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Thymic carcinoma. Clinical institutional experience with 15 patients

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Abstract

Objective: We retrospectively evaluated 15 patients with thymic carcinoma treated with various modalities and investigated overall management of this disease. **Methods**: From 1983 to 2003, we treated 15 patients with thymic carcinoma (12 squamous cell carcinomas, 2 undifferentiated carcinomas and one adenocarcinoma). According to Masaoka's staging system, they consisted of 2 at stage II, 5 at stage III, 4 at stage IVa and 4 at stage IVb. **Results**: Ten patients were histologically diagnosed preoperatively, and 5 patients underwent an exploratory procedure under the diagnosis of thymoma or benign teratoma. Complete resection was performed in 9 patients (2 stage II, 5 stage III and 2 stage IVa), which included 4 patients who received induction therapy, 4 who received postoperative radiation therapy, and 1 who received postoperative chemotherapy. Six patients with unresectable tumors were treated by irradiation (40–60 Gy) with or without chemotherapy. The median survival was 13 months for patients without resection, and 57 months for patients with a complete resection. Total 3-year and 5-year survival rates were 51.9 and 39.0%, respectively. **Conclusions**: We concluded that a complete resection is mainstay of therapy when possible, but chemoradiation therapy being potential benefit in the management of thymic carcinoma. However, considering the high prevalence of advanced stage patients, to establish the effective regimen of induction therapy in the additional multicenter trials should be mandatory.

Keywords: Thymic carcinoma; Thymic epithelial tumors

1. Introduction

Thymic carcinoma is a relatively rare tumor located in the anterior mediastinum that, until recently, has shown a difficult to determine histogenesis. In contrast thymomas, thymic carcinomas show aggressive behavior and often invade adjacent organs, such as the great vessels, pericardium, and lungs [1–3]. Histologically, thymic carcinomas show obvious cytologic atypia, therefore Levine and Rosai [4] first included these tumors in the group of so-called malignant thymomas. Snover and colleagues [5] later named this tumor thymic carcinoma and this disease entity definition was revised by Suster and Rosai [3]. They are usually represented as a solid anterior mediastinal mass, and a needle biopsy can offer histological diagnosis to determine therapeutic yield, though they are usually not found until an advanced stage. In patients with advanced stage thymic carcinoma, induction therapy should be first applied to improve the resectability, because of the aggressiveness of local invasion [1,4]. A differential diagnosis is also warranted from other anterior mediastinal tumors such as thymomas, lymphomas, and germ cell tumors. Clinical features and therapeutic modalities of thymic carcinoma have not been established, because of its rarity and long-standing confusion regarding pathological disease entity. Thymic carcinomas are now recognized as pathological and clinical entity, named C thymoma by Rosai and World Health Organization (WHO) [6]. We retrospectively reviewed 15 cases of primary thymic carcinoma, and present some unusual clinical and radiologic features, as well as treatment with various modalities, and also discuss overall management of this disease.

2. Patients and methods

From 1983 to 2003, we treated 15 cases of primary thymic carcinoma among 107 thymic neoplasms

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(61 thymomas and 32 germ cell tumors) out of a total 220 mediastinal tumors at our hospital. The diagnosis of thymic carcinoma was confirmed by a review of microscopic sections by a single pathologist (M.H) and reconfirmed by an independent pathologist (H.H). We used the criteria for diagnosis recently published by Rosai and WHO [6]. Clinical staging was done by surgical or histological examination after preoperative evaluation including chest X-ray, chest and abdominal computed tomogram (CT), brain CT, or magnetic resonance imaging (MRI). The stage was evaluated according to the classification of Masaoka and associates [7], which was originally described by surgical stage, i.e. stage I, microscopically encapsulated; stage II, microscopic invasion into capsule; stage III, macroscopic invasion into neighboring organs; stage IVa, pleural or pericardial dissemination; stage IVb, lymphogenous or hematogenous metastases. At the end of the study, 7 patients were alive and 8 patients had died of the disease. Survival time was calculated from the date of operation or surgical biopsy by the method of Kaplan and Meier, and the log-rank test was used to compare survival rates between the groups.

3. Results

Patient profiles are summarized in Table 1. There were 10 men and 5 women, whose ages ranged from 39 to 77 years old (mean 60.8 years). Ten patients (66.7%) presented symptoms directly attributable to the mass including cough, chest oppression or pain, and superior vena cava (SVC) syndrome (Table 1) while 5 patients without symptom were incidentally found at an annual check-up. The tumors were presented as a large anterior mass with a relatively irregular margin between the tumor and adjacent structures. Radiologically, the maximum tumor diameter ranged from 4 to 15 cm (mean 8.9 cm). As for CT findings, all our cases had typical radiologic features of a thymic carcinoma classified as WHO type C [6], such as a highly aggressive infiltrating solid mass with an irregular contour [1,3,6], and loss of mediastinal fat plane [8]. Fig. 1 shows CT images from before and after induction therapy of a patient (Case 4) with thymic carcinoma, in whom complete resection was achieved successfully after induction chemoradiotherapy. Three patients had intrapulmonary metastasis and 2 had bone metastasis at presentation. Additionally 4 patients showed mediastinal lymphadenopathy in CT findings, and mediastinal metastasis was histologically proven in 2 patients by VATS exploration or mediastinoscopic biopsy. None of these patients had concomitant paraneoplastic syndrome, including myasthenia gravis or other autoimmune diseases in the light of clinical and laboratory findings. Histological diagnosis of thymic carcinoma was made according to the WHO classification as type C [6]. There were 12 squamous cell carcinomas, 2 undifferentiated carcinomas, and 1 adenocarcinoma in the current cases. According to Masaoka's classification, they consisted of 2 of stage II, 5 at stage III, 4 at stage IVa, and 4 at stage IVb.

Ten patients were histologically diagnosed preoperatively and 5 patients underwent an exploratory procedure under a diagnosis of thymoma or benign cystic teratoma. Therefore, surgical resection was preceded in 5 patients who were not diagnosed with thymic carcinoma. Complete resection was performed in 9 patients (2 stage II, 5 stage III and 2 stage IVa), including 4 patients with induction therapy and 4 who received postoperative radiation therapy, and 1 who received chemotherapy. As for combined resection, 4 patients required resection of the SVC with/without innominate vein, followed by prosthetic polytetrafluoroethylene (PTFE) ring graft substitution. To avoid postoperative respiratory failure associated with diaphragmatic paralysis, 2 patients received concurrent diaphragmatic plication. Six patients

Table 1
Clinical profiles of 11 patients with thymic carcinoma

Case No.	Age/gender	Histology	Tumor size (cm)	Initial diagnosis	Initial symptoms
1.	53/M	Squamous cell	7 × 7 × 6	Thymic cancer	None
2.	77/M	Squamous cell	8.5 × 8 × 6	Thymic cancer	Cough, Chest pain
3.	58/M	Undifferentiated	15 × 10 × 10	Teratoma	Cought, Chest pain
4.	65/M	Squamous cell	12 × 10 × 10	Thymic cancer	Cough, Chest pain
5.	64/F	Adenocarcinoma	7 × 5 × 5	Thymic cancer	None
6.	59/M	Squamous cell	7 × 7 × 6	Thymic cancer	SVC syndrome
7.	55/F	Squamous cell	6 × 6 × 5	Thymic cancer	None
8.	59/M	Undifferentiated	15 × 10 × 10	Thymoma	Chest discomfort
9.	66/M	Squamous cell	8 × 8 × 7	Thymic cancer	Chest pain, SVC syndrome
10.	76/F	Squamous cell	9 × 9 × 7	Thymoma	Chest discomfort
11.	72/F	Squamous cell	9 × 8 × 7	Thymic cancer	Cough
12.	39/M	Squamous cell	6 × 5 × 5	Teratoma	None
13.	48/M	Squamous cell	5 × 4 × 4	Thymoma	None
14.	51/M	Squamous cell	13 × 12 × 10	Thymic cancer	Cough, Chest pain, SVC syndrome
15.	67/F	Squamous cell	7 × 6 × 5	Thymoma	Chest discomfort

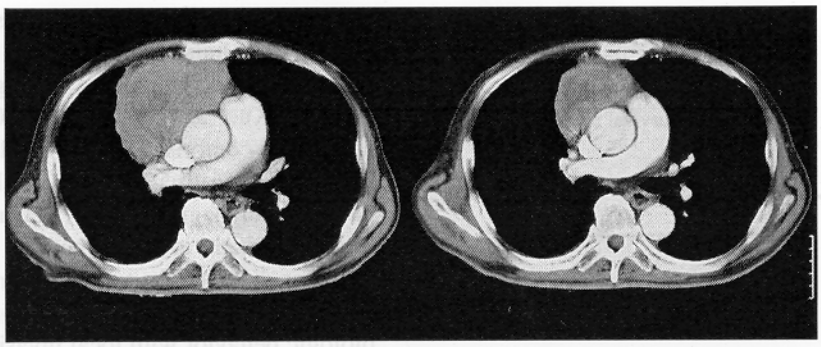
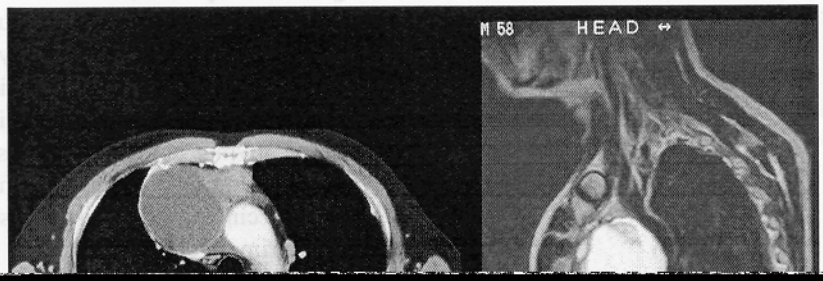


Fig. 1. Chest computed tomography (CT) scans of Case 4 before (A) and after (B) induction chemotherapy.

received combined resection of the pericardium and lung. Five patients having unresectable tumors were treated by irradiation (40–60 Gy) with or without chemotherapy.

We herein present a case with difficulty and peculiarity in preoperative diagnosis. In 1 patient (Case 3), a chest CT showed a well-circumscribed lobulated rounded mass with a predominantly cystic formation just adjacent to the heart border and SVC (Fig. 2A). Chest MRI (Fig. 2B) with T2 weighed images further revealed a fluid filled density, suggestive of a cystic mass. There were no lymphadenopathy, or pleural and pericardial effusions. A CT guided needle biopsy was performed to obtain histodiagnosis, which was compatible with cystic teratoma without malignant components. At surgery, the tumor was found as a thymic carcinoma with a pleural disseminated nodule in the left thoracic cavity. Histologically, the cystic wall was composed of fibrous tissue containing tumor nests and lined by neoplastic cells. From these results, we made a diagnosis of undifferentiated (squamous cell) carcinoma of the thymus. The tumor was extirpated, with resection and reconstruction of the SVC and innominate vein, followed by 2 cycles of chemotherapy. In Case 12 accompanying cystic structure, the malignant tumor cells were found in the solid mass, however the cyst was free of cancer invasion.

Four patients who did not receive a complete resection died of disease progression due to the primary disease. One recent patient (Case 2) who underwent chemoradiotherapy for locoregional control and was alive 25 months after the initial therapy. As for 9 patients who underwent complete resection, 5 patients (Cases 4, 8 and 11 to 13) were alive without relapse. One patient died of local recurrence in the thoracic cavity 26 months postoperatively, and other 3 patients died of multiple distant metastasis 25, 88, and 124 months, respectively, after resection. Overall 3-year and 5-year survival rates were 51.9 and 39.0%, respectively (Fig. 3). The median survival was 13 months for patients without resection and 57 months for patients who received a complete resection. Among these patients, those who received resection showed better survival than those without resection (Fig. 4).



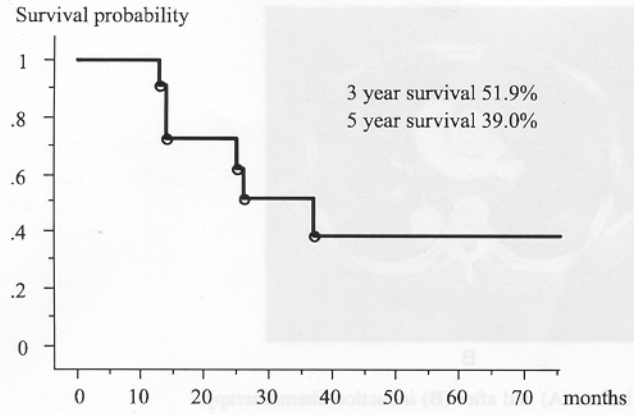


Fig. 3. Overall survival rates for 15 patients with thymic carcinoma.

4. Discussion

Until recently, a clinical entity of thymic carcinoma has been controversial among pathologists, especially regarding clinical behavior and histological definition. Before the early 1970s, all thymic neoplasms were classified as thymoma regardless of their malignancy. However, Shimosato et al. [2] first described 8 cases of thymic carcinomas as a new entity of thymic neoplasms, after which the tumor was described as entity distinct entity from malignant thymoma [3,4,9,10] as well as part of a new classification of thymic neoplasms [9,10]. The most important pathologic feature of thymic carcinoma is its potential to be categorized into versatile pathologic subtypes [4,11]. From the viewpoint of pathology, Suster [3] and Snover [4] described 7 unique and complex histologic subtypes of thymic carcinoma, which were squamous, mucoepidermoid, basaloid, sarcomatoid, small cell, lymphoepithelial, and clear cell tumors.

The prevalence of thymic carcinoma is regarded as to be rare Wick et al. found only 20 cases of thymic carcinoma among all large masses seen at the Mayo clinic over 75 years [9]. In the largest mass of mediastinal tumors reported from Japan [12], thymic carcinoma made up of 1.7% of all the mediastinal tumors, in contrast to 29.9% of thymoma. On the other hand, Blumberg and colleagues [13] found 43 cases of thymic carcinoma among 118 thymic neoplasms. Further, Kuo and associates [10] reported that thymic carcinoma comprised 21.3% of all thymic neoplasms seen in a Chinese institution, implying the difficulty of pathological diagnosis rather than race difference. However, it is important to note that the complicated pathologic subtypes did not have an impact on clinical behavior [1,13].

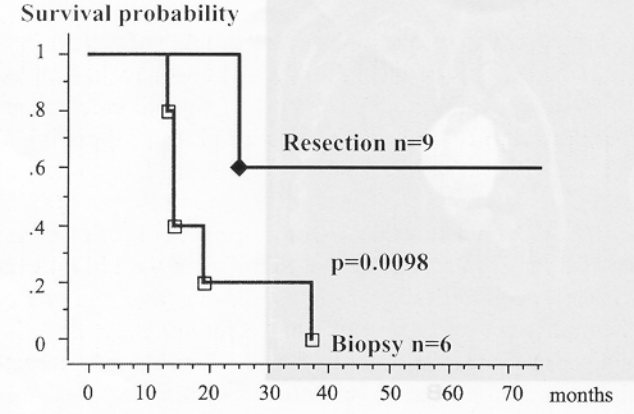


Fig. 4. Survival rates for 9 patients who received resection with thymic carcinoma compared with patients by biopsy.

Clinically, thymic carcinomas show malignant biologic behavior with local invasion and distant metastasis [1,10,11], and 68% of the cases were symptomatic at presentation [1]. Myasthenia gravis or other autoimmune diseases, often associated with thymoma, were not noted in the current series of thymic carcinoma, of which results were consistent with the clinical characteristics in the previously reports [2,3,5].

Compared to thymoma, thymic carcinoma shows different characteristics in CT findings [8] in terms of contour, shape, calcification and cystic changes. Thymic carcinomas classified as WHO type C have been characterized as a highly aggressive infiltrating solid mass with an irregular contour [8], loss of mediastinal fat plane, and extrathymic lymphadenopathy (56%) [8,13]. In the current series, however, since Case 3 did not show these characteristic CT findings as well as well as needle aspiration cytology negative, we reached a clinical diagnosis of cystic teratoma (germ cell tumor) that was based on a clinical overview of 129 primary mediastinal germ cell tumors [14]. In the English literature for thymic carcinomas, only 2 cases with a cystic mass were reported, 1 in the collective reviews of Truong et al. [11] and 1 by Lee and colleagues [15]. In the present Case 3, the solid part was found to be an undifferentiated squamous cell carcinoma of the thymus and, surprisingly, the cystic wall was replaced by malignant neoplastic cells. Accurate histological diagnosis of thymic carcinoma is an important issue in the management of this disease. Fujii et al. [16] recently analyzed the lymphocyte flow-cytometry and found that frequency of double positive cells in thymoma was different from that of thymic carcinoma. This characteristic may help diagnose thymic epithelial tumors [6,16]. In addition, we recently performed CD5 immunohistochemistry to confirm thymic carcinoma [17], distinguishing from carcinoma of various primary sites.

In the current series, we did not encounter stage I thymic carcinomas. Tsuchiya et al. [18] reviewed 16 patients with thymic carcinoma over 27 years and found only 2 cases at stage I or II. Yamakawa and colleagues [19] and Ogawa and associates [20] also stated that a high percentage of thymic carcinomas were at an advanced stage. Kondo et al. [21] stressed the importance of N factor on survival in cases with thymic carcinoma in contrast to the evidence that the prognosis of thymoma was dependent on the clinical stage of Masaoka. In this sense, establishment of TNM staging for

Table 2
Demographic data of 11 patients with thymic carcinoma

Case.	Stage	Intervention	Pleural dissemination	Involved organ	Metastatic organs	Postoperative therapy	Prognosis
1.	IVb	VATS exploratory	+	SVC In Ao	Lung, bone, LN	CRT (CDDP + VNR, 50Gy)	14 mos D
2.	IVb	Mediastinoscopy	−	SVC In	Lung, bone, LN	RT (60 Gy)	19 mos A
3.	IVa	Complete resection	+	SVC, In, RUL, pericardium	−	CT (CDDP + VNR)	26 mos D
4.	III	Complete resection (NA) (CDDP + VP16, 40 Gy)	−	SVC, In, RUL, pericardium	−	−	24 mos A
5.	III	Complete resection (NA) (CDDP + VP16, 40 Gy)	−	SVC, In, RUL, pericardium	−	−	27 mos D
6.	IVb	VATS exploratory	+	SVC, In, Ao	Lung, LN	CRT (CDDP + VP16 + MMC, 50 Gy)	38 mos D
7.	IVa	Needle biopsy	+	SVC, In, Ao	−	RT (40 Gy)	13 mos D
8.	III	Complete resection	−	Pericardium, LUL	−	RT (40 Gy)	57 mos A
9.	IVa	VATS exploratory	+	SVC, In, RUL	−	CT (CDDP + VP16)	14 mos D
10.	III	Complete resection	−	In, Pericardium, LUL	−	RT (40 Gy)	88 mos D
11.	III	Complete resection (NA) (CDDP + VNR, 40 Gy)	−	SVC, In, RUL	−	−	11 mos A
12.	II	Complete resection	−	Pleura	−	−	5 mos A
13.	II	Complete resection	−	Pleura	−	−	4 mos A
14.	IVb	VATS, needle biopsy	+	SVC, In, Ao	Lung, LN	CRT (CDDP + VP16, 60 Gy)	3 mos A
15.	III	Complete resection	−	Pericardium, LUL	−	RT (40 Gy)	124 mos D

VATS, video-assisted thoracic surgery; SVC, superior vena cava; In, Innominate vein; Ao, Aorta; CRT, chemoradiotherapy; CDDP, cis-platin; VNR, vinorelbin; RUL, right upper lobe; NA, neoadjuvant therapy; VP16, etoposide; CT, chemotherapy; RT, radiation therapy; LN, lymph node; A, alive; D, dead.

thymic carcinoma awaits investigation to decide patients' management and to estimate prognosis (Table 2).

Although therapeutic modalities have not been established in case with thymic carcinoma, induction therapy similar to that for an invasive thymoma has been applied [1,22] to ensure resectability, since more than 80% of the cases are found in an advanced stage [18–20]. In cases of unresectable thymic carcinoma, radiation therapy with or without chemotherapy has been employed, based on previous reports that thymic carcinoma seemed to be sensitive to irradiation like thymoma [22,23]. In contrast to thymoma of Masaoka stage III or IV [24,25], an incomplete resection does not result in a fair prognosis with radiation and/or chemotherapy in case of thymic carcinoma [25].

Lucchi et al. [22] stressed the importance of multimodality treatment adjuvant setting, and they did not perform aggressive extended resection such as SVC replacement because of high morbidity and mortality. However, we believed that the complete surgical resection of the entire thymus and tumors with en bloc resection of all involved adjacent structures remains the mainstay for treatment of thymic tumors. A complete resection was performed in 67% of the cases in our series. Seven of nine (78%) patients in the current study required a combined resection of adjacent organs including the SVC, innominate vein, pericardium, or lungs, without perioperative problems. The 30-day mortality of thymic carcinoma patients is reported to be 2.1%, with reference to thymoma in 0.1% of the cases in the annual report of the Japanese association of thoracic surgery [26]. We did not experience major morbidity or mortality in patients who received a complete resection.

In cases with non-seminomatous germ cell tumor, induction chemotherapy should be employed even in the resectable cases [14]. In contrast, it is not determined regarding the benefit of induction therapy for completely resectable thymic carcinomas. The role of chemotherapy is now possibly verified and new regimens are in progress [27,28], based on the experience that cisplatin-based chemotherapy were effective for patients with metastatic and unresectable thymic carcinomas [20,27]. Lucchi et al. [22] stressed that induction chemotherapy followed by complete resection and postoperative radiation improved the prognosis of patients with advanced thymic carcinomas.

From our experience with a small number of patients and preliminary trials of induction therapy, we have attempted to characterize the clinical impact of thymic carcinomas. Based on the results, we concluded that the best initial treatment is complete resection when possible, regardless of induction therapy, with chemoradiation therapy, to provide the best potential benefit in the management of patients with thymic carcinomas. However, considering the high prevalence of advanced stage patients, an effective regimen of chemotherapy with or without radiation, such as with malignant germ cell tumors [19,20], may improve resectability and prognosis. In order to establish new therapeutic strategies for thymic carcinoma, additional multicenter trials are required.

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