Surgical Staging and Advanced Surgical Techniques in Thymic Cancers

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Introduction

Thymoma and thymic carcinoma are the most frequent anterior mediastinal neoplasms that originates from epithelial tissue of the thymic gland. Histologic classification of thymomas has been under debate for many years until the World Health Organization (WHO) published and updated the histologic classification of thymomas in 1999 and 2004, respectively [1, 2]. In updated version, type C thymomas were classified in to separate type of thymic tumors as thymic carcinomas (Table 17.1). The widely used staging system, Masaoka classification published in 1981 and further refined with little modifications as the Masaoka-Koga staging system in 1994 (Table 17.2), was proved to be a significant factor for survival [3, 4].

Surgery in Thymic Malignancies

The treatment of thymic tumors depends on clinical stage; however, it is widely accepted that surgical resection is the mainstay of treatment [5]. Complete surgical resection which is proved to be one of the most important prognostic factors should be the goal even in advanced stage [6]. Patients with clinical stage III thymoma may require extended surgery to achieve complete resection.

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Table 17.1 WHO classification of thymic tumors

Thymoma	Thymic carcinoma	Neuroendocrine tumors
Type A, spindle cell; medullary	Squamous cell, epidermoid keratinizing	Well-differentiated neuroendocrine tumor/ carcinomas, including typical and atypical carcinoids
Type AB, mixed	Epidermoid nonkeratinizing	Poorly differentiated neuroendocrine carcinomas, including large and small cell neuroendocrine carcinoma
Type B1, lymphocyte-rich; lymphocytic; predominantly cortical; organoid	Basaloid	
Type B2 cortical	Lymphoepithelioma-like	
Type B3 epithelial; atypical; squamoid; well-differentiated thymic carcinoma	Mucoepidermoid carcinoma	
Micronodular thymoma	Sarcomatoid	
Metaplastic, sclerosing, microscopic thymoma	Clear cell	
Lipofibroadenoma	Mucoepidermoid	
	Papillary	
	Undifferentiated	
	Combined	

Table 17.2 The Masaoka-Koga staging system

Tumor stage	Description
I	Grossly and microscopically completely encapsulated tumor
II	(a) Microscopic transcapsular invasion
	(b) Macroscopic invasion into the thymic or surrounding fatty tissue or grossly adherent but not breaking through the mediastinal pleura or pericardium
III	Macroscopic invasion of neighboring organs (pericardium, great vessels, or lung)
IV	(a) Pleural or pericardial dissemination
	(b) Lymphatic or hematogenous metastasis

Clinical staging of thymic masses is crucial to determine appropriate treatment. A retrospective study published in 2014 showed that CT imaging had some features that were significantly correlated with the WHO classification, the Masaoka-Koga clinical staging and the completeness of resection; however, authors concluded that CT has no definite role to predict the survival rate of thymoma patients. CT features correlated with the WHO classification were tumor contours, homogeneity, degree of enhancement, fat plane obliteration with adjacent structures, the presence of mediastinal lymphadenopathy, irregular infiltration into the lung, and tumor shape. Lobulated or irregular tumor contours, the presence of calcifications, infiltration of surrounding fat, irregular infiltration into the lung, irregular infiltration into

vasculature, more abutment of vessels, and pulmonary changes adjacent to the tumor were associated with the more advanced Masaoka-Koga clinical stage [7].

Thymic type A tumors are more likely to have round shapes and smooth contours on CT images when comparing with other types of thymic epithelial tumors. Besides, thymic carcinomas had a higher prevalence of irregular contours, and calcification was more frequently seen in type B tumors [8]. To predict incomplete resection in patients with thymic tumors preoperatively by CT images is a key point for surgeons. Hayes et al. in 2014, reported on 133 patients underwent surgical resection for thymoma. In this study, lobulated tumor contour ($p=0.016$), ≥50 % abutment of the circumference of an adjacent vessel ($p<0.001$), thoracic lymphadenopathy ($p=0.029$), adjacent lung changes ($p=0.005$), and pleural nodularity ($p=0.001$) were found to be significantly correlated with incomplete resection [9].

The recommended treatment option is surgery alone for stage I thymic tumors with a nearly 80 % 10-year survival rate [10]. Median sternotomy (MS) is widely used surgical incision that allows a maximal exposure of the anterior mediastinum to radical surgical removal of the thymoma along with the entire thymus and the mediastinal fat; thus, MS is a gold standard for surgical treatment of thymomas [6]. Moreover, minimally invasive techniques including conventional VATS and robotic-assisted thoracic surgery (RATS) become increasingly popular for anterior mediastinal procedures such as thymectomy in patients with myasthenia gravis and mediastinal mass resection. However, minimally approach to thymoma is still controversial. The main concern is the possibility of damage at the tumor capsule which may increase the risk of spreading tumor cells during the minimally invasive procedure. There are several studies about comparison between open and minimally invasive techniques in early stage thymoma (Table 17.3).

Pennathur et al. reported on a retrospective review of 40 patients who underwent surgical resection of early stage thymoma with open or minimally invasive thymectomy. This study showed that no significant differences were found in the estimated recurrence-free and overall 5-year survival rates (83–100 %) between the two groups [14].

More recently, RATS have been a surgery of choice for mediastinal malignancies. A multicenter study, aimed to evaluate the safety and feasibility of robotic thymectomy with analyzing the oncologic outcomes, was published in 2012. A total of 79 patients who underwent RATS for early stage thymoma was analyzed in terms of perioperative data and oncological outcome. One patient (1.3 %) required conversion to an open approach because of a large diameter tumor interfering with a safe dissection. Ten patients (12.7 %) had postoperative complications. Median hospital stay was 3 days (range, 2–15 days). Median diameter of the resected tumors was 3 cm and 5-year thymoma-related survival was 97 %. The authors concluded that RATS for thymoma was a technically sound and safe procedure with acceptable oncologic outcome [15].

A comparison study of 74 patients between RATS and open approach for early stage thymoma, published in 2014, showed that the duration of surgery and the intraoperative blood loss was significantly less (61.3 ± 21.8 vs. 466.1 ± 91.4) and the postoperative hospital stay significantly shorter days in the RATS group than in the open approach group (3.7 ± 1.1 vs. 11.6 ± 10.4 days) ($p<0.01$). Within the

Table 17.3 Comparison studies between VATS and median sternotomy (VATS vs MS)

Author	n	MG (%)	MBL (ml)	LOD (days)	LHS (days)	C (n)	MS I (n)	MS II (n)	R (n)	Median FU (months)	Study design
Chao et al. (2015) [11]	48 vs 48	26 vs 26	40±66 vs 75±96	4.4±1.5 vs 4.9±1.9	5.8±2 vs 7±2.2	2 vs 6	17 vs 17	31 vs 31	2 vs 3	75.5	R
Maniscalco et al. (2015) [12]	13 vs 14	39 vs 36	NA	NA	2.6 vs 5.4	2 vs 3	8 vs 10	5 vs 4	0	123	R
Jurado et al. (2012) [13]	10 vs 62	NA	7.5 vs 200	NA	4 vs 5	NA	4 vs 16	6 vs 41	0	24.2 vs 81	R
Pennathur et al. (2011) [14]	18 vs 22	40 vs 19	NA	NA	3 vs 5	NA	5 vs 9	13 vs 13	NA	27 vs 58	R

MG myasthenia gravis, *MBL* mean blood loss, *LOD* length of drainage, *LHS* length of hospital stay, *C* complication, *MS I* Masaoka stage I, *MS II* Masaoka stage II, *R* recurrence, *FU* follow-up, *R* retrospective

postoperative follow-up period of 16.9 months (range, 1–48 months) in the RATS group and 18.1 months (range, 1–48 months) in the open approach group, no recurrence was observed [16].

RATS seems to be a good alternative for minimally invasive approach in early stage thymoma; however, thymoma requires longer follow-up data, such as more than 5 years, to determine the oncologic outcome of minimally invasive approaches; thus, additional randomized studies with a large number of patients are essential.

In case of clinically locally advance disease at Masaoka stage III, en bloc resection is essential; thus, resectability with tumor-free margins should be evaluated with contrast-enhanced spiral computerized tomography of the chest. If the patients have findings that suggested extensive invasion, large tumors with indistinct borders, or evidence of great vessel invasion, complete resection may not be achieved. In these circumstances, tru-cut biopsy followed by induction chemotherapy or chemoradiotherapy should be considered to increase the chance of complete resection. Along with CT, fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) may provide additional data to predict the WHO grade of malignancy [17] and Masaoka stage.

A phase II, multi-institutional clinical trial was conducted in 2014 to determine the response rate, toxicity, and rate of complete resection after induction chemoradiotherapy for locally advanced thymic tumors. In this study, the induction therapy consisted of cisplatin, etoposide, and concurrent radiotherapy ≤4,500 cGy. Among 22 patients, a total of ten patients had a partial response, and 11 had stable disease detected with computerized tomography. Of the 21 patients who completed induction therapy, 17 (77 %) underwent an R0 resection, three (14 %) underwent R1 resection, and one (5 %) underwent debulking. The complication and mortality rate were 36 % and 9 %, respectively. No patient had a complete pathologic response, but five specimens (24 %) had <10 % viable tumor [18]. Ruffini et al. [19] reported the results of database developed by European Society of Thoracic Surgeons in 2014. A total of 2,030 patients including 1,798 thymomas, 191 thymic carcinoma (TC), and 41 neuroendocrine thymic tumor (NETT) were analyzed. Recurrence occurred in 141 patients (8 %) among 1,709 patients with complete resection. Authors showed that risk of recurrence increased with stage (IV 40 %) and histology (TC 30 %, NETT 37 %). The probability of an incomplete resection was higher in male patients and increased with tumor size, whereas decreased with the presence of myasthenia gravis. When comparing with A-AB-B1 thymoma, the probability of an incomplete resection is higher in B2-B3 thymoma, TC, and NETT. Five- and 10-year OS and DFS rates were 85 % and 73 % and 84 % and 70 %, respectively.

The role of surgery in stage IV is still controversial; nevertheless, multimodality treatment including surgical resection should be considered as the treatment of choice in patients with stage IV thymic malignancies. There are several studies reported a wide range of survival rates between 0 % and 71 % at 5 years [20–22]. Hamaji reported on a population-based analysis of 282 patients with stage IV thymoma. Among 282 patients, 110 patients underwent surgical resection and 172 were managed nonsurgically. The 5- and 10-year cancer-specific survival (CSS) rates were 78.8 % and 53.8 %, respectively; however, CSS rates were 51.9 % and

35.9 %, respectively, in patients with nonsurgical management. Even though this database did not include detailed data on chemoradiotherapy, multimodality treatment including surgery at stage IV may improve overall survival [23].

Surgery in Recurrent Thymic Malignancies

Recurrence after surgery is another critical issue on the treatment of thymic malignancies. Published guidelines recommend surgery for recurrent thymoma in case of a localized recurrence after apparently successful initial therapy [24, 25]. In one of the largest series published by Kondo et al., recurrence rates for stages I, II, III, and IV were 0.9 %, 4.1 %, 28.4 %, and 34.3 %, respectively [22]. Okumura et al. reported on 67 patients with recurrence after resections for thymic epithelial tumors. Among 67 patients, 27 had re-resection for recurrence. The 10-year survival rate was 70 % for patients who underwent a re-resection and 35 % for those who did not. There was a significant difference between the two groups ($p=0.002$). In addition, study showed that 5-year survival rate after the re-resection was 100 % in patients with type B1 tumors, 56 % in those with type B2 tumors, and 60 % in those with type B3 tumors. Authors concluded that recurrence following resection of type AB and type B1 tumors demonstrated a greater chance of treatment by re-resection surgery [26].

Case 1

A 37-year-old female patient presented with chest pain. Chest computed tomography (CT) revealed anterior mediastinal mass (Fig. 17.1). Tru-cut biopsy of the anterior mediastinal mass revealed the diagnosis as thymoma type B1. The patient underwent anterior mediastinal mass resection with median sternotomy. Histopathologic examination confirmed the diagnosis. The patient was staged as Masaoka-Koga stage I. CT revealed pleuroparenchymal metastatic nodules with

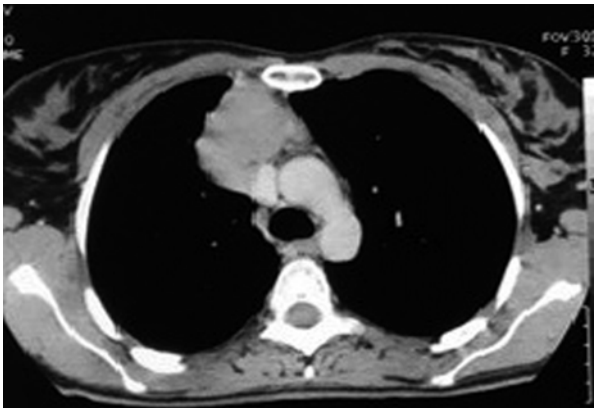

Fig. 17.1 CT revealed anterior mediastinal mass

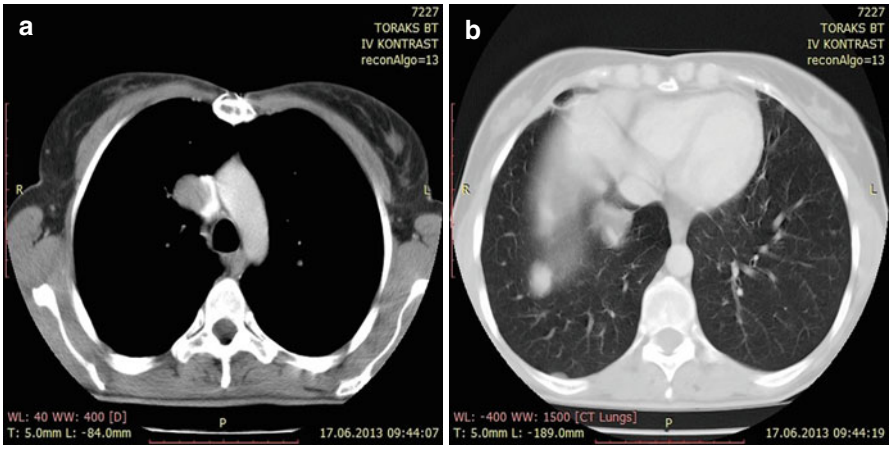

Fig. 17.2 (**a**, **b**) Pleuroparenchymal metastatic nodules with superior vena cava invasion

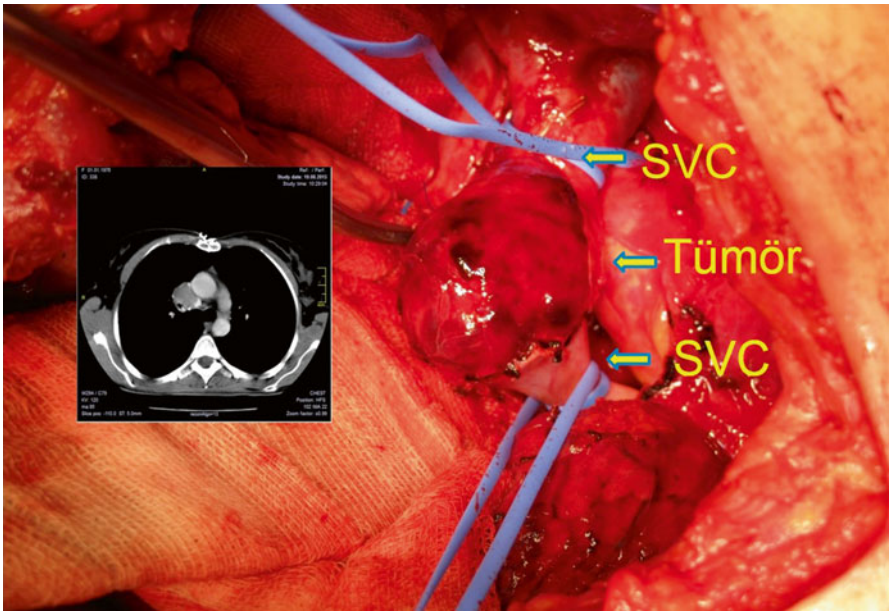

Fig. 17.3 Intraoperative view of tumor invading the superior vena cava

superior vena cava invasion at 3 years after the operation (Fig. 17.2a, b). Superior vena cava resection with graft interposition and resection of pleuroparenchymal nodules was performed following three courses of chemotherapy (cisplatin, cyclophosphamide, adriamycin) (Fig. 17.3). The patient underwent pleural implant resection at 1 year after the second operation. There is no recurrence detected on CT during the follow-up period of 1 year.

Case 2

A 47-year-old male patient presented with anterior mediastinal mass and right pleural nodular implants (Fig. 17.4). Tru-cut biopsy of the mass showed thymoma type B2. After four courses of cisplatin, cyclophosphamide, and adriamycin, CT revealed partial response. The patient underwent mediastinal mass resection with partial pericardial resection and right total parietal pleurectomy (Fig. 17.5a, b). The patient is in first year of follow-up without recurrence.

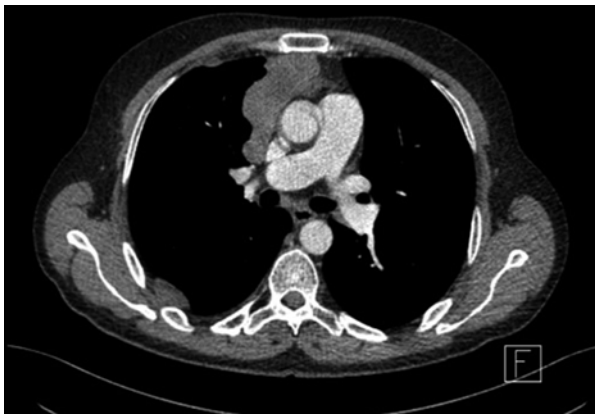

Fig. 17.4 Mediastinal mass with pleural implant

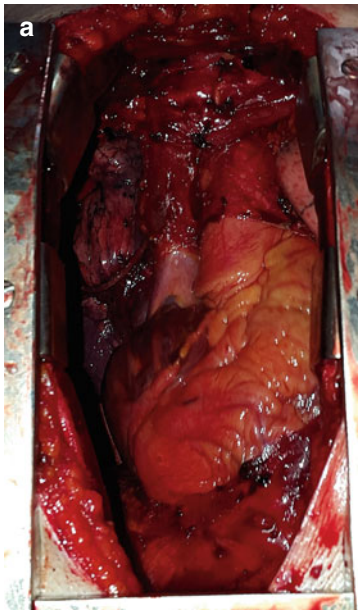

Fig. 17.5 (**a**) Intraoperative view of anterior mediastinum after resection. (**b**) Mediastinal mass and parietal pleura

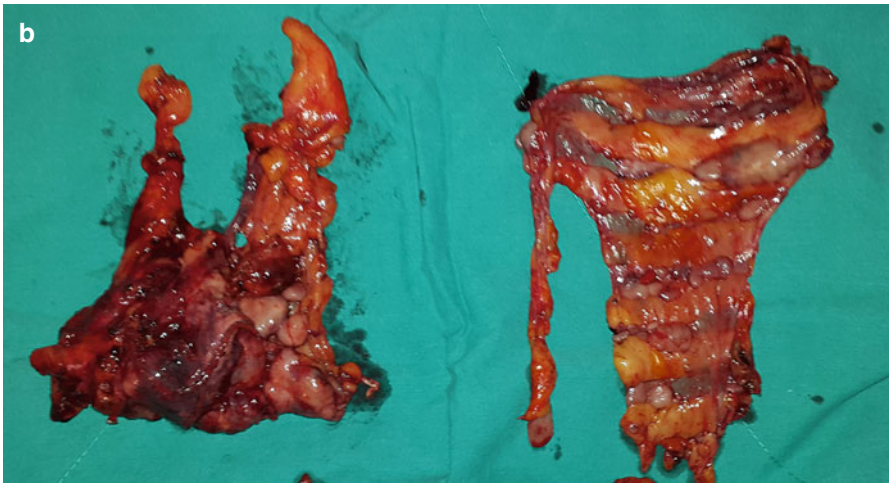

Fig. 17.5 (continued)

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