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

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Background: Optimal treatment for advanced thymoma remains controversial. This study aimed to elucidate the effectiveness of intended tumor reduction in multimodality therapy for patients with an unresectable thymoma.

Methods: Between 2007 and 2018, six patients with an unresectable Masaoka stage III or IV thymoma underwent surgical resection using multimodality therapy. These cases were retrospectively reviewed. Tumor resection rate was calculated based on pre- and post-surgery computed tomography (CT) findings using a modified commercially available software package to determine resection-targeted tumor volume change.

Results: The study population included four men and two women, with a mean age of 49 (range, 38–68) years. Preoperative Masaoka stage was III in one and IVa in five, while the histological type was B2 in four and B3 in two patients. Preoperative chemotherapy was performed for all except Case 5 because of encephalitis of unknown origin. All were treated with radiotherapy (RT) at a dose of 50–60 Gy. Each showed a grossly reduced tumor, with reduction ranging from 29–89% in the portion located adjacent to the aorta in four, arch vessels in one, and PA trunk in one. Postoperative Masaoka stage was III in one and IVa in five. One patient died from another disease 11 months after the operation, while the others remained alive at the time of writing with controlled disease after RT for a mean 89 (range, 27–149) months, with tumor reduction rates from 69–98%.

Conclusions: Tumor reduction surgery as part of multimodality therapy for advanced thymoma may be effective in selected patients.

Keywords: Thymoma; reduction surgery; multimodality therapy; chemotherapy; radiotherapy (RT)

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Introduction

In patients with a thymoma, complete surgical resection is the main determinant of outcome and postoperative survival. However, for those in an advanced stage, complete resection is not possible without causing damage to a main organ (1), thus no optimal treatment method has been established for thymoma patients with tumor invasion to vital organs like the aorta and heart. Surgical resection

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that includes a mediastinal great vessel structure, such as the aorta or main pulmonary artery (PA) trunk, in cases of thymic malignancy is challenging, because extracorporeal circulation is generally required (2,3). Furthermore, these patients often have pleural dissemination, thus a pathological complete resection for an advanced thymoma is not possible for those cases.

When considering the potential for a more favorable outcome for treatment of a thymoma as compared to thymic cancer patients, surgical debulking of a disseminated tumor as well as the primary tumor is thought to be acceptable for an invasive thymoma (4). Debulking surgery minimizes tumor size and the area for postoperative radiotherapy (PORT), resulting in less damage to adjacent tissues during PORT, thus it may be applicable for patients with advanced-stage thymoma in whom extensive radiotherapy (RT) will be required (5).

Although debulking surgery has been defined as a maximally tolerable resection or at least 90% resection of the main lesion (6), we have rarely experienced cases in which a less than 90% resection of the tumor is performed, termed "tumor reduction surgery". For the present study, tumor reduction surgery was defined as removal of as much of the tumor as possible in cases of unresectable advanced thymoma. To elucidate the effectiveness of reduction surgery for unresectable thymoma, we retrospectively analyzed our previous cases. We present the following article in accordance with the STROBE reporting checklist (available at https://jovs.amegroups.com/article/view/10.21037/jovs-21-59/rc).

Methods

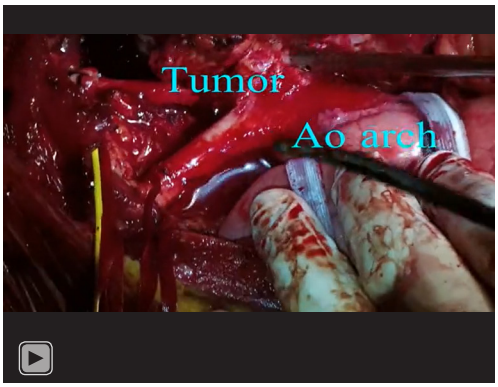
Patients

Between 2005 and 2018, 51 patients with a Masaoka stage III or IV thymoma underwent surgical resection at Osaka University Hospital. Of those, intended tumor reduction surgery in which a less than 90% resection of the primary tumor was performed followed by RT was performed in six and those cases were retrospectively reviewed. Disease stage was determined according to the Masaoka staging system for thymic epithelial tumors and tumor-node-metastasis (TNM) classification (7,8). Pathological diagnosis was determined according to the World Health Organization (WHO) classification (9). This study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and approved by the Institutional Review Board of Osaka University (Approval No. 18518). Need for individual consent was waived, as this was a retrospective analysis and data were accessed after masking patients' identity.

Treatment

All patients were preoperatively diagnosed with an invasive thymoma with or without pleural dissemination, and their treatment strategy was discussed by our multidisciplinary team. At our hospital, the following criteria are used for indicating preoperative chemotherapy: (I) detection of great vessel and/or adjacent organ invasion, or encirclement based on radiological examination findings and/or detection of a large amount of dissemination in preoperative radiological examinations; (II) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and (III) in patients with autoimmune disease, stable disease (SD) and chemotherapy considered to be tolerable (10). 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 (11,12).

A representative tumor reduction surgery procedure in one of the patients is presented in *Video 1*. A 50-year-old male underwent surgery for stage IVa thymoma following systemic chemotherapy. Preoperative computed tomography (CT) findings revealed that the tumor was located in the mediastinum surrounding the aortic arch as well as hilum of the left lung, thus it was resected along with the pericardium and left upper lobe (*Figure 1*). A median sternotomy and lateral thoracotomy were performed. Although the tumor was resected along with the pericardium and left upper lobe, a portion remained on the wall of the aortic arch. Because of invasion of the aortic arch, as well as root of the left common carotid artery and subclavian artery, the residual tumor was removed as much as possible. Clips were placed at the site of the residual tumor at the end of the reduction surgery procedure (*Video 1*). In another case, tumor reduction surgery was performed under a



Video 1 Case 4 intraoperative findings. A median sternotomy and lateral thoracotomy were performed. Although the tumor was resected along with the pericardium, left upper lobe, and left phrenic nerve, some remained on the wall of the aortic arch. Because of invasion of the aortic arch, and root of the left common carotid artery and subclavian artery, the residual tumor was removed as much as possible. Clips were placed at the site of the residual tumor at the end of the reduction surgery procedure.

cardiopulmonary bypass for acquisition of a surgical view in the pericardium. The patient was a 38-year-old male who showed extensive tumor development in the pericardium after undergoing systemic chemotherapy, which indicated the presence of cardiac compression and risk of mortality (*Figure 2*). A median sternotomy and lateral thoracotomy were performed. After opening the pericardium, massive bloody pericardial effusion was aspirated, the tumor was detached from the superior vena cava (SVC), and the left brachiocephalic vein was dissected. The upper lobe of the left lung had been invaded, thus a partial resection was performed, with the tumor detached along the ascending aorta and divided halfway through. Continuity of tumor invasion from the PA trunk to aorta dorsal side was noted, and surgery was continued under a cardiopulmonary bypass to maintain the visual field and for patient safety. The remaining tumor was then resected in pieces along the PA trunk. Invasion of the left coronary artery and left atrium was noted, with no resection performed there (*Video 2*).

In each of the present cases, reduction surgical surgery was performed without aortic replacement, PA trunk replacement, or heart resection, thus the residual tumor remained adjacent to vital organs following surgery. At the end of the procedure, clips were placed at the site of the residual tumor to facilitate identification of the target volume for PORT given for the residual tumor within 3 months.

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. Representative cases are presented in Figure S1. 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.

Follow-up

Follow-up assessments were conducted every 3 to 6 months after treatment for the first year, and every 6 months thereafter, with physical examination and chest CT results used. SD was defined as disease controlled and no evidence of enlargement of the residual tumor. Survival time was calculated from the date of surgery to date of death or final follow-up examination.

Tumor reduction rate

Tumor resection rate was calculated based on CT findings, and resection-targeted tumor volume change was compared between pre- (after induction chemotherapy) and post-surgery measurements. Volumetric measurements were semi-automatically obtained using a modified commercially available software package (LISIT, Co., Ltd., Tokyo, Japan) by one of the authors (YM) who was not informed regarding the clinical characteristics of the patients, as described previously in another study presented by our institution (13). Briefly, after a rough tracing of the tumor shown in a single CT slice with the computer cursor, tumor

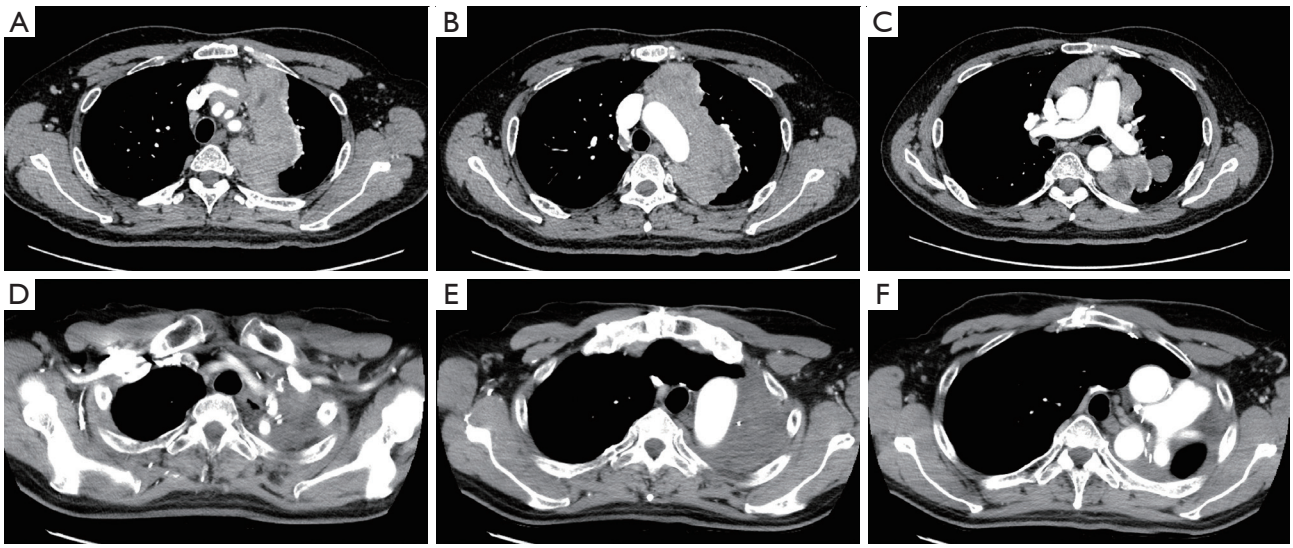


Figure 1 Chest CT imaging in Case 4. (A-C) Preoperative chest CT revealed an anterior mediastinal tumor surrounding the aortic arch as well as hilum of the left lung. (D-F) Chest CT after reduction surgery showed the tumor remaining on the wall of the aortic arch along with clips placed at the site of the residual tumor. CT, computed tomography.

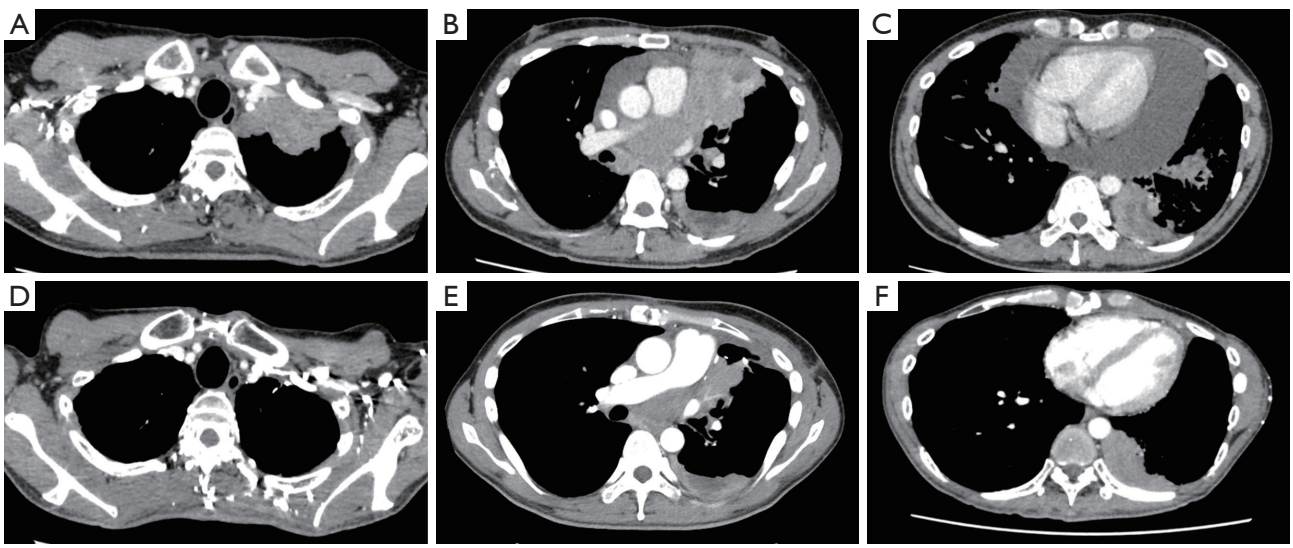
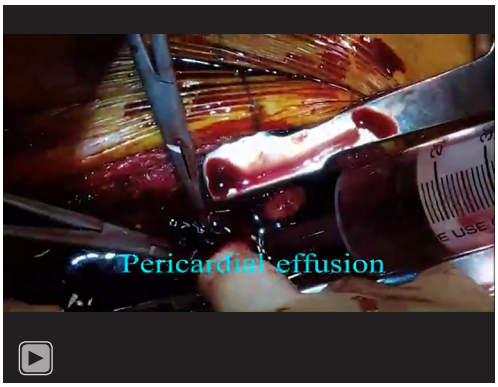


Figure 2 Chest CT imaging in Case 6. (A-C) Preoperative chest CT revealed an anterior mediastinal tumor invading intrapericardial space. (D-F) Chest CT after reduction surgery showed that the volume of the intrapericardial tumor was reduced as well as diminished pericardial effusion. CT, computed tomography.

volume was calculated automatically (*Figure 3*). Tumor reduction rate was then determined using the following formula: (preoperative tumor volume – tumor volume after surgery)/preoperative tumor volume × 100. In patients with stage IVa thymoma, the disseminated lesions were resected as much as possible with a partial pleurectomy procedure.

Results

Patient characteristics are presented in *Table 1*. The study



Video 2 Case 6 intraoperative findings. A median sternotomy and lateral thoracotomy were performed. After opening the pericardium, massive bloody pericardial effusion was aspirated, the tumor was detached from the superior vena cava (SVC), and the left brachiocephalic vein was dissected. The upper lobe of the left lung was invaded by the tumor, thus partial resection was performed. The tumor was detached along the ascending aorta and divided halfway through. Continuity of tumor invasion from the pulmonary trunk to aorta dorsal side was noted, and surgery was continued under a cardiopulmonary bypass to maintain the visual field and for patient safety. The rest of the tumor was then resected in pieces along the pulmonary trunk. Invasion of the left coronary artery and left atrium was noted, with no resection performed there.

population included four males and two females, with a mean age of 49 (range, 38–68) years. Preoperative Masaoka stage was III in one and IVa in five, while histological type was B2 and B3 in four and two, respectively. Preoperative chemotherapy was performed in all cases except Case 5, because of encephalitis of unknown origin. Using the calculation formula described above in the Methods section, the tumor reduction rates, based on comparisons of just before and after surgery, ranged from 29% to 89%. 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. The grossly reduced tumor was located in the aorta arch in four, arch vessels in one, and PA trunk in one. Postoperatively, two developed respiratory complications. Serial CT findings for all patients obtained in pre- and post-operative examinations, as well as a few years after the operation are shown in Figure S2. 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 (*Video 2*, *Table 1*, Figure S2).

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. All underwent PORT for mediastinal lesions, with a dose to the target of 50 Gy in two and 60 Gy in four. Consolidation chemotherapy with four courses of carboplatin and paclitaxel was given to a single patient after resection of massive pleural disseminations. This patient had re-growth lesions in the pleural cavity, thus received chemotherapy with docetaxel for controlling the disease. None of the other patients received adjuvant therapy other than PORT. One died at 11 months after the operation of respiratory failure due to atypical mycobacterial disease after RT, while the other patients were alive with controlled disease at the time of writing for a mean period of 89 (range, 27–149) months. The most recent CT findings showed tumor reduction rates ranging from 69% to 98%, based on the calculation formula described in the Methods section (Figure S2).

Discussion

Here, results of tumor reduction surgery for patients with unresectable thymoma are presented. When treating a case of unresectable thymoma, it is very important to control the disease by use of multimodality treatment. Based on our experience with the present patients, we propose tumor reduction surgery as a part of multimodality treatment for patients with an unresectable thymoma. Five of the six patients who underwent tumor reduction surgery were alive at the time of writing with a controlled tumor and sufficient tumor reduction rates noted.

While most studies have not found any survival benefit of debulking surgery for patients with advanced thymoma, Hamaji *et al.* reported a meta-analysis of published retrospective cohort studies indicating that debulking surgery for unresectable thymoma may be associated with improved overall survival and recommended that it should be considered for affected patients (4). Another report noted that for cases of unresectable or incomplete resected thymoma, not debulking surgery but definitive RT with a dose greater than 54 Gy may lead to long-term tumor control, though there is still no evidence supporting debulking surgery for treatment of unresectable thymoma (6). Each of the present patients had an extremely advanced thymoma showing extensive invasion to the aorta, PA trunk, and heart, thus complete resection

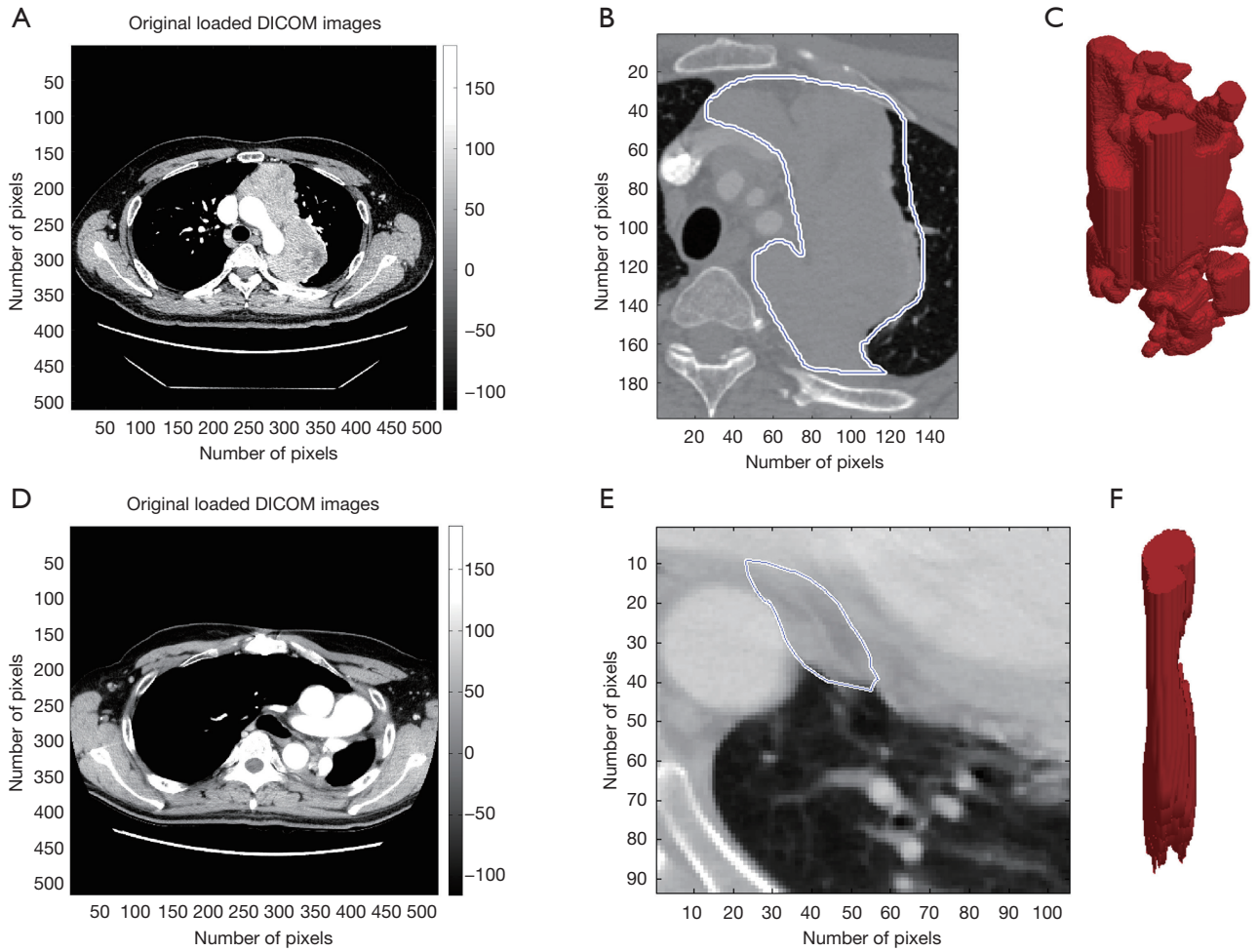


Figure 3 Volume measurement of the tumor using software package. (A,B,D,E) The tumor was roughly outlined on a single CT slice. (C,F) Tumor images were automatically chosen by level based on an image segmentation method. Roughly outlined images of the tumor which includes surrounding tissues are reconstructed three-dimensionally, and CT tumor volumes were calculated. Each measurement was performed semi-automatically using a modified version of the commercially available WatchinGGO software package (LISIT, Co., Ltd., Tokyo, Japan). (A) Preoperative chest CT imaging. (D) Postoperative chest CT imaging. CT, computed tomography.

was impossible based on preoperative workup results. The ability to perform lesion resection is dependent on the positional relationship between the primary tumor and vital organs. However, it is difficult for the attending surgeon to remove most of a tumor that has widely invaded a great vessel or the heart while also avoiding injury to such vital organs. Similar to debulking surgery for thymoma, even if the tumor reduction rate is less than 90% of the whole tumor, the aim of tumor reduction surgery is to minimize tumor size as well as remove dissemination, thus reducing the required amount of RT dosage to lower the amount of damage caused by that to adjacent tissues is necessary. Although a previous study found that survival of patients with advanced thymoma did not seem to be affected by surgery and also noted that the role of surgery as compared with definitive RT remained unclear (14), we consider that reduction surgery is a valuable option for advanced thymoma with disseminations. In such cases, irradiation of the residual mediastinal tumor after resection of disseminations is normally planned. The amount of RT dosage as well as irradiation region can be predicted before treatment, which should be taken into account to decide a treatment strategy. Indeed, three of the present patients with stage IVa thymoma showed SD without re-

Table 1 Patient characteristics and clinical course

Case	Age	Gender	Preope Masaoka stage	Histology (WHO type)	Preope CTx	Courses of CTx	Approach	Ope time (min)	Blood loss (g)	Transfusion (mL)	Residual tumor	Postope complication	Tumor reduction rate	Masaoka stage	TNM stage	Postope RT (Gy)	Postope CTx	Disease control	Tumor reduction rate*	Survival (months)
1	40	F	IVa	B2	ADOC	2	Sternotomy	315	880	0	Ao arch	None	35.1	IVa	T4N0M1a (IVa)	50	TJ	PD**	76.9	81
2	42	F	III	B2	ADOC	4	Neck + sternotomy	450	1,320	1,120	Arch vessels	None	35.5	III	T4N0M0 (IIIB)	50	–	SD	87.2	147
3	68	M	IVa	B3	ADOC	5	Sternotomy	215	275	0	PA trunk	None	40.9	IVa	T4N0M1a (IVa)	60	–	SD	78.9	149
4	50	M	IVa	B2	CDDP + VP16	4	Sternotmy + thoracotomy	567	2,280	1,800	Ao arch	None	89.1	IVa	T4N0M1a (IVa)	60	–	SD	98.4	40
5	53	M	IVa	B2	–	0	Sternotmy + thoracotomy	613	2,870	2,180	Ao arch	Atelectasis	29.1	IVa	T4N0M1a (IVa)	60	–	SD	69.1	27
6	38	M	IVa	B3	ADOC	4	Sternotmy + thoracotomy	368	2,730	1,400	Ao arch	Respitatory failure	52.4	IVa	T4N0M1a (IVa)	60	–	DOO	71.3	11

*, tumor reduction rate was calculated using the latest CT findings; **, the disease was treated with chemotherapy and controlled. Prepe, preoperative, WHO, World Health Organization; CTx, chemotherapy; ADOC, adriamycin + cisplatin + vincristine + cyclophosphamide; CDDP, cisplatin; VP-16, etoposide; ope, operation; RT, radiotherapy; postope, postoperative; Ao, aortic; PA, pulmonary artery; TJ, paclitaxel + carboplatin; TNM, tumor-node-metastasis; PD, progressive disease; SD, stable disease; DOO, died of other disease.

growth of disseminations after undergoing resection. 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.

For patients at our hospital with stage III thymoma who did not agree to undergo surgery, definitive RT is performed when poor performance status is present. We were not able to clarify the clinical outcomes of concurrent sequential chemoradiotherapy or definitive RT for patients with an unresectable thymoma, because they were often treated at other hospitals. However, a previous report of six thymoma patients (one stage 1 or 2, one stage III, three stage IVa, one stage IVb) noted median and progression-free survival after chemoradiotherapy of 64.1 and 38.2 months, respectively (16). It will be necessary to perform a prospective controlled trial of patients with an unresectable thymoma who undergo reduction surgery as part of multimodality treatment to definitively elucidate the results of chemoradiotherapy.

The risks of surgery in patients who receive multimodality treatment must be carefully assessed prior to initiation of treatment. One of the present patients died of respiratory failure within 1 year after treatment. In that case, extensive tumor development was seen in the pericardium, indicating that cardiac compression and mortality were possible, thus we performed tumor reduction surgery in consideration of the young age of the patent as a lifesaving procedure.

Limitations

This study has some limitations, including a sample size too small to fully discuss factors related to prognosis. Additionally, the enrolled patients underwent planned tumor reduction surgery and their clinical records were retrospectively investigated, thus case-selection bias was inevitable. Finally, we were not able to compare the outcomes of patients with tumor reduction surgery followed by RT with those of patients treated with definitive RT without surgery.

Conclusions

For patients with advanced thymoma, multimodality treatment, including chemotherapy, RT, and surgery, is often applied as curative therapy. Tumor reduction surgery as part of multimodality therapy for advanced thymoma may be effective in select cases.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jovs.amegroups.com/article/view/10.21037/jovs-21-59/rc

Data Sharing Statement: Available at https://jovs.amegroups.com/article/view/10.21037/jovs-21-59/dss

Peer Review File: Available at https://jovs.amegroups.com/article/view/10.21037/jovs-21-59/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jovs.amegroups.com/article/view/10.21037/jovs-21-59/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and approved by the Institutional Review Board of Osaka University (Approval No. 18518). Need for individual consent was waived, as this was a retrospective analysis and data were accessed after masking patients' identity.

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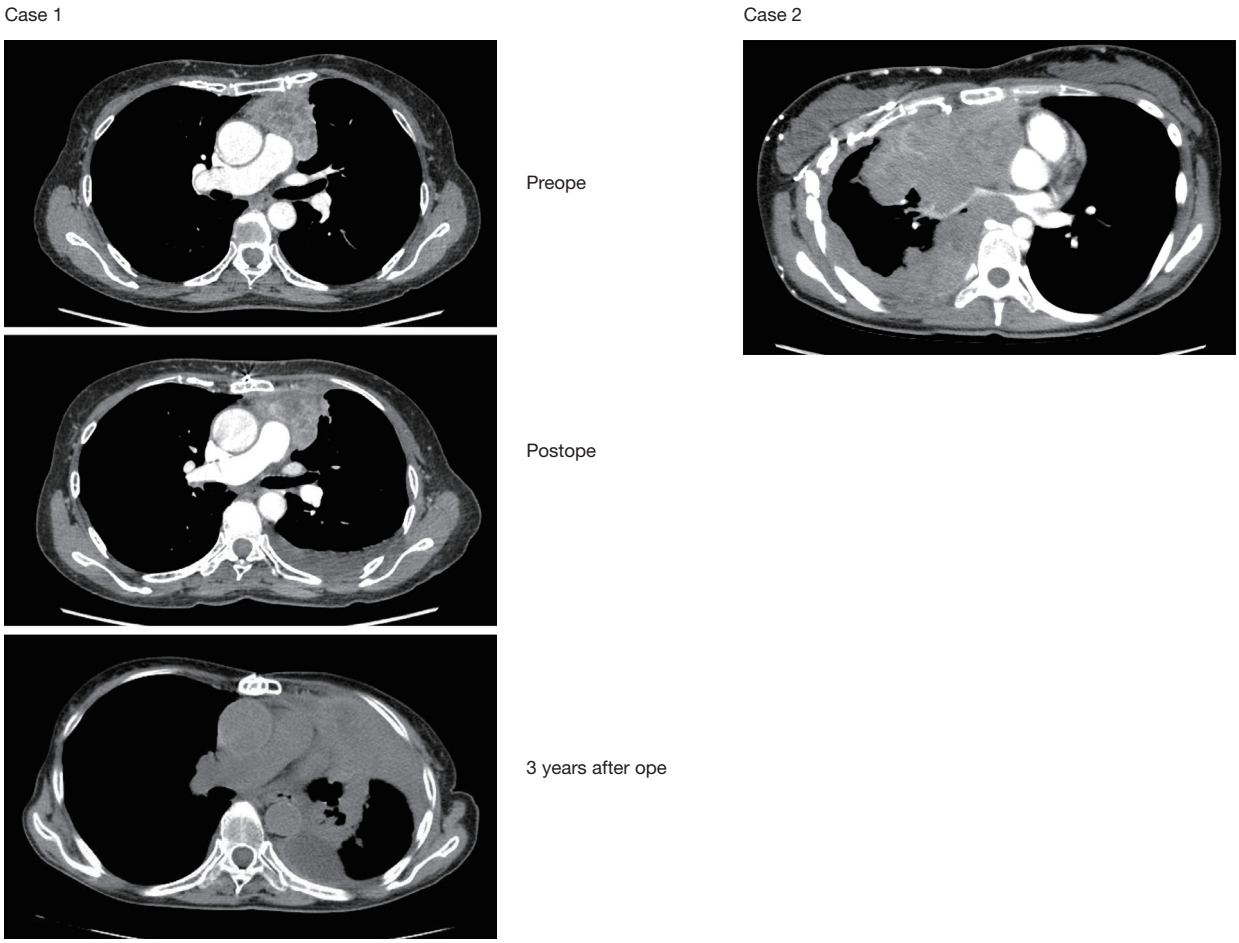

Figure S1 Representative cases that did not undergo reduction surgery. Case 1: the patient was a 66-year-old female shown to have a mediastinal tumor with pericardial effusion. Results of a tumor biopsy and pericardial fenestration performed under thoracoscopic surgery, the diagnosis was Masaoka stage 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 4 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 3 years after initiation of treatment with progressive disease. Prepe, preoperative, postope, postoperative; ope, operation; PA, pulmonary artery; PORT, postoperative radiotherapy.

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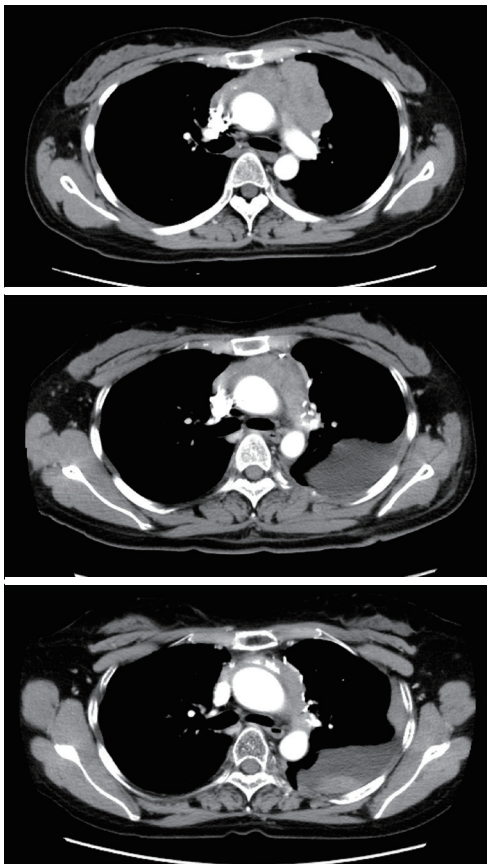
Case 1

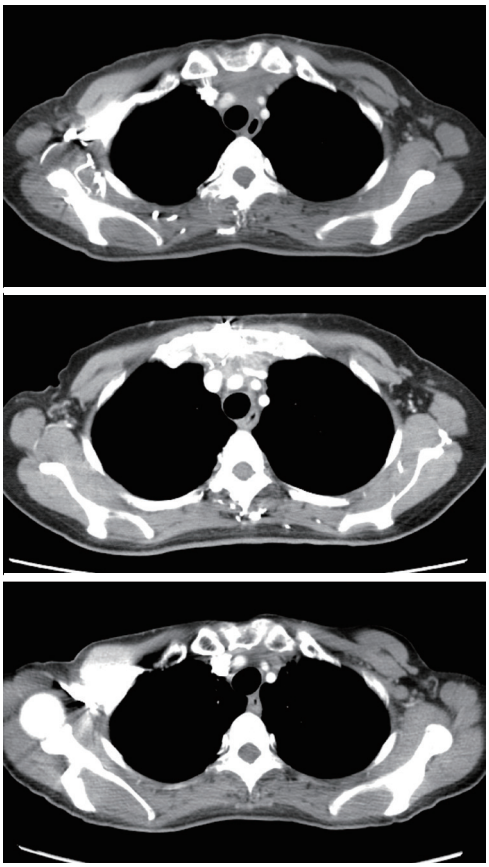


Preope
223994

Postope
145358
35.1%

6 years after ope
51754
76.9%

Case 2

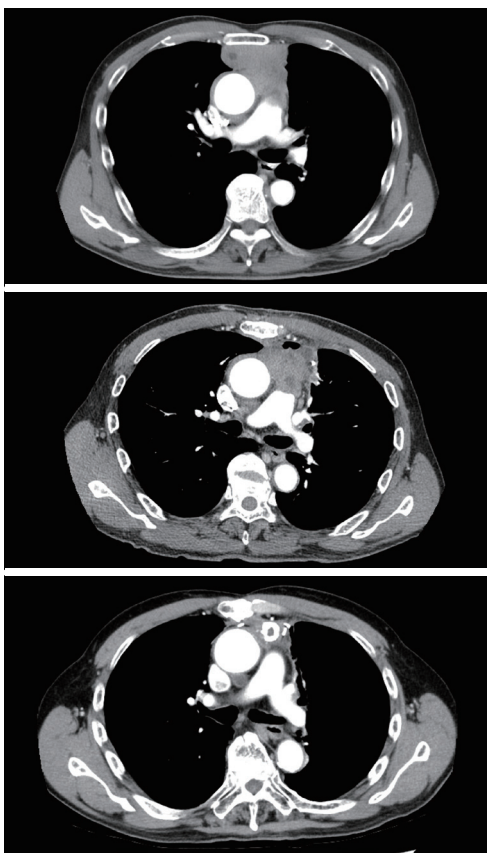


Preope
95997

Postope
61680
35.5%

5 years after ope
12262
87.2%

Case 3

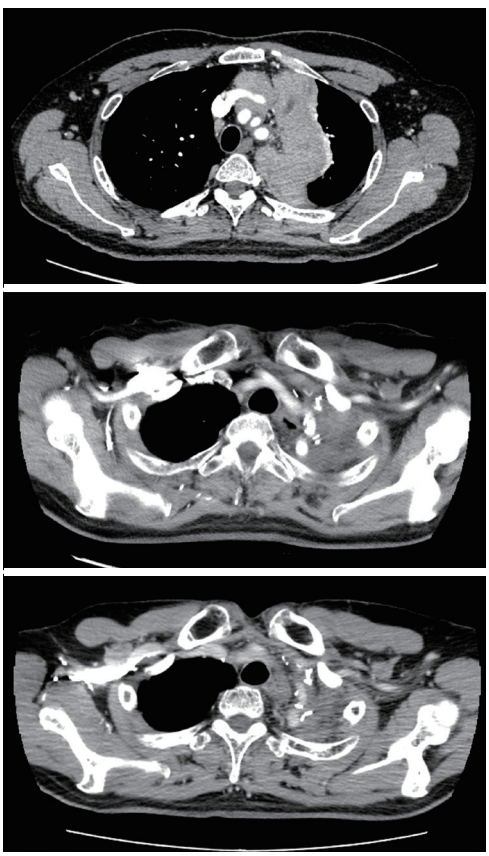


Preope
326013

Postope
192674
40.9%

8 years after ope
68666
78.9%

Case 4



Preope
605993

Postope
65582
89.1%

3 years after ope
9328
98.4%

https://dx.doi.org/10.21037/jovs-21-59

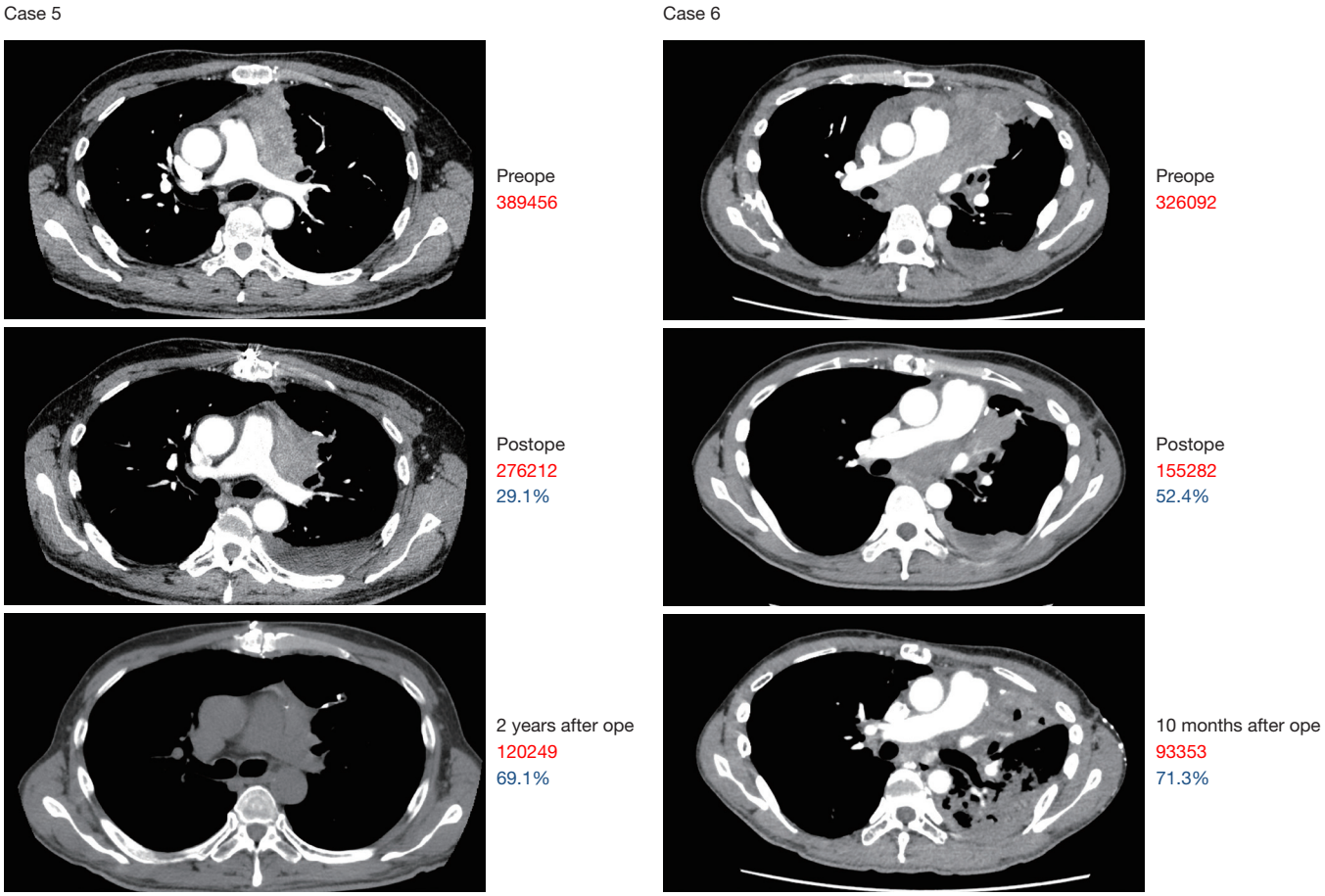


Figure S2 Chest CT imaging changes in all cases. Numbers in red indicate results of volumetric measurements obtained with a specialized software package (LISIT, Co., Ltd., Tokyo, Japan). Numbers in blue indicate tumor reduction rates which were calculated using the following formula: (preoperative tumor volume – tumor volume after surgery)/preoperative tumor volume × 100. Prepe, preoperative, postope, postoperative; ope, operation; CT, computed tomography.

https://dx.doi.org/10.21037/jovs-21-59