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Does the Type of Surgical Approach and the Use of Uterine Manipulators Influence the Disease-Free Survival and Recurrence Rates in Early-Stage Endometrial Cancer?

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Objective: The purpose of this study was to compare the long-term safety, disease-free survival, and recurrence rate of total laparoscopic hysterectomy using uterine manipulator and abdominal hysterectomy in the surgical treatment in early-stage endometrial cancer.
Study Design: This was a cohort study of 147 patients with clinical endometrial cancer (laparoscopic surgery group, 77 women; laparotomy group, 70 women). Data were evaluated and analyzed by intention-to-treat principle, and survival data of stage I endometrial cancer (129 patients; 66 from laparoscopic surgery group and 60 from laparotomy group) were estimated by using the Kaplan-Meier curves.
Results: After a follow-up period of 60 months for both laparoscopic surgery and laparotomy groups, no significant difference in the cumulative recurrence rates (7.4% and 13.1%, $P = 0.091$) and overall survival (97.1% and 95.1%, $P = 0.592$) was detected between both groups of stage I endometrial cancer. Conversion to laparotomy occurred in 10.4% (8/77) of the laparoscopic procedures. Laparoscopic hysterectomy was associated with less use of pain medication ($P = 0.001$) and a shorter hospital stay ($P < 0.001$), but the procedure took longer than laparotomic hysterectomy ($P < 0.001$). The proportion of patients with intraoperative and long-term complications was not significantly different between both groups. The use of uterine manipulators did not have increased recurrence rate in patients treated with laparoscopic approach.
Conclusions: The laparoscopic surgery approach to early-stage endometrial cancer using uterine manipulators is as safe and effective as the laparotomic approach.

Key Words: Disease free survival, Overall survival, Endometrial cancer, Hysterectomy, Laparoscopy, Laparotomy, Surgery, Uterine manipulator

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Endometrial cancer is the most common gynecologic malignancy in developed countries.[1] In approximately 80% of patients, their conditions were diagnosed at an early stage and the main treatment is surgery. The current standard treatment is total hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic and aortic lymph-node dissection, depending on histologic type and stage.[2]

The efficacy and safety of the laparoscopic approach to endometrial cancer have been clearly established by many publications, including randomized controlled trials[3–14] and meta-analyses.[15–18] Despite that, some surgeons have skepticism for laparoscopy in oncologic patients. On the contrary, for others, this surgical approach is routinely used in their practice for staging endometrial cancer.

Several authors have reported the feasibility and safety of the laparoscopic approach in early-stage endometrial cancer compared with laparotomic approach.[3,4,7] However, data related to recurrence rate and long-term survival are limited.[13]

During laparoscopic approach, the upward traction to the uterus turns to be fundamental to achieve a successful procedure. That fact can be possible with the use of uterine manipulators in hysterectomy. Some authors think that the use of uterine manipulators might increase the incidence of tumor cell dissemination among patients with endometrial cancers.[19,20] This assumption is suggested to be a derivative of common sense. In fact, the available clinical evidence suggests that the application of uterine manipulators has no clear correlation with the recurrence of the endometrial carcinoma.[21]

The aim of this study is to compare overall survival, disease-free survival, and recurrence rate of total laparoscopic hysterectomy using uterine manipulator and abdominal hysterectomy in the surgical treatment of early-stage endometrial cancer.

MATERIALS AND METHODS

The procedures used in this study were in accordance with the guidelines of the Helsinki Declaration on human experimentation. The study was approved by our institutional review board, and all women gave their informed consent to use their data.

Between February 1998 and November 2009, an observational cohort study was performed. We selected 147 women with clinical endometrial cancer, according to our inclusion criteria, at the Department of Obstetrics and Gynecology of the "Hospital General Universitario" of Alicante, in Spain. All patients entered on the study had their initial pathologic diagnosis confirmed at our institution. The staging of the tumor was done according to the International Federation of Gynecology and Obstetrics 2009 staging system.

The primary outcomes were rates of 60-month overall survival and 60-month disease-free survival. The secondary outcomes were the rate of 60-month local recurrence, postoperative and intraoperative complications, operative time, and recovery from surgery (length of hospital stay and need for postoperative analgesia).

We defined disease-free survival as the time from surgery to first reappearance of endometrial cancer or death from any cause. Patients who were known to be still alive and without recurrence at the time of the analysis were censored at the time of their last follow-up. Overall survival was calculated from the date of surgery to the date of death.

In the patients whose surgical approach was converted from laparoscopy to laparotomy, the evaluation was conducted after the intention-to-treat basis.

All patients were followed every 3 months for the first 2 years, every 6 months for 3 years, and yearly after until 5 years.

Inclusion criteria were the presence of histologically confirmed endometrial cancer treated with standard surgical staging.

Exclusion criteria were the absence of clear and complete clinical and histological data, not having undergone a hysterectomy, ovarian lesions, and obvious metastasis beyond the uterus.

According to these criteria, 77 patients were treated with a laparoscopic approach (laparoscopy group), whereas the other 70 patients were treated with a laparotomic approach (laparotomy group). All surgical procedures consisted of peritoneal washing, systematic inspection of the intraperitoneal cavity with biopsy of each suspected lesion, and total hysterectomy (including both totally laparoscopic/laparotomic approach and laparoscopically assisted vaginal approach, which was included in the laparoscopy group) with bilateral salpingo-oophorectomy and/or pelvic lymphadenectomy.

Thromboprophilaxis and prophylactic antibiotics were prescribed according to local practice.

In the laparotomy group, abdominal access was obtained through a vertical midline skin incision and the hysterectomy consisted of an extrafascial total hysterectomy.

In the laparoscopic surgery group, the abdominal access was obtained with a 10-mm trocar through the umbilicus for video laparoscopy, after pneumoperitoneum by Veress needle was induced. The suprapubic ancillary trocars were used; one 5-mm trocar was inserted in the midline 5 cm under the umbilicus and one in each iliac fossa (5 mm on the left side and 10 mm on the right side) laterally to inferior epigastric vessels, respectively. After dilatation with a Hegar dilator (no. 8), a uterine manipulator (Clermont-Ferrand, Karl Storz) was inserted. Before starting all the laparoscopic procedures, we routinely coagulated the fallopian tubes bilaterally to minimize the risk of tumor spread during manipulation of the uterus.

Pelvic lymphadenectomy consisted of the removal of the lymphatic tissue overlying the external, internal, and common iliac veins and arteries and the fossa obturatoria above the obturator nerve. When a serous papillary carcinoma was detected, an omentectomy was also performed.

In both groups, the patient characteristics reported were age, body mass index (BMI), menopausal state, previous major open surgery, stage, histologic type, operative time, estimated blood loss, perioperative blood transfusions, myometrial invasion, length of hospital stay, complications, overall survival, and disease-free survival.

Information regarding patients was obtained from the hospital records, physicians, and direct reports from the patients.

Statistical methods used were the Kaplan-Meier curves and log-rank test with regard to time-to-event analyses. Continuous variables were expressed as median and interquartile range and analyzed using Mann-Whitney *U* test. For categorical variables, the Pearson χ^2 test was applied. The independent-sample *t* test was used for comparison of median.

TABLE 1. Patients' characteristics according to treatment approach

	Laparoscopy (n = 77)	Laparotomy (n = 70)	*P*
Age, mean (SD)	65.2 (11.5)	63.2 (9.7)	0.275
BMI, median (range)	32.1 (28–36.5)	34.2 (32–34)	0.107
Parity, median (range)	2 (1.5–3)	2 (1–3)	0.187
Previous abdominal surgery, n (%)	29 (37.7)	28 (40.0)	0.771
Diabetes mellitus, n (%)	5 (6.5)	9 (12.9)	0.189
Arterial hypertension, n (%)	27 (35.1)	21 (30)	0.513
Hemoglobin, median (range), mg/dL	14 (13–14)	14 (13–14)	0.615
Hematocrit, median (range)	42 (40–44)	42 (40–44)	0.543
Ca125, median (range), UI/mL	11 (7–19)	10 (6–20)	0.426
Ca199, median (range), UI/mL	10 (4.2–27.7)	10 (6–20)	0.738
Myometrial invasion >50% suspected by ecography, n (%)	24 (31.2)	28 (40)	0.263
Surgical FIGO 2009 stage, n (%)			
IA	51 (66.2)	37 (52.9)	0.213
IB	17 (22.1)	24 (34.3)	0.213
II–IV	9 (11.7)	9 (12.9)	0.213
Grade, n (%)			
1	52 (67.5)	49 (70)	0.420
2	18 (23.4)	12 (17.1)	0.420
3	7 (9.1)	9 (12.4)	0.420
Histology endometrioid adenocarcinoma, n (%)	68 (88.3)	56 (80)	0.370
Papillary serous, n (%)	8 (10.4)	12 (17.1)	0.370
Clear cell, n (%)	1 (1.3)	2 (2.9)	0.370
Postoperative brachytherapy/radiotherapy, n (%)	23 (29.8)	32 (45.71)	0.610

CA-125, cancer antigen 125; CA 19-9, carbohydrate antigen 19-9; FIGO, International Federation of Gynecology and Obstetrics.

Data were managed with an Access database (Microsoft), and statistical analysis was performed using the SPSS 15.0 (SPSS Inc, Chicago, Ill) package. A *P* value of less than 0.05 was considered as statistically significant.

RESULTS

We reviewed 306 patients with endometrial carcinoma and 147 were included, 77 in the laparoscopy group and 70 in the laparotomy group. Age and BMI were similar in the 2 groups; likewise, no significant differences were found regarding histology type, grading, tumor stage, and postoperative treatment with brachytherapy or radiotherapy. Various patient characteristics are shown in Table 1. Operative data are summarized in Table 2.

The operating time was 150 minutes (range, 120–180 minutes) in the laparoscopy group and 90 minutes (range, 70–120 minutes) in the laparotomy group ($P < 0.001$). The

TABLE 2. Comparison of operative outcome

	Laparoscopy (n = 77)	Laparotomy (n = 70)	RR (CI 95%)	*P*
Operative time, median (range), min	150 (120–180)	90 (70–120)	—	<0.001
Intraoperative complications, n (%)	8 (10.4)	5 (7.1)	1.455 (0.499–4.238)	0.489
Postoperative complications, n (%)	15 (19.5)	18 (25.7)	0.759 (0.414–1.386)	0.366
Moderate bleeding, n (%)	19 (24.7)	21 (30)	0.823 (0.484–1.379)	0.469
Postoperative pain (need opioids), n (%)	11 (14.3)	27 (38.6)	0.370 (0.199–0.690)	0.001
Hemoglobin difference, median (range)	1.7 (1–2.4)	1.8 (1–2.3)	—	0.540
Hospital stay, median (range), d	3 (2–4)	7 (5–8)	—	<0.001
Stay > 4 d, n (%)	16 (20.8)	61 (79.2)	0.238 (0.153–0.372)	<0.001

CI, confidence interval; RR, relative risk.

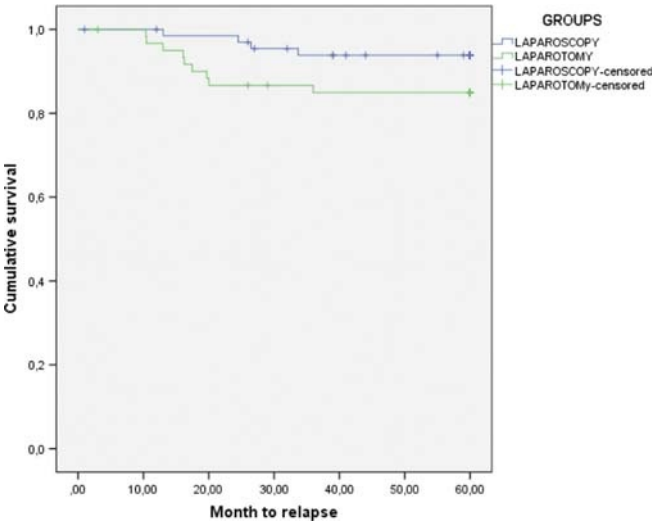

FIGURE 1. Disease-free survival of the laparoscopy and laparotomy groups.

percentage of patients with moderate bleeding (>250 mL) during the surgery in the laparoscopy group was 24.7% and 30% in the laparotomy group (P = 0.469). In only 1 case (laparotomy group), intraoperative transfusion was performed. The median length of hospital stay was 3 days in the laparoscopy group and 7 days in the laparotomy group ($P < 0.001$). There were no significant differences in intraoperative and postoperative complications between both groups (P = 0.489 and P = 0.366). No urinary complications were reported with the use of uterine manipulator. Eleven patients of the laparoscopy group needed opioids during the postoperative versus 27 of the laparotomy group (P = 0.001).

Pelvic lymphadenectomy was performed in 51% of patients. All the laparoscopic procedures were performed using a uterine manipulator, and conversion to laparotomy occurred in 10.4% (8/77) of the laparoscopic procedures.

The recurrence rate after a 60-month follow-up period was 20% (14/70 patients) in the laparotomy group and 7.8% (6/77 patients) in the laparoscopy group (P = 0.031). The disease-free survival was 51.2 months (SD, 2.2) for the laparotomy group and 56.8 months (SD, 1.23) for the laparoscopy group. Those differences were statistically significant (P = 0.031). The recurrences in the laparotomy group were peritoneal in 6 cases, ganglionar in 3 cases, 1 in lungs, 1 in the liver, and 3 in the vaginal cuff. Three peritoneal recurrences were observed in the laparoscopy group, 1 in the vaginal cuff, and 2 in the liver. None of those recurrences were in the laparoscopy port sites.

Nine patients (12.9%) of the laparotomy group died from the endometrial cancer and 3 patients (3.9%) of the laparoscopy group. Those differences were not statistically significant (P = 0.053).

Survival data of stage I endometrial cancer (129 patients; 66 from laparoscopic surgery group and 60 from laparotomy group) were estimated by using the Kaplan-Meier curves. After a follow-up period of 60 months for both groups, no significant difference in the cumulative recurrence rates (7.4% and 13.1%, P = 0.091, Fig. 1) and overall survival (97.1% and 95.1%, P = 0.592, Fig. 2) was detected between both groups of stage I endometrial cancer.

There were 2 cases of recurrence in the vaginal cuff in stage I endometrial cancer, 1 in the laparoscopy group and 1 in the laparotomy group, and both were papillary serous cancer. There were no recurrences in the laparoscopy port sites in early-stage endometrial cancer.

DISCUSSION

Data from the literature confirmed that laparoscopy is associated with safety and efficacy outcomes that are similar to those that have been reported for laparotomy for the treatment of endometrial cancer.[3–18]

Our results indicate that both laparoscopic and laparotomic approaches are feasible in patients with endometrial cancer but laparoscopy may have more advantages than laparotomy in postoperative pain and days of hospitalization, like other studies also concluded.[3–7,9,13] There were no significant differences for intraoperative and postoperative complications, and not also in blood loss. Many studies have reported less bleeding in laparoscopic procedures,[5,6,12,13,15–18] but there were no differences in a randomized trial.[3,4]

On the other hand, a longer operative time is needed for laparoscopic staging surgery. That fact is common in most of the studies published,[3,4,6,7,15] except of one.[13] It is also important to note that the development of the study coincided with the learning curve of the laparoscopic surgeons of our hospital, and this fact may have contributed to elongate the surgical procedure.

However, laparoscopy does not seem to improve the overall survival and the disease-free survival rate,[3,4,9,13–15,17,18] although multicenter randomized trials are required to evaluate the overall oncologic outcomes of this procedure.

It has been a topic of controversial in the recent years on the use of uterine manipulators during laparoscopic procedures, because of the role that they may play in endometrial cancer

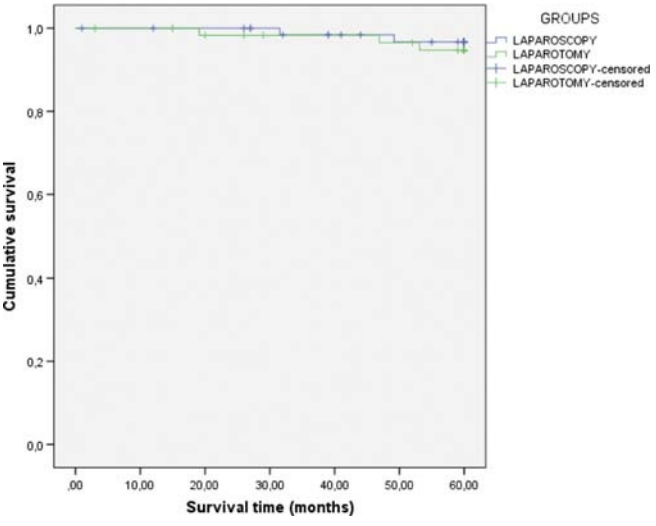

FIGURE 2. Overall survival of the laparoscopy and laparotomy groups.

recurrence. The uterine manipulator is essential to improve exposure and prevent ureteral complications. This has increased concerns regarding the dissemination of malignant cells to the vaginal cuff and the peritoneal cavity through the fallopian tubes. It was claimed that the fallopian tubes should be occluded at the beginning of the procedure. However, the findings that peritoneal washings before and after the insertion of the uterine manipulator were identical indicated that uterine manipulation during laparoscopic hysterectomy does not increase the incidence of positive peritoneal cytology in endometrial cancer.[21,22] In our study, we used a uterine manipulator in all the laparoscopic procedures, and there were no statistically significant differences between the rate of peritoneal recurrences and in vaginal cuff for both groups. Further investigation is needed for the clarification of the influence of uterine manipulators in cancer recurrence.

The main strengths of our study are the long-term follow-up (60 months) and the fact that all the surgical treatment in the laparoscopy group was performed using uterine manipulator. On the other hand, the weakness of it is that it is not a randomized controlled trial and the power of the study is limited because of the small sample size.

With our data, we can conclude that the type of surgical approach and the use of uterine manipulators do not seem to influence the disease-free survival and recurrence rates in early-stage endometrial cancer.

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