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Impact of Positive Peritoneal Cytology on Prognosis in Stage IA Endometrial Cancer: A Retrospective Cohort Study in the Era of Minimally Invasive Surgery

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Abstract

Objective: The prognostic significance of positive peritoneal cytology (PC) in early-stage endometrial cancer remains debated, particularly following its exclusion from the 2008 International Federation of Gynecology and Obstetrics (FIGO) staging system. This study aimed to evaluate the impact of positive PC on recurrence and survival outcomes in patients with stage IA endometrial cancer, considering contemporary surgical practices, including minimally invasive surgery.

Methods: This retrospective cohort study included 325 patients diagnosed with stage IA endometrial cancer who underwent primary surgical treatment at Kagoshima University Hospital between 2010 and 2022. PC was assessed intraoperatively, and patients were stratified into positive and negative cytology groups. Clinicopathological characteristics, recurrence-free survival (RFS), and overall survival (OS) were compared using Kaplan–Meier analysis. Cox proportional hazards regression was performed to identify independent prognostic factors.

Results: Positive PC was identified in 5.8% (19/325) of cases. Patients with positive cytology had significantly lower five-year RFS (72.7% vs. 93.7%, $p = 0.0001$) and OS (82.1% vs. 96.1%, $p = 0.0001$). Cox regression analysis identified positive PC as the strongest independent predictor of recurrence (HR 8.33, 95% CI: 2.41–25.8) and mortality (HR 14.2, 95% CI: 2.22–90.3). In addition, advanced age (≥ 60 years) was significantly associated with decreased survival.

Conclusion: Positive PC is a significant adverse prognostic factor in stage IA endometrial cancer, associated with increased recurrence and reduced survival. Future large-scale prospective studies are needed to determine its role in risk stratification and management of stage IA endometrial cancer.

Categories: Obstetrics/Gynecology

Keywords: endometrial cancer, peritoneal cytology, prognosis, recurrence, survival

Introduction

Endometrial cancer is among the most common gynecologic malignancies, generally associated with a favorable prognosis and an estimated five-year survival rate of approximately 80% [1]. The standard treatment for endometrial cancer involves a simple total hysterectomy with bilateral salpingo-oophorectomy, and lymph node dissection or biopsy when indicated [2]. The staging of endometrial cancer is determined based on multiple pathological factors identified in the resected specimens, which subsequently guide the need for adjuvant therapy [3]. Consequently, each prognostic factor is crucial in determining patient outcomes.

In the 2008 International Federation of Gynecology and Obstetrics (FIGO) classification, peritoneal cytology (PC) was excluded from the staging criteria for endometrial cancer, and stage IIIA was thereafter limited to cases involving serosal or adnexal invasion, excluding PC as a factor in stage determination [4]. This exclusion was largely influenced by studies suggesting that positive PC does not significantly impact prognosis [5,6]. However, recent studies have reported a significant association between positive PC and reduced survival in patients with endometrial cancer [7–9]. Although PC is no longer included in the FIGO staging system, the National Comprehensive Cancer Network guidelines still recommend its evaluation during surgery, indicating its potential prognostic relevance [3].

The exclusion of positive PC from the staging criteria may have had the greatest impact on stage IA endometrial cancer (FIGO 2008) with positive cytology. Previously classified as stage IIIA and typically managed with adjuvant therapy, these cases are now considered low risk for recurrence and do not routinely undergo adjuvant treatment. In addition, the surgical approach to endometrial cancer has shifted from open surgery to minimally invasive surgery (MIS), including laparoscopic and robot-assisted approaches, since the

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2008 FIGO classification update. Given these substantial changes, limited studies have evaluated the prognostic impact of positive PC in stage IA endometrial cancer (FIGO 2008), considering these recent advancements. This study aimed to analyze the prognostic impact of positive PC in stage IA endometrial cancer (FIGO 2008) and reassess its clinical significance.

Materials And Methods

Study population

This retrospective study included patients who underwent surgery at Kagoshima University Hospital between January 2010 and January 2022 and were pathologically diagnosed with stage IA endometrial cancer (FIGO 2008). Eligible cases included those who underwent at least a total hysterectomy and had histologically confirmed endometrial cancer with $\leq 50\%$ myometrial invasion. The exclusion criteria included patients who received neoadjuvant chemotherapy, those with sarcomatous histology (excluding carcinosarcoma), those with synchronous malignancies, and those for whom PC was not performed intraoperatively. Clinical and pathological data, including patient age, body mass index (BMI), final histological subtype, lymphovascular space invasion (LVSI), surgical approach (open surgery vs. MIS), adjuvant therapy, recurrence, and survival outcomes, were extracted from electronic medical records. The study was approved by the Institutional Review Board of Kagoshima University Hospital (Approval No. 240153).

Clinical data analysis

Surgical staging was determined based on the 2008 FIGO classification. PC was considered positive if malignant cells were identified, whereas negative cytology included cases without malignant cells or with atypical cells of uncertain malignancy. Patients were stratified into two groups based on age (< 60 vs. ≥ 60 years) and BMI (< 30 vs. ≥ 30). Histological subtypes were categorized as endometrioid carcinoma (grades 1, 2, and 3), serous carcinoma, clear cell carcinoma, and other types. Surgical procedures included simple hysterectomy with bilateral salpingo-oophorectomy, with or without lymphadenectomy/biopsy. Surgical approaches were classified as open surgery or MIS (laparoscopic or robotic-assisted surgery). MIS was introduced in December 2016. In all MIS cases, the external cervical OS was sutured closed before surgery, and uterine manipulators were not used. PC was collected before uterine extraction in both open and MIS procedures. Adjuvant therapy was administered in cases of grade 3 endometrioid carcinoma, non-endometrioid histology, or LVSI. Recurrence was diagnosed based on clinical examination, cytological/histological analysis, tumor markers, and imaging studies. Recurrence-free survival (RFS) was defined as the interval from primary surgery to the first recurrence, and overall survival (OS) was defined as the time from surgery to the last follow-up or death from endometrial cancer.

Statistical analysis

Comparisons of clinicopathological characteristics between the positive and negative PC groups were performed using the chi-square test. Survival analysis was conducted using Kaplan–Meier survival curves, with statistical significance assessed via the log-rank test. A p-value < 0.05 was considered statistically significant. Cox proportional hazards regression models were used to identify independent prognostic factors associated with recurrence and survival. Statistical analysis was performed using JMP software (version 14, SAS Institute Inc., Cary, NC, USA).

Results

A total of 325 patients with stage IA endometrial cancer were analyzed, including 19 (5.8%) with positive PC and 306 (94.2%) with negative PC. The overall clinicopathological characteristics are summarized in Table 1. The two groups were generally similar in terms of age distribution and histological subtype. Although BMI differed significantly between groups, other factors such as LVSI, surgical approach (open vs. MIS), and the proportion of patients receiving adjuvant therapy did not show statistically significant differences.

Characteristic	Positive PC (n = 19)	Negative PC (n = 306)	Test Statistic	P-value
Age <60/≥60	15 (79.0%)/4 (21.0%)	182 (59.5%)/124 (40.5%)	$\chi^2 = 2.85$	0.09
BMI <30/≥30	14 (73.7%)/5 (26.3%)	238 (77.8%)/68 (22.2%)	$\chi^2 = 15.24$	<0.0001
Final pathology	Endometrioid 18 (94.7%), serous 1 (5.3%), others 0	Endometrioid 276 (90.2%), serous 13 (4.3%), clear cell 9, others 8	$\chi^2 = 0.92$	0.77
LVSI (no/yes)	19 (100%)/0 (0%)	279 (91.2%)/27 (8.8%)	$\chi^2 = 1.80$	0.18
Surgical procedure (open/MIS)	11 (57.9%)/8 (42.1%)	135 (44.1%)/171 (55.9%)	$\chi^2 = 1.38$	0.24
Adjuvant therapy (no/yes)	13 (68.4%)/6 (31.6%)	249 (81.4%)/57 (18.6%)	$\chi^2 = 1.90$	0.17
Recurrence (no/yes)	14 (73.7%)/5 (26.3%)	288 (94.1%)/18 (5.9%)	$\chi^2 = 11.33$	0.0008

TABLE 1: Clinicopathological characteristics of 325 patients with stage IA endometrial cancer in this study

PC: peritoneal cytology, BMI: body mass index, LVSI: lymphovascular space invasion, MIS: minimally invasive surgery

Statistical comparisons were conducted using chi-square (χ^2) tests for categorical variables.

A p-value < 0.05 was considered statistically significant.

The recurrence rate was markedly higher in the positive PC group compared to the negative PC group, with peritoneal dissemination being the predominant site in the former. In contrast, recurrences in the negative group were more widely distributed, including the vaginal cuff, lymph nodes, and distant sites. Detailed recurrence patterns are presented in the text and summarized in Table 1.

Kaplan-Meier survival analysis demonstrated significantly reduced RFS and OS in the positive PC group, with five-year RFS and OS rates of 72.7% and 82.1%, respectively, compared to 93.7% and 96.1% in the negative PC group (p = 0.0001 for both; Figures 1, 2). These findings underscore the prognostic significance of positive cytology in stage IA endometrial cancer.

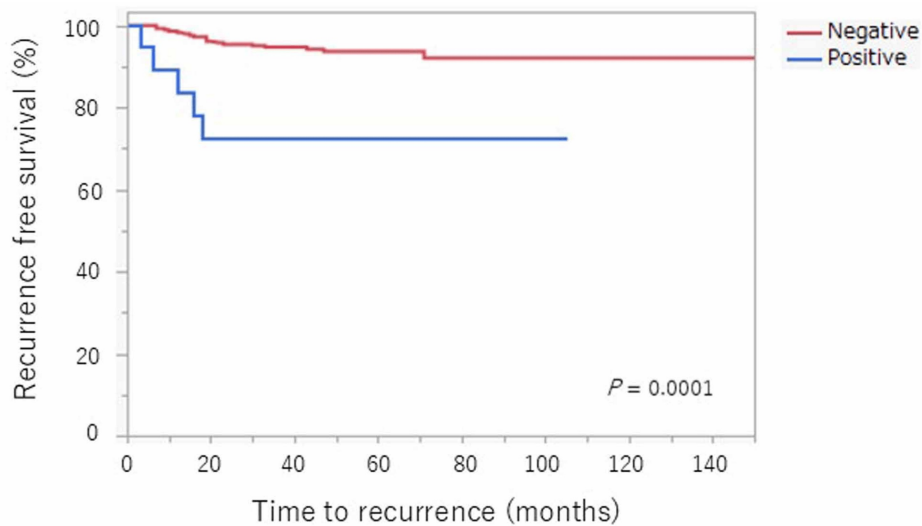


FIGURE 1: Five-year recurrence-free survival rate

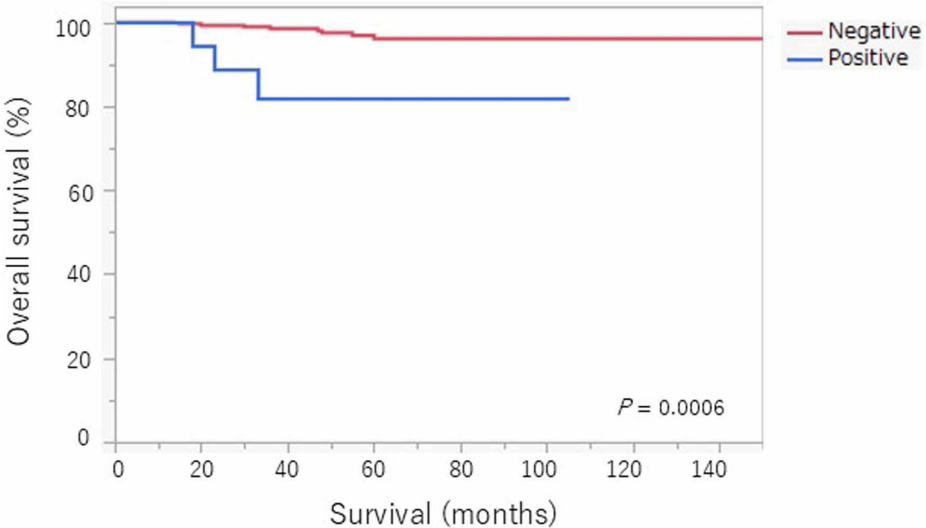


FIGURE 2: Five-year overall survival rate

Table 2 presents the Cox proportional hazards regression analysis for recurrence and survival. Older age (≥ 60 years), open surgery, and positive PC were significantly associated with increased recurrence risk, with positive cytology being the strongest predictor. Similarly, older age (≥ 60 years) and positive PC were significant factors associated with reduced OS, with positive cytology being the most strongly correlated factor.

Characteristic	RFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	-	-	-	-
<60	1	-	1	-
>60	4.0 (1.62–10.8)	0.0025	5.58 (1.46–28.4)	0.01
Median BMI (kg/m ²)	-	-	-	-
<30	1	-	1	-
>30	0.73 (0.17–2.27)	0.62	0.43 (0.02–2.42)	0.38
Final pathology	-	-	-	-
Endometrioid	1	-	1	-
Non-endometrioid	0.61 (0.09–2.44)	0.51	0.48 (0.02–3.07)	0.48
LVSI	-	-	-	-
No	1	-	1	-
Yes	2.20 (0.56–7.02)	0.24	4.0 (0.81–20.1)	0.86
Surgical procedure	-	-	-	-
Open surgery	1	-	1	-
Minimally invasive surgery	0.26 (0.08–0.70)	0.0073	0.47 (0.07–2.19)	0.35
Adjuvant therapy	-	-	-	-
No	1	-	1	-
Yes	0.89 (0.30–2.47)	0.82	3.9 (0.88–22.1)	0.07
Peritoneal cytology	-	-	-	-
Negative	1	-	1	-
Positive	8.33 (2.41–25.8)	0.0016	14.2 (2.22–90.3)	0.0067

TABLE 2: Multivariable Cox analysis with recurrence-free survival and overall survival in patients with stage IA endometrial cancer

RFS: recurrence-free survival, OS: overall survival, HR: hazard ratio, CI: confidence interval, BMI: body mass index, LVSI: lymphovascular space invasion,

Statistical significance of differences between groups was conducted using likelihood ratio test.

A p-value < 0.05 was considered statistically significant.

Discussion

In this study, we analyzed the prognostic impact of positive PC in stage IA endometrial cancer (FIGO 2008) and reassessed its clinical significance in the context of modern surgical practices. Among 325 patients, 19 (5.8%) had positive PC, which is consistent with previous reports indicating a positive PC incidence ranging from 3.3% to 13.7% in early-stage endometrial cancer [7–13].

Recurrence was observed in five of 19 patients with positive PC (26.3%), which was significantly higher than that in the negative PC group (18 of 306; 5.9%). Furthermore, the five-year RFS rate was 72.7% (14/19) in the positive PC group versus 93.7% (287/306) in the negative PC group ($p = 0.0001$), and the five-year OS rate was 82.1% (15/19) versus 96.1% (294/306), respectively (Figures 1, 2). These data underscore the clinical importance of Tables 1, 2, which demonstrate the disproportionate distribution of recurrence and survival based on PC status, despite similarity in most other clinicopathological characteristics.

Cox proportional hazards analysis identified positive PC as the most significant factor associated with both

recurrence (HR 8.33, 95% CI: 2.41-25.8) and OS (HR 14.2, 95% CI: 2.22-90.3). These findings are consistent with previous large-scale studies. For example, Seagle et al. [8] reported a four-year OS rate of 79.5% in patients with positive PC versus 92.2% in those with negative PC in stage I/II disease and identified positive PC as an independent prognostic factor (HR 1.85, 95% CI: 1.28-2.67). Similarly, Matsuo et al. [7] demonstrated an association between positive PC and decreased cause-specific survival even in low-risk endometrial cancer (HR 1.64, 95% CI: 1.01-2.68). However, the extent to which MIS was incorporated in those studies remains unclear.

In our cohort, 179 patients (55.1%) underwent MIS, reflecting current clinical practice. To reduce bias associated with surgical manipulation, no uterine manipulators were used, and the external cervical os was sutured prior to surgery to prevent tumor spillage into the peritoneal cavity. This procedural consistency allowed for a clearer evaluation of the true prognostic significance of positive PC, independent of iatrogenic dissemination.

Siegenthaler et al. [14] previously reported that patients with positive PC were more likely to experience intra-abdominal or distant recurrence, as opposed to local recurrence. In our study, of the five recurrences in the positive PC group, four involved peritoneal or distant metastases, and only one involved local recurrence. These recurrence patterns highlight the need for vigilant surveillance strategies targeting intra-abdominal and distant sites in patients with positive PC.

Additionally, it has been suggested that surgical instruments like uterine manipulators may facilitate tumor cell dissemination. The Laparoscopic Approach to Cervical Cancer (LACC) trial [15] indicated poorer oncologic outcomes in the MIS group, potentially due to peritoneal spread via manipulators. While MIS is now an established standard of care for early-stage endometrial cancer [16,17], few trials have examined the specific oncologic impact of manipulator use. A recent prospective study [14] observed cytologic conversion from negative to positive in 10 of 124 cases after manipulator use, suggesting a causal link. Our study, devoid of manipulator-related variables, supports the notion that positive PC is an independent adverse prognostic factor.

Regarding adjuvant therapy, six of 19 patients (31.6%) in the positive PC group received postoperative treatment, compared to 57 of 306 (18.6%) in the negative PC group ($p = 0.17$). Notably, two recurrences occurred in patients with positive PC who had no additional risk factors and did not receive adjuvant therapy. While the small number of positive PC cases limited our ability to evaluate the efficacy of adjuvant chemotherapy statistically, our findings align with previous reports suggesting that postoperative chemotherapy may improve survival outcomes in this population [8,18].

The strength of our study lies in the targeted analysis of positive PC in stage IA disease within a standardized surgical context, including contemporary MIS protocols without uterine manipulators. However, a key limitation is the relatively small number of positive PC cases, which may affect the statistical power and generalizability of the results. Furthermore, as a retrospective study based on medical record data, inherent biases cannot be excluded.

Conclusions

Our study demonstrated that positive PC is associated with significantly increased recurrence and reduced survival in patients with stage IA endometrial cancer. These findings were independent of surgical approach and highlight the importance of considering positive PC as a key prognostic factor. Given the risk of peritoneal or distant recurrence in these patients, careful postoperative monitoring and individualized consideration of adjuvant therapy may be warranted. These results support the reevaluation of current clinical strategies and underscore the need for prospective studies to clarify the role of PC in treatment decision-making for early-stage endometrial cancer.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Review Board of Kagoshima University Hospital, Kagoshima, Japan issued approval 240153. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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