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Benefit of combination chemotherapy and radiation stratified by grade of stage IIIC endometrial cancer☆

Pratibha S. Binder [a,*], Lindsay M. Kuroki [a], Peinan Zhao [b], Sarah Cusworth [b], Laura M. Divine [a], Andrea R. Hagemann [a], Carolyn K. McCourt [a], Premal H. Thaker [a], Matthew A. Powell [a], David G. Mutch [a], L. Stewart Massad [a]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University, St. Louis, MO, United States
[b] Department of Obstetrics and Gynecology, Washington University, St. Louis, MO, United States

HIGHLIGHTS

- Patients with stage IIIC endometrial cancer should receive adjuvant chemoradiation.
- Low-grade cancers have a survival benefit with radiation alone and chemoradiation.
- High-grade cancers have a survival benefit with chemotherapy and chemoradiation.

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ABSTRACT

Objective. The optimal strategy for adjuvant therapy in stage IIIC endometrial cancer has not been determined. Our aim was to evaluate survival benefit of different treatments and to investigate if benefit varied by histologic grade.

Methods. We identified 199 patients with stage IIIC endometrial cancer from 2000 to 2012 through the Siteman Cancer Center registry. All patients underwent surgical staging followed by no adjuvant therapy (NAT), radiation (RT), chemotherapy (CT) or chemoradiation (CRT). The association between adjuvant treatment and overall survival was explored using Kaplan-Meier plots and multivariable Cox regression analysis. Multivariable analysis was stratified by low- or high-grade to explore the interaction between grade and treatment.

Results. Most patients received CRT (50.3%) followed by CT (23.1%), RT (16.1%) and NAT (10.5%). Survival after CRT was superior to NAT ($p < 0.001$), RT ($p = 0.010$) and CT ($p < 0.001$). After adjusting for covariates, treatment with RT, CT and CRT led to a 57% ($p = 0.024$), 62% ($p = 0.003$) and 83% ($p < 0.001$) reduction in risk of death compared to NAT, respectively. With CRT as the reference, the adjusted hazard of death was higher with NAT (5.94, $p < 0.001$), RT (2.56, $p = 0.009$) and CT (2.24, $p = 0.004$). Stratifying by grade, RT and CRT led to a 67% ($p = 0.039$) and 85% ($p < 0.001$) reduction in death, compared to NAT in low-grade patients. CT and CRT led to a 72% ($p = 0.003$) and 83% ($p < 0.001$) reduction in death, compared to NAT in high-grade patients.

Conclusions. Our findings suggest that CRT should be the preferred adjuvant treatment strategy for patients with stage IIIC endometrial cancer.

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1. Introduction

Endometrial cancer (EC) is the leading gynecologic malignancy in the United States [1], and while most patients have early stage disease that can be cured with hysterectomy alone, 5–20% have nodal involvement at presentation and a significant risk of recurrence and cancer related death [2–5]. The EC death rate has increased 2% per year from 2010 to 2014 [1].

Although there is consensus that patients with advanced EC warrant adjuvant therapy, the optimal treatment strategy has yet to be determined. Patients with extrauterine disease confined to nodes and adnexa may be treated with pelvic or extended-field radiation therapy (RT) alone [6]. Chemotherapy (CT) showed a survival advantage in prospective trials but outcomes were suboptimal leading to the exploration of

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* Corresponding author at: Division of Gynecologic Oncology, Department of OB/Gyn, Campus Box 8064, 661 Euclid Ave., United States.
E-mail address: binderp@wustl.edu (P.S. Binder).

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combination chemotherapy and radiotherapy (CRT) [7,8]. Retrospective studies have attempted to review the benefit of multi-modality treatment; however, results are difficult to assess due to patient, tumor and treatment heterogeneity [9–14]. Studies have been conflicting, especially regarding the interaction of histologic grade with different treatment modalities [15–18].

The current study builds on the growing understanding from recent literature that individualized treatment approaches may be needed for stage IIIC EC patients. Our primary objectives were to determine whether RT, CT, or CRT is associated with improved PFS (progression-free survival) and OS (overall survival) in a cohort of stage IIIC EC patients and to investigate whether the results differed according to grade (G1–2 vs G3). Based on prior data, we hypothesized that CRT would be most beneficial, followed by RT and CT regardless of histologic grade. Our secondary objectives were to study the interactions between treatment type and grade, stage, or age in OS analysis.

2. Methods

2.1. Study design and cohort

We performed a retrospective cohort study of women diagnosed with node-positive stage IIIC endometrial cancer from 2000 to 2012. The analysis included surgically treated patients, all of whom underwent at least hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy. The standard of lymphadenectomy for apparent early stage endometrial cancer evolved from lymphadenectomy for all patients, unless contraindicated, to lymphadenectomy based on pre-operative histology/grade and intra-operative findings including myometrial invasion and obvious extra-uterine disease. Patients primarily treated with hormones, radiation or chemotherapy were excluded. Pathology was reviewed by gynecologic pathologists, and cases were presented at a multi-disciplinary conference for treatment planning. Adjuvant therapy options consisted of RT, CT or CRT. Radiation was delivered by external beam radiation therapy (EBRT) with image-guidance or intensity-modulated radiation therapy (IMRT) and most patients received vaginal-cuff brachytherapy. IMRT was used starting the second half of 2005. Chemotherapy usually consisted of multi-agent chemotherapy with carboplatin and paclitaxel being the most common regimen. Concurrent CRT was usually prescribed at our institution and was well tolerated [19]. Only patients with endometrioid, serous and clear cell adenocarcinoma were included in the analysis. Patients with mixed histology were considered serous or clear cell if that component consisted of >10% of the specimen. Thus, we excluded patients with uterine sarcomas and undifferentiated malignancy.

2.2. Data source and collection

After Institutional Review Board approval of this review, patients were identified from the prospectively maintained Siteman Cancer Center tumor registry. We extracted demographic and medical data including age of diagnosis, race, alcohol/tobacco habits, marital status, ACE-27 comorbidity score [20], surgical procedure, number of nodes removed/involved, cancer stage, grade, histology, lymphovascular space invasion (LVSI) and adjuvant treatment. Tumor stage was based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) guidelines. Pathology reports and charts were reviewed to exclude any patients with clinical stage 4 disease. Dates of diagnosis, recurrence, death and last follow-up were used to calculate PFS and OS. Recurrence date was based on pathologic or computed tomography confirmation. Recurrence and death data were updated in the database semiannually by contacting patients, their families, and their physicians. The National and Social Security Death Index was queried for the patients who were lost to follow-up.

2.3. Statistical methods

Prospective studies detailing surgical-pathological findings and patterns of spread of endometrial cancer have shown that grade 1 and 2 endometrioid adenocarcinomas have similar patterns of localized spread and comparable percentages of risk factors like myometrial invasion and lymph node metastasis when compared to grade 3 [21,22]. Therefore, the cohort was dichotomized as low-grade (G1–2) versus high-grade (G3) endometrial cancers. Patients with serous and clear cell histology were considered high-grade. Standard descriptive statistics were used to describe the demographic and clinicopathologic characteristics. Continuous variables were compared using Student's *t*-test and categorical variables were compared using χ^2 tests.

The independent variable of interest was adjuvant treatment type, which was divided into none, RT, CT, and CRT. The primary outcome was OS and was calculated from date of diagnosis to date of death or last follow-up. Patients who were alive at last follow-up were censored for OS analysis. Kaplan Meier survival analysis and log-rank tests with Šidák correction were used to compare unadjusted OS between the treatment types in all stage IIIC EC patients, as well as both low-grade and high-grade EC patients.

Multivariable Cox proportional hazard models were fit using a stepwise variable selection method and Akaike information criteria (AIC). Interaction between treatment type and grade differentiation, stage, and age were considered during model selection and only a significant interaction was included in the final model. All 2-sided *P*-values <0.05 were considered statistically significant. Statistical analyses were performed with SAS (version 9.3, SAS institution Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

We identified 2519 patients evaluated for endometrial cancer from 2000 to 2012. We excluded 175 patients who did not undergo surgery and 206 patients with ineligible histology. Of the remaining patients, 1712 had surgical and pathological evaluation of lymph nodes. Finally, 199 had surgically-staged node-positive EC, including 115 stage IIIC1 and 84 stage IIIC2 patients. The median follow-up was 40.1 months (95% CI 5.8–153.4 months) and 5-year OS was 36.2%. The distribution of variables between low-grade (G1–2) and high-grade (G3) patients is presented in Table 1. Patients with G1–2 disease were younger (median 60.0 vs. 66.5 years, $p < 0.001$), had fewer positive nodes (median 2.0 vs. 3.0, $p < 0.001$), were more likely to receive adjuvant treatment with RT alone (21.3% vs. 8.8%, $p < 0.001$), and less likely to receive CT alone (12.0% vs. 36.3%, $p < 0.001$) than patients with G3 disease. Adjuvant treatment with CRT was administered in 55.6% of patients with G1–2 disease compared to 44.0% of patients with G3 disease. Only 10–11% of patients in both groups received no adjuvant therapy. There was no difference between the groups in the number of nodes examined, prevalence of LVSI, pelvic washings, or comorbidity score.

3.2. Treatment arms

The distribution of variables between treatment arms is shown in Table 2. Most patients received CRT (50.3%) followed by CT (23.1%), then RT (16.1%), then no adjuvant treatment (10.5%). Median age of patients treated with CRT was lowest (60.5 years), followed by RT (63.0 years), then CT (67.5 years), then no adjuvant treatment (70.0 years). Patients with serous histology or G3 disease were more likely to get CT or CRT adjuvant treatment rather than RT or no treatment. There was no difference in number of positive lymph nodes, LVSI, pelvic washings, and comorbidity score between the different types of adjuvant therapies.

Of the 132 patients that received radiation therapy, 43 received IMRT, 80 received EBRT, not otherwise specified, 9 received

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