

Peer review file

Article information: <http://dx.doi.org/10.21037/jtd-20-1388>

Reviewer A:

Comment 1: What is TNM staging for patients with supraclavicular LN?

Reply 1: Considering the Reviewer's suggestion, The staging of patients with positive supraclavicular lymph node metastasis was M1.

Comment 2: Are supraclavicular LNs categorized regional or distal?

Reply 2: Considering the Reviewer's suggestion, Supraclavicular lymph nodes are classified by region According to the AJCC TNM classification.

Comment 3: So current staging of these patients is Stage IVB?

Reply 3: Considering the Reviewer's suggestion, The current staging of these patients is IVB. During the postoperative follow-up, some patients found that supraclavicular lymph nodes were enlarged, and some of them were pathologically confirmed to be positive for supraclavicular lymph nodes.

Comment 4: Introduction is way too long - you should stick to the "what is the issue and why it is a problem"

Reply 4: We are very sorry for our incorrect writing and we have re-written this part according to the Reviewer's suggestion as blow. (see Page 4-5, line 75-109)

Changes in the text: "In China, the incidence of esophageal squamous cell carcinoma (ESCC) is 20.9 out of 100,000, which is the highest in the world [1-3]. At the time of ESCC treatment, most patients are in the middle and late stages, and there are a large number of patients with supraclavicular lymph node metastasis (10.3%-17.6%). Lymph node surgery and radical surgery are considered to be the main diagnostic treatments for patients with resectable ESCC [4-5]. While there have been no strict prospective, randomized, controlled clinical studies to provide supporting evidence, with the use of a lymph node cleaning scope, the greater the surgical effect is, and the better the radical

cure effect; however, the operation risk will also increase, especially in the neck, such as with chest minor cleaning for cervical anastomotic fistula, resulting in laryngeal recurrent nerve injury and a high incidence of respiratory complications, affecting the patients' rapid recovery and quality of life[6-8]. Therefore, How to reasonably choose the range of lymph node dissection for patients with high risk of supraclavicular lymph node metastasis, and to ensure the curative effect while reducing the adverse reactions of surgery is the current problem.

In recent years, there are some "selective minor lymph node cleaning" studies[9-10]were perform , aiming at providing radical surgery, reducing operation risks, improving survival, and making treatment accuracy more robust. However, these studies have some limitations. First, even if preoperative supraclavicular lymph node metastasis was found and immediate salvage treatment was implemented, there was still a lag in treatment. Second, the risk of supraclavicular lymph node metastasis was not objectively quantified, and assessments based on subjective experience are not rigorous enough.

By searching multiple databases, including PubMed, the nomogram model has been widely and successfully used for prediction and survival analyses of a variety of cancers, quantifying risks by considering all known clinical variables, thus allowing individualized risk assessment and prognosis prediction of a variety of cancers[11-18]. However, a prediction model that can be applied for the clinical quantitative assessment [19-20] of supraclavicular lymph node metastasis in terms of the risks of ESCC surgery has not been established. Therefore, in this paper, a nomogram prediction model was established to analyze the known clinical data to quantify supraclavicular lymph node metastasis risk assessment in the postoperative period, aiming to target elderly patients with ESCC (two-field lymphadenectomy) if further retrospective radiation and chemotherapy or supraclavicular lymph node cleaning is needed after surgery and to provide an important reference for treatment decisions.”

Comment 5: I would increase the age to above 70-year-old, reflecting on the frailty of the patients that is sought after in this study (e.g. septuagenarians)

Reply 5: Considering the Reviewer's suggestion, The division of age in this study is mainly based on two considerations. Firstly, this study started in 2008. Before 2012, the United Nations World Health Organization (who) determined the global human quality and average life expectancy, and stipulated the age classification standard, that is, the elderly over 65 years old. Reference can be found in: World Health Day 2012: ageing and health: toolkit for event organizers[J].1.2012,1:10-11.Secondly, the reason why this study focuses on the elderly is that in clinical work, we found that esophageal squamous cell carcinoma is a high incidence in middle-aged and elderly patients, especially the elderly.

Comment 6: You state rejection criteria as M1 disease, but positive supraclavicular nodes ARE M1 disease. Were these patients incidental findings?

Reply 6: It is really true as Reviewer suggested, there patients were incidental findings whose supraclavicular lymph nodes were enlarged, and some of them were pathologically confirmed to be positive for supraclavicular lymph nodes during the postoperative follow-up. We included patients with positive supraclavicular lymph node metastasis during follow-up. We excluded cases whose intraoperative or postoperative pathologically confirmed staging was M1 , that is, no evidence of distant metastasis was found in preoperative examination, but metastasis was confirmed by intraoperative exploration or postoperative pathology.

Comment 7: I understand that preoperative chemoradiation is not utilized in China for Squamous cell cancer, but the audience of this paper is extensive -> i would take this into account.

Reply 7: It is really true as Reviewer suggested. Surgical resection is the best treatment to achieve local control of the disease. However, the 5-year survival rate of stage IIA - III esophageal squamous cell carcinoma treated by surgical resection alone is less than 30%. Many patients have metastasis or local recurrence soon after operation, resulting in unsatisfactory curative effect. The adverse prognosis of surgery alone and the pattern of recurrent disease prompt the addition of neoadjuvant radiotherapy, chemotherapy or

chemoradiotherapy in the treatment plan. The goal of neoadjuvant radiotherapy and chemotherapy is to reduce the tumor size and achieve local control to the maximum extent by using the radiosensitization effect of chemotherapy. But for the tumor patients who are ineffective in neoadjuvant therapy, the timing of surgical resection will be affected, and even the disease progression will occur. Neoadjuvant therapy may increase the incidence of perioperative complications and mortality, especially the incidence of anastomotic leakage and cardiopulmonary complications, and may lead to death related to radiotherapy and chemotherapy toxicity. At present, the efficacy of neoadjuvant therapy still needs to be further verified. In view of this, this study temporarily excluded this part of patients in order to better eliminate the offset. In the future further research, a more representative multi center sample of elderly esophageal squamous cell carcinoma patients will be included to further improve the risk assessment value and survival benefit of the nomogram prediction model.

Comment 8: You lack the limitations of the study segment

Reply 8: We are very sorry for our incorrect writing and We have made correction according to the Reviewer's comments as blow. (see Page 16, line 347-356)

Changes in the text: “We must acknowledge several limitations of this study. First, The current study was a retrospective design of a small population. Potential biases were inevitable because of the retrospective nature of our study. Although some advanced statistical methods were applied to balance the covariates among the arms, there were still some latent biases. Secondly, the risk stratification of postoperative supraclavicular lymph node metastasis is not mature. Most importantly, this study only included single center samples to establish the nomogram model. In future further research, a more representative multi center sample of elderly patients with esophageal squamous cell carcinoma is needed to further improve the risk assessment value and survival benefit of the nomogram prediction model.”

Comment 9: You should also write clear "conclusion" paragraph

Reply 9: We are very sorry for our incorrect writing and We have made correction according to the Reviewer's comments as blow. (see Page 16-17, line 357-365)

Changes in the text: "In conclusion, our results provide preliminary evidence that postoperative lymph node metastasis, vascular tumor thrombus, and tumor infiltration are independent risk factors for the development of supraclavicular lymph node metastasis in ESCC radical surgery based on the mathematical models of the column chart; these factors can be used to analyze risk assessment and survival in patients with indicators, as well as the risk of radical chest lymph node removal with two-field lymphadenectomy if further retrospective radiation and chemotherapy are needed postoperatively in patients with ESCC or supraclavicular lymph node cleaning treatment to provide a quantitative basis of risk."

Comment 10: I would be tempted to argue that neoadjuvant chemo-radiation would increase overall survival for these patients and would be more appealing to study than initial surgery with LN clearance during the same operation.

Reply 10: It is really true as Reviewer suggested that neoadjuvant chemo-radiation would increase overall survival for these patients and would be more appealing to study than initial surgery with LN clearance during the same operation, However, patients with esophageal squamous cell carcinoma who have supraclavicular lymph node metastasis have a poor prognosis. Even if supraclavicular lymph node metastasis is found before surgery, the corresponding salvage treatment will still be lagging behind. This article aims to calculate the risk of supraclavicular lymph node metastasis, screen high-risk elderly patients with lymph node metastasis, and then adopt treatments including neoadjuvant chemo-radiation to improve treatment efficiency.

Comment 11: Also, please reflect on both Chinese and Western publications on this matter: <https://onlinelibrary.wiley.com/doi/pdf/10.1111/1759-7714.13144>

Reply 11: As suggested by the reviewer, the Western article reviews the treatment strategies and results of patients with different lymph node status, and concludes that

the clinical significance of supraclavicular and abdominal lymph node metastasis of thoracic esophageal cancer should be reevaluated according to the primary site using different prognostic information.

In this paper, we calculated the risk of supraclavicular lymph node metastasis in elderly patients, and then gave different prognosis guidance for individuals with different risk. Although the intention of the article is different, it can provide a reference for the choice of treatment strategy of supraclavicular lymph node. The conclusions of the two papers have certain reference significance to each other.

Reviewer B:

The manuscript does need significant editing. For instance, ESCC is mentioned in the title without spelling its meaning. ESCC is not a worldwide recognized abbreviation for esophageal squamous cell cancer and should be spelled first.

More importantly, the background and the objective of the study should be stated more clearly. The inclusion criteria of Ivor Lewis esophagectomy without prior neoadjuvant treatment is very important to orient the reader to the study population. On that note, why limit the comparison to elderly patients only? A nomogram and predictors of SCLN would be helpful for all patients with sq. cell cancer of the esophagus, not just those above 65 years of age.

Not sure what is meant by vascular thrombectomy (vascular tumor thrombus?) or tumor infiltration, of what? What is organization infringement in the conclusion section? The conclusion seems to go over board, compared with the results section of the abstract.

Note worthy too that the prognostic indicators found by the authors (for instance pathological positive lymph nodes) are mostly helpful after surgery, and do not really help with pre-operative decision making on whether to proceed with neck dissection.

Additionally, there is no data on tumor location in the study population, clinical stage pre or post-operatively, tumor differentiation, etc.

The figures with the multiple different colors do not read well either.

Comment 1: The manuscript does need significant editing. For instance, ESCC is

mentioned in the title without spelling its meaning. ESCC is not a worldwide recognized abbreviation for esophageal squamous cell cancer and should be spelled first.

Reply 1: Thank you very much for your careful review and valuable comments, and We have made correction according to the Editor's comments. For instance, The abbreviation ESCC is spelled completely in the title as esophageal squamous cell carcinoma. (see Page 1 line 2)

Changes in the text: "Supraclavicular lymph node metastasis in elderly patients undergoing esophageal squamous cell carcinoma radical surgery: Construction of risk and prognostic predictive nomograms"

Comment 2: More importantly, the background and the objective of the study should be stated more clearly. The inclusion criteria of Ivor Lewis esophagectomy without prior neoadjuvant treatment is very important to orient the reader to the study population.

Reply 2: We are very sorry for our incorrect writing and we have re-written this part according to the Reviewer's suggestion as below. (see Page 4-5, line 75-109)

Changes in the text: "In China, the incidence of esophageal squamous cell carcinoma (ESCC) is 20.9 out of 100,000, which is the highest in the world [1-3]. At the time of ESCC treatment, most patients are in the middle and late stages, and there are a large number of patients with supraclavicular lymph node metastasis (10.3%-17.6%). Lymph node surgery and radical surgery are considered to be the main diagnostic treatments for patients with resectable ESCC [4-5]. While there have been no strict prospective, randomized, controlled clinical studies to provide supporting evidence, with the use of a lymph node cleaning scope, the greater the surgical effect is, and the better the radical cure effect; however, the operation risk will also increase, especially in the neck, such as with chest minor cleaning for cervical anastomotic fistula, resulting in laryngeal recurrent nerve injury and a high incidence of respiratory complications, affecting the patients' rapid recovery and quality of life[6-8]. Therefore, How to reasonably choose the range of lymph node dissection for patients with high risk of supraclavicular lymph node metastasis, and to ensure the curative effect while reducing the adverse reactions

of surgery is the current problem.

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Comment 3: On that note, why limit the comparison to elderly patients only? A

nomogram and predictors of SCLN would be helpful for all patients with sq. cell cancer of the esophagus, not just those above 65 years of age.

Reply 3: Thank you very much for your careful review and valuable comments , The division of age in this study is mainly based on two considerations. Firstly, this study started in 2008. Before 2012, the United Nations World Health Organization (who) determined the global human quality and average life expectancy, and stipulated the age classification standard, that is, the elderly over 65 years old. Reference can be found in: World Health Day 2012: ageing and health: toolkit for event organizers[J].1.2012,1:10-11.Secondly, the reason why this study focuses on the elderly is that in clinical work, we found that esophageal squamous cell carcinoma is a high incidence in middle-aged and elderly patients, especially the elderly.

Comment 4: Not sure what is meant by vascular thrombectomy (vascular tumor thrombus?) or tumor infiltration, of what? What is organization infringement in the conclusion section?

Reply 4: Thank you very much for your careful review and valuable comments, We are very sorry for our incorrect writing and we have made correction according to the Reviewer's comments. All the vascular thrombectomy mentioned in the manuscript were changed to tumor thrombus. Tumor infiltration and organization infilling are the same concept, which refers to the phenomenon that tumor cells and extracellular matrix interact with each other under the regulation of various factors of host, so as to distribute abnormally in the tissue space. It is the performance of a series of processes such as tumor cell adhesion, enzyme degradation, migration, and matrix proliferation. It is related to the biological characteristics of tumor cells, the role of surrounding stroma and local immunity.

Comment 5: The conclusion seems to go over board, compared with the results section of the abstract.

Reply 5: Thank you very much for your careful review and valuable comments, We are very sorry for our incorrect writing and we have made correction according to the

Reviewer's comments as below. (see Page 2-3, line 46-52)

Changes in the text: "Postoperative lymph node metastasis, tumor thrombus and tumor invasion are independent risk factors for recurrence and metastasis of supraclavicular lymph nodes in elderly patients with esophageal squamous cell carcinoma. The nomogram model based on these factors provides a preliminary reference for individualized risk assessment, prognosis guidance and decision-making of supraclavicular lymph node metastasis in elderly patients with esophageal squamous cell carcinoma (ESCC)."

Comment 6: Note worthy too that the prognostic indicators found by the authors (for instance pathological positive lymph nodes) are mostly helpful after surgery, and do not really help with pre-operative decision making on whether to proceed with neck dissection.

Reply 6: Thank you very much for your careful review and valuable comments, We must acknowledge several limitations of this study. First, the current study is a retrospective design of a small group. Due to the retrospective nature of our research, potential biases are inevitable. Although some advanced statistical methods are used to balance the covariates between the arms, there are still some potential deviations. Most importantly, this study only uses a single-center sample to establish a nomogram model. Therefore, in the process of data analysis, we found that the preoperative clinical indicators of patients are not risk factors for supraclavicular lymph node metastasis, which makes our predictions limited. However, with the rapid development of pathology technology and equipment, I believe that we can quickly perform intraoperative frozen pathological detection of lymph nodes and other specimens to achieve the goal of intraoperative prediction. At the same time, in future further research, a more representative sample of elderly patients with esophageal squamous cell carcinoma will be included to further improve the risk assessment value and survival benefit of the nomogram prediction model, and to make up for the shortcomings you mentioned.

Comment 7: Additionally, there is no data on tumor location in the study population, clinical stage pre or post-operatively, tumor differentiation, etc.

Reply 7: Thank you very much for your careful review and valuable comments, We have uploaded the relevant data according to the Reviewer's suggestion.

Comment 8: The figures with the multiple different colors do not read well either.

Reply 7: Thank you very much for your careful review and valuable comments, We have made a more detailed explanation of the annotation of the figures, in order to provide you with a better interpretation of the figures.