Surgical Management of Recurrent Thymic Epithelial Tumors

A Retrospective Analysis Based on the Japanese Nationwide Database

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Background: There is no standard treatment for recurrent thymic epithelial tumors. Although the efficacy has not been validated based on the large series studies, surgical resection is sometimes employed for patients with recurrent thymic tumors. The aim of this study is to evaluate the surgical outcomes for recurrent thymic epithelial tumors based on the Japanese nationwide database.

Methods: From the database of patients whose thymic epithelial tumors were treated surgically from 1991 through 2010, the cohort who developed recurrence after the initial resection was extracted. Clinicopathological factors were reviewed, and the prognostic factors of re-resected cases were examined.

Results: Twenty-eight hundred thirty-five patients who underwent surgical resection of thymic epithelial tumors were registered to the database. Among these patients, 420 (14.8%) experienced recurrence. One hundred sixty-two patients were treated surgically and 243 were treated nonsurgically for recurrent disease. The 5- and 10-year postrecurrence survival rates were 82.7% and 68.2%, respectively, in the surgery group and 43.5% and 25.4%, respectively, in the nonsurgery group ($p < 0.001$). According to univariate analyses, female sex and the pathological Masaoka I-II stage, nonthymic carcinoma, absence of preoperative treatment and longer recurrent-free interval (RFI) were significantly favorable factors for survival in the surgery group. According to the multivariate analysis, nonthymic carcinoma histology and longer RFI were identified to be independent prognostic factors.

Conclusions: The surgical outcomes of recurrent thymic epithelial tumors are favorable in selected patients. The role of re-resection may be limited in the setting of thymic carcinoma and/or a short RFI.

Key Words: Recurrent thymic epithelial tumors, Thymic cancer, Thymoma, Surgical resection, Disease-free interval.

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Thymic epithelial tumors are rare neoplasms, reported to account for 50% of the anterior mediastinal masses. In particular, the incidence of thymomas, which comprise a major portion of thymic epithelial tumors, is 0.15 per 100,000 person-years.[1–3] Tumors of this entity exhibit a heterogeneous malignant potential with progression, and clinicians often encounter long-term survivors who experience recurrence after the initial complete resection. Recurrence is often observed at local, regional, or distant sites in patients with other malignancies, including lung cancer. However, surgical resection of recurrent lesions is employed as a treatment option in such patients, although the efficacy and indications have not been elucidated. One possible reason for the lack of data regarding this issue is the rarity of these tumors, with only small series being evaluated in previous reports. Accordingly, an analysis of this issue in a large cohort is required.

The aim of this study was to analyze the outcomes of patients with thymic epithelial tumors who were surgically treated for recurrent disease after the initial resection and discuss the contribution of surgical intervention for recurrent disease based on the data found in the Japanese nationwide database.

MATERIALS AND METHODS

A Japanese nationwide registry study of thymic epithelial tumors was carried out by the Japanese Association for Research on the Thymus. The medical data of 2835 patients with thymic epithelial tumors treated surgically during the period from 1991 through 2010 were retrospectively collected and registered from 32 Japanese institutes. Seventy-eight variables, including patient demographics, clinical

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diagnosis, surgical procedure, pathological diagnosis, perioperative therapy and outcomes, were investigated. With regard to diagnosis of recurrence, the follow-up schedule and the introduced modalities depended on the respective institutions. The histological diagnoses were made according to the World Health Organization (WHO) classification of thymic epithelial tumors, and the stage of disease was determined based on the revised Masaoka staging system.[1,4]

In the present study, 420 patients who experienced recurrence after the initial resection were extracted from the entire cohort, as records concerning recurrence were not complete in 194 patients. Recurrence was defined as the clinical detection of new lesions after complete resection of the primary tumor and as the detection of new lesions and progression of residual diseases after incomplete resection. Fifteen patients without information regarding the presence of redo surgery were excluded to investigate the contribution of surgery to the survival of patients with recurrence.

Recurrence-free interval (RFI) was defined as the duration between the date of initial surgery for the primary tumor and the date of detection of recurrence. Postrecurrent survival time was calculated from the date of diagnosis of recurrence to the date of either death or the last follow-up. Categorical variables in each group were compared using the χ^2 test or Fischer's exact test. Survival curves were created according to the Kaplan–Meier method, with differences examined using the log-rank test. A multivariate analysis of prognostic factors in the re-resected cases was performed using a Cox proportional hazard model. The statistical analyses were carried out using the SPSS software package for Windows (version 12.0; Chicago, IL). In both the univariate and multivariate analyses, a p value of less than 0.05 was considered to be significant. This nationwide registry study was approved by the institutional review board of each participating institution, including Nagoya University Hospital.

RESULTS

The median follow-up period after diagnosis of recurrence was 59.8 months among all 405 patients and 73.3 months among the 267 surviving patients.

The patient demographics are shown in Table 1. The mean age of the patients at the time of initial resection was 54.8 years. The majority of the patients had advanced disease of stage III or IV (n = 329; 81.2%) and tumors of type B3 thymoma or a carcinoma histology (n = 235; 58.0%), which usually represented an aggressive behavior. The initial resection resulted in R0 in 254 patients (62.7%). A repeated resection was performed in 162 patients (40.0%) for recurrent disease (surgery group), whereas the remaining 243 patients (60.0%) were treated nonsurgically (nonsurgery group). In the nonsurgery group, 42 patients received chemoradiotherapy, 75 received chemotherapy, and 77 received radiotherapy for their recurrent disease. Ninety-one patients received supportive care.

Comparing the patient demographics of the surgery and nonsurgery groups, the mean age of the patients was lower in the surgery group (p = 0.408). The distribution of the WHO histologic classification also differed between the two groups ($p < 0.001$); more patients with a carcinoma histology were included in the nonsurgery group. Preoperative adjuvant therapy was introduced in the initial treatment regimen more frequently in the nonsurgery group (37.4% versus 25.9%, p = 0.017). Postoperative adjuvant therapy was also introduced more frequently in the nonsurgery group (27.6% versus 20.3%, p = 0.126). Fifty-three of 149 patients (35.6%) with incomplete resection at initial surgery received that treatment. In terms of the completeness of the initial surgery, a superior success rate was observed in the surgery group than in the nonsurgery group. Seventy-two percent of the patients underwent complete resection in the surgery group, whereas 56.8% of the patients received this treatment in the nonsurgery group. The RFI after the initial resection was longer in the surgery group than in the nonsurgery group, at 3.2 and 2.2 years, respectively ($p < 0.001$).

The most frequent metastatic site was the pleura, in which 219 patients (54.1%) experienced disease recurrence, followed by the lungs (21.0%) and the local sites (17.3%). The prevalence of metastasis to the bone and liver was significantly higher in the nonsurgery group. In the surgery group, more patients exhibited recurrence in the pleura, which was considered to be a favorable indication for resection. On the other hand, a limited number of patients, including four patients with bone metastasis, two patients with liver metastasis and one patient with brain metastasis, underwent surgical resection for recurrence (Table 1). Regarding the number of metastatic sites, a large portion of the patients (90.7%) developed single-site recurrence in the surgery group, compared with 76.1% of the patients in the nonsurgery group. Among the 147 patients with single-site recurrence in the surgery group, 85 (57.8%) exhibited pleural dissemination, followed by 24 (16.3%) with pulmonary metastasis and 20 (13.6%) with local disease.

The 5- and 10-year survival rates of all patients with recurrence were 59.9% and 42.5%, respectively (Fig. 1*A*). According to histology, the 5- and 10-year survival rates of thymoma patients were 76.2% and 50.0%, respectively, and those of thymic carcinoma patients were 30.8% and 28.2%, respectively ($p < 0.001$) (Fig. 1*B*). Although prevalence of re-resection was less frequent in Type B2-3 thymoma compared with Type A-B1 thymoma (47.6% versus 56.9%, p = 0.231), the WHO histological classification of thymoma did not demonstrate any significant trends with respect to the survival outcomes. The survival of the surgery group was significantly better than that of the nonsurgery group, with 5- and 10-year survival rates of 82.7% and 68.2%, respectively, in the surgery group and 43.5% and 25.4%, respectively, in the nonsurgery group ($p < 0.001$) (Fig. 2*A*). The trend that survival of the surgery group was significantly better than those with the nonsurgery group was also observed in subgroup analyses according to the completeness of initial resection for the primary tumor (Fig. 2*B*, *C*). According to a subgroup analysis of the thymoma and thymic carcinoma cases, the superiority of survival of the surgery group over the nonsurgery group remained for each histology ($p < 0.001$, p = 0.018, respectively). In addition, an analysis of the completeness of re-resections showed a survival advantage among the patients

TABLE 1. Patients Demographics

	Total		NonSurgery		Surgery		
Variables	**405**	**%**	**243**	**%**	**162**	**%**	***p***
Age (year)	54.8±13.9		57.1±13.5		51.4±13.9		0.408
Sex (male/female)	220/185	53.0/47.0	139/104	57.2/42.8	81/81	50.0/50.0	0.156
Masaoka stage							<0.001
I	22	5.4	6	2.5	16	9.9	
II	53	13.1	20	8.2	33	20.4	
III	153	37.8	91	37.4	62	38.3	
IVa	105	25.9	71	29.2	34	20.9	
IVb	71	17.5	55	22.7	16	9.9	
Unknown	1	0.3	0	0	1	0.6	
Histologic type							<0.001
A	7	1.7	3	1.2	4	2.5	
AB	14	3.5	7	2.9	7	4.3	
B1	37	9.1	15	6.2	22	13.6	
B2	106	26.2	54	22.2	52	32.1	
B3	79	19.5	43	17.7	36	22.2	
Cancer	156	38.5	118	48.6	38	23.5	
Others	6	1.5	3	1.2	3	1.8	
Myasthenia gravis	54	13.3	24	9.9	30	18.5	0.017
Preoperative treatment	133	32.8	91	37.4	42	25.9	0.017
Postoperative treatment	100	24.7	67	27.6	33	20.3	0.126
Postrecurrence nonsurgical treatment	241	59.5	152	62.6	89	54.9	0.126
Completeness of the initial surgery							0.009
R0	254	62.7	138	56.8	116	71.6	
R1	64	15.8	44	18.1	20	12.3	
R2	85	20.9	60	24.7	25	15.4	
Unknown	2	0.6	1	0.4	1	0.7	
Recurrent-free interval (year)	2.7±2.3		2.2±2.4		3.2±2.8		<0.001
No. of recurrent sites	1.3±0.7		1.4±0.7		1.3±0.7		0.165
Recurrent site							
Local	70	17.3	44	18.1	26	16.0	0.688
Pleura	219	54.1	132	54.3	97	59.9	0.067
Pericardium	9	2.2	7	2.9	2	1.2	0.326
Lung	85	21.0	53	21.8	32	19.8	0.709
Bone	26	6.4	22	9.1	4	2.5	0.007
Liver	15	3.7	13	5.3	2	1.2	0.033
Brain	5	1.2	4	1.6	1	0.6	0.652
Others	60	14.8	44	18.1	16	9.9	0.023

treated with R0-1 and R2 re-resections compared with that observed in the nonsurgery group ($p < 0.001$, $p = 0.004$) (Fig. 3*A*). A significant survival advantage was also noted among the patients treated with R0-1 re-resection compared with that observed in the nonsurgery group for each histology ($p < 0.001$, $p = 0.014$) (Fig. 3*B*, *C*). Meanwhile, the survival of the patients treated with R2 re-resection was intermediate between that of the patients treated with R0-1 re-resection and that observed in the nonsurgery group for thymomas, although the difference between the patients treated with R2 re-resection and the nonsurgery group was not significant for either histology ($p = 0.143$ and 0.809, respectively). The results of the univariate analyses and estimated postrecurrence survival rates of the surgery group according to each variable are presented in Table 2. These analyses demonstrated that female sex and the Masaoka I-II stage, nonthymic carcinoma, use of preoperative treatment and longer RFI (≥3 years) were significant prognostic factors in the surgery group, whereas the completeness of re-resection was not identified to be a significant factor ($p = 0.385$). Regarding the patients with single-site recurrence, the 5- and 10-year survival rates of the patients with pleural dissemination were 90.6% and 66.9%, respectively, which indicated a trend toward a more favorable survival compared with that observed in the patients with recurrence at the other sites (data not shown).

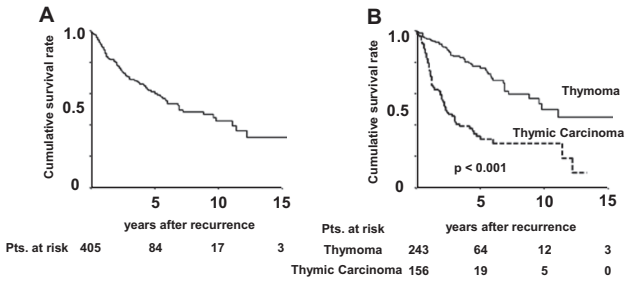

FIGURE 1. *A,* Overall survival after recurrence among the patients with recurrent thymic epithelial tumors, and (*B*) thymoma and thymic carcinoma. Pts, patients.

With regard to the extrathoracic metastases including those in the bone, liver, and brain, we identified six patients who underwent resection for their recurrences. Postrecurrence survival of them ranged from 0.7 to 4.8 years. Four patients were alive with disease, one was alive without disease, and one died of disease.

Furthermore, the multivariate analysis showed the WHO histologic type (nonthymic carcinoma) and longer RFI to be favorable prognostic factors in the patients who underwent surgery for recurrent disease (Table 3).

DISCUSSION

Thymic epithelial tumors are rare neoplasms, with recurrence after resection observed in 7% to 22.3% of the patients.[5–7] Our rate of 14.8% among the entire cohort is consistent with the findings of the previous reports. It has been demonstrated that the proportion of patients exhibiting recurrence is increased among those with advanced thymoma. For example, 5% to 10% of the patients with stage I or II disease experience recurrence, whereas this proportion is elevated, at approximately 30%, among those with more advanced stages of the disease.[8] Okumura et al.[9] reported that the incidence of tumor recurrence is closely correlated with the WHO histologic type of thymoma, which reflects the oncologic nature of the tumor; that is, the authors documented failure of surgical treatment in as many as 28.6% of the patients with resected type B3 thymoma. Thymic carcinoma is known to exhibit a more aggressive behavior and is considered to be a distinct subtype to thymoma, with recurrence reported in more than half of the affected patients.[5]

To date, several reports, including small series, have documented the outcomes of surgical management of recurrent thymic epithelial tumors. However, the efficacy of this modality remains controversial. In the present study, we aimed

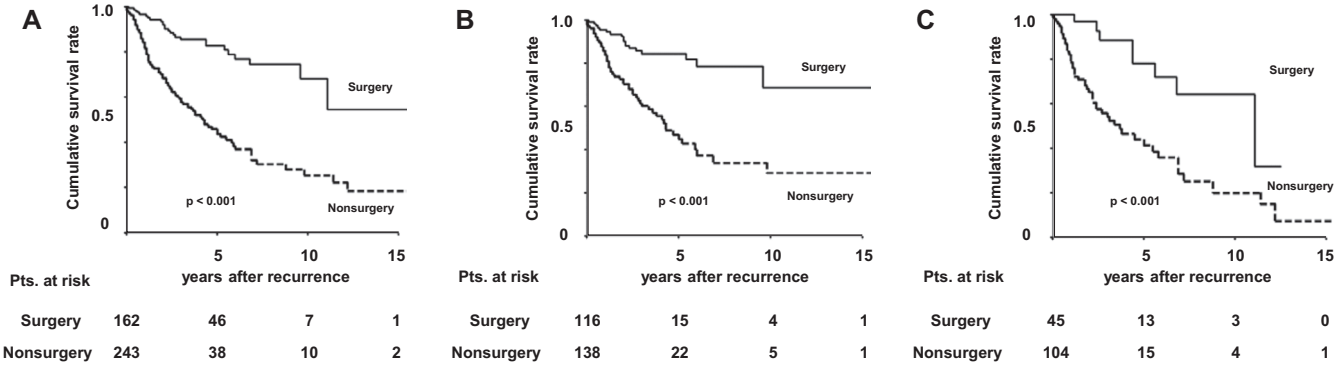

FIGURE 2. *A,* Overall survival after recurrence among the patients with recurrent thymic epithelial tumors, (*B*) thymic epithelial tumors treated with complete resection of the primary tumor, and (*C*) thymic epithelial tumors treated with incomplete resection of the primary tumor according to the treatment for recurrence. Pts, patients.

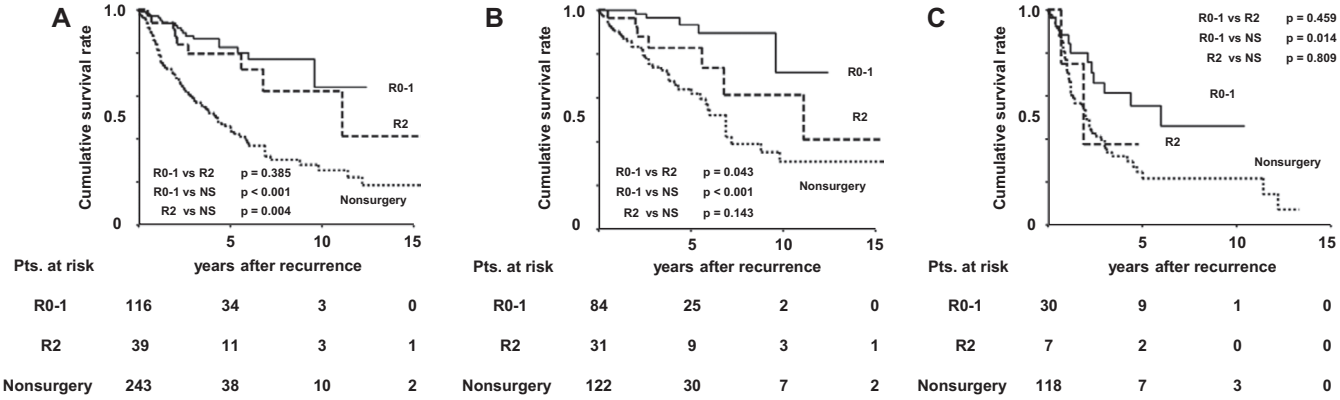

FIGURE 3. *A,* Overall survival after recurrence among the patients with recurrent thymic epithelial tumors, (*B*) thymoma, and (*C*) thymic carcinoma according to the treatment and completeness of re-resection for recurrence. Pts, patients; R0, no residual recurrent tumor; R1, microscopic residual recurrent tumor; R2, macroscopic residual recurrent tumor.

TABLE 2. Univariate Analysis of Prognostic Factors in Patients with Resected Recurrent Thymic Tumors

Variables	*n* = 162	Five-Year Survival (%)	Ten-Year Survival (%)	*p*
Sex				
Male	81	74.6	60.4	0.036
Female	81	90.5	76.7	
Age				
<50	65	86.7	59.3	0.525
≥50	92	78.8	69.6	
Masaoka stage				
I–II	49	89.5	89.5	0.033
III–IV	112	79.3	56.7	
Unknown	1			
Histologic type				
A–B3	121	92.0	73.7	< 0.001
Cancer	38	53.4	44.5	
Others	3			
Myasthenia gravis				
Present	30	95.6	86.1	0.292
Absent	132	79.6	65.3	
Preoperative treatment				
Present	42	73.4	51.5	0.025
Absent	120	85.8	75.3	
Postoperative treatment				
Present	88	77.6	62.1	0.097
Absent	74	85.8	80.5	
Postrecurrence nonsurgical treatment				
Present	33	77.6	62.1	0.097
Absent	129	91.2	80.5	
Completeness of the initial surgery				
Complete (R0)	115	84.4	68.7	0.565
Incomplete (R1-2)	45	78.0	64.0	
Unknown	1			
Recurrent-free interval (year)				
<3	92	76.9	55.6	0.012
≥3	65	90.3	90.3	
Unknown	5			
No. of recurrent sites				
One	147	84.3	68.1	0.219
Two or more	15	70.1	—	
Re-reresection				
Present	43	82.0	82	0.421
Absent	114	83.5	61.6	
Unknown	5			
Completeness of re-resection				
R0-1	116	82.5	64.1	0.385
R2	39	79.7	62.1	
Unknown	7			

to examine the surgical outcomes of treatment for recurrent thymic epithelial tumors based on a large cohort recruited from the Japanese nationwide database. Most previous reports have supported the presence of an association between surgical resection and survival as a treatment for recurrent thymic tumors compared with that observed in nonsurgical cases. For example, Margaritora et al.[10] showed a significant survival difference between patients treated with repeated surgery and those treated without surgery among subjects with recurrent thymoma, with 5-year survival rates of 77% and 35%, respectively. Bott et al.[7] also recently reported 5-year survival rates of surgery and nonsurgery cases of 82% and 58%, respectively.

TABLE 3. Multivariate Analysis of Prognostic Factors in Patients with Resected Recurrent Thymic Epithelial Tumors

Variables	Reference	HR	95% CI	*p*
Sex (male)	Female	1.92	0.801–4.585	0.144
Stage (I–II)	Stage III–IV	0.64	0.199–2.085	0.463
Histologic type (thymic carcinoma)	Others	3.23	1.392–7.518	0.006
Preoperative treatment (present)	Absent	1.657	0.695–3.951	0.255
Recurrent-free interval		0.744	0.565–0.979	0.035

HR, hazard ratio; CI, confidence interval.

Although the potential contribution of repeated resection for recurrent thymic tumors was suggested in these reports, the authors also emphasized the importance of patient selection. On the other hand, Haniuda et al.[11] did not find any significant survival benefits of repeated resection, reporting a 5-year survival rate of 46.9% among patients treated with repeated resection, which is lower than that of other reports. In their study, the authors referred to their low complete resection rate of 27% for recurrent disease and the possible inclusion of patients with a poor prognosis. In the present study, the 5- and 10-year survival rates were 82.7% and 68.2%, respectively, in the surgery group and 43.5% and 25.4%, respectively, in the nonsurgery group, which also supports the finding of improved survival among selected patients treated with repeated resection. As shown in Table 1, the patient demographics differed according to the Masaoka stage, WHO histological type, presence of MG, use of preoperative treatment and completeness of the initial surgery between the two groups. Although these differences may reflect the effects of patient selection with respect to the indications for repeated resection, we were unable to identify such candidates clearly due to our study design, which was based on the retrospective database.

In the present study, we demonstrated the survival advantage of re-resected thymic tumor, even in the patients with R2 re-resection of recurrent disease. Although survival of patients with R0-1 re-resection seemed to be slightly better than that with R2 re-resection, we did not detect a statistical difference as presented in Figure 3*A*. However, survival of the patients with R0-1 re-resection was significantly better than that with R2 re-resection, survival of patients treated with R2 resection was intermediate between R0-1 and nonsurgery in thymoma cases. We consider that these results suggested potential efficacy of debulking in thymoma cases, and not in thymic carcinoma cases. These biological differences between the two entities of the tumor and the small sample size might lead to failure in detecting statistical difference in the whole recurrent cases. We herein identified the nonthymic carcinoma histology and longer RFI to be the favorable prognostic factors among the patients with resected recurrent thymic epithelial tumors. Meanwhile, a comparison of patterns of recurrence of thymoma and thymic cancer revealed some differences between these two groups.[12] For example, thymic carcinoma presents more frequently with distant failure in addition to a shorter RFI and earlier onset of recurrence than thymoma, which appears to confirm the more aggressive nature of thymic carcinoma. Hamaji et al.[13] also found the WHO histology to be a significant prognostic factor after recurrence in a study of 48 patients with recurrent disease. In that report, the authors suggested that surgical management is associated with better survival rates among patients with recurrent thymoma, although the role of this modality is limited in those with thymic carcinoma. Our current results seem to support their conclusion, and therefore, careful patient selection, especially in cases of thymic carcinoma, is required.

Although RFI is generally considered to be a predictive factor of survival among patients with recurrent malignancies, several reports have failed to prove a significant association between RFI and survival in thymic epithelial tumors. One reason for the previous results is thought to be brought about by the small number of each study, which may be associated with a poor statistical power to detect significant differences.[11,14,15] Biologically, this factor may represent a phenotype of less aggressive thymic tumors.

As to the site of recurrence, more than half of the resected patients evaluated in this study experienced recurrence in the pleura, which was also the most frequent metastatic site. Limited to the cases of single-site recurrence, this site accounted for 57.8% of the cases (85 of 147 patients), with a favorable survival among the resected cases. Although there is currently no standard treatment for pleural recurrence, repeated resection is considered to be an acceptable option. According to a report by Lucchi et al.[16], the resection of pleural metastases may thus make it possible to achieve paraneoplastic syndrome control in addition to improving the survival outcome.

Due to the study design based on the retrospective database, our study includes several limitations. First, our study cannot exclude selection bias completely, and it subsequently led to the subtraction of patients with better prognosis for surgery case and to heterogeneous diagnosis of progression, which means that the modality used in the diagnoses of recurrence and the definition of recurrence may depend on the respective institutions. The lack of central pathology review may be also another limitation. It is well known that the distinction between thymic carcinoma and B3 thymona is challenging even for expert pathologists in diagnosis of thymic tumors. We should also remind that the pathological diagnoses in our study may impact our results strongly.

In conclusion, we demonstrate the survival advantages of patients who underwent surgical treatment for the recurrent lesions from thymic epithelial tumors, in comparison with the survival outcome obtained in patients treated nonsurgically. Therefore, re-resection can be indicated for selected patients in the management of recurrent disease after the initial surgical treatment for thymic epithelial tumors.

However, the efficacy of this modality is limited in patients with thymic carcinoma and/or a short RFI. Therefore, a multimodal approach should be considered in such cases.

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REFERENCES

1. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. *Cancer* 1981;48:2485–2492.
2. Blumberg D, Port JL, Weksler B, et al. Thymoma: a multivariate analysis of factors predicting survival. *Ann Thorac Surg* 1995;60:908–913.
3. Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and associations with subsequent malignancies. *Int J Cancer* 2003;105:546–551.
4. Masaoka A, Yamakawa Y, Niwa H, et al. Thymectomy and malignancy. *Eur J Cardiothorac Surg* 1994;8:251–253.
5. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. *Ann Thorac Surg* 2003;76:878–884.
6. Ströbel P, Bauer A, Puppe B, et al. Tumor recurrence and survival in patients treated for thymomas and thymic squamous cell carcinomas: a retrospective analysis. *J Clin Oncol* 2004;22:1501–1509.
7. Bott MJ, Wang H, Travis W, et al. Management and outcomes of relapse after treatment for thymoma and thymic carcinoma. *Ann Thorac Surg* 2011;92:1984–1991.
8. Ruffini E, Mancuso M, Oliaro A, et al. Recurrence of thymoma: analysis of clinicopathologic features, treatment, and outcome. *J Thorac Cardiovasc Surg* 1997;113:55–63.
9. Okumura M, Shiono H, Inoue M, et al. Outcome of surgical treatment for recurrent thymic epithelial tumors with reference to world health organization histologic classification system. *J Surg Oncol* 2007;95:40–44.
10. Margaritora S, Cesario A, Cusumano G, et al. Single-centre 40-year results of redo operation for recurrent thymomas. *Eur J Cardiothorac Surg* 2011;40:894–900.
11. Haniuda M, Kondo R, Numanami H, Makiuchi A, Machida E, Amano J. Recurrence of thymoma: clinicopathological features, re-operation, and outcome. *J Surg Oncol* 2001;78:183–188.
12. Huang J, Rizk NP, Travis WD, et al. Comparison of patterns of relapse in thymic carcinoma and thymoma. *J Thorac Cardiovasc Surg* 2009;138:26–31.
13. Hamaji M, Allen MS, Cassivi SD, et al. The role of surgical management in recurrent thymic tumors. *Ann Thorac Surg* 2012;94:247–54; discussion 254.
14. Yano M, Sasaki H, Moriyama S, et al. Number of recurrent lesions is a prognostic factor in recurrent thymoma. *Interact Cardiovasc Thorac Surg* 2011;13:21–24.
15. Bae MK, Byun CS, Lee CY, et al. Clinical outcomes and prognosis of recurrent thymoma management. *J Thorac Oncol* 2012;7:1304–1314.
16. Lucchi M, Davini F, Ricciardi R, et al. Management of pleural recurrence after curative resection of thymoma. *J Thorac Cardiovasc Surg* 2009;137:1185–1189.

