

CLINICAL INVESTIGATION

Mediastinum

STAGE III THYMOMA: PATTERN OF FAILURE AFTER SURGERY AND
POSTOPERATIVE RADIOTHERAPY AND ITS IMPLICATION FOR
FUTURE STUDY

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Purpose: With the conventional approach of surgery and postoperative radiotherapy for patients with Masaoka Stage III thymoma, progress has been slow for an improvement in the long-term survival rate over the past 20 years. The objective of this study was to evaluate the pattern of failure and survival after surgery and postoperative radiotherapy in Stage III thymoma and search for a new direction for better therapy outcome.
Methods and Materials: Between 1975 and 1993, 111 patients with thymoma were treated at Massachusetts General Hospital. Of these, 32 patients were determined to have Masaoka Stage III thymoma. The initial treatment included surgery for clinically resectable disease in 25 patients and preoperative therapy for unresectable disease in 7 patients. Surgical procedure consisted of thymectomy plus resection of involved tissues. For postoperative radiotherapy ($n = 23$), radiation dose consisted of 45–50 Gy for close resection margins, 54 Gy for microscopically positive resection margins, and 60 Gy for grossly positive margins administered in 1.8 to 2.0 Gy of daily dose fractions, 5 fractions a week, over a period of 5 to 6.6 weeks. In preoperative radiotherapy, a dose of 40 Gy was administered in 2.0 Gy of daily dose fractions, 5 days a week. For patients with large tumor requiring more than 30% of total lung volume included in the target volume ($n = 3$), a preoperative radiation dose of 30 Gy was administered and an additional dose of 24–30 Gy was given to the tumor bed region after surgery for positive resection margins.

Results: Patients with Stage III thymoma accounted for 29% (32/111 patients) of all patients. The median age was 57 years with a range from 27 to 81 years; gender ratio was 10:22 for male to female. The median follow-up time was 6 years. Histologic subtypes included well-differentiated thymic carcinoma in 19 (59%), high-grade carcinoma in 6 (19%), organoid thymoma in 4 (13%), and cortical thymoma in 3 (9%) according to the Marino and Müller-Hermelink classification. The overall survival rates were 71% and 54% at 5 and 10 years, respectively. Ten of the 25 patients who were subjected to surgery as initial treatment were found to have incomplete resection by histopathologic evaluation. The 5- and 10-year survival rates were 86% and 69% for patients ($n = 15$) with clear resection margins as compared with 28% and 14% for those ($n = 10$) with incomplete resection margins even after postoperative therapy, $p = 0.002$. Survival rates at 5 and 10 years were 100% and 67% for those with unresectable disease treated with preoperative radiation ($n = 6$) and subsequent surgery ($n = 3$). Recurrence was noted in 12 of 32 patients and 11 of these died of recurrent thymoma. Recurrences at pleura and tumor bed accounted for 77% of all relapses, and all pleural recurrences were observed among the patients who were treated with surgery initially.

Conclusion: Incomplete resection leads to poor results even with postoperative radiotherapy or chemoradiotherapy in Stage III thymoma. Pleural recurrence is also observed more often among patients treated with surgery first. These findings suggest that preoperative radiotherapy or chemoradiotherapy may result in an increase in survival by improving the rate of complete resection and reducing local and pleural recurrences. © 2000 Elsevier Science Inc.

Malignant thymoma, Stage III thymoma, Thymic carcinoma, Preoperative radiotherapy.

INTRODUCTION

The progress in the treatment of patients with Stage III thymoma (Masaoka staging system) has been slow (1). The conventional approach of surgery and postoperative radio-

therapy has resulted in a 5-year survival rate of about 60% without a noticeable improvement over the past 20 years (2–6). Surgery alone for Stage I and surgery plus postoperative radiation therapy for Stage II disease have resulted

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in a 5-year survival rate of 95% and 80–85% respectively. However, in a subset of patients within the Stage III thymoma, the conventional approach of surgery and postoperative radiotherapy results in a poor outcome even after postoperative radiation for an incomplete resection because of the involvement of major blood vessels including innominate vessels (3, 7–12). Although postoperative radiotherapy has been used after incomplete resection, the results remain less than desired with 5-year survival rate of 30–40% and local failure rate of 50% (4–6, 12–14).

For patients with unresectable thymoma, radiation therapy alone resulted in a 5-year survival rate of 30–50% (9, 13, 14). Loehrer *et al.* (15) treated 23 patients with inoperable thymoma (22 with Stage III and 1 with Stage IVa) with 2–4 cycles of induction chemotherapy (cisplatin, doxorubicin, and cyclophosphamide [PAC]) and subsequent radiation using 54 Gy in 30 fractions over a period of 6 weeks. Even though this approach of sequential chemotherapy and radiotherapy resulted in an overall response rate of 70%, 5-year survival rate was only 53%.

One of the characteristic features of Stage III thymoma is its invasion into surrounding tissue. Haniuda *et al.* (16) reported that the majority of patients with Stage III thymoma in his series presented with mediastinal pleural involvement and pleural recurrence was a major pattern of failure even after a complete resection. Distant metastasis remains uncommon until late in the course of disease.

The goal of this retrospective study was to evaluate the patterns of failure and survival following the conventional approach of surgery and postoperative radiotherapy in patients with Stage III thymoma and to search for new direction for better results.

METHODS AND MATERIALS

Patient population and initial evaluation

Between 1975 and 1993, 111 patients were treated for thymoma at this institution. According to the staging criteria of Masaoka *et al.* (1), there were 33 patients with Stage I, 43 with Stage II, 32 with Stage III, and 3 with Stage IVa thymoma. The 32 patients in the Stage III group had histologic evidence of invasion into the neighboring tissues and organs and were the subject of this study.

The initial evaluation included a complete history and physical examination with special attention to symptoms often associated with thymoma, laboratory tests including a complete blood cell count (CBC), blood urea nitrogen (BUN), creatinine, and liver function tests. Computed tomography and magnetic resonance imaging (MRI) of the chest were also included in the initial work-up for the evaluation of an involvement of major vessels and surrounding organs.

Treatment methods

The treatment policy for patients with a clinical diagnosis of anterior mediastinal tumor that was judged to be resectable was surgical exploration for both tissue diagnosis and

complete resection. The initial treatment plan of the 32 patients consisted of (a) surgical resection ($n = 25$) with postoperative radiation ($n = 21$) or chemoradiotherapy ($n = 2$), and (b) preoperative radiotherapy ($n = 6$) or chemotherapy ($n = 1$) for unresectable disease.

Surgery

Twenty-five of the 32 patients who were judged to be clinically resectable were subjected to surgery as initial treatment. The surgical procedure consisted of a total thymectomy through a median sternotomy and excision of involved tissues. The extent of surgery in these patients included the following: (1) thymectomy with resection of involved lung and pericardium in 16 patients (50%), (2) thymectomy with involved pericardium in 6 patients (19%), (3) thymectomy with resection of involved lung in 4 (13%), and (4) thymectomy with a lobectomy and resection of involved pericardium in 2 (6%). The involved major vessels which were resected included innominate veins in 9 patients and a combination of innominate veins and superior vena cava in 4 for a total of 13 patients. The surgical procedures for the 3 patients who were subjected to surgery after the preoperative radiotherapy included thymectomy and resection of involved lung and pericardium in 2 and thymectomy and resection of involved lung, pericardium, and superior vena cava with a venous graft in 1 patient.

Postoperative radiotherapy

Twenty-one of 25 patients were planned for postoperative radiotherapy because of resection margins positive for gross tumor in 2, microscopic tumor in 8, and close margins in 11 patients. However, this was administered to 17 patients only, for the following reasons: A slow recovery from pneumonia in 1, myasthenia gravis crisis in 1, distant metastasis in 1, and postoperative respiratory failure in 1. Postoperative chemotherapy and radiotherapy was planned in 2 patients, but it was administered to only 1.

The treatment volume for postoperative radiotherapy included the tumor bed with a margin of 4 cm for the cranial and caudal direction and a lateral margin of 3 cm toward the involved lung. All patients were treated with megavoltage radiation using 4–10 MeV photons. Total doses were 45 Gy to 50 Gy for close resection margins and 54 Gy for microscopic residual tumor administered by using 1.8 Gy to 2.0 Gy of daily dose fractions, 5 days per week. For gross residual tumor, a total dose of 60 Gy was administered in 2.0 Gy of daily dose fractions, 5 days per week. The arrangement of radiation portals consisted of a combination of antero-posterior and postero-anterior (AP-PA) fields for the initial 30 Gy to 34 Gy and anterior/right posterior oblique/left posterior oblique fields for the remaining 15 Gy to 30 Gy. The initial target volume was reduced at 26 Gy for patients in whom the initial treatment volume included more than 30% of the whole lung volume.

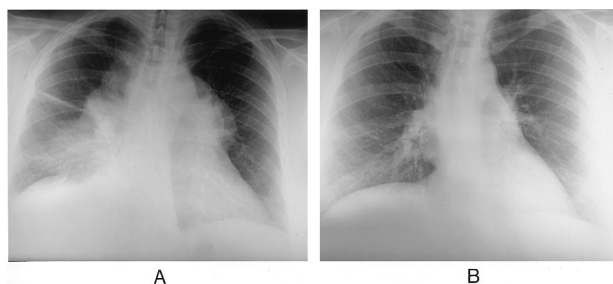


Fig. 1. Posteroanterior radiograph of chest of a patient with unresectable thymic carcinoma: before (A) and after (B) preoperative radiotherapy showing a dramatic tumor regression.

Preoperative therapy

There were 7 patients with clinically inoperable thymoma; preoperative radiation therapy was administered in 6 patients and preoperative chemotherapy in 1 patient with a plan for possible surgery later.

For the preoperative radiation therapy, a radiation dose of 40 Gy was administered in 20 fractions over a period of 4 weeks. When more than 30% of total lung volume was to be included in the AP/PA radiation portals for large tumors, the portal size was reduced at 24 Gy ($n = 2$). In 3 patients with large tumor mass, a preoperative radiation dose of 30 Gy was administered using 1.5 Gy of dose fractions given twice daily with an intertreatment interval of 5 hours over a period of 12 days. In this preoperative radiotherapy, the size of radiation portals was also reduced at 21 Gy as a significant decrease in the tumor volume was observed ($n = 2$). For those with residual tumor at the resection margin, an additional dose of 24 Gy to 30 Gy was administered using 2 Gy of daily dose fractions, 5 days a week postoperatively. Examples of a chest radiograph and an MRI scan of the chest before and after 30 Gy of preoperative radiotherapy are shown in Figs. 1 and 2.

Subsequent resection was performed in 3 patients, and the remaining 3 patients were not subjected to surgery because of a slow recovery from radiation pneumonitis in 1, poor pulmonary reserve in 1, and refusal of surgery in 1 patient.

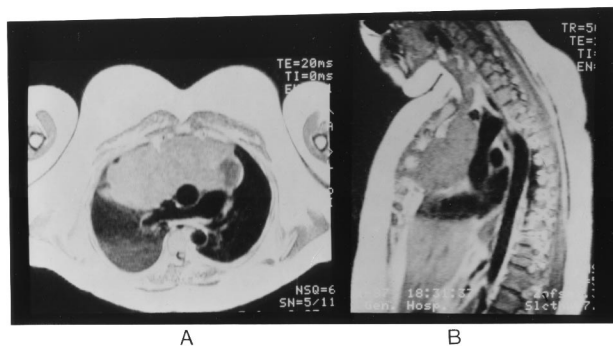


Fig. 2. MRI of chest before preoperative radiotherapy showing the tumor inseparable from major vessels: Axial (A) and sagittal (B) views.

Chemotherapy

Neoadjuvant chemotherapy was used in the last 2 years of the study period. One patient received two cycles of doxorubicin 40 mg/m² on day 1, vincristine 0.6 mg/m² on day 3, and cyclophosphamide 700 mg/m² on day 4 preoperatively in 1991. Postoperative chemotherapy was administered to two patients during the period of 1991 and 1992 which consisted of four cycles of cisplatin 50 mg/m² and doxorubicin 40 mg/m² on day 1, vincristine 0.6 mg/m² on day 3, and cyclophosphamide 700 mg/m² on day 4 every 3 to 4 weeks starting 4 weeks after surgery. The fourth patient was treated with a combination of cyclophosphamide, vincristine, prednisone, and procarbazine for recurrent well-differentiated thymic carcinoma between 1978 and 1980.

Histopathology

The histopathologic criteria for thymic epithelial tumors proposed by Marino and Müller-Hermelink, and Kirchner were used for the classification of thymoma (17, 18). The subtypes of thymoma among these 32 patients, reported in part by us previously (19), included well-differentiated (low-grade) thymic carcinoma in 19 (59%), high-grade carcinoma in 6 (19%), organoid thymoma in 4 (13%), and cortical thymoma in 3 (9%) patients. Therefore, thymic carcinoma, the most unfavorable subtype, accounted for 78% (25/32) of all patients.

Statistical method

Statistical methods used in this analysis included the life-table method for actuarial survival data (20). The comparisons of the survival data between patients with negative and those with positive margins were made using the log-rank test (21). The clinical factors relevant to selection for the initial treatment plan were investigated with Fisher's exact test (22).

RESULTS

Patient characteristics

Patients with Stage III thymoma accounted for 29% (32/111) of all patients who were treated for thymoma between 1975 and 1993. Demographic characteristics of the 32 patients included the following: median age of 57 years (range 27–81), male to female ratio of 10:22, and Karnofsky performance score of 90–100 in 11, 80 in 18, 70 in 2, and 50 in 1 patient.

Presenting symptoms included chest pain in 14 (44%), dyspnea in 8 (25%), weight loss of more than 10% in 5 (16%), cough in 3 (9%), superior vena cava syndrome in 3 (9%), and night sweats and fever in 2 (6%) patients. Three (9%) patients were without significant symptoms. Associated systemic syndromes among these patients included myasthenia gravis in 9 (28%), red cell aplasia in 1 (3%), and systemic lupus erythematosus in 1 (3%) patient. Three of the 9 patients with myasthenia gravis had marked generalized muscular weakness and the remaining 6 patients had

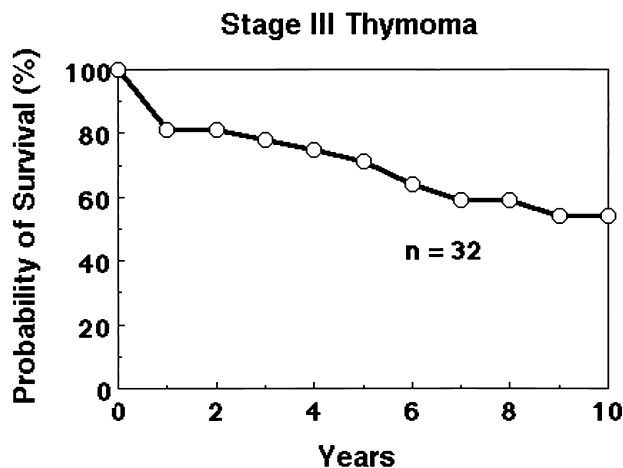


Fig. 3. Probability of survival of all patients by actuarial method. n: Number of patients.

ocular symptoms. One patient had both myasthenia gravis and systemic lupus erythematosus.

Treatment-related morbidities

Surgical morbidities: There were 4 deaths within 3 months after surgery from the following causes: pneumonia and myocardial infarction in 1 patient at 1 month after surgery and progressive worsening of thymoma in 3 patients between 2 and 3 months after surgery. None of these patients received preoperative therapy. There was a temporary exacerbation of myasthenia gravis during postoperative radiotherapy in 1 patient.

Radiation pneumonitis: Two patients developed Grade 2–3 radiation pneumonitis after preoperative radiation with a dose of 40 Gy in 20 fractions over a period of 4 weeks. Both patients were judged inoperable initially and radiation therapy was administered with a plan for reassessment of tumor response and possible surgery later. They did not undergo surgery because of a slow recovery from the pneumonitis in one and poor pulmonary reserve from the underlying chronic obstructive pulmonary disease and paralyzed left diaphragm in the other patient. One of these 2 patients recurred at the primary site 3 years later and was treated with chemotherapy. He subsequently died of leukoencephalopathy and uncontrolled thymoma in the chest 10 years after the initial treatment. The second patient remained free of recurrence 10 years after the initial radiotherapy.

Survival

The median follow-up time for all patients was 6 years. The overall survival rates for all patients were 71% and 54% at 5 and 10 years respectively, as shown in Fig. 3.

The overall survival was also evaluated for 25 patients who were treated with surgery initially and with subsequent postoperative therapy. Ten of these 25 patients were judged to have incomplete resection by histopathologic evaluation. The 5- and 10-year survival rates were 86% and 69% for

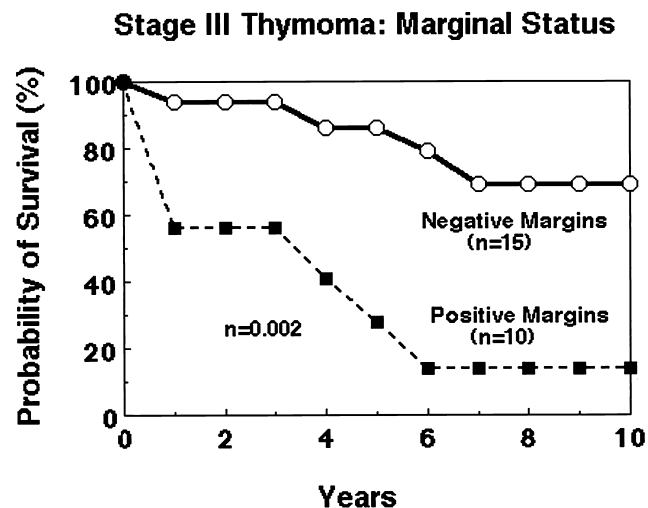


Fig. 4. Probability of survival of patients according to the status of resection margins in patients who were subjected to surgery as initial treatment. The actuarial method was used.

patients ($n = 15$) with clear resection margins as compared with 28% and 14% for those ($n = 10$) with incomplete resection margins as shown in Fig. 4, $p = 0.002$. Twenty-one of 25 patients received postoperative radiation and their 5- and 10-year survival rates were 66% and 39% respectively.

The therapeutic outcome of the 6 patients who presented with unresectable Stage III thymoma is of interest. All 6 patients were treated with radiation first and 3 of the 6 patients were able to undergo a subsequent resection. One patient died of recurrent tumor 10 years after the initial radiotherapy, and the remaining 5 patients were alive without recurrence. The 5- and 10-year survival rates of these patients were 100% and 67% respectively.

Patterns of failure

Recurrence was observed in 12 of 32 patients (38%) and 13 sites with 1 patient having two sites of relapse (tumor bed and pleura). Of these 12 patients, 11 died of recurrent thymoma and the remaining 1 patient was alive as of this writing without relapse 16 years from the initial surgery and 9 years after a salvage surgery and postoperative radiotherapy.

The majority of recurrences were noted at the pleura and tumor bed. The distribution of these 13 relapse sites (12 patients) was as follows: pleura in 7 of 13 (54%), tumor bed in 3 of 13 (23%), lung in 1 of 13 (8%), and distant metastasis in 2 of 13 sites (15%) as shown in Table 1.

According to the initial treatment methods, all pleural recurrences were observed in the cohorts of patients treated with either surgery alone (1/2), initial surgery and postoperative radiation (5/21), or surgery and postoperative chemoradiation (1/2). The initial treatments for the 3 patients with recurrences at the tumor bed included radiotherapy alone (40 Gy/20 fractions/4 weeks) in one (1/6 patients),

Table 1. Patterns of failure according to initial treatments

Initial treatment	<i>n</i> = 32	Tumor bed	Pleura	Lung	Distant metastasis
Preop RT → Surg	6	1/6	0/6	0/6	0/6
Surg → Postop RT	21	0/21	5/21	1/21	1/21
Surg → CT and RT	2	0/2	1/2	0/2	0/2
CT → Surg and RT	1	1/1	0/1	0/1	1/1
Surg alone	2	1/2	1/2	0/2	0/2
Site of Rec/Total Rec	13/32	3/13	7/13	1/13	2/13

Abbreviations: n = number of patients; Preop = preoperative; RT = radiotherapy; Surg = surgery; Postop = postoperative; CT = chemotherapy; Rec = recurrence.

preoperative chemotherapy and surgery in one (1/1), and surgery alone in another patient (1/2).

Cause of death

Of 32 patients in this study cohort, 17 patients have died. Recurrent thymoma accounted for 71% (12/17) of the deaths. The remainder included early postoperative death in 1, a crisis of myasthenia gravis in 1, depression resulting in suicide in 1, and congestive heart failure in 2 patients at the age of 80 and 88 years, 6 and 15 years after the treatment.

DISCUSSION

The conventional approach for clinically suspected thymoma has been surgical exploration of the anterior mediastinum with an aim for a complete resection whenever feasible (2, 3, 8–14). However, a significant proportion of patients with clinically suspected Stage III thymoma have tumor invasion into the adjacent vital structures, and a complete resection with clear margins may not be attainable (3, 6, 7, 9–11, 13, 14). Blumberg *et al.* and Urgesi *et al.* reported that 44% of their patients with Stage III thymoma were found to be unresectable at presentation (3, 12). In this series, a complete resection was not achieved in 40% of patients (10/25) who were subjected to definitive surgery on the basis of clinical and radiographic studies. When the 7 patients who were judged to be clinically unresectable and treated with either preoperative radiation (*n* = 6) or chemotherapy (*n* = 1) were taken into account, a complete resection was not feasible in 53% of patients (17/32).

Incomplete resection is associated with a poor therapy outcome even after added postoperative therapy. In this series, 40% of patients (10/25) who were subjected to surgery had incomplete resection by histopathologic evaluation. The 5- and 10-year survival rates for these patients (*n* = 10) were 28% and 14% as compared with 86% and 69% for those with clear resection margins (*n* = 15), *p* = 0.002. Similar poor outcome has also been reported by other investigators following postoperative radiotherapy or chemoradiotherapy for incomplete resection (3, 4, 6, 7, 10, 13, 14). Although postoperative radiotherapy has been used as a supplemental therapy to an incomplete resection, the long-term survival data may not reflect a significant gain by the postoperative radiotherapy.

When the 5- and 10-year survival rates of 28% and 14% in those (*n* = 10) with incomplete resection and postoperative radiotherapy are compared with the 100% and 67% in those treated with radiation first (*n* = 6) for unresectable disease, the administration of radiation before surgery may be an important factor in improving the result in patients with doubt about the feasibility of complete resection in Stage III thymoma.

The current CT scan and MRI are not sensitive enough in assessing the involvement of the major vessels in the mediastinum and predicting the feasibility of complete resection. Therefore, it seems reasonable to consider preoperative therapy whenever there is uncertainty about the feasibility for complete resection in Stage III thymoma.

The common sites of failure in this study were pleura (54%) and tumor bed (23%), as shown in Table 1. All pleural recurrences (7 of 7) were observed in the cohorts of patients who were treated with either surgery alone or surgery followed by postoperative therapy. None of the 6 patients who were treated with radiation first and subsequent surgery (3 of 6 patients) developed pleural recurrence. Haniuda *et al.* (16) evaluated the significance of involvement of the mediastinal pleura as a risk factor for subsequent pleural recurrence in 41 patients with completely resected Stage II and III thymoma. Recurrence was observed in 13 of 41 patients (32%), of whom 92% (12/13) were pleural, 46% (6/13) local plus pleural, and 8% (1/13) distant metastasis. In Haniuda's study, 17 of 18 patients with Stage III disease showed pleural involvement by microscopic tumor. These findings may suggest that patients with Stage III thymoma have a high incidence of mediastinal pleural involvement and that the risk for subsequent pleural recurrence is high even after added postoperative radiotherapy. Preoperative radiotherapy may reduce the risk for subsequent pleural recurrence after surgery.

Radiation therapy alone has been used for unresectable Stage III thymoma. Mornex *et al.* (13) and Cowen *et al.* (14) reported that radiation therapy using 50–54 Gy in 1.8 to 2.0 Gy of daily dose fractions, 5 fractions per week resulted in a 5-year survival rate of 41% and a local control rate of 41% (15/37) in patients with Stage III thymoma excluding thymic carcinoma. Curran *et al.* (4) also reported that overall failure was noted in 5 of 10 patients using 44 to 51.4 Gy in 1.8 to 2.0 Gy of daily dose fractions, 5 fractions a week for

unresectable Stage III thymoma. Even the addition of 2–4 cycles of chemotherapy prior to radiotherapy resulted in a 5-year survival rate of only 53% in the study by Loehrer *et al.* (15). In this sequential chemoradiotherapy study, a total radiation dose of 54 Gy was administered in 30 fractions over a period of 6 weeks. Therefore, an increase in radiation dose schedule to 60 Gy in 30 fractions over a period of 6 weeks may be necessary for an improvement in survival for patients with unresectable Stage III thymoma.

Histopathologic classification of thymoma remains controversial (17–19). Studies using the classification of Rosai and Levine (23, 24) excluded patients with thymic carcinoma from their analysis (4, 12–14, 16, 25–30). Unlike these reports in literature, 78% (25/32) of patients in this series had thymic carcinoma. Given the aggressive nature of Stage III thymoma and notably thymic carcinoma, it seems

logical to combine chemotherapy with radiation for the best possible tumor regression before surgery whenever feasible. Chemotherapy regimen such as platinum plus etoposide (PE) may be preferred over doxorubicin-containing regimen for this approach because of increased toxicities to thoracic organs when doxorubicin and radiation are combined (31–34).

In conclusion, the conventional approach of surgical exploration and attempts for complete resection whenever feasible along with administration of postoperative radiotherapy or chemoradiotherapy for incomplete resection needs to be reassessed in the absence of significant progress in improving survival in recent years. Preoperative therapy using radiotherapy or chemoradiotherapy needs to be explored for its potential in enhancing local tumor control and survival.

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