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Is Postoperative Radiotherapy for Thymoma Effective?

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Objective
The authors determined the effect of postoperative mediastinal irradiation in preventing local and pleural recurrences of thymoma.

Summary Background Data
The role of mediastinal irradiation after incomplete resection or biopsy of an invasive thymoma is well established. However, routine use of adjuvant mediastinal irradiation for patients with thymoma after complete resection remains controversial.

Methods
During the 19-year period from 1973 to 1992, operations were performed on 89 patients with thymoma. Of these 89 patients, 80 patients who underwent gross complete tumor resection including adjacent tissues that appeared to be invaded by tumor were selected for this study. The effects of postoperative mediastinal irradiation on the recurrence rate of thymoma were analyzed according to histologic type, clinical stage, and whether adhesions to or invasion of the pleura or pericardium were present.

Results
Recurrence of thymoma was observed in 13 of 80 (16.3%) patients. No recurrence was observed in 23 patients with noninvasive thymoma. In patients with invasive thymoma whose tumor was macroscopically adherent to the pleura but not microscopically invasive (p1), recurrence was observed in 4 of 11 patients (36.4%) when mediastinal irradiation was not performed, but in none of 10 patients who received mediastinal irradiation. However, in patients with microscopic pleural invasion (p2), a high recurrence rate was observed with mediastinal irradiation (40%, 6/15 patients) or without mediastinal irradiation (30%, 3/10 patients). Postoperative mediastinal irradiation for patients with microscopical invasion to pericardium (c2) did not decrease the recurrence rate. Analysis of the mode of recurrence showed that mediastinal irradiation may have been effective in preventing local recurrence, but it did not control the pleural dissemination that was observed in 12 of 13 recurrent cases.

Conclusions
Mediastinal irradiation is not necessary for patients with noninvasive thymoma. In patients with invasive thymoma, postoperative mediastinal irradiation is effective in preventing recurrence in patients with p1 thymoma, but not in patients with p2 or c2 tumors. Further adjuvant therapy should be performed to supplement mediastinal irradiation in patients with p2 or c2 thymoma, even after complete resection.

The role of postoperative mediastinal irradiation after incomplete resection or biopsy of an invasive thymoma is well established.[1-3] Although there seems to be general agreement that postoperative mediastinal irradiation is effective in preventing a recurrence of invasive thymoma,[4-11] routine use of adjuvant mediastinal irradiation after complete resection in patients with noninvasive thymoma remains controversial. In this report, the effects of postoperative mediastinal irradiation on the recurrence rate were analyzed according to microscopical invasion of thymoma to the mediastinal pleura and the pericardium.

MATERIALS AND METHODS

Clinical Features and Surgery

In the 19-year period from 1973 to 1992, operations were performed on 89 patients with thymoma. Of these 89 patients, 80 patients who underwent gross complete tumor resection including adjacent tissues that appeared to be invaded by tumor were selected for this study. All complete tumor resections were performed through a median sternotomy. Anterolateral thoracotomy was added in six advanced cases. Forty-three of the 80 patients were women, and 37 were men. Patient age ranged from 12 to 77 years, with a mean age of 51 years. Of the 80 patients, 44 had myasthenia gravis, 2 had pure red cell aplasia, and 1 had a benign thyroid tumor.

Pathologic Findings

The diagnosis of thymoma was based on pathologic criteria, *i.e.*, neoplasm of the thymic epithelial cells, regardless of the presence or absence of a lymphoid component. Patients with germinal tumor, malignant lymphoma, carcinoid tumor, and thymic carcinoma were excluded. The thymomas were classified histopathologically into three groups: lymphocyte predominant, mixed, and epithelial predominant.[12]

Staging

The clinical staging was based on surgical and pathologic criteria described by Masaoka et al.[13] In addition, these patients were subgrouped according to pleural[14] and pericardial invasion, as confirmed by histologic examination of the tumor after operation. The criteria used in this study are as follows:

Clinical Stages[13]

Stage I: completely encapsulated thymoma without microscopic invasion of the capsule;

Stage II: macroscopic invasion of the mediastinal fat or pleura, or microscopic invasion of the capsule;

Stage III: macroscopic invasion of surrounding tissues such as lung, pericardium, superior vena cava, and aorta;

Stage IVa: pleural or pericardial dissemination;

Stage IVb: lymphogenous or hematogenous metastasis.

Classification by pleural factors (p)[14] and pericardial factors (c);

p0/c0: no adhesion to the mediastinal pleura/the pericardium;

p1/c1: fibrous adhesion to the mediastinal pleura/the pericardium without microscopic invasion;

p2/c2: microscopic invasion to the mediastinal pleura/the pericardium.

Postoperative Adjuvant Therapy

Since 1973, mediastinal irradiation (40–50 Gy) has been added to the postoperative treatment of patients after complete resection for thymoma. However, when patients did not consent to the therapy or had an associated severe myasthenic condition, the postoperative radiotherapy was withheld. Adjuvant chemotherapy and radiotherapy were administered when recurrence was confirmed.

Statistics

Statistical correlations were determined by means of nonparametric tests, including Mann-Whitney *U* test or Kruskal-Wallis test, and chi-square test for independence. Statistical significance was defined as a p value of less than 0.05.

RESULTS

General and Histologic Type of the Patients with Recurrence

Recurrence of thymoma was observed in 13 of the 80 patients who underwent complete resection. The recurrence rate did not relate to gender, age, or presence of myasthenia gravis. Complete resection cases were distributed equally between the three histologic types of thymoma (Table 1). The recurrence rate of the lymphocyte predominant group was lower than the other histologic groups, but the difference was not statistically significant. Comparison of recurrence rates between the two groups with and without radiotherapy revealed no significant differences in any histologic type of thymoma.

Table 2 shows the mode of recurrence in the 13 pa-

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Table 1. EFFECT OF MEDIASTINAL IRRADIATION BY HISTOLOGIC TYPE ON RECURRENCE RATE OF THYMOMA

	Mediastinal Irradiation		
	With	Without	Total
Lymphocytic	2/16 (12.5)	0/15 (0)	2/31 (6.5)
Mixed	3/8 (37.5)	2/17 (11.8)	5/25 (20)
Epithelial	1/7 (14.3)	5/17 (29.4)	6/24 (25)
Total	6/31 (19.4)	7/49 (14.3)	13/80 (16.3)

Values are number of recurrences/total number of cases; numbers in parentheses indicate recurrence rate (%).

Table 3. EFFECT OF MEDIASTINAL IRRADIATION BY CLINICAL STAGE ON RECURRENCE RATE OF THYMOMA*

	Mediastinal Irradiation		
	With	Without	Total
Stage I	0/3 (0)	0/20 (0)	0/23 (0)†
Stage II	3/16 (18.8)	5/21 (23.8)	8/37 (21.6)
Stage III	3/12 (25)	2/8 (25)	5/20 (25)
Total	6/31 (19.4)	7/49 (14.3)	13/80 (16.3)

* Values are number of recurrences/total number of cases; numbers in parentheses indicate recurrence rate (%).
† Recurrent rate was significantly increased ($p < 0.05$) by clinical stage.

tients (types of recurrence overlap). Twelve of the 13 patients had pleural dissemination at the predominant tumor site, 6 patients (19.4%) with mediastinal irradiation and 6 patients (12.2%) without mediastinal irradiation. Seven patients (5 with mediastinal irradiation, 2 without mediastinal irradiation) suffered from the pleural recurrence without local recurrence or distant metastasis. Recurrence by pleural dissemination was not suppressed by mediastinal irradiation.

Local recurrence was observed in only one (3.2%) patient with mediastinal irradiation after complete resection. However, five (10.2%) patients without mediastinal irradiation suffered from local recurrence even after complete resection. This difference is not statistically significant.

Clinical Stage

Table 3 shows the effect of mediastinal irradiation on recurrence rate by clinical stage after complete resection. Twenty-three patients with stage I (noninvasive) thymoma underwent a gross total resection. Although adjuvant mediastinal irradiation was not performed in 20 of 23, no stage I patients had recurrence after complete resection. Thirty-seven stage II and 20 stage III patients underwent a visible complete resection, and 8 (21.6%) and 5 (25%) of them suffered from recurrence, respectively. In those patients with invasive thymoma, 3 of 16 stage II (18.8%) and 3 of 12 stage III (25%) patients suffered from recurrence after mediastinal irradiation. Recurrence rate was significantly increased by clinical stage ($p < 0.05$)

Pleural Factors

Of the 23 stage I patients, 10 were classified as p0 and 13 were classified as p1 (Table 4). The 37 patients with

Table 2. MODE OF THE RECURRENCE AFTER COMPLETE RESECTION OF THYMOMA

	Radiotherapy		
	With	Without	Total
Number of cases	31	49	80
Pleural dissemination	6 (19.4)	6 (12.2)	12 (15)
Local recurrence	1 (3.2)	5 (10.2)	6 (7.5)
Distant metastasis	2 (6.5)	1 (2.0)	3 (3.8)

Numbers in parentheses indicate the percent frequency of each recurrence type. The types of recurrence overlapped.

Table 4. RECURRENCE OF THYMOMA BY STAGE AND PERICARDIAL FACTOR AFTER COMPLETE RESECTION*

		Pleural Factor			
	MI	p0	p1	p2	Total
Clinical stage					
I	(−)	0/9 (0)	0/11 (0)	—	0/20 (0)
	(+)	0/1 (0)	0/2 (0)	—	0/3 (0)
II	(−)	0/8 (0)	4/11 (36.4)	1/2 (50)	5/21 (23.8)
	(+)	0/3 (0)	0/8 (0)†	3/5 (60)	3/16 (18.8)
III	(−)	—	—	2/8 (25)	2/8 (25)
	(+)	—	0/2 (0)	3/10 (30)	3/12 (25)
All patients	(−)	0/17 (0)	4/22 (18.2)	3/10 (30)	7/49 (14.3)
	(+)	0/4 (0)	0/12 (0)	6/15 (40)	6/31 (19.4)
	Total	0/21 (0)	4/34 (11.8)	9/25 (36)	13/80 (16.3)‡

MI = mediastinal irradiation.
* Values are number of recurrences/total number of cases; numbers in parentheses indicate recurrence rate (%).
† MI was significantly ($p < 0.05$) effective in preventing recurrence in stage II p1 patients.
‡ Recurrence rates were significantly increased by pleural factor ($p < 0.01$).

Table 5. RECURRENCE OF THYMOMA BY STAGE AND PERICARDIAL FACTOR AFTER COMPLETE RESECTION*

		Pericardial Factor			
	MI	c0	c1	c2	Total
Clinical stage					
I	(−)	0/20 (0)	—	—	0/20 (0)
	(+)	0/3 (0)	—	—	0/3 (0)
II	(−)	5/19 (26.3)	0/2 (0)	—	5/21 (23.8)
	(+)	1/12 (8.3)	1/3 (33.3)	1/1 (100)	3/16 (18.8)
III	(−)	0/2 (0)	1/2 (50)	1/4 (25)	2/8 (25)
	(+)	0/2 (0)	0/2 (0)	3/8 (37.5)	3/12 (25)
All patients	(−)	5/41 (12.2)	1/4 (25)	1/4 (25)	7/49 (14.3)
	(+)	1/17 (5.9)	1/5 (20)	4/9 (44.4)	6/31 (19.4)
	Total	6/58 (10.3)	2/9 (22.2)	5/13 (38.5)	13/80 (16.3)

MI = mediastinal irradiation.
* Values are number of recurrences/total number of cases; numbers in parentheses indicate recurrence rate (%).

stage II thymoma were distributed from p0 to p2, and in this stage, the recurrence rate increased with the pleural factor (p0, 0%; p1, 21.1%; p2, 57.1%; $p < 0.05$). All of the 20 stage III patients were classified in the p2 group, except for 2 patients who had only direct invasion to the pericardium and the superior vena cava. The recurrence rate of all the patients was significantly increased by the pleural factor ($p < 0.01$).

In 23 stage I and 11 stage II p0 patients, no recurrence was observed, regardless of mediastinal irradiation therapy. In stage II p1 patients, mediastinal irradiation was significantly ($p < 0.05$) effective in preventing recurrence after complete resection. In this group, recurrences were observed in 4 of 11 (36.4%) patients who did not receive mediastinal irradiation *versus* 0 of 8 (0%) patients who received mediastinal irradiation. There is no recurrence in two stage III p1 patients after mediastinal irradiation. However, 3 of 10 p2 patients (30%) without mediastinal irradiation and 6 of 15 p2 patients (40%) with mediastinal irradiation had recurrences. Postoperative mediastinal irradiation did not decrease the recurrence rate in patients with p2 tumor.

Pericardial Factors

Recurrence rates of the patients with thymoma are shown in Table 5 by the pericardial factor. All stage I patients were classified in c0 by pericardial factor, and there was no recurrence. Thirty one of the 37 stage II patients (83.8%) were classified in c0, 5 (13.5%) were classified in c1, and 1 (2.7%) was classified in c2. In 20 stage III patients, 4 (20%) patients were classified in c0, 4 (20%) were classified in c1, and 12 (60%) were classified in c2. Recurrence rate was 10.3% for c0 patients, 22.2% for c1 patients, and 38.5% for c2 patients. Although the recurrence rate increased by pericardial factor, these differences did not reach statistical significance. Effectiveness of mediastinal irradiation against recurrence in each pericardial factor group also is shown in Table 5. In the c0 group, mediastinal irradiation decreased the recurrence rate from 12.2% to 5.9%, but there was no statistical significance. In both c1 and c2 groups, recurrence rates also could not be suppressed by mediastinal irradiation.

The mode of the recurrence by the pericardial factor is shown in Table 6. Local recurrences were observed in six patients and were accompanied by pleural dissemination in five. In patients without mediastinal irradiation, 3 of 41 c0 patients, 1 of 4 c1 patients, and 1 of 4 c2 patients had recurrences. However, only one c0 patient suffered from local recurrence after mediastinal irradiation. Distant metastasis was observed in three patients (2 lung and 1 bone metastasis).

DISCUSSION

Although surgery remains the first choice of treatment for stage I to stage III thymomas,[15–17] there still is controversy concerning the optimum adjuvant treatment of thymoma after complete resection. For stage I thymoma, most studies report no or very few relapses after surgery without any adjuvant therapies.[2,14,18] In the current study, no recurrence of stage I thymoma after surgery with or without mediastinal irradiation was observed. These results suggest that routine postoperative mediastinal irradiation is not indicated for patients with stage I thymoma. However, 21.6% and 25% of stage II and stage III patients suffered from recurrences, respectively. In those groups, effect of mediastinal irradiation on recur-

Table 6. MODE OF THE RECURRENCE BY PERICARDIAL FACTOR

	Mediastinal Irradiation							
	With				Without			
Pericardial Factor	Cases	PD	Local	DM	Cases	PD	Local	DM
c0	17	3*	1	0	41	2	3	1
c1	5	0	0	0	4	2	1	0
c2	9	3	0	2	4	2	1	0
Total	31	6	1	2	49	6	5	0

PD = pleural dissemination; DM = distant metastasis.
* Types of recurrence overlapped.

rence rate was not evident when it was investigated by the clinical stage. These results suggest that it is very hard to select the patients who need the additional therapy based on clinical staging. These drawbacks of the clinical staging may derive from an equivocal classification on local invasion (particularly stage II patients) that has been recognized as the most important clinical parameter of thymoma.[8,19] To avoid the disadvantages of clinical staging, we proposed the classification by pleural[14] and pericardial factor.

Classification by pleural factor is based on microscopic confirmation of surgically observed adhesions to the mediastinal pleura. There is no recurrence in p0 patients, regardless of their clinical stage. In p1 patients with invasive thymoma, postoperative mediastinal irradiation is significantly effective in suppressing the recurrence. However, in p2 patients, high recurrence rates were observed with (37.5%) or without (33.3%) mediastinal irradiation. In our series, analysis of the recurrent cases in stage II and III patients showed that pleural dissemination was the most common mode of recurrence. These results indicate that thymomas classified in p0 and p1 are localized diseases, and mediastinal irradiation for these diseases will be effective enough. However, many p2 patients already have latent microscopic pleural dissemination at the time of their surgical treatment of thymoma, even though they were classified as stage II. In those p2 patients, mediastinal irradiation may have only a limited effect.

It has been reported that local recurrence occurs as frequently as pleural dissemination, even after complete resection of thymoma.[2,8,20] Postoperative mediastinal irradiation seems to be the most effective adjuvant therapy for reducing the risk of local recurrence and prolonging survival in patients with locally advanced thymoma.[7,21] In the current study, local recurrence was observed in only 3.6% of stage II and stage III patients after mediastinal irradiation. However, 17.2% of stage II and stage III patients without mediastinal irradiation suffered from local recurrence even after complete resection. Because the number of cases is too small, this difference is not statistically significant. Further investigations are necessary to elucidate whether mediastinal irradiation is effective to prevent the local recurrence of thymoma.

Local recurrence was observed in any pericardial factor groups without mediastinal irradiation, whereas it was present in only one c0 patient after mediastinal irradiation. Analysis of the mode of recurrence showed that mediastinal irradiation may have been effective in preventing local recurrence, although it did not control the pleural dissemination. Unfortunately, these results show that the classification by the pericardial factor is not suitable to predict the patients who will develop local recurrences after complete resection of thymoma. However, this classification by pericardial factor is the first objective analysis available to precisely describe the spread of thymoma to the pericardium. For a detailed study of thymoma, we believe that analysis of the pericardial factor, as well as of the pleural factor, will be an indispensable element.

Frequency of first failure of therapy in the pleural cavity has been reported to be less than 10% after complete resection of thymoma.[2,4] In the current study, recurrence rate by pleural dissemination was 15% (12/80 patients), higher than the other studies.[2,4] Overlapping of recurrent types may be one of the reasons why such a high recurrence was observed on the pleural surface. Regardless, this low frequency did not support routine additional prophylactic radiotherapy, including whole-lung or hemithorax irradiation and intrapleural instillation of chromic phosphate, and only patients who are at high risk of pleural recurrence should be selected for additional therapies. From our results, our current approach to treatment of thymoma after complete resection is as follows: 1) no further treatment for p0 patients; 2) postoperative mediastinal irradiation for p1 and c0-1 pa-

tients; and 3) mediastinal irradiation with additional irradiation for pleural lesions and/or chemotherapy for p2 or c2 patients.

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