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Original Research

The impact of the surgical routes and learning curve of radical hysterectomy on the survival outcomes in stage IB cervical cancer: A retrospective cohort study

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ABSTRACT

Objective: Little is known about the definite reasons of the disadvantage of minimally invasive surgery in the treatment of early stage cervical cancer. This study is to compare survival outcomes of patients with stage IB cervical cancer who received radical hysterectomy (RH) by one surgeon in different periods.

Methods: A retrospective analysis was performed on stage IB cervical cancer patients who received RH from February 2001 to November 2015 at a tertiary hospital. All the major procedures were performed by one surgeon. The clinicopathological characteristics and survival outcomes were compared with laparoscopic RH (LRH) and abdominal RH (ARH) groups in the periods of 2001–2005, 2006–2010, and 2011–2015.

Results: Totally 406 patients were included in the study, 135 (33.3%) and 271 (66.7%) in ARH and LRH groups respectively. The 5-year disease-free survival (DFS) of all patients increased from 2001 to 2005 to 2006–2010 but decreased in 2011–2015. No significant differences exist in the 5-year DFS and overall survival (OS) rates in the first 50 patients of LRH and ARH groups. The subgroup analysis in stage IB1 patients (68.2% of all participants) reached the same conclusions.

Conclusion: For RH patients, in which all major procedures were performed by one surgeon, the DFS did not exhibit substantial improvement in the period of 2001–2015 since the extensive adoption of LRH. The learning curve probably explains the disadvantage of LRH.

1. Introduction

Globally, cervical cancer is the third most common gynecologic malignancy, and the fourth cause of cancer-related mortality among women worldwide [1]. Current treatment for the early stage of this disease is radical hysterectomy (RH) and lymphadenectomy. Nezhat et al. [2] first reported laparoscopic RH (LRH) and dissection of the pelvic lymph nodes (LNs) in 1992, and since then, mini-invasive surgeries (MISs) have become the main operative approach. Numerous retrospective studies and even a meta-analysis [3,4] have supported MIS as a feasible and safe approach. However, a randomized controlled study (LACC trial) reported that minimally invasive RH was associated with lower rates of disease-free survival (DFS) and overall survival (OS) than abdominal RH (ARH) among women with early-stage cervical cancer [4]. The LACC trial had several limitations [4,5], and the covariate of surgeons' experiences was neglected by the LACC authors although some efforts had been made to clarify the issue. The learning curves of the surgeons were also rarely discussed. An epidemiologic study revealed that minimally invasive RH was associated with shorter OS than ARH among women with stage IA2 or IB1 cervical carcinoma. The adoption of MIS coincided with a decline in the 4-year relative survival rate of 0.8% per year after 2006 [6]. Such a phenomenon suggested that the learning curves of MIS probably caused the decline in survival outcomes, since the trend of survival after 2010 is little known.

In this study, we reported all RHs in one university hospital from February 2001 to November 2015, in which the principal procedures were all performed by Dr. MW. We tried to determine whether the surgeon's learning curves would affect the survival outcomes between MIS and ARH groups.

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2. Methods

2.1. Patient enrollment

The work has been reported in line with the STROCSS criteria [7]. All cervical cancer patients of International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB treated with RH between February 2001 and November 2015 in one university hospital were enrolled according to the following inclusion criteria: histopathologically proven primary cervical cancer, receiving LRH or ARH performed primarily by Dr. MW. The whole study period was divided into three phases: phase 1 (2001–2005), phase 2 (2006–2010) and phase 3 (2011–2015).

This report is part of a multicenter study of the "Longitudinal study of different surgical approaches in Chinese patients of uterine cervical cancer" (SACCC, NCT03738969 of *clinicaltrials.gov*), which has been approved by the Institutional Review Board of the hospital. All patients gave informed consent before surgical treatment. The primary measurement of the study was DFS and OS in the whole study period and in different phases.

2.2. Treatments and follow-up

Surgical procedures consisted of RH, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and para-aortic LN dissection (extension to the level of the inferior mesenteric artery and to the renal vein level when the metastasis was suspicious). For young patients requiring the preservation of ovaries, salpingectomy was performed along with suspension of the ovaries to the peritoneum above the level of the anterior superior spine. All the major procedures, including lymphadenectomy and parametrial resection with or without a nerve-sparing procedure, were primarily performed by one surgeon according to Class III or Meigs' surgeries of the Piver-Rutledge-Smith classification [8] (before 2011) and later according to Type C1 of the Q-M classification (after 2011) [9]. These procedures and adjuvant therapy have been described in a previous report [10]. Postoperative adjuvant therapies were provided for eligible patients, including systematic chemotherapy, radiotherapy, radiotherapy and concurrent chemotherapy of cisplatin or paclitaxel (CCRT) or a combination of these protocols.

Clinical and pathologic data were retrospectively collected by searching and reviewing medical records. Complications related to RH within 3 months were reviewed and collected in medical records as adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.8 [11]. The data of recurrence and mortality were drawn from the case reports. Recurrent sites were verified by surgeries and/or imaging evaluation. A detailed follow-up by telephone was also provided to patients with unknown or uncertain survival outcomes.

2.3. Statistical analysis

SPSS 22.0 software (IBM, USA) was used for statistical analysis. $p < 0.05$ was set to indicate statistical significance. Comparisons of continuous variables were conducted with parametric methods if assumptions of a normal distribution were confirmed. Nonnormally distributed variables and categorical data were compared between LRH and ARH groups with the use of nonparametric tests. Survival curves were generated by the Kaplan–Meier method, and Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the effect of surgical routes on DFS, progression-free survival, and OS. A multivariable analysis of DFS was performed with adjustment for important pathological risk factors of FIGO stage, tumor differentiation, lymph-vascular space invasion (LVSI), invasion depth of the stroma, metastasis to the LNs, and involvement status of the parametrial and vaginal margin.

3. Results

3.1. Patients' characteristics

In total, 406 patients were included in the study, with 135 cases (33.3%) in the ARH group and 271 cases (66.7%) in the LRH group. The epidemiological, clinical and pathological characteristics of the two groups are summarized in Table 1. The baseline epidemiological characteristics of patients in the ARH and LRH groups were well balanced. No conversion to the ARH from LRH occurred. Both groups had similar proportions of postoperative adjuvant therapy.

Regarding surgical outcomes, compared with the ARH group, the LRH group had a lower estimated blood loss (269.8 ± 303.5 vs 467.4 ± 292.0 ml, $p < 0.001$), lower blood transfusion rate (10% vs 26.7%, $p < 0.001$) and shorter length of hospital stay (14.3 ± 6.7 vs 21.9 ± 16.1 days, $p < 0.001$). The duration of the surgical procedures and the grade 3/4 complications showed no statistically significant differences between the two groups. Regarding the pathological characteristics, in the LRH group, there were a higher number of LNs resected ($p = 0.003$), a lower proportion of grade 2–3 tumor differentiation ($p = 0.015$) and deep stromal invasion ($p = 0.003$), fewer positive LVSI ($p = 0.001$) and more frequent parametrial involvement ($p = 0.007$).

3.2. Recurrent sites

The distribution of recurrent sites between LRH and ARH cases showed no significant differences. LRH and ARH groups exhibited 68.3% (28/41) and 75.9% (22/29) recurrence within the pelvic cavity or vaginal vault, respectively. However, the ARH group presented significantly more recurrences in the vaginal vault (55.2% [16/29] vs 31.7% [13/41] of LRH, $p = 0.05$).

3.3. Survival analysis

The median follow-up time was 49 months (range 12–189 months), and 371 (91.4%) patients had definite survival outcomes (87 and 214 cases in the ARH and LRH groups). In total, 70 patients (18.9%) experienced recurrence, including 41 (16.1%) in the LRH group and 29 (25.0%) in the ARH group ($p = 0.042$). The median DFS was 23.5 months (range 6–156).The 3-year and 5-year DFS in the LRH group was 83.8% and 80.2% vs 87.1% and 81.0% in the ARH group ($p = 0.467$). In total, 46 patients (12.4%) died, including 22 (8.6%) in the LRH group and 24 (20.7%) in the ARH group ($p = 0.001$). The median OS was 48.5 months (range, 12–189). The 3-year and 5-year OS in the LRH group was 95.0% and 92.5% vs 84.5% and 87.1% in the ARH group ($p = 0.043$).

In the Cox regression model adjusted for pathological risk factors, the LRH and ARH groups had no significant differences in 5-year DFS (HR, 0.8; 95% CI, 0.4–1.3; $p = 0.356$) or in 5-year OS (HR, 1.5; 95% CI, 0.8–3.0; $p = 0.237$) with the LRH group as a reference (Fig. 1).

3.4. Survival analysis of different phases

Survival outcomes of different phases are shown in Table 2, Figs. 2–3. There were few laparoscopy surgeries in phase 1 (2001–2005) and no open surgery in phase 3 (2011–2015). The adjusted 5-year rates of OS or DFS were not significant between the three phases; however, the 5-year DFS in phase 3 was lower than that in phase 2 (2006–2010) (Fig. 3).

Although the 5-year DFS of LRH and ARH increased with the chronicle years, the total 5-year DFS increased from phase 1 (2001–2005) to phase 2 (2006–2010) and dropped in phase 3 (2011–2015) to the level of phase 1. The subgroup analysis of Stage IB1 also showed the same "increase-decrease" trend. Kaplan–Meier analysis revealed no significant changes between the 5-year DFS rates of LRH

Table 1
Clinical and pathological characteristics of the LRH and ARH groups in total and in first 50 cases.

	LRH group (n = 271)	ARH group (n = 135)	*p*	First 50 cases in LRH group	First 50 cases in ARH group	*p*
Age (year) (mean ± SD)	42.9 ± 9.1	42.6 ± 7.9	0.548	42.7 ± 6.4	40.0 ± 9.4	0.003
Menopause n (%)	217 (80.1)	104 (77.0)	0.479	43 (86.0)	43 (86.0)	1.000
BMI (Kg/m^2) (mean ± SD)	23.1 ± 2.8	23.7 ± 3.0	0.056	23.6 ± 2.0	23.8 ± 3.2	0.022
Max diameter of tumor (cm) (mean ± SD))	3.2 ± 1.6	3.4 ± 1.4	0.250	3.3 ± 1.3	3.4 ± 1.5	0.345
FIGO stage n (%)			0.921	–	–	
IB1	184 (67.9)	91 (67.4)		–	–	
IB2	87 (32.1)	44 (32.6)		–	–	
Duration of surgery (min) (mean ± SD)	200.2 ± 40.6	209.5 ± 40.2	0.061	197.0 ± 44.0	213.5 ± 38.8	0.230
Estimated blood loss (ml) (mean ± SD)	269.8 ± 303.5	467.4 ± 292.0	< 0.001	162.4 ± 202.8	538.0 ± 320.8	0.004
Blood transfusion n (%)	27 (10.0)	36 (26.7)	< 0.001	4 (8.0)	12 (24.0)	< 0.001
Hospital stay (days) (mean ± SD)	14.3 ± 6.7	21.9 ± 16.1	< 0.001	14.8 ± 4.5	27.3 ± 22.9	< 0.001
Grade 3/4 complications[a]	16 (5.9)	12 (8.9)		1 (2.0)	3 (6.0)	0.309
No. of lymph nodes resected (mean ± SD)	28.7 ± 12.0	25.1 ± 11.3	0.003	27.5 ± 10.3	26.1 ± 9.6	0.334
Pathologic subtype			0.120			0.143
Squamous carcinoma	217 (80.1)	119 (88.1)		37 (74.0)	45 (90.0)	
Adenocarcinoma	43 (15.9)	12 (8.9)		12 (24.0)	3 (6.0)	
Adenosquamous carcinoma	11 (4.0)	4 (3.0)		1 (2.0)	2 (4.0)	
Differentiation of tumor			0.015			0.071
G1	147 (54.2)	56 (41.5)		31 (62.0)	19 (38.0)	
G2-G3	124 (45.8)	79 (58.5)		22 (44.0)	28 (56.0)	
Invasion depth of stroma			0.003			0.052
< 1/3	136 (50.2)	44 (32.6)		28 (56.0)	19 (38.0)	
> 1/3 but < 2/3	71 (26.2)	44 (32.6)		7 (14.0)	17 (34.0)	
> 2/3	64 (23.6)	47 (34.8)		15 (30.0)	14 (28.0)	
Positive LVSI n (%)	170 (62.7)	61 (45.2)	0.001	27 (54.0)	25 (50.0)	0.689
Parametrial involvement n (%)	10 (3.7)	14 (10.4)	0.007	4 (8.0)	10 (20.0)	0.084
Positive vaginal margin n (%)	2 (0.7)	1 (0.7)	0.998	1 (2.0)	0 (0.0)	0.500
Metastasis to lymph nodes n (%)	42 (15.5)	15 (11.1)	0.231	8 (18.0)	6 (12.0)	0.564
Postoperative adjuvant therapy n (%)	142 (52.4)	75 (55.6)	0.548	2 (4.0)	7 (14.0)	0.080

ARH, abdominal radical hysterectomy. BMI, body mass index. FIGO, International Federation of Gynecology and Obstetrics. G1, G2 and G3, grade of the differentiation. LRH, laparoscopic radical hysterectomy. LVSI, lymph-vascular space invasion. SD, standard deviation.

[a] These complications and their severity were defined as adverse events happened within 3 months after RH according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

and ARH in different phases (all p values > 0.05), except for the IB1 patients in phase 2 (2006–2010) (71% vs 90%; p = 0.05; HR, 0.3; 95% CI, 0.1–1.0, with the LRH group as a reference, Table 2). In Cox regression model, all these differences disappeared.

The 5-year OS of LRH, ARH and all patients increased with the chronicle years. The 5-year OS between different phases had no significant differences in the Kaplan–Meier analysis or in the regression model (all p values > 0.05). No significant changes between the 5-year OS rates of LRH and ARH in different phases (all p values > 0.05), including the IB1 patients.

3.5. Analysis of learning curves

During the entire study period, the epidemiological, surgical and pathological results among the first 50 cases in the LRH and ARH groups were compared (Table 1). LRH still had the advantage of significantly less estimated blood loss and transfusion and a shorter hospital stay. During the entire study period, the first 50 cases in the LRH and ARH groups had a similar 5-year DFS and OS in the Kaplan–Meier analysis and Cox regression analysis (Fig. 3). For the subgroup of stage IB1, analysis in the first 50 cases and later cases (41 in the ARH group and 136 in the LRH group) had the same findings.

4. Discussion

Current guidelines [12,13] indicate that either laparotomy (open surgery) or MIS is an acceptable approach to RH in patients with early-stage (IA2 to IIA) cervical cancer. These recommendations have led to widespread use of a minimally invasive approach. MIS had not been associated with lower 5-year rates of DFS or OS than the ARH [3,4,14–19]. However, the two studies [4,6] published recently had put forward objections, documented worse survival outcomes of LRH and decreased DFS since 2006 in the United States. Similarly in our report, the DFS did not exhibit substantial improvement in the period of 2001–2015 since the extensive adoption of LRH. Besides, our study also found that in phase 2 (2006–2010), the DFS of ARH was superior to the DFS of LRH, which had statistical significance in patients at stage IB1. It seems that the MIS should have a reputation for this trend, which was significantly different from the situation in early-stage uterine, colorectal, or gastric cancer [20–23].

The recurrent rate in our study is higher compared to the literature, especially the recent findings [4,6]. There are several possible reasons. The different stages in various studies may produce diverse survival outcomes. Plenty of stage IB2 patients and no IA2 patients in our study would cause more recurrence. The long follow-up period in our study may also be associated with high recurrent rate. Last, as we have illustrated, the learning curve of the surgeon would partially explain the shifting survival outcomes. Indeed, near-term 5-year DFS and OS of open surgeries (2006–2010) or laparoscopy (2011–2015) in all stage IB patients had achieved similar outcomes published in recent reports [4,6].

The reasons of inferior survival outcomes of MIS were little known despite of several assumptions. In our opinion, due the complex and complicated characteristics of radical hysterectomy, a longer learning probably is needed to achieve comparable survival outcomes, which is equally essential for laparotomy or laparoscopy. According to published data, 2006 was the year in which surgeons in the United States began to adopt minimally invasive RH for the treatment of cervical cancer [24]. In the study of Melamed et al. [6], the adoption of MIS was associated with a significant change in the trend and coincided with the beginning

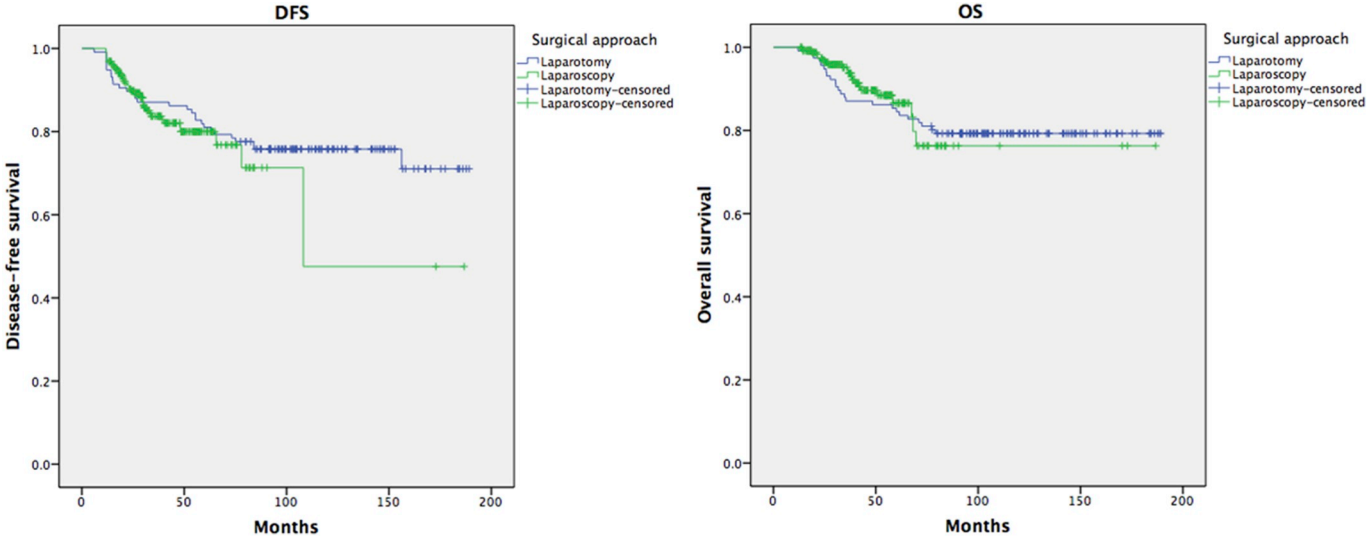

Fig. 1. The DFS and OS adjusted for pathological factors of laparoscopic and laparotomic patients.

Table 2
Survival outcomes of different phases.

Chronicle years	2001–2005	2006–2010	2011–2015
Laparotomy cases	52	83	0
Laparoscopy cases	3	26	242
Five-year DFS of all	79%	82%	79%
Five-year DFS of ARH	77%	83%	–
Five-year DFS of LRH	–	76%	79%
Five-year DFS of IB1 patients	84%	86%	82%
Five-year DFS of LRH in IB1 patients	–	71%	82%
Five-year DFS of ARH in IB1 patients	83%	90%	–
Five-year OS of all	81%	85%	87%
Five-year OS of ARH	80%	86%	–
Five-year OS of LRH	–	81%	87%
Five-year OS of IB1 patients	87%	90%	90%
Five-year OS of LRH in IB1 patients	–	79%	90%
Five-year OS of ARH in IB1 patients	86%	94%	–

ARH, abdominal radical hysterectomy. DFS, disease-free survival. LRH, laparoscopic radical hysterectomy. OS, overall survival.

of a decline in the 4-year relative survival rate of 0.8% per year between 2006 and 2010 in this population. There are almost no definite reasons that could explain this phenomenon, and very few studies have considered factors involving surgeons and their learning curves. Conrad et al. [25] evaluated the current patterns in the use of MIS procedures by SGO members and compared the results against those of their 2004 and 2007 surveys. There was an increase in conversion from MIS to laparotomy. Mastery of LRH required experience in at least 25 and up to 50 cases [26,27]. After completing the residency- and fellowship-training course on gynecologic laparoscopy, gynecologic oncologists, even without ARH experience, might reach an acceptable level of surgical proficiency in LRH after approximately 20 cases and showed a gentle slope of the learning curve, taking less effort to initially perform LRH [28]. According to Hwang et al. [29], the learning period for LRH and LN dissection to reach a turning point was calculated to be 40 cases. However, the DFS did not differ between the two groups of first 30 patients and next 30 patients [29]. The systematic review found a slow learning curve required for a surgeon to gain expertise in laparoscopically assisted vaginal RH [30]. These studies supported the necessity of evaluating the learning curves in a demanding surgical modality.

In our study, it is obvious that both LRH and ARH require learning curves to achieve improved survival outcomes, as the first 50 cases of LRH and ARH had almost the same 5-year DFS. Meanwhile, the 5-year DFS rate of LRH in 2011–2015 achieved a similar level to that of ARH in 2006–2010. As judged by the numbers of resected LNs, LRH and ARH exhibited a similar surgical quality in their first 50 cases (Table 1). The worse DFS rates and stable OS rates in phase 3 (2011–2015) in the total study population were probably caused by the effects of the learning curve. Most likely, the patients in the study of Melamed et al. [6] would have improved their survival outcomes in the following periods beyond year 2010, as described in our study, when most surgeons had achieved experienced training and skills. Such a hypothesis requires a longer

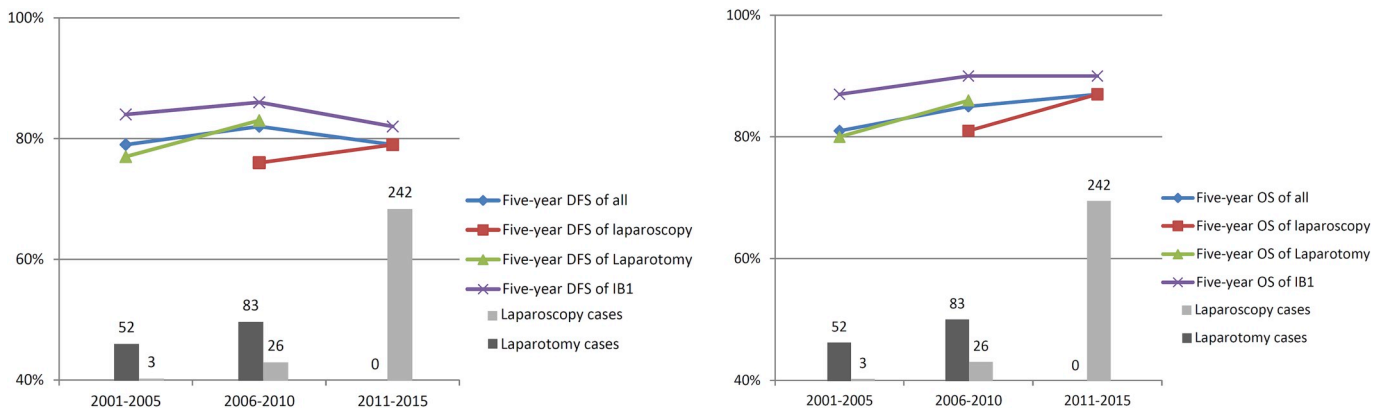

Fig. 2. The DFS and OS of different phases in all patients and in patients with laparoscopy, laparotomy, and FIGO stage IB1.

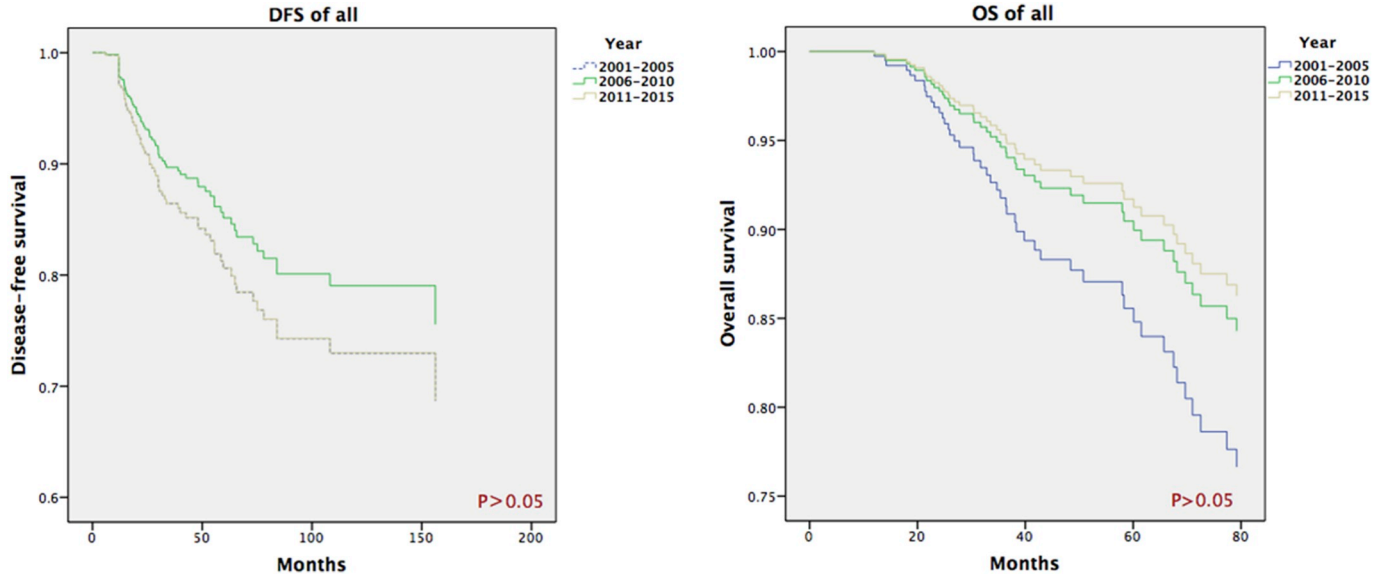

Fig. 3. The DFS and OS of different phases adjusted for pathological factors of laparoscopic and laparotomic patients.

follow-up to confirm or to disprove. As Melamed et al. stated, it may be that the MIS is not inherently inferior to ARH but that the patients in the LACC study were treated by surgeons who were more experienced with ARH than with MIS [6]. Cancer control after radical prostatectomy appears to be sensitive to surgeon experience [31]. We must judge the usefulness of MIS for early-stage cervical cancer dispassionately and objectively on the basis of all pertinent data [5]. As the learning curve could not completely explain the deteriorated DFS in the LACC trial, a randomized controlled trial taking into account the factors of individual surgeons should provide sound evidence of the advantages and disadvantages of LRH, such as the clinical trial of NCT03739944 of *clinicaltrials.gov*.

Other perspectives in our study need further consideration. In our study, no conversion occurred, which was different from the rates of 1.5%–3.5% in other reports [32]. It is hard to retrospectively judge whether all of the LRHs in our group were uneventful. However, a better description of the surgical procedure for the purpose of quality control is essential for further study. Although the total distribution of recurrent sites was similar in the LRH and ARH groups, the significantly higher recurrence at the vaginal vault in the ARH group was also similar to that in the LACC trial. However, in the LACC trial, the definite reasons were unknown. Total laparoscopic/robotic intracorporeal colpotomy under CO2 pneumoperitoneum may pose a risk of a positive vaginal cuff margin and of intraperitoneal tumor spread [33–35]. However, this fact could not explain the higher recurrence at the vaginal vault in the ARH group.

Our study had several limitations. Similar to previous reports, our study was also limited by low power, uncertain generalizability, and probable residual confounding. Data on long-term survival assessed in randomized trials or in large, well-designed observational studies are urgently needed. The insufficient number of stage IB1 patients and the lack of patients at stage IA1 with positive LVSI or patient at stage IA2 further limited the generalizability of our findings. As our study reports on a single center and a single team, selection bias would greatly interfere with the interpretation of the oncologic outcomes.

5. Conclusions

In a cohort stage IB cervical patients treated with RH, in which all the major procedures were performed by one surgeon, the DFS and OS did not achieve substantial improvement from 2001 to 2005 to 2011–2015. The major reason was the adoption of laparoscopy since 2006. However, the disadvantage of LRH is probably not from the assumptive inherent techniques itself, but rather from the learning curves, as the OS and DFS were familiar in the total and in the first 50 cases of LRH and ARH patients. The subgroup analysis of stage IB1 patients reached the same conclusions.

Ethical approval

The Institutional Review Board of Peking Union Medical College Hospital has approved this study (No. JS-1711).

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Conflicts of interest

None.

Research registration number

The registration No. is NCT03738969 NCT03738969 (*clinicaltrials.gov*).https://clinicaltrials.gov/ct2/show/NCT03738969.

Guarantor

Dr Lei Li and Dr Ming Wu accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Disclosure

All authors have nothing to disclose and no conflict of interests.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

Yuting Liu: Methodology, Software, Formal analysis, Data curation, Writing - original draft. **Lei Li:** Conceptualization, Conceptualization, Software, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Project administration, Funding acquisition. **Ming Wu:** Validation, Resources, Writing - review & editing, Supervision. **Shuiqing Ma:** Investigation, Resources. **Xianjie Tan:** Investigation, Resources. **Sen Zhong:** Investigation, Resources. **Jinghe Lang:** Visualization, Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.06.009.

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