TRANSLATIONAL LUNG CANCER RESEARCH

# Peer Review File

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**Review Comments**

**Reviewer A**

The authors presented a retrospective analysis regarding ERAS in patients undergoing VATS lobectomy for lung cancer. The study is well written and shows a slight improvement in post-operative outcomes for ERAS protocol compared to standard care. I suggest several issues that should be revised.

Comment 1

Does the institutional review board approve the study?

Reply 1

Thank you for this very important comment. The Local Ethics Committee approved our study and this was mentioned in the footnote of page 4. We also added this in our methodology section.

Changes in the text:

We modified our manuscript as followed: “The study was approved by the Local Ethics Committee (N°2019-02464) and individual consent was waived.” (page 4, line 8-9).

Comment 2

The control group is labelled as “non-ERAS” and corresponds to the standard care applied before the adoption of the ERAS protocol. Several of the ERAS items are not new to thoracic surgeons (e.g. early mobilization, i.v. fluid restriction, early chest drain removal…). I guess the authors applied these ERAS items also during the standard care period, may be with less standardization. The definition “non-ERAS” could be misleading, I suggest modifying in “pre-ERAS”.

Reply 2

That’s a good point. As you mentioned it, our pre-ERAS management was similar to the ERAS one in some respects. Thus, we applied your suggestion in our manuscript.

Changes in the text:

Through the entire manuscript, we changed the ”non-ERAS” label for a “pre-ERAS” label.

Comment 3

Authors shifted from “pre-ERAS” to “ERAS” in April 2017. Did the authors contemplated a training and washout period? Reported methods suggest that patients managed within staff’s learning curve were included in the ERAS “group”. These could

have masked some ERAS benefit. Furthermore, all the elements described in table 1 seem to be implemented in April 2017, is it right?

Reply 3

This is a good point. We elaborated the care maps with the dedicated clinical nurse, then educated the nurses, anesthesiologists and surgeons during 6 months. We launched the program in April 2017. Of course, we experienced some minor problems during the implementation phase, but we finally decided to include these patients in the ERAS group. We have published our preliminary results after 50 patients showing a decreased rate of complications and shortened length of stay (reference 13 in our manuscript).

Changes in the text:

"After six months of team education and training by a dedicated ERAS clinical nurse, surgeons and anaesthesiologists, an ERAS protocol for VATS anatomical pulmonary resection was finally launched in our thoracic surgery department in April 2017." (page 4, line 22-23).

Comment 4

Methods section: "Daily early mobilization started on the day of the operation and twice daily on the following days". Please define "Daily early mobilization". Early means to me few hours after surgery, "daily" is routine standard care. May be your objective was to mobilize patients soon after surgery and to maintain a daily mobilization/physiotherapy program. Please better define your goals about this ERAS item.

Reply 4

Our ERAS patients were mobilized on the day of surgery as soon as they were fully awake. Their objective was to eat dinner in a sitting position. On the first postoperative day, patients walked in the ward on two occasions and they maintained this routine on a daily basis.

Changes in the text:

We amended our manuscript: "Daily early mobilization, in the form of two short walks in the ward with the help of a nurse, started on the day of the operation as soon as patients were fully awake, and was carried out twice daily on the following days until discharge." (page 6, line 13-14).

Comment 5

Methods section: "The chest tube was removed as soon as there was no air leak and the amount of pleural fluid was <400 mL over 24 hours". The reported ERAS protocol included electronic drainage system. Were 24 hours a cutoff value also for absent air leak or did you use a different cut off between air and fluid outputs?

Reply 5

We used 24 hours as cut off value for fluid and 6h for air leak.

Changes in the text:

We added this precision in our methodology section: “The chest tube was removed as soon as there was no air leak over six hours and the amount of pleural fluid was <400 mL over 24 hours.” (page 6, line 15-16).

Comment 6

Methods section: “The PSM allowed us to simulate a randomized controlled trial”. This is not true, PSM helps to mitigate the selection bias regarding the distribution of the known covariates, but it has no effect of unknown ones. Please omit or better explain.

Reply 6

Thank you for your comment. We changed our manuscript according to your suggestions.

Changes in the text:

We changed our text as followed: “The PSM helped us to mitigate the selection bias regarding the distribution of the known covariates” (page 7, line 4-5).

Comment 7

Methods section: “We found it fair to assume that the distribution of measured baseline covariates was balanced between individuals treated under the ERAS and those under the non-ERAS protocol, due to the size of both groups. This condition had to be met to carry out a PSM”. I do not understand what the authors are stating. PSM is supposed to help balancing covariates between groups. After performing a good PSM, covariates should always result well balanced. Furthermore, I understand from table 2 that 3 baseline covariates (gender, history of arrhythmia and stage) were significantly related to the post-operative management protocol. It sounds strange to me, these odds deserve a comment. Did the PSM consider these covariates?

Reply 7

Thank you for this comment. You are right, this part of the statistical methodology is incorrect and thus we removed it.

Changes in the text:

We deleted this sentence: “We found it fair to assume that the distribution of measured baseline covariates was balanced between individuals treated under the ERAS and those under the non-ERAS protocol, due to the size of both groups. This condition had to be met to carry out a PSM”.

Comment 8

Result section: “There were fewer stage I (55.7% vs. 74.2%; p=0.0006) and more stage III (18.6% vs. 7.2%; p=0.0025) NSCLC in the ERAS group”. Authors observed in ERAS group a number of stage III lung cancer about twice than in the control group. Please comment this result. Did you modify the selection criteria for lung cancer surgery during the study period? Did you extend indication for multimodal treatments? This information is crucial when analyzing post-operative outcomes. Please also add a sentence (or a line in table 2) about the prevalence of neo-adjuvant treatments.

Reply 8

We observed fewer cases of stage I and more advanced stage NSCLCs in the ERAS group. We do not have a clear explanation since the rate of neo-adjuvant chemotherapy were similar in both groups. One possible explanation is that we may have operated larger lesions with growing experience and thus more incidental N1-2 were observed. Interestingly, even with difficult cases, we observed better post-operative outcomes.

Changes in the text:

We added a sentence about this observation in the discussion section (page 14, line 10-17).

Comment 9

Result section: “To harmonize the PSM analysis, one patient was removed from the non-ERAS group, thus making a cohort of 306 patients (non-ERAS: 166, ERAS: 140)”. When performing PSM (with three unbalanced baseline covariates!) removing one patient from the analysis was enough to harmonize the PSM. Firstly, this sentence should be moved to the methods section. Secondly, it is hard to me to understand the methodology. I suggest checking it with a statistician.

Reply 9

In fact, a statistician performed our analyses and the sentence as it was written was an unfortunate misrepresentation of his work. You are right, it was not to harmonize the PSM analysis that we removed one patient, but because this patient did not have any match in the common support.

Changes in the text:

We changed our methodology section as followed: “Only one patient had no match in the region of common support and was thus excluded from the analysis, making a cohort of 306 patients (pre-ERAS: 166, ERAS: 140)” (page 7, line 13-14).

Comment 10

Results section: “The overall compliance to the ERAS program was 81%”. I really appreciated that the authors focused on ERAS adherence; however, I have a few

considerations. Please define ERAS compliance in the methods section or better define ERAS goals in table 1 (which is the cut off value to consider a successful adherence to the "avoidance of fluid overload" item? which is the goal to consider a successful adherence to "post-operative analgesia"? what does "early" feeding mean? There is no information about pre-operative fasting). Adherence to ERAS was reported as one of the main factors influencing ERAS outcomes (Mazza F et al. Gen Thorac Cardiovasc Surg 2020 Sep;68(9):1003-1010; Rogers LJ et al. J Thorac Cardiovasc Surg 2018;155(4):1843–52). The present study is lacking about the evaluation of ERAS adherence effects. Early mobilization was reported as one of the most effective ERAS items in improving post-operative outcomes (Mazza F et al. Gen Thorac Cardiovasc Surg 2020 Sep;68(9):1003-1010; Rogers LJ et al. J Thorac Cardiovasc Surg 2018;155(4):1843–52). As I have already mentioned, a better definition of early mobilization is needed. Some data and/or a comment in discussion about the impact this item on post-operative course would be appreciated.

Reply 10

Thank you for this comment. Our previous study evaluating the ERAS program detailed the different items of the protocol (Forster C, Doucet V, Perentes JY, et al. Impact of compliance with components of an ERAS pathway on the outcomes of anatomic VATS pulmonary resections. Journal of Cardiothoracic and Vascular Anesthesia 2020;00:1-9 => reference 20 in our manuscript). As you suggested, we added more details in the present study.

We strongly agree that early mobilization (which we now clearly defined in the text) is a key element of an ERAS pathway. Several papers have reported the impact of early mobilization on post-operative length of stay and post-operative complications, but a generally accepted definition remains elusive. We decided to have a pragmatic approach and to mobilize the patients on the day of surgery, as soon as they were fully awake, if there were no associated cardiopulmonary comorbidities. This means that the exact timing of mobilization varied from one patient to another, but generally, we accepted that this was "as early" as feasible, depending on the status of each patient. We did add a paragraph in the Discussion section to give more details on the impact of this item.

Changes in the text:

We added the following precisions:

"The compliance was considered complete if the patient could meet all protagonists before surgery." (page 5, line 10-11).

Post-operative phase
Daily early mobilization, *in the form of short walks in the ward with the help of a nurse*, started on the day of the operation as soon as patients were fully awake (page 6, line 13-14)

"*Compliance*
The compliance to the ERAS protocol was based on the 16 individual items of the program described in Table 1, based on current evidence supporting their importance. The compliance rate was defined as the number of protocol items observed divided by the total number of items." (page 6, line 19-23).

We also added the following paragraph in the discussion section:
"Early mobilization has been reported to be a central element of the ERAS pathway (ERAS/ESTS guidelines) to avoid the deleterious effects of bed rest. Rogers et al. reported that early mobilization was a strong predictor of decreased postoperative complications and shortened length of stay, but this study was unclear about which type of mobilization [27]. Mazza et al. reported a shortened length of stay in their ERAS group patients when patients were mobilized into a sitting position within 4 hours from tracheal tube weaning and when physiotherapy started within 12 hours after surgery [30]. The series reported by Khendaar et al. reported an aggressive regimen of mobilization with VATS lobectomy patients placed on a chair as soon as possible with an ambulation target of 250 feet within one hour of extubation. A majority of patients (61.5%) achieved this ambulation goal[31]. In our protocol, 89% of patients were mobilized on day of surgery. They were seated for dinner and walked through the ward helped by nurses from the first day onwards." page 13, line 21-27 + page 14, line 1-4)

Comment 11
Discussion section: From page, 5 lines 44 to page 6 line 2 authors compare their results with the others from literature and they overall seem to be in keeping. Which is the novelty of the present study? Tahiri M et al. (Can J Surg. 2020 May 8;63(3):E233-E240) showed (by a PSM analysis) a reduction of post-operative length of stay in a cohort of patients who underwent VATS lobectomy and managed within an ERAS protocol, as compared to pre-ERAS care.
Reply 11
Thank you for this comment. We agree that the study mentioned by this reviewer is of similar nature to ours. We do however wish to point out several differences.

- We report on a European experience with a larger group of patients
- We report on a longer period of time

- We report on an established ERAS protocol, not on a developing pathway
- We represent a pioneering institution with a long expertise in ERAS pathways and generally very high compliance rates

We feel that our results not only complement, but add scientific solidity to the excellent study published by Tahiri et al. Finally, and in more general terms, our study is one of the very few reporting exclusively on VATS lobectomies for NSCLCs. Most other studies also include wedge resections and thoracotomy procedures.

Changes in the text:

We added a thorough discussion and differentiation of the Tahiri study in the Discussion section (page 12, line 15-25).

Comment 12

Discussion section: "Thereby, the first part of the cohort included only non-ERAS patients and the later part of the cohort represented only ERAS patients. However, the involved surgeons had a wide expertise in VATS lobectomy procedures before the start of the study and the surgical teams and techniques did not significantly change during the study period". How surgeon's expertise could have mitigated the time-related selection bias? Please omit or better explain. The absence of changing in surgical technique is a more reliable protective factor.

Reply 12

The surgeon's expertise was useful in mitigating selection bias insofar as it minimized possible biases introduced when the ERAS program was implemented. We started a VATS lobectomy program in 2010 and by the time the ERAS program was rolled in, each surgeon already had a good experience on VATS lobectomy with more than 100 cases. Thus, the ERAS program was not introduced during the surgeons VATS learning curve.

Changes in the text:

We amended the Discussion section to reflect your comment and clarify our point (page 11, line 14-26).

Comment 13

Please check table 2 for "arrythmia" (arrhythmia?) and "stage" (c-stage or p-stage?).

Reply 13

Thank you for this comment; we applied the change in table 2.

Changes in the text:

Table 2: changes as described above.

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**Reviewer B**

I appreciate the opportunity to review this manuscript on the use of an ERAS protocol. As Henry Ford discovered with modern manufacturing, standardizing any workflow will work and will improve efficiency. I am not surprised that the ERAS program patients had better outcomes.

The shortcoming of the paper is the lack of detail. Most of the discussion can be deleted. The authors do not need to discuss the role of ERAS, but should focus on the elements of the ERAS program.

General reply

We thank this reviewer for their comments. Generally speaking, we decided to not dwell on the details of the ERAS protocol because we published them before (Forster C, Doucet V, Perentes JY, et al. Impact of compliance with components of an ERAS pathway on the outcomes of anatomic VATS pulmonary resections. Journal of Cardiothoracic and Vascular Anesthesia 2020;00:1-9 => reference 20 in our manuscript). Thus, for the sake of clarity and in order to better suit the specific audience of this paper, we decided to only refer to such technical details in the reference list. We did however majorly amend the discussion to reflect the comments of this reviewer.

Comment 1

Table 1 is the heart of the paper. I would eliminate any factors that were in the control and the ERAS. For example, VTE and antibiotics are common to both.

Reply 1

We agree, but these two elements are important in the ERAS protocol and were recommended in the ERAS/ESTS guidelines, so we decided to include them in the protocol for the sake of completeness, clarity and alignment with guidelines.

Changes in the text:

No change.

Comment 2

Discussion of the baseline practice would help. At baseline, there was considerable use of an epidural. Was this put in preoperative assuming conversion to open surgery would happen?

Reply 2

Before 2017, in the pre-ERAS phase, some surgeons and anesthesiologists were more comfortable using an epidural catheter. However, in the ERAS phase, we decided to reserve the epidural for patients with high risk of conversion only. This explains why the reported rate of epidural use has significantly decreased.

Changes in the text:

We amended the MM section (peri-operative section) with the sentence: “Epidural catheter was reserved for patients with high risk of conversion to thoracotomy (as opposed to pre-2017, when its use was more frequent) or in case of intolerance to opioids” (page 6, line 5-6).

Comment 3

I noticed a digital drain was used in both groups, but the parameters to remove the drain changed. Please elaborate. (In my own practice, we send 50% of lobectomy patient’s home in under 48 hours... we pull the chest drain on the morning after surgery if the output is not bloody and there is no air leak.)

Reply 3

In the pre-ERAS group, the decision to remove the chest tube was based on the experience of the surgeons and based on the traditional value of fluid output smaller than 250ml/24h. More recently, data has shown that fluid output of <400ml was safe. We implemented this metric in the ERAS group and changed our approach accordingly.

Changes in the text:

The Table 1 contains already all information about chest tube management in both groups.

Comment 4

Elaborate on the TIVA protocol.

Reply 4

Our manuscript is more focused on the surgical technique, the ERAS protocol and the postoperative outcomes than on the anesthesia protocol. Still, we briefly described it in the M&M section. We decided against the option of making it a separate paragraph because it is not the focus of our article.

Changes in the text:

We did not amend the sentence: “In the majority of cases, the hypnotic used was Propofol by total intravenous anesthesia (TIVA) in order to reduce the likelihood of postoperative nausea and vomiting (PONV). The administration of volatiles was reserved for patients with moderate to severe chronic obstructive pulmonary disease (COPD) due to their bronchodilation properties.”

Comment 5

The LOS is much higher than the STS standard of 4 days, also accounting for the admission to hospital the day before. Please speculate on why that is.

Reply 5

We agree that the STS database reports a four-day hospital stay, but most of these patients have to leave the hospital as soon as possible for economical reason, to a hotel or with a Heimlich valve. The ESTS database reports a mean length of stay of 7 days after VATS lobectomy for lung cancer (Falcoz et al. EJCTS), better reflecting the general practice in Europe. In addition, patients residing in Switzerland all pay a mandatory health insurance that considers that they can leave the hospital once they have recovered. This point is of course largely discussed in pre-operative consultation with the clinical nurse and a date of discharge is planned. This is not to say that we cannot improve in that respect, but we must accept that local practices may differ from country to country.

Changes in the text:

No change.

Comment 6

Use of carbohydrate drink documented in the colorectal literature. How do you justify it in this group of patients? It may not do any harm, but please speculate on if it is doing anything of value.

Reply 6

We agree that the use of carbohydrate drinks in colorectal surgery is done to avoid the deleterious effect of fasting. However, some of the elements included in the ERAS pathways may have only a modest benefit by themselves, but the addition of all these small measures may have a synergistic effect. This is particularly the case for carbohydrate drinks. Finally, the EARS/ESTS guidelines for Thoracic surgery recommend their use and we wished to stick to these guidelines as much as possible.

Changes in the text:

No change.

Comment 7

Bottom line... the details of your protocol are what I care about. Please provide more information and steps on each of the interventions. That would be most useful to the reader.

Reply 7

We agree. Actually, we have already explained the protocol in details in a previous study (Forster C, Doucet V, Perentes JY, et al. Impact of compliance with components of an ERAS pathway on the outcomes of anatomic VATS pulmonary resections. Journal of Cardiothoracic and Vascular Anesthesia 2020;00:1-9 => reference 20 in our manuscript) and we decided to only briefly summarize the protocol. However, we added more details as you suggested.

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Changes in the text:
Page 4-5-6, “ERAS program” section.

**Reviewer C**
Thank you for invitation to this reviewing. In this manuscript title ’Impact of an Enhanced Recovery after surgery pathway on thoracoscopic lobectomy outcomes in non-small cell lung cancer patients. There are a lot of similar articles. The study is retrospective and no remarkable features. I cannot recommend this manuscript for publication of this Journal.

Reply
Thank you for reviewing our manuscript. Our study is innovative in the sense that it is the one of the very few focusing exclusively on VATS lobectomy for non-small cell lung cancer patients. Most other studies also include wedge resections and thoracotomy procedures. We clarified this point in the Discussion section.