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Impact of laparoscopic radical hysterectomy on survival outcome in patients with FIGO stage IB cervical cancer: A matching study of two institutional hospitals in Korea

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HIGHLIGHTS

- We conducted a matching study to investigate survival of laparoscopic radical hysterectomy (LRH) in stage IB cervical cancer.
- After matching, LRH group showed a higher recurrence rate compared to open group, whereas overall survival was not different.
- In stage IB1 patients with tumor size ≤2 cm, equivalent survival outcomes were observed regardless of the surgical approach.

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ABSTRACT

Objective. To compare survival outcomes of primary laparoscopic radical hysterectomy (LRH) and open radical hysterectomy (ORH) in patients with FIGO stage IB cervical cancer.

Methods. We retrospectively identified stage IB1–IB2 cervical cancer patients who received either LRH ($n = 343$) or ORH ($n = 222$) at two tertiary institutional hospitals between 2000 and 2018. To adjust for confounders, we conducted Mahalanobis distance-based sample matching for stage, histology, cervical mass size, parametrial invasion, and lymph node metastasis. Then, survival outcomes were compared between the matched groups. Through the independent matching processes, we narrowed the study population to stage IB1 patients and stage IB1 patients with tumor size ≤2 cm on pre-operative MRI.

Results. After matching, LRH group showed poorer progression-free survival (PFS) than ORH group (3-year: 85.4% vs. 91.8%; $P = 0.036$), whereas no significant difference in overall survival (OS) was found. Regarding recurrence patterns, no significant differences in the incidences of pelvic, retroperitoneal lymph node and abdominal recurrences, or distant metastasis were observed between the two groups. Among the matched patients with stage IB1 who had cervical mass size ≤2 cm, the LRH and ORH groups showed similar PFS (3-year: 90.0% vs. 93.1%; $P = 0.8$) and OS (5-year: 98.6% vs. 96.4%; $P = 0.6$).

Conclusions. Despite the retrospective design, our matched cohort study suggests that ORH might be preferable for the surgical treatment of FIGO stage IB cervical cancer. However, in stage IB1 patients with tumor size ≤2 cm, LRH might be applicable, as equivalent outcomes were found regardless of the surgical approach. Further prospective studies are warranted.

1. Introduction

Cervical cancer is a global burden; it is the fourth most common type of cancer in women and the most common gynecologic malignancy, with an estimated 569,847 new cases and 311,365 deaths worldwide in 2018 [1]. Cervical cancer shows a large geographic variation in its incidence and mortality, and it is more common and fatal in less developed countries.

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For decades, minimally invasive surgery (MIS) has been the mainstay of treatment for various cancer types. MIS has advantages over open surgery, including better operative morbidity and shorter hospital stays, without hindering survival outcomes [2–4]. Laparoscopic radical hysterectomy (LRH) was considered an oncologically safe alternative to open radical hysterectomy (ORH) in early-stage cervical cancer [5–7] until the surprising results of the phase III randomized controlled trial (RCT) "Laparoscopic Approach to Carcinoma of the Cervix (LACC)" were published [8].

According to the LACC trial, minimally invasive radical hysterectomy (RH) was associated with a higher recurrence rate and worse overall survival (OS) than ORH among women with International Federation of Gynecology and Obstetrics (FIGO) stage IA1 (lymphovascular invasion) to IB1 cervical cancer [8]. Despite some controversies surrounding the LACC trial [9–13], it was obvious that this study had a great impact on real-world practice.

We previously conducted a retrospective study comparing survival outcomes of ORH and LRH as primary treatment in patients with FIGO stage IB1–IIA2 cervical cancer [14]. In contrast to OS, which was not different between the two groups, the recurrence rate was higher in patients who underwent LRH than in those who underwent ORH in both stage IB1–IIA2 and stage IB1. We also found that LRH did not influence progression-free survival (PFS) in stage IB1 patients with cervical mass size ≤2 cm on pre-operative magnetic resonance imaging (MRI). However, the study was a single-institution study and there were some differences in baseline patient characteristics between the two groups.

To overcome these limitations of the previous study and to make a better comparison, we aimed to conduct a retrospective matched cohort study of patients in two high-volume tertiary institutional hospitals comparing the survival outcomes of primary LRH and ORH in patients with FIGO stage IB cervical cancer.

2. Material and methods

This study was approved by the Institutional Review Boards of both the Seoul National University Hospital (SNUH; No. H-1905-003-1030) and the Seoul National University Bundang Hospital (SNUBH; No. B-1903-526-102) and performed in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived.

2.1. Study population

Inclusion criteria for the study population were as follows: (1) patients who were diagnosed with and treated for stage IB cervical cancer according to the 2014 FIGO staging system [15] at the two institutional hospitals (SNUH and SNUBH) between January 2000 and June 2018; and (2) those who underwent primary Type C RH according to Querleu and Morrow's classification [16], performed by either open surgery or laparoscopic surgery. The exclusion criteria were as follows: (1) patients who received neoadjuvant chemotherapy prior to surgery; (2) those who had histologic types other than squamous cell carcinoma, usual type adenocarcinoma, or adenosquamous carcinoma; and (3) those who had insufficient clinical and/or pathologic data. Cases of robotic RH were also excluded in this analysis.

Among 724 patients who met the study criteria, 470 (64.9%) and 254 (35.1%) were in the ORH and LRH groups, respectively. Before conducting sample matching, we selected patients based on two points: 1) as MRI provides objective information on the cervical mass size, we chose only patients who underwent pre-operative MRI; and 2) allowing for a 2-year adaptation period after the introduction of LRH in SNUH and SNUBH, we chose patients who received LRH in 2009 or later. Consequently, 343 patients from the ORH group and 222 patients from the LRH group were selected as the study population. Of these, 384 patients from SNUH were also part of the study population assessed in our previous single-institution retrospective study [14].

2.2. Data collection

During the study period, five surgeons in SNUH and four surgeons in SNUBH performed all the surgical procedures. All of them were faculties of the two hospitals and had completed their gynecologic oncology fellowship training. Before the reports from the LACC trial, both two hospitals did not have any internal policies on selecting patients to undergo MIS or open surgery in early-stage cervical cancer. Instead, surgical approach was chosen in many respects according to the surgeons' preference. After RH, adjuvant radiation therapy was administered to patients with one or more pathologic high-risk factors (involvement of the parametrium, resection margin, or lymph node [LN]). If all three high-risk factors were negative, adjuvant radiation therapy was administered selectively according to the Sedlis criteria [17].

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 the pelvic and para-aortic LNs, and risk factors identified by pathological examination) and adjuvant treatments such as chemotherapy, radiation, or concurrent chemoradiation therapy.

2.3. Sample matching

Considering the complexity of data composition, we performed Mahalanobis distance-based sample matching, which is known to be more robust than the popular propensity score matching method [18], using the following variables: stage, histology, cervical mass size on pre-operative MRI, and pathologically confirmed parametrial invasion and LN metastasis. In total, we performed three individual sample matching processes: all patients (Matching I), stage IB1 patients (Matching II), and stage IB1 patients with cervical mass size ≤2 cm on pre-operative MRI (Matching III).

For each matching process, we performed one-to-one Mahalanobis distance-based sample matching using the R statistical software version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0; http://www.R-project.org). In order to evaluate the matching performance, we calculated the propensity scores for the two groups before and after sample matching.

2.4. Comparison of survival outcomes

After each sample matching process, survival outcomes were compared between the ORH and LRH groups. From the date of initial diagnosis, OS and PFS were defined as the period to the date of cancer-related death or the end of the study and the date of disease progression, respectively. Surveillance methods were the same between the two groups. In our institutions, computed tomography scanning is routinely performed during the surveillance, regardless of the surgical approach, as follows: every three to four months for the first two years, every six months for the next two years, and thereafter, every year or when symptoms or examination findings are suspicious for recurrence. Disease progression was assessed according to the Response Evaluation Criteria in Solid Tumours version 1.1 [19]. At the time of the first recurrence, specific locations of the recurrent lesions were categorized as follows: the pelvis, retroperitoneal LNs, abdomen, and distant metastases. The last included metastatic lesions in the liver and spleen parenchyma, thorax, supraclavicular LNs, and bone.

2.5. Statistical analysis

We evaluated differences in clinicopathologic characteristics between the ORH and LRH groups. For comparisons of continuous variables, Student's *t*-test and Mann-Whitney *U* test were used. For

comparisons of categorical variables, Pearson's chi-squared test and Fisher's exact test were used. Survival outcomes were compared using Kaplan-Meier analysis with log-rank test. In multivariate analyses, we calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression models. Statistical analyses were performed using the SPSS statistical software (version 25.0; SPSS Inc., Chicago, IL, USA). A $P < 0.05$ indicated statistical significance.

3. Results

The selection of the study population and consecutive processes of sample matching are presented in Fig. 1. In total, 565 patients with FIGO stage IB1–IB2 cervical cancer who underwent primary Type C ORH ($n = 343$) and LRH ($n = 222$) were included. In the three independent sample matching processes, 222, 196, and 122 patients from the ORH group were selected, respectively. As shown in Fig. 2, the propensity scores were highly variable between the two groups before matching, but those variabilities were adjusted after matching.

3.1. Analysis in matched patients with stage IB1–IB2 cervical cancer (matching I)

The clinicopathologic characteristics of the patients before and after matching are presented side by side in Table 1. After matching, the ORH and LRH groups had similar age, histologic type, FIGO stage, proportions of pre-operative conization, and cervical mass size measured by MRI. However, the para-aortic LNs were more frequently removed in the ORH group than in the LRH group (24.8% vs. 13.5%; $P = 0.003$). On pathologic examination, no differences between the two groups were observed in any of the three high-risk factors (parametrial involvement [$P > 0.9$], resection margin involvement [$P = 0.3$], and LN metastasis [$P = 0.9$]) or two intermediate-risk factors (lymphovascular space invasion [$P = 0.8$] and invasion depth [$P = 0.1$]). Patients in the ORH group more commonly received adjuvant treatment than those in the LRH group, without statistical significance (44.6% vs. 35.6%; $P = 0.1$). The modalities for adjuvant treatment were similar between the two groups ($P = 0.6$).

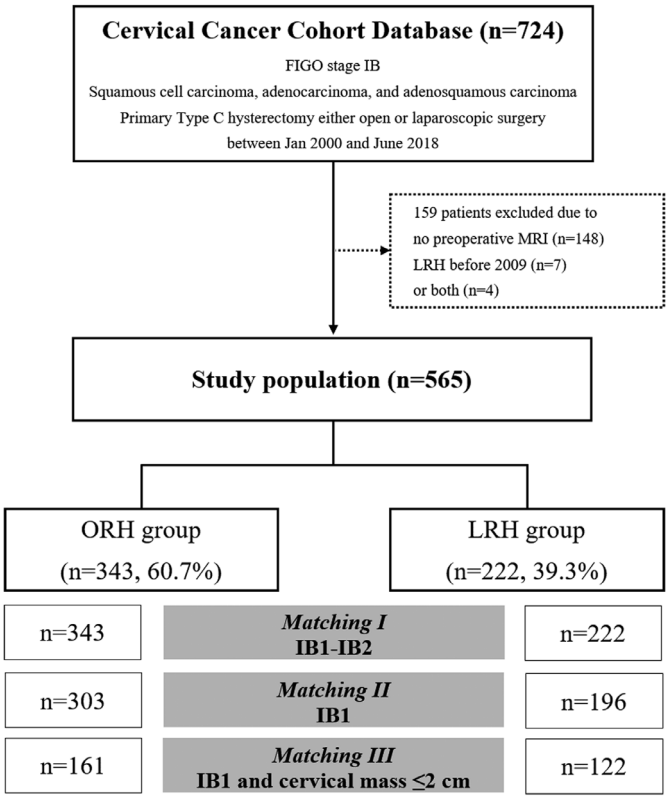


Fig. 1. Flow diagrams depicting the selection of the study population and consecutive processes of sample matching.

The median follow-up period was 59.1 months, during which 24 patients (5.4%) died and 51 patients (11.5%) experienced recurrence. Compared to the ORH group, the LRH group had significantly shorter follow-up period (median, 34.5 vs. 112.5 months; $P < 0.001$). Both groups showed similar OS (5-year: 96.9% vs. 94.6%; $P = 0.4$), whereas the LRH group had significantly worse PFS than the ORH group (3-year: 85.4% vs. 91.8%; $P = 0.036$) (Fig. 3A, B). Multivariate analysis adjusted for pre-operative conization, cervical mass size, pathologic high-risk factors, and adjuvant treatment identified LRH as an independent poor prognostic factor for PFS (adjusted HR, 1.923; 95% CI, 1.066–3.468; $P = 0.030$) (Table S1). In terms of recurrence patterns, there were no differences in the incidences of pelvic recurrence, recurrence to the retroperitoneal LNs, abdominal recurrence, or distant metastasis between the ORH and LRH groups (Table 2).

3.2. Analysis in matched patients with stage IB1 cervical cancer (matching II)

The left half of Table 3 depicts the clinicopathologic characteristics of the matched stage IB1 patients, which were not different according to the surgical approach, except for surgeries on the para-aortic LNs; para-aortic LN sampling or dissection was more frequent in the ORH group (24.5% vs. 11.7%; $P = 0.001$). Pathologic risk factors and administration of adjuvant treatment were also similar between the two groups.

The median follow-up period was 61.6 months, during which 22 patients (5.6%) died and 41 patients (10.5%) experienced recurrence. The median follow-up period was significantly shorter in the LRH group compared to the ORH group (37.1 vs. 121.6 months; $P < 0.001$). The ORH and LRH groups showed similar OS (5-year: 94.4% vs. 97.2%; $P = 0.3$) and PFS (3-year: 92.3% vs. 87.6%; $P = 0.1$) (Fig. 3C, D). In this subset of the study population, multivariate analysis adjusted for histologic type, pre-operative conization, cervical mass size, pathologic high- and intermediate-risk factors, and adjuvant treatment failed to prove LRH as an independent prognostic factor for PFS (adjusted HR, 1.620; 95% CI, 0.843–3.113; $P = 0.1$) (Table S2). In terms of recurrence patterns, there were no differences in the incidences of pelvic recurrence, recurrence to the retroperitoneal LNs, abdominal recurrence, or distant metastasis between the ORH and LRH groups (Table 2).

3.3. Analysis in matched patients with stage IB1 and mass size ≤2 cm on pre-operative MRI (matching III)

The right half of Table 3 depicts the clinicopathologic characteristics of the selected patients after the third matching analysis. As with the other matched analyses, all the characteristics other than surgeries on the para-aortic LNs were similar between the ORH and LRH groups. However, para-aortic LN sampling or dissection was more frequent in the ORH group (21.3% vs. 7.4%; $P = 0.002$).

The median follow-up period was 66.2 months, during which 11 patients (4.5%) died and 21 patients (8.6%) experienced disease recurrence. Significant difference in follow-up period was observed between the ORH and LRH groups (median, 133.4 vs. 46.8 months; $P < 0.001$). However, both two groups showed similar OS (5-year: 96.4% vs. 98.6%; $P = 0.6$) and PFS (3-year: 93.1% vs. 90.0%; $P = 0.8$) (Fig. 3E, F). In this subset of the study population, multivariate analysis adjusted for histologic type, pre-operative conization, pathologic high- and intermediate-risk factors, and adjuvant treatment proved that LRH was not a prognostic factor for PFS (adjusted HR, 1.054; 95% CI, 0.404–2.748; $P = 0.9$) (Table S3). In terms of recurrence patterns, there were no differences in the incidences of pelvic recurrence, recurrence to the retroperitoneal LNs, abdominal recurrence, or distant metastasis between the ORH and LRH groups (Table 2).

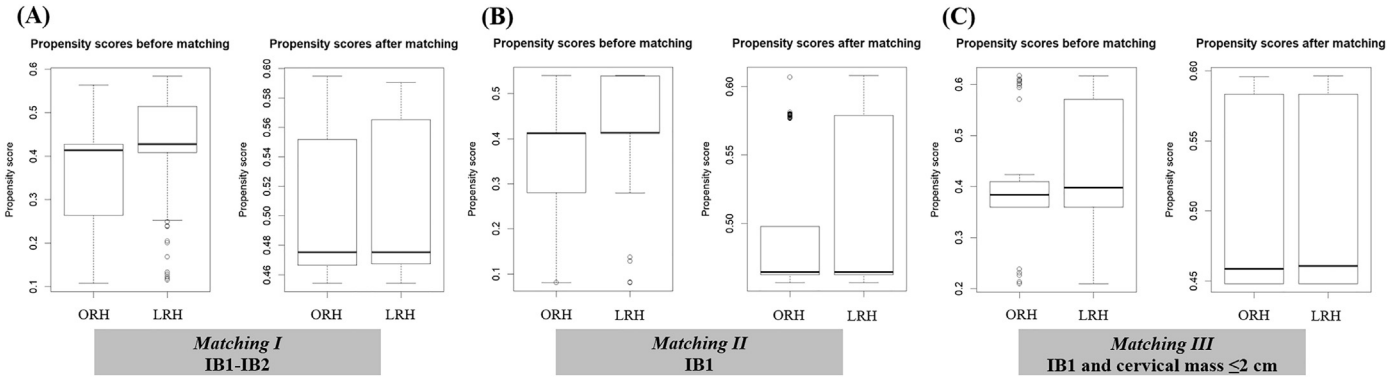


Fig. 2. Distribution of the propensity scores in the open radical hysterectomy and laparoscopic radical hysterectomy groups before and after sample matching. (A) Matching I (patients with stage IB1–IB2 cervical cancer); (B) Matching II (patients with stage IB1 cervical cancer); (3) Matching III (patients with stage IB1 and cervical mass size ≤2 cm on pre-operative MRI).

4. Discussion

In this study, we conducted three independent sample matching analyses among FIGO stage IB cervical cancer patients who received either primary LRH or ORH at two tertiary institutional hospitals. By doing so, we attempted to overcome some of the inherent limitations of retrospective studies and similarly align the baseline characteristics of patients between the two groups. Overall, LRH was associated with a significantly higher recurrence rate than ORH. However, this association was not observed among the matched stage IB1 patients or among those with stage IB1 with mass size ≤2 cm on pre-operative MRI.

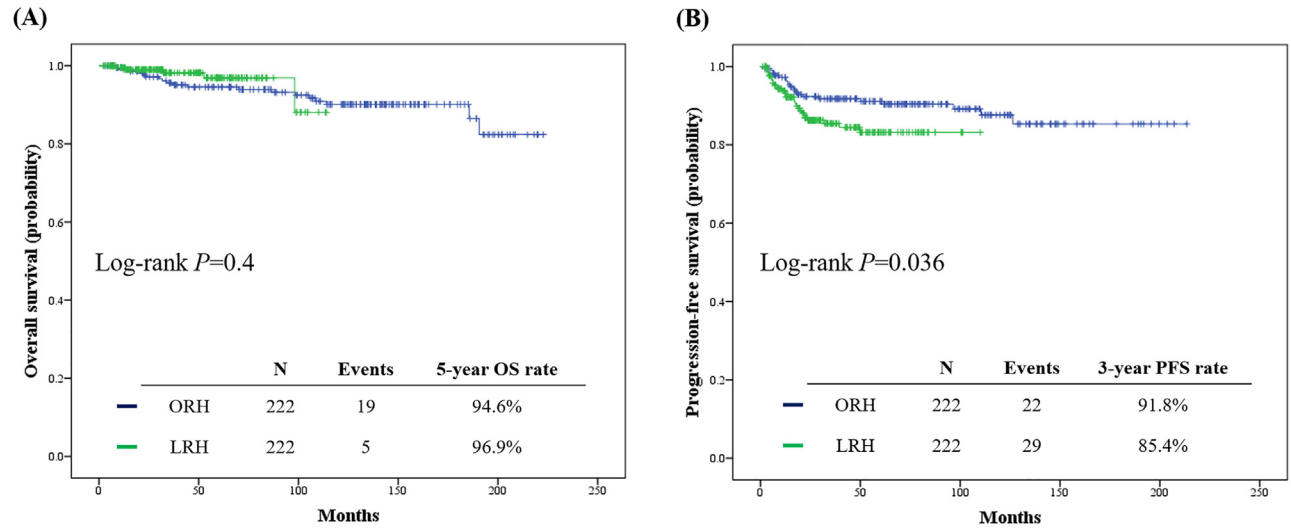
Although the incidence of cervical cancer has been gradually decreasing in Korea, it is still more prevalent than in Western countries [20]. According to the Korea National Cancer Incidence Database, 2856 new cervical cancer cases will be diagnosed in 2019, accounting for 2.8% of all new cancer cases in women [21]. LRH has also been widely used in Korea for the surgical management of newly diagnosed cervical cancer; approximately half (51.8%) of all RH procedures were performed by laparoscopy in 2014 [22]. However, this widespread use of LRH became problematic after the unexpected results from the LACC trial [8], supported by a retrospective study using the National Cancer Database of the United States [23].

Table 1
Clinicopathologic characteristics of study population before and after matching I.

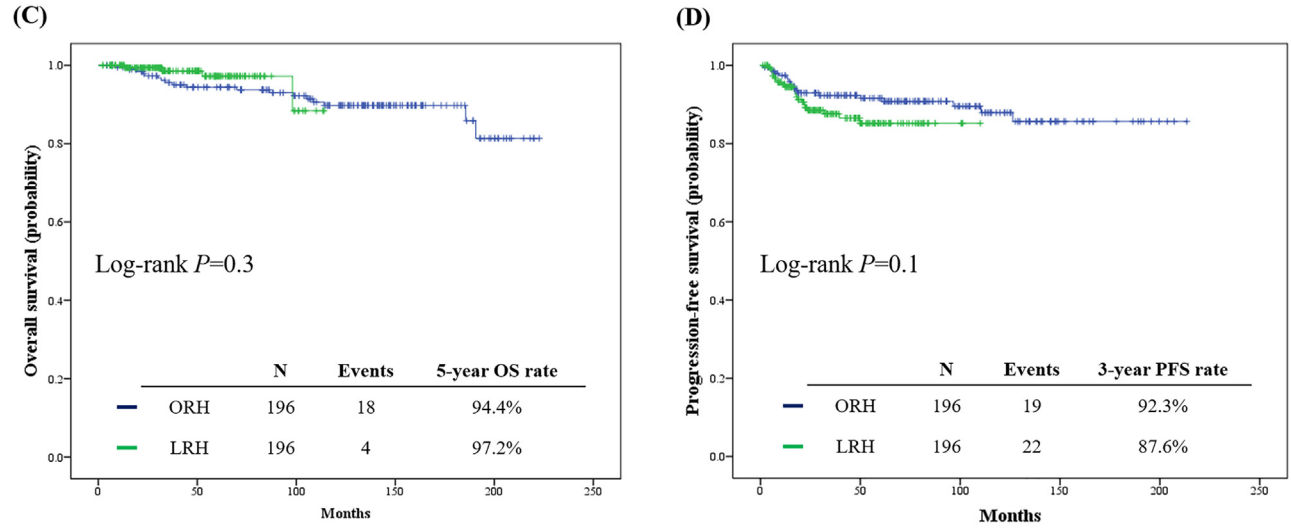
Characteristics	Before matching I			After matching I		
	ORH ($n = 343$, %)	LRH ($n = 222$, %)	*P*	ORH ($n = 222$, %)	LRH ($n = 222$, %)	*P*
Age, years						
Mean ± SD	49.3 ± 11.1	49.5 ± 11.2	0.9	49.0 ± 11.0	49.5 ± 11.2	0.7
Histologic type			0.013			0.1
SCC	261 (76.1)	148 (66.7)		167 (75.2)	148 (66.7)	
AC	60 (17.5)	62 (27.9)		42 (18.9)	62 (27.9)	
ASC	22 (6.4)	12 (5.4)		13 (5.9)	12 (5.4)	
FIGO stage			>0.9			>0.9
IB1	303 (88.3)	196 (88.3)		196 (88.3)	196 (88.3)	
IB2	40 (11.7)	26 (11.7)		26 (11.7)	26 (11.7)	
Pre-operative conization	121 (35.3)	88 (39.6)	0.3	85 (38.3)	88 (39.6)	0.8
Cervical mass size by MRI						
Mean ± SD, cm	2.2 ± 1.7	1.9 ± 1.6	0.1	1.9 ± 1.6	1.9 ± 1.6	0.8
≤2 cm	166 (48.4)	125 (56.3)	0.1	121 (54.5)	125 (56.3)	0.8
>2 cm, ≤4 cm	129 (37.6)	78 (35.1)		78 (35.1)	78 (35.1)	
>4 cm	48 (14.0)	19 (8.6)		23 (10.4)	19 (8.6)	
Pelvic LNs			0.4			>0.9
No	0	1 (0.5)		0	1 (0.5)	
Sampling/dissection	343 (100.0)	221 (99.5)		222 (100.0)	221 (99.5)	
Para-aortic LNs			0.001			0.003
No	255 (74.3)	192 (86.5)		167 (75.2)	192 (86.5)	
Sampling/dissection	88 (25.7)	30 (13.5)		55 (24.8)	30 (13.5)	
Risk factors						
PM involvement	59 (17.2)	12 (5.4)	<0.001	12 (5.4)	12 (5.4)	>0.9
RM involvement	13 (3.8)	2 (0.9)	0.037	6 (2.7)	2 (0.9)	0.3
LN metastasis	93 (27.1)	27 (12.2)	<0.001	28 (12.6)	27 (12.2)	0.9
LVSI	152 (44.3)	83 (37.4)	0.1	85 (38.3)	83 (37.4)	0.8
Invasion depth ≥ 1/2	196 (57.5)	97 (44.1)	0.002	117 (52.9)	97 (44.1)	0.1
Adjuvant treatment						
None	161 (46.9)	143 (64.4)	<0.001	123 (55.4)	143 (64.4)	0.1
Yes	182 (53.1)	79 (35.6)	<0.001	99 (44.6)	79 (35.6)	0.1
Chemotherapy only	5 (1.5)	2 (0.9)	0.037	4 (1.8)	2 (0.9)	0.6
Radiation only	28 (8.2)	23 (10.4)		23 (10.4)	23 (10.4)	
CCRT	149 (43.4)	54 (24.3)		72 (32.4)	54 (24.3)	

Abbreviations: AC, adenocarcinoma; ASC, adenosquamous carcinoma; CCRT, concurrent chemoradiation therapy; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space incision; LRH, laparoscopic radical hysterectomy; MRI, magnetic resonance imaging; ORH, open radical hysterectomy; PM, paramterium; RM, resection margin; SCC, squamous cell carcinoma; SD, standard deviation.

FIGO stage IB1-IB2



FIGO stage IB1



FIGO stage IB1 and cervical mass ≤2 cm on MRI

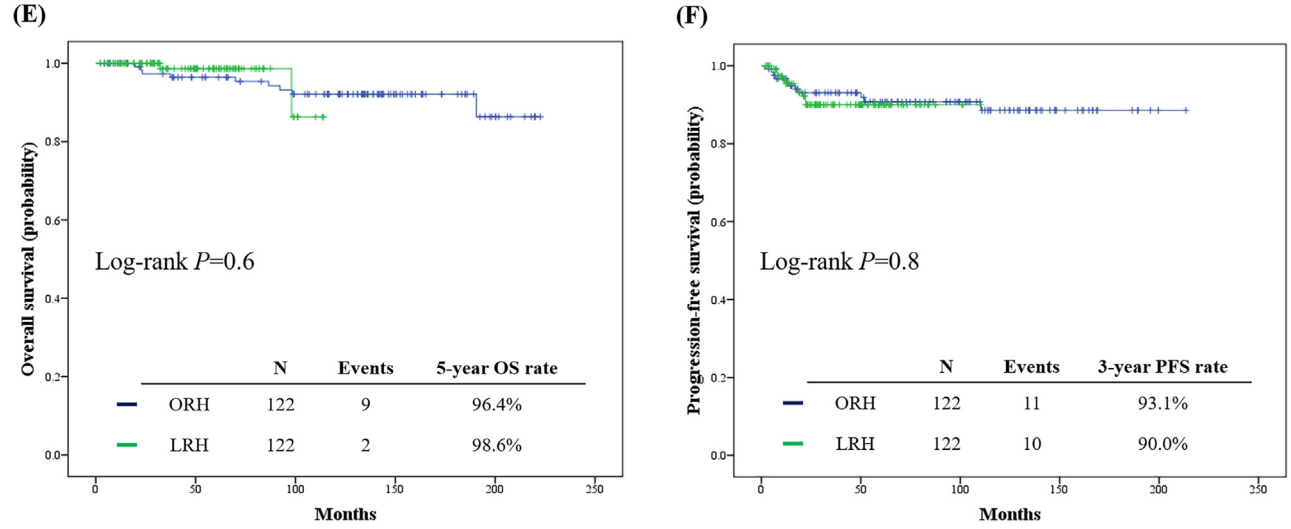


Fig. 3. Comparisons of survival outcomes for matched patients. (Upper) Matching I (patients with stage IB1–IB2 cervical cancer); (Middle) Matching II (patients with stage IB1 cervical cancer); (Lower) Matching III (patients with stage IB1 and cervical mass size ≤2 cm on pre-operative MRI). (A, C, E) Overall survival; (B, D, F) Progression-free survival.

Table 2
Comparisons of recurrence patterns between the two groups.

Characteristics	Matching I: IB1-IB2			Matching II: IB1			Matching III: IB1 and ≤2 cm		
	ORH ($n = 222$, %)	LRH ($n = 222$, %)	*P*	ORH ($n = 196$, %)	LRH ($n = 196$, %)	*P*	ORH ($n = 122$, %)	LRH ($n = 122$, %)	*P*
Recurrence									
Total	22 (9.9)	29 (13.1)	0.3	19 (9.7)	22 (11.2)	0.6	9 (7.4)	10 (8.2)	0.8
Pelvis	12 (5.4)	19 (8.6)	0.2	10 (5.1)	14 (7.1)	0.4	5 (4.1)	5 (4.1)	>0.9
Retroperitoneal LNs	5 (2.3)	4 (1.8)	>0.9	4 (2.0)	3 (1.5)	>0.9	3 (2.5)	1 (0.8)	0.6
Abdomen	1 (0.5)	6 (2.7)	0.1	0	2 (1.0)	0.5	1 (0.8)	1 (0.8)	>0.9
Distant site	7 (3.2)	10 (4.5)	0.5	7 (3.6)	8 (4.1)	0.8	2 (1.6)	5 (4.1)	0.4

Abbreviations: LN, lymph node; LRH, laparoscopic radical hysterectomy; ORH, open radical hysterectomy.

The results of the LACC trial showing that MIS in early-stage cervical cancer were controversial. Researchers pointed out limitations of the study, including early termination, incompleteness of data, unequal balance between LRH and robotic RH, and lack of surgical details and quality assessment of the surgeon's skills [9–13]. However, as the solitary level 1 evidence, the LACC trial has already significantly influenced real-world clinical practice. According to a recent survey performed by the European Society of Gynaecological Oncology, 57% of the members stated that they have changed their practice to open surgery. Half of the members stated that MIS would be appropriate for small tumors [24]. The Korean Society of Gynecologic Oncology also conducted a member survey on this issue, and 60% of the respondents stated that they would change surgical approaches after the trial, despite >80% of them having routinely performed MIS for early-stage cervical cancer [25]. However, before rejecting LRH and its accompanying benefits, we need robust scientific evidence from additional RCTs elucidating the exact effect of laparoscopic surgery on survival outcomes in early-stage cervical cancer. In addition, well-conducted retrospective studies may also provide valuable findings reflecting real-world clinical practice [26].

Previously, we performed a single-institution retrospective study comparing survival outcomes between FIGO stage IB1–IIA2 cervical cancer patients who underwent primary LRH and conventional ORH [14]. One shortcoming of our previous study was that the clinicopathologic characteristics were quite different between the two groups. For example, the LRH group had significantly lower stage disease, and parametrial invasion was less common. Therefore, in the current study, we focused on only IB disease and performed Mahalanobis distance-based sample matching for stage, histology, cervical mass size, parametrial invasion, and LN metastasis. After sample matching, we were able to successfully balance most confounders between the two groups.

In this matched study targeting FIGO stage IB1-IB2 cervical cancer, the LRH group had significantly worse PFS than the ORH group. The 3-year and 4.5-year PFS differences between the two groups were −6.4% and −7.9%, respectively. One possible reason for this might be

Table 3
Clinicopathologic characteristics of study population after matching II and III.

Characteristics	After matching II			After matching III		
	ORH ($n = 196$, %)	LRH ($n = 196$, %)	*P*	ORH ($n = 122$, %)	LRH ($n = 122$, %)	*P*
Age, years						
Mean ± SD	49.1 ± 11.1	50.1 ± 11.3	0.4	48.0 ± 11.4	49.7 ± 10.4	0.2
Histologic type			0.1			0.2
SCC	149 (76.0)	131 (66.8)		89 (73.0)	75 (61.5)	
AC	37 (18.9)	56 (28.6)		29 (23.8)	42 (34.4)	
ASC	10 (5.1)	9 (4.6)		4 (3.3)	5 (4.1)	
Pre-operative conization	83 (42.3)	83 (42.3)	>0.9	68 (55.7)	72 (59.0)	0.6
Cervical mass size by MRI						
Mean ± SD, cm	1.6 ± 1.4	1.6 ± 1.3	0.9	0.7 ± 0.8	0.7 ± 0.8	0.9
≤2 cm	119 (60.7)	122 (62.2)	0.4	122 (100.0)	122 (100.0)	>0.9
>2 cm, ≤4 cm	71 (36.2)	72 (36.7)		0	0	
>4 cm	6 (3.1)	2 (1.0)		0	0	
Pelvic LNs			>0.9			>0.9
No	0	1 (0.5)		0	0	
Sampling/dissection	196 (100.0)	195 (99.5)		122 (100.0)	122 (100.0)	
Para-aortic LNs			0.001			0.002
No	148 (75.5)	173 (88.3)		96 (78.7)	113 (92.6)	
Sampling/dissection	48 (24.5)	23 (11.7)		26 (21.3)	9 (7.4)	
Risk factors						
PM involvement	6 (3.1)	6 (3.1)	>0.9	3 (2.5)	3 (2.5)	>0.9
RM involvement	4 (2.0)	1 (0.5)	0.4	3 (2.5)	0	0.2
LN metastasis	23 (11.7)	23 (11.7)	>0.9	11 (9.0)	11 (9.0)	>0.9
LVSI	68 (34.7)	70 (35.7)	0.8	29 (23.8)	34 (27.9)	0.5
Invasion depth ≥ 1/2	92 (47.2)	78 (40.2)	0.2	40 (32.8)	26 (21.7)	0.1
Adjuvant treatment						
None	122 (62.2)	134 (68.4)	0.2	89 (73.0)	97 (79.5)	0.2
Yes	74 (37.8)	62 (31.6)	0.2	33 (27.0)	25 (20.5)	0.2
Chemotherapy only	3 (1.5)	2 (1.0)	0.8	2 (1.6)	2 (1.6)	0.9
Radiation only	17 (8.7)	17 (8.7)		9 (7.4)	8 (6.6)	
CCRT	54 (7.6)	43 (21.9)		22 (18.0)	15 (12.3)	

Abbreviations: AC, adenocarcinoma; ASC, adenosquamous carcinoma; CCRT, concurrent chemoradiation therapy; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space incision; LRH, laparoscopic radical hysterectomy; MRI, magnetic resonance imaging; ORH, open radical hysterectomy; PM, paramterium; RM, resection margin; SCC, squamous cell carcinoma; SD, standard deviation.

the increased risk of tumor spillage and dissemination from the use of a uterine manipulator, exacerbated by the intracorporeal colpotomy method and carbon dioxide gas insufflation [27]. In contrast, although both 3-year PFS rates of the LRH and ORH groups were lower than those rates in the LACC trial, the PFS of matched stage IB1 patients were not significantly different; neither were those of matched stage IB1 patients with tumor size ≤2 cm on pre-operative MRI. In the 2014 FIGO staging system, the difference between stage IB1 and IB2 is the size of the clinical lesions ≤4 cm or >4 cm [15]. Therefore, we believe that cervical mass size is directly associated with adverse outcome from LRH. As we discussed in our previous study, pre-operative conization might have a favorable impact on PFS, as the procedure reduces the primary cervical mass size and the potential for tumor spillage [14]. In addition, development of surgical techniques to prevent tumor spillage during LRH is necessary. For example, it would be worth applying the no-look no-touch technique proposed by Kanao et al. [28] for stage IB1 cervical cancer.

In terms of recurrence patterns, our hypothesis was that the LRH group would have a higher rate of pelvic and abdominal recurrence because of tumor spillage and dissemination during laparoscopic surgery, as mentioned above. Ramilez et al. reported a higher rate of locoregional recurrence in the MIS group compared to the open surgery group in their LACC trial [8]. We recognize that the LACC trial and the current study had different study populations (e.g., FIGO stage IA1 (lymphovascular invasion) to IB1 vs. FIGO stage IB1-IB2), nevertheless, we did not observe any differences in the rates of local recurrence, nodal recurrence, or distant metastasis between the LRH and ORH groups after the three independent matching processes. This might be owing to (1) the small sample size, which is not sufficient to compare recurrence patterns; (2) masking by adjuvant treatment, even though it was similarly administered in both groups; and (3) unknown surgical factors, such as sufficient irrigation in the abdominopelvic cavity, which is hard to assess in a retrospective setting.

Interestingly, OS was also not different between the LRH and ORH groups after the three independent matching processes. Particularly in patients with FIGO stage IB1–IB2 disease, OS was similar despite a significantly higher rate of disease recurrence in the LRH group. There are two potential reasons for these results: (1) compared to the ORH group, the LRH group had a shorter follow-up period, resulting in relatively fewer deaths; and (2) recurrent cases were salvaged regardless of the initial surgical approach. Although we balanced the two groups through the matching processes, we could not match the observation period. In addition, the optimal subsequent therapy for recurrent cervical cancer among patients who are primarily treated by LRH or ORH is still not known. Further prospective cohort studies might solve both issues in the near future.

The current study has several limitations. First, biases of the retrospective study design are problematic. Second, although we collected the relevant patients' data from two high-volume tertiary institutional hospitals in Korea, the sample size as well as the observation period might be insufficient for comparing the survival outcomes of primary LRH and ORH. Third, inter-institutional heterogeneity might exist, especially in surgical techniques, despite the two institutions having the same root and sharing training programs for gynecologic oncologists. Last, we did not compare quality of life outcomes between the LRH and ORH groups. The recent matching study by Bogani et al. reported that laparoscopic nerve-sparing RH was superior to open nerve-sparing RH in recovery of bladder function [29]. This benefit from the laparoscopic approach is thought to originate from its unique characteristics; for example, the magnified view of laparoscopic surgery enables a better visualization of the nervous system and more accurate dissection compared to open surgery [29]. It is necessary to remember that MIS has the additional benefit of improving functional outcomes after RH. These shortcomings mentioned might be overcome in a multi-institutional prospective cohort study.

Nevertheless, the current study has several strengths. We clarified the study population as FIGO stage IB cervical cancer patients who underwent primary type C RH by either open or laparoscopic surgery. To measure cervical mass size objectively, only patients who received pre-operative MRI were included [30]. Considering the surgeon's learning curve or proficiency for LRH, we excluded LRH cases performed within the first two years after LRH was introduced in the two hospitals. We also excluded robotic RH cases. Then, we conducted a systematic approach of sample selection to identify the impact of LRH on survival outcome. As shown in Table 1, our initial dataset had various confounders that could significantly affect the results of statistical analysis, and those confounders were highly likely to be nonlinear. Therefore, we applied Mahalanobis distance-based sample matching for optimal subset selection to identify true association and resolve the nonlinearity of confounders.

In conclusion, this two-center matched cohort study indicates that ORH might be preferable for FIGO stage IB cervical cancer as LRH is associated with a higher recurrence rate. However, in patients with stage IB1, especially in those with cervical mass size ≤2 cm on MRI, LRH might be an acceptable option, as equivalent survival outcomes were observed regardless of the surgical approach. Further prospective studies are warranted to support our findings.

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Declaration of Competing Interest

No conflict of interest relevant to this article was reported.

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