

Original Article

A prospective study of nerve-sparing radical hysterectomy for uterine cervical carcinoma in Taiwan

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Abstract

Objective: Surgical therapy for cervical carcinoma carries a significant risk of functional impairment to the bladder. This study evaluates the feasibility and complications of nerve-sparing radical hysterectomy (NRH) in Taiwan.

Methods: Between March 2010 and March 2011, consecutive patients diagnosed with early stage cervical cancer (FIGO stage Ia2 to Ib1) and tumor size < 3 cm were recruited prospectively to undergo NRH or conventional radical hysterectomy (RH). Patients with histories of urinary stress incontinence or bladder dysfunction disease were excluded. A modified Tokyo nerve-sparing radical hysterectomy was performed.

Results: A total of 30 patients were enrolled. Among these, 18 patients underwent NRH with successful bilaterally nerve-sparing procedures in 15 cases (83%), unilaterally nerve-sparing procedures in 2 cases (11%), and a failure in 1 case (6%). The indwelling catheter was removed on postoperative day 6. The mean \pm SD duration from operation to spontaneous voiding was 6.8 ± 1.5 days for women who underwent NRH; the corresponding duration for women who underwent RH or failed NRH was 20.6 ± 3 days. None of the patients who underwent NRH required intermittent catheterization. All 12 patients who underwent RH needed self-catheterization after discharge. There was a significant reduction in the incidence of postoperative self-catheterization ($p < 0.01$) and bladder dysfunction ($p < 0.006$). Average satisfaction score analyzed by the Likert-scale questionnaire was 4.5 for the NRH group and 1.9 for RH group ($p < 0.0001$).

Conclusions: We concluded that the new technique of NRH can reduce postoperative bladder dysfunctions.

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Keywords: nerve-sparing radical hysterectomy; cervical carcinoma; bladder function; Taiwan

Introduction

In 1969, Hanley first proposed that radical hysterectomy (RH) might have an effect on bladder function [1]. Several large epidemiological studies have addressed the relationship between RH, urinary incontinence and bladder dysfunction

[2–4]. The incidence of lower urinary tract dysfunction after RH has been reported to be 12%–40% [5,6]. This complication is thought to be caused by damage to the pelvic nerve plexus [7]. The severity of bladder dysfunction after RH appeared to be related to the extent of the procedure. Benedetti-Panici et al have suggested that the incidence of lower urinary tract dysfunction is related to the extent of resection of the rectovaginal ligaments and vaginal tissue [8]. Resection of these tissues would interrupt the autonomic fibers innervating the bladder, as would the resection of the parametrium, cardinal ligament, and utero-sacral ligament [9].

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By contrast, any operative procedures for invasive cancers should allow sufficient radicality for an optimal outcome. Extensive pelvic dissection would mean greater neurovascular disruption with increased urinary tract complications. Hence, achieving maximal therapeutic benefit in the surgical treatment of invasive cervical carcinoma, with minimal complications, remains a challenge for gynecologic oncologists.

Several studies have demonstrated a new nerve-sparing surgical technique that permits preservation of the hypogastric and splenic nerves during radical hysterectomy, with fewer lower urinary tract complications [10–19]. These studies have shown the feasibility of a nerve-sparing radical hysterectomy (NRH) and have documented fewer complications as compared to the conventional procedure for RH, in which the pelvic nerves are not preserved. Moreover, NRH does not appear to influence the disease-free survival of invasive cervical cancer [20,21].

Cervical carcinoma is still one of the most important female cancers in Taiwan. With the introduction of the universal Papanicolaou cervical smear screening program, early stage cervical carcinomas are increasingly detected at an earlier age. Surgical therapy is indicated in these young patients with early stage cervical cancer, as surgery could help preserve sexual function. However, traditional RH may induce lower urinary tract dysfunction and urinary incontinence, and affect the quality of life. NRH was developed as an alternative to traditional RH or modified RH. NRH can reduce complications associated with traditional RH and may hold a place in the therapeutic choices for treating early stage cervical carcinoma in Taiwan. Unfortunately, there is no data regarding this new technique and its related lower urinary tract morbidity in Taiwan.

This study was a prospective preliminary study to evaluate the effect of nerve-sparing RH versus traditional RH on lower urinary tract function on Taiwanese patients with early cervical carcinoma.

Materials and methods

This study was conducted prospectively in patients with early uterine cervical carcinoma (2009 FIGO staging Ia2 to Ib1) who received either nerve-sparing RH or non nerve-sparing RH at a tertiary referral hospital. Patients receiving either types of hysterectomy gave informed consent. This study was approved by the Ethics Committee of Chung Shan Medical University Hospital. Other eligibility criteria consist of a Karnofsky performance status index of $\geq 80\%$ an age of ≤ 70 years. Exclusion criteria included a history of voiding dysfunction, previous pelvic radiotherapy, previous pelvic reconstruction, and brain/spinal cord diseases. In addition, patients with pathologically confirmed metastasis to the lymph nodes were excluded.

Preoperatively, a detailed medical review, physical examination, routine laboratory tests, tumor markers, chest X ray, and contrast-enhanced computerized tomography of the abdomen and pelvis were carried out. During the operation, any enlarged or suspicious nodes were excised and sent for

histopathology. All operations were performed by board-certified gynecological oncology surgeons at the Chung Shan Medical University Hospital. The classification of hysterectomy was based on the new definition by Querleu and Morrow [22]. A conventional type C2 hysterectomy was performed on patients undergoing RH. A nerve-sparing type C1 RH was performed on patients undergoing NRH. In the type C1 RH, the pelvic splanchnic and hypogastric nerves were preserved during transection of the cardinal ligament as described by Possover and Trimbois [9,20]. In addition, efforts were made to preserve the caudal neural portion of the cardinal ligament. Moreover, the pelvic splanchnic nerve was preserved during lateral dissection of the hypogastric fascia. During the process of cardinal ligament complex dissection, the lymphatic tissue adjacent to the cardinal ligament was bluntly excised to facilitate the identification and resection of any associated vascular pedicle. The pelvic splanchnic nerves were preserved by freeing anteriorly the neural part of the cardinal ligament of fat and lymphatic tissue and dividing the vascular part of the cardinal ligament laterally, without transecting the middle rectal vessels.

Indwelling catheters were placed at the time of surgery, and were removed on postoperative day 6 after bladder training for 2 days. After the removal of the catheter, the voided volumes were recorded and the post-voiding residual urine volumes were measured by a computerized bladder sonography scan. Intermittent catheterization was performed if post-void residual urine volume exceeded 200 mL. Lower urinary tract function is considered preserved when residual urine volume is ≤ 50 mL, or if residual urine volume is $\leq 30\%$ of the total voided volume.

The lengths of operations, blood loss, indwelling catheter retention days, the need for postoperative intermittent catheterization, the duration of postoperative stay, operation-related complications, and immediate bladder function review at postoperative day 90, were compared in patients from the two groups. A urodynamic study was performed before surgery and 3 months after the operation. All women who underwent RH or NRH were asked to complete a questionnaire regarding symptoms of abnormal storage, abnormal voiding, and abnormal sensation, including urge incontinence, diurnal frequency, nocturia, nocturnal enuresis, strain to void, incomplete emptying, hesitancy, poor stream, post-micturition dribble, dysuria, urgency, suprapubic fullness, and unnoticed urinary incontinence. All patients completed the Likert-scale questionnaires about urinary symptoms at 3 months after RH or NRH. Patients were to answer a satisfaction questionnaire using a 5-point Likert scale, where: score 5 = very satisfied, score 4 = satisfied, score 3 = neutral, score 2 = dissatisfied and score 1 = very dissatisfied.

Statistical analysis: The results are expressed as means \pm standard deviation (SD) or percentage (%), as appropriate. We checked for normality of distribution of all variables with continuous data. The Mann-Whitney test was used to assess the difference in medians between NRH and RH because of non-normality of distribution SPSS17.0 statistical package (SPSS inc. CHICAGO, United States). Categorical data used

the Fisher's exact test. The SPSS17.0 statistical package was used for all analyses. All tests were two-tail and $p < 0.05$ was considered statistically significant.

Results

Between March 2010 and March 2011, 30 patients with early stage cervical cancer were recruited prospectively at a tertiary referral medical center to receive NRH or RH. Of these patients, 28 were stage FIGO Ib1 and two patients were stage Ia2. Of these patients, 18 underwent NRH and 12 underwent RH. The patients were aged from 32 to 61 years (mean age 43.2 years). Data analyzed on the characteristics between patients undergoing the two types of procedures included age, FIGO stage, tumor size, operation time, blood loss, and complications (Table 1). Of these parameters, there was no significant difference between the two groups.

Of the 18 patients who underwent NRH, the pelvic nerve was successfully spared bilaterally in only 15 patients (83%), and unilaterally in two patients (11%). In one patient, the pelvic nerves could not be preserved due to surgical constraints; namely, the presence of surgically difficult enlarged and fixed pelvic lymph nodes. Of the NRH group, 12/15 patients with successful bilateral nerve-sparing operations had spontaneous self-voiding on postoperative day 6. The remaining three cases self-voided successfully on days 7, 9, and 10, respectively. Of the two patients with successful unilateral nerve preservation, one had spontaneous voiding without urine retention on day 6 and the other patient on day 10. None of above patients required further intermittent self-catheterization. One patient who had failed bilateral nerve preservation, was discharged with intermittent self-catheterization. She resumed normal spontaneous voiding function on postoperative day 23. All the 12 patients who underwent RH, were discharged with intermittent self-catheterization. Among them, one patient resumed spontaneous self voiding on day 11, three patients on day 15, five

patients on day 21, and three patients on day 25. There was a significant reduction in the incidence of postoperative self-catheterization after NRH comparing with RH ($p < 0.01$). Catheter-associated urinary tract infection was observed in five cases (42%). These patients were treated with oral antibiotics for 14 days. In the 2 weeks after surgery, 41.7% of RH patients experienced a urinary tract infection compared with 5.6% of NRH patients ($p = 0.026$). The mean time to spontaneous self-voiding was 6.8 ± 1.5 days (range 5–12 days) in patients whose pelvic nerves were spared bilaterally, 8.0 ± 1.4 days (range 6–8 days) in those spared unilaterally, and 20.6 ± 3.0 days (range 9–30 days) in those whose nerves were not spared or failed to be spared (Table 2). Taken altogether, there was a significant reduction in the incidence of postoperative self-catheterization and a reduction in the period of bladder function recovery in those whose pelvic nerves were preserved versus those whose were not. Six months postoperatively, urinary complications such as nocturia, urgency and frequency, postoperative urine retention, dysuria, and voiding difficulty were significantly different (Table 3).

Personal satisfaction analysis revealed an increase in personal satisfaction score from 1.9 in the RH group to 4.5 in the NRH group ($p < 0.0001$).

None of the patients in either group presented pathologically positive surgical margins or positive parametrium. After the median follow-up of 12 months (range 9–16 months), all these cases were free of disease.

Discussion

Cervical carcinoma is the leading cause of gynecologic cancer death in women worldwide. In general, early invasive carcinoma of the cervix is treated with RH or radiation [23].

It has been recognized that RH is associated with varying degrees of complications, especially complications related to the urinary tract. Overall, bladder dysfunction is the most frequent postoperative complication and has been reported to be within the range of 10–50% [24–27]. In one large case series, Torres-Lobaton et al indicated that 21% of patients who have had a RH, have some degree of bladder dysfunction up to 3 months postoperatively [28]. In addition, Chen et al reported significant impairments in bladder sensation, bladder capacity, bladder compliance, detrusor function, reduction of maximal urethral pressure and maximal urethral closure pressure, and a decrease of the pressure transmission ratio in up to 53.1% of patients who have undergone RH [6].

RH would traditionally cause trauma to the bladder or to its surrounding supporting tissues that contain pelvic nerve fibers,

Table 1
Comparison of characteristics between patients undergoing RH with or without nerve-sparing techniques.

Characteristics	NRH (n = 18)	RH (n = 12)
Age (y)	42 (range, 32–54)	45 (range, 38–61)
Histology		
Squamous cell carcinoma	12	9
Adenocarcinoma	6	3
Operative time (min)	168 (range, 132–255)	152 (range, 116–223)
Blood loss (mL)	162 (range, 50–550)	205 (range, 50–750)
Hospital stay (days)	8.5 (range, 7–14)	14.7 (range, 8–18)
Tumor size (cm)	1.7	2.8
Parametrial involvement	0	0
Positive pelvic lymph node	1	3
Positive paraaortic lymph node	0	0
Positive section margin	0	0
Operation-related complications		
Bladder injuring	0	0
Fistula/ureter injuring	0	0
GI injury	0	0
Thromboembolism	0	0

Table 2
Mean duration of spontaneous voiding without urine retention.

	n	Days
NRH	18	
Bilateral success	15	6.8 ± 1.5
Unilateral success*	2	8.0 ± 1.4
RH/Failed bilateral	12/1	20.6 ± 3.0

*Data are presented as mean \pm standard deviation.

Table 3
Comparison of postoperative urinary symptoms and parameters between patients undergoing RH with or without nerve-sparing techniques.

Characteristics	NRH (n = 18)*	RH (n = 12)*	p
Duration of spontaneous voiding (days)	6.9 ± 1.5	20.6 ± 3.0	< 0.0001
Number of catheterizations (per woman)	0 (0%)	21.4 ± 9	< 0.01
Re-inserting indwelling catheter	0 (0%)	1 (8.3%)	0.4
Frequency/urgency symptoms	2 (11.1%)	9 (75.0%)	0.001
Nocturia	1 (5.6%)	9 (75.0%)	0.0001
Dysuria	1 (5.6%)	7 (58.3%)	0.003
Voiding difficulty	1 (5.6%)	8 (66.7%)	0.0006
Urinary retention	0 (0%)	7 (58.3%)	0.0004
Incontinence	0 (0%)	5 (41.7%)	0.006
Personal satisfaction scoring	4.5 ± 0.9	1.9 ± 0.5	< 0.0001

*Data are presented as n (%) and mean ± standard deviation.

such as the cardinal ligament and uterosacral ligament. Hence, transection of these tissues would also injure the autonomic nerves, both sympathetic and parasympathetic, extending from the inferior hypogastric plexus innervating the bladder [8]. By immunohistochemistry, Butler-Manuel et al reported that significantly more autonomic nerves are transected in the more lateral division of the uterine supporting ligaments during a RH as compared to a simple hysterectomy [8].

In order to reduce the morbidity of bladder dysfunction, various surgical strategies have been developed to spare the nervous component of the pelvic autonomic plexus, including the inferior segment of the cardinal ligament and the terminal bundle in the uterosacral and pubocervicovesical ligaments. The preservation of the pelvic autonomic nerves in RH can be achieved by separating the lateral and cardinal ligament between the deep uterine vein and the middle rectal vessel and resecting only the cardinal ligament [29]. This nerve sparing technique makes for a rapid recovery of lower urinary tract function. In the ensuing years, NRH has been modified by Kobayashi et al and many others [9–22]. These studies have shown the feasibility of a nerve-sparing radical pelvic surgery with fewer lower urinary tract complications.

The radicality of the operative procedure is critical in complete tumor resection. Anatomical studies demonstrated that the pelvic autonomic nerve plexus, namely, the hypogastric nerve and splanchnic nerves, lies within a loose tissue sheath underneath the ureter, lateral to the sacro-uterine ligaments, and within the dorsomedial side of the neural part of the cardinal ligament at the bottom of the pararectal space [30]. In addition, Kato et al revealed that fewer nerves were found in the cardinal ligament than in the uterosacral ligament [31]. Hence, Kato et al proposed that a complete dissection of the cardinal ligament be performed during nerve-sparing hysterectomy to allow for radicality. We concur in our study, that the removal of the anterior cardinal ligament, with preservation of the caudal neural portion, would help preserve bladder innervation and lower urinary tract function, without compromising the radicality of the procedure. In addition, our results also indicated a reduction in recovery time of lower urinary tract function when pelvic nerves were spared.

Interestingly, there was only a slight increase in the mean time to full voiding function when comparing patients who underwent unilateral pelvic nerve preservation versus those whose pelvic nerves were bilaterally preserved. Although this study sample size is small, it echoes several studies that have found similar results, showing that unilateral pelvic nerve damage does not result in the complete denervation of the lower urinary tract and that any remaining innervation may compensate for the contralateral denervation [14,32]. In conclusion, we suggest that all efforts should be made to spare the contralateral neurovascular bundles leading to the bladder, when success cannot be achieved on one side in order to preserve lower urinary tract function.

Our satisfaction questionnaire revealed an increase of troublesome disorders of the lower urinary tract function from 12% in the NRH group to 55% in the RH group. The incidence of catheter-associated urinary tract infection after surgery was significantly less in the RH group. Taken together, these results appear to show that nerve sparing RH improves the quality of life by reducing associated lower urinary tract complications.

In conclusion, our study suggests that nerve-sparing RH significantly reduces the incidence and severity of lower urinary tract dysfunctions. However, we did not look at whether subsequent radiation therapy and chemotherapy have any impact on the recovery of lower urinary tract function. A specifically designed prospective trial with larger patient numbers is needed to answer this question.

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