ASTRO ANNUAL refresher COURSE 2021

BEST PRACTICES AND EMERGING TRENDS

March 19-21 *Live* Interactive Virtual Conference

Welcome

Update on Management of Gynecologic Cancers

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Disclosures
none

Learning objectives

1. Discuss a compressed version of Standard management of gynecologic cancers

2. Apply the UPDATED HYBRID use of image guided brachytherapy for cervical cancer to your clinical practice.

3. A quick Peek at recent promising advances .

Promising advances in Management of Gyn Tumors 2021

1. Translational biology comes to the forefront

2. Radiation Treatment delivery tips and aids

3.Integration of RT with other agents .

Will try to point these areas during the talk

Management of Endometrial Cancer

Epidemiology:

- Main risk factors:
  - Obesity, nulliparity, tamoxifen
  - Unopposed estrogen
  - Diabetes, hypertension
  - Lynch syndrome
- Protective factors:
  - Breastfeeding, smoking, physical activity
- ~70% diagnosed at early state

Breast	266,120	30%
Lung & Bronchus	112,350	13%
Uterine corpus	63,230	7%
Thyroid	40,900	7%
Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	32,650	4%
Pancreas	26,240	3%
Leukemia	25,270	3%
Kidney & renal pelvis	22,660	3%
All sites	878,980	100%

Endometrial Cancer Subtypes

Type I: Endometrioid (70-80%)

Type II: Non-endometrioid (Papillary serous/clear cell/carcinosarcoma)

	Type I	Type II
Associated clinical features	Metabolic syndrome: obesity, hyperlipidaemia, hyperglycaemia, and increased oestrogen concentrations	None
Grade	Low	High
Hormone receptor expression	Positive	Negative
Histology	Endometrioid	Non-endometrioid (serous, clear-cell carcinoma)
Genomic stability	Diploid, frequent microsatellite instability (40%)	Aneuploid
TP53 mutation	No	Yes
Prognosis	Good (overall survival 85% at 5 years)	Poor (overall survival 55% at 5 years)

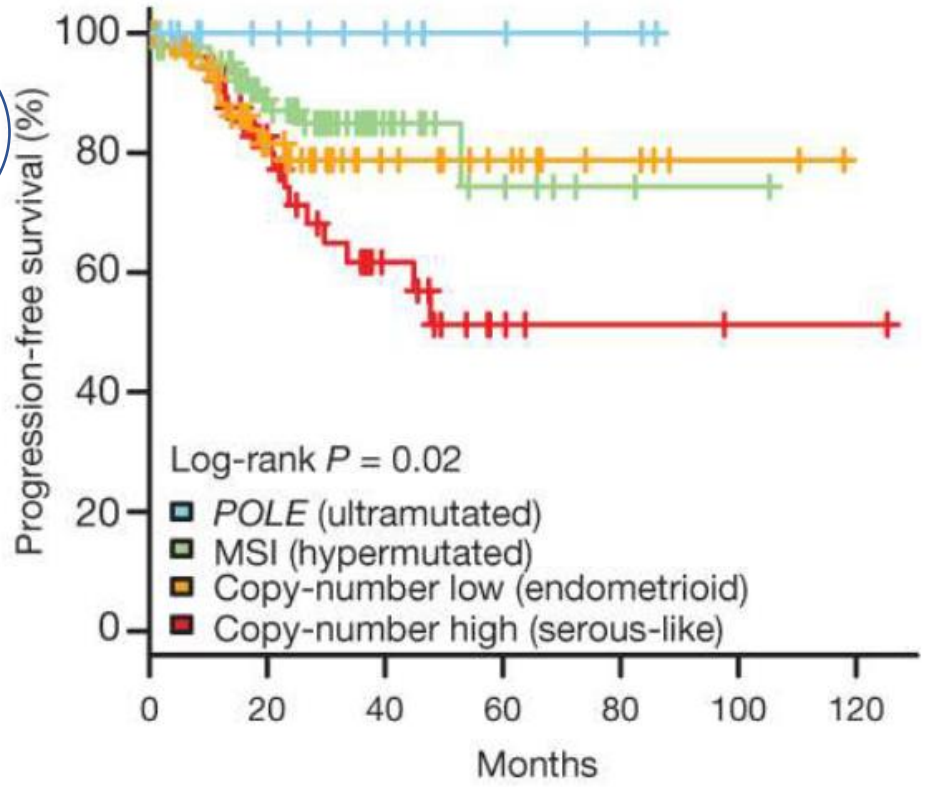
Table 1: **Dualistic classification of endometrial cancers, by Bokhman subtype**

Morice et al. Lancet. 2016

Histologies:

- **POLE:**
  - 6.4% of low grade
  - 17.4% of high grade
- **Hypermutated/MSI unstable**
  - 28.6% low grade
  - 54.3% high grade
- **Copy number low (endometrioid)**
  - 60% low grade endometrioid
  - 8.7% High grade endometrioid
  - 2.3% serous carcinomas
  - 25% mixed histology
- **Copy number high (serous like)**
  - Serous
  - 90% p53 mutations

Immuno Responsive



Cancer Genome Atlas Research Network, Nature 2013

FIGO Staging:

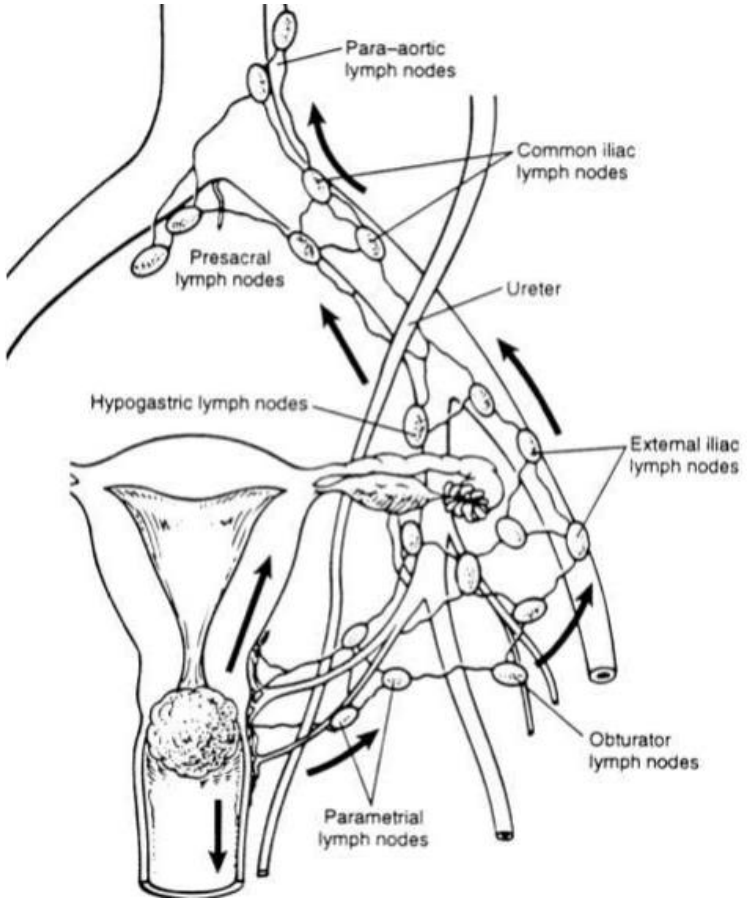
1988

IA	Endometrium only
IB	≤ 50% Invasion of myometrium
IC	> 50% Invasion of myometrium
IIA	Cervix - Endocervical glands
IIB	Cervix - Stromal invasion
IIIA	Serosa / adnexa / cytology
IIIB	Lower vagina
IIIC	Pelvic or PA nodes
IVA	Bladder or rectum
IVB	Distant

2009

IA	Endometrium only ≤ 50% Invasion of myometrium
IB	> 50% Invasion of myometrium
II	Cervix - Stromal invasion
IIIA	Serosa / adnexa /
IIIB	Lower vagina
IIIC1	Pelvic nodes
IIIC2	Para-aortic nodes
IVA	Bladder or rectum
IVB	Distant

Pelvic lymphatic drainage



Uterus/cervix: USA ME LIES

1. **U**pper Uterine: **S**uperficial inguinal and **A**ortic

2. **M**iddle portion (uterine body): **E**xternal iliac nodes

3. **L**ower portion (cervix): **I**nternal iliac nodes, **E**xternal iliac nodes, **S**acral nodes

Vagina:

1. Upper 2/3: external and internal iliac nodes.
2. Lower 1/3: superficial inguinal lymph nodes.

Benedetti-Panici
Gynecol Oncol 1996

GOG-33: Grade and invasion vs nodal metastases

	n	Grade 1 (180)	Grade 2 (288)	Grade 3 (153)
Depth		Pelvic LN	Pelvic LN	Pelvic LN
Superficial	281	3 (3%)	7 (5%)	5 (9%)
Middle	115	0 (0%)	6 (9%)	1 (4%)
Deep	139	2 (11%)	11 (19%)	22 (34%)

GOG-33: Relationship of Pelvic and Aortic Nodes

	Aorta		
Pelvic	Negative	Positive	Total
Negative	551 (89%)	12 (2%)	563 (91%)
Positive	36 (6%)	22 (3%)	58 (9%)
Total	587 (95%)	34 (5%)	621 (100%)

- Positive pelvic nodes were associated with a high risk of positive para-aortic nodes (22/58 – 37%)

Principles of Surgical evaluation and staging

- Total Hysterectomy/BSO and lymph node assessment by any surgical route though minimally invasive is better
- Lymph Node included Pelvic+/_ PA nodal dissection (esp for advanced stage and high risk histologies)
- PA Nodes dissected to level of IMA /or higher (see later)
- Sentinel Node mapping considered for uterine confined lower grade cancers (Update - now also being done for HIGH RISK PTS):nccn
- Omental and Peritoneal biopsy for serous and clear cell carcinoma
- NCCN, SGO guidelines

Surgico-pathologic risk factors for Recurrence :

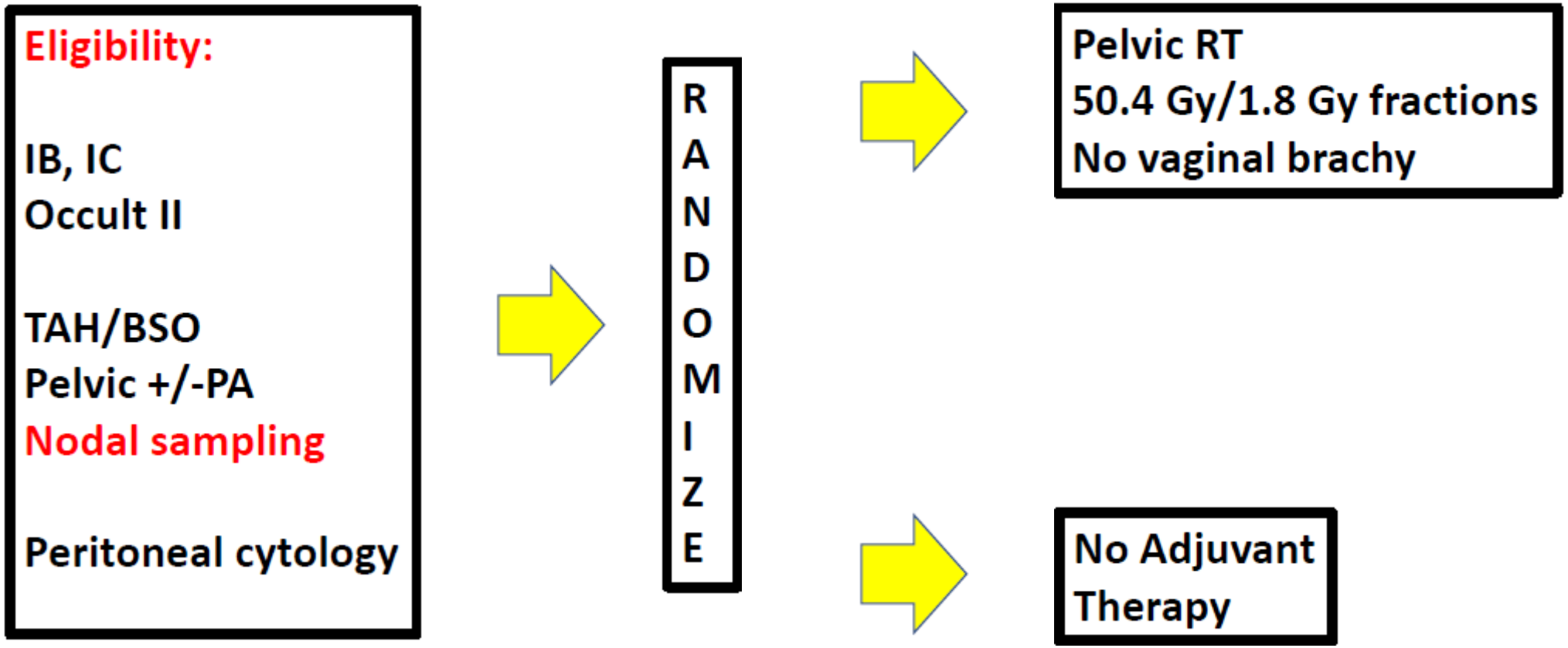
- Depth of myometrial invasion
- Cervical invasion
- Pathologic grade
- Histologic type
  - Higher risk: serous, clear cell, carcinosarcoma
- Lymphovascular space invasion
- Tumor size
- Low uterine segment extension

Adjuvant Radiation Trials

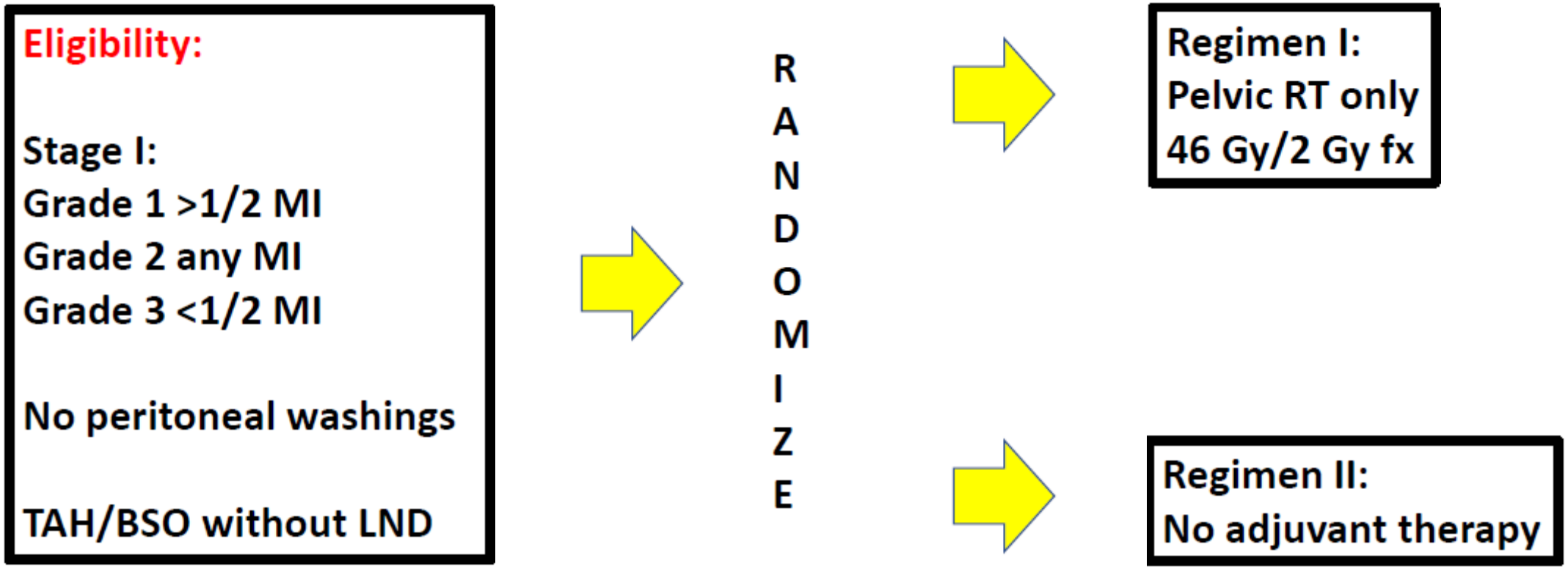
- **Norwegian**
- **PORTEC-1**
- **GOG 99**
- **PORTEC 2**
- **ASTEC**
- **Swedish**

@GynRadOnc

GOG 99:

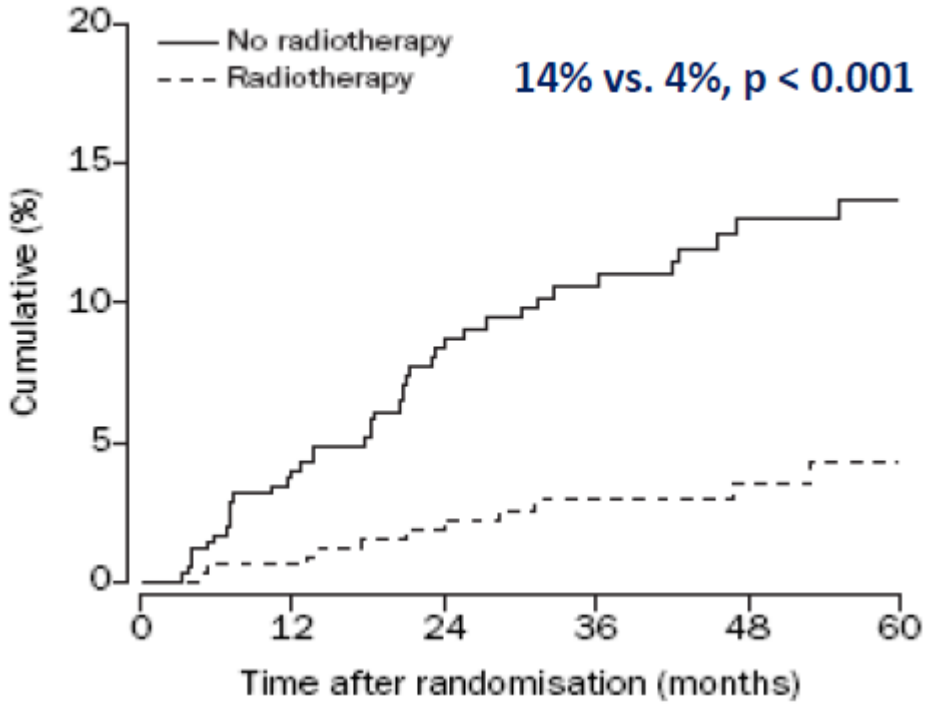

Eligibility:
IB, IC
Occult II
TAH/BSO
Pelvic +/-PA
Nodal sampling
Peritoneal cytology
RANDOMIZE
Pelvic RT
50.4 Gy/1.8 Gy fractions
No vaginal brachy
No Adjuvant Therapy

PORTEC-1 (Postoperative Radiation Therapy in Endometrial Cancer):



Pelvic Recurrence:

PORTEC-1
Recurrence Rate



GOG-99

Site	NAT	EBRT
Local Recurrence	18(8.9%)	3(1.6%)
Vagina	13	2*
Pelvis	4	0
Vagina and pelvic	1	1

Intermediate risk endometrial carcinoma: phase III studies

Study	# pts	Inclusion	Surgery	TX arms	LRR	Survival
Norwegian	540	I	TAH-BSO	VBT vs pelvic RT/VBT	7% vs 2% at 5 years *p*<0.01	89% vs 91% 5 years p=NS
PORTEC-I	714	IB G2-3 IC G1-2	TAH/BSO	NAT vs pelvic RT	14% vs 4% 5 years p<0.001	85% vs 81% 5 years p=0.31
GOG 99	392	IB/IC occult II	TAH/BSO LND	NAT vs pelvic RT	12% vs 3% at 2 years p<0.01	86% vs 92% 4 years p=0.56
ASTEC/EN5	905	IA/B G3, IC, II, **serous/cc**	TAH/BSO +/-LND	NAT vs pelvic RT	7% vs 4% 5 years p<0.01	84% vs 84% 5 years p=0.98
PORTEC-2	547	IB/IC G1-2 >60 yrs IIA G1-2 IIA G3 w/<50% MI	TAH/BSO	pelvic RT vs VBT	5.1% vs 2.1% 5 yrs p=0.17	79.6% vs 84.8% 5 yrs p=0.57
Swedish	527	I with at least 1 RF: g3, ≥MI, DNA aneuploidy, nuclear g1-2	TAH/BSO	EBRT/VB vs VBT	1.5% vs 5% (p=0.013)	89% vs 90% p=0.548

High intermediate risk groupings:

GOG 99	PORTEC
Risk factors: grade 2-3 LVSI outer 1/3 MI	Age >60 yo: G1 or G2 ≥50% MI G3 with <50% MI Any age: IIA G1 or G2 G3 with ≤50% MI
Age ≥ 70 yrs with 1 risk factor Age ≥ 50 yrs with 2 factors Any age with all 3 factors	
19% improvement in any recurrence at 2 years with RT (entire cohort)	20% benefit in <u>loco-regional recurrence in 10 years with RT</u>

Patterns of failure: PORTEC and GOG99

mostly in the vagina

PORTEC

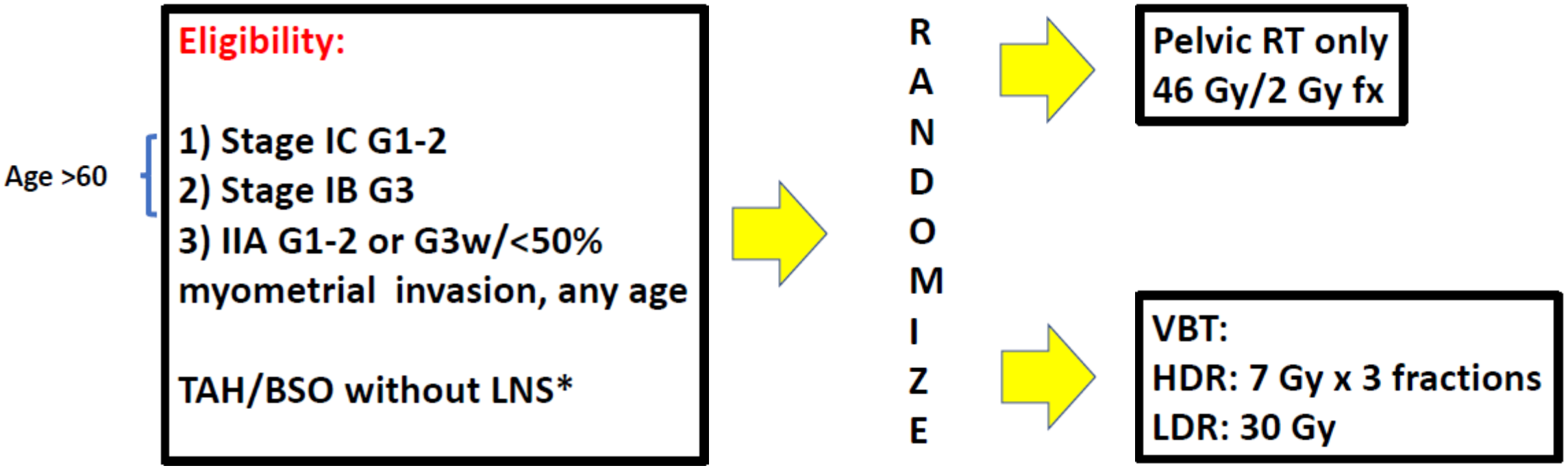
5 year	EBRT	NAT	
Locoregional recurrence	4.2%	13.7%	P<0.001
Vaginal recurrence	2.3%	10.2%	~67% of failures in vagina
Pelvic	2.0%	3.4%	

GOG99

Site	NAT	EBRT
Local Recurrence	18(8.9%)	3(1.6%)
Vagina	13	2*
Pelvic	4	
Vagina and pelvic	1	
Distant Recurrence	13(6.4%)	10(5.3%)

~2/3rds the risk of recurrence in the vagina

PORTEC-2 (Postoperative Radiation Therapy in Endometrial Cancer):



PORTEC-2: 5 and 10 yr data

	EBRT		VBT		*p* Value
	No.	5 yr %	No .	5 yr %	
Vaginal Recurrence	4	1.6%	3	1.8%	0.74
Pelvic recurrence	**1**	**0.5%**	**8**	**3.8%**	**0.02**
Locoregional recurrence	5	2.1%	10	5.1%	0.17
Distant metastases	13	5.7%	16	8.3%	0.46
First failure type					
Vaginal recurrence	2	1.1	1	0.9%	0.57
Pelvic recurrence	1	0.5%	3	1.5%	0.30
DFS		78.1%		82.7%	0.74
OS		79.6%		84.8%	0.57

*Median f/u of 45 months

Pelvic Recurrence 0.9 vs 6% AT 10 YRS sig

PORTEC-2 Toxicities:

N(%)	EBRT 214	VBT 213	*p* Value
Gastrointestinal			**<0.001**
Grade 1	74(35)	25(12)	
Grade 2	40(19)	1(1)	
Urinary			0.39
Grade 1	53(25)	41(20)	
Grade 2	4(2)	4(2)	
Vaginal			0.10
Grade 1	11(5)	19(9)	
Grade 2	3(2)	8(4)	
Skin			**<0.001**
Grade 1	13(6)	2(1)	
Grade 2	7(3)	0(0)	

PORTEC 2: Conclusions

- Risk of pelvic recurrence is low in this group(Increases with followup)
  - Criticism: lower risk population than PORTEC-1
- Vaginal Brachytherapy is sufficient for this unstaged population:
  - IB/IC G1-2 >60
  - IIA G1-2 or G3w/<50% myometrial invasion
- Side effects from VBT are low

ASTRO Stage I Guidelines(to be updated soon)

Characteristic	Recommendation	Strength of data
Grade 1-2, <50% MI, no high risk features	No adjuvant treatment	High
Grade 1-2, <50% MI; age >60, LVSI, or other risk factors	Observation or VBT	Medium
Grade 3 with no MI	Observation or VBT	Low
Grade 1-2, >50% MI	VBT / EBRT if risk factors *Ł	Medium
Grade 3, <50% MI	VBT	Medium
Grade 3, >50% MI	EBRT	High

*Risk factors: age >60, LVSI
unstaged also consider
Ł-substantial LVSI

Klopp Pro 2014

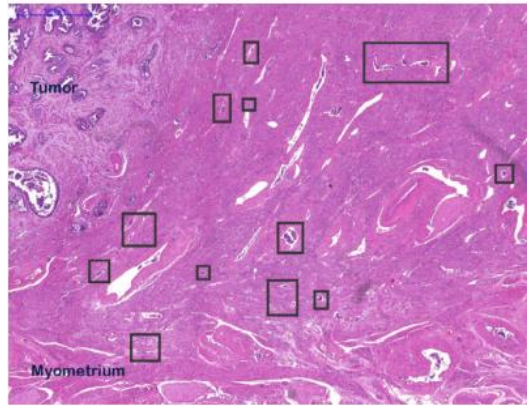
ESMO RISK GROUP CLASSIFICATIONS

Risk Group	Characteristic	Strength of data
Low	Grade 1-2, <50% MI, no high risk features ,Stage I	I
Intermediate	Stage I,Grade 1-2, >50% MI,no LVSI	I & III
High Intermediate	Stage I,Grade 3 <50% MI,regardless of LVI	III
	Stage I,Grade 1-2,LVSI+ regardless of depth	III
High Risk	Stage 1 Grade 3> 50% MI, Stage 2	III
	Non-Endometrioid (Serous / Clear cell)	I

- If LVSI is present and patient was not surgically staged, recommendation is to perform EBRT, esp if diffuse LVSI risk factor

Colombo Annals Onc 2016

Pooled PORTEC 1 & 2-LVSI five year Data



- 3 tired system had best prognostic value
  - No LVSI
  - Focal: Single focus LVSI was seen
  - Substantial: Diffuse or multifocal LVSI seen
- Substantial LVSI independent predictor for distant metastasis and OS
- In patients with substantial LVSI, risk of pelvic recurrence at 5 years was **4.3% with EBRT compared to 27.1% for vaginal brachytherapy and 30.7% for observation.(so consider EBRTfor diffuse LVI)**
- Limitation: only 4.8% of patients (44 patients) had substantial LVSI
- Difficult –not commonly done in most US centers, also pts were unstaged

Bosse, Eur J Cancer 2015

High risk histologies, early stage: VB±EBRT/chemo4-6

Reference	Year	N	Inclusion	Survival	Total pelvic Recurrence	Vaginal recurrence
Uterine serous and clear cell carcinoma						
DFCI	2013	37	Stage I-II USC or CC	2 yo OS 100% 2 yr DFS 89.3%	5.4	2.7
Mayo	2013	103	Stage I USC or CC	2 yo OS 79%	4.0%	2.0%
MSKCC	2012	41	I-II USC	5 yo OS 90%	9%	0%
Carcinosarcoma						
Mayo	2015	33	Stage I-II CS	2 yo OS 79%	9%	6%
Penn/Iowa	2016	42	I-II CS	2 yo OS 85%	7.1%	

Key take home point:

- Upper vagina main site of LRR in early stage uterine cancer
- Vaginal brachytherapy alone for intermediate risk stage I uterine ca, endometrioid type
  - EBRT reserved for highest risk patients (over 60 years old,deepinvasion+G3, sub LVSI,unstaged)
- Combined VB/EBRT and chemo for high risk histologies, early stage

Vaginal brachytherapy:

- Dose specification
  - 5 mm vs surface
- Length of vagina
  - Variable
  - 3-5 cm of upper vagina
- Applicators
  - Single channel vs multi-channel
- Treatment Planning
  - 3D vs 2D
  - 3D allows for air gap assessment, normal tissue dose

Vaginal brachytherapy: fractionation

Monotherapy

Dose	Rx point
7 Gy x 3	5 mm
5 Gy x 5	5 mm
2.5 Gy x 5	5 mm
6 Gy x 5	Surface[#]
4 Gy x 6	Surface[$]

[#]MDA
[$]BWH

Post EBRT

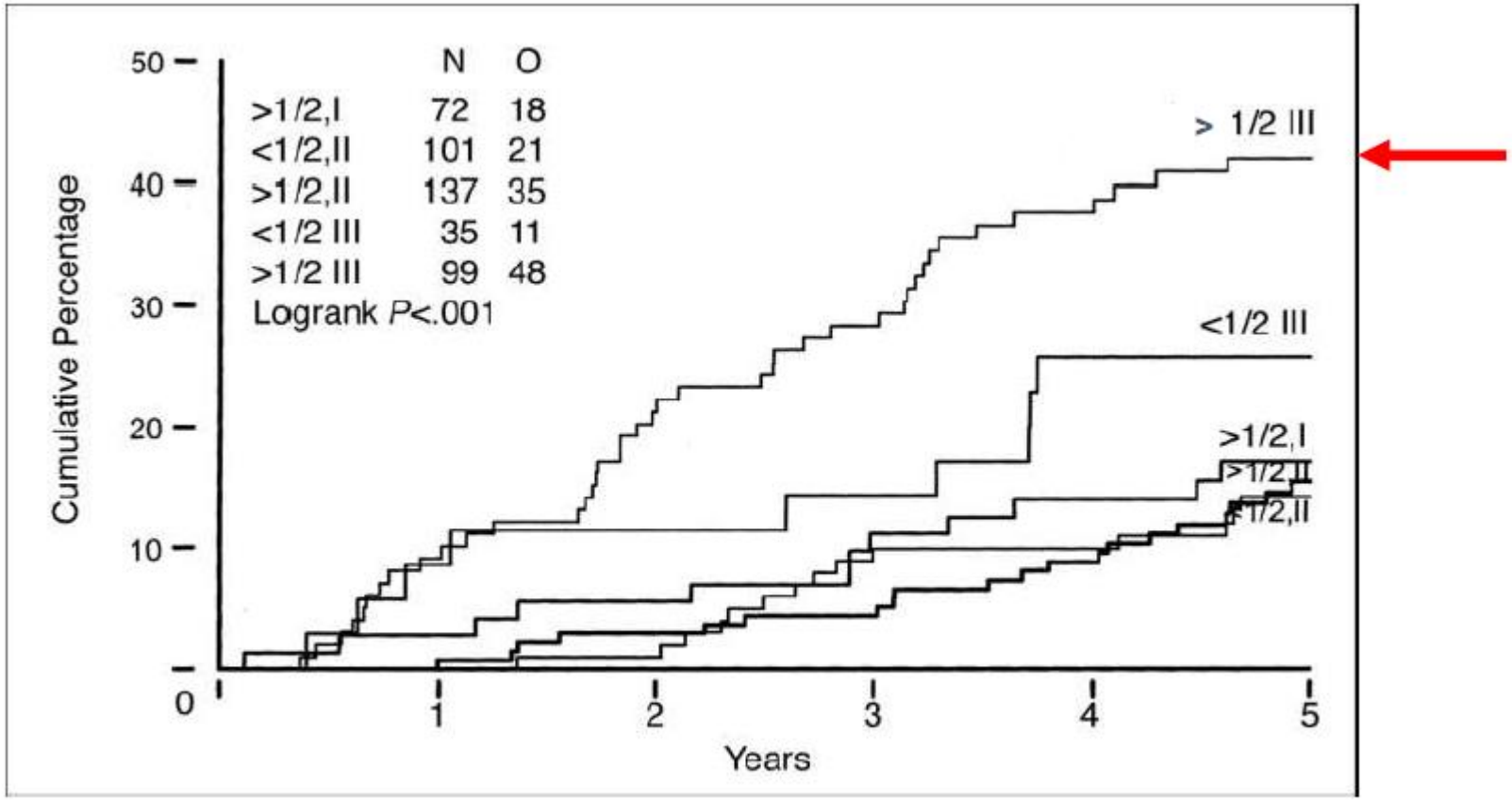
Dose	Rx point
6 Gy x 3	Surface*
6 Gy x 2	Surface*
5 Gy x 2	Surface[#]

*RTOG 0921 and 0418
[#]MDA

Q What would you recommend in your clinical practice? 61 yo IBG2, + sub.LVSI, met 0/5 LN

- Vaginal brachytherapy
- Vaginal brachytherapy and chemotherapy
- External beam radiotherapy
- External beam radiotherapy with concurrent chemo followed by adjuvant chemotherapy
- Observation

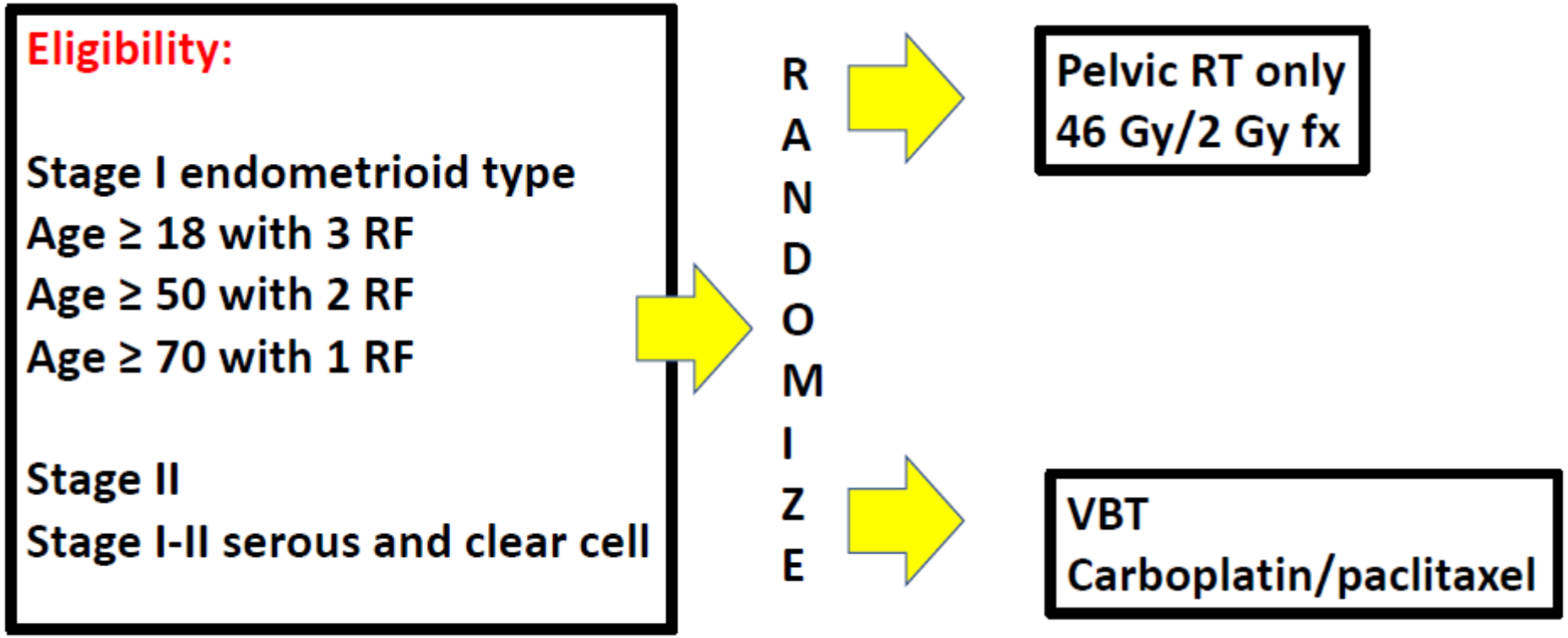
PORTEC-1 (IBG3) Probability of Death(all):



Creutzberg C L et al. JCO 2004;22:1234-1241

Risk of relapse is high: what about chemotherapy?

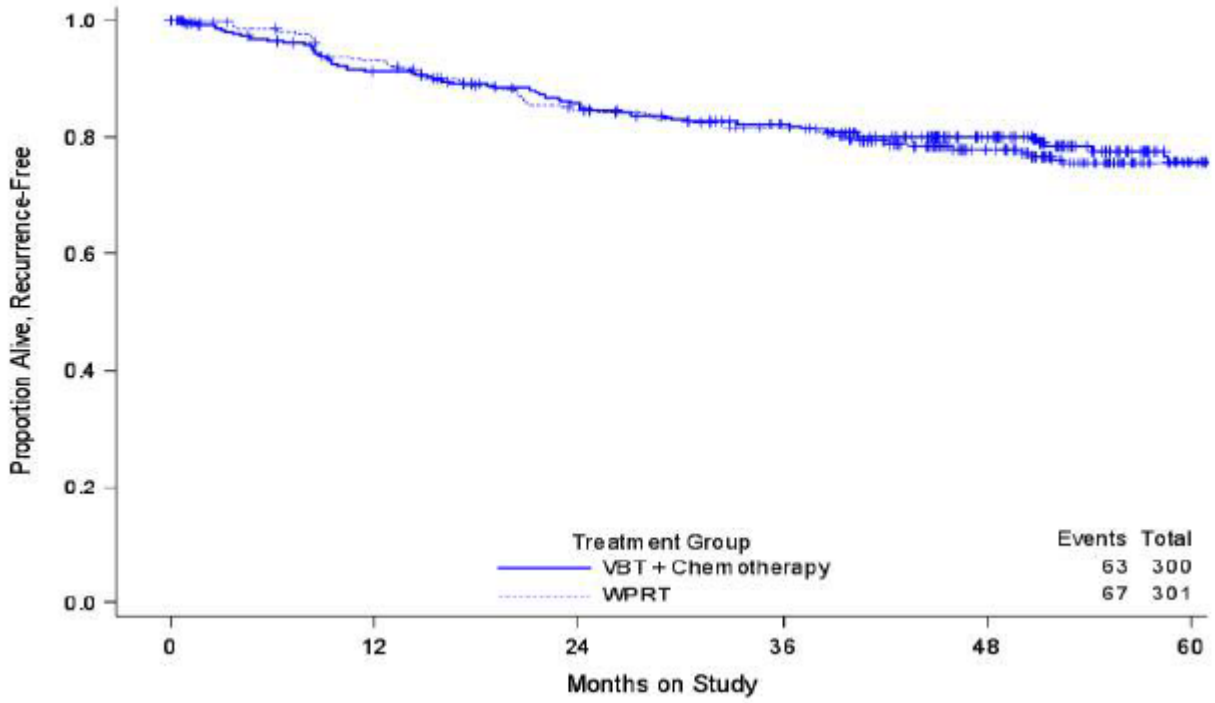
GOG249:



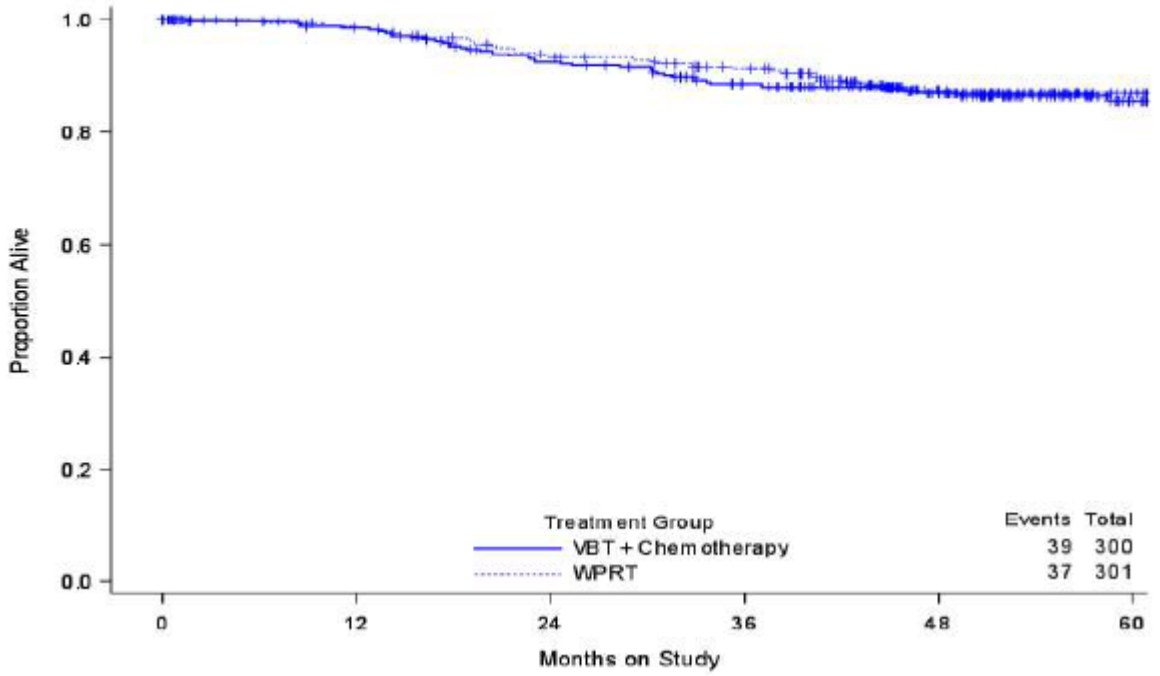
*high-intermediate risk uterine risk factors (endometrioid):
G2-3, outer ½ depth of MI, LVSI
89% lymphadenectomy

GOG249:

Relapse free survival



Overall Survival



Toxicities: GOG249:

- Acute toxicity ≥grade 3
  - EBRT 11% vs VB/C 64%

- Late toxicities ≥grade 3
  - EBRT 13% vs VB/C 12%

Summary and Key Points:

- Consider pelvic radiotherapy for highest risk stage I/II

- No evidence that addition of chemotherapy improves survival in this subset
- Cautionary points- lower percentage of high risk histology
- Cautionary points- heterogenous group of patients
- So we still use chemo in serous and clear cell uterine ca -> Portec3

Treatment technique

RTOG 1203, "Time-C": Standard 4-field vs IMRT for Post-op Endometrial and Cervical Cancer

STRATIFY		RANDOMIZE		
	XRT Dose 1. 45 Gy 2. 50.4 Gy **Chemotherapy** 1. No Chemotherapy 2. 5 cycles of weekly cisplatin at 40mg/m2 **Disease Site** 1. Endometrial 2. Cervix		**Arm 1** IMRT pelvic radiation treatment **6-MV or higher** **Normalize to IDL between 97-100%** **Field-in-field allowed**	n = 107
			Arm 2 4-field pelvic radiation treatment **Nodal CTV and vaginal ITV + 7 mm** **IMRT, VMAT, tomotherapy allowed**	n = 126

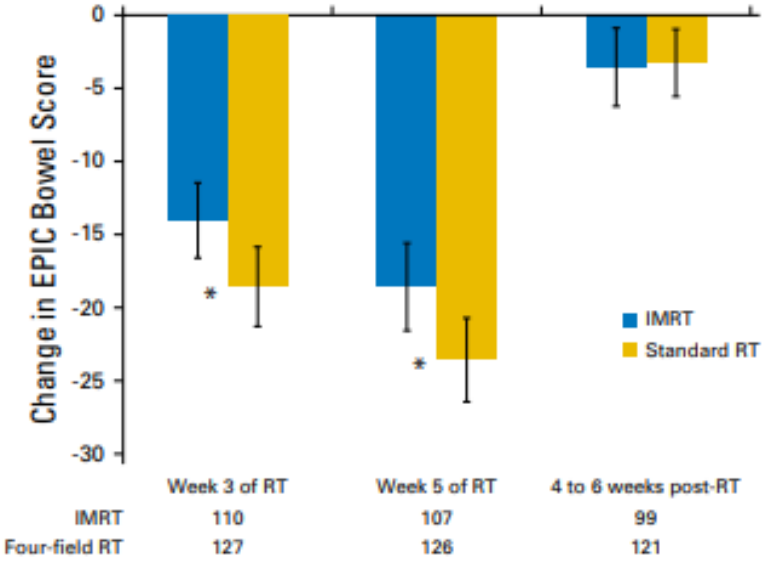
Primary endpoint: GI toxicity from baseline to 5 weeks measured with bowel domain of EPIC (Expanded Prostate Cancer Index Composite)

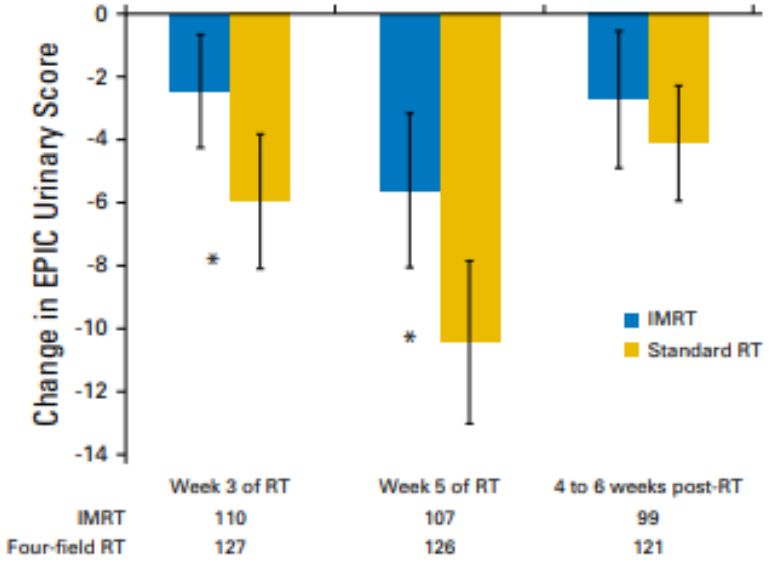
Secondary endpoints:

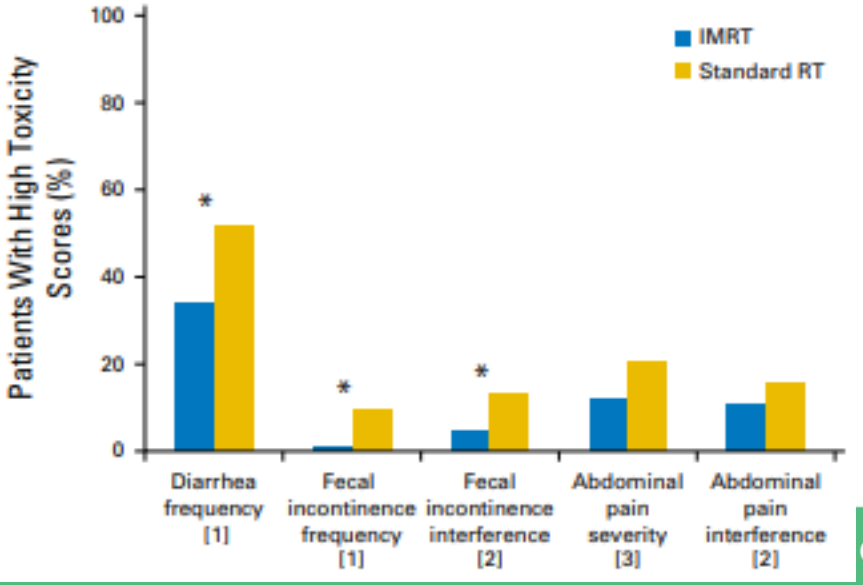
- **GU toxicity from baseline to 5 weeks measured with the urinary domain of the EPIC**
- **Toxicity measured with the PRO-CTCAE**
  QOL measured with the FACT-Cx

Klopp, JCO 2018

RTOG 1203, "Time-C": Standard 4-field vs IMRT for Post-op Endometrial and Cervical Cancer







Conclusion: Pelvic IMRT was associated with significantly less GI and urinary toxicity than standard RT from the patient's perspective.

Klopp, JCO 2018

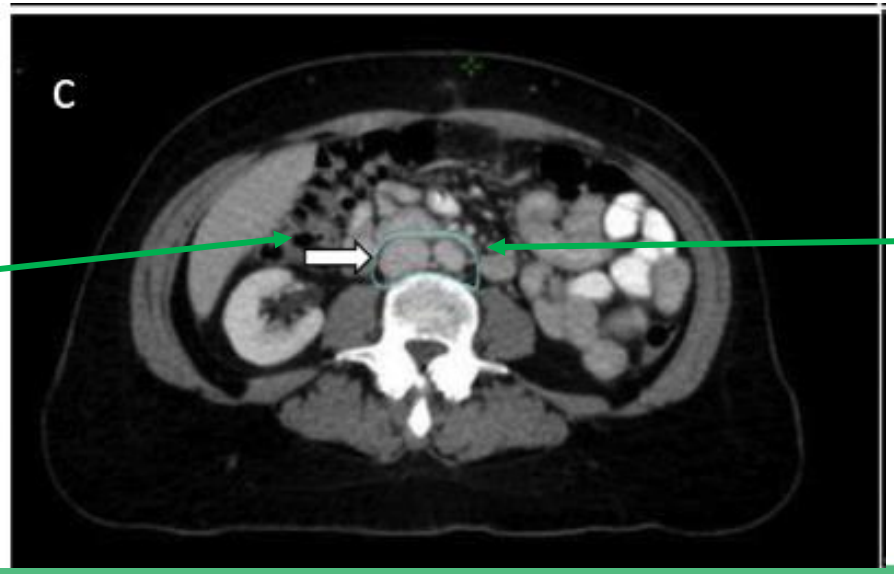
IMRT Contouring new:

NRG Oncology/RTOG Consensus Guidelines for Delineation of Clinical Target Volume for Intensity Modulated Pelvic Radiation Therapy in Postoperative Treatment of Endometrial and Cervical Cancer: An Update

William Small, Jr, MD,* Walter R. Bosch, DSc,†

- Updated and expanded Contouring postop GYN Atlas
- Highlights include Paraotic,Presacral,Obturator nodes
- Details about vaginal CTV

RtPC node-tighter margins
-3-5mm anterior



Lt PAN-extend out 1-1.5 cm out to med border Psoas

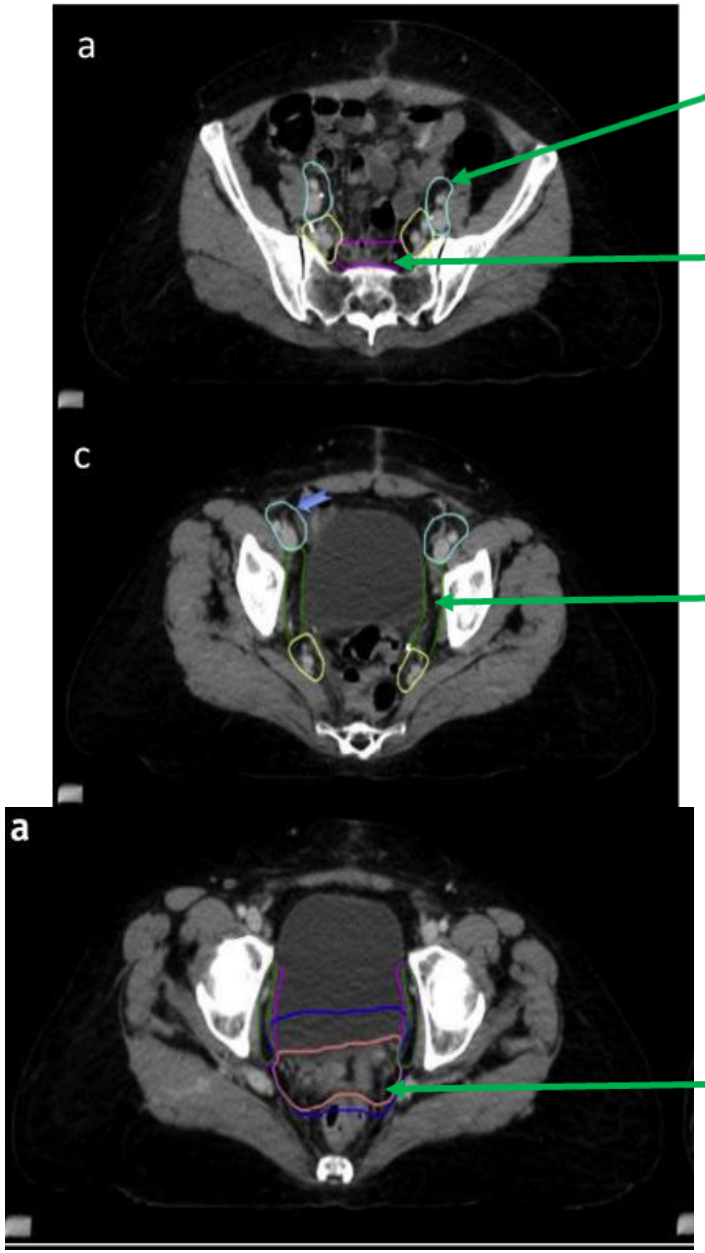
Para-Aortic (PA) Nodal CTV

- PA Nodal CTV borders * :
  - Superior: For cervical cancer: level of left renal vein; For endometrial cancer: 1-1.5cm above the left renal vessels.
  - Inferior: bifurcation of the aorta where it becomes common iliac CTV.
  - Anterior: 3-5mm anterior to IVC up to 7mm anterior to aorta; the CTV delineation at the aortocaval space should be straight rather than concave.
  - Posterior: vertebral body, excluding bone and muscle.
  - Lateral: A right lateral expansion of 3-5mm off the IVC is used; A left lateral expansion off the aorta of 1-2cm is typically used, extending to the medial border of the left psoas muscle.

* There are some exceptions to these recommendations. See manuscript for additional details

Vaginal CTV(should have ITV)

- The vaginal CTV should include the proximal 3.5-4cm* of the vaginal canal and any paravaginal or retracted parametrial tissue that can be visualized on the planning CT.
  - The urethra can be excluded from the CTV for routine cases.
- Consider using a flexible vaginal marker at the time of CT simulation to better visualize the vaginal cuff. Surgical clips at the cuff may also help with visualization.
- The CTV should extend posteriorly to the anterior rectal wall and should include the anterior 1/3 of the mesorectum *. The anterior border is the posterior aspect of the bladder wall.
- The lateral extent is the medial border of the obturator nodal CTV or the urogenital diaphragm more inferiorly.



Ext Iliac extend 1 cm anteriorly

Presacral 1-1.5cm

Obturator ITV

Vaginal CTV/ITV include part of Mesorectum

Advanced Endometrial Cancer

FIGO stages **IIIA-IVA**

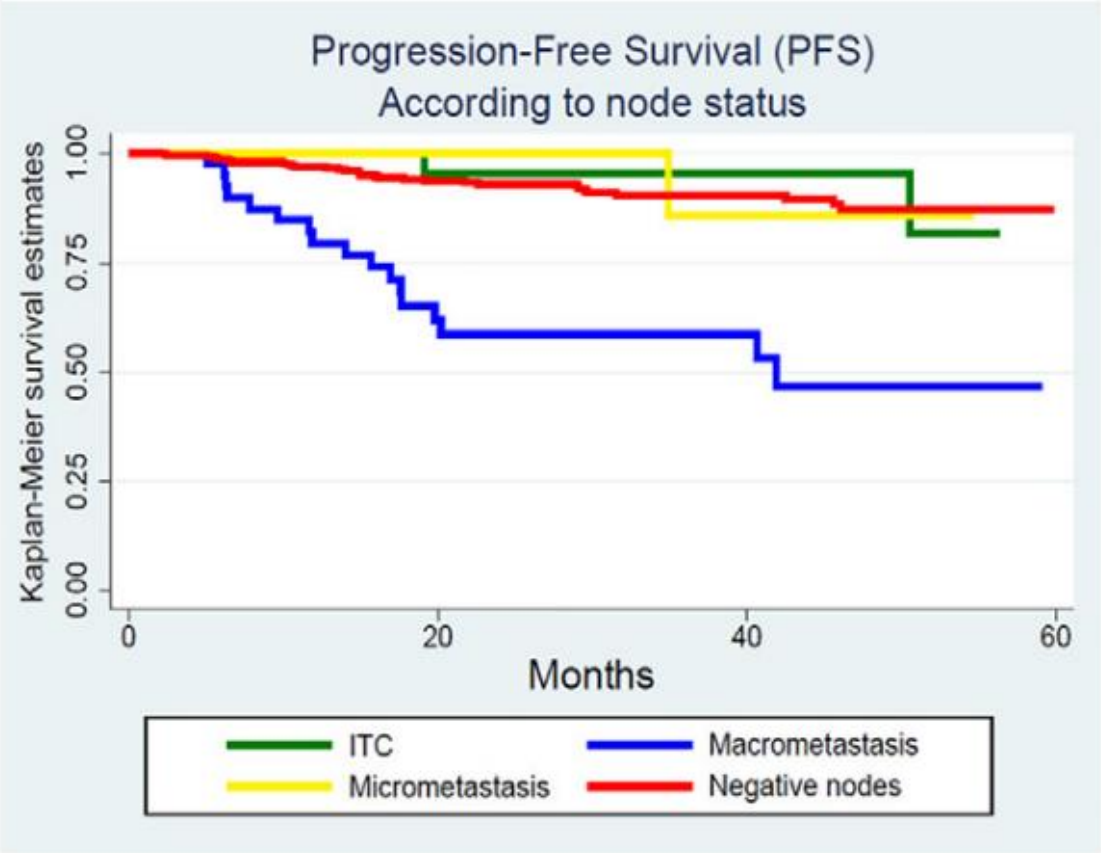
Case Presentation: Advanced Endometrial Ca

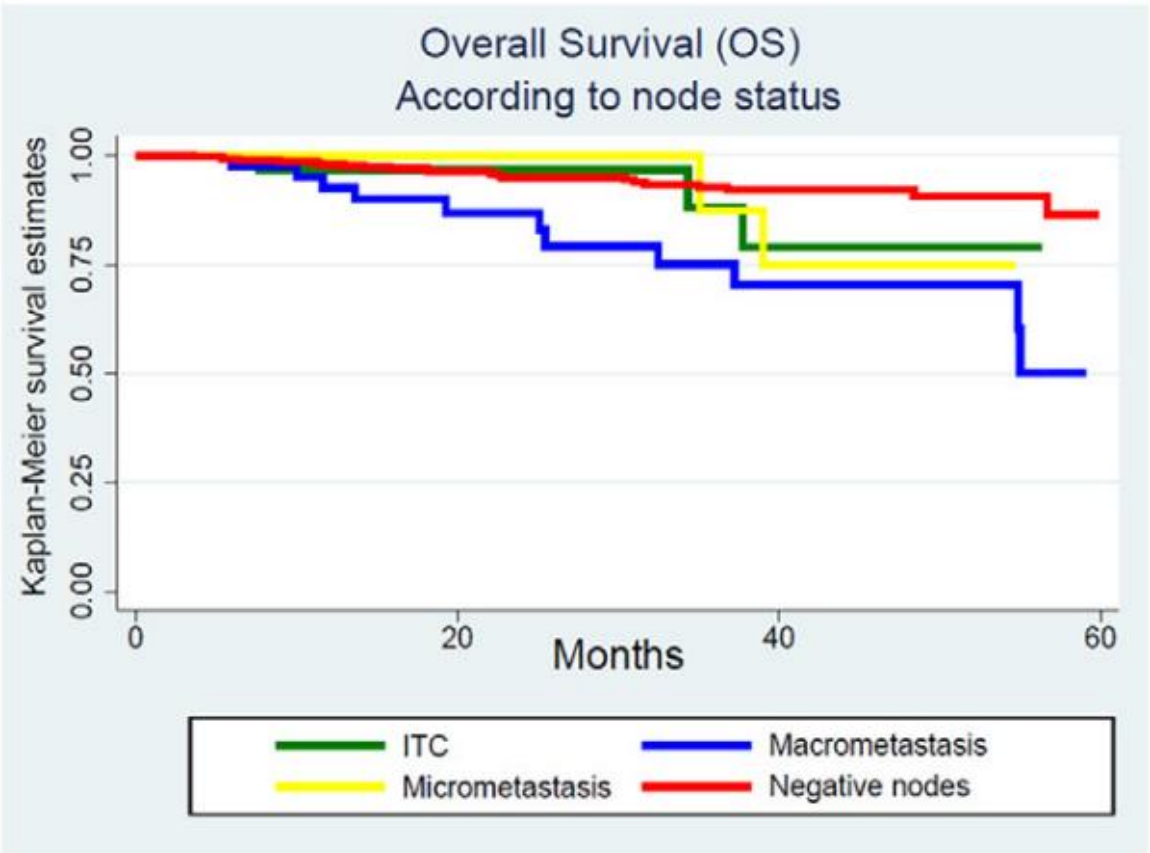
- 52 year old woman with IIIC1 endometrioid adenocarcinoma of the uterus s/p TLH, BSO and bilateral SLN mapping
- Pathology:
  - 4.1 cm FIGO grade 2 EAC
  - 8/19 mm invasion
  - +LVSI
  - SLN (1/2)
    - Positive left external iliac SLN(macromet)
    - Negative right obturator SLN

Q3: What would you recommend in your clinical practice? IIIC1 G2, + SLN

- External beam radiotherapy alone
- External beam radiotherapy and concurrent chemotherapy
- External beam radiotherapy with concurrent chemo followed by adjuvant chemo
- Chemotherapy alone
- Sandwich RT and chemo

Uterine SLN Micromets(0.2to 2mm) AND ITCs (<0.2) ITC behave like node negative patients





Plante et al, GynOnc 2017
Quebec

Predicting Non SLN Mets with ITC-what does the Radiation Oncologist do?
A Turkish Gynecologic Oncology Group Study (TRSGO-SLN-004)-using ESMO risk groups

- **395 Patients** who underwent at least bilateral pelvic lymphadenectomy after SLN mapping were retrospectively analyzed. Patients were categorized into low, intermediate, high-intermediate, and high-risk groups defined by ESMO-ESGO-ESTRO.

- **TABLE shows percent positive nodes and Non-SLN a/c to Risk group**

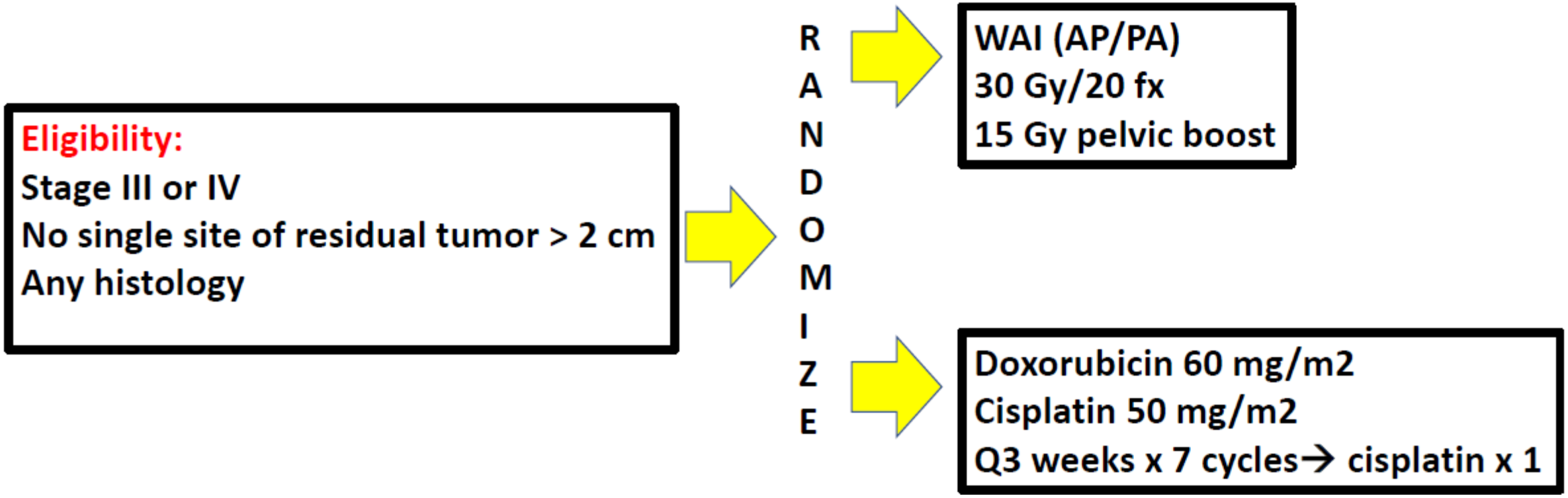
Patients	Low risk (*n* = 228)	Intermediate risk (*n* = 46)	High-intermediate (*n* = 53)	High risk (*n* = 68)
SLN metastasis	4 (1.8%)	5 (10.9%)	12 (22.6%)	21 (30.9%)
Macrometastasis	0	1	6	15
Micrometastasis	2	1	4	3
ITCs	2	3	2	3
Non-SLN metastasis	0/4 (0%)	2/5 (40%)	5/12 (41.7%)	9/21 (42.9%)

Altin et al Journal of Surgical Oncology Dec 2020

Advanced Endometrial Ca

Chemo vs RT

GOG 122:

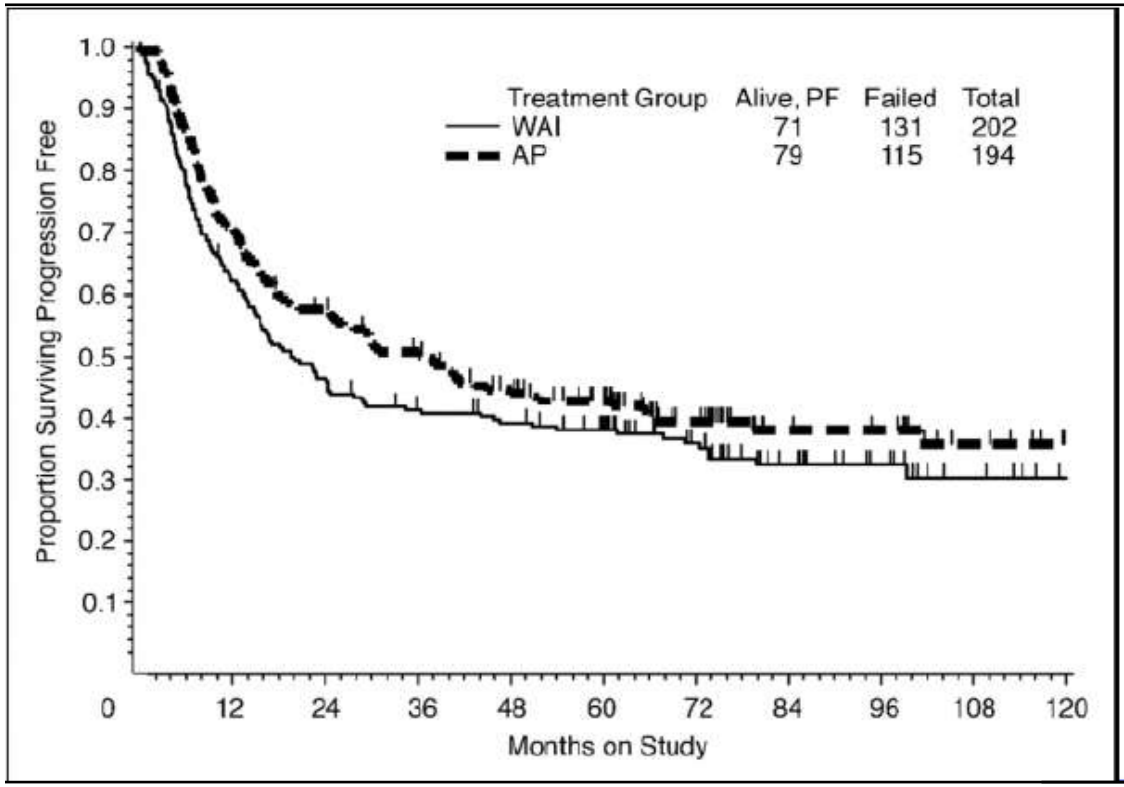


*Nodal sampling optional
+ PA nodes → required scalene biopsy and chest CT

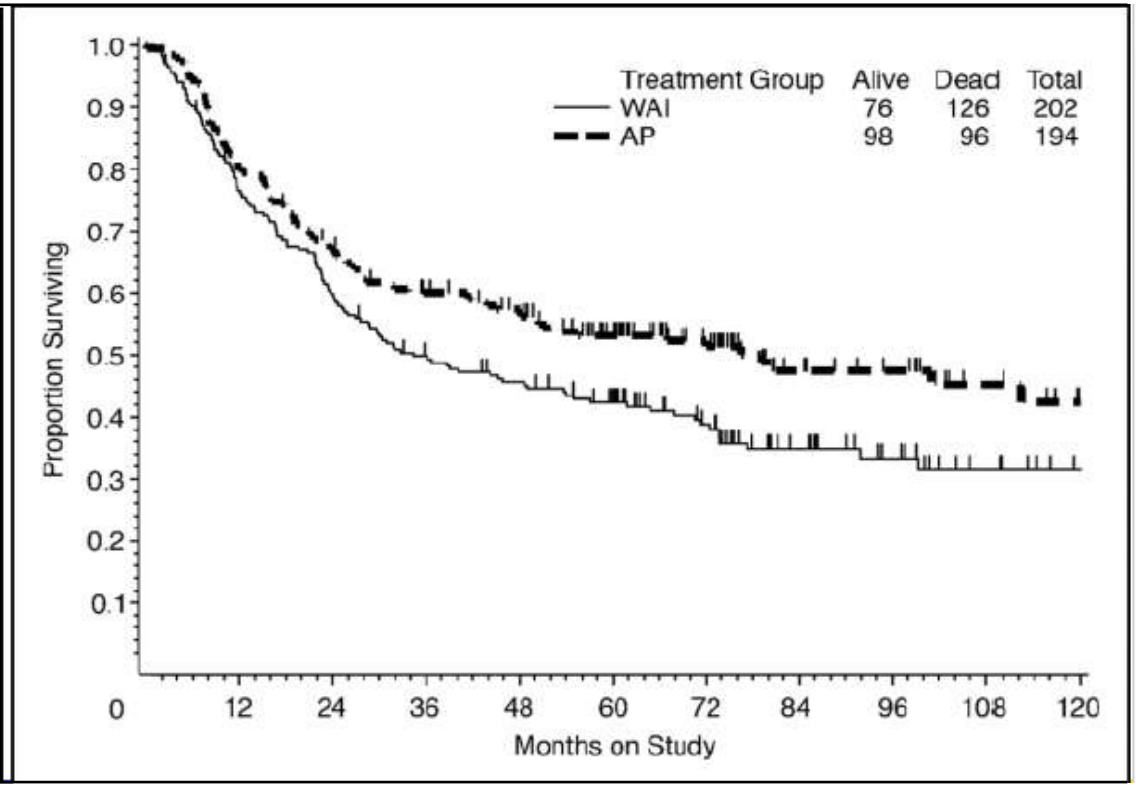
Randall et al JCO 2006

GOG 122:

PFS



Overall survival



GOG 122: Patterns of failure

	WAI	AP
Pelvis	13% (27/202)	18% (34/194)
Abdomen	16% (33/202)	14% (27/194)
Extra-abdominal/Liver	22% (45/202)	18% (34/194)
Distant (exclude liver)	19%	10%

Radiation reduced pelvic recurrence
Only Secondary stage adjusted analysis showed a benefit for chemo

Advanced Endometrial Ca

Sequential Chemo and RT

NSG09501/EORTC55991 and MaNGO:

NSGO/EORTC
Surgical Stage I-II
IIIA+cytology
IIIC (+pelvic LN only)
(optional LND)

MaNGO
IIB, IIIA(+cytology only excluded), IIIC
(included PA nodes)

Serous/clear cell/anaplastic
Ineligible

1996-2007

Primary Endpoint: PFS

RANDOMIZE

Regimen I:
Pelvic RT only
≥44 Gy
Optional VBT (39%)

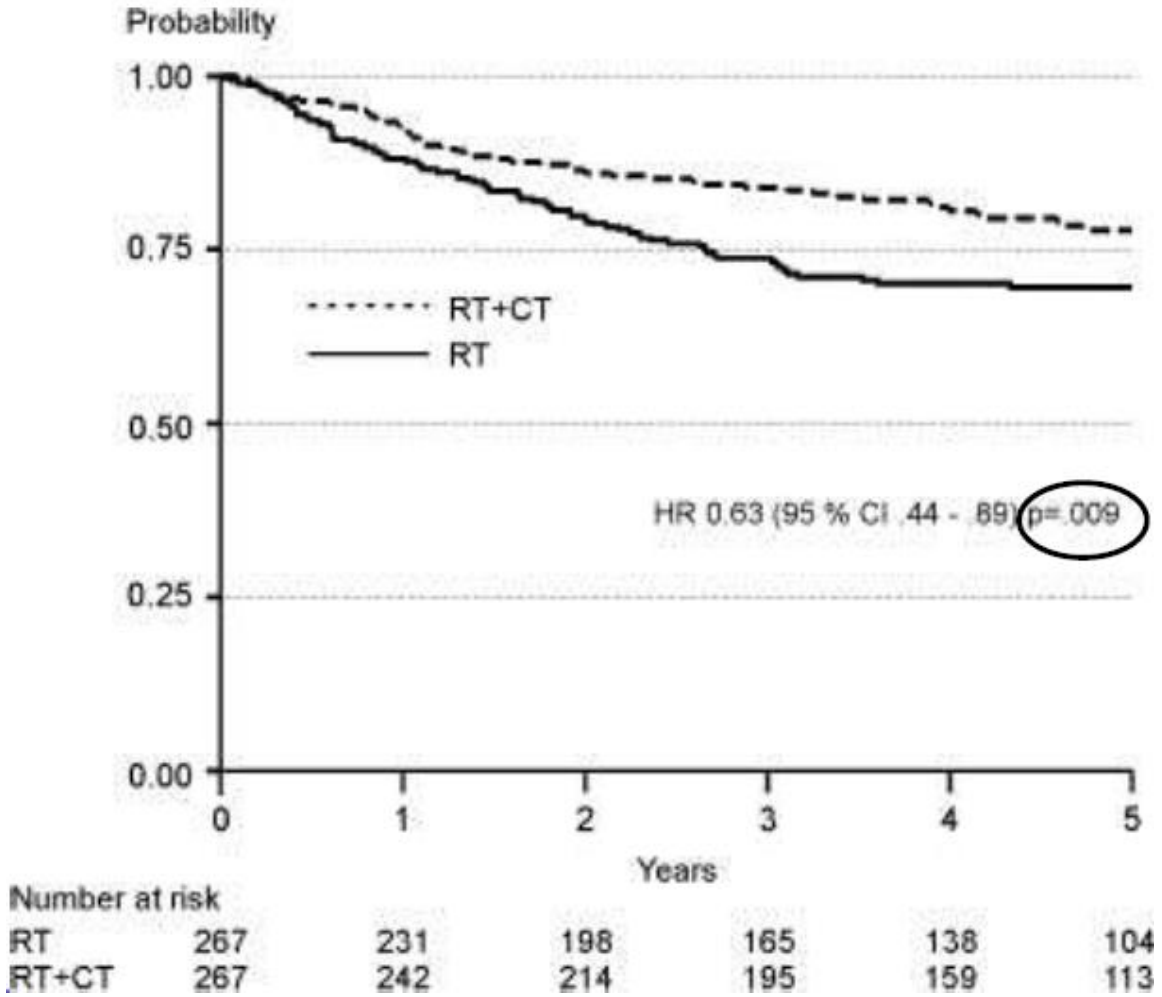
RT→CT or CT→RT
VBT (44%)
NSGO/EORTC CT: initially AP
Later AP, TcP, TAP, TEcP

MaNGO CT: AP

Hogberg et al Eur J Ca 2010

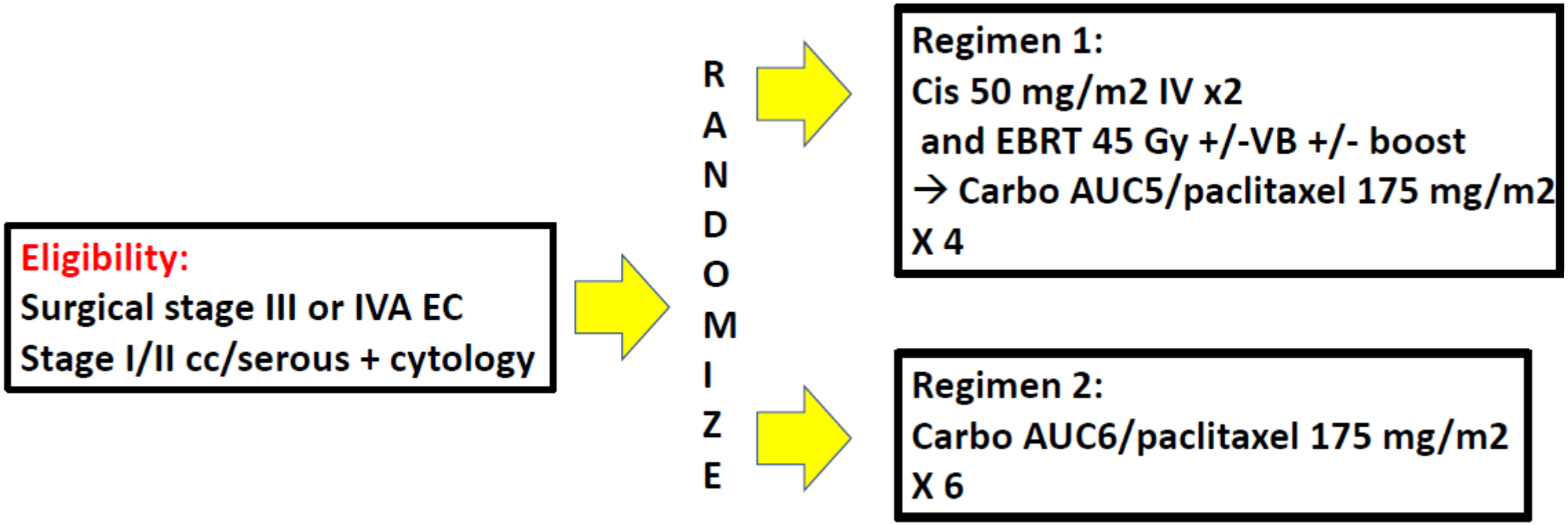
@GynRadonc

NSGO9501/EORTC55991 and MaNGO Pooled PFS:



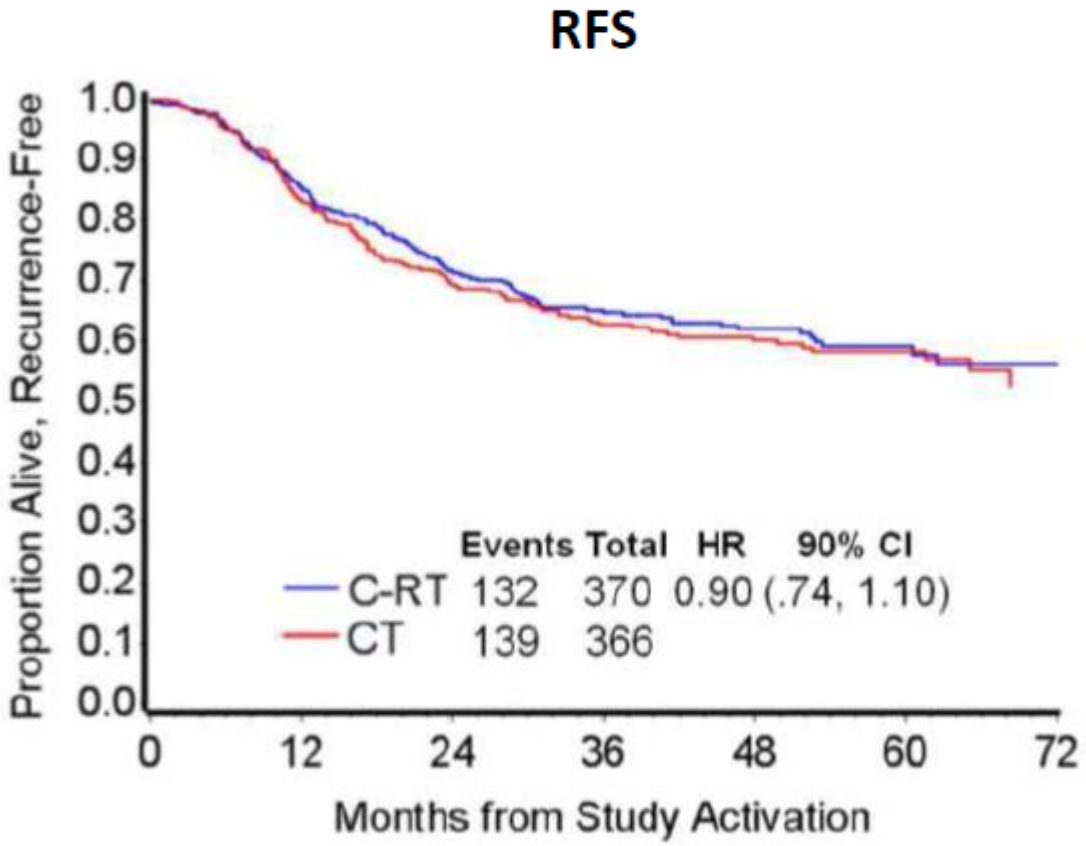
Concurrent CRT

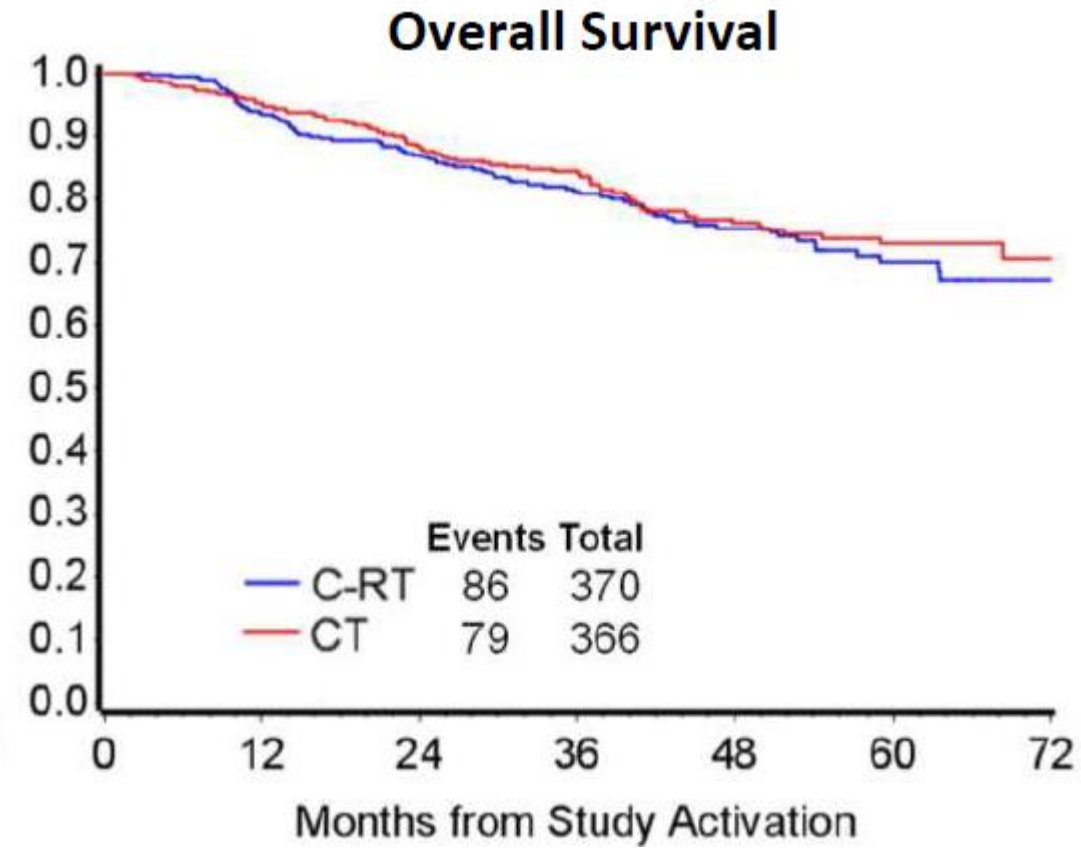
GOG258:



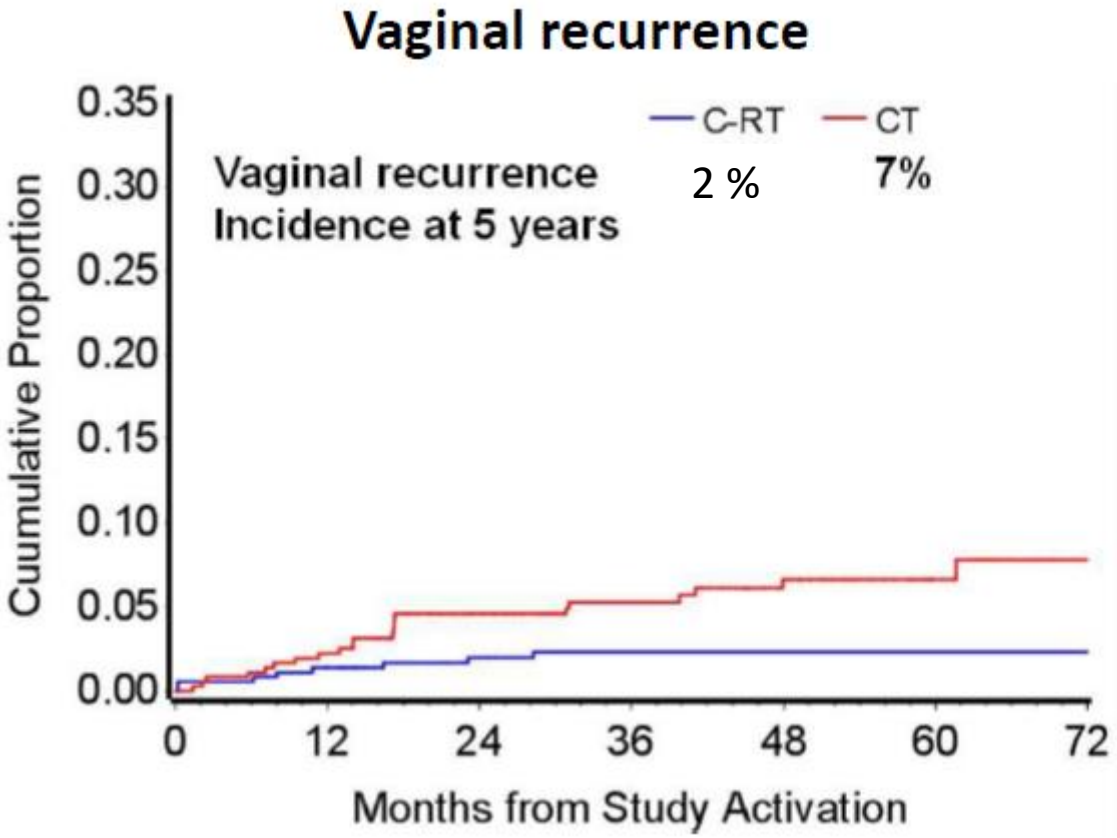
Matei et al, NEJM 2019

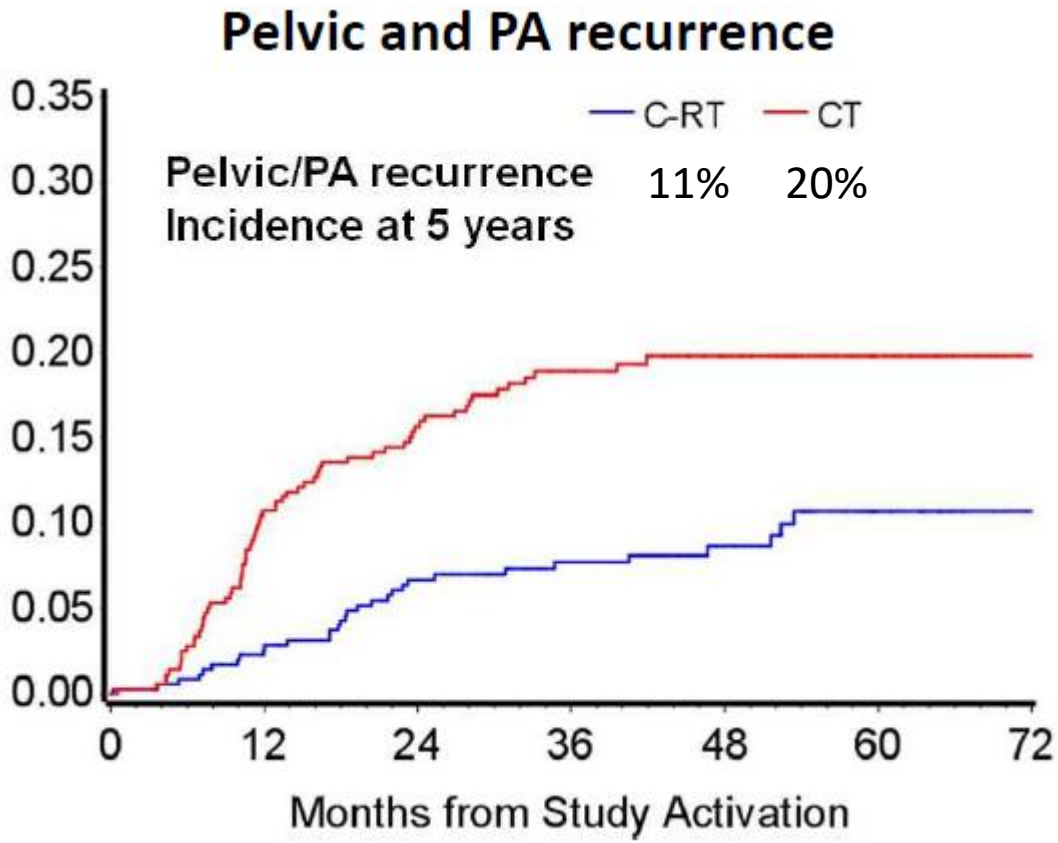
GOG258:


RFS
Proportion Alive, Recurrence-Free
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Events Total HR 90% CI
C-RT 132 370 0.90 (.74, 1.10)
CT 139 366
0 12 24 36 48 60 72
Months from Study Activation

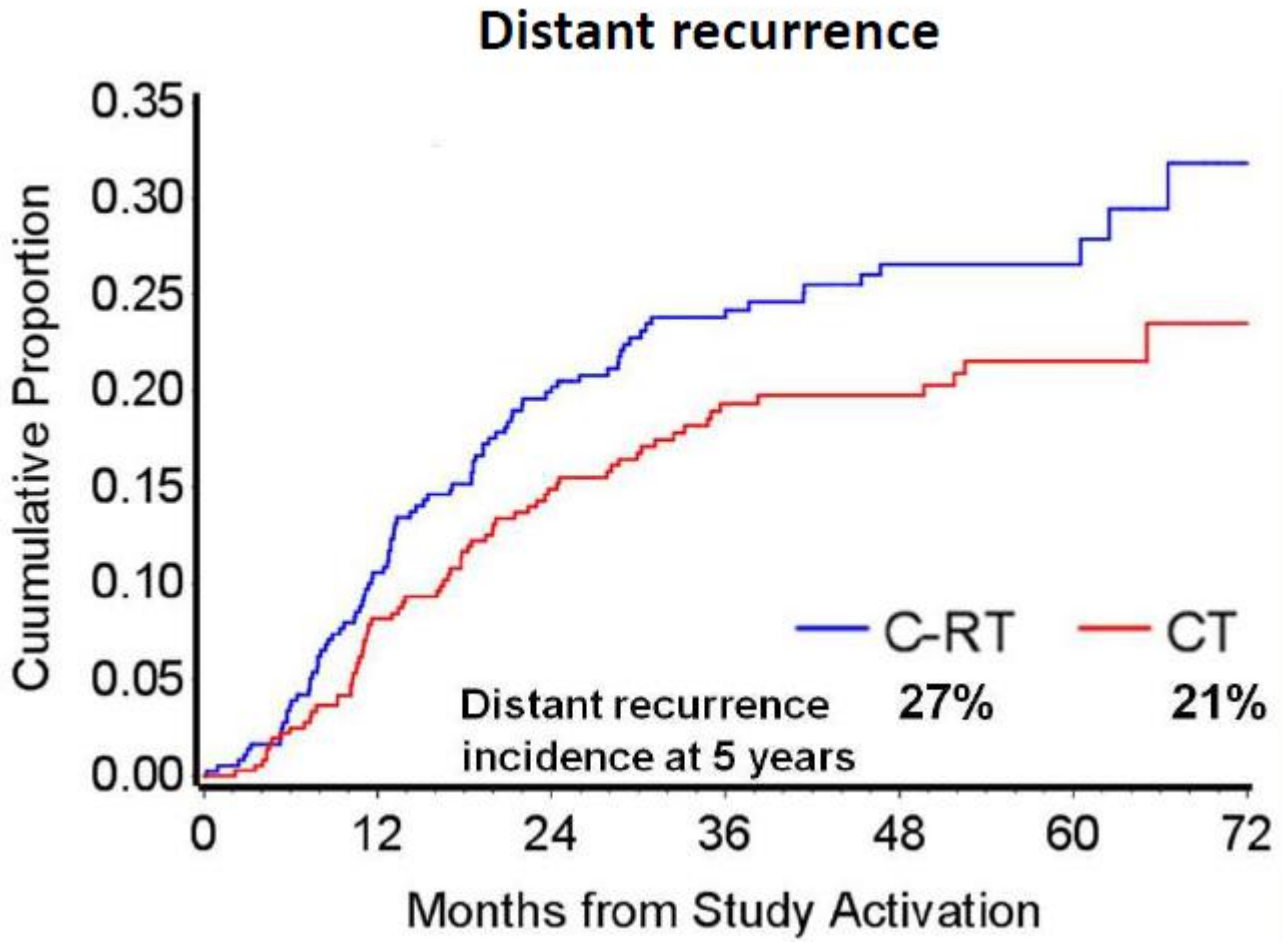

Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Events Total
C-RT 86 370
CT 79 366
0 12 24 36 48 60 72
Months from Study Activation

GOG 258: Cumulative incidence of recurrence





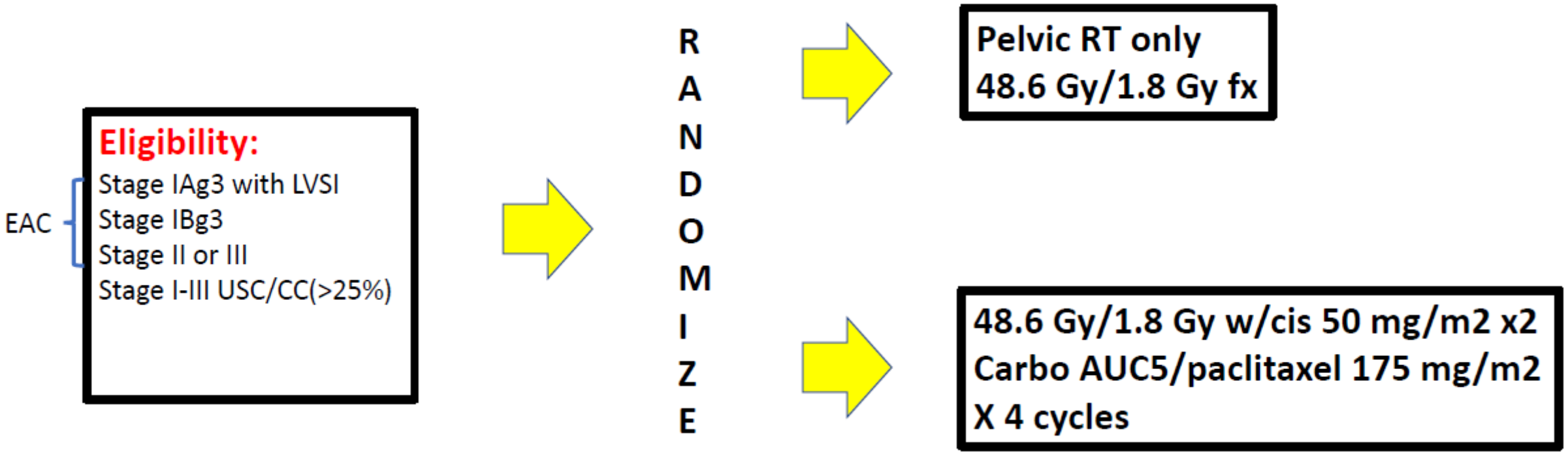
GOG 258: Cumulative incidence of recurrence



GOG 258: Summary

- No difference in OS or RFS with CRT vs Chemo
- Higher localregional relapse with chemo 27% 30% vs 13%
- 25% in CRT did not receive full chemo

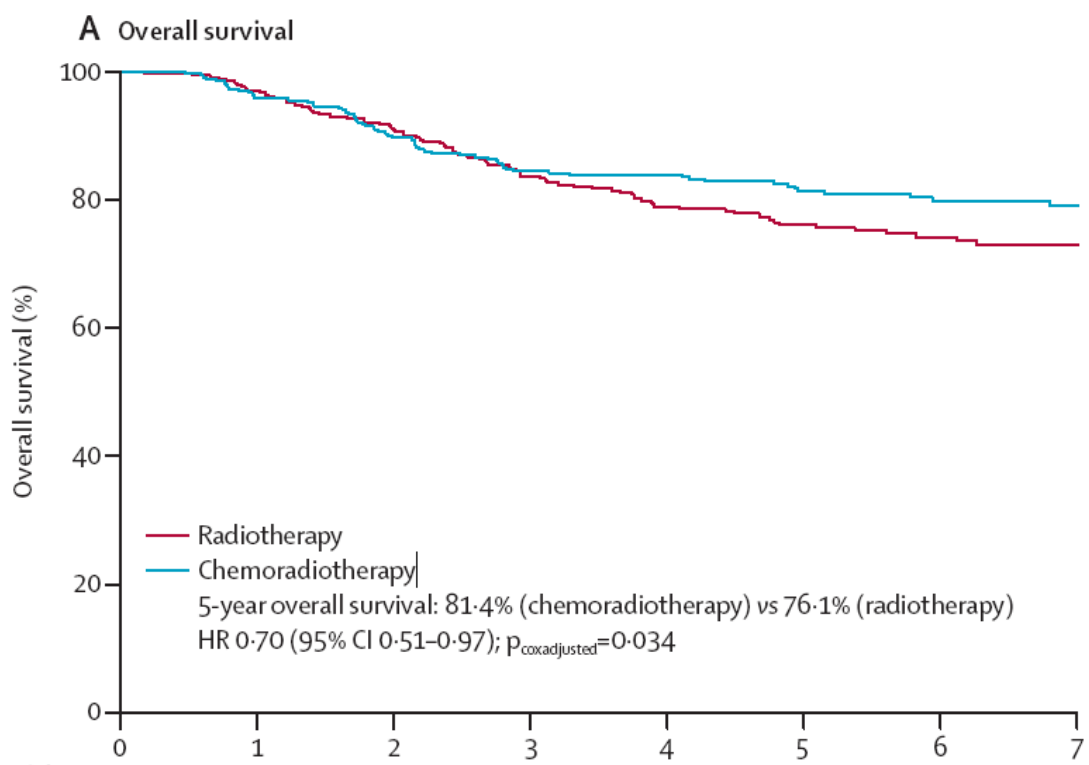
PORTEC-3 (Postoperative Radiation Therapy in Endometrial Cancer)



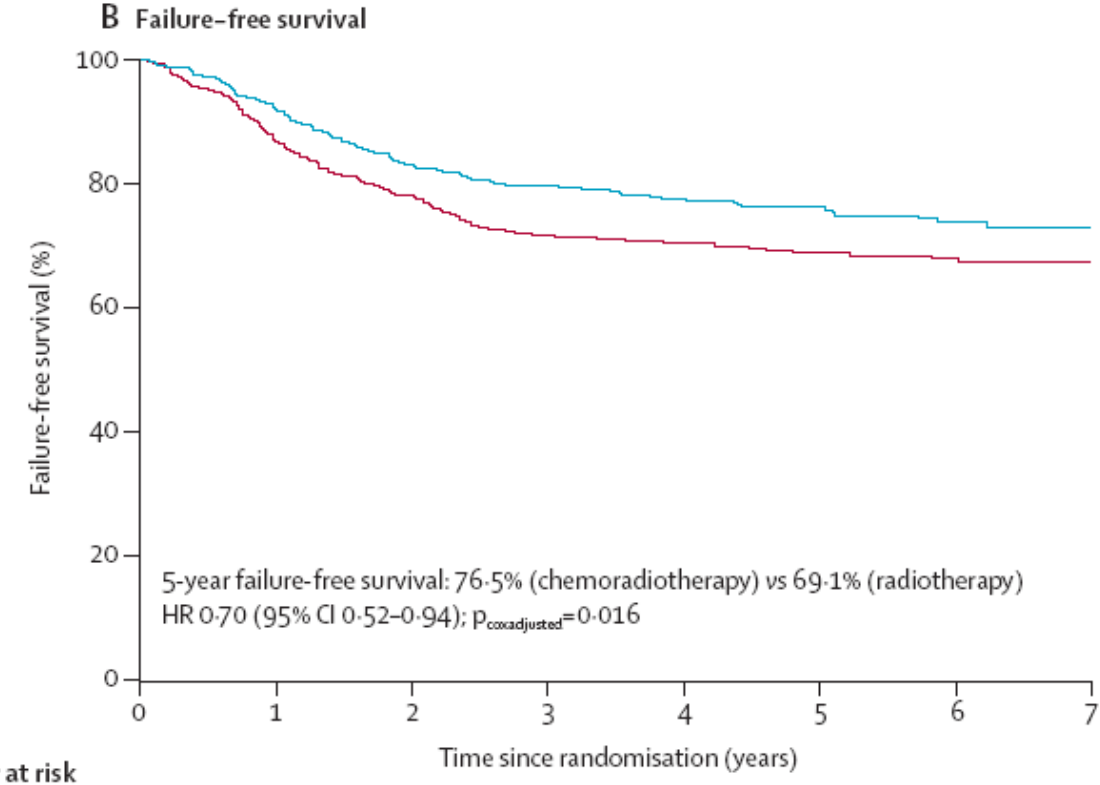
*No residual macroscopic tumor after surgery

De Boer et al Lancet Oncol 2018,19

5 Year Survival (OS and FFS)

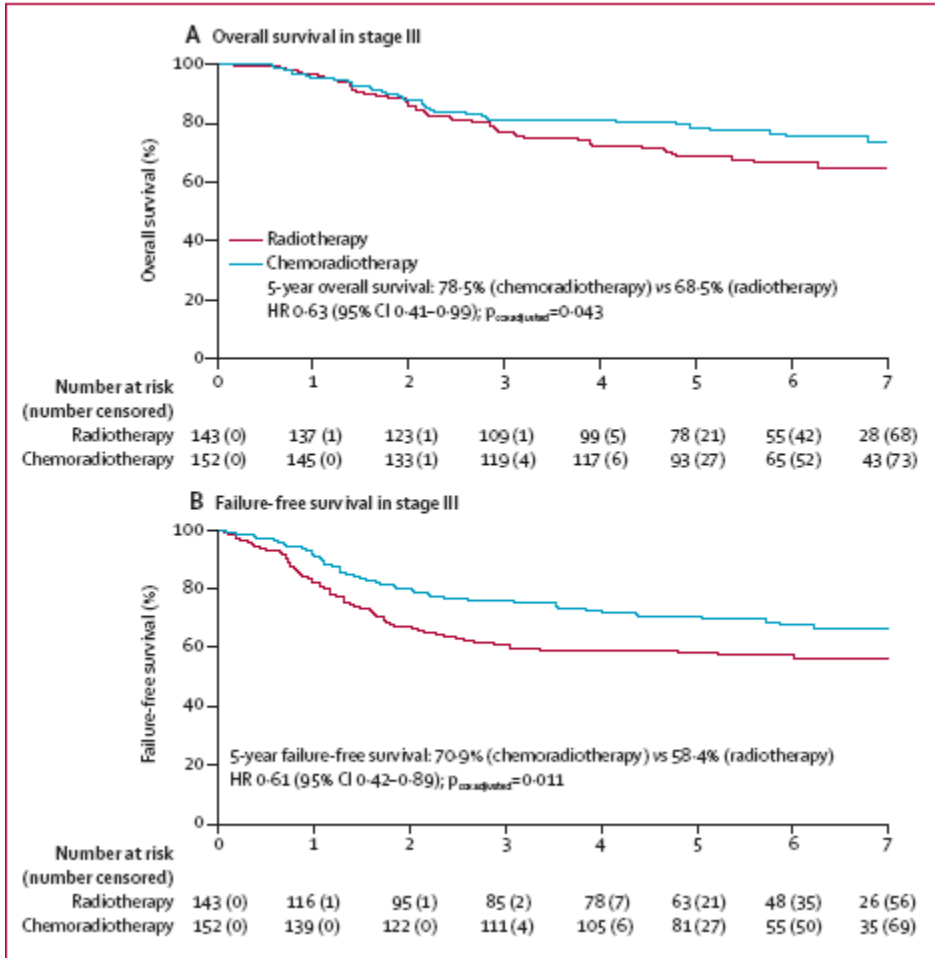


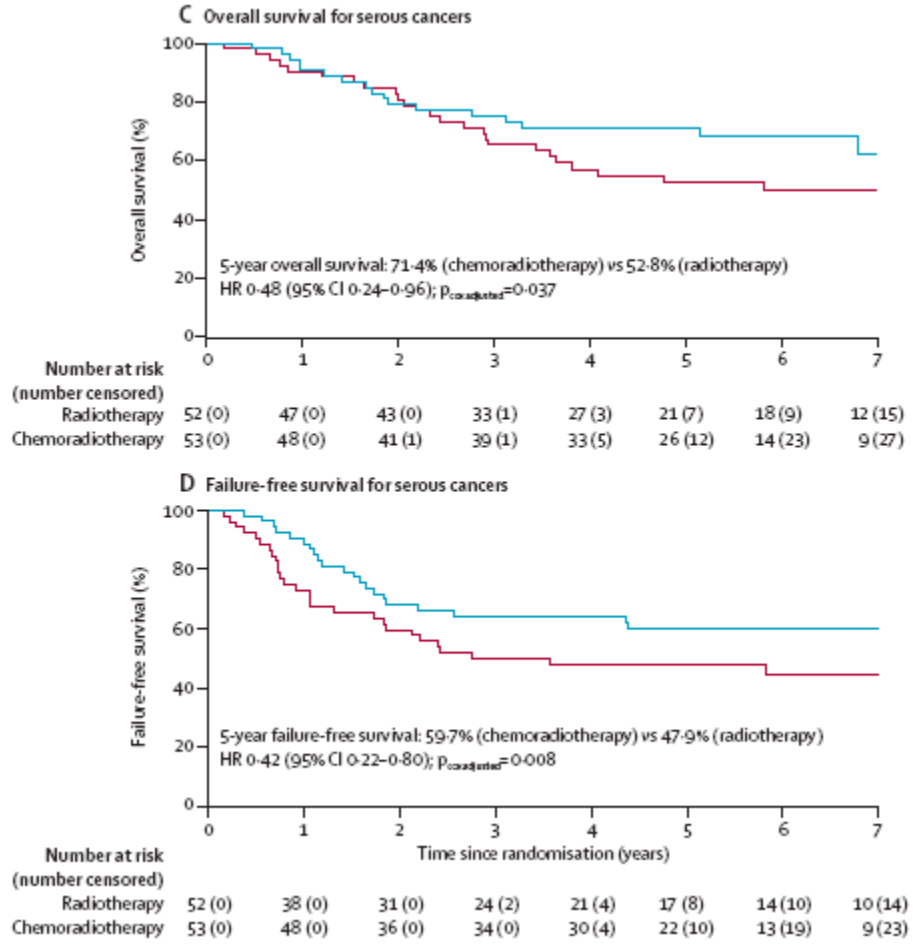
Number at risk (number censored)								
Radiotherapy	330 (0)	319 (1)	299 (1)	273 (3)	248 (13)	187 (66)	129 (120)	81 (166)
Chemoradiotherapy	330 (0)	316 (0)	295 (1)	272 (7)	258 (19)	201 (69)	137 (130)	89 (177)



Number at risk (number censored)								
Radiotherapy	330 (0)	286 (1)	257 (1)	230 (3)	215 (13)	163 (61)	116 (106)	75 (1
Chemoradiotherapy	330 (0)	304 (0)	275 (0)	256 (5)	237 (17)	182 (64)	120 (121)	78 (1

Stage III (OS and FFS) Serous Ca(OS and FFS)





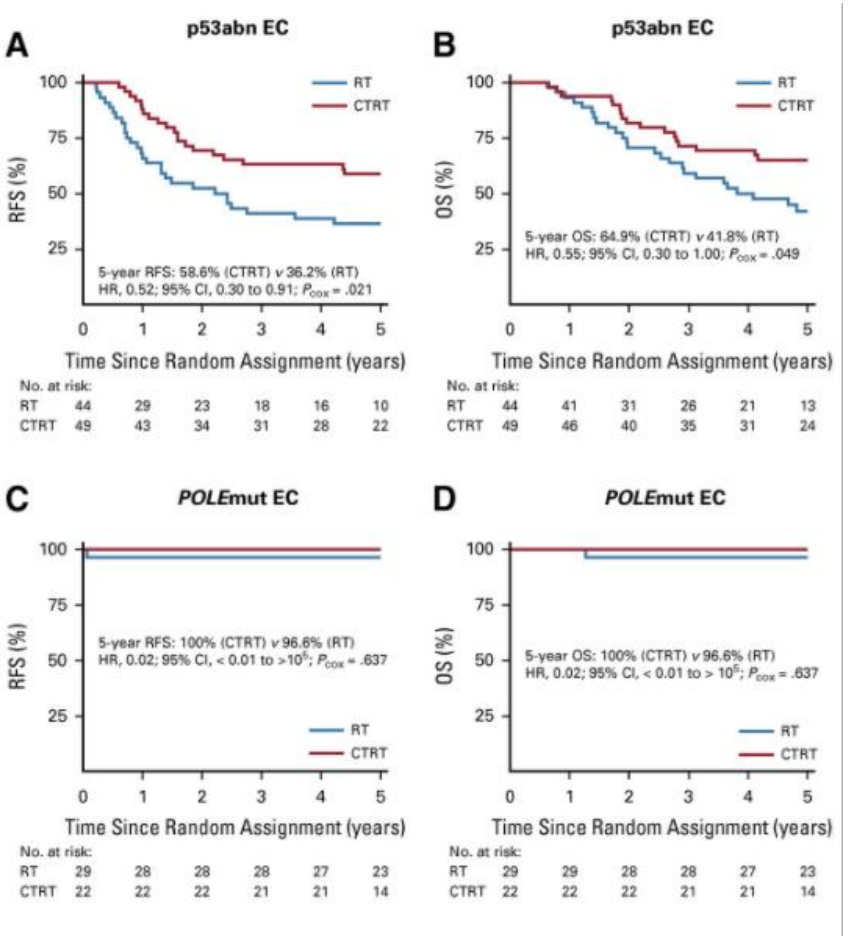
PORTEC-3: Summary

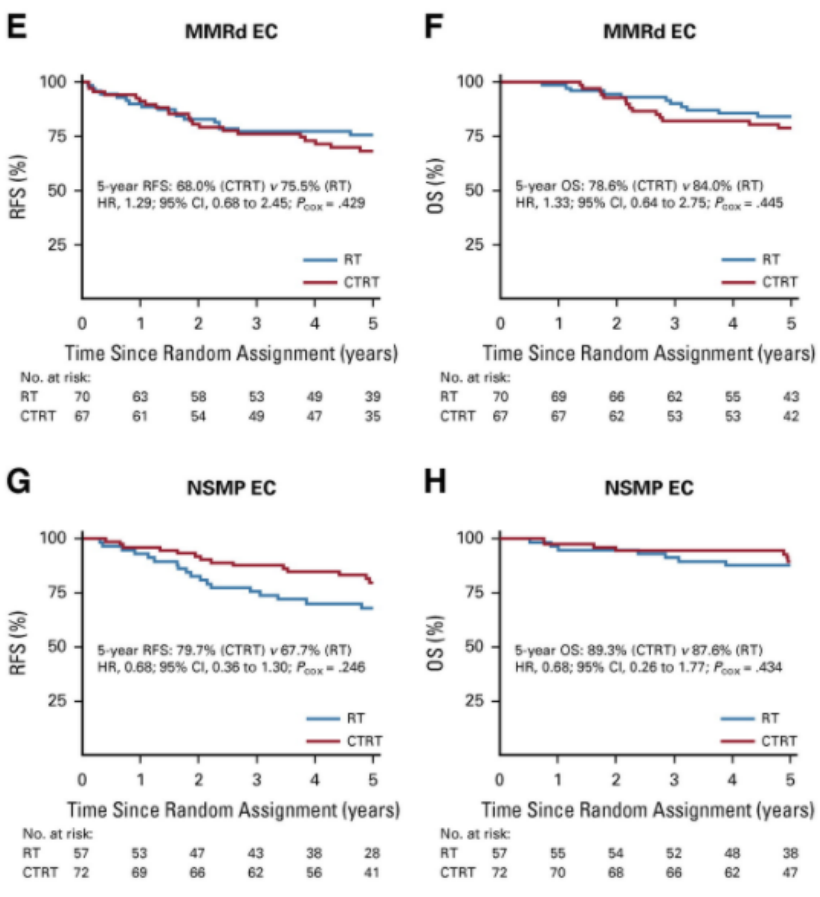
- 5 year OS and FFS better with CRT vs RT
  - Stage III HR 0.66, absolute 11% improvement in FFS
  - No difference in stage I-II
- Serous carcinoma
  - Lower FFS and OS than other subtypes
  - 5 year FFS 58% vs 48% CRT vs RT, p=0.11
- Higher incidence of AEs and decreased QOL with CRT

Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy

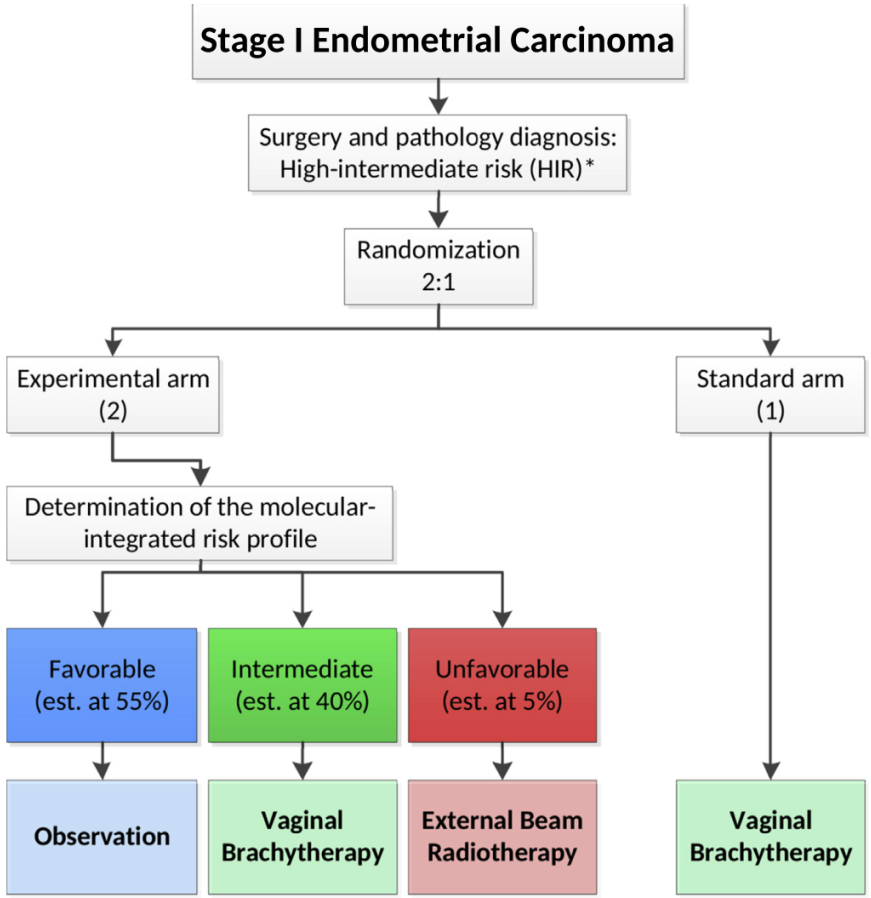
Alicia León-Castillo, MD[1]; Stephanie M. de Boer, MD[2]; Melanie E. Powell, MD[3]; Linda R.

- **METHODS**
- Paraffin-embedded tissues of 423 patients were collected. Molecular analysis done to classify tumors as p53 abnormal (p53abn), *POLE*-ultramutated (*POLE*mut), MMR-deficient (MMRd), or no specific molecular profile (NSMP). The primary end point was recurrence-free survival (RFS)..
- **RESULTS**
- Molecular analysis was successful in 410 high-risk EC (97%), identifying the 4 subgroups: Five-year RFS was 48% for patients with p53abn EC and 74% for NSMP EC ($P < .001$).
- The 5-year RFS with CTRT versus RT for p53abn EC was 59% versus 36% ($P = .019$); 100% versus 97% for patients with *POLE*mut EC ($P = .637$); 68% versus 76% ($P = .428$) for MMRd EC; and 80% versus 68% ($P = .243$) for NSMP EC.
-


A
p53abn EC
RFS (%)
100
75
50
25
RT
CTRT
5-year RFS: 58.6% (CTRT) v 36.2% (RT)
HR, 0.52; 95% CI, 0.30 to 0.91; P_{cox} = .021
0 1 2 3 4 5
Time Since Random Assignment (years)
No. at risk:
RT 44 29 23 18 16 10
CTRT 49 43 34 31 28 22
B
p53abn EC
OS (%)
5-year OS: 64.9% (CTRT) v 41.8% (RT)
HR, 0.55; 95% CI, 0.30 to 1.00; P_{cox} = .049
Time Since Random Assignment (years)
No. at risk:
RT 44 41 31 26 21 13
CTRT 49 46 40 35 31 24
C
POLEmut EC
RFS (%)
5-year RFS: 100% (CTRT) v 96.6% (RT)
HR, 0.02; 95% CI, < 0.01 to >10^6; P_{cox} = .637
Time Since Random Assignment (years)
No. at risk:
RT 29 28 28 28 27 23
CTRT 22 22 22 21 21 14
D
POLEmut EC
OS (%)
5-year OS: 100% (CTRT) v 96.6% (RT)
HR, 0.02; 95% CI, < 0.01 to > 10^6; P_{cox} = .637
Time Since Random Assignment (years)
No. at risk:
RT 29 29 28 28 27 23
CTRT 22 22 22 21 21 14


E
MMRd EC
RFS (%)
5-year RFS: 68.0% (CTRT) v 75.5% (RT)
HR, 1.29; 95% CI, 0.68 to 2.45; P_{cox} = .429
Time Since Random Assignment (years)
No. at risk:
RT 70 63 58 53 49 39
CTRT 67 61 54 49 47 35
F
MMRd EC
OS (%)
5-year OS: 78.6% (CTRT) v 84.0% (RT)
HR, 1.33; 95% CI, 0.64 to 2.75; P_{cox} = .445
Time Since Random Assignment (years)
No. at risk:
RT 70 69 66 62 55 43
CTRT 67 67 62 53 53 42
G
NSMP EC
RFS (%)
5-year RFS: 79.7% (CTRT) v 67.7% (RT)
HR, 0.68; 95% CI, 0.36 to 1.30; P_{cox} = .246
Time Since Random Assignment (years)
No. at risk:
RT 57 53 47 43 38 28
CTRT 72 69 66 62 56 41
H
NSMP EC
OS (%)
5-year OS: 89.3% (CTRT) v 87.6% (RT)
HR, 0.68; 95% CI, 0.26 to 1.77; P_{cox} = .434
Time Since Random Assignment (years)
No. at risk:
RT 57 55 54 52 48 38
CTRT 72 70 68 66 62 47

NEW PORTEC 4



- Stage IA Grade 3; IB G1-2 with >60yo or LVSI; IB G3 without LVSI
- 7 Gy * 3 fractions to 5mm surface
- Non-inferiority
- Primary endpoint is vaginal recurrence with 7% margin

- Favorable: Pole Mutation or MMR WT CTNNB1 WT
- Intermediate: MMR mutant or [MMR WT with CTNNB1 mutation]
- Unfavorable: Substantial LVSI, TP53, >10% LCAM

Wortman, Gynecology Onc 2018

Summary and Key Points:

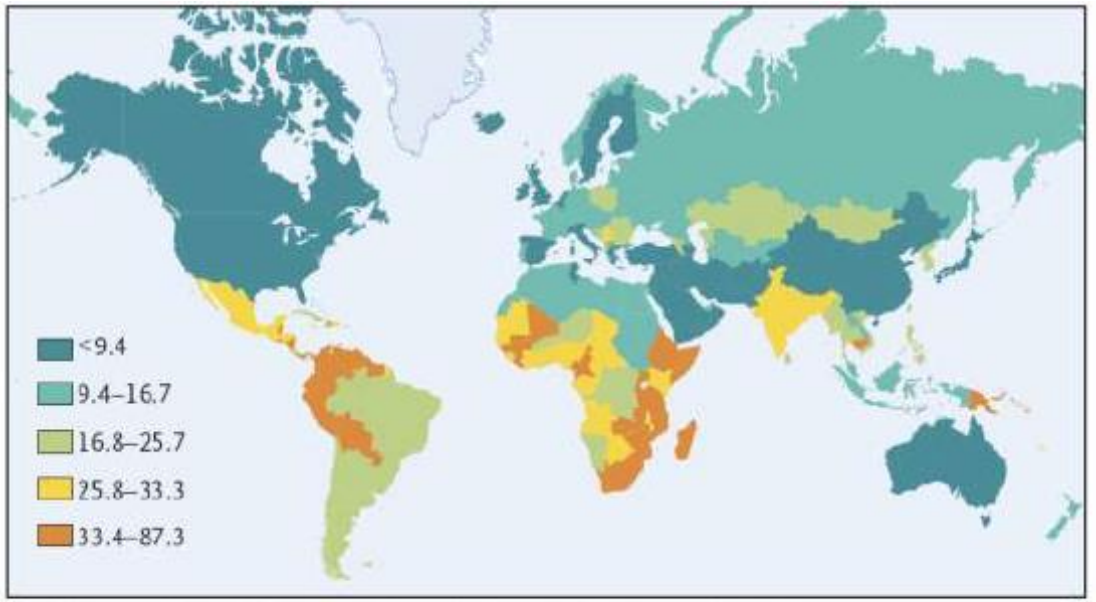
- Lack of survival benefit to combined CRT vs chemo alone in randomized studies

- Greatest benefit with CRT in stage III
  - CRT in stage IIIC
  - Other stage III dependent on uterine risk factors and/or risk of LRR
- Limited rationale for CRT in high risk stage I/II endometrioid
  - Trend towards improvement with CRT in serous histology

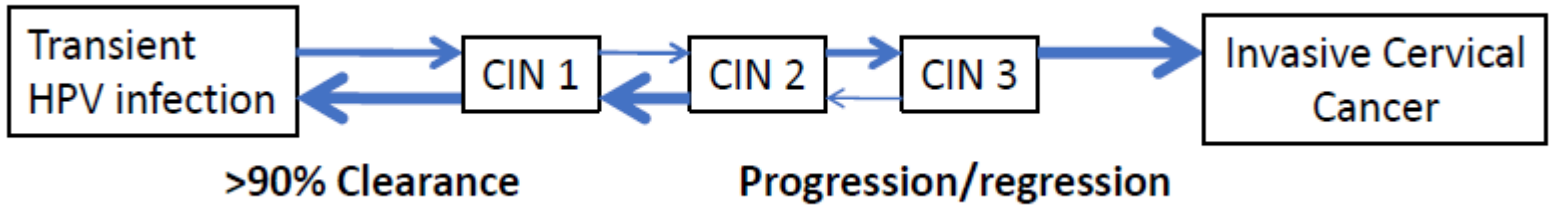
Management of Cervical Cancer

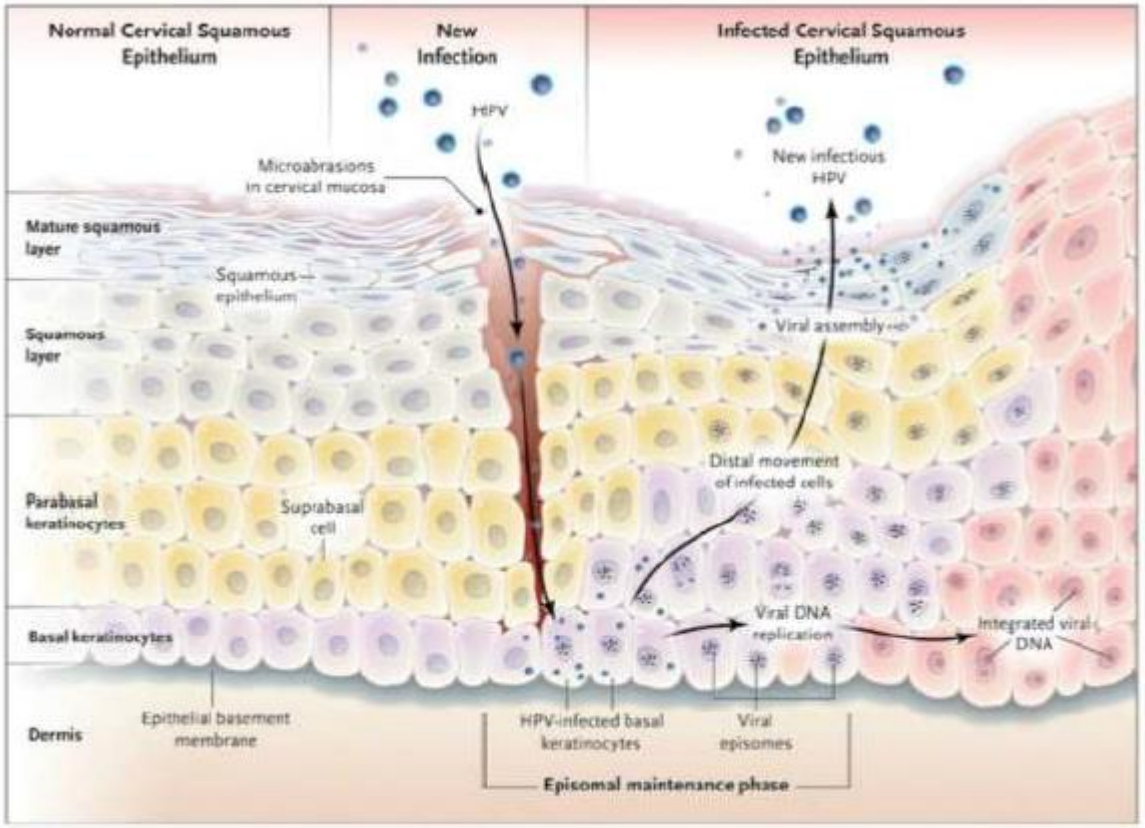
Global Statistics

- 2nd most female common cancer in the developing world
- ~ 500,000 new cases worldwide
- AIDS defining in the setting of HIV
- Lymph node evaluation
- ~ 13,000 new cases per year in the US



Age-Standardized Incidence Rates of Cervical Cancer per 100,000.





Cofactors for Persistence:

- Smoking
- Increased age
- HPV type
- Mutagens
- Immunosuppression
- Inflammation
- Hormones
- Genetic Factors

Kahn J, NEJM 2009

HPV

- High Risk Types:
  - 16 and 18 (responsible for 70% of cervical cancers)
  - 31 and 45 (responsible for 10%)
  - Others: 33, 35, 39, 51, 52, 56, 58, 59, 68, 73, and 82
- Low Risk types:
  - 6 and 11 (genital warts)

HISTOLOGY –mostly squamous , 10-15 % AdenoCa

Staging and Workup

2018 FIGO Staging

I – Confined to uterus

- IA: Depth of invasion < 5 mm
  - IA1: microscopic, ≤3 mm stromal invasion
  - IA2: microscopic, >3 to 5 mm stromal invasion
- IB: Depth of invasion ≥ 5 mm
  - IB1: ≥5 mm depth of stromal invasion and **<2 cm** in greatest dimension
  - IB2: **≥2 cm and <4 cm** in greatest dimension
  - IB3: **≥4 cm** in greatest dimension

II – Extends outside uterus but has not extended onto the lower third of the vagina or to the pelvic wall

- IIA: Involvement limited to the upper two-thirds of the vagina without parametrial involvement
  - IIA1: ≤4 cm diameter
  - IIA2: >4 cm diameter
- IIB: parametrial invasion but not up to pelvic wall

IIIA – Involves the lower third of the vagina, with no extension to the pelvic wall

IIIB – Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)

IIIC – Involvement of pelvic and/or para-aortic lymph nodes

IIIC1: **Pelvic lymph node metastasis only**
IIIC2: **Para-aortic lymph node metastasis**

IV: Extension beyond true pelvis or biopsy-proven involvement of the mucosa of the bladder or rectum

IVA: Spread to adjacent pelvic organs
IVB: Spread to distant organs

Risk of Lymph Node Metastases

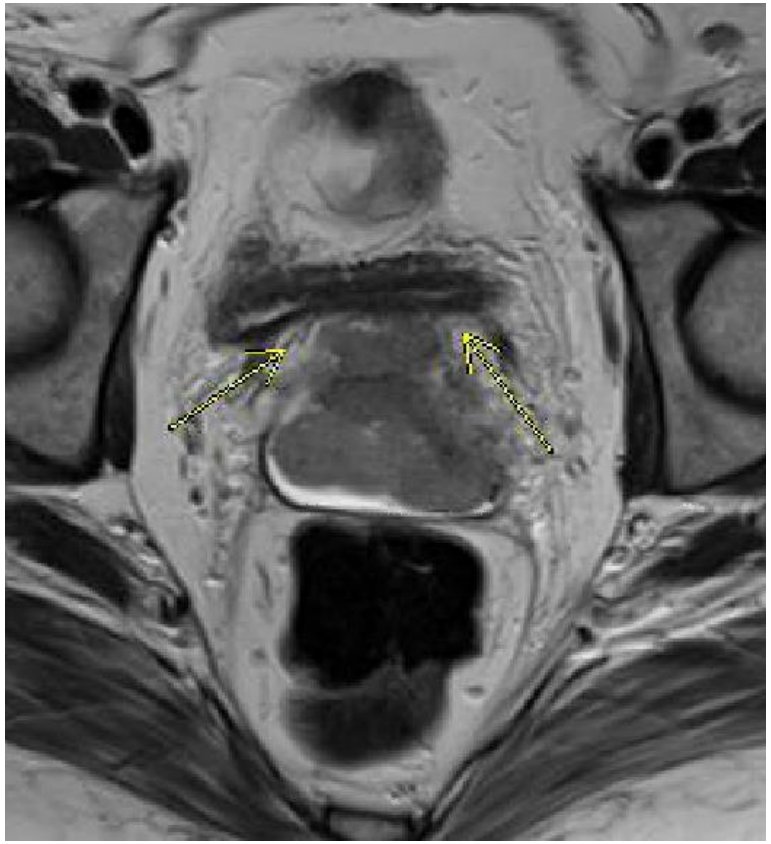
Stage	Pelvic LN	PA LN
IA1	<1%	
IA2	6-7%	<3%
IB	15%	10%
IIB	30%	20%
III	45%	30%

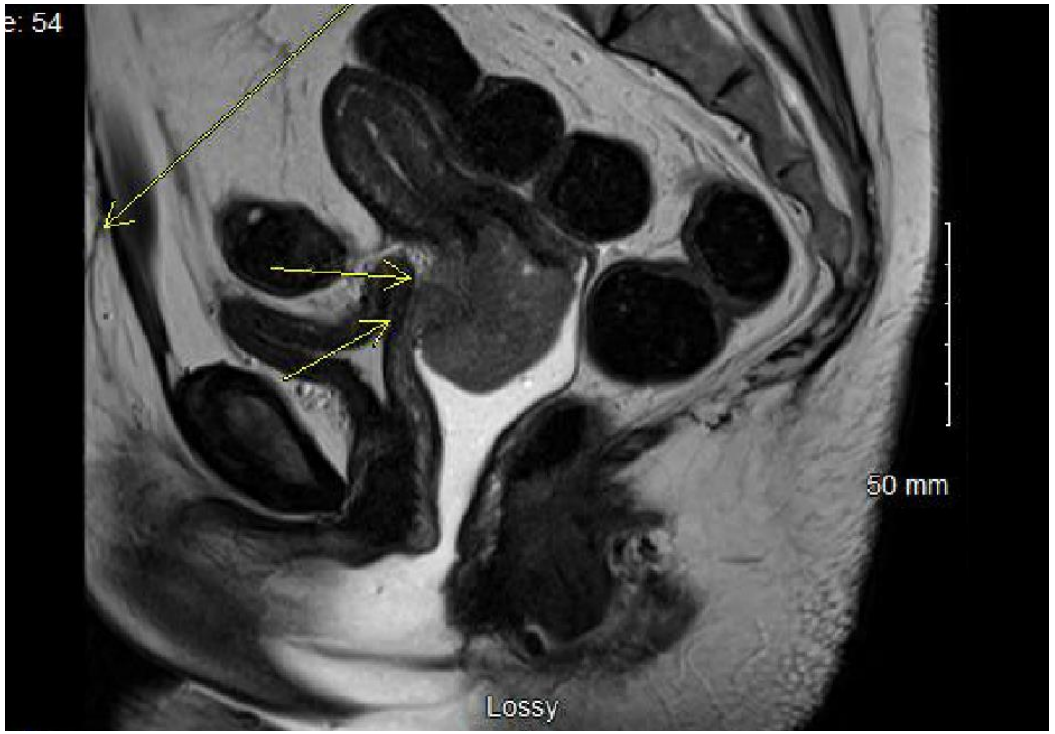
Determining Extent of Primary Tumor

- Pelvic examination
  - Staging Accuracy: 47%
    - Bipat et al, Gyn Onc 2003

- MRI vs CT
  - Staging Accuracy: 86%
  - MR is superior to CT for detecting uterine body involvement/PM invasion (ACRIN 6651/GOG 183)
    - JCO 2006
  - MR superior in detecting vaginal extension

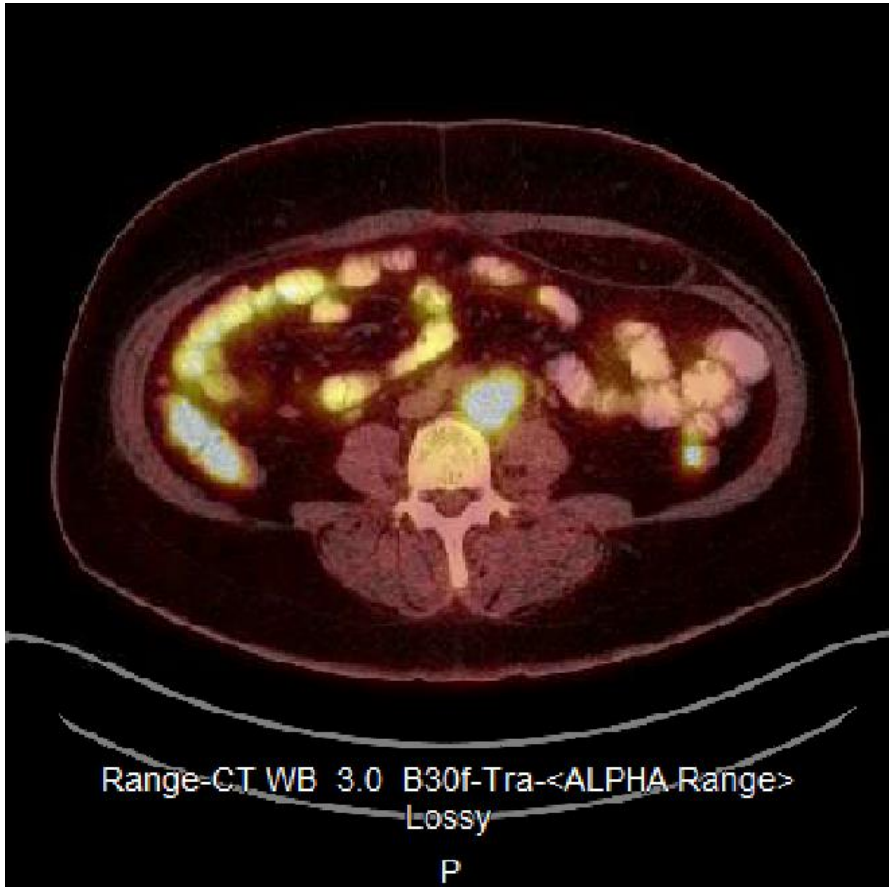
Determining Extent of Primary disease:Benefit of MR example



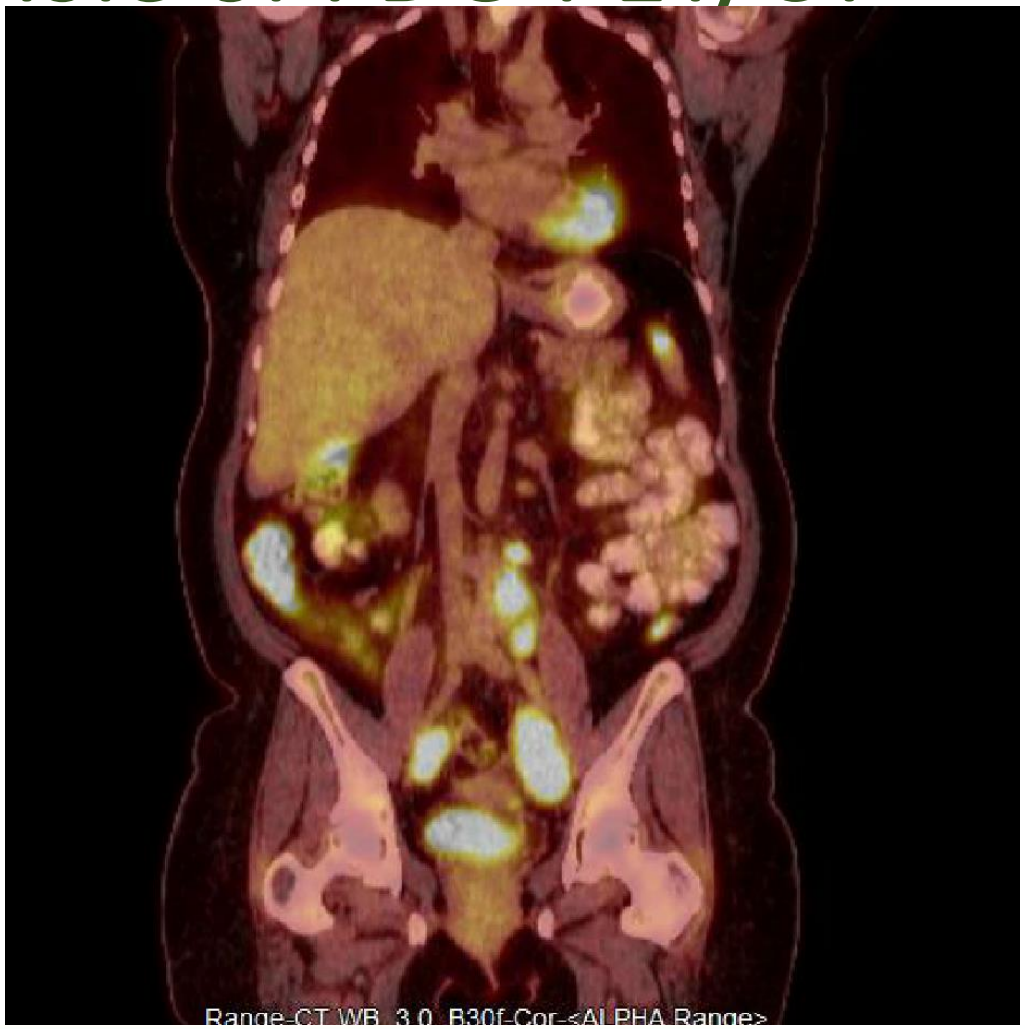


Arrows show involvement of vagina and vesico-vaginal space

Determining Extent of LN/Distant Metastases: example of Role of FDG-PET/CT

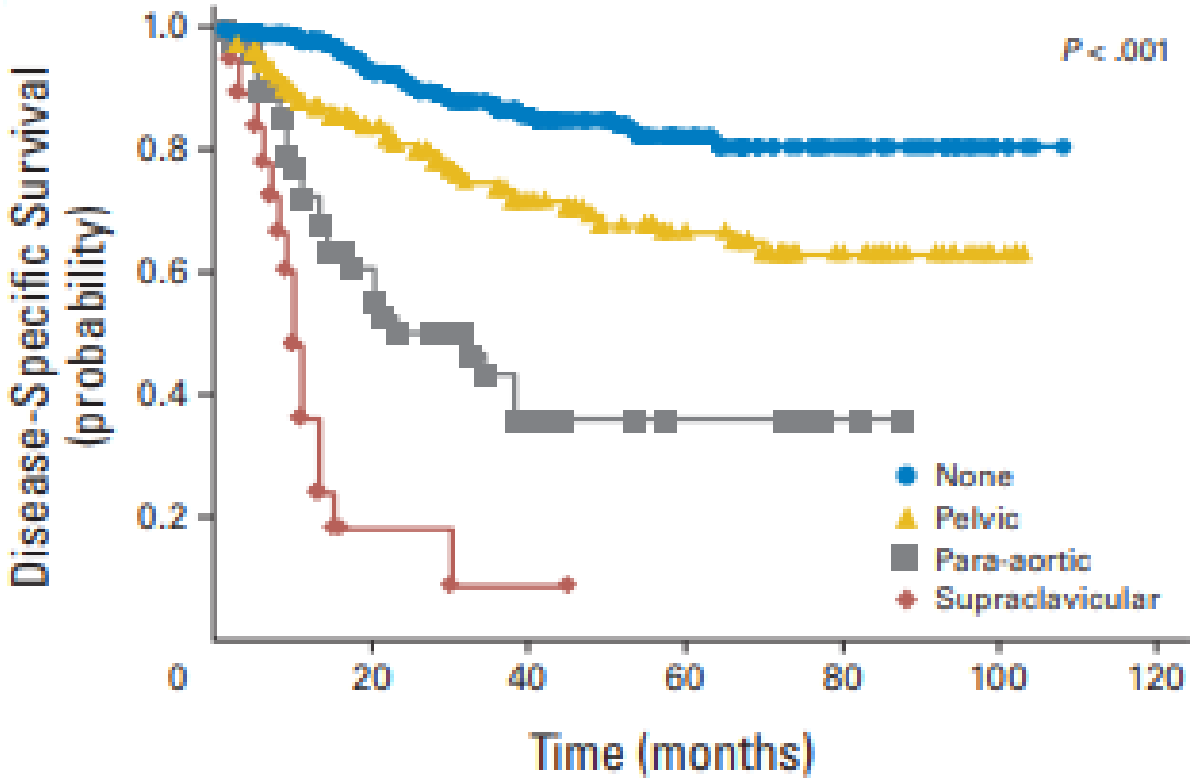


Large Pelvic and Paraortic nodal metastases



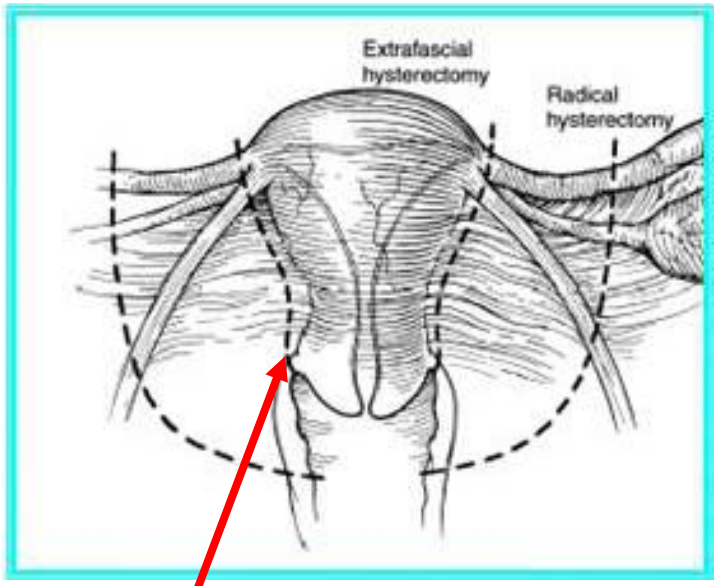
Impact of nodal involvement –worst prognostic factor

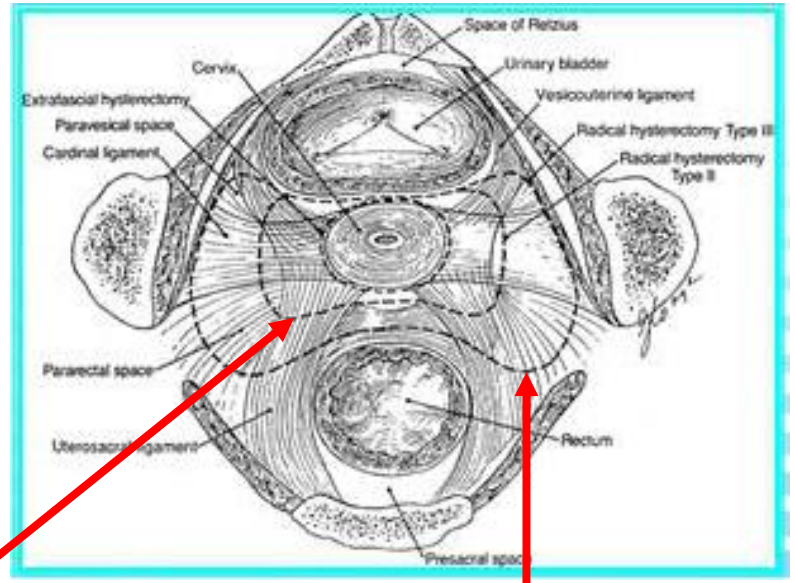
Retrospective study of 560 pts with cervical cancer underwent pretreatment FDG-PET lymph node staging.



Kidd et al, JCO 2010

Surgical Management: Early stage IA/IB1 (2018)





Type I: Extrafascial/Simple hysterectomy
- Remove uterus, cervix, rim vag cuff
- Does not remove parametria

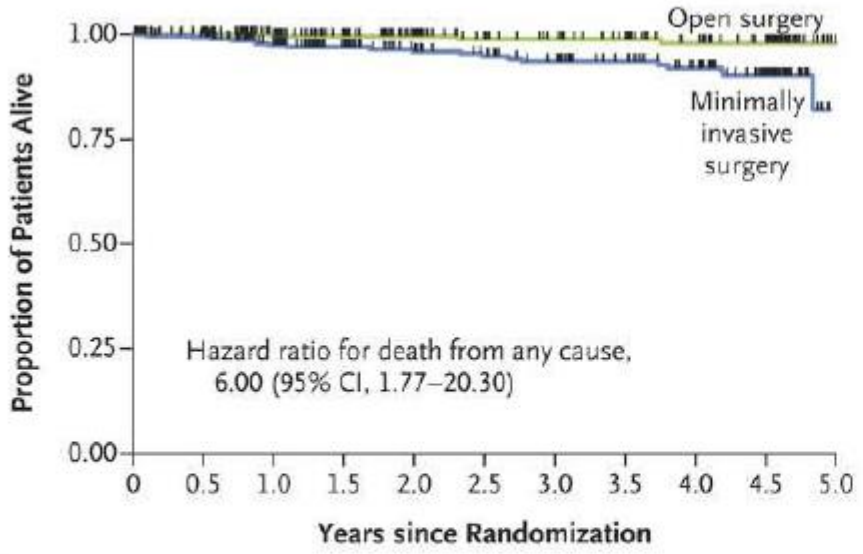
Type II: Modified radical hysterectomy
- Remove uterus, cervix, 1-2 cm vagina, WLE of parametria
- Resect parametria to where the ureter and uterine artery cross

Type III: Radical hysterectomy
- Removal of uterus, cervix, ¼ to 1/3 of vagina, parametria divided at pelvic sidewall or sacral origin.

Laparoscopic Approach to Cervical Cancer (LACC) Trial

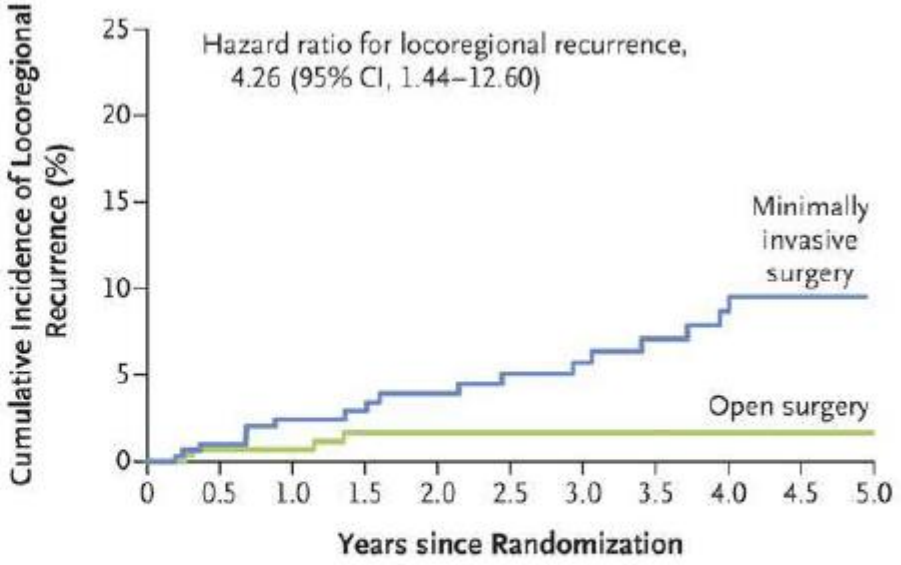
Open vs minimally invasive surgery

Overall Survival



No. at Risk											
Open surgery	312	282	237	190	164	146	136	125	104	90	7
Minimally invasive surgery	319	297	249	198	174	163	150	133	113	87	5

Locoregional recurrence was High for MIS



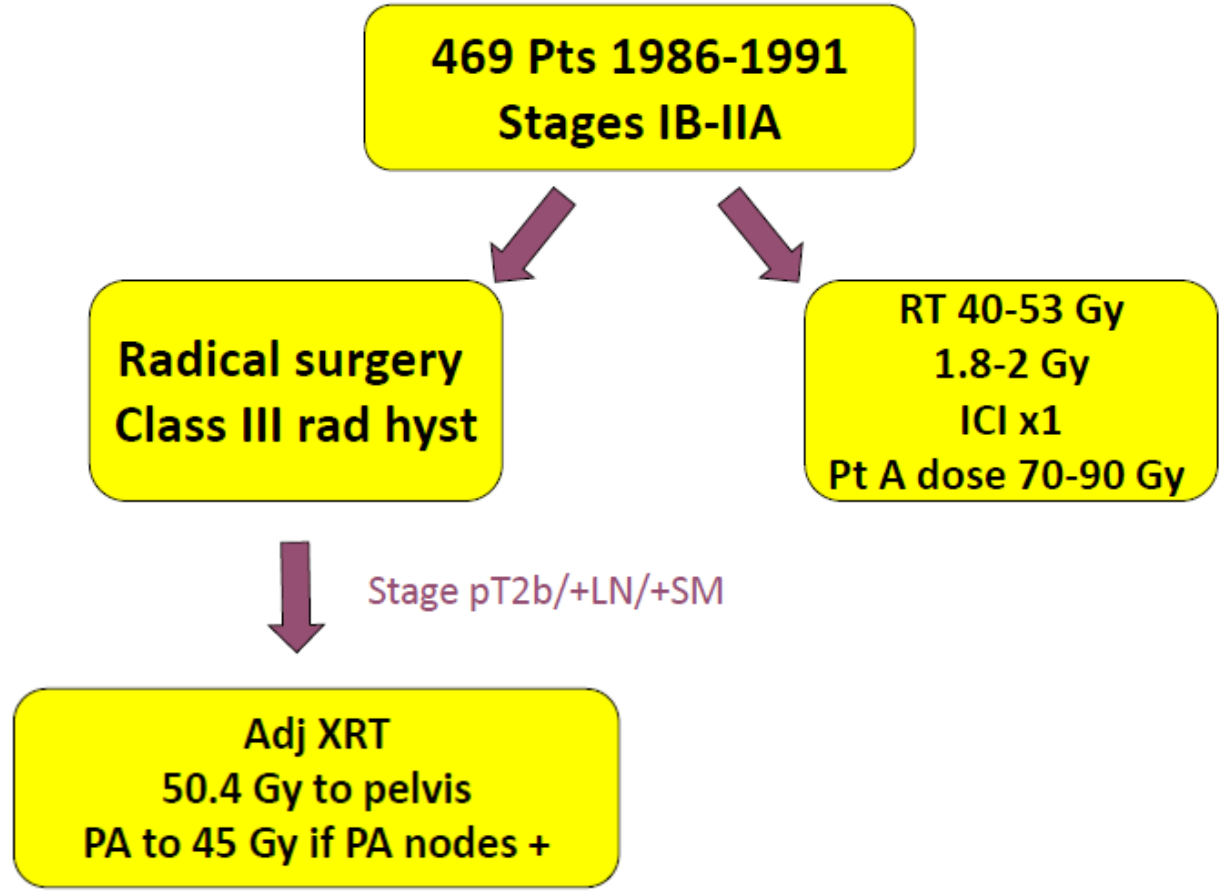
No. at Risk											
Open surgery	312	280	236	187	163	144	134	123	104	90	7
Minimally invasive surgery	319	292	244	192	167	155	142	121	102	80	5

Ramirez et al NEJM 2018

Stagewise Treatment Plan for Cervical Cancer

FIGO 2018	Treatment
IA1	Cervical conization or extrafascial hysterectomy; consider radical trachelectomy for fertility sparing in low risk
IA2	Modified radical hysterectomy and PLND
IB1	Radical hysterectomy and PLND +/- RT
IB2	
IB3	Definitive CRT → brachy boost
IIA1	Radical hysterectomy and PLND +/- RT
IIA2	Definitive CRT → brachy boost
IIB	
IIIA	
IIIB	
IIIC	
IVA	
IVB	Chemotherapy +/- palliative RT

Primary radiotherapy vs Radical Hysterectomy(Milan)



Landoni Lancet 1997

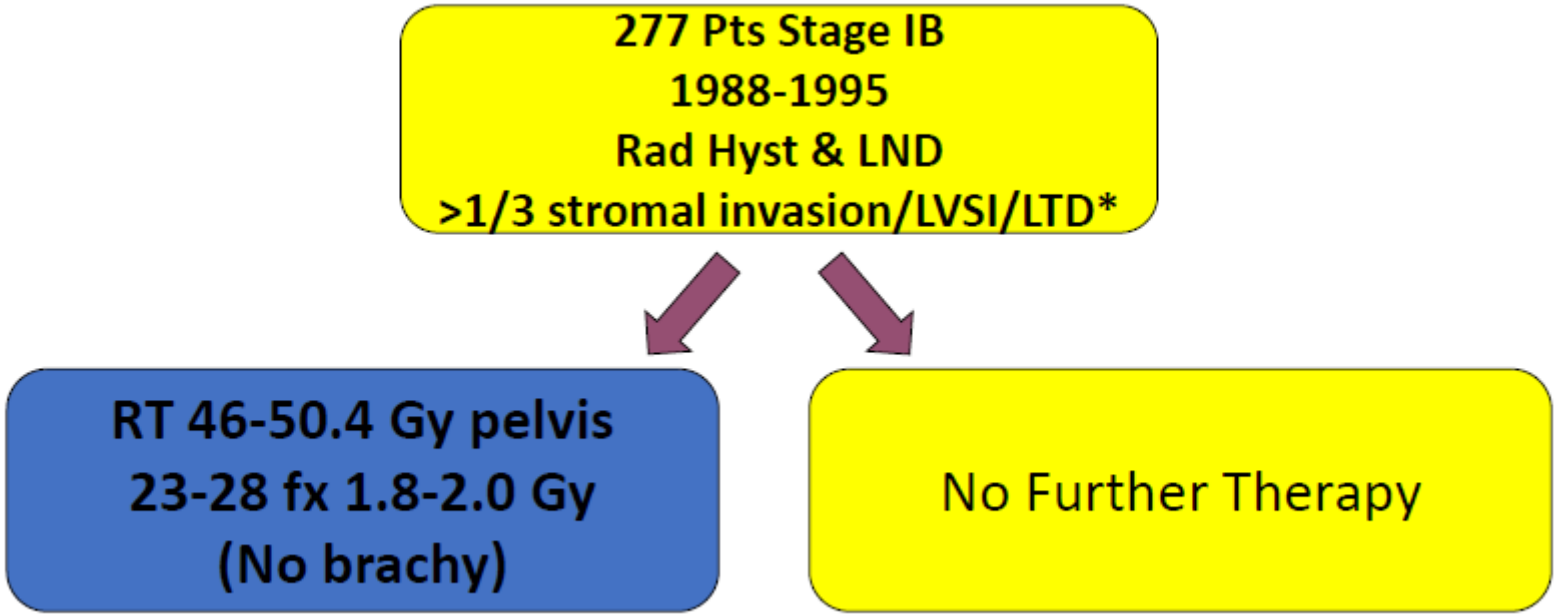
Primary radiotherapy vs Radical Hysterectomy

- Median follow-up 87 months
- No difference in survival/LC
- Adjuvant RT
  - 64% of patients overall
  - IB1 54%, IB2 88%
  - **Higher rates of urologic complications with combined surgery/adjuvant RT**

Role of Adjuvant Radiotherapy

GOG 92: LN Negative, Intermediate risk

Role of adjuvant post-operative radiotherapy



Sedlis, Gyn Onc 1999
Rotman, IJROBP 2006

GOG 92 Eligibility Criteria(Sedlis)

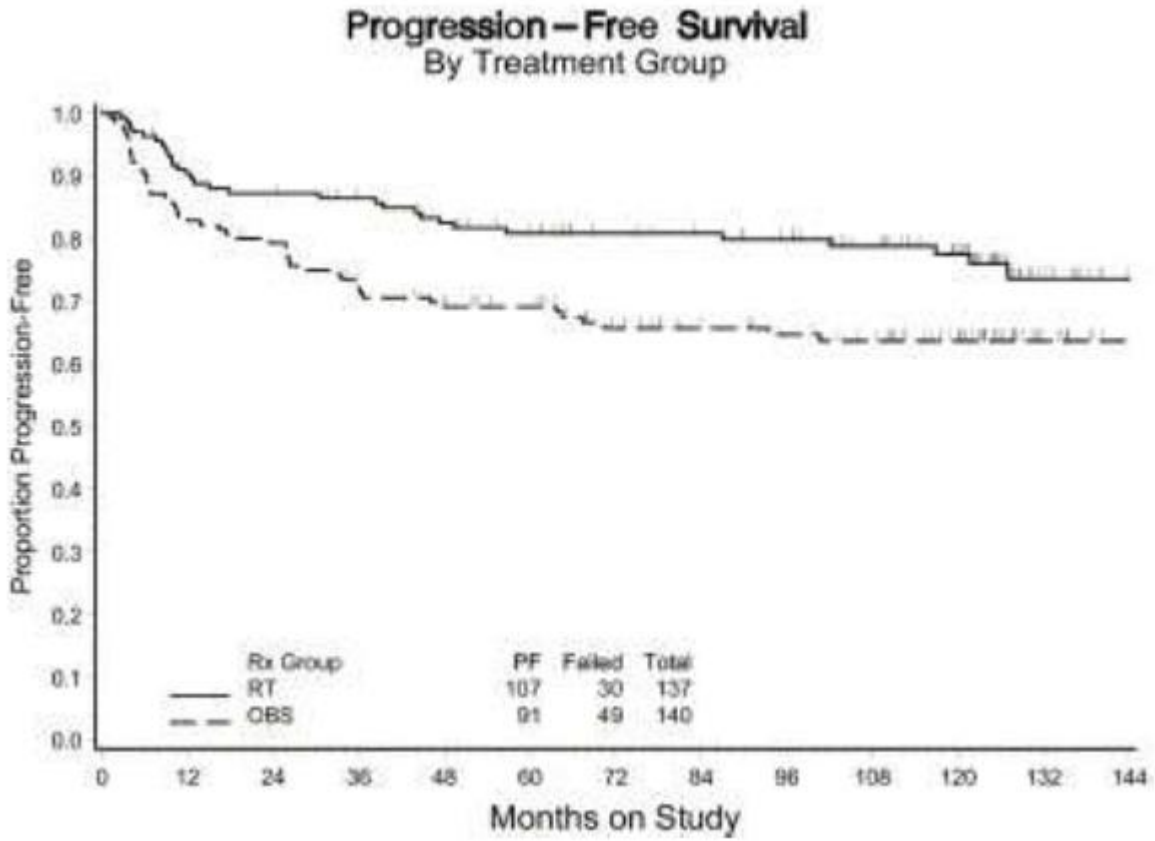
CLS	Stromal Invasion	Tumor Size
Positive	Deep 1/3	Any
Positive	Middle 1/3	≥2 cm
Positive	Superficial 1/3	≥5 cm
Negative	Deep or middle 1/3	≥4 cm

Need 2 of 3 factors: Positive CLS, Middle 1/3, ≥ 4 cm

GOG 92: Update

- Median f/u: 10 years
- PFS: 46% reduction in HR
- Overall survival:
- Grade ¾ toxicity:
- Adenocarcinoma and adenosquamous recurrence rate is highest

  :8.8% (RT) vs 44% (obs), P=0.019



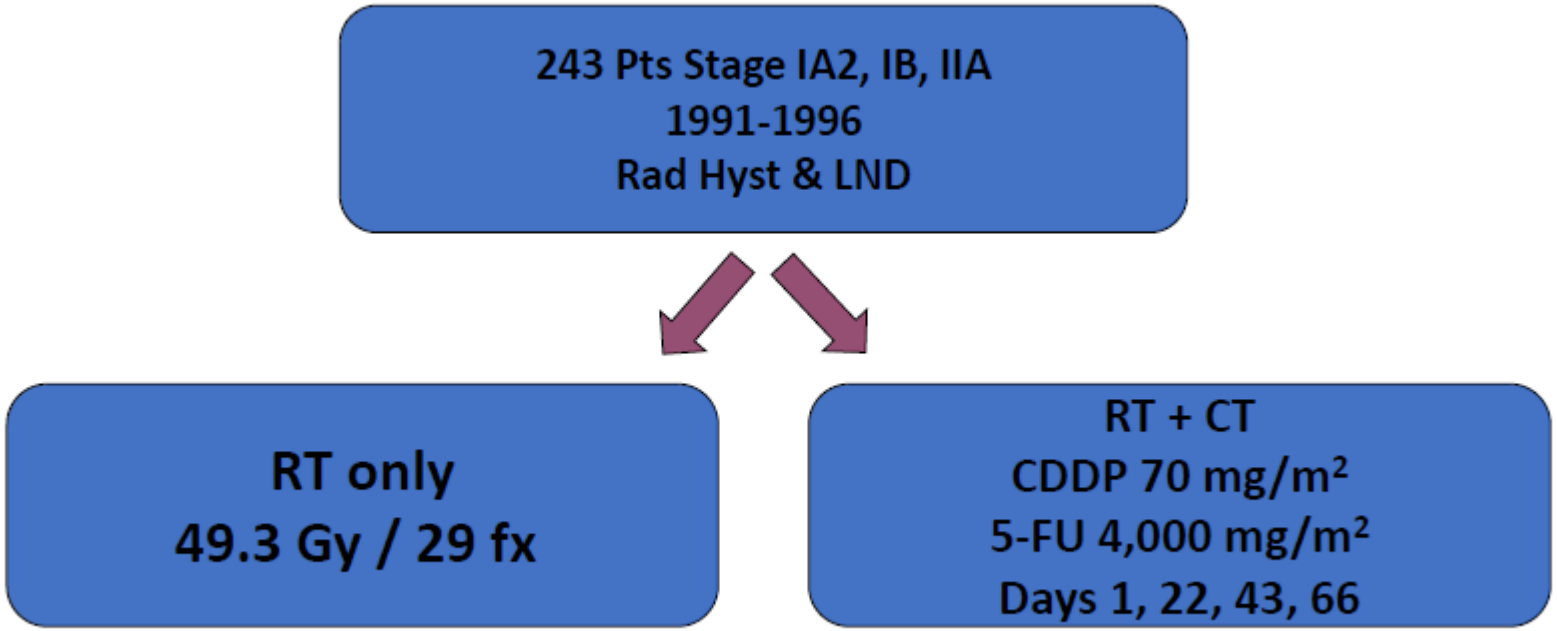
Sedlis, Gyn Onc 1999
Rotman, IJROBP 2006

Chemoradiation after Hysterectomy

GOG 109-High Risk Postop Cervix

Role of Chemo/RT

Positive margins, positive LN, +parametrial invasion(Peters)

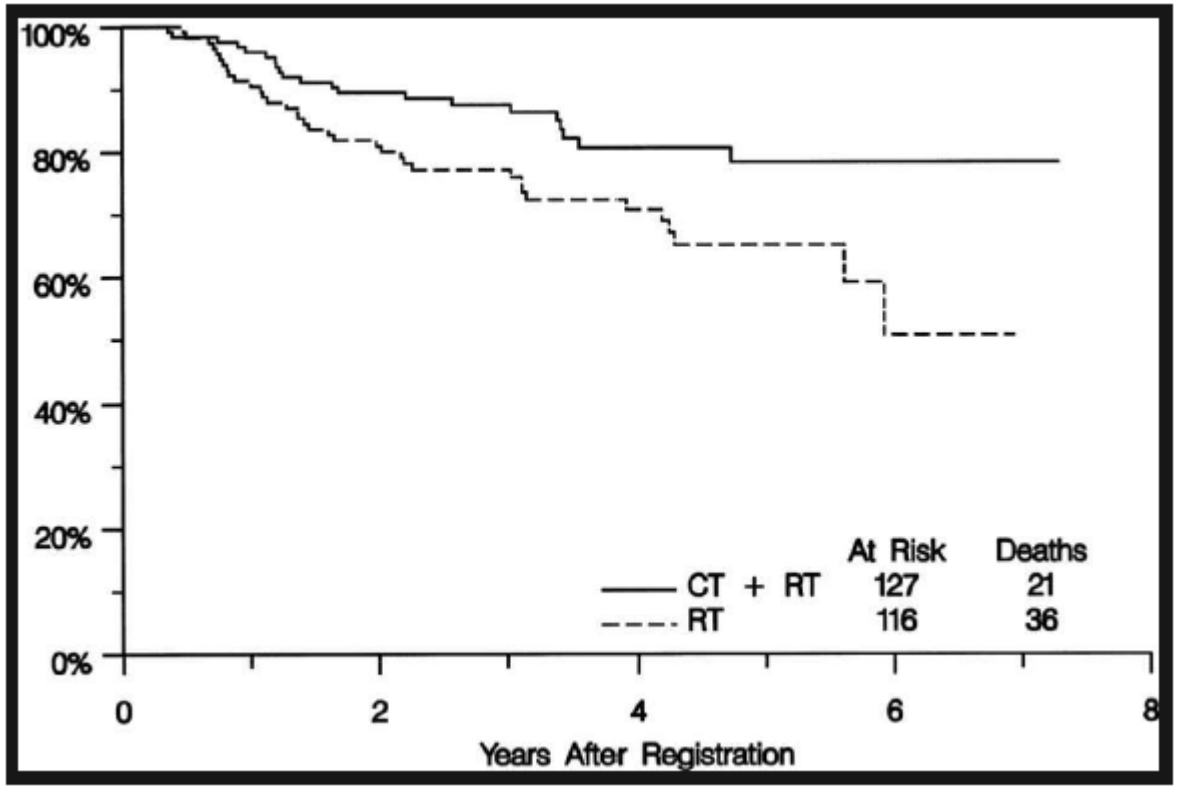


Peters, JCO 2000

GOG 109/SWOG 8797

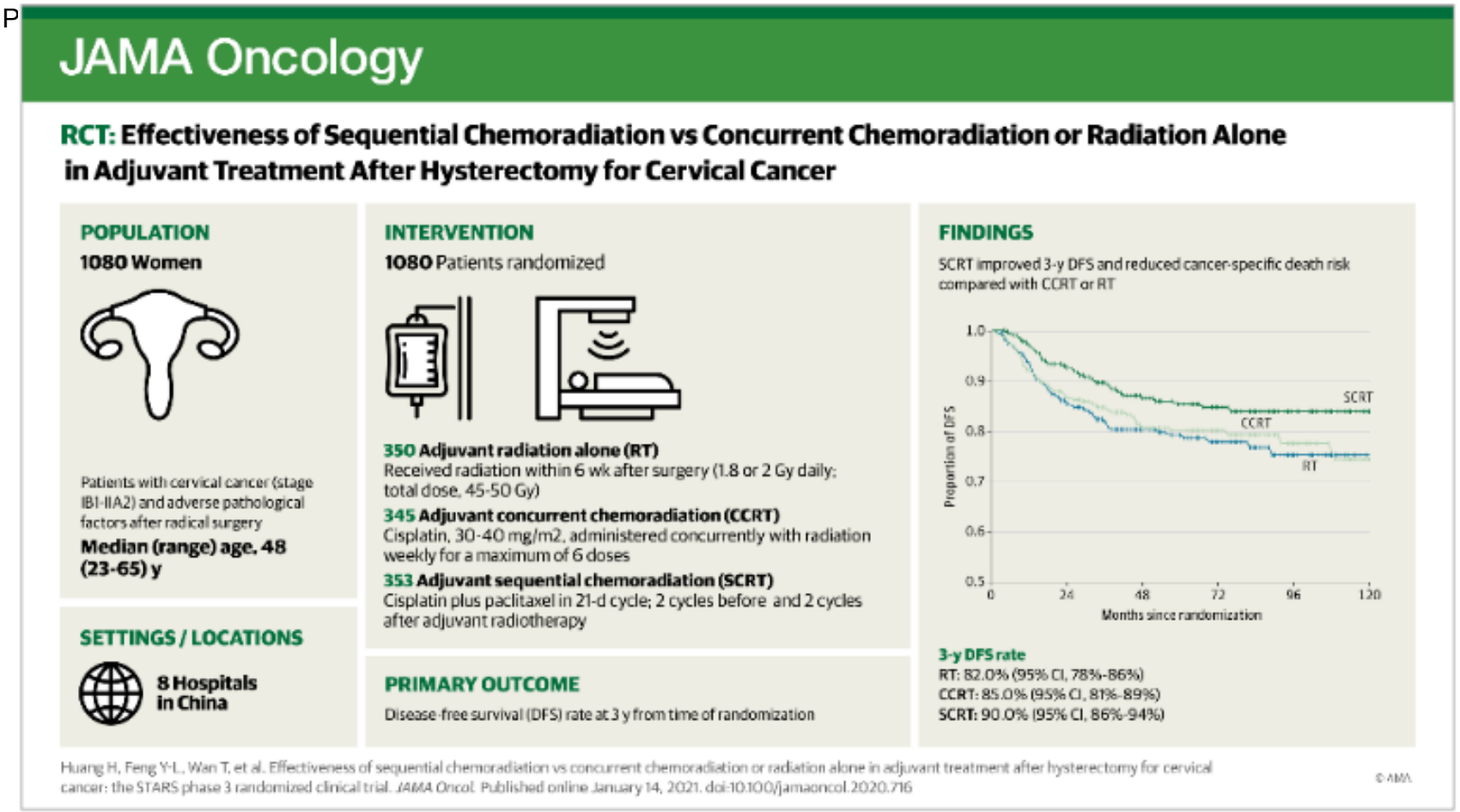
- 4 year PFS
  - 80% CT+RT vs. 63% RT alone
- 4 year OS:
  - 81% CT+RT vs. 71% RT alone

Not possible to determine impact of outback chemo component



Effectiveness of Sequential Chemoradiation vs Concurrent Chemoradiation or Radiation Alone in Adjuvant Treatment After Hysterectomy for Cervical Cancer: The STARS Phase 3 Randomized Clinical Trial

JAMA Oncol. P



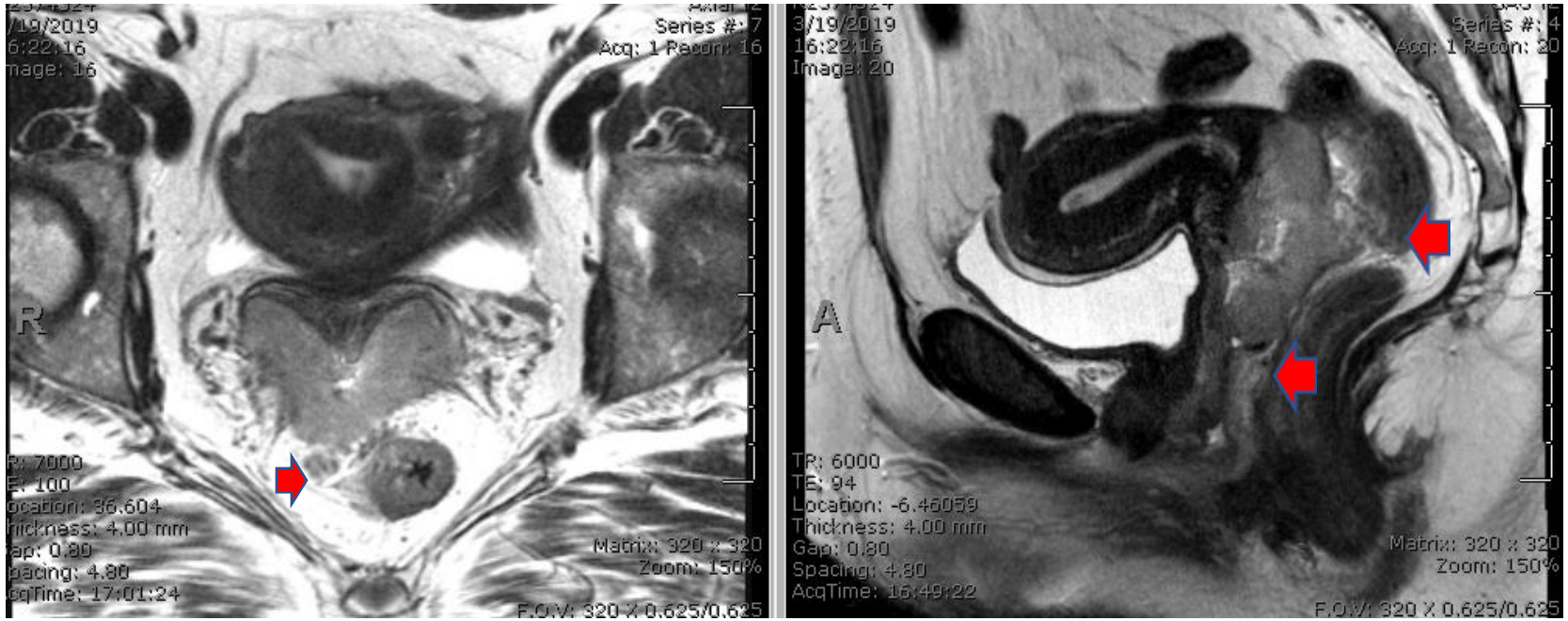
Issues

- Combined High and Intermediate risk patients together muddying results
- Approx 20% patients had neoadjuvant chemo prior to surgery-suggesting a higher risk population
- For intermediate risk group Seq CRT was no better than Concurrent CRT
- GOG studies

Treatment of Locally Advanced Cervical Cancer

Advanced Cervical Cancer –Treatment approach

42 yr pt with large cervix squamous cancer-extending to lower 1/3 vagina, invading rectovaginal septum on pre-treatment T2-W MRI

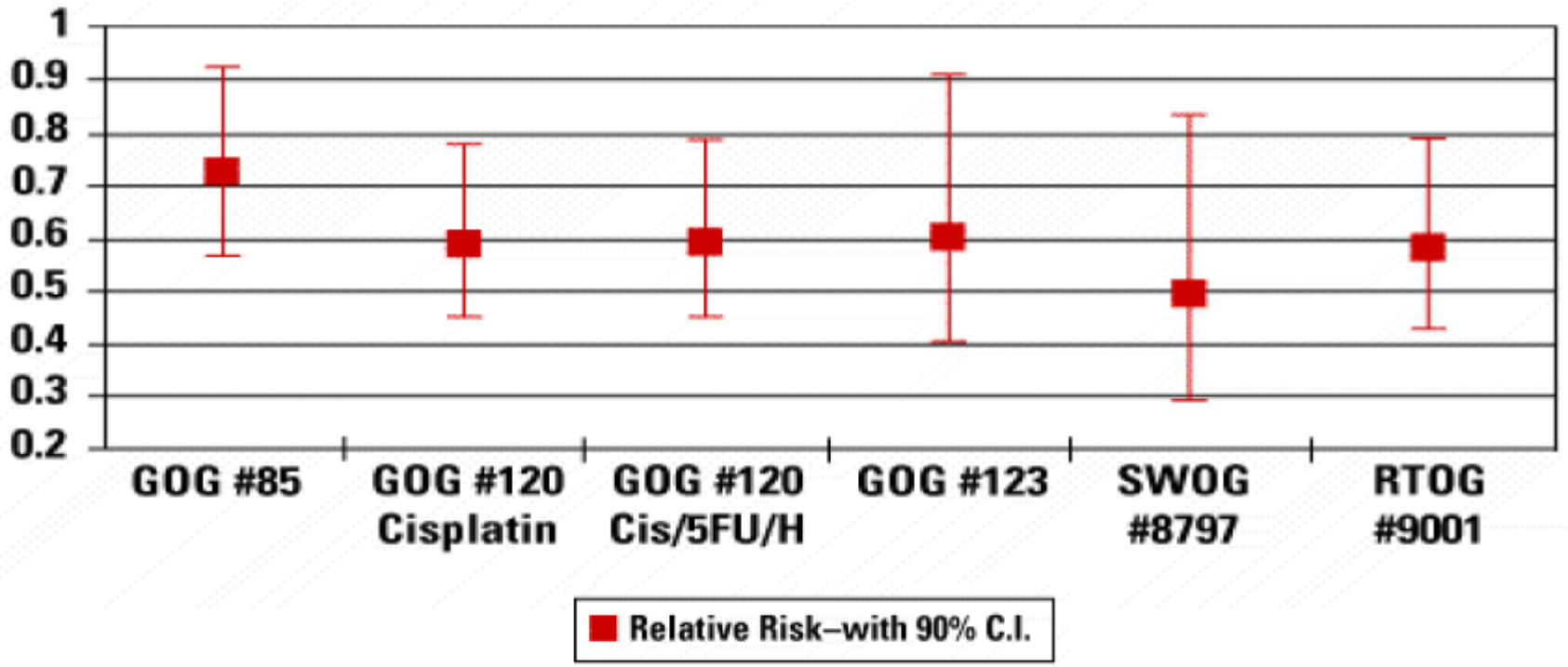


Q: What would you recommend in your clinical practice? Advanced Cervix Ca

- Concurrent ChemoRT with Tandem Ring Brachytherapy
- Neoadjuvant chemotherapy followed by Surgery
- Concurrent ChemoRT with Interstitial Brachytherapy
- Neoadjuvant Immunotherapy followed by Concurrent Chemoradiation

Cervical Cancer
Definitive Chemoradiation

Relative Risk Estimate of Survival from Five Chemoradiation Clinical Trials



Concurrent weekly CDDP/RT

	GOG 120 Rose, 1999	NCIC Pearcey, 2002	GOG 123 Keys, 1999
Stage	IIB-IVA	IA – IIA, > 5cm IIB	IB2
Arms	WPRT/B/H WPRT/B/cis/5FU/HU WPRT/B/weekly cis	WPRT/B WPRT/B + wkly cis	WPRT/B + SH WPRT/B/wkly cis + SH
OS	47% 65% (3 year)	62% 58% (5 year), p = NS	74% 83% (3 year)
LR			21% 37%
Notes	↓toxicity with cis or HU alone	Non-surgical staging of nodes	↑pCR with chemo (52 vs 41%)

RT vs. CRT: RTOG 90-01

n = 389
FIGO IIB-IVA cervical cancer or IB-IIA cervical cancer if tumor > 5 cm or +LN

Years: 1990-1997

Exclusion criteria:
- Pos. PA LN
- Disease outside pelvis
- Prior tx for cervical ca

RANDOMIZE

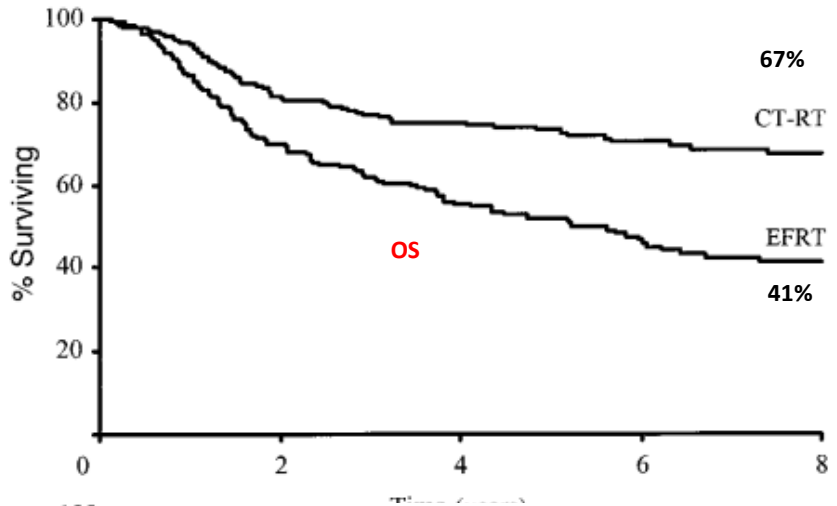
45 Gy to pelvis and para-aortic LN (EFRT) → LDR brachy

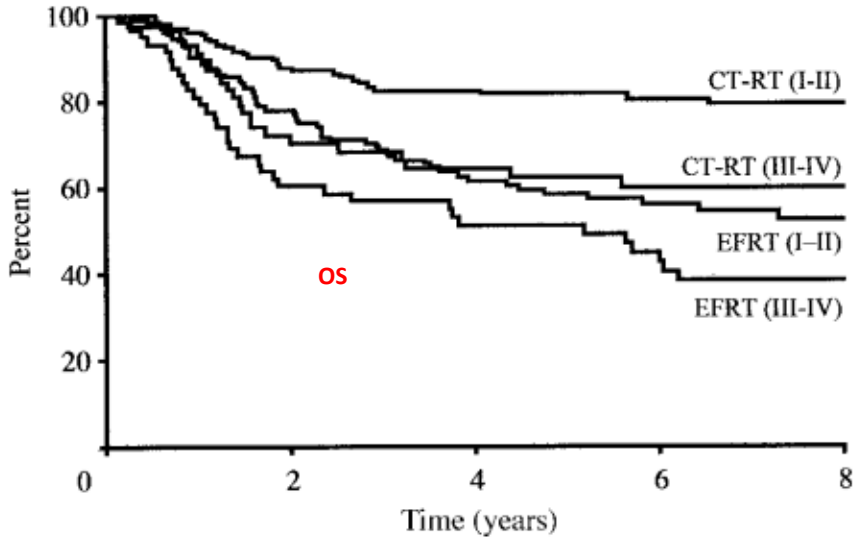
Cumulative point A dose ≥ 85 Gy

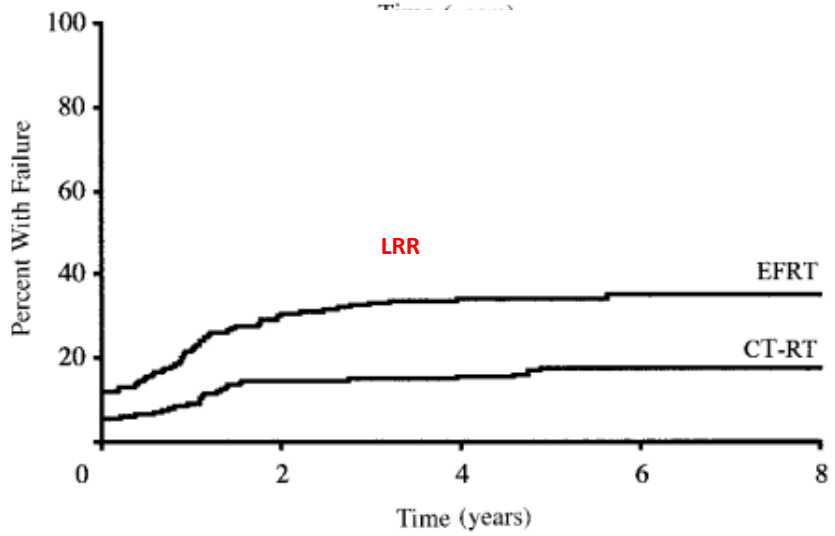
45 Gy to pelvis with concurrent CDDP/5-FU → LDR brachy
- **3 cycles chemo (Q3 weeks)**
  - **75 mg/m^2 cisplatin**
  - **4000 mg/m^2 5-FU over 4 days**

Eifel *NEJM* 2001 and *JCO* 2004

RT vs. CRT: RTOG 90-01





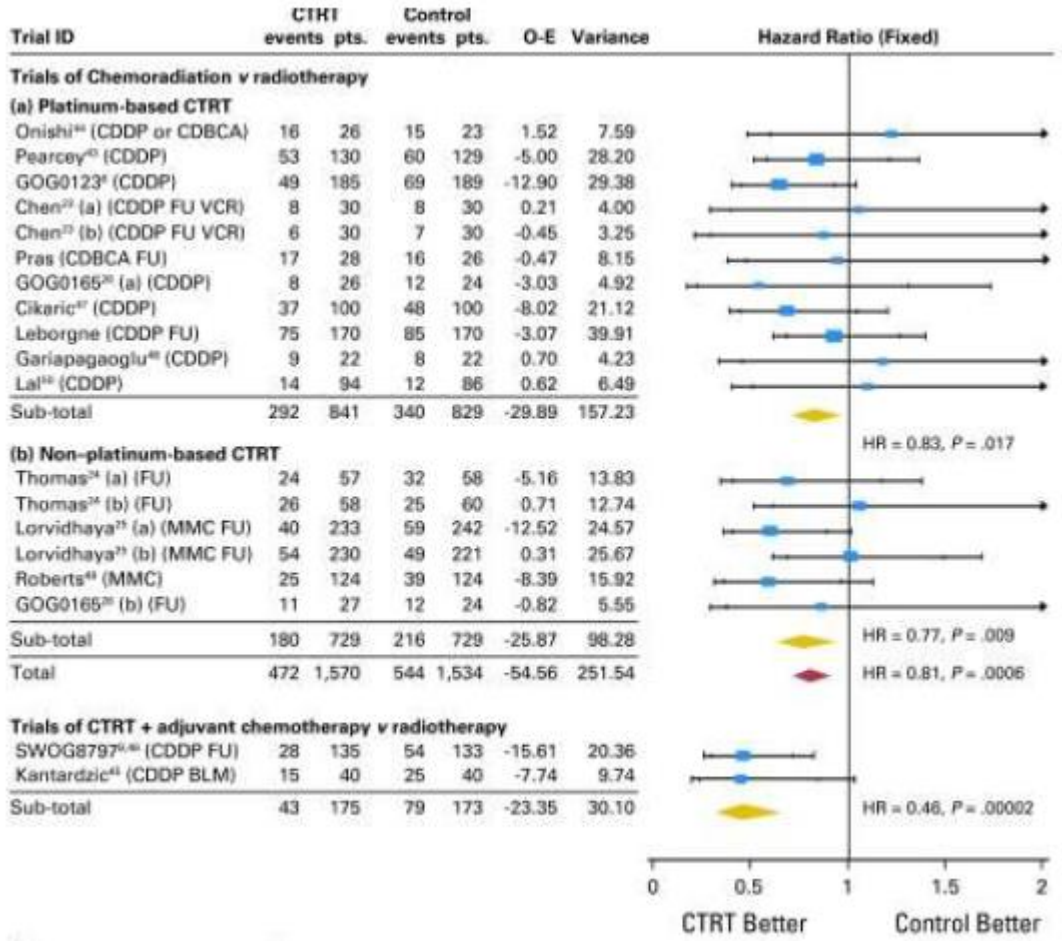


5 year LRR
FIGO stage IB or II: 13% (CRT) vs. 31% (EBRT), p=0.0002
FIGO stage III or IVA: 29% (CRT) vs. 44% (EBRT), p=0.065

Eifel *NEJM* 2001 and *JCO* 2004

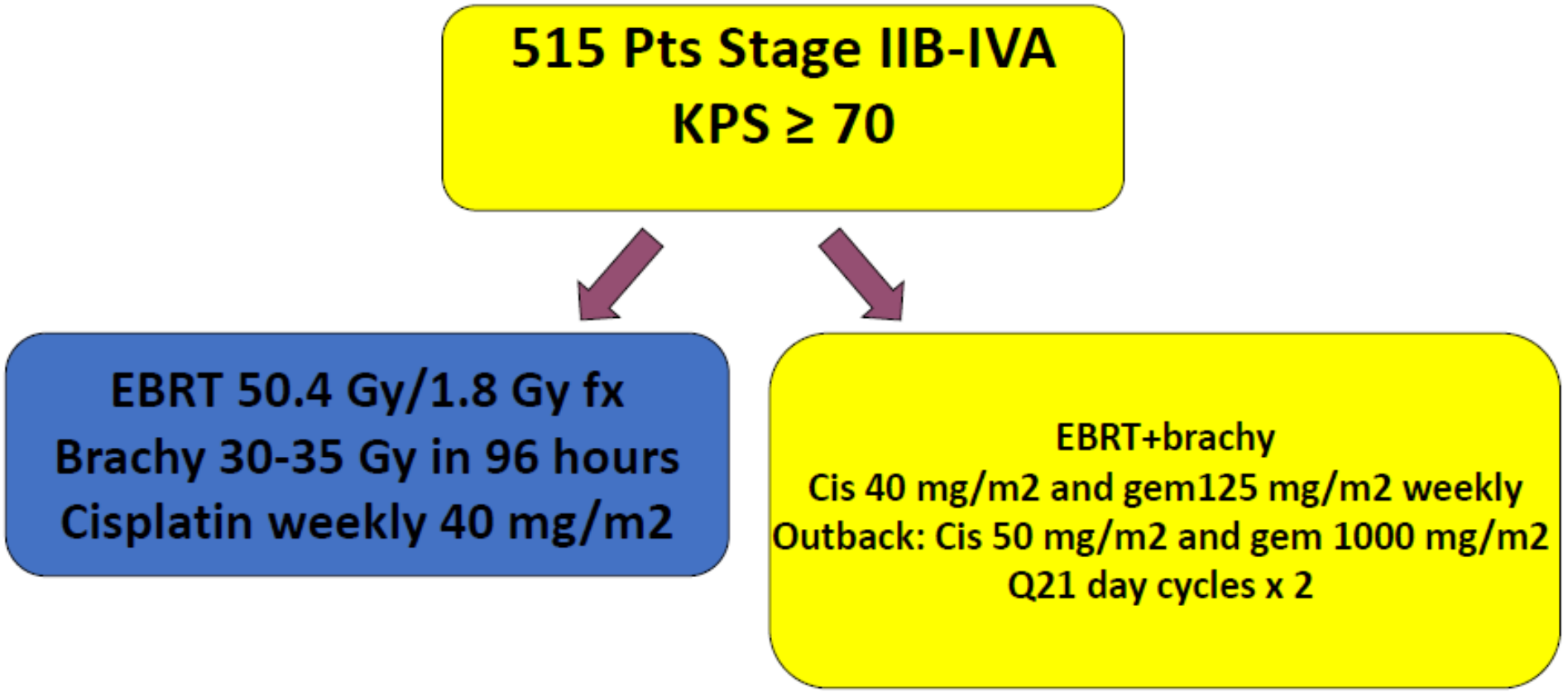
Chemo-radiotherapy Meta-analysis

- 15 randomized trials of CT+RT vs RT
  - 11 Platinum based
  - 3 Nonplatinum
- 3452 pts
- CT+RT vs RT
  - 8% absolute improvement in DFS (50% to 58%)
    - Also for locoregional DFS and distant metastases free survival
  - Overall survival benefit of 6% (60% to 66%) for CT+RT vs RT
- CT+RT→CT vs RT alone
  - Two trials
  - 19% absolute OS improvement (60% to 79%)



Trial ID	CTRT events	CTRT pts.	Control events	Control pts.	O-E	Variance
Trials of Chemoradiation *v* radiotherapy						
(a) Platinum-based CTRT						
Onishi[44] (CDDP or CDBCA)	16	26	15	23	1.52	7.59
Pearcey[45] (CDDP)	53	130	60	129	-5.00	28.20
GOG0123[3] (CDDP)	49	185	69	189	-12.90	29.38
Chen[23] (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00
Chen[23] (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15
GOG0165[26] (a) (CDDP)	8	26	12	24	-3.03	4.92
Cikaric[47] (CDDP)	37	100	48	100	-8.02	21.12
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91
Gariapagaoglu[48] (CDDP)	9	22	8	22	0.70	4.23
Lal[49] (CDDP)	14	94	12	86	0.62	6.49
Sub-total	292	841	340	829	-29.89	157.23
(b) Non-platinum-based CTRT						
Thomas[24] (a) (FU)	24	57	32	58	-5.16	13.83
Thomas[24] (b) (FU)	26	58	25	60	0.71	12.74
Lorvidhaya[25] (a) (MMC FU)	40	233	59	242	-12.52	24.57
Lorvidhaya[25] (b) (MMC FU)	54	230	49	221	0.31	25.67
Roberts[46] (MMC)	25	124	39	124	-8.39	15.92
GOG0165[26] (b) (FU)	11	27	12	24	-0.82	5.55
Sub-total	180	729	216	729	-25.87	98.28
Total	472	1,570	544	1,534	-54.56	251.54
Trials of CTRT + adjuvant chemotherapy *v* radiotherapy						
SWOG8797[50,51] (CDDP FU)	28	135	54	133	-15.61	20.36
Kantardzic[41] (CDDP BLM)	15	40	25	40	-7.74	9.74
Sub-total	43	175	79	173	-23.35	30.10

What is role of intensified + outback chemo?

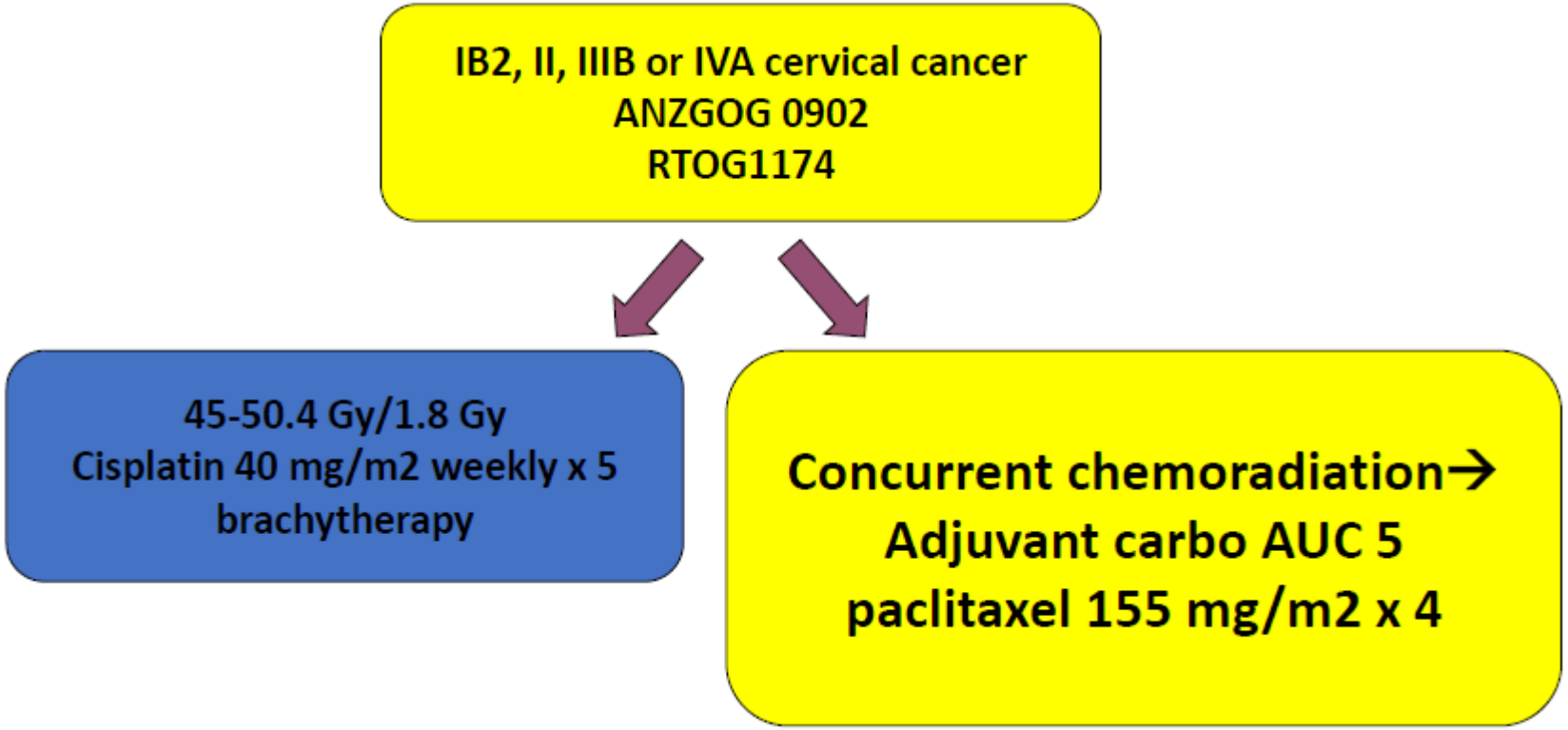


Duenas-Gonzalez, JCO 2011

Should we be giving outback chemo?

- Use of cisplatin plus gemcitabine resulted in
  - Improvement in PFS vs cis alone
    - 3 year PFS 74% versus 65%
  - An improvement in overall survival
  - Toxicities
    - More serious (grade ¾) toxicities (87% vs 43%)
    - More hospitalizations (30% vs 11%)

Should we be giving outback chemo?



OUTBACK STUDY-Results out soon?

NAC + surgery vs. CRT

Stage IB2, IIA, or IIB

RANDOMIZE

Chemo + Hysterectomy

3 cycles Carboplatin AUC 5-6

Paclitaxel 175 mg/m^2 q3wks

CRT

Cisplatin 40 mg/m^2 weekly x 5

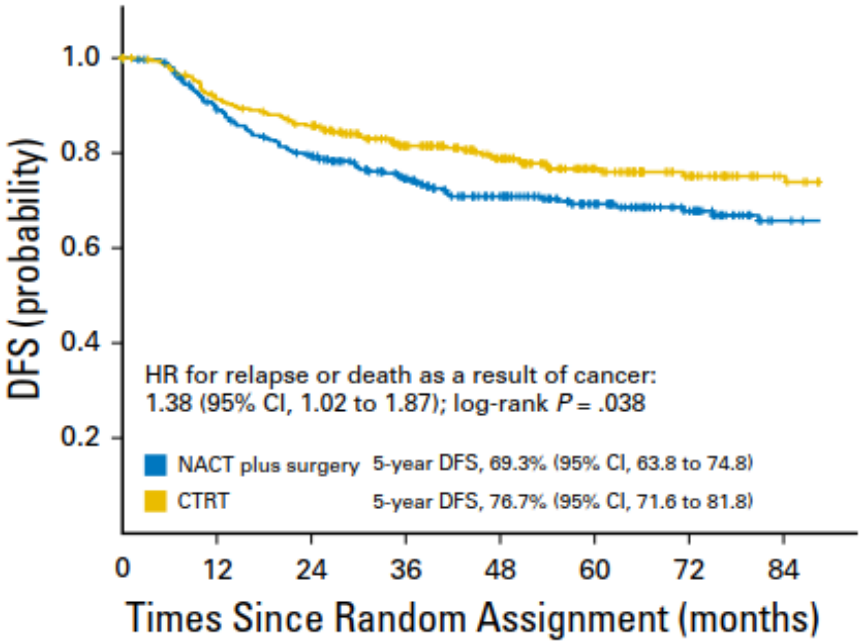
40 Gy in 20 fractions with 2 Gy per fraction and a midline shield at 20 Gy, followed by intracavitary radiation to point A as follows: either two ap-
plications of a low dose rate of 30 Gy each or five applications of a high dose
rate of 7 Gy each.

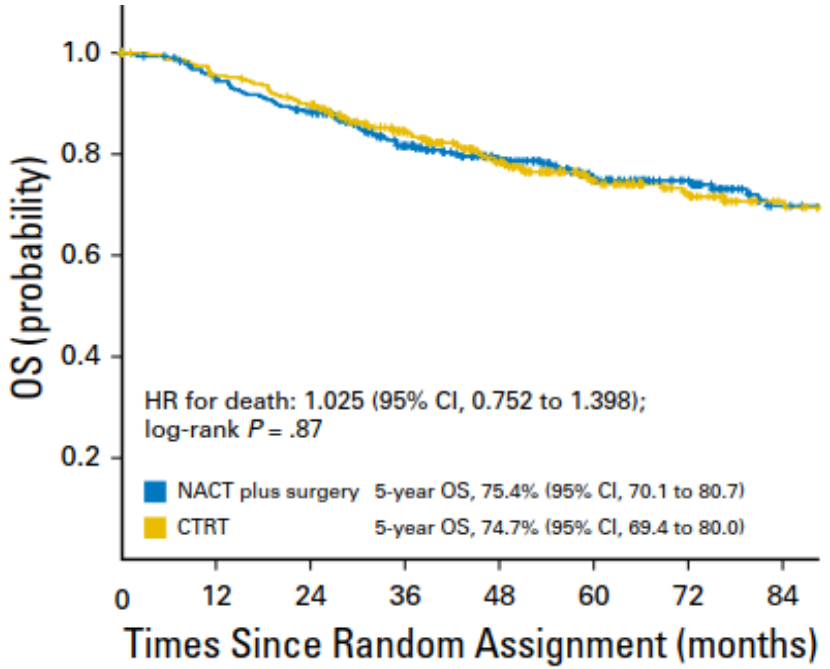
Primary endpoint: DFS

2nd endpoint: OS, toxicity

Gupta *JCO* 2018

NAC + surgery vs. CRT





Gupta *JCO* 2018

Treatment of Locally advanced IB2 – IVA cervical cancer

- EBRT 45 Gy (1.8 Gy fx)
  - 3D CRT, 4 fields
  - Boost to parametrial or sidewall disease
- Brachytherapy (total 85-90 Gy)
- Concurrent chemotherapy
  - (weekly CDDP 40 mg/m2)

Practical Radiation Oncology® (2020) 10, 220-234

Clinical Practice Guidelines

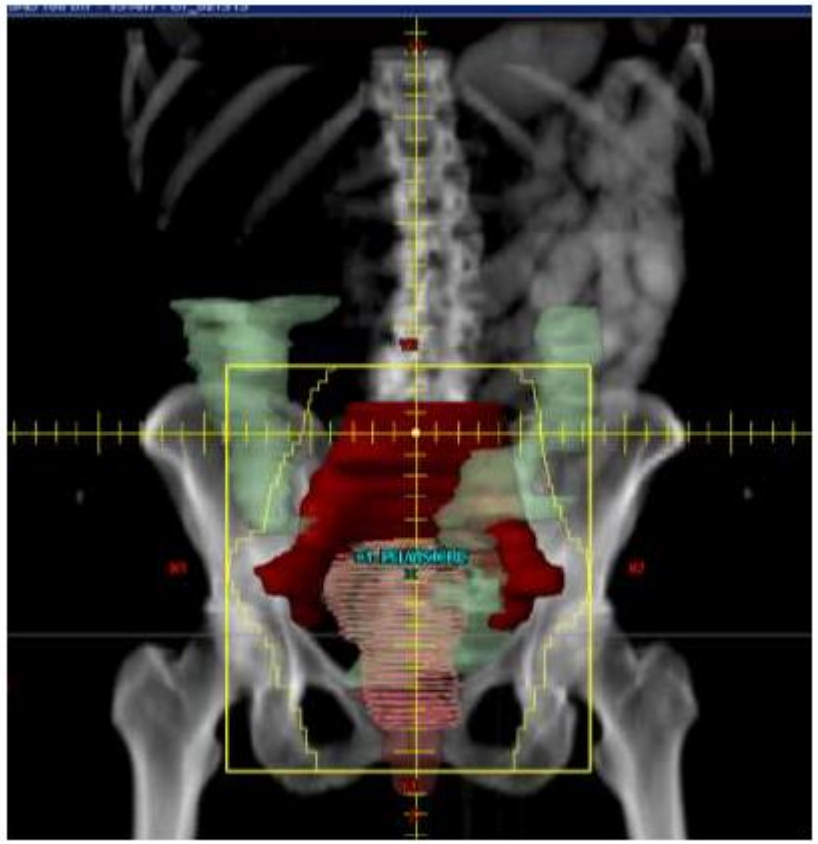
Radiation Therapy for Cervical Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

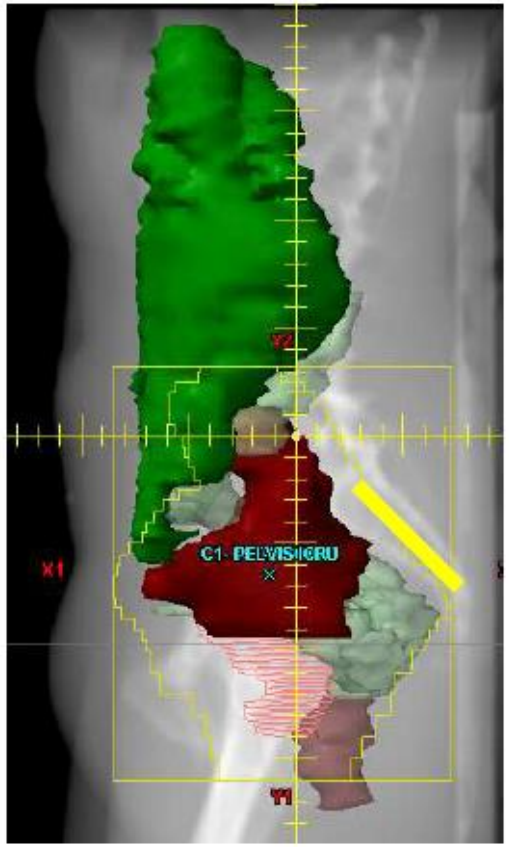
Junzo Chino, MD,[a,*] Christina M. Annunziata, MD, PhD,[b]

- IMPORTANT DOCUMENT
- 5KEY QUESTIONS

i. Postop RT for Early Stage cervix
ii. Definitive ChemoRT
iii. Use of IMRT-conditional for definitive treatment
    Creation of PTV
IV. When is Brachy indicated
V. Technique and Parameters of Brachy

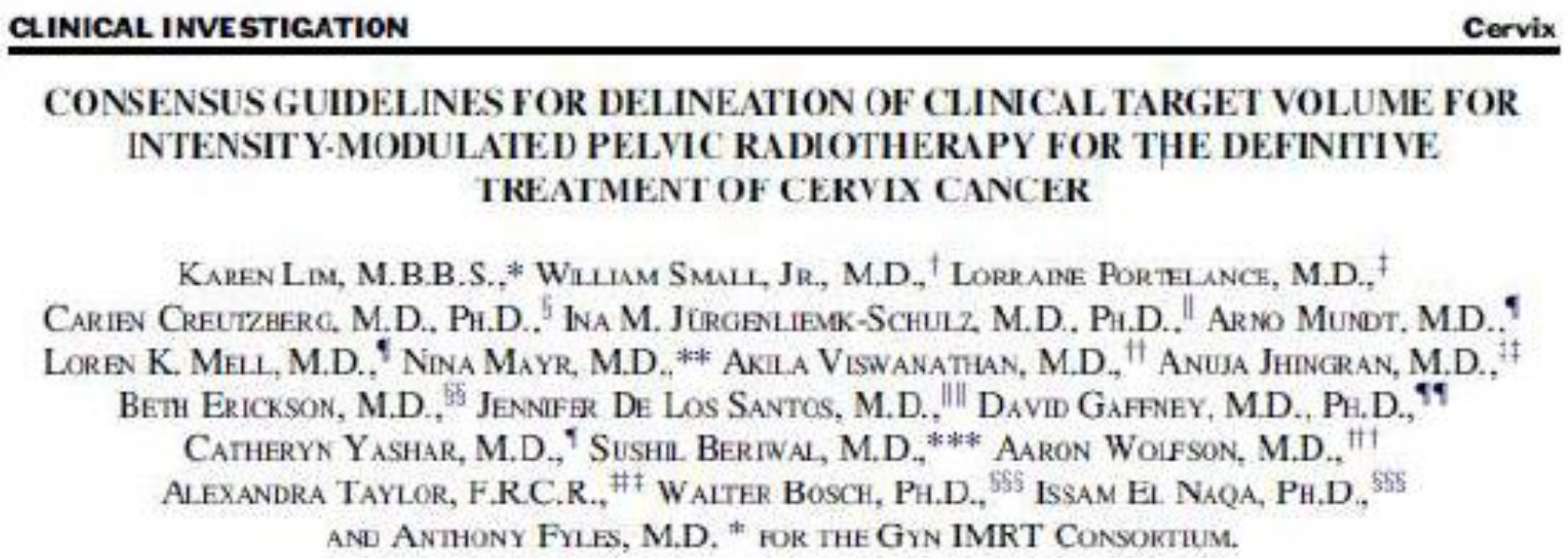
RT Fields





Use of IMRT for Intact Cervix: Controversies

- Contouring
- Organ Motion
- Simulation/Setup/IGRT



CLINICAL INVESTIGATION Cervix

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY FOR THE DEFINITIVE TREATMENT OF CERVIX CANCER

KAREN LIM, M.B.B.S.,* WILLIAM SMALL, JR., M.D.,† LORRAINE PORTELANCE, M.D.,‡ CARIEN CREUTZBERG, M.D., PH.D.,§ INA M. JÜRGENLIEMK-SCHULZ, M.D., PH.D.,‖ ARNO MUNDT, M.D.,¶ LOREN K. MELL, M.D.,¶ NINA MAYR, M.D.,** AKILA VISWANATHAN, M.D.,†† ANUJA JHINGRAN, M.D.,‡‡ BETH ERICKSON, M.D.,§§ JENNIFER DE LOS SANTOS, M.D.,‖‖ DAVID GAFFNEY, M.D., PH.D.,¶¶ CATHERYN YASHAR, M.D.,¶ SUSHIL BERTWAL, M.D.,*** AARON WOLFSON, M.D.,††† ALEXANDRA TAYLOR, F.R.C.R.,‡‡‡ WALTER BOSCH, PH.D.,§§§ ISSAM EL NAQA, PH.D.,§§§ AND ANTHONY FYLES, M.D. * FOR THE GYN IMRT CONSORTIUM.

http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx

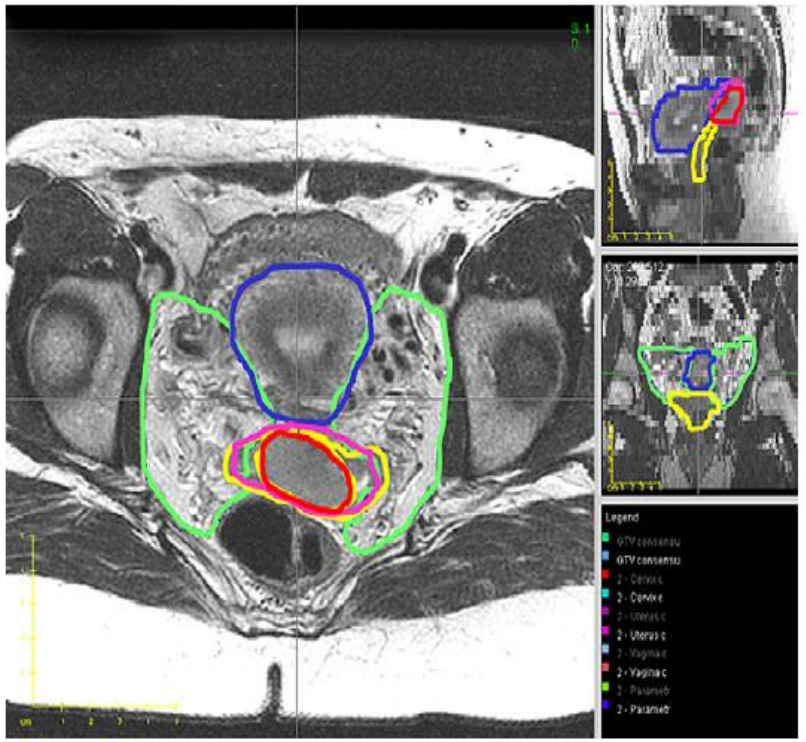
IMRT for Intact Cervix Cancer-CTV

- Accurate target definition is vitally important for definitive treatment of cervix cancer with IMRT, - as unlike 3D ,IMRT is not forgiving
- Definition of clinical target volume includes structures surgically removed in radical hysterectomy /MRI based

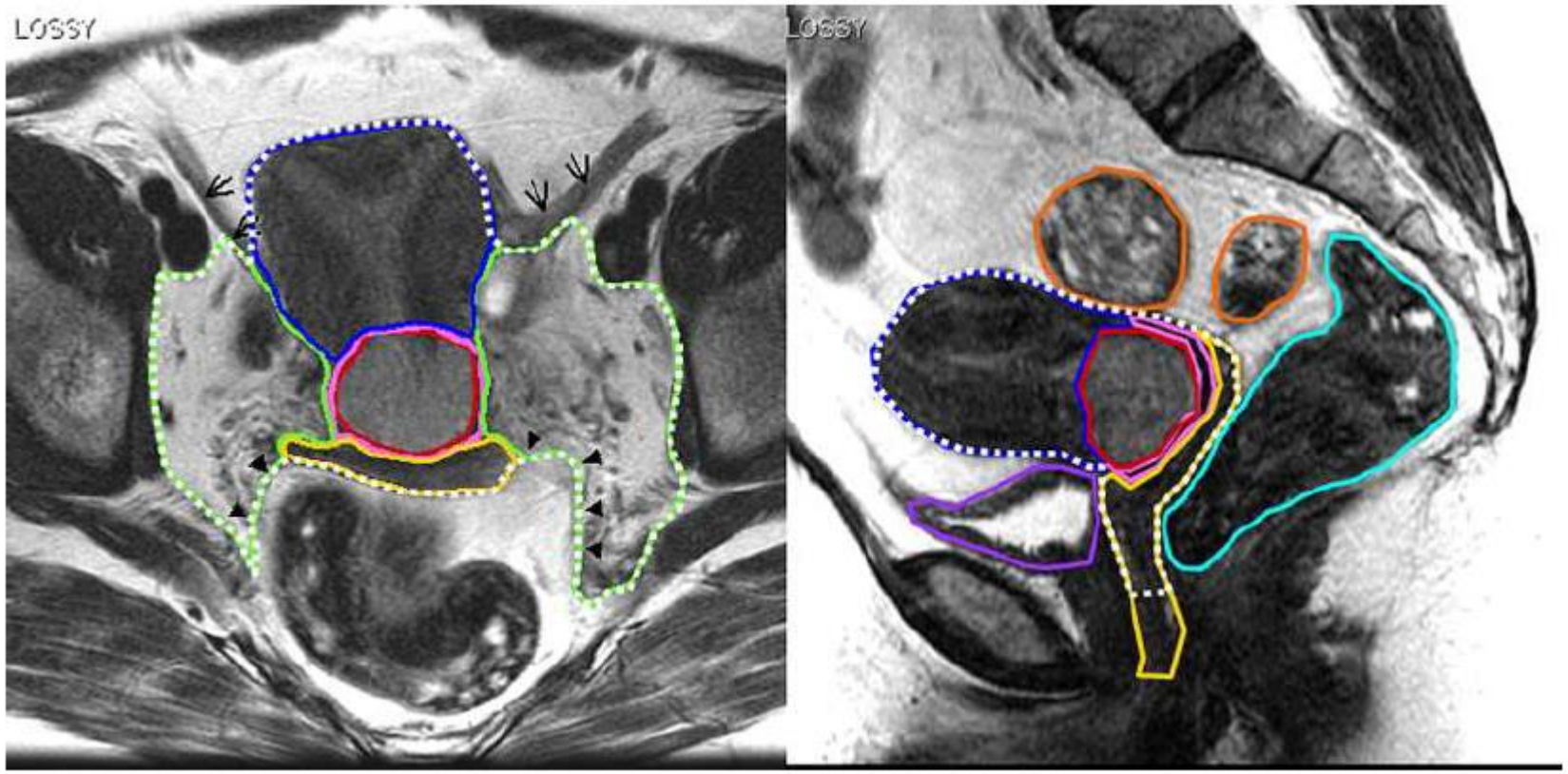
Table 2. CTV components

GTV	Entire GTV; intermediate/high signal seen on T_2-weighted MR images
Cervix	Entire cervix; if not already included within GTV contour
Uterus	Entire uterus
Parametrium	Entire parametrium, including ovaries; include entire mesorectum if uterosacral ligament involved
Vagina	Minimal or no vaginal extension: upper half of the vagina Upper vaginal involvement: upper two-thirds of the vagina Extensive vaginal involvement: entire vagina

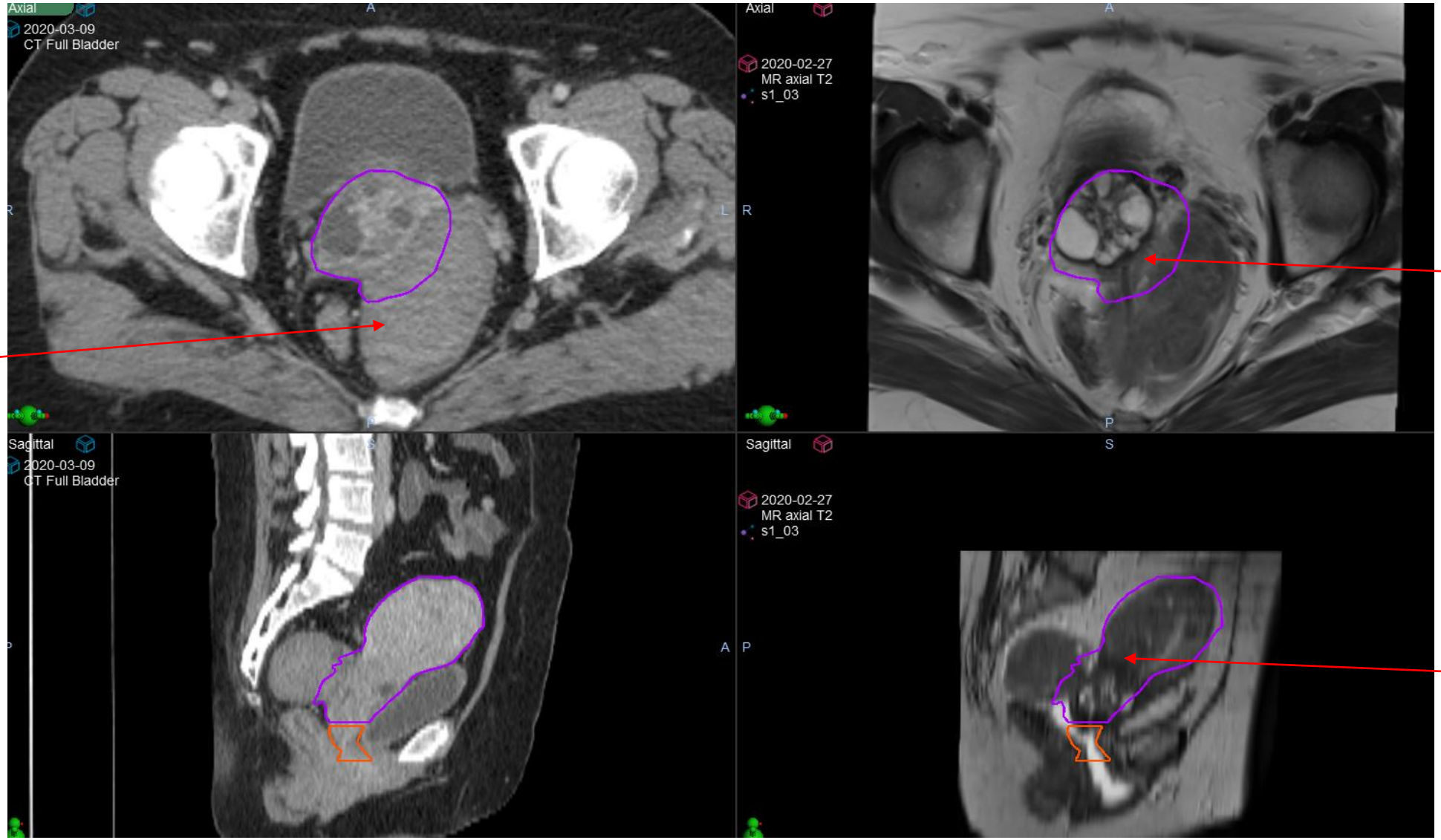
Onc



IMRT for Intact Cervix Cancer-CTV



FDG PET/CT and MR FUSION OR SIMULATION

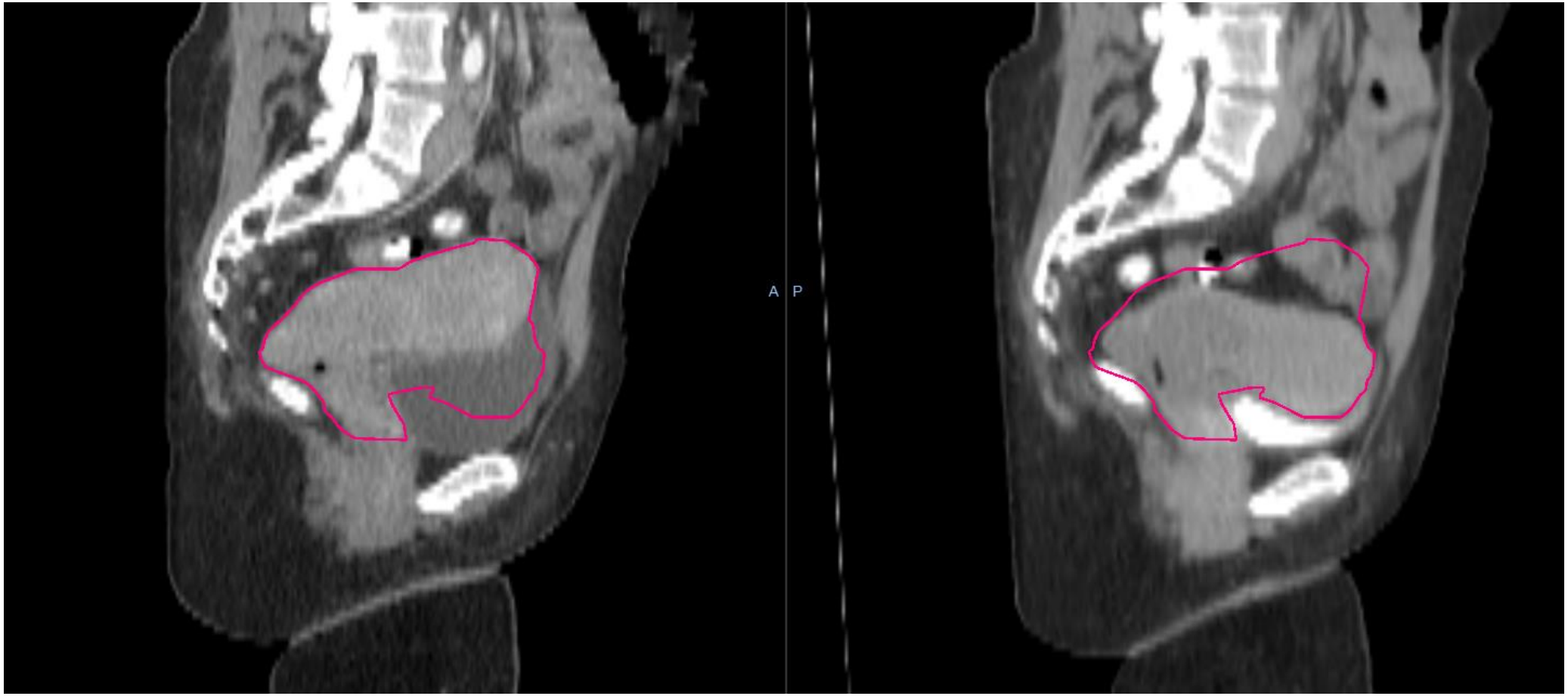


fibroid

PET avid jnx of fibroid and cervix

Cervix CTV

Cervix ITV (Pink) –from bladder full/empty



Maybe greater interfraction and Intrafraction Motion

IMRT Considerations for Intact Cervix Cancer

- Simulation: bladder full and bladder empty
- MRI pretreatment or at the time of simulation
- Use all available imaging for contouring ITV
- Margins
  - CTV – PTV margins for primary CTV: 1.5-2 cm
  - ITV – PTV margins for primary ITV: 7-10 mm
  - CTV – PTV margins for nodal CTV: 7 mm
- Daily soft tissue IGRT/ may need replanning at short notice

Motion of cervix can exceed 2 cm in some situations

So why do IMRT- Advantages of IMRT

- PA nodes-extended field IMRT-→spare bowel, kidney,duodenum
- Inguinal nodes--→ Spare femur, SIB boost
- Boost
  - Nodal boost(SIB)
  - Sidewall boost

- Potential reduced bowel,bone marrow toxicity
- Potential reduced pelvic fracture

Key Points:

- Concurrent chemo/RT remains standard of care for locally advanced cervical cancer
- IMRT may be appropriate particularly in select situations (groin or PA+) with careful accounting of cervix/uterine motion
- Use all available imagine to define uterine-cervix ITV.

Brachytherapy -saves Lives

Brachytherapy is a continuous process
Plan from the beginning,and strategize…

<u>Tumor Mapping done at initial exam</u>

Lower Vaginal involvement , adjacent organ invasion may preclude HDR-Intracavitary BTT

- Plan ahead for Hybrid Interstitial

If ICBT is possible is the… ?

Organ anatomy Favorable- think ahead about different applicator T/o,T/r,T/c,T/n

- Uterus Anteverted /retroverted –see diagnostic CT scan(saggital)/MRI
- Vaginal Fornices deep vs Obliterated

<u>Tumor Anatomy Favorable</u>

- Cervix destroyed , os difficult to visualize
- Endocervical tumor
- Tumor Size- will it be within prescription isodose?-if not Interstial /Hybrid Brachytherapy

ASTRO GUIDELINES CERVICAL CANCER-BRACHYTHERAPY

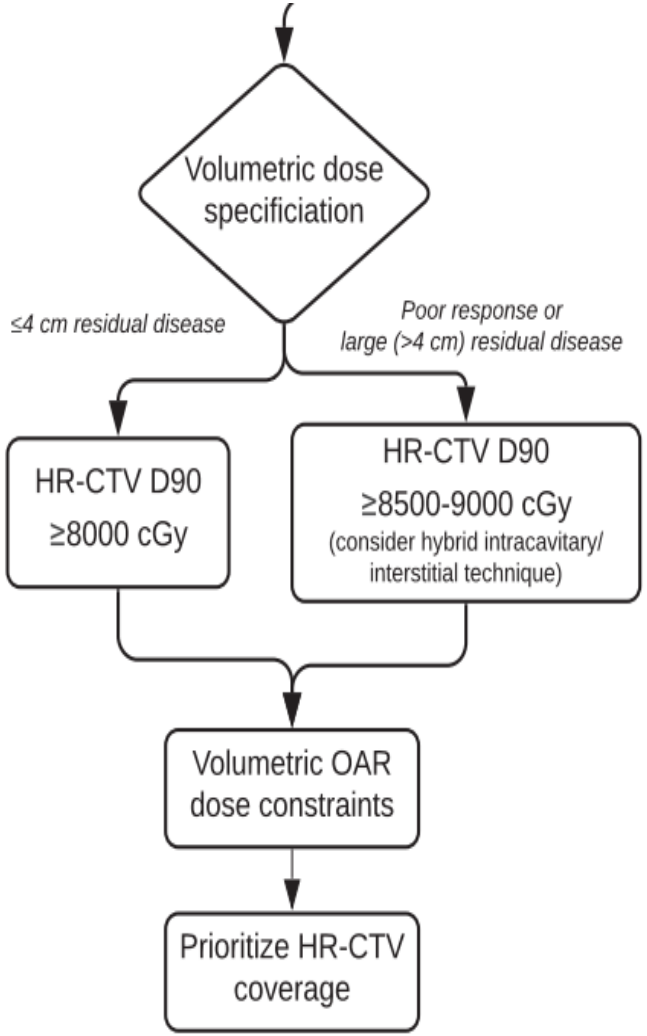


Table 7 Dose constraints

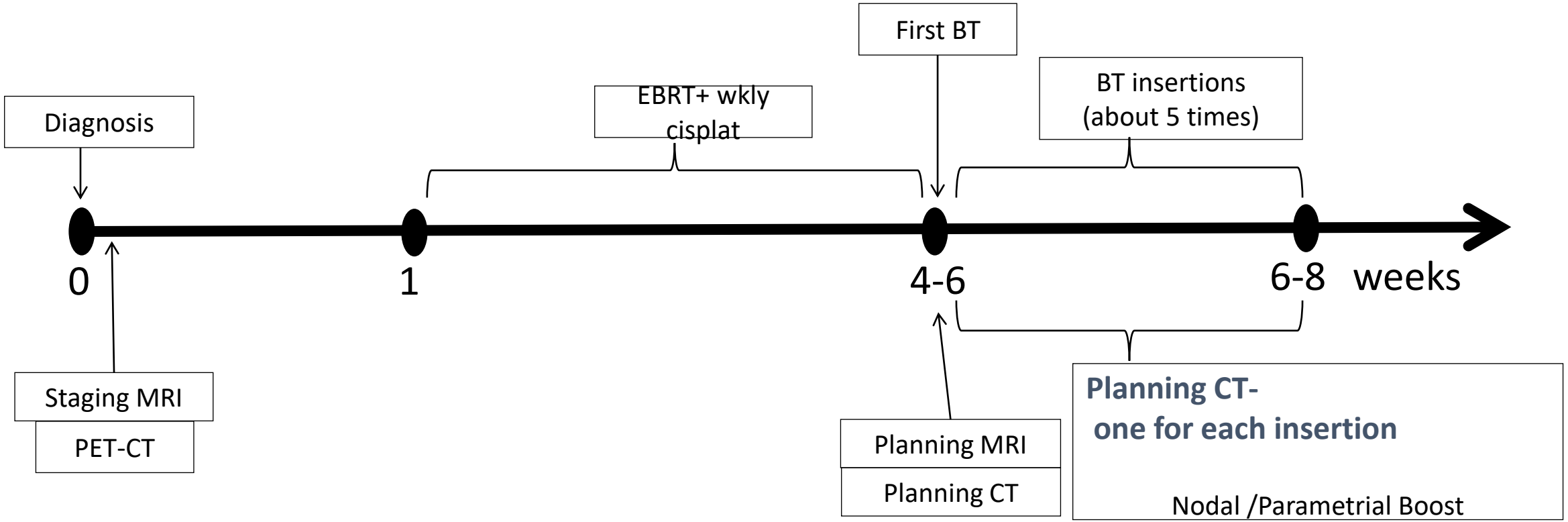
Organ at risk	Ideal dose constraint (cGy) ($EQD2_3$)	Maximum* dose constraint (cGy) ($EQD2_3$)	ICRU point (cGy) ($EQD2_3$)
Rectum	<6500 D2cc	<7500 D2cc	<7500 point dose
Bladder	<8000 D2cc	<9000 D2cc	<9000 point dose
Vagina (recto-vaginal point)†	<6500 point dose	<7500 point dose	—
Sigmoid‡	<7000 D2cc	<7500 D2cc	—
Bowel‡	<7000 D2cc	<7500 D2cc†	—

Abbreviations: ICRU = International Commission of Radiation Units and Measurements; $EQD2_3$ = dose calculation to an eq with an α-to-β ratio of 3. D2cc is the minimal dose to the 2 cm^3 (2 mL) of the organ at risk receiving the maximal dose.

* There will be occasions when exceeding these maximum constraints is necessary to adequately treat the targets of ther clinical judgment of the treating physician.

† The rectovaginal point is defined 5 mm posterior to the vaginal mucosa from the center of the vaginal sources.

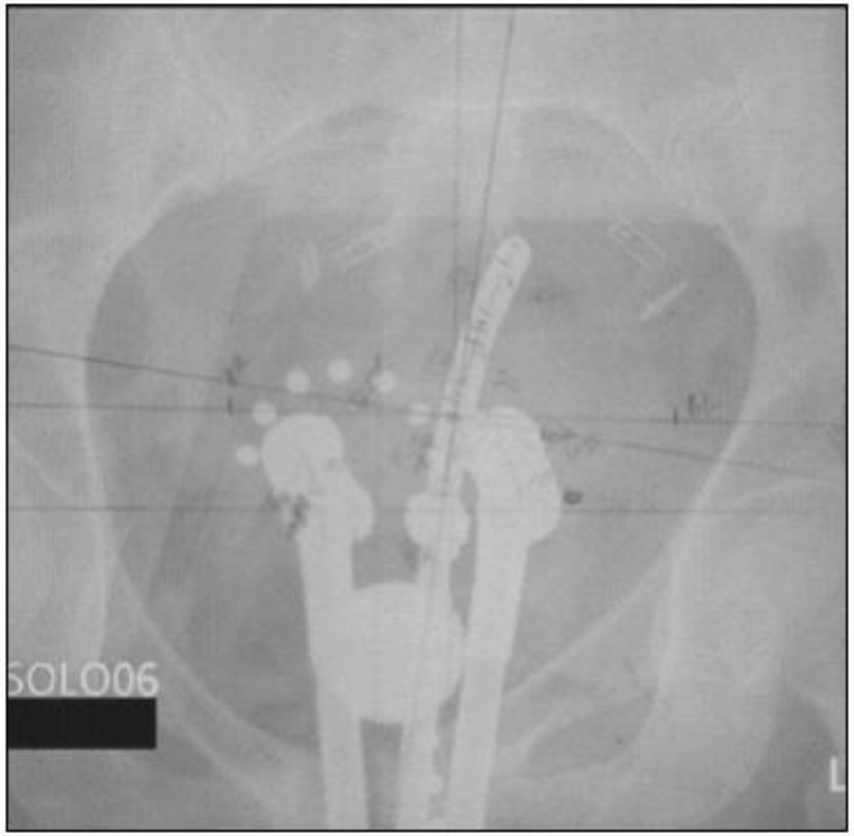
Timeline for advanced cervical cancer treatment-a veritable symphony



EBRT – external beam radiation therapy

BT - brachytherapy

Implant quality matters RTOG 0116 and 0128



- Mean f/u: 24.5 months
- Reviewed brachytherapy records
- Higher LR with unacceptable geometry
  - Displacement of ovoids relative to os HR 2.67
  - Unacceptable symmetry of ovoids and tandem HR2.50
  - Inappropriate packing placement HR 2.06

Viswanathan IJGC 2012

MR Brachytherapy Guidelines- ICRU 89

- GTV
  - Macroscopic tumor at brachytherapy
  - High signal intensity mass(es) (FSE, T2) in cervix/corpus, parametria, vagina, bladder and rectum
- High Risk-CTV
  - Includes gtv, whole cervix, and presumed extracervical tumor extension.
  - Grey zones in parametria, uterine corpus, vagina, or rectum, and bladder
- Intermediate Risk-CTV
  - Encompasses HRCTV with margins added according to tumor size and regression; minima margins of 5-15 mm
  - Extensive disease w/good remission: HR-CTV and initial tumor extension

MRI for Image Guided Brachytherapy

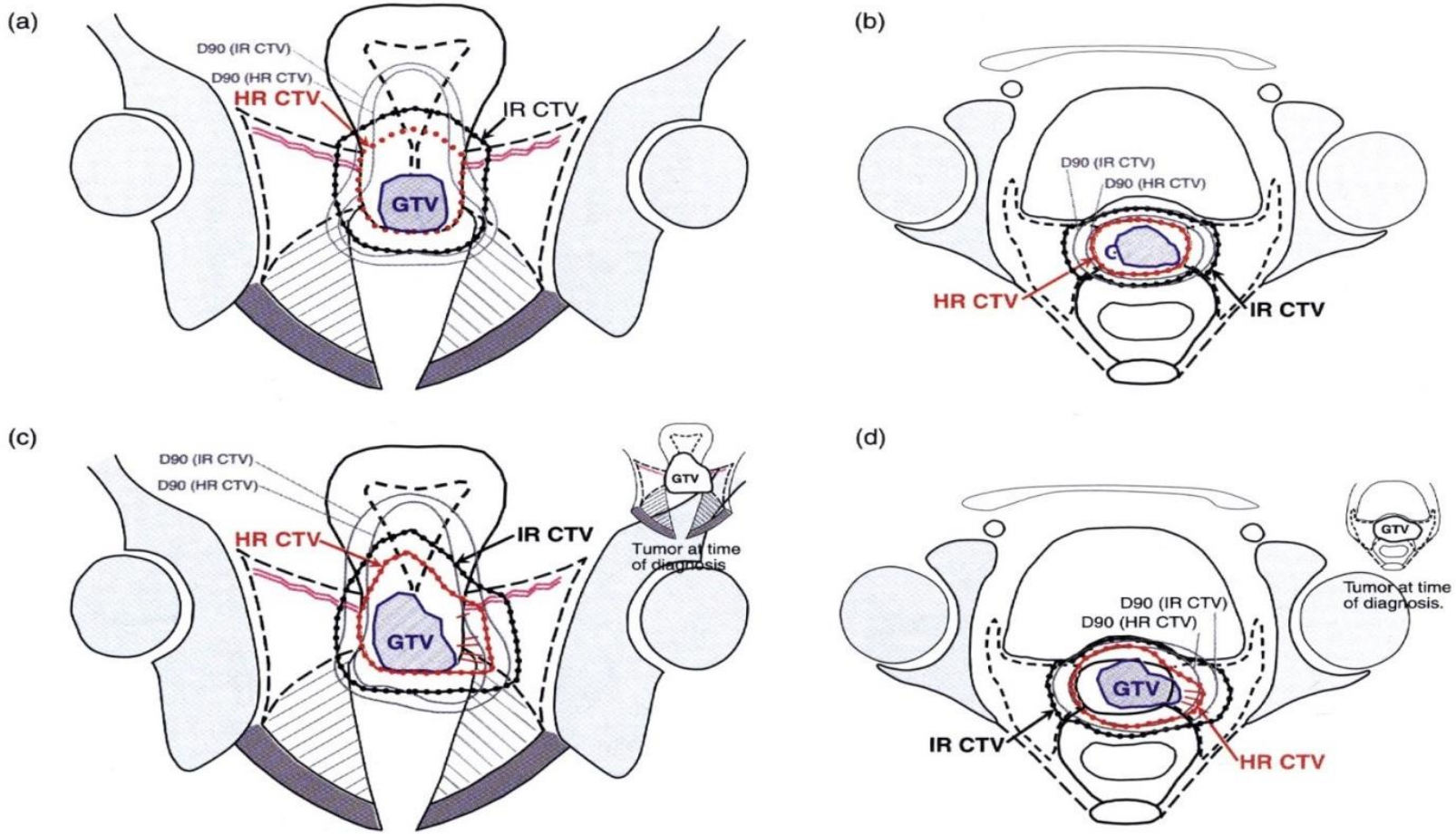
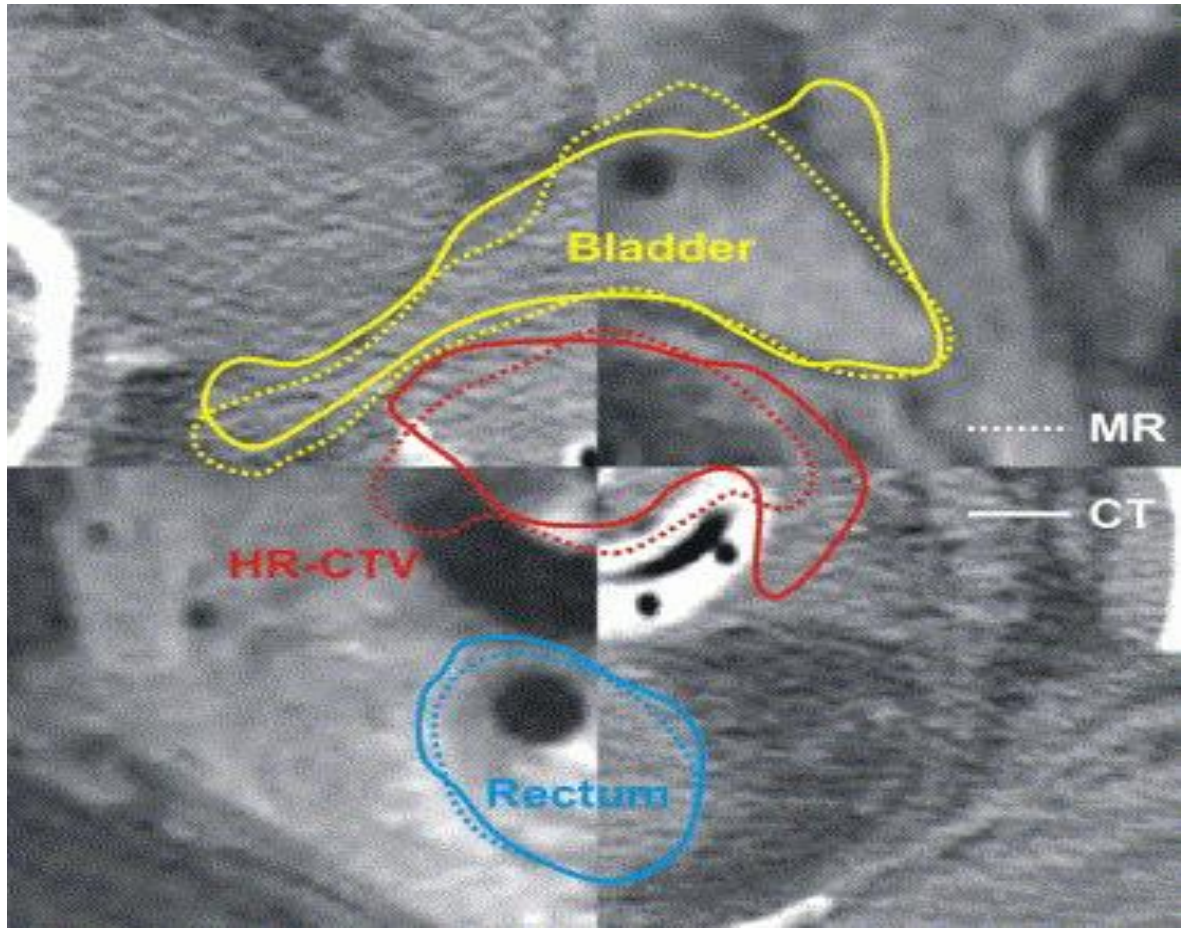


Fig. 2. Schematic diagram for cervix cancer with coronal (a, c) and transverse (b, d) sections of an optimised treatment plan for limited (a, b) and advanced (c, d) disease with partial remission after EBT (grey zones in left parametrium on MRI) (compare Figs. 5 and 7 in [16]). GTV, HR CTV and IR CTV and isodose lines for D90 of HR CTV and IR CTV are indicated. For advanced disease the extension at diagnosis is also indicated.

Potter R et al (Gyn) GEC ESTRO Recommendations,3d image based BT
In cervix cancer Radioth & Oncol 78: 67, 2006

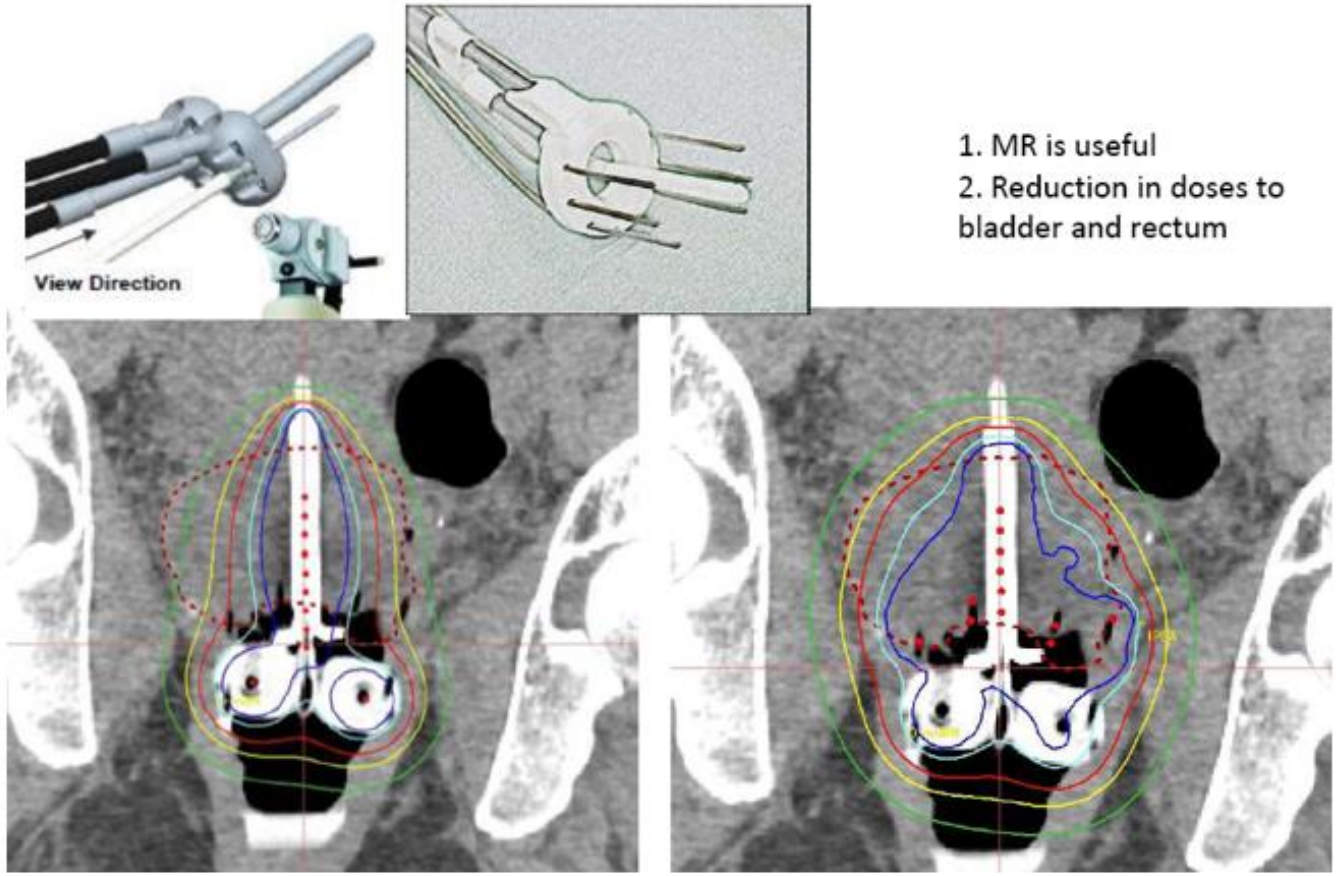
CT VS MR Image-Based Contouring in Cervix Brachytherapy



- Parametrial extension defines whether CT differs from MR contours
  - No parametrial extension=identical contours
  - Poor parametrial response = similar contours
  - Good parametrial response = largest discrepancy in contours

Viswanathan AN et al Int J Rad Oncol Bio Phys 68: 491, 2007

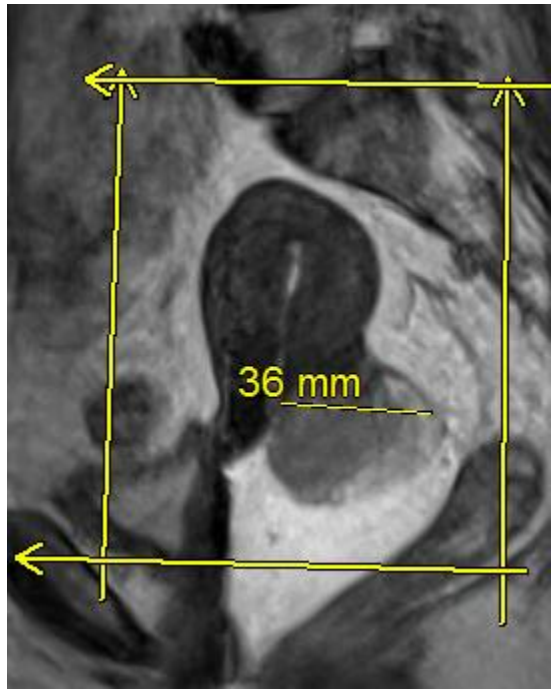
Large Tumor or poorly responding tumors: Consider combination applicators hybrid /interstitial.

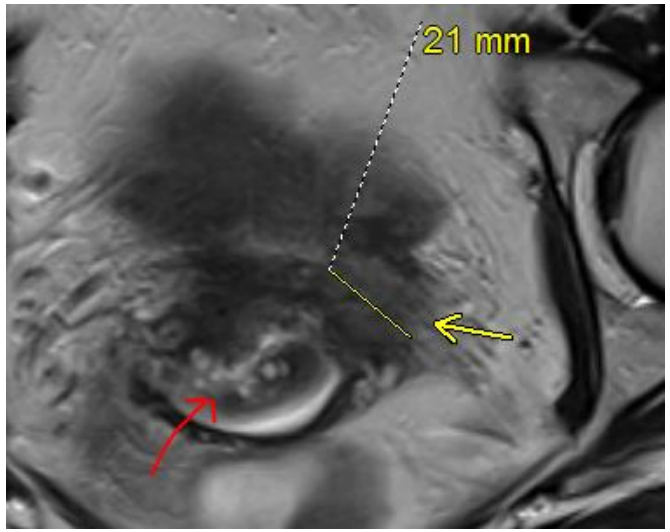


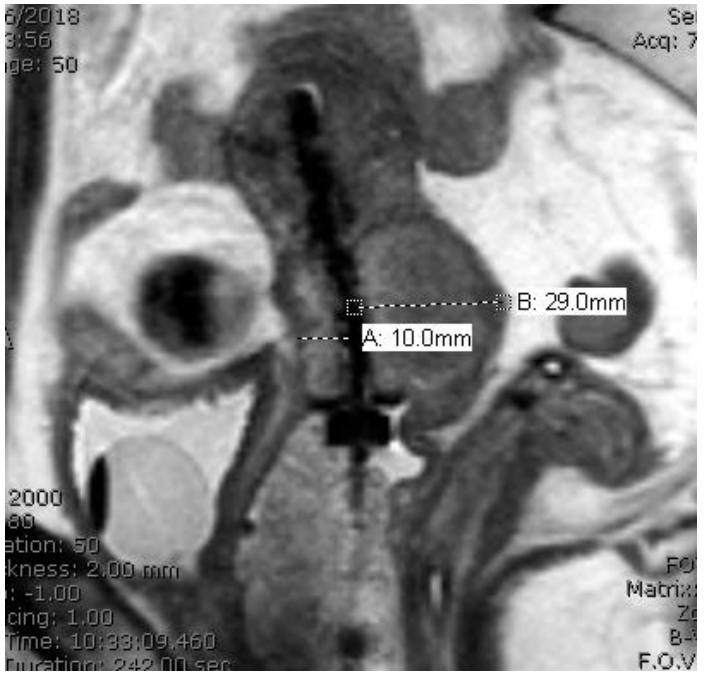
Selection for Hybrid Intracavitary (IC)with Needles(FHN)

- **Imaging at presentation- Bulky tumors >5cm**
- **----- Asymetrical tumor A/P or lateral**
- **------Thick upper vaginal involvement**

- **Interim MRI if necessary- assess for IC coverage**
- **First IC implant MR –assess HR-CTV volume and above features**







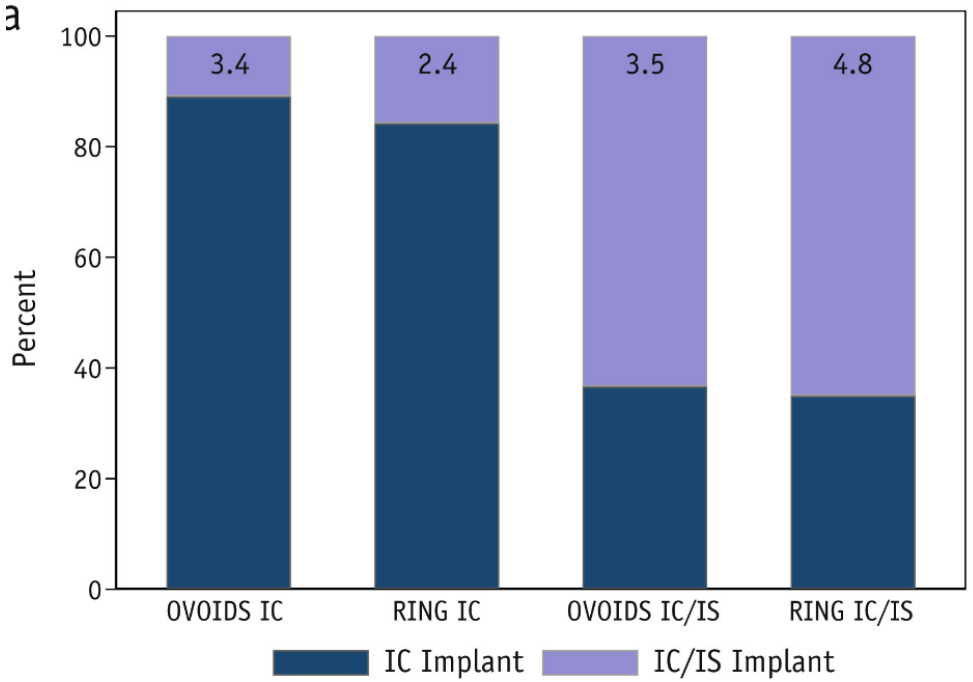
Choosing Applicator and Hybrid technique –EMBRACE 1
Serban et al ,IJRBOP
Volume 106, Issue 5, 1 April 2020, Pages 1052-1062

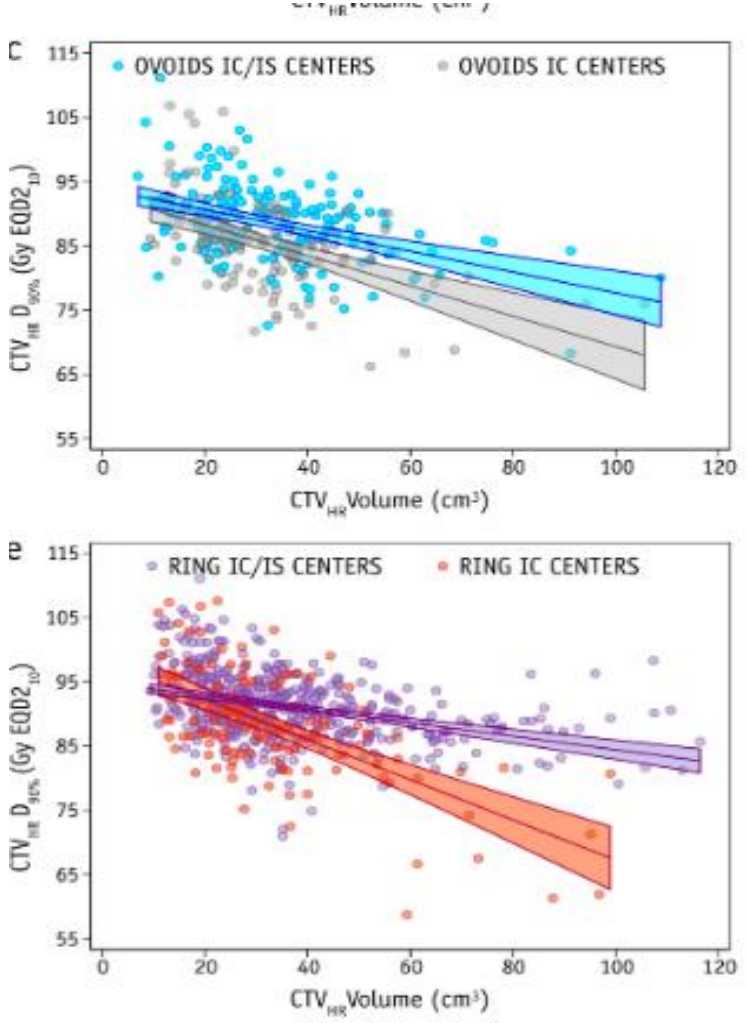
- 902 patients prospective has T/R T/O or IC/IS
- For similar point A doses, mean CTVHR D90% was 3.3 Gy higher and V85Gy(more conformal) was 23% lower for ring-IC compared with ovoids-IC centers (at median target volumes).

➢ Mean bladder/rectum doses (D_{2cm3} and ICRU-point) were 3.2 to 7.7 Gy smaller and vaginal 5-mm lateral-point was 19.6 Gy higher for ring-IC centers)

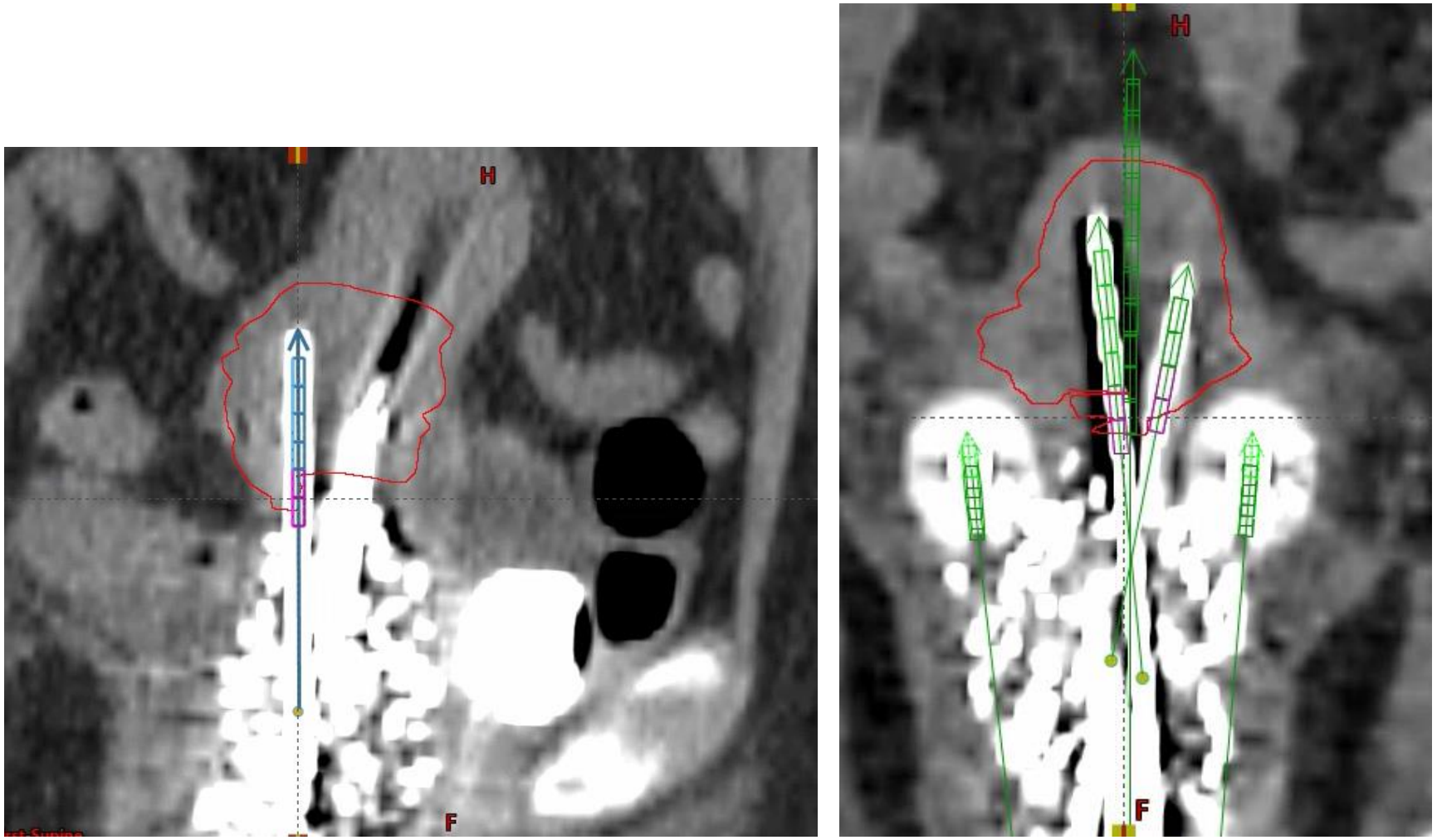
Choosing Applicator and Hybrid technique –EMBRACE 1

- Routine use of IC/IS technique resulted in increased target dose, whereas V85Gy was stable (T&R) or decreased (T&O)
- In the IC/IS centers,64% patients were selected IC/IS technique. **<u>For small CTVHR volumes <30 cm3 vs ≥30cc the IC/IS technique was used in 22% vs 60% of patients tumor confined to cervix</u>**





Tandem with 2 Needles



EMBRACE II Planning /Limit Constraints
European Study on MRI-guided brachytherapy in locally advanced cervical cancer.

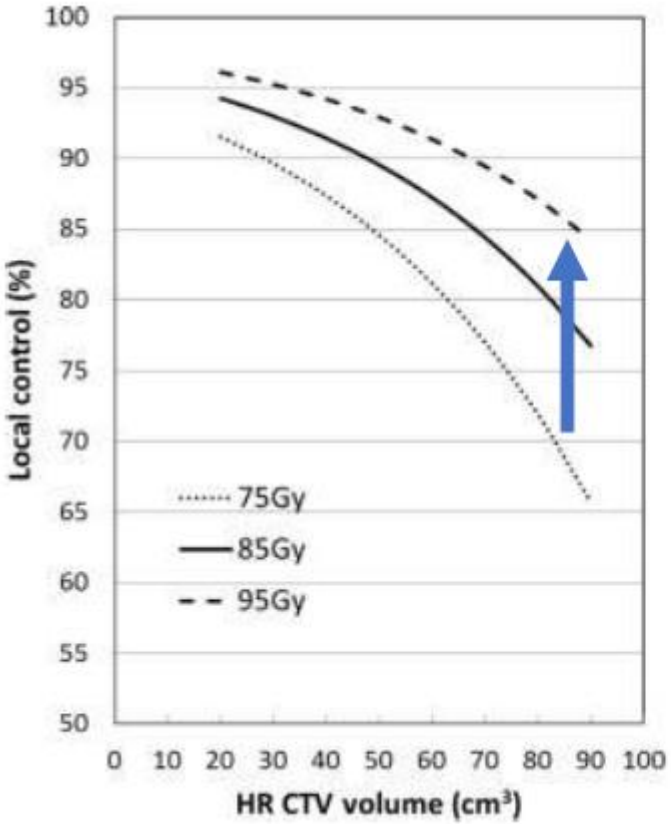
Target	D90 CTV_{HR} ($EQD2_{10}$)	D98 CTV_{HR} ($EQD2_{10}$)	D98 GTV_{res} ($EQD2_{10}$)	D98 CTV_{IR} ($EQD2_{10}$)	Point A ($EQD2_{10}$)
Aim	**>90 Gy <95Gy**	>75Gy	>95Gy	>60Gy	>65Gy
Limit	**>85Gy**		>90Gy		

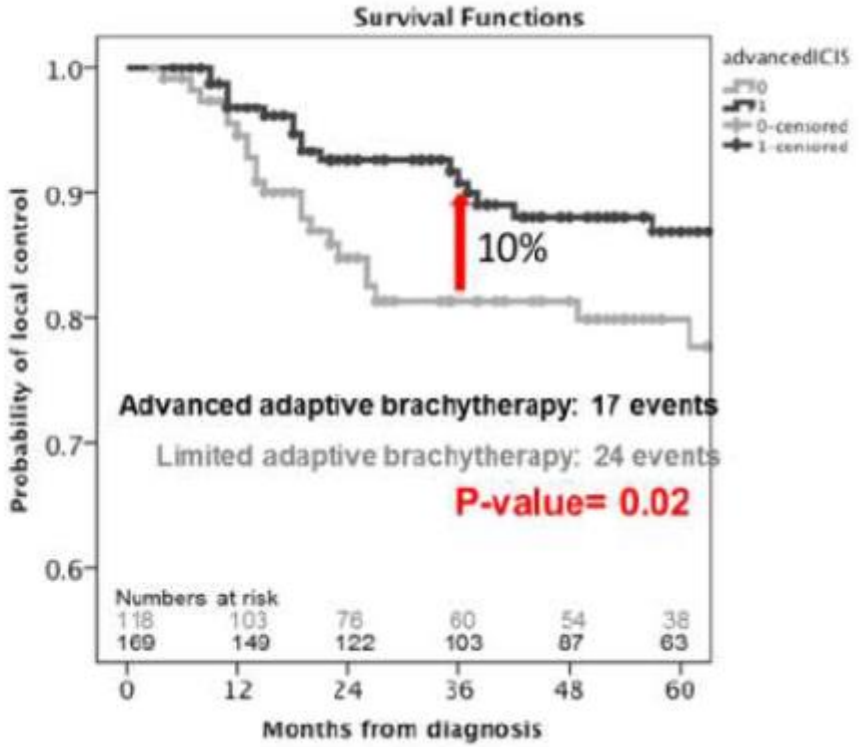
OAR	Bladder D_{2cc} ($EQD2_3$)	Rectum D_{2cc} ($EQD2_3$)	Sigmoid D_{2cc} ($EQD2_3$)	Recto-vaginal point ($EQD2_3$)	Bowel D_{2cc} ($EQD2_3$)
Aim	<80 Gy	<65Gy	<70Gy	<65Gy	<70Gy
Limit	<90Gy	<75Gy	<75Gy	<75Gy	<75Gy

Results of image guided brachytherapy

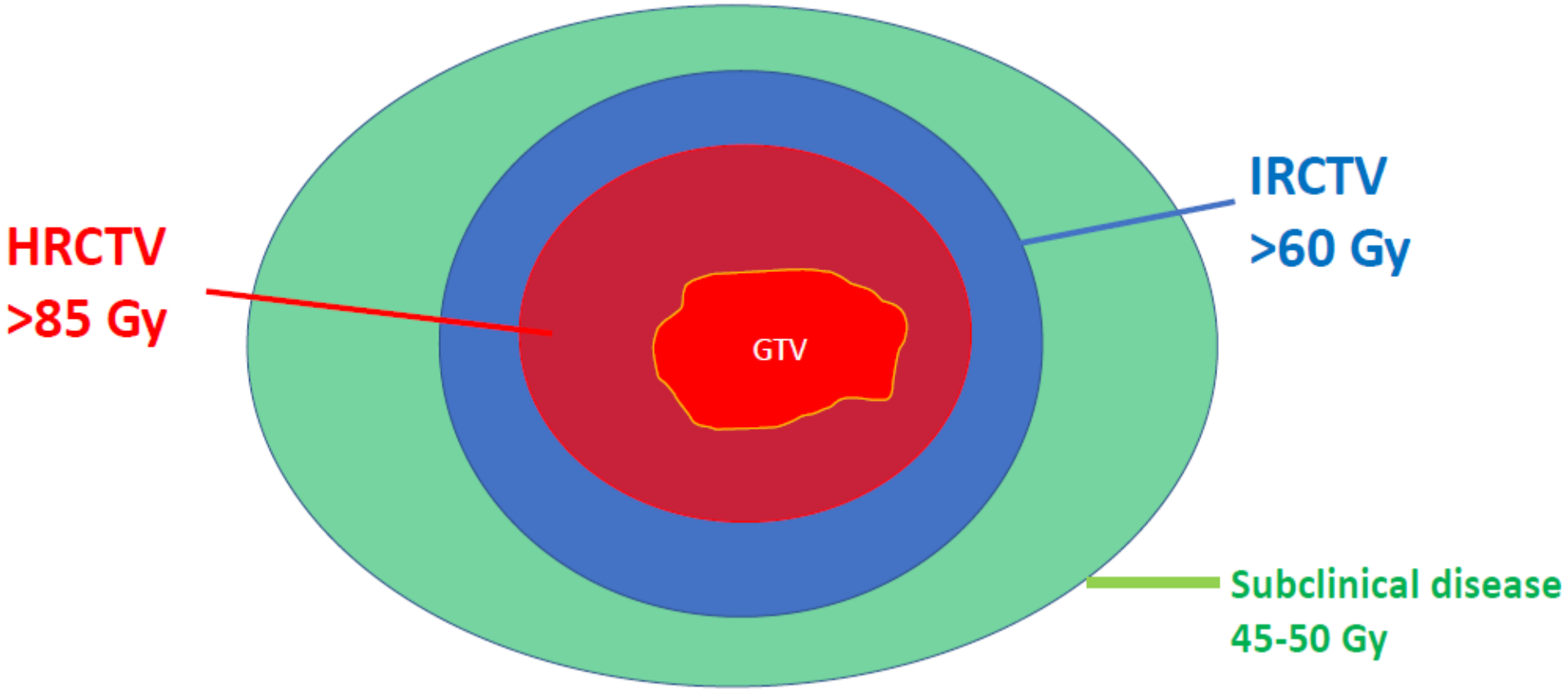
	# yr	Local control	Overall Survival	Late toxicity (Grade 3+)
STIC	2	78.5-100%	74-96%	2.6-8.9%
Pittsburgh	2	90%	82%	
Vienna	3	91%	94%	0%
Addenbrooke	3	96%	82%	11% crude (14% actuarial)
Korea	3	97%	NR	2%
Paris	4	91%	94%	0%
Australia	5	87-88%	60%	0.6-4.6%
Leuven	5	96%	65%	6%

RETROEMBRACE





Dose Levels per EMBRACE



Management of Vulvar Cancer- Crash Course

Workup

Physical exam: ~70% arise in labia majora/minora, ~20% are locally advanced

Assess for synchronous lesions (5-10%)

Vagina: manual exam, speculum exam
Cervix: colposcopy
Anus: DRE
If advanced/suspicious: cystoscopy/sigmoidoscopy

Imaging: CT scan

PET CT +/- MRI (**helps delineate extent of disease if advanced**

Biopsy: lesion *≤ 2cm & ≤1mm inv → bx w 1cm margin → path*

larger → incisional biopsy

CNode+(FNA)

cNode- → Sentinel lymph node biopsy

Vulvar Cancer Staging

AJCC		FIGO
Tis	Carcinoma in situ	
T1a	Confined to vulva/perineum, size ≤2cm, stromal invasion ≤1mm, N0	IA
T1b	Confined to vulva/perineum, size >2cm or any size with stromal invasion >1mm, N0	IB
T2	Any size with adjacent spread to lower 1/3 urethra, vagina, or anus	II
T3	Invades upper 2/3 urethral mucosa, upper 2/3 vagina, bladder mucosa, rectal mucosa, or is fixed to bone	IVA
N1a	1-2 Lymph Node Metastases each < 5 mm	IIIA1
N1b	Single Lymph Node Metastasis measuring > 5 mm	IIIA2
N2a	3 or more Lymph Node Metastases, Each < 5 mm	IIIB1
N2b	2 or more Lymph Node Metastases ≥ 5 mm	IIIB2
N2c	Lymph Node Metastases with ECE	IIIC
N3	Fixed or Ulcerated Regional Nodes	IVA
M1	Distant metastasis (including pelvic lymph node metastasis)	IVB

Vulvar Cancer – "functional" staging and Rx

- Early stage(T1N1-2)
  - **Can treat with primary surgery** (WLE, MRV, RV)

--- Adjuvant RT if indicated(separate into indications for primary and nodal disease)

- Locally advanced disease(most T2,allT3,N3)
  - **Unable to resect without 'ultra-radical' exenterative surgery**

  ----Neoadjuvant ChemoRT/Definitive Chemo RT

Risk factors for recurrence

- Large tumor size
- Multifocal disease
- Tumor free surgical margin (Heaps >8mm)
- New-dVIN and Lichen sclerosis
- Deep stromal invasion
- LVI

Gynecologic Oncology
Volume 154, Issue 2, August 2019, Pages 266-275

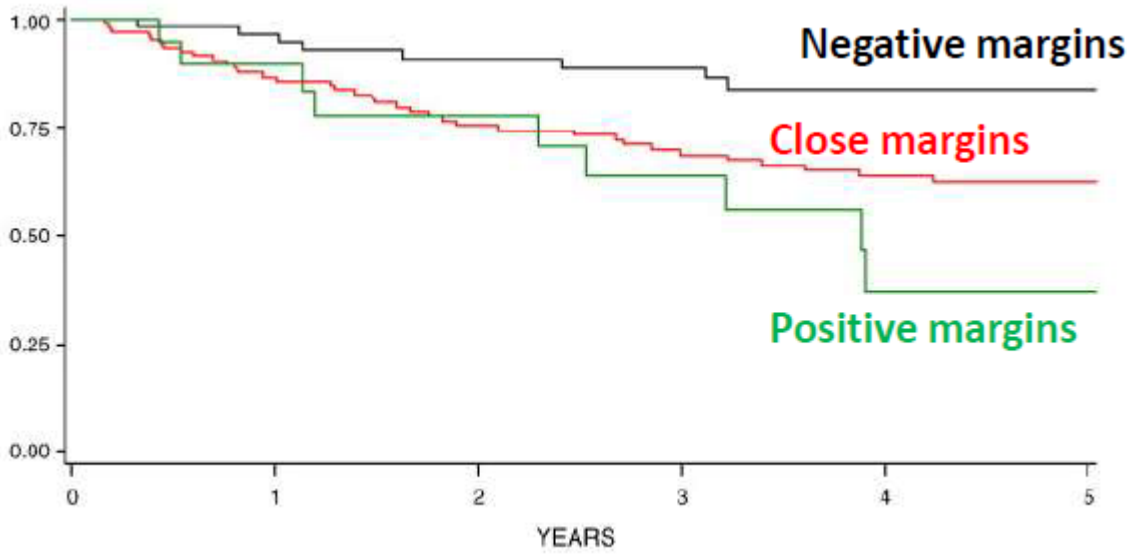
Margin status revisited in vulvar squamous cell carcinoma

N.C. te Grootenhuis [a, 1], A.W. Pouwer [b, 1], G.H. de Bock [c], H. Hollema [d], J. Bulten [e], A.G.J. van der Zee [a], J.A. de Hullu [b], M.H.M. Oonk [a]

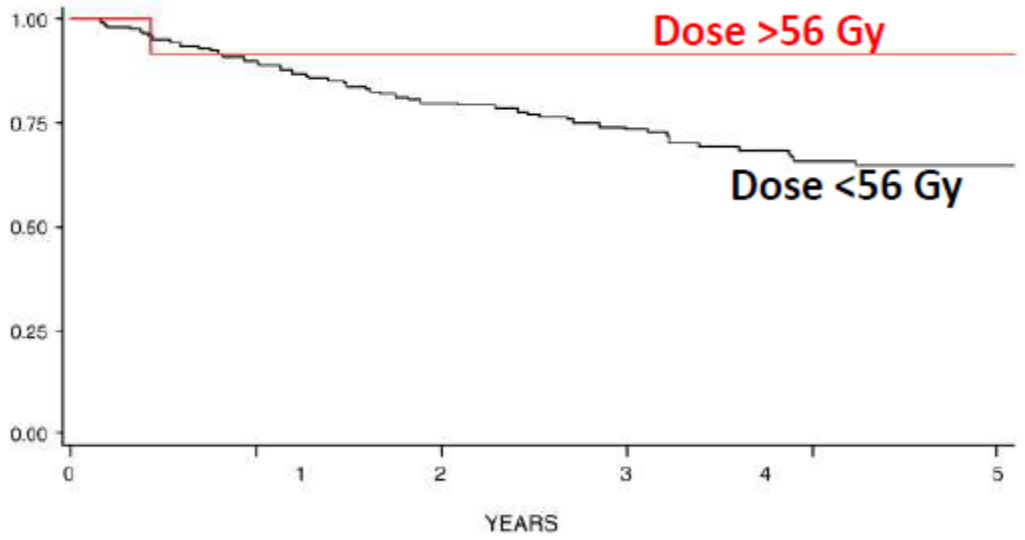
- 287 patients with a median follow-up of 80 months (range 0–204) were analyzed. The actuarial local recurrence rate ten years after treatment was 42.5%.
- Pathologic tumor free margin distance did not influence the risk on local recurrence (HR 1.03 (95% CI 0.99–1.06)), **neither using a cutoff of eight, five, or three millimeters**.
- Multivariable analyses showed a higher local recurrence rate in patients with dVIN(differentiated) and Lichen Sclerosis in the margin (HR 2.76 (95% CI 1.62–4.71)
- WORK IN PROGRESS- NEGATIVE MARGINS STILL REQUIRED
- RADIATION RECOMMENDED FOR CLOSE POSTIVE MARGINS

Margin status- adjuvant RT dose determination

Freedom from vulvar relapse by Margin status



By Radiation Dose



Viswanathan et al, Gyn Onc 2013

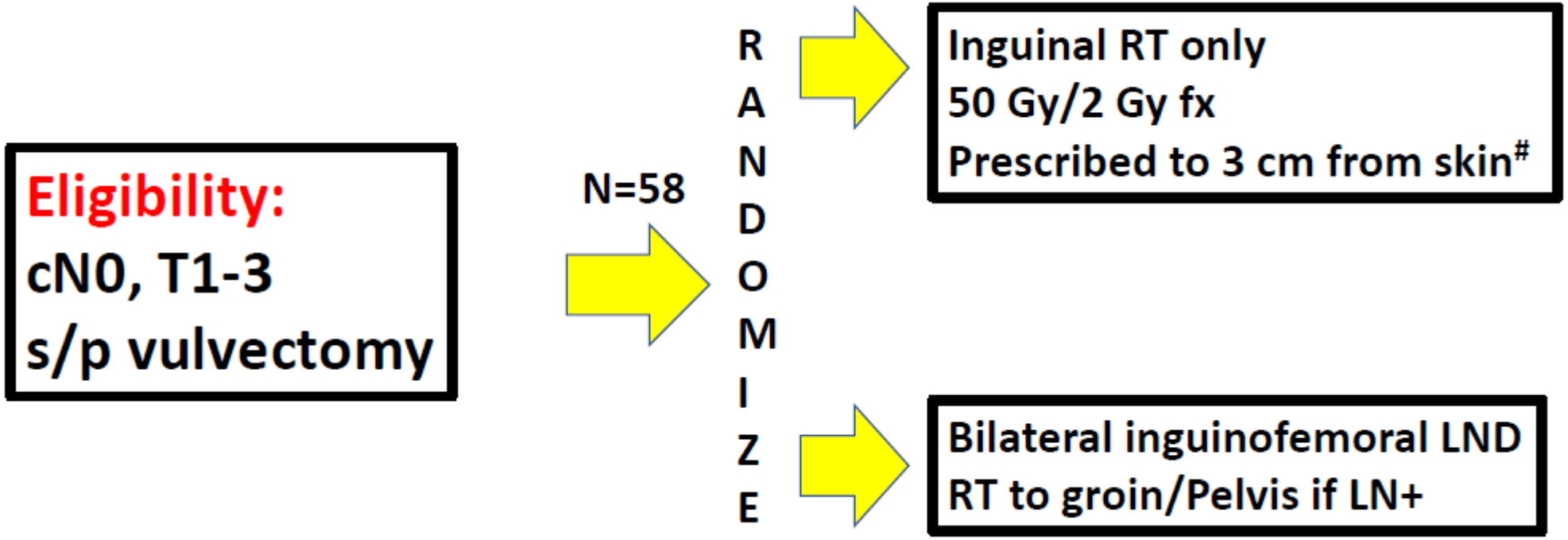
Adjuvant RT: Primary

Margin	Dose
5-10 mm	
>1-2mm, but <5 mm	
<1 to 2 mm	
Positive	60 Gy

56 Gy

Management of Groins

GOG88: Management of *clinical negative groins* (RT vs surgery)



- ***No CT Planning***
- Combined photon and 9 to 12MeV electrons

Stehman FB et al., IJROBP. 1992

GOG88: Management of groins (RT vs surgery)

Closed early due to increased failure and ↓survival at 2 years in RT arm

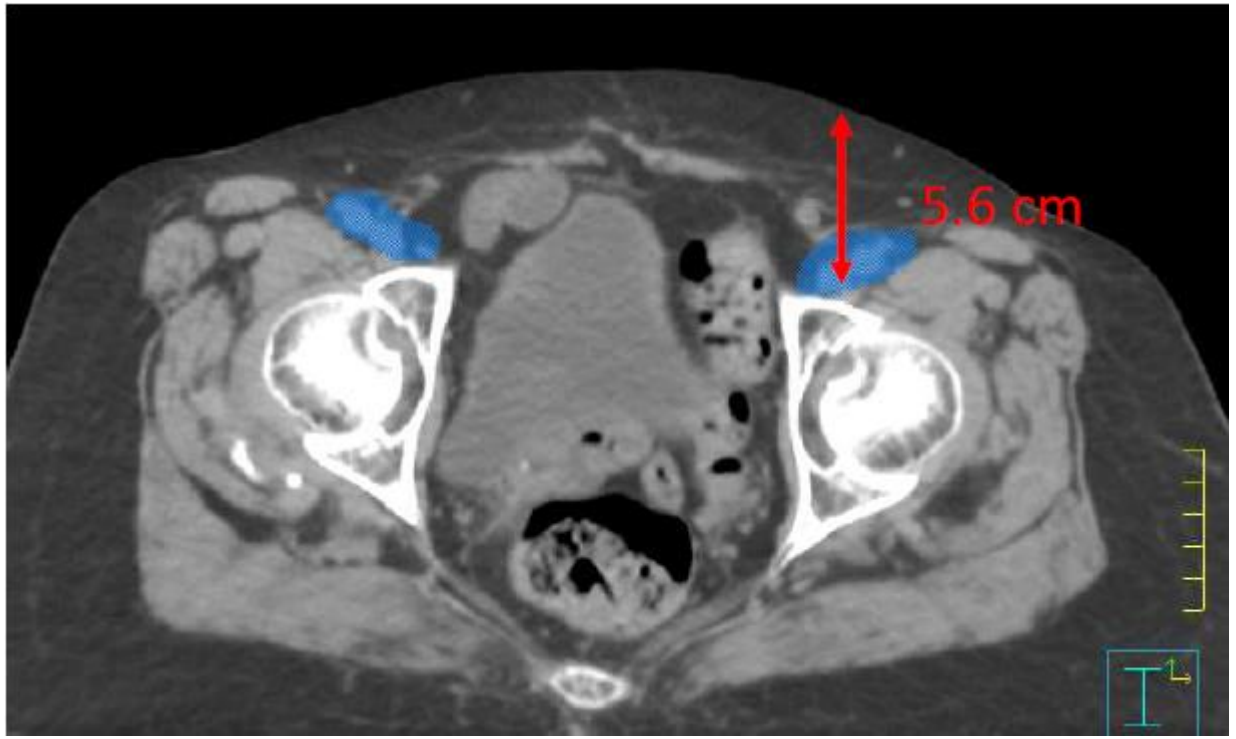
20% in surgery arm had +LN

	Groin Dissection	Groin XRT	
Groin Recurrence	0/25 (0%)	5/27 (18.5%)P+	P=0.033
Overall Survival	22/25 (88%)	17/27 (63%)	P=0.035

Conclusion: RT could not control groin disease

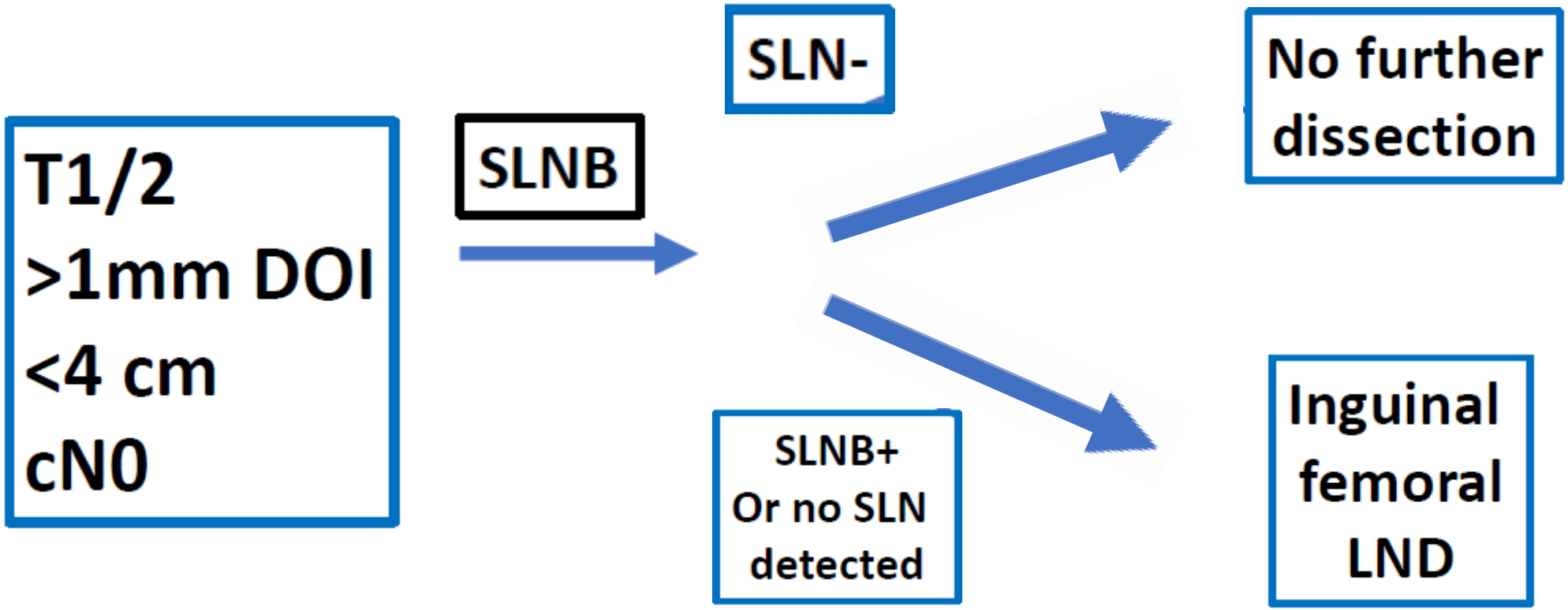
GOG88: Management of groins (RT vs surgery)

- Inguinal RT prescribed to 3 cm
- No CT planning, median depth>6 cm
- 3/5 patients w/inguinal recurrence underdosed by 30%



Koh et al, IJROBP 1993

Modern Era -Sentinel node biopsy: GROINSS-V I



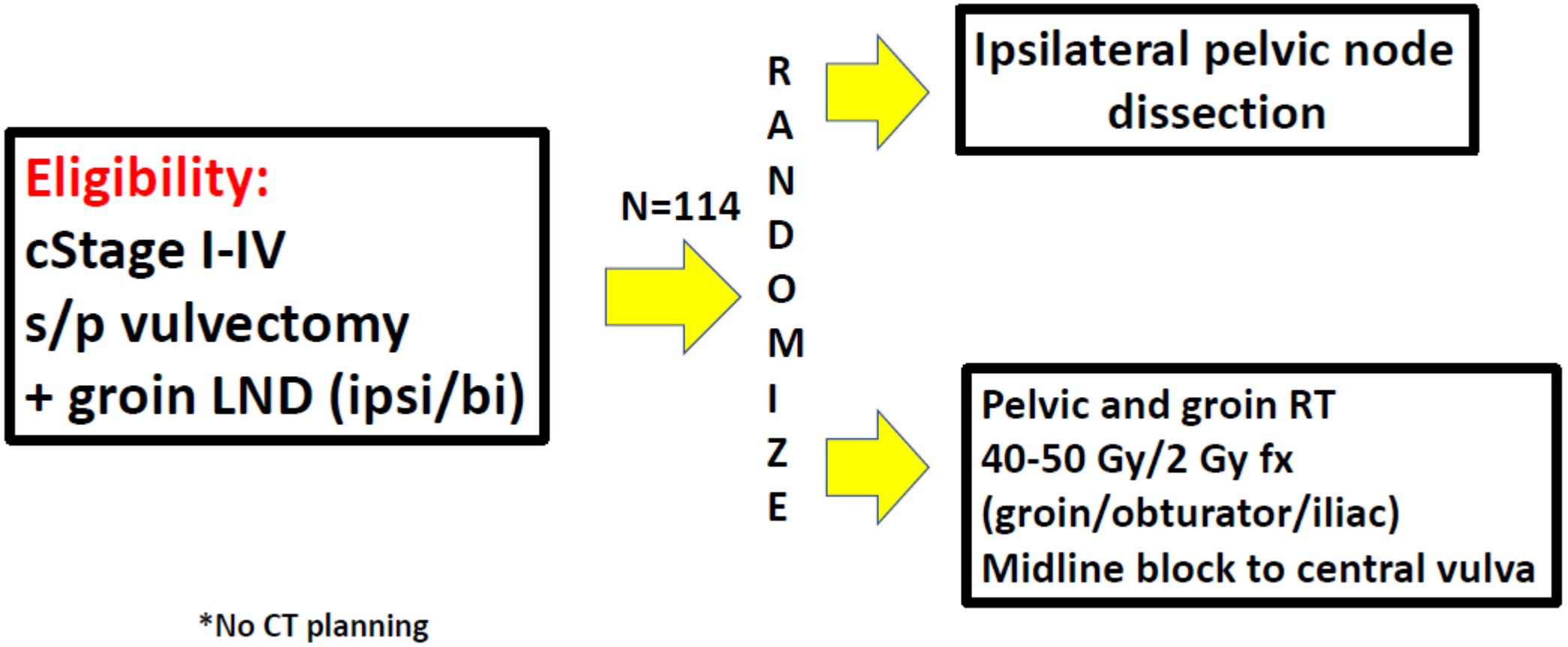
Van der Zee et al, JCO 2008 (GROINSS V)

Sentinel Lymph Node Biopsy:Less Morbidity GROINSS-VI

5yr isolated Groin REC 2.5% if SLN-ve

	SLNB	Completed LND	
Wound Breakdown	11.7%	34.0%	P<0.0001
Lymphedema	1.9%	25.2%	P<0.0001
Cellulitis	4.5%	21.3%	P<0.0001

GOG37: Groin Node positive



*No CT planning

Homesley ObsGyn 1986, Kunos ObsGyn 2009

GOG 37: Surgery vs RT-works for >1 node+

- Groin failures reduced with XRT from 23.6% (n=13) in the surgery arm to 5.1% (n=3) in the XRT arm (p=0.02)
- **No OS benefit in patients with 1 node positive**

	2yr OS Pelvic XRT	2 yr OS Surgery	
Clinical N2-3 Groin Nodes	59%	31%	P=0.01
≥ 2 Inguinal nodes Positive	63%	37%	P <0.0001

- Long Term followup (6 year)
-Groin recurrences 13/27(48%) v 14% (RT)
- **LN+ ratio >20%→** worse LRR, CSS, OS(6 yr 13 v 36%)

Adjuvant RT: Nodes

Node	Dose
Microscopic, no ECE, -RAD	45-50 Gy
Grossly enlarged nodes, no ECE, -RAD	50-56 Gy
ECE	60-66 Gy
Gross residual disease, +RAD	60-70 Gy

Key Points: Management of the Groins

- +SLN – Further groin treatment irrespective of size of LN metastases
- Completion groin dissection
- Adjuvant RT and concurrent chemo for >1 positive node

  - +SLN -if no further dissection _ Consider appropriate volume defined RT +chemo

Radiotherapy as an alternative treatment for inguinofemoral lymphadenectomy in vulvar cancer patients with a metastatic sentinel node: Results of GROINSS-V II

A.G. van Der Zee- Plenary SGO 2020

- **Methods:** . In case of a metastatic SN (metastasis of any size), radiotherapy was given to the groin(s) (50Gy). In case of a negative SN, patients were followed-up for ≥2 years. Stopping rules were defined for both groups to monitor groin recurrence rate.
- **Results** 1552 eligible patients were registered.
- After 54 months the stopping-rule for SN-positive patients was activated; interim analysis **showed an increased risk for groin recurrence in case of SN-metastasis >2 mm and/or extranodal extension (ENE).**

- For patients with SN-micrometastasis ≤2 mm radiotherapy was successful
- **Conclusion** For patients with SN metastasis >2 mm, radiotherapy with a total dose of 50Gy was noT safe alternative for IFL; dose escalation and/or chemoradiation should be investigated in these patients.

Advanced vulva cancer -Preoperative RT: GOG 205 Phase II Study of RT and weekly cis

- T3/T4
- Treatment:

- Results
  - 58 evaluable pts
  - 69% completed treatment
  - cCR 64% and **pCR 50%** (of total enrolled)
  - pCR 78% in those with cCR

Moore et al Gyn Onc 2012

GOG 279

Phase II trial of Gem + CDDP + RT

- T2-3 N0-3
- 64Gy to gross disease, 45-50Gy to elective volume
- Gem 50mg/m2, CDDP 40mg/m2 weekly
- Reassess 6-8 weeks afterward

  If cCR → confirmation biopsy performed, and no surgery

  If no cCR → surgery

- IMRT is allowed on trial
- **Goal: 70% pCR**

Primary Treatment-unresectable

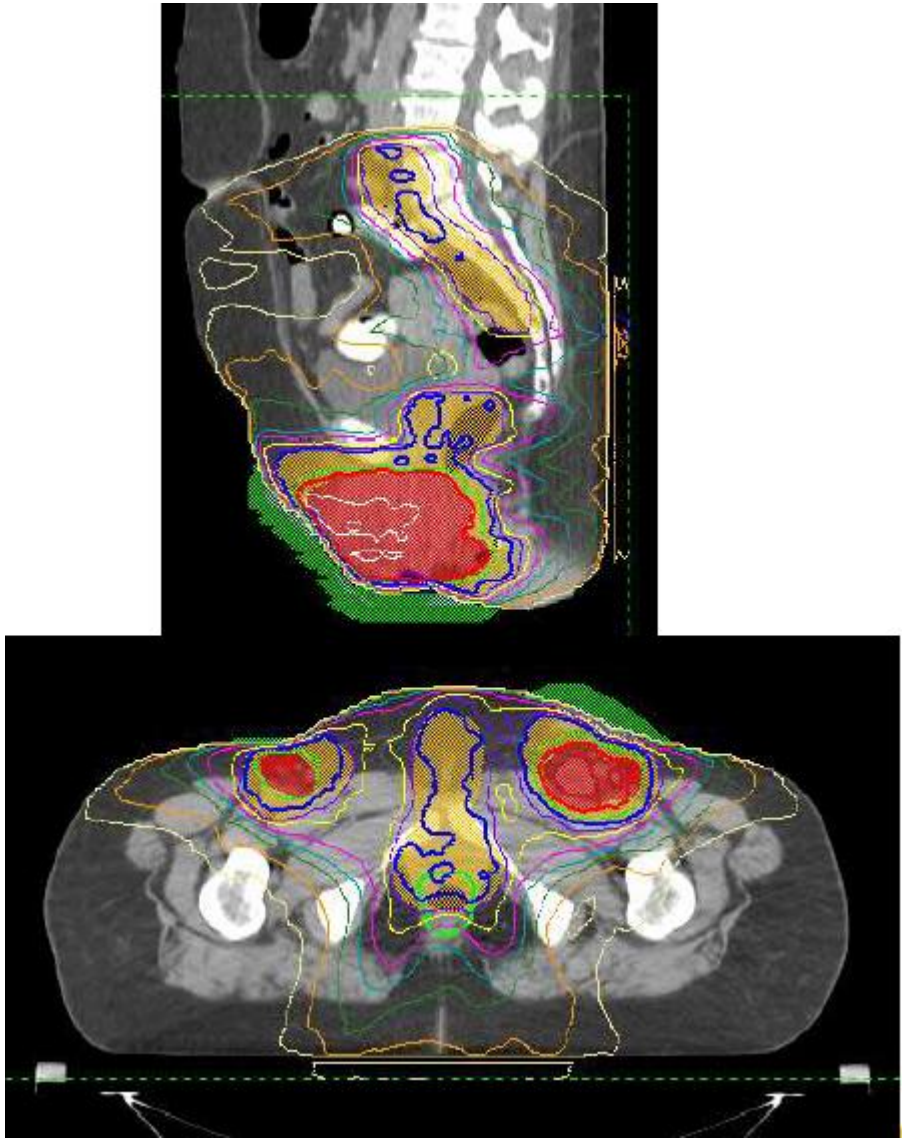
Site	Dose
Primary	64-68Gy
Nodes	
<1 cm	
1-2 cm	
Nodes >2 cm	64-68Gy
Massive or fixed nodes	**65-70 Gy**

Treatment technique

- At simulation:
  - Mark scars, tumor with “sticky wire”
  - Frog-legged, avoid overlapping regions of skin
  - Bolus-custom/3d bolus
- Fractionation
  - 1.8-2 Gy/day SIB-IMRT
  - Mild hypofractionation 2.1-2.2 Gy for nodal boost
- Use virtual PTV to get dose to skin
- Use of TLDs to check skin dose

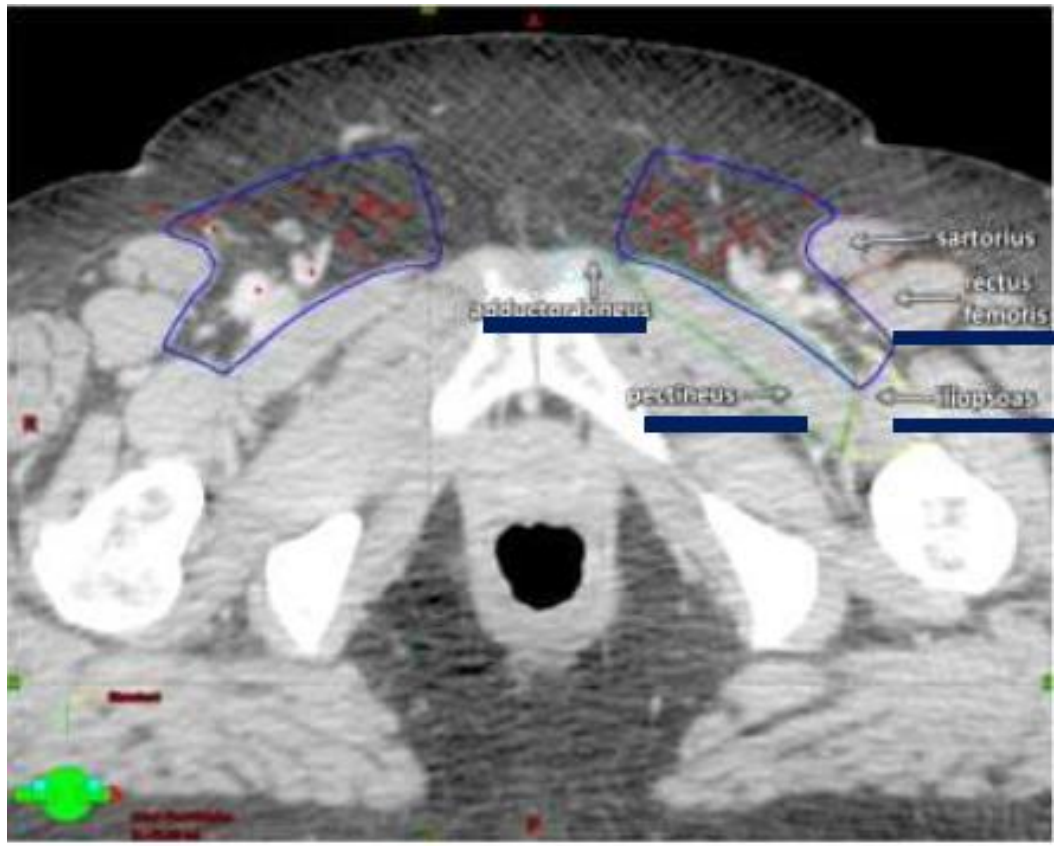
IMRT for vulvar cancer

- Advantages
  - Sparing of central bowel, femoral heads
  - Concurrent boost
  - Protection of skin outside PTV
  - Reduced acute and late toxicities
  - Better for obese patients
- Disadvantages
  - Steep learning curve
  - Controversies about target delineation
  - Daily Setup



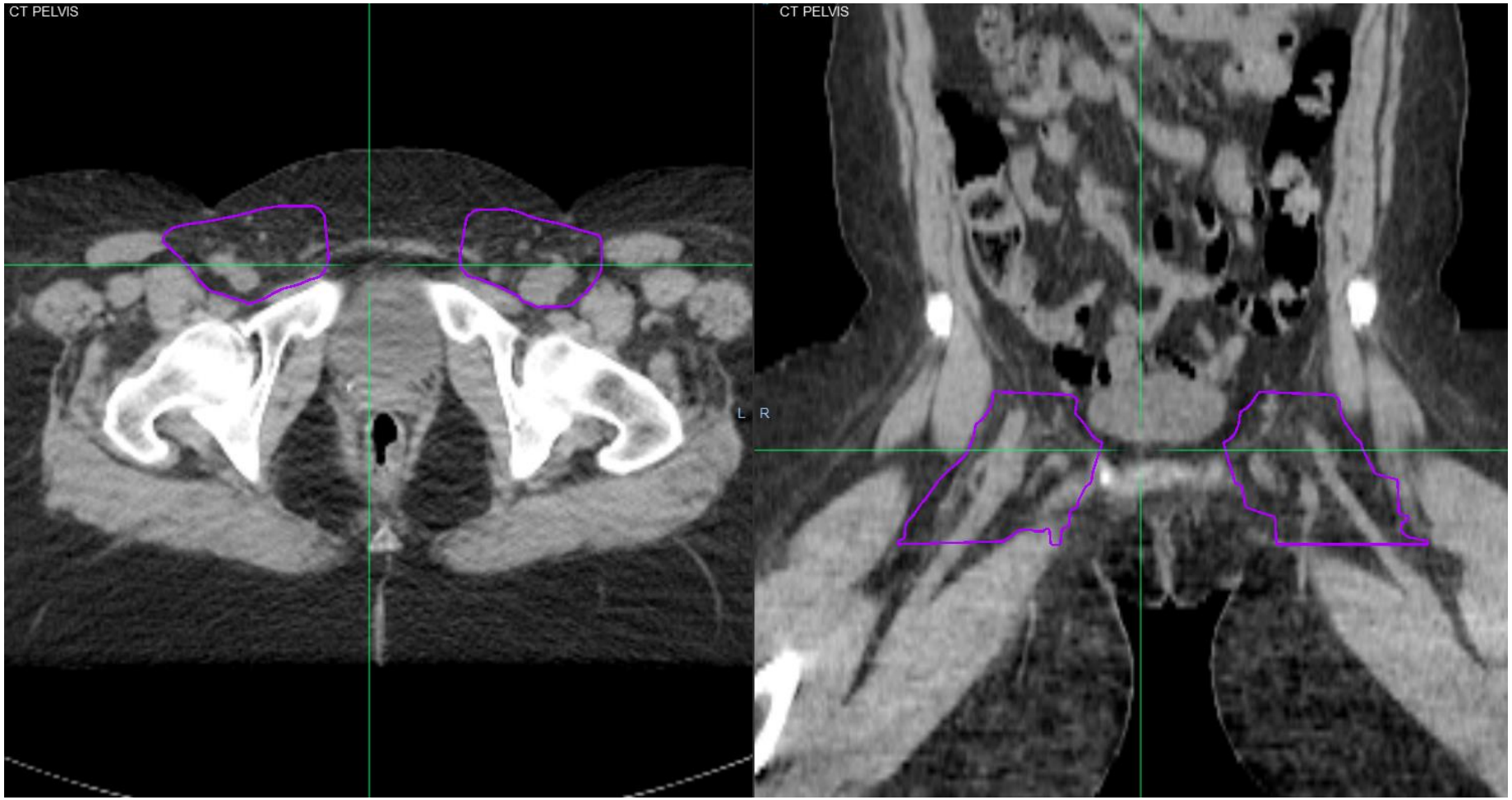
Contouring Inguinal nodes: How much margin is necessary?

- **Margin on nearest femoral vessel required to encompass ≥90% of the positive nodes:**
  - anteromedial ≥35 mm
  - anterior ≥23 mm
  - anterolateral ≥25 mm
  - medial ≥22 mm
  - posterior ≥9 mm
  - lateral ≥32 mm



Kim et al, PRO 2012

Contouring of inguinal nodes



Consensus contouring guidelines: Vulvar carcinoma

Gaffney et al, IJROBP 2016

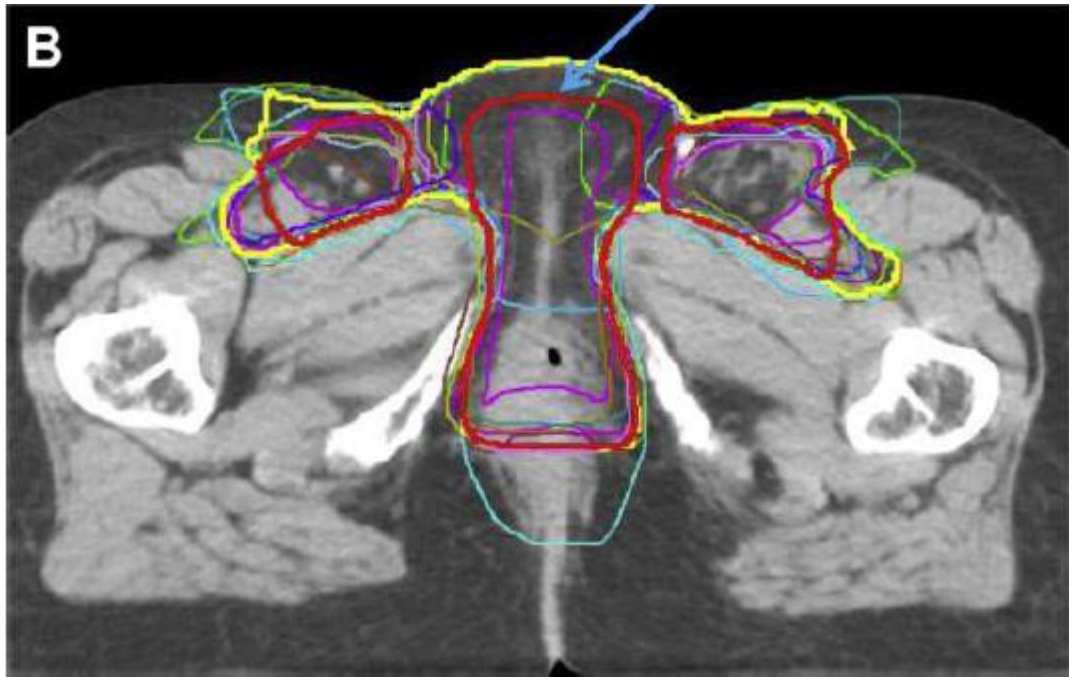
Locally advanced vulvar carcinoma

- Primary:
  - CTV = entire vulva
  - If GTV extends beyond vulva, add 1 cm margin
- Invasion of vagina
  - Gross disease + 3 cm of vagina
  - Entire vagina if uncertainty regarding extent or if LVSI
- Anus, anal canal, bladder or rectum invasion
  - Gross disease + 2 cm of anus
- Periurethral
  - Gross disease + 2 cm of urethra
- Periclitoral
  - Gross disease 2 cm

Consensus contouring guidelines: Vulvar carcinoma

Gaffney et al, IJROBP 2016

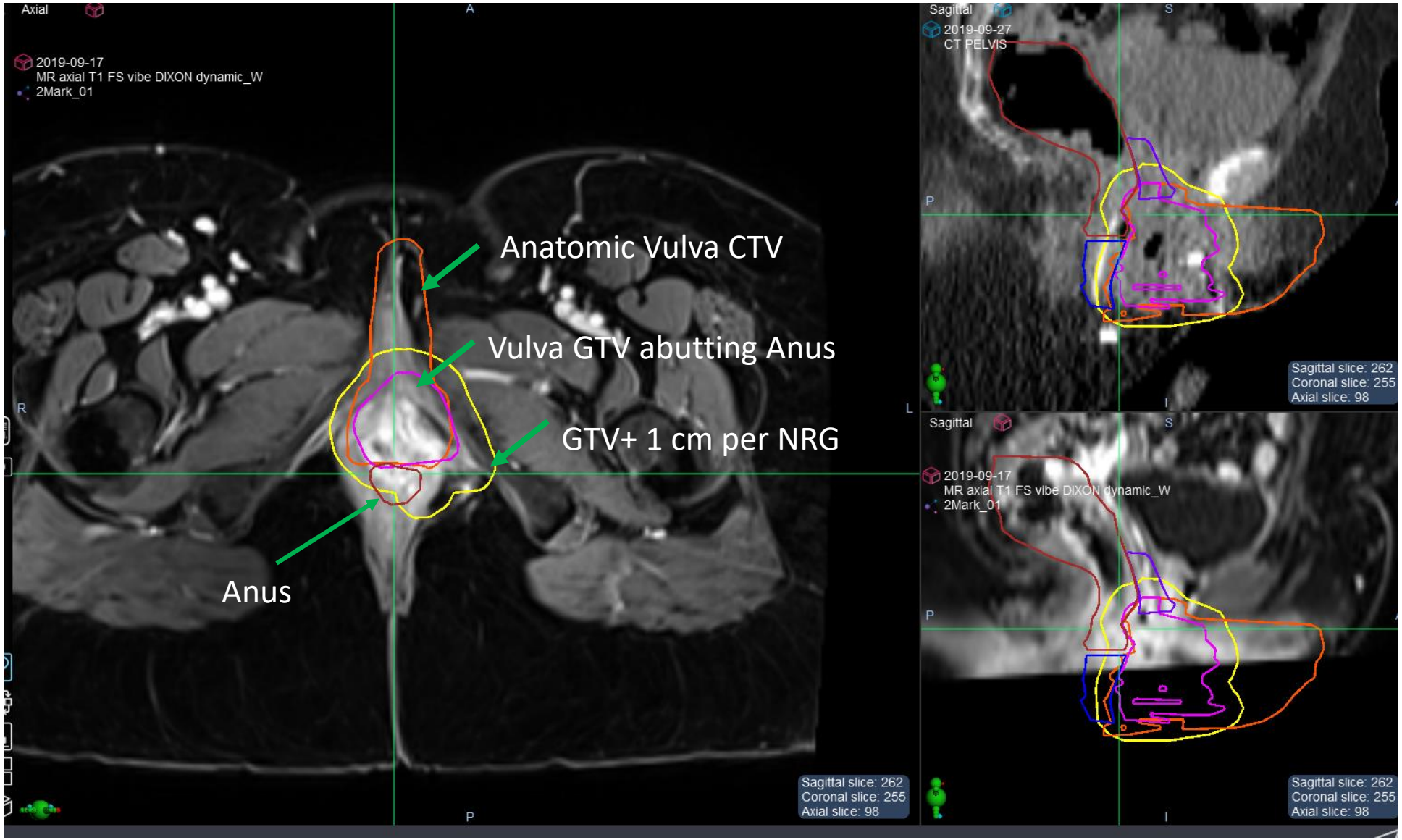
Locally advanced vulvar carcinoma



Postoperative vulvar carcinoma

CTV = entire operative bed (+2 cm if +margin)

Example of multimodality imaging and contours for Vulva Primary



Patient presents with vulva tumor abutting/invading anal sphincter-will include anus and vagina in extended Vulva CTV

American Journal of Obstetrics and Gynecology
Available online 14 January 2021
In Press, Corrected Proof

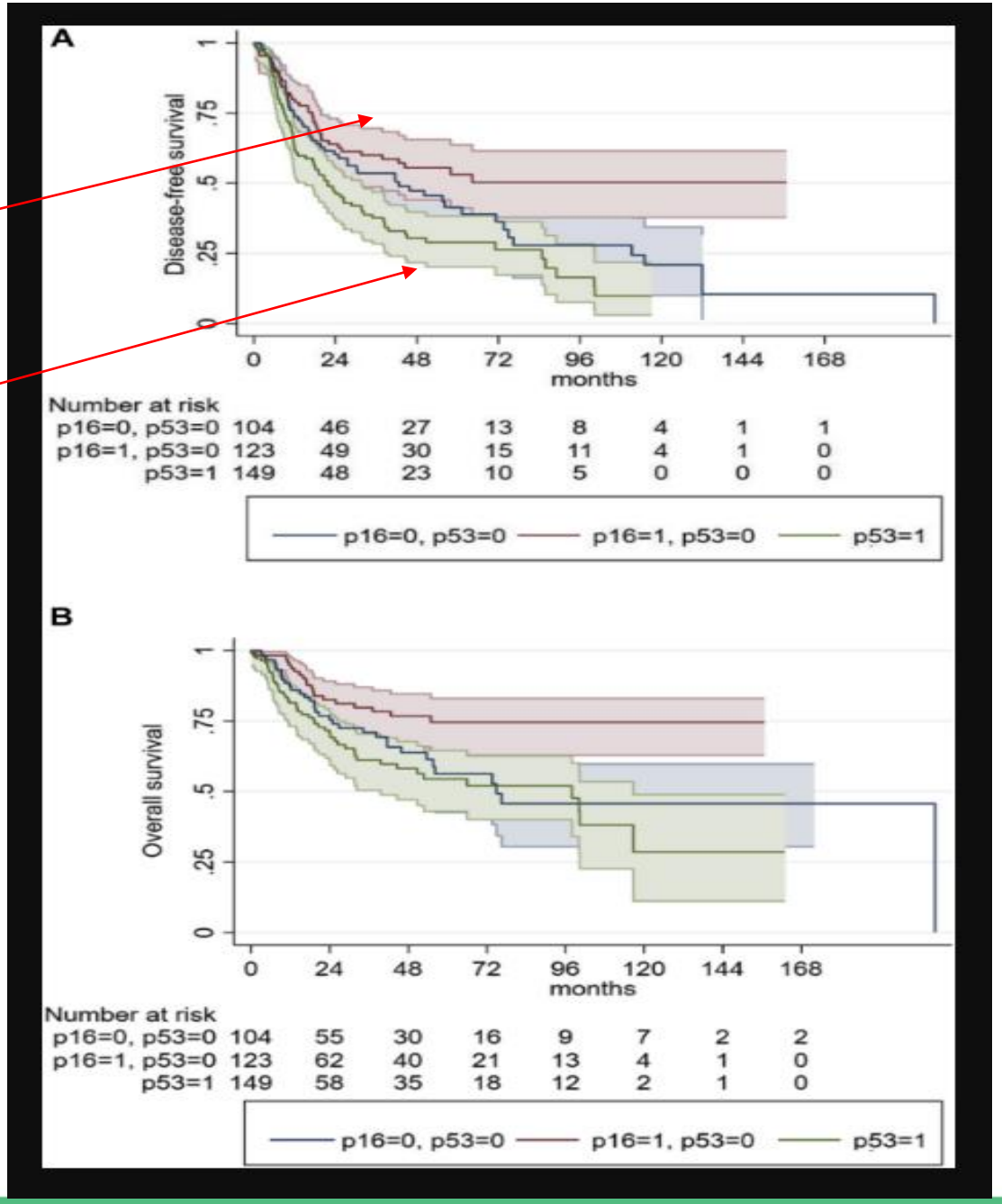
NEW biology -- p53 and p16 expression profiles in vulvar cancer: AGO-CARE1 BY L Woebler et al

- The AGO-CARE-1 study is a retrospective cohort study of 1618 patients with primary vulvar squamous cell carcinoma
- 411 pts subset with p16 and p53 test available analysed
- Patients with p16+ tumors were younger and showed lower rates of lymph-node involvement
- DFS/OS was worst with P16-P53+
- In multivariate analysis, the p16+/p53− phenotype showed a consistently improved prognosis compared with the other groups

P16+ does best

P53 + does worst

Can be used to intensify treatment



Key take home points:

- Treatment of vulvar carcinoma requires multidisciplinary management and individualization
- Separate treatment indications into “primary” and “nodes”
- IMRT can reduce acute/late toxicities and achieve tumor control but must be used carefully

Thank you all for participating virtually

Stay Healthy!

Email kevin.albuquerque@utsouthwestern.edu