Tohoku J. Exp. Med., 2024, **263**, 1-9

Long-Term and Short-Interval Assessment of Self-Reported Urinary and Sexual Functions after Nerve-Sparing Radical Hysterectomy: A Prospective Cohort Study

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The aim of this study was to determine the impact of nerve preservation confirmed by intraoperative electrical stimulation (IES) on subjective symptoms of urinary and sexual function in uterine cervical cancer patients who underwent radical hysterectomies. This study included 85 patients who underwent type C radical hysterectomy with IES. Pelvic splanchnic nerve preservation with IES after hysterectomy (nerve-stimulation positive group) was confirmed in 61 women and 24 women did not have nerve preservation (negative group). Urinary function was assessed with the Overactive Bladder Symptom Score (OABSS), International Prostate Symptom Score (IPSS), and International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) questionnaires. Sexual function was surveyed using the Female Sexual Function Index (FSFI). Longitudinal changes in those scores according to response to nerve-stimulation were evaluated using a generalized estimating equation. IPSS quality of life (QOL) scores were significantly better in the nerve-stimulation positive group compared with the scores in the negative group until 12 months after surgery, whereas OABSS, IPSS total, IPSS voiding, and ICIQ-SF scores evaluating urinary symptoms were not significantly different between the two groups. FSFI scores were better in the nerve-stimulation positive group 36 months after surgery compared with the scores in the negative group. In this study, we assessed self-reported urinary and sexual symptoms after nerve-sparing radical hysterectomy (NSRH) with IES in the long term. We demonstrated that nerve-sparing significantly reduced distress associated with QOL until 1 year, improved urinary storage symptoms at 2 years, and sexual symptoms 3 years after surgery.

Keywords: bladder function; intraoperative electrical stimulation; nerve-preserving radical hysterectomy; sexual function; uterine cervical cancer
Tohoku J. Exp. Med., 2024 May, **263** (1), 1-9.
doi: 10.1620/tjem.2024.J014

Introduction

Uterine cervical cancer (UCC) is a common cancer in women. Approximately 570,000 new cases and 311,000 deaths due to UCC occurred worldwide in 2018 (Arbyn et al. 2020). In Japan, 10,978 patients were newly diagnosed with UCC, and 2,871 patients died of the disease in 2018 (https://ganjoho.jp/reg_stat/statistics/stat/cancer/17_cervix_uteri.html.). Organized cervical cancer screening and the widespread implementation of human papilloma virus (HPV) vaccine programs have reduced the incidence of UCC (Melnikow et al. 2018). Nevertheless, UCC screen-

Received October 26, 2023; revised and accepted January 30, 2024; J-STAGE Advance online publication February 8, 2024
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ing, coverage and penetration of the HPV vaccine program is still low in Japan (Sekine et al. 2022). Therefore, the incidence and mortality of UCC are increasing in young and middle-aged Japanese adults (Tanaka et al. 2022).

Japanese treatment guidelines indicate that surgery is the treatment of choice for The International Federation of Gynecology and Obstetrics (FIGO) I–II and some IIIC stages of cervical cancer (Japan Society of Gynecologic Oncology 2022). Surgical treatment of gynecological diseases can lead to urinary dysfunction associated with nerve injury, decreased fertility, and hormonal changes. Conventional radical hysterectomy for UCC damages the pelvic splanchnic nerve branches and the hypogastric plexus, resulting in postoperative urinary and sexual dysfunction (Derks et al. 2016; Bakker et al. 2017; Wang et al. 2018). Nerve-sparing radical hysterectomy (NSRH), which was first reported by Kobayashi, reduces postoperative bladder dysfunction in UCC patients (Dursun et al. 2009; Sakuragi and Kaneuchi 2021a) without sacrificing cancer curability (Li et al. 2019; Yin et al. 2018). We previously confirmed the existence of cases in which the nerves were not preserved despite surgical manipulation, which is considered a nerve-sparing technique, by using electrical stimulation tests (Nagai et al. 2012). Confirming nerve preservation with intraoperative electrical stimulation (IES) can predict postoperative bladder function (Katahira et al. 2005; Nagai et al. 2012) evaluated by urodynamic studies. However, few studies have evaluated long-term bladder function preservation after NSRH, focusing on patient subjective symptoms rather than urodynamic studies.

Several non-Japanese studies demonstrated that vaginal secretion and sexual desire decreased after radical hysterectomy (Wang et al. 2018), and showed that NSRH results in better sexual function in women after surgery compared to non-NSRH (Chen et al. 2014; Bogani et al. 2018). However, no report has been described on sexual function after NSRH in Japanese women. The aim of this study was to determine the impact of nerve preservation confirmed by IES on urinary and sexual function, focusing on subjective symptoms using a questionnaire survey of UCC patients who underwent radical hysterectomies.

Methods

Ethical approval

This study was approved by the Ethics Committee of Tohoku University School of Medicine (approval number: 2017-1-346, approval date: August 8, 2017), and was conducted according to the guidelines of the Declaration of Helsinki. The patients received thorough explanations of the study using a written document, and all patients signed a written informed consent form before commencement of the study.

Study design

This study included 85 patients who underwent type C radical hysterectomy with IES. Pelvic splanchnic nerve preservation was confirmed with IES after hysterectomy, and participants were divided into nerve-stimulation positive group and negative group. Urinary symptom was assessed with the Overactive Bladder Symptom Score (OABSS), International Prostate Symptom Score (IPSS), and International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) questionnaires. Sexual function was surveyed using the Female Sexual Function Index (FSFI). Questionnaires were sent by mail at 1, 3, 6, 12, 24, and 36 months after surgery. Longitudinal changes in those scores according to response to nerve-stimulation were evaluated using a generalized estimating equation.

Patients

Patients were chosen from 1,060 patients admitted to Tohoku University Hospital from January, 2008 to April, 2018 who received initial surgical treatment for gynecological diseases. Of the patients who planned to have abdominal radical hysterectomies with pelvic lymphadenectomies, 139 of 158 patients agreed to participate in this study (Fig. 1). Eighty-five patients with stage IA- IIB UCC underwent type C radical hysterectomy (Marin et al. 2014) with IES. Pelvic splanchnic nerve preservation with IES after hysterectomy (nerve-stimulation positive group) was confirmed in 61 patients and the pelvic splanchnic nerves were not preserved in 24 women (negative group). Patient selection is shown in Fig. 1.

Patient medical information, including age, FIGO stage, pathological findings, adjuvant treatment after radical hysterectomy, response to IES, operation time, and blood loss during surgery, was collected from medical records.

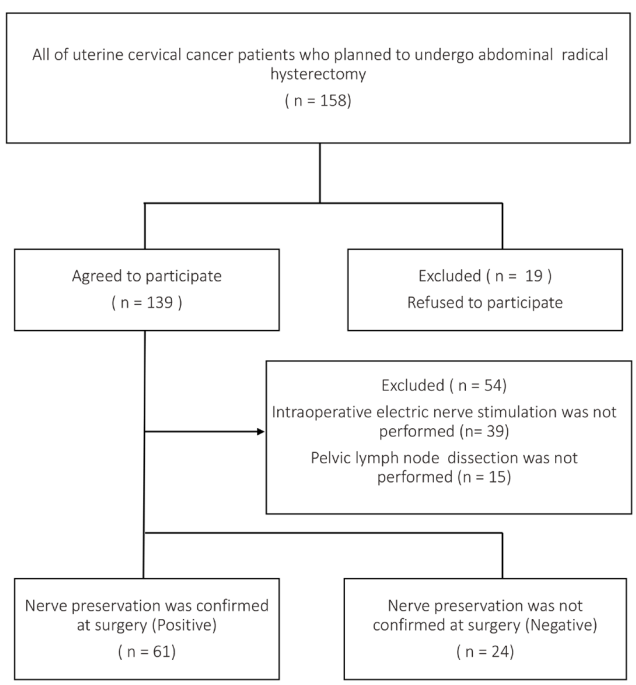

Fig. 1. Flowchart of study selection.

Patients were informed about the questionnaire survey before surgery. Questionnaires were sent by mail at 1, 3, 6, 12, 24, and 36 months after surgery.

Questionnaires

The following score indices for the subjective evaluation of lower urinary tract symptoms were used: i) OABSS: scores daytime frequency, nocturia, urinary urgency, and urge urinary incontinence in the past week by self-assessment (Honma 2005), ii) IPSS: evaluates lower urinary tract symptoms by rating residual urine, frequency, urinary line interruption, difficulty with retention, decreased urinary output, and abdominal pressure urination on a 6-point scale over the past month (Barry et al. 1992; Study Group on Standardization of Treatment in Urology 2001), iii) ICIQ-SF: consists of questions about frequency of urinary incontinence in the past week, degree of urinary incontinence, and degree of disruption of daily life due to urinary incontinence. The IPSS score was divided into IPSS voiding subscore (IPSS-V) and IPSS storage subscore (IPSS-S). Incomplete emptying, intermittency, weak stream and straining to void were defined as "IPSS-V" and frequency, urgency and nocturia were defined as "IPSS-S", each score was summed to evaluate. The IPSS quality of life (QOL) score evaluates satisfaction with urination on a 7-point scale from very satisfied to very dissatisfied. In these urinary function evaluation scores, lower scores indicate normal or favorable conditions (Avery et al. 2004; Study Group on Standardization of Treatment in Urology 2004).

FSFI (tentative plan of the Department of Urology at Sapporo Medical University) was used to survey sexual function. The FSFI surveys the status of sexual desire, sexual arousal, vaginal wetness, orgasm, sexual satisfaction, and painful intercourse in the past month. Higher scores indicate more favorable states (Takahashi et al. 2011).

Intraoperative electrical stimulation (IES)

IES was performed as previously reported (Nagai et al. 2012). In all cases, electrical stimulation of the pelvic plexus after hysterectomy was performed to check for increased pressure in the bladder. Both right and left pelvic splanchnic nerves were evaluated. "Nerve-sparing

Table 1. Clinical and pathologic data in nerve-stimulation positive and negative group. FIGO, The International Federation of Gynecology and Obstetrics.

	Negative (n = 24)	Positive (n = 61)	p
Age, years, median (min-max)	46.5 (29-70)	41 (28-66)	0.73
< 50 years, n (%)	17 (70.8)	38 (62.2)	0.45
≥ 50 years, n (%)	7 (29.2)	23 (37.7)	
Marriage or partnership, n (%)			0.4
No	4 (16.6)	14 (22.9)	
Yes	20 (83.3)	47 (77.1)	
Histological type, n (%)			0.17
Squamous cell carcinoma	17 (70.8)	38 (62.2)	
Adenocarcinoma	5 (20.8)	13 (21.3)	
Adenosquamous carcinoma	0 (0)	1 (1.6)	
Others	1 (0.4)	4 (6.5)	
FIGO stage (FIGO 2008), n (%)			1.18
IA	0 (0)	3 (4.9)	
IB	19 (79.1)	49 (80.3)	
IIA	3 (12.5)	3 (4.9)	
IIB	2 (8.3)	6 (9.8)	
Ovarian preservation, n (%)			0.96
No	16 (66.6)	41 (67.2)	
Yes	8 (33.3)	20 (32.7)	
Operative time, min, median (min-max)	278 (179-431)	264 (161-408)	0.4
Blood loss, ml, median (min-max)	770 (255-1,710)	493 (136-1,490)	0.1
Postsurgical therapy, n (%)			0.12
No	5 (20.8)	23 (37.7)	
Yes	19 (79.1)	38 (62.2)	
Radiotherapy	3 (12.5)	16 (26.2)	
Chemoradiation	16 (66.6)	22 (36.0)	

FIGO, The International Federation of Gynecology and Obstetrics.

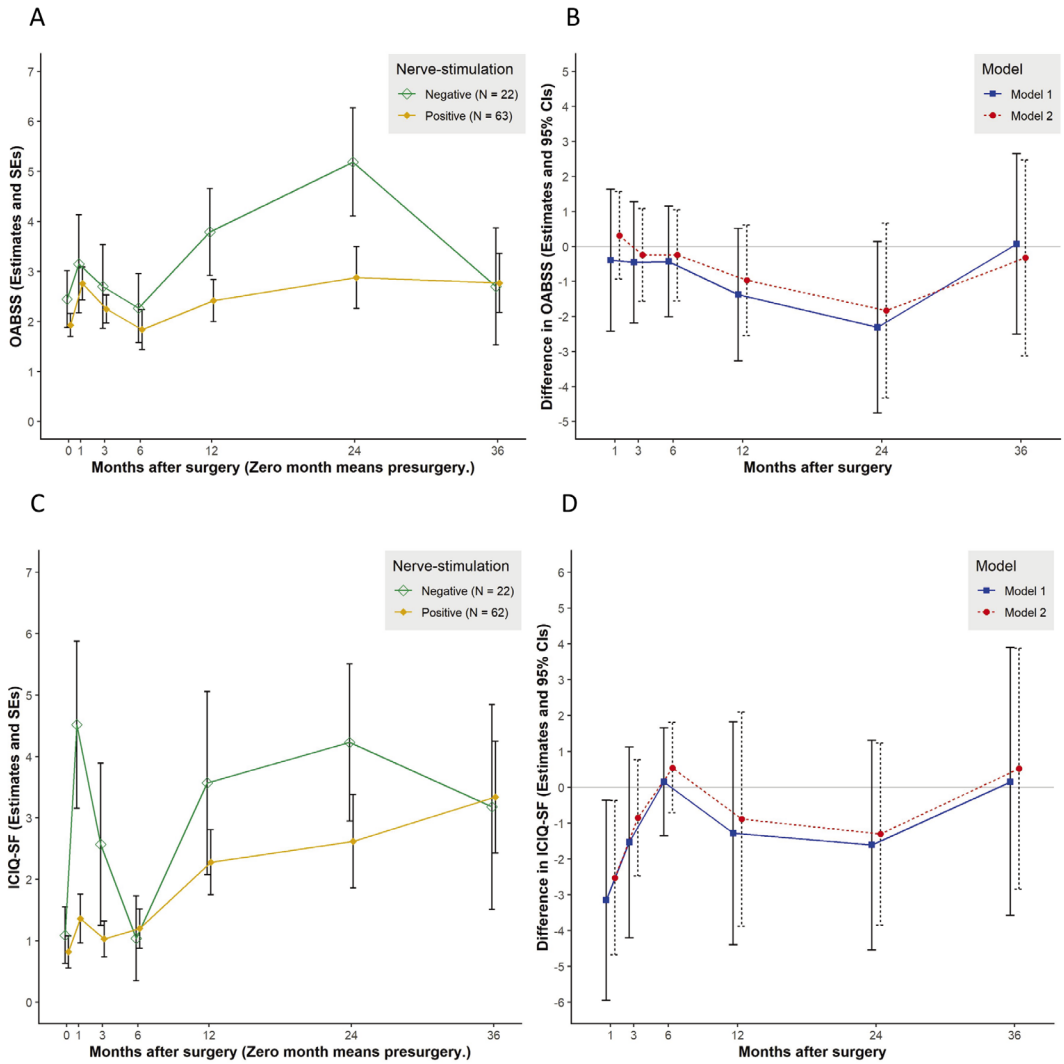

Fig. 2. Comparison of postoperative Overactive Bladder Symptom Score (OABSS) and International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) scores in the nerve-stimulation positive and negative groups.
A. Longitudinal changes in OABSS scores in model 1 (Crude model). B. Longitudinal changes in differences in OABSS scores [Positive vs. Negative (Reference)]. C. Longitudinal changes in ICIQ-SF scores in model 1 (Crude model). D. Longitudinal changes in the differences in ICIQ-SF score [Positive vs. Negative (Reference)]. Model 1 was the crude model. Model 2 was adjusted for the baseline values for each outcome, the interaction term of months and baseline values for each outcome, age (≥ 50 or < 50 years), FIGO stage (I or II), bilateral salpingo-oophorectomy (BSO), postsurgical therapy, and presence of a partner. *$p < 0.05$. The error bars indicate 95% control limit (CL). Detailed P values of each point and 95% CL were described in Supplementary Table S2.

Positive" was defined as a response to nerve-stimulation on at least one side of the pelvic splanchnic nerves.

Statistical analysis

Patient characteristics such as age, partnership, ovarian preservation, and postsurgical therapy were compared using χ^2 test. FIGO stage and histological type were compared using Kruskal-Wallis test. OABSS, ICIQ-SF, Total IPSS (IPSS-T), PSS-V, IPSS-S, IPSS-QOL score, and FSFI were continuous variables. Longitudinal changes in OABSS, ICIQ-SF, IPSS-T, IPSS-V, IPSS-S, QOL score, FSFI, and the number of sexual intercourse episodes per four weeks according to the response to nerve-stimulation were evaluated using a generalized estimating equation (GEE).

The logit link function was used to analyze longitudinal changes in OABSS. A negative binomial regression model, rather than a Poisson regression model, was used to analyze the number of sexual intercourse episodes per four weeks based on the GEE, due to over-dispersion. Months after surgery were treated as a categorical variable.

Furthermore, an interaction term of months and response to nerve-stimulation (i.e., positive, or negative) was also included in the model. Because the GEE using an unstructured working correlation did not converge, a compound symmetry working correlation structure was used to consider the serial correlation between months after NSRH.

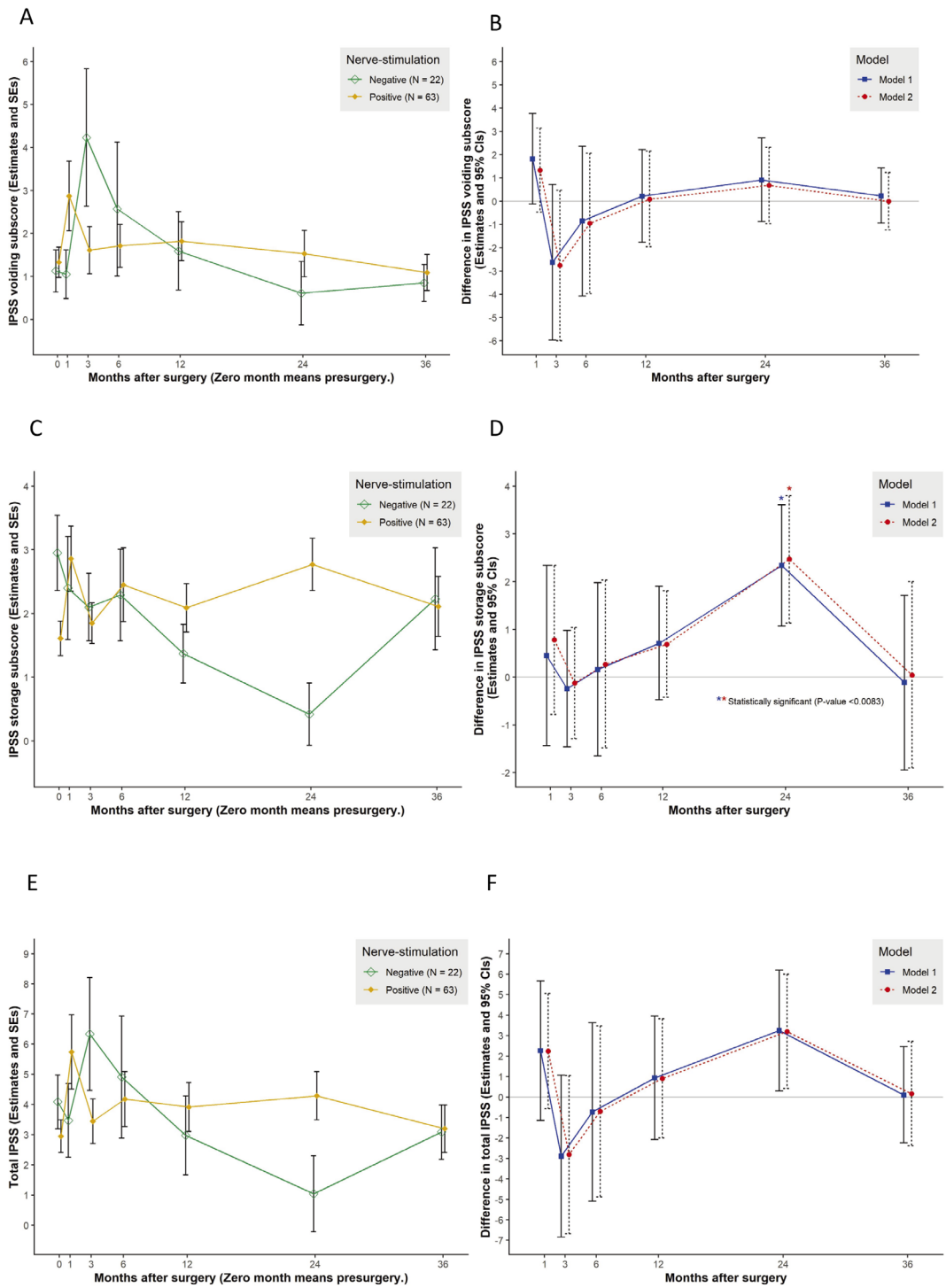

Fig. 3. Comparison of postoperative International Prostate Symptom Score (IPSS) between the nerve-stimulation positive and negative groups.
A. Longitudinal changes in IPSS voiding scores in model 1 (Crude model). B. Longitudinal changes in the differences in IPSS voiding scores [Positive vs. Negative (Reference)]. C. Longitudinal changes in IPSS storage scores in model 1 (Crude model). D. Longitudinal changes in the differences in IPSS storage scores (Positive vs. Negative [Reference]). E. Longitudinal changes in IPSS total scores in model 1 (Crude model). F. Longitudinal changes in the differences in IPSS total scores (Positive vs. Negative [Reference]). *$p < 0.05$. The error bars indicate 95% control limit (CL). Detailed p values of each point and 95% CL were described in Supplementary Table S2.

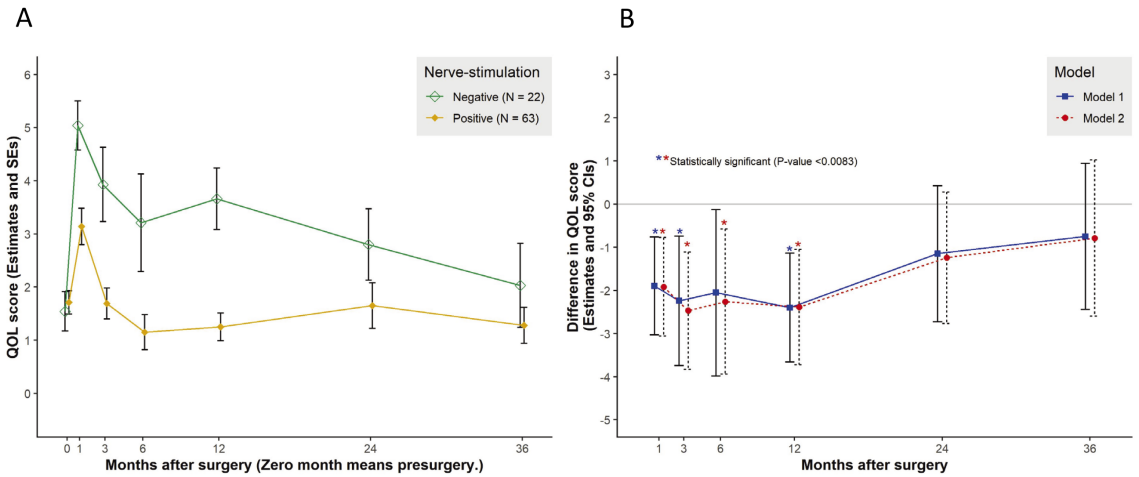

Fig. 4. Comparison of postoperative IPSS quality of life (QOL) scores between the nerve-stimulation positive and negative groups.
A. Longitudinal changes in IPSS QOL scores in model 1 (Crude model). B. Longitudinal changes in the differences in IPSS QOL scores [Positive vs. Negative (Reference)]. Model 1 was the crude model. Model 2 was adjusted for the baseline value of each outcome, the interaction term of months and baseline values of each outcome, age (≥ 50 or < 50 years), FIGO stage (I or II), bilateral salpingo-oophorectomy (BSO), postsurgical therapy, and the presence of a partner. *p < 0.05. The error bars indicate 95% control limit (CL). Detailed P values of each point and 95% CL were described in Supplementary Table S2.

An empirical sandwich estimator was also used in GEE.

The differences in OABSS, ICIQ-SF, IPSS-T, IPSS-V, IPSS-S, QOL score, FSFI, and the number of sexual intercourse episodes per four weeks between the nerve-stimulation positive and negative groups at 1, 3, 6, 12, 24, and 36 months after surgery were also tested with the latter group set as a reference group. Model 1 was defined as a crude model. Model 2 was adjusted for the baseline values of each outcome, interaction terms of months and baseline values of each outcome, age (≥ 50 or < 50 years), FIGO stage (I or II), Bilateral salpingo-oophorectomy (BSO), postsurgical therapy, and presence of a partner. In the analysis of differences in the number of sexual intercourse episodes per four weeks between the nerve-stimulation positive and negative groups, neither FIGO stage nor the presence of a sexual partner was included in model 2 due to non-convergence of GEE. Considering the multiple comparisons, a two-sided p-value of < 0.0083 (i.e., 0.05/6 using Bonferroni correction) was considered statistically significant. SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the GEE analysis.

Results

Basic patient characteristics

The clinicopathological characteristics of the nerve-stimulation positive and negative groups are summarized in Table 1. Patient ages ranged from 28 to 70 years (median = 44.9). Seventy-eight percent of the women had sexual partners (n = 67). In over half of the patients, the histopathologic type was squamous cell carcinoma (69%, n = 55), and 22% of patients had adenocarcinoma (n = 18). The postoperative diagnosis in 80% of patients was FIGO stage IB (n = 68). The operating times ranged from 161 to 431 minutes (median 271 minutes). The amount of blood loss ranged from 136 to 1,710 ml (median 526 ml). BSOs were performed in 57 patients (67%). Postsurgical radiotherapy or chemoradiation was administered to 57 patients (67%). There were no significant differences between stimulation positive and negative group in all characteristics.

Nerve-sparing radical hysterectomies improved urinary subjective symptoms after surgery

The response rate of the questionnaires is described in Supplementary Table S1. According to the OABSS score, urinary symptom tended to improve after surgery in the nerve-stimulation positive group compared to the negative group, but the difference was not statistically significant in model 1 and 2 (Fig. 2A, B). No statistically significant differences in ICIQ-SF scores for urinary incontinence (Fig. 2C, D). No statistically significant differences in IPSS voiding subscores were detected between the two groups in model 1 and 2 (Fig. 3A, B). The nerve-stimulation positive group had higher IPSS storage subscores than the negative group 24 months after surgery in model 1 and 2 (Fig. 3C, D). No statistically significant differences in total IPSS scores were detected between the two groups in model 1 and 2 (Fig. 3E, F). However, QOL was significantly better in the nerve-stimulation positive group compared to QOL in the negative group until up to 12 months after surgery (Fig. 4A, B). Differences between nerve-stimulation positive and negative group, and p-values are given in Supplementary Table S2.

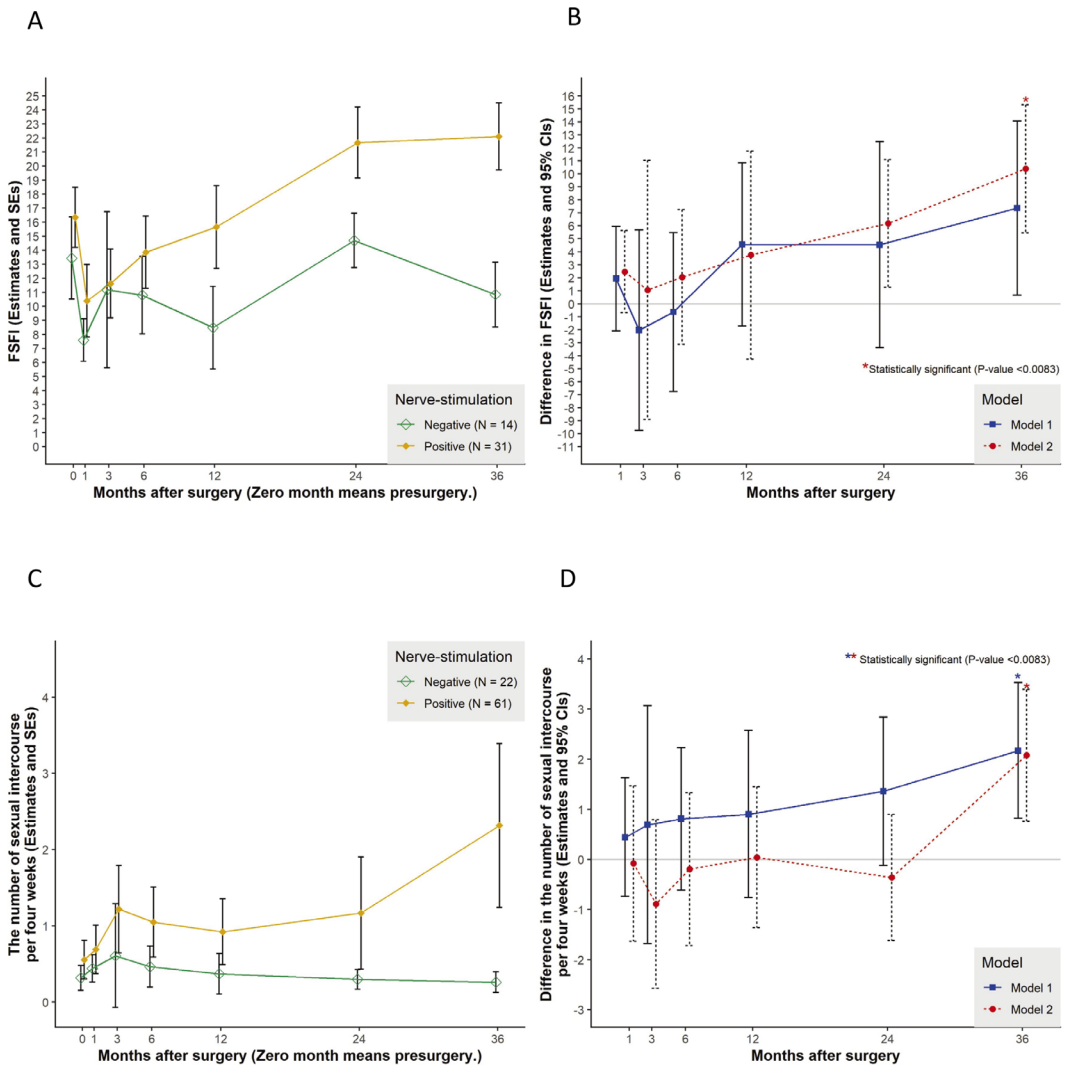

Fig. 5. Comparison of postoperative Female Sexual Function Index (FSFI) total scores between the nerve-stimulation positive and negative groups.
A. Longitudinal change in FSFI total scores in model 1 (Crude model). B. Longitudinal changes in the differences in FSFI total scores [Positive vs. Negative (Reference)]. C. Longitudinal changes in the frequency of sexual intercourse per four weeks in model 1 (Crude model). D. Longitudinal changes of the differences in frequency of intercourse per four weeks [Positive vs. Negative (Reference)]. Model 1 was the crude model. Model 2 was adjusted for the baseline values of each outcome, the interaction term of months and baseline value of each outcome, age (≥ 50 or < 50 years), FIGO stage (I or II), bilateral salpingo-oophorectomy (BSO), postsurgical therapy, and the presence of a partner. *p < 0.05. The error bars indicate 95% control limit (CL). Detailed p values of each point and 95% CL were described in Supplementary Table S2.

Nerve-sparing radical hysterectomies improve sexual subjective symptoms in the late postoperative period

FSFI scores significantly improved 36 months after radical hysterectomy in the nerve-sparing positive group compared to the scores in the negative group in model 2 (Fig. 5A, B). Sexual intercourse frequencies over 4 weeks were very low in both groups. However, 36 months after surgery, women in the nerve-stimulation positive group had significantly more sexual intercourse than the negative group in model 1 and 2 (Fig. 5C, D). Differences between nerve-stimulation positive and negative group, and p-values are given in Supplementary Table S2.

Discussion

In the present study, we evaluated the effects of pelvic splanchnic nerve preservation on urinary and sexual symptom. We found that nerve sparing proved by objective electrical stimulation of the nerve plexus to be effective in improving early postoperative urinary symptoms and late postoperative sexual symptoms.

In Japan, the incidence of cervical cancer is increasing among young women (Tanaka et al. 2022). Therefore, the

evaluation of postoperative QOL is very important, considering the long survival time after cancer therapy. NSRH is a technique that preserves the pelvic splanchnic nerves by isolating the vascular and neural parts during the dissection of the lateral parametrium (Sakuragi and Kaneuchi 2021b). In several studies, bladder function after radical hysterectomy was evaluated using urodynamic studies (Todo et al. 2006; Chen et al. 2012). Pieterse et al. (2013) compared self-reported bladder symptoms in cervical cancer patients before and 1 and 2 years after treatment; no significant differences were detected between patients who underwent NSRH and non-NSRH. Although many reports focused on the recovery of bladder function after NSRH, no studies assessed subjective long-term urinary symptoms in detail. In this study, we assessed self-reported urinary symptoms after NSRH in a long-term study with detailed observations and demonstrated that nerve-sparing significantly improved IPSS-QOL score until 12 months after surgery and IPSS-S score at 24 months after surgery, whereas not affect other scores in the long-term. IPSS-S score evaluates the symptoms such as frequent of urination, which assumes that the desire to urinate is maintained. This result suggests that the nerve preservation, which is confirmed by intraoperative electrical stimulation, affects storage rather than urinary output symptom. In the group in which the nerves were not preserved, it can be inferred that patients feel a vague sense of discomfort regarding urination during the first postoperative year and are clearly aware of it as frequent urination symptoms during the second postoperative year, and the symptoms are improved 3 years after surgery. The detailed mechanism of this urinary symptom after NSRH will require further study.

It is not known whether damage to the bladder branch of the pelvic visceral nerve is related to sexual function. Carter et al. (2010) reported that sexual function improved gradually during the first year after radical hysterectomy, reaching a plateau between years 1 and 2. In this study, observation period was longer than previous studies (Carter et al. 2010; Wang et al. 2018; Novackova et al. 2022) and our result revealed that FSFI scores significantly differed between the nerve-sparing positive and negative groups three years after surgery. Based on this result, long-term monitoring of sexual function is needed.

One of the limitations of this study is that the frequency of sexual intercourse was very low in the participants of this study. Since the FSFI questionnaire contained many questions that were difficult to answer for women who have had sexual intercourses less frequently, it is questionable whether it is appropriate to use this questionnaire to evaluate the sexual function in this study. The sexual response in women is very complicated, and nerve preservation alone may not resolve problems related to sexual function. Another limitation is that there is insufficient study of factors other than nerve preservation that affect sexual and urinary symptoms. In the future, we will investigate these other factors that affect urinary and sexual function.

NSRH has been developed and adopted around the world over the last 20 years world (Trimbos et al. 2001), and, recently, laparoscopic and robotic approaches have increased (Oyama et al. 2019; Ceccaroni et al. 2021). Reliable preservation of nerves may help improve QOL, and endoscopic surgery such as robotic surgery, which allows delicate procedures, may be useful for this purpose.

In conclusion, we assessed self-reported urinary and sexual symptoms after NSRH with IES on the long-term in this study. We demonstrated that nerve-sparing significantly reduced distress associated with QOL until 1 year, improved urinary storage symptoms at 2 years and sexual symptoms 3 years after surgery.

Acknowledgments

This study was supported by the JSPS Grants-in-Aids for Scientific Research (22592515 to M.I.). The authors thank Enago (https://www.enago.jp) for English language review.

Author Contributions

Masumi Ishibashi: Data curation, manuscript writing and editing. H.N.: Conceptualization, data curation, manuscript review and editing. Motoko Ishida: Data curation. N.I.: Data analysis, manuscript review and editing. H.M.: Data analysis, and data interpretation. S.S.: Data curation. T.N.: Data curation, and conceptualization. H.T.: Data curation, and conceptualization. M.S.: Manuscript review and editing. N.Y.: Conceptualization, manuscript review and editing.

Conflict of Interest

The authors declare no conflict of interest.

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Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1620/tjem.2024.J014