Observational Study

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Intraperitoneal cytology after laparoscopic hysterectomy in patients with endometrial cancer

A retrospective observational study

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Abstract

The aim of this study was to evaluate the dissemination of cancer cells at laparoscopic hysterectomy according to the intraperitoneal cytology.

Patients with endometrial cancer underwent total laparoscopic modified radical hysterectomy. Peritoneal wash cytology was performed on entering the peritoneal cavity before surgical preparation and just after hysterectomy.

Seventy-eight patients underwent laparoscopic hysterectomy for endometrial cancer. Among the 15 patients who had positive intraperitoneal cytology on entering the peritoneal cavity, 10 converted to negative intraperitoneal cytology after hysterectomy. In contrast, among the 63 patients who had negative intraperitoneal cytology on entering the peritoneal cavity, 2 converted to positive intraperitoneal cytology after hysterectomy.

While surgery can reduce the number of cancer cells in the peritoneal cavity, leakage can occur, as seen in some cases of hysterectomy. Careful washing must be performed after hysterectomy.

Abbreviations: BMI = body mass index, FIGO = International Federation of Gynecology and Obstetrics, GOG = Gynecologic Oncology Group, NCCN = National Comprehensive Cancer Network, SD = standard deviation.

Keywords: endometrial cancer, intraperitoneal cytology, laparoscope

1. Introduction

Positive peritoneal cytology in the setting of endometrial cancer is not part of the current International Federation of Gynecology and Obstetrics (FIGO) staging system, because several authors showed that it was not independent prognostic factor in endometrial carcinoma confined to the uterus.[1,2] However, others showed that the positive peritoneal cytology was important factor of prognosis[3,4] especially in patients with extrauterine disease.[5,6] Although cytology by itself does not affect FIGO staging, National Comprehensive Cancer Network guideline recommend peritoneal cytology because positive cytology is an adverse risk factor especially in patients with extrauterine disease.[7]

Historically, endometrial cancer has been treated by abdominal hysterectomy; however, laparoscopic procedures have been practiced increasingly frequently worldwide over the past decade. Several studies have demonstrated the feasibility of laparoscopic surgery for patients with endometrial cancer. In these studies, laparoscopic surgery involved less intraoperative blood loss and a shorter hospital stay than laparotomic surgery.[8–13] The Gynecologic Oncology Group LAP 2 study, which was a multicenter randomized trial comparing the treatment of endometrial cancer by laparoscopy versus laparotomy, demonstrated not only the short-term feasibility of laparoscopy but also its noninferiority with regard to the long-term prognosis compared with laparotomy. However, few studies have so far examined whether or not laparoscopic surgery can lead to intraperitoneal tumor cell dissemination.

In this study, we evaluated the dissemination of cancer cells during laparoscopic hysterectomy according to the intraperitoneal cytology.

2. Materials and methods

2.1. Participants

Between September 2014 and December 2016, a total of 78 Japanese endometrial cancer patients underwent a laparoscopic procedure at Osaka Medical College in Japan. All of the patients underwent total laparoscopic modified radical hysterectomy with bilateral salpingo-oophorectomy and lymph node dissection. The present study was approved by the institutional review board of Osaka Medical College, and the participants gave their written informed consent.

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2.2. Cytopathologic procedure

All patients had no abnormal findings including atypical squamous cells, squamous intraepithelial lesion or atypical glandular cells on preoperative cervical cytology. The first peritoneal wash cytology was collected on entering the peritoneal cavity before surgical preparation and just after hysterectomy. The peritoneal cavity was washed with 20 mL of sterile physiologic saline solution. The ascites was aspirated after peritoneal dispersion from the Douglas pouch and then sent for a cytological analysis. Thin-layer cell preparation was performed with a Shandon CytoSpin III Cytocentrifuge. The slide was stained with Papanicolaou and interpreted by experienced cytologists. The criteria for malignancy were adapted from Ziselman et al.[15]

2.3. Surgical procedure

All patients underwent dilatation and curettage with hysteroscope within 6 weeks before surgery. In all cases, the surgical procedure was performed in the same way as below. Total laparoscopic modified radical hysterectomy was performed as a standard 5-port technique without intrauterine manipulation in the lithotomy position. Briefly, a 12-mm balloon trocar (Auto Suture Blunt Tip Trocar; Tyco), used for a 30° 10-mm laparoscope, was inserted under direct visualization (open laparoscopy) through an intra-umbilical incision of 1.5 cm. Three lateral 5-mm trocars were inserted (left and right lower abdominal quadrant, and left under the costal arch) for the ancillary instruments, and one 12-mm trocar was placed midline suprapubically for further manipulations and the extraction of lymph nodes. The uterus was retracted using 5-mm grasping forceps that were inserted into the left under the costal arch. Tubal ligation or coagulation was not performed. A sentinel node biopsy was performed after the first cytology sampling on entering the peritoneal cavity; after collecting peritoneal fluid or washings for cytological examination, the round and broad ligaments were coagulated and transected by an Enseal (Ethicon Endo-surgery) or bipolar coagulation device. After deploying the retroperitoneum, the sentinel lymph node was excised when it was detected. After clamping the uterine artery lateral to the ureters and opening of the ureteral tunnels, the ureters were unroofed and rolled laterally. The bilateral infundibulopelvic ligaments were coagulated and transected by an Enseal. The vesicouterine and uterosacral ligaments were also transected. After the bilateral paracolpium were ligated by 1–0 polydioxanone suture, the vaginal cuff (10–20 mm) and the corresponding paracolpos were resected. A circumferential colpotomy was performed on the rim of the Vagi-pipe (Hakko) with monopolar scissors. When it was difficult to remove uterus because of large myoma or narrow vagina, the uterus was put into retrieval bag (Memo Bag, Teleflex co.). Just after removal of the uterus or adnexa, or both, through the vagina, the second intraperitoneal wash cytology was collected and the vaginal cuff was closed laparoscopically with running absorbable sutures. Then a laparoscopic pelvic with or without para-aortic lymphadenectomy was performed. We previously reported the procedure of total laparoscopic modified radical hysterectomy and sentinel lymph node biopsy.[16,17]

2.4. Statistical analyses

All of the statistical analyses were performed using the JMP software package (version. 11.1.1). Continuous variables are expressed as the mean ± standard deviation. The Mann–Whitney *U*-test was used to compare continuous variables, and Fisher's exact test was used to compare frequencies. *P* values of $<.05$ were considered to indicate statistical significance.

Table 1

Characteristics of patients with endometrial cancer who underwent laparoscopic surgery.

Total number of patients	78
Age,* years	55.8 ± 10.5
BMI	24.1 ± 4.8
Nulliparous, %	27 (34.6)
FIGO stage, %	
IA	60 (76.9)
IB	8 (10.3)
IIIA	6 (6.4)
IIIB	1 (1.3)
IIIC	3 (6.4)
Histological type, %	
Grade 1	54 (69.2)
Grade 2	15 (19.2)
Grade 3	6 (11.5)
Serous	3 (3.8)

BMI = body mass index, FIGO = International Federation of Gynecology and Obstetrics.
* Based on an analysis of variance (mean ± standard deviation).

3. Results

Table 1 shows the characteristics of 78 patients with uterine endometrial cancer who underwent laparoscopic modified radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy with or without para-aortic lymphadenectomy. The mean (±standard deviation [SD]) age of the patients was 55.8 ± 10.5 years, and the mean body mass index (BMI) was 24.1 ± 4.8. Twenty-seven (34.6%) patients were nulliparous. A total of 60 patients had FIGO stage IA disease, 8 had stage IB disease, 6 had stage IIIA disease, 1 had stage IIIB disease, and 3 had stage IIIC disease. Histologically, 54 patients had endometrioid carcinoma of grade 1, 15 had endometrioid carcinoma of grade 2, 6 had endometrioid carcinoma of grade 3, and 3 had serous carcinoma.

Figure 1 shows the results of intraperitoneal cytology during surgery. Among the 15 patients who had positive intraperitoneal

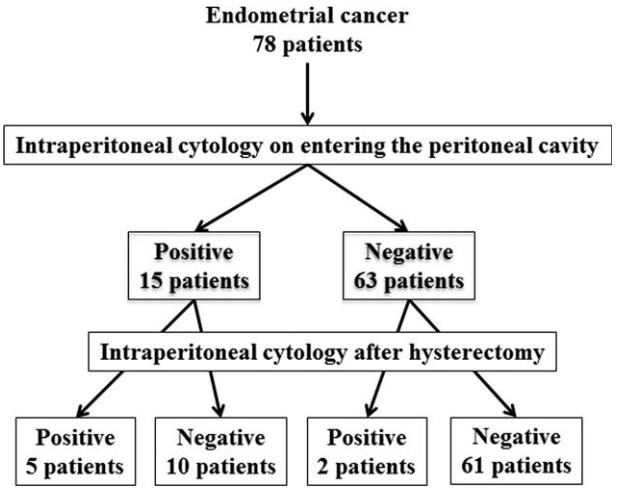

Figure 1. The results of intraperitoneal cytology during surgery. Among the 15 patients who had positive intraperitoneal cytology on entering the peritoneal cavity, 10 converted to negative intraperitoneal cytology after hysterectomy. In contrast, among the 63 patients who had negative intraperitoneal cytology on entering the peritoneal cavity, 2 converted to positive intraperitoneal cytology after hysterectomy.

cytology on entering the peritoneal cavity, 10 converted to negative intraperitoneal cytology after hysterectomy. In contrast, among the 63 patients who had negative intraperitoneal cytology on entering the peritoneal cavity, 2 converted to positive intraperitoneal cytology after hysterectomy. Two patients who converted to positive intraperitoneal cytology had no recurrent disease at 6 and 15 months' follow-up. Although all of the patients underwent a sentinel node biopsy after the first cytology sampling and 3 patients had lymph node metastasis, none of these 3 converted from negative to positive intraperitoneal cytology.

4. Discussion

In the present study, among the 15 patients who had positive intraperitoneal cytology on entering the peritoneal cavity, 10 converted to negative intraperitoneal cytology after hysterectomy. In contrast, among the 63 patients who had negative intraperitoneal cytology on entering the peritoneal cavity, 2 converted to positive intraperitoneal cytology after hysterectomy. These findings suggest that while surgery can reduce the number of cancer cells in the peritoneal cavity, leakage can occur, as seen in some cases of hysterectomy.

Several studies have demonstrated the feasibility of laparoscopic surgery for patients with endometrial cancer, showing not only the short-term feasibility of laparoscopy but also its noninferiority with regard to the long-term prognosis compared with laparotomy.[8–14] For these reasons, laparoscopic surgery has been performed increasingly frequently worldwide as therapy, especially in low-risk endometrial cancer patients. However, there is substantial variation between procedures, including the use of intrauterine manipulators, wrapping, or tying the uterine cervix and tubal ligation.

Several retrospective studies have assessed the relationship between malignant cytology results and laparoscopic surgery or laparotomy. However, these reports did not mention the timing of the collection of pelvic cytology samples in detail.[18–20] In contrast, a recent retrospective study with a large sample size found that laparoscopic surgical staging, including hysterectomy for endometrial cancer, was not associated with an increased risk of malignant cells in pelvic cytology samples compared with conventional abdominal hysterectomy.[21] In addition, according to several prospective studies describing the timing of the collection of pelvic cytology samples in detail, the incidence of malignant cytology was not significantly different from that with laparotomy surgery.[22–24]

A uterine manipulator is a useful adjunct for total laparoscopic hysterectomy because it can improve the maneuverability of the uterus during surgery.[25] In early-stage endometrial cancer, the rate of positive intraperitoneal cytology ranges from 0% to 14.3% in women undergoing TLH using a uterine manipulator[18–20,22–24] and from 5% to 21% in women undergoing conventional laparotomy.[26–28] Machida et al[29] found no association between the timing of intrauterine manipulator use and pelvic cytology results in laparoscopic hysterectomy. They also observed that a history of tubal ligation was associated with a decreased risk of malignant pelvic cytology, although it did not remain an independent risk factor in a multivariate analysis. Felix et al[30] found that tubal ligation was associated with a lower disease stage and lower cancer-related mortality in high-grade tumors, suggesting the prominent hypothesis of endometrial cancer spreading in a retrograde fashion through the fallopian tube. In the present study, the rate of positive peritoneal cytology at last evaluation was 22% (17/78). All patients in our study underwent dilatation and curettage with hysteroscope within 6 weeks before surgery. We consider that these procedures caused this high prevalence.

von Heesen et al[31] reported on the conversion of pelvic cytology during laparoscopic surgery in endometrial cancer patients. In this study, intraperitoneal cytology at the beginning and end of surgery was assessed. Among 24 patients with endometrial cancer, only 1 had tumor cells on a cytological analysis both before and after surgery. Another patient showed cytological conversion from negative to positive during surgery. They concluded that laparoscopy does not appear to increase the rate of intraoperative tumor cell dissemination.[31] In our study, among the 15 patients who had positive intraperitoneal cytology on entering the peritoneal cavity, 10 converted to negative intraperitoneal cytology after hysterectomy. Surgery procedures, including washing and suction for keep the field clean, may reduce the number of cancer cells in the peritoneal cavity.

This study is associated with several major limitations that may reduce its value. First, the sample size was too small to conduct a multivariate analysis. Second, the study did not include conventional laparotomic surgery patients. Third, the study did not include much variation in the surgical procedure, such as the use of an intrauterine manipulator, wrapping, or tying the uterine cervix and tubal ligation. As such, our conclusion is not definitive.

In conclusion, while laparoscopic surgery can reduce the number of cancer cells in the peritoneal cavity, some cells may still become scattered during the procedure.

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