

Peer Review File

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Reviewer A

The authors have retrospectively evaluated the impact of extended N2 MLND in patients with GGO lesions with a consolidation tumor ratio (CTR) of 0.3–0.7.

After a quick review of the literature, there are different scientific papers about this issue. Thus, the manuscript does not add more to the general knowledge on this subject. The Authors did not perform a literature review to compare their results with that of other authors more experienced.

Finally, the manuscript is written well enough, and the English language needs to be checked to avoid only minor grammar mistakes.

The authors retrospectively reviewed 138 patients with a CTR of 0.3–0.7. They were divided into the following two groups by MLND: limited N2 MLND (<3 N2 stations; n=38) and extended N2 MLND (≥ 3 N2 stations; n=100).

The Authors did not perform a literature review to compare their results with that of other authors more experienced.

My recommendation to the authors is for a further major revision. Probably it is needed to better select and analyze their data.

According to Michaelson HB (1) the elements required for a high-quality manuscript could be summarized as below:

- a) Scientific content: 10 points (maximum 20 points)
- b) Validity of the results: 10 points (maximum 20 points)
- b) Importance of results: 10 points (maximum 20 points)
- d) Organization: 10 points (maximum 20 points)
- e) Literary style: 10 points (maximum 20 points)

Overall manuscript rating: 50 points (Range 1-100).

1) Michaelson H.B., How to write and publish engineering papers and reports, Phoenix, Oryx Press, 3rd ed., 1990.

Reply:

It is great honor to have your comments about our study. We appreciate all your assessments in detail. As you mentioned, this study has several drawbacks, and it is mostly due to its retrospective design and small sample size. However, this study compared the extent of MLND in terms of long-term and postoperative outcomes. Though there are many studies comparing MLND and lymph node metastasis among GGO or solid dominant, there is not many for pulmonary lesions with comparable two different radiologic characteristics. As we tried to focus on lesions with CTR around 0.5, this study still has some value to add evidence related to this subject. It would be appreciated if our study is published in your journal and adds more knowledge in terms of early-lung cancer with GGO. We addressed following comments from seven reviewers. Thank you for giving this opportunity.

Reviewer B

I thank the Editor to give me the opportunity to review this interesting paper about the mediastinal lymphadenectomy in stage I adenocarcinoma (GGO). The study is well written; however, I have few questions for the authors:

Comment 1: How the authors have chosen the cut-off of 3 mediastinal stations to split the patients in the different group? IALSC recommendations stated that at least 3 mediastinal stations of which mandatory station 7 must be resected, all the patients included in the study underwent station 7 dissection?

Reply 1:

Thank you for your insightful comment. Regarding the completeness of MLND, there are several guidelines from different surgical societies. The following table is reproduced with permission from Osarogiagbon et al. (1).

Table 1 Minimum recommended surgical mediastinal lymph node staging quality parameters

Tumor location	Guideline group and recommended surgical lymph node collection stations				
	ACOSOG (33)	CoC (34)	ESTS (32)	IASLC (31)	NCCN (35)
Right lung					
Upper	2R, 4R, 7, 10R	≥10	2R, 4R, 7	3, 4R, 7	≥3 N2 stations
Middle	Same	Nodes*	Same	Same	
Lower	Same		4R, 7, 8, 9	3, 4R, 7, 8, 9	
Left lung					
Upper	5, 6, 7, 10L	≥10	5, 6, 7	3, 5, 6, 7	≥3 N2 stations
Lower	Same	Nodes*	7, 8, 9	7, 8, 9	

*, no nodal station specification. ACOSOG, American College of Surgeons Oncology Group; CoC, American College of Surgery Commission on Cancer; ESTS, European Society of Thoracic Surgeons; IASLC, International Association for the Study of Lung Cancer; NCCN, National Comprehensive Cancer Network; L, left; R, right.

As you can see above, MLND of three N2 stations can be commonly recognized as a key component for complete MLND. Therefore, we applied this same criterion to evaluate the quality of MLND. Among 38 patients in the extended N2 MLND group, 36 had their station 7 removed. Therefore, it meets the criteria from the IASLC also. We think different perspectives on the quality of MLND should be also considered and defined three or more N2 MLND as the extended N2 MLND group.

Changes in the text:

We have modified our text as advised to give more explanation in background and method.

(Revised Line 77-82, 115-119)

Comment 2: The authors analyze the GGO lesions but the solid component should be specified. Indeed, in some cases, despite a little part solid of the lesion the tumor had the visceral pleura infiltrated.

Reply 2:

We truly agree with your suggestion and presented data about the solid portion size in Table 1 and 2.

Changes in the text:

We have modified our table as advised.

(Revised Table 1 and 2, Line 327, 336)

Reviewer C

In this study, the authors compared mediastinal lymph node dissection involving ≥ 3 stations (extended dissection) and dissection involving fewer stations with regard to prognosis of stage I adenocarcinoma with a consolidation/tumor ratio (CTR) ranging from 0.3 to 0.7. Additionally, the authors compared the incidence of complications between the aforementioned groups.

In my opinion, the following concerns should be addressed before the manuscript could be considered for publication:

Comment 1: It is necessary to clearly describe the rationale to set the target CTR range as 0.3–0.7. Previous studies have reported that dissection is ineffective in patients with CTR < 0.5 and use of this CTR value in the study population complicates result interpretation.

Reply 1:

We appreciate your comment. In previous studies about GGO, CTR under 0.25 was recognized as a radiologically non-invasive pulmonary lesion. And CTR over 0.75 was also recognized as solid-predominant group. However, these criteria are still not generalized and need to be improved. Also, the preciseness of CTR measurement based on axial two-dimensional image is still debatable; it can be different from three-dimensional analysis.

The reason why that we applied 0.3 to 0.7 criterion was to analyze patients with comparably significant GGO and solid component. These lesions can not be classified as GGO or solid dominant. We attempted to focus on lesions with CTR around 0.5.

Changes in the text:

We added further explanations regarding this as advised.

(Revised line 89-90, 100-101)

Comment 2: Considering the limited number of cases included in the study, the relevance of performing further subgroup analysis is questionable. However, tumor size and fluorodeoxyglucose accumulation are important prognostic factors and should be analyzed if possible.

Reply 2:

Yes. We truly agree with your opinion. Even though the sample size is not big enough, we performed propensity-score matching for tumor size, PET activity, and surgical extent. After the propensity score matching, both groups (33 patients in each group) did not exhibit difference in clinical outcome (Figure 2). Therefore, we believe that impacts on early postoperative complication should be considered in these specific groups when we perform mediastinal lymph node dissection.

Changes in the text:

We added further analysis, figure and changed text as advised

Revised line 38-40, 44-45, 124-126, 148-152, Table 2, Figure 2

Comment 3: In my opinion, inclusion of both lobectomy and segmental lung resection as surgical procedures is a concern that should be addressed (in fact, previous studies have reported high local recurrence rates associated with segmental resection).

Therefore, it is possible that the comparison was made between different populations owing to potential differences in background factors.

Reply 3:

That is important point. As we answered in previous comment, we performed subgroup analysis after propensity score matching. I hope this can give you further information regarding the impact of MLND extent. In addition, we think that we need more patients to compare the impact of sublobar resection and lobectomy. This was added in our limitation. Thank you for your suggestions.

Changes in the text:

We added further analysis, figure and changed text as advised

Revised line 38-40, 44-45, 124-126, 148-152, 213-216, Table 2, Figure 2

Comment 4: Lymph node dissection is important not only for local control but also for accurate evaluation of the N-factor to determine disease stage. Therefore, it is necessary to confirm the accuracy of staging in addition to assessment of prognosis, and evaluation of the rates of N1 or N2 metastasis is important for patients with CTR 0.3–0.7.

Reply 4:

Thank you. We truly believe that accurate staging with N1 or N2 node evaluation is a critical component of surgery. In our study population, median number of N1, N2, and total dissected lymph nodes were 3, 3, and 7, respectively. We think this number is

sufficient for pulmonary lesions with CTR 0.3-0.7. In a recently published prospective study about lobe-specific MLND by Zhang et al., they even did not perform MLND for lesions with CTR under 0.5 (2). We believe it is very difficult to make a decision regarding accurate staging without compromising clinical results in MLND. We just would like to emphasize the need for different criteria for pulmonary lesions with significant proportion of GGO. We need more studies to be done in this topic. Thank you for your comments.

Reviewer D

This study aimed to evaluate the impact of extended N2 MLND in patients with GGO lesions with a consolidation tumor ratio (CTR) of 0.3–0.7. The authors concluded that GGO lesions with a CTR of 0.3–0.7, the extended MLND strategy may not be optimal in terms of clinical outcome. It could lead to more frequent early complications with no oncologic benefits. Due to the limited number of cases in this study, further prospective research on MLND for part-solid lesions is required.

This study is very interesting.

I also think that the extent of the lymph node dissection for tumors with GGO should be more minimized.

However, I have several questions about this article.

Comment 1: Why were tumors with a CTR (0.3-0.7) investigated in this study? Do you have the previous report of study targeting similar CTR (0.3-0.7)? Please tell me.

Reply 1:

We appreciate your comment. In previous studies with GGN, CTR under 0.25 was recognized as a radiologically non-invasive pulmonary lesion. And CTR over 0.75 was also recognized as solid-predominant group. However, these criteria are still not generalized and need to be improved. Also, the preciseness of CTR measurement based on axial two-dimensional image is still debatable; it can be different from three-dimensional analysis.

The reason why that we applied 0.3 to 0.7 criterion was to analyze patients with comparably significant GGO and solid component. These lesions can not be classified as GGO or solid dominant. We attempted to focus on lesions with CTR around 0.5.

Changes in the text:

We added further explanations regarding this as advised.

(Revised line 89-90, 100-101)

Comment 2: You should show the criteria for performing a limited N2 dissection or an extended N2 dissection in this study.

Reply 2:

Thank you for your comment. As this study is based on retrospective review of our record, we cannot give a definite criterion for applying different MLND strategies. However, there are several factors that could influence the MLND strategy from our experience. First, radiologic characteristics of tumor was important factor. As our table shows the difference in solid component size, we applied extended N2 dissection for lesions with large solid lesions over 5mm. Second factor is surgeons' preferences or discretion based on patients' risk factors such as cardiovascular or respiratory disease. Third, intraoperative frozen biopsy results were also used to make a decision. If minimally invasive adenocarcinoma is diagnosed, further MLND was avoided.

Changes in the text:

We added further explanations regarding this as advised.

(Revised line 108-119)

Comment 3:

I think the details of postoperative complications should be shown. And it is necessary to confirm whether the complications are related to MLND.

Reply 3:

We agree with your opinion. Therefore, we further added information regarding the details of postoperative complications. Most of them were prolonged air leakage requiring chemical pleurodesis. The numbers were not sufficient to check whether the different MLND strategy affected the development of PoC. However, chylothorax and recurrent laryngeal nerve damage in the extended group could explain possible negative impacts of it.

Changes in the text)

We added further explanations regarding this as advised.

(Revised line 158-160, Table 1, Table 2)

Comment 4:

I think it is necessary to describe the comparison of preoperative comorbidities between the two groups.

Reply 4:

Thank you. As there was no significant difference regarding preoperative comorbidities, we excluded in the presentation. For a better understanding, here we added information related to patients' medical history.

Changes in the text) Table 1 and 2

Comment 5:

This trial compares 38 and 100 patients, is it statistically power enough?

Reply 5:

Due to limited number of patients, we also agree that it is still early to draw conclusion based on our data. However, this type of approach could be further validated in the long-term and we expect others do perform similar studies. We described our small number as one of the limitations in this study.

Reviewer E

Woo et al performed retrospective analysis of patients who had stage I GGO with solid component who underwent removal of 3 or more vs < 3 N2 lymph node dissection and evaluated the long term survival and complications in their study "Impact of extended mediastinal lymph node dissection for stage I ground-glass opacity lesions." The manuscript can be improved with following

Comment 1:

Clarify why 3 N2 LN station was used as cutoff

Reply 1:

Thank you for your insightful comment. Regarding the completeness of MLND, there are several guidelines from different surgical societies. The following table is reproduced with permission from Osarogiagbon et al. (1).

Table 1 Minimum recommended surgical mediastinal lymph node staging quality parameters

Tumor location	Guideline group and recommended surgical lymph node collection stations				
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Upper	2R, 4R, 7, 10R	≥10	2R, 4R, 7	3, 4R, 7	≥3 N2 stations
Middle	Same	Nodes*	Same	Same	
Lower	Same		4R, 7, 8, 9	3, 4R, 7, 8, 9	
Left lung					
Upper	5, 6, 7, 10L	≥10	5, 6, 7	3, 5, 6, 7	≥3 N2 stations
Lower	Same	Nodes*	7, 8, 9	7, 8, 9	

*, no nodal station specification. ACOSOG, American College of Surgeons Oncology Group; CoC, American College of Surgery Commission on Cancer; ESTS, European Society of Thoracic Surgeons; IASLC, International Association for the Study of Lung Cancer; NCCN, National Comprehensive Cancer Network; L, left; R, right.

As you can see above, MLND of three N2 stations can be commonly recognized as a key component for complete MLND. Therefore, we applied this same criterion to evaluate the quality of MLND. We think different perspectives on the quality of MLND should be also considered and defined three or more N2 MLND as the extended N2 MLND group.

Changes in the text:

We have modified our text as advised to give more explanation in background and method.

(Revised Line 77-82, 115-119)

Comment 2:

Clarify MLND mean full dissection of the lymph node station or sampling of lymph node

Reply 2:

Thank you. MLND here implies that full dissection of lymph nodes stations. We revised our text to clarify.

Changes in the text:

We have modified our text as advised.

(Revised Line 115-119)

Comment 3:

Patient with "extended N2" have significantly larger tumor with larger solid lesion. Please perform a propensity match analysis. Please perform UV and MV analysis for survival.

Reply 3:

Yes. We truly agree with your opinion. Even though the sample size is not big enough, we performed propensity-score matching for tumor size, PET activity, and surgical extent. After the propensity score matching, both groups (33 patients in each group) did not exhibit difference in clinical outcome (Figure 2). In risk factor UV and MV analysis for RFS, patients' history of cardiovascular disease was found as a sole significant factor. Impacts of extended N2 MLND on long-term outcomes was not obvious. Therefore, we believe that impacts on early postoperative complication should be considered in these specific groups when we perform mediastinal lymph node dissection.

Changes in the text:

We added further analysis, figure and changed text as advised

Revised line 38-40, 44-45, 124-126, 148-152, Table 2 and 3, Figure 2

Comment 4:

Please add details of postoperative complications - need to understand if this is related to the different dissection vs most patients who had "extended N2" had lobectomy compared to "limited N2". Since patients who undergo lobectomy have higher complication vs wedge resection, the postoperative complication may be due to difference in the extent of resection

Reply 4:

We agree with your opinion. Therefore, we further added information regarding the details of postoperative complications. Most of them were prolonged air leakage requiring chemical pleurodesis. The numbers were not sufficient to check whether the different MLND strategy affected the development of PoC. However, chylothorax and recurrent laryngeal nerve damage in the extended group could explain possible negative impacts of it.

Changes in the text:

We added further explanations regarding this as advised.
(Revised line 158-160, Table 1, Table 2)

Comment 5:

Please clarify the length of follow up for patients.

Reply 5:

Thank you. We added information related to follow-up duration in the table.

Changes in the text:

We added further explanations regarding this as advised.
(Revised line 138, Table 1, Table 2)

Reviewer F

Comment 1:

It is unclear that why the authors included patients with CTR 0.3-0.7 carcinoma. That is not a common standard. So, it is difficult to generalize their results.

Reply 1:

We appreciate your comment. In previous studies with GGN, CTR under 0.25 was recognized as a radiologically non-invasive pulmonary lesion. And CTR over 0.75 was also recognized as solid-predominant group. However, these criteria are still not generalized and need to be improved. Also, the preciseness of CTR measurement based on axial two-dimensional image is still debatable; it can be different from three-dimensional analysis.

The reason why that we applied 0.3 to 0.7 criterion was to analyze patients with comparably significant GGO and solid component. These lesions can not be classified

as GGO or solid dominant. We attempted to focus on lesions with CTR around 0.5.

Changes in the text :

We added further explanations regarding this as advised.

(Revised line 89-90, 100-101)

Comment 2:

The difference between "Extended" and "systemic" is not unclear. The latter is the more common definition.

Reply 2:

We appreciate your suggestion. Systemic MLND has been used more consistently in other studies. However, it is based on the pattern that which stations are removed and mostly includes station 7 removed. It is usually compared with Lobe-specific MLND. However, here we applied the number of N2 node stations which were dissected to compare the extent of N2 MLND. We added further description to clarify this.

Changes in the text:

We have modified our text as advised to give more explanation in background and method.

(Revised Line 115-119)

Comment 3:

Patient backgrounds of the two groups in this study are different, making comparisons difficult.

Reply 3:

Yes. We truly agree with your opinion. Even though the sample size is not big enough, we performed propensity-score matching for tumor size, PET activity, and surgical extent. After the propensity score matching, both groups (33 patients in each group) did not exhibit difference in clinical outcome (Figure 2). Impacts of extended N2 MLND on long-term outcomes was not obvious. We hope this additional analysis give you further explanation regarding difference in patient backgrounds.

Changes in the text:

We added further analysis, figure and changed text as advised

Revised line 38-40, 44-45, 124-126, 148-152, 213-216, Table 2, Figure 2

Comment 4:

It is obvious that there is no difference in outcome because the subject was only patients with stage I disease.

Reply 4:

Thank you for your comment. This study population is composed of very early-stage

lung cancer. Therefore, it is hard to expect to have many events such as mortality or recurrence. However, we think it is still important to improve surgical outcome among these patients. With the expansion of lung cancer screening program, we expect that we will continue to have these types of patients with GGO proportions. We would like to find an optimal surgical strategy for these patients.

Reviewer G

This is a study which examining the postoperative outcome according to the extent of mediastinal lymph node dissection in patients with stage I lung adenocarcinoma with GGO.

Based on the results of previous studies, the frequency of mediastinal lymph node metastasis in the patients of this study is estimated to be about 1%. Therefore, the number of cases in this study (n=138) is too small to validate the outcome in mediastinal lymph node dissection. In fact, no mediastinal lymph node metastasis seems to have been observed in this study. (To begin with, although the study included patients with stage I lung adenocarcinoma, it is unclear whether this was clinical stage or pathological stage). In addition, since this study only examined the number of lymph node stations, it is not possible to examine which stations should be dissected. This study is also highly influenced by selection bias.

My Comments are listed below.

Comment 1:

Abstract (lines 34-35)

The number of cases in the limited N2 MLND group and the extended N2 MLND group are reversed from Table 1. Please confirm.

Reply 1:

Thank you for your detailed review and apologize for our mistake. We corrected it.

Changes in the text)

Revised line 36.

Comment 2:

This study includes patients who underwent mediastinal lymph node dissection. Does the author's institution routinely perform mediastinal lymph node dissection even when wedge resection is performed?

Reply 2:

Yes. We applied same mediastinal lymph node dissection strategy in sublobar resection. However, the number of stations assessed depend on various factors such as patients risk factor, surgeon's preference, or intraoperative frozen biopsy. We added further information regarding our MLND strategy in the text.

Changes in the text:

We revised as advised.

Revised line 115-119

Comment 3: (Table 1)

Why are there so few cases in the PET-CT and postoperative complications section? I think that it is better to exclude all cases with insufficient information.

Reply 3:

Thank you for your comment. There were 23 patients who did not undergo PET-CT and 5 patients' medical records were not sufficient to determine whether they had complications during hospitalization. For early-stage lung cancer patients, the benefit of routine PET-CT is questionable. In this study cohort, 47 patients (34.0%) had no activity on PET scan. Therefore, we think this number would not affect the entire results as PET would not be critical in patients with large GGO component.

For 5 patients without medical records about their postoperative complications, they seemed to have not experienced complications. However, we think that these numbers would not affect the entire results.

Comment 4: (Table 1)

What is the definition of the classification of FDG accumulation on PET-CT? It would be better to use "SUVmax" or "Deauville score" for classification.

Reply 4:

Thank you. We applied SUVmax to classify patients' PET-CT results. We added further information in the table.

Changes in the text:

Table 1 and 2.

Comment 5: (Table 1)

What about histopathological findings such as histological subtype, STAS, lymphatic invasion, venous invasion, etc.?

Reply 5:

Thank you. We added more information related to pathologic results.

Changes in the text:

Table 1 and 2.

Comment 6:

Details of postoperative complications should be described.

Reply 6:

We agree with your opinion. Therefore, we further added information regarding the details of postoperative complications. Most of them were prolonged air leakage requiring chemical pleurodesis. The numbers were not sufficient to check whether the different MLND strategy affected the development of PoC. However, chylothorax and recurrent laryngeal nerve damage in the extended group could explain possible negative impacts of it.

Changes in the text:

We added further explanations regarding this as advised.

(Revised line 158-160, Table 1, Table 2)

Comment 7:

In this study, there were 12 cases with postoperative complications. In Table 2, a multivariable analysis is performed on risk factors for postoperative complications, but the variables of multivariable analysis should be approximately one-tenth of the number of events. Therefore, a maximum of two variables for multivariate analysis would be appropriate in this study.

Reply 7:

Thank you. In the multivariate analysis, two factors were found significant in postoperative complications. I hope this can give you further information.

Comment 8:

English editing should be performed by native English speakers.

Reply 8:

Thank you very much. This article was edited by an editing service.

References

1. Osarogiagbon RU, Hilsenbeck HL, Sales EW et al. Spencer D. Improving the pathologic evaluation of lung cancer resection specimens. *Transl Lung Cancer Res.* 2015 Aug;4(4):432-7. doi: 10.3978/j.issn.2218-6751.2015.07.07. PMID: 26380184; PMCID: PMC4549477
2. Zhang Y, Deng C, Zheng Q et al. Selective Mediastinal Lymph Node Dissection Strategy for Clinical T1N0 Invasive Lung Cancer: A Prospective, Multicenter, Clinical Trial. *J Thorac Oncol* 2023;S1556-0864(23)00138-7.