Peer Review File

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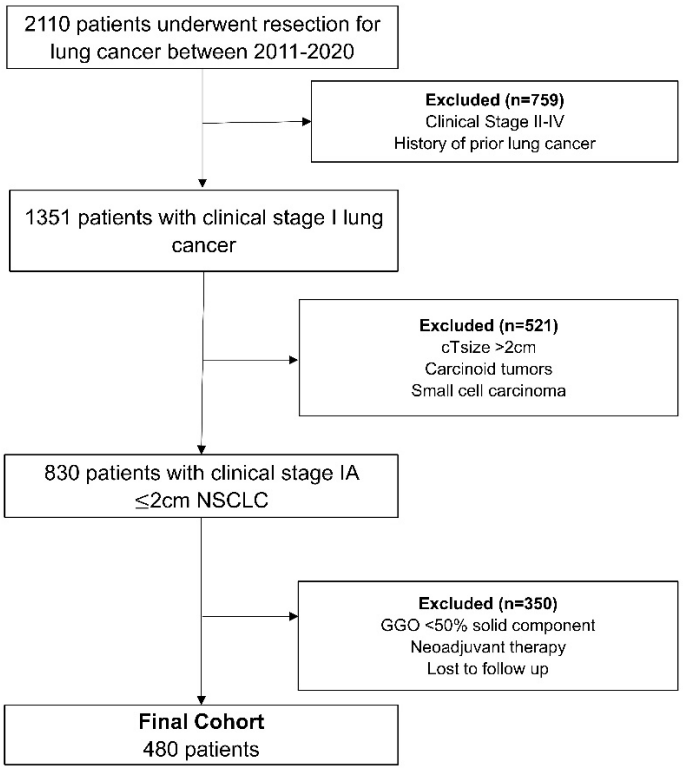
Reviewer A

The reviewer is honored to review an article about the extent of surgical resection in lung cancer. As the authors stated in the limitation of the manuscript, this study was a retrospective study with approximately 500 clinical stage 1A1 and 1A2 NSCLC in a single institution, which potentially included several limitations. However, the results of this study were overall consistent with the 2 large scale randomized clinical trials (JCOG0802 and CALGB 140503). This study was well constructed and easy to understand, but there are several points to be revised, as follows:

1) In supplementary Figure 1, “from 2011-2020” should be “between 2011 and 2020”. “Stage 2-4“, “stage I”, and “stage 1A” should be unified.

<u>Author’s response:</u> We thank the reviewer for the comments. We have modified the supplementary figure 1 as suggested. A new figure was submitted (see below).



2) In methods, the authors excluded patients with GGO with less than 50% solid component. Is it necessary? Tumor size (equal to or less than 2 cm) was determined by the size of solid component.

<u>Author’s response:</u> A lot of the cohort was treated prior to AJCC TNM 8th edition

was established, and so the clinical tumor size is based on both solid and part solid components. Based on the literature, individuals with a higher solid component ratio had worse prognosis and so if we included patients with pure GGO or <50% solid component we might have skewed our survival results to a better prognosis.

3) In the first sentence of the discussion, the authors stated "large", but this study is not based on the large cohort. Please delete this word.

Author's response: These changes have been made as advised (see page 8, line 158).

Reviewer B

As noted by the authors, there has been a large number of similar studies in recent years on the extent of lung resection for sub-2 cm non-small cell lung cancer.
In this situation, the study is not unique in its methodology in terms of patients, endpoints, or study items, and the results do not reveal any new findings unfortunately.

Author's response: While we appreciate this reviewer's time in reviewing this paper and the expressed opinion, we respectfully disagree with the implied assertion that only studies with unique methodology and new findings are worthy of publication. The long-standing controversy regarding the extent of resection for early-stage NSCLC is of critical importance, especially given the recent randomized trial results of JCOG and CALGB. Studies of how these practices play out in real-world cohorts outside of the strict clinical trial settings are – at least in our opinion – entirely worthwhile for such a common clinical scenario. For us, the findings of our study demonstrating that these patients achieve similar oncologic and survival outcomes regardless of extent of resection, despite the fact that the population selected for sublobar resections have worse baseline pulmonary function and performance status, is still an important and timely message (see page 8, lines 161-166).

Reviewer C

In this study, basically authors are saying that:
They did smaller resections to wedge and segmentectomy to patients with worse pulmonary function capacity. The outcomes were found to be similar. So they do not think doing a wedge or a segmentectomy to a patient with poor pulmonary function in patients with lung cancer smaller than 2 cm.

1- Patients who underwent wedge resection had smaller mean pathologic tumor size compared to segmentectomy and lobectomy; 1.23cm vs. 1.50cm and 1.76cm, respectively. (Shows groups are not uniform)
2- Nodal upstaging was significantly greater for lobectomy compared with sublobar resection. N1 upstaging was observed in 1.1% of wedge resection, 3.3% of

segmentectomy, and 6.4% of lobectomy, and N2 upstaging was observed in 1.1%, 4.4%, and 5.1%, 110 respectively (P<0.05). (shows groups are not uniform)

Author's response: **We thank the reviewer for the additional comments. In comments 1 and 2, we agree that the groups are not uniform, this is a retrospective study and so this certainly reflects a degree of patient selection bias. To us, this bias is important to recognize and document as it reflects how surgeons may be inclined to determine extent of resection and we have further clarified this in the discussion (see page 8, line 160-166).**

3- Factors associated with worse DFS on univariate analysis were older age, squamous histology, thoracotomy and pathologic stage III/IV. What does pathologic stage 3-4 mean here? Were not they excluded?

Author's response: **The study is based on clinical stage IA NSCLC ≤2cm, with all patients staged by PET/CT and/or EBUS and found to be clinically node negative, which was clarified on page 5, line 86. Some of these patients subsequently had pathologic upstaging due to occult nodal positivity or pleural invasion.**

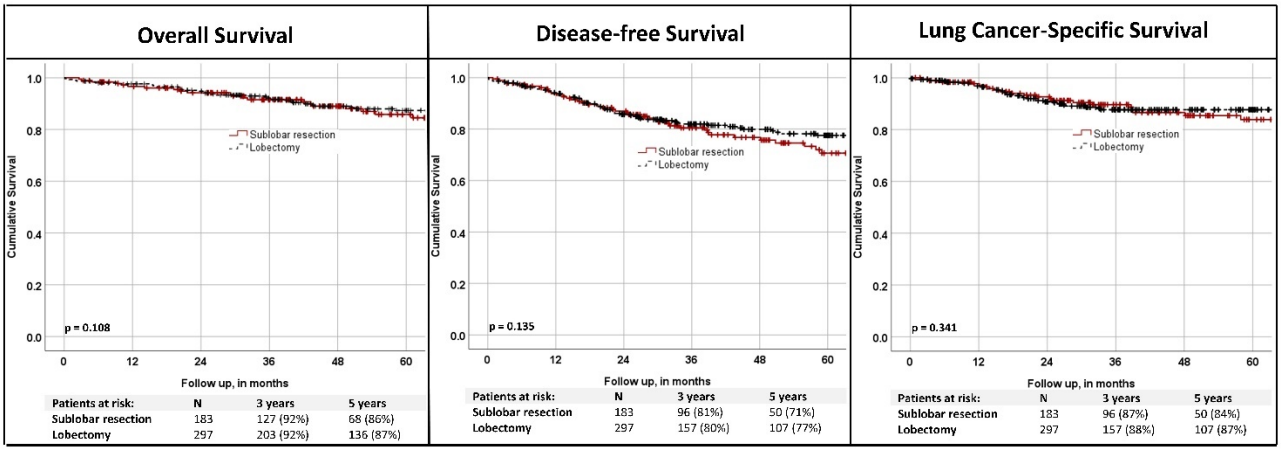
4- Would the authors have similar conclusions if they have compared sublobar resections with the lobectomy? By this way groups could have been similar.

Author's response: **When consolidating groups to sublobar resection vs lobar resection the results remain similar, refer to Tables A-D below and figure A. We deliberately kept the types of sublobar resection separated between wedge resection and segmentectomy in this study because we find it provides a more granular view of our cohort.**

Table A: Demographics and Clinical variables			
	Sublobar N = 183	**Lobar N = 297**	**p-value**
Age			
Mean (±SD)	71.1 (±9.0)	70.0 (±9.0)	0.165
Sex			0.736
Female	107 (58.5%)	169 (56.9%)	
Male	76 (41.5%)	128 (43.1%)	
Race			0.015
White	112 (61.2%)	187 (63%)	
African American	19 (10.4%)	24 (8.1%)	
Asian	16 (8.7%)	50 (16.8%)	
Other	36 (19.7%)	36 (12.1%)	
Smoking status			0.636
Never	37 (20.2%)	71 (23.9%)	
Former	45 (24.6%)	68 (22.9%)	
Current	101 (55.2%)	158 (53.2%)	
ECOG performance status			**<0.001**
0	156 (85.2%)	281 (94.6%)	
1 or 2	27 (14.8%)	16 (5.4%)	
Pulmonary function test			
%FVC (Mean (±SD))	87.1 (±18.2)	89.8 (±19.4)	0.156
% FEV_1 (Mean (±SD))	82.4 (±22.7)	89.6 (±19.0)	**<0.001**
% DLCO (Mean (±SD))	79.2 (±24.3)	85.3 (±23.2)	**0.016**
Surgical approach			**0.048**
Thoracotomy	3 (1.6%)	7 (2.4%)	
VATS	173 (94.5%)	258 (86.9%)	
VATS converted to thoracotomy	0 (0%)	1 (0.3%)	
Robotic	7 (3.8%)	31 (10.4%)	
Histologic Subtype			0.202
Adenocarcinoma	148 (80.9%)	257 (86.5%)	
Squamous cell carcinoma	30 (16.4%)	32 (10.8%)	
Other	5 (2.7%)	8 (2.7%)	
Recurrence			0.106
No recurrence	157 (85.8%)	264 (88.9%)	
Local	14 (7.7%)	10 (3.4%)	
Distant	12 (6.6%)	23 (7.7%)	

Table B: Comorbidities			
	Sublobar N = 183	**Lobar N = 297**	**p-value**
Hypertension	100 (54.6%)	178 (59.9%)	0.254
Hypercholesterolemia	86 (47%)	123 (41.4%)	0.231
Coronary artery disease	24 (13.1%)	47 (15.8%)	0.417
Interstitial lung fibrosis	11 (6%)	4 (1.3%)	**0.004**
Myocardial infarction	8 (4.4%)	15 (5.1%)	0.735
Peripheral vascular disease	10 (5.5%)	14 (4.7%)	0.714
Congestive heart failure	7 (3.8%)	4 (1.3%)	0.078
Chronic obstructive pulmonary disease	59 (32.2%)	54 (18.2%)	**<0.001**
Atrial fibrillation	17 (9.3%)	23 (7.7%)	0.552
Diabetes mellitus	39 (21.3%)	45 (15.2%)	0.085
Renal disease	13 (7.1%)	14 (4.7%)	0.270
Charlson Comorbidity Index			**0.002**
0	57 (31.2%)	143 (48.2%)	
1	52 (28.4%)	68 (22.9%)	
2	41 (22.4%)	55 (18.5%)	
3 or greater	33 (18%)	31 (10.4%)	

Table C: Pathologic variables			
	Sublobar N = 183	**Lobar N = 297**	**p-value**
Pathologic stage			0.255
Stage 0	1 (0.5%)	2 (0.7%)	
Stage I	169 (92.3%)	257 (86.5%)	
Stage II	7 (3.8%)	23 (7.7%)	
Stage III	6 (3.3%)	15 (5.1%)	
Pathologic T stage			0.471
Tis	1 (0.6%)	2 (0.7%)	
T1	155 (84.7%)	239 (80.5%)	
T2	23 (12.5%)	52 (17.5%)	
T3/T4	4 (2.2%)	4 (1.3%)	
Mean Pathologic Tumor Size (±SD)	1.38 (±0.52)	1.76 (±0.80)	**<0.001**
Pathology N stage			**<0.001**
Nx	7 (3.8%)	0 (0%)	
N0	167 (91.3%)	263 (88.6%)	
N1	4 (2.2%)	19 (6.4%)	
N2	5 (2.7%)	15 (5.1%)	
Number of LN sampled			
Median (IQR)	7 (4 – 11)	13 (9 – 18)	**<0.001**



5- Authors claim that their study corroborate the results of JCOG 0802 and CALGB 140503, the only two randomized trials comparing extent of surgical resection for small early-stage lung cancer in the modern era. However, I disagree with the authors on this. First of all both studies are randomized and in CALBG trial most of the surgeries were wedge resection. However, both studies have strict mediastinal lymph node dissection criteria intraoperatively and frozen sections were performed to proceed. Follow up was routine and longer than 7 years in CALBG. This study being retrospective and having limited number of LND and no long term follow up could not Do the authors compare clinical stage 1A 1-2 patients or pathologic IA1-2 patients. It is confusing.

<u>Author's response:</u> This study is based on clinically staged IA1-2 patients, and this has been further clarified in the methods section (see page 8, line 86). We still assert that the findings of the study corroborate/support the results of the randomized trials and importantly – since this study was retrospective and from a single institution – represents real-world experience outside of the highly controlled confines of a randomized trial to support the conclusions of those clinical trials (see page 8, lines 160-166).

While patients in this cohort were not subject to the same strict intraoperative frozen analysis of lymph nodes to confirm N0 status and allow inclusion as in CALGB 140503 or to ensure adequacy of resection as in JCOG 0802, the assessment of mediastinal lymph nodes in all three subgroups (wedge, segment, and lobectomy) in our cohort included 2 or more N2 lymph node stations in the vast majority of cases. The extent of nodal dissection has been added to Table 3 to further elucidate this important aspect of our study.

6- Why do the authors have T3 and T4 patients in the Tables. Please show in the flow Chart which patients were included. This is same with N1 and N2 patients.
Also a better design of this study is required.

<u>Author's response:</u> This study included patients with clinical stage IA 1-2 patients based on PETCT scans +/- invasive mediastinal staging. Table 3 represents

pathologic findings, which include patients who were pathologically upstaged.

Reviewer D

Thank you for the opportunity to review this manuscript focused on difference in oncologic outcomes for patients with small <2cm NSCLC treated with either wedge, segmentectomy, or lobectomy.

Introduction:

1. The introduction is clear and provides the context for the study. No significant comments.

Methods:

1. How was written consent obtained for patients in the retrospective study? Were patients queried in follow up clinic visits or called via telephone? I do not think many IRBs would require consent for this type of retrospective study, but I am curious how it was obtained.

Author's response: Thank you for the comments. The patient consent was waived given that this is a retrospective study (see page 5, line 96 in the methods section).

2. The authors should specify if the size and nodal status for the inclusion status was based on clinical or pathologic staging (I assume clinical).

Author's response: The inclusion criteria is based on clinical staging, this was further clarified in the methods section page 5, line 86 and also in Supplementary Figure 1.

Results:

1. In table 1 there is an error in smoking status. I believe in Lobar column in never row is should read 23.9% not 239%. In addition, please rerun your Chi square for this block, when I calculate it I get <0.001.

Author's response: We appreciate this comment and important pick-up from the reviewer. The percentage was modified as advised. The number of former and current smokers in wedge resections and segmentectomy were flipped and this was corrected, and the chi square test was recalculated. Please see these modifications in table 1.

2. Do the authors have any information on distance of staple line from margin? This would be especially helpful in the wedge resection and segmentectomy groups.

Author's response: Based on pathology reports, all the margins were noted to be negative. The median distance from the parenchymal margin staple line for wedge

resections was 1.20cm (0.60 – 2.00) and 1.80cm (0.98 – 3.10) for segmentectomy group and 3.00 (1.50 – 5.00), this information was added to table 3 and results section (see page 6, lines 125-127).

3. Is there any information on stations of lymph nodes sampled? For example, how regularly were mediastinal nodal stations being sampled?

Author's response:

	Wedge resection	**Segmentectomy**	**Lobectomy**	**p-value**
Number of N2 stations sampled				**0.012**
0 N2 stations	8 (8.6%)	4 (4.4%)	6 (2%)	
1 N2 station	23 (24.7%)	14 (15.6%)	39 (13.1%)	
2 N2 station	43 (46.2%)	49 (54.4%)	157 (52.9%)	
3 N2 station	15 (16.1%)	18 (20%)	79 (26.6%)	
4 N2 station	3 (3.2%)	3 (3.3%)	15 (5.1%)	
5 N2 station	1 (1.1%)	2 (2.2%)	1 (0.3%)	

Based on the retrospective data available, patients who underwent a wedge resection had overall a smaller number of N2 stations examined and the highest number of 0 N2 stations examined (8.6%), while segmentectomy and lobectomy were more likely to have a higher number of N2 stations sampled. This was added to table 3 and to the results section (see page 6, line 129)

Discussion:
1. The authors should expand on the difference in survival in their study compared to the CALGB study. The authors survival is more similar to the JCOG study and may reflect inclusion of part solid nodule or other differences in the populations.

Author's response: The differences in survival might be attributed to the inclusion of GGO in our cohort, but it constitutes 10.6% of this study population. The distribution of the type of nodule (solid/part solid) in each group were added in table 1 (see below).

	Wedge	**Segmentectomy**	**Lobectomy**	**Total**
Solid	83 (89.2%)	77 (85.6%)	269 (90.6%)	429 (89.4%)
Part solid	10 (10.8%)	13 (14.4%)	28 (9.4%)	51 (10.6%)
Total	93 (100%)	90 (100%)	297 (100%)	480 (100%)

Additionally, the population in the CALGB trial had a higher rate of individuals with ECOG performance status 1 and 2 (>20% in each arm) as compared to JCOG 0802 which had <3% in each arm with ECOG performance status 1 and 2.

Reviewer E

The authors report oncologic outcomes in patients with c-stage IA NSCLC < 2cm who underwent wedge resection, segmentectomy of lobectomy, suggesting that overall survival and recurrence-free survival were not significantly different regardless of type of surgery. Although this manuscript is well written, several points should be clarified. My comments and questions are given below.

Major concern:
I reckon that the reason why sublobar resection (wedge resection or segmentectomy) provided similar long-term results with lobectomy may be selection bias. Part-solid nodules, which often grow slowly, and small nodules localized in the peripheral side might be included in sublobar resection groups more frequently than in the lobectomy group. In fact, median tumor size was smaller in the wedge resection group than in the lobectomy group. Therefore, univariate and multivariate analyses should be performed by adding the following factors: part-solid or solid, tumor size, and peripheral or central.

Author's response: Noted and appreciated. These changes were added as advised to the univariable and multivariable analysis in supplementary table 1. Clinical tumor size was not significantly associated with DFS on univariable analysis (HR 1.293 (0.842 – 1.986), p = 0.239) and therefore was not added to the multivariable analysis. Solid nodules were significantly associated with DFS in univariable analysis (HR 2.558 (95% CI 1.044 – 6.268), p = 0.40) but was not statistically significant in the multivariable model (HR 2.135 (95%CI (0.851 – 5.354), p = 0.106). Factors that were associated with worse DFS on multivariable analysis included older age, squamous histology, and higher pathologic staging (p<0.05). These modifications were also made in the results section: see page 7, lines 142-147.

Minor concerns:
1. Line 68: Did you use TNM ver8? If so, please mention it.

Author's response: These modifications were made as advised (see page 5, line 86-87 in the methods section).

2. Line 107-110: How did you perform lymph node sampling for wedge resection or segmentectomy? You should mention the surgical procedure if there are any criteria.

Author's response: Sampling was performed per surgeon judgement. Our institutional guideline is to perform mediastinal lymph node dissection on all lung cancer resections that include at least 2 N2 stations and 1 N1 station, and the large majority (>80%) of the resections included in this cohort met that guideline. The extent of lymph node dissection performed has been added to Table 3.

3. Line 125-126: The rate of complication in the wedge resection group seemed to be

lower than in the segmentectomy and lobectomy groups. This result should not be compared among the three groups; wedge resection vs. segmentectomy or lobectomy.

Author's response: While the complication rate was lower in the wedge resection group than the segmentectomy and lobectomy group, this finding was not statistically significant (p=0.41, Supplementary Table 2).

4. Table 1: Predicted % FVC should be added in the table because some patients had interstitial pneumonia.

Author's response: There is no significant difference between the three groups in %FVC (p = 0.17). This has been added to table 1 under pulmonary function test as recommended.

Reviewer F

Congratulations to the authors for the work done. The topic covered is certainly of current interest due to the importance of the minimally invasive impact of treatments in thoracic surgery in early stages of NSCLC. From the experience of the Center it is clear that the complications are similar in the various groups, but seeing the ratio of the greater number of patients in the major resection it is easy to understand how the value is stronger. The data and literature support how sublobar treatments are suitable in stage I, but as well underlined in the discussion, it is essential that a good lymphadenectomy is completed even in minor resections. I recommend simple in-depth analysis in describing the type of follow up followed with timing and radiological methods. Otherwise favorable and still good work.

Author's response: Thank you for reviewing the manuscript and the comments. The database used for this research study does not have specific details regarding follow up plan or frequency of the follow up for each patient. The dataset only provides the last date of follow up. Patients that are in this study follow the institutional follow up protocol per the National Comprehensive Cancer Network guidelines in terms of frequency of follow up and imaging, which include: post operative follow up 10-14 days after surgery, followed by visits and CT chest for radiographic surveillance every 6 months for the first 2-3 years, and annually thereafter. We have included the follow-up performed for this cohort in the methods section (page 5, line 99-102).