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Important trials in management of endometrial cancer

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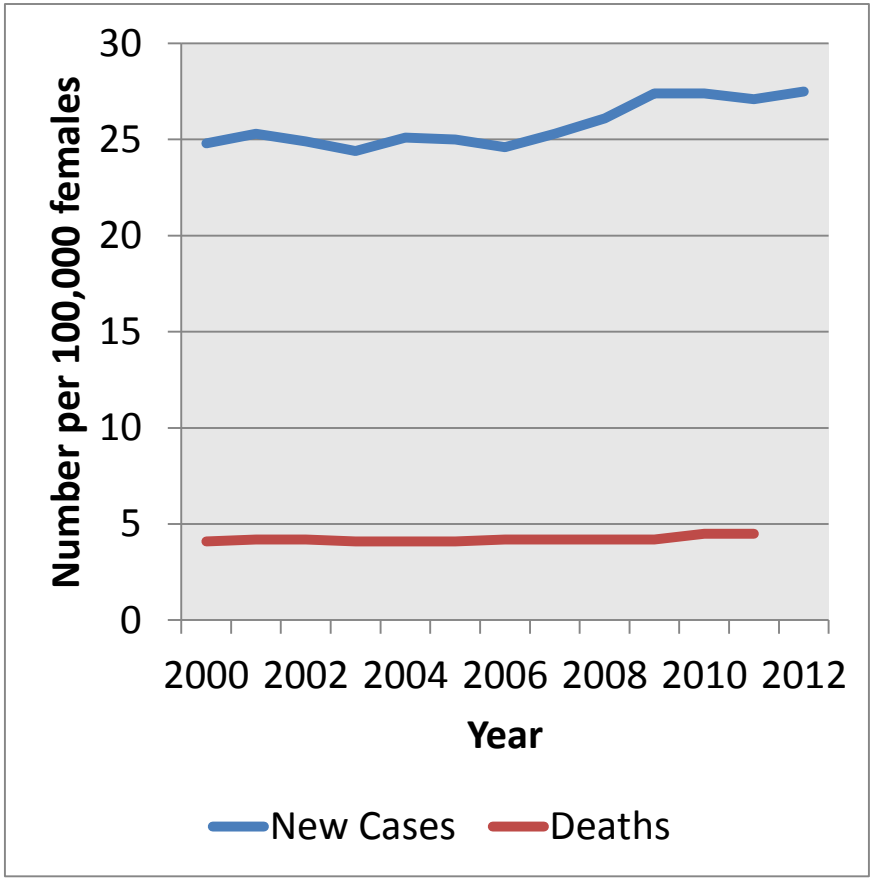
Introduction

- Most common gynecologic cancer in developed countries
- In 2012, occurred in 320,000 women and caused 76,000 deaths
- 3rd most common cause of female malignancy death (behind ovarian and cervical cancer)
- Rising incidence due to the increasing number of elderly people and increasing rates of obesity



Graph adapted from SEER Cancer Statistics

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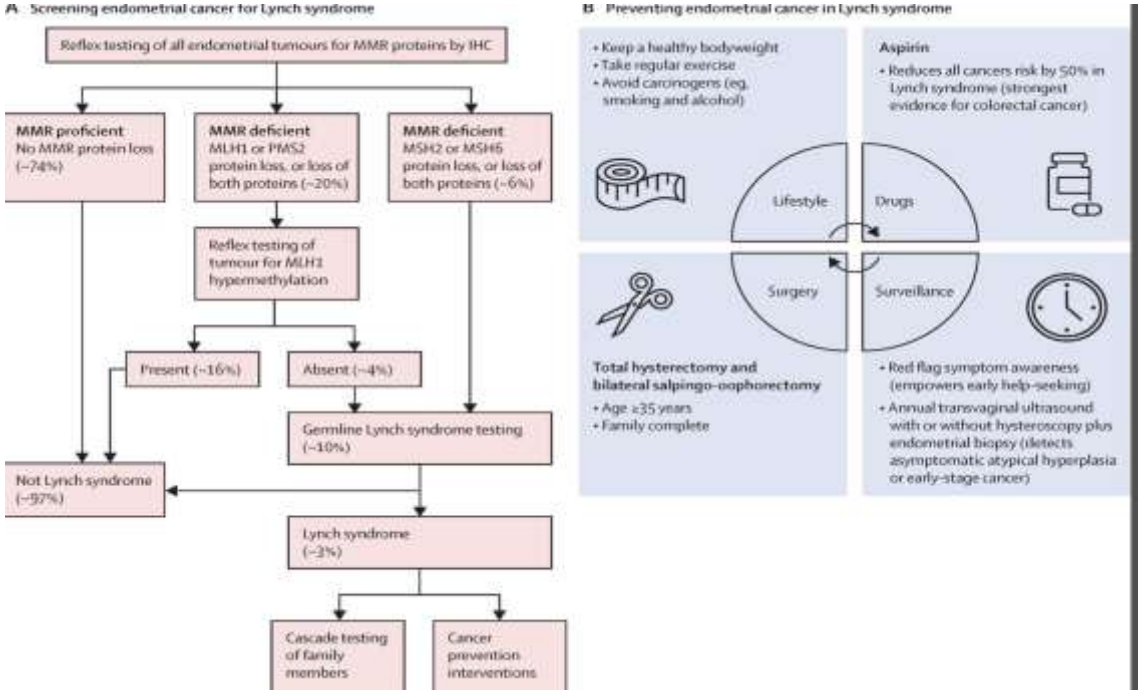
Screening for lynch syndrome



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Lymph Node Dissection
Early Stage Disease

Global Controversy
Prognostic, not therapeutic
Risk factors associated with LN metastasis
- Grade and histology
- Depth of invasion
- LVSI
- Tumor size
- ?LUS/Cervical involvement

Routine vs Selective Lymphadenectomy?

MRC ASTEC LND Trial

Lymphadenectomy upstaged 10% of patients who had High/Intermediate risk disease

- Grade 3 or >50% myometrial invasion

No oncologic benefit on adjusted analysis

- Overall Survival
- Disease Specific Survival
- Recurrence free survival

Higher morbidity with lymphadenectomy

- Moderate/severe morbidity (17% vs 12%)
- Lymphedema (4% vs 0.2%)

Lymphadenectomy is useful for staging but not therapeutic

Italian LND Trial

Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial

Pierluigi Benedetti Panici, Stefano Basile, Francesco Maneschi, Andrea Alberto Lissoni, Mauro Signorelli, Giovanni Scambia, Roberto Angioli, Saverio Tateo, Giorgia Mangili, Dionyssios Katsaros, Gaetano Garozzo, Elio Campagnutta, Nicoletta Donadello, Stefano Greggi, Mauro Melpignano, Francesco Raspagliesi, Nicola Ragni, Gennaro Cormio, Roberto Grassi, Massimo Franchi, Diana Giannarelli, Roldano Fossati, Valter Torri, Mariangela Amoroso, Clara Crocè, Costantino Mangioni

J Natl Cancer Inst 2008;100:1707–1716

Italian LND Trial

Eligible patients

- Presumed Stage I at time of surgery
- Excluded <50% myometrial invasion + G1 DZ

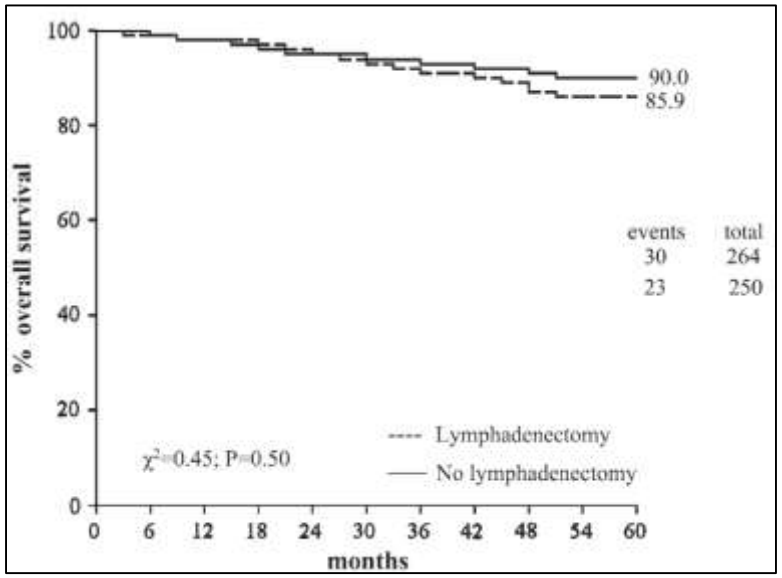
Randomized to TAH +/- Lymphadenectomy

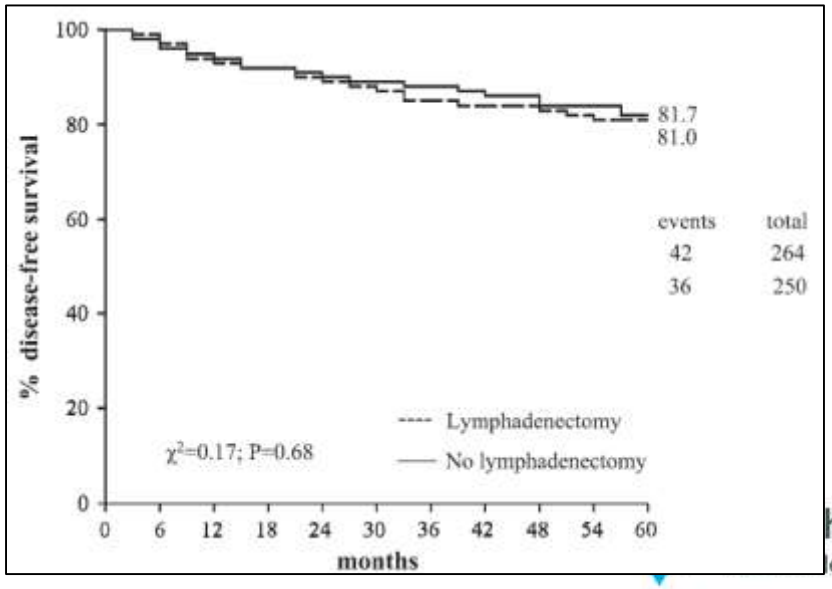
PLND upstaged ~10% of patients

- 13% vs 3% with pathologic positive nodes

No difference in OS or DFS

Important b/c European studies do not utilize PNLD while American studies do





PLND summary

Useful for staging

- Upstage 10% of HIR disease

No therapeutic benefit in RCTs

- ASTEC and Italian trials

Has increased morbidity

Can we use SNBx instead?

- May have same staging accuracy wrt nodes
- Minimize toxicity vs. lymphadenectomy

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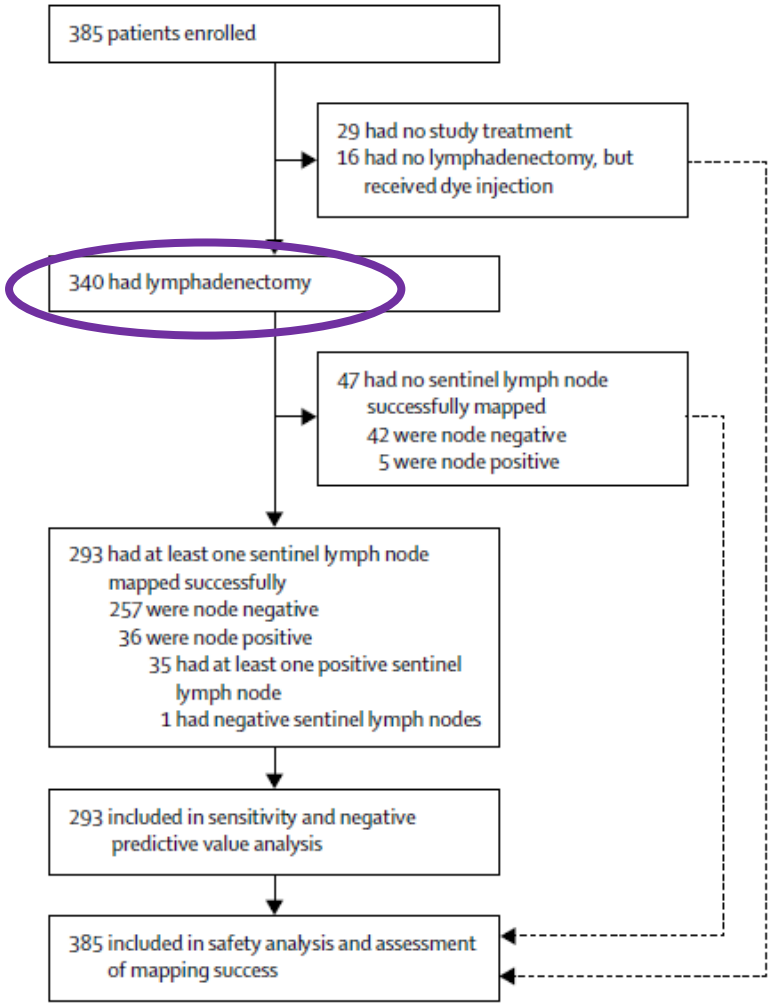
FIRES Trial- SNLN

- Multicenter, prospective cohort study, 10 US centers, 18 surgeons
- Clinical Stage I, any histology
- No prior therapy, retroperitoneal surgery, or extra uterine disease
- 0.5mg/mL ICG tracer, cervical injection 1cm deep at 3 & 9 o'clock
- Pelvic lymphadenectomy required, para-aortics optional
- Ultra-staging of SLN (3mm cuts)
- Primary endpoints: Sensitivity & NPV

Rossi *et al*, Lancet Oncol, 2017, 18:384



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FIRES Trial

Prospective cohort study 385 of clinical stage I endometrial cancer, all histologies (19% type II) and grades (11% G3), undergoing robotic staging

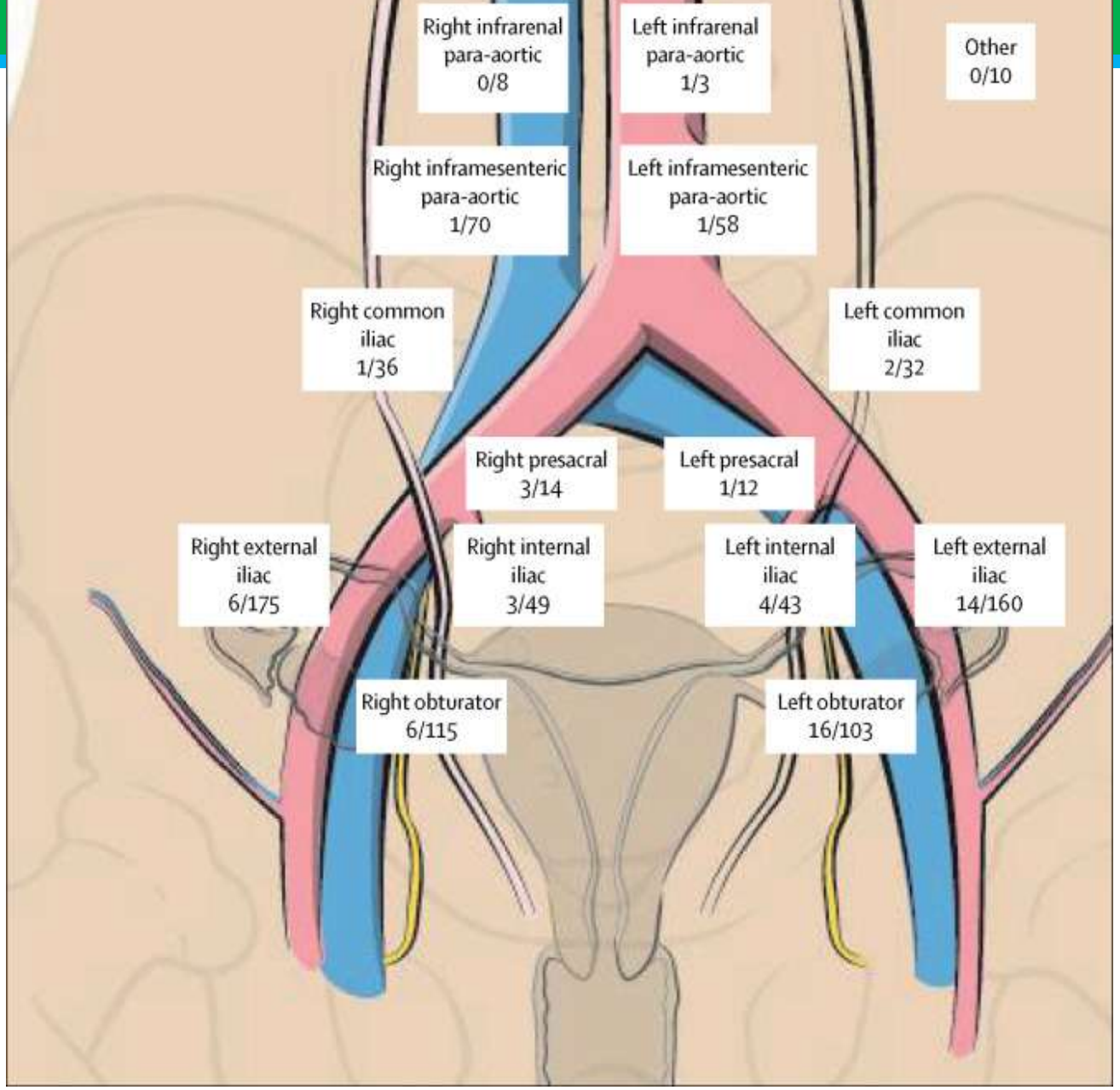
ICG mapping SLN biopsy followed by PLND, 58% also had PALND

86% had mapping of at least 1 sentinel LN, 52% bilateral mapping

+LN 12%

Sensitivity of 97.2%, NPV 99.6%

28% of the study population had high-grade histology, but not powered for this sub-group



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Rad Onc

Six (17%) patients had positive sentinel lymph nodes found exclusively in regions the surgeon identified as lying outside of routine lymphadenectomy (such as pre-sacral or internal iliac regions)

Six (29%) of the 21 patients with low-volume metastatic sentinel lymph node disease found on ultra-staging had accompanying positive non-sentinel lymph nodes

For macro-metastatic disease nine (64%) of 14 patients with high-volume sentinel lymph-node metastases.

Sentinel Lymph Node Biopsy

Ongoing randomized trial to quantify benefit

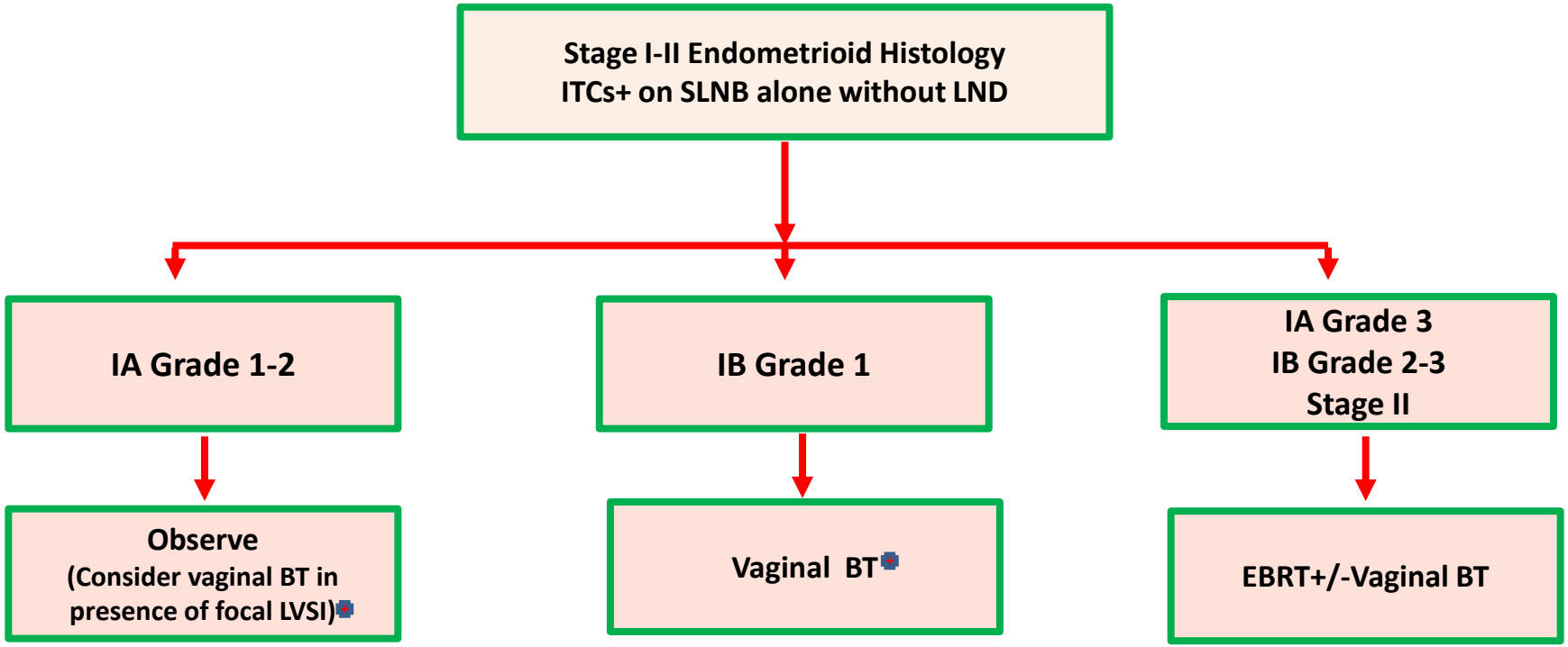
Accepted standard of care if access available as data shows high sensitivity (97%) and NPV (99%) when protocol is followed

Ultrastaging is picking up more ITC of which the clinical significance is unclear and may result in overtreatment.

Currently we treat ITC based on intrauterine factors with RT if has otherwise high risk disease

Macro and micro metastases is treated like node positive disease with chemo + RT (PORTEC3 and GOG 258)

Can we skip RT in all SNLN negative patients ?



● EBRT in presence of substantial LVSI irrespective of extent of myometrial invasion or grade of disease

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Adjuvant treatment for early stage endometrial cancer

Risk stratification

Low risk

Intermediate risk

High intermediate risk

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Low risk

Stage IA (<50% myometrial invasion) grade 1-2 endometrioid histology

- Lacks high risk features such as LVSI
- Estimated absolute risk of recurrence <5%

Management of low risk

- Randomized trial by Swedish group
  - Stage IA grade 1-2 endometrioid s/p surgical staging
  - Vaginal brachytherapy (VCBT) vs. observation
- Results
  - Non-significant reduction in vaginal recurrences with VCBT
    - 3.1→1.2%, p=0.11
  - Side effects limited to grade 1-2:
    - Dysuria, frequency and incontinence slightly more common after VCBT (2.8 vs. 0.6%)
- These findings support observing patients with low-risk findings following hysterectomy.

Sorbe et al. Int J Gynecol Cancer 2009.

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Intermediate risk

Variable definitions but generally group includes stage I-II disease with risk factors such as deep myometrial invasion (MI), higher grade, LVSI, and/or older age

The PORTEC and the GOG-99 studies enrolled patients at “intermediate risk” and defined a subset of these patients who were at higher risk and thus referred to as “high-intermediate risk”

Randomized studies For intermediate risk patients

PORTEC 1 and 2

GOG 99/GOG 249

Swedish x2

Norwegian

ASTEC

JGOG 2033

Adjuvant RT vs. observation

	GOG 99	PORTEC1
Inclusion	Stages IA-IB and occult II, any grade	Stage IA (G2-3) or IB (G1-2), ***no IC G3***
Risk category	intermediate	Intermediate
Nodal sampling	Yes	No
Randomization	Observation vs. EBRT	Observation vs. EBRT
Dose	50.4 Gy/28 fractions	46 Gy/23 fractions
Risk of any relapse	12→3% (70% in vagina) 26→6% (HIR)	15.5→5.8% 23→4% (HIR)
Overall survival	86→92% (NS)	80→84% (NS) 52→60% (HIR)
Morbidity	8% GI	4→26% 0→3%
QOL		Long-term urinary and bowel symptoms and lower functioning

Creutzberg et al. Lancet 2000./Nout et al. J Clin Oncol 2011.
Keys et al. Gynecol Oncol 2004.

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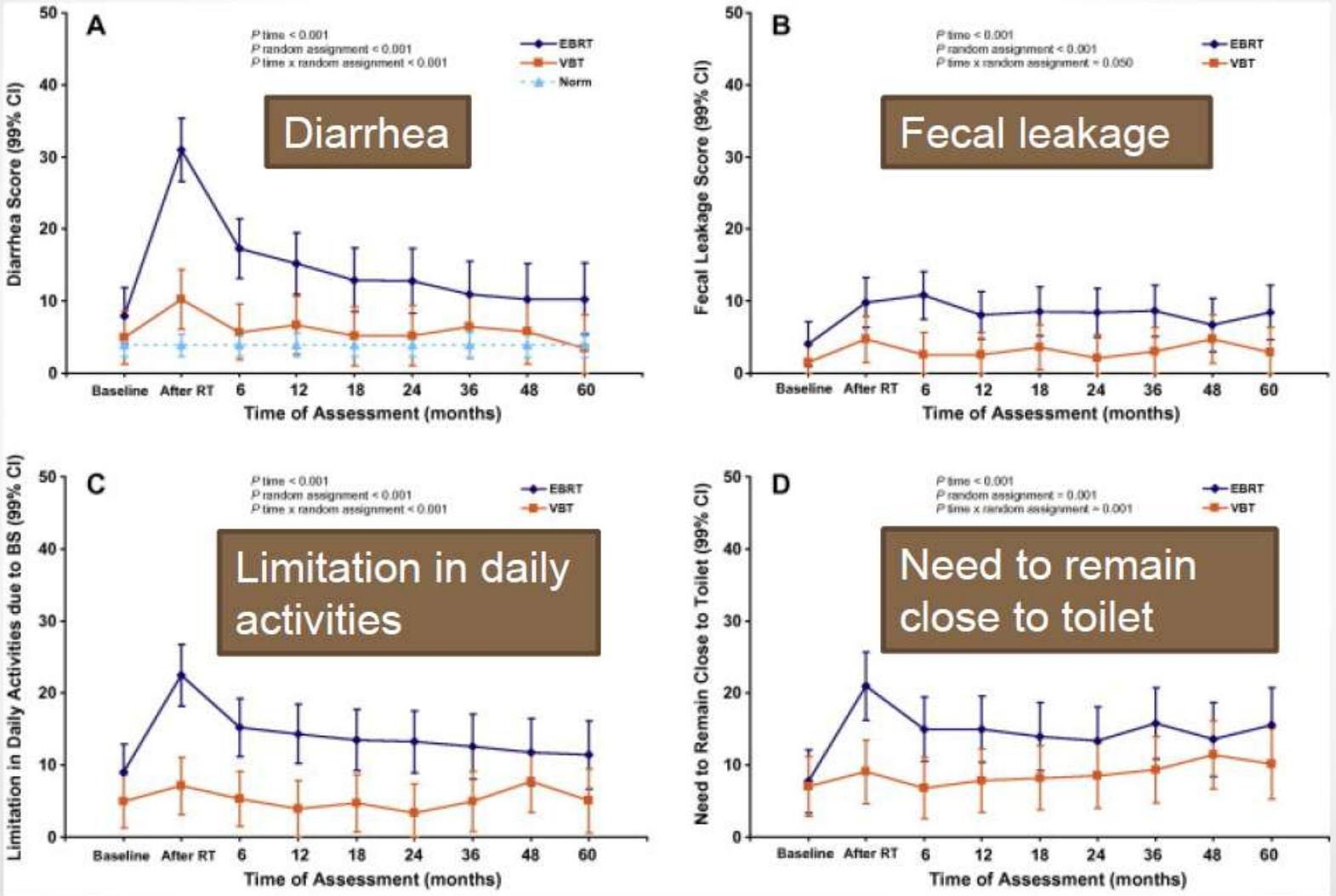
PORTEC 1



Nout et al. J Clin Oncol 2011.

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Summary

EBRT reduces risk of pelvic relapse by about 75%

Majority of pelvic recurrences in vagina

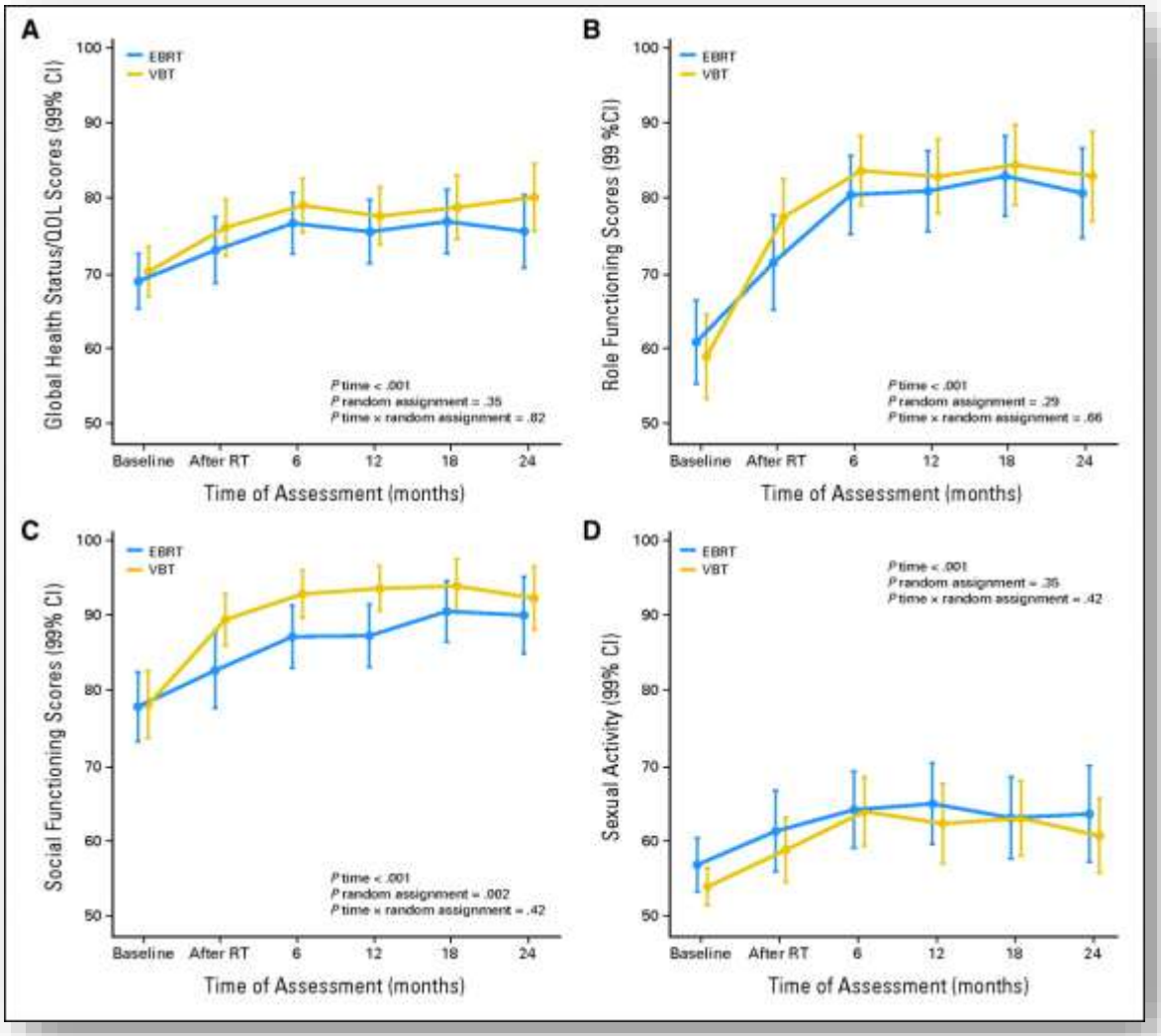
Increased GI morbidities with affect on QOL with EBRT

No difference in survival

VCBT vs. EBRT

	Norwegian	ASTEC/NCIC	Swedish	PORTEC 2
Inclusion	All stage I	IA-IB Grade 3, IC Grade 1-3, Adverse Path	Grade 3, IB, or DNA aneuploid	>60y and IB grade 1-2 or IA grade 3
Risk Group	LR/IR/HIR	HIR	HIR	HIR
Nodal staging	None	+/- 50%	Not routine	None
Treatment	VCBT vs. EBRT+VCBT	Obs (50% VCBT) vs. EBRT+VCBT	VCBT vs. EBRT+VCBT	VCBT vs. EBRT
EBRT Dose	40 Gy	40-46 Gy	46 Gy	46 Gy
Local relapse	7→2% 20→5% (HIR)	6→3%	5→1.5%	5.1→2.1%
Overall survival	90→87% NS	84 vs. 84%	89→90%	85→80% NS
Grade 3 morbidity	<60y had 2x cancer risk	Any 45→61% G3-4 3→8%	0→<2%	Acute G1-2 13→54%
QOL	-	-	Bowel and urinary sx and QOL	Diarrhea and worse social functioning

Quality of Life from Portec 2



Nout et al. J Clin Oncol 2009.

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Summary

EBRT associated with slightly lower risk of loco regional relapse (3 to 5%) in comparison to VBT

No difference in overall survival

VBT associated with less impact on long term QOL in comparison to EBT

VBT is reasonable option for most patients with intermediate risk disease

Brachytherapy

Most common site of relapse for patients with early stage endometrial cancer treated with observation is the vaginal cuff

Vaginal cuff brachytherapy (VCBT) reduces the risk of recurrence in the vagina and causes significantly less toxicity than pelvic radiation therapy.

The side effects of vaginal cuff irradiation are generally limited to vaginal complications and mild urinary side effects.

Sorbe 2009

- Randomized trial of observation vs. VCBT for low risk patients
- Grade 1-2 vaginal toxicity: 1.5→9% with VCBT
- Grade 1-2 urinary toxicity: 0.6→2.8% (p=0.06)
- No difference in GI toxicity

Sorbe et al. Int J Gynecol Cancer 2009.

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Dose and volume

Brachytherapy dose has been shown to impact vaginal toxicity

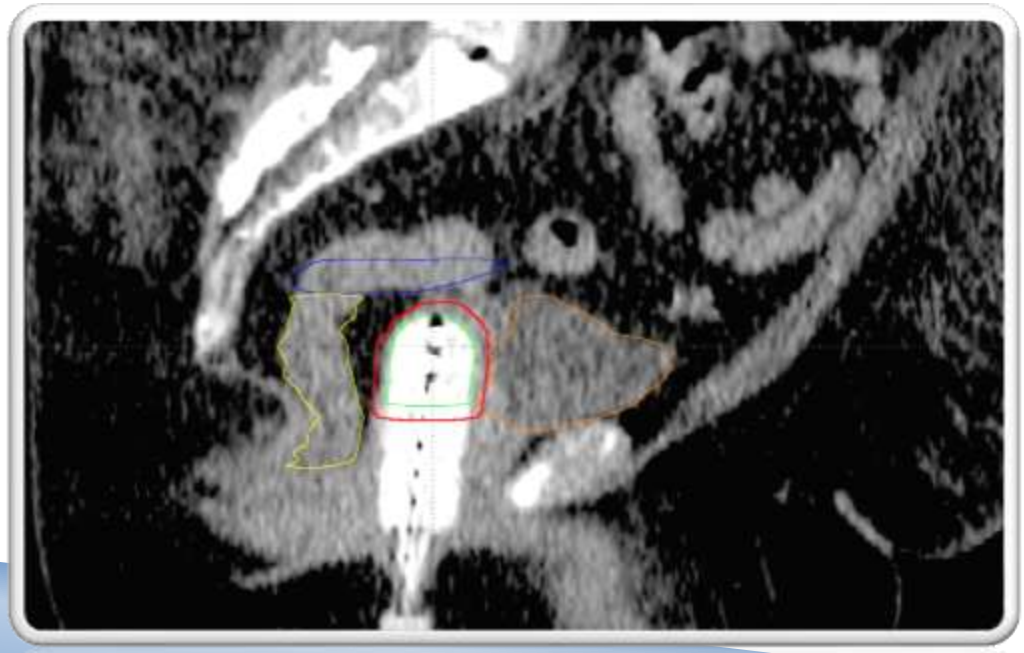
Most commonly used fractionation in PORTEC 2 and GOG 249:

- 7 Gy x 3 fractions prescribed to 5 mm depth
- Delivers comparable dose for late effects to Sorbe randomized trial
- However, expected to lead to increased vaginal fibrosis as compared with lower dose per fraction regimens

Effective lower dose regimens (6 Gy ×5 or 4 Gy ×6 prescribed to the vaginal surface) have been reported with excellent vaginal control rates and minimal vaginal toxicity.

Benefits of CT simulation

- Confirms placement of applicator to the apex
- Identifies rare but possible cuff dehiscence
- Dosimetry for critical organs



High risk/HIR

Stage IB grade 3 and stage II disease (not represented in PORTEC 2)

Stage IA grade 3 with LVSI and nodes not dissected

- Under represented in PORTEC 2 and are now part of PORTEC 3 which is high risk study looking at chemo RT vs. RT

Risk of extrapelvic relapse as high as pelvic relapse in these patients

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Chemo vs. EBRT for high/HIR

	GOG 249	JGOG 2033
Inclusion	Stage I (HIR) , Stage II endometrial, Stage I-II serous or clear cell.	IC 61%, II 14%, IIIA 13%, IIIC 12%.
Risk Group	HIR	HIR and High risk
Nodal staging	Sampled	Sampled
Treatment	VCBT/Chemo vs. EBRT	EBRT vs. Chemo (CAP)
LR	19 vs. 2%	6.7 vs. 7.3%
DM	24 vs. 32%	13.5 vs. 16.5%
OS	92 vs. 93%	85 vs. 87% 74 vs. 90% (HR)
Morbidity	Increased GI and heme toxicity with chemo	No difference

McMeekin et al. SGO 2014.
Susumu et al. Gynecol Oncol 2008.

GOG 249 (SGO 2014)

AE	Gr 2		Gr 3		Gr 4	
	PXRT	VCB/C	PXRT	VCB/C	PXRT	VCB/C
Constitutional						
Fatigue	25	60	1	9	0	1
Weight Loss	0	2	0	0	0	0
GI						
Nausea	7	17	0	4	0	0
Vomiting	3	8	0	4	0	0
Diarrhea/Constipation	33/1	16/21	8/0	5/1	0/0	0/0
Dehydration	3	6	0	3	0	0
Heme						
ANC	8	46	0	73	0	94
Hb	3	62	0	5	0	2
PLT	0	11	0	4	0	5
Febrile Neutropenia	0	0	0	6	0	1
Neurologic						
Sensory	2	20	0	5	0	0

McMeekin et al. SGO 2014.

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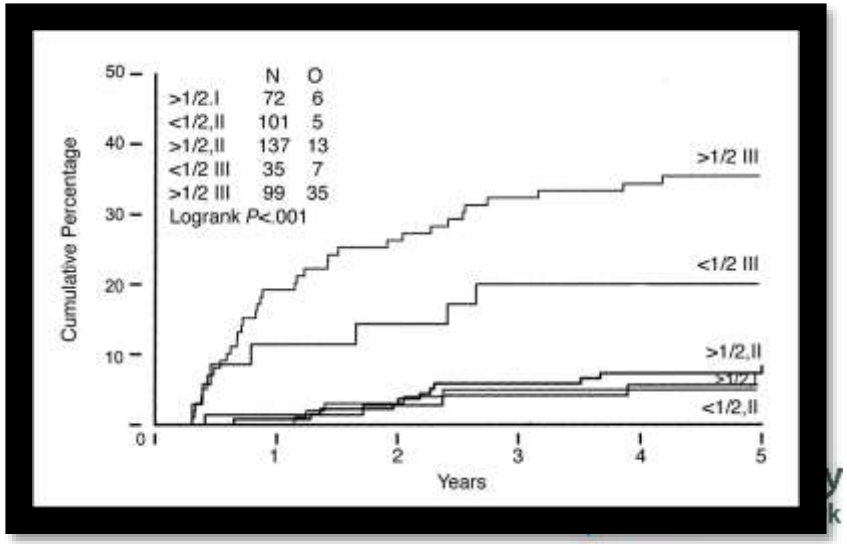
PORTEC 1: Stage IC grade 3 patients

- Analysis of patients with IC G3 disease registered but ineligible
  - n=99
  - Treated per same protocol
- Median follow-up 6.9 years
- 5-year outcomes
  - Overall survival: IB-C G1-2 83-85%, IB G3 74%, IC G3 58%
  - DM rates: IB-C G1-2 3-8%, IB G3 20%, and IC G3 31%
- IC G3 had a high risk of DM and cancer-related death



Cruetzberg et al. J Clin Oncol 2004.

Cochrane meta-analysis

Meta-analysis for early stage endometrial cancer treated with adjuvant therapy

5 randomized trials, stratified patients by risk

- **Low-risk disease** (IA, IB G1-2):
  - EBRT worsens survival (OR for death without RT 0.71, SS)
- **Intermediate-risk disease** (IB G3, IC G1-2)
  - EBRT doesn't alter survival (OR 0.97, NS)
- **High-risk disease** (IC G3)
  - EBRT offers DFS benefit (OR 1.76, SS) and benefits 1/10 women

Adjuvant EBRT should not be used for IA, IB, or IC G1-2 disease

There is a 10% survival advantage for IC G3 patients

Johnson et al. BGOG 2007.

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Summary

EBRT is preferred for this subset of high risk early stage disease

Chemo plus VBT was not superior to EBRT associated with higher morbidity

Risk of Secondary malignancy

Norwegian study (VCBT vs. EBRT+VCBT)[1]

- Median follow-up 20.5 years
- Women <60 years had higher mortality after EBRT (HR 1.36)
- Risk of 2nd cancer increased after EBRT, particularly in this age group (HR 2.02)

Pooled analysis of TME and PORTEC trials[2]

- Median follow-up 13 years
- No difference in the risk of 2nd cancer treated with or without RT
  - 15-year rate 26.5 (no RT) vs. 25.6% (with RT)
  - 10-year rate 15.4% (EBRT) and 14.9% (VCBT)

[1]Onsrug et al. J Clin Oncol 2013.
[2]Wiltink et al. J Clin Oncol 2015.

IMRT vs. 3D: Dosimetry

	↓ in volume receiving prescription dose		
	Bowel	**Bladder**	**Rectum**
Roeske	50%	23%	23%
Ahamad	40-63%	NS	NS
Chen	70%	-	-
Heron	51%	31%	66%

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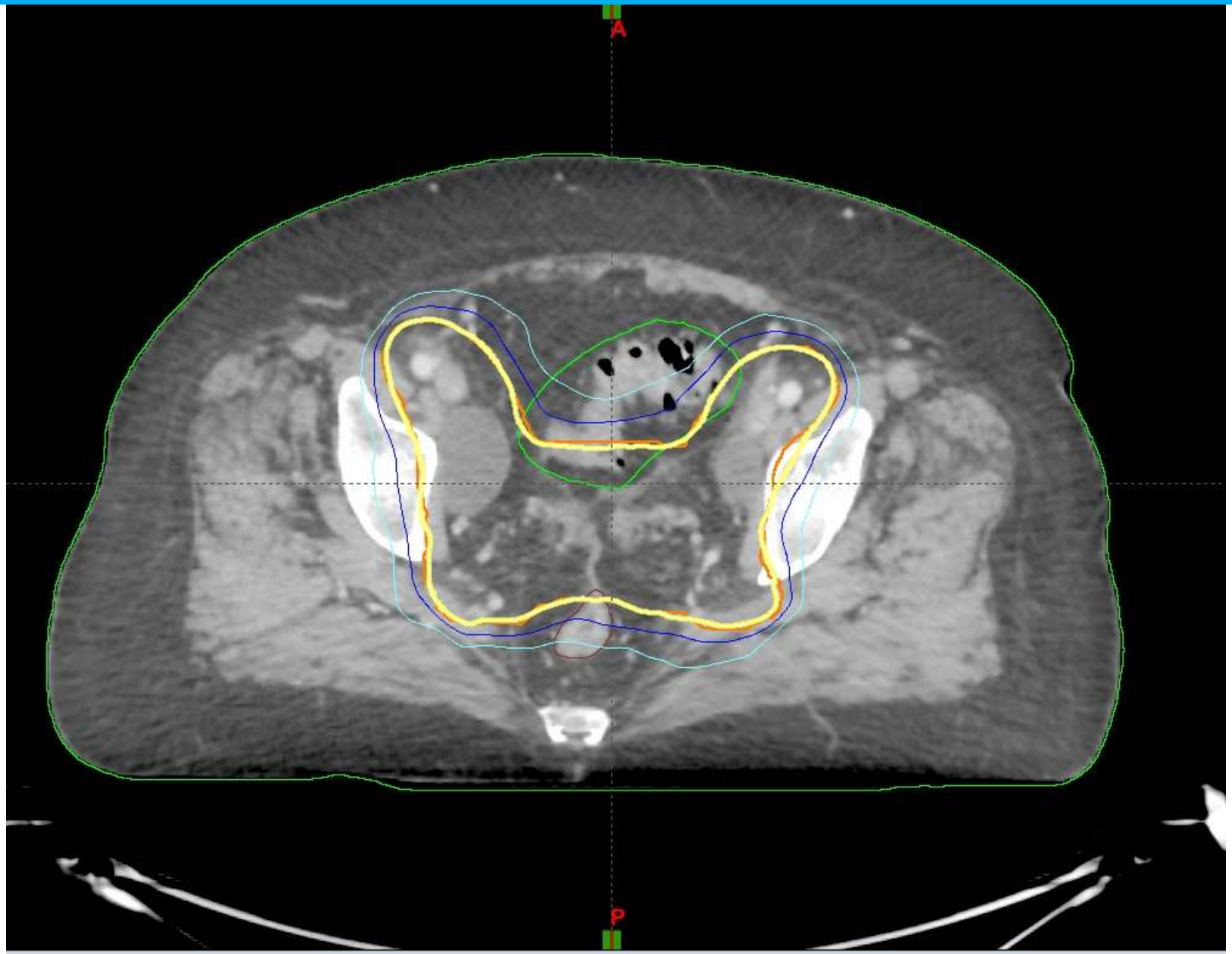

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RTOG 1203/Time-C

Phase III Multicenter Study

Eligibility

- Confirmed histologic diagnosis of invasive cervical or endometrial cancer
- Indication for adjuvant RT on the basis of pathologic risk factors
  - Excluded if required extended-field RT

Randomization (all radiation 45-50.4Gy per physician preference)

- Four-field pelvic RT
- Pelvic IMRT

Primary Endpoint

- Change in patient-reported acute GI toxicity from baseline to end of RT measured with EPIC bowel domain

Klopp JCO 2018

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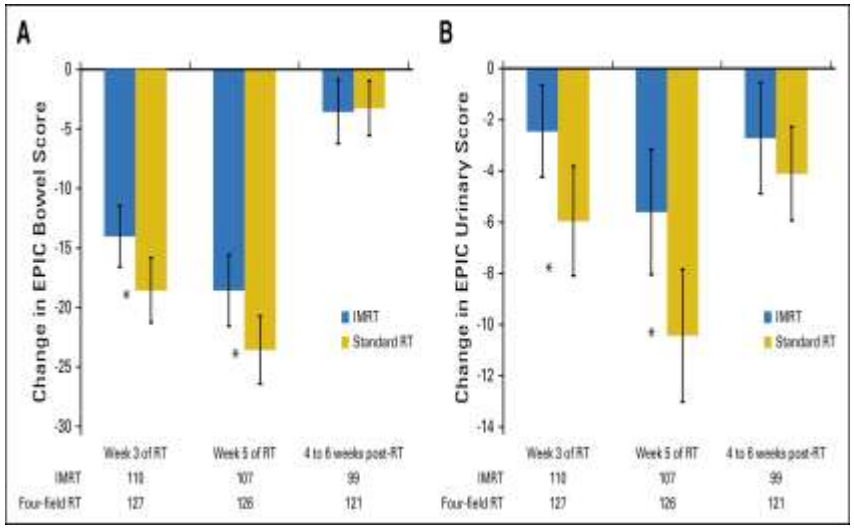
RTOG 1203/Time-C Outcomes

- Mean decreases in EPIC bowel summary scores significantly improved for IMRT group vs. Standard RT group
  - Effect size at 5 weeks = 0.26 SD
- Between baseline and end of RT
  - Mean EPIC bowel score declined 23.6 points in the standard RT group and 18.6 points in the IMRT group (*P* = .048)
  - Mean EPIC urinary score declined 10.4 points in the standard RT group and 5.6 points in the IMRT group (*P* = .03)
- Patient-Reported
  - Frequent or almost constant diarrhea higher in standard RT arm
    - 51.9% v 33.7% (P=0.01)
  - More women in standard RT arm taking anti-diarrheal medications
    - 20.4% v 7.8% (p= 0.04)



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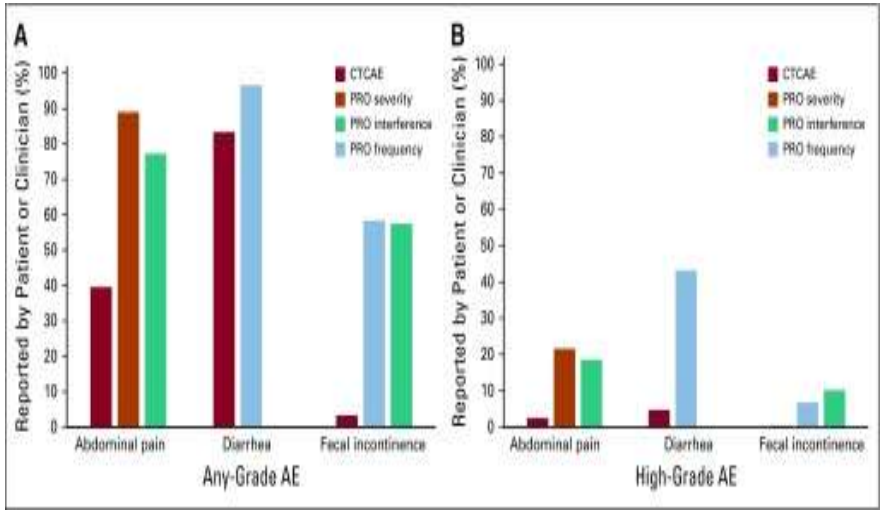
RTOG 1203/Time-C Update

- Patients reported toxicity more frequently than physicians
  - High-grade abdominal pain
    - 19.1% more ($P < .0001$)
  - High-grade diarrhea
    - 38.5% more ($P < .0001$)
  - Fecal incontinence
    - 6.8% more
- Similar effects seen between grade 1 or higher and any grade toxicity
- Clinician reported any-grade CTCAE abdominal pain rate
  - 35.6%, compared with 80.1% of patients reporting at least mild abdominal pain
  - 69.5% reported interference with usual activities at least a little bit
- With IMRT patients reported fewer GI adverse events with respect to
  - Frequency of diarrhea (18.2% difference; $P = .01$)
  - Frequency of fecal incontinence (8.2% difference; $P = .01$)
  - Interference of fecal incontinence (8.5% difference; $P = .04$)
- G3+ CTCAE toxicity was 2.5%, 21.6% of women reported severe or very severe abdominal pain
  - 18.6% reported abdominal pain interfered with activities quite a bit or very much



Yeung JCO 2020

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PARCER

Phase II RCT

Inclusion Criteria

- Diagnosis of cervical cancer
- An indication for PORT alone (any 2 of tumor size ≥ 4 cm, deep stromal invasion, and lymphovascular space invasion) or chemoradiation

Intervention

- Pelvic radiation therapy 50y/25fx over 5 weeks
- And high-dose-rate vaginal brachytherapy 12Gy/2fx over 1 week prescribed to 5mm from the cylinder

Randomization

- IMRT vs. 3D-CRT

Primary outcome

- 3-year Grade 2 or higher GI toxicity assessed on CTCAE v 3.0

Chopra JCO 2021

PARCER Outcomes

Acute Toxicity

- No difference in overall grade ≥ 2 acute GI toxicity
  - 29.8% *v* 28.8%, *P* = .38

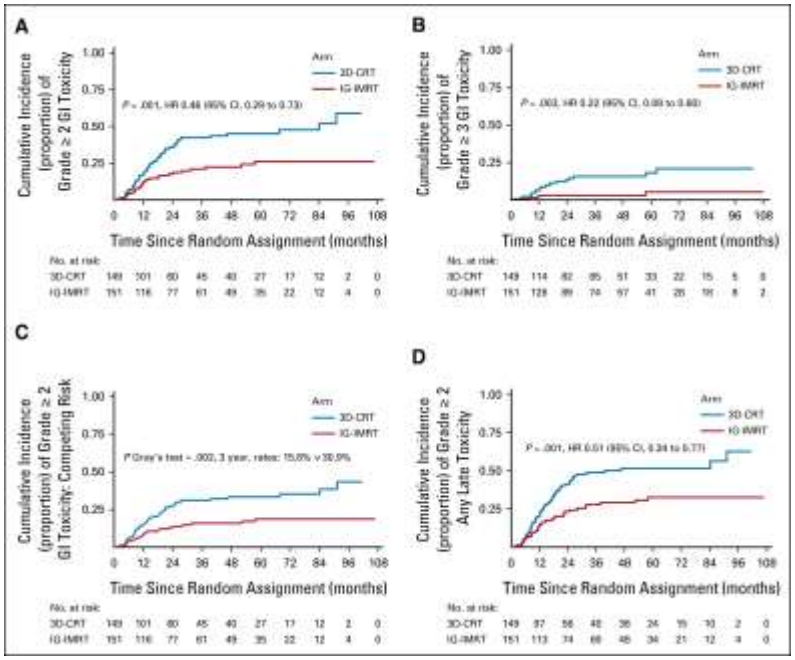
Late Toxicity

- 3-year incidence of grade ≥ 2 late GI toxicity improved with IMRT
  - 21.1% versus 42.4% *P* < .001
- 3-year cumulative incidence of grade ≥ 2 late toxicity was significantly lower in the IG-IMRT arm
  - 28.1% *v* 48.9%, *P* < .001
- Grade ≥ 3 any late toxicity were 4.0% *v* 15.5%, *P* = .004

Patients reported IG-IMRT improved

- Diarrhea (*P* = .04)
- Appetite (*P* = .008)
- Bowel symptoms (*P* = .002)

No difference in 3-year RFS or DFS in IG-IMRT vs. 3D-CRT arms



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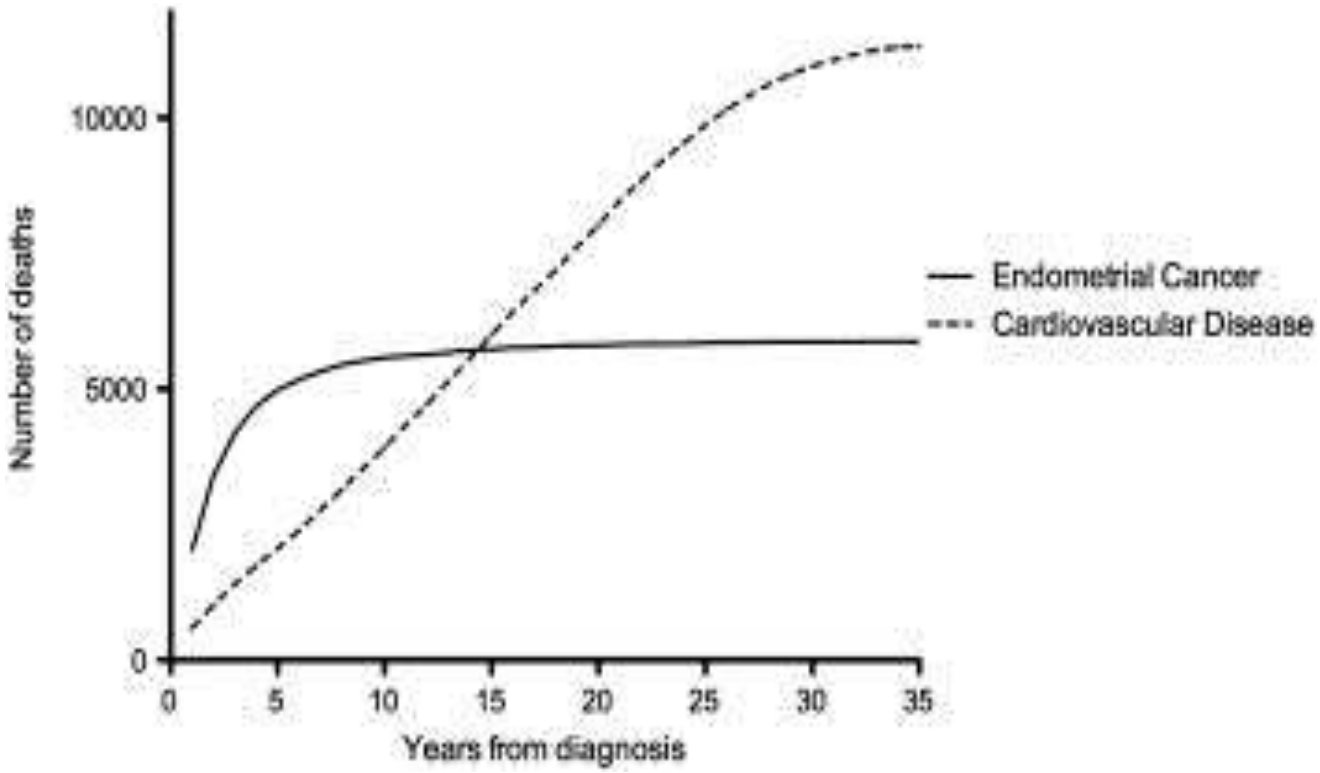
Competing causes of death



Ward et al. Gynecol Oncol 2012.

Conclusions- early stage

Low risk:	Observe
Intermediate risk:	Brachytherapy alone
High risk:	EBRT +/- brachytherapy

For EBRT, IMRT is preferred as less acute and late PRO

Focus on the overall health for this population due to the high, competing risk of cardiovascular disease

PORTEC Extensive LVSI

Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer – A pooled analysis of PORTEC 1 and 2 trials

Tjalling Bosse [a,1], Elke E.M. Peters [a,1], Carien L. Creutzberg [b], Ina M. Jürgenliemk-Schulz [c], Jan J. Jobsen [d], Jan Willem M. Mens [e], Ludy C.H.W. Lutgens [f], Elzbieta M. van der Steen-Banasik [g], Vincent T.H.B.M. Smit [a], Remi A. Nout [b,*]

European Journal of Cancer (2015) 51, 1742–1750

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PORTEC Extensive LVSI

Substantial LVSI the strongest independent prognostic factor for pelvic regional recurrence

Tier	5yr pelvic recurrence rate
No LVSI	1.7%
Focal LVSI	2.5%
Substantial LVSI	15.3%

Substantial LVSI is also an independent prognostic factor for

- Distant Metastasis
- Overall Survival

PORTEC Extensive LVSI

Subgroup analysis of Substantial LVSI group

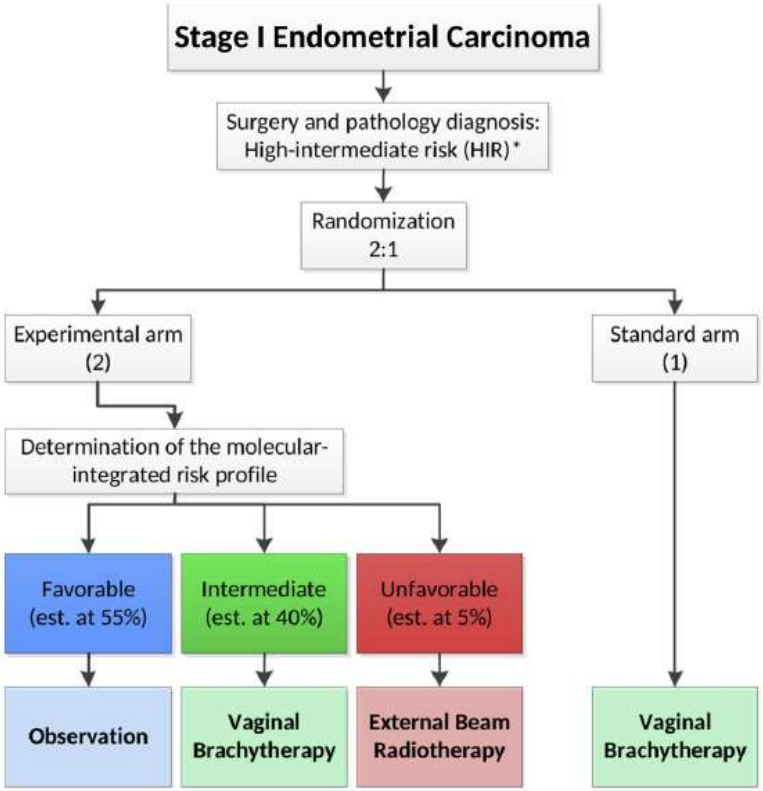
- EBRT improves rate of pelvis regional recurrence
- Vaginal Brachytherapy does not

Treatment	5yr pelvic recurrence rate
No Additional Treatment	30.7%
Vaginal Brachytherapy	27.1%
EBRT to the pelvis	4.3%

Adjuvant Pelvic EBRT is indicated in patients who have substantial/multifocal LVSI

PORTEC 4

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

Is the risk of substantial LVSI in stage I endometrial cancer similar to PORTEC in the North American population? - A single-institution study- Beriwal et al Gyne onc 2021

A retrospective review was conducted on patients with clinically uterine-confined, endometrioid type endometrial cancer who underwent surgical staging and were found to have pT1a-b disease.

In the overall cohort and in the subset meeting PORTEC-1 inclusion criteria (n = 195), no LVSI was present in 67.4% and 50.8%; focal LVSI was present in 16.7% and 24.1%; and substantial LVSI was present in **16.0% and 25.1%,** respectively.

Among patients who underwent surgical LN assessment (79.2%, n = 347), LNs were involved in 3.3% without LVSI, 7.5% with focal LVSI (OR 2.4), and 15.2% with substantial LVSI (OR 5.3) (p = .005),.

Our incidence of substantial LVSI was three to five times higher than reported by PORTEC and correlated with LN involvement.

This questions the reproducibility of the three-tier LVSI reporting system and emphasizes the need for multi-institutional data outside PORTEC for confirmation of our findings.

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Adjuvant treatment for advanced stage endometrial cancer

RTOG 9708

Final analysis of RTOG 9708: Adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer

Kathryn Greven [a,*], Kathryn Winter [b], Kelly Underhill [c], Jim Fontenesci [d], Jay Cooper [e], Tom Burke [f]

Gynecologic Oncology 103 (2006) 155–159

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RTOG 9708

Final analysis of RTOG 9708: Adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer

Kathryn Greven [a,*], Kathryn Winter [b], Kelly Underhill [c], Jim Fontenesci [d], Jay Cooper [e], Tom Burke [f]

Gynecologic Oncology 103 (2006) 155–159

Purpose. A phase II study was completed by the RTOG to assess the feasibility, safety, toxicity, and patterns of recurrence and survival when chemotherapy was combined with adjuvant radiation for patients with high-risk endometrial cancer.

Materials and methods. Pathologic requirements included grade 2 or 3 endometrial adenocarcinoma with either >50% myometrial invasion, cervical stromal invasion, or pelvic-confined extrauterine disease. Radiation included 45 Gy in 25 fractions to the pelvis along with cisplatin (50 mg/m^2) on days 1 and 28. Vaginal brachytherapy was performed after the external beam radiation. Four courses of cisplatin (50 mg/m^2) and paclitaxel (175 mg/m^2) were given at 4-week intervals following completion of radiotherapy.

Results. Forty-six patients were entered between 10/97 and 4/99. Follow-up times range from 6.8 to 72 months with a median of 4.3 years. Maximum late toxicity was grade 1 in 16%, grade 2 in 41%, grade 3 in 16%, and grade 4 in 5%. At 4 years pelvic, regional and distant recurrence rates are 2%, 2%, and 19%, respectively. Overall survival and disease-free survival (DFS) rates at 4 years are 85% and 81%, respectively. Four-year rates for survival and DFS for Stage III patients are 77% and 72%, respectively. There have been no recurrences for patients with stage IC, IIA, or IIB.

Conclusion. Local–regional control is excellent following combined modality treatment in all patients suggesting additive effects of chemotherapy and radiation. Distant metastases continue to occur in more advanced staged patients. This regimen appears reasonable to be tested for efficacy in randomized studies.

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MaNGO ILIADE III + EORTC 55991

Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer – Results from two randomised studies

Thomas Hogberg [a,*], *Mauro Signorelli* [b], *Carlos Freire de Oliveira* [c], *Roldano Fossati* [d], *Andrea Alberto Lissoni* [e], *Bengt Sorbe* [f], *Håkan Andersson* [g], *Seija Grenman* [h], *Caroline Lundgren* [i], *Per Rosenberg* [j], *Karin Boman* [k], *Bengt Tholander* [l], *Giovanni Scambia* [m], *Nicholas Reed* [n], *Gennaro Cormio* [o], *Germana Tognon* [p], *Jackie Clarke* [q], *Tomasz Sawicki* [r], *Paolo Zola* [s], *Gunnar Kristensen* [t]

EUROPEAN JOURNAL OF CANCER 46 (2010) 2422–2431

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MaNGO ILIADE III + EORTC 55991

Two trials with similar design analyzed together

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

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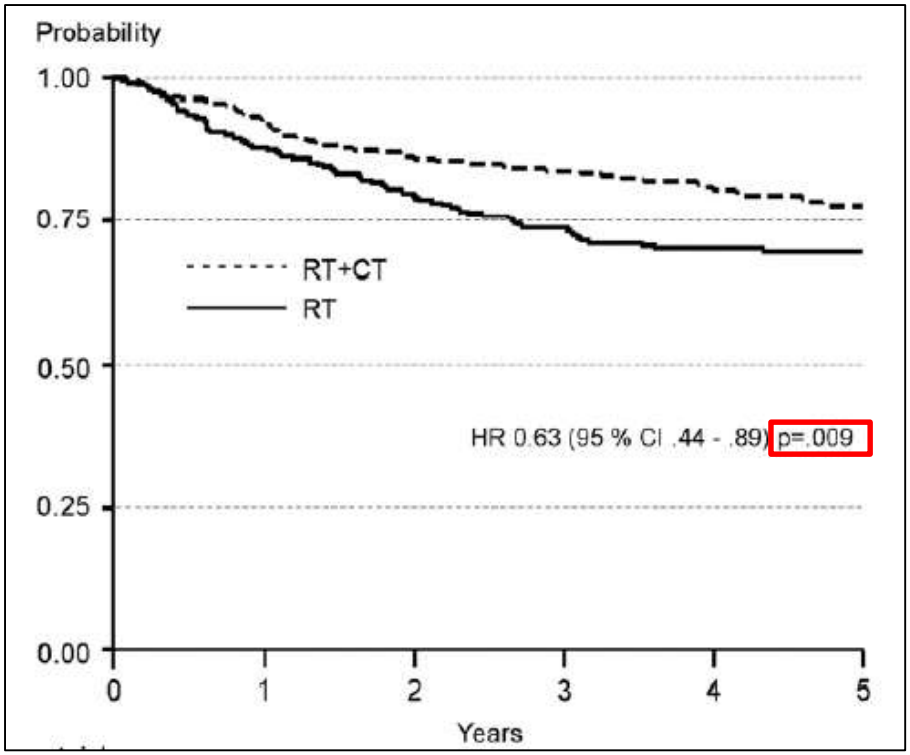
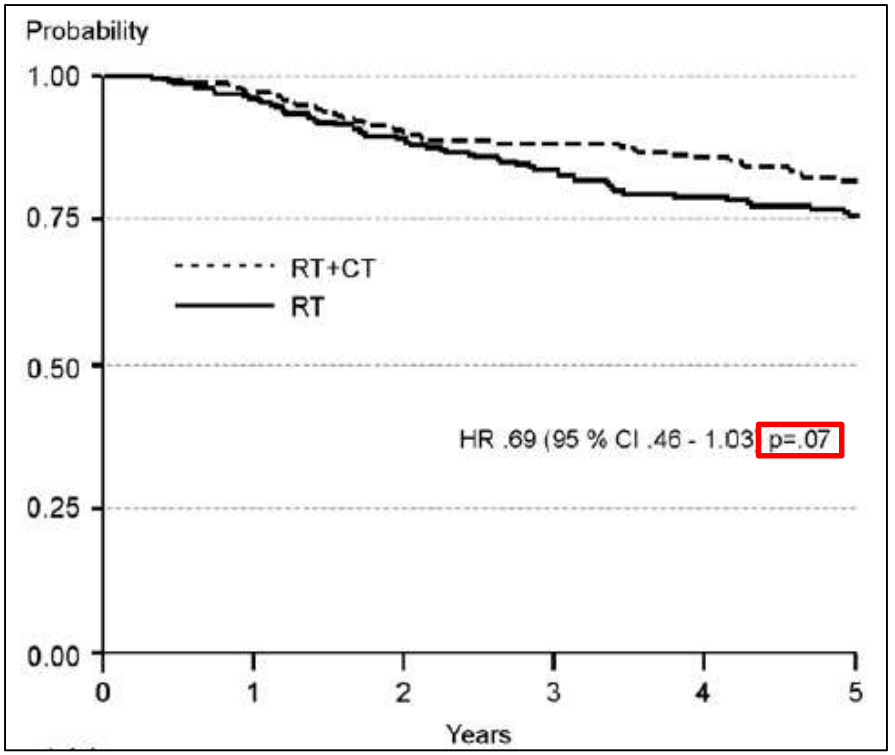
MaNGO ILIADE III + EORTC 55991

- Two trials with similar design analyzed together
- Inclusion Criteria
  - Stage I-III endometrial cancer
  - Primary treatment with surgery
  - No residual macroscopic tumor
- Randomized
  - Pelvic RT alone (≥44Gy)
  - RT with Chemotherapy
    - RT -> CTx in EORTC 55991
    - CTx -> RT in MaNGO ILIADE III

MaNGO ILIADE III + EORTC 55991





Sequential treatment improves PFS

But not OS…Trend

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	PORTEC 3	PORTEC 3	GOG 258	GOG 258
Inclusion	295/660 were stage III	295/660 were stage III	707/694	707/698
Treatment	EBRT alone 45-50.4 Gy	Concurrent chemo RT plus adjuvant chemo	Chemo alone	Concurrent chemo RT (45 Gy) plus adjuvant chemo
Brachytherapy boost	48%	46%		54%
Completion	98%	71-79%	85%	75%
DFS OS	68%/58% 76.7%	75%/69.3% 81.8%	58%	59%
Nodal relapse	3%/9.2%	2%/4.9%	13.5%/21%	6.2%/10%
Vaginal relapse	<1%	<1%	7%/4.9%	3%/1.9%
Distant metastases	28%	22%	21%	28%
Complications				

Adjuvant Therapy in 2021

- How to synthesize?
  - GOG-258:
    - No benefit to CMT over chemo alone
    - Higher DM vs. lower LRR (sequencing issue)
    - No subset analyses
  - PORTEC-3:
    - Benefit to CMT especially in stage III/serous over RT alone
    - Limited surgical staging
  - Applicability in SLNBx era?

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Chemo RT studies

Dose & Fractionation

GOG 249	PORTEC 3	GOG 258	RTOG 1203	NSGO/EORTC 55991	MaNGO ILIADE-III	Ontario "sandwich" trial
45-50.4Gy*	**48.6Gy/27fx**	**45Gy/25fx***	**45Gy/25fx or 50.4Gy/28fx**	**≥ 44Gy**	**Pelvic RT 45/25**	**45Gy/25fx**
None	Cisplatin x2c*	Cisplatin x2c*	Cisplatin x5c**	None	None	None
None	-> Chemo* (4c Carbo/Taxol)	Carbo/Pac x4c*	none	Various regimens*	doxorubicin 60 mg/m2 and cisplatin 50 mg/m2 Q3W x 3 cycles*	Pac/Carbo x4c & Pac/Carb x2c
BT boost: Cervical/serous /clear cell pts	10Gy/2fx when cervical involvement	Boost allowed	Physician discretion: 6Gy/2fx	Optional, decided before randomization	Cervical stromal invasion	Physician discretion: 5-7.5Gy/3fx

What do we do actually used in practice?

Sequential chemotherapy followed by RT

45 Gy in 25 fractions with IMRT followed by vaginal brachy of 5 Gy x 2

If persistent residual node after surgery sometimes do PORTEC3/GOG258 concurrent CTRT regimen

Volume of RT pelvic or pelvic plus PA based on nodal location and extent of PA nodal assessment

Molecular Classification

PORTEC 3 Molecular Classification

Methods

Parafinn-embedded tissue from 423 patients

Classified tumors as:

- P53 abdnormal (p53abn)
- POLE-ultramutated (POLEmut)
- MMR-deficient (MMRd)
- No specific molecular profile (NSMP)

Evaluate response to chemotherapy in each subset

- CRT vs. RT alone

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PORTEC 3 Molecular Classification

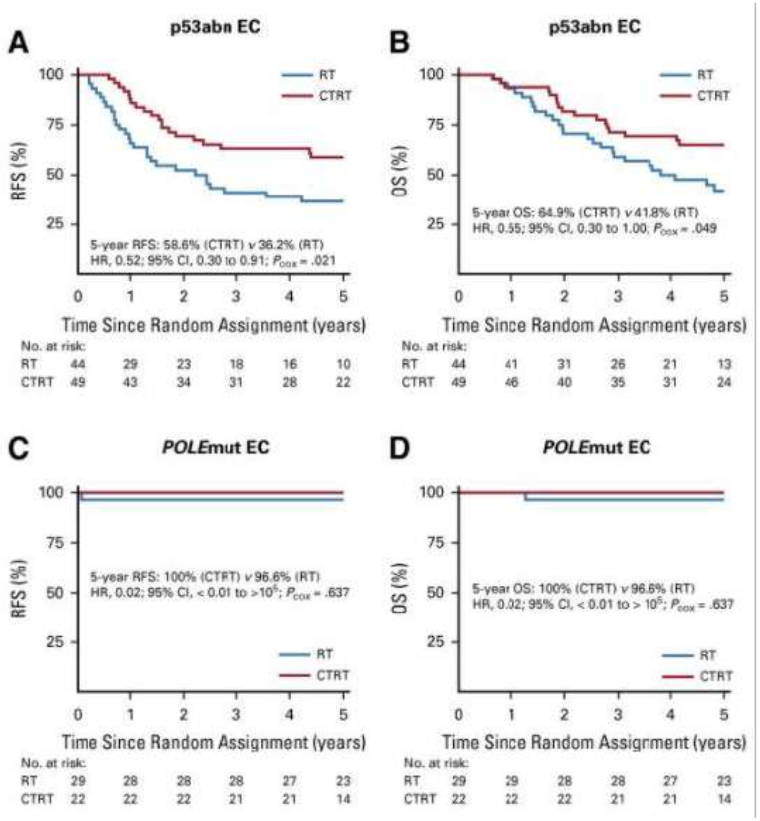
Risk of recurrence is dependent on the molecular profile

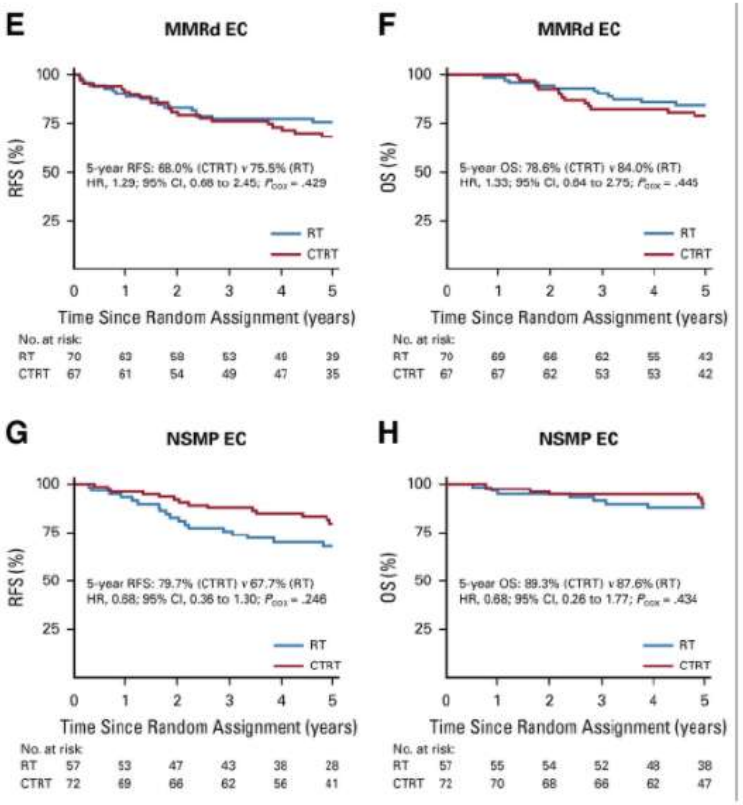
Molecular Classification	5yr RFS
POLEm	98%
NSMP	74%
MMRd	72%
P53	48%

PORTEC 3 Molecular Classification

Addition of chemotherapy to EBRT only improved 5yr outcomes for p53abn
RFS = 59% v 36%; OS = 65% v 42%

Slight trend to worse OS in MMRd





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ESGO/ESTRO guidelines

Endometrial cancer

Histopathological prognostic factors

Molecular classification known *	Stage I–II *POLE* -mutant no residual disease Stage IA, MMRd or NSMP, endometrioid, low-grade, with negative or focal LVSI	Stage IB, MMRd or NSMP, endometrioid, low-grade, with negative or focal LVSI Stage IA, MMRd or NSMP, endometrioid, high-grade, with negative or focal LVSI Stage IA, p53-abnormal, or non-endometroid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, or mixed), or any combination thereof, without myometrial invasion	Stage I, MMRd or NSMP, endometrioid with substantial LVSI, regardless of grade or depth of invasion Stage IB, MMRd or NSMP, endometrioid high-grade regardless of LVSI Stage II, MMRd or NSMP, endometrioid	Stage III–IVA, MMRd or NSMP, endometrioid with no residual disease Stage I–IVA, MMRd or NSMP, serous, undifferentiated carcinoma, or carcinosarcoma with myometrial invasion and no residual disease Stage I–IVA, p53-abnormal, with myometrial invasion and no residual disease	Stage III–IVA with residual disease of any molecular type Stage IVB of any molecular type

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ESGO/ESTRO guidelines

- **Stage I–II *POLE*mut endometrial carcinoma, no residual disease- low risk**

- **Stage IB–IVA p53abn endometrial carcinoma with myometrial invasion, with no residual disease- high risk**

- **For stage III–IVA *POLE*mut endometrial carcinoma insufficient data are available to allocate these patients to a prognostic risk group in the molecular classification**

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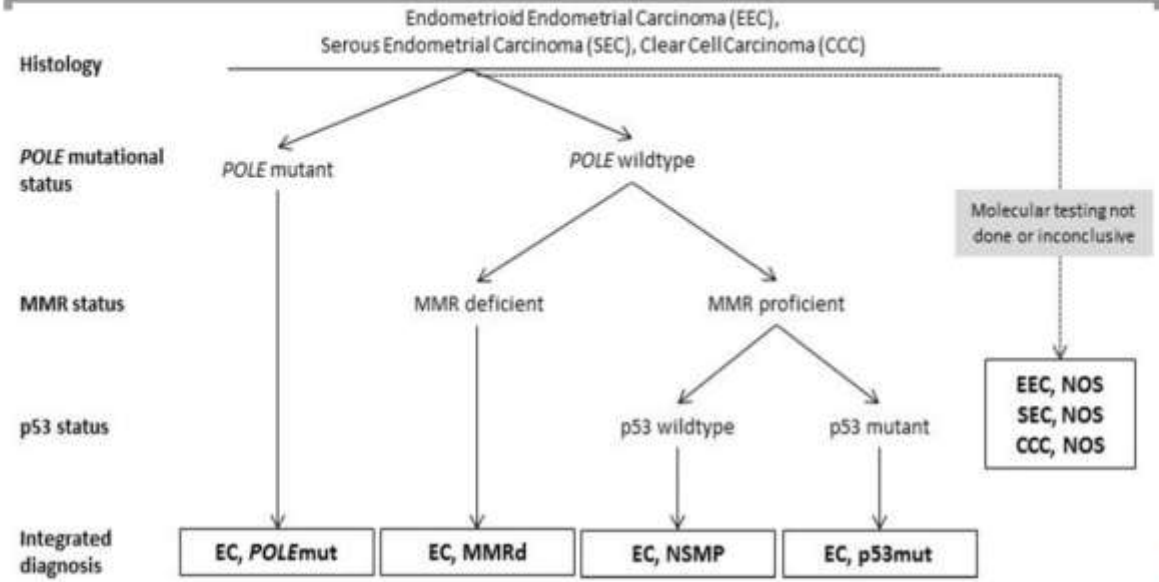
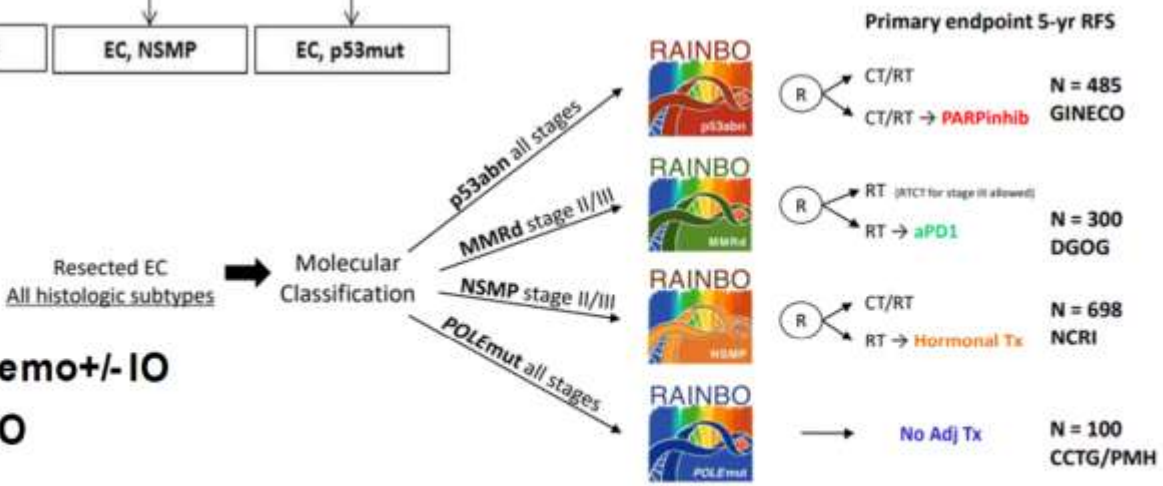
Rational Selection of Adjuvant Therapy





Also

GY-018 MMRd/MMRp → chemo+/-IO

GY-020 MMRd HIR → RT+/-IO

TAPER trial

Vermij Histopathology 2020
RAINBO Umbrella Program

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Future Directions

- GOG-3053[17]
  - Stage I/II Type II
  - Stage III/IVA Type IVA
  - Any p53mut
  - Chemotherapy ± pembrolizumab
    - VBT or XRT @ discretion of physician
  - Pembrolizumab vs placebo x6 cycles

17. Van Gorp T et al, JCO 2021.

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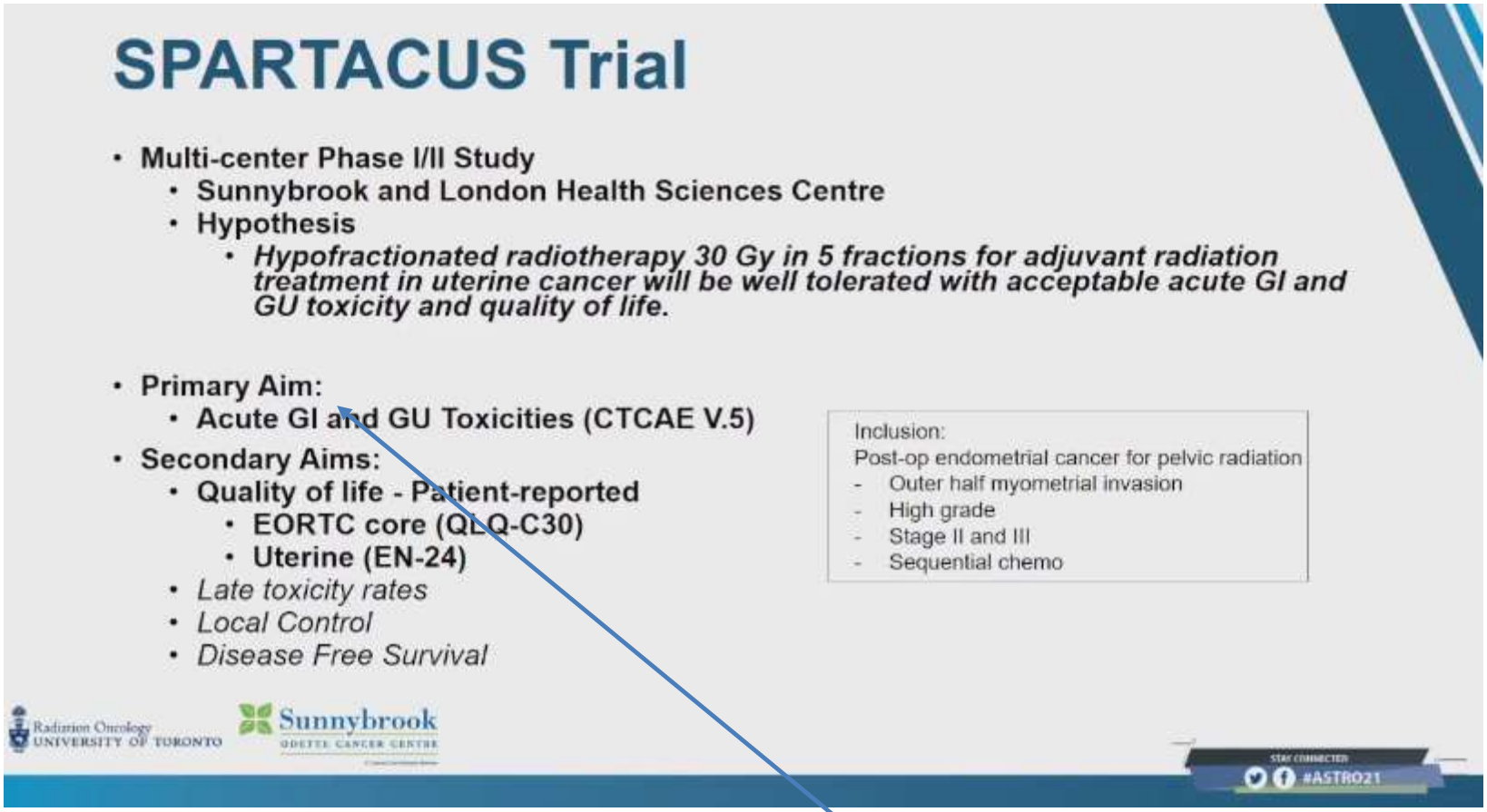
Future Directions

- GOG-3041/DUO-E[18]
  - Stage III (measurable)/IV
  - Chemotherapy ± durvalumab ± olaparib maintenance
  - No radiation

18. Westin SN et al, JCO 2020.

SPARTACUS



Goal of this Presentation at ASTRO

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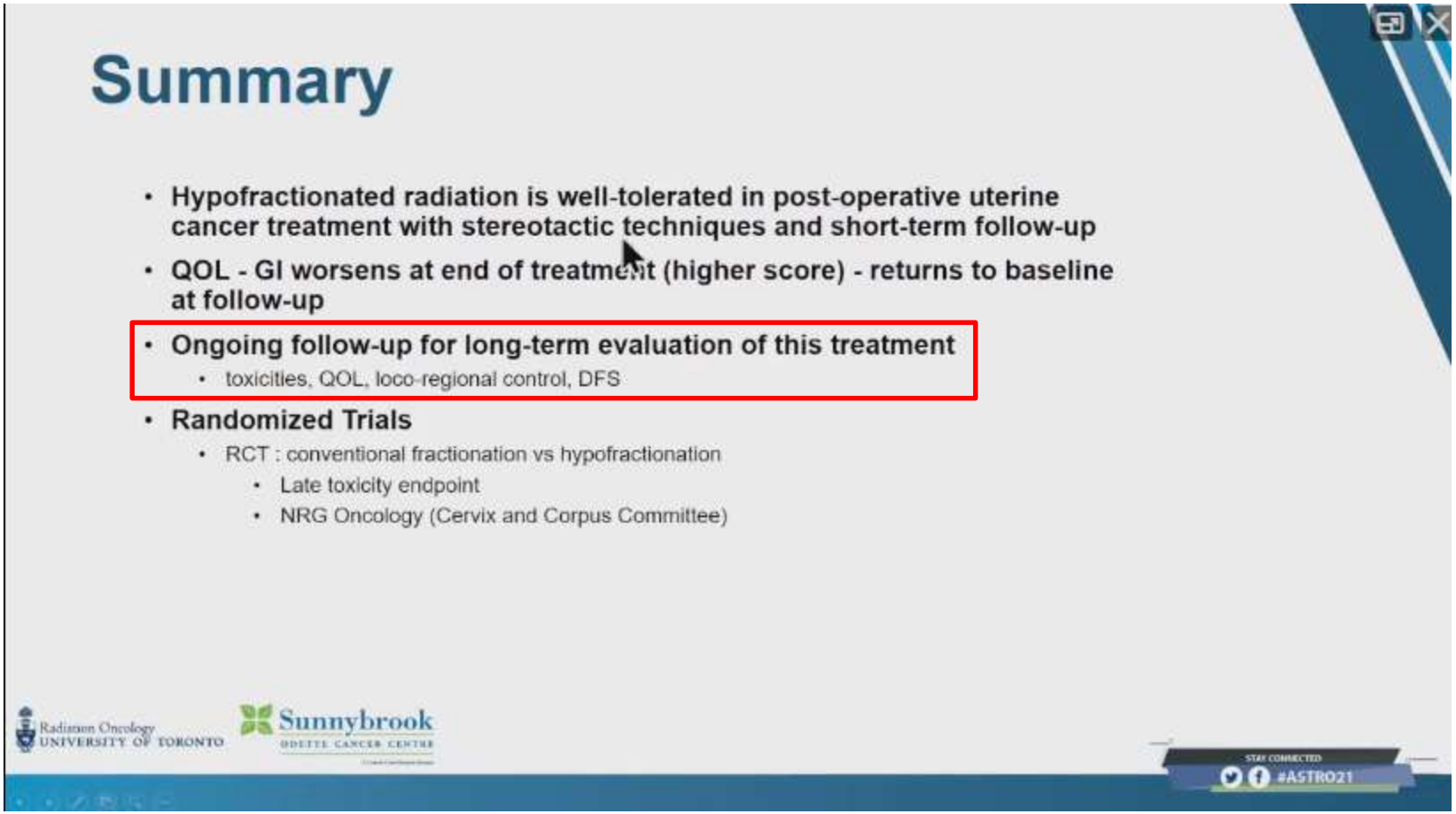
SPARTACUS



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THANK YOU for attention

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