Efficacy of laparoscopic nerve-sparing radical hysterectomy in the treatment of early cervical cancer

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Summary

Purpose: To evaluate the efficacy and safety of laparoscopic nerve-sparing radical hysterectomy (LNSRH) in the treatment of early cervical cancer.

Methods: The clinical data of 152 patients with early cervical cancer undergoing radical hysterectomy (RH) were retrospectively analyzed, and the patients were divided into LNSRH group (n=76) and laparoscopic RH (LRH) group (n=76) according to the surgical approaches. The tumor recurrence and survival were recorded during postoperative follow-up, and the disease-free survival (DFS) and overall survival (OS) were compared between the two groups of patients.

Results: The general clinical characteristics were comparable between the two groups of patients. LNSRH group had a remarkably longer operation time (p<0.001) and a notably shorter length of hospital stay (p<0.001) than LRH group. The postoperative in-dwelling time of urinary catheter in LNSRH group was evidently shorter than that in LRH group (p<0.001). Besides, the time of first flatus and defecation after operation was markedly shortened in LNSRH group compared with that in LRH group, with statistically significant differences (p<0.001). In comparison with those in LRH group, the incidence rate of bladder dysfunction was obviously decreased (p<0.001), while the urodynamic indexes at 6 months after operation were prominently better in LNSRH group (p<0.05). According to the follow-up results, the 5-year OS was 84.9% and 88% in LNSRH group and LRH group, respectively, and the DFS was 74.0% and 78.7%, respectively. Log-rank test showed that the differences in OS and DFS between the two groups of patients were not statistically significant (p=0.275, p=0.213).

Conclusions: LNSRH is safe and effective in treating early cervical cancer and can result in similar tumor recurrence and long-term survival to LRH. However, it has superior protective effects on the bladder and bowel functions, which is worthy of popularization and application.

Key words: cervical cancer, early, nerve-sparing, radical hysterectomy, laparoscope

Introduction

Cervical cancer is a common malignant tumor in women, and laparoscopic nerve-sparing radical hysterectomy (LNSRH) is the standard procedure for the treatment of early cervical cancer [1,2]. However, the damaged pelvic autonomic nerve (PAN) during the operation will cause postoperative complications such as bladder, rectum and sexual dysfunctions, seriously affecting the patients' quality of life after operation. In particular, the incidence rate of bladder dysfunction is as high as 50-85% [3,4].

In 1921, the Japanese researcher Okabayashi proposed the hypothesis of improving the bladder function of the patients by preserving the pelvic nerves during cervical cancer operation. In 2000, the German researcher Possover [5] started to explore the laparoscopic nerve-sparing operations. It was until 2008 that the PAN-sparing radical hysterectomy was formally included into the new classification of radical hysterectomy (Querleu-Morrow classification) by Japanese authors [6,7]. With the

development of laparoscopic technique and its wide application in the field of gynecologic tumors, the safety and feasibility of LNSRH are beneficial to the postoperative recovery of bladder, rectum and sexual function according to some research reports, but there is still a lack of long-term follow-up data about the clinical efficacy of the procedure [7-9]. In this research, the clinical efficacy of LNSRH and LRH in 152 patients with early cervical cancer in our hospital was retrospectively analyzed, the influence on the postoperative recovery of bladder and rectum functions and quality of life were investigated, and the safety and feasibility of LNSRH were further explored.

Methods

General data

A total of 76 patients with early cervical cancer receiving LNSRH and another 76 patients undergoing LRH in our hospital from January 2013 to March 2016 were selected as the study subjects. Enrolled were patients aged ≤65 years, those definitely diagnosed with cervical cancer in clinical stage of IA2-IIA stage by pathological examination before operation, those who had no symptoms such as frequent micturition, urgent micturition, painful micturition and dysuria before operation, those without diabetes, severe medical and surgical diseases and mental diseases, and those who did not receive chemotherapy, radiotherapy and other adjunctive therapies before operation. There were no statistically significant differences in the age, pathological type and clinical stage between the two groups, which were comparable (Table 1). In this research, the *Declaration of Helsinki* was followed, the duty of disclosure was performed,

and all the patients enrolled signed informed consent. This study was approved by the Ethics Committee of Shanxian Central Hospital.

Therapeutic methods

LNSRH group: The principle of operation is to preserve the PAN as much as possible without affecting the range of operation, namely type III LNSRH. The operative key points were as follows: The patients were placed in the bladder lithotomy position after general anesthesia, and pneumoperitoneum was established by means of 4-port technique. Meanwhile, the uterus was held up using a cup-type uterine manipulator, with attention that the manipulator was not processed into the cervical canal in any case. Then, bilateral pelvic lymph nodes were excised under a laparoscope, the ureters and mesenteria below were isolated, and the para-uterine connective tissues at the perirectal and paravesical fossae were separated. The uterine artery was cut using a pair of scissors after electrocoagulation via Biclamp, then the cut end was lifted up to expose the pelvic plexus below, and the bladder and uterine nerve branches originating from the pelvic plexus were found and preserved. Next, the uterosacral ligament was bluntly dissected, and the beginning parts of the lateral hypogastric nerve and inferior hypogastric plexus were located. It should be noted that the exposed pelvic nerve fibers, fat, lymph, blood vessels and compact connective tissue below the cardinal ligament were identified, and the pelvic nerve fibers of the pelvic plexus were reserved. Subsequently, the anterior leaf of vesicocervical ligament was cut, the ureters were dissociated, the vesicocervical ligament and paracolpium were bluntly dissected, the middle and inferior vesical veins were severed to expose the bladder branch of hypogastric plexus, and the neurological levels of the hypogastric plexus and the bladder branch were reserved. Finally, the uterine branch of hypogastric

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	LNSRH group (n=76)	LRH group (n=76)	p value
Age	48.53±10.06	47.28±9.71	0.437
BMI (kg/m^2)	22.61±2.26	22.33±2.11	0.431
Histology			0.097
Squamous cell carcinoma	68 (89.5%)	58 (76.3%)	
Adenocarcinoma	6 (7.9%)	14 (18.4%)	
Others	2 (2.6%)	4 (5.3%)	
FIGO stage			0.685
I A2	8 (10.5%)	11 (14.5%)	
I B1	37 (48.7%)	35 (46.1%)	
I B2	18 (23.7%)	21 (27.6%)	
II A	13 (17.1%)	9 (11.8%)	
Differentiation grade			0.414
High-middle	45 (59.2%)	40 (52.6%)	
Low	31 (40.8%)	36 (47.4%)	

LNSRH: Laparoscopic nerve-sparing radical hysterectomy; LRH: Laparoscopic radical hysterectomy; BMI: body mass index; FIGO: Federation of Gynecology and Obstetrics

plexus was cut, the bladder was push down, a circular incision was made on the vagina at 3-4 cm below the fornix, the resected uterus was taken out, and the vaginal stump was sutured under the laparoscope, followed by flushing of pelvic cavity, hemostasis and completion of operation.

LRH group: After routine disinfection and draping, pneumoperitoneum was established using the 4-port technique, and the uterus was held up by the cup-type uterine manipulator at the same time. The laparoscope was utilized to probe whether there was metastasis in the pelvic cavity and abdominal cavity. Then, the lateral third of unilateral round ligament was coagulated and severed using the Biclamp or BiSect, the posterior peritoneum was opened along the pelvic ligament, and the right ovarian artery and vein were separated at the branch of right common iliac artery, followed by high electrocoagulation and cutting. The anterior branches of internal iliac artery were isolated, and the uterine artery was dissected to the beginning part, then coagulated and cut. After that, the reflexed peritoneum of uterus and rectum were opened, the rectum was separated and pushed down along the rectovaginal space, the perirectal fossa was dissected, and the ureters were pushed away to expose the uterosacral ligament which was coagulated and severed. Next, the uterine artery was isolated to the cervix across the ureters, and the ureters were dissociated. The paravesical fossa was separated to expose the cardinal ligament on the same side, followed by electrocoagulation and cutting of the cardinal ligament at the place close to the pelvic wall. The bladder was pushed down continually, the paracolpium on both sides was coagulated, a circular incision was made on the vagina, and specimens were acquired. After washing of the pelvic cavity and hemostasis, the operation was completed. The contralateral side was treated using the same methods, while the pelvic nerves were not reserved during isolation.

Observation indexes

The operation time, intraoperative blood loss, length of resected cardinal ligament, uterosacral ligament and vagina as well as intraoperative complications in the two groups of patients were recorded. After operation, the patients were given dual anti-inflammatory therapy with second-generation cephalosporin antibiotics+ornidazole for 3-5 days, which was smeared on or used to wash the perineum. The volume of pelvic drainage was recorded every day until the drainage volume was <100 mL twice, then the pelvic drainage tube was extracted, and, finally, the total in-dwelling days of pelvic drainage tube were counted. Complications such as vesicovaginal fistula, intestinal obstruction and infection were observed, and the time of anal flatus and defecation after operation was recorded.

From the 3rd day after operation, the urinary catheter was clipped intermittently (3-4 per day) to exercise the bladder function. When the patients had the urge to urinate or feeling of bladder filling and at 7 days after operation, color ultrasonography of urinary system and examination of bladder residual urine volume were

performed within 30 min after the removal of the urinary catheter. Bladder residual urine volume >100 mL indicated urinary retention, so a silicone catheter was indwelled again until the residual urine volume was <100 mL, and the total in-dwelling days of urinary catheter was recorded.

The patients were followed up every month up to 6 months after operation, during which the postoperative recovery was recorded. After that, the patients were reexamined every 3 months and subjected to gynecological examination, color ultrasonography of the pelvic cavity, color ultrasonography of the urinary system and tumor cervical marker CA 125. Further, pelvic MRI was performed in case of any abnormality, and vaginal exfoliative cytology examination and chest X-ray were conducted if necessary or once every 6 months. At 3-5 years after operation, the patients were reexamined once every year. The postoperative recurrence and death of the patients were recorded. The survival time (in months) of the patients refers to the duration from the day of operation to the day of last follow-up or death.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was adopted for statistical analyses. The measurement data were expressed by mean ± standard deviation (SD), and two-sample t-test was performed for inter-group comparison. The enumeration data were presented as ratio (%), and x^2 test was conducted for inter-group comparison. P<0.05 suggested that the difference was statistically significant. Kaplan-Meier method was applied to plot the survival curves, log-rank test was utilized to compare the difference in survival rate between the two groups, and p<0.05 suggested that the difference was statistically significant.

Results

Comparisons of operation-related indexes

The LNSRH group had a remarkably longer operation time [(251.37±22.30) min *vs.* (209.72±29.47) min, p<0.001] and a notably shorter length of hospital stay [(10.2±1.3) d *vs.* (11.8±1.7) d, p<0.001] than the LRH group. The differences in the intraoperative blood loss and postoperative in-dwelling time of pelvic drainage tube between the two groups were not statistically significant (p=0.155, p=0.061). The length of resected cardinal and uterosacral ligament, length of resected vagina and number of resected lymph nodes stood for the range of operation. There were no statistical differences in those indexes between LNSRH group and LRH group (p>0.05). No vascular injury, organ injury and other complications occurred in the patients during operation. In the LNSRH group, there were 15 cases of complications after operation, including 1 case of vesicovaginal fistula, 2 cases of in-

complete intestinal obstruction, 2 cases of pelvic infection, 1 case of chylous fistula and 15 cases of bladder dysfunction. Seventeen cases of complications occurred after operation in the LRH group, including 3 cases of incomplete intestinal obstruction, 2 cases of pelvic infection and 39 cases of bladder dysfunction. The incidence rate of bladder dysfunction-related complications in the LNSRH group (19.7%) was evidently lower than that in the LRH group (51.3%) (p<0.001), while no statistically significant differences in the complications related to non-bladder dysfunction were detected between the two groups (p>0.05) (Table 2).

Comparisons of postoperative bladder and rectum functions

The postoperative in-dwelling time of urinary catheter in the LNSRH group was distinctly shorter than that in the LRH group [(8.6±2.3) d *vs.* (10.8±3.1) d, p<0.001]. Besides, the time of flatus and defecation after operation was decreased markedly in the LNSRH group compared with that in the LRH group, with statistically significant differences (p=0.034, p<0.001).

Among the 15 cases of bladder dysfunction in LNSRH group after operation, there were 4 cases

of abdominal pressure voiding, 1 case of urinary incontinence, 2 cases of urinary retention and 8 cases of irritation symptoms of bladder manifested as frequent micturition and urgent micturition. In the LNSRH group, the 39 cases of bladder dysfunction after operation included 10 cases of urinary retention, 3 case of urinary incontinence, 12 cases of abdominal pressure voiding and 14 cases of irritation symptoms of bladder manifested as frequent micturition and urgent micturition. In addition, there was a statistically significant difference in the incidence rate of bladder dysfunction between groups (p<0.001) (Table 3).

In terms of the urodynamic parameters reexamined at 6 months after operation, the bladder capacity at the time of first urination and maximum bladder capacity in the LNSR group was notably smaller than those in the LRH group [(168.8±20.5) mL *vs.* (188.7±32.8) mL, p<0.001, and (456.4±44.3) mL *vs.* (506.2±41.2) mL, p<0.001]. However, the LNSRH group exhibited obviously raised maximum urinary flow rate and urethral closure pressure compared with the LRH group [(21.5±4.4) mL/s *vs.* (19.8±4.7) mL/s, p=0.022, and (27.6±4.1) cm H_2O *vs.* (25.1±4.8) cm H_2O, p<0.001] (Table 4).

Table 2. Comparison of perioperative parameters

Parameters	LNSRH group (n=76)	LRH group (n=76)	p value
Operation time (min)	251.37±22.30	209.72±29.47	0.001
Blood loss (ml)	117.51±73.66	135.48±81.14	0.155
Lymph node dissection number	16.3±2.1	15.7±2.5	0.111
Pelvic catheter removal time (day)	3.5±0.7	3.7±0.6	0.061
In-hospital time (day)	10.2±1.3	11.8±1.7	0.001
Length of cardinal ligament resection (cm)	3.3±0.3	3.4±0.2	0.168
Length of uterosacral ligament resection (cm)	3.5±0.3	3.4±0.3	0.416
Length of vagina resection (cm)	3.4±0.2	3.3±0.2	0.240

LNSRH: Laparoscopic nerve-sparing radical hysterectomy; LRH: Laparoscopic radical hysterectomy

Table 3. Comparison of bladder and rectum function of patients in the two groups

| Parameters	LNSRH group (n=76)	LRH group (n=76)	p value
Postoperative catheter removal time (day)	8.6±2.3	10.8±3.1	0.001
Gas passage after surgery (d)	3.65±7.7	3.93±8.4	0.034
Bowel movement time after surgery (d)	5.87±11.1	7.02±9.5	0.001
Bladder dysfunction (n,%)	15 (19.7)	39 (51.3)	0.001
Abdominal pressure-helped urination (n,%)	4 (5.3)	12 (15.8)	
Urinary incontinence (n,%)	1 (1.3)	3 (3.9)	
Urinary Retentron (n,%)	2 (2.6)	10 (13.2)	
Irritation sign of bladder (n,%)	8 (10.5)	14 (18.4)	

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Table 4. Comparison of urodynamic parameters of patients in the two groups

Parameters	LNSRH group (n=76)	LRH group (n=76)	p value
Bladder volume at first urination (mL)			
Preoperative	158.9±18.9	163.4±17.3	0.128
Postoperative	168.8±20.5	188.7±32.8	0.001
Maximum cystometric capacity (mL)			
Preoperative	416.7±37.6	424.6±27.8	0.143
Postoperative	456.4±44.3	506.2±41.2	0.001
Maximum flow rate (mL/s)			
Preoperative	24.2±3.3	23.7±2.7	0.308
Postoperative	21.5±4.4	19.8±4.7	0.022
Urethral closure pressure (cmH$_2$O)			
Preoperative	28.9±3.7	28.1±3.6	0.179
Postoperative	27.6±4.1	25.1±4.8	0.001

LNSRH: Laparoscopic nerve-sparing radical hysterectomy; LRH: Laparoscopic radical hysterectomy
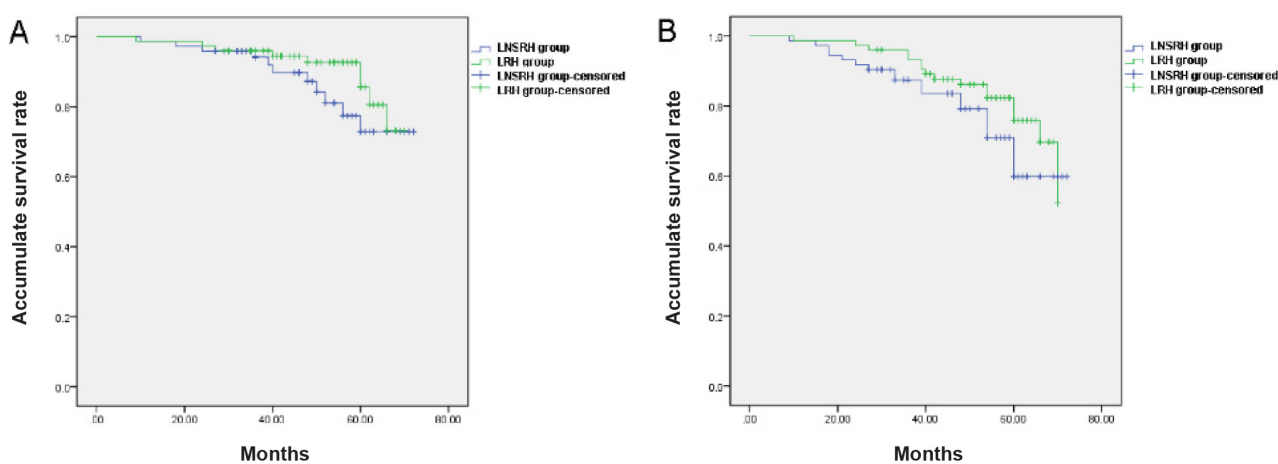
Figure 1. Kaplan-Meier survival curves of patients in LNSRH group and LRH group. **A:** The difference of overall survival rate of patients in the two group had no statistical significance (p=0.275). **B:** The difference of disease-free survival rate of patients in the two group had no statistical significance (p=0.213).

Follow-up results of patient's survival

The follow-up terminated in March 2019. The follow-up time was 48 months (10-72), and 3 patients were lost to follow-up in the LNSRH group. The follow-up time was 45 months (9-70), and 1 patient was lost to follow-up in the LRH group. In the LNSRH group, 19 patients had recurrence, including 8 cases of local recurrence and 11 cases of cervical cancer recurrence-induced death. Sixteen patients in the LRH group had recurrence, and there were 7 and 9 cases of local recurrence and cervical cancer recurrence-induced death, respectively. The 5-year OS was 84.9% (62/73) and 88% (66/75) in the LNSRH group and LRH group, respectively, and the DFS was 74.0% (54/73) and 78.7% (59/75), respectively. The Kaplan-Meier survival curves of the patients are shown in Figure 1. The log-rank test indicated that both OS and DFS had no statistically significant differences between the two groups (p=0.275, p=0.213).

Discussion

As a standard procedure for the treatment of early cervical cancer, LRH can not only realize the the scope of surgical resection but also possesses advantages such as smaller trauma, less intraoperative blood loss and faster postoperative recovery in comparison with laparotomy [10,11]. Nevertheless, the PANs are severed during operation, which will lead to postoperative bladder, rectum and sexual dysfunctions, seriously affecting the quality of life after operation. Surgeons are constantly looking for approaches to preserve the PANs to reduce the aforementioned complications and improve the patient's quality of life after operation, and they have discovered that the pelvic nerves can be precisely dissected, recognized and reserved under the laparoscope by virtue of its superiority of amplification and minimal invasion, so the LNSRH procedure is proposed [12,13].

A large amount of literature in recent years has reported that LNSRH exerts great effects in protecting the pelvic floor function. According to the study on 64 patients of Shi et al [14], the time of removing the urinary catheter after operation in LNSRH group [(10.2±3.7) d] is obviously shorter than that in LRH group [(17.8±6.7) d], and the incidence rate of pelvic floor dysfunction at 1 year after operation is 7.8% and 31%, respectively, in the two groups, displaying statistically significant differences. Ceccaroni et al [15] divided 56 cervical cancer patients into RH group (n=31) and NSRH group (n=25) and carried out follow-up via questionnaire for 36 months after operation. The questionnaire for postoperative quality of life revealed that the incidence rates of urinary incontinence, urinary retention, fecal incontinence and constipation after operation in RH group were remarkably higher than those in the NSRH group, and the differences were statistically significant (p<0.05). However, no statistically significant differences were observed in orgasm and sexual desire between the two groups of patients, so it is concluded that NSRH is capable of ameliorating the postoperative bladder and rectum functions [15].

According to the results in this research, the postoperative in-dwelling time of urinary catheter in the LNSRH group was shortened evidently in comparison with that in the LRH group (p<0.001), and the time of first flatus and defecation after operation was also decreased markedly in the LNSRH group compared with that in the LRH group (p=0.034, p<0.001). The incidence rate of bladder dysfunction was notably lower (p<0.001), while the urodynamic indexes at 6 months after operation were obviously better (p<0.05) in the LNSRH group than those in the LRH group. Those findings suggest that LNSRH can reduce the damage to nerves dominating the bladder and other organs, thus shortening the in-dwelling time of urinary catheter and reducing the occurrence of complications such as urinary retention after operation. Therefore, it is of positive significance for the postoperative recovery of bladder function in the cervical cancer patients. In this research, the postoperative recovery of anal first flatus and defecation and postoperative abnormal defecation were used to reflect the rectum function. It was indicated that the anal flatus and defecation in the LNSRH group were recovered earlier after operation, and there was a statistically significant difference in the time of rectum function recovery between the two groups (p<0.05).

van den Tillaart et al [16] conducted a cohort study in which the data of 246 patients with cervical cancer were analyzed. The results manifested that the local recurrence rate was 8.3% and 4.9%, the 2-year cumulative recurrence rate was 20% and 10.7%, and the average local DFS within 2 years was 22.7 months and 22.0 months in nerve-sparing group and non-nerve-sparing group, respectively. The univariate and multivariate regression analyses displayed that the nerve-sparing therapy was not an influencing factor for local recurrence, and the OS had no statistically significant difference between the two groups (p=0.4) [16]. Park et al [17] performed follow-up for 125 cervical cancer patients undergoing LNSRH and found that for the patients in stages Ib1 and Ib2, the 5-year DFS was 92% and 78%, respectively, and the 5-year OS was 96% and 83%, respectively, so it is believed that LNSRH has no impact on the postoperative survival time of the patients with early cervical cancer. Liang et al [4] conducted a prospective non-randomized study involving 163 cervical cancer patients in stages Ia-Ib, with a tumor diameter smaller than 5 cm and without preoperative imaging evidence of lymph node metastasis. After 5-42 months of follow-up, no local recurrence or distant metastasis occurred. The team of Van gent implemented a meta-analysis including 27 studies and revealed that there were no statistical differences in 2-, 3- and 5-year OS and DFS between NSRH group and RH group, which is similar to the majority of meta-analyses [18-20]. In this research, the 5-year OS after operation was 84.9% and 88% in the LNSRH group and LRH group, respectively, and the DFS was 74.0% and 78.7%, respectively. Log-rank test indicated that the differences in OS and DFS between the two groups of patients were not statistically significant (p=0.275, p=0.213), which are in line with the previous literature reports.

There is certain data bias in this research since it is a retrospective study, with lack of subjective evaluation indexes of postoperative quality of life, bladder and rectum functions and sexual life of the patients. Hence, more well-designed, multicenter, prospective, randomized controlled study are needed to further verify the influence of treatment with LNSRH on the long-term quality of life, survival and prognosis of the patients with early cervical cancer in the future.

Conclusions

LNSRH is safe and effective in treating early cervical cancer and can result in similar tumor recurrence and long-term survival to LRH. However, it has superior protective effects on the bladder and bowel functions, which is worthy of popularization and application.

Conflict of interests

The authors declare no conflict of interests.

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