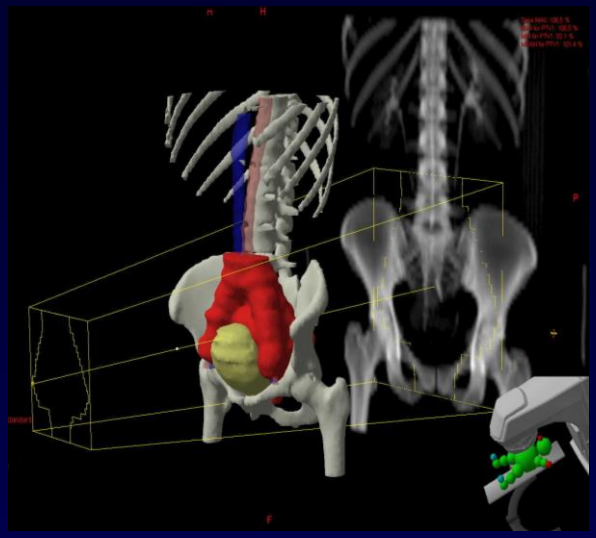
Role of Radiotherapy in Grade 3 FIGO IB Endometrial Cancer



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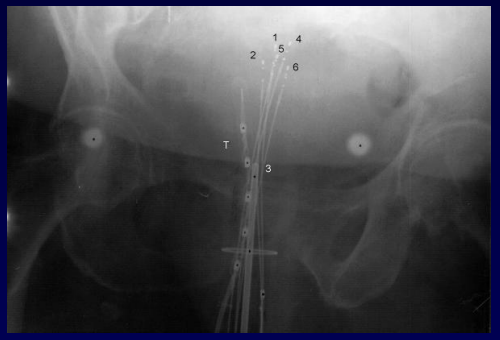
London, United Kingdom

Adjuvant Treatment Endpoints

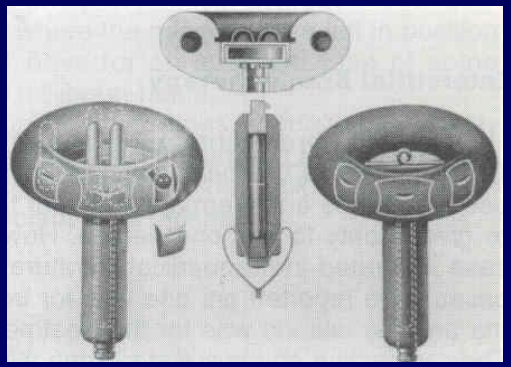
- Overall Survival
- Locoregional control
  - Prevention of uncontrolled pelvic disease
  - Prevention of stress and morbidity of diagnosis and treatment of pelvic relapse
- Quality of life
  - Treatment toxicity
  - Disease

Radiotherapy for Endometrial Cancer Historical Background

- 1901: First use of radium for intrauterine insertion
- Pre-operative radiotherapy became standard
- 1970s: Move to tailored post-operative radiotherapy based on pathology
- Excellent outcomes for stage I disease in retrospective studies with adjuvant RT
  - Pelvic control >95%
  - 5-year survival 80%-98%
  - Concerns about over-treatment

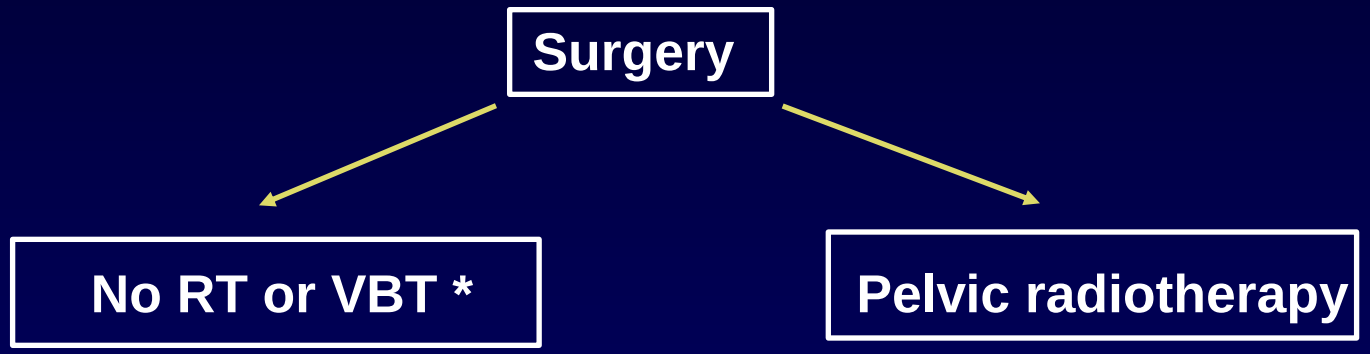


Intrauterine applicators



Vaginal applicators 1920

Post-Operative Radiotherapy for Stage I Endometrial Cancer Randomised Trials



Norwegian Radium Hospital *	n = 540	1968-74
GOG 99	n = 392	1987-95
PORTEC	n = 715	1990-97
ASTEC + NCIC EN.5 *	n = 905	1996/8-2004
PORTEC 2 *	n = 427	2002-06
Sorbe (Swedish) *	n = 527	1997-2008

FIGO Staging 1998 Endometrium

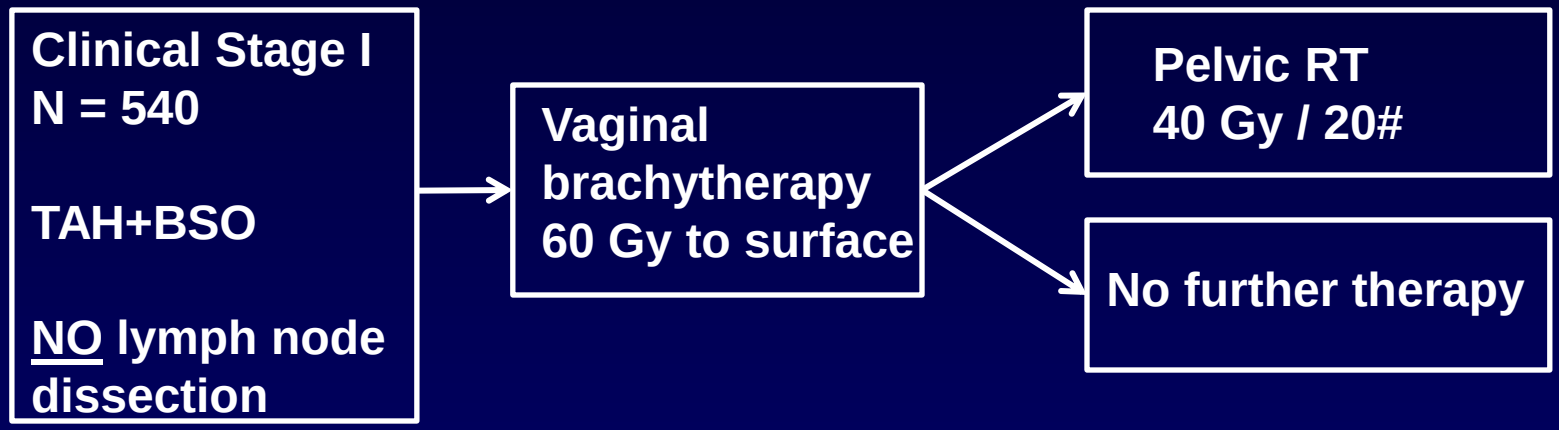
I	Confined to corpus uteri
IA	Limited to endometrium
IB	Invades up to one half of myometrium
IC	Invades more than half of myometrium
II	Invades cervix
IIA	Endocervical glands only
IIB	Cervical stromal invasion
IIIA	Involves serosa, adnexa +/or +ve peritoneal washings
IIIB	Vaginal involvement
IIIC	Pelvic +/or para-aortic LNs
IVA	Invades bladder or bowel mucosa
IVB	Distant metastases

Revised FIGO Staging 2009 Endometrium

I	Confined to corpus uteri
IA	Invades up to one half of myometrium
IB	Invades more than half of myometrium
II	Invades cervical stroma
IIIA	Involves serosa or adnexae
IIIB	Vaginal or parametrial involvement
IIIC 1	Pelvic LN
IIIC2	Para-aortic LN
IVA	Invades bladder or bowel mucosa
IVB	Distant metastases

Norwegian Radium Hospital Trial

Aalders et al, Obs Gyn 1980

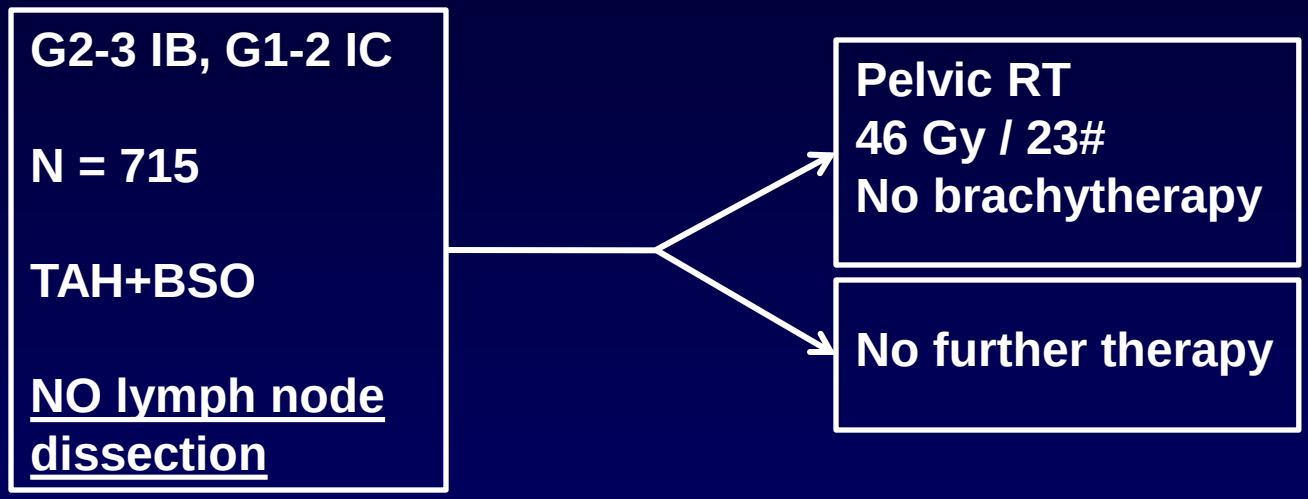


9-year outcomes	No EBRT	EBRT
Overall survival	90%	87%
Local recurrence (all)	7%	2%
Local recurrence (G3 IC)	20%	5%
Distant metastases	5%	10%

Aalders J, et al. *Obstet Gynecol.* 1980;56(4):419-427.

PORTEC Trial

Creutzberg et al, Lancet 2000

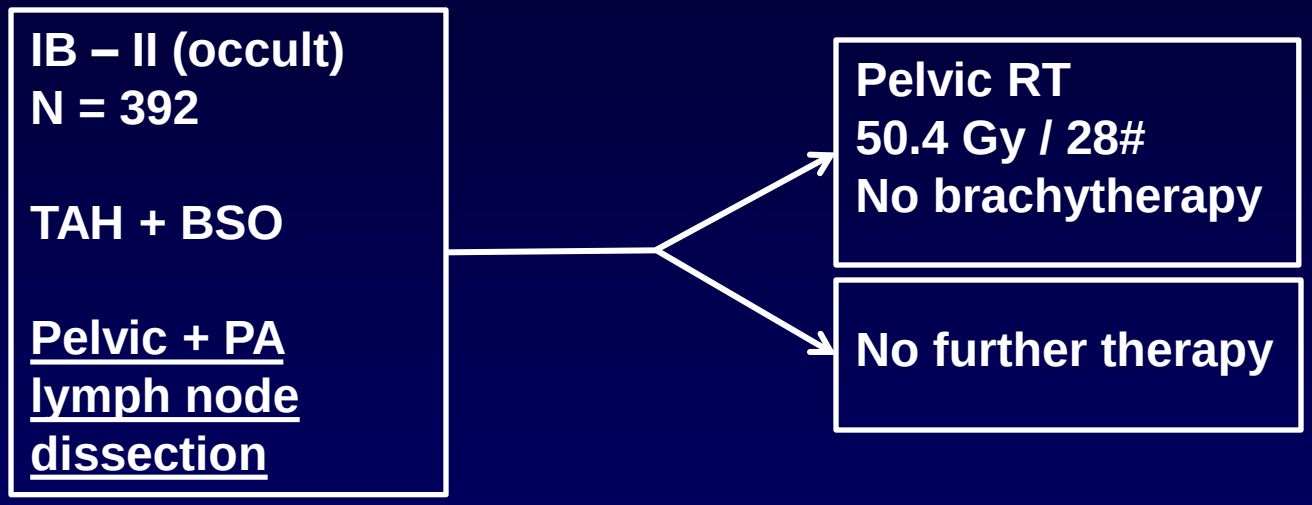


	No EBRT	EBRT
5-yr overall survival	84%	80%
5-yr local recurrence	14%	4%
Toxicity: All grades	4%	26%

Creutzberg CL, et al. *Lancet.* 2000;355(9213):1404-1411.

GOG 99

Keys et al, Gyn Onc 2004



	No EBRT	EBRT	
4-yr overall survival	86%	92%	*P* = .57
4-yr local recurrence	9%	1%	
Toxicity: lymphoedema	3%	5%	
severe GI	1%	7%	

Keys HM, et al. *Gynecol Oncol.* 2004;92(3):744-751.

High Risk Factors - Subset Analysis

GOG 99

High risk factors

- G2, 3
- Age
- LVSI
- Deep myometrial invasion

High intermediate risk group

- >70 yrs and 1 factor
- 50-70 yrs and 2 factors
- <50 yrs and 3 factors

HIR 2-yr locoregional relapse:
26% vs 6%

PORTEC

High risk factors

- >60 yrs
- G3
- Deep myometrial invasion

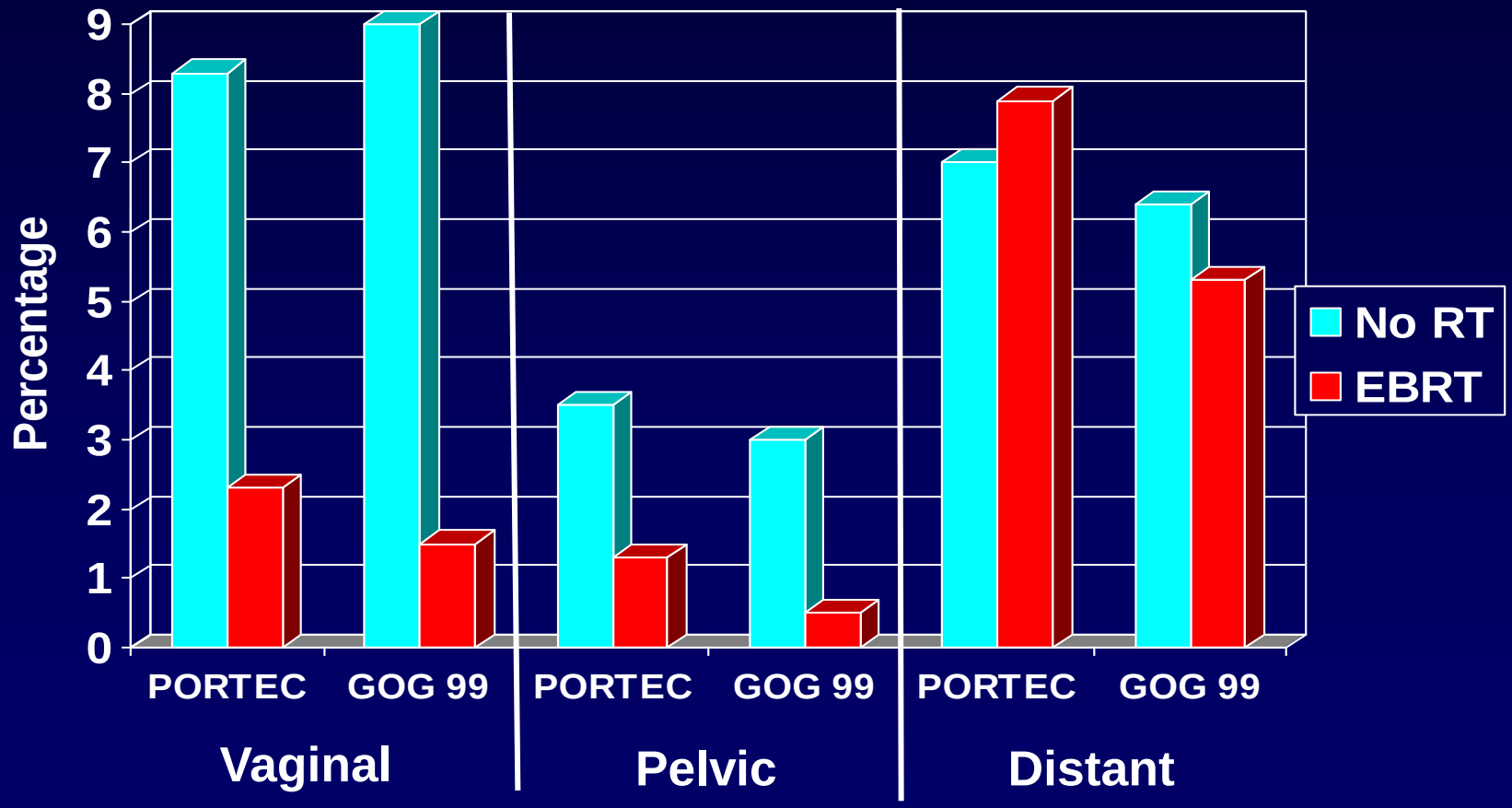
2 factors

- 10 yr LRR 23% vs 5%

Using GOG 99 criteria for HIR

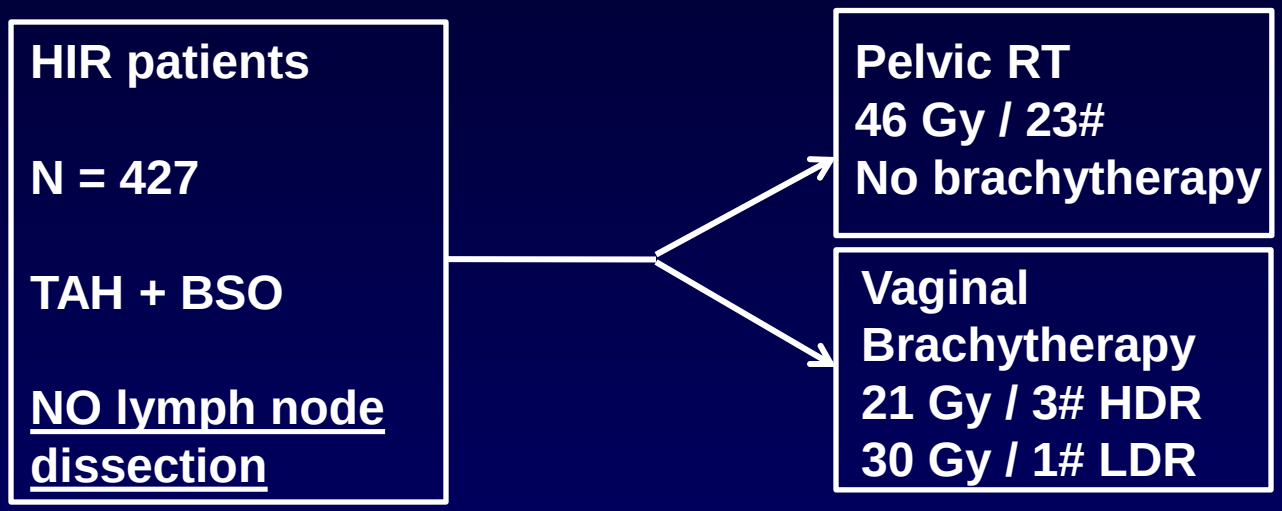
- 10 yr LRR 22% vs 8%

Sites of Relapse
GOG-99 and PORTEC-1



PORTEC 2 Study

Nout et al, Lancet 2010

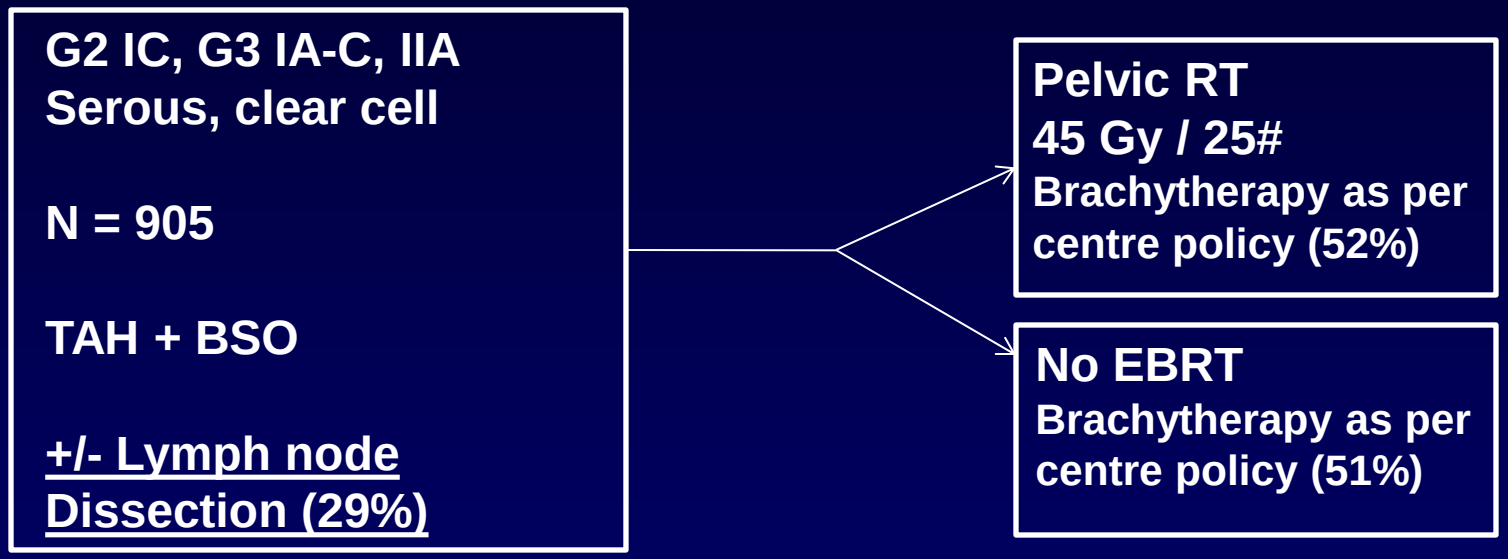


	EBRT	VBT	
3-yr overall survival	84%	84%	*P* = .55
3-yr disease-specific survival	89%	89%	*P* = .38

Nout RA, et al. *Lancet.* 2010;375(9717):816-823.

ASTEC Trial and NCIC EN5 Trial

ASTEC/EN.5 Study Group, Blake et al, Lancet 2009



	No EBRT	EBRT
5-yr overall survival	84%	84%
5-yr disease-specific survival	89%	89%

ASTEC/EN.5 Study Group, et al. *Lancet.* 2009;373(9658):137-146.

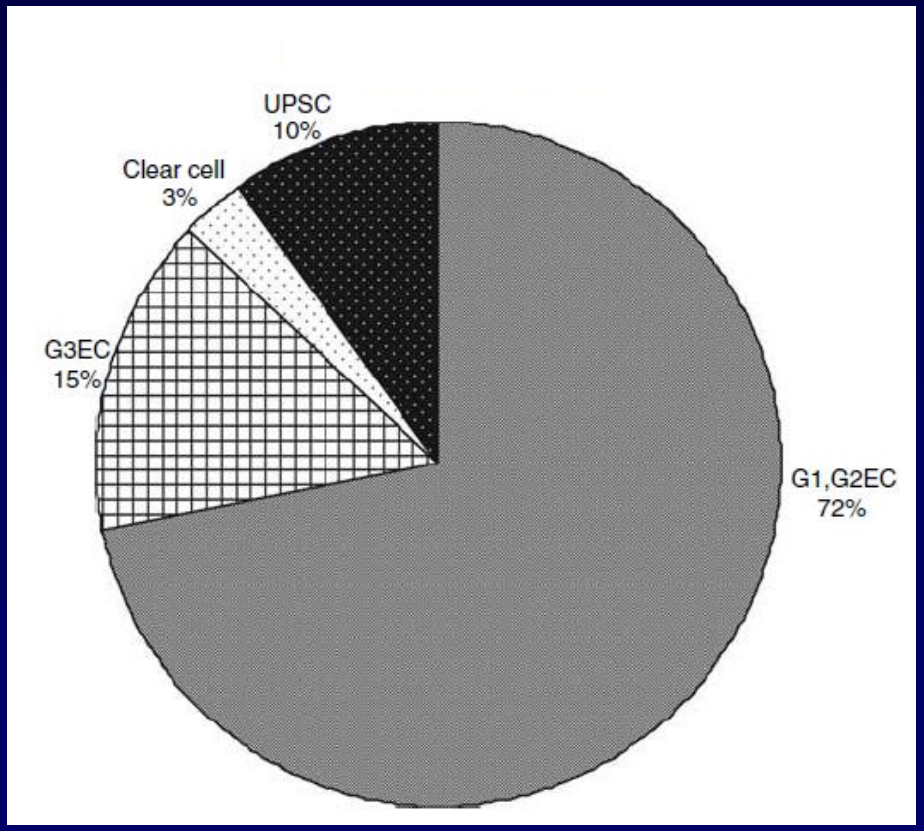
Randomised Trials: Conclusions

- RT improves local control, particularly in subset with high-risk features
- No impact on overall survival
- High salvage rate for recurrences
- Increases toxicity

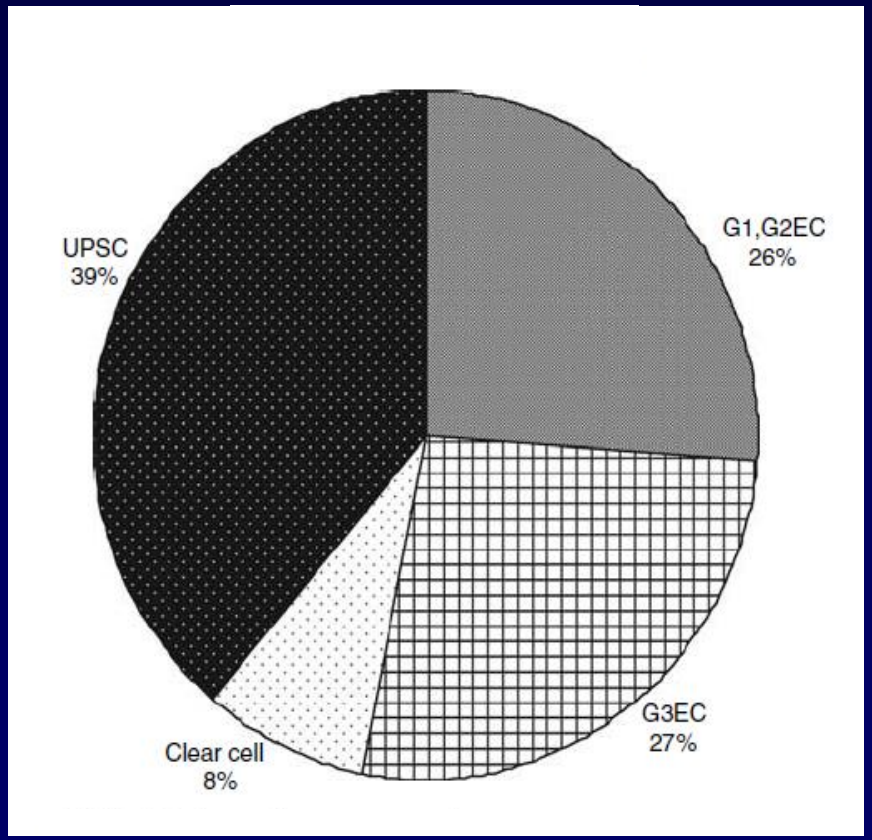
Radiotherapy has no effect on survival?

SEER Registry

Proportion of diagnosed uterine cancers

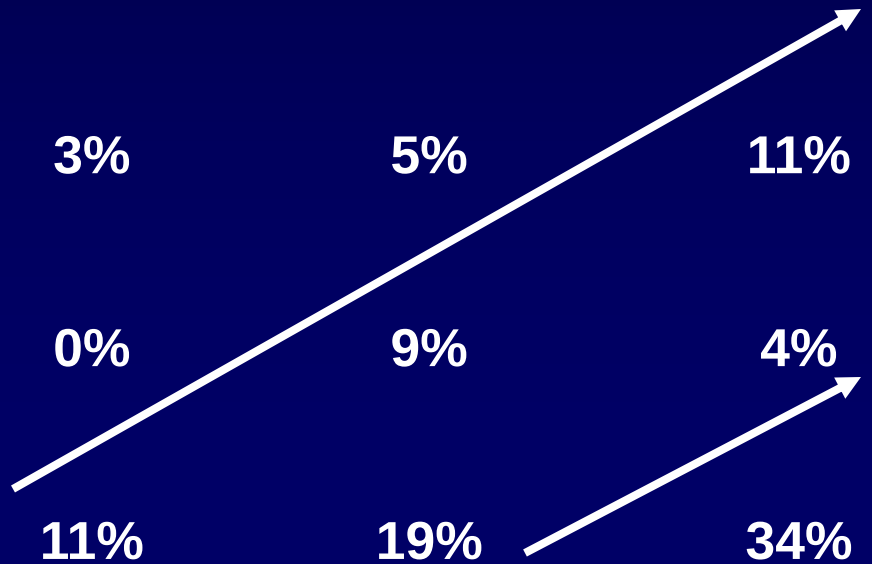


Proportion of deaths from uterine cancer



GOG 33: Surgicopathologic Risk Factors Incidence of Pelvic Lymph Nodes

Depth of myometrial invasion	G1	G2	G3
None	0%	3%	0%
Inner 1/3	3%	5%	11%
Middle 1/3	0%	9%	4%
Outer 1/3	11%	19%	34%



Creasman WT, et al. *Cancer.* 1987;60(8 Suppl):2035-2041.

Risk Groups in Endometrial Cancer

- **Low Risk**
  - **Stage 1A, G1-2**

No RT

- **Intermediate Risk**
  - **Stage IB G1-2; Stage IA G3**

ICRT
?EBRT

- **High risk**
  - **Stage IB G3; Stage II**
  - **Stage III or IV**
  - **Serous or clear cell carcinoma**
  - **Carcinosarcoma**

G3 IC Outcomes Compared to Stage I PORTEC Trial

Creutzberg et al, JCO 2004

- **99 patients with G3 IC disease**
- **Received adjuvant pelvic RT**

	G3 IC	PORTEC	
Locoregional recurrence	14%		3%
Distant metastases	31%		8%
Overall survival	58%	G1-2	85%
		G3 IB	74%

Creutzberg CL, et al. *J Clin Oncol.* 2004;22(7):1234-1241.

Radiotherapy for Stage One Disease: SEER Database

Lee et al, J Clin Oncol 2006

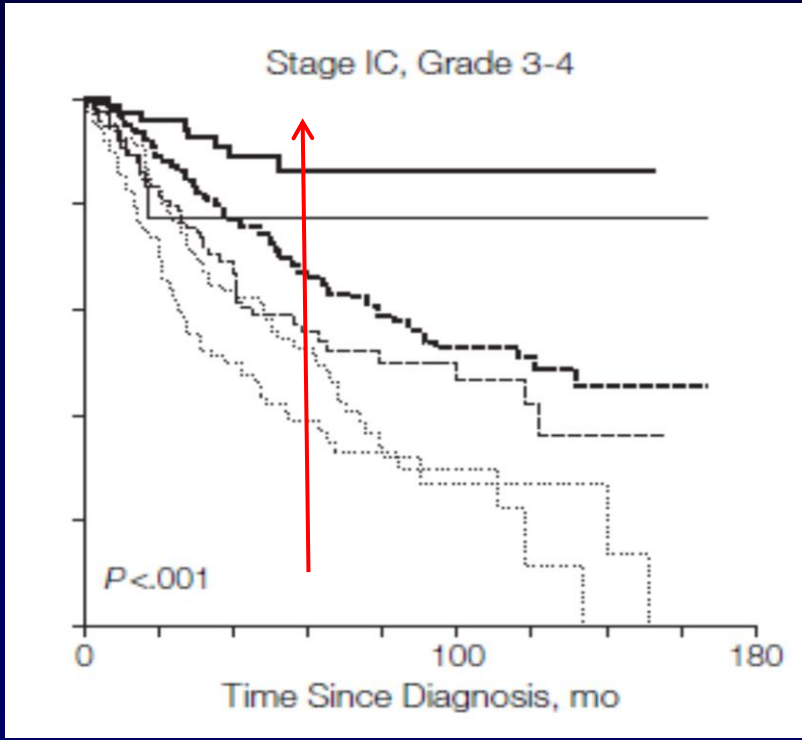
n = 21,249 **19% received RT**

G3 IC

886 patients: 66% received RT

Hazard ratio for survival

- **All patients** **0.72 (0.57-0.92)**
- **LND** **0.73 (0.55-0.96)**



Lee CM, et al. *J AMA.* 2006;295(4):389-397.

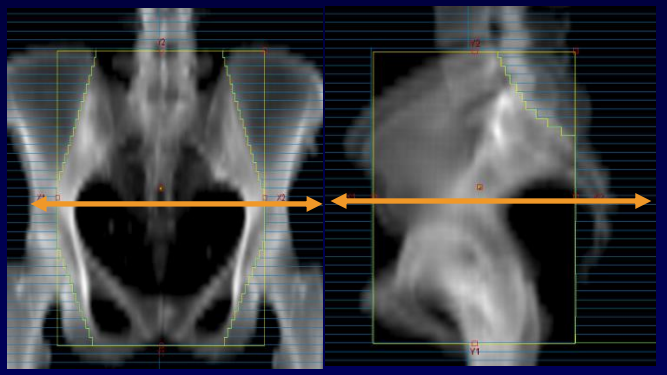
Can Pelvic RT Improve Survival?

		No RT	RT
FIGO report, 2006			
IC disease	5YS	75%	86%
Norwegian Radium Hospital Trial			
G3 IC	9YS	72%	82%
GOG 99			
HIR	4YS	74%	88%
ASTEC			
High risk	No difference		

Radiotherapy causes unacceptable toxicity?

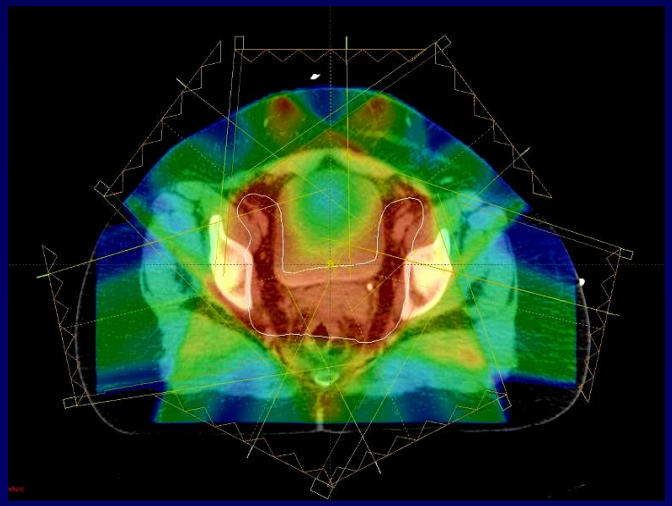
External Beam Radiotherapy

Target volume:
Pelvic lymph nodes, parametrium, and upper vagina



Conventional RT:
2D planning
Toxicity: G1+ 20%-30%, G2+ 9%

Intensity-modulated radiotherapy:
Reduces dose to bowel, bladder, and rectum by 40%-60%

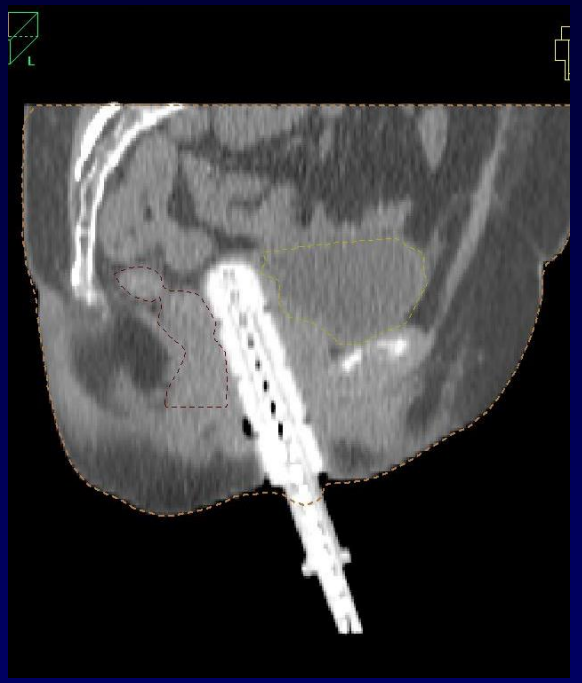


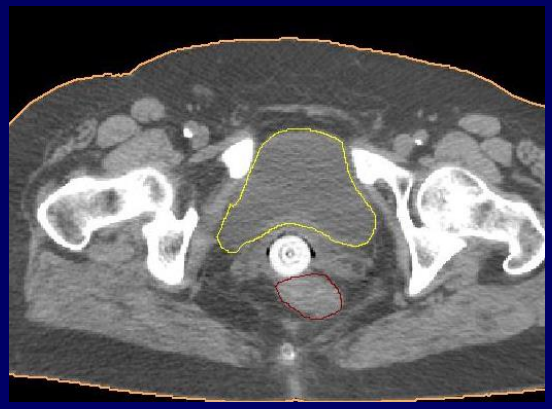
Chen LA, et al. *Gynecol Oncol.* 2015 Jan 3. [Epub ahead of print].
3-yr late toxicity 16% vs 45%

Vaginal Vault Brachytherapy (VBT)

Target volume
Vaginal vault only

Late toxicity
G3 0%
QoL studies: impact on sexual function





Vaginal Vault Brachytherapy Alone After Negative Lymphadenectomy

Straughan, Gynecol Onceol 2004

	No RT (n = 121)	RT (EBRT n = 33 / VBT n = 56)
Local relapse	**7%**	**1%**
3-yr DFS	**71%**	**93%**
3-yr OS	**90%**	**92%**

- **In several series with G3 or IC disease, overall pelvic relapse 4% (14/381)**

Long-Term Risk of Second Cancer After Radiotherapy

Witlink et al, JCO 2014

- **Pooled data from 3 trials:**

  Rectal cancer TME trial (n = 1530) **EBRT vs No RT**

  PORTEC-1 (n = 714) **EBRT vs No RT**

  PORTEC-2 (n = 427) **EBRT vs VBT**

  Total: 2554 patients

- **No difference in incidence between RT and no RT**
- **All survivors higher risk of second cancer compared to general population**
  - **HR 2.98 (2.82-3.14)**

	No RT	EBRT	VBT
10 years	16%	15%	15%
15 years	26%	26%	-

Witlink LM, et al. *J Clin Oncol.* 2014 Dec 22. [Epub ahead of print].

Adjuvant radiotherapy or treatment upon relapse?

Vaginal Recurrence of Endometrial Cancer

Multiple case series

Complete response: up to 95%

Local control

Confined to mucosa	80%-90%
More advanced disease	60%-70%
Sidewall relapse	15%-30%

5-yr overall survival 25%-68%

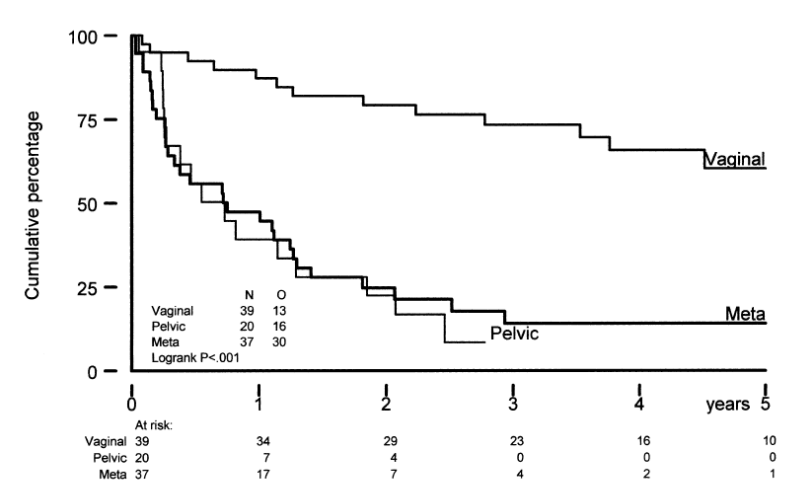


Fig. 2. Probability of survival after relapse by site of relapse: vaginal, pelvic, and distant relapse (both study groups combined).

Creutzberg CL, et al. *Gynecol Oncol.* 2003:80(2);201-209.

IMRT With Image Guided Brachytherapy for Vaginal Recurrence of Endometrial Cancer

Vargo et al, Radiother Oncol 2014

- **41 patients**
- **EBRT with IMRT**
- **Image guided HDR brachytherapy**

CR	**95%**
3 yr LC	**95%**
3 yr RFS	**68%**
3 yr OS	**67%**

Late Toxicity: G3+ 8% (2 patients)

Vargo JA, et al. *Radiother Oncol.* 2014;113(1):126-131.

IMRT With Image-Guided Brachytherapy for Vaginal Recurrence of Endometrial Cancer Interplay of PORTEC Risk Stratification

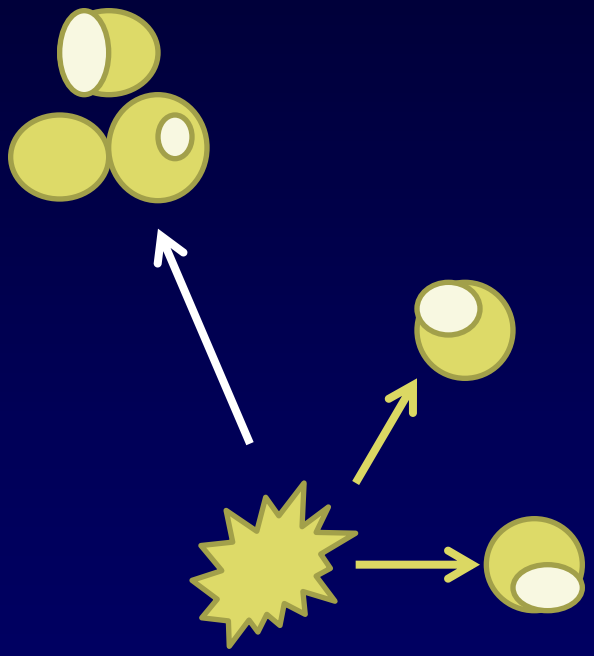
Vargo et al, Radiother Oncol 2014

	Univariate – 2-year distant control (±SE)	Univariate – 2-year overall survival (±SE)
PORTEC 1 (included vs. excluded)	95% (±4.9) vs. 19% (±16.3), $p < 0.0001$[a]	96% (±4.4) vs. 72% (±17.8), $p = 0.001$[a]
FIGO stage (I vs. II–IV)	88% (±6.5) vs. 24% (±20.3), $p = 0.003$	92% (±5.3) vs. 80% (±17.9), $p = 0.021$
FIGO grade (I–II vs. III)	87% (±7.3) vs. 43% (±20.8), $p = 0.010$	96% (±4.3) vs. 67% (±20.8), $p = 0.042$
Histology (endometrioid vs. non)	88% (±6.9) vs. 30% (±23.1), $p = 0.031$	93% (±5.2) vs. 75% (±21.7), $p = 0.338$[a]
Depth of myometrial invasion (<50% vs. ⩾50%)	91% (±6.3) vs. 30% (±17.5), $p = 0.001$	95% (±4.6) vs. 70% (±18.2), $p = 0.003$
Type of recurrence (vagina only vs. vagina + lymph node)	87% (±7.0) vs. 45% (±18.8), $p = 0.018$	90% (±6.8) vs. 88% (±11.7), $p = 0.159$[a]
	Multivariate – distant control	Multivariate – overall survival
Depth of myometrial invasion	HR = 7.694, 95% CI 1.815–32.614, $p = 0.006$	HR = 15.145, 95% CI 1.505–152.424, $p = 0.$

Vargo JA, et al. *Radiother Oncol.* 2014;113(1):126-131.

With the high risk of distant spread, is there any benefit in local therapy?

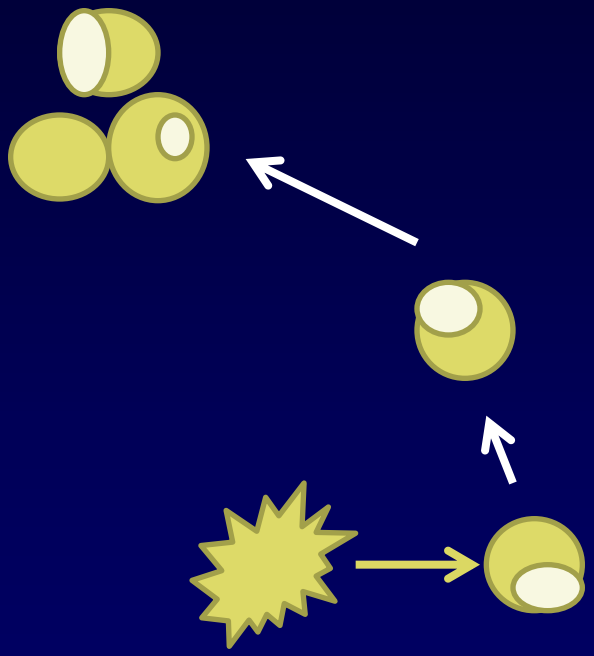
Potential Models of Spread



Pathway One

- Early dissemination of disease
- Lymph node involvement prognostic
- Improved locoregional control may prevent local complications, but unlikely to improve survival
- Requires effective systemic therapy

Models of Spread



Pathway Two

- Early nodal involvement
- Sequential spread
- Remains locoregional, so can still potentially cure distant nodal disease
- Improvement in local control does impact on survival

Node-Positive Disease

Klopp et al, Gyn Onc 2009

68 patients: 50 received RT and 18 no RT (+chemo/hormones)

61% pelvic node positive, 39% PAN positive

	RT	No RT
Pelvic control	98%	61%
DSS	78%	39%
OS	73%	40%

Klopp AH, et al. *Gynecol Oncol.* 2009;115(1):6-11.

Node-Positive Disease

Secord et al, Gynecol Oncol 2013

265 optimally resected stage IIIC

	RT	Chemo	Chemo+RT
RFS	73%	56%	73%
OS	95%	78%	90%

***P* = .0005**

Secord AA, et al. *Gynecol Oncol.* 2013;128(1):65-70.

Can Chemotherapy Replace Radiotherapy?

Mundt et al, IJROBP 2001

- **43 high risk patients**
- **4-6 cycles of chemotherapy**
- **67% relapsed:**
  - **40% pelvis**
  - **56% extra-pelvis**
- **31% first site of relapse in pelvis**
- **20% only ever pelvic disease**

NO

Mundt AJ, et al. *Int J Radiat Oncol Biol Phys.* 2001;50(5):1145-1153.

Chemotherapy and Radiotherapy?

- Need to determine optimal schedule
  - NSGO-EORTC/MaNGO — EBRT vs EBRT+CT
  - PORTEC-3 — EBRT vs Chemo-RT + CT
  - GOG 0249 — EBRT vs VBT + CT

Conclusions
Radiotherapy for G3 IB disease

- **Risk of local relapse 30%-40%**
- **Risk of distant relapse 30%-40%**

Recommendation

- **No / limited LND or extensive LVSI EBRT**
- **LND – node negative VBT**
- **Consider chemotherapy**

2015

Progress and Controversies in Gynecologic Oncology Conference