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Uterine serous carcinoma: Reassessing effectiveness of platinum-based adjuvant therapy

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HIGHLIGHTS

- Most uterine serous carcinomas fail to respond to platinum-based chemotherapy.
- Critical lag times precede declaration of platinum refractory microscopic disease.
- Truncated survival/systemic failures compel a search for more effective therapy.

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ABSTRACT

Objective. Two randomized trials failed to demonstrate efficacy of platinum-based chemotherapy (PbCT) for uterine serous carcinoma (USC). Our objective was to reassess the value of PbCT for patients with microscopic residuum (R0).

Methods. Progression-free survival (PFS) after surgery was analyzed for 409 patients and correlated with adjuvant therapies: vaginal brachytherapy (VBRT), external beam radiotherapy (EBRT), PbCT, or combinations.

Results. The estimated 5-year PFS for stage I ($n = 209$) USC was 65.1% for observation only; 90.7%, VBRT only; and 91.1%, PbCT ± VBRT (85% received VBRT); VBRT significantly ($P = .004$) impacted PFS, but the added value of PbCT remains uncertain. Of 58 stage IIIC, PbCT-treated patients (±EBRT), 5-year PFS was 33.9%; most failures had a vascular disseminated component. Median PFS for 72 stage IV, PbCT-treated patients was 18.6 months for R0; 8.0, R1 ≤ 1 cm residual disease; and 4.6, R2 > 1 cm ($P = .008$). The progression rate (PR) during 1 to 2 year follow-up for R0 was similar to PR during 0–1 year follow-up for R1 ($P = .31$), suggesting recurrences in patients with R0 disease before 2 years are likely platinum resistant. PRs during follow-up were nearly identical for R0 ≥ 2 years and R1 ≥ 1 year ($P = .95$), presumably showing limited numbers of platinum-sensitive tumors.

Conclusions. A comparison of PR for patients treated with PbCT for stage IV R0 and R1 disease suggested that a 1-year lag interval precedes clinical recognition of PbCT refractory/resistant R0 disease. Most patients treated with PbCT who had microscopic residuum had recurrences within 2 years (across stages), emphasizing the need for more effective therapy.

1. Introduction

The current therapeutic algorithm for advanced-stage, high-grade uterine epithelial cancers generally includes surgical staging, cytoreduction, and administration of adjuvant platinum-based chemotherapy (PbCT) [1]. These principles have been extrapolated from the management of advanced-stage, high-grade serous ovarian cancer (HGSOC), for which the response rate to PbCT is 80%, and median

Abbreviations: CT, chemotherapy; EBRT, external beam radiotherapy; EEC, endometrial endometrioid carcinoma; HGSOC, high-grade serous ovarian cancer; HR, hazard ratio; IQR, interquartile range; OS, overall survival; PbCT, platinum-based chemotherapy; PFS, progression-free survival; PR, progression rate; R0, no macroscopic residual disease; R1, residual disease ≤1 cm; R2, residual disease >1 cm; RT, radiotherapy; USC, uterine serous carcinoma; VBRT, vaginal brachytherapy.

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overall survival (OS) rates exceed 5 years in patients whose tumors are completely cytoreduced [2]. This experiential model has been advocated for both advanced endometrial endometrioid carcinoma (EEC) and uterine serous carcinoma (USC). However, in the protocol based on Gynecologic Oncology Group 122, a clinical trial that randomized patients with advanced and recurrent endometrial cancer to either abdominal irradiation or PbCT, a survival advantage was readily shown with PbCT for EEC (progression-free survival [PFS] hazard ratio [HR], 0.687; OS HR, 0.482) but not for USC (PFS HR, 0.909; OS HR, 1.025) [3]. Similarly, a prospective clinical trial of pelvic radiotherapy (RT) alone vs RT plus PbCT for patients with stage I/II endometrial cancer showed a survival advantage with added PbCT for patients with EEC but not for those with USC or clear cell carcinomas [4]. Nevertheless, the increasing use of PbCT for treating USC at our institution and others, even for stage I patients, presupposes an evolving standard of care with uncertain justification [1].

This transition in clinical practice patterns is based on numerous retrospective studies, reviewed in detail by Sagae et al. [1], which reported clinical outcomes for small cohorts of patients with the majority having no measurable disease at initiation of chemotherapy (CT). Without randomized comparisons for defining platinum-refractory, resistant, or sensitive USC in the adjuvant setting, ascertaining therapeutic efficacy is indeed challenging. PFS is the current metric of choice for determining drug sensitivity for patients harboring tumors with reliable biomarkers or measurable disease. The use of such parameters for primary USC is limited and infrequently applicable, except in stage IV with macroscopic residual disease. The lag time requisite for microscopic refractory or resistant residual USC to become clinically detectable and afford reliable assessment of PFS is undefined.

USC has an aggressive natural history, and the effectiveness of contemporary, adjuvant PbCT in the absence of measurable disease has not been established. Clinical trial data and current observations as well as the experiential transition in managing USC at our institution over the past 18 years were incentives to conduct a more detailed assessment of the effectiveness of adjuvant therapies for USC.

2. Methods

The number of new cases of endometrial cancer is increasing in the United States [5]. In our tertiary care practice, the volume is also increasing, with the prevalence of USC (approximately 14%) somewhat higher than expected. From January 1, 1999, through June 30, 2016, 409 patients diagnosed with serous carcinoma or serous carcinoma with either endometrioid or clear cell carcinomas of documented uterine origin were eligible for inclusion in this study. Patients were excluded if they declined research authorization, had invasive synchronous cancers, or had received neoadjuvant CT. This study was approved by the Mayo Clinic Institutional Review Board. Only those patients who consented to use of their medical records for research were included in the analyses, in accordance with the Minnesota Statute for Use of Medical Information in Research.

During the study period, surgical staging and cytoreduction followed by selective adjuvant therapies were the main therapies. The benchmarks used for staging were based on the 2009 International Federation of Gynecology and Obstetrics criteria for endometrial cancer [6]. During the first tertile of this study, the standardized treatment algorithm was adjusted periodically after outcomes were assessed. Beginning in 2004, specific surgical guidelines were developed for staging, and periodic quality assessments of the results were begun [7]. Shortly thereafter (first tertile of this study), we demonstrated a need for adjuvant vaginal brachytherapy (VBRT) in patients with early stage disease who had vaginal recurrences, grade 3 histologic findings, and lymphovascular space involvement [8]. The primary adjuvant therapy for stage I disease was VBRT ± PbCT; however, PbCT ± external beam radiotherapy (EBRT) was considered standard treatment for eligible patients with advanced-stage disease. Combined therapy was preferably administered sequentially, although PbCT was infrequently "sandwiched" around EBRT. Pelvic EBRT was administered at 45 to 50 Gy in 5 to 7 weeks, with fields extended for paraaortic metastases. Of 190 patients who received adjuvant CT, treatment methods were not available for 8. PbCT, either cisplatin or carboplatin in standard doses, was given to the remaining 182 patients (94.8%) in combination with paclitaxel ($n = 168$) or doxorubicin ($n = 7$), or both ($n = 7$).

Pathologic criteria used to diagnose USC typically included foci of papillary growth, high-grade cytologic findings, hob-nail cells, and cells exfoliated into luminal spaces. In cases where the diagnosis was suspected from high-grade cytologic findings alone, p53 over expression or loss, and strong, block-like p16 expression were used for confirmation. In specimens with mixed differentiation, the serous component was considered the principal histologic finding. Systematic histologic reassessment of specimens accrued before 2009 and intermittently thereafter was conducted by a senior gynecologic pathologist (G.L.K).

2.1. Statistical analyses

Statistical analyses were performed using SAS version 9.3 software (SAS Institute Inc). PFS after surgery was estimated using the Kaplan-Meier method; the duration of follow-up for patients without a documented progression was censored at the date of their last relevant clinical follow-up. Comparisons of PFS between groups were evaluated using the log-rank test. Multivariable Cox proportional hazards regression models were fit to identify factors independently associated with progression. Progression rates (PRs), stratified by extent of residual disease and follow-up intervals, were calculated as the number of patients in each stratum, with progression divided by the total duration of follow-up during each follow-up interval and expressed per 1 person-year of follow-up. Exact 95% CIs were constructed, assuming the observed number of patients with progressions followed a Poisson distribution and the number of person-years was fixed. All calculated P values were 2-sided, and P values $< .05$ were considered statistically significant.

3. Results

During the study period, 409 patients with USC met the inclusion criteria. Table 1 shows age at surgery, histologic findings, stage, and therapeutic interventions for early localized and advanced disease. Patients with stage III/IV disease more often had positive cytologic findings, tumor size >2 cm, myometrial invasion ≥50%, and adjuvant systemic therapy. Of the patients with stage III/IV disease, 64.9% underwent cytoreduction to no residual disease (R0) (87.4% had residual disease ≤1 cm [R1]).

Of 218 patients with early stage disease, 209 had stage I disease. Postoperative adjuvant therapy for the patients with stage I disease included VBRT alone in 79 patients; PbCT alone, 8 patients; PbCT plus VBRT, 44 patients; and EBRT only, 4 patients. Fifty-six patients were observed only, and the initiation/completion of adjuvant therapy was not documented for 18 patients. Of the 209 patients with stage I disease, 26 (12.4%) had a documented progression at a median of 1.3 years after surgery (interquartile range [IQR], 0.8–2.9 years). The median duration of relevant clinical follow-up for the remaining 183 patients with stage I disease was 3.1 years (IQR, 0.7–7.7 years). Overall, the estimated 5-year PFS for patients with stage I disease was 81.3% (95% CI, 74.7–88.5). In multivariable analysis, adjuvant therapy was the strongest predictor of PFS; none of the other variables (Table 1) were significant after adjuvant therapy was included in the model (results not shown). Compared with observation only, clinical outcomes (PFS) were better after either VBRT only or PbCT ± VBRT ($P = .004$) (Fig. 1). The estimated 5-year PFS for observation only was 65.1% (95% CI, 51.3–82.7); VBRT only, 90.7% (95% CI, 83.1–99.0); and PbCT ± VBRT, 91.1% (95% CI, 81.3–100.0).

Of the patients with advanced disease, 72 had stage IIIC disease. Of these patients, 67 (93.1%) had systemic lymphadenectomy, including

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