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Research Paper

Does the lymph node yield affect survival in patients with esophageal cancer receiving neoadjuvant therapy plus esophagectomy? A systematic review and updated meta-analysis

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ABSTRACT

Background: Conflicting data have been reported on the prognostic impact of the extent of lymphadenectomy during esophagectomy for esophageal cancer (EC) after neoadjuvant therapy, especially after neoadjuvant chemoradiotherapy (nCRT).
Methods: A comprehensive online search was performed to explore the association between increased lymph node yield (LNY) and survival of patients with EC, in which the overall survival (OS) was set as the primary outcome. In addition to analysis of the entire cohort, subgroup analyses of different induction therapy and different populations were also performed.
Findings: A total of 19528 patients from twelve studies were included in our study. The pooled data revealed that more lymph node harvested was associated with better OS (HR = 0·87; 95% CI: 0·79−0·95, $p < 0·001$). Notably, a higher LNY was associated with better OS if the threshold was less than 18. However, more thorough lymphadenectomy might not bring additional survival benefits when it came to a cutoff value more than 18. The subgroup analysis further revealed that a higher LNY after nCRT was associated favorable survival. In terms of subset analysis of different populations, increased LNY was associated with longer OS in Western populations but not in Eastern.
Interpretation: Increased LNY during esophagectomy after neoadjuvant therapy, especially after nCRT, might be associated with improved OS. More studies are warranted to assess the survival benefits of a higher LNY receiving neoadjuvant therapy plus esophagectomy, especially in Eastern populations.
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1. Introduction

Esophageal cancer (EC) is the sixth most common cause of cancer-related death around the world with an estimated 508,585 deaths each year [1]. Surgery remains the fundamental modality for patients with operable EC. Nowadays, neoadjuvant therapy, especially neoadjuvant chemoradiotherapy (nCRT), followed by surgery has been confirmed as a preferential treatment strategy for patients with locally advanced EC, which is associated with favorable long-term survival [2−6].

The extent of lymphadenectomy is one of the most important issues during esophagectomy [7−10]. Adequate lymphadenectomy provides correct pathologic staging and potentially affects the prognosis [11]. It is recommended that in patients undergoing esophagectomy without nCRT, at least 15 lymph nodes should be removed [8]. However, it remains controversial whether high lymph node yields (LNY) are associated with better survival in

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Research in Context

Evidence Before This Study

Conflicting data have been reported on the prognostic impact of the extent of lymphadenectomy during esophagectomy for esophageal cancer (EC) after neoadjuvant therapy.

Added Value of This Study

A systematic review and updated meta-analysis was performed, which is the largest and latest pooled analysis so far evaluating the impact of lymph node yield (LNY) on long-term survival in patients undergoing neoadjuvant therapy followed by esophagectomy for EC. Subgroup analyses of different induction therapy and different populations were also performed.

Implications of all the Available Evidence

The pooled data revealed that a higher LNY was associated with better OS in patients with EC receiving neoadjuvant therapy plus esophagectomy. Increased LNY was associated with longer OS in Western populations but not in Eastern, which merits further exploration to corroborate the implication of a higher LNY in Eastern populations receiving neoadjuvant therapy plus esophagectomy.

patients undergoing esophagectomy after neoadjuvant therapy [11–14].

In 2010, Vallböhmer et al. [15] reported that the number of resected lymph nodes was not a predictor of survival for ypT0N0M0R0 EC. Studies also indicated that the number of harvested lymph nodes during esophagectomy after nCRT could not affect survival irrespective of pathologic response [14] or histologic type of the primary lesion [16]. Meanwhile, the number of positive nodes, not the number of resected nodes, was reported to be a risk factor for patients with EC undergoing neoadjuvant chemotherapy [10]. In contrast, some studies reported that the number of resected nodes was an independent prognosticator in EC patients receiving preoperative radiotherapy plus cancer-directed surgery or esophagectomy after nCRT [17,11,18,19]. Since the heterogeneous preoperative treatment could result in different associations between LNY and OS, there is an urgent need to address the debate.

The present study investigated the impact of LNY on survival in EC patients with neoadjuvant therapy followed by surgery by performing a pooled analysis.

2. Methods

2.1. Search strategy

This meta-analysis was conducted in line with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [20]. We waived the registration of the protocol at the PROSPERO database before initial of the literature search. Studies were identified by searching four public databases including PubMed, EMBASE, Web of science and Cochrane Library without language restrictions. Search date was from the inception to October 2019. The main search terms included "Esophageal Neoplasms", "Carcinoma, Esophagus", "Neoadjuvant", "Lymphadenectomy", "Lymph Node retrieval", "Lymph Node Yield" and "Esophagectomy". The full search strategies are presented in Supplementary Table 1. We also manually searched the reference lists of the previously published review article or meta-analysis concerning "lymphadenectomy" and "esophageal cancer" until no additional articles could be identified.

2.2. Study selection and inclusion criteria

The population for inclusion was patients with primary EC. The intervention was neoadjuvant therapy followed by esophagectomy (transthoracic or transhiatal esophagectomy with limited or 2-field or 3-field lymphadenectomy); the survival of patients were reported as outcomes. Comparison of the survival between patients with a higher LNY and those with a lower LNY must be performed, while the hazard ratio (HR) with the corresponding 95% confidence interval (CI) for survival was planned for meta-analysis. Studies reporting combined results of both surgery after neoadjuvant therapy and upfront surgery were eligible provided the majority of the study population had neoadjuvant therapy followed by surgery. Two independent reviewers (C.D. and M.Y.) were in charge of identifying the eligible studies. First, the titles and abstracts were screened to assess the eligibility and then the full text was reviewed. Any disagreement could be resolved by discussion or by a third reviewer (X.Y.) until a consensus was reached. Studies that met the following criteria were included: (1) Studies about lymph node dissection in esophagectomy after induction therapy; (2) Studies providing the hazard ratio (HR) with a 95% confidence interval (CI) for overall survival (OS), or indirect information such as Kaplan-Meier curves used to estimate patient survival; (3) If two or more studies used the same population, only the study with the largest sample size or the latest information was included; (4) The full text was available. Exclusion criteria were as follows: (1) Non-human research. (2) Case report, reviews, comments, editorials and letters.

2.3. Data extraction and quality assessment

Two reviewers (C.D. and M.Y.) independently extracted the useful data from the identified studies. The HRs estimates (with the corresponding 95% CIs) for OS were extracted from the studies which were uniformly adjusted as high/low LNY. Any discrepancies between reviewers were resolved by consensus. The following information was recorded for each study: first author's name, year of publication, research country, inclusion period, study design, number of patients, patient age, histology type, tumor stage, types of neoadjuvant treatment, number of harvested lymph nodes, follow-up period and study endpoints. Two reviewers (M.Y. and W.W) independently investigated the risk of bias of the included studies using a set of modified predefined criteria [21]: (1) Representativeness of population; (2) Non-exposed cohort; (3) Ascertainment of exposure; (4) Outcome not present at start of study; (5) Appropriate confounding measurement and account; (6) Sufficient measurement of outcomes; (7) Completeness of follow-up. The quality of the included studies was assess according to a set of predefined criteria as described previously [22,23]. Scores of 7 or higher were defined as high-quality scores whereas scores of less than 7 were considered low-quality scores.

2.4. Definitions of study endpoints

The primary outcome of interest was the prognostic value of a higher LNY based on time-to-event variables including OS. OS was defined as the period from initial treatment until death due to any cause or last follow-up. The secondary outcome was disease-free survival (DFS), which was defined as the time from the initial surgery to the time of the first documentation of recurrence.

2.5. Statistical analyses

Statistical Package for Social Sciences (SPSS) software (version 21·0 for Windows) was employed for the general data analysis and STATA 12·0 software (StatCorp, College Station, TX, USA) to conduct the meta-analysis. Subgroup Analyses of the associations between LNY and OS were performed which were stratified by the different demographic or clinical characteristics. Meanwhile, pooled analyses were performed to assess the relationships between LNY and OS after neoadjuvant therapy in Eastern and Western populations, respectively. Cochran's Q test and Higgins I-squared statistic were used to test the heterogeneity of different studies. A p value of less than 0·1 was considered significant. $I^2 > 50\%$ was deemed as of substantial heterogeneity [24]. A random-effect model was used in our study because of the significant heterogeneity of the included studies. The reasons for inter-study heterogeneity were explored using subgroup analysis. Meanwhile, a meta-regression was performed to determine sources of heterogeneity in HRs estimates between studies. We also conducted sensitivity analysis by omission of each single study to evaluate stability of the results. Publication bias was assessed by visual inspection of funnel plots, Begg's and Egger's tests. All statistical tests were two-sided, and statistical significance was defined as p less than 0·05.

2.6. Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Selection of eligible studies

The flow-chart of the literature searching strategy is shown in Fig. 1. Initially, 1268 studies were identified after searching the relevant online databases. Twelve studies were eventually eligible for our study after careful screening and assessment.

3.2. Study characteristics

A total of 19,528 patients were included in our analysis with a median number of 305 cases. The baseline information and main characteristics are listed in Table 1 and Supplementary Table 2, respectively. In summary, 11 retrospective studies and 1 prospective nonrandomized studies met our inclusion criteria in which the relationship between LNY after neoajuvant therapy and survival were assessed. Among them, 4 were large-scale population-based studies. In terms of neoadjuvant therapy, five studies investigated the association between LNY after nCRT and OS with a median of 358 patients included. Three studies with a median number of 305 cases assessed the association between LNY after neoadjuvant chemotherapy and patient survival, one of which merely reported DFS as the endpoint. Notably, the median cutoff value of LNY was 18 which varied considerably from 11 to 60 among the 12 eligible studies. The cutoff value of LNY was pre-specified in five of the 12 studies and was set as the median of the number of resected nodes in the rest. The follow-up duration was reported in half of the included studies, among which the median was 34 months. The quality score of the 12 eligible studies are listed in Supplementary Table 3. According to the quality assessment scale, eight studies had a quality score of 7 and the rest had a score of 8.

3.3. Prognostic impact of LNY after neoadjuvant therapy

Eleven studies [9–12,14,15,17–19,25,26] with 19,477 individuals were involved in the analysis of LNY and OS. As shown in Fig. 2, a greater number of lymph nodes harvested was associated with better OS (HR = 0·87; 95% CI: 0·79–0·95, $p < 0·001$) with significant heterogeneity (I^2 = 90·1%, $p < 0·001$). As shown in Table 2, the subgroup analysis stratified by types of neoadjuvant therapy revealed that a higher LNY (lymph nodes harvested > 18) after nCRT was associated favorable survival (n = 5, HR = 0·81; 95% CI: 0·70–0·93, $p < 0·001$; I^2 = 88·7%, $p < 0·001$). However, the subgroup analysis indicated that increased LNY after neoadjuvant chemotherapy might not be associated with improved OS (n = 2, HR = 1·16; 95% CI: 0·93–1·38, p = 0·39; I^2 = 69·7%, p = 0·68). Interestingly, the subgroup analysis stratified by the cutoff value of lymph nodes revealed that a higher LNY was associated with better OS if the threshold was less than 18 (n = 6, HR = 0·81; 95% CI: 0·67–0·95, $p < 0·001$; I^2 = 91·6%, $p < 0·001$). However, more thorough lymphadenectomy might not bring additional survival benefits when it came to a cutoff value more than 18 (n = 5, HR = 0·97; 95% CI: 0·79–1·16, p = 0·21; I^2 = 81·7%, $p < 0·001$).

The relationship between LNY and DFS were investigated in two studies [14,27] with 409 patients included. Our analysis indicated that a higher LNY might not prolong DFS (n = 2, HR = 0·91; 95% CI: 0·58–1·23, p = 0·50; I^2 = 46·3%, p = 0·17).

Finally, we assessed the impact of LNY after neoadjuvant therapy on OS in Western populations and Eastern populations (Fig. 3). The results showed that a higher number of lymph nodes harvested might be associated with better OS in Western populations (n = 8, HR = 0·87; 95% CI: 0·78–0·96, $p < 0·001$) but not in Eastern (n = 3, HR = 0·95; 95% CI: 0·60–1·30, p = 0·315). There was evidence of statistical heterogeneity for the results (Western: I^2 = 91·5%, $p < 0·001$; Eastern: I^2 = 80·3%, p = 0·006).

To determine the sources of heterogeneity, we also performed a meta-regression on several important factors, in which the number of pathologic stages in each study was calculated and included in the analysis (Supplementary Table 4). Interestingly, none of the moderator variables were found to significantly affect the pooled HR of a higher LNY.

3.4. Publication bias

The potential presence of publication bias, namely the association between publication probability and the statistical significance of study result, was explored by visualizing asymmetry in funnel plots for each pooled analysis. As shown in Fig. 4 and Supplementary Table 5, no publication bias in terms of HRs of OS was observed in our sensitivity analysis.

4. Discussion

Up till now, for therapeutic purposes, the extent of lymphadenectomy after nCRT has remained as a matter of debate [19]. It is known to surgeons that limited lymph node dissection may result in underestimation of pathological stage since positive nodes can be missed, whereas extensive lymphadenectomy might bring unexpected complications. Recently, Visser et al. [28] conducted a meta-analysis on the prognostic value of LNY on OS. In their pooled analysis, 25 studies concerning LNY during esophagectomy with or without induction therapy for EC were all included, seven of which aimed to demonstrate improved OS with a higher LNY in patients receiving neoadjuvant therapy followed by esophagectomy (HR = 0·82; 95% CI = 0·73–0·92; $p < 0·01$) [28]. However, not only did the researchers miss several relevant studies, but they also failed to perform subgroup analysis on the role of LNY after nCRT. Therefore, the present study is the largest and latest meta-analysis so far evaluating the

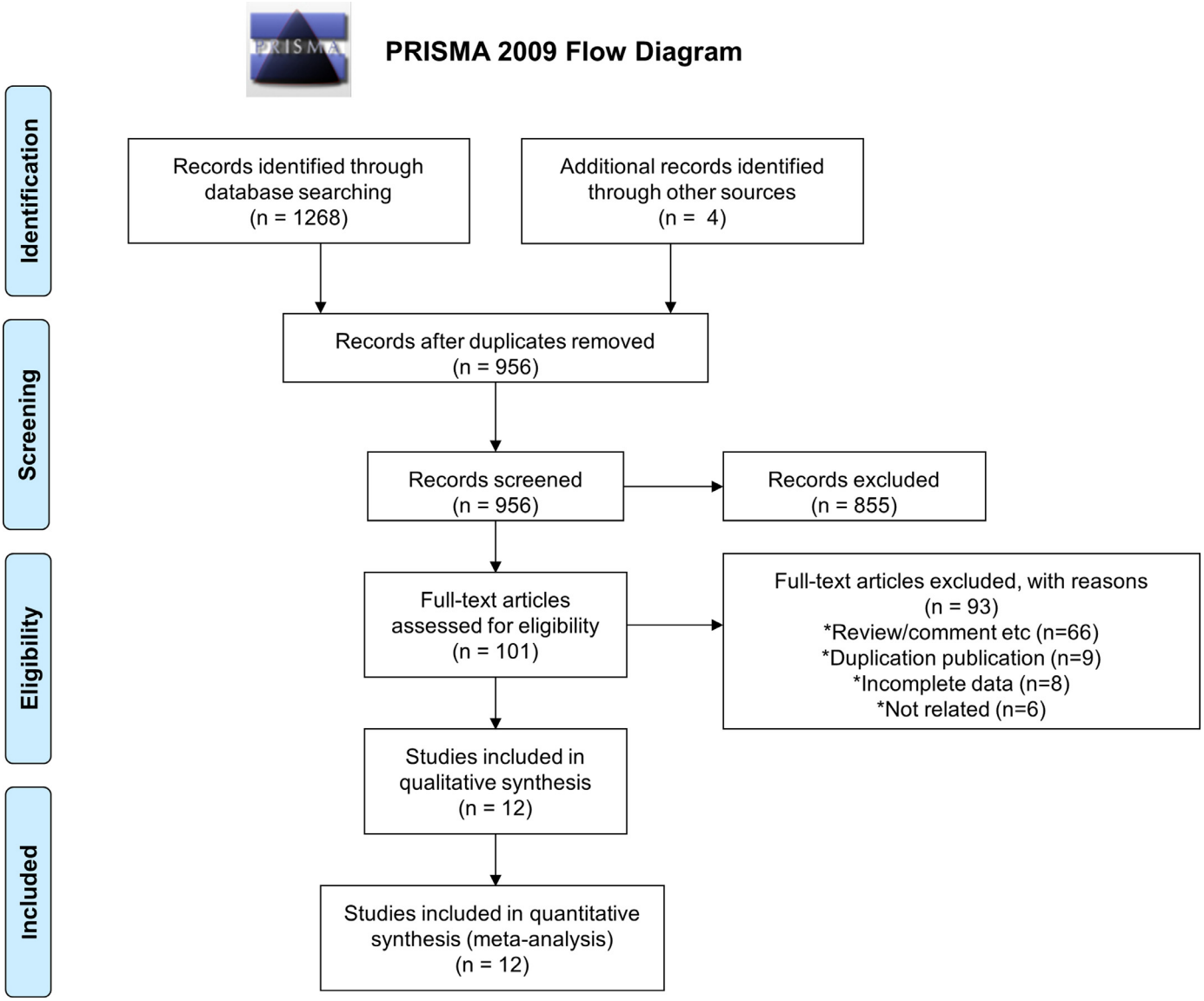

Fig. 1. Literature search of eligible studies.

impact of LNY on survival in patients with EC undergoing neoadjuvant therapy followed by esophagectomy.

Our results demonstrated that increased LNY was associated with improved OS but not DFS. Furthermore, a higher LNY was associated with favorable HRs in several subgroups, especially in patients treated with nCRT and in the subgroup with a cutoff value of lymph nodes less than 18. To be noted, four large-scale studies [9,11,17,19] among the 11 retrospective ones draw the similar conclusion that an extended lymphadenectomy during esophagectomy after neoadjuvant therapy was associated with better survival. However, the findings may be different among patient cohorts, as no association was found between LNY after nCRT and OS in a post hoc analysis on a randomized controlled trial [25]. Additionally, increased LNY after neoadjuvant radiotherapy was considered to benefit EC patients undergoing esophagectomy which was derived from a study on the Surveillance, Epidemiology, and End Results (SEER) database [17]. However, Solomon et al. [29] who also performed a retrospective study on SEER data including patients with esophageal adenocarcinoma from 1988 to 2005 revealed that adequate lymphadenectomy after neoadjuvant radiation could exert a positive impact on patients with node-positive disease but not those with node-negative. Different findings could also be observed in Western and Eastern populations. Notably, the negative result in Eastern populations could be explained by the limited number of studies into analysis.

Surprisingly, the subgroup analysis indicated that increased LNY after neoadjuvant chemotherapy might not improve OS (n = 2, HR = 1·16; 95% CI: 0·93–1·38, p = 0·39; I^2 = 69·7%, p = 0·68). The negative result might be attributed to the following three aspects: (1) one of the two studies [18,27] assessing the prognostic impact of LNY after neoadjuvant chemotherapy was a small-sized nonrandomized study; (2) the HRs of LNY as a predictor into multivariable analysis were unavailable in both studies; (3) the threshold of resected lymph nodes was set as a yield of more than 50 in both studies, which seemed too high to produce statistical significance. Additionally, given that only two studies were available to assess the relationship of LNY and OS after neoadjuvant chemotherapy, the negative result should be interpreted with great caution.

Several limitations should be acknowledged in our present analysis. First, the number of lymph nodes retrieved does not necessarily correlate with the extent of the lymphadenectomy [30]. A number of factors may contribute to the number of nodes identified by the pathologist, including the use of neoadjuvant chemotherapy and radiotherapy, and whether the specimen was dissected by the operating surgeon [31]. Extent of lymphadenectomy can, however, only

Table 1
Baseline Characteristics of Included Studies Investigating the Association between LNY after Neoadjuvant Therapy and Patient Survival (n = 12).

No.	Authors	Country or region (year)	Study design (Inclusion period)	Number of cases (F/M)	Age (years) median (range)	Tumor stage	ypT	ypN	Types of neo-adjuvant therapy	Regimens (number of patients)	Types of esophagectomy	Histology	Number of resected LN	LN cutoff value	Number of patients with different LNY in the surgical specimen (high/low)	Follow-up period (month)	Study endpoints	Analysis of hazard ratio	Quality score
1	Vallböhmer D et al	Europe &USA (2010)	Retrospective study (1985−2009)	282 (216 /66)	60 (29−79)	I-III	T0=282	N0=282	Neoadjuvant Radiotherapy/ Chemotherapy	5-FU-based chemo-therapy regimen (14) and a radia-tion dose of 40 to 45 Gy (268)	Open surgery/ VATS	SCC/ADC	20(1−77)	20	116/166	NR	OS	Multi-variable	8
2	Miyata H et al	Japan (2019)	Retrospective study (2000−2013)	561 (498 /63)	64.0 ± 7.8	I-III	T0=37 T1=112 T2=87 T3=306 T4=19	N0=170 N1=181 N2=106 N3=104	Neoadjuvant Chemo-therapy	Adriamycin, cisplatin and 5-FU (ACF:414); doce-taxel, cisplatin and 5-FU (DCF:132); Cisplatin plus 5-FU (CF:15)	NR	SCC/ADC	70.4 ± 31.0	60	NR	NR	OS	Uni-variable	7
3	Samson P et al	USA (2017)	Retrospective study (2006−2012)	10,411	NR	I-III	NR	NR	NR	NR	NR	SCC/ADC	NR	15	NR	NR	OS	Multi-variable	7
4	Visser E et al	Netherland (2017)	Retrospective study (2005−2014)	2698 (2086 /612)	63.1 ± 8.75	I-III	T0=764 T1=446 T2=511 T3=866 T4=9 NR=102	N0=1794 N1=553 N2=254 N3=89 NR=8	Neoadjuvant Chemoradio-therapy	Carboplatin AUC2 and paclitaxel 50 mg/m^2 and concurrent radio-therapy with a dose of 41.4 Gy in 23 fractions of 1.8 Gy(2698)	NR	SCC/ADC	16(11−22)	15	NR	34(4−143)	OS	Multi-variable	7
5	Wu SG et al	USA (2016)	Retrospective study (1988−2012)	3159 (2656 /503)	62(20−87)	I-III	T1=357 T2=408 T3=1358 T4=140	N0=2039 N1=715 N2=308 N3=97	Neoadjuvant Radiotherapy	NR	NR	SCC/ADC /Other	10(1−71)	11	NR	21(1−241)	OS;CSS	Multi-variable	7
6	Guo JC et al	China (2018)	Retrospective study (2000−2012)	139 (131 /8)	53.8(34.3 −74.3)	II-IV	T0=57 T1=18 T2=29 T3=31 NR=4	N0=100 N1=26 N2=12 N3=1	Neoadjuvant Chemoradio-therapy	TP-CRT: chemora-diotherapy with twice weekly pac-litaxel and cis-platin(56); Cetuximab plus TP-CRT(37); TP-HDFL: one cycle induction chemo-therapy with pac-litaxel and cisplatin plus 24-h infusion of high-dose 5-FU and leucovorin followed by TP-CRT(46)	Open surgery/ VATS	SCC	19(2−96)	19	NR	NR	OS;PFS	Uni-variable	8
7	Yasuda T et al	Japan (2015)	Prospective study (NR)	51 (10 /41)	NR	I-IV	T1=4 T2=10 T3=37	N0=3 N1=48	Neoadjuvant Chemo-therapy	Daily 5-FU for 7 days by continuous intravenous infu-sion plus doxoru-bicin and cisplatin by intravenous bolus on day 1 (51)	NR	SCC	65.2(29−112)	60	NR	81.5(48.2−120.9)	DFS	Uni-variable	8
8	Ho HJ et al	Taiwan (2018)	Retrospective study (2008−2014)	1399 (1333 /66)	54 (23−84)	I-III	T1=26 T2=149 T3=1043 T4=174 NR=7	N0=179 N1=658 N2=441 N3=119 NR=2	Neoadjuvant Chemoradio-therapy	NR	Open surgery/ VATS	SCC	19(0−90)	21	642/757	NR	OS	Multi-variable	7

(*continued on next page*)

Table 1 (*Continued*)

No.	Authors	Country or region (year)	Study design (Inclusion period)	Number of cases (F/M)	Age (years) median (range)	Tumor stage	ypT	ypN	Types of neo-adjuvant therapy	Regimens (number of patients)	Types of esophagectomy	Histology	Number of resected LN	LN cutoff value	Number of patients with different LNY in the surgical specimen (high/low)	Follow-up period (month)	Study endpoints	Analysis of hazard ratio	Quality score
9	Robb WB et al	France (2015)	Retrospective study (2000–2009)	81 (73/8)	57.8 (40.1–76.4)	I-III	T1=21 T2=47 T3=13	N0=58 N1=31	Neoadjuvant Chemoradio-therapy	Chemotherapy was delivered concomitantly with radiotherapy and comprised 2 cycles of 5-fluorouracil and cisplatin. A total dose of 45 Gy was delivered in 25 fractions (5 fractions per week) over a period of 5 weeks(81)	Open surgery	SCC/ADC	16.0(0–47.0)	15	48/33	NR	OS	Multi-variable	7
10	Phillips AW et al	UK (2017)	Retrospective study (2000–2013)	305 (263/42)	64 (23–79)	I-III	T0=2 T1=4 T2=13 T3=266 T4=20	N0=33 N1=209 N2=50 N3=11 Nx=2	Neoadjuvant Chemo-therapy	Cisplatin and 5-FU (168); epirubicin, cisplatin, and either 5-FU or capecitabine (131); epirubicin, oxaliplatin, and capecitabine(2); other(4)	Open surgery	SCC/ADC /Other	33(10–77)	33	NR	37.7(29–46)	OS	Uni-variable	8
11	Shridhar R et al	USA (2013)	Retrospective study (2000–2011)	358 (300/58)	63.5 (28–86)	I-IV	T1–2 = 52 T3–4 = 277	N0=74 N1=251	Neoadjuvant Chemoradio-therapy	Concurrent chemotherapy regimens included cisplatin and bolus 5-FU, cisplatin and protracted infusion 5-FU, carboplatin and paclitaxel, and oxaliplatin and protracted infusion 5-FU. Patients were either treated with 3D conformal therapy or intensity modulated radiation therapy with a median radiation dose of 50.4 Gy (358)	Open surgery /VATS	SCC/ADC	8(0–32)	12	NR	19 (0.3–116.8)	OS;DFS	Multi-variable	7
12	Torgersen Z et al	USA (2011)	Retrospective study (2004–2010)	84 (72/12)	NR	I-III	NR	NR	NR	NR	Open surgery /VATS	SCC/ADC	18.6(5–53)	18	41/43	51.4 (39.1–63.7)	OS	Uni-variable	7

Abbreviations: NR, not reported; VATS, video-assisted thoracoscopic surgery; SCC, squamous cell carcinoma; ADC, adenocarcinoma; OS, LN, lymph nodes; LNY, lymph node yield; overall survival; DFS, disease-free survival; 5-FU, 5-fluorouracil.

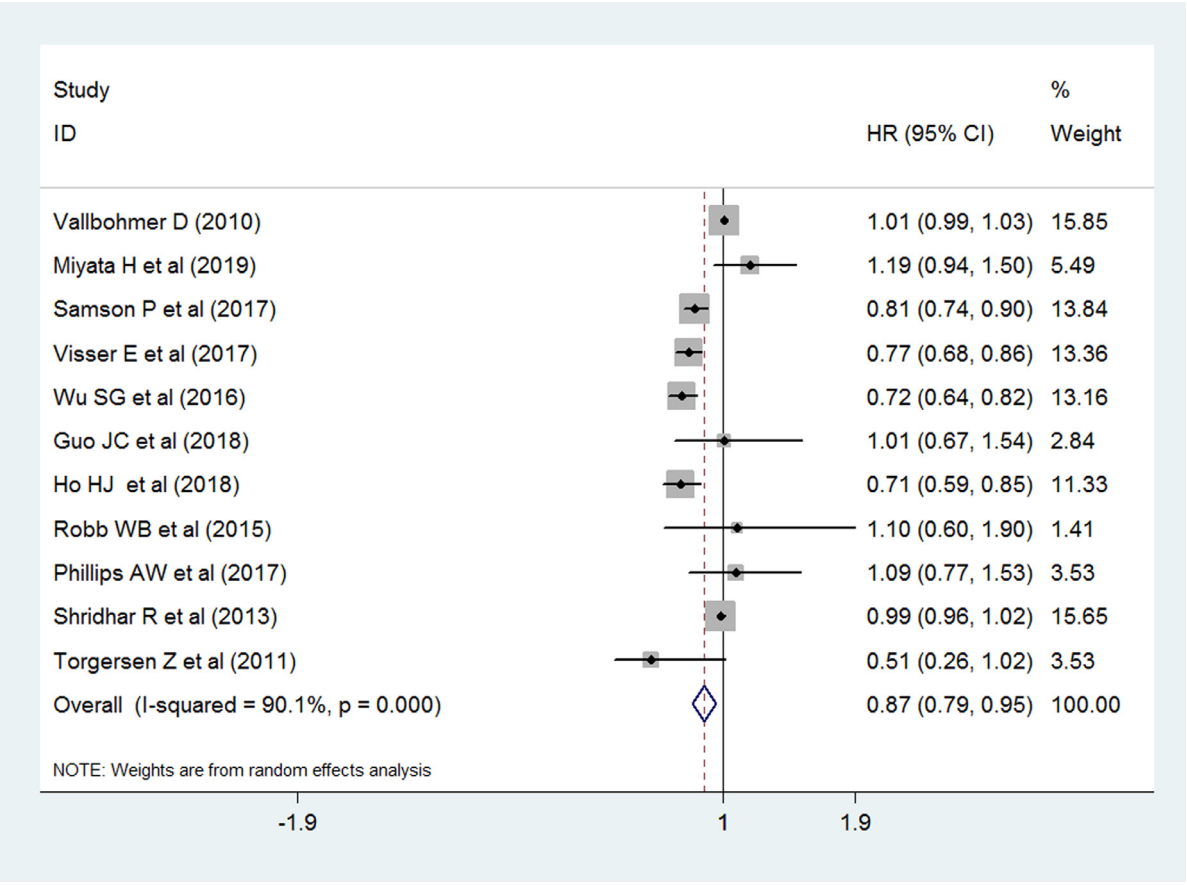

Fig. 2. Forrest plot demonstrating improved overall survival with a high lymph node yield in patients receiving neoadjuvant therapy followed by esophagectomy.

Table 2
Subgroup Analyses of the Associations Between LNY and OS.

Variables	Number of studies	Test of association			Test of heterogeneity	
		HR	95%CI	*P* value	I^2	*P* value
Total	11	0.872	0.791−0.953	<0.001	90.10%	<0.001
Publication year						
≤2016	5	0.910	0.823−0.998	<0.001	91.10%	<0.001
>2016	6	0.842	0.737−1.530	0.341	61.30%	0.024
Initial inclusion period						
≤2000	7	0.956	0.879−1.032	0.124	83.50%	<0.001
>2000	4	0.769	0.707−0.830	<0.001	15.90%	0.312
Research region						
National or regional database	4	0.764	0.717−0.811	<0.001	0.00%	0.45
Multiple countries	1	1.010	0.990−1.030	0.141	−−	−−
Japan	1	1.190	0.910−1.470	0.229	−−	−−
China	1	1.010	0.575−1.445	0.213	−−	−−
France	1	1.100	0.450−1.750	0.463	−−	−−
UK	1	1.090	0.710−1.470	0.392	−−	−−
USA	2	0.789	0.324−1.255	0.248	83.60%	0.013
Study design						
Retrospective study	11	0.872	0.791−0.953	<0.001	90.10%	<0.001
Number of cases						
≤305	5	0.950	0.768−1.132	0.184	41.90%	0.142
>305	6	0.872	0.791−0.953	<0.001	92.70%	<0.001
Median age(years)						
≤60	4	0.913	0.686−1.141	0.197	85.10%	<0.001
>60	5	0.913	0.751−1.074	0.135	91.60%	<0.001
NR	2	0.720	0.450−0.989	<0.001	56.40%	0.130
Histology						
Squamous cell cancer	2	0.785	0.530−1.040	0.134	40.40%	0.195
Squamous cell cancer/Adenocarcinoma	7	0.913	0.833−0.992	<0.001	89.00%	<0.001
Squamous cell cancer/Adenocarcinoma/Other	2	0.859	0.513−1.205	0.254	70.20%	0.067
Type of neoadjuvant therapy						
Neoadjuvant Chemoradiotherapy	5	0.814	0.695−0.933	<0.001	88.70%	<0.001
Neoadjuvant Radiotherapy/Chemotherapy	1	1.010	0.990−1.030	0.178	−−	−−

(*continued*)

Table 2 (*Continued*)

Variables	Number of studies	Test of association			Test of heterogeneity	
		HR	95%CI	*P* value	I^2	*P* value
Neoadjuvant Chemotherapy	2	1.155	0.929–1.380	0.389	0.00%	0.678
Neoadjuvant Radiotherapy	1	0.724	0.630–0.818	<0.001	––	––
NR	2	0.720	0.450–0.989	<0.001	56.40%	0.130
Type of esophagectomy						
Open surgery/VATS	5	0.931	0.856–1.006	0.121	85.10%	<0.001
Open surgery	2	1.093	0.764–1.421	0.368	0.00%	0.979
NR	4	0.810	0.709–0.910	<0.001	70.40%	0.017
Lymph nodes cutoff value						
≤18	6	0.811	0.671–0.950	<0.001	91.60%	<0.001
>18	5	0.973	0.789–1.156	0.212	81.70%	<0.001
Follow-up period (months)						
≤34	3	0.832	0.641–1.023	0.124	95.50%	<0.001
>34	2	0.800	0.232–1.368	0.257	77.70%	0.034
NR	6	0.923	0.772–1.074	0.143	88.40%	<0.001
Populations						
Eastern	3	0.949	0.602–1.295	0.213	80.30%	0.006
Western	8	0.869	0.784–0.955	0.007	91.50%	<0.001
Quality score						
7	8	0.831	0.707–0.955	<0.001	90.50%	<0.001
8	3	1.010	0.990–1.030	0.108	0.00%	0.919
Analysis of hazard ratio						
Multivariable	7	0.853	0.766–0.940	<0.001	93.50%	<0.001
Univariable	4	0.961	0.657–1.264	0.352	64.10%	0.039

Abbreviations:LNY, lymph node yield; OS, overall survival; HR, hazard ratio; CI, confidence interval; NR, not reported; VATS, video-assisted thoracoscopic surgery.

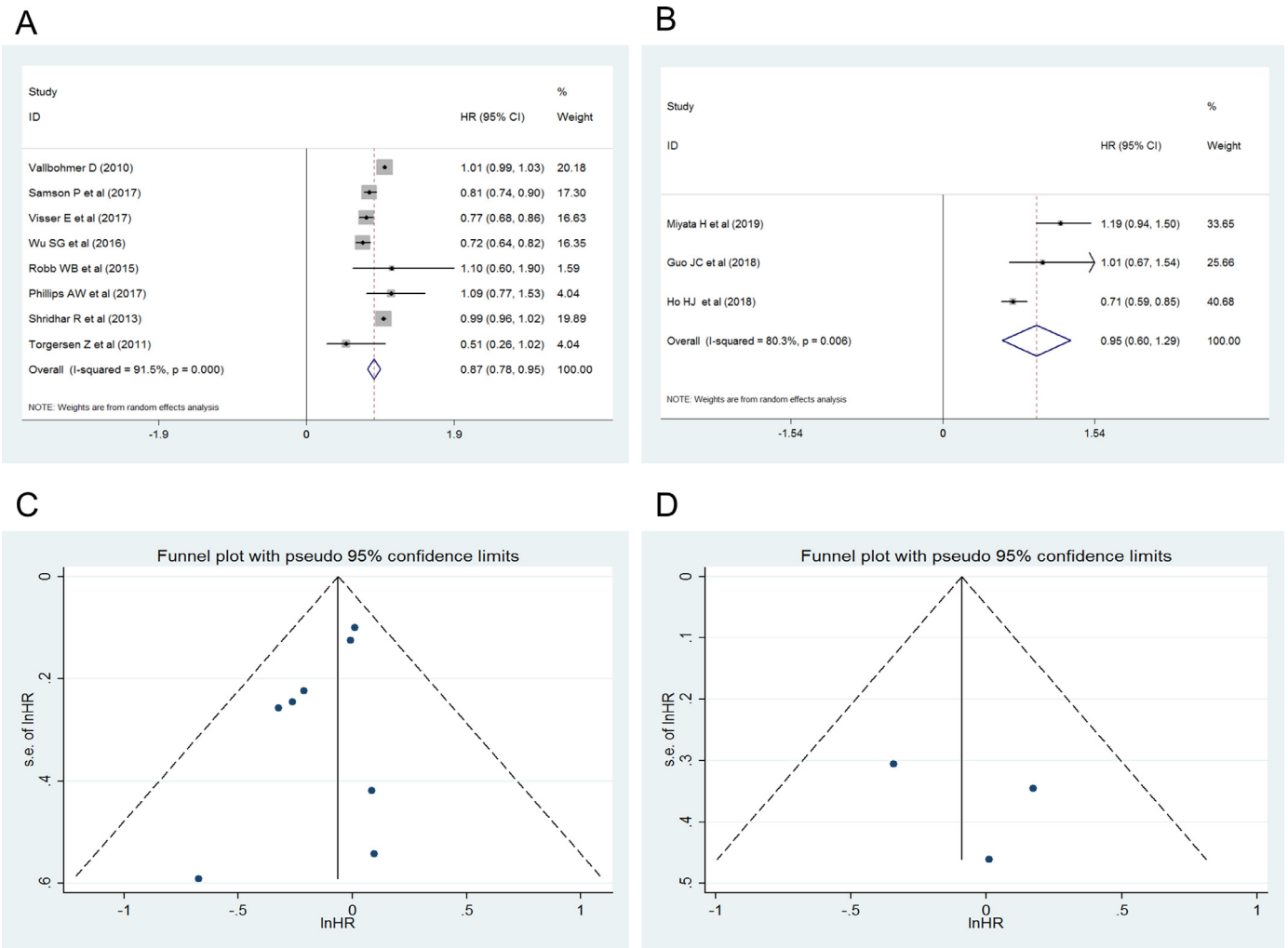

Fig. 3. Forrest plot demonstrating improved overall survival with a high lymph node yield after neoadjuvant therapy from (A) Western populations and (B) Eastern populations. Funnel plot demonstrating the hazard ratios of overall survival in (C) Western populations and (D) Eastern populations.

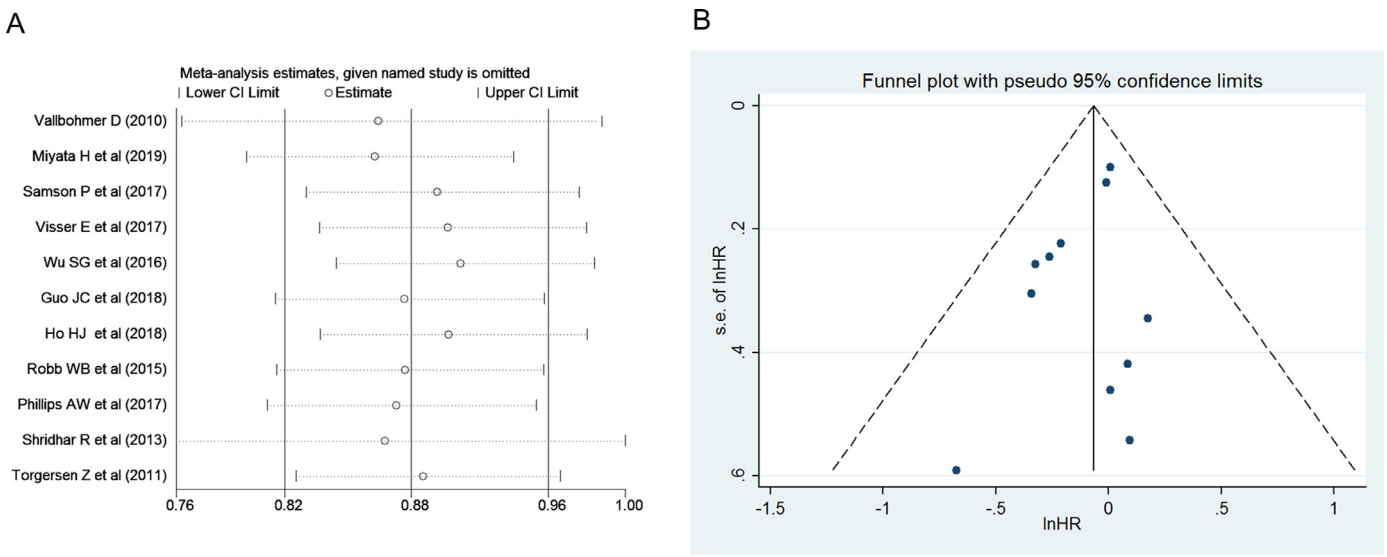

Fig. 4. Sensitivity analysis and publication bias regarding the hazard ratios of overall survival in the entire cohort.

be fully evaluated if the location of these nodes can also be determined [10]. Second, though additional studies were included compared with the previous meta-analysis [28], the number of eligible studies was still relatively small, and statistical significant heterogeneity was observed across subgroup analyses. In other word, the interpretation of our analytical results requires caution. Moreover, the cutoff value of LNY varying considerably among studies, combining these studies with their cutoff value might result in an amplification effect in the HRs, such as a bias results deviating the HR towards a better effect compared to the reality. Therefore, the difference in cutoff value of LNY in each study posed a major limitation to our pooled analysis. Last but not least, the present meta-analysis cannot replace the need for a randomized controlled trial; rather it underlines the difficulties in the design of a trial comparing a limited with more extended lymphadenectomy after neoadjuvant therapy.

In conclusion, increased LNY from esophagectomy after neoadjuvant therapy, especially after nCRT, might be associated with improved OS. More studies are warranted to assess the survival benefits of a higher LNY receiving neoadjuvant therapy plus esophagectomy, especially in Eastern populations.

Author contribution

Chen D., Mao Y. and Xue Y.: Conception and design; Collection and assembly of data; Data analysis and interpretation.

Sang Y., Liu D. and Chen Y.: Review and editing; Administrative support; Supervision; Acquisition of funds.

Manuscript writing: All authors.

Final approval of manuscript: All authors.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Supplementary materials

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