BRACHYTHERAPY IN CARCINOMA CERVIX: NEW DEVELOPMENTS

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- Brachytherapy (Greek "brachos"=short) describes a technique of treatment of malignant tumors with sealed radioisotopes, where the source of radiation is placed within or very close to the patient's body.
- Brachytherapy is an essential component in the non-surgical treatment of uterine cervical cancer, alone (very early stage) or in combination with external beam radiotherapy.

Physical properties of some nuclides

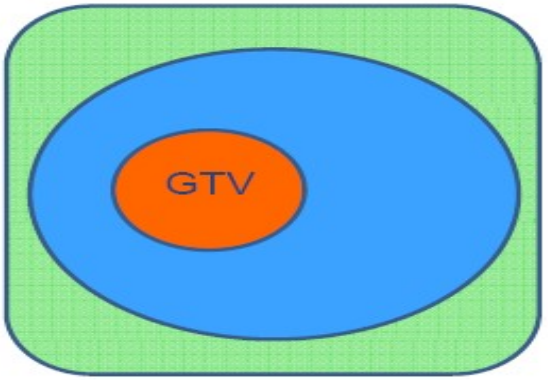
Radio Nuclide	Half time $T_{1/2}$	λ (s^{-1})	Average Photon Energy (keV)	Mass for 100 MBq (µg)
^{226}Ra	1600 y	$1.37\ 10^{-11}$	830	45
^{137}Cs	30 y	$7.27\ 10^{-10}$	662	31
^{60}Co	5.26 y	$4.18\ 10^{-9}$	1253	2.4
^{192}Ir	74.2 d	$1.08\ 10^{-7}$	380	0.29
^{125}I	60.2 d	$1.34\ 10^{-7}$	28	0.16
^{103}Pd	17 d	$4.72\ 10^{-7}$	21	0.04

Khan

Background: Target concepts (ICRU)

Gross Tumor Volume (GTV)

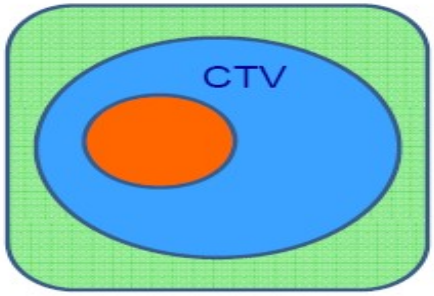
- The GTV is the gross palpable or visible/demonstrable extent and location of the malignant growth



Clinical Target Volume (CTV)

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

This volume has to be treated adequately in order to achieve the aim of therapy: cure or palliation. The CTV is an anatomical-clinical concept, that has to be defined before a choice of treatment modality and technique is made.



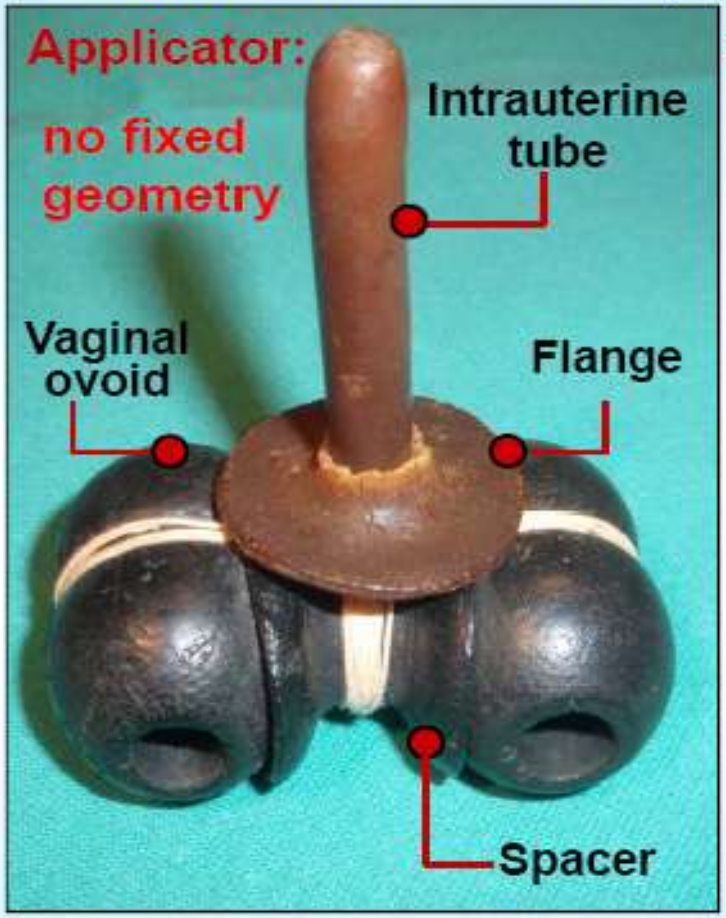
Classical systems of brachytherapy

- Brachytherapy dosage & application were based on certain systems developed in the early part of the 20th century
- The three main systems were :
- Paris
- Stockholm
- Manchester (& Fletcher)

- The latter has become a standard & modern computerised planning techniques are basically developments of the Manchester & Fletcher techniques.

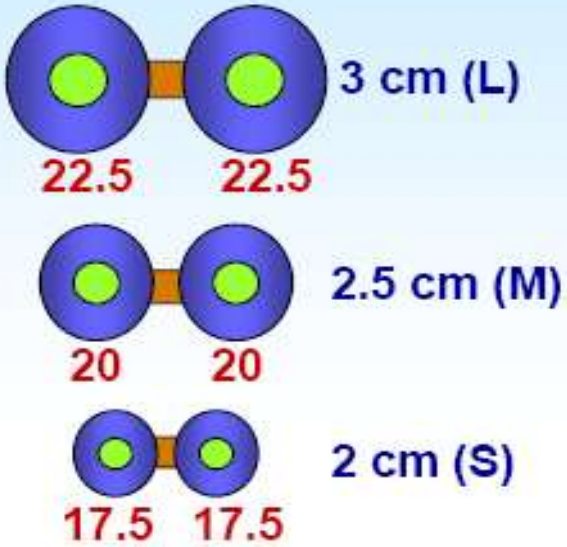
Historical Manchester System

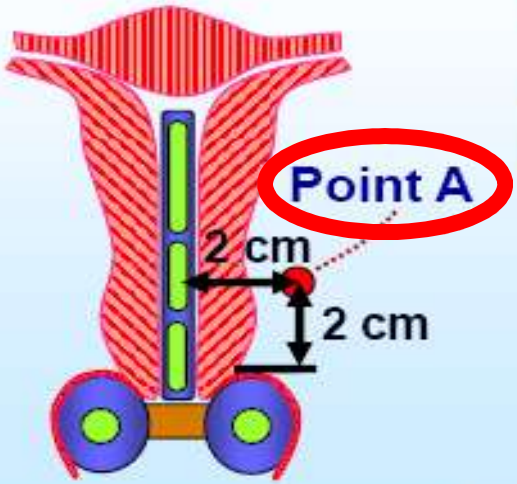
Related to historical Paris technique



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.

Limitations of Manchester system

- Dosage is defined in terms of dose to Point A
- Point A represents the point where the uterine artery & ureter cross
- The maximum dose allowed should respect the tolerance of these structures
- Point A is located 2 cm above the mucosa of the vaginal fornices and 2 cm lateral to the central axis of the uterus
- BUT, point A has no fixed relation to the actual tumor, which may extend beyond point A easily.

Modern-day Intracavitary Applicators

Modern day Remote Afterloading HDR Brachytherapy machine

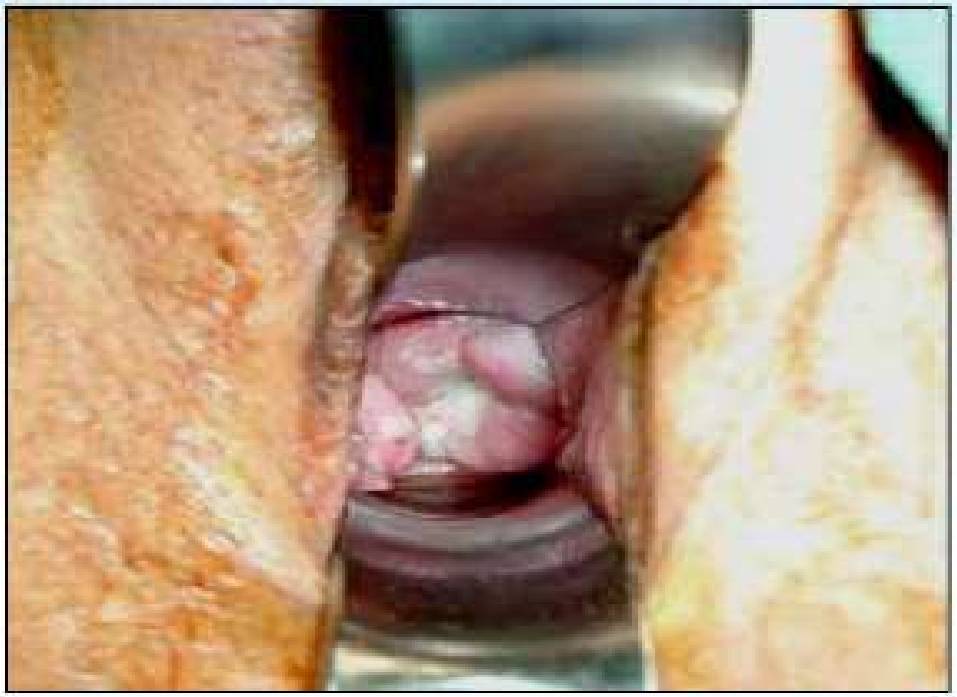
Instruments

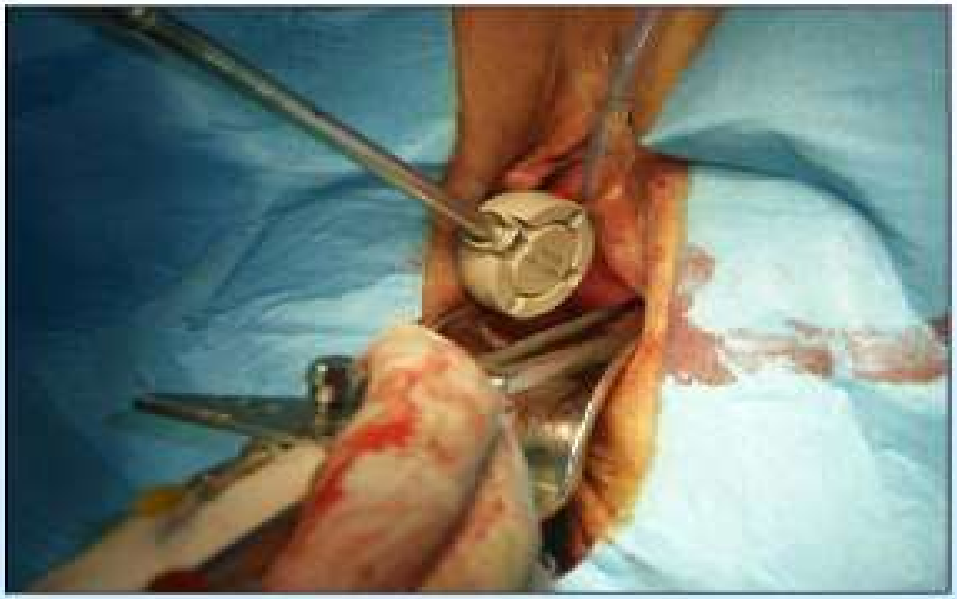
Preparation

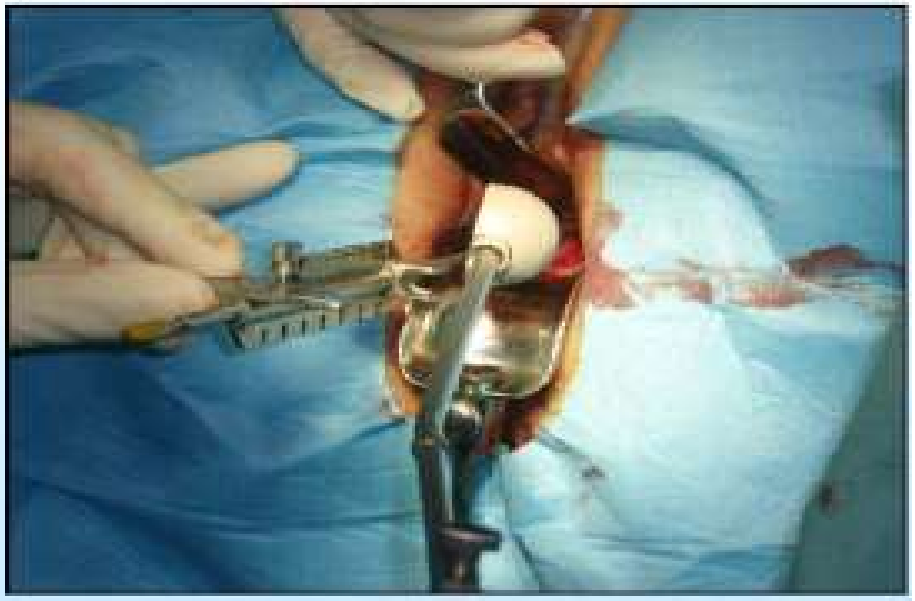
Dressing & Draping

Examination under anaesthesia

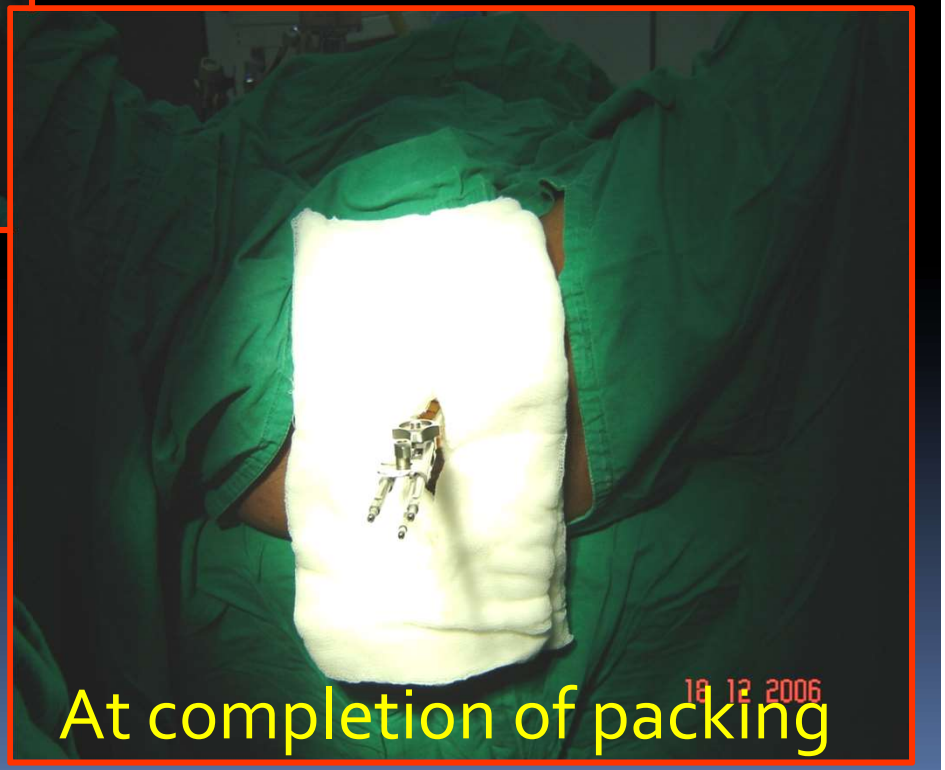
Applicator insertion







Packing of vagina

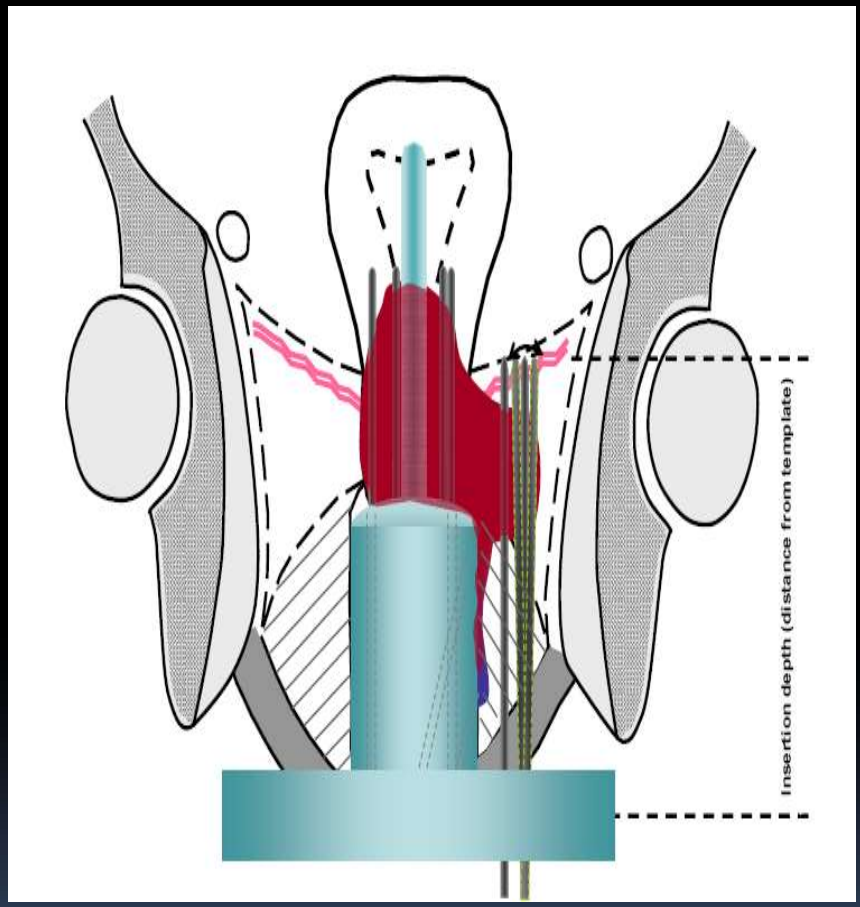


At completion of packing

Limitations of pure intracavitary techniques with conventional applicators

- distal intravaginal + parametrial tumor growth
- para-vaginal tumor growth
- middle/distal parametrial tumor extension
- unfavourable topography/unfavourable relation to the applicator (e.g. asymmetrical tumors)
  (depending on applicator position)
- unfavourable topography of organs at risk
  (not predictable – correction within the frame of subsequent applications)

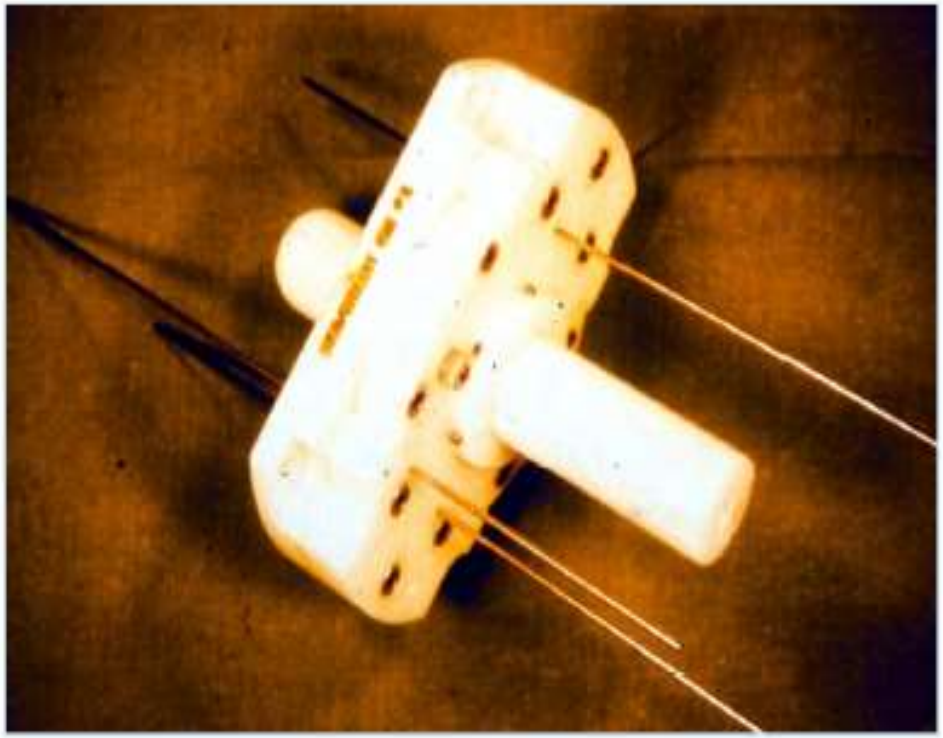
- In these situations, interstitial applications have advantage.
- They may be free-hand but are usually template-guided.
- The 2 commonest templates used are the Syed-Neblett & the Martinez Universal Perineal Interstitial Template (MUPIT).



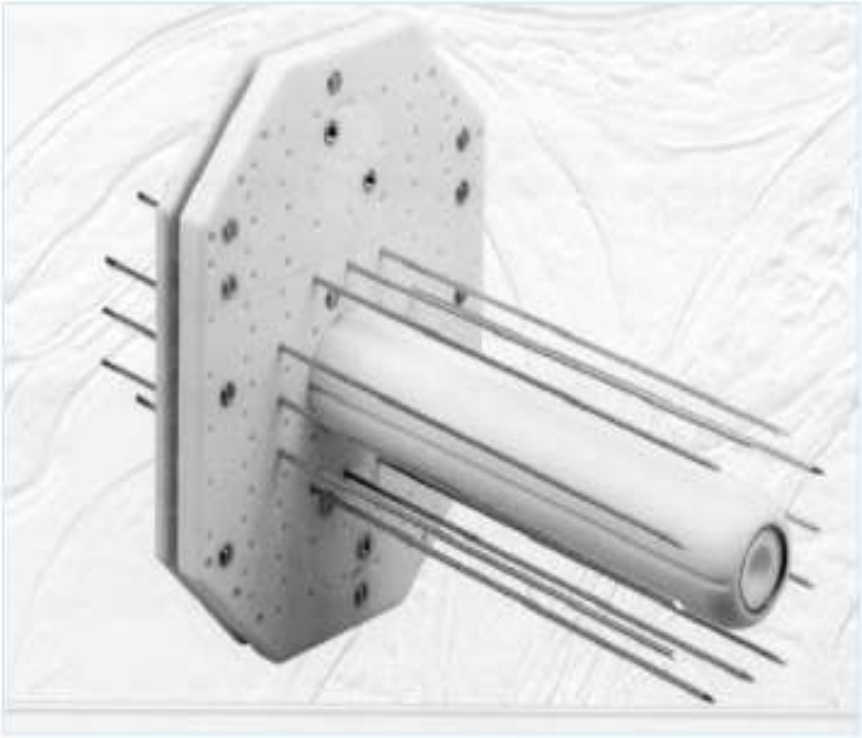
Classical interstitial techniques

Perineal Templates

Syed

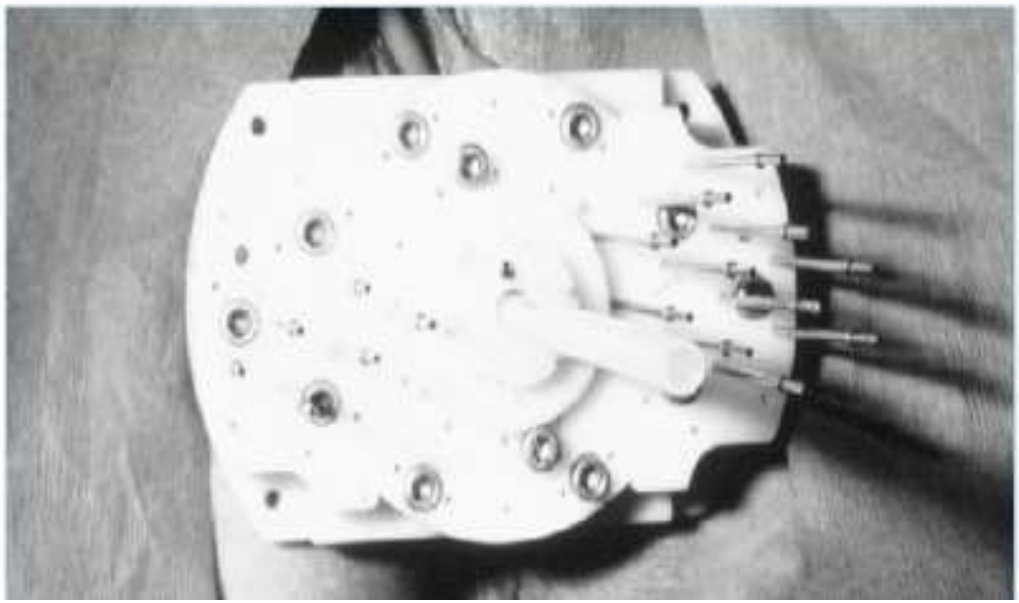


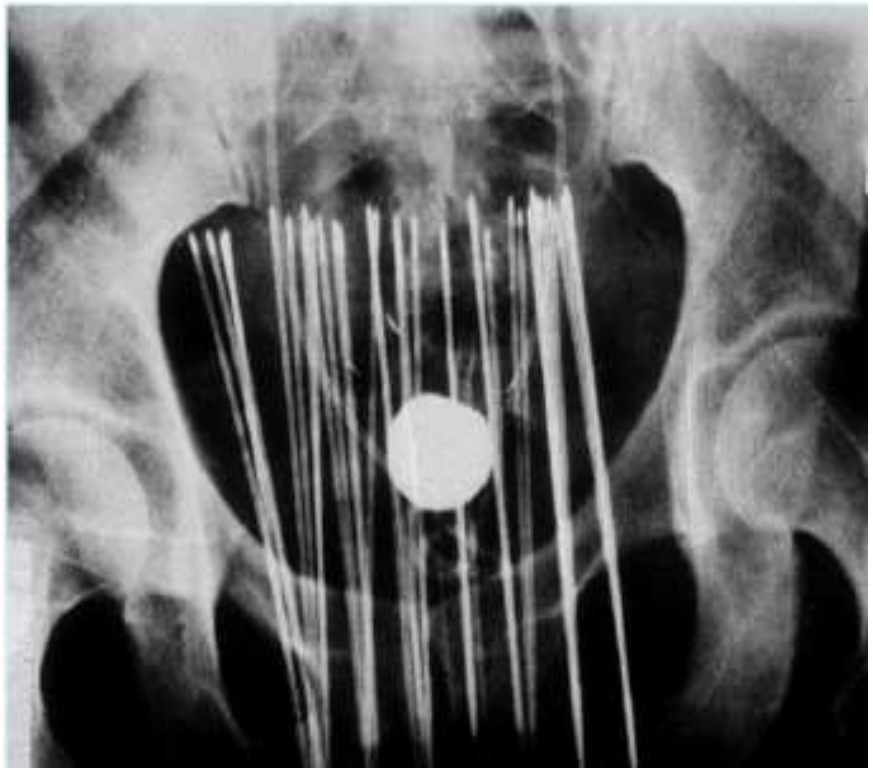
MUPIT



Classical interstitial techniques

Syed

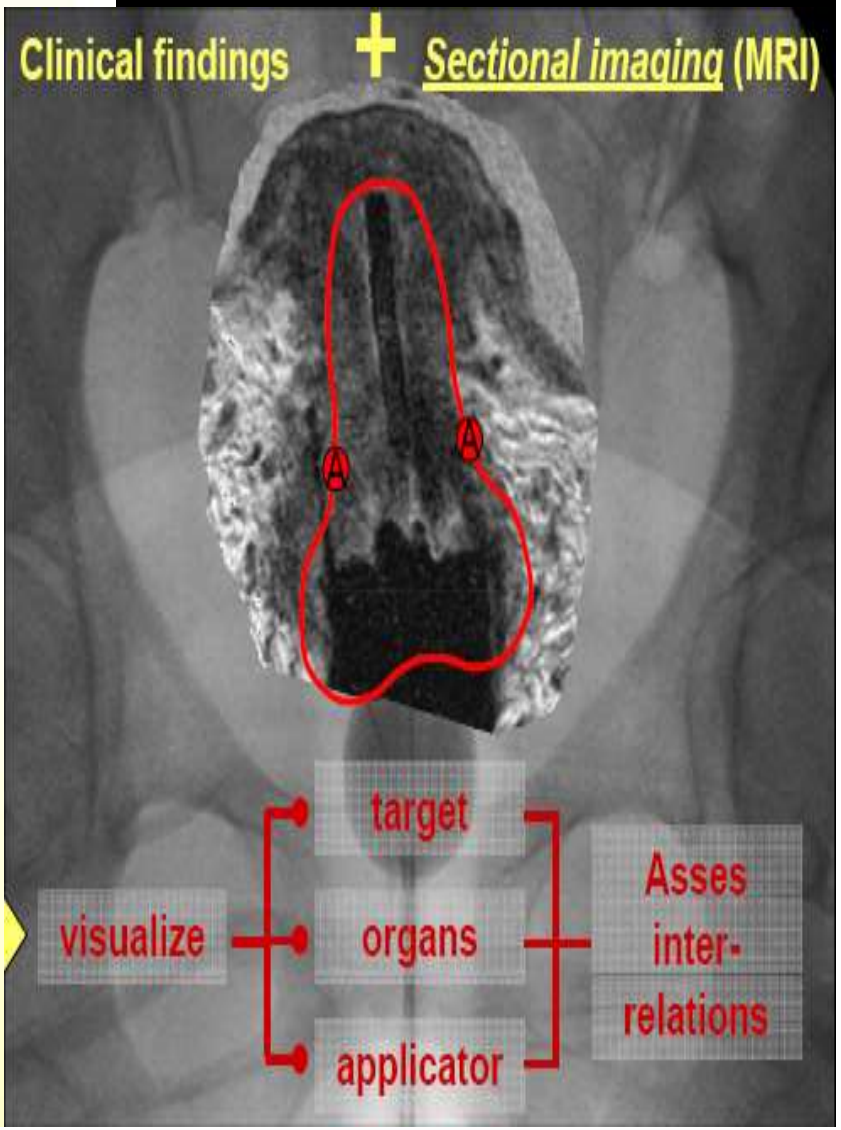




Limitations of 2D approaches

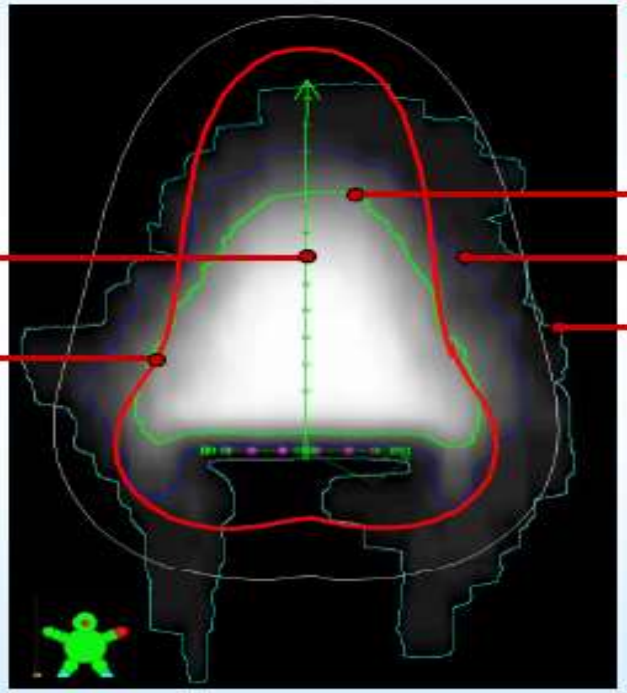
Main limitation of 2D approaches:

Absence of visual information on spatial relations between tumour and applicator



Prescribing to Point A may not deliver sufficient dose to the

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



Intracavitary applicator (Stockholm type)

Prescribed dose

Standard point A

Patient population (n>200):
Lubljana, Aarhus, Vienna

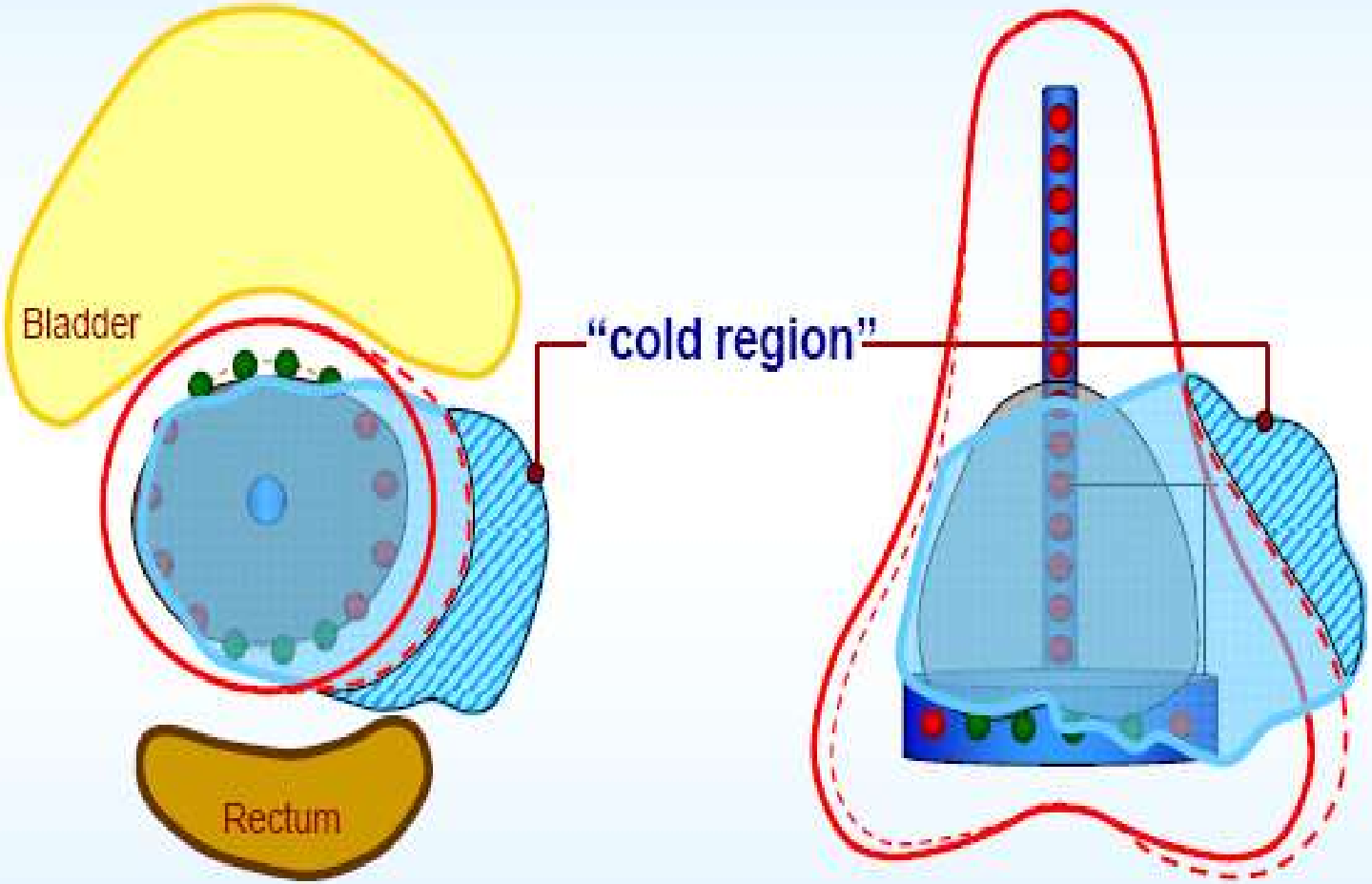
75 % of target volumes

95 % of target volumes

100 % of target volumes

Petric P, et al. GEC ESTRO, Porto 2009

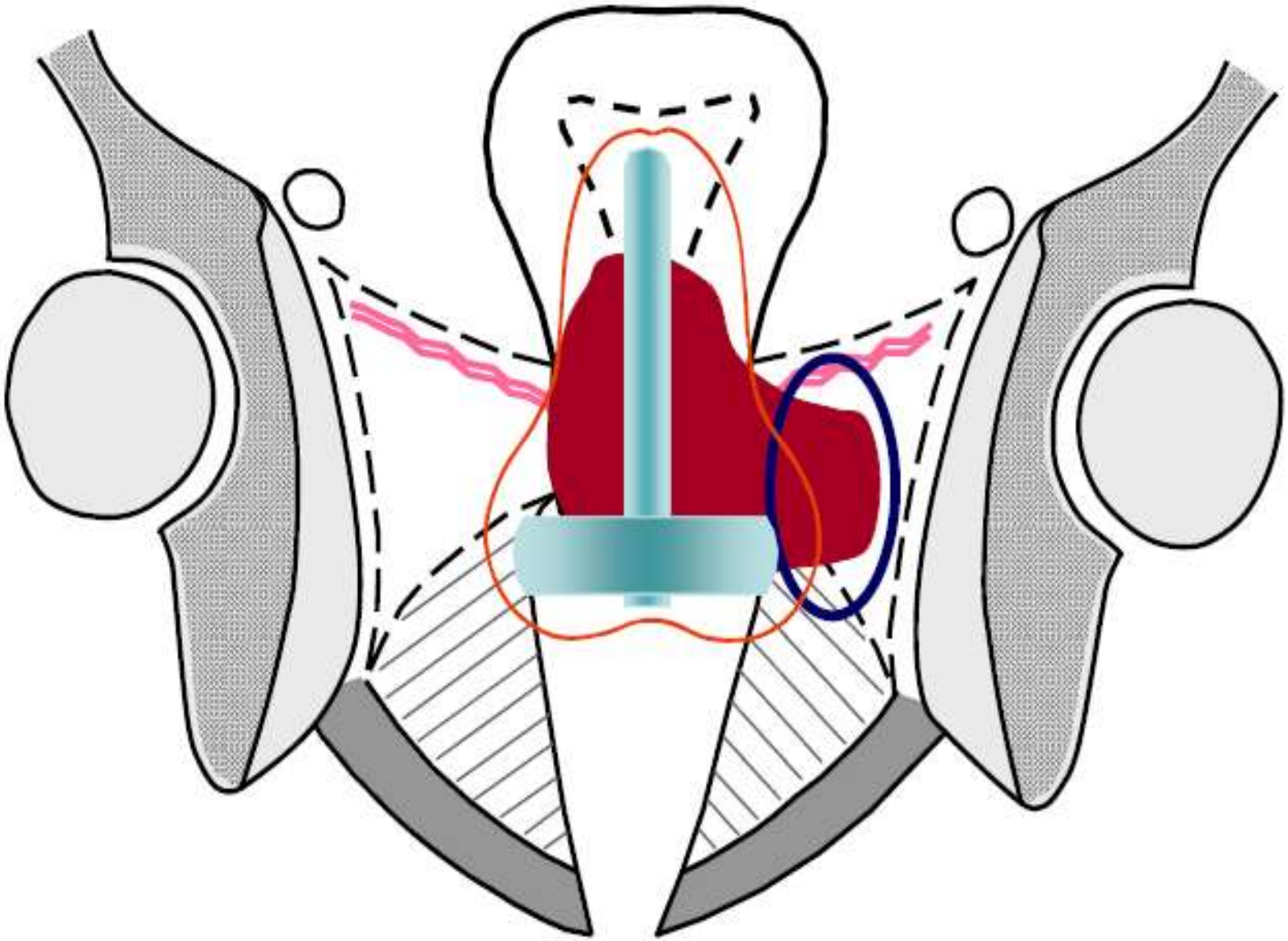
Covering the target volume with *prescribed dose* (—)



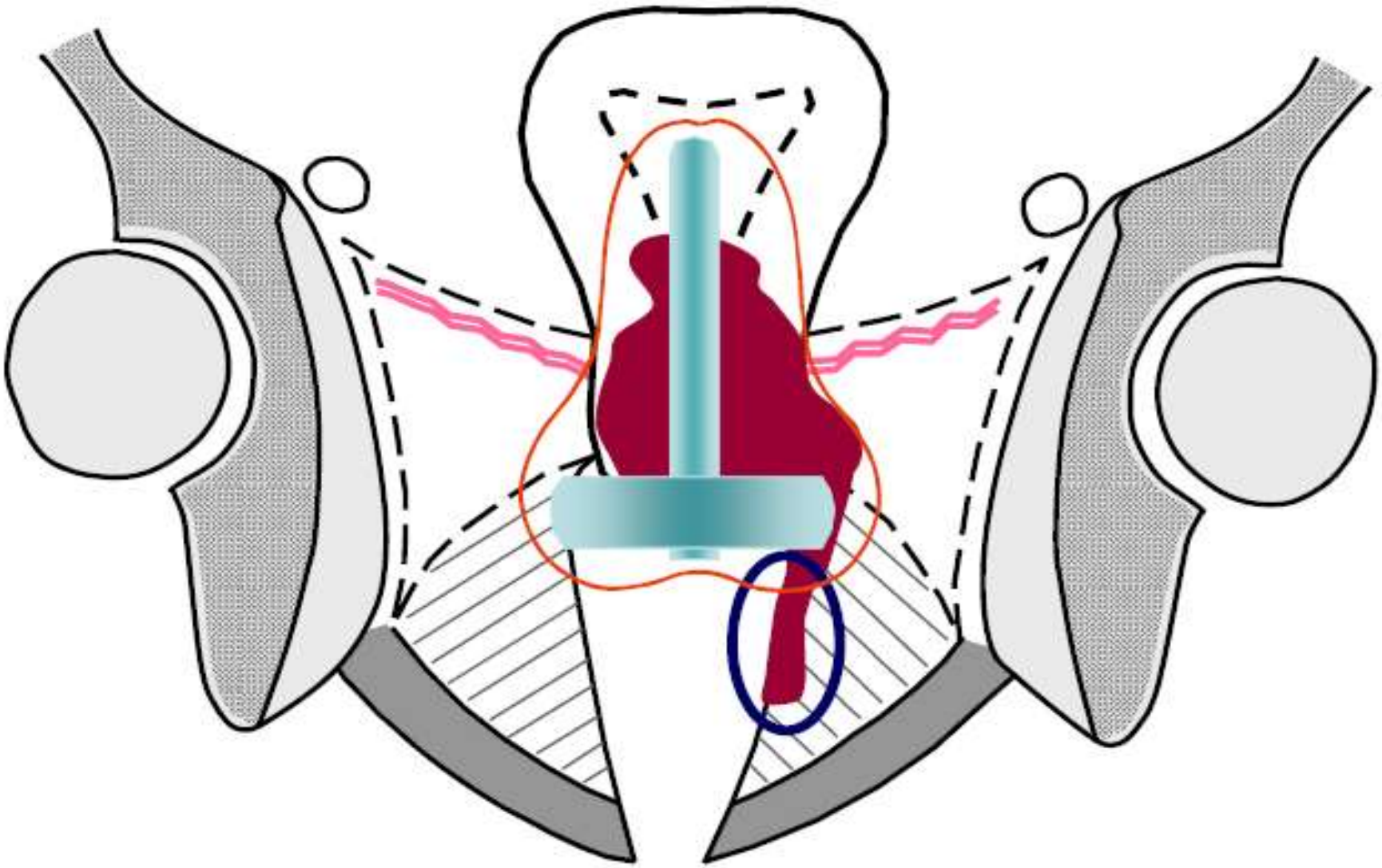
Transversal view, point A level

Mid-coronal view

Detection of inappropriate coverage



Detection of inappropriate coverage



Measures to improve applications: Imaging

- H.S. 47 years old patient with FIGO Stage IIIB, SCC, G3, cervical cancer
  - Post laparoscopic lymph node staging (6/24)
  - Proximal/middle involvement of left parametrium
  - Involvement of right parametrium to pelvic wall
  - Invasion of right fornix
  - Treatment: 45 Gy EBT+ 4x7Gy HDR-BT+Cisplatin

Patient: HS

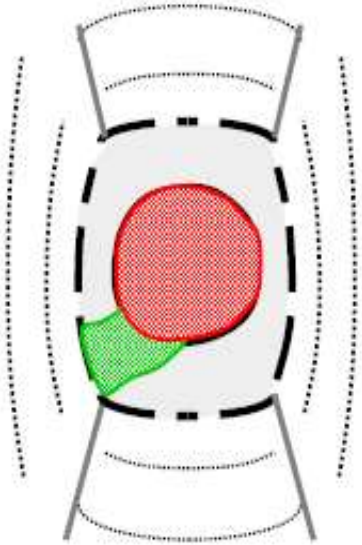
Clinical Drawing

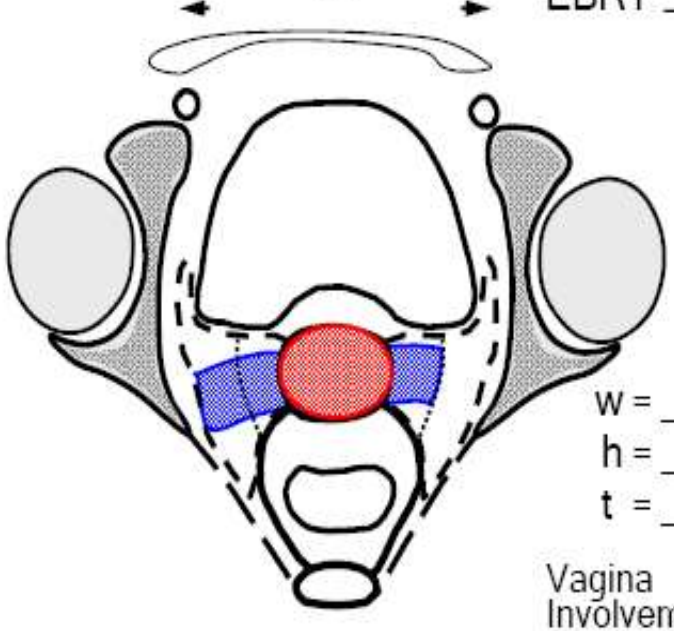
At Diagnosis [X]

At Brachytherapy [ ]

EBRT ___ Gy

	Infiltrative	Exophytic
Cervix		
Vagina		
Parametria		
Rectum or Bladder		



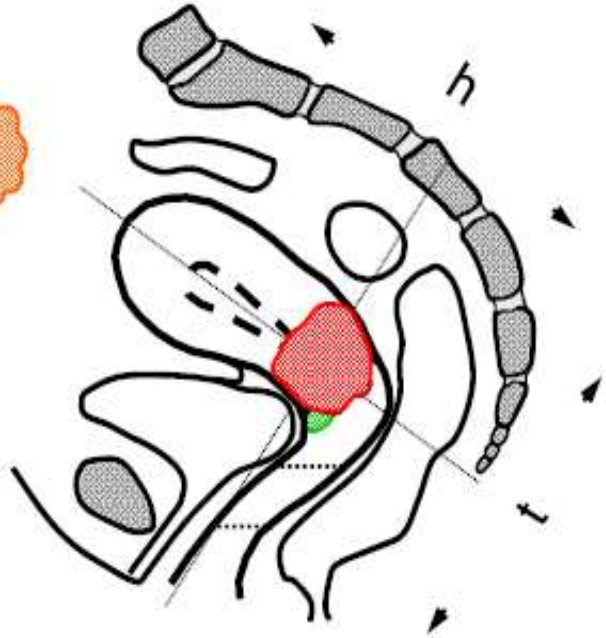


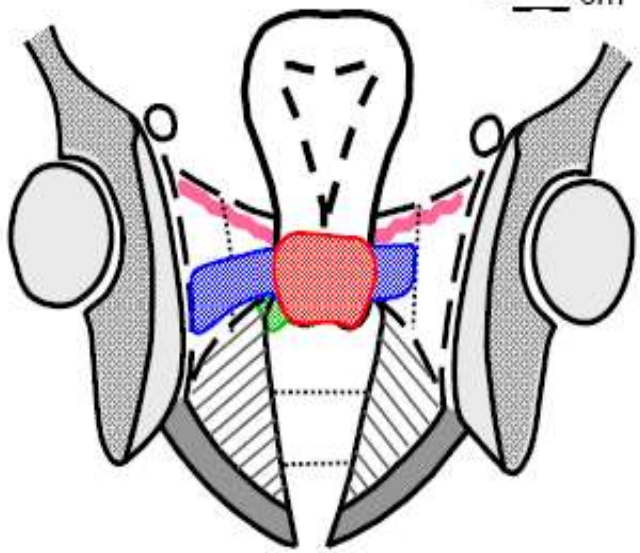
w = ___ cm

h = ___ cm

t = ___ cm

Vagina Involvement = ___ cm



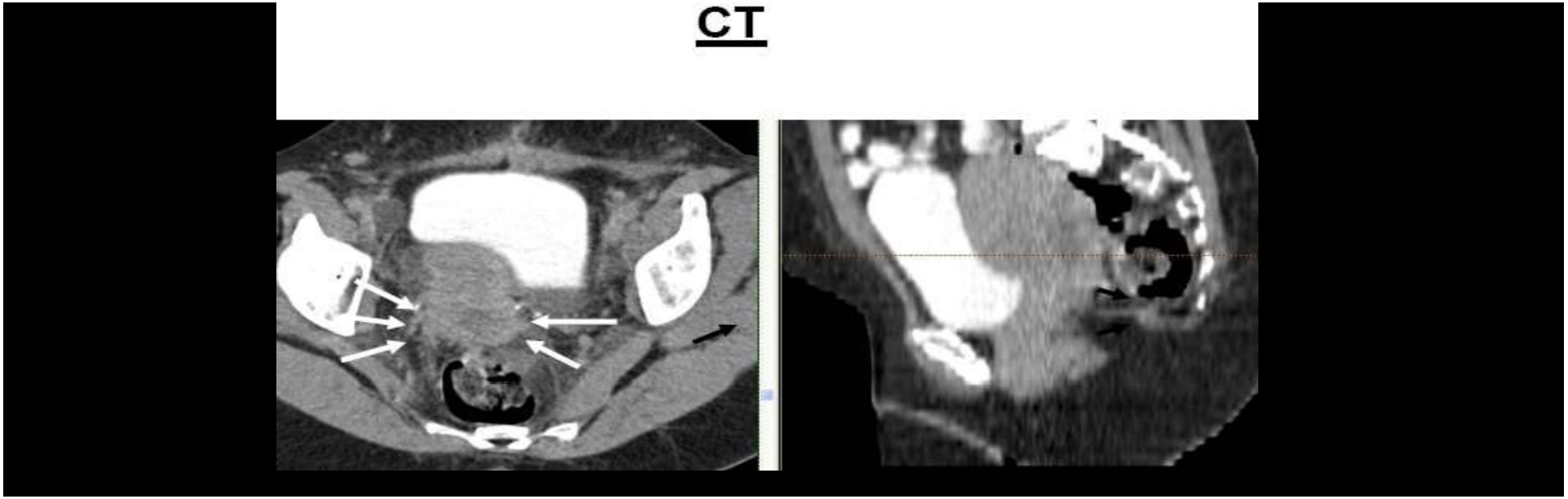


dd/mm/yy

___/___/___

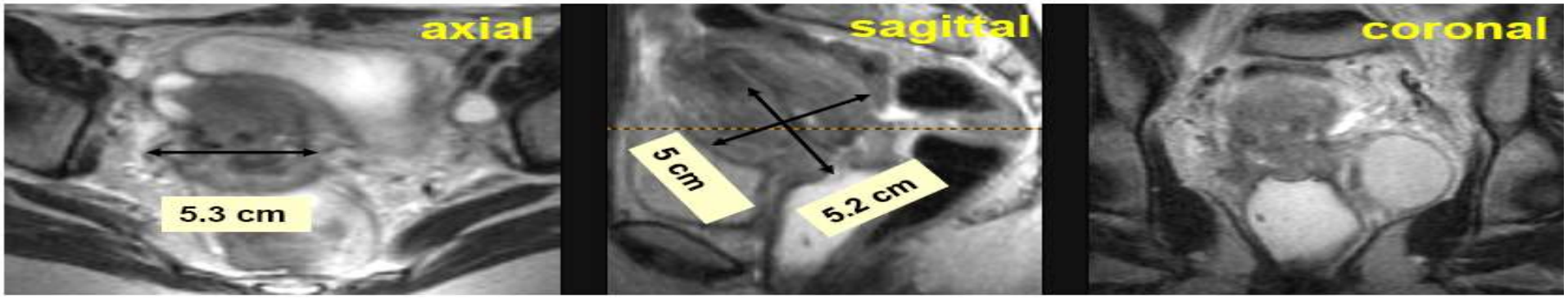
Signature

CT

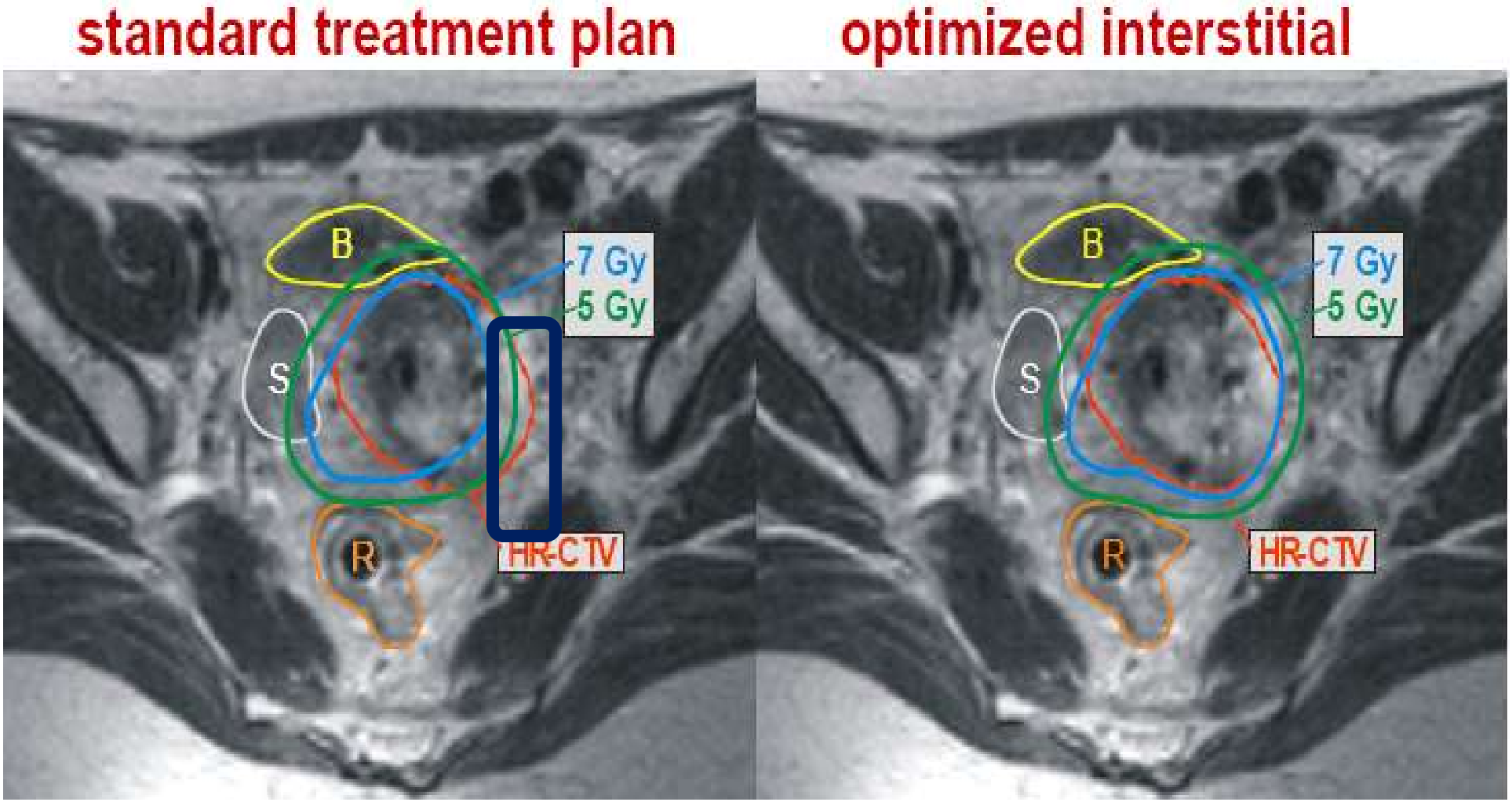


MRI

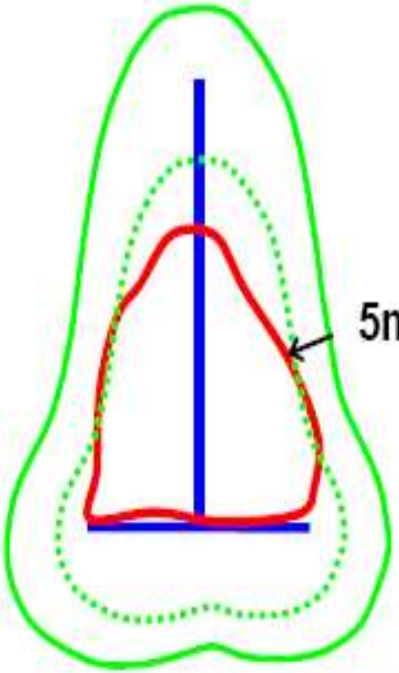
	Volume	Width	Thickness	Height
Diagnosis	69 cm^3	5.3 cm	5.2 cm	5 cm



Measures to improve applications
Optimised planning

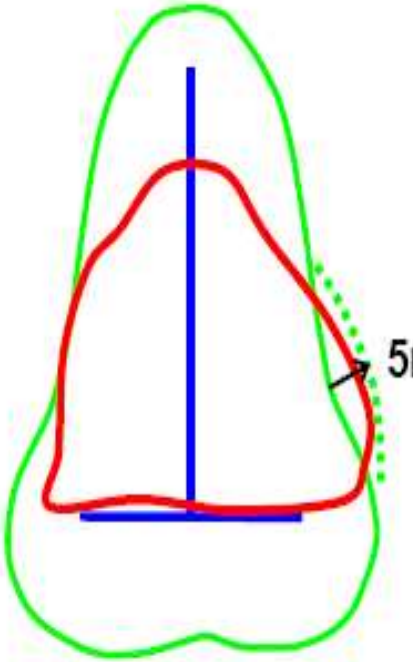


HR-CTV vol < 20cc



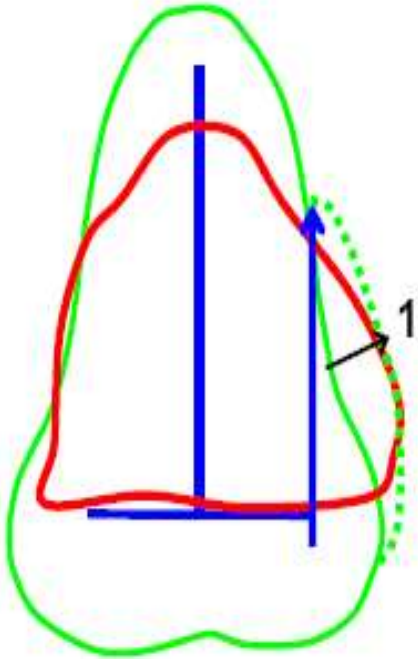
Intracavitary optimisation

HR-CTV vol ~ 30cc



Intracavitary optimisation

HR-CTV vol > 40-50cc



Optimisation with needles

- The biggest impact is actually redefining the whole target concept
- Moving from the point A concept on 2D imaging
- To 3D visualisation of the disease on sectional imaging & prescribing to this volume.

GEC-ESTRO recommendations

ELSEVIER

Radiotherapy and Oncology 74 (2005) 235–245

RADIOTHERAPY & ONCOLOGY

www.elsevier.com/locate/radonline

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group☆ (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV

Christine Haie-Meder[a,*], Richard Pötter[b], Erik Van Limbergen[c], Edith Briot[a], Marisol De Brabandere[c], Johannes Dimopoulos[b], Isabelle Dumas[a], Taran Paulsen Hellebust[d], Christian Kirisits[b], Stefan Lang[b], Sabine Muschitz[b], Juliana Nevinson[e], An Nulens[c], Peter Petrow[f], Natascha Wachter-Gerstner[b]

ESTRO project

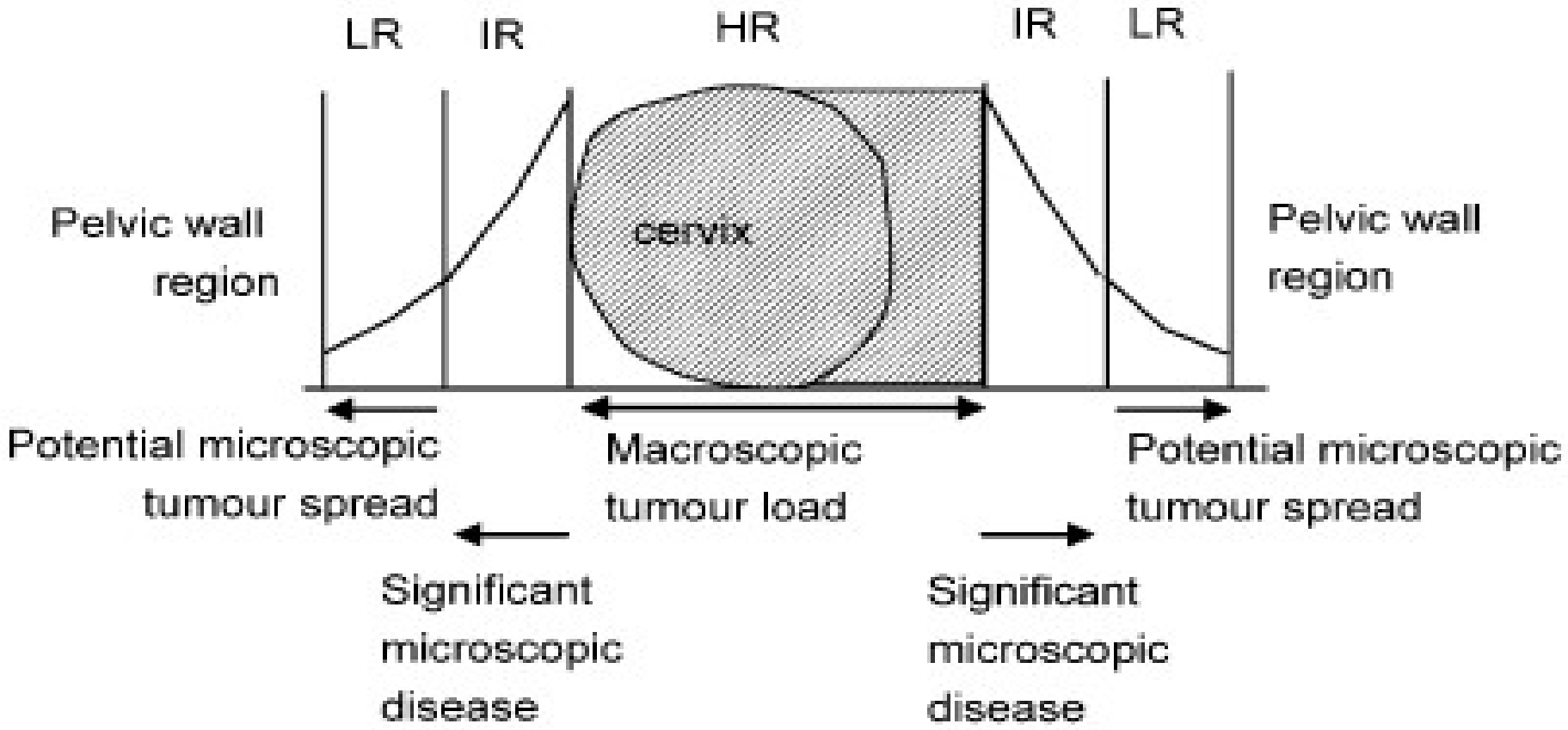
Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology

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]

3D sectional image based brachytherapy:

Targets

Three different target volumes according to cancer cell density



HR: High risk CTV
IR : Intermediate risk CTV
LR: Low risk CTV

GEC-ESTRO recommendations

Target definition

2 CTVs

A first target related to the extent of GTV **at diagnosis** :

with an intermediate dose prescribed to this target (60 Gy)

Intermediate risk CTV

A second target related to the extent of GTV **at time of BT** :

taking into account tumour extent at diagnosis.

with a high dose prescribed to this target (80-90 Gy)

High risk CTV

Gross tumour volume (diagnosis) (GTV_D) includes macroscopic tumour extension at diagnosis as detected by clinical examination (visualisation and palpation) and as visualised on MRI: high signal intensity mass(es) at fast spin echo sequences (FSE) T2 in cervix/corpus, parametria, vagina, bladder and rectum

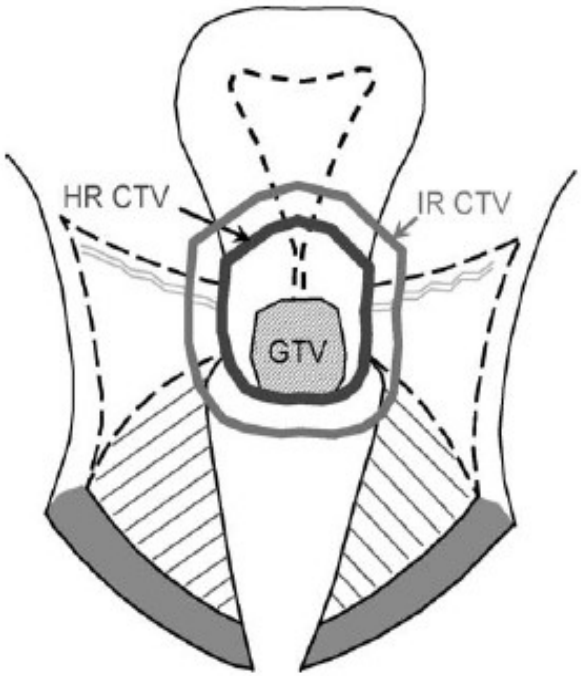
Gross tumour volume (BT) (GTV_{B1}, GTV_{B2}, GTV_{B3},...) for BT includes macroscopic tumour extension at time of BT as detected by clinical examination and as visualised on MRI: High signal intensity mass(es) (FSE, T2) in cervix/-corpus, parametria, vagina, bladder and rectum. In patients treated with upfront BT or with BT alone, GTV_B is identical with GTV_D.

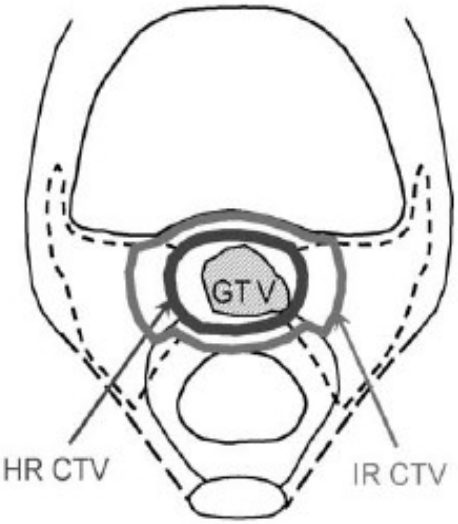
High risk CTV for BT (HR CTV_{B1}, HR CTV_{B2},...) carrying a high tumour load, includes $GTV_{B1, B2,...}$, always the whole cervix and the presumed extracervical tumour extension at time of BT.

Intermediate risk CTV for BT (IR CTV_{B1}, IR CTV_{B2},...) carrying a significant microscopic tumour load, encompasses high risk CTV[1] with a safety margin of 5–15 mm. Amount of safety margin is chosen according to tumour size and location, potential tumour spread, tumour regression and treatment strategy.

In case of good remission the IR CTV includes the HR CTV and the initial tumour extension at diagnosis and (b)). In case of poor tumour remission less than 10 mm including extracervical residual disease (e.g. parametria), a safety margin of minimum 10 mm into the direction of potential spread (parametria, vagina, uterus) is added to the HR CTV

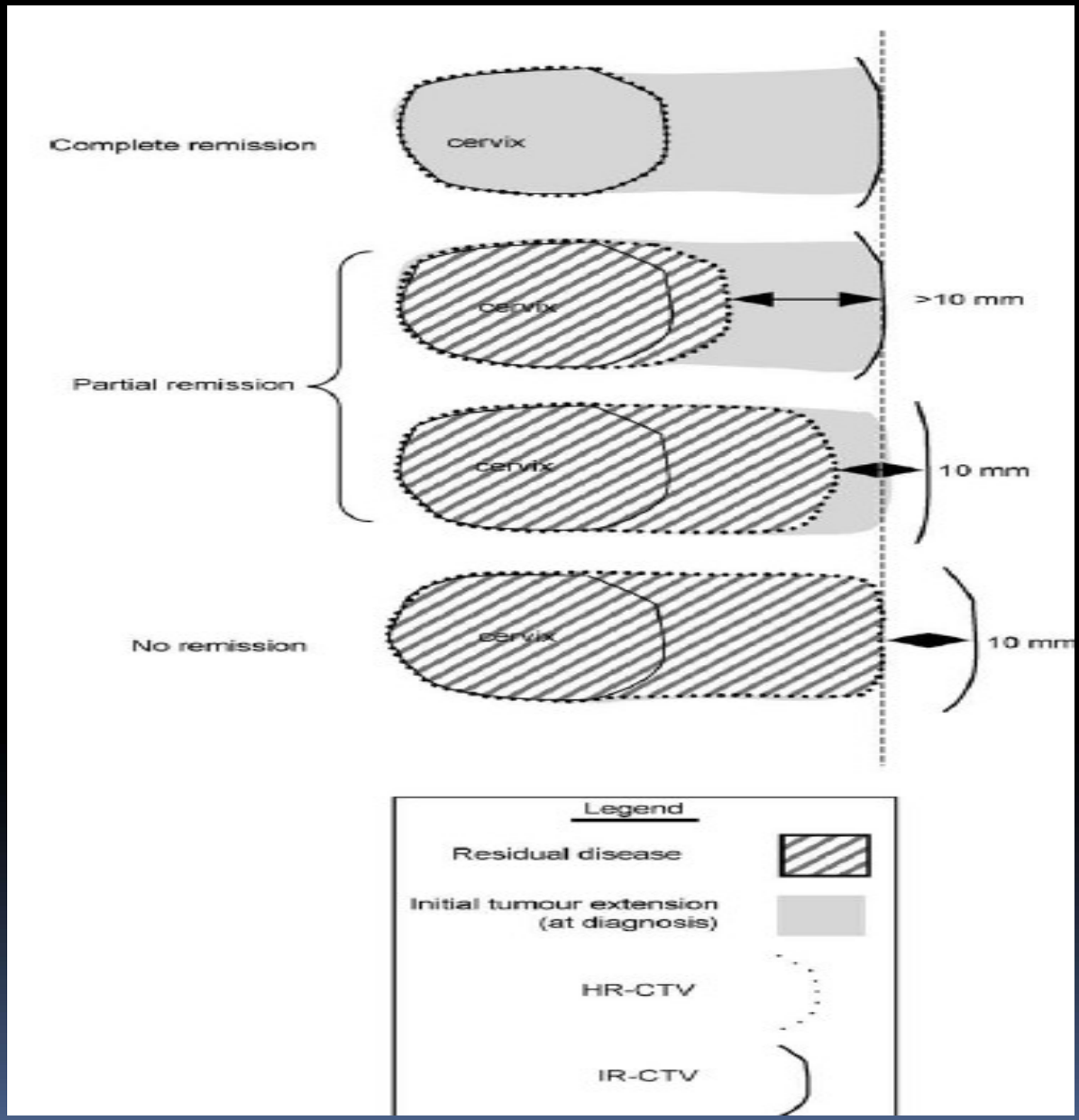
In case of stable disease a safety margin of 10 mm is added to the initial tumour extension at diagnosis which is superimposed on the anatomy as it presents at time of BT





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.*

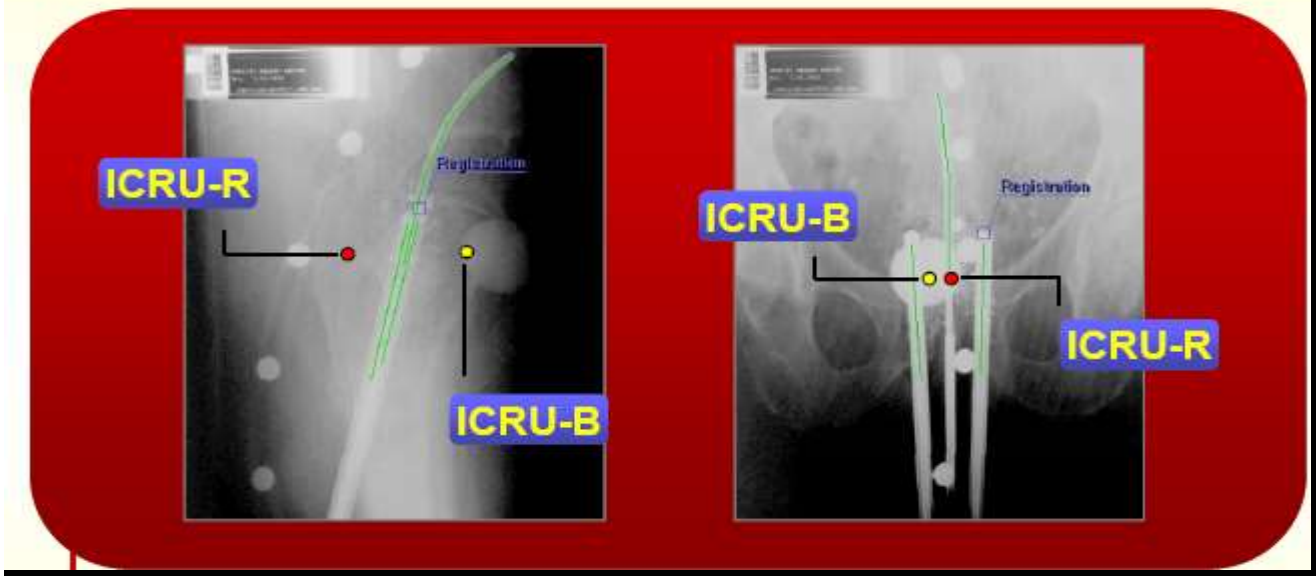
An *'intermediate risk' CTV* (IR CTV) with a major risk of local recurrence in areas that correspond to initial macroscopic extent of disease with at most residual microscopic disease at time of BT. The intent is to deliver a total radiation dose appropriate to cure significant *microscopic disease*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


Complete remission
cervix
Partial remission
cervix
>10 mm
cervix
10 mm
No remission
cervix
10 mm
Legend
Residual disease
Initial tumour extension
(at diagnosis)
HR-CTV
IR-CTV

3D sectional image based brachytherapy:

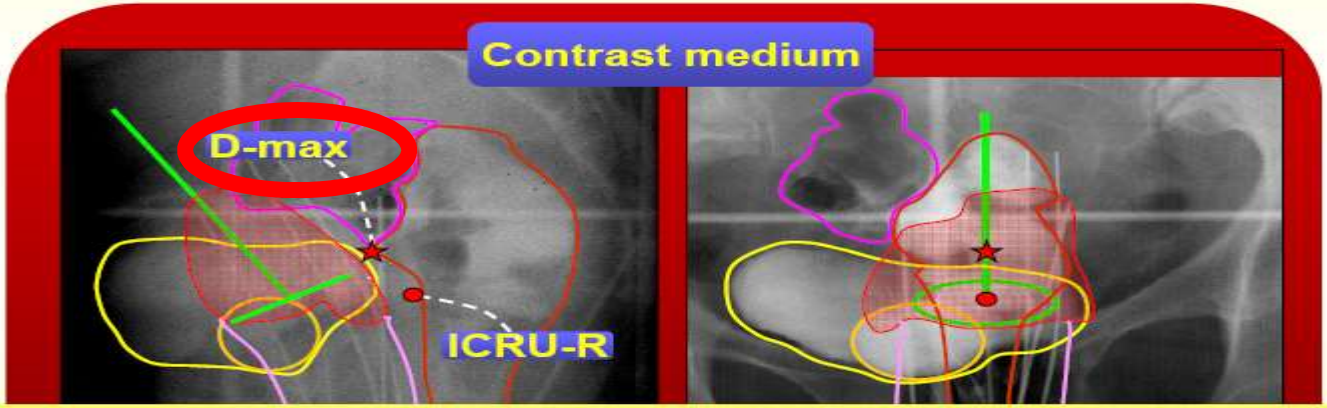
Organs at Risk (OARs)

Dose to bladder and rectum: ICRU Points



Do ICRU point-doses represent true D-max?

Looking for D-max: orthogonal radiographs

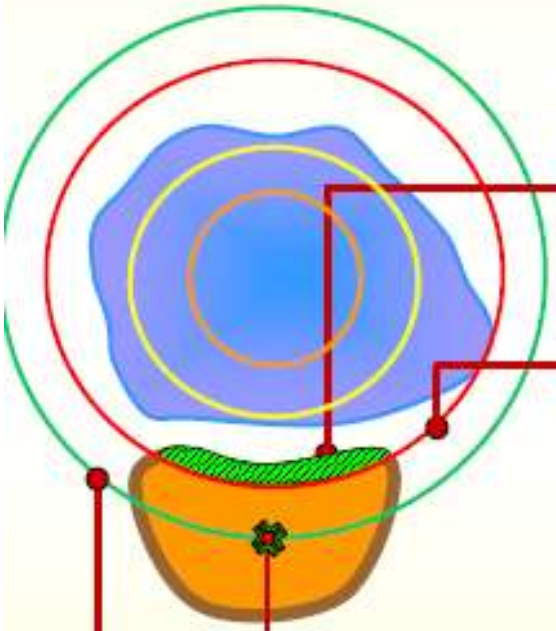


- ★ D-max located at proximal rectal points in 89%
- ★ D-max: better correlation with morbidity than ICRU-R

→Contrasting and multiple dose-points calculation advocated

Correlating tissue effect(s) with doses

More appropriate to correlate tissue effects with doses to tissue volumes (at different times-4D), rather than points...



Most exposed V of OAR

Minimum dose to this V

D, V of clinical relevance?

0.1 cm3	D0.1cc
1 cm3	D1cc
2 cm3	D2cc
5 cm3	D5cc

OAR Point (i.e. ICRU-R)

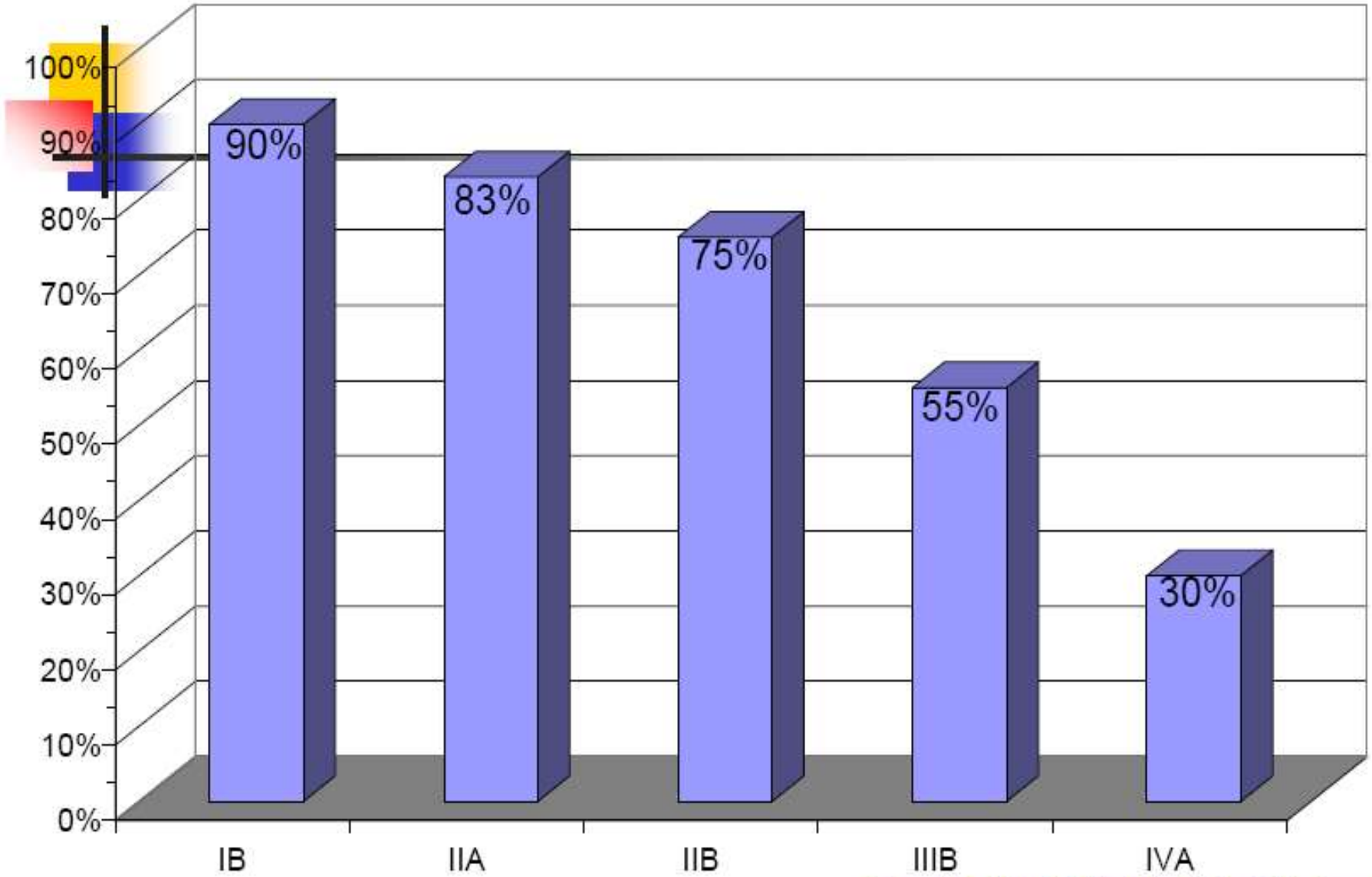
Dose to OAR Point

TISSUE EFFECT: damage to OAR

Pötter et al. Radioth Oncol 2006. Haie-Meder et al. Radiother Oncol 2005.

Results of treatment: classical & modern

TREATMENT RESULTS DEFINITIVE RADIOTHERAPY
2D X-RAY BASED PLANNING/POINT A



Gerbaulet A, Pötter R, Haie-Meder C. Cervix Carcinoma.
In: Gerbaulet A, Pötter R, Mazeron JJ, Meertens H, Van Limbergen E, eds. (2002)
The GEC ESTRO Handbook of Brachytherapy. Brussels:ESTRO

CONTINUOUS COMPLETE REMISSION
3 YEARS*

VIENNA 1993-2003: 335 patients

TREATMENT PERIOD	CCR	
	2-5cm (REC.)	>5cm (REC.)
2001-2003**	**96%** (1/34)	**90%** (3/34)
1998-2000**	**96%** (1/33)	**71%** (9/37)
1993-1997***	**90%** (5/65)	**67%** (27/124)

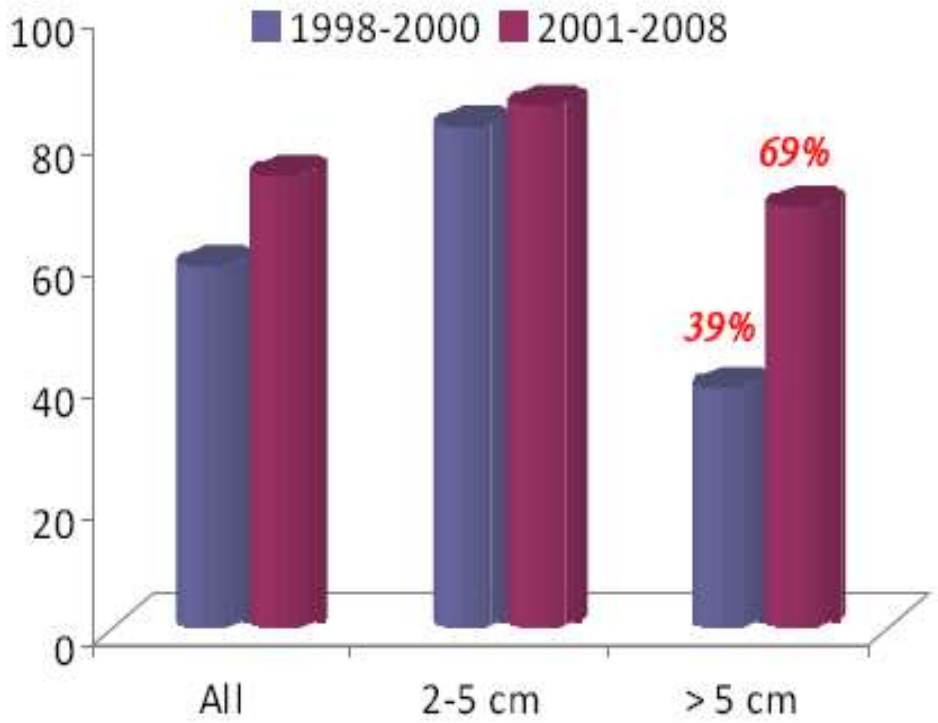
** *Pötter et al. 2007 Radioth Oncol*

*** *Pötter et al. Cancer Radioth 2000*

* *Actuarial data (Kaplan Meier)*

TREATMENT OUTCOME

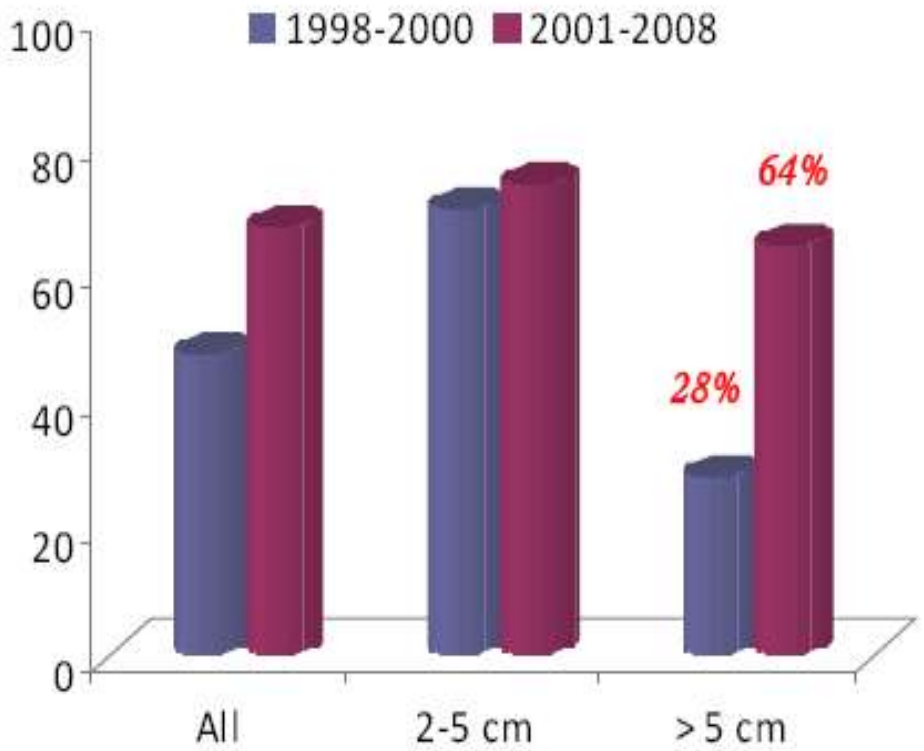
Cancer Specific Survival at 3 years (Vienna)



228 patients

TREATMENT OUTCOME

Overall Survival at 3 years (Vienna)



228 patients

Universitätsklinik für Strahlentherapie und Strahlenbiologie Wien

CONCLUSIONS

MRI assisted treatment planning
in defintive intracavitary cervical cancer brachytherapy
Plus risk adapted interstitial brachytherapy
plus 3D CRT +/- cis-PLATINUM

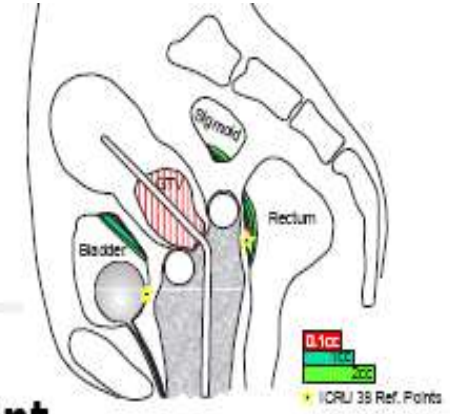
- **Local control**

  tumours < 5 cm: ~95% **D90: 85 Gy**

  tumours ≥ 5 cm: ~85-90% **D90: 90+ Gy**

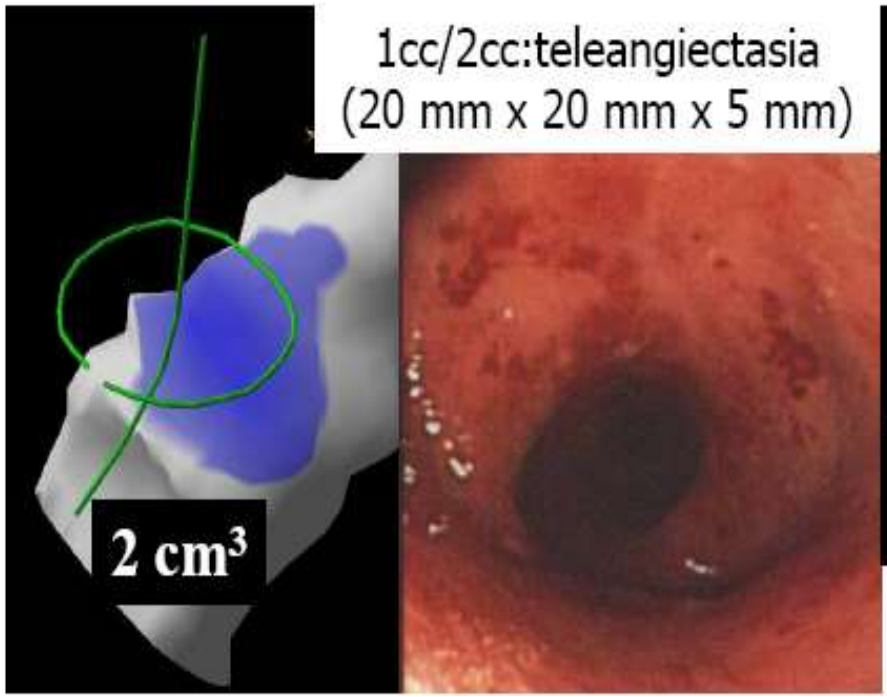
- **Low rate of late side effects**

3D-BASED DOSE VOLUME CONSTRAINTS FOR OAR

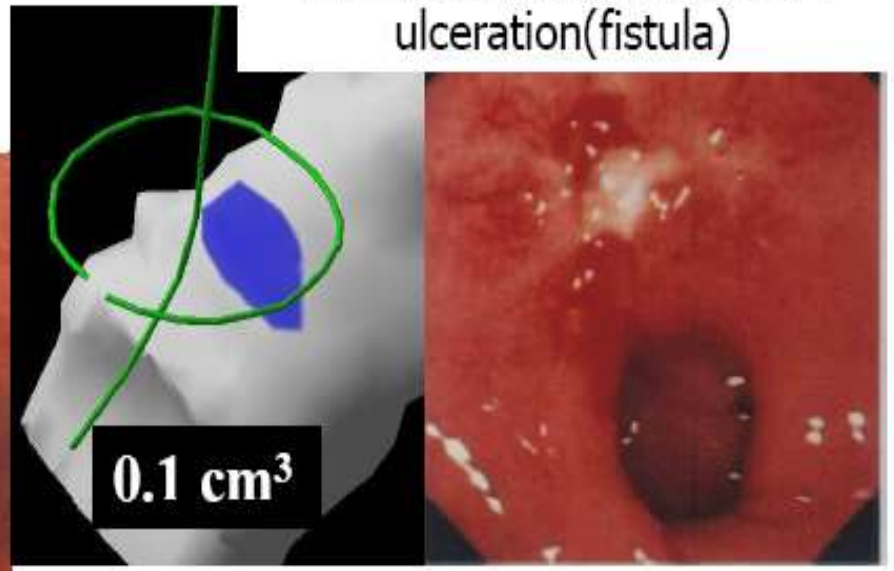


CLASSICAL MAX DOSE : in 3D no clinical relevant endpoint

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



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



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

*GYN GEC ESTRO Recommendations(II)
Radiotherapy and Oncology 2006

3D radiotherapy : dose to volumes and morbidity

Recommended constraints

Bladder : D2cc < 90Gy EQD2

Rectum : D2cc < 70 Gy EQD2

Sigmoid : D2cc < 70 Gy EQD2

Vagina : ???

2D radiotherapy : dose at points and outcome

MORBIDITY RATES AFTER RADIOTHERAPY (EBRT+BT)

	STAGE				
	IB	*IIA*	*IIB*	*IIIB*	*IVA*
Total no. of patients	415	137	391	326	23
G2 complications	51 (12%)	14 (10%)	65 (17%)	38 (12%)	3 (13%)
G3 complications	26 (6%)	23 (17%)	57 (15%)	45 (14%)	2 (9%)

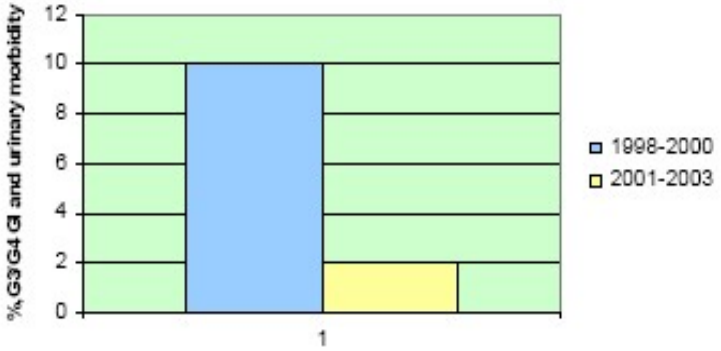
G3 morbidity > 10% ~ all stages

„Refinements in brachytherapy techniques are necessary to improve the present results“

Perez CA in Perez/Brady 1998

3D radiotherapy:dose to volumes and morbidity
Results-Vienna

LENT/ SOMA	G1 n	G2 n	G3 n	G4 n
BLADDER	7	11	1	2
RECTUM/ SIGMOID	2	7	2	2
SMALL BOWEL/COLON	5	0	0	0
VAGINA	78	36	5	0



•145 consecutive patients (1998-2003)

D2cm^3

Bladder 95 Gy EQD2

Rectum 55 Gy EQD2

Sigmoid 62 Gy EQD2

Dose escalation from 81 to 90 Gy and volume adaptation

ACTUARIAL SEVERE (G3/G4) OVERALL MORBIDITY RATE (GASTROINTESTINAL AND URINARY)

Pötter R, et al Radiother Oncol 2007

The Way Forward:
EMBRACE the change

EMBRACE

(European Study on MRI Based 3D Brachytherapy in Locally Advanced Cervical Cancer): A PROSPECTIVE OBSERVATIONAL MULTI-CENTRE STUDY

AIMS:

- Implementation of 3D MRI based cervix cancer brachytherapy in a multi-centre setting in Europe and outside Europe
- Quality control of MRI based brachytherapy in a multi-centre setting applying Gyn GEC ESTRO Recommendations for reporting
- Prospective assessment of outcome for disease, morbidity and quality of life in patients receiving MRI based cervix cancer brachytherapy
- Correlation of local control and dose volume parameters for GTV, HR CTV and IR CTV with the establishment of hazard ratios and dose effect curves for the primary tumour
- Correlation of late morbidity and dose volume parameters for the OAR (rectum, sigmoid, bladder) with the establishment of hazard ratios and dose effect curves for OAR.
- Validation of the GYN GEC ESTRO recommendations in a multi-centre setting

Study Centers

Vienna
Aarhus
Utrecht
Leiden
Leuven
Ljubljana
London
Arnhem
Paris
Mumbai

Pittsburgh
Milwaukee
Kaposvar
Maastricht
Trondheim
Leeds
Chandigarh

17 Centres
Europe-13
N.America-2
Asia-2

Thank you!