Efficacy of nerve-sparing radical hysterectomy vs. conventional radical hysterectomy in early-stage cervical cancer: A systematic review and meta-analysis

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Abstract. The aim of the present study was to compare the oncological outcome of nerve-sparing radical hysterectomy (NSRH) and conventional radical hysterectomy (CRH) for early-stage cervical cancer using a meta-analysis. A systematic review and meta-analysis was conducted, including 4 randomized controlled trials (RCT), 8 case-control and 11 comparative cohort studies comparing the morbidity, pelvic dysfunctions and oncological outcome between the two surgical methods. A total of 23 studies were included in this meta-analysis. The studies reported data of patients affected by cervical cancer; were written in English; included ≥20 patients; and reported data of patients with a comparison of clinical outcomes between NSRH and CRH. Data were extracted and risk of bias was assessed by four independent reviewers. A total of 1,796 patients were included: 884 patients (49.2%) undergoing NSRH and 912 (50.8%) undergoing CRH. The meta-analyses were conducted using Review Manager version 5.3 software, which is designed for conducting Cochrane reviews. As regards perioperative parameters, NSRH was found to be associated with a lower intraoperative blood loss and a shorter length of hospital stay in comparison with CRH. Patients undergoing NSRH experienced lower incidence of urinary, colorectal and sexual dysfunction compared with patients undergoing CRH. However, the resected parametrial width was favorable in patients with CRH, suggesting that NSRH was inferior to CRH in terms of radicality. The 5-year disease-free and overall survival rates were similar between the two groups. In this systematic review and meta-analysis, the collected data to date demonstrated that the nerve-sparing approach guarantees minimized surgical-related pelvic dysfunction, with similar oncological outcomes as CRH. However, further RCTs should be conducted to confirm the superiority and safety of NSRH.

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Key words: cervical cancer, nerve-sparing, hysterectomy, oncological outcome

Introduction

Despite the large-scale screening programs in developed countries, cervical cancer remains a major health concern in the United States, accounting for >12,800 and 4,200 new diagnoses and deaths, respectively, in 2017 (1). In addition, cervical cancer is the second most common cause of death from cancer among women aged 20-39 years (2). Early cervical cancer (ECC), which can be treated with radical hysterectomy, has been reported to have 5-year survival rates of 88-97% after surgery (3,4).

Various types of conventional radical surgery, such as radical hysterectomy, trachelectomy, and parametrectomy, remain the standard treatment for ECC (International Federation of Gynecology and Obstetrics stage I-IIA) (5,6). According to the Querleu and Morrow classification, conventional radical hysterectomy (CRH) means type C2 hysterectomy. Following this procedure, the hypogastric nerve (sympathetic nerve), the pelvic splanchnic nerve (parasympathetic nerve), and the vesical branch of the pelvic plexus (both sympathetic and parasympathetic nerves) are damaged during the dissection of the uterosacral ligament, vesicouterine ligament and parametrium. These injuries are the leading cause of postoperative pelvic dysfunction, typically including bladder, sexual and colorectal dysfunction (7,8).

As ECC has a high 5-year survival rate, the long-term quality of life of the patients is important. It is also important how quickly the pelvic dysfunction is restored. The concept of 'nerve-sparing' surgery was first described by Höckel *et al* (9) in 1998 as part of an effort to improve the oncological outcome of radical hysterectomy by extending the resection of parametrial tissue without further impairing pelvic autonomic nerve functions. Since then, this surgical procedure has been actively performed and studied, mainly by the Japanese research group (9). However, nerve-sparing radical hysterectomy (NSRH) remains controversial in gynecological oncology.

Although this technique may have a positive impact on the quality of life of the patients, the heterogeneity of the technique itself is substantial and there is ongoing debate regarding the oncological outcome (3,4,10).

Although five systematic reviews with meta-analyses and three randomized controlled trials (RCTs) have been published to date, they are not sufficient to verify the efficacy and safety of NSRH in ECC (4,10-16). In the present systematic review and meta-analysis, pooled data may provide evidence regarding both comparative effectiveness and safety between NSRH and CRH in ECC. The aim was to review the currently available relevant literature and compare morbidity, pelvic dysfunction and oncological outcomes between the two surgical methods.

Materials and methods

Search strategy. The present systematic review and meta-analysis followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (17). For this meta-analysis, the Cochrane Central Register of controlled Trials (CENTRAL), MedLine and Embase were searched for relevant studies published between 2000 and 2018, using the terms 'cervical AND cancer OR malignancy OR carcinoma' AND 'nerve AND sparing' AND 'radical AND hysterectomy'.

Study selection and inclusion criteria. Published articles were included if they met the following criteria: i) Studies reporting data of patients affected by cervical cancer; ii) English language studies; iii) series including ≥20 patients and iv) studies reporting data of patients with comparison of clinical outcomes between NSRH and CRH. If there were duplicate studies, the studies that were published first or provided more information were included.

Data extraction. Two authors (KHY, KSJ) independently extracted the data, and disagreements were re-evaluated by two other authors (YJH, CSE). Two reviewers (KHY, KSJ) worked independently, and examined the potential eligibility of all studies retrieved from the databases based on selection and exclusion criteria. The third and fourth reviewers (YJH, CSE) resolved inconsistencies between the first two reviewers through consensus and discussion. The data investigated were perioperative outcomes, quality of life indicators, progression-free survival (PFS) and overall survival (OS).

Quality assessment. The questionnaire for methodological quality of the Cochrane Collaboration's Risk of Bias assessment tool was answered for each article to determine the risk of bias. The level of bias of the included studies was assessed based on the Cochrane Collaboration system (18). Furthermore, the quality of outcomes was rated using the Grading of Recommendations, Assessment, Development and Evaluation system (19). The meta-analyses were conducted using Review Manager software, version 5.3 (20), which is designed for conducting Cochrane reviews.

Statistical analysis. Dichotomous outcomes eligible in each study are demonstrated as risk ratio (RR) with estimated 95% confidence interval (CI). Continuous outcomes are shown as the weighted mean difference (WMD) with 95% CI, which were calculated from mean, standard deviation (SD), P-value and sample size in each study. Heterogeneity was assessed using Higgins I^2, evaluating the percentage of total variation across studies that was due to heterogeneity rather than chance. Thus, an I^2 of >50% was considered to reflect substantial heterogeneity, and thereby the random effects model using the DerSimonian and Laird method was used. The fixed effects model, using the Mantel-Haenszel method, was employed when I^2 was ≤50%, indicating no heterogeneity. The Cochrane Review software (Review Manager version 5.3) was used in order to assess the heterogeneity of the included studies and to evaluate pooled results of the included investigations. The level of heterogeneity was studied for each comparison. On the basis of the level of heterogeneity, the random and fixed effects models were used to compare outcomes between groups. Random and fixed effects models were used as appropriate. Forest plots were created for each comparison and RR, WMD and 95% CI are presented; P-values <0.05 were considered to indicate statistically significant differences.

Results

Eligible studies. A total of 211 studies were identified, and 26 duplicated articles were excluded. In addition, 153 studies, including non-cervical cancer (n=35), non-English language studies (n=27), case reports and reviewed articles (n=91), were excluded. After assessment of full-text articles for eligibility, an additional 9 studies were excluded due to the following criteria: Number of patients <20 (n=5), no control group (n=2), and ineligible statistical information (n=2). Finally, 4 RCTs, 8 case control and 11 comparative cohort studies were included in the present meta-analysis. A total of 23 articles were selected for data extraction. Detailed information of study acquisition may be found in Fig. 1.

Study characteristics. A total of 23 articles were selected for inclusion in this meta-analysis, 4 of which were RCTs and the remaining 19 were case control or comparative cohort studies. Overall, 1,769 patients were included: 912 (50.8%) and 884 (49.2%) patients had undergone CRH and NSRH, respectively. The risk of bias was assessed for all studies. A summary of the included studies (11,21-42) is presented in Table I.

Study quality. All 23 studies included were retrospective. The risk of bias was deemed to be high in all the studies due to the lack of blinding of the participants or personnel and outcome assessors. Moreover, all studies were characterized by high risk of allocation bias. A detailed risk of bias assessment is described in Fig. 2.

Meta-analysis results. Outcomes included the following perioperative parameters: Mean operative time, mean estimated blood loss and length of hospital stay. Outcomes as an indicator of quality of life were as follows: Duration of postoperative catheter (days), urinary dysfunction, rectal dysfunction and sexual dysfunction. The analysis of oncological outcome was performed through radicality, PFS and OS. Radicality was measured by the resected parametrium and vagina. The operative time (WMD, 8.45 min; 95% CI: -2.79 to 19.67; P=0.14)

Table I. Main characteristics of the included studies.

First author	Year	Study design	Evaluation	Study period	Patients, n	CRH, n	NSRH, n	(Refs.)
Bogani	2014	CC	PS	2004-2012	96	63	33	(21)
Ceccaroni	2012	CC	RS	1997-2009	56	31	25	(22)
Chen	2012	RCT	PS	NS	NS	NS	NS	(12)
Chen	2014	RCT	PS	NS	NS	NS	NS	(23)
Ditto	2011	CC	NS	NS	NS	NS	NS	(25)
Ditto	2018	CC	NS	NS	NS	NS	NS	(26)
van Gent	2017	CC	PS	1994-2005	246	124	122	(27)
Kuwabara	2000	CC	PS	1993-1994	37	18	19	(28)
Liang	2010	CC	PS	2006-2009	163	81	82	(29)
Liu	2016	CC	PS	2011-2012	120	60	60	(30)
Makowski	2014	CC	NS	2001-2012	73	53	20	(31)
Possover	2000	CC	PS	1997-1999	38	28	10	(32)
Querleu	2002	CC	RS	1991-1996	95	47	48	(33)
Raspagliesi	2006	CC	PS	NS	110	51	59	(34)
Raspagliesi	2017	CC	PS	2009-2016	83	36	47	(35)
Roh	2015	RCT	PS	2003-2005	86	40	46	(36)
Sakuragi	2005	CC	PS	2000-2002	27	5	22	(37)
Shi	2016	CC	RS	2003-2013	108	42	64	(38)
Skret-Magierlo	2010	CC	PS	2007-2008	20	10	10	(39)
van den Tillaart	2009	CC	PS	1994-1999 2001-2005	246	124	122	(40)
Tseng	2012	CC	PS	2010-2011	30	12	18	(41)
Wu	2010	RCT	PS	2007-2008	31	16	15	(11)
Yang	2016	CC	PS	2012-2015	76	38	38	(42)

CC, case-control; PS, prospective study; RS, retrospective study; RCT, randomized controlled trial; NSRH nerve-sparing radical hysterectomy; CRH, conventional radical hysterectomy; NS, non-specified.

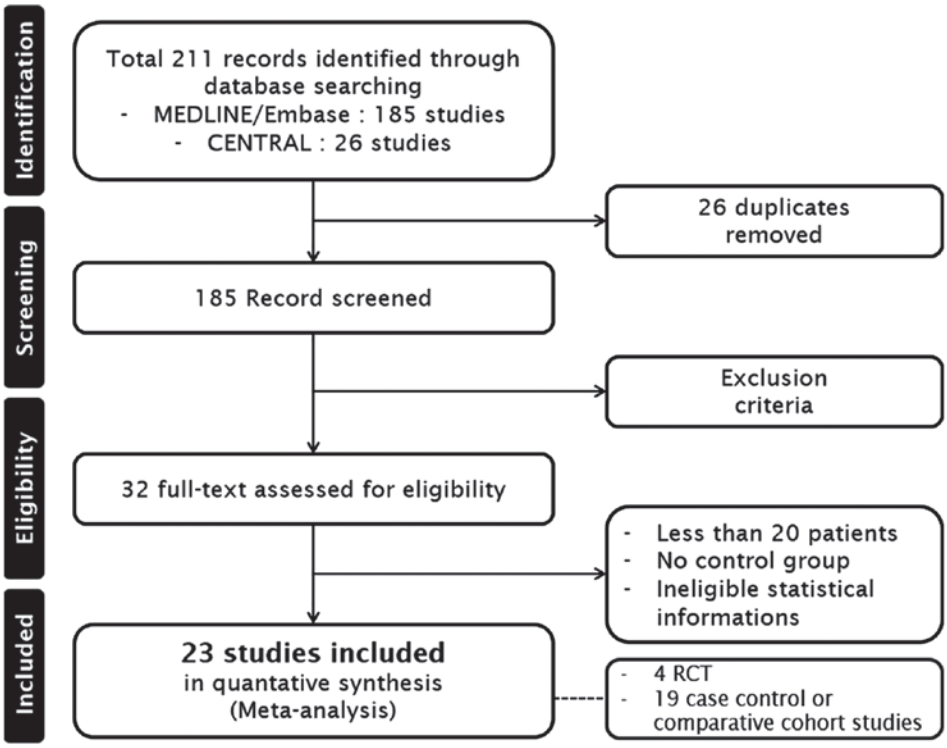

Figure 1. Flowchart of study selection process for the systematic review and meta-analysis.

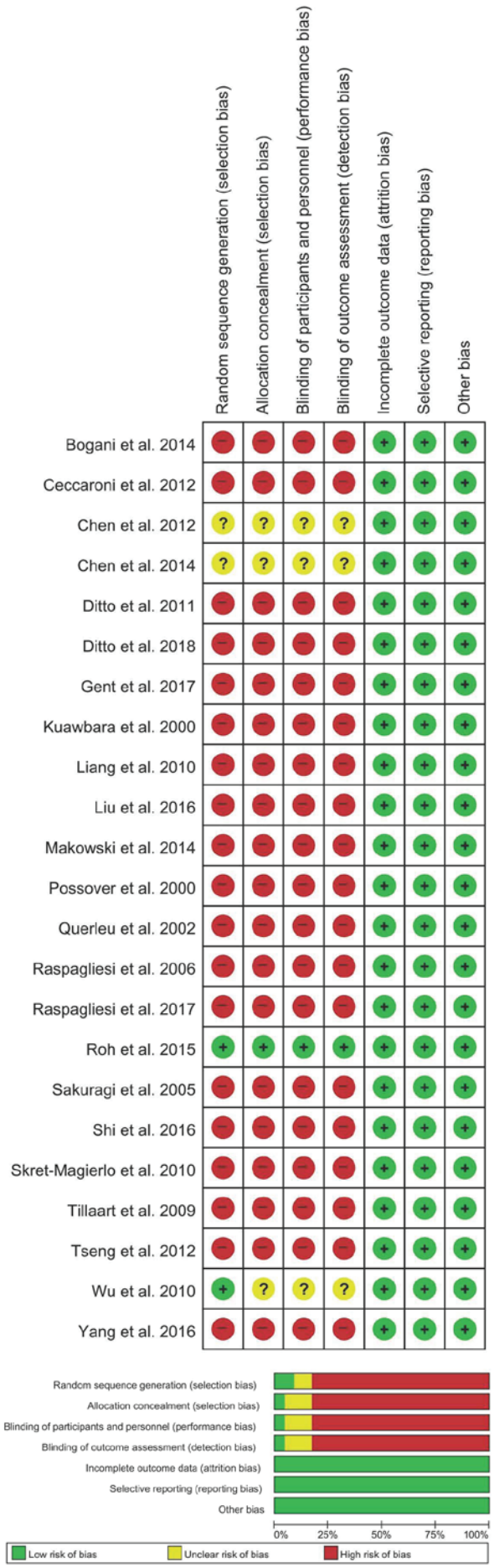

Figure 2. Risk of bias.

did not differ statistically significantly between patients undergoing CRH and NSRH (Fig. 3). As regards perioperative parameters, NSRH was found to be associated with lower intraoperative blood loss (WMD, -87.29 ml; 95% CI: -139.91 to -34.66; P=0.001) and a shorter length of hospital stay (WMD, -5.37 days; 95% CI: -8.08 to -2.67; P<0.0001) in comparison with CRH.

Data on pelvic floor dysfunction rates are presented in Fig. 4. Patients undergoing NSRH experienced lower urinary (RR=0.34; 95% CI: 0.18 to 0.63; P=0.0007), colorectal (RR=0.24; 95% CI: 0.13 to 0.45; P<0.00001) and sexual (RR=0.27; 95% CI; 0.08 to 0.86; P=0.03) dysfunction rates compared with patients undergoing CRH (Fig. 4A). In particular, a shorter duration of postoperative catheterization (WMD, -8.59 days; 95% CI: -12.17 to -5.02; P<0.00001) was observed among patients undergoing NSRH compared with patients undergoing CRH (Fig. 4B). Resected parametrial width was a favorable factor in patients with CRH (WMD, -0.78 cm; 95% CI: -1.45 to -0.11; P=0.02). This result suggests that NSRH is inferior to CRH in terms of radicality (Fig. 5). The 5-year disease free survival (RR=0.98; 95% CI: 0.90 to 1.06; P=0.62) and 5-year OS (RR=0.97; 95% CI: 0.92 to 1.02; P=0.26) rates were similar between groups (Fig.6).

Discussion

The present study was a systematic review and meta-analysis of the current evidence on the role of the nerve-sparing approach to surgical treatment for ECC, collecting data from studies comparing NSRH with CRH. Considering the heterogeneity between studies, we were able to obtain valuable data regarding pelvic dysfunction rate and oncological outcome. First, our findings supported the results of studies reporting that NSRH was associated with a shorter duration of postoperative catheterization compared with CRH. These findings indicated that bladder function recovered faster and the incidence of bladder dysfunction was lower compared with that of CRH when using the NSRH approach. Second, postoperative flatulence, constipation and fecal incontinence are the main manifestations of anorectal dysfunction, and the results are more favorable for NSRH compared with CRH. The negative effect of CRH on bowel function was also reported in other studies (43). Similarly, the nerve-sparing approach was associated with a lower rate of sexual dysfunction. There was no difference in operative time between the two groups. However, estimated blood loss and length of hospital stay were favorable for NSRH. In a meta-analysis with a non-randomized study, NSRH was reported to be associated with a longer operative time compared with CRH (44). Unlike our results, estimated blood loss and length of hospital stay were similar between the two groups in this non-randomized study.

The results of present systematic review and meta-analysis suggest that NSRH is associated with fewer complications and faster recovery of pelvic function compared with CRH. Therefore, the radicality and oncological outcome were compared between the two groups. Radicality was analyzed by resected parametrium width and vaginal length, and NSRH exhibited lower radicality compared with CRH. Liang *et al* investigated the safety of 163 ECC patients and observed a

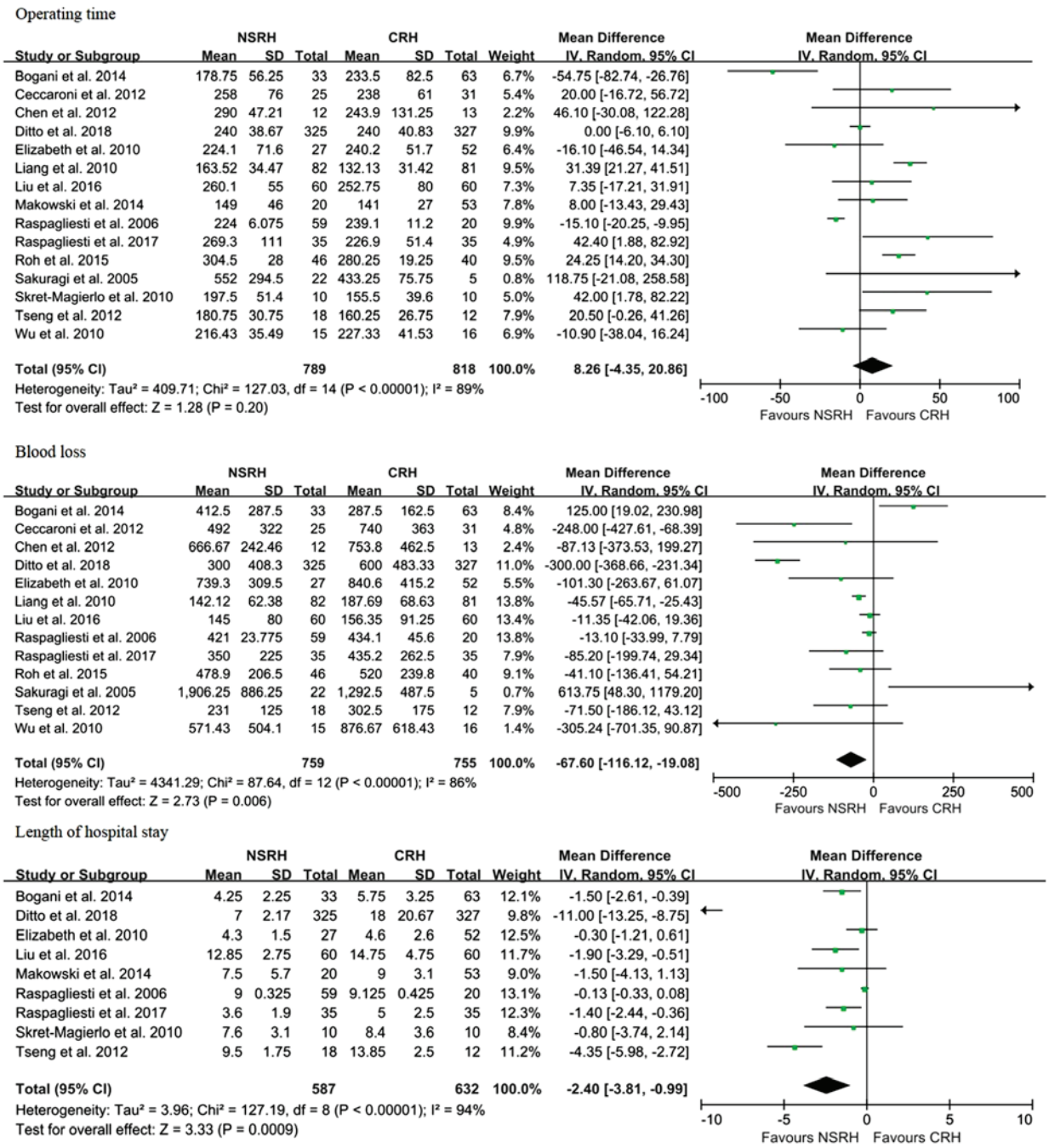

Figure 3. Pooled results for operative time, blood loss and length of hospital stay. NSRH, nerve-sparing radical hysterectomy; CRH, conventional radical hysterectomy; SD, standard deviation; CI, confidence interval.

statistically significant reduction in the length of the resected parametrium and vagina in the NSRH group (29). The lower radicality *per se* may also be a concern. However, other studies have reported favorable results of less radical surgery in combination with neoadjuvant chemotherapy (45). There was no significant difference in the 5-year PFS and OS between NSRH and CRH. The reason for the less radical approach not affecting the oncological outcome may be explained by previous studies (12,36,39). Chen *et al* (12) analyzed the cardinal ligament tissue specimens of 12 and 13 patients undergoing NSRH and CRH, respectively, and found that, compared with CRH, fewer pelvic nerves were removed in NSRH during cardinal ligament dissection. In addition, they confirmed that the same number of blood and lymphatic vessels were eliminated with both approaches. The metastasis of cervical cancer occurs mainly through the blood vessels and the lymphatic system, whereas metastasis through the nerves is extremely rare, with only one such case reported to date (46). However, even this single case was one with advanced cervical cancer, rather than ECC. These results may clarify why oncological outcome did not differ between the two groups, and why the pelvic dysfunction rate was lower in the NSRH group.

However, only 4 RCTs were included in the evaluated studies, whereas the majority were case-control and comparative cohort studies. There was also heterogeneity between studies, and there was no level A evidence on this

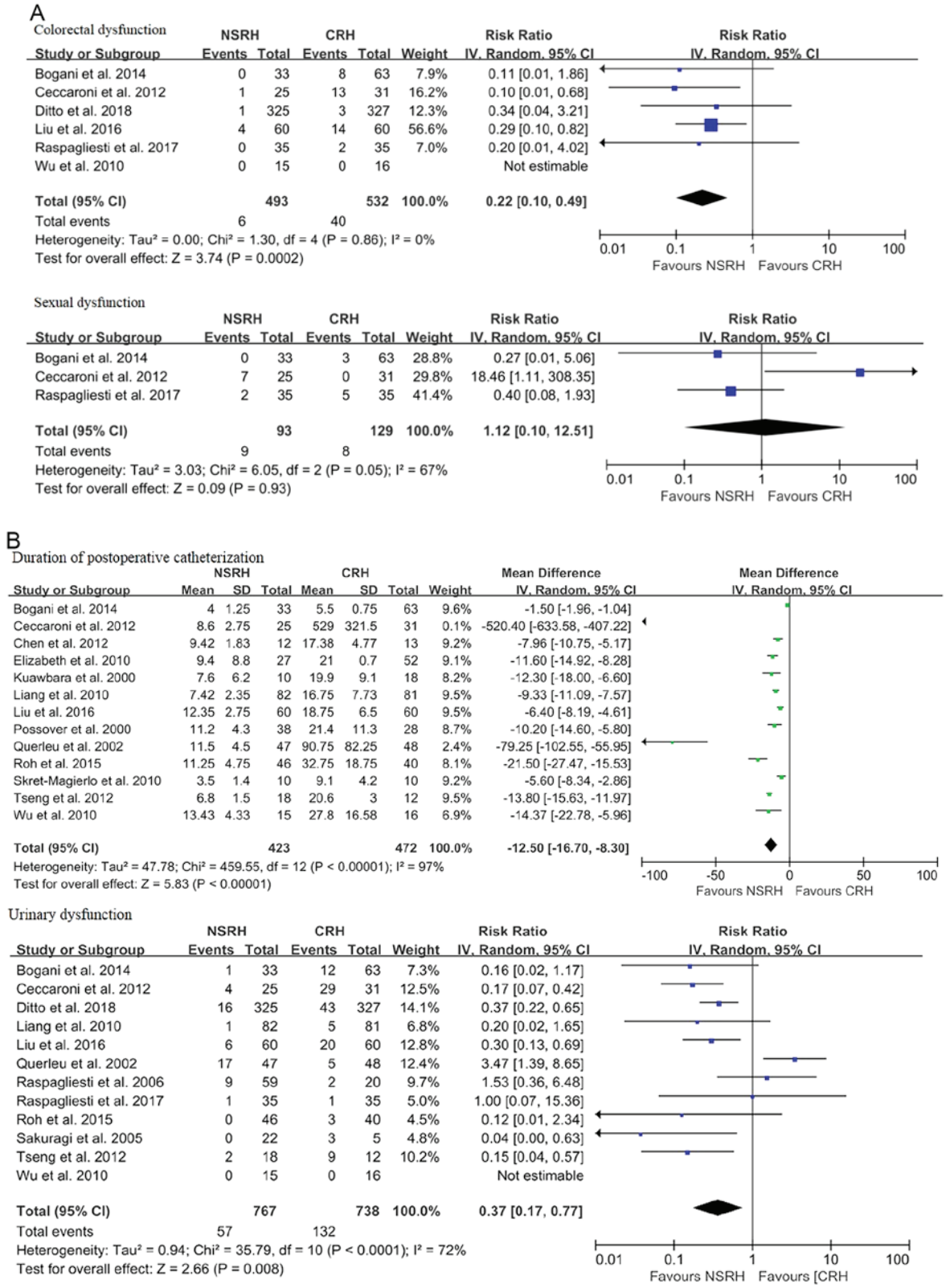

Figure 4. (A) Pooled results for colorectal and sexual dysfunction. (B) Pooled results for duration of postoperative catheterization and urinary dysfunction. NSRH, nerve-sparing radical hysterectomy; CRH, conventional radical hysterectomy; SD, standard deviation; CI, confidence interval.

issue. However, the studies were well-conducted and the data extracted were sufficient to understand the impact of the nerve-sparing approach compared with CRH. Recently, Chinese study groups conducted larger studies (28,29,47), and a total of 172 patients (82, 60 and 30 patients, respectively) underwent NSRH. Lower pelvic dysfunction rate and improved safety were confirmed with the nerve-sparing approach in these studies.

There were certain limitations to the present study: i) As mentioned earlier, the first limitation of this meta-analysis was

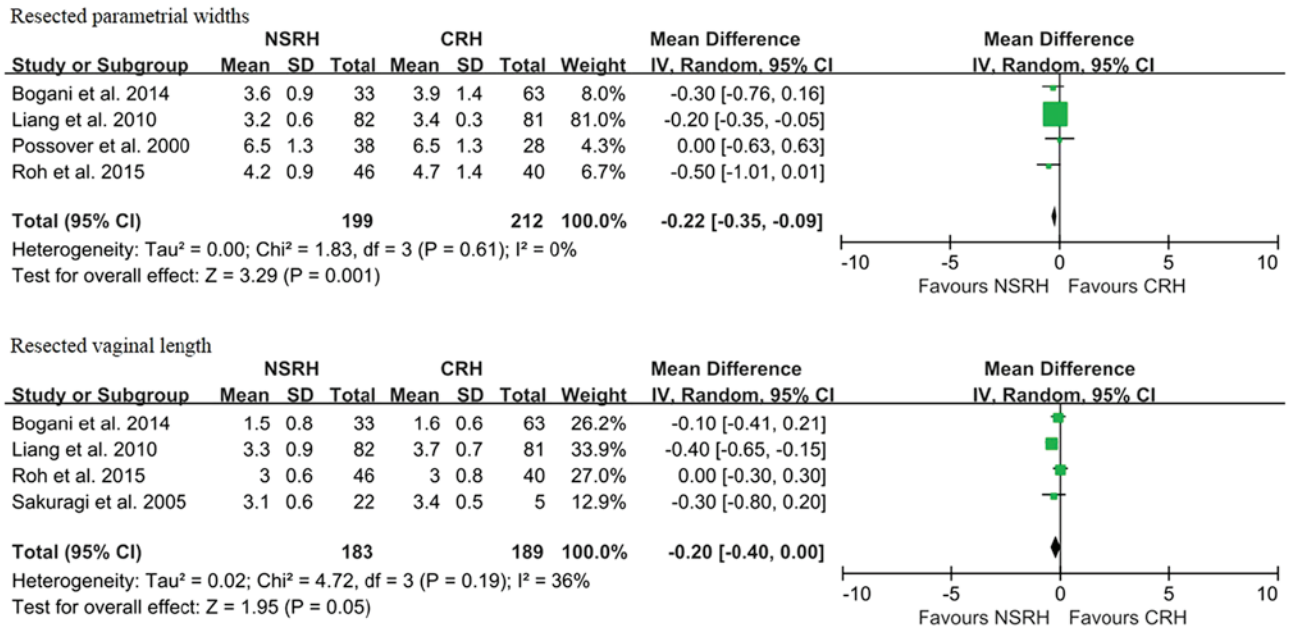

Figure 5. Pooled results for oncological outcome. NSRH, nerve-sparing radical hysterectomy; CRH, conventional radical hysterectomy; SD, standard deviation; CI, confidence interval.

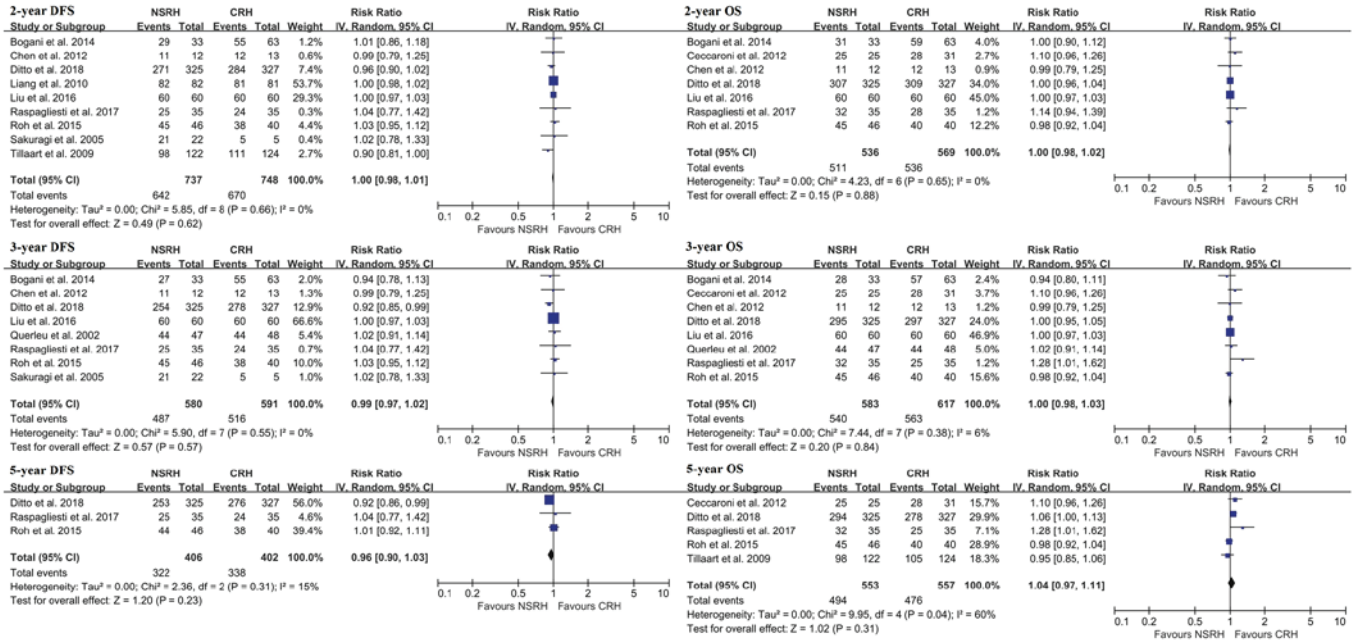

Figure 6. Pooled results for 2-, 3- and 5-year OS and DFS. OS, overall survival; DFS, disease-free survival; NSRH, nerve-sparing radical hysterectomy; CRH, conventional radical hysterectomy; CI, confidence interval.

the considerable heterogeneity among the studies. There are inherent biases in the various-design papers included in the present study. Therefore, this must be taken into consideration when interpreting the results. The risk of bias of the included studies was systematically assessed, as seen in Fig. 6. ii) There were several omitted data across different studies. Therefore, the results should be interpreted with caution. iii) The mean number of patients included in the reviewed studies was only 50 per group, which is relatively small. iv) RR rather than hazard ratio was used to assess survival outcomes. RR only measures the number of events and takes no account of when they occur; thus, it is suitable for measuring dichotomous outcomes, but less appropriate for analyzing time-to-event outcomes (48). When the total number of events reported for each study is used to calculate RR, the result is an estimate that is difficult to interpret. Although interpretation may be difficult, RRs can be calculated at specific time points, making estimates comparable and easier to interpret, at least at those time points.

In conclusion, the data collected in this systematic review and meta-analysis demonstrated that the nerve-sparing approach guarantees minimized risk of surgical-related pelvic

dysfunction, while achieving a similar oncological outcome as CRH, supporting the preferred use of NSRH over CRH as a treatment for ECC patients. However, further RCTs should be conducted to establish the superiority and safety of NSRH in ECC.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SHL wrote the manuscript and analyzed the data. JWB, MH, YJC, JWP and SRO analyzed the data. SJK, SYC, JHY and YL collected the data. All authors have read and approved the final version of this manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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