

Peer Review File

Article information: <https://dx.doi.org/10.21037/ccts-21-24>

Review Comments - Round 1

Reviewer A

The authors are very detailed in their literature review, however the paper is non-specific to thoracic surgery and does not focus on key ERATS components. Recommend revision that focuses on thoracic surgery and a more concise approach.

1. Introduction – no changes needed

2. Discussion

a. Recommend capitalizing Table 1 for stylistic choice.

Reply: Thank you for the suggestion.

Changes in text: Table Capitalized.

3. The nutrition and smoking cessation sections are well done.

4. Methods

a. Articles that referred to the non-thoracic surgical population were excluded except were specifically mentioned because of a lack of thoracic surgery-specific literature. – This sentence is confusing and worded poorly.

Reply: Thank you for drawing our attention to this, “were” was supposed to be “where”.

Changes in text: The sentence was rewritten; see page 5 lines 102 – 104.

5. Perioperative techniques

a. Recommend combining some sections that are relevant across specialties (post-operative nausea and vomiting, normothermia, surgical site prophylaxis) into one section that is more concise.

Reply: Thank you for the suggestion. We elected to give each of these topics their own section because they are all individually important parts of the enhanced recovery framework.

6. Atrial Fibrillation prevention

a. This section is nicely outlined for AATS guidelines.

7. Regional Anesthesia and Pain Relief

a. A variety of ERATS protocols give Tylenol and gabapentin preoperatively. This is worth mentioning in the context of an ERATS discussion.

Reply: Thank you, we absolutely agree with your comment. In an attempt to maintain

a thoracic surgery focused approach and keep the review to a reasonable length we elected to focus mostly on the debate between different and in some cases novel regional techniques as opposed to an in depth review of the evidence for all of the many adjuncts that may be included under the umbrella of multimodal oral/IV analgesia (gabapentin, ketamine, dexmedetomidine etc...). We do not include gabapentin in our thoracic ERAS pathways and did not specifically mention it given the concerns expressed by the FDA regarding concomitant use with opioids in patients with underlying respiratory impairment.

Changes in text: See page 15, line 372. We elaborated on what we meant by multimodal analgesia.

8. Surgical Technique

a. This section is nicely outlined.

b. Would recommend discussion of robotic assisted thoracoscopic surgery which has been demonstrated to higher lymphadenectomy achieved as compared to VATS.

Reply: Thank you very much for the suggestion. Robotic VATS is a very interesting emerging technique in lung resection and its adoption is becoming more widespread. While we did not feel there was room for a full in depth review of robotic VATS in this paper focused on enhanced recovery, having read your comment we did agree that this issue does deserve mention.

Changes in text: See page 18, lines 420 – 424: Other novel or non-routine approaches to thoracic surgical procedures are being adopted and researched with increasing interest. These include robotic-assisted lung resections, non-intubated lung surgery and prone esophagectomy, each with their own various purported benefits. An in depth review of all of these novel techniques is beyond the scope of this review but as the body of literature around them increases they may work their way into routine practice.

9. Case discussion:

a. The idea of a case discussion is well done. I would recommend introducing the case earlier in the paper (i.e. after methods section) so as to frame the narrative.

Thank you for the suggestion. In the introduction we do mention that a short case will be used to illustrate how prehabilitation programs can aid in perioperative decision making for these patients. The reference provided by the journal editors for guidelines for narrative reviews did not give any specific suggestions for how a case should be introduced or included in a review but if the editors or reviewers feel strongly that the case should appear earlier in the text we can revise this.

10. Table 1:

a. Recommend consistent use of capital vs. lowercase letters (pre/intraoperative s. post-operative).

Reply: Thank you for the suggestion.

Changes in text: Table Capitalized.

Reviewer B

Thank you for giving me the opportunity to review your article. I was just wondering how you can propose such a review article on ERAS with discussion of several points of the ERAS items and not include or cite the ESTS/ERAS guidelines published on January 2019 (Batchelor et al EJCTS 2019). This is just a summary of these guidelines... and I am not mentioning all articles on ERAS in thoracic surgery.

Reply: Thank you very much for your comment. We are of course familiar with the 2019 guidelines from the ERAS society/ESTS that provide excellent evidence-based recommendations for lung (mostly lung resection) surgery. In our review we included literature published up to March 2021 (those guidelines reviewed the literature up to 2017). Additionally, we did not focus solely on lung resection surgery but also included the esophagectomy population. The guidelines that you mention did not appear in our references likely because we were only citing original research articles. After reading your comment however, I can imagine that other readers may have the same question. Therefore, we added some text to clarify this.

Changes in the text: See page 4, lines 88- 92.

Guideline recommendations have been published by the ERAS society for specific surgical procedures (lung resection, esophagectomy) (4,5). As these pathways consist of bundles of interventions throughout the perioperative period, the relative contribution of each individual component of these programs remains to be elucidated. The aim of this article is to summarize the current state of the literature on various individual elements of ERAS pathways in thoracic surgery in both lung resection and esophagectomy populations, including evidence for the role of prehabilitation interventions.

Reviewer C

I want to congratulate the authors for a very thoughtful review of current ERAS practices in thoracic surgery.

I have been surprised by all the aspects included by the authors in their review, but I have missed to read the current status of patient information and follow up.

I would appreciate if the authors could comment on this.

Reply: Thank you for reviewing our paper. I am not sure if you are referring to postoperative follow up? This is one area that we did not focus on, as we did not come across a lot of literature on this topic and we are focusing more on the immediate perioperative period.

Reviewer D

Thank you for the opportunity to review this article describing the prehabilitation and Enhanced Recovery After Surgery (ERAS). I think there are several points to revise before publication.

In this review, although the authors investigated lung resection and esophagectomy, these two types of surgery are completely different in their management and surgical stress. I think that the authors had better focus on the lung resection. Robinson et al. also investigated the clinical impact of ERAS after excluding esophageal surgery (1).

Reply: Thank you for taking the time to read and give feedback on our review. I certainly appreciate your comment that esophagectomy and lung resection do differ in terms of patient population, and of course management. While you recommend focusing on lung resection, another reviewer felt that we should have been broader in our scope and included procedures such as lung transplant. We were approached for this review of ERAS and prehab in thoracic surgery based on our local expertise at the Montreal General as we are an ERAS centre of excellence and apply these principles to both our lung resection and esophagectomy patients and have extensive experience in prehabilitation with these populations. As this is a narrative review and not a systematic review used to generate concise guidelines, we felt this it was a reasonable compromise to include both lung resection and esophagectomy.

Although I think the authors showed the best scientific evidence in the perioperative management, they included unnecessary information. For example, the description of preoperative skin management might not be essential for lung cancer surgery.

Reply: Thank you for your comment. We chose to include a review of the evidence on preoperative skin preparation in our section on surgical site infection because it is included on our local ERAS pathways, we felt the prevention of SSI is an important element in the care of these patients and there is a strong body of evidence to support the practice.

In the discussion of surgical technique, I think that VATS and robotic surgery should be mentioned in detail.

Reply: Thank you very much for the suggestion. Robotic VATS is a very interesting emerging technique in lung resection and its adoption is becoming more widespread. While we did not feel there was room for a full in depth discussion of robotic VATS in this paper focused specifically on enhanced recovery, having read your comment we did agree that this issue does at least deserve mention.

Changes in text: See page 18, lines 420 – 424: Other novel or non-routine approaches to thoracic surgical procedures are being adopted and researched with increasing interest. These include robotic-assisted lung resections, non-intubated lung surgery and prone esophagectomy, each with their own various purported benefits. An in depth review of all of these novel techniques is beyond the scope of this review but as the body of literature around them increases they may work their way into routine practice.

In table 1, the words of postoperative management are capital.

Reply: Thank you for pointing this out.

Changes in text: Table capitalized to be consistent.

Reviewer E

The authors reviewed the application of enhanced recovery after surgery (ERAS) principles to the thoracic surgery population. They searched a lot of relevant studies in this field and finished a narrative review which covers the most important aspects of ERAS during the whole perioperative period including perioperative nutrition, smoking cessation, anemia management, preoperative fasting and carbohydrate treatment, prehabilitation, prevention of venous thromboembolism, prevention of surgical site infection, management of core temperature, lung isolation, mechanical ventilation, anesthetic technique, perioperative fluid management, postoperative nausea and vomiting control, atrial fibrillation prevention, regional anaesthesia and pain relief, surgical technique, chest drain management and postoperative mobilization and physiotherapy. Several issues should be revised before publication

- 1) As one of the reviewers mentioned, this review was based on several guidelines and consensus, while they were not cited, especially Batchelor et al EJCTS 2019. A plagiarism is not allowed, and normative and reasonable citation was the most basic rule. Thus, corresponding revisions are encouraged.

Reply: Thank you for taking the time to read and give feedback on our review. We are of course familiar with the 2019 guidelines from the ERAS society/ESTS that provide excellent evidence-based recommendations for lung (mostly lung resection) surgery based on systematic review of the literature. Our paper was intended as a narrative review and we included literature published up to March 2021 (those guidelines reviewed the literature up to 2017). Additionally, we did not focus solely on lung resection surgery but also included the esophagectomy population. The comprehensive guidelines that you mention did not appear in our references likely because we were only citing original research articles. After your comments however, we added some text to clarify this including citing those guidelines.

Changes in the text: See page 4, lines 88- 92.

Guideline recommendations have been published by the ERAS society for specific surgical procedures (lung resection, esophagectomy) (4,5). As these pathways consist of bundles of interventions throughout the perioperative period, the relative contribution of each individual component of these programs remains to be elucidated. The aim of this article is to summarize the current state of the literature on various individual elements of ERAS pathways in thoracic surgery in both lung resection and esophagectomy populations, including evidence for the role of prehabilitation interventions.

- 2) Thoracic operations included lung, mediastinal, esophageal, tracheal, and transplantation surgery. This review particularly focused on the lung and esophageal surgery, while mediastinal, tracheal, and transplantation surgery were largely unmentioned. It will be more comprehensive for this review to cover these surgical procedures.

Reply: Thank you for your comment. While you recommend broadening the scope of the cases we included in this review, another reviewer suggested we revise and focus solely on lung resection. We were approached for this review of ERAS and prehab in thoracic surgery based on our local expertise at the Montreal General as we are an ERAS centre of excellence and we apply these principles specifically to both our lung resection and esophagectomy patients and have extensive experience in prehabilitation with these specific populations. As a result we felt that limiting the scope of our review to these procedures was a reasonable compromise. This was the rationale for focusing on these subsets of thoracic surgical cases.

3) The postoperative outcomes of prehabilitation in lung resection surgery reported shorter length of stay, shorter chest tube drainage time and decreased complications. The authors did not introduce the details of prehabilitation program. Please clarify.

4) The authors gave several recommendations for ERAS. Please provide the evidence level and grade of your recommendation.

Reply: This article was not designed as a systematic review used to generate guidelines, but instead a narrative review of the literature. We followed the structure recommended by the editorial office for writing a narrative review.¹ As a result we are not intending to generate guideline recommendations.

1 - Green BN, Johnson CD, Adams A. Writing narrative literature reviews for peer-reviewed journals: secrets of the trade. *J Chiropr Med.* 2006;5(3):101-117. doi:10.1016/S0899-3467(07)60142-6

5) Tubeless surgery (chest tube, tracheal intubation, urinary drainage), one of the hot topics in thoracic surgery, is also one of the latest progresses of ERAS. The authors are suggested to include this topic.

Reply: Thank you for the comment. We agree that these are certainly interesting topics. While it is not standard of care in ERAS pathways, we addressed the omission of chest tubes on page 18, lines 419-421. Endotracheal tube-less surgery is a very interesting emerging technique in lung resection. We did not review it because we felt it is still a fairly novel technique that is not used widely. Having read your comment we did agree that this issue does at least deserve mention.

Changes in text: See page 18, lines 420 – 424: Other novel or non-routine approaches to thoracic surgical procedures are being adopted and researched with increasing interest. These include robotic-assisted lung resections, non-intubated lung surgery and prone esophagectomy, each with their own various purported benefits. An in-depth review of all of these novel techniques is beyond the scope of this review but as the body of literature around them increases they may work their way into routine practice.

6) Minimally invasive surgery including VATS and RATS was different in ERAS when compared with open surgery. Please introduce the specific aspects of ERAS for minimally invasive surgery.

Reply: Thank you for your comment. We agree that when making guidelines or

devising ERAS pathways there are certainly differences based on whether a minimally invasive or open approach was taken. We were not aiming to generate guidelines but simply to review the current state of the evidence for different elements of these pathways. Wherever possible we would describe if a study included open or minimally invasive or both techniques for lung resection. A similar approach was applied to lung resection vs thoracotomy.

Reviewer F

The guest editors thank the authors for their submission and feel that overall this is a very good paper.

We appreciate you taking the time to review and give your detailed feedback.

It covers the relevant topics in a very structured way, and was a pleasure to read. I am certain that all readers, from surgeons to anesthetists to other specialists involved in the care of thoracic surgery patients will have learned something useful and practical that they can take « back to the patient's bedside ». Nevertheless, the reviewers felt that there was still some room for improvement.

The reviewers had several comments that we encourage the authors to consider. We should add that the current format (addressing both pulmonary and some instances of non-pulmonary thoracic surgery) is adequate, provided the text is clear on this point.

Thank you. The rationale for this choice was that we were approached for this review of ERAS and prehab in thoracic surgery based on our local expertise at the Montreal General as we are an ERAS centre of excellence and we apply these principles specifically to both our lung resection and esophagectomy patients and have extensive experience in prehabilitation with these specific populations. Therefore, we felt that including these two categories of procedures was a reasonable approach. Based on this comment and those from other reviewers we chose to make this explicitly clear.

Changes in the text: Page 4, lines 91-93. The aim of this article is to summarize the current state of the literature on various individual elements of ERAS pathways in thoracic surgery in both lung resection and esophagectomy populations, including evidence for the role of prehabilitation interventions.

The guest editors also added the few comments below.

- « ERAS » is a registered trademark and as such requires an « ® », or equivalent.

Reply: We thank you for bringing this to our attention. We will discuss this with the editorial office as often this acronym does appear in the literature without the “®” symbol although the term is indeed trademarked by the ERAS Society.

Changes in the text: The registered trademark logo has been added to all mentions of ERAS.

Editorial Office: It is ok to keep ERAS without the logo “®”.

- The authors mention their « institution », their « site », their « center » at several

points in the text. Each time please be sure to specify which institution is being referred to, as the authors are affiliated with more than one institution.

Reply: Thank you for pointing this out. One of the authors was a clinical fellow at the Montreal General Hospital during the writing of this manuscript but as they have returned to their home institution that is the institution listed next to their name. We have clarified in the text that we are referring to the Montreal General Hospital.

Changes in the text: See page 4, line 86, we clarify that our institution refers to the Montreal General Hospital.

- In the section on smoking cessation (p. 4 lines 98-107) : there seem to be a couple of conflicting statements; it is mentioned that smoking cessation makes no difference at a cutoff of 6 weeks preop, whereas on lines 103-104, a study is cited that found smoking cessation to be of benefit even less than 1 month preop. Are these 2 different studies? Please be sure to mention explicitly in the text.

Reply: Thank you for pointing this out, we have revised the text to be clearer.

Changes in the text: Page 6, lines 132-140

A decrease in postoperative pulmonary complications (PPCs) and ICU admission has been demonstrated among never vs active smokers undergoing lung resection, however only a trend to reduced PPC and ICU admission was observed for ex-smokers with no difference between those who stopped more than or less than 6 weeks prior to surgery (13). Two large database studies have shown constant but gradual reduction in risk of PPCs (and in one study perioperative mortality) with increased duration of smoking cessation, with benefits seemingly continuing to increase with more than one year of cessation (12,14). While PPCs trended towards a decrease even with less than one month of cessation in both studies, this finding has not been reproduced consistently (15) and delaying surgery for the “full” benefit which may extend beyond one year is clearly not reasonable.

- Please define the following acronyms the first time they appear in the text: ASRA, (line 175), TIVA (line 249), PONV (line 255), AKI (line 268), POAF (line 328), TEA (line 340).

Reply: Thank you for this suggestion

Changes in text: The first appearance of each acronym was defined

- Line 122: please specify whether or not anemia guidelines are specific to thoracic surgery.

Reply: Thank you for the suggestion, we clarified this in the text.

Changes in text: Page 7, lines 155-158: The largest RCT to date, not included in the aforementioned meta-analysis, did not replicate these findings but was specific to abdominal procedures and was criticized for not specifically targeting iron deficient anemia and not outlining a transfusion strategy (24).

- Line 177: please provide a reference for the « Caprini » score, for the benefit of the reader.

Reply: Thank you for the suggestion. As the ACCP guidelines do not actually follow the validated Caprini score but in fact used this score (and another model) to create their own risk assessment tool, the sentence was modified to clarify this.

Changes in text: Page 9, lines 213-218. The American College of Chest Physicians (ACCP) guidelines propose an outline to determine individual patient risk, and recommend using either pharmacologic prophylaxis or intermittent pneumatic compression (IPC) for most thoracic surgery patients, and a combined pharmacologic/mechanical approach for high risk patients and procedures (including extended resections, pneumonectomy and esophagectomy) who are not at major risk of bleeding (in which case IPC is favoured)

- Line 186: Please specify whether the effectiveness of antibiotic prophylaxis is limited to cases where a hollow viscus (esophagus, bronchus) is entered or divided, or whether the effectiveness extends to « clean » cases as well (ex : pulmonary wedge resections).

Reply: The studies supporting antibiotic prophylaxis discussed in the reference we cited by Chang and Krupnick include a wide variety of thoracic surgical procedures including ones where a hollow viscus was not entered.

Changes in the text: Page 10, lines 223-225: Good evidence supports the use of first generation cephalosporins such as cefazolin in a wide range of thoracic surgical procedures, whether or not a hollow viscus is entered.

- Line 254: the authors mention they prefer sevoflurane. For the benefit of non-anesthetists, can the authors mention whether the benefits of sevoflurane are generalizable to other volatile anesthetics, of which sevoflurane has the best profile? It is implied on line 255 that volatile anesthetics are more prone to PONV, and that this is particularly the case with sevoflurane; once again, for non-anesthetists, please mention explicitly.

Reply: Thank you for pointing out the lack of clarity here. While evidence exists for decreased inflammatory mediators in the lung post OLV with various volatiles, a larger body of evidence exists supporting the anti-inflammatory and immunomodulatory role of sevoflurane in this context. The comment about PONV was not meant to imply that use of sevoflurane in particular increases risk of PONV (when compared to other volatiles). We were suggesting that high risk factors for PONV would be an indication for TIVA (foregoing volatiles altogether).

Changes in text: Page 12, lines 292-294. The authors prefer sevoflurane both for its bronchodilating effects and the larger body of evidence supporting the potential immunomodulatory benefits with regards to lung injury, unless there are strong risk factors for postoperative nausea and vomiting (PONV) in which case TIVA may be indicated

Line 326: any concern about lung toxicity with amiodarone? (in the context of lung resection surgery)?

Reply: Thank you for pointing out this concern. Cases of acute pulmonary toxicity

that may occur with short term amiodarone administration (as in the context of perioperative atrial fibrillation prophylaxis) have for the vast majority been limited to patients receiving doses much higher than currently recommended prophylactic doses in the American Association for Thoracic Surgery guidelines. Nevertheless we agree that it is a concern worth mentioning.

Changes in the text: Page 15, lines, 365-367: While concern exists for acute pulmonary toxicity with amiodarone use particularly in the pneumonectomy population, reports of such toxicity at doses currently recommended for prophylaxis are exceedingly rare (107).

Line 396: « atrium express mini » is a commercial name; please mark appropriately (with an « ® » or equivalent).

Reply: We thank you for bringing this to our attention!

Changes in the text: The registered trademark logo has been added.

Regarding the overall presentation of the paper and visuals, we would suggest presenting the « Case » in a « box » that accompanies the main text. We find that this would neatly isolate this element visually.

Reply: Thank you for this suggestion. We agree and will discuss this with the editorial office.

Editorial Office: We would suggest the authors to present the case as Appendix 1 and mention it in the main text to isolate this element visually with better presentation of the paper and visuals.

If the authors had a prehab/ERAS® booklet they use at their institution (as are often used as a patient education tool), I think that the inclusion of salient figures or visual elements from such would really enhance the paper, perhaps they could even accompany corresponding sections in the text. This would also address the comments of reviewer C.

Reply: We appreciate this suggestion. While we do have some patient information brochures the figures relate more to the patient experience and are not really pertinent to most of the content of this narrative review.

Review Comments - Round 2

The authors have improved their manuscript. I have one last concern. I believe that lung resection and esophagectomy are completely different surgery in the management and surgical stress. I suggest that the authors had better focus on the lung resection.

Thank you very much for your time and thoughtful comments.

Reply: We agree that they differ substantially. The reason we chose to include both is that among all thoracic surgical procedures, when it comes to enhanced recovery

pathways, there is a very large body of experience and evidence for these two populations. While there is certainly overlap in terms of the way in which many ERAS principles are applied to these patients, where the evidence pertains specifically to one or the other, this is always mentioned in the text. This way the article is more broadly relevant vs having a narrower scope. After the first round of review, another reviewer felt that we should have been broader in our scope and included procedures such as lung transplant. Based on our local expertise at the Montreal General (as an ERAS centre of excellence) where we apply these principles to both our lung resection and esophagectomy patients we felt these populations were the most pertinent and chose to focus here.

Changes in text: A sentence explaining this rationale was added on line 66.

This is an excellent manuscript that covers all the important aspects of enhanced recovery pathways. The authors did a good job of presenting this complex subject in a clear, structured, and comprehensive way. They have addressed most of the reviewers' comments.

I would suggest a couple of tweaks before the paper is accepted for publication.

One of the reviewers' comments dealt with the prehab protocol at the authors' institution. While the authors refer to this protocol, it is not further outlined. Could the authors briefly summarize their prehab protocol? This could probably most easily be done in the form of a figure.

An initial suggestion to the authors addressed including some pictorial « ERAS » content, perhaps from a patient information booklet. As another paper in this series will deal with patients' experiences of minimally invasive vs open surgery, in addition to enhancing the paper's visual content this would be a neat way to highlight a common thread through different papers in this series. If ever the authors would like suggestions regarding the creation of visual content (figures, etc.), we would be happy to suggest resources.

Reply: Thank you for taking the time to read and re-review our submission! We appreciate your comments. Thank you for this suggestion. We have added a descriptive outline of the components of our own protocol. An important part of prehab is that the protocol be tailored to the individual of course, but the elements are always the same where applicable. We would be open to having an illustration to highlight this! Unfortunately I don't think we can simply take something from our patient information materials for copyright reasons. We would be happy to work with an illustrator on a simple image if such resources are available.

Changes in the text: Line 167 outlines the elements of our program.

Also, lines 412-419, in the section on postoperative pain, the authors described different minimally invasive approaches. However, they did not mention their impact on postoperative pain. Although this is covered in more detail in another paper in this series, could the authors briefly mention the impact of minimally invasive approaches on pain in one or two sentences? This can also be an opportunity to mention in what ways (other than issues of pain control) ERAS may differ in minimally invasive as compared to open surgery, as per an initial suggestion by reviewer E.

Reply: Thank you for the comments. While the overarching principles of ERAS can be applied to both minimally invasive and open surgical techniques, your comments about differences between these techniques with regards to postoperative pain led us to make some modifications to the text.

Changes in the text: Page 17 line 294-396

Below are a few specific minor comments.

We would like to thank the authors and look forward to the revised manuscript.

Line 433: « duration of chest tube insertion »; the term « insertion » may cause a bit of confusion; perhaps « duration of chest tube drainage » would be more clear and consistent with other mentions of this issue in the text.

Reply: We appreciate the time you have taken to review our manuscript. Thank you for this suggestion.

Changes in the text: Line 414 changed to “duration of chest tube drainage”

There are still several undefined acronyms in the paper, which may not be familiar to all readers. Could the authors please make sure they define all acronyms at first mention in the text? These include MWT line 182, DVT line 199, LMWH line 208, UFH line 209, TEE line 323.

Reply: Thank you for this suggestion, we agree that this will make it clearer

Changes in the text: the above mentioned acronyms were defined upon first mention

Please add ® where trademark names are mentioned: IMAPCT® line 119; Flotrac® line 324.

Reply: Thank you for bringing this to our attention. We consulted with the editorial office via email exchange with Anne Lu (science editor) and she advised not to put the registered trademark symbol. I have no objection to putting it if it is appropriate. I know that ERAS is a trademarked phrase but there are many examples in the literature where it is not accompanied by that symbol. I leave it at the discretion of the editors, I am happy to do whatever they feel is appropriate.