

The Impaction of Laparoscopic versus Laparotomy for Lymphovascular Space Invasion of Early Cervical Cancer: A Multicenter Retrospective Study

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Abstract

Objectives: The aim of this study was to compare the lymphovascular space invasion between laparoscopic radical hysterectomy (LRH) and abdominal radical hysterectomy (ARH).

Materials and Methods: One retrospective study was conducted with 391 patients treated with 242 patients underwent ARH and 149 patients underwent LRH between May 2010 and August 2019. We collected clinicopathological and perioperative outcome from medical records. We adopt Student's *t*-test and Chi-square test was used to compare continuous and categorical variables between LRH and ARH.

Results: Our research found that there was no difference in tumor size, histology grades, positive lymph nodes, and postoperative complications between LRH and ARH ($P > 0.05$). The estimated bleeding loss (EBL) and length of postoperative hospital stay were less for LRH than ARH (248.12 ml vs. 412.56 ml, $P < 0.05$, and 10.48 days vs. 15.16 days, $P < 0.05$). The mean operative time was longer for LRH than ARH (227.51 min vs. 215.62 min, $P < 0.05$). Significant difference was found in intraoperative complications ($P < 0.05$). However, LVSI was higher for LRH than ARH (36.8% vs. 19.8%, $P < 0.05$). We discovered that the LVSI was related with International Federation of Obstetrics and Gynecology stage and tumor size.

Conclusion: Compared to ARH, the LRH would be advantageous for early cervical cancer in terms of EBL, length of postoperative hospital stay, and intraoperative complications. The ARH was superior to LRH in operative time. In addition to, LRH was more likely to lead to LVSI. Furthermore, when tumor size or stage was increasing, LRH was easily to generate LVSI. But, we cannot confirm recurrence rate is related to LVSI.

Keywords: Abdominal radical hysterectomy, early cervical cancer, laparoscopic radical hysterectomy, lymphovascular space invasion

INTRODUCTION

Cervical cancer is the fourth malignancy in the world, which the main treatment is surgery and the standard model is radical hysterectomy (RH). Many retrospective reports suggested that overall survival (OS) and disease-free survival, there was no significant difference between laparoscopic RH (LRH) and abdominal RH (ARH).^[1-3] However, in 2018, both a prospective

study that Laparoscopic Approach to Cervical Cancer and a cohort study indicated that ARH is better than minimally invasive surgery such as laparoscopic or robot-assisted in OS and PFS. The result may be associated with the uterine manipulator squeezing of the uterine cervix, intraperitoneal colpotomy in laparoscopic, and CO₂ set up an acid environment, which can lead to tumor cell spillage, shedding, and dissemination.^[4-6]

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LVSI is that tumor cell shedding into surrounding tissues in that the injury of connective tissues that belong to paramerrium contain abundant blood vessels and lymphatic tissues by forming cancer embolus. In addition, it closely related to paramerrium infiltration and lymph node metastasis.^[7,8] Ernsr reported that tumor cell can infiltrate lymphatic tissues in the perineurium and endoneurium and the phenomenon existed in breast cancer, pancreatic cancer, and gastric cancer.^[9] Now, a number of studies report that lymph node metastasis, tumor size, and LVSI are prognostic factors for cervical cancer.^[7,10] Moreover, lymph node metastasis has been used as clinical stages according to 2018 International Federation of Obstetrics and gynecology (FIGO) stages, and it also suggests that LVSI is closely associated with prognosis.^[11] However, few reports suggest that how to cause LVSI. We speculate that different surgical methods may be associated with it according to our research. Therefore, the study focuses on the effects of different surgical methods such as LRH and ARH on LVSI.

MATERIALS AND METHODS

Patients

The retrospective study contained patients who were diagnosed with stage IA-IIA cervical cancer according to 2018 FIGO stages. Patients were underwent LRH or ARH from May 2010 to August 2019 at the Department of Gynecology and Obstetrics, Gynecology, and Obstetrics, Yangpu District Central Hospital Affiliated to Tongji University, Shanghai, Department of Gynecology and Obstetrics, Tenth People's Hospital Affiliated to Tongji University, Shanghai and Department of Gynecology and Obstetrics, and Yan Cheng Third People's Hospital.

All patients were diagnosed with cervical cancer by pathological feature, magnetic resonance imaging (MRI), computed tomography (CT), and pelvic examination before surgery. The pretreatment evaluation covered physical examination, vaginal/pelvic examination, ultrasonic testing, and pelvic MRI. In addition to, before surgery, patients were undertaken all perioperative examination such as electrocardiogram, X-rays, biochemical examination, blood routine examination, coagulation function, and so on. Moreover, we need to be evaluated performance status and function of important organs, for instance, cardiac, kidneys, and spleens, which were tested by ultrasonography or CT.

Surgical management

Stage IA1 patients were operated using Piver Type I techniques. Stage IA1 with positive LVSI and stage IA2 patients who were adopted Piver Type II. Stage IB1-IIA2 stage patients were operated with Piver Type III RH.^[12] All patients were operated on by gynecologists who were deputy chief physician above.

Eligibility criteria and patient counseling

The exclusion criteria were as follows: (1) The pathological examination was errored; (2) the patients who were performed only loop electrosurgical excision procedure or total hysterectomy with bilateral adnexectomy; (3) the patients information was incompleted or errored; (4) the patients who were operated in other hospitals. Between May 2010 and August 2019, 242 patients underwent ARH and 149 patients underwent LRH. We had to talked with patients and their agents about the benefits and potential risks of the treatment.

Data collections

We had to collect and interpret data regarding disease and therapy. The following data were collected: Age, body mass index (BMI), histology of tumor, histological grades, tumor size, positive lymph nodes, and LVSI. The surgical outcomes such as operation time, estimated blood loss (EBL), perioperative complications, and the length of postoperative hospital stay. The histology of tumor contained squamous carcinoma, adenocarcinoma, adenosquamous carcinoma, and others included neuroendocrine carcinoma, clear cell carcinoma. The operative time was calculated from the first incision to the end of the suture. The EBL was estimated by calculating the difference between the total amount of suctioned fluids, the weight of the sponges, and the irrigated fluids. Intraoperative complications were defined as intestinal, bladder, ureters, and vessels injury. Postoperative complications were defined: (1) bladder dysfunction, lymphocele, lymphedema, intestinal obstruction, and fistula; (2) surgical site complications were included incisional abscess or rupture and incisional hernia; (3) medical complications were contained venous thromboembolism (VTE), infection, shock, bacteremia/sepsis, and so on. Moreover, the bladder dysfunction was diagnosed if patient who was removed of the catheter showed that residual urine was >100 ml using ultrasonography 2 weeks after surgery. The infection was diagnosed as the presence of bacteria was founded by microbial culture after surgery. LVSI defined that starting from edge, pathologist observed it using optical microscope at a ratio of 10 × 10, when the morphology of the cell was inconsistent with surface in the lacunae, after that further diagnosis was interpreted with 10 × 20.10 × 40 magnification, and adopted immunohistochemical markers such as CD-34 and D-240 were used for identification. All pathological results were interpreted by experienced pathologists.

Ethical statements

The data of medical records were used in our study. However, according to the ethics statements, informed consent was obtained from all the participating patients in the study. Besides, the Ethical Committee of the Shanghai Tenth People's

Hospital approved the study by SHSY-IEC-BG/04.03/04.0 code on September 9, 2020.

Statistical analysis

SPSS software 20.0 (SPSS version 20. IBM, Shanghai, China) was used for data analysis. Student's *t*-test was used to compare each group's continuous variables. In case of measurement data, Chi-square test was used to compare categorical variables between LRH and ARH. The level of significance was set at $P < 0.05$.

RESULTS

According to exclusion criteria, between May 2010 and August 2019, 242 patients underwent ARH and 149 patients underwent LRH. The clinicopathologic factors of surgical groups are shown in Table 1. The results demonstrated that there was no difference between LRH and ARH in regrade to age, BMI, tumor size, lymph node metastasis, 2018 FIGO stages, histology of tumor, and histology grades ($P > 0.05$).

Table 2 indicates that a surgical outcomes in the LRH and

ARH. The mean operative time of LRH was significantly longer than ARH (227.51 min vs. 215.62 min, $P < 0.05$). The mean EBL and length of postoperative hospital stay were significantly lower in LRH compared with ARH (248.12 ml vs. 412.56 ml, $P < 0.05$ and 10.48 days vs. 15.16 days, $P < 0.05$). In addition, it illustrated that the difference between LRH and ARH in perioperative complications. First, concerning intracomplications, we found that there was observable significance between LRH and ARH ($P < 0.05$). LRH had no complications, but ARH had 12 cases. It contained one ureter injury patient and 11 vessel injury patients. Second, we showed that there was no difference between LRH and ARH in postoperative complications. With regard to postoperative complications, one patient in LRH group and ten patients in ARH group suffered bladder dysfunction and VTE (2 in each group). In LRH group, one patient had ureterovaginal fistula and two patients had infection. In ARH group, three patients had infection, two patients had intestinal dysfunction, two patients had incisional rupture, and one patient had lymphocele.

Tables 3 and 4 demonstrate that an observable significance between two groups in LVSI (36.9% vs. 19.8%, $P < 0.05$) and we speculate that LRH was tended to lead to LVSI. We also compared in case of different 2018 FIGO stages and tumor size. These results were as followed. Table 4 depicts that there was no difference between LRH and ARH in I stage ($P > 0.05$) other than IB3 stage ($P < 0.05$). However, in II stage tumor, it showed significance between LRH and ARH ($P < 0.05$). It suggested that the difference of LVSI was related with FIGO stage. In addition to Table 4 illustrates that, in different tumor size, LRH or ARH has effect on LVSI. We found except tumor size < 2 cm, there was significant between LRH and ARH ($P < 0.05$).

DISCUSSION

According to the obtained procedures, in terms of study size, the retrospective study appears to contain the largest relative number of subjects. Our results demonstrated that LRH had significantly longer operative time than ARH; the result was coincided to other studies. Because laparoscopic surgery has long learning curve, many gynecologists are good at open surgery.^[13-16] However, the review of previous studies of LRH versus ARH including this study suggested that EBL was significantly lower LRH than ARH.^[17,18] During the surgical procedure, the LRH is better to expose the surgical zone, stop bleeding, and using advanced equipment than ARH. In addition to, we adopted a special method that our team established the Cheng's triangular area and Cheng's Cross in surgical procedure.^[19] Kim *et al.*^[17] studied morbidity, cost of care, and survival between ARH and LRH. There were suggested that LRH had lower complications, EBL, and shorter postoperative

Table 1: Comparison of clinicopathologic characteristics of patients (n=391)

Characteristics	LRH (n=149)	ARH (n=242)	P ^a
Age			
Median (range), (years)	50 (30-76)	51 (22-84)	0.335
BMI			
Median (range), (kg/m ²)	23 (18-37)	23 (18-41)	0.173
FIGO stage, n (%)			
IA1	11 (7.38)	10 (4.13)	0.347
IA2	7 (4.70)	12 (4.96)	
IB1	40 (26.85)	60 (24.79)	
IB2	31 (20.80)	61 (25.20)	
IB3	20 (13.42)	21 (8.68)	
IIA1	25 (16.78)	54 (22.31)	
IIA2	15 (10.07)	24 (9.93)	
Histology of tumour, n (%)			
Squamous	129 (86.58)	211 (87.19)	0.877
Adenocarcinoma	16 (10.74)	24 (9.91)	
Adenosquamous	3 (2.01)	3 (1.24)	
Others	1 (0.67)	4 (1.66)	
Histological grading, n (%)			
Keratinizing	23 (15.43)	26 (10.74)	0.174
Nonkeratinizing	126 (84.57)	216 (89.26)	
Tumour size (cm), n (%)			
< 2	71 (47.65)	127 (52.48)	0.884
$2 \leq$ tumour < 4	43 (28.86)	70 (28.92)	
≥ 4	35 (23.49)	45 (18.60)	
Positive lymph nodes			
No	120 (80.54)	187 (77.27)	0.446
Yes	29 (19.46)	55 (22.73)	

^aStudent's *t*-test or nonparametric tests as appropriate. BMI: Body mass index, FIGO: International federation of obstetrics and gynecology, LRH: Laparoscopic radical hysterectomy with pelvic lymphadenectomy, ARH: Abdominal radical hysterectomy with pelvic lymphadenectomy

Table 2: Comparison of surgical outcomes in laparotomy and Laparoscopic patients (n=391)

Characteristics	LRH (n=149)	ARH (n=242)	P ^a
Operative time			
Average, (min)	210 (120-460)	209 (95-430)	0.044
Blood loss			
Average, (mL)	200 (30-700)	300 (50-2500)	<0.001
Postoperative hospital stay			<0.001
Average, (days)	8 (3-34)	4 (5-51)	
Intraoperative complications, n (%)	0	12 (3.1)	
Ureter injury		1 (0.25)	0.006
Vessel injury		11 (2.85)	
Postoperation complications, n (%)	6 (1.50)	20 (5.10)	
Uretero vaginal fistula	1 (0.25)		0.079
Infection	2 (0.50)	3 (0.77)	
VTE	2 (0.50)	2 (0.50)	
Bladder dysfunction	1 (0.25)	10 (3.35)	
Intestinal dysfunction		2 (0.50)	
Incisional rupture		2 (0.50)	
Lymphocele		1 (0.25)	

^aStudent's *t*-test or Nonparametric tests as appropriate. LRH: Laparoscopic radical hysterectomy with pelvic lymphadenectomy, ARH: Abdominal radical hysterectomy with pelvic lymphadenectomy, VTE: Venous thromboembolism

Table 3: According to 2018 international federation of gynecology and obstetrics stage, comparison of difference stage's lymphovascular space invasion in laparotomy and laparoscopic patients (n=391)

Groups	Total	LVSI (-)		LVSI (+)		P ^a
		LRH	ARH	LRH	ARH	
I stage	391	94	194	55	48	<0.001
IA1	273	77	132	32	32	0.060
IA2	21	10	10	1	0	0.524
IB1	19	6	12	1	0	0.368
IB2	100	29	51	11	9	0.126
IB3	92	25	45	6	16	0.465
IB3	41	7	14	13	7	0.043
II stage	118	17	62	23	16	<0.001
IIA1	79	10	41	15	13	0.002
IIA2	39	7	21	8	3	0.010

^aChi-square test as appropriate. LRH: Laparoscopic radical hysterectomy with pelvic lymphadenectomy, ARH: Abdominal radical hysterectomy with pelvic lymphadenectomy, LVSI: Lymphovascular space invasion

Table 4: Comparison of difference tumour size's lymphovascular space invasion in laparotomy and laparoscopic patients (n=391)

Groups	Total	LVSI (-)		LVSI (+)		P ^a
		LRH	ARH	LRH	ARH	
	391	94	194	55	48	<0.001
<2 cm	198	56	107	15	20	0.341
2 cm≤tumour size<4 cm	113	24	52	19	18	0.042
≥4 cm	80	14	35	21	10	0.001

^aChi-square test as appropriate. LRH: Laparoscopic radical hysterectomy with pelvic lymphadenectomy, ARH: Abdominal radical hysterectomy with pelvic lymphadenectomy, LVSI: Lymphovascular space invasion

hospital stay. Our results were compatible to it, which demonstrated the length of postoperative hospital stay was significantly shorter LRH than ARH in that patients could move early and the advantage of laparoscopic was that incisions are small and not susceptible to infection.^[20] Concerning surgical complications, many gynecologists think that ARH is more likely to lead to complications.^[21,22] Our results found that LRH is superior to ARH in intraoperative complications due to its advantage that the visualization of the surgical field that contains nervous tissue be separated clearly by magnification of the laparoscopic optical systems, which enables clear surgical area.^[18,21] However, there did not differ significantly between LRH and ARH in postoperative complications. It may not be completely accurate due to the retrospective nature of the study. Now, a lot of research reported that LVSI is closely associated with parametrial invasion and the prognosis of patients with cervical cancer.^[23-26] However, few studies have shown what kind of surgical methods are more likely to result in LVSI. We assumed that the use of uterine manipulator, the circulating pneumoperitoneum CO₂ gas and the disturbance of the superficial mesothelial layer caused through the high CO₂ pressure, and the compression of tumor tissue during LRH may further disrupt the tumor and lead to the dissemination of tumor cells into the surrounding vessels and lymphatics, which more likely to cause LVSI.^[5,6,27,28] However, adequate number of tumor cells required to establish the metastasis.^[29] Our research found that, when we compared the conditions with postoperative LVSI, it was higher significantly LRH than ARH. Moreover, according to 2018 FIGO stages, we also researched that the LVSI was closely connected with stages with the stage increasing. Hence, we need to standardize

the surgical area and our team is working it. Beyond that, we researched that, in different tumor size, we found except tumor size <2 cm, there was different between LRH and ARH with the tumor size increasing, LRH is more likely to cause cancer cell spread to blood or lymphatic vessel by extruding tumor tissue. In LRH patients, the number of lymph node positive is inconsistent with LVSI positive. Subsequently, we discovered an obvious fact that it did not differ significantly between LRH and ARH in IB1 and IB2 stages according to 2018 FIGO stages. The result further illustrated that, when the tumor size, in particular tumor size ≥ 4 cm, was increasing, the LRH had higher probability than ARH. However, it also demonstrated that LRH may be safe in IB1, the consequence is similar with some experts such as Kim and David.^[7,25,30,31] However, whether LRH is easily to cause LVSI is related to recurrence rates needs further research. In a meta-analysis study,^[32] LRH in women diagnosed early-stage cervical cancer do not increase recurrent rate death rate a decrease in survival. Moreover, LRH do not affect the negative cancer factors which drives adjuvant therapy. Our study provides strong evidence for patients with early cervical cancer who select more reasonable surgical methods in future, but prospective study is needed to confirm the result. In this research, certain limitations were present. First, the study is retrospective; therefore, there might be selective biases. Second, the study currently lacks survival analysis, so we need further follow-up information which related to patient's survival. Third, the research demonstrate that LRH is more likely lead to LVSI and LVSI is relate to parametrium infiltration and lymph node metastasis, we need further follow-up of patients with recurrence rate is associate with LVSI.

CONCLUSION

On the basis of the present data, LRH has many advantages. However, LRH may be more likely to cause LVSI than ARH, it is important for postoperative adjuvant treatment and we need to consider what cause it. In addition, owing to the natural limitations of the retrospective study, multi-institutional prospective be performed to confirm the clinical value.

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Conflicts of interest

Dr. Zhongping Cheng, an editorial board member at *Gynecology and Minimally Invasive Therapy*, had no role in the peer review process of or decision to publish this article.

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