# 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  $\geq$ 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.

### 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.

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

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  $\geq$ 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<sup>2</sup>, 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  $\leq 50\%$ , 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)

First author Year S		Study design	Evaluation	Study period	Patients, n	CRH, n	NSRH, n	(Refs.) (21)	
Bogani	ni 2014 CC		PS	2004-2012	96	63	33		
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	2011-2003	30	12	18	(41)	
Wu	2012	RCT	PS	2007-2008	31	16	15	(11)	
Yang	2016	CC	PS	2012-2015	76	38	38	(42)	

Table I. Main characteristics of the included studies.

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.

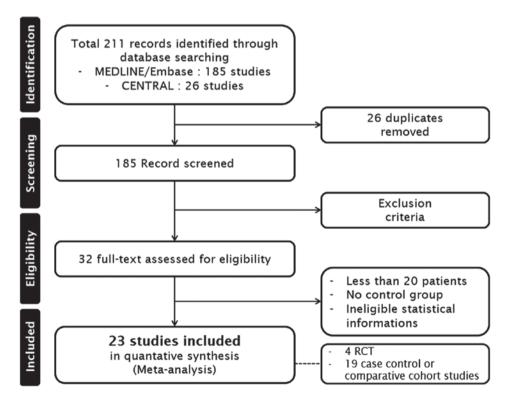


Figure 1. Flowchart of study selection process for the systematic review and meta-analysis.

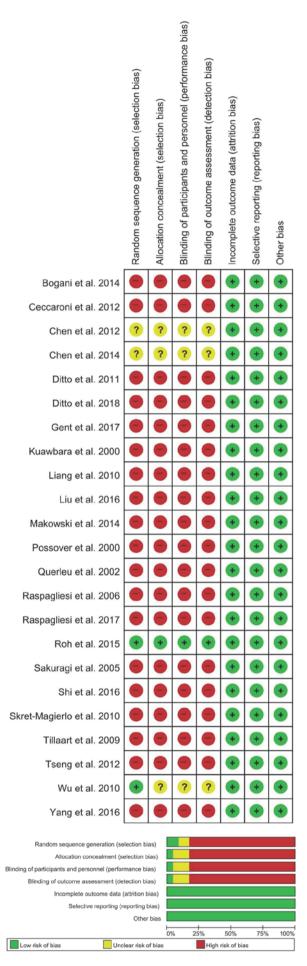


Figure 2. Risk of bias.

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



Study or Subarrows		NSRH	Total	Mean	CRH	Tatal	Weinht	Mean Difference	Mean Difference
Study or Subgroup	Mean		Total	Mean			Weight	IV. Random. 95% CI	IV. Random. 95% Cl
Bogani et al. 2014	178.75		33	233.5	82.5	63	6.7%	-54.75 [-82.74, -26.76]	
Ceccaroni et al. 2012	258		25	238	61	31	5.4%	20.00 [-16.72, 56.72]	
Chen et al. 2012	290		12		131.25	13	2.2%	46.10 [-30.08, 122.28]	
Ditto et al. 2018	240		325	240	40.83	327	9.9%	0.00 [-6.10, 6.10]	T
Elizabeth et al. 2010	224.1		27	240.2	51.7	52	6.4%	-16.10 [-46.54, 14.34]	
Liang et al. 2010	163.52			132.13	31.42	81	9.5%	31.39 [21.27, 41.51]	
Liu et al. 2016	260.1			252.75	80	60	7.3%	7.35 [-17.21, 31.91]	
Makowski et al. 2014	149		20	141	27	53	7.8%	8.00 [-13.43, 29.43]	
Raspagliesti et al. 2006	224	6.075	59	239.1	11.2	20	9.9%	-15.10 [-20.25, -9.95]	-
Raspagliesti et al. 2017	269.3	111	35	226.9	51.4	35	4.9%	42.40 [1.88, 82.92]	
Roh et al. 2015	304.5	28	46	280.25	19.25	40	9.5%	24.25 [14.20, 34.30]	
Sakuragi et al. 2005	552	294.5	22	433.25	75.75	5	0.8%	118.75 [-21.08, 258.58]	
Skret-Magierlo et al. 2010	197.5	51.4	10	155.5	39.6	10	5.0%	42.00 [1.78, 82.22]	
Tseng et al. 2012	180.75	30.75	18	160.25	26.75	12	7.9%	20.50 [-0.26, 41.26]	
Wu et al. 2010	216.43		15	227.33	41.53	16	6.9%	-10.90 [-38.04, 16.24]	
5-1-1 (05% ON			700				400.00/	0.007.4.05.00.001	
Total (95% CI) Heterogeneity: Tau² = 409.	71· Chi2 -	= 127 02	789 df = 14		00011		100.0%	8.26 [-4.35, 20.86]	⊢ <b>├</b>
Test for overall effect: Z = 1			UI - 14		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	- 00%	,		-100 -50 0 50 100
resciol overall effect. Z =	1.20 (F =	0.20)							Favours NSRH Favours CRH
Blood loss									
B1000 1035	N	SRH			CRH			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95%	CI IV. Random, 95% CI
Bogani et al. 2014	412.5	287.5	33	287.5	162.5	63	8.4%	125.00 [19.02, 230.98	
Ceccaroni et al. 2012	492	322	25	740	363	31	4.8%	-248.00 [-427.61, -68.39	
Chen et al. 2012	666.67		12	753.8	462.5	13	2.4%	-87.13 [-373.53, 199.27	
Ditto et al. 2018	300	408.3	325	600		327	11.0%	-300.00 [-368.66, -231.34	
Elizabeth et al. 2010	739.3	309.5	27	840.6	415.2	52	5.5%	-101.30 [-263.67, 61.07	
Liang et al. 2010	142.12	62.38	82	187.69	68.63	81	13.8%	-45.57 [-65.71, -25.43	
Liu et al. 2016	145	80	60	156.35	91.25	60	13.4%	-11.35 [-42.06, 19.36	•
Raspagliesti et al. 2006		23.775	59	434.1	45.6	20	13.8%	-13.10 [-33.99, 7.79	
Raspagliesti et al. 2017	350	225	35	435.2	262.5	35	7.9%	-85.20 [-199.74, 29.34	
Roh et al. 2015	478.9	206.5	46	520	239.8	40	9.1%	-41.10 [-136.41, 54.21	
		886.25		1,292.5	487.5	5	0.7%	613.75 [48.30, 1179.20	
Tseng et al. 2012	231	125	18	302.5	175	12	7.9%	-71.50 [-186.12, 43.12	
Wu et al. 2010	571.43	504.1	15		618.43	16	1.4%	-305.24 [-701.35, 90.87	
								-	
Total (95% CI)			759			755	100.0%	-67.60 [-116.12, -19.08]	
Heterogeneity: Tau <sup>2</sup> = 4341 Test for overall effect: Z = 2	,	,	af = 12	(P < 0.00	JUU1); I*	= 86%			-500 -250 0 250 5
	2.75 (F - C								Favours NSRH Favours CRH
Length of hospital stay									
o		NSRH	-		CRH	-		Mean Difference	Mean Difference
Study or Subgroup	Mean			I Mean			Weight		IV. Random. 95% Cl
Bogani et al. 2014	4.2					63	12.1%		← <sup>-</sup>
Ditto et al. 2018		7 2.17				327	9.8%		·
Elizabeth et al. 2010	4.3					52	12.5%		
Liu et al. 2016	12.8					60	11.7%	• • •	
Makowski et al. 2014	7.	5 5.7	20	) 9	3.1	53	9.0%	-1.50 [-4.13, 1.13]	
Raspagliesti et al. 2006	9	9 0.325	59	9.125	0.425	20	13.1%	-0.13 [-0.33, 0.08]	1
	3.0	6 1.9	35	5 5	2.5	35	12.3%	-1.40 [-2.44, -0.36]	
Raspagliesti et al. 2017				-		10	8.4%		
1.0	) (1								
Raspagliesti et al. 2017 Skret-Magierlo et al. 2010 Tseng et al. 2012	0 7.0 9.9		18	3 13.85	2.5	12	11.2%	-4.35 [-5.98, -2.72]	· ·
Skret-Magierlo et al. 2010 Tseng et al. 2012					2.5				
Skret-Magierlo et al. 2010 Tseng et al. 2012 Total (95% CI)	9.9	5 1.75	587	,		632	100.0%		<b>•</b>
Skret-Magierlo et al. 2010 Tseng et al. 2012	9.9 96; Chi² =	5 1.75 127.19,	587 df = 8	,		632	100.0%		-10 -5 0 5

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

Colorectal dysfunction	l dysfunction NSRH			1		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% C	CI IV. Random, 95% CI
Bogani et al. 2014	0	33	8	63	7.9%	0.11 [0.01, 1.86]	] ←
Ceccaroni et al. 2012	1	25	13	31	16.2%	0.10 [0.01, 0.68]	]
Ditto et al. 2018	1	325	3	327	12.3%	0.34 [0.04, 3.21]	
Liu et al. 2016	4	60	14	60	56.6%	0.29 [0.10, 0.82]	
Raspagliesti et al. 2017	0	35	2	35	7.0%	0.20 [0.01, 4.02]	• • •
Wu et al. 2010	0	15	0	16		Not estimable	9
Total (95% CI)		493		532	100.0%	0.22 [0.10, 0.49]	• •
Total events	6		40				
Heterogeneity: Tau <sup>2</sup> = 0.0	0; Chi <sup>2</sup> = 1	1.30, df	= 4 (P =	0.86); I	<sup>2</sup> = 0%		
Test for overall effect: Z =	= 3.74 (P =	0.0002	2)				0.01 0.1 1 10 100 Favours NSRH Favours CRH

Sexual dystatetion	NSR	н	CRH	4		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events Total		Events	Total	Weight	IV, Random, 95% CI		IV, Rando	om, 95% Cl		
Bogani et al. 2014	0	33	3	63	28.8%	0.27 [0.01, 5.06]					
Ceccaroni et al. 2012	7	25	0	31	29.8%	18.46 [1.11, 308.35]				$\rightarrow$	
Raspagliesti et al. 2017	2	35	5	35	41.4%	0.40 [0.08, 1.93]					
Total (95% CI)		93		129	100.0%	1.12 [0.10, 12.51]					
Total events	9		8								
Heterogeneity: Tau <sup>2</sup> = 3.0	3; Chi <sup>2</sup> = 0	6.05, df	f = 2 (P =	0.05);	l² = 67%			0.1		100	
Test for overall effect: Z =	: 0.09 (P =	0.93)					0.01	0.1 Favours NSRH	1 10 Favours CRH	100	

B Duration of postoperative catheterization

Sexual dysfunction

	catheter								
	N	SRH			CRH			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean		Total V	-	IV, Random, 95% Cl	IV, Random, 95% CI
Bogani et al. 2014		1.25	33	5.5	0.75	63	9.6%	-1.50 [-1.96, -1.04]	. 1
Ceccaroni et al. 2012		2.75	25	529	321.5	31			
Chen et al. 2012	9.42			17.38	4.77	13	9.2%	-7.96 [-10.75, -5.17]	-
Elizabeth et al. 2010	9.4	8.8	27	21	0.7	52	9.1%	-11.60 [-14.92, -8.28]	-
Kuawbara et al. 2000	7.6	6.2	10	19.9	9.1	18	8.2%	-12.30 [-18.00, -6.60]	-
Liang et al. 2010	7.42		82		7.73	81	9.5%	-9.33 [-11.09, -7.57]	•
Liu et al. 2016	12.35		60	18.75	6.5	60	9.5%	-6.40 [-8.19, -4.61]	
Possover et al. 2000	11.2	4.3	38	21.4	11.3	28	8.7%	-10.20 [-14.60, -5.80]	
Querleu et al. 2002	11.5	4.5	47			48	2.4%	-79.25 [-102.55, -55.95]	
Roh et al. 2015		4.75	46	32.75		40	8.1%	-21.50 [-27.47, -15.53]	
Skret-Magierlo et al. 2010	3.5	1.4	10	9.1	4.2	10	9.2%	-5.60 [-8.34, -2.86]	
Tseng et al. 2012	6.8	1.5	18	20.6	3	12	9.5%	-13.80 [-15.63, -11.97]	-
Wu et al. 2010	13.43	4.33	15	27.8	16.58	16	6.9%	-14.37 [-22.78, -5.96]	
Total (95% CI)			423			472 1	00.0%	-12.50 [-16.70, -8.30]	◆
Heterogeneity: Tau <sup>2</sup> = 47.78	: Chi <sup>2</sup> = 4	459.55	5. df =	12 (P < (	0.00001	); l <sup>2</sup> = 97	%		
Test for overall effect: Z = 5.	,					,,			-100 -50 0 50 100
			,						Favours NSRH Favours CRH
Urinary dysfunction				0.01					
		SRH		CRH				Risk Ratio	Risk Ratio
Study or Subgroup					Tatal	10/- 1-1-		Developer OFM OI	IV Developer OFAC OI
	Lven					Weigh		Random, 95% Cl	IV, Random, 95% CI
Bogani et al. 2014	Lven	1	33	12	63	7.3%	6	0.16 [0.02, 1.17]	IV, Random, 95% Cl
Ceccaroni et al. 2012		1 4	33 25	12 29	63 31	7.3% 12.5%	/o /o	0.16 [0.02, 1.17]	IV. Random, 95% Cl
•		1 4	33 25 325	12	63	7.3% 12.5% 14.1%	/o /o /o	0.16 [0.02, 1.17]	IV. Random, 95% Cl
Ceccaroni et al. 2012		1 4	33 25	12 29	63 31	7.3% 12.5%	/o /o /o	0.16 [0.02, 1.17]	IV. Random. 95% Cl
Ceccaroni et al. 2012 Ditto et al. 2018		1 4 16 3	33 25 325	12 29 43	63 31 327	7.3% 12.5% 14.1%	,0 ,0 ,0 ,0	0.16 [0.02, 1.17] 0.17 [0.07, 0.42] 0.37 [0.22, 0.65]	IV. Random. 95% Cl
Ceccaroni et al. 2012 Ditto et al. 2018 Liang et al. 2010	1	1 4 16 3	33 25 325 82	12 29 43 5	63 31 327 81	7.3% 12.5% 14.1% 6.8%	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.16 [0.02, 1.17] 0.17 [0.07, 0.42] 0.37 [0.22, 0.65] 0.20 [0.02, 1.65]	IV. Random. 95% Cl
Ceccaroni et al. 2012 Ditto et al. 2018 Liang et al. 2010 Liu et al. 2016	1	1 4 16 : 1 6	33 25 325 82 60	12 29 43 5 20	63 31 327 81 60	7.3% 12.5% 14.1% 6.8% 12.8%	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.16 [0.02, 1.17] 0.17 [0.07, 0.42] 0.37 [0.22, 0.65] 0.20 [0.02, 1.65] 0.30 [0.13, 0.69]	IV. Random, 95% Cl
Ceccaroni et al. 2012 Ditto et al. 2018 Liang et al. 2010 Liu et al. 2016 Querleu et al. 2002	1	1 4 16 5 1 6	33 25 325 82 60 47	12 29 43 5 20 5	63 31 327 81 60 48	7.3% 12.5% 14.1% 6.8% 12.8% 12.4%	0,0,0,0,0,0,0	0.16 [0.02, 1.17] 0.17 [0.07, 0.42] 0.37 [0.22, 0.65] 0.20 [0.02, 1.65] 0.30 [0.13, 0.69] 3.47 [1.39, 8.65]	IV. Random, 95% Cl
Ceccaroni et al. 2012 Ditto et al. 2018 Liang et al. 2010 Liu et al. 2016 Querleu et al. 2002 Raspagliesti et al. 2006	1	1 4 16 5 1 7 9	33 25 325 82 60 47 59	12 29 43 5 20 5 2	63 31 327 81 60 48 20	7.3% 12.5% 14.1% 6.8% 12.8% 12.4% 9.7%	, o , o , o , o , o , o , o , o , o , o	0.16 [0.02, 1.17] 0.17 [0.07, 0.42] 0.37 [0.22, 0.65] 0.20 [0.02, 1.65] 0.30 [0.13, 0.69] 3.47 [1.39, 8.65] 1.53 [0.36, 6.48]	IV. Random, 95% Cl
Ceccaroni et al. 2012 Ditto et al. 2018 Liang et al. 2010 Liu et al. 2016 Querleu et al. 2002 Raspagliesti et al. 2006 Raspagliesti et al. 2017	1	1 4 16 5 7 9 1	33 25 325 82 60 47 59 35	12 29 43 5 20 5 2 1	63 31 327 81 60 48 20 35	7.3% 12.5% 14.1% 6.8% 12.8% 12.4% 9.7% 5.0%	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.16 [0.02, 1.17] 0.17 [0.07, 0.42] 0.37 [0.22, 0.65] 0.20 [0.02, 1.65] 0.30 [0.13, 0.69] 3.47 [1.39, 8.65] 1.53 [0.36, 6.48] 1.00 [0.07, 15.36]	IV. Random, 95% Cl
Ceccaroni et al. 2012 Ditto et al. 2018 Liang et al. 2010 Liu et al. 2016 Querleu et al. 2002 Raspagliesti et al. 2006 Raspagliesti et al. 2017 Roh et al. 2015 Sakuragi et al. 2005	1	1 4 16 3 1 7 9 1 0	33 25 325 82 60 47 59 35 46	12 29 43 5 20 5 2 1 3	63 31 327 81 60 48 20 35 40 5	7.3% 12.5% 14.1% 6.8% 12.8% 12.4% 9.7% 5.0% 4.5% 4.8%	, o , o , o , o , o , o , o , o , o , o	0.16 [0.02, 1.17] 0.17 [0.07, 0.42] 0.37 [0.22, 0.65] 0.20 [0.02, 1.65] 0.30 [0.13, 0.69] 3.47 [1.39, 8.65] 1.53 [0.36, 6.48] 1.00 [0.07, 15.36] 0.12 [0.01, 2.34] 0.04 [0.00, 0.63]	IV. Random, 95% Cl
Ceccaroni et al. 2012 Ditto et al. 2018 Liang et al. 2010 Liu et al. 2016 Querleu et al. 2002 Raspagliesti et al. 2006 Raspagliesti et al. 2017 Roh et al. 2015	1	1 4 1 6 7 9 1 0	33 25 325 82 60 47 59 35 46 22	12 29 43 5 20 5 2 1 3 3 3	63 31 327 81 60 48 20 35 40 5 12	7.3% 12.5% 14.1% 6.8% 12.8% 12.4% 9.7% 5.0% 4.5%	, o , o , o , o , o , o , o , o , o , o	0.16 [0.02, 1.17] 0.17 [0.07, 0.42] 0.37 [0.22, 0.65] 0.20 [0.02, 1.65] 0.30 [0.13, 0.69] 3.47 [1.39, 8.65] 1.53 [0.36, 6.48] 1.00 [0.07, 15.36] 0.12 [0.01, 2.34]	IV. Random, 95% Cl
Ceccaroni et al. 2012 Ditto et al. 2018 Liang et al. 2010 Liu et al. 2016 Querleu et al. 2002 Raspagliesti et al. 2007 Roh et al. 2015 Sakuragi et al. 2015 Tseng et al. 2012	1	1 4 16 7 9 1 0 2	33 25 325 82 60 47 59 35 46 22 18	12 29 43 5 20 5 2 1 3 3 9	63 31 327 81 60 48 20 35 40 5	7.3% 12.5% 14.1% 6.8% 12.8% 12.4% 9.7% 5.0% 4.5% 4.8%	, o , o , o , o , o , o , o , o , o , o	0.16 [0.02, 1.17] 0.17 [0.07, 0.42] 0.37 [0.22, 0.65] 0.20 [0.02, 1.65] 0.30 [0.13, 0.69] 3.47 [1.39, 8.65] 1.53 [0.36, 6.48] 1.00 [0.07, 15.36] 0.12 [0.01, 2.34] 0.04 [0.00, 0.63] 0.15 [0.04, 0.57]	IV. Random, 95% Cl

Total events 132 57 Heterogeneity: Tau<sup>2</sup> = 0.94; Chi<sup>2</sup> = 35.79, df = 10 (P < 0.0001); I<sup>2</sup> = 72% 0.01 0.1 Test for overall effect: Z = 2.66 (P = 0.008) Favours NSRH Favours [CRH

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.

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

Resected parametrial w									
NSRH				(	CRH			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Bogani et al. 2014	3.6	0.9	33	3.9	1.4	63	8.0%	-0.30 [-0.76, 0.16]	±
Liang et al. 2010	3.2	0.6	82	3.4	0.3	81	81.0%	-0.20 [-0.35, -0.05]	
Possover et al. 2000	6.5	1.3	38	6.5	1.3	28	4.3%	0.00 [-0.63, 0.63]	+
Roh et al. 2015	4.2	0.9	46	4.7	1.4	40	6.7%	-0.50 [-1.01, 0.01]	7
Total (95% CI)			199			212	100.0%	-0.22 [-0.35, -0.09]	4
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 1	.83, df	= 3 (P	= 0.6	1); I² =	0%		
Test for overall effect:	Z = 3.29	(P =	0.001)						-10 -5 0 5 10 Favours NSRH Favours CRH
Resected vaginal lengtl	1								
	N	SRH		(	CRH			Mean Difference	Mean Difference

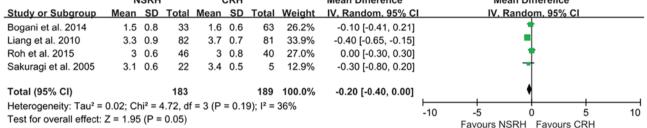


Figure 5. Pooled results for oncological outcome. NSRH, nerve-sparing radical hysterectomy; CRH, conventional radical hysterectomy; SD, standard deviation; CI, confidence interval.

2-year DFS	NSRH	CRH			Risk Ratio	Risk Ratio	2-year OS	NSRH		CRH			Risk Ratio	Risk Ratio
Study or Subgroup	Events Total				IV, Random, 95% C	IV. Random, 95% Cl	Study or Subgroup						IV, Random, 95% C	IV. Random, 95% CI
Bogani et al. 2014	29 33	55	63	1.2%	1.01 [0.86, 1.18]	-	Bogani et al. 2014	31	33	59	63	4.0%	1.00 [0.90, 1.12]	Ť
Chen et al. 2012	11 12	12	13	0.6%	0.99 [0.79, 1.25]	-	Ceccaroni et al. 2012	25	25	28	31	2.7%	1.10 [0.96, 1.26]	
Ditto et al. 2018	271 325	284	327	7.4%	0.96 [0.90, 1.02]	1	Chen et al. 2012	11	12	12	13	0.9%	0.99 [0.79, 1.25]	+
Liang et al. 2010	82 82	81	81	53.7%	1.00 [0.98, 1.02]		Ditto et al. 2018	307	325	309	327	34.0%	1.00 [0.96, 1.04]	•
Liu et al. 2016	60 60	60	60	29.3%	1.00 [0.97, 1.03]	•	Liu et al. 2016	60	60	60	60	45.0%	1.00 [0.97, 1.03]	
Raspagliesti et al. 2017	25 35	24	35	0.3%	1.04 [0.77, 1.42]	-	Raspagliesti et al. 2017	32	35	28	35	1.2%	1.14 [0.94, 1.39]	+
Roh et al. 2015	45 46	38	40	4.4%	1.03 [0.95, 1.12]	+	Roh et al. 2015	45	46	40	40	12.2%	0.98 [0.92, 1.04]	+
Sakuragi et al. 2005	21 22	5	5	0.4%	1.02 [0.78, 1.33]	+								
Tillaart et al. 2009	98 122	111	124	2.7%	0.90 [0.81, 1.00]	-	Total (95% CI)		536		569	100.0%	1.00 [0.98, 1.02]	1
							Total events	511		536				
Total (95% CI)	737		748	100.0%	1.00 [0.98, 1.01]		Heterogeneity: Tau <sup>2</sup> = 0.0		23. df =		65) P	t = 0%		
Total events	642	670					Test for overall effect: Z =			0 () 0		0.10		0.1 0.2 0.5 1 2 5 10
Heterogeneity: Tau <sup>2</sup> = 0.0			1 66)- F	<sup>2</sup> = 0%			rest for orefail ender E	0.10 (1 - 0	1.00)					Favours NSRH Favours CRH
Test for overall effect Z =			0.00), 1	- 010		0.1 0.2 0.5 1 2 5 10 Favours NSRH Favours CRH								
3-year DFS	NSRH	CRH			Risk Ratio	Risk Ratio	3-year OS	NSRH		CRH			Risk Ratio	Risk Ratio
Study or Subgroup	Events Total	Events	Total	Weight	IV. Random, 95% C	IV. Random, 95% CI	Study or Subgroup	Events 1	Total E	Events	Total	Weight	IV. Random, 95% C	IV. Random, 95% Cl
Bogani et al. 2014	27 33	55	63	2.0%	0.94 [0.78, 1.13]		Bogani et al. 2014	28	33	57	63	2.4%	0.94 [0.80, 1.11]	-
Chen et al. 2012	11 12	12	13	1.3%	0.99 [0.79, 1.25]	+	Ceccaroni et al. 2012	25	25	28	31	3.7%	1,10 [0.96, 1,26]	
Ditto et al. 2018	254 325	278	327	12.9%	0.92 [0.85, 0.99]	-	Chen et al. 2012	11	12	12	13	1.2%	0.99 [0.79, 1.25]	+
Liu et al. 2016	60 60	60	60	66.6%	1.00 [0.97, 1.03]		Ditto et al. 2018	295	325	297	327	24.0%	1.00 [0.95, 1.05]	+
Querieu et al. 2002	44 47	44	48	5.4%	1.02 [0.91, 1.14]	+	Liu et al. 2016	60	60	60	60	46.9%	1.00 [0.97, 1.03]	
Raspagliesti et al. 2017	25 35	24	35	0.7%	1.04 [0.77, 1.42]	+	Quedeu et al. 2002	44	47	44	48	5.0%	1.02 [0.91, 1.14]	+
Roh et al. 2015	45 46	38	40	10.0%	1.03 [0.95, 1.12]	+	Raspagliesti et al. 2017	32	35	25	35	1.2%	1.28 [1.01, 1.62]	
Sakuragi et al. 2005	21 22	5	5	1.0%	1.02 [0.78, 1.33]	+	Roh et al. 2015	45	46	40	40	15.6%	0.98 [0.92, 1.04]	+
control of the second					tion [otto; tioo]		1001 01 01 00 10					101010	orea faranti ria il	
Total (95% CI)	580		591	100.0%	0.99 [0.97, 1.02]	(	Total (95% CI)		583		617	100.0%	1.00 [0.98, 1.03]	•
Total events	487	516					Total events	540		563				
Heterogeneity: Tau <sup>2</sup> = 0.0	0: Chi <sup>2</sup> = 5.90. df		0.55): F	<sup>2</sup> = 0%			Heterogeneity: Tau <sup>2</sup> = 0.0		44. df =		38): P	= 6%		
Test for overall effect: Z =		. (	0.007,1			0.1 0.2 0.5 1 2 5 10	Test for overall effect: Z =			. (		0.10		0.1 0.2 0.5 1 2 5 10
						Favours NSRH Favours CRH								Favours NSRH Favours CRH
5-year DFS	NSRH	CRH			Risk Ratio	Risk Ratio	5-year OS	NSRH		CRH			Risk Ratio	Risk Ratio
Study or Subgroup	Events Total	Events	Total	Weight	IV. Random, 95% C	IV. Random, 95% CI	Study or Subgroup	Events 1	Total E	vents	Total	Weight	IV. Random, 95% C	IV. Random, 95% Cl
Ditto et al. 2018	253 325	276	327	56.0%	0.92 [0.86, 0.99]		Ceccaroni et al. 2012	25	25	28	31	15.7%	1.10 [0.96, 1.26]	
Raspagliesti et al. 2017	25 35	24	35	4.6%	1.04 [0.77, 1.42]	+-	Ditto et al. 2018	294	325	278	327	29.9%	1.06 [1.00, 1.13]	•
Roh et al. 2015	44 46	38	40		1.01 [0.92, 1.11]	+	Raspagliesti et al. 2017	32	35	25	35	7.1%	1.28 [1.01, 1.62]	
							Roh et al. 2015	45	46	40	40	28.9%	0.98 [0.92, 1.04]	+
Total (95% CI)	406		402	100.0%	0.96 [0.90, 1.03]	•	Tillaart et al. 2009	98	122	105	124	18.3%	0.95 [0.85, 1.06]	+
Total events	322	338											0.000 (0.000) 1.000/	
Heterogeneity: Tau <sup>2</sup> = 0.0			0.31): F	<sup>2</sup> = 15%			Total (95% CI)		553		557	100.0%	1.04 [0.97, 1.11]	•
Test for overall effect: Z =		. ę. – ę				0.1 0.2 0.5 1 2 5 10	Total events	494		476				
Control of State of Order E						Favours NSRH Favours CRH	Heterogeneity: Tau <sup>2</sup> = 0.0		95. df =		04): P	t = 60%		
							Test for overall effect: Z =					2410		0.1 0.2 0.5 1 2 5 10
														Favours NSRH Favours CRH

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

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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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