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Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report

Edward S. Kim[a,*], Joe B. Putnam[a], Ritsuko Komaki[a], Garrett L. Walsh[a], Jae Y. Ro[a], Hyung Ju Shin[b], Mylene Truong[a], Hojin Moon[a], Steven G. Swisher[a], Frank V. Fossella[a], Fadlo R. Khuri[b], Waun K. Hong[a], Dong M. Shin[b]

[a] *Department of Thoracic/Head and Neck Medical Oncology, Thoracic/Cardiovascular Surgery, Radiation Therapy, Pathology, Radiology, and Biostatistics, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Box 432, Houston, TX 77030, USA*
[b] *The Division of Hematology—Oncology, Winship Cancer Institute, Emory University School of Medicine, 1365 Clifton Road, N.E., Atlanta, GA 30322, USA*

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Summary *Purpose:* To evaluate tumor resectability after induction chemotherapy and to determine disease-free and overall survival rates of patients with locally advanced unresectable thymoma that received a multimodal treatment regimen. *Patients and methods:* Twenty-two patients (9 men, 13 women) with histologically confirmed invasive thymoma were treated with a multidisciplinary regimen consisting of three courses of induction chemotherapy, surgical resection, and radiation therapy, followed by three courses of consolidation chemotherapy. The median age was 47 years (range, 25—70). Eleven patients had stage III disease, 10 patients, stage IVA, and one patient, IVB. The most common histologic type was lymphocytic. Induction chemotherapy consisted of 500 mg/m^2 of cyclophosphamide on day 1; doxorubicin (20 mg/m^2 per day) on days 1—3 via continuous infusion (a total of 60 mg/m^2); cisplatin (30 mg/m^2 per day) on days 1—3 (a total of 90 mg/m^2); and prednisone (100 mg per day) on days 1—5. This cycle was repeated three times at 3—4-week intervals. Patients then underwent surgery for tumor resection and received radiotherapy. Consolidation chemotherapy given at 80% of the induction chemotherapy doses of cyclophosphamide, doxorubicin, and cisplatin and 100% of the dose of prednisone was then repeated every 3—4 weeks for a total of three courses. *Results:* Induction chemotherapy

* Corresponding author. Tel.: +1-713-792-6363; fax: +1-713-796-8655.
E-mail address: edkim@mdanderson.org (E.S. Kim).

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produced major responses in 17 (77%) of the 22 patients including 3 (14%) complete responses (CR) and 14 (63%) partial responses (PR). Twenty-one patients underwent surgical exploration: 16 (76%) had complete resection and 5 (24%) had incomplete resection; one patient refused surgery. All 22 patients received radiation therapy. Nineteen of 22 patients completed the planned therapy, and all but one had completed consolidation chemotherapy at the time of analysis. With a median follow-up time of 50.3 months, 18 of the 19 patients who completed the multidisciplinary approach were disease-free. Of the 22 patients originally registered, 20 were alive at the time of analysis (one patient died of endocarditis, and one died of recurrent disease). The overall survival rate was 95% at 5 years (95% confidence interval (CI), 0.87—1.0) and 79% at 7 years (95% CI, 0.55—1.0). The progression-free survival rates were 77% at 5 years (95% CI, 0.58—1.0) and 77% at 7 years (95% CI, 0.58—1.0). The major side effect from induction and consolidation chemotherapy was myelosuppression. Nine patients experienced grade III/IV neutropenia, which included neutropenic fever in two patients, and grade III thrombocytopenia in two patients. The most common nonhematologic side effects were fatigue, nausea and vomiting, and decreased appetite. One patient experienced acute respiratory distress syndrome after surgical resection and required a prolonged hospitalization. No patients developed cardiac toxic effects, and no surgical mortality occurred. *Conclusions:* The use of induction chemotherapy to optimize surgical resectability of thymoma followed by radiation therapy and consolidation chemotherapy lead to good control of residual disease and high overall survival rates. We believe that this combined multidisciplinary approach prolongs lives and may cure locally advanced unresectable malignant thymomas. Future prospective multi-institutional studies are needed to further verify or define the best treatment for this patient population.

1. Introduction

Thymomas are rare mediastinal tumors that comprise the majority of thymic lesions in the anterior mediastinum in the adult humans [1—4]. About half of the patients with thymic tumors are asymptomatic, their lesion being discovered serendipitously on chest radiograph. Of symptomatic patients, most that present will have myasthenia gravis, red cell aplasia, or hypogammaglobulinemia [5]. As disease stage and complete surgical resectability are important prognostic factors, early-stage encapsulated tumors are easily resected with curative intent [6—8]. Patients with malignant thymoma who undergo complete resection and who receive postoperative irradiation have a low risk of recurrent disease. However, patients with advanced invasive disease whose tumors cannot be completely resected have a lower cure rate with or without postoperative radiotherapy [9—12]. These patients, because of gross residual disease or microinvasion of surrounding structures including the pleura and pericardium, have a high incidence of disease recurrence. Patients whose disease recurs have a much poorer prognosis [13,14].

Chemotherapy has shown significant antitumor activity in metastatic, unresectable, or recurrent thymomas [15—17]. Cisplatin and doxorubicin-based combination chemotherapy regimens produce overall major response rates between 50 and 90% in chemotherapy-naïve patients. However, in patients with recurrent disease previously treated with chemotherapy, response rates to chemotherapy are lower.

We designed a prospective study using a multimodal treatment regimen consisting of chemotherapy surgery, and radiotherapy to improve tumor resectability and to determine the disease-free and overall survival times of patients with locally advanced unresectable malignant thymoma. Consolidation chemotherapy was added to target microscopic disease that potentially recurs outside of the radiation portals. This report describes the final results of this study.

2. Patients and methods

2.1. Patients

Patients with Masaoka et al. [6] stage III or IV tumors were eligible for this prospective study. The thoracic surgeons determined disease resectability before patients entered the protocol. Patients had to have Zubrod performance status of two or less, bidimensionally measurable disease, adequate bone marrow function (absolute granulocyte counts $\geq$1500 cells/mm^3 and platelet counts $\geq$100,000 cells/mm^3), adequate hepatic function (serum total bilirubin level $\leq$1.5 mg/dl, and

adequate renal function (serum creatinine level $\leq$1.5 mg/dl or creatinine clearance $\geq$60 ml/min). The left ventricular ejection fraction was examined in all participants using two-dimensional echocardiography or a cardiac scan before treatment. The Institutional Review Board at The University of Texas, M.D. Anderson Cancer Center, approved the protocol, and signed informed consent was obtained from all patients. Ineligibility criteria included prior chemotherapy with doxorubicin, cyclophosphamide, or cisplatin, prior malignancy within the previous 5 years (except nonmelanomatous skin cancer, stage I colon carcinoma, uterine cervical cancer, prostate cancer, and head and neck cancer), thymic carcinoma or prior history of congestive heart failure.

The pretreatment evaluation included a medical history and physical examination, chest radiographs (posteroanterior and lateral), a complete blood cell count, serum electrolytes, chemistry panel, and serum creatinine. Computed tomography (CT) of the chest was performed to obtain tumor measurements.

During treatment, history and physical examination, serum chemistry panel, and complete blood cell counts were performed prior to each course of treatment. Chest CT scans were repeated after three courses of induction chemotherapy, after radiation therapy, or to confirm a complete response (CR).

2.2. Treatment regimen

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 (Fig. 1).

Induction chemotherapy consisted of cyclophosphamide at 500 mg/m^2 on day 1; doxorubicin at 20 mg/m^2 per day on days 1–3, via continuous infusion (a total of 60 mg/m^2); cisplatin at 30 mg/m^2 per day on days 1–3 (a total of 90 mg/m^2); and prednisone at 100 mg per day for 5 days on days 1–5. This cycle was repeated three times at 3–4-week intervals. Patients were pretreated with metoclopramide (1 mg/kg IV) and diphenhydramine (25 mg IV) before each chemotherapy treatment. Prophylactic granulocyte colony-stimulating factor was not used.

After induction chemotherapy, we assessed clinical response by measuring tumor size on CT scans. Within 3–4 weeks after the last chemotherapy cycle, we used computed tomography to assess tumor resectability. Resection was performed and the surgical specimen was assessed for the degree of tumor necrosis. Patients who underwent complete resection and whose tumors were at least 80% necrotic began radiation therapy with a total dose of 50 Gy within 3–6 weeks of surgery. Patients were irradiated with a total dose of 60 Gy if resection was incomplete or if less than 80% of the tumor was necrotic. Two pathologists assessed the degree of necrosis before patients began radiation therapy.

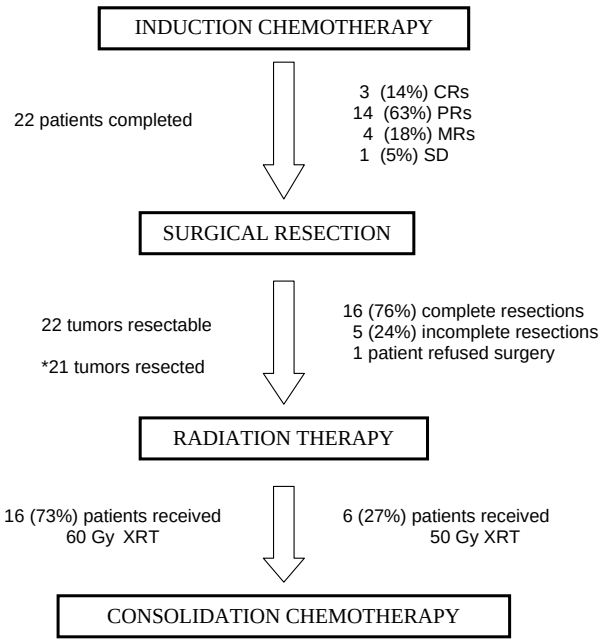

Fig. 1 Treatment schema of the multidisciplinary approach. Patients and responses are included.

Consolidation chemotherapy was given at 80% of the induction chemotherapy doses of cyclophosphamide, doxorubicin, and cisplatin and 100% of the dose of prednisone. It was repeated every 3–4 weeks for a total of three courses.

The chemotherapy dose modifications were considered for patients demonstrating hematologic toxic effects including granulocyte and platelet nadir levels. For nonhematologic toxic effects of grade 3 or higher, dosage adjustments were made. Therapy was discontinued for the following reasons: development of unacceptable side effects, which was defined as unpredictable, irreversible, or grade 4, noncompliance by the patient with protocol requirements, or patient refusal. To minimize toxicity from radiation therapy, dosage limits were applied to the spinal cord (45 Gy), lung (18 Gy), and heart (36 Gy).

A complete response was defined as the disappearance of all evidence of tumor for at least

one cycle of therapy or 4 weeks, and a partial response (PR) was defined as a 50% or greater reduction in the sum of the products of diameters of all measured lesions persisting for at least one cycle of therapy or 4 weeks. A minor response was a measurable decrease in lesions that was too small or too brief to qualify as a partial response. Any increase of greater than 25% in this sum or in the estimated size of nonmeasurable lesions, or the appearance of an unequivocal new lesion was defined as progressive disease. Overall survival time was measured from the date of registration for induction chemotherapy to the date of the last follow-up contact or death (from all causes). Progression-free survival time was measured from the date of last treatment to the date of last follow-up visit or disease progression. We estimated survival curves by using the method of Kaplan and Meier [18].

3. Results

3.1. Patients

From February 1990 to April 2000, a total of 22 patients with advanced malignant thymoma were consecutively entered into the trial. Patient characteristics are listed in Table 1. The median age of the 22 eligible patients was 47 years (range, 25—70), and the study group included 9 men and 13 women. Patients had a mean Zubrod performance status of one (range, 0—2). Twenty-one patients had had no prior treatment, and one had recurrent disease (previous treatment included surgery and radiotherapy). Masaoka et al. [6] staging revealed 11 (50%) patients with stage III, 10 (45%) with stage IVA, and 1 (5%) with stage IVB. Thymoma cell types included 7 (32%) epithelial tumors, 10 (45%) lymphocytic tumors, and 5 (23%) mixed tumors. The detailed tumor characteristics are described in Table 2.

Table 1 Patient characteristics

Characteristics	Number (%)
Age	
Median	47
Range	25—70
Sex	
Female	13 (59)
Male	9 (41)
Performance status	
0	9 (41)
1	11 (50)
2	2 (9)
Masaoka stage	
III	11 (50)
IVA	10 (45)
IVB	1 (5)
Histology	
Epithelial	7 (32)
Lymphocytic	10 (45)
Mixed	5 (23)
Prior treatment	
No (newly diagnosed)	21 (95)
Yes (recurrent tumor)	1 (5)

3.2. Disease response and survival times

Induction chemotherapy produced major responses in 17 (77%) of the 22 patients, including 3 (14%) complete responses and 14 (67%) partial responses. Twenty-one patients underwent surgical exploration, and one patient refused surgery. Of the 21 patients undergoing surgical resection, 16 (76%) had complete resections and 5 (24%) had incomplete resections. Tumors were completely resected in all three patients (100%) whose disease responded completely, in 10 of the 14 patients (71%) whose disease responded partially, and in two of the three patients (67%) who had minimal response. One patient who had stable disease after induction chemotherapy needed two surgical procedures for complete tumor resection.

All pathologic specimens obtained during surgery were evaluated for extent of tumor necrosis. Of the 16 patients whose tumors were completely resected, 6 (38%) had tumors that were more than 80% necrotic. All three of the patients who had a CR after induction chemotherapy had tumor specimens with greater than 80% tumor necrosis, including two that were 100% necrotic. Of 14 patients who had a PR, three patients had tumors with more than 80% tumor necrosis (Fig. 2). No patient with a minor response or stable disease had a tumor with more than 80% necrosis (Table 3).

All 22 patients received radiation therapy. Patients who had tumors more than 80% necrotic and complete surgical resection received 50 Gy, while those patients who had incomplete surgical resection or less than 80% tumor necrosis received 60 Gy. The patient who refused surgery chose to finish only 54 Gy of the planned 60 Gy. One other patient completed only 34 Gy before he died of endocarditis. Twenty completed the planned multidisciplinary regimen. In median follow-up time of

Table 2 Tumor characteristics

Patient	Cell type	Masaoka stage	Tumor dimensions (cm)	Tumor volume (cm^3)	Remarks
1	Epithelial	III	9 × 7 × 7	441	Invasion of mediastinal soft tissue
2	Lymphocytic	III	8 × 8 × 7	448	Invasion of pulmonary arteries and pericardium
3	Epithelial	IVA	8 × 6 × 5	240	Incomplete resection at outside hospital before study entry
4	Mixed	III	7 × 7 × 4.5	220.5	Abutted pericardium and aorta
5	Mixed	IVA	14 × 10 × 9	1260	Invasion of pericardium and aorta; massive recurrence after surgery and radiation
6	Lymphocytic	IVA	15 × 12 × 6.5	1170	Pleural effusion with lung collapse
7	Mixed	IVA	10 × 9 × 7	630	Pleural seeding with extension to diaphragm
8	Epithelial	III	11 × 7 × 10	770	Large mass with central necrosis with invasion of mediastinal fatty tissue
9	Mixed	IVA	7 × 5 × 8	280	Invasion of pericardium and controlled myasthenia gravis
10	Epithelial	IVA	9 × 7.5 × 5	337.5	Invasion of pericardium, pleura and diaphragm; lung metastases
11	Lymphocytic	IVA	12 × 17.5 × 6	1260	Associated with mycosis fungoides and pulmonary vesselcompression
12	Mixed	IVA	9 × 7.5 × 5	337.5	Superior vena cava syndrome, pleural effusion, and encasement of great vessels
13	Epithelial	IVA	11 × 7 × 6	462	Pericardial effusion and encasement of aorta
14	Lymphocytic	III	4 × 6 × 4	96	Invasion of pulmonary artery
15	Epithelial	III	10 × 7 × 7	490	Invasion of pleura
16	Lymphocytic	III	6 × 5 × 5	150	Invasion of pleura
17	Lymphocytic	III	5 × 3 × 6	90	Pleural effusion
18	Lymphocytic	III	11 × 7 × 13	1001	Pleural effusion, pulmonary metastases, and lobar collapse
19	Lymphocytic	IVB	18.5 × 8 × 5	740	Invasion of pleura, aorta, and pulmonary artery
20	Epithelial	III	7 × 5 × 10	350	Abutting right atrium, right ventricle, and pulmonary veins
21	Lymphocytic	III	9 × 9 × 4	324	Encasement of pulmonary artery and veins
22	Lymphocytic	IVA	5 × 4 × 3	60	Pleural metastases and controlled myasthenia gravis

Table 3 Tumor necrosis in relation to response

Response to induction chemotherapy	Resection at surgery	No. of patients, $N = 21$ (%)	Tumor necrosis at surgery	
			$\geq$80%	<80%
Complete	Complete	3 (14)	3	0
	Incomplete	0 (0)	0	0
Partial	Complete	10 (47)	3	7
	Incomplete	4 (19)	0	4
Minor	Complete	2 (10)	0	2
	Incomplete	1 (5)	0	1
Stable disease	Complete	1 (5)	0	1
	Incomplete	0 (0)	0	0
Overall	Complete	16 (76)		
	Incomplete	5 (24)		

50.3 months, 19 of the 20 achieved disease-free status. At the time of analysis, 20 were alive; one patient died of endocarditis, and one patient died of recurrent disease. The overall survival rate was 95% at 5 years (95% confidence interval (CI), 0.87—1.0) and 79% at 7 years (95% CI, 0.55—1.0) (Fig. 3A). The progression-free survival rates were 77% at 5 years (95% CI, 0.58—1.0) and 77% at 7 years (95% CI, 0.58—1.0) (Fig. 3B).

3.3. Toxic effects

Toxicity was graded according to the NCI common toxicity criteria for all patients. The toxic effects from chemotherapy were modest and well tolerated (Table 4). The major side effect from induction chemotherapy was myelosuppression. Seven patients experienced grade III/IV neutropenia, including neutropenic fever in three patients

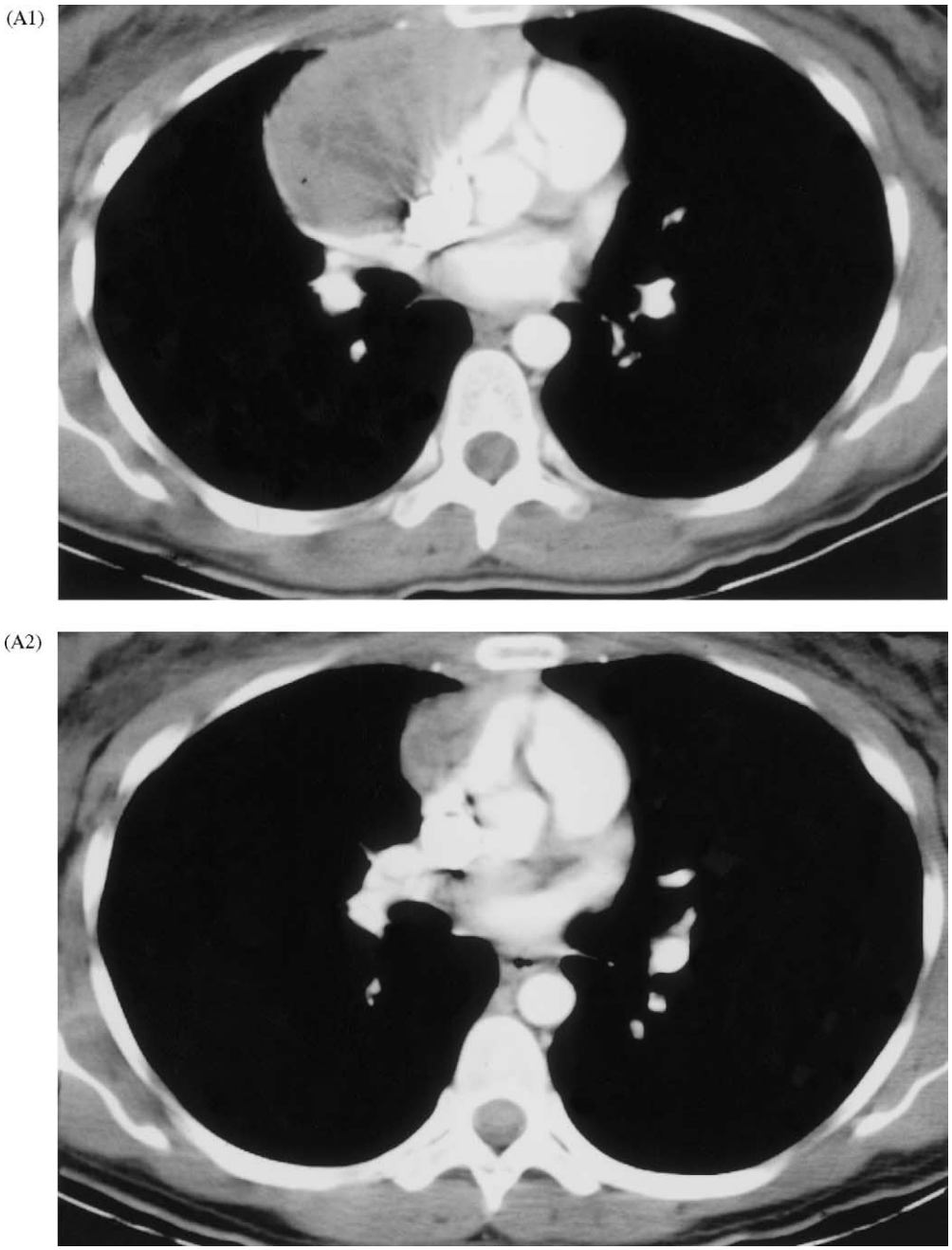

Fig. 2 The baseline chest CT scan (A1) showing a bulky tumor compressing pericardium with pleural effusion. (A2) Post-induction chemotherapy CT scan demonstrating an excellent partial response. (B1) Pathological findings indicated epithelial-predominant type malignant thymoma showing bland polygonal tumor cells with distinct collagenous band before chemotherapy and (B2) extensive tumor necrosis (near 100%) after chemotherapy.

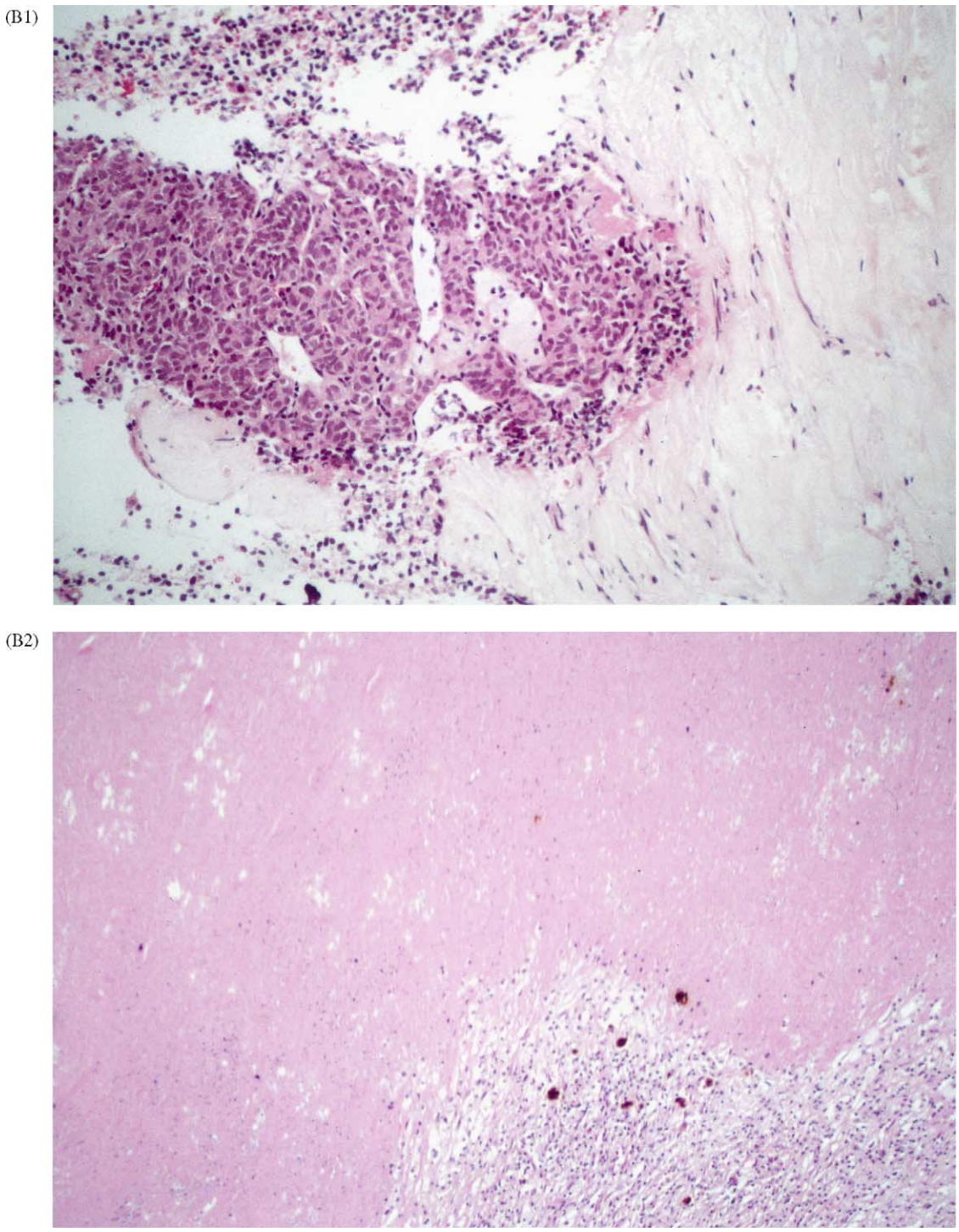

Fig. 2 (*Continued*).

who recovered following antibiotic therapy and three patients with grade III thrombocytopenia. Two patients experienced grade 3 myelosuppression during consolidation chemotherapy. The most common nonhematologic side effects were fatigue, nausea and vomiting, and decreased appetite. Grade 3 toxic effects included esophagitis (four), pain (four), fatigue (three), diarrhea (two), nausea (one), and respiratory distress (two). One patient experienced adult respiratory distress syndrome after surgical resection and required prolonged hospitalization. She eventually completed her therapy. No patients had myocardial toxicity, and no surgical mortality occurred.

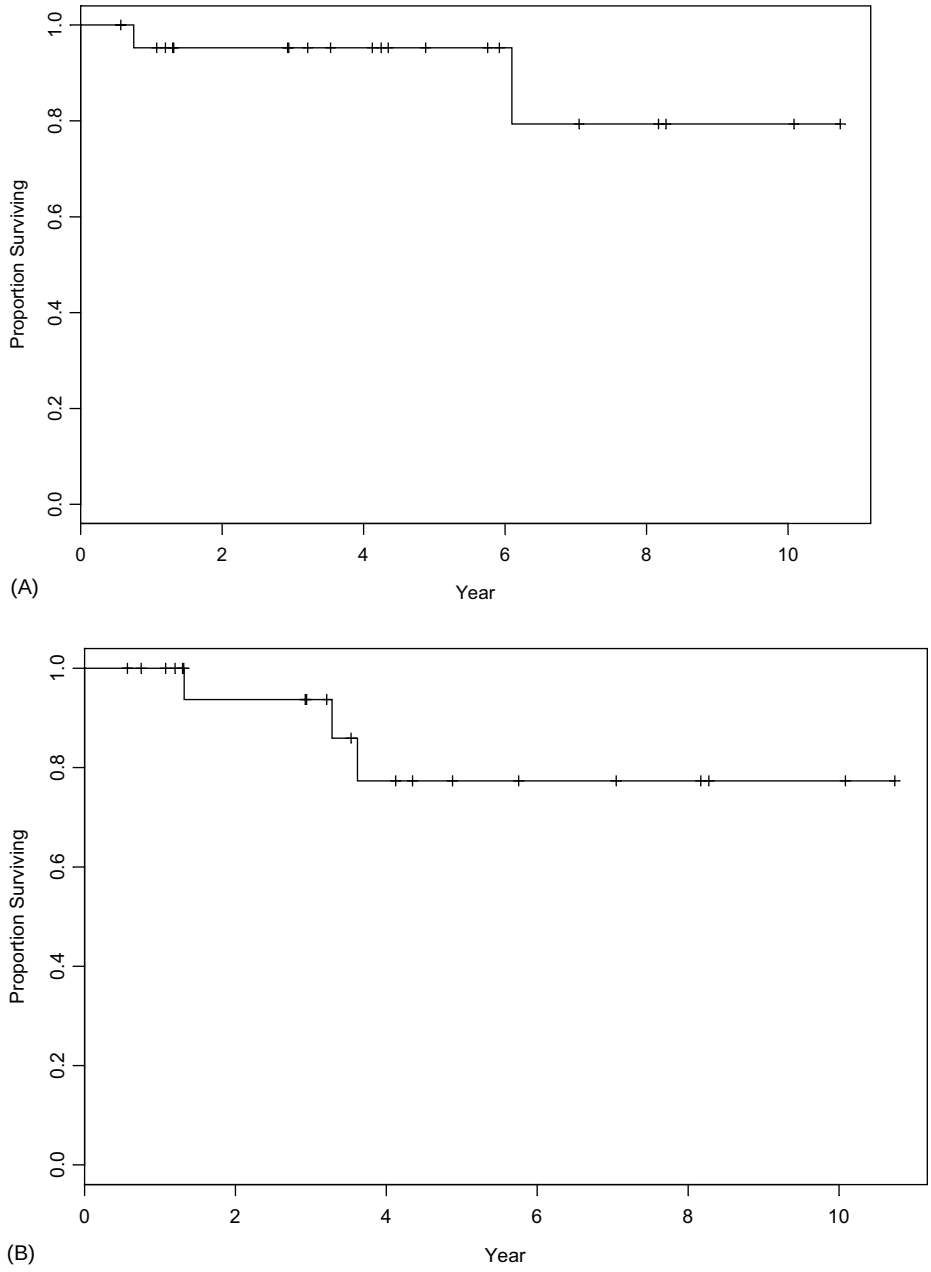

Fig. 3 (A) Overall survival time of patients (22 patients). Overall survival was 95% at 5 years (95% confidence interval (CI), 0.87—1.0) and 79% at 7 years (95% CI, 0.55—1.0). (B) Progression-free survival time of patients (22 patients). Progression-free survival was 77% at 5 years (95% CI, 0.58—1.0) and 77% at 7 years (95% CI, 0.58—1.0).

4. Discussion

Malignant thymoma is a rare tumor that is usually located in the anterior mediastinum. A majority of patients will present with a localized tumor in which surgical resection is the standard procedure of choice. The addition of adjuvant radiotherapy may improve local disease control. In more advanced and recurrent disease, systemic chemotherapy produces objective response rates of 50—80%. Therefore, complete surgical resection is an important factor for locally advanced malignant thymoma [19], making it critical to convert locally advanced unresectable tumors (stages III and IVA) to resectable ones. However, complete surgical resection of advanced tumors is not feasible because of local invasion into mediastinal structures including major blood vessels, the pericardium, or other vital structures. Furthermore, microscopic invasion and gross residual disease lead to an increased incidence of recurrence and, overall, a poorer prognosis.

Table 4 Toxic effects

	After induction chemotherapy ($N = 22$)		After surgery, XRT, and consolidation chemotherapy ($N = 21$)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic				
Myelosuppression	4	0	2	0
Thrombocytopenia	3	0	0	0
Neutropenia	2	4	1	0
Neutropenic fever	3	0	0	0
Anemia	1	0	0	0
Nonhematologic				
Fatigue	0	0	3	0
Nausea	0	0	1	0
Vomiting	0	0	0	0
Pain	0	0	4	0
Esophagitis	1	0	4	0
Diarrhea	0	0	2	0
Respiratory distress	0	0	2	1
Anorexia/weight loss	0	0	0	1
Dehydration	1	0	0	0
Fever	2	0	0	0

No cardiotoxicity was observed. No surgical mortality occurred. XRT: radiation therapy.

Uematsu et al. [10] reported on 165 patients with malignant thymoma and retrospectively obtained survival time data. Patients with invasive thymoma survived for a shorter period than patients with noninvasive tumors (67% versus 85% at 5 years). However, when the tumor could be completely resected, no difference in survival rates between the two groups was detectable. Therefore, complete tumor resectability seems to be a critical component for disease control. Thymomas are historically described as chemosensitive tumors [21—23]. To enhance tumor resectability, preoperative induction or neoadjuvant chemotherapy may be used. We previously reported results of such a regimen for 12 patients [20]. At that time (1998), all 12 patients (100%) were alive 7 years after treatment, and 10 patients (73%) were disease-free at 7 years. In the current analysis, we continuously accrued in the prospective phase II study settings, and 22 patients received induction chemotherapy. The major response rate was 77%, including 14% CR. Patients tolerated therapy well, and no surgical mortality occurred.

Postoperative radiation therapy is an important modality of treatment for locally advanced thymoma. We retrospectively analyzed 87 patients with malignant thymoma treated at M.D. Anderson Cancer Center between 1951 and 1990 [24]. Recurrent disease usually occurred in the pleura, mediastinum, or pulmonary parenchyma. Many of the recurrences within the chest occurred outside the radiation field, an observation that was consistent throughout the 40-year retrospective study period.

In advanced malignant thymoma, the total dose of radiation therapy in the postoperative setting has not been well established. The doses of radiation used in our study were derived from those that have proved effective in patients with lung cancer. For patients whose tumors were completely resected but in whom microscopic disease may have persisted, 50 Gy of radiation was used. For patients whose tumors were incompletely resected and had gross residual disease, 60 Gy was delivered. Komaki and Cox demonstrated that in patients who received postoperative radiation therapy, recurrent disease was found in 25% compared with 57% of those who did not receive radiotherapy [23]. Postoperative radiation therapy clearly further reduces the risk of recurrence in the radiated field, even in patients with complete resections.

Our decision to administer consolidation chemotherapy was based on patterns of treatment failure in advanced disease. Among 87 patients with malignant thymoma, 30% of these patients also experienced metastases outside of the chest [24]. Thus, after radiation therapy is delivered to the chest in order to control the microscopic disease intrathoracically, further systemic treatment is necessary to eradicate microscopic disease in

distant sites. Therefore, further consolidation with systemic chemotherapy may be beneficial.

The patients in our current study presented with advanced malignant thymomas that were deemed unresectable. Our initial strategy was to convert these clearly unresectable tumors to resectable ones, which was accomplished in all patients with the use of chemotherapy. In addition, however, we wished to further control recurrence by eradicating potential microscopic disease outside of the radiation port with consolidation chemotherapy. Additionally, the two patients with controlled myasthenia gravis at study entry did not require further therapy after completion on protocol. This unique multidisciplinary approach may have helped to lengthen overall and disease-free survival times in our patients.

Rea et al. [25] 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, three (27%) died of recurrent disease. Of the five patients whose tumors were partially resected, three (60%) died after surgery. Such data strongly indicates that postoperative radiation alone or chemotherapy alone may not optimally control residual disease and that multidisciplinary approaches may be needed.

Loehrer et al. [26] treated patients with limited-stage unresectable thymoma who were chemotherapy-naïve with induction chemotherapy followed by radiotherapy. Patients received two to four cycles of induction chemotherapy repeated every 3 weeks. This included cisplatin at 50 mg/m^2, doxorubicin at 50 mg/m^2, and cyclophosphamide at 500 mg/m^2 followed by 54 Gy of thoracic radiation without surgical resection. Of 23 assessable patients, induction chemotherapy produced a 69.6% response rate (5 CR, 11 PR) before radiotherapy. The 5-year survival rate reported was 52.5%. Our study produced a similar response rate (77% versus 69.6%) with induction chemotherapy. However, as discussed previously, the favorable difference in overall 5-year survival rate (95% versus 52.5% 5-year survival) in our study can most likely be attributed to complete surgical resection of the disease as well as the addition of consolidation chemotherapy. to eradicate microscopic disease outside the radiation field. None of our patients experienced recurrence outside the radiation field.

Highly et al. [27] recently reported a trial in which 15 patients with stage III or IV invasive thymoma were treated with single-agent ifosfamide at 1.5 g/m^2 with mesna for 5 days every 3 weeks. Patients received between two and nine cycles. In the 13 patients whose disease response could be evaluated, there were five (38.5%) complete responses and one (7.7%) partial response. This study suggested that the use of ifosfamide as a single agent is suboptimal and that it may be used in combination chemotherapy for thymoma.

The treatment of malignant thymoma continues to evolve. It is becoming clearer that multimodal approaches that can integrate surgical resection lead to more favorable outcomes in advanced malignant thymoma. As the disease has been shown in previous studies to be sensitive to radiation and chemotherapy, our strategy has been to provide a combined multidisciplinary approach for patients with malignant thymoma. Induction chemotherapy to optimize surgical respectability, radiation therapy to definitively treat local disease, Surgery to remove visible disease, and consolidation chemotherapy to eradicate microscopic disease seem to be key components. The results of our study clearly indicate the importance of using multiple modalities as demonstrated by our patients' overall survival and progression-free survival times. Still, five patients did not have a major disease response after induction chemotherapy on our trial. Prednisone was used in this regimen in an attempt to increase the cytotoxic activity against the lymphocytic components of the tumors.

New chemotherapy regimens are needed to further improve the response rate, particularly the rate of complete response, and thus improve surgical resectability. Palmieri et al. [28] have been described as being potentially useful in combination. Also, as novel molecularly targeted agents are developed, octreotide or other specifically targeted molecules may play a role in the primary treatment of malignant thymoma or in recurrent disease.

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