

## Peer Review File

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### Reviewer A

The reviewer is honored to review an article about a narrative review of NITS. The paper is well written, but there are several points to be revised, as follows:

#### Major points

- 1) In this article, the authors did not mention about long-term outcomes regarding NITS. Please mention about this point.
- 2) In NITS, some centers perform carinal resection. Please mention about this procedure.
- 3) The authors provided thoracotomy and VATS for NITS. Are there any difference for these procedures in terms of anesthesia?
- 4) The authors provided ICG utilization, but all the cited papers did not provide the data of NITS. They should change the references (12-14) if they want to mention about this.

Thank you for your precise revisions. We modified the text following your suggestions:

- 1) Even though long-term outcomes of NITS major procedures are still being investigated and only few published papers reported convincing results, we added some data about that. Please see page 17, lines 389-394, reference # 31.
- 2) We included some data about NITS airway surgery, please see page 11, lines 261-276, references # 20, 21.
- 3) Anaesthetic management of NITS thoracotomy is well described by Furak et al (Furák J, Szabó Z, Tanczos T, et al. Conversion method to manage surgical difficulties in non-intubated uniportal video-assisted thoracic surgery for major lung resection: simple thoracotomy without intubation. *J Thorac Dis* 2020;12(5):2061-2069. doi: 10.21037/jtd-19-3830). In particular, it is reported that: “for the thoracotomy, we do not change the anesthesia and no additional drugs are necessary”.
- 4) We included a paper describing technical features of ICG utilization during NITS segmentectomies. Please see reference # 16.

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### Reviewer B

First of all I would like to commend you on a very nice manuscript, that nonetheless would benefit from some work-over.

- historical notes: the first reports on what could be considered niVATS are from the late 90ies (Tschopp JM, Brutsche M, Frey JG. Treatment of complicated spontaneous pneumothorax by simple talc pleurodesis under thoracoscopy and local anaesthesia. *Thorax*. 1997 Apr;52(4):329-32, Mukaida T, Andou A, Date H, Aoe M, Shimizu N. Thoracoscopic operation for secondary pneumothorax under local and epidural anesthesia in high-risk patients. *Ann Thorac Surg*. 1998 Apr;65(4):924-6), the first niVATS major resections from 2007 (Al-Abdullatief M, Wahood A, Al-

Shirawi N, Arabi Y, Wahba M, Al-Jumah M, Al-Sheha S, Yamani N. Awake anaesthesia for major thoracic surgical procedures: an observational study . Eur J Cardiothorac Surg. 2007 Aug;32(2):346-50. Epub 2007 Jun 18) and Diego published the first Uniportal niVATS in 2014. The concept of awake thoracoscopy itself is from the late 1800s (Sir Francis Richard Cruise, Thoracoscopy before Jacobaeus. Hoksch B, Birken-Bertsch H, Müller JM. Ann Thorac Surg. 2002 Oct; 74(4):1288-90.)

- not to be nitpicking: ICG is utilized in NEAR infrared spectroscopy

- try to elucidate the differences between major and minor procedures by niVATS a bit more in depth; while anatomical resections are challenging and only large volume surgeons publish their experience (especially Diego Rivas and Jin-Shing-Chen, the true pioneer in the field), minor procedures are generally easily feasible as corroborated by large amounts of publications dealing with it.

- a very good point is the possibility of conversion to ni thoracotomy. This concept itself has been proven to be a feasible in the 1950ies by Russian surgeon Alexander Wischnewski.

- anesthesia: a European group reported their experience in major niVATS utilizing dexmedetomidine (Starke, Henning, et al. "Developing a minimally-invasive anaesthesiological approach to non-intubated uniportal video-assisted thoracoscopic surgery in minor and major thoracic surgery." Journal of Thoracic Disease 12.12 (2020)). Maybe you could comment on this.

Thank you for your clarifications about NITS historical evolution and your suggestions about anaesthesiological management.

- We modified historical references (see page 2, lines 42-43) and mention the first successful NITS major procedures (see page 5, lines 101-103, references #3,4).

-We rectified the reference about infrared in near-infrared, which is the correct spectroscopy using ICG.

- We tried to better explain the differences performing NITS minor and major procedures in terms of technical skills and expertise; please see page 5, lines 104-107.

- We added some information about the use of dexmedetomidine in major niVATS procedures; please see page 6, lines 148-151, reference # 9.

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### Reviewer C

I suggest that the authors incorporate a table that summarizes the results of the main comparative studies described in the bibliography.

It would also be interesting if you could provide a video in the surgical technique section on vagal block or emergent intubation in lateral decubitus. I miss a section that assesses desoyó the different options for conversion to general anesthesia with intubation in an emergent intraoperative situation, in test point I recommend incorporating this article to the bibliography

Navarro-Martínez J, Galiana-Ivars M, Rivera-Cogollos MJ, Gálvez C, Nadal SB, Lampaignère MO, Mazo ED. Management of Intraoperative Crisis During Nonintubated Thoracic Surgery. *Thorac Surg Clin.* 2020 Feb; 30 (1): 101-110

Thank you for your suggestions.

We added a summary table with main results of the studies mentioned in the discussion (see page 15-16, Table 1).

Unfortunately, we don't have video materials that can be attached to the paper.

We mentioned emergency management during NITS applying crisis resource management (CRM) protocols, referring to the interesting work of Navarro-Martinez et al, as suggested (see page 9, lines 215-220, reference #15).

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#### Reviewer D

It is the best summary on NITS I know. Most important aspects are addressed in a short, concise manner. I have only few comments:

1. The techniques of NITS are much older than 20 or 30 years, only the technical term NITS is new. Minor pleural procedures have been performed by pulmologists (not surgeons!) for decades, using local anaesthesia, sedation and spontaneous ventilation. The Russian have been performing major lung and even chest wall resections, see Ossipov 1960, *Anaesthesia and Analgesia*, volume 39, no 4 "local anaesthesia in thoracic surgery: 20 years experience in 3265 cases", and Pschenichnikov 1959, *Anaesthesia*, Vol 14 no 3, "local anaesthesia in thoracic surgery", both describing techniques of vagal nerve block etc. very precisely. These are techniques which have been abandoned when "modern" but invasive thoracic anaesthesia (DLT, OLV) occurred, and they are now rediscovered. So these early achievements should be acknowledged when you write about History (line 63++).
2. Lines 110-114 Delirium as postoperative complication should be mentioned, the more so as patients get older. Delirium can end in persisting neurological deficits which decide whether an elderly patient will be able to live a self-sustained life after surgery.
3. "Patients' selection" Lines 116-125: One contraindication for NITS is suspected difficult airway, which should be mentioned explicitly (see lines 193-195).
4. Lines 231-233: I do not agree that in NITS segmentectomy frozen section of hilar lymphnodes is mandatory. Usually, if you decide to perform NITS segmentectomy, the patient is in marginal condition, not capable to tolerate lobectomy, and the tumour smaller than 2cm, otherwise you would chose radiotherapy instead of surgery,. So, if incidentally N1 or N2 occurs postoperatively, the patient will receive adjuvant therapy instead of completion lobectomy. Why act different in NITS segmentectomy than in DLT-segmentectomy? Please shortly discuss.
5. Discussion: Your view on the oncological radicality of NITS is a bit too euphemistic. The

hypothesis that less inflammation during NITS leads to better immunoresponse and better oncological outcome (lines 332-347) is speculative and not based on convincing data. To my knowledge, there are no current long-term data on the oncologic outcome of NITS vs. DLT-surgery. You should mention this aspect and discuss a little more neutral.

Thank you for your nice comment about our work, we are glad to see your appreciation.

- 1) We modified some imprecise historical references and really appreciated your detailed specifications about terminology referring to non-intubated thoracic surgery.
- 2) We added a reference about possible neurological complications occurring in elderly patients after general anaesthesia; please see page 5, lines 116-119, reference # 6.
- 3) Difficult airways is mentioned among the relative contraindications of NITS (see page 6, line 132).
- 4) We modified the text as you suggested, including the possibility of intentional segmentectomy in compromised patients. Please see pages 10-11, lines 254-257.
- 5) Considering the oncological radicality of NITS major resections, most of the studies comparing NITS and intubated procedures reported no differences in nodal dissection. In addition, it should be considered that NITS is proposed for early stage NSCLC (often GGO lesions), in which nodal sampling is considered adequate. Considering the oncological outcomes after NITS, we referred to the interesting retrospective analysis by Furak et al, in which the reported data showed an oncological advantage in patients who underwent NITS procedures (see reference #29). We also added some data about long-term outcomes after NITS (see page 17, lines 389-394, reference # 30). However, we explicitly write that more studies and a longer follow up are needed to support these results.

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#### Reviewer E

This review is about non-intubated thoracic surgery. It is informative, but there are some issues.

Major issues

1. The contents is well-organized, but make further revisions to the information in greater depth.
2. Pg 4~5, ln 92~107 Please describe more information about advantages of NiVATS in detail. (I think this point is the highlight of this review article.)
3. Pg 7, ln 167~ I think you misunderstand the mechanism of ventilation in NiVATS (i.e., paradoxical respiration..) Please revise this section.
4. Pg 9, ln 225 What is “balloon-assisted ventilation?”

Minor issues

5. Pg 6, ln 1~8 Please revise “the intubation” into “airway management”
6. British and American English are mixed. Please correct them.

Thank you for your comments and suggestions.

- 2) We described the advantages of NiVATS both in the introduction section (page 5, lines 108-119), patients' selection (page 6, lines 128-131) and in the discussion section (mainly oncological advantages, page 16-17 lines 373-394)
- 3) We modified the text in order to make clearer the mechanism of ventilation in NiVATS. Please

see page 8, lines 188-195.

4) We mean AMBU-bag ventilation. We correct the term in the text. See page 10, line 246.

5) We modified the text as you suggested (see page 6, line 134)

6) We corrected the text as you suggested

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#### Reviewer F

The feasibility and advantages of NITS for lobectomy or segmentectomy have been popularly reported. However, this review present the oncological adequacy of operations as well as oncological advantages on immune responses. The conclusion is clear, therefore I suggest the authors make this manuscript more concise.

minor comments:

technical aspect: I think spontaneous breathing is more physical.

line 136, without inhalational agents

line 149, locoregional anesthesia provides adequate analgesia, to prevent accidentally movement

180,during time-consuming procedures without an optimal anesthetic management.

NITS could be safely applied for 4-6 hour operations.

line194,rapid intubation, lung seperation, to secure the airway, protect the dependent lung from injuries

line 225, replace balloon with ambu bag or mask

line 351-355

intubation conversion is suggested to be take place after the artificial pneumothorax with dense pleural adhesion, conditions with difficult VATS operations. at this time, tracheal intubation and lung separation could be safely performed. However, emergent intubation conversion may be necessary when massive bleeding happened. For tumors adjacent to vessels, the benefits of NITS should be discussed between team members.

Thank you for your accurate comments. We think a more concise paper could result less clear especially for readers at the beginning of their NITS knowledge. We tried to be didactic and to explore various aspects of NITS, from anaesthesiologic and technical aspects to the oncologic adequacy of non-intubated procedures, in order to give the reader a wide overview about the topic. We modified the text as you suggested (see page 6, line 143, page 8, lines 194-195, page 9, line 209, page 10, line 246)

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#### Reviewer G

Thank you for giving me the opportunity to review the manuscript.

This manuscript was well organized, and we can easily understand past history or current status of major lung resection under spontaneous ventilation by reading it.

I have some recommendations to make the manuscript better.

1. Content in lines 255-274 might be better to be moved to the introduction section.
2. I totally agree with the author's opinion that a longer follow up was needed to investigate the feasibility in daily clinical practice.

Long-term result is most important matter in oncological perspective. I recommend that the author describe it if there have been previous reports showing the long-term results of NITS.

Thank you for you appreciation and your comments.

1) To be honest, similar contents are reported both in the abstract/introduction section and in the first part of the discussion; even if a little redundant, we think it makes the reading more pleasant and comprehensible.

2) We added some recent data about long-term outcomes of NITS major procedures. Please see page 17, lines 389-394, reference # 31.

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