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BRIEF COMMUNICATION

A Multidisciplinary Approach to Therapy for Unresectable Malignant Thymoma

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Background: The therapeutic outcome for unresectable, locally advanced, malignant thymoma has been poor.

Objective: To improve tumor resectability and patient survival rates by studying a multimodal approach to therapy for unresectable malignant thymoma.

Design: Prospective cohort study.

Setting: Tertiary care cancer center.

Participants: All eligible patients had newly diagnosed, histologically proven, unresectable malignant thymoma.

Intervention: The treatment regimen consisted of induction chemotherapy (three courses of cyclophosphamide, doxorubicin, cisplatin, and prednisone), surgical resection, postoperative radiation therapy, and consolidation chemotherapy (three courses of cyclophosphamide, doxorubicin, cisplatin, and prednisone). Tissue samples were taken at the time of surgical resection for assessment of tumor necrosis and Ki-67 expression.

Measurements: Tumor response and resectability (both overall and after induction chemotherapy) and disease-free survival rate in patients who received multimodal therapy.

Results: 13 patients were consecutively enrolled from February 1990 to December 1996, and 12 evaluable patients were assessed for response. Disease responded to induction chemotherapy completely in 3 patients (25%) and partially in 8 patients (67%); 1 patient had a minor response (8%). Eleven patients had surgical resection; 1 refused surgery. Tumors were removed completely in 9 (82%) and incompletely in 2 (18%) of 11 patients who had been receiving radiation therapy and consolidation chemotherapy. All 12 patients are alive (100% at 7 years), with a median follow-up of 43 months, and 10 patients are disease free (73% disease-free survival at 7 years). A high correlation was seen between tumor necrosis after induction chemotherapy and Ki-67 expression ($r = -0.88$).

Conclusions: Aggressive multimodal treatment is highly effective and may cure locally advanced, unresectable malignant thymoma.

Malignant thymoma is a rare mediastinal tumor [1]. The important prognostic factors in this condition are disease stage and completeness of surgical resection [2-4]. In the early stages, the tumor can be completely resected. However, complete resection of advanced-stage tumors has been difficult [4], and surgery in such cases has not substantially changed the biology of the tumor because gross residual disease or microinvasion of surrounding structures, including the pleura and the pericardium, has led to a high incidence of eventual recurrence.

Ki-67 has been used as an important indicator of the biological behavior of tumor cells [5,6]. In cases of invasive thymoma, expression of Ki-67 has correlated with proliferating activity of tumor cells and clinical stage. There is also a general correlation between the labeling index of Ki-67 and both invasiveness and histologic subtype [6]. We investigated whether such correlations were valid in tissue samples obtained from our patients.

Radiation therapy has been important in the management of patients with advanced thymoma. Postoperative irradiation of tumors graded stage II or beyond has been shown to reduce the risk for recurrence in patients with invasive thymoma who have had complete resection [7,8]. However, in cases of incomplete resection, postoperative irradiation has not substantially changed overall survival rates; disease tends to recur both locally and distantly [9,10].

Chemotherapy has shown significant antitumor activity against unresectable, recurrent, or metastatic thymomas [11,12]. Our experience and that of others has indicated that overall major response rates with combination chemotherapy based on cisplatin and doxorubicin were between 50% and 90% in chemotherapy-naive patients [11-14].

To improve tumor resectability and to determine the disease-free and overall survival times of patients with locally advanced unresectable thymoma, we designed a prospective study of a multimodal treatment regimen.

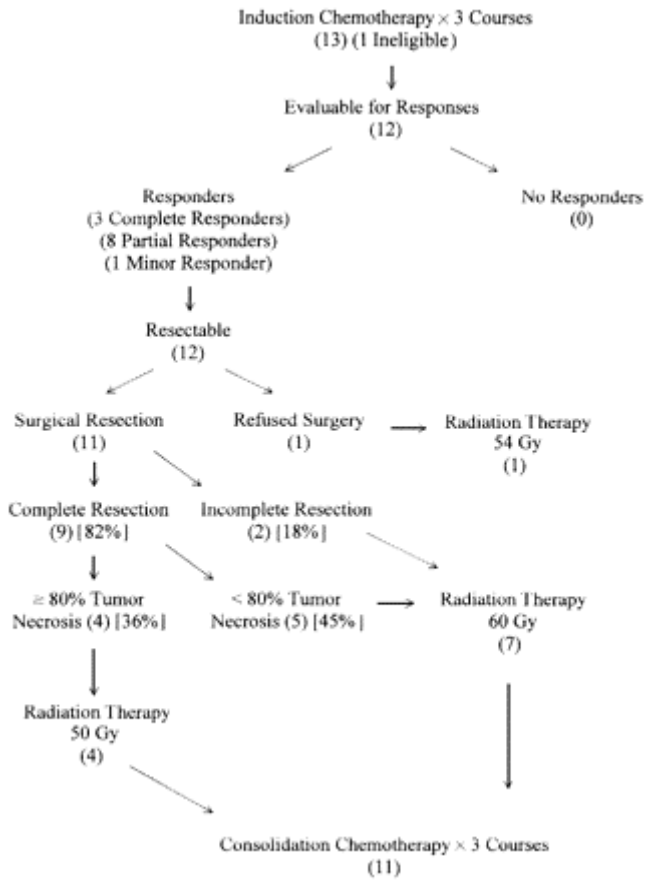
Methods

Patients

Patients with Masaoka stage III or IVA tumors [2] were eligible for this study. The resectability of disease was determined by the thoracic surgeons before patients entered the protocol. Patients had a performance status of less than 2 on the Zubrod scale, bidimensional measurable disease, adequate bone marrow (absolute granulocyte counts > 1500 cells/mm^3 and platelet counts > 100 000 cells/mm^3), adequate hepatic function (serum total bilirubin level < 1.5 mg/dL [25.65 [micro sign]mol/L]), and adequate renal function (serum creatinine level < 1.5 mg/dL [132.6 [micro sign]mol/L]). Left ventricular ejection fraction in all participants was examined by using two-dimensional echocardiography before treatment. Signed informed consent was obtained, and the protocol was approved by the institutional review board at the M.D. Anderson Cancer Center.

Protocol

We designed this prospective study for patients with pathologically confirmed malignant thymoma. The study schema consisted of three courses of induction chemotherapy, surgical resection, radiation therapy, and three courses of consolidation chemotherapy (Figure 1).



Induction chemotherapy consisted of cyclophosphamide, 500 mg/m^2, on day 1; continuous infusion of doxorubicin, 20 mg/m^2 per day, on days 1 to 3 (total, 60 mg/m^2); cisplatin, 30 mg/m^2 per day, on days 1 to 3 (total, 90 mg/m^2); and prednisone (100 mg/d for 5 days). This cycle was repeated three times at 3- to 4-week intervals. Prophylactic granulocyte colony-stimulating factor was not used.

After induction chemotherapy, we assessed clinical response by measuring tumor size on computed tomography [13]. Within 3 to 4 weeks after the last chemotherapy cycle, we used computed tomography to assess tumor resectability. Resection was done during this exploration, and the pathologic specimen was assessed for the degree of tumor necrosis. Within 3 to 6 weeks of surgery, patients who had had complete resection and whose tumors were at least 80% necrotic began radiation therapy with a total dose of 50 Gy. Patients were irradiated with a total dose of 60 Gy if resection was incomplete or if less than 80% of the tumor was necrotic.

Consolidation chemotherapy with 80% doses of cyclophosphamide, doxorubicin, and cisplatin and a 100% dose of prednisone was repeated every 3 to 4 weeks for three courses.

Ki-67 Expression

After induction chemotherapy, 11 patients had surgical resection (1 patient did not have surgery) and 16 tissue samples were obtained. All samples underwent immunohistochemical analysis so that we could determine whether Ki-67 expression correlated with tumor necrosis after chemotherapy. Anti-Ki-67 antibody (clone MIB1) was obtained from Zymed Laboratory, Inc. (San Francisco, California), and immunohistochemistry was done by using the standard procedure [6].

Statistical Analysis

Overall survival was measured from the date of registration for induction chemotherapy to the date of last follow-up or death. Disease-free survival was measured from the date of last treatment to the date of last follow-up or recurrence. We estimated survival curves by using the method of Kaplan and Meier [15]. We calculated the Pearson correlation coefficient between Ki-67 expression and percentage of tumor necrosis, using the average if a participant had multiple observations. All calculations were done by using SAS software (SAS Institute, Inc., Cary, North Carolina).

Results

From February 1990 to December 1996, a total of 13 patients were consecutively enrolled in the study. One of these patients was later deemed ineligible because a final pathologic diagnosis of thymic carcinoma was made. Patient characteristics are shown in Table 1.

Patient	Sex	Age	Performance Status (Zubrod Scale)	Cell Type	Masaoka Stage	Tumor Size	Remarks
		y				*cm*	
1	Female	31	0	Epithelial	III	9 × 7 × 7	Large anterior and superior mediastinal mass with invasion of mediastinal soft tissue
2	Female	55	1	Lymphocytic	III	8 × 8 × 7	Invasion of pulmonary arteries and pericardium
3	Male	42	0	Mixed	III	7 × 7 × 4.5	Abutted pericardium and aorta
4	Male	24	0	Epithelial	IVA	8 × 6 × 5	Incomplete resection at outside hospital before study entry
5	Female	33	1	Mixed	IVA	14 × 10 × 9	Invasion of pericardium and aorta; massive recurrence after surgery and radiation therapy
6	Female	23	1	Lymphocytic	IVA	15 × 12 × 6.5	Pleural effusion with lung collapse
7	Male	33	1	Mixed	IVA	10 × 9 × 7	Pleural seeding with extension to diaphragm
8	Female	30	0	Epithelial	III	11 × 10 × 7	Large mass with central necrosis with invasion of mediastinal fatty tissue
9	Male	40	1	Mixed	IVA	9 × 8 × 7	Invasion of pericardium and controlled myasthenia gravis*
10	Male	59	1	Epithelial	IVA	9 × 7.5 × 5	Invasion of pericardium and pleura
11	Female	39	0	Lymphocytic	IVA	17.5 × 12 × 6	Associated with mycosis fungoides and compressing the pulmonary vessels
12	Female	66	1	Mixed	IVA	9 × 7.5 × 5	Superior vena cava syndrome and pleural effusion

* Patient presented with myasthenia gravis, but the symptoms were controlled with medication before he started chemotherapy. After the second course of chemotherapy, his medication was tapered off.

Induction chemotherapy produced three complete responses, eight partial responses, and one minor response, for an overall major response rate of 92%. Eleven patients had surgical exploration; 1 patient refused surgical resection. Tumors were completely resected in all 3 patients whose disease responded completely and in 6 of the 8 patients whose disease responded partially; thus, 9 of 11 patients (82%) were responders. Resection was incomplete in 2 patients (18%), including 1 of the patients with partial response and the 1 patient with a minor response.

All pathologic specimens obtained during surgery were evaluated for extent of tumor necrosis. Two of the three complete responders had 100% tumor necrosis, and one complete responder and one partial responder had tumor necrosis greater than 80%. Seven other patients had tumor necrosis less than 80%.

All 12 patients received radiation therapy. The 4 patients (36%) whose tumors had more than 80% necrosis on complete resection received 50 Gy; the 7 patients who had less than 80% necrosis or had incomplete resection received 60 Gy. The patient who refused surgery received only 54 Gy of the planned 60 Gy because of insufficient compliance. All 11 patients who underwent surgery had consolidation chemotherapy (Figure 1).

Overall, after completion of the planned therapy, 10 patients remain disease free at a median follow-up period of 43 months (disease-free survival rate at 7 years, 73%). Two patients who had incomplete tumor resection had locoregional recurrent disease but are still alive (overall survival rate at 7 years, 100%).

The major side effect during induction and consolidation chemotherapy was myelosuppression. One patient required a prophylactic platelet transfusion but had no bleeding. Other hematologic side effects were modest. The most common nonhematologic side effects were fatigue, nausea and vomiting, and decreased appetite. Two patients developed neutropenic fever during induction chemotherapy but recovered fully with intravenous antibiotics. One patient developed radiation-induced mild pneumonitis and esophagitis. No patients developed cardiac toxicity. No surgical morbidity or mortality occurred.

We correlated the degree of tumor necrosis with Ki-67 expression in the samples after induction chemotherapy. The samples with tumor necrosis greater than 80% expressed a minimal degree of Ki-67 (mean labeling index, 0.02 [range, 0.01 to 0.03]). The overall correlation between tumor necrosis and Ki-67 expression was high (Pearson r = -0.88).

Discussion

Complete surgical resection is an important prognostic factor for locally advanced malignant thymoma [16]. It is critical to convert locally advanced unresectable tumors (stage III and IVA) to resectable tumors. Complete resection of these advanced tumors is often unfeasible because the tumors invade adjacent mediastinal structures, including major blood vessels and the pericardium.

Preoperative (neoadjuvant or induction) chemotherapy may enhance tumor resectability. With this goal in mind, we administered induction chemotherapy to all patients and achieved a major response rate of 92%. Our results and those of others [17-19] suggest that malignant thymoma is highly responsive to chemotherapy. More important, disease in all of our patients became resectable with this preoperative chemotherapy.

Another striking finding was the degree of tumor necrosis in tissue specimens. Almost half of the patients whose tumors were completely resected had tumor necrosis greater than 80% in resected specimens. All patients received postoperative radiation therapy. Komaki and Cox [7] summarized data from the literature showing that recurrence (local or distant) was found in 25% of patients who received postoperative radiation therapy and 57% of patients who did not receive this therapy. These data clearly show that postoperative radiation therapy for tumors graded stage II or higher further reduces risk for recurrence in patients who have had even complete resection. The total dose of radiation therapy in the postoperative setting has not been well established in thymoma; we used doses similar to those that palliate microscopic residual disease (50 Gy) and those that palliate gross residual disease (60 Gy) in patients with lung carcinoma.

Rea and colleagues [19] treated 16 patients with invasive thymoma (stage III or IV) with three to four courses of induction chemotherapy followed by surgery. The patients who had viable tumors at surgery then received radiation therapy only. Patients whose tumors were not viable at surgery received three more courses of chemotherapy without radiation therapy. Of 11 patients who had complete resection at surgery and received radiation therapy alone, 3 (27%) died of recurrent disease. Of the 5 patients whose tumors were partially resected, 3 (60%) died after surgery. Such data clearly indicate that postoperative radiation therapy alone or chemotherapy alone may not optimally control residual disease.

An intergroup trial [20] recently reported on patients with unresectable thymomas who received induction chemotherapy followed by radiation therapy alone without surgical resection. The 5-year survival rate in this study was 52.5%. The data also indicated that surgery (particularly complete resection) is an important part of a multimodal approach to therapy. Therefore, the strategy used in our trial, which included surgery followed by both postoperative radiation therapy and consolidation chemotherapy, seems to be critical to better control of residual disease. However, the optimal number of courses of chemotherapy and combination of systemic agents have yet to be determined. Other limiting factors of our study are the small number of patients, the lack of controls, and the nonrandomized design. Nevertheless, the overall survival and disease-free survival rates seen with this multidisciplinary approach to malignant thymoma are excellent and seem to be better than those in any other reported studies [17-20]. Incorporation of a biomarker, such as Ki-67, into clinical trials may promote better understanding of the biological behavior of tumor cells and better therapeutic outcomes.

In conclusion, we believe that a multimodal approach to therapy may prolong lives and may cure locally advanced unresectable malignant thymomas. Patient accrual in this study continues.

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