GYNECOLOGY

Impact of uterine manipulator on oncological outcome in endometrial cancer surgery

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BACKGROUND: There are limited data available to indicate whether oncological outcomes might be influenced by the uterine manipulator, which is used at the time of hysterectomy for minimally invasive surgery in patients with endometrial cancer. The current evidence derives from retrospective studies with limited sample sizes. Without substantial evidence to support its use, surgeons are required to make decisions about its use based only on their personal choice and surgical experience.

OBJECTIVE: To evaluate the use of the uterine manipulator on oncological outcomes after minimally invasive surgery, for apparent early-stage endometrial cancer.

STUDY DESIGN: We performed a retrospective multicentric study to assess the oncological safety of uterine manipulator use in patients with apparent early-stage endometrial cancer, treated with minimally invasive surgery. The type of manipulator, surgical staging, histology, lymphovascular space invasion, International Federation of Gynecology and Obstetrics stage, adjuvant treatment, recurrence, and pattern of recurrence were evaluated. The primary objective was to determine the relapse rate. The secondary objective was to determine recurrence-free survival, overall survival, and the pattern of recurrence.

RESULTS: A total of 2661 women from 15 centers were included; 1756 patients underwent hysterectomy with a uterine manipulator and 905 without it. Both groups were balanced with respect to histology, tumor grade, myometrial invasion, International Federation of Gynecology and Obstetrics stage, and adjuvant therapy. The rate of recurrence was 11.69% in the uterine manipulator group and 7.4% in the no-manipulator group ($P<.001$). The use of the uterine manipulator was associated with a higher risk of recurrence (hazard ratio, 2.31; 95% confidence interval, 1.27–4.20; $P=.006$). The use of uterine manipulator in uterus-confined endometrial cancer (International Federation of Gynecology and Obstetrics [FIGO] I–II) was associated with lower disease-free survival (hazard ratio, 1.74; 95% confidence interval, 0.57–0.97; $P=.027$) and higher risk of death (hazard ratio, 1.74; 95% confidence interval, 1.07–2.83; $P=.026$). No differences were found regarding the pattern of recurrence between both groups (chi-square statistic, 1.74; $P=.63$).

CONCLUSION: In this study, the use of a uterine manipulator was associated with a worse oncological outcome in patients with uterus-confined endometrial cancer (International Federation of Gynecology and Obstetrics I–II) who underwent minimally invasive surgery. Prospective trials are essential to confirm these results.

Key words: endometrial cancer, minimally invasive surgery, oncological safety, overall survival, recurrence, recurrence-free survival, uterine manipulator

The primary treatment for early-stage endometrial cancer is surgery, performing a total hysterectomy and bilateral salpingo-oophorectomy with surgical staging, if it is indicated.[1] The National Comprehensive Cancer Network and the European Society of Gynaecological Oncology consensus recommends minimally invasive approaches (laparoscopic/robotic) in patients with a disease limited to the uterus, according to evidence reported from randomized prospective studies (Gynecologic Oncology Group LAP_2 trial).[2] This approach leads to lower operative morbidity and a shorter hospital stay than open surgery, without compromising oncological outcomes.[3]

The uterine manipulator is a device commonly used in minimally invasive gynecologic hysterectomy for benign disease. It is inserted vaginally through the cervical canal into the endometrial cavity. It facilitates the uterus mobilization during the surgery, generating tension on the main supporting elements of the uterus to improve surgical field exposure and provide a landmark for the colpotomy.[4]

With the introduction of minimally invasive approaches in gynecologic oncology treatments, this uterine device has been utilized for endometrial and cervical cancers, with controversy regarding its influence on the spread of tumor cells and the risk of recurrence. Recently, the Laparoscopic Approach to Cervical Cancer trial reported a worse than expected oncological outcome after a laparoscopic/robotic approach in early-stage cervical cancer.[5] One of the hypotheses generated was that the uterine manipulator might influence this worse prognosis.[6] The retrospective European Surgery in Cervical Cancer Comparing Different Surgical Approaches in Stage IB1 Cervical Cancer study found the use of a manipulator was associated with a decrease in

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AJOG at a Glance

Why was this study conducted?

The uterine manipulator is a device commonly used in minimally invasive hysterectomy surgery for endometrial cancer. However, without substantial evidence to support its use, surgeons are required to make decisions about its use based only on their personal choice and surgical experience.

Key findings

This study demonstrated how the use of uterine manipulator in early-stage endometrial cancer (International Federation of Gynecology and Obstetrics [FIGO] I–II) for minimally invasive surgery was associated with a higher recurrence rate, lower disease-free survival, and higher risk of death than the same surgery without its use.

What does this add to what is known?

This large, multicenter, retrospective study suggests that the use of a uterine manipulator is associated with worse oncological outcomes in patients with uterus-confined endometrial cancer. The use of a uterine device in oncological minimally invasive surgery should be reconsidered.

disease-free survival in cervical cancer in the minimally invasive group.[7] Therefore, there are reasonable doubts about the uterine manipulator's safety in hysterectomy performed because of cancer.

In endometrial cancer, the presence of the uterine device in a cavity lined with neoplastic tissues leads to a potential tumor-manipulator interaction. Multiple mechanisms are potentially involved in this relationship but are poorly understood; however, the concept of uterus-confined disease is important to evaluate these interactions.[8] Nonetheless, we have limited evidence from retrospective studies about the uterine manipulator in endometrial cancer surgery, in which no impact of the uterine manipulator's use on oncological outcome has been found.[9–12] To date, it remains a controversial conclusion that the theoretical tumor manipulation has no clear impact on the oncological prognosis in endometrial cancer.

In this retrospective multicenter study, we hypothesized that the use of the uterine manipulator might have an impact on oncological outcomes after minimally invasive surgery in patients with apparent early-stage endometrial cancer.

Materials and Methods

This is a multicenter retrospective study endorsed by the Spanish Investigational Network Gynecologic Oncology Group (Spain-GOG) and conducted after obtaining the Institutional Review Board approval. All researchers involved in the study agreed to treat the data confidentially in accordance with the General Data Protection Regulation.[13]

Study design

We retrospectively evaluated the influence of the uterine manipulator on the oncological outcomes in a large cohort of endometrial cancer patients coming from multicenter Spanish participation. Two cohorts of patients with apparent early-stage endometrial cancer treated with minimally invasive surgery were evaluated, with and without uterine manipulator use. The primary objective was to determine the relapse rate. The secondary objective was to determine recurrence-free survival, overall survival, and pattern of recurrence.

Cohort selection and study variables

We included patients with the disease apparently confined in the uterus at the time of surgery, with histologic confirmation of endometrial cancer in which a hysterectomy and bilateral salpingo-oophorectomy were performed. Patients with surgical staging according to the International Federation of Gynecology and Obstetrics (FIGO) recommendations were also included.[14]

Apparent early-stage disease was preoperatively defined as the disease being confined to the uterus according to myometrial imaging assessment (transvaginal ultrasound and pelvic magnetic resonance imaging) and/or intraoperative assessment of the surgical specimen by the pathologist. In type II histology, to evaluate extrauterine involvement, additional imaging procedures were performed (computed tomography [CT] or positron emission tomography–CT scanner).[3] Patients with suspected disease beyond the uterus in preoperative assessment or confirmed disease during surgical exploration were excluded. Cases with no pathologic confirmation of endometrial cancer in the final surgical specimen (vanishing endometrial carcinoma) or final histology of atypical hyperplasia/endometrial intraepithelial neoplasia were also excluded.[15] Therefore, only patients with suspected endometrial cancer confined in the uterus at the time of surgery were included.

All surgeries were performed by minimally invasive approach, performed either by laparoscopic hysterectomy, robotic hysterectomy, or laparoscopically assisted vaginal hysterectomy. Open surgery, conversion to laparotomy, or only vaginal hysterectomy was excluded. Patients unfit for standard surgery owing to their medical condition were also excluded (Figure 1).

The surgical variables collected were the use of a uterine manipulator (the type of uterine manipulator and subtype classification with or without intrauterine balloon), sealing of the fallopian tubes, surgical staging procedure, surgical time, and hospital stay. Final surgery histology data were gathered as the tumor type and grade according to the World Health Organization classification, myometrial invasion, presence of lymphovascular space invasion (LVSI), and the number of pelvic and paraaortic lymph nodes.[16] Bokhman's dualistic classification of

endometrial cancer was used, and the tumors were classified using FIGO staging.[17,18] Finally, the data of adjuvant treatment (vaginal brachytherapy, external beam radiation (EBRT), and chemotherapy scheme), time of follow-up, time to relapse, and type and pattern of recurrence were collected.

Statistical analysis

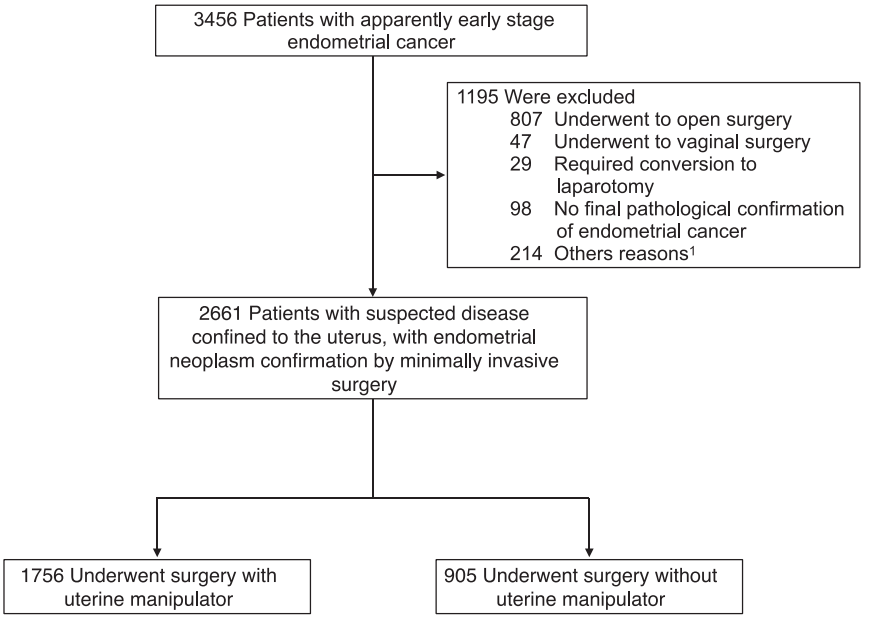
Data were summarized using the mean (standard deviation) in the case of numeric variables and absolute and relative frequencies in the case of categorical variables. To assess the effect of the uterine manipulator on disease-free survival, a mixed-effects Cox regression model was adjusted.[19]

The factors in our survival model were adapted from 2 validated nomograms predicting survival in endometrial cancer: type II histology, vaginal brachytherapy, EBRT, chemotherapy, FIGO stage, and the interaction between the manipulator used and FIGO stage, as explicative variables.[20,21] A random intercept was included for each center to control for the nonindependence of the observations. Because FIGO did not indicate a linear trend, the model was segmented for these variables with a breakpoint at FIGO III. In this model, LVSI was not included owing to the high number of missing values. Therefore, we performed a sensitivity analysis by imputing the missing values of LVSI and readjusting the survival model. The missing values of LVSI were imputed using the nonparametric imputation method provided in the missForest package.[22]

Differences in the pattern of recurrence between both groups were also assessed using multinomial logistic regression. The effect of the uterine manipulator use on overall survival was also evaluated using a competing risks model.[23] In addition, a sensitivity analysis using propensity score matching, based on the same covariates used to fit the multivariable model, was performed. Thus, the Rosenbaum method for matched data was used to estimate the degree of robustness of the observed differences to changes in the odds of differential assignment to the manipulator group owing to unobserved confounders.[24]

For all estimates, 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using R (version 3.6.2) and the R packages clickR (version 0.4.47), coxme (version 2.2-16), cmprsk (version 2.2-9), and rms (version 5.1-4).

FIGURE 1
Study population



[1]Other reasons included lack of data on whether a uterine manipulator was used or not, type of uterine device, final histologic diagnosis on nonendometrial cancer, and lack of data on relapse and/or pattern of recurrence.

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Results

Study population

The retrospective study was conducted using the data collected from 15 national centers with a mean recruitment period of 8.3±3.6 years (range, 3−13). A total of 2661 women underwent primary surgery for endometrial cancer by a minimally invasive approach and met the inclusion criteria: 1756 with a uterine manipulator and 905 without a uterine manipulator. Both groups were balanced with respect to baseline characteristics (Table 1).

Of the 1756 patients in whom a uterine manipulator was used, in 909 patients (51.77%), an intrauterine inflated balloon manipulator was used: VCare (ConMed Corporation, Utica, NY) in 41.4% and Rumi-Koh (CooperSurgical Inc, Trumbull, CT) in 10.36% of the patients. In 847 patients, a no-balloon manipulator was used: Cohen intrauterine cannula (Sklar Surgical Instruments, West Chester, PA) in 17.2%, Clermont-Ferrand (Karl Storz SE & Co KG, Tuttlingen, Germany) in 26.94%, and Valtchev uterine mobilizer (Conkin Surgical Instruments Ltd, Vancouver, Canada) in 4.1%.

There were relevant differences between the uterine manipulator and no-uterine manipulator groups with respect to surgical procedures: pelvic and paraaortic lymphadenectomy ($P<.001$). There were no differences between the 2 groups with respect to the final Bokhman's classification types I and II, tumor grade, myometrial invasion, maximum tumor diameter, or the number of lymph nodes harvested. There was a higher rate of LVSI in the uterine manipulator group (24.56% vs 11.76%; $P<.001$).

TABLE 1
Characteristics, surgical procedures, and histologic data of patients

Variable	Uterine manipulator (n=1756)	No uterine manipulator (n=905)
Age, y (mean [SD])	64.71 (10.93)	65.34 (10.86)
BMI, kg/m^2 (mean [SD])	30.36 (6.17)	29.26 (5.95)
Balloon manipulator	909 (51.77)	0
Pelvic lymphadenectomy	1084 (61.73)	475 (52.49)
Paraaortic lymphadenectomy	574 (40.65)	223 (24.67)
Infracolic omentectomy	118 (6.72)	49 (5.43)
Surgical time, min (mean [SD])	191.76 (78.43)	190.67 (82.99)
Hospitalization time, d (mean [SD])	4.22 (4.42)	3.05 (3.50)
Bokhman's classification[a]		
Type I	1345 (76.73)	692 (77.06)
Type II	408 (23.27)	206 (22.94)
Myometrial invasion		
≤50%	1239 (70.68)	591 (65.38)
>50%	514 (29.32)	313 (34.62)
Maximum tumor diameter, mm (mean [SD])	29.37 (18.85)	30.80 (22.40)
LVSI	379 (24.56)	102 (11.76)
Histologic data		
Endometrioid G1	718 (40.96)	467 (52.00)
Endometrioid G2	619 (35.31)	220 (24.50)
Endometrioid G3	200 (11.41)	100 (11.14)
Serous	97 (5.53)	54 (6.01)
Clear cells	47 (2.68)	23 (2.56)
Carcinosarcoma	24 (1.37)	16 (1.78)
Pelvic lymph nodes removed (mean [SD])	12.87 (6.37)	13.66 (6.94)
Paraaortic lymph nodes removed (mean [SD])	8.63 (6.89)	10.13 (6.17)

Data are presented as number (percentage) unless indicated otherwise.

BMI, body mass index; LVSI, lymphovascular space invasion in surgical specimen; *SD*, standard deviation.

[a] Bokhman's type dualistic model.

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The final FIGO classification is summarized in Table 2. Most of the tumors were confined to the uterus (90.88% in the uterine manipulator group and 91.09% in the no-manipulator group). There were no relevant differences between the 2 groups in lymph nodes metastasis (5.18% vs 5.97%). Half of the patients in both groups received adjuvant radiotherapy, with combined EBRT with vaginal brachytherapy as the most commonly used modality. There were no differences in the mean follow-up period (45.67 vs 43.35 months).

Survival analysis

A total of 272 patients presented a recurrence during the follow-up period, 205 patients with uterine manipulator use (11.67%) and 67 patients without uterine manipulator (7.4%) ($P<.001$). Most of the recurrences in both groups occurred as peritoneal carcinomatosis (34.63% and 37.31%, respectively) or visceral metastasis (35.12% and 34.32%, respectively). Recurrences in the vaginal vault were similar in both groups (12.69% and 11.92%, respectively; $P=.26$). A total of 176 patients died directly because of endometrial cancer: 137 patients in the uterine manipulator group (7.8%) and 39 patients in the no-uterine manipulator group (4.3%).

After adjusting for type II histology, adjuvant administration of vaginal brachytherapy, EBRT, chemotherapy, and FIGO stage, the uterine manipulator use was associated with a higher risk of recurrence than the no-uterine manipulator group (hazard ratio [HR], 2.31; 95% CI, 1.27−4.20; $P=.006$) (Table 3).

The decrease in recurrence-free survival with uterine manipulator use was only statistically significant in FIGO I−II (HR for the interaction with FIGO IA to II, 1.74; 95% CI, 0.57−0.97; $P=.027$) but not in FIGO III (HR for the interaction with FIGO IIIA to IIIC2, 2.22; 95% CI, 0.85−5.83; $P=.1$). No differences were found regarding the pattern of recurrence between both groups according to the multinomial regression model (chi-square statistic, 1.74; $P=.63$).

The differences in recurrence-free survival based on the subtype of the manipulator used (balloon vs no-balloon device) were also assessed. With this goal, a Cox regression model was only adjusted to the group that used a uterine manipulator. Results revealed no statistically significant differences between both groups (HR, 1.41 balloon manipulator vs no-balloon manipulator group; 95% CI, 0.71−2.78; $P=.33$).

Regarding overall survival, after adjustment for type II histology, adjuvant administration of vaginal brachytherapy, EBRT, chemotherapy, and FIGO stage, a statistically significant association was found between the use of a uterine manipulator and higher risk of death in FIGO I−II (HR, 1.74; 95% CI, 1.07−2.83; $P=.026$) but not in FIGO III (HR, 1.02; 95% CI, 0.54−1.9; $P=.96$) (Figure 2).

Unfortunately, because of the high number of missing values, the LVSI could not be included in the statistical model. For this reason, a sensitivity analysis by imputing the missing values of LVSI was performed, adjusting the

survival model once again. Results were very similar between both models, so we concluded that the noninclusion of LVSI in our original model did not represent bias to our results (Supplemental Table).

Results of the sensitivity analysis using propensity score matching yielded a critical Γ value of 1.4, which means that 1 patient in the matched pair may be up to 1.4 times more likely to be in the manipulator group than in the no-manipulator group because of different values on unobserved covariates, and the difference in relapse rates would still be significant in favor of the no-manipulator group (Supplemental Figures 1 and 2).

Discussion

Principal findings

This multicentric cohort study suggests that patients who underwent a minimally invasive surgery for early-stage endometrial cancer in whom a uterine manipulator was used presented a higher rate of recurrence, lower recurrence-free survival, and lower overall survival than patients in whom a uterine manipulator was not used. Our results contradict previously published findings and call into question the oncological safety of the uterine manipulator use in endometrial cancer.[8–12] Uccella et al[9] reported the effect of a uterine manipulator in patients with endometrial cancer by laparoscopic approach (579 patients with uterine manipulator vs 372 with no uterine manipulator). They found no statistical differences in recurrence rate (11.6% and 13.5%, respectively) (odds ratio, 1.00; 95% CI, 0.60–1.70; P=.99), with a comparable site of recurrence and no differences among different types of manipulators.

These differences may be explained by different factors. The low rate of recurrence in endometrial cancer is one factor. The overall risk of recurrence is 13% for all patients and ≤3% for patients at low risk.[25] When the magnitude of the differences to test is low, large samples are required to detect statistical significance; therefore, conclusions from a small sample size should be interpreted with caution.[26] In this scenario, previously published studies included 534, 951, 110, 110, and 147 patients, respectively.[8–12] The relapse rate in the no-uterine manipulator group was lower, but not statistically significant. Nevertheless, the sample size of those studies seems to limit their power to find differences in the recurrence rate.

TABLE 2
FIGO classification, adjuvant therapy, and patterns of recurrence

Variable	Uterine manipulator (n=1756)	No uterine manipulator (n=905)
FIGO staging		
FIGO IA	1139 (64.90)	554 (61.22)
FIGO IB	351 (20.00)	216 (23.87)
FIGO II	105 (5.98)	47 (5.19)
FIGO IIIA	44 (2.51)	26 (2.87)
FIGO IIIB	25 (1.42)	8 (0.88)
FIGO IIIC1	52 (2.96)	35 (3.87)
FIGO IIIC2	39 (2.22)	19 (2.10)
Adjuvant therapy		
VBT[a]	388 (22.09)	214 (23.64)
EBRT[b]	34 (1.94)	11 (1.10)
VBT+EBRT[c]	507 (28.87)	219 (24.20)
Combined EBRT+chemotherapy[d]	126 (7.17)	73 (8.07)
Chemotherapy alone[e]	10 (0.57)	12 (1.33)
Relapse	205 (11.69)	67 (7.40)
Patterns of recurrence		
Vaginal vault	26 (1.48)	8 (0.88)
Peritoneal carcinomatosis	71 (4.04)	25 (2.76)
Metastatic lymph nodes	32 (1.82)	6 (0.66)
Visceral metastases	72 (4.10)	23 (2.54)

Data are presented as number (percentage).

AUC, area under the curve; *EBRT*, external beam radiotherapy; *FIGO*, International Federation of Gynecology and Obstetrics; *VBT*, vaginal brachytherapy.

[a] Most common schedule for exclusive vaginal cuff brachytherapy was 7 Gy for 3 fractions with a total dose of 21 Gy in vaginal cuff; [b] Most common fractionation at 1.8–2 Gy per session with 5 sessions per wk, with a total dose of 45–50.4 Gy in the pelvis, increasing to 50–55 Gy if there was microscopic pelvic lymph node involvement. Extended-field radiotherapy with 45 Gy, if microscopic paraaortic lymphatic node involvement was present; [c] Vaginal brachytherapy with 4.5–6 Gy after total pelvic irradiation with 45Gy or VBT with 6 Gy if pelvis received 50.5 Gy; [d] There were several modalities. The most common was 6 cycles of chemotherapy (carboplatin AUC 5+paclitaxel 175 mg/m^2 every 3 wk) and subsequent external beam radiotherapy (45 Gy) with vaginal brachytherapy (20 Gy); [e] The most commonly used chemotherapy regimen was carboplatin AUC 5+paclitaxel 175 mg/m^2 every 3 wk during 4–6 cycles.

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Results

The uterine manipulator is widely used in benign gynecologic surgery because it hypothetically decreases the complication rate and facilitates the surgery. However, none of the data published to date have indicated that a uterine device reduces surgical complications.[8] In endometrial cancer, the use of a uterine device may be useful, because of high rates of obesity in this population.[25] Notwithstanding, current evidence supports that there is a real and safe possibility to perform hysterectomy without any uterine manipulator, even in adverse situations.[27,28]

As is already known in other gynecologic tumors (such as early-stage epithelial ovarian cancer or morcellation in unexpected uterine sarcoma), when the confined disease is exposed to

TABLE 3
Results of the mixed-effects Cox proportional hazards model for recurrence-free survival

Variables	Estimate	Standard error	HR (95% CI)	*P* value
Uterine manipulator	0.84	0.30	2.31 (1.27–4.20)	.006
Type II histology	1.33	0.14	3.76 (2.83–4.99)	<.001
Vaginal brachytherapy	−0.28	0.16	0.76 (0.55–1.05)	.092
EBRT	0.28	0.19	1.33 (0.92–1.92)	.13
Chemotherapy	−0.04	0.19	0.96 (0.67–1.40)	.85
FIGO (IA to II)	0.49	0.12	1.64 (1.29–2.08)	<.001
FIGO (IIIA to IIIC2)	−0.77	0.43	0.46 (0.20–1.08)	.074
FIGO (uterus-confined endometrial cancer) and uterine manipulator	−0.30	0.14	1.74 (0.57–0.97)	.027
FIGO (no uterus-confined endometrial cancer) and uterine manipulator	0.80	0.49	2.22 (0.85–5.83)	.10

CI, confidence interval; *EBRT*, external beam radiation; *FIGO*, International Federation of Gynecology and Obstetrics; *HR*, hazard ratio.
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the peritoneal cavity, the oncological outcome worsens.[29] Therefore, the concept of organ-confined disease is an essential idea to understand our results. In early-stage endometrial cancer, the myometrium acts as a containment barrier, which may be iatrogenically injured by the uterine manipulator.

Clinical implications

We observed a worse prognosis when the uterine manipulator was used in patients with uterus-confined diseases (FIGO I–II), which was not present in patients without uterus-confined diseases (FIGO III), at the time of surgery. These results support the concept that the uterine manipulator might act in breaking the uterus-confined disease and worsen the oncological outcomes.

The different potential interferences, summarized in Figure 3 and the Video, may explain the alteration of the myometrial barrier by the uterine device. Therefore, 2 hypotheses are presented to explain the relationship between the uterine manipulator and endometrial cancer.

First is the macroscopic injury hypothesis. During the insertion of any uterine manipulator (with or without balloon) and its use (especially in the atrophic uterus), the manipulator's shank may weaken the myometrium, iatrogenically leading to uterine rupture and opening of the tumor to the peritoneal cavity and surgical field.[30,31] The uterine rupture is rarely reflected in surgical reports, and it has not been considered in previous analyses. Machida et al[32] reported a 0.4% to 1% perforation rate with a balloon manipulator; thus, other factors could be involved.

The second hypothesis is the microscopic pathway of dissemination. The uterine device generates a significant increase in pressure inside the endometrial cavity, generating global distension according to Pascal's principle, which is additionally increased by the maintained push needed during uterine mobilization and colpotomy.[33] This increased pressure might be involved in the improved ability of tumor cells to exceed the myometrial barrier, spreading outside the uterus cavity by a passive effect through the fallopian tubes and lymphovascular space.[34]

Research implications

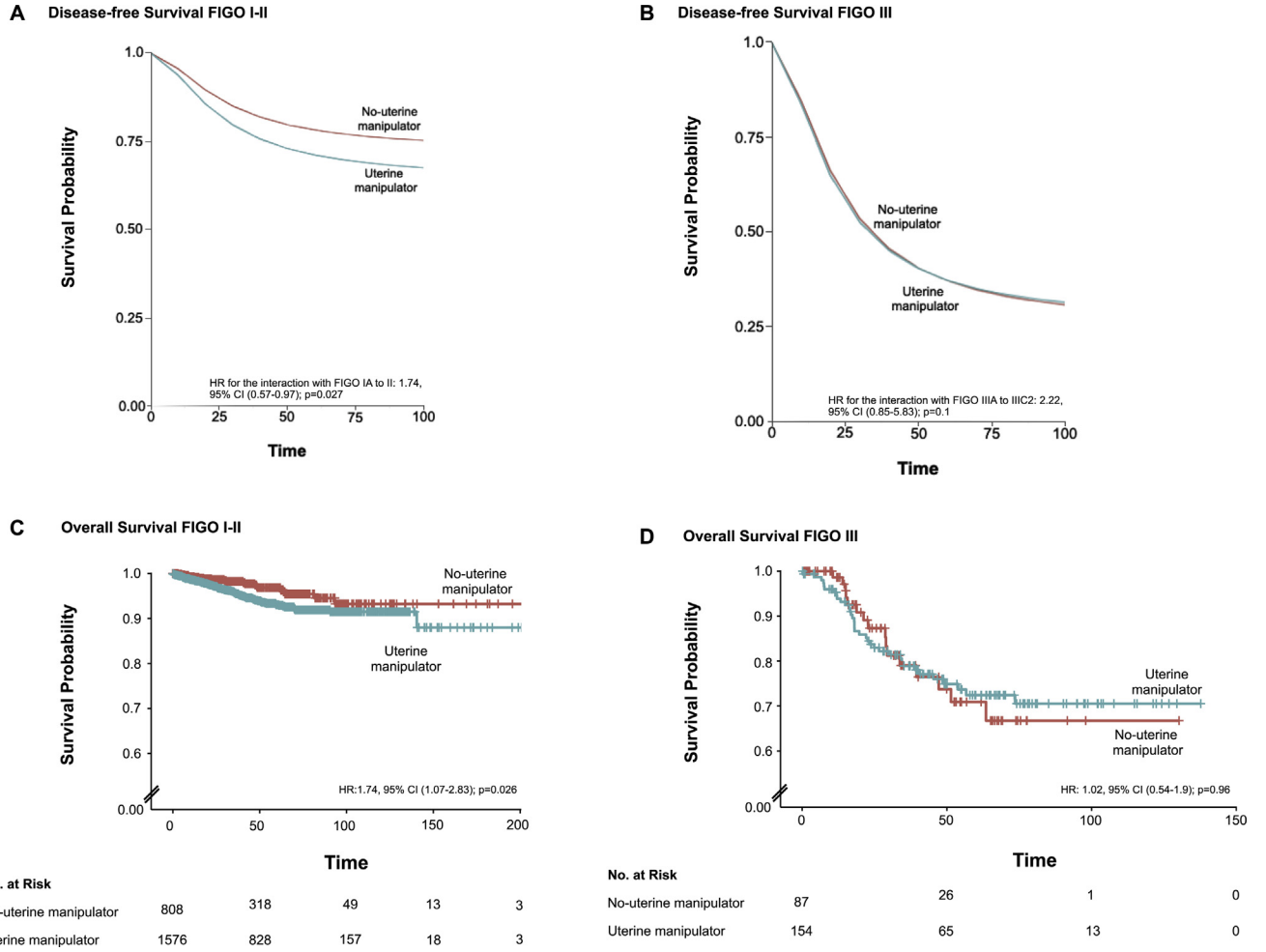
The pressure effect discussed has an impact on the tumor microenvironment, potentially helping to spread tumor cells into the blood circulation intraoperatively. This fact may also explain the higher rate of distance recurrences related to the use of uterine manipulators found in this study. Tohme et al[35] reported that a higher trauma and manipulation of the tumor enhanced the potential of metastatic disease. Nevertheless, it remains unclear why the increase in relapses is not strongly associated with the lymphovascular invasion.[34] Some limitations in the evaluation of LVSI in the surgical specimen, such as tumor size, autolysis, delayed formalin fixation, interobserver variability, and pseudovascular artifact, may lead to misinterpretation by pathologists and justify this lack of association.[36–38]

Strengths and limitations

The main strength of our study is that the sample size rose owing to multicenter participation, which made an accurate analysis possible because of the low rate of recurrences in endometrial cancer. We also included all different types of minimally invasive approaches and long-term survival data, which powered the results of the study. To decrease the risk of bias, we only recruited patients with histologic confirmation in the final surgical specimen to guarantee that, theoretically, all uterine manipulators were in touch with the tumor. We also performed the subanalysis in patients with the organ-confined disease to demonstrate the manipulator's effect.

Our trial has several limitations: above all, the retrospective nature of the study

FIGURE 2
Survival analysis



Survival analysis in patients with endometrial cancer by minimally invasive surgery in the uterine manipulator group (*green line*) and no-manipulator group (*red line*). The top of the figure represented the disease-free survival estimates using marginal effect plots of the mixed-effects Cox regression model. **A,** The disease-free survival estimates for FIGO I—II. **B,** The disease-free survival estimates for FIGO III. The bottom of the figure represented the overall survival in use of uterine manipulator and nonuse of uterine manipulator using the Kaplan-Meier curves. **C,** The overall estimates for FIGO I—II. **D,** The overall estimates for FIGO III.

CI, confidence interval; *FIGO*, International Federation of Gynecology and Obstetrics; *HR*, hazard ratio.

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and the fact that there are centers that contributed to only 1 branch of the study. The surgical staging indication depended on each center, which could have affected the adjuvant therapy indications. The pathologist assessment of LVSI was not standardized. In the same way, the coagulation of the fallopian tubes was collected, but we could not use this in the analysis because the quality of the data was insufficient. The missing LVSI data could influence our results, and its relationship with the uterine device remains unclear. Finally, we were only able to hypothesize about the relationship between tumors and uterine manipulator, and more knowledge must be sought.

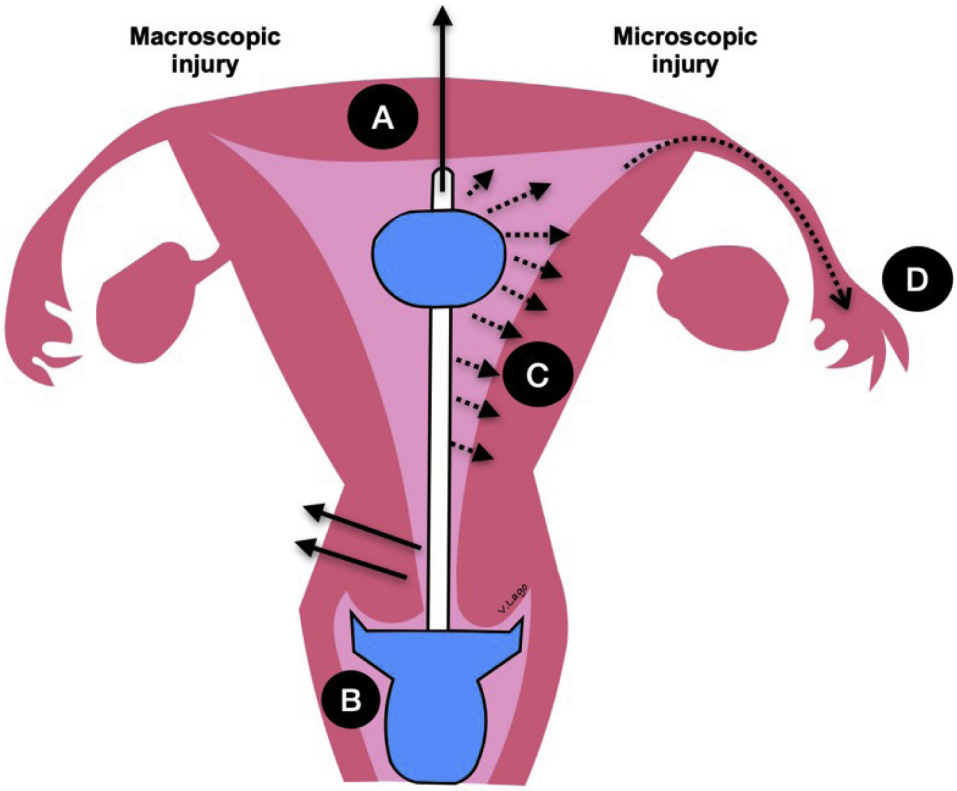
Conclusion

This single study suggests that the use of a uterine manipulator is associated with worse oncological outcomes in patients with uterus-confined endometrial cancer (FIGO I—II) at the time of surgery; it also presented a lower recurrence-free survival and lower overall survival, regardless of the type of manipulator used, with no differences in the pattern of recurrence. These results must be confirmed in a prospective trial, with a strict surgical reporting policy (including reporting of tubal sealing, uterine perforation, and intraoperative complication) and standard pathologist assessment. ■

Acknowledgments

We thank the Spanish Society of Gynecology and Obstetrics Spain-GOG and the Society of

FIGURE 3
Potential interferences between endometrial tumor and uterine manipulator



Interferences between tumor and uterine manipulator may explain the alteration in the myometrial barrier. Macroscopic hypothesis: **A,** weakening and accidental uterine rupture because of manipulator's shank; and **B,** tumor manipulation during insertion and colpotomy. Microscopic hypothesis: an increase of pressure inside the endometrial cavity might spread malignant cells through the **C,** lymphovascular space and **D,** fallopian tubes.

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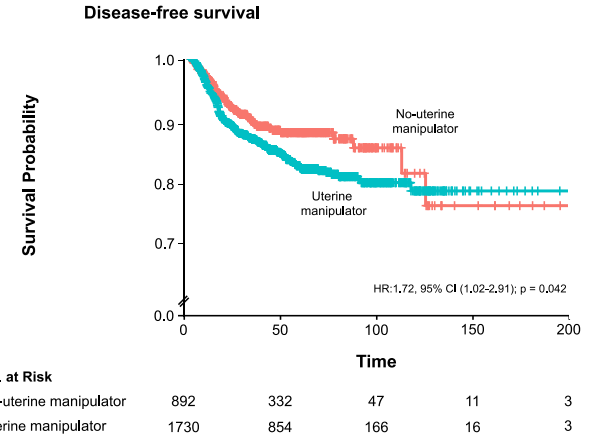
SUPPLEMENTAL FIGURE 1
Kaplan-Meier curves for disease-free survival in use of uterine manipulator and nonuse of uterine manipulator



No. at Risk					
No-uterine manipulator	892	332	47	11	3
Uterine manipulator	1730	854	166	16	3

CI, confidence interval; *HR*, hazard ratio.

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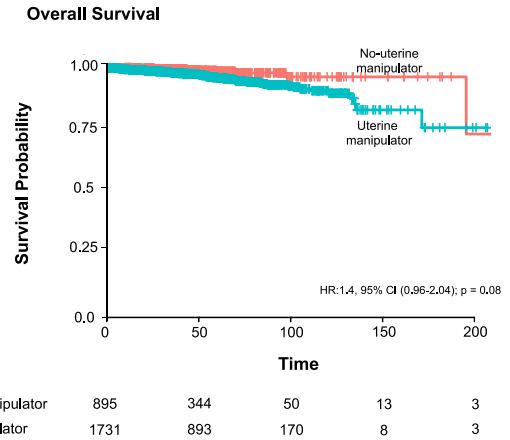
SUPPLEMENTAL FIGURE 2
Kaplan-Meier curves for overall survival in use of uterine manipulator and nonuse of uterine manipulator



No. at Risk					
No-uterine manipulator	895	344	50	13	3
Uterine manipulator	1731	893	170	8	3

CI, confidence interval; *HR*, hazard ratio.

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SUPPLEMENTAL TABLE

Results of the mixed-effects Cox proportional hazards model for recurrence-free survival imputing the missing values of LVSI

Variables	Estimate	Standard error	HR (95% CI)	*P* value
Uterine manipulator	0.80	0.30	2.25 (1.24–4.06)	.007
Type II histology	1.28	0.14	3.61 (2.71–4.82)	<.001
Vaginal brachytherapy	−0.27	0.16	0.76 (0.55–1.04)	.09
EBRT	0.25	0.19	1.29 (0.89–1.86)	.13
Chemotherapy	0.06	0.19	0.94 (0.65–1.36)	.73
LVSI	0.25	0.16	1.28 (0.94–1.75)	.11
FIGO (IA to II)	0.48	0.12	1.62 (1.27–2.06)	<.001
FIGO (IIIA to IIIC2)	−0.76	0.43	0.43 (0.20–1.08)	.076
FIGO (uterus-confined endometrial cancer) and uterine manipulator	−0.31	0.14	1.73 (0.56–0.95)	.021
FIGO (no uterus-confined endometrial cancer) and uterine manipulator	0.83	0.49	2.29 (0.87–6.03)	.09

CI, confidence interval; *EBRT*, external beam radiation; *FIGO*, International Federation of Gynecology and Obstetrics; *HR*, hazard ratio; *LVSI*, lymphovascular space invasion.

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