Gynecologic Oncology 133 (2014) 494–498

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Predictive factors of recurrence following adjuvant vaginal cuff brachytherapy alone for stage I endometrial cancer

Emily F. Dunn [a,*], Heather Geye [a], Chris S. Platta [a], Vinai Gondi [c], Stephen Rose [b], Kristin A. Bradley [a], Bethany M. Anderson [a]

[a] Department of Radiation Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[b] Department of Gynecology Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[c] CDH Cancer Center, Warrenville, IL, USA

HIGHLIGHTS

- Stage I endometrial cancer patients have excellent treatment outcomes.
- A subset of stage I endometrial cancer patients may benefit from chemotherapy.

ARTICLE INFO

Article history:
Received 25 November 2013
Accepted 16 March 2014
Available online 20 March 2014

Keywords:
Brachytherapy
Endometrial cancer
Radiation

ABSTRACT

Purpose. The purpose of this study is to identify risk factors for recurrence in a cohort of stage I endometrial cancer patients treated with vaginal cuff brachytherapy at a single academic institution.

Methods and materials. From 1989 to 2011, 424 patients with stage I endometrial cancer underwent total hysterectomy and bilateral salpingo-oophorectomy, with or without lymphadenectomy (LND), followed by high-dose-rate vaginal cuff brachytherapy (VCB) to patients felt to be high or intermediate risk FIGO stage IA and IB disease. Covariates included: 2009 FIGO stage, age, grade, histology, presence of lymphovascular space invasion, LND, and receipt of chemotherapy.

Results. With a median follow-up of 3.7 years, the 5 and 10-year disease free survival were 98.4% and 95.9%, respectively. A total of 30 patients developed recurrence, with the predominant pattern of isolated distant recurrence (57.0%). On multivariate analysis, grade 3 ($p = 0.039$) and LND ($p = 0.048$) independently predicted of increased recurrence risk. χ^2 analysis suggested that higher-risk patients were selected for LND, with significant differences in age, stage, and grade noted between cohorts. Distant metastatic rate was significantly higher for patients who qualified for GOG 0249 at 23.1% (95% CI 10.7–35.5%) compared to those who did not at 6.8% (95% CI 1.8–11.8%, $p < 0.001$).

Conclusion. Overall disease-free survival for this cohort of patients was >95% at 10 years. Univariate analysis confirmed previously identified risk factors as predictors for recurrence. Multivariate analysis found that grade 3 and LND correlated with risk for recurrence. Of those that did recur, the initial site of relapse included distant metastasis in most cases.

Introduction

Studies such as GOG 99 and PORTEC-1 have demonstrated that pelvic external beam radiation therapy (EBRT) improves local control in patients with intermediate risk early stage endometrial cancer, primarily by reducing the risk for vaginal cuff recurrence [1,2]. Vaginal cuff brachytherapy (VCB) has, therefore, emerged as an effective adjuvant treatment option for this patient population [3,4]. PORTEC-2 randomized patients with FIGO 1988 stage I-IIA endometrial carcinoma to pelvic EBRT vs. VCB, and found that patients treated with VCB had equivalent overall local control and significantly reduced acute and chronic gastrointestinal toxicity [2].

Chemotherapy has been shown to improve progression-free and overall survival in women with advanced endometrial cancer [5,6]. However, its role in early stage disease is currently unclear. Certain women with high-risk features, such as deeply invasive and high-grade disease, may be at particularly high risk for developing distant metastasis [7]. Currently, the potential benefits of chemotherapy are being studied via GOG 0249, a prospective phase III trial randomizing

* Corresponding author at: University of Wisconsin – Madison, School of Medicine and Public Health, Department of Human Oncology, 600 Highland Ave., K4/B143, Madison, WI 53792, USA. Fax: +1 608 263 9167.
E-mail address: Dunn@humonc.wisc.edu (E.F. Dunn).

http://dx.doi.org/10.1016/j.ygyno.2014.03.554
0090-8258/

patients with high-risk stage I-II endometrial cancer to pelvic EBRT alone vs. VCB plus 3 cycles of carboplatin and paclitaxel.

The purpose of our retrospective study was to evaluate the recurrence patterns and identify factors predictive of recurrence. Patients with stage IA and IB endometrial cancer were selected for VCB based risk for recurrence and were reviewed retrospectively. In addition, patient eligibility for GOG 0249 was assessed retrospectively, and correlation with eligibility for this trial and distant metastatic rate was completed.

Methods and materials

Study population

From 1989 to 2011, 424 patients with FIGO Stage IA and IB endometrial cancer underwent total hysterectomy with bilateral salpingo-oophorectomy (BSO), with or without lymphadenectomy (LND), followed by high-dose-rate VCB. A total of 10 patients were lost to follow up, yielding a total of 414 analyzable patients. Standardly, patients were treated with full surgical staging including pelvic and paraaortic LND with pelvic washings and sampling of the omentum. A portion of patients did not undergo a LND for various reasons including body mass index, medical comorbidities, or surgery completed at an outside institution. All patients in this cohort received post-operative VCB as a portion of their therapy. At our institution, VCB was generally offered for stage I patients felt to be at high or intermediate risk for local recurrence: deep myometrial invasion, higher grade, non-endometrioid histology, and those with the presence of LVSI. The ultimate recommendation for VCB was based upon discussion at a multidisciplinary tumor board, as well as the treating radiation oncologist's individual practice. Radiation was prescribed to the vaginal mucosa, utilizing the following treatment regimens: 32.4 Gy in 2 fractions (1989–2000), 36.6 Gy in 3 fractions (2001–2009), and 31.5 Gy in 3 fractions (2010–2011). The majority of these treatments were completed using ovoids assembled into colpostats, with 6% receiving treatment with cylinders to an individualized length determined on the basis of the patient's anatomy and tumor histology. A small minority of patients (6% of entire cohort) also received between 3 and 6 cycles of carboplatin and paclitaxel between the years 2002 and 2011. No patient in this series received EBRT. Late toxicities were defined as 6 months or more from the end of treatment based on CTCAE version 4.0. Distant metastasis was defined as outside of pelvis or in patients with peritoneal carcinomatosis. Pelvic recurrence was defined as a pelvic lymph node recurrence or other location of disease not including the vaginal cuff or carcinomatosis. Vaginal cuff recurrence was defined as recurrent disease only at the vaginal apex, present on imaging and/or physical exam.

Patients were eligible for GOG 0249 according to the trial specifications [8]. Risk factors included grade 2 or 3 tumor, evidence of LVSI, and outer half of myometrial invasion. Patients age 70 and older required one risk factor to be eligible, patients 50–69 required two risk factors, and patients 18–49 required three risk factors. In addition, patients with stage I–II clear cell or serious histology were eligible despite age or other risk factors present. Staging with peritoneal cytology was routinely performed in all patients, but positive cytology was an exclusion criterion only for patients with serous or clear cell histology.

Patients from our institution were routinely followed with physical exam every 3 months for two years, followed by every 6 months for two years and annually until 5 years from completion of therapy. Pelvic exam was completed at all follow up visits unless distant metastatic disease was defined. Patients referred from outside institutions were followed in a similar fashion, though limited follow up was allowed due to patient ability to travel or insurance limiting long term follow up.

Data was collected retrospectively, after obtaining approval from the institutional review board.

Statistical analysis

All FIGO staging was updated to the 2009 FIGO system for comparison. Patients were censored at the time of first recurrence. Presence of LVSI, histology, age, grade, LND, use of chemotherapy, and 2009 FIGO stage were used as covariates. Incidence of recurrence and distant metastatic rate was estimated by the Kaplan–Meier method and defined as stated in Materials and methods. Univariate comparisons were made using log-rank statistic. Multivariate analysis used the Cox proportional hazards model. χ^2 analysis was utilized to compare cohorts of patients who did and did not undergo LND.

Results

The study population consisted of 414 consecutively treated patients with 2009 FIGO stage IA and IB endometrial cancer, diagnosed between 1989 and 2011, who were selected for VCB following surgical resection. Patient and tumor characteristics are shown in Table 1. The median age in our patient cohort was 62 years. Endometrioid adenocarcinoma was the primary histology (96%), with other histologies including papillary serous (3.5%), clear cell (<1%), carcinosarcoma (<1%), and mixed histology (<1%). The majority of patients treated in this group, 77%, had Stage IB disease. Most patients had grade 1 (51.5%) or grade 2 (33.8%) disease. The majority of patients (65.9%) underwent LND, with a median of 14 lymph nodes removed at the time of surgery. Due to the 22-year time period encompassed by our study, the presence or absence of LVSI was unknown in the majority of our patient cohort (59.9%). Of the patients with known LVSI status, 80.7% did not demonstrate LVSI on pathological evaluation.

With a median follow up of 3.7 years, the actuarial 5- and 10-year recurrence rates were 1.6% ± 0.01% and 4.1% ± 0.01%, respectively. A total of 30 patients out of 414 developed a recurrence at the time of analysis. The majority of patients who recurred had distant metastasis

Table 1
Characteristics of endometrial cancer patients ($N = 414$).

Patient and tumor characteristics	
Characteristic	% (n)
Age (years)	
<40 years	3.1 (13)
40–49	7.5 (31)
50–59	30.9 (128)
60–69	32.1 (133)
>70	26.3 (109)
Stage	
IA	22.5 (93)
IB	77.5 (321)
Histology	
Adenocarcinoma	95.9 (397)
Papillary serous	3.6 (15)
Carcinosarcoma	<1.0 (1)
Clear cell	<1.0 (1)
Grade	
1	51.5 (213)
2	33.8 (140)
3	14.7 (61)
Lymph node dissection	
Yes	65.7 (272)
No	30.4 (126)
Unknown	3.9 (16)
LVSI	
Yes	7.7 (32)
No	32.3 (134)
Unknown	60.0 (248)
Chemotherapy	
Yes	6.0 (25)
No	94.0 (389)