

Peer review file

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Reviewer A

Comment 1: Authors conducted this study for the patients less than 25 years. Why did the authors use 25 years as a age limitation?

Reply 1: Sudduth et al. showed that age is significantly associated with recurrence rates in patients undergoing wedge resection + pleural abrasion for PSP. In a meta-analysis, these authors also showed that younger patients tend to have higher recurrence rates compared to older patients, with a negative correlation with age in the 15-35 age range. Therefore, we selected a cut-off of 25 years old, which is a high-risk group based on this meta-analysis.

Changes in the text: We have added new sentences on this issue (Page 7, Lines 117-118)

Comment 2: The authors demonstrated that the PGA sheet induces the sever adhesion. However, in reference 9, the paper revealed that PGA sheet did not always induce the adhesion and this data was not from the surgery in PSP.

Reply 2: We apologize for this mistake. We agree with the reviewer that a PGA sheet does not always induce adhesion. However, the rate of induction of adhesion is not clear because the presence or absence of adhesion is only seen in patients who receive PGA sheet covering and undergo a second surgery for postoperative recurrence of PSP. Takeshita et al. found that all 5 patients who underwent a second surgery after use of a PGA sheet showed strong adhesion, which led to longer operative times and greater intraoperative bleeding. In addition, Isaka et al. showed that a PGA sheet caused strong adhesion, rather than ORC, in rats.

Changes in the text: We have added the two articles mentioned above (Page 6, Line 87 and Page 21, Line 374 to Page 22, Line 381)

Comment 3: The authors indicated that Integran sheet induces the minimal inflammation and adhesion. However, the reference paper reviewed only 2 cases so I think the evidence is weak.

Reply 3: As indicated by the reviewer, there is weak evidence for the effect of Integran because only two cases (both lung cancer patients) have been reported. There is no previous study of Integran in PSP patients. Therefore, verification and establishment of safety of use of an Integran sheet for young patients is needed, and this is the basis of our feasibility study.

Changes in the text: To address this point, we have added a new sentence. (Page 6, Line 101 to Page 7, Line 104)

Comment 4: In the study group, apical wedge resection was performed in 24 cases, I think the patients with non apical bulla have to be excluded because the recurrence rate is different between apical lesion and non apical lesion.

Reply 4: We agree that the recurrence rate may differ between patients with non-apical bulla and those with apical bulla. However, the main purpose of our study is to evaluate the safety, and we calculated the sample size based on the safety factor. Therefore, we would like to show data for 25 patients to maintain the statistical power for feasibility evaluation.

Changes in the text: No changes.

Comment 5: I wondered whether the resected lung volume is correlated with the recurrence. They used number of staple cartridge (median 2: 1-6). This value did not influence the recurrence?

Reply 5: We thank the reviewer for this interesting comment. Choi et al. found a relationship between resected lung volume and postoperative recurrence (J Thorac Dis 2018;10(3):1622-1627). However, we could not calculate the resected volume in our 25 patients. On the other hand, there is no evidence that the length of resected line or the number of staple cartridges used is correlated with recurrence. However, Choi et al. found that new occurrence of bullae around the staple-line in wedge resection is a risk factor for postoperative recurrence, and we consider that the extent of the staple-line in the risk area for new bullae, as represented by the used staple-line number, is an important factor in PSP recurrence.

Changes in the text: No changes.

Comment 6: The authors revealed that recurrence rate is 12 %. I think the rate is high. In addition, it was a only 1 year recurrence rate. F/U period is too short to evaluate the feasibility and efficacy.

Reply 6: We agree with the reviewer that the recurrence rate of 12% is high for all PSP patients. However, our study was conducted in young adults, a high-risk patient cohort. As mentioned in the manuscript, the postoperative recurrence rate in young adults is 17.9-40.0%, even if intraoperative additional procedures are performed. Thus, we consider that our results are acceptable compared to previous reports. However, the follow-up period is short and we

recognize that a RCT (or comparative study) is needed to evaluate the efficacy of INTEGRAN. Thus, in this study, we focus on evaluation of the safety of INTEGRAN.

Changes in the text: To clarify the focus on evaluation of safety, we have delated sentences concerned with efficacy (Page 4, Line 54-58; Page 7, Line 105-107; Page 8, Line 132-134) and the “old” Figure 4 showing a Kaplan-Meier curve for postoperative recurrence.

Comment 7: It was a single prospective study. To evaluate the efficacy, the authors should compare with the control group. (ex, wedge + pleurectomy or wedge + PGA sheet).

Reply 7: As mentioned above, we have focused on evaluation of safety in this manuscript and we leave the evaluation of efficacy for comparative studies planned in the future.

Changes in the text: To clarify the focus on evaluation of safety, we have delated sentences concerned with efficacy (Page 4, Line 54-58; Page 7, Line 105-107; Page 8, Line 132-134) and the “old” Figure 4 showing a Kaplan-Meier curve for postoperative recurrence.

Comment 8: Without other risk factors analysis, we could not indicate the efficacy of the INTEGRAN sheet but we could indicate the feasibility.

Reply 8: As mentioned above, we have focused on evaluation of safety in this manuscript and we leave the evaluation of efficacy for comparative studies planned in the future.

Changes in the text: To clarify the focus on evaluation of safety, we have delated sentences concerned with efficacy (Page 4, Line 54-58; Page 7, Line 105-107; Page 8, Line 132-134) and the “old” Figure 4 showing a Kaplan-Meier curve for postoperative recurrence.

Reviewer B

Comment 1: One of surgical indications for PSP was prolonged air leak. How long do you usually wait for the cessation of the air leak?

Reply 1: We usually wait for cessation of the air leak for about 1 week after insertion of a chest tube. At 4-5 days after chest tube insertion, we prepare for an operation, and we perform surgery as soon as possible after 7 days following insertion if the air leak continues.

Changes in the text: We have added new sentences to clarify the indication (Page 11, Line 183-185).

Comment 2: On Figure 2, postoperative maximal body temperatures were depicted as box

plot. Two box plots for postoperative day 1 and 2 may be better to be shown.

Reply 2: We have modified Figure 2 as advised.

Change in the text: We have modified the “old” Figure 2 and renamed it “Figure 3” in the revised manuscript, with a figure legend (Page 26, Line 456-460).

Comment 3: It may also be better to show postoperative blood test results of postoperative day 1 and 14 respectively.

Reply 3: We have modified Figure 3 as advised and added a new Figure as “Figure 4”.

Change in the text: We have modified Figure 3 and added a new “Figure 4” in the revised manuscript, with changes to the figure legends (Page 26, Line 459-460).

Comment 4: 1-year follow-up may not be long enough to evaluate the efficacy of this treatment.

Reply 4: As in the reply to Reviewer A, we agree that our follow-up period is short and we recognize that a RCT (or a comparative study) is needed to examine the efficacy of INTEGRAN. Therefore, we have focused on evaluation of safety in this manuscript and we leave the evaluation of efficacy for comparative studies planned in the future.

Changes in the text: To clarify the focus on evaluation of safety, we have delated sentences concerned with efficacy (Page 4, Line 54-58; Page 7, Line 105-107; Page 8, Line 132-134) and the “old” Figure 4 showing a Kaplan-Meier curve for postoperative recurrence.

Reviewer C

Comment 1: I think your title should be rephrased into "Feasibility of application of absorbable collagen hemostat sheet for prevention of postoperative recurrence of pneumothorax in youths".

Reply 1: We have modified the Title and Running title along the lines advised.

Change in the text: Title and Running title modified (Page 1, Line 1-3; Page 2, Line 20-21).

Comment 2: Your recurrence rate is still high. According to the literatures and my thirty years' experience, 4-7% is acceptable and reasonable.

Reply 2: We agree with the reviewer that a recurrence rate of 12% is high for all PSP patients. However, our study was conducted in young adults, which is a high-risk cohort according to

Sudduth et al. The postoperative recurrence rate in young patients is 17.9-40.0%, even with additional intraoperative procedures. Thus, we consider that our results are equivalent to previous reports and are acceptable.

Change in the text: We have modified the text (Page 4, Line 56-57; Page 16, Line 290 to Page 17, Line 302).

Comment 3: The 'Background' is too lengthy and should be shortened.

Reply 3: We have shortened the Background section.

Change in the text: We have modified the text as suggested (Page 5, Line 67 to Page 7, Line 107).

Comment 4: I suggest the entire studied population were operated by the same surgeon for reducing the discrepancy of surgical dexterity.

Reply 4: We agree that operations by the same surgeon are favorable for reducing discrepancies due to surgical dexterity. However, this is somewhat difficult in daily medical practice. To minimize the differences in surgical dexterity among surgeons, we provided the surgical procedure as written in the manuscript when planning this study. We will use the comment from Reviewer C as a reference when we plan an RCT in the future.

Changes in the text: No changes.

Comment 5: Sealing test with airway pressure 20 cm H₂O, will it be too low? I will use at least 25.

Reply 5: We thank the reviewer for this interesting comment. We could not find a study of the relationship between airway pressure in an intraoperative sealing test and postoperative air leak. We and our colleagues usually perform a sealing test with 20 cm H₂O in testing an air leak from lung parenchyma, although we use 25 cm H₂O for testing an air leak from the bronchial stump in lung cancer surgery. We have not experienced any problems in a sealing test with 20 cm H₂O, and thus, we consider that 20 cm H₂O of airway pressure is sufficient for a sealing test in PSP surgery.

Changes in the text: No changes.

Comment 6: The description of placement of the sheet is not clear enough. Maybe using a picture or drawing can help.

Reply 6: As suggested, we have added a new Figure to explain our surgical procedure.

Changes in the text: New “Figure 2” explains the procedure (Page 9, Line 151; Page 26, Line 455).

Comment 7: What is your purpose of performing blood tests in the postoperative acute period?

Reply 7: Blood tests in the postoperative acute period were performed to identify abnormal inflammatory reactions against INTEGRAN. As stated in the text, AEs of INTEGRAN when used as an absorbable topical hemostat include fever, local inflammation, and local abscess formation, as inflammatory reactions against an INTEGRAN sheet. We used WBC and CRP as indexes of inflammatory reactions.

Changes in the text: No changes.

Comment 8: Also CT scan on POM 12, what is your purpose?

Reply 8: The CT scan on POM 12 was performed to identify formation of new bullae around the staple-line. Choi et al. reported that such formation of new bullae was a significant risk factor for postoperative PSP recurrence. Also, we have experienced cases with recurrence after surgery without staple-line coverage that showed formation of new bullae around the staple-line in a second surgery. As the concept of staple-line coverage is mainly prevention of this formation of new bullae, we performed a CT scan to evaluate the effect of INTEGRAN for prevention of the formation of new bullae around the staple-line.

Changes in the text: New sentence added on the purpose of CT (Page 9, Line 160 to Page 10, Line 161).

Comment 9: You stated WBC less than 18000/mm³ considered normal. It is not a usual reference.

Reply 9: We apologize for our insufficient explanation. WBC and CRP are usually elevated by surgical invasion, even with a satisfactory postoperative course. Therefore, we cannot distinguish an abnormal inflammatory reaction against INTEGRAN from a normal postoperative reaction using a normal cut-off, such as WBC >12000/mm³. To identify an abnormal inflammatory reaction against INTEGRAN, we set the cut-off as WBC >18000 /mm³ and/or CRP >15mg/dL, which were about 1.5 times the usual abnormal value.

Changes in the text: New sentence added on this issue (Page 8, Line 130-132).

Comment 10: Your 'Discussion' is also too lengthy. Just state the materials or make up of the

sheet, its advantages and disadvantages, its side effects.

Reply 10: We have made the Discussion section more concise.

Change in the text: Text modified as suggested (Page 12, Line 217 to Page 18, Line 318).

Comment 11: Fig. 1,2 and 3 are not necessary.

Reply 11: Other reviewers recommended revisions to Figure 1 to 3, and therefore, we would like to leave these Figures in the manuscript.

Change in the text: We have modified Figures 1, 2, and 3 (“new” Figures 1 and 3-5).

Comment 12: One of the major defects of the article is the language which should be thoroughly revised by native professionals. It consists of too many weird medical terms, sentence structures and context.

Reply 12: The manuscript was checked and revised by a native-English speaker before the first submission, and the revised manuscript has also been checked.

Change in the text: The revised manuscript was checked by a native-English speaker.

Reviewer D

Comment 1: Authors investigated the feasibility of a sheet-type absorbable topical collagen hemostat for prevention of postoperative recurrence of pneumothorax. They reported 12.0% of postoperative recurrence and none of material-related adverse events. The main limitation of this study is absence of control group. Authors decided recurrence as secondary end points and adverse events as primary end points. I think that important point of pneumothorax is recurrence. Prevention or reducing is the objectives of use of another options for pneumothorax. Fever and inflammatory reactions could occur in the absence of additional material. Authors’ no case of adverse event is able to related with the lower cases. As authors described in the manuscript, randomized study combined with control group would improve the study.

Reply 1: We appreciate the insightful comments of the reviewer. We agree that the most important point in treatment for PSP is recurrence. Additional intraoperative procedures have been introduced to minimize postoperative recurrence of PSP, but all of these have some disadvantages. Thus, there remains controversy with regard to procedures for prevention of PSP. There is a need for an ideal procedure for prevention of PSP that has a low recurrence

rate with few disadvantages. As part of this research, we focused on INTEGRAN and evaluated its potential for prevention of PSP recurrence. INTEGRAN has not previously been examined for this purpose. Therefore, we conducted this study to verify the safety of INTEGRAN as a first step of evaluating the potential of this material. We agree with the reviewer that a randomized study with a control group is necessary to evaluate the efficacy of INTEGRAN for prevention of PSP recurrence. In this study, we verified the safety of INTEGRAN for use for staple-line coverage in PSP surgery. We plan to conduct a new study to evaluate the efficacy of INTEGRAN with comparison to a control group.

Changes in the text: To clarify the focus on evaluation of safety, we have delated sentences concerned with efficacy (Page 4, Line 54-58; Page 7, Line 105-107; Page 8, Line 132-134) and the “old” Figure 4 showing a Kaplan-Meier curve for postoperative recurrence.

Reviewer E

Comment 1: We know now from meta-analysis, that some sort of pleurodesis dramatically reduced the rates of recurrence in these patients. As you described in your paper, the 3 patients who did have the recurrence had bullae present elsewhere (which is at S6, a common area for bullae to form) and not from the previous staple line. This is the reason for performing pleurodesis, to get the rest of the lung to form adhesions or bridging fibrosis with the chest wall, so if other bullae develop somewhere else, and does rupture, most of the lung will remain adhered to the chest wall and would not collapse due to leaking bullae. How would you address this issue with patients, as the recurrence rates of just a wedge only is 10-20% which is similar to your recurrence of 12.5%. How does INTEGRAN then help to reduce the risk of postoperative pneumothorax if it does not address the new bullae formation, which pleurodesis addresses? Could you alternatively place INTEGRAN prophylactically over S6 during your surgery to address this issue?

Reply 1: We appreciate the insightful comments made by the reviewer. We agree that some cases with PSP recurrence have bulla rupture in a different area from the previous resection. As mentioned in the manuscript, the concept of staple-line coverage is to thicken the visceral pleura and prevent new occurrence of bullae around the staple-line in wedge resection, and consequently prevent postoperative recurrence. Therefore, staple-line coverage with INTEGRAN or a PGA sheet cannot prevent recurrence in patients with recurrence due to bulla rupture in a different area, and pleurodesis is superior to staple-line coverage for such

cases. To prevent such recurrence, total pleural covering with an oxidized regenerated cellulose sheet is used in some Japanese centers and is reported to be effective for prevention of recurrence of pneumothorax due to lymphangiomyomatosis. Theoretically, the same procedure with use of INTEGRAN is possible, but the efficacy for PSP recurrence is unknown. As is well known, the frequency of natural bullae development (not around the staple-line) decreases in older patients, which indicates that the risk of occurrence of PSP not due to bullae around the staple-line in wedge resection is limited to younger patients. On the other hand, there are disadvantages of pleurodesis, including respiratory dysfunction or complication of future ipsilateral chest surgery. The best approach is still controversial and there is a need to identify the ideal method for prevention of PSP recurrence.

Changes in the text: No changes.

Comment 2: From your study, you also stated that the post operative CT scan at 1 year showed new bullae formation over the staple line lined with INTEGRAN in 4 of the 25 patients. This rate of new bullae formation is 16.7%. My question here is How deep is the margin of normal lung tissue from the bullae? Is the bullae wedged close to the normal lung tissue or is there a good margin between the bullae and normal lung. What this indicates is that close to 20% of patients with INTEGRAN can develop new bullae at the site of the sheet which is 1 in 5 after a one year follow up. Do you feel if the study was longer, would you find more patients developing bullae in the same place? This would tell us the efficacy of INTEGRAN then.

Reply 2: We always intended to resect bullae with about a 1-cm margin between bullae and normal lung. If the margin is close to bullae, the visceral pleura of the resected site may be thin and lead to occurrence of bullae around the staple-line. On the other hand, bulky resection with a large margin is associated with greater tension in the stapling-line and leads to occurrence of bullae around the staple-line (Choi et al. Influence of lung resection volume on risk of primary spontaneous pneumothorax recurrence. *J Thorac Dis* 2018;10(3):1622-1627). Thus, we consider that a 1-cm margin is suitable for bulla resection. With regard to development of new bullae at the site of the sheet, we cannot address this tendency without a longer study period, but our study is the first to observe the occurrence of bullae around the staple-line prospectively. Choi et al. reported in their retrospective study that 60 new bullae, including 39 new bullae around the staple-line, were found on CT in 85 patients after VATS surgery for PSP, in a mean follow-up period between surgery and CT of 24.9 months (*J Thorac Dis* 2018;10(7):4287-4292). This result shows a higher rate of bullae around the

staple-line (39/85 = 45.9%) than in our patients, which may suggest that coverage with INTEGRAN prevents this occurrence of bullae. Choi et al. also only performed CT for patients with symptoms suggesting recurrence of PSP, which may also account for differences in the results of the two studies. It is also difficult to assess the details of the occurrence of bullae around the staple-line based on only two studies.

Changes in the text: No changes.

Comment 3: I do agree that there are reports of reduction of lung function post pleurodesis, however the long term findings are not significant. below 2 papers.

1. Cardillo et al. Long-term lung function following videothoroscopic talc poudrage for primary spontaneous recurrent pneumothorax. *Eur J Cardio-thorac Surg Off J Eur Assoc Cardio-thorac Surg* 31(5):802–805 □ there was no significant deterioration in lung function of patients who had talc poudrage at 5 years.

2. Tschopp et al. (1997) Treatment of complicated spontaneous pneumothorax by simple talc pleurodesis under thoracoscopy and local anaesthesia. *Thorax* 52(4):329–332 □ reported mild lung restriction in the early months that improved at 12 months post-procedure.

Lastly, thou the amount of adhesions by using INTEGRAN is reduced and the authors comments that this can ease future surgery for patients if they need a re-operation. However, the need for re-operation in patients who undergo surgery with pleurodesis is relatively low.

Cardillo et al. (2001) Recurrences following videothoroscopic treatment of primary spontaneous pneumothorax: the role of redo videothoracoscopy. *Eur J Cardio-thorac Surg Off J Eur Assoc Cardio-thorac Surg* 19(4):396–399. In his paper, he has a recurrence rate of 3.85% (23 patients) in a cohort of 597 patients who underwent surgery for VATS and pleurodesis. He deemed the re-operation feasible by VATS, with only one patient who requiring conversion to open thoracotomy. Again, performing a re-operation for pleurodesis will be more challenging, but the surgery is feasible. How would the authors then justify a higher risk of re-op to patients with just INTEGRAN thou easier to perform as there are minimal adhesions, as the risk of re-op is almost 2-3x higher?

Reply 3: We thank the reviewer for the insightful comments and for pointing out the new articles. In one of these articles, respiratory function recovered 1-year after talc pleurodesis, which suggests that pleurodesis by talc poudrage is a safe procedure for PSP patients from the lung function perspective. However, Lange et al. showed that a patient had extensive pleural calcification and a substantial reduction in lung function (TLC 58% predicted) with some evidence of lung fibrosis more than 20 years after pleurodesis with talc poudrage

(Thorax 1988;43(7):559-61). We also experienced a patient who received pleurodesis with talc 10 years earlier, and showed extensive pleural calcification on chest X-ray with a presumed significant decrease in TLC. Moreover, we are concerned that strong adhesion induced by pleurodesis is an obstacle in future ipsilateral chest surgery, especially in anatomical resection for lung tumors. Cardillo et al. reported that reoperation after pleurodesis was feasible by VATS, with only one patient requiring conversion to open thoracotomy. We agree with this opinion that reoperation with partial lung resection after pleurodesis is feasible. However, reoperation with anatomical resection pleurodesis can be much difficult. In anatomical resection, the pulmonary artery and vein and bronchi must be dissected and exposed, then cut with ligation or by auto-suture. Under normal conditions, these procedures are safe with VATS (even with uniport VATS) or robot-assisted surgery. However, the procedures are troublesome even in open thoracotomy due to strong adhesion if pleurodesis was introduced previously. Thus, pleurodesis has a risk of eliminating the future chance to receive minimally invasive thoracic surgery for treatment of lung disease. As mentioned above, there is still controversy with regard to the best scenario: minimization of the recurrence rate of PSP with strong adhesion or tolerating some recurrence while maintaining the chance for a future minimally invasive operation. The best way is clearly to develop a procedure with a low recurrence rate without adhesion, and there is a need to identify such a method for prevention of PSP recurrence. In regards to INTEGRAN, the recurrence rate of 12% is high for all PSP patients. However, our study was conducted in young adults, a high-risk cohort. The postoperative recurrence rate in young patients is 17.9-40.0% even if additional intraoperative procedures are performed. Thus, we consider that our results are acceptable compared to previous reports. However, our follow-up period is short and we recognize that a RCT (or a comparative study) is needed to examine the efficacy of INTEGRAN. Therefore, we have focused on evaluation of safety in this manuscript and we leave the evaluation of efficacy for comparative studies planned in the future.

Changes in the text: To clarify the focus on evaluation of safety, we have delated sentences concerned with efficacy (Page 4, Line 54-58; Page 7, Line 105-107; Page 8, Line 132-134) and the “old” Figure 4 showing a Kaplan-Meier curve for postoperative recurrence.

Reviewer F

Comment 1: [The primary endpoint \(adverse effect\) is somewhat ambiguous due to](#)

postoperative fever or leukocytosis, elevation of CRP is common with atelectasis in early postoperative days and normalized within 2 days. How about the preventive antibiotic protocol?

Reply 1: Thank you for all of your comments. We administer preventive antibiotics only at the start of surgery and no additional antibiotics were introduced. We agree that WBC and CRP are usually elevated by surgical invasion, even with a satisfactory postoperative course. Therefore, we cannot distinguish an abnormal inflammatory reaction against INTEGRAN from a normal postoperative reaction using a normal cut-off, such as WBC >12000/mm³. To identify an abnormal inflammatory reaction against INTEGRAN, we set the cut-off as WBC >18000 /mm³ and/or CRP >15mg/dL, which were about 1.5 times the usual abnormal value.

Changes in the text: We have added new text to clarify these points (Page 8, Line 130-132 and Page 9, Line 153-154).

Comment 2: A secondary endpoint of 1 year recurrence showed 12%, but which seems relatively high in pneumothorax surgery with recent studies (<5%) using varied materials and techniques. Thus, combination or comparative study is thought to be required to enhance the efficacy of Integran® usage.

Reply 2: We agree that a RCT (or a comparative study) is needed to evaluate the efficacy of INTEGRAN. Therefore, we have focused on evaluation of safety in this study and we leave the evaluation of efficacy for comparative studies planned in the future.

Changes in the text: To clarify the focus on evaluation of safety, we have deleted sentences concerned with efficacy (Page 4, Line 54-58; Page 7, Line 105-107; Page 8, Line 132-134) and the “old” Figure 4 showing a Kaplan-Meier curve for postoperative recurrence.

Comment 3: In figure 1. Initial inclusion criteria defined for PSP in young patients that “secondary spontaneous pneumothorax” in exclusion line seems not suitable.

Reply 3: We have deleted “secondary spontaneous pneumothorax” in Figure 1.

Changes in the text: We deleted “secondary spontaneous pneumothorax” in Figure 1.

Comment 4: In figure 2 and 3. It may be informative to show changes between POD 1, POD 14, and POM 1, as described surveillances.

Reply 4: Concerning body temperature, all patients were discharged on POD 2; thus, we could record body temperature only on POD 1 and POD 2. We have revised the “old” Figure 2 to show changes between POD 1 and POD 2, and we have revised the Figures to show

changes in WBC and CRP among POD 1, POD 14, and POM 1.

Changes in the text: We revised the “old” Figures 2 and 3, and renamed these figures as “Figure 3” and “Figure 4” with addition of “Figure 5”.

Comment 5: [In study design, treatment options \(tube drainage or reoperation\) in cases of recurrence or acute empyema were explained prior to surgery?](#)

Reply 5: Our treatment policy for recurrence or acute empyema was explained to patients, but not in detail. Details were provided as necessary based on the status of recurrence or if empyema occurred.

Changes in the text: No changes.

Comment 6: [In line 238, reference \[6\] is not associated with the study using PGA sheets.](#)

Reply 6: We apologize for this mistake.

Changes in the text: We have corrected the reference number (Page 21, Line 374 to Page 22, Page 381).

Comment 7: [What is the authors’ opinion about application of surgical glue regardless of the coverage materials around the stapling line?](#)

Reply 7: Thank you for this comment. We believe that surgical glue, such as fibrin sealant, is useful to prevent both postoperative air leak and new occurrence of bullae around the staple-line. In addition, surgical glue has been suggested to prevent adherence to the lung surface and chest wall. However, surgical glue has the risk of blood infection because the material is produced from animal or human blood components, which is a concern, especially for young patients. INTEGRAN has theoretically no risk of such infection and we selected this material as a candidate material for staple-line coverage.

Changes in the text: No changes.

Comment 8: [What about reactive adhesions \(material related or not\) around stapling lines without abrasion or chemical pleurodesis, as preventive effects to lower recurrences of pneumothorax.](#)

Reply 8: We again appreciate this comment. Adhesions around the staple-line often occur, even if no coverage technique is performed. However, as is well known, the recurrence rate of PSP after bullectomy without any additional procedure is high, which indicates that adhesion only in a small area around the staple-line is not enough to prevent postoperative

recurrence. This phenomenon also suggests that the covering technique exerts a preventive effect through thickening the visceral pleura and prevention of new occurrence of bullae around the staple-line, rather than through adhesion. Therefore, we consider that a procedure with no adhesion and prevention of PSP recurrence can be developed.

Changes in the text: No changes.