Invasive Thymoma: The Role of Mediastinal Irradiation Following Complete or Incomplete Surgical Resection

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To evaluate the role of mediastinal irradiation (RT) following surgery for invasive thymomas, a clinical and pathologic review of 117 patients with the diagnosis of thymoma was completed. Fourteen cases were excluded because of the lack of histologic criteria for a thymic tumor, and the remaining 103 were classified according to a staging system as follows: stage I, completely encapsulated (43); stage II, extension through the capsule or pericapsular fat invasion (21); stage III, invasion of adjacent structures (36); and stage IV, thoracic dissemination or metastases (3). The 5-year actuarial survival and relapse-free survival rates were 67% and 100% for stage I, 86% and 58% for stage II, and 69% and 53% for stage III. No recurrences occurred among stage I patients after total resection without RT. However, eight of 21 patients with invasive (stage II or III) thymomas had mediastinal recurrence as the first site of failure following total resection without RT. The 5-year actuarial mediastinal relapse rate of 53% in this group compares unfavorably with the mediastinal relapse rate seen among stage II or III cases following total resection with RT (0%) or following subtotal resection/ biopsy with RT (21%). Despite attempted salvage therapy, five of eight patients with mediastinal relapse following total resection alone died of progressive disease. No significant difference was observed in the local relapse rate, overall relapse rate, or survival between those patients undergoing biopsy and RT *v* subtotal resection and RT for invasive thymomas (stages II and III). Total resection alone appears to be inadequate therapy resulting in an unacceptably high local failure rate with poor salvage therapy results.

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THYMOMAS are mediastinal neoplasms of thymic origin that occur with or without myasthenia gravis. When a thymoma is completely encapsulated (stage I), total resection by thymectomy is usually curative. When a thymoma has invaded through the capsule into the pericapsular fat (stage II) or adjacent thoracic structures (stage III), total resection is more technically difficult and of less certain value. Radiation therapy (RT) is used for unresectable or subtotally resected invasive thymomas (stages II and III), resulting in freedom from tumor progression in 50% to 100% of cases and what appears to be prolonged disease-free survival.[1-8] However, several issues in the management of thymomas remain unresolved and will be the focus of this report.

The surgical management of an unresectable, invasive thymoma may be confined to a biopsy or may involve an aggressive attempt at tumor debulking. Either procedure is usually followed by postoperative mediastinal RT. Little information is available as to whether the more aggressive surgical approach results in an improved rate of local control without increased morbidity.[4,7] While the role of postoperative RT following subtotal resection or biopsy of an invasive thymoma is well established,[1-8] conflicting reports exist regarding the role of RT following a visibly complete resection of an invasive (stage II or III) thymoma. Following complete resection of stage II or III thymomas without RT, reported relapse rates range from 0% to 100% without a consensus on the role of postoperative RT.[3,9-12]

A review of 117 patients with the diagnosis of thymoma treated at three institutions between 1960 and 1985 was completed to address these questions. Both the diagnosis of a thymic epithelial tumor and the extent of tumor involvement

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were verified by pathologic review in over 90% of these cases.

METHODS AND MATERIALS

Pathology Review

One hundred seventeen patients with the diagnosis of thymoma were identified from the tumor registries at three institutions: Hospital of the University of Pennsylvania 1971 to 1985; Medical College of Virginia 1960 to 1985; and the Fox Chase Cancer Center 1970 to 1985. Pathology slides were available for 113 cases and reviewed by two of the authors (M.K., J.B.). Using the pathologic definition of an epithelial tumor of the thymus proposed by Rosai and Levine,[13] 14 patients were excluded for failing to meet the pathologic criteria. Their diagnoses were revised to non-Hodgkin's lymphoma (5), bronchogenic carcinoma (2), carcinoma of the thymus (5), thymic carcinoid (1), and no confirmed malignancy (1). These revised diagnoses are listed in Table 1. The remaining 99 cases were histologically classified as lymphocytic, epithelial, mixed cell, or spindle cell according to the morphological characteristics of the predominant cell type. The presence or absence of capsular invasion or invasion into adjacent thoracic structures was confirmed on microscopic review whenever possible.

Clinical Review

The operative notes of all patients were reviewed to determine the presence of (1) capsular invasion, (2) tumor extension to adjacent structures, and (3) completeness of resection. Patients were assigned retrospectively to stages I, II, III, and IV by applying a staging system adapted from those proposed by Bergh et al[14] and modified by Masaoka et al.[7] The criteria for this staging system and the distribution of patients are shown in Table 2. There are 43 stage I patients, 21 stage II, 36 stage III, and three stage IV patients. As in the Bergh staging system and in distinction to the Masaoka system, patients with microscopic evidence of invasion into, but not through, the thymic capsule are assigned to stage I.

There are seven stage I patients noted by their surgeons to have dense adhesions between the thymoma and adjacent structures without microscopic evidence of invasion through the capsule by tumor. Table 3 groups these patients according to stage and the extent of their surgical procedure: total resection (100%); subtotal resection (10% to < 100%); or biopsy (< 10%).

Table 1. Pathologic Review

Diagnosis	N
Confirmed thymoma	99
Non-Hodgkin's lymphoma	5
Non–small-cell carcinoma	2
Thymic carcinoma	5
Thymic carcinoid	1
No malignancy	1
No pathology review	4
Total	117

Table 2. Thymoma Staging System

Stage	Description	Total No.
I	Macroscopic complete encapsulation; microscopic invasion into, but not through the capsule	43
II	Macroscopic invasion into surrounding fatty tissues or mediastinal pleura or microscopic invasion through the capsule	21
III	Macroscopic invasion into neighboring structure, ie, pericardium, great vessels, or lung	36
IV	Pleural or pericardial dissemination or metastases	3
Total		103

Adapted with permission.[7,14]

Patient Profile

Of the 103 patients, 57 were men, and 46 were women. The median age was 57 with a range from 21 to 82. Thirty-seven patients (36%) had myasthesia gravis, and six patients had other syndromes associated with thymoma including pure red cell aplasia (2), aplastic anemia (1), essential thrombocytosis (1), hypogammaglobulinemia (1), and dermatomyositis (1). The remaining 67 patients had no known thymoma-associated syndrome. These characteristics are summarized in Table 4.

Radiation Therapy

Twenty-eight patients with invasive thymomas received external beam RT following surgery. Two have been excluded from analysis because orthovoltage therapy was used. For the remaining 26 patients, treatment was delivered via a linear accelerator or cobalt-60 unit using opposing anterior-posterior technique until spinal cord tolerance was approached. Prescribed doses ranged from 32.0 to 60.0 Gy, with a median dose of 50.0 Gy. All but four patients received doses between 44.0 and 51.4 Gy, and all but one patient received five treatments per week at 1.8 to 2.0 Gy/d. When the prescribed dose exceeded 45.0 Gy, the additional therapy was delivered using angled fields sparing spinal cord. Treatment volume included the mediastinum and adjacent lung and pleura, except in four cases when residual disease extended more laterally.

Table 3. Extent of Surgery *v* Stage

Stage	Total Resection	Subtotal Resection	Biopsy	Unknown	Total
I	42	0	0	1	43
II	19	0	0	2	21
III	7	13	15	1	36
IV	0	1	2	0	3
Total	68	14	17	4	103

Table 4. Patient Profile

Patients (no.)	103
Age range (yr)	21-82
Median age	57
Associated syndromes	43
Myasthenia gravis	37
RBC aplasia	2
Aplastic anemia	1
Thrombocytosis	1
Hypogammaglobulinemia	1
Dermatomyositis	1

Statistical Methods

All time intervals were measured from the date of initial surgery. Survival and local control data were calculated by the product limit method,[15] and the determination of the *P* value between two groups was performed using the long-rank test.[16] Multivariate analysis by means of Cox's proportional hazard regression model[17] was used to assess the relationship of local relapse and overall relapse with pretreatment variables, adjusting for the effects of concomitant variables.

RESULTS

Stage I

Of the 43 patients with stage I thymomas, 42 underwent a gross total resection, and only one received postoperative RT. With follow-up ranging from 1.1 to 25 years or until death (median, 4.1 years), no recurrences were noted among these patients. This group includes the seven patients with adhesions between the thymoma and adjacent structures without tumor invasion through the capsule.

Stages II and III: Total Resection

Twenty-six patients underwent a visibly complete resection of either an invasive stage II (19) or stage III (7) thymoma. Five of these patients received postoperative RT. Of the 21 not receiving RT, eight recurred within the mediastinum as site of first failure. The time to recurrence for these patients ranged from 0.7 to 7.0 years with a median of 3.8 years. The 5-year actuarial mediastinal relapse rate was 53% for this group. No relapses were noted among the five patients receiving RT following a total resection for stage II (1) or stage III (4) thymoma. Six of the 18 stage II patients not receiving RT suffered a mediastinal recurrence, with a 5-year relapse rate of 47%. Figure 1 compares the relapse patterns following total resection for stage II and III thymomas with or without mediastinal RT (P = .12).

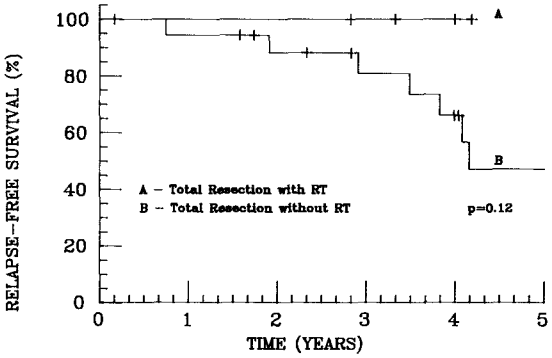

Fig 1. Comparison of percent relapse-free survival between those patients with invasive thymoma after total resection with RT (5) and total resection without RT (21).

Stage III: Biopsy of Subtotal Resection

Twenty-eight patients underwent either biopsy (13) or subtotal resection (15) for stage III thymoma. Excluding the two orthovoltage patients, 20 underwent postoperative mediastinal RT. Of the six nonirradiated patients, all three with follow-up of 12 months or longer had local tumor progression. Among the 20 irradiated patients, four experienced mediastinal recurrence as the site of first failure 0.1 to 3.3 years following surgery. Five additional patients suffered relapses outside the mediastinum as the site of first failure 0.3 to 5.0 years (median, 3.4 years) following surgery. The sites of non-mediastinal relapses were osseous (2), lung (2), and lateral pleura (1). One of these five patients subsequently recurred in the mediastinum. The 5-year actuarial rate of mediastinal recurrence for this group was 21%, and the overall relapse rate at 5 years was 49%. Local failure was not different between the irradiated patients undergoing biopsy (2/10) or subtotal resection (2/10) or in the incidence of overall failure (5/10 *v* 4/10). Figure 2 shows both the mediastinal and overall relapse pattern for these patients.

Salvage Therapy

Among the eight non-irradiated patients who relapsed solely in the mediastinum following complete resection, a variety of treatments were attempted. Salvage therapy consisted of RT

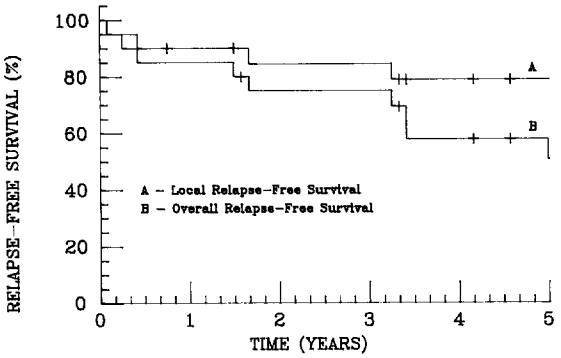

Fig 2. Percent local relapse-free survival and overall relapse-free survival for 20 patients with invasive thymoma after subtotal resection/biopsy and RT.

alone for three patients, resection followed by RT for two, surgery and chemotherapy for two, and surgery alone for one. Three patients were rendered free of disease by this salvage therapy, and two remain free of disease. Five have died of progressive disease, and one patient is alive with disease.

Relapse-Free Survival and Survival

Figures 3 and 4 show actuarial relapse-free survival and survival curves according to stage. The 5-year survival and relapse-free survival rates were 67% and 100% for stage I, 86% and 58% for stage II, and 69% and 53% for stage III. The relapse-free survival and survival rates at 5 years for the entire group were 67% and 70%.

Prognostic Factors

A multivariate analysis was performed on four variables to evaluate their influence on the patient's likelihood of disease relapse. These were histopathologic category (lymphocytic,

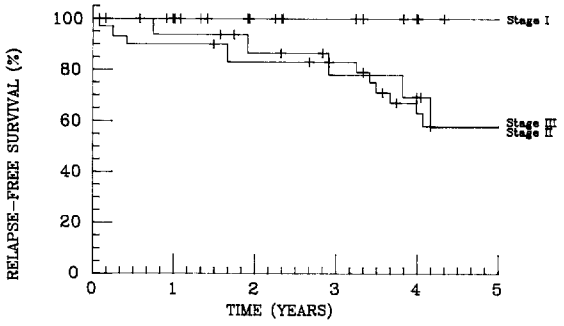

Fig 3. Percent relapse-free survival by stage.

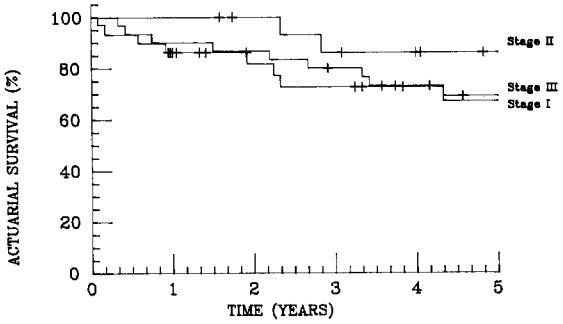

Fig 4. Percent actuarial survival by stage.

epithelial, mixed cell, or spindle cell), the presence of myasthenia gravis, stage, and the extent of resection. With overall relapse as an end point, the factors predicting for a significantly lower recurrence rate were the presence of myasthenia gravis, stage I compared with other stages, and total resection compared with biopsy or subtotal resection. With mediastinal relapse as an end point, only stage predicted significantly for outcome. While a greater proportion of patients without myasthenia gravis experienced overall tumor recurrence than those with myasthenia (27% *v* 16%), the frequency of mediastinal recurrence in both groups was similar (18% *v* 14%). Histopathologic category had no significant influence on outcome. Table 5 displays the results of this analysis.

Complications

Two patients died within 1 month of surgery from complications related to their severe myasthenia gravis. One patient who received a significantly higher RT dose than the other patients (60.0 Gy in 3.0 Gy fractions in split course) died 2.7 years following surgery of exsanguination from a tracheoinnominate artery fistula. Autopsy confirmed RT changes and no tumor.[18] No other serious complications have been noted.

Table 5. Multivariate Analysis for Overall and Local Relapse

Variable	Overall Relapse	Local Relapse
Extent of resection	0.0004	0.13
Stage	<0.0001	0.002
Histology	0.59	0.35
Myasthenia gravis	0.04	0.34

DISCUSSION

Pathologic material was reviewed on 97% of the cases initially diagnosed as thymoma at our institutions, and the diagnosis was revised in 11% of these cases on the basis of morphology and in selected cases, immunohistochemistry. Of 19 previously published clinical series on thymoma, pathologic review was performed in six,[1,3,8,10,14,19] and the conclusions presented in the 13 reports without pathologic review[2,4-7,9,11,12,20-24] should be viewed with caution.

No recurrences occurred among totally resected stage I thymomas. Of note is the absence of recurrence among those stage I patients with adhesions between the thymic capsule and adjacent structures as well as those with microscopic invasion into, but not through, the capsule. Total resection alone is adequate therapy for such patients, and there is no rationale for the use of adjuvant RT. Despite a relapse-free survival of 100%, the 5-year survival for stage I was only 67%, a figure comparable to the survival in stage III. This decrease in survival was primarily due to the higher frequency of severe myasthenia gravis seen among stage I patients than in other stages in this series.

Total resection alone is inadequate therapy for either stage II or III invasive thymoma patients. A 53% mediastinal recurrence rate at 5 years was observed among 21 patients treated in this manner. This rate compares unfavorably with the local failure rate seen among patients after total resection and RT (0%), subtotal resection and RT (21%), or biopsy and RT (21%). Table 6 shows the intrathoracic tumor relapse following total resection of invasive thymoma with or without RT. Including the present series and seven previous studies,[3,6,9-12,22] the intrathoracic relapse rate following total resection alone is 28%, compared with 5% after total resection and RT. In this series, salvage therapy for such local recurrences was poor, with five of eight patients dying of progressive disease despite aggressive surgical and radiotherapeutic treatment. The available data support the use of postoperative RT following total resection of all stage II or III thymomas. This includes those patients without visible invasion noted during surgery but with pathologic evidence of microscopic invasion through the thymic capsule.

Table 6. Thoracic Failure Following Total Resection ± RT for Invasive Thymoma (Stages II and III)

Series	Total Resection Without RT (%)	Total Resection With RT (%)
Batata et al[3]	6/6	–
Chahinian et al[9]	3/3	–
Maggi et al[10]	1/32	0/2
Marks et al[6]	–	0/3
Monden et al[11]	2/7	2/25
Norstrom et al[12]	0/5	0/2
Penn & Hope-Stone[22]	–	0/6
Present Series	8/19	0/5
Total	20/72 (28)	2/43 (5)

No conclusion can be made from the present series regarding whether aggressive surgery before irradiation improves outcome in unresectable stage III thymomas. The in-field and overall recurrence rates, as well as survival, were similar between those patients undergoing biopsy or subtotal resection when this surgery was followed by RT. One advantage of aggressive debulking is the reduced size of the RT portals necessary to encompass tumor. Smaller RT field sizes would expose less adjacent normal tissues to radiation and lessen the potential for complications.

Because invasive thymomas disseminate along pleural surfaces, several authors have advocated low-dose prophylactic whole lung or hemithorax irradiation[2,14,25] or intrapleural instillation of chromic phosphate (P-32)[3] to supplement mediastinal RT. In this series, only three (7%) relapsed outside the mediastinum and within the thorax as their site of first failure. While additional patients subsequently developed intrathoracic dissemination following mediastinal failure, this low frequency of first failure in the pleura or lung does not support such prophylactic therapy.

No association between histologic subtyping of thymoma and outcome was noted in this study, a finding frequently observed in earlier reports. Marino and Muller-Hermelink[26] have recently reported on light microscopic features of thymic epithelial tumors which distinguish between medullary and cortical morphology. In a separate report we will examine whether this system will more successfully predict for tumor recurrence and survival than the current histological categories. For the present, the strongest predictor for recurrence and the strongest indi-

cation for postoperative RT remains surgical and pathologic evidence of tumor invasion.

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