The effect of intrauterine manipulator on oncological outcome in early-stage, low-grade endometrial cancer: A retrospective cohort study

Yexin Ye[1,4], Maite Timmermans[2,4], Maaike A. van der Aa[4], Saskia le Cessie[3], Trudy N. Jonges[5], Juliënne A. Janse[2], Cornelis G. Gerestein[1]

[1] *Department of Gynaecological Oncology, Division of Imaging and Oncology, University Medical Centre Utrecht, Utrecht, the Netherlands.*

[2] *Department of Obstetrics and Gynaecology, Leiden University Medical Centre, Leiden, The Netherlands.*

[3] *Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands.*

[4] *Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, The Netherlands.*

[5] *Department of Pathology, Division of Laboratory, Pharmacy and Biomedical Genetics, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands.*

ABSTRACT

Objective To evaluate the influence of intrauterine (IU) or non-IU manipulators on oncological outcome in early-stage, low-grade endometrioid endometrial cancer (EEC).

Design Retrospective cohort study

Setting Nationwide population-based study in the Netherlands

Population Women with FIGO stage I, low-grade EEC who received total laparoscopic hysterectomy between 2010 and 2020.

Methods Patient data were identified from the Netherlands Cancer Registry. Data regarding hospital manipulator preferences were retrieved through an online survey. Patients were categorized based on hospital manipulator preference. Survival analyses were performed using univariable and multivariable cox regression analysis.

Main outcome measures Recurrence of cancer, disease-free survival (DFS), overall survival (OS), site of recurrence, and manipulator preference according to type of hospital.

Results Of the total study population (N = 5,205), 1524 (29.3%) patients underwent surgery in hospitals that used non-IU manipulators and 3681 (70.7%) in hospitals that used IU manipulators. Recurrence of cancer was experienced by 195 patients, 49 (3.2%) in the non-IU

group and 146 (4.0%) in the IU group. No significant difference in site of recurrence was observed (p=0.778). After adjusting for potential confounders, type of uterus manipulator did not affect DFS (hazard ratio [HR] 0.93, 95% confidence interval [CI] 0.78–1.11) and OS (HR 0.90, 95% CI 0.75–1.09).

Conclusion IU manipulators are not inferior to non-IU manipulators with respect to oncological outcome in early-stage, low-grade EEC.

KEYWORDS endometrial cancer, manipulator, hysterectomy, recurrence, survival

1. INTRODUCTION

The primary treatment for early-stage, low-grade endometrial cancer is a total laparoscopic hysterectomy (TLH) with bilateral salpingo-oophorectomy (BSO)[1–3]. During this procedure, uterine manipulators are commonly used. These instruments facilitate transection of uterine pedicles, delineation of vaginal fornices, colpotomy, and maintenance of pneumoperitoneum[4,5]. Amongst the numerous manipulators available, the vast majority possesses an intrauterine (IU) tip. Only few are without IU tip, such as the McCartney tube[6]. Especially manipulators with tip provide the added advantage of optimal uterine mobilization and enhanced exposure of the surgical field. Therefore, using IU manipulators may minimalize damage during surgery to surrounding tissues, including the ureters[4]. However, the use of uterine devices for malignant diseases has been subject to controversy. Some surgeons have argued that using IU manipulators may cause iatrogenic lymph vascular space invasion (LVSI) and spillage of malignant cells into the peritoneal cavity, which have both been associated with poor outcome in endometrial cancer[7–11].

Several studies demonstrated that using IU manipulators during hysterectomy did not influence the incidence of LVSI, peritoneal cytology, recurrence rate, and survival in endometrial cancer[12–14]. On the contrary, Padilla-Iserte et al. previously showed that oncological outcome was worse when IU manipulators were used in terms of recurrence rate and survival. However, this association was only observed in early-stage cancer[15]. In line with the latter results, Siegenthaler et al. showed that positive peritoneal cytology (PPC) conversion occurred in 8% of endometrial cancer patients following laparoscopic surgery with IU manipulators, which had a negative impact on oncological outcome[16].

While there has been growing interest in the effect of uterine manipulators on oncological outcome in endometrial cancer, none of the previous studies specifically compared IU with non-IU manipulators. IU manipulators are theoretically more likely to cause

dissemination of tumour cells than non-IU manipulators due to potential tumour manipulation. In light of this, it should be stressed that the introduction of TLH as a safe approach for endometrial cancer is predominantly based on studies in which non-IU manipulators were used[1,2,17]. Furthermore, while tumour stage, grade, and histotype are important prognostic factors, most of the studies did not restrict their focus to one consistent subset of patients.

The aim of this study was to determine whether hospital manipulator preference for IU manipulators or non-IU manipulators during TLH influences oncological outcome in early-stage, low-grade endometrioid endometrial cancer (EEC).

2. METHODS

2.1 Study design

This retrospective, nationwide, multicentre, comparative effectiveness study assessed the influence of hospital manipulator preference for IU manipulators or non-IU manipulators on oncological outcome in a large cohort of EEC patients. All patients with early-stage, low-grade EEC who received TLH between 01-01-2010 and 31-12-2020 within the Netherlands were included. Inclusion criteria were: i) histologically confirmed grade 1 or 2 EEC; ii) Federation of Gynaecology and Obstetrics (FIGO) stage I; and iii) surgery performed by laparoscopy or robotic-assisted laparoscopy. Exclusion criteria were: i) patients younger than 18 years; ii) patients with concurrent adnexal malignancy; and iii) patients with missing histopathology report. Eligible patients were categorized based on manipulator preference of the hospital at which they received surgery.

2.2 Data collection

Patients were identified from the Netherlands Cancer Registry (NCR), which is a population-based registry with coverage of all newly diagnosed malignancies in the Netherlands since

1989. Dedicated registration clerks routinely extract patient information from medical records within the hospitals. Information on vital status and date of death were obtained from the municipal demography registries[18]. The NCR database was linked with patient files in the Pathological Anatomical National Automated Archive (PALGA), which is a national histo- and cytopathology register that archives all pathology reports in the Netherlands[19]. Patients' age at time of diagnosis, treatment information, final surgery histopathology, and follow-up data were obtained for each patient. Treatment information consisted of date of surgery, type of surgery (e.g., with or without BSO), details about the hospital at which surgery was performed, and information regarding adjuvant treatment (e.g., radiotherapy, chemotherapy, hormone therapy). Final surgery histopathology data collected were histotype according to the International Classification of Diseases for Oncology (ICD-O), differentiation grade, FIGO stage 2009[20], maximum tumour diameter and presence of LVSI. Follow-up data was available on histologically confirmed recurrence of cancer, including date and site of recurrence, vital status, and date of death. In case of incoherent data, the PALGA histopathology records were leading for histotype and differentiation grade, and the NCR database was leading for disease stage.

National hospitals were contacted to retrieve data regarding hospital manipulator preference (i.e., IU or non-IU manipulator) between 2010 and 2020 by means of an online survey. The survey was formatted via Microsoft Forms and distributed to the appointed representative, a gynaecologist who performs minimally invasive hysterectomy for endometrial cancer, of each national hospital. Questions included in the survey are displayed in Table S1. In the absence of response, reminder emails were sent to those hospitals. Hospitals with disputable responses were contacted again for further clarification (by means of a phone call or an email). If the manipulator preference within a hospital changed between 2010 and 2020, these hospitals were analysed as independent institutions before and after the date of change in manipulator preference. Hospitals that used both IU and non-IU manipulators simultaneously between 2010

and 2020 and their corresponding patients were excluded from the analysis, as patients were categorized into IU group and non-IU group according to hospital manipulator preference rather than manipulator use at patient level.

2.3 Outcomes

The primary outcome measures were recurrence, disease-free survival (DFS), and overall survival (OS). Recurrence was defined as histologically confirmed recurrence during follow-up. DFS was defined as date of surgery to date of first recurrence or last follow-up date. OS was defined as date of surgery to date of death or last follow-up date for patients who were still alive (1 February 2022). Secondary outcome measures were site of recurrence and manipulator preference in relation to the type of hospital. Site of recurrence was categorized as local, regional, or distant according to the site of first recurrence. Local recurrences included vaginal recurrences. Regional recurrences referred to pelvic recurrences, including pelvic lymph node involvement and spread to the vulva, rectum, urethra, or bladder, as well as paraaortic and iliac lymph node involvement. Distant recurrences were defined as extra-pelvic recurrences, including peritoneal carcinomatosis, omental metastasis, involvement of other lymph node stations, and metastasis to bowels, lung, liver, bone, or muscle. Type of hospital was defined as general, teaching hospital or academic.

2.4 Statistical analysis

Data were summarized as absolute frequency (percentage) for nominal variables and as mean (standard deviation [SD]) for continuous variables. Percentages were compared with the Chi-square or Fisher's exact test. Continuous data were compared using the Student's t-test or Mann-Whitney U-test. Survival curves for DFS and OS were generated using Kaplan-Meier survival curves and compared using the log-rank test. The effect of uterine manipulator type on DFS

and OS were evaluated using univariable and multivariable Cox proportional hazards regression analysis, expressed as hazard ratio (HR) and 95% confidence interval (CI). The following baseline variables were added as potential confounders in the multivariable analysis: age at onset, FIGO stage, and presence of LVSI. Also, the type of hospital (academic versus non-academic) was added in the multivariable analyses. A p-value of less than 0.05 was considered significant. Data were analysed with the statistical package STATA/SE (version 14.1; STATA CORP., College Station, Texas, USA).

3. RESULTS

A total of 5,995 patients were identified with early-stage, low-grade EEC who received TLH between 2010 and 2020 from the NCR database. After linkage of the NCR database with the PALGA records, 86 patients did not meet the inclusion criteria. Moreover, 49 patients were excluded based on concurrent adnexal malignancy and 45 patients were excluded due to (partly) missing histopathology records. The online survey was distributed to 70 national hospitals. Amongst the hospitals, 9 underwent a change in hospital manipulator preference between 2010 and 2020. Therefore, these hospitals were seen as independent institutions before and after the date of change in manipulator preference, resulting in a total of 79 hospitals between 2010 and 2020. Of these hospitals, 5 were excluded from the analysis due to absence of response or inadequate data regarding hospital manipulator preference (N = 420 patients), and 4 because of simultaneous use of IU and non-IU manipulators (N = 190 patients). The remaining 70 (88.6%) hospitals, comprised of 5,205 patients (89.5%), were included in the analysis (Figure S1).

Of the total study population, 1,524 (29.3%) patients underwent surgery in hospitals that preferred non-IU manipulators (non-IU group) and 3,681 (70.7%) in hospitals that preferred IU manipulators (IU group). TLH with BSO was performed in 94.1% of patients in the non-IU group and 93.5% of patients in the IU group. The remaining patients underwent no or other

types of (salpingo-)oophorectomy due to unknown reasons. In the non-IU group, 330 patients received adjuvant radiotherapy (21.7%), 1 patient received chemotherapy (0.1%), and 13 patients received (neo)adjuvant hormone therapy (0.8%). In the IU-group, 890 patients received adjuvant radiotherapy (24.2%), 1 patient underwent chemotherapy (0.0%), and 11 patients received adjuvant hormone therapy (0.3%). Mean age at diagnosis was 65.5 years (SD 10 years) in the non-IU group and 66.5 years (SD 9.7 years) in the IU group (p=0.001). In both non-IU and IU groups, most patients were diagnosed with FIGO IA disease (70.8% vs 67.8%, respectively, p=0.034) and without LVSI (89.5% vs 87.3%, p=0.036). No significant difference was observed between groups in maximum tumour diameter (p=0.485) (Table 1).

TABLE 1. Baseline characteristics of study population

Variable	All cases N = 5205		Non-IU N = 1524		IU N = 3681		P value
Age at onset, years							**0.004**
30 – 49	214		84	(5.5)	130	(3.5)	
50 – 59	1097		326	(21.4)	771	(20.9)	
60 – 69	1934		583	(38.3)	1351	(36.7)	
70 – 79	1496		407	(26.7)	1089	(29.6)	
> 80	464		124	(8.1)	340	(9.2)	
Mean (SD)	66.2	(9.8)	65.5	(10)	66.5	(9.7)	**0.001**
FIGO stage*							**0.034**
IA	3573		1079	(70.8)	2494	(67.8)	
IB	1629		445	(29.2)	1184	(32.2)	
LVSI±							**0.036**
No	4205		1238	(89.5)	2967	(87.3)	
Yes	579		146	(10.5)	433	(12.7)	
Maximum diameter of tumour, mm§							0.485
< 20	622		196	(21.8)	426	(23.3)	
20 – 50	1821		614	(68.2)	1207	(65.9)	
> 50	288		90	(10.0)	198	(10.8)	

Note: Data are presented as number (percentage) unless indicated otherwise. Statistically significant differences are highlighted in bold font. * Information available for 5202/5205 patients. ± Information available for 4784/5205 patients. § Information available for 2731/5205 patients. Abbreviations: FIGO, Federation of Gynaecology and Obstetrics; IU, intrauterine; LVSI, lymphovascular space invasion; N, number; SD, standard deviation.

A total of 195 (3.7%) patients experienced recurrence of cancer during follow-up, involving 49/1524 (3.2%) patients in the non-IU group and 146/3681 (4.0%) patients in the IU group. There were no significant differences in site of recurrence (p=0.778). In both groups, the majority of the recurrences were distant (46.9% vs 41.8%, respectively), followed by local (32.7% vs 37.0%) and regional recurrences (20.4% vs 19.9%) (Table 2). There were 456 deaths during follow-up, including 142/1524 (9.3%) deaths in the non-IU group and 314/3681 (8.5%) in the IU group.

TABLE 2. Site of recurrence according to hospital manipulator preference

Site of recurrence	**All cases N = 195**	**Non-IU N = 49**	**IU N = 146**	**P value**
Local	70 (35.9)	16 (32.7)	54 (37.0)	0.778
Regional	39 (20.0)	10 (20.4)	29 (19.9)	
Distant	84 (43.1)	23 (46.9)	61 (41.8)	
Unknown	2 (1.0)	0 (0.0)	2 (1.4)	

Note: Data are presented as number (percentage) unless indicated otherwise. Statistically significant differences are highlighted in bold font.

Abbreviations: IU, intrauterine; N, number.

The median follow-up time was 64 months (interquartile range [IQR] 42.1–86.5 months) for the whole study population. Five-year DFS was 89.9% in the non-IU group and 89.5% in the IU group (Figure 1A). Five-year OS was 91.0% in the non-IU group and 91.5% in the IU group (Figure 1B). On univariable analysis, the risk of recurrence was comparable between the IU and non-IU groups (HR 1.04, 95% CI 0.87–1.23). After adjusting for age at onset, FIGO stage, type of hospital, and presence of LVSI, the risk of recurrence remained similar in both groups (HR 0.93, 95% CI 0.78–1.11). Similarly, manipulator preference did not affect the risk of death by any cause both at univariable (HR 1.02, 95% CI 0.85–1.22) and multivariable analyses (HR 0.90, 95% CI 0.75–1.09).

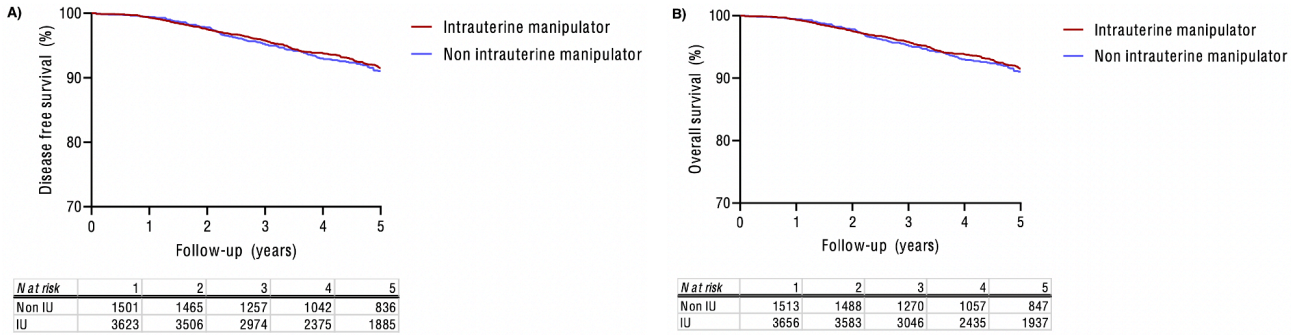

Figure 1. Survival analysis in patients with early-stage, low-grade endometrioid endometrial cancer according to hospital manipulator preference. **A** Disease-free survival in patients treated in hospitals at which only non-IU manipulators (non-IU group) or IU manipulators (IU group) were used. **B** Overall survival in patients treated in hospitals at which only non-IU manipulators (non-IU group) or IU manipulators (IU group) were used. Abbreviations: IU, intrauterine; N; number.

Of all patients, 1907 were treated in general hospitals, 2979 in teaching hospitals, and 319 in academic hospitals. The majority of patients seen in academic hospitals were treated with non-IU manipulators (66.8%), while patients in general and teaching hospitals were mainly operated on with IU manipulators (84.2% and 66.1%, respectively) (Table 3).

TABLE 3. Manipulator preference according to type of hospital

Type of hospital	**All cases N = 5205**	**Non-IU N = 1524**	**IU N = 3681**	**P value**
General	1907	301 (15.8)	1606 (84.2)	**0.001**
Teaching	2979	1010 (33.9)	1969 (66.1)	
Academic	319	213 (66.8)	106 (33.2)	

Note: Data are presented as number (percentage) unless indicated otherwise. Statistically significant differences are highlighted in bold font.

Abbreviations: IU, intrauterine; N, number.

4. DISCUSSION

4.1 Main findings

We demonstrated that the use of IU manipulators did not result in poorer oncological outcome than the use of non-IU manipulators during TLH in early-stage, low-grade EEC in a longitudinal and nationwide study in the Netherlands. No differences were observed between IU and non-IU manipulators in recurrence, DFS, and OS. Secondarily, no association was found between

site of recurrence and type of manipulator. However, manipulator preferences differed significantly by type of hospital. Non-IU manipulators were predominantly used in academic hospitals, whereas IU manipulators were mostly used in general and teaching hospitals. Our survey also revealed that these preferences changed within some hospitals over the years.

4.2 Strengths and limitations

The main strength of this study is that it is the largest to date to compare IU with non-IU manipulators in a homogeneous cohort of patients with early-stage, low-grade EEC. The study's nationwide multicentre design and 10-year inclusion period contributed to its large sample size (N = 5,205), which substantially increased the statistical power and allowed robust analysis. Moreover, the median follow-up period of 64 months was relatively long. This provided a higher chance of detecting differences in recurrence and survival, as most recurrences occur during the first two years after initial treatment[29,30].

The current work has some drawbacks, including its retrospective nature. Our study population was categorized according to hospital manipulator preference, as data extraction on manipulator use at patient level was not feasible. Obtaining data on hospital manipulator preference through a survey appeared challenging, as it was not always documented well which uterine manipulators were used over the years. However, we addressed this by contacting hospitals with questionable survey answers for further clarification and, therefore, do not expect this to influence the current results. Another limitation is the variability in other treatment practices across hospitals, including the surgical procedure and systemic therapy indications. However, these variations reflect clinical practice and make our findings more applicable. Also, early-stage, low-grade EEC is normally not an indication for an academic referral. It could be that a part of the patients was treated in academic hospitals because of e.g., severe co-morbidity or high BMI, which may have influenced our results.

4.3 Interpretation

The oncological safety of IU manipulators in endometrial cancer remains a subject of debate. Although previous studies did not specifically compare IU with non-IU manipulators, our findings support earlier research in a homogenous population with low risk EEC patients[12–14,21–23]. A recent meta-analysis by Scutiero et al. demonstrated that the use of IU manipulators did not impact the recurrence rate compared to when no manipulators were used in TLH for clinically early-stage endometrial cancer (risk ratio [RR] 1.11, 95% CI 0.71–1.74)[13]. Furthermore, Uccella et al. found no association between different IU manipulators used and the risk of recurrence. Additionally, no difference in recurrence pattern, DFS, and OS between the use and non-use of manipulators during TLH were observed[22]. In line with this, Alletti et al. illustrated similar DFS and OS after TLH with and without IU manipulator in a multicentric randomized controlled trial[14].

On the contrary, several research groups have indicated that the use of IU manipulators negatively affects oncological outcome[15,16]. Padilla-Iserte et al. showed that the recurrence rate (HR 2.31, 95% CI 1.27–4.20) and survival were worse after TLH with IU manipulator than without manipulator, but no difference in recurrence pattern was found. Interestingly, the decrease in DFS and OS was only observed in patients with FIGO I-II endometrial cancer (HR 0.74, 95% CI 0.57–0.97 vs HR 1.74, 95% CI 1.07–2.83, respectively) and not in those with FIGO III endometrial cancer[15].

In our cohort, the positive LVSI rate was significantly higher in the IU group (12.7%) than in the non-IU group (10.5%), but no correlation was observed with worse survival. LVSI and PPC have both been considered poor prognostic factors for recurrence and survival in endometrial cancer. However, it remains disputable whether these factors are associated with the use of uterine manipulators[7–11]. Scutiero et al. reported that there were no differences in LVSI and PPC rate between the use and non-use of IU manipulators during TLH. Moreover,

the incidence of PPC before and after insertion of the IU manipulator was similar, which suggested that the use of IU manipulators was not associated with PPC conversion[13]. In disagreement with these findings, Siegenthaler et al. showed that laparoscopy with IU manipulation was followed by PPC conversion in 8.1% of patients, which was significantly associated with higher recurrence rate and lower DFS and OS. In their study, peritoneal washings were taken at three time points: at the beginning of surgery, after manipulator insertion, and after vaginal vault closure. They found that 80% of cytology conversions occurred at the third washing, implying that the presence of the manipulator in the uterine cavity during the whole procedure is the main issue, rather than the insertion of the manipulator itself[16]. Interestingly, hysteroscopy has been associated with higher PPC rates, but without worse oncological outcome[24–27]. This discrepancy might result from different ways of handling the IU device. During hysterectomy, the IU manipulator is in theory more likely to induce trauma, which might lead to cancer recurrence by disrupting the containment barrier, whereas hysteroscopy involves passively rinsing out tumour cells[16]. Our observation of no significant differences in site of recurrence argues against this theory.

One explanation for the contrasting results observed across studies is the small sample size of the majority of research, combined with the low recurrence rate in endometrial cancer[14,21,23]. Although studies with small sample sizes should not be disregarded, their results are limited in statistical power. In addition, the variation in follow-up duration between studies, ranging from 19[23] to 120 months[16], contributes to the inconsistency in earlier findings, as time is important when evaluating oncological outcomes. Furthermore, most studies included a heterogeneous population of patients in terms of tumour stage, grade, and histotype[15,16,21–23]. Alletti et al. was the only study that specifically focused on clinically early-stage, low-grade EEC patients, but only included 154 patients[14]. Another contributing factor could be the different manipulators used during surgery[12,13]. Since favourable and adverse effects of tumour

manipulation may be affected by the type of manipulator, potential manipulator-specific differences should be considered.

Moreover, the overall recurrence in our study was 3.7%, which is lower than the 9.7% reported by Reijntjes et al. in the same low-risk population[28]. This suggests a relative underreporting of recurrence in our data. One explanation is that we defined recurrence as histologically confirmed recurrence according to PALGA, leading to some patients with not-histologically confirmed recurrences being missed in our study. Although NCR has not systematically recorded cancer recurrence, NCR has documented recurrence data between 2015 and 2017 in a pilot study. By comparing the NCR pilot data to the PALGA data, we established that the number of missed recurrences was similar between the IU and non-IU group in this period.

5. CONCLUSION

Overall, relying on the robustness of our study, we were able to confirm that the use of IU and non-IU manipulators during TLH results in comparable oncological outcome in early-stage, low-grade EEC. Future work should specifically focus on investigating the role of manipulators in other subsets of endometrial cancer patients in terms of tumour stage, grade, and histotype. In patients with high-risk endometrial cancer, implementation of solely those manipulators that do not compromise oncological prognosis will not only facilitate gynaecologists in their choice of manipulator, but also further improve patient care. Additionally, potential advantages of IU manipulators should be explored, including their impact on surgery time, complication rate, and learning curve.

CONFLICT OF INTEREST STATEMENT

None declared. Completed disclosure of interests forms are available to view online as supporting information.

AUTHOR CONTRIBUTIONS

CG, JJ, MT, and YY were all involved in the conception and planning of the research. MA and TJ were responsible for data acquisition. YY participated in patient record review and data abstraction. KC and JJ reviewed and supervised the study conduct. SC evaluated and finetuned the statistical plan. MT analysed the data. YY wrote the first draft, which was critically revised by all authors. All authors have approved the final version of the article for publication.

ETHICS APPROVAL

This study was approved by the Privacy Review Board of the NCR and PALGA (25-2-2022;K21.270)

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No funding was received for the research presented in this article.

DATA AVAILABILITY STATEMENT

Because the data collected for this study contain information that is potentially traceable to the hospitals that provided the data, the data cannot be shared in open data depositories. De-identified aggregated data that support the findings of this study can be made available from the corresponding author to qualified investigators upon reasonable request.

REFERENCES

1. Janda M, Gebski V, Davies LC, Forder P, Brand A, Hogg R, et al. Effect of Total Laparoscopic Hysterectomy vs Total Abdominal Hysterectomy on Disease-Free Survival Among Women With Stage I Endometrial Cancer: A Randomized Clinical Trial. JAMA. 2017 Mar 28;317(12):1224–33.

2. Mourits MJE, Bijen CB, Arts HJ, ter Brugge HG, van der Sijde R, Paulsen L, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. Lancet Oncol. 2010 Aug;11(8):763–71.

3. Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG). Richtlijn Endometriumcarcinoom [Internet]. Endometriumcarcinoom. [cited 2023 Aug 8]. Available from: https://richtlijnendatabase.nl/richtlijn/endometriumcarcinoom/algemeen.html

4. Mettler L, Nikam YA. A comparative survey of various uterine manipulators used in operative laparoscopy. Gynecol Surg. 2006 Dec;3(4):239–43.

5. van den Haak L, Alleblas C, Nieboer TE, Rhemrev JP, Jansen FW. Efficacy and safety of uterine manipulators in laparoscopic surgery: a review. Arch Gynecol Obstet. 2015 Nov;292(5):1003–11.

6. McCartney AJ, Obermair A. Total laparoscopic hysterectomy with a transvaginal tube. J Am Assoc Gynecol Laparosc. 2004 Feb;11(1):79–82.

7. Machida H, Hom MS, Adams CL, Eckhardt SE, Garcia-Sayre J, Mikami M, et al. Intrauterine Manipulator Use During Minimally Invasive Hysterectomy and Risk of Lymphovascular Space Invasion in Endometrial Cancer. Int J Gynecol Cancer. 2018 Feb;28(2):208–19.

8. Sonoda Y, Zerbe M, Smith A, Lin O, Barakat RR, Hoskins WJ. High incidence of positive peritoneal cytology in low-risk endometrial cancer treated by laparoscopically assisted vaginal hysterectomy. Gynecol Oncol. 2001 Mar;80(3):378–82.

9. Weinberg LE, Kunos CA, Zanotti KM. Lymphovascular space invasion (LVSI) is an isolated poor prognostic factor for recurrence and survival among women with intermediate- to high-risk early-stage endometrioid endometrial cancer. Int J Gynecol Cancer. 2013 Oct;23(8):1438–45.

10. Garg G, Gao F, Wright JD, Hagemann AR, Mutch DG, Powell MA. Positive peritoneal cytology is an independent risk-factor in early stage endometrial cancer. Gynecol Oncol. 2013 Jan;128(1):77–82.

11. Oliver-Perez MR, Padilla-Iserte P, Arencibia-Sanchez O, Martin-Arriscado C, Muruzabal JC, Diaz-Feijóo B, et al. Lymphovascular Space Invasion in Early-Stage Endometrial Cancer (LySEC): Patterns of Recurrence and Predictors. A Multicentre Retrospective Cohort Study of the Spain Gynecologic Oncology Group. Cancers (Basel). 2023 May 4;15(9):2612.

12. Meng Y, Liu Y, Lin S, Cao C, Wu P, Gao P, et al. The effects of uterine manipulators in minimally invasive hysterectomy for endometrial cancer: A systematic review and meta-analysis. Eur J Surg Oncol. 2020 Jul 1;46(7):1225–32.

13. Scutiero G, Vizzielli G, Taliento C, Bernardi G, Martinello R, Cianci S, et al. Influence of uterine manipulator on oncological outcome in minimally invasive surgery of endometrial cancer: A systematic review and meta-analysis. Eur J Surg Oncol. 2022 Oct;48(10):2112–8.

14. Alletti SG, Perrone E, Fedele C, Cianci S, Pasciuto T, Chiantera V, et al. A Multicentric Randomized Trial to Evaluate the ROle of Uterine MANipulator on Laparoscopic/Robotic HYsterectomy for the Treatment of Early-Stage Endometrial Cancer: The ROMANHY Trial. Front Oncol. 2021 Sep 10;11:720894.

15. Padilla-Iserte P, Lago V, Tauste C, Díaz-Feijoo B, Gil-Moreno A, Oliver R, et al. Impact of uterine manipulator on oncological outcome in endometrial cancer surgery. Am J Obstet Gynecol. 2021 Jan 1;224(1):65.e1-65.e11.

16. Siegenthaler F, Johann S, Imboden S, Samartzis N, Ledermann-Liu H, Sarlos D, et al. Prospective Multicenter Trial Assessing the Impact of Positive Peritoneal Cytology Conversion on Oncological Outcome in Patients with Endometrial Cancer Undergoing Minimally Invasive Surgery with the use of an Intrauterine Manipulator. Ann Surg Oncol. 2022 Dec 1;29(13):8320–33.

17. Obermair A, Manolitsas TP, Leung Y, Hammond IG, McCartney AJ. Total laparoscopic hysterectomy for endometrial cancer: patterns of recurrence and survival. Gynecol Oncol. 2004 Mar 1;92(3):789–93.

18. van der Sanden GA, Coebergh JW, Schouten LJ, Visser O, van Leeuwen FE. Cancer incidence in The Netherlands in 1989 and 1990: first results of the nationwide Netherlands cancer registry. Coordinating Committee for Regional Cancer Registries. Eur J Cancer. 1995 Oct;31A(11):1822–9.

19. Casparie M, Tiebosch ATMG, Burger G, Blauwgeers H, van de Pol A, van Krieken JHJM, et al. Pathology Databanking and Biobanking in The Netherlands, a Central Role for PALGA, the Nationwide Histopathology and Cytopathology Data Network and Archive. Cell Oncol. 2007;29(1):19–24.

20. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 2009 May;105(2):103–4.

21. Tinelli R, Cicinelli E, Tinelli A, Bettocchi S, Angioni S, Litta P. Laparoscopic treatment of early-stage endometrial cancer with and without uterine manipulator: Our experience and review of literature. Surg Oncol. 2016 Jun;25(2):98–103.

22. Uccella S, Bonzini M, Malzoni M, Fanfani F, Palomba S, Aletti G, et al. The effect of a uterine manipulator on the recurrence and mortality of endometrial cancer: a multi-centric study by the Italian Society of Gynecological Endoscopy. Am J Obstet Gynecol. 2017 Jun;216(6):592.e1-592.e11.

23. Lee M, Kim Y, Kim S, Kim S, Kim J, Nam E. Effects of Uterine Manipulation on Surgical Outcomes in Laparoscopic Management of Endometrial Cancer A Prospective Randomized Clinical Trial. Int J Gynaecol Cancer. 2012 Dec 20;23.

24. Polyzos NP, Mauri D, Tsioras S, Messini CI, Valachis A, Messinis IE. Intraperitoneal dissemination of endometrial cancer cells after hysteroscopy: a systematic review and meta-analysis. Int J Gynecol Cancer. 2010 Feb;20(2):261–7.

25. Du Y, Xu Y, Qin Z, Sun L, Chen Y, Han L, et al. The Oncology Safety of Diagnostic Hysteroscopy in Early-Stage Endometrial Cancer: A Systematic Review and Meta-Analysis. Front Oncol. 2021;11:742761.

26. Zhou H, Lai KF, Xiang Q, Xu Y, Zhang QW, Hu C, et al. Oncological Safety of Diagnostic Hysteroscopy for Apparent Early-Stage Type II Endometrial Cancer: A Multicenter Retrospective Cohort Study. Front Oncol. 2022;12:918693.

27. Chang YN, Zhang Y, Wang YJ, Wang LP, Duan H. Effect of hysteroscopy on the peritoneal dissemination of endometrial cancer cells: a meta-analysis. Fertil Steril. 2011 Oct;96(4):957–61.

28. Reijntjes B, van Suijlichem M, Woolderink JM, Bongers MY, Reesink-Peters N, Paulsen L, et al. Recurrence and survival after laparoscopy versus laparotomy without lymphadenectomy in early-stage endometrial cancer: Long-term outcomes of a randomised trial. Gynecol Oncol. 2022 Feb;164(2):265–70.

29. Legge F, Restaino S, Leone L, Carone V, Ronsini C, Di Fiore GLM, et al. Clinical outcome of recurrent endometrial cancer: analysis of post-relapse survival by pattern of recurrence and secondary treatment. Int J Gynecol Cancer. 2020 Feb;30(2):193–200.

30. Siegenthaler F, Lindemann K, Epstein E, Rau TT, Nastic D, Ghaderi M, et al. Time to first recurrence, pattern of recurrence, and survival after recurrence in endometrial cancer according to the molecular classification. Gynecol Oncol. 2022 May 1;165(2):230–8.