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Original Research

Effect of positive peritoneal cytology on the prognosis of patients with FIGO stage I endometrial cancer

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Objective: Peritoneal cytology is routinely analyzed during surgical treatment of endometrial cancer. We investigated the effect of positive peritoneal cytology on the prognosis of patients with International Federation of Gynecology and Obstetrics (FIGO) stage I endometrial cancer. *Methods*: The medical records of 364 patients diagnosed with FIGO stage I endometrial cancer between January 2006 and December 2017 were retrospectively reviewed. Twenty-five patients (6.8%) had positive whereas 339 had negative peritoneal cytology results (93.2%). Demographics, recurrence-free survival, and 5-year overall survival were compared. The clinical factors affecting survival and recurrence were evaluated by univariate and multivariate analyses. *Results*: The median age was 53 years and median follow-up was 85 months (range, 6–142). There was no significant difference in the demographics and pathologic results between the groups. Recurrence occurred in only one patient with positive peritoneal cytology. The differences in recurrence-free (p = 0.815) and 5-year overall survival (p = 0.938) between the patients with positive and those with negative peritoneal cytology were not significant. In the univariate analysis, lymphovascular invasion (p = 0.030) and non-endometrioid histology ($p < 0.001$) were significantly associated with an increased recurrence risk, but only non-endometrioid histology was associated with recurrence and reduced survival in the multivariate analysis. *Discussion*: Positive peritoneal cytology did not seem to be associated with recurrence or overall survival in this series of patients with FIGO stage I endometrial cancer.

Keywords

Endometrial neoplasm; Multivariate analysis; Peritoneum; Prognosis

1. Introduction

The standard initial treatment of International Federation of Gynecology and Obstetrics (FIGO) early-stage endometrial cancer is surgery, which includes total hysterectomy, ovarian resection, and pelvic and para-aortic lymphadenectomy to confirm the pathological stage and determine whether adjuvant treatment is indicated. Cytological evaluation of the pelvic peritoneal washing is also performed for most patients. Before 2009, positive peritoneal cytology (PPC) was classified by FIGO as stage IIIA and was considered an indicator of systemic disease. In 2009, the FIGO staging criteria were changed, and the peritoneal cytology status was no longer a part of the staging criteria, but cytological evaluation of the pelvic washings done during surgery was recommended. The National Comprehensive Cancer Network (NCCN) guidelines consider that PPC may enhance the effect of other risk factors [1]. However, there are numerous contradictory reports regarding the effect of PPC on the prognosis of patients with early-stage endometrial cancer [2–15].

Only one prospective clinical trial involving PPC has previously been reported. Dede *et al.* [4] analyzed 12 PPC patients and 12 negative peritoneal cytologic patients. The researchers concluded that no significance was observed between the two groups. In 2018, Matsuo *et al.* [12] found that PPC was associated with decreased survival in women with FIGO stage I–II endometrioid endometrial cancer and recommended adjuvant treatment for such patients. A report by Scott *et al.* [10] in 2017 did not find a significant association between PPC and decreased disease-free survival in patients with early-stage endometrial cancer. They did not recommend changing the treatment plan for all early-stage endometrial cancer patients with PPC just because of a small risk of recurrence and because chemotherapy for low and intermediate-risk early-stage endometrial cancer patients would not be cost-effective. Lee *et al.* [9] undertook a systematic review and meta-analysis, where they investigated the association between PPC and various prognostic factors. They analyzed 11 studies and concluded that PPC is associated with other prognostic factors and survival, therefore PPC has potential as a useful prognostic factor. Previous retrospective studies have estimated that 2–5% of the patients with early-stage endometrial cancer will have PPC. Because of the very small percentage, it is difficult to conduct a prospective study on the clinical significance of PPC in early-stage endometrial cancer. Even without a standard treatment recommendation for patients with PPC, optimal management is important for these patients. This study retrospectively evaluated the treatment history of FIGO stage I and II endometrial cancer patients with all histological types to determine the influence of PPC on prognosis in real-world practice.

2. Materials and methods

2.1 Study population

We reviewed the electronic medical records of patients who were newly diagnosed with endometrial cancer according to the endometrial biopsy result and were treated at the National Cancer Center in South Korea between January 2006 and December 2017. Patients with neuroendocrine tumor (NET), uterine sarcoma, and carcinosarcoma were excluded. NET does not display all the typical characteristics of endometrial cancer as it can be found in other organs. Moreover, sarcoma is not categorized as a carcinoma. Although carcinosarcoma is classified as carcinoma, its manifestation differs slightly from carcinoma. Of the 1578 endometrial cancer patients who visited our outpatient clinics, 497 patients visited only once for counseling or a second opinion, and 439 patients had recurrent disease. The FIGO stages of the patients diagnosed between 2006 and 2009 were adjusted to account for the removal of PPC from the IIIA classification. One hundred and twenty-three patients with current FIGO stage II, III, or IV, 125 patients whose peritoneal cytology report was not present in the pathology results, and 30 with other synchronous cancers were excluded from the analysis. The remaining 364 patients with FIGO stage I endometrial cancer who were diagnosed and treated at our center were included in the analysis (Fig. 1). Patients' baseline characteristics, such as age at diagnosis, tumor size, radicality of hysterectomy, lymph node dissection, lympho-vascular space invasion (LVSI), endocervical invasion (although this was not included in staging, it can function as a prognostic factor), FIGO stage, FIGO grade, histology of the endometrium, and the history of adjuvant chemotherapy or radiotherapy, were extracted.

2.2 Statistical analysis

Correlations of variables were assessed with Fisher's exact or Student *t*-tests. The log-rank tests were used for determining significance of the differences. Five-year overall survival (OS) and recurrence-free survival (RFS) were analyzed using the Kaplan-Meier method. For identifying the prognostic factors in patient characteristics, univariate and multivariate Cox regression analyses were performed. Hazard ratios were calculated. *p*-values of <0.05 were considered significant.

3. Results

Twenty-five patients (6.8%), out of 364, had PPC, whereas 339 had negative peritoneal cytology results (93.2%). The patients' characteristics are shown in Table 1. Differences in age, tumor size, hysterectomy type, proportion of patients who underwent lymph node dissection, LVSI endometrial invasion depth, endocervical invasion, histology, FIGO grade, and FIGO stage between the two patient groups were not statistically different. Only one patient with PPC experienced recurrence. Recurrence occurred in 13 patients with negative peritoneal cytology. The Kaplan-Meier analysis of RFS and 5-year OS is shown in Fig. 2. Differences in RFS and OS were not significant between the groups. Univariate analysis found that histology ($p < 0.037$) and LVSI ($p = 0.022$) were associated with recurrence (Table 2). According to the multivariate analysis, non-endometrioid histology ($p = 0.042$) was independently associated with recurrence risk (Table 3). Histology ($p = 0.001$) and LVSI ($p = 0.030$) were associated with lower OS according to the univariate analysis (Table 2). Non-endometrioid histology was independently associated with decreased OS according to the multivariate analysis (Table 3).

4. Discussion

There is no consensus on the optimal management of early-stage endometrial cancer patients with PPC. In this study, non-endometrioid histology and LVSI were identified as factors associated with worse RFS and OS in patients with FIGO stage I endometrial cancer. PPC did not affect the patient prognosis. The patients' characteristics and postsurgical treatment or management of all 25 patients with PPC are shown in **Supplementary Table 1** (Supplementary data). Recurrence occurred in only one patient with PPC. Histology of the cancer in this patient was serous type but no other risk factors were present. Two patients received adjuvant chemotherapy, seven patients received radiotherapy, and one patient received both adjuvant treatments. The results of this study are consistent with those presented by Scott *et al.* [10] who reported that the adjuvant treatment after surgery did not affect the risk of recurrence in patients with PPC. There is no evidence that any patient would have relapsed if they had not received adjuvant therapy. In this study, only one patient with PPC had a recurrence, but the lack of sufficient recurrence events may due to the small sample size. Therefore, we cannot state definitively that PPC does not affect the prognosis just by analyzing the study results. However, when reviewing the medical records of these 25 patients with PPC, it was found that 15 patients received no additional treatment, but they did experience cancer recurrence. Therefore, we cannot conclude with certainty that PPC had a negative effect on the prognosis and that additional treatment was required for the patients with PPC. There were only 25 patients with PPC, but most of them showed endometrioid histology; 22 of these 25 patients were LVSI-negative and had a very early-stage disease. Early-stage endometrial cancer patients with PPC appeared to do well without adjuvant systemic treatment, and systemic treatment did not change the prognosis.

Comparing prognostic factors, LVSI and non-endometrioid histology were associated with lower survival. In patients with these risk factors, proper adjuvant treatment would be beneficial; however, adjuvant treatment for patients with PPC alone may not be effective.

It is worth paying attention to the origin of the malignant cells in the abdominal cavity. Peritoneal dissemination of cancer, serosal invasion, lymphatic dissemination, and reflux

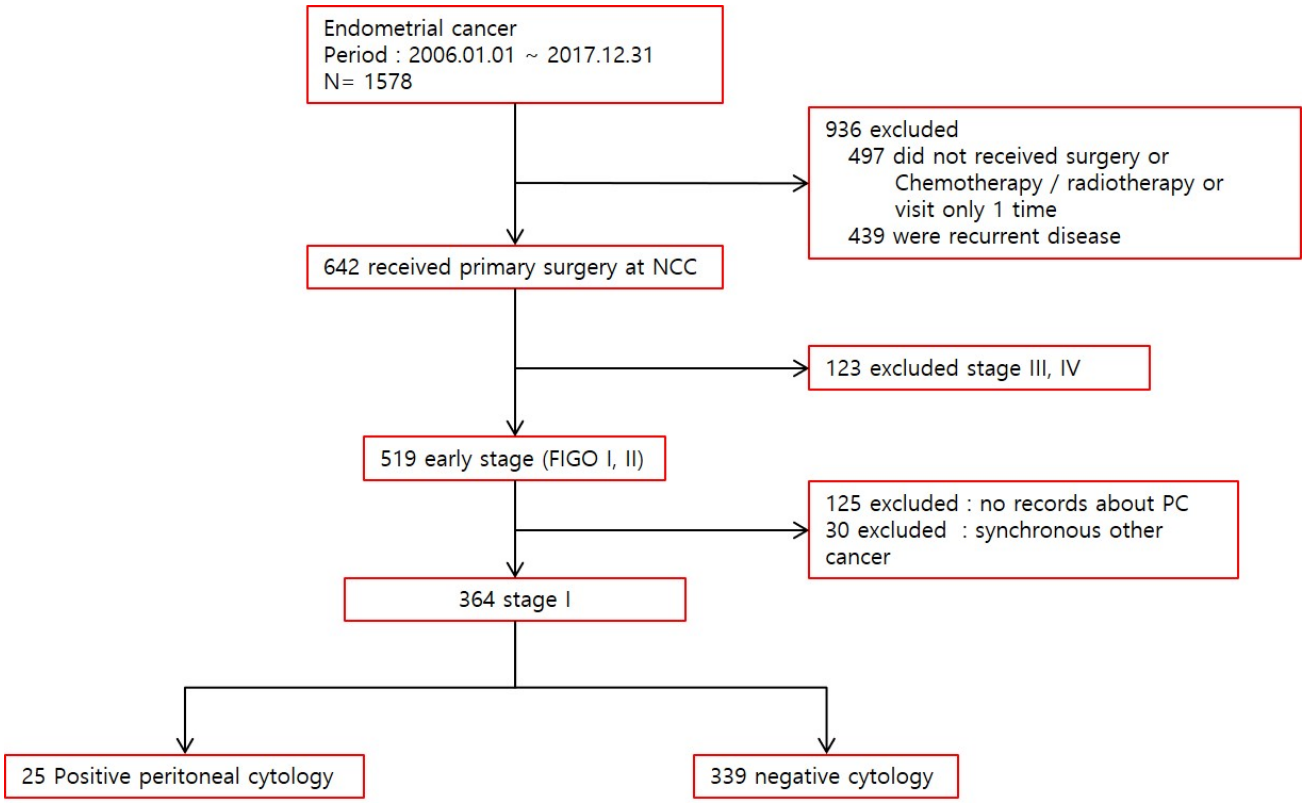

Fig. 1. Patient selection flow chart. PC, peritoneal cytology.

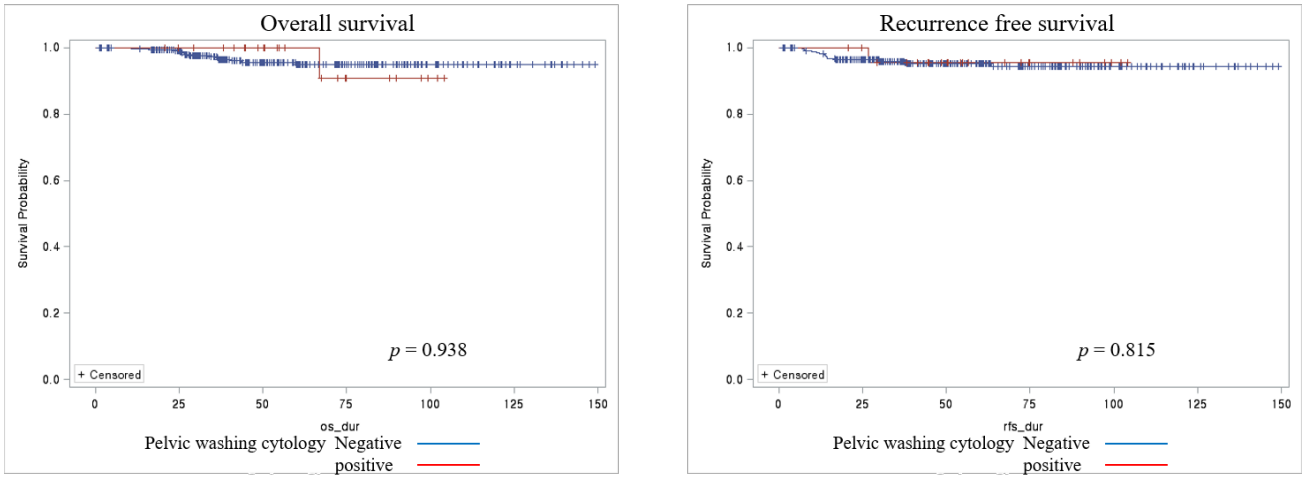

Fig. 2. Kaplan-Meier survival curves of overall survival and recurrence free survival.

through the fallopian tubes can be considered as the source of these peritoneal malignant cells. In this study, only FIGO I/II patients were included [14]. Therefore, uterine serosal invasion and peritoneal and lymphatic dissemination would not occur. The only possible cause is the reflux of the endometrial malignant cells through the fallopian tubes. The cause of this regurgitation is probably related to menstruation, preoperative biopsy, or hysteroscopic or cervical dilatation and curettage.

The five-tier system of International System for Reporting Serous Fluid Cytology (TIS) is the standard classification system for peritoneal cytology, following non-diagnostic (ND), negative for malignancy (NFM), atypia of undetermined significance (AUS), suspicious for malignancy (SFM), and malignant (MAL) [16]. In our institution, many patients had been processed before this standard was established. Moreover, in the case of AUS in the TIS system, it is difficult to precisely determine malignancy [17]. In our present study, only the presence of malignant cells was de-

Table 1. Baseline characteristics of patients.

Variables	Total	Negative	Positive	*p*-value
	(N = 364)	(N = 339)	(N = 25)	
Age (mean ± SD)	53.1 ± 10.13	53.18 ± 10.24	52.08 ± 8.71	0.602
Tumor size (median (min–max))	2 (0–10)	2 (0–10)	2.5 (0–7)	0.756
Pelvic_washing_cytology				
Negative	339 (93.2)			
Positive	25 (6.8)			
Approach				0.555
Laparoscopy	289 (79.4)	268 (79.1)	21 (84)	
Laparotomy	75 (20.6)	71 (20.9)	4 (16)	
Hysterectomy - radicality				0.416
Simple	337 (92.6)	315 (92.9)	22 (88)	
Radical	27 (7.4)	24 (7.1)	3 (12)	
BSO				1.000
No	47 (12.9)	44 (13)	3 (12)	
Yes	317 (87.1)	295 (87)	22 (88)	
PLND				0.798
No	70 (19.2)	66 (19.5)	4 (16)	
Yes	294 (80.8)	273 (80.5)	21 (84)	
PALND				0.233
No	158 (43.4)	150 (44.3)	8 (32)	
Yes	206 (56.6)	189 (55.8)	17 (68)	
LVI	(miss = 19)			0.778
No	287 (83.2)	266 (82.9)	21 (87.5)	
Yes	58 (16.8)	55 (17.1)	3 (12.5)	
Histology_group				0.554
Non-endometrioid	48 (13.2)	46 (13.6)	2 (8)	
Endometrioid	316 (86.8)	293 (86.4)	23 (92)	
FIGO grade	(miss = 31)			0.645
1	190 (57.1)	174 (56.5)	16 (64)	
2	108 (32.4)	102 (33.1)	6 (24)	
3	35 (10.5)	32 (10.4)	3 (12)	
Endocervix				0.647
No	343 (94.2)	320 (94.4)	23 (92)	
Yes	21 (5.8)	19 (5.6)	2 (8)	
FIGO stage				0.190
IA	294 (80.8)	271 (79.9)	23 (92)	
IB	70 (19.2)	68 (20.1)	2 (8)	
Adjuvant chemotherapy				0.126
No	315 (86.5)	296 (87.3)	19 (76)	
Yes	49 (13.5)	43 (12.7)	6 (24)	
Adjuvant radiotherapy				0.347
No	317 (87.1)	297 (87.6)	20 (80)	
Yes	47 (12.9)	42 (12.4)	5 (20)	
Myometrial invasion depth	(miss = 34)			0.186
<0.5	262 (79.4)	241 (78.5)	21 (91.3)	
≥0.5	68 (20.6)	66 (21.5)	2 (8.7)	

termined, ND may have been overlooked, therefore affecting the measurement of the PPC rate.

However, simply moving malignant cells from one area to another does not result in successful metastasis. Successful metastasis requires various conditions such as a particular vascular and tumor microenvironment [18, 19]. Transfer of a small amount of cells in the endometrium to the peritoneal cavity does not mean successful settlement.

Peritoneal cytology is also performed for other solid cancers such as ovarian and gastric cancers. Malignant ascites or PPC is included in the FIGO IC3 stage for ovarian cancer. PPC is considered peritoneal dissemination, and adjuvant systemic chemotherapy is the standard treatment for ovarian cancers. PPC in gastric cancer is associated with poor prognosis and is considered stage IV [20]. In gastric cancer, the reliability of negative cytology results is an impor-

Table 2. Univariate analysis of clinical factors related to overall survival and recurrence free survival.

	Overall survival			Recurrence free survival		
	Univariable			Univariable		
Variables	N (event)	HR (95% CI)	*p*-value	N (event)	HR (95% CI)	*p*-value
Age	364 (14)	1.08 (1.02–1.14)	0.008	364 (17)	1.01 (0.96–1.06)	0.766
Tumor size	364 (14)	1.20 (0.96–1.49)	0.109	364 (17)	1.11 (0.90–1.37)	0.340
Pelvic_washing_cytology						
Negative	339 (13)	1		339 (16)	1	
Positive	25 (1)	0.92 (0.12–7.06)	0.938	25 (1)	0.79 (0.10–5.93)	0.816
hysterectomy - radicality						
Simple	337 (13)	1		337 (15)	1	
Radical	27 (1)	1.03 (0.13–7.84)	0.98	27 (2)	1.67 (0.38–7.29)	0.498
BSO						
No	47 (0)			47 (2)	1	
Yes	317 (14)			317 (15)	1.17 (0.27–5.13)	0.833
PLND						
No	70 (3)	1		70 (3)	1	
Yes	294 (11)	0.87 (0.24–3.11)	0.826	294 (14)	1.10 (0.32–3.83)	0.879
PALND						
No	158 (5)	1		158 (7)	1	
Yes	206 (9)	1.44 (0.48–4.31)	0.511	206 (10)	1.11 (0.42–2.91)	0.839
LVI						
No	287 (8)	1		287 (10)	1	
Yes	58 (5)	3.46 (1.13–10.60)	0.03	58 (6)	3.28 (1.19–9.04)	0.022
Histology_group						
Non-endometrioid	48 (6)	1		48 (5)	1	
Endometrioid	316 (8)	0.17 (0.06–0.49)	0.001	316 (12)	0.33 (0.12–0.94)	0.037
FIGO grade						
1	190 (3)	1	–0.144	190 (4)	1	–0.054
2	108 (6)	3.71 (0.93–14.86)	0.064	108 (9)	4.08 (1.26–13.27)	0.019
3	35 (2)	4.03 (0.67–24.14)	0.127	35 (1)	1.44 (0.16–12.86)	0.746
Endocervix						
No	343 (12)	1		343 (15)	1	
Yes	21 (2)	2.49 (0.56–11.13)	0.233	21 (2)	2.18 (0.50–9.55)	0.299
Figo stage						
Ia	294 (10)	1		294 (11)	1	
Ib	70 (4)	1.81 (0.57–5.77)	0.317	70 (6)	2.46 (0.91–6.64)	0.077

tant clinical issue since recurrence has been reported even for those patients with negative cytology [21].

Likewise, we should consider the possibility of false-negative results of cytology in patients with endometrial cancer recurrence who had a negative cytology result initially. It is necessary to establish a standard method of obtaining peritoneal washings for cytology as well.

As this study was a retrospective study, there is the possibility of selection bias. This, and the small number of PPC cases in our institution may limit the significance of the findings. However, as our study used data from a single large institution to enroll the endometrial cancer patients, this achieved a relatively large sample size. Real-world experience has also led us to the conclusion that PPC does not affect patient survival and recurrence, which may serve as a counterpoint to the controversy regarding endometrial cancer with PPC.

5. Conclusions

PPC alone does not affect survival and RFS in FIGO stage I endometrial cancer patients. Further research with larger sample sizes is needed to determine the optimal treatment of early-stage endometrial cancer patients with PPC to exclude the peritoneal cytology results from the pathologic results.

Author contributions

WS and SSS conceived and designed the study. WS performed the data analysis and wrote the paper. DOL, MCL, SYP, and SK reviewed and revised the manuscript. SSS supervised the entire study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Table 3. Multivariate analysis of clinical factors.

	Overall survival			Recurrence free survival		
	Multivariable (N = 364)			Multivariable (N = 364)		
Variables	N (event)	HR (95% CI)	*p*-value	N (event)	HR (95% CI)	*p*-value
Age	364 (14)	1.07 (1.01–1.13)	0.029	364 (17)		
Pelvic_washing_cytology						
negative	339 (13)	1		339 (16)	1	
positive	25 (1)	0.97 (0.13–7.43)	0.976	25 (1)	0.66 (0.09–5.03)	0.689
Histology_group						
Non-endometrioid	48 (6)	1		48 (5)	1	
Endometrioid	316 (8)	0.22 (0.07–0.64)	0.006	316 (12)	0.34 (0.12–0.96)	0.042

Ethics approval and consent to participate

This retrospective study was approved and the requirement for informed consent was waived by the institutional review board of our institution (IRB No. NCC2019-0272). The study was conducted in accordance with the Declaration of Helsinki.

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Conflict of interest

The authors declare no competing interests.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://ejgo.imrpress.com/EN/10.31083/j.ejgo4204110.

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