

## The Role of Radiotherapy for Thymic Carcinoma

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Received June 16, 2004; accepted October 15, 2004

**Objective:** The aim of this study is to evaluate retrospectively the role of radiotherapy for thymic carcinoma.

**Methods:** Between 1973 and 1998, 14 patients with thymic carcinoma were treated at Gunma Prefectural Cancer Center. Two patients who had hematogenous metastasis were excluded from this study, therefore 12 patients were analyzed. The Masaoka staging system was used; four patients were diagnosed with stage III disease and eight patients with stage IV disease. The pathological subtype according to the World Health Organization histological criteria for thymic tumors was squamous cell carcinoma (low-grade histology) in six cases and undifferentiated carcinoma (high-grade histology) in six. Ten patients underwent thoracotomy, and two patients underwent excisional biopsy without thoracotomy. Ten patients (83%) received radiotherapy as a curative intent, and the median dose was 60 Gy. Systemic chemotherapy was administered to four patients (33%), and the majority (75%) of the regimens contained cisplatin.

**Results:** The 3-year overall survival rate was 25%. Histological subtype (low-grade versus high-grade), surgical resection (complete versus incomplete), radiotherapy and chemotherapy were evaluated as prognostic factors in a univariate analysis. Low-grade histology and complete resection were good prognostic factors, although these were not statistically significant. Patients who received radiotherapy had a better outcome than those who did not. The major sites of recurrence were the pleura and pericardium. Recurrence within the radiation field was observed in one of seven patients in whom failure patterns could be evaluated.

**Conclusion:** Complete resection is mandatory if possible. Radiotherapy plays an important role in treating thymic carcinoma in terms of reducing local recurrence and prolonging survival time. Establishment of an innovative treatment protocol that includes chemotherapy is necessary to control intrathoracic relapse and distant metastasis.

*Key words: thymic carcinoma – radiotherapy – complete resection*

### INTRODUCTION

Thymic carcinoma is a relatively rare neoplasm of the anterior mediastinum (1–3), and has caused a great deal of controversy. There is still confusion in the terminology and classification of tumors of the thymus: for example, some authors use ‘malignant thymoma’ as thymic carcinoma and others use the term to refer to thymoma with invasiveness or metastasis. Recent studies, however, have defined thymic carcinoma as a distinct thymic neoplasm that differs from other thymic tumors, such as thymomas (2–6). In 1977, Shimosato et al. (4) analyzed eight

cases of squamous cell carcinoma of the thymus and presented the concept of thymic carcinoma, and the following year Levine and Rosai (5) proposed a classification of thymic carcinomas into five types: squamous cell, lymphoepithelioma-like, clear cell, sarcomatoid and undifferentiated. Three histological types of thymic carcinoma were added later: basaloid, mucoepidermoid and small cell, and Suster and Rosai (3) divided these eight types of thymic carcinoma into two groups: low-grade and high-grade histology. A new scheme for the classification of thymic epithelial tumors has been proposed recently by the International Committee of the World Health Organization (WHO) (7), in which thymic carcinoma is classified as type C thymoma consisting of epidermoid keratinizing (squamous cell) carcinoma, lymphoepithelioma-like carcinoma, sarcomatoid carcinoma (carcinosarcoma), clear cell carcinoma, basaloid

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carcinoma, mucoepidermoid carcinoma, papillary carcinoma and undifferentiated carcinoma.

Several investigators have reported that postoperative radiotherapy plays an important role in local control in stage II and more advanced stages of thymoma after incomplete resection and that it improves local control (8–11). Myojin et al. (12) reported that incomplete resection leads to poor results, and suggested that preoperative radiotherapy or chemotherapy might reduce the risk of pleural recurrence after surgery for locally advanced thymoma. Thymic carcinoma is reported to exhibit worse behavior and poorer prognosis than thymoma (8,9,13,14); however, because of the rarity of thymic carcinoma, no consensus has yet been established on a therapeutic strategy that includes radiotherapy.

In this study, we retrospectively studied the data from 12 cases of thymic carcinoma treated at Gunma Prefectural Cancer Center, and we evaluated the role of radiotherapy for this disease.

## SUBJECTS AND METHODS

### PATIENTS AND EVALUATION

Between 1973 and 1998, 68 patients were diagnosed with thymic neoplasms and treated at Gunma Prefectural Cancer Center, and thymic carcinoma was confirmed histologically in 14 of them in a review of all microscopic sections by two pathologists. Two patients who had hematogenous metastasis stage IVb disease were excluded from this study, therefore 12 patients were analyzed. Tumors exhibiting pathological features of well-differentiated thymic carcinoma, which is classified as type B3 tumor in the WHO classification, were excluded. Patient age at the start of treatment ranged from 39 to 78 years (median 50 years). Three patients were women and nine were men (Table 1).

All patients were examined by chest X-ray, and computed tomography of the thorax was performed in 10 patients who had been treated since 1979. At diagnosis, nine patients (75%) had symptoms attributable to mediastinal compression by their tumor, such as cough, dyspnea, chest pain and hoarseness. No patient had a history or manifestations of myasthenia gravis, pure red cell aplasia or other paraneoplastic syndromes associated with the tumors.

### STAGING AND HISTOLOGICAL DIAGNOSIS

Since Hsu et al. (15) reported that the Masaoka staging system for thymoma was the most important prognostic factor in primary thymic carcinoma patients receiving postoperative radiotherapy, we applied the criteria of Masaoka et al. (16) for thymomas to the postoperative clinicopathological staging. Briefly, the Masaoka staging system was determined as follows: stage I, encapsuled tumor; stage II, infiltration of mediastinal fat; stage III, infiltration of neighboring organs; stage IVa, pleural or pericardial dissemination; and stage IVb, lymphatic or hematogenous metastases.

**Table 1.** Patient characteristics

Characteristics	No. of cases
Total cases	12
Gender	
Male/Female	9/3
Age (median)	39–78 (50)
Masaoka stage	
III/IVa/IVb (LYM)	3/4/5
Histology	
SCC/UN	6/6

LYM, lymphogenous metastasis; SCC, squamous cell carcinoma; UN, undifferentiated carcinoma.

**Table 2.** Distribution of patients undergoing surgery, radiotherapy and chemotherapy

Treatment	No. of cases
Surgery	
Complete resection	5
Partial resection	1
Biopsy alone (without thoracotomy)	6 (2)
Radiotherapy	
Yes	10
No	2
Chemotherapy	
Yes	4
No	8

Three patients had stage III disease, four patients had stage IVa and five patients had stage IVb with lymphogenous metastases. No patients had stage I or II disease. The criteria for the pathological diagnosis of thymic carcinoma were based on the WHO histological classification (7). The pathological subtype of thymic carcinoma was squamous cell carcinoma which is classified into low-grade histology (3) in six cases, and undifferentiated carcinoma which is classified into high-grade histology (3) in six.

### SURGERY

Table 2 summarizes the treatment for the 12 patients. All except two underwent thoracotomy: five patients underwent complete resection, one patient underwent partial resection and four patients underwent biopsy alone. Excisional biopsy without thoracotomy was performed in the other two patients.

### RADIOTHERAPY

Ten patients (83%) received radiotherapy with curative intent by <sup>60</sup>Co teletherapy or a 6 or 10 MV linear accelerator. The

treatment volume included the primary tumor bed with approximately 1–2 cm margin. The supraclavicular fossa was included in the irradiation field in one patient, and hemithorax irradiation (25 Gy per 25 fractions) followed by mediastinal irradiation (36 Gy per 18 fractions) was administered to one patient. The range of total dose was 47–70 Gy (median dose 60 Gy), and it was administered in daily dose fractions of 1.8 or 2.0 Gy, 5 days a week. A 78-year-old man who received radiotherapy in a dose of 32 Gy to the right lower neck lymph node metastasis without any irradiation to the primary site to reduce intolerable pain was excluded from these 10 patients of the radiotherapy group.

#### CHEMOTHERAPY

Chemotherapy was administered to four patients (33%) including one patient with stage III, two patients with stage IVa and one patient with stage IVb. Three of them received chemotherapy as induction therapy: two patients were treated with a combination of cisplatin (CDDP), doxorubicin, cyclophosphamide and vincristine, and the other with a combination of CDDP, doxorubicin and etoposide. The remaining one patient received chemotherapy after surgery and radiotherapy with a combination of cyclophosphamide and vincristine.

#### STATISTICAL ANALYSIS

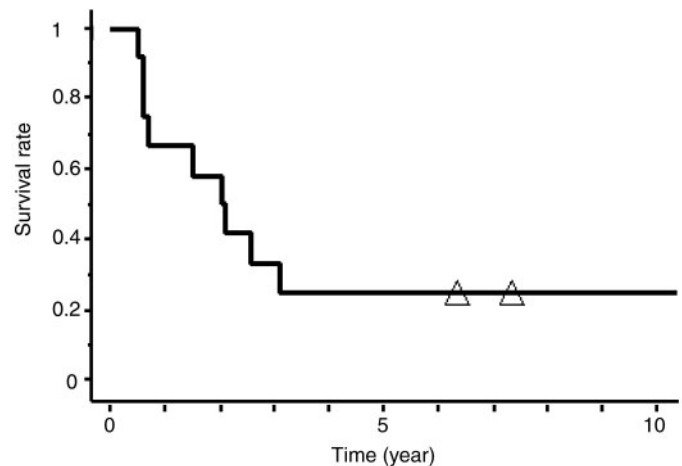
The overall survival was calculated from the start of the treatment, including excisional biopsy, by the Kaplan–Meier non-parametric estimation. Differences between the groups were analyzed by using the log rank test, and significance was defined as a  $P$ -value  $<0.05$ .

## RESULTS

#### SURVIVAL

The median follow-up period of survivors was 82 months. At the end of the study, seven patients had died of their disease within 37 months from the start of the treatment, three had died of other causes, and two patients are alive with no evidence of disease for 88 months in one, and for 76 months in the other. One of the three patients who died from other causes died with a brain infarction 31 months after the initiation of treatment; the cause of death was not confirmed in the other two patients. The survival time of the two patients who were lost to follow-up was 18 and 254 months, respectively. The overall cumulative survival rate at 3 years was 25%, and the median survival time was 24 months (Fig. 1). The treatment outcome is summarized in Table 3.

The six patients with a pathological type of squamous cell carcinoma had a survival rate of 33% at 3 years, and their median survival time was 34 months. The 3-year survival rate and the median survival time of the other six patients were 17% and 21 months, respectively. Patients with squamous cell carcinoma had a better outcome than the others, but the



**Figure 1.** Overall survival rate of 12 patients with thymic carcinoma. The survival rate was calculated by the Kaplan–Meier method. Open triangles represent survivors.

**Table 3.** Results of univariate analysis of different prognostic factors

	No. of patients	3-year survival	MST (months)
Histological type			
SCC (low grade)	6	33%	34
UN (high grade)	6	17%	21
Resection			
Complete	5	40%	31
Incomplete	7	14%	8
Radiotherapy			
Yes	10	33%	28
No	2	0%	12
Chemotherapy			
Yes	4	25%	30
No	8	25%	21

MST, median survival time; SCC, squamous cell carcinoma; UN, undifferentiated carcinoma.

difference between the two groups was not statistically significant ( $P = 0.31$ ).

The resection was complete in five patients, and incomplete in seven patients (partial resection in one, biopsy in six). The overall survival rate at 3 years in the complete resection group was 40%, and the median survival time was 31 months. These results were better than the incomplete resection group (overall survival rate at 3 years 14%, median survival time 8 months).

The overall survival rate of the patients who received radiotherapy was 33% at 3 years, and their median survival time was 28 months, whereas two patients who did not receive radiotherapy died at 6 months from the start of the treatment in one, and 18 months in the other.

When the subjects are limited to the 10 patients who received radiotherapy with curative intent consisting of four patients who underwent complete resection and six who underwent

**Table 4.** Patterns of failure

Patient no.	Age/gender	Stage	Histology	Initial treatment	Recurrence site
1	68/M	III	SCC	Bx-RT (52 Gy)	Pericardium
2	76/M	III	SCC	Bx-chemo-RT (70 Gy)	Pleura
3	39/M	IVa	UN	Chemo-Bx-RT (57.5 Gy)	Locally uncontrolled
4	49/F	IVa	UN	CR-RT (60 Gy)	Distant
5	70/M	IVb	SCC	Bx-RT (60 Gy)	Pleura, pericardium
6	48/F	IVb	UN	CR-RT (60 Gy)	Pleura
7	78/M	IVb	UN	Bx-chemo	Locally uncontrolled

Bx, biopsy; chemo, chemotherapy; CR, complete resection; RT, radiotherapy; SCC, squamous cell carcinoma; UN, undifferentiated carcinoma.

incomplete resection, the overall survival rate at 3 years in the complete resection group and incomplete resection group was 50 and 17%, respectively. The outcome tended to be more favorable in the complete resection group, although the difference was not statistically significant ( $P = 0.20$ ) (data not shown).

The overall survival rate at 3 years and median survival time of the patients who received chemotherapy were 25% and 30 months, respectively, as opposed to 25% and 21 months, respectively, in the patients who did not receive chemotherapy. The difference in survival rate and median survival time between the two groups was not statistically significant ( $P = 0.86$ ).

#### PATTERNS OF FAILURE

Recurrent sites were identified in seven of the 12 patients (58%), and all seven patients died of their disease. Patient characteristics, initial treatment methods and sites of recurrence of these seven patients are shown in Table 4. The major sites of recurrence were the pleura and pericardium (57%). The primary tumor was not controlled in two patients (29%). Six of the 10 patients who received radiotherapy to the mediastinum in the course of the initial treatment developed recurrence. Recurrence within the radiation field was observed in only one patient whose primary lesion was not controlled (patient no. 3 in Table 4). No recurrence at the pericardium or pleura within the radiation field was observed.

#### DISCUSSION

The histological grade of thymic carcinoma is regarded as one of the prognostic factors. Suster and Rosai (3) showed in their analysis of 60 thymic carcinoma cases that histological grade was the most important prognostic factor, and low-grade tumors were characterized by a relatively favorable clinical course. In our series, the six patients with squamous cell carcinoma in the low-grade group had a better outcome than the other six patients with undifferentiated carcinoma in the high-grade group. However, the difference between the two groups was not statistically significant because of the small number of patients.

Thymic carcinoma is a relatively rare neoplasm of the anterior mediastinum, and its true incidence is still unclear (1–3). Because of its rarity, no treatment method has been properly established, and the treatment guidelines established for thymoma are currently being adopted. Surgery is the basic method for treating thymoma, and complete resection is recommended if possible (17). The resection was complete only in five patients in this study, and it was incomplete in the other seven patients. The difference in survival time between the complete and incomplete resection groups was not statistically significant. However, when the subjects were limited to the 10 patients who received radiotherapy in the course of their initial treatment, survival time tended to be more favorable in the complete resection group. These findings support the view that complete resection is as necessary in thymic carcinoma as in thymoma.

Several investigators have reported that postoperative radiotherapy can reduce local failure in thymoma and contribute to the prolongation of survival time (8–11). A total dose of 45–50 Gy is needed for completely resected stage II disease, and a dose of >50 Gy is recommended if the resection is incomplete. However, the role of radiotherapy for thymic carcinoma has not been satisfactorily investigated. Hsu et al. (13) studied 20 cases of thymic carcinoma retrospectively and reported that there was a tendency that favors postoperative radiotherapy, although the data did not reveal a statistical difference in survival time between the radiotherapy group and non-radiotherapy group.

In our study, the patients who received radiotherapy had a better outcome than the patients who did not, although the number of patients was too small. Moreover, no patients who received radiotherapy to the mediastinum in the course of the initial treatment developed recurrence within the radiation field, except one patient in whom the primary lesion was not completely regressed. These findings strongly suggest that radiotherapy plays an important role in treating thymic carcinoma and can reduce local recurrence. Regarding the total dose of radiotherapy for thymic carcinoma, a dose of 60 Gy or more is required for local control, especially in cases with incomplete resection.

In this study, the major sites of recurrence were the pleura and pericardium, hence a novel strategy to reduce

these recurrences is needed. Uematsu et al. (18) reported the efficacy of irradiation of the entire hemithorax for stage II and III thymoma to prevent pleural dissemination. In our series, one patient with stage IVa squamous cell carcinoma received hemithorax irradiation with a dose of 25 Gy in 25 fractions, and he is alive >5 years later without any evidence of recurrence or pulmonary sequela. Thus, hemithorax irradiation may be one of the strategies for reducing intrathoracic relapse, but it has not been completely accepted because of the risk of pulmonary complications.

Chemotherapy may be a key to reduce pleural relapse and manage distant metastasis. Although some investigators have reported that patients who responded to chemotherapy received regimens that included CDDP, the role and regimen of chemotherapy for thymic carcinoma are still controversial (13,19,20). In our study, four patients (33%) received systemic chemotherapy, and in three of them the regimen contained CDDP. However, there was no significant benefit in terms of survival time.

With regard to preoperative therapy, Myojin et al. (12) suggested that preoperative radiotherapy or chemotherapy might increase survival by improving the rate of complete resection and reducing the risk of pleural recurrence after surgery for locally advanced thymoma. In a study by Hsu et al. (13), a patient with stage IVb thymic carcinoma received preoperative radiotherapy and chemotherapy for possible downstaging of the tumor and ultimately underwent successful extended thoracotomy. Based on these findings, preoperative therapy, including radiotherapy and chemotherapy, might be a new approach to improve the outcome of thymic carcinoma.

In conclusion, we have reported the efficacy of radiotherapy for thymic carcinoma in reducing local tumor relapse. The precise role and proper regimen of chemotherapy is still unclear. Further accumulation of clinical experience with this disease and establishment of a treatment protocol are needed.

### Acknowledgments

This work was partly supported by a Grant-in-Aid for Cancer Research 14-9 from the Ministry of Health, Labor and Welfare of Japan. The authors wish to thank Dr Yukio Shimizu, who was on the staff of the Department of Thoracic Surgery, Gunma Prefectural Cancer Center from 1978 to 2001, for his kindness and helpful advice.

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