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Multimodality Treatment for Thymic Carcinoma: Review of 11 Cases at a Single Institute

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ABSTRACT

Background: We reported our experience with thymic carcinomas and review their clinical features, treatment strategies, and prognoses. **Methods:** From April 1998 to November 2012, 11 patients pathologically diagnosed with thymic carcinoma and treated in our hospital were investigated. **Results:** There were 7 men and 4 women, with a median age of 62 years (range, 35 - 72). According to the Masaoka staging system, 3 patients had stage II, 1 stage III disease, 3 stage IVa disease and 4 stage IVb disease. Ten patients had squamous cell carcinoma, whereas 1 had large cell neuroendocrine carcinoma (LCNEC). We performed surgery or multimodality therapy including surgery as the initial therapy for 8 patients. Of the non-surgical cases, 1 patient received chemoradiotherapy and survived for over 6 years without recurrence, whereas 2 received palliative care. Three of 4 patients who underwent complete resection survived without disease recurrence, whereas only 1 patient with LCNEC survived in the incomplete resection group. Multimodality therapy with cisplatin and docetaxel was provided to 3 patients, and recurrence has not been observed in any of the cases. **Conclusions:** Favorable outcomes could be achieved in patients with thymic carcinoma who underwent intensive treatment. In particular, surgery combined with cisplatin and docetaxel plus thoracic irradiation may be an attractive approach for thymic carcinoma.

Keywords: Thymic Carcinoma; Multimodality Treatment; Cisplatin; Docetaxel

1. Introduction

Thymic carcinoma is a rare tumor arising from the thymic epithelium that accounts for approximately 14.1% of thymic epithelial neoplasms and differs from thymoma with respect to morphological and biological features. The most common histologic type in Japan is squamous cell carcinoma [1]. The prognosis of thymic carcinoma is worse than that of thymoma, with a 5-year survival rate of 33.3% to 50.5%, which correlates with the Masaoka staging system [1,2]. Unfortunately, 80% to 90% of cases are diagnosed at an advanced stage (stage III or IV) [1,3]. Treatment with surgery, radiotherapy, and chemotherapy has been described in some reports, but there is no consensus as to which modality or combined modality is the gold standard. We report our experience with 11 cases of thymic carcinoma and review their clinical features, treatment, and prognoses.

2. Patients and Methods

From April 1998 to November 2012, 11 patients were pathologically diagnosed with thymic carcinoma and treated in our hospital. We retrospectively reviewed their clinical features, treatment, and prognoses. The clinical or pathological stage of the disease was determined according to the staging system described by Masaoka *et al.* [4]. The pathological diagnosis of thymic carcinoma was established according to the histopathological criteria proposed by the World Health Organization (WHO) [5].

Overall survival time was calculated from the date of diagnosis until death or the last follow-up visit using the Kaplan-Meier method. Statistical analyses were performed using SPSS version 20 for Windows (IBM).

3. Results

3.1. Patient Characteristics

The study included 7 men and 4 women, with a median age of 62 years (range, 35 - 72). According to the Masaoka staging system, 3 patients had stage II disease, 1 stage III disease, 3 stage IVa disease and 4 stage IVb disease. Pathologically, 10 patients had squamous cell carcinoma, whereas 1 had large cell neuroendocrine carcinoma (LCNEC). We performed surgery or multimodality therapy including surgery as the initial therapy for 8 patients. Of the non-surgical cases, 1 patient received chemoradiotherapy, whereas 2 received palliative care.

3.2. Treatment Strategies and Clinical Outcomes

Table 1 summarizes all cases with respect to their initial treatment and respective outcomes. One patient (case 7) from the non-surgery group received pericardial drainage and died 21 months after the diagnosis. A second patient (case 8) was treated with radiotherapy to the site of bone metastasis followed by chemotherapy and eventually died 23 months later. Another patient (case 9) received chemotherapy consisting of cisplatin and docetaxel with concurrent thoracic irradiation in accordance with the OLCSG 0007 protocol [6]; this patient is still alive 6 years later without disease progression (**Figure 1**).

In the surgical intervention group, 1 patient received surgery alone, 2 patients received surgery and adjuvant radiotherapy, 3 patients received surgery with adjuvant chemotherapy and subsequent radiotherapy, and 2 patients received preoperative chemoradiotherapy, surgery, and adjuvant chemotherapy. Complete resection was performed in 4 of the 8 cases (**Table 2**). In the complete resection group, 3 of 4 patients were alive and disease free at the time of reporting, whereas the other patient (case 2) had recurrence of pleural dissemination. In the incomplete resection group, 1 patient with LCNEC was alive with no evidence of disease following postoperative radiotherapy and chemotherapy consisting of carboplatin and etoposide at the time of reporting.

However, the other 3 patients experienced disease recurrence. As shown in **Table 2**, better outcomes were achieved in patients at an early Masaoka stage and in those who underwent complete resection together with radiotherapy and chemotherapy.

Table 3 shows the site of disease recurrence in each patient who received surgery. Manifestations of disease recurrence were dissemination to the pleura, supraclavicular lymph nodes, and lungs. Seven of the 11 patients are still alive. The median survival time and 5-year survival rate were 63.7 months and 58.3%, respectively.

3.3. Treatment Outcomes According to Chemotherapy Regimens

Recurrence was not observed in any of the 3 patients treated with this regimen (cisplatin and docetaxel) at the time of reporting. As mentioned above, 1 of the patients was alive for over 6 years with no further need for surgery. In another patient, complete resection was achieved by performing preoperative chemoradiotherapy. In contrast, 2 of 3 patients treated with cisplatin alone or with the adriamycin, cisplatin, vincristine, and cyclophosphamide (ADOC) regimen experienced recurrent diseases (**Table 4**).

Table 1. Summary of 11 cases of thymic carcinoma.

Case	Age	Sex	Histology	Stage	Initial treatment			Recurrence	DFS(M)	Status
					Surgery	RT	Cx			
1	66	F	LCNEC	II	+	+	+	No	43.1	Alive
2	35	M	Sq	II	+	+	-	Yes	8.0	Alive
3	60	M	Sq	II	+	+	-	No	20.6	Alive
4	70	F	Sq	III	+	+	+	Yes	17.9	Dead
5	56	F	Sq	IVa	+	-	-	Yes	26.5	Alive
6	67	M	Sq	IVa	+	+	+	Yes	32.9	Dead
7	42	M	Sq	IVa	-	-	-	-	-	Dead
8	62	M	Sq	IVb	-	+	-	-	-	Dead
9	70	M	Sq	IVb	-	+	+	No	80.7	Alive
10	72	M	Sq	IVb	+	+	+	No	46.2	Alive
11	59	F	Sq	IVb	+	+	+	No	14.8	Alive

Abbreviations: DFS, disease-free survival; LCNEC, large cell neuroendocrine carcinoma; Sq, squamous cell carcinoma; RT, radiotherapy; Cx, chemotherapy.

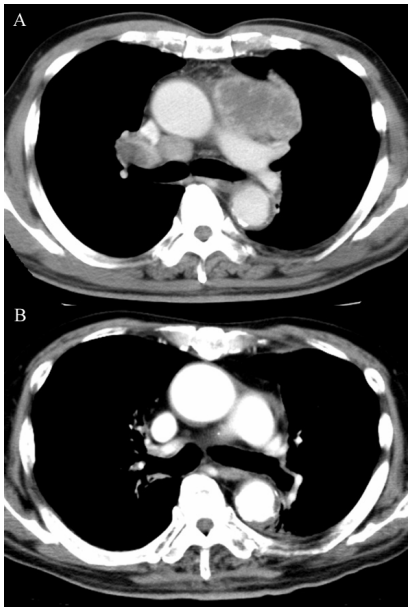

Figure 1. Computed tomography scan of the chest in case 9 showed a bulky mass in the anterior mediastinum with mediastinal and right hailer lymphadenopathy in April 2006 (A); Complete remission was achieved by treatment with cisplatin and docetaxel accompanied by concurrent thoracic irradiation, and the patient was alive for over 6 years without disease progression at the time of reporting (B).

Table 2. Outcomes according to clinical stage and treatment modality.

		Recurrence		Total
		Yes	No	
Stage	II	2 (67%)	1 (33%)	3
	III or IV	3 (38%)	5 (62%)	8
Resection	Complete	3 (75%)	1 (25%)	4
	Incomplete	1 (25%)	3 (75%)	4
	Non-Resection	1 (33%)	2 (67%)	3
Radiotherapy	+	4 (50%)	4 (50%)	8
	-	0 (0%)	3 (100%)	3
Chemotherapy	+	4 (67%)	2 (33%)	6
	-	1 (20%)	4 (80%)	5

Table 3. Recurrent sites in patients who underwent surgical resection.

	Recurrence site	Status	OS (M)
2	Pleura	alive	40.3
4	Supraclavicular Lymph Node	dead	64.6
5	Pleura	alive	176
6	Lung	dead	53.0

Abbreviation: OS, overall survival.

4. Discussion

Surgery is considered to be the mainstay of treatment for thymic carcinoma. Complete resection is particularly important [7]. Kondo *et al.* showed 5-year survival rates of 66.9%, 29.8%, and 19.4% in the complete resection group, incomplete resection group, and non-surgery groups, respectively [1]. In accordance with these findings, 3 of our 4 patients who underwent complete resection survived without recurrence, highlighting the importance of complete resection. However, extensive invasion or metastasis at diagnosis is a frequent finding. Even with complete resection, 50% of patients are reported to experience disease recurrence [1]. As a result, treatment with multiple modalities including surgery, radiotherapy, and chemotherapy has been attempted [8], but without general consensus on the optimal approach.

Multimodality treatment is expected to be more effective, and some studies have reported its high efficacy [3, 8]. However, other studies have suggested that adjuvant radiotherapy and adjuvant chemotherapy do not contribute to a favorable prognosis [1,9]. In our study, local recurrence was detected in only 1 of the 8 patients who underwent mediastinal radiotherapy. However, 3 of these patients experienced distant metastases. Therefore, we speculate that radiotherapy has potential for good in-field control but is insufficient to control distant metastases. In contrast, chemotherapy is effective not only on primary lesions but also on distant metastases. Platinum-based regimens have been widely used, and the response rate

Table 4. Treatment outcome according to chemotherapy regimen.

Case	Histology	Stage	Initial Treatment			Recurrence	DFS(M)	Status
			Surgery	RT	Regimen			
1	LCNEC	II	+	+	CE	No	43.1	Alive
3	Sq	III	+	+	CDDP	Yes	20.6	Alive
6	Sq	IVa	+	+	ADOC, 5FU	Yes	32.9	Dead
9	Sq	IVb	-	+	DP	No	80.7	Alive
10	Sq	IVb	+	+	DP	No	46.2	Alive
11	Sq	IVb	+	+	DP	No	14.8	Alive

Abbreviations: RT, radiotherapy; DFS, disease-free survival; LCNEC, large cell neuroendocrine carcinoma; Sq, squamous cell carcinoma; CE, carboplatin, etoposide; CDDP, cisplatin; ADOC, doxorubicin, cisplatin, vincristine, cyclophosphamide; DP, cisplatin, docetaxel.

has been reported to be 22% to 75% [10-13]. In addition, recent reports have shown the efficacy of third-generation anti-cancer agents. However, we do know that complete response is very rare and that local control in particular is difficult to achieve by means of chemotherapy alone. Therefore, the use of multimodality therapy is worthwhile when aiming to cure the disease.

Indeed, we treated 3 patients with combination chemotherapy consisting of cisplatin and docetaxel accompanied by radiotherapy, and none of these patients experienced recurrent diseases. Surprisingly, 1 patient (case 9) treated with this regimen and concurrent thoracic irradiation survived for over 6 years without any recurrence, indicating that this chemoradiotherapy controlled the primary lesion and micrometastases and has potential for the cure of thymic carcinomas. Recently, Segawa *et al.* showed the efficacy of docetaxel and cisplatin with concomitant radiotherapy in locally advanced non-small cell lung cancer (NSCLC) [6]. Therefore, this strategy appears to be an attractive approach for the treatment of thymic carcinoma.

Additionally, because many studies have emphasized the importance of complete resection, preoperative chemoradiotherapy to improve the resectability of the tumor may be a useful strategy. Some studies have evaluated preoperative chemoradiotherapy [14-16], but there is still no definitive consensus regarding this approach. Toyooka *et al.* recently reported the superiority of induction chemoradiotherapy using cisplatin and docetaxel together with concurrent radiotherapy in comparison with induction chemotherapy for locally advanced NSCLC [17]. In this report, they described that the rate of pathological downstaging was significantly higher in the chemoradiotherapy group than in the chemotherapy group, resulting in significantly longer overall survival and disease-free survival in the chemoradiotherapy group. We also observed good outcomes when we treated patients with preoperative cisplatin and docetaxel in combination with radiotherapy and believe that this preoperative approach may improve tumor resectability.

Our study has some limitations. First, this is simply a study of a series of cases of thymic carcinoma, and the sample size is too small to conclusively determine the efficacy of multimodal approaches. Second, we cannot simply compare each of our cases because of differences in pathological differentiation and clinical stage. Thymic carcinoma is a rare malignant tumor, and therefore, we cannot develop a new strategy based on a study at a single institute. Further studies are warranted to establish evidence for the treatment of thymic carcinoma in a multi-center clinical study setting.

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