



Minimally invasive surgery without a uterine manipulator versus open radical hysterectomy for early-stage cervical cancer: A retrospective propensity-score-matched single-center cohort study

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HIGHLIGHTS

- Largest cohort to date of manipulator-free radical hysterectomy for cervical cancer.
- Propensity matching yielded 539 patients in each surgical group.
- Disease-free and overall survival did not differ significantly between approaches.
- Oncologic findings remained consistent in calendar-year and 24-month analyses.
- Manipulator-free minimally invasive surgery showed favorable perioperative outcomes.

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ABSTRACT

Objective. To compare oncologic and perioperative outcomes between minimally invasive radical hysterectomy (MIS-RH) without a uterine manipulator and open radical hysterectomy (O-RH) for early-stage cervical cancer (CC).

Methods. This retrospective propensity-score-matched cohort study included 1798 patients treated from 2019 to 2023 (539 MIS-RH and 1259 O-RH). All MIS-RH procedures were performed without a uterine manipulator and incorporated uterine-exposure techniques and protective vaginal transection. After 1:1 matching, 539 patients remained in each group. The primary outcome was disease-free survival (DFS); secondary outcomes included overall survival (OS), perioperative outcomes, and postoperative complications.

Results. Median potential follow-up was shorter after MIS-RH (18.93 vs 31.30 months). Recurrence occurred in 18 and 30 patients, respectively, and 17 deaths were recorded (9 vs 8). DFS did not differ significantly between MIS-RH and O-RH (HR, 0.863; 95% CI, 0.480–1.553; $P = .623$), nor did OS (HR, 1.735; 95% CI, 0.666–4.518; $P = .259$). Results remained consistent after calendar-year adjustment and administrative censoring at 24 months. MIS-RH was associated with lower estimated blood loss (100 vs 300 mL), fewer intraoperative transfusions (0.56% vs 6.31%), shorter time to first flatus (48 vs 60 h), and shorter postoperative hospitalization (6 vs 7 days), but longer operative time (260 vs 235 min; all $P < .001$).

Conclusion. No statistically significant DFS or OS differences were detected between manipulator-free MIS-RH and O-RH. MIS-RH was associated with several favorable perioperative outcomes, but shorter follow-up and the small number of deaths preclude conclusions of equivalence or noninferiority. Longer follow-up and prospective validation are required.

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1. Introduction

Cervical cancer (CC) is the fourth leading cause of cancer-related death among women worldwide, with approximately 600,000 new cases and 340,000 deaths worldwide in 2020 [1]. In China, an estimated 150,700 new cases and 55,700 deaths occurred in 2022 [2]. Radical hysterectomy (RH) is an important treatment for selected patients with

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early-stage disease, and open radical hysterectomy (O-RH) was traditionally regarded as the standard surgical approach. With advances in surgical technology, minimally invasive surgery (MIS) evolved from conventional laparoscopy to transumbilical laparoscopic single-site and robotic approaches [3–5]. Earlier retrospective studies and meta-analyses reported survival outcomes similar to those of open surgery, together with potential perioperative advantages including less blood loss, shorter hospitalization, and reduced postoperative morbidity [6–11]. On the basis of these findings, MIS was incorporated as an acceptable surgical approach in earlier clinical guidelines [12].

Clinical practice changed substantially after publication of the Laparoscopic Approach to Cervical Cancer (LACC) trial in 2018, which demonstrated inferior progression-free survival (PFS) and overall survival (OS) after minimally invasive radical hysterectomy (MIS-RH) compared with O-RH [13]. A contemporaneous real-world study reported similar findings [14], and several subsequent studies supported an oncologic disadvantage associated with MIS [15–17], although others did not identify significant survival differences [18–20]. These findings prompted major guideline bodies to recommend open surgery as the standard surgical approach for early-stage CC [21–23]. The mechanisms underlying the poorer outcomes observed after MIS remain incompletely understood. Uterine-manipulator use and unprotected intracorporeal colpotomy have been proposed as potential contributors to tumor spillage and dissemination [16,17]. Consequently, modified minimally invasive techniques based on tumor-containment principles have been developed, including avoidance of uterine manipulators, protective vaginal closure or transection, and contained specimen retrieval. Observational studies using such modified approaches have reported encouraging oncologic outcomes [24–26]. However, comparative evidence specifically evaluating manipulator-free MIS-RH with tumor-protective measures against O-RH remains limited.

We therefore conducted a retrospective propensity-score-matched cohort study comparing manipulator-free MIS-RH with O-RH in patients with early-stage CC treated at a high-volume tertiary referral center from 2019 to 2023. Disease-free survival (DFS) was the primary outcome; OS, perioperative outcomes, and postoperative complications were secondary outcomes.

2. Materials and methods

2.1. Patients and data sources

This retrospective cohort study included patients with early-stage CC who underwent RH at West China Second University Hospital between January 2019 and December 2023. Surgical approach was selected through shared decision-making between the patient and the treating gynecologic oncology team. Preoperative counseling included discussion of the perioperative characteristics of O-RH and MIS-RH, evidence from the LACC trial and then-current guideline recommendations, the oncologic uncertainties associated with MIS-RH, and the manipulator-free and tumor-containment techniques used at our institution. For patients considering MIS-RH, the minimally invasive platforms available at the time and their technical characteristics were also discussed. Patients were given the opportunity to ask questions and express their treatment preferences before the surgical approach was selected. No random allocation or protocol-mandated assignment of surgical approach was used. All procedures were performed by senior gynecologic oncologists; approach- and platform-specific surgeon experience is summarized in Supplementary Table S1. Inclusion criteria were: (1) Histopathologically confirmed invasive CC, including squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and neuroendocrine subtypes; (2) Clinical stage IB1, IB2, or IIA1 according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system [12]; (3) Querleu–Morrow type C RH [27] with pelvic lymph-node assessment, including sentinel lymph-node biopsy

(SLNB) and/or pelvic lymphadenectomy; and (4) surgery performed using manipulator-free multiport laparoscopic radical hysterectomy (MPLS-RH), transumbilical laparoscopic single-site radical hysterectomy (TU-LESS-RH), robot-assisted radical hysterectomy, or O-RH. Exclusion criteria encompassed: (1) concurrent primary or metastatic malignancies; (2) receipt of neoadjuvant chemotherapy or radiotherapy; (3) pregnancy. After application of these criteria, 1798 patients were included: 539 underwent MIS-RH and 1259 underwent O-RH (Supplementary Fig. S1). This investigation received ethical approval from the Institutional Review Board of West China Second University Hospital (Protocol ID: 2023332).

2.2. Tumor-free measures adopted to prevent tumor spillage during MIS-RH

2.2.1. Manipulator-free uterine exposure

During MPLS-RH, uterine traction was achieved using fundal sutures exteriorized through a suprapubic trocar (Fig. 1A–F). During TU-LESS-RH, uterine exposure was obtained using Zheng's 4C Suspension Method [28] (Fig. 1G–J). During robot-assisted RH, a sterilized cable tie placed at the cervico-isthmic junction was used for assistant-controlled traction (Supplementary Fig. S2). Detailed descriptions and video demonstrations of the suspension and tumor-containment techniques used in TU-LESS-RH and robot-assisted TU-LESS-RH have been published previously [28–30].

2.2.2. Specimen bagging and protective vaginal transection

Resected specimens were placed in impermeable retrieval bags. Before vaginal transection, the vagina was circumferentially ligated with a suture or sterilized cable tie to isolate the cervix from the abdominopelvic cavity (Supplementary Fig. S3). Vaginal transection was then performed 1.5–2.0 cm distal to the tumor margin, followed by transvaginal specimen extraction.

2.3. Study outcomes and definitions

The primary outcome was DFS, defined as the interval from surgery to first recurrence or death from any cause; patients without an event were censored at last follow-up. Secondary outcomes were OS, perioperative outcomes, and postoperative complications. OS was defined as the interval from surgery to death from any cause, with survivors censored at last follow-up. Perioperative outcomes included operative time, estimated blood loss, intraoperative transfusion and complications, time to first flatus, pelvic drainage duration, visual analogue scale (VAS) pain scores, supplemental analgesic use, and postoperative length of stay. Time to first flatus was measured from completion of surgery to first passage of flatus. Postoperative complications included urinary, thromboembolic, lymphatic, bowel-obstruction, infectious or hemorrhagic, vaginal-cuff, and wound-healing complications and were graded according to the Clavien–Dindo classification [31]. Postoperative pathological characteristics included pelvic lymph-node yield and positivity, lymphovascular space invasion (LVSI), differentiation, stromal invasion depth, pathological tumor size, vaginal resection length, and final pathological stage. LVSI was determined from final surgical pathology. Adjuvant-treatment status reflected treatment actually received rather than a standardized assessment of treatment indication and was categorized as none, radiotherapy alone, chemotherapy alone, or combined radiotherapy and chemotherapy. Treatment decisions were based on final pathological findings, institutional practice, and individualized clinical assessment.

2.4. Postoperative surveillance and follow-up

Patients underwent follow-up every 3 months during the first 2 postoperative years, every 6 months during years 3–5, and annually thereafter. Follow-up generally included clinical assessment and imaging examinations as clinically indicated. Vital status and disease outcomes were last updated in May 2024.

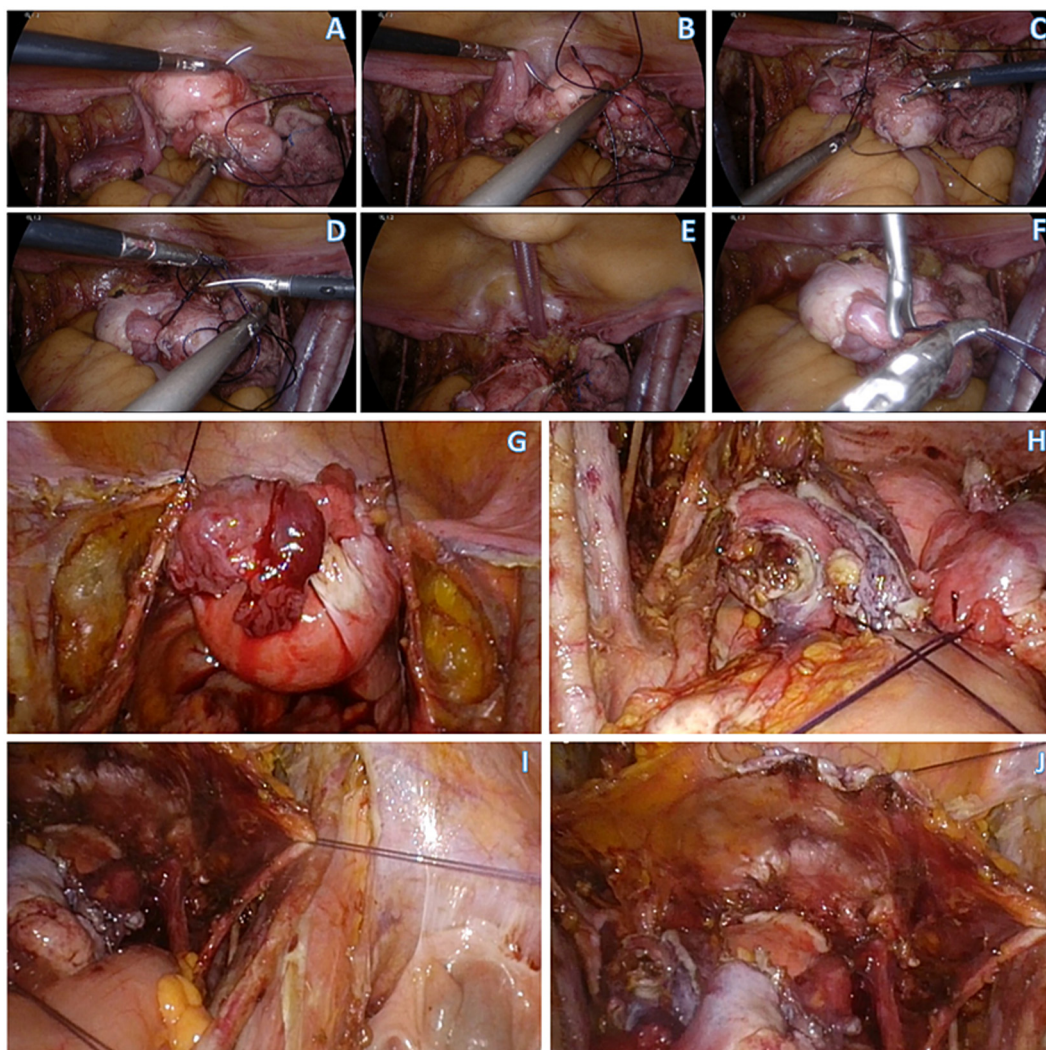


Fig. 1. Manipulator-free uterine suspension techniques used for uterine exposure during minimally invasive radical hysterectomy.

(A–F) Fundal suture suspension during multiport laparoscopic radical hysterectomy (MPLS-RH): (A) suspension of the right uterine cornu and adnexa; (B) suspension of the left uterine cornu and adnexa; (C) tying the figure-of-eight suture knot; (D) cutting the suture distal to the knot; (E) suprapubic trocar insertion; and (F) grasping the suture knot with an instrument and applying traction to the uterus. (G–J) Uterine suspension during transumbilical laparoendoscopic single-site radical hysterectomy (TU-LESS-RH) using Zheng's 4C Suspension Method: (G) center suspension; (H) crab suspension; and (I–J) cross suspension.

2.5. Statistical analysis

Propensity scores were estimated using multivariable logistic regression including age, body mass index (BMI), preoperative histologic subtype, clinical stage, history of abdominal surgery, and comorbidity. Patients were matched 1:1 by nearest-neighbor matching without replacement, using a maximum absolute propensity-score difference of 0.02 on the propensity-score scale. Balance was assessed using standardized mean differences (SMDs; absolute SMD <0.10 considered adequate), with variance ratios for continuous variables and a Love plot. Conversions from MIS-RH to O-RH were analyzed in the MIS-RH group according to the initial surgical approach. Continuous-variable distributions were assessed using the D'Agostino–Pearson omnibus test. Normally distributed variables are presented as mean $\pm$ standard deviation and were compared using the independent-samples Student's *t*-test; non-normally distributed variables are presented as median (interquartile range) and were compared using the Mann–Whitney *U* test. Categorical variables are presented as *n* (%) and were compared using Pearson's chi-square test; Fisher's exact test was used for 2 $\times$ 2 contingency tables when any expected cell count was <5. For the overall comparison of final pathological stage groups I, II, III, and IV, the

Fisher–Freeman–Halton exact test was used because of sparse expected cell counts. The association between calendar year and surgical approach was assessed using Pearson's chi-square test. DFS and OS were estimated by Kaplan–Meier analysis and compared using the log-rank test. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs), with O-RH as the reference. The proportional hazards assumption for surgical approach was assessed separately for DFS and OS using a time-dependent interaction between surgical approach and follow-up time; the interaction coefficient was evaluated by the Wald test. Median potential follow-up was estimated using reverse Kaplan–Meier analysis and compared between groups using the log-rank test. Because surgical approach changed over calendar time, additional Cox proportional hazards models were fitted with year of surgery included as a categorical covariate (2019, 2020, 2021, 2022, and 2023). To address the unequal follow-up resulting from the later adoption of MIS-RH, a post hoc common-horizon sensitivity analysis administratively censored event-free follow-up at 24 months. The 24-month horizon was selected as a pragmatic two-year observation window before substantial attrition of the MIS-RH risk set at later time points. Kaplan–Meier and unadjusted and year-adjusted Cox analyses were repeated. One post hoc sensitivity analysis excluded

complete matched pairs in which either patient had a pure or mixed neuroendocrine carcinoma component, after which survival analyses were repeated. A separate post hoc sensitivity analysis excluded matched pairs in which either patient underwent SLNB alone, after which perioperative analyses were repeated. Exploratory Kaplan–Meier analyses compared DFS and OS by surgical approach within pathological tumor-size (≤ 2 vs > 2 cm) and LVSI (negative vs positive) strata; no interaction tests were performed. Recurrence and all-cause mortality were also descriptively compared by surgical approach after joint stratification by adjuvant treatment actually received and final pathological stage: group 1, IB1–IB2/IIA1; group 2, IB3/IIA2/IIIB; and group 3, III–IV. Pearson's chi-square or Fisher's exact test was used as appropriate; no multivariable estimates were calculated because of sparse strata. No adjustment for multiple comparisons was applied. Secondary outcome analyses were considered supportive, whereas exploratory analyses were considered hypothesis-generating. All tests were two-sided with $P < .05$ considered statistically significant. Analyses used IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Pre- and post-matching cohort characteristics

Of 1798 eligible patients, 539 underwent MIS-RH and 1259 underwent O-RH. Pre-matching analysis revealed meaningful imbalances in age, clinical stage and history of abdominal surgery. After 1:1 propensity-score matching ($n = 539$ per cohort), baseline characteristics achieved balance (Table 1 and Supplementary Fig. S4).

3.2. Perioperative outcomes

Among the secondary perioperative outcomes, MIS-RH was associated with longer operative time (260 vs 235 min) but lower estimated blood loss (100 vs 300 mL), fewer intraoperative transfusions (0.56% vs 6.31%), shorter time to first flatus (48 vs 60 h), and shorter postoperative hospitalization (6 vs 7 days; all $P < .001$). Intraoperative complication rates were similar between groups, and two MIS-RH procedures (0.37%) were converted to O-RH. MIS-RH was also associated with lower VAS pain scores at 2, 24, and 36 h postoperatively and less supplemental analgesic use (Table 2). SLNB alone was more frequent after MIS-RH than O-RH (14.47% vs 0.37%; $P < .001$). After excluding the 78 matched pairs in which either patient underwent SLNB alone,

the principal perioperative findings remained unchanged, while pelvic lymph-node yield and intraoperative complication rates remained similar between groups (Supplementary Table S2).

3.3. Postoperative pathological and treatment characteristics

Postoperative pathological characteristics, including lymph-node status, LVSI, tumor differentiation, stromal invasion, tumor size, and final pathological stage, were similar between groups. MIS-RH was associated with a longer vaginal resection length (2.30 vs 2.05 cm; $P < .001$) and a lower rate of postoperative adjuvant treatment (57.14% vs 67.35%; $P < .001$); the distribution of adjuvant-treatment regimens also differed between groups ($P = .021$) (Table 3).

3.4. Postoperative morbidity

The overall postoperative complication rate and the proportions of minor and serious complications according to the Clavien–Dindo classification [31] did not differ significantly between groups (Table 4). However, MIS-RH had a higher incidence of urinary retention (22.26% vs 11.13%; $P < .001$) and bowel obstruction (2.23% vs 0.74%; $P = .044$). All bowel-obstruction events were partial. No cases of poor incision healing occurred in the MIS-RH group, compared with 12 cases in the O-RH group.

3.5. Oncologic outcomes

3.5.1. Follow-up and oncologic outcomes

Median potential follow-up was 18.93 months (95% CI, 16.76–21.11) after MIS-RH and 31.30 months (95% CI, 29.36–33.24) after O-RH ($P < .001$). Recurrence occurred in 18 (3.34%) and 30 (5.57%) patients, respectively, and all-cause deaths in 9 (1.67%) and 8 (1.48%). DFS did not differ significantly between groups (log-rank $P = .623$; HR, 0.863; 95% CI, 0.480–1.553; $P = .623$), nor did OS (log-rank $P = .253$; HR, 1.735; 95% CI, 0.666–4.518; $P = .259$) (Fig. 2; Supplementary Table S3). No evidence of violation of the proportional hazards assumption was identified for surgical approach in either DFS or OS analyses (time-dependent interaction $P = .304$ and $P = .777$, respectively).

3.5.2. Sensitivity analyses

MIS-RH use increased from 23.47% in 2019 to 86.88% in 2023 ($P < .001$; Supplementary Table S4). After adjustment for calendar year, surgical approach was not significantly associated with DFS (HR,

Table 1
Baseline characteristics and covariate balance before and after PSM (propensity-score matching).

Characteristics	Before PSM				After PSM			
	MIS-RH ($n = 539$)	O-RH ($n = 1259$)	Absolute SMD ^a	Variance ratio ^b	MIS-RH ($n = 539$)	O-RH ($n = 539$)	Absolute SMD ^a	Variance ratio ^b
Age, years, mean $\pm$ SD	49.38 $\pm$ 9.98	50.67 $\pm$ 9.74	0.131	1.048	49.38 $\pm$ 9.98	48.65 $\pm$ 9.48	0.075	1.107
BMI, kg/m ² , mean $\pm$ SD	23.27 $\pm$ 3.13	23.25 $\pm$ 3.05	0.006	1.053	23.27 $\pm$ 3.13	22.99 $\pm$ 2.92	0.093	1.153
Preoperative histologic subtype, n (%)			0.038	–			0.013	–
Squamous cell carcinoma	400 (74.21)	955 (75.85)			400 (74.21)	397 (73.65)		
Other histologic subtypes	139 (25.79)	304 (24.15)			139 (25.79)	142 (26.35)		
Clinical stage, n (%)								
IB1	286 (53.06)	385 (30.58)	0.468	–	286 (53.06)	294 (54.55)	0.030	–
IB2	190 (35.25)	321 (25.50)	0.213	–	190 (35.25)	182 (33.77)	0.031	–
IIA1	63 (11.69)	553 (43.92)	0.771	–	63 (11.69)	63 (11.69)	0.000	–
Comorbidity, yes, n (%)	92 (17.07)	211 (16.76)	0.008	–	92 (17.07)	75 (13.91)	0.087	–
History of abdominal surgery, yes, n (%)	231 (42.86)	472 (37.49)	0.110	–	231 (42.86)	220 (40.82)	0.041	–

BMI, body mass index; MIS-RH, minimally invasive radical hysterectomy; O-RH, open radical hysterectomy; PSM, propensity-score matching; SD, standard deviation; SMD, standardized mean difference.

^a Absolute standardized mean differences are reported, with an absolute SMD < 0.10 considered indicative of adequate covariate balance.

^b Variance ratios are reported for continuous variables only, with values closer to 1 indicating greater similarity in dispersion between groups.

Table 2
Perioperative outcomes after propensity-score matching.

Outcomes	MIS-RH (n = 539)	O-RH (n = 539)	P value
Surgical procedures, n (%)			
Unilateral/bilateral salpingectomy	533 (98.89)	537 (99.63)	0.287*
Unilateral/bilateral oophorectomy	417 (77.37)	442 (82.00)	0.058
SLNB alone	78 (14.47)	2 (0.37)	< 0.001
Pelvic lymphadenectomy alone	447 (82.93)	536 (99.44)	< 0.001
SLNB plus pelvic lymphadenectomy	14 (2.60)	1 (0.19)	< 0.001
Para-aortic lymphadenectomy	408 (75.70)	431 (79.96)	0.092
Operative time and blood loss			
Operative time [min, median (IQR)]	260 (221,310)	235 (195, 280)	< 0.001
Estimated blood loss [mL, median (IQR)]	100 (50, 200)	300 (200, 500)	< 0.001
Intraoperative transfusion, n (%)	3 (0.56)	34 (6.31)	< 0.001
Intraoperative complications, n (%)	18 (3.34)	20 (3.71)	0.741
Ureteral injury	9 (1.67)	4 (0.74)	0.163
Bladder injury	2 (0.37)	5 (0.93)	0.452*
Vascular injury	4 (0.74)	5 (0.93)	1.000*
Intestinal injury	3 (0.56)	6 (1.11)	0.506*
MIS-RH to O-RH conversion, n (%)	2 (0.37) ^a	–	–
Time to first flatus [h, median (IQR)]	48 (36, 60)	60 (60, 84)	< 0.001
Pelvic drainage duration [d, median (IQR)]	4 (3, 5)	4 (3, 5)	0.698
Postoperative length of stay [d, median (IQR)]	6 (5, 7)	7 (6, 8)	< 0.001
VAS score, mean ± SD			
2 h	2.92 ± 0.97	3.68 ± 1.73	< 0.001
12 h	2.13 ± 1.09	2.28 ± 1.27	0.050
24 h	2.13 ± 0.91	2.37 ± 1.08	< 0.001
36 h	1.70 ± 0.75	1.83 ± 0.87	0.009
Supplemental analgesic use, n (%)	200 (37.11)	261 (48.42)	< 0.001

IQR, interquartile range; MIS-RH, minimally invasive radical hysterectomy; O-RH, open radical hysterectomy; SD, standard deviation; SLNB, sentinel lymph-node biopsy; VAS, visual analogue scale.

^a Patients converted from MIS-RH to O-RH were retained in the MIS-RH group according to the initially selected surgical approach.

* Fisher's exact test.

0.784; 95% CI, 0.428–1.435; $P = .430$) or OS (HR, 1.917; 95% CI, 0.735–4.996; $P = .183$). No significant DFS or OS differences were observed in the 24-month common-horizon analysis (Supplementary Table S5). Excluding 33 matched pairs containing a neuroendocrine carcinoma component left 506 patients per group and again yielded no significant DFS or OS differences in unadjusted or year-adjusted analyses (Supplementary Table S6).

3.5.3. Exploratory analyses

Exploratory analyses stratified by pathological tumor size (≤ 2 vs > 2 cm) or LVSI status identified no significant between-group differences in DFS or OS (Supplementary Figs. S5 and S6). In analyses jointly stratified by final pathological stage and postoperative adjuvant treatment actually received, recurrence and all-cause mortality did not differ significantly between surgical approaches. Because several strata contained few patients and events, these comparisons were considered descriptive (Supplementary Table S7).

4. Discussion

In this propensity-score-matched cohort, no statistically significant difference was detected in the primary outcome of DFS between manipulator-free MIS-RH and O-RH, and no significant difference was identified in OS. These findings remained consistent after adjustment for calendar year and across sensitivity analyses, although the limited number of events resulted in imprecise estimates, particularly for OS. MIS-RH was associated with lower blood loss, fewer intraoperative transfusions, earlier return of bowel function, and shorter

Table 3
Postoperative pathological and treatment characteristics after propensity-score matching.

Characteristics	MIS-RH (n = 539)	O-RH (n = 539)	P value
Final histopathologic finding, n (%)			
Squamous cell carcinoma	355 (65.86)	369 (68.46)	0.352
Adenocarcinoma	97 (18.00)	91 (16.88)	
Adenosquamous carcinoma	42 (7.79)	30 (5.57)	
Neuroendocrine carcinoma	5 (0.93)	11 (2.04)	
Mixed histology	10 (1.86)	13 (2.41)	
No residual tumor	30 (5.57)	25 (4.64)	
Number of pelvic lymph nodes, median (IQR)	26 (22,31)	26 (21,31)	0.456
Lymph node positivity, n (%)	83 (15.40)	85 (15.77)	0.867
LVSI positive, n (%)	262 (48.61)	285 (52.88)	0.161
Poorly differentiated, n (%)	340 (63.08)	345 (64.01)	0.752
Deep stromal invasion, n (%)	232 (43.04)	258 (47.87)	0.112
Tumor size, n (%)			
≤ 2 cm	278 (51.58)	264 (48.98)	0.394
> 2 cm	261 (48.42)	275 (51.02)	
Final pathological stage, n (%) ^a			
IB1	238 (44.16)	221 (41.00)	0.834
IB2	136 (25.23)	152 (28.20)	
IB3	1 (0.19)	5 (0.93)	
IIA1	63 (11.69)	64 (11.87)	
IIA2	5 (0.93)	1 (0.19)	
IIB	11 (2.04)	9 (1.67)	
IIIA	1 (0.19)	0	
IIIC1p	69 (12.80)	77 (14.29)	
IIIC2p	11 (2.04)	8 (1.48)	
IV	4 (0.74)	2 (0.37)	
Vaginal resection length, cm, mean ± SD	2.30 ± 0.86	2.05 ± 0.72	< 0.001
Receipt of adjuvant treatment, n (%) ^b			
No adjuvant treatment	231 (42.86)	176 (32.65)	< 0.001
Any adjuvant treatment	308 (57.14)	363 (67.35)	
Adjuvant treatment regimen, n (%) ^c			
Radiotherapy	64 (11.87)	48 (8.91)	0.021
Chemotherapy	19 (3.53)	32 (5.94)	
Radiotherapy and chemotherapy	225 (41.74)	283 (52.50)	

FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LVSI, lymphovascular space invasion; MIS-RH, minimally invasive radical hysterectomy; O-RH, open radical hysterectomy; SD, standard deviation.

^a The P value for final pathological stage was calculated by comparing overall FIGO stage groups I, II, III, and IV using the Fisher–Freeman–Halton exact test because of sparse expected cell counts.

^b Adjuvant-treatment status represents treatment actually received rather than a standardized clinical indication for treatment.

^c Percentages for individual adjuvant-treatment regimens are expressed relative to the total surgical group ($n = 539$ in each group), whereas the P value for regimen distribution compares only patients who actually received postoperative adjuvant treatment (MIS-RH, $n = 308$; O-RH, $n = 363$).

hospitalization, but also with longer operative time and more postoperative urinary retention.

4.1. Comparative perioperative outcomes and technical considerations

The perioperative profile observed after MIS-RH is consistent with the expected advantages of MIS, particularly reduced blood loss and faster postoperative recovery. The longer operative time may reflect the additional manipulator-free suspension and exposure procedures required during MIS-RH, as well as differences in technical complexity across laparoscopic, single-site, and robotic platforms. The one-day difference in length of stay was smaller than that reported in some previous studies. The LACC trial reported median hospitalization of 3 days after MIS-RH and 5 days after O-RH [13], whereas the SUCCOR study reported corresponding durations of 4 and 7 days [17]. Such variation likely reflects differences in discharge criteria, perioperative care pathways, urinary-catheter and drain management, and healthcare-system practice. Thus, the shorter hospitalization observed in our cohort should

Table 4
Postoperative complications after propensity-score matching.

Complications	MIS-RH (n = 539)	O-RH (n = 539)	P value
Overall complications, n (%) ^a	173 (32.10)	149 (27.64)	0.110
Urinary system, n (%)			
Urinary retention	120 (22.26)	60 (11.13)	< 0.001
Hydronephrosis or hydroureter	4 (0.74)	5 (0.93)	1.000*
Ureterovaginal fistula	9 (1.67)	3 (0.56)	0.082
Vesicovaginal fistula	1 (0.19)	2 (0.37)	1.000*
DVT (without pulmonary embolism), n (%)	23 (4.27)	31 (5.75)	0.264
Pulmonary embolism, n (%)	6 (1.11)	12 (2.23)	0.154
Postoperative blood transfusion, n (%)	3 (0.56)	24 (4.45)	< 0.001
Lymphocele with infection or hemorrhage, n (%)	10 (1.86)	15 (2.78)	0.312
Bowel obstruction, n (%)	12 (2.23)	4 (0.74)	0.044
Pelvic infection, n (%)	3 (0.56)	2 (0.37)	1.000*
Pelvic hemorrhage, n (%)	1 (0.19)	1 (0.19)	1.000*
Vaginal stump hemorrhage or dehiscence, n (%)	3 (0.56)	1 (0.19)	0.624*
Vaginal stump infection, n (%)	6 (1.11)	2 (0.37)	0.287*
Poor incision healing, n (%)	0	12 (2.23)	< 0.001
Clavien–Dindo severity category, n (%) ^a			
Minor complications	150 (27.83)	126 (23.38)	0.094
Grade I	104 (19.29)	45 (8.35)	
Grade II	46 (8.53)	81 (15.03)	
Serious complications	23 (4.27)	23 (4.27)	1.000
Grade III	23 (4.27)	23 (4.27)	
Grade IV	0	0	
Grade V	0	0	

DVT, deep-vein thrombosis; MIS-RH, minimally invasive radical hysterectomy; O-RH, open radical hysterectomy.

^a Overall complication rates and Clavien–Dindo categories represent numbers of individual patients. For patients with multiple complications, Clavien–Dindo classification was based on the highest-grade complication experienced. Individual complication categories represent recorded complication events; therefore, a patient could contribute to more than one individual complication category.

* Fisher's exact test.

be interpreted as a center-specific perioperative association rather than evidence of superior recovery in all settings. Intraoperative and overall postoperative complication rates did not differ significantly between groups, nor did pelvic lymph-node yield, while vaginal resection length was greater in the MIS-RH group. These findings suggest that the observed perioperative benefits were not accompanied by evidence of

reduced surgical extent. SLNB alone was substantially more frequent in the MIS-RH group, raising concern that a less extensive lymph-node assessment might partly explain the perioperative differences. However, after exclusion of the 78 affected matched pairs, the principal differences in blood loss, transfusion, bowel recovery, hospitalization, and operative time persisted, whereas lymph-node yield and intraoperative complication rates remained similar. Thus, the perioperative findings were not explained solely by the imbalance in SLNB use. Urinary retention was more frequent after MIS-RH (22.26% vs 11.13%). The mechanism cannot be established from this retrospective study, but potential contributors include differences in parametrial dissection, energy-device use near the pelvic autonomic nerves, and postoperative bladder-management practices. This finding warrants further evaluation using standardized definitions of bladder dysfunction and nerve-sparing procedures.

4.2. Manipulator-free MIS-RH in the context of post-LACC evidence

An important question in the post-LACC era is whether the adverse oncologic outcomes observed with conventional MIS-RH apply equally to modified minimally invasive procedures incorporating tumor-protective measures. In our propensity-score-matched cohort, no statistically significant differences in DFS or OS were detected between manipulator-free MIS-RH and O-RH. These findings were materially unchanged after adjustment for calendar year and remained consistent in the 24-month common-horizon analysis. However, the limited numbers of oncologic events, particularly deaths, resulted in wide confidence intervals and restricted the precision of these estimates.

Modifications in minimally invasive surgical technique may partly explain why some studies of modified MIS-RH have reported findings different from those of the LACC trial. Uterine-manipulator use and unprotected intracorporeal colpotomy have been proposed as potentially modifiable factors that may contribute to tumor compression, disruption, or spillage [16,17]. These concerns have prompted the development of tumor-protective strategies incorporating avoidance of uterine manipulators, protective vaginal closure or transection, and contained specimen retrieval, with several observational studies reporting encouraging oncologic outcomes [24–26]. In the present study, all MIS-RH procedures were performed without a uterine manipulator and incorporated uterine-suspension techniques, protective

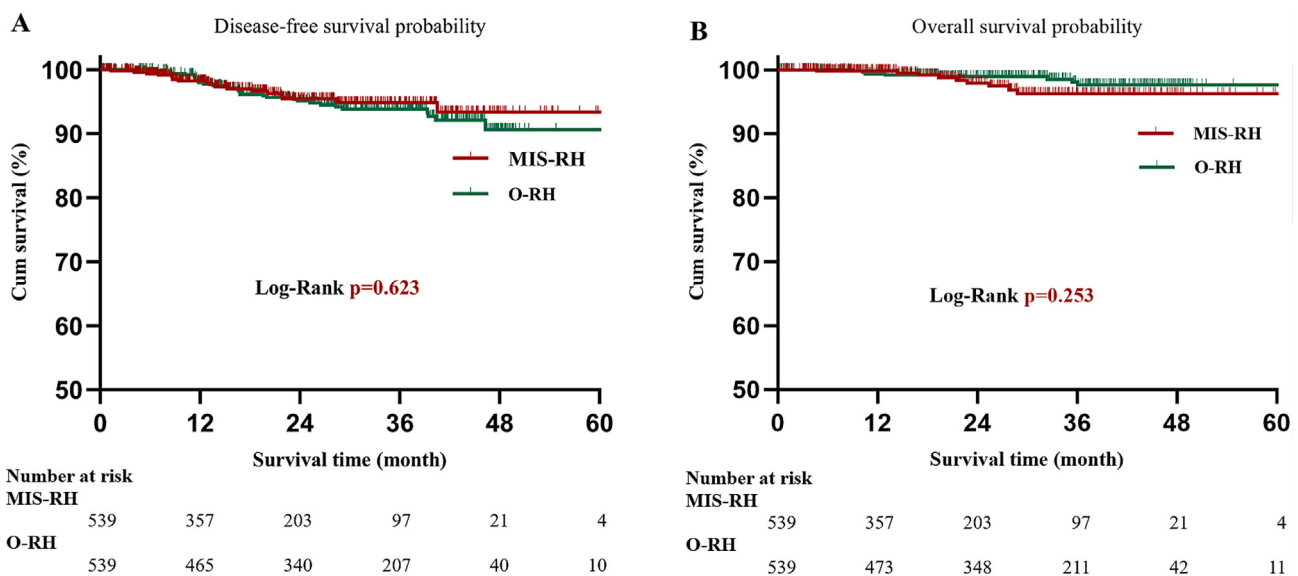


Fig. 2. Kaplan–Meier curves for disease-free survival and overall survival in the propensity-score-matched cohort.

(A) Disease-free survival (DFS) and (B) overall survival (OS) according to surgical approach. Tick marks indicate censored observations, and numbers at risk are shown below each panel. MIS-RH, minimally invasive radical hysterectomy; O-RH, open radical hysterectomy.

vaginal transection, and contained specimen retrieval based on previously described institutional techniques [28–30]. These technical characteristics distinguish the surgical strategy evaluated in our cohort from conventional MIS-RH and may represent one source of heterogeneity across studies. Nevertheless, because these measures were implemented as a combined strategy, our study cannot determine whether any individual modification independently influenced oncologic outcomes or establish a causal relationship between technical modification and survival.

Surgeon experience may represent another source of between-study heterogeneity. RH is technically demanding, and previous studies have demonstrated a learning curve for minimally invasive approaches [9]. In the LACC trial, participating centers were required to provide perioperative outcome data from at least 10 previous minimally invasive radical hysterectomies and submit two unedited surgical videos for quality review [13]. Although these requirements provided an important framework for surgical quality assurance, detailed surgeon-specific experience was not incorporated into the outcome analyses. In our study, all procedures were performed by senior gynecologic oncologists, with approach- and platform-specific experience summarized in Supplementary Table S1. Such experience may have reduced variability related to technical proficiency; however, surgeon experience was not identical across approaches and platforms, and residual operator-related confounding cannot be excluded. Accordingly, the survival findings in our cohort should not be attributed solely to surgeon experience or technical modification.

Study setting may also contribute to heterogeneity. Single-center studies may provide greater consistency in surgical technique, perioperative management, and follow-up, whereas multicenter studies generally provide broader external validity and better reflect variations in clinical practice [32–34]. Thus, although the relatively standardized single-center setting of our study should not be considered methodologically superior, it may have reduced variability in operative protocols and clinical management. Conversely, our findings may not be directly generalizable to institutions with different levels of surgical expertise, tumor-containment strategies, or perioperative practices.

Despite these potential sources of heterogeneity in surgical technique, surgeon experience, and study setting, the LACC trial remains the highest-level randomized evidence comparing MIS-RH with O-RH and supports open surgery as the preferred surgical approach for early-stage CC [13]. Therefore, our observational findings should not be interpreted as challenging the conclusions of the LACC trial or as establishing equivalence or noninferiority of manipulator-free MIS-RH relative to O-RH. Rather, they provide technique-specific observational evidence supporting further evaluation of standardized manipulator-free, tumor-protective MIS-RH. Prospective multicenter studies with standardized surgical techniques, detailed reporting of surgeon experience, adequate numbers of oncologic events, and longer follow-up are needed to clarify the long-term oncologic outcomes of these modified approaches.

4.3. Exploratory analyses according to LVSI and tumor size

LVSI is an established adverse prognostic factor in CC [35]. Uterine manipulation has been hypothesized to facilitate tumor-cell entry into lymphovascular spaces through cervical compression. Previous studies, however, have not been consistent. Yang et al. reported a higher frequency of LVSI with manipulator-assisted laparoscopy, whereas Liu et al. found no association between either surgical approach or manipulator use and LVSI [36,37]. This inconsistency supports cautious interpretation of the proposed mechanical pathway. In our cohort, LVSI prevalence was similar between MIS-RH and O-RH, and exploratory analyses identified no statistically significant differences in DFS or OS within either LVSI stratum. Because LVSI was determined from postoperative pathology and event numbers were limited, these results

represent exploratory prognostic stratification and should not be used to guide preoperative selection of surgical approach.

Evidence regarding tumor size is similarly heterogeneous. The SUCCOR study suggested that the excess recurrence associated with MIS was concentrated among patients with tumors ≥ 2 cm [17]. In contrast, a matched study from China reported similar oncologic outcomes between MIS and open surgery among patients with stage IB1 tumors ≤ 2 cm [38]. A Korean study found poorer DFS after MIS in patients with tumors > 2 cm, but not in those with tumors ≤ 2 cm [39]. However, a 2024 retrospective cohort study from China reported no significant differences in survival outcomes between MIS and open surgery across tumor-size subgroups of < 2 cm, 2–4 cm, and > 4 cm [40]. Differences in stage distribution, tumor-size assessment, surgical technique, and patient selection may partly account for these discrepant findings. In our exploratory analysis, no statistically significant differences in DFS or OS were detected between MIS-RH and O-RH within either pathological tumor-size subgroup (≤ 2 or > 2 cm). Because tumor size was determined postoperatively and the number of events within each subgroup was limited, these findings should be regarded as hypothesis-generating and do not establish equivalence or identify a subgroup in which MIS-RH can be considered oncologically noninferior to O-RH.

4.4. Methodological considerations and future directions

This study has several strengths, including a relatively large propensity-score-matched cohort, a consistently applied manipulator-free and tumor-protective MIS strategy, detailed perioperative and pathological data, and multiple sensitivity analyses addressing calendar-time imbalance, unequal follow-up, neuroendocrine carcinoma, and differences in lymph-node assessment. Nevertheless, several limitations should be considered. First, the retrospective, nonrandomized design remains susceptible to selection bias and residual confounding despite propensity-score matching, particularly from unmeasured patient-, disease-, surgeon-, and platform-related factors. Second, MIS-RH was increasingly adopted during the later study years, resulting in substantially shorter follow-up in the MIS-RH group and potential temporal confounding. Although calendar-year-adjusted analyses and the 24-month common-horizon sensitivity analysis yielded results consistent with the primary analysis, the limited numbers of recurrences and, particularly, deaths resulted in wide confidence intervals and preclude conclusions of equivalence or noninferiority. Secular changes in surgical experience, perioperative management, and institutional practice may also have influenced perioperative outcomes and cannot be fully addressed by adjustment for calendar year. Third, the single-center setting, while providing greater consistency in surgical technique and clinical management, may limit the generalizability of the findings to institutions with different levels of surgical expertise and perioperative practice. Finally, multiple secondary and exploratory analyses were performed without adjustment for multiplicity and should therefore be interpreted as supportive or hypothesis-generating. Prospective multicenter studies with standardized eligibility criteria, tumor-containment techniques, detailed reporting of surgeon experience and longer follow-up are needed to further clarify the long-term oncologic outcomes of modified MIS-RH.

5. Conclusions

In this propensity-score-matched retrospective cohort, no statistically significant difference was detected in the primary outcome of DFS between manipulator-free MIS-RH and O-RH. Similarly, no statistically significant difference was observed in the secondary oncologic outcome of OS, although precision was limited by the small number of deaths. MIS-RH was associated with lower estimated blood loss, fewer intraoperative transfusions, earlier return of bowel function, and a shorter postoperative hospital stay, but also with a longer operative time and a higher incidence of postoperative urinary retention. Because

of the nonrandomized design, shorter follow-up in the MIS-RH group, and limited number of outcome events, these findings do not establish equivalence or noninferiority. Further prospective studies with standardized surgical techniques and longer follow-up are warranted.

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CRedit authorship contribution statement

Lusi Deng: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ying Zheng:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Fan Yang:** Writing – review & editing, Resources, Investigation, Data curation. **Qiao Wang:** Writing – review & editing, Resources, Investigation, Data curation. **Yu Chen:** Writing – review & editing, Resources, Investigation, Data curation. **Jianhong Liu:** Writing – review & editing, Validation, Software, Methodology, Formal analysis. **Xu Yang:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Informed consent

Written informed consent was obtained from all participants.

Ethical approval

This investigation received ethical approval from the Institutional Review Board of West China Second University Hospital (Protocol ID: 2023332).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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