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The role of radiotherapy in the management of resected uterine papillary serous and clear cell carcinoma

Emma C. Batchelor [a,*], John M. Watkins [a], William T. Creasman [b], Matthew F. Kohler [b], Debajyoti Sinha [c], Joseph M. Jenrette [a]

[a] Department of Radiation Oncology, Medical University of South Carolina, Charleston, SC 29425, USA
[b] Department of Obstetrics and Gynecology, Medical University of South Carolina, Charleston, SC, USA
[c] Department of Biostatistics, Bioinformatics, and Epidemiology, Medical University of South Carolina, Charleston, SC, USA

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ABSTRACT

Objective: Primary uterine papillary serous (PS) and clear cell (CC) carcinoma are aggressive histologies characterized by elevated risk of loco-regional recurrence and disease-specific mortality following hysterectomy. The impact of adjuvant radiotherapy remains to be elucidated. The present study is a single institution, retrospective cohort comparison to determine whether post-hysterectomy radiotherapy improves loco-regional control and/or disease-specific survival outcomes in a population of women with PS and/or CC.

Study design: Between June 1992 and November 2006, 50 women underwent hysterectomy alone (H) or hysterectomy with adjuvant radiotherapy (H + RT) for primary uterine PS and/or CC. RT involved either high dose-rate (HDR) brachytherapy, external beam RT, or both.

Results: At a median survivor follow-up of 27 months (range 2.7–137.3) for the H + RT group and 61 months (range 11.9–114.6) for the H group (range 3–137), patients in the H + RT group demonstrated a trend toward superior disease-free survival (not yet attained at 26 months versus 25 months; $p = 0.0625$). For patients with ≥24 months of follow-up, disease recurrence was significantly higher in H patients over H + RT patients (45% versus 12.5%; $p < 0.05$). Additionally, the H + RT group demonstrated significant improvement in loco-regional control (0% versus 37.5%; $p < 0.001$), most pronounced within FIGO stages I–II H + RT patients (0% versus 70%; $p < 0.001$). Overall survival was not significantly different between the two cohorts (H = 32 months, H + RT = not yet attained at 26 months; p = non-significant).

Conclusions: Hysterectomy with adjuvant radiotherapy significantly improves disease-free survival within 2 years post-hysterectomy and significantly reduces loco-regional failures over hysterectomy alone.

1. Introduction

Of the anticipated 39,000 cases of primary uterine cancer that will be diagnosed in the United States this year, approximately 6–15% will be papillary serous (PS) and/or clear cell (CC) histology [1,2]. Both variants are locally aggressive and have high rates of deep myometrial invasion and extensive lymphovascular space invasion at diagnosis [3]. These high risk features translate into advanced stage at hysterectomy, increased rates of loco-regional recurrence, and reduced overall survival even in early-stage disease [4–6]. Five-year overall survivals of 42–72% have been described for FIGO stages I–II PS or CC [7–10], compared with 75–87% for similarly staged endometrioid adenocarcinomas [11,12].

Definitive therapy for early-stage endometrial cancer involves primary hysterectomy and bilateral salpingo-oophorectomy, with stage-dependent lymphadenectomy and peritoneal cytology. Adjuvant therapy is highly individualized. The 2008 National Comprehensive Cancer Network guidelines recommend observation or vaginal brachytherapy for stage IA confined to a polyp and chemotherapy plus radiotherapy (RT) for all other stage IA. For stages IB, IC, II, and adequately debulked III and IV, the recommendations are chemotherapy plus or minus RT or a regimen of whole abdominopelvic RT plus or minus vaginal brachytherapy. Chemotherapy alone is recommended for inadequately debulked stages III and IV. The most commonly used chemotherapy regimens are platinum-based regimens including cisplatin and carboplatin. Others commonly used are paclitaxel and doxorubicin [13].

Adjuvant RT is generally recommended when the risk for loco-regional recurrence exceeds 10%, as with high risk histology (high-

* Corresponding author. Tel.: +1 843 412 4843; fax: +1 843 792 5498.
E-mail address: batchele@musc.edu (E.C. Batchelor).

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grade adenocarcinoma, PS, CC), myometrial invasion ≥50%, lymph node involvement, or insufficient nodal sampling. Specific to PS and CC, recurrence rates of 50–80% have been described following hysterectomy alone, with up to 50% isolated loco-regional failures [3–5,14–16]. The precise role of RT in resected PS and CC remains to be defined. The present study describes a single institution retrospective cohort comparison of women with PS and/or CC who underwent hysterectomy with or without adjuvant RT, focusing on loco-regional control, patterns of failure, and disease-free and overall survivals.

2. Methods

Patients diagnosed with primary uterine PS or CC between 1992 and 2006 were identified from diagnosis-based searches of departmental electronic medical records and/or institutional cancer registry records. Eligibility criteria for inclusion in the present study included: primary uterine PS or CC (with or without associated adenocarcinoma), hysterectomy as initial intervention, and treatment with curative intent. Exclusion criteria included: residual metastatic disease at diagnosis, serous carcinoma with concurrent or previous ovarian stromal carcinoma, inadequate treatment-related data for the present analysis, and/or insufficient patient follow-up. The histological criteria to define PS and CC endometrial cancers at the Medical University of South Carolina are the presence of papillary serous or clear cells noted in the biopsy or resection samples. To be considered a mixed histological subtype at least 10% of another cell type must be present in addition to papillary serous or clear cells in the resection or biopsy. All pathology specimens were reviewed in our pathology department.

Following institutional review board approval of this project, data were retrospectively identified from institutional and departmental electronic and paper records, and recorded into the study database. Data extracted included patient- (age, race), tumor- (stage, histology), treatment- (type and timing of interventions), and outcome-related data fields. The primary objective of this study was to describe differences in local control between patients who underwent hysterectomy alone versus hysterectomy plus adjuvant RT. Local control was measured from date of hysterectomy to date of pelvic failure (or last follow-up if no failure). Disease-free survival and overall survival were also recorded as secondary endpoints. Disease-free survival was measured from date of hysterectomy to disease recurrence or last follow-up (if no recurrence); overall survival was measured from date of hysterectomy to last follow-up or death. Clinical or radiographic initial sites of disease recurrence were recorded as site of failure, regardless of subsequent manifestation of disease. Recurrence location was recorded as ''local'' (vaginal cuff), ''regional'' (pelvic lymph nodes), ''distant,'' or ''loco-regional and distant.'' Biopsy of suspected recurrence was generally performed, though not required for definition of failure.

Radical and total abdominal hysterectomies were generally performed when a prior biopsy had confirmed presence of uterine cancer, with the former reserved for locally advanced disease. On occasion, uterine carcinoma was identified during pathologic examination for simple hysterectomy performed for other reason (symptomatic leiomyomata, etc.). In general, surgical staging involved para-aortic lymph node sampling, peritoneal washing cytology, and resection of concerning omental/peritoneal nodules; however, complete omentectomy was not routinely performed.

The recommendations for adjuvant RT were based upon referral from gynecologic oncologists, with non-uniformity due to individual differences in opinion regarding the relative merit (loco-regional control versus survival) of RT. When patients were referred to radiation oncology for consideration of adjuvant RT for PS, CC, or endometrial adenocarcinoma with either high-grade component, recommendation for post-operative RT was generally made. However, not all patients were referred to radiation oncology, and as such not all received RT. This heterogeneity allows for the present study, delineating a referral bias rather than patient selection bias. RT intervention recommendations (high dose-rate (HDR) brachytherapy, external beam RT, or both) were related to both chronological and clinical factors. External beam pelvic RT was employed as a sole modality for all patients from 1995 to 1998. From 1999 to 2004, 45 Gy external beam pelvic RT was coupled with two fractions of HDR brachytherapy (13.5 Gy) for early-stage (FIGO IA–IB) patients. Since 2005, patients with stages IA–IIA disease have been recommended HDR brachytherapy alone (21 Gy in 3 fractions), while higher stage patients have been recommended external beam pelvic RT alone.

HDR brachytherapy involved placement of a vaginal cylinder specifically fitted with a central hollow catheter. The diameter of the vaginal cylinder was specifically selected for each patient, allowing for uniform and maximal displacement of vaginal mucosa from the catheter. A lubricated synthetic condom was fitted over the cylinder prior to each placement, and the cylinder was advanced until resistance from the vaginal cuff was appreciated. A permanent ink pen was used to mark the patient's thigh adjacent to the distal edge of the catheter to assist placement verification during future cylinder placements. Next, the cylinder was stabilized with mesh underwear, and a plain anteroposterior film radiograph was taken to verify position following each cylinder placement (Fig. 1). Next, a staff medical physicist created the HDR treatment plan specific to the physician's prescription. In general, patients undergoing adjuvant HDR alone were prescribed 2100 cGy in 3 treatment fractions delivered every other day, prescribed to 0.5 cm depth beyond the cylinder surface, to the superior-most 3–4 cm of the vaginal cuff. Treatment planning was performed using Nucletron Planning System version 3.5 (Nucletron, BV, Veenendaal, The Netherlands). Following treatment planning, the patient would be transported to a shielded treatment room (vault), and the catheter connected to the HDR remote afterloading device, which contained the ^{192}Ir HDR source (activity 3.8–9.8 mCi). External beam RT consisted of whole pelvis fields, typically delivered in a ''four-field box'' technique, utilizing opposed anteroposterior/posteroanterior and

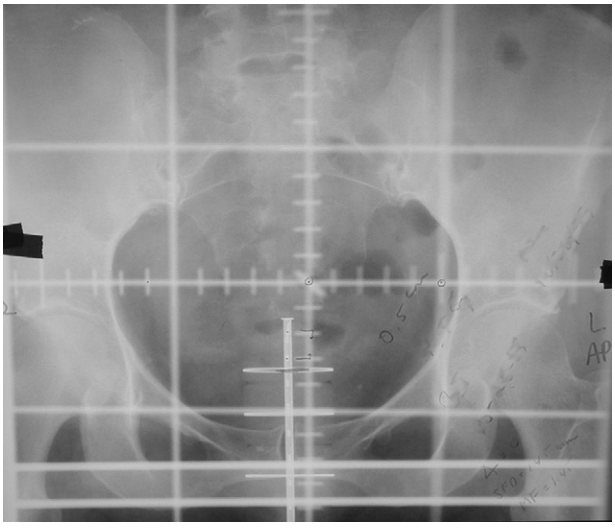

Fig. 1. Simulation film for vaginal cuff high dose-rate brachytherapy; anteroposterior view.