The influence of interval between conization and laparoscopic radical hysterectomy on the morbidity of patients with cervical cancer

H. Li[1, 2], J.Y. Jang[2], H. Li[1], K. Chen[3], X.G. Shao[2]

[1]*The Second Affliated Hospital of China Medical University, ShenYang*
[2]*The Affliated Obstertrics and Gynecology Hospital of DaLian Medical University, DaLian*
[3]*The Maternal-Fetus Center of YingKou, LiaoNing (China)*

Summary

Objective: To evaluate the correlations between postoperative sequelae and the intervals between conization and subsequent laparoscopic radical hysterectomy (LRH) and pelvic lymphadenectomy in patients with cervical cancer. *Materials and Methods:* A retrospective study was conducted in a tertiary care university hospital. The medical records of cervical cancer patients undergoing LRH and pelvic lymphadenectomy between April 2005 and August 2011 were reviewed. The subjects were divided into three groups according to time from conization to LRH: group 1 (within six weeks, n = 17), group 2 (> six weeks, n = 38), and group 3 (no previous conization, n = 40). *Results:* The three groups showed no significant differences with respect to patient and tumor characteristics, intraoperative variables such as surgical time, blood loss, conversion to laparotomy, and perioperative morbidity, while the complications in group 1 showed a significant difference compared to groups 2 and 3. *Conclusions:* LRH is feasible for the treatment of cervical cancer patients with previous conization and the appropriate time interval is after six weeks. A careful separation of the bladder and ureters from the cervix is recommended to minimize morbidity associated with this surgery.

Key words: Cervical cancer; Laparoscopic radical hysterectomy; Conization; Learning curve.

Introduction

Since the first laparoscopic radical hysterectomy (LRH) and lymphadenectomy for cervical carcinoma was performed in 1992, laparoscopy for uterine malignancies has evolved rapidly [1]. The advantages of laparoscopy vs open uterine surgery are clear, including decreased postoperative pain, shorter length of hospital stay, more rapid return to normal activities, and a substantial equivalent of lymph nodes removed [1, 2]. In the management of early invasive cancer of the cervix, LRH with proper patient selection and performance of the surgery by an experienced gynecologist that is well-trained in laparoscopic surgery is encouraged in the practice of gynecologic oncology. However, it is associated with unique challenges and complications [3]. To reduce perioperative complications, the determination of an appropriate time for LRH in patients who have undergone cervical conization is required and this study was undertaken to verify a possible correlation between the clinical aspects and the time interval.

Materials and Methods

Patient groups

Data of patients who underwent total LRH and pelvic lymphadenectomy for cervical cancer between April 2005 and August 2011 were retrospectively collected and recorded. During this period, 1,167 cervical cancer patients received

radical hysterectomy and systematic lymphnode dissection, and 167 patients were eligible to undergo LRH; of these, 55 (32.9%) had recent conization of the cervix and were the basis of this report. Surgery was performed by the team including six surgeons under the direction of Dr Jiyong Jiang, who had previous and extensive experience in gynecologic oncology and laparoscopic procedures. Inclusion criteria were: good general condition, no evidence of lymph node metastasis according to imaging study, before Stage IIA. All patients were staged based on clinical evaluation according to the most recent FIGO clinical staging system, conversion to laparotomy was mandatory if safety of the patient and the tumor incision margin could not be assured during the laparoscopic procedure. Patients were informed of risks and possible complications of the laparoscopic procedure and signed a written informed consent for conversion to laparotomy. All patients received a preoperative bowel preparation, antibiotic prophylaxis, and antithrombotic treatment with subcutaneous low molecular weight heparin for five to seven days.

Total LRH technique

Many authors have described the techniques used to perform LRH [4, 5]. Briefly, with the patient in the Trendelenburg position with the foot raised at 1-15° after the placement of a uterine manipulator, a 10-mm trocar for the 0° laparoscope was placed at the level of the umbilicus. Once the trocar had been safely introduced into the abdominal cavity, insufflation was performed and the intra-abdominal pressure was maintained at 11-12 mmHg. Two additional 5 mm trocars in the right and left quadrants and one suprapubic trocar were placed. The round ligaments were transected bilaterally, and the paravesical and pararectal spaces were developed with ultrasonic energy instruments to achieve a blunt dissection. Complete pelvic lymphadenectomy up to the common iliac nodes and para-aortic

Table 1. — *Patients and tumor characteristics.*

	Previous Group 1 [17]	Conizazion Group 2 [38]	No conization Group 3 [40]	pᵃ	pᵇ	pᶜ
Age (years)	44.2 ± 4.6	43.5 ± 8.9	46.2 ± 5.5	0.65*	0.051	1.0
BMI (kg/m)	22.5 ± 2.1	21.4 ± 3.4	22.7 ± 3.7	1.0*	0.067*	0.9*
Parity	1.4 ± 0.5	1.2 ± 0.6	1.3 ± 0.6	1.0*	1.0*	1.0*
Previous cervical excision						
LEEP, n (%)	5 (29.4%)	13 (34.2%)		1.0#		
Cold knife, n (%)	12 (70.6%)	25 (65.8%)		1.0#		

pᵃ: Group 1 (previous conization < 6 weeks) vs group 2 (previous conization > 6 weeks).
pᵇ: Group 1 (previous conization < 6 weeks) versus group 3 (no previous conization).
pᶜ: Group 2 (previous conization > 6 weeks) versus group 3 (no previous conization).
*Bonferroni test.
Fisher exact test.

Table 2. — *Tumor characteristics.*

	Previous Group 1 [17]	Conizazion Group 2 [38]	No conization Group 3 [40]
Stage IA2	6 (35.3%)	11 (28.9%)	0
Stage IB1	9 (52.9%)	24 (63.2%)	26 (65.0%)
Stage IB2	2 (11.8%)	3 (7.9%)	14 (35.0%)
Hystology			
Squamous cell	14 (82.3%)	33 (86.9%)	35 (87.5%)
Adenocarcinoma	1 (5.9%)	4 (10.5%)	2 (5.0%)
Adenosquamous	1 (5.9%)	1 (2.6%)	2 (5.0%)
Other	1 (5.9%)	0	1 (2.5%)
Positive pelvic nodes, n	2 (11.6%)	5 (13.2%)	4 (10.0%)
Positive parametrium, n (%)	1 (5.9%)	2 (5.2%)	3 (7.5%)
Positive resection margin, n (%)	0	0	0

Group 1 (previous conization < 6 weeks) vs group 2 (previous conization > 6 weeks).
Group 1 (previous conization < 6weeks) vs group 3 (no previous conization).
Group 2 (previous conization > 6 weeks) vs group 3 (no previous conization).
*Bonferroni test.
Fisher exact test.

Table 3. — *Surgical data.*

	Previous conization Group 1 [n = 17]	Group 2 [n = 38]	No conization Group 3 [n = 40]	pᵃ	pᵇ	pᶜ
Uterine dimension (cm)	10.5 ± 2.1	11.8 ± 1.8	10.4 ± 2.3	1.2*	1.0*	0.592*
Surgical time (min)	263 ± 65	217 ± 74	210 ± 65	0.01*	0.001	0.057*
Estimated blood loss (ml)	367 ± 115	229 ± 123	240 ± 119	0.01*	0.01*	0.058*
Pelvic node	24.1 ± 4.2	25.3 ± 5.0	23.7 ± 7.4	1.0*	1.0*	0.556*
Conversion to laparotomy	2 (11.6%)	1 (2.6%)	1 (2.5%)	0.01#	0.01#	1.0#

pᵃ: Group 1 (previous conization < 6 weeks) vs group 2 (previous conization > 6 weeks).
pᵇ: Group 1 (previous conization < 6 weeks) versus group 3 (no previous conization).
pᶜ: Group 2 (previous conization > 6 weeks) versus group 3 (no previous conization).
*Bonferroni test.
Fisher exact test.

Table 4. — *Perioperative morbidity and complications.*

Type	Previous conization Group 1 n (%)	Group 2 n (%)	No conization Group 3 n (%)	pᵃ	pᵇ	pᶜ
Bladder injury	1 (5.8%)	1 (2.6%)	1 (2.5%)			
Ureter injury	1 (5.8%)	0	1 (2.5%)			
Vascular injury	0	1 (2.6%)	1 (2.5%)			
Fever of unknown origin	2 (11.6%)	1 (2.6%)	0 (2.5%)			
Vaginal cuff cellulitis	1	0	0			
Ureterovaginal fistula	1 (11.7%)	0	1 (2.5%			
Vesicovaginal fistula	0	0	0			
Bowel obstruction	1 (5.8%)	1 (5.2%)	1 (2.5%)			
Hematoma	0	1 (2.6%)	1 (2.5%)	0.033#	0.029#	1.0#
Total	7 (41.2%)	5 (13.2%)	6 (15.0%)			

pᵃ: Group 1 (previous conization < 6 weeks) vs group 2 (previous conization > 6 weeks).
pᵇ: Group 1 (previous conization < 6 weeks) versus group 3 (no previous conization).
pᶜ: Group 2 (previous conization > 6 weeks) versus group 3 (no previous conization).
Fisher exact test.

nodes was performed and the lymph nodes were placed into a bag and removed vaginally at the end of the operation. Total LRH was performed identifying and cutting uterine vessels at their origin from hypogastric vessels using a bipolar knife. With the transected uterine vessels in tension, the ureter was then unroofed and dissected out of the tunnel, and the uterosacral and cardinal ligaments were isolated and resected as close as possible to the pelvic sidewalls. The bladder was mobilized inferiorly to ensure adequate vaginal margins. Finally, the vaginal wall was transected by monopolar coagulation and all the specimens were then retrieved from the vagina. In patients less than 40 years and with squamous cervical cancer, the ovaries were preserved, and the vaginal cuff was sutured vaginally. In order to facilitate laparoscopic ureteral manipulation and minimize risk of ureteral damage, ureteral bilateral stents were placed preoperatively and removed at 7-14 days postoperatively.

Postoperative treatment

The vital signs of the patients, the characteristics, and quantity of liquid from the drainage tube were observed. Febrile morbidity was defined as a temperature of 38°C on two separate occasional days at least four hours apart, excluding the initial 24 hours post-surgery. Adjuvant therapy was proposed to patients according to risk factors, such as parametrial involvement, positive resection margins, and positive lymph nodes. Follow-up consisted in a pelvic examination every three months during the first two years, three times annually from the third to the fifth year, then annually from then onwards.

Statistical analysis

The SPSS software (version 13.0) was used for statistical analysis, differences between continuous variables were evaluated through one-way ANOVA for normally distributed variables and by the Bonferroni test for variables that were not normally distributed, differences of proportions were compared with the Fisher exact test, and $p < 0.05$ was considered statistically significant.

Results

Patients' characteristics

A total of 95 patients were subdivided into 17 patients in group 1 (previous conization within six weeks), 38 patients in group 2 (previous conization > six weeks), and 40 patients in group 3 (no previous conization) were enrolled. The mean age was 44.2, 43.5, and 46.2 years, the mean delivery histories were 1.4, 1.2, and 1.3 times, and mean body mass index (BMI) was 22.5, 21.4, and 22.7 kg/m², and previous cervix LEEP was 5 (29.4%), 13 (34.2%), previous cold knife was 12 (70.6%), 25 (65.8%), respectively. The aforementioned data showed no significant differences between the three groups (Table 1).

Comparison of intraoperative variables

The uterine dimension was 10.5 cm, 11.8 cm, and 10.4 cm, pelvic lymph nodes were 24.1, 25.3, and 23.7, respectively, and there was no statistical difference between the three groups. Mean blood loss was 367 ml, 229 ml, and 240 ml; mean surgical time was 263 min, 217 min, and 210 min, conversion to laparotomy was 2

(11.6%), 1 (2.6%), and 1 (2.5%) respectively. Group 1 and 2 patients experienced uncontrolled parametrial bleeding during dissection of the vesicocervical ligament to unroof the ureter. In group 2, one patient experienced right external iliac vein laceration during debulking lymphadenectomy and thrombosis occurred on the fifth day. In group 3, one patient experienced left internal iliac vein injury when the uterosacral ligaments were transected. The patients in group 1 therefore had more blood loss, longer surgical time, and more risks of conversion to laparotomy, compared to the patients in groups 2 and 3, and there was no difference between these latter two groups (Table 3).

Comparison of postoperative morbidity and complications

In group 1, one patient with previous transverse incision Cesarean section at the lower uterine segment experienced bladder injury during opening of the cervicovesical space and there was extensive intraoperative bleeding during the course of hemostasis, which was repaired laparoscopically. One patient experienced inadvertent ureteric injury during retroperitoneal ureteric dissection and was then rapaired lapasocopically. One patient complained of water vaginal discharge from the tenth postoperative day, the ureteric injury (ureterovaginal fistula) was discovered 18 days postoperatively and required surgical repair. One patient experienced pyrexia ranging from 38.0°C to 39.8°C and more vaginal discharge for seven days postoperatively, and vaginal cuff cellulitis and cuff separation were found, but then successfully repaired. Two women experienced fever of unknown origin, but disappeared ten days later. In group 2, one patient had acute renal failure and retroperitoneal hematoma was found; she then received a blood transfusion of 800 ml, and healed by conservative treatment after three days. In group 3, one patient experienced bowel obstruction on the fourth day postoperatively and recovered by means of gastrointestinal decompression. In all cases, the aforementioned data showed perioperative morbidity and complications in group 1 was significantly higher compared to groups 2 and 3, and there was no significant difference between the same groups (Table 4).

Discussion

This study showed that LRH can be successfully performed in women with cervical carcinoma undergoing prior excision of the cervix. Although the study sample was small, in most (95.8%) of these patients, the procedure was completed laparoscopically.

The topic of interval between conization and subsequent hysterectomy seems surpassed. Concerns of hysterectomy in women with previous electrical loop or cold knife excision of the cervix include: the risk of urinary injury, infectious morbidity, and severe hemorrhage due to inflammatory reaction of the paracervical tissue. It has been proposed that subsequent hysterectomy after conization should be conducted within 48 hours or after six weeks [6]. Many patients had conization performed elsewhere, and these patients were frequently referred at varying intervals after conization and often had a radical surgical procedure at that time. Hysterectomy cannot be easily conducted within 48 hours, especiallly for cervical cancer patients, because the histotype cannot be determined early. Furthermore, a hysterectomy after six weeks after conization can lead to several problems, such as fear and anxiety about cancer metastasis during the waiting period. Attributing to the efficacies of antibiotics, to rapid and sufficient transfusion, and to advances in surgical techniques, the appropriate time is of current debate and each hospital has different guidelines. Korean doctors report that abdominal extended hysterectomies could be conducted at any time when the patient is in a good condition, not precisely within 48 hours or > six weeks after LEEP [7]. Thailand doctors reported that total laparoscopic hysterectomy could be feasible and safe in patients with prior diagnostic excision of the cervix [8], but in a brief review of articles of LRH, no information regarding the significance of conization -LRH interval was found [9-11] thus this study was undertaken to verify a possible correlation between the clinical aspects and the time interval.

The paracervix has two parts: the medial part is a condensation of connective tissue, and the lateral part is made of fatty tissue that contains lymph nodes and surrounds vessels and nerves; the stable anatomical landmark that marks the limit between these two parts is the terminal ureter. It has been recognized that prior operation of the cervix may lead to inflammatory reaction and hypervascularity of the paracervical tissue [12], and these changes continue until six weeks postoperatively. If hysterectomy is performed after 48 hours or before the cervix has healed, the risk of severe intraoperative bleeding and serious postoperative infectious morbidity is increased. In this surgical procedure in group 1, during the course of ligation of uterine artery, dissection of the ureteral tunnel and resection of the cardinal ligament of the vagina, the authors found that the parametrial blood vessel was dilated, the fatty tissue was in edema, and the authors experienced more hemorrhage, more time with ultrasonic energy, and bipolar device was required to arrest hemorrhage. Increased surgical time often associated with increased technical difficulty, predisposes the patient to increased perioperative morbidity [13]. One patient suffered from febrile, watery diarrhea, peritonitis, and leakage of urine through the vagina nine days postoperatively, ureteroneocystomy was performed abdominally, but in groups 2 and 3, these complications did not exist.

Urologic structures are at risk for injuries at the time of LRH and pelvic lymphadenectomy procedures, in particular this injury is mainly related to injury of the bladder or ureter because the authors dissected part of the vesicocervical ligament. In this series, the incidence of bladder injury was 5.8% and the incidence of uretal injury was 5.8% in group 1, 2.6% in group 2, and 2.5% in group 3 Steed [13] and Milad [14] reported similar high numbers of urinary tract complications of 8% and 6%. Although it

has been argued that the restriction of the technique can be overcome with suitable training, the authors' experience still indicated a reduction in such complications within the proper interval between conization and subsequent LRH.

The authors also found that in group 1, the febrile morbidity was higher than the other two groups and this was in accordance to the previous work of Osoba [15], but Cavannagh [16] reported that while febrile morbidity may be increased when hysterectomy was performed within six weeks of cone biopsy, no conclusive evidence could be found for this; however even if it did increase, it was apparently not a serious problem. If hysterectomy was not postponed for six weeks, it was unimportant if it was performed within that period.

Compared to abdominal and vaginal hysterectomies, laparoscopic hysterectomy requires greater surgical expertise, a longer time to master, longer surgical time, and increased incidence of urinary tract injury. To prevent and reduce these complications, gynecologists must acquire skilled laparoscopic tecniques through repeated training based on a slow learning curve with the aim to improve these laparoscopic skills. In a recent review of laparoscopic gynecologic complications, Possover [17] suggested that a minimum of 50 LRH and lymphadenectomy cases are needed for a surgeon to acquire adequate laparoscopic skills. Furthermore, complications decreased with increased experience, therefore it is important to respect the learning curve. In this department, the initial learning experience of the primary complications was from laparoscopic hysterectomy as well as LRH. In this study, four patients (23.5%) in group 1, ten patients (26.3%) in group 2, and 11 patients (27.5%) in group 3 were included in the first 50 cases; the proportion had no significant difference, therefore the authors could exclude the impact of the learning curve.

In conclusion, the data revealed differences in surgical morbidity at distinct time intervals between conization and subsequent LRH. LRH within six weeks of conization of the cervix is fraught with the danger of high morbidity and it is reasonable to perform LRH six weeks after conization; moreover, careful dissection of the bladder from the cervix and identification of both ureters are recommended to minimize morbidity associated with this procedure.

References

[1] Childers J.M., Hatch K.D., Tran An, Surwit E.A.: "Laparoscopic paraaortic lymphadenectomy in gynecologic malignancies". *Obstet. Gynecol.*, 1993, *82*, 741.
[2] Eltabbakh G.H., Shamonki M.I., Moody J.M., Garafano L.L.: "Laparoscopy as the primary modality for the treatment of women with endometrial cancer". *Gynecol. Oncol.*, 2001, *78*, 58.
[3] Steed H., Rosen B., Murphy J., Laframbosis S., De Petrillo D., Covens A.: "A comparison of laparoscopic-assisted radical vaginal hysterectomy and radical abdominal hysterectomy in the treatment of cervical cancer". *Gynecol. Oncol.*, 2004, *93*, 588.
[4] Xu H., Chen Y., Li Y., Zhang Q., Wang D., Liang Z.: "Complications of laparoscopic radical hysterectomy and lymadenectomy for invasive cervical cancer:experience based on 317 procedures". *Surg. Endose,* 2007, *21*, 96.
[5] Possover M., Krause N., Kuhhne-Heid R., Schneider A: "Laparoscopic assistance for extended radicality of radical vaginal hysterectomy:description of a technique". *Gynecol. Oncol.*, 1998, *70*, 94.
[6] Webb M.J., Symmmonds R.E.: "Radical hysterectomy influence of recent conization on morbidity and complications". *Obstet. Gynecol.,* 1979, *53*, 290.
[7] Young Tae Kim, Bo Sung Yoon, Sung Hoon Kim, Jae Hoon Kim: "The influence of time intervals between loop electrosurgical excision and subsequent hysterectomy on the morbidity of patients with cervical neoplasia". *Gynecol. Oncol.*, 2005, *96*, 500.
[8] Phongnarisorn C., Srisomboon J.: "Surgical morbidity associated with total laparoscopic hysterectomy in women with prior diagnostic excision of the cervix". *J. Obstet. Gynaecol. Res.*, 2007, *33*, 519.
[9] Cavanagh D., Rutledge F.: "The cervical cone biopsy-hysterectomy sequence and factors affecting the febrile morbidity". *Am. J. Obstet. Gynecol.*, 1960, *80*, 53.
[10] Williams T.J., Johnson T.R., Pratt J.H.: "Time interval between cervical conization and hysterectomy". *Am. J. Obstet. Gynecol.,* 1970, *107*, 790.
[11] Orr J.W. Jr, Shingleton H.M., Hatch K.D., Mann W.J., Austin J.M., Soong S.J.: "Correlation of perioperative morbidity and conization and radical hysterectomy interval". *Obstet. Gynecol.,* 1982, *59*, 726.
[12] Malinak L.R., Jeffrey R.A., Dunn W.J.: "The conization-hysterectomy time interval: a clinical and pathologic study". *Obstet. Gynecol.,* 1964, *23*, 317.
[13] Steed H., Rosen B., Murphy J., Laframboise S., De Petrillo D., Covens A.: "A comparison of laparoscopic assisted radical vaginal hysterectomy and radical abdominal hysterectomy in the treatment of cervical cancer". *Gynecol. Oncol.*, 2004, *93*, 588.
[14] Milad M.P., Morrison K., Sokol A., Miller D., Kirkpatrick L.: "A comparison of laparoscopic supracervical hysterectomy vs laparoscopically assisted vaginal hysterectomy". *Surg. Endosc.*, 2001, *15*, 286.
[15] Osoba D.: "Febrile morbidity in relation to cone biopsy followed by hysterectomy;A study of 38 patients". *Canad. M.A.J.*, 1958, *79*, 85.
[16] Cavnagh D., Rutledge F.: "The cervical cone biopsy: hysterectomy sequence and factors affecting the febrile morbidity". *Am. J. Obstet. & Gynecol.*, 1960, *80*, 53.
[17] Possover M., Krause N., Plaul K., Kuhne-Heid R., Schneider A.: "Laparoscopic paraaortic and pelvic lymphadenectomy: experience with 15 patients and review of the literature". *Gynecol. Oncol.*, 1998, *71*, 19.

Address reprint requests to:
J.Y. JANG, M.D.
The 10 floor of Dalian
Maternity Hospital
1 Dunhuang Road
Shahekou District DaLian City
116033 Liaonung Province (P.R. China)
e-mail: jiangjiyong@dl.cn.