# Minimally Invasive Versus Open Surgery for Radical Hysterectomy Followed By Adjuvant Radiotherapy in Intermediate- or High-Risk Early-Stage Cancer of The Cervix: A Retrospective Study

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## Abstract

# Background

Postoperative radiotherapy (RT) or chemoradiotherapy (CRT) improves outcomes of cervical cancer patients with risk factors. Minimally invasive surgery (MIS) has an inferior survival than open radical hysterectomy (ORH), however, the impact of MIS on postoperative RT remains uncertain. The study compared the impacts of MIS versus ORH on delivering of adjuvant RT or CRT for intermediate- or high-risk early-stage cervical cancer.

# Methods

Data on stage IB1-IIA2 patients who underwent radical hysterectomy and postoperative RT/CRT in our institution, from 2014 to 2017, were retrospectively collected. Patients with high or intermediate-risk factors who met the Sedlis criteria received postoperative pelvic external beam radiotherapy (50Gy/25f) with platinum-based chemotherapy (0–6 cycles) according to guidelines. Disease-free survival (DFS) and overall survival (OS) were compared in the two surgical groups.

# Results

One hundred and twenty-nine patients eligible for the study (68 in ORH; 61 in MIS groups) had similar clinicopathologic features except for the stage (highest in MIS was IB1; IIA1 in ORH) and presence of lymph vascular space invasion (higher in MIS group). The median time interval from surgery to chemotherapy and to RT was shorter in the MIS group. Three-year DFS and OS were similar in both groups. Further sub-analysis indicated that the DFS and OS in intermediate/high-risk groups had no significant difference. Cox-multivariate analyses found that tumor size > 4 cm and time interval from surgery to RT beyond seven weeks were adverse independent prognostic factors for DFS.

# Conclusions

In early-stage (IB1-IIA2) cervical cancer patients with intermediate or high-risk factors who received postoperative RT or CRT, no matter they received ORH or MIS as their primary treatment, the DFS and OS had no significant difference, despite TI from surgery to postoperative adjuvant therapy being shorter in the MIS group than ORH.

## Introduction

Surgery or radiotherapy (RT), with or without chemotherapy (CT)[1], is the recommended treatment for early-stage cervical cancer. Most patients opt for surgical management. Surgical options for cervical cancer include minimally invasive surgery (MIS) or open radical hysterectomy (ORH). These surgical

methods have comparable 5-year overall survival (OS) and disease-free survival (DFS) rates[2–4], and the National Comprehensive Cancer Network (NCCN) recommendations for cervical cancer (versions before 2018) state that either ORH or MIS are acceptable approaches for radical hysterectomy (RH). However, a multicenter, prospective randomized clinical trial (Laparoscopic Approach to cervical cancer, LACC)conducted in 2018 provided a higher level of evidence for the use of laparoscopy and demonstrated that in patients with early-stage (IA1, IA2, and IB1) cervical cancer, MIS had a higher recurrence rate and a lower DFS and OS rate than open surgery[5]. Comparable results were reported by Melamed *et al.* [6]in their cohort study of 2461 stage IA2-IB1 cervical cancer patients, which compared the survival outcomes of MIS and ORH and demonstrated shorter OS in the MIS group. Hence, these unsatisfactory oncologic outcomes with MIS prompted considerable debate regarding the appropriateness of MIS for cervical cancer.

Postoperative RT or chemoradiotherapy (CRT) can reduce the risk of recurrence and prolongs progression-free survival (PFS) in cervical cancer patients [7–9]. It was recommended for patients with one or more high-risk factors or a combination of intermediate-risk factors to receive adjuvant therapy[10]. In the LACC trial [5], the percentage of patients who received adjuvant therapy was similar in MIS and ORH groups; however, this group does not include all patients who should receive adjuvant therapy but did not. Adjuvant therapy might be a significant confounding factor in MIS and open surgery[11]. Therefore, we collected and analyzed the data of early-stage cervical cancer patients with intermediate- or high-risk factors and had received RT or CRT following MIS or open surgery in our institution.

## Methods

# Patients

This study included patients diagnosed with stage IB1-IIA2 cervical cancer according to the 2009 FIGO staging system[12]. All patients underwent a type III RH[13] with pelvic lymph node dissection, and patients with high or intermediate-risk factors that met the Sedlis criteria had received postoperative external beam radiotherapy (EBRT), with or without CT in our hospital, from 2014 to 2017 (Fig. 1). Patients were excluded from the study if they had previously received RT, had missing clinical or pathological data or had relapsed before receiving RT. Patients were divided into two groups based on the surgical approach: the open radical hysterectomy (ORH) and minimally invasive surgery (MIS) groups.

# Treatment regimen

Following RH, patients with intermediate or high-risk factors should receive postoperative adjuvant therapy, as recommended by the NCCN guidelines[10]. Intermediate-risk factors include lympho vascular involvement (LVSI), stromal invasion, and tumor size[14], and high-risk factors include lymph node-positive, parametrial involvement, and margin status [7]. We implemented adjuvant RT and 4–6 cycles of platinum-based CT when one or more high-risk characteristics were present. Patients with multiple intermediate-risk factors that met the Sedis criteria received adjuvant RT and 2–4 cycles of platinum-

based CT[10]. All patients received EBRT following surgery utilizing pelvic intensity-modulated radiotherapy (IMRT) or three-dimensional conformal radiation therapy (3D-CRT) with computed tomography-based treatment planning. The clinical target volume was determined using the criteria of the Radiation Therapy Oncology Group[15]. EBRT was delivered at a dose of 2 Gy/d on five days per week (total dose 50 Gy). Brachytherapy was given to patients with positive vaginal margins or vaginal invasion close to the surgical margin (0.5 cm).

# Data collection and follow-up

Patient data were retrospectively collected by reviewing the medical record system of our hospital. The following data were obtained: baseline demographics, histologic type, FIGO stage, tumor size, surgical approach, pelvic lymph nodes involvement, and other risk factors identified by pathological examination. We also collected data regarding adjuvant treatments such as CT, RT, or brachytherapy, the initiation of CT or RT, and the number of CT cycles.

Follow-up information was obtained through outpatient clinic appointments and a telephone questionnaire. The primary outcome was DFS, defined as the period from surgery to the detection of recurrence or cervical cancer-related death. The secondary outcome was OS, defined as the period from initial surgery to cervical cancer-related death.

# Statistical analysis

For continuous variables, we used the non-paired Student's t-test and the Mann-Whitney U test, and used Pearson’s chi-squared test or Fisher’s exact test for categorical variables. To compare and analyze survival data between the two surgery groups, Kaplan-Meier methods and the log-rank test were utilized. The threshold for statistical significance was fixed at $P < 0.05$. Clinical risk factors affecting survival outcomes were analyzed by using Cox regression models. SPSS version 22 was used to conduct all statistical analyses.

## Results

# Patient characteristics

One hundred twenty-nine cervical cancer patients with stage IB1–IIA2 were included in the study: 68 (52.7%) in the ORH group and 61 (47.2%) in the MIS group (78.7% laparoscopic and 21.3% robotic surgery). Table 1 summarizes the clinicopathological information. The clinicopathological parameters of the two surgery groups had no significant difference except for the stage and the presence of LVSI. In terms of the FIGO stage, the highest percentage was stage IB1 (45.9%) in the MIS group and IIA1 (47.1%) in the ORH group ($P = 0.046$). The proportion of patients with LVSI was higher in the MIS group (42.6% vs. 19.1%. $P = 0.004$). There were 21 (30.9%) patients with high-risk factors in the ORH group and 29 (47.5%) in the MIS group ($P = 0.053$).

Table 1
**Baseline characteristics in different group**

| Characteristic | ORH(n = 68) | MIS(n = 61) | *P* value |
|---|---|---|---|
| Age, years | 46(27–61) | 47(35–59) | 0.4 |
| FIGO stage | | | 0.046 |
| IB1 | 24(35.3) | 28(45.9) | |
| IB2 | 5(7.4) | 12(19.7) | |
| IIA1 | 32(47.1) | 17(27.9) | |
| IIA2 | 7(10.3) | 4(6.6) | |
| Tumor size | | | 0.097 |
| > 4.0cm | 11(16.2) | 14(23) | |
| > 2cm,≤4cm | 44(64.7) | 28(45.9) | |
| ≤ 2.0cm | 13(19.1) | 19(31.1) | |
| Histology | | | 0.510 |
| Squamous cell carcinoma | 62(91.2) | 58(95.1) | |
| Adenocarcinoma | 4(5.9) | 1(1.6) | |
| Others | 2(2.9) | 2(3.3) | |
| Grade | | | 0.09 |
| 1 | 3(4.4) | 2(3.3) | |
| 2 | 45(66.2) | 32(52.5) | |
| 3 | 20(29.4) | 27(44.3) | |
| Pelvic node | | | 0.053 |
| Positive | 20(29.4) | 28(45.9) | |
| Negative | 48(70.6) | 33(54.1) | |
| LVSI | | | 0.004 |
| Positive | 13(19.1) | 26(42.6) | |
| Negative | 55(80.9) | 35(57.4) | |
| Stromal invasion | | | 0.753 |
| Invasion depth > 1/2 | 58(85.3) | 47(77.0) | |

Data are given as the median (range) or number (%).

| Characteristic | ORH(n = 68) | MIS(n = 61) | *P* value |
|---|---|---|---|
| Invasion depth < 1/2 | 10(14.7) | 12(19.7) | |
| No | 0(0) | 2(3.3) | |
| Surgical margin | | | 0.212 |
| Positive | 5(7.4) | 1(1.6) | |
| Negative | 63(92.6) | 60(98.4) | |
| Prognostic risk group | | | 0.053 |
| High-risk | 21(30.9) | 29(47.5) | |
| Intermediate-risk | 47(69.1) | 32(52.5) | |
| Data are given as the median (range) or number (%). | | | |

**FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymph vascular space invasion; Treatment**

Table 2 summarizes the postoperative adjuvant therapy protocol. Gynecologists and radiation oncologists administered the treatments. The most common radiation technique in the study was IMRT (76.5% in the ORH group and 83.6% in the MIS group, $P = 0.313$), with only a few patients receiving 3D-CRT. Most patients were treated with postoperative CRT (88.2% in the ORH group and 88.5% in the MIS group, $P = 0.959$), and only a few patients received postoperative RT alone. The two groups had equivalent rates of postoperative RT, CT, and intracavitary radiotherapy. However, the MIS group had a shorter median time interval (TI) from surgery to CT (7 days vs. 8 days, $P = 0.014$) and from surgery to RT (28 days vs. 35 days, $P = 0.00$) compared with the ORH group. The number of patients who suffered from grade 3 or 4 gastrointestinal (GI) and genitourinary (GU) toxicity was slight, and hematologic (HT) toxicity was the most common severe side effect (47.1% in the ORH group and 26.2% in the MIS group, respectively; P = 0.015).

Table 2
Treatment details for two groups

| Treatment | ORH(n = 68) | MIS(n = 61) | *P* value |
|---|---|---|---|
| Technique | | | 0.313 |
| IMRT | 52(76.5) | 51(83.6) | |
| 3D-CRT | 16(23.5) | 10(16.4) | |
| Postoperative treatment | | | 0.959 |
| RT alone | 8(11.8) | 7(11.5) | |
| RT + CT | 60(88.2) | 54(88.5) | |
| Intracavitary radiotherapy | 7(10.4) | 3(5.0) | 0.332 |
| Chemotherapy before RT | | | 0.242 |
| YES | 53(77.9) | 42(68.9) | |
| NO | 15(22.1) | 19(31.1) | |
| CT cycles before RT | 1(0–3) | 1(0–4) | 0.1 |
| TI (surgery to CT), days | 8(5–17) | 7(5–14) | 0.014 |
| TI (Surgery to RT), days | 35(18–100) | 28(16–120) | 0.00 |
| ≤ 42 | 45(66.2) | 51(83.6) | |
| 43–49 | 13(19.1) | 3(4.9) | |
| ≥ 49 | 10(14.7) | 7(11.6) | |
| Total CT cycles | 3.5(0–6) | 4(0–6) | 0.089 |
| Grade 3–4 adverse effect | | | |
| Hematologic | 32(47.1) | 16(26.2) | 0.015 |
| Gastrointestinal | 2(2.9) | 0(0) | 0.506 |
| Genitourinary | 4(5.9) | 2(3.3) | 0.683 |

Data are given as the median (range), or number (%)

RT: radiotherapy; CT: chemotherapy; TI: time interval.

# Survival Outcomes

The last follow-up time was April 2021. The average follow-up duration was 67.5 months (interquartile range: 52–78 months). The data were censored at the time of last follow-up or cancer-related death.

Patients in the MIS group who underwent postoperative RT or CRT had a slightly lower 3-year DFS and OS than those in the ORH group (85.2% vs 89.7%, $P = 0.274$; 89.9% vs 98.5%, $P = 0.499$, respectively) (Fig. 2A,2B). Subgroup survival analyses in the intermediate-risk and high-risk groups revealed no significant differences in DFS and OS between the two surgical approaches (Fig. 2C-2F). Univariate and multivariate analysis for DFS is shown in Table 3. In the univariate analysis, only the FIGO stage, tumor size, and TI from surgery to RT (> 7 weeks) were significantly associated with DFS. After being adjusted for age, histologic type, tumor grade, intermediate- and high-risk factors, the tumor size (> 4 cm) and TI from surgery to RT (> 7 weeks) were independent poor predictive variables for DFS.

The recurrence and mortality rates were summarized in Table 4; there was no difference in the recurrence rate or pattern between the two groups ($P = 0.463$ and $P = 0.709$, respectively). Until the last follow-up, five (7.3%) patients in the ORH group and six (9.8%) patients in the MIS group had died of cervical cancer ($P = 0.614$).

Table 3
Univariate and multivariate analysis for DFS

| characteristics | Univariate analysis | | | multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | P value | Adjusted HR | 95%CI | P value |
| Age (≥ 45 VS < 45) | 1.16 | 0.47–2.88 | 0.75 | | | |
| FIGO stage | 1.79 | 1.11–2.87 | 0.016 | | | |
| Tumor size (> 4cm VS ≤ 4cm) | 4.33 | 1.76–10.67 | 0.001 | 4.42 | 1.79–10.92 | 0.001 |
| Histology (SC VS Others) | 0.66 | 0.15–2.84 | 0.57 | | | |
| differentiation | 0.97 | 0.42–2.25 | 0.94 | | | |
| Deep invasion | 0.62 | 0.22–1.72 | 0.36 | | | |
| Surgical margin | 1.13 | 0.15–8.47 | 0.91 | | | |
| LVSI | 1.15 | 0.44–3.02 | 0.78 | | | |
| LN metastasis | 1.22 | 0.49–3.04 | 0.67 | | | |
| TI (surgery to CT) (> 7d vs ≤ 7d) | 0.77 | 0.25–2.39 | 0.65 | | | |
| TI (surgery to RT) (> 7 weeks VS ≤ 7 weeks) | 4.22 | 1.60-11.22 | 0.004 | 4.34 | 1.64–11.50 | 0.003 |
| CT cycles (> 4) | 2.01 | 0.82–4.94 | 0.13 | | | |

SC: Squamous arcinoma; Others: include adenocarcinoma, adenosquamous carcinoma; LN: lymph node; TI: time interval; CT: chemotherapy; RT: radiotherapy:

Table 4
Recurrences and death

| characteristics | ORH (n, %) | MIS(n,%) | *P* value |
|---|---|---|---|
| Patients with recurrences | 8(11.8) | 11(18) | 0.463 |
| Recurrence site | | | 0.709 |
| Local | 5(62.5) | 5(45.5) | |
| Vagina | 4 | 4 | |
| Pelvis | 1 | 1 | |
| Distal | 3(37.5) | 6(54.5) | |
| Lung | 1 | 2 | |
| Multi recurrence | 1 | 2 | |
| unknown | 1 | 2 | |
| Total death | 5(7.3) | 6(9.8) | 0.614 |

# Discussion

Adjuvant RT or CRT is typically delivered after RH for early-stage cervical cancer patients with certain risk factors. One study from Levine Cancer Institute (one of the LACC trial centers) indicated that adjuvant therapy might be an important confounder for the survival outcomes of MIS and open surgery [11]. MIS is associated with a shorter recovery time and a lower risk of postoperative complications than ORH [5], and the TI from surgery to adjuvant may differ. We hypothesized that the initiation of postoperative RT or CRT might impact survival outcomes among the treatment-related variables. The results of the present study have confirmed the hypothesis.

We found that the DFS and OS had no significant difference in both groups, despite the TI from surgery to postoperative CT or RT being shorter in the MIS group. Tumor size > 4 cm and TI from surgery to RT beyond seven weeks were revealed to be independent predictive variables for DFS after being adjusted for important prognostic parameters.

The study results showed that the DFS and OS were similar between the MIS and ORH groups, which were different from the outcomes of the LACC trial. The following factors might explain the different results. Firstly, the surgical-related factors that may result in poor survival, such as utilizing uterine manipulator, the effect of insufflation gas (CO2), and the degree of resection, can be improved by postoperative RT or CRT [5, 6, 8, 16]. Furthermore, the TI from surgery to postoperative CT and RT were shorter in the MIS group, resulting in a shorter overall treatment time, which was a critical factor for pelvic control and survival in cervical cancer[17].

Most patients in the study received pelvic IMRT, which could reduce the toxicity of postoperative RT with a non-inferior survival outcome[18, 19]. The update of GOG 92[9], a randomized trial of postoperative RT versus no further therapy in stage IB cervical cancer after RH, revealed that the 3-year PFS and OS was around 86% and 88% for patients with intermediate-risk factors. In high-risk patients, the three-year PFS and OS were around 84% and 88% [7]. Similarly, our research indicated that the 3-year DFS rates and OS rates in ORH and MIS groups were 89.7% vs. 85.2% and 98.5% vs. 89.9%, respectively. Meanwhile, IMRT helps decrease GI and GU toxicity, with a greater incidence of grade 3 or higher acute HT complications[20].

Tumor size is generally accepted as an independent prognostic factor [21, 22]. However, the optimal time to start postoperative RT in individuals with risk factors has not been well defined. The role of postoperative adjuvant therapy is to control the residual subclinical disease. Some animal studies revealed that surgery might stimulate angiogenesis by releasing circulating growth factors and accelerating the growth of minimal residual disease[23, 24]. The delay in postoperative adjuvant therapy could allow more time for a tumor cell to proliferate, and the early initiation of postoperative adjuvant treatment might improve oncological outcomes. In the present study, the median time for patients to receive postoperative adjuvant CT and RT were seven days vs. eight days, and 28 days vs. 35 days in MIS and ORH groups, respectively. We delivered adjuvant therapy in such a short TI and got a favorable survival outcome. It showed that patients received postoperative adjuvant treatment timely is very important to ensure the treatment outcome.

We found that the median TI from surgery to RT beyond seven weeks had an independent significant adverse effect on survival. The median TI from surgery to RT was within seven weeks; despite some differences in both groups, the slight disparity has little impact on DFS. Consistent with our results, Hanprasertpong J. et al. [25] found that delaying adjuvant therapy in patients with early-stage squamous cell cervical cancer beyond four weeks after surgery resulted in a lower RFS. And Jhawar. et al. [26] concluded that postoperative therapy should be administered within eight weeks after surgery whenever possible. Although the definite initiate time of postoperative adjuvant therapy is not clear in cervical cancer, it is recommended for postoperative RT to be delivered as early as possible.

This study has some limitations worth noting. It is a retrospective study performed at a single institution, and the retrospective study design has inherent biases and limitations. A multicenter study with larger sample size and longer follow-up duration is needed to verify these results.

In conclusion, for the early-stage (IB1-IIA2) cervical cancer patients with intermediate or high-risk factors who received postoperative RT or CRT, no matter they received ORH or MIS as their primary treatment, the DFS and OS had no significant difference, despite TI from surgery to postoperative adjuvant therapy being shorter in the MIS group than ORH.

# Abbreviations

| RT | Radiotherapy |
|---|---|
| CRT | Chemoradiotherapy |
| MIS | Minimally invasive surgery |
| ORH | Open radical hysterectomy |
| DFS | Disease-free survival |
| OS | Overall survival |
| CT | Chemotherapy |
| NCCN | National Comprehensive Cancer Network |
| RH | Radical hysterectomy |
| LACC | Laparoscopic Approach to cervical cancer |
| PFS | Progression-free survival |
| LVSI | Lymph vascular involvement |
| IMRT | Intensity-modulated radiotherapy |
| EBRT | External beam radiotherapy |
| 3D-CRT | Three-dimensional conformal radiation therapy |
| TI | Time interval |
| GI | Gastrointestinal |
| GU | Genitourinary |
| HT | Hematologic |

# Declarations


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### Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiao Tong University (No. XJTU1AF2021LSK-257). The informed consent was exempted due to the retrospective nature of the study. We confirm that all methods were performed in accordance with the relevant guidelines and regulations.

### Consent for publication

Not applicable.

## Availability of data and materials

The data used and analyzed in the current study are available from the corresponding author upon reasonable request.

## Conflict of interest statement

The authors declare that they have no competing interests.


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None


## Author Contribution

Study concept and design: Zi Liu, Ya-li Wang

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Analysis and interpretation of data: Qi-ying Zhang, Juan Wang, Jin Su.

Wrote, reviewed, and/or revised the manuscript: Qi-ying Zhang, Zi Liu, Tao Wang, Fan Shi

All authors read and approved the final manuscript.

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# References

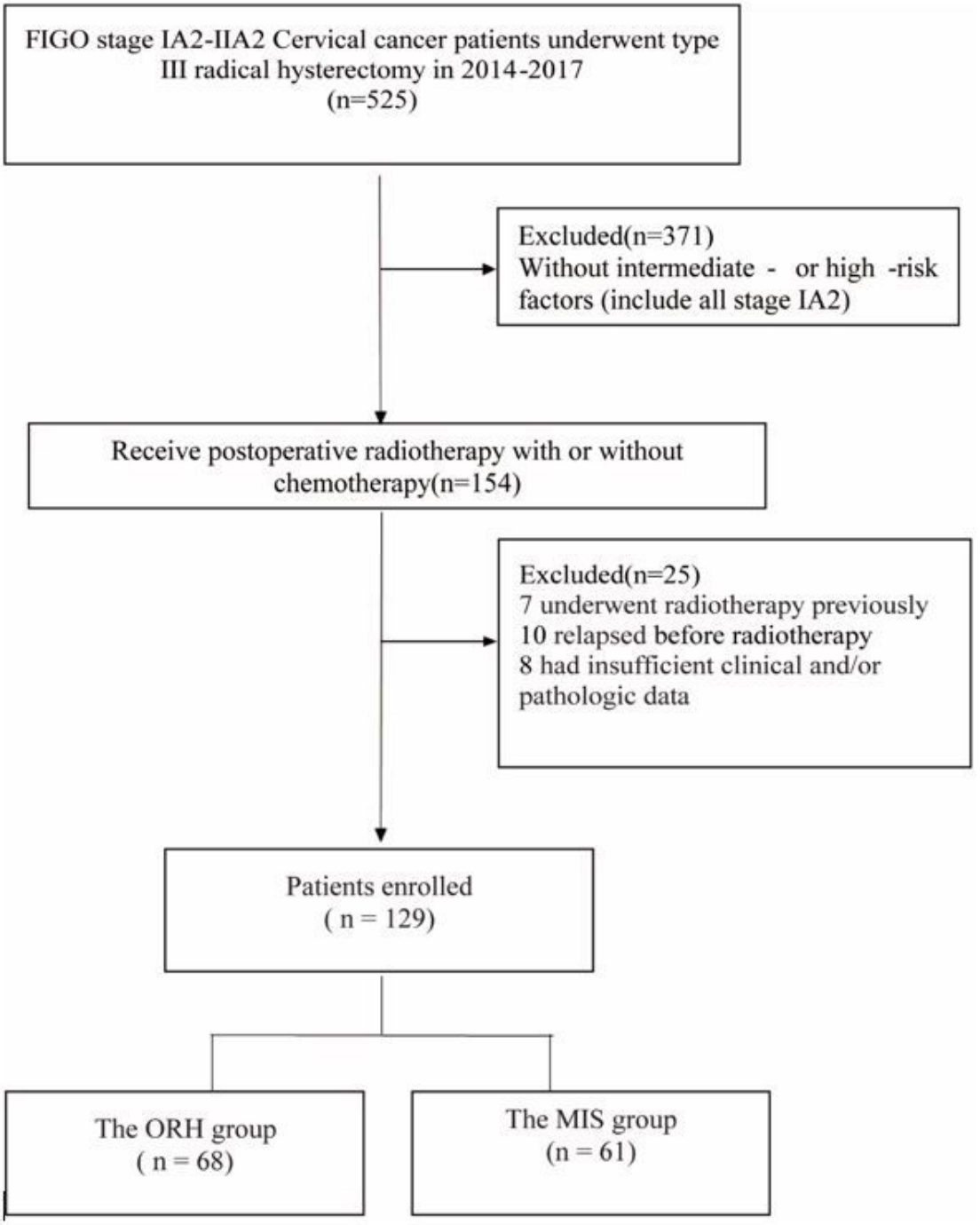
1. Landoni F, Colombo A, Milani R, Placa F, Zanagnolo V, Mangioni C: **Randomized study between radical surgery and radiotherapy for the treatment of stage IB-IIA cervical cancer: 20-year update**. *Journal of Gynecologic Oncology* 2017, **28**(3).
2. Kwon BS, Roh HJ, Lee S, Yang J, Song YJ, Lee SH, Kim KH, Suh DS: **Comparison of long-term survival of total abdominal radical hysterectomy and laparoscopy-assisted radical vaginal hysterectomy in patients with early cervical cancer: Korean multicenter, retrospective analysis**. *Gynecologic Oncology* 2020, **159**(3):642–648.
3. Mendivil AA, Rettenmaier MA, Abaid LN, Brown JV, Micha JP, Lopez KL, Goldstein BH: **Survival rate comparisons amongst cervical cancer patients treated with an open, robotic-assisted or laparoscopic radical hysterectomy: A five year experience**. *Surg Oncol* 2016, **25**(1):66–71.
4. Brandt B, Sioulas V, Basaran D, Kuhn T, LaVigne K, Gardner GJ, Sonoda Y, Chi DS, Roche KCL, Mueller JJ *et al*: **Minimally invasive surgery versus laparotomy for radical hysterectomy in the management of early-stage cervical cancer: Survival outcomes**. *Gynecologic Oncology* 2020, **156**(3):591–597.
5. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, Buda A, Yan X, Shuzhong Y, Chetty N *et al*: **Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer**. *N Engl J Med* 2018, **379**(20):1895–1904.
6. Melamed A, Margul DJ, Chen L, Keating NL, Del Carmen MG, Yang J, Seagle BL, Alexander A, Barber EL, Rice LW *et al*: **Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer**. *N Engl J Med* 2018, **379**(20):1905–1914.
7. Peters WA, Liu PY, Barrett RJ, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon W, Alberts DS: **Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix**. *Journal of Clinical Oncology* 2000, **18**(8):1606–1613.
8. Kim SI, Kim TH, Lee M, Kim HS, Chung HH, Lee TS, Jeon HW, Kim JW, Park NH, Song YS: **Impact of Adjuvant Radiotherapy on Survival Outcomes in Intermediate-Risk, Early-Stage Cervical Cancer: Analyses Regarding Surgical Approach of Radical Hysterectomy**. *J Clin Med* 2020, **9**(11).
9. Rotman M, Sedlis A, Piedmonte MR, Bundy B, Lentz SS, Muderspach LI, Zaino RJ: **A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor**

**prognostic features: follow-up of a gynecologic oncology group study**. *Int J Radiat Oncol Biol Phys* 2006, **65**(1):169–176.

10. Koh WJ, Greer BE, Abu-Rustum NR, Apte SM, Campos SM, Chan J, Cho KR, Cohn D, Crispens MA, DuPont N *et al*: **Cervical cancer**. *J Natl Compr Canc Netw* 2013, **11**(3):320–343.
11. Levine MD, Brown J, Crane EK, Tait DL, Naumann RW: **Outcomes of Minimally Invasive versus Open Radical Hysterectomy for Early Stage Cervical Cancer Incorporating 2018 FIGO Staging**. *J Minim Invasive Gynecol* 2021, **28**(4):824–828.
12. Pecorelli S: **Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium**. *Int J Gynaecol Obstet* 2009, **105**(2):103–104.
13. Piver MS, Rutledge F, Smith JP: **Five classes of extended hysterectomy for women with cervical cancer**. *Obstet Gynecol* 1974, **44**(2):265–272.
14. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ: **A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study**. *Gynecol Oncol* 1999, **73**(2):177–183.
15. Small W, Jr., Mell LK, Anderson P, Creutzberg C, De Los Santos J, Gaffney D, Jhingran A, Portelance L, Schefter T, Iyer R *et al*: **Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer**. *Int J Radiat Oncol Biol Phys* 2008, **71**(2):428–434.
16. Nie JC, Wu QJ, Yan AQ, Wu ZY: **Impact of different therapies on the survival of patients with stage I-IIA cervical cancer with intermediate risk factors**. *Ann Transl Med* 2021, **9**(2).
17. Huang EY, Lin H, Wang CJ, Chanchien CC, Ou YC: **Impact of treatment time-related factors on prognoses and radiation proctitis after definitive chemoradiotherapy for cervical cancer**. *Cancer Med* 2016, **5**(9):2205–2212.
18. Tsuchida K, Murakami N, Kato T, Okuma K, Okamoto H, Kashihara T, Takahashi K, Inaba K, Igaki H, Nakayama Y *et al*: **Postoperative pelvic intensity-modulated radiation therapy reduced the incidence of late gastrointestinal complications for uterine cervical cancer patients**. *J Radiat Res* 2019, **60**(5):650–657.
19. Yamamoto T, Umezawa R, Tokunaga H, Kubozono M, Kozumi M, Takahashi N, Matsushita H, Kadoya N, Ito K, Sato K *et al*: **Clinical experience of pelvic radiotherapy or chemoradiotherapy for postoperative uterine cervical cancer using intensity-modulated radiation therapy**. *J Radiat Res* 2020, **61**(3):470–478.
20. Isohashi F, Mabuchi S, Yoshioka Y, Seo Y, Suzuki O, Tamari K, Yamashita M, Unno H, Kinose Y, Kozasa K *et al*: **Intensity-modulated radiation therapy versus three-dimensional conformal radiation therapy with concurrent nedaplatin-based chemotherapy after radical hysterectomy for uterine cervical cancer: comparison of outcomes, complications, and dose-volume histogram parameters**. *Radiat Oncol* 2015, **10**:180.

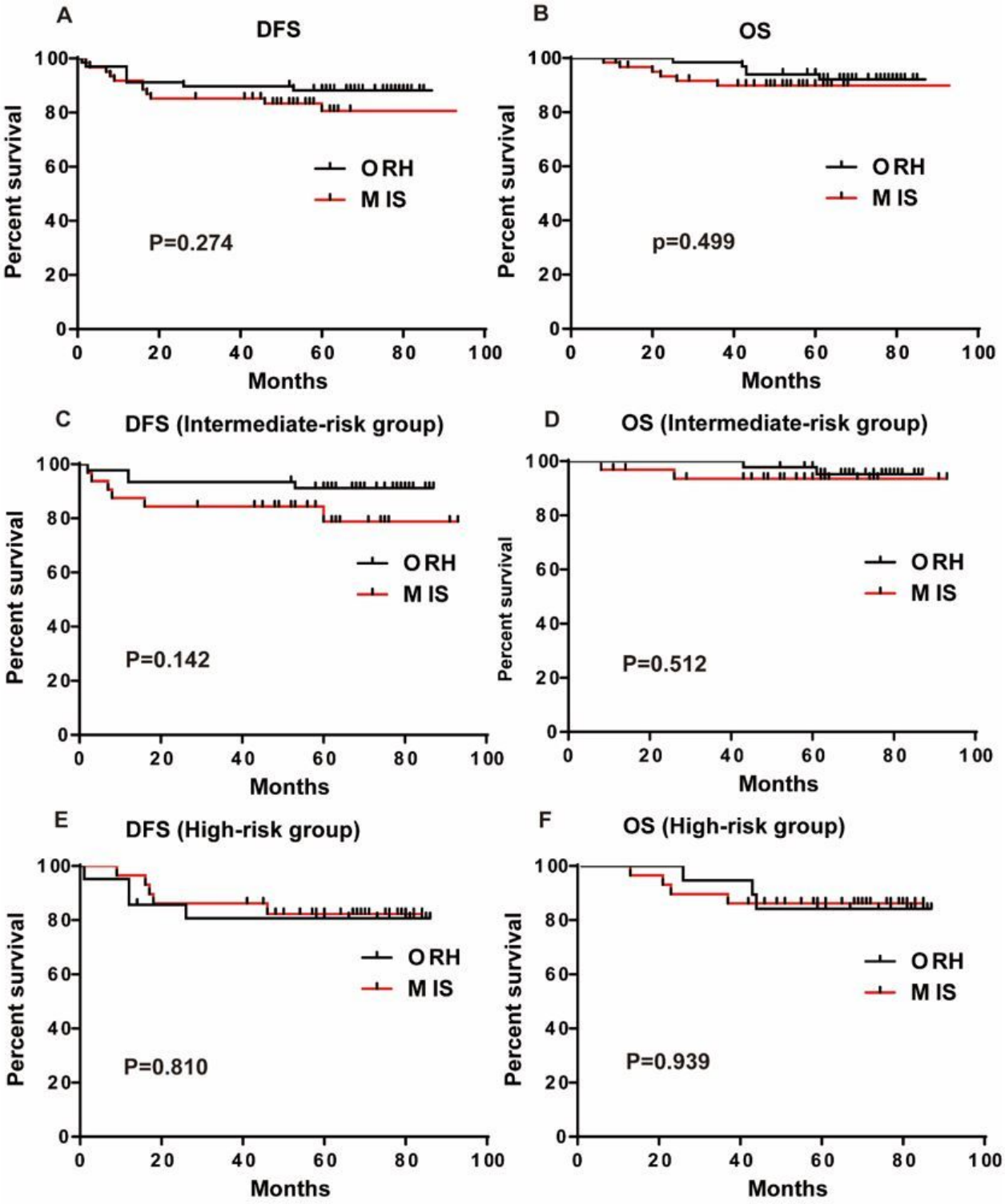
21. Li D, Xu X, Yan D, Yuan S, Ni J, Lou H: **Prognostic factors affecting survival and recurrence in patients with early cervical squamous cell cancer following radical hysterectomy**. *J Int Med Res* 2020, **48**(4):300060519889741.
22. Casarin J, Buda A, Bogani G, Fanfani F, Papadia A, Ceccaroni M, Malzoni M, Pellegrino A, Ferrari F, Greggi S *et al*: **Predictors of recurrence following laparoscopic radical hysterectomy for early-stage cervical cancer: A multi-institutional study**. *Gynecol Oncol* 2020, **159**(1):164–170.
23. Biagi JJ, Raphael MJ, Mackillop WJ, Kong WD, King WD, Booth CM: **Association Between Time to Initiation of Adjuvant Chemotherapy and Survival in Colorectal Cancer A Systematic Review and Meta-analysis**. *Jama-J Am Med Assoc* 2011, **305**(22):2335–2342.
24. Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E: **Presence of a growth-stimulating factor in serum following primary tumor removal in mice**. *Cancer Res* 1989, **49**(8):1996–2001.
25. Hanprasertpong J, Jiamset I, Geater A, Leetanaporn K, Peerawong T: **Impact of time interval between radical hysterectomy with pelvic node dissection and initial adjuvant therapy on oncological outcomes of early stage cervical cancer**. *Journal of Gynecologic Oncology* 2017, **28**(4).
26. Jhawar S, Hathout L, Elshaikh MA, Beriwal S, Small W, Jr., Mahmoud O: **Adjuvant Chemoradiation Therapy for Cervical Cancer and Effect of Timing and Duration on Treatment Outcome**. *Int J Radiat Oncol Biol Phys* 2017, **98**(5):1132–1141.

# Figures




## Figure 1

Flow diagram. ORH: open abdominal radical hysterectomy; MIS: minimally invasive surgery, include laparoscopic or robot-assisted radical hysterectomy.




## Figure 2

Comparisons of survival outcomes in MIS and ORH groups. Comparisons of survival outcomes of early-stage patients with intermediate- or high-risk factors in MIS and ORH groups. (A) Disease-free survival (DFS). (B)Overall survival (OS). (C) DFS in intermediate-risk patients. (D) OS in intermediate-risk patients. (E) DFS in high-risk patients. (F) OS in high-risk patients.