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THE ROLE OF PREOPERATIVE RADIOTHERAPY FOR INVASIVE THYMOMA

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Abstract

Six patients with large invasive thymomas were treated by preoperative irradiation with 12 to 20 Gy before total or partial resection of the tumor. The responses of these 6 thymomas were estimated on the chest radiograms as follows; complete response in 2 patients, partial response in 3 and no response in one. Although the clinical responses varied, the surgical specimens of all the tumors pronounced severe fibrosis, probably not related to irradiation, and necrotic foci with a few viable tumor cells. Total resection of the thymoma was performed in 3 patients and subtotal resection in 3. Adhered or involved surrounding tissues such as the pericardium, pleura and/or veins were also resected in most patients. Preoperative radiotherapy facilitated total or subtotal resection of the invasive thymoma mass by reducing the tumor volume.

Key words: Thymoma, preoperative radiotherapy.

Thymoma is a rare neoplasm located in the anterior mediastinum (1). Most thymomas are potentially malignant even though they may show non-invasive growth at an early stage. The malignancy of thymoma is frequently manifested by local recurrence or distant metastasis following radical resection of the tumors (2–6). Many reports suggest that a combination of operation and irradiation, especially postoperative, gives better results than either modality alone (6–13).

In this report we present 6 patients with thymomas which at the time of clinical diagnosis were considered too large or invasive for total or subtotal resection. Therefore, we decided to try preoperative radiotherapy in order to improve tumor-resectability, since thymoma is known sometimes to be highly radiosensitive (6, 13–15).

Material and Methods

Six patients with large thymomas received preoperative radiotherapy in Tsukuba University Hospital between 1982 and 1987. There were 3 males and 3 females, aged from 19 to 67 years (Table 1).

All the patients had complained of various symptoms, such as cough, dyspnea, chest pain and superior vena cava syndrome, that were suggestive of invasive extension of thymomas. Associated syndromes and diseases such as autoimmune phenomena and endocrine disorders were not found. Radiological examinations revealed large tumor masses in the anterior mediastinum. Computed tomography and/or superior venacavography showed tumor involvement of the great vessels, marked displacement of the mediastinal structures and pericardial or pleural effusion, which have been described as invasive signs of the tumors (16, 17). In one patient (case No. 1) a metastatic tumor was detected in the lung.

Mediastinal needle biopsy for histopathology was performed in all the patients for preoperative diagnosis. A definite diagnosis of thymoma was established in 2 patients, while it was difficult to distinguish the tumor from malignant lymphoma in another 2 patients as the specimens contained only a lymphocytic component. The fibrous specimens obtained from the remaining 2 patients were inadequate for histological verification.

Preoperative irradiation was given with a total tumor dose of 12 to 20 Gy over 2 or 3 weeks. We limited the tumor dose to 20 Gy or less with the intention of giving additional postoperative radiotherapy if prompted by findings during the operation. Cobalt 60 gamma-rays or 6 or 12 MV x-rays were used with portals covering the whole mediastinum in 4 patients and the tumor masses with generous margins in 2. Two patients were irradiated through a single anterior portal, while two opposing anteroposterior beams were used in the other 4 patients. In

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Table 1

Symptoms, biopsy diagnosis and tumor size before treatments, and doses in preoperative radiotherapy in 6 patients with clinical diagnosis of invasive thymoma

Patient No.	Age/ sex	Symptoms	Histologic diagnosis by biopsy	Tumor size* (cm)	Radiation dose (Gy/fractions/ days)
1	35/M	Chest pain	Thymoma (definite)	5	20.0/10/17
2	67/F	Cough, chest pain, dyspnea	Thymoma (definite)	6	18.0/10/14
3	24/M	Cough, dyspnea, SVC syndrome	Thymoma (probable)	18	18.0/10/12
4	53/F	Cough, dyspnea	Thymoma (probable)	13	18.8/12/16
5	31/F	Back pain	Fibrous tissue only	19	18.4/11/15
6	19/M	Cough, SVC syndrome	Fibrous tissue only	12	12.0/8/10

* The largest diameter of the tumor on the chest x-ray.
SVC = superior vena cava.

Table 2

Clinical responses to preoperative radiotherapy and surgical resection methods

Patient No.	Responses		Intervals* (days)	Resection methods	Resected tissues*
	Subjective	Objective			
1	Ameliorated	PR	5	Subtotal	IV, BCV, PuM
2	Ameliorated	CR	10	Total	SVC, BCV, PuL, Per, Pl
3	Completely relieved	CR	4	Total	IV, Per, Pl
4	Ameliorated	PR	20	Subtotal	IV, Per, Pl
5	Ameliorated	NR	5	Subtotal	Per, Pl
6	Completely relieved	PR	1	Total	SVC, BCV, Per, Pl

* Intervals between the last day of the irradiation and the operation day.
** Tissues resected with the tumors.
IV: Innominate vein. BCV: Brachiocephalic vein. PuM: Pulmonary metastatic tumors. Per: Pericardium. Pl: Pleura and/or a part of the lung. Ao: Adventitia of the aorta. SVC: Superior vena cava. PuL: Pulmonary lobectomy.

Table 3

Histological findings in the surgical specimens, postsurgical treatment and outcome

Patient No.	Histology in surgical specimens			Postsurgical treatment	Outcome (months)
	Remaining cells	Fibrosis	Necrosis		
1	Epi (1), Lym [1]	2+	1+	Radiotherapy (40.0 Gy)	DoM (36)
2	Epi (2), Lym [2]	3+	3+	–	DoC (2)
3	Epi (2), Lym [1]	1+	1+	Radiotherapy (27.6 Gy)	NED (53)
4	Epi (1), Lym [3]	3+	2+	Radiotherapy (43.0 Gy)	NED (8)
5	Epi (2), Lym [3]	3+	1+	Radiotherapy (36.2 Gy)	NED (51)
6	Epi (2), Lym [2]	2+	2+	Radiotherapy (39.9 Gy)	NED (44)

* Months after the beginning of the preoperative radiotherapy till the time of writing (May, 1988). DoM: dead of metastases. NED: No evidence of disease. DoC: Dead of complication. Epi: Epithelial component. Lym: Lymphocytic component. (1) Scattered cells. (2) scattered cell-clusters. Lymphocyte numbers are classified into 3 grades. [1] is the fewest. 1+ mild: 2+ moderate: 3+ severe.

two of the latter patients, the AP/PA dose ratio was 1 : 1 and in the remaining two it was 2 : 1. A shrinking field technique could be used in 3 patients. Operation was performed 1 to 20 days after radiotherapy.

Results

The clinical and histological responses and the course after the preoperative radiotherapy are summarized in Tables 2 and 3.

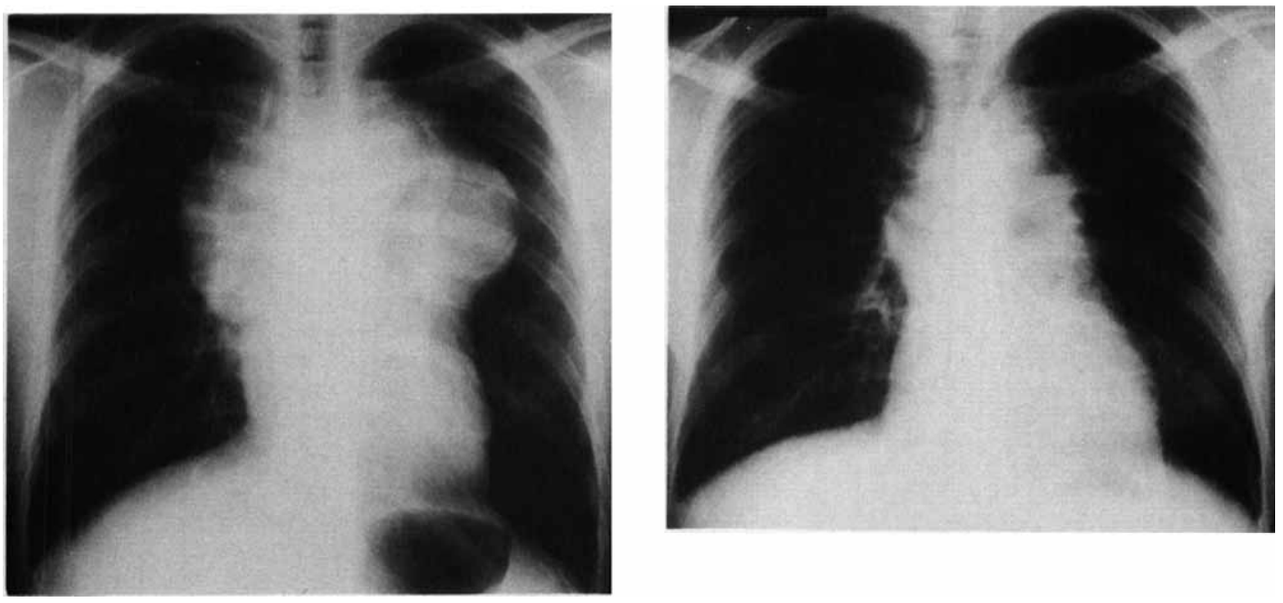

Fig. 1. Chest radiogram of patient No. 3. a) before irradiation, b) after 9 Gy/5 fractions.

More or less pronounced subjective improvement occurred in all patients during or after radiotherapy. The symptoms were completely relieved in 2 patients and ameliorated in the other 4. Chest radiography showed complete disappearance (CR) of the mediastinal mass in 2 patients (Fig. 1). A decrease by more than 30% of the tumor transverse diameter (partial response, PR), was observed in 3 patients, and a decrease by less than 30% (no response, NR) in one patient.

The tumor surgery was performed as an extensive resection including removal of the tumor and surrounding involved or adherent mediastinal structures. Transected vessels were reconstructed with vascular prostheses. However, the greater arteries involved by the tumor were always preserved. Total macroscopical resection of the tumor was achieved in 3 patients and subtotal resection in the remaining 3 patients.

The histologic findings in the irradiated thymomas were characterized by dominant fibrous lesions with scattered foci of necrosis and a rather small number of lymphocytic and/or epithelial cells. The proportion of fibrous areas and necrosis were crudely classified by 3 grades, of epithelial component by 2 grades and of lymphocytes by 3 grades (Table 3, Figs 2 and 3).

One patient (No. 2) died of pneumonia 44 days after the operation. Three patients (Nos 3, 4 and 5) developed postoperative recurrent nerve and/or phrenic nerve palsy. Five patients received additional postoperative radiotherapy from portals covering the whole mediastinum and with boost doses given to the areas macroscopically invaded. Total tumor doses from 45.6 to 61.8 Gy were given including the preoperative irradiation and with a planning that implied that the total spinal cord dose did not exceed 50 Gy. Four patients have been alive for 8 to 53 months since the beginning of the radiotherapy without evidence of recurrence. One patient who had pulmonary metastases before operation died with extensive lung and bone metastases after 36 months but without locoregional recurrence.

Discussion

Preoperative radiotherapy has been used sporadically in the management of thymoma. Weissberg et al. (18) reported their experience in 35 patients with thymoma, of whom 9 had received preoperative radiotherapy. They stated that preoperative radiotherapy might be useful for minimizing the risk of tumor cell implantation during the operation and reported that none of their 9 patients developed pleural metastases. However, only 4 of these 9 patients had invasive tumors and the data for the radiotherapy were not specified.

Sellors et al. (19) showed effectiveness of preoperative radiotherapy in patients with large tumor mass or rapidly growing tumors. The dose ranged from 4000 to 6000 R. They reported that the tumors became less extensive but that the operation was technically difficult which might have been due to the high radiation doses.

Batata et al. (8) reported that total regression was achieved in 8 of their 23 patients with invasive thymomas, partial regression in 10 and no response in 5, with a dose around 40 Gy. To judge both from the literatures and our own series thymoma seems to have a varying degree of radiosensitivity as far as regression of the tumor volume is concerned.

In our series the surgical specimens were histologically

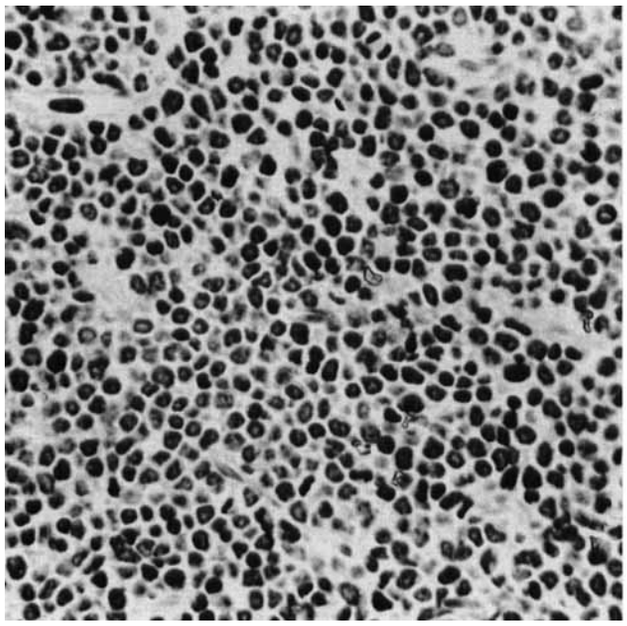

Fig. 2. Biopsy specimen from patient No. 3. Lymphocytes are observed in most part of the specimen. (HE ×100.)

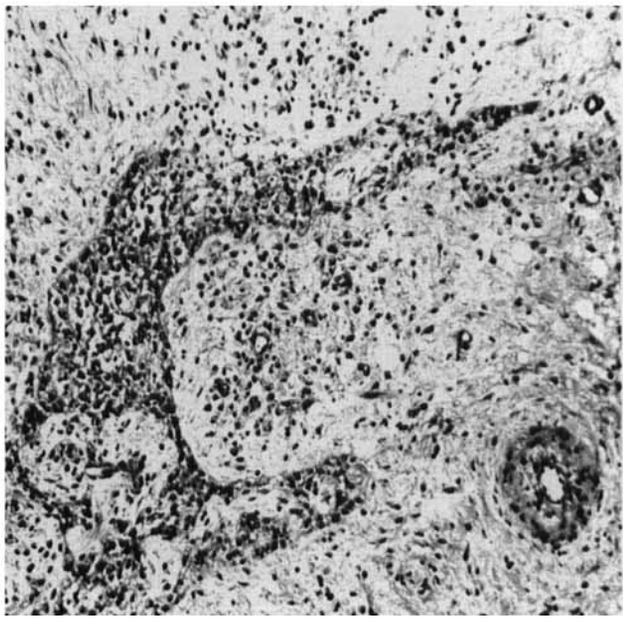

Fig. 3. Surgical specimen from patient No. 3. A few scattered lymphocytes and an epithelial cell-cluster are seen in the fibrous tissue. (HE ×25.)

characterized by the dominance of fibrous areas and a various number of necrotic foci while the number of lymphocytic cells and epithelial cells seemed to be less abundant than expected. A probable explanation for this picture is that the last mentioned cells (especially the lymphocytic cells) were most radiosensitive. This explanation corresponds to conjecture by Marks et al. (14) that the lymphocyte-predominant thymoma might be more radiosensitive. On the other hand, in view of the low radiation doses and the short time between radiotherapy and surgery, it does not seem likely that fibrosis and necrosis should have been induced by the irradiation and it was probably a spontaneous feature of the tumors.

In recent years it has been demonstrated that the behavior of thymoma is to some degree predictable by the morphologic features. Verley & Hollmann (20) showed that there was a good correlation between the degree of differentiation of the tumors and prognosis. Monden et al. (21) reported that the degree of differentiation of the epithelial tumor component showed strong correlation with both invasiveness and prognosis. Therefore, when preoperative radiotherapy is planned, it is desirable to obtain adequate biopsy specimens for both histological diagnosis and grading before the irradiation. Adler et al. (22) reported fine-needle aspiration biopsy under computed tomography guidance, as an easy method to get adequate specimens, especially in cases with vascular involvement as superior vena cava syndrome.

In conclusion, preoperative radiotherapy with a tumor dose of 12 to 20 Gy seemed to improve resectability of symptomatic invasive thymomas by improving the patients' general condition and by making surgical manipulation easier after reduction of the tumor volume. The rather small radiation dose does not impede a definite histopathological diagnosis of the surgical specimen or additional postoperative irradiation if indicated by the surgical or histological findings.

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