

Peer Review File

Article information: <https://dx.doi.org/10.21037/jovs-21-59>

Reviewer A

Comment 1:

Can you explain and conclude the subsequent management of adjuvant therapy after tumor reduction surgery?

Reply 1:

We sincerely appreciate this important question. As the reviewer pointed out, the benefits of adjuvant chemotherapy following macroscopical complete resection for patients with advanced thymoma are unclear. In the present case series, adjuvant chemotherapy was given to a single patient after undergoing a pleurectomy for massive pleural disseminations, as no evidence showing that adjuvant chemotherapy can improve survival in such cases has been presented. Related sentences have been added to the Discussion section, as shown following.

Changes in the text:

In general, adjuvant RT or chemoradiotherapy should be considered for Masaoka stage III or above, though there is no evidence that adjuvant chemotherapy improves survival in completely resected stage III and IV thymoma cases (15). In the present series, adjuvant chemotherapy was given to a single patient following a pleurectomy for massive pleural disseminations, after which re-growth of pleural disseminations was noted and then continuous systemic chemotherapy was given (Case 1). None of the other patients received adjuvant therapy other than PORT, as no evidence of a beneficial effect of adjuvant chemotherapy on survival has been presented. (Page 14, lines 257-265)

Comment 2:

What is the surgical plan for these huge tumors in general?

Reply 2:

At our hospital, the treatment strategy for advanced thymoma patients is discussed with our multidisciplinary team. We generally perform chemotherapy as neoadjuvant therapy,

expecting that to downsize the tumor and reduce the area invading adjacent organs. Thereafter, when reduction surgery seems to be tolerable, surgery is planned so as to minimize the area of postoperative radiation therapy (PORT) and cause less damage to adjacent tissues during that therapy. We have added sentences in this regard to the Methods section in the revised version, as shown following.

Changes in the text:

When invasion of adjacent great vessels or the heart was obvious, and dissemination lesions were considered to be controllable by a pleurectomy procedure after chemotherapy, tumor reduction surgery including resection of the primary tumor as well as dissemination lesions as much as possible was planned. Otherwise, additional chemotherapy was considered for disease control. For avoiding injury to vital organs such as the aortic arch and PA trunk during surgery, the intention was to leave the tumor adjacent to them. The surgery for patients with advanced thymoma was performed as a median sternotomy or that with a lateral thoracotomy. (Page 6, lines 115-122)

Tumor reduction surgery minimizes the area of PORT, resulting in less damage to adjacent tissues during that therapy. However, when that surgical procedure seems to be intolerable for a patient due to poor cardiac or respiratory function, or systemic disease, we select conservative treatment such as chemotherapy and/or RT for advanced thymoma patients. (Page 8, lines 155-159)

Comment 3:

Limited cases could not give conclusive results. However, could you supply some cases without surgery for competition? Therefore, we could understand the benefit of debulking surgery.

Reply 3:

We agree with the reviewer and our grateful for this good suggestion. We have added text regarding representative inoperable cases to the Methods section, as shown following.

Changes in the text:

Representative cases are presented in Supplemental Figure 2. For one of those with advanced thymoma, reduction surgery was planned. A thoracotomy was performed, during which innumerable small intrapericardial lesions and pleural dissemination, as

well as the primary tumor were found invading the PA trunk, thus an exploratory thoracotomy was selected because tumor reduction surgery did not affect the range of PORT due to uncontrollable disseminations. Another patient had an advanced thymoma invading the heart after systemic chemotherapy. In this case, the tumor was mainly located in intracardiac space, a life-threatening condition. Respiratory function was too poor for the patient to undergo surgery under a cardiopulmonary bypass and we considered that tumor reduction outside the heart might not have a beneficial effect, thus chemotherapy and immunotherapy were performed. (Page 9, lines 159-169; Supplemental Figure 2)

Supplemental Figure 2 legends

Representative cases that did not undergo reduction surgery.

Case 1. The patient was a 66-year old female shown to have a mediastinal tumor with pericardial effusion. Results of a tumor biopsy and pericardial fenestration performed under thoracoscopic surgery, the diagnosis was Masaoka-stage IVa thymoma type B3. Although we planned to perform reduction surgery to control pericardial effusion, thoracotomy findings showed innumerable small intrapericardial and pleural dissemination, as well as the primary tumor invading the PA trunk, thus an exploratory thoracotomy was selected because tumor reduction surgery did not affect the range of PORT due to uncontrollable disseminations. This patient died of disease four years after surgery, even sequential chemoradiotherapy was given.

Case 2. The patient was a 30-year old female who underwent systemic chemotherapy for Masaoka-stage IVa thymoma type B3. The tumor was mainly located in intracardiac space after chemotherapy, a life-threatening condition. Respiratory function was too poor for the patient to undergo surgery under a cardiopulmonary bypass, and we considered that tumor reduction outside the heart might not have a beneficial effect, thus chemotherapy and immunotherapy were performed. The patient was alive three years after initiation of treatment with progressive disease.

Reviewer B

This case series focused on tumor reduction surgery in advanced thymoma is very interesting. The quality of the provided videos is very good!

Reply:

We are grateful for the kind comments from the reviewer.

Comment 1:

How do you selected the patients? "intended tumor reduction surgery in which a less than 90% resection of the primary tumor was performed followed by RT" was the only inclusion criterion? could you precise better inclusion and exclusion criteria in the methods section?

Reply 1:

At our hospital, the treatment strategy for advanced thymoma patients is discussed with our multidisciplinary team. We generally perform chemotherapy as neoadjuvant therapy, expecting that to downsize the tumor and reduce the area invading adjacent organs. Thereafter, when reduction surgery seems to be intolerable, that is not planned. We have added details regarding the criteria used for considering reduction surgery for advanced thymoma to the revised Methods section, as shown following. Additionally, based on a suggestion from reviewer A, details regarding inoperable cases after chemotherapy are now also included in the Methods section (page 9, lines159-169; also Supplemental Figure 2).

Changes in the text:

Tumor reduction surgery minimizes the area of PORT, resulting in less damage to adjacent tissues during that therapy. However, when that surgical procedure seems to be intolerable for a patient due to poor cardiac or respiratory function, or systemic disease, we select conservative treatment such as chemotherapy and/or RT for advanced thymoma patients. (Page 8, lines 155-159)

Comment 2:

According to the strobe guidelines you should precise in the title.

Reply 2:

The title of the revised manuscript has been changed, as shown following.

Changes in the title:

Role of tumor reduction surgery in multimodality therapy for advanced thymoma – case series

Comment 3:

Line 91: Eastern instead of astern

Line 157: IVa instead of Iva

Reply 3:

We sincerely appreciate the reviewer for pointing these out and have corrected the text.

Reviewer C

Comment 1:

You present a total of n= 6 patients with advanced thymomas who underwent tumor reduction surgery over a period of 14 years and analyzed the results retrospectively. The manuscript is well written and understandable. The problem of these mostly young patients with unresectable thymoma hits us thoracic surgeons again and again and I too believe that these patients should be evaluated for multimodality therapy at an experienced center. In selected cases tumor reduction surgery can be offered and also the literature has already shown some positive data.

In my view, your analysis is more a case series than a retrospective study. The data collection period of 14 years was very long, which seems understandable in such special cases.

Reply 1:

We agree with the reviewer's comments and our grateful for the suggestions. The title of the revised manuscript has been changed, as shown following.

Changes in the title:

Role of tumor reduction surgery in multimodality therapy for advanced thymoma – case series

Comment 2:

Please still specify the stage n. IASLC/ITMIG, there should be differences to the Masaoka-Koga stage.

Reply 2:

Accordingly, we now indicate TNM stage for each of the cases in the revised Results

section, as shown following.

Changes in the text:

Postoperative Masaoka stage was III in one and IV in five patients, while 8th edition TNM stage was IIIB in one and IVa in five patients. (Page 11, lines 210-211; Table 1)

Comment 3:

How do you care for a stage IVa with pleural metastasis? Primarily resection of the mediastinal tumor and secondarily the pleural tumor components via thoracotomy?

Pleurectomy/decortication or extended pleurectomy/decortication?

How often did you use the heart-lung machine?

Reply 3:

For patients with advanced thymoma, we generally perform reduction surgery for the primary tumor as well as disseminated lesions via a pleurectomy using a median sternotomy or that with a lateral thoracotomy (hemi-clamshell approach). Although we often perform resection of pleural disseminations as a secondary surgical procedure in such cases, for all of the present patients, except Case 6, surgery including resection of pleural disseminations was performed. As for the purpose of reduction surgery before subsequent PORT, we attempted to perform resection of both the primary tumor and pleural disseminations at the same time. In Case 6, pleural disseminations in the dorsal thoracic cavity were left so as to avoid excessive surgical stress when reduction surgery was performed under a cardiopulmonary bypass. Changes in the text are noted following.

Changes in the text:

Two patients underwent a gross tumor volume removal of more than 50% and four of less than 50%, while pleural or pericardial disseminations were macroscopically resected using a pleurectomy in all except for Case 6. (Page 11, lines 199-202)

Surgery was performed under a cardiopulmonary bypass only for Case 6, with pleural disseminations in the dorsal thoracic cavity left to avoid excessive surgical stress. (Page 11, lines 206-208)

Comment 3:

Please clarify your criteria for surgery for these primarily unresectable tumors. When

did you decide not to proceed with surgery?

Reply 3:

At our hospital, the treatment strategy for advanced thymoma patients is discussed with our multidisciplinary team. We generally perform chemotherapy as neoadjuvant therapy expecting that to downsize the tumor and reduce the area invading adjacent organs. However, when reduction surgery seems to be intolerable, that is not planned. We have added details regarding the criteria used for considering reduction surgery for advanced thymoma to the revised Methods section, as shown following. Additionally, based on a suggestion from reviewer A, details regarding inoperable cases after chemotherapy are now also included in the Methods section (page 9, lines 159-169, also Supplemental Figure 2)

Changes in the text:

Tumor reduction surgery minimizes the area of PORT, resulting in less damage to adjacent tissues during that therapy. However, when that surgical procedure seems to be intolerable for a patient due to poor cardiac or respiratory function, or systemic disease, we select conservative treatment such as chemotherapy and/or RT for advanced thymoma patients. (Page 8, lines 155-159)