Outcome of Surgical treatment for Recurrent Thymic Epithelial Tumors With Reference to World Health Organization Histologic Classification System

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Background and Objectives: The aim of this study was to clarify the significance of surgical treatment for recurrent thymic epithelial tumors with reference to the World Health Organization (WHO) histological classification system.

Patients: Among 67 patients with tumor recurrence, 22 underwent a re-resection. There were 1 patient with a type AB tumor, 5 with type B1 tumors, 10 with type B2 tumors, 5 with type B3 tumors, and 1 with a carcinoma.

Results: The 10-year survival rate following the initial resection was 70% in patients who underwent a re-resection and 35% in those who did not. The average intervals from the initial resection to re-resection were 10.3, 7.8, 6.0, 2.4, and 2.6 years for patients with type AB, B1, B2, B3 tumors, and carcinoma, respectively. The patient with a type AB tumor was alive at 2.4 years after re-resection, 12.7 years after the initial resection. The 5-year survival rates following re-resection in the patients with type B1, B2, and B3 tumors were 100, 56, and 60, respectively. The patient with a carcinoma died as a result of the tumor 2 years after re-resection.

Conclusion: WHO histological classification indicates the outcome of surgical treatment for recurrent thymic epithelial tumors.


KEY WORDS: thymoma; thymic carcinoma; re-resection

INTRODUCTION

Thymomas and thymic carcinomas are epithelial tumors of the thymus, and representative of neoplasms that arise in the anterior mediastinum. The clinical features of these thymic epithelial tumors are heterogeneity in terms of oncological behavior and an association with paraneoplastic autoimmune diseases, such as myasthenia gravis [1,2].

Recent progress in clinical research of thymic epithelial tumors has been accomplished because of the establishment of the novel histological classification proposed by the World Health Organization (WHO) in 1999 [3], which is based on the ontogenic classification system of Müller-Hermelink et al. [4–6]. According to the WHO classification, thymic epithelial tumors are categorized into types A, AB, B1, B2, B3, and C, and the clinical significance of this classification has been revealed [7–10]. More recently, WHO histological classification of thymic epithelial tumors was modified and type C tumor was finally defined as thymic carcinoma. [11]

The main strategy for treatment of primary thymic epithelial tumors is surgical resection [12–14]; however, tumor recurrence is sometimes encountered even after...
complete resection [15]. Re-resection of recurrent thymomas has been shown to contribute to long-term patient survival in several studies [16–18] and is accepted as an option when a complete resection seems to be attainable.

The WHO histological classification has been shown to reflect the clinical features of primary thymic epithelial tumors and the outcome of surgical treatment; however, there is no known study that focused on the relationship between that classification system and recurrent thymic epithelial tumors. The aim of the present study was to clarify the significance of re-resection for recurrent thymic epithelial tumors from the standpoint of histological background.

**PATIENTS AND METHODS**

We reviewed the records of 395 patients who underwent resections for thymic epithelial tumors at Osaka University Hospital and affiliated hospitals during the 45-year period from 1957 to 2002. Seven patients who underwent a biopsy alone during that period were not included. Of the 395 patients, 67 had tumor recurrence. The tumor stages established according to Masaoka’s classification [12] at the time of initial resection in those 67 patients were stage I in 4 patients, stage II in 6 patients, stage III in 29 patients, stage IVa in 18 patients, and stage IVb in 10 patients. The pathological types according to the WHO histological classification [11] were as follows: 4 patients with type AB, 10 with type B1, 25 with type B2, 15 with type B3, and 13 with carcinoma. Among them, 45 patients died as a direct result of the tumor. The Masaoka stage in those 45 patients were stage I in 3 patients, stage II in 3, stage III in 19, stage IVa in 11, and stage IVb in 9, while WHO histological type classification showed 3 patients with type AB, 3 with type B1, 18 with type B2, 10 with type B3, and 11 with type C.

Surgical treatment was considered as an option even for recurrent thymic epithelial tumors and chosen when determined to be resectable. In total, 22 of 67 patients with tumor recurrence underwent a re-resection procedure.

Adjuvant therapy before or after the initial resection had been given to 16 of these 22 patients, while preoperative chemotherapy, radiation, or both were administered to 6 patients. Further, postoperative adjuvant therapy was administered to 12, radiation therapy to 8, chemotherapy to 1, and both to 3 patients. Two patients underwent both pre- and post-operative adjuvant therapies. Standard chemotherapy protocols for thymic epithelial tumors have not been established, thus the administered reagents differed among the cases, though cisplatin-based chemotherapy was most often chosen, with seven of eight cases receiving that administration. In two of those cases, a combination of cisplatin, Adriamycin, vincristine, and cyclophosphamide (ADOC protocol) was given. The remaining patient underwent an administration of Adriamycin and cyclophosphamide.

The age at first re-resection for recurrent tumor ranged from 29 to 75 years, with an average of 51 years. In all, 8 patients underwent a re-resection twice and 1 patient 3 times, for a total number of 32 re-resections.

No deaths were related to re-resection, though eight patients died from tumor-related causes and one patient from respiratory failure caused by myasthenic crisis. At the final follow-up examination in 2004, 12 patients were alive, though 8 of those had recurrent tumors. One patient with tumor recurrence who survived was lost to follow-up at 1 year 2 months after re-resection.

Actuarial survival rates were calculated using the method of Kaplan and Meier, and statistical difference between survival curves were examined using a log rank test. To focus on oncological behavior, the patient who died of myasthenia gravis was dealt with as a drop-out case at the time of the event. Therefore, survival refers to freedom from tumor death in the present study. Statistical analyses were performed with the commercially available personal computer program SPSS (SPSS, Inc., Chicago, IL).

**RESULTS**

Survival of the entire patient population with tumor recurrence after the initial resection was examined with reference to the presence or absence of a re-resection. As shown in Figure 1, the 10-year survival rate was 70% for patients who underwent a re-resection and 35% for those who did not, which was a significant difference ($P = 0.002$). The clinical characteristics of the 22 patients who underwent a re-resection are shown in Table I along with WHO histologic type. According to Masaoka’s staging system, the primary lesions were in stage III or IV in the majority of our patients (18 of 22, 82%).

![Actuarial survival rates following initial resection according to the presence or absence of re-resection. Survival refers to freedom from tumor death.](image-url)
We previously reported the significance of involvement of the great vessels and completeness of resection as prognostic factors [19]. In the present series, 10 patients had primary lesions that invaded the great vessels. A complete resection was performed in all 6 patients with type AB or B1 tumors, while the resection was incomplete in 2 of 10 patients with a type B2 tumor, in 1 of 5 patients with a type B3 tumor, and in the 1 patient with a carcinoma.

The intervals between the initial resection and re-resection with reference to WHO histological classification are shown in Figure 2. The one patient with a type AB tumor and one patient with a carcinoma underwent re-resection at 10.3 and 2.6 years, respectively, after the initial resection. The mean interval periods were 7.8, 6.0, and 2.4 years in patients with type B1, B2, and B3 tumors, respectively. Among patients with type AB and B1 tumors, three underwent a re-resection more than 10 years after the initial resection, while re-resection was performed within 4 years after the initial resection in all the patients with type B3 and carcinoma.

Completeness of the first re-resection was also examined. Re-resection was incomplete in one patient with a type B1 tumor, who had local recurrence in the mediastinum. Further, the re-resection was incomplete in four patients with type B2 tumors and in one patient with a type B3 tumor, in whom tumor recurrence occurred in the pleural cavity, and four of those had multiple tumors.

Re-resection was performed at least twice in 2 patients (40%) with type B1 tumors, 2 patients (20%) with type B2 tumors, 4 patients (80%) with type B3 tumors, and 1 patient in a carcinoma. The sites of the 32 re-resected tumors are shown in Table II, with the pleura shown to be the most common site of recurrence. In the patients with type B3 tumors, lung metastasis was the most frequent lesion of resection. One patient, whose primary tumor was type AB with stage I disease, had tumor recurrence in the chest wall that occurred at the site of needle biopsy more than 10 years after the initial resection. In that case, recurrence was presumed to have occurred due to tumor implantation at the needle biopsy site prior to the initial operation.

The patient who had the type AB tumor was alive with no evidence of disease at 2.4 years after re-resection, 12.7 years after the initial resection. In the group of patients with type B1 tumors, 2 (40%) were alive with no evidence of disease, 2 were alive with recurrent tumors, and 1 died from a myasthenic crisis. In the group of patients with type B2 tumors, only 1 patient (10%) was alive with no evidence of disease, 4 were alive with recurrent tumors, and these 5 patients had disseminated tumors. Five patients had died from tumor-related disease. In these five patients, two with mediastinal recurrent tumors and one with a disseminated tumor died within 3 years after re-resection. In the group of patients with type B3 tumors, there was no patient alive with no evidence of disease. Three patients were alive with recurrent tumors, and two patients with lung metastasis died as a result of tumors within 3 years after re-resection. The one patient with a carcinoma died as a result of the tumor 2 years after re-resection, which was 4.6 years after the initial resection. The survival rates of patients with type B1, B2, and B3 tumors after the initial resection and after re-resection are shown in Figures 3 and 4, respectively. The 10-year survival rate after the initial operation

<table>
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<tr>
<th>Table I. Clinical Features and WHO Histologic Type for Primary Tumors Resected From 22 Patients Who Underwent Re-Resection</th>
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<tr>
<td><strong>WHO type</strong></td>
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<td>-------------------</td>
</tr>
<tr>
<td>Number of patients</td>
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<tr>
<td>Myasthenia gravis</td>
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<td>Masaoka stage I</td>
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<tr>
<td>II</td>
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<td>III</td>
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<tr>
<td>IVa</td>
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<td>IVb</td>
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<tr>
<td>Involvement of the great vessels Complete</td>
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<td>Subtotal</td>
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<th>Table II. Site of Re-Resected Tumors</th>
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<td><strong>WHO type</strong></td>
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<td>-------------------</td>
</tr>
<tr>
<td>Mediastinum (local)</td>
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<td>Pleura</td>
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RESECTION was 100% in patients with type B1 tumors, 67% in those with type B2 tumors, and 53% in those with type B3 tumors. The 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.

DISCUSSION

Clinical studies of the long-term outcome of re-resection for recurrent thymic epithelial tumors have been limited because of the small number of patients. Regnard et al. published their findings following re-resection of recurrent thymomas in 28 patients, which is the largest known series of recurrent thymomas, and reported overall actuarial survival rates of 51 and 43% after 5 and 10 years, respectively, and actuarial survival rates following complete resection of 64 and 53%, respectively [18]. Ruffini et al. reported re-resections of 16 recurrent thymomas and concluded that surgical resection for local recurrence is recommended when a total resection can be achieved, while the presence of distant metastasis is likely to result in a poor prognosis [16]. Kirschner et al. also reported favorable outcomes following re-resection of recurrent thymomas in the thoracic cavity based on their experiences with seven patients [17]. The present study revealed that the overall 10-year survival (freedom from tumor death) rate after the initial resection was 70% in the re-resected patients and was significantly higher than in the patients who did not undergo surgical treatment for recurrence. Thus, re-resection for recurrent thymoma is considered to be an effective and acceptable option of treatment. It is important to note, however, that the patients who underwent a re-resection in the present study came from a selected group whose recurrent tumors were considered to be resectable.

The significance of histological findings in view of long-term survival after thymoma re-resection has not been reported, and the present is the first study describing the relationships between histological appearance and outcome of surgical treatment for recurrent thymic epithelial tumors. There is some confusion in the histological classification for thymic epithelial tumors, because various kinds of classification systems have been presented [4–6, 20–22]. Our previous clinical study of patients with thymomas revealed that the 20-year survival rate following initial resection was more than 90% for those with type A, AB, and B1 tumors, while that rate declined in the order of type B2 and B3 tumors [9]. Similar findings have been reported by other groups [10, 23–26] and the clinical significance of the WHO histological classification has come to be accepted. Further, studies on the genomes of neoplastic cells have revealed that genetic aberrations increase from type A to carcinoma [27–29], suggesting the genetic significance of this classification system. Therefore, we focused on the relationship between WHO histological subtype and clinical outcome in patients who underwent a re-resection for recurrent tumors in the present study.

In the present series, the interval from the primary operation to re-resection in patients with type B3 tumors or carcinoma was less than 4 years, while in those with type AB, B1, and B2 tumors, it was less than 5 years in five patients, between 5 and 10 years in seven patients, and more than 10 years in four patients. In addition, patients with type AB and B1 tumors lived longer than those with type B3 tumors and carcinoma. These results suggest that type B3 tumors and thymic carcinomas grow faster than type AB, B1, and B2 tumors, as well as the importance of the histological type of the primary tumor for treatment of recurrent thymic epithelial tumors. Re-resection is more likely to result in disease-free survival for patients with type AB and B1 tumors. Long-term survival was also obtained for some of our patients with type B2 and type B3 tumors, and some of those were alive with recurrent tumors at the time of writing, suggesting the significance of re-resection for patients with type B2 and B3 tumors when it is feasible.

An interesting finding in our series is that some patients survived for more than 10 years despite an

CONCLUSION

In the present study, the WHO histological classification of thymic epithelial tumors was shown to indicate the outcome of surgical treatment in patients with recurrent tumors. Recurrence following resection of type AB and type B1 tumors demonstrated a greater chance of treatment by re-resection surgery. In patients with type B2 and type B3 thymomas, re-resection of disseminated tumors is likely to contribute to long-term survival. On the other hand, re-resection of lung metastasis from type B3 tumors and carcinomas fails to achieve long-term survival. Thus, the WHO histological classification should be taken into consideration before deciding treatment for recurrence.

REFERENCES