The Effect of Laparoscopic Radical Hysterectomy Surgical Volume on Oncology Outcomes in Early-Stage Cervical Cancer

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Abstract

Objective: To analyze the effect of surgical experience with laparoscopic radical hysterectomy (LRH) on oncological outcome in cervical cancer patients. Methods: We retrospectively compared the oncological outcomes of 1469 patients with stage IB1 cervical cancer receiving LRH from 2004 to 2016. The surgical volume for each surgeon was defined as low (fewer than 50 surgeries), mid (51-100 surgeries), and high (100 surgeries or more). Kaplan-Meier curves and the Cox proportional hazards model were used to estimate the effect of surgical experience on the oncological outcomes of patients. Results:A total of 1405 cases were included in this study. The average operative times of the low-volume (n = 427), mid-volume (n = 396) and high-volume (n=582) groups were 270, 260 and 227 minutes, respectively (P < 0·001), and mean blood loss was 218 ml, 197 ml and 179 ml, respectively (P = 0·004). The 5-year OS of the low-volume, mid-volume and high-volume groups was 96·1%, 93·1% and 92·5%, with 5-year DFS rates of 92·0%, 87·5% and 87·6%, respectively. There was no significant difference among the three groups. However, surgery volume was not an independent risk factor for shorter OS or DFS after controlling for case mix, nor was surgeons' experience after 1:1 PSM (Propensity score matching) between each two of the three groups. Conclusion: The results showed that surgeons' surgical volume did not affect the oncological outcome of LRH but that operative time and blood loss were significantly improved with a higher surgical volume.

Introduction

Radical hysterectomy (RH) is one of the traditional treatments for early-stage cervical cancer. The laparoscopic technique was first used for RH in 1992, and minimally invasive surgery has become a common surgical approach that has advantages of less intraoperative blood loss and complications and shorter hospital stay when compared with traditional open surgery[1-5]. However, the Laparoscopic Approach to Cervical Cancer (LACC) trial, a high-quality international multicenter randomized controlled trial, reported that LRH was

closely related to worse oncology outcomes, though without explaining the reasons. In general, surgeons' surgical volume may be one of the reasons influencing oncology outcomes. For example, for other malignant tumors, it is considered that a greater surgery volume is an important factor related to better oncological outcomes[6]. Meta-analysis to investigate the relationship between the number of gynecology surgeries and surgical outcomes has been conducted, and it is believed that intraoperative and postoperative complications are significantly reduced with high-volume surgeons[7].

Nonetheless, previous studies have focused on the relationship between surgical skills and perioperative period outcomes and surgical volume, whereas long-term oncological outcomes have seldom been discussed[8-11]. Moreover, previous studies mostly involve single centers and surgeons, with few cases included. Therefore, this multicenter, retrospective cohort database study based on the large clinical diagnosis and treatment database of cervical cancer in China was carried out. The aims were to explore the association between the LRH volume of surgeons and long-term oncological outcomes of early cervical cancer to discuss whether the volume of LRH by gynecologists will affect survival outcomes of early cervical cancer patients.

Methods

Data Source

The data of this study derive from the clinical diagnosis and treatment for cervical cancer in mainland China (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 Ethics Committee of Nanfang Hospital, Southern Medical University, approved this retrospective study (ethics number NFEC-2017-135). Written informed consent was waived by the ethics committee, as the information of human medical documents was retrospectively gathered and analyzed and patient data were unidentifiable in this study. The identifier of the clinical trial is CHiCTR1800017778 (International Clinical Trials Registry Platform Search Port,*http://apps.who.int/trialsearch/*).

Using standardized data collection and quality control procedures, trained gynecological oncology staff collected the clinical data from patient files and the medical record management system in the hospitals. The details of the data sources and methods were the same those as previously reported[12, 13]. For patients undergoing surgical treatment, the collected data, including demographic details, preoperative examination results, surgical information, pathological results, preoperative and postoperative adjuvant treatment details, complications, hospitalization time, expenses, and follow-up, contained almost all the information during the treatment of cervical cancer. In this database, the FIGO stage was recorded and corrected by tumor size according to the FIGO 2009 staging system. Tumor size was evaluated by pathological records. To ensure the accuracy of the collected data, two uniformly trained staff members 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 gynecological oncology staff at each center to keep the patients' personal data confidential and to provide disease management guidance. The follow-up information, including survival status, time of death, recurrence time, recurrence site, and treatment after recurrence, was gathered through the return visit system or telephone follow-up. Oncological outcomes were assessed according to the recorded information, and the last day of the return visit or telephone follow-up was defined as the last follow-up. The follow-up rate of oncological outcomes in this database is 72·7%.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) age $>$ 18 years old; (2) FIGO stage IB1; (3) squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma; (4) QM type B or type C hysterectomy + pelvic lymphadenectomy $\pm$ para-abdominal aortic lymphadenectomy; (5) available survival outcomes; (6) no preoperative treatments; and (7) standard postoperative adjuvant treatment after operation.

The exclusion criteria were as follows: (1) pregnancy; (2) cervical stump cancer; (3) combined with other malignant tumors; and (4) did not meet the inclusion criteria.

Definitions and outcome measures

In this study, patients treated by surgeons with different LRH experiences were divided into three groups[14]: low-volume surgeons (< 51), mid-volume surgeons (51-100) and high-volume surgeons (> 100). Outcome measures included operative technique (operative time and blood loss) and oncological outcome (5-year OS and DFS).

OS was defined as the time from the date of surgery to the date of death from any cause. DFS was defined as the time from the date of surgery to the date of disease recurrence or death from cervical cancer, and patients with no evidence of recurrence or death were censored at the date of the last follow-up or return visit.

According to FIGO guidelines[15], standard postoperative treatment was defined by any one pathological high-risk factor (positive para-aortic or pelvic nodes, parametrial extension, and positive margins) or any two or more pathological medium-risk factors (tumor size > 4 cm, LVSI, stromal invasion) who received radiotherapy or radiochemotherapy or those with no postoperative high-risk factor and one or more medium-risk factors who did not receive postoperative radiotherapy or radiochemotherapy.

Statistical methods

All statistical procedures were processed with SPSS 23.0 statistical software (SPSS, Inc., Chicago, IL, USA). Between-group differences in the baseline characteristics were assessed through independent two-sample t tests or Pearson's chi-squared test. Quantitative data are shown as the mean ± standard deviation (x ± s), and nominal-scale data are shown as percentages (%). The 5-year OS and DFS rates of LRH and ARH were calculated and compared using the Kaplan–Meier curve and the log-rank test. A Cox proportional hazards model was used to estimate HRs and 95% confidence intervals for the effect of treatment on 5-year OS and DFS; known factors that may affect the oncological outcome of cervical cancer were included in this multivariate model to adjust for case mix, including age, hospital type, region, city class, finance, year, histology, LVSI, stromal invasion, uterine corpus invasion, parametrial tumor involvement, surgical margin invasion, lymph node metastasis, preoperative treatment condition, and postoperative adjuvant treatment. Propensity score matching (PSM, 1:1) was used to balance differences in the data analysis; the variables included were the same as those above. A P value <0·05 from two-sided tests was regarded as significant.

Results

Among the 46,313 patients described in the database, 1405 were included in this study (427 patients in the low-volume group, 396 patients in the mid-volume group and 582 patients in the high-volume group). The flow diagram of recruitment and exclusion is illustrated in Figure 1. The median follow-up time was 30 months (interquartile range, 19·0-45·0). The clinicopathologic characteristics of the three groups are provided in Table 1. The patients in the high-volume group were more likely to have LVSI (P = 0·004) and lymph node metastasis (P = 0·002); those in the mid- and high-volume groups were more likely to have deep stromal and uterine invasion than were those in the low-volume group (all P < 0·05).

Perioperative outcome

The average operative times was 249 minutes for the low-, mid- and high-volume groups, at 270 minutes, 260 minutes and 227 minutes, respectively (P < 0·001). Although there was no significant difference in operative time between the low- and mid-volume groups, that of the high-volume group was significantly shorter than that of the low-and mid-volume groups (P < 0·001). Among the 1405 patients, the average intraoperative blood loss was 196 ml; the values were 218 ml, 197 ml and 179 ml in the low-, mid- and high-groups, respectively (P = 0·005). There was no significant difference between the mid-volume group and the low- and high-volume groups, but blood loss in the high-volume group was significantly less than that in the low-volume group (P = 0·001).

Oncology outcome

In 1405 cases, 48 cases died and 104 cases recurred. The clinicopathologic characteristics of the two groups are shown in Table 1. in the low-, mid- and high-volume groups ,the 5-year DFS was 92·0%, 87·5% and 87·6%; the 5-years OS was 96·1%, 93·1% and 92·5%; there was no significant difference between the three groups (DFS: P=0·215; OS: P = 0·155)· The Kaplan–Meier survival curves are shown in Figures 2· In the multivariable analysis, adjusting for the case mix, patients in different volume groups were not an independent worse prognostic factor for a worse 5-year DFS or OS (DFS: p=0·508;OS: p=0*353, Table 2)

After 1:1 PSM between each two of the three groups, the clinicopathological characteristics were well balanced (Table 3). For the low group vs the mid group, including 254 patients in each, there was no significant difference in 5-year DFS or OS (DFS: 90*0% vs 91*6%, P = 0*729; OS: 94*3% vs 93*8%; P = 0*137). In Cox regression analysis adjusting for the above factors, the volume of surgery was not an independent risk factor for DFS and OS (DFS: P = 0*489; OS: P = 0*131). There was also no significant difference in OS and DFS between the low and high groups, including 218 patients in each (DFS: P = 0*651, OS: P = 0*474). After eliminating the case mix factors by Cox regression analysis, the volume of surgery was not an independent risk factor for DFS and OS (DFS: P = 0*289; OS: P = 0*583). Between the mid and high groups, with 444 patients in each. there was no significant difference in DFS and OS (DFS: P = 0*754; OS: P = 0*788). After eliminating the case mix factors by Cox regression analysis, the surgical volume of surgeons was not an independent risk factor for DFS and OS (DFS: P = 0*598; OS: P = 0*959).

Discussion

In this study, we divided patients into three groups according to the total volume of surgeons' LRH experience, low-, mid- and high-volume groups, and analyzed their effects on surgical skills (operative time, blood loss) and patients' long-term oncological outcomes (DFS, OS). We found that intraoperative blood loss decreased and operative time was significantly shortened with an increase in surgical volume, demonstrating that operative technology improves as surgeons gain more experience. This conclusion was consistent with that of most previous learning curve studies. Laparoscopic surgery involves new technologies and equipment, with the surgical field being transformed from traditional three-dimensional open surgery to two-dimensional laparoscopic surgery. The increase in surgical experience means repeated practice of surgical skills. In general, theoretical and practical research results confirm that laparoscopic surgery skills can be improved with an increase in surgical volume.

The LACC trial considered that the oncological outcomes of minimally invasive surgery for early cervical cancer were worse than those of traditional open surgery[16,17]. Many studies have explored the causes of the higher mortality and recurrence rate of LRH. In addition to the necessary technologies required for minimally invasive surgery, such as carbon dioxide pneumoperitoneum, uterine manipulators[18-21] and other possible factors, the surgical experience of surgeons has also attracted more attention. However, there are few studies to date about laparoscopic surgery experience, and most are focused on the influence of surgical experience on surgical skills and perioperative outcomes, with little emphasis on oncological outcomes. This study explored the surgical volume of LRH and the long-term oncological outcomes of early cervical cancer patients based on the clinical diagnosis and treatment for cervical cancer in a mainland China (Four C) database (n=46313).

In a study of 4702 cases of prostate cancer patients involving 29 doctors, Vickers et al[6] found 5-year recurrence rates of 17%, 16% and 9% for patients who underwent laparoscopic radical prostatectomy and whose surgeons had performed 10, 250 and 750 surgeries, respectively, suggesting that the 5-year recurrence rate of patients decreases with an increase in laparoscopic surgeon experience. In a recent multicenter study in Japan, Matsuo et al[22]defined low-volume hospitals as less than 32 cases of RH (radical hysterectomy) in 5 years, mid-volume hospitals as 32-104 cases, and high-volume hospitals as [?] 105 cases. Based on analysis of the oncological outcomes of RH of 116 medical institutions, they considered that high-volume hospitals may be associated with the risk of local recurrence and the improvement of survival rate.

The results above are different from our findings. However, there are many differences in surgical difficulties and skills and the use of instruments between LRH and laparoscopic radical prostatectomy, such as the

use of uterine manipulators in LRH. Nevertheless, previous results cannot be used to represent the impact of laparoscopic experience on the long-term prognosis of cervical cancer. For example, Matsuo et al[22] overlooked the possible effect of the surgical approach on RH oncological outcomes. Moreover, the surgical volume of hospitals does not fully represent the surgical volume of surgeons, and there are also surgeons with poor surgical experience in high-volume hospitals and surgeons with rich surgical experience in low-volume hospitals; moreover, their grouping method of surgical volume, the minimum P-value method, might be flawed. They use this approach to identify the cutoff for surgical volume related to disease-free survival via an unadjusted Cox proportional hazard regression model. The first surgical volume exhibiting statistical significance is used to define low-volume centers, and the smallest P-value was defined for high-volume centers. This grouping led to differences in oncological outcomes between groups prior to analysis, making the differences controversial. Our study makes up for the deficiency of Matsuo et al. in not studying the experience of surgeons and unclear surgical approaches, and the grouping method of this study is not suspected of making analysis on the basis of known outcomes.

Chong et al[23] analyzed the oncological outcomes of the first 50 LRH patients and the second 50 LRH patients of the same doctor and found that the long-term prognosis of the patients did not show significant improvement with the increase in surgical experience. However, it is undeniable that the operative time, hospital stay, time to restore normal residual urine volume, blood loss, intraoperative and postoperative complications are significantly reduced and that the number of lymph nodes acquired is increased with an increase in surgical experience. Based on analysis of the experience of a single surgeon in LRH, this study concludes that the increase in LRH experience may improve surgical skills but have no effect on oncological outcomes, which is consistent with our results. The previous study focused on the analysis of the results of the first 50 cases and the second 50 cases of a single doctor, with good consistency, but the sample size was small. In contrast, our study was a multicenter, multisurgeon, large-sample analysis, and Cox regression analysis and PSM were used to balance the case mix factors; thus, the results are more convincing.

However, we acknowledge several limitations in this study. First, this was a retrospective study with confounding factors. For example, in the high-volume group, the proportion of patients with LVSI and lymph node metastasis was higher than that in the mid- and low-volume groups. Nonetheless, we attempted to balance these differences through propensity score matching. Second, the case and report writing standards among hospitals might have been different, leading to the absence of clinical data. Third, although our study covered a total of 46,313 cases of cervical cancer inpatients in 37 hospitals in most of China, it did not cover all regions nationwide. Regardless, the database can comprehensively represent the diagnosis and treatment of cervical cancer in China. Fourth, because this database was a cervical cancer-specialized disease database, a small number of endometrial cancer patients who will also receive LRH may have been considered in this study, which might have affected the analysis of the effects of LRH surgical experience on surgical skills and oncology outcomes. Fifth, we only analyzed surgical skills and long-term oncological outcomes, without further exploration of the occurrence of near- and long-term complications. However, our team has conducted special discussions on complications, and we believe that a conclusion will be reached soon to compensate for the deficiencies in this study. Finally, there may be methodological flaws in defining the volume of surgery in this study. According to previous literature, we used 50 cases as the cutoff point to define low- and mid-surgical volumes and 100 cases as the cutoff point to define medium and high surgical volumes[23-25], but others believe that LRH requires at least 23 cases to reach the proficiency level[27]. Although many studies on surgical experience take previous studies and experience as the basis of high and low surgical volumes, some studies have utilized the median method, the minimum p-value method, and the Jordan index methods to define the grouping of surgical volume[22,27-28]. The grouping method of surgical volume should be explored in future research.

Despite the above flaws, based on the large sample size of the study, we conclude the following clinical significance. First, we consider that surgical skills can be improved with rich experience. Shortening of the operative time and the reduction of intraoperative blood loss can minimize harm to patients during the operation. Second, surgical experience may not be the factor that affects long-term oncological outcomes of LRH. Therefore, we need to further explore the limitations of laparoscopic technology itself.

Conflicts of interest: All authors have no conflicts of interest to disclose.

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Author contributions

All authors approved the final version of the study. Study design: CLC, PL, LW, JHL. Literature search: PFL, JQL, ZQL. Figures: PFL,JQL. Data analysis: CLC, PFL, XNB,. Data interpretation: All authors. Data collection: PFL, ZQL. Drafting of the manuscript: PFL, JQL. Obtained funding: CLC. Supervision: CLC, LW, PL, JHL.

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Competing interests : All authors have completed the ICMJE uniform disclosure form at*www.icmje.org/coi_disclosure.pdf*; no financial relationships with any organizations that might have an interest in the submitted work; and all authors have no conflicts of interest to disclose.

Ethical approval : The establishment of the clinical diagnosis and treatment for cervical cancer in mainland China (Four C) database was approved by the Ethics Committee of the Southern Hospital of Southern Medical University. The ethical approval number is NEEC-2017-135, and the clinical research registration number is CHiCTR1800017778 (International Clinical Trials Registry Platform Search Port,*http://apps.who.int/trialsearch/*).

Data sharing : Additional data available from the corresponding author at *ccl1@smu.edu.cn*. The lead author (CC) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies(and, if relevant, registered) from the study as planned have been explain.

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Figure 1 Flowchart of patients included in the analysis

Figure 2. Kaplan-Meier survival curves of the three groups.

Figure 3. Kaplan-Meier survival curves after PSM matching.

(A) Low-volume group vs mid-volume group. **(B)**Low-volume group vs high-volume group. **(C)** Mid-volume group vs high-volume group.

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