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Number of recurrent lesions is a prognostic factor in recurrent thymoma

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Abstract

In advanced stage thymomas, recurrence is not uncommon but prognostic factors in recurrent thymoma have not been determined and standardized treatment for recurrence has not yet been established. A retrospective analysis was conducted on 24 thymoma patients who underwent treatment for recurrence in our institution to determine the prognostic factors for overall survival. Recurrence of thymoma appeared 11.6—109.6 months after the primary operation (34.6±25.7 months). Pleural disseminated recurrence was common (n=21) as the primary recurrent lesions. Single or combined modality therapy was performed in 19 patients; surgical resection in 12, radiotherapy in 10, and chemotherapy in six patients. A third surgical resection was performed in two patients. There was no difference in overall survival between the groups with or without treatment nor in those with or without resection. Old age and chemotherapy were factors for poorer prognosis. Patients with one or two recurrent lesions detected on CT examinations showed better prognosis. Prognosis in thymoma patients with recurrence was reviewed in the present study. Patients with a small number of recurrent lesions showed better prognosis irrespective of the treatment.

Keywords: Thymoma; Recurrence

1. Introduction

Thymoma is the most common tumor of the anterior mediastinum. The neoplasm arises from thymic epithelial cells, and is associated with non-neoplastic T lymphocytes to varying degrees. Surgical resection has been advocated as the principal treatment and completeness of resection has been considered to be the most important determinant of long-term survival in thymomas [1—3]. In advanced stage thymomas, recurrence is not uncommon and surgical resection or radiotherapy (RT) is often selected for treatment. Some reports of treatment for recurrences in thymoma have been presented [4—6]. Complete resection of the recurrent lesions seemed to be more effective for survival than incomplete resection [4, 5]. RT, also, may be effective for recurrence [5, 7]. However, the efficacy of surgical resection or other modalities remains uncertain [6].

In the present retrospective study, 25 thymoma patients with recurrences were reviewed to analyze clinicopathological factors in recurrent thymoma, to study the efficacy of each modality for recurrent thymoma, and to determine the prognostic factors.

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2. Patients and methods

A retrospective review was conducted of clinical and pathological data in all thymoma patients undergoing treatment at Nagoya City University Hospital between January 1994 and December 2009. During this time period, 159 patients underwent macroscopically total resection for thymoma. In 24 of these, recurrences were observed.

The present study was approved by the Institutional Review Board (IRB) of Nagoya City University Hospital.

There were no strict rules for postoperative follow-up in thymoma patients. However, it was common practice to obtain a chest-RT every three or four months and a chest computed tomography at least once a year. In advanced thymoma, chest computed tomography examination has been performed twice a year. This frequency of follow-up imaging was similar to recommendation as reported [8].

2.1. Statistical analysis

Survival analysis was performed by the Kaplan–Meier method and univariate log-rank test. A outcome measure was utilized with overall survival [8] and it was calculated from the primary diagnosis of thymoma to death. Disease free interval (DFI) was calculated from the date of the primary surgery to the date of the first radiographic study demonstrating recurrent disease or most recent study dem-

onstrating absence of disease [8]. Statistical significance was defined as $P<0.05$.

3. Results

3.1. Clinical and pathological data (Table 1)

There were 12 males and 12 females, with a mean age of 52 years ranging between 30 and 80 years. Six patients were complicated with myasthenia gravis (MR), four with pure red cell aplasia (PRCA) and one patient with myotonic dystrophy. Masaoka–Koga staging system [9] was utilized for staging in the present study. Masaoka–Koga staging system [9] which was modified with Masaoka staging system [1] has been recommended by the International Thymic Malignancy Interest Group (ITMIG) [8]. At the time of the primary operation, eight patients were diagnosed as stage III, 11 as stage IVa, and five as stage IVb.

All patients basically underwent extended thymothymomectomy at the primary operation. In stage III disease, resection of involved organs was performed. When all of the disseminated nodules were resected macroscopically in patients with pleural dissemination, the operation was regarded as a subtotal resection and included in the present study. All patients underwent macroscopically total resections ($n=24$) of the tumor. Of these, 12 patients had T4 disease (pleural dissemination) and diagnosed as stage IVa ($n=10$) and IVb ($n=2$) and all disseminated nodules have been resected completely. Postoperative adjuvant radiation was performed in 18 patients. One patient underwent postoperative adjuvant chemotherapy with carboplatin and gemcitabine.

3.2. Recurrence and treatment

Recurrence of thymoma appeared 11.6–109.6 months after the primary operation. Mean DFI was 34.6±25.7 months. Primary recurrent lesions were disseminated pleural nodules in 21 patients, pulmonary metastasis in one patient, retroperitoneal lymph node metastasis in one patient, and local recurrence in one patient. The number of recurrent lesions (NRL) was counted on a CT at the beginning of treatment. The mean number of lesions was 5.2 (1–34) ($n=24$). Actual NRL found at an operation ($n=12$) was 9.8 (1–52). There were 1.88 times more lesions diagnosed intraoperatively when compared with the counts on a CT.

Single or combined modality therapy were selected in 19 patients; surgical resection in 12 patients, RT in 10 patients, and chemotherapy in six patients. Primary regimen of chemotherapy was cisplatin alone in two patients and carboplatin and paclitaxel in five patients. Five patients were followed without treatment for the recurrent lesions. The interval between the primary and second operations was 33.9±17.1 months (range: 12.4–58.3) ($n=12$). A third surgical resection was performed in two patients. The interval between the second and third operations was 21.2±4.5 months (range: 18.0–24.3) ($n=2$).

3.3. Prognosis and prognostic factors

The observation period was from 26.8 to 187.1 months after the primary operation [mean±standard deviation (S.D.): 86.8±44.6 months]. Eight patients died 44.4–142.9 months after the primary operation (mean±S.D.: 90.7±30.0 months). Six patients died of thymoma and two patients died from complications of the treatment. One patient died of respiratory distress due to recurrence and radiation pneumonitis. Another patient died of acute leukemia during chemotherapy. The overall survival in 24 patients was 89.3% at five years and 45.2% at 10 years after the primary operation (Fig. 1). Overall survival after recurrence was 73.3% at five years and 25.1% at 10 years (Fig. 1). DFI, recurrence, survival length and prognosis in individual cases are shown in Fig. 2.

For prognostic factors, the following factors were analyzed: age, gender, complications, Masaoka–Koga stage [9], WHO histological classification [10], resectability of the

Table 1. Clinical and pathological data and prognosis

Factors	Numbers	Five- and 10-year survival after relapse	*P*-value
Total	$n=24$	73.3% and 25.1%	-
Age (years)	52±13 (30-80)		
	<65 ($n=20$)	85.6% and 29.3%	0.023
	>65 ($n=4$)	0% and 0%	
Gender	M ($n=12$)	64.3% and 42.9%	0.552
	F ($n=12$)	90. % and 0%	
Complications	-($n=15$)	68.2% and N.A.	0.902
	+($n=9$)*	83.3% and 27.8%	
	MG: 5		
	PRCA: 4		
	Myotonic dystorophy: 1		
Masaoka-Koga stage	III ($n=8$)	33.3% and N.A.	0.924
	IVa and IVb ($n=16$)	84.6% and 17.6%	
	IVa: 11		
	IVb: 5		
WHO stage	III ($n=11$)	37.5% and N.A.	0.747
	IV ($n=13$)	81.8% and 17.0%	
WHO histology	AB and B1 ($n=5$)	100% and 0%	0.963
	B2 ($n=14$)	78.6% and 29.5%	
	B2+3 and B3 ($n=5$)	50.0% and N.A.	
	AB: 2		
	B1: 3		
	B2: 14		
	B2+3: 1		
	B3: 4		
Adjuvant RT after primary operation	-($n=5$)	100% and 0%	0.973
	+($n=19$)	68.9% and N.A.	
Adjuvant CT after primary operation	-($n=23$)	72.3% and 24.8%	N.A.
	+($n=1$)	100% and N.A	
DFI (months)	34.6±25.7		
	(11.6-109.6)	75.8% and 50.5%	0.079
	24≤($n=12$)	71.1% and N.A.	
	24>($n=12$)		
NRL	5.1±7.0 (1-34)		
	1 or 2 ($n=12$)	100% and 88.9%	0.006
	3≤($n=12$)	41.5% and N.A.	
Treatment for rec.	-($n=5$)	66.7% and N.A.	0.484
	+($n=19$)	78.4% and 16.3%	
Operation for rec.	-($n=12$)	66.7% and N.A.	0.423
	+($n=12$)	83.3% and 55.6%	
RT for rec.	-($n=14$)	64.0% and 21.3%	0.393
	+($n=10$)	85.7% and N.A.	
CT for rec.	-($n=18$)	85.7% and 45.7%	0.007
	+($n=6$)	40.0% and 0%	

*One patient had both MG and PRCA. MG, myasthenia gravis; PRCA, pure red cell aplasia; N.A., not applicable; WHO, World Health Organization; RT, radiotherapy; CT, chemotherapy; DFI, disease free interval; NRL, number of rec. lesion; rec., recurrence.

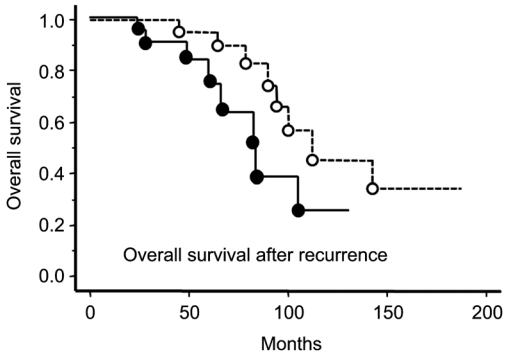

Fig. 1. Overall survival after primary operation and after recurrence in recurrent thymoma patients.

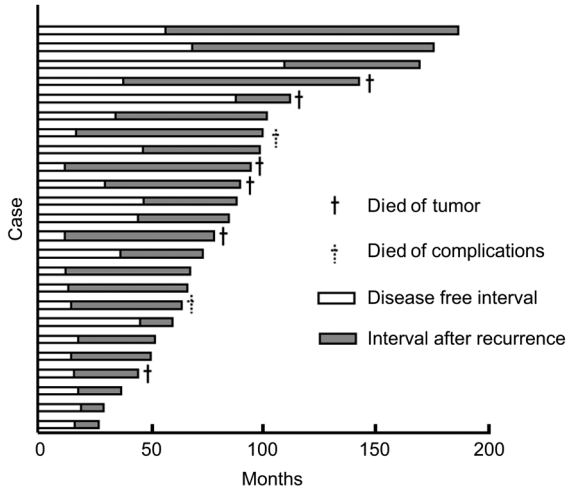

Fig. 2. Disease free interval, recurrence, survival length and prognosis in individual cases.

primary operation, adjuvant chemotherapy or RT after the primary operation, DFI, NRL, treatment (operation, RT, and chemotherapy) for recurrence (Table 1). Younger age (<65) (P=0.023) (Fig. 3), small NRL (1 or 2) (P=0.006), (Fig. 4) and absence of chemotherapy for recurrence (P=0.007) (Fig. 5) were factors for better overall survival after recurrence. Though statistical significances was not obvious because of the number of small samples, DFI (P=0.079) was likely to be a candidate of prognostic factors (Fig. 6). The hazard ratios of these candidates are shown in Table 2. The hazard ratio for younger patients was 0.139 [95% confidence interval (CI), 0.019-1.010]. The hazard ratio for patients with small NRL (1 or 2) was 0.251 (95% CI, 0.011-0.768). The hazard ratio for patients without chemotherapy for recurrence was 0.148 (95% CI, 0.027–0.733). The hazard ratio for patients with longer DFI (over 24 months) was 0.251 (95% CI, 0.048-1.318).

4. Discussion

In the present study, our aim was to search for better prognostic factors in recurrent thymoma. Postoperative recurrence of thymoma is infrequently observed. The recurrence rate was recently reported as ranging from 8% to 19% of operated patients [4–6, 11], which was similar to that in our study. Treatment for recurrence is not easy. We have

Table 2. Hazard ratios of candidates of better prognosis

Factors	Hazard ratio (95% CI)
Age (years)	Age <65 0.139 (0.019-1.010)
DFI (months)	DFI ≥24 months 0.251 (0.048-1.318)
NRL	NRL: 1 or 2 0.091 (0.011-0.768)
Chemotherapy for recurrence	Chemotherapy (-) 0.141 (0.027-0.733)

DFI, disease free interval; NRL, number of recurrence lesion; CI, confidence intervals.

recommended patients for surgical resection or RT. If these modalities are not applicable, chemotherapy with a platinum-based regimen has been considered [12]. Similar treatment strategies have been suggested [13]. However, prognostic factors and optimal strategy for recurrence has not been determined.

In our series, the DFI from the primary operation to diagnosis of recurrence was shorter than in other reports. Two possible explanations for this are: (1) patients in the present study might have more advanced disease than in other reports. Sixteen of 24 cases (67%) were diagnosed as Masaoka–Koga stage IV disease (11 of stage IVa and five of stage IVb). We have positively performed total resection for thymoma and disseminated nodules in stage IV thymoma and reported its efficacy [14]; (2) follow-up might be performed more frequently and recurrent lesions might have been diagnosed in the early period. Five- and 10-year survival rates were 37-51% and 16–43% [5-7, 12], respec-

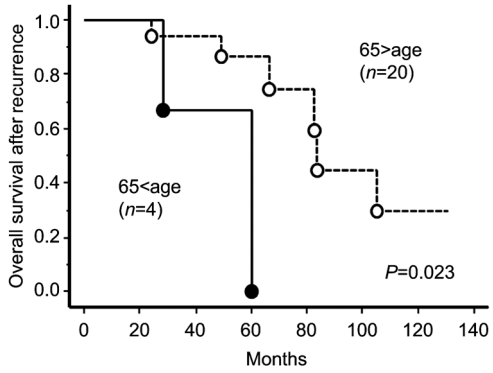

Fig. 3. Overall survival after recurrence and age.

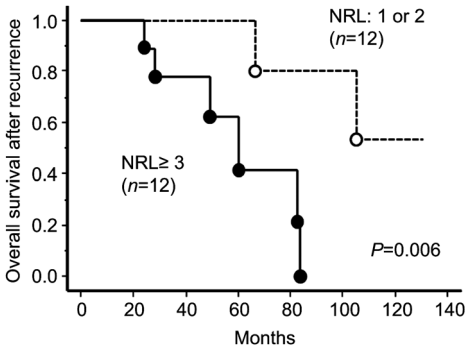

Fig. 4. Overall survival after recurrence and number of recurrent lesions (NRL).

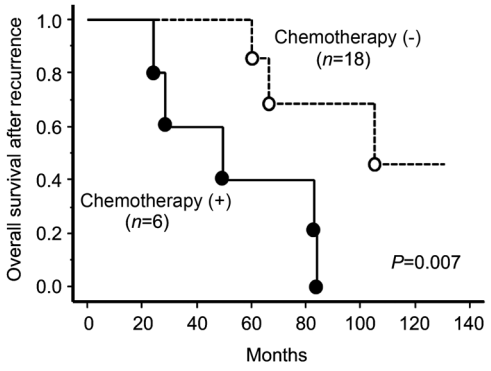

Fig. 5. Overall survival after recurrence and chemotherapy.

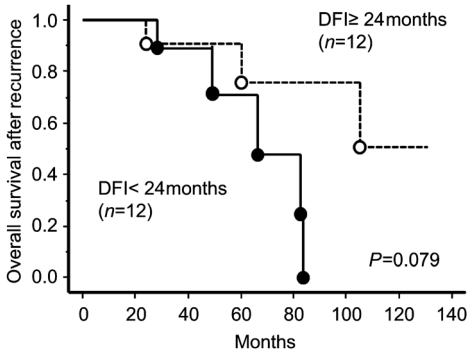

Fig. 6. Overall survival after recurrence and disease free interval (DFI).

tively in other reports; our overall survival rates for five and 10 years in the present study were better 73.3% and 25.1%, respectively.

Surgical resection for recurrent lesions has been recommended in some reports [4, 5, 15]. In our series, the data suggests that surgical resection may be efficacious in the limited cases with a small NRL. These cases with small NRL showed better prognosis. In these patients, six patients underwent a second operation with or without another modality. Five of these patients are alive and one patient died of tumor 66 months after recurrence. In six other patients, three patients underwent only RT for recurrence. One patient died of tumor but two patients are alive at over 40 months after recurrence. Three other patients were followed up without treatment and they are alive at 14, 60, and 107 months after recurrence. Therefore, the patients with a small NRL showed better prognosis irrespective of the treatment. Surgical resection or RT for the patients with a small NRL may be useful. We have newly suggested the NRL as a prognostic factor. Lucchi et al. reported a series of pleural recurrences of thymoma and better prognosis in cases with single recurrent lesion [15]. As the number of cases with single recurrent lesion was too small in our series, we have combined the cases with single lesion and two recurrent lesions and evaluated.

There is still a problem in treatment of patients with many recurrent lesions. Chemotherapy is considered as a candidate of modality for these patients. However, we have proposed chemotherapy for those with the poorest prognostic factors in the present study. Chemotherapy was usually performed with many recurrent lesions or repeated recurrences. These patients are not suitable for surgery or RT because the disease is more advanced or more widely spread.

In the present study with a limited number of patients it was difficult to determine the modality of choice to prolong the survival. However, the small NRL has associated with a better prognosis irrespective of the treatment.

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, Delgado R, Rosai J, Bains MS, Ginsberg RJ, Martini N, McCormack PM, Rusch V, Burt ME. Thymoma: a multivariate analysis of factors predicting survival. Ann Thorac Surg 1995;60:908—913.

[3] 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.

[4] Regnard JF, Zinzindohoue F, Magdeleinat P, Guibert L, Spaggiari L, Levasseur P. Results of re-resection for recurrent thymomas. Ann Thorac Surg 1997;64:1593—1598.

[5] Ruffini E, Mancuso M, Oliaro A, Casadio C, Cavallo A, Cianci R, Filosso PL, Molinatti M, Porrello C, Cappello N, Maggi G. Recurrence of thymoma: analysis of clinicopathologic features, treatment, and outcome. J Thorac Cardiovasc Surg 1997;113:55—63.

[6] 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.

[7] Urgesi A, Monetti U, Rossi G, Ricardi U, Maggi G, Sannazzari GL. Aggressive treatment of intrathoracic recurrences of thymoma. Radiother Oncol 1992;24:221—225.

[8] Huang J, Detterbeck FC, Wang Z, Loehrer PJ Sr. Standard outcome measures for thymic malignancies. J Thorac Oncol 2010;12:2017—2023.

[9] Koga K, Matsuno Y, Noguchi M, Mukai K, Asamura H, Goya T, Shimosato Y. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. Pathol Int 1994;44:359—367.

[10] Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. World Health Organization classification of tumours. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: International Agency for Research on Cancer Press 2004:146—151.

[11] Wright CD, Wain JC, Wong DR, Donahue DM, Gaissert HA, Grillo HC, Mathisen DJ. Predictors of recurrence in thymic tumors: importance of invasion, World Health Organization histology, and size. J Thorac Cardiovasc Surg 2005;130:1413—1421.

[12] Loehrer PJ Sr, Kim K, Aisner SC, Livingston R, Einhorn LH, Johnson D, Blum R. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. J Clin Oncol 1994;12:1164—1168.

[13] Girard N, Mornex F, Van Houtte P, Cordier JF, van Schil P. Thymoma: a focus on current therapeutic management. J Thorac Oncol 2009;4:119-126.

[14] Yano M, Sasaki H, Yukiue H, Kawano O, Okuda K, Hikosaka Y, Fujii Y. Thymoma with dissemination: efficacy of macroscopic total resection of disseminated nodules. World J Surg 2009;33:1425—1431.

[15] Lucchi M, Davini F, Ricciardi R, Duranti L, Boldrini L, Palmiero G, Basolo F, Mussi A. Management of pleural recurrence after curative resection of thymoma. J Thorac Cardiovasc Surg 2009;137:1185—1189.