

We thank the reviewers for providing constructive feedback. These comments are very helpful to improve the quality of the manuscript. We have fully revised our manuscript (91363). Now I respond to the reviewers' comments point by point and highlight the changes in the revised manuscript. All the page and line numbers refer to the revised version of the manuscript. We sincerely hope that you find our responses and modifications satisfactory.

Reviewer 1:

I read with interest the retrospective study demonstrating that 21 nodes and more harvested improves survival outcomes of ESCC patients. This is a retrospective study including large number of patients and my comments serve to improve the content of report.

1. The abstract has short forms that are not explained to readers what the full forms mean. NRLN and RPLN

Reply: Thank you for your suggestion. We have now included the full forms and a brief explanation of NRLN (Number of Removed Lymph Nodes) and RPLN (Ratio of Positive Lymph Nodes) in the abstract to ensure clarity for our readers. (line 59-61)

2. Line 69 the NCCN statement needs a citation

Reply: Thank you for pointing this out. We have added the appropriate citation for the National Comprehensive Cancer Network (NCCN) guidelines. (line 106)

3. Dissection of node does not mean resection. So use resection to convey removal of node. Dissection is not appropriate.

Reply: Thank you for your suggestions. We have revised the terminology in our manuscript from "dissection" to "resection" to more accurately describe the removal of lymph nodes.

4. Line 89 2 times pathology - pathologically confirmed. Omit one.

Reply: We agree with your observation and have corrected this redundancy by removing the repeated term to streamline the text. (line 126)

5. Line 90-92 exclusion reasons - please tell in brackets how many patients excluded for each reason. This is mandatory as you have a lot of exclusions 1821 minus 1042 patients (about 780 patients are excluded and is a large number that readers need to know.

Reply: We appreciate your insightful suggestion. 1821 patients with esophageal cancer who underwent esophagectomy at Guangdong Provincial People's Hospital and The First Affiliated Hospital of Shantou University Medical College were eligible for further selection. 1470 patients met the inclusion criteria. Patients with a lack of lymph node information (N=364), lack of follow-up information (N=29), positive resection margins (n=22), and death within one month after surgery (N=13) were excluded. We have now detailed the number of patients excluded for each reason within brackets, providing clarity on the cohort composition. (line 126-130)

6. Line 102 you need to define and tell readers what is standard lymphadenectomy, extended lymphadenectomy and total lymphadenectomy. All 3 needs clarification and also tell how many of 1042 patients had which category of lymphadenectomy in your series.

Reply: Thank you for your suggestions. We understand the need for clarity. Definitions for standard, extended, and total lymphadenectomy have been added, along with the distribution of these procedures among the 1042 patients. Based on the International Society for the Diseases of the Esophagus consensus meeting in 1995, the two-field lymph node dissection can be divided into three types: **Standard 2-field lymphadenectomy** encompasses a comprehensive removal of the primary tumor, including a lymphadenectomy that covers the entire posterior mediastinum – from the diaphragm up to the subcarinal nodes and the aortopulmonary window. In the abdomen, this approach includes the

dissection of lymph nodes along the celiac trunk, common hepatic and splenic arteries, and those along the lesser curvature of the stomach and in the lesser omentum; Extended 2-field lymphadenectomy includes all lymph nodes addressed in the standard 2-field, with additional clearance of the nodes in the right paratracheal gutter, extending to include those along the right recurrent nerve and the brachiocephalic trunk; Total 2-field lymphadenectomy expands upon the extended 2-field dissection by also removing the lymph nodes in the left paratracheal gutter, including those alongside the left recurrent nerve. Among the included patients, 519 received standard 2-field lymphadenectomy, 335 received extended 2-field lymphadenectomy, and 188 received total 2-field lymphadenectomy. (line 140-150)

7. Line 133 need to tell age range along with median

Reply: We appreciate the need for a comprehensive demographic profile. The age (median, Interquartile range) has been added. (line 189-190)

8. Is this propensity score matched study? If so this has to be told in title, abstract, and in method section. Also need to add details on what variables were matched for and process of matching and you need to give pre-matching as well as post-matching demography details, clinical details, etc.

Reply: Thank you for highlighting this. We have explicitly stated that this study uses propensity score matching in the title, abstract, and methods section, and included detailed information on the variables used for matching and the matching process. Pre-/post-matching details are included as supplementary tables. (line 1-3, 56, 178-183, Supplementary Table 1)

9. Tables 1 and 2 do not contain a lot of essential details like albumin, comorbidities, weight, nutritional status, hemoglobin, liver function, performance status etc that are relevant in predicting outcomes. Missing too many clinically important prognostic variables.

Reply: Thank you for your insightful feedback regarding the inclusion of additional prognostic variables in Tables 1 and 2. As a retrospective analysis, our ability to include specific variables such as albumin levels, nutritional status, and liver function was constrained by the data that were originally recorded in patient files at the time of treatment. Unfortunately, this limitation meant we were unable to incorporate these potentially significant variables into our analysis.

We acknowledge this as a limitation of our study, which is discussed in the limitations section of our discussion. It is important to note that similar retrospective studies published in reputable journals such as JAMA Surgery and the Journal of the National Cancer Institute (JNCI) have also faced challenges in including these so-called prognostic factors. This observation underscores a common challenge in retrospective oncological research, where the availability of comprehensive historical data can be variable.

This limitation not only clarifies the scope of our findings but also emphasizes the importance of prospective studies where data collection can be more controlled and systematic. Our discussion aims to provide a clear perspective on how the absence of these variables might impact the study outcomes and to guide future research protocols that can address these gaps. (line 352-362)

Reference:

van der Schaaf M, Johar A, Wijnhoven B, Lagergren P, Lagergren J. Extent of lymph node removal during esophageal cancer surgery and survival. J Natl Cancer Inst. 2015 Mar 5;107(5):djv043. doi: 10.1093/jnci/djv043. PMID: 25748792.

Lagergren J, Mattsson F, Zylstra J, Chang F, Gossage J, Mason R, Lagergren P, Davies A. Extent of Lymphadenectomy and Prognosis After Esophageal Cancer Surgery. JAMA Surg. 2016 Jan;151(1):32-9. doi: 10.1001/jamasurg.2015.2611. PMID: 26331431.

10. The figure 4 i am unsure what the 6 graphs means for the 2 subgroups of <21 and >21 nodes. What does each figure mean?

Reply: We apologize for any confusion caused by the presentation of Figure 4 and appreciate the opportunity to provide further clarity. The figure comprises six Kaplan-Meier survival curves that are segmented into two primary cohorts based on the number of lymph nodes resected: those with ≤ 21 nodes removed, and those with > 21 nodes removed.

Within these primary groups, patients are further stratified based on their positive lymph node ratio, which is categorized into three ranges: 0, between 0 and 0.16, and greater than 0.16. This ratio represents the proportion of removed lymph nodes that were found to be cancerous.

The first figure (upper left) pertains to patients with ≤ 21 removed lymph nodes and a positive lymph node ratio of 0, indicating no detectable cancer in the resected nodes. Here, the survival curves for both adjuvant chemotherapy and non-adjuvant groups closely overlap, suggesting no observable survival benefit from adjuvant chemotherapy within this subgroup.

The second figure (upper center) reflects patients with ≤ 21 removed lymph nodes and a positive lymph node ratio between 0 and 0.16. This graph also shows overlapping survival curves, implying a lack of significant survival benefit from adjuvant chemotherapy in this specific context.

The third figure (upper right) shows patients with ≤ 21 lymph nodes removed but a higher positive lymph node ratio of > 0.16 . Unlike the previous graphs, a divergence in the curves indicates a statistical difference in survival favoring the adjuvant chemotherapy group, as evidenced by the log-rank p-value.

The fourth figure (lower left) corresponds to patients with > 21 lymph nodes removed and a positive lymph node ratio of 0. Here, the survival curves demonstrate a similar outcome for patients regardless of adjuvant chemotherapy, indicating no added survival advantage from the treatment for this subgroup.

The fifth figure (lower center) includes patients with > 21 lymph nodes removed

and a positive lymph node ratio between 0 and 0.16. The curves in this scenario suggest a survival benefit for the adjuvant chemotherapy group, as reflected in the log-rank p-value.

The final figure (lower right) focuses on patients with >21 lymph nodes removed with a positive lymph node ratio of >0.16. The survival curves indicate no significant difference between the groups receiving adjuvant chemotherapy and those who did not, as the curves converge.

11. I am also unsure why and how did you determine cut off as 21 nodes and not 15 or 16 or 17 or 18 or 19 etc node number. What is the basis? You have not told how you derived this magic number.

Reply: Thank you for pointing this out. We acknowledge the importance of justifying our methodology. The optimal cutoff values of the total lymph nodes number were determined by the "surv_cutpoint" function of the "survminer" R package. We have mentioned the process of obtaining best cutoff value and provided the supplementary figure to illustrate that 21 is the optimal value. (line 171-172, supplementary Figure 1)

12. The AUC is below 70 which is 'okay, not a very good'. In relation to models, an AUC value of <0.60 means poor discriminatory ability, 0.60–0.80 means moderate discriminatory ability, 0.8–0.9 means good discriminatory ability and a value of >0.9 mean an excellent discriminator between different prediction models. This has to be discussed and acknowledged as a limitation.

Reply: Thank you for your suggestions. We recognize the importance of addressing this issue. The AUC values have been discussed in the context of model performance, and this has been acknowledged as a limitation in our discussion section. (line 317-323)

13. Line 253-254 -- tell why subgroup of patients did not derive benefit from

adjuvant therapy. Why? Discuss this.

& 14. Similarly line 258-261 - why subgroup had worse prognosis despite adjuvant? I.e. adjuvant was harmful? Please discuss why so.

Reply: We thank the reviewer for their astute observations regarding the lack of benefit from adjuvant therapy in certain subgroups as noted on lines 253-254. In our analysis, we observed that patients within the lymph node-negative cohort who underwent extensive lymph node dissection (NRLN>21) exhibited higher long-term overall survival without adjuvant therapy compared to those who received such treatment. One plausible explanation for this finding, which we now explore further in the discussion section, could be the detrimental side effects associated with chemotherapy. These adverse effects can significantly impact the survival of patients, particularly in cases where the surgical outcome is already favorable, such as in patients with no lymph node metastasis and a high number of lymph nodes removed.

Moreover, we appreciate the opportunity to clarify the outcomes observed in the subgroup with NRLN >21 and RPLN >0.16, where no survival benefit was associated with adjuvant chemotherapy. Our analysis suggests that the intensity or efficacy of the adjuvant chemotherapy regimen may not have been sufficient to demonstrate a survival advantage in patients with a more extensive nodal disease, as indicated by a higher RPLN. Despite the extended lymphadenectomy providing a clearer and more comprehensive nodal staging, the adjuvant treatment administered might not have been adequately potent to improve outcomes in this patient subset.

It is also imperative to recognize that the utility of adjuvant chemotherapy in esophageal cancer remains a complex and debated issue within the medical community. The findings related to subgroups in our study underscore the intricate nature of cancer treatment and response, revealing that there is not a one-size-fits-all solution, particularly in a disease as heterogeneous as esophageal cancer.

Reference:

1. Ando, N., et al., Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study--JCOG9204. J Clin Oncol, 2003. 21(24): p. 4592-6.
2. Wong, A.T., et al., The Impact of Adjuvant Postoperative Radiation Therapy and Chemotherapy on Survival After Esophagectomy for Esophageal Carcinoma. 2017. 265(6): p. 1146-1151.
3. Burt, B.M., et al., Utility of Adjuvant Chemotherapy After Neoadjuvant Chemoradiation and Esophagectomy for Esophageal Cancer. Ann Surg, 2017. 266(2): p. 297-304.

15. Could nutrition have a role due to foregut cancers causing eating/nutrition issues secondary to dysphagia or vomiting?

Reply: We agree with the reviewer that nutrition likely plays a crucial role in the treatment outcomes and prognosis of foregut cancers, where dysphagia or vomiting secondary to the malignancy can significantly affect a patient's nutritional status. Recognizing the importance of this factor, we have expanded the discussion in our manuscript to address the potential impact of nutrition on patient outcomes. (line 306-312)

16. There is no mention or discussion about other issues relevant to perioperative care such as advances in anesthesia, pain management, ERAS or prehabilitation protocols similar to other foregut cancers which could impact survival outcomes or perioperative morbidity.

Reply: We appreciate your observations concerning the broader aspects of perioperative care, such as advances in anesthesia, pain management, and Enhanced Recovery After Surgery (ERAS) protocols. While these elements are undoubtedly crucial to patient outcomes, our study primarily focuses on investigating the prognostic value of the extent of lymphadenectomy in

esophageal cancer. Nonetheless, we recognize that perioperative care factors significantly influence patient recovery and morbidity. To address this, we have included a brief discussion on these aspects to contextualize their role within the scope of our study focused on surgical outcomes. (line 301-306)

17. Esophagus surgery is technically complex. Similar to pancreas surgery, 90-day mortality outcomes and 1-year mortality outcomes must be reported. These are key performance indicators of a unit . Please report and also discuss the results. Thanks

Reply: Your emphasis on outcome reporting is well-founded. 12 patients died within 90 days, with a 90-day mortality rate of 1.15%. 130 patients died within 1 year, with a 1-year mortality rate of 12.18%. We have included 90-day and 1-year mortality data and discussed these outcomes in the context of surgery complexity and performance indicators. (line 193-195)

Reviewer 2

Authors performed an examination of the large study group and proved between number of removed lymph nodes and NRLN > 21 was an independent prognostic factor after ESCC surgery. Authors used a meticulous statistical analysis, formed nomograms for confirmation of the discussed hypothesis.

Reply: We are immensely grateful for your encouraging feedback and for recommending the acceptance of our manuscript. It is heartening to know that our efforts to explore the prognostic significance of the number of removed lymph nodes in ESCC surgery have been recognized. We truly appreciate your acknowledgment of the meticulous statistical analysis and the development of nomograms that we employed to confirm our hypothesis.

Revision reviewer

Specific Comments to Authors:nil

Reply: Thanks for your comments.