

**Reviewer A**

I would like to summarize what to present in general.

**Comment 1:** - Please, precisely describe the treatment in Stage 3 and 4. You may make a Table from the following information. For sure it changes from Department to Department but there should be a baseline for everybody to agree up on. Your paper is a little bit confusing. Please describe the situations clearly. Thymoma and Thymic carcinoma is such a complex situation. Please also include Recurrent thymomas.

Here is the standard information. Please make certain that the readers get this after reading your article:

Standard treatment of stage III and stage IV thymoma that may be completely removed by surgery includes the following:

- Surgery followed by radiation therapy.
- Neoadjuvant chemotherapy followed by surgery and radiation therapy.

Treatment of stage III and stage IV thymoma that cannot be completely removed by surgery includes the following:

Chemotherapy.

Chemotherapy followed by radiation therapy.

Neoadjuvant chemotherapy followed by surgery (if operable) and radiation therapy.

Treatment of thymic carcinoma that may be completely removed by surgery

- Surgery followed by radiation therapy with or without chemotherapy.
- Not completely removed by surgery:

Chemotherapy.

Chemotherapy with radiation therapy.

Chemotherapy followed surgery, if the tumor may be completely removed, and radiation therapy.

Treatment of Recurrent Thymoma and Thymic Carcinoma

- Chemotherapy.
- Hormone therapy (octreotide) with or without prednisone.
- Targeted therapy.
- Surgery.
- Radiation therapy.
- A clinical trial of immune checkpoint inhibitor therapy with pembrolizumab.

**Reply 1:** We modified the main text as advised.

**Changes in the text:** We performed a global review of the following sections in the following sections (text highlighted in blue): CLINICAL ASSESSMENT (lines 19-45), RADIOLOGICAL ASSESSMENT (lines 46-83), and MULTIMODALITY TREATMENT (lines 84-138). In the section RADIOLOGICAL ASSESSMENT, we created three additional sub-paragraphs entitled: Computed Tomography (CT) (lines 58-64); Fluorodeoxyglucose F18Positron Emission Tomography/Computerised Tomography (18FDG PET/CT) (lines 65-77); Magnetic Resonance Imaging (MRI) (lines 78-83), in which we detailed each single technique.

In the MULTIMODALITY TREATMENT section (lines 84-138), we performed a more schematic description of the treatments for the different stages of thymic malignancies. We also added Table1, with a schematic overview of the current therapeutic approaches for locally advanced, advanced and recurrent thymic malignancies.

We also deep reviewed the SURGERY section (modified text in the manuscript is highlighted in blue).

2- Please check the following references for further detailed analyzes.

Choe G, Ghanie A, Riely G et al, Long-term, disease-specific outcomes of thymic malignancies presenting with de novo pleural metastasis. JTCVS. 2020;159(2):705-14.

Park S, Park IK, Kim YT, et al. Comparison of neoadjuvant chemotherapy followed by surgery to upfront surgery for thymic malignancy. Ann Thorac Surg. 2019;107(2):355-62.

Merveilleux duVignaux C, Dansin E, Mhanna L, et al. Systemic therapy in advanced thymic epithelial tumors: Insight from RYTHMIC prospective Cohort. J Thorac Oncol. 2018;13(11):1762-70.

Toker A, Hayanga JWA, Dhamija A, Kaba E, Ozkan B, Ayalp K, Cimenoglu B, Abbas G, Superior Vena Cava Reconstruction in Masaoka Stage III and IVa Thymic Epithelial Tumors, The Annals of Thoracic Surgery (2021), doi: <https://doi.org/10.1016/j.athoracsur.2021.05.077>.

## **Reviewer B**

The authors have reported a very interesting “narrative review” to analyze the outcomes of extended surgical resections for locally advanced thymic malignancies. In general, this manuscript is logical and interesting, and discussed a hot topic in thymic malignancies treatment. This review would be helpful for journal readers to update knowledge of thymic malignancies. However, the following points should be addressed.

The author should discuss as follows:

Major points

**Comment 1:** The authors focused on extended surgical resections for locally advanced thymic malignancies. There have been several reviews or reports of SVC replacement for a curative resection for thymic malignancies. Thus I think that if the authors describe the role of aortic resection (even reported in case report) or treatment for stage IVa thymic malignancies, debulking,

as well as treatment for recurrent thymic malignancies, the manuscript will be more valuable for readers.

**Reply 1:** We modified text following Reviewer's suggestions (modified text in the manuscript is highlighted in blue).

**Changes in the text:** In the SURGERY section we added the following sentences: "Overall, only a few reports describe ascending aorta or aortic arch replacement; such scarcity is due to the extreme surgical challenges posed by the procedure. (29-31) In case of pleural metastases (stage IVa) surgical options range from regional or complete parietal pleurectomy to extrapleural pleuropneumectomy (EPP); yet, the benefits of the latter are still under debate. (32)." (lines 219-223) Moreover, in Table 1, we schematic reported an overview of the recommended therapeutic approaches for stage IV thymic malignancies.

In DISCUSSION, we explained that the combination of debulking surgery followed by radiotherapy have been reported to be more efficient than radiotherapy alone (lines 318-320)

Minor points

**Comment 2:** Please describe the role of PET-CT in detail such as SUVmax for thymic cancer or other malignancies (lymphoma, germ cell tumor).

**Reply 2:** We modified the text as advised (modified text in the manuscript is highlighted in blue).

**Changes in the text:** We deep revised the RADIOLOGICAL ASSESSMENT section, with particular regard to PET/CT sub-paragraph (text highlighted in blue) (lines 65-77).

**Comment 3:** The regime of chemotherapy for thymoma or thymic carcinoma would be useful for readers.

**Reply 3:** We modified the text as advised (modified text in the manuscript is highlighted in blue).

**Changes in the text:** We deep revised the MULTIMODALITY TREATMENT section (lines 84-138) in which we explored the therapeutic approaches for thymic malignancies, moreover in Table 1, we schematic reported the current treatment strategies, according with NCCN Guidelines, version 1.2021 (Ref 2).

**Comment 4:** The "nerve-sparing" surgery means the preservation of phrenic nerve.

**Reply 4:** We modified text following Reviewer's suggestions (modified text in the manuscript is highlighted in blue).

**Changes in the text:** in the SURGERY section (lines 153-156) we added the following sentence: "Resection of the PN is particularly dreaded in myasthenic patients because of the risk of hemidiaphragmatic paralysis, which causes impairment of pulmonary function; therefore, some authors suggest using a nerve-sparing technique, which entails the skeletonization of the neural layer. (12)"

**Comment 5:** Please discuss the indication of aggressive surgery for locally advanced thymic malignancies.

**Reply 5:** We clarified in the text (modified text in the manuscript is highlighted in blue).

**Changes in the text:** In Table 1 we schematic reported the current therapeutic options for locally advanced thymic malignancies.

**Comment 6:** Some spell check or is required. Some abbreviation should be explained (AFP, HCG etc). In page 9, line 23, “superior vena cava” should be “SVC”.

**Reply 6:** We explained in the main text (modified text in the manuscript is highlighted in blue).

**Changes in the text:** We provided explanations for the abbreviations: AFP (alpha-phetoprotein), (line 41); HCG (beta-human chorionic gonadotropin), (lines 41-42). In page 9 we replaced “superior vena cava” with SVC.

## Reviewer C

This review article was conducted to explore the recent literature to investigate clinical and radiological assessment, multimodality approach and outcomes of locally advanced thymic tumors. They concluded that extended surgery should be indicated when a complete resection suspected to be gained preoperatively, and the multidisciplinary treatment plan is mandatory when managing advanced staged thymic epithelial tumors. However, the study contains several fundamental limitations consistent with their conclusions. Therefore, I would not recommend this manuscript for publication in the GS.

Major problems:

**Comment 1:** This review research was not conducted with systematic review. The article treating ITMIG database contained results of other studies in Table 1, therefore, the article should not be incorporated in this review analyses.

**Reply 1:** We revised the text as advised (modified text in the manuscript is highlighted in blue).

**Changes in the text :** We clarified in the section MATERIALS AND METHODS that our Narrative Review was carried out in a non-systematic way (line 12). Moreover, in Table 2 and in the References section we removed the Bibliographic Reference Rimmer et al. 2016, referring to ITMIG Database.

**Comment 2:** Authors should mention with regard to limitations that this review was not conducted in systematic methods.

**Reply 2 :** We precised in the main text (modified text in the manuscript is highlighted in blue).

**Changes in the text :** We precised, with regard to limitations, that our manuscript has been conducted in a non-systematic way (line 344).

**Comment 3:** In this study, English was poorly written. Authors should consult for native English proofreading.

**Reply 3:** We submitted our manuscript to a native English reviewer for proofreading.

Although, this paper does not worthy to be published in GS based on their materials and methods, when a major revision is made that corrects a major problems, it should be considered for publication in GS after rigorous peer re-review.

## Reviewer D

This narrative review makes a good read and the content of the manuscript is easy to follow. However, in some points, the reader is left behind. For example:

**Comment 1:** Page 3: what does it mean direct and indirect CT signs (please specify)

**Reply 1:** We modified the text as advised (modified text in the manuscript is highlighted in blue).

**Changes in the text:** We performed a deep revision of the RADIOLOGICAL ASSESSMENT, with particular regard to CT and the sentence referring to indirect CT has been removed (lines 58-64).

**Comment 2:** Page 3: size does not correlate with more advanced disease (I can not understand this statement, please explain)

**Reply 2:** We modified the text as advised (modified text in the manuscript is highlighted in blue).

**Changes in the text:** As for Comment 1, we revised the entire section RADIOLOGICAL ASSESSMENT (lines 58-64), and the sentence has been removed.

**Comment 3:** Page 4: CT is equal to or superior to MRI for evaluating mediastinal mass? This is a new message to me, please provide the evidence and literature

**Reply 3:** We modified the text as advised (modified text in the manuscript is highlighted in blue).

**Changes in the text:** The RADIOLOGICAL ASSESSMENT section has been deep re-organised (lines 58-83), we removed the sentence.

**Comment 4:** Page 5: You stated, that tissue biopsy like needle aspiration may have the possible adverse effect such as tumor seeding. This is an enormous statement, which has to be proven, you should provide the evidence and quantify the risk for this assumption.

**Reply 5:** We modified accordingly (modified text in the manuscript is highlighted in blue).

**Changes in the text:** We removed the sentence “A tissue biopsy is obtainable via transthoracic or transbronchial needle aspiration, mediastinoscopy, anterior mediastinotomy, or video-assisted thoracoscopic surgery (VATS), considering possible adverse effects such as tumor seeding (21)”.

**Comment 6:** Page 5: The indication for PORT should be more detailed because this is often discussed in the multidisciplinary tumor board (when, what group of patients, dose).

**Reply 6:** We modified the section MULTIMODALITY TREATMENT (modified text in the manuscript is highlighted in blue).

**Changes in the text:** In the section MULTIMODALITY TREATMENT (lines 84-138) we better described the PORT approach (lines 131-138); we also created Table 1 in which we schematic summarized the current treatments for locally advanced, advanced and recurrent thymic malignancies.

**Comment 7:** Page 9: Within the surgical community it is more recently discussed the value of lymph node dissection (systematic, sampling or no dissection) for staging and further adjuvant therapy, you should this surgical issue in detail - it's important to have an educated comment and advice.

**Reply 7:** We modified text as advised (modified text in the manuscript is highlighted in blue).

**Changes in the text:** In lines 157-160, we replaced our previous sentence with the following “The effectiveness of lymph node dissections is still debated, as the incidence of lymph node metastasis in thymic malignancy has not been clearly established yet. As reported in several studies, lymphadenectomy should not affect long-term survival but seems to improve the staging as suggested by the ITMIG. (20)”

**Comment 8:** Overall, you should expand on the role of different thymoma histologies (thymoma type A-B3) for the multimodality treatment and prognosis

**Reply 8:** We modified text following Reviewer’s suggestions (modified text in the manuscript is highlighted in blue).

**Changes in the text :** In Table 1 we schematic reviewed the current treatment strategies for different stages thymic malignancies.

## **Reviewer E**

Congratulations on this informative and well-structured review article on the diagnosis and treatment of locally advanced tumours of the thymus. In my view, you have clearly formulated the problems in the treatment of these tumours and described clinically important recommendations based on the existing international literature.

I still have the following comments, which should please be commented on or implemented in the manuscript:

**Comment 1:** Please describe briefly the now established and clinically recommended IASLC/ITMIG classification of UICC stage III. Please elaborate the differences between stage IIIA and IIIB, as this is crucial for treatment planning. For example, stage IIIa tumours are usually operable, whereas stage IIIB tumours are usually no longer operable. From my point of view, this is important for the reader.

**Reply 1:** We modified the text following Reviewer’s suggestions (modified text in the manuscript is highlighted in blue).

**Changes in the text:** We created Table 1 in which we schematic reported the current therapeutic options for locally advanced, advanced thymic malignancies (stage I to IV) and for recurrent disease.

**Comment 2:** You have described tips and recommendations on the multimodal approach and also the surgical technique (pages 5 and 9), with which I agree. For the reader, two suitable illustrations, e.g. as a flow chart, would be easier to understand. Please add to this.

**Reply 2:** We modified text as advised (modified text in the manuscript is highlighted in blue).

**Changes in the text:** In the section MULTIMODALITY TREATMENT (lines 84-138), we schematic explained recommendations for each Masaoka-Koga stage, I to IV, referring to Table 1.

**Comment 3:** The main focus of your article is stage III and this should be the complete focus. Please state this in the introduction and also in the discussion.

**Reply 3:** In our narrative review, we explored the current literature on the therapeutic approaches for the treatment of locally advanced and advanced thymic malignancies; we also reported recurrent disease. Stage III thymic tumours could enter in the locally advanced category.

**Comment 4:** What about intrathoracic lymph node involvement? Difference N1 and N2 according to IASLC/ITMIG? Recommendation for lymph node dissection and to what extent? Please describe and discuss this in your manuscript, as mediastinal lymph nodes may also be involved in locally advanced thymomas. If yes, then postoperatively it is a stage IV. Please present this connection in a comprehensible way.

**Reply 4:** We explained in the text (modified text in the manuscript is highlighted in blue).

**Changes in the text:** Lymph node has been treated in the section SURGERY: at present lymph node dissection is still an open question, since the incidence of lymph node metastases in thymic malignancies has not clearly established, as reported by current literature (Hwang et al 2018) (lines 157-160).