Chemo- and Radiotherapy in Adjuvant Management of Optimally Debulked Endometrial Cancer

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Key Words
Endometrial cancer, surgery, surgical staging, adjuvant radiotherapy, adjuvant chemotherapy, chemoradiotherapy

Abstract
The role of chemotherapy and radiotherapy in adjuvant management of optimally debulked endometrial cancer with extrauterine involvement is evolving. Recent studies have suggested an expanded role for chemotherapy and questioned the benefit of radiation therapy. Ongoing and planned clinical trials should provide clarification. (JNCCN 2009;7:535–541)

The most common scenario in which adjuvant therapy is considered for patients who have undergone optimal debulking of endometrial cancer with extrauterine involvement typically involves patients with FIGO stage III disease with metastases to the pelvic or peri-aortic lymph nodes, or the less common patients with stage IV disease who underwent optimal resection of intraperitoneal disease. Traditionally, patients in these circumstances were offered radiation therapy (RT), particularly if the volume of tissue at risk could be safely contained within a radiation treatment field. If not, chemotherapy was offered. However, recently published and presented trials have suggested that these approaches could be improved. These studies have addressed which modality might be better, whether they should be combined, and, if combined, what chemotherapy should be used. However, results are often difficult to interpret and apply because of the disparate stages of disease addressed by the different trials.

Which is Better? RT Versus Chemotherapy

Gynecologic Oncology Group Study 122
Gynecologic Oncology Group (GOG) protocol 122 compared whole abdominal RT with doxorubicin-cisplatin chemotherapy in patients with optimally debulked (no single site of residual > 2 cm) stage III/IV endometrial carcinoma. Within 8 weeks of surgery, patients randomized to the radiation arm began whole abdominal RT to 30 Gy in 20 daily fractions followed by a pelvic boost of 15 Gy in 8 fractions. Patients with positive para-aortic nodes also received a 15-Gy boost to that region. Patients randomized to the chemotherapy arm received doxorubicin 60 mg/m² plus cisplatin 50 mg/m² every 3 weeks for 7 cycles, followed by 1 cycle of cisplatin. Of 396 evaluable patients, 202 underwent whole abdominal RT and 194 underwent chemotherapy, with a median follow-up of 74 months. Of the patients who underwent whole abdominal RT, 109 (54%) experienced tumor recurrence versus 97 who underwent chemotherapy (50%).

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At final analysis, 38% in the whole abdominal RT arm were predicted to be alive and disease-free compared with 50% in the chemotherapy arm. The difference in progression-free survival between treatment arms was statistically significant \((P = .007)\). Patients in the chemotherapy arm had a 55% 5-year overall survival versus 42% in the whole abdominal RT arm, which also represented a statistically significant difference \((P = .004)\). Furthermore, the data suggest that doxorubicin/cisplatin (AP) chemotherapy favorably affected the distant failure rate, reducing the crude percentage of initial extra-abdominal failure from 18% to 10%. Similarly, patients in the whole abdominal RT arm had a lower risk for first failure occurring in the pelvis.

Importantly, a greater acute grade 3 to 4 hematologic and gastrointestinal toxicity occurred in the chemotherapy arm. In fact, 17% of patients in that arm did not complete protocol treatment compared with 3% in the RT arm.

**Italian Study**

An Italian group conducted a randomized clinical trial comparing adjuvant chemotherapy versus radiotherapy in high-risk endometrial carcinoma. This trial randomized 345 patients with either stage III disease or stage IC to II grade 3 with myometrial invasion greater than 50% to receive either adjuvant cisplatin/doxorubicin/cyclophosphamide or external beam RT (45–50 Gy). Approximately two thirds of the enrolled patients had stage III disease. After a median follow-up of 95.5 months, no significant difference was seen in overall or progression-free survival. The 3-, 5-, and 7-year overall survivals were 78%, 69%, and 62% in the RT group, and 76%, 66%, and 62% in the chemotherapy group. RT delayed local relapses and chemotherapy delayed metastases, but these trends were not statistically significant. The difference in results compared with the GOG trial is likely related to different populations. GOG 122 included a significant proportion of patients with aggressive histologies (e.g., uterine papillary serous and clear cell carcinomas), stage IV disease, and residual tumor up to 2 cm.

**Japanese Gynecologic Oncology Group Study**

The Japanese Gynecologic Oncology Group (JGOG) trial randomized 385 eligible women, 193 to pelvic RT (at least 40 Gy; 45–50 Gy planned) and 192 to CAP (cyclophosphamide 333 mg/m², doxorubicin 40 mg/m², and cisplatin 50 mg/m² every 4 weeks for ≥ 3 courses) chemotherapy. The dosage of chemotherapy used was substantially lower than in the GOG 122 trial. Eligibility criteria included endometrioid histology and at least 50% myometrial invasion. Pelvic lymphadenectomy was performed in 96% of patients and a para-aortic lymphadenectomy in 29%. No overall difference was seen in 5-year progression-free survival (pelvic RT 83%, CAP 82%) or 5-year overall survival (pelvic RT 85%, CAP 87%). As suggested by the good overall outcomes, most patients had a fairly low risk for recurrence; all were of endometrioid histology, 60% had stage IC disease, 55% had grade 1 tumors, and only 14% had grade 3 tumors. By way of contrast in GOG 122, only 50% were reported to have endometrioid histology and 52% had grade 3 disease.

A retrospective subgroup analysis identified a “high-intermediate risk” group of 120 patients with either 1) stage IC disease with grade 3 tumors, 2) stage IC disease and age older than 70 years, 3) stage II disease, or 4) stage IIIb based on positive cytology. In this group, CAP produced a higher progression-free (84% vs. 66%) and overall survival (90% vs. 74%). However, for the 75 high-risk patients (stage IIIb, IIIC, or IIIa based on factors other than positive cytology),...
outcomes were not statistically different between the arms, and the trend favored RT alone (5-year progression-free survival was 79% for pelvic RT and 64% for CAP; 5-year overall survival was 76% and 71%, respectively). Because the subgroup analyses are retrospective and small, the JGOG trial does not convincingly support superiority of either pelvic RT or chemotherapy in any particular group of patients.

**RT With or Without Chemotherapy**

Several retrospective series have used chemotherapy alone in patients with stage III disease, only to note poor outcomes or predominantly local failure patterns that might be improved with local (pelvic or pelvic plus para-aortic) RT.\(^5\)\(^-\)\(^8\)

**GOG 34**

This early trial, published in 1990 and conducted before the adoption of a surgical staging system for endometrial cancer, randomly assigned 181 eligible women with high-risk clinical stage I or occult stage II disease to undergo postoperative pelvic RT (along with aortic field RT in those who had documented aortic node metastases) followed by observation, or the same RT followed by doxorubicin, 60 mg/m\(^2\), every 3 weeks to a maximum cumulative dose of 500 mg/m\(^2\).\(^9\) High risk was defined as greater than 50% myometrial invasion, pelvic or aortic node metastasis, cervical involvement, or adnexal metastasis. Among the patients, 32% had nodal involvement (stage III in the current staging system). No significant difference in overall or progression-free survival was seen between the arms. However, the study had a particularly high rate of refusal in the experimental arm: 27 of the 92 patients assigned to receive doxorubicin never received any. In addition, an imbalance occurred in the treatment arms, with more patients assigned to doxorubicin having pelvic node metastases or grade 3 disease. Twelve patients (7%) developed bowel obstructions: 4 in the doxorubicin group and 8 in the non-doxorubicin group.

**Finnish Study**

Kuoppala et al.\(^10\) reported a randomized study comparing postoperative RT with RT plus chemotherapy in 156 patients, most of whom (128) had stage IC to IIIA disease, and 19 of these had stage IIIA. Chemotherapy consisted of 3 courses of cisplatin, epirubicin, and cyclophosphamide. The follow-up was excellent, with patients followed up for a minimum of 5 years or until recurrence. In this study, the addition of chemotherapy to RT did not improve overall survival or lower the recurrence rate.

**NSGO-EC-9501/EORTC-55991**

Eligibility for the NSGO-EC-9501/EORTC-55991 trial included surgical stage I, II, IIIA (positive cytology only), or IIC (positive pelvic nodes only) disease considered high enough risk for chemotherapy according to institutional guidelines.\(^11\) Most of the 367 evaluable patients had 2 or more of the following: grade 3 disease, deep myometrial invasion, or DNA nondiploidy; some had only 1 of these risk factors. Patients with serous, clear cell, or anaplastic carcinomas were eligible regardless of risk factors; those with para-aortic node involvement were not. All patients underwent pelvic RT with or without vaginal brachytherapy. Chemotherapy could be given before or after RT. Chemotherapy regimens allowed included doxorubicin/cisplatin; epirubicin/cisplatin; paclitaxel/epirubicin/carboplatin; and paclitaxel/carboplatin. This trial was presented only in abstract form. Chemotherapy was reported to produce a significant benefit in progression-free survival (hazard ratio [HR], 0.62; \(P = .03\)); 22% of patients progressed in the radiotherapy group versus 12% in the combination therapy group. A trend toward a benefit in overall survival was also seen (HR, 0.65; \(P = .08\)).

**Which Chemotherapy?**

**GOG 184**

GOG 184 compared 2 different chemotherapy regimens in the high-risk adjuvant setting.\(^12\) All women underwent volume-directed RT (pelvic or pelvic plus para-aortic) followed by either AP (6 cycles of cisplatin, 50 mg/m\(^2\), plus doxorubicin, 45 mg/m\(^2\)) or paclitaxel/doxorubicin/cisplatin (TAP; 6 cycles of cisplatin, 50 mg/m\(^2\), plus doxorubicin, 45 mg/m\(^2\), plus paclitaxel, 160 mg/m\(^2\)). The choice of regimens was based on a trial in women with advanced or recurrent endometrial carcinoma (GOG 177) in which TAP significantly improved response rates, progression-free survival, and overall survival (15.3 vs. 12.3 months) compared with AP.\(^13\)

GOG 184 initially included patients who had stage IV (debulked to < 2 cm) and III disease, the same population included in GOG 122. However, af-
Ongoing Studies

GOG 209
GOG 209 is a large study designed to test the noninferiority of carboplatin (area under the curve [AUC] of 6)/paclitaxel (175 mg/m²) compared with paclitaxel (160 mg/m²)/cisplatin (50 mg/m²)/doxorubicin (45 mg/m²)/G-CSF support. Carboplatin/paclitaxel is already widely used in the therapy of endometrial cancer based on promising results in phase II studies. The doublet’s advantage is that it is given over 1 day rather than 2 and does not always require growth factor administration. However full-dose carboplatin/paclitaxel is not tolerated by all patients in this population; GOG 209 was recently amended to require an initial dose-reduction to carboplatin AUC of 5 and paclitaxel dose of 135 mg/m² in those who underwent prior whole pelvic radiotherapy. More importantly, carboplatin/paclitaxel avoids doxorubicin-related cardiac toxicity, which is of particular concern in the adjuvant disease setting. Finally, doxorubicin may be difficult to safely combine with newer biologic agents, some of which also can cause cardiac toxicity. GOG 209 includes patients with measurable advanced/recurrent disease; those with nonmeasurable stage IV disease, such as those with “optimally debulked” stage IV disease studied on GOG 122; and those with stage III disease. The study is expected to be completed by 2010.

PORTEC-3
An ongoing European trial (PORTEC-3) is randomizing patients with stages IBG3, ICG3, and IIG3, and all patients with stage IIIA and IIIC disease to either pelvic RT alone or combination chemoradiation followed by consolidation chemotherapy. The chemoradiation regimen incorporates cisplatin at 50 mg/m² days 1 and 22. Consolidation chemotherapy consists of carboplatin (AUC 5) and paclitaxel (175 mg/m²) for 4 cycles. This trial is anticipated to accrue 800 patients.

Stage III Disease
None of the trials addressing the value of chemotherapy has targeted only stage III disease. As seen from the overall survivals shown in Table 1, many patients included were not even particularly high risk. A couple of the trials have not been published in full, and retrospective analysis of small higher-risk subsets is likely to yield wide variation in results based on chance. GOG 122 included the highest-risk population, and convincingly showed benefit to adding chemotherapy. Currently, chemotherapy should be considered for all women with stage III disease. Information from the ongoing PORTEC-3 trial should be very informative. However, future trials must incorporate evaluation of factors that will predict which patients benefit most from treatment.

Optimally Debulked Stage IV Disease
This situation is exemplified by a patient with serous carcinoma of the uterus who is managed with a treatment algorithm similar to that used for ovarian cancer, undergoes initial debulking surgery, and is left with no measurable residual disease. Most chemotherapy trials addressing the role of chemotherapy in the treatment of optimally debulked endometrial cancer with extracavitary involvement have not included patients with stage IV disease. The excep-
tions have been GOG 122 (whole abdominal radiotherapy vs. chemotherapy) and GOG 209 (currently ongoing; testing paclitaxel/carboplatin vs. TAP). Patients with stage IV disease clearly did better with chemotherapy than whole abdominal RT on GOG 122, although it was noted that maximum residual disease of up to 2 cm was allowed, which is perhaps a larger bulk than is optimally managed by the radiation doses achievable with whole abdominal RT. Five-year survival for patients with stage IV disease treated with chemotherapy on GOG 122 ranged from 25% to 30%; however, that trial required no more than 1 cm maximum postoperative residual disease, whereas up to 2 cm was permitted on GOG 122.

Role of Hormonal Therapy

No trials of hormonal therapy have been conducted specifically in patients with optimally debulked endometrial cancer with extraterine involvement. Numerous trials have addressed the use of adjuvant hormonal therapy (progestins) in stage I disease. Gien et al.14 recently reviewed the literature in this area and found 9 randomized trials and 1 published meta-analysis. Among the trials, 7 found no significant differences in recurrence rates and 2 found an advantage to hormonal therapy. Of these 2 trials, 1 showed a 5% difference between the rates of recurrence and the other showed a 16% difference, but methodological concerns were believed to limit the relevance of the results. The authors concluded that hormonal therapy has no role in the treatment of stage I endometrial carcinoma.

An earlier meta-analysis (which included 6 of the 9 trials mentioned by Gien et al.14) had concluded that endometrial cancer deaths and disease relapse seemed to be nonsignificantly reduced by adjuvant progestins (odds ratio [OR], 0.88; 95% CI,

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<th>Table 1 Randomized Trials Including Adjuvant Chemotherapy and at Least Some Stage III Patients</th>
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<td><strong>Radiotherapy Versus Chemotherapy</strong></td>
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**Radiotherapy Versus Radiotherapy Plus Chemotherapy**

| **GOG 34** | 181 | Clinical /occult II 31% node-positive | RT vs. RT + doxorubicin | No difference |
| **Finland** | 156 | IA, B Gr3 IC–IIIA* Gr1–3 | RT vs. RT + CEP | No difference |
| | | | 5-y DSS, 85% RT and 82% CT |
| **NSGO/EORTC** | 367 | I, II, IIIA, IIIC with selected high-risk factors | RT vs. RT + CT (various regimens) | Addition of chemotherapy superior: |
| | | | HR for PFS, 0.58; P = .046 |
| | | | 5-y PFS, 75% RT and 82% CT |

**Trials Addressing Differences Between Chemotherapy Regimens**

| **GOG 184** | 659 | III IV optimal | RT + AP vs. RT + TAP | No difference |
| | | | 36-mo PFS, 62% AP and 64% TAP |

*Only 19 patients had stage IIIA disease.*

Abbreviations: AP, doxorubicin plus cisplatin; CAP, cyclophosphamide plus doxorubicin plus cisplatin; CEP, cyclophosphamide plus epirubicin plus cisplatin; CT, chemotherapy; DSS, disease-specific survival; GOG, Gynecologic Oncology Group; HR, hazard ratio; JGOG, Japanese Gynecologic Oncology Group; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; TAP, paclitaxel plus doxorubicin plus cisplatin.
The trial will test this hypothesis by using modern tumor volume-directed RT administered with cisplatin and followed by systemic chemotherapy. The study builds on the previous experience of the GOG and Radiation Therapy Oncology Group. GOG 122 has clearly shown that systemic chemotherapy should be part of the treatment for this patient population. RT is also predicted to decrease the rate of local failure. However, whether adding volume-directed chemoradiation to chemotherapy alters recurrence-free and overall survival in a significant manner is unknown. This trial is the logical follow-up to the previous research questions addressed by GOG protocols (122, 177, 184, and 209). The trial will determine the impact of chemoradiation in this setting, the tolerability of this approach compared with the standard of care, and the short- and long-term impact on the quality of life.

Conclusions

It can be reasonably concluded that chemotherapy has a role in adjuvant management of optimally debulked endometrial cancer with extraterine involvement. The results of GOG 209 should identify the best regimen. The role of biologics, particularly mTOR inhibitors, remains to be defined in adjuvant therapy, but likely will play a role. GOG 258 will define whether RT adds to patient survival and local control.

References


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