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Adjuvant radiation in early stage, unfavorable histology endometrial carcinoma is associated with improved local control and survival

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HIGHLIGHTS

- We compared the association of adjuvant radiation therapy and outcomes in patients with unfavorable histology, FIGO IA endometrial cancer.
- Adjuvant radiation therapy was associated with a significant improvement in local–regional control.
- Adjuvant radiation therapy was associated with a significant improvement in overall survival.

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ABSTRACT

Objective. Unfavorable histology endometrial carcinomas confer worse prognosis. We determined the association of adjuvant radiation on local recurrence and survival for unfavorable, early stage endometrial cancer.

Methods. We retrospectively identified 125 patients who had a hysterectomy for early stage (FIGO IA), unfavorable histology (clear cell, papillary serous or grade 3 endometrioid), endometrial carcinoma treated between 1992 and 2011. Patients were restaged according to current FIGO 2009 guidelines. Primary endpoint was local control and secondary endpoints were distant recurrence and overall survival.

Results. The median age of the cohort was 67 years old with a mean follow up 152 months. Adjuvant radiation was delivered in 60 patients (48%). There were a total of 24 recurrences; 5 had local–regional recurrences, 4 local and distant recurrence, 12 distant only recurrences, and 3 had unspecified recurrences. The 5-year local–regional control was 97.8% in patients who received radiation and 80.1% in patients who did not receive radiation ($p = 0.018$). The 5-year overall survival rate was 68.1% if patients did not receive radiation and 84.9% if they did receive radiation ($p = 0.0062$). On univariate analysis, only radiation (HR 0.12, 95% CI: 0.03 to 0.49, p-value $= 0.018$) was associated with a significant increase in local relapse free survival.

Conclusions. Adjuvant radiation therapy was significantly associated with an improvement in local–regional control and overall survival in patients with unfavorable histology, early stage endometrial cancer.

Introduction

Endometrial carcinoma is the most common gynecologic malignancy in the United States with an incidence of 40,000 cases a year. Approximately 80% of endometrial carcinomas are of Type I origin (endometrioid adenocarcinomas) while the second most common histologies are of Type II origin (clear cell and papillary serous). Type I tumors are estrogen dependent tumors, and patients are more likely to be diagnosed at an earlier stage. Type II tumors are estrogen independent, more frequently harbor a p53 mutation, and are more likely to be diagnosed with metastatic disease. Grade 3 adenocarcinomas, clear cell and papillary serous endometrial cancers are thought to have poorer prognosis compared to their low or intermediate grade histologic counterparts [1,2]. A study of patients from the SEER database demonstrates poorer survival in patients with clear cell and papillary serous subtypes compared to grade 3 endometrial adenocarcinomas [3]. However, a review from the annual report of FIGO demonstrates equivalent survival for papillary serous and clear cell subtypes compared to grade 3 endometrial adenocarcinomas [4]. Grade 3 endometrioid adenocarcinomas portend a worse prognosis compared to their grade 1 and 2

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counterparts [5]. Because of poorer outcomes, adjuvant radiation therapy has been used to improve local control. Recent recommendation guidelines by the Society of Gynecologic Oncology note that vaginal brachytherapy may be considered in the management of Stage IA uterine papillary serous cancer [6]. In a subsequent review by the Society of Gynecologic Oncology, no definitive recommendations could be made for adjuvant treatment of clear cell endometrial cancer [7]. Randomized trials that have evaluated the role of radiation therapy in early stage endometrial cancer patients have not been conclusive for patients with high risk histologies [8–10].

Several retrospective studies have attempted to examine the importance of vaginal cuff brachytherapy in early stage endometrial cancer. FIGO Stage I, unfavorable histology endometrial cancers are quite rare, and constitute approximately 9–14% of all endometrial cancers [3,4,11]; FIGO IA cancers are even more rare. Barney, et al. showed that in a retrospective review of Stage I endometrial carcinoma patients with clear cell and/or papillary serous histology following surgery and vaginal brachytherapy, the 5 year estimates of vaginal recurrence were 3% [12]. Similarly, a retrospective review of 37 patients of Stage I and II clear cell or papillary serous histology who had adjuvant vaginal brachytherapy had a 2 year vaginal recurrence rate of 3.2% [13]. However, these studies did not evaluate a comparison group of women who did not receive vaginal brachytherapy. In addition, these studies did not evaluate FIGO IA patients alone.

Our hypothesis is that very, early stage (FIGO IA) endometrial cancer patients with unfavorable histologies have high local recurrence rates and adjuvant radiation therapy can improve local–regional relapse.

Methods

We retrospectively identified 2816 patients with endometrial carcinoma at Intermountain Healthcare and the University of Utah who had a hysterectomy between 1992 and 2011. Based upon previously constructed databases, we identified patients with less than half myometrial invasion. We excluded patients with positive lymph nodes and patients with Grade 1 or Grade 2 histology. This would, therefore, lead to inclusion of patients who were staged as FIGO IIIa (FIGO 1998 staging). Pathology reports were then re-reviewed to ensure patient eligibility. Based upon these criteria, we then identified 125 patients with endometrial carcinoma who had a hysterectomy for early stage (FIGO IA), unfavorable histology (clear cell, papillary serous or grade 3 endometrioid adenocarcinoma), endometrial carcinoma treated between 1992 and 2011. Data regarding demographics, surgical report, pathology, radiation delivery, and follow-up were obtained.

Patient cohort

Patients were staged according to current FIGO 2009 guidelines. This was an IRB approved study, IRB number 1024494. Exclusion criteria included uterine sarcoma histology, prior or concurrent diagnosis of other non-cutaneous malignancy, prior chemotherapy or previous pelvic radiation therapy. All patients who were enrolled on the study had less than <50% myometrial invasion (FIGO IA) and negative margins after surgery. Additionally, the precise myometrial depth of penetration were obtained in 78 patients (62.4%), lymphovascular space invasion was available in 88 patients (70.4%), largest tumor diameter was available in 94 patients (75.2%), tumor volume was available in 37 patients (29.6%), and cytology was available in 77 patients (61.6%). Univariate analysis was performed on the data that was available.

Radiation

Adjuvant radiotherapy was routinely offered in this patient cohort; however, patients and their physicians could refuse adjuvant treatment. Radiation therapy was delivered by external beam radiotherapy and/or brachytherapy. External beam radiotherapy was delivered using traditional pelvic fields utilizing either a 3 or 4 field techniques and treated using high energy photons. In more recent years, CT-based planning was utilized. Brachytherapy was administered either using a high dose rate (HDR) or low dose rate (LDR) technique. The majority of patients received HDR brachytherapy via a vaginal cylinder, which was prescribed to either the vaginal surface or 0.5 cm depth. LDR therapy was prescribed to the vaginal surface. The length of the vagina that was treated by brachytherapy included the entire vaginal length that was l–2 cm proximal from the end of the vaginal canal.

Endpoints

Primary endpoint is for local–regional control, which is defined as any recurrent disease in the pelvis identified by physical examination, biopsy or imaging. In addition, we further defined local–regional recurrence as vaginal recurrence or pelvic recurrence. Secondary endpoints are distant recurrence and overall survival.

Statistics

Demographics were evaluated using an unpaired Student's t test (two sided test) and chi-squared test for comparison of means. Kaplan–Meier method was utilized to determine time to endpoint. The endpoints were calculated from the date of surgery to the date of the outcome. Patients were censored at the last date of follow up if the above endpoints did not occur. Endpoint and survival data was obtained from the written paper or electronic medical record. The log-rank test was used to compare the outcomes between groups. For univariate analysis, chi-square test examined the association with the given outcome. Because there were far too few events in our cohort, we did not complete a multivariate model. A p-value of ≤ 0.05 was considered significant.

Results

We identified 125 subjects who had pathologic confirmation of FIGO IA disease with unfavorable histology and had a margin negative resection; 86 subjects obtained care at Intermountain Healthcare and 39 subjects obtained care at the University of Utah. The median age of the cohort was 67 years old and median follow up of 30.4 months (range: 0.03 to 244.7 months). Adjuvant radiation therapy was delivered in 60 patients (48%) and 65 patients did not have any adjuvant radiation therapy (52%). Complete list of demographics is available in Table 1. The radiation therapy cohort was more likely to have worse prognostic features such as LVSI, and deeper myometrial invasion. The radiation therapy group was more likely to have a greater number of lymph nodes dissected. In comparison, the group that did not undergo radiotherapy had a higher frequency of papillary serous histology; however, the histologic difference was not statistically significant. The radiotherapy group was more likely to undergo pelvic lymph node dissection (87%) compared to the non-radiotherapy group (71%) ($p = 0.03$). The radiotherapy group was more likely to undergo chemotherapy (11.6%) compared to the non-radiotherapy group (0%) ($p = .007$). Of the 7 patients that had chemotherapy, 4 had HDR brachytherapy, 1 had pelvic radiotherapy alone, 1 had a combination of pelvic and HDR brachytherapy and the last patient did not have radiation records that were available.

Radiation therapy

Of the 60 patients who had radiation administered, 18 (30%) patients had external beam radiation therapy to the pelvis with a median dose of 4860 cGy (range: 4500 cGy to 5400 cGy) in 27 fractions (range: 25 to 30 fractions). Brachytherapy was administered in 38 (63.3%) patients. Two patients had a combination of both external