Extranodal extension of lymph node metastasis is a marker of poor prognosis in oesophageal cancer: a systematic review with meta-analysis

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jclinpath-2016-203830).

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Received 26 April 2016
Revised 14 June 2016
Accepted 18 June 2016
Published Online First 7 July 2016

ABSTRACT

The extranodal extension (ENE) of nodal metastasis is the extension of neoplastic cells through the nodal capsule into the perinodal adipose tissue. This histological feature has recently been indicated as an important prognostic factor in different types of malignancies; in this manuscript, we aim at defining its role in the prognosis of oesophageal cancer with the tool of meta-analysis. Two independent authors searched SCOPUS and PubMed until 31 August 2015 without language restrictions. The studies with available data about prognostic parameters in subjects with oesophageal cancer, comparing patients with the presence of ENE (ENE+) versus only intranodal extension (ENE−), were considered as eligible. Data were summarised using risk ratios (RRs) for number of deaths/recurrences and HRs together with 95% CIs for time-dependent risk related to ENE+, adjusted for potential confounders. Fourteen studies were selected; they followed-up 1437 patients with oesophageal cancer for a median follow-up of 39.4 months. The presence of ENE was associated with a significantly increased risk of all-cause mortality (RR=1.33; 95% CI 1.18 to 1.50, p<0.0001, I^2=49%; HR=2.72, 95% CI 2.03 to 3.64, p<0.0001, I^2=0%), cancer-specific mortality (RR=1.35; 95% CI 1.14 to 1.59, p=0.001, I^2=57%; HR=1.97, 95% CI 1.41 to 2.75, p<0.0001, I^2=41%) and of risk of recurrence (RR=1.50, 95% CI 1.20 to 1.88, p<0.0001, I^2=9%; HR=2.27, 95% CI 1.72 to 2.90, p<0.0001, I^2=0%). On the basis of these results, in oesophageal cancer, ENE should be considered from the gross sampling to the pathology report, and in future oncological staging system.

INTRODUCTION

Upper gastrointestinal malignancies are common and the incidence and mortality is second only to lung cancer.[1 2] Surgical resection, with or without chemoradiation, represents the gold standard of curative treatment for oesophageal cancer. Advances in perioperative techniques, staging methods and surgical management have clearly improved operative mortality and morbidity.[2] However, despite improvements in diagnostic and therapeutic strategies, the prognosis of such patients remains poor. The prognosis of this cancer, indeed, seems to mainly depend on clinical features (eg, performance status), tumour status (eg, tumour node metastasis system—TNM), extent of surgical resection and response to chemoradiotherapy.[1–5]

Oesophageal cancer is classically staged using the TNM staging system, in which the N category is subdivided in N0, N1, N2 and N3 only on the basis of the number of metastatic lymph nodes.[6] The histological features of lymph node metastasis have received no attention. Particularly, the extranodal extension (ENE) of nodal metastasis, that is the extension of tumour cells through the nodal capsule into the perinodal adipose tissue (figure 1), has recently emerged as an important prognostic factor in several types of malignancies.[7–10] Furthermore, a previous systematic review with a last search date of almost a decade old,[11] suggested that ENE should be considered as a prognostic factor in all the gastrointestinal malignancies. Although this review indicated ENE to be a potential prognostic factor for this cancer, the small number of the studies included encourages further research about the possible prognostic role of ENE in this cancer.[11] Moreover, no formal meta-analysis currently exists on this field, but could be of importance for having a better evidence of the association between ENE and poor prognosis in oesophageal cancer.

Since several new studies in the last years have investigated this issue and the last review date was over a decade old, we aimed to weight and clarify the prognostic role of ENE in patients with lymph node positive oesophageal cancer with the first meta-analysis on this topic.

METHODS

This systematic review adhered to the Meta-analysis Of Observational Studies in Epidemiology guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[12 13] following a predetermined protocol.

Inclusion and exclusion criteria

Studies were considered eligible for inclusion if they satisfy the following criteria: (1) retrospective/prospective, observational cohort studies, (2) contained a comparison of prognostic factors, among N+ patients, between ENE+ versus ENE−, (3) diagnosis of cancer of oesophagus±gastro-oesophageal junction, (4) contained data about the incidence of mortality or recurrence of disease, (5) were published in a peer review journal or published abstract.

To cite: Luchini C, Wood LD, Cheng L, *et al*. *J Clin Pathol* 2016;**69**:956–961.

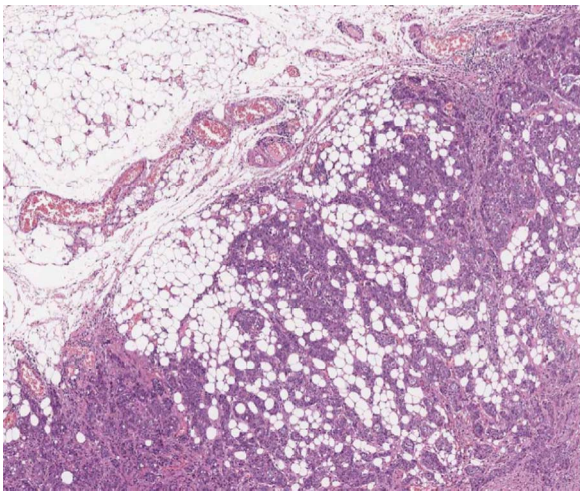

Figure 1 A classic example of extranodal extension of nodal metastasis in a case of oesophageal adenocarcinoma (10× original magnification). The marginal zone of a metastatic lymph node is totally occupied by a metastasis, which has broken the nodal capsule to massively infiltrate the perinodal adipose tissue (only a small portion of residue lymphoid tissue is present).

Exclusion criteria were: (1) no presence of cancer, (2) no data about prognostic parameters in the title/abstract, (3) comparison between ENE+ versus no lymph nodes metastases (N0), (4) diagnosis of non-epithelial malignancies (ie, lymphomas), (5) diagnosis only of gastro-oesophageal junction (no data about oesophagus) and (6) in vitro or animal studies. We considered articles written in any language.

Data sources and literature search strategy

Two investigators (CL and NV) independently searched PubMed and SCOPUS until 31 August 2015. The search terms used in PubMed included combinations of the following keywords: ((extracapsular OR pericapsular OR extranodal OR perilymphatic OR perinodal OR 'extra capsular' OR 'peri-capsular' OR 'extra nodal' OR 'peri lymphatic' OR 'peri nodal' OR 'extra-capsular' OR peri-capsular OR 'extra-nodal' OR 'peri-lymphatic' OR 'peri-nodal') AND (esophagus OR oesophagus OR esophageal OR oesophageal OR junction OR junctional) AND (mortality OR mortalities OR fatality OR fatalities OR death* OR survival OR prognosis OR 'hazard ratio' OR HR OR 'relative risk' OR RR OR prognosis OR progression OR recurrence)). A similar search was repeated in SCOPUS. We considered also the reference lists of all included articles and of all previous related reviews.[11]

Study selection

Following the searches as outlined above, after removal of duplicates (in the cases of same/similar cohort of patients in different paper, we selected the largest, the most comprehensive one and/or the most recent one), two reviewers (MS and GS) independently screened titles and abstracts of all potentially eligible articles. The two authors applied the criteria of eligibility, considered the full texts and a final list of included articles was reached through consensus with a third author (BS) if necessary.

Data extraction

Two authors were involved in data extraction in a predetermined database. One author (AN) extracted data from the included articles and a second independent author (CL) validated the data extraction. For each article, we extracted information about authors, year of publication, country, location of cancer, exclusion criteria, histotype, type number of adjustments in survival analyses and duration of mean follow-up. Moreover, number of females, T stage, tumour grading, number of patients with metastatic lymph nodes, age were extracting by ENE status (see online supplementary table S1).

Outcomes

The primary outcomes were number of deaths independently from all the causes, that is, all-cause mortality (ACM), number of deaths due to cancer, that is, cancer-specific mortality (CSM) and number of recurrences after treatment during follow-up period in those with ENE+ versus ENE−, that is, risk of recurrence (ROR). Secondary outcomes were HRs, adjusted for the maximum number of confounders available, about the same issues, taking those with ENE− as reference. All these outcomes were considered at 5 years of follow-up.

Assessment of study quality

The Newcastle-Ottawa Scale (NOS) was used to evaluate study quality.[14] The NOS provides an assessment of the methodological quality of non-randomised trials and its content validity and reliability have been already established.[12] Included studies are judged on eight items across three key areas: selection of the participants, comparability of the participants and outcomes. Two authors (CL and NV) completed the NOS and each study receives an overall score for methodological quality of up to nine points with a score of ≤5 (out of nine) indicating high risk of bias (see online supplementary tables S2 and S3).[14]

Data synthesis and statistical analysis

All analyses were conducted using Comprehensive Meta-Analysis 3. In our primary analyses, pooled risk ratios (RRs) and 95% CIs of ACM, CSM and ROR between ENE+ versus ENE− were calculated using DerSimonian-Laird random-effects models.[15] In secondary analyses, pooled, HRs with 95% CIs adjusted for the maximum number of covariates available in the articles, were also calculated for providing additional information if the relationship between ENE status and outcomes was influenced by potential confounders. Heterogeneity across studies was assessed by the I^2 metric and χ^2 statistics.[16] In the presence of significant heterogeneity (indicated by $I^2 \geq 50\%$ and/or $p<0.05$) and for outcomes having at least four studies, we planned to conduct a series of meta-regression analyses according to ENE status and each of prognostic parameters considered. However, since the outcomes with at least four studies resulted poorly heterogeneous, we made only a meta-regression analysis for the adjusted HRs for ACM taking as moderator the number of adjustments.

Finally, we investigated publication bias for our primary meta-analysis with a visual inspection of funnel plots and with the Begg–Mazumdar Kendall's τ and Egger bias test.[17 18] Moreover, in the presence of publication bias for the main analyses, we performed a trim and fill adjusted analysis to remove the most extreme small studies from the positive side of the funnel plot, recalculating the effect size at each iteration, until the funnel plot was symmetric about the (new) effect size.[19]

RESULTS

Search results

Altogether, 164 non-duplicated articles were identified through the literature search. After excluding 137 articles based on title/abstract review, 27 articles were retrieved for full text review and, following the application of the inclusion criteria, 14

unique articles resulted as eligible for this meta-analysis (see online supplementary figure S1).[20–33]

Study and patient characteristics

The studies were conducted in Europe (eight studies, 57.1%),[21 22 24–28 30] in Asia (five studies, 35.7%)[20 23 29 31 32] or in Australia (one study, 7.2%),[33] with no studies identified in America. Globally, 1437 patients (745 ENE+ and 692 ENE−), with a median follow-up of 39.4 months, were included in this meta-analysis. Eleven studies specifically investigated oesophageal cancer only,[20–23 26 27 29–33] while three studies considered together cancers of oesophagus and gastro-oesophageal junction.[24 25 28] About the histotype, three studies are focused on oesophageal squamous cell carcinoma (SCC),[20 23 31] five on oesophageal AC,[21 24 25 28 30] while five considered together these tumour subtypes,[22 26 27 29 32] sometimes without a specific separation of the data.[29 32]

The median NOS score was five points (range: 5–8) with five studies at possible high risk of bias for quality (ie, NOS score ≤5) (see online supplementary tables S1 and S2).

Nine out of 14 studies assessed ENE with a classic definition,[20–25 28 30 33] that is the extension of lymph node metastatic cells through the nodal capsule into the perinodal fatty tissue, with,[22 30 33] or without,[20 21 23–25 28] specific details about capsule infiltration. The remaining five studies used alternative definitions of ENE.[26 27 29 31 32] Particularly, in the two studies by Metzger *et al*,[26 27] and in the one by Sakai *et al*,[31] ENE is defined as metastatic cancer extending through the nodal capsule into the perinodal fatty tissue, but deposits of metastatic cancer cells without a recognisable lymph node were also considered as ENE, unless these deposits were associated with perineural and/or vessel involvement. Furthermore, for Nakano *et al*,[29] ENE is the presence of cancer cells in the connective tissues around the removed nodes detected by histological examination, while for Tachikawa *et al*,[32] it is defined as a metastasis apparently penetrating the capsule or accompanied by carcinomatous nodules such as extracapsular vessel invasion, excluding carcinomatous nodules of the oesophageal wall.

Only three studies reported the use of preoperative therapy (neoadjuvant chemotherapy and/or radiotherapy), but we cannot specifically obtain the total number of N1 (ENE− vs ENE+) patients from these three studies.[22 27 33]

There were very few studies (three studies on ENE+ patients and two on ENE−) that reported complete clinical–pathological data, divided between ENE+ and ENE−, to make a reliable comparison; however, where provided, there is not a clear differences in such parameters, like TNM status at the time of diagnosis or tumour grading, between ENE+ and ENE− patients.

Furthermore, five studies reported data about the total number of resected and identified lymph nodes,[22 25–28] of which the mean number per patients was 31.7. Two studies reported this kind of data also divided on the basis of the presence of ENE;[25 28] particularly, in these studies the mean number of lymph nodes was 35.1 in ENE+ patients versus 33.9 in ENE− patients, without a statistically significant difference.

RRs on ACM, CSM and ROR

Pooling data from eight studies reporting data on ACM,[23 26 27 29–33] 86.2% with ENE+ were dead versus 64.5% with ENE−, leading to a significant increased risk of mortality for all cause (RR=1.33; 95% CI 1.18 to 1.50, p<0.0001, I^2=49%) (table 1, figure 2).

Moreover, CSM was reported in three studies,[24 25 28] and resulted significantly higher in ENE+ than ENE− patients (RR=1.35; 95% CI 1.14 to 1.59, p=0.001, I^2=57%) (table 1, see online supplementary figure S2).

Lastly, ENE+ was further associated to a significant higher ROR (three studies);[20 22 31] 69.7% in ENE+ versus 46.5% in ENE− patients experienced a recurrence, equating to an RR=1.50 (95% CI 1.20 to 1.88, p<0.0001, I^2=9%) (table 1; see online supplementary figure S3).

The analysis for identifying a publication bias was possible only for ACM outcome, since this analysis requires at least four studies. As shown in the funnel plot of the studies taking as outcome ACM (see online supplementary figure S4) there was an evidence of publication bias, due to a higher proportion of studies at the right side of the mean (indicating a significant association between ENE+ with reduced ACM). These findings were confirmed by the Egger's test (bias=3.4; 95% CI 0.78 to 1.52, p=0.005) and Begg–Mazumdar test (Kendall's τ=0.61, p=0.04). Given the publication bias observed, we calculated the trim and fill adjusted analysis which demonstrated a pooled RR of 1.22 (95% CI 1.06 to 1.41) suggesting that the publication bias for this outcome is unlikely.[17]

Adjusted HRs on ACM, CSM and ROR

In our secondary analyses, we investigated whether using HRs (adjusted for the maximum number of the covariates reported in each study) instead of RRs could influence our results. Altogether, the median number of adjustments used was 3 (range: 0–9) (see online supplementary tables S1 and S3).

Table 2 shows the adjusted HRs according to ENE status: ENE+ was associated to a significant poorer prognosis, being associated with a higher risk of ACM (four studies;[21 26 27 31] median number of adjustments=5 (range: 4–7); HR=2.72, 95% CI 2.03 to 3.64, p<0.0001, I^2=0%) (see online supplementary figure S5), CSM (three studies;[24 25 28] median number of adjustments=4 (range: 2–7); HR=1.97, 95% CI 1.41 to 2.75, p<0.0001, I^2=41%) (see online supplementary figure S6) and ROR (three studies;[21 22 24] median number of

Table 1 Pooled risk ratio estimates for ACM, CSM and ROR according to presence or not of ENE

Parameter	No of studies	No of events* in ENE+	No of ENE+	No of events* in ENE−	No of ENE−	Risk ratio (95% CI)	p Value	Heterogeneity
ACM	8	288	334	253	392	1.33 (1.18 to 1.50)	<0.0001	τ^2=0.01; χ^2=13.80, df=7 (p=0.06); I^2=49%
CSM	3	319	371	143	223	1.35 (1.14 to 1.59)	0.001	τ^2=0.11; χ^2=4.67, df=2 (p=0.10); I^2=57%
ROR	3	69	99	73	157	1.50 (1.20 to 1.88)	<0.0001	τ^2=0.06; χ^2=2.21, df=2 (p=0.33); I^2=9%

*Events stand for death for ACM and CSM, and for recurrence for ROR.
ACM, all-cause mortality; CSM, cancer-specific mortality; ENE, extranodal extension; ROR, risk of recurrence.

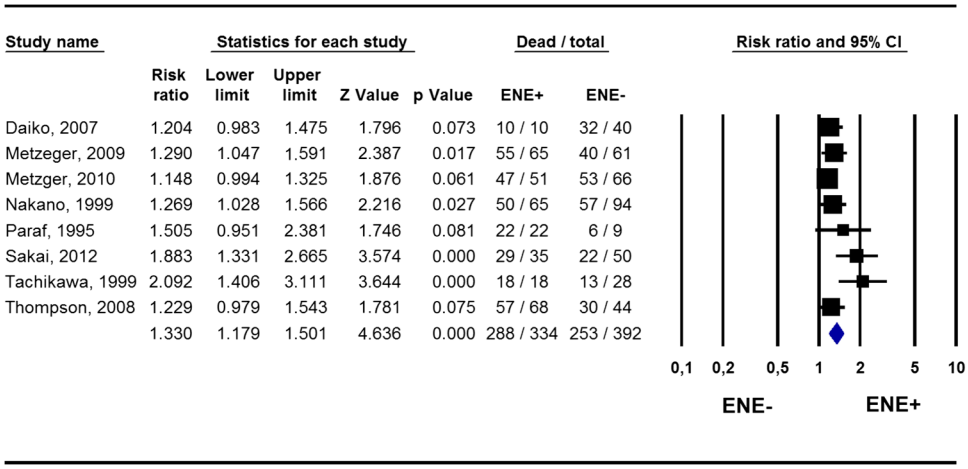

Figure 2 Forest plot for relative risk of overall survival. ENE, extranodal extension.

Table 2 Pooled risk ratio estimates for adjusted HRs for overall and disease free survival according to presence or not of ENE

Parameter	No of studies	HRs (95% CI)	p Value	Heterogeneity
ACM	4	2.72 (2.03 to 3.64)	<0.0001	τ^2=0.00; χ^2=0.24, df=3 (p=0.97); I^2=0%
CSM	3	1.97 (1.41 to 2.75)	<0.0001	τ^2=0.04; χ^2=3.43, df=2 (p=0.18); I^2=41%
ROR	3	2.27 (1.72 to 2.90)	<0.0001	τ^2=0.00; χ^2=1.48, df=2 (p=0.48); I^2=0%

ACM, all-cause mortality; CSM, cancer-specific mortality; ENE, extranodal extension; ROR, risk of recurrence.

adjustments=6 (range: 1–7); HR=2.27, 95% CI 1.72 to 2.90, p<0.0001, I^2=0%) (see online supplementary figure S7).

No publication bias evident using adjusted HRs instead of RR for ACM (see online supplementary figure S8) (Egger's test: bias=0.97; 95% CI −6.98 to 8.94, p=0.65; Begg–Mazumdar test: Kendall's τ=0.00, p=1.00).

Meta-regression analysis

Among the outcomes investigated, only RR for CSM showed a high heterogeneity (I^2=57%). However, this outcome included only three studies, thus precluding a meta-regression analysis.

Since it is conceivable that the strength of the association between ENE+ and reduced ACM in adjusted HRs estimates may depend on the number of adjustments, we conducted a meta-regression analysis between these two estimates that, however, did not show any significant association (β=−0.04; 95% CI −0.45 to 0.37, p=0.86, R^2=0%).

DISCUSSION

In this study, we analysed 14 observational studies involving 1437 patients affected by oesophageal cancer with metastatic lymph nodes. Of them, 745 presented ENE+, while 692 showed only intranodal metastasis. Our findings suggest that the presence of ENE is strongly associated to a poor prognosis in all the most important prognostic indexes, namely ACM, CSM and ROR. Although a potential publication bias was evident, it seems that the relationship was evident after the trim and fill adjusted analysis. Moreover, the association between ENE and poor prognosis was also maintained considering HR adjusted for potential confounders. Furthermore, reinforcing the robustness of our findings, the vast majority of prognostic outcomes were not characterised by a significant heterogeneity.

It is noteworthy that in three studies all the node-positive patients with ENE died within 5 years,[23 30 32] highlighting the important prognostic significance of this morphologic aspect. There are several potential implications derived from this study. The first regards the surgical pathology approach and particularly the gross sampling. Indeed, on the basis of the shown importance of ENE in oesophageal cancer, and knowing that ENE can be very focal in a metastatic lymph node, a fundamental consequence is that all the lymph nodes with their surrounding adipose tissue have to be completely included, and not simply isolated from the fatty tissue. The most common approach for surgical pathologists during grossing starts with the manual isolation of lymph nodes; if there is an enlarged lymph node with a metastatic aspect, the pathologists often start to include only a portion of this, because the only thing required is the demonstration of a metastasis, and also because of an economic reason. However, on the basis of this systematic review and meta-analysis, a complete inclusion of all the lymph nodes, even if very large, and also of the perinodal adipose tissue is recommended.

There is not a statistically significant difference between the total number of resected and identified lymph nodes and the detection of ENE. However, some authors indicated that the number of lymph nodes with ENE was significantly correlated with the number of positive nodes and lymph node ratio (ie, number of positive lymph nodes/total number of lymph nodes).[22 26 27 31] Particularly, ENE was seen more often if the number of positive nodes and the lymph node ratio were higher, highlighting the role of ENE as a marker of poor prognosis.

Notably, the prevalence of ENE resulted more frequently in AC than in SCC. Metzger *et al* presented separately data between these two subtypes, showing a prevalence of ENE of 66% in AC and of 35% in SCC.[26] Similar results, with a predominance of ENE in AC, have been shown by Thompson *et al*.[33] For SCC, Tachikawa *et al* found a prevalence of ENE in 39% of node-positive patients, and Nakano *et al* in 41%.[29 32] However, both Nakano *et al* and Tachikawa *et al* considered also tumour cells found in the perinodal soft tissue as ENE, and this may explain the slightly higher frequencies than Metzger *et al*. At the same time, Lerut *et al* and Lagarde *et al* analysed relatively uniform cohorts of patients with AC,

producing similar results about this tumour histotype, with a prevalence of ENE of 63% and 66%, respectively.[24 25] Despite of a reliable importance of ENE in both AC and SCC, further studies are needed to investigate more in depth and separately the role of ENE in influencing the prognosis in these different tumour types.

Other considerations can be made about neoadjuvant chemotherapy (CHT). Interestingly, Metzger *et al* indicated that neoadjuvant therapy did not reduce the occurrence of ENE, with similar percentages in a cohort with and in a second without neoadjuvant CHT.[27] These results were substantially confirmed also by Thompson *et al*.[33] The conservation of ENE after neo-adjuvant treatment increases its importance, since this prognostic parameter can be assessed also in post-CHT specimens, with the same value of a marker of poor prognosis.

Furthermore, another aspect that has to be addressed is a standard definition of ENE, since this parameter, on the basis of this meta-analysis, should be considered by the staging systems and reported in the final pathology report. Nine out of 14 studies assessed ENE classically, that is, as the extension of metastatic cells through the nodal capsule into the perinodal adipose tissue.[20–25 28 30 33] Five studies,[26 27 29 31 32] however, used alternative definitions of ENE. Particularly, also deposits of metastatic cancer cells without a recognisable lymph node, unless these deposits were associated with perineural and/or vessel involvement,[26 27 31] or the presence of cancer cells in the connective tissues around the removed nodes,[32] were considered as part of ENE definition. Using these definitions, also free tumour deposits could be included in our meta-analysis, introducing a possible bias. However, the results of our meta-analysis seem to be robust (as shown by low heterogeneity by the outcomes included) to be affected significantly by this issue, that moreover concerns only four out of 14 studies. Furthermore, this point highlights the importance of looking for a standard definition of ENE. We recommend considering true ENE only a non-debatable ENE, that is demonstrated histologically and characterised by a structural rupture of the lymph node capsule by the metastasis. Neoplastic emboli, free tumour cells deposits in soft tissue and metastasis in the marginal sinus and should not be considered as true ENE. Notably, the presence of tumour cells in the adipose tissue is recognised as associated to a poor prognosis: for example, in the TNM staging system for colorectal cancer, the free tumour deposits in the adipose tissue are recognised as important prognostic parameters, constituting a specific subcategory in N group, named N1c.[6 8] Furthermore, ENE has also been taken into account in the last staging systems of squamous cell carcinoma of the vulva, playing an important and adverse prognostic role.[10] On the basis of this meta-analysis, and if further studies and/or nomograms will confirm our results, the presence of ENE should be included in the staging system also for oesophageal cancer.

Considering implications for therapy pointed out by this meta-analysis, it has to be reported that patients with ENE in pancreatic cancer seem to benefit from adjuvant chemoradiation, but not from chemotherapy alone.[7 34] This aspect has to be investigated by future studies, and could address particular therapeutic approaches if confirmed for oesophageal cancers.

While the results of this meta-analysis are clear and novel, we have also to consider some limitations of our paper. First, data about other comorbidities (like cardiovascular diseases) were not consistently reported by the primary studies, but it is known that they have an important role in the prognosis also of patients with cancer. Second, while the evidence for ACM seems to be exhaustive since it includes eight studies in both not adjusted and adjusted analyses, the evidence about CSM and ROR is more limited. This issue is probably due to the fact that oesophageal cancer has one of the most lethality among all cancers and so the possibility of recurrence is limited and ACM is probably similar to CSM. However, future research is needed about the role of ENE for these specific outcomes.

In conclusion, our results indicate that ENE seems to be strongly associated with a poorer prognosis in oesophageal cancer, also independent of potential confounders. This condition is present in a remarkable proportion of the patients affected by such malignancy. Therefore, its consideration becomes fundamental from the gross sampling to the histopathological evaluation and the oncological staging. A final consideration regards the recent development of techniques of DNA sequencing: it has been already proposed an integration of the pathology report with a complete molecular characterisation of cancer;[35 36] however, before this, all the prognostic roles of the pure morphological features and of the histological aspects, as ENE, should be clarified.

Take home messages

- ENE is important in influencing the prognosis of some solid cancers.
- We investigate if ENE may be important also for oesophageal cancer.
- We demonstrate its importance with the tool of meta-analysis.
- Thanks to our results, it should be considered by future staging system.

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Handling editor Cheok Soon Lee

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Funding MB was supported by Trentino Biomolecular Oncologic Network—TreBiONet: 'Fondazione Cassa di Risparmio di Trento e Rovereto'. AS is supported by Ministry of University (FIRB RBAP10AHJB) and AIRC (grant n. 12182).

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Bosman FT, Carneiro F, Hruban RH, *et al*. WHO classification of tumours of the digestive system. Lyon: IARC Press, 2010.
2 Murphy AG, Lynch D, Kelly RJ. State of the art management of metastatic gastroesophageal cancer. *Ann Transl Med* 2015;3:236.

3 Yodying H, Matsuda A, Miyashita M, *et al*. Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2016;23:646–54.
4 Ohashi S, Miyamoto S, Kikuchi O, *et al*. Recent advances from basic and clinical studies of esophageal squamous cell carcinoma. *Gastroenterology* 2015;149:1700–15.
5 Noordman BJ, Wijnhoven BP, van Lanschot JJ. Optimal surgical approach for esophageal cancer in the era of minimally invasive esophagectomy and neoadjuvant therapy. *Dis Esophagus* Published Online First: 18 Sep 2015. doi: 10.1111/dote.12407.
6 Edge SB, Byrd DR, Compton CC, *et al*. *AJCC cancer staging manual*. 7th edn. New York: Springer-Verlag, 2010.
7 Luchini C, Veronese N, Pea A, *et al*. Extranodal extension in N1-adenocarcinoma of the pancreas and papilla of Vater: a systematic review and meta-analysis of its prognostic significance. *Eur J Gastroenterol Hepatol* 2016;28:205–9.
8 Veronese N, Nottegar A, Pea A, *et al*. Prognostic impact and implications of extra-capsular lymph node involvement in colorectal cancer: a systematic review with meta-analysis. *Ann Oncol* 2016;27:42–8.
9 Veronese N, Luchini C, Nottegar A, *et al*. Prognostic impact of extra-nodal extension in thyroid cancer: a meta-analysis. *J Surg Oncol* 2015;112:828–33.
10 Luchini C, Nottegar A, Solmi M, *et al*. Prognostic implications of extra-nodal extension in node-positive squamous cell carcinoma of the vulva: a systematic review and meta-analysis. *Surg Oncol* 2016;25:60–5.
11 Wind J, Lagarde SM, Ten Kate FJ, *et al*. A systematic review on the significance of extracapsular lymph node involvement in gastrointestinal malignancies. *Eur J Surg Oncol* 2007;33:401–8.
12 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
13 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
14 Wells GA, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (accessed 13 Oct 2015).
15 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
16 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
17 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
18 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
19 Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.
20 Baba M, Aikou T, Natsugoe S, *et al*. Lymph node and perinodal tissue tumor involvement in patients with esophagectomy and three-field lymphadenectomy for carcinoma of the esophagus. *J Surg Oncol* 1997;64:12–16.
21 Courrech Staal EF, Wouters MW, van Sandick JW. The stromal part of adenocarcinomas of the oesophagus: does it conceal targets for therapy? *Eur J Cancer* 2010;46:720–8.
22 D'Annoville T, D'Journo XB, Loundou A, *et al*. Prognostic impact of the extracapsular lymph node involvement on disease-free survival according to the 7th edition of American Joint Committee on Cancer Staging System. *Eur J Cardiothorac Surg* 2013;44:e207–11.
23 Daiko H, Hayashi R, Saikawa M, *et al*. Surgical management of carcinoma of the cervical esophagus. *J Surg Oncol* 2007;96:166–72.
24 Lagarde SM, de Boer JD, ten Kate FJ, *et al*. Postoperative complications after esophagectomy for adenocarcinoma of the esophagus are related to timing of death due to recurrence. *Ann Surg* 2008;247:71–6.
25 Lerut T, Coosemans W, Decker G, *et al*. Extracapsular lymph node involvement is a negative prognostic factor in T3 adenocarcinoma of the distal esophagus and gastroesophageal junction. *J Thorac Cardiovasc Surg* 2003;126:1121–8.
26 Metzger R, Drebber U, Baldus SE, *et al*. Extracapsular lymph node involvement differs between squamous cell and adenocarcinoma of the esophagus. *Ann Surg Oncol* 2009;16:447–53.
27 Metzger R, Bollschweiler E, Drebber U, *et al*. Neoadjuvant chemoradiotherapy for esophageal cancer: impact on extracapsular lymph node involvement. *World J Gastroenterol* 2010;16:1986–92.
28 Nafteux P, Lerut T, De Hertogh G, *et al*. Can extracapsular lymph node involvement be a tool to fine-tune pN1 for adenocarcinoma of the oesophagus and gastro-oesophageal junction in the Union Internationale contre le Cancer (UICC) TNM 7th edition? *Eur J Cardiothorac Surg* 2014;45:1001–10.
29 Nakano S, Baba M, Shimada M, *et al*. How the lymph node metastases toward cervico-upper mediastinal region affect the outcome of patients with carcinoma of the thoracic esophagus. *Jpn J Clin Oncol* 1999;29:248–51.
30 Paraf F, Fléjou JF, Pignon JP, *et al*. Surgical pathology of adenocarcinoma arising in Barrett's esophagus. Analysis of 67 cases. *Am J Surg Pathol* 1995;19:183–91.
31 Sakai M, Suzuki S, Sano A, *et al*. Significance of lymph node capsular invasion in esophageal squamous cell carcinoma. *Ann Surg Oncol* 2012;19:1911–7.
32 Tachikawa D, Inada S, Kotoh T, *et al*. An evaluation of malignancy and prognostic factors based on mode of lymph node metastasis in esophageal carcinoma. *Surg Today* 1999;29:1131–5.
33 Thompson SK, Ruszkiewicz AR, Jamieson GG, *et al*. Improving the accuracy of TNM staging in esophageal cancer: a pathological review of resected specimens. *Ann Surg Oncol* 2008;15:3447–58.
34 Sergeant G, Ectors N, Fieuws S, *et al*. Prognostic relevance of extracapsular lymph node involvement in pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 2009;16:3070–9.
35 Luchini C, Capelli P, Fassan M, *et al*. Next-generation histopathologic diagnosis: a lesson from a hepatic carcinosarcoma. *J Clin Oncol* 2014;32:e63–6.
36 Luchini C, Veronese N, Solmi M, *et al*. Prognostic role and implications of mutation status of tumor suppressor gene ARID1A in cancer: a systematic review and meta-analysis. *Oncotarget* 2015;6:39088–97.

Extranodal extension of lymph node metastasis is a marker of poor prognosis in oesophageal cancer: a systematic review with meta-analysis

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J Clin Pathol 2016 69: 956-961 originally published online July 7, 2016
doi: 10.1136/jclinpath-2016-203830