

Basics of Cervix Cancer Brachytherapy

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Incidence Cervix:
445,000

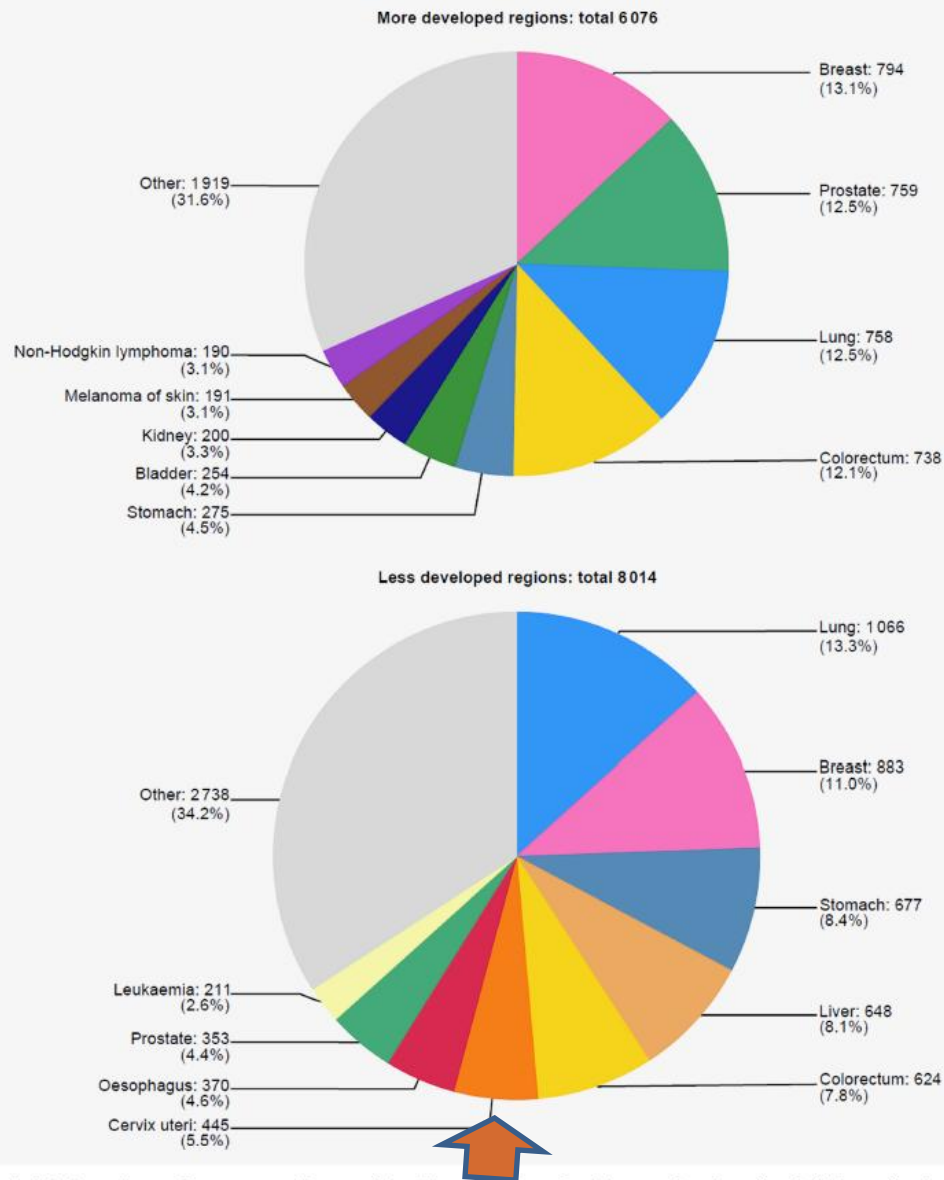


Figure 3. Estimated global numbers of new cases (thousands) with proportions for (a) more developed and (b) less developed regions, both sexes combined, 2012. The area of the pie is proportional to the number of new cases.

Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012

Int J Cancer 2015

Jacques Ferlay¹, Isabelle Soerjomataram¹, Rajesh Dikshit², Sultan Eser³, Colin Mathers⁴, Marise Rebelo⁵, Donald Maxwell Parkin⁶, David Forman¹ and Freddie Bray¹

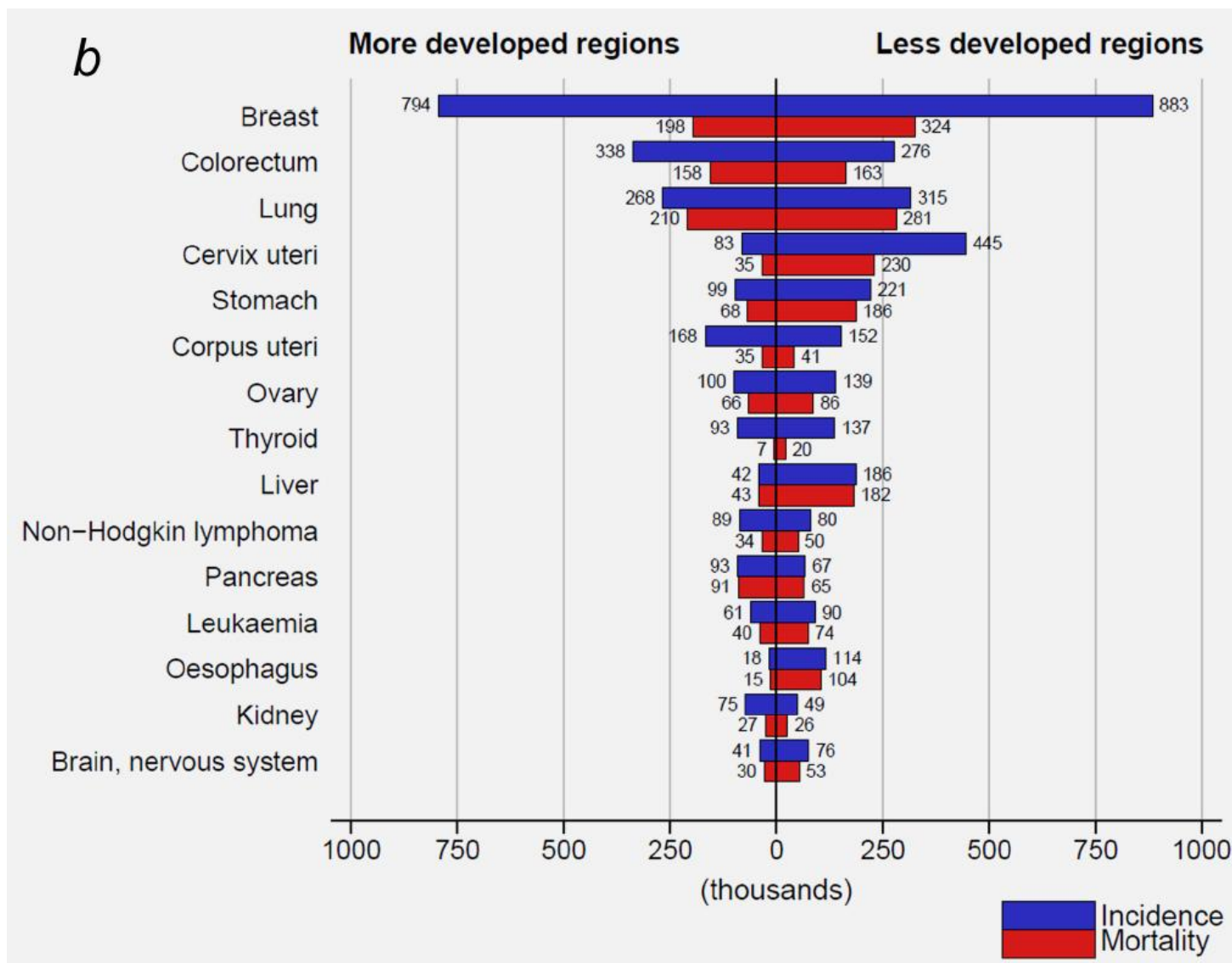
Cervix Cancer Demographics

- 87% of cervix cancer occurs in less developed regions of the world
- 18 fold difference in mortality rate for cervix cancer depending on region of the world

Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012 Int J Cancer 2015

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Incidence and Mortality in More and Less Developed Regions for Women



Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012

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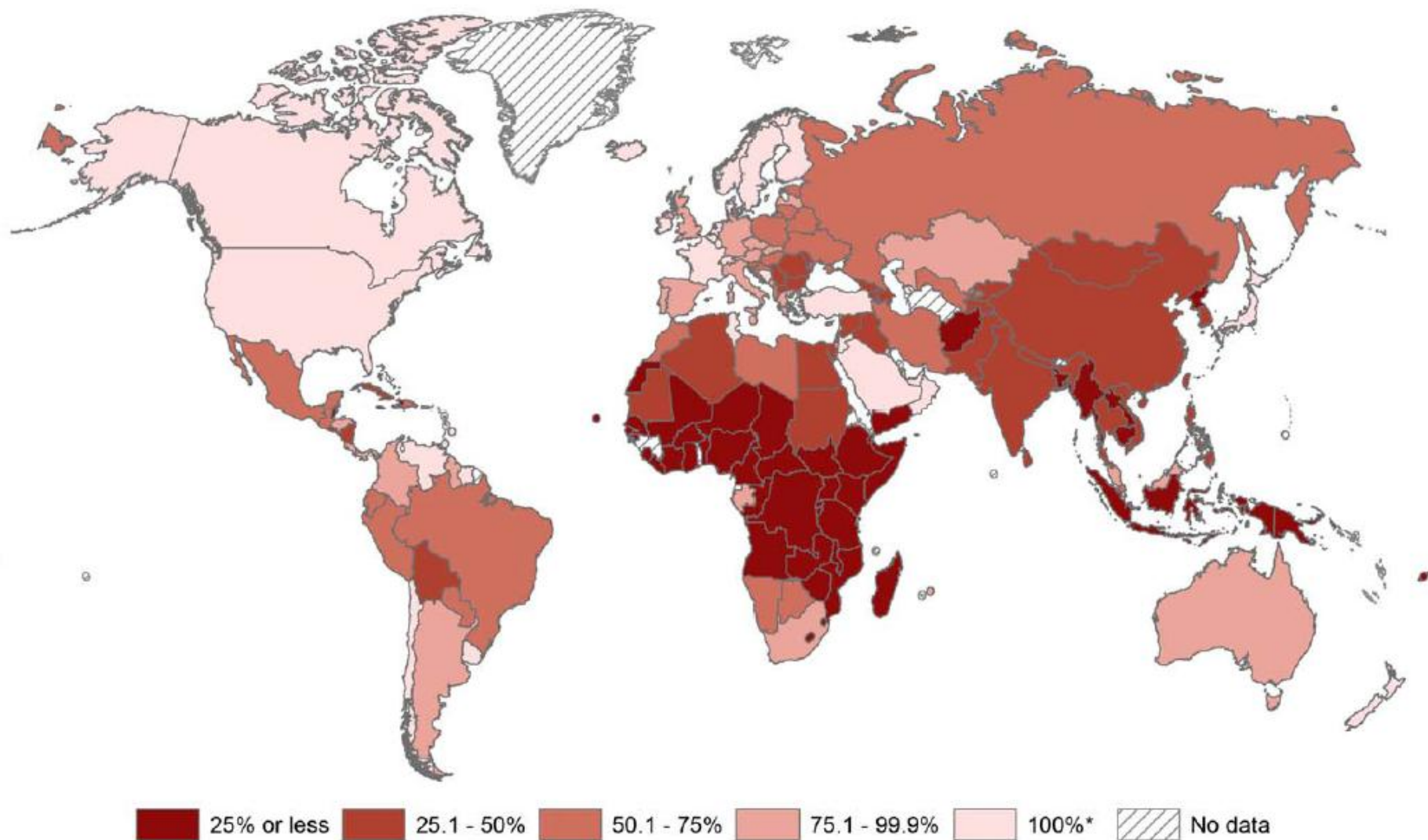
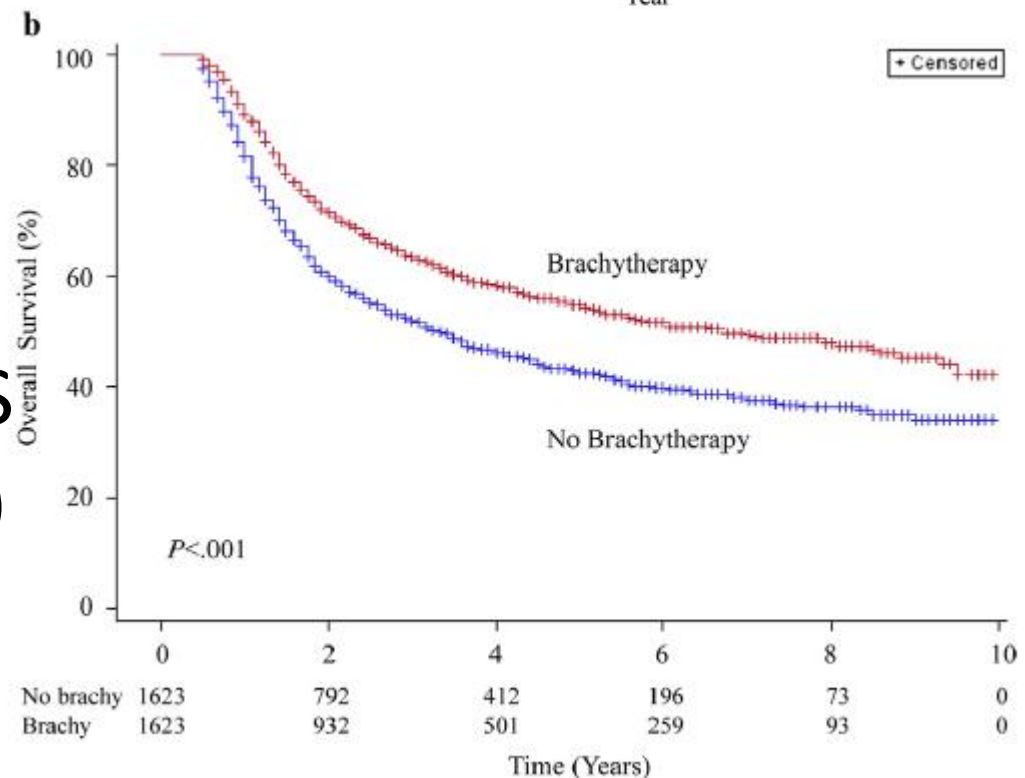
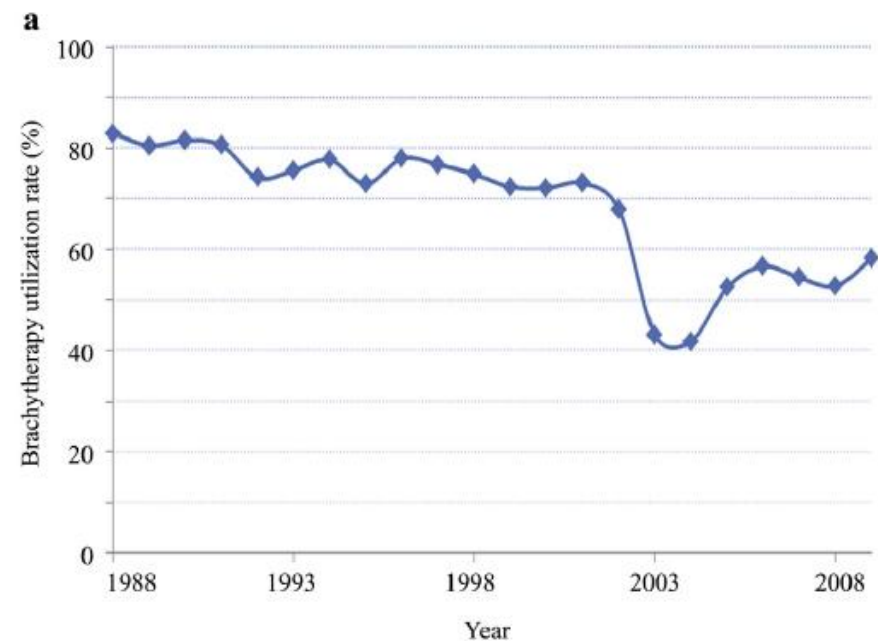


FIGURE 3. Estimated Percentage of Patients Able to Access Radiotherapy, 2013.

Trends in Brachytherapy in the US

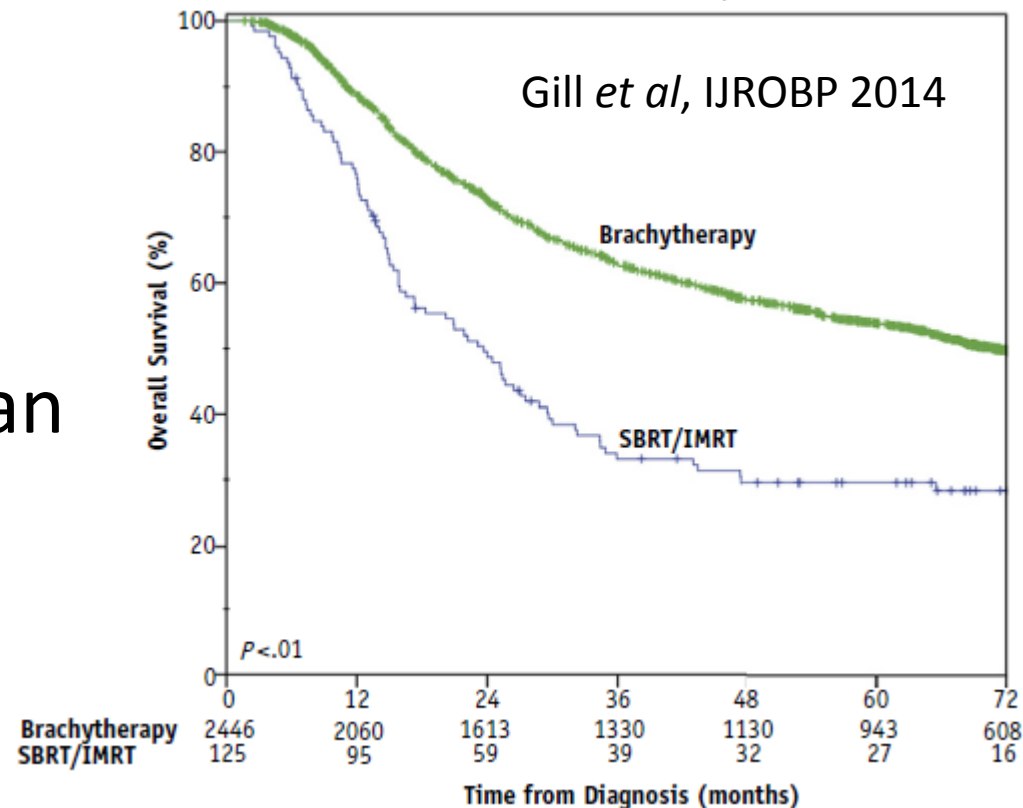
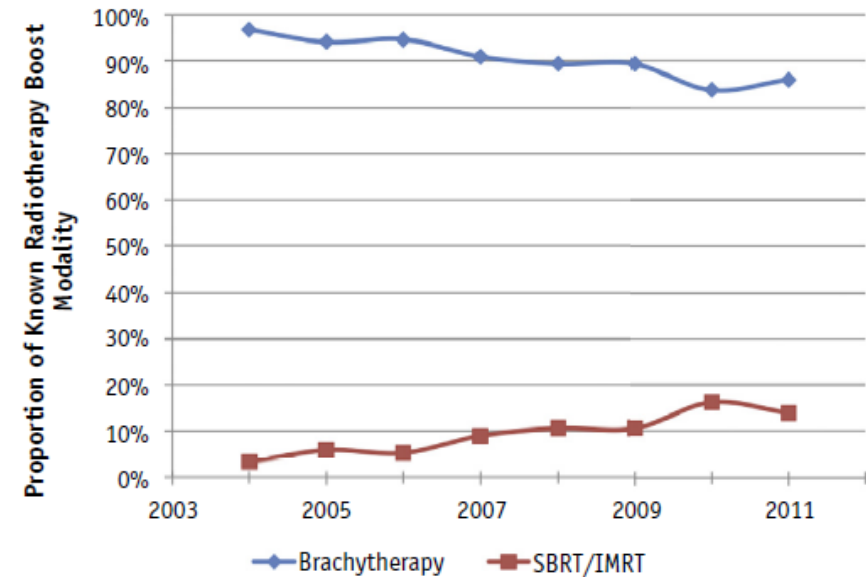
Han *et al* IJROBP 2013

- SEER study
- 7359 patients
- 1988-2009
- 37% EBRT alone
- Brachytherapy use \uparrow OS
HR 0.66 (95% CI 0.6-.74)

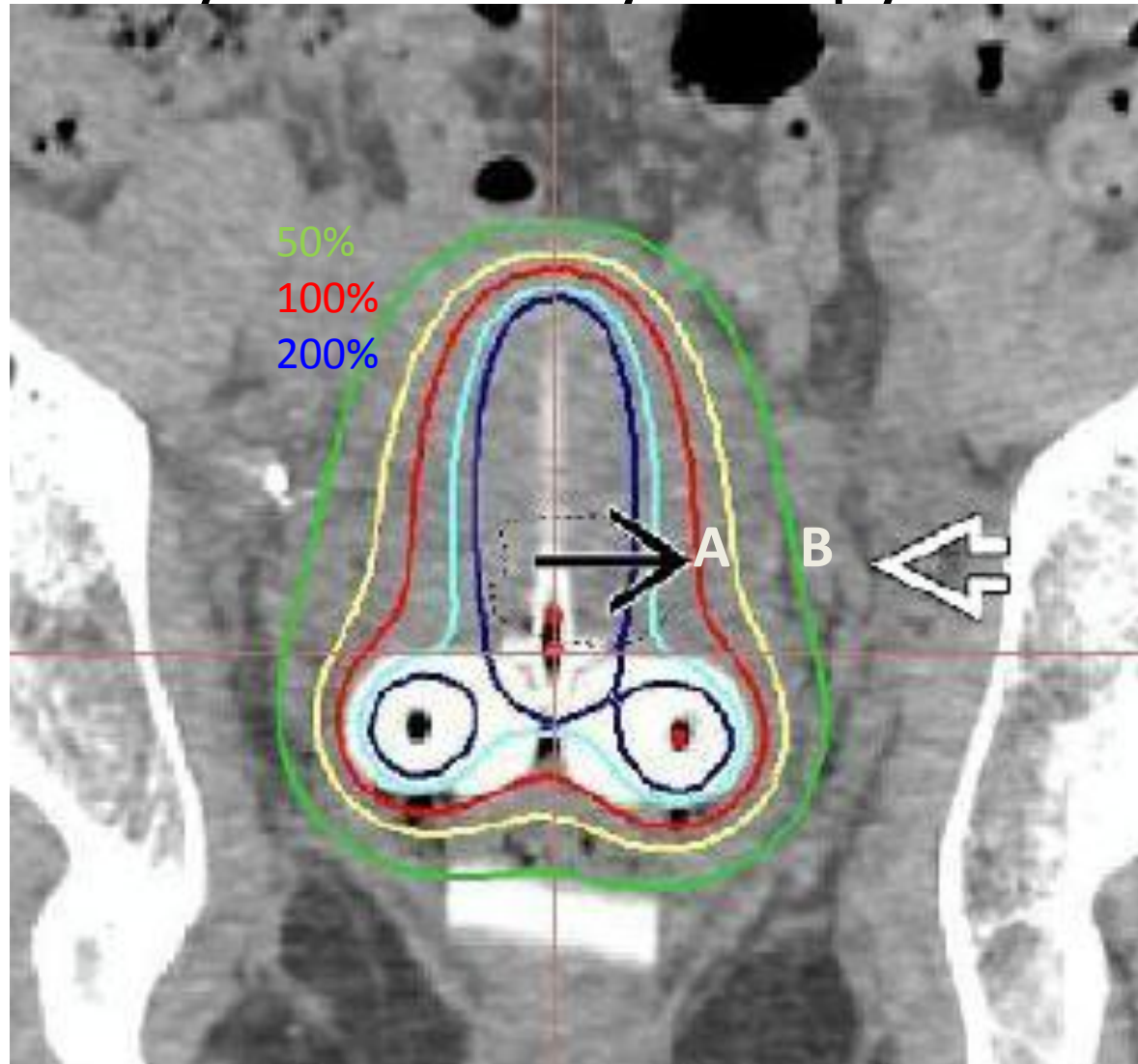


Is type of boost important in cervix cancer?

- NCDB analysis
- 2004-2011
- 7654 patients
- SBRT/IMRT survival decrement was > than omission of chemo ($p < 0.01$)



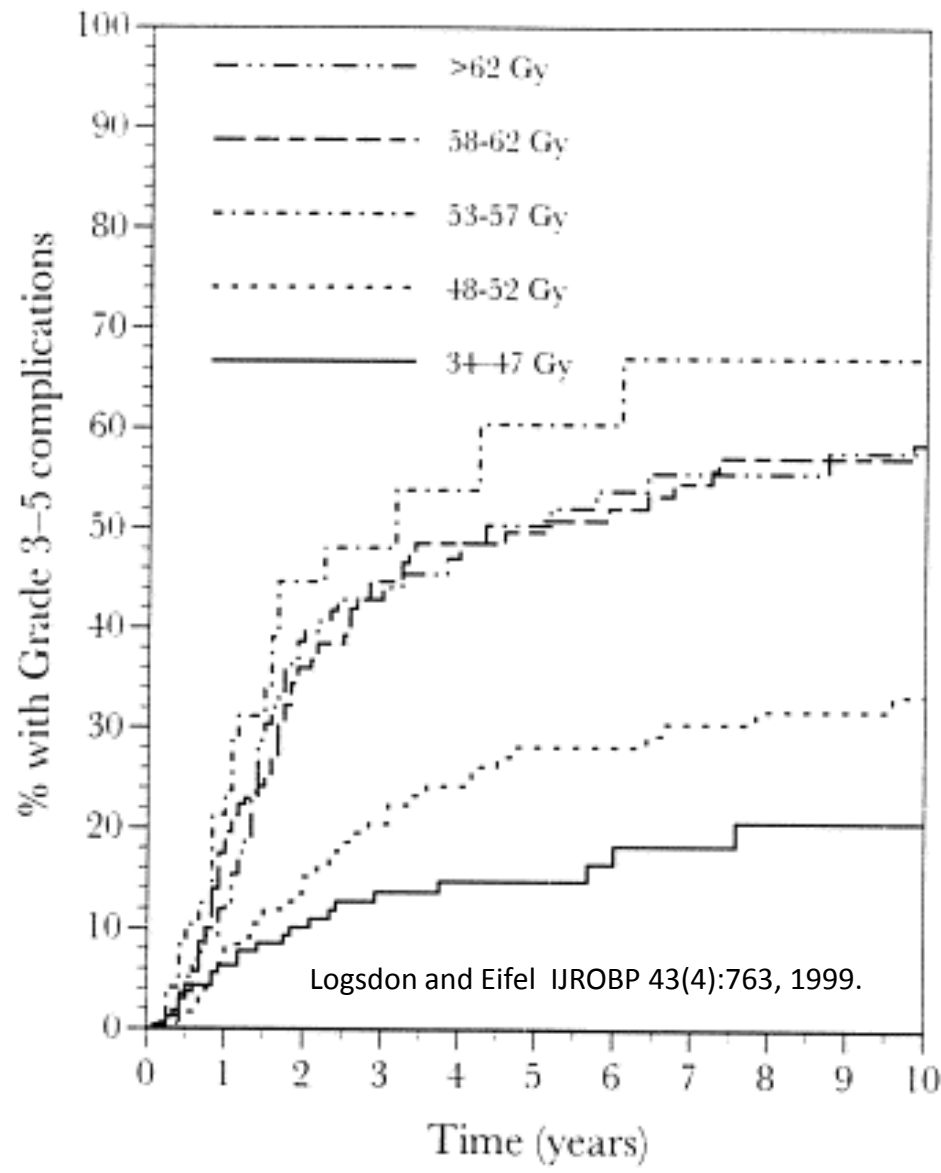
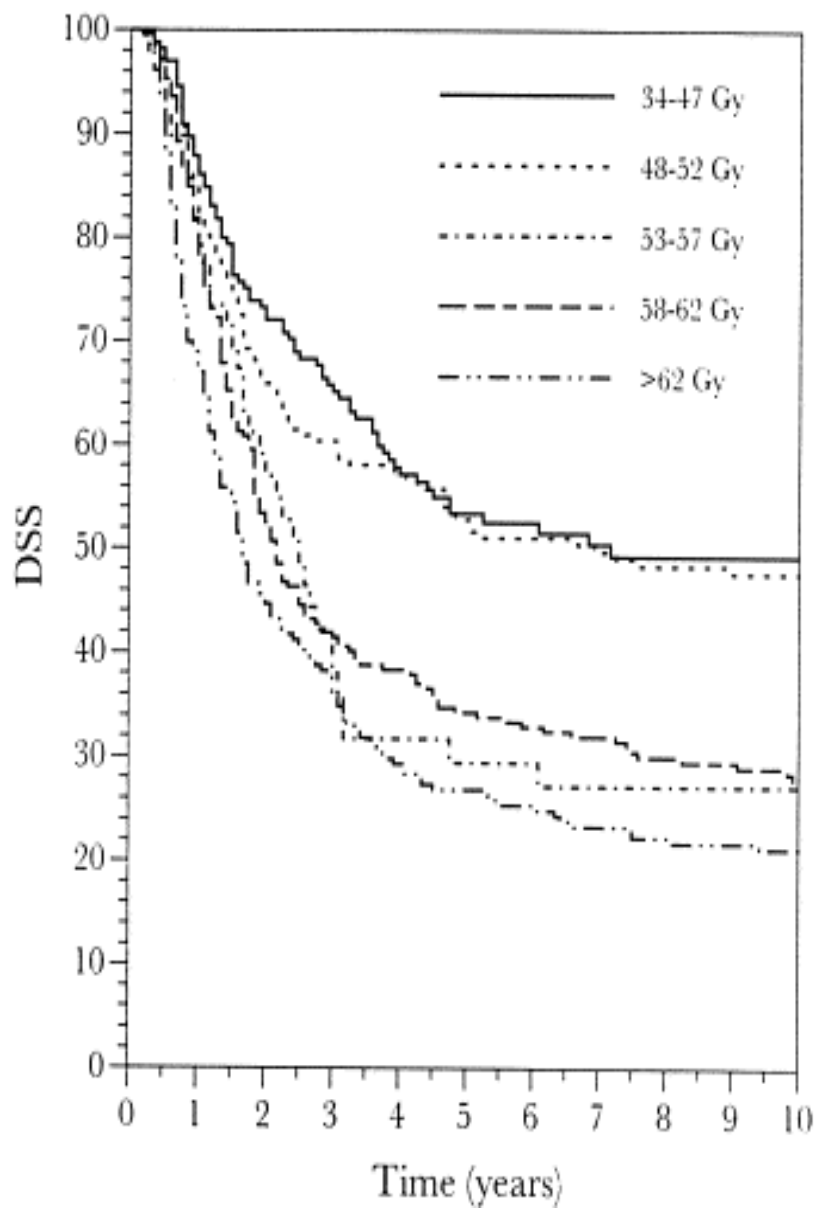
Why does Brachytherapy work?



In a study of 125 patients from Washington University, probit analysis estimated the mean dose required for $\geq 90\%$ local control to be 260 Gy ($P < .001$).

Dyk et al IJROBP, 90:794-801, 2014

Successful Tx of advanced cervix cancer requires combination of external beam and brachytherapy



Logsdon and Eifel IJROBP 43(4):763, 1999.

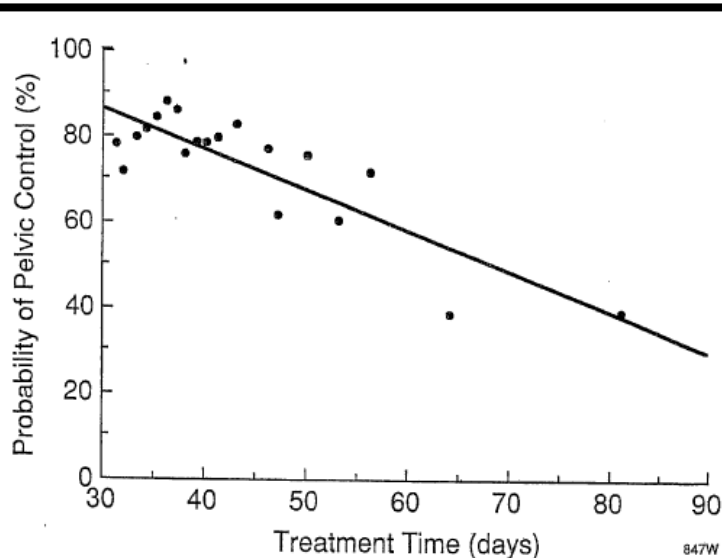
High dose rate vs low dose rate intracavity brachytherapy for carcinoma of the uterine cervix cancer: Systematic review and meta-analysis

Lee KK et al Brachytherapy 14:449-457, 2015

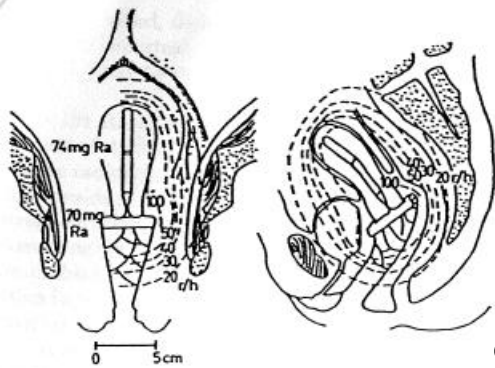
- 18,937 patients
- 15 articles
 - 3 randomized trials
 - 12 retrospective studies
- No difference in survival, pelvic recurrence, rectal and bladder complications
- Liu et al Cochrane Meta-analysis: same conclusion

Importance of Overall Treatment Time

Study	Year	N	Outcome
PMH	1992	830	LC
Inst. Gustave Roussy	1993	386	LC OS
Patterns of Care	1993	837	LC OS
Washington Univ.	1995	1224	LC CSS
Univ. of Wisconsin	2013	206 RT 166 CRT	DFS not sig.

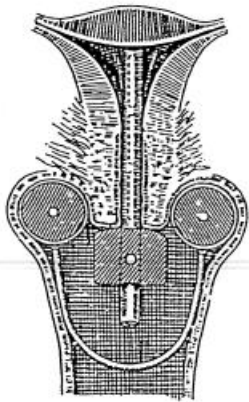


~1% loss of local control per day

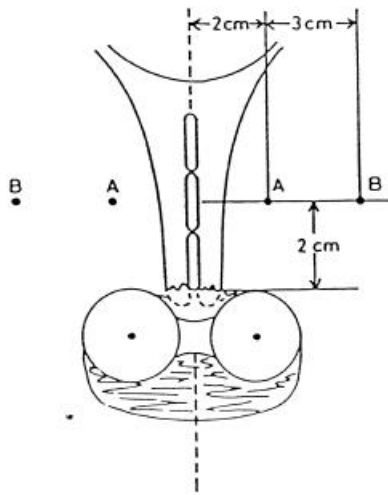


Stockholm

1. Historic Good Results
2. Imaging → Renaissance



Paris



Manchester

Stage	% 5 yr cure (RT)
I	79
II	41
III	27
Regaud, Paris: 1922-26, n=329	

Anesthesia

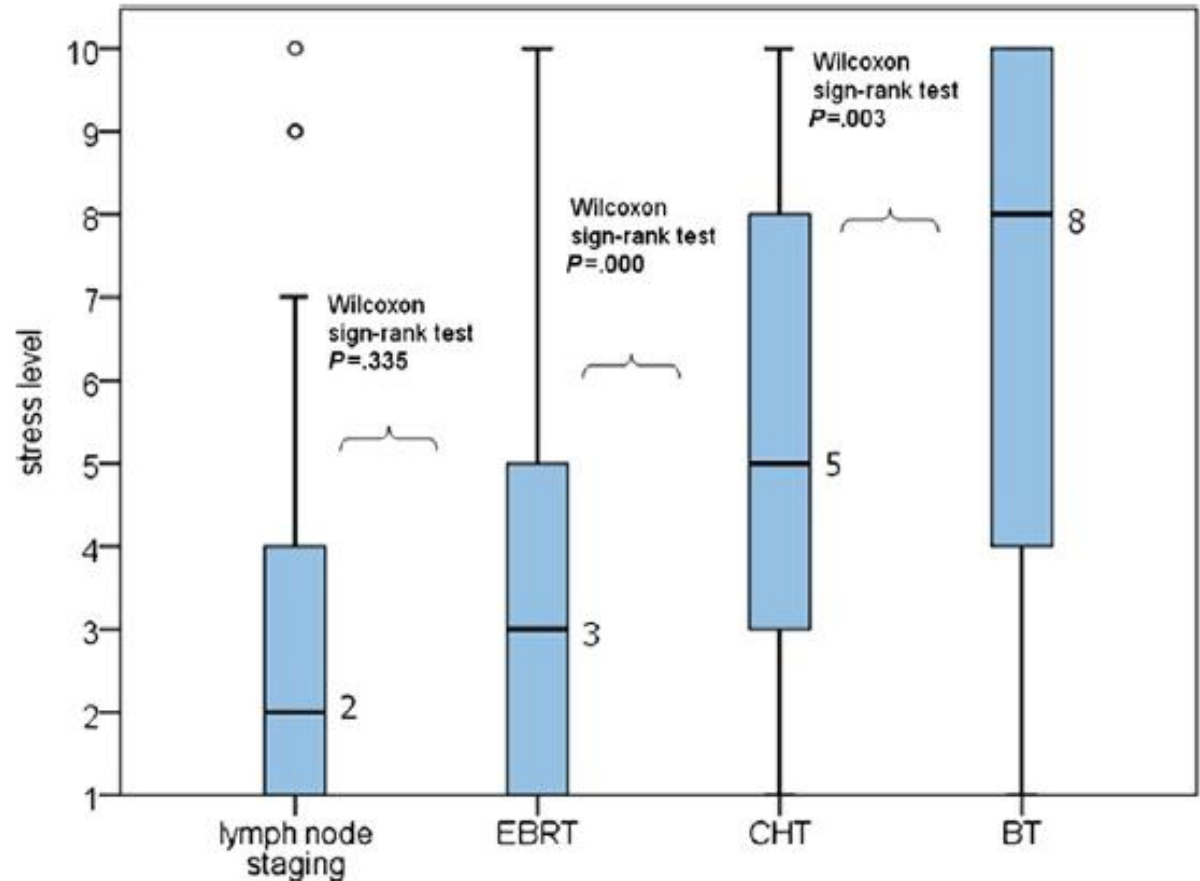
- General
 - Laryngeal Mask Airway
 - Intubation
- Regional
 - Spinal
 - Epidural
- Monitored Anesthesia Care (MAC)
 - Procedural sedation
- Local
 - Pudendal block
- Oral medicines (Smit sleeve in place)
 - Narcotics
 - Benzodiazepines



Posttraumatic Stress Disorder After High-Dose-Rate Brachytherapy for Cervical Cancer With 2 Fractions in 1 Application Under Spinal/Epidural Anesthesia: Incidence and Risk Factors

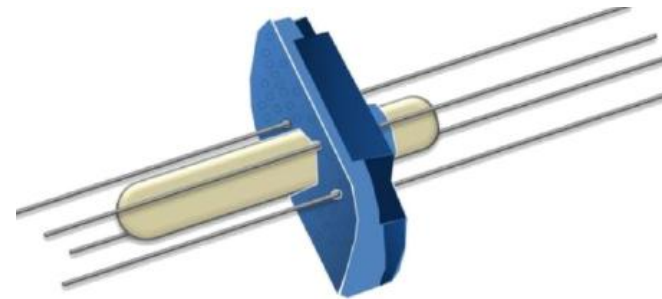
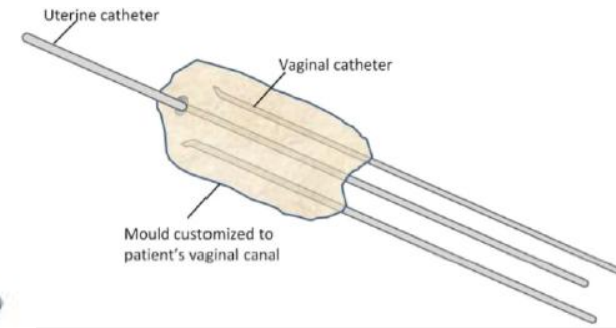
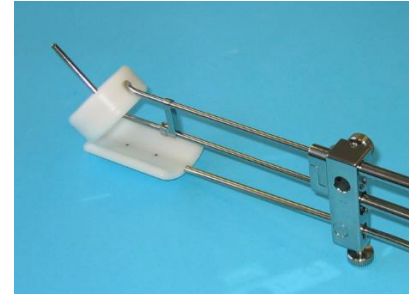
Kirchheiner K et al IJROBP 89(1):260-7, 2014.

- N=50
- Validated questionnaires
- Acute Stress in 30%
- PTSD in 41%
- Helpful Experiences
 - Treatment team
 - Psychological support
 - Positive attitude
- Stressful Factors
 - Pain
 - Organizational problems
 - Immobility



Applicator Choice

- Tandem and Ovoids
 - Fletcher
 - Henschke
 - Rotterdam
- Tandem and Ring
- Vaginal Mold
- Combination applicators
 - Utrecht
 - Vienna
- Tandem and Cylinder
 - Miami
- Interstitial
 - Template based
 - Free hand
- Angle of tandem
- Diameter of upper vagina



INTRAOP US

- CT-based study showed a perforation rate of 14% (experienced investigators)
 - Still occurred 8% when physician was confident of correct placement
 - Physician concern, age > 60, and tumor size were predictors of perforation
- US should be used to avoid perforation
 - If perforation: consider antibiotics
- US can be used for treatment planning and IGBT

Barnes et al IJGC 17(4):821-6, 2007

Importance of Vaginal Packing

- Essential aspect of good technique
- For MRI packing
 - Ultrasound gel (best contrast)
 - Conjugated estrogen cream + ultrasound gel
 - Gadolinium
- For Xray or CT packing
 - Radiopaque wire impregnated gauze
 - Contrast soaked gauze

Swanick et al. Brachytherapy, 14(3):385-9, 2015

Does Implant Technique Effect Survival?

Corn et al. Gyn Onc 53:294300,1994

Ideal

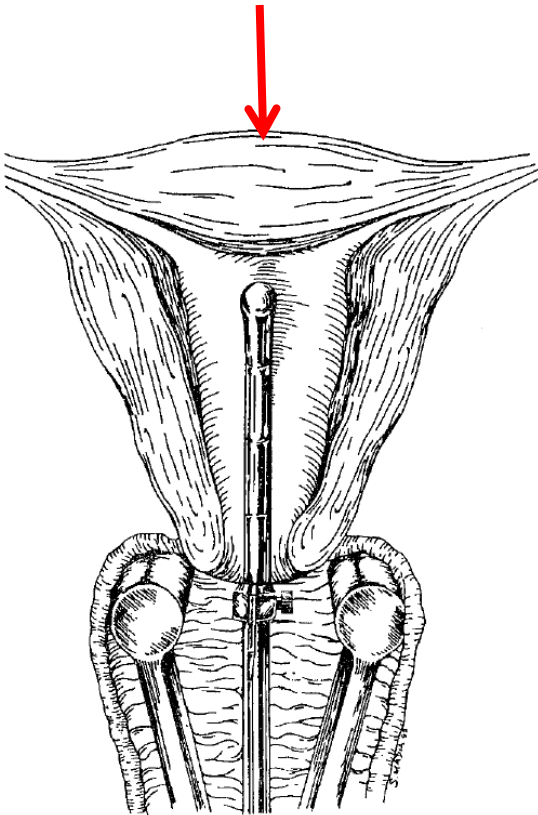


FIG. 3. Idealized brachytherapy implant for patients with carcinoma of the uterine cervix.

Displaced

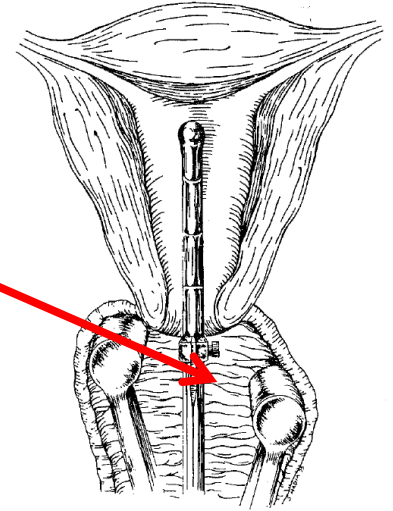


FIG. 2. Displacement of left colpostat. Note that the inferior tip of the caudal tandem source is separated from the left colpostat source.

Asymmetric

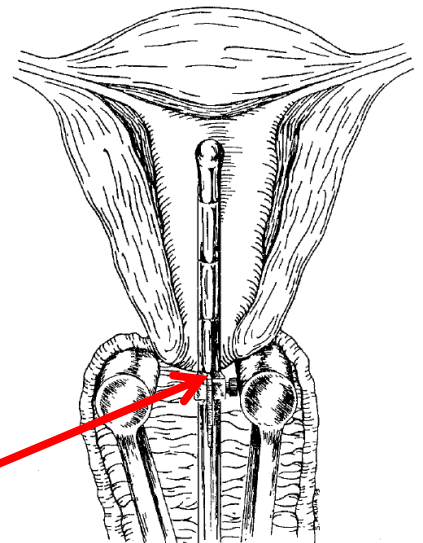


FIG. 1. Asymmetric implant. Note that the distance between the tandem and right colpostat is greater than the distance between the tandem and left colpostat.

Local Control Impacts Survival

- > 85Gy, Multivariate Analysis $p=0.01$
- Technical adequacy of implant
important determinant of local control

	Acceptable implant	Unacceptable implant
5 yr Local Control	68%	35%
5 yr Overall Survival	61%	42%

Use standard reference points (ICRU 38)

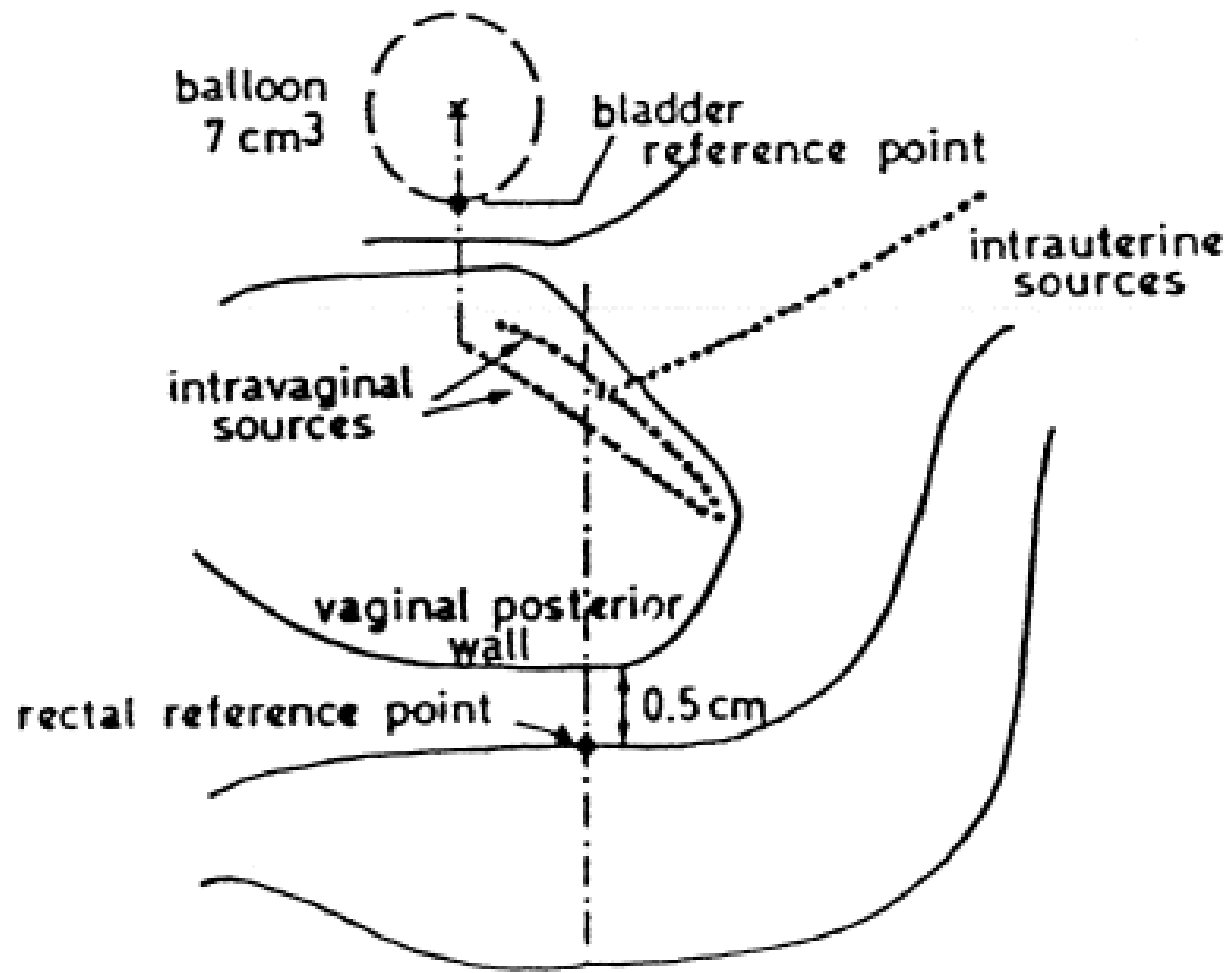
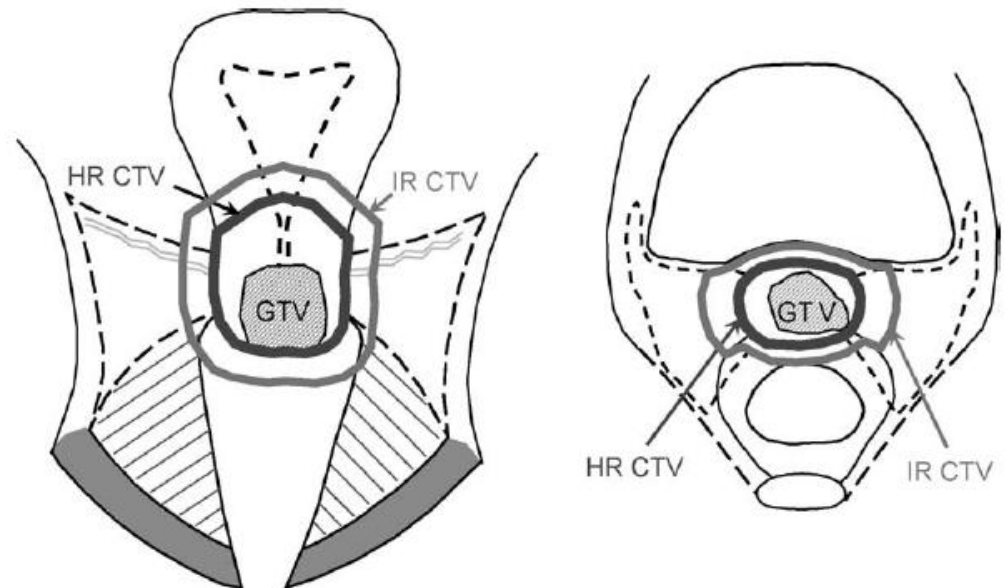


Fig. 3.2. Determination of the reference points for bladder and rectum (see text).

2D to 3D to 4D: Image Guided Brachytherapy

- Reduction in dose to OARs
- Dose escalation (improved tumor control)
- MR, CT and US can be used for IGBT
- Continue to use standard reference points
- Document HRCTV, D90, D2cc for bladder, rectum, and sigmoid
- Iterative Brachy

C. Haie-Meder et al. / Radiotherapy and Oncology 74 (2005) 235–245



Brachytherapy Dose

- Standard regimens
 - 5-6 Gy x 5
 - 7 Gy x 4
 - 8 Gy x 3
 - 9 Gy x 2
- 2 LDR implants preferable to 1
- Guiding principle: mitigating late toxicity

OAR Targets

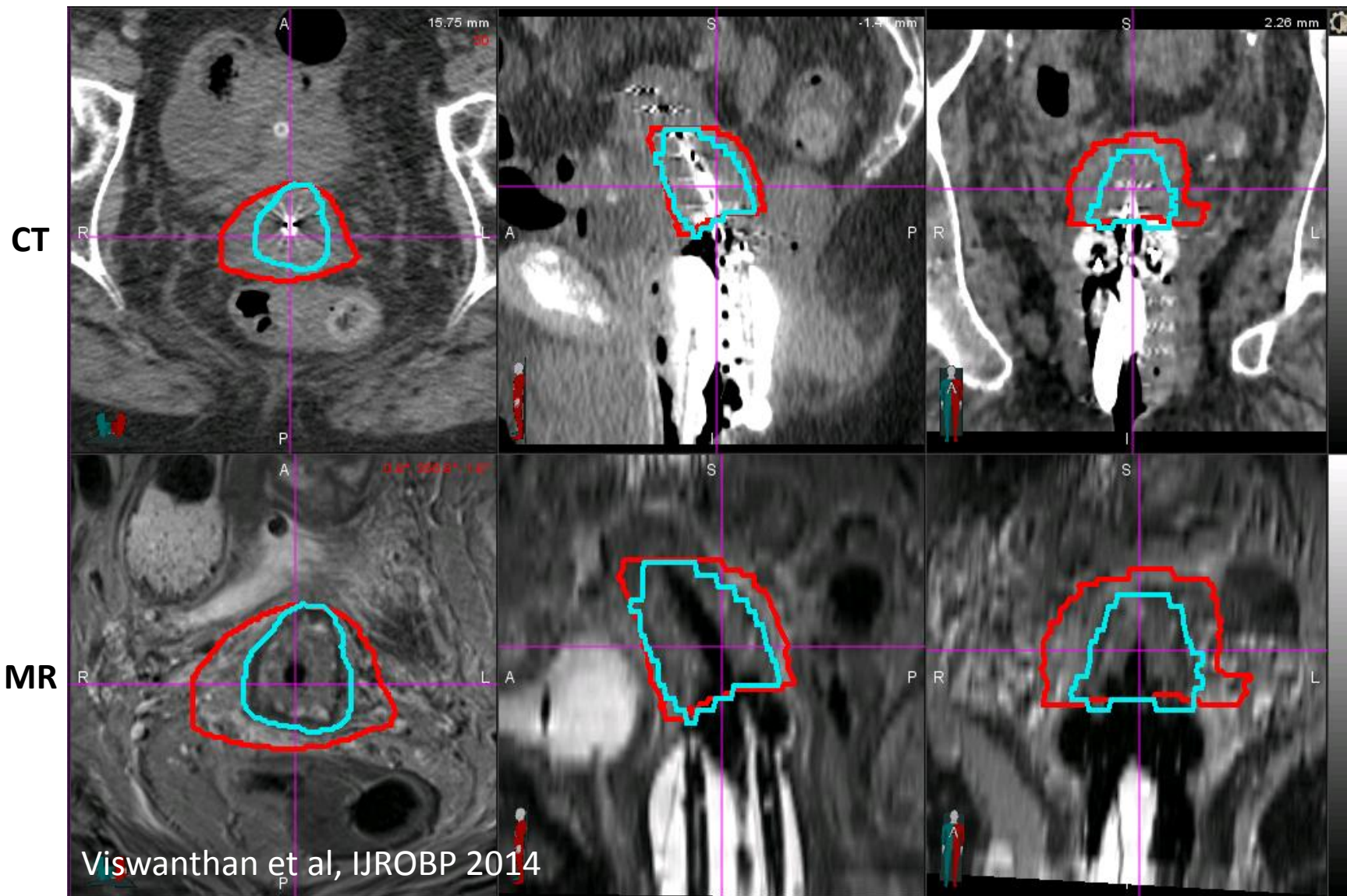
Volume	ABS	EMBRACE	Geortg <i>et al</i> ED10
D2cc bladder	≤ 90 Gy	< 90 Gy	101 Gy
D2cc rectum	≤ 75 Gy	$\leq 70-75$ Gy	78 Gy
D2cc Sigmoid	≤ 75 Gy	≤ 75 Gy	No recommendation

Doses in EQD2. Modified from Harkendrider *et al* IJROBP, 2015. ED10=dose corresponding to 10% rate of toxicity.

- ICRU rectal point/D2cc correspond
 - Limit to 70-75 Gy EQD2
- ICRU bladder point/D2cc do not correspond
 - 75 Gy for ICRU point dose
 - 90 Gy for D2cc dose

CT (red) vs. MR (blue) for IGBT

For all 3 cases, the mean tumor volume was smaller on MR than on CT ($P < .001$)



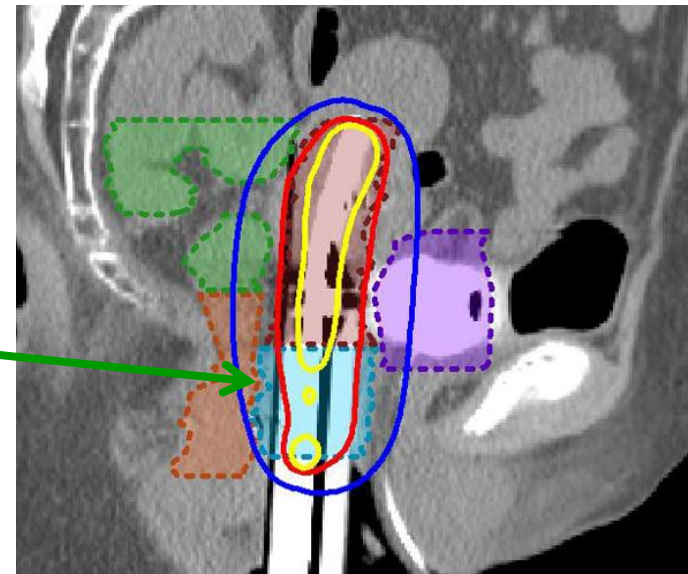
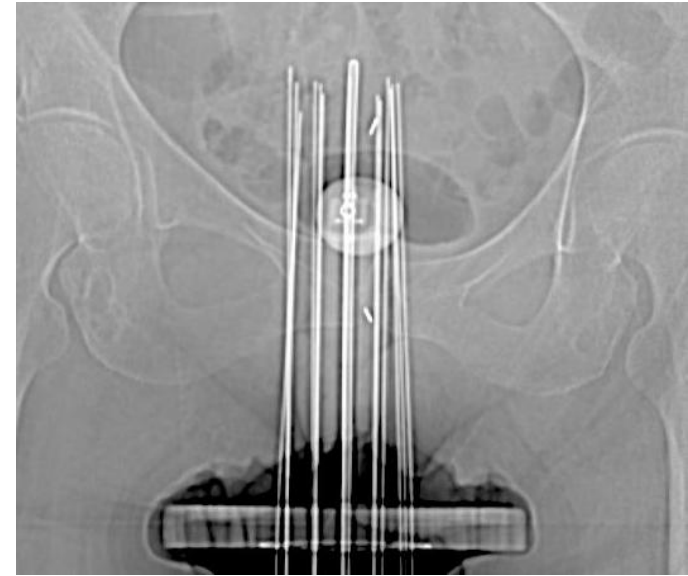
MR at the time of brachytherapy may be of greatest benefit in patients with large tumors with parametrial extension that have a partial or complete response to external beam.

Issues with MRI

- Superior soft tissue resolution
- HRCTV smaller than on CT
- Greater conformality will lead to decrease dose to OARs
 - More critical for large lesions
- First fraction or every fraction
 - Beware of significant tumor response
 - $T_{1/2}$ for tumor response 20-21 days (CT, MR, clinical exam)

Indications for Interstitial Implant for Cervix Cancer

- Stage IIIA
- Large cancer not amenable to intracavitary approaches
- Recurrence after hysterectomy/radiation therapy
- Cervical stump cancer
 - Post supracervical hyst.
- Tandem should always be used (if possible)
- Subvolumes can easily be defined



Treatment planning

- Develop a standard
 - Team approach: Physician, Physicist, Nurse
- Plan each implant
- D90, V100, V150, V200, point A
 - Inverse Planning: watch the hot spots
- Combination applicators (Intracavitary + Interstitial)
 - Start with intracavitary positions, add ~10-15% of activity from the needle dwell positions
- Iterative approach

Conclusions

- The goal of treatment is cure with minimal side effects in most women
 - Stages I-IVa
- Brachytherapy works
- Incorporate advanced imaging
- Thanks for your attention!

Definitive CRT: Trial Example

45 Gy/25
fractions

37.5 Gy/15
fractions

7 Gy x 4
Brachy

9 Gy x 2
Brachy

EBRT +
SURGERY

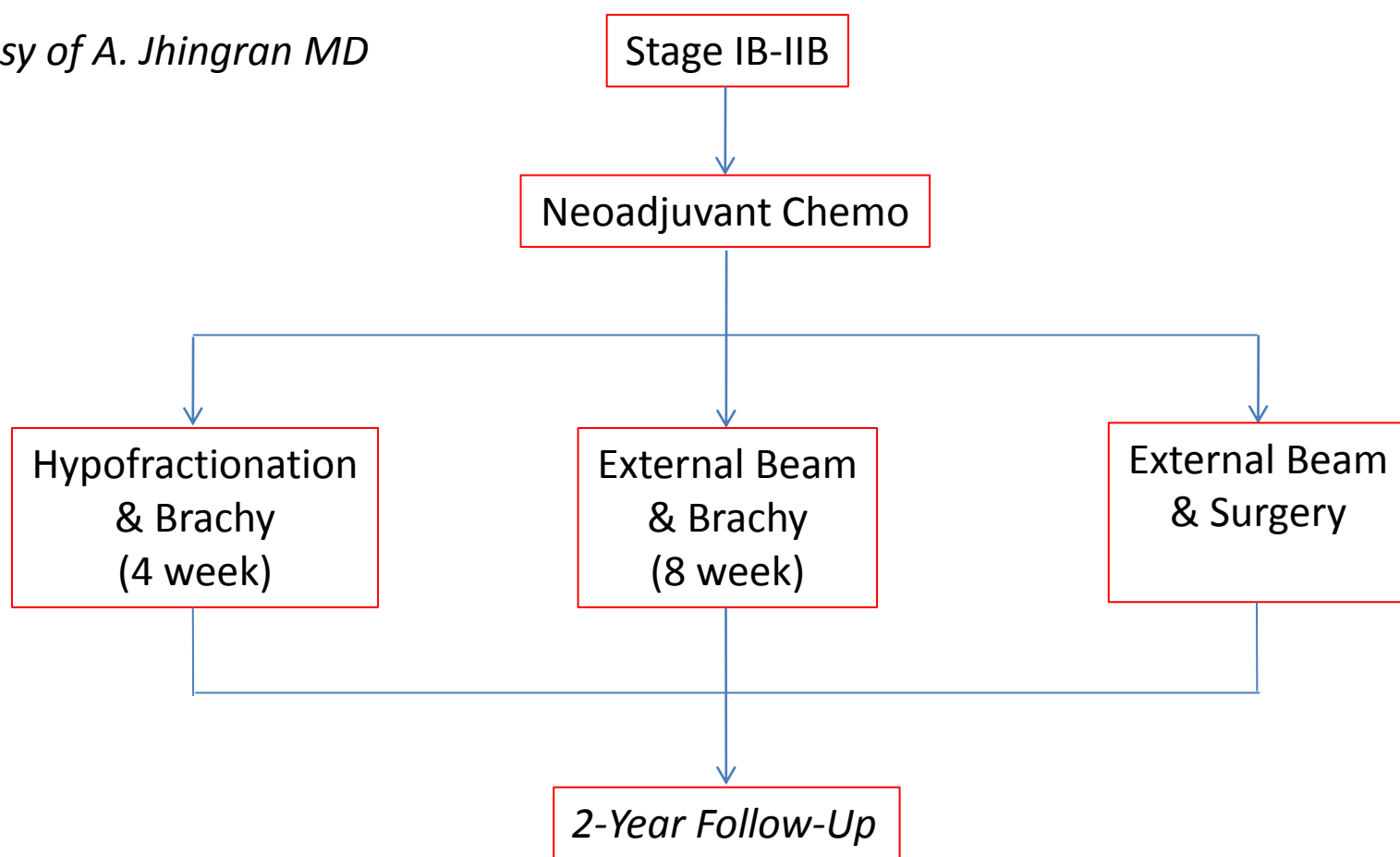
ENDPOINT: RFS

Hypofraction: BED and EQD2

Dose	Dose per fraction	Alpha/Beta	BED	EQD2
45	1.8	3	72.0	43.2
44	2.0	3	73.2	44.0
37.5	2.5	3	68.8	41.3
30	3.0	3	60.0	36.0
45	1.8	10	53.1	44.3
44	2.0	10	52.8	44.0
37.5	2.5	10	46.9	39.1
30	3.0	10	39.0	32.5
Brachy				
30	6.0	3	90.0	54.0
28	7.0	3	93.3	56.0
24	8.0	3	88.0	52.8
18	9.0	3	72.0	43.2
30	6.0	10	48.0	40.0
28	7.0	10	47.6	39.7
24	8.0	10	43.2	36.0
18	9.0	10	34.2	28.5

$45/1.8 + 30/6 = \mathbf{97.2 \text{ EQD2}}$ vs $37.5/2.5 + 24/8 = \mathbf{94.1 \text{ EQD2}}$ for alpha/beta 3
30 fractions vs 18 fractions

Courtesy of A. Jhingran MD



Outcomes: Non-inferiority to External Beam & Brachy for 2-year survival; Equivalence for Toxicity/QoL

Analysis: Stratify on Stage and Node Involvement

Data: Standardized; Tissues (Genetics; HPV type); Blood (Nutritional Status)

Sites: Brazil and Mexico; Minimum requirement---CT image of Abdomen and Pelvis and Chest x-ray

In close or positive margins, what is the role for a brachytherapy boost after hysterectomy?

Viswanathan *et al* IJROBP 2006

- 230 patients negative margins
 - LR 10% to 0% with RT
- 46 patients close margins (< 1 cm)
 - LR 17% to 0% with RT
- 8 patients with positive margins
 - LR 50% to 25% with RT
- Significant factors on univariate for RFS
 - Depth of invasion
 - Margin status and margin width
 - Tumor Size
 - LVSI

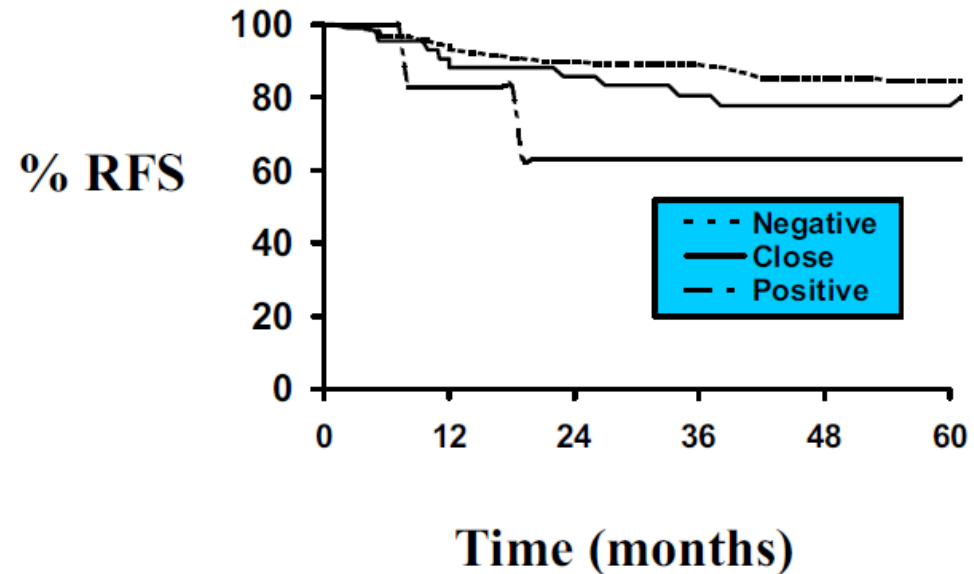


Table 5. Retrospective studies assessing patients with positive/close margins treated with RT

	<i>n</i>	RT	Relapse rate (%)	Margins
Estape <i>et al.</i> (33)	51	EB + VB	12.5	Close (≤ 5 mm) paravaginal
Hong <i>et al.</i> (34)	29	EB + VB*	25	Close (<3 mm) and positive [†]
Kim <i>et al.</i> (35)	11	VB \pm EB	55	Close (<1 cm) and positive [†]
Russell <i>et al.</i> (29)	16	EB	36	Close (not defined)
Hogan <i>et al.</i> (30)	6	EB	33	Positive
Snijders-Keilholz <i>et al.</i> (32)	17	EB + VB	6	Positive
Snijders-Keilholz <i>et al.</i> (32)	6	EB + VB	Not given	Close (<5 mm)