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Positive Peritoneal Cytology is an Independent Risk-Factor in Early Stage Endometrial Cancer

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Abstract

Objective—In light of the recent changes in the International Federation of Gynecology and Obstetrics (FIGO) staging system, the objective of this study was to determine the prognostic significance of positive peritoneal cytology (PPC) among patients with early stage endometrial cancer.

Methods—Data were extracted from the Surveillance, Epidemiology, and End Results database between 1988 and 2005. Only those patients with stage I/II endometrial cancer who had

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undergone a complete staging procedure (lymph-node removal) were included. Statistical analyses used Chi-square test, Kaplan-Meier log rank, and Cox proportional hazards models.

Results—A total of 14,704 patients were identified: 14,219 with negative peritoneal cytology (NPC) and 485 with positive peritoneal cytology. More patients with PPC compared to those with NPC were diagnosed with high-risk factors such grade III disease (40.2% vs. 23.8%, $p<0.0001$), and unfavorable histologic types such as clear cell/serous carcinoma (17.5% vs. 7.5%, $p<0.0001$) and carcinosarcoma (9.3% vs. 5.6%, $p<0.0001$). When compared to patients with negative peritoneal cytology, survival was significantly worse among patients with positive peritoneal cytology ($p<0.0001$): 5-year disease specific survival 95.1% vs. 80.8% in endometrioid adenocarcinoma; 78.0% vs. 50.4% in clear cell/serous cancer; and 64.7% vs. 32.3% in carcinosarcoma. After adjusting for other contributing factors in the multivariable model, PPC remained an independent predictor of poor survival ($p<0.0001$) in all histologic types examined.

Conclusion—PPC is an independent risk factor in patients with early stage endometrial cancer. Although, no longer a part of the current FIGO staging criteria, peritoneal cytology status should still be considered for accurate risk-stratification of these patients.

Keywords

Peritoneal cytology; endometrial cancer; prognostic significance; risk-factor

Introduction

Until recently, peritoneal cytology was used as a stage defining variable in the 1988 International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer. Based on this staging schema, patients with stage I or stage II endometrial cancer who had positive peritoneal cytology were upstaged to stage IIIA endometrial cancer, even in the absence of any other evidence of extrauterine disease spread.

Several reports have failed to show a negative correlation between positive peritoneal cytology and survival or recurrence among patients with stage I endometrial cancer (1-3). As a result, there exists an uncertainty regarding the true significance of positive peritoneal cytology in these patients, and is why positive cytology was recently dropped from the revised 2009 FIGO staging criteria for endometrial cancer (4). Given that most previous studies on this topic were not adequately powered to perform a detailed analysis, the primary objective of current study was to determine the impact of positive peritoneal cytology on survival in patients diagnosed with endometrial cancer otherwise confined to the uterus, utilizing a large cohort of patients from the Surveillance Epidemiology and End Results (SEER) database of the U.S. National Cancer Institute.

Materials and Methods

Demographic, clinicopathologic, and survival information for women diagnosed with endometrial cancer from January 1, 1988, to December 31, 2005, were extracted from the Surveillance, Epidemiology and End Results (SEER) database of the U.S. National Cancer Institute (5). SEER is a population-based cancer registry that includes approximately 26% of the United States population. The demographic characteristics of the SEER registries are

representative of the general population within the United States. Data from the 17 SEER registries were used. All patients with endometrial cancer were extracted in tabular format in the “Case Listing” option of the SEER* Stat software. Eligibility criteria included (1) patients with only one primary tumor, (2) patients deemed to have stage I or stage II endometrial cancer according to the 2009 FIGO staging criteria, after a complete staging procedure (total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and/or para-aortic lymphadenectomy) and pathological review (3) pathological diagnosis of endometrioid adenocarcinoma, mucinous adenocarcinoma, serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma (4) diagnosis between 1988 and 2005. Data recorded included date of diagnosis, age at diagnosis, race, extent of disease spread, tumor grade, histology, surgical procedure, performance of lymphadenectomy, number of lymph nodes removed, lymph node status, administration of radiation treatment, and disease specific survival.

Patients were divided into three age groups; age less than 50 years, 50 to 65 years, and greater than 65 years. Race was categorized as white, black, and other. Grade, when reported, was described by a three-grade system; grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated and undifferentiated). Serous carcinomas, clear cell carcinomas, and carcinosarcomas were not graded, but were all considered grade 3. Stage was assigned from the recorded extent of disease (EOD) codes based on the 2009 FIGO staging criteria as follows: stage IA: myometrial invasion less than 50%; stage IB: myometrial invasion greater than or equal to 50%; stage II: cervical stromal invasion. Only patients with negative peritoneal cytology (NPC) could be classified in such manner. A separate category “positive peritoneal cytology (PPC)” was created to include those patients with stage I-II endometrial cancer found to have positive peritoneal cytology. The “PPC group” could not be sub-classified into different stage categories (IA, IB, and II), because this information is not available from the SEER data. Surgical procedure data were derived from site-specific surgery codes. Data concerning the performance of lymph node dissection and lymph node metastasis were derived from pathology codes, and classified as 10 vs. >10 for lymph nodes removed. Use of adjuvant radiation therapy was collected. Each patient's cause specific death was recorded. Survival was calculated as the number of months from cancer diagnosis to date of death due to disease.

The distribution of demographic and clinical characteristics between patients with positive peritoneal cytology and those with negative peritoneal cytology were compared using Chi-square tests. Survival was estimated using the Kaplan-Meier method and differences between groups were compared using the log rank test. Cox proportional hazards regression models were developed to examine the effect of positive peritoneal cytology on disease specific survival while controlling for other clinical and demographic characteristics. Statistical analyses were performed using SAS 9.2 (SAS Institutes, Cary, NC). All p values reported are two-tailed, and a p value of less than 0.05 was considered to be statistically significant. This study was exempt from review by the Institutional Review Board of Washington University School of Medicine.

Results

A total of 14,704 patients matched the inclusion criteria: 14,219 with negative peritoneal cytology (NPC) and 485 with positive peritoneal cytology. Demographic and clinical features of the entire cohort were as shown in Table 1. The mean age of patients was 62 years (range: 20-99). When comparing patients with and without positive peritoneal cytology; there were no significant differences with regards to either patient age at diagnosis or distribution of race ($p=0.4$). However, patients with PPC were more frequently diagnosed with high-risk factors such as grade III disease (40.2% vs. 23.8%, $p<0.0001$), and unfavorable histologic types such as clear cell/serous carcinoma (17.5% vs. 7.5%, $p<0.0001$) and carcinosarcoma (9.3% vs. 5.6%, $p<0.0001$). Similarly, adjuvant radiation was administered more frequently in patients with PPC compared to those with NPC (53.4% vs. 29.7%, $p<0.0001$). Although removal of more than 10 lymph nodes (56.1% vs. 52.9%) was more common among patients with positive peritoneal cytology than those with negative peritoneal cytology, it did not reach statistical significance ($p=0.2$).

On univariate analysis, the following variables were found to be significantly associated with survival: age ($p<0.0001$), race ($p<0.0001$), histology ($p<0.0001$), grade ($p<0.0001$), peritoneal cytology ($p<0.0001$), and number of lymph nodes removed ($p=0.002$). Patients with positive peritoneal cytology had a significantly poorer survival compared to those with negative peritoneal cytology, and this difference was observed across all histologic types examined: endometrioid/mucinous adenocarcinoma; 80.8% vs. 95.1%, clear cell/serous carcinoma; 50.4% vs. 78.0%, and carcinosarcoma; 32.3% vs. 64.7%. When examined by grade, the survival was found to be significantly worse for those patients with endometrioid/mucinous adenocarcinoma who had positive peritoneal cytology compared to those in whom the cytology was negative for grade I (88.2% vs. 98.6%), grade II (87.8% vs. 95.7%), as well as grade III disease (68.6% vs. 87.4%). The survival rates in the PPC group were also compared to the different stage categories within the NPC group (stages IA, IB, and II). The survival was noted to be significantly worse in the PPC group relative to all individual stage categories of the NPC group for all histologic types and tumor grades examined (Table 2, Figure 1).

In a multivariable analysis, positive peritoneal cytology was found to be an independent predictor of survival after adjusting for other contributory factors ($P<0.0001$) (Table 3). The risk of death with PPC was 4.7 times higher compared to stage IA disease and negative peritoneal cytology, 2.0 times more compared to stage IB disease and negative peritoneal cytology, and 1.7 times increased compared to stage II disease and negative peritoneal cytology. Other factors significantly associated with survival were age ($p<0.0001$), race ($p<0.0001$), histology ($p<0.0001$), tumor grade ($p<0.0001$), and number of lymph nodes removed ($p=0.0002$).

Separate models were developed to examine the association of positive peritoneal cytology with survival for individual histologic sub-types (endometrioid/mucinous, adenocarcinoma NOS, papillary serous/clear cell, and carcinosarcoma) (Table 4). The hazard ratio for death in patients with PPC compared to those with NPC and apparent stage IA disease was 5.8 for endometrioid/mucinous histology, 4.3 for clear cell/serous cancer, and 3.6 for

carcinosarcoma. The corresponding hazard ratios for PPC vs. NPC and apparent stage IB disease were 2.4, 1.7, and 1.9, respectively, and for PPC vs. NPC and apparent stage II disease, 1.8, 1.7, and 1.8, respectively.

Discussion

Malignant cells in peritoneal washings may be the result of trans-tubal dissemination of primary tumor, tumor extension via myometrium/serosal lymphatics, or exfoliation of cells from disease at other extrauterine sites (6, 7). Kadar et al reported that malignant cytology was associated with an adverse effect on survival only when accompanied by disease at other extrauterine sites and not if endometrial cancer was still limited to the uterus (8). They rationalized that intraperitoneal dispersion of primary tumor cells not possessing the metastatic phenotype may not be capable of forming metastases. Others have speculated that malignant cytology serves as an indicator of aggressive tumor behavior rather than intraperitoneal disease spread (9, 10). Indeed, malignant cytology has been reported in association with other adverse prognostic features such as high grade disease, non-endometrioid histology, and deep myometrial invasion in a majority of studies including the current study (8, 11-13).

Our results indicate that positive peritoneal cytology is an independent predictor of survival among patients with 2009 FIGO stage I and stage II endometrial cancer. Although the PPC group (unlike the NPC group) could not be further classified into individual stage categories (stages IA, IB, and II) precluding a stage matched comparison between patients with negative- and positive cytology, survival outcomes in the PPC group were individually compared to different stage categories within the NPC group (stages IA, IB, and II). The survival was found to be significantly worse in patients with PPC compared to those with NPC and deep myometrial invasion, as well as those with NPC and cervical stromal invasion, after adjusting for different clinico-pathologic variables including tumor grade and histology. Data regarding the depth of myometrial invasion or cervical stromal invasion were not available independent of the stage at diagnosis and for patients with PPC, hence not included in the multivariate model. However, even if one presumes that most patients in the PPC group in the current study had deep myometrial invasion and/or cervical stromal invasion, the fact that their survival was worse compared to the corresponding patients with negative peritoneal cytology provides indirect evidence that positive cytology is indeed an independent prognostic factor in these patients. Furthermore, similar results were obtained when separate multivariable analyses were performed by individual histologic subtypes, reinforcing the prognostic significance of PPC in patients with early stage endometrial cancer.

Although, a number of studies have failed to corroborate the prognostic significance of PPC in patients with early stage endometrial cancer (14-16), most large studies have found it to be an independent predictor of survival (17-19). Furthermore, multiple studies have shown that outcomes in patients with endometrial cancer otherwise confined to the uterus were similar to those of women with serosal or adnexal metastasis in presence of PPC (12, 20). These results support the placement of patients with stage I/II endometrial cancer and PPC in a more advanced stage group, as opposed to the current FIGO staging criteria for

accurate risk-stratification. In fact, in a survey study of the members of the society of gynecologic oncologists, a majority of respondents supported the retention of PPC in the current FIGO stage IIIA classification (21). Unfortunately, we are not able to comment on whether or not the presence of PPC should influence postoperative adjuvant therapy recommendations in patients with stage I-II endometrial cancer. Due to a higher incidence of concurrent high-risk or high-intermediate risk features (non-endometrioid histology, deep myometrial invasion, high-grade disease), more patients with PPC than NPC could be speculated to have received adjuvant chemotherapy. The impact of chemotherapy administration on prognosis of patients with PPC however could not be determined, because this information was not available from the SEER database.

Although our study benefits from inclusion of a large number of patients, several limitations must be acknowledged. The major shortcoming of this study was the inability to sub-classify patients in the PPC group into individual stage categories as mentioned before. Additionally, information regarding lymphovascular space invasion, and depth of myometrial invasion could not be obtained. Both lymphovascular space invasion and extent of myometrial invasion are well recognized prognostic factors in endometrial cancer, which could not be incorporated in the multivariable analysis. Similarly, we were not able to determine if (and which) patients in the PPC and NPC groups received chemotherapy or adjust for chemotherapy usage in the multivariate model, because this information is not available from the SEER database. Had patients more likely to be treated with chemotherapy (i.e. PPC group) shown better outcome than those less likely to receive chemotherapy (i.e. NPC group), this lack of adjustment for chemotherapy administration could be considered to have significantly influenced our results. Although radiation use was recorded, it was not possible to determine the dose of radiation, fields that were treated, or compliance with radiation. Finally, as with any registry study, centralized pathology review was not performed.

In conclusion, our study shows that positive peritoneal cytology is an independent prognostic factor in patients with early stage endometrial cancer. The risk of death is increased considerably for all histologies in the presence of positive peritoneal cytology. Although, peritoneal cytology is no longer a part of the FIGO staging criteria, it is still requested by the FIGO to be reported separately. We hope that with further data peritoneal cytology will be added back into the surgical staging for endometrial cancer. Until then, it should still be taken into consideration for accurate risk-stratification of patients with early stage endometrial cancer.

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Research Highlights

1. Positive peritoneal cytology is frequently associated with uterine high-risk factors.
2. It is an independent risk- factor in patients with early-stage endometrial cancer.
3. Survival is decreased for all histologies in the presence of malignant cytology.

Figure 1.
Kaplan-Meier Disease Specific Survival by Peritoneal Cytology Status in (A) Endometrioid Adenocarcinoma; (B) Clear cell/Serous Adenocarcinoma; and (C) Carcinosarcoma

Table 1

Comparison of Demographic and Clinical Features between Endometrial Cancer Patients with Negative Peritoneal Cytology and those with Positive Peritoneal Cytology

Variable		Overall (N=14,704)	Negative Peritoneal Cytology (NPC) (N=14,219)	Positive Peritoneal Cytology (PPC) (N=485)	P value
Age at diagnosis	<50	1961 (13.3%)	1902(13.4%)	59(12.2%)	0.4
	50-65	6976 (47.4%)	6755 (47.5%)	221 (45.6%)	
	>65	5767 (39.2%)	5562 (39.1%)	205(42.3%)	
Race	White	12609 (85.8%)	12204 (85.8%)	405 (83.5%)	0.4
	Black	914 (6.2%)	877(6.2%)	37 (7.6%)	
	Other	1122 (7.6%)	1080(7.6%)	42 (8.7%)	
	Unknown	59 (0.4%)	58 (0.4%)	1 (0.2%)	
Grade	I	4664 (31.7%)	4593 (32.3%)	71 (14.6%)	<0.0001
	II	5149 (35.0%)	4981(35.0%)	168 (34.6%)	
	III	3584 (24.4%)	3389(23.8%)	195 (40.2%)	
	Unknown	1307 (8.9%)	1256 (8.8%)	51 (10.5%)	
Histology	Endometrioid/Mucinous	12709 (86.4%)	12354 (86.9%)	355 (73.2%)	<0.0001
	Clear cell/Serous	1153 (7.8%)	1068 (7.5%)	85 (17.5%)	
	Carcinosarcoma	842 (5.8%)	797 (5.6%)	45 (9.3%)	
Radiation	No	10044 (68.3%)	9829 (69.1%)	215 (44.3%)	<0.0001
	Yes	4475 (30.4%)	4216 (29.7%)	259 (53.4%)	
	Unknown	185 (1.3%)	174 (1.2%)	11 (2.3%)	
Lymph node removed	<10	5727 (38.9%)	5543 (39.0%)	184 (37.9%)	0.2
	10	7791 (53.0%)	7519 (52.9%)	272 (56.1%)	
	Unknown	1186 (8.1%)	1157 (8.1%)	29 (6.0%)	

NOS: Not otherwise specified

Table 2

Univariate Analysis of Disease Specific Survival by Histology and Grade

Stage	Endometrioid/Mucinous					Clear cell/Serous	Carcinosarcoma
	Overall	G 1	G 2	G 3			
		5-yr DSS (95% CI)	5-yr DSS (95% CI)	5-yr DSS (95% CI)	5-yr DSS (95% CI)		
Negative Peritoneal Cytology	Overall (stages I-II)	95.1% (94.7%-95.5%)	98.6% (98.2%-99.0%)	95.7% (95.0%-96.3%)	87.4% (85.8%-88.8%)	78.0% (75.1%-80.6%)	64.7% (61.0%-68.2%)
	IA	97.2% (96.8%-97.5%)	99.0% (98.5%-99.3%)	97.3% (96.6%-97.8%)	92.8% (91.2%-94.1%)	85.0% (81.9%-87.5%)	72.9% (68.5%-76.9%)
	IB	90.3% (88.9%-91.6%)	97.3% (95.3%-98.4%)	92.1% (90.0%-93.9%)	80.1% (76.3%-83.3%)	59.1% (49.5%-67.5%)	52.3% (44.0%-60.0%)
	II	88.3% (85.9%-90.2%)	96.3% (92.8%-98.2%)	91.8% (88.5%-94.1%)	74.9% (68.7%-80.1%)	64.7% (56.7%-71.6%)	48.2% (37.6%-57.9%)
Positive Peritoneal Cytology		80.8% (75.7%-85.0%)	88.2% (77.6%-94.0%)	87.8% (80.5%-92.5%)	68.6% (57.2%-77.5%)	50.4% (37.1%-62.2%)	32.3% (17.8%-47.8%)

Table 3

Multivariate Analysis of Factors Associated with Survival

Variables			Disease Specific Survival
Age	>65		Referent
	50-65		* 0.52 (0.46-0.58)
	<50		* 0.24 (0.18-0.32)
Race	White		Referent
	Black		* 1.68 (1.42-2.0)
	Other		0.86 (0.66-1.12)
Histology	Endometrioid/Mucinous		Referent
	Clear cell/Serous		* 2.13 (1.81-2.50)
	Carcinosarcoma		* 4.09 (3.48-4.80)
Grade	I		Referent
	II		* 1.86 (1.47-2.36)
	III		* 4.38 (3.49-5.52)
Stage	NPC	IA	Referent
		IB	* 2.29 (1.98-2.64)
		II	* 2.70 (2.30-3.18)
	PPC		* 4.63 (3.79-5.66)
Radiation	No		Referent
	Yes		1.12 (1.00-1.26)
Lymph nodes removed	<10		Referent
	10		* 0.79 (0.70-0.89)

(95% confidence interval).

*
p<0.05

Table 4

Multivariate Analysis of Factors Associated with Disease Specific Survival by Histologic Sub-type

	Variables		Endometrioid/Mucinous	Clear cell/Serous Cancer	Carcinosarcoma
			Hazards Ratio (95% CI)	Hazards Ratio (95% CI)	Hazards Ratio (95% CI)
Age	>65		Referent	Referent	Referent
	50-65		* 0.49 (0.41-0.58)	* 0.50 (0.38-0.66)	* 0.66 (0.51-0.85)
	<50		* 0.31 (0.22-0.43)	*****	* 0.14 (0.05-0.39)
Race	White		Referent	Referent	Referent
	Black		* 2.07 (1.59-2.70)	1.20 (0.87-1.67)	* 1.71 (1.25-2.33)
	Other		0.75 (0.52-1.10)	0.87 (0.52-1.45)	1.09 (0.64-1.84)
Grade	I		Referent	Referent	Referent
	II		* 1.83 (1.42-2.36)	--	--
	III		* 5.02 (3.93-6.42)	--	--
	Unknown		* 2.38 (1.59-3.55)	--	--
Stage	Negative Peritoneal Cytology	IA	Referent	Referent	Referent
		IB	* 2.45 (2.02-2.98)	* 2.46 (1.75-3.46)	* 1.90 (1.43-2.54)
		II	* 3.18 (2.52-4.01)	* 2.53 (1.84-3.48)	* 1.96 (1.41-2.71)
	Positive Peritoneal Cytology		* 5.82 (4.35-7.78)	* 4.28 (2.92-6.27)	* 3.59 (2.36-5.46)
Radiation	No		Referent	Referent	Referent
	Yes		1.12 (0.95-1.33)	1.04 (0.81-1.33)	1.06 (0.84-1.34)
Lymph Nodes Removed	<10		Referent	Referent	Referent
	10		* 0.84 (0.72-0.99)	* 0.64 (0.50-0.83)	0.85 (0.66-1.09)
	Unknown		0.75 (0.55-1.015)	* 0.57 (0.36-0.90)	1.04 (0.71-1.53)

*
p<0.05*****
sample size too small to generate reliable estimates