Peer Review File

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Reviewer A

Comment 1: Please check for spelling/grammatical errors in the text. Consider getting the paper checked by a native English speaker for better vocabulary and better structured sentences.

Reply 1: Thank you for your comment. We already had a native English speaker proofread. However, we ask them to further check our manuscript again.

Comment 2: In the title, “thymic tumor” should be revised “thymic epithelial tumor”.

Reply 2: Thank you for your comment. The title was revised as follows.

Changes in the text 2: “Surgical outcomes of patients with locally advanced thymic epithelial tumor undergoing induction therapy followed by surgery: a narrative review”

Comment 3: Thymoma and thymic cancer should not be discussed together, and that the structure should be revised to make it easy to understand by readers.

Reply 3: Thank you for your valuable feedback. In response to the reviewer's comments, we have carefully distinguished between thymoma and thymic cancers throughout the manuscript. Additionally, we have updated the tables related to thymoma and thymic cancers to reflect these distinctions more clearly.

Changes in the text 3:

Table 2

Summary of studies on induction therapy followed by surgery for locally advanced thymomas

Studies	Study period	No. of all patients	Sex (Female)	Age	The rate of InT (%)	Study type	Stage
Leuzzi et al. (2016 Italy)	1990-2010	370	195	54	24.9	Retrospective	III
Yamada et al. (2015 Japan)	1991-2010	310	140	58	13.5	Retrospective	III
Mineo et al. (2010 Italy)	1989 - 2008	33	13	55.5	100	Retrospective	III
Kunitoh et al. (2010 Japan)	1997-2005	23	6	56	100	Prospective (Phase II)	III
Rena et al. (2012 Italy)	1998-2008	18	8	54.5	100	Retrospective	IVa
Yang et al. (2011 Korea)	1994-2009	7	3	49	57	Retrospective	IVa
Nakamura et al. (2019 Japan)	2003-2017	19	8	49	100	Retrospective	IV
Huang et al. (2007 USA)	1996-2006	18	10	43.5	100	Retrospective	IV
Jalil et al. (2023 Jordan)	2015-2021	23	5	46.3	52	Retrospective	III 12 IV 5
Yokoi et al. (2007 Japan)	1998-2003	17	8	50.6	82	Retrospective	III 4 IVa 9 IVb 4
Lucchi et al. (2006 Italy)	1989-2004	30	17	53.7	100	Retrospective	III 20 IVa 10
Kim et al. (2004 USA)	1990-2000	22	13	47	100	Prospective (Phase II)	III 11 IVa 10 IVb 1
Bretti et al. (2004 Italy)	1989-2000	63	26	51	52	Retrospective	III 43 IVa 20

InT, Induction therapy; Stage, Clinical Masaoka (-Koga) stage.

Table 3

Summary of studies on induction therapy followed by surgery for locally advanced thymic cancers

Studies	Study period	No. of all patients	Sex (Female)	Age	The rate of InT or PrT (%)	Study type	Stage
Shintani et al. (2015 Japan)	1998-2014	16	5	52	100	Retrospective	III 11 IVb 5
Kawasaki et al. (2014 Japan)	2001-2010	7	1	47.3	100	Retrospective	III 5 IV 2
Filosso et al. (2014 Italy)	2000-2011	31 (40*)	15*	54.5*	35	Retrospective	III 24 IVa 7
Okereke et al. (2012 USA)	1990-2011	9 (16*)	7*	52*	56	Retrospective	III 8 IVa 1
Yano et al. (2008 Japan)	1983-2006	28 (30*)	14*	59*	18	Retrospective	III 13 IVa 7 IVb 8
Suzuki et al. (2005 Japan)	1997-2003	11	7	49	36	Retrospective	III 4 IVa 1 IVb 6
Takeda et al. (2004 Japan)	1983-2003	13 (15*)	5*	60.8*	31	Retrospective	III 5 IVa 4 IVb 4

InT, Induction therapy; PrT, Preceding treatment; Stage, Clinical Masaoka (-Koga) stage; *, including stage I or II patients.

Comment 4: It should be included “thymoma”, “thymic cancer”, and “advanced” in the keywords to search.

Reply 4: Thank you for your comment. According to the reviewer’s comment, we added those words to search articles as follows.

Changes in the text 4: **Keywords:** Thymoma; Thymic cancer, Survival, Induction therapy; Surgery, Advanced (P4, L53)

Comment 5: What do the authors compare the data of advanced TET treated with induction therapy followed by surgery with and on what basis do they conclude that induction therapy is promising long-term OS rates?
It merely lists the results of previously published papers, and there are no novel opinions or findings.

Reply 5: Thank you very much for your critical insights. We concur that the current literature does not definitively establish the prognostic benefits of induction therapy for locally advanced thymic epithelial tumors TETs. Notwithstanding, for cases of exclusively invasive thymomas, the reported median rate of complete surgical resection is 76%, and the 5-year OS rate is 85%. These outcomes are notably favorable, considering the advanced stage of these TETs. It is true that the absence of randomized trials on this topic precludes us from asserting significant advantages of this therapeutic approach. Therefore, we aim to suggest that this strategy appears promising rather than conclusively advantageous.

Comment 6: Line 61, “the chance of systemic relapse” should be fixed.

Reply 6: Thank you for the reviewer’s comment. According to this, we revised the resentence as follows.

Changes in the text 6: In advanced cases deemed inoperable during preoperative evaluations, the preference leans toward induction therapy, as it may increase the resection rate and decreases the incidence of systemic relapse. (P5, L63)

Comment 7: Line 70, September 2023. Please describe the exact date. “Ther”?

Reply 7: Thank you for this notice. According to this, we revised it as follows.

Changes in the text 7: The search strategy is summarized in *Table 1*. Briefly, we searched PubMed without date restrictions up to January 31, 2024. We only considered manuscripts written in English. The search strategy included the terms “surgery,” “survival,” “thymoma,” “thymic cancer,” “advance,” “induction therapy.” (P6, L73)

Comment 8: Line 83, “Main body”?

Reply 8: Thank you for your comment. According to this, we revised it as

follows.

Changes in the text 8: Literature review method (P8 L87)

Comment 9: Line 221-222, “overall OS”?

Reply 9: Thank you for your comment. According to this, we revised the point.

Comment 10: Line 229, “between studies”?

Reply 10: Thank you again, we revised the point too.

Comment 11: Line 247, “in sampler sample sizes”?

Reply 11: Thank you again, we revised the point too.

Reviewer B

Comment 1: - Thymoma and thymic carcinoma are two different diseases and should be divided in the results analysis as well as in the tables.

Reply 1: Thank you for your valuable feedback. In response to the reviewer's comments, we have carefully distinguished between thymoma and thymic cancers throughout the manuscript. Additionally, we have updated the tables related to thymoma and thymic cancers to reflect these distinctions more clearly.

Changes in the text 1:

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InT, Induction therapy; Stage, Clinical Masaoka (-Koga) stage.

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InT, Induction therapy; PrT, Preceding treatment; Stage, Clinical Masaoka (-Koga) stage; *, including stage I or II patients.

Comment 2: Radicality and tumor invasion should be better defined, stage III thymoma could be easily resected in case of phrenic nerve infiltration (see PMID: 30336118) or lung invasion compared to great vessels infiltration. This aspect should be reported in the analysis (pre and post treatment) if available. Moreover, a sub analysis of R+ surgery could be interesting to evaluate the role of the adjuvant treatment.

Reply 2: Thank you for your insightful comment. In response, we have included additional commentary on the phrenic nerve-sparing technique. Conversely, literature exploring the relationship between the extent of resection and the role of adjuvant therapy remains limited. Notably, a study by Yokoi et al., which discusses thymoma, has been pertinent to our discussion. We have accordingly incorporated this reference into our manuscript as follows.

Changes in the text 2: The phrenic nerve is an organ commonly invaded by

locally advanced TETs. However, Aprile has reported techniques for sparing the phrenic nerve in the context of locally advanced TETs. These techniques can be applied even in cases undergoing induction therapy, particularly for patients with severe comorbidities or poor performance status. (P12, L193)

Yokoi et al. found that out of 14 patients who received induction chemotherapy (cisplatin, doxorubicin, and prednisolone), 9 proceeded to surgical resection. Of these, only 2 achieved R0 resection, while the others had incomplete resections. PORT was administered to 8 patients, including 7 with incomplete resections. Notably, 2 of these patients with incomplete resections achieved long-term survival, lasting 72 and 180 months post-surgery. (P14, L233)

Comment 3: - Masaoka stage IV is a large and heterogeneous group of TET, authors should make an effort to get data on the T stage (tumor extension) even in case of stage IV because small tumor with few droplet metastases are different by invasive thymoma with diffuse and unresectable carcinosis.

Reply 3: Thank you for your comment. We acknowledge the importance of distinguishing stage IV tumors based on tumor status, including organ invasion and dissemination. However, the majority of the published studies have combined these two statuses, making it challenging to differentiate between them at this time. This limitation was also noted in previous systematic reviews, which were unable to separate these two aspects. Given this, we plan to address this distinction in a future review study, focusing more closely on each specific status.

Changes in the text 3: Stage IV diseases could not be classified based on disease status, such as local invasion or dissemination, due to a lack of information in some studies. (P8, L109)

Finally, the inability to distinguish between stage IV tumors that are locally invaded and those with pleural nodules, due to the limited information available even after reviewing a large corpus of literature, remains a

significant constraint. It is our hope that future reviews will differentiate these two statuses, thereby shedding light on the clinical significance of induction treatment for locally advanced TETs. (P18, L290)

Comment 4: - More data on the surgical treatment with eventual prosthetic reconstruction or eventual HITHOC (see PMID: 32170942) should be reported.

Reply 4: Thank you very much for your valuable suggestion. However, our narrative review is specifically centered on the role of induction treatment strategies for locally advanced TETs. The study recommended by the reviewer primarily encompasses recurrent thymoma, which, while insightful, falls outside the scope of our current review. We will certainly consider referencing this study in future work where it may be more directly relevant.

Comment 5: - Tables should be divided according to the pathology (thymoma or thymic carcinoma) as well as Stage III and Stage IV.

Reply 5: Thank you for the comment. We agree it is better to understand for readers by dividing the two diseases. According to the comment, we revised tables as follows.

Changes in the text 5:

Table 2

Summary of studies on induction therapy followed by surgery for locally advanced thymomas

Studies	Study period	No. of all patients	Sex (Female)	Age	The rate of InT (%)	Study type	Stage
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InT, Induction therapy; Stage, Clinical Masaoka (-Koga) stage.

Comment 6: - In the Induction therapy section, there is an unclear repeated sentence (line 136).

Reply 6: Thank you for this comment. According to this, we delated the sentence.

Comment 7: - Reported studies of the same authors or the same groups could include the same patients two times. This Bias could affect result and the discussion.

Reply 7: Thank you for your comment. According to this, studies written by the same authors were omitted.

Reviewer C

Comment 1: The title should be changed from “thymic tumor” to “thymic epithelial tumor”, because germ cell tumor, not included in this study”, is also originated from thymus.

Reply 1: Thank you for your comment. The title was revised as follows.

Changes in the text 1: “Surgical outcomes of patients with locally advanced thymic epithelial tumor undergoing induction therapy followed by surgery: a narrative review”

Comment 2: The last paragraph for limitation should be included the feasible outcome after surgery could be caused by the patient selection bias among stage III-IV advanced diseases.

Reply 2: Thank you for this comment. According to this, we added the following sentence.

Changes in the text 2: This narrative review faces multiple limitations. The inherent rarity of TETs leads to small sample sizes in the reviewed studies, which, along with the extensive time span these studies cover, contributes to the heterogeneity of their populations. Additionally, the positive outcomes observed post-surgery in patients with stage III-IV advanced diseases may be influenced by selection bias. (P17, L284)