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Early stage papillary serous or clear cell carcinoma confined to or involving an endometrial polyp: outcomes with and without adjuvant therapy

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HIGHLIGHTS

- Clinical outcomes of patients with stage IA UPSC/CC involving a polyp were reviewed
- 3/32 patients with disease confined to a polyp and 1/19 patients with endometrial surface spread or myometrial invasion progressed
- No vaginal recurrences occurred

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ABSTRACT

Objective. To investigate clinical outcomes of stage IA uterine papillary serous (UPSC) and clear cell carcinoma (CC) arising from or associated with a polyp.

Methods. From 1995 to 2011, we identified 51 cases of stage IA UPSC (67%), CC (8%) or mixed histology (26%) endometrial cancer. Of these, 32 had disease confined to polyp (seven with no residual disease after hysterectomy), 14 had surface spread, 1 had myometrial invasion (MMI) and 4 had both. The majority of patients did not receive adjuvant therapy (80%). Patients given adjuvant treatment (either platinum-based chemotherapy alone, radiation alone, or a combination of the two) had incomplete staging or abnormal cytology.

Results. At mean follow-up of 58.3 months, only 4 patients had progressed, via pelvic adenopathy, carcinomatosis or both. There were no vaginal cuff recurrences. Kaplan–Meier 5 year estimates were pelvic control of 92.1%, disease-free survival 93% and OS 80.6%. Only 9% (3/32) of cases confined to polyp progressed. One responded to salvage chemoradiation, but two died despite salvage. Only 5% (1/19) of cases with surface and MMI progressed. On univariate analysis, only MMI and abnormal/positive cytology were significantly associated with increased pelvic recurrence (MMI $p = 0.0059$, cytology $p = 0.0036$) and worse DFS (MMI $p = 0.0018$, cytology $p = 0.0054$). Two patients given adjuvant treatment developed new gynecologic malignancies.

Conclusion. In our study, patients with limited UPSC/CC disease involving a polyp who have complete workup did well without adjuvant therapy, with recurrence rates similar to UPSC/CC stage IA disease. Late and extensive pelvic relapses may occur in the few who do relapse.

Introduction

Endometrial cancer is the fourth most common cancer diagnosis in women with 49,560 new cases expected from 2013 [1]. While the 5 year survival for stage IA endometrioid adenocarcinoma is approximately 99% [2], type II subtypes are known to carry a worse prognosis. Included among type II are uterine papillary serous carcinoma (UPSC) and clear cell (CC) carcinoma, considered more high-risk endometrial carcinoma subtypes compared to endometrial adenocarcinoma.

UPSC and CC appear to have higher tendency for lymphovascular invasion, with pattern of failure commonly involving spread via intraperitoneal or extra-abdominal invasion [3,4]. Prognostic factors for UPSC/CC appear to differ from endometrioid adenocarcinoma. Only stage has consistently been shown to correlate with survival, while myometrial invasion (MMI) has prognostic significance in some but not all studies [4–8]. No standard treatment regimen exists for early stage UPSC or CC, and stage I–II disease has variably been treated with observation, radiation, chemotherapy or combination modality treatment [8–11]. In addition, radiation options include therapy given by external beam (EBRT) to the pelvis or by high-dose rate vaginal

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brachytherapy (VB). Recent papers suggest VB alone may be adequate adjuvant treatment for patients with surgical stage I papillary serous or clear cell carcinoma, given subsequent low vaginal recurrence rates after VB from 0% to 3% and pelvic recurrence of 4–9% [12–14]. Overall recurrence rates for FIGO 2002 stage IA UPSC from retrospective studies have been reported from 9% to 11%, and up to 13% for stage IA by currently used FIGO 2009 criteria [7,15]. Observation has been proposed as a reasonable option for stage IA disease, particularly if no myometrial invasion is present [15].

Endometrial cancer confined to a polyp is a clinical scenario that offers particular difficulty given rarity of disease and limited available published data. Given the limited extent of disease but aggressive biologic behavior of UPSC/CC it is unclear whether adjuvant therapy is warranted. While case reports and small series have been published mainly in the pathology literature [16–19], these often include all stages of UPSC, with inconsistent description of the adjuvant treatment given or details of patients' clinical outcomes. We conducted a retrospective review of our institution's incidence and clinical outcomes of patients with surgical stage IA UPSC/CC involving a polyp observed after surgery or given adjuvant therapy (radiation, chemotherapy, or both).

Materials and methods

Following Institutional Review Board approval, we queried our institution's Cancer Registry for cases of endometrial cancer. Based on stage and histology, we identified 236 cases of stage IA pure UPSC, pure CC or mixed endometrial cancer, diagnosed from 1995 to 2011. The mixed endometrial cancer patients included data of all histologic subtypes, which we then sorted for UPSC/CC. The International Federation of Gynecology and Obstetrics (FIGO) previously defined stage IA disease as endometrial cancer with no myometrial invasion (MMI). Starting in 2009, patients with less than half MMI were also included in our study based on changes in definition of FIGO IA criteria. Pathology reports were reviewed for mention of polyp involvement with carcinoma. Classically, the pathological definition of a polyp is a grossly pedunculated mass composed of cystically dilated glands with fibrous stroma and thick walled blood vessels, associated with a stalk. Endometrial cancer found only in the polyp was considered confined to and arising from polyp. It is possible that cases with MMI or surface invasion had cancer arising from elsewhere in the endometrium instead of from the polyp itself, but typically there was limited extension outside of polyp since only stage IA disease was included.

Statistical analysis included Kaplan–Meier estimates for 5 year pelvic recurrence-free survival (RFS), disease-free survival (DFS) and overall survival (OS). Time to event was calculated from date of surgical staging. Log-rank analysis was used for univariate analysis to determine possible prognostic variables. The variables looked at in our study were age (≤60 or >60 years), adjuvant treatment (yes/no), LVI (yes/no), cytology (abnormal or positive versus negative), adenomyosis (yes/no), endometrial intraepithelial neoplasia (yes/no), MMI (yes/no), and tumor spread on endometrial surface (yes/no). Due to small number of events, multivariate analysis was not conducted. GraphPad Prism (version 6.0) was used for analysis.

Results

We identified 51 cases of stage IA UPSC, CC or mixed UPSC/CC involving a polyp, from 1997 to 2011. An additional two patients qualified, but lacked sufficient follow-up data. Medical records of the 51 patients were reviewed for work-up, potential prognostic factors, and clinical outcomes. Slides were reviewed with a gynecological-oncology pathologist specialist if there were incomplete reports, if patients had later progression of disease, or if later development of other gynecologic malignancies occurred.

All patients underwent surgical staging with hysterectomy (typically abdominal or laparoscopic, one with radical hysterectomy) and bilateral salpingo-oophrectomy. Cytology specimens were collected from peritoneal fluid obtained during hysterectomy. Lymph node dissection of para-aortic (PA) and pelvic lymph nodes (PLND) was done for 32 patients (63%) with average of 20 dissected nodes. One patient had PA dissection only, 9 had PLND only and an additional 9 either refused or did not have any dissection done. Cytology was known for 40 patients (78.4%), of which 2 were positive for malignant cells and 3 had "atypical" cells. Omental biopsy was done for 26 patients (51%), all negative.

Mean follow-up from date of surgical staging was 58.3 months (median follow-up 45.2 months, from 1.8 to 188.2 months). Median follow-up for patients treated who are NED and still alive was 33.6 months. The majority of patients had pure UPSC (66.7%), the fewest had pure CC (7.8%) and the remainder had mixed UPSC/CC/adenocarcinoma (25.5%). Median age was 65 years at time of diagnosis. Six patients were nulliparous (11.7%). Median BMI was 41 and 20% of patients had previous endocrine treatment for breast cancer. See Table 1 for additional characteristics. Five patients had MMI and extent of MMI ranged from 3% to 30%. Polyp size was reported for 36 patients and tumor size reported for 15 patients. Six patients had multiple polyps on gross pathology, of which two had multiple polyps involved with tumor (one superficial and limited to polyps and the other appearing to arise from polyps and limited to endometrium with no MMI). Twenty-five patients had disease confined to polyp, defined as only involving the polyp with no MMI or endometrial surface spread beyond polyp (see Fig. 1). An additional 7 patients had cancer on endometrial biopsy or curettage (arising in a polyp) but no residual disease at time of hysterectomy. Thus, in total, 32 patients had disease confined to polyp, either before or after hysterectomy.

Table 1
Clinical and pathologic characteristics.

Characteristics		Value (%)
Median age		65 (51–85) years
Race	Asian	2 (4%)
	Black	16 (31%)
	Hispanic	9 (18%)
	White	24 (47%)
History of endocrine therapy for breast cancer		10 (20%)
Presenting symptoms	Vaginal bleeding	35 (68.6%)
	Abnormal pap	6 (11.8%)
	Abnormal imaging	6 (11.8%)
	Abdominal pain/pressure	4 (7.8%)
	Unknown	3 (5.9%)
Preoperative imaging		21 (41%)
	CT chest, abdomen, pelvis	13 (25.5%)
	CT abdomen, pelvis	7 (13.7%)
	MRI pelvis	1 (2%)
Lymph node dissection	Para-aortic and pelvic	32 (63%)
	Mean# dissected	20
	Para-aortic only	1 (2%)
	Mean# dissected	2
	Pelvic only	9 (18%)
	Mean# dissected	11
	Refused/not done	9 (18%)
Cytology	Positive	2 (4%)
	Atypical	3 (6%)
Omental biopsy performed	Yes	26 (51%)
Histology	UPSC	34 (66.7%)
	CC	4 (7.8%)
	Mixed UPSC/CC	13 (25.5%)
Confined to polyp before or after TAH		32 (63%)
	Polyp only after TAH	25 (49%)
	No residual disease after TAH	7 (14%)
Endometrial surface spread only		14 (27%)
Myometrial invasion (MMI) only		1 (2%)
Both surface spread and MMI		4 (7.7%)
Size of tumor (median)		1.2 (0.5 to 4) cm
Size of polyp (median)		3 (0.6 to 8.5) cm
Adenomyosis		17 (33%)
Lymphovascular invasion	Outside of polyp	1 (2%)
	Within polyp	2 (4%)
Endometrial intraepithelial neoplasia		8 (16%)