

Peer Review File

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Answer to the Reviewer A.

Thank you very much for your time and very helpful comments. I agree with all of your recommendations and criticism. I think our article with your kind help will be more obvious.

Our answers are as follows:

1. The number of cases is small and unbalanced between patients with and without myasthenia gravis, so I think it would be more appropriate to propose it **as a case series.**

Answer: Yes, you are right. This is few number of clinical observation. We have accepted your proposal to add “case series” to the end of the title. Because the reviewer B recommended the same but the “PILOT STUDY” was recommended with capital letters, we used this one.

Correction:

Spontaneous ventilation with double-lumen tube intubation for video-assisted thoracic surgery thymectomy: **A pilot study**

2. I would recommend creating **a single table including** all the characteristics of the patients in the two groups. Furthermore, it would be useful to summarize **in a table concerning the drugs used for anesthesia, the need for intubation, surgical times and complications, hospitalization times.**

With the recommended Tables, the article is more understandable. Thank you!

Correction:

Table 1. Clinical details of the patients

Females/males	10/5
Mean age (year)	38.9 (19–74)

Mean BMI	24.6 (15.9–33.7)
Osserman classification of MG (n = 11)	
I	3
IIa	4
IIb	3
III	0
IV	1
Preoperative treatment of MG (n = 11)	
No pharmaceutical treatment	1
PB alone	7
PB + CS + AZA	1
PB + CS + AZA + IVIG	1
AC + RIX	1
TPE	0

MG: myasthenia gravis. BMI: body mass index. PB, pyridostigmine bromide (Mestinon); CS, corticosteroid; AZA, azathioprine (Imuran); IVIG, intravenous immunoglobulin; AC, ambenonium chloride (Mytelase); RIX, rituximab; TPE, therapeutic plasma exchange (also known as plasmapheresis).

3. Data relating to the risk of complications with the standard technique, including myasthenic crises, are available in the literature, which should be reported and studied in depth in order to highlight what the real advantages of SVI-VATS could be.

Answer: This is a really debated point of the study. Because of the limited number of the cases we can not make a serious conclusion about the advantage of the SVI in MG cases. That is why we changed the title, the MG as the main line of the paper was deleted, and we just focused on the technical point of view of the technique.

Correction:

Introduction

~~Thymectomy is considered as a beneficial curative surgical treatment for myasthenia gravis (MG), with approximately 35% of cases achieving either complete remission without further pharmaceutical treatment or significant symptomatic improvement (1).~~

~~In the case of MG, the occurrence of ectopic thymic tissue in the perithymic fatty tissue ranges from 21–63%. Therefore, the currently accepted surgical resection is the removal of the thymus gland with extrathymic fatty tissue (2,3).~~

Answer: But we think an advantage can be the spontaneous ventilation period during the surgery, which periode can be respect as a biological test if the relaxant agent ceased or not?

Correction:

“During the spontaneous ventilation period of SVI surgery, patients with MG should be closely monitored for the development of a possible residual neuromuscular blockade, in which a ‘biological test’ provides a safe postoperative period.”

4- In fact, both in the background and in the discussion, the potential differences in terms not only of advantages but also of disadvantages between the SVI VATS and the standard technique should be underlined: **the limited number does not allow to make significant differences**, therefore the data available up to now should be used to then comment on the results obtained in these patients.

Answer: Your comment is absolutely correct. We have expanded the limitation of this study.

Correction:

“This pilot study has some limitations. First, this was a retrospective, monocentric, interventional cohort study. Second, the small number of patients, as the most important limitation, is the key to many further limitations. In this pilot study, we aimed to demonstrate a new and safe method for spontaneous ventilation VATS thymectomy which is applicable in MG cases. Third, the small sample size of this study prevented a broad statistical analysis of the data, which were mainly reported descriptively. Fourth, owing to the lack of a control group, the results of the SVI VATS thymectomy cases were not compared with those of the relaxed series. In the future, with an extended number of SVI VATS thymectomy cases, a comparison between SVI VATS thymectomy and the standard techniques will be presented.”

5. We have reported a clinical case, which could be cited (Patelli, Giorgio et al. *Journal of medical case reports* vol. 15,1 32. 2 Feb. 2021, <https://pubmed.ncbi.nlm.nih.gov/33526108/>), of a very young patient with thymoma who developed a myasthenic crisis during the start of the chemotherapy cycle which required intubation. Other similar cases above all related to anesthesia and surgery should be cited.

Answer:

Thank you very much for this useful information. We referred this article and mentioned in the text.

Correction:

1. Patelli G, Bencardino K, Tosi F et al. Chemotherapy-induced myasthenic crisis in thymoma treated with primary chemotherapy with curative intent on mechanical ventilation: A case report and review of the literature. *J Med Case Rep.* 2021;15:32. doi: 10.1186/s13256-020-02601-8.

6. The heterogeneity of these patients is also a limit in this sense since the thymoma itself, surgery, chemotherapy, anesthesia can represent triggers for a myasthenic crisis which, however, occur through different mechanisms. All of this obviously affects not only the way the potential crisis develops but also the real indication, considering risks and benefits, of a surgical technique such as SVI VATS.

Answer:

Thank you for this recommendation. We used it.

Correction:

A special risk can occur after neoadjuvant treatment of a thymoma when spontaneous ventilation during thymectomy is helpful (25).

Answer to the Reviewer B.

Thank you for your helpful review. You are absolutely right in all the topics you mentioned, and we agree with you. We have reviewed and modified our article: we gave up to focus on make conclusions on the basis of a very limited number of MG cases, and the SVI VATS thymectomy is in the focus of the paper.

Our answers to your proposals are as follows:

I have carefully reviewed the article by Dr. József Furák and Co-Authors, that stands as an interesting contribution to the field of thoracic surgery and anesthesiology.

The study focuses on the advantages of the spontaneous ventilation with double-lumen tube intubation (SVI) technique for video-assisted thoracic surgery (VATS) thymectomy. The Authors included both patients with and without myasthenia gravis (MG), with an indication to thymectomy. The main findings of the study suggest that SVI VATS thymectomy is feasible and safe. Indeed, SVI VATS procedures for other indications were previously reported by the group through peer-reviewed publication.

Overall, the study has potential implications for the management of patients undergoing thymectomy, especially those with MG.

However, there are some limitations that should be at least discussed and partially hampers generalizability of these findings, ensuring that readers have a clear understanding of the scope and applicability of the findings:

1. **small sample size**: the study cohorts of patients with MG (N=11) and without MG (N=4) are relatively small. While small sample size is not uncommon in studies involving rare diseases, such as MG, **it is essential to acknowledge in the paper that the small sample size in this study has prevented broad statistical analysis of the data, that are mainly reported descriptively.** This should be contextualized in the title as follows: “**Spontaneous ventilation with double lumen tube intubation for video-assisted thoracic surgery thymectomy for myasthenia gravis: A PILOT STUDY**”; abstract (method section): “**This is a retrospective, monocentric, interventional cohort study that stands as a pilot evaluation for SVI VATS thymectomy**”; methods section, discussion and conclusions in the main text. Besides,

Answer:

After your recommendation we have changed the title and the abstract:

Correction:

Spontaneous ventilation with double-lumen tube intubation for video-assisted thoracic surgery thymectomy: A pilot study

Background: Spontaneous ventilation is considered the most physiological anaesthesia method in thoracic surgery; however, this procedure is controversial because of the potential risk of an unsafe airway. **We conducted a retrospective, monocentric, interventional cohort study, which was a pilot evaluation of** spontaneous ventilation using a double-lumen tube intubation (SVI) technique for video-assisted thoracic surgery (VATS) thymectomy.

2. I recommend the Authors to report results **as median and not by mean**, given that the latter is more susceptible of influence in case of any outlier result, especially with this low numerosity;

Answer:

We changed the mean to median in the Text:

Correction:

Results: SVI VATS thymectomy was performed without conversion to sternotomy, thoracotomy, or mechanical ventilation. The patients breathed spontaneously for 77.56% of the operative time. **The median minimal arterial oxygen tension (mmHg),**

median maximal arterial carbon dioxide tension (mmHg), and median operative time were 82.4 (56.1–247.2), 59.2 (44.8–67.8), and 75 min (60–120), respectively. The median chest tube duration and length of postoperative hospital stay were 1 and 4 days, respectively

Table 2. Perioperative results

Median operative time (min)	75 (60–120)
Median chest tube duration (days)	1 (1–5)
Median hospital stays (days)	4 (4–7)
Abnormality in the radiological results of the chest X-ray	
Fluid (no required intervention)	5/15
Pneumothorax (no required intervention)	2/15
Pneumothorax (required intervention)	1/15
Atelectasis (no required intervention)	3/15
Infiltration	0/15
Median minimal arterial oxygen tension (mmHg)	82.4 (56.1–247.2)
Median maximal arterial carbon-dioxide tension (mmHg)	59.2 (44.8–67.8)
Histology (n = 15)	
Persistent thymus	9
Follicular hyperplasia	4
Micronodular thymoma	1
Lobulated fatty tissue + lymphoid infiltration	1

3. **lack of control group**: the study lacks a control group of patients who underwent a conventional thymectomy technique. **A comparison between the SVI VATS thymectomy and the standard technique would provide a clearer understanding**

of the advantages and potential benefits of the SVI approach. I understand the work was not conceived as a case-control study; however, this should be reported as a limitation;

Answer:

Unfortunately, we have low numbers in this study, but the main purpose was to mention the feasibility of this process. In the limitations we discussed this problem.

Correction:

“This pilot study has some limitations. First, this was a retrospective, monocentric, interventional cohort study. Second, the small number of patients, as the most important limitation, is the key to many further limitations. In this pilot study, we aimed to demonstrate a new and safe method for spontaneous ventilation VATS thymectomy which is applicable in MG cases. Third, the small sample size of this study prevented a broad statistical analysis of the data, which were mainly reported descriptively. Fourth, owing to the lack of a control group, the results of the SVI VATS thymectomy cases were not compared with those of the relaxed series. In the future, with an extended number of SVI VATS thymectomy cases, a comparison between SVI VATS thymectomy and the standard techniques will be presented.”

4 . **unclear follow-up duration:** the Authors do not provide clear information on the follow-up duration for the patients included. **In fact, the Authors just report that the follow-up care time ranged between 4 and 29 months. A median follow-up time is required** to be calculated to contextualize the data;

Answer:

We added the correct period of the study and the follow-up period.

Correction:

Study design

All patients who underwent SVI VATS thymectomy in our clinic between October 9, 2020 and December 31, 2022 were included in this study. Patient characteristics (sex

and age), indications for surgery, intraoperative and postoperative data, and results were analysed. The follow-up period ended on March 31, 2023, so the median follow-up period was 13.5 months (4–29).

5 . methods are reported incorrectly; the number of patients enrolled, the descriptive analysis of the categories (MG versus non-MG group), and BMI or other clinical data are not part of the methods but instead part of the results.

Answer

We relocated these data from the methods to the results part:

Correction:

“Results

In total, 155 surgeries were performed using the SVI technique. Among these, 58, 82, and 15 were SVI VATS lobectomies, sublobar resections, and SVI VATS thymectomies, respectively.

Fifteen patients with symptoms of MG (n = 11) or radiologically suspected thymoma (non-MG) (n = 4) who underwent SVI VATS resection for thymectomy were retrospectively included in this study.

Four patients without symptoms or a clinical diagnosis of MG were included in the non-MG group, three of whom had a preoperative diagnosis of thymoma, and one patient had a post-COVID accidental chest CT scan diagnosis of persistent thymus without myasthenia.

The mean preoperative American Society of Anesthesiologists (ASA) score was 2.067, and three patients had ASA grade III. Patient characteristics are listed in Table 1. “

5/1 In the methods, please report the study design (point 1), inclusion and exclusion criteria (i.e., indication to thymectomy as inclusion, BMI 30 kg/sqm is a contraindication for SVI VATS, however in the results BMI ranges up to 33 kg/sqm. Please explain why.

Answer:

We have made the study design more obvious and discussed the BMI question. I would like to mention, as we have more experience with the SVI VAZTS thymectomy, we extended the inclusion criteria in terms of the BMI. Sometimes we accepted BMI more than 30 without any surgical difficulties.

Correction:*Study design*

All patients who underwent SVI VATS thymectomy in our clinic between October 9, 2020 and December 31, 2022 were included in this study. Patient characteristics (sex and age), indications for surgery, intraoperative and postoperative data, and results were analysed. The follow-up period ended on March 31, 2023, so the median follow-up period was 13.5 months (4–29).

Patient selection

The only exclusion criterion for SVI surgery was a body mass index (BMI) of >30 . In some cases, a BMI of >30 was accepted for the SVI technique if the fatty tissue of the patient was located in the lower part of the body, away from the chest or abdomen.