Peer Review File

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Reviewer A

The authors provide a narrative review on induction therapy for malignant thymic epithelial tumors. The topic is certainly interesting and timely. A comprehensive review of recent literature is provided divided in several subheadings.

Comments:

- the authors should follow specific guidelines for narrative reviews, an example is provided by https://familymedicine.med.wayne.edu/mph/project/green_2006_narrative_literature_reviews.pdf

Reply: Thank you for important indication. We have revised the manuscript to conform to the stipulations regarding the guidelines and have submitted the checklist as an attachment.

- how many papers were found in literature; how many were excluded and why?

Reply: Thank you for important indication. We accepted the papers as listed in Table 1 and made exclusions in accordance with the Criteria.

- for many papers the level of evidence is low to very low; for the readers these levels of evidence should be indicated in the tables

Reply: Thank you for important indication. We have described the level of evidence for the papers listed in Tables.

- at the end there is a good summary but this should be transferred to a general discussion which is currently missing

Reply: Thank you for important indication. Discussion part was changed to Results and Summary part was changed to Discussions and Conclusions.

- the authors often refer to "complete resection"; what is their definition of complete resection (negative margins, encapsulated lymph nodes, no positive N2 nodes, ...?). It is advisable to include a thoracic surgeon as co-author to provide more details on surgical therapy

Reply: Thank you for indication. This paper on “Indication and management of induction therapy” is part of the special series “Locally Advanced Thymic Epithelial Tumors”. The overall series covers a wide range of topics such as gene mutation, tumor pathology, radiological findings, treatment options including postoperative radiotherapy and induction therapy management, perioperative management and postoperative outcomes, long-term outcomes, re-staging and operative indications after induction therapy, and lymph node evaluation.

This paper does not focus on details of surgical therapy, as those aspects are covered in other manuscripts within the series.

- which is the ideal approach after induction therapy: sternotomy, VATS, RATS?

Reply: Thank you for indication. As with the above response, this section describes medical therapy, and subsequent surgical therapy will be described in a separate section.

- when do the authors advise a preoperative surgical biopsy?

Reply: Thank you for indication. As with the above response, this section is the medical treatment part of the series and does not deal with the pros and cons of preoperative surgical biopsy.

In addition, preoperative surgical biopsy may be considered when the tumor is considered unresectable, when preoperative treatment is planned even if resection is the final goal, and when the possibility of malignant lymphoma cannot be ruled out based on imaging findings and clinical information. However, percutaneous needle biopsy has been reported to have a certain diagnostic yield, and it is generally recommended that preoperative "surgical" biopsy not be performed if resectable.

- in most studies there is a clear selection bias with a so-called shrinking denominator ; this should be mentioned in the discussion
Reply: Thank you for your important remarks. Thymic tumors are difficult to exclude selection bias, due to their small population size. I mentioned it in the discussion.

- lines 217-224: the data in the manuscript don't seem to correspond with the data in table 3, please check carefully
Reply: Thank you for indication. Main text and figure were corrected.

- page 10 induction immunotherapy: there is certainly a concern of induction immunotherapy in patients presenting with myasthenia gravis; this should be clearly mentioned (also in the discussion)
Reply: Thank you for your indication. In addition to the text, the toxicity of immunotherapy is described in the Discussion.

- tables 1, 3-5: it would be more logical to first mention author + year, then reference followed by regimen in separate columns; also indicate levels of evidence
Reply: Thank you for indication. All tables have been revised; study forms have also been included.

- what does abbreviation PII mean?
Reply: Thank you for indication. PII referred to the Phase 2 study, but when listed as an abbreviation, the official name should have been listed. The abbreviation PII has been deleted.

- table 2: mention reference in a separate column
Reply: Thank you for your suggestion. We have created a separate column for Tables and References from the main text.

Reviewer B
I carefully read and appreciated your paper entitled "Indication and management of induction therapy for malignant epithelial tumors".
Here are my comments:
1) In the title is missing the word "thymic" before "malignant epithelial tumors".
Reply: Thank you for indication. We have corrected the description.

2) The title should contain information about the type of the article (narrative review/systematic review).
Reply: Thank you for indication. We have added Narrative review in the title.

3) Methods section in Abstracts is missing.
3) In the Abstract, the "Methods" section is missing.
Reply: Thank you for indication. The Method section of the abstract has been added.

4) Page 3, line 76: the 5-y survival rates reported by Masaoka in the cited article are 100%, 98% and 85% for stages I, II and III thymoma, respectively.
Reply: Thank you for indication. We have corrected the manuscript.

5) Page 3, lines 81-82: since TETs has already been defined in the text, it is not

necessary to rewrite "tumors of thymic epithelial origin".
Reply: Thank you for indication. We have corrected the manuscript.

6) Methods: why did you search only PubMed and no other scientific search engines such as Embase, Web of Science etc.?
Reply: Thank you for indication. At the time of writing the paper, after searching with the scientific search engines listed, we thought the Pubmed search covered the major papers. As you indicated, we thought it necessary to cover the contents of the searches in other engines, so we have listed them after the searches.

7) The Methods section should be enriched with details on the exclusion criteria.
Reply: Thank you for indication. Table 1 has been renewed, detailing the exclusion criteria.

8) The "Discussion" section should be renamed "Results" and the "Summary" should be renamed "Discussions and conclusions".
Reply: Thank you for indication. We renamed "Discussion" section to "Results" and "Summary" section to "Discussions and conclusions".

9) Since postoperative radiotherapy is a very common treatment after stage >II thymomas resection, the risks of a postoperative re-irradiation should be mentioned when debating on neoadjuvant radiotherapy.
Reply: Thank you for your indication. We considered this an important point and mentioned it in line 190-192, 209-210.

10) Page 8, lines 220-221: please verify if the number of patients in the chemotherapy group of the cited study is correct, since you wrote 12 patients and then described the group as follows: 5 thymomas, 3 TC and 2 unclassified tumors (5+2+3=10, not 12).
Reply: Thank you for your indication. There were four unclassifiable tumor (5+3+4=12). The text has been corrected.

11) Page 8, lines 228-234: please check the cited article to ensure if the reported data are correct, since there is some inconsistency. Actually, if all the patients were affected by unresectable thymoma and 6 patients did not show any response after induction therapy, how could it be possible that 8 patients underwent R0 resection? I expected that those six patients would have at least undergone R+ resection/debulking.
Reply: Thank you for your indication.
I have checked the original paper again. In the paper, the clinical stage, pathological stage, and presence or absence of PET-CT in all cases are listed as Figures. Indeed, 60% of the cases were judged to be stable disease, which means that no partial response consistent with RECIST was achieved in the CT measurements. However, in cases of SD, those with a trend toward reduction from the original tumor size or with decreased or absent accumulation on PET-CT led to complete resection, and the authors note that there were no incomplete resections or debulking among the 8 cases. On the other hand, the authors note in the text that the definition of "unresectable" is somewhat ambiguous. For those cases that were considered unresectable clinical stage 3, the authors stated that the diagnosis was CT findings suggestive of extensive invasion, a large tumor with indistinct borders or macrovascular invasion, and a thymoma or suspected thymic carcinoma on initial biopsy.

12) Page 8-9, lines 236-242: the study by Korst et al. has been already described (lines 207-217).
Reply: Thank you for your indication. We have removed the relevant section.

13) Page 10, lines 271-271: please report on what kind of sample the PD-L1 expression is measured in TET patients and in the control group. Since the control group is not affected by TET, I guess that the sample cannot be represented by the tumor cells.
Reply: Thank you for your indication. In the paper, thymic tumors and thymic tissue

(non-tumor) were microarrayed, stained for PDL1, and scored by epithelial cell staining. We added this point to the manuscript, line 280-286.

14) Although the English language command is good, I suggest a native speaker revision of the text.
Reply: Thank you for your indication. This revised text was submitted to English proofreading and corrected by a native speaker.