

Peer review file

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Reviewer A

Comment: As the rapid development of minimal invasive esophagectomy, the anesthetic managements have changed a lot to prevent major complications and enhance recovery in advance. In this article, the most important evidence-based progress in perioperative approach was reviewed. This manuscript provides a concise concept up to date for anesthesiologists to optimize the perioperative care. However, there remains some gap between concept to clinical practice. For example, what could we do to achieve intraoperative zero balance and which monitor could indicate the tissue perfusion?

I suggest the authors address more on multimodal analgesia for different esophagectomy except the conventional epidural analgesia and nerve blocks.

Reply: According to your suggestions and trying to fill in the gap between concept and clinical practice, we better highlighted some practical advices in the revised version. Fluid management in thoracic surgery is complex. As suggested in our previous work, ("Liberal or restricted fluid administration: are we ready for a proposal of a restricted intraoperative approach? BMC Anesthesiol. 2014 Aug 1;14:62. DOI: 10.1186/1471-2253-14-62") we propose to achieve zero balance or optimize fluids with GDT during esophagectomy. Consequently, to clarify, we changed figure 5 with a new one that takes into account fluid management and hemodynamic monitoring from low to high-risk surgical patients. Please see new figures 5.

In regards to your second question and following your suggestions, we expanded the discussion about multimodal analgesia for different types esophagectomy.

Changes in the text:

Evidence demonstrated that "perspiratio insensibilis" is about 1 mL/kg/h during open abdominal surgery; in addition, thanks to mini-invasive procedures, blood loss during

esophagectomy is scarce. As a consequence, maintenance infusion rate of 1-3 mL/Kg/h of balanced fluid solutions seems to be a reasonable approach to obtain a “zero balance” at the end of surgery.

New version of Figure 5. Peri-operative fluid and hemodynamic management for esophagectomy.

Fluid strategy and hemodynamic approach consider the patient’s anesthesiological peri-operative risk and the risk of surgery itself. For low-risk patients undergoing low risk surgery, standard monitoring and a liberal fluid strategy (green triangles) are considered a valuable option. Esophagectomy should be considered an intermediate-high risk surgery. Consequently, “zero balance” (light blue triangles) or GDT (blue triangles) approach are the proposed options: the former should be considered if the patient is at low-intermediate risk, the latter when a high-risk patient will face to esophagectomy. Hemodynamic monitoring is also included in the figure: patient at low-intermediate risk would benefit from mini-invasive approach, high-risk patients need more invasive tools.

Legend: HR=heart rate, NIBP=non-invasive arterial blood pressure, IAP=invasive arterial blood pressure, SVV=stroke volume variation, PPV=pulse pressure variation, ScVO₂= central venous oxygen saturation, SVI=stroke volume index, CI=cardiac index, DO₂I= indexed oxygen delivery, GDT=goal directed fluid therapy.

Paravertebral blocks (PVB) and erector spine block (ESP) are two valid options. Sometimes a combination of spinal opioids with PVB or ESP is used. These approaches are less invasive and less risky than EDA and could be the right choice in a multimodal approach. They give less hypotension than EDA, leading to less fluid load and the need for vasopressors. These aspects improve the early post-operative mobilization of the patients.

These techniques could also be useful in cases of patients under peri-operative anticoagulation. An ongoing trial (PEPMEN trial) is recruiting patients undergoing MIE comparing the postoperative quality of recovery between paravertebral catheter

versus thoracic epidural analgesia. Transversus abdominis plane block (TAP) represents another option in the postoperative pain treatment armamentarium. Intravenous analgesia with or without opioids probably continues to be the most used type of analgesic regimen due to its easy application and its usually sufficient pain control in conjunction with its low risk for postoperative adverse events. Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are largely used. Postoperative scheduled acetaminophen has been demonstrated to reduce opioid use without drawbacks on postoperative pain control. Its efficacy, with the easiness of administration, make acetaminophen a valid analgesic option within multimodal analgesia. Ketorolac and other NSAIDs have raised concerns about their possible role in the development of anastomotic leakage. Dexmedetomidine and sufentanil patient-controlled analgesia (PCA) was demonstrated to reduce inflammation, improve postoperative pain relief, and reduce delirium after MIE in a recent randomized controlled trial. However, the sample size was low, and further research is needed. The role of adjuncts, such as gabapentinoids, magnesium, lignocaine, and ketamine, is not well established.

In summary, pain control must be tailored for every patient, considering the comorbidities, the type of surgery (open versus laparoscopic surgery) and the resources available in each specific centre, respecting the safety and efficacy of the treatment itself.

Reviewer B

Comment 1: In line 115, McKeown esophagectomy is written as easier for leak management, but it is not accurate from the surgical point of view. The difficulty of the leak management is purely depending on the route of the reconstruction, i.e., the anastomotic site of posterior mediastinal McKeown and Ivor-Lewis is behind the trachea in the mediastinum and almost identical, while the anastomotic site of retrosternal McKeown locates just under the cervical skin incision.

Reply 1: We are grateful with the reviewer for this technical comment and we add it in

the text as it is. Thank you!

Changes in the text:

To be more precise, the reconstruction route characterizes the leak's management difficulty: the posterior mediastinal anastomotic site of McKeown and Ivor-Lewis is behind the trachea. In contrast, the retrosternal anastomotic site of McKeown locates just under the cervical skin incision. In the first scenario, the site of the anastomotic leakage is more difficult to reach and treat.

Comment 2: In line 196, "laparoscopic MIE" is "thoroscopic" instead.

Reply 2: Right!

Changes in the text://

Comment 3: In line 232, PCV and VCV need to be spelled out.

Reply 3: Done!

Changes in the text: pressure-controlled ventilation (PCV) and volume-controlled ventilation (VCV).

Comment 4: Description of AI regarding preoperative diagnosis sounds out of the scope of this review.

Reply 4: Considering your suggestion, we have omitted this part in the revised version.

Changes in the text://

Comment 5: MIE in the prone position without OLV is much more protective to the lung compared to MIE in the left decubitus position which always requires OLV and retraction of the lung to access the esophagus. Such points need to be discussed further.

Reply 5: This is a very nice suggestion and we add it as it is in the new version. Thank you.

Changes in the text:

Some centers perform thoracoscopic MIE in the prone position without OLV, which results in more protection to the lung than MIE in the left lateral decubitus with OLV, a known risk factor for lung damage.

Reviewer C

Comment 1:

introduction:

line 60: You are correct that squamous cell carcinoma world-wide is still the most common type but it is important to mention that adenocarcinoma is increasing and becoming more important in the western world. AC is different patient group and less live style related and thus asking for a different peri-operative approach.

Reply 1: Thank you for this important detail, we added it!

Changes in the text:

The second most frequent form is adenocarcinoma, which is rapidly rising in the western world, whereas that of the former is declining.

Comment 2:

Discussion

types of surgery

Line129: Technical limitation of MIE are not only resolved through RAMIE. A broad European collaboration found out that MIE has a learning curve of +/- 75 patients or an individual surgeon. After this learning curve complications are on a stable level and operation time is decreasing. Introducing MIE in a hospital needs intense training and proctoring for both surgeons and anesthesiologist.

Reply 2: Following your suggestion, we identified an important article about that and modified the text and references.

Changes in the text:

MIE has a learning curve of about 75 patients for an individual surgeon; after that, complication's rates are on a stable level with decreased operative time...

Consequently, introducing MIE program in a hospital needs intense training and proctoring for both surgeons and anesthesiologists...

Comment 3:

Pre-operative optimization:

In this part, the future role of e-health applications can be mentioned to increase the communication between care-giver (physiotherapists and dietists) and patient.

Reply 3: thank you for this suggestion. We added it in the new version.

Changes in the text:

Home-based pre-habilitation programs could overcome transport-related problems (the most frequently quoted problems) of these patients who often are elderly or in non-optimal physical conditions. Moreover, adding visits to these patients could be another limiting factor that reduces pre-habilitation program adherence.

Recent investigations explored the possibility of tele-rehabilitation programs delivered through web-based platforms from 2 to 4 weeks before surgery. The main results highlighted the feasibility, safety and satisfaction of this intervention.

Comment 4:

intra-operative management

Airway.

204 FOB is Fiber Optic Bronchoscopy

Reply 4: Right!

Changes in the text: fiber optic bronchoscopy (FOB).

Comment 5: 228 Two-Lung ventilation is becoming more popular and several studies are showing that is safe and (obvious) less invasive than DLT. There is more to say about the ventilation's strategy and the absence of PEEP. in my experience positioning of the patient in prone position is very important and the use of a very high (or two) thoracic pillows is extremely helpful in achieving good surgical exposure.

Reply 5: Thank you for these comments. Evidence-based medicine is poor to the best of our knowledge about ZEEP during general anesthesia and mechanical ventilation. We perform MIE in the prone position (without OLV), applying 3-5 cmH20 without any surgical impairment.

We agree to underline that the patient's position is extremely important in optimising surgical area exposure and avoiding skin or nerve injury.

Our standard positioning during prone MIE can be assessed in: "Postoperative complications after minimally invasive esophagectomy in the prone position: any anesthesia-related factor? Tumori. 2020 Dec 15:300891620979358. doi: 10.1177/0300891620979358".

Changes in the text://

Comment 6:

Fluid management

274 The less invasive the GDT device, the more drifting and discussion about the measurements. The role of OLV and prone position on GDT is uncertain.

Reply 6: As for your suggestion and reviewer #1 we better highlighted some practical advices in the revised version in red. Please, see reply to Reviewer #1.

Changes in the text://

Comment 7:

Post operative management:

321 the role of early extubation is probably not in the ventilation physiology but in avoiding fluid load due to hypotension by sedation given by a less dedicated team in the ICU/HDU.

Reply 7: Thank you for this comment. Very early extubation represents the result of all peri-operative esophagectomy features, including proper pre-operative optimization, intra-operative “protective” anesthesia, optimal pain management, use of less invasive surgical techniques and adequate postoperative HDU admission. Only high-volume centers can provide these practices. In our review, we emphasized this concept. We believe that early extubation is a positive clinical outcome in different settings such as esophagectomy or liver transplantation.

Changes in the text://

Comment 8:

324 I agree that the department after surgery: ICU or HDU is dependent on local organization and logistics. I think that 24 our minvasive monitoring is still common in most hospitals and I suggest the term advanced care unit.

Reply 8: Thank you! We use HDU for the advanced care unit.

Changes in the text: high dependency unit (HDU or advanced care unit).

Comment 9:

Analgesia:

351 paravertebral and erector Spine blocks are giving less hypotension leading to less fluid load and need for vaso-pressors. They also improve early mobilization compared to TDA. Sometimes they are combined with spinal opioids (morphine) besides intravenous opioids.

Reply 9: Thank you for this suggestion. We included it in the revised version.

Changes in the text: Paravertebral blocks (PVB) and erector spine blocks (ESP) are two valid alternatives. These approaches are less invasive and less risky than EDA and could be the right choice in a multimodal approach. They give less hypotension than EDA, leading to less fluid load and the need for vasopressors. Sometimes a combination of spinal opioids with PVB or ESP is used.

These aspects improve the early post-operative mobilization of the patients. These techniques could also be useful in cases of patients under peri-operative anticoagulation.

Comment 10:

Post-operative respiratory support.

369 I think you should mention increasing the risk of aspiration by using NIPPV and HFNC because of loss of the lower esophageal sphincter in combination with pyloric spasm.

Reply 10: Thank you for the comment. Many physicians are concerned about NIPPV after esophagectomy due to the anastomosis leak risk. However, more and more evidence support the safety of HFNC and NIPPV in respiratory failure after esophagectomy. The role of HFNC after extubation to prevent postoperative pulmonary complications is under investigation. We have just started at our Center a prospective study about this!

Changes in the text: Indeed, concern for neo-conduit dehiscence or increased risk of aspiration (due to the loss of the lower esophageal sphincter combined with pyloric spasm) has limited the adoption of this kind of ventilation as a preventive treatment

following Extubation.

Comment 11:

Conclusion

429 Communication is the 4th crucial issue

Reply 11: we agree with you.

Changes in the text://

Comment 12:

Figure 4. please explain LRMs

Reply 12: Thank you. We added legend to the figure.

Changes in the text: Legend: DLV=double lung ventilation, OLV=one lung ventilation, TV=tidal volume, PEEP=positive end expiratory pressure, LRMs=lung recruiting maneuvers, VCV=volume-controlled ventilation, PCV=pressure-controlled ventilation.

Comment 13:

In general: In the western world, there is a rapid movement that MIE is replacing open surgery in this review most of the conclusion/recommendations are given by using data of both the procedures. In the last five years tremendous progression is made in reducing LOS in hospital and ICU and conclusion of studies older than 10/15 years are probably no longer directly correlated to general clinical practice. perhaps it is good to mention this in the introduction

Reply 13: Thank you for this comment. Fortunately, knowledge progression is rapidly changing, and evidence sometimes cannot keep up! We are in line with the reviewer; however, to be comprehensive, we decided to use MIE and open surgery data.

Changes in the text://

Reviewer D

This review focuses on the anesthesiological aspects of esophagectomy for cancer. This article provides a useful overview and should be considered for publication.

Reply: thank you!

However, the following comments should be addressed:

Comment 1: The evidence for superiority of RAMIE to conventional MIE is very scarce (level 3 at best since no RCTs have been completed yet). Although robotic surgery might offer advantages during complex parts of the procedure such as the upper mediastinal dissection, RAMIE is expected to have the same rate of pulmonary complications as MIE. Moreover, semi-prone positioning can also be used in MIE. Therefore, the statements regarding RAMIE should be nuanced in the manuscript.

Reply 1: Thank you for this clarification. The work by Tsunoda et al. Lower Incidence of Post-operative Pulmonary Complications Following Robot-Assisted Minimally Invasive Esophagectomy for Esophageal Cancer: Propensity Score-Matched Comparison to Conventional Minimally Invasive Esophagectomy. *Ann Surg Oncol.* 2021 Feb;28(2):639-647”) support of this. However, following the reviewer suggestion, we have nuanced the statement.

Changes in the text: An additional benefit of RAMIE is its lower rate of postoperative pulmonary complications, although randomized controlled trials are highly advocated in this regard.

Comment 2; The 30-day mortality of esophagectomy is currently about 2-3% in expert centers (Low et al. Benchmarking complications associated with esophagectomy. *Ann Surg* 2019). This is a substantial improvement and nowadays more realistic than the >5% 30-day mortality that is cited from the ESC/ESA guidelines from 2014.

Reply 2: Thank you for this comment. We have included it.

Changes in the text: The 2014 ESC/ESA guidelines on noncardiac surgery consider esophagectomy a high-risk surgical procedure with an expected 30-day cardiovascular death or myocardial infarction risk > 5%. However, high volume centers have a lower mortality rate.

Comment 3: The authors mention several strategies to evaluate perioperative risk of morbidity and mortality. Can the authors make any recommendations on the possible role of such evaluations to select patients for either a transthoracic or a transhiatal approach in clinical practice, based on current literature?

Reply 3: Thank you for this comment. As for ESA or ASA perioperative guidelines, esophagectomy should be considered major surgery as described in our paper. However, we are aware that in high volume centers 30th day post-operative mortality is lower than 5%. Please see the answer above.

Changes in the text://

Comment 4: It is hard to understand how totally intravenous anesthesia would lead to improved survival compared to volatile anesthesia in cancer surgery. Please elaborate on this hypothesis, also in the context of esophagectomy.

Reply 4: Thank you for this interesting question. The mechanism by which survival could be related to the type of anesthetic regimen is unknown.

However, one of the experimental proposed mechanisms is that volatile anesthetics may suppress the activity of natural killers. These cells play an important role in the innate immune system against the invasion of cancer cells (released into the circulation during surgery). In addition, the activity of NK during the perioperative period is inversely related to the development of metastasis.

In contrast, it has been reported that propofol did not suppress the natural killer activity.

Propofol may also inhibit matrix metalloproteinases that are the key enzyme involved in the basement membrane breakdown, thus promoting tumour spread.

These mechanisms need future in vivo investigations, above all in the specific context of esophagectomy.

We added a new reference specific for esophagectomy (Jun IJ, Jo JY, Kim JI, Chin JH, Kim WJ, Kim HR, Lee EH, Choi IC. Impact of anesthetic agents on overall and recurrence-free survival in patients undergoing esophageal cancer surgery: A retrospective observational study. *Sci Rep.* 2017 Oct 25;7(1):14020. doi: 10.1038/s41598-017-14147-9.)

Changes in the text: A retrospective study found that TIVA during esophageal cancer surgery was associated with better postoperative survival rates than volatile anesthesia. The proposed mechanism is that volatile anesthetics may suppress the activity of natural killers.

In contrast, it has been reported that propofol did not suppress the natural killer cells activity.

Propofol may also inhibit matrix metalloproteinases that are the key enzyme involved in the basement membrane breakdown, thus promoting tumour spread.

These mechanisms need future in vivo investigations, above all in the specific context of esophagectomy.

Comment 5: Can the authors make any evidence-based statements regarding the role of deep versus moderate neuromuscular block during an esophagectomy procedure?

Reply 5: To the best of our knowledge, no evidence-based statements can be done in this regard. We can suggest, however, that neuromuscular monitoring is fundamental as for every type of surgery requiring paralytic agents.

Changes in the text://

Comment 6: Regarding pain management, recent research is focusing on paravertebral analgesia. The authors should discuss the currently ongoing PEPMEN trial, which is an

RCT comparing epidural vs paravertebral analgesia. The research protocol has been published in BMC Cancer in 2020.

Reply 6: Thank you for highlight this suggestion about this important research. We found it very interesting, and we included a statement about that.

Changes in the text: An ongoing trial (PEPMEN trial) is recruiting patients undergoing MIE comparing the postoperative quality of recovery between paravertebral catheter versus thoracic epidural analgesia.

Comment 7: The paragraph on the role of artificial intelligence is probably beyond the scope of this anesthesia-oriented paper.

Reply 7: We adjusted accordingly!

Changes in the text://

Comment 8: In the conclusion, provide bullet points with clear recommendations on the discussed topics.

Reply 8: Following your suggestion, we provided three bullets point with clear recommendations.

Changes in the text:

- Only multidisciplinary team in high volume centers must take care of patients undergoing esophagectomy;
- Protective intra-operative ventilation and proper fluid management are the cornerstones of “protective anesthesia”;
- Multimodal post-operative analgesia is essential for rapid mobilization and return to normal daily activity for these patients