17th ESO-ESMO Masterclass in clinical Oncology

Cervical and endometrial Cancer

Cristiana Sessa
IOSI Bellinzona, Switzerland

Berlin, March 28th, 2018
Presenter Disclosures

None
Cervical Cancer
Estimated Incidence, Mortality and Prevalence Worldwide in 2012
CERVICAL CANCER

Epidemiology

- In female in less developed countries
  second most commonly diagnosed
  third leading cause of cancer death
- Third most common cause of female mortality
- In 2012 worldwide
  527'600 new cases
  265'700 deaths
- In 2012 in Europe
  58'000 new cases
  24'000 cancer deaths
- Incidence and mortality higher in developing countries
  (85% of cases, 90% of deaths)
Cervical Cancer

Diagnosis and staging

- Bimanual P/V examination, colposcopy, biopsy and/or endocervical curettage (ECC)
- MRI: to determine tumor size, degree of stromal penetration, vaginal and corpus extension.
- CT: to detect pathologic lymphnodes
- Chest xray
- Cystoscopy, rectoscopy (stages IIB-IV)
FIGO Staging is based on the extent of tumor lesion

<table>
<thead>
<tr>
<th>Extent of Tumor</th>
<th>Stage 0</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Location</td>
<td>Carcinoma in situ</td>
<td>Confined to cervix</td>
<td>Disease beyond cervix but not to pelvic wall or lower 1/3 of vagina</td>
<td>Disease to pelvic wall or lower 1/3 of vagina</td>
<td>Invades bladder, rectum or metastasis</td>
</tr>
<tr>
<td>Stage at presentation</td>
<td></td>
<td>47%</td>
<td>28%</td>
<td>21%</td>
<td>4%</td>
</tr>
</tbody>
</table>

- Fallopian tube
- Uterine cavity
- Uterine wall
- Internal OS
- External OS
- Fundus
- Corpus
- Cervix
- Vagina
- Pelvic side wall
- Rectum
- Bladder
Survival by FIGO stage
CERVICAL CANCER
Histopathological assessment

Timer size stromal invasion / depth of the wall involved, tumour differentiation, LVSI, status of resection margin, status of parametrial and vaginal cuff, number and status of lymph nodes

Risk factors

- Tumour size
- Deep stromal invasion
- LVSI
- Positive margins
- Positive lymph nodes
- Microscopic parametrial involvement

Intermediate-risk
High-risk

17th ESO-ESMO Masterclass in Clinical Oncology
CERVICAL CANCER

ESMO algorithm for cervical cancer – Early stage

Positive Pap smear / HPV – high risk positive / suspected cervix

Colposcopy / Biopsy

CIN2 / CIN3

Conisation

Invasive cervical cancer

Early disease

FIGO IA1

Invasive disease

Radical hysterectomy

Simple hysterectomy + PLND + PALND

LVSI: simple hysterectomy + PLND + PALND

Only if negative margins

Adjuvant treatment depending on risk factors

FIGO IA2

Radical hysterectomy + PLND + PALND

Frozen section, tracheotomy, CRT

Adjunctive treatment depending on risk factors

FIGO IB2 + IIA

CIN, cervical intraepithelial neoplasia; CRT, chemoradiotherapy; LVSI, lymphovascular space invasion; PALND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection; RT, radiotherapy; SLN, sentinel lymph node.

ESMO Guidelines
Radical hysterectomy vs radiotherapy in patients with stage I B, II A cervical cancer

- DFS = disease-free survival; OS = overall survival


5-year OS (83%) and DFS (74%) did not differ significantly between the two groups

- DFS = disease-free survival; OS = overall survival
The addition of concurrent cisplatin-based chemotherapy to radiation therapy significantly improves PFS and OS for high-risk, early-stage patients who undergo radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix.
CERVICAL CANCER

ESMO algorithm for cervical cancer

CIN, cervical intraepithelial neoplasia; CRT, chemoradiotherapy; LVSI, lymphovascular space invasion; PALND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection; RT, radiotherapy; SLN, sentinel lymph node.

CRT standard of care

CT (C) RT
Pelvic exenteration

CT + bevacizumab standard of care

RT

ESMO Guidelines
The results of 5 large studies have shown that women with bulky IB₂-IVA cervical cancer have better survival when they receive chemotherapy which includes the drug cisplatin along with radiation therapy.
CERVICAL CANCER

Concurrent chemoradiotherapy for cervical cancer: a meta-analysis of 18 randomized trials

- Greater effect for stage IB2-IIA/IIB with 10% survival improvement, 3% for stage III / IVA

- Better results for platinum based therapy (40mg / m² / wk)

- Greater benefit in overall survival with additional adjuvant CT (to be confirmed in ongoing studies: INTERLACE)
CISPLATIN CHEMORADIOThERAPY VS RADIOTHERAPY IN FIGO STAGE IIIB SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX
A RANDOMIZED CLINICAL TRIAL

SHRIVSTAVA S. ET AL

Jama Oncol, 2018
STUDY DESIGN
Open label phase randomized III Trial

INCLUSION CRITERIA
- FIGO Stage IIIB
- Squamous carcinoma histology
- Age > 18 years and < 65 years
- WHO performance status: 0 or 1
- Hemoglobin > 10 gm %
- Normal WBC and platelet counts
- Normal renal functions

Exclusion Criteria
- Bilateral Hydronephrosis
- HIV positive
- Medical Renal Disease
- Gross PA nodes on Imaging

STUDY ARM
Concomitant Chemo-radiation
(Cisplatin weekly 40 mg/m² for 5 cycles atleast)
N = 424

STANDARD ARM
Definitive Radiation
N = 426

1:1 randomization

Definitive Radiation:
- External Beam: 50 Gy / 25 # (MLB at 40 Gy when ever feasible)
- Brachytherapy: LDR (25-30 Gy to point ‘A’ 1#) or HDR (7 Gy to point ‘A’ x 3# once weekly)
- Total RT (Physical) Doses: 76 Gy – 81 Gy (LDR Equivalent) to Point ‘A’*

Overall Survival by Arms: ITT Analysis

Overall survival at 5 years
- Chemo-radiation arm: 54% (95% CI, 53.95 – 54.05)
- Radiation Arm: 46% (95% CI, 45.95 – 46.05)

HR=0.82 (95% CI = 0.68 - 0.98), p=0.033
CONCLUSIONS

- Our study is the largest trial in a homogenous group of advanced stage (IIIB) cervical cancer to prove the benefit of relatively simple and well tolerated concomitant cisplatin chemotherapy regimen over adequately delivered radiation therapy.

*Our study confirms that concomitant weekly cisplatin based chemo-radiation should be the standard of care in FIGO Stage IIIB Squamous Cell Cervical Cancer*
CERVICAL CANCER
ESMO algorithm for cervical cancer

CIN, cervical intraepithelial neoplasia; CRT, chemoradiotherapy; LVSI, lymphovascular space invasion; PALND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection; RT, radiotherapy; SLN, sentinel lymph node.

CRT standard of care

CT (C) RT
Pelvic exenteration

CT + bevacizumab standard of care

ESMO Guidelines
CERVICAL CANCER

Phase III trial four cisplatin-containing doublet combinations in stage IVB, recurrent or persistent cervical carcinoma

Conclusion: Experimental arms NOT superior – Trend favors control arm of cisplatin/paclitaxel

Monk et al., JCO, 2009
CERVICAL CANCER

GOG 240: final protocol-specified Overall survival
Cisplatin-Paclitaxel versus Cisplatin-Paclitaxel-Bevacizumab

<table>
<thead>
<tr>
<th></th>
<th>Cis+Pac (n=114)</th>
<th>Cis+Pac+Bev (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>92 (81)</td>
<td>83 (72)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>15.0</td>
<td>17.5</td>
</tr>
<tr>
<td>HR</td>
<td>0.73 (95% CI, 0.54–0.99)</td>
<td><em>P</em> = 0.04</td>
</tr>
</tbody>
</table>

Months on Study

Bev, bevacizumab; CI, confidence interval; cis, cisplatin; HR, hazard ratio; OS, overall survival; pac, paclitaxel.

Tewari et al ESMO Madrid 2014
**CERVICAL CANCER**

Randomised trial comparing cisplatin/paclitaxel with carboplatin/paclitaxel: a non inferiority study (JCOG 0505)

| Stage IV B, persistent or recurrent cervical cancer, not amenable to curative surgery radiotherapy | Standard: TP  
| Paclitaxel 135 mg/m² 24h d1  
| Cisplatin 50 mg/m² d2  |
| Balancing factors:  
| Tumors outside of the prior irradiation field (yes or no)  
| PS 0-1 or 2  
| SCC or non SCC  
| Institution  | Every 21 days for 6 cycles  
| Experimental: TC  
| Paclitaxel 175 mg/m² 3h d1  
| Carboplatin AUC 5 d1  |
Randomised trial comparing cisplatin/paclitaxel with carboplatin /paclitaxel: a non inferiority study (JCOG 0505)

Stage IV B, persistent or recurrent cervical cancer, not amenable to curative surgery radiotherapy

Balancing factors:
- Tumors outside of the prior irradiation field (yes or no)
- PS 0-1 or 2
- SCC or non SCC
- Institution

Standard: TP
- Paclitaxel 135 mg/m² 24h d1
- Cisplatin 50 mg/m² d2
- Every 21 days for 6 cycles

Experimental: TC
- Paclitaxel 175 mg/m² 3h d1
- Carboplatin AUC 5 d1
Cisplatin / paclitaxel versus carboplatin/paclitaxel in metastatic or recurrent cervical cancer

Overall survival

Kitagawa et al, JCO, 2015.
Cisplatin / paclitaxel versus carboplatin/paclitaxel in metastatic or recurrent cervical cancer

Subgroups analysis of overall survival

<table>
<thead>
<tr>
<th>Category</th>
<th>TP (n)</th>
<th>TC (n)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>56</td>
<td>48</td>
<td>1.16</td>
<td>0.77 to 1.75</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>67</td>
<td>73</td>
<td>0.94</td>
<td>0.65 to 1.38</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>94</td>
<td>91</td>
<td>0.90</td>
<td>0.65 to 1.24</td>
</tr>
<tr>
<td>1 or 2</td>
<td>29</td>
<td>30</td>
<td>1.44</td>
<td>0.94 to 2.47</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>102</td>
<td>100</td>
<td>0.96</td>
<td>0.71 to 1.29</td>
</tr>
<tr>
<td>Non-SCC</td>
<td>21</td>
<td>21</td>
<td>1.28</td>
<td>0.68 to 2.48</td>
</tr>
<tr>
<td>Nonirradiated tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one tumor</td>
<td>79</td>
<td>73</td>
<td>0.97</td>
<td>0.69 to 1.37</td>
</tr>
<tr>
<td>is nonirradiated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All the tumors are irradiated</td>
<td>44</td>
<td>48</td>
<td>1.03</td>
<td>0.65 to 1.64</td>
</tr>
<tr>
<td>Prior platinum therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (most CDDP)</td>
<td>69</td>
<td>68</td>
<td>0.69</td>
<td>0.47 to 1.02</td>
</tr>
<tr>
<td>No</td>
<td>64</td>
<td>53</td>
<td>1.57</td>
<td>1.06 to 2.32</td>
</tr>
<tr>
<td>Platinum-free interval, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>20</td>
<td>12</td>
<td>1.69</td>
<td>0.78 to 3.65</td>
</tr>
<tr>
<td>≥ 6, &lt; 12</td>
<td>18</td>
<td>22</td>
<td>0.57</td>
<td>0.29 to 1.11</td>
</tr>
<tr>
<td>≥ 12</td>
<td>21</td>
<td>34</td>
<td>0.71</td>
<td>0.38 to 1.38</td>
</tr>
<tr>
<td>No prior platinum therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>123</td>
<td>121</td>
<td>0.99</td>
<td>0.76 to 1.31</td>
</tr>
</tbody>
</table>

Kitagawa et al, JCO, 2015.
Why T-cell based immunotherapy is promising in cervical cancer?

The HPV oncoproteins E6 and E7 are attractive therapeutic targets because:

- Completely foreign viral protein
- No antigen loss

Still limited results with vaccines because of low vaccine induced immune-response and tumor mediated immuno-suppression.
Immunotherapy for cervical cancer

Several T cell based immunotherapy approaches in early clinical trials

- Checkpoint inhibitors / immune modulators
- Therapeutic vaccines
  - Bacterial vector
  - Viral vector
  - Peptide / protein based
- Adoptive T cell therapy
Emerging strategies in recurrent cervical cancer immune checkpoint inhibitors

Pembrolizumab in patients with advanced cervical Ca
Phase 1b Keynote-028 study

Key eligibility criteria
- Unresectable or metastatic Cervical Ca
- Failure of standard therapy
- PD-L1 positive

Primary endpoints
ORR (Recist)

Pembrolizumab
10mg/Kg IV
q 2 wks

CR, PR, SD
Continue for 24 mos or PD

PD
Unacceptable toxicity
Off study

Frenel, JCO 2017
**Pembrolizumab in patients with advanced cervical cancer**

**STUDY RESULTS**

<table>
<thead>
<tr>
<th>Patients treated (%) (n=24)</th>
<th>Antitumor activity (%)</th>
<th>Grade 3 TRAE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic disease</td>
<td>63 ORR</td>
<td>17 Any</td>
</tr>
<tr>
<td>Prior RT</td>
<td>96 PR</td>
<td>17 Rash</td>
</tr>
<tr>
<td>Prior lines CT (≥3)</td>
<td>38 SD</td>
<td>13 Colitis</td>
</tr>
<tr>
<td>Prior Bev</td>
<td>42 PD</td>
<td>67 Guillain Barrè</td>
</tr>
</tbody>
</table>

Median response duration 26 wks (18-52)

Frenel, JCO 2017
Endometrial cancer

Epidemiology

- The most common gynecological cancer in Western countries
- Incidence 13/100'000 women/yr Europe
- Mortality 2-3/100'000 women/yr
- 80-90% post menopausal; 5% in <40 yrs old
- Median age 63 yrs
- 80% Stage I 5yr survival 95%
- 10% stage IV 5 yr survival 17%

Risk factors
- RR 1.89
- nulliparity, early menarche/late menopause, diabetes
- treatment with tamoxifen in postmenopause

Genetic susceptibility
- Lynch syndrome/ Hereditary Non-Polyposis
- Colorectal Cancer: 40-60% lifetime risk of both endometrial and CRC
**Endometrial cancer**

<table>
<thead>
<tr>
<th>Clinical, endocrinological, and morphological components (Bokhman classification²)</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>60–70%</td>
<td>30–40%</td>
</tr>
<tr>
<td>Reproductive function</td>
<td>Decreased</td>
<td>No disturbances</td>
</tr>
<tr>
<td>Onset of menopause</td>
<td>After age 50 years</td>
<td>Younger than age 50 years</td>
</tr>
<tr>
<td>Background endometrium</td>
<td>Hyperplasia</td>
<td>Atrophy</td>
</tr>
<tr>
<td>Oestrogen associated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Associated obesity, hyperlipidaemia, and diabetes mellitus</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tumour grade</td>
<td>Low (grades 1–2)</td>
<td>High (grade 3)</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td>Superficial</td>
<td>Deep</td>
</tr>
<tr>
<td>Potential for lymphogenic metastatic spread</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Favourable</td>
<td>Unfavourable</td>
</tr>
<tr>
<td>Sensitivity to progestagens</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Outcome (5-year survival)</td>
<td>86%</td>
<td>59%</td>
</tr>
<tr>
<td>Prototypical histological type</td>
<td>Endometrioid</td>
<td>Serous</td>
</tr>
<tr>
<td>Oestrogen-receptor or progesterone-receptor expression</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td>Early (FIGO stage I–II)</td>
<td>Advanced (FIGO stage III–IV)</td>
</tr>
</tbody>
</table>
### Four genomic classes

<table>
<thead>
<tr>
<th>Copy-number aberrations</th>
<th>POLE (ultramutated)</th>
<th>MSI (hypermutated)</th>
<th>Copy-number low (endometrioid)</th>
<th>Copy-number high (serous-like)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSL/MLH1 methylation</td>
<td>Low</td>
<td>Mixed MSH high, low, stable</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Mutation rate</td>
<td>Very high (232 × 10^6 mutations/Mb)</td>
<td>High (18 × 10^5 mutations/Mb)</td>
<td>Low (2.9 × 10^6 mutations/Mb)</td>
<td>Low (2.3 × 10^6 mutations/Mb)</td>
</tr>
<tr>
<td>Genes commonly mutated</td>
<td>POLE (100%)</td>
<td>PTEN (88%)</td>
<td>PTEN (77%)</td>
<td>TP53 (92%)</td>
</tr>
<tr>
<td>(prevalence)</td>
<td>PTEN (94%)</td>
<td>RPL22 (37%)</td>
<td>CTNNB1 (52%)</td>
<td>PPP2R1A (22%)</td>
</tr>
<tr>
<td></td>
<td>PIK3CA (71%)</td>
<td>KRAS (35%)</td>
<td>PIK3CA (53%)</td>
<td>PIK3CA (47%)</td>
</tr>
<tr>
<td></td>
<td>PIK3R1 (65%)</td>
<td>PIK3CA (54%)</td>
<td>PIK3R1 (33%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FBXW7 (82%)</td>
<td>PIK3R1 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARID1A (76%)</td>
<td>ARID1A (37%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
<td>Endometrioid</td>
<td>Endometrioid</td>
<td>Endometrioid</td>
<td>Serous, endometrioid, and mixed serous and endometrioid</td>
</tr>
<tr>
<td>Tumour grade</td>
<td>Mixed (grades 1-3)</td>
<td>Mixed (grades 1-3)</td>
<td>Grades 1 and 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>Good</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Cancer Genome Atlas Research Network

Comprehensive genomic and transcriptomic analysis of endometrial cancer

Murali R, Lancet Oncol, 2014
## ENDOMETRIAL CANCER

### Risk factors for adjuvant therapy

<table>
<thead>
<tr>
<th>LOE</th>
<th>Stage</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>I</td>
<td>Endometrioid + gr 1-2 + &lt;50% myometrial invasion + LVSI neg</td>
</tr>
<tr>
<td>Low</td>
<td>I</td>
<td>Endometrioid + gr 1-2 + ≥50% myometrial invasion + LVSI neg</td>
</tr>
<tr>
<td>High</td>
<td>II</td>
<td>Endometrioid + gr 3 + &lt;50% myometrial invasion, regardless of LVSI status</td>
</tr>
<tr>
<td>High</td>
<td>II</td>
<td>Endometrioid + gr 1-2 + LVSI unequivocal positive, regardless of depth of invasion</td>
</tr>
<tr>
<td>High</td>
<td>I</td>
<td>Endometrioid + gr 3 + ≥50% myometrial invasion, regardless of LVSI status</td>
</tr>
<tr>
<td>Adv</td>
<td>I</td>
<td>Stage II &amp; stage III no residual disease</td>
</tr>
<tr>
<td>M+</td>
<td>I</td>
<td>Non endometrioid (serous or clear cell or undifferentiated carcinoma, carcinosarcoma)</td>
</tr>
<tr>
<td>M+</td>
<td>I</td>
<td>Stage III residual disease &amp; IVa</td>
</tr>
<tr>
<td>M+</td>
<td>I</td>
<td>Stage IVB</td>
</tr>
</tbody>
</table>

**FIGO 2009 staging used**

- Molecular factors were considered but not included
- Tumor size was considered but not included
- Nodal status may be considered for treatment recommendations
PORTEC 3

Phase III trial comparing concurrent chemo radiation (CTRT) and adjuvant CT with pelvic RT alone in high-risk and advanced stage endometrial carcinoma (EC) S. de Boer et al.

Question

Is the combination of RT and CT better than RT alone in improving PFS and OS in high-risk EC patients?

ASGO 2017
PORTEC 3

Trial design

High risk Endometrial Cancer (HREC)

Pelvic RT 48.6 Gy + 2x Cisplatin 50mg/m²
4x Carboplatin AUC5 Paclitaxel 175mg/m²

- uniform treatment schedule
- upfront pathology review
- quality of life analysis
PorTEC 3

Inclusion criteria

- Endometrial carcinoma
  - stage I grade 3, with deep invasion or LVI+ 
  - stage II - III 
  - stage I-III serous or clear cell cancers (>25%)
- WHO PS 0-2
- No residual macroscopic tumor after surgery
- Pathology review before randomisation
### PORTEC 3

#### Tumour characteristics

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
<th>RT alone</th>
<th>CTRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrioid grade 1-2</td>
<td>39.7%</td>
<td>38.5%</td>
</tr>
<tr>
<td>Endometrioid grade 3</td>
<td>32.4%</td>
<td>32.4%</td>
</tr>
<tr>
<td>Serous/ clear cell/ other</td>
<td>28.2%</td>
<td>29.1%</td>
</tr>
<tr>
<td><strong>LVI/SI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58.2%</td>
<td>59.7%</td>
</tr>
<tr>
<td>No</td>
<td>41.8%</td>
<td>40.3%</td>
</tr>
<tr>
<td><strong>Stage (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>29.4%</td>
<td>29.7%</td>
</tr>
<tr>
<td>II</td>
<td>27.3%</td>
<td>24.2%</td>
</tr>
<tr>
<td>III</td>
<td>43.3%</td>
<td>46.1%</td>
</tr>
</tbody>
</table>
PORTEC 3

Survival (Os and FFS)

5 yr OS: 82% (CTRT) versus 77% (RT)

HR 0.79 [0.57-1.12], p=0.18

5 yr FFS: 76% (CTRT) versus 69% (RT)

HR 0.77 [0.58-1.03], p=0.078
PORTEC 3

Survival results per stage

Patients with stage III EC:
• Lower 5-year FFS and OS:
  • FFS: 64% stage III versus 79% for stage I-II (p<0.001)
  • OS: 74% vs 83% (p=0.003)

• Greatest benefit of CTRT
  • 5-year FFS 69% for CTRT vs 58% for RT
    [HR 0.66, 95% CI 0.45-0.97, p=0.032]
  • 5-year OS 79% vs 70%  
    [HR 0.69, 0.44-1.09, p=0.114]
PORTEC 3

Conclusions

- Risk reduction of 7% (FFS) and 5% (OS)
- Significant 11% FFS benefit with CTRT for stage III → Recommended
- Significant more toxicity with CTRT in the first 12 mos
- Good pelvic control with RT alone
- OS analysis may need a longer follow up
ENDOMETRIAL CANCER
Adjuvant treatment algorithm stage I

Low risk (stage I endometrioid G1-G2, <50% myometrial invasion):
No adjuvant treatment

Intermediate risk (stage I endometrioid, G1-G2, >50% myometrial invasion, LVSI neg.):
Adjuvant BT
No adjuvant BT is an option in younger patients
Surgical nodal staging performed, node negative: adjuvant BT, no BT is an option
No surgical node staging: adjuvant EBRT
If LVSI positive adjuvant BT for G3 and LVSI negative

High intermediate risk (stage I endometrioid, G3, <50% myometrial invasion or G1-G2 LVSI positive):
Surgical nodal staging performed, node negative: adjuvant EBRT, adjuvant CT can be considered
No surgical node staging: adjuvant EBRT with limited fields

High risk: stage I EEC (G3, >50% myometrial invasion):
No surgical nodal staging: adjuvant EBRT, adjuvant CT can be considered

BT = brachytherapy; EBRT = radiotherapy; LVSI: lymphovascular space invasion; CT: chemotherapy

ESMO Guidelines

ESMO-ESMO Masterclass in Clinical Oncology
ENDOMETRIAL CANCER

Adjuvant treatment algorithm stage II-III high-risk pts

- High risk stage II
- High risk stage III EEC no residual disease
- High risk non endometrioid (serous or clear cell or undifferentiated or carcinosarcoma)

Hysterectomy, surgical nodal staging performed node negative: G1-G2, LVSI negative vaginal BT
G3 or LVSI positive limited EBRT

No surgical nodal staging: adjuvant EBRT; G3 or LVSI positive consider adjuvant CT

III A, III B, III C1
CT + EBRT

III C2 CT + EBRT

Serous and clear cell after staging: stage I A, LVSI negative: vaginal BT
stage ≥ IB: EBRT + CT

Carcinosarcoma: CT, consider EBRT

ESMO Guidelines

RT green
CT + RT light blue
PORTEC 3

BT = brachytherapy; EBRT = radiotherapy; LVSI: lymphovascular space invasion; CT: chemotherapy
## Endometrial Cancer

### Advanced / Recurrent Disease Treatment Algorithms

<table>
<thead>
<tr>
<th>Isolated Vaginal Relapse</th>
<th>Central Local Relapse</th>
<th>Advanced / Metastatic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Only if optimal cytoreduction (RO) can be achieved</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exenteration considered for stage III A and central local relapse after RT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Resection of oligometastases if feasible</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Palliative surgery to alleviate specific symptoms</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard Treatment Curative RT</th>
<th>Radical RT for Primary Unresectable Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT + RT can be considered for high risk vaginal or pelvic nodal relapse</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Standard of care CT 6 cy carbo / tax</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Palliative RT to alleviate specific symptoms</strong></td>
<td></td>
</tr>
</tbody>
</table>

| No Biomarker Approved for Clinical Use; Biomarker Driven Clinical Trials Needed
| Hormonal treatment for G1 / G2 endometrioid hormone receptor positive in PTS without visceral involvement or rapidly PD |

**ESMO Guidelines**

*17th ESO-ESMO Masterclass in Clinical Oncology*
THANK YOU