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Surgical, Urinary, and Survival Outcomes of Nerve-sparing Versus Traditional Radical Hysterectomy

A Retrospective Cohort Study in China

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Purpose: The purpose of this retrospective study was to compare the surgical, urinary, and survival outcomes between nerve-sparing radical hysterectomy (NSRH) and traditional radical hysterectomy (TRH) for stage IB cervical cancer, in which all the primary procedures were performed by a single physician.

Methods: Patients with cervical cancer of International Federation of Gynecology and Obstetrics (FIGO) stage IB were included if they received radical hysterectomy of class III or type C in 1 center between February 2001 and November 2015. The epidemiological, clinicopathologic, surgical, and urinary data were collected and compared between the NSRH and TRH groups. The follow-up period ended in December 2016.

Results: A total of 406 patients were identified, including 111 (27.3%) in the TRH group and 295 (72.7%) in the NSRH group. Most epidemiological and clinicopathologic characteristics were balanced between the 2 groups. The NSRH and TRH groups had similar mean operating times and comparable short-term postoperative complications, but NSRH had less mean estimated blood loss and a shorter mean postoperative stay (all P <0.001). Within 12 months from surgeries, patients in the NSRH group had less residual urine and fewer urinary dysfunctions. For the 371 patients with definite survival outcomes, in the multivariate analysis, both overall survival (hazard ratio = 1.79, 95% confidence interval: 0.64-5.02) and disease-free survival (hazard ratio = 1.50, 95% confidence interval: 0.72-3.11, P = 0.280) of the NSRH group were similar to those of the TRH group.

Conclusion: NSRH for stage IB cervical cancer patients had better urinary outcomes than TRH without sacrificing the safety and survival benefits.

Key Words: cervical cancer, nerve-sparing radical hysterectomy, residual urine, survival, adverse events

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Cervical cancer has the highest incidence and mortality of female genital tract cancers in China.[1] Radical hysterectomy (RH) established by Ernst Wertheim has been the classical approach for the surgical treatment of early-stage cervical cancer.[2] However, the quality of life of patients is intensively influenced by RH due to a high rate of postoperative morbidities involving the pelvic autonomic nervous system, including bladder dysfunction, colorectal disorder, and sexual dissatisfaction.[3] Takashi Kobayashi introduced the nerve-sparing radical hysterectomy (NSRH) procedure to preserve pelvic autonomic nerves,[2] which was then modified and improved by other gynecologists during the last 2 decades.[4] Although NSRH was probably associated with less bladder dysfunction, the surgical and oncologic outcomes for these patients could not be fully assessed because of scarcity and heterogeneity of effect estimates, and various limitations in study designs addressing the advantages of NSRH versus traditional radical hysterectomy (TRH).[5] More meticulous data and well-designed studies were needed to clarify the superiority of NSRH over TRH.

This retrospective study aimed to reveal the safety of NSRH and the survival outcomes in patients with stage IB cervical cancer who received NSRH compared with patients who received TRH in a Chinese tertiary teaching hospital. All the primary procedures of NSRH or TRH for patients included in this cohort were performed by a single physician (M.W.).

METHODS

Ethical Approval

The Institutional Review Board had approved this study. Informed consent was obtained from all individual participants included in the study before any treatment. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Study Design

This retrospective cohort study was conducted at the Department of Obstetrics and Gynecology of a tertiary teaching hospital. We identified all patients diagnosed with cervical cancer of stage IB from February 1, 2001, to November 31, 2015, through the medical records system. All patients were followed-up in outpatient clinics, and the follow-up ended on December 31, 2016. The primary objectives were the disease-free survival (DFS) and overall survival (OS) of patients treated with NSRH and TRH. The secondary objectives were the residual urine volume at 14 days, at 4 months, and 12 months after the surgeries. The urinary comorbidities after surgeries were also evaluated in the study.

Study Participants

All stage IB patients who accepted the NSRH or TRH by the corresponding author were included. The inclusion criteria consisted of the following (and they are): histopathologically proven primary cervical cancer of squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma; stage IB of International Federation of Gynecology and Obstetrics (FIGO) 2009[6] diagnosed using imaging evaluations (pelvic magnetic resonance imaging with computed tomography or positron emission tomography for evaluation of other sites) and pelvic examinations by 2 experienced physicians of gynecologic oncology; and normal bladder filling and voiding function based on patients' complaints before and after surgeries. The definite diagnosis was made by transferring to the urologic clinics. Patients were excluded if they had distant metastasis in preoperative imaging or postoperative pathologic examinations. For patients who accepted surgical interventions, their pathologic outcomes were reviewed again by L.L. and S.Z. and modified according to FIGO 2009 criteria.

Surgical Interventions, Adjuvant Therapy, and Follow-Up

Surgical treatment consisted of RH, bilateral salpingo-oophorectomy or salpingectomy, and lymphadenectomy of pelvic lymph nodes (LNs) with or without para-aortic LNs. For young patients with the requirement of preserving ovaries, salpingectomy was undertaken along with suspension of the ovaries to the peritoneum above the level of the anterior superior spine. All the primary procedures, including the resection of the parametrium and retroperitoneal LNs, were performed by the corresponding author in accordance with class III or with Meigs' surgeries of Piver-Rutledge-Smith classification[7] before 2011, and in accordance with type C of the Querleu-Morrow classification[8] after 2011. Type C1, that is, NSRH, requires the separation of 2 parts of the dorsal parametria: the medial part, which contains the rectouterine and rectovaginal ligaments, and the lateral part, which is a laminar structure and which contains the hypogastric plexus.[8,9] Although type C2 surgery represents RH without preservation of the autonomic nerves, the paracervix is resected completely, including the part close to the end of the deep uterine vein. Surgical years were further divided into 3 phases: 2001 to 2005, 2006 to 2010, and 2011 to 2015. The decision of NSRH or TRH was made due to the judgment and learning curve of the surgeon (M.W.). Since 2011, all the RH surgeries belonged to nerve-sparing procedures.

All histologic specimens underwent thorough pathologic examinations. Neoadjuvant chemotherapy was administered to some patients with stage IB2. Postoperative adjuvant therapies, including systematic chemotherapy, radiotherapy, concurrent chemoradiotherapy, or a combination of these therapies, were provided for patients according to relevant contemporary guidelines. Regimens of chemotherapy consisted of paclitaxel/carboplatin, paclitaxel/cisplatin, or fluorouracil/cisplatin. Complications such as adverse events within 3 months after the surgery were reviewed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.[10] These complications included pulmonary, renal, and cerebrovascular morbidity; wound and vault complications (infection, breakdown, and dehiscence); septicemia and thromboembolic complications (deep vein thrombosis, pulmonary embolism); and lymphocyst or abscess formation lymphedema, incisional hernia formation, vaginal evisceration.[11]

Postoperative catheters were preserved until 14 days after NSRH. Bladder training was performed for all participants over 3 to 4 days by intermittently closing the catheters. On the morning of the 14th day, the urinary catheters were removed for all participants. After sufficient hydration by routine diet and drinking, the first spontaneous voiding was recorded. Clean catheterization was used to obtain precise residual urine volume. At residual urine volume > 100 mL, the catheter was kept in place until a second removal of the catheter was appropriate. At 14 days, 4 months, and 1 year from the surgery, the residual urine volumes were measured by clean catheterization. The potential urinary dysfunctions were identified and obtained a definite diagnosis during the follow-up consistent with the recommendations of the International Urogynecological Association/International Continence Society.[12]

A close follow-up according to the customed protocol was provided for all patients, who would visit the outpatient clinics every 3 to 4 months for the first year, every 6 months for the second to third year, and every year for the rest of the follow-up period. Patients will accept physical examinations, cytology test, and imaging evaluation. Recurrence was validated by imaging examination and/or biopsy. DFS was defined as the time interval from the date of primary surgery to the date of disease progression and/or recurrence. OS was defined in months as the time interval from the date of the primary surgery to the date of death or censoring at the date of the last contact.

Statistical Analysis

Comparisons of continuous variables were conducted with parametric methods if assumptions of normal distribution were confirmed. Non-normally distributed variables and categorical data were compared between 2 groups with the use of nonparametric tests. Survival curves were generated with the use of the Kaplan-Meier method, and proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the effect of epidemiological and clinicopathologic factors on DFS, progression-free survival, and OS. Multivariable analysis of DFS was performed with adjustment for important baseline risk factors. Unless otherwise stated, all analyses were performed with a 2-sided significance level of 0.05 and conducted with the use of the software SPSS 23.0 (SPSS Inc., Chicago, IL; Supplement 1, Supplemental Digital Content 1, http://links.lww.com/AJCO/A282).

RESULTS

Epidemiological and Preoperative Clinical Characteristics of Patients

A total of 406 patients diagnosed with clinical stage IB and treated were identified, with 111 (27.3%) patients in the TRH group and 295 (72.7%) patients in the NSRH group. Table 1 shows the demographic and clinical characteristics of all the patients, with comparisons between the TRH group and NSRH group shown as well. There was no statistically significant difference observed in FIGO stage, histologic subtype, differentiation, neoadjuvant chemotherapy, ovarian preservation, residual tumor, invasion of stroma, lymphovascular space invasion, uterine involvement, vaginal margin involvement, LN positivity, radiotherapy, chemotherapy, or complications within 3 months after surgery, as shown in Table 1. However, patients in the NSRH groups had more conization procedures, more laparoscopic surgeries, and less parametrium involvement. Since 2011, all RH procedures belonged to NSRH. A more detailed description was listed in Supplement 1 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A282).

Surgical Outcomes and Complications

The NSRH group and RH group had similar mean operating times and mean number of LNs harvested. However, the

TABLE 1. Epidemiological, Clinicopathologic, and Surgical Characteristics of the Patients

Characteristics	n (%)/Mean ± SD TRH (N = 111)	NSRH (N = 295)	*P*
Age (y)	43.86 ± 9.03	42.29 ± 7.99	0.090
BMI (kg/m^2)	24.23 ± 2.77	22.98 ± 2.86	< 0.001
Gravidity	2.98 ± 1.43	2.57 ± 1.29	0.639
Parity	1.50 ± 1.35	1.26 ± 0.79	0.004
FIGO stage			0.170
IB1	70 (63.06)	207 (70.17)	
IB2	41 (36.94)	88 (29.83)	
Pathologic subtype			0.257
Squamous	97 (87.39)	239 (81.02)	
Adenocarcinoma	12 (10.81)	43 (14.58)	
Adenosquamous	2 (1.8)	13 (4.41)	
Conization			0.035
Yes	16 (14.41)	71 (24.07)	
No	95 (85.59)	224 (75.93)	
Neoadjuvant chemotherapy			0.070
Yes	50 (45.05)	104 (35.25)	
No	61 (54.95)	191 (64.75)	
Surgical approach			< 0.001
Laparotomy	97 (87.39)	38 (12.88)	
Laparoscopy	14 (12.61)	257 (87.12)	
Operating time (min)	205.23 ± 36.47	202.56 ± 42.15	0.557
Surgical year			< 0.001
2000-2005	48 (43.2)	7 (2.4)	
2006-2010	63 (56.8)	46 (15.6)	
2011-2015	0 (0)	242 (82.0)	
Estimated blood loss (mL)	439.64 ± 318.03	296.31 ± 303.2	< 0.001
Postoperative stay (d)	17.11 ± 15.41	11.07 ± 6.43	< 0.001
Ovarian preservation			0.355
Yes	44 (39.64)	132 (44.75)	
No	67 (60.36)	163 (55.25)	
Differentiation			0.231
Grade 1	50 (45.05)	153 (51.86)	
Grade 2	47 (42.34)	98 (33.22)	
Grade 3	14 (12.61)	44 (14.92)	
Residual tumor			0.791
Yes	89 (80.18)	233 (78.98)	
No	22 (19.82)	62 (21.02)	
Invasion depth of stroma			0.056
< 1/3	40 (36.04)	140 (47.46)	
1/3-2/3	32 (28.83)	83 (28.14)	
> 2/3	39 (35.14)	72 (24.41)	
LVSI			0.194
Yes	50 (45.05)	112 (37.97)	
No	61 (54.95)	183 (62.03)	
Uterine involvement			0.472
Yes	93 (83.78)	238 (80.68)	
No	18 (16.22)	57 (19.32)	
Parametrial involvement			0.010
Yes	12 (10.81)	12 (4.07)	
No	99 (89.19)	283 (95.93)	
Vaginal margin involvement			0.125
Yes	2 (1.8)	1 (0.34)	
No	109 (98.2)	294 (99.66)	
LNs harvested	40.12 ± 6.5	43.61 ± 7.8	0.566
General number of LNs involved	13 (11.71)	44 (14.92)	0.408
Postoperative radiotherapy			0.080
Yes	65 (58.56)	144 (48.81)	
No	46 (41.44)	151 (51.19)	
Postoperative chemotherapy			0.335
Yes	12 (10.81)	23 (7.8)	
No	99 (89.19)	272 (92.2)	
Complications within 3 mo			0.467
Yes	6 (5.41)	22 (7.46)	
No	105 (94.59)	273 (92.54)	
Recurrent sites			0.390
Local	17/26 (65.4)	33/44 (75.0)	
Beyond the pelvic cavity	9/26 (34.6)	11/44 (25.0)	

BMI indicates body mass index; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space invasion; NSRH, nerve-sparing radical hysterectomy; TRH, traditional radical hysterectomy.

TRH group had more mean blood loss during the operation (439.64 vs. 296.31 mL, $P < 0.05$) and longer mean postoperative stay (11 vs. 17 d, $P < 0.05$) than the NSRH group. The cases with severe (grade 3/4) complications comprised 5.41% (6/111) of the TRH group and 7.46% (22/295) of the NSRH group, between which no significant difference was observed ($P = 0.467$). Severe lower limb lymphedema and lymphocysts demanding drainage occurred in 6 and 8 patients, respectively. No large vessel or visceral damage was found during the operation. However, ureteral fistula occurred in 1 case in the TRH group and in 2 cases in the NSRH group. No mortality occurred during the operation or the early postoperative period in either of the groups.

Urinary Outcomes

At 14 days, 4 months, and 12 months from the surgery, 398, 366, and 338 patients had their residual urine measured, respectively. At each phase in the NSRH group, there were fewer patients having residual urine volumes <50 mL compared with those in the TRH group (Table 2). The significances still exist in the subgroup analysis of various surgical years, various surgical approaches, and the utilization of neoadjuvant chemotherapy.

TABLE 2. Residual Urine Volumes Measured by Clean Catheterization

Residual Urine Volumes	n (%) NSRH Group	TRH Group	*P*
At 14 d from surgeries (mL)	N = 292	N = 106	
> 50	61 (20.9)	39 (36.8)	0.001
> 100	28 (9.6)	20 (18.9)	0.012
At 4 mo from surgeries (mL)	N = 266	N = 100	
> 50	11 (4.1)	10 (10.0)	0.032
At 12 mo from surgeries (mL)	N = 249	N = 89	
> 50	2 (0.8)	5 (5.6)	0.015

NSRH indicates nerve-sparing radical hysterectomy; TRH, traditional radical hysterectomy.

TABLE 3. Comparison of OS and DFS in the Multivariate-Adjusted Model Between the NSRH and TRH Groups

	NSRH (n = 295)	TRH (n = 111)	*P*
OS			
Unadjusted HR (95% CI)	Reference	1.98 (1.02-3.82)	0.043
Multivariate-adjusted HR (95% CI)	Reference	1.79 (0.64-5.02)	0.268
DFS			
Unadjusted HR (95% CI)	Reference	2.33 (1.20-4.50)	0.012
Multivariate-adjusted HR (95% CI)	Reference	1.50 (0.72-3.11)	0.280

CI indicates confidence interval; DFS, disease-free survival; HR, hazard ratio; NSRH, nerve-sparing radical hysterectomy; OS, overall survival; TRH, traditional radical hysterectomy.

At 1 year from surgery, NSRH patients had fewer urinary dysfunction incidents than TRH patients (4/295 [1.4%] and 11/111 [9.9], $P < 0.001$). In the NSRH groups, detrusor dysfunction, low compliance, and stress urinary incontinence were diagnosed in 1, 1, and 2 cases, respectively. In the NSRH groups, detrusor dysfunction, low compliance, stress urinary incontinence and mixed urinary incontinence were diagnosed in 2, 4, 3 and 2 cases, respectively. There were 3 and 0 patients with the diagnosis of neurogenic adynamia of detrusor muscle in the TRH and NSRH groups, respectively, who needed clean intermittent self-catheterization.

Survival Outcomes

A total of 371 cases (91.4%) with definite survival outcomes were included in the survival analysis. The cases with recurrence confirmed by imaging methods or pathologic examinations comprised 28.9% (26/90) of the TRH group and 15.7% (44/281) of the NSRH group, which showed a significant difference ($P < 0.05$). The recurrent sites had no significant differences (Table 1). Table 3 shows the comparisons of survival outcomes between the 2 groups. In the univariate analyses, the OS and DFS for patients in the NSRH group were significantly better than those for patients in the TRH group (Fig. 1). In the multivariate analysis (Fig. 2), both OS and DFS in the NSRH group were similar to those in the TRH group (with NSRH as a reference, HR of OS 1.79, 95% CI: 0.64-5.02, $P = 0.268$; HR of DFS 1.50, 95% CI: 0.72-3.11, $P = 0.280$), after adjusting for the following variables: age, body mass index, gravidity, parity, surgical years, FIGO stage, neoadjuvant chemotherapy, surgical approach, and postoperative adjuvant therapy.

DISCUSSION

Our report supports the superior bladder functions in the NSRH patients, who had similar surgical and survival outcomes as the non-NSRH patients. Despite ample evidence of favorable urinary, sexual, and anorectal outcomes for patients with cervical cancer after NSRH,[13–15] it has not yet become a widely applied procedure among gynecologic surgeons, mainly because of the difficulty of recognizing and protecting nerve fibers in the operation.[16] Although the Querleu-Morrow classification[8,9] provides a reproducible anatomic terminology for NSRH, it was not designed to impose a universal surgical technique. The description of surgical procedures and energy instruments for NSRH and TRH differ considerably among different studies,[17,18] suggesting that different surgeons are performing operations without standardized techniques and processes, even though the autonomic nerves form well-defined anatomic boundaries for NSRH. The success determining factors of nerve-sparing, such as FIGO stage or pathologic subtype, were little known.[5,19,20] Thus far, NSRH still lacks standardization in surgical techniques and procedures, resulting in the large heterogeneity among different studies, which makes it difficult to compare the results of NSRH and TRH.[21] In our study, all the surgeries were performed by a single surgeon, which probably could decrease the bias from surgical techniques. However, the learning curve of surgical experiences would interfere with the interpretation of survival outcomes.

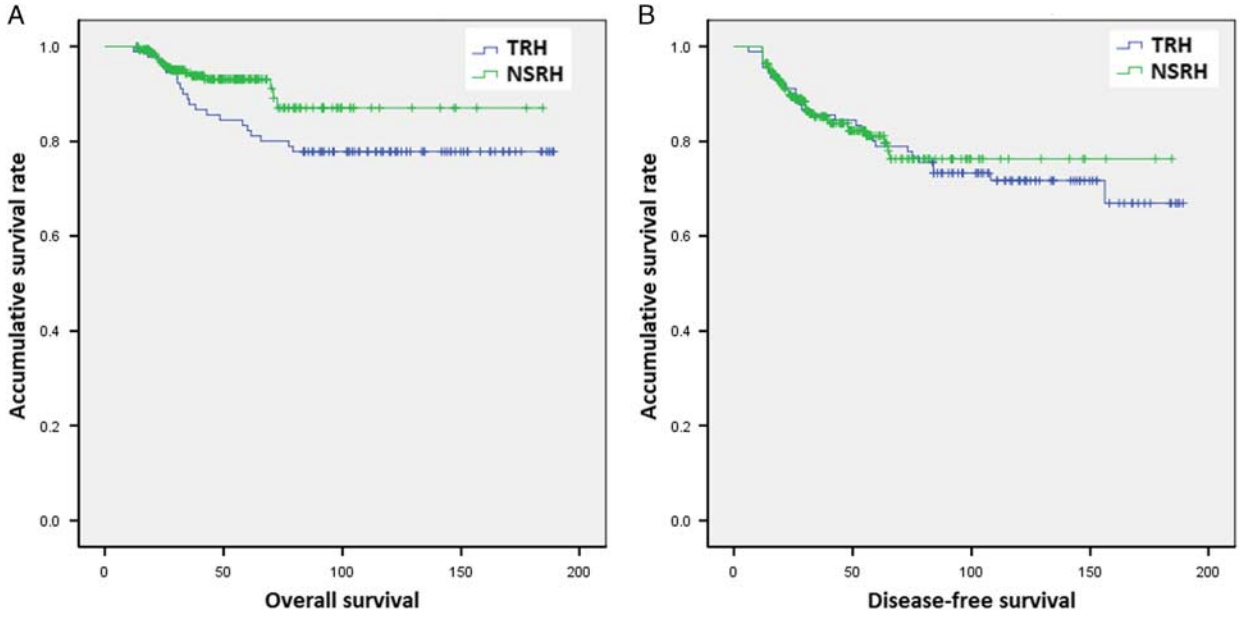

FIGURE 1. Overall survival and disease-free survival curves of the TRH and NSRH patients described by Kaplan-Meier tests. A, Overall survival curve. B, Disease-free survival curve. NSRH indicates nerve-sparing radical hysterectomy; TRH, traditional radical hysterectomy.

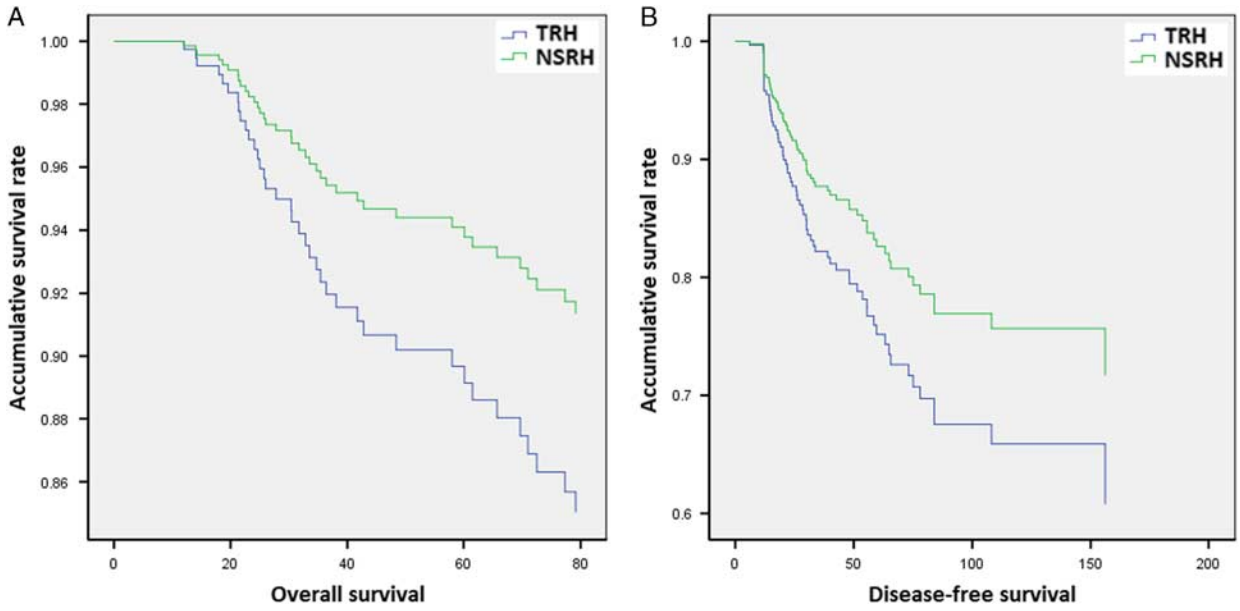

FIGURE 2. Overall survival and disease-free survival curves of the TRH and NSRH patients described by multivariate analysis. A, Overall survival curve. B, Disease-free survival curve. NSRH indicates nerve-sparing radical hysterectomy; TRH, traditional radical hysterectomy.

The definite pathologic outcomes in our report had given enough evidence of the surgical scope of RH procedures. Few studies had reported the comparison of surgical scope between NSRH and TRH. One of the concerns with regard to NSRH is the possibility that, by taking measures to preserve the nerves, NSRH may restrict the scope of the operation and lead to insufficient treatment, which will eventually have effects on patients' survival.[22] This problem is hard to determine even for skilled surgeons who are familiar with the pelvic anatomy and the procedure of RH. Some authors found NSRH resulted in a shorter length of the resected vagina.[23] A strict randomized study with a longer follow-up with regard to survival outcomes would indirectly explain the equivalence of surgical scope. More careful evaluation and pathologic examination of the uterine specimen would also probably provide valuable perspectives for such an issue. In our study, the mean number of LNs was 43.61 and 40.12 in the NSRH group and RH group, respectively, showing no significant difference ($P > 0.05$). In addition, Bogani et al[24] even reported more LNs in NSRH than in TRH. However, the numbers of harvested LNs did not offer enough evidence sustaining the extent of RH. A full-description of pathology by independent pathologists, including the length and/or width of the parametrium, uterosacral ligaments, and vagina, would provide more substantial verification of surgical scope in a prospective study.

Overall, our data suggested NSRH had favorable surgical outcomes. Compared with TRH, NSRH was reported to have no significant differences in blood loss, in the proportion of patients who required a blood transfusion, or in severe complications during the operation.[23,25–27] The operating time exhibited differences among many studies, which were considered to be related to differences in the surgeons' experiences, techniques, and surgical procedures for NSRH. In our study, there was no statistically significant difference observed in the mean operating time or in the complications during the operation, whereas the mean blood loss during operation in the TRH group was significantly greater than that in the NSRH group. In previous studies, the incidence of postoperative complications in NSRH was reported to be lower than that in TRH, perhaps because of the protection of bladder and rectal functions.[28] Consistent with previous studies, our results showed that the mean postoperative stay of the TRH group was significantly longer than that of the NSRH group, suggesting that NSRH was generally associated with a shorter postoperative stay, which might be associated with less bladder dysfunction and fewer postoperative complications.[28,29]

Our data suggested that NSRH had favorable oncologic outcomes. As NSRH has not been connected with a reduced scope of operation, theoretically, patients who received NSRH will not have worse survival than those who received TRH. Although it is proposed that patients with cervical cancer who received NSRH might have an increased rate of recurrence because of the perineural invasiveness of residual tumor tissues that may have attached to the reserved nerve fibers, this concern had little evidence to support to date. Almost no report had reported that NSRH was associated with worse survival, even for locally advanced stage cervical cancer.[30,31] A randomized controlled trial reported that patients who underwent NSRH had no difference in the 10-year rate of DFS compared with that of patients who underwent TRH.[32] Systematic review and meta-analysis revealed that the local and overall recurrence rate data did not show significant differences between NSRH and TRH procedures.[33,34] The results of our study showed that both OS and DFS in the NSRH group were similar to those in the TRH group, after adjusting for preoperative factors, operative approaches, and adjuvant therapy. These findings support the safety and survival benefits of NSRH. However, according to the study of Basaran et al,[5] the evidence addressing the oncologic safety of NSRH over that of conventional RH in cervical cancer is neither adequate nor statistically relevant. The current knowledge on oncologic outcomes may not be insufficient to assess the equality of survival between NSRH and TRH.

As a retrospective cohort study, the main limitations of our study were the recall bias and selection bias. A lack of consistent criteria for pathologic examinations is an important confounding factor in our study. The limited number of cases of TRH might have influenced the results and restricted the

extrapolation of related conclusions. We did not apply urodynamic analysis with multiparameters for the comparison of urinary outcomes, which would hinder the extrapolation of our findings. Although the LACC trial[35] and another epidemiological study[36] suggested minimally invasive surgeries could cause significant deteriorative survival outcomes, we could not support meaningful evidence in the field of NSRH. First, this is a cohort study in a single center; second, almost all the NSRH procedures were performed in recent periods and in laparoscopic routs. The learning curves of a single physician would significantly distract the stratification analysis.

CONCLUSION

In conclusion, the results of this study showed that NSRH might be a promising surgical approach for early-stage cervical cancer patients without sacrificing oncologic safety. The NSRH procedure should be standardized to create uniform assessment criteria. More well-designed and large-scale multicenter clinical trials are needed to evaluate the efficacy and oncologic safety of NSRH before it is recommended as a standard approach for cervical cancer treatment.

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