PROGNOSTIC FACTORS FOR INVASIVE THYMOMA TREATED WITH RADIATION THERAPY ALONE OR COMBINATION OF SURGERY AND RADIATION THERAPY

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Abstract : The prognostic factors and the correlation between local control and total dose were investigated for the patients with invasive thymoma treated by a combination of radiation therapy and surgery or radiation therapy alone. Eighteen patients were retrospectively analyzed. Our treatment strategy was to give the target volume a total dose of at least 50 Gy for patients with microscopic residual and 60 Gy or more for macroscopic residual. The actuarial survival rates were 61 % at 5 years and 54 % at 10 years in all patients. All patients having a complete resection survived disease-free for more than 6 years while the survival rates of patients with macroscopic residual or unresected tumors were 38 % at 5 years and 25 % at 10 years ($p < 0.005$). For macroscopic residual local recurrence rate within a radiation field was 0 % at a dose of 60 Gy or more, 67 % from 50 to 58 Gy and 100 % under 40 Gy, respectively. Invasive thymoma may be preferable to be treated at the dose of 50 Gy or more for microscopic residual and 60 Gy or more for macroscopic residual. Good prognosis may be expected in the patients undergoing complete resection and radiation therapy.

Key words : Invasive thymoma, Radiation therapy, Operation, Local control, Prognosis
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INTRODUCTION

Thymoma, the morphologic criteria of which was defined by Rosai and Levine¹⁾, is the most common neoplasm found in the anterior mediastinum²⁾. It is a slow-growing tumor with a local invasion and rarely metastasizes outside the thorax³⁾. Good prognosis, such as survival rates of 75-100 % at 5-years and 63-100 % at 10-years, was reported in patients with non-invasive tumors^{3~6)}. In invasive tumors, survival rates were about 50-73 % at 5 years and 30-60 % at 10 years, respectively^{4~8)}. On the other hand, thymic carcinoma recognized by a high degree of histologic anaplasia and close resemblance to carcinomas are distinguished from thymoma^{9~11)}. Treatment strategy and prognosis are very different in these tumors. The complete resec-

tion is the treatment of choice though sometimes it is impossible because of invasion to surrounding structures. A tumor relapse may be observed in 0-12 % of non-invasive thymoma^{3~6,12~13)}. Even if complete resection is performed, approximately 20 % of invasive thymoma may recur locally⁴⁾. It remains controversial whether postoperative irradiation is necessary for the patients receiving complete resection^{4,6,7)}. However, radiation therapy has been recommended for the patients with postoperative residual tumors^{4,6,7,14,15)}. The purpose of this article is to present the prognostic factors and the correlation between local control and total dose in the patients with invasive thymoma treated by our treatment strategy.

MATERIALS AND METHODS

There were eighteen patients with invasive thymoma treated in our department from 1973 to 1989. Their initial investigation and surgery had been performed at surgical departments in our or other hospitals prior to consultation with our department. Twelve patients were male and six female. Mean age was 59 years with a range of 34 to 74 years.

Pathology and Staging

Tumors were classified to epithelial, lymphocytic and mixed type according to the predominant cell type. All patients were staged according to the classification of MASAOKA⁵⁾(Table 1) except for two patients who did not undergo thoracotomy (Table 2). There were two patients with Stage II invading only pleura and twelve with Stage III invading a lung or an adjacent vasculature and two with Stage IV having pleural dissemination. Myasthenia gravis was associated in 5 of 18 patients.

Surgery

Eight patients had a complete resection and three had an incomplete resection. Four patients had only open biopsy.

Radiation therapy

Eight patients, including four with open biopsy and one undergoing radiation therapy because of recurrence after surgery, were treated with radiation

therapy alone. Eight patients with complete resection and two with incomplete resection assessed by surgical inspection were treated with radiation therapy after surgery (Table 2). Radiation therapy was given with a 10 MeV linear accelerator. Anterior fields or anteroposterior parallel opposed fields weighted 2:1 were employed by tumor sites. The fraction size was 2 Gy/day. The treatment volume encompassed all tumors visible on pre-treatment chest radiographs with a 1 to 2 cm margin when a tumor was incompletely resected. When a tumor was completely resected the radiation field included pleura and pericardium adjacent to tumor. After 40 Gy, the radiation field was decreased to include the most possible residual tumor site as the dose of the spinal cord was under 50 Gy with a fraction size of 1.4 to 1.8 Gy. From 1980, computed tomography has been used in 14 patients for the confirmation of treatment volume. Our treatment strategy is to give the target a total dose of at least 50 Gy for patients with microscopic residual tumors and 60 Gy or more for macroscopic residual tumors. The target dose given varied from 50 to 70 Gy (mean 57 Gy) except for two under 40 Gy because at first these patients were diagnosed as a lymphoma. Two patients received 70 Gy because a tumor shadow remained on chest radiography.

Survival curves were calculated by the Kaplan-Meier method. The curve was not age-adjusted and the death from unknown reason was calculated as cancer death. The comparisons between the curves were obtained by logrank test. The minimum follow-up period was 6 years.

RESULTS

The actuarial survival rates were 61 % at 5 years and 54 % at 10 years in all patients (Fig. 1.). Two patients with Stage II disease undergoing a complete resection survived disease-free for more than 6 years. For twelve

Table 1 Clinical Stages by Masaoka

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 IV a	Pleural or pericardial dissemination
Stage IVb	Lymphogenous or hematogeneous metastasis

Table 2 Patients Characteristics and Prognosis

Histological Type	Number of Patients	Survival Rates (except for Stage IV)		Stage (Masaoka)			
		5 years (%)	10 years (%)	II	III	IV a	Unknown
Epithelial	8	86	86				
Lymphocytic	5	60	40				
Mixed	5	50	50				
Treatment methods		Radiation alone		Radiation+Operation		Total	
with Operation							
Complete Resection	8		8	2	6		
Incomplete Resection	3	1*	2		2	1	
Open Biopsy	4	4			4		
without Operation	3	3				1	2
Total	18	8	10	2	12	2	2

*This patient was treated with radiation therapy due to recurrence after surgery.

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Fig. 1. Cumulative survival curves for all patients and patients with Stage III disease

Fig. 2. Cumulative survival curves by the extent of operation

patients with Stage III disease who underwent a complete resection in 50 % of them, survival rates were 75 % at 5 years and 63 % at 10 years, respectively. Two patients with Stage IV disease died of thymoma at 18 and 38 months after radiation therapy. All patients having a complete resection survived disease-free while the survival rates of Stage III patients having macroscopic residual tumors or unresected tumors were 38 % at 5 years and 25 % at 10 years, respectively (Fig. 2., $p < 0.005$). In histological types survival rates of Stage II or III patients were 86 % for epithelial type, 60 % for lymphocytic type and 50 % for mixed type at 5 years and 86 %, 40 % and 50 % at 10 years, respectively (Table 2). Myasthenia gravis did not have a significant impact on treatment outcome.

In Stage II or III disease, infield recurrence rates for microscopic residual tumors were 0 % at a dose of 50 Gy or more. Those for macroscopic residual tumors were 0 % at 60 Gy or more, 67 % at 50-58 Gy and 100 %

less than 40 Gy, respectively (Table 3). Two patients treated less than 40 Gy were diagnosed as a malignant lymphoma at first. Intrathoracic recurrences were seen in seven patients, in whom five infield recurrences were included, and distant recurrence in four (two pulmonary metastases, one bone metastasis and one axillary lymph node metastasis) (Table 4). There were 11 patients who survived for more than 5 years (Table 5). Almost all patients had slight radiation esophagitis unnecessary for treatment. No serious radiation se-

Table 3 In-field Recurrence Rate by Total Dose

Total Dose	Infield Recurrence Rate		Total
	Microscopic residual	Macroscopic residual	
~40Gy		2/2(100%)	2
50~58Gy	0/5(0%)	2/3(67%)	8
60Gy~	0/3(0%)	0/2(0%)	5
Total	8	7	15

Three patients were excluded from analysis because of Stage IV or uncertain records.

Table 4 Pattern of Failure by the Extent of Operation

Operation	Number of patients	Recurrence			Unknown
		Intrathoracic Infield ()	Distant	Both	
Complete	8	0	0	0	0
Incomplete or Open Biopsy	7	4(3)	1	1(1)	1
without Operation	3	1(1)	1	1	0
Total	18	5(4)	2	2(1)	1

Table 5 Characteristics of 5-Year Survivors

Sex/Age	Stage	Histological type	Operation	Radiotherapy	Prognosis
1 F/47	II	mixed	complete	after surgery	alive with disease-free
2 M/63	II	lymphocytic	complete	after surgery	alive with disease-free
3 M/45	III	epithelial	complete	after surgery	alive with disease-free
4 F/72	III	epithelial	complete	after surgery	alive with disease-free
5 M/44	III	epithelial	complete	after surgery	alive with disease-free
6 M/69	III	epithelial	complete	after surgery	alive with disease-free
7 M/71	III	epithelial	complete	after surgery	alive with disease-free
8 M/62	III	mixed	complete	after surgery	alive with disease-free
9 M/34	III	lymphocytic	incomplete	recurrence	dead with local recurrence
10 M/54	III	lymphocytic	biopsy	alone	dead with local and distant recurrence
11 M/55	III	epithelial	biopsy	alone	alive with distant metastases

quela was seen in any of the patients.

DISCUSSION

Irradiation following surgery has been reported to be necessary for invasive thymoma^{4,6,15,16}. The outcome of our patients with invasive thymoma was similar to those in previous reports^{3,4,7,8}. Patients, who had a complete resection or had Stage II disease, were locally controlled for a long-term though patients with an incomplete resection were not. The extent of operation and stage of disease were already reported to be important prognostic factors^{3,4,7,12,16~18}. Pollack et al.¹⁹ and Mornex et al.²⁰ reported the patients with the incomplete resection had a better prognosis than those with biopsy though in some papers a debulking operation followed by irradiation did not have better survival benefits than a radiation therapy alone^{16,18,21}. In our data no difference of survivals was seen between the patients who had an incomplete resection and those who had only biopsy. Intra-thoracic recurrence which resulted from local invasion or pleural dissemination was recognized in the patients with these advanced tumors.

Urgesi²² reported that infield relapses after irradiation correlated with the type of resection. He did not mention anything about the correlation between infield recurrence and total dose. The optimal dose for controlling microscopic or macroscopic residual tumor was controversial. Pollack et al.¹⁹ and Mornex et al.²⁰ recommended 50 Gy for completely resected invasive thymoma and more than 50 Gy for unresectable tumors. In our data, a total dose less than 60 Gy was insufficient for the eradication of macroscopic residual tumors. For microscopic residual no infield recurrence was observed at a dose of 50 Gy or more, suggesting these doses may be preferable to sterilize microscopic residual tumors.

No clear difference of prognosis was seen by histological subtypes. Prognosis for the patients with epithelial type may be superior to those with other histological types due to different numbers of complete resection which is larger in epithelial type. So far, histological subtypes have been reported not to correlate with prognosis^{4,16,18,22} though some papers suggested that the predominant epithelial type with an exception of the spindle cell variant carried a worse prognosis⁸. Marino and müller-Hermelink²³ proposed a new classification which classified thymoma into cortical, medullary and mixed type from cytological similarity to normal cortical and medullary epithelial cells. Ricci²⁴ and other authors²⁵ reported medullary thymoma was better prognosis than cortical thymoma and mixed type was intermediate prognosis by a new

classification.

There were four patients with distant metastases in our data. Distant metastases were rare, in about 3~26 % and much more in advanced cases^{3,7,18}. In advanced cases reduction surgery may be ineffective in prognosis because of pleural dissemination or distant metastases.

Jackson⁷ reported that three patients (11 %) developed significant side effects by radiation therapy. No serious radiation sequela such as radiation myelopathy or severe radiation pneumonitis was seen in any of our patients.

In conclusion, invasive thymoma may be preferable to be treated at the dose of 50 Gy or more for microscopic residual tumor and 60 Gy or more for macroscopic residual tumor. A fruitful outcome will be expected by undergoing complete resection and radiation therapy.

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