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The result of Radiotherapy in Malignant Thymona

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Twenty one patients of malignant thymoma treated with curative aim at the Department of Therapeutic Radiology of Seoul National University Hospital from 1979 to 1987 were analysed retrospectively.

The 3 year overall and relapse free survival rate was 80.5% and 78.6%, respectively.

Myasthenia gravis (MG) was seen in 43.5% at presentation and disappeared in 40% (4/10) after radiotherapy with or without operation. The 3 year cumulative survival rate with and without MG was 90% and 78.8%, respectively. We could consider that MG was no longer adverse prognostic factor.

The complete response rate after partial resection was 100% (3/3), and that after biopsy was 20% (3/15). The overall local control rate including complete and partial response rate (33% vs 56%) was 89% and the 3 year actuarial survival rate by the response rate was 88.9% and 81.7%, respectively. There was no statistically significant survival difference between two groups.

The crude rate of relapse at 3 years was 23.8% (5/21), and 80% (4/5) were locoregional failures. All failures were observed in biopsy only group, while no failure was observed in resected group. The major pattern of the treatment failure was the locoregional failure and the distant metastases was rarely observed.

Key Words: Malignant thymoma, Radiotherapy, Myasthenia gravis

INTRODUCTION

Thymoma refers to a neoplastic change of thymic epithelial cells, with the lymphocytes representing merely an accompanying population coexisting within the neoplastic epithelial cells[1].

They are usually known as relatively localized, slowly growing tumors with low incidence of distant metastases. Rosai et al reported that some tumors have stayed the same size for as long as 15 years[1]. Sometimes it may produce the morbidity and even death by extensive infiltration of surrounding mediastinal structures.

The treatment of choice is complete resection of the lesion but, it is not always feasible due to invasive characteristics and surgical inaccessibility of surrounding critical mediastinal structures.

Although the place of radiotherapy in the management of thymoma is still a matter of dispute, the current treatment policy of the invasive thymoma is combined modality of surgery and radiation therapy. Several authors reported the improved local tumor control and survival rates of invasive thymoma with the approach of combined modality therapy[2~5].

In this article we report the outcome of all the cases of malignant thymoma patients treated by radiotherapy at the Departmemt of Therapeutic Radiology of Seoul National University Hospital from 1979 to 1987.

The purpose of this study is to assess more fully the results of radiotherapy with respects to the local control and the overall survival.

MATERIALS AND METHODS

1. Patient Characteristics

Twenty four patients with malignant thymoma were treated at the Department of Therapeutic Radiology of Seoul National University Hospital during the eight year period from 1979 to 1987. Of them twenty one patients' records were available for this study.

Most of the patients were adults with an average age of 47 and a median age of 48 years. The age range was 27 to 67 years. The sexes were evenly distributed (Table 1).

Table 1. Patients Characteristics

Characteristics	No. of Patients
Age	
– 30	1 (4.7)
31 – 40	6 (28.6)
41 – 50	8 (38.1)
51 – 60	3 (14.3)
61 –	3 (14.3)
Sex	
Male	11 (52.4)
Female	10 (47.6)
Histology	
Epithelial	5 (23.8)
Lymphocytic	2 (9.5)
Lymphoepithelial	6 (28.6)
Spindle cell	2 (9.5)
Unclassified	6 (28.6)

The neoplasms were classified into four types on the basis of their predominant histologic pattern: epithelial, lymphocytic, mixed lymphoepithelial, and spindle cell. But in a few patients the subtype is not defined. So we grouped them to the unclassified cases.

MG, the most common associated disease of thymoma was shown in 10 patients (47.6%) at diagnosis and the male to female sex ratio was 6:4. The primary tumor size was ranged from 5 to 9 cm in greatest dimensions.

To assist in the specification of invasion, the method of surgical pathological staging defined by Bergh and collaborators were adopted[6], as pathological stsging defined by Bergh and collaborators were adopted[6], as follows.

Stage I; Intact capsule or growth within the capsule

Stage II; Pericapsular growth into the mediastinal fat tissues or adjacent pleura or pericardium

Stage III; Invasive growth into the surrounding organs, intrathoracic metastases, or both

Eingteen patients (85.7%) were stage III and the other three patients (14.3%0 were stage II.

The median follow-up period was 5 years and the minimum follow-up period was 3 years. The survival time was calculated by assumming the first date of the irradiation as the base of follow-up. The survival curves were plotted using life table method and the log-rank test was used for comparison.

Table 2. Distribution by the Extent of Operation

Resection	No. of Patients
No (viopsy only)	15 (71.4)
Partial	3 (14.3)
Complete	3 (14.3)

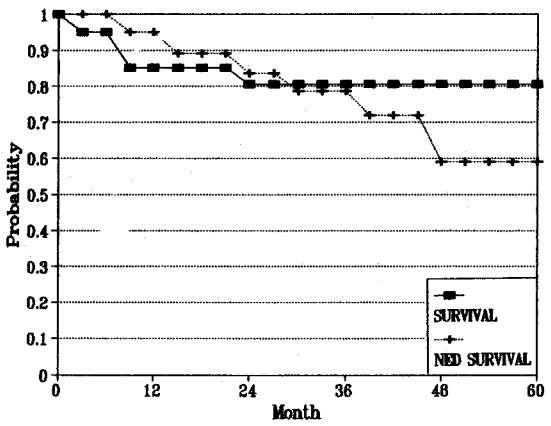

Fig. 1. Survival and NED survival.

2. Treatment

Initially surgical removal was tried in all patients and then applied radiotherapy according to their operative findings (Table 2). The resectable cases including complete and partial resection were 28.6% (6/21).

Radiation was delivered with Co-60 teletherapy unit or 6 MV or 10 MV linear accelerator and directed to the primary tumor and subclinical potential region of invasion with 2~2.5 cm margin. A midplane dose of 4500cGy was planned and boost dose of 500~1000 cGy was added to the primary tumor bed with conventional fractional schedule. If the tumor was relatively small, a technique using two large anterior oblique wedge fields were used. Field size was of the order of 15×8 cm. In the more extensive lesion, large parallel opposing fields or parallel oposing fields supplemented with a wedge pair or additional directed anterior field were used. Field size were up to 20×15 cm for the parallel opposing fields, and up to 20×8 cm for the wedge fields.

RESULTS

The overall actuarial 3 year survival rate was 80.5% and the 3 year relapse free survival rate was 78.

6% (Fig. 1).

The remission rate of myasthenic symptons after radiotherapy was 40% and the extent of surgery was variable.

The overall response rate after radiation therapy was 89%, and the complete response was shown in 6 patients (33%) and the partial respose in 10 (56%). All of the resectable patients (3/3) had the complete response (Table 3). The actuarial 3 year survival rate by the local control rate (complete vs partial) was 88.9% and 81.7%, respectively and the difference was not statistically significant (Fig. 2).

The survival rate was analysed according to the various factors known to affect the outcomes of malignant thymoma patients (Table 4). The actuarial 3 year survival rate with or without MG was 90% and 78.8% and with or without resection was 100% and 78.2%, respectively.

During the follow-up period, the bone metastases was identified in 1 patient (4.8%) and the locoregional failure was identified in 4 patients (19%). All failures were observed in unresectable patients (Table 5). The general features of 4 patients with locoregional failures are shown in Table 6. The recurrence time was ranged from 2 years to 4 years and the main salvage treatment was palliative chemotherapy due to the limited tolearnce of the critical organ to further irradiation.

The lifespan of patients who had been treated by chemotherapy for recurrent diseases seemed to be

Table 3. Response to Radiation Therapy

Resection	CR	PR	NR
Partial (N=3)	3	—	—
Biopsy only (N=15)	3	10	2
Total (N=18)	6	10	2

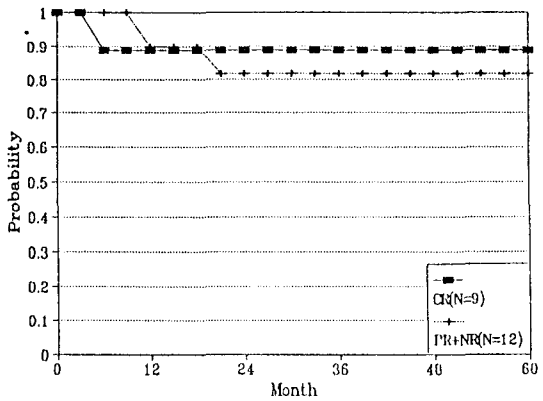

Fig. 2. Survival by response rate.

Table 4. Prognostic Factors

Prognostic factors	No. of Patients	3-YSR (%)
Myasthenia		
Present	10	90.0
Absent	11	78.8
Staye		
II	3	100.0
III	18	77.2
Resection		
Yes	6	100.0
No	15	78.2

Table 5. Patterns of Failure

Extent of surgery	No. of Patients	L-R	DM
Resection	6	—	—
Biopsy only	15	4	1
Total	21	4	1

L-R : Locoregional, DM : Distant metastases.

Table 6. Details on 4 Patients with Locoregional Failures

Patients No.	Age/Sex	Cell Type	MG	RT Dose	Recur Time	Salvage Tx.	Survival (Year)
1	39/F	M	+	4000	3Y	CT.	7^+
2	59/M	E	—	5000	4Y	CT.	9^+
3	48/F	M	—	5100	2Y	—	2
4	39/F	E	—	5040	2Y	CT.	3^+

prolonged but the stastistical significance was not identified.

DISCUSSION

The malignant nature of a thymoma is determined by invasive characteristics rather than the microscopic appearance of the tumor, which is most often diagnosed during surgery. Histologically benign tumors may assume malignant characteristics by invading adjacent tissues, whereas histologically malignant tumors may remain well encapsulated and noninvasive. For a convinence, benign thymomas are defined as well-encapsulated and otherwise invasion features are present, it is defined as malignant thymoma, generally comprising of 60% of all cases[2,6].

The incidence is most frequent in middle aged person. In our report the average age was 47 years old and similar to the reports of others[2,7,8]. Age relates to the prognosis and children have more malignant course than those in adults[9]. De Muth et al[10] reported that patients less than 25 years of age had an extremely poor prognosis, with a 2 year survival approximately 0%.

The sex distribution for all thymoma was approximately equal for males and females and no survival difference was in relation to sex[8,11]. We had the male to female sex ratio of 1.1:1.

A variety of disease occurs in association with thymoma, of which the most common is myasthenia gravis. Myasthenia gravis is known to be an autoimmune disease causing neuromuscular fatigue. In this study 10 patients (47.6%) showed the myasthenic symptoms and this incidence was similar to the other reports[6,12]. But Verley et al[7] reported somewhat higher incidence rate than that of ours. The most common presenting symptoms of malignant thymoma were related to myasthenia gravis and symptoms due to compression on mediastinal structure were next in frequency[8].

The remission rate of myasthenics after the radiotherapy with or without operation was reported to be quite as low as 7%[5]. The remission rate of our study was 40% (4/10), higher than the other result. The effect of myasthenia gravis on the survival of patients with invasive thymoma remains controversial[9]. By the recent report[7,11,13,14]. myasthenia gravis no longer carries the stigma as poor prgnostic factor. Probably the better postoperative supportive care plus long-term medicinal management of myasthenia gravis seem to the essential factors for the improved survival. According to the Massachusettes General Hospital experience, the cumulative survival at 5 years with or without myasthenia gravis was 94% and 68%, respectively[11]. Our data revealed that the 3 year cumulative survival rate with or without MG was 90% and 78.8%, respectively. From these results it can be no longer stated that myasthenia gravis diminishes the prospect for long-term survival.

In the mangement of malignant thymoma, surgery is always attempted in the first instance, even if the lesion is inoperable. This may be the only way to establish a histologic diagnosis.

In encapsulated noninvasive thymoma, the recurrence after the complete removal was very unusual and was estimated by Fechner to be less than 2%[15], so the adjuvant postoperative radiotherapy was not recommended. But some favors radiotherapy, even in patients who have had a complete operative resection because they consider all thymomas are potentially invasive and malignant[3,4].

In about 36% of invasive thymoma, resection alone resulted in the recurrent tumor within 5 years and subsequently died of the disease[7]. Also the response of late recurrent disease to irradiation is so poor, it would seem reasonable to suggest that all cases of infiltrating tumor could be reserved for postoperative radiotherapy even if the surgical resection was macroscopically complete[2~4,16].

Thymomas are relatively radiosensitive and radiation therapy constitutes excellent adjuvant therapy. Marks et al[4]. reported the excellent local control rate of 100% with the doses of more than 4000 rads, average follow-up 5.5 years and minimum follow-up, 30months. In our results the overall response rate was 89%.

A dose of 4000 rads to the tumor bed is adequate in 4 to 5 weeks if the invasive thymoma is completely removed, and the least 1000rads should be given with a paired anterior oblique fields to reduce the total doses to the spinal cord. In addition, all locally inoperable cases should perhaps be given a chance to respond to a course of radical irradiation.

The overall 5 year survival rate was in the range from 50% to 72% by various authors[10~12,17,18]. In our study the actuarial 3 year survival rate was 80.5% and the 3 year relapse free survival rate was 78.6%. The local invasion of adjacent structures and lymphatic metastases are the two main forms of tumor spread in malignant thymoma[2]. Linder and associates[17] treated 25 patients with radiotherapy

and had the local recurrence rate of about 20% and remote metastases in 30% of patients. In our study distant metastases was identified in only one patient (4.8%) and the locoregional failure was in 4 patients (19%). The mortality due to recurrent and infiltrative thymoma was reported to be around 17%[8]. The mortality rate of our cases due to recurrent tumor was 40% (2/5) but the remaining 3 patients had survived with disease for 1, 4, 5 years after recurrene at the time of study and all of them had palliative chemotherapy. Recent information on chemotherapy and steroidal therapy indicates that invasive thymomas are sensitive to cytotoxic agents[18,19]. Especially steroids was known to have the thymolytic effect[18]. But no outstanding drugs are known in their effectiveness and their overall response rate was less than 50% with short duration. Boston[19] reported that adriamycin produced symptom remission for 4 weeks and the longest remission described was a 13 months remission using cis-platinum for 5 days repeated every 4 weeks[19]. So we can consider that there is no known role of chemotherapy until now. Only future study will be able to show the optimal role of combination chemotherapy integrated with surgery and radiotherapy.

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═ 국문초록 ═

흉선암의 방사선치료 성적

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1979년부터 1987년까지 서울대학교병원 치료방사선과에서 흉선암으로 근치목적의 방사선치료를 받은 21명을 대상으로 조사하였다.

전체환자의 3년생존율은 80.5%, 3년 무병생존율은 78.6%였다.

근무력증을 동반한 환자는 43.5%였고 치료후 40% (4/10)에서 증상의 호전을 보였다. 증상의 유무에 따른 3년생존율을 비교하여보면 각각 90%, 78.8%였으며 근무력증이 예후에 나쁜 영향을 주는 인자가 아님을 알 수 있었다.

방사선치료후 완전관해율은 절제술을 시행한 경우는 100%(3/3)인 반면, 절제가 불가능한 경우는 20%(3/15)였다. 완전관해율 및 부분관해율은(33% vs 56%) 89%였고 이에 따른 3년생존율은 각각 88.9%, 81.7%로 통계학적으로 유의한 차이는 보이지 않았다.

수술정도에 따른 치료실패율을 비교하여보면 절제가 가능한 환자에서는 치료실패가 없었으나, 절제가 불가능하였던 환자 15명중 4명에서 국소실패, 1명이 골전이 소견을 보였다. 국소치료실패가 대부분으로 원격전이율은 낮은 양상을 보였다.