

## Original Article

# Systematic lymphadenectomy in early-stage endometrial cancer: a systematic review of the literature with meta-analysis

Lili Wang, Huanwen Wu, Li Wang, Hui Zhang, Junliang Lu, Zhiyong Liang, Tonghua Liu

*Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China.*

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**Abstract:** Background: The value of systematic lymphadenectomy (SL) in the treatment of early endometrial cancer (ECC) is still being debated. The purpose of the present study was to assess the benefit of SL for ECC by performing a systematic review of the published literatures. Methods: Systematic research was performed on Pubmed Database, Embase, Medline, Web of Science and CENTRAL for studies from 2003 January to 2015 January. Firstly, the search was limited to clinical trials concerning the surgical treatments of endometrial cancer patients which were written in English. Then, we included articles according the following criteria: 1) content of included study: comparison between SL group and no SL group; 2) ECC: stage I or II endometrial cancer according the International Federation of Gynecology and Obstetrics (FIGO) staging system in 1998 or 2009; 3) definition of SL versus no SL: removal of  $\geq 10$  lymph nodes or pelvic lymphadenectomy versus removal of versus  $< 10$  lymph nodes or pelvic and para-aortic lymphadenectomy. Methodological quality was assessed with the Jadad scale. Result: Eight studies were eligible for our analysis (including three randomized controlled trials and five observational studies), which included 13892 clinically ECC patients. On one hand, the results indicated that there was obvious difference between SL and no SL group in 5 year survival rate for ECC patients with high risk of lymph node metastasis (LNM) (OR 0.42, 95% CI, 0.26 to 0.68;  $P=0.0004$ ). However, there was no statistical difference between SL and no SL group in 5 year survival rate for all ECC patients (OR 0.85, 95% CI, 0.60 to 1.21;  $P=0.37$ ) and ECC patients with low risk of LNM (OR 0.73, 95% CI, 0.38 to 1.73;  $P=0.32$ ). On the other hand, SL group has a higher incidence of long-term complications than no SL group ( $P<0.05$ ). Conclusion: The present systematic review indicates that SL may improve 5 year survival rate for ECC patients with high risk of LNM, while risking then of long term complications.

**Keywords:** Endometrial cancer, systematic lymphadenectomy, meta-analysis

## Background

Endometrial cancer is the most common gynecologic malignancy in the United States. Most patients are in early stage upon diagnosis and the 5 year survival rates is more than 90% [1]. Previous study showed that the regional lymph nodes (LNs) are the most common sites of ECC metastasis [2]. The impact of LNM on survival rate is indisputable. Different locations of LN metastasis lead to different surgical staging and prognosis for endometrial cancer [3, 4]. SL has been performed on ECC for a long time and current clinical practice completely depends on the preferences of surgeons and institutions [5, 6]. There is no doubt that SL is a useful procedure to detect early occult metastatic mic-

rolesion in regional LN for an accurate surgical staging and good prognosis. However, in the presence of low LNM rate of ECC, especially in those at low risk, as well as the risk of peri-operative complications, especially in women more than 50 years old, and those who comrbid obese, hypertension and diabetes mellitus, the necessity and potential benefit of SL well deserve a second thought. In 2005 and 2006, there were two retrospective studies reporting that SL could improve the 5 year survival rate for ECC patients with high risk of LNM [7, 8]. However, later in 2008 and 2009, two more retrospective randomized controlled trials (RCTs) revealed that SL had no benefit for overall 5 year survival rate in all ECC patients [9, 10]. Recently, the accuracy of the two RCTs was

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doubted by some scholars, because of the lack of subgroup analysis and the inclusion of too many ECC patients with low risk of LNM. To date, there has been no meta-analysis on the peri-operative complications between SL group and no SL group of ECC. Therefore, in the present study, patients who underwent SL were grouped according to the risk of LNM [11], and peri-operative complications of SL were taken into consideration. By doing that, we aimed to assess the therapeutic value of SL in ECC patients with low or high risk of LNM in systematic review of the published literatures.

## Methods

### *Trial selection*

Studies available for our analysis were published RCTs and observational studies in all available biomedical databases (Pubmed Database, Embase, Medline, Web of Science, and CENTRAL) from 2003 January to 2015 January. Search strategy was provided by the biomedical specialists in Peking Union Medical College Hospital (PUMCH). Two reviewers independently read titles, abstracts and full text of the papers, and included or excluded studies based on criteria specified as follows: 1) content of study: comparison between SL group and non-SL group; 2) ECC: stage I or II endometrial cancer according to the International Federation of Gynecology and Obstetrics (FIGO) staging system in 1998 or 2009; 3) definition of SL versus non-SL: removal of  $\geq 10$  lymph nodes or systematic dissection of lymphatic tissues by surgeons' experience or pelvic lymphadenectomy versus removal of  $< 10$  pelvic lymph nodes or no pelvic lymphadenectomy or para-aortic lymphadenectomy. Then, they extracted essential data from included papers. The third reviewer handled incomplete or unclear data of the studies and difference of opinions between the previous two reviewers.

All the included ECC patients were first divided into two groups: SL group and no SL group according to the surgical procedures they had received. Then, all the patients in the two different groups were divided again according to the risk of LN metastasis.

### *Methodological assessment*

Methodological quality of randomized controlled trials and observational studies was as-

essed by Jadad and colleagues' scales [12]. There were 4 aspects in Jadad scoring system. 1) Whether all patients were grouped according to the randomization principle or not? 2) Whether all researches were double-blinded or not? 3) Whether the method of concealment and allocation was appropriate or not? 4) Whether there were descriptions of dropouts and withdrawals or not? The quality of the studies was evaluated by four authors. The final scores ranged from 0 (weakest) to 7 (strongest) for each aspect. Using a standardized protocol, the characteristics of each study were extracted into a reporting form. The disagreement was resolved through group discussion.

### *Statistical analysis*

Statistical analysis was performed using the Review Manager 5.2. Odds ratio (OR) and 95% confidence intervals (95% CI) were used as summary statistics. Categorical variables were analyzed using a chi-square test. The pooled OR was calculated using a random-effect with the Mante-Haenszel method and the Breslow-Day test was used to examine the statistical evidence of heterogeneity across the studies ( $P < 0.01$ ). The effects of selected measures of study quality were assessed by sensitivity analyses. The influence of each study was estimated by deleting each in turn from the analysis, then observing the degree to which the effect size and significance of the treatment effect changed. This analysis was performed for each outcome. If the deleted study induced more than 20% difference in the final conclusion or the estimate effect, the excluded study was considered influential.

## Results

Two randomized clinical trials and five observational studies published between 2004 and 2010 were eligible for our review. Their main characteristics were summarized in **Table 1**. The total number of eligible patients included was 13221; the number of patients by study ranged from 130 to 12333 patients. The duration of follow-up was 60 months.

### *Methodological quality of included studies*

Among all the included studies, about 85.7% reached an agreement between the initial reviewers. Then, after a consensus meeting, no

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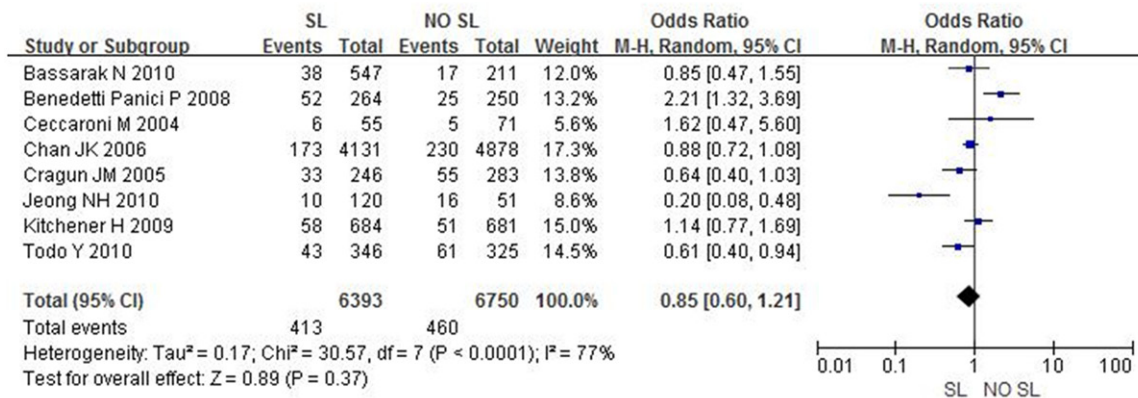
**Table 1.** Characteristics of the seven studies included in the meta-analysis

Author	Country	Year of publication	Number of patients		Surgical Methods of SL Group and no SL Group	Follow-up
			SL	NO SL		
Ceccaroni M, et al. [13]	Italy	2004	55	75	SL group: TAH-BSO combined with removal of pelvic LNs No SL: TAH-BSO	5 years
Cragun JM, et al. [14]	America	2005	246	243	SL: TAH-BSO combined with removal of more than 11 LNs No SL: TAH-BSO combined with removal of less than 11 LNs	5 years
Chan JK, et al. [15]	America	2006	5755	6578	SL: TAH-BSO combined with removal of more than 11 LNs No SL: TAH-BSO combined with removal of less than 10 LNs	5 years
Benedetti Panici P, et al. [9]	America	2008	264	250	SL: TAH-BSO combined with the pelvic lymphadenectomy and sampling of para-aortic LNs No SL: TAH-BSO combined with suspicious LNs sampling	5 years
Kitchener H, et al. [10]	UK	2009	704	704	SL: TAH-BSO combined with the pelvic lymphadenectomy and para-aortic LNs No SL: TAH-BSO combined with suspicious LNs sampling	5 years
Bassarak N, et al. [16]	Germany	2010	151	63	SL: TAH-BSO combined with the pelvic lymphadenectomy and sampling of para-aortic LNs No SL: TAH-BSO combined with suspicious LNs sampling	5 years
Jeong NH, et al. [17]	Korea	2010	151	211	SL: TAH-BSO combined with removal of more than 10 LNs No SL: TAH-BSO combined with removal of less than 10 LNs	5 years
Todo Y, et al. [18]	Japan	2010	325	346	SL: TAH-BSO combined with the pelvic lymphadenectomy and para-aortic LNs No SL: TAH-BSO combined with the pelvic lymphadenectomy	5 year

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**Table 2.** Jadad quality scores of the seven trials included in the meta-analysis

	Randomization	Concealment of allocation	Double blinding	Withdrawals and dropouts	Total
Ceccaroni M, et al. 2004	1	0	0	0	1
Cragun JM, et al. 2005	1	1	0	0	2
Chan JK, et al. 2006	1	1	0	0	2
Benedetti PP, et al. 2008	1	1	1	0	3
Kitchener H, et al. 2009	1	1	1	0	3
Bassarak N, et al. 2010	1	1	0	0	2
Jeong NH, et al. 2010	1	1	0	0	2
Todo Y, et al. 2010	2	1	1	1	5



**Figure 1.** Comparison of 5 year survival rate between SL group and no SL group. Seven studies presented 5 year survival rate of early-stage endometrial cancer patients in SL group and no SL group. The results revealed that there was no difference ( $P = 0.37$ ) in 5 year survival rate between SL group and no SL group, with a pooled OR of 0.85 (95% CI, 0.60 to 1.21).

disagreement persisted. **Table 2** shows the Jadad quality scores of all the included studies. Any study with a Jadad score below 3 was considered to be of poor quality.

### Overall 5 year survival rate

Seven studies presented 5 year survival rate of early-stage endometrial cancer patients in SL group and no SL group. The results revealed that there was no difference ( $P = 0.37$ ) in 5 year survival rate between SL group and no SL group, with a pooled OR of 0.85 (95% CI, 0.60 to 1.21) (**Figure 1**).

### 5 year survival rate in low risk group

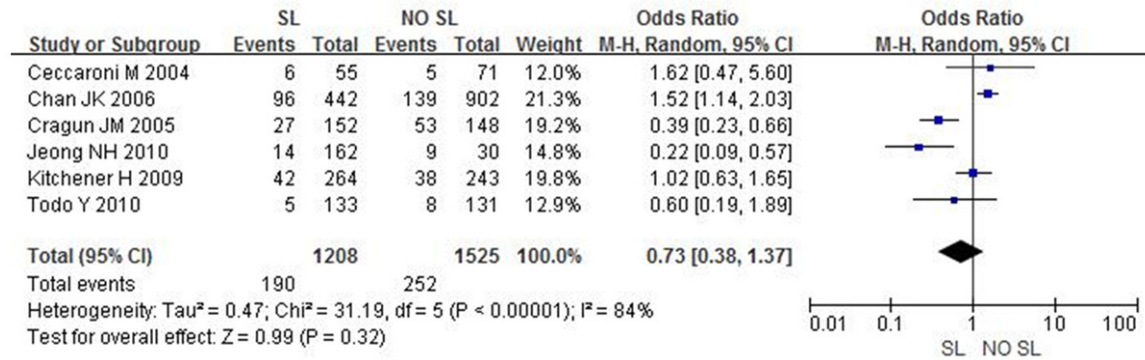
Patients were classified by the degree of tissue differentiation, myometrial invasion and histologic type. Patients who had well or moderately differentiated lesions, less than 1/2 myometrial invasion, and histologic subtypes (other than

papillary serous or clear-cell) carcinoma were categorized as low risk. Six out of the eight studies enrolled low risk ECC patients, all of which compared 5 year survival rate of ECC patients between SL group and no SL group. The final results revealed that there was no difference in 5 year survival rate between SL group and no SL group in low risk ECC patients ( $P = 0.32$ ), with a pooled OR of 0.73 (95% CI, 0.38 to 1.73) (**Figure 2**).

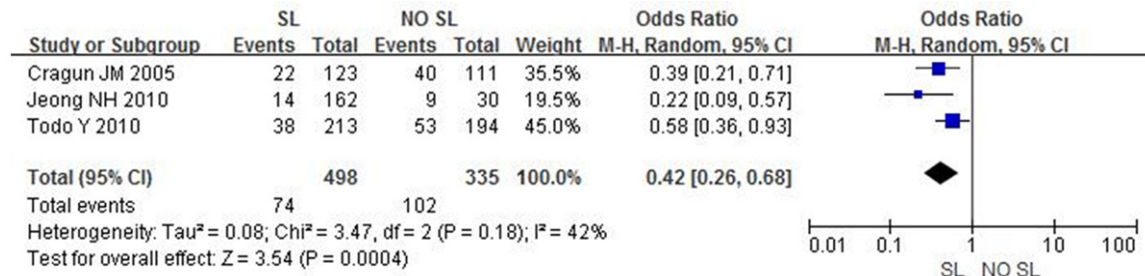
### 5 year survival rate in high risk group

Patients who had poorly differentiated lesions, more than 1/2 myometrial invasion, and papillary serous or clear-cell histologic type were categorized as high risk. Three of the eight studies included high risk ECC patients. All of them compared 5 year survival rate between SL group and no SL group. The results revealed that there was obvious difference ( $P < 0.001$ ) in 5 year survival rate between SL group and no

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**Figure 2.** Comparison of 5 year survival rate between SL group and no SL in ECC patients with low risk of LN metastasis. Patients were classified by the degree of tissue differentiation, myometrial invasion and histologic type. Patients who had well or moderately differentiated lesions, less than 1/2 myometrial invasion, and histologic subtypes (other than papillary serous or clear-cell) carcinoma were categorized as low risk. Six out of the eight studies enrolled low risk ECC patients, all of which compared 5 year survival rate of ECC patients between SL group and no SL group. The final results revealed that there was no difference in 5 year survival rate between SL group and no SL group in low risk ECC patients (P = 0.32), with a pooled OR of 0.73 (95% CI, 0.38 to 1.73).



**Figure 3.** Comparison of 5 year survival rate between SL group and no SL in ECC patients with high risk of LN metastasis. Patients who had poorly differentiated lesions, more than 1/2 myometrial invasion, and papillary serous or clear-cell histologic type were categorized as high risk. Three of the eight studies included high risk ECC patients. All of them compared 5 year survival rate between SL group and no SL group. The results revealed that there was obvious difference (P < 0.001) in 5 year survival rate between SL group and no SL group, with a pooled OR of 0.42 (95% CI, 0.26 to 0.68).

**Table 3.** The incidence of major adverse events of SL versus no SL group

Author	Year of publication	Medical Adverse Events		Surgical Adverse Events	
		SBO (%)	DVT (%)	Lymphocyst (%)	WD (%)
Cragun	2005	2.6 vs 2.5	2.6 vs 2.4	2.4 vs 2.6	0.6 vs 0.7
Kitchener	2009	3.0 vs 1.0	1.0 vs 0.1	1.0 vs 0.3	1.0 vs 0.1

Abbreviations: SBO, small bowel obstruction; DVT, deep venous thrombus; WD, Wound Dehiscence.

SL group, with a pooled OR of 0.42 (95% CI, 0.26 to 0.68) (Figure 3).

### Peri-operative complications

Only two studies compared the incidence of major postoperative complications of the included studies (Table 3). Our analysis revealed

that there was no significant difference in the short term complications between SL and no SL group (P > 0.05), but SL group suffered more long term complication than no SL group (P < 0.05).

### Discussion

With obvious early symptoms, endometrial cancer is usually diagnosed in early-stage [19]. According to FIGO and American College of Obstetricians and Gynecologists (ACOG), LNM is one of the most important factors for surgical staging and prognosis evaluation in endometrial cancer [20, 21]. Thus, in order to figure out the accurate surgical staging and guide the



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decision for appropriate adjuvant therapies, SL has been performed on ECC for a long time. However, with the increasing reports of peri-operative complications [10], the overall benefit of SL to ECC patients is being doubted. Recently, it was proposed that a complete surgical staging for ECC patients with low risk of LNM should be avoided, and only perform SL in patients at intermediate or high risk of LNM [23, 24].

In the present study, we revealed that SL did not improve 5 year survival rate for combined or low risk subgroup of ECC patients, while improved the 5 year survival rate of ECC patients with high risk of LNM, which was consistent with the previous studies [7, 9, 10, 17, 22]. On the other hand, some included studies in our analysis showed that ECC patients who had undergone SL were more likely to be upgraded [13, 14, 16]. Therefore, it is important to evaluate the risk of LNM comprehensively before and in the surgical procedure. In a multicenter study, a risk scoring system for evaluating the risk of LNM in ECC was proposed, and aged  $\geq 60$  years, histological grade III and/or type 2, primary tumor diameter  $\geq 1.5$  cm, depth of myometrial invasion  $\geq 50\%$  and a positive lympho vascular space invasion (LVSI) status were associated with LNM [25].

Adverse event of SL is a great issue for ECC patients. Short term surgical complications and long term surgical complications were thought to result in different prognosis. Many short term surgical complications usually recover completely, but most of the long term postoperative complications permanently impair the quality of life for ECC patients. In the present analysis, we found that the incidence of long term surgery-related complications of SL group was much higher than those of no SL group, which was consistent with Kitchener's study [10]. In addition, compared with no SL group, SL group patients suffered from larger surgical incision, more blood loss, longer anesthesia duration, longer hospital stay and higher hospital fee.

Given all the above considerations, we propose that a careful characterization on the risk of LNM should be performed on all ECC patients before and during surgery, and SL shall only be performed in high risk subgroup.

The limitation of the present study was mainly a result of the lack of consistent grouping criteria for ECC patients in all enrolled studies, making the result of our subgroup analysis less compelling. A large cohort study with well pre-specified grouping criteria is anticipated to further evaluate the value and risk of SL in different subgroups of ECC patients.

### Conclusion

We conclude that 1) SL improved the 5 year survival rate of ECC patients with high risk LNM; 2) The risk of long term postoperative complications of ECC patients who underwent SL was higher than those who did not.

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### Disclosure of conflict of interest

None.

### Authors' contribution

WLL, LZ Y and LTH have made substantial contributions to design the study. WLL, WL and LJL have screened papers and conducted the quality rating and meta-analysis. The statistical analyses were conducted by WLL, WHW and WL. WLL, LJL and WL have been involved in drafting the manuscript. WHW, WL and WHW have been involved in critically revising the manuscript. All authors read and approved the final manuscript.

**Address correspondence to:** Zhiyong Liang and Tonghua Liu Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China. E-mail: liangzhiyong1220@yahoo.com (LZY); Tonghua\_liu@163.com (THL)

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