

Peer Review File

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Reviewer A

First of all, I would like to commend the authors on their approach to pain management. With an increasing commitment to ERAS-principles, we as surgeons do need to be deeply involved into all our patient's treatment phases. After reviewing your manuscript, I would like to address a couple of issues:

- Even though you addressed the fact that UVATS was performed by a single surgeon in your limitations section, you should discuss this major bias issue more in depth.
- Why did you switch from epidural analgesia to no regional anesthesia at all? How about erector spinae plane block or paravertebral blockade as viable alternative?
- Your methods section, at least the "Surgeons" part, would benefit from a re-write.

Reply:

Thank you for your valuable comments.

Comment 1: Even though you addressed the fact that UVATS was performed by a single surgeon in your limitations section, you should discuss this major bias issue more in depth.

Reply 1:

Other reviewers pointed out the same thing, so we rewrote the results according to the result of one chief surgeon.

Changes in the text:

Abstract-Results (see page 3, line 53-56)

Methods-Surgeons (see page 8, line 155-156)

Methods-Data management and statistical analyses (see page 14, line 277-281)

Results (see page 15, line 296-316)

Figure 2

Table 2, 3

Supplement table 2, 3

Discussion (see page 17, line 343-346)

Limitations (see page 20, line 417-419)

Conclusions (see page 20, line 434)

Comment 2: Why did you switch from epidural analgesia to no regional anesthesia at all? How about erector spinae plane block or paravertebral blockade as viable alternative?

Reply 2: As described in the results and discussion, 42.4% patients showed epidural anesthesia-related adverse events. Adverse events increase the workload of medical staff. We thought that good pain control could be obtained without epidural anesthesia.

Comment 3: Your methods section, at least the “Surgeons” part, would benefit from a re-write.

Reply 3: We have corrected them according to your indications.

Change in the text:

Methods-Surgeons (see page 8, line 155-156)

Reviewer B

This is a retrospective review describing their experience with developing a uniportal VATS program at their institution

The principal findings were;

uVATS had less bleeding, shorter operating time, less hospital stay, fewer complications and less pain

I have several major concerns with this manuscript. This retrospective study involves 3 phases, phase 1) mVATS (all tumors treated)

Phase 2) early learning curve of uVATS – where there was some patient selection for easier cases

Phase 3) uVATS -where all cases were tackled

In addition all uVATS cases were performed by the chief surgeon. In the mVATS procedures, operations were performed by a variety of surgeons with variable experience.

The above significantly decreases the impact of any differences in operating time, and complications reported by the authors, since the mVATS cases were likely more complex operations, and also performed by more inexperienced surgeons.

The authors have also performed propensity matching to compare the patient groups, however only limited patient variables are included for this analysis.

Tumor factors that could make the operation more challenging such as tumor size, central versus peripheral location, clinical N1 disease were not included in the

propensity matching.

If this manuscript is eventually accepted, I would recommend removing the discussion of morbidity and operating time from the abstract, as this analysis is severely flawed, and a casual review of the abstract would be misleading.

The most significant contribution of their manuscript is their pain analysis. If this manuscript is resubmitted, I would provide a more detailed pain analysis and how pain differed between the groups, as this is likely where uVATS has its biggest advantages over mVATS.

In its current form, I do not feel that this manuscript should be accepted

Reply: Thank you for your valuable comments. Other reviewers pointed out the same thing, so we rewrote the results according to the result of one chief surgeon. And we included clinical N disease information.

New table 3 showed that no difference in acute pain between U-VATS and M-VATS. However, when the data of all surgeons were analyzed, U-VATS patients had significantly less acute pain. Postoperative acute pain may be affected by the skill of the surgeon.

Change in the text:

Abstract-Results (see page 3, line 53-56)

Methods-Surgeons (see page 8, line 155-156)

Methods-Data management and statistical analyses (see page 14, line 277-281)

Results (see page 15, line 296-316)

Figure 2

Table 2, 3

Supplement table 2, 3, 4

Discussion (see page 17, line 343-346)

Limitations (see page 20, line 417-419)

Conclusions (see page 20, line 434)

Reviewer C

The authors performed a retrospective review of patients who underwent lobectomy or segmentectomy by M-VATS or U-VATS through three phases of their U-VATS learning curve. They found that U-VATS is associated with less neuropathic pain even without epidural anesthesia. This is an important question in assessing whether there are clinical advantages of U-VATS.

- The description of the port placement is a bit confusing. Perhaps replacing it with a better figure would be helpful. Was one port incision extended to extract the specimen in the M-VATS procedures?
- It's very interesting to read about differences in pain management. We very rarely use fentanyl infusions but instead patient controlled analgesia. And we never leave an epidural in for 14 days.
- The statistical analysis may benefit from review. The propensity matching does not seem to take into account tumor size, and U-VATS was used only for tumors less than 2cm initially.
- A major limitation is that the chief surgeon performed all of the U-VATS cases, but other surgeons (presumably less experience) performed the M-VATS cases. This should be acknowledged.
- Another major limitation in comparing U-VATS with or without epidural anesthesia is that the chief surgeon was more experienced with U-VATS during the time without the epidural.
- Surgical time seems to be very important to pain control. Did the authors see what effect this had over which VATS approach?
- Of note, this manuscript would benefit from editing for clarity. For example, there is a very long sentence at lines 79-83.

Reply: Thank you for your valuable comments.

Comment 1: The description of the port placement is a bit confusing. Perhaps replacing it with a better figure would be helpful. Was one port incision extended to extract the specimen in the M-VATS procedures?

Reply 1: We added some sentence in the Figure 1 legend and port placement.

Change in the text:

Figure legends (see page 26, line 547-550)

Comment 2: It's very interesting to read about differences in pain management. We very rarely use fentanyl infusions but instead patient controlled analgesia. And we never leave an epidural in for 14 days.

Reply 2: We have generally used intravenous fentanyl for patients who cannot use epidural anesthesia. It is one of the useful methods for pain control. Epidural

anesthesia may be used for up to 14 days, but it is generally removed the day after chest tube removal.

Comment 3: The statistical analysis may benefit from review. The propensity matching does not seem to take into account tumor size, and U-VATS was used only for tumors less than 2cm initially.

Reply 3: Propensity matching analyzed by considering the tumor size. It is also described in the method.

Change in the text:

Please see page 14, line 279-281

Comment 4: A major limitation is that the chief surgeon performed all of the U-VATS cases, but other surgeons (presumably less experience) performed the M-VATS cases. This should be acknowledged.

Reply 4: Other reviewers pointed out the same thing, so we rewrote the results according to the result of one chief surgeon.

Change in the text:

Abstract-Results (see page 3, line 53-56)

Methods-Surgeons (see page 8, line 155-156)

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Results (see page 15, line 296-316)

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Comment 5: Another major limitation in comparing U-VATS with or without epidural anesthesia is that the chief surgeon was more experienced with U-VATS during the time without the epidural.

Reply 5: We think that in the early stage of introduction for U-VATS, it would be unavoidable to keep safety. We added about the experience during early introduction time in the limitation.

Change in the text:

Please see page 20, line 415-420

Comment 6: Surgical time seems to be very important to pain control. Did the authors see what effect this had over which VATS approach?

Reply 6: Yes. We have already reported on surgery time and postoperative neuropathic pain (Reference 17: Homma T, Shimada Y, Tanabe K, et al. Adverse factors and postoperative neuropathic pain in challenging video-assisted thoracoscopic surgery. *Ann Palliat Med* 2021; Feb 5;apm-20-1729. doi: 10.21037/apm-20-1729.

Comment 7: Of note, this manuscript would benefit from editing for clarity. For example, there is a very long sentence at lines 79-83.

Reply 7: Exactly. We corrected it.

Change in the text:

Introduction (please see page 5, line 79-82)

Reviewer D

I would like to thank the authors and the research team for clearly presenting this paper in background, rationale and study findings. This is extremely interesting in the context of increasing numbers of procedures performed via minimally-invasive means. The analysis proposed is concise and precise, both in statistical data and contextually to available literature.

In order to further the implications of the paper, I would suggest the followings:

1. It may be useful to clarify how the three phases of the study were chosen and analysed, especially with regards to the current routine use of U-VATS at your institution. Has this become your sole VATS approach to lung resection?
2. The paper suggests that a single chief surgeon performed U-VATS procedures at your centre. However, variability will be introduced when the approach is shared to other qualified and training surgeons, can you suggested additional difficulties which were encouraged during the dissection and resection of lung tissue and how this may affect the preference of U-VATS over M-VATS?
3. It could be speculated that U-VATS patients expected to experience less pain if they had previously been told that they would undergo a more minimally-invasive procedure compared to standard surgical approach worldwide. Were patients surveys about their experiences and beliefs around pain prior to the procedure? This may lead M-VATS patients to report subjectively higher pain scores than U-VATS.

4. As mentioned in the limitations, these findings are significant for thoracic surgery and approach to lung resection, but this single-centre experience on a limited sample population may be difficult to replicate across various centres and surgeons. Have the centre developed a training protocol for the approach to be shared across other centres in order to audit these findings in a wider patient and surgeon population?

Reply: Thank you for your valuable comments. Other reviewers pointed out the same thing, so we rewrote the results according to the result of one chief surgeon.

Comment 1: It may be useful to clarify how the three phases of the study were chosen and analysed, especially with regards to the current routine use of U-VATS at your institution. Has this become your sole VATS approach to lung resection?

Reply 1: For the chief surgeon, U-VATS has become almost the only approach. However, for inexperienced surgeons, U-VATS is technically difficult. Therefore, M-VATS may be safer and more educational for them. It is unclear how many surgeries should be performed with M-VATS in order to move to U-VATS, and it is considered to be one of the problems in the future. We added these sentences.

Change in the text:

Discussion (please see page 19, line 404-408)

Comment 2: The paper suggests that a single chief surgeon performed U-VATS procedures at your centre. However, variability will be introduced when the approach is shared to other qualified and training surgeons, can you suggested additional difficulties which were encountered during the dissection and resection of lung tissue and how this may affect the preference of U-VATS over M-VATS?

Reply 2: As described in the discussion, lymph node dissection and middle lobe lobectomy were initially difficult with U-VATS. In addition, in cases of severe adhesion of the vascular sheath, tumors of 5 cm or more, and locally invasive tumors, U-VATS is considered to be challenging as well as M-VATS.

Change in the text:

Discussion (please see page 19, line 392-394)

Comment 3: It could be speculated that U-VATS patients expected to experience less pain if they had previously been told that they would undergo a more minimally-invasive procedure compared to standard surgical approach worldwide. Were patients surveyed about their experiences and beliefs around pain prior to the procedure? This may lead M-VATS patients to report subjectively higher pain scores than U-VATS.

Reply 3: We explain that we manage patients to be as painless as possible after surgery, but we do not talk about the potential changes in pain with a surgical approach. Because there is always the potential to convert to thoracotomy.

Comment 4: As mentioned in the limitations, these findings are significant for thoracic surgery and approach to lung resection, but this single-centre experience on a limited sample population may be difficult to replicate across various centres and surgeons. Have the centre developed a training protocol for the approach to be shared across other centres in order to audit these findings in a wider patient and surgeon population?

Reply 4: Yes. Currently, we have already conducting multicenter training and study in the Japanese Uniportal VATS Interest Group.