ROLE OF RADIOTHERAPY IN CERVICAL AND ENDOMETRIAL CANCER

Vesna Plesinac Karapandzic
Institute of Oncology and Radiology of Serbia
ESO BELGRADE 2018
Introduction

Radiotherapy (RT) in gynaecological cancer
Cervical & Endometrial cancer

- In past decades the role of RT in the treatment of gynaecological cancer change based on:
  1. developments in other oncology modality (surgery, chemotherapy, target therapy...)
  2. Incorporation of imaging (PET-CT, MR..)
  3. new pathological features
  4. on implementation of new 3D conformal RT technique

- IMRT, IGRT, adaptive RT...
- image based brachytherapy (BT)

With Resultus:
- Better local tumour control
- Decreased adverse effects
- Better OS

Role of radiotherapy:
- **Adjuvant** (post-operative)
- **Definitive** (radical treatment)
- **Salvage** (locoregional recurrence post surgery)
- **Palliation**

- increase dose in target volume
- decrease dose in normal organ
RT in gynaecological cancer

Typically a combination of external beam whole pelvic RT (EBRT) & intracavitary brachytherapy (BT)
• EBRT - treat the primary tumor/tumor bed plus the regional lymphatics
• BT - boost the primary tumor/tumor bed safely to high doses

The art of radiation oncology: possibility to balance between the high probability to control tumor with the low probability of causing a side effect
  • accept some mild side effects to increase
  • Not accept high (severe) side effect
## Cervical cancer treatment options

**Management: Multidisciplinary**

### Clinical Staging

<table>
<thead>
<tr>
<th>Limited disease</th>
<th>Locally extended disease</th>
<th>Recurrence or persistent disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA/B1</td>
<td>IB2, IIA/B (&gt;4cm)</td>
<td>• Surgery</td>
</tr>
<tr>
<td>IIA/B (&lt;4cm)</td>
<td>IIA, IIIB, IVA, IVB</td>
<td>• Radiotherapy (Paliative)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiotherapy (postoperative or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>definitive)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiotherapy (Paliative)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chemotherapy</td>
</tr>
</tbody>
</table>

---

![Graph showing percentage of patients by stage and treatment options.](image-url)
3D-Conformal radiotherapy vs 2D

- 2 or 4 field (or more field)
- Avoidance of geographical miss
- More homogenous dose distribution
- Reduction of treated volume
- **OAR: limited sparing possible** (rectum, bladder, partly bowel)
- Change in irradiated volume
  - Non-adjacent tissues: larger volumes with small dose

4 versus 6 field technique: reduction in treated volume
The Role of IMRT - Intensity modulated radiotherapy

- Reduction of dose to normal structures - ‘conformal avoidance’
  - Less morbidity (less dose to bowel, bladder, bone marrow)
  - Larger volumes with small doses (clinical effect?)
- Deliver multiple dose levels at one time
  - Simultaneous in-field boost
  - Boost after large field
- Dose escalation – more dose in better defined target-improved disease control
- Mimicking brachytherapy distribution

Adjuvant RT- irradiation of pelvic lymph node
Urbano et al. British Journal of Radiology, 2004
TUMOR REGRESSION AND MOTION DURING RT

Uncertainties due to:
- Tumor regression during RT
- Tumor-uterus movement
- Organ movement (bowel, sigmoid)

AT ADVANCED STAGE DURING IMRT - REPETITIVE SECTIONAL IMAGING IS NECESSARY TO AVOID SIGNIFICANT CHANGES IN TOPOGRAPHY
Brachytherapy today

- Diferent:
  - applicators,
  - dose prescribing related to historical tradition (dose to point A)
  - dose rates, schedules and fractionation
- 2D planning BT at 80%
- Implementation of 3D CT/MR imaging
- based BT

CT/ MR compatible applicator:
- Combination of intracavitary and interstitial BT
3D- image based BT

- **MRI** - ability to define the tumour extension in relation to the applicator

- **CT/MRI compatible applicators**

- **GYN GEC ESTRO group** - developed a systematic approach for the 3D sectional imaging based BT treatment planning recommendations

- The aim:
  - an individualised adaption of dose distribution to the target and organ at risk

- **3D BT allowed: Dose escalation**
  - until dose volume constraints are reached for organ at risk (70-75Gy for 2cm³ rectum)
  - Until defined values are reached for CTV (D90 of 90Gy for HR-CTV)

HR-CTV 43,7cm³, D90 7,1Gy, D100 4,2 Gy, V100 90% - small tumors had better coverage by prescribed dose.

IORS
Outcome after radiotherapy ± chemotherapy and IGBT. (a) Local control, cancer specific survival and overall survival for all 156 patients. (b) Local control and tumour size. (c) Cancer specific survival for FIGO stages IB, IIB, IIIB. (d) Local control for FIGO stages IB, IIB, IIIB.

Actuarial rate for G3 + G4 morbidity was 2%/3% for the bladder, 4%/4% for the rectum, 0%/0%, for the bowel and 1%/3% for the vagina at 3/5 years, respectively.

Combination of image guided IC-BT and applicator guided IMRT. (with either interstitial brachytherapy or IMRT-patch-plan)

- provided dosimetrically options for boost
- dose coverage for large and/or topographically unfavourable cervical tumours could be significantly increased
- It depended on the patient anatomy which of the two techniques was the most favourable

- IMRT alone cannot be advocated as a replacement of BT for boost in cervical cancer.
  - IMRT alone with a tight margin of 3 mm significantly increased the volume irradiated to more than 60Gy

Assenholt M. A dose planning study on applicator guided stereotactic IMRT boost in combination with 3D MRI based brachytherapy in locally advanced Cervical cancer Acta Oncologica, 2008; 47: 1337-1343
ADJUVANT - POSTOPERATIVE PELVIC RT

- At patients with:

  - **Intermediate risk features**: presence of 2 of 3 risk features
    - Large tu size, LVI, deep stromal invasion
    - GOG 92 trial: 46% reduction in the risk of recurrence in the RT arm vs. observation arm and adverse effect in 7% vs 2.1%

  - **High risk**: positive lymph node, margins or parametria
    - Intergroup Trial SWOG, GOG and RTOG: OS 3-years-87% for st.Ia2,Ib,IIa with concurrent RT-CH (vs. 77% only RT group)
A Phase III Randomized Trial Of Postoperative Pelvic Irradiation In Stage Ib Cervical Carcinoma With Poor Prognostic Features: Follow-up Of A Gynecologic Oncology Group Study

Cumulative incidence of recurrences by treatment group:
- 24 RT patients and 43 OBS patients recurred.
- RT significantly reduced recurrence risk ($p=0.007$).
- OBS=observation; RT=irradiation.

Progression-free survival by treatment group:
- 30 RT patients and 49 OBS patients recurred or died.
- RT significantly increased progression-free survival ($p=0.009$).
- OBS=observation; RT=irradiation.

OS; n.s.

Rotman 2006
Concurrent Chemotherapy and Pelvic Radiation Therapy Compared With Pelvic Radiation Therapy Alone as Adjuvant Therapy After Radical Surgery in High-Risk Early-Stage Cancer of the Cervix

RT: 49.3 GY RT in 29 fractions to a standard pelvic field. Chemotherapy: consisted of bolus cisplatin 70 mg/m2 and a 96-hour infusion of fluorouracil 1,000 mg/m2/d every 3 weeks for four cycles, with the first and second cycles given concurrent to RT.

Progression-free survival for 127 patients randomized to receive CT + RT and for 116 patients randomized to receive RT alone. Overall survival for 127 patients randomized to receive CT + RT and for 116 patients randomized to receive RT alone.

Peters 2000
ADJUVANT CT-RT
GOG 109

• 243 pts.
• 5y. OS with CT (less evident at small tu)
  – tu < 2cm only 5% (77% vs. 82%)
  – tu > 2cm is 19% (58% vs 77%)
• 5y. OS benefit less evident at pts.
  – 1 positive LN. (79% vs 83%)
  VS.
  – 2 and more positive LN (55% vs 75%)

• Monk BJ Gynecol Oncol 2005; 96(3).
Postoperative HT-RT

Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a GOG / SWOG / RTOG trial.

Cervix Cancer GOG Scores: As a guide in utility of adjuvant RT at LN negative pts.

- score >120 - adjuvant whole pelvic RT with
- score 40-120 - consider for adjuvant central pelvic RT
- Score = Relative risks assigned to depth of tumour penetration x clinical tumour size x presence LVSI
G. Delgado et al. **Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study**. Gynecol Oncol, 1990; 38: 352-357

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depth of tumor penetration (mm)</strong></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
</tr>
<tr>
<td>5</td>
<td>7.2</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Middle</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>Deep</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
</tr>
<tr>
<td>12</td>
<td>37</td>
</tr>
<tr>
<td>14</td>
<td>41</td>
</tr>
<tr>
<td>16</td>
<td>45</td>
</tr>
<tr>
<td>18</td>
<td>49</td>
</tr>
<tr>
<td>19</td>
<td>54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical tumor size (cm)</strong></td>
<td></td>
</tr>
<tr>
<td>Occult tumor</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>3</td>
<td>2.4</td>
</tr>
<tr>
<td>4</td>
<td>2.9</td>
</tr>
<tr>
<td>6</td>
<td>4.4</td>
</tr>
<tr>
<td>8</td>
<td>6.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capillary-lymphatic space involvement</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*GOG score* is calculated by multiplying the relative risk for the depth × tumor size × capillary space involvement e.g. 8 mm superficial tumor, measuring 2 cm with LVS would be $26 \times 1.9 \times 1.7 = 84$.

Table 1. Delgado’s prognostic risk scoring system.

Relative risk of recurrence after radical hysterectomy for cervical cancer.
Elective / prophylactically/ RT - Occult involvement / from 5% at I b to 36% in IIlb/

Possible indications: positive PET scans, high pelvic lymph node involved (common iliac), gross nodal metastases in pelvis, bilateral positive pelvic node, adeno Ca histology with any number of positive pelvic lymph, planoCa with 4 positive pelvic lymph nodes

5 years-OS: 67% vs 55% /RTOG 7920 / and G3-4 complications 11% vs 2%

Therapeutic RT - long-term survival of 25% to 50%

Chemotherapy can be feasibly added with expected increased of acute toxicity

IMRT - extended of dose to 60-65Gy / conventional technique to 45Gy/
Individual radiosensitivity / genetics

• A variation in normal tissue radiosensitivity: some individuals being more sensitive (greater reactions) or respectively more resistant (less reactions) than the average.
  — first highlighted at patient with ataxiatelangiectasia who developed severe reactions to RT. Fibroblast from this individual show a marked sensitivity to radiation compared to fibroblasts from normal donors.
  — investigation of acute erythema in patients treated to the same radical dose show variation in response

• rapid reduction in cost of genotyping- increase interest in exploring new genes associated with toxicity.

• Prospective study of cervix cancer – SF2 of lymphocytes was significant prognostic factor for developing any late effects

• many studies at last 2 decades – try to confirm and measure radiosensitivity as a significant prognostic factor

• radiogenomics consortium establish in 2009/ consortium - should provide a route for developing studies and quality assurance procedures
Individual radiosensitivity / genetics

- affecting RT toxicity
- GSTP1 and GSTA1 genes associated with free radical causing alterations (processes have been linked with acute and late reactions following RT)
- TGFB1 has been the most widely studied gene (role in inflammatory response processes after irradiation and radiation-induced fibrosis)
- Although positive associations have been reported between genetic variation and risk of radiotherapy toxicity, validation analyses have often failed to confirm it

<table>
<thead>
<tr>
<th>Free radical scavenging</th>
<th>Anti-inflammatory</th>
<th>DNA damage recognition and cell cycle control</th>
<th>DNA damage repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT</td>
<td>TGFB1</td>
<td>ATM gene - 62 exons</td>
<td>XRCC1</td>
</tr>
<tr>
<td>SOD2</td>
<td>TNF</td>
<td></td>
<td>XRCC3</td>
</tr>
<tr>
<td>GSTP1</td>
<td></td>
<td></td>
<td>ERCC4</td>
</tr>
<tr>
<td>GSTA1</td>
<td></td>
<td></td>
<td>LIG4</td>
</tr>
<tr>
<td>GSTM1</td>
<td></td>
<td></td>
<td>RAD51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RAD52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>XRCC1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>XRCC2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>XRCC3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NBN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LIG4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA2</td>
</tr>
</tbody>
</table>
radiogenetic/radiogenomic studies predicts test

• long-term goal - develop a test that predicts the likelihood of a patient suffering side effects

• **Predictive clinical models are developed** - models integrate clinical (diabetes, age, smoking, hormonal therapy) and dosimetric (mean doses to critical normal tissues) data to estimate the probability of developing toxicity.

• models can easily be extended to incorporate genotyping data.

• such test should improve the therapeutic ratio of RT - by allowing dose escalation in radioresistant patients


**MATHEMATICAL/BIOLOGICAL MODELS**

Graphic representation of the Baglan–Robertson threshold model for risk of acute small bowel toxicity. Here, “low risk” implies 10% and “high risk” 40%. Note that the y-axis represents absolute volume of individual bowel loops and not the peritoneal space.
Radiotherapy- Secondary cancer

- 3 Studies - from Scandinavia, USA, and Japan.
- In high doses region
- **induced bladder cancer** - relative risk (RR) was about 1.6 (i.e. 60% greater) compared to the incidence in cervix cancer patients treated with nonradiation methods, and about 3.3 compared to the incidence of primary cancers in the general population.
- **induced rectal cancer** - RR values were about 1.2 and 1.5
- **induced colon cancer** - were about 1.0 and about 1.1.
- **RT cervical cancer patients** has a higher incidence for primary cancer in bladder and rectum than general population
- **IMRT concentrated RT dose** (increase dose in the tumor volume while sparing normal tissues) - potential to increase induced cancers
  - involves more fields and more monitor units
  - much higher in children (not be acceptable)
Cervical cancer

Results of treatment: 5 year survival approximately

- Stage I 80-90%
- Stage IIA - 78%, IIB - 65-70%
- Stage IIIA - 60%, IIIB - 34-52%
- Stage IVA - 0-20%

- Routine follow-up: early detect/treat recurrences and to diagnose treatment complications
  - Local only recurrence (node negative, mobile cervix) can be surgically salvaged

- After 5 years (without recurrence) annually visit (until to year 10)
INTRODUCTION
ENDOMETRIAL CANCER

• Majority of cases - stage I and II
• Stage III - in 5% to 10% of patients
• Stage IV - less than 5%
• Most common cell type is endometrioid adenocarcinoma (75%-80%)
• Clear cell, papillary serous and undifferentiated carcinoma are tumors with the worse prognosis
PROGNOSTIC FACTORS
demonstrated in GOG33- surgical pathologic study on 621 pts. St.I

- Tumor differentiation
- Myometrial invasion - strong correlation with lymph node involvement, distant metastases and is often independent of the degree of differentiation
- Involvement of the capillary - lymphatic space correlate with extrauterine and nodal spread of tumor
- Cervical spread
- Nodal spread
- Abdominal spread
- Age

GOG 33
- IA and IB high grade pathology: 5-9% positive LN
- IC or IIA 10-34% positive LN
**Myometrial invasion** - strong correlation with lymph node involvement, distant metastases and is often independent of the degree of differentiation

<table>
<thead>
<tr>
<th>Invasion</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Inner</td>
<td>3%</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Middle</td>
<td>0%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Deep</td>
<td>11%</td>
<td>19%</td>
<td>34%</td>
</tr>
</tbody>
</table>

---

Positive Pelvic LNs

<table>
<thead>
<tr>
<th>Invasion</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Inner</td>
<td>1%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Middle</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Deep</td>
<td>6%</td>
<td>14%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Creasman WT et al, Cancer 1984;60:2035
Corellation between pathologic factors and vaginal failure
Price 1965

<table>
<thead>
<tr>
<th></th>
<th>Vaginal Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>14%</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4.4</td>
</tr>
<tr>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>3</td>
<td>13.6</td>
</tr>
<tr>
<td>MI</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3.7</td>
</tr>
<tr>
<td>&lt; half</td>
<td>4.7</td>
</tr>
<tr>
<td>&gt; half</td>
<td>15.1</td>
</tr>
</tbody>
</table>

Number of pts. 41, stage I. Surgery sole Price et al. Am J Obstet Gynecol 1965;91:1060
RT  Management paradigm operabile stage FIGO I depend on risk groupe

• **Low Risk**
  – G1/2
  – Endometrioid histology
  – <50% myo invasion

• **Intermediate Risk**
  – G1/2 endometrioid AND >50% myo invasion
  – G3 endometrioid AND <50% myo invasion

• **High Risk**
  – G3 endometrioid AND >50% myo invasion
  – All Non endometrioid histology
Adjuvant Radiotherapy for Stage I Endometrial Cancer: An Updated Cochrane Systematic Review and Meta-analysis
Anthony Kong,* Nick Johnson, Henry C. Kitchener, Theresa A. Lawrie*
Manuscript received April 19, 2012; revised July 23, 2012; accepted July 25, 2012.


CONCLUSION
- routine EBRT cannot be recommended to improve survival in stage I endometrial carcinoma.
- further evidence may be needed for high risk or high–intermediate risk-
- No definitive conclusions about VBT
- VBT - useful in preventing vaginal tumor recurrence in high–intermediate subgroups compared with EBRT.

Adjuvant radiotherapy for stage I endometrial cancer (Review)
2015 The Cochrane Collaboration
Adjuvant Radiotherapy for Stage I Endometrial Cancer: An Updated Cochrane Systematic Review and Meta-analysis

Anthony Kong,* Nick Johnson, Henry C. Kitchener, Theresa A. Lawrie*

Manuscript received April 19, 2012; revised July 23, 2012; accepted July 25, 2012.

OVERALL SURVIVAL

0.2% differences in 5y. OS (87.7% in EBRT vs. 88% No EBRT)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>EBRT vs no additional treatment</th>
<th>EBRT</th>
<th>No EBRT</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio (IV, Random, 95% CI)</th>
<th>Hazard Ratio (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GOG 99</td>
<td>-0.15</td>
<td>0.25</td>
<td>190</td>
<td>0.25</td>
<td>202</td>
<td>15.0%</td>
<td>0.86 [0.53, 1.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PORTEC-1</td>
<td>0.2</td>
<td>0.2</td>
<td>354</td>
<td>0.2</td>
<td>360</td>
<td>23.5%</td>
<td>1.22 [0.83, 1.81]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>544</td>
<td></td>
<td>562</td>
<td>38.5%</td>
<td>1.06 [0.76, 1.48]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.01; Chi² = 1.20, df =</td>
<td>1</td>
<td>(P = .27)</td>
<td>P = 16%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>effect: Z = 0.33 (P = .74)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EBRT vs no additional treatment (VBT balanced across groups)</th>
<th>EBRT</th>
<th>No EBRT</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio (IV, Random, 95% CI)</th>
<th>Hazard Ratio (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTEC/EN.5 (1)</td>
<td>0.05</td>
<td>0.175</td>
<td>462</td>
<td>0.175</td>
<td>453</td>
<td>30.7%</td>
<td>1.05 [0.75, 1.48]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorbe 2011 (2)</td>
<td>-0.14</td>
<td>0.23</td>
<td>264</td>
<td>0.23</td>
<td>263</td>
<td>17.8%</td>
<td>0.87 [0.55, 1.36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>716</td>
<td>716</td>
<td></td>
<td></td>
<td></td>
<td>48.4%</td>
<td>0.96 [0.75, 1.29]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.00; Chi² = 0.43, df =</td>
<td>1 (P = .51)</td>
<td>P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.14 (P = .89)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EBRT vs VBT</th>
<th>EBRT</th>
<th>No EBRT</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio (IV, Random, 95% CI)</th>
<th>Hazard Ratio (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PORTEC-2 (3)</td>
<td>-0.16</td>
<td>0.268</td>
<td>214</td>
<td>0.268</td>
<td>213</td>
<td>13.1%</td>
<td>0.85 [0.50, 1.44]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>214</td>
<td>213</td>
<td></td>
<td></td>
<td></td>
<td>13.1%</td>
<td>0.85 [0.50, 1.44]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.60 (P = .55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI)                                     1474 | 1491 | 100.0% | 0.99 [0.82, 1.20] | 0.99 [0.82, 1.20] |

Heterogeneity: Tau² = 0.00; Chi² = 2.16, df = 4 (P = .71); P = 0%
Test for overall effect: Z = 0.06 (P = .95)
Test for subgroup differences: Chi² = 0.47, df = 2 (P = .79); P = 0%
(1) 54% in EBRT group and 52% in the No EBRT group received VBT
(2) All women received VBT. This trial expressed HRs in terms of VBT; we have expressed the HR in terms of EBRT.
(3) This trial expressed HRs in terms of VBT vs EBRT; we have expressed the HR in terms of EBRT.

Figure 2. Forest plot of hazard ratios (HRs) comparing overall survival (OS) for stage I endometrial carcinoma patients who received external beam radiotherapy (EBRT) treatment vs those who received no EBRT treatment. HRs for each trial are represented by the squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis random effect of all trials. Inverse variance (IV) and random effects methods were used to calculate HRs, 95% CIs, P values, and the test for overall effect; these calculations were two-sided. The χ² test was used to calculate heterogeneity. Random = random effects method; SE = standard error; VBT = vaginal brachytherapy.
2012 Cochrane meta-analysis of eight trials examining adjuvant RT in stage I EC showed no significant difference in OS (HR 0.88, 95% CI 0.63–1.22)
- the meta-analyses were underpowered in examining the impact of adjuvant RT on a specific high-intermediate or high-risk group.

Gupta et al. - to examine the relationship between adjuvant RT and OS specifically in HIR EC patient population by performing a retrospective analysis of the National Cancer Data Base (NCDB)
- 33,600 pts.
  - 18,070 patients (53.8%) received surgery alone
  - 15,530 patients (46.2%) received surgery + adjuvant RT.
    - adjuvant RT: 42.2% EBRT and 44.7% BT (13.1% EBRT+B)

5-year OS: 79.2% surgery alone group vs. 83.3% surgery + adjuvant RT (p < 0.0001). On multivariate analysis, adjuvant RT was independently associated with improved OS vs. surgery alone (HR 0.7; 95% CI 0.8–0.9, p < 0.0001).

Conclusion:
1. surgery+adjuvant RT was associated with a statistically significant 4.1% improvement in 5-year OS vs. surgery alone in stage I HIR EC.
2. the improvement in local control with adjuvant RT leads to improved OS.
Adjuvant radiation therapy is associated with improved overall survival in high-intermediate risk stage I endometrial cancer: A national cancer data base analysis

Vishal Gupta, MD *, Mary McGunigal, BA, Monica Prasad-Hayes, MD, Tamara Kalir, MD, PhD, Jerry Liu, MD

Icahn School of Medicine at Mount Sinai, Radiation Oncology, 1184 Fifth Avenue, 10029 New York, NY, United States

HIGHLIGHTS

• FIGO 2009 criteria
• Of the entire HIR cohort, 53.8% received surgery alone and 46.2% received surgery followed by adjuvant RT.
• 5y- OS HIR group was 81.0%.
  – **79.2% surgery alone vs. 83.3% surgery + adjuvant RT cohort (p < 0.0001)**

Overall survival of high intermediate risk patients who received surgery alone vs. surgery and adjuvant radiotherapy.
Adjuvant radiation therapy is associated with improved overall survival in high-intermediate risk stage I endometrial cancer: A national cancer database analysis☆

Vishal Gupta, MD *, Mary McGunigal, BA, Monica Prasad-Hayes, MD, Tamara Kalir, MD, PhD, Jerry Liu, MD

John School of Medicine at Mount Sinai, Radiation Oncology, 1184 Fifth Avenue, 10029 New York, NY, United States

HIGHLIGHTS

• Subgroup analysis - 5y OS according to ASTRO-ASCO guidelines
  - surgery + EBRT group 80.9%,
  - surgery+VB group 85.4%
  - surgery+EBRT/VB (combination) 81.5% (p < 0.0001).

Overall survival of high intermediate risk patients who received no adjuvant radiotherapy vs. external beam radiotherapy vs. vaginal brachytherapy vs. external beam radiotherapy + vaginal brachytherapy.
• **consensus conference on endometrial cancer** was held on 11-13 December 2014 in Milan, Italy, and comprised a multidisciplinary panel of 40 leading experts in the management of endometrial cancer.

**Recommendations**
What is the Current Best Definition of Risk Groups for Adjuvant Therapy?
ESMO-ESGO- ESTRO consensus conference
International Journal of Gynecological Cancer & Volume 26, Number 1, January 2016

What are the Best Evidence-Based Adjuvant Treatment Strategies for Patients With Low- and Intermediate-Risk Endometrial Cancer?

**Low-Risk** - no adjuvant treatment is recommended

**Intermediate-Risk**

- 1: Adjuvant brachytherapy is recommended to decrease vaginal recurrence
  - Level of evidence: I
  - Strength of recommendation: B

- 2: No adjuvant treatment is an option, especially for patients Aged less of 60 years
  - Level of evidence: II
  - Strength of recommendation: C

---

**TABLE 2. New risk groups to guide adjuvant therapy use**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Description</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Stage I endometrioid, grade 1–2, &lt;50% myometrial invasion, LVSI negative</td>
<td>I</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative</td>
<td>I</td>
</tr>
<tr>
<td>High-intermediate</td>
<td>Stage I endometrioid, grade 3, &lt;50% myometrial invasion, regardless of LVSI status</td>
<td>I</td>
</tr>
<tr>
<td>High</td>
<td>Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>1–2, LVSI unequivocally positive, regardless of depth of invasion</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Stage III endometrioid, no residual disease</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Non endometrioid (serous or clear cell or undifferentiated carcinoma, or carcinosarcoma)</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>Stage III residual disease and stage IVA</td>
<td>I</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Stage IVB</td>
<td>I</td>
</tr>
</tbody>
</table>

FIGO 2009 staging used; molecular factors were considered but not included; tumour size was considered but not included; nodal status may be considered for treatment recommendations. LOE, level of evidence; LVSI, lymphovascular space invasion.
High-Intermediate-Risk Endometrial Cancer
ESTRO-ESMO recommendations

1: Surgical nodal staging performed, node negative:
   A. *Adjuvant BT* - is recommended to decrease vaginal recurrence
   • Level of evidence: III, Strength of recommendation: B
   B. *No adjuvant therapy is an option*
   • Level of evidence: III, Strength of recommendation: C

2: No surgical nodal staging:
   A. *Adjuvant EBRT* recommended for LVSI unequivocally positive to decrease pelvic recurrence
   • Level of evidence: III, Strength of recommendation: B
   B. *Adjuvant BT* - alone is recommended for grade 3 and LVSI negative to decrease vaginal recurrence
   • Level of evidence: III, Strength of recommendation: B

3: Systemic therapy is of uncertain benefit; clinical studies are encouraged
   • Level of evidence: III, Strength of recommendation: C
R. Maggi et al. **Adjuvant chemotherapy versus radiotherapy in high risk EC: result of a randomised trial.** BJC, 2006;95-266.

- Median follow up 95.5 months
- High risk: Stage IC G3, II G3, III
- **No difference in 5y OS or DFS**
- **RT (pelvic) reduced local failure and CT distant**
- Sugesting: combine of RT and CT (published trials mixed results)
- CT ARM: failure
  - Locoregional 11%
  - Distant 16%
  - Both 5%

- RT ARM: failure
  - Locoregional 7%
  - Distant 21%
  - Both 5%

Combined modality trials ongoing: GOG 258 (advanced disease), PORTEC-3 (in high risk patients), GOG 249 (intermediate risk st. I and Iia)
OVERAL FIVE - YEAR SURVIVAL

• St. I – 86% (low risk 100%; high risk 70%)
• St. II – 66%
• St. III - 44%
• St IV - 14%

• **Primary RT:**
  • for patients who cannot undergo hysterectomy (surgical staging) - remains option for locoregional disease control.
  • 5-year OS following primary RT ranges from 39% to 71%

• **Paraaortic + LN:**
  • investigators evaluated pat. with involved para-aortic lymph nodes treated with chemotherapy followed by pelvic and paraaortic radiation
  • An outcome of 75% survival rate (superior to any previous survival rates reported with radiation alone)
  • combining chemotherapy with radiation has a therapeutic benefit
PREOPERATIVE RADIOTHERAPY

• Few aims:
  – to decrease the chance of distant dissemination and local recurrence of the tumor at the time of surgery (St. II, III)
  – tumor sterilization, to reduce inflammation,
  – external beam techniques, brachytherapy, or the combination of both can be used (extrauterine spread).


• retrospective study: analysis of the operative specimen after preoperative RT FIGO (1971) st. I or II EC

• From 1976 - 1996, 221 patients were treated with EBRT) and/or LDR BT followed by surgery .
  – Aim- to reduce the pelvic failure rate in high-risk patients.

• tumors were sterilized in 37 patients (17%), sterilized but with dystrophic glands in 34 patients (16%), only modified and altered in 21 patients (9.5%), with viable cells in 56 patients (26%).

• The mean follow-up is 78 months (12–216)
  – The 5-year survival was 90% for FIGO Ia, 80% for FIGO Ib, and 84% for FIGO II (p 5 0.51)
WART (Whole abdominal RT) vs. CT

GOG 122

Survival
By Treatment Group

Dox/CDDP

WART

P - .01
Extended Fields (Whole Abdomen)
MSKCC

EC - 10 pts.
• conventional WART(kidney blocks) vs. IMRT
  • IMRT =
    ↑target coverage with comparable kidney dose
  • ↓dose to the bones
    Volume of pelvic bones irradiated ↓60%
  • Improved coverage of peritoneal cavity

Change the possibility of WART

Consensus Guidelines for the Delineation of the CTV in the Postoperative Pelvis in Patients with Endometrial and Cervical Cancer
Efficacy and safety of IMRT after surgery in patients with endometrial cancer RTOG 0418 phase II study

Anuja Jhingran, Kathryn Winter, Lorraine Portelance, Brigitte Miller, Mohammad Salehpour, Rakesh Gaur, Louis Souhami, William Small, and David Gaffney

Supported by RTOG U10 CA21661, CCOP U10 CA37422, and ATC U24 CA 81647 NCI grants.

- G2 nad higher small Bowel toxicity reduced from 40% in conventional RT to 28% in IMRT
- Vaginal volumes are influenced by bladder and rectal filling and nodal volumes will follow bony markes (integral target motion)-ITV
- Simple daily cone beams CT
evaluate dose distribution within uterus [CTV]) and tumor [GTV]) and the resulting clinical outcome based on 3D- treatment planning with dose–volume adaptation (16 pts.)

Heyman packing was performed with mean 11 Norman-Simon applicators (3–18).
- high-dose-rate brachytherapy (7 Gy per fraction) corresponding to a total dose of 60 Gy (2 Gy per fraction) to the CTV. (4pts had EBRT 10-40Gy)
- On average, 68% of the CTV and 92% of the GTV were encompassed by the 60 Gy reference volume.

3D treatment planning based on CT or MRI (n 29)

All patients treated with curative intent had complete remission (12/12)

After median follow-up of 47 months: 5 pts. are alive without tumor. 7 patients died without tumor from intercurrent disease

GTV on NMR only CTV on CT
LONG-TERM RESULTS OF HIGH-DOSE-RATE BRACHYTHERAPY IN PRIMARY TREATMENT OF MEDICALLY INOPERABLE STAGE I–II ENDOMETRIAL CARCINOMA

- 1984 - 2003, 38 pts. St.I and II considered high operative risk received RT as the primary treatment – BT (brachytherapy)
- median age was 74.1 years
- 8/38 pts. Had combined RT (EBRT+BT)
- 15-year DSS was 78% for all stages
  - (St. I- 90%, St. II- 42% , \( p < 0.0001 \)).

Butterfly applicator:
optimized dose distribution at the level of right lateral wall of the uterus (arrow) and fundus of the uterus (arrow).
**Conclusion**

- Optimal place of RT is still evolving
- Novel techniques (IMRT and IGRT) shall improve delivery and quality of RT and change the role of RT in complex modality treatment approach
- Further gains will require a better understanding of molecular mechanisms and personalized treatment based on an individual patient’s biology (radiogenomics)

Enjoy Belgrade