Therapeutic value of lymph node dissection for Siewert type II and III adenocarcinoma: meta-analysis

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Abstract

Background: Adenocarcinoma of the oesophagogastric junction presents an increasing incidence. Surgical resection with lymphadenectomy is the only curative treatment modality at the present time, but the optimal extent of lymphadenectomy is debatable. The aim of the present meta-analysis was to estimate the therapeutic value of each nodal station.

Methods: Studies reporting the therapeutic value index of each nodal station in Siewert types II/III oesophagogastric junction (EGJ) were searched in PubMed, Web of Science and Embase up to October 2022. This index was calculated by multiplication of metastatic incidence and 5-year overall survival rate at each nodal station. Risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Prevalence Studies. Pooled metastatic incidence and therapeutic value index were calculated using RevMan 5.4.

Results: Twelve studies involving 3513 patients were included. Nodes No. 3, 1, 7 and 2 were routinely dissected and achieved a high (≥10) or moderate (5–10) therapeutic value index in decreasing order, due to their high metastatic incidence and favourable survival rate. The index was relatively low (2–5) in suprapancreatic nodes No. 9, 11p and 8a. The index for nodes No. 4d and 10 was relatively low in Siewert type III EGJ but very low (<2) in type II. The index was very low for nodes No. 5, 6, 11d and 12a, due to their low metastatic incidence and poor survival if positive. Para-aortic, parahiatal and mediastinal nodes were dissected only in highly selected cases. Dissection of the lower mediastinal nodes, especially No. 110, could improve survival rates in type II EGJ.

Conclusion: These data could help assess the optimal extent of lymphadenectomy for EGJ. Nodes No. 1, 2, 3, 7, 8a, 9 and 11p need routine dissection in both Siewert types II/III EGJ; nodes around the lower oesophagus (especially No. 110) in Siewert type II EGJ and nodes No. 4d and 10 in Siewert type III EGJ might be considered for dissection.

Introduction

Adenocarcinoma of the oesophagogastric junction (AEG) is the tumour that straddles the oesophagogastric junction (EGJ) and has been considered separately since 2000 in the WHO Classification of Tumors1. The Siewert classification, based on the location of the tumour epicentre in relation to the EGJ, has been universally used as a surgical guide2. The 7th edition UICC TNM Classification was the first which staged AEG using the oesophageal scheme3. In the 8th edition, tumours with an epicentre within the proximal 2 cm of the cardia (Siewert types I/II) are staged as oesophageal cancers, while tumours with an epicentre more than 2 cm distal from the EGJ (Siewert type III) are staged as stomach cancers4. AEG treatment depends on the above definition.

Surgical resection with lymph node dissection (LND) is still the only potentially curative treatment for AEG, which is considered to be one of the most challenging surgical procedures due to the high postoperative morbidity rate and poor long-term prognosis. Due to the borderline location, lymphatic drainage in AEG is both in abdominal and in mediastinal nodes and the extent of LND is still debatable5,6. Recently, a systematic review was conducted to determine the incidence of metastasis in Siewert types II/III AEG at each nodal station to guide the lymphadenectomy7, but high-quality data from randomized controlled trials are still not available.

An index of the therapeutic value of each nodal station in gastric cancer was introduced by Sasako et al. in 1995 and it considered that patients with lymph node metastasis alive 5 years after resection would not have been so if the involved lymph nodes had been left in situ8. This index was calculated by multiplication of metastatic incidence and 5-year overall survival (OS) rate at each nodal station. The aim of this systematic review was to elucidate the therapeutic value of each nodal station in Siewert types II/III AEG.

Methods

This review was reported according to the PRISMA guideline and registered at the PROSPERO (https://www.crd.york.ac.uk/prospero/)
as CRD42021237978 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021237978). Because no individual patient data were involved, neither ethical approval from an institutional review board nor written consent from patients was needed.

**Search strategy**

Two reviewers independently searched PubMed, Embase and Web of Science using the following terms: (esophagogastric junction OR oesophagogastric junction OR gastroesophageal junction) AND (cancer OR carcinoma OR adenocarcinoma) AND (lymph node excision OR lymph node dissection OR nodal excision OR nodal dissection) AND (therapeutic value OR therapeutic benefit OR therapeutic index OR therapeutic effect OR survival benefit OR index of estimated benefit). A manual search of reference lists was also conducted and updated on 10 October, 2022.

Studies reporting the therapeutic value index of each nodal station in Siewert types II/III AEG were included. Involved patients were diagnosed with histologically confirmed AEG, treated by LND with retrieval of lymph node status, and followed up for 5 years. Reporting of the therapeutic value index for each nodal station was mandatory for inclusion. If the study reported multiple types of tumours, the results for AEG patients
had to be presented separately. Exclusion criteria were tumours other than AEG and duplicate material. Two reviewers independently read the title and abstract to select eligible studies and then the full text was evaluated for inclusion. Risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Prevalence Studies and classified into low risk with 7 or more “Yes” answers. Two reviewers independently extracted all relevant information in a data collection form, including study characteristics, patient features, the number of patients included, metastatic incidence, 5-year OS rate and the therapeutic value index for each nodal station.
Statistical analysis
The dissection rate and 5-year OS rate of each nodal station are presented in boxplots as median, quartiles and range. The results of metastatic incidence, 5-year OS rate and the therapeutic value index of each nodal station are shown in scatter diagrams with the metastatic incidence (×100%) on the horizontal axis and the 5-year OS rate (%) on the vertical axis, and each dot represented the therapeutic value index of each study. Pooled estimates with 95% c.i. of metastatic incidence and the therapeutic value index were calculated using Review Manager 5.4 via the Inverse-variance method (The Cochrane Collaboration, 2020). Statistical heterogeneity was evaluated using the \( \chi^2 \) test and the \( I^2 \) statistic and was considered high when \( P < 0.10 \) or \( I^2 > 50\% \). The random-effects model was always applied due to the high heterogeneity in observational studies. The presence of publication bias was evaluated using funnel plots.

Results
Study characteristics and patient features
Twelve studies were eligible \(^{11-22} \) (Fig. 1). All studies were retrospective and performed in East Asia (Table 1 and Table S1). In six studies, only abdominal lymph nodes were analysed, while the other six also included the mediastinal nodes. The clinicopathological features of involved patients are presented in Table 2 and Table S2. In total, 3513 patients were analysed, including 2090 with Siewert type II and 1423 with Siewert type III. The mean/median age varied from 60 to 69 years old. The mean/median tumour size exceeded 40 mm in all studies, ranging from 42 mm to 81.8 mm. Only one study included a small number of patients receiving neoadjuvant chemotherapy (41 of 3513, 1.2\%). A transhiatal approach was adopted in the majority of patients (3104 of 3513, 88.4\%), with most patients (3110 of 3513, 88.5\%) undergoing total gastrectomy.

Dissection rate
Nodes around the cardia (No. 1 dissected in 1687 of 1745 and 1214 of 1297 patients for Siewert types II and III respectively; No. 2 in 1702 of 1745 and 1259 of 1297 patients), along the lesser curvature (No. 3 in 1726 of 1937 and 1157 of 1297 patients) and the left gastric artery (No. 7 in 1837 of 1937 and 1262 of 1297 patients) were routinely dissected, closely followed by nodes along the greater curvature (No. 4sa, 4sb, 4d), suprapancreatic (No. 8a, 9, 11p) and parapyloric (No. 5, 6), as shown in Fig. 2 and Tables 3 and 4. Dissection rates in No. 10, 11d and 12a substantially varied across studies, from less than 10 to 100\%. In marked contrast, dissection of other abdominal (No. 16a2, 16b1, 19, 20), middle (No. 107, 108, 109) and lower (No. 110, 111, 112) mediastinal nodal areas was performed in highly selected cases, since the frequency of dissection for these nodes in Siewert type II, even for No. 110 (dissected in 216 of 684 patients), was less than 40\% (Fig. 2).

Metastatic incidence
The pooled metastatic incidence with 95% c.i. for each nodal station is summarized in Tables 3 and 4 (Figs S1–S28 for detailed results). The metastatic incidence was the highest in No. 3 (N: 815, 47.4\% (41.9\%, 52.9\%) and N: 740, 64.0\% (60.8\%, 67.3\%) for Siewert types II and III respectively), closely followed by No. 1

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**Fig. 2** Boxplots with median, quartiles and range of dissection rate
LMLN, lower mediastinal lymph nodes (including No. 110, 111 and 112 stations); MMLN, middle mediastinal lymph nodes (including No. 107, 108 and 109 stations); UMLN, upper mediastinal lymph nodes (including No. 105 and 106 stations). * and o for outlier.
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<th>No. of LND</th>
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<td>39</td>
<td>224</td>
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*LN, lymph node; LND, lymph node dissection; LNM, lymph node metastasis; c.i., confidence interval; RD, risk difference; IV, inverse variance; R, random; F, fixed; NA, not applicable; NE, not estimable (due to no survivor); MMLN, middle mediastinal lymph nodes (including No. 107, 108 and 109 stations); LMLN, lower mediastinal lymph nodes (including No. 110, 111 and 112 stations); *not subdivided into No. 11p and 11d stations.*
It was moderate in No. 9 (N: 260, 16.3% (12.2%, 20.3%) and N: 266, 19.9% (14.5%, 25.3%)) and No. 11p (N: 134, 13.5% (10.3%, 16.7%) and N: 75, 15.8% (11.2%, 20.4%)); incidence was around 10% in No. 8a and 10 (N:133 and N: 60 in Siewert II, N:156 and N:81 in Siewert III), while less than 5% in nodes along the greater curvature (No. 4sa, 4sb, 4d), around the pylorus (No. 5, 6), No. 11d and No. 12a. Regarding other abdominal and mediastinal nodes, the metastatic incidence exceeded 10% in the para-aortic (No. 16a2, 16b1) and paraoesophageal (No. 110, 108) nodes, and was approximately 5% in other middle and lower mediastinal (No. 107, 109, 111, 112) as well as parahiatal (No. 19, 20) nodes in Siewert type II AEG.

Survival rate

No. 1, 2, 3 and 7 were associated with the best 5-year OS rate, ranging from 25 to 50%, followed by the suprapancreatic nodes (No. 8a, 9, 11p) with the 5-year OS rate from 15 to 40% (Fig. 3). Involvement of nodes along the distal greater curvature in Siewert type II markedly reduced survival rate (0 to 50% with a median of 0% and 12.5% in No. 4d and No. 6 respectively) although the metastatic incidence was low. Metastasis to the suprapyloric nodes (No. 5, 12a) in Siewert type II and to the distal splenic nodes (No. 11d) in Siewert type III showed very poor survival. In contrast, involvement of No. 10 was associated with an acceptable survival rate with a median of 17.9% and 19.5% for Siewert types II and III respectively. Data on other abdominal and mediastinal lymph nodes were insufficient (Fig. 3). Of note, nodes around the lower oesophagus (No. 110, 20, 108) had a survival rate ranging from 15 to 45%; nevertheless, no patients with involvement of No. 16b1, 19 and 111 survived after 5 years.

Therapeutic value index

The therapeutic value index for each nodal station is shown in forest plots (Figs S1–S28) and scatter diagrams (Figs S29–S50). The pooled estimates are summarized in Tables 3 and 4, and also illustrated in scatter diagrams (Fig. 4) and on lymph node maps (Fig. 5). The index was high (≥10) and moderate (5–10) for No. 3, 1, 7 and 2 in decreasing order for both Siewert types II and III. The index was relatively low (2–5) for No. 9, 11p and 8a, except for No. 8a in Siewert type II. The index for No. 10 was apparently equivalent to that for No. 8a, but with a much lower dissection rate. By contrast, dissection rates in No. 11d and 12a were similar to No. 10, while the index for the first ones was very low (<2). In Siewert type III, the index for nodes along the greater curvature (No. 4sa, 4sb, 4d) and around the pylorus (No. 5, 6) was also very low (<2), corresponding to their low metastatic incidence; furthermore, the index for these nodes was very low (~0) in Siewert type II. It seemed that Siewert type III had a relatively higher index at the above abdominal nodes than Siewert type II. Regarding other abdominal and mediastinal lymph nodes, the index values ranged widely from 0 to 9.7 due to their varied and relatively low dissection rates. Dissection of the lower mediastinal nodes, especially No. 110, achieved promising survival benefit in Siewert type II.
Publication bias

The shapes of the funnel plots based on therapeutic value indices for No. 1, 2, 3 and 7 stations in Siewert type II did not reveal evidence of obvious asymmetry, suggesting that publication biases were not serious (Fig. S51).

Discussion

The present study was the first to show the dissection rate, metastatic incidence, 5-year OS rate and therapeutic value index for each nodal station in Siewert types II and III adenocarcinoma. Two nationwide Japanese studies reported the metastasis rate and therapeutic value of each nodal station for EGJ carcinoma, regardless of histological subtypes. Differences in anatomical location and histological type between EGJ carcinoma and AEG do not allow the generalization of previous results.

A higher therapeutic value index was found in No. 1, 2, 3 and 7 regardless of Siewert type, even in early tumours, making dissection necessary. Although lymph node metastasis in early tumours was almost limited to these nodes and incidence was low (2–7% versus 30–60% in advanced tumours), the survival rate was high, ranging from 70 to 90%, and the therapeutic value index ranged from 2 to 5 (versus 9 to 20).

Fig. 4 Pooled metastatic incidence, 5-year overall survival and the therapeutic value index (TVI) for each nodal station

a Lymph node No.1–12a in Siewert type II tumour; b Para-aortic, parahiatal and mediastinal lymph nodes in Siewert type II tumour; c Lymph node No.1–12a in Siewert type III tumour; d Para-aortic, parahiatal and mediastinal lymph nodes in Siewert type III tumour.
Due to their moderate therapeutic value index, suprapancreatic nodes No. 8a, 9 and 11p could require routine dissection in advanced AEG, but in Siewert type II most studies found just a weak survival benefit. In a Danish retrospective study, not based on Siewert classification, no significant difference in overall survival was found if No. 8 and/or 11 were dissected. Although No. 11d was recommended to be dissected for EGJ carcinoma in the Japanese guideline, its therapeutic value index was low in AEG and further data are needed.

Metastasis in No. 4d, 5, 6 and 12a was seen in larger tumours, at a longer distance from the EGJ and with a more extended involvement of lymph nodes. As a result, patients with involvement of these stations suffered extremely poor prognosis, similar to those with stage IV disease. In Siewert type II, lower metastatic incidence as well as poorer survival rate resulted in an extremely low therapeutic value index, suggesting that dissection of No. 4d, 5, 6 and 12a may be omitted from the routine surgical procedure and proximal gastrectomy may be sufficient for Siewert type II tumours. Some authors recommended dissection of these stations and a total gastrectomy procedure if the tumour size or the distance from the EGJ to the tumour was greater than 4 to 5 cm. By contrast, the relatively higher metastatic incidence and better survival rate offered a marginal therapeutic value for Siewert type III, implying that dissection of these stations is worthwhile. Dissection of No. 12a is debatable, as its index was consistently 0 in both types.

Although prophylactic splenectomy is denied in total gastrectomy for proximal gastric cancer, dissection of No. 10 through splenectomy or a spleen-preserving procedure was performed only for patients with tumours involving the greater curvature or with suspected nodal metastasis in the splenic hilum. Its metastatic incidence exceeded 10% with an index up to 4 in Siewert type III, which indicated improved prognosis. In Siewert type II, metastatic incidence and the therapeutic value index were significantly lower, which means that splenic hilar dissection may be omitted.

Metastasis to para-aortic nodes has been classified as M1 and para-aortic nodal dissection (PAND) does not improve survival in curable gastric cancer. Previously, No. 16a2 and 16b1 were classified into compartment 3. Metastatic incidence is not low in advanced gastric cancer, which is significantly associated with macroscopic N stage, tumour size and status of No. 7. Several studies performed PAND for selective patients, with the metastasis rate exceeding 10%. The therapeutic value index was consistent for No. 16a2, but not for No. 16b1.

Although the parahiatal nodes are included as regional nodes in tumours invading the oesophagus, the dissection rate was unexpectedly low. The survival for patients with involvement of No. 19 was surprisingly poor, in contrast with dissection of No. 20 which achieved some long-term survivors.

Regarding the mediastinal field, the situation remained unclear. High therapeutic value was seen in No. 110, but not in No. 111 or 112, suggesting that anatomical border could not be clearly defined. The lower mediastinal nodes should be treated as one station. The middle mediastinal nodes are less understood, since only a few studies have reported results in a very small population. Of note, the mediastinal lymph node metastasis may be an independent survival factor, associated with distant metastasis and poor survival, even if radical upper mediastinal lymphadenectomy was performed. The length of oesophageal invasion, defined as the distance from the EGJ to the proximal edge of the tumour, may be a significant indicator of metastasis or recurrence in the mediastinal lymph nodes, which could guide the extent of mediastinal lymphadenectomy. Special attention should be paid to these nodal stations in future studies.

This study has some limitations to consider: all articles included were retrospective, leading to a possible lack of data (for example unavailable para-aortic, parahiatal and mediastinal station status or inaccurate metastasis rate calculations), they were all performed in East Asia where a standard D2 or greater lymphadenectomy is routinely performed. Patients who received neoadjuvant treatment were not included and therefore the results cannot be generalized. Data on para-aortic, parahiatal and other mediastinal lymph nodes were inadequate, not allowing a data-driven conclusion. Validation of these findings in Western countries is needed.

These results may serve as a reference for determining the optimal extent of LND for AEG and underpin future prospective studies.

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Disclosure
The authors declare no conflict of interest.

Supplementary material
Supplementary material is available at BJS Open online.

Data availability
Research data for this study can be shared upon reasonable request to the corresponding author.

Author contributions
Xiao-Dong Chen (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing), Qing-Chuan Chen (Data curation, Formal analysis, Investigation, Software, Writing—original draft), Rui Xu (Data curation, Formal analysis, Writing—review & editing) and Fa-Zhi Zhao (Formal analysis, Investigation, Software, Writing— review & editing).

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