

Peer Review File

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Reviewer A

1) A massive flaw associated with the manuscript by Natsumi and colleagues is that granuloma and granulation are not equivalent terms. It is not clear from the description by Natsumi and co-authors if they are referring to the former or the latter. Fundamentally it would seem they are referring to granulation tissue, rather than granulomas. Please remain accurate and consistent in the use of their terminology..

Reply: We have modified our text as advised (Page 3, line 30, Page 5, line 61 and 65, Page 14, line 220, and Page 15, line 249).

Changes in the text: This study aimed to identify the frequency, shape, and course of staple line thickening and **granuloma** formation after sublobar resection for primary lung cancer, and to identify factors that help distinguish them from recurrent cancer cases. (Page 3, line 30)

In those cases, it is very difficult to distinguish between benign **granuloma** and recurrence of lung cancer only with imaging such as computed tomography (CT) or positron emission tomography (PET)-CT. (Page 5, line 61 and 65)

This study aimed to identify the frequency, shape, and course of staple line thickening and **granuloma** formation after sublobar resection for primary NSCLC, and to identify factors that help distinguish them from recurrent cancer cases.

There have also been some reports that infection involving the staple line was a factor in the formation of **granuloma** (10,11). (Page 14, line 220)

It is still difficult to distinguish by morphology alone, but in most of the present cases, the **granuloma** had a smooth margin (Figure 1), which may help in the differentiation. (Page 15, line 249)

2) The authors state in their methods that “Postoperative recurrence was clinically diagnosed by these tests with or without a pathologic diagnosis.” Since the authors do not have tissue confirmation of actual recurrence for all of their patients it is not clear how they know that the 57 patients who they deem as not having recurrence actually did not have recurrence. How can this group be a true comparator?

Reply: As you point out, that is the weakest point of this study. In the present cases, none underwent biopsy. CT-guided fine needle aspiration biopsy may be useful, but it is often difficult in cases deep in the lung or near the hilum, and there also may be differences between institutions. However, follow-up evaluations included physical examination, chest radiography, blood tests including tumor marker levels, CT of the chest and abdomen, and PET-CT if necessary. Based on these results, we believe that it is possible to clinically diagnose that there is no suspicion of recurrence.

3) The authors indicated that “...thickening size was measured in the longest diameter

perpendicular to the staple line...” This value seems unusual since some patients may have a singular point of thickening greater than 3 mm whereas others have a more consistent 3 mm thickening throughout the course of staple line. Were there other qualitative aspects of the CTR images that were employed to make a better distinction as to what could be a true recurrence?

Reply: There is no clear-cut definition about staple line thickening. In the present study, linear thickening is defined as uniformly thickening along the staple line, whereas nodular thickening is defined as a nodule that protrudes or surrounds the staple line.

4) One piece of information that would be useful to know is what were the preoperative characters of the lesions and, in particular, those that were ground glass in nature, do they have more information about these? Also, perhaps in this same line of thinking, what were the determinants for a wedge resection versus a segmentectomy?

Reply: The tumor size and invasive component size of the primary tumor are shown in Table 1. For patients who could not tolerate radical surgery due to complications and poor pulmonary function, segmentectomy or wedge resection was also performed as passive limited surgery. Which one to use depends on the tumor location, tumor size, lung function, and performance status of the patient.

In patients with metastatic lung tumors, segmentectomy was performed only when it was difficult to secure enough margin in wedge resection due to the location and size of tumor.

5) They based the clinical decision on those they thought had cN0 disease. Did these patients all have confirmed pN0 disease?

Reply: We sampled hilar lymph nodes during the operation.

6) Some patients underwent a completion lobectomy due to concerns of recurrence. It is not clear why patients underwent a sublobar resection when they must have met the criteria to under a lobectomy?

Reply: In this case, intentional sublobar resection was performed because the tumor was diagnosed with non-invasive preoperatively.

7) In their discussion they state, “Based on the results of this study, patients with staple line thickening and predisposing factors for recurrence... should be actively followed for further scrutiny.” This statement is a general one that does not impart any information that the reader does not already know. They have not provided meaningful data as well as an explanation that adds a deeper level to this sentiment.

Reply: In the present study, staple line thickening was observed in many cases, but most of which were linear. Nodular thickening and tendency to progress were

significantly correlated with recurrence. We believe that it is meaningful to show this result in the data.

8) In the discussion, the paragraph that occupy lines 242-250, are of very little impact and does not leave the reader with information that is particularly helpful. They may want to either refocus this paragraph or delete it.

Reply: We believe that it is useful to mention about the other proposed methods that may be helpful in the differentiation.

9) Their conclusion is one that is obvious. This type of statement does not provide a strong endorsement of their study. They should reconsider the nuances of their main message. Presently, this message is challenging to accept given that their recommendation is made essentially based upon 7 patients. Please revise.

Reply: As you pointed out, the total number of cases was relatively small; in particular, there were only 7 cases of recurrences. A multicenter study is required.

10) There is some scar tissue that waxes and wanes on serial imaging. Did they ever observe this phenomenon and, if so, do they have any words of guidance regarding this issue?

Reply: I'm afraid that we don't have the data about that phenomenon.

11) In Table 1 they do not include any patients with Right middle lobe tumors. I would simply remove this line because knowing there are none does not matter and not many perform segmentectomies of lesions in the right middle lobe.

Reply: We have modified Table 1 as advised (Page 23, Table 1).

Reviewer B

Comments

1- It is a too much and unnecessary exposure of the patients to radiation if you do CT scan every 6 months. Is that the protocol at your institution?

Reply: Yes, that is the protocol at our institution.

2- What do you mean by "intentional sub-lobar resection"? do you mean that it was pre-operatively planned? if so, does "unintentional" means that something unexpected happened during surgery and the plan was changed because of that? Please, explain.

Reply: "Intentional sub-lobar resection" means that sublobar resection is actively performed because the tumor is clinically diagnosed as stage 0-IA1 by careful preoperative staging. On the other hand, "unintentional" means that sublobar

resection is passively performed due to complications and poor pulmonary function.

3- You mentioned invasive size; how do you measure the invasive size?

Reply: We measured the solid component size of the tumor by high-resolution CT (thickness ≤ 1 mm).

4- You mentioned that segmentectomy was done in 3 patients with stage 2 and beyond in in table S1. I am wondering if there was a specific reason why lobectomy was not performed in these 3 patients with this relatively advanced stage?

Reply: We performed sublobar resections in these 3 patients due to complications and poor pulmonary function.

Edits

1- Line 1 (the title): Please, start every word with Upper Case letter (except “and” & “for”)

Reply: I’m afraid that there is no need to start every word with Upper Case letter.

2- Please, It is better not to use abbreviations in the abstract

Reply: I’m afraid that we did not use.

3- Line 90: Please, add “upon” after “operated”

Reply: I’m afraid that there is no need to add that word.

4- Line 91: Please, write “All surgeries were” instead of “All surgery was”

Reply: We have modified our text as advised. (Page7, line91)

5- Line 123 (statistical analysis): You need to add: "Data are shown as mean \pm standard deviation or number (%)"

Reply: That is described in each table.

6- Line 134: No need to mention female number (percentage)

Reply: We describe that for clarity.

7- Line 136: Please, add “%” to “51.6”. It is a percentage not a number.

Reply: We have modified our text as pointed out. (Page9, line136)

8- Line 146: you left a space at the start of the line. Please, eliminate this space.

Reply: This space is needed because we are changing the paragraph.

9- In the caption of table 4: Please, correct “Light” to “ Left”

Reply: We have modified our text as pointed out. (Page26 line358)

