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Prognostic Factors and Treatment Outcome for Thymoma

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Purpose : In this retrospective study, we attempted to evaluate the treatment outcome and the prognostic factors of thymoma treated with surgery, radiotherapy and chemotherapy.

Methods and materials : Between 1979 and 1998, 55 patients with thymoma were treated at the Seoul National University Hospital. Of these, 11 patients underwent surgery only, 33 patients received post-operative radiotherapy and 11 patients received radiotherapy only. Twenty-three patients had gross total resection and 21 patients subtotal resection. For postoperative radiotherapy, the radiation dose consisted of 41.4~55.8 Gy. The average follow-up was 64 months, and ranged from 2 to 160 months. The sex ratio was 1:1 and the median age was 48 years (15~74 years). Overall survival and disease-free survival were determined via the Kaplan-Meier method, and the log-rank was employed to evaluate for differences in prognostic factor.

Results : The five- and 10-year survival rates were 87% and 65% respectively, and the median survival was 103 months. By univariate analysis, only stage (p=0.0017) turned out to be significant prognostic factors of overall survival. Also, stage (p=0.0007) was significantly predictive for overall survival in muti-variated analysis.

Conclusion : This study showed the stage was found to be important prognostic factors, which influenced survival. Especially, as incomplete resection is related with poor results, complete resection is important to cure the invasive thymoma.

Key Words : Thymoma, Prognostic factor, Surgery, Radiotherapy

Introduction

Invasive thymoma is a rare disease, accounting for approximately 20~30% of all mediastinal tumors in adults.[1] Invasive thymomas appear as an asymptomatic and incidental finding on X-ray, but sometimes are associated with a spectrum of autoimmune diseases including myasthenia gravis, polymyositis, and hypogammaglobulinemia.[2] Even though they are generally slow-growing epithelial neoplasms, thymomas are potentially invasive, and therefore, should be considered as malignant tumors.[3] Invasive epithelial tumors of the thymus are cytologically divided into two groups. Invasive thymomas appear to be cytologically benign, but invade the surrounding tissue or tumor capsule, whereas thymic carcinoma has a cytologically malignant appearance, and is predominantly composed of squamous cell carcinoma.[4]

Although there are many prognostic factors associated with thymoma, the most significant factor is believed to be its invasiveness. Numerous authors have reported on the other significant prognostic factors, including tumor histology, paraneoplastic syndrome, performance, extent of resection and treatment modality.

Complete surgical resection remains the treatment of choice for all thymomas, regardless of invasiveness, and the preponderance of evidence indicates that all thymomas except the completely encapsulated stage I tumors should be treated with postoperative adjuvant radiation therapy in the hope of

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reducing the incidence of local relapse.[5] The recommended radiation dose for malignant thymoma after resection is 45~50 Gy in 23 to 25 fractions, but the optimal postoperative radiation dose is unclear. In this report, we retrospectively reviewed the outcome of 55 patients, treated primarily at the Seoul National University Hospital.

Methods and Materials

1. Clinical feature and the patient characteristics

From 1979 to 1998, 88 patients were diagnosed with thymic neoplasm. Of these patients, pathology was unavailable in 10, 17 were thymic carcinoma patients, 2 patients were transferred to another medical center, 2 patients died of other diseases (esophageal cancer, and acute ALL), and 2 patients refused treatment and were excluded from this study. Therefore, 55 patients were involved in this study. Eleven patients were treated by surgery alone, 33 patients were treated by surgery and radiotherapy, and 11 patients were treated by radiotherapy alone. The median follow-up was 64 months with a range of 2 to 160 months. The mean age was 48 years and ranged from 15 to 74 years, and the sex ratio was 1:1. At last follow-up, 41 patients were alive and 14 patients were dead. On presentation, only 14 thymomas were asymptomatic, and in terms of initial symptom, 18 patients were myasthenia gravis, 12 had chest pain. The patient characteristics are summarized in Table 1. Pathologic staging was performed according to Maskoka et al.[6] Staging was accomplished retrospectively using the operation and pathology reports. In this study, 8 patients were stage I, 10 stage II, 27 stage III, and 10 stage IV (1 stage IVb). The histologic specimens were reviewed by a pathologist at SNUH. The diagnosis of thymoma was based on the pathologic criteria described by Rosai & Levine. According to these criteria, we excluded thymic carcinoma. Lymphoepithelial type cells were most common, occurring in 23 cases, followed by lymphocytic type cells in 14 cases, epithelial type cells in 12 cases and spindle type cells in 6 cases.

Table 1. Patient Characteristics

	Number
Age 15~74 (48)	
Gender	
Female	28
Male	27
Stage	
I	8
II	10
III	27
IV	10 (IVB:1)
Performance	
ECOG 1	37
ECOG 2	16
ECOG 3	2
Histology	
Lymphocytic	14
Lymphoepithelial	23
Epithelial	12
Spindle	6
Associated symptom	
Myasthenia Gravis	18
Red cell aplasia	2
Pancytopenia	1
Myositis	2

2. Treatment method

1) Surgery

Forty-four patients were subjected to surgery as an initial treatment. The surgical procedures consisted of total or subtotal thymectomy through median sternotomy. Most of the stage III thymomas were treated by thymectomy of the involved lung, pleura or pericardium. Of these, 33 patients were treated by postoperative radiotherapy, and all stage I thymomas were treated by surgery alone. Twenty-three of the 55 patients underwent gross total resection (stage I : 8, stage II : 5, and stage III: 10), 21 had subtotal resection (100% >, > 50%) and 11 patients had biopsy alone.

2) Radiotherapy

Forty-four patients were treated at SNUH with Megavoltage irradiation using 4~10 MeV photons, excluding 8 stage I and 3 stage II thymomas that underwent total resection. Of these, 33 patients were scheduled to receive postoperative radiotherapy. Eleven patients received radiation alone, because they couldn't undergo surgery due to their general condition or surgery refusal. There was no preoperative radiotherapy case. Among those who were treated by total resection, 2 stage II thymomas and 10 stage III thymomas were treated by postoperative RT.

In the case of a negative resection margin, the total radiation dose was mainly 45 Gy, and for residual tumor the total dose was 50 to 55 Gy. Most of the patients were treated with ventral and dorsal opposed portals, in daily fractions of 1.8 Gy, 5 days per week; up to a dose of 36 Gy, AP/PA opposed fields were used. Off cord oblique

fields were used to limit the dose to the spinal cord, boosting the mediastinum. Radiation fields encompassed the tumors with a 1.5~2 cm margin. SCL field was included, if the operation was not performed. The median target volume dose was 50.4 Gy (41.4~55.8 Gy), except in one patient with SVC syndrome, who was treated in daily fractions of 3 Gy up to 30 Gy. Only one patient received combined treatment with multiagent chemotherapy, followed by radiotherapy. Of stage II thymomas, one refused surgery and received radical radiotherapy, and he was alive after 48 months of follow-up with no evidence of disease. The treatment modalities are described in Table 2.

3) Chemotherapy

Of 55 patients, only 8 received chemotherapy. Seven patients were treated for palliation after recurrence or distant metastasis, and one patient, in stage III, was treated with neoadjuvant and radiotherapy, using a CAP (Cyclophosphamide/Doxorubicin/Cisplatin) regimen. After 40 months of follow-up, he was diagnosed with pleural metastasis and the chemotherapy treatment continued. At 44 months, he expired of disease progression. Among the other patients who were treated with palliative chemotherapy, a CAP regimen was used in 6, and CHOP (Cyclophosphamide/Doxorubicin/ Vincristine/Prednisone) in one.

3. Statistics

Survival results including the estimation of median, overall and disease free survival (DFS) were generated using the Kaplan-Meier product limit method and the significance of differences was tested with the log-rank test.

Results

Of the 55 patients who were diagnosed with thymoma, and after a median follow-up of 64 months (2~160 months), 41 patients were alive, 13 patients died of disease progression and 1 died of intercurrent disease. Median overlall survival was 103 months and median disease free survival was 61 months. Five-year and 10-year overall survival rates were 87% and 62%, respectively (Fig. 1).

Table 2. Treatment Modalities

	Number of patients				
	Surgery		Surgery+ Radiotherpy		Radiotherapy
Stage	Total	Subtotal	Total	Subtotal	
I	8				
II	3		2	4	1
III			10	12	5
IV				5	5

1. Prognostic factor

By univariate analysis, stage (p=0.0017) was only significant predictors for OS. Other variables including age, gender, histology, and size had no influence on survival. The variables including age, gender, stage, performance status, and MG were also tested using the Cox proportional hazards model to establish independent significance. By multivariate analysis, stage (p=0.0007) was significantly predictive of OS. MG (p=0.0705) was of marginal significance. Thirty-seven of the patients who enrolled in this study were in a state of ECOG 1. Prognostic factors and their significance are described in Table 3.

The 5-year DFS by stage was 100% for stage I, 67% for stage II, 58% for stage III, and 10% for stage IV. Overall, there was a statistically significant difference by stage (p= 0.0077) (Fig. 2). The 5-year OS was 100% for stage I, 88% for stage II, 93% for stage III, and 50% for stage IV. The 5-year DFS and OS by the extent of surgery was 97.7% and 100% for those who had total resection, 36.6% and 80% for subtotal resection, and 8.33% and 46.8% for biopsy only, respectively.

2. Complications

Nine patients developed complications after radiotherapy.

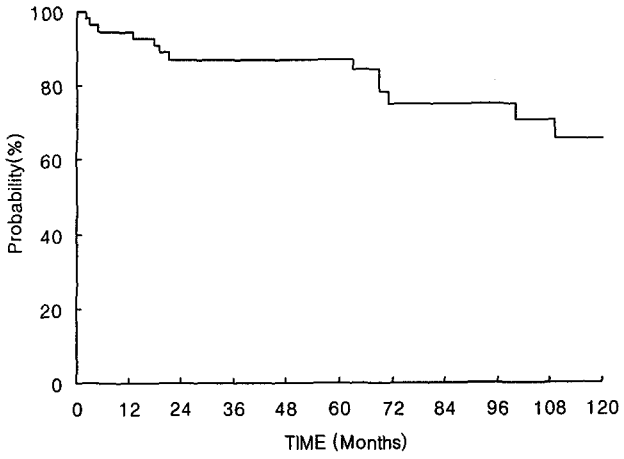

Fig. 1. Overall survival curve using Kaplan-Meier method.

Table 3. Prognostic Factors

Variables	OS*			DFS†		
	RR†	95 % CI§	*p*	RR	95 % CI	*p*
Stage	4.870	1.521~15.59	0.0007	3.890	1.778~8.509	0.0077
ECOG (1 vs. 2-3)	1.663	0.675~4.099	0.2690	1.077	0.551~2.107	0.8275
Histology	0.759	0.371~1.551	0.4497	0.7462	0.450~1.237	0.2557
Age (48< vs. ≥48)	0.311	0.080~1.208	0.0916	0.649	0.258~1.632	0.3585
Gender (male vs. female)	0.843	0.236~1.208	0.8384	0.820	0.331~2.036	0.6693

*overall suvival, †disease free survival, †relative risk, §confidence interval

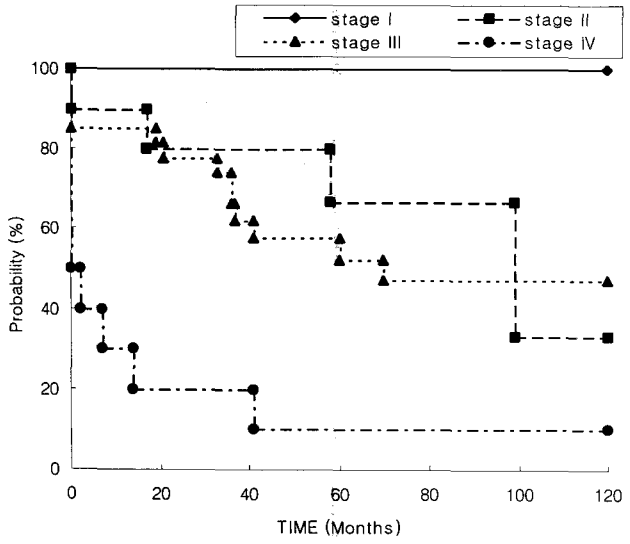

Fig. 2. Disease free survival by stage (p=0.0077).

Of these, 2 patients developed GII esophagitis, and 6 GI esophagitis. Pneumonitis was noted in one patient and he received steroid treatment; 3 weeks later, the pneumonitis su bsided.

Discussion

Thymoma is a rare disease of the thymic epithelium, and unlike thymic carcinoma, is known to carry a good prognosis. Of patients with myasthenia gravis, 75% are associated with thymic abnormalities, and of these, 15% have thymoma. Also, of all diagnoses of thymoma, about 50% are associated with myasthenia gravis, and 5% with hypogammaglobulinemia.[7] It has been reported that five-year and 10-year survival rates for a well-encapsulated thymoma without invasion are almost 100%. Even in the case of invasive thymoma, the ten-year survival rates have been reported to range from 27 to 69%.8) In the present study, the five-and 10-year survival rates for thymoma were 87% and 66%, respectively.

Many studies have reported upon the various prognostic factors of invasive thymoma. Of these, the most important prognostic factor in thymoma is believed to be invasiveness of the tumor. The extent of surgery is also important prognostic factor, but the value of incomplete surgical resection is debatable for prognosis. Many authors believe that incomplete resection has no survival or recurrence value over biopsy alone.[9, 10] Other authors found that survival was better after partial resection than after biopsy alone. Local relapse was observed in 16% of patients after partial resection and in 45% after biopsy (p<0.05). Nakahara et al. also found a significant difference in survival between patients that underwent subtotal resection and those that received biopsy alone (p<0.01),[11] and this study also supported the benefit of subtotal resection. The 5-year DFS of subtotal resection and biopsy alone were 37% and 8%, respectively (p<0.01). Although arguments exist, recent reports have found no influence of coexisting myasthenia gravis on prognosis.[8, 12] It may even confer a survival advantage, but this may be due to the preponderance of early stage tumors discovered incidentally in myasthenic patients.[5] Histopathologic classification of thymoma remains controversial. The classification system of Rosai and Levine grades tumors based on the characteristics of the epithelial cell component and the presence or absence of lymphocytic infiltration. Nowadays, a newer system by Marino and Muller-Hermelink divides tumors into cortical, mixed, and medullary types.[13]

Lymphocytic and spindle cell type thymoma according to the Rosai & Levine classification have been reported to show particularly good prognosis.[14] In the present study, presence of myasthenia gravis had marginal significance and histology was not found to influence prognosis. Although patient's performance status in this study showed no signi-

ficance in terms of its influence on prognosis, in general, performance is believed to be an important prognostic factor.

The conventional approach for clinically suspected thymoma has been surgical exploration of the anterior mediastinum with the aim of complete resection whenever feasible.[9~11] As the disease does not recur in patients with stage I thymoma treated with surgery alone, adjuvant treatment is not indicated in this group, but controversy continues regarding postoperative radiotherapy for invasive thymoma with surgically clear margins. After apparent complete resection, invasive thymomas are said to relapse in 20% of patients, and less than 5% develop extrathoracic metastasis.[15] Curran et al.[10] concluded that radiotherapy reduced the local failure rate after complete resection of invasive thymoma from 28% to 5%. The Torino group[16] emphasized radiotherapy for invasive thymoma, even after total resection. As there were few non-irradiated thymomas after complete resection, definite recommendations concerning adjuvant treatment cannot be drawn from this subgroup. The preponderance of evidence indicates that all thymomas except completely encapsulated stage I tumors should be treated with postoperative adjuvant radiation therapy in hope of reducing the incidence of local relapse. The recommended radiation dose for malignant thymoma, after resection, is not well established. Local recurrences have been reported with doses lower than 40 Gy.

The role of chemotherapy is uncertain, as chemotherapy is usually used as in a palliative setting after recurrence or distant metastasis. The Eastern Cooperative Oncology Group published a report upon the first American cooperative group effort to study chemotherapy in invasive thymoma.[17] The authors concluded that cisplatin was ineffective in producing regression of recurrent or metastatic thymoma. Our study used chemotherapy as a palliative treatment only. Of 55 patients, only 8 patients received chemotherapy. Seven patients were treated for palliation after recurrence. So, definite information cannot be obtained from our study. In contrast with the ECOG study, Park et al. observed a significant response rate to cisplatin with or without prednisone (6/17 CR, 5/17 PR, for overall response rate of 64%).[12] These authors now recommend preoperative induction chemotherapy, surgical resection, postoperative radiotherapy, and consolidative chemotherapy after radiotherapy. The role of chemotherapy should be investigated with respect to reducing distant metastasis and promoting the survival.

In conclusion, we found that only the stage was important prognostic factors for invasive thymomas and total resection is important to cure invasive thymoma.

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국문 초록

흉선종의 방사선치료 : 예후인자 및 치료성적

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목 적 : 흉선종에 있어서 수술과 방사선치료에 따른 결과와 생존율에 영향을 주는 여러 예후인자를 파악하기 위하여 후향적 연구를 시행하였다.

방 법 : 1979년부터 1998년까지 서울대학병원에서 수술과 방사선치료를 받은 55명의 환자를 대상으로 하였다. 그 중 수술만 받은 환자는 11명, 수술 후 방사선치료를 받은 환자는 33명이었고, 방사선치료만을 받은 환자는 11명이었다. 추적 관찰 기간은 2~160개월(중앙값 : 64개월)이었다. 남녀의 구성비는 1:1, 대상 환자의 연령은 15~74세(중앙값 : 48세)였다. 종양의 크기와 조직학적 분류, 병기, 수술의 범위 정도, ECOG활동도, 종양 수반 증후군, 치료 방법에 따라 생존율을 분석하였다. 통계방법은 생존율은 Kaplan-Meier, 생존율의 차이는 log rank test, 다변수 분석은 Cox regression 방법을 이용하였다.

결 과 : 전체 환자의 5년 생존율은 87%, 10년 생존율은 65%이었고, 중앙생존기간은 103개월이었다. 단변량분석상 생존에 통계적으로 유의한 예후인자는 병기(p=0.0017)였고, 다변량분석상에서도 역시 병기(p=0.0007) 만이 유일한 예후인자였다.

결 론 : 흉선종에 있어서 병기가 주요 예후인자임을 알 수 있었고, 특히 수술의 절제 범위가 생존율과 무병생존율에 큰 영향을 주므로 완전절제를 하는 것이 생존율을 높일 수 있을 것으로 생각된다.

핵심용어 : 흉선종, 예후인자, 수술, 방사선치료