

# Effectiveness and Long-term Outcomes of Nerve-Sparing Radical Hysterectomy for Cervical Cancer

Akihito Yamamoto, Seiryu Kamoi, Mariko Ikeda,  
Takashi Yamada, Koichi Yoneyama and Toshiyuki Takeshita

Department of Obstetrics and Gynecology, Nippon Medical School, Tokyo, Japan

**Background:** Radical hysterectomy (RH) is a type of radical surgery for cervical cancer. Urinary dysfunction due to RH worsens postoperative quality of life of patients with cervical cancer. Nerve-sparing RH (NSRH) technique has been used as an effective means to conserve urinary function. However, few reports have examined long-term outcomes after NSRH. This study describes the details and long-term outcomes of our nerve-sparing technique.

**Methods:** Sixty-one patients underwent radical hysterectomy in a 5-year period during which nerve-sparing technique was introduced; of these, 31 patients underwent NSRH and 30 underwent conventional RH. We retrospectively examined their medical records and compared postoperative urinary function and treatment outcomes between these two groups.

**Results:** The median time required for urinary residual volume to fall to  $\leq 50$  mL after removal of the urinary catheter was 6 days (range, 2-20 days) in the NSRH group and 13.5 days (range, 3-46 days) in the RH group. The results were significantly better in the NSRH group ( $p < 0.05$ ). The mean follow-up period was 2456.3 days (range, 48-4,213 days). Analysis of curability revealed no significant difference between the two groups in local recurrence or long-term survival rates. The 5-year survival rate was 0.861 in the NSRH group and 0.782 in the RH group; the 10-year survival rate was 0.861 in the NSRH group and 0.679 in the RH group.

**Conclusions:** NSRH significantly improved postoperative urinary function without worsening local recurrence rates or long-term outcomes. (J Nippon Med Sch 2021; 88: 386–397)

**Key words:** uterine cervical neoplasms, radical hysterectomy, urination disorders, prognosis, organ-sparing treatments

## Introduction

Radical hysterectomy (RH), a surgical treatment for cervical cancer, includes removal of the uterus, as well as the parametrium and upper vagina, and also includes bilateral pelvic lymphadenectomy. This surgical approach, which can cure cervical cancer, was first described by Wertheim more than 100 years ago, subsequently modified by Okabayashi in 1921, and repopularized by Meigs in the 1950s and by Piver in the 1970s<sup>1-4</sup>. In Japan, Okabayashi-style RH has been used as optimal therapy for International Federation of Gynecology and Obstetrics (FIGO) stage Ib-IIb cervical cancer. Although RH has

good therapeutic efficacy, it may result in damage to the pelvic autonomic nervous system that causes bladder dysfunction as a long-term postoperative complication<sup>5-8</sup>. The incidence of postoperative bladder dysfunction has been reported to be 70%-85%<sup>9</sup>. The pelvic splanchnic nerve is the pathway for neural control of the rectum, bladder, and sexual function. The hypogastric nerve is a sympathetic nerve fiber involved in relaxation of the bladder detrusor and contraction of the urethral sphincter. To maintain postoperative bladder function, these neural networks should be preserved, to the extent possible, without sacrificing the benefits of surgery.

Correspondence to Akihito Yamamoto, Department of Obstetrics and Gynecology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan

E-mail: s7095@nms.ac.jp

[https://doi.org/10.1272/jnms.JNMS.2021\\_88-503](https://doi.org/10.1272/jnms.JNMS.2021_88-503)

Journal Website (<https://www.nms.ac.jp/sh/jnms/>)

Cervical cancer is one of the most important cancers affecting women. Age of onset is lower than that of other cancers, and maintaining postoperative quality of life is a critical issue. Achieving maximum therapeutic effect with minimal invasiveness in the surgical treatment of invasive cervical cancer has always been a challenge for gynecological oncologists. In 1961, Kobayashi proposed a surgical procedure to preserve the pelvic plexus and its bladder branch<sup>10</sup>. Nerve-sparing radical hysterectomy (NSRH) was later improved and is now widely accepted as a procedure that can maintain postoperative urinary function<sup>11-22</sup>. However, the anatomical structures of the pelvic autonomic nerves have not been completely described, and it is extremely difficult to clearly visualize these structures in all patients. Therefore, to completely preserve postoperative urinary function, surgeons should familiarize themselves with the nerve fiber tracts, which cannot be clearly seen, and spare them to the greatest extent possible.

We have improved these surgical procedures and established nerve-sparing techniques. The most important surgical procedure we perform is to completely dissect and preserve nerve fibers around the pelvic plexus, from the paracolpium outward, as described below. In addition, although results after nerve-sparing surgery are frequently reported in the short-term, reports of outcomes after more than 5 years are rare. In this study, we report long-term outcomes of nerve-sparing surgery.

## Materials and Methods

### Patient Selection

The patient enrollment period was 5 years—from March 2007 through February 2012—which included the time before and after modification of the surgical procedure. The period until February 2020 was established as the prognostic study period, and data were extracted from medical records. This patient enrollment period was the operative transition period; most patients underwent RH during the first half of the study, and most underwent NSRH during the second half. All consecutive patients who received a diagnosis of cervical cancer during this period and underwent RH at our hospital were included in this study. The exclusion criteria included preoperative voiding dysfunction, previous pelvic radiation therapy, previous pelvic reconstruction surgery, and history of cerebrospinal disease. Before surgery, all patients underwent a detailed medical review, physical examination, serum biochemical examination, analysis of tumor markers, and chest radiography, abdominal and pelvic

computed tomography, and pelvic magnetic resonance imaging studies. Tumor tissue resected during surgery was sent for histopathological examination, and the stage of tumor progression was confirmed by microscopy in all cases. All surgeries were performed by gynecological oncologists.

This study was approved by the ethics committee at our institution (No. 30-01-1068). All patients received a written explanation of and provided consent for the surgery performed. This study was conducted retrospectively by examining the patients' medical records. The data analyzed were age, body mass index, histopathological type, staging, operation time, intraoperative blood loss, operation-related complications, postoperative urination, number of days to establish urinary function, presence or absence of local recurrence, disease-free survival, and overall survival. Local recurrence was defined as any recurrence in the lesser pelvis, including the vagina and pelvic lymph nodes.

## Surgical Techniques

### RH

Even when using conventional methods, some consideration is given to avoiding damage to the autonomic nerve, but this is not sufficient. Nerve injury due to amputation of the cardinal ligament is considered the leading cause of urination disorders. The nerve-sparing method that we have conventionally performed involves one additional step in which cutting of the cardinal ligament was moved to the uterine side—by cutting the blood vessel part of the cardinal ligament and then lifting the end to the uterine side.

### NSRH

The key points of the nerve-sparing procedure we developed and performed are described below.

1. The ureter and hypogastric nerve are detached from the dorsal pelvic peritoneum, marked with tape, and kept outside the body. The pararectal space is developed by advancing the detachment to the dorsal side.
2. Detachment of the hypogastric nerve is advanced caudally to the uterosacral ligament. Beyond this ligament, the hypogastric nerve is joined to the pelvic plexus. To avoid damage to the pelvic plexus, we do not advance the dissection beyond it.
3. The uterine artery is cut from the internal iliac artery bifurcation and isolated toward the uterus. Sufficient isolation beyond the intersection with the ureter is then performed.
4. The anterior layer of the vesicouterine ligament is

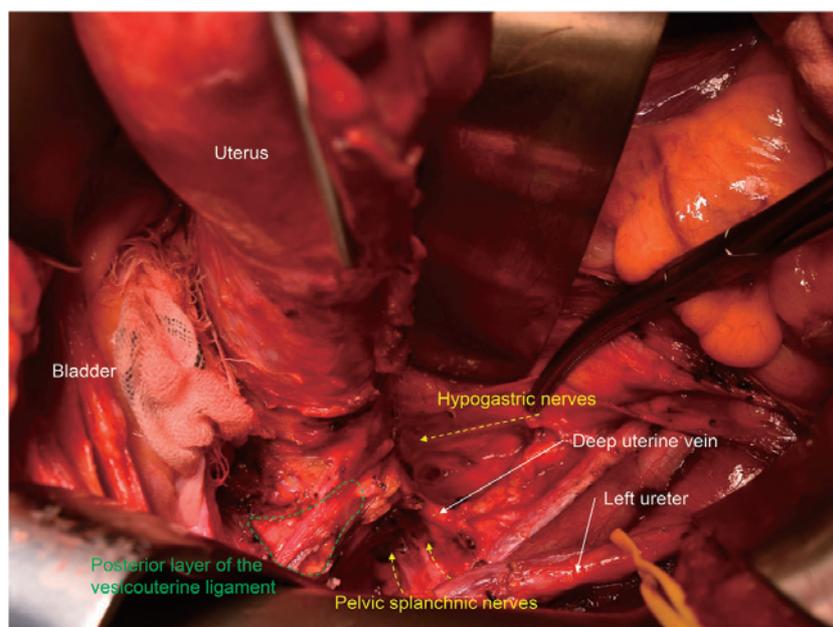


Fig. 1 The point at which resection of the anterior layer of the vesicouterine ligament was completed.

The left ureter was moved completely and laterally.

excised and the ureter is moved outward. It is excised from the entrance of the ureter tunnel, and instead of being cut all at once, it is divided into small parts of approximately several millimeters each, as if the roof of the tunnel is broken down gradually. Because blood vessels are abundant in the vesicouterine ligament, severe bleeding interferes with subsequent detailed operations; thus, these resections are performed carefully. The anterior layer of the vesicouterine ligament is unfolded, and the ureter moved outward up to the site where the vesicoureteral junction is completely exposed (Fig. 1). When the ureter is sufficiently removed, the ureteral insertion angle into the bladder is observed horizontally. Sufficient separation between the back of the bladder and anterior vaginal wall is necessary for subsequent development of the paravaginal space. If the bladder detaches in a shallow manner, the paravaginal tissue including the autonomic nervous bladder branch is not visible during subsequent procedures.

5. The posterior layer of the vesicouterine ligament is carefully separated and ligated in small portions. During this procedure, a venous plexus is observed between the bladder and the cervix. In our experience, two or three bladder veins are usually found, which are cut from the deep uterine veins (Fig. 2). The posterior layer of the vesicouterine ligament and paracolpium, including the autonomic bladder branch, is continuous and borderless. Therefore, damage to the bladder branch must be pre-

vented. The point of processing is, first, to exfoliate the tissue from the position on the uterine side from the middle part of the ligament and, second, to finish exfoliation at the depth that the bladder veins are cut and separated from the deep uterine vein. A wide incision in the caudal and dorsal layers of the posterior vesicouterine ligament would damage the bladder branch of the pelvic plexus.

6. A portion of the cardinal ligament vessel, which is well-exposed after lymphadenectomy, is cut distally and lifted toward the uterus. Because the bladder veins that meet from the anterior have already been cut, the deep uterine vein can be easily lifted to a shallow position. The pelvic nerve plexus is located inside and dorsal to the venous plexus (Fig. 3).

7. The nerve plexus is formed where the autonomic nerves exit S2-S4 and the hypogastric nerve exits the cranial side and is joined at the site of the cardinal ligament. Branches of the nerve are then advanced toward the uterus and bladder, from the plexus. A procedure is performed to protect this bladder branch passing through the lateral portion of the paracolpium that was exposed in the previous step. The outer portion of the paracolpium is detached from the vagina toward the paravesical space, taking care not to damage the vascular plexus inside the paracolpium. This is marked and protected by using tape and moving it outward.

8. The hypogastric nerve and pelvic splanchnic nerve

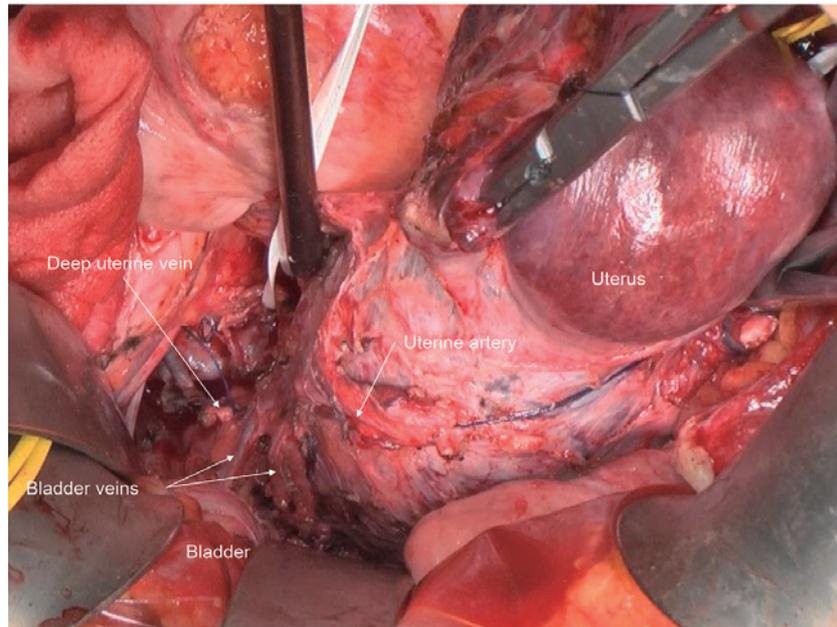


Fig. 2 A photograph showing resection of the posterior layer of the vesicouterine ligament. Several bladder veins were present in the ligament.

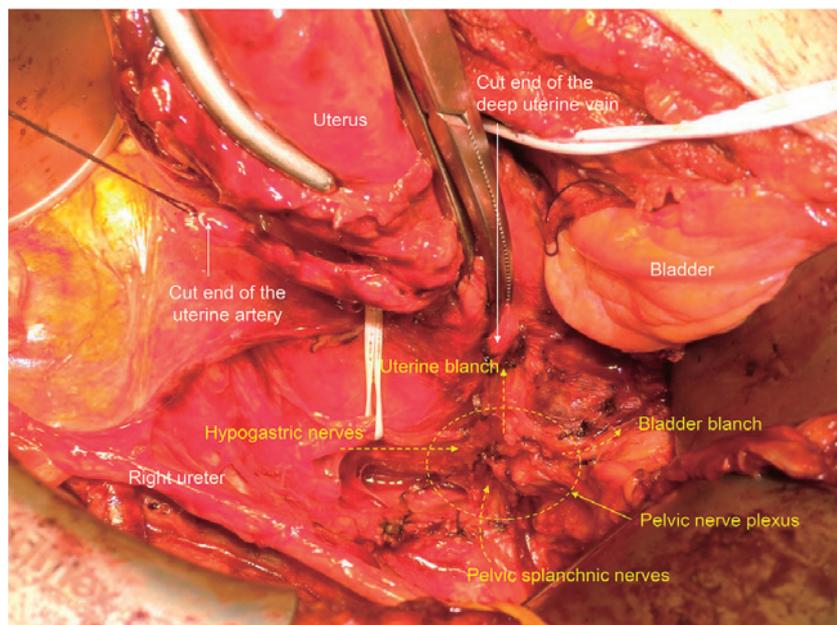


Fig. 3 The deep uterine vein was cut distally and lifted toward the uterus. The pelvic nerve plexus was located inside and dorsal to the venous plexus. Intersections formed by the hypogastric nerve and pelvic splanchnic nerve, which merged around the pelvic plexus, and those of the uterine and bladder branches—ie, the branching nerves—were confirmed.

are crossed; these nerves, which are located around the pelvic plexus, and the branching nerves (i.e., the uterine branch and bladder branch), are confirmed. Only the uterine branch is cut from this cross, and the pelvic plexus is peeled outward with the cut site as a starting point (Fig. 4). After careful dissection of the pelvic plexus

toward the dorsal side, the paravesical space and pararectal space are made continuous as the lateral vaginal space, and the pelvic plexus is laterally displaced in a plate-like form (Fig. 5). This plate-like tissue, including nerve fibers completely separated from the uterus and parametrium, assumes a T-shape without the uterine

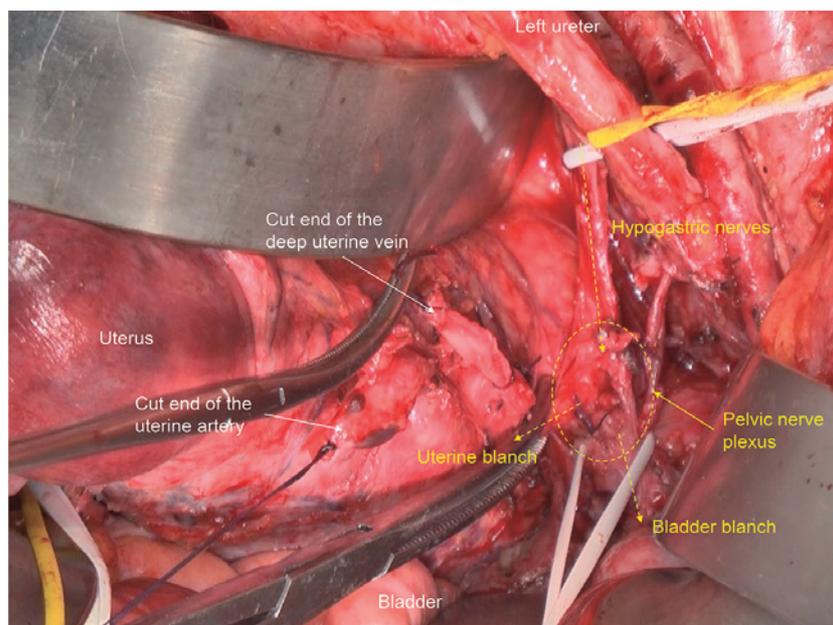


Fig. 4 Only the uterine branch was cut from the intersection, and the pelvic plexus was peeled outward, with the cut site as the starting point.

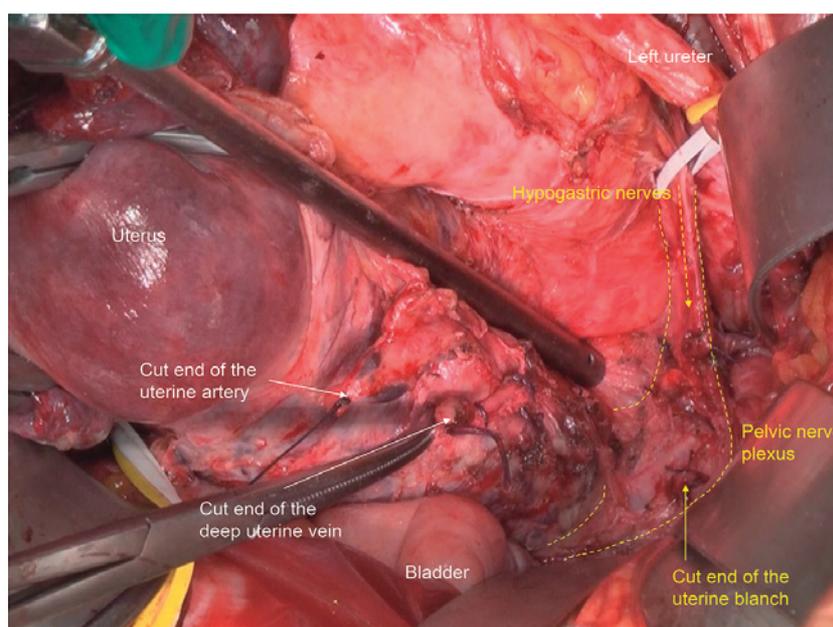


Fig. 5 The paravesical space and pararectal space were continuous as the lateral vaginal space, and the pelvic nerve plexus was laterally displaced in a plate-like form.

branch from the cross (Fig. 6).

9. The rectovaginal septum is developed, and the rectum is detached from the posterior wall of the vagina. After resection of the uterosacral ligament and the remaining paracolpium, the uterus is connected only to the vagina. The vagina is cut to the required length, depending on the degree of tumor invasion. In accordance with the previous step, the pelvic plexus and its branches are

completely outside the surgical field, and thus undamaged.

The difference between our improved surgical technique and the conventional method is that the pelvic plexus and bladder branch are completely outwardly separated. A crucial goal of the procedure is to maximize protection of nerves by ensuring nerve plexus detachment, which has been unpopular because of the severe

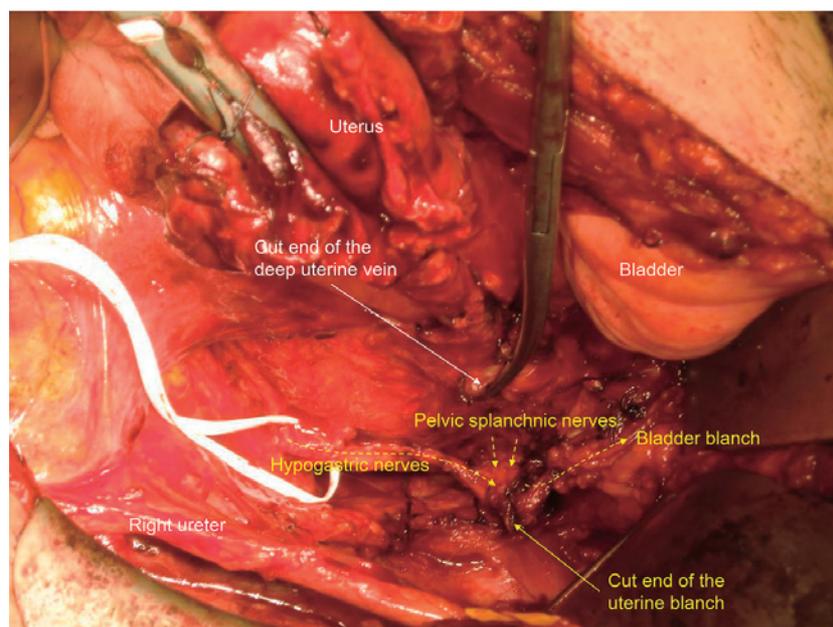


Fig. 6 The plate-like tissue, including nerve fibers that were completely separated from the uterus and parametrium, assumed a T-shape without the uterine branch from the intersection of fibers.

bleeding caused by damage to the venous plexus. Therefore, the procedure, as it relates to hysterectomy, was modified. The procedure that was historically performed from the cranial side to the caudal side (in the order of cardinal ligament, uterosacral ligament, vesicouterine ligament, paracolpium, vagina) was modified and is now performed from the ventral side to the dorsal side (in the order of vesicouterine ligament, cardinal ligament, nerve plexus dissection, uterosacral ligament, paracolpium, vagina). This was done because completing excision of the posterior layer of the vesicouterine ligament and substantially raising the cardinal ligament to the uterine corpus are essential steps in the outward detachment of the pelvic plexus and its bladder branch.

#### Residual Urine Measurement

An indwelling bladder catheter was placed at the time of surgery and removed 7 days later. After removal of the catheter, patients were free to urinate, and urination volume and residual urine volume were recorded at six pre-specified times each day. On-time measurement of residual urine volume was performed at 3:00, 7:00, 11:00, 15:00, 19:00, and 23:00. The residual urine volume was accurately measured by a nurse immediately after urination, by inserting a catheter into the bladder cavity of the patient. When residual urine volume was 50 mL or less at the same time of day for 2 consecutive days, measurement of residual urine was stopped only at that time.

When all measurement times were cleared, urination ability was considered completely established. In addition to measurement of residual urine volume, micturition desire was also recorded. If no improvement in urinary function was observed even after more than 3 weeks after the start of residual urine measurement, the patient was given instruction on the method of self-catheterization and withdrawn from residual urine measurement. If urinary function improved over time, even after more than 3 weeks, measurement of residual urine was continued until urination was established.

#### Follow-up

All patients were staged according to the FIGO and TNM classification systems. Patients at high risk for recurrence received additional postoperative adjuvant therapy. After treatment, patients underwent medical checkups for the number of months equal to the number of years passed. After more than 6 years, all patients underwent regular medical examinations every 6 months for at least 10 years after treatment was completed. At the regular medical examinations, patients underwent an internal examination, transvaginal ultrasonography, and serum biochemistry tests, including detection of tumor markers, to assess recurrence. In addition, patients underwent annual computed tomography scans of the chest, abdomen, and pelvis to evaluate the presence or absence of recurrent lesions, including those at distant sites. All patient clinical

data were stored in an in-hospital electronic medical records system.

### Statistical Analysis

The results are expressed as means  $\pm$  SD, or medians, as appropriate. The normality of the distribution was examined for all continuous variables. The t-test was used for comparisons of age and body mass index between the two groups, when the data were normally distributed. For comparisons between the two groups with respect to operative time, amount of blood loss, and number of days until establishment of urination, the difference between medians was evaluated with the Mann-Whitney U test when the data were not normally distributed. Fisher's exact test was used to compare nominal variables between the two groups. The log-rank test was used to compare outcomes between the two groups. All tests were two-sided, and  $p < 0.05$  was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander that is designed to add statistical functions frequently used in biostatistics<sup>23</sup>.

### Results

During the 5-year period from March 2007 to February 2012, 61 patients with cervical cancer underwent RH. The patients were divided into two groups according to the type of treatment received: 31 patients were in the NSRH group and 30 were in the RH group. No significant differences in the measured variables, including staging and histology, were observed between the two groups (Table 1). In the NSRH group, one patient had diabetes, two had depression, one had panic disorder, and one had Hashimoto's disease. In the RH group, two patients had diabetes, one had schizophrenia, and four had hypertension. All patients in both groups received appropriate treatment for complications, which were controlled. In the NSRH group, five patients underwent unilateral nerve-sparing surgery after preoperative evaluation of tumor invasion and intraoperative findings. Postoperative histopathological examination revealed tumor invasion of the cardinal ligaments in seven patients in the NSRH group and in six patients in the RH group; however, the resected margins were negative in all cases. Pelvic lymph node metastases were diagnosed pathologically in six patients in the NSRH group and in nine patients in the RH

group. On the basis of the stage of postoperative pathological diagnosis, 23 patients in the NSRH group and 21 patients in the RH group received postoperative adjuvant therapy. In the NSRH group, 19 patients received chemotherapy and four patients received concurrent chemoradiotherapy. In the RH group, 15 patients received chemotherapy, four patients received radiotherapy, and two patients received concurrent chemoradiotherapy.

To evaluate surgical invasiveness, we compared operative time, intraoperative blood loss, and intraoperative complications between groups. In the NSRH group, median operative time was 390.0 minutes (range, 253-580 minutes) and median blood loss was 1,212.0 g (range, 500-3,195 g). In the RH group, median operative time was 361.5 minutes (range, 255-555 minutes) and median blood loss was 1,562.5 g (range, 500-4,780 g). No significant difference was observed between the two groups (Table 2), and no intraoperative complications occurred in either group.

To evaluate urinary function, postoperative micturition desire and the number of days required to establish urination without a catheter were compared between the two groups. A self-reported subjective survey showed that 80.6% (25/31) of patients in the NSRH group were aware of urination after removal of the indwelling bladder catheter, while 46.7% (14/30) of patients in the RH group were aware. The median time required to establish urination after removal of the indwelling bladder catheter was 6 days (range, 2-20 days) in the NSRH group and 13.5 days (range, 3-46 days) in the RH group. The results were significantly better in the NSRH group ( $p < 0.05$ ). No patient in the NSRH group required self-catheterization at discharge, whereas five patients in the RH group required self-catheterization (Table 2). The prevalence of dysuria was reported to be higher in patients with diabetes or mental illnesses such as depression<sup>24-27</sup>. However, in this study, postoperative urinary function did not differ significantly between patients with and without these conditions.

The results for the five patients who underwent a unilateral nerve-sparing procedure in the NSRH group were analyzed. The median time required to establish urination was 7 days (range, 5-15 days) in those patients. This value was slightly worse than that of patients who underwent the bilateral nerve-sparing procedure but was significantly better than that of patients in the RH group. This result is consistent with the findings of a previous study, which reported that the contractile function of the detrusor muscle of the bladder was maintained if unilat-

Table 1 Patient characteristics

	NSRH (n = 31)	RH (n = 30)	P value
Age (years)	50.8 ± 10.3	49.7 ± 11.3	0.682
BMI (kg/m <sup>2</sup> )	22.6 ± 3.0	23.1 ± 4.2	0.619
FIGO stage (%)			0.742
IA	1 (3.2)	0 (0.0)	
IA2	2 (6.5)	0 (0.0)	
IB1	14 (45.2)	15 (50.0)	
IB2	6 (19.4)	4 (13.3)	
IIA	1 (3.2)	1 (3.3)	
IIB	7 (22.6)	9 (30.0)	
IIIB	0 (0.0)	1 (3.3)	
TNM stage			
pT (%)			0.895
1a	1 (3.2)	0 (0.0)	
1a1	1 (3.2)	1 (3.3)	
1a2	2 (6.5)	0 (0.0)	
1b	1 (3.2)	0 (0.0)	
1b1	12 (38.7)	14 (46.7)	
1b2	4 (12.9)	4 (13.3)	
2a	2 (6.5)	4 (13.3)	
2b	7 (22.6)	6 (20.0)	
3a	1 (3.2)	1 (3.3)	
pN (%)	6 (19.4)	9 (30.0)	0.384
pM (%)	0 (0)	0 (0)	N/A
Postoperative treatment (%)	23 (76.7)	21 (70.0)	0.771
Histology (%)			0.097
Squamous cell carcinoma	19 (61.3)	25 (83.3)	
Adenosquamous carcinoma	1 (3.2)	0 (0.0)	
Mucinous carcinoma	7 (22.6)	4 (13.3)	
Endometrioid carcinoma	3 (9.7)	0 (0.0)	
Serous carcinoma	1 (3.2)	0 (0.0)	
Small-cell carcinoma	0 (0.0)	1 (3.3)	

Values are number (%) or mean ± SD

BMI, body mass index; TNM stage, the TNM classification of malignant tumors established by the Union for International Cancer Control; pT, pN, pM, TNM classification determined by histopathologic examination of a surgical specimen

Table 2 Postoperative urination and surgical invasiveness

	NSRH (n = 31)	RH (n = 30)	P value
Operative time (min)	390.0 [253.0, 580.0]	361.5 [255.0, 555.0]	0.155
Blood loss (g)	1,212.0 [500.0, 3,195.0]	1,562.5 [500.0, 4,780.0]	0.074
Micturition desire (%)	25 (80.6)	14 (46.7)	0.008*
Time to establish urination (days)	6.0 [2.0, 20.0]	13.5 [3.0, 46.0]	0.002*
Self-catheterization (%)	0 (0.0)	5 (16.7)	0.024*

Values are number (%) or median [range]

\*p<0.05

eral nerve preservation was successful<sup>22</sup>.

To assess curability, we compared the local recurrence-free rate, disease-free survival, and overall survival between the two groups. The local recurrence-free rate was 87.1% (27/31) for patients in the NSRH group and 83.3%

(25/30) for the RH group. The disease-free survival rate in the NSRH group was 70.0% at 5 years (70.0% at 10 years); in the RH group, it was 68.3% at 5 years (63.1% at 10 years). The overall survival rate was 86.1% in the NSRH group at 5 years (86.1% at 10 years) and 78.2% at

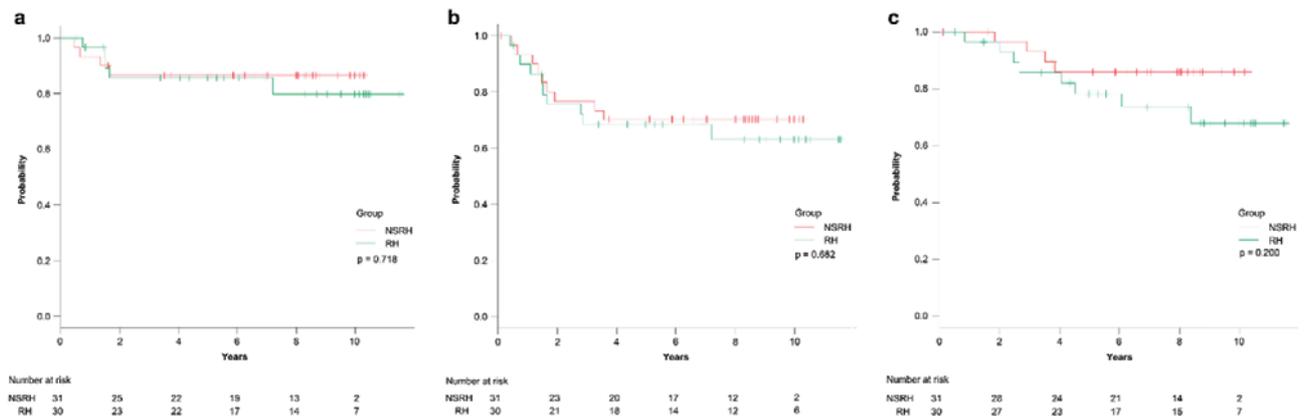


Fig. 7 Kaplan-Meier curves are shown. Panel a shows local recurrence-free rate, Panel b shows disease-free survival, and Panel c shows overall survival. The log-rank test showed no significant difference between the curves shown in a, b, and c.

5 years in the RH group (67.9% at 10 years). No difference was observed between groups in local recurrence-free rate, disease-free survival, or overall survival (Fig. 7). The mean follow-up period after treatment was 2,456.3 days (range, 48-4,213 days).

### Discussion

RH has long been the standard surgical treatment for cervical cancer worldwide. In Western countries, the resection line for RH is defined according to the classification of Piver, Rutledge, and Smith, while in Japan, it is defined according to Okabayashi<sup>4,28</sup>. Okabayashi surgery is more radical than Piver type III surgery and usually involves sacrifice of the pelvic plexus. Because the sympathetic and parasympathetic nervous systems throughout the pelvic plexus play a key role in normal urinary function, damage to these autonomic nerves caused by RH is strongly associated with the risk of consequent bladder dysfunction<sup>8,19-21,29-32</sup>. The importance of carefully identifying and preserving autonomic nerves in order to minimize bladder dysfunction has recently been emphasized in the practice of RH. Preserving pelvic autonomic nerves, without limiting the extent of RH resection, has been important for gynecological oncologists. Therefore, many studies include descriptions of nerve-sparing surgical techniques and patient outcomes<sup>5,6,12,13,15,17,18,20,21,29-38</sup>.

The present results showed that, as reported by the authors, our improved nerve-sparing technique resulted in well-preserved bladder function and helped maintain the postoperative quality of life of these patients. However, some patients had insufficient bladder function despite nerve-sparing surgery, perhaps because of nerve damage caused by surgical procedures unnoticed by the surgeon or non-visible thermal damage from powered

devices. In addition, a few patients had unexpectedly poor bladder function outcomes, despite complete intraoperative progress and careful adherence to nerve-sparing techniques. We believe the preservation rate of the pelvic plexus may be low in some persons because of substantial individual differences in how nerve tracts run, and that this could cause unexpectedly poor results. It is difficult to focus on nerves that are not present as single distinct nerve bundles, such as the obturator nerve. The hypogastric nerve runs like a membrane, while multiple thin nerve fibers cross each other, this resembling a mesh. Similarly, the bladder branch diverging from the pelvic plexus also spreads to the bladder as narrow nerve fibers. Most bladder branches pass through the posterior layer of the vesicouterine ligament and reach the area at the back of the bladder, mainly from the vesicoureteral junction to the bladder neck. However, these nerve tracts show atypical differences in terms of location, eg, some fibers run along the ureter, some fibers pass through the anterior layer of the vesicouterine ligament that is located further on the ventral side of the typical nerve tract, and some fibers pass through the anterior vaginal wall<sup>39-42</sup>. Fibers that run in relatively shallow layers must be cut, and a reduction in the nerve preservation rate is inevitable in such patients. Nerve-sparing technique is not a technique of isolating only nerve fibers, but rather, of preserving the lateral parametrium and paracolpium, which are expected to contain most nerve fibers. For that reason, it is extremely difficult to achieve 100% complete nerve preservation. We believe that variability in outcomes of nerve-sparing surgery is attributable to such individual differences in nerve tracts. In addition, previous descriptions of nerve-sparing technique are ambiguous and replication of the technique is

sometimes challenging because of individual differences in nerve tracts.

The main point of the present surgical procedure is that when the posterior layer of the vesicouterine ligament is dissected, it should not be cut from the outside more than is necessary, to avoid damage to the bladder branch that runs in the dorsolateral direction. In addition, the procedure of peeling the pelvic plexus outward after dissecting the uterine branch is stopped at the minimum necessary depth. These precautions reduce the risk of damage to the nerve plexus during the dissection procedure and avoid nerve damage during hemostasis for bleeding caused by vascular damage of the parametrium. There is some concern that these procedures sacrifice curability because they are clearly more limited surgically than those used in conventional surgeries, which do not consider nerve preservation. However, nerve-sparing surgery was reported to have no short-term adverse effects on outcomes, and the present results indicate that nerve-sparing surgery has no long-term adverse effects on outcomes.

As stated above, nerve-sparing technique is a limited surgery. However, modifications of radical surgery that change it to a limited surgery present a conflict. Radical surgery has long been performed as a standard treatment for early-stage cervical cancer and has remained unchanged for almost a century. However, is highly invasive surgery, such as surgery involving dissection of the pelvic floor, really necessary for patients with relatively early-stage cervical cancer that has not spread outside the cervix? In developed countries today, preoperative staging is performed by using various examinations, including diagnostic imaging. In Japan, both computed tomography and magnetic resonance imaging are now mandatory preoperative examinations. In other words, accurate preoperative diagnosis is possible, which was not the case when RH was first developed. In addition, postoperative adjuvant therapy has advanced significantly, and some surgeons have questioned whether radical surgery is required for early-stage cervical cancer. Currently, patients with a high risk of relapse are usually treated with additional chemotherapy or radiation therapy or concurrent chemoradiotherapy. In this study, 72.1% of the patients received adjuvant therapy (55.7% received chemotherapy and 16.4% received either radiotherapy or concurrent chemoradiotherapy). This high rate of additional treatment may be a reason why outcomes did not differ between the two groups. If so, radical surgery may not be needed for relatively early invasive can-

cers, such as FIGO IB stage cancers. The 2018 revision of the FIGO classification acknowledged the use of diagnostic imaging modalities, such as computed tomography or magnetic resonance imaging, to determine preoperative FIGO classification, as global medical capabilities have improved<sup>43</sup>. Thus, a large-scale prospective study should be conducted to identify the optimal surgical method based on accurate preoperative diagnoses.

The results of this study indicate that nerve-sparing technique is effective for preserving bladder function and does not adversely affect short-term or long-term outcomes. However, this study has several limitations. First, this study was a historical-controlled study. During the enrollment period, patients in the RH group tended to receive treatment earlier than those in the NSRH group. By setting the enrollment period around the transition period of the operative procedure, patients were almost equally assigned to the two groups. In addition, no fundamental treatment changes were implemented during this enrollment period, except for the introduction of nerve-sparing techniques. Second, this was a single-center study with a small sample size. This study evaluated the results of surgical procedures, and the accuracy of the procedures should not vary. At this stage, we consider it appropriate to conduct single-center studies to perform accurate nerve-sparing techniques for all patients. In the future, it will be necessary to perform more extensive studies that involve multiple surgeons who can perform nerve-sparing surgery with uniformly high quality.

Our findings indicate that NSRH for cervical cancer maintains satisfactory postoperative bladder function. No difference was observed in local recurrence rates, and no adverse effects on outcomes were seen beyond 5 years. Therefore, NSRH appears to be one of the best treatment options for early cervical cancer.

**Conflict of Interest:** The authors declare no conflicts of interest.

#### References

1. Wertheim E. The extended abdominal operation for carcinoma uteri (based on 500 operative cases). *Am J Obstet Dis Women Child.* 1912;66:169–232.
2. Okabayashi H. Radical abdominal hysterectomy for cancer of the cervix uteri, modification of the Takayama operation. *Surg Gynecol Obstet.* 1921;33:335–41.
3. Meigs JV. Radical hysterectomy with bilateral pelvic lymph node dissections; a report of 100 patients operated on five or more years ago. *Am J Obstet Gynecol [Internet].* 1951 Oct;62(4):854–70. Available from: <https://www>.

- ncbi.nlm.nih.gov/pubmed/14885271
4. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. *Obstet Gynecol* [Internet]. 1974 Aug;44(2):265–72. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/4417035>
  5. Ercoli A, Delmas V, Gadonneix P, et al. Classical and nerve-sparing radical hysterectomy: an evaluation of the risk of injury to the autonomous pelvic nerves. *Surg Radiol Anat*. 2003 Jul-Aug;25(3-4):200–6.
  6. Maas CP, Trimbos JB, DeRuiter MC, van de Velde CJ, Kenter GG. Nerve sparing radical hysterectomy: latest developments and historical perspective. *Crit Rev Oncol Hematol* [Internet]. 2003 Dec;48(3):271–9. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/14693339>
  7. Zullo MA, Mancini N, Angioli R, Muzii L, Panici PB. Vesical dysfunctions after radical hysterectomy for cervical cancer: a critical review. *Crit Rev Oncol Hematol* [Internet]. 2003 Dec;48(3):287–93. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/14693341>
  8. Landoni F, Maneo A, Cormio G, et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. *Gynecol Oncol* [Internet]. 2001 Jan;80(1):3–12. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/11136561>
  9. Kindermann G, Debus-Thiede G. Postoperative urological complications after radical surgery for cervical cancer. *Baillieres Clin Obstet Gynaecol* [Internet]. 1988 Dec;2(4):933–41. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/3229061>
  10. Kobayashi T. [Abdominal radical hysterectomy with pelvic lymphadenectomy for cancer of cervix]. *Shikyukeigan Shujutsu* [Cervical cancer surgery]. Tokyo: Nanzando; 1961. p. 178–87. Japanese.
  11. Höckel M, Konerding MA, Heussel CP. Liposuction-assisted nerve-sparing extended radical hysterectomy: oncologic rationale, surgical anatomy, and feasibility study. *Am J Obstet Gynecol* [Internet]. 1998 May;178(5):971–6. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/9609569>
  12. Possover M, Stober S, Plaul K, Schneider A. Identification and preservation of the motoric innervation of the bladder in radical hysterectomy type III. *Gynecol Oncol*. 2000 Nov;79(2):154–7.
  13. Trimbos JB, Maas CP, Deruiter MC, Peters AA, Kenter GG. A nerve-sparing radical hysterectomy: guidelines and feasibility in Western patients. *Int J Gynecol Cancer* [Internet]. 2001 May-Jun;11(3):180–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11437922>
  14. Querleu D, Narducci F, Poulard V, et al. Modified radical vaginal hysterectomy with or without laparoscopic nerve-sparing dissection: a comparative study. *Gynecol Oncol* [Internet]. 2002 Apr;85(1):154–8. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/11925136>
  15. Raspagliesi F, Ditto A, Fontanelli R, et al. Nerve-sparing radical hysterectomy: a surgical technique for preserving the autonomic hypogastric nerve. *Gynecol Oncol* [Internet]. 2004 May;93(2):307–14. Available from: <http://www.sciencedirect.com/science/article/pii/S0090825804000733>
  16. Papp Z, Csapó Z, Hupucz P, Mayer A. Nerve-sparing radical hysterectomy for stage IA2-IIb cervical cancer: 5-year survival of 501 consecutive cases. *Eur J Gynaecol Oncol* [Internet]. 2006;27(6):553–60. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17290582>
  17. Sakamoto S, Takizawa K. An improved radical hysterectomy with fewer urological complications and with no loss of therapeutic results for invasive cervical cancer. *Baillieres Clin Obstet Gynaecol* [Internet]. 1988 Dec;2(4):953–62. Available from: <http://www.sciencedirect.com/science/article/pii/S0950355298800229>
  18. Yabuki Y, Asamoto A, Hoshiba T, Nishimoto H, Nishikawa Y, Nakajima T. Radical hysterectomy: An anatomic evaluation of parametrial dissection. *Gynecol Oncol* [Internet]. 2000;77(1):155–63. Available from: <http://www.sciencedirect.com/science/article/pii/S009082589957232>
  19. Kuwabara Y, Suzuki M, Hashimoto M, Furugen Y, Yoshida K, Mitsunashi N. New method to prevent bladder dysfunction after radical hysterectomy for uterine cervical cancer. *J Obstet Gynaecol Res* [Internet]. 2000 Feb;26(1):1–8. Available from: <https://doi.org/10.1111/j.1447-0756.2000.tb01192.x>
  20. Fujii S, Takakura K, Matsumura N, et al. Anatomic identification and functional outcomes of the nerve sparing Okabayashi radical hysterectomy. *Gynecol Oncol* [Internet]. 2007 Oct;107(1):4–13. Available from: <http://www.sciencedirect.com/science/article/pii/S009082580700652X>
  21. Sakuragi N, Todo Y, Kudo M, Yamamoto R, Sato T. A systematic nerve-sparing radical hysterectomy technique in invasive cervical cancer for preserving postsurgical bladder function. *Int J Gynecol Cancer* [Internet]. 2005 Mar-Apr;15(2):389–97. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/15823132>
  22. Katahira A, Niikura H, Kaiho Y, et al. Intraoperative electrical stimulation of the pelvic splanchnic nerves during nerve-sparing radical hysterectomy. *Gynecol Oncol*. 2005 Sep;98(3):462–6.
  23. Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant*. 2013 Mar;48(3):452–8.
  24. Yamaguchi C, Sakakibara R, Uchiyama T, et al. Overactive bladder in diabetes: a peripheral or central mechanism? *Neurourol Urodyn* [Internet]. 2007;26(6):807–13. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/17357115>
  25. Daneshgari F, Liu G, Birdler L, Hanna-Mitchell AT, Chacko S. Diabetic bladder dysfunction: current translational knowledge. *J Urol* [Internet]. 2009 Dec;182(6 Suppl):S18–26. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/19846137>
  26. Kirschner-Hermanns R, Daneshgari F, Vahabi B, Birdler L, Oelke M, Chacko S. Does diabetes mellitus-induced bladder remodeling affect lower urinary tract function? *ICI-RS 2011. Neurourol Urodyn* [Internet]. 2012 Mar;31(3):359–64. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22415965>
  27. Sakakibara R, Ito T, Yamamoto T, et al. Depression, anxiety and the bladder. *Low Urin Tract Symptoms* [Internet]. 2013 Sep;5(3):109–20. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26663445>
  28. Okabayashi H. Radical abdominal hysterectomy for cancer of the cervix uteri, modification of the Takayama operation. *Surg Gynecol Obstet*. 1921;33:335–41.
  29. Yabuki Y, Asamoto A, Hoshiba T, Nishimoto H, Satou N. A new proposal for radical hysterectomy. *Gynecol Oncol* [Internet]. 1996 Sep;62(3):370–8. Available from: <http://www.sciencedirect.com/science/article/pii/S0090825896902516>
  30. Kato T, Murakami G, Yabuki Y. A new perspective on nerve-sparing radical hysterectomy: nerve topography and over-preservation of the cardinal ligament. *Jpn J Clin Oncol* [Internet]. 2003 Nov;33(11):589–91. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/14711985>

31. Mantzaris G, Rodolakis A, Vlachos G, et al. Magnifying lenses assisted nerve-sparing radical hysterectomy and prevention of nerve plexus trauma. *Int J Gynecol Cancer* [Internet]. 2008 Jul-Aug;18(4):868-75. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17892457>
32. Possover M, Quakernack J, Chiantera V. The LANN technique to reduce postoperative functional morbidity in laparoscopic radical pelvic surgery. *J Am Coll Surg* [Internet]. 2005 Dec;201(6):913-7. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/16310695>
33. Fujii S. Original film of the Okabayashi's radical hysterectomy by Okabayashi himself in 1932, and two films of the precise anatomy necessary for nerve-sparing Okabayashi's radical hysterectomy clarified by Shingo Fujii. *Int J Gynecol Cancer* [Internet]. 2008 Mar-Apr;18(2):383-5. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/17587316>
34. Maas K, Moriya Y, Kenter G, Trimbos B, van de Velde C. A plea for preservation of the pelvic autonomic nerves. *Lancet* [Internet]. 1999 Aug;35(9180):772-3. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/10475214>
35. Kato K, Suzuka K, Osaki T, Tanaka N. Unilateral or bilateral nerve-sparing radical hysterectomy: a surgical technique to preserve the pelvic autonomic nerves while increasing radicality. *Int J Gynecol Cancer*. 2007 Sep-Oct;17(5):1172-8.
36. Höckel M, Horn LC, Hentschel B, Höckel S, Naumann G. Total mesometrial resection: high resolution nerve-sparing radical hysterectomy based on developmentally defined surgical anatomy. *Int J Gynecol Cancer* [Internet]. 2003 Nov-Dec;13(6):791-803. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/14675316>
37. Raspagliesi F, Ditto A, Kusamura S, et al. Nerve-sparing radical hysterectomy: a pilot study. *Tumori* [Internet]. 2003 Sep-Oct;89(5):497-501. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/14870771>
38. Fujii S. Anatomic identification of nerve-sparing radical hysterectomy: A step-by-step procedure. *Gynecologic Oncology* [Internet]. 2008 Nov;111(2, Supplement):S33-41. Available from: <http://www.sciencedirect.com/science/article/pii/S0090825808005398>
39. Spradling K, Khoyilar C, Abedi G, et al. Redefining the autonomic nerve distribution of the bladder using 3-dimensional image reconstruction. *J Urol* [Internet]. 2015 Dec;194(6):1661-7. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26003207>
40. Kraima AC, Derks M, Smit NN, Van De Velde CJ, Kenter GG, DeRuiter MC. Careful dissection of the distal ureter is highly important in nerve-sparing radical pelvic surgery: A 3D reconstruction and immunohistochemical characterization of the vesical plexus. *Int J Gynecol Cancer* [Internet]. 2016 Jun;26(5):959-66. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27101584>
41. Purves JT, Spruill L, Rovner E, et al. A three dimensional nerve map of human bladder trigone. *Neurourol Urodyn*. 2017 Apr;36(4):1015-9.
42. Ripperda CM, Jackson LA, Phelan JN, Carrick KS, Corton MM. Anatomic relationships of the pelvic autonomic nervous system in female cadavers: clinical applications to pelvic surgery. *Am J Obstet Gynecol* [Internet]. 2017 Apr;216(4):388.e1-e7. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/27956200>
43. Bhatla N, Berek JS, Cuello Fredes M, et al. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet* [Internet]. 2019 Apr;145(1):129-35. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/30656645>

(Received, April 29, 2020)

(Accepted, July 2, 2020)

(J-STAGE Advance Publication, August 1, 2020)

Journal of Nippon Medical School has adopted the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>) for this article. The Medical Association of Nippon Medical School remains the copyright holder of all articles. Anyone may download, reuse, copy, reprint, or distribute articles for non-profit purposes under this license, on condition that the authors of the articles are properly credited.