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Recurrence of Thymoma: Clinicopathological Features, Re-Operation, and Outcome

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Background: Even after complete resection, recurrence of thymoma is not infrequently observed, and treatment of recurrent thymoma remains controversial.
Study Design: One hundred and twenty-six patients underwent surgically complete resection for thymoma, and 24 of them had a recurrence. Surgical treatment of recurrent thymoma was attempted in 15 patients for a total of 18 times. In the present study, the relevance of clinicopathological features and the re-operation on the survival rate after the recurrence were determined.
Results: The most frequent recurrent type was pleural dissemination (92%), with local recurrence observed in 5%. Overall 5- and 10-year survivals after recurrence were 37 and 16%, respectively. Disease-free interval after initial operation and complication of myasthenia gravis had no significant effect on postrecurrent survival. The use of postoperative mediastinal irradiation had no effect on reducing the recurrence rate or improving survival after recurrence. Two of 15 patients who underwent re-operation died of major complications after It. pleuropneumonectomy for severe pleural dissemination. In the present study, the re-operation was not significantly effective for prolongation of postrecurrence survival.
Conclusion: Our study showed that re-operation should not be attempted for all patients with recurrent thymoma. Because effect of subtotal resection for severe pleural recurrence is disappointing, total resection for minimal pleural dissemination or small local recurrence will be undertaken to improve postrecurrent survival. Careful follow-up for >10 years will increase the chance of the total resection of the recurrent thymoma.
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KEY WORDS: **thymoma; recurrence; re-operation; radiotherapy; pleural factor**

INTRODUCTION

Thymoma is the most common neoplasm in the anterior mediastinum, and is known as a low-grade malignant tumor generally associated with a good clinical course after surgical treatment [1, 2]. Recent reports, however, show that recurrence even after complete resection is not uncommon [3–5]. Different from other malignant tumors, the frequency of recurrence with hematogenous metastasis is low, with most recurrent patients showing pleural dissemination or local relapse [3,6]. Many reports have presented a relatively long clinical course after recurrence of thymoma, and indicated the efficacy of re-operation [3,4,7,8]. But because of the limitations of clinical studies in which selection bias is unavoidable, the effect of re-operation on recurrent thymoma is still not confirmed.

In this study, we analyzed a series of recurrent thymoma cases after complete resection focusing on the

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clinicopathological features of thymoma, and re-operation on the survival of patients with recurrent thymoma.

PATIENTS AND METHODS

From 1963 to 1999, 140 thymoma patients underwent surgery at Shinshu University Hospital. One hundred and twenty-six patients underwent surgically complete resection. Twenty-four of these 126 patients developed a recurrence of the initial thymoma, and they represent the population of the present study. There were 14 men and 10 women with a mean age at the time of the original operation of 48 years (range 12–71 years). The surgical approach in the original operation was median sternotomy in all cases. Surgical–pathological staging of the initial thymoma according to Masaoka et al. [1] (Table I) was done (Table II).

In 1996, Haniuda et al. [5] proposed a pathological approach focused on the relation between thymoma and parietal pleura (pleural factor, p) and pericardium (pericardial factor, c) (Table I). They showed that patients with fibrous adhesion (p1/c1) or microscopic invasion to the mediastinal pleura or pericardium (p2/c2) are at increased risk for recurrence. Table III shows the distribution of thymoma patients according to their classification and recurrence rate of each group.

Since 1973, the original operation for all patients with and without myasthenia gravis (MG) has included resection of the thymoma and thymectomy. In this study, Stage IVa patients were classified into a complete resection group when pleural dissemination was macroscopically resected at the original operation. Histologic study of the recurrent patients revealed nine predominantly epithelial, nine mixed lymphoepithelial, five predominantly lymphocytic, and one spindle cell thymoma. Twelve patients (50%) had MG (6 women and 6 men) before the initial operation.

None of the 24 patients received preoperative adjuvant chemo and/or radiotherapy. After the initial operation, 14 of 24 patients received prophylactic mediastinal irradiation but not chemotherapy. The treatment of the recurrent tumor varied according to the extent of the recurrence, the control of MG, and general condition of the patients. In their first recurrence, 22 patients had pleural recurrence, 6 had local, and 5 had distant metastasis (4 lung and 1 bone, Table IV). After the recurrence, radiotherapy as definitive treatment was used in 17 cases (4 for mediastinum and 13 costodiaphragmatic lesions), and 9 patients had adjuvant chemotherapy.

The statistical significance of recurrence proportions was tested with a 2×2 contingency table. Survival and disease free survival were calculated by the methods of Kaplan and Meier and compared by the log-rank test. A probability value of $<5\%$ ($P < 0.05$) was regarded as significant.

RESULTS

Overall 5- and 10-year survivals in the 24 cases from the time of recurrence were 37.1 and 15.9% (Fig. 1).

Clinical Stage and Disease-Free Interval

The recurrence rate of thymoma after complete resection increased according to clinical stage ($P < 0.05$). Analysis of the postrecurrent survival curve between stage II patients ($n = 10$) and stage III + IVa patients ($n = 14$) did not show significant difference (Fig. 2).

Disease-free interval of the 24 patients ranged from 4 to 175 months (mean 68). Although the disease-free interval significantly decreased according to the clinical stage (stage II—112 months, stage III—94 months, stage IV—40 months, $P < 0.01$), disease-free interval shorter or longer than 60 months had no influence on postrecurrent survival (Fig. 3).

Pleural (p) and Pericardial (c) Factors

Table III shows the distribution of the 126 patients according to the pleural (p) and pericardial (c) factor. The recurrence rate significantly ($P < 0.05$) increased by both p and c factors. The p0 patients (35 cases) had no recurrence, and many of the recurrent patients were distributed in p2 and/or c2. In the analysis of the postrecurrent survival curve, no significant differences

TABLE I. Masaoka Staging Systems and Pleural and Pericardial Factors

Criteria of Masaoka clinical stage [1]	
Stage I:	Macroscopically completely encapsulated and microscopically no capsular invasion
Stage II:	1. Macroscopic invasion into surrounding fatty tissue or mediastinal pleura, or 2. Microscopic invasion into capsule
Stage III:	Macroscopic invasion into neighboring organ, i.e. pericardium, great vessels, or lung
Stage IVa:	Pleural or pericardial dissemination
Stage IVb:	Lymphogenous or hematogenous metastasis
Pericardials (p) and pericardial (c) factors [5]	
p0/c0:	No adhesion to the mediastinal pleura (p0)/the pericardium (c0)
p1/c1:	Fibrous adhesion to the mediastinal pleura/the pericardium without microscopic invasion
p2/c2:	Microscopic invasion to the mediastinal pleura/the pericardium

TABLE II. Recurrence of Thymoma According to Clinical Stage

	No. of cases	No. of patients who relapsed	Recurrence rate (%)
Stage I	39	0	0
Stage II	55	10	18
Stage III	26	9	35
Stage IVa	6	5	83*
Total	126	24	19

*Recurrence rate significantly increased with clinical stage ($P < 0.05$).

in survival were observed for these patients having p2 and/or c2 compared with those having less invasive disease (Fig. 4).

Myasthenia Gravis (MG)

In this series of 126 patients, 58 (46%) patients had MG at the original operation, and no patient died of MG after complete resection of the thymoma. Thirteen of the 24 recurrent patients (54%) had MG before the original operation. There is no significant difference in incidence of recurrence between MG and non-MG thymomas. Remission of MG was obtained in five patients and improvement in eight by the original operation. According to the development of recurrence, however, deterioration of the MG was observed in eight patients. The recurrence in seven of the eight patients was noticed because of this deterioration. The analysis of the survival curve between MG and non-MG recurrent thymomas did not show a statistically significant difference in postrecurrent survival (Fig. 5).

Mode of Recurrence and Postoperative Mediastinal Irradiation

Of the 126 patients, 60 patients (47.6%) received adjuvant mediastinal irradiation (Table IV). Pleural cavity is the most common recurrent site (22/24), and local recurrence was observed in six cases. Fewer local recurrences were observed after the adjuvant mediastinal irradiation, but there is no statistically significant effect on the recurrence rate. With or without adjuvant radiotherapy also had no significant effect on postrecurrence survival (Fig. 6).

Re-Operation

Re-operation was done in 15 patients for a total of 18 times. Recurrent thymomas were approached by a posterolateral thoracotomy in 17 operations and median sternotomy in 1. A presumably total resection of the recurrent tumor was obtained in only four cases with minimal pleural dissemination and/or lung metastasis. The remaining 11 patients underwent only a subtotal resection with debulking intent because of the extent of the recurrence. Two of the 15 patients died during the postoperative course (2/15, 13%). Both patients developed severe MG paralleling the recurrence of thymoma, and they required oral administration of daily 50–60 mg prednisolone for more than 1 year before the re-operation. They underwent pleuro-peumonectomy to treat the recurrent tumor and MG, but one patient died of bleeding and the other of respiratory failure due to pneumonia. The remaining 13 patients had no major complications in the postoperative course. Patients who underwent total resection of the recurrent tumor are all alive after an average follow-up period of 48 months. In the survival study, however, re-operation had no beneficial effect on postrecurrent survival (Fig. 7).

DISCUSSION

The surgical approach is still considered the mainstay of thymoma therapy, and complete resection of the thymoma has been found to have a marked effect on the long-term postoperative survival. However, even after complete resection, recurrence of thymoma occurs in 10–29% of patients [2,4,9]. In this study, we observed a 19% (24/126) recurrence rate after total resection. No stage I patients developed recurrence, and the recurrence rate increased with increasing clinical stage. Table III shows the relation between pleural (p) and pericardial (c) factors in the 24 recurrent patients, with the

TABLE III. Recurrence of Thymoma According to Pleural and Pericardial Factors

Pleural factor	No. of cases	No. of patients who relapsed	Recurrence rate (%)
p0	35	0	0
p1	56	5	9
p2	35	19	54*
Pericardial factor	**No. of cases**	**No. of patients who relapsed**	**Recurrence rate (%)**
c0	84	7	8
c1	23	6	26
c2	19	11	58*

*Recurrence rate significantly increased with pleural (p) and pericardial (c) factors ($P < 0.05$).

TABLE IV. Mode of Recurrence After Complete Resection of Thymoma

	Mediastinal irradiation		
	With	Without	Total
No. of patients	60	66	126
No. of recurrent patients	17 (28.3)	7 (10.6)	24 (19.0)
Local	1 (1.7)	5 (7.6)	6 (4.8)
Pleural dissemination	16 (26.7)	6 (9.1)	22 (17.5)
Distant metastasis	4 (6.7)	1 (1.5)	5 (4.0)

Numbers in parentheses indicate the percent frequency of each recurrence type. The types of recurrence overlapped.

recurrence rate significantly increased by these factors ($P < 0.05$). This table reveals that both factors as well as clinical staging are important in predicting the risk of recurrence.

Incidence of recurrence increased according to clinical stage, p and c factors, but these parameters had no significant influence on postrecurrent survival. Furthermore, we did not find an association between longer disease-free intervals and a better survival rate. In the present series, multimodal treatment for the recurrent tumor, including radiation and chemotherapy after recurrence and re-operation, may have some effects on postrecurrent survival rate, and presumably modified the results.

Adequate management of patients with recurrent thymoma, however, is still not established. Second operation is one of the main therapeutic options, and several reports demonstrated the effectiveness of second operation and the less effective nature of nonsurgical therapy [4,7,8]. Furthermore, Ruffini et al. [3] revealed that complete resection of recurrent thymoma offers the best chance for the long-term survival, with subtotal resection usually associated with a poor prognosis, even with the addition of radiation therapy. It should be noted that the

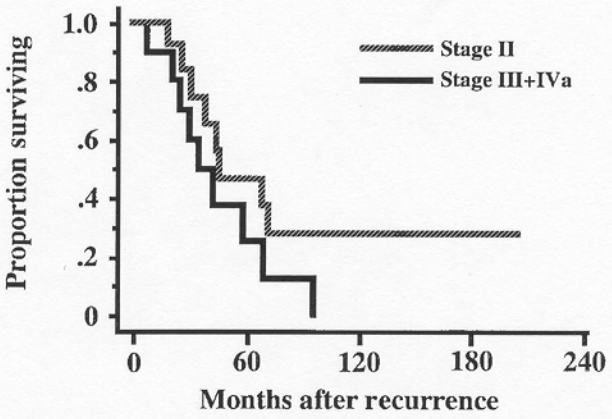

Fig. 2. Survival by the clinical stage; $P = 0.15$.

patients of these series were not randomly recruited for the surgical treatment of recurrent thymoma. Only patients with presumably resectable recurrent tumors were offered surgical treatment, while other patients with supposedly more advanced recurrence or severe MG were given chemo-and/or radiotherapy. This clinical selection bias for re-operation makes it difficult to evaluate the effect of re-operation.

Our results, unfortunately, could not show any significant beneficial effects of re-operation on the survival after recurrence. Five- and 10-year survival rates after re-operation were 46.9 and 35.2% in this study, and are lower than those of some reports from other institutions [3,4,7,8]. On the other hand, it is reported that a poor prognosis is anticipated when radical re-operation is not done [3]. In the current study, we applied re-operation for patients with recurrent tumor to reduce mass volume, or resect the tumor completely if possible. However, only 27% (4/15) of patients underwent complete resection of the recurrent tumor. Furthermore,

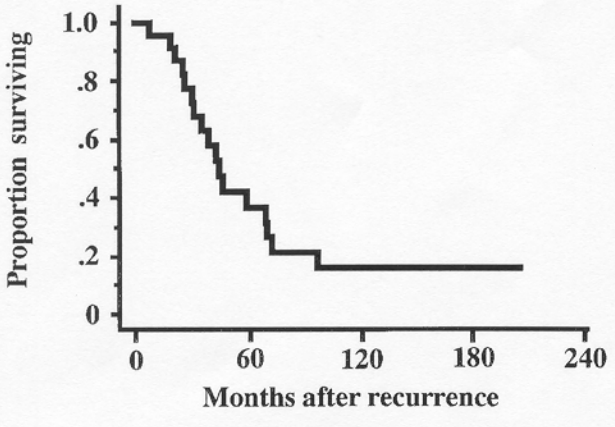

Fig. 1. Overall survival in the 24 cases of recurrent thymoma from time of recurrence to death or most recent follow-up.

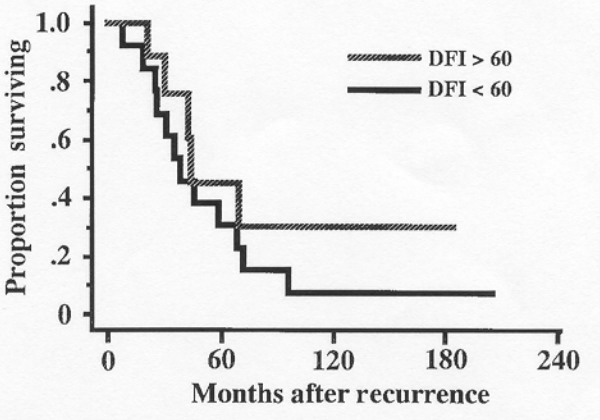

Fig. 3. Survival by the disease-free interval. DFI <60, Disease-free interval from the original operation shorter than 60 months; DFI >60, disease-free interval longer than 60 months; $P = 0.25$.

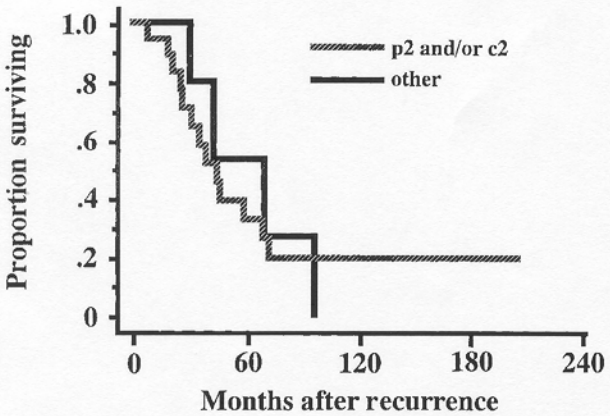

Fig. 4. Survival by the pleural (p) and pericardial (c) factors. Patients with p2 and/or c2 disease at initial resection did not have poorer prognosis than the others. $P = 0.82$.

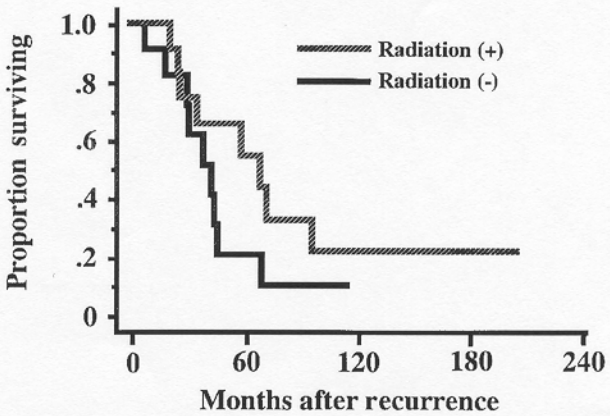

Fig. 6. Survival by presence of associated myasthenia gravis. $P = 0.45$.

two patients who underwent left pleuropneumonectomy for massive pleural dissemination died of postoperative complications, probably due to the high dose of oral steroid administered for MG. Our wide indication for re-operation may result in the lower survival rate in the present study.

Efficacy of surgical approach for patients with pleural recurrence is another problem. It is not questionable that "complete resection" for pleural disease, if possible, is quite effective in prolonging survival. However, total resection of severe intrathoracic dissemination, which is most frequently observed at recurrence, is exceedingly difficult. As in many previous reports [2,4,10], stage IVa patients were classified into the complete resection group in the present study, when pleural dissemination was macroscopically resected completely at the original operation. However, 83% of these patients relapsed within a relatively short disease-free time (average 39.7 months). Blumberg et al. [4] also showed these high recurrence rate (80%) in stage IVa patients even after "complete resection". These data clearly suggest that surgical "complete resection" for pleural dissemination is a considerably uncertain procedure. Because the effect of re-operation for pleural dissemination is still uncertain, excessive surgical intervention should not be undertaken for patients with massive pleural relapse, regardless of the development of severe MG due to the recurrence of thymoma.

Recently, Shin et al. [11] revealed interesting result that aggressive multimodal treatment is highly effective for locally advanced, unresectable thymoma. Their treatment regimen consist of induction chemotherapy (three courses of cyclophosphamide, doxolubicin, cisplatin, and prodnisone), surgical resection, postoperative radiation therapy, and consolidation chemotherapy. In the patients with recurrent thymoma, this multidisciplinary approach

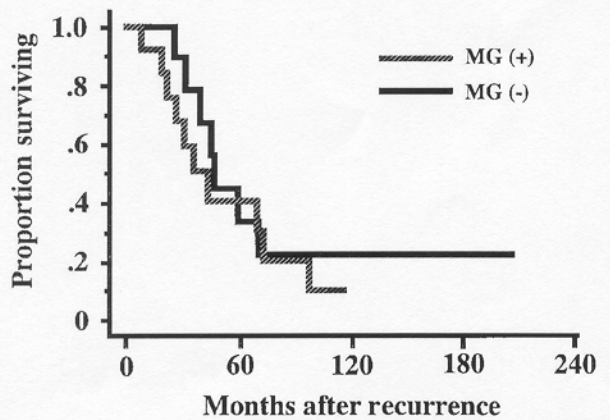

Fig. 5. Survival in cases of recurrent thymoma by the use of adjuvant radiotherapy after the resection of initial thymoma. $P = 0.22$.

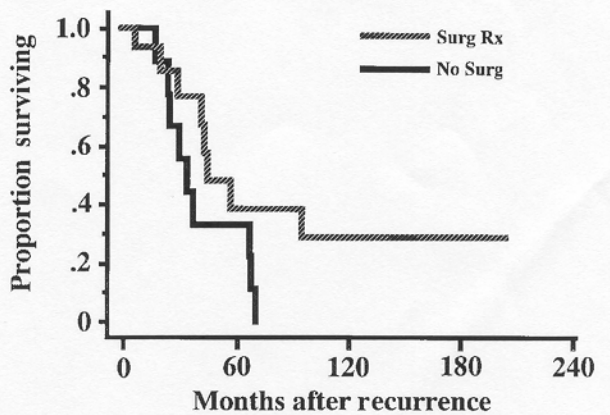

Fig. 7. Survival of patients with recurrence treated by surgical resection (Surg Rx, n = 15), and with recurrence not treated surgically (No surgery, n = 9). $P = 0.08$.

may increase the effect of re-operation and elevate their survival rate.

The average disease-free period of the present report amounted to 68 months. Reports from other institution also show longer disease-free period of around 80 months [3,4]. This long disease-free interval in recurrent cases makes it difficult to conduct regular follow-up and examination of thymoma patients to detect early stage recurrence, i.e., small local recurrence and minimal pleural dissemination. Re-operation for early stage recurrence would possibly increase the survival rate after recurrence. To improve the survival rate after recurrence, therefore, we should make greater efforts to detect recurrences of thymoma in the early stage. Because of the long disease-free interval of more than 5 years, regular follow-up will be necessary for at least 10 years in patients who underwent complete resection for invasive (more than stage II) thymoma regardless of postoperative mediastinal irradiation. Development or deterioration of MG may be a useful clue to the presence of recurrent thymoma.

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