

Peer Review File

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Reviewer A

I regret rejecting the publication of your article. All the research you have done is noteworthy, but nowadays there is not enough evidence to support some of your statements. In the “Extended thymectomy” section, you explain the controversy between extended thymectomy (or total/complete thymectomy) and thymothymectomy (or thymomectomy or simple thymectomy) as the recommended type of resection in early-stage non-myasthenic thymoma.

It is true that some recent articles have described that disease-free and thymoma-related survivals are comparable, but studies of the Japanese Association for Research on the Thymus, the Chinese Alliance for Research in Thymoma and a European Society of Thoracic Surgeons Thymic Working Group have found a higher rate of local recurrence in the thymomectomy group than in the thymectomy group. Therefore, there is not sufficiently strong evidence to support the algorithm shown in figure 2, which suggests that thymomectomy should be the preferred extend of resection in early-stage non-myasthenic thymoma.

Reply: We consulted the studies of the Japanese Association for Research on the Thymus, and the European Society of Thoracic Surgeons Thymic Working Group. We removed Figure 2 because its content lacked a clear basis.

Changes in the text: We removed Figure 2.

Reviewer B

Herein, authors summarized the standard of care in TET’s treatment and treated exhaustively the new and interesting topic of immune checkpoint inhibitor (ICI) as systemic chemotherapy.

The manuscript could be interesting but there are some major and minor issues and concerns that could be issued.

Comment 1: Background is not focused on the topic of review, diagnosis and paraneoplastic syndrome are not really related to the surgical treatment or to the new

perspectives on TET.

Reply 1: We have revised the background to focus on the topic of the review. The content on diagnosis and paraneoplastic syndromes has been reduced, and content related to ICI treatment has been added.

Changes in the text: We have modified our text as advised (see Page 4, line 55-66).

Comment 2: “there are no clear standards for which surgical method to choose” is not correct, main guidelines and thoracic societies suggest the extended thymectomy as preferred operation for thymomas (PMID: 34023891, PMID: 34165529)

Reply 2: We have deleted the text marked with “there are no clear standards for which surgical method to choose”. We confirmed the main guidelines, revised the wording, and added references.

Changes in the text: We have modified our text as advised (see Page 4, line 71-73).

Comment 3: 3.1 Paragraph could be omitted since it has already been reported in Table 1.

Reply 3: We have omitted the content that overlaps with Table 1 in paragraph 3.1.

Changes in the text: Contents that overlap with Table 1 in paragraph 3.1 have been omitted.

Comment 4: 3.1 Paragraph included in a confusing manner surgical, oncological and neurological outcomes. A methodical description of indications and outcomes is required.

Reply 4: Paragraph 3.1 contained surgical, oncological, and neurological outcomes confusingly, so we systematically revised the wording.

Changes in the text: We have modified our text as advised (see Page 6-7, line 113-128).

Comment 5: Why authors separated thymic tumors from thymic cancers (3.4 paragraph)?

Reply 5: We unified the paragraphs on thymic tumors and thymic cancer.

Changes in the text: We unified the paragraphs on thymic tumors and thymic cancer.

Comment 6: MDB should be offered to all the patients despite the stage, dimensions, or the presence of paraneoplastic syndromes.

Reply 6: Multidisciplinary treatment should be offered to all patients regardless of stage, size, or presence of paraneoplastic syndromes, and we have added text.

Changes in the text: We have modified our text as advised (see Page 7, line 126-128).

Comment 7: Discussion on biomarker or genetic mutations should be improved PMID: PMC10475716

Reply 7: We have improved the discussion of biomarkers or genetic variants. Added references.

Changes in the text: We have modified our text as advised (see Page 10-11, line 206-212 and page 11, line 225-227).

Reviewer C

While your manuscript provides valuable insights into an important clinical topic, there are some areas that could be refined to further augment the quality and impact of the work. Here are some respectful suggestions that could potentially improve the paper if you choose to implement them:

Comment 1: Initiating the background section with a succinct introductory sentence that offers a clear definition of thymic epithelial tumours prior to delving into specific details would assist in orienting general readers.

Reply 1: We have added a clear definition of thymic epithelial tumors in the background section.

Changes in the text: We have modified our text as advised (see Page 4, line 55-57).

Comment 2: Further elaboration on the composition of the 69 studies included would enhance the understanding of the evidence base. Including details such as the

distribution among retrospective and prospective studies, randomized controlled trials, case studies, and other relevant classifications will offer a clearer picture of the diverse range of evidence underpinning the analysis.

Reply 2: We have added a detailed distribution of retrospective and prospective studies to the composition of the studies in the 69 literatures.

Changes in the text: We have modified our text as advised (see Page 13, line 259-262).

Comment 3: Expanding the discussion on robotic-assisted surgery would enrich the manuscript, particularly considering the escalating adoption of this surgical approach. Offering a more comprehensive exploration of its distinct advantages and limitations in comparison to conventional open surgeries or video-assisted thoracic surgery approaches could enhance the depth of understanding.

Reply 3: We expanded the discussion on robot-assisted surgery. Compared with conventional open surgeries and video-assisted thoracic surgery approaches its distinct advantages and limitations were more comprehensively explored.

Changes in the text: We have modified our text as advised (see Page 9, line 168-175).

Comment 4: Incorporating a concise section dedicated to optimal perioperative management strategies aimed at minimizing complications and mitigating myasthenia gravis flares would augment the manuscript. This addition would serve to outline practical approaches essential for enhancing patient outcomes and could include a spectrum of effective perioperative interventions.

Reply 4: We have added a concise section dedicated to optimal perioperative management strategies aimed at minimizing complications and reducing recurrence of myasthenia gravis.

Changes in the text: We have modified our text as advised (see Page 12-13, line 249-256).

Comment 5: Further elaboration on the mechanisms and rates of treatment response, as well as resistance to emerging immunotherapies, such as checkpoint inhibitors in thymic tumours, would enrich the manuscript. This deeper exploration would offer a more comprehensive understanding of the landscape surrounding these novel therapies, allowing for a contextualized assessment of their potential role in clinical applications.

Reply 5: We added mechanisms of therapeutic response and resistance to new immunotherapies such as checkpoint inhibitors in thymic tumors.

Changes in the text: We have modified our text as advised (see Page 4, line 61-66 and page 11, line 225-227.).

Comment 6: Engaging in a discussion about limitations associated with the heterogeneity in defining and measuring outcomes across studies would significantly bolster the manuscript. Highlighting concerns regarding potential publication bias, overrepresentation of positive findings, and the challenges posed by varying definitions and measurement methodologies for outcomes would add depth to the analysis. Additionally, addressing the predominance of retrospective, single-centre studies and their implications on the generalizability of findings would offer valuable insights into the broader applicability of the research.

Reply 6: We added limitations related to heterogeneity in outcome definition and measurement across studies. Added concerns about potential publication bias, overrepresentation of positive results, and challenges posed by changes in how outcomes are defined and measured. Furthermore, we added the advantages of a retrospective, single-center study and the generalizability of the study results.

Changes in the text: We have modified our text as advised (see Page 13-14, line 263-277).

Comment 7: Assigning specific titles to Tables 1 and 2 would enhance clarity and organization within the manuscript. Moreover, introducing another table summarizing the advantages and disadvantages of the various surgical techniques discussed would effectively highlight ongoing debates and facilitate a nuanced understanding of the comparative merits and limitations of these approaches.

Reply 7: We have assigned specific titles to Tables 1 and 2. In addition, we introduced a separate table summarizing the advantages and disadvantages of the various surgical techniques discussed.

Changes in the text: We have modified our text as advised (see Page 9, line 180-181).

Comment 8: Restricting the use of passive voice statements throughout the manuscript can significantly enhance engagement by opting for active voice, thereby imparting a

more dynamic narrative. Additionally, reviewing the manuscript for consistency in verb tense between sections is pivotal. Considering the nature of a review, favouring the past tense predominantly might better align with the overall context and improve coherence across the document.

Reply 8: In revising it, we limited the use of passive voice statements throughout the manuscript and opted for active voice statements. Furthermore, the text was revised to give priority to the past tense.

Changes in the text: We have modified our text as advised (see Page 6, line 98-99 and page 6, line 108-110).