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Comparative outcomes assessment of uterine grade 3 endometrioid, serous, and clear cell carcinomas

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HIGHLIGHTS

- Overall survival as a function of histologic subtypes dies not differ statistically, even when controlling for disease stage.
- Age, lymphovascular space involvement, residual nodal disease, and radiotherapy independently affect survival in stage III high-risk uterine cancers.
- Lymphovascular space involvement, cervical stromal invasion, and chemotherapy independently affect survival in stage IV high-risk uterine cancers.

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ABSTRACT

Objective. The objective of this study is to assess effects of clinicopathologic risk factors and contemporary therapeutic interventions on high-risk uterine epithelial carcinoma outcomes.

Methods. Patient-, disease-, and treatment-specific variables were annotated. Survival was estimated via the Kaplan–Meier method. Associations were evaluated with Cox proportional hazard regression and summarized using hazard ratios.

Results. From 1999 through 2008, therapy with curative intent was initiated for 119 grade 3 endometrioid (G3EC), 211 serous (USC), and 40 clear cell (CCC) carcinomas. Although clinicopathologic risk factors varied among the histologic subtypes, overall survival (OS) did not differ statistically between subtypes ($P = .10$) or in stage-for-stage comparative analyses (stage I/II, $P = .45$; stage III, $P = .46$; stage IV, $P = .65$). The 5-year cause-specific survival in stage I/II was 84.8%, 89.8%, and 83.9% for G3EC, USC, and CCC, respectively; multivariable modeling identified lymphovascular space involvement (LVSI) as the only independent prognostic factor ($P = .02$). For stage III, 5-year OS was 49.2% and 40.0% for G3EC and USC, respectively; multivariable modeling identified age ($P < .001$), LVSI ($P < .001$), unresectable nodal disease ($P = .03$), and regional radiotherapy ($P = .01$) as independent prognostic factors. For stage IV, 5-year OS was 8.7% and 12.1% for G3EC and USC, respectively; multivariable modeling identified LVSI ($P = .002$), cervical stromal invasion ($P = .02$), and adjuvant chemotherapy ($P = .02$) but not residual disease as independent prognostic factors.

Conclusions. When controlled for disease stage, outcomes did not differ among high-risk histologic subtypes. LVSI was a significant adverse prognostic factor within all stages. The lack of improved outcomes with contemporary therapy suggests that more innovative therapeutic approaches should be given higher priority.

Introduction

It has been 30 years since Hendrickson et al. [1] described the clinicopathologic characteristics of uterine serous carcinoma (USC) as being distinct from the more common endometrioid adenocarcinoma. Although recognition of uterine clear cell carcinoma (CCC) predated USC, their diverse histologic subtypes and aggressive natural histories relative to their endometrioid counterpart favored their designation as type II endometrial cancers (ECs) [1,2]. However, poorly differentiated

Abbreviations: CCC, clear cell carcinoma; EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group; G3EC, grade 3 endometrioid carcinoma; HR, hazard ratio; LND, lymphadenectomy; LVSI, lymphovascular space involvement; OS, overall survival; R0, no residual disease; USC, uterine serous carcinoma.

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or grade 3 endometrioid carcinomas (G3EC), which account for a limited percentage of type I cancers, have historically been recognized to also portend a poor prognosis [3–5]. Collectively, these 3 epithelial carcinomas reportedly comprise approximately 25% of new cases but account for nearly 75% of EC deaths annually [6]. These sobering figures attest to the exigency for the elucidation of the pathogenesis and the development of more innovative therapies for these virulent cancers.

The clinicopathologic characteristics and molecular profiles attributed to type I EC are representative of well- and moderately well-differentiated endometrioid EC but differ distinctly from type II cancers [7–12]. By contrast, G3EC harbors genomic and epigenomic alterations commonly ascribed to both histologic subtypes [12,13]. Furthermore, the similarities in the clinical behaviors of G3EC and type II cancers and the frequency of their coexistence have generated debate about whether G3EC should be classified as a type I or type II EC [14–19]. Comparative clinical analyses of G3EC, USC, and CCC are very limited, reflecting the low prevalence of each of these histologic subtypes. Consequently, the existing reports are restrictive and conflicting because of sample size, inclusion criteria (primary with or without recurrent disease), treatment variability (staging, cytoreduction, adjuvant therapy), definitions and assignment of histologic subtype (pure vs mixed), or a combination of these factors [6,19–21]. The aim of this study was to conduct a comparative clinical outcomes assessment of G3EC, USC, and CCC cases in a 10-year period; patients were managed in a consistent manner by gynecologic oncologists within a tertiary referral center.

Methods

Study patients

This retrospective investigation was approved by the Mayo Clinic Institutional Review Board. From January 1999 through December 2008, 1415 patients presenting with epithelial EC for primary intervention were surgically managed at Mayo Clinic (Rochester, Minnesota). In accordance with the Minnesota Statute for Use of Medical Information in Research, women who did not consent to use of information in their medical records were excluded from the study population (n = 22). Initiation of accrual for this report coincided with the transition to more uniform individualized treatment algorithms for EC; this was further standardized with the integration of a surgical quality assessment instrument in January 2004.

Treatment

The surgical treatment algorithm consisted of removal of the uterus and adnexa and prompt intraoperative histologic assessment of the primary tumor, which dictated subsequent surgical intervention. The technique for processing and examining intraoperative frozen sections has been detailed previously [22]. The taxonomy proposed by the World Health Organization was used to distinguish histologic subtypes [23]. Prior reports demonstrated that minor components of serous carcinoma coexisting with endometrioid carcinoma confer clinical behavior and outcomes more consistent with serous than endometrioid EC [15,17]; thus, tumors with mixed histologic subtypes were assigned according to a hierarchy with 1) any evidence of USC superseding CCC and G3EC and 2) CCC dominant to G3EC. The degree of glandular differentiation and cytologic atypia was used to determine architectural grading according to the International Federation for Gynecology and Obstetrics (FIGO) [24]. All pathologic review was performed by 1 gynecologic pathologist (G.L.K.). Stage assignment utilized the 2009 FIGO staging classification criteria [25].

Unless contraindicated by excessive medical comorbidities or advanced disease, the surgical management of high-risk EC included bilateral pelvic and para-aortic lymphadenectomy (LND). The superior anatomic landmarks for the latter were the renal vessels. Staging biopsies, omentectomy, and cytoreductive procedures were performed as dictated by frozen section assessment and the extent of disease. The cytoreductive objective was no residual disease (R0).

The rationale for adjuvant therapy was predicated on the documented presence of extrauterine disease and clinical scenarios judged to have high risk of occult extrauterine dissemination. Patients with deep myometrial invasion were considered at-risk for hematogenous dissemination and were candidates for systemic therapy. Patients with lymphovascular space involvement (LVSI) were considered at-risk for occult vaginal spread and were candidates for vaginal brachytherapy. Pelvic external-beam radiotherapy was administered for regional nodal involvement and extended to include the para-aortic region, with spread to this site. Platinum-based combination chemotherapy, invariably with paclitaxel or doxorubicin or both, was the treatment of choice for patients with histologic evidence of intraperitoneal or extra-abdominal disease or judged to have substantial risk of recurrence. Serial administration of chemotherapy and radiotherapy was frequently chosen when patients fulfilled the above criteria for both modalities. Similarly, vaginal brachytherapy was judiciously added (29.5%) to treatment, regardless of the dominant adjuvant modality.

Data collection and statistical analysis

Patient-, treatment-, and disease-specific parameters were abstracted from clinic records by a dedicated nurse following the American College of Surgeons National Surgical Quality Improvement Program platform [26,27]. Rigorous efforts were expended to secure accurate surveillance histories through clinic and tumor registry records. When information regarding survival or recurrences was not current or sufficiently detailed in the records, we reviewed death certificates, sent letters to patients or their personal physicians, or conducted telephone interviews to obtain the necessary information.

Comparisons of the patient-, disease-, and treatment-specific variables between the histologic subtypes were evaluated using the χ^2 test for the categorical variables and the F-test from a 1-way analysis of variable model for age and body mass index. 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, and cumulative incidence of recurrence (i.e., 100 − [recurrence − free survival]) were each estimated using the Kaplan–Meier method. Univariable and multivariable Cox proportional hazard models were fit for each time-to-event outcome and fit separately for stages I/II, III, and IV. Multivariable models were fit by first adjusting for histologic subtype and then by identifying any statistically significant factors using stepwise and backward variable selection techniques. Associations were summarized by calculating hazard ratios (HRs) and corresponding 95% CIs. All calculated *P* values were 2-sided and *P* values less than .05 were considered statistically significant. Analyses were performed using the SAS software package, version 9.2 (SAS Institute Inc.).

Results

Of 1393 patients who authorized use of their records for research, high-risk EC was diagnosed in 388 patients (27.9%). After excluding 18 patients with synchronous cancers, 370 were eligible for evaluation, including 119 with G3EC, 211 with USC, and 40 with CCC. Comparative assessments of patient-, disease-, and treatment-specific variables associated with the 3 epithelial cancers are shown in Table 1. Demographic characteristics were not statistically dissimilar among the histologic subtypes. CCC more frequently harbored disease confined to the uterus. Conversely, G3EC had a higher prevalence of deep myometrial invasion and stage III disease, whereas USC had a higher prevalence of positive peritoneal washings and stage IV disease. Adjuvant therapy was administered more frequently in patients with USC. Among patients undergoing LND (median node count, 44), pelvic node metastases were encountered in 32.7%, 34.9%, and 20.6%