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
Screening for Lynch syndrome

(A) Screening endometrial cancer for Lynch syndrome

Reflex testing of all endometrial tumours for MMR proteins by IHC

- MMR proficient
  - MMR proficient: MLH1 or PMS2 protein loss, or loss of both proteins (20%) or (6%)
  - Reflex testing of tumour for MLH1 hypermethylation
    - Present (~16%)
    - Absent (~4%)
  - Not Lynch syndrome (~97%)

- MMR deficient
  - MMR deficient: MSH2 or MSH6 protein loss, or loss of both proteins (~20%)
  - Lynch syndrome (~2%)
    - Cascade testing of family members
    - Cancer prevention interventions

(B) Preventing endometrial cancer in Lynch syndrome

- Aspirin
  - Red flag symptom awareness (empowers early help-seeking)
  - Annual transvaginal ultrasound with or without hysteroscopy plus endometrial biopsy (detects asymptomatic atypical hyperplasia or early-stage cancer)

- Lifestyle
  - Keep a healthy bodyweight
  - Take regular exercise
  - Avoid carcinogens (eg, smoking and alcohol)
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
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

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
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 ?
IA Grade 1 - Stage I-II Endometrioid Histology ITCs+ on SLNB alone without LND

IA Grade 1-2
- Observe (Consider vaginal BT in presence of focal LVSI)

IB Grade 1
- Vaginal BT

IA Grade 3
- EBRT+/-Vaginal BT

IB Grade 2-3 Stage II
- Observe (Consider vaginal BT in presence of focal LVSI)

EBRT in presence of substantial LVSI irrespective of extent of myometrial invasion or grade of disease
Adjuvant treatment for early stage endometrial cancer
Risk stratification

Low risk
Intermediate risk
High intermediate risk
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.

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

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

PORTEC 1


A. Diarrhea
B. Fecal leakage
C. Limitation in daily activities
D. Need to remain close to toilet
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

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

A

Global Health Status/QOL Scores (99% CI)

B

Role Functioning Scores (99% CI)

C

Social Functioning Scores (99% CI)

D

Sexual Activity (99% CI)
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

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 x 5 or 4 Gy x 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
## Chemo vs. EBRT for high/HIR

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

McMeekin et al. SGO 2014.
# GOG 249 (SGO 2014)

<table>
<thead>
<tr>
<th>AE</th>
<th>Gr 2 PXRT</th>
<th>Gr 2 VCB/C</th>
<th>Gr 3 PXRT</th>
<th>Gr 3 VCB/C</th>
<th>Gr 4 PXRT</th>
<th>Gr 4 VCB/C</th>
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<td>Constitutional Fatigue</td>
<td>25</td>
<td>60</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>1</td>
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<td>Weight Loss</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>GI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>17</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Vomiting</td>
<td>3</td>
<td>8</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Diarrhea/Constipation</td>
<td>33/1</td>
<td>16/21</td>
<td>8/0</td>
<td>5/1</td>
<td>0/0</td>
<td>0/0</td>
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<tr>
<td>Dehydration</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heme</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ANC</td>
<td>8</td>
<td>46</td>
<td>0</td>
<td>73</td>
<td>0</td>
<td>94</td>
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<tr>
<td>Hb</td>
<td>3</td>
<td>62</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>2</td>
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<td>PLT</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Febrile Neutropenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Neurologic Sensory</td>
<td>2</td>
<td>20</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
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
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.
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 2\(^{nd}\) 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 2\(^{nd}\) 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)

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## IMRT vs. 3D: Dosimetry

<table>
<thead>
<tr>
<th></th>
<th>↓ in volume receiving prescription dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bowel</td>
</tr>
<tr>
<td>Roeske</td>
<td>50%</td>
</tr>
<tr>
<td>Ahamad</td>
<td>40-63%</td>
</tr>
<tr>
<td>Chen</td>
<td>70%</td>
</tr>
<tr>
<td>Heron</td>
<td>51%</td>
</tr>
</tbody>
</table>
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
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)
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
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
Competing causes of death

- Endometrial Cancer
- Cardiovascular Disease

Years from diagnosis

Number of deaths

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

PORTEC Extensive LVSI

Substantial LVSI the strongest independent prognostic factor for pelvic regional recurrence

<table>
<thead>
<tr>
<th>Tier</th>
<th>5yr pelvic recurrence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No LVSI</td>
<td>1.7%</td>
</tr>
<tr>
<td>Focal LVSI</td>
<td>2.5%</td>
</tr>
<tr>
<td>Substantial LVSI</td>
<td>15.3%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5yr pelvic recurrence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Additional Treatment</td>
<td>30.7%</td>
</tr>
<tr>
<td>Vaginal Brachytherapy</td>
<td>27.1%</td>
</tr>
<tr>
<td>EBRT to the pelvis</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Adjuvant Pelvic EBRT is indicated in patients who have substantial/multifocal LVSI
PORTEC 4

NEW PORTEC 4

Stage I Endometrial Carcinoma

Surgery and pathology diagnosis: High-intermediate risk (HIR) *

Randomization 2:1

Experimental arm (2)

Determination of the molecular-integrated risk profile

- Favorable (est. at 55%)
- Intermediate (est. at 40%)
- Unfavorable (est. at 5%)

- Observation
- Vaginal Brachytherapy
- External Beam Radiotherapy

Standard arm (1)

- Vaginal Brachytherapy

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

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

Wortman, Gynecology Onc 2018
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.
Adjuvant treatment for advanced stage endometrial cancer
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 Fontenesce d, Jay Cooper e, Tom Burke f

Gynecologic Oncology 103 (2006) 155–159
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 Fontenesi 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 extraterine disease. Radiation included 45 Gy in 25 fractions to the pelvis along with cisplatin (50 mg/m²) on days 1 and 28. Vaginal brachytherapy was performed after the external beam radiation. Four courses of cisplatin (50 mg/m²) and paclitaxel (175 mg/m²) 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.
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
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
IIIB, IIIA(+cytology only excluded), IIIC
(included PA nodes)

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

Primary Endpoint: PFS
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
<table>
<thead>
<tr>
<th></th>
<th>PORTEC 3</th>
<th>PORTEC 3</th>
<th>GOG 258</th>
<th>GOG 258</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>295/660 were stage III</td>
<td>295/660 were stage III</td>
<td>707/694</td>
<td>707/698</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>EBRT alone 45-50.4 Gy</td>
<td>Concurrent chemo RT plus adjuvant chemo</td>
<td>Chemo alone</td>
<td>Concurrent chemo RT (45 Gy) plus adjuvant chemo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachytherapy boost</td>
<td>48%</td>
<td>46%</td>
<td></td>
<td>54%</td>
</tr>
<tr>
<td><strong>Completion</strong></td>
<td>98%</td>
<td>71-79%</td>
<td>85%</td>
<td>75%</td>
</tr>
<tr>
<td>DFS/OS</td>
<td>68%/58% 76.7%</td>
<td>75%/69.3% 81.8%</td>
<td>58%</td>
<td>59%</td>
</tr>
<tr>
<td>Nodal relapse</td>
<td>3%/9.2%</td>
<td>2%/4.9%</td>
<td>13.5%/21%</td>
<td>6.2%/10%</td>
</tr>
<tr>
<td>Vaginal relapse</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>7%/4.9%</td>
<td>3%/1.9%</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>28%</td>
<td>22%</td>
<td>21%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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?
# Chemo RT studies

## Dose & Fractionation

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

@kjopferma

[Allegeny Health Network]
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 abnormal (p53abn)
- POLE-ultramutated (POLEmut)
- MMR-deficient (MMRd)
- No specific molecular profile (NSMP)

Evaluate response to chemotherapy in each subset
- CRT vs. RT alone
PORTEC 3 Molecular Classification

Risk of recurrence is dependent on the molecular profile

<table>
<thead>
<tr>
<th>Molecular Classification</th>
<th>5yr RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLEm</td>
<td>98%</td>
</tr>
<tr>
<td>NSMP</td>
<td>74%</td>
</tr>
<tr>
<td>MMRd</td>
<td>72%</td>
</tr>
<tr>
<td>P53</td>
<td>48%</td>
</tr>
</tbody>
</table>
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
# ESGO/ESTRO guidelines

<table>
<thead>
<tr>
<th>Endometrial cancer</th>
<th>Histopathological prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular classification known *</td>
<td>Stage I–II&lt;br&gt; POLE - mutant no residual disease&lt;br&gt; Stage IA, MMRd or NSMP, endometrioid, low-grade, with negative or focal LVSI</td>
</tr>
<tr>
<td></td>
<td>Stage I, MMRd or NSMP, endometrioid with substantial LVSI, regardless of grade or depth of invasion&lt;br&gt; Stage IB, MMRd or NSMP, endometrioid high-grade regardless of LVSI&lt;br&gt; Stage II, MMRd or NSMP, endometrioid</td>
</tr>
<tr>
<td></td>
<td>Stage III–IVA with residual disease of any molecular type&lt;br&gt; Stage IVB of any molecular type</td>
</tr>
</tbody>
</table>
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
Rational Selection of Adjuvant Therapy

Histology

Endometrioid Endometrial Carcinoma (EEC), Serous Endometrial Carcinoma (SEC), Clear Cell Carcinoma (CCC)

POLE mutational status

- POLE mutant
- POLE wildtype

MMR status

- MMR deficient
- MMR proficient

p53 status

- p53 wildtype
- p53 mutant

Integrated diagnosis

- EC, POLEmut
- EC, MMRd
- EC, NSMP
- EC, p53mut

Molecular testing not done or inconclusive

EEC, NOS SEC, NOS CCC, NOS

Primary endpoint 5-yr RFS

GY-018 MMRd/MMRp → chemo+/- IO
GY-020 MMRd HIR → RT+/- IO
TAPER trial

Also

Vermij Histopathology 2020
RAINBO Umbrella Program
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

Future Directions

- GOG-3041/DUO-E\(^{18}\)
  - Stage III (measurable)/IV
  - Chemotherapy ± durvalumab ± olaparib maintenance
  - No radiation

SPARTACUS

SPARTACUS Trial

- Multi-center Phase I/II Study
  - Sunnybrook and London Health Sciences Centre
  - Hypothesis
    - *Hypofractionated radiotherapy 30 Gy in 5 fractions for adjuvant radiation treatment in uterine cancer will be well tolerated with acceptable acute GI and GU toxicity and quality of life.*

- Primary Aim:
  - Acute GI and GU Toxicities (CTCAE V.5)

- Secondary Aims:
  - Quality of life - Patient-reported
    - EORTC core (QLQ-C30)
    - Uterine (EN-24)
  - Late toxicity rates
  - Local Control
  - Disease Free Survival

Inclusion:
- Post-op endometrial cancer for pelvic radiation
  - Outer half myometrial invasion
  - High grade
  - Stage II and III
  - Sequential chemo

Goal of this Presentation at ASTRO
Summary

- Hypofractionated radiation is well-tolerated in post-operative uterine cancer treatment with stereotactic techniques and short-term follow-up
- QOL - GI worsens at end of treatment (higher score) - returns to baseline at follow-up
  - Ongoing follow-up for long-term evaluation of this treatment
    - toxicities, QOL, loco-regional control, DFS
- Randomized Trials
  - RCT: conventional fractionation vs hypofractionation
    - Late toxicity endpoint
    - NRG Oncology (Cervix and Corpus Committee)
THANK YOU for attention