

Standardized radical hysterectomy promises the clinical outcomes of laparoscopic surgery for early-stage cervical cancer

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Research

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Abstract

Background: The recent publication of LACC Clinical Trial (NCT00614211) stated that minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy among women with early-stage cervical cancer (ECC). The purpose of this present study is to evaluate clinical outcomes of laparoscopic standardized radical hysterectomy for ECC.

Methods: This is a retrospective controlled study. 328 women with ECC (IA1, IA2, IB1 or IIA1) underwent primary surgery treatments by laparoscopy or laparotomy in Tenth's People Hospitals. The women diagnosed as stage IB1 or IIA1 performed radical hysterectomy (RH). The total parametrium excision in process of radical hysterectomy was clarified specially in the study.

Results: 186 patients underwent open surgery and 142 ones were performed laparoscopic surgery. Laparoscopic surgery was associated with less blood loss (194.43 ± 84.40 ml vs. 362.68 ± 253.36 ml, $P < 0.01$), shorter hospital staying (11day vs. 14day, $P < 0.01$) and fewer risk of blood transfusion (2.8% vs. 18.8%, $P < 0.01$). There was no statistical difference in postoperative complications between two groups (18/142, 12.7% vs. 21/186, 11.3% $P > 0.05$). The rate of 5-years overall survival (OS) was 92.8% in laparoscopy group similar to that of 94.4% in open group ($p = 0.762$). Disease-free survival (DFS) rate at 3 years in laparoscopy group significantly decreased when compared to open group (91.8% vs 95.0%, $p = 0.030$). But there was no difference in 3-years DFS among the women with tumor size < 2 cm (100% vs 97.0%, $p = 0.818$).

Discussion: Laparoscopic surgery was associated with preferable surgical quality compared to open surgery in ECC. Laparoscopic radical hysterectomy may be fit to the women with tumor < 2 cm. Standardized radical hysterectomy helps to promise the clinical outcomes of LRH in ECC.

Introduction

The recent study from the publication of Laparoscopic Approach to Cervical Cancer Trial (LACC) questioned the survival outcomes of minimally invasive surgery (MIS) for early-stage cervical cancer (ECC)[1, 2]. It concluded that minimally invasive radical hysterectomy (RH) was associated with lower rates of disease-free survival (DFS) and overall survival (OS) in ECC. The related reasons affecting the outcomes of MIS were thought to be CO₂ pneumoperitoneum, the uterine manipulator, unenclosed colpotomy, as well as the surgeon's skills and learning curve. As the results differ from the previous conventional viewpoints, it triggers the discussion whether LRH is suitable for the treatment of ECC.

Following the Piver classification in 1970s and QM classification in 2008[3, 4], RH for cervical cancer has been progressively standardized. Some clinical studies showed the similar therapeutic outcomes between LRH and abdominal radical hysterectomy (ARH). Moreover, LRH presented the advantages in the reduced morbidity and improved quality of postoperative life[5–9]. Laparoscopic surgery had seen to be the popular surgical approach for treatment of ECC at one time.

It's very important to perform the standardized RH for ensuring the surgical quality. We proposed the concept of radical regional excision of parametrium based on the precise anatomy in parametrial ligament and pararectal and paravesical spaces. In the article, we retrospectively analyzed the clinical data of patients with IA1, IA2, IB1, and IIA1 staging cervical cancer (FIGO 2009), who underwent LRH or ARH in Tenth People's Hospital from 2011 to 2016. The purpose of the paper is to compare the survival outcomes between laparoscopic and open surgery, and evaluate the value of standardized RH focusing on regional excision of parametrium in ECC.

Methods

Patients

This investigation was designed as the retrospective case-control study. The patients undergoing the surgical therapy by laparotomy or laparoscopy from 2011 to 2016 for primary early cervical cancer (FIGO stage of IA1, IA2, IB1 and IIA1) were enrolled. They were from Tenth People's Hospital affiliated to Tongji University Medical School. The diagnosis of cervical cancer was confirmed by pathological exam before surgery. The tumor size depended on the reports from magnetic resonance imaging (MRI) or transvaginal sonography (TVS). Exclusion criteria included the treatments of only radiotherapy or chemoradiotherapy, loop electrosurgical excision (LEEP) and fertility-sparing surgery. The recruited patients were divided into two groups, laparoscopic surgery group and open surgery group. The demographics such as age, BMI and education background were collected and compared between two groups.

The study was approved by the ethical committee of Tenth People's Hospital affiliated to Tongji University School of Medicine. Informed consent was obtained from all participants included in the study.

Standardized radical hysterectomy

All surgeries were carried out after the patients were under general anesthesia. The special gynecologic oncologists who were proficient in the procedures of both laparoscopy and laparotomy performed the surgery. The patients diagnosed as stage IA1 no lymphovascular space invasion (LVSI) underwent extrafascial hysterectomy, stage IA2 received modified radical hysterectomy and stage IB1 and IIA1 performed radical hysterectomy. Surgical technique obeyed the principles of Piver classification or QM classification of radical hysterectomy[3, 4, 10].

In the study, laparoscopic standardized radical hysterectomy (Type C) focusing on the total parametrium excision was emphasized, the key steps of which were described as followings. (1)We opened the lateral peritoneum of pelvic wall in Cheng's Triangle area and made the iliac vessels and ureter visible [11]. The pararectal space and paravesical space were separated by removing the covering fascia and fatty tissue until the muscle or fascia tissue of pelvic floor was exposed (Fig1A). (2)The transection of cardinal ligament was required to laterally extend the pelvic wall and vertically touched the pelvic floor's fascia (Fig1B). The total paracervix excision contains the removal of both the vessels part and caudal neural part of cardinal ligament except the Type C1 radical hysterectomy. We named the complete removal of

cardinal ligament as “regional excision” (Fig1B). (3) We dissected the vesico-cervix space and exposed the shape of ureter (Fig1C). Then the anterior, posterior and lateral components of vesicouterine ligament were transected at the bladder to mobilize the ureter completely (Fig1D). (4) The uterosacral ligament was cut off near the rectum. When considering the automatic nerve preservation in Type C1 radical hysterectomy, the uterosacral ligament was transected after the hypogastric nerve was mobilized previously (Fig1C). The cervical branches and bladder branches of pelvic plexus were also identified[12]. The bladder nerves should be preserved carefully in the lateral and posterior ligaments of bladder. Lastly, the uterus was removed radically along with the routine pelvic lymphadenectomy. In the course of surgery, the uterine manipulator was used and the vaginal was opened laparoscopically.

The operative parameters containing operative time, intraoperative blood loss, postoperative length of hospital stay were recorded, as well as the perioperative complications were reported. In addition, the data of post-operative adjuvant therapy were collected.

Follow-up

The patients were required for the following-up of 3-months interval in the first 2 years after surgery and 6-months follow-up for following 3 years and yearly follow-up thereafter. The median follow-up time of was calculated. Routinely, the patients underwent the laboratory testing and CT/MRI exams every time. Recurrent diseases included the locoregional recurrence and distant metastasis. The death cases owing to cervical cancer was labelled. Disease-free survival (DFS) was defined as the time from primary surgery to recurrence or death from cervical cancer. The rate of DFS at 3 years and overall survival (OS) at 5 years were evaluated as the primary oncologic outcomes.

Statistics

The Statistical Package for the Social Sciences version 19.0(IBM Corp., Armonk, NY) was used for statistical analysis. Data were presented as mean \pm standard deviation or percentages. Continuous variables were compared using independent sample t test (between 2 groups), and categorical variables were compared using χ^2 test or Fisher exact test, as appropriate. A $p < .05$ was considered statistically significant. Kaplan–Meier survival curve was described to compare the differences of DFS rate at 3 years and OS rate at 5 years between the two groups. Long-rank p value was assessed and recorded, as well as 95% CI (confidence interval).

Results

A total of 479 patients with cervical cancer were treated in Tenth People’s Hospital, Tongji University Medical School from Nov 2011 to Des 2016. A total of 328 patients received primarily hysterectomy surgeries and were enrolled. The mean age of patients was 49 years old. Of these patients, 56 was diagnosed with stage IA1 no LVS, 67 with stage IA2, 138 with IB1 and 67 with IIA1. One hundred and

eighty-six patients underwent open surgery and 142 ones were performed laparoscopic surgery. The conversion from minimally invasive surgery to laparotomy didn't happen. The comparisons of demographic data between laparoscopy group and laparotomy group were listed in Table 1. The baseline characteristics including histologic subtype, tumor size and positive lymph node were similar in two groups (Table 1).

Table 1
Baseline Characteristics

Characteristic	Open surgery (n = 186)	Laparoscopic surgery (n = 142)	P/X ² value (t value)
Age	49.45 ± 8.78	49.20 ± 8.85	0.824 (0.222)
Body mass index	23.46 ± 4.20	23.74 ± 2.68	0.110 (1.604))
Education			0.873
University or above	18(9.7%)	13(9.2%)	
High school	168(90.3%)	129(90.8%)	
Stage of disease			0.796
IA1	26 (14.0%)	30 (21.1%)	
IA2	31 (16.7%)	36 (25.4%)	
IB1	86 (46.2%)	52 (36.6%)	
IIA1	43 (23.1%)	24 (16.9%)	
Histologic subtype			0.132
Squamous cell carcinoma	161 (86.6%)	114 (80.3%)	
Adenocarcinoma	20 (10.8%)	16 (11.3%)	
Adenosquamous	2 (1.1%)	4 (2.8%)	
others	3 (1.6%)	8 (5.6%)	
Positive lymph node	2 (1.1%)	3 (2.1%)	0.447
Tumor size*			0.114
< 2 cm	34 (26.4%)	28 (36.8%)	
≥ 2 cm	95 (73.6%)	48 (63.2%)	

*Only the women with the FIGO staging of IB1 or IIA1 were compared. Among of them, 129 patients performed open surgery, the others of 76 patients underwent laparoscopic surgery.

As showed in Table 2, laparoscopic surgery was associated with less blood loss (194.43 ± 84.40 ml vs. 362.68 ± 253.36 ml, $P < 0.01$), shorter hospital staying (11 day vs. 14 day, $P < 0.01$) and fewer risk of blood transfusion (2.8% vs. 18.8%, $P < 0.01$) when compared with open surgery. Twenty-one patients in open group encountered postoperative complications and 18 patients in laparoscopic group (11.3% vs 12.7% $P > 0.05$). The main complications included infection (22 patients), dysuria/urinary retention (11 patients), deep vein thrombosis (4 patients), intestinal obstruction (1 patient) and postoperative blood loss (1 patient). Adjuvant treatment were carried out for patients had pathologic risk factors (large primary tumors, deep stromal invasion, and/or LVS)[13, 14]. The postoperative radiochemotherapy were indicated in 32 cases of laparoscopic group (32/142, 22.5%) and 55 ones of open group (55/186, 29.6%). There was no significant difference in postoperative adjuvant treatments between two groups($P > 0.05$).

Table 2
Operative Parameters and Adjuvant Therapy

	Open surgery (n = 186)	Laparoscopic surgery (n = 142)	P/X ² value (t value)
Operative Parameters			
Operation time (min)	199.72 ± 62.35	215.15 ± 53.71	0.039 (-2.074)
Blood loss (ml)	362.68 ± 253.36	194.43 ± 84.40	< 0.001 (6.962)
Intraoperative transfusion	35 (18.8%)	4 (2.8%)	< 0.001
Postoperative length of hospital stays (day)	14.53 ± 7.55	11.21 ± 3.94	< 0.001 (4.768)
30-d Postoperative complications	21 (11.3%)	18 (12.7%)	0.701
Adjuvant Therapy			
Postoperative radiochemotherapy	55 (29.6%)	32 (22.5%)	0.153

In the present trial, the median follow-up time was 41 months (range, 20–84) in laparoscopic group and 49 months (range, 22–89) in open group. Thirteen (6.99%) recurrent cases of open group were observed. Among of them, 12 patients had locoregional recurrences and 1 patient underwent a new primary breast cancer after the follow-up of 59 months. Eighteen patients (12.68%) in laparoscopic group had locoregional recurrences. A total of 15 deaths were noted, 9 in the open surgery group and 6 in the minimally invasive surgery group. All of the recurrences or deaths occurred in the patients with stage IA2, IB1 and IIA1 who underwent modified radical or radical hysterectomy. The rate of 5-years OS in laparoscopic surgery group was 92.8% similar to that of 94.4% in open group ($p = 0.763$) (Fig. 2A). The DFS at 3 years in laparoscopy group significantly decreased when compared to open group (91.8% vs 95.0%, $p = 0.030$) (Fig. 2B). However, there was no difference in 3-years DFS rate between two groups with

stage IA1-IA2 cervical cancer (100% vs 98.2%, $p = 0.472$) (Fig. 3A). Likewise, the rate of DFS at 3 years was not obviously various among two groups with stage IB1-IIA1 accompanying tumor < 2 cm (100% vs 97.0%, $p = 0.818$) (Fig. 3B). But the 3-years DFS rate in laparoscopic surgery groups was remarkably lower than in open surgery group among the women with stage IB1-IIA1 associated with tumor size of ≥ 2 cm (75% vs 92.4%, $p < 0.001$) (Fig. 3C).

Discussion

Surgical treatment has been the preferred modality for the treatment of ECC. But the recent publication of LACC trial stated that conventional open surgery appeared the preferable survival outcomes compared with MIS.[1, 2]. In this study, we retrospectively compared the perioperative parameters and the results of follow-up after laparoscopic or open radical hysterectomy for ECC. Our data showed that LRH was superior to RAH in blood loss, the length of hospital stay and the risk of blood transfusion (Table 2). The results consisted with the published researches by other authors[6–9]. Jin Hee Kim et al. showed that laparoscopic radical hysterectomy was associated with fewer intraoperative complications (9.9% vs. 12.0%, $P < 0.001$) and shorter median length of stay ($P < 0.001$), compared with abdominal radical hysterectomy[9]. Dong-Ho Kim's team indicated that the mean estimated blood loss and length of hospital stay in laparoscopic radical hysterectomy group were significantly less than those in radical abdominal hysterectomy group (414.3 ml and 836.0 ml, respectively; $P < 0.001$; 10.7 days and 18.8 days, respectively; $P < 0.01$) [5]. The study from Bogani G et al. stated that patients undergoing laparoscopic radical hysterectomy experienced less blood loss (200 vs 500 mL; $P < 0.001$) and shorter length of hospital stay (4 vs 8 days; $P < 0.001$), compared with the radical abdominal hysterectomy group. No between-group differences in intraoperative complications were recorded ($P = 1.0$)[15]. It's seemingly suggested that laparoscopic radical hysterectomy was safe and feasible in management of ECC.

Over the median follow-up of 41 months in laparoscopic group and 49 months in abdominal surgery group, our data found that there were no differences in 5-years OS rate between two groups (92.8% vs 94.4%, long-rank $p = 0.763$, Fig. 2A). Though the rate of DFS at 3 years in laparoscopic surgery group was significantly lower than in laparotomic groups (91.8% vs 95.0 long-rank $p = 0.030$, Fig. 2B), the difference of DFS was attributed to the existence of subgroup with IB1-IIA1 staging cervical cancer combined with tumor ≥ 2 cm (Fig. 3C). For the patients with the diagnose of IA1-IA2 or IB1-IIA1 accompanying tumor < 2 cm, the rate of DFS was not statistically various between laparoscopic route and open approach (Fig. 3A, Fig. 3B). We believed that the standardized radical hysterectomy was an important fact associated with the surgical quality and clinical outcomes. In the present study, we had an insight to the precise anatomy of paracervical structure focusing on the dissection of cardinal ligament, sacral ligament and vesico-cervical ligament. The view of regional excision of parametrium was proposed by us in order to perform the standardized radical hysterectomy (Supplemental Fig. 1). According to the criterion of Class III or Type C radical hysterectomy, the cardinal ligament transection obeyed the principles of boundary near the pelvic floor vertically and at the pelvic side-wall laterally (Fig. 1A, Fig. 1B). The anterior, lateral and posterior parts of vesico-cervical ligament were transected near the bladder (Fig. 1D). Based on the elaborate anatomy of cardinal ligament and sacral ligament, hypogastric nerves

as well as bladder and cervical branches of pelvic plexus were dissected and separated orderly from the ventral and caudal part of the paracervix[12], which facilitated the nerve-sparing Type C1 radical hysterectomy. It was concluded that standardized radical hysterectomy based on regional excision of parametrium promised the surgical quality and clinical outcomes.

Of course, the adoption of LRH for ECC remains debatable. The reasons affecting therapeutic results were considered to associate with the use of uterine manipulation, virginal colpotomy and the circulating CO₂. The tumor surface was exposed to circulating CO₂ when intracorporeal colpotomy was performed. This may lead to the increasing risk of tumor spillage[16–19]. Uterine manipulators which were frequently used for visualization and retraction during minimally invasive hysterectomy may also disseminate tumor cells. In our study, for the patients with stage IB1-IIA1 combined with tumor ≥ 2 cm, the rate of 3-years DFS in LRH group was remarkably lower than in ARH group (75.0% vs 92.4%, $p < 0.001$). It was suggested that the worse survival outcomes of LRH was closely linked to the tumor size. The tumor ≥ 2 cm may have the increasing risk of cancer cells spillage if the uterine manipulation was used and the unenclosed colpotomy was carried out in LRH. Some scholars have tried to perform the enclosed colpotomy without the use of uterine manipulation to obtain a relatively tumor-free removal and improve the surgical quality of LRH for ECC[20].

In addition, the previous documents suggested laparoscopic hysterectomy for women with early-stage endometrial cancer was not associated with the inferior oncologic outcomes. In the clinical trial of NCT 00096408, the use of total abdominal hysterectomy compared with total laparoscopic hysterectomy resulted in the equivalent rate of DFS at 4.5 years (81.6% vs. 81.3%, $P < 0.01$) and OS (risk difference, $P = 0.76$)[21]. An update of a previous Cochrane Review published in 2012, Issue 9 concluded that laparoscopy for the management of early endometrial cancer was associated with the similar rates of OS and DFS compared with laparotomy approach[22]. It was unreasonable to completely explain the differences in OS and DFS after laparoscopy or laparotomy treatment from the perspective of CO₂ pneumoperitoneum and/or uterine manipulation. Now, we are trying to use Air-Seal pneumoperitoneum system to reduce the possible adverse effects of smoke dust. Our trial was not designed to attempt the new method to replace the conventional intracorporeal colpotomy. Further investigation is warranted for evaluating the survival outcomes with minimally invasive surgery.

There are some concerns that should be recognized when interpreting the results of the study. Firstly, LRH and ARH were performed by senior gynecologic oncologist who are both skillful at laparotomy and laparoscopy surgeries. This evaded the shortcomings of less experiences and techniques influencing the surgical quality of standardized radical hysterectomy. Secondly, the effects of regional excision of parametrium on the postoperative urination, defecation and the risk of perioperative infection and bleeding need be more checked in the following trial. Lastly, the cohort study was designed as a retrospective study with a small sample size. In the future, multicenter prospective randomized study especially taking into account methods for enclosed colpotomy not using a manipulator is necessary for further evaluating the values and feasibility of LRH for ECC.

Conclusion

Laparoscopic surgery was associated with less blood loss, shorter hospital staying and fewer risk of blood transfusion when compared to open surgery for treatment of ECC. Standardized radical hysterectomy based on total parametrium excision played an important role on promising the surgical quality and clinical outcomes in management of ECC. For the patients with IB1-IIA1 staging cervical cancer accompanying tumor <2cm, the rate of 3-years DFS after LRH was similar to that of ARH. The larger tumor (2-4cm) treated by laparoscopic surgery may give rise to the risk of poor outcomes.

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of Tenth People's Hospital affiliated to Tongji University School of Medicine (NO. SHSY-IEC-4.1/19-177/01).

Consent for publication

Informed consent for publication was obtained from all participants included in the study.

Availability of data and material

The data that support the findings of this study are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Ethical Committee of Tenth People's Hospital.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZP C was responsible for the design of study, data interpretation and surgeries. WH Y contributed to the data collection and analysis, surgeries, statistical analysis and manuscript preparation. R C took charge of the data collection, surgeries and patient recruitment. CX L and L L took part in the data collection, statistical analysis and patient recruitment. N L contributed to the data collection, surgeries and statistical analysis. All authors read and approved the final manuscript.

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Figures

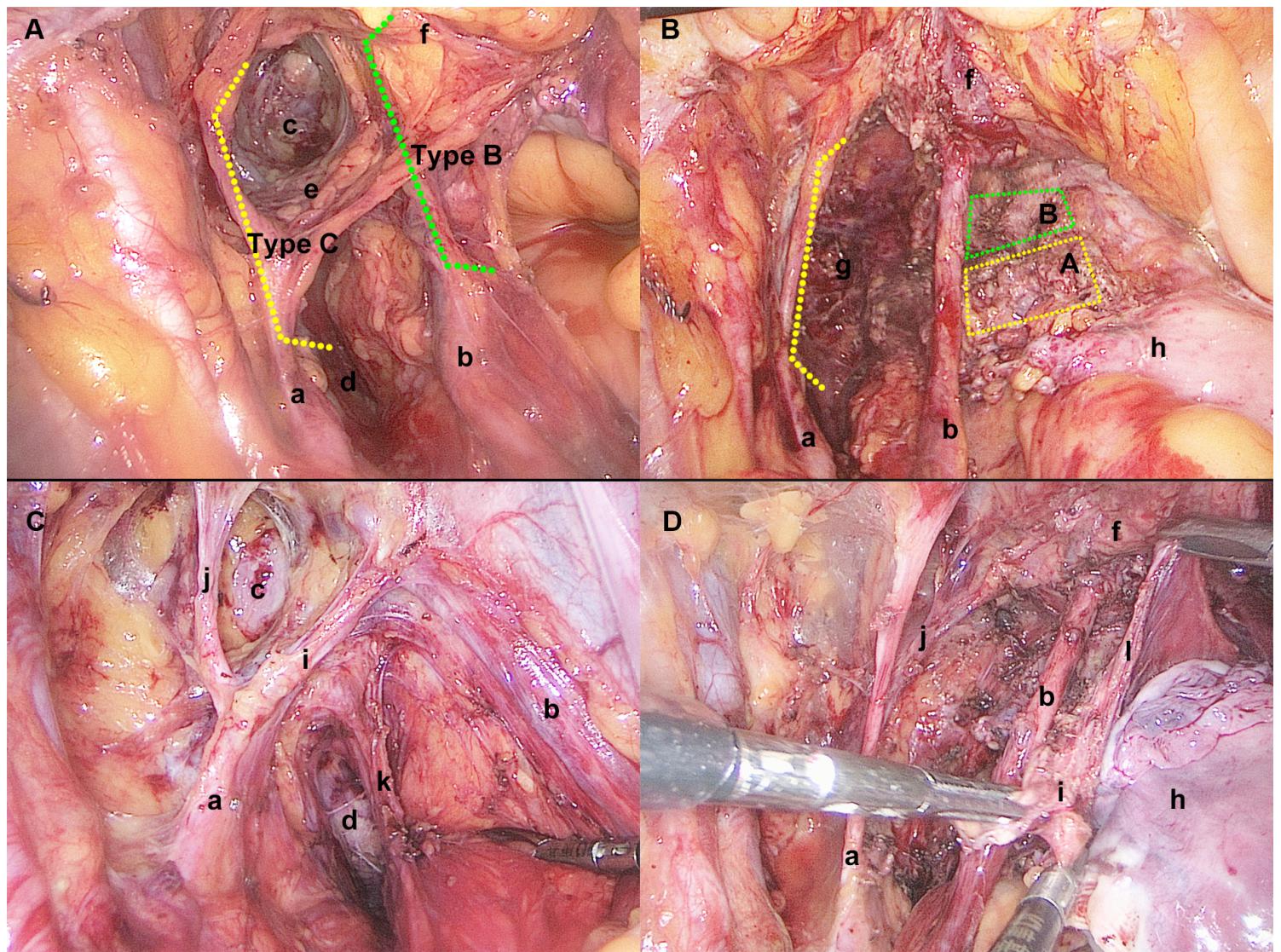
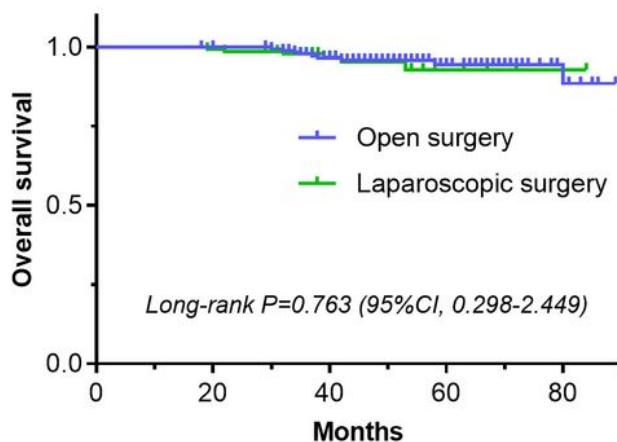
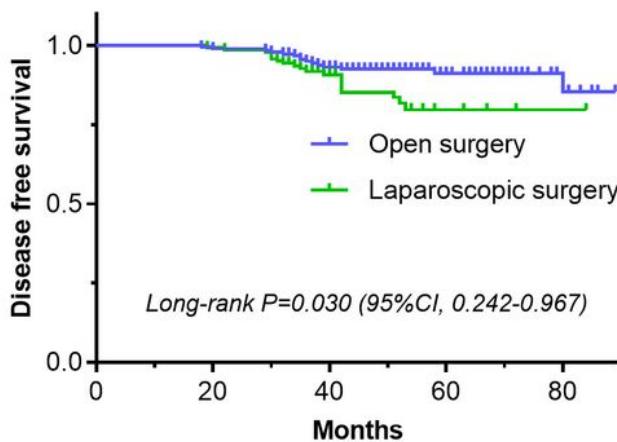


Figure 1

Before the cardinal ligament resection(A) and after the cardinal ligament resection(B); before the vesical-cervical ligament transection(C) and after the vesical-cervical ligament transection(D): a. internal iliac artery, b. ureter, c. lateral vesical space, d. lateral rectal space, e. cardinal ligament, f. bladder, g. the muscle and fascia tissue of pelvic floor, h. uterus, i. uterine artery, j. superior vesical artery, k. pelvic nerve plexus, l. anterior vesical-cervical ligament after transection, h. uterus. A region. the complete removal of cardinal ligament; B region. the complete removal of paravaginal tissue, Type B. extent of Type B radical hysterectomy, Type C. extent of Type C radical hysterectomy.

A Overall Survival**No. at Risk**

Laparoscopic surgery	142	142	77	22	7
Open surgery	186	185	150	62	16

B Disease Free Survival**No. at Risk**

Laparoscopic surgery	142	142	77	22	7
Open surgery	186	185	150	62	16

Figure 2

The rate of 5-years overall survival (OS) and 3-years disease-free survival (DFS) were compared between laparoscopic group and open group by Kaplan–Meier survival curve method. (A) At 5 years after surgery, 14 patients had died, 6 in laparoscopic surgery group and 8 in open surgery group, accounting for an OS rate of 92.8% in the laparoscopic group and 94.4% in the open group ($p=0.763$). (B) At 3 years, a total of

33 recurrences or deaths were noted, 19 in laparoscopic surgery group and 14 in open surgery group. The rate of 3-years DFS was 91.8% in the laparoscopic group and 94.4% in the open group ($p=0.030$).

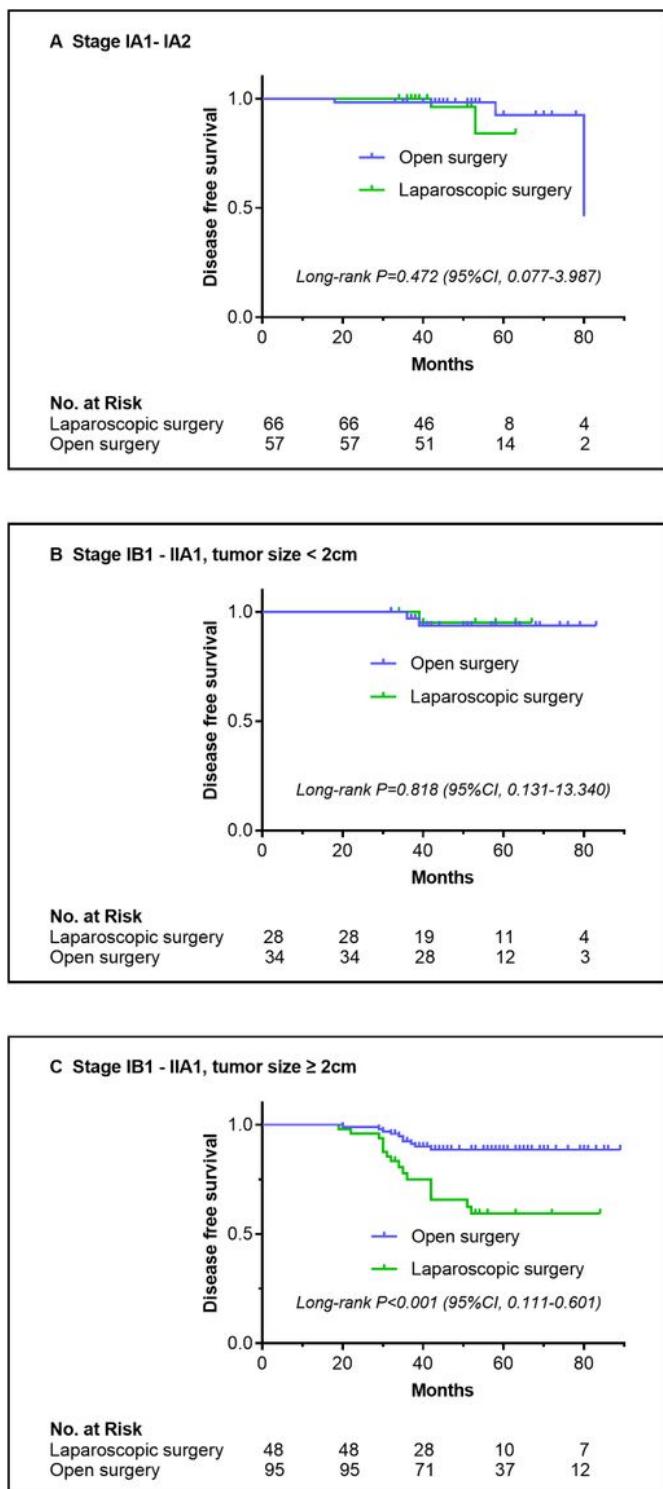


Figure 3

Three -years DFS rate based on disease stage and tumor size. (A) Among the women with IA1-IA2 stage, only one recurrence occurred in open group. The rate of 3-years DFS was 100% in the laparoscopic group and 98.2% in the open group ($p=0.472$). (B) In the women with IB1-IIA1 accompanying tumor $<2\text{cm}$, one

patient had a recurrence in open surgery. The rate of 3-years DFS was 100% in the laparoscopic group and 97.0% in the open group ($p=0.818$). (C) In the women with IB1-IIA1 accompanying tumor $\geq 2\text{cm}$, 18 patient had a recurrence, 11 in laparoscopic surgery group and 7 in open surgery group. The rate of 3-years DFS was 75% in the laparoscopic group and 92.4% in the open group ($p<0.001$).

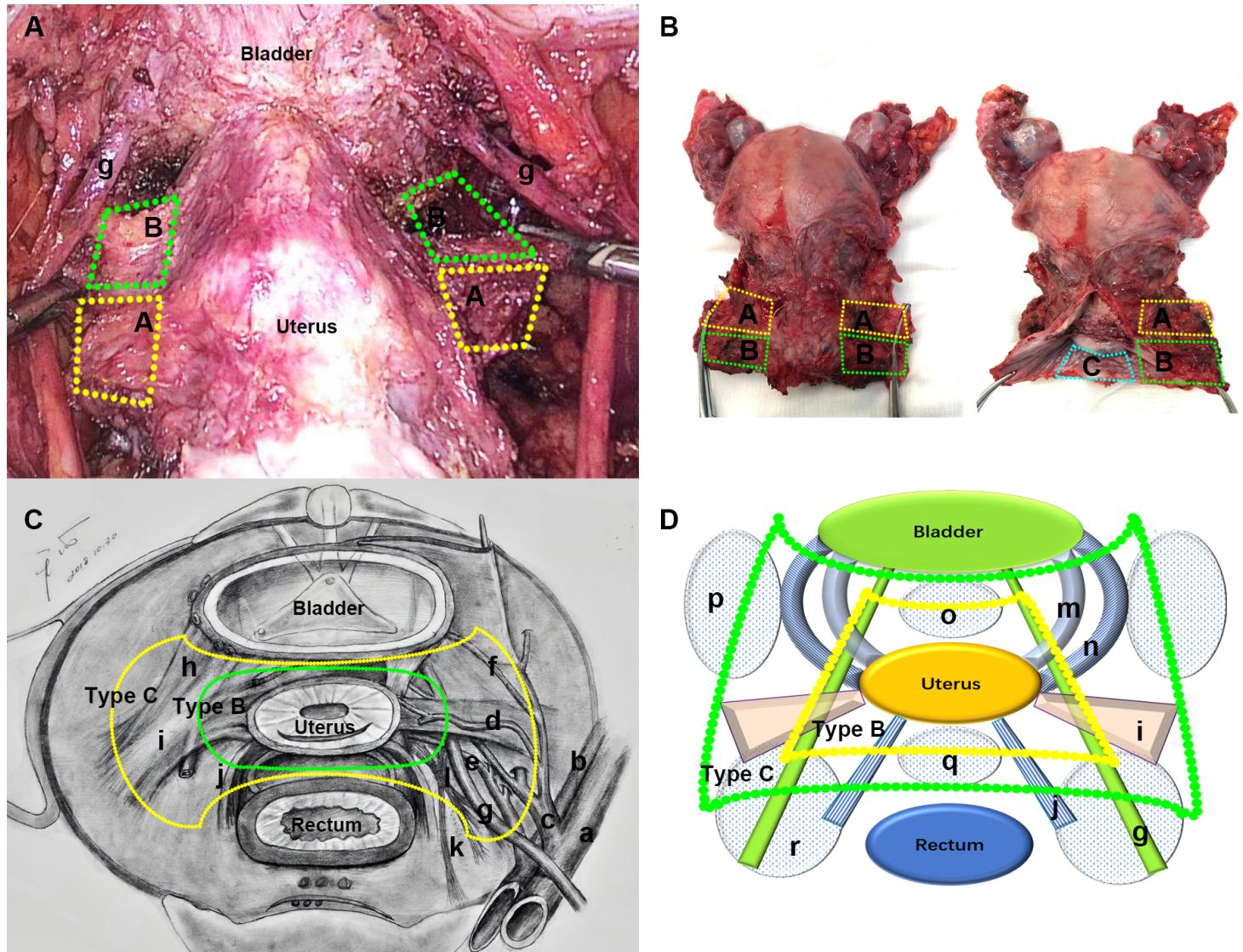


Figure 4

(A) Show the total excision of parametrium before colpotomy; (B) Reveal the regional excision of parametrium and extent of vagina transection; Show the resection boundary of Type B and Type C radical hysterectomy by a sketch picture(C) or by a diagrammatic figure(D): a. external iliac artery, b. external iliac vein, c. internal iliac artery, d. uterine artery, e. uterine deep vein, f. superior vesical artery, g. ureter, h. vesical-cervical ligament, i. cardinal ligament, j. uterosacral ligament, k. hypogastric nerve, l. inferior hypogastric plexus(IHP), m. ventral leaf of vesical-cervical ligament, n. dorsal leaf of vesico-cervical ligament, o. vesico-cervical space, p. lateral vesical space, q. uterine rectal space, r. lateral rectal space, A region. the complete removal of cardinal ligament, B region. the complete removal of paravaginal tissue; C region. the enough length of vaginal resection(more than 1.5 to 2.0cm away from tumor), Type B. extent of Type B radical hysterectomy, Type C. extent of Type C radical hysterectomy.