

## Peer Review File

**Article information:** <https://dx.doi.org/10.21037/jtd-22-80>

### Reviewer A

**Comment:** Thank you for the opportunity to review this article. The article is a narrative review of the evolution, progression of minimally invasive techniques of thoracic surgery, specifically Non-intubated techniques. The article is well written, covering the basics, from pathophysiology to different schools of thought in different geographic areas. It serves as an excellent educational read and will add to the body of literature on NIVATS. I would only add that the abstract may benefit from mentioning the 3 schools of thought for further clarification /description of the article.

**Reply:** Thank you for your time to review our article and your supporting opinion. We created a table and added in the text with advantages and limitation of these procedures.

(Table 2)

### **Changes in the text:**

#### **Thoracic surgery with spontaneous breathing**

Based on the literature data preserving of spontaneous breathing can diminish the potential harmful effect of conventional approach. But it is very important to emphasise the spontaneous breathing during thoracic procedure can be dangerous due to unusual circumstances (ie. paradoxical breathing, mediastinal movement) that's why the application of NIVATS in the training programs of the professional perioperative teams is essential to ensure maximal patient safety and comfort for the teams (51,52).

After reviewing the literature, we identified different methods with very similar clinical results. Theirs main characteristics, advantages, limitations, exclusion criteria and indications for

conversion are summarized in table 2,3 and 4.

## **Reviewer B**

**Comment 1:** The article represents the current state of anesthesiologic methods in a very well researched manner. The conclusions are correct and give an important indication of the direction in which thoracic surgery will develop. Overall, I would suggest a little more emphasis on the necessary size of the performing center, the case numbers of the center and the case number of the individual anesthesiologist. Also, the inclusion of such training programs and the NIVATS method in the curricula of the professional societies seems to me an important aspect that should be mentioned. A hint may be provided by the article on this topic recently published in Current Opinion of Anaesthesiology (PMID: 34889801).

**Reply 1:** Thank you for your constructive remark. I absolutely agreed with your opinion. One of the most important things is the training of the team due to ensure maximal comfort for them and also ensure the maximal patient safety. We added your recommended reference in the text.

**Changes in the text:** Added:

### **Thoracic surgery with spontaneous breathing**

Based on the literature data preserving of spontaneous breathing can diminish the potential harmful effect of conventional approach. But it is very important to emphasize the spontaneous breathing during thoracic procedure can be dangerous due to unusual circumstances (ie. paradoxical breathing, mediastinal movement) that's why the application of NIVATS in the training programs of the professional perioperative teams is essential to ensure maximal patient safety and comfort for the teams (51, 52).

After reviewing the literature, we identified different methods with very similar clinical results.

Their main characteristics, advantages, limitations, exclusion criteria and indications for conversion are summarized in table 2,3 and 4.

**Comment 2:** When it comes to the issue of patient safety, my recommendation in this article is also to compare the training programs of the Asian, Italian, and Hungarian methods.

Why Asia is mentioned as a continent and Italy and Hungary as national states is not apparent to the reader. Either one differentiates between Chinese, Korean and Indian methods and the Italian and Hungarian methods, or one stays with Asia and Europe in the context of continents, or one admits that the method is useful independent of the place of implementation and describes the approaches independently of continents and nation states. My recommendation is the latter.

**Reply 2:** Thank you for your advice. I think, we are in very complicated situation. Many centres perform excellent scientific and publicational performance. It is very difficult to differentiate from each other namely the techniques come near. We tried to introduce the different centres based on their main characteristic difference and these can associate to countries, not just centres alone. The Asian label can conclude the several very important centres in the Asian region. In our opinion, the assignment of these numerous centres exceeds the aim of these review but other reviews are under preparation which try to introduce the different scientific aspects focused on inflammatory background, surgical aspects, detailed anesthesiological methods.

### **Reviewer C**

**Comment 1:** The term, “dogmatic” in the title is worthy of discussion and might be a matter of opinion.

**Reply 1:** Thank you for your reflection. I have also felt a bit strong word in the term before.

Changes in the text: Anesthetic (r)evolution from the ~~dogmatic~~ **conventional** concept to the minimally invasive techniques in thoracic surgery – Narrative review”

**Comment 2:** The abstract is written in an intricate way and there is no coherence between the sentences.

**Reply 2:** Thank you for your opinion. Abstract has been reedited.

**Comment 3:** There are abbreviations in the abstract which are not described.

Thank you. List of abbreviations is attached.

**Comment 4:** In the “Background” in the abstract you mention anesthetized patients, but you should mention that they are not intubated or without muscle relaxants.

**Changes in the text:** An adequate analgesic approach (regional or epidural anesthesia) allows VATS to be performed **in non intubated** anesthetized patients and thus the potential adverse effects related to general anesthesia and mechanical one-lung ventilation (OLV) can be avoided.

**Comment 5:** You announce “gold standard procedures” in the Conclusions. But there is no explanation in the abstract what are “gold standard procedures”.

**Reply 5:** Thank you for your annotations. It is missing indeed what gold standard procedures is. It is explained later in the text (ln 255-257). Gold standard procedures has been changed to conventional methods which is explained in the abstract.

**Changes in the text:** Based on the results, non-intubated thoracic surgery appears to be an increasingly widespread, safe procedure, that will be available to a wider range of patients as experience expands and by the implication of the constantly evolving, new processes, featured by an efficiency equal to or greater than that of the ~~gold standard procedures~~

conventional methods.

**Comment 6:** In the introduction, you mention the decreased amount of lymphocyte cells after NIVATS and depict as a secret fact. Actually, several authors showed this up in their reviews about NIVATS. But none explained any benefit in clinical management or patients process of the lower amount. Are you able to explain if there is a better outcome in oncologic or infectious disease?

**Reply 6:** This is a very important question. Many papers showed great scientific numbers during different procedures and we are able to convert them in practical benefits. The main theory in postoperative systematic inflammation response (SIR) is how pro- and anti-inflammatory responses can affect the clinical picture. Based on the changes in the cellular defense and cytokine levels, this kind of postoperative SIR period can take for around 3–12 days, but it affects not only on the early postoperative morbidity, but also the 30-day mortality (1,2,3). Regarding the early postoperative morbidity, the reduced levels and functions of lymphocytes and NK cells can cause diminished cellular defense ability. This can manifest as postoperative pneumonia, wound infection, or other inflammation. Postoperative pneumonia rates were 5% and 10%, and wound infection rates were 0.4% and 1% after VATS and open lobectomies. (4). Because of the less pro-inflammatory response, some postoperative morbidities can be reduced further during NIVATS (5). Postoperative morbidity is lower (5%) than in relaxed surgery cases (23%) (3). Generally, NIVATS lung resection, the postoperative fasting time, drainage time, and hospital stay were shorter than those in relaxed VATS cases (5) furthermore better compliance with adjuvant chemotherapy was found after non-intubated VATS lobectomies than after relaxed VATS lobectomies, with less toxicity, and more patients (92%) could receive the adjuvant chemotherapy protocol, compared with 72% in relaxed surgery cases (6).

1. Mineo TC, Ambrogi V. Immune effects after uniportal nonintubated video-thoroscopic operations. *Video-assist. J Thorac Surg* (2018) 3:4–10.
2. Breunig A, Gambazzi F, Beck-Schimmer B, Tamm M, Lardinois D, Oertli D, Zingg U. Cytokine& chemokine response in the lungs, pleural fluid and serum in thoracic surgery using one-lung ventilation. *J Inflamm (Lond)* (2011) 8:32. doi:10.1186/1476-9255-8-32.
3. Mineo TC, Sellitri F, Vanni G, Gallina FT, Ambrogi V. Immunological and inflammatory impact of non-intubated lung metastasectomy. *Int J Mol Sci* (2017) 18:1466. doi:10.3390/ijms18071466.
4. Villamizar NR, Darrabie MD, Burfeind WR, Petersen RP, Onaitis MW, Toloza E, Harpole DH, D'Amico TA. Thoracoscopic lobectomy is associated with lower morbidity compared with thoracotomy. *J Thorac Cardiovasc Surg* (2009) 138:419–25. doi:10.1016/j.jtcvs.2009.04.026.
5. Liu J, Cui F, Pompeo E, Gonzalez-Rivas D, Chen H, Yin W et al. The impact of non-intubated versus intubated anaesthesia on early outcomes of video-assisted thoracoscopic anatomical resection in non-small-cell lung cancer: a propensity score matching analysis. *Eur J Cardiothorac Surg* (2016) 50:920–5. DOI: 10.1093/ejcts/ezw160.
6. Furák J, Paróczai D, Burián K, Szabó Z, Zombori T. Oncological advantage of nonintubated thoracic surgery: better compliance of adjuvant treatment after lung lobectomy. *Thorac Cancer* (2020) 11:3309–16. doi: 10.1111/1759-7714.13672.

**Changes in the text:**

Postoperative systematic inflammation response (SIR) can affect the clinical picture. Based on the changes in the cellular defense and cytokine levels, SIR period can take for around 3–12 days, but it affects not only on the early postoperative morbidity, but also the 30-day mortality(5,41,42). Regarding the early postoperative morbidity, the reduced levels and functions of lymphocytes and NK cells can cause diminished cellular defense ability. This can manifest as postoperative pneumonia, wound infection, or other inflammation response. Postoperative pneumonia rates were 5% and 10%, and wound infection rates were 0.4% and 1% after VATS and open lobectomies(43). Postoperative morbidity is lower (5%) than in relaxed surgery cases (23%)(41). Generally due to less pro-inflammatory response, some postoperative morbidities can be reduced further during NIVATS, the postoperative fasting time, drainage time, and hospital stay were shorter than those in relaxed VATS cases(44). Furthermore better compliance with adjuvant chemotherapy was found after non-intubated VATS lobectomies than after relaxed VATS lobectomies, with less toxicity, and more patients (92%) could receive the adjuvant chemotherapy protocol, compared with 72% in relaxed surgery cases(45).

**Comment 7:** The explanations about physiology and pathophysiology of breathing and ventilation are well described and missing in most reviews.

**Reply 7:** Thank you. Our opinion is the same. It is very important to identify what factors can be beneficial or potentially harmful based on our physiological and pathophysiological knowledge.

**Comment 8:** You present differences in NIVATS and that there are varieties of application of oxygen and sedation of the patients, up to intubation and sedation

and just waiving muscle relaxation. Recommendations of implementing NIVATS in units for thoracic surgery are missing at all, but I think this was not the aim of this review.

**Reply 8:** Yes, we tried to push in all of the different methods of implementing NIVATS but unfortunately it has exceeded the word limit. We are planning to do another review focusing the practical aspects and the typical problems (patient selection, hypoxia, hypercapnia, acid-base imbalance, conversion methods) and their solution. It can be important especially in the beginning of the learning curve.

#### **Reviewer D**

##### **Comment 1:**

Abstract

L 53

potential adverse effects related to general anesthesia and mechanical one-lung ventilation can be avoided.

Change avoided for minimized

**Reply 1:** Thank you. Changed.

##### **Comment 2:**

L60

We identified three “schools” with very similar results.

In your results section you have a fourth “school” : Other methods (Saudi Arabia)

##### **Changes in the text:**

**Results:** After reviewing the literature, we identified ~~three~~ “schools” **with different techniques** but with very similar results. Most of the differences were in the anesthetic technique,



oxygenation and analgesia, however, the immunological results, and the qualitative parameters (inpatient hospital care days, complication rate, mortality) of the perioperative period showed great similarity, in addition, all three schools identified the same risk factors (hypoxia, hypercapnia, airway safety).

**Comment 3:**

L 64

Please defined SVI in the abstract or simply write it in full length without abbreviation.

**Reply 3:** Than you. SVI defined in the abstract.

**Changes in the text:** The combination of spontaneous ventilation with double lumen tube intubation, called VATS - SVI method seems to be suitable for reducing these risk factors, which may serve as an alternative for patients not suitable for the non-intubated technique in the near future.

**Comment 4:**

L70

Featured by an efficiency equal to or greater than that of the gold standard procedures.

You cannot conclude like this.

You did not present clinical results obtained with these techniques, and even less you did not compare any results.

**Reply 4:** Modified

**Changes in the text: Conclusions:** Based on the results, non-intubated thoracic surgery appears to be an increasingly widespread, safe procedure, that will be available to a wider range of patients as experience expands and by the implication of the constantly evolving new processes. ~~featured by an efficiency equal to or greater than that of the gold standard procedures.~~

**Comment 5:**

Introduction

Lines 76 to 239 introduction (5 pages!!!) vs results (3 pages) and conclusion ( less than 1 page)

The introduction is too much long and contain too much details.

Your introduction is a very extensive review of the history of the physiology and pathophysiology of different factors implicated in the anesthetic management for NITS.

All this content of this section should be reduced extensively.

**Reply 5:** Thank you for your remark. We constructed many versions of this narrative review with different focus. Our perception -after the overview of the relevant literature- is not easy to build in all of the clinical and theoretical relevant aspects in one review due to formal regulations. Therefore, we are planning to write another review focused on the clinically relevant aspects. We tried to keep now the focus principally of the theoretical backgrounds and the introducing of different approaches. We hope you can help again to improve quality of another review which based on the referred viewpoint.

**Comment 6:**

L 184-186

During mechanical one-lung ventilation (OLV) only the dependent lung is ventilated while the nondependent lung is excluded from the gas exchange with maintained perfusion.

I suggest to you with lower perfusion.

**Reply 6:** Modified

**Comment 7:**

L 187-188

This can lead to as high a shunt fraction as 20-30%, that understandably decreases the arterial oxygen content, as a higher fraction of the cardiac output is passed through from left to right without gas exchange.

It is probably right to left...

**Reply 7:** Than you. Erratum corrected.

**Comment 8:**

L 204-206

HPV reversibility after a short hypoxic episode: how is short? 10-15 minutes, 60 minutes, or 90 minutes or more?

HPV disappearance after hours of re-oxygenation: how many hours? One, three, five?

**Reply 8:** Thank you for your question. HPV is a huge topic, we tried to introduce the probably not very well-known aspects of this phenomenon.

Changes in the text: When normoxia is restored after a short hypoxic phase (<20 min), the HPV declines and PVR normalizes as pulmonary blood flow increases in the re-oxygenated areas. In contrast, after a prolonged period of hypoxia, the HPV only disappears after several hours despite full re-oxygenation, resulting in greater ventilation-perfusion (V/Q) mismatch and consequently larger alveolar-to-arterial O<sub>2</sub> pressure gradient (A-aPO<sub>2</sub>). However, after a longer hypoxic period, HPV disappears completely only after hours of re-oxygenation (24–26).

**Comment 9:**

L 238

Please defined SVI when used it for the first time in your text

**Reply 9:** Thank you. SVI is defined.

**Changes in the text:** Be it the increasingly popular non-intubated thoracic surgeries (NITS) or the recently introduced **spontaneous ventilation with intubation** (SVI) method. It seems that the advantages of the maintained SB can overcome concerns (46,47).

**Comment 10:**

Methods

L 242-246

The first part is OK until "...papers focusing"

L 246-249

You began by being negative, "you excluded... other than..." and "you pay attention to this particular technique"

Please be more specific and positive in your text,

We looked for anesthetic technique for NIVATS.

**Reply 10:** Thank you. Our approach is positive but this topic is very broad, some restrictions might be needed. Language error and our approach corrected.

**Changes in the text:** The editorials, commentaries, letters were excluded and papers focusing on other than the non-intubated (aka awake or tubeless) video-assisted thoracic surgery (*NIVATS*) technique, as well as the full text scientific papers available in languages other than English. The findings of these articles are shown in table 1.

**Comment 11:**

Results

L 253, 175, 290, 308, 314

Gold standard: OK

Italian approach; Asian perspective; Other methods; and Hungarian method.

Please change nomenclature to use the same “word” for each section: may you can use “technique”.

**Reply 11:** Thank you. Words are modified to technique.

**Comment 12:**

L275-333

Your text only includes “recipes” of techniques without any clinical results and even less any comparisons between each technic and mainly with the “gold standard.”

Maybe you can use a table to present the different technics.

**Reply 12:** Thank you. Table with characteristics of different techniques is attached. Please find as table 2.

**Comment 13:**

Conclusion

L336

NIVATS is a safe and acceptable method...

You cannot conclude like this as you never present any results: number of cases, type of patients, data from operating room and postoperative care...

**Reply 13:** Thank you for your remark. It is corrected.

**Changes in the text:** NIVATS is **can be** a safe and acceptable method for performing minor or even major pulmonary resections. Patient safety is a cornerstone of the non-intubated techniques, and can be enhanced by using clear inclusion and exclusion criterias, completed with well-defined conversion strategies. The combination of regional anesthesia and

intravenous sedation strategies gives the opportunity to prevent perioperative complications like hemodynamic imbalance, hypoxia, or severe hypercapnia.

**Comment 14:**

L 338

You never defined inclusion and exclusion criteria's and even less conversion strategies.

**Reply 14:** Thank you. Table 3 with criteria is attached

**Reviewer E**

The authors have prepared a narrative review to minimally invasive techniques in thoracic surgery. The scope of this topic is broad, but the contents and the depth of review is not sufficient to cover recent/important development in this area. There are areas where additional details would contribute to the impact of this review, as I have noted below.

**Comment 1:** Ln 64: In the abstract, the abbreviation "SVI" was not defined in its first use.

**Reply 1:** Thank you for pointing out that. We have modified our text as you advised.

**Changes in the text:** "The combination of spontaneous ventilation with double lumen tube intubation, called VATS - SVI method seems to be suitable for reducing these risk factors, which may serve as an alternative for patients not suitable for the non-intubated technique in the near future.

**Comment 2:** Ln 63-66: In the abstract, the authors mentioned "all three schools identified the same risk factors. The SVI method seems to be suitable for reducing these risk factors". I am not quite sure what risk factors the authors are referring to. Is the information missing?

**Reply 2:** Thank you for your suggestion, we added most often mentioned concerns about the

non intubated techniques.

**Changes in the text:** “Most of the differences were in the anesthetic technique, oxygenation and analgesia, however, the immunological results, and the qualitative parameters (inpatient hospital care days, complication rate, mortality) of the perioperative period showed great similarity, in addition, all three schools identified the same risk factors (hypoxia, hypercapnia, airway safety).”

**Comment 3:** Ln 155-157: More elaboration on how the respiratory parameters could be monitored or adjusted in clinical practice, or leading to differential diagnosis is recommended.

**Reply 3:** Thank you for your remark. We did many versions of this narrative review with different focus. Our perception -after the overview of the relevant literature- is not easy to build in all of the clinical and theoretical relevant aspects in one review due to formal regulations. Therefore, we are planning to write another review focused on the clinically relevant aspects. We tried to keep now the focus principally of the theoretical backgrounds and the introducing of different approaches. We hope you can help again to improve quality of another review which based on the referred viewpoint.

**Comment 4:** Ln 242-250: A flow chart showing the characteristics of included articles, records screened/identified, full-text articles assessed... etc. is recommended.

**Reply 4:** Thank you for your suggestion. Flow chart is attached, please find in the appendix.

**Comment 5:** Ln 309-312: The authors did not mention the type of analgesic used in Al-Abdullatif et al. study. (although such information could be found in table 1). I recommend adding this information so that reader will find it easier to follow.

**Reply 5:** Thank you for your suggestion, we have modified the text as you advised

**Changes in the text:** “Besides the Italian and Asian approaches, other modifications to the NITS procedure have also been developed. Al-Abdullatif et al. from Saudi Arabia performed major operations, such as lobectomy and thymectomy, in awake or mildly sedated individuals. After iv. midazolam – fentanyl premedication thoracic epidural anesthesia was done and ~~blocked~~ the ipsilateral stellate ganglion was blocked to diminish the cough reflex (64)”

**Comment 6:** Ln 315-321: VATS with spontaneous breathing through laryngeal mask has been published by an Italian study in 2012. (J Thorac Cardiovasc Surg. 2012 Aug;144(2):514-5. doi: 10.1016/j.jtcvs.2012.01.077. Epub 2012 Feb 22. PMID: 22361250.). Whether it is appropriate to defined this technique as the "The Hungarian method" is questionable.

**Reply 6:** Thank you for your constructive suggestion. It is absolutely true that Italians published the method in which we gained most of our experience in the last few years. We are thankful to all groups paying attention to minimally invasive surgical and anesthetic techniques in the field of thoracic surgery, as it gives an opportunity to learn from each other. The Hungarian method should refer to the evolution/alteration of our anesthetic strategy from NITS to VATS - SVI

**Changes in the text:** -

**Comment 7:** Ln 324-333: The authors mentioned the " VATS-SVI" technique to combine the advantage of double lumen tube and spontaneous ventilation. As this is not a common practice, more details on the practical issue on short-term neuromuscular paralysis/relaxation for double lumen tube insertion is recommended.

**Reply 7:** Thank you for your remark. More detailed description of VATS SVI has been



added to the text, although now we only would like present the brief summary of that method, as we are about to publish an article focusing mainly on VATS – SVI method and our results in the topic.

**Changes in the text:** “The same workgroup published a new method, called VATS-SVI, which combined the positive physiological effects of the non-intubated technique with those of the gold standard technique applying double-lumen tube intubation and providing a safe airway. ~~and~~ Anesthetic management for VATS-SVI has been described previously (11).

Briefly, patients received premedication with midazolam and fentanyl. Induction and maintenance of anesthesia was guaranteed by propofol target controlled infusion dosed to reach a BIS value between 40 to 60.

They found better intraoperative cardiopulmonary stability and similar postoperative results of spontaneous ventilation combined with intubation than non intubated thoracic surgery (11,66).”

**Comment 8:** The authors have covered numerous anesthesia approaches including different ventilation method (spontaneous/mechanical), airway devices (double lumen/LMA) and anesthesia/sedation (propofol/midazolam/awake) and analgesia (ICB/TEA/remifentanyl). I recommend adding a table to summarize and comparing the strength and weakness of the individual approaches.

**Reply 8:** Thank you for your constructive comment, a table has been added to the article

**Changes in the text: Thoracic surgery with spontaneous breathing**

Based on the literature data preserving of spontaneous breathing can diminish the potential harmful effect of conventional approach. But it is very important to emphasise the spontaneous breathing during thoracic procedure can be dangerous due to unusual circumstances (ie. paradoxical breathing, mediastinal movement) that's why the application of NIVATS in the

training programs of the professional perioperative teams is essential to ensure maximal patient safety and comfort for the teams (51,52).

After reviewing the literature, we identified different methods with very similar clinical results. Theirs main characteristics, advantages and limitations are summarized in table 2.

**Comment 9:** The reference number of studies in table 1 were inconsistent with the reference list.

**Reply 9:** Thank you for pointing out that. The studies have been expanded according to reviewer's advice and the reference numbers have been corrected.