J Gynecol Oncol. 2022 Sep;33(5):e69
https://doi.org/10.3802/jgo.2022.33.e69
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Review Article

Systematic lymph node dissection during interval debulking surgery for advanced epithelial ovarian cancer: a systematic review and meta-analysis

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Received: Mar 29, 2022
Revised: May 27, 2022
Accepted: Jun 21, 2022
Published online: Jul 6, 2022

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ABSTRACT

Objective: To evaluate the efficacy and safety of systematic lymph node dissection (SyLND) at the time of interval debulking surgery (IDS) for advanced epithelial ovarian cancer (AEOC).
Methods: Systematic literature review of studies including AEOC patients undergoing SyLND versus selective lymph node dissection (SeLND) or no lymph node dissection (NoLND) after neoadjuvant chemotherapy (NACT). Primary endpoints included progression-free survival (PFS) and overall survival (OS). Secondary endpoints included severe postoperative complications, lymphocele, lymphedema, blood loss, blood transfusions, operative time, and hospital stay.
Results: Nine retrospective studies met the eligibility criteria, involving a total of 1,660 patients: 827 (49.8%) SyLND, 490 (29.5%) SeLND, and 343 (20.7%) NoLND. The pooled estimated hazard ratios (HR) for PFS and OS were, respectively, 0.88 (95% confidence interval [CI]=0.65–1.20; p=0.43) and 0.80 (95% CI=0.50–1.30; p=0.37). The pooled estimated odds ratios (ORs) for severe postoperative complications, lymphocele, lymphedema, and blood transfusions were, respectively, 1.83 (95% CI=1.19–2.82; p=0.006), 3.38 (95% CI=1.71–6.70; p<0.001), 7.23 (95% CI=3.40–15.36; p<0.0001), and 1.22 (95% CI=0.50–2.96; p=0.67).
Conclusion: Despite the heterogeneity in the study designs, SyLND after NACT failed to demonstrate a significant improvement in PFS and OS and resulted in a higher risk of severe postoperative complications.

Trial Registration: PROSPERO Identifier: CRD42022303577

Keywords: Ovarian Cancer; Neoadjuvant Chemotherapy; Cytoreductive Surgery; Lymphadenectomy; Survival

Synopsis

Systematic lymph node dissection (SyLND) during interval debulking surgery (IDS) for advanced epithelial ovarian cancer failed to demonstrate a significant improvement in survival rates. The risk of postoperative complications was higher when SyLND was performed. The role of imaging for nodal evaluation after neoadjuvant chemotherapy remains a matter of debate. Further high-quality evidence is required before definitively omitting SyLND during IDS.

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Trial Registration
PROSPERO Identifier: CRD42022303577

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: C.G.; Data curation: C.G., D.D.V.; Formal analysis: C.G., P.I., B.G., T.F., P.G.; Investigation: C.G.; Methodology: C.G., D.D.V., B.G.; Project administration: C.G., D.D.V.; Resources: C.G., D.D.V.; Supervision: C.G., P.I., B.G, D.D.V.; Validation: C.G., P.I., B.G., M.L., D.D.V.; Visualization: C.G., P.I., B.G., T.F., P.G.; Writing - original draft: C.G.; Writing - review & editing: P.I., B.G., T.F., P.G., B.P.P., M.L., D.D.V.

INTRODUCTION

The cornerstone of the surgical treatment for advanced epithelial ovarian cancer (AEOC) is to achieve complete cytoreduction of all macroscopic peritoneal lesions with no gross residual disease (NGRD) [1-3]. The standard surgical staging for AEOC currently includes hysterectomy, salpingo-oophorectomy, omentectomy, peritoneal washing, and peritoneal biopsies [4,5]. In the past, pelvic and paraaortic systematic lymph node dissection (SyLND) has been also performed as a staging procedure [6-8] for AEOC until in 2018 the LION trial [9] definitively put an end to a longstanding debate on the role of SyLND in the PDS setting, confirming the results from other randomized trials [10,11] that demonstrated only a prognostic role for SyLND without any therapeutic value.

The LION trial [9] demonstrated that pelvic and paraaortic SyLND in patients undergoing primary debulking surgery (PDS) for AEOC and with radiologically and surgically negative lymph nodes (LNs) was not associated with longer progression-free survival (PFS) or overall survival (OS) and resulted in a higher rate of postoperative complications. Nowadays, however, almost 70% of AEOC patients are treated with neoadjuvant chemotherapy (NACT) and interval cytoreductive surgery (IDS) [12,13], owing to the presence of unresectable widespread disease or poor performance status [14], with apparently similar oncological outcomes compared with PDS [15-19]. While recent robust data allow for omitting SyLND during PDS for AEOC patients without any suspicion of LN involvement [20-25], the evidence supporting the same assumption for IDS is limited. Patients submitted to NACT-IDS generally present with more extensive disease and thus may have an increased risk of occult lymphadenopathy in case of negative radiological and surgical assessment [26,27]. Furthermore, NACT may act as a game-changer leading to the negativization of initially positive LNs, which though are not totally chemoresponsive and may hide chemoresistant microscopic disease. Therefore, whether SyLND may still find a role in case of non-suspicious LNs after NACT remains unclear.

The present analysis aimed to evaluate the prognostic impact of SyLND in patients undergoing IDS for AEOC.

MATERIALS AND METHODS

1. Search strategy

We conducted this systematic review and meta-analysis using a prospectively registered protocol (PROSPERO CRD42022303577) and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [28].

A search was performed up to January 31, 2022 by 2 authors (C.G., D.D.V.) independently within several databases (MEDLINE, Embase, Cochrane Library, Scopus, Google Scholar, ClinicalTrials.gov) to ensure all relevant studies evaluating the role of SyLND during IDS for AEOC. The process of evidence acquisition combined the following keywords and their MESH terms: “advanced ovarian cancer,” “neoadjuvant chemotherapy,” “interval debulking surgery,” “lymphadenectomy,” “lymph node dissection.” Article abstracts, full text of articles and cross-referenced studies identified from retrieved articles were screened for pertinent information. Duplicate records were excluded.

2. Inclusion criteria and trial selection

Key criteria for inclusion were: 1) original studies published in English, in peer-reviewed journals; 2) advanced epithelial ovarian cancer; 3) IDS after NACT; 4) SyLND versus selective lymph node dissection (SeLND) or no lymph node dissection (NoLND). Exclusion criteria were: 1) editorials, review articles and conference abstracts; 2) PDS; 3) non-epithelial ovarian cancer; 4) early-stage ovarian cancer; 5) series where PDS and IDS patients were mixed and no separate results could be obtained.

The selected studies were comprehensively examined, and relevant data extracted for each paper were inputted to the spreadsheet. The information selected included: authors, year of publication, study design and setting, number of patients, period of enrollment, age, body mass index (BMI), International Federation of Gynecology and Obstetrics (FIGO) stage, histotype, grading, BRCA mutation, preoperative CA125 serum level, number of NACT cycles, clinical response to NACT, positive LNs on preoperative imaging assessment, residual tumor (RT), number of resected LNs, number of positive LNs, perioperative complications, follow-up, overall recurrence rate, site of recurrence (LNs, peritoneal or distant), PFS, and OS. The 2 authors (C.G., D.D.V.) carried out data extraction and quality assessment from all the retrieved studies based on full-text articles. Discrepancies between the investigators were resolved by consensus.

3. Quality assessment

All identified controlled studies were included in the meta-analysis. The studies were then classified qualitatively according to the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions [29]. The Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used for assessing the risk of bias in non-randomized studies of interventions included in the meta-analysis [30].

4. Outcomes

Two groups of outcomes were considered to be meaningful and therefore addressed in the present analysis: survival and surgical outcomes.

Survival outcomes

The primary outcome was to evaluate the impact of SyLND on survival. The primary endpoints were PFS and OS. The PFS was defined as the time from surgery until progression of disease. The OS was defined as the time from surgery to death.

Surgical outcomes

The secondary outcome was to evaluate the impact of SyLND on perioperative outcomes in terms of:

- Severe postoperative complications: occurrence of severe complications (grade III–IV) according to the Clavien-Dindo classification [31];
- Lymphocele and lymphedema;
- Blood loss: changes from baseline in terms of hemoglobin level (g/dL);
- Blood transfusions: occurrence of perioperative transfusions of red cell concentrates (RCC);
- Operative time: duration of surgery;
- Hospital stay: length of postoperative hospital stay (days).

https://doi.org/10.3802/jgo.2022.33.e69

5. Statistical analysis

All analyses were carried out using RevMan software (Review Manager version 5.4; Cochrane Collaboration, London, UK). Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). HRs from multivariate analyses (Cox regression model) were used to assess the endpoints (time-to-event outcomes). Dichotomous outcomes from each study were expressed as an odds ratio (OR) with a 95% CI. Continuous outcomes were expressed as standardized mean difference (SMD). Heterogeneity among studies was reported with I^2 statistics. A random-effect model was used at meta-analysis if any heterogeneity was detected, whereas a fixed-effect model was used if no heterogeneity was identified. We decided to examine publication bias with Egger's test and funnel plots if the number of studies was 10 or above, since these analyses are underpowered otherwise.

RESULTS

1. Study selection

The study selection is illustrated in **Fig. 1**. A search of the MEDLINE (PubMed) database resulted in 282 relevant articles and further search in the Embase, Cochrane Library, Google Scholar databases yielded no additional articles. No additional eligible studies were retrieved by hand-searching bibliographies. Nine fulfilled the inclusion criteria for this systematic review, involving a total of 1,660 patients [32-40].

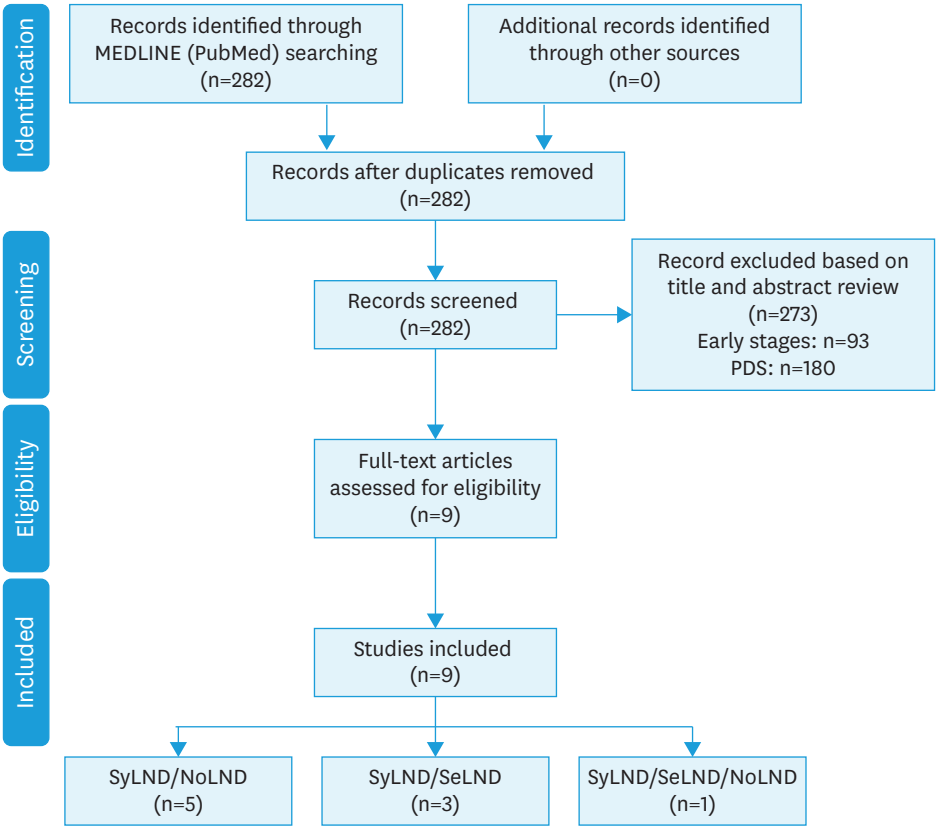

Fig. 1. PRISMA diagram.
NoLND, no lymph node dissection; PDS, primary debulking surgery; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SeLND selective lymph node dissection; SyLND, systematic lymph node dissection.

https://doi.org/10.3802/jgo.2022.33.e69

2. Study and population characteristics

The characteristics of included studies are detailed in **Table 1**. All nine studies were retrospective [32-40]. No randomized controlled trials were found. Six studies (66.7%) [33,35,36,38-40] were monocentric and 3 (33.3%) [32,34,37] were multicentric. The studies were published between 2012 and 2021, while the period of patient enrollment varied from 1996 and 2018 across the series. The risk of bias assessment for the included studies is detailed in the **Table S1**.

Depending on the series, patients underwent different patterns of nodal surgery procedures: 1) systematic pelvic and para-aortic LN dissection (SyLND); 2) resection of bulky nodes or radiologically suspicious lymph nodes (SeLND); 3) no lymph node dissection (NoLND). Five studies compared SyLND to NoLND [33,34,37,38,40], three studies compared SyLND to SeLND [32,35,39], and one compared the 3 groups [36]. Of the 1,660 patients included, 827 (49.8%) underwent SyLND, 490 (29.5%) SeLND, and 343 (20.7%) NoLND. When the information was available, the extent of paraaortic lymph node dissection (LND) was performed up to the level of the inferior mesenteric artery in one study [36] and the left renal vein in three studies [32,35,38].

Regarding the demographic and preoperative clinical characteristics (**Table 1**), there were no statistically significant differences between the compared groups (SyLND vs. SeLND/NoLND), except for the following: 1) 3 studies [37,38,40] reported a lower age in the SyLND cohort; 2) Schwartz et al. [34] described more FIGO stage III and less stage IV in the SyLND group; 3) Bund et al. [37] reported less ASA (American Society of Anesthesiologists) score 3-4 among SyLND patients; 4) Fagotti et al. [32] reported a higher number of NACT cycles while another study [37] a lower number in the SyLND group; (5) Bund et al. [37] described a higher complete response to NACT in SyLND patients. The vast majority (80%–100%) of patients across all studies had high grade serous ovarian cancers (HGSOC) and underwent platinum-based NACT before IDS and platinum-based adjuvant chemotherapy after surgery. There were no significant differences in terms of treatment regimens and number of NACT cycles between compared groups across the studies.

The surgical data of the included studies are detailed in **Table 2**. The surgical approach during IDS was exclusively laparotomy in all studies except for the Lopes' and Bund's series. In particular, Lopes et al. reported that laparotomy was performed in 90% of SyLND patients and 95% of NoLND patients, while laparoscopy in 10% and 5%, respectively [38]. Bund et al. [37] reported significant differences in the surgical approach for IDS between SyLND and NoLND groups (p=0.01): the rates of laparoscopy, laparoconversion and laparotomy were 33%, 4%, and 63%, respectively, in the SyLND group, and 16%, 7%, and 77%, respectively, in the NoLND group. The ancillary surgical procedures performed during IDS (e.g., rectosigmoidectomy, right diaphragm stripping, cholecystectomy, splenectomy, etc.) were similar between compared groups across the series.

No RT was achieved from 80% up to 100%, except for: 1) the Eoh's series [35] and the He's series [39], where the rate of complete cytoreduction was 35% and 54%, respectively; 2) the Bund's series [37] and the Benoit's series [40], where the NoLND group achieved 50% and 69%, respectively. Two studies [38,39] reported the percentage of suspicious LNs on initial imaging before NACT, ranging from 40% to 82% and 2 studies [35,39] after NACT, ranging from 37% and 55%. The median number of LNs removed ranged from 23 to 46 in SyLND groups and varied from 4 to 10 in SeLND groups. The percentage of positive LNs on pathological assessment ranged from 11% to 66%. The overall recurrence varied from 40.2%

https://doi.org/10.3802/jgo.2022.33.e69

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Table 1. Main characteristics of the studies included and clinical data.

Author (yr)	Design	Period	Sample size	Age (yr), median (range)	p	BMI (kg/m²)	p	FIGO stage	p	Histotype	p	Grading	p	BRCA	p	PS	p	NACT cycles, median (range)	p	CA125	p	Clinical response to NACT (RECIST)	p
Fagotti et al., 2012 [32]	R, Mu	2005–2010	Total 151 SeLND 101	62 (31–80)	0.61	NA		III: 81 (80.2%) IV: 20 (19.8%)	0.408	HGSOC: 99 (98%) Others: 2 (2%)	0.19	See histotype		NA		NA		4 (3–9)	0.0001	NA		CR/PR: 79 (78.2%) SD: 22 (21.8%)	0.588
			SyLND 50	63 (35–76)				III: 37 (74%) IV: 13 (36%)		HGSOC: 47 (94%) Others: 3 (6%)								6 (6–10)				CR/PR: 41 (82%) SD: 9 (18%)	
Iwase et al., 2015 [33]	R, Mo	2000–2008	Total 124	58 (29–83)		NA		IIIB: 6 (4.8%)		Serous: 105 (84.6%)		NA		NA		NA		6 (2–9)		Pre-NACT: 1,569.4 (13.5–24,821)		NA	
			NoLND 38 SyLND 86					IIIC: 77 (62.1%) IV: 41 (33.1%)		Others: 19 (15.4%)										Post-NACT: 15.8 (2.3–1,965.1)			
Schwartz et al., 2015 [34]	R, Mu	1998–2012	Total 101 NoLND 47	≤55: 14 (29.8%) 56–69: 22 (46.8%) ≥71: 11 (23.4%)	0.40	25.2 (22.6–28.7)	0.79	III: 27 (57.4%) IV: 20 (42.6%)	0.01	Serous: 38 (80.9%) Others: 9 (19.1%)	0.22	1–2: 12 (33.3%) 3: 24 (66.7%) NA: 11	0.60	5 (10.6%)	0.73	ECOG 0–1: 22 (50%) 2–4: 22 (50%) NA: 3	0.60	6 (4–6)	0.15	NA		CR: 6 (18.7%) PR: 19 (59.4%) SD: 7 (21.9%) NA: 15	0.30
			SyLND 54	≤55: 22 (40.8%) 56–69: 24 (44.4%) ≥71: 11 (23.4%)		24.5 (22.4–27.3)		III: 43 (79.6%) IV: 11 (20.4%)		Serous: 43 (79.6%) Others: 11 (20.4%)		1–2: 12 (25.6%) 3: 31 (74.4%) NA: 11		4 (7.4%)		ECOG 0–1: 27 (50%) 2–4: 25 (50%) NA: 2		5 (4–6)		NA		CR: 9 (33.3%) PR: 16 (53.4%) SD: 4 (13.3%) NA: 24	

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https://doi.org/10.3802/jgo.2022.33.e69

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Table 1. (Continued) Main characteristics of the studies included and clinical data.

Author (yr)	Design	Period	Sample size		Age (yr), median (range)	p	BMI (kg/m²)	p	FIGO stage	p	Histotype	p	Grading	p	BRCA	p	PS	p	NACT cycles, median (range)	p	CA125	p	Clinical response to NACT (RECIST)	p
Eoh et al., 2017 [35]	R, Mo	2009–2015	Total	133		0.33	NA			0.2		0.523		0.89	NA			0.431		0.307		0.54	NA	
			SeLND	68	60.5 (38–79)				IIIC: 27 (39.7%) IV: 41 (60.3%)		Serous: 62 (91.2%) Others: 6 (8.8%)		1: 4 (5.9%) 2: 11 (16.2%) 3: 53 (77.9%)				ASA 1: 19 (27.9%) 2: 35 (51.5%) 3: 14 (20.6%)		3 (2–6)		Pre-NACT: 3,677.1 (6.2–20,685.7)			
			SyLND	65	53.8 (27–75)				IIIC: 33 (50.8%) IV: 32 (49.2%)		Serous: 56 (86.2%) Others: 9 (13.8%)		1: 4 (6.2%) 2: 14 (21.5%) 3: 47 (72.3%)				ASA 1: 25 (38.5%) 2: 28 (43.1%) 3: 12 (18.5%)		3 (3–6)		Pre-NACT: 3,938.5 (141.7–30,000)			
Song and Gao, 2019 [36]	R, Mo	1996–2016	Total	330		0.55		0.87		0.51		0.29		0.96		0.87	NA			0.43	NA			0.80
			NoLND	67	56 (51–62)		21.7 (20.2–24.2)		III: 52 (77.6%) IV: (15 (22.4%)		Serous: 54 (80.6%) Others: 13 (19.4%)		1: 7 (10.4%) 2–3: 60 (89.6%)		5 (22.7%)				3 (2–3)				CR: 11 (16.4%) PR: 56 (83.6%)	
			SeLND (ref.)	145	54 (50–61.5)		22.3 (20.3–24.9)		III: 108 (75.5%) IV: 37 (25.5%)		Serous: 124 (85.5%) Others: 21 (14.5%)		1: 17 (11.7%) 2–3: 128 (88.3%)		14 (28.6%)				3 (3–3)				CR: 27 (18.6%) PR: 118 (81.4%)	
			SyLND	118	55.5 (51–61)		21.9 (20.0–24.3)		III: 95 (80.5%) IV: 23 (19.5%)		Serous: 105 (89%) Others: 13 (11%)		1: 13 (11%) 2–3: 105 (89%)		10 (27.8%)				3 (2–3)				CR: 24 (20.3%) PR: 94 (79.7%)	
Bund et al., 2020 [37]	R, Mu	2000–2017	Total	255		<0.0001		0.63		0.4				0.8		0.19		0.03		0.02		0.36		0.08
			NoLND	100	67.5 (31–83)		<25: 38 (49.4%) 25–30: 27 (35%) >30: 12 (15.6%) NA: 23		III: 78 (78%) IV: 22 (22%)		Serous: 100 (100%)		1–2: 10 (17.9%) 3: 46 (82.1%) NA: 44		2 (25%) NA: 92		ASA 0–2: 54 (54%) 3–4: 21 (21%) NA: 25		≤3: 5 (5.1%) 4–6: 74 (76.3%) ≥7: 18 (18.6%) NA: 3		Pre-NACT ≤1,500: 58 (65.2%) >1,500: 31 (34.8%) NA: 11		CR: 5 (27.8%) PR: 13 (72.2%) NA: 82	
			SyLND	155	59 (31–82)		<25: 70 (54.3%) 25–30: 37 (28.7%) >30: 22 (17.1%) NA: 26		III: 127 (81.9%) IV: 28 (18.1%)		Serous: 155 (100%)		1–2: 23 (19.3%) 3: 96 (80.7%) NA: 36		19 (58%) NA: 122		ASA 0–2: 94 (60.6%) 3–4: 24 (15.5%) NA: 37		≤3: 25 (16.7%) 4–6: 107 (71.3% ≥7: 18 (12%) NA: 5		Pre-NACT ≤1,500: 102 (70.8%) >1,500: 42 (29.2%) NA: 11		CR: 19 (52.8%) PR: 17 (47.2%) NA: 119	

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Table 1. (Continued) Main characteristics of the studies included and clinical data.

Author (yr)	Design	Period	Sample size		Age (yr), median (range)	p	BMI (kg/m²)	p	FIGO stage	p	Histotype	p	Grading	p	BRCA	p	PS	p	NACT cycles, median (range)	p	CA125	p	Clinical response to NACT (RECIST)	p
Lopes et al., 2021 [38]	R, Mo	2008–2016	Total	60		0.03		0.58		0.64	HGSOC		HGSOC		NA			1						1
			NoLND	21	61.5 (46–82)		24.4 (20.1–34.9)		IIIC: 16 (76.2%) IC: 5 (23.8%)								ECOG 2: 9.5%		6		CA125 at diagnosis: 1,422 Post-NACT CA125: 19.6		CR: 3 (14.3%)	
			SyLND	39	55.7 (41–73)		25.8 (17.6–42)		IIIC: 30 (76.9%) IV: 9 (23.1%)								ECOG 3: 7.7%		6				CR: 7 (17.9%)	
He et al., 2021 [39]	R, Mo	2000–2014	Total	303		0.36	NA			0.19		0.45		0.32	NA		NA			NS		0.46		
			SeLND	176	44.5 (23–75)				IIIB: 10 (5.7%) IIIC: 124 (70.5%) IV:		Serous: 110 (62.5%) Others: 66 (37.5%)		1: 4 (2.3%) 2–3: 127 (72.2%) NA: 45						2 (1–6)		Pre-NACT: 1,320.5 (13.4–47,422)		NA	
			SyLND	127	53 (32–74)				IIIB: 11 (8.7%) IIIC: 77 (60.6%) IV: 39 (30.7%)		Serous: 77 (60.6%) Others: 50 (39.4%)		1: 1 (0.7%) 2–3: 115 (90.6%) NA: 11						2 (1–6)		Pre-NACT: 1,233 (10.1–31,521)			
Benoit et al., 2021 [40]	R, Mo	2005–2018	Total	203		<0.001		0.57		0.30	HGSOC		HGSOC			0.43		0.06		0.34		0.28		
			NoLND	70	68.37± 10.95		24.07± 5.35		III: 44 (62.9%) IV: 19 (27.1%) NA: 7						6 (8.6%)		ASA 1–2: 40 (57.1%) 3–4: 12 (17.1%) NA: 18		4.6± 1.55		Pre-NACT: 2,587± 3,865		NA	
			SyLND	133	62.33± 10.5		23.62± 4.71		III: 83 (62.4%) IV: 42 (31.6%) NA: 8						22 (16.5%)		ASA 1–2: 76 (57.1%) 3–4: 12 (9%) NA: 45		4.39± 1.42		Pre-NACT: 1,976± 3,504			

BMI, body mass index; BRCA, BReast CAncer gene; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; HGSOC, high grade serous ovarian cancer; Mo, monocentric; Mu, multicentric; NA, not available; NACT, neoadjuvant chemotherapy; NoLND, no lymph node dissection; PR, partial response; PS, performance status; R, retrospective; RECIST, response evaluation criteria in solid tumors; Ref., reference; SD, stable disease; SeLND, selective lymph node dissection; SyLND, systematic lymph node dissection.

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Table 2. Surgical data and oncological outcomes

Author	LND	Image (+) LNs		RT	p	No. of removed LNs, median (range)	p	Positive LNs	p	FU	Recurrence rate	p	Site of recurrence						PFS	p	OS	p
		Pre-NACT	Post-NACT										LNs		Peritoneal		Distant					
Fagotti et al. [32]	SeLND	NA	NA	0: 81 (80.2%) <1: 20 (19.8%)	0.79	4 (1–14)	0.0001	33.3%	0.708	Mean: 35 (95% CI, 32–38)	62.4%	0.37	17.8%	p=0.56	28.8%	0.70	7.9%	0.67	2-yr PFS: 25%	0.83	2-yr OS: 69%	0.77
	SyLND			0: 41 (82%) <1: 9 (18%)		38 (15–84)		28%		Mean: 36 (95% CI, 31–41)	70%		24%		30%		6%		2-yr PFS: 36%		2-yr OS: 88%	
Iwase et al. [33]	NoLND	NA	NA	0: 98 (79%) <1: 15 (12.1%)		46 (19–96)		39.5%		Median: 39.5 (5–142)	80.5%		29.6%	p=0.53	62.9%	NS	14.8%	NA	2-yr PFS: 26.1%	0.89	5-yr OS: 19.1%	0.62
	SyLND			≥1: 11 (8.9%)									19.8%		61.6%		10.5%		2-yr PFS: 56.1% (LN–) 24.5% (LN+)		5-yr OS: 62% (LN–) 26.2% (LN+)	
Schwartz et al. [34]	NoLND	NA	NA	0: 47 (100%)	NS	Pelvic: 11.5 (8–15.8)		40.7%		Median: 34	NA		NA		NA		NA		9.7	0.79	36.3	0.42
	SyLND			0: 54 (100%)		Paraaortic: 15.5 (8–23.8)													10.4		33.1	
Eoh et al. [35]	SeLND	NA	32 (47.1%)	0: 25 (36.8%) <1: 43 (63.2%)	0.76	10.5 (0–19)	<0.001	66.2%	0.16	NA	80.9%	0.73	45.5%	p=0.02	32.7%	p=0.04	22.1%	NS	12 (3–45)	0.74	28 (5–123)	0.001
	SyLND		41 (63.1%) p=0.06	0: 22 (33.8%) <1: 43 (66.2%)		27.7 (20–128)		53.8%			78.5%		23.5%		15.7%		18.5%		17 (1–88)		37 (13–150)	
Song and Gao [36]	NoLND	NA	0 (inclusion criteria)	0: 67 (100%)	NS	-	NA	-	0.43	69 (IQR, 31.5–84)	70.1%	NA	31.9%	p=0.02	NA		NA		22 (IQR, 16–34)	0.57	57 (IQR, 43–67)	0.049
	SeLND			0: 145 (100%)		8 (IQR, 6–11)		22.1%		65 (IQR, 38–102)	69.7%		15.8%						28 (IQR, 20.5–46)		50 (IQR, 41–78)	
	SyLND			0: 118 (100%)		31 (IQR, 29–36)		26.3%		53 (IQR, 32–87)	66.9%		12.7%						30.5 (IQR, 19–45)		59 (IQR, 44–76)	
Bund et al. [37]	NoLND	NA	NA	0: 50 (50%) ≤0.25: 23 (23%) >0.25: 27 (27%)	<0.0001	28 (15 paraaortic, 13 pelvic)		11% (13% paraaortic, 10% pelvic)		NA	NA		15%	0.67	44%	0.2	41%	0.76	16.6 (95% CI, 14.9–18.7)	0.70	27.6 (95% CI, 20.7–36)	0.48
	SyLND			0: 137 (88.4%) ≤0.25: 9 (5.8%) >0.25: 9 (5.8%)									22%		61%		34%		18.3 (95% CI, 16.3–20.1)		26.8 (95% CI, 21.6–36.4)	

(continued to the next page)

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Table 2. (Continued) Surgical data and oncological outcomes

Author	LND	Image (+) LNs		RT	p	No. of removed LNs, median (range)	p	Positive LNs	p	FU	Recurrence rate	p	Site of recurrence						PFS	p	OS	p
		Pre-NACT	Post-NACT										LNs		Peritoneal		Distant					
Lopes et al. [38]	NoLND	11 (57.9%)	0 (inclusion criteria)	0: 18 (85.7%) <0.25: 3 (14.3%)	0.33	23 (8 paraaortic, 12 pelvic)		30.8%		39.7 (14.4–127.5)	90.5%	0.41	4.8%	NA	NA		NA		8.3 (95% CI, 5.1–11.6)	0.878	61.2 (95% CI, 21.4–101)	0.93
	SyLND	13 (33.3%) p=0.08		0: 37 (94.9%) <0.25: 2 (5.1%)						49.3 (13.5–115.5)	89.7%		12.8%						8.1 (95% CI, 6.2–10.1)		56.7 (95% CI, 43.4–70.1)	
He et al. [39]	SeLND	82.2%	36.6%	0: 90 (51.1%) <1: 32 (18.2%) ≥1: 54 (30.7%)	NA	Pelvic: 20 (8–59) Paraaortic: 10 (8–24)		55.7%		38.6 (1.7–177.9)	44.9%	NA	4.5%	p=0.94	Overall: 44.9%			NA	3-yr PFS (RT=0): 48.6%	0.324	5-yr OS (RT=0): 55.2%	0.22
	SyLND			0: 73 (57.5%) <1: 37 (29.1%) ≥1: 17 (13.4%)							40.2%		4.7%		Overall: 40.2%				3-yr PFS (RT=0): 52.4%		5-yr OS (RT=0): 64.5%	
Benoit et al. [40]	NoLND	NA	NA	0: 48 (68.6%) ≤0.25: 5 (7.1%) >0.25: 15 (21.4%) NA: 2	<0.001	31.4±17		57.9%		26 (5–103)	62.8%	1	38.6%	0.68	45.7%	0.77	27.1%	0.23	2-yr PFS: 48.6%	0.87	5-yr OS: 58.6%	0.41
	SyLND			0: 116 (87.2%) ≤0.25: 15 (11.3%) >0.25: 1 (0.75%) NA: 1						32 (4–120)	65.4%		34.6%		48.9%		18.8%		2-yr PFS: 47.4% 42.5% (LN+) 60.7% (LN–)		5-yr OS: 63.2% 49.9% (LN+) 82.2% (LN–)	

IQR, interquartile range; LN, lymph node; LND, lymph node dissection; NA, not available; NoLND, no lymph node dissection; NA, not available; NS, not significant; OS, overall survival; PFS, progression-free survival; SeLND, selective lymph node dissection; SyLND, systematic lymph node dissection.

https://doi.org/10.3802/jgo.2022.33.e69

to 89.7% in the SyLND groups, 44.9% to 80.9% in the SeLND groups, and 62.8% to 90.5% in the NoLND. When the information was available, LN recurrence occurred in 4.7% to 23.5% in the SyLND groups, 4.5% to 45.5% in the SeLND groups, and 4.8% to 31.7% in the NoLND groups. Regarding the specific site of recurrence (LNs, peritoneal or distant), most studies reported no differences according to the type of LND performed. However, Eoh's series [35] reported LN recurrences in 45.5% of SyLND cases compared with 23.5% in the SeLND group (p=0.02) and peritoneal metastases in 32.7% vs 15.7% (p=0.04), respectively. Moreover, Song et al. [36] described a significantly higher rate of LN metastasis in the NoLND group (31.9%) compared with SeLND (15.8%) and SyLND (12.7%) (p=0.02).

3. Outcomes

Survival outcomes

Survival outcomes in terms of PFS and OS are detailed in **Table 2**.

1) PFS

Six studies [34-38,40] provided PFS data. Three studies were excluded from the analysis: 1) He et al. [39] reported only a subgroup analysis of PFS according to the RT status; 2) Iwase et al. [33] reported a subgroup analysis of PFS according to the presence of LN metastasis; 3) Fagotti et al. [32] did not report the HR for PFS.

No statistically significant differences in terms of PFS were shown between cohorts who underwent SyLND and SeLND/NoLND (HR=0.88; 95% CI=0.65–1.20; p=0.43) (**Fig. 2A**). The heterogeneity for this comparison was I^2=60% (95% CI=1.8%–83.7%).

The subgroup analysis of PFS data according to NGRD included two studies and revealed no statistically significant differences in terms of PFS between cohorts who underwent SyLND and SeLND/NoLND (HR=1.17; 95% CI=0.91–1.52; p=0.23) (**Fig. 2B**).

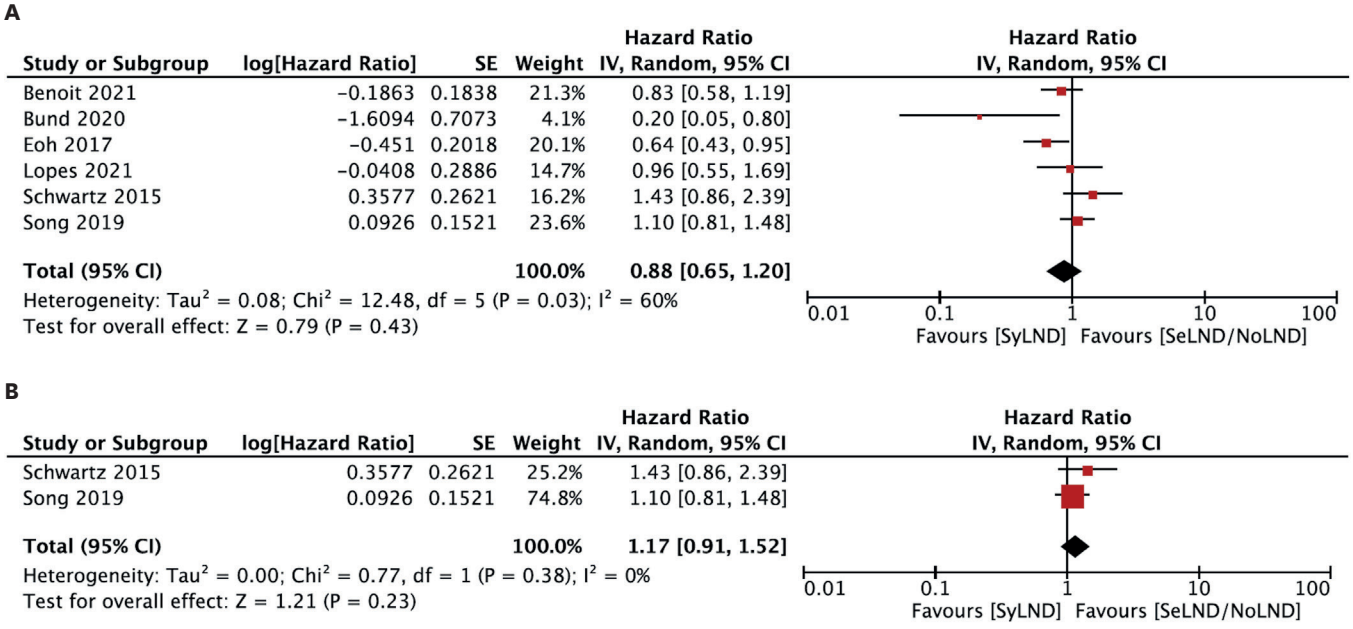

Fig. 2. Forest plots. (A) Forest plot of comparison: PFS and (B) Forest plot of comparison: subgroup analysis of PFS according to NGRD.
CI, confidence interval; HR, hazard ratio; IV, interval variable; NGRD, no gross residual disease; NoLND, no lymph node dissection; PFS, progression-free survival; SE, standard error; SeLND, selective lymph node dissection; SyLND, systematic lymph node dissection.

https://doi.org/10.3802/jgo.2022.33.e69

2) OS

Seven studies provided OS data [33–38,40]. Two studies were excluded from the analysis: 1) He et al. [39] reported only a subgroup analysis of OS according to the RT status; (2) Fagotti et al. [32] did not report the HR for OS.

No statistically significant differences in terms of OS were shown between patients who underwent SyLND and SeLND/NoLND (HR=0.80; 95% CI=0.50–1.30; p=0.37) (**Fig. 3A**). The heterogeneity for this comparison was I^2=83% (95% CI=66.3%–91.4%).

The subgroup analysis of OS data according to NGRD included two studies and revealed no statistically significant differences in terms of OS between cohorts who underwent SyLND and SeLND/NoLND (HR=1.33; 95% CI=0.92–1.91; p=0.13) (**Fig. 3B**).

Surgical outcomes

The perioperative surgical data of included studies are detailed in **Table 3**.

1) Severe postoperative complications

Seven studies [32,34,36-40] with a total of 1,336 patients (676 in the SyLND and 660 in the SeLND/NoLND group) reported the rate of severe postoperative complications. Overall, 104 (7.8%) patients experienced grade III–IV postoperative complications: a statistically significant increase in grade III–IV postoperative complications was shown in the SyLND group compared with SeLND/NoLND group. The pooled estimated OR was 1.83 (95% CI=1.19–2.82; p=0.006) (**Fig. 4**). The heterogeneity for this comparison was 0% (95% CI=0%–70.8%).

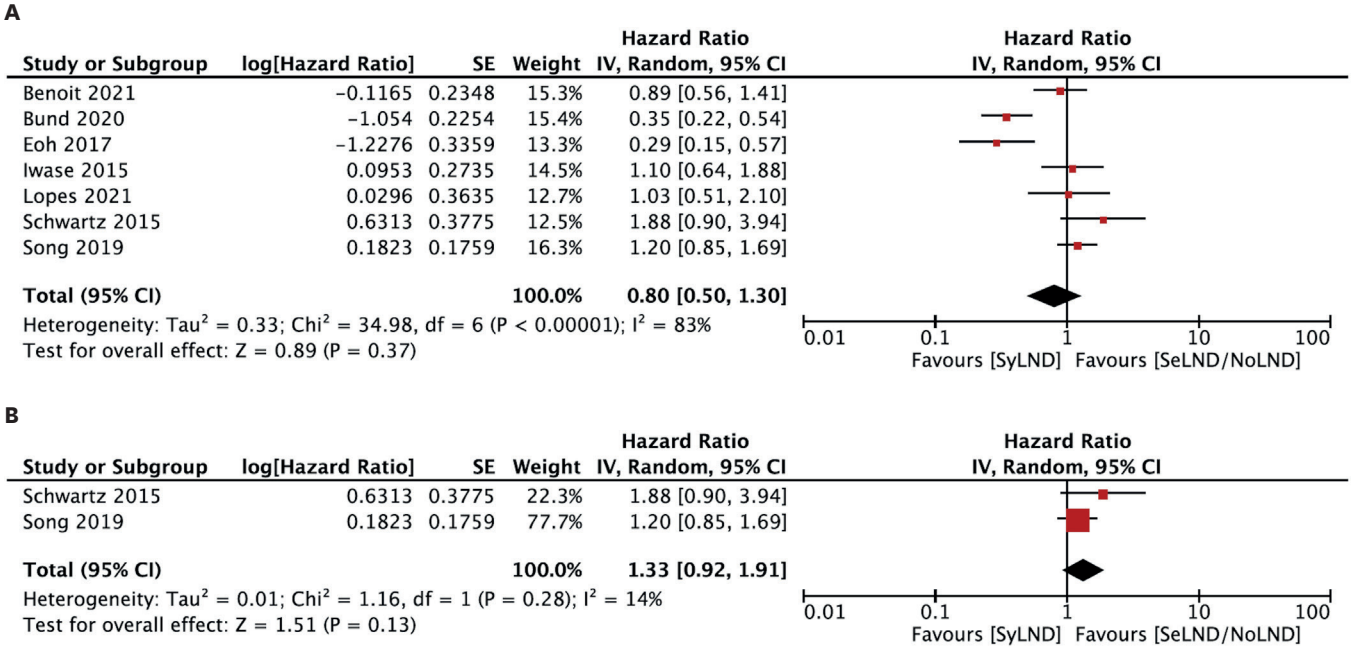

Fig. 3. Forest plots. (A) Forest plot of comparison: OS and (B) Forest plot of comparison: subgroup analysis of OS according to NGRD.
CI, confidence interval; HR, hazard ratio; IV, interval variable; NGRD, no gross residual disease; NoLND, no lymph node dissection; OS, overall survival; SE, standard error; SeLND, selective lymph node dissection; SyLND, systematic lymph node dissection.

https://doi.org/10.3802/jgo.2022.33.e69

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Table 3. Perioperative surgical complications

Author	LND	Operative time (min), median (range)	p	Blood loss (DHb g/dL), median (range)	p	Blood transfusions	p	Hospital stay (days), median (range)	p	Surgical complication				Lymphocele	p
										Grade I–II		Grade III–IV			
Fagotti et al. [32]	SeLND	210 (90–400)	0.023	1.40 (0.01–6.20)	0.0001	23 (22.8%)	0.0001	9 (4–20)	0.232	89 (88.2%)	p<0.001	12 (11.8%)	p=NS	0.9%	NS
	SyLND	225 (125–390)		3.25 (0.02–5.10)		27 (54%)		8 (4–23)		41 (82%)		9 (18%)		26%	
Iwase et al. [33]	NoLND	419 (185–611)		1,291 (220–5,640)		70.6%		NA		NA		NA		NA	
	SyLND														
Schwartz et al. [34]	NoLND	240 (177.5–295)	<0.001	NA		11 (33.3%) NA: 14	0.002	10 (8–15)	0.67	28 (63.6%)	p=0.43	2 (4.6%)	p=0.43	NA	
	SyLND	320 (270–370)				33 (70.2%) NA: 7		10.5 (9.0–14.2)		32 (62.7%)		6 (11.8)			
Eoh et al. [35]	SeLND	265 (108–900)	0.27	1.0 (−2.1–3.4)	0.19	41 (60.3%)	0.29	11 (7–51)	0.83	ICU admission: 22 (32.4%)			p=0.08	13 (19.1%)	0.31
	SyLND	283 (104–735)		1.0 (−3.0–4.4)		33 (50.8%)		10 (6–31)		ICU admission: 12 (18.5%)				18 (7.2%)	
Song and Gao [36]	NoLND	NA		NA		NA		7 (6–10)	0.045	65 (97%)	p=0.718	2 (3%)	p=0.718	-	<0.001
	SeLND							7 (6–8.5)		140 (96.6%)		5 (3.4%)		9 (6.2%)	
	SyLND							7 (6–10)		112 (94.9%)		6 (5.1%)		32 (27.1%)	
Bund et al. [37]	NoLND	242 (155–405)	<0.0001	NA		9 (60%) NA: 85	0.7	NA		10 (10.5%)	p=0.15	4 (4.2%)	p=0.15	NA	
	SyLND	383 (170–660)				16 (55.2%) NA: 126				29 (20%)		9 (6.2%)			
Lopes et al. [38]	NoLND	164	<0.001	NA		3 (14%)	0.85	3	0.02	NA		2 (9.5%)	p=0.80	NA	
	SyLND	299				6 (15%)		5		NA		3 (7.5%)			
He et al. [39]	SeLND	NA		NA		NA		NA		10 (5.7%)			p=0.03	0	NA
	SyLND									15 (11.8%)				3 (1.8%)	
Benoit et al. [40]	NoLND	NA		NA		NA		NA		9 (69.2%)	p=0.48	4 (30.8%)	p=0.48	NA	
	SyLND									25 (59.5%)		17 (40.5%)			

ICU, intensive care unit; NA, not available; LND, lymph node dissection; NS, not significant; NoLND, no lymph node dissection; SeLND, selective lymph node dissection; SyLND, systematic lymph node dissection.

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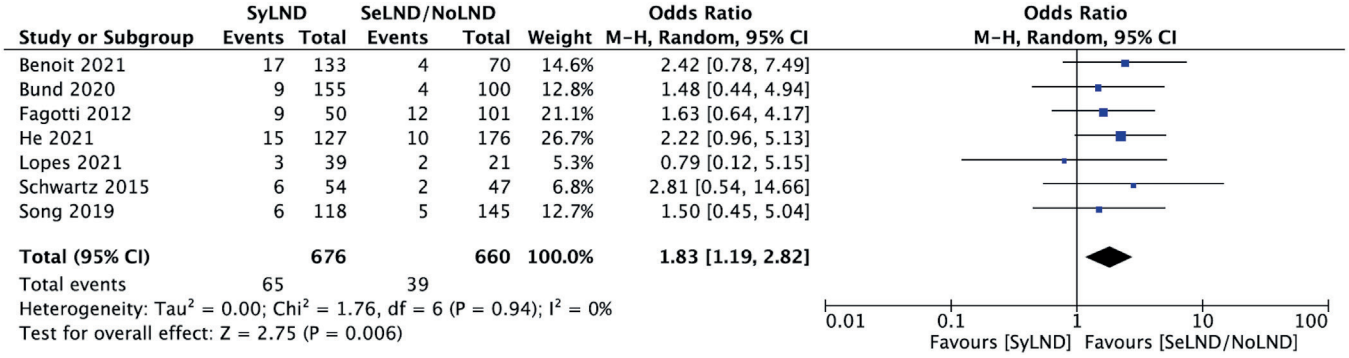

Fig. 4. Forest plot of comparison: grade III–IV postoperative complications.
CI, confidence interval; M-H, Mantel-Haenszel test; NoLND, no lymph node dissection; OR, odds ratio; SeLND, selective lymphadenectomy; SyLND, systematic lymphadenectomy.

2) Lymphocele

Four studies [32,35,36,39] with a total of 850 patients (360 in the SyLND and 490 in the SeLND/NoLND group) reported the rate of postoperative lymphocele. Overall, 97 (11.4%%) patients experienced lymphocele: a statistically significant increase was shown in the SyLND compared with SeLND/NoLND group. The pooled estimated OR was 3.38 (95% CI=1.71–6.70; p<0.001) (**Fig. 5**). The heterogeneity for this comparison was 43% (95% CI=0%–80.9%).

3) Lymphedema

Two studies [36,39] with a total of 566 patients (245 in the SyLND and 321 in the SeLND/NoLND group) reported the rate of postoperative lymphedema of the lower limbs. Overall, 49 (11.4%%) patients experienced lymphedema: 16.3% for the SyLND groups and 2.8% for the SeLND/NoLND group. The pooled estimated OR was 7.23 (95% CI=3.40–15.36; p<0.0001) (**Fig. 6**).

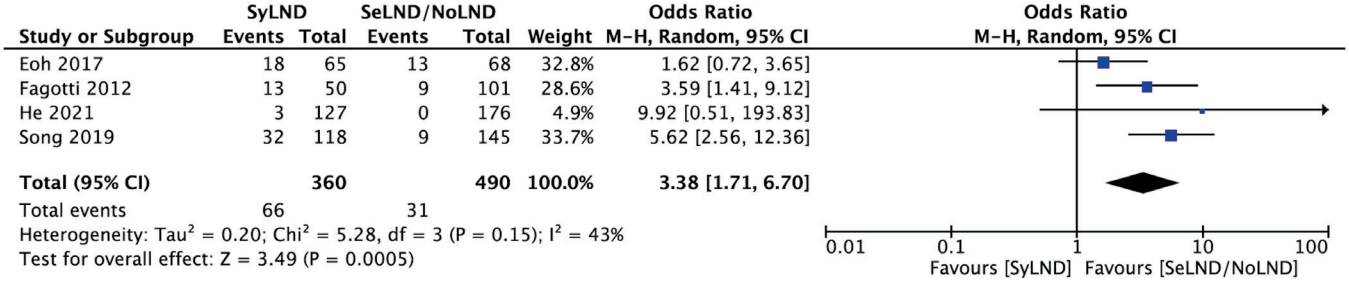

Fig. 5. Forest plot of comparison: lymphocele.
CI, confidence interval; M-H, Mantel-Haenszel test; NoLND, no lymph node dissection; OR, odds ratio; SeLND, selective lymph node dissection; SyLND, systematic lymph node dissection.

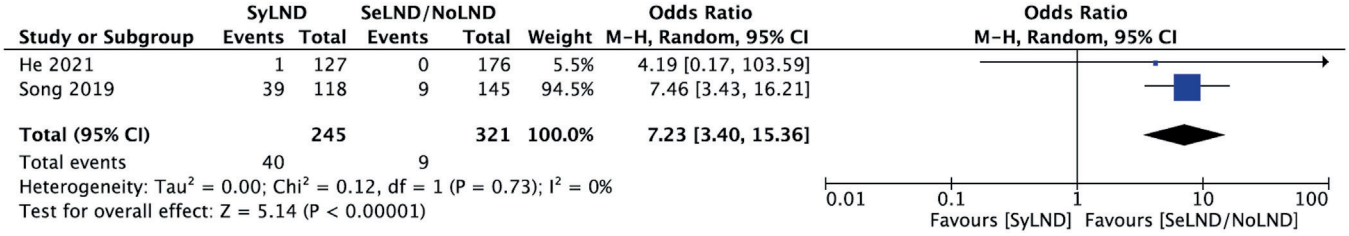

Fig. 6. Forest plot of comparison: lymphedema.
CI, confidence interval; M-H, Mantel-Haenszel test; NoLND, no lymph node dissection; OR, odds ratio; SeLND, selective lymph node dissection; SyLND, systematic lymph node dissection.

https://doi.org/10.3802/jgo.2022.33.e69

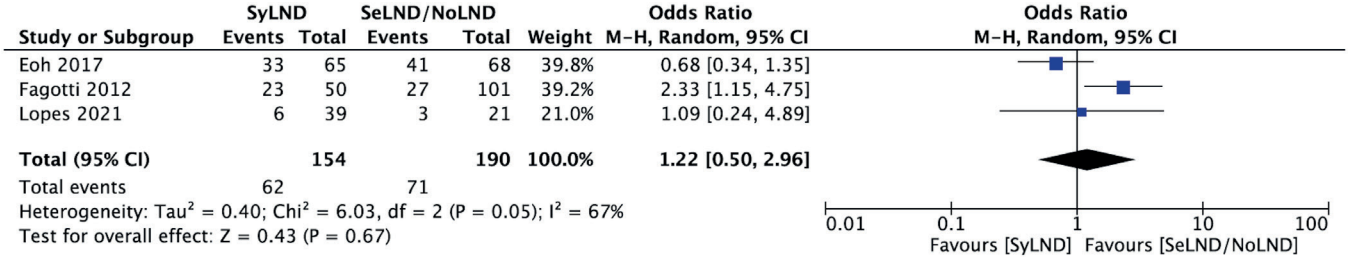

Fig. 7. Forest plot of comparison: blood transfusions.
CI, confidence interval; M-H, Mantel-Haenszel test; NoLND, no lymph node dissection; OR, odds ratio; SeLND, selective lymph node dissection; SyLND, systematic lymph node dissection.

4) Blood loss

Three studies [32,33,35] reported data about blood loss but none reported the mean value with standard deviation; therefore, meta-analysis was not feasible. Two studies reported the median blood loss comparing the SyLND and the SeLND/NoLND groups: one study [32] showed a statistically significant higher blood loss in SyLND patients compared with SeLND, while the other one not [35].

5) Blood transfusions

Six studies [32-35,37,38] reported data about blood transfusions. Data were incomplete in three of them [33,34,37]. The remaining three studies [32,35,38] showed no statistically significant difference in terms of blood transfusions between groups. The pooled estimated OR was 1.22 (95% CI=0.50–2.96; p=0.67) (**Fig. 7**). The heterogeneity for this comparison was 67% (95% CI=0%–90.5%).

6) Operative time

Six studies [32-35,37,38] reported data about operative time but none reported the mean value with standard deviation; therefore, meta-analysis was not feasible. Five studies reported the median operative time comparing the SyLND and the SeLND/NoLND groups: 4 studies [32,34,37,38] showed a statistically significant higher operative time in SyLND patients compared with SeLND, while one [35] reported no relevant difference.

7) Hospital stay

Five studies [32,33,35] reported data about the length of hospital stay but none reported the mean value with standard deviation; therefore, meta-analysis was not feasible. Two studies [36,38] showed a statistically significant higher length of hospital in SyLND patients compared with SeLND, while three [32,34,35] reported no relevant difference.

DISCUSSION

The present meta-analysis summarizes the highest-quality evidence available in the English-language gynecologic oncology literature on the prognostic and surgical impact of systematic lymphadenectomy in patients undergoing interval debulking surgery for advanced epithelial ovarian cancer.

Cumulative results failed to demonstrate any beneficial effect of SyLND on survival rates, neither on OS nor PFS, while reporting a higher risk of postoperative complications for patients undergoing SyLND. Currently, international guidelines recommend performing only

selective lymph node dissection in case of radiological or intraoperative suspicious nodal metastases [4,41]. This meta-analysis supports the current recommendations and does not provide any evidence of a prognostic advantage in performing SyLND as a routine procedure during IDS. In the absence of a clear survival benefit, preserving patients from the SyLND-related morbidity and potential delay in adjuvant chemotherapy is advisable [14,42,43]. Additionally, the lymphadenectomy after neoadjuvant chemotherapy could be even more invasive and technically difficult as a result of the potential fibrotic reaction.

The rationale for pursuing the assessment of SyLND during IDS could be to evaluate the potential therapeutic benefit of removing microscopic nodal disease. Indeed, clinically negative LNs at the time of IDS might be either effectively negative or positive nodes at diagnosis which then became negative after NACT. In this scenario, the therapeutic role of SyLND during IDS could be theoretically related to the removal of occult and/or chemoresistant microscopic nodal disease after NACT. However, despite speculation about a potential prognostic role for nodal micrometastases, so far, no data have demonstrated an effective improvement in survival rates when performing SyLND in the course of IDS. On the contrary, the persistence of bulky nodes after NACT could be a proxy for chemoresistant nodal disease suggesting a potential benefit for selective lymph node dissection.

To complicate matters even further, the role of preoperative imaging for the evaluation of lymph node status after NACT is still a matter of debate. The radiologic evaluation of lymph nodes, which is already difficult in chemotherapy-naive patients, is even more challenging after chemotherapy. Indeed, lymph nodes radiologically interpreted as suspicious may actually be the result of a fibrotic or inflammatory response, while apparently negative lymph nodes may hide neoplastic foci. In the present meta-analysis, the rate of radiologically suspicious nodal metastases ranged from 40% to 82% before NACT [38,39] and from 37% to 55% after NACT [35,39]. Even in case of radiologically negative lymph nodes after NACT, there was still a rate of occult nodal micrometastases, ranging from 19% to 31% [35,36,38,39]. Conversely, only 22%–66% of radiologically suspicious nodes were histologically-proven positive [32,35,36].

The present meta-analysis has some limitations. First, all included studies were retrospective and the sample size was small in some cases. Second, the inclusion criteria, indications and extension of SyLND were heterogeneous across the studies, as well as the timing of the radiological nodal evaluation. Third, in more than half of the studies data were collected for a period of more than 10 years [34,36,37,39,40]. Finally, an additional potential limitation is the heterogeneity level that often remains undetected in small meta-analyses and that leads to poor pooled estimates [44]. However, in most of our meta-analysis heterogeneity was successfully modeled using random-effects meta-analysis methods.

In conclusion, SyLND during IDS appears to be not beneficial for preventing relapse or prolonging overall survival in AEOC patients. Due to the limited number of high-quality studies, a global patient assessment is mandatory to properly tailor the surgical strategy, especially when treating frail patients who are at higher risk for postoperative morbidity. Further evidence is warranted to confirm these results.

https://doi.org/10.3802/jgo.2022.33.e69

SUPPLEMENTARY MATERIAL

Table S1

Quality assessment of the included studies (ROBINS-I tool)

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