Am J Cancer Res 2026;16(6):2577-2611
www.ajcr.us /ISSN:2156-6976/ajcr0172498

Original Article

Impact of laparoscopic versus open surgery on 5-year survival in patients with stage IA2-IB1 cervical cancer: a retrospective cohort study

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Received March 9, 2026; Accepted May 19, 2026; Epub June 15, 2026; Published June 30, 2026

Abstract: Utilizing inverse probability of treatment weighting (IPTW), this retrospective, multicenter study examined the association between laparoscopic versus open radical hysterectomy and 5-year overall survival (OS) and disease-free survival (DFS) in patients with FIGO stage IA2-IB1 cervical cancer. A total of 840 patients who underwent surgery between January 2016 and January 2021 were recruited (laparoscopic group, N=512; open group, N=328). These patients were randomly assigned to a training cohort (N=529) and a validation cohort (N=311). In the training cohort, a propensity score model including 27 covariates was constructed, and IPTW achieved good covariate balance (all standardized mean difference <0.1). IPTW-weighted Cox regression analysis showed that, in comparison to open surgery, laparoscopic surgery was associated with worse DFS in both the training cohort (HR: 1.73, 95% CI: 1.25-2.40) and the validation cohort (HR: 3.80, 95% CI: 2.25-6.41). The findings were consistent in multivariable Cox analysis. For OS, Kaplan-Meier analysis suggested that laparoscopic surgery was associated with lower survival probability; however, after multivariable adjustment, this association was not statistically significant in the training cohort, while a similar unfavorable association was noted in the validation cohort. Subgroup analysis suggested a potential interaction between lymphovascular space invasion (LVSI) and surgical approach, with laparoscopic surgery showing worse outcomes in patients without LVSI. Alternative sensitivity analyses yielded consistent trends. Other independent prognostic factors for both DFS and OS included deep stromal invasion of at least 50%, positive LVSI, non-R0 margins, and lymph node metastasis. In summary, after adjustment, laparoscopic radical hysterectomy was associated with poorer DFS compared with open surgery, and the association with OS was less consistent. These findings should be interpreted with caution due to the observational design and lack of detailed characteristics regarding surgical techniques.

Keywords: Cervical cancer, laparoscopic surgery, open surgery, propensity score, survival

Introduction

Cervical cancer is one of the most common cancers among women. According to the GLOBOCAN 2022 database, it accounts for around 660,000 new cases and 350,000 deaths annually, ranking fourth among women in both incidence and mortality [1]. Although widespread human papillomavirus (HPV) vaccination and cervical screening programs have reduced the incidence in some high-income countries, the global disease burden remains considerable. Countries with low Human Development Index (HDI) values exhibit incidence and mortality rates around 2-5 times higher than very high HDI countries. Global cervical cancer cases and deaths are projected to rise by 14.8% and 17.8% by 2030 [2]. For early-stage cervical cancer (FIGO stage IA2-IB1), international guidelines recommend radical hysterectomy with pelvic lymphadenectomy as the treatment of choice. Open radical hysterectomy has long been established as the stan-

https://doi.org/10.62347/VGJF7110

dard approach, with reported 5-year OS rates exceeding 90% [3].

Since the 1990s, there has been rapid development and wide adoption of laparoscopy techniques for gynecological oncology. Numerous retrospective studies and meta-analyses have observed that laparoscopic radical hysterectomy provides perioperative benefits over open approach, including reduced intraoperative blood loss, shorter hospital stay, and faster postoperative recovery [4]. Regarding oncologic outcomes, earlier observational studies generally suggested no significant differences in overall survival (OS) and disease-free survival (DFS) [5]. These data contributed to rapid globe adoption of laparoscopic radical hysterectomy, making it the preferred approach for early cervical cancers [6].

The Laparoscopic Approach to Cervical Cancer (LACC) trial by Ramirez et al. in 2018 [7] remains the only large prospective randomized controlled trial (RCT) in this field. The trial recruited 631 patients with early-stage cervical cancer and reported a 4.5-year DFS rate of 86% in the minimally invasive surgery (MIS) group, compared with 96.5% in the open surgery group (HR=3.74, 95% CI: 1.63-8.58). Similar trend was observed on OS. The publication of the LACC trial led to substantial changes in clinical practice, with the proportion of MIS procedures in the US decreasing from 58% to approximately 43% [8]. Subsequent systematic review and meta-analysis echoed these findings. Nitecki et al. analyzed 15 high-quality observational studies involving 9,499 patients and reported that MIS was associated with a greater risk of recurrence or death (HR=1.71) and all-cause mortality (HR=1.56) compared with open surgery [9]. The European SUCCOR study, using inverse probability of treatment weighting (IPTW) analysis of 693 patients with stage IB1 disease, found that MIS was associated with a 2.07-fold higher recurrence risk. Notably, in the SUCCOR study, the use of a uterine manipulator was avoided and a protective vaginal closure was performed, resulting in comparable MIS outcomes to open surgery [10]. However, the LACC trial has been subject to criticism due to limited sample size. The trial also did not standardize the use of uterine manipulator and other important surgical details [6, 11].

Subsequent studies have reported conflicting results. Di Donato et al., in a 10-year follow-up of patients with early-stage “low-risk” cervical cancer, found no significant OS or DFS benefit in MIS over open surgery [12]. Similarly, Kim et al. reported that in patients with tumor diameter ≤2 cm, laparoscopic surgery did not significantly worsen outcomes, provided high-risk pathological features were identified postoperatively and appropriate adjuvant therapy was administered [13]. A meta-analysis by Nasioudis et al. also reported no significant survival difference between the two methods in patients with tumors smaller than 2 cm [14]. These findings suggest that the adverse effects of laparoscopic surgery may not be universal but limited to only certain subgroups.

Despite existing literature, several gap remain. First, most observational studies have relied on traditional multivariable regression or propensity score matching (PSM) to adjust for confounding. However, PSM often results in substantial sample loss because only matched pairs are retained, which reduces statistical power and limits generalizability. In contrast, IPTW keeps the entire sample and was successfully used in the SUCCOR study [10]. IPTW is a causal inference method that remains relatively uncommon in this field. Second, few studies implement a training-validation split framework for independent verification, making it difficult to assess reproducibility. Third, investigations into the interaction between surgical approach and key pathologic covariates, such as lymphovascular space invasion (LVSI) status and histologic type, were mostly conducted post hoc, exploratory, and often lacked systematic robustness checks [6, 15]. Fourth, Chinese cervical cancer patients may differ from Western populations in histology, HPV genotype distribution, and treatment patterns, and high-quality, large-scale evidence from Chinese populations remains scarce.

To address these gaps, we conducted a large multicenter retrospective cohort (n=840) using IPTW to minimize baseline confounding between laparoscopic and open radical hysterectomy cohorts. We evaluated the impact of surgical approach on 5-year OS and DFS in patients with stage IA2-IB1 cervical cancer in both training cohort and independent validation cohort. Subgroup analyses were performed to further

explore potential interactions between surgical approach and key clinicopathological factors. In addition, trimmed IPTW, overlap weights, PSM, and multivariable Cox regression were also employed as sensitivity analyses to verify the robustness of our findings. The objective of this study was to provide high-quality evidence to inform clinical decision-making regarding surgical approach in early-stage cervical cancer.

Materials and methods

Sample size estimation

This retrospective cohort study aimed to evaluate DFS. The Schoenfeld formula for the Cox proportional hazards model was used to determine sample size. The required number of events (E) can be calculated as: $E = \frac{(Z_{\alpha/2} + Z_{\beta})^2}{p1 \times p2 \times (\ln HR)^2}$, where $Z_{\alpha/2}$ corresponds to the two-sided significance level, Z_{β} corresponds to the desired statistical power, HR is the expected hazard ratio, and p1 and p2 are the proportions of patients in the two comparison groups. In this study, we assumed a two-sided significance level of α=0.05 ($Z_{\alpha/2}$=1.96), a statistical power of 1-β=0.80 (Z_{β}=0.842), an expected HR of 2.0 as per previous studies, and equal group allocation i.e. p1=p2=0.5. Substituting these values, the required minimum number of events was calculated to be approximately 65. To account for a possible 15% loss to follow up, this was conservatively adjusted to 75 events [16].

Study population

This multicenter retrospective cohort study employed January 2026 as the data cutoff date, ensuring a complete 5-year follow-up for all patients. Patients with stage IA2-IB1 cervical cancer who received radical hysterectomy with pelvic lymphadenectomy at Henan Provincial People's Hospital (Zhengzhou, China) and Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine (Shanghai, China) between January 2016 and January 2021. The study was approved by the Institutional Ethics Committee of Henan Provincial People's Hospital (the coordinating center) and the Institutional Review Board of Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine. Given the retrospective nature of the study and use of anonymized clinical data, the requirement for written informed consent was waived by both ethics committees. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria: (1) Pathologically confirmed cervical cancer staged as International Federation of Gynecology and Obstetrics (FIGO) 2009 IA2 or IB1 [17]; (2) Radical hysterectomy (open or laparoscopic) with systematic pelvic lymphadenectomy performed between January 2016 and January 2021; (3) Histology of squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; (4) Complete clinicopathological and follow-up data available through January 2026.

Exclusion criteria: (1) Neoadjuvant chemotherapy or radiotherapy before surgery; (2) Rare histological subtypes such as small cell neuroendocrine carcinoma, clear cell carcinoma, or carcinosarcoma; (3) Concurrent primary malignancy of another organ; (4) Follow-up less than 6 months or loss to follow-up.

Clinical data collection

A total of 840 eligible patients were included in this study, of whom 512 patients underwent laparoscopic radical hysterectomy and 328 underwent open radical hysterectomy. Data were collected using a standardized Case Report Form (CRF). Collected variables included demographics and general characteristics like age, menopausal status, smoking history, parity, and body mass index (BMI). Comorbidities and surgical risk were assessed using the Charlson Comorbidity Index (CCI; <1 vs. ≥1) and American Society of Anesthesiologist (ASA) grade (I-II vs. III). Pathological tumor features considered included FIGO stage (IA2 vs. IB1), maximum tumor diameter (<2 cm vs. ≥2 cm), histological type (adenocarcinoma/adenosquamous vs. others), tumor grade (G1-2 vs. G3), depth of stromal invasion (<50% vs. ≥50%), lymphovascular space invasion (LVSI; negative vs. positive), margin status (R0 vs. non-R0), lymph node status (negative vs. positive), parametrial invasion (no vs. yes), perineural invasion (PNI; negative vs. positive), and HPV status (positive vs. negative). Preoperative laboratory markers include hemoglobin (Hb), albumin (ALB), platelet count (PLT), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and squamous cell carcinoma antigen

(SCC-Ag). Information on surgical approach (laparoscopic vs. open) and adjuvant therapy, including adjuvant radiotherapy, chemotherapy, or concurrent chemoradiotherapy (no vs. yes) was also collected. To ensure data consistency across centers, the study co-ordinator checked all entries against a common variable definition manual prior to finalizing the data. Missing or questionable value ware cross-checked and confirmed with source records.

Laboratory methods

All preoperative laboratory tests were performed on fasting peripheral venous blood samples drawn within one week before surgery. Hb, PLT, and white blood cell differential counts (used to calculate NLR and PLR) were measured using an automated hematology analyzer (Sysmex XN-9000, Sysmex Corporation, Kobe, Japan). Serum ALB was determined by the bromocresol green method on an automated biochemistry analyzer (Beckman Coulter AU5800, Beckman Coulter Inc., Brea, CA, USA). SCC-Ag was measured by chemiluminescent microparticle immunoassay on the Architect i2000SR platform (Abbott Laboratories, Chicago, IL, USA) using assay kits provided by Abbott. Carbohydrate antigen 125 (CA125) and carcinoembryonic antigen (CEA) were measured by electrochemiluminescence immunoassay on the Cobas e 801 platform (Roche Diagnostics, Basel, Switzerland) using Roche-supplied reagent kits (CA125 kit, catalog no. 11776223 322; CEA kit, catalog no. 11731629 322). NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, and PLR was defined as the platelet count divided by the absolute lymphocyte count.

HPV testing was performed using a PCR-reverse dot blot hybridization method (HPV genotyping kit, Hybribio Ltd., Guangdong, China) capable of simultaneously detecting 23 HPV subtypes (14 high-risk and 9 low-risk types). HPV positivity was defined as detection of any high-risk HPV type.

Maximum tumor diameter was measured on preoperative pelvic magnetic resonance imaging (MRI). Depth of stromal invasion, LVSI, margin status, lymph node status, parametrial invasion, and perineural invasion (PNI) were assessed on postoperative pathology reports. Pathological specimens at each center were independently reviewed by two senior pathologists, with discrepancies resolved by consensus discussion. Before study initiation, pathologists from all participating centers received training based on a standardized interpretation protocol to ensure consistency in pathological diagnosis across sites.

Outcome measures

The primary endpoint was OS, defined as the time from surgery to death from any cause or last follow-up (censored at January 2026). Patients alive at last follow-up were censored.

The secondary endpoint was DFS, defined as the time from surgery to the first occurrence of disease recurrence (local or distant metastasis) or death from any cause. Patients alive without recurrence at last follow-up were censored.

Follow-up schedules included evaluations every 3 months for the first 2 years after surgery, every 6 months during years 3-5, and annually thereafter. Follow-up assessments included gynecological examination, cervical/vaginal cuff cytology, pelvic and abdominal ultrasound or CT/MRI, chest imaging, and tumor marker testing. Disease recurrence was confirmed by imaging and/or histopathological examination.

Statistical analysis

All statistical analyses were performed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 27.0 (IBM Corp., Armonk, NY, USA). A two-sided $P<0.05$ was considered statistically significant.

(1) Cohort partition and baseline comparisons: Patients were randomly divided into a training cohort (n=529) and a validation cohort (n=311) at a 7:3 ratio. Categorical variables were presented as frequencies (percentages) and compared using the chi-square test or Fisher's exact test. Normally distributed continuous variables were presented as mean ± standard deviation ($\bar{x} \pm s$) and compared using independent-samples t-tests. Non-normally distributed continuous variables were presented as median [interquartile range] (M [Q_1, Q_3]) and compared using the Mann-Whitney U test.

(2) Collinearity diagnostics: Multicollinearity among the 27 covariates in the training cohort was assessed. Spearman correlation analysis was used for continuous variables, with $|r|>0.5$ indicating high collinearity. Variance inflation factors (VIF) were computed for all variables, with VIF≥5 considered indicative of multicollinearity.

(3) Propensity score estimation and IPTW: In the training cohort, a logistic regression model was fitted with surgical approach (laparoscopic vs. open) as the dependent variable and all 27 covariates as independent variables to estimate the propensity score (PS). IPTW was applied to balance the groups, with weights of 1/PS for the laparoscopic group and 1/(1-PS) for the open group. Balance was evaluated using standardized mean differences (SMD), with SMD<0.1 considered adequate for all covariates. PS distributions and IPTW weight distributions were visualized using kernel density plots and histograms. The IPTW procedure was independently replicated in the validation cohort, with weights trimmed at the 99th percentile to prevent extreme values.

(4) Proportional hazards assumption testing: The proportional hazards (PH) assumption for Cox regression models in the training cohort was tested using the Schoenfeld residuals, supplemented by visual assessment of locally estimated scatterplot smoothing (LOESS) curves. Variables with borderline *P* values (near 0.05) were evaluated jointly with the global test result and residual plots.

(5) Cox regression analysis: Unweighted and IPTW-weighted univariable Cox regression analyses were performed in the training cohort. In the unweighted analysis, variables with P<0.1 in univariable analysis were entered into the multivariable Cox regression model. In the IPTW-weighted analysis, variables with P<0.05 were included in the multivariable model. Results were reported as β coefficients, hazard ratios (HR), and 95% confidence intervals (CI).

(6) Kaplan-Meier survival analysis: Kaplan-Meier curves were constructed and compared between groups using the log-rank test, both before and after IPTW weighting. Stratified survival analyses were performed for surgical approach and for variables identified as significant in multivariable analysis.

(7) Subgroup analysis: Subgroup analyses were performed for eight key variables: age, FIGO stage, tumor size, histological type, depth of stromal invasion, LVSI, lymph node status, and adjuvant therapy. Analyses were performed both before and after IPTW weighting. Heterogeneity was assessed by including interaction terms between surgical approach and each subgroup variable in the Cox regression model (P_interaction <0.05 indicated significant interaction). Given the exploratory nature of these analyses, no correction for multiple comparisons (e.g., Bonferroni correction) was applied, and the results should be interpreted accordingly.

(8) Sensitivity analysis: Four alternative methods were used to test the robustness of the primary IPTW findings: (a) trimmed IPTW (weights truncated at the 1st-99th percentiles); (b) overlap weights estimating the average treatment effect among the overlap population (ATO); (c) 1:1 PSM with a caliper of 0.2 times the standard deviation of the PS logit; (d) multivariable Cox regression including all 27 covariates and surgical approach. HR point estimates and 95% CIs from all five methods (including the original IPTW) were summarized in forest plots.

(9) Validation cohort: An independent logistic regression PS model and IPTW weights were constructed in the validation cohort. Covariate balance before and after weighting was assessed. IPTW-weighted Kaplan-Meier survival curves were plotted for both cohorts, and forest plots were used to compare the direction and magnitude of treatment effects across the overall population and key subgroups between the two cohorts.

Results

Patient enrollment and cohort composition

A total of 840 patients with FIGO stage IA2-IB1 cervical cancer were enrolled, including 512 patients undergoing laparoscopic radical hysterectomy and 328 undergoing open surgery. Patients were randomly assigned to a training cohort (n=529) and a validation cohort (n=311) at approximately a 7:3 ratio. This radon allocation achieved good balance, with no significant difference in the distribution of surgical approaches between cohorts (P=0.458).

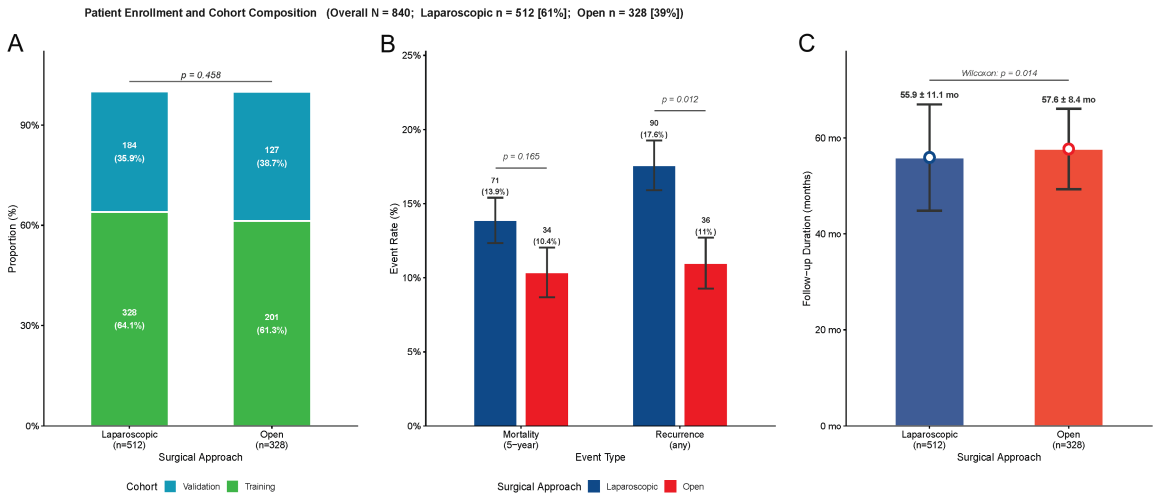


Figure 1. Patient enrollment and cohort composition by surgical approach. A. Training and validation cohort distribution stratified by surgical approach. B. Comparison of 5-year mortality and recurrence rates between the laparoscopic and open surgery groups. C. Comparison of mean follow-up duration between the laparoscopic and open surgery groups. Notes: OS, Overall Survival; DFS, Disease-Free Survival.

Regarding clinical outcomes, the 5-year mortality rate did not differ significantly between the two groups (P=0.165); however, the recurrence rate was significantly higher in the laparoscopic group (P=0.012). Median follow-up was significantly longer in the open group (P=0.014) (**Figure 1**).

Baseline characteristics of the training and validation cohorts

No significant differences were found between the training and validation cohorts in terms of baseline characteristics, including age (P=0.126), menopausal status (P=0.731), smoking history (P=0.139), parity (P=0.587), CCI category (P=0.550), ASA grade (P=0.771), FIGO stage (P=0.975), tumor size (P=0.870), histological type (P=0.372), tumor grade (P=0.662), depth of stromal invasion (P=0.121), LVSI (P=0.071), margin status (P=0.936), lymph node status (P=0.257), parametrial invasion (P=0.490), PNI (P=0.939), HPV status (P=0.808), adjuvant therapy (P=0.251), BMI (P=0.215), hemoglobin (P=0.230), albumin (P=0.460), platelet count (P=0.050), NLR (P=0.586), PLR (P=0.659), SCC-Ag (P=0.131), CA125 (P=0.937), and CEA (P=0.681). These results confirm that the two cohorts were well balanced at baseline, supporting valid model construction and verification (**Table 1**).

Propensity score estimation and IPTW balancing assessment

In the training cohort, a logistic regression PS model was constructed using all 27 covariates, and IPTW was applied to balance the two surgical groups. Before weighting, several covariates exceeded the SMD threshold of 0.1, including PS (SMD=0.821), albumin (SMD=0.209), tumor size (SMD=0.152), adjuvant therapy (SMD=0.132), SCC-Ag (SMD=0.101), and CCI category (SMD=0.100), indicating substantial baseline imbalance. After IPTW, all covariates achieved SMD<0.1, with the largest post-weighting SMD observed for CA125 (SMD=0.066), showing effective removal of inter-group confounding. The effective sample sizes after weighting were 294.31 for the laparoscopic group and 151.34 for the open group.

PS distributions showed adequate overlap between groups after weighting, and IPTW weight distributions were concentrated in the low-value range with no extreme weights (**Figure 2**). The PS model demonstrated acceptable discrimination, with a C-statistic (AUC) of 0.717 (95% CI: 0.671-0.762) in the training cohort and 0.789 (95% CI: 0.739-0.840) in the validation cohort.

Table 1. Baseline characteristics of patients in the training and validation cohorts

Variable	Total	Training cohort (n=529)	Validation cohort (n=311)	Statistic	*P* value
Age (years)				2.337	0.126
≥45 years (ref)	369 (43.93%)	243 (45.94%)	126 (40.51%)		
<45 years	471 (56.07%)	286 (54.06%)	185 (59.49%)		
Menopausal status				0.118	0.731
Premenopausal (ref)	675 (80.36%)	427 (80.72%)	248 (79.74%)		
Postmenopausal	165 (19.64%)	102 (19.28%)	63 (20.26%)		
Smoking history				2.187	0.139
No (ref)	795 (94.64%)	496 (93.76%)	299 (96.14%)		
Yes	45 (5.36%)	33 (6.24%)	12 (3.86%)		
Parity				0.296	0.587
Nulliparous (ref)	83 (9.88%)	50 (9.45%)	33 (10.61%)		
≥1 delivery	757 (90.12%)	479 (90.55%)	278 (89.39%)		
CCI				0.357	0.550
<1 (ref)	623 (74.17%)	396 (74.86%)	227 (72.99%)		
≥1	217 (25.83%)	133 (25.14%)	84 (27.01%)		
ASA grade				0.085	0.771
I-II (ref)	720 (85.71%)	452 (85.44%)	268 (86.17%)		
III	120 (14.29%)	77 (14.56%)	43 (13.83%)		
FIGO stage				0.001	0.975
IA2 (ref)	149 (17.74%)	94 (17.77%)	55 (17.68%)		
IB1	691 (82.26%)	435 (82.23%)	256 (82.32%)		
Tumor size				0.027	0.870
<2 cm (ref)	562 (66.90%)	355 (67.11%)	207 (66.56%)		
≥2 cm	278 (33.10%)	174 (32.89%)	104 (33.44%)		
Histology				0.797	0.372
Adenocarcinoma/Adenosquamous (ref)	173 (20.60%)	114 (21.55%)	59 (18.97%)		
Other	667 (79.40%)	415 (78.45%)	252 (81.03%)		
Tumor grade				0.192	0.662
G1-G2 (ref)	633 (75.36%)	396 (74.86%)	237 (76.21%)		
G3	207 (24.64%)	133 (25.14%)	74 (23.79%)		
Deep stromal invasion				2.408	0.121
<1/2 (ref)	620 (73.81%)	400 (75.61%)	220 (70.74%)		
≥1/2	220 (26.19%)	129 (24.39%)	91 (29.26%)		

LVSI				3.267	0.071
Negative (ref)	576 (68.57%)	351 (66.35%)	225 (72.35%)		
Positive	264 (31.43%)	178 (33.65%)	86 (27.65%)		
Surgical margin				0.006	0.936
R0 (ref)	807 (96.07%)	508 (96.03%)	299 (96.14%)		
Non-R0	33 (3.93%)	21 (3.97%)	12 (3.86%)		
Lymph node status				1.283	0.257
Negative (ref)	757 (90.12%)	472 (89.22%)	285 (91.64%)		
Positive	83 (9.88%)	57 (10.78%)	26 (8.36%)		
Parametrial invasion				0.476	0.490
No (ref)	808 (96.19%)	507 (95.84%)	301 (96.78%)		
Yes	32 (3.81%)	22 (4.16%)	10 (3.22%)		
PNI				0.006	0.939
Negative (ref)	784 (93.33%)	494 (93.38%)	290 (93.25%)		
Positive	56 (6.67%)	35 (6.62%)	21 (6.75%)		
HPV				0.059	0.808
Positive (ref)	735 (87.50%)	464 (87.71%)	271 (87.14%)		
Negative	105 (12.50%)	65 (12.29%)	40 (12.86%)		
Adjuvant therapy				1.315	0.251
No (ref)	550 (65.48%)	354 (66.92%)	196 (63.02%)		
Yes	290 (34.52%)	175 (33.08%)	115 (36.98%)		
BMI (kg/m^2)	23.39 [21.38, 25.59]	23.48 [21.47, 25.75]	23.27 [21.34, 25.25]	1.239	0.215
Hemoglobin (g/L)	124.00 [115.00, 131.00]	123.00 [115.00, 131.00]	125.00 [115.00, 133.00]	1.201	0.230
Albumin (g/L)	40.94±3.92	41.02±4.01	40.81±3.77	0.739	0.460
Platelet (×10^9/L)	268.39±62.14	265.17±59.72	273.87±65.79	-1.962	0.050
NLR	2.37 [1.49, 3.13]	2.37 [1.45, 3.08]	2.37 [1.53, 3.21]	0.545	0.586
PLR	140.47±58.55	139.78±58.12	141.63±59.34	-0.441	0.659
SCC-Ag (ng/mL)	2.12 [1.35, 2.99]	2.08 [1.28, 2.89]	2.19 [1.42, 3.14]	1.512	0.131
CA125 (U/mL)	18.35 [12.53, 24.63]	18.71 [12.57, 24.79]	18.06 [12.43, 24.30]	0.079	0.937
CEA (ng/mL)	2.24 [1.53, 2.99]	2.27 [1.52, 2.95]	2.21 [1.57, 3.02]	0.411	0.681

Note: BMI, Body Mass Index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion; PNI, Perineural Invasion; HPV, Human Papillomavirus; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SCC-Ag, Squamous Cell Carcinoma Antigen; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen.

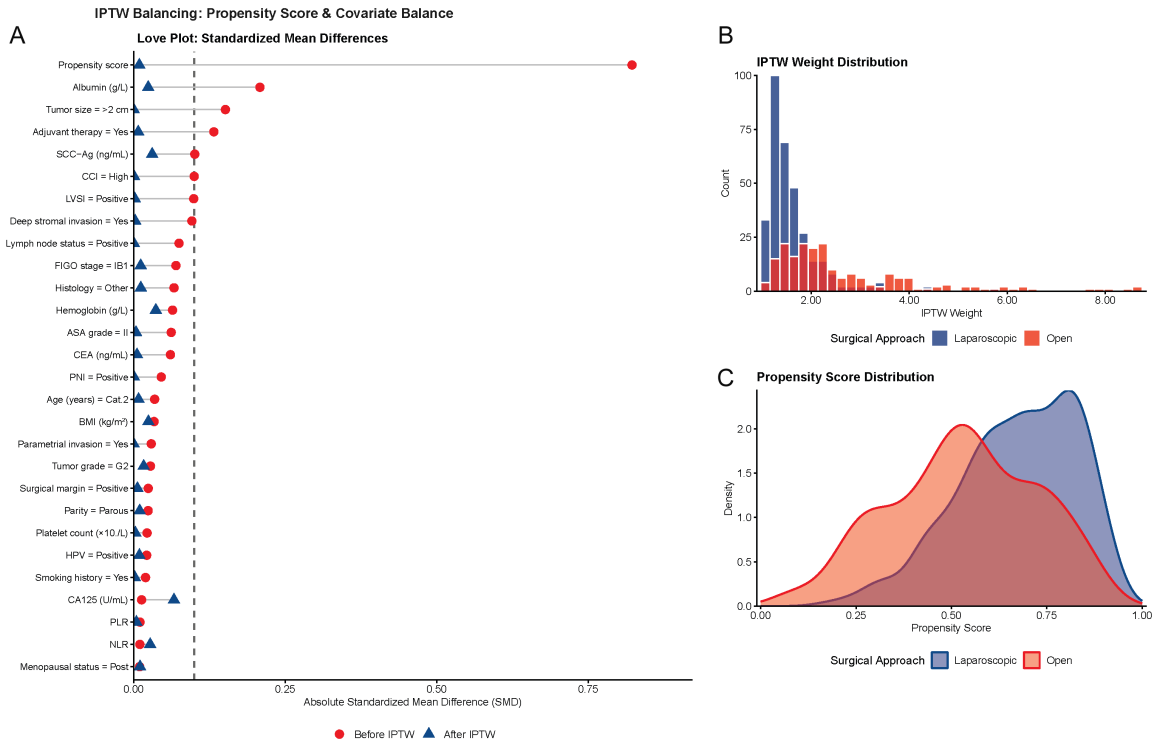


Figure 2. IPTW balancing diagnostics in the training cohort. A. Love plot displaying the absolute standardized mean differences for all covariates before and after IPTW, with the dashed line indicating the 0.1 threshold. B. Distribution of IPTW weights stratified by surgical approach. C. Kernel density plots of propensity scores for the laparoscopic and open surgery groups. Notes: IPTW, Inverse Probability of Treatment Weighting; SMD, Standardized Mean Difference; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion; PNI, Perineural Invasion; HPV, Human Papillomavirus; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SCC-Ag, Squamous Cell Carcinoma Antigen; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen; BMI, Body Mass Index.

IPTW-weighted baseline characteristics in the training cohort

After IPTW weighting, no statistically significant differences remained between the laparoscopic and open groups for any baseline variable (all P>0.05). Among continuous variables, BMI (P=0.813), Hb (P=0.716), ALB (P=0.820), PLT (P=0.976), NLR (P=0.964), PLR (P=0.967), SCC-Ag (P=0.384), CA125 (P=0.544), and CEA (P=0.963) were all well balanced. Among categorical variables, age (P=0.787), menopausal status (P=0.661), smoking history (P=0.887), parity (P=0.580), CCI (P=0.977), ASA grade (P=0.852), FIGO stage (P=0.623), tumor size (P=0.995), histological type (P=0.635), tumor grade (P=0.524), depth of stromal invasion (P=0.917), LVSI (P=0.945), margin status (P=0.614), lymph node status (P=0.985), parametrial invasion (P=0.994), PNI (P=0.967), HPV (P=0.638), and adjuvant therapy (P=0.789) showed balanced distributions as well. These findings confirmed that IPTW effectively eliminated baseline confounding, producing a pseudo-randomized sample suitable for causal inference (**Table 2**).

Collinearity diagnostics

Prior to model development, multicollinearity was assessed among all 27 covariates in the training cohort. Spearman correlation analysis of the 11 continuous variables showed a maximum absolute correlation coefficient of 0.089, observed between CEA and PLR, with no variable pair exceeding the |r|>0.5 threshold, suggesting no high collinearity among continuous variables. VIF for all 27 covariates were below the cutoff of 5, with the maximum VIF of 1.20 for the FIGO stage and VIF of 1.03 for both menopausal status and HPV. No covariate simultaneously met the criteria of |r|>0.5 and VIF≥5, indicating absence of significant multicollinearity. Hence, all covariates were retained for subsequent multivariable modeling (**Figure 3**).

Table 2. IPTW-weighted baseline characteristics of the training cohort by surgical approach

Variable	Overall	Laparoscopic (weighted)	Open (weighted)	Statistic	*P*-value
BMI (kg/m^2)	23.61±3.41	23.65±3.23	23.57±3.57	0.237	0.813
Hemoglobin (g/L)	122.72±12.93	122.96±11.81	122.48±13.94	0.364	0.716
Albumin (g/L)	41.06±4.10	41.11±3.84	41.02±4.33	0.228	0.820
Platelet (×10^9/L)	264.50±60.51	264.59±57.36	264.40±63.43	0.031	0.976
NLR	2.37 (1.72)	2.37 [1.46, 3.10]	2.35 [1.39, 3.12]	-	0.964
PLR	140.20±60.61	140.06±56.18	140.34±64.65	-0.042	0.967
SCC-Ag (ng/mL)	2.02 (1.66)	2.12 [1.41, 2.88]	1.90 [1.04, 2.88]	-	0.384
CA125 (U/mL)	19.14 (13.38)	18.57 [12.74, 24.45]	19.94 [11.49, 26.56]	-	0.544
CEA (ng/mL)	2.26 (1.49)	2.19 [1.59, 2.92]	2.31 [1.33, 3.14]	-	0.963
Age (years)				0.073	0.787
≥45 years (ref)	487.2 (45.98%)	238.4 (45.56%)	248.9 (46.39%)		
<45 years	572.4 (54.02%)	284.8 (54.44%)	287.6 (53.61%)		
Menopausal status				0.192	0.661
Premenopausal (ref)	852.1 (80.41%)	423.5 (80.96%)	428.6 (79.89%)		
Postmenopausal	207.5 (19.59%)	99.6 (19.04%)	107.9 (20.11%)		
Smoking history				0.020	0.887
No (ref)	992.4 (93.66%)	490.5 (93.77%)	501.9 (93.55%)		
Yes	67.2 (6.34%)	32.6 (6.23%)	34.6 (6.45%)		
Parity				0.306	0.580
Nulliparous (ref)	104.9 (9.90%)	49.1 (9.39%)	55.8 (10.40%)		
≥1 delivery	954.7 (90.10%)	474.0 (90.61%)	480.7 (89.60%)		
CCI				0.001	0.977
<1 (ref)	787.6 (74.33%)	388.6 (74.29%)	399.0 (74.37%)		
≥1	272.0 (25.67%)	134.5 (25.71%)	137.5 (25.63%)		
ASA grade				0.035	0.852
I-II (ref)	910.0 (85.88%)	450.3 (86.08%)	459.7 (85.68%)		
III	149.6 (14.12%)	72.8 (13.92%)	76.8 (14.32%)		
FIGO stage				0.241	0.623
IA2 (ref)	198.9 (18.78%)	95.1 (18.18%)	103.8 (19.36%)		
IB1	860.7 (81.22%)	428.0 (81.82%)	432.6 (80.64%)		
Tumor size				0.000	0.995
<2 cm (ref)	721.4 (68.08%)	356.2 (68.09%)	365.2 (68.07%)		
≥2 cm	338.2 (31.92%)	167.0 (31.91%)	171.3 (31.93%)		
Histology				0.226	0.635
Adenocarcinoma/Adenosquamous (ref)	227.0 (21.42%)	115.2 (22.03%)	111.8 (20.83%)		
Other	832.6 (78.58%)	407.9 (77.97%)	424.7 (79.17%)		
Tumor grade				0.406	0.524
G1-G2 (ref)	806.7 (76.13%)	393.9 (75.29%)	412.9 (76.96%)		
G3	252.9 (23.87%)	129.3 (24.71%)	123.6 (23.04%)		
Deep stromal invasion				0.011	0.917
<1/2 (ref)	797.7 (75.28%)	394.5 (75.42%)	403.1 (75.14%)		
≥1/2	262.0 (24.72%)	128.6 (24.58%)	133.4 (24.86%)		
LVSI				0.005	0.945
Negative (ref)	705.8 (66.61%)	347.9 (66.51%)	357.9 (66.71%)		
Positive	353.8 (33.39%)	175.2 (33.49%)	178.6 (33.29%)		
Surgical margin				0.255	0.614
R0 (ref)	1012.3 (95.54%)	498.1 (95.21%)	514.2 (95.85%)		
Non-R0	47.3 (4.46%)	25.0 (4.79%)	22.2 (4.15%)		
Lymph node status				0.000	0.985
Negative (ref)	953.1 (89.94%)	470.6 (89.96%)	482.4 (89.93%)		
Positive	106.5 (10.06%)	52.5 (10.04%)	54.0 (10.07%)		

Parametrial invasion				0.000	0.994
No (ref)	1018.9 (96.16%)	503.1 (96.16%)	515.9 (96.16%)		
Yes	40.7 (3.84%)	20.1 (3.84%)	20.6 (3.84%)		
PNI				0.002	0.967
Negative (ref)	991.5 (93.57%)	489.7 (93.60%)	501.8 (93.54%)		
Positive	68.1 (6.43%)	33.5 (6.40%)	34.6 (6.46%)		
HPV				0.222	0.638
Positive (ref)	924.8 (87.28%)	459.1 (87.77%)	465.7 (86.80%)		
Negative	134.8 (12.72%)	64.0 (12.23%)	70.8 (13.20%)		
Adjuvant therapy				0.072	0.789
No (ref)	717.3 (67.70%)	356.2 (68.08%)	361.1 (67.32%)		
Yes	342.3 (32.30%)	167.0 (31.92%)	175.3 (32.68%)		

Note: IPTW, Inverse Probability of Treatment Weighting; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion; PNI, Perineural Invasion; HPV, Human Papillomavirus; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SCC-Ag, Squamous Cell Carcinoma Antigen; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen.

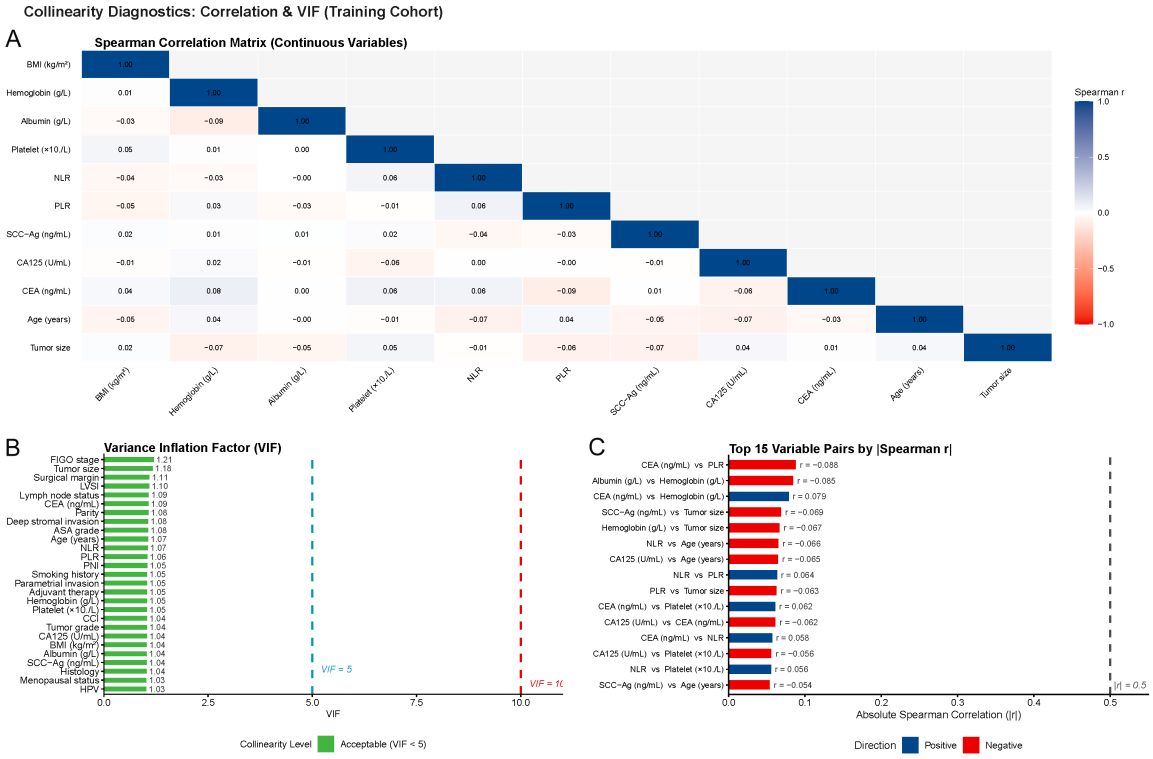


Figure 3. Collinearity diagnostics of covariates in the training cohort. A. Spearman correlation heatmap of the continuous variables, with correlation coefficients displayed in each cell. B. Variance inflation factor values for all 27 covariates, with dashed lines indicating VIF thresholds of 5 and 10. C. Top 15 variable pairs ranked by the absolute Spearman correlation coefficient, with the dashed line indicating the |r|=0.5 threshold. Notes: VIF, Variance Inflation Factor; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SCC-Ag, Squamous Cell Carcinoma Antigen; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion; PNI, Perineural Invasion; HPV, Human Papillomavirus.

Proportional hazards assumption testing

The proportional hazards (PH) assumption for Cox regression models in the training cohort was assessed using Schoenfeld residuals. In the OS model, only surgical approach had a borderline *P* value (P=0.049) among the 28 covariates; the remaining 27 variables all satis-

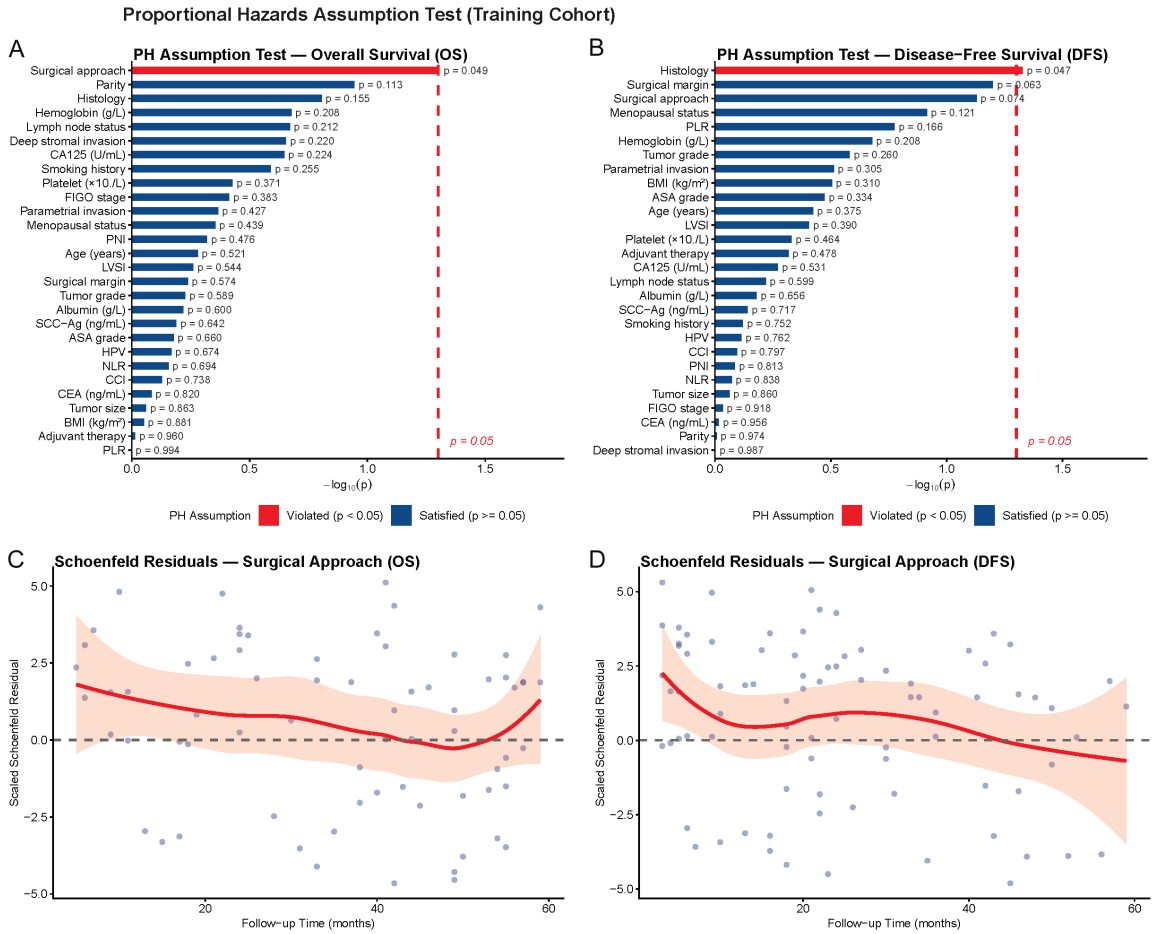


Figure 4. Proportional hazards assumption test for Cox regression models in the training cohort. A. Bar plot of -$\log_{10}$(P) values from the Schoenfeld residuals test for each covariate in the OS model, with the dashed line indicating the P=0.05 threshold. B. Bar plot of -$\log_{10}$(P) values from the Schoenfeld residuals test for each covariate in the DFS model. C. Schoenfeld residual plot for surgical approach over follow-up time in the OS model, with LOESS smoothing curve and 95% confidence band. D. Schoenfeld residual plot for surgical approach over follow-up time in the DFS model. Notes: PH, Proportional Hazards; OS, Overall Survival; DFS, Disease-Free Survival; LOESS, Locally Estimated Scatterplot Smoothing; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion; PNI, Perineural Invasion; HPV, Human Papillomavirus; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SCC-Ag, Squamous Cell Carcinoma Antigen; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen; BMI, Body Mass Index.

fied the PH assumption (all P>0.05). The global test indicated that the OS model as a whole met the PH assumption (χ^2=20.948, df=28, P=0.828). In the DFS model, only histological type had a borderline *P* value (P=0.047), with all other variables satisfying the assumption (all P>0.05). The global test similarly supported the PH assumption for the DFS model as a whole (χ^2=27.188, df=28, P=0.508). Schoenfeld residual scatter plots for surgical approach (OS model) and histological type (DFS model) showed LOESS smoothing curves fluctuating around the zero line without obvious time-dependent trends. Combined with the global test results, these marginal violations were judged not to compromise the overall validity of the Cox regression models (**Figure 4**).

Unadjusted Cox regression analysis for overall survival

In the training cohort, unadjusted univariable Cox regression was performed for all 28 covariates. Histological type (P=0.021), depth of stromal invasion (P<0.001), LVSI (P<0.001), margin status (P<0.001), and lymph node sta-

Table 3. Unadjusted univariable and multivariable Cox regression analysis for overall survival in the training cohort

Variable	Univariable			Multivariable		
	Beta	P	HR_95 CI	Beta	P	HR_95 CI
Surgical approach						
Open (ref)			1.000 (ref)			
Laparoscopic	0.042	0.865	1.043 (0.641-1.697)			
BMI (kg/m^2)	-0.006	0.869	0.994 (0.926-1.067)			
Hemoglobin (g/L)	-0.015	0.110	0.985 (0.967-1.003)			
Albumin (g/L)	0	0.991	1 (0.943-1.061)			
Platelet (×10^9/L)	-0.002	0.253	0.998 (0.994-1.002)			
NLR	0.018	0.857	1.018 (0.835-1.241)			
PLR	-0.001	0.586	0.999 (0.995-1.003)			
SCC-Ag (ng/mL)	-0.067	0.512	0.935 (0.766-1.142)			
CA125 (U/mL)	0.011	0.429	1.011 (0.984-1.04)			
CEA (ng/mL)	-0.097	0.395	0.907 (0.725-1.135)			
Age (years)						
≥45 years (ref)			1.000 (ref)			
<45 years	0.166	0.497	1.18 (0.732-1.903)			
Menopausal status						
Premenopausal (ref)			1.000 (ref)			
Postmenopausal	-0.004	0.989	0.996 (0.545-1.821)			
Smoking history						
No (ref)			1.000 (ref)			
Yes	0.367	0.391	1.443 (0.624-3.333)			
Parity						
Nulliparous (ref)			1.000 (ref)			
≥1 delivery	-0.372	0.298	0.689 (0.342-1.389)			
CCI						
<1 (ref)			1.000 (ref)			
≥1	-0.601	0.068	0.548 (0.288-1.045)			
ASA grade						
I-II (ref)			1.000 (ref)			
III	-0.13	0.716	0.878 (0.436-1.769)			
FIGO stage						
IA2 (ref)			1.000 (ref)			
IB1	0.25	0.465	1.284 (0.657-2.51)			
Tumor size						
<2 cm (ref)			1.000 (ref)			
≥2 cm	0.42	0.085	1.522 (0.943-2.454)			
Histology						
Adenocarcinoma/Adenosquamous (ref)			1.000 (ref)			
Other	-0.594	0.021	0.552 (0.333-0.916)	-0.512	0.049	0.599 (0.36-0.997)
Tumor grade						
G1-G2 (ref)			1.000 (ref)			
G3	-0.115	0.687	0.891 (0.51-1.559)			
Deep stromal invasion						
<1/2 (ref)			1.000 (ref)			
≥1/2	0.865	<0.001	2.374 (1.472-3.83)	0.743	0.003	2.102 (1.298-3.404)
LVSI						
Negative (ref)			1.000 (ref)			
Positive	0.822	<0.001	2.274 (1.418-3.648)	0.649	0.009	1.913 (1.176-3.112)

Surgical margin						
R0 (ref)			1.000 (ref)			
Non-R0	1.718	<0.001	5.571 (2.847-10.903)	1.138	0.002	3.12 (1.535-6.343)
Lymph node status						
Negative (ref)			1.000 (ref)			
Positive	1.272	<0.001	3.569 (2.103-6.055)	0.975	<0.001	2.652 (1.53-4.597)
Parametrial invasion						
No (ref)			1.000 (ref)			
Yes	0.062	0.917	1.064 (0.334-3.383)			
PNI						
Negative (ref)			1.000 (ref)			
Positive	0.085	0.855	1.089 (0.438-2.705)			
HPV						
Positive (ref)			1.000 (ref)			
Negative	-0.081	0.829	0.922 (0.441-1.927)			
Adjuvant therapy						
No (ref)			1.000 (ref)			
Yes	0.081	0.749	1.084 (0.661-1.78)			

Note: OS, Overall Survival; HR, Hazard Ratio;95% CI, 95% Confidence Interval; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion; PNI, Perineural Invasion; HPV, Human Papillomavirus; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SCC-Ag, Squamous Cell Carcinoma Antigen; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen.

tus (P<0.001) were significantly associated with OS. Surgical approach (P=0.865) and the remaining 21 variables showed no significant association with OS (all P>0.05). Variables with P<0.1 in univariable analysis were entered into the multivariable Cox model. In the multivariable analysis, depth of stromal invasion ≥1/2 (P=0.005), positive LVSI (P=0.009), non-R0 margins (P<0.001), and positive lymph nodes (P<0.001) were identified as independent risk factors for OS, whereas histological type did not reach statistical significance (P=0.064). Kaplan-Meier curves further illustrated the stratified OS differences for these significant variables. The unadjusted Kaplan-Meier curve for surgical approach showed no significant OS difference between the laparoscopic and open groups (P=0.865) (**Table 3**; **Figure 5**).

IPTW-weighted Cox regression analysis for overall survival

After IPTW weighting, weighted Cox regression was performed in the training cohort. In univariable analysis, histological type (P=0.011), depth of stromal invasion (P=0.003), LVSI (P< 0.001), margin status (P<0.001), and lymph node status (P<0.001) remained significantly associated with OS. Surgical approach did not reach statistical significance in the weighted univariable Cox model (P=0.141). However, the IPTW-weighted Kaplan-Meier curves showed significantly lower OS in the laparoscopic group compared with the open group (P=0.024).

In the multivariable IPTW-weighted model, non-adenocarcinoma/adenosquamous histological type was identified as an independent protective factor for OS (P=0.027). Independent risk factors included depth of stromal invasion ≥1/2 (P=0.022), positive LVSI (P=0.002), non-R0 margins (P=0.012), and positive lymph nodes (P<0.001). Surgical approach was not an independent predictor after adjustment for these pathological risk factors (all P>0.05) (**Table 4**; **Figure 6**).

Unadjusted Cox regression analysis for disease-free survival

Unadjusted univariable Cox regression was performed for all 28 covariates to assess their association with DFS. Depth of stromal invasion (P=0.001), LVSI (P=0.004), margin status (P<0.001), and lymph node status (P<0.001) were significantly associated with DFS. Surgical approach (P=0.239) and the remaining 23 variables were not significantly associated with DFS (all P>0.05).

The four significant variables were entered into the multivariable model, and all four remained

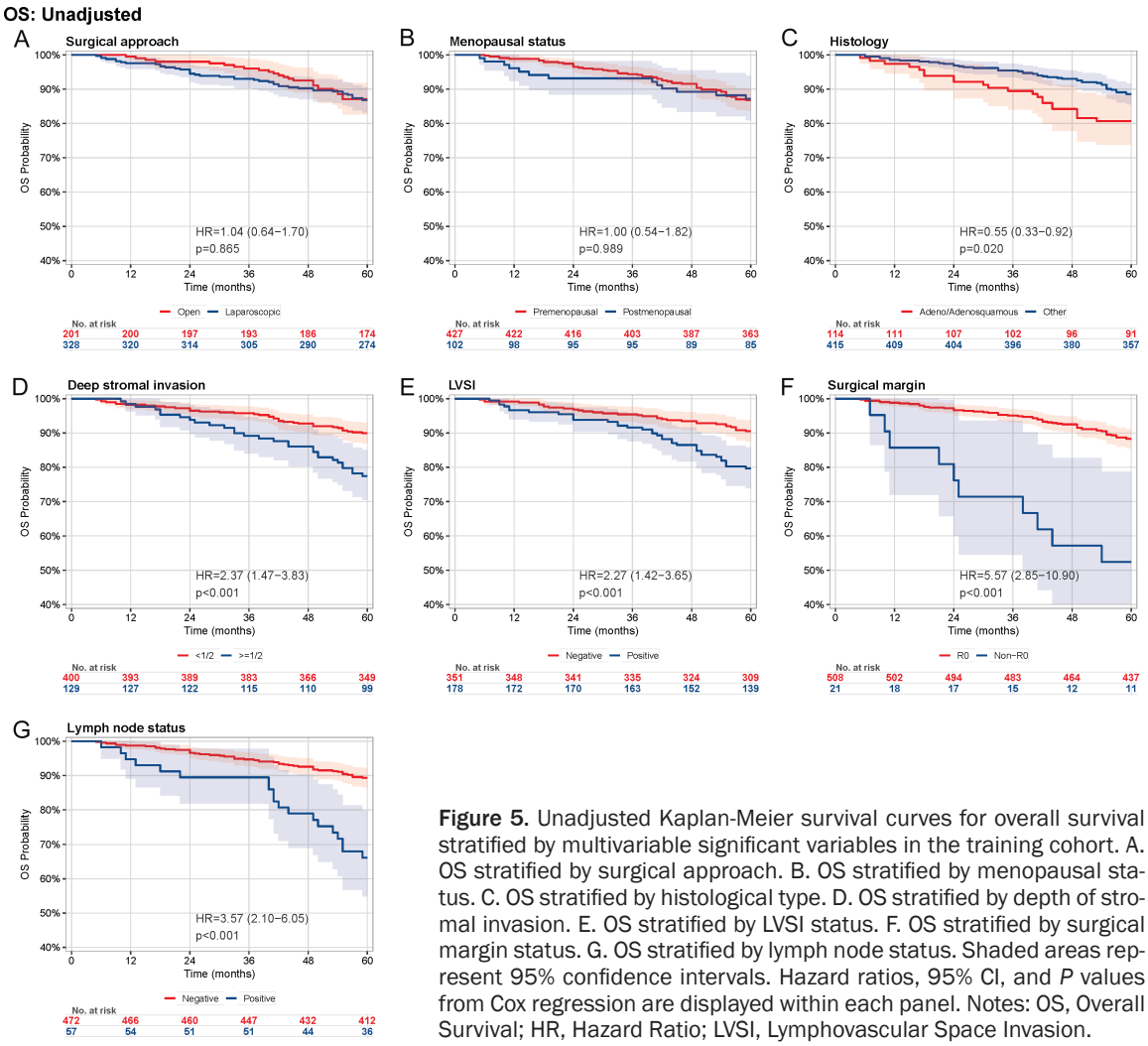


Figure 5. Unadjusted Kaplan-Meier survival curves for overall survival stratified by multivariable significant variables in the training cohort. A. OS stratified by surgical approach. B. OS stratified by menopausal status. C. OS stratified by histological type. D. OS stratified by depth of stromal invasion. E. OS stratified by LVSI status. F. OS stratified by surgical margin status. G. OS stratified by lymph node status. Shaded areas represent 95% confidence intervals. Hazard ratios, 95% CI, and *P* values from Cox regression are displayed within each panel. Notes: OS, Overall Survival; HR, Hazard Ratio; LVSI, Lymphovascular Space Invasion.

Table 4. IPTW-weighted univariable and multivariable Cox regression analysis for overall survival in the training cohort

Variable	Univariable			Multivariable		
	Beta	P	HR_95 CI	Beta	P	HR_95 CI
Surgical approach						
Open (ref)			1.000 (ref)			
Laparoscopic	0.395	0.141	1.484 (1.05-2.097)			
BMI (kg/m^2)	-0.014	0.703	0.986 (0.937-1.037)			
Hemoglobin (g/L)	-0.014	0.172	0.986 (0.974-0.999)			
Albumin (g/L)	-0.018	0.545	0.982 (0.942-1.024)			
Platelet (×10^9/L)	-0.002	0.409	0.998 (0.995-1.001)			
NLR	0.072	0.446	1.074 (0.936-1.233)			
PLR	-0.001	0.573	0.999 (0.996-1.002)			
SCC-Ag (ng/mL)	0.01	0.899	1.01 (0.878-1.162)			
CA125 (U/mL)	0.003	0.876	1.003 (0.984-1.022)			
CEA (ng/mL)	-0.106	0.331	0.899 (0.767-1.054)			
Age (years)						
≥45 years (ref)			1.000 (ref)			
<45 years	0.314	0.235	1.369 (0.964-1.943)			

Menopausal status						
Premenopausal (ref)			1.000 (ref)			
Postmenopausal	0.071	0.835	1.074 (0.703-1.64)			
Smoking history						
No (ref)			1.000 (ref)			
Yes	0.358	0.444	1.431 (0.782-2.62)			
Parity						
Nulliparous (ref)			1.000 (ref)			
≥1 delivery	-0.359	0.365	0.698 (0.424-1.151)			
CCI						
<1 (ref)			1.000 (ref)			
≥1	-0.627	0.089	0.534 (0.335-0.852)			
ASA grade						
I-II (ref)			1.000 (ref)			
III	0.178	0.636	1.195 (0.753-1.897)			
FIGO stage						
IA2 (ref)			1.000 (ref)			
IB1	0.626	0.096	1.871 (1.088-3.215)			
Tumor size						
<2 cm (ref)			1.000 (ref)			
≥2 cm	0.495	0.060	1.641 (1.162-2.318)			
Histology						
Adenocarcinoma/Adenosquamous (ref)			1.000 (ref)			
Other	-0.733	0.011	0.481 (0.336-0.688)	-0.641	0.025	0.527 (0.367-0.756)
Tumor grade						
G1-G2 (ref)			1.000 (ref)			
G3	0.154	0.614	1.167 (0.792-1.718)			
Deep stromal invasion						
<1/2 (ref)			1.000 (ref)			
≥1/2	0.785	0.003	2.193 (1.549-3.106)	0.638	0.017	1.892 (1.33-2.69)
LVSI						
Negative (ref)			1.000 (ref)			
Positive	1.003	<0.001	2.725 (1.932-3.845)	0.835	0.002	2.304 (1.615-3.286)
Surgical margin						
R0 (ref)			1.000 (ref)			
Non-R0	1.612	<0.001	5.011 (3.107-8.083)	0.938	0.016	2.555 (1.542-4.234)
Lymph node status						
Negative (ref)			1.000 (ref)			
Positive	1.463	<0.001	4.317 (2.962-6.291)	1.201	<0.001	3.322 (2.255-4.895)
Parametrial invasion						
No (ref)			1.000 (ref)			
Yes	0.403	0.496	1.497 (0.704-3.185)			
PNI						
Negative (ref)			1.000 (ref)			
Positive	-0.056	0.909	0.945 (0.465-1.92)			
HPV						
Positive (ref)			1.000 (ref)			
Negative	-0.181	0.650	0.834 (0.484-1.438)			
Adjuvant therapy						
No (ref)			1.000 (ref)			
Yes	0.064	0.815	1.066 (0.742-1.53)			

Note: IPTW, Inverse Probability of Treatment Weighting; OS, Overall Survival; HR, Hazard Ratio; 95% CI, 95% Confidence Interval; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion; PNI, Perineural Invasion; HPV, Human Papillomavirus; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SCC-Ag, Squamous Cell Carcinoma Antigen; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen.

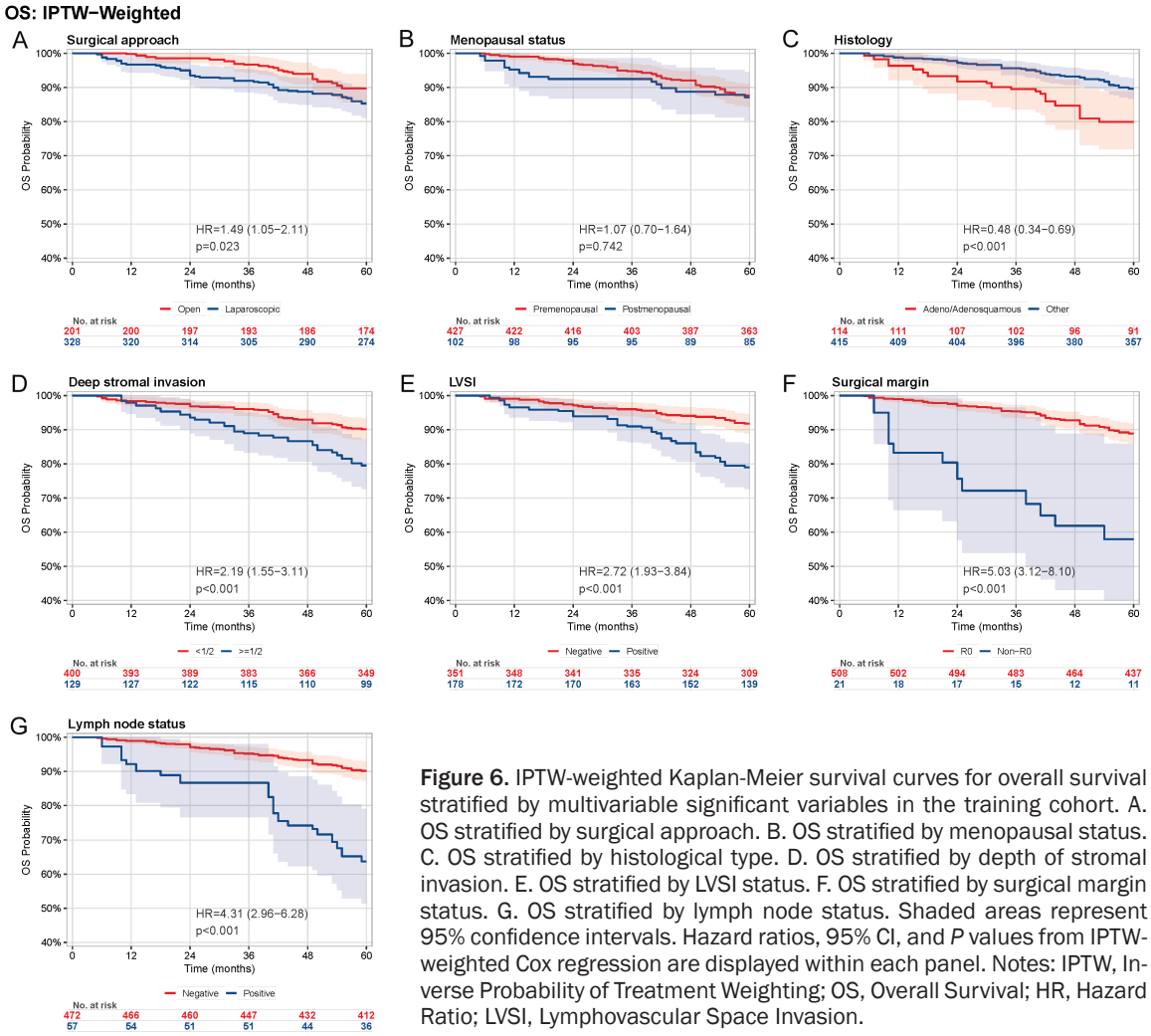


Figure 6. IPTW-weighted Kaplan-Meier survival curves for overall survival stratified by multivariable significant variables in the training cohort. A. OS stratified by surgical approach. B. OS stratified by menopausal status. C. OS stratified by histological type. D. OS stratified by depth of stromal invasion. E. OS stratified by LVSI status. F. OS stratified by surgical margin status. G. OS stratified by lymph node status. Shaded areas represent 95% confidence intervals. Hazard ratios, 95% CI, and *P* values from IPTW-weighted Cox regression are displayed within each panel. Notes: IPTW, Inverse Probability of Treatment Weighting; OS, Overall Survival; HR, Hazard Ratio; LVSI, Lymphovascular Space Invasion.

independent risk factors for DFS: depth of stromal invasion ≥1/2 (P=0.004), positive LVSI (P=0.033), non-R0 margins (P=0.001), and positive lymph nodes (P<0.001). Of note, unlike the OS analysis, menopausal status (P=0.123) and histological type (P=0.056) did not reach statistical significance in univariable analysis for DFS. Kaplan-Meier curves illustrated the stratified DFS differences for these significant variables, and the unadjusted K-M curve for surgical approach showed no significant DFS difference between the laparoscopic and open groups (P=0.237) (**Table 5**; **Figure 7**).

IPTW-weighted Cox regression analysis for disease-free survival

After IPTW weighting, weighted Cox regression analysis was performed to evaluate the association between each covariate and DFS. In univariable analysis, surgical approach (P=0.030), histological type (P=0.033), depth of stromal invasion (P=0.007), LVSI (P<0.001), margin status (P<0.001), and lymph node status (P<0.001) were significantly associated with DFS. The remaining 22 variables were not significant (all P>0.05). Notably, surgical approach became a significant factor for DFS after IPTW weighting, with the laparoscopic group showing a significantly higher risk of recurrence or death compared with the open group. When these six significant variables were entered into the multivariable Cox model, laparoscopic surgery (P=0.022) was confirmed as an independent risk factor for DFS. Other independent risk factors included depth of stromal invasion ≥1/2 (P=0.034), positive LVSI (P=0.010), non-R0 margins (P=0.019), and positive lymph nodes (P<0.001), whereas

Table 5. Unadjusted univariable and multivariable Cox regression analysis for disease-free survival in the training cohort

Variable	Univariable			Multivariable		
	Beta	P	HR_95 CI	Beta	P	HR_95 CI
Surgical approach						
Open (ref)			1.000 (ref)			
Laparoscopic	0.276	0.239	1.318 (0.833-2.086)			
BMI (kg/m^2)	0.004	0.906	1.004 (0.941-1.071)			
Hemoglobin (g/L)	-0.013	0.121	0.987 (0.97-1.003)			
Albumin (g/L)	0.023	0.407	1.023 (0.97-1.079)			
Platelet (×10^9/L)	-0.002	0.279	0.998 (0.994-1.002)			
NLR	-0.038	0.679	0.962 (0.802-1.154)			
PLR	-0.003	0.172	0.997 (0.994-1.001)			
SCC-Ag (ng/mL)	-0.038	0.680	0.963 (0.804-1.153)			
CA125 (U/mL)	0.001	0.944	1.001 (0.976-1.027)			
CEA (ng/mL)	-0.101	0.331	0.904 (0.737-1.108)			
Age (years)						
≥45 years (ref)			1.000 (ref)			
<45 years	0.212	0.342	1.236 (0.798-1.915)			
Menopausal status						
Premenopausal (ref)			1.000 (ref)			
Postmenopausal	-0.499	0.123	0.607 (0.322-1.145)			
Smoking history						
No (ref)			1.000 (ref)			
Yes	0.176	0.677	1.193 (0.52-2.738)			
Parity						
Nulliparous (ref)			1.000 (ref)			
≥1 delivery	-0.306	0.364	0.736 (0.38-1.426)			
CCI						
<1 (ref)			1.000 (ref)			
≥1	-0.542	0.064	0.582 (0.327-1.033)			
ASA grade						
I-II (ref)			1.000 (ref)			
III	0.077	0.799	1.08 (0.598-1.952)			
FIGO stage						
IA2 (ref)			1.000 (ref)			
IB1	0.071	0.808	1.074 (0.605-1.908)			
Tumor size						
<2 cm (ref)			1.000 (ref)			
≥2 cm	0.219	0.336	1.244 (0.798-1.941)			
Histology						
Adenocarcinoma/Adenosquamous (ref)			1.000 (ref)			
Other	-0.462	0.056	0.63 (0.392-1.013)			
Tumor grade						
G1-G2 (ref)			1.000 (ref)			
G3	-0.273	0.315	0.761 (0.446-1.297)			
Deep stromal invasion						
<1/2 (ref)			1.000 (ref)			
≥1/2	0.739	0.001	2.094 (1.346-3.259)	0.653	0.004	1.922 (1.233-2.994)
LVSI						
Negative (ref)			1.000 (ref)			
Positive	0.625	0.004	1.868 (1.214-2.875)	0.481	0.033	1.617 (1.039-2.516)

Surgical margin						
R0 (ref)			1.000 (ref)			
Non-R0	1.562	<0.001	4.769 (2.461-9.243)	1.143	0.001	3.136 (1.579-6.228)
Lymph node status						
Negative (ref)			1.000 (ref)			
Positive	1.174	<0.001	3.234 (1.971-5.307)	0.953	<0.001	2.593 (1.558-4.314)
Parametrial invasion						
No (ref)			1.000 (ref)			
Yes	-0.131	0.824	0.878 (0.277-2.779)			
PNI						
Negative (ref)			1.000 (ref)			
Positive	-0.113	0.807	0.894 (0.362-2.207)			
HPV						
Positive (ref)			1.000 (ref)			
Negative	-0.154	0.663	0.857 (0.429-1.713)			
Adjuvant therapy						
No (ref)			1.000 (ref)			
Yes	-0.016	0.946	0.984 (0.622-1.558)			

Note: DFS, Disease-Free Survival; HR, Hazard Ratio;95% CI, 95% Confidence Interval; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion; PNI, Perineural Invasion; HPV, Human Papillomavirus; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SCC-Ag, Squamous Cell Carcinoma Antigen; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen.

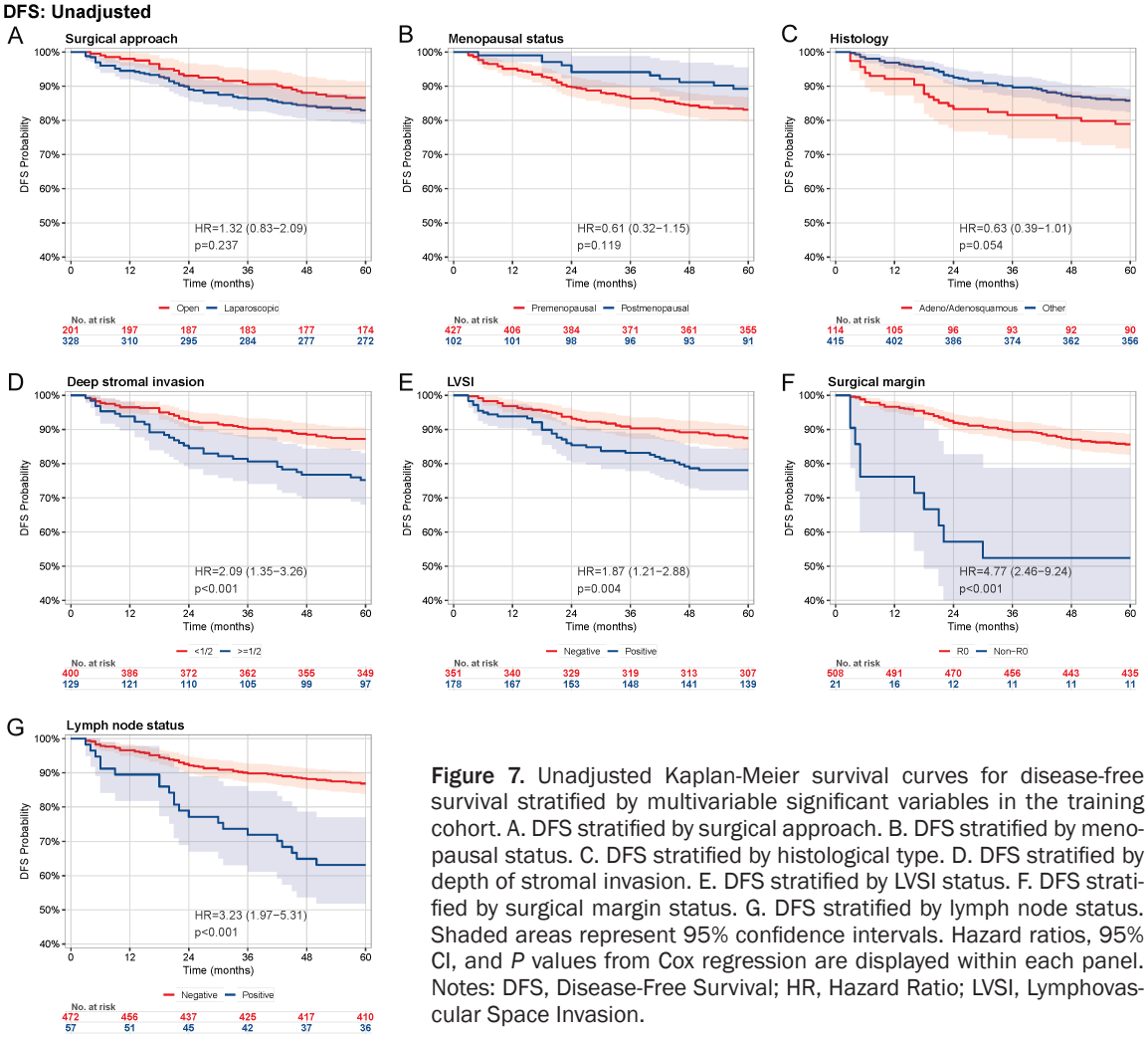


Figure 7. Unadjusted Kaplan-Meier survival curves for disease-free survival stratified by multivariable significant variables in the training cohort. A. DFS stratified by surgical approach. B. DFS stratified by menopausal status. C. DFS stratified by histological type. D. DFS stratified by depth of stromal invasion. E. DFS stratified by LVSI status. F. DFS stratified by surgical margin status. G. DFS stratified by lymph node status. Shaded areas represent 95% confidence intervals. Hazard ratios, 95% CI, and *P* values from Cox regression are displayed within each panel. Notes: DFS, Disease-Free Survival; HR, Hazard Ratio; LVSI, Lymphovascular Space Invasion.

Table 6. IPTW-weighted univariable and multivariable Cox regression analysis for disease-free survival in the training cohort

Variable	Univariable			Multivariable		
	Beta	P	HR_95 CI	Beta	P	HR_95 CI
Surgical approach						
Open (ref)			1.000 (ref)			
Laparoscopic	0.55	0.030	1.733 (1.253-2.396)	0.635	0.022	1.887 (1.358-2.622)
BMI (kg/m^2)	-0.009	0.799	0.991 (0.946-1.038)			
Hemoglobin (g/L)	-0.011	0.237	0.989 (0.977-1.001)			
Albumin (g/L)	0.001	0.977	1.001 (0.963-1.04)			
Platelet (×10^9/L)	-0.001	0.535	0.999 (0.996-1.001)			
NLR	0.002	0.982	1.002 (0.882-1.139)			
PLR	-0.002	0.270	0.998 (0.995-1.001)			
SCC-Ag (ng/mL)	0.008	0.925	1.008 (0.885-1.147)			
CA125 (U/mL)	-0.007	0.634	0.993 (0.976-1.01)			
CEA (ng/mL)	-0.105	0.289	0.9 (0.777-1.043)			
Age (years)						
≥45 years (ref)			1.000 (ref)			
<45 years	0.349	0.151	1.418 (1.024-1.963)			
Menopausal status						
Premenopausal (ref)			1.000 (ref)			
Postmenopausal	-0.599	0.083	0.549 (0.339-0.888)			
Smoking history						
No (ref)			1.000 (ref)			
Yes	0.196	0.677	1.217 (0.667-2.218)			
Parity						
Nulliparous (ref)			1.000 (ref)			
≥1 delivery	-0.284	0.456	0.753 (0.467-1.213)			
CCI						
<1 (ref)			1.000 (ref)			
≥1	-0.607	0.066	0.545 (0.355-0.836)			
ASA grade						
I-II (ref)			1.000 (ref)			
III	0.29	0.366	1.336 (0.886-2.016)			
FIGO stage						
IA2 (ref)			1.000 (ref)			
IB1	0.451	0.163	1.571 (0.984-2.508)			
Tumor size						
<2 cm (ref)			1.000 (ref)			
≥2 cm	0.309	0.208	1.362 (0.984-1.884)			
Histology						
Adenocarcinoma/Adenosquamous (ref)			1.000 (ref)			
Other	-0.58	0.033	0.56 (0.398-0.787)	-0.501	0.075	0.606 (0.43-0.853)
Tumor grade						
G1-G2 (ref)			1.000 (ref)			
G3	-0.011	0.971	0.989 (0.681-1.436)			
Deep stromal invasion						
<1/2 (ref)			1.000 (ref)			
≥1/2	0.668	0.007	1.951 (1.407-2.703)	0.542	0.034	1.72 (1.237-2.392)
LVSI						
Negative (ref)			1.000 (ref)			
Positive	0.81	<0.001	2.248 (1.639-3.082)	0.654	0.010	1.923 (1.39-2.659)

Surgical margin						
R0 (ref)			1.000 (ref)			
Non-R0	1.475	<0.001	4.373 (2.728-7.008)	1.021	0.019	2.776 (1.701-4.53)
Lymph node status						
Negative (ref)			1.000 (ref)			
Positive	1.372	<0.001	3.943 (2.759-5.634)	1.271	<0.001	3.565 (2.48-5.124)
Parametrial invasion						
No (ref)			1.000 (ref)			
Yes	0.243	0.684	1.275 (0.601-2.704)			
PNI						
Negative (ref)			1.000 (ref)			
Positive	-0.222	0.653	0.801 (0.396-1.622)			
HPV						
Positive (ref)			1.000 (ref)			
Negative	-0.266	0.485	0.767 (0.456-1.29)			
Adjuvant therapy						
No (ref)			1.000 (ref)			
Yes	0.069	0.785	1.072 (0.767-1.497)			

Note: IPTW, Inverse Probability of Treatment Weighting; DFS, Disease-Free Survival; HR, Hazard Ratio; 95% CI, 95% Confidence Interval; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion; PNI, Perineural Invasion; HPV, Human Papillomavirus; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SCC-Ag, Squamous Cell Carcinoma Antigen; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen.

histological type did not reach significance in the multivariable model (P=0.075).

IPTW-weighted Kaplan-Meier curves likewise confirmed significantly worse DFS in the laparoscopic group compared with the open group (P<0.001), indicating that after adjustment for baseline confounding, laparoscopic surgery was independently associated with poorer DFS in patients with early-stage cervical cancer (**Table 6**; **Figure 8**).

Subgroup analysis: effect of surgical approach on DFS and OS

To explore whether the effect of surgical approach on prognosis varied across patient subgroups, subgroup analyses were performed for eight key variables: age, FIGO stage, tumor size, histological type, depth of stromal invasion, LVSI, lymph node status, and adjuvant therapy. Both unadjusted and IPTW-weighted results are presented.

DFS subgroup analysis: In the unadjusted overall analysis, no significant DFS difference was found between the laparoscopic and open groups (P=0.239). After IPTW weighting, the laparoscopic group showed significantly worse DFS (P=0.030). In unadjusted subgroup analysis, laparoscopic surgery was associated with significantly worse DFS only in the LVSI-negative subgroup (P=0.041). A significant interaction was detected for histological type (P_interaction =0.035), suggesting that the effect of surgical approach on DFS differed between adenocarcinoma/adenosquamous and other histological types. After IPTW weighting, laparoscopic surgery was associated with significantly worse DFS in several subgroups: FIGO stage IA2 (P=0.029), tumor <2 cm (P=0.028), non-adenocarcinoma/adenosquamous histology (P=0.007), LVSI-negative (P=0.004), and no adjuvant therapy (P=0.020). A significant interaction was found for LVSI (P_interaction =0.037), indicating that the adverse effect of laparoscopic surgery on DFS was concentrated among LVSI-negative patients. In LVSI-positive patients, DFS did not differ significantly between the two surgical approaches (P=0.904). No other subgroup interactions reached significance (all P_interaction >0.05).

OS subgroup analysis: In the unadjusted overall analysis, OS did not differ significantly between the two groups (P=0.865), and this remained non-significant after IPTW weighting (P=0.141). Unadjusted subgroup analyses detected no significant interactions (all P_interaction >0.05), and no subgroup showed a significant effect of surgical approach on OS. After

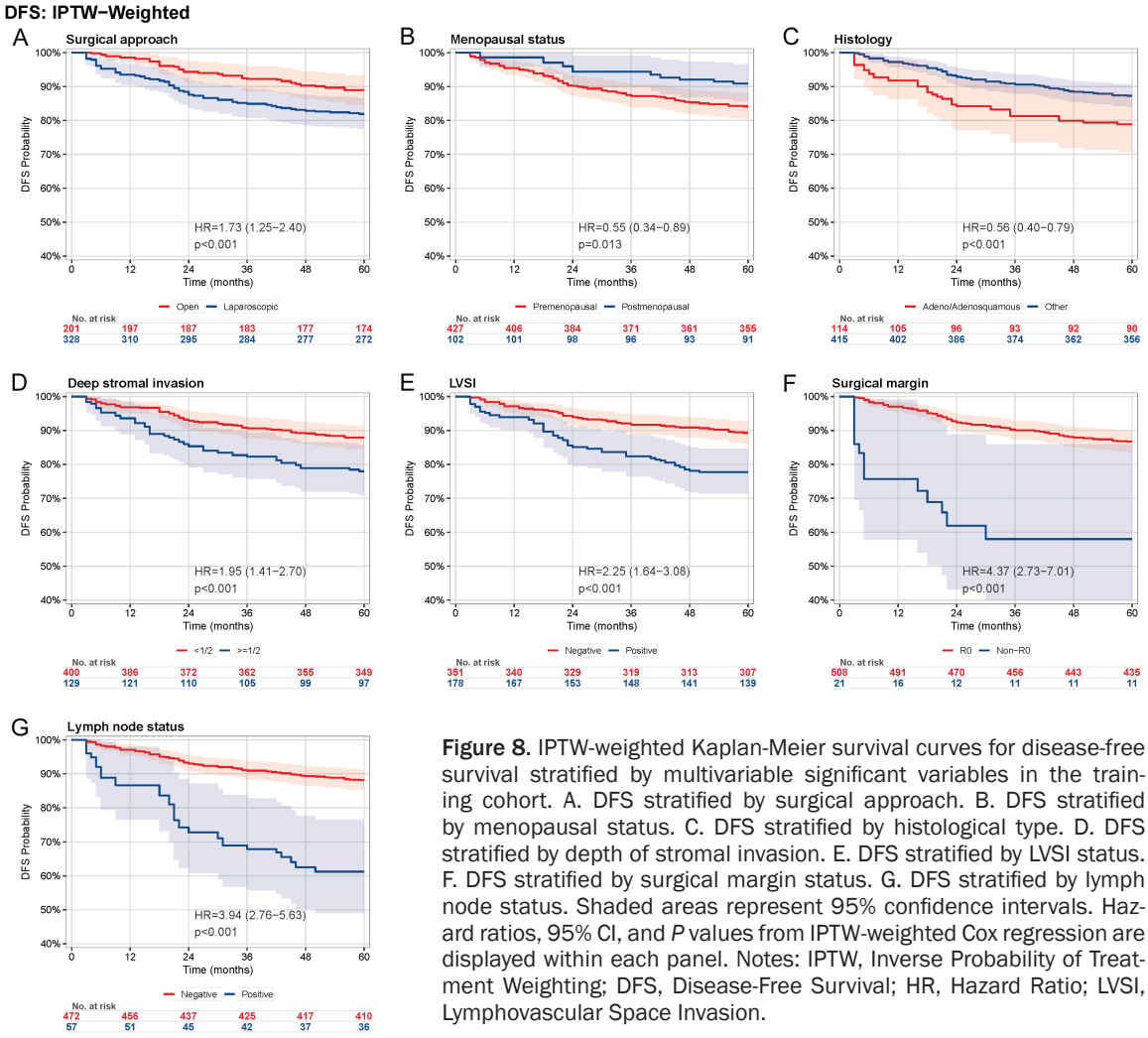


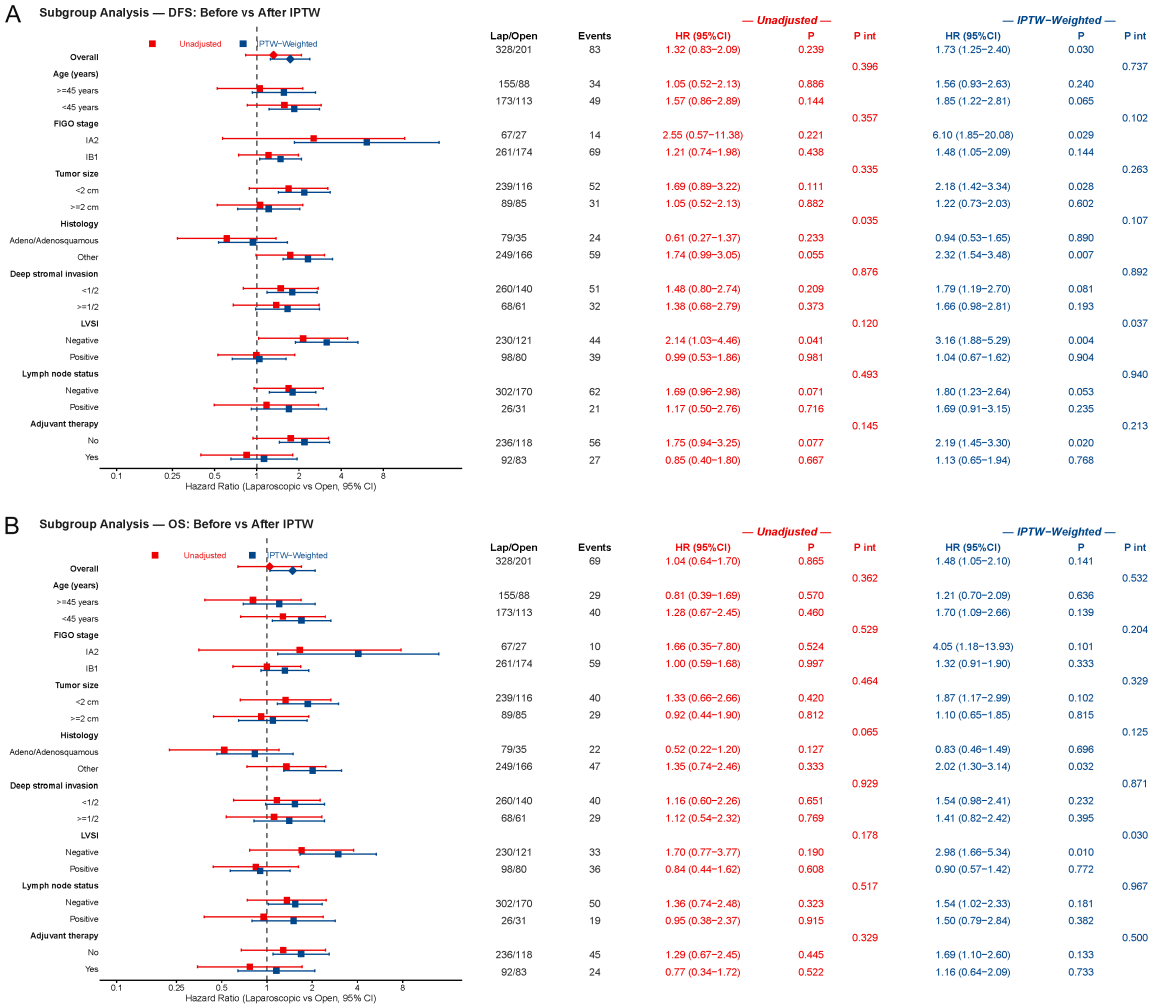
Figure 8. IPTW-weighted Kaplan-Meier survival curves for disease-free survival stratified by multivariable significant variables in the training cohort. A. DFS stratified by surgical approach. B. DFS stratified by menopausal status. C. DFS stratified by histological type. D. DFS stratified by depth of stromal invasion. E. DFS stratified by LVSI status. F. DFS stratified by surgical margin status. G. DFS stratified by lymph node status. Shaded areas represent 95% confidence intervals. Hazard ratios, 95% CI, and *P* values from IPTW-weighted Cox regression are displayed within each panel. Notes: IPTW, Inverse Probability of Treatment Weighting; DFS, Disease-Free Survival; HR, Hazard Ratio; LVSI, Lymphovascular Space Invasion.

IPTW weighting, laparoscopic surgery was associated with significantly worse OS in the non-adenocarcinoma/adenosquamous histology subgroup (P=0.032) and the LVSI-negative subgroup (P=0.010). LVSI showed a significant interaction (P_interaction =0.030), consistent with the DFS findings. The adverse effect of laparoscopic surgery on OS was concentrated in LVSI-negative patients, while no significant difference was observed between approaches in LVSI-positive patients (P=0.772). No other subgroup interactions were significant (all P_interaction >0.05) (**Figure 9**).

Sensitivity analysis: robustness of the effect of surgical approach on DFS and OS

The reliability of the primary IPTW findings was validated using four alternative methods, including trimmed IPTW (1st-99th percentile), overlap weights (ATO), 1:1 PSM, and multivariable Cox regression including all covariates. For DFS, all five analytical methods produced HR point estimates >1, suggesting an increased risk of recurrence or death with laparoscopic surgery (HR=1.434-1.956). Statistical significance was achieved in four of five methods: original IPTW (P=0.030), trimmed IPTW (P=0.033), overlap weights (P=0.049), and multivariable Cox regression (P=0.012). Only 1:1 PSM was not significant (P=0.208), likely due to reduced sample size after matching (n=342, events =50), although the effect remained in the same direction. Multivariable Cox regression produced the largest effect size (HR=1.956), confirming the adverse effect of laparoscopic surgery on DFS.

For OS, all five methods reported HR point estimates >1 (range: 1.182-1.613) indicating a



	Lap/Open	Events	— Unadjusted — HR (95%CI)	P	P int	— IPTW−Weighted — HR (95%CI)	P	P int
Overall	328/201	83	1.32 (0.83−2.09)	0.239		1.73 (1.25−2.40)	0.030	
Age (years)					0.396			0.737
>=45 years	155/88	34	1.05 (0.52−2.13)	0.886		1.56 (0.93−2.63)	0.240	
<45 years	173/113	49	1.57 (0.86−2.89)	0.144		1.85 (1.22−2.81)	0.065	
FIGO stage					0.357			0.102
IA2	67/27	14	2.55 (0.57−11.38)	0.221		6.10 (1.85−20.08)	0.029	
IB1	261/174	69	1.21 (0.74−1.98)	0.438		1.48 (1.05−2.09)	0.144	
Tumor size					0.335			0.263
<2 cm	239/116	52	1.69 (0.89−3.22)	0.111		2.18 (1.42−3.34)	0.028	
>=2 cm	89/85	31	1.05 (0.52−2.13)	0.882		1.22 (0.73−2.03)	0.602	
Histology					0.035			0.107
Adeno/Adenosquamous	79/35	24	0.61 (0.27−1.37)	0.233		0.94 (0.53−1.65)	0.890	
Other	249/166	59	1.74 (0.99−3.05)	0.055		2.32 (1.54−3.48)	0.007	
Deep stromal invasion					0.876			0.892
<1/2	260/140	51	1.48 (0.80−2.74)	0.209		1.79 (1.19−2.70)	0.081	
>=1/2	68/61	32	1.38 (0.68−2.79)	0.373		1.66 (0.98−2.81)	0.193	
LVSI					0.120			0.037
Negative	230/121	44	2.14 (1.03−4.46)	0.041		3.16 (1.88−5.29)	0.004	
Positive	98/80	39	0.99 (0.53−1.86)	0.981		1.04 (0.67−1.62)	0.904	
Lymph node status					0.493			0.940
Negative	302/170	62	1.69 (0.96−2.98)	0.071		1.80 (1.23−2.64)	0.053	
Positive	26/31	21	1.17 (0.50−2.76)	0.716		1.69 (0.91−3.15)	0.235	
Adjuvant therapy					0.145			0.213
No	236/118	56	1.75 (0.94−3.25)	0.077		2.19 (1.45−3.30)	0.020	
Yes	92/83	27	0.85 (0.40−1.80)	0.667		1.13 (0.65−1.94)	0.768	

	Lap/Open	Events	— Unadjusted — HR (95%CI)	P	P int	— IPTW−Weighted — HR (95%CI)	P	P int
Overall	328/201	69	1.04 (0.64−1.70)	0.865		1.48 (1.05−2.10)	0.141	
Age (years)					0.362			0.532
>=45 years	155/88	29	0.81 (0.39−1.69)	0.570		1.21 (0.70−2.09)	0.636	
<45 years	173/113	40	1.28 (0.67−2.45)	0.460		1.70 (1.09−2.66)	0.139	
FIGO stage					0.529			0.204
IA2	67/27	10	1.66 (0.35−7.80)	0.524		4.05 (1.18−13.93)	0.101	
IB1	261/174	59	1.00 (0.59−1.68)	0.997		1.32 (0.91−1.90)	0.333	
Tumor size					0.464			0.329
<2 cm	239/116	40	1.33 (0.66−2.66)	0.420		1.87 (1.17−2.99)	0.102	
>=2 cm	89/85	29	0.92 (0.44−1.90)	0.812		1.10 (0.65−1.85)	0.815	
Histology					0.065			0.125
Adeno/Adenosquamous	79/35	22	0.52 (0.22−1.20)	0.127		0.83 (0.46−1.49)	0.696	
Other	249/166	47	1.35 (0.74−2.46)	0.333		2.02 (1.30−3.14)	0.032	
Deep stromal invasion					0.929			0.871
<1/2	260/140	40	1.16 (0.60−2.26)	0.651		1.54 (0.98−2.41)	0.232	
>=1/2	68/61	29	1.12 (0.54−2.32)	0.769		1.41 (0.82−2.42)	0.395	
LVSI					0.178			0.030
Negative	230/121	33	1.70 (0.77−3.77)	0.190		2.98 (1.66−5.34)	0.010	
Positive	98/80	36	0.84 (0.44−1.62)	0.608		0.90 (0.57−1.42)	0.772	
Lymph node status					0.517			0.967
Negative	302/170	50	1.36 (0.74−2.48)	0.323		1.54 (1.02−2.33)	0.181	
Positive	26/31	19	0.95 (0.38−2.37)	0.915		1.50 (0.79−2.84)	0.382	
Adjuvant therapy					0.329			0.500
No	236/118	45	1.29 (0.67−2.45)	0.445		1.69 (1.10−2.60)	0.133	
Yes	92/83	24	0.77 (0.34−1.72)	0.522		1.16 (0.64−2.09)	0.733	

Figure 9. Forest plots of subgroup analyses comparing the effect of surgical approach (laparoscopic vs. open) on disease-free survival and overall survival, before and after IPTW adjustment in the training cohort. A. Subgroup analysis for DFS showing unadjusted (red) and IPTW-weighted (blue) hazard ratios with 95% confidence intervals across eight clinical subgroups. B. Subgroup analysis for OS showing unadjusted (red) and IPTW-weighted (blue) hazard ratios with 95% confidence intervals across the same subgroups. Diamonds represent overall estimates; squares represent subgroup-specific estimates. P int denotes the *P* value for interaction between surgical approach and the subgroup variable. Notes: DFS, Disease-Free Survival; OS, Overall Survival; HR, Hazard Ratio; 95% CI, 95% Confidence Interval; IPTW, Inverse Probability of Treatment Weighting; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion.

trend toward higher mortality with laparoscopic surgery. None of the results were statistically significant (P=0.096-0.584), with multivariable Cox regression being closest to significance (P=0.096), and 1:1 PSM showing the smallest effect (HR=1.182, P=0.584). Overall, sensitivity analyses supported the robustness of the main IPTW finding: laparoscopic surgery was consistently associated with worse DFS in early-stage cervical cancer. The adverse effect on OS showed a similar trend but did not achieve statistical significance (**Figure 10**).

Independent IPTW validation in the validation cohort

In the validation cohort (n=311), an independent logistic regression PS model was built, and IPTW weights were calculated. Before weighting, multiple covariates showed substantial imbalance between the laparoscopic and open groups. CCI had the largest SMD at 0.474, followed by tumor grade (SMD=0.367), tumor size (SMD=0.326), LVSI (SMD=0.323), ASA grade (SMD=0.282), adjuvant therapy (SMD=0.278),

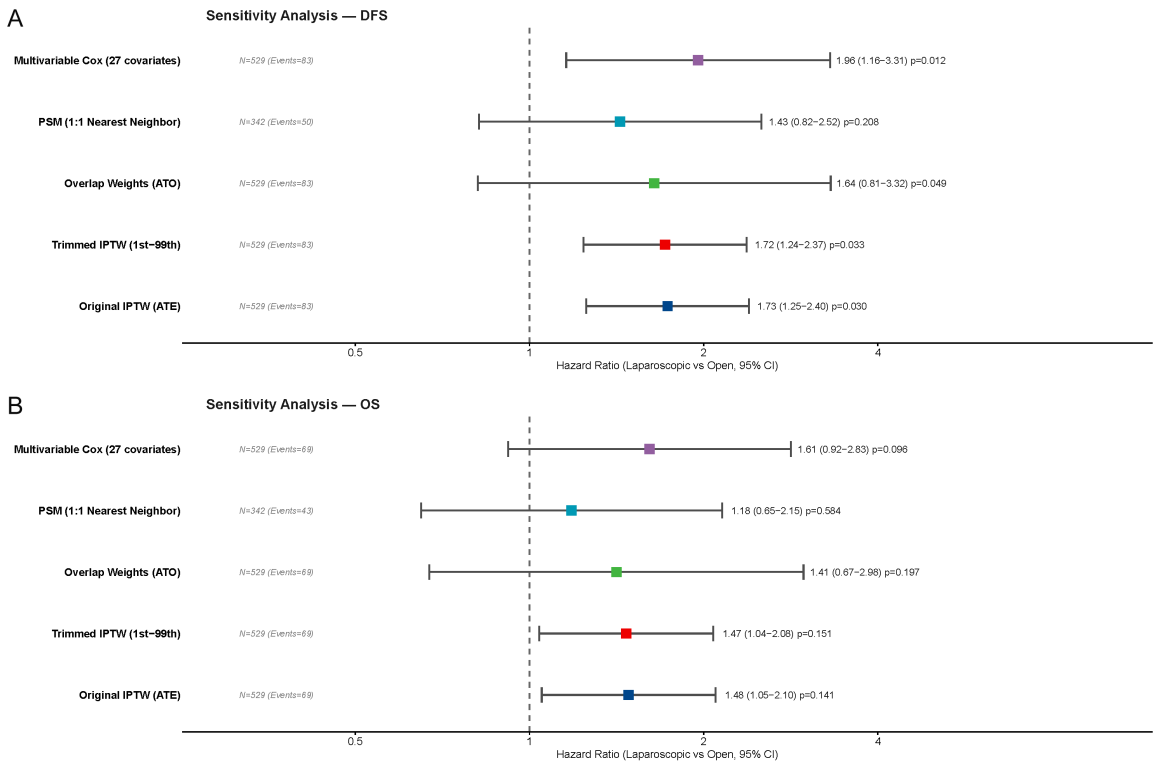


Figure 10. Sensitivity analysis of the effect of surgical approach (laparoscopic vs. open) on disease-free survival and overall survival using five analytical methods in the training cohort. A. Forest plot showing hazard ratios with 95% confidence intervals for DFS across five analytical methods: original IPTW, trimmed IPTW, overlap weights, propensity score matching, and multivariable Cox regression. B. Corresponding forest plot for OS across the same five methods. The dashed line indicates HR=1 (no difference). Sample sizes and event counts are annotated for each method. Notes: DFS, Disease-Free Survival; OS, Overall Survival; HR, Hazard Ratio; 95% CI, 95% Confidence Interval; IPTW, Inverse Probability of Treatment Weighting; ATE, Average Treatment Effect; ATO, Average Treatment Effect among the Overlap Population; PSM, Propensity Score Matching.

menopausal status (SMD=0.272), smoking history (SMD=0.270), HPV (SMD=0.261), CA125 (SMD=0.242), FIGO stage (SMD=0.231), depth of stromal invasion (SMD=0.229), and parametrial invasion (SMD=0.210).

After IPTW weighting, with weights trimmed at the 99th percentile, all covariates achieved SMD below 0.1. The largest post-weighting SMD was for smoking history (SMD=0.099), confirming that IPTW effectively eliminated baseline confounding in the validation cohort as well (**Figure 11**).

IPTW-weighted Kaplan-Meier survival analysis in the training and validation cohorts

IPTW-weighted Kaplan-Meier curves were plotted separately for the training and validation cohorts to assess the reproducibility of the observed effect of surgical approach on OS and DFS.

For OS, the laparoscopic group had significantly worse survival in the training cohort (HR=1.47, 95% CI: 1.04-2.08, P=0.028). The validation cohort yielded a consistent effect in the same direction, with an even larger magnitude (HR=3.10, 95% CI: 1.79-5.38, P<0.001), confirming the adverse impact of laparoscopic surgery on OS in an independent sample.

For DFS, the laparoscopic group again showed significantly worse outcomes in the training cohort (HR=1.72, 95% CI: 1.24-2.37, P<0.001). The validation cohort demonstrated a consistent and even more pronounced result (HR=3.80, 95% CI: 2.25-6.41, P<0.001). The survival curve shapes were similar in both cohorts, with the laparoscopic group's curve

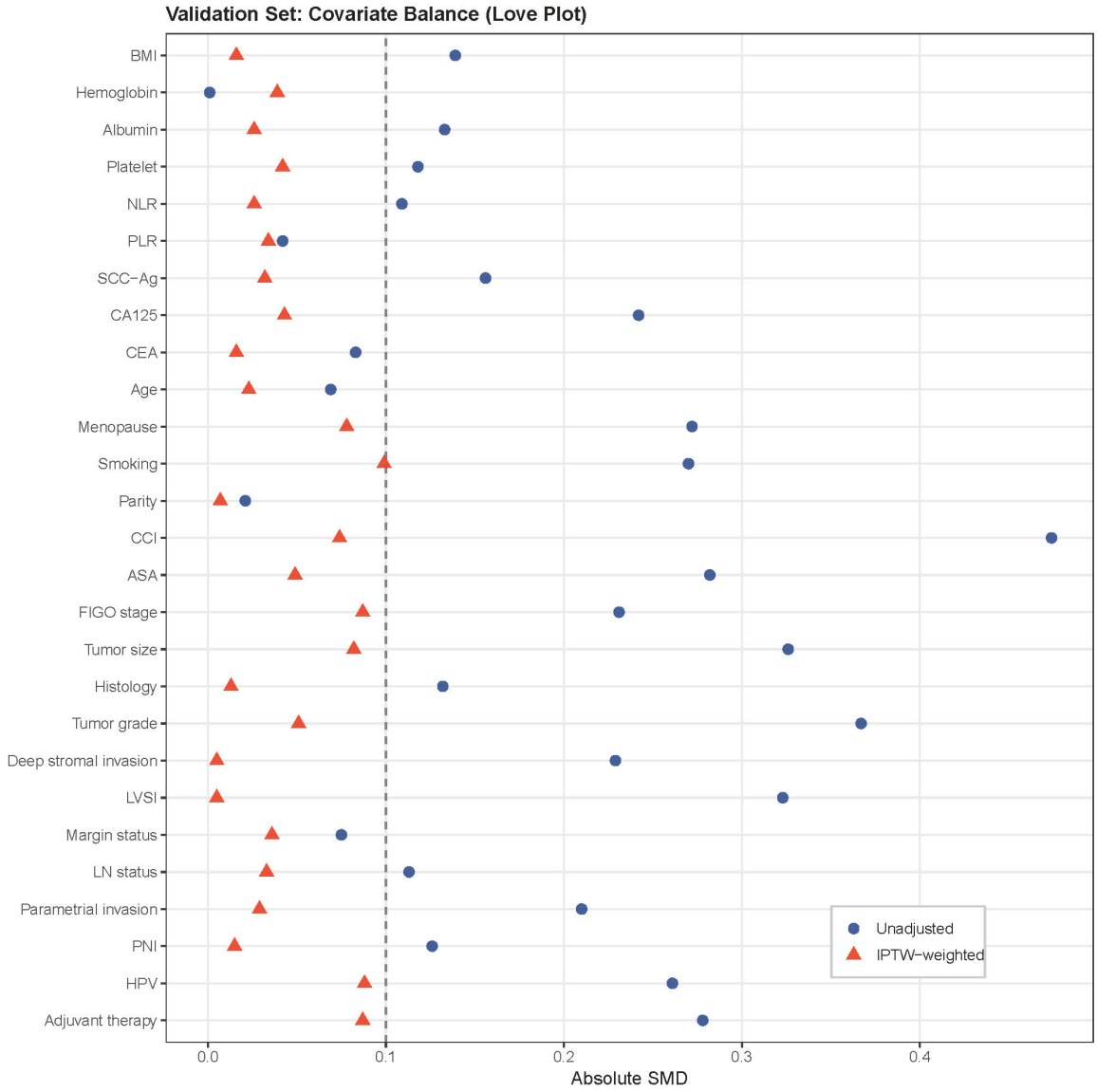


Figure 11. Love plot of covariate balance before and after IPTW weighting in the validation cohort. Love plot displaying the absolute standardized mean differences for all 27 covariates before (unadjusted, blue circles) and after IPTW weighting (red triangles) in the validation cohort. The dashed line indicates the SMD=0.1 threshold. Notes: IPTW, Inverse Probability of Treatment Weighting; SMD, Standardized Mean Difference; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion; HPV, Human Papillomavirus; CA125, Carbohydrate Antigen 125; BMI, Body Mass Index.

consistently below that of the open group, and the separation widening over follow-up time (**Figure 12**).

Consistency of treatment effects between training and validation cohorts

Forest plots were used to comprehensively compare the IPTW-weighted treatment effects of surgical approach on OS and PFS between the training and validation cohorts. For OS, the overall HR was 1.47 (95% CI: 1.04-2.08) in the training cohort and 3.10 (95% CI: 1.79-5.38) in the validation cohort, demonstrating consistent directionality: laparoscopic surgery increased mortality risk in both cohorts. Subgroup analyses also showed consistent effect directions across cohorts: in the non-adenocarcinoma/adenosquamous histology, LVSI-

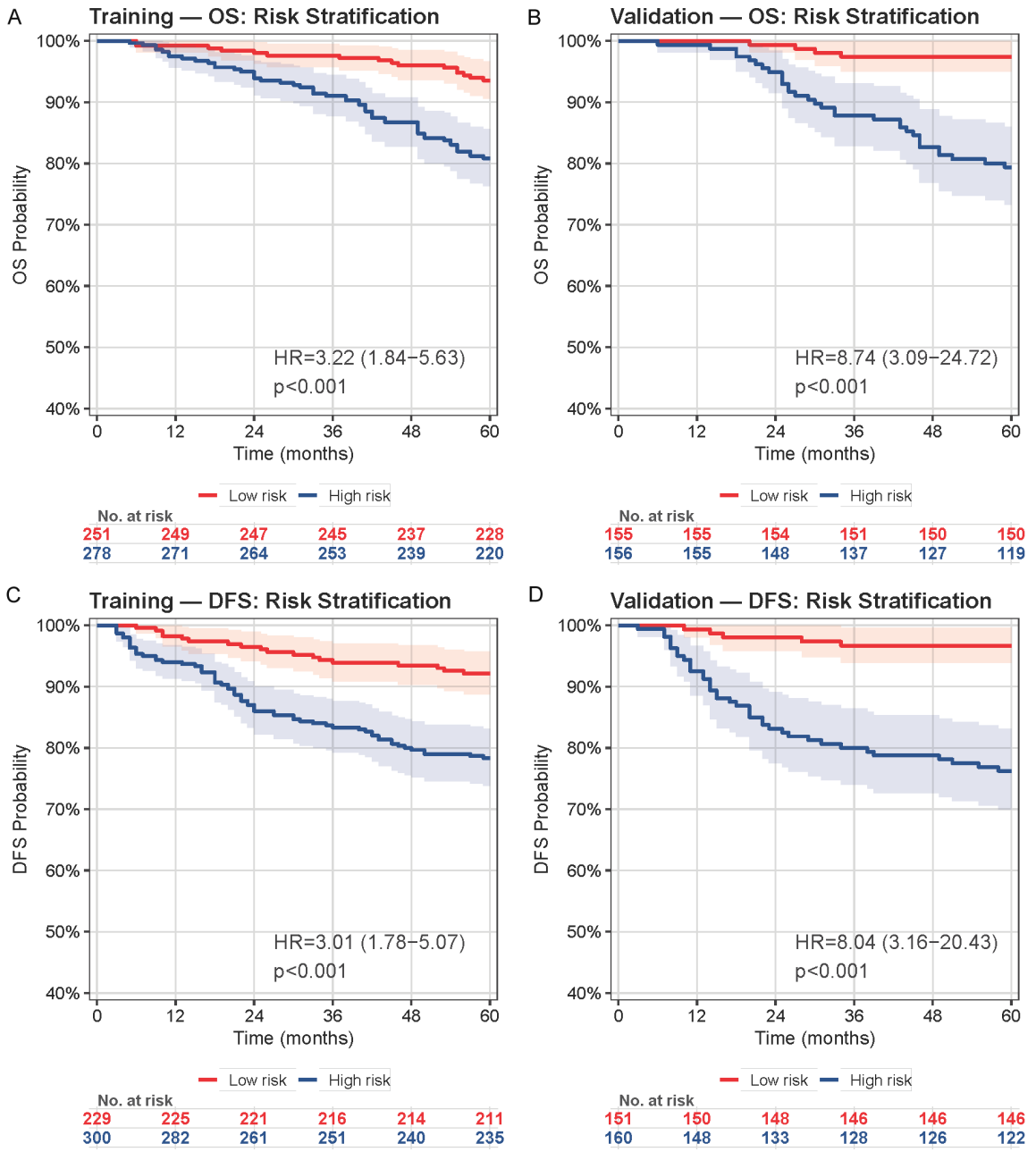


Figure 12. IPTW-weighted Kaplan-Meier survival curves for overall survival and disease-free survival in the training and validation cohorts. A. IPTW-weighted OS curves in the training cohort. B. IPTW-weighted OS curves in the validation cohort. C. IPTW-weighted DFS curves in the training cohort. D. IPTW-weighted DFS curves in the validation cohort. Shaded areas represent 95% confidence intervals. Hazard ratios, 95% CI, and *P* values from IPTW-weighted Cox regression are displayed within each panel. Number at risk tables are shown below each curve. Note: OS, Overall Survival; DFS, Disease-Free Survival; IPTW, Inverse Probability of Treatment Weighting; HR, Hazard Ratio; 95% CI, 95% Confidence Interval.

negative, and lymph node-negative subgroups, HRs were greater than 1 for the laparoscopic group in both cohorts. In contrast, the LVSI-positive subgroup showed a much larger effect size in the validation cohort than in the training cohort (HR=5.18 vs. HR=0.90). The FIGO IA2 subgroup was excluded from the forest plot because the small number of events in the validation cohort, which produced extreme and unstable HR estimates.

For DFS, the overall HR was 1.72 (95% CI: 1.24-2.37) in the training cohort and 3.80 (95% CI: 2.25-6.41) in the validation cohort, confirming that laparoscopic surgery was associated with an increased risk of recurrence or death. However, the larger HR observed in the validation cohort should be interpreted cautiously, as the smaller sample size and fewer outcome events likely increased statistical variability. This effect was further amplified in subgroup analyses, where sparse events in some strata resulted in wide confidence intervals and occasionally extreme HR estimates. Nevertheless, the direction of effect in the validation cohort was largely consistent with the training cohort across almost all subgroups. Notably, the lymph node-negative subgroup (validation HR=6.20 vs. training HR=1.78) and the depth of stromal invasion <1/2 subgroup (validation HR=14.43 vs. training HR=1.77) showed notably amplified effects in the validation cohort. Overall, the validation cohort strongly supported the core findings from the training cohort: after IPTW adjustment, laparoscopic surgery had an adverse impact on both DFS and OS in early-stage cervical cancer patients (**Figure 13**).

Subgroup event distribution in training and validation cohorts

The numbers of patients and outcome events across overall and subgroup analyses are summarized in Table S1. In the validation cohort, total number of events was relatively limited (43 DFS events and 36 OS events overall), which was further reduced after stratification by subgroup factors. Several subgroups contained very few events, particularly after stratification by surgical approach. This limited number of events likely contributed to statistical instability, wide confidence intervals, and some extreme hazard ratio estimates observed in the validation cohort subgroup analyses.

Discussion

In this multicenter retrospective cohort of 840 patients with stage IA2-IB1 cervical cancer, we used IPTW to systematically evaluate the impact of laparoscopic versus open radical hysterectomy on 5-year OS and DFS. The most robust finding of this study was that laparoscopic surgery was associated with significantly worse DFS after IPTW adjustment, a result consistent in direction between the training cohort (HR=1.73) and the validation cohort (HR=3.80), and confirmed as an independent risk factor in multivariable Cox regression (HR=1.89, P=0.022). The larger HR in the validation cohort likely reflects statistical instability due to smaller sample size, fewer outcome events, and differences in weight trimming, rather than true heterogeneity of treatment effect. This is especially relevant in subgroup analyses, where few event numbers result in broader confidence intervals and occasional extreme HR estimates. Thus, under these conditions, consistency in the direction of the effect across the training and validation cohorts is more informative than the absolute magnitude of the subgroup-specific point estimates.

For OS, HRs for the laparoscopic group were consistently >1 across analyses, indicating a constant negative direction, but surgical approach was not an independent predictor in the IPTW-weighted multivariable Cox model (P=0.141). Although IPTW-weighted Kaplan-Meier analysis showed a significant OS difference (P=0.024), this effect disappeared after adjusting for established pathological risk factors. Potential explanations for this discordance between the DFS and OS include limited statistical power due to low overall mortality, the use all-cause rather than cancer-specific mortality, and the standard 5-year follow-up period potentially missing late mortality events. Thus, DFS finding should be considered the primary and most reliable endpoint. The OS trend is directionally consistent but greater confirmation in larger studies with longer follow-up on cancer-specific mortality will be needed. Subgroup analysis suggested that LVSI status may be an essential stratifying factor, with laparoscopic surgery exerting greater adverse effects in LVSI-negative patients. The robustness of these conclusions was tested by trimmed IPTW, overlap weights, 1:1 PSM, and multivariable Cox regression, all of which yielded HR point estimates pointing in the same direction.

Comparison with the LACC trial and other key studies

The main fining of this study - that laparoscopic surgery is an independent risk factor for

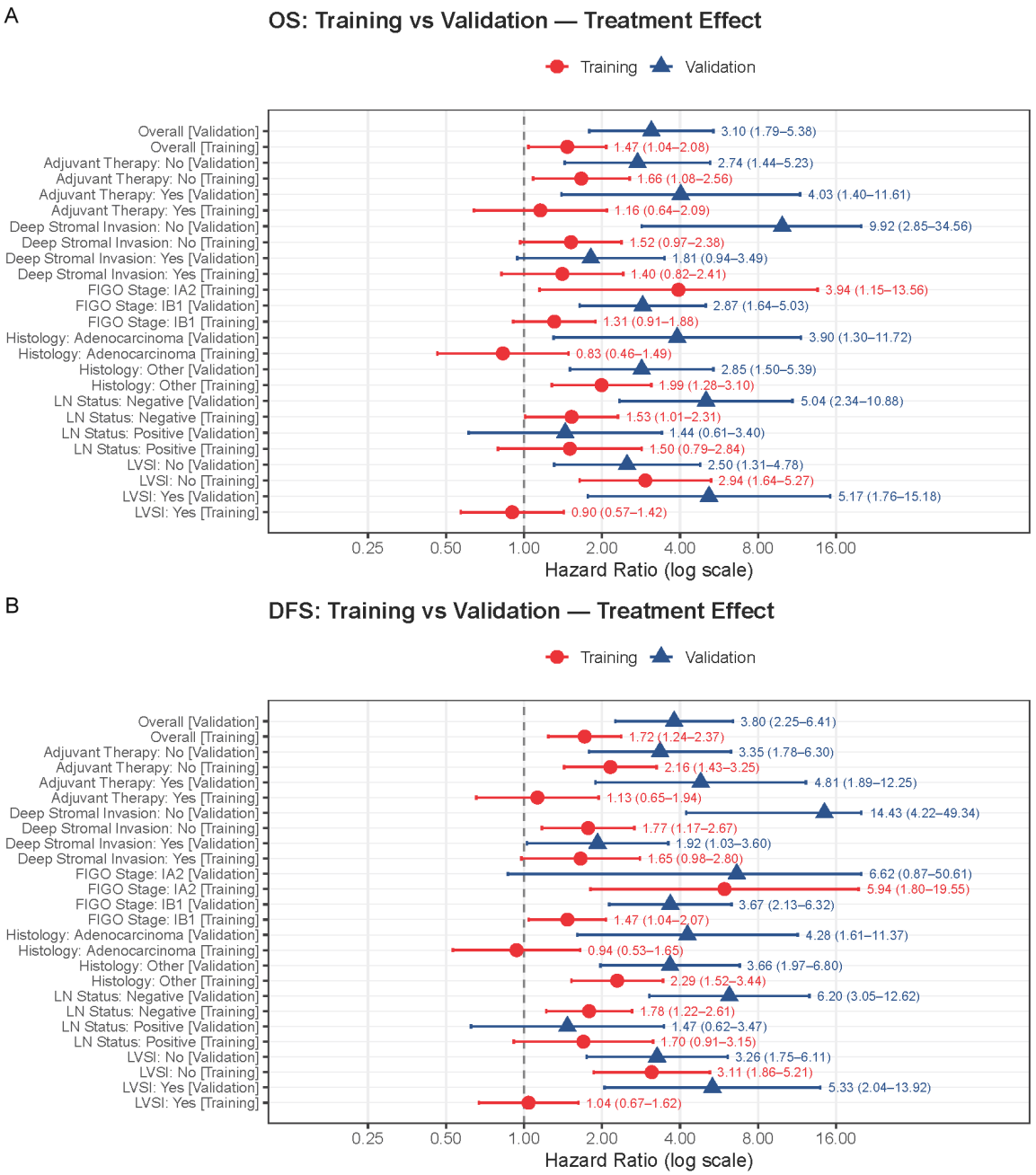


Figure 13. Forest plots comparing the IPTW-weighted treatment effect of surgical approach (laparoscopic vs. open) between the training and validation cohorts across overall and subgroup analyses. A. Comparison of hazard ratios for OS between the training (red circles) and validation (blue triangles) cohorts for overall and six key subgroup analyses. B. Corresponding comparison for DFS. The dashed line indicates HR=1 (no difference). Extreme HR estimates due to sparse events (e.g., FIGO IA2 in the validation OS analysis) were excluded from the plot. Note: OS, Overall Survival; DFS, Disease-Free Survival; HR, Hazard Ratio; 95% CI, 95% Confidence Interval; IPTW, Inverse Probability of Treatment Weighting; FIGO, International Federation of Gynecology and Obstetrics; LVSI, Lymphovascular Space Invasion.

worse DFS in early-stage cervical cancer - is consistent with the 2018 LACC trial [7], which reported that a 4.5-year DFS rate of 86% for MIS versus 96.5% for open surgery (HR=3.74). In our training set, the IPTW-weighted DFS HR was 1.73, smaller than the LACC estimate but directionally consistent, and confirmed as independent in multivariable analysis (HR=1.89,

P=0.022). The higher HR (3.80) in the validation cohort is likely attributable to several factors. The validation cohort included only 311 patients with a smaller open surgery group. Furthermore, the limited number of events in some subgroups increased variability in HR point estimates, and the weight trimming strategy applied in the validation cohort (99th percentile) differed slightly from that in the training cohort. Therefore, the difference in effect size is more likely due to random variation from sample size limitations rather than true heterogeneity. In this contest, the absolute magnitude of HRs is less important than direction and consistency of estimates. Additionally, because the LACC trial was stopped early and had a limited number of events, the precision of its effect size estimate is uncertain [18]. Our finding of a directionally consistent result in a real-world cohort may offer complementary evidence regarding the effect of surgical approach across populations. According to the LACC trial and several observational studies, there does not seem to be a significant independent effect of surgical approach on OS in multivariable analyses. In our study, the OS HR consistently favored open surgery across all five analytical techniques (HR range: 1.18-1.61), but none reached statistical significance in sensitivity analyses. This implies that, if surgical approach affects OS, the effect is likely modest, and detection would require larger samples and longer follow-up.

At the observational study level, our results are consistent with several large cohort studies and meta-analyses. Wenzel et al. [18], using data from the US National Cancer Database (NCDB), found that MIS was associated with worse OS in patients with stage IA2-IB1 cervical cancer (HR=1.28). Chen et al. [19] reported higher recurrence rates in the laparoscopic group in a Chinese multicenter analysis. Pedone Anchora et al. [20] found that in patients with IB1 tumors larger than 2 cm, MIS was associated with significantly worse DFS and OS. Our study extends these findings by introducing a training-validation internal split framework, which provides a more direct form of internal verification and strengthens the credibility of the conclusions.

However, not all studies have reached the same conclusions. Di Donato et al. [12] followed "low-risk" early-stage patients for 10 years and found no significant difference in OS or DFS between MIS and open surgery. Kim et al. [13] reported that laparoscopic surgery did not significantly worsen prognosis in patients with tumors ≤2 cm who received adjuvant therapy after detection of high-risk pathological factors. In our study, the tumor <2 cm subgroup still showed significantly worse DFS in the laparoscopic group after IPTW weighting (P=0.028), which differs from the meta-analysis by Nasioudis et al. [14]. These differences may be due to several factors. First, confounding control method varies; our analysis used IPTW with full-sample weighting, whereas referenced studies mainly used PSM or standard regression, which could be affected by matched sample loss or residual confounding. Second, population differences can also be significant; Chinese patients have a higher prevalence of squamous cell carcinoma, and HPV genotype distributions may also be different [21], potentially affecting the relationship between the surgical approach and outcomes. Residual confounding cannot be fully excluded. Finally, multiple comparisons were made in the subgroup analyses: we evaluated interactions for eight subgroup variables, without adjustment for multiple testing (e.g., the Bonferroni correction). Therefore, these stratified results should be regarded as exploratory and need validation in further independent cohorts.

LVSI interaction: an exploratory finding

A key observation of this study was a significant interaction between LVSI status and surgical approach. The negative effect of laparoscopic surgery was more pronounced in LVSI-negative patients, whereas no statistically significant difference was observed between approaches in LVSI positive patients. This result can be interpreted from several perspectives; however, it should be emphasized that these explanations are mostly based on indirect evidence and need further validation.

From a surgical technique perspective, the application of a uterine manipulator during laparoscopic surgery has been suggested as a potential mechanism of tumor dissemination. Klapdor et al. [22] have shown that mechanical compression exerted by the manipulator on cervical tumor tissue could facilitate tumor cell

spread via vascular channels. In the multicenter retrospective SUCCOR study, Chiva et al. [10] found that in patients undergoing MIS radical hysterectomy, the use of a uterine manipulator was associated with a higher recurrence risk (HR=2.76), while patients who avoided its use had DFS similar to the open surgery group. In LVSI-positive patients, vascular invasion has already occurred, and such patients are often treated with adjuvant chemoradiotherapy postoperatively [23], which may mitigate the disadvantage associated with surgical approach.

Another hypothesized mechanism involves CO_2 pneumoperitoneum. The pneumoperitoneum environment may facilitate intra-abdominal migration and possible trocar-site implantation of free tumor cells. A recent review indicated that port-site metastasis (PSM) could result from: (1) direct contamination of instruments or incision sites; (2) spillage of tumor cells spillage of tumor cells during manipulation; and (3) a "chimney effect", in which gas flow and leakage during pneumoperitoneum may carry free tumor cells toward the abdominal wall or surrounding tissues, promoting effective cell implantation [24]. An experimental study using inert carbon particles as surrogates for tumor cells has shown that pneumoperitoneum pressure and flow/leakage patterns can influence the particle migration and deposition [25]. Nonetheless, these findings remain largely mechanistic, and our cohort lacks direct evidence on insufflation pressure, leakage control, specimen retrieval, or peritoneal lavage. In addition, PSM for cervical cancer is rare overall (approximately 0.43% across reviews) [24], thus caution is warranted when extrapolating these mechanisms to clinical outcomes. Clinically relevant factors that can be directly addressed during surgery include tumor handling at the vaginal cuff (e.g., whether protective vaginal closure was performed) and the mechanical effects of the uterine manipulator.

The LVSI-related findings are consistent, to some extent, with the SUCCOR study. When protective surgical measures were adopted (e.g., avoiding the uterine manipulator, performing vaginal closure), the prognostic differences between MIS and open surgery were abolished [10]. Similarly, Kanao et al. [26] recently reported that a strict no-manipulator strategy resulted in DFS and OS comparable to open surgery. Collectively, these results indicate that the potential disadvantages of laparoscopic surgery may not stem solely from the surgical route but are closely related to particular intraoperative techniques.

It should be noted that LVSI is determined postoperatively, limiting its utility in preoperative surgical decision-making. LVSI may help explain prognostic heterogeneity by surgical approach and inform postoperative risk stratification and adjuvant therapy decision-making rather serving as the sole criterion for surgical approach selection. In our study, interactions were tested for eight subgroup variables without correction for multiple testing (e.g., Bonferroni testing), and detailed information regarding intraoperative practice such use of uterine manipulator and vaginal closure were unavailable. Therefore, we cannot definitively assess the modifying effect of surgical approach on outcomes. Findings from SUCCOR and subsequent investigations indicate that technical variations can significantly influence the risk of tumor dissemination during MIS. Thus, the observed interaction between LVSI status and surgical approach in the present work should be interpreted cautiously, as it may reflect unmeasured heterogeneity in surgical technique rather than true biological interaction.

Other independent prognostic factors

Multivariable Cox-regression consistently identified depth of stromal invasion ≥1/2, positive LVSI, non-R0 margins, and positive lymph nodes as common independent risk factors for both OS and DFS in this study. These findings are well-aligned with the international literature. Matsuo et al. [27], in a large cohort from the SEER database, demonstrated that deep stromal invasion and lymph node metastasis are strongest predictors of recurrence after surgery for early-stage cervical cancer. Similarly, as pointed out by Cibula et al. [28] in the European Society of Gynaecological Oncology (ESGO) guidelines, positive or close margins (non-R0) influence the decision on adjuvant therapy. The adverse prognostic impact of non-R0 margins in our study (OS HR=2.56; DFS HR=2.78) is in line with these guidelines.

Histological type was an independent factor for OS (non-adenocarcinoma/adenosquamous as protective) but not for DFS. Adenocarcinoma/adenosquamous carcinoma is known to respond less favorably to radiotherapy and concurrent chemoradiotherapy as compared with squamous cell carcinoma, which may limit the OS benefit. Recent evidence regarding salvage therapy post recurrence indicates that the adenocarcinoma subtypes may have worse outcomes post-salvage therapy, possibly manifesting more in OS than DFS [29, 30]. Galic et al. [31] showed that cervical adenocarcinoma has a poorer long-term prognosis than squamous cell carcinoma, and that adjuvant radiotherapy did not significantly reduce this difference. These explanations are limited by the lack of detailed information on post-recurrence treatment in our cohort.

Preoperative laboratory markers examined in this study (NLR, PLR, SCC-Ag, CA125, CEA) did not demonstrate independent prognostic value in multivariable analysis. Although some studies have reported associations between NLR, PLR, and cervical cancer prognosis [32], their independent predictive value in early-stage disease may be overshadowed by established pathological factors such as LVSI, stromal invasion depth, and lymph node involvement. A meta-analysis by Leng et al. [33] similarly concluded that the prognostic utility of inflammatory markers is primarily observed in locally advanced cervical cancer, with limited independent predictive ability in early-stage patients.

Methodological interpretation of pre- and post-weighting differences

An important observation in this study was that surgical approach showed no significant effect on either DFS (P=0.239) or OS (P=0.865) in the unadjusted analysis, whereas after IPTW weighting, the laparoscopic group demonstrated significantly worse DFS. The “reverse after weighting” pattern is consistent with confounding by indication. In clinical practice, open surgery is mostly performed in patients with larger tumors, more advanced stage, or higher-risk pathological features, whereas laparoscopic surgery is preferentially performed in patients considered as “low-risk”. Consequently, the unadjusted analysis did not reflect the true effect of surgical approach on outcomes due to baseline bias. For example, SMD before weighting exceeded 0.1 for albumin (SMD=0.209), tumor size (SMD=0.152), and adjuvant therapy (SMD=0.132), indicating considerable baseline imbalance.

IPTW assigns each patient a weight equal to the inverse probability of receiving the treatment actually received, thereby creating a pseudo-randomized cohort balanced on all measured confounders. In this study, IPTW weights were concentrated in lower ranges without extreme values, and propensity score distributions after weighting exhibited good overlap, supporting stable estimation. Unlike PSM, IPTW uses the full sample and avoids information loss due to matching. For instance, the sensitivity analysis using 1:1 PSM reduced the sample size to 342 patients with just 50 events, resulting in a non-significant DFS HR (P=0.208) that remained directionally consistent. This demonstrates the methodological advantage of IPTW in limited-sample cohort studies. As noted by Austin et al. [34], IPTW is considered superior to PSM regarding control of bias and statistical power in observational studies, particularly for survival analyses with rare events.

Nevertheless, IPTW can only adjust for measured confounders. Residual confounding may persist due to unmeasured factors, such as surgeon experience, composition of the surgical team, and specific intraoperative details. The lack of a significant OS effect is expected, as OS captures fewer death events compared with DFS, which includes both recurrence plus death. The greater number of events in DFS confers higher statistical power explaining why DFS reached strong statistical significance while OS did not.

Value of evidence from a Chinese population

According to GLOBOCAN [35], China has one of the highest cervical cancer burdens worldwide, with approximately 110,000 new cases per year. However, high-quality population-based data on the impact of surgical approach on prognosis in Chinese patients remain limited. This study, encompassing 840 Chinese patients, provides valuable insight in several aspects. First, squamous cell carcinoma predominates among Chinese cervical cancer patients (approximately 79%), highlighting poten-

tial regional variation in HPV genotype distribution [36], although HP genotyping data were not collected in this study. Whether these differences modify the relationship between surgical approach and oncologic outcomes warrants further investigation. Second, laparoscopic surgery remains a common procedure in Chinese hospitals. Although its use has decreased somewhat since the LACC trial, it still represents a significant portion of procedures [37]. Consequently, data from this study are directly relevant to current clinical practice in China. Finally, the application of IPTW combined with a training-validation internal split framework on a Chinese population strengthens the methodological rigor and adds to the existing evidence based on minimally invasive surgery in a Chinese population.

Limitations

There are some limitations to this study. First, as a retrospective cohort, selection and information bias may exist. Despite the use of IPTW, residual confounding couldn't be entirely excluded, particularly from unmeasured factors such as surgeon experience, surgical team composition, and the learning curve. Second, specific intraoperative details, such as the uterine manipulator use and vaginal cuff closure, were not documented. Prior investigations, including the SUCCOR study and Uppal S et al. [38], suggest that these variables may influence oncologic outcomes, making it unclear whether the observed disparities are due to the surgical route or technique-related tumor cell dissemination. Third, laparoscopic procedures were not distinguished between standard and robot-assisted approaches, which differ in technical execution and learning curve. Although robotic surgery may confer certain technical advantages, meta-analyses have not demonstrated a significant difference in oncologic outcomes [39]. Fourth, the study period (2016-2021) precedes the full publication and widespread adoption of the LACC trial results, introducing potential temporal confounding in MIS practice patterns. Fifth, OS was defined as all-cause mortality and cause-specific mortality data were unavailable, which may partly explain discrepancies between OS and DFS results. Sixth, small sample size and few events in some validation-subgroups resulted in wide confidence interval and unstable HR estimates. Multiple subgroup interaction tests were performed without adjustment for multiplicity; therefore, these results should be interpreted cautiously as exploratory and require validation in independent external cohorts. Seventh, follow-up duration varied due to staggered enrollment. Consequently, not all patients achieved a complete 5-year follow-up by the data cutoff (January 2026), with earlier enrollees contributing disproportionally to outcome events. All time-to-event analyses were conducted using right-censoring from the date of surgery, and Cox proportional hazards models account for varying follow-up durations. Calendar year of surgery was included in multivariable models to partially adjust for temporal trends. Despite these measures, residual impact of follow-up variability on observed associations cannot be entirely excluded. Finally, despite the multicenter design, all centers came were located in South China, potentially limiting external generalizability to other regions.

Future directions and clinical implications

High-quality prospective evidence is needed to clarify the safety of MIS for early-stage cervical cancer. Currently ongoing randomized controlled trials, such as the LAGCC trial in China [15] and the CIRCLE trial in South Korean [40], are anticipated to provide further insights, particularly under standardized technical conditions (e.g., avoidance of uterine manipulator and use of adequate vaginal closure). Further validation of LVSI as a prognostic factor, along with advances in preoperative prediction methods (e.g. radiomics or molecular biomarkers) may allow for more individualized surgical decision-making. Comparative studies between robot-assisted and conventional laparoscopy, as well as temporal trend analyses of MIS outcomes, are also warranted.

Clinically, MIS for early-stage cervical cancer should be performed with strict oncologic protection techniques. Comprehensive informed consent regarding potential risks is essential. Among patients with high-risk features, such as positive LVSI, this study did not detect a clear difference between surgical approaches, though this may have been influenced by adjuvant therapy and limited subgroup sample sizes. Surgical decision-making should priori-

tize oncologic safety over other considerations.

Conclusions

In this retrospective multicenter cohort of patients with IA2-IB1 cervical cancer, laparoscopic surgery was associated with inferior disease-free survival compared with open surgery after IPTW adjustment, while no significant difference was observed in overall survival. The findings of LVSI subgroup should be interpreted with caution, as they are exploratory. Due to the lack of detailed documentation of key surgical techniques, it is unclear whether such factors influenced outcomes. Although previous studies suggest that protective measures during minimally invasive surgery may improve oncologic safety, they were not assessed in this study and require further validation. Therefore, selection of surgical approach must be made with caution.

Disclosure of conflict of interest

None.

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