Prognostic value of systematic lymphadenectomy in patients with ovarian cancer: A systematic review and meta-analysis

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Abstract

Background: Standard management of ovarian cancer is surgical debulking and adjuvant chemotherapy. The role of systematic lymphadenectomy, as a part of debulking, has been controversial. Objective: To assess prognostic value of systematic lymphadenectomy in women with ovarian cancer based on stage, control group and type of chemotherapy Search strategy: A literature search was conducted on SCOPUS, PUBMED, COCHRANE, MEDLINE, and WEB OF SCIENCE databases. Selection criteria: All comparative studies that assess outcomes of systematic lymphadenectomy in patients with ovarian cancer were eligible. Data Collection and Analysis: overall survival was analyzed by pooling log hazard ratio (HR) and standard error of multivariable Cox regression models. MOGGE Meta-analysis Matrix is a novel illustration tool that was used to demonstrate multiple subgroup analyses of included studies. Main results: Twenty-two studies were eligible. Systematic lymphadenectomy was associated with better overall survival, that was close to significance, compared to control group (HR 0.93, 95%CI 0.86-1.00). Among women treated with adjuvant chemotherapy, overall survival improved in women with stage IIB-IV who underwent systematic lymphadenectomy (HR 0.91, 95%CI 0.84-0.99) and was most significant among patients with III to IV (HR 0.85, 95%CI 0.73-0.99). Systematic lymphadenectomy did not improve survival in women who received neoadjuvant chemotherapy (HR 0.97, 95%CI 0.73-1.29). Systematic lymphadenectomy was associated with improved progress-free survival compared to control group (HR 0.88, 95%CI 0.79-0.99). Conclusion: Data from clinical trials do not support role of systematic lymphadenectomy in advanced ovarian cancer. However, further studies may be warranted to assess substage-specific survival outcomes in women with advanced stages.

Introduction:

Ovarian cancer is the seventh most common cancer in women worldwide (1). It accounts for 5% of cancer-related female deaths, primarily due to late diagnosis. Approximately, 51% of patients are diagnosed at stage III and 29% at stage IV, which yields 5-year cause-specific survival of 42% and 26%, respectively (2). In 2018, 295,414 patients were newly diagnosed with ovarian cancer and 184,799 died of the disease worldwide (3).

Standard treatment of ovarian cancer is primary debulking surgery, aiming to achieve complete resection of macroscopic disease, followed by platinum/taxane-based chemotherapy (4). A residual tumor less than 1 cm after completion of surgery is considered “optimal debulking” (5). Society of Gynecologic Oncology and American Society of Clinical Oncology clinical practice guideline recommend that all women with suspected stage IIIC or IV epithelial ovarian cancer receive neoadjuvant chemotherapy if optimal debulking is unlikely with primary surgery (6).

Whether systematic lymphadenectomy (sysLA) should be considered a routine part of debulking surgery has been controversial. Lymphatic spread is commonly encountered even in early stages of ovarian cancer. Lymph node (LN) metastasis is reported in 6.5% and 40.7% of women with stage I and stage II disease, respectively (7). However, several studies failed to disclose significant impact of sysLA on overall survival of ovarian cancer, including a recent clinical trial on 647 patients with stage IIB to IV disease (8-10). Surgical morbidity associated with sysLA should be weighed by clear evidence of survival benefit, if any, to consider sysLA as a part of surgical debulking (11). In this review, our objective is to appraise clinical outcomes of sysLA in women with ovarian cancer and to determine prognostic value of sysLA in relation to disease stage and treatment approach.

Materials and methods:

Literature search

A literature search for "lymphadenectomy for ovarian cancer" was conducted using SCOPUS, PUBMED, COCHRANE, MEDLINE, and WEB OF SCIENCE databases. The search was conducted from the date of database inception to January 29th, 2020. The following search terminology was used: ("lymphadenectomy" OR "lymph node excision" OR "lymph node dissection") AND ("ovarian cancer" OR "ovarian neoplasm" OR "ovarian epithelial carcinoma"), ("systematic lymphadenectomy") AND ("ovarian cancer" OR "ovarian neoplasm" OR "ovarian tumor" OR "ovarian carcinoma" OR "ovarian malignancy").

Eligibility criteria and study selection

All comparative studies that assess clinical outcomes and prognostic value of sysLN in patients with ovarian cancer were considered eligible. Studies were included regardless of disease stage, chemotherapy (adjuvant or neoadjuvant), or control group (no lymphadenectomy [noLND] or selective lymphadenectomy [selLND]). Exclusion criteria included non-comparative studies, review articles, conference papers, and case series. Neither language nor sample size were considered during study selection.

Retrieved studies were screened through 3 stages by two independent reviewers. The first stage involves screening of titles for irrelevance. Abstracts of remaining articles were screened for eligibility. Eventually, full texts of selected abstracts were reviewed for final inclusion. Overall survival (OS) and progress free survival (PFS) present our primary outcomes. Secondary outcomes include: (l) Intraoperative outcomes: operative time, and intraoperative complications. (II) postoperative outcomes: hospital stay, postoperative complications.

Data abstraction

Data abstraction was done using a standardized spreadsheet designed for the study. Data include study characteristics (authors, year of publication, study setting, type of the study, comparison arms, and sample size), patient characteristics (selection frame, patient demographics, disease stage, pathological grade, histologic type, serum CA125), surgical management, tumor size, intraoperative findings, number of removed lymph nodes, lymph nodes status, residual disease after surgery, adjuvant or neoadjuvant treatment and duration of follow up. The data were abstracted from article text, tables, and figures. Quality assessment of included studies was assessed using US National Heart, Lung and Blood Institute Quality Assessment Tool (9).

Data analysis

Primary outcomes (OS, PFS) were analyzed by pooling log hazard ratio (HR) and standard error using generic inverse variance. These values are calculated from HR and 95% confidence interval (CI) of multivariable Cox regression models using Cochrane approved formulas (12). Secondary dichotomous outcomes (intraoperative complications, postoperative complications) were expressed as pooled odds ratios and 95% CI. Effect size of continuous data are expressed as weighted mean difference (WMD) and 95% CI using means and standard deviation. Data presented as medians and ranges were converted to mean and standard deviation using Hozo's formula (13). Random effect model was opted due to anticipated heterogeneity.

MOGGE Meta-analysis Matrix (MMM) is a novel illustration tool that is used to present all possible subgroup analyses. Because of heterogenicity of study cohorts, a matrix was created using 3 axes: disease stage, type of chemotherapy (adjuvant and neoadjuvant), and control group (selLND, noLND). "Disease stage" axis is divided into columns based on grouped studies covering the same range of stages. These columns are further transected by "type of chemotherapy" and "control group". Thus, each cell of this matrix presents a subgroup analysis of a group of studies that correspond to the stage above, chemotherapy to the left and control group to the right. Each cell contains the pooled HR and 95% CI, number of studies and patients in each subgroup analysis. The right column presents the total for each row.

Results

A total of 651 studies were initially retrieved from database search. Fifteen results were duplicates. Through 3 phases of screening, 614 studies were excluded (466 irrelevant studies, 79 review articles, 61 conference abstracts, 6 ineligible study designs, and a single case study). Eventually, 22 comparative studies (6,825 patients) met our inclusion criteria and were eligible for pooled analysis. Flowchart of selection process is demonstrated in figure 1.

Study design and selection criteria of included studies are summarized in Table S1. Of all studies, 19 were retrospectively conducted (9, 14-31) and three were randomized clinical trials (RCTs) (10, 32, 33). All studies were published between 1995 and 2019 and included patient data collected between 1985 and 2019. Sixteen studies investigated women with advanced disease; 7 studies included patients with FIGO stage III and IV (9, 18, 20, 22, 24, 26, 27), 4 studies included FIGO stage IIIC to IV (14-16, 28), 2 study included stages IIIB to IV (19, 33), 2 included stage IIB to IV (10, 25), and 1 study included stage IIIC only (23). Early stages were addressed by 3 studies (stage I- IIIa (21), stage I and II (32), and stage I (34)). Three studies include all stage in their cohort (17, 29, 30). Women who received neoadjuvant chemotherapy followed by debulking surgery were exclusively selected in 7 studies (9, 14, 15, 19, 20, 28, 34). Assessment of risk of bias is summarized in Figure S1.

Short-term outcomes

Eight studies compared operative time between sysLA and either noLND or silLND; operative time of debulking surgery involving sysLA was significantly longer compared to control group (WMD 63.5, 95% CI 32.5 - 94.5) (Figure 2a). Hospital stay in days was not significantly different (WMD -0.21, 95% CI -1.09 - 0.68) (Figure 2b). Incidence of intraoperative complications was significantly higher among women who underwent sysLA compared to control group (OR 2.18, 95% CI 1.35 - 3.51) (figure 2c). However, incidence of postoperative complications was not significantly different (OR 0.81, 95% CI 0.45 - 1.46) (Figure 2d).

Long-term outcomes

Fifteen studies conducted multivariate cox regression analysis of OS and were eligible for our analysis (10, 14-25, 32, 33). Pooled analysis of all studies showed superiority of OS in women who had sysLA was close to significance, compared to control group (HR 0.93, 95% CI 0.86 - 1.00). Subgroup analysis of 3 RCTs did not show significant difference in OS between both groups (HR 1.01, 95% CI 0.94 - 1.08) (Figure 3). Due to heterogeneity of study population, a matrix subgroup analysis was conducted using 3 parameters: disease stage, timing of chemotherapy in relation to surgery, and control group (Figure 4). Stagewise, sysLA did not improve survival when performed in early stages (HR 1.04, 95% CI 0.84 - 1.29) (Figure 4: A0). Superiority of sysLA was close to significance in advanced stages (Figure 4: D-F0) and was statistically significant in stage IIB-IV (HR 0.91, 95% CI 0.84 - 0.99, 12 studies) (Figure 4: C0). SysLA did not improve survival in women who received neoadjuvant chemotherapy (HR 0.97, 95% CI 0.73 - 1.29, 4 studies) (Figure 4: T6) regardless of control group (Figure 4: T4-5). In contrast, sysLA significantly improved OS in women treated with adjuvant chemotherapy following surgery (HR 0.91, 95% CI 0.84 - 0.99, 11 studies) (Figure 4: T3). Among women who received adjuvant chemotherapy, sysLA was significantly associated with improved OS in stage IIB to IV (HR 0.90, 95% CI 0.82, 0.98, 8 studies) and III to IV (HR 0.85, 95% CI 0.73 - 0.99, 6 studies) (Figure 4: C3 and D3, respectively). OS benefit of sysLA was most significant in patients with stage III to IV when compared to noLND (HR 0.86, 95% CI 0.77 - 0.96, 3 studies) (Figure 4: D2). Analysis of

studies including either optimal debulking only or optimal and suboptimal debulking yielded similar results (HR 0.88, 95% CI 0.76 - 1.01, HR 0.91, 95% CI 0.84 - 1.00). PFS was reported in 8 studies. SysLA was associated with improved PFS compared to control group (HR 0.88, 95% CI 0.79 - 0.99). Subgroup analysis of RCTs (2 studies) was consistent with total analysis (HR 0.88, 95% CI 0.81 - 0.96) (Figure 5).

Discussion

The debate about the efficacy of systematic lymphadenectomy in ovarian cancer in the literature remains unsettled. In this meta-analysis, we observed marginal significance in OS among sysLA in all stage ovarian cancer. In addition, sysLA was associated with improved PFS in all stage ovarian cancer. However, sysLA was associated with significantly higher intraoperative, but not postoperative, complications rate.

Early stage (Stage I-IIA) ovarian cancer should be distinguished from advanced stage (Stage IIB-IV) as the prognosis of the two diseases is quite different. Early stage ovarian cancer has a 10-year survival of more than 80%, while advanced stage ovarian cancer has a 5-year survival rate less than 40% (35-38). In early stage ovarian cancer, sysLA allows complete staging by confirming no distant microscopic disease and provides prognostic information that can guide treatment. Also, accurate staging may prevent unnecessary adjuvant chemotherapy. While the role of sysLA in advanced stage is still controversial. It was hypothesized that radical lymphadenectomy may benefit those who may have extensive lymph node metastasis since the surgery goal is to achieve optimal debulking. Another hypothesis pushed the case for the therapeutic role of lymphadenectomy in advanced disease is the pharmacologic sanctuary hypothesis. This hypothesis assumed that nodal metastasis of ovarian cancer may be less sensitive to systemic chemotherapy due to diminished blood supply, hence sysLA may be therapeutic in advanced disease to remove the occult lymph node metastasis and improve the survival (39-41).

There are 6 meta-analyses in the literature that addressed this debate. Those conducted before the Lymphadenectomy in Ovarian Neoplasm (LION) RCT provided a survival benefit of sysLA in all stage disease. Kim et al concluded that sysLA is efficient in improving OS in all stage disease compared to unsystematic lymphadenectomy (USL). However, this study did not clearly define follow up period for survival analysis and there were no data regarding PFS or recurrence rate (42). Similarly, Gao et al concluded that sysLA was efficient in improving 5-year OS in all stage disease and advanced ovarian cancer compared to USL. This study is limited by inconsistency of definition of USL, lack of data on impact of residual tumor status, PFS or recurrence rate (43). Zhou et al reported that SysLA was efficient in improving 5-year OS in all stage, early and advanced disease compared to USL in addition to improving PFS in advanced disease. Similarly, definition of unsystematic lymphadenectomy was not consistent among the included studies, and impact of residual tumor status was not considered (44).

When the LION trial was published, the results tipped the balance in favor of abandoning sysLA in advanced ovarian cancer because of no survival benefit in addition to higher incidence of postoperative complications. The LION trial results weighted in heavily in the meta-analyses that were conducted this year. Lin et al concluded that SysLA did not improve OS or PFS in optimally cytoreduction all stage ovarian cancer patients. However, definition of unsystematic lymphadenectomy was not consistent and no subgroup analysis was conducted according to cancer stage (45). Xu et al reported that analysis of RCT demonstrated that sysLA cannot improve OS or PFS in advanced ovarian cancer which is quite the opposite of his analysis of observational studies (46). Wang et al revealed that sysLA may improve OS but not PFS in optimally debulked advanced ovarian cancer (47).

Our metanalysis included 22 studies with 6,825 patients with ovarian cancer. The meta-analysis pooled results show that sysLA did not improve OS in all stage disease. Since the studies included a range of study population questioning whether pooled data may present a mixed effect of sysLA, we performed a thorough subgroup analysis. While results were close to significance, subgroup analysis of OS by splitting studies into RCTs and retrospective demonstrated that RCTs showed no significance, but retrospective studies were close to significance. However, subgroup analysis by RCT demonstrated statistical significance of sysLA regarding PFS in both RCT and observational studies. The LION trial was a prospectively randomized, well

powered, multicenter international trial with large sample size. While the LION weight in the meta-analyses that included RCTs will affect the results heavily, the controversy between observational studies and the LION questions whether this discrepancy is a result of inherited pitfalls in observational studies. However, another explanation may be related to LION study design. First, the LION assessed the participating centers and deemed them to be proficient in performing sysLA and the patients who participated in the trial were of median age 60 years and had good performance score. However, morbidity and mortality figures in the lymphadenectomy group were relatively high. Also, the LION excluded 65% of the registered population before randomization for different reasons, one must question the possible survival benefit that lymphadenectomy could have provided if patients with poor prognosis indicators were included. Nevertheless, LION still presents the best available evidence and should be considered over other observational studies.

Our novel MOGGE Meta-analysis Matrix (MMM) revealed interesting findings. Subgroup analysis by stage revealed statistically significant superiority of sysLA in OS in advanced disease (stage IIB-IV) whether they received adjuvant or neoadjuvant chemotherapy (C0). The clear advantage of sysLA on OS in advanced ovarian cancer was consolidated by a further subgroup analysis in the adjuvant chemotherapy group (C3). So, while the LION trial was among the included studies in this subgroup analysis, the scales here were tipped in favor of sysLA in this particular population. Survival benefit of sysLA was more prominent in studies covering particularly stage III-IV compared to stage IIB-IV (D3). This may be attributed to the weight of LION trial, which is included in the first, but not the second subgroup analysis. Although this may be apparently reflective of superiority of LION trial study design, impact of disease stage was investigated. Approximately 78% of study population in LION trial were staged as IIIB to IV (10). Similarly, Du Bios el al. is another study included in the first but not the second analysis (included population was stage IIB to IV). Of their cohort, only 79.6% were staged as IIIB to IV. In comparison, all patients reported by Chang et al. were staged as IIIC (23), all patients reported by Eoh et. al. were stage IIIC-IV (16), and 94% of patients reported by Paik et. al. were stage IIIB-IV (18). In addition, LION trial did not present subgroup results based on disease stage. Therefore, study design may not be the only contributing factor, and OS benefit of sysLA may be associated with more advanced stages, including stage IIIB or IIIC, compared to earlier stages, including stage IIB. Unfortunately, specific studies on stage IIIB or IIIC are too few to draw a direct conclusion. Therefore, it seems that although LION study provides the most robust level of evidence, our current results may warrant further assessment/subgroup analysis that narrows the spectrum toward more advanced stages specifically stage IIIB, IIIC.

Unlike women who received adjuvant chemotherapy, there was clearly no survival benefit of sysLA among women who received neoadjuvant chemotherapy regardless of disease stage. Therefore, neoadjuvant chemotherapy seems to omit need for sysLA if ever needed. This outcome may reflect either that: (1) neoadjuvant chemotherapy provides therapeutic benefit that deems sysLA unnecessary, or (2) selected patients for neoadjuvant chemotherapy who responded to treatment may still yield a poor prognosis that limits survival benefit of sysLA. However, recent evidence reflects that prognosis among women with advanced ovarian cancer receiving neoadjuvant chemotherapy is non inferior to adjuvant chemotherapy after surgery (6, 48). Given surgical complications of sysLA, these findings raise a question whether neoadjuvant chemotherapy may be considered in women with stage III-IV to avert sysLA if the latter is anticipated to improve survival.

Our metanalysis is the first to date to evaluate intraoperative complications of sysLA in ovarian cancer. It is of crucial importance in determining the benefit risk of performing a complex procedure as lymphadenectomy. Our metanalysis overcame the common limitation that most of the previously published metanalyses faced which is non-consistent definition of unsystematic lymphadenectomy among the included studies by dividing the control groups into selective lymphadenectomy and no lymphadenectomy groups. This meta-analysis provides a novel and comprehensive subgroup analysis to reveal specific conclusions.

However, this meta-analysis is limited by heterogeneity of the included studies. Since most of the studies were retrospective, they might contain selection and confounding biases. No subgroup analysis was conducted with regard to histological type because of no individual patient data or aggregate level data available.

Histological subtype may present different biological tumor behaviors and hence different therapy lines.

In conclusion, sysLA was associated with improved PFS, but not improved OS, in all stages of ovarian cancer. Current evidence, based on a well-designed RCT, did not endorse a prognostic role of sysLA in women with advanced ovarian cancer. Nevertheless, future studies on a narrow spectrum of patients with stage IIIB and IIIC may be warranted particularly those who received adjuvant chemotherapy. On the contrary, women who received neoadjuvant chemotherapy did not seem to benefit from sysLA regardless of study design or disease stage.

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AMA: literature search, data abstraction, manuscript writing, manuscript reviewing

GME: literature search, data abstraction, manuscript writing, manuscript reviewing

AYA: literature search, manuscript writing, manuscript reviewing

AYA: Data abstraction, quality assessment of included studies, manuscript writing, manuscript reviewing

FA: literature search, selection of eligible studies, manuscript writing, manuscript reviewing

IAA: literature search, selection of eligible studies, manuscript writing, manuscript reviewing

EGS: Data abstraction, creation of figures, manuscript writing, manuscript reviewing

MAS: Data abstraction, creation of figures, manuscript writing, manuscript reviewing

AKA: Data abstraction, creation of figures, manuscript writing, manuscript reviewing

EYR: selection of eligible studies, creation of supplementary tables, manuscript writing, manuscript reviewing

HSA: data abstraction, selection of eligible studies, creation of supplementary tables, manuscript writing, manuscript reviewing

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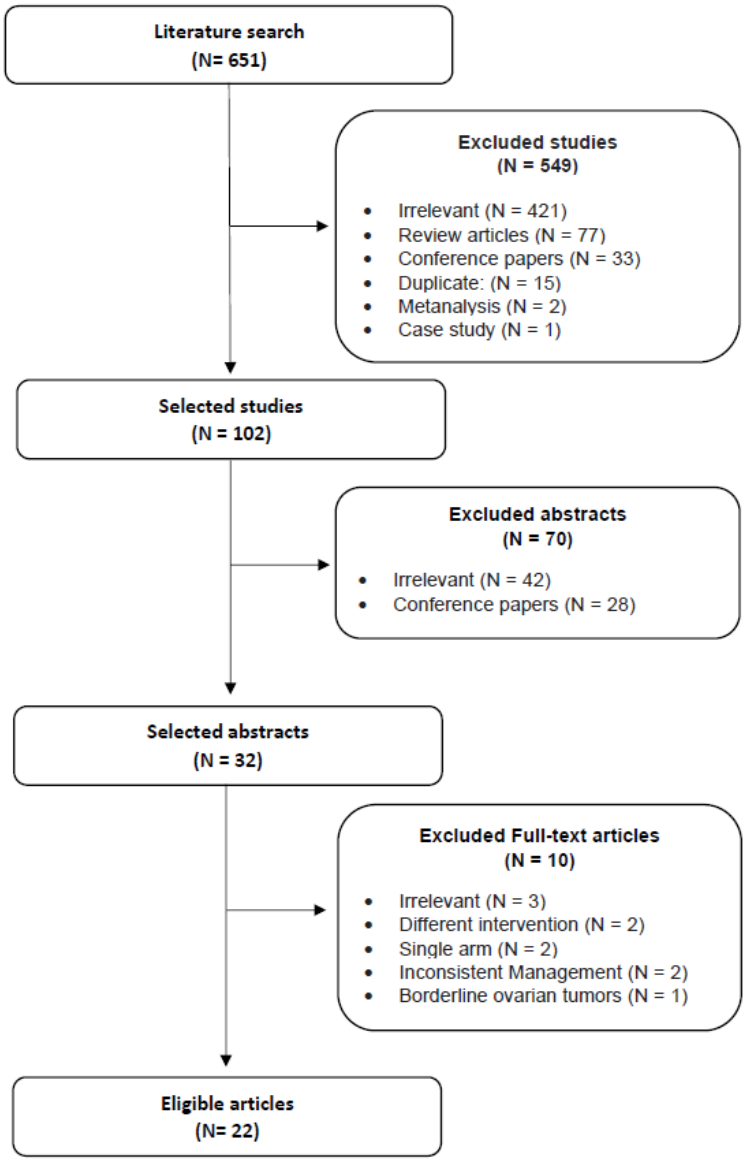
Figure Legand

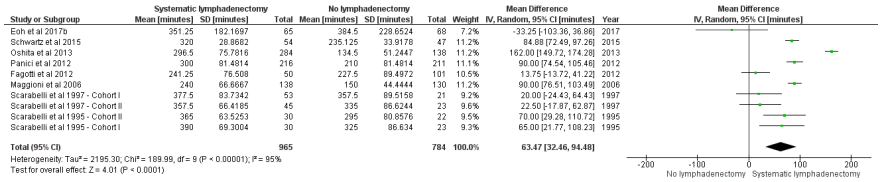
Figure 1. Stud selection flow chart

Figure 2. Short-term outcomes of women with ovarian cancer who underwent systematic lmphadenectomy (sysLA) versus control group

Figure 3. Forest plot of overall survival in women with ovarian cancer who underwent systematic lmphadenectomy (sysLA) versus control group

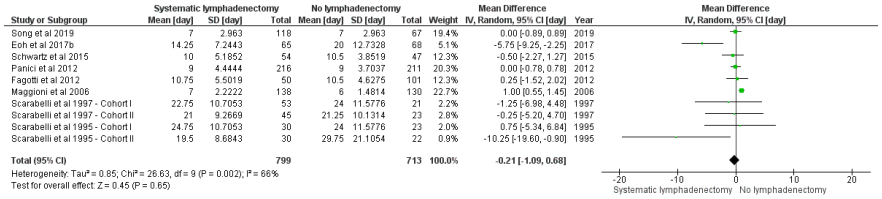
Figure 4. MOGGE Meta-analysis Matrix (MMM) of overall survival in women with ovarian cancer who underwent systematic lmphadenectomy (sysLA) versus control group





Study or Subgroup	Systematic lymphadenectomy Mean [minutes]	SD [minutes]	Total	No lymphadenectomy Mean [minutes]	SD [minutes]	Total	Weight	Mean Difference IV, Random, 95% CI [minutes]	Year
Eoh et al 2017b	351.25	182.1697	65	384.5	228.6524	68	7.2%	-33.25 [-103.36, 36.86]	2017
Schwartz et al 2015	320	28.8682	54	235.125	33.9178	47	11.2%	84.88 [72.49, 97.26]	2015
Oshita et al 2013	296.5	75.7816	284	134.5	51.2447	138	11.2%	162.00 [149.72, 174.28]	2013
Panici et al 2012	300	81.4814	216	210	81.4814	211	11.1%	90.00 [74.54, 105.46]	2012
Fagotti et al 2012	241.25	76.508	50	227.5	89.4972	101	10.5%	13.75 [-13.72, 41.22]	2012
Maggioni et al 2006	240	66.6667	138	150	44.4444	130	11.2%	90.00 [76.51, 103.49]	2006
Scarabelli et al 1997 - Cohort I	377.5	93.7342	53	357.5	89.5158	21	9.2%	20.00 [-24.43, 64.43]	1997
Scarabelli et al 1997 - Cohort II	357.5	66.4185	45	335	86.6244	23	9.6%	22.50 [-17.87, 62.87]	1997
Scarabelli et al 1995 - Cohort II	365	63.5253	30	295	80.8576	22	9.5%	70.00 [29.28, 110.72]	1995
Scarabelli et al 1995 - Cohort I	390	69.3004	30	325	86.634	23	9.3%	65.00 [21.77, 108.23]	1995
Total (95% CI)			**965**			**784**	**100.0%**	**63.47 [32.46, 94.48]**	

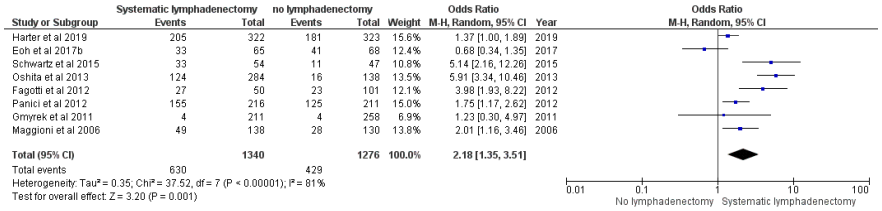
Heterogeneity: Tau² = 2195.30; Chi² = 189.99, df = 9 (P < 0.00001); I² = 95%
Test for overall effect: Z = 4.01 (P < 0.0001)



Study or Subgroup	Systematic lymphadenectomy Mean [day]	SD [day]	Total	No lymphadenectomy Mean [day]	SD [day]	Total	Weight	Mean Difference IV, Random, 95% CI [day]	Year
Song et al 2019	7	2.963	118	7	2.963	67	19.4%	0.00 [-0.89, 0.89]	2019
Eoh et al 2017b	14.25	7.2443	65	20	12.7328	68	5.1%	-5.75 [-9.25, -2.25]	2017
Schwartz et al 2015	10	5.1852	54	10.5	3.8519	47	12.3%	-0.50 [-2.27, 1.27]	2015
Panici et al 2012	9	4.4444	216	9	3.7037	211	20.3%	0.00 [-0.78, 0.78]	2012
Fagotti et al 2012	10.75	5.5019	50	10.5	4.6275	101	12.3%	0.25 [-1.52, 2.02]	2012
Maggioni et al 2006	7	2.2222	138	6	1.4814	130	22.7%	1.00 [0.55, 1.45]	2006
Scarabelli et al 1997 - Cohort I	22.75	10.7053	53	24	11.5776	21	2.2%	-1.25 [-6.98, 4.48]	1997
Scarabelli et al 1997 - Cohort II	21	9.2669	45	21.25	10.1314	23	2.8%	-0.25 [-5.20, 4.70]	1997
Scarabelli et al 1995 - Cohort I	24.75	10.7053	30	24	11.5776	23	2.0%	0.75 [-5.34, 6.84]	1995
Scarabelli et al 1995 - Cohort II	19.5	8.6843	30	29.75	21.1054	22	0.9%	-10.25 [-19.60, -0.90]	1995
Total (95% CI)			**799**			**713**	**100.0%**	**-0.21 [-1.09, 0.68]**	

Heterogeneity: Tau² = 0.85; Chi² = 26.63, df = 9 (P = 0.002); I² = 66%
Test for overall effect: Z = 0.45 (P = 0.65)

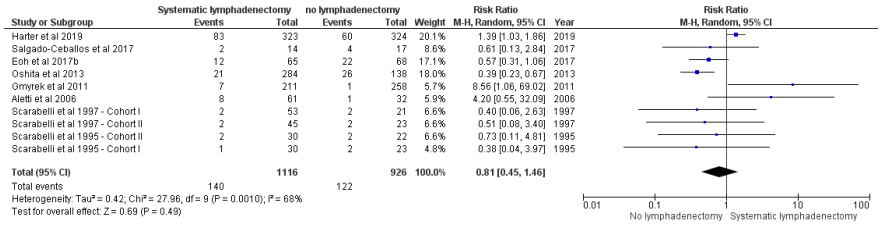
Mean Difference
IV, Random, 95% CI [day]
-20 -10 0 10 20
Systematic lymphadenectomy No lymphadenectomy



Study or Subgroup	Systematic lymphadenectomy Events	Total	no lymphadenectomy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Harter et al 2019	205	322	181	323	15.6%	1.37 [1.00, 1.89]	2019
Eoh et al 2017b	33	65	41	68	12.4%	0.68 [0.34, 1.35]	2017
Schwartz et al 2015	33	54	11	47	10.8%	5.14 [2.16, 12.26]	2015
Oshita et al 2013	124	284	16	138	13.5%	5.91 [3.34, 10.46]	2013
Fagotti et al 2012	27	50	23	101	12.1%	3.98 [1.93, 8.22]	2012
Panici et al 2012	155	216	125	211	15.0%	1.75 [1.17, 2.62]	2012
Gmyrek et al 2011	4	211	4	258	6.9%	1.23 [0.30, 4.97]	2011
Maggioni et al 2006	49	138	28	130	13.8%	2.01 [1.16, 3.46]	2006
Total (95% CI)		**1340**		**1276**	**100.0%**	**2.18 [1.35, 3.51]**	
Total events	630		429				

Heterogeneity: Tau² = 0.35; Chi² = 37.52, df = 7 (P < 0.00001); I² = 81%
Test for overall effect: Z = 3.20 (P = 0.001)

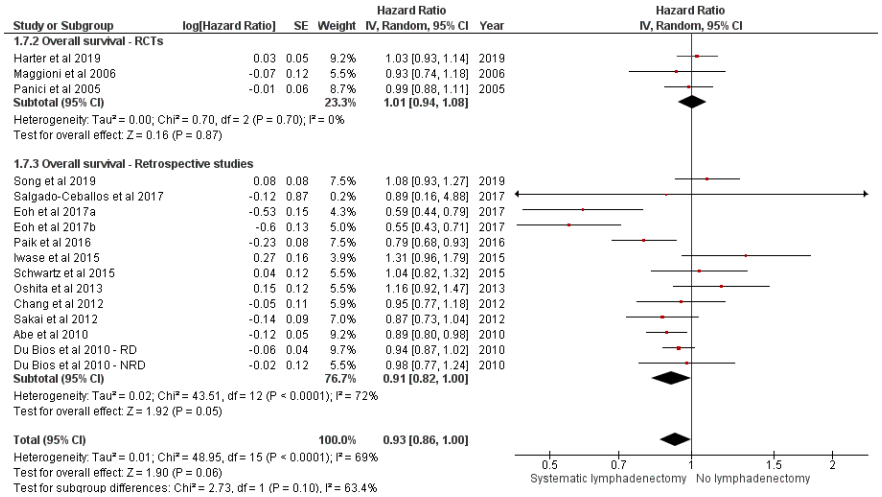
Odds Ratio
M-H, Random, 95% CI
0.01 0.1 1 10 100
No lymphadenectomy Systematic lymphadenectomy



Study or Subgroup	Systematic lymphadenectomy Events	Total	no lymphadenectomy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Harter et al 2019	83	323	60	324	20.1%	1.39 [1.03, 1.86]	2019
Salgado-Ceballos et al 2017	2	14	4	17	8.6%	0.61 [0.13, 2.84]	2017
Eoh et al 2017b	12	65	22	68	17.1%	0.57 [0.31, 1.06]	2017
Oshita et al 2013	21	284	26	138	18.0%	0.39 [0.23, 0.67]	2013
Gmyrek et al 2011	7	211	1	258	5.7%	8.56 [1.06, 69.02]	2011
Aletti et al 2006	8	61	1	32	5.9%	4.20 [0.55, 32.09]	2006
Scarabelli et al 1997 - Cohort I	2	53	2	21	6.6%	0.40 [0.06, 2.63]	1997
Scarabelli et al 1997 - Cohort II	2	45	2	23	6.6%	0.51 [0.08, 3.40]	1997
Scarabelli et al 1995 - Cohort II	2	30	2	22	6.6%	0.73 [0.11, 4.81]	1995
Scarabelli et al 1995 - Cohort I	1	30	2	23	4.8%	0.38 [0.04, 3.97]	1995
Total (95% CI)		**1116**		**926**	**100.0%**	**0.81 [0.45, 1.46]**	
Total events	140		122				

Heterogeneity: Tau² = 0.42; Chi² = 27.96, df = 9 (P = 0.0010); I² = 68%
Test for overall effect: Z = 0.69 (P = 0.49)

Risk Ratio
M-H, Random, 95% CI
0.01 0.1 1 10 100
No lymphadenectomy Systematic lymphadenectomy



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
1.7.2 Overall survival - RCTs					
Harter et al 2019	0.03	0.05	9.2%	1.03 [0.93, 1.14]	2019
Maggioni et al 2006	-0.07	0.12	5.5%	0.93 [0.74, 1.18]	2006
Panici et al 2005	-0.01	0.06	8.7%	0.99 [0.88, 1.11]	2005
Subtotal (95% CI)			**23.3%**	**1.01 [0.94, 1.08]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 2 (P = 0.70); I² = 0%					
Test for overall effect: Z = 0.16 (P = 0.87)					
1.7.3 Overall survival - Retrospective studies					
Song et al 2019	0.08	0.08	7.5%	1.08 [0.93, 1.27]	2019
Salgado-Ceballos et al 2017	-0.12	0.87	0.2%	0.89 [0.16, 4.88]	2017
Eoh et al 2017a	-0.53	0.15	4.3%	0.59 [0.44, 0.79]	2017
Eoh et al 2017b	-0.6	0.13	5.0%	0.55 [0.43, 0.71]	2017
Paik et al 2016	-0.23	0.08	7.5%	0.79 [0.68, 0.93]	2016
Iwase et al 2015	0.27	0.16	3.9%	1.31 [0.96, 1.79]	2015
Schwartz et al 2015	0.04	0.12	5.5%	1.04 [0.82, 1.32]	2015
Oshita et al 2013	0.15	0.12	5.5%	1.16 [0.92, 1.47]	2013
Chang et al 2012	-0.05	0.11	5.9%	0.95 [0.77, 1.18]	2012
Sakai et al 2012	-0.14	0.09	7.0%	0.87 [0.73, 1.04]	2012
Abe et al 2010	-0.12	0.05	9.2%	0.89 [0.80, 0.98]	2010
Du Bois et al 2010 - RD	-0.06	0.04	9.7%	0.94 [0.87, 1.02]	2010
Du Bois et al 2010 - NRD	-0.02	0.12	5.5%	0.98 [0.77, 1.24]	2010
Subtotal (95% CI)			**76.7%**	**0.91 [0.82, 1.00]**	
Heterogeneity: Tau² = 0.02; Chi² = 43.51, df = 12 (P < 0.0001); I² = 72%					
Test for overall effect: Z = 1.92 (P = 0.05)					
Total (95% CI)			**100.0%**	**0.93 [0.86, 1.00]**	
Heterogeneity: Tau² = 0.01; Chi² = 48.95, df = 15 (P < 0.0001); I² = 69%					
Test for overall effect: Z = 1.90 (P = 0.06)					
Test for subgroup differences: Chi² = 2.73, df = 1 (P = 0.10), I² = 63.4%					

Hazard Ratio
IV, Random, 95% CI
0.5 0.7 1 1.5 2
Systematic lymphadenectomy No lymphadenectomy