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Comparison of survival outcomes between minimally invasive surgery and conventional open surgery for radical hysterectomy as primary treatment in patients with stage IB1–IIA2 cervical cancer

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HIGHLIGHTS

- We investigated survival outcome of radical hysterectomy (RH) by laparoscopic surgery in early-stage cervical cancer.
- Compared to open RH, minimally invasive surgery (MIS) was associated with higher recurrence rates.
- MIS RH was not a poor prognostic factor in patients with stage IB1 and cervical mass size ≤2 cm on pre-operative MRI.

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ABSTRACT

Objective. To compare survival outcomes of minimally invasive surgery (MIS) and conventional open surgery for radical hysterectomy (RH) among patients with early-stage cervical cancer (CC).

Methods. We retrospectively identified stage IB1-IIA2 CC patients who underwent either laparoscopic or open Type C RH between 2000 and 2018. Patients' clinicopathologic characteristics and survival outcomes were compared according to the surgical approach. For a more robust statistical analysis, we narrowed the study population down to the patients with stage IB1 who underwent pre-operative MRI.

Results. In total, 435 and 158 patients were assigned to open surgery and MIS groups, respectively. MIS group had significantly less parametrial invasion (6.3% vs. 15.4%; $P = 0.004$). Despite similar proportions of patients received adjuvant treatment, concurrent chemoradiation therapy was performed less frequently in MIS group. After a median follow up of 114.8 months, the groups showed similar overall survival; however, MIS group displayed poorer progression-free survival (PFS; 5-year rate, 78.5% vs. 89.7%; $P < 0.001$). Multivariate analyses identified MIS as an independent poor prognostic factor for PFS (adjusted HR, 2.883; 95% CI, 1.711–4.859; $P < 0.001$). Consistent results were observed among 349 patients with stage IB1: MIS was associated with higher recurrence rates (adjusted HR, 2.276; 95% CI, 1.039–4.986; $P = 0.040$). However, MIS did not influence PFS of stage IB1 patients with cervical mass size ≤2 cm on pre-operative MRI (adjusted HR, 1.146; 95% CI, 0.278–4.724; $P = 0.850$).

Conclusions. Overall, MIS RH was associated with higher recurrence rates than open RH in patients with early-stage CC. However, MIS was not a poor prognostic factor among those with stage IB1 and cervical mass size ≤2 cm on pre-operative MRI.

1. Introduction

Cervical cancer (CC) is the fourth most common cancer in women, accounting for 527,600 new cases and 265,700 deaths each year globally [1]. In 2018, CC is estimated to account for 1.5% (13,240) of new cancer cases among women in the United States [2]. In Korea, although its incidence has been decreasing, CC is still more prevalent than in Western countries and is expected to account for 3.1% (2910) of new cancer cases among women [3,4].

Radical hysterectomy (RH) with bilateral pelvic lymph node dissection is recommended as the standard treatment for early-stage CC [International Federation of Gynecology and Obstetrics (FIGO) stage IB1 or IIA1 disease]. RH accompanied by adjuvant treatment is also a

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recommended treatment option for bulky tumors in stage IB2 or IIA2 [5–8]. In the era of minimally invasive surgery (MIS), RH is commonly performed by laparoscopic surgery or robot-assisted surgery, both supported by evidence of oncologic safety in real-world clinical practice [9–12].

MIS has been accepted in cancer treatment because compared with conventional laparotomic surgery in patients with various cancer types, it reduces operative morbidity and shortens hospital stays without compromising survival outcomes [13–16]. A recent phase III randomized trial in patients with CC, named as the "Laparoscopic Approach to Carcinoma of the Cervix (LACC) trial," reported discouraging results, however: patients that underwent MIS for RH had higher recurrence rates and worse overall survival compared with patients that underwent open surgery for RH [17].

There are some controversies surrounding the LACC trial. For example, the recurrence rate was low compared with that in other studies, probably because of a short follow-up period, and the proficiency of the surgeons performing the MIS has been questioned [18–21]. In addition, confirmation studies that consider the medical circumstances of different countries are warranted. Furthermore, subgroup analyses to identify specific patients for whom MIS might entail an especially low risk would be very important in real-world practice.

Thus, we aimed to compare the survival outcomes of RH performed by MIS and open surgery, respectively, in patients with FIGO stage IB1–IIA2 CC at a high-volume tertiary institutional hospital in Korea. We also investigated prognostic factors that might affect survival outcomes in those patients.

2. Methods

This retrospective case-control study was performed with approval from the Institutional Review Board of Seoul National University Hospital (No. 1807-046-957).

2.1. Study population

From our institution's cancer registry, we identified patients with FIGO stage IB1–IIA2 disease that received primary surgical treatment at Seoul National University Hospital between January 2000 and June 2018. We excluded patients with any of the following characteristics from our analysis: (1) underwent fertility-sparing surgery, total mesometrial resection, or vaginal total hysterectomy; (2) received neoadjuvant chemotherapy prior to surgery; (3) had histologic types other than squamous cell carcinoma (SCC), usual type adenocarcinoma, or adenosquamous carcinoma; and (4) had insufficient clinical and/or pathologic data. In addition, we included only patients that underwent Type C RH according to Querleu and Morrow's classification [22] in the study populations. We divided the patients that met the study inclusion criteria into to two groups: those who underwent RH by conventional laparotomic surgery (open surgery group) and those who underwent RH by laparoscopic surgery (MIS group). Thirteen patients who received RH by robot-assisted surgery were excluded in this analysis.

Laparoscopic RH was first introduced in Seoul National University Hospital in 2007 and has been performed there in earnest since 2012. After RH, we implement adjuvant radiation therapy when one or more pathologic risk factors are present (involvement of parametrium, resection margin, or lymph node). In node-negative, margin-negative, parametrium-negative cases, we perform adjuvant radiation therapy selectively according to the presence of intermediate risk factors (lymphovascular space invasion, stromal invasion, and tumor size), defined as Sedlis criteria [23].

The majority (81.8%) of study population in this study were FIGO stage IB1 disease. In addition, patients diagnosed with CC commonly undergo MRI in our institution. The MRI is usually performed between diagnostic conization and RH, and provides additional information on objective cervical mass size and risk of parametrial invasion. To minimize the heterogeneity between the two groups and elucidate the pure effect of MIS on patients' survival outcome, we selected the subset of patients who were diagnosed with FIGO stage IB1 disease and had pre-operative MRI for further detailed analysis.

2.2. Data collection

We reviewed the patients' medical records, pathologic reports, and MRI studies and collected information about clinicopathologic characteristics (age, histologic type, FIGO stage, pre-operative cervical mass size on MRI, surgeries on pelvic and para-aortic lymph nodes, and risk factors identified by pathological examination) and adjuvant treatments such as chemotherapy, radiation, or concurrent chemoradiation therapy (CCRT). The patients that underwent MIS received colpotomy, either intracorporeal (IC) or vaginal (VC), during RH; colpotomy methods were also collected.

We obtained information about the survival status of all the patients from Statistics Korea, a service of the South Korean government, using the patients' resident registration numbers. We defined overall survival (OS) as the time interval between the date of initial diagnosis and the date of cancer-related death or the end of the study. We defined progression-free survival (PFS) as the time interval between the date of initial diagnosis and the date of disease progression based on the Response Evaluation Criteria in Solid Tumours version 1.1 [24].

2.3. Statistical analysis

Differences in clinicopathologic characteristics were evaluated between the patients that underwent MIS and those that underwent open surgery. We used Student's *t*-test and Mann-Whitney *U* test to compare continuous variables and Pearson's chi-squared test and Fisher's exact test to compare categorical variables. We used Kaplan-Meier methods with log-rank test to compare survival outcomes between the two groups. In multivariate analyses, we calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression models. All statistical analyses were performed using the SPSS statistical software (version 21.0; SPSS Inc., Chicago, IL, USA). We defined the threshold for statistical significance as $P < 0.05$.

3. Results

The selection of the study population is depicted in Fig. S1. In total, we included 593 patients with FIGO stage IB1–IIA2 disease who underwent primary Type C RH: 435 (73.4%) and 158 (26.6%) patients were assigned to open surgery group and MIS group, respectively.

3.1. Analysis in patients with FIGO stage IB1-IIA2 cervical cancer

The clinicopathologic characteristics of the patients are presented in Table S1. There were no differences between the open surgery and MIS groups except surgery on para-aortic lymph nodes (21.1% vs. 12.7%; $P = 0.020$) and parametrial involvement (15.4% vs. 6.3%; $P = 0.004$). Other high risk factors as well as intermediate risk factors were not different between the two groups. In terms of adjuvant treatment, 216 patients (49.7%) that underwent open surgery and 91 patients (57.6%) that underwent MIS did not receive any type of adjuvant treatment ($P = 0.087$). CCRT was the most common modality of adjuvant treatment in both groups and was performed more frequently for the patients that underwent open surgery than for those that underwent MIS (40.9% vs. 28.5%; $P = 0.006$; Table S1).

During a median length of observation of 114.8 months, 74 patients (12.5%) experienced disease recurrence and 68 patients (11.5%) died. While there was no significant difference in OS based on the type of surgery ($P = 0.788$), patients that underwent MIS had significantly worse PFS than those that underwent open surgery (5-year survival rate,

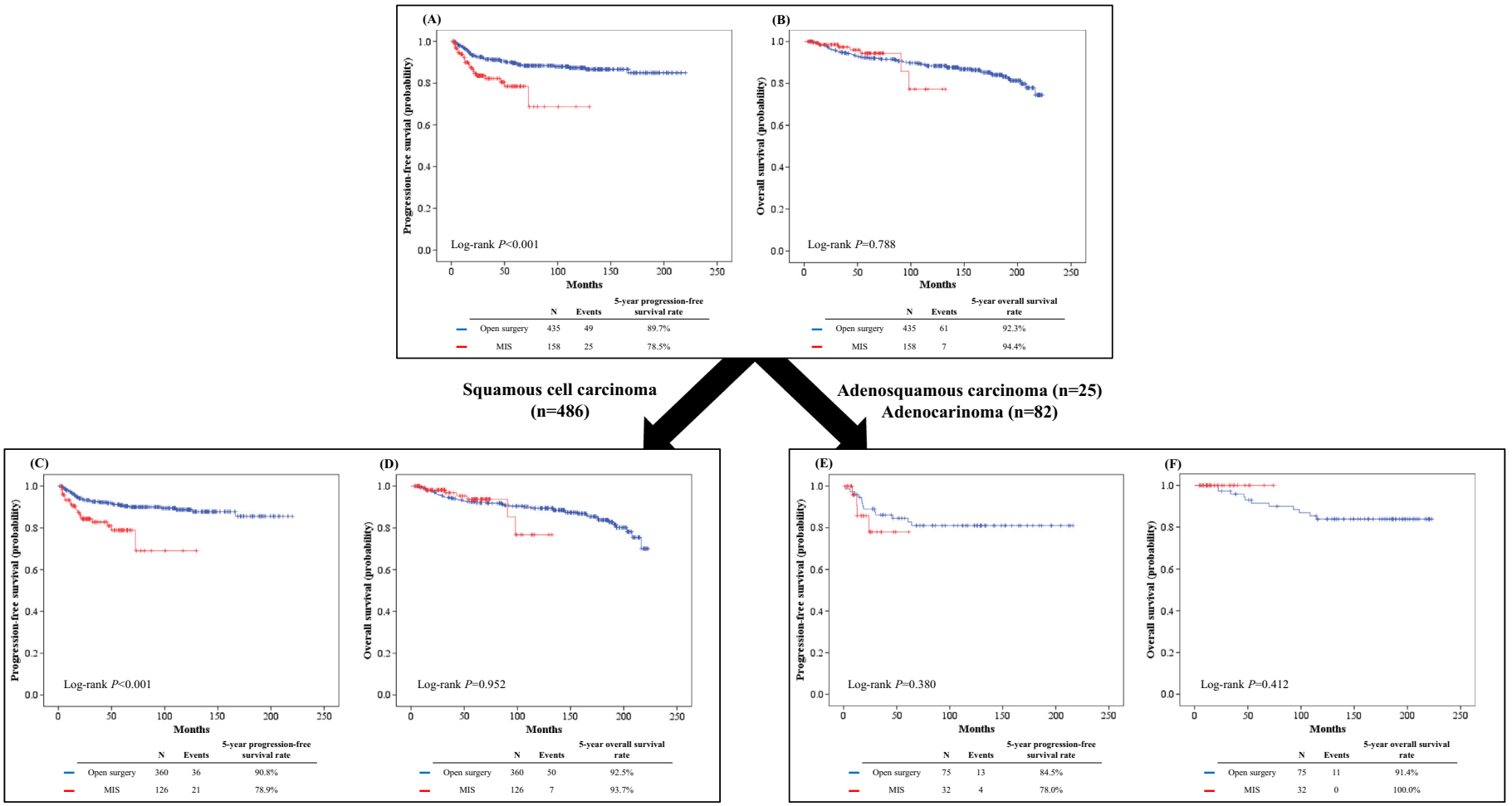

Fig. 1. Survival outcomes of open surgery and minimally invasive surgery in study population. All patients, (A) progression-free survival and (B) overall survival; among the patients with squamous cell carcinoma, (C) progression-free survival and (D) overall survival; among the patients with adenocarcinoma and adenosquamous carcinoma, (E) progression-free survival and (F) overall survival.

89.7% vs. 78.5%; $P < 0.001$). The patients that underwent open surgery and MIS had recurrence rates of 11.3% and 15.8%, respectively (Fig. 1A, B).

Next, we performed subgroup analyses according to the histologic type. In patients with SCC histologic type ($n = 486$), the MIS group showed significantly worse PFS compared to the open surgery group (5-year survival rate, 90.8% vs. 78.9%; $P < 0.001$), whereas OS was similar between the two groups ($P = 0.952$; Fig. 1C, D). In patients with non-SCC histologic type, adenocarcinoma ($n = 82$) and adenosquamous carcinoma ($n = 25$), there were no significant differences in PFS and OS based on the type of surgery ($P = 0.380$ and $P = 0.412$, respectively; Fig. 1E, F).

Multivariate analyses identified MIS as an independent poor prognostic factor for PFS (adjusted HR, 2.883; 95% CI, 1.711–4.859; $P < 0.001$; Table S2). Non-SCC histologic type (adjusted HR, 2.054; 95% CI, 1.159–3.640; $P = 0.014$) and resection margin involvement (adjusted HR, 2.321; 95% CI, 1.020–5.283; $P = 0.045$) were also poor prognostic factors for PFS, whereas pre-operative conization was a favorable prognostic factor for PFS (adjusted HR, 0.319; 95% CI, 0.148–0.689; $P = 0.004$).

3.2. Analysis in patients with FIGO stage IB1 and pre-operative MRI

The clinicopathologic characteristics of the patients with FIGO stage IB1 disease who underwent MRI prior to surgery are presented in Table 1. The patients that underwent MIS were significantly older than those that underwent open surgery (mean, 49.5 vs. 52.9 years; $P = 0.012$). Sampling/biopsy or dissection of para-aortic lymph nodes was performed significantly less in the MIS group (22.4% vs. 9.7%; $P = 0.006$). There was no difference in the proportion of patients who underwent pre-operative conization based on the type of surgery (41.5% vs. 34.0%; $P = 0.192$). Pre-operative MRI revealed no residual tumor in 35.8% of the patients that underwent open surgery and 29.1% of the patients that underwent MIS. Tumor sizes measured by MRI were also similar between the two groups (mean, 15.6 vs. 17.8 mm; $P = 0.195$). Pathologic examination confirmed that parametrial involvement was significantly more common among the patients that underwent open surgery than among those that underwent MIS (12.2% vs. 3.9%; $P = 0.017$). Other pathologic risk factors were not different between the two groups. The proportion of patients who received adjuvant treatment was also similar between the two groups. However, CCRT was performed significantly less in the MIS group (34.1% vs. 22.3%; $P = 0.029$; Table 1).

We compared the survival outcomes between the open surgery and MIS groups in this subset of study population (Fig. 2). The median length of observation was 106.0 months, during which 40 patients (11.5%) experienced disease recurrence and 35 patients (10.0%) died. Patients that underwent open surgery and those that underwent MIS showed similar PFS (5-year survival rate, 89.6% vs. 83.5%; $P = 0.093$) and OS (5-year survival rate, 92.7% vs. 94.4%; $P = 0.848$). The patients in the open surgery and MIS groups had recurrence rates of 11.4% and 11.7%, respectively (Fig. 2A, B).

In patients with SCC histologic type ($n = 280$), the MIS group showed a trend towards worse PFS (5-year survival rate, 91.5% vs. 85.3%; $P = 0.070$), whereas OS was similar between the two groups ($P = 0.713$; Fig. 2C, D). In patients with non-SCC histologic type, adenocarcinoma ($n = 52$) and adenosquamous carcinoma ($n = 17$), there were no significant differences in PFS and OS based on the type of surgery ($P = 0.675$ and $P = 0.231$, respectively; Fig. 2E, F).

Fig. S2 depicts the survival outcomes according to the type of surgery and the tumor size on pre-operative MRI. PFS and OS worsened as the pre-operative tumor size increased ($P < 0.001$ and $P = 0.010$, respectively). We divided the patients into two subgroups based on the tumor size as measured by MRI: those with cervical mass size ≤2 cm and those with cervical mass size >2 cm and ≤4 cm. In the subgroup with cervical mass size ≤2 cm, patients with open surgery and MIS had similar PFS (5-year survival rate, 93.5% vs. 92.4%; $P = 0.749$) and OS (5-year survival rate, 96.5% vs. 96.2%; $P = 0.570$). However, in the subgroup with cervical mass size >2 cm and ≤4 cm, patients that underwent MIS had significantly poorer PFS than those that underwent open surgery (5-year survival rate, 86.9% vs. 72.1%; $P = 0.044$), although OS was similar between the two subgroups (5-year survival rate, 87.6% vs. 91.5%; $P = 0.907$; Fig. 3).

Multivariate analyses adjusted for age, histologic type, pre-operative conization, cervical mass size measured by MRI, high and intermediate pathologic risk factors, and adjuvant treatment identified MIS as an independent poor prognostic factor for PFS (adjusted HR, 2.276; 95% CI, 1.039–4.986; $P = 0.040$; Table 2). Non-SCC histologic type (adjusted HR, 2.406; 95% CI, 1.144–5.058; $P = 0.021$) and parametrial involvement (adjusted HR, 2.829; 95% CI, 1.157–6.920; $P = 0.023$) were also poor prognostic factors for PFS, whereas pre-operative conization was a favorable prognostic factor for PFS (adjusted HR, 0.342; 95% CI, 0.137–0.856; $P = 0.022$). Cervical mass size >2 cm on MRI showed a trend towards worse PFS (adjusted HR, 2.020; 95% CI, 0.971–4.200; $P = 0.060$; Table 2).

We performed further multivariate analyses confined to the patients with FIGO stage IB1 disease and cervical mass size ≤2 cm on pre-

Table 1
Clinicopathologic characteristics of patients with FIGO stage IB1 and pre-operative MRI.

Characteristics	All ($n = 349$, %)	Open surgery group ($n = 246$, %)	MIS group ($n = 103$, %)	P
Age, years				
Mean ± SD	50.5 ± 11.7	49.5 ± 11.5	52.9 ± 12.0	0.012
<40	82 (23.5)	60 (24.4)	22 (21.4)	0.051
40–49	91 (26.1)	73 (29.7)	18 (17.5)	
50–59	96 (27.5)	62 (25.2)	34 (33.0)	
≥60	80 (22.9)	51 (20.7)	29 (28.2)	
Histologic type				0.724
Squamous cell carcinoma	280 (80.2)	200 (81.3)	80 (77.7)	
Adenocarcinoma	52 (14.9)	35 (14.2)	17 (16.5)	
Adenosquamous carcinoma	17 (4.9)	11 (4.5)	6 (5.8)	
Pre-operative conization				0.192
No	212 (60.7)	144 (58.5)	68 (66.0)	
Yes	137 (39.3)	102 (41.5)	35 (34.0)	
Cervical mass size by MRI				
Mean ± SD, mm	16.3 ± 14.0	15.6 ± 13.9	17.8 ± 14.1	0.195
No residual tumor	118 (33.8)	88 (35.8)	30 (29.1)	0.216
≤2 cm	89 (25.5)	65 (26.4)	24 (23.3)	
>2 cm, ≤4 cm	131 (37.5)	84 (34.1)	47 (45.6)	
>4 cm	11 (3.2)	9 (3.7)	2 (1.9)	
Pelvic lymph nodes				0.295
No	1 (0.3)	0	1 (1.0)	
Sampling/biopsy	0	0	0	
Dissection	348 (99.7)	246 (100.0)	102 (99.0)	
Para-aortic lymph nodes				0.006
No	284 (81.4)	191 (77.6)	93 (90.3)	
Sampling/biopsy or dissection	65 (18.6)	55 (22.4)	10 (9.7)	
Risk factors				
Parametrial involvement	34 (9.7)	30 (12.2)	4 (3.9)	0.017
Resection margin involvement	10 (2.9)	9 (3.7)	1 (1.0)	0.292
Lymph node involvement	65 (18.6)	50 (20.3)	15 (14.6)	0.207
LVSI	128 (36.7)	94 (38.2)	34 (33.0)	0.358
Invasion depth ≥ 1/2	167 (47.9)	116 (47.2)	51 (49.5)	0.687
Adjuvant treatment				
None	207 (59.3)	140 (56.9)	67 (65.0)	0.158
Yes	142 (40.7)	106 (43.1)	36 (35.0)	0.158
Chemotherapy only	4 (1.1)	3 (1.2)	1 (1.0)	1.000
Radiation only	31 (8.9)	19 (7.7)	12 (11.7)	0.240
CCRT	107 (30.7)	84 (34.1)	23 (22.3)	0.029

Abbreviations: CCRT, concurrent chemoradiation therapy; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space incision; MIS, minimally invasive surgery; MRI, magnetic resonance imaging; SD, standard deviation.

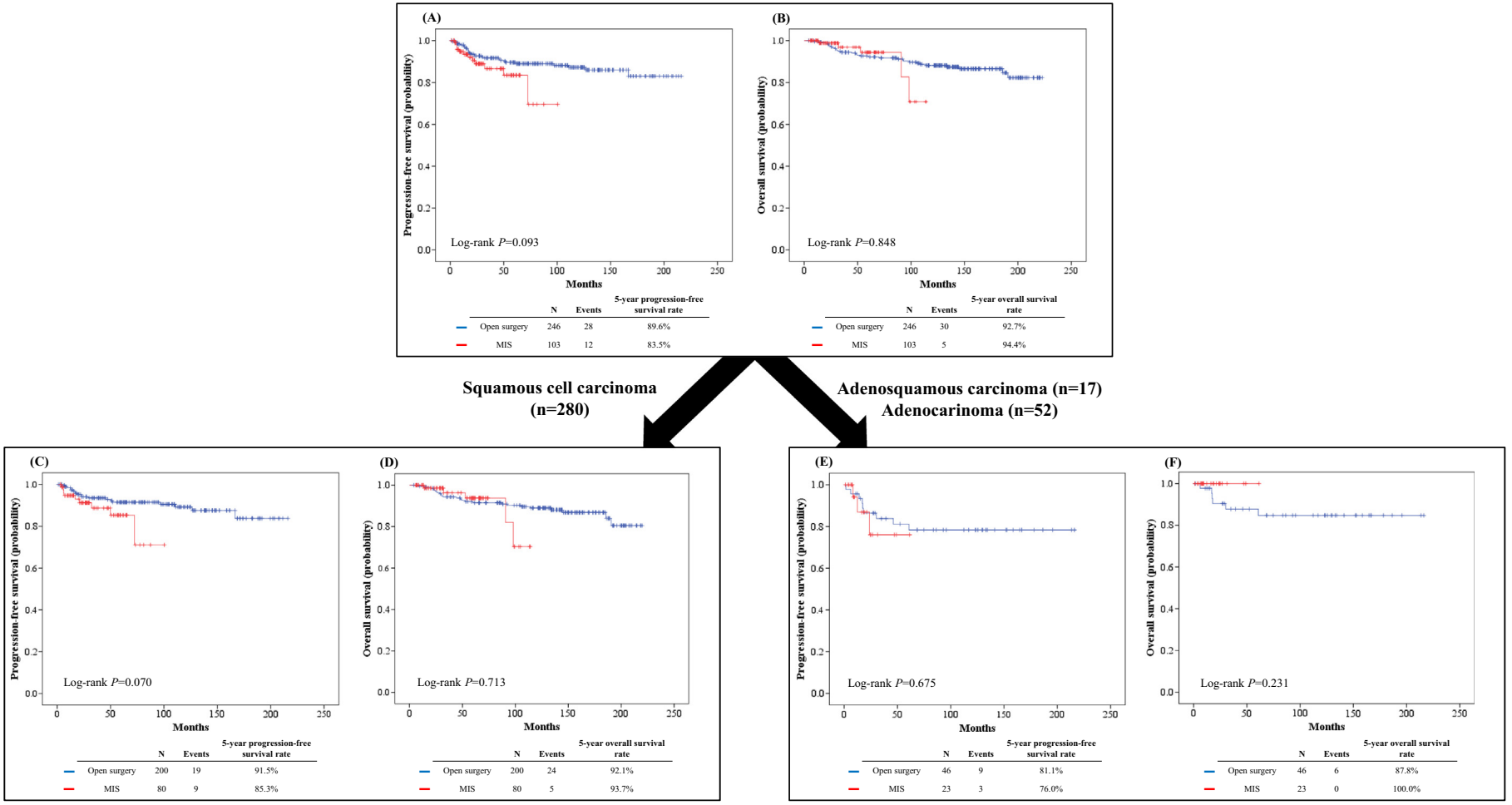

Fig. 2. Survival outcomes of open surgery and minimally invasive surgery in patients with FIGO stage IB1 disease who underwent pre-operative MRI. All patients, (A) progression-free survival and (B) overall survival; among the patients with squamous cell carcinoma, (C) progression-free survival and (D) overall survival; among the patients with adenocarcinoma and adenosquamous carcinoma, (E) progression-free survival and (F) overall survival.

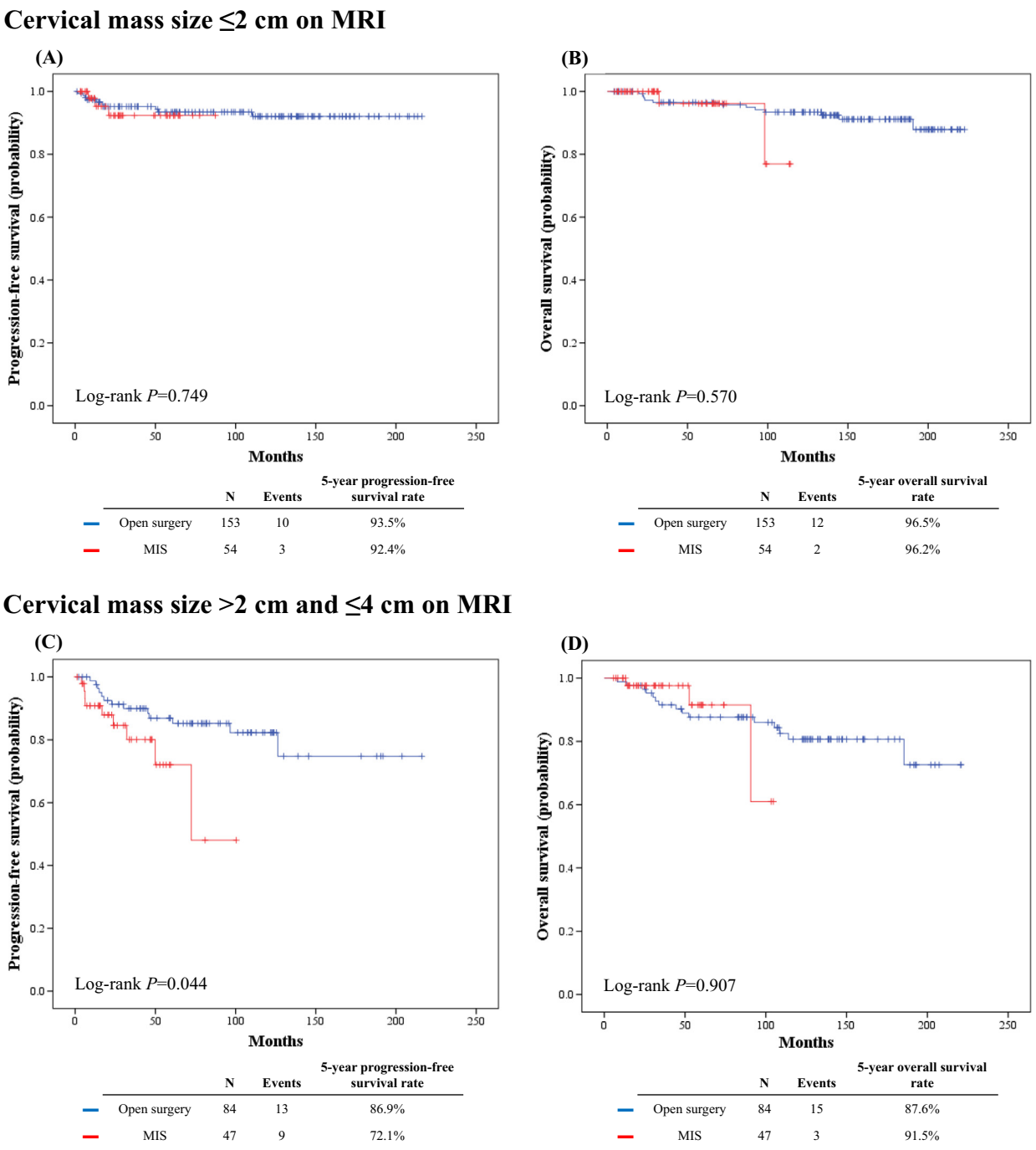

Fig. 3. Comparisons of survival outcomes for patients with FIGO stage IB1 disease and cervical mass size ≤2 cm (upper) and cervical mass size >2 cm and ≤4 cm (lower) as measured by pre-operative MRI. (A, C) Progression-free survival. (B, D) Overall survival.

operative MRI ($n = 207$; Table 3). In that subset of the study population, the surgical approach (open surgery or MIS) did not affect PFS (adjusted HR, 1.146; 95% CI, 0.278–4.724; $P = 0.850$).

3.3. Comparison of survival outcome according to the colpotomy method in MIS group

Of the 158 patients that underwent MIS for FIGO stage IB1-IIA2 disease, 83 (52.5%) and 75 (47.5%) had IC and VC during RH, respectively. PFS and OS were not different according to the method of colpotomy ($P = 0.571$ and $P = 0.177$, respectively; Fig. S3A, B). Sequent univariate and multivariate analyses revealed that the colpotomy method was not a prognostic factor for PFS (Table S3).

Similar results were also observed in the subset of patients who were diagnosed with FIGO stage IB1 disease and had pre-operative MRI. Of the 103 patients that underwent MIS, 66 (64.1%) and 37 (35.9%) patients received IC and VC, respectively. There were no differences in PFS and OS based on the method of colpotomy ($P = 0.164$ and $P = 0.272$, respectively; Fig. S3C, D). Sequent univariate and multivariate analyses revealed that the colpotomy method was not a prognostic factor for PFS (Table S4).

3.4. Comparison of survival outcome according to the study period in MIS group

Considering the time of introduction of laparoscopic RH in our institutional hospital, patients in MIS group were classified into two groups

Table 2
Factors associated with progression-free survival in patients with FIGO stage IB1 and pre-operative MRI.

Characteristics	*N*	Univariate analysis			Multivariate analysis		
		HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Age, years							
<50	173	1 (Ref)	–	–	1 (Ref)	–	–
≥50	176	1.516	0.809–2.841	0.194	1.372	0.714–2.636	0.342
Histology							
SCC	280	1 (Ref)	–	–	1 (Ref)	–	–
Non-SCC	69	1.938	0.985–3.814	0.055	2.406	1.144–5.058	0.021
Pre-operative conization							
No	212	1 (Ref)	–	–	1 (Ref)	–	–
Yes	137	0.248	0.104–0.594	<0.001	0.342	0.137–0.856	0.022
Cervical mass size on MRI							
≤2 cm	207	1 (Ref)	–	–	1 (Ref)	–	–
>2 cm	142	3.350	1.723–6.513	<0.001	2.020	0.971–4.200	0.060
Para-aortic lymph nodes							
No	284	1 (Ref)	–	–	1 (Ref)	–	–
Sampling/biopsy or dissection	65	1.411	0.689–2.889	0.346	1.369	0.634–2.954	0.424
Parametrial involvement							
No	315	1 (Ref)	–	–	1 (Ref)	–	–
Yes	34	3.370	1.683–6.749	0.001	2.829	1.157–6.920	0.023
Resection margin involvement							
No	339	1 (Ref)	–	–	1 (Ref)	–	–
Yes	10	3.888	1.380–10.952	0.010	2.418	0.756–7.737	0.137
Lymph node involvement							
No	284	1 (Ref)	–	–	1 (Ref)	–	–
Yes	65	1.898	0.965–3.734	0.063	1.476	0.635–3.433	0.366
LVSI							
No	221	1 (Ref)	–	–	1 (Ref)	–	–
Yes	128	1.691	0.910–3.144	0.097	1.715	0.733–4.013	0.213
Invasion depth							
<1/2	182	1 (Ref)	–	–			
≥1/2	167	2.900	1.446–5.816	0.003			
Adjuvant treatment							
No	207	1 (Ref)	–	–	1 (Ref)	–	–
Yes	142	1.907	1.018–3.570	0.044	0.518	0.185–1.447	0.209
Surgical approach							
Open surgery	246	1 (Ref)	–	–	1 (Ref)	–	–
MIS	103	1.810	0.896–3.657	0.098	2.276	1.039–4.986	0.040

Abbreviations: LVSI, lymphovascular space invasion; MIS, minimally invasive surgery; MRI, magnetic resonance imaging; SCC, squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; Ref, reference.

according to the year they received laparoscopic RH: 2007–2012 (early introduction stage, $n = 29$) and 2013 and thereafter (post-dissemination stage, $n = 129$). There were no differences in PFS and OS during the two study periods ($P = 0.132$ and $P = 0.524$, respectively; Fig. S4A, B). Further, confined to the FIGO stage IB1 patients who underwent MRI prior to surgery, no differences in survival outcomes were observed between the two study periods, either (PFS, $P = 0.227$; OS, $P = 0.221$; Fig. S4C, D).

4. Discussion

We evaluated survival outcomes of patients that underwent MIS for RH due to early-stage CC and compared them with those of patients that underwent open surgery. In contrast to OS, which showed no differences based on the type of surgery, PFS after MIS was significantly inferior compared with that after open surgery, among patients with FIGO stage IB1–IIA2 disease. MIS for RH was definitely associated with higher rates of recurrence.

In 2018, unexpected results from the LACC trial, the only randomized trial comparing survival outcomes between MIS and open surgery in patients with CC ranging from IA1 stage plus lymphovascular space invasion to IB1 stage, were released at the Society of Gynecologic Oncology Annual Meeting [17]. Before that, numerous retrospective studies from various institutions had consistently reported that MIS for RH was not inferior to open surgery in terms of survival outcomes and, furthermore, was superior in terms of reduced operative and postoperative morbidity [9–11,25–27]. Therefore, MIS for RH was considered not only as a reasonable alternative to open surgery but also as the preferred surgical procedure.

In Korea, the use of laparoscopy for RH increased from 46.1% of surgeries in 2011 to 51.8% of surgeries in 2014 [28]. Those rates are substantially higher than that in the United States: during 2006–2010, only 11.5% of RH cases were performed by laparoscopy [26]. At our hospital, the rate of laparoscopic RH is even higher than the average rate in Korea, reaching 68.0% of all RH procedures in 2012 and 81.1% of all RH procedures in 2017. Such widespread use of laparoscopic RH might be the result of several factors, including Korean gynecologic oncologists' great interest in MIS as well as patients' preferences for a fast return to daily life and cosmetic benefits. In addition, the cost of laparoscopic RH is much lower in Korea than in Western countries, resulting in decreased entry barriers and increased access for patients.

In our study, we observed some differences in clinicopathologic characteristics between patients that underwent open surgery and those that underwent MIS. In patients with FIGO stage IB1-IIA2 disease, the patients that underwent MIS had less parametrial involvement and application of CCRT than those that underwent open surgery. In patients with FIGO stage IB1 disease, surgeries on para-aortic lymph nodes were performed less frequently on patients who underwent MIS. Those differences suggest that the surgeons tended to choose the surgical approach on the basis of certain patient characteristics. In order to make comparisons between matched patients, we tried to balance the two groups by performing propensity score matching for clinicopathologic characteristics and adjuvant treatment. However, there was a significant difference in the observation period between the two groups owing to an extremely high rate of MIS, especially within the last five

Table 3
Factors associated with progression-free survival in patients with FIGO stage IB1 and cervical mass size ≤2 cm on pre-operative MRI.

Characteristics	*N*	Univariate analysis			Multivariate analysis		
		HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Age, years							
<50	111	1 (Ref)	–	–			
≥50	96	1.110	0.372–3.311	0.851			
Histology							
SCC	160	1 (Ref)	–	–	1 (Ref)	–	–
Non-SCC	47	3.429	1.149–10.229	0.027	3.168	0.853–11.769	0.085
Pre-operative conization							
No	96	1 (Ref)	–	–	1 (Ref)	–	–
Yes	111	0.389	0.120–1.264	0.116	0.476	0.132–1.708	0.255
Para-aortic lymph nodes							
No	175	1 (Ref)	–	–	1 (Ref)	–	–
Sampling/biopsy or dissection	32	0.431	0.056–3.317	0.419	0.391	0.047–3.245	0.384
Parametrial involvement							
No	198	1 (Ref)	–	–	1 (Ref)	–	–
Yes	9	6.485	1.781–23.614	0.005	6.735	0.958–47.339	0.055
Resection margin involvement							
No	204	1 (Ref)	–	–	1 (Ref)	–	–
Yes	3	7.699	0.991–59.812	0.051	1.337	0.113–15.827	0.818
Lymph node involvement							
No	184	1 (Ref)	–	–			
Yes	23	1.373	0.304–6.200	0.680			
LVSI							
No	152	1 (Ref)	–	–	1 (Ref)	–	–
Yes	55	1.132	0.348–3.680	0.836	1.336	0.252–7.088	0.733
Invasion depth							
<1/2	148	1 (Ref)	–	–	1 (Ref)	–	–
≥1/2	59	2.738	0.919–8.155	0.070	2.376	0.577–9.782	0.231
Adjuvant treatment							
No	153	1 (Ref)	–	–	1 (Ref)	–	–
Yes	54	1.565	0.512–4.785	0.432	0.361	0.050–2.633	0.315
Surgical approach							
Open surgery	153	1 (Ref)	–	–	1 (Ref)	–	–
MIS	54	1.239	0.333–4.613	0.750	1.146	0.278–4.724	0.850

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; MIS, minimally invasive surgery; SCC, squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; Ref, reference.

years, which hindered effective matching. That shortcoming might be overcome in a multi-institutional study with proper matching.

In contrast to the results of the LACC trial, the type of surgery did not affect OS in our study [17]. On the other hand, consistent with the results of the LACC trial, the patients in our study that underwent MIS had higher recurrence rates than those that underwent open surgery. The adjusted HR of MIS for PFS was lower in our study than in the LACC trial (2.883 [IB1-IIA2] and 2.276 [IB1] vs. 3.74) [17]. That difference might be explained by the higher recurrence rates in our study compared with those in the LACC trial. In the LACC trial, the recurrence rate among the patients that underwent open surgery was only 2.2%, with a 4.5-year PFS rate of 96.5%, which deviated strongly from the results of previously published studies, resulting in a relative increase in the adjusted HR [18].

Although we included only patients that underwent Type C RH according to Querleu and Morrow's classification, there may be criticism pointing out that even if it is namely the same Type C RH, radicality could vary depending on the surgeons. This is an inevitable issue and quality assurance for RH might be necessary. However, in a prospective randomized study comparing Piver-Rutledge-Smith class II and class III RH in stage IB-IIA CC, recurrence rate as well as survival were not different [29], suggesting it may not be a bigger issue than we expected: Other factors might have a greater impact on survival outcomes.

The possible reasons or factors for higher recurrence rates in the MIS group might be listed as follows: First, CO2 pneumoperitoneum during laparoscopic surgery might promote inflammation and tumor progression. Second, steep Trendelenburg position during MIS might be related with fluid and/or tumor tissue collection in upper abdomen. Third, use of uterine manipulator during MIS might promote breakdown of cervical tumor and its dissemination. Lastly, although we failed to show difference in survival outcome between IC and VC during laparoscopic RH, IC might adversely affect the survival outcome in fact. Altogether, these surgery-related factors potentially may cause an increased risk of relapse in MIS group.

In the current study, survival curves showed different features depending on the histologic type: In SCC, the MIS group showed significantly worse PFS compared to the open surgery group, while no difference in PFS were observed in non-SCC. We also found that non-SCC was an independent poor prognostic factor for PFS. Non-SCC, especially adenocarcinoma, is well known to have a higher recurrence rate as well as a lower survival rate than SCC [30]. Aggressive tumor nature itself and multi focal lesions, commonly referred to as “skip lesions” in adenocarcinoma of cervix [31], together might have masked adverse effect of MIS. Similarly, in a previous retrospective study of 293 patients with early-stage cervical adenocarcinoma, both PFS and OS were comparable between patients that underwent laparoscopic RH and those that underwent laparotomic RH [32].

Interestingly, pre-operative conization was an independent favorable prognostic factor for PFS both in patients with FIGO stage IB1–IIA2 disease and in those with stage IB1 disease. At our institution, pre-operative conization is commonly performed to make an accurate diagnosis when punch biopsy results are ambiguous or the tumor size is small, to treat microinvasive CC, or to confirm accompanying pathologic risk factors, such as tumor size, histology, and depth of invasion, prior to deciding on a surgical plan. In our study, 32.4% of the patients received pre-operative conization, and the proportion was not different between the open surgery and MIS groups. Our hypothesis to explain the favorable impact of pre-operative conization on disease recurrence

is that the procedure reduced the primary cervical mass size, thus reducing the potential for tumor spillage during MIS, especially at the time of uterine manipulation and colpotomy.

Although it is not incorporated into the formal staging process, MRI is widely used at our hospital. Adding to the objective measurement of cervical mass size, pre-operative MRI identifies patients with either low or high risk of parametrial invasion, which is very helpful in making decisions to perform less radical surgery or fertility-sparing surgery [33–35]. MRI-invisible IB1 cancer is also known to be associated with better postoperative outcomes [36]. Our study revealed that the cervical mass size on pre-operative MRI significantly affected both PFS and OS in stage IB1 CC. In multivariate analysis, although it was not statistically significant, cervical mass size >2 cm on MRI definitely showed a trend towards worse PFS.

Our results indicate that MIS did not compromise survival in patients with stage IB1 disease and cervical mass size ≤2 cm on pre-operative MRI. MIS was not a poor prognostic factor for survival in those populations. However, patients with MIS had significantly poorer PFS than those with open surgery in the subgroup with cervical mass size >2 cm and ≤4 cm. The conflicting results are observed in a previous study that analyzed long-term survival outcomes among patients with stage IA2–IIA: laparoscopic RH and laparotomic RH resulted in similar risks of recurrence even in patients with tumors >2 cm in diameter [9]. Our study differed from the previous study in terms of the study design and study population with the main difference being that we measured the cervical mass by MRI, whereas the previous study measured it clinically.

Nevertheless, our study result suggests that MIS RH might be performed safely in much selected patients with early-stage cervical cancer. Before the current study, surgeons at our institutional hospital have not considered the size of cervical mass, whether cervical mass size ≤2 cm or not, in their choice of surgical approach. However, from now on, selection of patients for MIS considering cervical mass size seems to be critical in the real-world clinical practice.

We compared survival outcomes according to the colpotomy method in the patients that underwent MIS. We found no differences in OS or PFS between patients that had IC and those that had VC both in patients with FIGO stage IB1–IIA2 disease and in those with stage IB1 disease. The colpotomy method was not a prognostic factor for PFS in multivariate analyses. Those results contrast with the results of a previous retrospective study that reported that IC rather than VC during MIS for RH was a strong prognostic factor for disease recurrence in stage IB–IIA CC [37]. As a possible explanation, the authors pointed out that the patients that had IC were exposed to CO2 pneumoperitoneum during the procedure and a higher rate of positivity in the resection margin, especially for the vaginal cuff. Similarly, another study reported a higher stump recurrence rate in patients that underwent laparoscopic RH compared with that in patients that underwent laparoscopic-assisted radical vaginal hysterectomy, although the difference was not statistically significant ($P = 0.08$) [38].

The study populations might be heterogeneous between our study and previous studies. As described above, pre-operative conization might reduce the risk of relapse from IC. There might also be differences among studies in the procedures used to prevent tumor spillage into the abdominopelvic cavity, such as intraperitoneal handling of the cervical mass and intraperitoneal irrigation. Further comparative studies with large sample sizes are necessary to make conclusions about the impact of the different colpotomy methods on survival outcomes.

Our study has several limitations. First, although we included consecutive patients from our cancer registry as long as they met clearly defined eligibility criteria, inevitable issues due to the retrospective study design, such as selection bias, might exist. Second, while we used Sedlis criteria to apply adjuvant treatment for the patients with intermediate risk factors, other institutions might use different criteria, such as "four-factor model" [39]. However, in the current study, multivariate analyses adjusting other factors revealed that adjuvant treatment did not influence the PFS both in stage IB1-IIA2 disease and in stage IB1 disease. Third, despite a long observation period, the observation period itself and the sample size, as well as the numbers of recurrence and death events, might be insufficient to properly compare PFS and OS between the two types of surgery. Lastly, we did not evaluate operative morbidity according to the surgical approach. Nevertheless, we specifically selected our study population step by step for the purpose of making comparisons between our groups of interest.

In conclusion, MIS was associated with higher recurrence rates than open surgery in patients that underwent RH for early-stage CC. This retrospective study provides additional evidence that the application of MIS has a significant influence on the prognosis of CC. However, a specific group of patients may undergo MIS for RH safely, without compromising survival: patients with FIGO stage IB1 disease with cervical mass size ≤2 cm on pre-operative MRI. Thus, we insist that advantages of laparoscopic RH should not be given up at all: MIS RH must continue to be implemented through the delicate patient selection as well as careful surgical techniques. We hope that laparoscopic RH will flourish, rather than decay, by the current study results and those from further studies.

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Conflict of interest

No conflict of interest relevant to this article was reported.

Author contributions

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References

[1] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, CA Cancer J. Clin. 65 (2015) 87–108.
[2] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 68 (2018) 7–30.
[3] K.W. Jung, Y.J. Won, H.J. Kong, E.S. Lee, Prediction of cancer incidence and mortality in Korea, 2018, Cancer Res. Treat. 50 (2018) 317–323.
[4] M.C. Lim, E.K. Moon, A. Shin, K.W. Jung, Y.J. Won, S.S. Seo, et al., Incidence of cervical, endometrial, and ovarian cancer in Korea, 1999–2010, J. Gynecol. Oncol. 24 (2013) 298–302.
[5] W.J. Koh, B.E. Greer, N.R. Abu-Rustum, S.M. Apte, S.M. Campos, K.R. Cho, et al., Cervical cancer, version 2.2015, J. Natl. Compr. Cancer Netw. 13 (2015) 395–404.
[6] D. Cibula, R. Potter, F. Planchamp, E. Avall-Lundqvist, D. Fischerova, C. Haie Meder, et al., The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer, Radiother. Oncol. 127 (2018) 404–416.
[7] M.C. Lim, M. Lee, S.H. Shim, E.J. Nam, J.Y. Lee, H.J. Kim, et al., Practice guidelines for management of cervical cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement, J. Gynecol. Oncol. 28 (2017), e22. .
[8] Y. Ebina, N. Yaegashi, H. Katabuchi, S. Nagase, Y. Udagawa, T. Hachisuga, et al., Japan Society of Gynecologic Oncology guidelines 2011 for the treatment of uterine cervical cancer, Int. J. Clin. Oncol. 20 (2015) 240–248.
[9] J.H. Nam, J.Y. Park, D.Y. Kim, J.H. Kim, Y.M. Kim, Y.T. Kim, Laparoscopic versus open radical hysterectomy in early-stage cervical cancer: long-term survival outcomes in a matched cohort study, Ann. Oncol. 23 (2012) 903–911.
[10] W. Wang, H.J. Chu, C.L. Shang, X. Gong, T.Y. Liu, Y.H. Zhao, et al., Long-term oncological outcomes after laparoscopic versus abdominal radical hysterectomy in stage IA2 to IIA2 cervical cancer: a matched cohort study, Int. J. Gynecol. Cancer 26 (2016) 1264–1273.
[11] Y.M. Jin, S.S. Liu, J. Chen, Y.N. Chen, C.C. Ren, Robotic radical hysterectomy is superior to laparoscopic radical hysterectomy and open radical hysterectomy in the treatment of cervical cancer, PLoS One 13 (2018), e0193033. .
[12] L.B. Conrad, P.T. Ramirez, W. Burke, R.W. Naumann, K.L. Ring, M.F. Munsell, et al., Role of minimally invasive surgery in gynecologic oncology: an updated survey of

members of the Society of Gynecologic Oncology, Int. J. Gynecol. Cancer 25 (2015) 1121–1127.
[13] J.L. Walker, M.R. Piedmonte, N.M. Spirtos, S.M. Eisenkop, J.B. Schlaerth, R.S. Mannel, et al., Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2, J. Clin. Oncol. 27 (2009) 5331–5336.
[14] J.L. Walker, M.R. Piedmonte, N.M. Spirtos, S.M. Eisenkop, J.B. Schlaerth, R.S. Mannel, et al., Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study, J. Clin. Oncol. 30 (2012) 695–700.
[15] W. Schwenk, O. Haase, J. Neudecker, J.M. Muller, Short term benefits for laparoscopic colorectal resection, Cochrane Database Syst. Rev. (3) (2005 Jul 20), CD003145. https://www.ncbi.nlm.nih.gov/pubmed/16034888.
[16] E. Kuhry, W.F. Schwenk, R. Gaupset, U. Romild, H.J. Bonjer, Long-term results of laparoscopic colorectal cancer resection, Cochrane Database Syst. Rev. (2) (2008 Apr 16), CD003432. https://www.ncbi.nlm.nih.gov/pubmed/16034888.
[17] P.T. Ramirez, M. Frumovitz, R. Pareja, A. Lopez, M. Vieira, R. Ribeiro, et al., Minimally invasive versus abdominal radical hysterectomy for cervical cancer, N. Engl. J. Med. 379 (2018) 1895–1904.
[18] M.M. Leitao Jr., The LACC trial: has minimally invasive surgery for early-stage cervical cancer been dealt a knockout punch? Int. J. Gynecol. Cancer 28 (2018) 1248–1250.
[19] H. Kanao, Y. Aoki, N. Takeshima, Unexpected result of minimally invasive surgery for cervical cancer, J. Gynecol. Oncol. 29 (2018), e73. .
[20] J.Y. Park, J.H. Nam, How should gynecologic oncologists react to the unexpected results of LACC trial? J. Gynecol. Oncol. 29 (2018), e74. .
[21] R. Kimmig, T. Ind, Minimally invasive surgery for cervical cancer: consequences for treatment after LACC Study, J. Gynecol. Oncol. 29 (2018), e75. .
[22] D. Querleu, C.P. Morrow, Classification of radical hysterectomy, Lancet Oncol. 9 (2008) 297–303.
[23] A. Sedlis, B.N. Bundy, M.Z. Rotman, S.S. Lentz, L.I. Muderspach, R.J. Zaino, 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. 73 (1999) 177–183.
[24] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2009) 228–247.
[25] M. Frumovitz, R. dos Reis, C.C. Sun, M.R. Milam, M.W. Bevers, J. Brown, et al., Comparison of total laparoscopic and abdominal radical hysterectomy for patients with early-stage cervical cancer, Obstet. Gynecol. 110 (2007) 96–102.
[26] J.D. Wright, T.J. Herzog, A.I. Neugut, W.M. Burke, Y.S. Lu, S.N. Lewin, et al., Comparative effectiveness of minimally invasive and abdominal radical hysterectomy for cervical cancer, Gynecol. Oncol. 127 (2012) 11–17.
[27] G. Bogani, A. Cromi, S. Uccella, M. Serati, J. Casarin, C. Pinelli, et al., Laparoscopic versus open abdominal management of cervical cancer: long-term results from a propensity-matched analysis, J. Minim. Invasive Gynecol. 21 (2014) 857–862.
[28] J.H. Kim, K. Kim, S.J. Park, J.Y. Lee, M.C. Lim, J.W. Kim, Comparative effectiveness of abdominal versus laparoscopic radical hysterectomy for cervical cancer in the postdissemination era, Cancer Res. Treat. (2018 Sep 11)https://doi.org/10.4143/crt.2018.120 , [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30205416.
[29] F. Landoni, A. Maneo, G. Cormio, P. Perego, R. Milani, O. Caruso, et al., Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study, Gynecol. Oncol. 80 (2001) 3–12.
[30] L.T. Gien, M.C. Beauchemin, G. Thomas, Adenocarcinoma: a unique cervical cancer, Gynecol. Oncol. 116 (2010) 140–146.
[31] T.C. Krivak, B. Retherford, S. Voskuil, G.S. Rose, T. Alagoz, Recurrent invasive adenocarcinoma after hysterectomy for cervical adenocarcinoma in situ, Gynecol. Oncol. 77 (2000) 334–335.
[32] J.Y. Park, D. Kim, D.S. Suh, J.H. Kim, Y.M. Kim, Y.T. Kim, et al., The role of laparoscopic radical hysterectomy in early-stage adenocarcinoma of the uterine cervix, Ann. Surg. Oncol. 23 (2016) 825–833.
[33] J.Y. Lee, J. Youm, T.H. Kim, J.Y. Cho, M.A. Kim, D.H. Suh, et al., Preoperative MRI criteria for trials on less radical surgery in Stage IB1 cervical cancer, Gynecol. Oncol. 134 (2014) 47–51.
[34] M. Kim, D.H. Suh, K. Kim, H.J. Lee, Y.B. Kim, J.H. No, Magnetic resonance imaging as a valuable tool for predicting parametrial invasion in stage IB1 to IIA2 cervical cancer, Int. J. Gynecol. Cancer 27 (2017) 332–338.
[35] Y. Lakhman, O. Akin, K.J. Park, D.M. Sarasohn, J. Zheng, D.A. Goldman, et al., Stage IB1 cervical cancer: role of preoperative MR imaging in selection of patients for fertility-sparing radical trachelectomy, Radiology 269 (2013) 149–158.
[36] J.Y. Park, J.W. Lee, B.K. Park, Y.Y. Lee, C.H. Choi, T.J. Kim, et al., Postoperative outcomes of MR-invisible stage IB1 cervical cancer, Am. J. Obstet. Gynecol. 211 (2014) 168 e1-7.
[37] T.W. Kong, S.J. Chang, X. Piao, J. Paek, Y. Lee, E.J. Lee, et al., Patterns of recurrence and survival after abdominal versus laparoscopic/robotic radical hysterectomy in patients with early cervical cancer, J. Obstet. Gynaecol. Res. 42 (2016) 77–86.
[38] C.H. Choi, J.W. Lee, Y.Y. Lee, H.J. Kim, T. Song, M.K. Kim, et al., Comparison of laparoscopic-assisted radical vaginal hysterectomy and laparoscopic radical hysterectomy in the treatment of cervical cancer, Ann. Surg. Oncol. 19 (2012) 3839–3848.
[39] S.Y. Ryu, M.H. Kim, B.H. Nam, T.S. Lee, E.S. Song, C.Y. Park, et al., Intermediate-risk grouping of cervical cancer patients treated with radical hysterectomy: a Korean Gynecologic Oncology Group study, Br. J. Cancer 110 (2014) 278–285.