A meta-analysis of lymph node metastasis rate for patients with thoracic oesophageal cancer and its implication in delineation of clinical target volume for radiation therapy

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Objectives: The objective of this study was to pool the lymph node metastasis rate (LNMR) in patients with thoracic oesophageal cancer (TOC) and to determine which node level should be included when undergoing radiation therapy.
Methods: Qualified studies were identified on Medline, Embase, CBM and the Cochrane Library through to the end of April 2011. Pooled estimates of LNMR were obtained through a random-effect model. Possible effect modifiers which might lead to the statistical heterogeneity were identified through meta-regression, and further subgroup analyses of factors influencing LNMR were performed.
Results: 45 observational studies with a total of 18 415 patients were included in the meta-analysis. The pooled estimates of LNMR in upper, middle and lower TOC were 30.7%, 16.8% and 11.0% cervical, 42.0%, 21.1% and 10.5% upper mediastinal, 12.9%, 28.1% and 19.6% middle mediastinal, 2.6%, 7.8% and 23.0% lower mediastinal, and 9%, 21.4% and 39.9% abdominal, respectively. Lymph node metastasis most frequently happened to paratracheal, paraoesophageal, perigastric 106recR and station 7. The most obvious difference (≥15%) of LNMR between two-field and three-field lymphatic dissection occurred in cervical, paratracheal, 106recR and 108.
Conclusions: Through the meta-analysis, more useful information was obtained about clinical target volume (CTV) delineation of TOC patients treated with radiotherapy. However, our study is predominantly a description of squamous carcinoma and the results may not be valid for adenocarcinoma.

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Globally, oesophageal carcinoma is the eighth most common malignancy and sixth most fatal, with approximately 460 000 new diagnoses and >380 000 deaths annually [1]. In Asia (especially China) it usually occurs as squamous cell carcinoma in the middle or upper third of the oesophagus. But in Europe and the United States, most oesophageal tumours are adenocarcinomas and most commonly arise in the distal end of the oesophagus and at the gastro-oesophageal junction [2]. Among the various treatment modalities, surgery is still the mainstay of treatment for potentially resectable oesophageal carcinoma, but consensus has not been reached on surgical approach and extent of lymph node dissection [3], that is, two-field dissection (2FLD, including mediastinal and abdominal stations) *vs* three-field dissection (3FLD, including cervical, mediastinal and abdominal stations).

However, surgery is inappropriate in 40–60% of patients, because most oesophageal carcinomas are in an advanced stage at diagnosis [4], and there is no clear evidence for the superiority of surgery over primary (chemo-)radiotherapy for these patients. Despite some controversy about whether post-operative radiotherapy improves survival in all cases [5, 6], there seems to be a survival benefit in cases involving lymph node metastasis [7]. In patients with thoracic oesophageal carcinoma (TOC), the locoregional recurrence is still the main reason for failure [8], and the dismal prognosis primarily attributes to lymph node metastasis. As reported by many studies [9–11], the lymph node metastasis rate (LNMR) was affected by invasion depth, lymphatic vessel invasion, length, histological type and differentiation of the tumour. The sample sizes and LNMRs reported in different studies varied, so it is difficult for clinical oncologists to reach an agreement on the pattern of lymph node metastasis of TOC and to determine the optimal radiotherapy target volumes. To date, the common radiotherapy target volume for TOC has been studied often, including:

- large T-shaped, bilateral supraclavicular areas, the whole mediastinum and left gastric lymph nodes included [12]
- bilateral supraclavicular areas and mediastinum [13]
- tumour bed only [14]

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- 5–8 cm outside the tumour bed vertically and 2 cm horizontally without prophylactic irradiation of bilateral supraclavicular areas [15]
- a small T-shaped field including bilateral lower cervical, supraclavicular areas, and the upper portion of the mediastinum [16].

Exploratory meta-analysis of observational studies may provide useful information to understand and quantify sources of variability in results across studies and become a method for assessing efficacy and effectiveness [17] of a treatment. In this work, we conducted a meta-analysis by pooling the reported LNMR data to determine the clinical parameters that may be used in the current clinical practice for the target delineation of post-operative or radical radiotherapy for patients with TOC.

Methods and materials

This meta-analysis was performed in accordance with the guidelines proposed by the Meta-analysis Of Observational Studies in Epidemiology group (MOOSE) [18].

Literature search strategy

Medline (1950–2011), EMBASE (1974–2011), CBM (1978–2011) and the Cochrane Library were searched to identify relevant published articles. The search included the following terms: ((''lymph nodes'' [mesh])) AND (''esophageal neoplasm/pathology'' [mesh] OR ''esophageal neoplasm/radiotherapy'' [mesh] OR ''esophageal neoplasm/surgery'' [mesh]). The computer search was supplemented with manual searches for reference lists of full text articles.

Selection criteria

Lists of articles identified through the above search strategy were further assessed. An article was included in the subsequent analysis if the following criteria were satisfied:

- it included thoracic oesophageal carcinoma
- it included patients undergoing surgical treatment, two-field dissection or three-field dissection
- it described the lymph node metastasis of different sites in detail
- it had been published
- it included 50 or more patients.

To decide whether a study qualified for the analysis, two reviewers applied the inclusion criteria, to ensure the judgment is reproducible.

Data extraction

Relevant data from the qualified studies were extracted by two investigators (XD and JZ) independently. To resolve disagreement between reviewers, a third reviewer assessed all discrepant items and the majority opinion was used for analysis. The LNMRs of total, upper, middle, and lower TOC and of every detailed site were extracted from each study. Lymph nodes were named according to the guideline of the Japanese Society for Esophageal Diseases (JSED) [19], among which paraoesophageal nodes include 105, 108 and 110, paratracheal nodes include cervical and thoracic paratracheal nodes, and perigastric nodes include stations 1, 2, 3 and 4 (Table 1).

Data and statistical analysis

To obtain the pooled estimates of LNMR, the data were combined using a fixed-effects model if the results appeared homogeneous. If significant heterogeneity existed (if the χ^2 test for homogeneity had $p<0.10$) after careful verification of the data, a random-effect meta-analysis was performed and reasons for the heterogeneity were explored through a subgroup analysis or meta-regression analysis. In addition, publication bias was assessed using tests of funnel plot asymmetry [20]. Missing data on the characteristics of the studies were handled with Rubin's multiple imputation [21].

The data were analysed in SPSS v. 19.0 (IBM Inc, Armonk, NY), and meta-analysis and meta-regression were performed in Comprehensive Meta Analysis Version 2 (Englewood, NJ).

Results

Selected articles and description of the studies

The search is illustrated in a flow diagram (Figure 1). Potentially relevant reports included 3648 articles, of which 45 [3, 9–11, 22–62] ($n=18\,415$) satisfied the selection criteria. In so far as different articles and authors reported on patients in the same study at different time [25, 63], only the article with detailed data was permitted, to prevent duplication [20], and the data of the same population in different studies were integrated artificially [31, 32]. If the same author reported different patient populations in the same article, it was included as two studies [3]. Study characteristics for the included studies are summarised in Table 2. General characteristics for each study are listed in Table 3. No randomised controlled trials (RCTs) were found. Of the 45 studies, 29 were done in China, 11 in Japan, 4 in Europe and 1 in Russia.

Exploration of influencing baseline characteristics

Introducing the characteristics of the studies, our meta-regression analysis showed that the differences in the mean number of resected lymph nodes, the percentage of male patients, the percentage of patients with 3FLD and the percentage of patients with middle or low TOC statistically significantly influenced the regression coefficients.

Pooled lymph node metastasis rates in different site and subgroup analysis

The LNMR of TOC patients in five node levels is shown in Figure 2. The commonly metastatic areas were

Table 1. Terminology of regional lymph node in oesophageal carcinoma by the Japanese Society for Esophageal Diseases

Numbering	Cervical and mediastinal lymph nodes	Numbering	Abdominal lymph nodes
100	Superficial cervical	1	Right cardiac
101	Paraoesophageal	2	Left cardiac
102	Deep cervical	3	Lesser curvature
103	Peripharygeal	4	Greater curvature
104	Supraclavicular	7	Left gastric artery
105	Upper thoracic paraoesophageal	8	Common hepatic artery
106	Thoracic paratracheal	9	
106rec	Recurrent nerve	10	Coeliac artery
106pre	Pretracheal	11	Splenic hilar
106tb	Tracheobronchial		Splenic artery
107	Subcarinal		
108	Middle thoracic paraoesophageal		
109	Main bronchus		
110	Lower thoracic paraoesophageal		
111	Supradiaphragmatic		
112	Posterior mediastinal		

cervical, upper and mid-mediastinal nodes in upper TOC (30.7%, 42.0% and 12.9%, respectively); cervical, upper, mid-mediastinal and abdominal nodes in mid-TOC (16.8%, 21.1%, 28.1% and 21.4%, respectively); and cervical, upper, middle and lower mediastinal and abdominal nodes in lower TOC (11.0%, 10.5%, 19.6%, 23.0% and 39.9%, respectively). The areas with LNMR higher than 15% are also marked with shadow in Figure 2. The LNMRs in the subgroups of nodes (JSED) are listed in Table 4 in descending order.

LNMRs in different sites of the TOC patients undergoing 2FLD and 3FLD are shown in Figure 3. The total LNMR of 3FLD patients was generally higher than that of 2FLD patients (61.5% *vs* 52.4%). This difference was especially significant in the LNMR of cervical and upper mediastinal nodes in all parts of thoracic oesophagus.

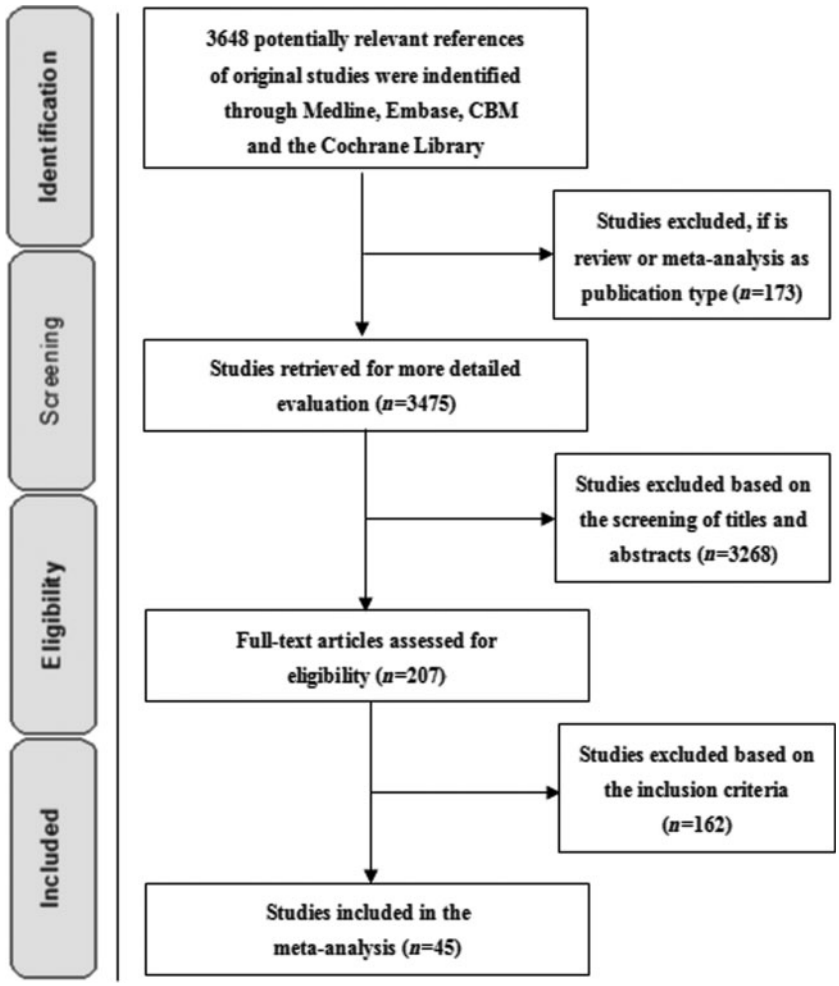

Figure 1. Flow diagram of the search results in this meta-analysis.

Table 2. Patient and tumour characteristics of 45 studies

Characteristic	*n*	%
No. of patients	18 415	
Sex		
Male	12 950	70.3
Female	5465	29.7
Mean age	57.6	
Histology		
Squamous		92.5
Good differentiation		22.8
Moderate differentiation		57.3
Poor differentiation		19.9
Non-squamous		7.5
Tumour location		
Upper	2350	12.8
Middle	11 366	61.7
Lower	4699	25.5
Surgical approach		
Two-field		50.3
Three-field		49.7
Mean nodes per patient	18.2	
T stage		
Tis–T1		11.0
T2		24.0
T3		50.3
T4		14.7

Furthermore, the results of further subgroup analysis about T stage, pathological type and differentiation are shown in Table 5. First, as the T stage increased, higher pooled LNMR followed with 28.0%, 46.2%, 61.0% and 72.9% in patients with T1 to T4, respectively. Second, the pooled LNMR estimates of squamous cell carcinoma were higher than adenocarcinoma (61.4% *vs* 57.6%). Third, LNMRs in TOC from well to poor differentiation had a tendency to increase (37.4%, 52.8% and 67.5%, respectively), and the LNMR in other differentiation TOC was 57.7%.

Analysis of publication bias

The publication bias was assessed through testing of funnel plot asymmetry. This analysis gives no indication of publication bias (classic fail-safe *N* ranged from 87 to 6086).

Discussion

Implications for radiotherapy

Generally, surgery, post-operative radiotherapy and definitive (chemo-)radiotherapy are frequently used treatments in oesophageal cancer. For patients treated with radiotherapy, accurate delivery is crucial, as inaccurate or inappropriate nodal target volumes potentially will lead to locoregional recurrence due to missed nodes within a clinical target volume (CTV) or excess toxicity due to unnecessarily large treatment volumes. Commonly, the gross tumour volume includes the primary tumour and positive lymph nodes (with diameter ≥1 cm on CT scan), while the CTV, including subclinical invasion and high-risk lymph nodes, is currently defined as 5 cm outside the tumour bed vertically and 1.5–2 cm horizontally [64]. However, global consensus is lacking on which high-risk nodal levels should be prophylactically irradiated. From the meta-analysis, it is expected to obtain useful information on how to define CTV of patients with TOC who will undergo definitive (chemo-)radiotherapy or post-operative radiotherapy.

In our present study, those sites with LNMR > 15%, an empirical cut-off value, were considered as high-risk areas and should be involved in the target volume of patients with TOC. For patients who will undergo definitive (chemo-)radiotherapy, we suggest that cervical and upper mediastinal nodes should be included in the CTV, especially lymph nodes of 101 (especially 101R), 104, 105 and 106 (especially 106 RecR) for the upper TOC. This result is in accordance with Nishimura et al's small T-shaped field radiation [16]. Tumours located in the mid-oesophagus can skip not only up to the cervical lymph nodes, but also down to the abdomen. Thus, the CTV for middle TOC should include cervical, upper, middle mediastinal and abdominal portions, especially 106 (106 recR), 107, 108, stations 1, 2 and 7 lymph nodes. As to the lower TOC from our results, the CTV should cover the middle, lower mediastinal and abdominal regions, especially including lymph nodes of 110, stations 1, 2, 3 and 7, which is consistent with the CTV definition in our institution [10]. Moreover, TOC patients of every site suffered high lymph node metastasis in paraoesophageal and paratracheal portion, from 16.9% to 34.8% and from 18.2% to 43.3%, respectively, which conformed to the nearest transferred pattern of TOC lymphatic metastasis.Thus, it is necessary to note that no matter which part of oesophagus the tumour is located in, the corresponding paraoesophageal and paratracheal nodes are considered to be covered in the CTV.

It is reported that for each part of TOC, the LNMR of cervical and upper mediastinal lymph nodes is high [8]. The anatomical complexity of the lower neck and upper mediastinum, being rich in lymphatic vessels and nerves with large blood vessels adjacent to organs, makes the exposure of lymph nodes inadequate during surgery. Therefore, completely resecting involved nodes seems to be impractical, the subclinical lesions remain, and result in lymph node metastasis and recurrence [65]. For this reason, cervical and upper mediastinal lymph nodes theoretically need to be irradiated for all TOC patients. However, our meta-analysis showed that LNMR of cervical and upper mediastinal sites for lower TOC were 11.0% and 10.5%, respectively. Although these two sites were once suggested in radiation therapy for lower TOC [65], we advocate that it be free of irradiation because of the toxicity and complications of extensive radiotherapy.

Currently, it is unclear whether the survival after 3FLD can be improved, compared with 2FLD [66], but it is becoming clear that adequate lymph node sampling is beneficial to more accurate staging [67] and lowers the recurrence rate [68]. However, 3FLD has been reported to be invasive, and has a high incidence of complications such as recurrent nerve paralysis [68]. In addition, although there is no evidence from randomised phase III trials to support the use of post-operative radiotherapy, several studies [69–71] have indicated that the locoregional control rate was significantly better for those who had undergone post-operative radiotherapy.

Table 3. Study and population characteristics for studies of thoracic oesophageal carcinoma

Study	Year	Country	Sample size	Male (%)	Mean age (years)	Mean lymph nodes	Squamous cell carcinoma (%)	Three-field dissection (%)	Upper (%)	Middle (%)	Lower (%)
Kawaguchi et al [22]	1973	Japan	65	82.2	60.0	20.0	100.0	100.0	0	69.2	30.8
Matsubara [23]	1992	Japan	110	UR (62.0)	UR (54.9)	UR (24.0)	UR (75.9)	100.0	16.4	62.7	20.9
Kakegawa et al [24]	1991	Japan	715	UR (78.6)	UR (54.4)	UR (14.2)	UR (96.9)	100.0	11.0	63.1	25.9
Fujita et al [25]	1994	Japan	70	88.6	58.5	81.8	100.0	100.0	14.3	52.9	32.8
Sayama et al [26]	1994	Japan	226	85.0	61.4	UR (55.5)	95.1	UR (100.0)	7.5	56.2	36.3
Shao et al [27]	1994	China	216	74.9	UR (62.8)	7.5	94.0	UR (7.4)	18.1	81.9	0
Su et al [28]	1994	China	175	UR (55.3)	UR (57.7)	16.3	UR (63.7)	21.7	21.7	64.6	13.7
Fu and Lian [29]	1996	China	1063	77.8	54.0	UR (26.7)	100.0	UR (99.1)	4.1	72.9	23.0
Bhansali et al [30]	1997	Japan	90	90.0	58.0	UR (59.6)	100.0	100.0	12.2	54.5	33.3
Nishimaki et al [31,32]	1997	Japan	154	92.9	60.5	77.2	94.8	100.0	6.5	51.3	42.2
Wang et al [33]	1997	China	130	86.2	57.5	UR (40.2)	90.8	UR (57.8)	47.7	52.3	0
She et al [34]	1998	China	230	76.1	56.4	25.0	100.0	100.0	23.5	63.5	13.0
Guo et al [35]	1999	China	616	63.0	UR (52.6)	UR (6.5)	100.0	100.0	10.3	72.4	17.3
Zheng et al [36]	1999	China	988	59.2	56.3	UR (3.4)	95.1	0	12.1	66.1	21.8
Wang et al [37]	2000	China	243	72.8	UR (61.0)	15.7	100.0	5.3	17.3	57.2	25.5
Xiang et al [38]	2001	China	100	79.0	56.1	30.1	91.0	100.0	14.3	75.5	10.2
Dresner et al [39]	2001	UK	104	86.5	62.9	22.0	0.0	0	0	0	100.0
Sato et al [40]	2002	Japan	155	82.0	63.9	41.7	100.0	51.6	12.3	64.5	23.2
An et al [41]	2003	China	217	66.8	56.0	18.4	100.0	100.0	18.9	54.4	26.7
He et al [42]	2003	China	150	78.7	UR (66.0)	UR (27.5)	100.0	4.7	14.0	58.7	27.3
Nakagawa et al [43]	2003	Japan	199	91.5	61.0	UR (52.0)	96.5	100.0	8.0	59.8	32.2
Stilidi et al [44]	2003	Russia	147	76.9	57.0	43.0	94.6	0	8.8	58.5	32.7
Li et al [45]	2004	China	104	63.5	56.8	UR (34.2)	100.0	100.0	100.0	0	0
Lerut et al [46]	2004	Belgium	174	85.6	59.3	59.2	44.8	100.0	6.5	30.4	63.1
Liu et al [47]	2005	China	472	77.8	57.0	21.7	94.3	100.0	11.2	71.4	17.4
Feith et al [43]	2006	Germany	621	63.0	61.0	UR (7.3)	0	0	0	0	100.0
Xu et al [49]	2007	China	308	63.0	57.5	UR (14.8)	100.0	100.0	10.4	73.4	16.2
Li et al [9]	2007	China	230	79.6	55.6	25.3	100.0	100.0	15.7	65.2	19.1
Sun et al [50]	2007	China	152	58.6	56.1	21.1	100.0	100.0	23.7	51.3	25.0
Fang et al [51]	2007	China	87	78.2	59.0	12.4	100.0	59.8	27.6	60.9	11.5
Xue et al [52]	2007	China	1412	51.0	58.0	UR (14.5)	98.2	0	14.3	68.8	16.9
Xiao et al [53]	2008	China	549	UR (71.0)	UR (58.8)	17.0	100.0	0	13.1	66.1	20.8
Liu et al [54]	2008	China	886	72.1	58.2	6.7	94.7	UR (38.6)	12.1	72.7	15.2
Wang et al [55]	2008	China	161	59.0	56.0	UR (6.6)	90.1	0	19.9	55.3	24.8
Meier et al [56]	2008	Germany	111	82.5	63.0	37.0	0	0	0	0	100.0
Chen et al [11]	2009	China	1850	73.0	55.0	26.0	100.0	100.0	15.6	74.7	9.7
Zhu et al [57]	2009	China	1690	53.6	57.3	UR (6.5)	98.0	0	14.0	65.0	21.0
Yang et al [58]	2010	China	160	70.6	UR (63.1)	UR (3.6)	100.0	0	18.8	55.0	26.2
Abula et al [59]	2010	China	215	74.4	61.0	21.9	100.0	100.0	9.6	57.7	32.7
Zhao et al [60]	2010	China	612	88.9	58.0	25.0	100.0	11.9	2.0	48.9	49.1
Huang et al [10]	2010	China	1077	78.1	UR (60.2)	19.7	100.0	UR (36.7)	5.0	63.2	31.8
Wu et al [61]	2010	China	262	81.7	55.2	22.0	94.3	100.0	36.6	48.1	15.3
Li et al [62]	2010	China Japan	763	68.9	59.0	7.7	93.4	11.1	15.4	61.5	23.1
Tachimori et al [3]	2011	Japan	127	90.6	62.7	UR (19.3)	100.0	100.0	17.3	52.8	29.9
Tachimori et al [3]	2011		229	86.9	62.8	UR (64.0)	100.0	100.0	14.4	46.3	39.3

UR, unreported (multiple imputation value in parentheses).

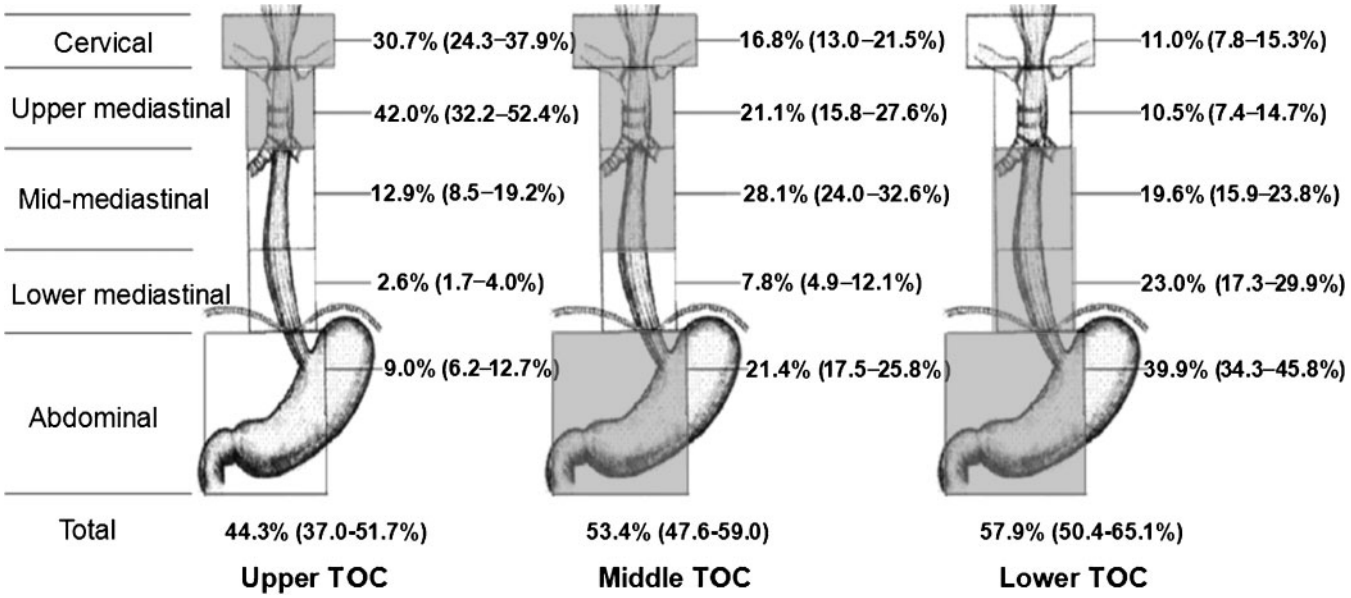

Figure 2. Pooled lymph node metastasis rates (95% confidence interval) in five lymph node regions for thoracic oesophageal carcinoma (TOC). Areas in shadow represent high-risk nodal sites with lymph node metastasis rates >15%.

For these patient cohorts, the following questions are raised:

- Is the CTV of patients with 2FLD different from that of 3FLD?
- Is it possible to narrow down the CTV of patients with 3FLD?

In our subgroup analysis results of the LNMRs of TOC patients undergoing 2FLD *vs* 3FLD, the higher the LNMR is in some sites, the more radical the dissection may be regarded as. For post-operative radiotherapy, we consider it is necessary to focus on some lymph node regions with subgroup differences of more than 15%. For the post-operative patients with 2FLD, cervical and 106recR lymph nodes of upper TOC should receive extra attention, as well as the cervical node for mid-TOC. For the post-operative patients with 3FLD, particular emphasis might be placed on the 106recL, 106pre and station 1 lymph nodes of upper TOC, 108 lymph nodes of mid-TOC, and paratracheal, station 1, 3, 4 and 9 nodes of lower TOC. Because these results obtained from subgroup analysis only describe nodes found at surgery of 2FLD and 3FLD, the role of radiotherapy to the areas outside the standard surgical field cannot be drawn from this work alone. Thus, its implication on the CTV definition of post-operative radiotherapy should be interpreted with caution.

When no RCTs are available, as is the case in the study, the appropriateness of performing a meta-analysis may be challenged because of the differences in baseline characteristics of each study. As with any meta-analysis of observational studies, this review comes with a number of caveats that we acknowledge. We explored the statistical

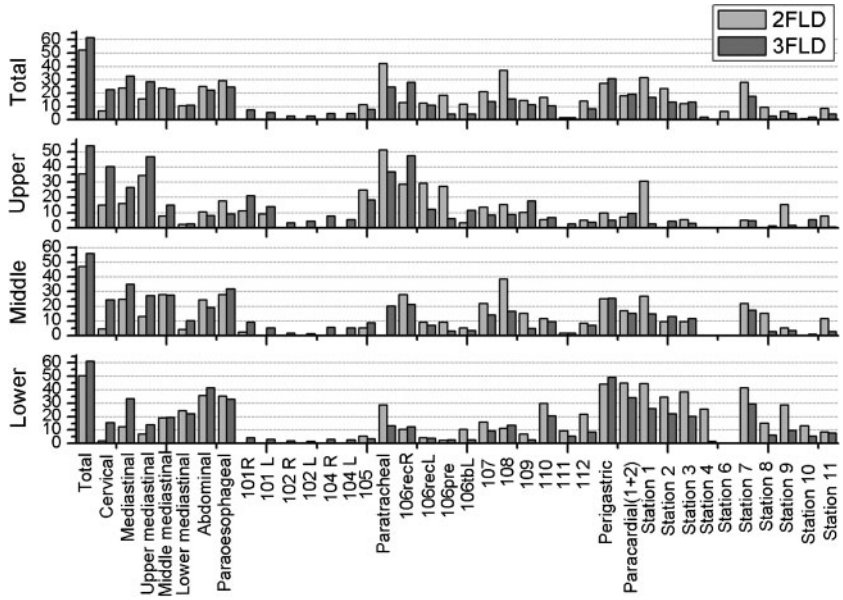

Figure 3. Lymph node metastasis rate percentages in different sites of 2FLD and 3FLD subgroups. 2FLD, two-field lymphatic dissection; 3FLD, three-field lymphatic dissection.

Table 4. Pooled lymph node metastasis rates (%) in lymph node subgroups defined by JSED

Order of rates	TOC		Upper TOC		Middle TOC		Lower TOC	
	Subgroup	%	Subgroup	%	Subgroup	%	Subgroup	%
1	Paratracheal	31.7	Paratracheal	43.3	Paraoesophageal	28.7	Perigastric	47.9
2	Perigastric	30.0	106recR	35.6	Perigastric	26.3	1+2	42.4
3	Paraoesophageal	28.4	101	23.3	108	23.6	7	36.3
4	106recR	24.3	105	20.5	106recR	23.0	Paraoesophageal	34.8
5	7	22.6	101R	18.5	Paratracheal	20.1	1	33.4
6	1	22.4	104	18.0	7	19.7	2	27.9
7	1+2	18.3	106recL	17.7	107	18.6	3	27.6
8	107	16.7	Paraoesophageal	16.9	1	17.6	110	22.6
9	2	16.4	106	15.2	1+2	16.6	Paratracheal	18.2
10	104	15.7	106pre	13.2	109	12.9	9	14.4
11	109	13.8	101L	13.0	106	12.0	108	12.7
12	3	13.0	107	11.5	2	11.8	10	12.6
13	110	11.8	109	11.4	3	10.8	107	12.4
14	106recL	11.5	108	11.2	110	10.4	106recR	12.1
15	101	11.0	106tbL	9.6	101	9.9	112	11.8
16	112	10.3	Perigastric	8.4	104	9.7	11	8.3
17	105	8.2	1+2	7.7	105	7.5	101	7.7
18	101R	7.4	104R	7.7	112	7.5	4	6.7
19	106pre	6.5	110	6.2	106recL	7.1	109	6.5
20	106tbL	6.5	1	5.3	101R	6.6	111	5.8
21	109R	5.8	104L	5.3	104R	5.6	104	5.6
22	11	5.6	10	5.3	101L	5.2	106tbL	5.1
23	101L	5.4	7	4.8	104L	5.1	101R	4.4
24	9	5.2	9	4.7	106pre	4.9	109R	4.4
25	104L	4.7	102L	4.3	11	4.8	106recL	3.9
26	104R	4.6	2	4.2	109L	4.2	105	3.8
27	106	4.4	112	3.9	106tbL	3.7	109L	3.7
28	109L	3.7	102R	3.4	9	3.7	104R	3.3
29	8	3.7	3	3.2	109R	3.7	106pre	3.2
30	102R	2.9	109R	3.0	8	3.2	101L	3.1
31	102L	2.8	11	2.7	102R	2.2	106	3.0
32	108	2.0	109L	2.6	102L	1.3	104L	3.0
33	111	1.8	111	2.5	111	1.2	102R	2.0
34	10	1.8	8	1.4	10	1.0	102L	1.7
35	4	0.9	4	0	4	0.6	8	0.8

JSED, Japanese Society for Esophageal Diseases; LNMR, lymph node metastasis rate; TOC, thoracic oesophageal cancer.

heterogeneity among studies by conducting subgroup analysis or meta-regression. Regarding potential effect modifiers, the meta-regression analysis in the present study found that the differences in the mean number of resected lymph nodes, percentage of male patients, percentage of patients with 3FLD, and the percentage of patients with middle or low TOC significantly influenced the outcome (*i.e.* the LNMR). Of these, the percentage of middle TOC patients had a negative effect on LNMR (slope coefficient less than zero). Subgroup analysis also suggested that TOC patients with different tumour stages, pathological types, tumour locations, lymphatic dissection ranges and tumour cell differentiations had different LNMRs. Although the analysis of impact of tumour length on the LNMR of TOC patients was unable to be performed because the length data extracted from the included studies were quite non-uniform, it is noteworthy that the impact of tumour length on the LNMR of patients with TOC cannot be ignored [11, 72].

Study limitations

Our study also has some limitations and the results may be misleading. First of all, among the 45 studies identified for the analysis, 41 were from Asia and 97.4% had squamous histology. These biased the data towards a population with squamous cell carcinoma in Asian

Table 5. Lymph node metastasis rate percentages in T classification, histology type and differentiation subgroups

T classification	% LNMR	*n/N*	Histology type	% LNMR	*n/N*	Differentiation	% LNMR	*n/N*
Tis–T1	28.0	15/586	Squamous cell carcinoma	57.6	21/7879	Well	37.4	6/597
T2	46.2	16/1531				Moderate	52.8	6/1474
T3	61.0	17/3587	Adenocarcinoma	61.4	3/836	Poor	67.5	6/509
T4	72.9	15/1084				Others	57.7	6/122

LNMR, lymph node metastasis rate; *n/N*, the number of studies referred to the characteristic/the total number of patients in the referred studies.

countries. Second, though we conducted subgroup analysis and meta-regression, the results needed to be cautiously interpreted because statistical heterogeneity among studies was significant ($I^2 \leq 90$). Additionally, some subgroup analyses were based on the data of a few studies, which should be re-evaluated in further studies.

In conclusion, through the pooled data of LNMR in TOC patients in the meta-analysis, we obtained some useful information about how to define the CTV of patients with TOC who would undergo definitive (chemo-)radiotherapy or post-operative radiotherapy. However, considering the bias in the initial studies, the heterogeneity among studies and the self-limitation of meta-analysis of observational studies, more evidence is needed to define the CTV delineation for TOC. Currently, the CTV should be delineated individually by experienced oncologists according to different clinical factors influencing lymph node metastasis. In addition, the fields for radiotherapy should be guided by radiological investigations, such as endoscopic ultrasound and positron emission tomography/CT. The relationship between different CTV coverage and survival benefit is expected to be assessed in future RCTs.

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