Chemotherapy for Early Stage High-Risk Endometrial Cancer: Opposed

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The Emperor’s New Clothing
The Emperor’s New Chemotherapy
Outline

- Staging of Endometrial Cancer
- Risk Factors for Recurrence
- Results of Randomized Studies
- Unanswered Questions
- Summary and Conclusions
## FIGO Staging of Endometrial Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Absence of myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Less than 50% myometrial invasion</td>
</tr>
<tr>
<td>IC</td>
<td>At least 50% myometrial invasion</td>
</tr>
<tr>
<td>IIA</td>
<td>Extension to the cervical glands only</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension to the cervical stroma</td>
</tr>
<tr>
<td>IIIA</td>
<td>Malignant peritoneal washings, adnexal involvement, or uterine serosal involvement</td>
</tr>
<tr>
<td>IIIIB</td>
<td>Extension to the vagina</td>
</tr>
<tr>
<td>IIIC</td>
<td>Pelvic or para-aortic lymphatic dissemination</td>
</tr>
<tr>
<td>IVA</td>
<td>Extension to bowel or bladder serosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases, including peritoneal or inguinal lymph nodes</td>
</tr>
</tbody>
</table>
Risk Factors For Recurrence

- Uterine
  - Histologic grade
  - Depth of myometrial invasion
  - Vascular space invasion
  - Cervical extension

- Extrauterine
  - Pelvic node metastases
  - Aortic node metastases
  - Adnexal metastases
  - Positive peritoneal cytology
  - Gross tumour breakthrough of the uterine serosa
# Histologic Grade and Depth of Invasion

<table>
<thead>
<tr>
<th>Depth</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium only</td>
<td>44 (24%)</td>
<td>31 (11%)</td>
<td>11 (7%)</td>
<td>86 (14%)</td>
</tr>
<tr>
<td>Superficial</td>
<td>96 (53%)</td>
<td>131 (45%)</td>
<td>54 (35%)</td>
<td>281 (45%)</td>
</tr>
<tr>
<td>Middle</td>
<td>22 (12%)</td>
<td>69 (24%)</td>
<td>24 (16%)</td>
<td>115 (19%)</td>
</tr>
<tr>
<td>Deep</td>
<td>18 (10%)</td>
<td>57 (20%)</td>
<td>64 (42%)</td>
<td>139 (22%)</td>
</tr>
<tr>
<td>Total</td>
<td>180 (100%)</td>
<td>288 (100%)</td>
<td>153 (100%)</td>
<td>621 (100%)</td>
</tr>
</tbody>
</table>

Creasman et al. Cancer 1987; 60:2035
Grade, Depth of Invasion and Node Metastasis

### Table 5. Grade, Depth of Invasion and Pelvic Node Metastasis

<table>
<thead>
<tr>
<th>Depth of invasion</th>
<th>Grade</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>G1 (N = 180)</td>
<td>G2 (N = 288)</td>
</tr>
<tr>
<td>Endometrium only</td>
<td></td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>(N = 86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inner (N = 281)</td>
<td></td>
<td>3 (3%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Middle (N = 115)</td>
<td></td>
<td>0 (0%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Deep (N = 139)</td>
<td></td>
<td>2 (11%)</td>
<td>11 (19%)</td>
</tr>
</tbody>
</table>

### Table 6. Grade, Depth of Invasion, and Aortic Node Metastasis

<table>
<thead>
<tr>
<th>Depth of invasion</th>
<th>Grade</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>G1 (N = 180)</td>
<td>G2 (N = 288)</td>
</tr>
<tr>
<td>Endometrium only</td>
<td></td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>(N = 86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inner (N = 281)</td>
<td></td>
<td>1 (1%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Middle (N = 115)</td>
<td></td>
<td>1 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Deep (N = 139)</td>
<td></td>
<td>1 (6%)</td>
<td>8 (14%)</td>
</tr>
</tbody>
</table>

Creasman et al. Cancer 1987; 60:2035
Recurrence-Free Interval and Grade

FIG. 2.  Recurrence-free interval by histologic grade.

Morrow et al, Gynecol Oncol 1991; 40:55
Recurrence-Free Interval and Depth of Invasion

FIG. 3. Recurrence-free interval by depth of myometrial invasion.

Morrow et al, Gynecol Oncol 1991; 40:55
## Risk of Recurrence Within Stage I Endometrial Cancer

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(limited to endometrium)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;50% myometrial invasion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt;50% myometrial invasion)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Low-risk, risk of recurrence
Intermediate-risk
High-risk, risk of recurrence

Lukka et al. Gynecol Oncol 2006; 102:361
Results of 4 Randomized Studies Reported to Date

- Radiotherapy ± chemotherapy (2)
- Radiotherapy versus chemotherapy (2)
Doxorubicin as an Adjuvant following Surgery and Radiation Therapy in Patients with High-Risk Endometrial Carcinoma, Stage I and Occult Stage II: A Gynecologic Oncology Group Study*

C. Paul Morrow, M.D.,1 Brian N. Bundy, Ph.D.,2 Howard D. Homesley, M.D.,3 William T. Creasman, M.D.,4 Ned B. Hornback, M.D.,5 Robert Kurman, M.D.,6 and J. Tate Thigpen, M.D.7

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Morrow et al (GOG-34)

FIGO clinical Stage I or II (occult):
- greater than 50% myometrial invasion
- pelvic or aortic node metastasis
- cervical involvement
- adnexal involvement

Radiation – 5000 cGy to whole pelvis at 160-180 cGy/day

Chemotherapy – doxorubicin 60 mg/m² iv q3weekly to maximum dose of 500 mg/m² (N=92)

Control – observation (N=89)
Results

**FIG. 1.** Survival by treatment.
Conclusions

- Study was terminated prematurely because of slow recruitment
- 27% of patients randomized to doxorubicin did not receive it
- No significant difference in OS or PFS
- Study unable to determine effect of doxorubicin on recurrence due to protocol violations, small sample size and number of patients lost to follow-up
Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial

R Maggi¹, A Lissoni², F Spina¹, M Melpignano³, P Zola⁴, G Favalli⁵, A Colombo⁶ and R Fossati*⁷

¹Clinica ‘L. Mangiagalli’, Università degli Studi di Milano, Milano, Italy; ²Ospedale ‘San Gerardo’, Università degli Studi Milano ‘Bicocca’, Monza, Italy; ³Azienda Ospedaliero-Universitaria di Parma, Università degli Studi di Parma, Italy; ⁴Ospedale Mauriziano ‘Umberto I’, Università degli Studi di Torino, Italy; ⁵Ospedali Civili di Brescia, Università degli Studi di Brescia, Italy; ⁶Ospedale ‘A. Manzoni’, Lecco, Italy; ⁷Department of Oncology, Istituto ‘Mario Negri’, Via Ertetta 62, 20157 Milano, Italy
Maggi et al

FIGO stage IC gr 3, stage IIA-B gr 3 with $\geq 50\%$ myometrial invasion, stage III

Randomize

Chemotherapy:
cyclophosphamide 600 mg/m$^2$
doxorubicin 45 mg/m$^2$
cisplatin 50 mg/m$^2$
qu4weeks X 5 cycles (n=174)

Pelvic XRT:
45-50 Gy in 5-7 weeks + para-aortics if involved (n=166)
Results

Figure 2  Overall survival of patients with high-risk endometrial carcinoma (stage IcG3, IIIG3 with myometrial invasion > 50%, and III) receiving adjuvant radiotherapy (Radio) or chemotherapy (Chemio). Five-year overall survival was 69% and 66% respectively for adjuvant radiotherapy and chemotherapy.
Conclusions

- No improvement in PFS or OS for patients treated with chemotherapy
- Trend for radiotherapy to delay local relapses and chemotherapy to delay distant relapses
Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: A Japanese Gynecologic Oncology Group study

Nobuyuki Susumu a, Satoru Sagae b,*, Yasuhiro Udagawa c, Kenji Niwa d, Hiroyuki Kuramoto c, Shinji Satoh f, Ryuichi Kudo g

a School of Medicine, Keio University, Shinjuku-ku, Tokyo
b Sapporo Railway Hospital, Sapporo, Hokkaido, Tokyo, Japan
c Fujita Health University School of Medicine, Toyoake, Aichi, Japan
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f Tohoku University, School of Medicine, Sendai, Miyagi, Japan
g Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan
Susumu et al (JGOG-2033)

FIGO stage IC to III
with ≥ 50% myometrial invasion

Randomize

Chemotherapy:
cyclophosphamide 333 mg/m²
doxorubicin 40 mg/m²
cisplatin 50 mg/m²
defined X 3 or more cycles
(N=188)

Pelvic XRT:
45-50 Gy in 4-6 weeks
+ para-aortics if involved
(N=186)
Results

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Alive</th>
<th>Failed</th>
<th>Total</th>
<th>5ys rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>170</td>
<td>22</td>
<td>192</td>
<td>86.7%</td>
</tr>
<tr>
<td>PRT</td>
<td>166</td>
<td>26</td>
<td>192</td>
<td>85.3%</td>
</tr>
</tbody>
</table>

Hazard Ratio: 0.72
Confidence Interval: 0.40 - 1.29

Log-Rank Test p=0.462
Conclusions

- No improvement in PFS or OS for patients treated with chemotherapy.
- Retrospective subgroup analysis of “high to intermediate risk” group (stage IC > 70 years, IC grade 3, stage II or IIIA n=120) found that chemotherapy significantly improved PFS and OS, however no PFS or OS difference found in “high risk” group (stage IIIA-IIIC n=75).
Hogberg et al (NSGO/EORTC)

A randomized phase-III study on adjuvant treatment with radiation (RT) ± chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991).

T. Hogberg, P. Rosenberg, G. Kristensen, C. F. de Oliveira, R. de Pont Christensen, B. Sorbe, C. Lundgren, T. Salmi, H. Andersson, N. S. Reed

Hogberg et al (NSGO/EORTC)

FIGO stage I, II, IIIA (cytology), or IIIC with high risk for recurrence:
One or more of
- grade 3 tumour
- deep myometrial invasion
- non-diploid DNA
- serous or clear cell or anaplastic histology

Pelvic radiotherapy ± vaginal brachytherapy
Given to dose of ≥ 44 Gy

Chemotherapy given before OR after XRT:
- doxorubicin 40 mg/m², cisplatin ±50 mg/m² X 4 cycles
- epirubicin 75 mg/m², cisplatin ±50 mg/m² X 4 cycles
- paclitaxel 175 mg/m², epirubicin 60 mg/m², carboplatin AUC5
- paclitaxel 175 mg/m², carboplatin AUC5-6

(n=177)

No chemotherapy (n=190)
Results

- Improved PFS on the chemotherapy arm
  - 7% improvement at 5 years, p=0.03
- Survival data too early to draw conclusions
Conclusions

- Not clear if this was truly a randomized study since a variety of chemotherapy regimens could be given either before or after radiation, thus casting doubt about PFS benefits attributed to chemotherapy.
- Study terminated before target of 400 patients reached due to slow recruitment and thus underpowered.
- 27% of patients received no or only part of prescribed chemotherapy.
Unanswered Questions in Adjuvant Therapy of High Risk Early Stage Endometrial Carcinoma

- Would adjuvant chemotherapy be efficacious if optimal chemotherapy were used?
- What is optimal sequencing of combined therapy?
Chemotherapeutic Agents

- In advanced disease, chemotherapeutic agents with activity (response rates of over 20%) demonstrated in phase II studies include:
  - doxorubicin
  - cisplatin/carboplatin
  - paclitaxel
  - cyclophosphamide
  - ifosfamide

- Role of combinations such as carboplatin/paclitaxel
Optimal Sequencing of Chemotherapy and Radiation

- Concurrent with radiation?
- Following radiation?
- Both concurrent and sequential?
- Chemotherapy can be safely combined with radiation and the outcomes of such treatment compared to radiation alone are being tested
PORTEC-3 (NCIC EN.7) Study

TAH-BSO + peritoneal cytology +/- other biopsies
No residual disease

Pathology diagnosis

High-risk or advanced stage

Radiotherapy referral
Pathology review <1 wk*

Stage IB grade 3 + LVSI
Stage IC or IIA grade 3
Stage IIB
Stage IIIA or IIIC
Stage IB, IC, II or III with serous or clear cell histology

Eligible:
Medical oncology consultation
Informed consent procedure

Randomisation

Radiotherapy plus concurrent and adjuvant chemotherapy
Concurrent: 2x cisplatin 50 mg/m²
Adjuvant: 4x carboplatin AUC 5 and paclitaxel 175 mg/m² @ 3 wk intervals

Radiotherapy alone
Pelvic RT: 27 fractions of 1.8 Gy -> 48.6 Gy
Brachytherapy if cervical invasion
Final Conclusions

- No evidence exists to support the routine use of adjuvant chemotherapy in patients with high risk early stage endometrial carcinoma from the 4 randomized studies reported to date.

- Strategies to evaluate potentially more effective combination chemotherapy together with radiation remain to be tested.

- Patients with high risk early stage disease should be encouraged to participate in clinical trials addressing these questions.
The Emperor has no new clothes!