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# Prognosis of positive peritoneal cytology in minimally invasive surgery for early-stage endometrial cancer

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*Objective*: In this decade, minimally invasive surgery for endometrial cancer has spread rapidly worldwide. This study aimed to evaluate the clinical significance of peritoneal cytology in minimally invasive surgery for early-stage endometrial cancer. *Methods*: The subjects were patients who underwent minimally invasive surgery for endometrial cancer stages I–III (FIGO2008) between 2014 and 2019. We classified patients into three groups (group A: surgical stage I/II and peritoneal cytology negative, group B: surgical stage I/II and peritoneal cytology positive, and group C: surgical stage III), and examined oncological outcomes retrospectively on the basis of the patients' medical records. *Results*: Of the 225 patients, 176, 19, and 30 were classified into groups A, B, and C, respectively. Kaplan–Meier curve analysis with a log-rank test demonstrated that group A had a better progression free survival (PFS) than that of group B ($p < 0.0001$), and there was no statistical difference in PFS between groups B and C ($p = 0.748$). Furthermore, group A had a better overall survival than that of group B ($p = 0.001$), and there was no statistical difference in OS between groups B and C ($p = 0.766$). In multivariate analyses for PFS in groups A and B, peritoneal cytology, along with lymph-vascular space invasion, were significant poor prognosis factors. *Conclusions*: Our results suggest that positive peritoneal cytology is a poor prognosis factor in laparoscopic surgery for early-stage endometrial cancer.

*Keywords*

Endometrial cancer; Peritoneal cytology; Prognostic factor; Laparoscopic surgery

## 1. Introduction

Endometrial cancer is the most common malignant tumor of the female genital tract [1], affecting over 38,000 patients annually [2].

In 1988, the International Federation of Gynecologists and Obstetricians (FIGO) developed a surgical staging system for endometrial cancer. After that, data from more than 42,000 cases were analyzed, and a new stage classification of surgery was revised in 2008 [3]. One of the major changes was that only positive peritoneal cytology was excluded from stage IIIA, because some reports showed a small impact of peritoneal cytology as a prognostic factor [4, 5]. However, since the revision, multiple studies have demonstrated a poor prognosis of positive peritoneal cytology in endometrial cancer patients [6–8]. The significance of ascites cytology in endometrial cancer is still controversial. Furthermore, to the best of our knowledge, there are no reports investigating peritoneal cytology as a prognostic factor in endometrial cancer patients specifically treated with minimally invasive surgery. In 2009, the LAP2 study [9] reported that laparoscopic surgery for early-stage endometrial cancer is not inferior to open surgery in terms of surgical and oncological outcomes. Since then, laparoscopic surgery for endometrial cancer has spread rapidly around the world. In contrast, prognosis was poor after minimally invasive surgery (MIS) in cervical cancer during the LACC trial [10]. Cell scattering during colpotomy and the use of a manipulator and tumor spread via pneumo-peritoneal $CO_2$ were presumed to be the causes of poor prognosis [11]. Tumor spread via pneumo-peritoneal $CO_2$ is unique to MIS and may be particularly relevant in patients with positive ascites cytology.

The object of this study was to investigate the clinical significance of peritoneal cytology in laparoscopic surgery for early-stage endometrial cancer.

## 2. Material and methods

### 2.1 Study design

A single-institute, retrospective observational study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Yokohama Citizens Municipal Hospital, Kanagawa, Japan.

### 2.2 Patients

The subjects were patients who underwent laparoscopic surgery for endometrial cancer stages I–III (FIGO2008) at the Yokohama Municipal Citizen's Hospital between January 2014 and December 2019. We excluded patients who underwent palliative surgery due to old age, complications, and performance status. We classified patients into three groups (group A: surgical stage I/II and peritoneal cytology negative, group B: surgical stage I/II and peritoneal cytology positive, and group C: surgical stage III) and examined oncological outcomes retrospectively based on the patients' medical records.

**Table 1. Surgical procedure selection.**

| Presurgical diagnosis | Operation |
|---|---|
| Stage IA and endometrioid adenocarcinoma G1/G2 (tumor thickness <10 mm) | TLmRH and BSO |
| Stage IA and endometrioid adenocarcinoma G1/G2 (tumor thickness >10 mm) | TLmRH, BSO, and PLA |
| Other cases of type I (No cervical stromal invasion) | TLmRH, BSO, PLA, and EpPALA |
| Other cases of type I (With cervical stromal invasion) | TLRH, BSO, PLA, and EpPALA |
| Type II or carcinosarcoma (No cervical stromal invasion) | TLmRH, BSO, PLA, EpPALA, and OMT |
| Type II or carcinosarcoma (With cervical stromal invasion) | TLRH, BSO, PLA, EpPALA, and OMT |

TLmRH, laparoscopic modified radical hysterectomy; TLRH, laparoscopic radical hysterectomy; BSO, laparoscopic bilateral adnexectomy; PLA, laparoscopic pelvic lymph node dissection; OMT, laparoscopic omentectomy; EpPALA, extraperitoneal para-aortic lymph node dissection.

### *2.3 Surgery*

Laparoscopic surgery was first introduced in 2014, and the proportion of this type of surgery has gradually increased. In 2019, 97.6% of patients with endometrial cancer underwent laparoscopic surgery. The surgical procedure selection is shown in Table 1.

Ascites in the abdominal cavity was collected as the first step. A vaginal cuff closure was generated to prevent malignant cell spillage during colpotomy. A uterine manipulator was not inserted. Bilateral fallopian tubes were obstructed with coagulation to prevent the leaking of cancer cells through the fallopian tubes into the abdominal cavity. Para-aortic lymph node dissection was performed through the extraperitoneal approach [12]. The excised lymph nodes were stored in a plastic bag and carried out through the vagina after hysterectomy. A large uterus that could not be smoothly removed from the vagina was placed in a bag and carried out through an extended umbilical incision. At the end of the procedure, the retroperitoneal and abdominal cavities were washed thoroughly with 1 L and 2 L of warm saline, respectively.

### *2.4 Statistical analyses*

The Chi-squared ($\chi^2$) test was used to compare categorical data, and numeric data were analyzed using the Mann–Whitney U test for independent variables with a normal distribution. Progression free survival (PFS) and overall survival (OS) were analyzed by the Kaplan–Meier method and compared by the log-rank test. In groups A and B, Cox hazard model analysis was applied to detect the risk factors for recurrence. Independent variables did not include histological types (type I or type II and carcinosarcoma), because no recurrence was observed in patients with type 1. $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the IBM SPSS version.27.0 software (SPSS Inc., Chicago, IL, USA).

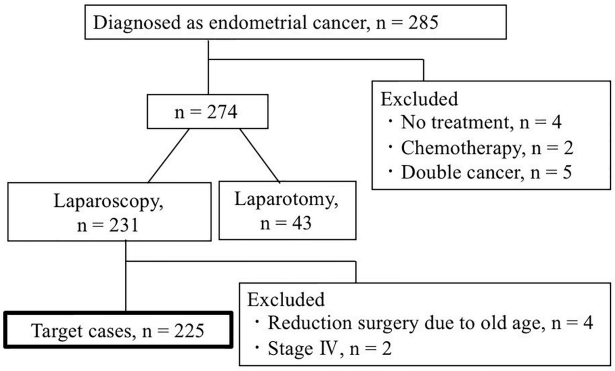


**Fig. 1. The case selection flowchart.**

## 3. Results

Fig. 1 shows the case selection flowchart. Of the 285 endometrial cancer cases, 4 without treatment, 2 treated with chemotherapy alone, and 5 with double cancers were excluded from the analysis. No cases received neoadjuvant chemotherapy. Among the remaining 274 patients, 43 underwent laparotomy and 231 underwent laparoscopic surgery. Among the latter, 4 who underwent a palliative surgery due to old age and 2 who had a stage IV disease were excluded. Finally, 225 patients were enrolled in this study and classified into three groups as follows: 176, 19, and 30 patients in groups A, group B, group C, respectively. Table 2 shows the patients' characteristics in each group. The median number of removed lymph nodes was 35 (range, 12–75) in pelvic lymph node dissection alone and 91 (41–183) in both pelvic and para-aortic lymph node dissection. Of the FIGO stage IIIC stages, 13 patients (52.0%) had multiple lymph node metastases. The median follow-up periods (months) were 48.4 (range, 14.0–89.5), 40.6 (14.0–72.8), and 35.5 (12.0–73.8) in groups A, B, and C, respectively. Recurrence was found in 3 cases (1.7%), 4 cases (21.1%), and 7 cases (23.3%) in groups A, B, and C, respectively.

**Table 2. Patient characteristics.**

| Characteristics | Group A (n = 176) | Group B (n = 19) | Group C (n = 30) | *p (A vs B)* | *p (B vs C)* |
|---|---|---|---|---|---|
| | Surgical Stage I/II and Ascites-negative | Surgical Stage I/II and Ascites-positive | Surgical Stage III | | |
| Age (years) | 59.4 ± 11.4 | 57.8 ± 11.0 | 61.0 ± 9.5 | 0.554 | 0.283 |
| BMI (kg/m$^2$) | 23.1 (16.3–51.8) | 22.0 (17.8–39.1) | 23.8 (17.6–37.8) | 0.730 | 0.514 |
| Gravida | 2 (0–9) | 1 (0–3) | 1 (0–5) | 0.177 | 0.977 |
| Parity | 2 (0–5) | 1 (0–3) | 1 (0–3) | 0.306 | 0.445 |
| Lymph node dissection | | | | | |
| none | 68 (38.6%) | 2 (10.5%) | 1 (3.3%) | **0.039** | **0.009** |
| pelvic | 27 (15.3%) | 6 (31.6%) | 1 (3.3%) | | |
| pelvic and para-aortic | 81 (46.0%) | 11 (57.9%) | 28 (93.3) | | |
| Surgical stage (FIGO2008) | | | | | |
| IA | 118 (67.0%) | 13 (68.4%) | | 0.965 | N/A |
| IB | 46 (26.1%) | 5 (26.3%) | | | |
| II | 12 (6.8%) | 1 (5.3%) | | | |
| IIIA | | | 4 (13.3%) | | |
| IIIB | | | 1 (3.3%) | | |
| IIIC1 | | | 9 (30.0%) | | |
| IIIC2 | | | 16 (53.3%) | | |
| Histological type | | | | | |
| Type I | 141 (80.1%) | 12 (63.2%) | 16 (53.3%) | 0.087 | 0.498 |
| Type II, carcinosarcoma | 35 (19.9%) | 7 (36.9%) | 14 (46.7%) | | |
| LVSI | | | | | |
| Positive | 24 (13.6%) | 6 (31.6%) | 25 (83.3%) | **0.041** | **<0.0001** |
| Negative | 152 (86.4%) | 13 (64.8%) | 5 (16.7%) | | |
| Tumor size (mm) | 30.0 (0–110.0) | 40.0 (10.0–70.0) | 54.5 (25.0–110.0) | 0.069 | **0.023** |
| Myometrial invasion | | | | | |
| <1/2 | 123 (69.9%) | 14 (73.7%) | 10 (33.3%) | 0.720 | **0.006** |
| ≥1/2 | 53 (30.1%) | 5 (26.3%) | 20 (66.7%) | | |
| Cervical involvement | | | | | |
| Positive | 12 (6.8%) | 1 (5.3%) | 2 (6.7%) | 0.792 | 0.631 |
| Negative | 164 (93.2%) | 18 (94.7%) | 28 (93.3%) | | |
| Adjuvant therapy | | | | | |
| Yes | 120 (68.2%) | 11 (57.9%) | 29 (96.7%) | 0.374 | **<0.0001** |
| No | 56 (31.8%) | 8 (42.1%) | 1 (3.3%) | | |

The values are numbers (%) and means ± SD, or median (range); significance at $p < 0.05$ is indicated in bold letters. BMI, body mass index; LVSI, lymph-vascular space invasion.

Table 3 shows details of the cases in which recurrence occurred. All recurrent cases in groups A and B were type 2. Cancer-related death was found in 0 (0%), 2 cases (10.5%), and 2 cases (6.7%) in groups A, B, and C, respectively.

Kaplan–Meier curve analysis with log-rank test demonstrated that group A had a better PFS than did group B ($p < 0.0001$), and there was no statistical difference in PFS between groups B and C ($p = 0.748$) (Fig. 2). Furthermore, group A had a better OS than did group B ($p = 0.001$), and there was no statistical difference in OS between groups B and C ($p = 0.766$) (Fig. 2).

Table 4 shows univariate and multivariate analyses of PFS in groups A and B. Peritoneal cytology and lymph-vascular space invasion were significantly poor prognosis factors in univariate and multivariate analyses. The pathological type was not included in this analysis because there was no recurrence of type 1 in groups A and B, only type II cases in groups A and B were further analyzed (Table 5). Ascites cytology was detected as a poor prognostic factor in the univariate analysis.

## 4. Discussion

In present study, among surgical stage I/II endometrial cancer patients, cases with positive peritoneal cytology had a worse PFS and OS than cases with negative peritoneal ascites. Surgical stage I/II with positive peritoneal cytology had a similar prognosis to surgical stage III. In 2013, Garg *et al.* [6] analyzed 14,704 women with surgical stage I/II endometrial cancer from the Surveillance epidemiology and end results (SEER) database and found that positive peritoneal cytology was an independent poor prognostic factor for early-

**Table 3. Recurrence cases.**

| Group | Age (years) | Stage (FIGO2008) | Histology | Surgery | LSVI | Site of recurrence | Adjuvant therapy | Disease-free survival (months) |
|---|---|---|---|---|---|---|---|---|
| A | 58 | II | endometrioid carcinoma, G3 | c | + | lung | Yes | 13 |
| A | 75 | IB | carcinosarcoma | c | + | lung, mediastinal lymph nodes | No | 11 |
| A | 70 | IA | serous carcinoma | c | + | lung | Yes | 15 |
| B | 60 | IB | carcinosarcoma | c | + | peritoneal dissemination | Yes | 6 |
| B | 63 | IB | carcinosarcoma | c | + | peritoneal dissemination | Yes | 20 |
| B | 59 | IA | serous carcinoma | c | - | vagina | No | 18 |
| B | 67 | IA | endometrioid carcinoma, G3 | c | + | lung | Yes | 35 |
| C | 61 | IIIC2 | serous carcinoma | c | + | peritoneal dissemination | Yes | 3 |
| C | 70 | IIIB | carcinosarcoma | c | - | peritoneal dissemination | Yes | 8 |
| C | 54 | IIIC2 | carcinosarcoma | c | + | retro-peritoneal dissemination | Yes | 9 |
| C | 72 | IIIC1 | carcinosarcoma | c | + | peritoneal dissemination | Yes | 9 |
| C | 53 | IIIC1 | endometrioid carcinoma, G1 | c | + | groin lymph nodes | No | 12 |
| C | 68 | IIIC1 | carcinosarcoma | c | + | skeletal muscle (iliopsoas) | Yes | 15 |
| C | 51 | IIIA | endometrioid carcinoma, G2 | c | - | skeletal muscle (iliopsoas) | Yes | 40 |

LSVI, lymph-vascular space invasion.

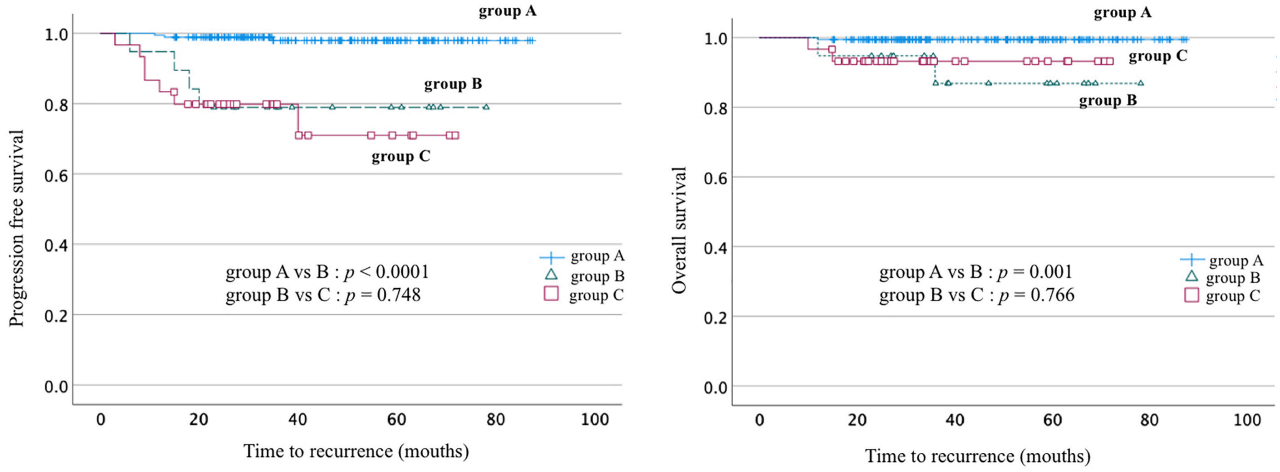


**Fig. 2. Kaplan–Meier curves for progression-free survival and overall survival in groups A, B, and C.**

**Table 4. Univariate and Multivariate analyses of PFS in groups A and B.**

| | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | *p* value | Hazard ratio (95% CI) | *p* value |
| Myometrial invasion | <1/2 | referent | 0.111 | referent | 0.753 |
| | ≥1/2 | 3.379 (0.755–15.131) | | 0.770 (0.151–3.920) | |
| Cervical involvement | Negative | referent | 0.440 | referent | 0.128 |
| | Positive | 2.305 (0.277–19.173) | | 6.466 (0.83–71.769) | |
| Ascites cytology | Negative | referent | **0.001** | referent | **0.008** |
| | Positive | 13.176 (2.948–58.891) | | 8.439 (1.766–40.329) | |
| LVSI | Negative | referent | **0.001** | referent | **0.003** |
| | Positive | 435.986 (4.330–229.056) | | 37.227 (3.541–391.300) | |

Significant at $p < 0.05$ are indicated in bold letters. LVSI, lymph-vascular space invasion.

stage endometrial cancer. In 2018, Seagle *et al.* [7] analyzed 16,851 early-stage endometrial cancers from the National Cancer Database's cohort analysis, and found positive peritoneal cytology as an independent poor prognosis factor in early-stage endometrial cancers, including low-grade endometrioid adenocarcinoma. Recently, Matsuo *et al.* [8] analyzed 24,800 women with stage I endometrioid endometrial carcinoma who had peritoneal cytology testing and reported malignant peritoneal cytology was associated with poor prognosis in stage I endometrioid endometrial cancer. Contro-

**Table 5. Univariate analyses of progression free survival in groups A and B (only type 2).**

| | | Univariate | *p* value |
|---|---|---|---|
| | | Hazard ratio (95% CI) | |
| Myometrial invasion | <1/2 | referent | 0.166 |
| | >1/2 | 2.887 (0.643–12.955) | |
| Cervical involvement | Negative | referent | **0.014** |
| | Positive | 19.994 (1.813–220.527) | |
| Ascites cytology | Negative | referent | **0.006** |
| | Positive | 8.149 (1.817–36.541) | |
| LVSI | Negative | referent | **0.012** |
| | Positive | 15.361 (1.839–128.288) | |
| Tumor size | <4 cm | referent | 0.347 |
| | >4 cm | 2.197 (0.426–11.332) | |
| Lymph node dissection | No | referent | 0.693 |
| | Yes | 0.652 (0.078–5.435) | |
| Adjuvant therapy | No | referent | 0.322 |
| | Yes | 0.436 (0.084–2.257) | |

Significant differences at $p < 0.05$ are indicated in bold letters. LVSI, lymph-vascular space invasion.

versy around peritoneal cytology and prognosis may be due to a lack of stratification in stage, histology, and others. There are no prospective studies on the association between peritoneal cytology and oncological outcome in early endometrial cancer, and no conclusions have been reached yet. The results of the population-based data analyses are in line with our data. Our study differed from previous studies because it only focused on laparoscopic surgery. The relationship between cell spillage due to pneumoperitoneum pressure in MIS and prognosis is unknown, but is meaningful to discuss when focusing only on laparoscopic surgery.

Here, the recurrence site was distant metastasis in all patients in group A, whereas recurrence in group B involved in dissemination of cancer cells in the pelvis in 3 of 4 patients. This result indicated that a patient with positive peritoneal cytology could tend to relapse as peritoneal dissemination. In our study, the minimally invasive surgical technique was performed by minimizing cancer cell spillage. Our surgical procedure differed from previous MIS methods for endometrial cancer in several aspects. We did not insert a manipulator to prevent artificial cell spillage during surgery, tubal obstruction was performed just after intraperitoneal observation, and the uterine os was closed with a vaginal cuff to prevent spillage during the colpotomy. Therefore, the population of patients with positive cytology in our study may have been enriched for those with true intraperitoneal disease. Also, the use of manipulators may be associated with the prognosis due to the risk of intraperitoneal tumor cell dispersal in the MIS of endometrial cancer [13]. Similar to previous reports for laparotomies, our study showed that patients with true positive ascites cytology had a poor prognosis using laparoscopic surgery. Furthermore, peritoneal dissemination recurrence is a common recurrence site in laparoscopic surgery in patients with true ascites cytology in endometrial cancer, which is a new finding of this study.

In our study, the number of harvested lymph nodes is larger than that in previous reports [14, 15]. Papathemeli *et al.* [15] reported that the removal of 25 or more pelvic and para-aortic lymph nodes lowers the recurrence rate and improves prognosis in high-grade endometrial cancer. Kim *et al.* [16] reported that removal of as many pelvic lymph nodes as possible determines an accurate stage and improves prognosis, in intermediate- or high-risk endometrial cancer. In the present study, the oncological outcomes of group C may be closer to those of group B by sufficient removal of the pelvic and para-aortic lymph nodes, including those with positive lymph node metastasis. In our study, a large number of lymph nodes were removed, which may have improved the outcomes in groups A and B, as those groups would otherwise contain more patients with occult nodal metastases.

The limitations of this study are its retrospective nature, use of single-facility data from a small number of cases, and an insufficient follow-up period.

## 5. Conclusions

In conclusion, positive peritoneal cytology was a factor associated with poor prognosis in laparoscopic surgery for early-stage endometrial cancer. Although positive peritoneal cytology is excluded from the FIGO stage criteria currently, it may be necessary to reconsider positive peritoneal cytology as a FIGO stage criteria when performing thorough lymph node dissection. Larger scale studies are necessary to clarify the clinical significance of ascites cytology for early-stage endometrial cancer.

## Author contributions

MY and HY designed the research study. MY and HY performed the research. MY analyzed the data. MY and HY wrote the manuscript. MY and HY contributed to editorial changes in the manuscript. MY and HY read and approved the final manuscript.

## Ethics approval and consent to participate

The IRB in Yokohama Municipal Citizen's Hospital approved this study; the trial registration number was 19-05-06. Written informed consent was obtained from all patients for the publication of this study.


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## Conflict of interest

The authors declare no conflict of interest.

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