

Reviewer A

General comments

In this paper, the authors investigated the significance and accuracy of dynamic chest radiography (DCR) for the presence of pleural adhesions before pulmonary surgery in preoperative patients. They demonstrated that DCR showed high or acceptable sensitivity, specificity, positive and negative predictive value (PPV and NPV) to detect pleural adhesions at the preoperative evaluation. The text was well described and data analysis was fairly adequate. The following points, however, should be addressed.

Major points:

In major medical institutes where chest surgery is available, computer tomography (CT) must be set up and more available than DCR. Comparing the accuracy between DCR and CT to predict pleural adhesion would be needed. Sensitivity, specificity, PPV and NPV of CT and the combination of CT with DCR for detecting pleural adhesion should be presented in study subjects of this investigation although previous studies were described at the reference. In cases presentations, figures of CT or MRI in 4 patients would be demonstrated. Although I agree with authors description that DCR is superior to other modalities including CT, MRI and radioisotope studies in points of medical cost and radiation exposure, readers may be interested in the superiority or inferiority of DCR as compared with CT or other radiographical modalities.

Reply: Thank you for your great comments. We consider that simple CT cannot detect the pleural adhesion (dynamic CT can detect). In our study, dynamic CT was not taken for the objective patients. So, we cannot compare them. Thank you very much.

1. Method; Imaging analysis: Page 7, line 114-118: This description and figures about PH-mode and PH2 mode may be not necessary in this paper because these modes to assess pulmonary circulation was not used for the following analysis and case presentations. Just a minimum explanation in the introduction may be enough.

Reply: As you say, it is not needed. I deleted the sentence (Revised manuscript, Page 7, Line 114-118). Thank you very much.

2. Results: Page 9, line 167-168: This sentence can be deleted because it is easily understood after reading Introduction and Methods.

Reply: As you say, it is not needed. I deleted the sentence (Revised manuscript, Page 9, Line 169-170). Thank you very much.

3. Results: Page 10, line 175-178: Cases of false negative were often appeared in patients having pleural adhesion on the side of mediastinum (6/11) . This may be from weakness of DCR that is difficult to assess left lung and neighborhood of the heart because of heartbeats. This concerns would be emphasized in the Discussion.

Reply: Heartbeats is said to be unaffected for DCR. The reason is mentioned in the Discussion (Revised manuscript, Page 14, Line 255-258). Thank you.

4. Figure 2: Figures of PH-mode and PH2-Mode can be deleted.

Reply: As you say, it is not needed. I deleted them (Figure 2). Thank you very much.

5. Figure 3, 4 and 6: The analysis using CT would be presented. Data analysis when combined DCR with CT would be further evaluated.

Reply: Thank you. We consider using only CT is not able to detect pleural adhesions.

6. Figure 5: Case presentations: Similarly, figures of CT would be demonstrated.

There are 2 reasons: 1) comparing accuracy between DCR and CT, 2) Were there emphysematous or fibrotic changes in lungs, especially in cases B and D who showed pulmonary ventilation defect in PL-mode?

Reply: Reply: Thank you. The one slice of CT cannot describe the lung fields, so we decide to not demonstrate findings of CT.

Reviewer B

This is an interesting manuscript, and the authors are to be congratulated for applying several interesting imaging techniques to a relevant clinical problem. Overall I think the manuscript is of a high quality, however there are some points that need addressing before acceptance.

Line 120 Who performed DCR analyses and interpretation of the images? How much experience/training did they have in image interpretation? Were the readers blinded to the case history, and if there was more than one, to each other's interpretation?

Reply: It is very important. Two expert surgeons did. I added it in the Methods (Revised manuscript, Page 7, Line 121-122). Thank you very much.

Line 122 What metrics used to determine 'disappeared'? I think it's important to clarify the objective measure used to determine this, or qualify in the methods that it is a user-dependent subjective measure if this is the case.

Reply: If you can, please watch the supplemental movie. In fact, the blue shadow disappeared in the low motion area.

Line 133 Was the operating surgeon blinded to the results pre-op DCR analysis? How

many surgeons performed operations within this study? If the surgeon was not blinded, this should be acknowledged as a potential source of bias in the limitations.

Reply: This study is prospective, and not blind. And then, the surgeon had the findings of DCR before surgery. However, within this study, the findings of DCR did not make surgery change. However, according to the results of this study, we may change surgery by the findings of DCR from now on. Thank you.

Line 160 / 265 Is it valid to compare operating times when including both VATS and RATS? Presumably operating time differs somewhat between these two techniques, and surgical case selection will be dependent on the presumed diagnosis (which might affect DCR findings), thus introducing a source of selection bias.

Reply: This study did not aim at the operation time. According to the results of this study, we may consider which VATS or RATS selected by the findings of DCR from now on. Thank you.

Line 153-156 I am surprised at the inclusion of both malignancy and benign pathologies in this study. It would seem more sensible to me to separate the two into different analyses, or at least remove non-malignant entities from the final analysis, as it is plausible that DCR results may differ in cancer vs benign conditions. A subgroup analysis of malignant cases only using only one surgical technique (e.g. VATS alone) may be interesting.

Reply: At first, we want to demonstrate the utility of DCR for all kinds of tumors. So, both malignancy and benign pathologies were included. Thank you.

Line 215 – I would avoid subjective terms when describing other authors within this field.

Reply: Exactly. I deleted it. (Revised manuscript, Page 12, Line 222). Thank you very much.

Line 235 – Quality in what sense? There is no formal comparison made to dynamic CT or MRI, limiting the ability to compare the two techniques to the findings of DCR. Why was CT not performed in this study?

Reply: Your comment is very nice. I revised the term to "results". (Revised manuscript, Page 13, Line 244). And, we consider that simple CT cannot detect the pleural adhesion (dynamic CT can detect). In our study, dynamic CT was not taken for the objective patients. So, we cannot compare them. Thank you for your cooperation.

Reviewer C

Simple, well-written, easy flowing article about the novel use of dynamic chest radiography to evaluate pleural adhesions. The methods section is incomplete. The

results are overstated and need to be downplayed in the discussion.

-I have difficulty understanding which patients were included from your methods section. All consecutive patients undergoing thoracic surgery without pneumothorax or mesothelioma who consented? The way the manuscript is phrased currently leaves place to interpretation for the inclusion and exclusion criteria.

Reply: It is very important, and I added the sentence in the Methods. (Revised manuscript, Page 5, Line 81). Thank you very much

-Were there any patients who did not consent? This should be stated in the results section.

Reply: No patients gave inconsent. I added the sentence in the Results. (Revised manuscript, Page 9, Line 155-156). Thank you very much

-The imaging technique is well explained for a neophyte as myself in DCR. The description and technique used should be reviewed by a more experience reviewer in the technique.

Reply: Yes, the description was reviewed by the experts of DCR.

-Why were the 20% and "5min to dissect" thresholds used to define significant adhesions? As this is the main outcome, the definition should be backed by litterature or, at least, the reason for this choice should be explained. The thresholds should be clinically significant. Was the primary outcome evaluated by a single observer? Who was that observer? The treating surgeon? What was there experience with DCR prior to the study?

Reply: Unfortunately, the definition backed by literatures were none. So, we had no choice, and I decided it was the first standard. The evaluation methods are very inportant. So, I added them in the Methods (Revised manuscript, Page 7, Line 121-122, Page 8, Line 134-135).

-The statistical analysis section describes analysis which were not performed and does not discuss the ROC curve which was designed.

Reply: Thank you for your kind comments. It is my fault, so I revised it (Revised manuscript, Page 8, Line 147-148).

-"DCR was able to be performed even for patients over 80 years old." This should not appear in the results but is more a discussion point.

Reply: Exactly. I revised it in the Discussion (Revised manuscript, Page 13, Line 239-240).

-Ultrasound to assess pleural adhesions should be discussed.

Reply: Thank you for your great comments. It is very important. So, I added the assessment in the Discussion, and added some references (Revised manuscript, Page 14, Line 245-253).

- "In the preoperative evaluation of pleural invasion⁷, pleural adhesion or invasion is often evaluated with dynamic computed tomography (CT)¹⁷⁻¹⁹ or magnetic resonance imaging (MRI).²⁰⁻²²" This phrase seems to suggest that these techniques are regular practice which is not the case.

Reply: As you say, my sentence was not suitable. So, I revised (Revised manuscript, Page 12, Line 219-220).

- The authors should make a better argument for the clinical application of their findings than the paragraph ranging from lines 225-229.

Reply: Thank you, and I added some sentence in the Discussion (Revised manuscript, Page 13, Line 237-238).

- "As a result, the utility of DCR for preoperatively detecting pleural adhesions was thus demonstrated." What is stated before does not demonstrate the utility of DCR but that it is feasible.

Reply: Thank you. The results of DCR were about equal with the results of other imaging modalities. So, we considered DCR is useful. Thank you very much.

- The authors overstate their findings. We are looking for a technique which is good at ruling out pleural adhesions at does not lead to too many false positives.

Reply: Thank you. The point is mentioned in the limitations. DCR has a potential for progress. Thank you very much.

- I do not understand the ROC curve findings discussed. The presented ROC curve was built using a cutoff for positive and negative LMA images for adhesions. What is this cutoff? The authors should explain how such a cutoff was found. The ROC curve is rather unimpressive to me and very close to the diagonal line representing a test that is not better than flipping a coin.

Reply: Thank you. The cut-off was set according to the ROC curve. The 50% is simple, and the statistical significance was confirmed. But, it was just a retrospective analysis. Thank you very much.

- I strongly disagree with the conclusion. This is not high specificity or sensitivity.

Reply: Thank you. The results of DCR were about equal with the results of other imaging modalities. So, we considered DCR is useful. Thank you very much.

- "In conclusion, we evaluated the consistency of the preoperative detection of pleural adhesions using DCR." Consistency was not evaluated according to what is written in the manuscript.

Reply: Thank you. "Consistency" means the negative predictive value and the positive predictive value. In addition, The results of DCR were about equal with the results of other imaging modalities. Thank you very much.

- "Based on our findings, DCR is expected to become a common preoperative examination for predicting the operative time or bleeding volume and deciding on the surgical approach, such as uVATS and RATS." Speculating that DCR will gain in popularity after your findings is not an appropriate conclusion.

Reply: Exactly. I revised the expression (Revised manuscript, Page 15, Line 281). Thank you for your kind comments.

Reviewer D

Thank you for the opportunity to review a manuscript entitled "Preoperative Detection of Pleural Adhesions Using Dynamic Chest Radiography: Prospective Analysis."

The authors developed a method, DCR, to predict pleural adhesions before surgery. The author emphasized that the radiation exposure during DCR was acceptable. Despite low sensitivity, it showed feasible specificity and negative predictive value, which may be helpful to plan a surgical approach and expect operation time and blood loss. Although I enjoyed reading the manuscript, there are some points to be addressed.

Reply: Thank you for your great comments.

1. Proofreading is strongly recommended.

Reply: This manuscript has already been proofread by an expert whose first language is English. Thank you.

2. For an original study, it is recommended to clarify the objectives or hypothesis of the study at the end of Introduction.

Reply: Thank you, and it is mentioned in Page 4, Line 70-72.

3. Page 5, Line 81. Please provide sample size. Also, I wonder if authors conducted the study for sequential cases. I mean, please describe how many patients were considered eligible during the study period, and how many patients did not agree to participate. If there was a bias in selection besides the exclusion criteria, it should be included in limitation.

Reply: Thank you, and I added it in the Methods (Revised manuscript, Page 5, Line 81).

4. Page 7, Line 121. Please specify who evaluated. Similarly, Page 7, Line 131: please specify who assessed the degree of adhesion. Were these determined by only one thoracic surgeon? Or by discussion? What was the level of clinical experience of the evaluators? If there were multiple evaluators, how did you calibrate the difference between evaluators? Were the evaluators blinded to the clinical information of the

patients? In addition, how did authors measure 20% of the pleural cavity? 5 minutes dissection seems too short to have any expectations of blood loss and total operation time, please provide the rationale.

Reply: Thank you, and it is very important. We added them in the Methods (Revised manuscript, Page 7, Line 121-122, Page 8, Line 134-135).

5. Page 8, Line 160-161. What do the numbers of 63, 28, 12 and 17 mean? Please specify the unit (probably patients or cases)?

Reply: Thank you. We revised them in the Results (Revised manuscript, Page 9, Line 162-163).

6. Page 10, Line 178. Please specify what intra-lobar means. Should it be inter-lobar?

Reply: Thank you. We revised it in the Results (Revised manuscript, Page 10, Line 182).

7. Page 11, Line 189, 193, 196, 200. I wonder if “correct” and “incorrect” are appropriate. Accurate/inaccurate sounds better.

Reply: Thank you. We revised them in the Results (Revised manuscript, Page 11, Line 194-205).

8. Page 13, Line 231. Did authors have any sub analysis among patients with emphysema or interstitial lung disease? Do the results of sensitivity, specificity or other parameters change? Since one third of patients had emphysema, I wonder how the condition affected the results.

Reply: Thank you very much. It is very important. So, we added the results of the patients with emphysema (Revised manuscript, Page 10, Line 177-179).

9. Page 12, Line 203-211. This paragraph is redundant since there is almost the same paragraph in Introduction. Please provide a more insightful implication instead.

Reply: Thank you. We deleted it in the Discussion (Revised manuscript, Page 12, Line 210-213).

10. The methodology the authors took seems to be overall evaluation if there is adhesion or not. In other words, specific locations of adhesion would not be detected even when some adhesions are predicted. To have an approach like VATS or RATS, surgeons should be mindful not to injure the lung when they open the first port. Please address if authors believe DCR is useful to decide where to install the first port.

Reply: Thank you. We consider not only the first port placement, but also the surgical approach including U-VATS or RATS. According to the results of this study, we may change surgery by the findings of DCR from now on. Thank you.

11. Again, when authors predicted some adhesions preoperatively, were there any cases in which initial planning of approach needed to be rearranged? What did authors do after detecting pleural adhesions. This is a crucial question. As the point above,

surgeons are always aware of the risk of intraoperative bleeding regardless of pleural adhesion and critical points are mediastinum and apex. Since DCR is not good at detection of adhesion around mediastinum and apex, I wonder how practically it is useful for preoperative evaluation.

Reply: Thank you. According to the results of this study, we may change surgery by the findings of DCR from now on. As you say, especially, DCR can detect NO adhesion. So, U-VATS and/or RATS will have good surgery indications when no findings of adhesions are found by DCR. Thank you for your great comments.