Original Article

The role systematic lymphadenectomy plays in determining the survival outcome for advanced ovarian cancer patients: a meta-analysis

Dan Xu[1], Jinling Xue[2], Rafi Rozan[3], Li Li[4]

[1]Department of Gynecology Oncology, Affiliated Tumor Hospital of Guangxi Medical University, Nanning 530021, China; [2]Department of Obstetrics and Gynecology, Yancheng No. 1 People's Hospital, Yancheng 224000, China; [3]Department of Obstetrics and Gynecology, Georgetown Public Hospital Corporation, Georgetown, Guyana; [4]Department of Gynecology Oncology, Affiliated Tumor Hospital of Guangxi Medical University, Nanning 530021, China

Contributions: (I) Conception and design: L Li, D Xu; (II) Administrative support: Guangxi Medical University Cancer Hospital; (III) Provision of study materials or patients: L Li, J Xue, D Xu; (IV) Collection and assembly of data: D Xu, R Rozan; (V) Data analysis and interpretation: D Xu, L Li, R Rozan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Li Li. Department of Gynecology Oncology, Affiliated Tumor Hospital of Guangxi Medical University, Nanning 530021, China. Email: lili@gxmu.edu.cn.

Background: This study aims to evaluate the role systematic lymphadenectomy (SL) plays in advanced ovarian cancer (OC) patients. A meta-analysis was done to compare the progression-free survival (PFS) rates and overall survival (OS) rates between SL and unsystematic lymphadenectomy (USL).

Methods: An extensive literature search from the dates of January 1, 1994, to today was performed. In total, we analyzed 15 studies [3 randomized controlled trials (RCTs) and 12 observation studies], which included 33,257 patients with advanced OC who underwent SL or USL. We compared the survival outcomes of PFS and OS between SL and USL stratified by research type, respectively. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were combined and analyzed by using the Revman 5.3 software.

Results: For RCTs, SL did not improve the survival outcomes for advanced OC. Only 2 RCTs compared PFS, and 3 RCTs compared the OS rates between SL and USL. Two RCTs demonstrated that there was no difference in PFS between SL and USL (HR: 0.91; 95% CI: 0.81–1.04; P=0.16>0.05); at the same time, 3 RCTs also demonstrated that there were no difference in OS between SL and USL (HR: 0.94, 95% CI: 0.88–1.00; P=0.07>0.05). However, in observational studies, SL showed increased PFS (HR: 0.93, 95% CI: 0.92–0.95; P<0.00001) and OS (HR: 0.91, 95% CI: 0.89–0.93, P<0.00001) for advanced OC patients. The heterogeneity and publication bias in the included studies were within acceptable thresholds.

Conclusions: These findings suggest the possibility that SL cannot improve survival outcomes for advanced OC patients. However, we cannot completely ignore the results of observational studies. More relevant RCTs are needed to investigate the role of SL for advanced OC patients.

Keywords: Ovarian cancer (OC); systematic lymphadenectomy (SL)

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Introduction

According to a 2018 global report from the International Agency for Research on Cancer, the number of new cases of ovarian cancer (OC) was 295,144, and the number of deaths was 184,799 (1). OC accounts for 2.5% of all malignancies and 5% of female cancer deaths due to its low survival rates, primarily driven by advanced-stage diagnoses (2). Because of a lack of typical early symptoms

and the absence of practical measurements for early detection, more than 70% of patients, are newly diagnosed with advanced OC (3). Epithelial ovarian cancers (EOCs) are common in women of all racial groups, accounting for 90% of all OC cases. The mortality rate of EOC declined by 33% between 1976 and 2015 because of reductions in incidence and improvements in treatment (4).

Lymphatic spread is an important prognostic factor for EOC (5); however, the therapeutic role of systematic lymphadenectomy (SL) for advanced EOC is still controversial. The core issue of the controversy is whether an SL should be performed to stage or improve survival. "NCCN Guidelines Ovarian Cancer Version 1.2019" suggests that if macroscopically complete resection is possible, resection of clinically negative nodes is not required. Retrospective studies have shown that the rate of lymph node involvement in advanced EOC ranges between 48% and 75% (6). If we miss these involved lymph nodes, which are also resistant to chemotherapy, patients of advanced EOC will develop recurrent disease and eventually die.

The controversy between randomized controlled trials (RCTs) and retrospective studies raises has given rise to a number of meta-analyses on SL for OC in recent years (7-9). However, none of the meta-analyses arrived at definite conclusions. Since then, many new studies including 1 well-designed RCT have been conducted, but it is still necessary to reevaluate the effect of SL. Moreover, the above-mentioned meta-analyses (7-9) mostly focused on all-stage OC; however, most gynecology oncologists agree that the effect of SL is mainly on early stage EOC. The present meta-analysis was designed to compare the survival outcome of progression-free survival (PFS) and overall survival (OS) between SL and unsystematic lymphadenectomy (USL) in advanced EOC.

Methods

Search strategy

Possible eligible studies were searched for in the PubMed, Embase, and Cochrane Library databases by two independent reviewers. Bibliographies of relevant studies were also scanned by us to identify additional studies. The literature search was limited to the period between January 1, 1994, and March 31, 2019. The following keywords were used for the search: "ovarian neoplasm", "ovarian cancer", "ovarian tumor", "ovarian carcinoma", "lymphadenectomy", "lymph node dissection", and "lymph node sampling". All terms were expanded to include all subcategories to identify all published studies that fit the selection criteria. Only studies published in English were included in this meta-analysis.

Study selection

Studies included had to meet all of the following criteria: (I) used an RCT or observation study design, (II) examined advanced EOC (stage II–IV) patients, and (III) compared survival outcome (PFS or OS) between SL and USL. Exclusion criteria were as follows: (I) other histological types; (II) patients undergoing other treatments like surgery or chemotherapy before SL which could influence the survival outcome; (III) a lack of comparison of survival outcome (PFS or OS).

Data abstraction

Two reviewers independently abstracted the following parameters for each eligible study: first author, year of publication, study design, clinical stage, number of patients, period of follow-up, definition of SL and USL, hazard ratio (HR), and 95% confidence interval (CI) [upper limitation (UL), lower limitation (LL)] of PFS and OS. Any discrepancies between the two reviewers were discussed until consensus was reached, or the third reviewer served as a tiebreaker.

Statistical analysis

The aim of this meta-analysis was to compare the survival outcome between SL and USL. There were many studies that did not present the direct results of HRs and 95% CIs. Among some approaches for resolving this problem, the method by Meng *et al.* (10) was used to extract survival data (HRs and 95% CIs) from survival curves by using R software.

This meta-analysis was performed using Review Manager 5.3. Heterogeneity was assessed by using Higgins I^2, which measures the percentage of the total variation across studies that is due to heterogeneity rather than chance (11). It usually ranges from 0% (no observed heterogeneity) to 100% (maximal heterogeneity). $I^2 \leq 50\%$ indicates no heterogeneity when using the fixed-effects model. $I^2 > 50\%$ may indicate substantial heterogeneity when using a random-effects model. In this meta-analysis, we used the

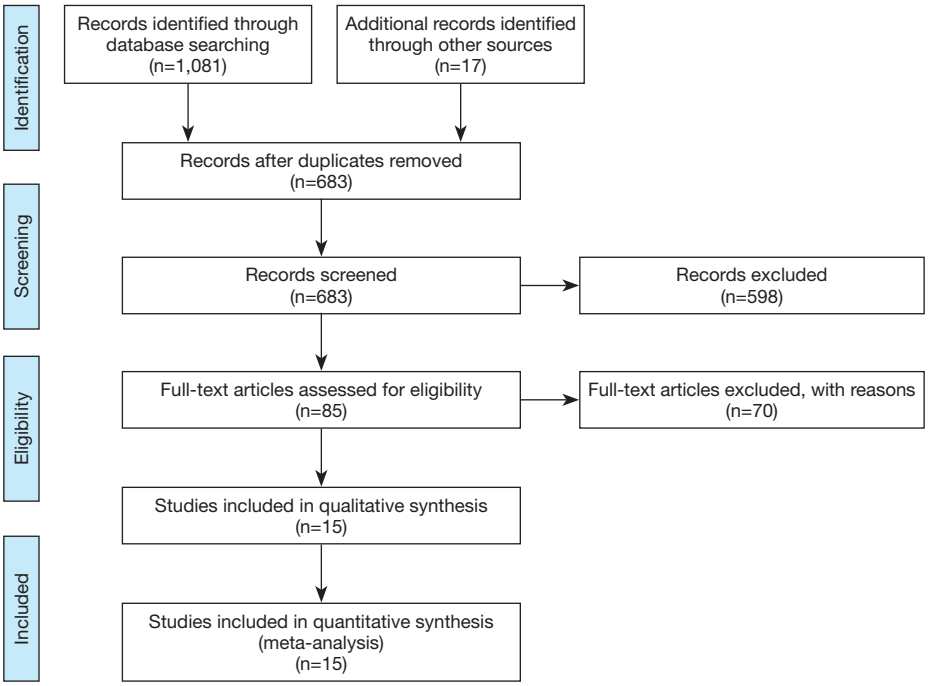

Figure 1 Flow diagram of the study selection process.

Table 1 Modified Jadad Assessments Scale for RCTs

Included studies	Randomization (2')	Concealment of allocation (2')	Double-blinding (2')	Withdraws and drop-outs (1')	Score
Panici 2005 (13)	2	1	2	1	6
du Bois 2010 (14)	1	1	1	1	4
Harter 2019 (15)	2	2	2	1	7

genetics inverse variance data type to combine Log HRs and SElogHRs, which were calculated by the following formula: SElogHR = (LogUL – LogLL)/3.92. P<0.05 was considered statistically significant.

Results

Search results

A total of 1,098 records were initially found based on the search criteria. After screening and exclusion, a total of 15 studies including 33,257 patients were eligible for this meta-analysis. A flow diagram of the study selection process is shown in *Figure 1*.

Quality assessment

For RCTs, we used a modified Jadad assessment scale (12), in which a study is judged according to four broad aspects: randomization, concealment of allocation, double-blinding and withdraws, and drop-outs. A full score is 7, and a high-quality study is defined as >4 (see *Table 1*).

For observational studies, we used the Newcastle-Ottawa Assessment Scale (16), in which a study is judged according to three broad aspects: selection, comparability, and outcome. A full score is 9, and a high-quality study is defined as score >7 (see *Table 2*).

Study characteristics

Of the literature included in this meta-analysis study, 3 studies were RCTs, and 12 studies were observational. Among the 12 observational studies, 3 studies were from the Surveillance, Epidemiology, and End Results (SEER) database. For this study, we divided patients into two

Table 2 Newcastle-Ottawa Assessment Scale for observation studies

Included studies	Selection				Comparability		Outcome		
	A	B	C	D	E		F	G	H
Kigawa 1994 (17)	☆	☆	☆	☆	☆	☆	☆	☆	☆
di Re 1996 (18)	☆	☆	☆	☆	☆		☆		☆
Allen 1999 (19)	☆	☆	☆	☆	☆	☆	☆	☆	☆
Saygili 2002 (20)	☆	☆	☆	☆	☆	☆	☆		
Isonishi 2004 (21)	☆	☆	☆	☆	☆	☆	☆		
Aletti 2006 (22)	☆	☆	☆	☆	☆		☆	☆	☆
Chan 2007 (23)	☆	☆	☆	☆	☆	☆	☆		
Abe 2010 (24)	☆	☆	☆	☆	☆		☆	☆	☆
Rouzier 2010 (25)	☆	☆	☆		☆		☆	☆	☆
Chang 2012 (26)	☆	☆	☆	☆	☆	☆	☆	☆	☆
Rungruang 2017 (27)	☆	☆	☆	☆	☆		☆	☆	☆
Zhou 2018 (28)	☆	☆	☆	☆	☆	☆	☆		

A: representative of SL; if truly representative of the average, 1 star was given. B: selection of USL; if they were from the same community as SL, 1 star was given. C: ascertainment of lymphadenectomy: if they had surgical records, 1 star was given. D: if there was no demonstration of outcome interest, 1 star was given. E: comparability of SL and unsystematic lymphadenectomy (USL) on the basis of some important factors including age, stage, chemotherapy; a maximum of 2 stars could be given. F: assessment of outcome; if the study was blind and independent, 1 star was given. G: if follow-up periods were longer than PFS or OS, 1 star was given. H: if there was an adequate number of SL subjects or no subject drop-out, 1 star was given. In the Newcastle-Ottawa Assessment Scale, studies with a score >7 were considered of good quality.

groups based on whether SL was performed or not. There were 7,829 patients in the SL group and 25,428 patients in the USL group. The definitions of SL and USL are shown in *Table 3*. Likewise, the detailed characteristics are also shown in *Table 3*.

Survival outcome

Primary outcomes: PFS

To investigate the role of SL in advanced OC on survival outcome, we conducted a meta-analysis using available information from 15 studies. Through considering some critical factors like selection bias, we separated RCTs and observational studies to compare the survival outcomes between SL and USL. There were two RCTs and three observational studies that conducted primary outcome (PFS) research. When we performed this meta-analysis according to the study design, no significant heterogeneities were detected (RCTs: I^2=26%; observational studies: I^2=0%), so the fixed-effects model was used. Two RCTs indicated that there was no difference in PFS between SL and USL (HR: 0.91; 95% CI: 0.81–1.04; P>0.05; *Figure 2*). On the other hand, 3 observational studies showed that SL improved PFS (HR: 0.93; 95% CI: 0.92–0.95; P<0.00001; *Figure 3*).

Secondary outcomes: OS

Regarding the survival benefits, we also investigated the role of SL on OS. All 15 studies were conducted to compare the OS between SL and USL. Because of the different proof strengths between RCTs and observational studies, the analysis was performed based on the research type. A fixed-effects model was used due to there being no significant heterogeneities (I^2=0% in RCTs, I^2=25% in observational studies). The overall pooled HR for RCTs (3 trials) was 0.94 (95% CI: 0.88–1.00; P=0.07>0.05; *Figure 4*), indicating SL had no effect in improving the OS of advanced EOC. On the other hand, the pooled HR for observational studies (12 studies) was 0.91 (95% CI: 0.89–0.93; P<0.00001; *Figure 5*), showing SL was an important factor for improved OS in observational studies.

Table 3 Clinical characteristics of 15 studies in the meta-analysis

First author	Year of publication	Design of study	Clinical stage	Follow-up time	Participant country	No. of patients		Definition of SL and USL
						SL	USL	
Kigawa	1994	Retrospective	III	14–123 months	Japan	29	24	SL: pelvic and para-aortic SL. USL: not performed
di Re	1996	Retrospective	II–IV	12–240 months	Italy	248	240	SL: ≥20 resected pelvic and para-aortic LNs. USL: <20 resected pelvic and para-aortic LNs
Allen	1999	Retrospective	III	10 years	Australia	33	97	SL: pelvic and para-aortic SL. USL: not performed
Saygili	2002	Retrospective	IIIC	19–46 months	Turkey	29	32	SL: pelvic and para-aortic SL. USL: not performed
Isonishi	2004	Retrospective	IIIC–IV	24 months	Japan	51	47	SL: pelvic and para-aortic SL. USL: not performed
Panici	2005	Prospective	IIIB–IV	35.2–90.7 months	Italy; Australia; Germany; England	216	211	SL: pelvic and para-aortic SL. USL: removal of macroscopic (>1 cm) pelvic and para-aortic LNs
Aletti	2006	Retrospective	IIIC–IV	5 years	The United States	61	158	SL: pelvic and para-aortic SL. USL: not performed or sampling
Chan*	2007	Retrospective	III–IV	4 years	The United States	1,520	12,398	SL: ≥10 resected pelvic and para-aortic LNs. USL: <10 resected pelvic and para-aortic LNs
du Bois	2010	Prospective	IIb–IV	7 years	Germany; France	610	1,332	SL: pelvic and para-aortic SL. USL: not performed or sampling
Abe	2010	Retrospective	IIII–IV	2–83 months	Japan	28	28	SL: pelvic and para-aortic SL. USL: not performed
Rouzier*	2010	Retrospective	IIIC	0–203 months	France	1953	8157	SL: ≥10 resected pelvic and para-aortic LNs. USL: <10 resected pelvic and para-aortic LNs
Chang	2012	Retrospective	IIIC	12 years	Korea	135	54	SL: pelvic and para-aortic SL. USL: not performed
Rungruang	2017	Retrospective	IIIC	45 months	The United States	689	1,182	SL: ≥1 resected pelvic and para-aortic LNs. USL: not performed
Zhou*	2018	Retrospective	IIIC–IV	4 years	The United States	1,904	1,144	SL: ≥10 resected pelvic and para-aortic LNs. USL: <10 resected pelvic and para-aortic LNs
Harter	2019	Prospective	IIB-IV	4 years	Germany; Italy; Belgium; Austria; Korea; Czech Republic	323	324	SL: pelvic and para-aortic SL. USL: not performed

*, studies from Surveillance, Epidemiology and End Results (SEER). LNs, lymph nodes.

Heterogeneity and publication bias

Tests for heterogeneity demonstrated that there was no significant difference between study variation (I^2=0–26%). Also, the funnel plot for 15 studies in this meta-analysis revealed that all studies were distributed evenly across the graph, suggesting no publication bias in this meta-analysis (*Figure 6*).

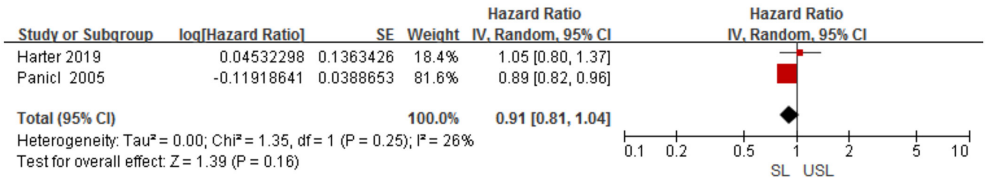

Figure 2 Comparison of PFS between SL and USL in two RCTs. PFS, progression-free survival; SL, systematic lymphadenectomy; USL, unsystematic lymphadenectomy; RCTs, randomized controlled trials.

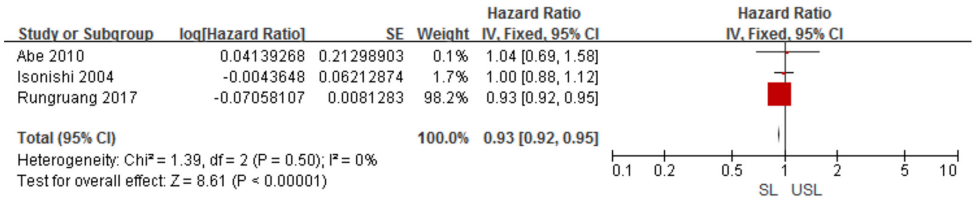

Figure 3 Comparison of PFS between SL and USL in three observation studies. PFS, progression-free survival; SL, systematic lymphadenectomy; USL, unsystematic lymphadenectomy; RCTs, randomized controlled trials.

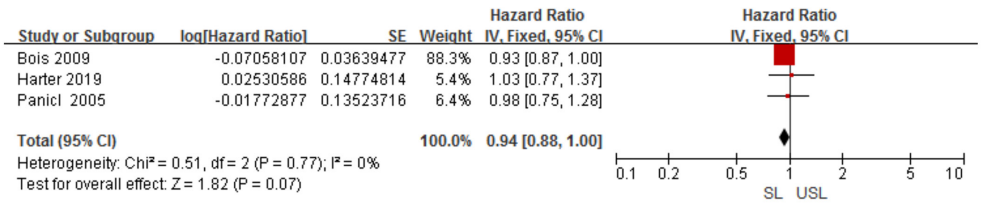

Figure 4 Comparison of OS between SL and USL in three RCTs. OS, overall survival; SL, systematic lymphadenectomy; USL, unsystematic lymphadenectomy; RCTs, randomized controlled trials.

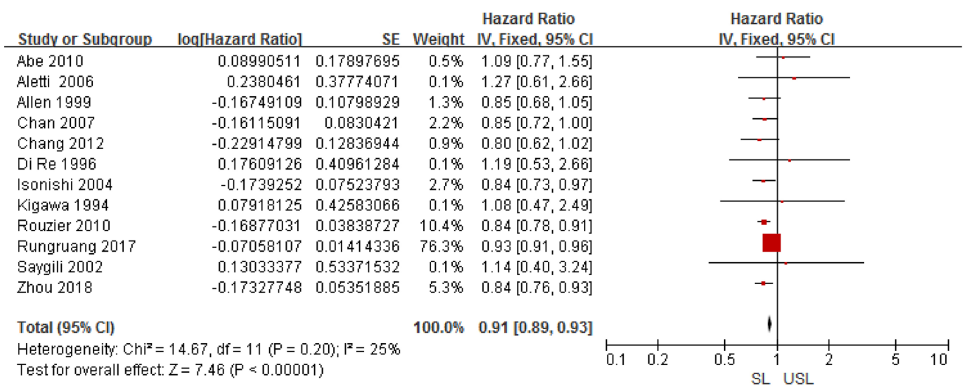

Figure 5 Comparison of OS between SL and USL in all observation studies. OS, overall survival; SL, systematic lymphadenectomy; USL, unsystematic lymphadenectomy; RCTs, randomized controlled trials.

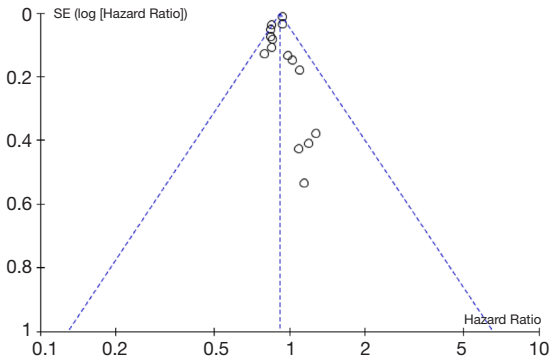

Figure 6 The funnel plot for 15 eligible studies in the meta-analysis.

Discussion

To clarify the effect of SL on survival outcome in advanced EOC, we performed this meta-analysis. After an extensive literature search, 3 RCTs and 12 observational studies were enrolled. Due to different research designs, we combined the RCTs and observational studies, respectively. PFS and OS are the most common survival outcomes for patient evaluation, which, in turn, represents the quality and quantity of life of women with advanced EOC. However, only 2 RCTs and 3 observational studies included in this meta-analysis published PFS results up. On the other hand, 15 included studies all reported the OS results of women with advanced EOC.

In our analysis, RCTs showed that SL may not improve PFS in advanced EOC, but three observational studies showed that SL can improve PFS compared with USL in advanced EOC. The discrepancy between RCTs and observational studies may be due to the different research designs: we believe the RCTs were well-designed, while the observational studies could not avoid selection bias. However, even among two RCTs, the conclusions differed. The former RCT reported that SL could improve PFS while the lymphadenectomy in ovarian neoplasm (LION) RCT reported the opposite result. However, the pooling of the meta-analysis indicated that SL cannot improve PFS. There are two explanations for this, as far as we can surmise. Firstly, the LION RCT was more precise and homogeneous. It amended some flaws in the former RCT like a more extended follow-up period. It added level 1 evidence to the long-standing research. Secondly, the greater number of cases in the LION RCT increased the weight of this RCT, and thus the combined result indicated that SL does not improve PFS in women with advanced EOC.

There are more studies focusing on the role of SL for OS in advanced EOC. A similar result has been documented for the secondary outcome-OS. Three RCTs showed that SL does not improve OS, while 12 observation studies showed that SL can improve OS. Unfortunately, but not surprisingly, we could not obtain a consensus conclusion as to whether SL improves the survival outcome in advanced EOC from this meta-analysis. There were only 3 included RCTs in which the number of patients involved was not large enough to describe the effect of survival outcome of SL in advanced EOC. Although 12 observational studies were included in this meta-analysis supporting the benefit of SL in women with advanced EOC, we think they are less convincing because of obvious selection bias and the deviation of weight by 3 large scale studies from SEER. In addition, most of the early observation studies compared OS of patients who underwent lymphadenectomy, which ranged from SL to node sampling with USL. These studies showed considerable differences in OS between groups. Hence, these studies were limited and did not account for the selection bias that SL has more favorable prognostic features than USL in advanced EOC.

It is well known that residual tumor size is particularly crucial to survival benefit (29). Lymph node metastasis rate was detected in 74.6% of advanced EOC patients (30). In our meta-analysis, 12 observational studies demonstrated the survival benefit of SL. Kigawa *et al.* (17) reported that omentum and retroperitoneal lymph nodes were the most frequent sites of metastasis. Similarly, Paik *et al.* (31) investigated recurrent EOC patients with no gross residual disease after primary debulking surgery and concluded that lymph nodes were at higher risk of recurrence. If these tumor cells were removed, further residual tumor burden could be reduced, which can affect survival outcomes. Keyver-Paik *et al.* (32) evaluated the lymph nodes of advanced OC undergoing neoadjuvant chemotherapy and reported that lymph node dissection even of unsuspicious nodes should be performed. However, the LION trial, which is a powered, international, multicenter trial, found that a macroscopically complete resection did not improve according to the increased radicality of the procedure. Thus far, there have been 3 well-designed RCTs for advanced EOC all stating the same conclusion: SL does not improve survival outcomes but results in treatment burden and harm in patients. Some meta-analyses (7-9) have been performed to study the role of SL. Gao *et al.* (7) and Zhou *et al.* (9) concluded that SL could improve OS in advanced EOC while Kim *et al.* (8) suspected the

active role of SL in advanced EOC. These meta-analyses included all stage OC studies, while the role of SL in stage I OC has already been confirmed. However, there were previously not many prospectively randomized, powered, international, multicenter trials. Nowadays, we included 1 necessary LION trial in our meta-analysis to update and reevaluate the role of SL in advanced EOC. Our meta-analysis is the first to include 3 RCTs to evaluate the role of SL in advanced OC. However, the controversy in the results between observational studies and LION raises several questions related to follow-up periods and the application of chemotherapy. In our meta-analysis, we included 15 studies which had OS and PFS results, but they rarely had data concerning side effects. Therefore, we did not analyze the side effects of SL, which is a limitation of our analysis. As a result, future randomized trials are needed to balance the risks and benefits of SL in advanced EOC (33). CARACO, an ongoing French trial (NCT0128490), scheduled to finish in 2022, is aimed at evaluating the impact of SL survival in patients with advanced EOC (34).

We look forward to this trial result to confirm the 3 RCTs result, so this issue can be conclusively resolved.

Conclusions

These findings suggest the possibility that SL cannot improve survival outcomes for advanced OC patients. However, we can not completely ignore the results of observational studies. More relevant RCTs are needed to investigate the role of SL for advanced OC patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm.2020.04.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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