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Adjuvant chemotherapy and radiation therapy with the “sandwich” method for endometrial cancer: an institutional analysis

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ABSTRACT

Introduction. Choice of adjuvant therapy for high risk endometrial cancers is controversial. The so-called “sandwich” regimen of pelvic external beam radiation administered between cycles of Carboplatin/Paclitaxel (CT-RT-CT) is commonly used in clinical practice but has not been evaluated in randomized endometrial cancer trials. There is relatively little published data regarding toxicity, patient tolerance, and efficacy of this regimen. Here, we report our institutional experience of CT-RT-CT for locally advanced endometrial cancer, focusing on toxicity and rates of compliance with study therapy.

Material and methods. Medical records of consecutive patients treated for surgically staged endometrial cancer at a tertiary care academic medical center between 2010 and 2017 were reviewed. All patients received adjuvant CT-RT-CT. Progression-free and overall survival were recorded from the date of surgery. Toxicity data was obtained from patient medical records and graded according to Common Terminology for Adverse Events Criteria, version 3.0.

Results. Thirty-eight patients with histologically proven stage I–IV endometrial cancer were included. Eighty-four percent of patients were able to complete all 6 planned cycles of chemotherapy and 92% completed at least 4 cycles. Cumulative incidence of grade 3–4 hematologic toxicity was 55%. Locoregional recurrence was the first site of failure in 2 patients (5.1%) while distant failure was the first site of recurrence in 8 patients (21%). Two year overall survival and progression-free survival were 76% and 77% respectively.

Conclusion. Our results suggest that adjuvant chemotherapy and radiation therapy with the “sandwich” regimen is associated with acceptable toxicity and satisfactory rates of completion of planned therapy.

Key words: endometrial cancer, sandwich therapy, radiation, carboplatin, paclitaxel

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Introduction

Endometrial cancer is the most common gynecologic cancer in the United States, with an estimated 63,230 cases and 11,350 deaths annually [1]. Standard therapy includes surgical staging followed by adjuvant chemotherapy and/or radiation therapy in patients with high-risk clinical or pathologic characteristics [2, 3]. For patients with advanced-stage endometrial

cancer, the choice of adjuvant therapy remains controversial.

Several early phase clinical trials and single institution clinical series have demonstrated the efficacy of adjuvant radiation or chemotherapy used as single modality treatments. Studies of adjuvant chemotherapy alone show high rates of local disease recurrence in the pelvis compared to trials in which radiation is given. Conversely, patients treated with radiation alone show

higher rates of distant failure. These observations were confirmed in GOG 122, a multi-institutional randomized clinical trial directly comparing chemotherapy versus whole abdominal radiation [4].

To optimize both distant and local control, combination chemotherapy and radiation therapy regimens are often favored in current practice and are endorsed in published treatment guidelines from the American Society for Radiation Oncology (ASTRO), and in a joint statement by the Society of Obstetrics and Gynecologists of Canada/Society of Gynecologic Oncology of Canada/Society of Canadian Colposcopists [3, 5]. However, there is significant institutional and provider variation in the specific adjuvant regimens used, with commonly employed regimens based primarily on results from early phase studies or retrospective reviews of institutional experiences [6–8]. Published data from randomized clinical trials providing direct comparisons between combination regimens are limited.

Results of two recently completed randomized trials (GOG 258 and PORTEC 3) provide important insights into the relative benefits of various adjuvant regimens [9, 10]. In these trials, patients were randomized to a regimen of concurrent cisplatin based chemotherapy and pelvic radiation followed by 4 cycles of adjuvant carboplatin and paclitaxel (C-RT) versus a regimen of six cycles of carboplatin and paclitaxel alone (CT) in GOG 258 or pelvic external beam radiation alone (RT) in PORTEC 3. Published results of these trials confirmed a relative local control benefit with C-RT relative to CT, a distant control benefit to CT relative to C-RT. In PORTEC 3, an overall survival benefit was demonstrated with C-RT compared to RT alone [9–11]. However, C-RT was associated with increased toxicity and decreased rates of compliance with the 4 cycles of adjuvant carboplatin/paclitaxel. Survival analysis is pending for GOG 258.

A third treatment regimen, commonly referred to as “sandwich” therapy, is often used in clinical practice and consists of pelvic external beam radiation administered between the 3rd and 4th cycles of a six-cycle regimen of carboplatin and paclitaxel chemotherapy [12]. Sandwich chemotherapy and radiation (CT-RT-CT) has the potential advantage of providing the local control benefit associated with pelvic radiation as well as the distant control associated with the completion of 6 cycles of carboplatin/paclitaxel chemotherapy. However, this regimen has never been evaluated in a randomized trial and published literature regarding efficacy and toxicity is relatively sparse. Additional clinical data regarding this regimen is needed. Here, we report our institutional experience with CT-RT-CT for endometrial cancer, focusing on treatment efficacy, toxicity, and rates of compliance with planned therapy.

Material and methods

Patient selection

Following IRB approval, we retrospectively identified patients treated at a single, tertiary care academic medical center who were diagnosed and treated for FIGO 2009 stage IA–IVB high risk endometrial cancer. High risk features included cervical stromal invasion, serosal/adnexal involvement, vaginal/parametrial involvement, bladder/rectal involvement, nodal involvement, and non-endometrioid histology. All patients were treated with hysterectomy and adjuvant CT-RT-CT between June 2011 and May 2017. Only patients treated with three cycles of carboplatin and paclitaxel followed by pelvic radiation and then additional cycles of chemotherapy were included. Patients who received concurrent chemotherapy with radiation were excluded, as were any patients treated with neoadjuvant chemotherapy.

Patient and tumor characteristic

Patient tumor and treatment characteristics were obtained from the electronic medical record. Variables recorded include age, race, tobacco, T stage, N stage, FIGO stage, surgical technique, pathologic findings, chemotherapy characteristics, radiation characteristics, hematologic toxicity, and recurrence. Length of follow-up was calculated from the date of surgery and the date of the most recent follow-up documented in the medical record. Progression-free and overall survival were recorded from the date of surgery. Toxicity was graded according to Common Terminology for Adverse Events Criteria, version 3.0.

Statistical analysis

Univariate and multivariable logistic regression models were used to test for associations between patient characteristics and clinical outcomes. P values < 0.05 were considered significant. All statistical analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC)

Results

Patient characteristics

We identified a total of 38 patients who met the inclusion criteria. Median age was 65 years and ranged from 38–88 years (Tab. 1). Eighty-three percent of patients were Caucasian. Forty-two percent of patients had a history of tobacco use. Bilateral pelvic lymph node dissection was performed in 90% of patients

Table 1. Patient and cancer characteristics (n = 38)

| Characteristic | n (%) |
|--------------------------------|------------------|
| Age at surgery (median, years) | 65 (range 38–88) |
| Race | |
| Caucasian | 31 (82%) |
| African American | 4 (11%) |
| Other | 3 (8%) |
| Tobacco use | |
| Yes | 16 (42%) |
| No | 22 (58%) |
| Histology | |
| Endometrioid | 18 (48%) |
| Clear cell | 0 |
| Serous | 9 (25%) |
| Mixed/Undifferentiated/Other | 11 (28%) |
| Tumor grade | |
| 1 | 3 (8%) |
| 2 | 10 (26%) |
| 3 | 25 (66%) |
| AJCC stage | |
| IA | 2 (5%) |
| IB | 0 |
| II | 5 (13%) |
| IIIA | 5 (13%) |
| IIIC1 | 14 (37%) |
| IIIC2 | 9 (24%) |
| IVA | 1 (3%) |
| IVB | 2 (5%) |

and para-aortic dissection was performed in 65% of patients. The majority of patients (74%) had stage III disease and 8% of patients had stage IV disease.

Chemotherapy

Six cycles of chemotherapy were planned for each patient. All patients completed the 3 cycles of chemotherapy delivered before radiation therapy. Eighty-four percent of patients were able to complete all 6 planned cycles of chemotherapy and 92% of patients were able to complete at least 4 cycles (Tab. 2). Seventy-five percent of patients received Pegfilgrastim. Chemotherapy was not completed due to neuropathy for two patients, thrombocytopenia for one patient, progression of disease for one patient, personal decision in one case, and unknown in one case. Seventy-three percent experienced no toxicity related delays in administration of chemotherapy during their treatment course. There were 11 patients whose chemotherapy treatments were

Table 2. Treatment characteristics

| Characteristic | N (%) |
|--|--------------------|
| Chemotherapy — number of cycles completed | |
| 3 | 3 (8%) |
| 4 | 1 (2.7%) |
| 5 | 2 (5%) |
| 6 | 32 (84%) |
| External beam radiation dose (median, Gy)* | 45 (range 45–55.8) |
| 45 Gy | 34 (92%) |
| 50.4 Gy | 2 (5%) |
| 55.8 Gy | 1 (2.7%) |
| Radiation technique* | |
| 3D | 12 (32%) |
| IMRT | 25 (68%) |
| Radiation field* | |
| Pelvic | 24 (65%) |
| Pelvic + para-aortic | 13 (35%) |
| Brachytherapy | |
| Yes | 24 (65%) |
| Brachytherapy dose (median, Gy) | 18 (range 10–18) |
| No | 13 (35%) |

*Radiation records for one patient was not available

delayed: 5 for thrombocytopenia, 1 for pancytopenia, 3 for neutropenia, 1 for an unrelated hospitalization, and 1 for influenza.

Radiation therapy

The majority of patients received 45 Gy of external beam radiation (EBRT) (range 45–55.8 Gy). All patients completed their planned external beam radiation treatment course. Sixty-eight percent of patients received intensity-modulated radiation therapy (IMRT) while 32% received 3-dimensional conformal radiation therapy (3D CRT). High dose rate vaginal brachytherapy was used in 65% of cases, with a median dose of 18Gy in 3 fractions.

Toxicity

Over the course of chemotherapy and radiation therapy, grade 3 anemia was experienced by 21% of patients and grade 4 anemia by 3% of patients (Tab. 3). Grade 3 and 4 thrombocytopenia were each experienced by 8% of patients. Twenty-six percent of patients developed grade 3 leukopenia and 13% of patients developed grade 4 leukopenia. Grade 3 and 4 neutropenia were each experienced by 24% of patients. The overall cumulative incidence of grade 3–4 hematologic toxicity was 55%. There were no grade 5 hematologic toxicities.

Treatment outcomes

Median follow up in our patient population was 24 months. The 2-year overall survival was 76.4% and the 2-year progression free survival (Fig. 1) was 76.6%. Time to progression ranged from 6 to 39 months (median 12 months). Distant metastasis was the first site of failure in 8 patients (21%), while locoregional recur-

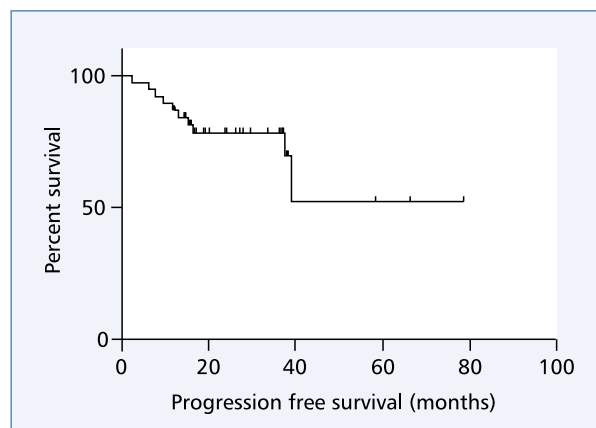


Figure 1. Kaplan-Meier analysis for progression-free survival

rence was the first site of failure in 2 patients (5.1%). Characteristics of patients who experienced recurrences are provided in Table 4. Both patients with locoregional recurrence presented with vaginal disease recurrence as the first site of failure.

On univariate analysis, the only predictor for improved overall survival was the completion of planned chemotherapy (HR 4.3; 95% CI 1.03–18.3). Kaplan Meier analysis of overall survival, stratified by whether or not patients completed all planned cycles of chemotherapy, is shown in Figure 2. The only significant predictor for improved progression-free survival was lower age (HR 1.03, 95% CI 1.0–1.2), which was calculated as a continuous variable. Distant metastasis free survival was significantly improved among patients who completed all planned cycles of chemotherapy (HR 6.3; 95% CI 1.5–27.5) and amongst patients who had no delayed or missed cycles of chemotherapy (HR 2.4; 95% CI > 1.0–5.7).

Discussion

We report our institutional experience treating patients with high risk endometrial cancer using adjuvant

Table 3. Hematologic toxicity during chemotherapy and radiation therapy

| Grade | Anemia | Thrombocytopenia | Leukopenia | Neutropenia |
|-------|----------|------------------|------------|-------------|
| 0 | 1 (3%) | 5 (13%) | 4 (11%) | 9 (24%) |
| 1 | 7 (18%) | 21 (55%) | 7 (18%) | 7 (18%) |
| 2 | 21 (55%) | 6 (16%) | 12 (32%) | 4 (11%) |
| 3 | 8 (21%) | 3 (8%) | 10 (26%) | 9 (24%) |
| 4 | 1 (3%) | 3 (8%) | 5 (13%) | 9 (24%) |

Table 4. Characteristics of patients with recurrences

| Age at surgery | Stage | #Cycles chemo completed | Radiation dose (Gy) | Brachytherapy dose (Gy) | PA field | Time to recurrence (months) | Location of recurrence |
|----------------|-------|-------------------------|---------------------|-------------------------|---------------|-----------------------------|-------------------------|
| 56 | IIIC2 | 6 | 45 | 18 | Yes | 15 | Mediastinum |
| 65 | IIIC2 | 6 | 45 | 18 | Yes | 39 | Peritoneal cavity/Liver |
| 71 | IIIC2 | 3 | 45 | 10 | Yes | 38 | Peritoneal cavity |
| 72 | IIIC1 | 6 | 45 | 0 | No | 13 | Vaginal cuff |
| 73 | IVB | 6 | 45 | 18 | No | 16 | Pulmonary and pelvic |
| 73 | IIIC2 | 6 | 45 | 0 | Yes | 2.5 | Pulmonary |
| 73 | IIIC2 | 4 | 45 | 10 | Yes | 6.2 | Peritoneal cavity |
| 75 | II | 6 | Not available | Not available | Not available | 7.8 | Pulmonary |
| 79 | IVB | 6 | 45 | 0 | Yes | 9.6 | Vaginal cuff |
| 81 | IIIA | 5 | 45 | 18 | Yes | 12 | Liver |

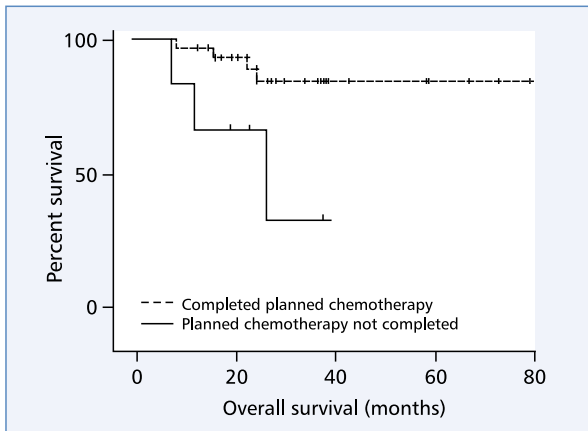


Figure 2. Kaplan-Meier analysis for overall survival stratified by the completion of all planned cycles of chemotherapy versus early termination of chemotherapy ($p = 0.01$)

“sandwich” therapy with pelvic external beam radiation administered between cycles 3 and 4 of a planned 6 cycles of carboplatin/paclitaxel chemotherapy. Our results show this regimen is associated with high rates of compliance with planned therapy, with 92% of patients completing at least 4 cycles of carboplatin/paclitaxel chemotherapy and 100% completing planned radiation treatments. In addition, we found low rates of locoregional failure (5%) and distant metastases (21%). Lower age was found to be a significant predictor for improved progression-free survival. This is in line with current literature reports of older age as a risk factor for recurrence and poor outcomes [13, 14].

Given the limited published clinical data regarding sandwich therapy, our findings provide important additional information regarding efficacy and toxicity of this regimen in a patient population that closely resembles results from recent randomized trials (GOG 258 and PORTEC 3) using combination adjuvant therapy regimens with radiation and chemotherapy. Our results show similar rates of locoregional disease control relative to other series of sandwich therapy, with reported rates or locoregional failure ranging from 2–15% in a recently published meta-analysis [12]. Our findings are also in line with the 5-year overall survival of 70% and 5-year progression free survival of 66% reported for stage III, IV and recurrent endometrial cancer patients treated with sandwich therapy in a recently published long term follow-up of a phase II study [15]. Our patient population did have a large proportion (25%) of serous histology. A study of 81 patients with uterine papillary serous carcinoma treated with the sandwich regimen found overall progression free survival and overall survival of 65.5% and 76.5% in early-stage patients and 25.8% and 35.9% in advanced stage patients [16]. These numbers compare

similarly with our 2-year overall survival of 76.4% and the 2-year progression free survival of 76.6% for our entire patient population.

Our findings also compare favourably with patients treated with radiation in both PORTEC 3 and GOG 258. In PORTEC 3, 5-year rates of pelvic or vaginal recurrence as the first site of failure among patients treated with C-RT and RT were 1.3% and 1.8%, respectively [10]. In GOG 258, the incidence of vaginal recurrence was 2% at 5 years, and locoregional recurrence 11% at 5 years among patients treated with pelvic radiation on the C-RT treatment arm [9]. The patients in GOG 258 did have higher risk disease with 97.3% having stage III or higher disease as compared to patients in PORTEC 3 in which only 43% of patients had stage III disease (there were no patients with stage IV disease). The patients in our study had more similar disease severity to the patients in GOG 258, with 82% of patients having stage III or above disease.

An important observation from both PORTEC 3 and GOG 258 is that distant metastasis remains the primary mode of treatment failure for high-risk endometrial cancer patients. Also of note, patients treated with CT alone showed lower rates of distant failure at 5 years than patients treated with C-RT on GOG 258 (27% vs. 21%). Reasons for the increased rates of distant failure observed with combination therapy are uncertain, though possibilities include: 1) planned treatment with 4 (CRT) versus 6 (CT) cycles of carboplatin and paclitaxel is less effective at eradicating subclinical metastatic disease; 2) delay in initiation of systemic carboplatin paclitaxel due to administration of pelvic radiation on the CRT arm resulted in decreased treatment efficacy; or, 3) increased toxicity with combination cisplatin and radiation resulted in decreased bone marrow reserve and associated poor compliance with adjuvant carboplatin/paclitaxel. In support of this final possibility, approximately 75% of patients completed 4 or more cycles of carboplatin/paclitaxel chemotherapy in the CRT arms of GOG 258 and PORTEC 3, while 92% of patients completed 4 or more cycles of chemotherapy in the CT arm of GOG 258. In comparison, 93% of patients in our series completed 4 or more cycles of carboplatin and paclitaxel, and 84% completed all six planned cycles. The cumulative incidence of grade 3–5 hematologic toxicity in our study was 55%, which again compares favourably with the 52% rates observed on the CT arm of GOG 258. In addition, we found that lack of completion of chemotherapy, and delays in chemotherapy significantly correlated with decreased rates of distant metastasis-free survival. A recently published SEER-Medicare database report of patients with advanced endometrial cancer found similarly that more cycles of chemotherapy administered correlated with increased overall survival [17]. These findings suggest that CT-RT-CT, in comparison with other commonly used adjuvant regimens, may optimally impart

local and distant disease control by allowing greater rates of completion of planned chemotherapy regimens among patients who receive radiation.

In summation, results of our study and others in which adjuvant sandwich therapy was used to reveal favourable disease-specific outcomes, including low rates of locoregional and distant recurrence. In addition, our results demonstrate that this regimen is associated with acceptable toxicity and high rates of compliance with planned chemotherapies. This is especially important as the completion of planned chemotherapy was a predictor for improved overall survival and given that distant failure is the primary failure pattern amongst high-risk endometrial cancer patients. Though our relatively small patient numbers do not allow us to draw definitive conclusions, our findings support further evaluation of sandwich therapy in future clinical trials evaluating combination therapy regimens in high-risk endometrial cancer patients.

Conclusions

Our results are consistent with literature suggesting that the adjuvant therapy regimen of chemotherapy followed by radiation therapy followed by additional chemotherapy for high-risk endometrial cancer leads to acceptable toxicity and does not impede patients' ability to complete chemotherapy. Randomized prospective studies are needed to compare the efficacy of this regimen with other commonly used regimens.

Conflict of interest

The authors report no conflicts of interest.

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