Original Article

J Gynecol Oncol Vol. 26, No. 2:100-110
http://dx.doi.org/10.3802/jgo.2015.26.2.100
pISSN 2005-0380 · eISSN 2005-0399

Journal of Gynecologic Oncology
JGO

Conventional versus nerve-sparing radical surgery for cervical cancer: a meta-analysis

Hee Seung Kim[1,2], Keewon Kim[3], Seung-Bum Ryoo[4], Joung Hwa Seo[5], Sang Youn Kim[6], Ji Won Park[4], Min A Kim[7], Kyoung Sup Hong[8], Chang Wook Jeong[9], Yong Sang Song[1,2,10]; On behalf of FUSION Study Group*

[1]Cancer Research Institute, Departments of [2]Obstetrics and Gynecology, [3]Rehabilitation Medicine, [4]Surgery, [5]Anesthesiology and Pain Medicine, [6]Radiology, [7]Pathology, [8]Internal Medicine, and [9]Urology, Seoul National University College of Medicine, Seoul; [10]Major in Biomodulation, World Class University, Seoul National University, Seoul, Korea

See accompanying editorial by Sakuragi on page 81.

Objective: Although nerve-sparing radical surgery (NSRS) is an emerging technique for reducing surgery-related dysfunctions, its efficacy is controversial in patients with cervical cancer. Thus, we performed a meta-analysis to compare clinical outcomes, and urinary, anorectal, and sexual dysfunctions between conventional radical surgery (CRS) and NSRS.

Methods: After searching PubMed, Embase, and the Cochrane Library, two randomized controlled trials, seven prospective and eleven retrospective cohort studies were included with 2,253 patients from January 2000 to February 2014. We performed crude analyses and then conducted subgroup analyses according to study design, quality of study, surgical approach, radicality, and adjustment for potential confounding factors.

Results: Crude analyses showed decreases in blood loss, hospital stay, frequency of intraoperative complications, length of the resected vagina, duration of postoperative catheterization (DPC), urinary frequency, and abnormal sensation in NSRS, whereas there were no significant differences in other clinical parameters and dysfunctions between CRS and NSRS. In subgroup analyses, operative time was longer (standardized difference in means, 0.948; 95% confidence interval [CI], 0.642 to 1.253), while intraoperative complications were less common (odds ratio, 0.147; 95% CI, 0.035 to 0.621) in NSRS. Furthermore, subgroup analyses showed that DPC was shorter, urinary incontinence or frequency, and constipation were less frequent in NSRS without adverse effects on survival and sexual functions.

Conclusion: NSRS may not affect prognosis and sexual dysfunctions in patients with cervical cancer, whereas it may decrease intraoperative complications, and urinary and anorectal dysfunctions despite long operative time and short length of the resected vagina when compared with CRS.

Keywords: Hysterectomy; Intraoperative Complications; Meta-Analysis; Radical Surgery; Urinary Retention; Uterine Cervical Neoplasms

INTRODUCTION

Various types of conventional radical surgery (CRS), such as radical hysterectomy, radical trachelectomy, and radical parametrectomy, have shown 5-year survival rates of more than 90%, and remain the standard treatment for patients with early-stage cervical cancer [1,2]. However, CRS is known to cause urinary dysfunctions, such as bladder hypotonia, urinary incontinence, and abnormal sensation, in 12% to 85% of patients [3-5]. Furthermore, anorectal dysfunctions, including constipation, have been reported in 5% to 10% of patients after CRS [6,7]. Considerable sexual dysfunctions, including decrease in sexual interest and orgasm, and vaginal dryness, are also noticed after CRS, which compromise sexual activity

Received Jan 2, 2015, **Revised** Mar 17, 2015, **Accepted** Mar 17, 2015

*All authors are included in FUSION (Functional Surgery and Imaging on Neoplasms) Study Group.

Correspondence to Yong Sang Song
Department of Obstetrics and Gynecology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea.
E-mail: yssong@snu.ac.kr

Copyright © 2015. Asian Society of Gynecologic Oncology, Korean Society of Gynecologic Oncology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

and result in substantial distress [8].

Urinary, anorectal, and sexual dysfunctions are known to be caused by injury to of the pelvic autonomic nerves during CRS. These nerves play a major role for the neurogenic control of urinary and anorectal functions. Moreover, they supply blood vessels of the female genital tract and thereby affect sexual activity by neurogenically controlling its lubrication or swelling response [9]. Thus, nerve-sparing radical surgery (NSRS) has emerged in the last 30 years for reducing surgery-related dysfunctions without compromising oncologic outcomes [10]. However, the efficacy and safety of NSRS are still controversial in comparison with CRS despite a growing number of studies addressing the issue of NSRS. In particular, major limitations are no consensus on which part of the uterine-supporting ligaments the nerve-sparing technique should be directed to, an unresolved concern about whether NSRS may interfere with radicality necessary for treating cervical cancer, and a debate on the discrepancy in prognosis between CRS and NSRS.

Although three prospective randomized controlled trials (RCTs) and one systematic review with a meta-analysis have been published up to now [11-14], they are not enough to clarify the efficacy and safety of NSRS in cervical cancer due to small numbers of enrolled patients and non-English literature that hinder extraction of relevant data. Thus, this meta-analysis was performed to compare clinical outcomes, and urinary, anorectal, and sexual dysfunctions between CRS and NSRS in patients with early-stage cervical cancer.

MATERIALS AND METHODS

1. Search strategy and selection criteria

This meta-analysis was conducted in line with the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. For this meta-analysis, we searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library for relevant studies published from January 2000 to February 2014 inclusive using the following terms: "cervical neoplasm(s)" or "cervical cancer" or "cervical carcinoma," and "nerve sparing."

We included relevant studies that met the following criteria: cervical cancer; comparison of clinical outcomes between CRS and NSRS; and comparison of urinary, anorectal, or sexual dysfunctions between CRS and NSRS. However, review articles, case reports, editorials or letters to the editor, and non-English studies that did not meet the selection criteria were excluded from this meta-analysis.

2. Selection of studies

Two of the authors (HSK and KK) independently evaluated the potential eligibility of all studies retrieved from the database based on the predetermined selection and exclusion criteria, and the third author (CWJ) resolved disagreement between the two authors through consensus conference. A total of 166 studies were identified, and we excluded 27 duplicates and 51 studies, including reviews (n=23), non-English literature (n=13), editorials or letters to the editor (n=9), and case reports (n=6). In addition, we excluded 54 studies due to non-comparative studies (n=41) and non-cervical cancer (n=13). Thirteen studies were also excluded due to data on surgical technique or anatomy only (n=8), and lack of data for comparison (n=5). Finally, two RCTs [12,13], seven prospective cohort [7,9,16-20], and 11 retrospective cohort studies [10,21-30] were included in this meta-analysis (**Fig. 1**).

3. Data collection

Data extraction was performed by two authors (HSK and SBR), and any discrepancies were addressed by a joint re-evaluation of the article with the third author (KSH). The following data were independently extracted from each study for this meta-analysis: the first author; period of enrollment; study design; the International Federation of Gynecology and Obstetrics (FIGO) stage; surgical approach; surgical types such as radical hysterectomy, radical trachelectomy, or radical parametrectomy; radicality of surgery; number of patients with cervical cancer who underwent CRS or NSRS; neoadjuvant chemotherapy (NAC); adjustment for potential confounding factors; clinical outcomes, including operative time (minute), blood loss (mL), hospital stay (day), intraoperative or postoperative complications, length of the resected vagina or parametrium (mm), disease-free survival (DFS), and overall survival (OS); urinary dysfunctions, including duration of postoperative catheterization (DPC, day), urinary incontinence and frequency, urinary retention and urgency and dysuria; anorectal dysfunctions including constipation, diarrhea and fecal incontinence; and sexual dysfunctions, including a decrease in sexual interest, dyspareunia, decreases in orgasm and sexual satisfaction, and vaginal dryness.

Since the classification of radical surgeries for cervical cancer has been changed from the Piver-Rutledge system to the Querleu-Morrow system since 2008 [31,32], we considered that types II and III were similar to types B and C, respectively. In particular, NSRS was evaluated by full review of some studies where the Piver-Rutledge system was used due to no subtype for defining NSRS [7,9,10,12,13,16-18,20-22,27-30], whereas type C1 was considered to be NSRS in other studies based on the Querleu-Morrow system [19,23-26].

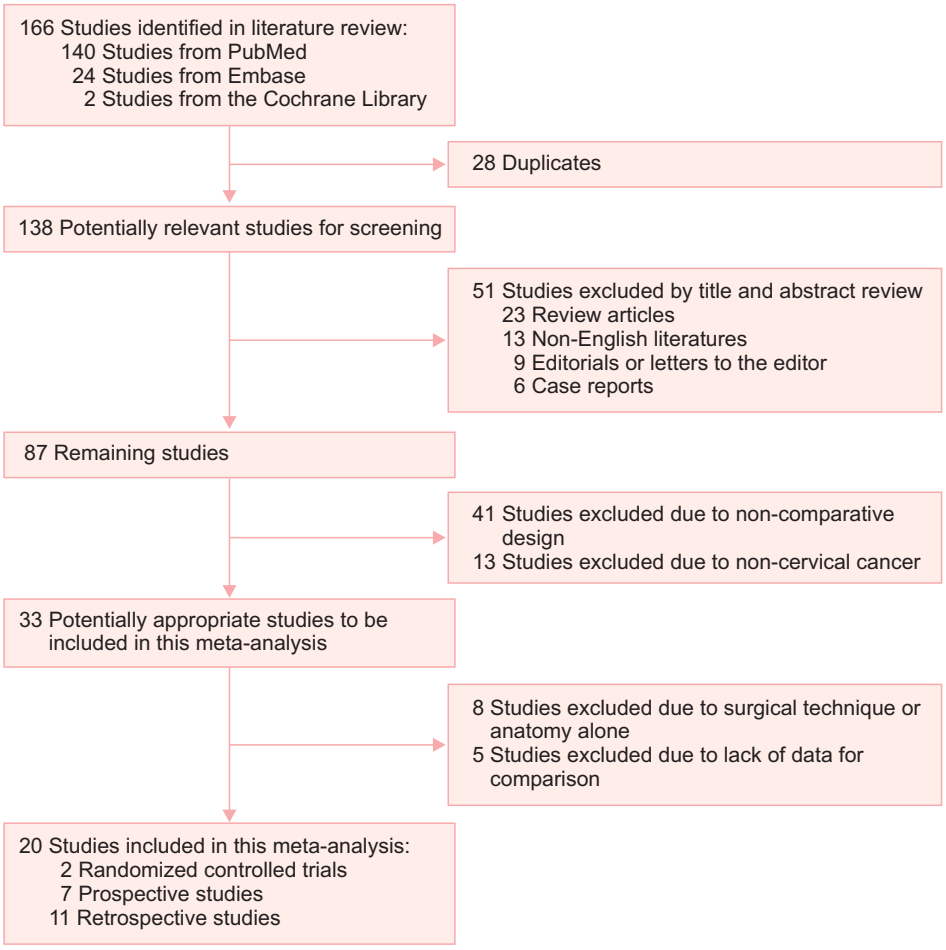


Fig. 1. PRISMA diagram. The search strategy and number of studies identified for inclusion in this meta-analysis.

Bladder injury, bowel perforation, vessel injury, and hemorrhage with estimated blood loss >1,000 mL were considered to be intraoperative complications [25,27,28]. Postoperative complications included acute renal failure, bleeding from surgical sites, dysesthesia, febrile morbidity, ileus, infection on surgical sites, lymphocele, metabolic complications, pyelonephritis, reoperation, thromboembolism, and ureteral fistula or stenosis [10,12,18,21,24, 27, 28, 30]. DPC was defined as the time to achieve postvoid residual urine of ≤50 [13,16,18,19,23,25] or ≤100 mL [12,21,24,28,30]. Urinary, anorectal, and sexual dysfunctions were evaluated through interviews or self-reports 6 [19,30] or 12 months after surgery [9,12,20,22,28,29].

4. Quality assessment

In CRS sacrificing the pelvic autonomic nerves—the hypogastric nerve containing sympathetic nerves, the pelvic splanchnic nerve containing parasympathetic nerves, and the vesical branch of pelvic plexus containing both sympathetic and parasympathetic nerves—are known to be easily injured during dissection of the uterosacral ligament, the parametrium, and the posterior part of the vesicouterine ligament, respectively [9]. Thus, we focused on whether each of the three nerves was preserved by NSRS to assess the quality of individual studies because they used different nerve-sparing techniques. As a result, it was found that the three nerves were preserved in all except one study [16], and only five studies confirmed the success rate of the nerve-sparing technique on at least one side (**Supplementary Table 1**) [17-19,22,29].

Furthermore, we assessed the quality of individual studies using the Newcastle-Ottawa Scale (NOS) for 18 enrolled cohort studies [33]. The NOS consists of the following three parameters of quality: selection, comparability, and outcome. It assigns a maximum of four points for selection, two points for comparability, and three points for outcome. In this meta-analysis, we considered a study with an NOS score of ≥8 to be a high-quality study because the mean NOS score was 7.6. As a result, 10 studies (55.6%) showed high quality (**Supplementary Table 2**).

 http://dx.doi.org/10.3802/jgo.2015.26.2.100

5. Statistical analyses

Continuous variables were shown as standard difference in means (SDMs) with 95% confidence intervals (CIs), which were calculated from mean, SD or p-value, and sample size in each study. Dichotomous data eligible in each study were demonstrated as an odds ratio (OR) with 95% CIs. Furthermore, we conducted survival analysis using a statistical method describer by Tierney et al. [34]. Heterogeneity was assessed using Higgins I^2, evaluating the percentage of total variation across studies which was due to heterogeneity rather than chance [35]. Thus, an I^2 of >50% was considered to represent substantial heterogeneity, and thereby we used the random effects model using the DerSimonian and Laird method. On the other hand, the fixed effect model using the Mantel-Haenszel method was employed when I^2 was ≤50% because it meant no heterogeneity.

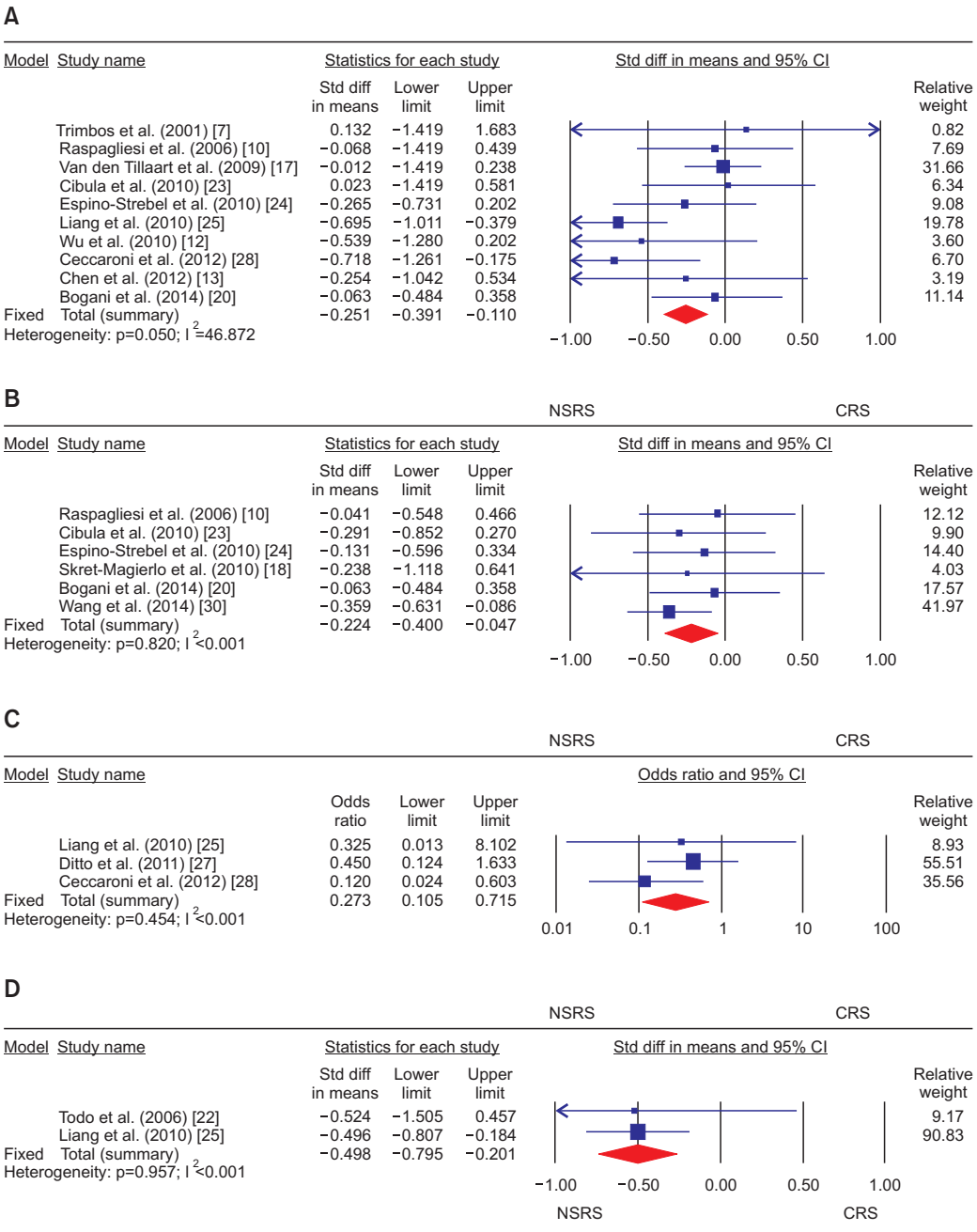


Fig. 2. Forest plots for standard differences (Std diffs) in means or odds ratios with 95% confidence intervals (CIs) to compare (A) blood loss, (B) hospital stay, (C) intraoperative complications, and (D) the length of the resected vagina between conventional radical surgery (CRS) and nerve-sparing radical surgery (NSRS) for cervical cancer.

Funnel plots were represented to identify publication bias, which were scattered plots of SMDs, ORs, or hazard ratios of individual studies on the *x* axis against the standard error on the y axis. As a result, all funnel plots resembled symmetric inverter funnels, suggesting no publication bias in this meta-analysis. Moreover, we performed Egger's test if at least three studies were included for each outcome and thereby found no publication bias (p>0.05) (**Supplementary Fig. 1**). For this meta-analysis, we used SPSS ver. 19.0 (SPSS Inc., Chicago, IL, USA) and Comprehensive Meta-Analysis ver. 2.0 (Biostat Inc., Englewood, NJ, USA). A p-value of <0.05 was considered to be statistically significant.

RESULTS

Supplementary Table 3 shows the general characteristics of 20 comparative studies that included 2,253 patients with cervical cancer. Among them, 1,130 (50.2%) underwent CRS, while 1,145 (49.8%) received NSRS, and there was no significant difference in the frequency of NAC between CRS and NSRS in all except two studies [27,30]. Furthermore, potential confounding factors, including age, adjuvant treatment, body mass index, FIGO stage, depth of stromal invasion, extent of lymphadenectomy, grade, histology, lymph node metastasis, number of resected lymph nodes, parametrial invasion, positive resection margin, and tumor size were adjusted in most of the studies.

As a result, crude analyses showed that blood loss (SDM, –0.251; 95% CI, –0.391 to –0.110) and hospital stay (SDM, –0.224; 95% CI, –0.400 to –0.047) were less, and intraoperative complications (OR, 0.273; 95% CI, 0.105 to 0.715) were less common in patients treated with NSRS. Moreover, the length of the resected vagina was significantly shorter in NSRS than in CRS (SDM, –0.498; 95% CI, –0.795 to –0.201) (**Fig. 2**). However, there were no significant differences in operative time, postoperative complications, the length of the resected parametrium, DFS, and OS between the two groups (**Supplementary Fig. 2**).

Table 1. Subgroup analyses for comparing clinical outcomes between conventional and nerve sparing radical surgery for cervical cancer

Category	No. of studies	SDM or OR	95% CI	Heterogeneity		Model used
				p-value	I^2	
Operative time*						
Study design						
RCT	2	0.263	–0.834 to 1.360	0.046	74.987	Random effects
Prospective	4	–0.691	–1.809 to 0.426	<0.001	93.027	Random effects
Retrospective	6	0.253	–0.141 to 0.647	<0.001	81.160	Random effects
Quality of study (NOS)						
≥8	6	–0.186	–1.088 to 0.717	<0.001	97.305	Random effects
<8	4	0.086	–0.574 to 0.747	0.024	65.709	Random effects
Surgical approach						
Laparotomy	9	–0.141	–0.861 to 0.579	<0.001	94.381	Random effects
Laparoscopy	2	0.174	–1.364 to 1.711	<0.001	96.935	Random effects
Radicality						
Type III or C	11	0.328	–0.635 to 0.652	<0.001	94.333	Random effects
Adjustment for potential confounding factors						
Age, BMI, FIGO stage	7	0.253	–0.255 to 0.735	<0.001	85.516	Random effects
Age, BMI, extent of lymphadenetomy, FIGO stage,	6	0.275	–0.380 to 0.697	<0.001	88.314	Random effects
Age, BMI, extent of lymphadenectomy, FIGO stage, no. of resected LNs	2	0.948	0.642 to 1.253	0.942	<0.001	Fixed effect
Intraoperative complications†						
Adjustment for potential confounding factors						
Age, extent of lymphadenectomy, FIGO stage, no. of resected LNs	2	0.147	0.035 to 0.621	0.588	<0.001	Fixed effect

BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LNs, lymph nodes; NOS, the Newcastle-Ottawa Scale; RCT, randomized controlled trial.
*SDM, standard difference in mean; †OR, odds ratio.

http://dx.doi.org/10.3802/jgo.2015.26.2.100

Table 2. Subgroup analyses for comparing survival between conventional and nerve sparing radical surgery for cervical cancer

Category	No. of studies	HR	95% CI	Heterogeneity		Model used
				p-value	I^2	
Disease-free survival						
Study design, and quality of study (NOS)						
Prospective and NOS=8	3	1.026	0.673–1.565	0.468	<0.001	Fixed effect
Surgical approach						
Laparotomy	3	1.038	0.666–1.618	0.403	<0.001	Fixed effect
Radicality						
Type III or C	2	1.003	0.635–1.585	0.228	31.146	Fixed effect
Adjustment for potential confounding factors						
Age, adjuvant treatment, extent of lymphadenectomy, FIGO stage, LNM	2	1.453	0.691–3.054	0.598	<0.001	Fixed effect
Overall survival						
Study design, and quality of study (NOS)						
Prospective, and NOS=8	3	1.075	0.433–2.611	0.054	65.805	Random effects
Surgical approach						
Laparotomy	3	1.124	0.422–2.944	0.044	68.098	Random effects
Radicality						
Type III or C	3	0.862	0.324–2.293	0.095	57.436	Random effects
Adjustment for potential confounding factors						
Age, adjuvant treatment, extent of lymphadenectomy, FIGO stage, LNM	2	1.680	0.862–3.274	0.774	<0.001	Fixed effect

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; LNM, lymph node metastasis; NOS, the Newcastle-Ottawa Scale.

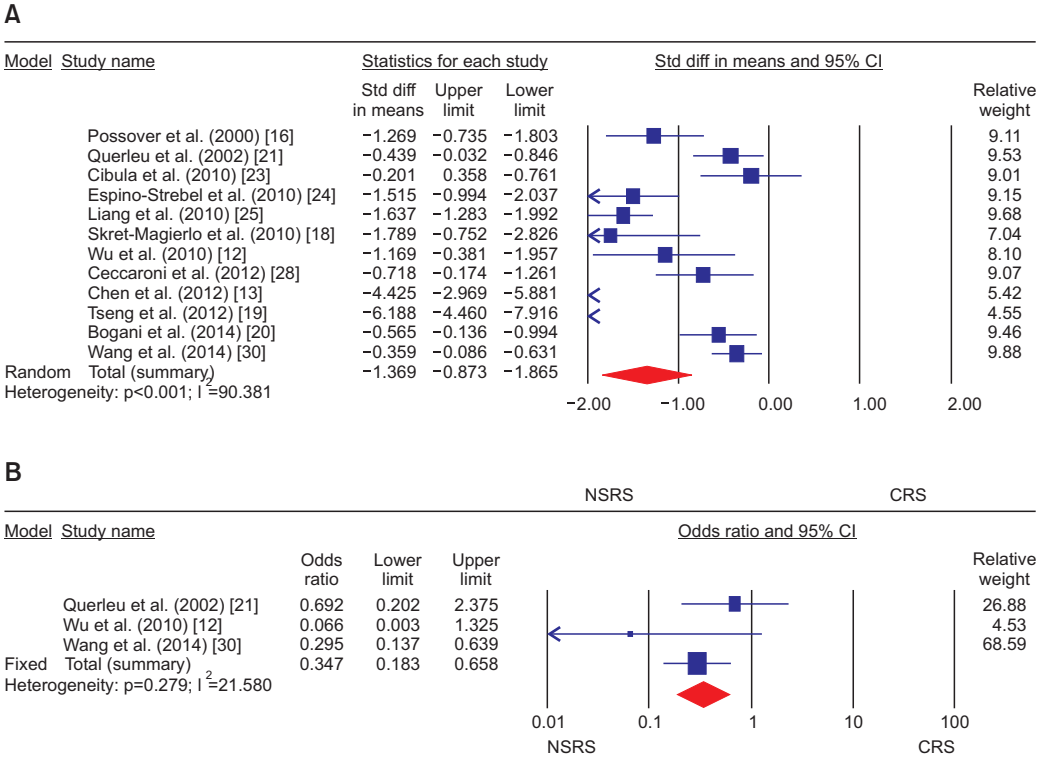


Fig. 3. Forest plots for standard differences (Std diffs) in means or odds ratios with 95% confidence intervals (CIs) to compare (A) the duration of post-operative catheterization, (B) urinary frequency between conventional radical surgery (CRS) and nerve-sparing radical surgery (NSRS) for cervical cancer.

When we performed subgroup analyses for at least three studies to evaluate each outcome according to study design, quality of study, surgical approach, radicality, and adjustment for potential confounding factors, operative time (SDM, 0.948; 95% CI, 0.642 to 1.253) was longer, and intraoperative complications were less common (OR, 0.147; 95% CI, 0.035 to 0.621) in NSRS (**Table 1**), whereas there were no differences in blood loss, hospital stay, and postoperative complications between NSRS and CRS after adjustment for age, body mass index, extent of lymphadenectomy, FIGO stage, and number of resected lymph nodes (**Supplementary Table 4**). In terms of survival, DFS and OS were not different between the two treatments (**Table 2**).

In regard to urinary dysfunctions, crude analyses demonstrated that DPC was shorter (SDM, –1.369; 95% CI, –1.865 to –0.873), and urinary frequency and abnormal sensation were less common in NSRS (OR, 0.347 and 0.067; 95% CI, 0.183 to 0.658 and 0.013 to 0.340, respectively) (**Fig. 3**). However, there were no significant differences in urinary incontinence, urinary retention, dysuria, and urinary urgency between CRS and NSRS (**Supplementary Fig. 3**). In terms of anorectal dysfunctions, there were no significant differences in constipation, diarrhea, and fecal incontinence between the two treatments. Furthermore, a decrease in sexual interest, dyspareunia, a decrease in orgasm, or sexual satisfaction, and vaginal dryness were not significantly different between CRS and NSRS (**Supplementary Fig. 4**).

In subgroup analyses based on study design, quality of study, surgical approach, radicality, postvoid residual urine volume not requiring DPC, follow-up for evaluating dysfunctions, and adjustment for potential confounding factors, DPC was still shorter, and urinary incontinence and urinary frequency were less common in NSRS. Furthermore, constipation was less frequent in NSRS after adjustment for age, adjuvant treatment, extent of lymphadenectomy, and FIGO stage (OR, 0.177; 95% CI, 0.078 to 0.401) (**Table 3**). However, there were no significant differences in sexual dysfunctions between CRS and NSRS (**Supplementary Table 5**).

Table 3. Subgroup analyses for comparing postoperative urinary and anorectal functions between conventional and nerve sparing radical surgery for cervical cancer

Category	No. of studies	SDM or OR	95% CI	Heterogeneity		Model used
				p-value	I^2	
DPC*						
Study design						
RCT	2	–1.907	–2.600 to –1.214	<0.001	93.268	Random effects
Prospective	4	–2.167	–3.524 to –0.810	<0.001	92.750	Random effects
Retrospective	6	–0.813	–1.330 to –0.296	<0.001	89.152	Random effects
Quality of study (NOS)						
≥8	6	–1.002	–1.495 to –0.508	<0.001	88.011	Random effects
<8	4	–1.874	–3.331 to –0.418	<0.001	93.695	Random effects
Surgical approach						
Laparotomy	7	–1.958	–2.914 to –1.003	<0.001	93.118	Random effects
Laparoscopy	4	–0.978	–1.586 to –0.370	<0.001	87.814	Random effects
Radicality						
Type III or C	10	–1.622	–2.236 to –1.007	<0.001	91.472	Random effects
Postvoid residual urine not requiring DPC (mL)						
<50	6	–2.178	–3.243 to –1.113	<0.001	93.632	Random effects
<100	5	–0.616	–0.805 to –0.428	0.001	77.275	Random effects
Adjustment for potential confounding factors						
Age, extent of lymphadenectomy, FIGO stage	6	–0.982	–1.510 to –0.454	<0.001	86.496	Random effects
Age, extent of lymphadenectomy, FIGO stage, no. of resected LNs	2	–1.653	–1.989 to –1.318	0.786	<0.001	Fixed effect

CI, confidence interval; DPC, duration of postoperative catheterization; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; NOS, the Newcastle-Ottawa Scale; RCT, randomized controlled trial.
*SDM, standard difference in mean; †OR, odds ratio.

http://dx.doi.org/10.3802/jgo.2015.26.2.100

Table 3. Continued

Category	No. of studies	SDM or OR	95% CI	Heterogeneity		Model used
				p-value	I^2	
Urinary incontinence†						
Study design						
Prospective	3	0.325	0.023 to 4.634	0.041	68.702	Random effects
Retrospective	5	0.592	0.403 to 0.869	0.103	48.005	Fixed effect
Quality of study (NOS)						
≥8	4	0.519	0.242 to 1.117	0.105	51.099	Random effects
<8	3	0.750	0.121 to 4.639	0.057	65.199	Random effects
Radicality						
Type III or C	7	0.509	0.230 to 1.128	0.050	52.390	Random effects
Follow-up for evaluating dysfunctions (mo)						
6	2	0.214	0.018 to 2.507	0.090	65.272	Random effects
12	6	0.743	0.273 to 2.025	0.072	50.492	Random effects
Adjustment for potential confounding factors						
Age, adjuvant treatment, FIGO stage	5	0.539	0.361 to 0.803	0.159	39.262	Fixed effect
Age, adjuvant treatment, extent of lymphadenectomy, FIGO stage	4	0.489	0.288 to 0.830	0.098	52.298	Random effects
Urinary frequency†						
Surgical approach, radicality, and adjustment for potential confounding factors						
Laparotomy, and type III or C, and age, adjuvant treatment, extent of lymphadenectomy, FIGO stage	2	0.269	0.914 to 0.568	0.342	<0.001	Fixed effect
Urinary retention†						
Follow-up for evaluating dysfunctions (mo)						
6	2	0.143	0.006 to 3.183	0.039	76.601	Random effects
Quality of study (NOS), and adjustment for potential confounding factors						
≥8, and age, adjuvant treatment, extent of lymphadenectomy, FIGO stage	2	0.301	0.051 to 1.762	0.173	46.252	Fixed effect
Constipation†						
Study design						
Prospective	2	0.648	0.153 to 2.749	0.491	<0.001	Fixed effect
Retrospective	3	0.353	0.088 to 1.420	0.005	81.351	Random effects
Quality of study (NOS)						
≥8	4	0.343	0.102 to 1.159	0.012	72.430	Random effects
Surgical approach						
Laparotomy	3	0.457	0.106 to 1.965	0.005	81.459	Random effects
Radicality						
Type III or C	4	0.426	0.140 to 1.292	0.011	73.119	Random effects
Follow-up for evaluating dysfunctions (mo)						
12	4	0.765	0.426 to 1.371	0.519	<0.001	Fixed effect
Adjustment for potential confounding factors						
Age, adjuvant treatment, FIGO stage	4	0.343	0.102 to 1.159	0.012	72.430	Random effects
Age, adjuvant treatment, extent of lymphadenectomy, FIGO stage	3	0.177	0.078 to 0.401	0.509	<0.001	Fixed effect

CI, confidence interval; DPC, duration of postoperative catheterization; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; NOS, the Newcastle-Ottawa Scale; RCT, randomized controlled trial.
*SDM, standard difference in mean; †OR, odds ratio.

DISCUSSION

Recent RCTs and one systematic review with a meta-analysis have reported the advantages of NSRS [11,14]. However, they have some limitations as follows: small numbers of studies with low quality of RCTs: seven studies (41.2%) published in the Chinese literature in the systematic review with a meta-analysis, which can act as a bias to interpret meta-analytic results because of difficulty in accessing full papers and the disadvantage that most of the relevant studies have been performed in the limited area [11,36-41]; a lack of relevant studies comparing prognosis, anorectal or sexual dysfunctions between the two treatments. Although this meta-analysis could not also overcome these limitations completely, it has major advantages as follows: (1) inclusion of the largest number of relevant English literature which enabled us to compare most of the surgery-related issues between CRS and NSRS; (2) definition of the pelvic autonomic nerves which should be spared in NSRS in spite of different techniques; (3) comparison of urinary, anorectal, and sexual dysfunctions between the two treatments in terms of long-term outcomes (6 or 12 months after surgery); (4) subgroup analyses based on study design, quality of study, surgical approach, radicality, and adjustment for potential confounding factors in order to minimize bias.

As a result, we found that operative time was longer, and intraoperative complications were less common in NSRS despite no significant differences in blood loss, hospital stay, and postoperative complications. Longer operative time and less frequent intraoperative complications may result from more care taken to avoid damaging the pelvic nerves during NSRS. Thus, the surgical field can be dissected even wider than CRS, and meticulous and precise dissection can contribute to decreases in blood loss and injury to adjacent organs [12,42].

Secondly, the length of the resected vagina was shorter in NSRS, while the length of the resected parametrium, DFS, and OS were not significantly different between CRS and NSRS. These finding can be supported by some studies suggesting that the level of colpectomy should be restricted to 2 cm in order to preserve the most distal portion of the vesical branch of the pelvic plexus [16,24,43]. On the other hand, the safety of NSRS still remains controversial because of the concerns of less radicality of NSRS [44,45]. Although this meta-analysis was performed under the conditions that radicality could affect prognosis (up to 90% of patients with a large tumor of >4 cm, and less than 50% of them who received adjuvant radiotherapy), it demonstrated that NSRS may not reduce the radicality affecting prognosis.

Thirdly, DPC was shorter, and urinary incontinence and frequency were less common in NSRS. Sympathetic nerves in the hypogastric nerve and the vesical branch of the pelvic plexus stimulate the urethral sphincter and inhibit the detrusor muscle of the bladder, whereas parasympathetic nerves in the pelvic splanchnic nerve and the vesical branch of the pelvic plexus relax the urethral sphincter and stimulate the detrusor muscle of the bladder [10,46]. Thus, CRS may increase DPC, and urinary incontinence and frequency can be expected by autonomic dysregulation after surgical disruption [21,22,47,48]. Thus, these meta-analyses is meaningful in supporting the efficacy of autonomic nerve preservation by NSRS on urinary functions.

Fourthly, constipation was less common in NSRS. Sympathetic nerves inhibit the expulsion of feces and stimulate the internal sphincter of the anus, whereas parasympathetic nerves show opposite effects [10,46]. In particular, a previous study has suggested the hypothesis that injury to the pelvic autonomic nerves by CRS disrupts the spinal reflex, which causes internal sphincter dysregulation and decreased rectal sensation [6]. Thus, this meta-analysis supports the hypothesis and suggests that NSRS may reduce the incidence of functional defecation disorders, such as constipation.

Fifthly, there were no significant differences in sexual dysfunctions between CRS and NSRS. Theoretically, autonomic nerve fibers in the vascular smooth muscle cells of the vagina innervate reproductive organs and are responsive to circulating steroids [49]. Thus, damage to autonomic nerves caused by CRS may change the neurogenic control of the blood vessels of the vagina wall and thereby disturbs vaginal blood flow during sexual arousal and lubrication-swelling response [9,49-51]. However, this meta-analysis failed to show a decrease in sexual dysfunctions by NSRS in comparison with CRS, which means that autonomic nerve preservation may not be associated with the improvement in sexual functions and that multiple factors, including vaginal shortness, tissue fibrosis, radiotherapy, a decrease in ovarian function, and psychological factors, may be more important to improve sexual functions [30].

When we consider that the nerve-sparing technique is not currently uniform, and thereby a large-scale RCT is not easy to perform, this meta-analysis is important because it showed the possibility that NSRS can give better quality of life by preserving urinary and anorectal functions without adverse effects on clinical outcomes and sexual functions in patients with early-stage cervical cancer. Furthermore, it is helpful in planning large-scale prospective randomized trials for valuable epidemiologic evidence.

http://dx.doi.org/10.3802/jgo.2015.26.2.100

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

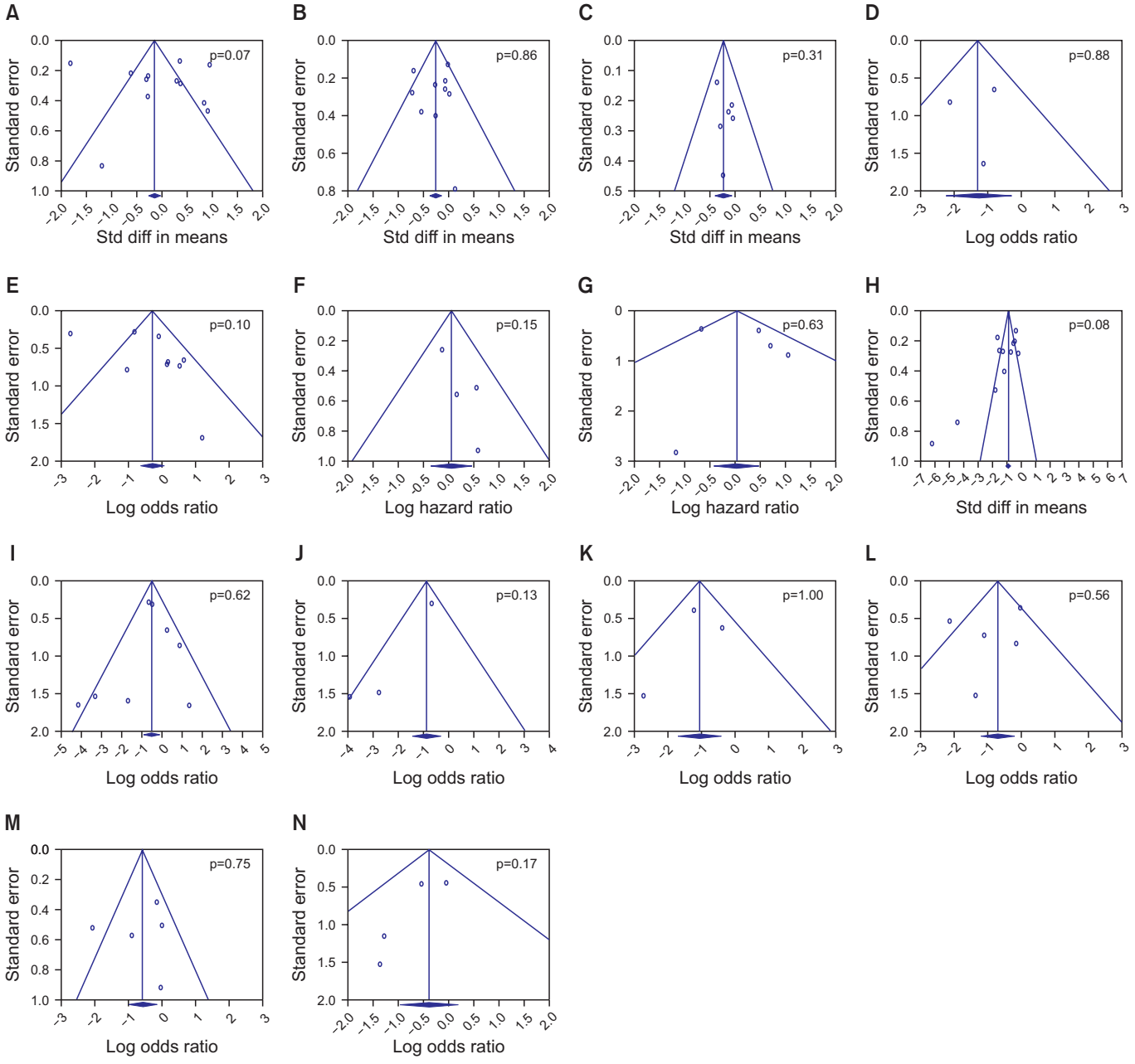
We appreciate the Medical Research Collaborating Center (MRCC) of Seoul National University Hospital for statistical analysis. This research was supported by grants (No. 04-2012-0890; 03-2012-0170) from the Seoul National University Hospital research fund and the Priority Research Centers Program (No. 2009-0093820), Basic Science Research Program (No. 2011-0025394), and BK21 plus program (No. 5256-20140100) through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology. Moreover, it was also supported by a grant of the Korean Health Technology R&D Project, Ministry of Health of Welfare (HI14C2404).

REFERENCES

1. Ditto A, Martinelli F, Borreani C, Kusamura S, Hanozet F, Brunelli C, et al. Quality of life and sexual, bladder, and intestinal dysfunctions after class III nerve-sparing and class II radical hysterectomies: a questionnaire-based study. Int J Gynecol Cancer 2009;19:953-7.
2. Kim HS, Choi CH, Lim MC, Chang SJ, Kim YB, Kim MA, et al. Safe criteria for less radical trachelectomy in patients with early-stage cervical cancer: a multicenter clinicopathologic study. Ann Surg Oncol 2012;19:1973-9.
3. Suh DH, Kim JW, Kang S, Kim HJ, Lee KH. Major clinical research advances in gynecologic cancer in 2013. J Gynecol Oncol 2014;25:236-48.
4. Choi SY, Lee KH, Suk HJ, Chae HD, Kang BM, Kim CH. Successful pregnancy by direct intraperitoneal insemination in an infertile patient with failure of recanalization of isthmic stenosis after laparoscopic radical trachelectomy. Obstet Gynecol Sci 2014;57:82-5.
5. Zullo MA, Manci N, Angioli R, Muzii L, Panici PB. Vesical dysfunctions after radical hysterectomy for cervical cancer: a critical review. Crit Rev Oncol Hematol 2003;48:287-93.
6. Barnes W, Waggoner S, Delgado G, Maher K, Potkul R, Barter J, et al. Manometric characterization of rectal dysfunction following radical hysterectomy. Gynecol Oncol 1991;42:116-9.
7. 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 2001;11:180-6.
8. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. N Engl J Med 1999;340:1383-9.
9. Pieterse QD, Ter Kuile MM, Deruiter MC, Trimbos JB, Kenter GG, Maas CP. Vaginal blood flow after radical hysterectomy with and without nerve sparing. A preliminary report. Int J Gynecol Cancer 2008;18:576-83.
10. Raspagliesi F, Ditto A, Fontanelli R, Zanaboni F, Solima E, Spatti G, et al. Type II versus type III nerve-sparing radical hysterectomy: comparison of lower urinary tract dysfunctions. Gynecol Oncol 2006;102:256-62.
11. Li B, Zhang R, Wu LY, Zhang GY, Li X, Yu GZ. A prospective study on nerve-sparing radical hysterectomy in patients with cervical cancer. Zhonghua Fu Chan Ke Za Zhi 2008;43:606-10.
12. Wu J, Liu X, Hua K, Hu C, Chen X, Lu X. Effect of nerve-sparing radical hysterectomy on bladder function recovery and quality of life in patients with cervical carcinoma. Int J Gynecol Cancer 2010;20:905-9.
13. Chen C, Li W, Li F, Liu P, Zhou J, Lu L, et al. Classical and nerve-sparing radical hysterectomy: an evaluation of the nerve trauma in cardinal ligament. Gynecol Oncol 2012;125:245-51.
14. Long Y, Yao DS, Pan XW, Ou TY. Clinical efficacy and safety of nerve-sparing radical hysterectomy for cervical cancer: a systematic review and meta-analysis. PLoS One 2014;9:e94116.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62:e1-34.
16. 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;79:154-7.
17. van den Tillaart SA, Kenter GG, Peters AA, Dekker FW, Gaarenstroom KN, Fleuren GJ, et al. Nerve-sparing radical hysterectomy: local recurrence rate, feasibility, and safety in cervical cancer patients stage IA to IIA. Int J Gynecol Cancer 2009;19:39-45.
18. Skret-Magierlo J, Narog M, Kruczek A, Kluza R, Kluz T, Magon T, et al. Radical hysterectomy during the transition period from traditional to nerve-sparing technique. Gynecol Oncol 2010;116:502-5.
19. Tseng CJ, Shen HP, Lin YH, Lee CY, Wei-Cheng Chiu W. A prospective study of nerve-sparing radical hysterectomy for uterine cervical carcinoma in Taiwan. Taiwan J Obstet Gynecol 2012;51:55-9.
20. Bogani G, Cromi A, Uccella S, Serati M, Casarin J, Pinelli C, et al. Nerve-sparing versus conventional laparoscopic radical hysterectomy: a minimum 12 months' follow-up study. Int J Gynecol Cancer 2014;24:787-93.
21. Querleu D, Narducci F, Poulard V, Lacaze S, Occelli B, Leblanc E, et al. Modified radical vaginal hysterectomy with or without laparoscopic nerve-sparing dissection: a comparative study. Gynecol Oncol 2002;85:154-8.
22. Todo Y, Kuwabara M, Watari H, Ebina Y, Takeda M, Kudo M, et al. Urodynamic study on postsurgical bladder function in cervical cancer treated with systematic nerve-sparing radical hysterectomy. Int J Gynecol Cancer 2006;16:369-75.
23. Cibula D, Slama J, Velechovska P, Fischerova D, Zikan M, Pinkavova

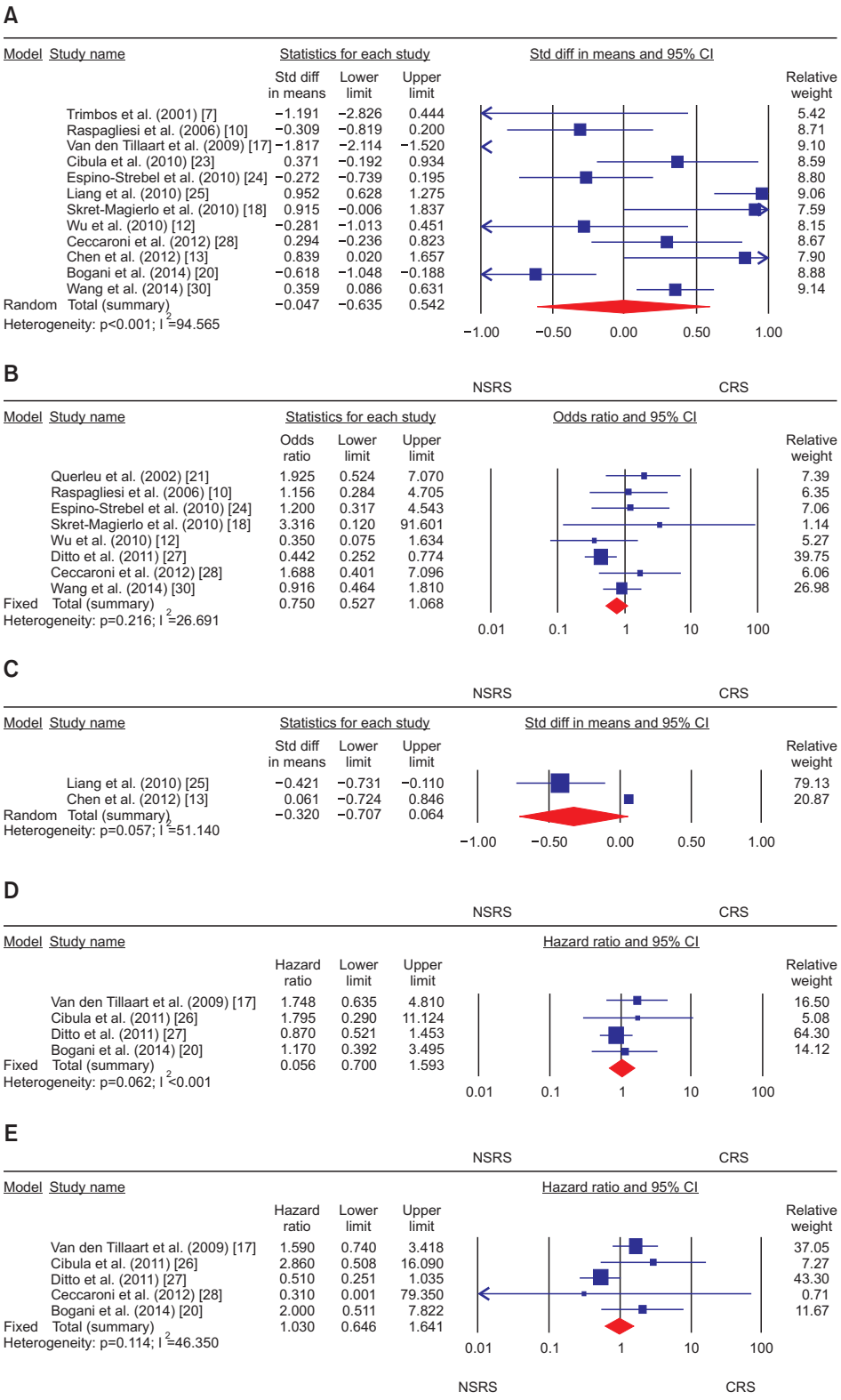
I, et al. Factors affecting spontaneous voiding recovery after radical hysterectomy. Int J Gynecol Cancer 2010;20:685-90.
24. Espino-Strebel EE, Luna JT, Domingo EJ. A comparison of the feasibility and safety of nerve-sparing radical hysterectomy with the conventional radical hysterectomy. Int J Gynecol Cancer 2010;20:1274-83.
25. Liang Z, Chen Y, Xu H, Li Y, Wang D. Laparoscopic nerve-sparing radical hysterectomy with fascia space dissection technique for cervical cancer: description of technique and outcomes. Gynecol Oncol 2010;119:202-7.
26. Cibula D, Pinkavova I, Dusek L, Slama J, Zikan M, Fischerova D, et al. Local control after tailored surgical treatment of early cervical cancer. Int J Gynecol Cancer 2011;21:690-8.
27. Ditto A, Martinelli F, Mattana F, Reato C, Solima E, Carcangiu M, et al. Class III nerve-sparing radical hysterectomy versus standard class III radical hysterectomy: an observational study. Ann Surg Oncol 2011;18:3469-78.
28. Ceccaroni M, Roviglione G, Spagnolo E, Casadio P, Clarizia R, Peiretti M, et al. Pelvic dysfunctions and quality of life after nerve-sparing radical hysterectomy: a multicenter comparative study. Anticancer Res 2012;32:581-8.
29. Pieterse QD, Kenter GG, Maas CP, de Kroon CD, Creutzberg CL, Trimbos JB, et al. Self-reported sexual, bowel and bladder function in cervical cancer patients following different treatment modalities: longitudinal prospective cohort study. Int J Gynecol Cancer 2013;23:1717-25.
30. Wang W, Li B, Zuo J, Zhang G, Yang Y, Zeng H, et al. Evaluation of pelvic visceral functions after modified nerve-sparing radical hysterectomy. Chin Med J (Engl) 2014;127:696-701.
31. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol 1974;44:265-72.
32. Querleu D, Morrow CP. Classification of radical hysterectomy. Lancet Oncol 2008;9:297-303.
33. Wells GA, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa: Ottawa Hospital Research Institute; c2014 [cited 2015 Mar 17]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
34. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
35. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
36. Sun L, Wu LY, Zhang WH, Li XG, Song Y, Zhang X. Preliminary study of nerve sparing radical hysterectomy in patients with cervical cancer. Zhonghua Zhong Liu Za Zhi 2009;31:607-11.
37. Long Y, Yao DS, Gao K, Xie XL. Preliminary study on clinical effect of nerve sparing radical hysterectomy for cervical cancer. Chin Clin Oncol 2010;15:1083-90.
38. Zhu T, Yu AJ, Shou HF, Chen X, Zhu JQ, Yang ZY, et al. Feasibility of unilateral or bilateral nerve-sparing radical hysterectomy in patients with cervical cancer and evaluation of the post-surgery recovery of the bladder and rectal function. Zhonghua Zhong Liu Za Zhi 2011;33:53-7.
39. Chen Y, Li Y, Xu HC, Li JN, Li YY, Liang ZQ. Laparoscopic anatomical nerve sparing radical hysterectomy for cervical cancer: a clinical analysis of 37 cases. Zhonghua Fu Chan Ke Za Zhi 2009;44:359-63.
40. Zhang Y, Wang D, Ma Y, Pan CQ. A clinical study of surgical treatment of the cervical cancer with laparoscopic nerve sparing radical hysterectomy. Prog Obstet Gynecol 2010;19:31-2.
41. Lu Y, Yao DS, Mo LZ, Li F, Pan ZM. Preliminary clinical study of laparoscopic pelvic autonomic nerve-plane sparing radical hystrectomy. Chin Clin Oncol 2012;17:347-50.
42. Liang JT, Chien CT, Chang KJ, Hsu HC, Chu SH, Lai MK, et al. Neurophysiological basis of sympathetic nerve-preserving surgery for lower rectal cancer: a canine model. Hepatogastroenterology 1998;45:2206-14.
43. Raspagliesi F, Ditto A, Fontanelli R, Solima E, Hanozet F, Zanaboni F, et al. Nerve-sparing radical hysterectomy: a surgical technique for preserving the autonomic hypogastric nerve. Gynecol Oncol 2004;93:307-14.
44. Hockel M. Do we need a new classification for radical hysterectomy? Insights in surgical anatomy and local tumor spread from human embryology. Gynecol Oncol 2007;107(1 Suppl 1):S106-12.
45. Dursun P, LeBlanc E, Nogueira MC. Radical vaginal trachelectomy (Dargent's operation): a critical review of the literature. Eur J Surg Oncol 2007;33:933-41.
46. Rob L, Halaska M, Robova H. Nerve-sparing and individually tailored surgery for cervical cancer. Lancet Oncol 2010;11:292-301.
47. Brown JS, Sawaya G, Thom DH, Grady D. Hysterectomy and urinary incontinence: a systematic review. Lancet 2000;356:535-9.
48. Raspagliesi F, Ditto A, Hanozet F, Martinelli F, Solima E, Zanaboni F, et al. Nerve-sparing radical hysterectomy in cervical cancer: evolution of concepts. Gynecol Oncol 2007;107(1 Suppl 1):S119-21.
49. Papka RE, Mowa CN. Estrogen receptors in the spinal cord, sensory ganglia, and pelvic autonomic ganglia. Int Rev Cytol 2003;231:91-127.
50. Maas CP, ter Kuile MM, Laan E, Tuijnman CC, Weijenborg PT, Trimbos JB, et al. Objective assessment of sexual arousal in women with a history of hysterectomy. BJOG 2004;111:456-62.
51. Ercoli A, Delmas V, Gadonneix P, Fanfani F, Villet R, Paparella 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;25:200-6.

 http://dx.doi.org/10.3802/jgo.2015.26.2.100

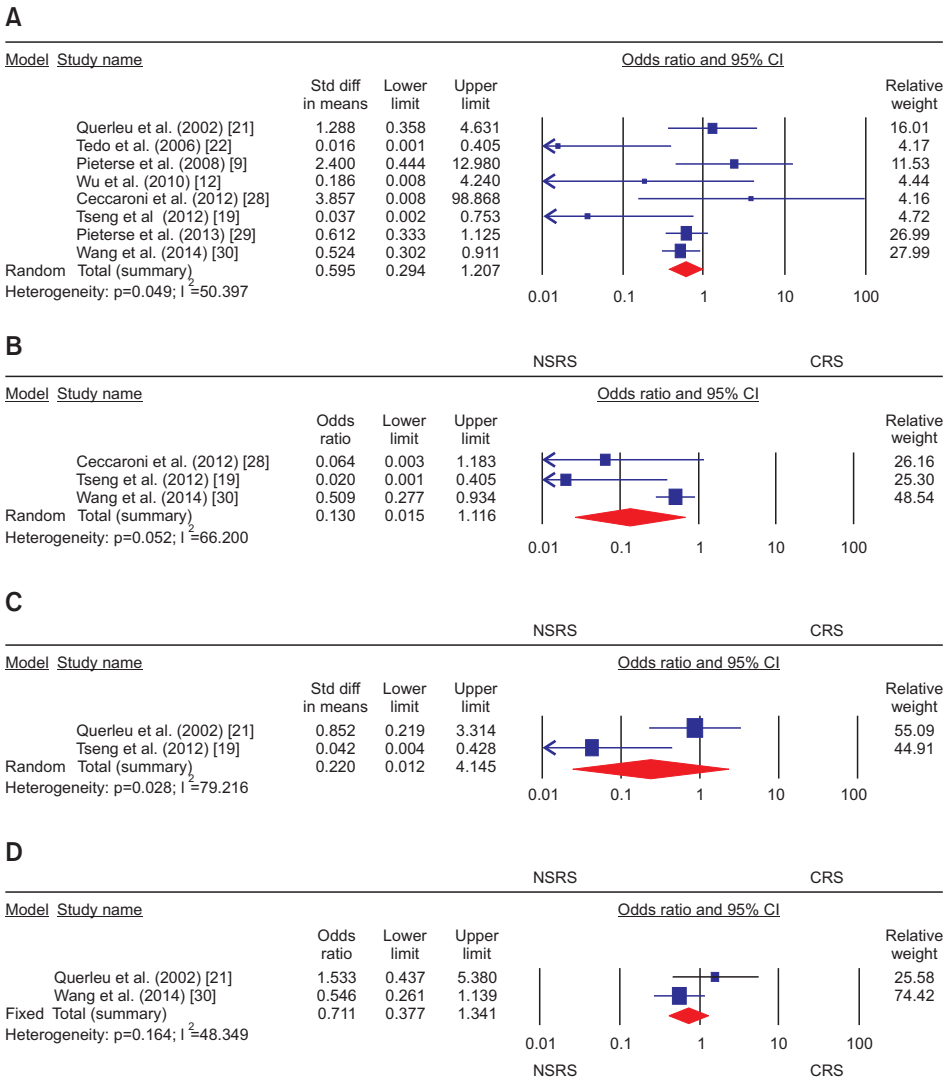


Supplementary Fig. 1. Funnel plots with Egger's test representing no publication bias in this meta-analysis for comparing clinical outcomes: (A) operative time, (B) blood loss, (C) hospital stay, (D) intraoperative complications, (E) postoperative complications, (F) disease-free survival, (G) overall survival, (H) duration of postoperative catheterization, (I) urinary incontinence, (J) urinary retention, (K) urinary frequency, (L) constipation, (M) decrease in sexual interest, and (N) dyspareunia between conventional and nerve-sparing radical surgery for cervical cancer.

http://dx.doi.org/10.3802/jgo.2015.26.2.100

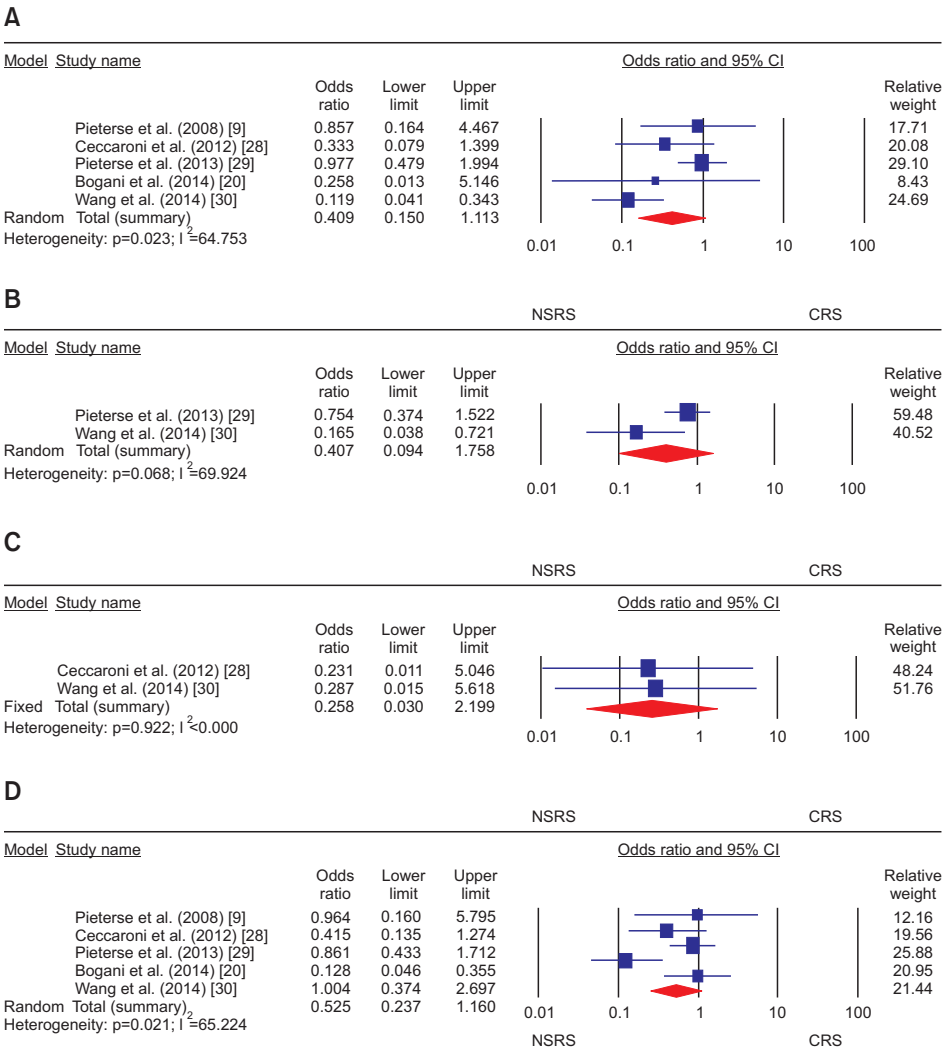


Supplementary Fig. 2. Forest plots for standard differences (Std diffs) in means or odds ratios with 95% confidence intervals (CIs) to compare (A) operative time, (B) postoperative complications, (C) the length of the resected parametrium, (D) disease-free survival, and (E) overall survival between conventional radical surgery (CRS) and nerve-sparing radical surgery (NSRS) for cervical cancer.

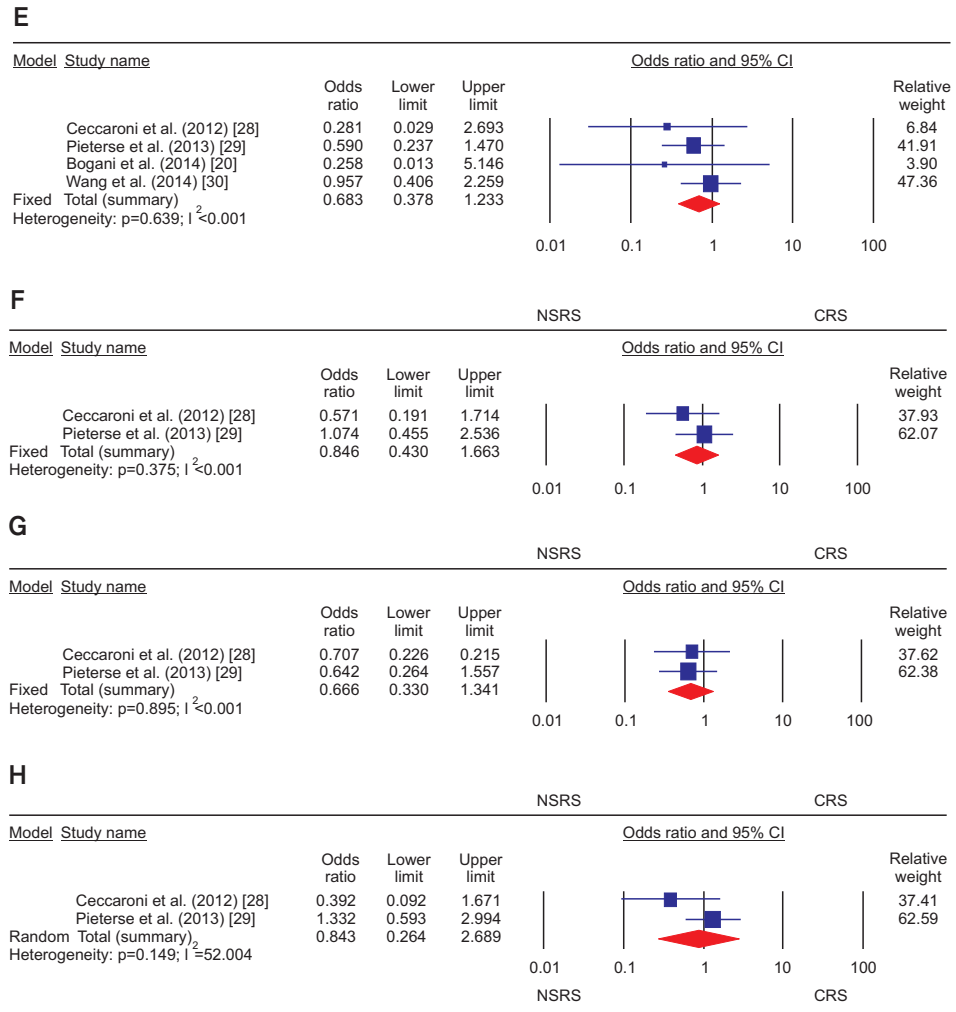


Supplementary Fig. 3. Forest plots for standard differences (Std diffs) in means or odds ratios with 95% confidence intervals (CIs) to compare (A) urinary incontinence, (B) urinary retention, (C) dysuria, and (D) urinary urgency between conventional radical surgery (CRS) and nerve-sparing radical surgery (NSRS) for cervical cancer.

http://dx.doi.org/10.3802/jgo.2015.26.2.100



Supplementary Fig. 4. Forest plots for odds ratios with 95% confidence intervals (CIs) to compare (A) constipation, (B) diarrhea, (C) fecal incontinence, (D) a decrease in sexual interest, (E) dyspareunia, (F) decrease in orgasm, (G) decrease in sexual satisfaction, and (H) vaginal dryness between conventional radical surgery (CRS) and nerve-sparing radical surgery (NSRS) for cervical cancer.



Supplementary Fig. 4. Continued.

http://dx.doi.org/10.3802/jgo.2015.26.2.100

Supplementary Table 1. Assessment of nerve sparing radical surgery for cervical cancer

Study	Sites of nerve preservation			Success rate (%)	
	Hypogastric nerve	Pelvic splanchnic nerve	Vesical branch of pelvic plexus	Failure	At least one side
Possover et al. (2000) [16]	△	O	△	△	△
Trimbos et al. (2001) [7]	O	O	O	△	△
Querleu et al. (2002) [21]	O*	O*	O*	△	△
Todo et al. (2006) [22]	O	O	O	0	100
Raspagliesi et al. (2006) [10]	O†	O†	O†	△	△
Pieterse et al. (2008) [9]	O	O	O	△	△
Van den Tillaart et al. (2009) [17]	O	O	O	19.7	80.3
Cibula et al. (2010) [23]	O‡	O‡	O‡	△	△
Espino-Strebel et al. (2010) [24]	O	O	O	△	△
Liang et al. (2010) [25]	O	O	O	△	△
Skret-Magierlo et al. (2010) [18]	O	O	O	0	100
Wu et al. (2010) [12]	O	O	O	△	△
Cibula et al. (2011) [26]	O	O	O	△	△
Ditto et al. (2011) [27]	O	O	O	△	△
Ceccaroni et al. (2012) [28]	O	O	O	△	△
Chen et al. (2012) [13]	O	O	O	△	△
Tseng et al. (2012) [19]	O	O	O	5.6	94.4
Pieterse et al. (2013) [29]	O	O	O	0	100
Bogani et al. (2014) [20]	O	O	O	△	△
Wang et al. (2014) [30]	O	O	O	△	△

△ not mentioned. *27.1% of patients who received nerve sparing surgery underwent radical trachelectomy. †6.8% of patients who underwent nerve sparing radical hysterectomy received neoadjuvant chemotherapy. ‡7.1% and 14.1% of all patients underwent radical parametrectomy and trachelectomy, respectively.

Supplementary Table 2. The Newcastle-Ottawa Scale for assessing qualities of 19 included cohort studies

Study	Selection (score)				Comparability (score)	Outcome(score)			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome interest not present at start of study	Control of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Possover et al. (2000) [16]	1	1	1	1	1	1	1	0	9
Trimbos et al. (2001) [7]	0	0	1	1	1	1	0	0	4
Querleu et al. (2002) [21]	1	1	1	0	1	1	1	1	7
Todo et al. (2006) [22]	1	0	1	1	2	1	1	1	8
Raspagliesi et al. (2006) [10]	1	1	1	0	2	1	1	0	7
Pieterse et al. (2008) [9]	0	0	1	1	1	1	1	0	5
Van den Tillaart et al. (2009) [17]	1	1	1	1	2	1	1	1	9
Cibula et al. (2010) [23]	1	0	1	0	2	1	1	1	7
Espino-Strebel et al. (2010) [24]	1	1	1	1	1	1	1	1	8
Liang et al. (2010) [25]	1	1	1	1	2	1	1	1	9
Skret-Magierlo et al. (2010) [18]	0	0	1	1	2	1	1	1	7
Cibula et al. (2011) [26]	0	0	1	1	0	1	1	1	5
Ditto et al. (2011) [27]	1	1	1	0	2	1	1	1	8
Ceccaroni et al. (2012) [28]	1	1	1	1	2	1	1	1	9
Tseng et al. (2012) [19]	0	0	1	1	2	1	1	1	7
Pieterse et al. (2013) [29]	1	1	1	1	2	1	1	1	9
Bogani et al. (2014) [20]	1	1	1	1	2	1	1	1	9
Wang et al. (2014) [30]	1	1	1	1	2	1	1	1	9

http://dx.doi.org/10.3802/jgo.2015.26.2.100

Supplementary Table 3. Demographic characteristics of 20 included studies

Study	Period of enrollment	Study design	FIGO stage	Surgical approach or type	Radicality	Sample size		Adjustment of potential confounding factors
						Conventional	Nerve sparing	
Possover et al. (2000) [16]	1996–	Prospective	IB2-IIA	LPS RH	III	28	38	Length of resected parametrium
Trimbos et al. (2001) [7]	2000	Prospective	Not mentioned	LPT RH	III	2	8	Age, adjuvant treatment, BMI, histology, NAC, tumor size
Querleu et al. (2002) [21]	1991–1995* 1996–†	Retrospective	IA2-II	LPS RH or RT	II	47	48 (RT, n=13)	Extent of lymphadenectomy, FIGO stage, LNM, LVSI, no. of resected LNs, parametrial invasion, positive resection margin, tumor size
Todo et al. (2006) [22]	2000–2002	Retrospective	IB1-IIB	LPT RH	III	5	22	Age, adjuvant treatment, extent of lymphadenectomy, FIGO stage, length of resected vagina, tumor size
Raspagliesi et al. (2006) [10]	Not mentioned	Retrospective	IB1-III	LPT RH	III	20	59 (NAC, n=4)	Age, BMI, extent of lymphadenectomy, FIGO stage, grade, histology, LVSI, parametrial invasion, parity, positive resection margin, tumor size
Pieterse et al. (2008) [9]	2006	Prospective	I-IIA	LPT RH	III	13	10	Adjuvant treatment, menopause
Van den Tillaart et al. (2009) [17]	1994–1999* 2001–2005†	Prospective	I-IIA	LPT RH	III	124	122	Age, adjuvant treatment, depth of stromal invasion, extent of lymphadenectomy, FIGO stage, histology, LNM, LVSI, parametrial invasion, positive resection margin, tumor size
Cibula et al. (2010) [23]	2006–2008	Retrospective	IA2-IIB	LPT RH or RP (7.1%) or RT (14.1%)	C	19	35	Age, adjuvant treatment, BMI, extent of lymphadenectomy, no. of resected LNs, tumor size
Espino-Strebel et al. (2010) [24]	2002–2007	Retrospective	IB1	LPT RH	C	52	27	Extent of lymphadenectomy, depth of stromal invasion, parametrial invasion, positive resection margin, tumor size
Liang et al. (2010) [25]	2006–2009	Retrospective	IA2-IB2	LPS RH	C	81	82	Age, BMI, extent of lymphadenectomy, FIGO stage, histology, length of resected parametrium, length of resected vagina, no. of resected LNs, tumor size
Skret-Magierlo et al. (2010) [18]	2007–2008	Prospective	IB1-IIA	LPT RH	III	10	10	Age, adjuvant treatment, BMI, extent of lymphadenectomy, FIGO stage. histology, LVSI, no. of resected LNs, tumor size
Wu et al. (2010) [11]	2007–2008	RCT	IB1-IIA	LPT RH	III	15	14	Age, adjuvant chemotherapy or radiotherapy, body mass index, extent of lymphadenectomy, FIGO stage, histology, LVSI, lymph node metastasis
Cibula et al. (2011) [26]	2003–2007	Retrospective	IA-IIB	LPT RH, RP (6.3%) or RT (4.7%)	B or C	17‡	175§	–
Ditto et al. (2011) [27]	1980–1995* 2001–2009†	Retrospective	IA2-IIB	LPT RH	III	311 (NAC, n=56)	185 (NAC, n=162)	Age, depth of stromal invasion, extent of lymphadenectomy, FIGO stage, histology, LNM, LVSI, parametrial invasion, positive resection margin
Ceccaroni et al. (2012) [28]	1997–2009	Retrospective	IA2-IIB	LPS or LPT RH	III	31 (NAC, n=3)	25 (NAC, n=4)	Age, adjuvant treatment, extent of lymphadenectomy, FIGO stage, grade, histology, NAC, no. of resected LNs, surgical approach
Chen et al. (2012) [13]	2007–2008	RCT	IB1-IIA	LPT RH	III	13	12	Age, adjuvant treatment, BMI, FIGO stage, LNM, positive resection margin
Tseng et al. (2012) [19]	2010–2011	Prospective	IA2-IB1	LPT RH	C	12	18	Age, extent of lymphadenectomy, histology, LNM, parametrial invasion, positive resection margin, tumor size
Pieterse et al. (2013) [29]	1998–2008	Retrospective	IA-IIB	LPT RH	III	106 (>stage IIB, n=1)	123	Age, adjuvant treatment, FIGO stage, hormone replacement therapy, menopause
Bogani et al. (2014) [20]	2004–2012	Prospective	IA-IIB	LPS RH	II or III	63 (NAC, n=12)	33 (NAC, n=7)	Age, adjuvant treatment, BMI, extent of lymphadenectomy, FIGO stage, grade, histology, length of resected parametrium, length of resected vagina, LNM, NAC
Wang et al. (2014) [30]	2008–2012	Retrospective	IB1-IIA	LPT RH	III	160 (NAC, n=42)	78 (NAC, n=25)	Age, adjuvant treatment, BMI, depth of stromal invasion, extent of lymphadenectomy, FIGO stage, histology, LNM, NAC, ovarian transposition, parametrial invasion, positive resection margin

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LNM, lymph node metastasis; LPS, laparoscopy; LPT, laparotomy; LVSI, lymphovascular space invasion; NAC, neoadjuvant chemotherapy; RCT, randomized controlled trial; RH, radical hysterectomy; RP, radical parametrectomy; RT, radical trachelectomy.
*Conventional radical surgery was performed. †Nerve sparing radical surgery was performed. ‡Type C2 radical surgery was performed. §Type B or C1 radical surgery was performed.

Supplementary Table 4. Subgroup analyses for comparing clinical outcomes between conventional and nerve sparing radical surgery for cervical cancer

Category	No. of studies	SDM or OR	95% CI	Heterogeneity		Model used
				p-value	I^2	
Blood loss (SDM)						
Study design						
RCT	2	−0.405	−0.945 to 0.135	0.605	<0.001	Fixed effect
Prospective	3	−0.022	−0.235 to 0.191	0.960	<0.001	Fixed effect
Retrospective	5	−0.374	−0.683 to 0.066	0.068	54.220	Random effects
Quality of study (NOS)						
≥8	5	−0.332	−0.656 to 0.009	0.006	72.541	Random effects
<8	3	−0.018	−0.383 to 0.347	0.954	<0.001	Fixed effect
Surgical approach						
Laparotomy	7	−0.093	−0.271 to 0.085	0.842	<0.001	Fixed effect
Laparoscopy	2	−0.395	−1.014 to 0.224	0.019	81.924	Random effects
Radicality						
Type III or C	9	−0.297	−0.536 to 0.057	0.041	50.258	Random effects
Adjustment for potential confounding factors						
Age, BMI, FIGO stage	5	−0.339	−0.655 to 0.024	0.103	48.091	Fixed effect
Age, BMI, extent of lymphadenetomy, FIGO stage	4	−0.346	−0.717 to 0.024	0.056	60.430	Fixed effect
Hospital stay (SDM)						
Study design						
Prospective	2	−0.096	−0.476 to 0.284	0.725	<0.001	Fixed effect
Retrospective	4	−0.259	−0.459 to 0.060	0.676	<0.001	Fixed effect
Quality of study (NOS)						
≥8	3	−0.244	−0.449 to 0.039	0.446	<0.001	Fixed effect
<8	3	−0.166	−0.512 to 0.180	0.798	<0.001	Fixed effect
Surgical approach, and type						
Laparotomy, and type III or C	5	−0.258	−0.453 to 0.064	0.822	<0.001	Fixed effect
Adjustment for potential confounding factors						
Age, BMI, extent of lymphadenetomy, FIGO stage	4	−0.233	−0.436 to 0.030	0.574	<0.001	Fixed effect
Postoperative complications (OR)						
Study design						
Prospective	3	0.452	0.269 to 0.761	0.473	<0.001	Fixed effect
Retrospective	5	1.157	0.715 to 1.874	0.860	<0.001	Fixed effect
Quality of study (NOS)						
≥8	4	0.684	0.460 to 1.016	0.155	42.800	Fixed effect
<8	4	1.082	0.492 to 2.380	0.353	8.005	Fixed effect
Radicality						
Type III or C	7	0.696	0.482 to 1.005	0.288	18.594	Fixed effect
Adjustment for potential confounding factors						
Age, BMI, extent of lymphadenectomy, FIGO stage	4	0.868	0.496 to 1.522	0.543	<0.001	Fixed effect

BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; NOS, the Newcastle-Ottawa Scale; OR, odds ratio; RCT, randomized controlled trial; SDM, standard difference in mean.

http://dx.doi.org/10.3802/jgo.2015.26.2.100

Supplementary Table 5. Subgroup analyses for comparing postoperative sexual functions between conventional and nerve sparing radical surgery for cervical cancer

Category	No. of studies	OR	95% CI	Heterogeneity		Model used
				p-value	I^2	
Decrease of sexual interest						
Study design						
Prospective	2	0.305	0.043–2.170	0.055	72.839	Random effects
Retrospective	3	0.774	0.467–1.281	0.461	<0.001	Fixed effect
Quality of study (NOS)						
≥8	4	0.480	0.194–1.185	0.011	73.057	Random effects
Surgical approach						
Laparotomy	3	0.911	0.532–1.560	0.967	<0.001	Fixed effect
Radicality						
Type III or C	4	0.786	0.484–1.277	0.659	<0.001	Fixed effect
Follow-up for evaluating dysfunctions (mo)						
12	4	0.440	0.166–1.166	0.020	69.574	Random effects
Adjustment for potential confounding factors						
Age, adjuvant treatment, FIGO stage	4	0.480	0.194–1.185	0.011	73.057	Random effects
Age, adjuvant treatment, extent of lymphadenectomy, FIGO stage	3	0.378	0.112–1.269	0.017	75.327	Random effects
Dyspareunia						
Surgical approach						
Laparotomy	2	0.763	0.408–1.426	0.449	<0.001	Fixed effect
Radicality						
Type III or C	2	0.711	0.389–1.298	0.530	<0.001	Fixed effect
Follow-up for evaluating dysfunctions (mo)						
12	2	0.504	0.223–1.138	0.754	<0.001	Fixed effect
Adjustment for potential confounding factors						
Age, adjuvant treatment, extent of lymphadenectomy, FIGO stage	3	0.759	0.350–1.648	0.467	75.327	Fixed effect

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; NOS, the Newcastle-Ottawa Scale; OR, odds ratio.