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Prognostic significance of peritoneal cytology in low-intermediate risk endometrial cancer

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HIGHLIGHTS

- A retrospective population-based cohort study of endometrial cancer patients was carried out.
- Grade, depth of myometrial invasion, LVSI, age and adjuvant therapy were controlled for.
- Cytology was not an independent prognostic factor in low or intermediate risk endometrial cancer.

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ABSTRACT

Objectives. There is uncertainty surrounding the prognostic value and clinical utility of peritoneal cytology in endometrial cancer. Our primary objective was to determine if positive cytology is associated with disease-free and overall survival in women treated surgically for endometrial cancer, specifically those with low or intermediate risk disease.

Methods. This was a retrospective population-based cohort study of British Columbia Cancer Registry patients who underwent surgery with peritoneal washings for endometrioid-type endometrial cancer from 2003 to 2009. Low risk was defined as Stage IA grade 1 or 2, and intermediate risk defined as Stage IA grade 3, or Stage IB grade 1 or 2 tumours. Five-year overall and disease free-survival were assessed using Kaplan-Meier estimation. Potential covariates including peritoneal cytology, grade, depth of myometrial invasion, LVSI, age, and adjuvant therapy were evaluated in a multivariable Cox proportional hazards model.

Results. There were 849 patients, of whom 370 (43.6%) and 298 (35.1%) had low- and intermediate-risk disease, respectively. Overall, forty-nine (5.8%) patients had positive cytology, including 6 and 9 with low- and intermediate-risk respectively (2.2% within low and intermediate risk combined). Positive peritoneal cytology was not significantly associated with disease-free (HR 3.17, 95% CI 0.91–11.03) or overall survival (HR 1.33, 95% CI 0.47–3.76) in low and intermediate risk patients. Only age and extensive LVSI were associated with lower overall survival (HR 1.10, 95% CI 1.08–1.13, and HR 2.39, 95% CI 1.02–5.61, respectively).

Conclusions. Positive peritoneal cytology was not associated with disease-free and overall survival in women with low and intermediate risk endometrial cancer.

1. Introduction

Prior to 2009 positive peritoneal cytology was utilized in endometrial cancer staging and influenced adjuvant treatment decisions [1]. However, there was limited evidence demonstrating an independent association between positive cytology and adverse outcome in endometrial cancer. Although positive cytology is correlated with established adverse prognostic factors in endometrial cancer, the prognostic significance of positive cytology in isolation continues to be debated [1–10]. Although not an invasive or time-consuming intervention the cost associated with this practice is not insignificant [12].

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In 2013, Garg et al. reported a superior disease-free survival in women with Stage I and II endometrial cancer with negative cytology [8]. The authors concluded that positive peritoneal cytology is an independent risk factor for patients with early stage endometrial cancer. Notably absent from the multivariate analysis within the aforementioned study were depth of myometrial invasion, LVSI, and adjuvant chemotherapy, all recognized to influence outcomes in endometrial cancer [13–15].

The primary objective of this study was to determine if positive cytology is independently associated with disease-free and overall survival in women treated surgically for endometrial cancer within a population, and specifically among those with low or intermediate risk disease. The secondary objective was to estimate what proportion of patients would have their treatment plan altered as a result of peritoneal cytology.

2. Methods

We carried out a population-based retrospective cohort study of British Columbia Cancer Registry patients who had surgery for endometrioid-type endometrial cancer between January 1, 2003 and December 31, 2009. Although peritoneal cytology was excluded from the new FIGO staging classification for endometrial cancer in 2009, the procedure of obtaining washings for cytologic analysis (peritoneal cytology) was routinely done through most of 2009, and consistently for the preceding 5 years. Approval for this study was granted by the Research Ethics Board of the University of British Columbia/BC Cancer Agency.

Data was extracted from patient records through the Cancer Agency Information System (CAIS) at the BC Cancer Agency, including age at diagnosis, surgical procedure, surgical stage, peritoneal cytology, tumour grade, histotype, depth of myometrial invasion, cervical stromal invasion, presence or absence of extrauterine disease including adnexal and/or serosal involvement, nodal metastases, distant metastases, LVSI, type of adjuvant therapy, date and status at last follow-up, date and site(s) of recurrence, and date of death if applicable. Patients were excluded if they had non-endometrioid histology, if they did not have peritoneal cytology performed as part of their initial surgery, or if they had neoadjuvant therapy (chemotherapy and/or radiotherapy).

Kaplan-Meier method was used to estimate the survival probabilities of patients until death from any cause (overall survival) or recurrence (disease-free survival). Kaplan-Meier plots were generated while stratifying by peritoneal cytology results, and log-rank tests were used to assess the difference in survival according to peritoneal cytology status.

Cox proportional hazards regression was used to model the hazard of death or recurrence. This analysis was performed on the entire cohort as well as on only those patients with low or intermediate risk Stage I disease. Patients with Stage I disease were categorized as low, intermediate and high risk, based on ESMO (European Society of Medical Oncology) criteria, according to the number of high-risk uterine factors present within the hysterectomy specimen [16]. Low risk was defined as grade 1 or 2 endometrioid cancers confined to the endometrium or <50% myometrial invasion. Intermediate risk patients included those who had Stage 1A grade 3 or Stage 1B grade 1 or 2 disease. High-risk was defined as those with Stage IB grade 3 disease, Stage II, III, or IV disease.

In British Columbia, women with low-risk disease endometrial cancer do not require adjuvant therapy, and those with intermediate risk are offered vault brachytherapy [17]. The only exception is the presence of LVSI, in which case they are offered pelvic radiotherapy. Women with high-risk disease (Stage IB grade 3 endometrioid carcinomas, and all non-endometrioid types) are generally offered adjuvant chemotherapy and involved field radiotherapy [17]. Because positive peritoneal cytology implies the possibility of intraperitoneal spread and may be associated with a worse outcome (higher risk of recurrence and mortality), positive peritoneal cytology could arguably justify adjuvant chemotherapy, which has been shown to improve survival in both early and advanced stage disease [13,18,19]. This would be particularly relevant to the low- and intermediate-risk group patients, whose adjuvant treatment recommendations would change as a result of peritoneal cytology results. For this reason, we combined the low- and intermediate risk group patients and estimated the number of patients requiring washings for peritoneal cytology in order to alter one adjuvant treatment decision (number needed to treat, or NNT), assuming that positive cytology would justify adjuvant chemotherapy. Based on this NNT and assuming a survival benefit from chemotherapy, we estimated the potential survival benefit from washings in low-intermediate risk patients.

3. Results

We identified 849 patients who had primary surgery for endometrioid-type endometrial cancer including washings for peritoneal cytology between 2003 and 2009 in British Columbia. The median follow-up was 40 months (1–143 months). Within this cohort, there were 370 women with low-risk, 298 with intermediate-risk, 56 with high-risk Stage I, 66 with Stage II and 59 with Stage III or IV disease. An additional 12 patients were found to have synchronous primaries of the endometrium and ovary, who were excluded from the remainder of the analysis.

Within the entire population the rate of positive cytology was 5.8% (49/849). Of the combined 668 patients with low or intermediate risk disease (comprising 78.7% of the entire cohort), we found a positive cytology rate of 2.2% (15/668) (Table 1). Within the combined low/intermediate risk group, patients with positive cytology had inferior disease-free and overall survival rates compared to those with negative cytology (Fig. 1). However, after controlling for grade, myometrial invasion, cervical stromal invasion, stage, LVSI, age at surgery and adjuvant treatment in the multivariable Cox model, positive cytology was no longer associated with disease-free or overall survival (Table 2). Only age,

Table 1
Peritoneal cytology and other covariates in low-intermediate risk endometrial cancer

	Peritoneal Cytology Test Result						P-value
	Positive		Negative		All		
	N	%	N	%	N	%	
All Patients	15	100.0	653	100.0	668	100.0	
Stage	6	40.0	364	55.7	370	55.4	0.2635
1 - Low							
1 - Intermediate	9	60.0	289	44.3	298	44.6	
Lymphovascular Space Involvement	6	40.0	117	17.9	123	18.4	0.0089
Focal							
Extensive	2	13.3	22	3.4	24	3.6	
None	7	46.7	514	78.7	521	78.0	
Depth of Myometrial Invasion	6	40.0	296	45.3	302	45.2	0.3559
< 50%							
> 50%	8	53.3	223	34.2	231	34.6	
Negative	1	6.7	134	20.5	135	20.2	
Nodes	14	93.3	436	66.8	450	67.4	0.0703
Not Sampled							
Negative	1	6.7	217	33.2	218	32.6	
Depth of Cervical Invasion	2	13.3	45	6.9	47	7.0	1.0000
Mucosal							
None	13	86.7	608	93.1	621	93.0	
Tumour Grade	5	33.3	311	47.6	316	47.3	0.3733
1							
2	9	60.0	276	42.3	285	42.7	
3	1	6.7	66	10.1	67	10.0	
External Beam Radiation Therapy	9	60.0	128	19.6	137	20.5	0.00096
Yes							
No	6	40.0	525	80.4	531	79.5	
Vaginal Vault Brachytherapy	11	73.3	201	30.8	212	31.7	0.00073
Yes							
No	4	26.7	452	69.2	456	68.3	
Chemotherapy (Adjuvant)	8	53.3	19	2.9	27	4.0	< 0.0001
Yes							
No	7	46.7	634	97.1	641	96.0	

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