Review Article on Thymoma

Surgical treatment strategies for invasive thymoma

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Abstract: A thymoma is a common anterior thymus mediastinal tumor composed of atypical epithelial tumor cells, though the morbidity rate is lower as compared to other types of thoracic malignancy such as lung cancer and lung metastasis from another primary cancer. As a result, clinical data regarding thymomas have not been well discussed as compared to those of other carcinomas. Also, because of the low morbidity rate and insufficient clinical experience, oncological characteristics and clinical treatment options are poorly understood. Surgical complete resection is the most reliable option for clinical treatment of a thymoma. This tumor can easily develop adjacent to several different structures and nearby organs, such as the pericardium, lungs, and great vessels, which are easily invaded when the size is large, and a combined resection is then needed. When *en bloc* resection is considered to be difficult based on evaluation with preoperative modalities, induction chemotherapy followed by surgery is recommended. Moreover, when pleural dissemination is revealed during pre- or peri-operative procedures, volume reduction surgery has been reported by several groups to extend prognosis. On the other hand, in cases with a small-sized tumor, a minimally invasive surgical procedure, such as video-assisted thoracic surgery (VATS) or robotic-assisted thoracic surgery (RATS), is usually selected. Because of the wide variety of cases with thymoma, a deliberate strategy and skillful techniques are necessary for effectual surgical treatment. In this review, we discuss strategies that have been shown to be effective for treating patients with early and advanced thymoma, including those with involved adjacent organs.

Keywords: Surgical approach; advanced thymoma; *en bloc* resection

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Introduction

It is well accepted that the main effective treatment for a thymic epithelial tumor (TET), including thymoma and thymic cancer, is complete resection surgery. Among TETs, a thymoma is most frequent, though still relatively rare as compared to all types of thoracic malignancy including lung cancer, thus no standard therapy has been established. A TET usually develops in the anterior mediastinum in close proximity to several important structures and organs, such as pericardium, great vessels, lungs, and heart, as well as others. When small in size and early Masaoka stage, no invasion of surrounding adjacent organs occurs and tumor resection in such early-stage cases is relatively easily completed. Preoperatively, an appropriate surgical method must be considered, such as a conventional median sternotomy (MS) or minimal invasive approach. In cases with advanced Masaoka stage, or a large sized tumor and aggressive histological types, such as type B2/B3 or thymic cancer, invasion of adjacent organs can easily occur. For

those cases, an *en bloc* resection is generally considered to be difficult and only incomplete resection is sometimes achieved. Surgery alone in affected patients often does not control the disease or improve curability, thus a therapeutic strategy with surgical treatment as well as multimodality therapy (MT) should be planned. Several studies have reported that induction therapy (IT) followed by surgery resulted in improved outcomes (1,2).

For this study, we focused on potential pitfalls when treating these cases and review recently published reports concerning surgical treatment for advanced stage TETs. Our findings show that the most effective surgical strategy will differ depending on what organs have been invaded by the tumor, and we present possible surgical strategies and approaches to be considered, especially for advanced TET cases. Recently, minimally invasive surgery (MIS) procedures including robotic-assisted thoracic surgery (RATS) have become prominent (3). Here, we also introduce an MIS approach for patients with advanced stage TET.

Fundamental surgical treatment principles

Surgical treatment for advanced thymoma cases is generally radical resection of the tumor and involved organs. Imaging to determine whether the tumor has invaded adjacent structures is very important, with enhanced high-resolution computed tomography, magnetic resonance imaging (MRI), and positron emission tomography (PET) examinations performed preoperatively (4). When a combined resection including invaded organs is necessary, a MS is the generally chosen surgical approach. To determine dissemination into the thoracic cavity and evaluate involved organs, thoracoscopy is a useful tool. When tumor invasion includes a wide area of a lung, resection of that organ is required, for which a one-lung ventilation technique should be chosen to provide a wide surgical field for easy surgical manipulation. Mainstem methods used to achieve lung separation include utilization of a double-lumen endotracheal tube or placement of a bronchial blocker through a single-lumen endotracheal tube.

MIS for advanced thymoma

Video-assisted thoracic surgery (VATS) is a minimally invasive technique usually applied to cases with early stage malignancy including TET. However, VATS for an anterior thoracic tumor has disadvantages for advanced cases as compared to a conventional MS, because surgical manipulation for resection and reconstruction is difficult with the mediastinum space is limited. Obtaining a wide surgical space in narrow mediastinum tissue is a significant issue with a VATS approach, though several groups have reported surgical procedures to solve associated problems. Kido *et al.* demonstrated an intrasternal technique termed the subxiphoid approach (5). Sakamaki *et al.* showed the utility of a sternal lifting technique by use of the Laparolift system and reported favorable intermediate-term oncologic outcomes after a VATS thymectomy (VATS-T) for early-stage thymoma in patients who underwent an open thymectomy (6,7). Additionally, Takeo *et al.* and Ohta *et al.* presented a sternum lifting method that utilizes retractors and costal hooks (8-10). Most of those explained sternum lifting techniques, which subsequently have been widely used for extended thymectomy and thymothymectomy procedures via VATS for myasthenia gravis (MG) and early stage thymoma patients who had no invasion to other organs.

More recently, several groups have reported surgical techniques for treating cases of advanced thymoma with VATS. Hirai *et al.* introduced a method that combines video-assisted thoracoscopic thymectomy (VAT-T) with lateral thoracotomy for stage II and some stage III thymomas with local lung and/or pericardium invasion, and Yano *et al.* reported a case in which a thoracoscopic thymectomy with partial resection of the brachiocephalic vein (BCV) was performed by use of a subxiphoid approach (11,12). Quite recently, a retractor with a gas insufflation tube and multiple access ports was developed, and shown able to create a wide surgical view and space, thus providing easier surgical manipulation. In addition, Okuda *et al.* reported a case of thymothymectomy with pulmonary partial resection using VATS for a subxiphoid approach with use of a CO_2 insufflation multiport system (13). However, the feasibility of VATS for an advanced thymoma and resulting clinical outcomes remain unclear. Kimura *et al.* noted that careful attention is required for MIS in cases with a large or cystic thymoma, because of potential risk for intraoperative capsule injury and subsequent pleural dissemination (14).

RATS

Along with progress in imaging quality and medical technology, new systems such as RATS have been developed, with the da Vinci Surgical System® a pioneer in

this field. That system has been shown to provide surgeons with superior visualization, enhanced dexterity, and greater precision, as well as intraoperative patient comfort. Moreover, with it the surgeon is able to perform procedures with lower levels of invasion for complex dissection or reconstruction as compared to traditional VATS. Several reports have also demonstrated cases of early as well as advanced thymoma treatment completed by use of RATS (15-17). On the other hand, the feasibility of RATS for TET along with resulting clinical outcomes remain unclear.

Advanced staging, Masaoka stage III-IV

Principles of treatment for advanced TET

An advanced thymoma is typically Masaoka stage III or IV, with a large size and possible invasion of nearby organs and structures. When an advanced stage TET is suspected in pretreatment imaging findings, such as those obtained by CT, MRI, or PET, the treatment plan should be carefully discussed and decided together with an experienced surgeon. Prior to finalizing the treatment plan, a histopathological examination is needed, for which a CT-guided biopsy is useful and can provide sufficient specimens. Furthermore, the risk of tumor dissemination into the thoracic cavity with a CT-guided biopsy is lower as compared to a biopsy using a VATS approach. When histopathological analysis results reveal thymoma or thymic carcinoma, with great vessel invasion or dissemination to thoracic cavity suspected, and complete resection considered to be difficult, IT followed by surgery should be the strategy used (1,2).

Multimodality treatment

Treatment of a locally invasive thymoma is considered to be difficult, because the high rate of incomplete resection results in a high rate of recurrence. To achieve complete resection of such an advanced thymoma, IT is sometimes performed, including chemotherapy or chemoradiation therapy. A multimodality therapeutic approach such as IT followed by complete resection is considered to improve the outcome of patients with an advanced thymoma (18). In fact, several reports discussing MT for advanced thymoma and thymic carcinoma have been presented, including induction chemotherapy regimens. Yokoi *et al.* reported cisplatin, doxorubicin, and methylprednisolone (CAMP) IT to be effective chemotherapy for advanced thymoma (2), and Korst *et al.* noted that induction chemoradiotherapy is a viable option for patients with a locally advanced thymic tumor and that its use resulted in a high rate of complete surgical resection (19). Use of adjuvant therapy has also been discussed, with Leuzzi *et al.* showing its benefits for locally advanced thymoma (20). On the other hand, postoperative radiation therapy (PORT) is controversial. Omasa found that PORT did not increase recurrence-free or overall survival for stage II or III thymoma cases, though recurrence-free survival was increased in stage II and III thymic carcinoma cases (21), with the same results demonstrated by Utsumi *et al.* (22).

Selection of surgical approach

A MS is the standard surgical approach for locally advanced TET. That procedure provides a wide surgical view with multiple diversity when used with a usual thymothymectomy or extended thymectomy, including combined resection and reconstruction with an involved adjacent organ located near the center of the mediastinum, such as left BCV, pericardium, and deep lymphoid node dissection. Moreover, for partial resection of an involved lung near the anterior hilum, MS also provides a sufficient surgical view. However, when the tumor involves the hilum including a wide area of the lung or pulmonary artery, resection of lung parenchyma greater than a single lobe is needed and the surgical view provided by only MS may sometimes be insufficient. To obtain a wider view during surgery and increase the safety of surgical manipulation, a hemi-clamshell (HCS) incision is useful. Recently, our group reported that an HCS approach was helpful for lung resection and dissemination around the thoracic cavity performed for advanced thymic malignancy with hilar invasion by providing multiple access paths to the tumor and hilum, allowing for a sufficient surgical margin (23).

Combined resection with adjacent involved organs

Phrenic nerve (PN) resection

A locally advanced thymoma (greater than Masaoka stage III) often involves the PN due to a mediastina tumor location. For only tumor curability, an *en bloc* resection with the PN is better than preserving that nerve. However, a combined resection including the PN is controversial in patients with severe MG or extensive comorbidities. Whether a combined resection including the PN should be performed has been discussed. Yano *et al.* reported that PN resection

decreased pulmonary function, though there was no significant difference between cases with and without resection (24). Also, Hamdi *et al.* noted that sparing the PN during thymoma resection achieved good long-term and disease-free survival in high-risk patients as compared with an *en bloc* PN resection, though concluded that it introduced a higher risk of recurrence despite performance of adjuvant radiation therapy (ART) (25). Moreover, Aprile *et al.* recently documented that PN preservation in cases of invasive thymoma is feasible and may result in acceptable local control of disease (26). On the other hand, when a combined resection including the PN is truly necessary or the nerve has received accidental injury resulting in paralysis during the operation, diaphragm plication is recommended. Tokunaga *et al.* reported that diaphragm plication following PN resection can prevent pulmonary dysfunction (27).

Superior vena cava resection and reconstruction

Radical resection of the tumor along with involved neighboring structures is key to prolonging overall survival of patients with an invasive thymoma. Additionally, combined resection and reconstruction of involved mediastinal great vessels is also considered to be feasible though challenging, as shown in retrospective findings (28,29). Most of those studies noted that a combined resection of the superior vena cava (SVC) and BCV is widely performed for cases of invasion by thymoma or thymic carcinoma. When the tumor has invaded a part of the vessel, resection of the invaded wall and direct suturing of the defect may be feasible. However, when a wide area of the vessel shows invasion, vessel replacement is required. There is variety of choices for vessel replacement that includes anastomosis of the SVC and BCV, including SVC-SVC, left BCV-right atrial appendage (RAA), and right/left BCV-RAA. As for the procedure used for reconstruction of those vessels, when a double BCV resection and reconstruction are performed, it is recommended that the graft first be anastomosed between the right appendage and left BCV in order to reduce clamping time. For SVC replacement, a polytetrafluoroethylene (PTFE) Gore-Tex synthetic prosthesis is usually employed, and a recent report noted use of an autologous pericardium conduit in cases of SVC replacement in which graft patency showed a good outcome (28,29).

Aortic arch combined resection and reconstruction

The combination of resection of an invaded artery and graft replacement in association with TET is rarely performed. As for cases of thymoma, a few reports have noted combined resection of the aortic arch, though we do not usually perform combined resection of the artery and reconstruction at our institution (30).

The feasibility as well as clinical outcomes of combined arterial resection in patients with an advanced thymoma remain unclear. We usually perform debulking surgery for volume reduction in thymoma cases (31). In those with a thymic carcinoma that has invaded an artery, especially the aortic arch, we aim to perform an *en bloc* resection of the tumor and invaded aortic arch, along with reconstruction for complete resection (32). In such complicated cases, careful preoperative evaluations should be made in discussions with an experienced board-certificated thoracic surgeon team with extensive experience as well as the cardiovascular surgeon team, with careful planning the goal. Recently, Shintani *et al.* presented a new surgical approach for *en bloc* resection of a tumor invading the aortic arch and replacement using total rerouting of supra-arch vessels, which may be useful for *en bloc* resection in cases with an advanced TET showing invasion of the aortic arch (33).

Surgical resection of recurrent thymoma

When possible, surgical resection is the primary treatment for a thymoma, as it provides the best assurance of good long-term prognosis. However, recurrence following such an operation can occur in 10–30% of treated patients, even years after the initial surgery. The most common is dissemination into the thoracic cavity. Several retrospective studies have found that surgical treatment for a recurrent thymoma may improve clinical outcome (34-39). Of various sites of metastasis reported, including local, distant, and dissemination, the optimal treatment method for a thymoma with pleural dissemination remains challenging. A number of different groups have reported results of surgical treatment for pleural recurrent thymoma. Lucchi *et al.* and Kimura *et al.* noted that surgical resection of a thymoma with pleural dissemination is feasible and safe (36-38). As for surgical procedures employed for pleural dissemination, extrapleural pneumonectomy (EPP), total pleurectomy (TP), and local pleurectomy (LP) have been demonstrated in previous reports (40-44). For an advanced thymoma with multiple dissemination sites throughout the thoracic cavity, as well as cases with severe invasion of the main pulmonary artery or a wide area of lung parenchyma, an EPP can sometimes be adapted, as noted in several retrospective

studies of EPP for advanced thymoma. Some Japanese groups have also reported that use of an EPP as part of MT for selected patients showed potential for improving local control, leading to a cure (40-44). The indications for an EPP should be considered for selected patients whose cardiopulmonary function has been preoperatively evaluated and found to be sufficient for undergoing a pneumonectomy. In addition, an EPP should be performed by a surgical team with ample experience. As part of MT for a thymoma with pleural dissemination, EPP offers good local control and may lead to a cure.

Adjuvant therapy

Disease control for an advanced thymoma by surgery alone is sometimes difficult, thus strategies that include other modalities such as induction and radiation therapy are necessary. However, the effects of adjuvant therapy remain unclear because of the paucity of reports presented thus far. Furthermore, the effects of adjuvant chemotherapy (ACT) and radiation therapy (ART) are controversial, as Utsumi *et al.* reported that ART did not improve outcome and a review by Hamaji *et al.* showed that outcomes were also not improved by ACT (22,45,46).

Concluding remarks

TET occurrence is relatively rare and no standard therapy has been established. For early stage cases, VATS and RATS have become standard approaches. As for advanced stage thymoma, a radical resection is considered to be the primary therapy, though, since surgery alone does not necessarily control disease, a multimodality treatment strategy is often needed. Careful preoperative evaluations and surgical indication decisions should be made in consultations with an established cancer board comprised of doctors from various related departments, while surgical procedures should be performed by an experienced surgeon.

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