criteria:**
  - Stage IB – IVA cervical cancer treated between 1988 – 2009 with RT
- **Exclusion Criteria:**
  - Rare histologies
  - Treated with surgery
  - History of other malignancy

Han et al, Int J Rad Oncol Bio Phys, 2013

Patient & Tumor Characteristics by Brachytherapy Use

Characteristics (n = 7359)	No Brachytherapy (n = 2690)	Brachytherapy (n = 4669)	*P*
Age, mean (SD)	55 (16)	54 (14)	< .001
Married, %	34	40	< .001
Race—White, %	69	71	< .001
Hispanic, %	75	79	< .001
Urban, %	89	85	< .001
Grade 3, %	37	36	.90
Histology—SCC, %	84	85	.13
Stage IB/II, %	53	65	< .001
Registry			< .001

Brachytherapy utilization rate in 18 SEER registries

Independent Predictors of Brachytherapy Use

- Younger age
- Married (vs not)
- Earlier year of diagnosis
- Earlier stage
- Certain SEER regions

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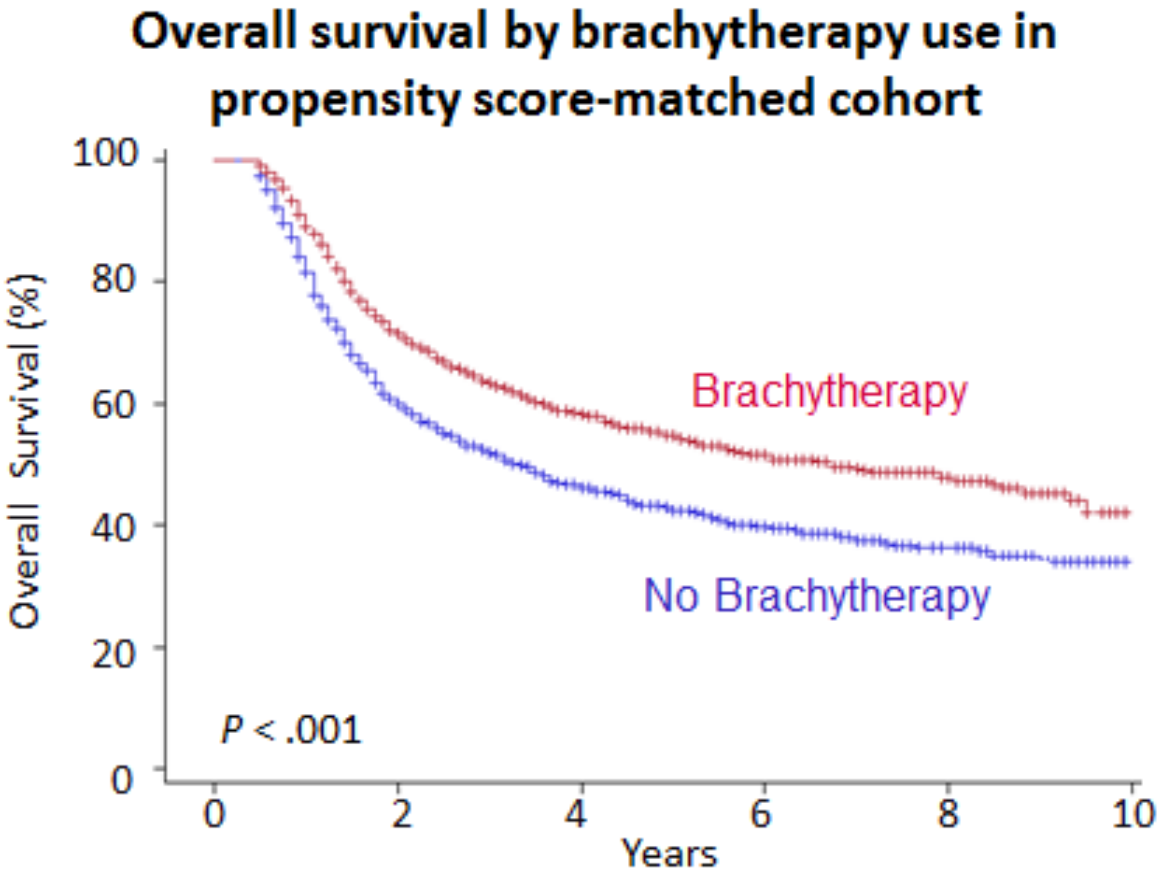

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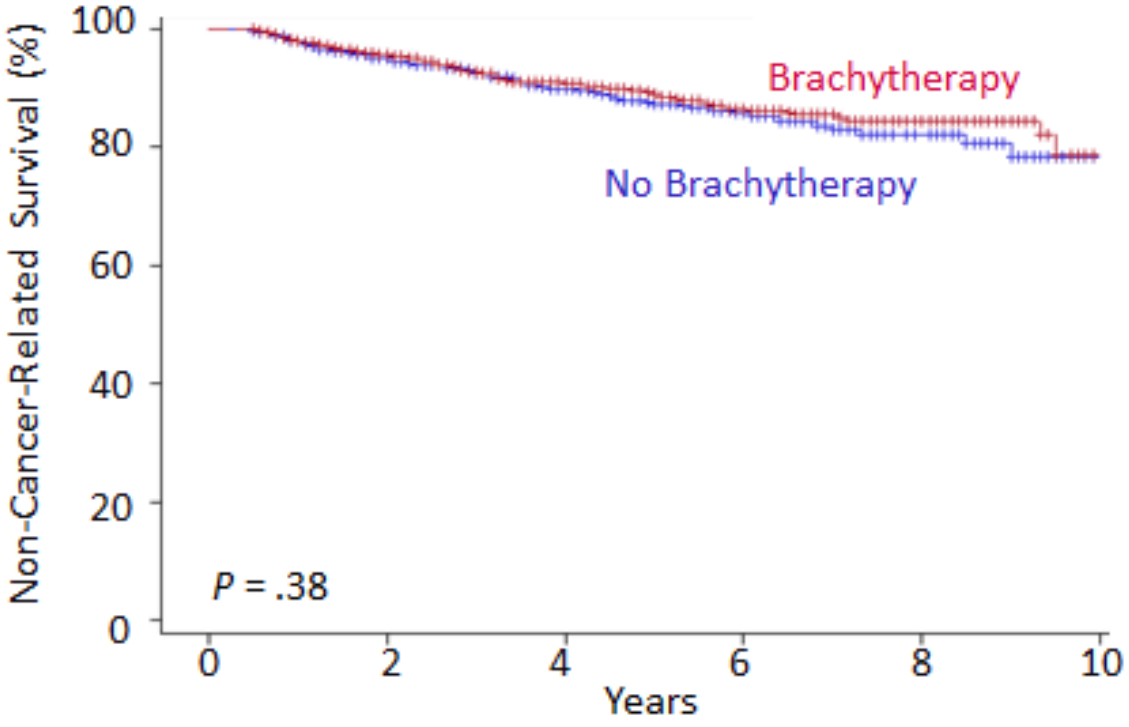
Non-cancer-related survival by brachytherapy use in propensity score-matched cohort



Multivariable Cox Regression

Characteristics	Cancer-Specific Survival		Overall Survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Brachytherapy				
No	1 (reference)		1 (reference)	
Yes	**0.64** (0.57-0.71)	<.001	**0.66** (0.60-0.74)	<.001
Stage				
IB2	1 (reference)		1 (reference)	
II	1.18 (0.93-1.49)	.17	1.16 (0.93-1.44)	.18
III	2.28 (1.80-2.88)	<.001	2.14 (1.72-2.67)	<.001
IVA	3.50 (2.49-4.92)	<.001	3.08 (2.24-4.22)	<.001
Histology				
SCC	1 (reference)		1 (reference)	
Adenocarcinoma	1.32 (1.10-1.60)	.004	1.28 (1.08-1.52)	.005
Other	1.26 (0.97-1.64)	.08	1.26 (0.98-1.60)	.07

Other significant factors: Age; Marital Status; Race; Ethnicity; Registry

Conclusions

- Recent decline in brachytherapy utilization in the U.S.
- Brachytherapy use is independently associated with significantly higher CSS and OS.
- Brachytherapy should be implemented in all feasible cases.

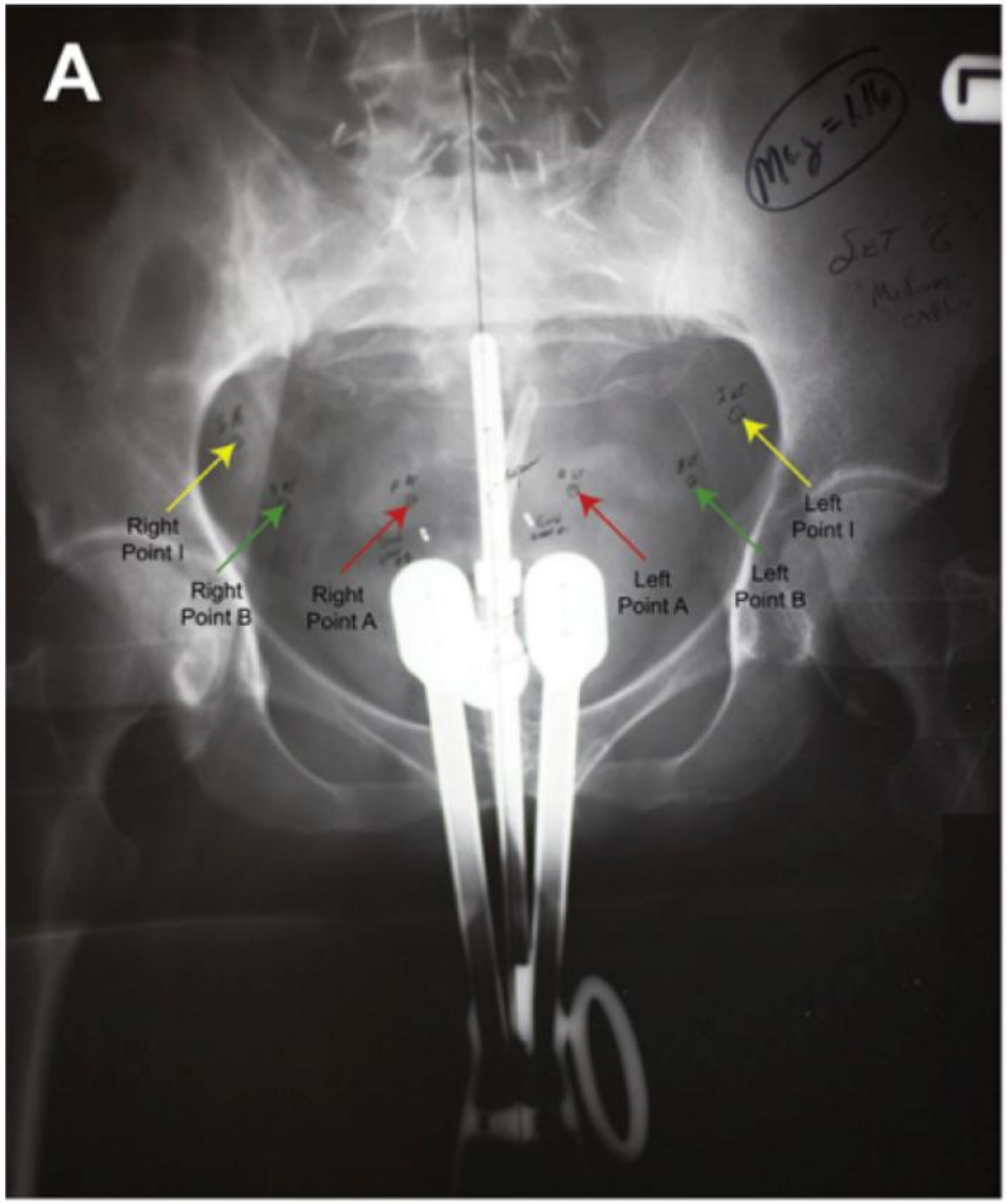
ORIGINAL ARTICLE

Low-Dose-Rate Brachytherapy Boosting Concurrent Chemoradiation as a Definitive Treatment Modality for Cervical Cancer

Long-term Clinical Results of Outcomes and Associated Toxicity

Tamer Refaat, MD, PhD, MSCI,† Eric D. Donnelly, MD,* Michelle Gentile, MD,* Caroline Novak, MD,* Ye Yuan, PhD,* Gehan A. Khedr, MD, PhD,† Irene Helenowksi, PhD,‡ John Lurain, MD,§ Julian Schink, MD,§ Alfred Rademaker, PhD,‡ Vythialinga Sathiaseelan, PhD,* Jonathan B. Strauss, MD,* and William Small, Jr, MD, FACRO, FACR, FASTRO‖*

Refaat et al. Am J Clin Oncol. 2014 Jan 30. [Epub ahead of print]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Point I
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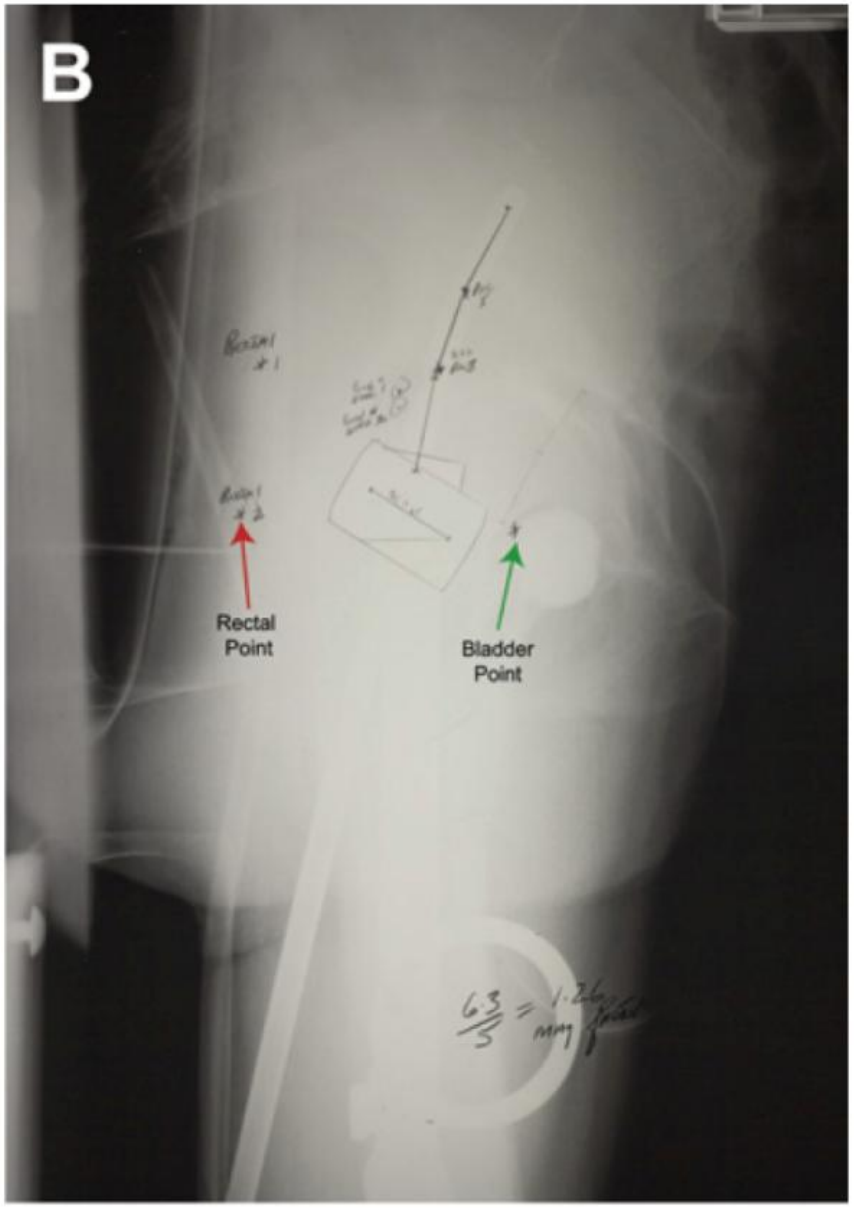
B
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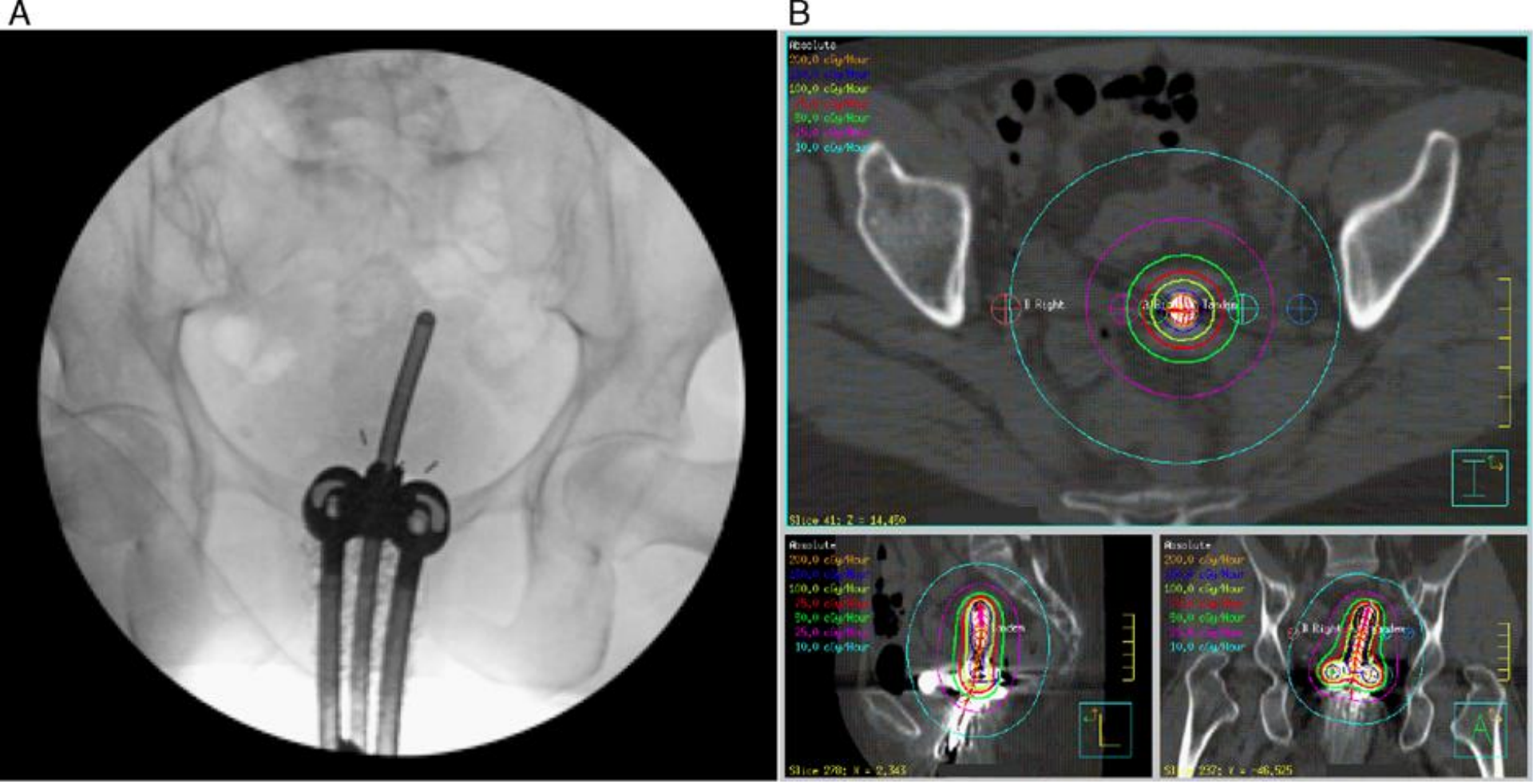
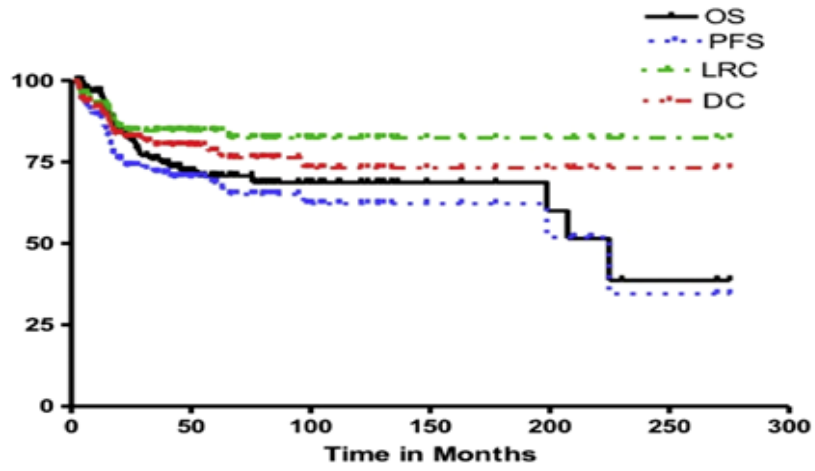
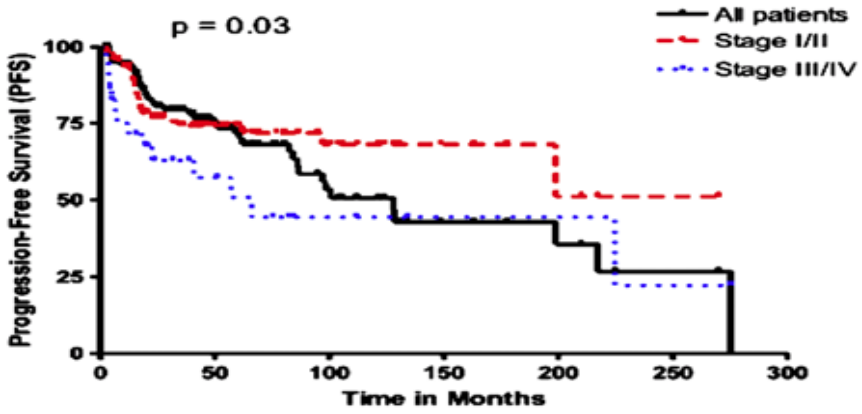
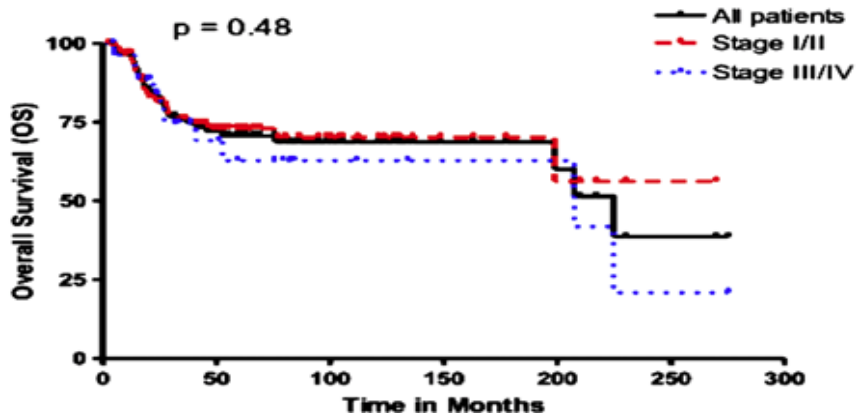


A) Intraoperative imaging at the time of first implant
B) Isodose distribution with 2002 cGy delivered continuously to point A over 43.83 hours using Cs-137 for the first implant with a total activity of 124.38 mCi.

Refaat et al. Am J Clin Oncol. 2014 Jan 30. [Epub ahead of print]







- ✓ 129 eligible cervical cancer patients
- ✓ The median age was 46 years
- ✓ stages I, II, III, IV (29.5%, 48.1%, 17.8% and 4.6% respectively).
- ✓ The median follow up was 37 months (mean 58 ± 59, range 3 – 275).
- ✓ The 3-years OS, PFS, LRC, and DC were 75.9%, 71.6%, 84.7%, and 80.2%, respectively.
- ✓ The 5-years OS, PFS, LRC, and DC were 70.7%, 68.7%, 84.7%, and 78.3%, respectively.
- ✓ The 10-years OS, PFS, LRC, and DC were 68.7%, 62.3%, 82.5%, and 73.2%, respectively.

Refaat et al. Am J Clin Oncol. 2014 Jan 30. [Epub ahead of print]

TABLE 4. Adverse Events

Adverse Events	N (%) None	Acute CTCAE Grades 3-4	Chronic CTCAE Grades 3-4
Skin	124 (96.1)	5 (3.9)	0 (0.0)
GI toxicity	97 (75.2)	5 (3.9)	27 (20.9)
GU toxicity	113 (87.6)	0 (0.0)	16 (12.4)
Others	126 (97.7)	3 (2.3)	0 (0.0)

CTCAE indicates Common Terminology Criteria for Adverse Events; GI, gastrointestinal; GU, genitourinary.

Refaat et al. Am J Clin Oncol. 2014 Jan 30. [Epub ahead of print]

Conclusion

- Standard LDR Brachytherapy cures significant percentage of patients – although there is room for improvement.
- There is not insignificant long term toxicities.

HDR - Sources
CO60 vs IR192

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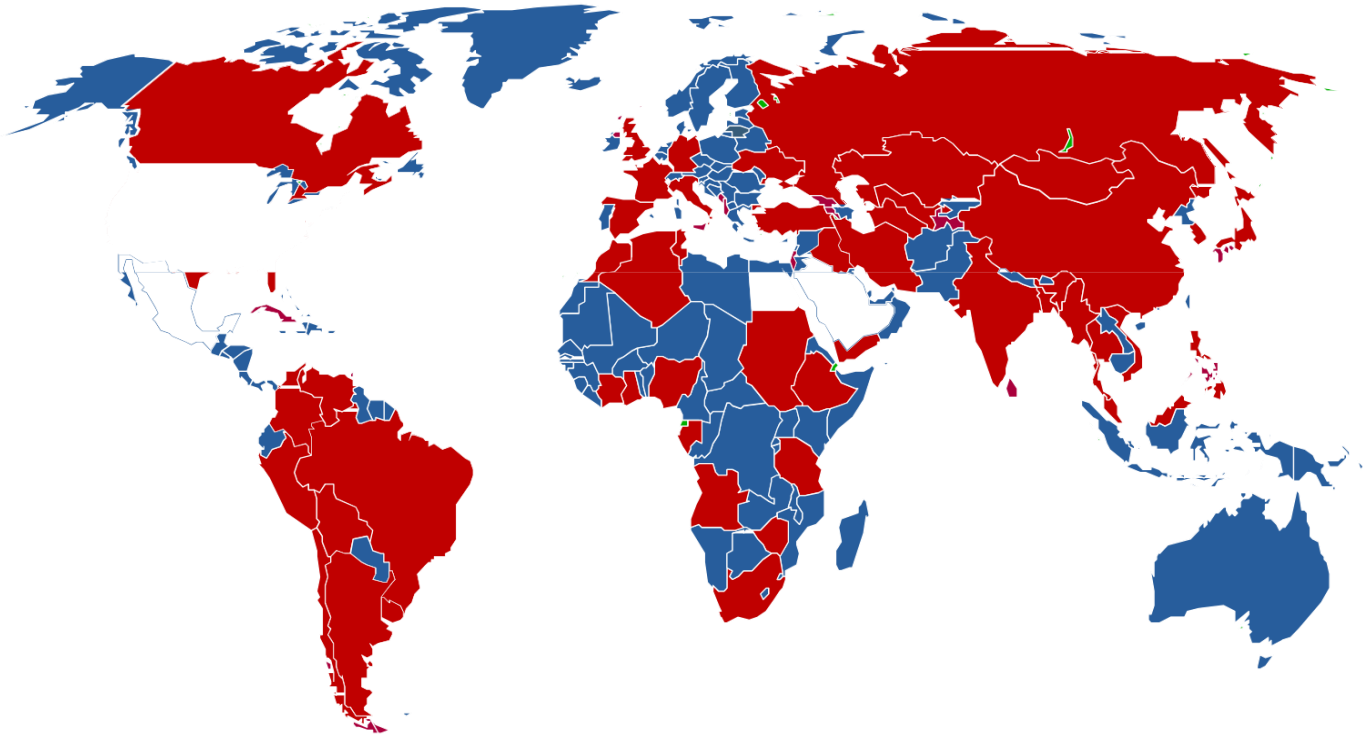
More than 300 installed Systems in more than 50 Countries
Most using Co60 sources



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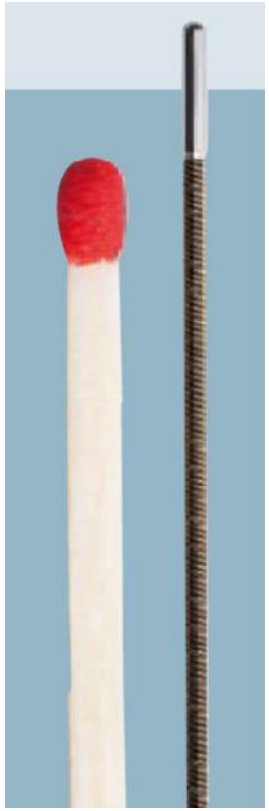

Important parameter for a HDR source

- **Doserate : must be in the HDR-Doserate range**
  - •Biological effects
  - •Treatment time
- **Dimension : as small as possible**
  - • For interstitial and intraop treatment
  - • small applicators
- **Dose - distribution :**
  - • strong dose gradient
  - • high dose to target volume but low dose to OAR

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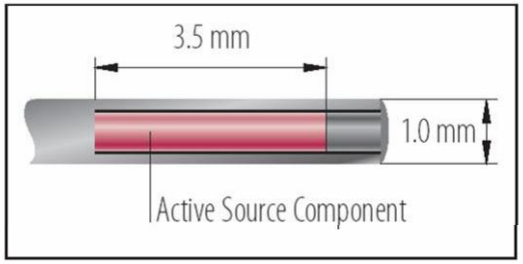
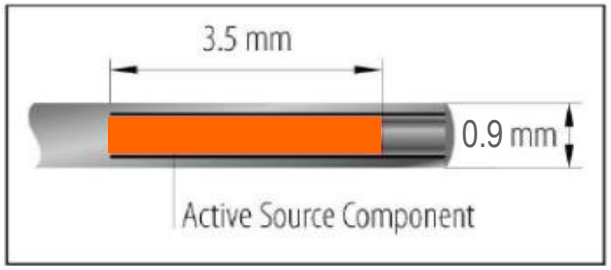


Miniaturized Co-60 Source

Co-60 Source (Co0.A86)

- 100.000 source transfers
- use for 5 years



Ir-192 Source

Ir-192 Source (Ir2.A85-2)

- 25.000 source transfers
- use for 3 ,4 (5) month

Co-60 Sources are not large anymore

Co-60 source is suitable for all BT applications

Source Specifications

	Cobalt-60	Iridium-192
ISO Classification 2919-1998	C 65444	C 63333
Half-life	5,27 years	73,8 days
Physical-Chemical form	solid, metal	solid, metal
Source activity	74 GBq ± 10%	370 GBq + 30%; -10%
Outer dimensions of the source: Diameter Total length of the wire:	 1 mm 2180 mm	 0,9 mm 2180 mm
Dimensions of active part Diameter: Length:	0,5 mm 3,5 mm	0,6 mm 3,5 mm
Working life	max 100.000 source transfers or 5 years	max 25.000 source transfers or 4 months

Eckert & Ziegler

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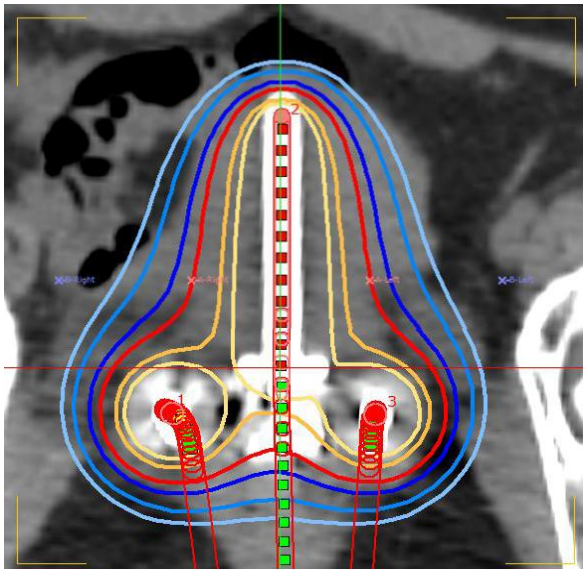
Physical Data

The air kerma-rate-constant is almost three times higher for Co-60 than for Ir-192

Nuclide	$\bar{E}$ (MeV)	$T_{1/2}$	(Ci/g)	Γ (μGy m² GBq⁻¹ h⁻¹)	$d_{1/10}$ 1) (lead)	$d_{1/10}$ (concrete)
	mean energy	half-life	specific activity	kerma-rate constant	tenth value layer	tenth value layer
Co-60	**1.253**	**5,27a**	330	**309**	4,8cm	32cm
Ir-192	0.38	73,8d	450	108	1,2cm	23cm

Co-60 vs. Ir-192: factor 2.86

Sample treatment time Ir-192 vs Co-60



Cervix cancer

- Fletcher Applicator
- Standard loading
- 5 Gy to Manchester A point

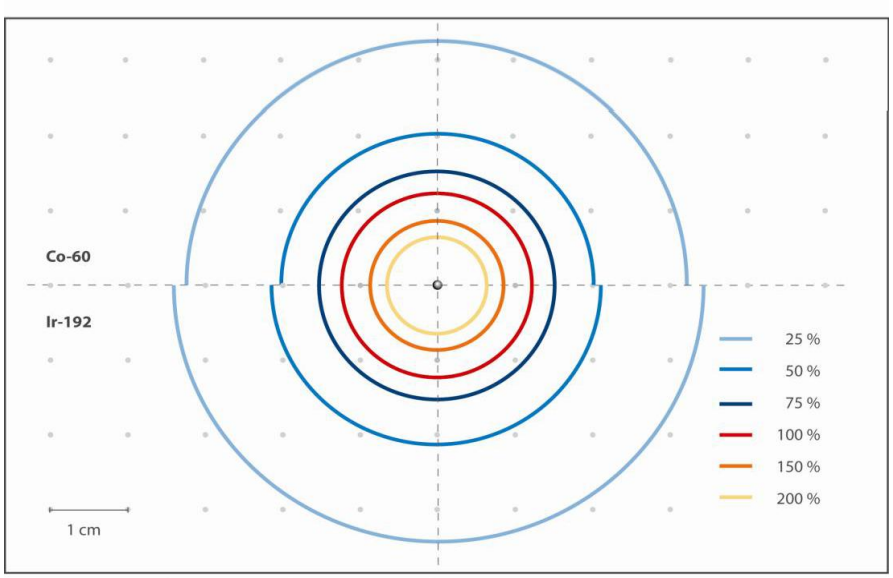
IR192 (2 month)

- 22,8 mGy/h ➔ 207 GBq
- ~ 11 Min

Co60 (1 years)

- 18,5 mGy/h ➔ 56,9 GBq
- ~ 11 Min

Dose at the OAR even little bit lower for Co-60 than for Ir-192

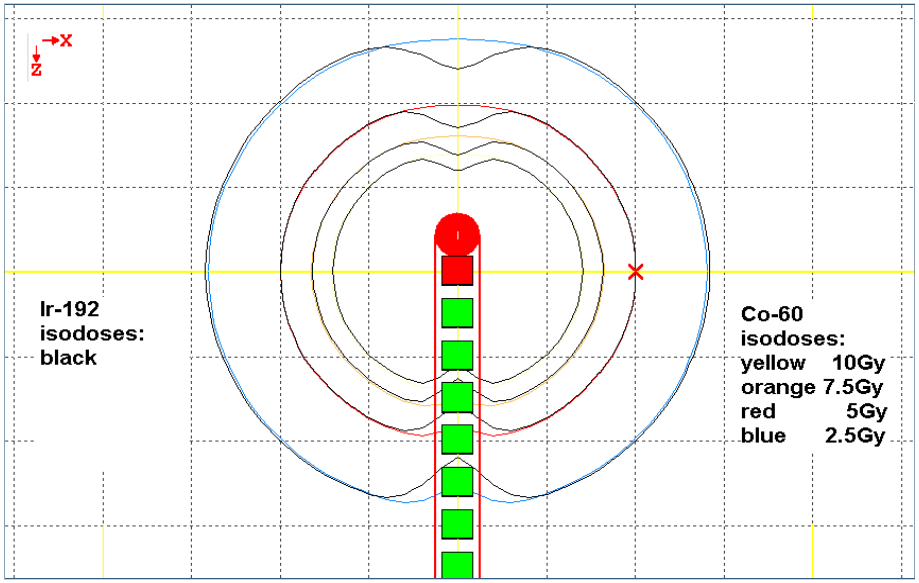


Radiation in tissue: isodose comparison between Co-60 and Ir-192

- Comparable dose distribution of Co-60 and Ir-192: Vaginal applicator

Anisotropy

Almost no difference between Co-60 and Ir-192 except the dip in direction of the source axis



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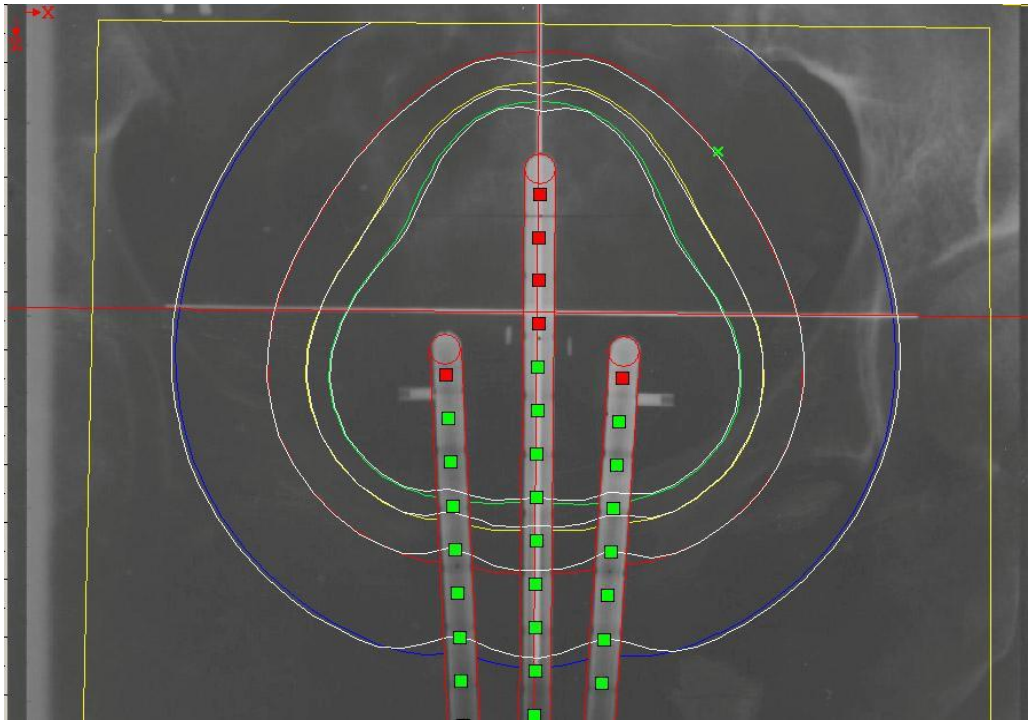

- Isodoses:
- Co-60:
- green: 10Gy
- yellow: 7.5Gy
- red: 5Gy
- blue: 2.5Gy

- Ir-192:
- all white

Number of source

	Ir-192 (every 4 months)	Co-60 (every 5 years)
10 years	**30**	**2**
15 years	**45**	**3**

→source exchanges using Co-60 mean:

- less expenses for sources
- less QC workload
- less logistic problems, less paperwork

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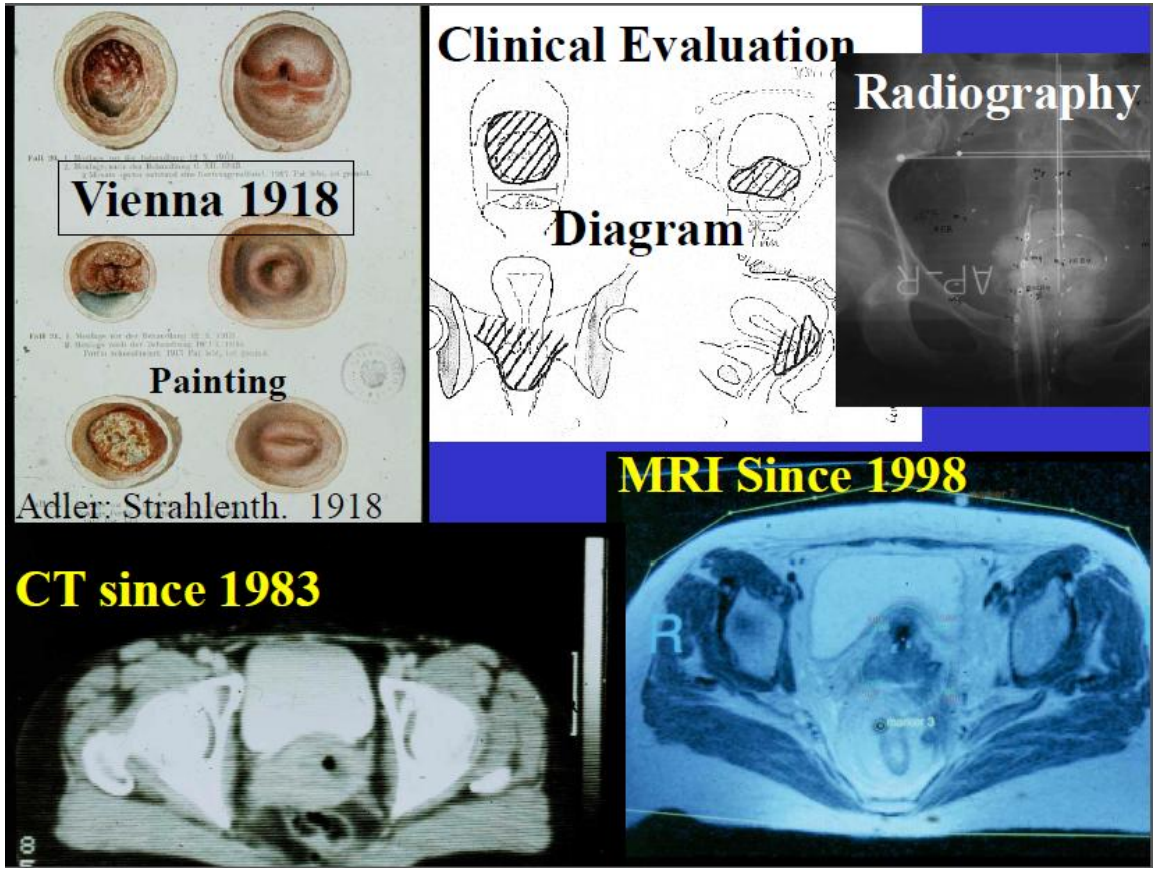

Current State of The Art Brachytherapy

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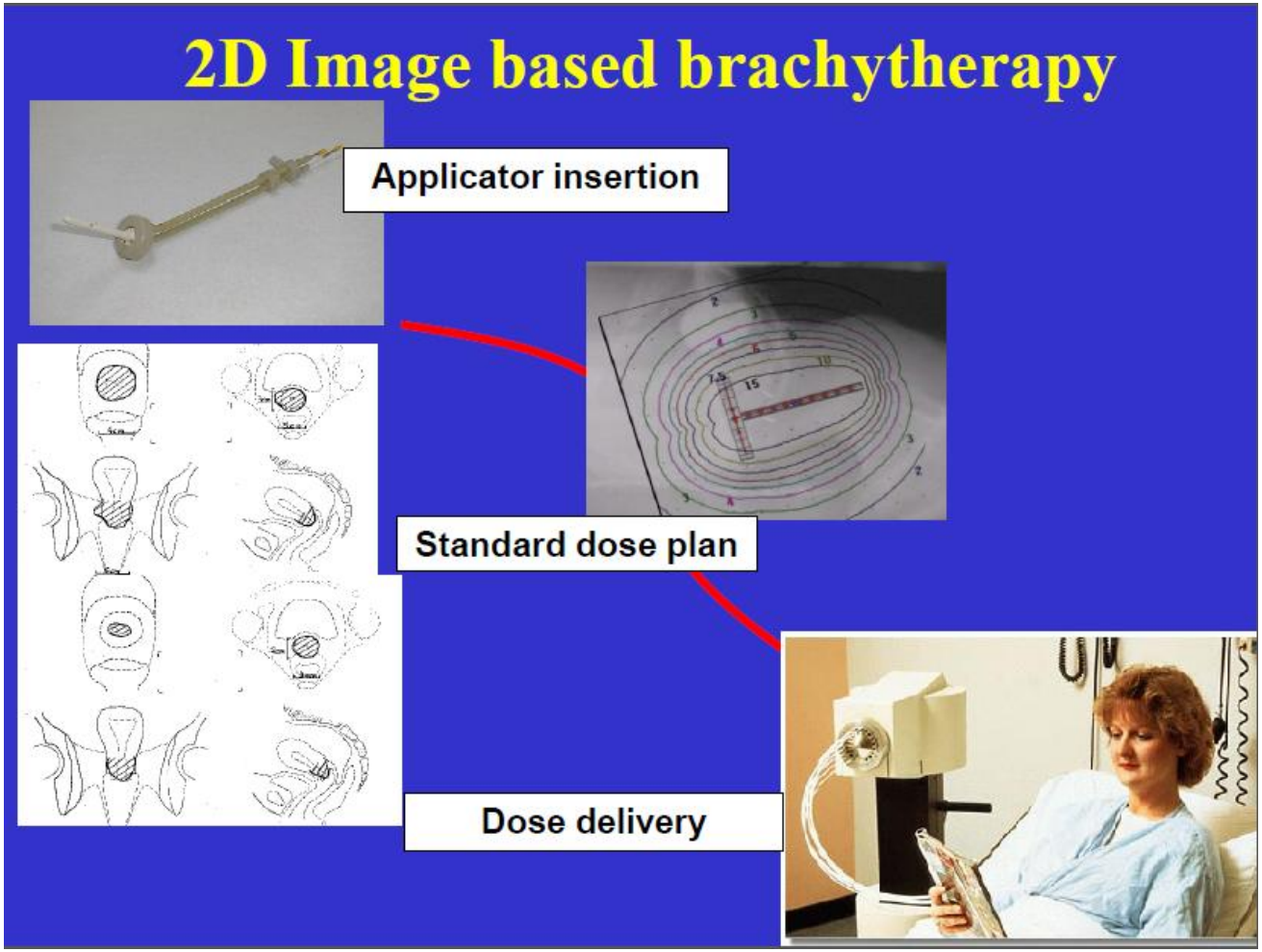

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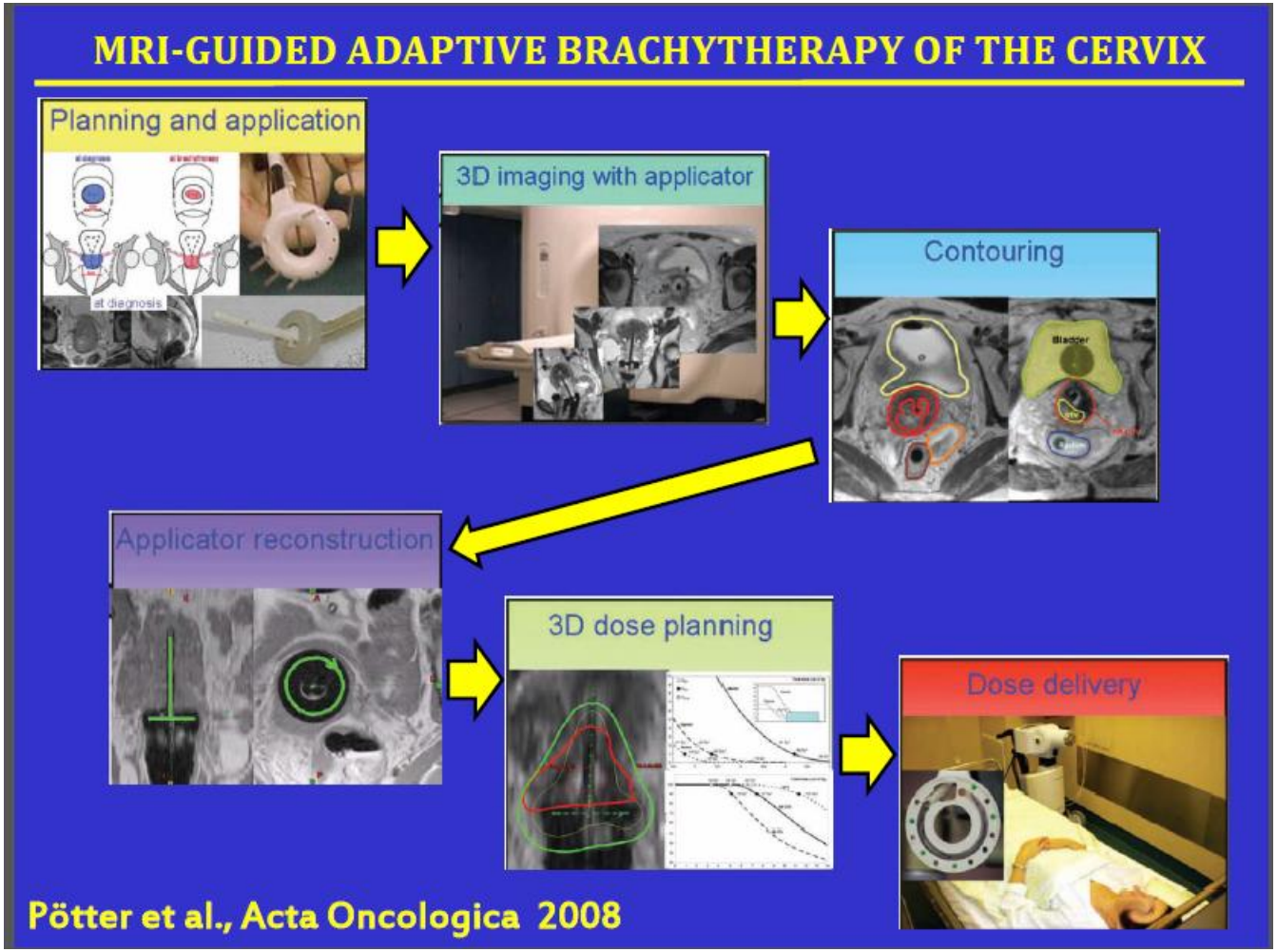

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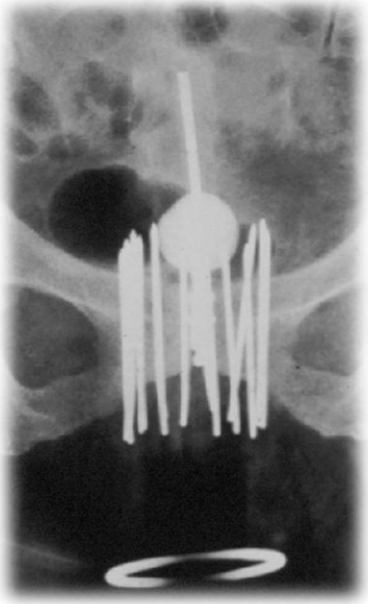
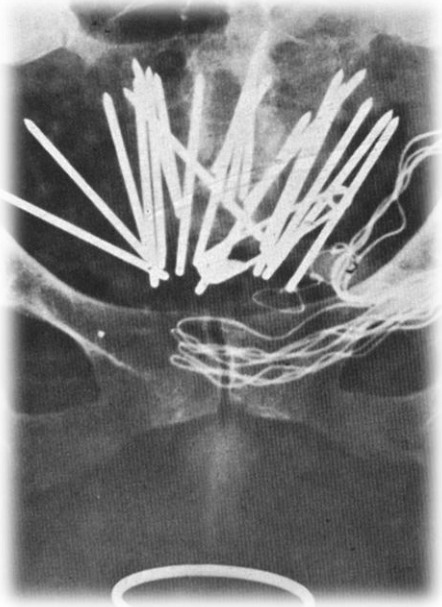
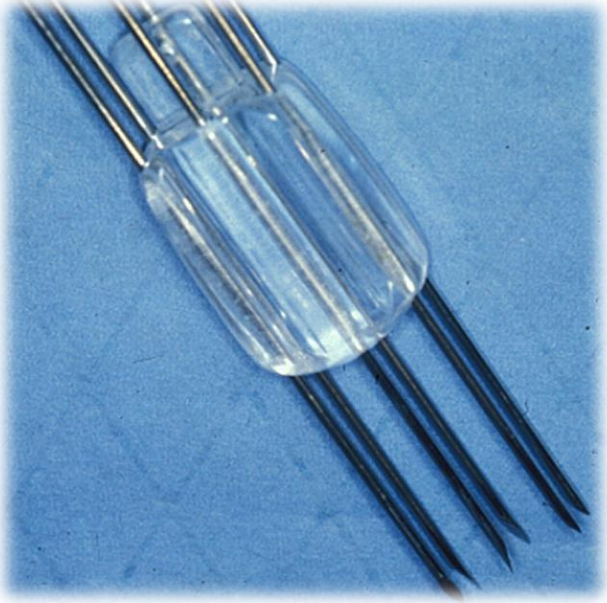
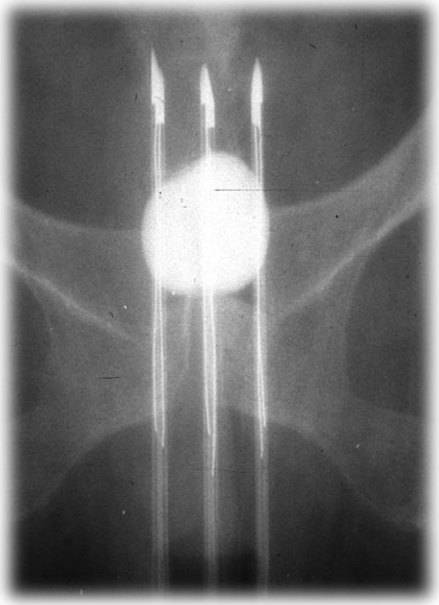
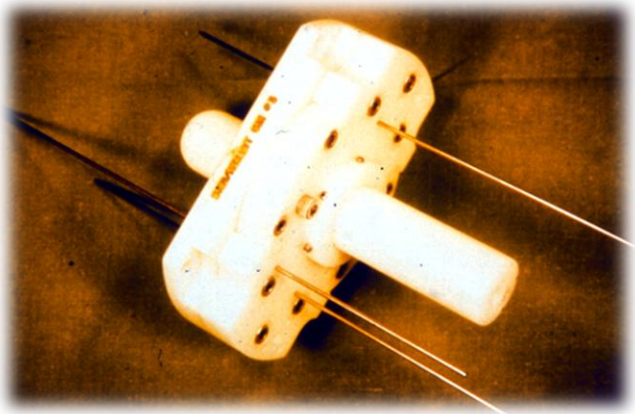
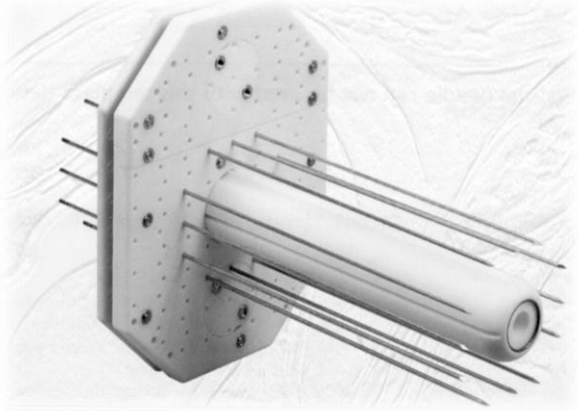
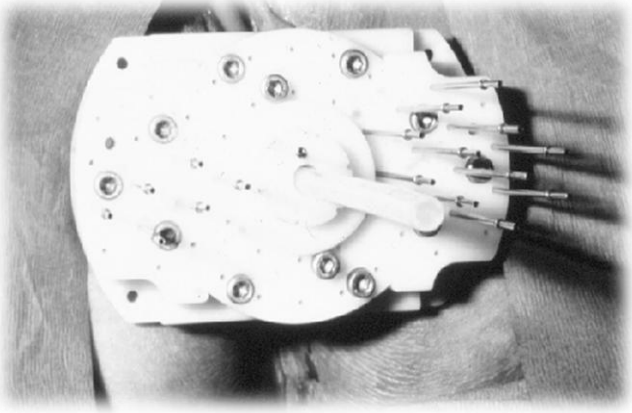
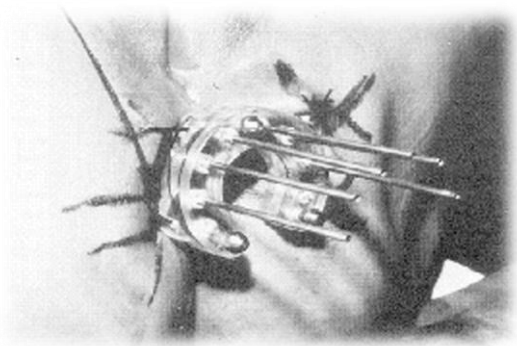
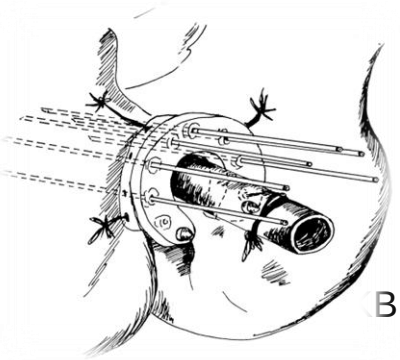
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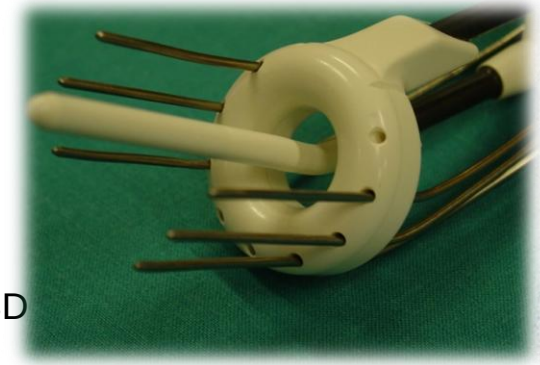
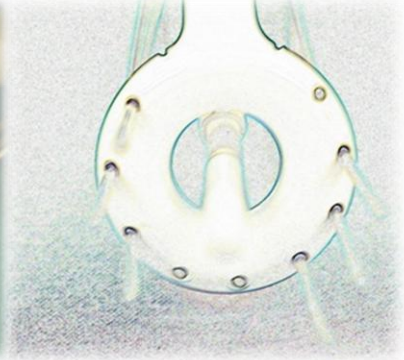

Gynecologic Cancer InterGroup
Cervix Cancer Research Network

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

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

ICRU-GEC-ESTRO recommendations on dose volume reporting

Richard Pötter

Cervix Cancer Education Symposium, January 2017, Mexico

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An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Recommendations, DVH parameters

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

ESTRO project

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

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

[a]*Department of Radiotherapy and Radiobiology, Medical University of Vienna, Austria,* [b]*Department of Radiotherapy, Brachytherapy Unit, Institut Gustave Roussy, Villejuif, France,* [c]*Department of Radiotherapy, University Hospital Gasthuisberg, Leuven, Belgium,* [d]*Department of Radiation Oncology, Centre George-Francois Leclerc, Dijon, France,* [e]*Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, USA,* [f]*Service de Radiodiagnostic, Institut Curie, Paris, France*

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At Diagnosis [X]

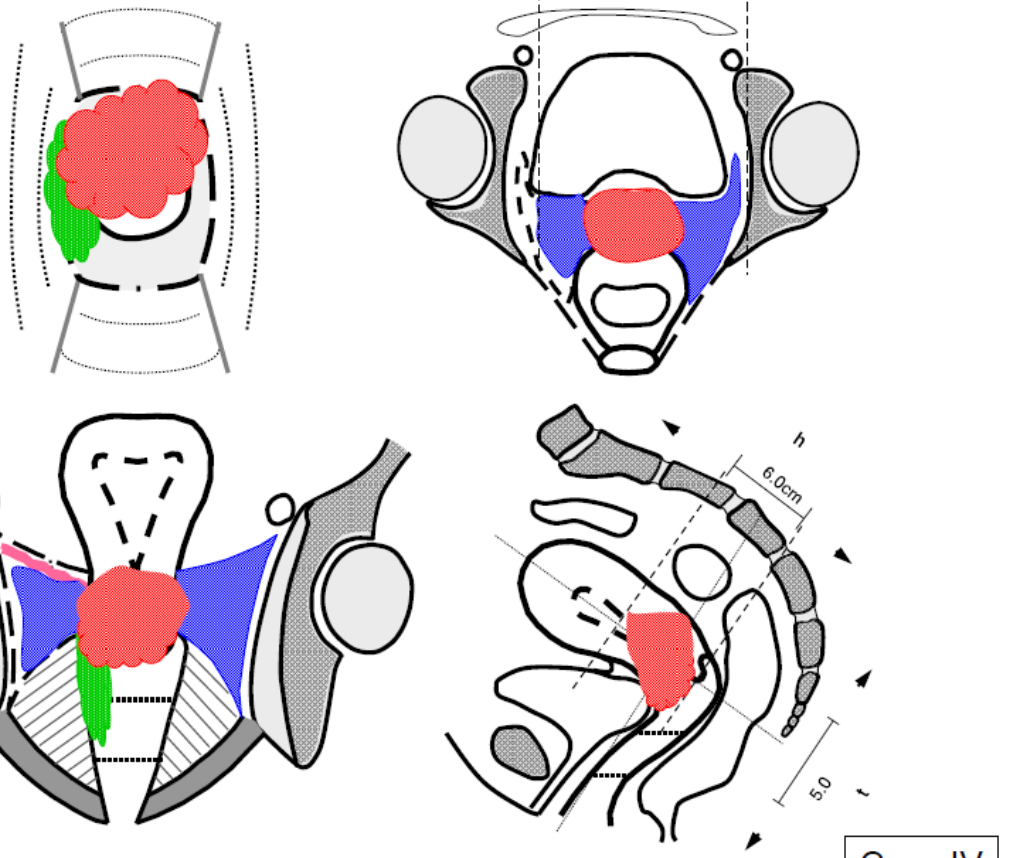
At Brachytherapy [ ]

Dose of EBRT___ Gy

IIIB

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

Vagina: 5 cm



dd/mm/yy
/ /

Signature

Note: vagina and parametria not included in h

Case IV

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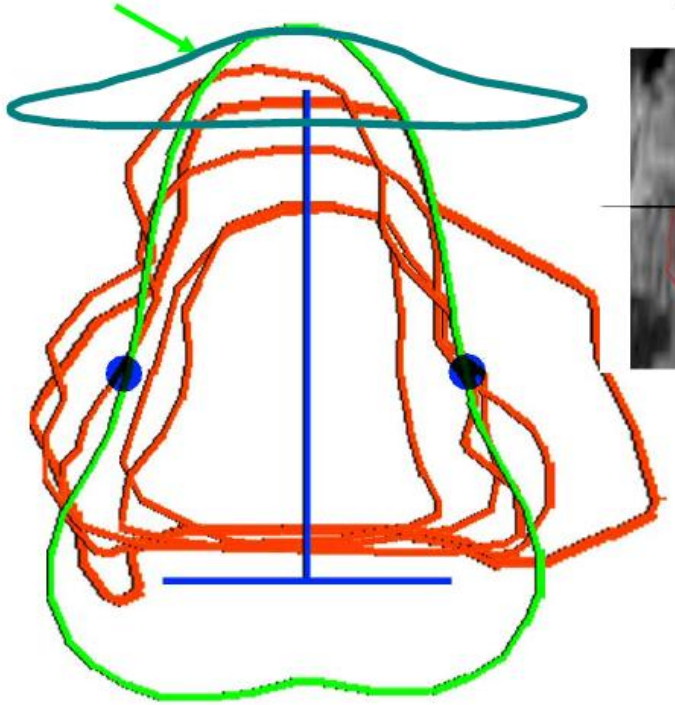
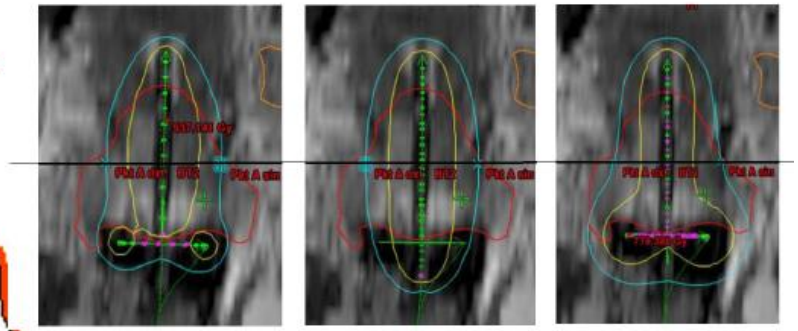
Point-A based brachytherapy

Point A isodose



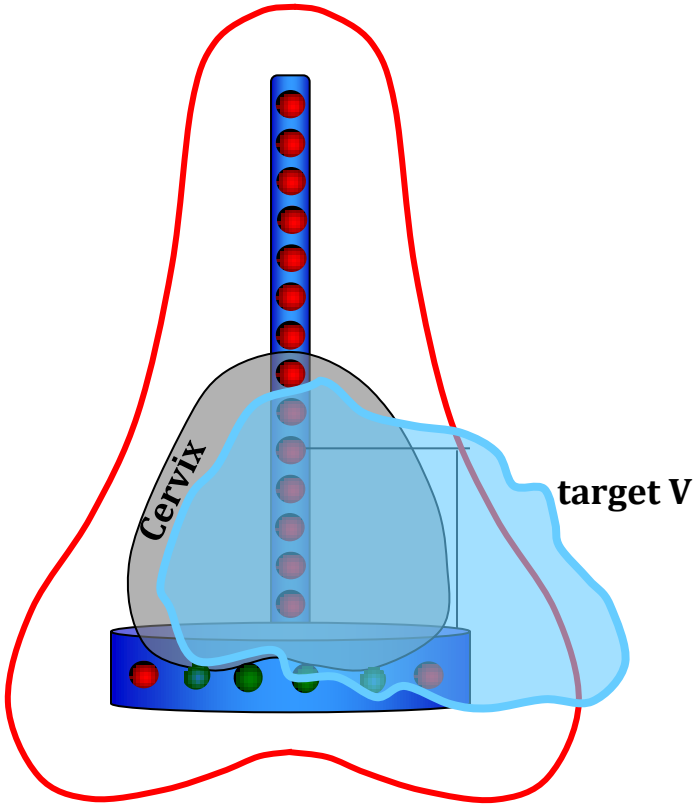
Milwaukee Toronto Vienna



Modern Intracavitary Techniques

Covering the target volume with *prescribed dose* (—)

Standard loading

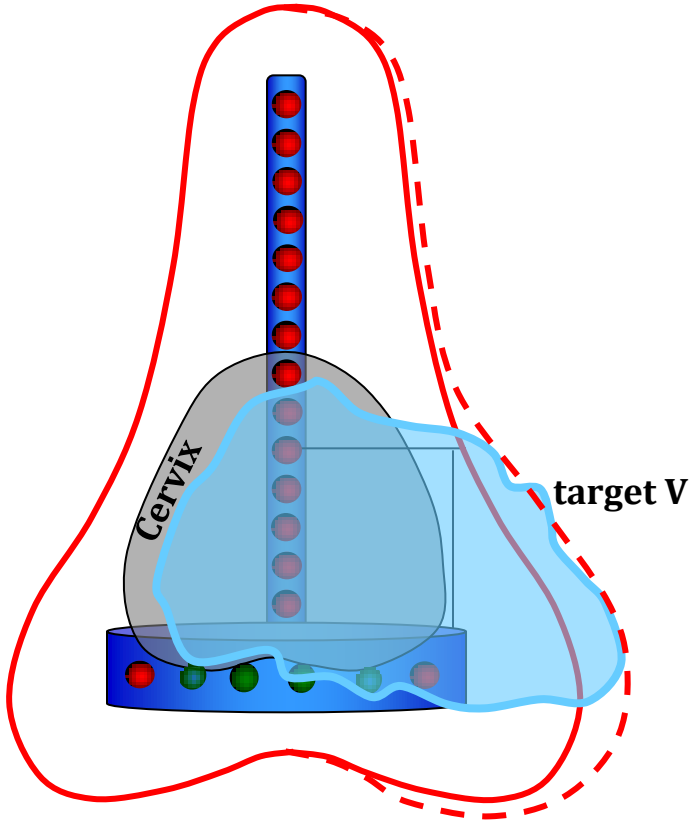


Mid-coronal view

Modern Intracavitary Techniques

Covering the target volume with *prescribed dose* (—)

Modified loading



Mid-coronal view

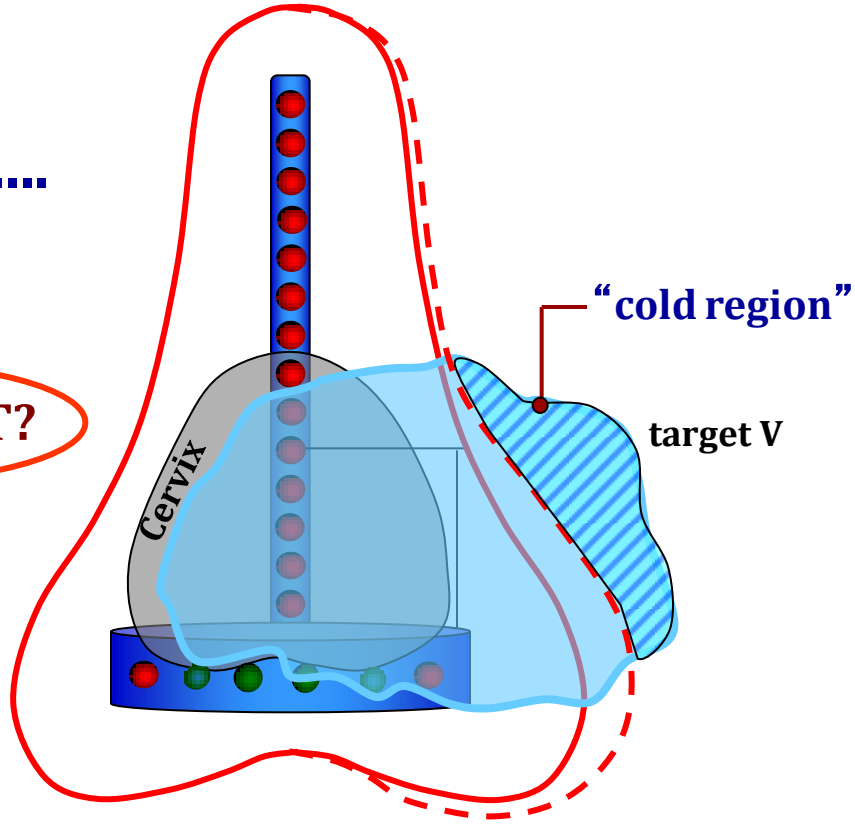
Modern Intracavitary Techniques

Covering the target volume with *prescribed dose* (—)

Modified loading

Boost needed....

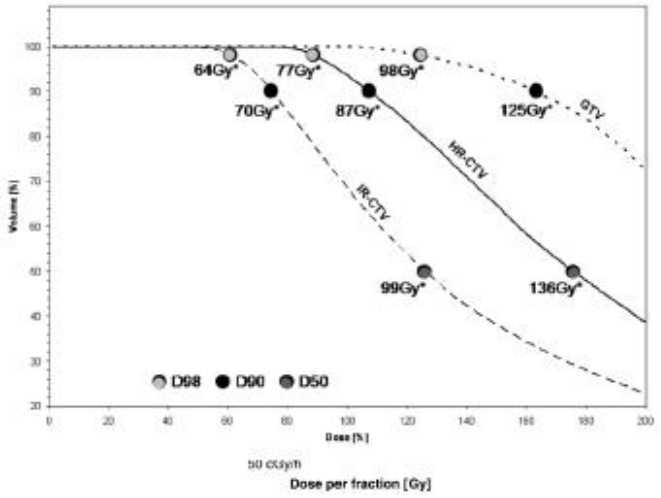
- EBRT?
- Interstitial BT?

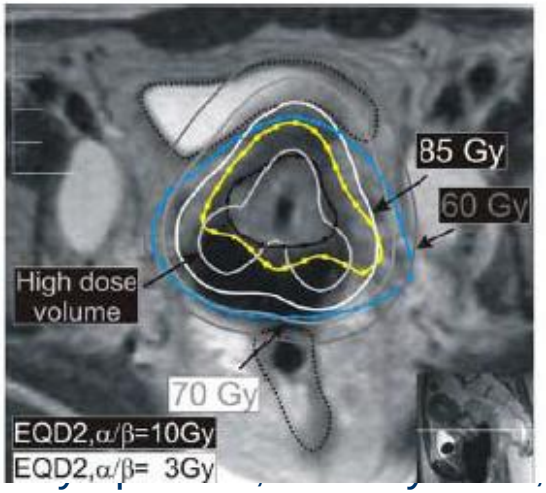


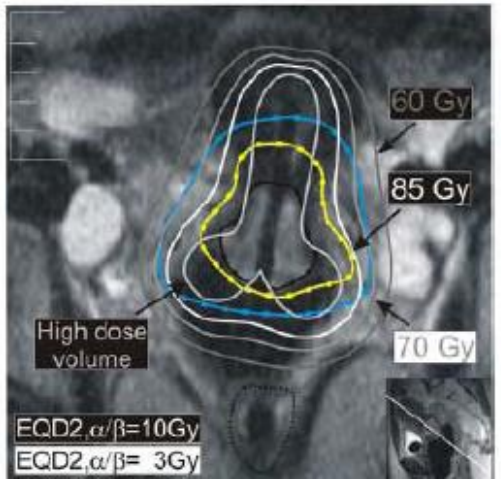
Mid-coronal view

DVH-parameters (GTV-T), CTV-T

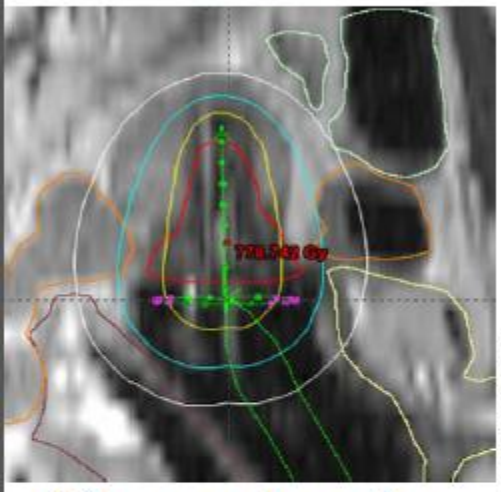
- **D90: Minimum dose within most exposed 90% of volume of interest**
  - **reliable and reproducible, but 10% „neglected“ (clin relevance)**
- **D 98: Minimum dose within most exposed 98% of volume of interest**
  - **reliable and reproducible, 2% not included**
- **[V100: Volume recieving prescribed physical dose (V150%/V200%)]**
  - **indicates target coverage;**
    only relevant within a specific dose (rate) and fractionation schedule
- **D50: Minimum dose within most exposed 50% of volume of interest**



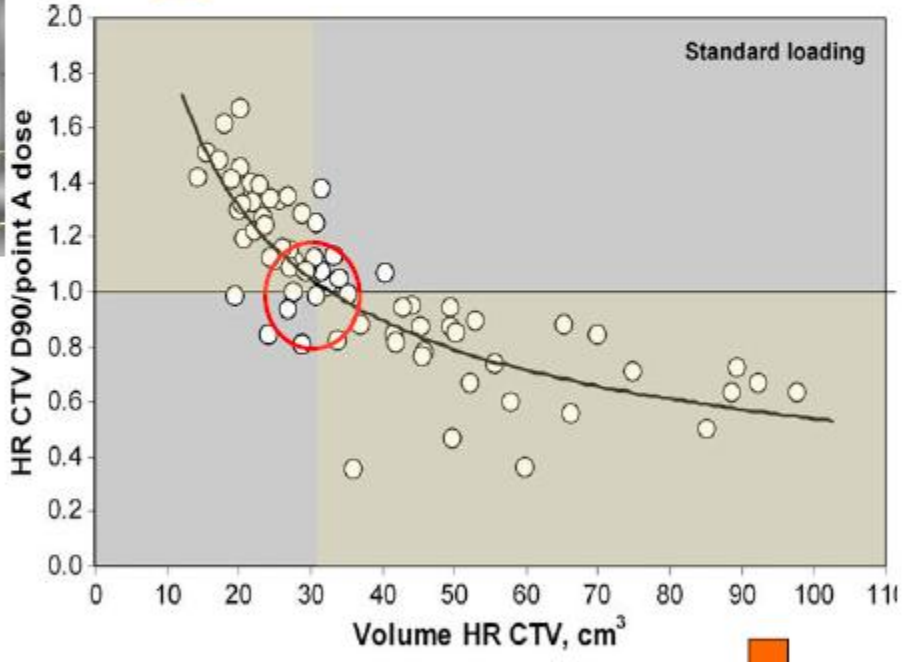




Consequences of prescribing to Point-A

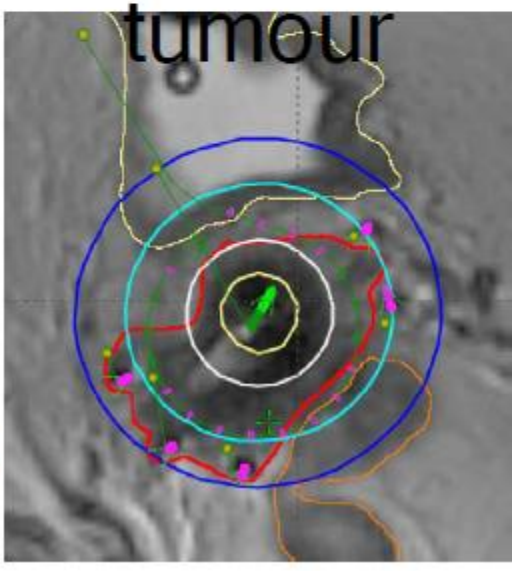


Overdosing organs at risk



Tanderup et al, Radiotherapy Oncol 2010

Underdosing the tumour



GEC-ESTRO Recommendations:

Specific requirements for MRI

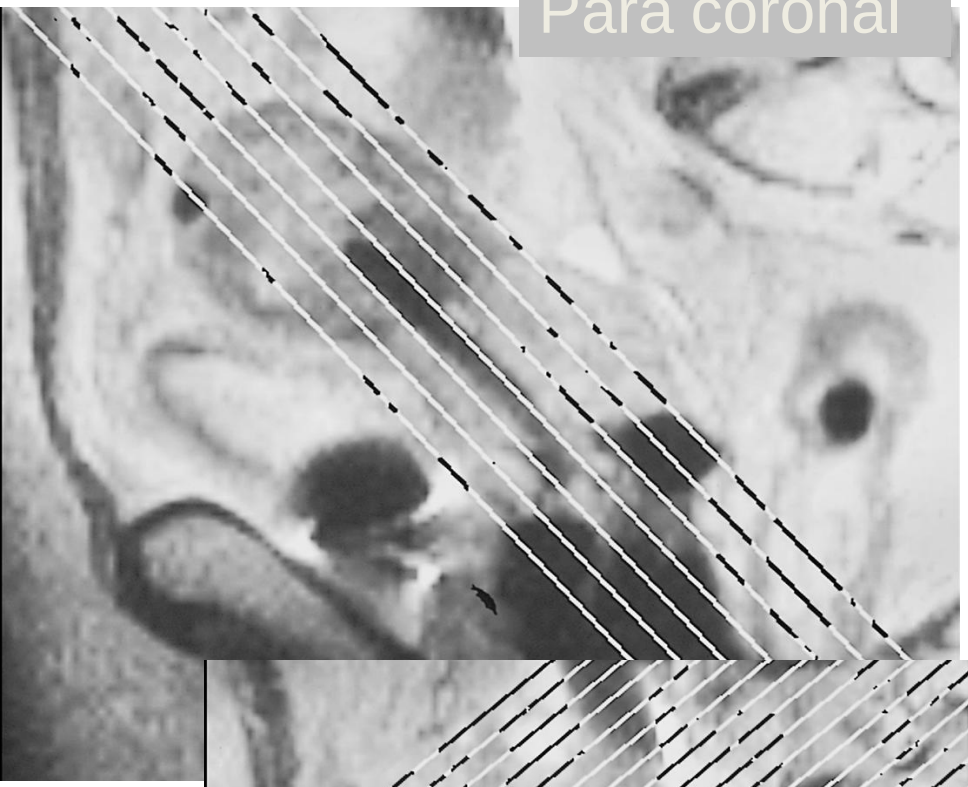
T2-weighted images:
High signal intensity
After EBRT : intermediate signal intensity (« grey zones »)

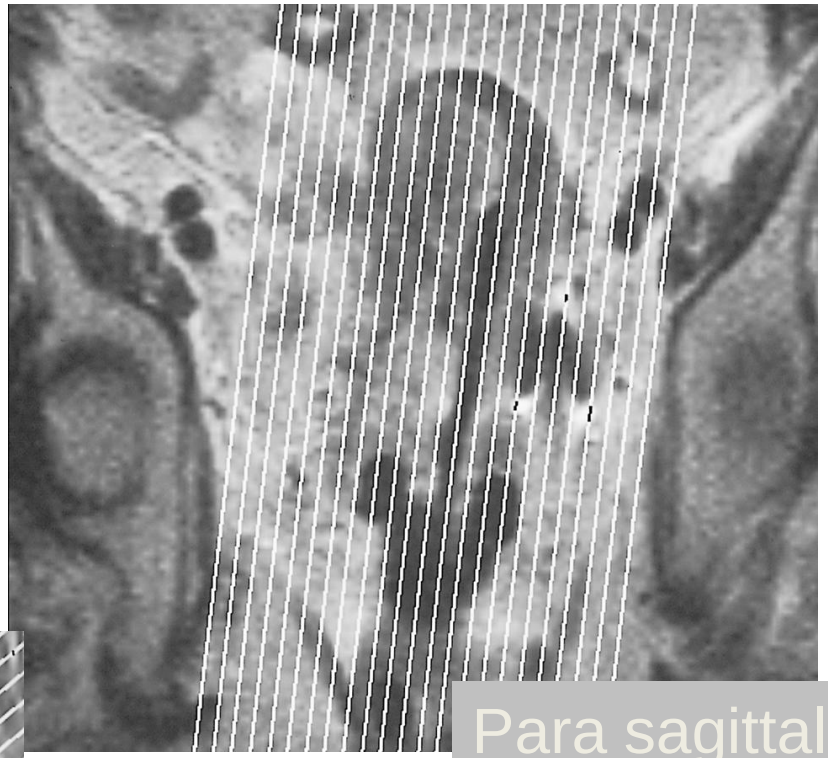
Image orientation:

- parallel
- orthogonal
- para-transversal
- para-coronal
- para-sagittal

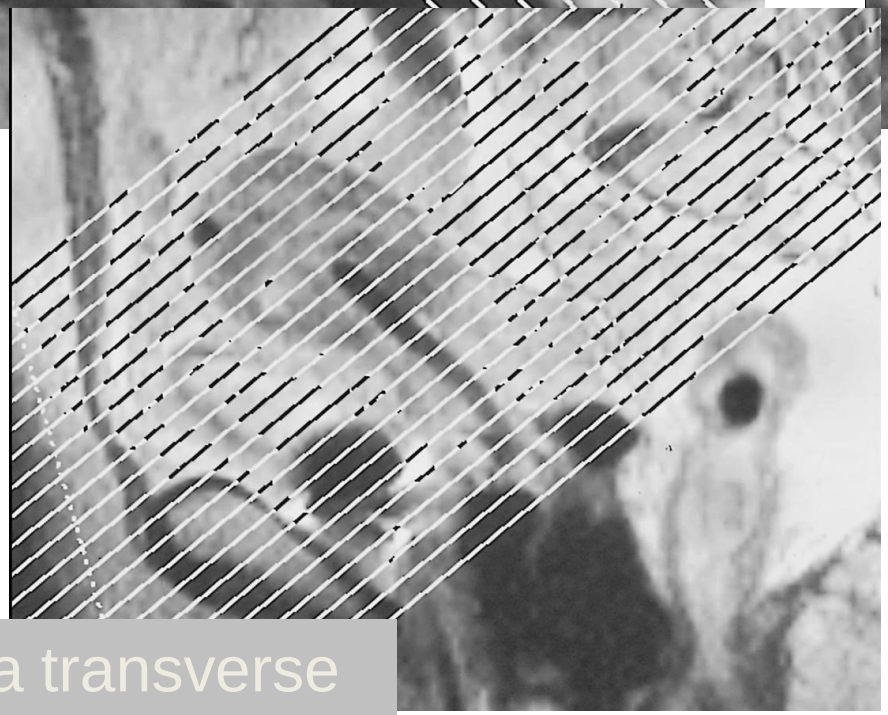
} to applicator axes

Para coronal





Para sagittal



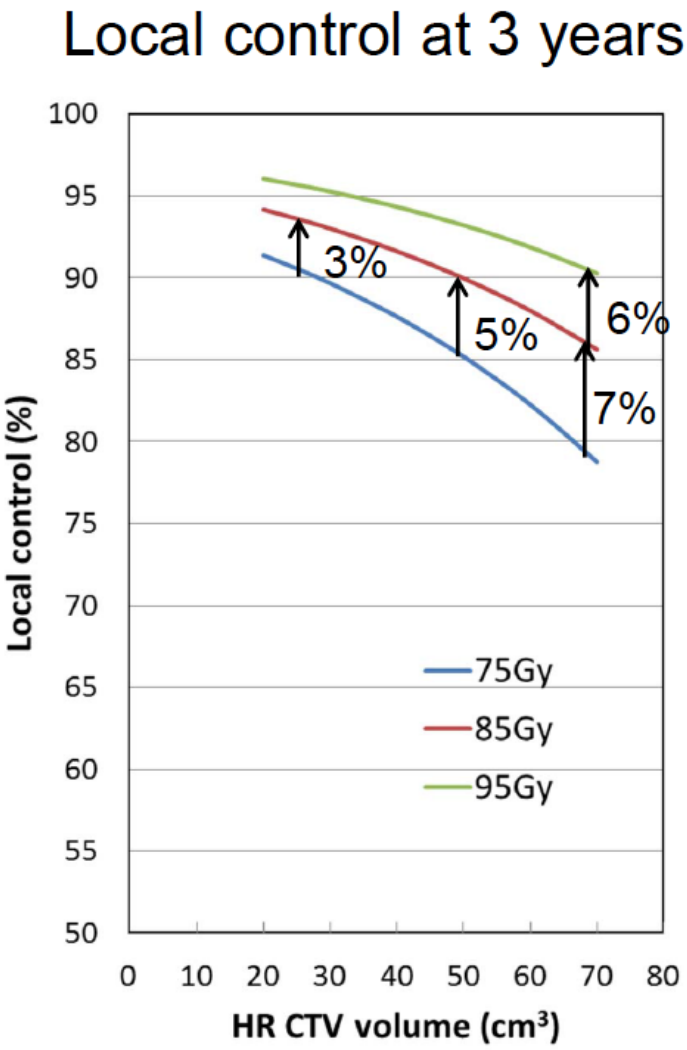
Para transverse

Specific requirements
for MRI

Are we making any difference?
Why to change from long-used practice to image guidance??!!

Volume and D90 HRCTV, local control 7 centres: multi-center cohort (n=488)

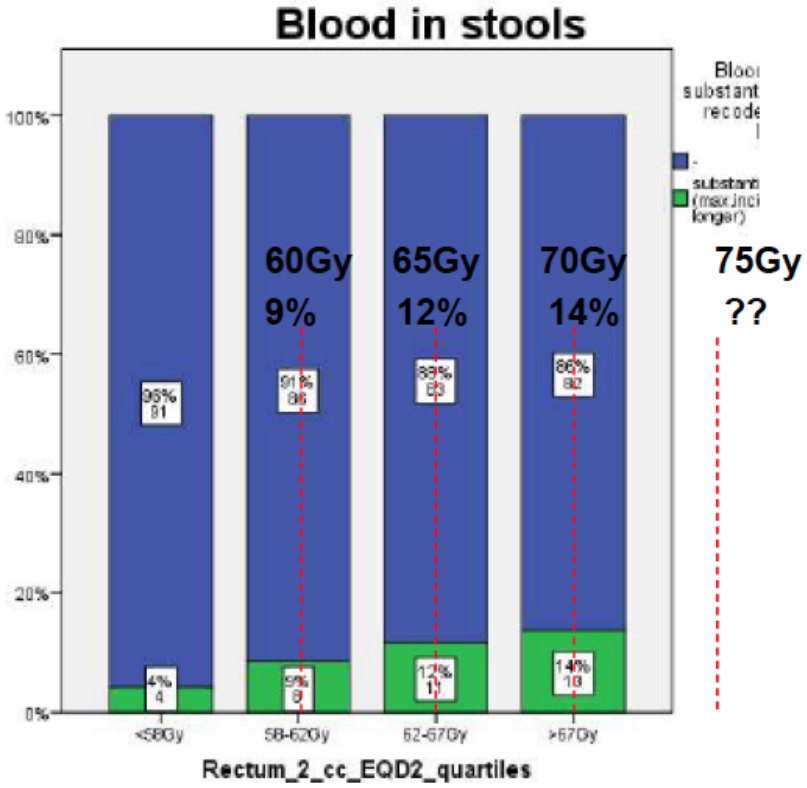
- Cox regression
- Dose and volume continous co-variates
- Significance:
  - p=0.07 for CTV_{HR} D90
  - p=0.01 for CTV_{HR} volume
- Hazard ratios:
  - 0.962 for CTV_{HR} D90 (per Gy)
  - 1.018 for CTV_{HR} volume (per cm^3)



Tanderup et al. , ASTRO 2014

Rectum: D 2 cm^3 and bleeding mono- and multi-centre evidence, Level II/III

EMBRACE data extraction
Oct 2013
Patient reported (≥12m FU)



Georg et al 2011, 141 pts
≥G2 (mainly rectal bleeding)

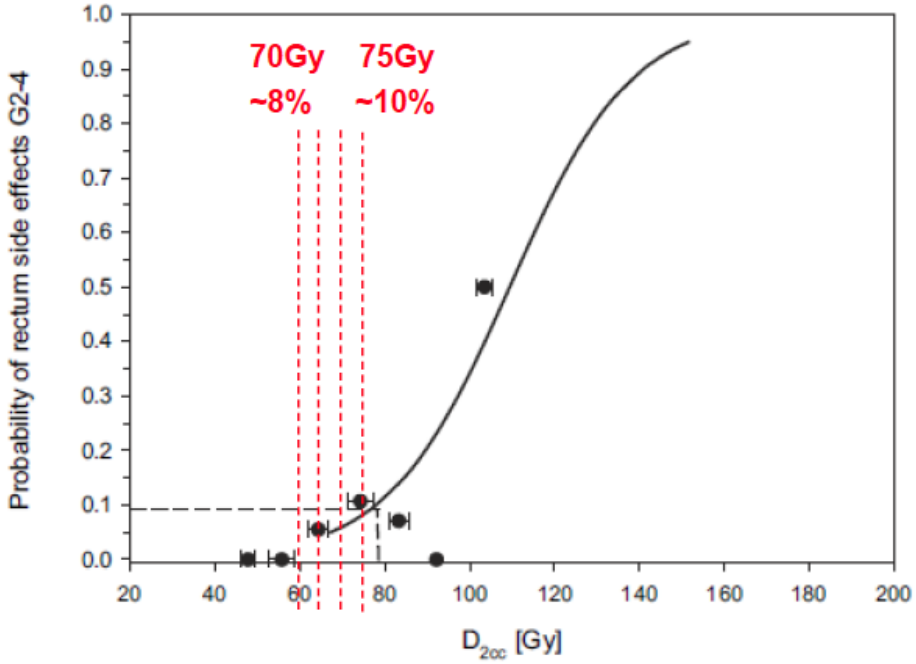


Fig. 1. Relationship between D_{2cc} and late side effects in the rectum.

Bladder: D 2 cm^3 and frequeny, urge, incontinence; mono- /multi-centre evid.

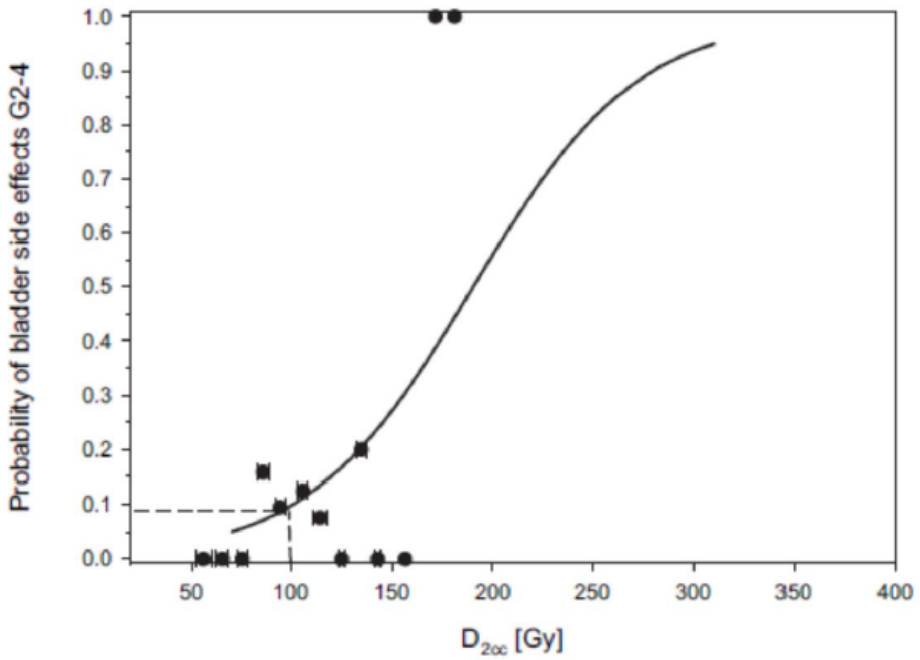
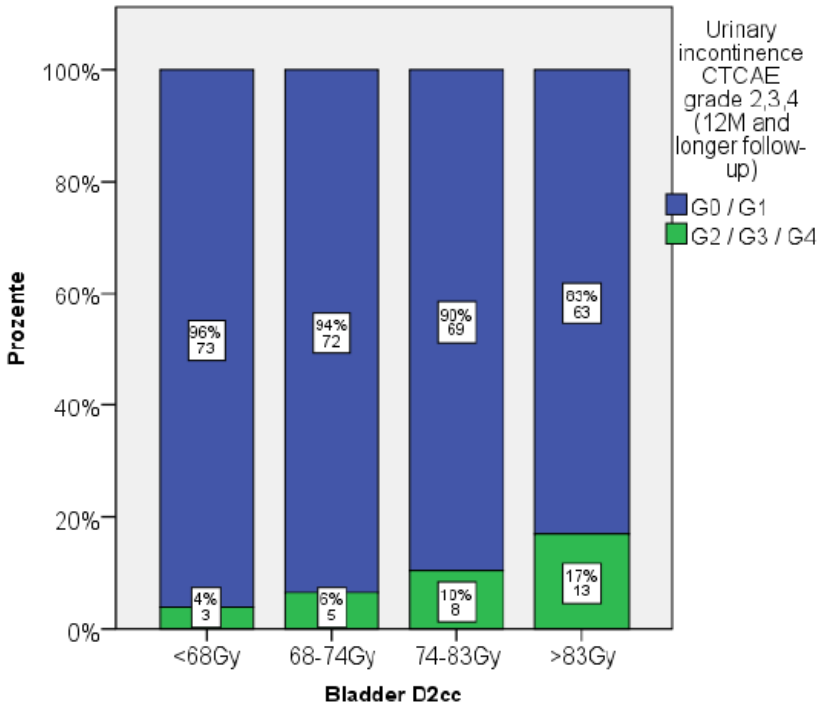


Fig. 2. Relationship between D_{2cc} and late side effects in the urinary bladder.

P. Georg et al. 2011 IJROBP
(Vienna data, n=141)



Significant dose response
for Bladder D_{2cm^3}
on urinary incontinence (frequ)
(EMBRACE)

Conclusion

- Brachytherapy is critical in the treatment of locally advanced cervical cancer.
- LDR or HDR are reasonable choices.
- Modern brachytherapy includes MRI image guidance.