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Comparison between laparoscopic and abdominal radical hysterectomy for stage IB1 and tumor size ‹2 cm cervical cancer with visible or invisible tumors: a multicentre retrospective study

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ABSTRACT

Objective: To compare 5-year disease-free survival (DFS) and overall survival (OS) rates of laparoscopic radical hysterectomy (LRH) and abdominal radical hysterectomy (ARH) for stage IB1 and tumor size <2 cm with visible or invisible tumors.

Methods: We retrospectively compared the oncological outcomes of 1,484 cervical cancer patients with IB1 and tumor size <2 cm on final pathology, who received ARH (n=899) or LRH (n=585) between January 2004 and December 2016. Patients were divided into visible tumor subgroup (ARH: n=668, LRH: n=444) and invisible tumor subgroup (ARH: n=231, LRH: n=141) according to tumor type.

Results: LRH and ARH showed similar 5-year DFS and OS rates (93.3% vs. 93.1%, p=0.997; 96.2% vs. 97.5%, p=0.351) in total study population. LRH was not associated with worse 5-year DFS rate (hazard ratio [HR]=0.96; 95% confidence interval [CI]=0.58–1.58; p=0.871) or OS rate (HR=1.37; 95% CI=0.65–2.89; p=0.409) by multivariable analysis. In the visible tumor subgroups, LRH and ARH showed similar 5-year DFS and OS rates (91.9% vs. 91.9%, p=0.933; 95.0% vs. 96.9%, p=0.276), and LRH was not associated with worse 5-year DFS or OS rate (p=0.804, p=0.324). In the invisible tumor subgroups, LRH and ARH also showed similar 5-year DFS and OS rates (97.3% vs. 97.1%, p=0.815; 100% vs. 99.5%, p=0.449), and LRH was not associated with worse 5-year DFS rate (p=0.723).

Conclusions: Among patients with stage IB1 and tumor size <2 cm, whether the tumor is visible or not, the oncological outcomes of LRH and ARH among cervical cancer patients are comparable. This suggests that LRH may be suitable for stage IB1 and tumor size <2 cm with visible or invisible tumors.

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INTRODUCTION

Since laparoscopic radical hysterectomy (LRH) was reported in 1992 [1], minimally invasive surgery (MIS) for cervical cancer has been used worldwide. Previous studies [2-5] revealed that patients with early stage cervical cancer can benefit from laparoscopic surgery, the oncology outcomes of laparoscopic and open radical hysterectomy are similar, and laparoscopic surgery has the advantages of short hospital stay, less bleeding, low blood transfusion rate, more lymph nodes removed, fast recovery and fewer postoperative complications.

However, a high-quality and international multicentre randomized controlled trial, the Laparoscopic Approach to Cervical Cancer (LACC) Trial [6], demonstrated that minimally invasive radical hysterectomy was associated with lower rates of 4.5 years disease-free survival (DFS) and overall survival (OS) than abdominal radical hysterectomy (ARH). A retrospective epidemiological study based on the National Cancer Database and the Surveillance, Epidemiology, and End Results database also reached similar conclusions [7]. Subsequently, several retrospective cohort studies from other countries demonstrated that minimally invasive radical hysterectomy was associated with worse oncological outcomes than open radical hysterectomy among patients with early stage cervical cancer [8,9]. Based on these clinical evidences, open surgery has been recommended as the only standard approach for radical hysterectomy starting with Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology [10].

Meanwhile, several studies suggest that MIS has similar oncological outcomes as open surgery in cervical cancer patients with stage IB1 and tumor size <2 cm [7,9]. However, articles suggestive of no difference in outcomes in patients with tumors <2 cm often are hindered by low volume of patients in such group and are not powered nor designed to demonstrate a difference. There were also some studies have come to the opposite conclusion [11,12]. Whether MIS is suitable for stage IB1 cervical cancer with tumor size <2 cm is still controversial. In addition, there has not been further analysis for patients with stage IB1and tumor size <2 cm with visible or invisible tumors.

Therefore, based on the clinical diagnosis and treatment for cervical cancer in mainland China (Four C) database, this study aimed to compare the 5-year OS and DFS of ARH and LRH in patients with stage IB1and tumor size <2 cm with visible or invisible tumors.

MATERIALS AND METHODS

1. Data source

This study was a multicentre, retrospective, observational study, and the data used in this study originated from the Four C database, a cervical cancer specialized disease database (n=46 313) that covers consecutive patients with cervical cancer in 37 hospitals in mainland China treated between January 2004 and December 2016. The establishment of the cervical cancer database was reviewed by the Ethics Committee of Nanfang Hospital, Southern

Medical University (ethics number NFEC-2017-135) and written informed consent was waived by the Ethics Committee. The identifier of the clinical trial is CHiCTR180017778 (International Clinical Trials Registry Platform Search Port, http://apps.who.int/trialsearch/).

Clinical data were collected from patient files and the medical record management system in the hospitals by trained gynaecological oncology staff using standardized data collection and quality control procedures. The details of the data sources and methods were the same as those previously reported [13-15]. For patients underwent surgical treatment, the collected data contained almost all the information during the treatment of cervical cancer, including demographic details, preoperative examination results, surgical information, pathological results, preoperative and postoperative adjuvant treatment details, complications, hospitalization time and expenses, and follow-up. To ensure the accuracy of the collected data, two uniformly trained staff used EpiData software (EpiData Association, Odense M, Denmark) to input and proofread the same data from each hospital.

All follow-up procedures were carried out by trained gynaecological oncology staff at each centre to keep the patients' personal data confidential and to simultaneously provide disease management guidance. Follow-up information, including the survival status, time of death, recurrence time, recurrence site, and treatment after recurrence, was gathered through the return visit system or through a telephone follow-up. Vaginal stump recurrence was usually confirmed by pathological biopsy, abdominal and pelvic recurrence is detected by computer tomography (CT) or magnetic resonance imaging (MRI), and a few patients are detected by positron emission tomography-CT. The oncological outcomes were estimated according to the recorded information, and the last day of the return visit or telephone follow-up was defined as the last follow-up. In this database, the final International Federation of Gynecology and Obstetrics (FIGO) stage was corrected by tumor size according to the FIGO 2009 staging system. Tumor size was determined by final pathological records.

2. Inclusion and exclusion criteria
The inclusion criteria were as follows: 1) FIGO stage IB1 (FIGO 2009 staging system) and tumor size <2 cm on postoperative pathology; 2) squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma; 3) Q-M type B or type C radical hysterectomy + pelvic lymphadenectomy ± para-abdominal aortic lymphadenectomy; and 4) laparoscopic or open surgery.

The exclusion criteria were as follows: 1) patients underwent preoperative adjuvant treatment; 2) conversion from laparoscopic surgery to open approach; 3) patients with pregnancy; 4) cervical stump cancer; 5) patients combined with other malignancies.

3. Definition
Visible tumors were defined as patients who were diagnosed with stage IB1 cervical cancer by cervical biopsy under naked eye or colposcope without cervical conization, and the tumor size measured by pathologic examination was less than 2 cm. Invisible tumors were defined as patients with no visible tumor by gynaecological examination, patients were diagnosed with stage IB1 cervical cancer by cervical conization with vertical interstitial infiltration >5 mm or horizontal infiltration >7 mm and tumor size <2 cm.

The 5-year DFS was defined as the date from the operation to the date of death due to cervical cancer or recurrence of cervical cancer. OS was defined as the date from the operation to the

date of death from any cause. Patients with no evidence of recurrence or death were defined by the date of the last follow-up date or the last outpatient visit.

4. Postoperative adjuvant treatment

Patients with one or more high-risk factors (lymph node metastasis, parametrial tumor involvement, and surgical margin invasion) were recommended to receive postoperative adjuvant chemoradiation therapy. Patient with two or more intermediate-risk factors (deep cervical stromal invasion, tumor size >4 cm, and lymphovascular space invasion [LVSI]) were recommended to receive postoperative adjuvant radiation or chemoradiation therapy. In real clinical practice, there were still a small number of patients receiving chemotherapy alone. In this study, there were also some patients who received postoperative chemotherapy; we included them as an influencing variable in the multivariate analysis to minimize the impact of postoperative adjuvant treatment on the results of this study.

5. Statistical methods

Two-independent samples t-test and the χ^2 test were used to analyse the clinicopathologic characteristics of the LRH and ARH groups. Kaplan-Meier curves were used to describe the survival outcomes of different surgical approaches. Cox proportional risk regression models were used to adjust for mixed cases and estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the effect of surgical approaches on the 5-year OS and DFS rates. The statistical software used was Statistical Product and Service Solutions 23.0 (SPSS, Inc., Chicago, IL, USA). The p-value <0.05 was considered statistically significant.

In the Cox proportional risk regression models, we included clinical variables regarded as known factors affecting the oncological outcomes of cervical cancer (age, histology, tumor type, depth of stromal invasion, LVSI, lymph node metastasis, surgical margin invasion, parametrial tumor involvement, and postoperative adjuvant treatment).

In the propensity score matching analysis, patients in the LRH group were matched to patients in the ARH group based on propensity score to reduce bias. Then, a new cohort of patients who differed with surgical approaches but were similar with other clinicopathological characteristics was constructed. The propensity score of each patient's propensity to undergo LRH was calculated by a logistic-regression model that included clinical variables (age, histology, tumor type, depth of stromal invasion, LVSI, lymph node metastasis, surgical margin invasion, parametrial tumor involvement, and postoperative adjuvant treatment) regarded as known factors affecting the oncological outcomes of cervical cancer. This propensity score was used for one-to-one matching cases with the nearest neighbour matching with variance of 0.02.

RESULTS

1. Study population and clinicopathologic characteristics

A total of 1484 patients met the inclusion and exclusion criteria, 585 patients in LRH group and 899 patients in ARH group (**Fig. 1**). The median follow-up time was 42 months in LRH group and 48 months in ARH group (p=0.521). The distribution of hospital function, region, and city scale in LRH group and ARH group was not balanced (all p>0.05), the urban-rural distribution in the 2 groups was similar, as shown in **Supplementary Table 1**. The clinicopathologic characteristics of the 2 groups are shown in **Table 1**. Patients in the LRH group were more likely to have LVSI
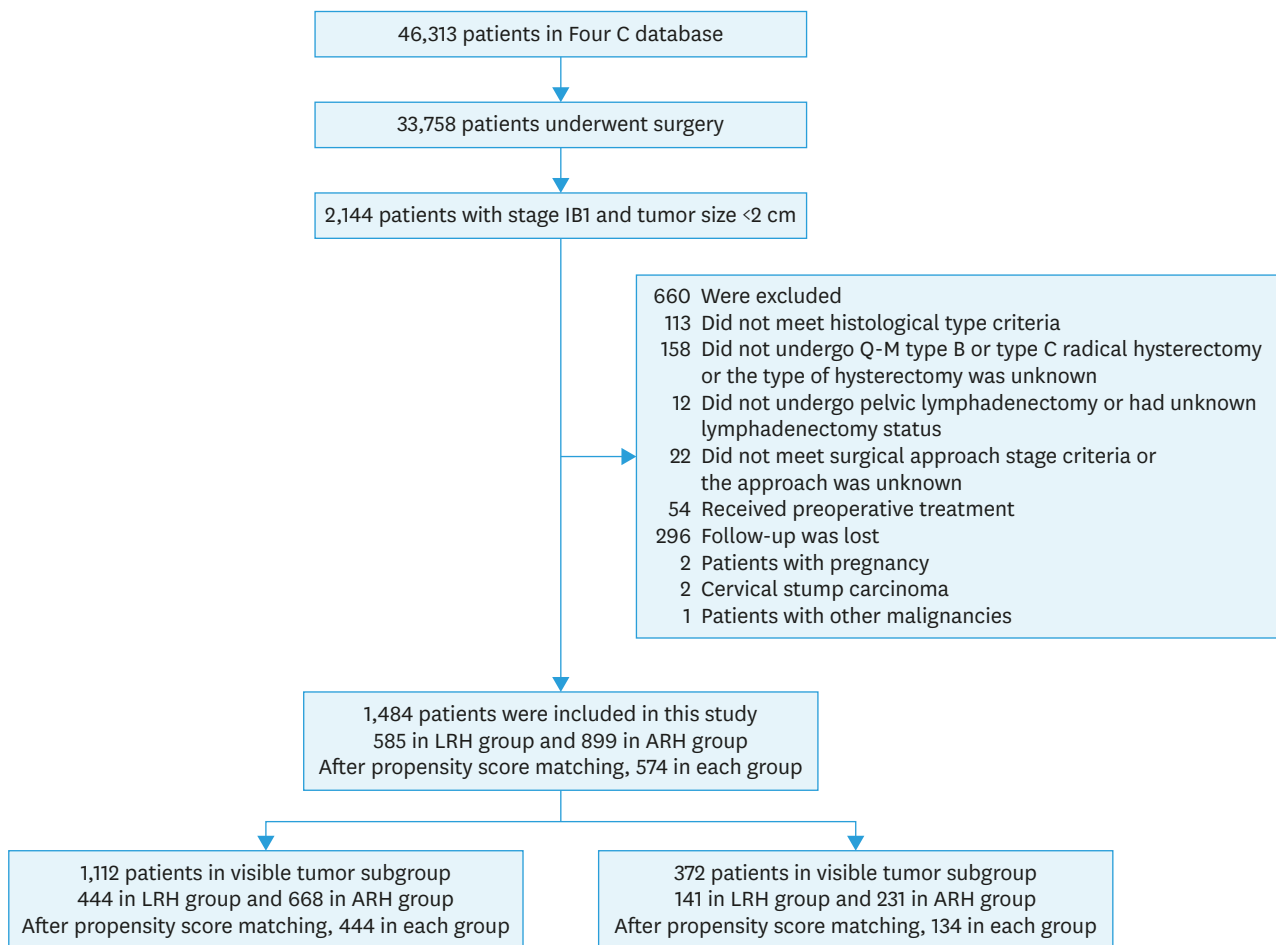
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┌─────────────────────────────────────────┐
│   46,313 patients in Four C database     │
└─────────────────────────────────────────┘
                    │
                    ▼
┌─────────────────────────────────────────┐
│   33,758 patients underwent surgery      │
└─────────────────────────────────────────┘
                    │
                    ▼
┌──────────────────────────────────────────────┐
│ 2,144 patients with stage IB1 and tumor size <2 cm │
└──────────────────────────────────────────────┘
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660 Were excluded
 113 Did not meet histological type criteria
 158 Did not undergo Q-M type B or type C radical hysterectomy
      or the type of hysterectomy was unknown
  12 Did not undergo pelvic lymphadenectomy or had unknown
      lymphadenectomy status
  22 Did not meet surgical approach stage criteria or
      the approach was unknown
  54 Received preoperative treatment
 296 Follow-up was lost
   2 Patients with pregnancy
   2 Cervical stump carcinoma
   1 Patients with other malignancies

1,484 patients were included in this study
585 in LRH group and 899 in ARH group
After propensity score matching, 574 in each group

1,112 patients in visible tumor subgroup	372 patients in visible tumor subgroup
444 in LRH group and 668 in ARH group	141 in LRH group and 231 in ARH group
After propensity score matching, 444 in each group	After propensity score matching, 134 in each group

Fig. 1. Flow diagram of recruitment and exclusions.
ARH, abdominal radical hysterectomy; LRH, laparoscopic radical hysterectomy.

than those in the ARH group (p=0.014). Patients in the LRH group were less likely to have no postoperative adjuvant treatment than those in the ARH group (p=0.008). The baseline differences in age, histology, infiltration depth of cervical stroma, positive parametrium, positive vaginal surgery margin, positive pelvic lymph nodes and positive para-aortic lymph nodes were not significantly different between the LRH and ARH groups (all p>0.05).

2. DFS and OS in total study population

Among patients with stage IB1 and tumor size <2 cm, the 5-year DFS was 93.3% and 93.1% in LRH and ARH groups, respectively, with no significant difference (p=0.997), as shown in **Figure 2A**. Multivariable analysis controlling for demographic, socioeconomic and clinical variables indicated that surgical approaches were not an independent risk factor for worse 5-year DFS (HR=0.96; 95% CI=0.58–1.58; p=0.871, as shown in **Table 2**). The 5-year OS was 96.2% and 97.5% in LRH and ARH groups, respectively, with no significant difference (p=0.351), as shown in **Figure 2B**, and surgical approaches were not an independent risk factor for worse 5-year OS (HR=1.37; 95% CI=0.65–2.89; p=0.409, as shown in **Table 2**).

After propensity score matching (n=1,148), the clinicopathologic characteristics were well balanced between the LRH and ARH groups (**Table 1**). LRH and ARH showed similar 5-year DFS

Table 1. The clinicopathologic characteristics of patients in LRH group and ARH group

Characteristics	Before matching			After matching		
	ARH (n=899)	LRH (n=585)	p	ARH (n=574)	LRH (n=574)	p
Age (yr)	46.33±9.505	46.86±9.423	0.638	46.29±8.836	46.54±9.086	0.640
Histologic type			0.403			0.142
Squamous cell	760 (84.5)	483 (82.6)		489 (85.2)	473 (82.4)	
Adenocarcinoma	114 (12.7)	88 (15.0)		66 (11.5)	87 (15.2)	
Adenosquamous	25 (2.8)	14 (2.4)		19 (3.3)	14 (2.4)	
Tumor type			0.489			0.155
Invisible tumor	231 (25.7)	141 (24.1)		157 (27.4)	136 (23.7)	
Visible tumor	668 (74.3)	444 (75.9)		417 (72.6)	438 (76.3)	
Stromal invasion			0.192			0.808
Superficial	664 (73.9)	410 (70.1)		414 (72.1)	404 (70.4)	
Deep	135 (15.0)	108 (18.5)		99 (17.2)	105 (18.3)	
Unreported	100 (11.1)	67 (11.5)		61 (10.6)	65 (11.3)	
LVSI			**0.014**			0.671
Negative	805 (89.5)	499 (85.3)		496 (86.4)	491 (85.5)	
Positive	94 (10.5)	86 (14.7)		78 (13.6)	83 (14.5)	
Parametrium			0.290			>0.999
Negative	892 (99.2)	583 (99.7)		572 (99.7)	572 (99.7)	
Positive	7 (0.8)	2 (0.3)		2 (0.3)	2 (0.3)	
Surgical margin			0.791			>0.999
Negative	891 (99.1)	579 (99.0)		568 (99.0)	568 (99.0)	
Positive	8 (0.9)	6 (1.0)		6 (1.0)	6 (1.0)	
Pelvic lymph nodes			0.114			0.675
Negative	835 (92.9)	530 (90.6)		526 (91.6)	522 (90.9)	
Positive	64 (7.1)	55 (9.4)		48 (8.4)	52 (9.1)	
Para-aortic lymph nodes			0.145			0.316
Negative or non-resection	898 (99.9)	582 (99.5)		573 (99.8)	571 (99.5)	
Positive	1 (0.1)	3 (0.5)		1 (0.2)	3 (0.5)	
Adjuvant therapy			**0.008**			0.063
None	549 (61.1)	339 (57.9)		342 (59.6)	331 (57.7)	
Chemotherapy	149 (16.6)	134 (22.9)		102 (17.8)	132 (23.0)	
Radiotherapy/radiochemotherapy	201 (22.4)	112 (22.4)		130 (22.6)	111 (19.3)	

Values are presented as mean±standard deviation or number (%). Bold indicates significant p-value.
ARH, abdominal radical hysterectomy; LRH, laparoscopic radical hysterectomy; LVSI, lymphovascular space invasion.

and OS (93.7% vs. 94.3%, p=0.490; 96.5% vs. 96.5%, p=0.831; as shown in **Fig. 2C and D**), and surgical approaches were not an independent risk factor for worse 5-year DFS (HR=1.17; 95% CI=0.66–2.09; p=0.590) or OS (HR=0.89; 95% CI=0.41–1.92; p=0.766), as shown in **Table 3**.

3. DFS and OS in visible tumor subgroup

Among 1112 patients with a visible tumor, 668 patients had ARH and 444 patients LRH (**Supplementary Table 2**). LRH showed similar 5-year DFS (91.9% vs. 91.9%, p=0.933) and OS (95.0% vs. 96.9%, p=0.276) compared to ARH (**Fig. 2E and F**). Surgical approaches were not an independent risk factor for worse 5-year DFS (HR=0.94; 95% CI=0.55–1.59; p=0.804) or OS (HR=1.46; 95% CI=0.69–3.11; p=0.324).

After propensity score matching, 444 patients were in each group, and the 5-year DFS (91.9% vs. 89.0%, p=0.173; HR=0.66; 95% CI=0.39–1.11; p=0.119) and OS (95.0% vs. 95.8%, p=0.811; HR=1.05; 95% CI=0.49–2.24; p=0.901) were comparable between LRH and ARH, as shown in **Fig. 2G and H**.

4. DFS and OS in invisible tumor subgroup

Among 372 patients with invisible tumors, 231 patients had ARH and 141 patients had LRH (**Supplementary Table 3**). In this subgroup, LRH showed similar 5-year DFS (97.3% vs. 97.1%,
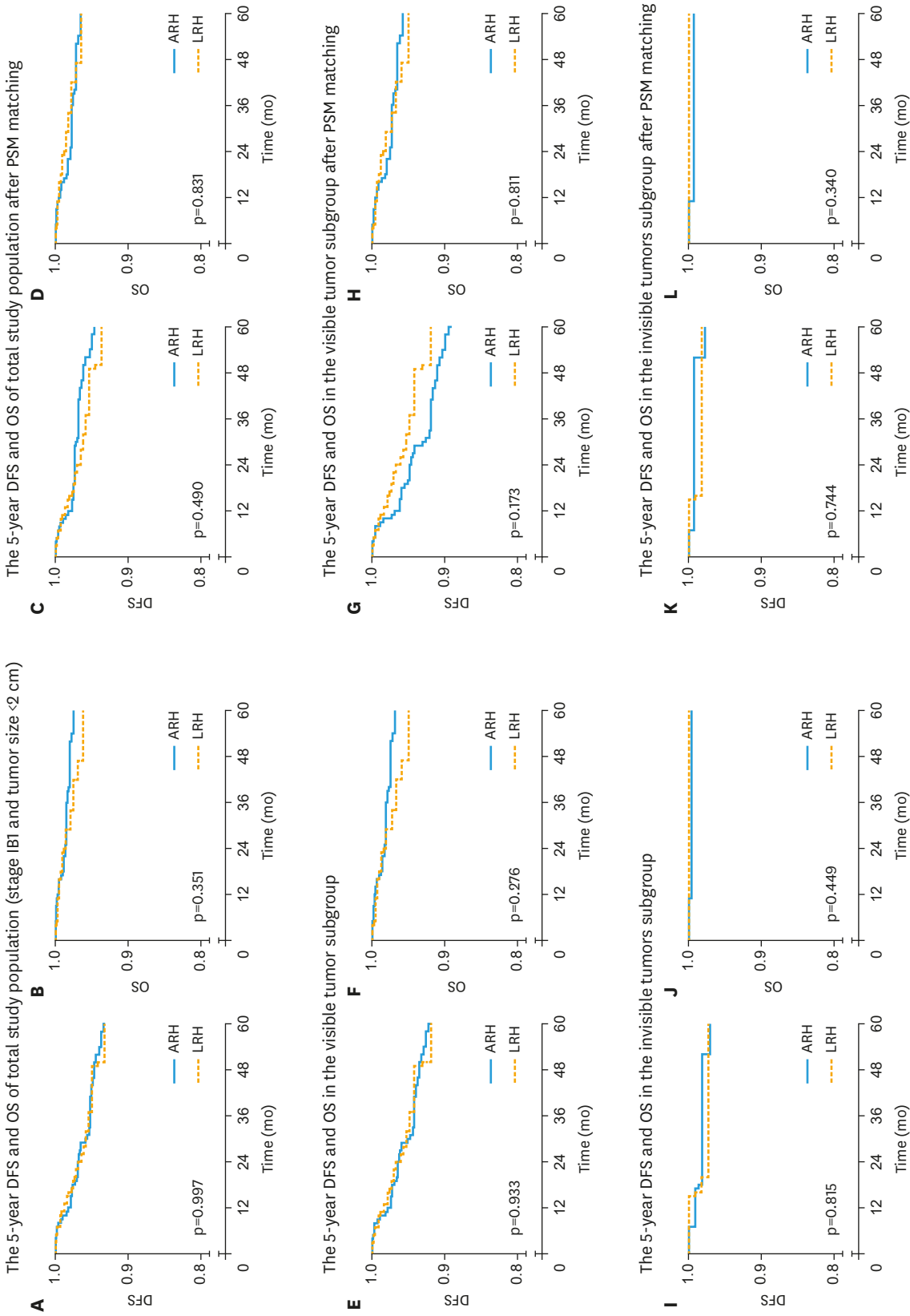
Fig. 2. Survival outcomes of open and laparoscopic surgery in study population and different subgroups.
ARH, abdominal radical hysterectomy; DFS, disease-free survival; LRH, laparoscopic radical hysterectomy; OS, overall survival; PSM, propensity score matching.

Table 2. Association of surgical approach and survival in cervical cancer by multivariablem analysis

Characteristics	Multivariate analysis for 5-year DFS			Multivariate analysis for 5-year OS		
	HR	95% CI	p	HR	95% CI	p
Surgical approach			0.871			0.409
Abdominal	1 (Ref)			1 (Ref)		
Laparoscopic	0.96	0.58–1.58	0.871	1.37	0.65–2.89	0.409
Age (yr)	1.02	0.99–1.04	0.200	1.06	1.02–1.10	**0.001**
Histologic type			0.649			0.880
Squamous cell	1 (Ref)			1 (Ref)		
Adenocarcinoma	1.05	0.55–2.03	0.878	0.76	0.26–2.23	0.614
Adenosquamous	0.40	0.05–2.92	0.364	1.00	0.13–7.45	0.996
Tumor type			**0.001**			**0.003**
Invisible tumor	1 (Ref)			1 (Ref)		
Visible tumor	2.67	1.26–5.65	0.001	9.21	1.24–68.55	0.003
LVSI			0.989			0.946
Negative	1 (Ref)			1 (Ref)		
Positive	1.01	0.48–2.09	0.989	0.96	0.33–2.83	0.946
Stromal invasion			0.109			0.222
Superficial	1 (Ref)			1 (Ref)		
Deep	1.04	0.54–1.98	0.911	0.72	0.26–1.96	0.517
Unreported	1.91	1.04–3.49	0.037	2.00	0.79–5.12	0.146
Parametrium			0.707			0.987
Negative	1 (Ref)			1 (Ref)		
Positive	1.50	0.18–12.11	0.707	0	-	0.987
Surgical margin			0.959			0.985
Negative	1 (Ref)			1 (Ref)		
Positive	0	0-2.584E+163	0.959	0	-	0.985
Lymph node metastasis			**<0.001**			**<0.001**
Negative	1 (Ref)			1 (Ref)		
Positive	3.53	1.84–6.76	<0.001	7.19	2.84–18.21	<0.001
Adjuvant therapy			0.643			0.880
None	1 (Ref)			1 (Ref)		
Chemotherapy	0.76	0.39–1.46	0.403	1.04	0.39–2.76	0.935
Radiochemotherapy/radiotherapy	0.79	0.40–1.54	0.485	0.80	0.28–2.30	0.679

Multicollinearity test and cox proportional hazard regression models were used for analysis. Proportional hazard assumption was tested and showed no interaction with time. Bold indicates significant p-value.
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LVSI, lymphovascular space invasion; OS, overall survival

p=0.815) and OS (100.0% vs. 99.5%, p=0.449) compared to ARH (**Fig. 2I and J**). Surgical approaches were not an independent risk factor for worse 5-year DFS (HR=0.72; 95% CI=0.14–3.76; p=0.701). After propensity score matching, 134 patients were in each group, and the 5-year DFS (98.2% vs. 97.7%, p=0.744; HR=0.76; 95% CI=0.10–22.39; p=0.759) and OS (100.0% vs. 99.3%, p=0.340) were comparable between ARH and LRH, as shown in **Fig. 2K and L**.

5. DFS and OS in different tumor type
After adjusting for case mix, including age, histology, depth of stromal invasion, LVSI, lymph node metastasis, surgical margin invasion, parametrial tumor involvement, and postoperative adjuvant treatment, visible tumor was independently associated with for worse 5-year DFS (HR=2.67; 95% CI=1.26–5.65; p=0.001) and OS (HR=9.21; 95% CI=1.24–68.55; p=0.003), as shown in **Table 2**.

DISCUSSION

In this study, we found that the 5-year DFS and OS were similar among patients with stage IB1 cervical cancer and tumor size <2 cm on final pathology. These patients were then subdivided

Table 3. Association of surgical approach and survival in cervical cancer by multivariable analysis after PSM matching

Characteristics	Multivariate analysis for 5-year DFS			Multivariate analysis for 5-year OS		
	HR	95% CI	p	HR	95% CI	p
Surgical approach			0.590			0.766
Abdominal	1 (Ref)			1 (Ref)		
Laparoscopic	1.17	0.66–2.09	0.590	0.89	0.41–1.92	0.766
Age (yr)	1.03	0.10–1.06	0.094	1.06	1.02–1.11	**0.002**
Histologic type			0.875			0.886
Squamous cell	1 (Ref)			1 (Ref)		
Adenocarcinoma	1.09	0.50–2.38	0.825	0.76	0.26–2.26	0.626
Adenosquamous	0.63	0.09–4.64	0.653	0.90	0.12–6.71	0.917
Tumor type			0.010			**0.024**
Invisible tumor	1 (Ref)			1 (Ref)		
Visible tumor	3.91	1.38–11.08	0.010	10.07	1.35–75.19	0.024
LVSI			0.846			0.483
Negative	1 (Ref)			1 (Ref)		
Positive	1.09	0.47–2.53	0.846	0	-	0.483
Stromal invasion			0.147			0.141
Superficial	1 (Ref)			1 (Ref)		
Deep	0.86	0.39–1.91	0.705	0.56	0.19–1.64	0.289
Unreported	1.95	0.94–4.01	0.072	1.99	0.78–5.10	0.150
Parametrium			0.985	0		0.987
Negative	1 (Ref)			1 (Ref)		
Positive	0	-	0.985	0	-	0.979
Surgical margin			0.976	0		0.979
Negative	1 (Ref)			1 (Ref)		
Positive	0	-	0.976	0	-	0.977
Lymph node metastasis			0.002			**<0.001**
Negative	1 (Ref)			1 (Ref)		
Positive	3.44	1.59–7.45	0.002	6.00	2.37–15.24	<0.001
Adjuvant therapy			0.769			0.921
None	1 (Ref)			1 (Ref)		
Chemotherapy	0.79	0.37–1.70	0.549	1.90	0.42–2.84	0.862
Radiochemotherapy/radiotherapy	0.77	0.33–1.80	0.551	0.87	0.23–2.52	0.791

Multicollinearity test and cox proportional hazard regression models were used for analysis. Proportional hazard assumption was tested and showed no interaction with time. Bold indicates significant p-value.

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LVSI, lymphovascular space invasion; OS, overall survival; PSM, propensity score matching.

into visible tumor and invisible tumor subgroups. In the visible tumor subgroup, the tumor was found by gynaecological examination. In the invisible tumor subgroup, the tumor was not found by gynaecological examination; patients were diagnosed by cervical conization with vertical interstitial infiltration >5 mm or horizontal infiltration >7 mm and tumor size <2 cm on conization and final pathology. We obtained the same results in these subgroups compared to the total study population. This suggests that patients with stage IB1 and tumor size <2 cm with visible or invisible tumors can benefit from laparoscopic surgery, considering the advantages of LRH in terms of hospital stay, blood transfusion, number of lymph nodes removed, postoperative complications, and recovery time [2-5]. In the analysis of 5-year OS in the invisible tumor subgroup, we did not conduct a multivariate analysis of the associations between surgical approaches and 5-year OS because there was no death in this group.

This large multicentre retrospective cohort study complements the evidence that laparoscopic surgery may be appropriate for cervical cancer patients with stage IB1 and tumor size <2 cm. The results of this study are similar to those of several recent retrospective studies. Melamed et al. [7] found that MIS was not associated with shorter overall survival than ARH among women with stage IA2 or IB1 and tumor size <2 cm (ARH vs. MIS, 459 vs. 534). Kim et al. [9] found that open surgery and MIS had similar PFS and OS among patients

with stage IB1 and ≤2 cm tumors (ARH vs. MIS, 65 vs. 24). Doo et al. [8] found that there was no difference in progression-free survival (PFS) or OS for stage IB1 and <2 cm tumors (ARH vs. LRH, 21 vs. 30). Pedone et al. [16] found laparoscopy showed DFS equivalent to ARH among IA1 with LVSI to IB1/IIA1 patient with tumor size ≤2 cm (ARH vs. LRH, 114 vs. 137).

There are also 2 studies with different results. Paik et al. [12] found LRH was associated with lower rate of DFS among patient with IB–IIA and tumor size <2 cm (ARH vs. LRH, 186 vs. 62). Uppal et al. [11] found that the MIS was associated with a higher likelihood of recurrence in the risk-adjusted analysis of IA1 with LVSI to IB1 patients with tumor size ≤2 cm (ARH vs. MIS, 82 vs. 182). In Paik's study, tumor size was determined by clinical palpation or inspection, but tumor size classification on clinical evaluation seemed to be different from the tumor size classification on final pathology, so some patients with tumor size >2 cm on final pathology may be included in the analysis. A larger percentage of MIS was robotic-assisted surgery in Uppal's study, while all of MIS was laparoscopic surgery in our study, which is a possible cause of the different results between the two studies.

Several potential reasons are regarded as contributing to the inferior oncological outcomes for LRH: uterine manipulator increasing tumor spillage, CO_2 pneumoperitoneum promoting tumor cell growth or spread, and intracorporeal colpotomy increasing the risk of tumor dissemination in abdominal and pelvic cavity [6,17]. But few studies have been designed to answer this question. In this study, we analyzed patients with IB1 tumor size <2 cm, small tumor was less likely to be broken during intracorporeal colpotomy or promoted to spread by insufflation gas. We performed a subgroup analysis of visible and invisible tumor based on the hypothesis that visible tumor has a high opportunity to be squeezed and tumor spillage during the use of uterine manipulator, and found that LRH and ARH had similar 5-year OS and DFS both in visible tumor and invisible tumor subgroups. This suggests that the role of uterine manipulator may not cause poor oncological outcomes of laparoscopic surgery for patients with small tumor, and more specialized research needs to be designed to answer this question.

The strengths of our study are that large number of stage IB1 and tumors size <2 cm patients were included and further stratification analysis for patients with visible or invisible tumors was conducted. However, this study had several limitations. First, the patient files and medical records may be different among hospitals, leading to a lack of certain clinical data. Second, although the study included cervical cancer patients from 37 hospitals, it did not completely cover all institutions in mainland China. Third, there was no pathological centre, so the determination of invisible tumor was based only on the medical records of cervical conization, and the infiltration depth of cervical stroma and horizontal extension width of the lesions were not assessed by homogenization. Fourth, the FIGO 2009 staging system was adopted in this study, and the horizontal invasion width of cancer tumor >7 mm was taken as the diagnosis standard of IB1, although the horizontal invasion was cancelled in the latest FIGO 2018 staging system. The results of the invisible tumor subgroup may be affected by this change in diagnostic criteria. Fifth, we chose the pathologic tumor size as the final tumor size, when the clinical tumor size was not inconsistent with pathology. However, cervical and uterine specimens were usually cut and unfolded when measuring tumor size, resulting in pathologic tumor size tended to be larger than its actual size, especially for patients with visible tumor. It may be more appropriate to determine visible tumors by preoperative MRI, but the rate of patients received MRI was low in this database. Sixth, the data on colpotomy methods and type of uterine manipulator was not available in the database, this may limit

our interpretation of the results. Seventh, this study was a retrospective study, and the oncological outcomes of 27.3% of patients in the database are unknown.

In conclusion, among cervical cancer patients with stage IB1 disease and tumor size <2 cm, the oncological outcomes of ARH and LRH are similar whether the tumor is visible or not, suggesting that laparoscopic surgery may be suitable for these patients. This study also adds to the evidence that LRH may be suitable for select patients with stage IB1 disease, but more studies are needed to clarify the indications of LRH for cervical cancer.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
The distribution of urban-rural areas, hospital function, region, and city scale in LRH group and ARH group

Click here to view

Supplementary Table 2
Characteristics of patients in the visible tumor subgroup

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Supplementary Table 3

Characteristics of patients in the invisible tumor subgroup

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