Peer Review File

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Reviewer A

Comment 1: Line 137. There are different types of tumor markers depending on the context. It should be mentioned that the NSE was used as a serum tumor marker in the NEJ023 study. Moreover, the reference 26 focused on advanced thymic carcinoma instead thymic carcinoma.

Reply 1: Thank you for your point. We revised the section accordingly.

Change in the text 1: Line 159, 165-173

Comment 2: Line 143-145. The diagnostic potential of cytokeratin 19 fragment was reported in the reference 28. However, the same marker was not associated with OS or PFS in the reference 26. The authors may want to discuss this point.

Reply 2: Thank you indeed for your comment.

We revised the section according to your comment.

Change in the text 2: Line 165-171

Comment 3: Line 301-303. The main focus of this manuscript is induction therapy. PDL1 and TMB are usually used as biomarker for response to immunotherapy. It is essential to add a few sentences into this part to briefly mention immunotherapy in TETs (Eg. Efficacy, predictive markers…).

Reply 3: Thank you for your suggestions. We revised the section and added the information regarding immunotherapy.

Change in the text 3: Line 353-387

Comment 4: Line 305 “as GFT2I” is a typo. GTF2I is the most frequently observed mutation in TETs, the original paper in which the mutation was first identified should be cited in this case. In addition, HRAS, NRAS and TP53 should be mentioned since these are potential founder mutations based on the reference 60.

Reply 4: We appreciate your comment. Due to the use of the sans-serif font Arial, it was challenging to distinguish between characters, but I intended to use "I," the uppercase letter "i."

Also, we revised the section according to your suggestion.

Change in the text 4: Line 353-360

Comment 5: Line 309-310. “we can now delve into a tumor’s genomic landscape, identifying mutations and alterations that might influence the treatment response.”
Are there any reported potential mutations/alterations that can be used for prediction of responses of TETs to different type of treatments? If so, the authors may want to provide a few examples.
Reply 5: Thank you indeed. We updated and added an example using a biomarker in TETs.
Change in the text 5: Line 368-372

Reviewer B

Comment: I only want to comment about the purpose of re-biopsy after neoadjuvant treatment in thymic epithelial tumors (lines 170-171) . Although it has been used to change systemic treatment when there is a tumor regrowth or an ineffective response, re-biopsy to decide surgery after induction therapy has not yet been shown to be effective. Indeed, biopsy-guided pathological response assessment has been explored in breast cancer and melanoma, with promising but not real application in clinical practice. I think this needs to be reflected more clearly in the manuscript.
Reply: Thank you so much for your constructive suggestion.
We revised the manuscript.
Change in the text: Line 194-200

Reviewer C

Comment 1: 53 - authors should stress for which types of thymoma the considerations described in the paper are valid.
Reply 1: Thank you for your constructive advice.
Thymic epithelial tumors (TETs) encompass both thymoma and thymic carcinoma. While recognizing the distinct oncological and clinical behaviors of thymoma and thymic carcinoma, the limited evidence in this field necessitates a discussion of these issues under the broader category of TETs, including both thymoma and thymic carcinoma. Where possible, we have endeavored to discuss them separately, acknowledging the nuances between the two.
Change in the text 1: Line 77-81, 405-412

Comment 2: 124 - The reference to the PET classification of response to induction therapy should be detailed, to the benefit of a better understanding by readers. In fact, not everyone could be familiar with this type of classification.
Reply 2: We appreciate your comment. We agree that the term "SUVindex" might not be familiar to the readers. We revised the section to align with the arguments presented in the cited paper.
Change in the text 2: Line 146

Comment 3: 228 - After induction therapy, when there is indication to radical surgery or debulking, it should be emphasized that the approach can only be the sternotomy or the sterno-thoracotomy. These invasive options have an impact on global survival that needs to be described and if possible, analysed in the light of publications on the subject.
Reply 3: Thank you indeed for your suggestions. We added the section regarding the surgical approach.
Change in the text 3: Line 287-296

Reviewer D

Comment 1: Pg. 3, Line 75: It would be better to use the term 'reference standard' instead of 'gold standard'.
Reply 1: Thank you for your suggestion. We changed the word.
Change in the text 1: Line 88

Comment 2: Pg. 5, Line 107-110: Cite the following reference and briefly mention that for tumor size, in forthcoming 9th edition of the TNM classification of malignant tumors (for thymic epithelial tumor staging) 5-cm is adopted as the threshold for T1 category.
Okumura M, et al. J Thorac Oncol 2023; 18: 1638-54.
Reply 2: Thank you indeed. We added a recent literature assessing the impact of tumor size on survival, and the nineth edition of TNM classification.
Change in the text 2: Line 120-126, Reference 17

Reviewer E

Comment 1: In this manuscript the authors provide a general review on "Re-evaluation and operative indications after induction therapy for thymic epithelial tumors". The subject is timely and clinically interesting. However, this manuscript cannot be

considered to be a systematic review nor even a narrative review, as search methodology and evaluation of the different studies have not been described in detail. How was search strategy performed? How many papers were included and excluded? Level of evidence of those papers is not given and detailed critical analysis has not been performed (generally, the evidence is very low).

Reply 1: We appreciate your thoughtful comments.

Regrettably, direct evidence on this topic is scarce, leading us to compile information from relevant literature to draft this review. Consequently, it may not strictly qualify as a narrative review in the precise sense.

Given the paucity of evidence, discussing how re-evaluation should be conducted post-induction therapy presents challenges. Our review primarily explores current practices through the lens of available literature. It is not aimed at directly answering questions about what should be done based on evidence. However, we believe that by accumulating and discussing current clinical experiences and practices, this review can pave the way for future recommendations on how to proceed in the face of such evidence gaps.

Change in the text 1: Line 46, 400-404

Comment 2: The authorship consists of 3 thoracic surgeons and no thoracic radiologist (mediastinal restaging) or medical oncologist has been included (induction therapy).

No recommendations (with level of evidence) are given for current practice and for this reason this paper is of less interest to the readership of Mediastinum.

Reply 2: We appreciate your advice on the manuscript.

As we mentioned in the text, we consider that a multidisciplinary oncology committee plays an important role in the process of the re-evaluation. This review is part of a series focusing on induction therapy for thymic epithelial tumors, in which colleagues from oncology, radiology, pathology, and surgery at our institution participate. We engage in discussions on each topic. Therefore, we included oncological physicians (HA and YS) and a radiologist (SK) as co-authors.

Change in the text 2: Line 5-7, Line 333-4

Reviewer F

Comment 1: Some more details could be provided especially in the paragraph related to the "tumor markers" (line 134) I would suggest reverting the order of the paragraph and rephrasing the Line 149-150, as the lack of evidence in terms of validated biomarkers is an issue for their use in cases of TETs, putting this sentence at the beginning of the

paragraph (e.g. Line 135).
Reply 1: Thank you indeed for your suggestion. We revised the paragraph.
Change in the text 1: Line 156-173

Comment 2: Line 164 to 171, the reference used is interesting. It would be even more interesting to mention data from that study in terms of population/sample size.
Reply 2: Thank you indeed. We added the sample size of the study.
Change in the text 2: Line 189

Comment 3: Line 187 to 193, it could be useful to specify the population characteristics, and what sort of induction therapy had been used before the re-evaluation.
Reply 3: We appreciate your comment. We added the sample size of the study.
Change in the text 3: Line 226-229

Comment 4: An additional discussion point of practical interest is the exact timing for the re-evaluation. Would the authors suggest a specific time window? If yes, on what basis? Should the time window for re-evaluation be the same regardless of the treatment (radiation, chemotherapy, chemoradiation)?
Reply 4: Thank you for pointing out an important issue. We added the section regarding when to assess.
Change in the text 4: Line 204-210

Comment 5: Table 1, The font of some columns does not seem consistent with the rest of the cells.
Reply 5: Thank you for pointing out. I unified the font of the tables.
Change in the text 5: Table 1

Reviewer G

Comment 1: One thing which makes this review difficult to read is that thymoma and thymic carcinoma are discussed together. I request the authors to discuss these 2 neoplasms separately, and if possible, Type B3 thymoma separately.
Furthermore, some figures to make the readers understand essence of this review easily are necessary.
Reply 1: We appreciate your comments. Thymic epithelial tumors (TETs) encompass both thymoma and thymic carcinoma. While recognizing the distinct oncological and

clinical behaviors of thymoma and thymic carcinoma, the limited evidence in this field necessitates a discussion of these issues under the broader category of TETs, including both thymoma and thymic carcinoma. Where possible, we have endeavored to discuss them separately, acknowledging the nuances between the two.
We added Figure 1 to depict the process of the re-evaluation.
Change in the text 1: Line 77-81, 405-412, Figure 1

Comment 2: I do not understand the following phrase in Page 11, Line 263 to 264.
"as an option in cases where radical resection is unachievable post-induction therapy".
Do the authors want to describe "as an option in cases where radical resection is unachievable after post-induction therapy"?
Reply 2: We apologize for the confusion. We revised the section.
Change in the text 2: Line 312-314

Reviewer H
Comment: interesting review.
Reply: Thank you so much.