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Efficacy of contemporary chemotherapy in stage IIIC endometrial cancer: A histologic dichotomy

Jamie N. Bakkum-Gamez [a], Andrea Mariani [a], Sean C. Dowdy [a], Amy L. Weaver [b], Michaela E. McGree [b], Janice R. Martin [a], Gary L. Keeney [c], Aminah Jatoi [d], Bobbie S. Gostout [a], Karl C. Podratz [a]

[a] Division of Gynecologic Surgery, Mayo Clinic, Rochester, MN, USA
[b] Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA
[c] Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, USA
[d] Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA

HIGHLIGHTS

- Occult extra-pelvic metastases account for greater than 85% of recurrences in stage IIIC endometrial cancer.
- Contemporary adjuvant chemotherapy substantially attenuates extra-pelvic recurrences in stage IIIC grade 1 and 2 endometrioid carcinomas.
- Chemotherapy does not impact extra-pelvic recurrences in stage IIIC grade 3 endometrioid, serous and clear cell carcinomas.

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ABSTRACT

Background. Treatment failures in stage IIIC endometrial carcinoma (EC) are predominantly due to occult extrapelvic metastases (EPM). The impact of chemotherapy on occult EPM was investigated according to grade (G), G1/2EC vs G3EC.

Methods. All surgical-stage IIIC EC cases from January 1, 1999, through December 31, 2008, from Mayo Clinic were included. Patient-, disease-, and treatment-specific risk factors were assessed for association with overall survival, cause-specific survival, and extrapelvic disease-free survival (DFS) using Cox proportional hazards regression.

Results. 109 cases met criteria, with 92 (84%) having systematic lymphadenectomy (>10 pelvic and >5 paraaortic lymph nodes resected). In patients with documented recurrence sites, occult EPM accounted for 88%. Among G1/2EC cases (n = 48), the sole independent predictor of extrapelvic DFS was grade 2 histology (hazard ratio [HR], 0.28; 95% CI, 0.08–0.91; $P = .03$) while receipt of adjuvant chemotherapy approached significance (HR 0.13; 95% CI, 0.02, 1.01; $P = .0511$). The 5-year extrapelvic DFS with and without adjuvant chemotherapy was 93% and 54%, respectively (log-rank, $P = .02$). Among G3EC (n = 61), the sole independent predictor of extrapelvic DFS was lymphovascular space involvement (HR, 2.63; 95% CI, 1.16–5.97; $P = .02$). Adjuvant chemotherapy did not affect occult EPM in G3EC; the 5-year extrapelvic DFS for G3EC with and without adjuvant chemotherapy was 43% and 42%, respectively (log-rank, $P = .91$).

Conclusions. Chemotherapy improves extrapelvic DFS for stage IIIC G1/2EC but not stage IIIC G3EC. Future efforts should focus on prospectively assessing the impact of chemotherapy on DFS in G3EC and developing innovative phase I and II trials of novel systemic therapies for advanced G3EC.

Introduction

Metastatic involvement of regional or distant lymph nodes is well established as a principal prognostic determinant in solid tumors, including endometrial carcinoma (EC). Nevertheless, the indications for lymphadenectomy (LND) and the merits of this procedure in the overall management of EC continue to be debated [1–8]. Proponents of LND in managing at-risk EC contend that the histologic status of regional lymph nodes facilitates the selection of adjuvant therapy [3,6,9]. Accepting this premise, the therapeutic options available in node-positive patients are radiotherapy or chemotherapy or a combination of these modalities. Nonetheless, contemporary therapeutic algorithms for stage IIIC disease have yielded disparate posttreatment recurrence rates [10–15]. Although multiple studies have demonstrated the efficacy of external-beam radiotherapy (EBRT) in minimizing pelvic

Abbreviations: CI, confidence interval; CSS, cause-specific survival; DFS, disease-free survival; EBRT, external-beam radiotherapy; EC, endometrial carcinoma; FIGO, International Federation of Gynecology and Obstetrics; G1/2EC, FIGO grade 1 and 2 endometrioid endometrial carcinoma; G3EC, FIGO grade 3 endometrial carcinoma; GOG, Gynecologic Oncology Group; HR, hazard ratio; LND, lymphadenectomy; OS, overall survival; PORTEC, Post Operative Radiation Therapy in Endometrial Carcinoma.

E-mail address: bakkum.jamie@mayo.edu (J.N. Bakkum-Gamez).

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relapses, treatment failures at distant sites, including the paraaortic area, are frequently observed [15–19]. Consequently, systemic therapy alone or in combination with EBRT has been advocated, but outcomes are inconsistent [10,11,15,20–22].

Optimal management of stage IIIC EC remains unclear, partly because of inconsistencies in addressing and stratifying relevant disease-specific parameters. Although more than 50% of patients with lymphatic dissemination have paraaortic metastasis [9,23,24], the impact of extended-field radiotherapy on lymphatic recurrences beyond the pelvis remains uncertain [2,4,11,12,25,26]. Similarly, the efficacy of contemporary systemic therapy in effectively managing lymphatic and occult distant metastatic disease in EC has not been elucidated [10,15,16,18,19,21,27–31]. Furthermore, emerging reports suggest marked differences in the therapeutic indices comparing endometrioid to type II EC; the latter shows relative recalcitrance to contemporary chemotherapy [10,15,27,30]. Hence, the objective of this investigation was to critically assess the efficacy of existing therapeutic strategies in controlling regional, but more notably occult, distant lymphatic, hematogenous, and peritoneal disease in stage IIIC EC as a function of uterine histology.

Methods

Study patients

This retrospective outcome analysis was approved by the Mayo Clinic Institutional Review Board. We identified women who presented with EC, were counseled, and elected primary surgical management of their disease at Mayo Clinic (Rochester, Minnesota) from January 1, 1999, through December 31, 2008.

Treatment

The surgical treatment algorithm for EC used at our institution previously has been described in detail [9]. Briefly, in the absence of macroscopic extrauterine disease, hysterectomy with removal of the adnexal structures is performed with immediate frozen-section assessment to determine the need for definitive surgical staging. LND is intentionally omitted in approximately 80% of low-risk patients according to the Mayo algorithm (grade 1 or 2 endometrioid with ≤50% myometrial invasion and tumor diameter ≤2 cm, as well as noninvasive endometrioid, regardless of grade). The remaining cohort is considered to have sufficient risk for lymph node metastases and thus requires a pelvic and paraaortic LND; the superior landmark for the latter is the left renal vein. With a diagnosis of uterine serous or clear cell carcinoma, multiple staging biopsies and omentectomy are performed in the absence of detectable macroscopic disease. Cytoreductive surgery is routinely performed in the presence of extrauterine spread, regardless of histology.

In this study, the taxonomy proposed by the World Health Organization was used to designate histologic subtypes [32]. The degree of glandular differentiation and cytologic atypia to determine architectural grade and surgical stage was in accord with International Federation of Gynecology and Obstetrics (FIGO) criteria [33,34]. Pathology review of all cases was conducted by a single gynecologic pathologist (G.L.K.).

For patients electing not to enter available clinical trials, counseling included detailed discussion of the merits and risks of the available adjuvant therapies based on contemporary practice patterns. Apropos to this outcome analysis, consultations regarding radiotherapy focused on local control but acknowledged the risk of distant treatment failures. Radiation-associated untoward sequelae were detailed, including the potential added risks with extended fields. Standard doses of 45.0 to 50.4 Gy to the pelvis, and 45.0 Gy to the paraaortic fields when indicated for lymph node metastases, were recommended. Likewise, the potential merits and associated sequelae of systemic therapy alone or in combination with EBRT were discussed. Platinum-based combination chemotherapy, invariably with paclitaxel or doxorubicin (or both), was the treatment of choice, preferably commencing within 6 weeks postoperatively. Chemoradiation was administered in a serial schema, planning 4 to 6 cycles of systemic therapy before administration of EBRT. When chemotherapy was the sole adjuvant modality, 4 to 6 cycles (more commonly 6 cycles) were recommended and delivered in standard doses. Vaginal brachytherapy was judiciously administered, regardless of the primary adjuvant therapy.

Data collection and statistical analysis

Patient-, disease-, and treatment-specific risk factors were abstracted from the medical records by a dedicated registered nurse following the American College of Surgeons' National Quality Improvement Program platform [35,36]. When surveillance information from the clinic or tumor registry records was insufficient, rigorous efforts were expended to update patient and disease status, including sending letters to patients or their physicians, conducting telephone interviews, and securing death certificates.

Data were summarized using standard descriptive statistics. Demographic and clinicopathologic characteristics were compared between groups using the 2-sample t test for age and the χ^2 test for categorical variables. Duration of follow-up was calculated from the date of surgical treatment to the date of death or last follow-up. Overall survival (OS), cause-specific survival (CSS), and disease-free survival (DFS) were each estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Risk factors were evaluated for an association with DFS based on fitting univariable Cox proportional hazards models. Multivariable models were fit using stepwise and backward variable selection methods considering all variables with a P value < .20 based on univariable analysis. Associations were summarized by calculating hazard ratios (HRs) and corresponding 95% CIs. All calculated P values were 2-sided, and P values < .05 were considered statistically significant. Analyses were performed using the SAS software package, version 9.2 (SAS Institute Inc.).

Results

Patients

During the study period, 1415 women presented with EC, were counseled, and elected primary surgical management of their disease. In accordance with the Minnesota statute for use of medical information in research [37], women who declined consent for use of recorded clinical information for research purposes were excluded from the study population (n = 22). In addition, 79 patients were diagnosed with synchronous cancers and were excluded, rendering an eligible study population of 1314 patients.

Clinicopathologic characteristics

Among the 1314 surgically managed EC patients, 109 received the diagnosis of stage IIIC disease. Forty-eight cases had FIGO grade 1 and 2 endometrioid carcinoma (G1/2EC), and 61 had grade 3 histology (G3EC), including endometrioid, serous, and clear cell carcinomas. Table 1 provides a comparative assessment of the clinical and pathologic characteristics of the 2 cohorts. The mean age of the G1/2EC cohort exceeded the age of the G3EC cohort; this finding was unexpected, but it also was not a statistically significant difference. A systematic LND (defined as removal and histologic assessment of ≥10 pelvic and ≥5 paraaortic nodes) was performed in 85% of G1/2EC and 84% of G3EC patients. The prevalence of stage IIIC2 was independent of grade (P = .21); of the 100 patients with a paraaortic LND, 33.3%, 69.0%, and 55.4% of the patients with grades 1, 2, and 3 had positive paraaortic nodes, respectively. Noteworthy was the absence of lymphovascular space invasion in 73% of the G1/2EC cohort, nearly double that witnessed among the G3EC cases. Overall, 52 (47.7%) patients received