

Peer Review File

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Reviewer A:

Comments to the authors:

The authors evaluate the surgical outcome such as chest tube removal time and admission time comparing three different surgical approaches respectively RATS, VATS and open surgery in the surgical treatment of thymomas. Whereas the RATS patients had a significantly higher Masaoka-Koga stage compared to the VATS and sternotomy groups, surgical outcome was similar to VATS group. RATS and VATS were associated with a lower blood loss through surgery, shorter admission time and shorter chest tube time compared to open resection, therefore they concluded that RATS surgery might be considered for patients with a more advanced thymoma stage. Robotic surgery for thymoma has been becoming popular, thus this manuscript is helpful for studying thymoma treatment. In general, this manuscript is interesting, and discussed a hot topic in surgery for thymoma. However, the article does not really extend our understanding of surgery for thymoma. The following points should be addressed.

Major points

1. The authors used data from a single center database extracted throughout the period from 2005 until 2016. The duration of surgical treatment should be inconsistent. This seems to be one of serious problems.

Reply:

Thank you for the comment regarding the period for the inclusion of the patients. The permission to evaluate patients reports from the hospital was given for this period by Secretariat of the Executive Board from Odense University Hospital and following not decided by the authors

2. The number of patients who underwent each surgical treatment was too small to discuss the surgical outcomes.

Reply:

We agree with the reviewer that a larger number of patients in each group would have been preferential but despite thymomas is the most common tumor in the anterior mediastinum they contribute with a limited number of cases each year in most thoracic centers.

3.

a) Whereas the authors performed thymectomy from one side via RATS or VATS, the phrenic nerve was visualized on both sides and spared. This seems to be overstatement because the phrenic nerve in opposite side was not easily visualized using those methods.

b) Actually four patients in the RATS had incomplete resection in this study. Radical treatment is the most important in surgery for thymoma, thus open surgery should be applied for those patients.

Reply:

3 a) We agree with the reviewer that visualization of the phrenic nerve is difficult with minimal invasive surgery. In cases where the resection of the thymoma and thymus resulted in opening of the pleura on the opposite side we had to visualize the nerve despite it was difficult. In our experience the CO₂-insufflation help to solve the difficulties regarding this problem. “under CO₂-insufflation” has been added to the manuscript under VATS thymectomy as it was not mentioned at first.

3 b) We agree with the reviewer that the achieved radicality is an important prognostic factor. Four patients in the RATS group had a pathology report where the capsule was destroyed in small areas due to spreading of heat from the permanent cautery spatula.

The resection border between the pericardium and the thymus is limited to less than a 1mm and therefore spreading of heat was not possible to eliminate from the permanent cautery spatula but the instrument has now been changed to an electro device with less spreading of heat with good results. In all patients the border between the pericardium and the specimen was clearly free and without invasion macroscopically but these patients were recorded with discontinuous capsula in small

areas and following complete radicality could not be warranted by the pathologist. We believe that these patients had radical surgery microscopically too which is consistent with the finding that the three patients have not had any recurrences in their follow-up program and the fourth patient we reoperated with the same finding did not have any malignant tissue left.

This has been added to the manuscript in the discussion section

4. Minor points

“Figures” should be corrected as “Tables”.

Reply:

This has now been corrected in the manuscript.

There are some spelling errors.

“Myastenia” in line 42

“thymomoma” in line 211

Reply:

Mystenia has been changed to Mysthenia

Thymomoma has been changed to thymoma

Reviewer B:

Comments to the authors:

The authors reported a retrospective analysis on outcomes after surgical resection for thymoma comparing VATS, RATS and open surgery. But this study is not quite innovative compared to what is already reported in the current literature on the topic.

Major points:

1. The number of patients reporteds is limited (80 patients in more than 11 years)

Reply:

We agree with the reviewer that a larger number of patients in each group would have been preferential but despite thymomas is the most common tumor in the anterior mediastinum they contribute with a limited number of cases each year in most thoracic centers. We have not been able to find studies comparing the three different surgical approaches in **one** thoracic center with this volume of patients.

2. The authors reported that patients submitted to RATS had more advanced stage thymomas than patients who underwent open surgery, in opposition to general findings. For this reason, this point should be better clarified.

Reply:

Thank you for giving us the opportunity to clarify this point. In the literature we find that after the introduction of minimal invasive surgery open surgery (sternotomy) is often reserved for the more advanced stages please see reference 13.

3. The references reported are poor and all quite dated (it would be better to include the most up-to-date references).

Reply:

The references have been updated according to the reference list

4. Concerning the analysis of the outcomes, no data on relapse of the disease and on survival are reported and this is one of the biggest limitations.

Reply:

We agree with the reviewer that we have not reported anything about relapse of disease and survival rate. We believe that a follow up time for at least 10 years for all

patients would be preferential in order to conclude any differences related to surgical approach as relapses are often seen after ten years and the disease in general have a good prognosis and therefore relapse rate and survival rate would not be reliable yet.

This has been added to limitations for the study

5. Minor points

1) There are some spelling errors, for example:

- Page 1 line 38: thimectomi – should be “thimectomy”
- Page 2 line 40: represents – should be “represent”
- Page 3 line 95: thorascopical- should be “thorascopic”

2) English grammar should be revised.

Reply:

The mentioned spelling errors have been corrected and the grammar has now been revised

3) Surgical complications of each surgical approach could be reported also in an additional table.

Reply:

Postoperative results have been merged to a single table (table 4). Furthermore, another table have been added (table 1) presenting complications.

Reviewer C:

Comments to the authors:

The authors presented comparative analysis between VATS, RATS and open thymectomy. They included 80 patients with thymoma for 10 years. VATS and RATS achieved better results compared to open surgery in early outcomes. The followings are my questions and comments.

1. *Please use generic name instead of commercial name of drugs.*

2. *“Thoracoscopic” is a correct term, not “thoracoscopical”*

Reply:

This has been corrected.

3. *Full names of all abbreviations should be presented when it is used first time (for example, TREND, NSAID, and EPI etc.)*

Reply:

This has been corrected, and abbreviations are now presented.

4. *Overall, 3 patients died after operation. It is quite high mortality rate considering most of the patients had early stage thymoma. The reason should be presented in the discussion section.*

Reply:

We agree with the reviewer that it is a high mortality if the mortality was related with the surgery. In the results section, we describe the three cases and we agree that it is misleading to include the two first cases.

- a) “hemothorax caused by fall episode at home resulting in death of the patient”
- b) “a patient died from pneumonia and sepsis 3 months postoperatively”
- c) “a patient died during admission due to sepsis”

We have deleted case a and b from the results section

5. *Considering the differences in sex ratio and stages between 3 surgical methods, comparing with propensity score matching is necessary.*

Reply:

We agree with the reviewer that with a larger number of patients in each group propensity match scoring would eliminate bias related to difference in sex ratio but with subgrouping of the limited number in each group propensity match scoring can accomplish the opposite of its intended goal --- thus increasing imbalance, model dependence, and bias therefore we decided not to do it.

6. It is necessary to present the criteria of chest tube removal in terms of amount of drainage.

Reply:

Thank you for the commentary regarding chest tube removal.

The following text has been added on page 5 in the section “postoperative treatment”

Chest tube removal

All patients followed the same guideline at our clinic regarding chest tube removal, which is production of less than 400 ml of pleural fluid chest tube over a period of 24 hours after surgery or less than 100 ml during the first 6 hours after surgery.

7. What is the meaning of “admission time”? Is it the length of hospital stay?

Reply:

We agree with the reviewer that the term length of stay is more precise and following it has been changed in the text

8. How about the difference in pain score and the use of analgesics?

Reply:

We agree with the reviewer that it would have been valuable with standardized VAS scoring of the patients but unfortunately, we do not have these data.

Regarding the use of analgetics, the medication has been described in the methods section.

9. WHO types of thymoma should be presented.

Reply:

We agree with the reviewer that other types of staging system for thymomas could have been presented too. According to a recent publication in J Thorac Oncol 2020 Mar;15(3) :436-447 focused on the topic Ruffine E. et al. concluded that the Masaoka

Koga system was most frequently used as staging system even more than the TNM system and WHO.

We added this reference to the manuscript in section for postoperative treatment.

10. How many patients had myasthenia gravis? How many were improved? Any difference among 3 surgical groups?

Reply:

We find that subgrouping of the data would not add further value to clarify our contribution therefore we have not evaluated patients with myasthenia gravis and surgical approach but would certainly consider doing it when we have a larger group of operated patients.

11. The proportion of R0 resection should be presented in result section.

Reply:

R0 resection has been added to the result section. However, we did not perform statistical analysis on this matter due to differences in stage and the uncertainty of the pathological report as described in the answer to Ad 14.

12. I think all the tables can be merged into single table.

Reply:

Two tables have been merged. However, another table is added presenting complications as requested.

13. I recommend using the 8th edition of AJCC staging system than Masaoka-Koga stage.

Reply:

We agree with the reviewer that other types of staging systems for thymomas could have been presented too. According to a recent publication in J Thorac Oncol 2020 Mar;15(3) :436-447 focused on the topic Ruffine E. et al. concluded that the Masaoka- Koga system was most frequently used as staging system even more than the TNM system.

We added this reference to the manuscript in the postoperative treatment section.

14. In discussion section, the comment on the inaccuracy of pathologic examination determining complete resection is not evidence-based and too subjective description. If the authors cannot believe in the report of pathologist, what else can be a gold standard for assessing complete resection? It should be removed.

Reply:

We agree with the reviewer that inaccuracy of pathologic examination determining complete resection is not evidence-based but more a matter of how it is in the clinic. Four patients in the RATS group had a pathology report where the capsule was destroyed in small areas due to spreading of heat from the permanent cautery spatula. The resection border between the pericardium and the thymus is limited to less than a 1mm and therefore spreading of heat was not possible to eliminate from the permanent cautery spatula but the instrument has now been changed to an electro device with less spreading of heat with good results.

In all patients the border between the pericardium and the specimen was clearly free and without invasion macroscopically but these patients were recorded with discontinuous capsula in small areas and following complete radicality could not be warranted by the pathologist. We believe that these patients had radical surgery microscopically too which is consistent with the finding that the three patients have not had any recurrences in their follow-up program and the fourth patient we reoperated with the same finding did not have any malignant tissue left.

This has been added to the manuscript in the discussion section

15. I cannot agree that this paper is “one of the largest single center study”. There are many other studies with sufficient larger volume of robotic or thoracoscopic surgical cases.

Reply:

We agree with the reviewer that there a larger multi center studies comparing two surgical approaches but we have not been able to find any single center studies focused on surgical approach for thymoma where all three surgical approaches have been compared.

Reviewer D:

The paper includes valuable information. However, much important information is lacking. Major revision is needed for this article.

1. In l.65-68, the author stated “Stage III and stage IV patients would receive adjuvant radiotherapy to reduce the risk of local recurrence (11) Patients treated surgically for stage II thymoma with an incomplete resection would also receive adjuvant radiotherapy to reduce the risk of local recurrence (11).” About this sentence, adjuvant radiotherapy is not considered as a gold standard. There is no recommendation on adjuvant radiotherapy in Reference 11 as well. The authors must explain why adjuvant radiotherapy is used in the author’s institution.

Reply:

We agree with the reviewer that radiotherapy is not considered as a gold standard. Oncological treatment of these patients has been centralized in Denmark to another hospital. They follow the ITMIG group recommendation for the oncological treatment but it was not the scope of our submission.

Following has been added to methods section

Patients with Masaoka stage II thymomas without complete microscopic resection and patients with stage III and IV thymomas, would be referred to Rigshospitalet, Denmark for further oncological treatment and follow-up.

2. l.75-76, the authors stated that patients with invasion in great vessels, thoracic wall and disseminated disease are excluded. It is not clear whether these patients are excluded from indication for surgery itself or excluded from the study. Because pleural dissemination and SVC invasion are not considered as contraindications to surgery in some institutions (Long-Term Outcomes After Surgical Resection for Pleural Dissemination of Thymoma. Kimura K, Kanzaki R, Kimura T, Kanou T, Ose N, Funaki S, Minami M, Shintani Y, Okumura M. Ann Surg Oncol. 2019 Jul;26(7):2073-2080. doi: 10.1245/s10434-019-07330-x. Long-term outcomes of advanced thymoma in patients undergoing preoperative chemotherapy or chemoradiotherapy followed by surgery: a 20-year experience. Kanzaki R, Kanou T, Ose N, Funaki S, Shintani Y, Minami M, Kida H, Ogawa K, Kumanogoh A, Okumura M. Interact Cardiovasc

Thorac Surg. 2019 Mar 1;28(3):360-367. doi:10.1093/icvts/ivy276.), the authors must explain indication of surgery for Stage III, IV disease in detail.

Reply:

We agree with the reviewer that pleural dissemination and SVC invasion are not considered as contraindications to surgery but treatment of these patients has been centralized in Denmark to another hospital following it excludes these patients from the study in those circumstances where pleural dissemination and SVC invasion were known prior to surgery. It has been added to the manuscript. The benefit of the centralization for our study is that our groups will be homogenous and have more similarities than if open surgery was reserved for the most advanced cases.

Following has been added to the methods section.

Treatment of patients with Masaoka stage III and IV has been centralized at Rigshospitalet, Copenhagen in Denmark and are not included in this study. A few number of patients were treated surgically for stage III thymoma at our clinic in cases where the stage was not known prior to surgery but were referred to Rigshospitalet, Denmark for further oncological treatment and followup.

3. Indication of VATS, RATS, Open should be stated more precisely. Because RATS or VATS for Stage III disease is not generally performed, the authors must explain the rationale for such surgery.

Reply:

Open surgery was the primary operation in the beginning of the period while VATS thymectomies followed when minimal invasive surgery was introduced. After the introduction of robotic assisted surgery this has been the surgery of choice for thymectomies. In the five cases with stage III these stages were not known before surgery and following operated in our hospital.

Following has been added

Surgical techniques

The surgical approach has changed throughout the inclusion time in this study. In 2006, the patients were treated through open surgery until the shift towards minimal invasive surgery and finally to robotic assisted surgery.

4. Patient characteristics should be placed in Table 1 for better understanding. Not only age and sex but also comorbid conditions of patients such as autoimmune disease should be provided. Basic information on tumor such as tumor size, site of invasion of stage III disease, histologic type should be provided.

Reply:

Thank you for valuable input to the tables. We have added the longest length axes measurement for the patients and we have added information about tumor invasion site on all stage III tumors. Information about myasthenia and comorbidities cannot be added due to the European Communittee ratified the General Data Protection Regulation law in 2016 which does not allow us to study each patient report after the patient has been discharged from the hospital.

Regarding the different staging modalities it has been mentioned in the manuscript (Background line 4) that MK staging is the most frequent used staging system therefore it has been chosen in our manuscript.

5. Information on combined resection in patients with 5 patients with Stage III disease should be provided.

Reply:

We have added information about the five patients with stage III.

Radical resection by the pathology report was not obtained for four RATS patients and two patients in the open surgery group (table 4). The four patients in the RATS group were all in stage II. The site for incomplete resection were in three cases discontinuous capsula caused by electro-cauterization while the fourth patient was re-resected with open surgery afterwards without malignant finding. None of the patients have had recurrence during 4,5,5 and 6 years. Among stage III patients, two patients with open surgery had invasion of the brachiocephalic vein and mediastinal pleura and did not achieve radical surgery at the site of the mediastinal pleura which was treated at Rigshospitalet, Denmark with radiation therapy with no recurrence for nine years in one patient while the other died the year after surgery. In the RATS group one patient had invasion of the pericardium and had radical surgery while two patients operated respectively by VATS and RATS, we found invasion of the mediastinal pleura and both had radical surgery.

6. l.168-171, information on details of incomplete resection of 6 cases suchas preoperative stage, site of residual tumor, indication of adjuvant therapy should be provided.

Reply:

The four cases registered with incomplete resection in the RATS group have already been described in the discussion section but in addition we have added the following to the results section line 168.

Radical resection by the pathology report was not obtained for four RATS patients and two patients in the open surgery group (table 4). The four patients in the RATS group were all in stage II. The site for incomplete resection were in three cases discontinuous capsula caused by electro-cauterization while the fourth patient was re-resected with open surgery afterwards without malignant finding. None of the patients have had recurrence during 4,5,5 and 6 years. The two patients operated with sternotomy have been described earlier.

7. It is better follow up information until now (i.e., follow up period, recurrence, death) is added. The authors should be able to calculate at least 3-year recurrence rates now (2020 November), why don't you show this information?

Reply:

We agree with the reviewer that recurrence rates, mortality rates could be valuable to add to a study with this scope but unfortunately the European Communittee ratified the General Data Protection Regulation law in 2016 which does not allow us to study each patient report after the patient has been discharged from the hospital. The law has in general limited our possibilities on follow up of the patients which I hope the reviewer can understand.

Apart from the above, calculation of recurrence rate would require that the study had been powered to support if a certain surgical was approach was in favour of another. With the given numbers in each group this message would be based on severe underpowered calculations which first of all not was the scope of this study and secondly would run the risk of drawing wrong conclusions.

8. R0 resection rate of RATS group (35/39) seems low. The authors should explain these results. As a surgeon, we should think about indication maybe wrong or procedure was not good. The authors have responsibility to draw a take home message from these results.

Reply:

We thank the reviewer for the question regarding R0 resection in the RATS group. In the discussion section we explain that our pathologist had difficulties defining a continuous resection border due spreading of heat from the cautery we used on these patients. By changing to another instrument with less spreading of heat we have solved the problem and feel sure that the patients had radical resections while these patients have had no recurrence in their follow up program with yearly CT scan.

9. Discussion section should be strengthened based on the points described above.

Reply:

The following has been added to the discussion

In all patients the border between the pericardium and the specimen was clearly free and without invasion macroscopically but these patients were recorded with discontinuous capsula in small areas and following, complete radicality could not be warranted by the pathologist. We believe that these patients had radical surgery microscopically too which is consistent with the finding that none of the patients have had recurrences in their follow-up program and the patient we reoperated with the same finding did not have any malignant tissue left.

The resection border between the pericardium and the thymus is limited to less than a 1mm and therefore spreading of heat was not possible to eliminate from the permanent cautery spatula but the instrument has now been changed to an electro device with less spreading of heat which solved the problem for the pathologist.

With the aid of the valuable input from the reviewer/editor we have put in an effort to strengthen the discussion with the focus on the aim of the study : Impact of the surgical approach on morbidity and length of stay on patients treated surgically for thymomas comparing three surgical techniques. Our groups are more homogenous as you normally would expect when you compare minimal invasive surgery with open surgery as the most advanced stages are excluded due to how it is organized in our

country. The treatment after surgery is without great differences as all patients have been treated in the same department with same procedures for medication, chest tube removal and discharge from the hospital and follow up.

Following has been added

The groups in this retrospective study are close to homogenous in terms of choice for the surgical approach and postoperative treatment. The treatment after surgery is without great differences as all patients have been treated in the same department with the same procedures for medication, chest tube removal, discharge from the hospital and follow up.