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Original Article

Systematic lymphadenectomy for survival in patients with early-stage endometrial cancer: a meta-analysis

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Abstract: The efficacy of systematic lymphadenectomy is controversial for improving overall survival in patients with early-stage endometrial cancer. Thus, we performed a meta-analysis comparing the efficacy for overall survival between systematic and unsystematic lymphadenectomies. After an extensive literature search between January 2000 and August 2015, we analyzed nine studies (two randomized controlled trials and seven observational studies) involving 3871 patients with early-stage endometrial cancer. In all nine studies, systematic lymphadenectomy (SL) didn't improve overall survival (OS), compared with unsystematic lymphadenectomies (USL) (OR, 0.77; 95% CI, 0.52-1.13). Moreover, two RCTs showed no difference in OS between SL and USL (OR, 1.30; 95% CI, 0.94-1.79), whereas seven observational studies demonstrated that SL improved OS, compared with USL (OR, 0.57; 95% CI, 0.42-0.77). In three studies in which patients with low-risk endometrial cancer were included, SL failed to improve OS (OR, 0.96; 95% CI, 0.59-1.55), and two observational studies also showed that there was no difference in OS between SL and USL in the patients (OR, 0.70; 95% CI, 0.37-1.33). On the other hand, three studies in which patients with high-risk endometrial cancer were enrolled showed that SL didn't increase OS (OR, 0.47; 95% CI, 0.20-1.14), but two observational studies demonstrated that SL improved OS when compared with USL (OR, 0.34; 95% CI, 0.20-0.57). This meta-analysis suggests that SL failed to improve OS in patients in early-stage endometrial cancer, especially those with low-risk disease.

Keywords: Systematic lymphadenectomy, overall survival, early-stage, endometrial cancer, meta-analysis

Introduction

Endometrial cancer is the most common malignancy of the female reproductive tract in developed countries and stands as second most common in developing countries [1], accounting for approximately 319,498 newly diagnosed cases of cancer worldwide. Fortunately, since vaginal bleeding is commonly associated with the presence of disease, approximately 80% of patients with endometrial cancer are diagnosed at an early-stage (stage I or II) and have a favorable prognosis [2]. The criteria for accurate surgical staging in endometrial cancer patients established in 1988 and updated in 2009 by the International Federation of Gynecology and Obstetrics (FIGO) including abdominal exploration, hysterectomy with salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy [3]. The guidelines of the National Comprehensive Cancer Network (NCCN) also recommend that surgical staging include pelvic and para-aortic lymphadenectomies for women with endometrial cancer [4]. Although lymphadenectomy is recommended as part of accurate surgical staging, and several retrospective studies have suggested a therapeutic benefit associated with lymphadenectomy in early-stage endometrial cancer, it is not rigorously performed around the world [5]. Recent two randomized trials have failed to show a survival advantage [6, 7]. Until now, there has been no convincing evidence as to whether systematic lymphadenectomy (SL) or unsystematic lymphadenectomy (USL) is more appropriate for patients, it remains a matter of great debate for years, especially in the early-stage endometrial cancer. Therefore, we performed a meta-analysis of relevant studies which compared the efficacy between SL and USL to evaluate the efficacy of SL for improving OS in patients with early-stage endometrial cancer.

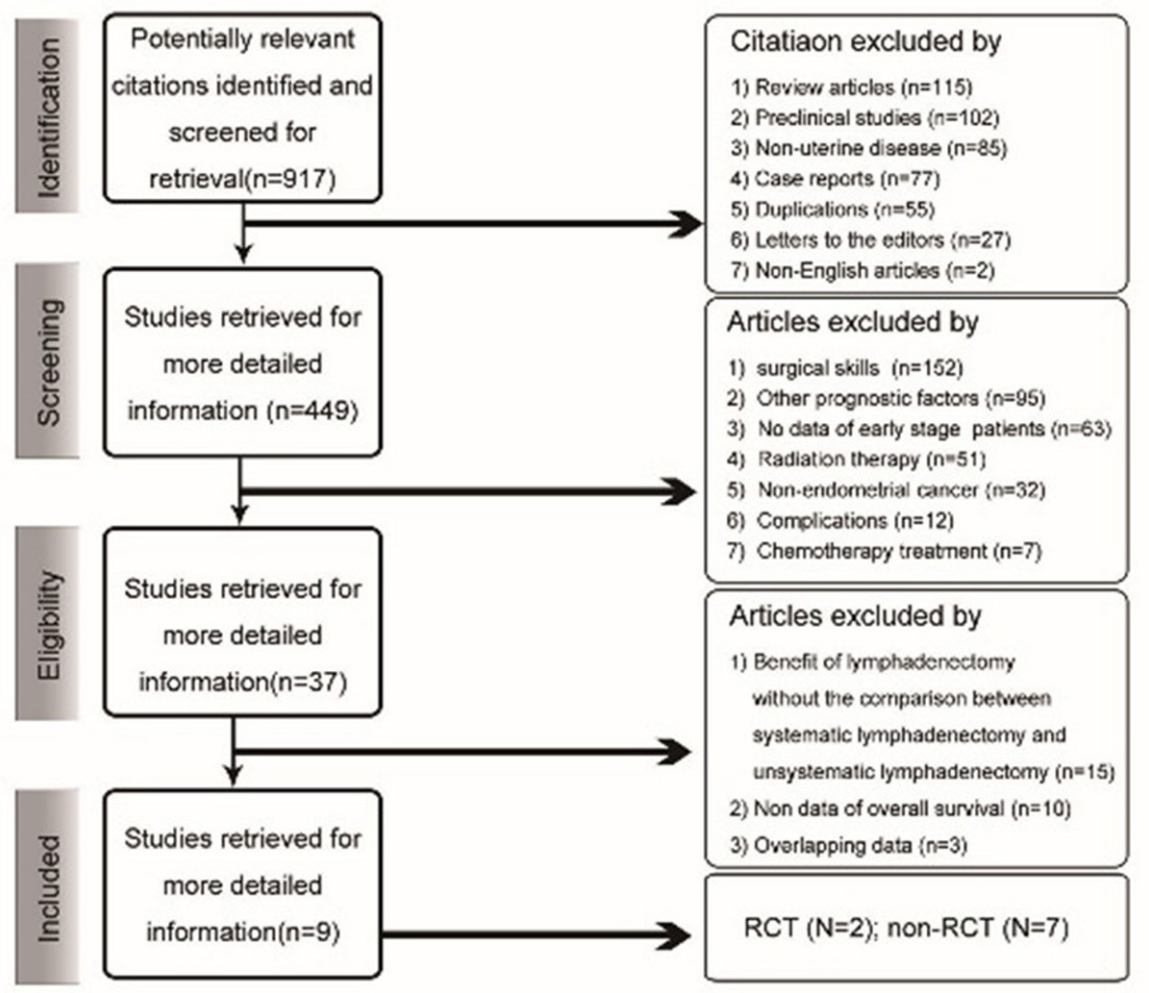

Figure 1. Preferred reporting items for meta-analyses flow diagram.

Patients and methods

search strategy

Two authors designed the protocol and extraction forms in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guideline [8]. For this meta-analysis, a National Library of Medicine and National Institutes of Health (PubMed), EmBase and Cochrane Controlled Trials Register (CENTRAL) electronic database search were performed on all studies between 2000 and 2015. The following MeSH terms and their combinations were searched in Title/Abstract: *lymphadenectomy/lymph nodes dissection/lymph nodes resection, endometrial cancer/endometrial carcinoma/endometrial neoplasm/endometrioid uterine cancer/endometrium cancer, early-stage/stage I/stage II/low risk*. The related articles function was also used to broaden the search, and the computer search was supplemented with manual searches of the reference lists of all retrieved studies, review articles, and conference abstracts. The most recent or complete report was used when multiple reports describing the same population were published.

Selection criteria

All retrieved studies had to meet the following inclusion criteria: early-stage endometrial cancer (stage I or stage II) and the comparison of OS between SL and USL. The exclusion criteria included uterine cancer with the exception of endometrial cancer, studies in which the comparison of OS was not performed between SL and USL, and publications in the non-English literature. Two investigators independently ex-

Table 1. Demographic characteristics of nine eligible studies

Study	Year of publication	Design of study	Study location	Ethnicity	Preoperative stage	No. of patients			No. of lymph nodes removed
						Total	SL	USL	
Vizza E et al	2003	Observational (cohort study)	Italy	Caucasians	STAGE I	111	72	39	NR
Ceccaroni et al	2004	Observational (cohort study)	Italy	Caucasians	STAGE I	131	55	76	29 (median)
A. Tserkezoglou et al	2005	Observational (cohort study)	Greece	Caucasians	STAGE I	173	55	118	NR
Cragun et al	2005	Observational (cohort study)	America	Caucasians	Stage I or occult Stage II	509	246	263	15 (median)
					Low risk	275	123	152	
					High risk	234	123	111	
Benedetti Panici et al	2008	RCT	Italy	Caucasians	STAGE I	514	264	250	30 (median)
Kitchener et al	2009	RCT	UK, South Africa, Poland, and New Zealand	Caucasians, African, Latinos	STAGE I	1119	546	573	12 (median)
					Low risk	612	282	330	
					High risk	507	264	243	
Bassarak et al	2010	Observational (cohort study)	Germany	Caucasians	Stage I	171	120	51	NR
Nan-HeeJeong et al	2010	Observational (cohort study)	Korea	Asians	Stage I	758	547	211	11 (median)
					Low risk	566	385	181	
					High risk	192	162	30	
dowdy et al	2012	Observational (cohort study)	America	Caucasians	Stage I	385	80	305	30 (mean)

Table 2. Assessment of methodological quality of randomized controlled trials included in the current review

Study	Random allocation (description of procedure)	Concealment of random allocation	Blinding of persons who assess treatment effects	Intention-to-treat analysis
Benedetti et al	+	+	+	+
Kitchener et al	+	+	+	-

Table 3. Assessment of methodological quality of non-randomized trials included in the current review

Study	Selection	Comparability	Outcome/Exposure	Stars
Vizza E et al	***	**	**	7
Ceccaroni et al	***	***	***	9
A. Tserkezoglou et al	***	**	***	8
Cragun et al	***	***	***	9
Bassarak et al	***	**	**	7
Nan-HeeJeong et al	***	**	**	7
dowdy et al	***	***	***	9

tracted the data of interest from studies using a checklist for data recording, and the full article texts were obtained for further evaluation in cases in which abstracts did not provide sufficient details for the determination of eligibility. Disagreements between reviewers regarding data abstraction were resolved through discussion.

Studies identified and quality assessment

A total of 912 potentially relevant studies were identified based on the above search terms. All of the studies retrieved from the database were independently evaluated. After screening the titles and abstracts, 463 studies were excluded due to review articles (n=115), preclinical studies (n=102), non-uterine diseases (n=85), case reports (n=77), duplications (n=55), letters to the editors (n=27) and non-English articles (n=2). Further assessment of more detailed information identified 412 ineligible studies associated with surgical skill (n=152), other prognostic factors, including histology and grade (n=95), no early-stage patients included (n=63), radiation therapy (n=51), non-endometrial cancer (n=32), complications (n=12) and chemotherapy treatment (n=7). After we reviewed the full manuscripts of the remaining studies, 28 studies were excluded due to the benefit of lymphadenectomy without a comparison between SL and USL (n=15), no data of OS (n=10) and overlapping data (n=3). Finally, two RCTs [6, 7] and seven observational studies [9-14] were intended to be appropriate (**Figure 1**).

According to the guidelines in the 2008 version of the Cochrane Handbook for Systematic Reviews of Interventions [15], the methodological quality of included RCTs was assessed: The methodological quality of the included RCTs were considered to be high-quality if they reported at least three items, which included random allocation, concealment of random allocation, blinding of persons who assess treatment effects and intention-to-treat analysis. Non-RCTs was assessed using the star scoring system based on the Newcastle-OttawaScale [16], which examines the method used to select patients, the comparability of the study groups, and the number of outcomes reported.

Statistical analysis

The following data were independently extracted for the current study: first author, year of publication, design of study, disease status, number of patients treated with SL or USL, and data of OS.

This meta-analysis was performed using Review Manager Version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark), The odds ratio (OR) was used to compare dichotomous variables. Statistical heterogeneity between studies was assessed using the chi-square test with significance set at $P<0.10$, and heterogeneity was quantified using the I^2 statistic. The value of I^2 ranges from 0% (no observed heterogeneity) to 100% (maximal heterogeneity). An $I^2>50\%$ is considered to represent substantial heterogeneity. The random-effects model was used if there was heterogeneity between studies. However, only the fixed-effect model using the Mantel-Haenszel method was used in this

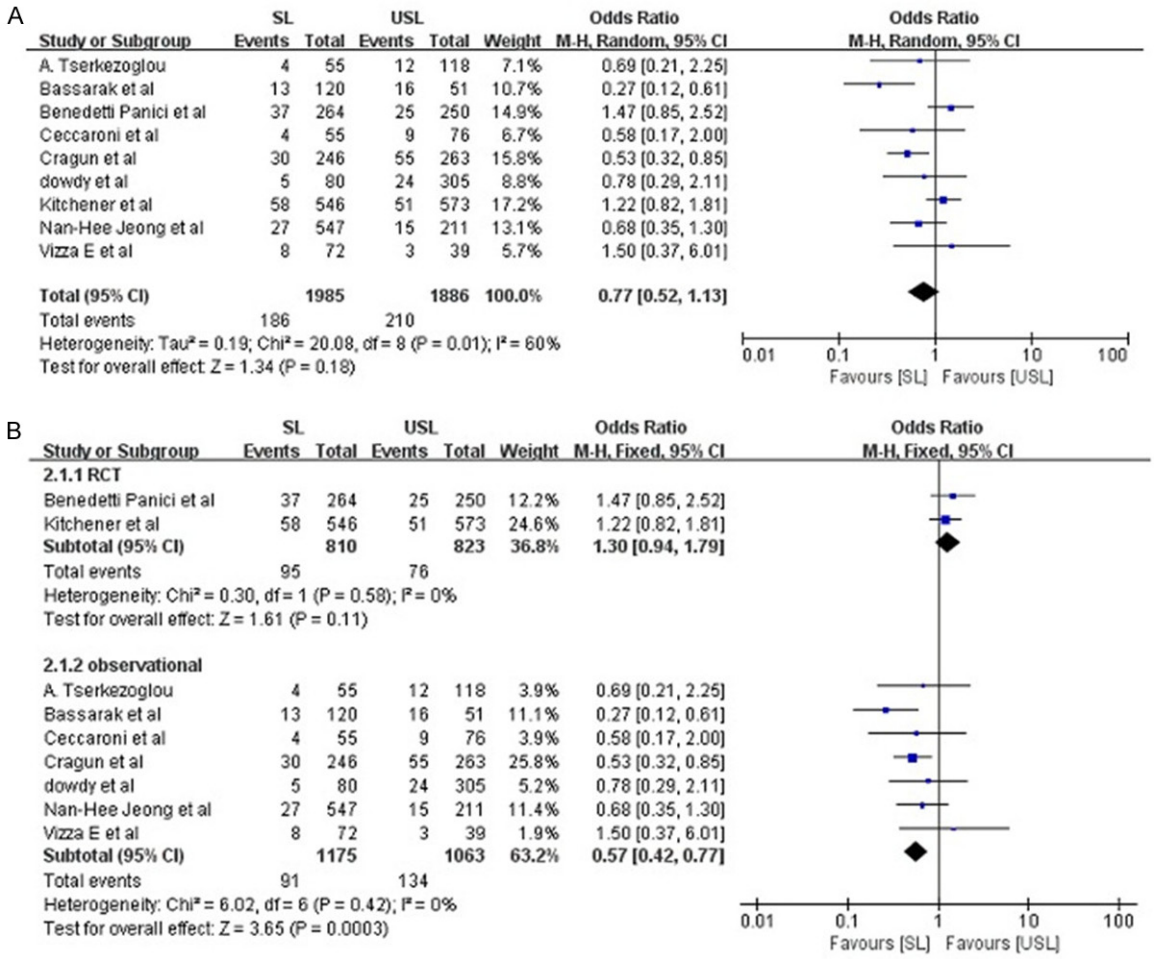

Figure 2. Comparison of overall survival between systematic lymphadenectomy (SL) and unsystematic lymphadenectomy (USL). A. SL didn't improve OS, compared with USL In all nine studies (OR, 0.77; 95% CI, 0.52-1.13). B. Two RCTs showed no difference in OS between SL and USL (OR, 1.30; 95% CI, 0.94-1.79), whereas seven observational studies demonstrated that SL improved OS, compared with USL (OR, 0.57; 95% CI, 0.42-0.77).

meta-analysis when I^2 was ≤50% because it indicated no heterogeneity. All results were reported with 95% confidence intervals (CIs), and a value of $P<0.05$ was considered to be statistically significant.

Results

Clinical characteristics

Nine studies including 3871 cases (1985 patients for SL group and 1886 patients for USL group) fulfilled the predefined inclusion criteria and were included in the final analysis. Eight publications were full-text articles, and one publication was conference abstract. The eligible population was classified as patients with Stage I or II according to the surgical staging systems, and the preoperative stage of eight studies involved was stage I, whereas only one study involved was Stage I or occult Stage II. Study recruitment periods extended from 2003 to 2012. Three studies did not report the number of lymph nodes dissected in the SL and USL groups. The quality of included studies was generally low. True randomization was used in only two RCTs. None of the observational studies adopted an appropriate protocol for treatment assignment, with distributions usually at the discretion of the physician, and none of them provided information about allocation concealment or the blinding method. Matching criteria between the groups were variable, and little matching information was identified from the conference abstracts. The key characteristics of the studies are presented in **Table 1**.

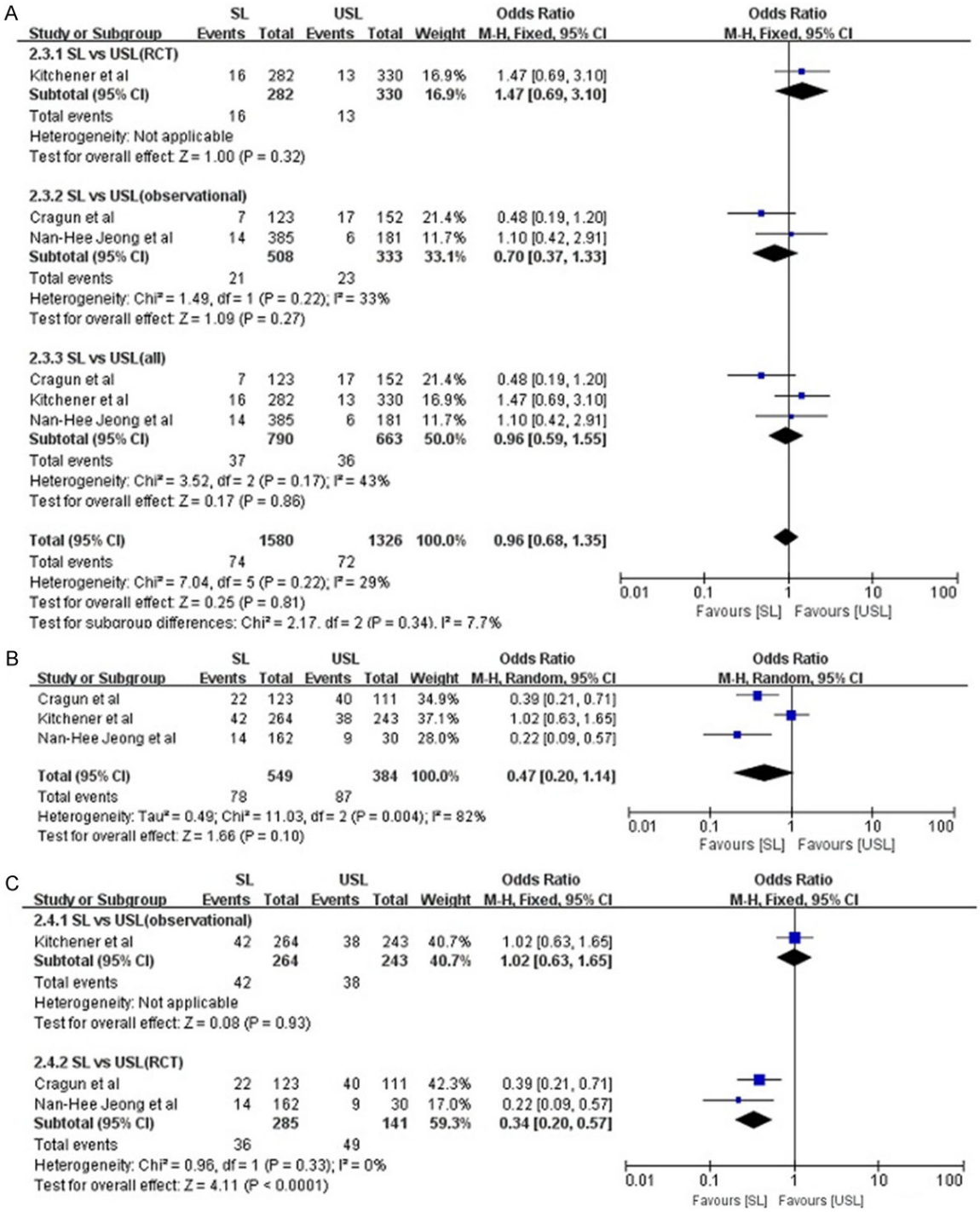

Figure 3. Comparison of overall survival between SL and USL in patients with low-risk and high-risk endometrial cancer. A. In three studies with low-risk endometrial cancer, SL failed to improve OS (OR, 0.96; 95% CI, 0.59-1.55), and two observational studies also showed there was no difference in OS between SL and USL in the patients (OR, 0.70; 95% CI, 0.37-1.33). B. In three studies with high-risk endometrial cancer, SL didn't increase OS (OR, 0.47; 95% CI, 0.20-1.14). C. In two observational studies with high-risk endometrial cancer, SL improved OS compared with USL (OR, 0.34; 95% CI, 0.20-0.57).

Methodological quality

Quality assessment scores of the included studies are summarized in **Tables 2** and **3**. The RCTs were considered to be high quality as they reported on three or four of the items. Similarly, the non-RCTs were judged to be of moderate to high quality, scoring 7-9 stars.

Survival

In all nine studies, SL didn't improve OS, compared with USL (OR, 0.77; 95% CI, 0.52-1.13 **Figure 2A**). Moreover, two RCTs showed no difference in OS between SL and USL (OR, 1.30; 95% CI, 0.94-1.79) [6, 7], whereas seven observational studies demonstrated that SL improved OS, compared with USL (OR, 0.57; 95% CI, 0.42-0.77; **Figure 2B**) [9-14].

In three studies in which patients with low-risk endometrial cancer were included, SL failed to improve OS (OR, 0.96; 95% CI, 0.59-1.55) [7, 11, 13], and two observational studies also showed that there was no difference in OS between SL and USL in the patients (OR, 0.70; 95% CI, 0.37-1.33; **Figure 3A**) [11, 13]. On the other hand, three studies in which patients with high-risk endometrial cancer were enrolled showed that SL didn't increase OS (OR, 0.47; 95% CI, 0.20-1.14; **Figure 3B**) [7, 11, 13], but two observational studies demonstrated that SL improved OS when compared with USL (OR, 0.34; 95% CI, 0.20-0.57; **Figure 3C**) [11, 13].

Discussion

FIGO changed the endometrial cancer staging system from a clinically to surgically based system in 1988, and revised in 2009, debate continues regarding the roles, candidates for, and extent of surgical staging procedures especially in regards to lymphadenectomy. In the early-stages of endometrial cancer, whether SL or USL is more appropriate for patients is controversial for years. Although Pelvic lymph node metastases in endometrial cancer at pre-surgical early stages are expected in 4.6% of cases [17], several studies suggest that lymph node resection is more reliable than surgery alone to determine whether endometrial cancer has metastasized and to reduce the risk of metastasis. And lymphadenectomy remains the most direct way to assess and reduce risk of metastasis [18-20]. Previous studies reported that high-risk patients who undergo para-aortic lymphadenectomy as part of their surgical staging procedure exhibit higher survival rates than those who undergo simple surgical staging [21], two randomized controlled trials (RCTs) have shown that SL does not improve overall survival (OS) [6, 7]. Furthermore, SL may be associated with higher rates of lymph cysts and lymphedema [22].

HeeSeung Kim et al [23] did a meta-analysis in 2012 about SL for survival in patients with endometrial cancer of all stages, and found that the efficacy of SL, defined as removal of more than about 10 lymph nodes, is limited for improving overall survival in patients with low-risk endometrial cancer, whereas it is efficient to increase overall survival in patients with intermediate- or high-risk endometrial cancer. Our aim of the current study was to determine the efficacy of SL for OS in patients specialized in early-stage endometrial cancer using a meta-analysis. The results were not consistent and we found that no difference in OS rates between SL and USL in all nine studies (OR, 0.77; 95% CI, 0.52-1.13). But seven observational studies indicated that SL improved OS (OR, 0.57; 95% CI, 0.42-0.77), two RCTs demonstrated no difference in OS between SL and USL (OR, 1.30; 95% CI, 0.94-1.79). These results must be interpreted carefully for a number of reasons. Firstly, the diverse definitions of SL may be the cause of the different efficacies of SL for OS in patients with endometrial cancer, it is possible that a high proportion of patients in the SL group did not, in fact, undergo such extensive dissection. However, no definitive guidelines are available regarding the number of lymph nodes that should be dissected. Although nodal count is indicative of the extent of lymphadenectomy, the number of nodes reported by the pathologist depends not only on anatomical variations in patients, but also on surgical expertise and the comprehensiveness of pathological analysis.

Secondly, the role of adjuvant radiation in early-stage endometrial cancer is also controversial. There may be potential for bias due to adjuvant radiation blunting the effect of SL. The accurate detection of LN metastasis by SL may lead to the avoidance of the potential risk of adjuvant radiotherapy [24], and it may not add significant morbidity by radiotherapy compared with patients not undergoing SL. Therefore, future investigation is required to define the role of adjuvant radiation in early-stage endometrial cancer.

Furthermore, three studies showed that the efficacy of SL for improved OS was not identified in patients with low-risk endometrial cancer (OR, 0.96; 95% CI, 0.59-1.55) [7, 11, 13]. Moreover, this finding was not changed in two observational studies, with the exception for

one RCT (OR, 0.70; 95% CI, 0.37-1.33) [11, 13]. On the other hand, SL increased OS in patients with high-risk endometrial cancer in two observational studies (OR, 0.34; 95% CI, 0.20-0.57) [11, 13]. Although one RCT demonstrated no difference in OS between SL and USL (OR, 1.02; 95% CI, 0.63-1.65) [7]. These findings provide evidence that the efficacy of SL is limited for improving the OS in patients with low-risk endometrial cancer, whereas it may increase OS in patients with high-risk endometrial cancer. The current systematic review suggests that SL should be applied carefully to patients with early-stage endometrial cancer, as it is unlikely to produce clinical benefits in a high proportion of patients. What we need are better guidances to select out the true low risk from the high risk patients who need adjuvant radiotherapy or lymphadenectomy plus or minus chemotherapy.

While this systematic review contributes significantly to the literature by examining a large number of patients in several countries and ethnic groups, its findings are nevertheless subject to several limitations. Firstly, only two of the included trials are RCTs, while the remaining seven are retrospective non-RCTs, which did not include control groups, and the results could have been biased by stage migration. Secondly, patient selection, techniques used to dissect lymph nodes and perform surgery, and postoperative care and follow-up varied substantially across the included studies, which weakens the strength of the conclusions.

In conclusion, this meta-analysis suggests that SL failed to improve OS in patients in early-stage endometrial cancer, especially those with low-risk disease. We may conclude that pelvic lymphadenectomy for endometrial carcinoma at in early-stage endometrial cancer is a useful procedure for prognostic and staging purposes, but does not improve survival. These findings are expected to be helpful in planning well-designed RCTs in the future. These findings argue that the use of SL in carefully selected patients may improve endometrial cancer staging, choice of adjuvant therapy and prognosis prediction. The accurate detection of LN metastasis should be still considered to be important because it can lead to upstaging pre-operative low-risk disease. In the future, major prospective randomized multicentric studies should yield conclusive data regarding its therapeutic value.

Disclosure of conflict of interest

None.

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