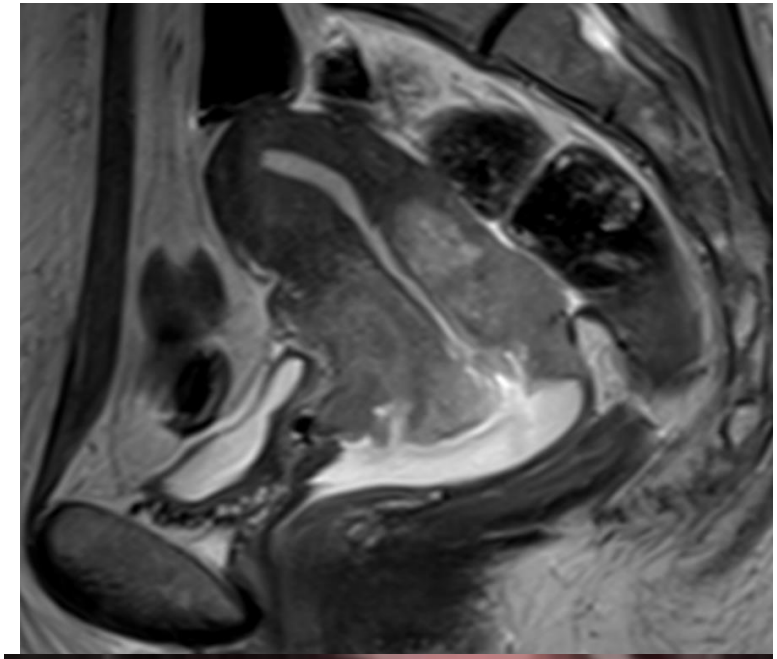
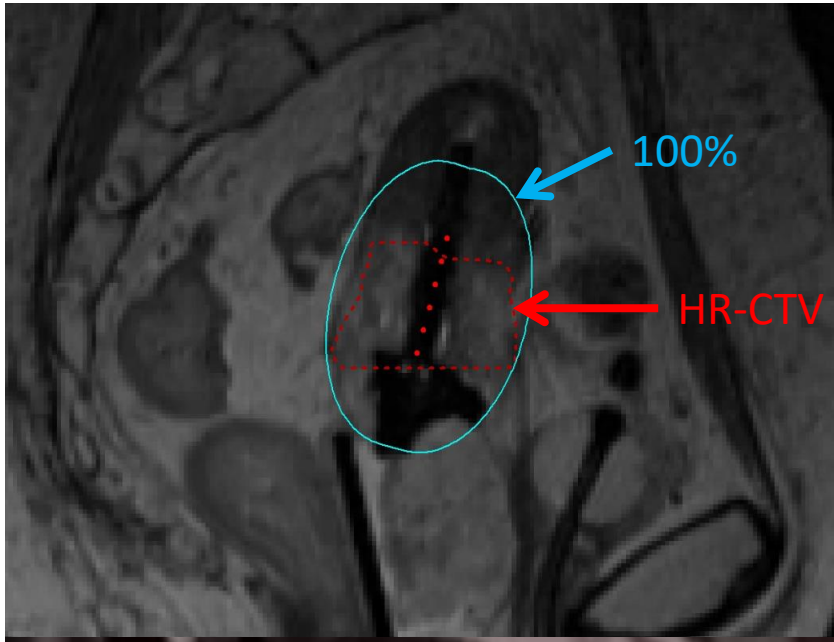
Pretreatment Imaging: Cervix Cancer

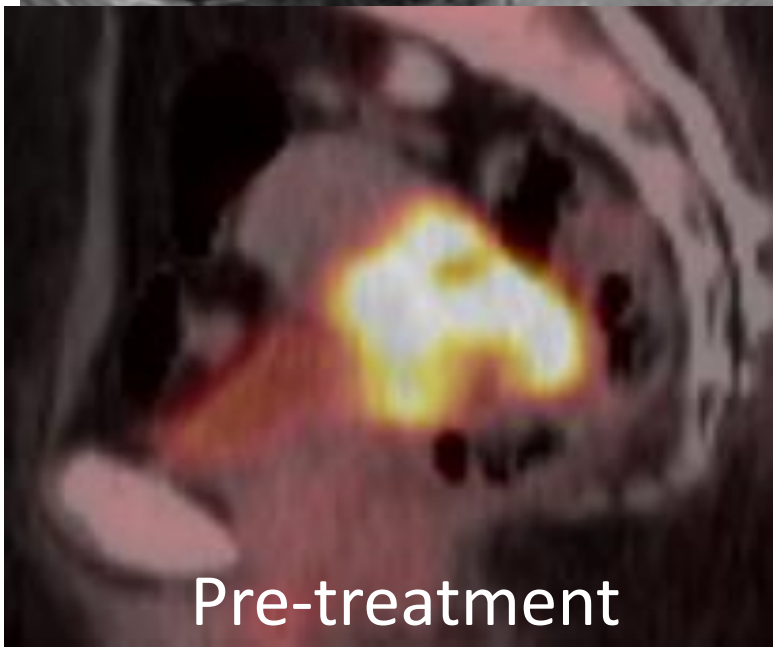
David Gaffney MDPhD

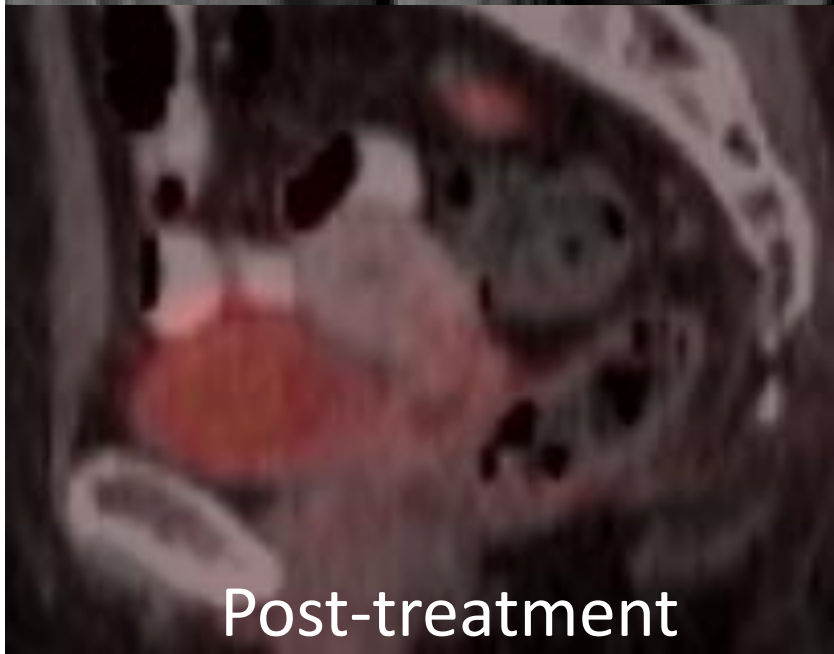
Univ of Utah

Cervix Cancer Education Symposium, January 2017, Mexico

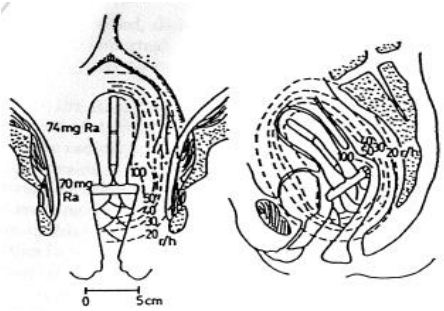



100%
HR-CTV

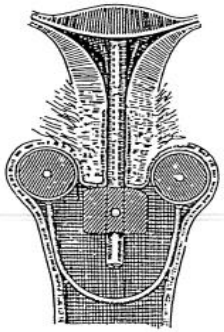

Pre-treatment


Post-treatment

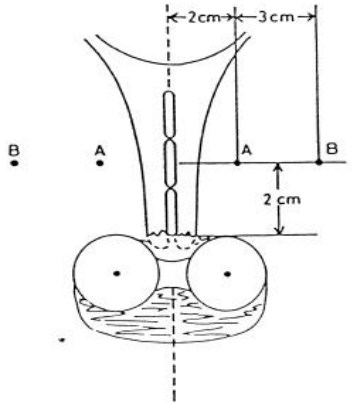
Is Imaging Imperative in Cancer of the Cervix?



Stockholm



Paris



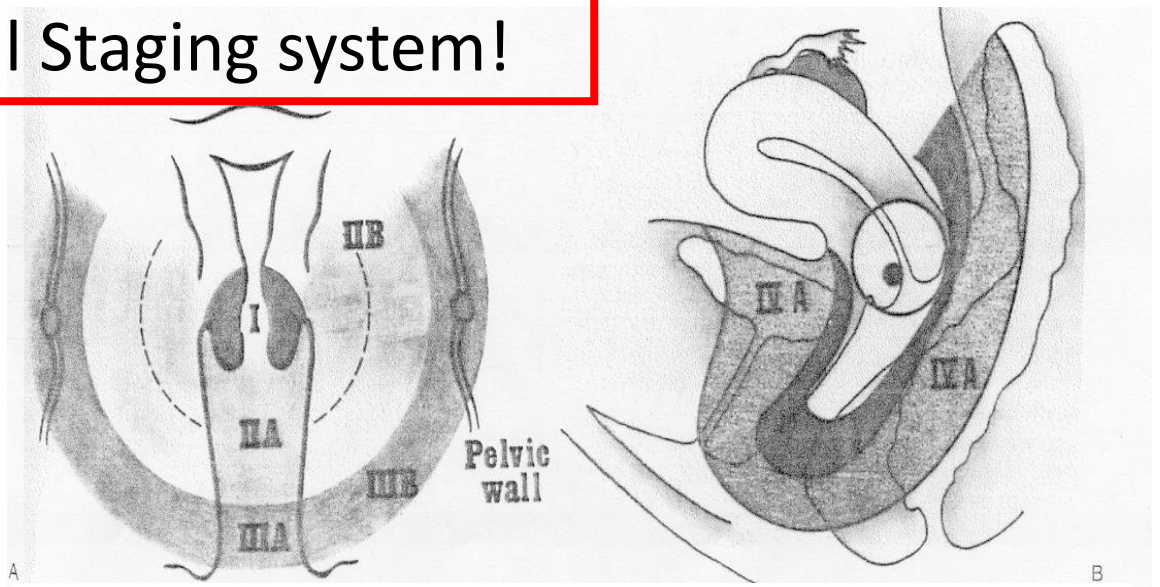
Manchester

1. Historic Good Results
2. Imaging → Renaissance

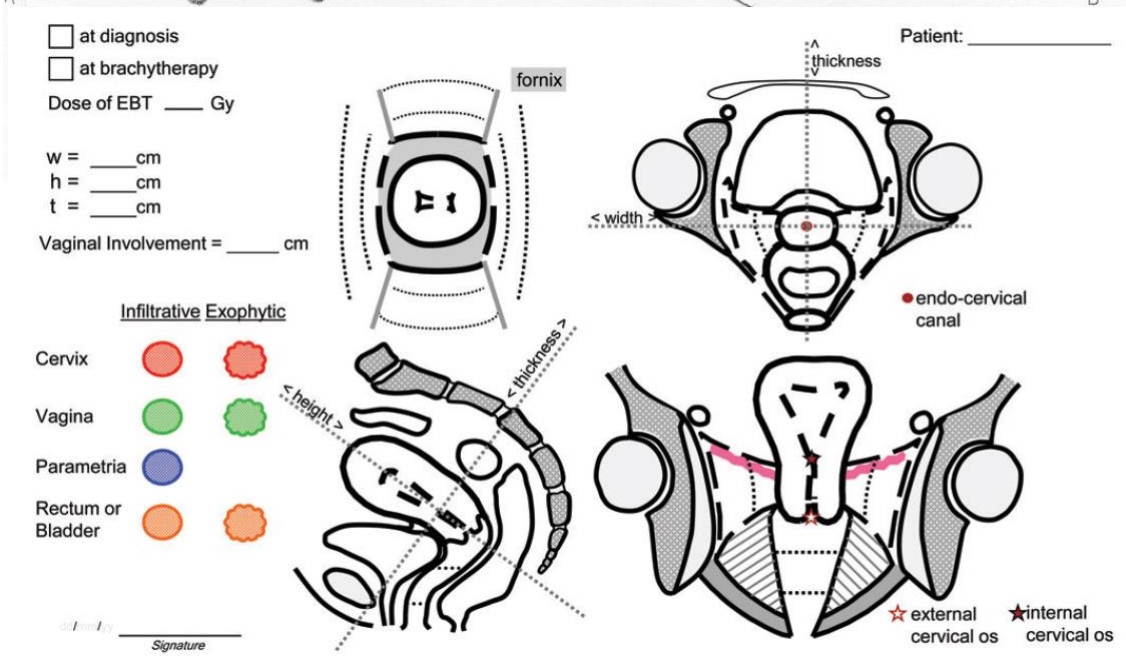
Stage	% 5 yr cure (RT)
I	79
II	41
III	27

Regaud, Paris: 1922-26, n=329

FIGO: Clincal Staging system!



ICRU 89 →



IA1 ≤ 3 mm invasion, IA2 3-5 mm invasion (< 7 mm horizontal spread)

IB1 ≤ 4 cm, IB2 > 4 cm

IIA1 ≤ 4 cm, IIA2 > 4 cm* *FIGO 2009 change.*

Staging and Imaging in Cervix Cancer

- FIGO permits:
  - EUA, colposcopy, endocervical curretage, hysteroscopy,
  - Cystoscopy, proctoscopy, IVP, chest Xray, skeletal Xrays
- Imaging (my preference)
  - PET/CT pretreatment for nodal evaluation and to evaluate response 3 months post treatment
  - MRI for evaluation of local tumor extent (eg brachy planning)
  - MRI at first brachy insertion (Image guided brachy)

MRI vs CT in cervix cancer staging?

Radiological Evaluation of Lymph NodeMetastases in Patients With Cervical Cancer: A Meta-analysis
Scheidler J JAMA 278:1096-1101, 1997

- 17 studies comparing CT, MRI and LAG
- LAG, CT, and MR imaging perform similarly in the detection of lymph node metastasis from cervical cancer.

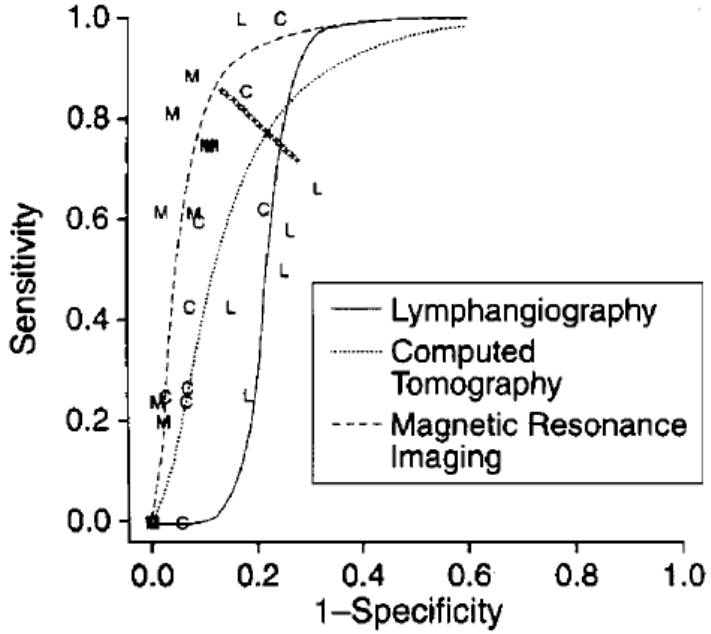
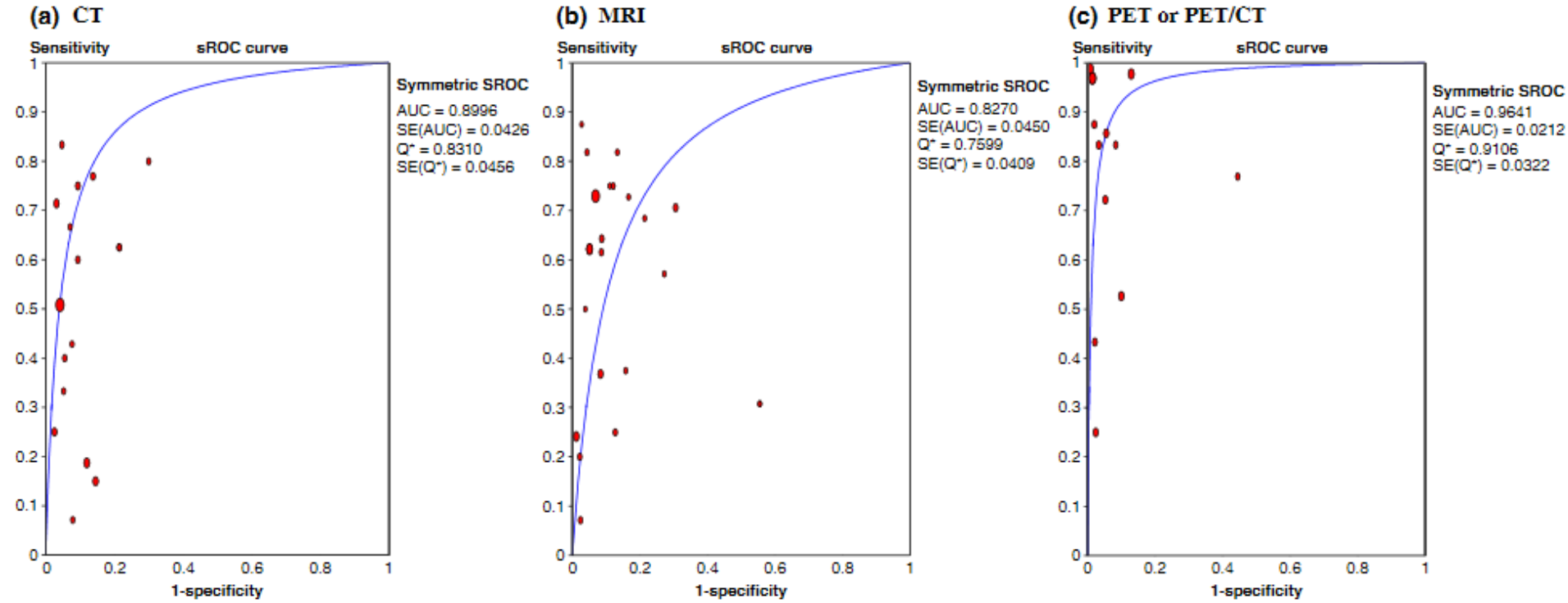


Figure 3.—Summary receiver operating characteristic analysis. Comparison of lymphangiography (L), computed tomography (C), and magnetic resonance imaging (M) in pelvic lymph node metastases. The diagonal line of *x*'s represents *Q**. The differences in *Q** values did not reach statistical significance.

MRI vs CT vs PET in cervix cancer staging?

Diagnostic performance of CT, MRI, and PET or PET/CT for detection of metastatic lymph nodes in patients with cervical cancer:Meta-analysis
Choi H, et al. Cancer Sci 101:1471-9, 2010

- 41 studies with histologic confirmation



- PET or PET/CT had an overall higher diagnostic performance than did CT or MRI in detecting metastatic lymph nodes in patients with cervical cancer

MRI vs CT vs PET in cervix cancer staging?

Diagnostic performance of CT, MRI, and PET or PET/CT for detection of metastatic lymph nodes in patients with cervical cancer:Meta-analysis
Choi H, et al. Cancer Sci 101:1471-9, 2010

Table 4. Summary sensitivity and specificity of CT, MRI, and PET or PET/CT

Category	No. of studies	Summary sensitivity, % (95% CI)	I^{2}* (%)	Summary specificity, % (95% CI)	I^{2}* (%)
Patient-based comparison					
CT	16	50 (43–57)	71.1	92 (90–94)	31.6
MRI	21	56 (51–62)	70.7	91 (90–93)	80.1
PET or PET/CT	12	82 (75–87)	80.7	95 (93–97)	69.7
Region/node-based comparison					
CT	4	52 (42–62)	78.0	92 (90–94)	81.5
MRI	9	38 (32–43)	67.7	97 (97–98)	95.0
PET or PET/CT	8	54 (46–61)	57.3	97 (96–98)	70.9

*Test for heterogeneity: An I^{2} value greater than 50% was considered to indicate substantial heterogeneity across the studies included in the analysis. CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

- PET or PET/CT had an overall higher diagnostic performance than did CT or MRI in detecting metastatic lymph nodes in patients with cervical cancer

PET in Cervix Cancer: Is it any good?

- Staging?
- Predictive of outcome?
- Asymptomatic recurrences?
- Can PET + LN's be cured with standard doses?

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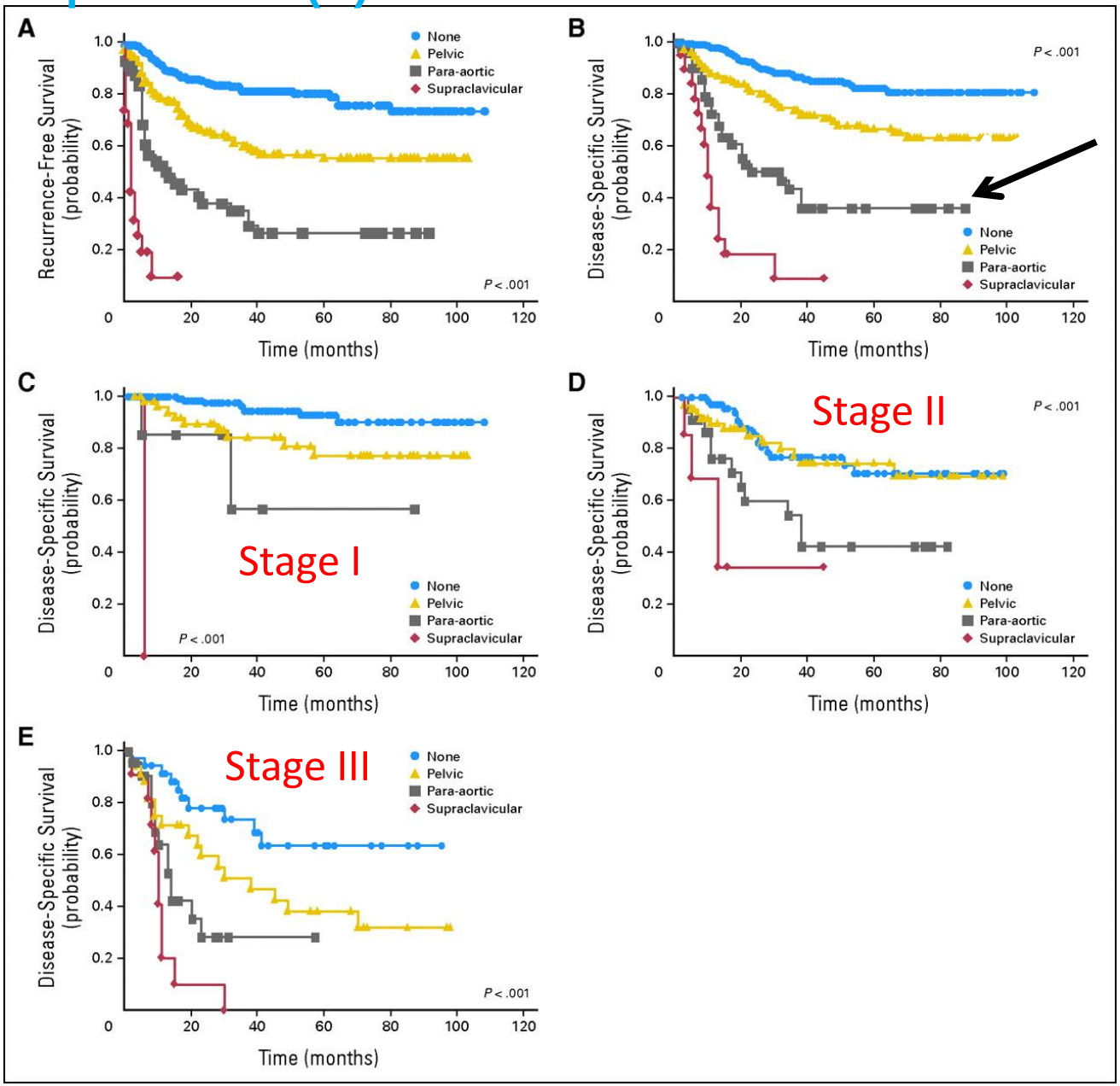
Fig 2. Kaplan-Meier (A) recurrence-free survival for all 513 patients



> 35% DSS

Kidd, E. A. et al. J Clin Oncol; 28:2108-2113 2010

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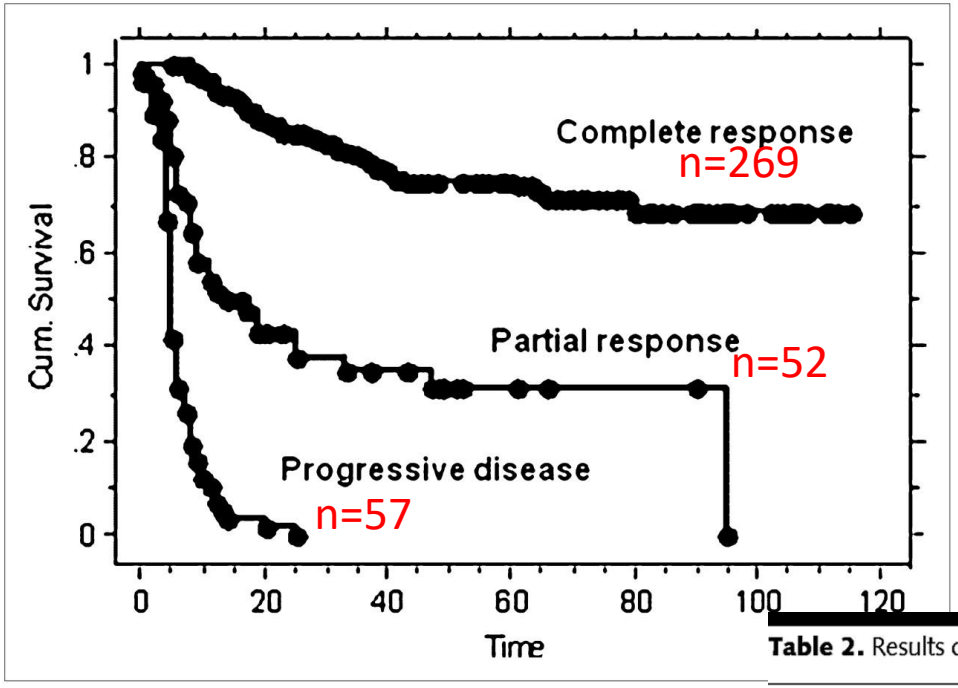
Post treatment PET can be highly predictive

The Role of ^{18}F-FDG PET in Assessing Therapy Response in Cancer of the Cervix and Ovaries

Schwarz et al J Nucl Med, 50(1):64-73, 2009



RFS by PET

Table 2. Results of Final Multivariate Proportional Hazards Model for Survival Outcome

	Posttherapy PET		Lymph Node Status by Pretreatment PET
	Progressive Disease	Persistent Disease	
Coefficient	3.48	1.84	1.26
SE	0.59	0.43	0.42
Coefficient/SE	5.89	4.31	2.99
χ^2	34.69	18.56	8.92
Hazard ratio (95% CI)	32.57 (10.22-103.82)	6.30 (2.73-14.56)	3.54 (1.54-8.09)
P value	<.001	<.001	.003

Abbreviations: CI, confidence interval; PET, positron emission tomography; SE, standard error.

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Surveillance FDG-PET detection of asymptomatic recurrences in patients with cervical cancer☆

Rebecca A. Brooks [c,d], Janet S. Rader [c,d], Farrokh Dehdashti [b,d], David G. Mutch [c,d], Matthew A. Powell [c,d], Premal H. Thaker [c,d], Barry A. Siegel [b,d], Perry W. Grigsby [a,b,c,d,*]

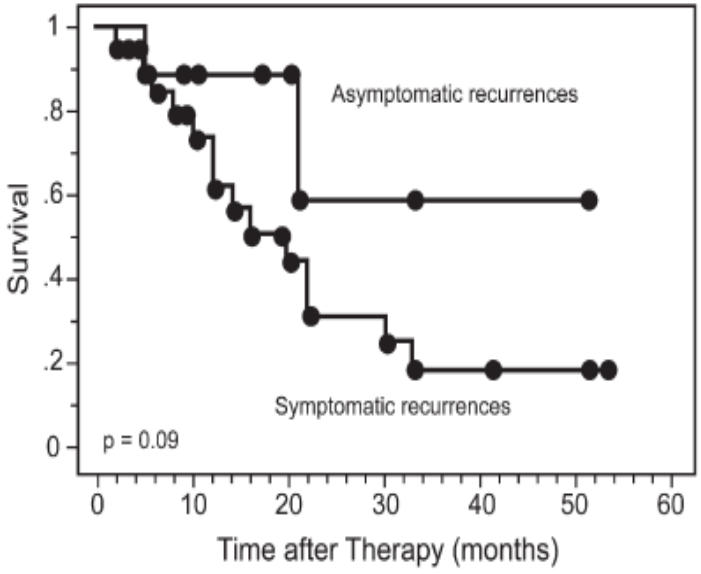

Fig. 2. Cause-specific survival for patients with symptomatic (n=21) versus asymptomatic (n=9) recurrences on their first surveillance FDG-PET scan.

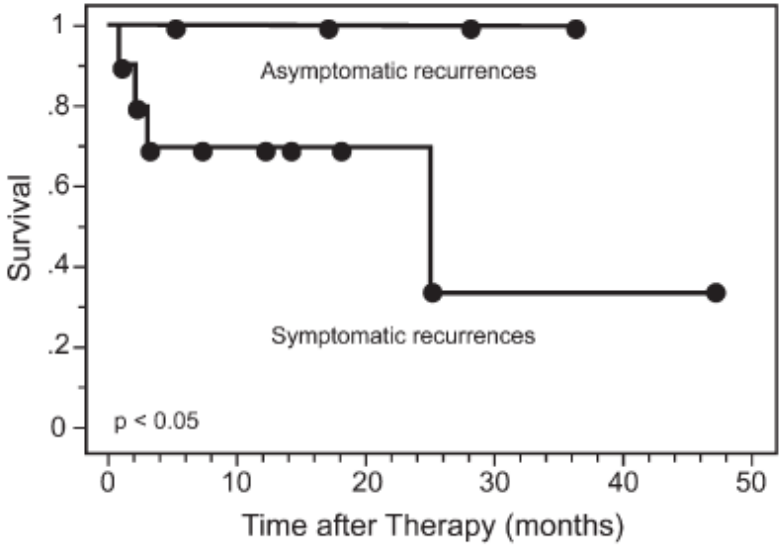

Fig. 3. Cause-specific survival for patients with symptomatic (n=10) versus asymptomatic (n=4) recurrences on their second surveillance FDG-PET scan.

12% (9/78) of patients had an asymptomatic recurrence with a median time to recurrence of 16 months

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Can PET + lymph nodes be adequtely treated with RT?

Table 2. Para-aortic lymph nodes

Lymph node status	Patients (no.)	Mean lymph node dose (Gy)	Paraaortic lymph node failure
PET negative	175	0	1/175
PET positive/CT ≤1 cm	24	43.9*	0/24
PET positive/CT >1 cm to ≤2 cm	5	45*	0/5
PET positive/CT >2 cm to ≤3 cm	4	33.9	0/4
Total	208	—	1/208

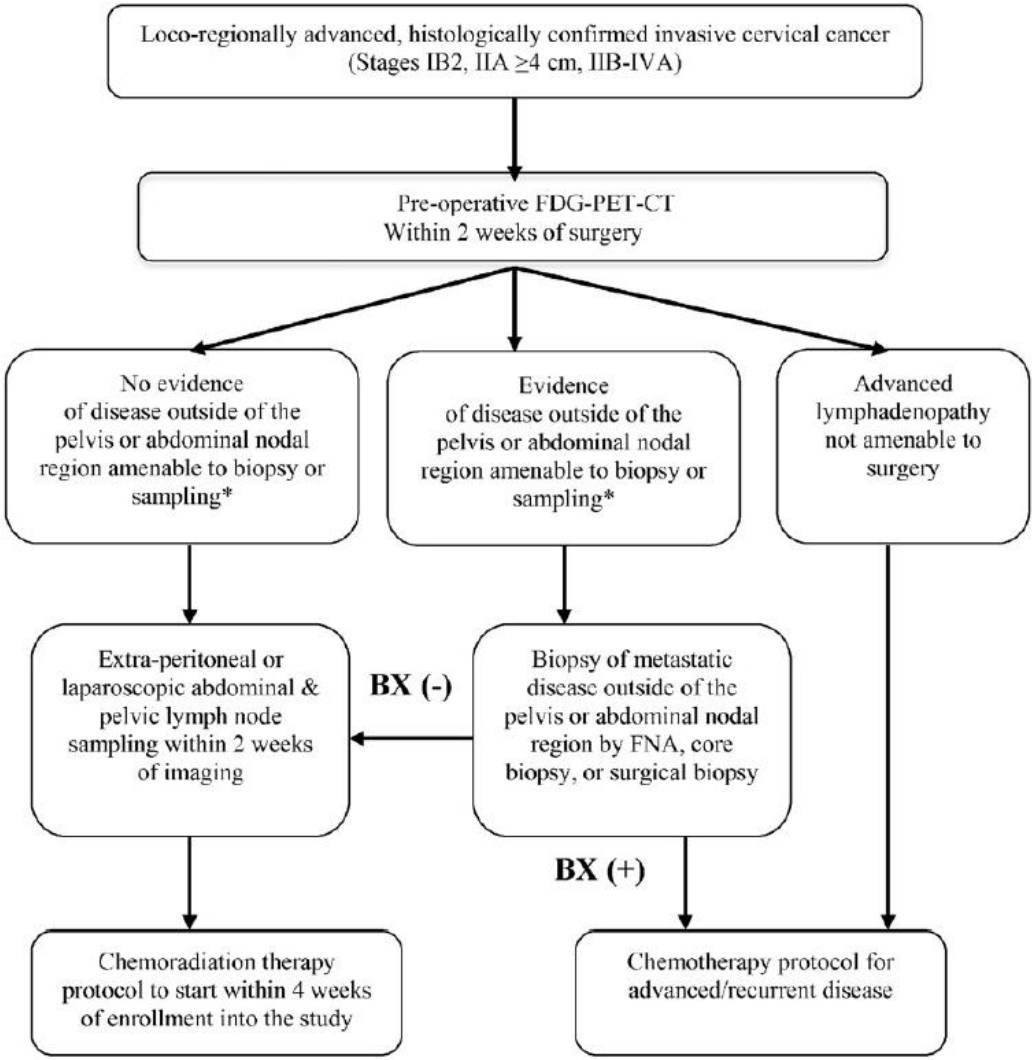
0/33 relapsed in PA LN's.

Utility of PET-CT to evaluate retroperitoneal lymph node metastasis in advanced cervical cancer: Results of ACRIN6671/GOG0233 trial☆,☆☆

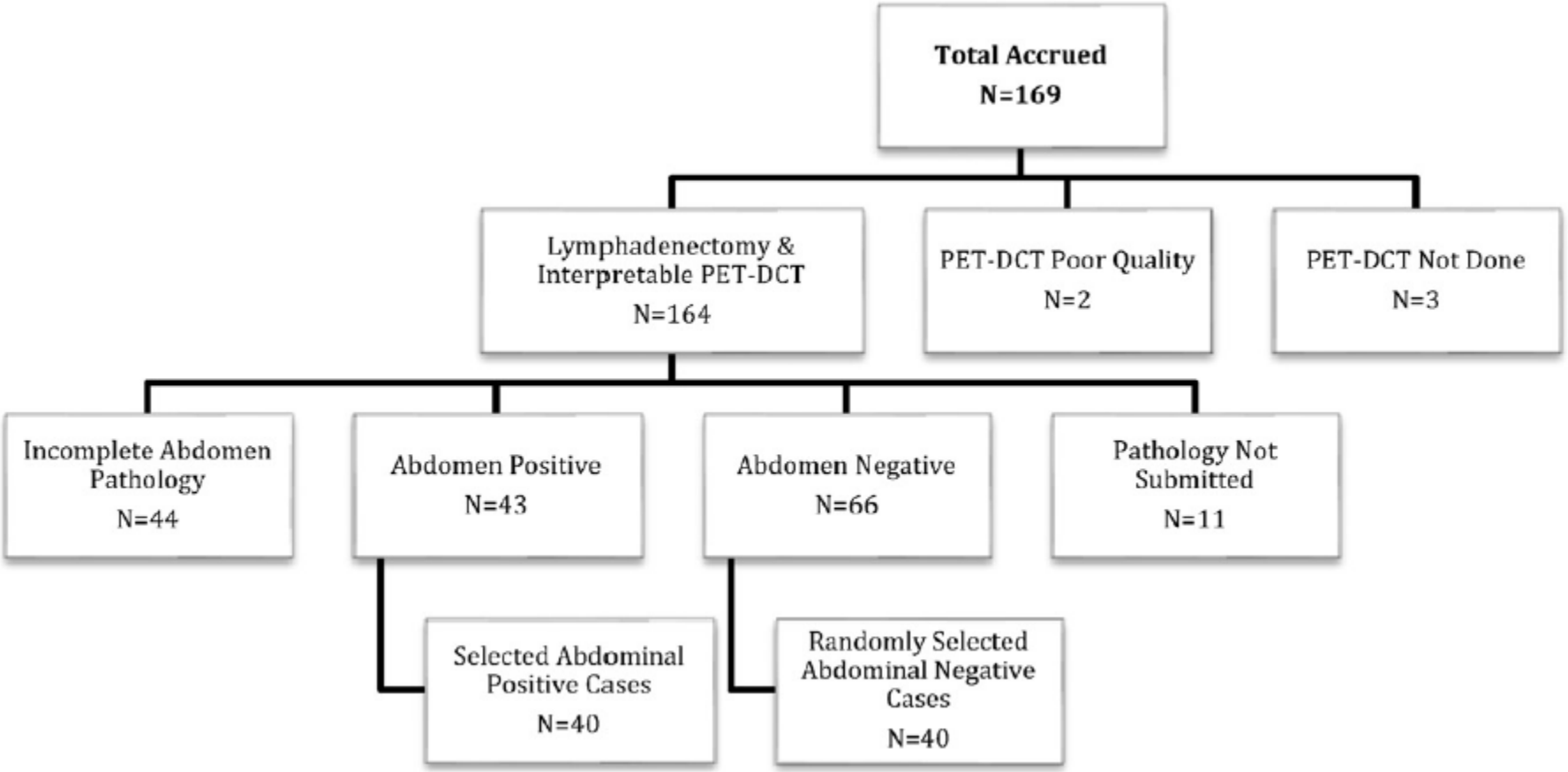
Mostafa Atri [a,*], Zheng Zhang [b], Farrokh Dehdashti [c], Susanna I. Lee [d], Shamshad Ali [e], Helga Marques [b], Wui-Jin Koh [f], Kathleen Moore [g], Lisa Landrum [g], Jae Weon Kim [h], Paul DiSilvestro [i], Eric Eisenhauer [j], Frederick Schnell [k], Michael Gold [l]

Gyn Oncol 146:413-9, 2016

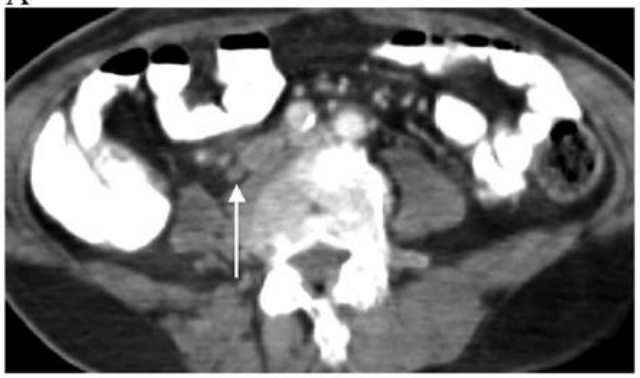
- Eligibility: IB2, IIA2, IIB-IVA
- 153 patients had PET and CT and Pathology
- 43 patients had positive lymph nodes



Patient Flow Chart



A



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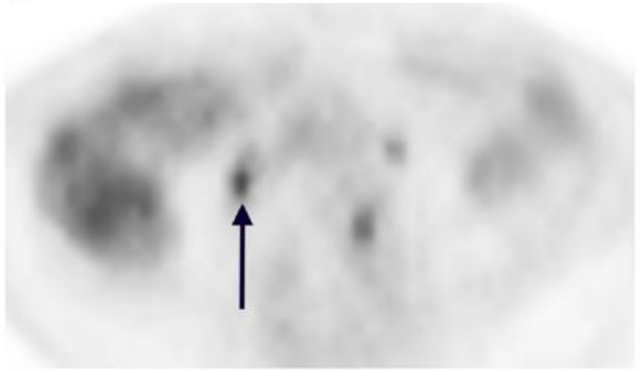


C

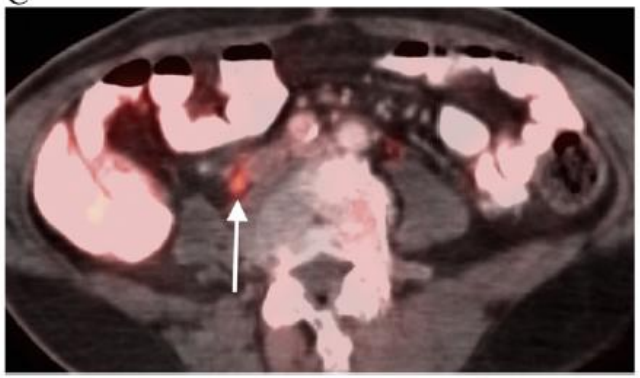


Table 1
Accuracy values with 95% CI of PET-DCT and diagnostic CT in the abdomen. AUC: Area Under Curve.

Abdomen	PET-DCT	CT	*p* value
Sensitivity	0.50 (CI: 0.44.0.56) 0.45–0.55	0.42 (CI: 0.36.0.48) 0.33–0.48	0.052
Specificity	0.85 (CI: 0.80.0.89) 0.75–0.90	0.89 (CI: 0.84.0.92) 0.83–0.95	0.21
AUC	0.70 (CI: 0.61.0.79) 0.65–0.73	0.68 (CI: 0.59.0.77) 0.61–0.70	0.43

Table 2
Accuracy values with 95% CI of PET-DCT and diagnostic CT in the pelvis and abdomen/pelvis combined. AUC: Area Under Curve.

	PET-DCT	CT	*p* value
Pelvis			
Sensitivity	0.83 (CI: 0.78.0.87) 0.65–0.90	0.79 (CI: 0.73.0.83) 0.71–0.84	0.15
Specificity	0.63 (CI: 0.54.0.70) 0.54–0.73	0.62 (CI: 0.53.0.69) 0.38–0.73	0.83
AUC	0.80 (CI: 0.71.0.88) 0.65–0.84	0.76 (CI: 0.67.0.85) 0.67–0.83	0.21
Combined abdomen/pelvis			
Sensitivity	0.81 (CI: 0.77.0.85) 0.69–0.86	0.77 (CI: 0.73.0.81) 0.71–0.81	0.17
Specificity	0.69 (CI: 0.59.0.77) 0.57–0.86	0.63 (CI: 0.54.0.72) 0.48–0.81	0.32
AUC	0.83 (CI: 0.75.0.91) 0.72–0.90	0.77 (CI: 0.69.0.85) 0.72–0.86	0.03

Table 3
Inter-observer agreement between seven readers for PET-DCT and diagnostic CT.

	Kappa		
	Abdomen	Pelvis	Combined
PET-DCT 7 readers	0.77	0.65	0.71
CT 7 readers	0.65	0.61	0.67

Table 4
Number of lymph nodes removed during lymphadenectomy.

		Range	Mean (SD)	Median
Number OF LNS	Abdomen ($N = 80$)	1–33	10.7 ± 7.6	9
	Pelvis ($N = 80$)	0–35	14.1 ± 7.5	13
Number OF positive LNS	Abdomen ($N = 40$)	1–24	3.6 ± 4.5	2
	Pelvis ($N = 51$)	1–14	4.0 ± 3.2	3

"Conclusion. Addition of PET to DCT resulted in statistically borderline increase in sensitivity to detect LN metastasis in abdomen in advanced cervical cancer."
**Modern CT is very good.*

Comparison of MRI and High-Resolution Transvaginal Sonography for the Local Staging of Cervical Cancer

J Clin Ultrasound 2016

Fiachra Moloney, MD,[1] David Ryan, MD,[1] Maria Twomey, MD,[1] Matt Hewitt, MD,[2] Josephine Barry, MD[1]

- N=46

TABLE 2
Diagnostic Accuracy of Disease Staging with MRI and TVS in the Detection of Stromal Invasion in 46 Women with Invasive Cervical Cancer

	Histopathologically Positive, n	Histopathologically Negative, n	
MRI positive	12	9	Sensitivity, 80% Specificity, 50% Positive predictive value, 57% Negative predictive value, 75% Kappa, 0.29 (“fair”)
MRI negative	3	9	
TVS positive	12	9	Sensitivity, 80% Specificity, 50% Positive predictive value, 57% Negative predictive value, 75% Kappa, 0.29 (“fair”)
TVS negative	3	9	

TABLE 3
Diagnostic Accuracy of Disease Staging with MRI and TVS in the Detection of Parametrial Invasion in 46 Women with Invasive Cervical Cancer

	Histopathologically Positive, n	Histopathologically Negative, n	
MRI positive	2	4	Sensitivity, 40% Specificity, 86% Positive predictive value, 33% Negative predictive value, 89% Kappa, 0.238 (“fair”)
MRI negative	3	24	
TVS positive	1	3	Sensitivity, 20% Specificity, 89% Positive predictive value, 25% Negative predictive value, 86% Kappa, 0.101 (“poor”)
TVS negative	4	25	

Conclusions: TVS performed by a dedicated gynecologic radiologist is a feasible and economic imaging modality with a diagnostic accuracy comparable to that of MRI.

THREE-DIMENSIONAL TRANSVAGINAL TOMOGRAPHIC ULTRASOUND IMAGING FOR CERVICAL CANCER STAGING

XUE-SONG HAN,* CHUN-PING NING,† LI-TAO SUN,* XIAO-YING LI,* YAN-QING PENG,* and MEI-ZHENG DANG*

Ultrasound Med Biol. 2015

- N=80
- Tomographic transvaginal US

Table 3. Comparison of clinical, US and MRI staging

		Clinical staging			US staging			MRI staging		
Stage	Final staging	Accurate	Under-staged	Over-staged	Accurate	Under-staged	Over-staged	Accurate	Under-staged	Over-staged
IA	5	5	—	—	1	2	2	0	3	2
IB	50	42	2	6	48	—	2	45	1	4
IIA	15	13	—	2	15	—	—	15	—	—
IIB	10	3	5	2	10	—	1	6	2	2
Accuracy		(63/80) 78.75%			(74/80) 92.50%			66/80 (82.50%)		
Comparisons										
Clinical vs. US					$\chi^2 = 4.902, p = 0.022$					
US vs. MRI					$\chi^2 = 2.686, p = 0.079$					

US = ultrasound; MRI = magnetic resonance imaging.

INTRAOPERATIVE ULTRASOUND

- 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

ICRU 89: Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix

(Produced in collaboration with GEC-ESTRO, June 2016)

ICRU reports:

Internationally acceptable recommendations regarding;

(1) quantities and units of ionizing radiation and radioactivity,
(2) procedures suitable for the measurement and application of these quantities
(3) physical data needed in the application of these procedures

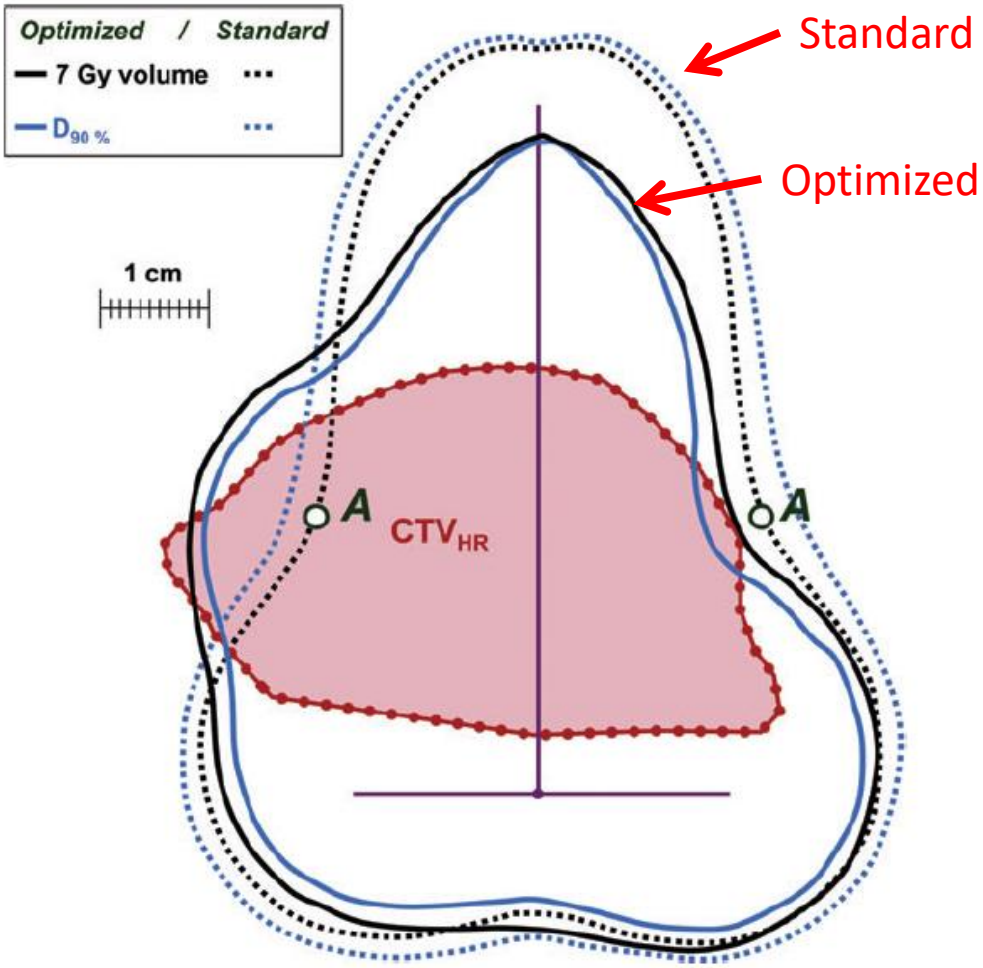
- ICRU 38 was published in 1985
- Formalization of GEC-ESTRO guidelines
- Describes prescribing, recording, and reporting cervix cancer brachytherapy
- Beautifully written, 258 pages

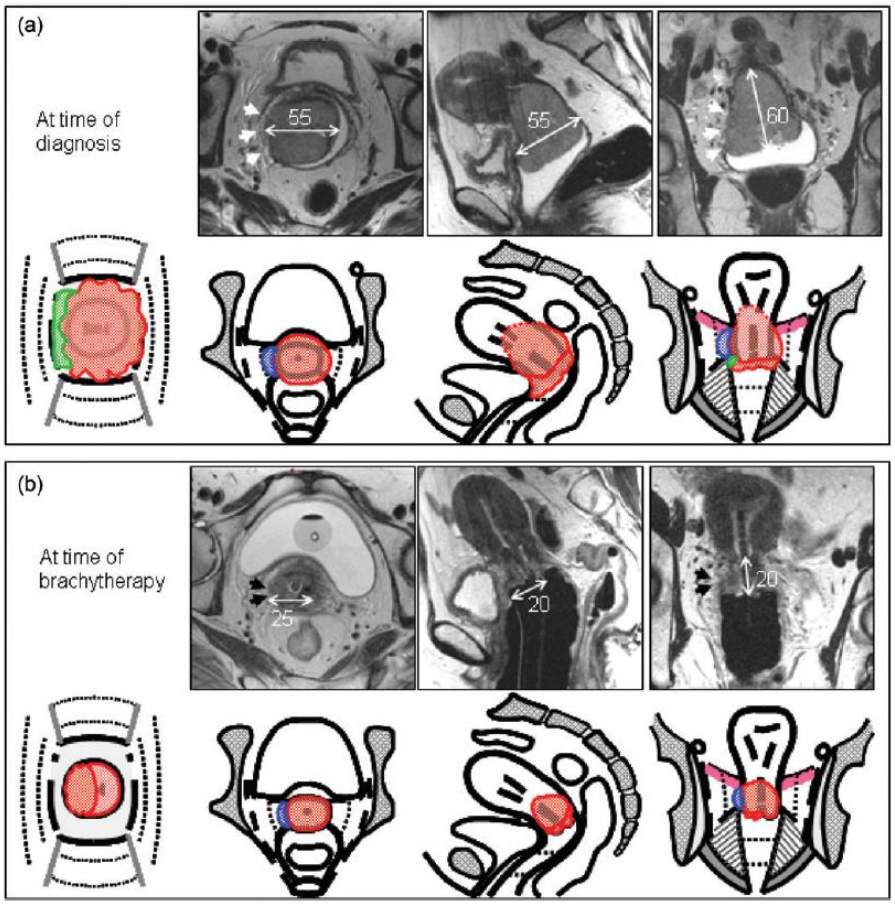
ICRU 89: Outline (abridged)

- Brachytherapy Techniques and Systems
- Imaging for Treatment Planning
- Tumor and Target Volumes and Adaptive Radiotherapy
- Organs At Risk
- Radiobiological Considerations
- Parameters for Prescribing, Recording, and Reporting
- Volumetric Dose Assessment
- Radiographic Dose Assessment
- Sources and Absorbed-Dose Calculation
- Treatment Planning
- Summary
- Examples

ICRU 89 Principle

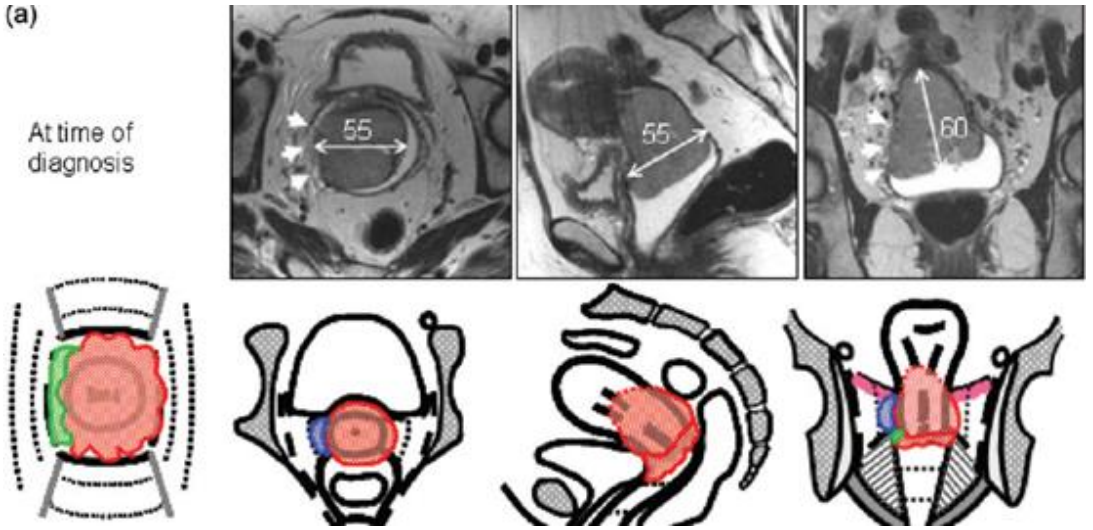
1. Use imaging to conform the dose to the target
2. Effectively spares OARs





ICRU 89: Imaging Key Messages

- The initial evaluation begins with clinical gynecologic examination and documentation and by drawing of the findings on clinical diagrams.

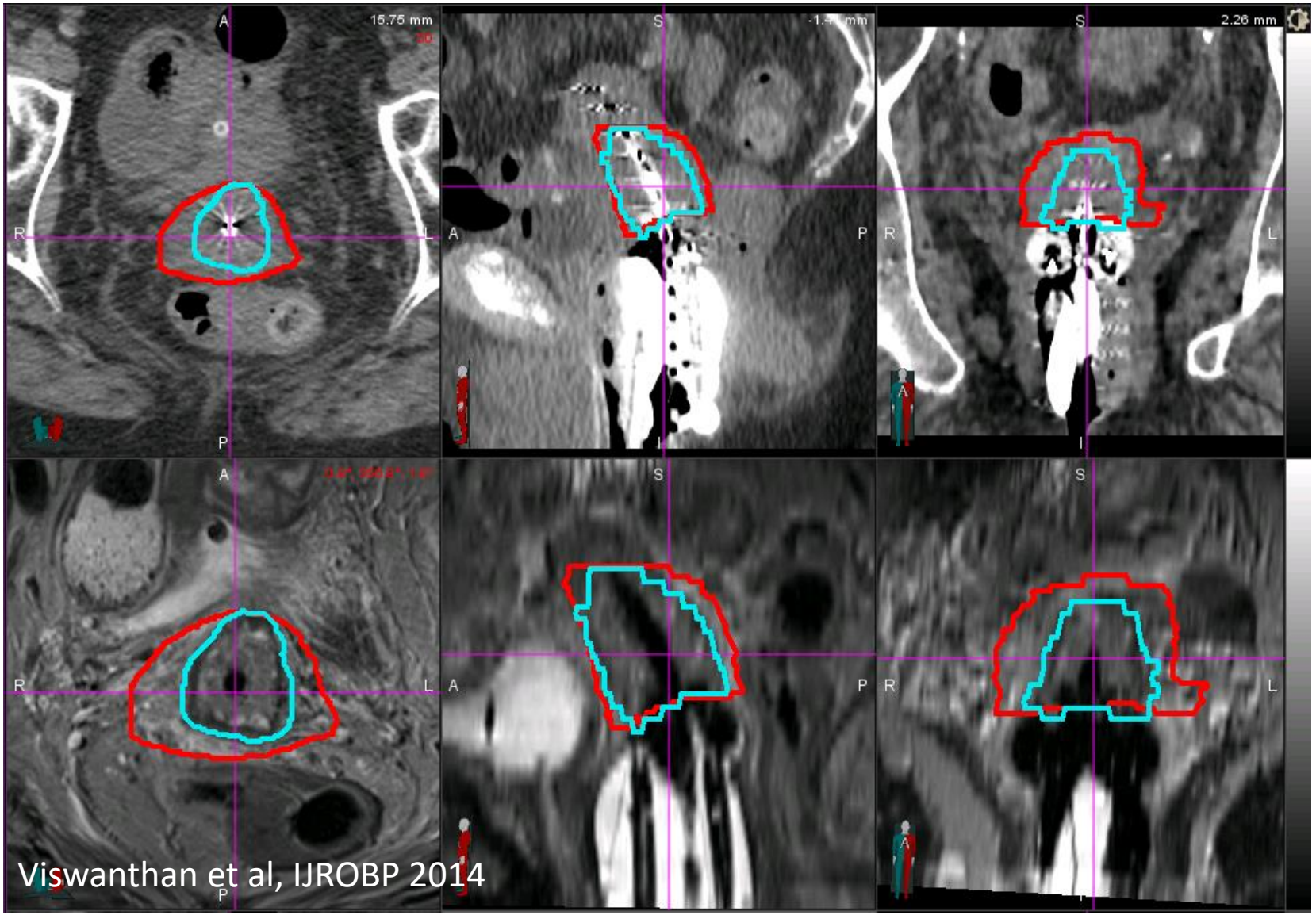


- Initial staging involves MRI, CT, or PET-CT, where available... The use of US, radiography (chest, IVU, skeletal), and scintigraphy can also be helpful, but the information they provide is more limited.

- Monitoring of disease regression during radiation treatment is important and is done through the use of repeated gynecologic examinations and imaging studies, before and at the time of brachytherapy to document disease regression and to plan brachytherapy.

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

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

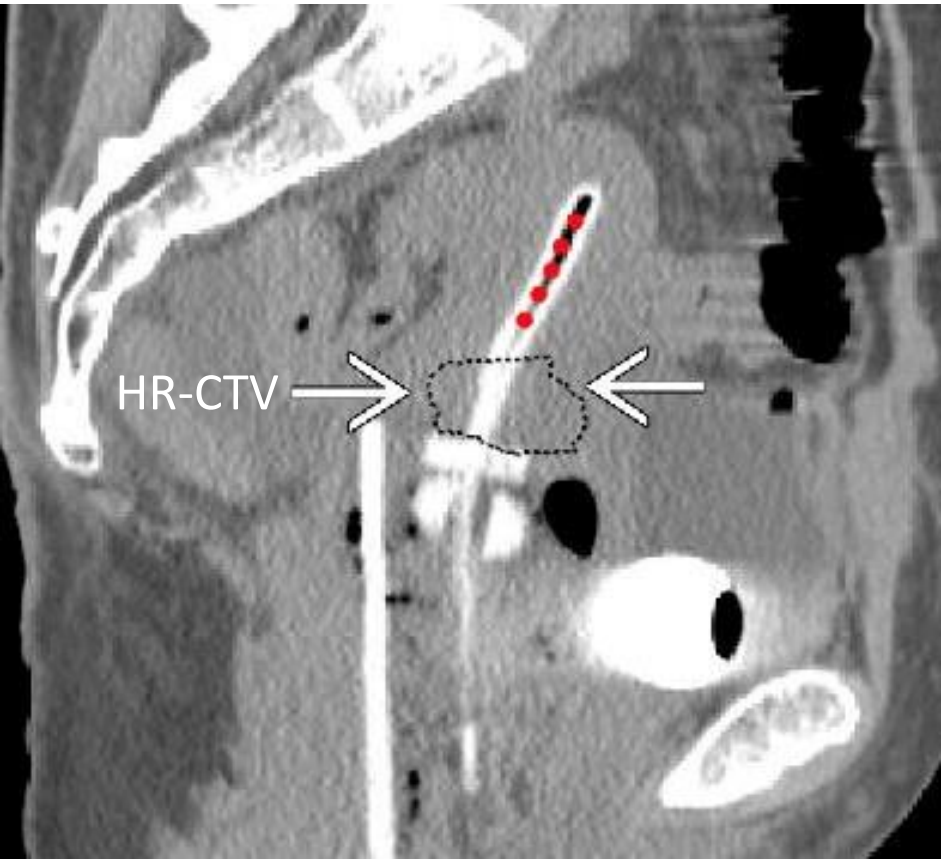


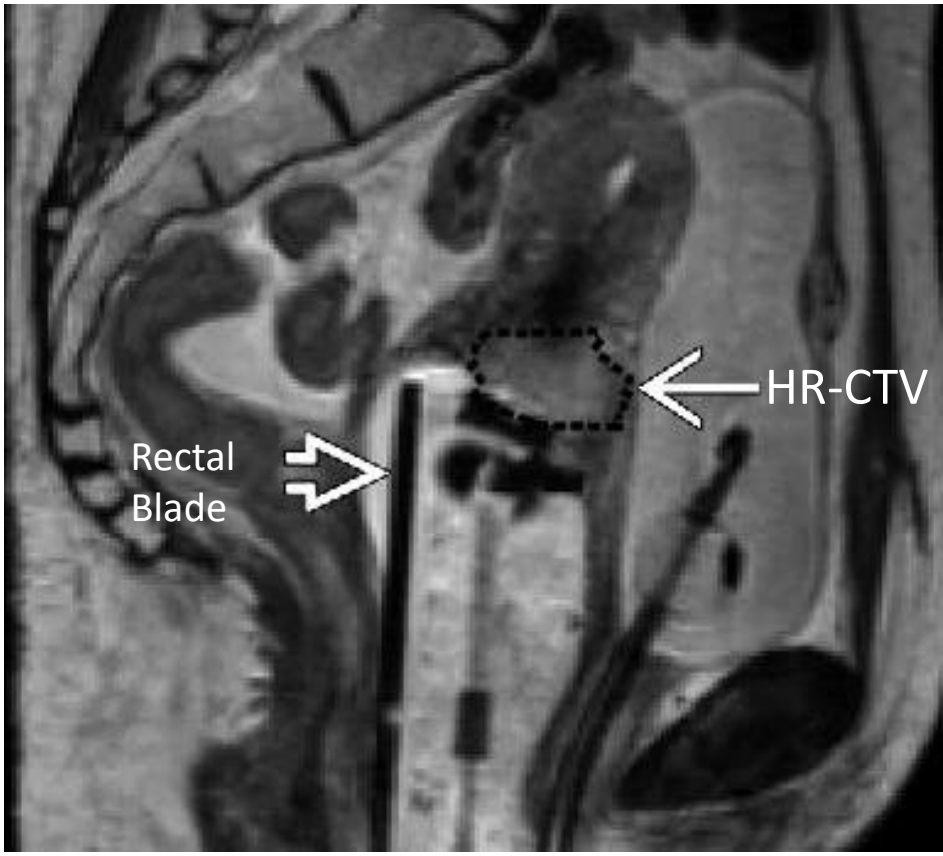
MR at the time of brachytherapy may be of greatest benefit in patients with large tumors with parametrial extension that have a partial or complete response to external beam.

Issues with MRI

- Superior soft tissue resolution
- HRCTV smaller than on CT
- Greater conformality will lead to decrease dose to OARs
  - Possibly 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)

CT vs MRI





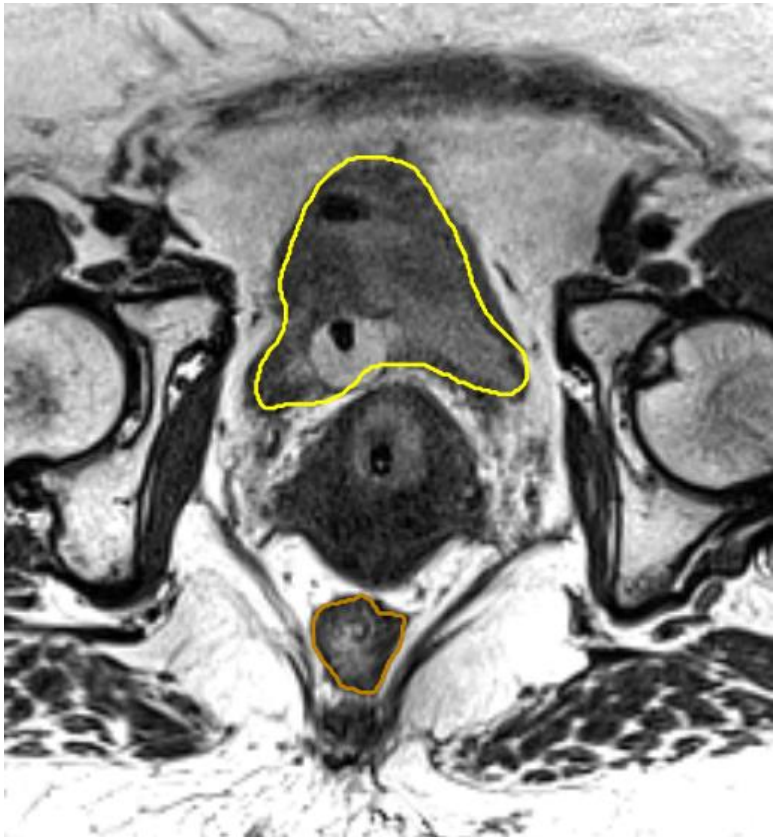
- Use all 3 planes when contouring: axial, sagittal, and coronal

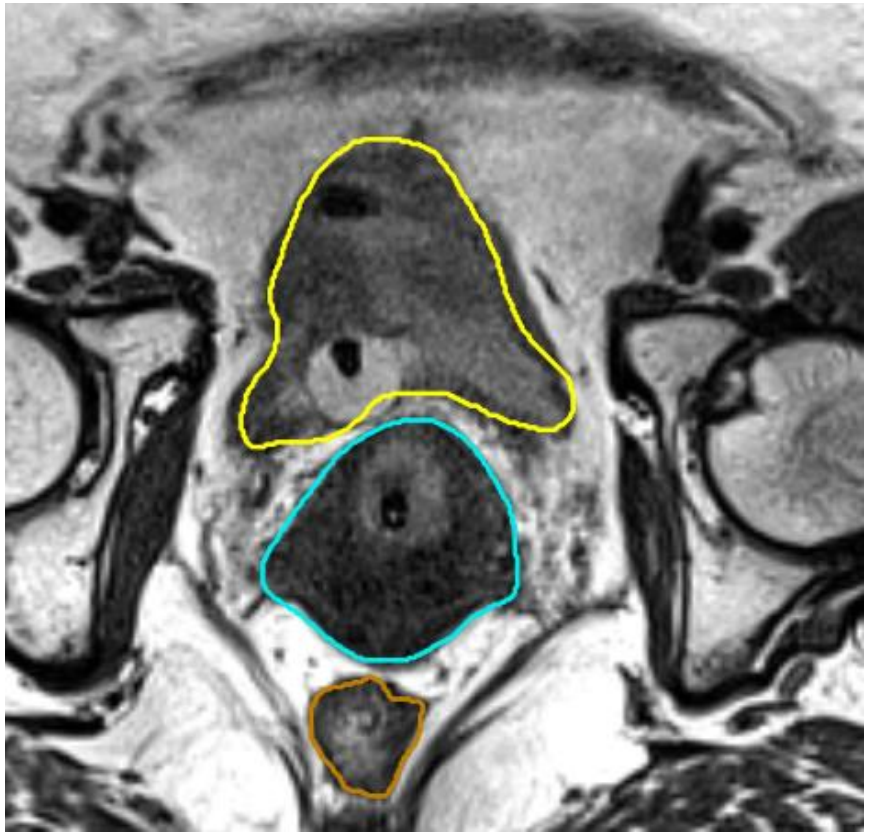
Pretreatment Imaging: Conclusions

- Imaging is useful in patient selection
- Use what you have!
  - US, CT, MRI, PET

Practice your brachy contouring for both CT and MR

(https://www.nrgoncology.org/Resources/Contouring-Atlases/GYN-Cervical-Brachytherapy)





Rules of 15 and 50 for cervical cancer

Stage	% 5 year survival	% + Pelvic LN	% + PA LN	%LR control (+ PA LN)	% + DM (+PA LN)
I	85	15	50	50	50
II	70	30	50	50	50
III	55	45	50	50	50

No role for unselective, prophylaxis of para-aortic (PA) lymph nodes.

If + PA LN at L2 and above: low cure rate. Palliate or protocol.
If + pelvic LNs consider PA RT.
Resect or boost LN's >3 cm.