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Vaginal brachytherapy for early stage uterine papillary serous and clear cell endometrial cancer

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HIGHLIGHTS

- Early-stage papillary serous and clear cell endometrial cancer patients received HDR vaginal brachytherapy.
- A low-dose brachytherapy regimen of 24 Gy in 6 fractions resulted in a low rate of vaginal relapse.
- This low-dose regimen was safe and without toxicity.

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ABSTRACT

Objective. To report clinical outcomes following adjuvant high-dose-rate (HDR) vaginal brachytherapy (VB) for early-stage uterine papillary serous (UPSC) and clear cell (CC) endometrial cancer.

Methods. A retrospective study of Stage I and II papillary serous and clear cell endometrial cancer treated with post-operative HDR VB between October 2005 and May 2012 was performed. A total of 37 patients were identified, 26 with UPSC, 9 with CC and 2 with mixed UPSC/CC. After total hysterectomy and bilateral salpingo-oophorectomy, VB was administered without external-beam radiation with a dose of 24 Gy in 6 fractions prescribed to the vaginal surface. Chemotherapy was given to 30 patients (75%).

Results. The median follow up time was 24.8 months (range, 2.0 to 71.5 months). Four patients relapsed, 2 with UPSC and 2 with CC. The initial site of relapse was concurrent vagina, pelvic/para-aortic nodes and abdominal wall (1), pelvic/para-aortic nodes (1) and para-aortic nodes alone (2). The 2-year vaginal-control rate was 96.8%. The pelvic-control rate including vaginal and nodal relapse was 93.5%. The 2-year disease-free and overall survival rates were 89.3% and 100%, respectively.

Conclusion. HDR VB as the sole adjuvant treatment modality for early-stage UPSC/CC is associated with a low rate of vaginal relapse and excellent survival outcomes. This novel low-dose regimen for VB is safe and effective.

Introduction

Uterine papillary serous carcinoma (UPSC) and clear cell (CC) carcinoma account for approximately 10% of endometrial-cancer diagnoses. These variants have a more aggressive natural history than the endometrioid subtype of endometrial cancer [1,2]. Patients with UPSC and CC present with more advanced-stage disease than those with endometrioid histology and have a higher rate of recurrence after primary treatment. Up to 40% of UPSC and CC patients may present with extrauterine disease even in the absence of myometrial invasion [3,4]. Given these high-risk features, several authors have advocated for the use of chemotherapy [3–9] after comprehensive surgical staging, including total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO), lymph-node removal, peritoneal cytology, and omentectomy.

Recommendations regarding the use of radiation for UPSC and CC have varied widely, with the 2012 National Comprehensive Cancer Network (NCCN) recommendations referring to chemotherapy, tumor-directed (pelvic and/or para-aortic nodal) radiation, whole-abdominal radiation and/or vaginal brachytherapy (VB) as options [10]. Some retrospective studies report a benefit for adjuvant radiation therapy (RT) in decreasing the rates of pelvic recurrence [1,7,11–14]. For patients with endometrioid endometrial adenocarcinoma, the use of VB alone has significantly increased since a randomized trial showed lower GI toxicity rates with VB [15]. In the U.S. the use of VB alone increased concomitant with the use of lymph-node dissection [16]. Studies of chemotherapy with VB have used a regimen of 7 Gy prescribed at 5-mm depth in vaginal tissue over 3 fractions for UPSC patients [8,17,18]. This 7Gy for 3

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fraction VB regimen provides a biologically equivalent dose (BED) of 35.7 Gy or an equivalent dose in 2-Gy fractions (EQD2) of 27.4 Gy at 5-mm depth, which corresponds to a vaginal surface dose BED of approximately 60 Gy or an EQD2 of approximately 50 Gy (alpha/beta of 10), with a rectal dose of approximately 42 Gy (EQD2 for normal tissues using alpha/beta of 3). A dose of 60 Gy of VB prescribed at the vaginal surface was traditionally used for low-dose-rate (LDR) VB. A survey of U.S. physicians identified the most common fractionation regimen as 7 Gy for 3 fractions prescribed at 0.5 cm from the surface; the next most common regimen is 5 Gy for 6 fractions [19,20]. In this report, we evaluate the effectiveness of a novel low-dose regimen of HDR brachytherapy for UPSC and CC, with an EQD2 of 28 Gy, approximately half the dose routinely given for patients treated with VB without external-beam RT. We found in our series of 157 endometrioid endometrial-cancer patients that this low-dose regimen of 4 Gy to the vaginal surface in 6 fractions resulted in low rates of vaginal relapse, with no grade 2 or higher vaginal stenosis and only 1% developing grade 1 vaginal stenosis based on clinical assessment in follow up [21]. Such a low-dose regimen has not been previously assessed in UPSC or CC.

Materials and methods

With IRB approval, the medical records between October 2005 and May 2012 from the gynecologic radiation databases of Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) were reviewed. A total of 414 endometrial-cancer patients treated with post-operative VB were identified. Of these, 37 patients with Stage I–II UPSC/CC were treated with VB without external beam radiation, with a dose of 4 Gy prescribed to the vaginal surface in 6 fractions. Pathology was reviewed as part of initial diagnosis by gynecologic pathologists at our institution. Patients with mixed components of UPSC or CC with endometrioid type (more than 10% UPSC or CC) were included in this study. All cases were classified using the FIGO 2009 surgical staging system [22].

All patients underwent surgical treatment including a hysterectomy and oophorectomy, peritoneal washings and omental biopsy or resection with pelvic and/or para-aortic nodal dissection (n = 30) or sampling (n = 7). Thirty patients received chemotherapy. HDR VB was delivered as outpatient treatment. The largest vaginal cylinder that fit each individual patient was inserted. Computed tomography (CT) scanning was performed immediately prior to each treatment to identify the exact cylinder position and confirm the size of the cylinder for quality assurance (QA). All insertions were performed in a dedicated CT brachytherapy suite and all patients had a CT scan after initial placement to confirm that the cylinder was placed snugly next to the vaginal apex. In addition, a measurement of vaginal length was obtained (from apex to below the public symphysis), and this measurement minus 1 cm (to avoid scatter dose to the labia) was used for the prescription length. Each treatment delivered 4 Gy at the vaginal surface. VB was administered in 6 fractions twice weekly over approximately 3 weeks. Patient follow-up post-treatment included a pelvic examination by her gynecologist, gynecologic oncologist or radiation oncologist every 3 months for 2 years, then every 6 months to 5 years, then annually thereafter; radiologic imaging was performed based on the recommendations of the medical oncologist and no routine surveillance imaging program was followed. The presence of vaginal stenosis was recorded during follow-up visits using speculum insertion then manual assessment. Of note, Common Toxicity Criteria for Adverse Events (CTCAE version 4.0) includes only vaginal fibrosis and not telangiectasia, though follow up reports were reviewed for bleeding or other symptoms.

Statistical analysis was performed using the Kaplan–Meier method to determine the rates of, local–regional control (pelvic and vaginal), disease-free survival (DFS) and overall survival (OS). *Disease-free survival* (PFS) was defined as the interval from diagnosis of primary or recurrent disease to the date of first evidence of disease recurrence or progression or death from any cause. Patients without progression, recurrence or death were censored at the last follow-up visit. *Overall survival* (OS) was defined as time from diagnosis to death from any cause.

Clinical outcome was measured from the date of surgery to the most recent visit for endometrial cancer or death date. All acute and late toxicity was scored using the CTCAE. To determine prognostic factors, Cox proportional hazards models were generated. Multivariable analysis was not performed given the small number of events. SPSS (version 18, IBM Inc.) was used for statistical analyses.

Results

Clinical characteristics of the 37 patients with Stage I–II UPSC or CC who underwent adjuvant VB are shown in Table 1. The median age at diagnosis was 64 years (range [rg], 43–81 years). Twenty-six patients (70%) had UPSC histology (22 pure UPSC, 4 mixed UPSC and endometrioid). CC histology was found in 9 patients (24%) (all pure CC) and 2 patients (5%) had mixed UPSC/CC. The FIGO 2009 stage was IA in 29 patients (78%), IB in 5 patients (14%) and II in 3 patients (8%). Chemotherapy was administered in 30 patients (81%). All patients received platinum-based chemotherapy; 28 patients received carboplatin and paclitaxel, 1 received cisplatin and docetaxel, and 1 received cisplatin, paclitaxel and doxorubicin. Chemotherapy was given before brachytherapy in 24 (80%). Other sequences were

Table 1
Patient characteristics.

		All patients (n = 37)	Papillary serous (n = 26)	Clear cell (N = 9)	Mixed serous and clear cell (n = 2)
		# (%)	# (%)	# (%)	# (%)
Age	Median	64	63	72	69.5
	Range	43–81	52–80	43–78	58–81
Stage	IA	29 (78.4)	21 (80.8)	6 (66.7)	2 (100)
	IB	5 (13.5)	3 (11.5)	2 (22.2)	0
	II	3 (8.1)	2 (7.7)	1 (11.1)	0
Peritoneal washing	Negative	31 (83.8)	22 (84.6)	7 (77.8)	0
	Positive	6 (16.2)	4 (15.4)	2 (22.2)	2 (100)
Lymph node dissection	Complete	33 (89.2)	22 (84.6)	9 (100)	2 (100)
	Sampling	2 (5.4)	2 (7.7)	0	0
	No	2 (5.4)	2 (7.7)	0	0
Number of nodes dissected	Median	21	21	19	7.5
	Range	3–38	3–36	4–38	6–9
Lymphovascular invasion	Yes	3 (8.1)	3 (11.5)	0	0
	No	34 (91.9)	23 (88.5)	9 (100)	2 (100)
Chemotherapy	Yes	30 (81.1)	25 (96.2)	5 (55.6)	0
	No	7 (18.9)	1 (3.8)	4 (44.4)	2 (100)
Chemotherapy type	Carboplatin + paclitaxel	28 (93.3)	23(92)	5(100)	0
	Other	2(6.7)	2(8)	0	0