Controversies in the Management of Malignant Thymoma*

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The management of most thymomas is relatively straightforward: surgical resection remains the primary mode of therapy. However, the literature contains many contradictory points of view regarding histology and pathology, staging and its usefulness, the need for adjuvant therapy, and recently, the place of video-assisted surgery in the treatment of this tumor. This article is not a comprehensive guide to management but rather explores several of these controversial areas. Conclusions include the following: invasiveness remains the single most consistent factor in predicting outcome; surgery is the treatment of choice for thymoma whenever a complete resection can be accomplished; and incomplete resection may have some advantage over biopsy alone. The preponderance of evidence indicates that all thymomas except completely encapsulated stage I tumors should be treated with postoperative adjuvant radiation therapy in the hope of reducing the incidence of local relapse. Myasthenia can no longer be considered an adverse prognostic factor in thymoma; it may even confer a survival advantage, but this may be due to the preponderance of early-stage tumors discovered incidentally in myasthenic patients. Other associated autoimmune diseases confer a survival disadvantage. Demonstrating the equivalence of minimally invasive thoracoscopic approaches to standard thymectomy will take many years of investigation. Some promising reports on response to chemotherapy have led to the development of a phase II intergroup study to assess the value of chemotherapy in advanced thymoma.

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Various staging systems have been defined, based on the degree of invasiveness; these systems are totally independent of histology and cytology. Perhaps the most common and useful system is that devised by Masaoka et al1 (Table 1). Stage I (completely encapsulated tumor) corresponds to the benign form of thymoma, which rarely, if ever, recurs; 70 to 80% of thymomas fall into this category.2 Stages II through IV are divided into two types. Type I tumors, also called malignant thymomas, have all the clinical, morphologic, and cytologic attributes of encapsulated thymoma but exhibit local invasion, pleural or pericardial implants, or distant metastases. The features of local invasiveness may be apparent to the surgeon at the time of operation or may become evident only after microscopic examination; they cannot be distinguished from the encapsulated types on cytologic or architectural grounds. Type II tumors, also called thymic carcinomas, are clearly identified by a variety of cytologic attributes characteristic of malignancy. These are very aggressive neoplasms, and local invasion and distant metastases are common.2

Two major classification systems based on microscopic appearance are in common use. The system of Rosai and Levine3 classifies tumors based on characteristics of the epithelial cell component (round, spindle, mixed) and the presence or absence of lymphocytic infiltration. A newer system by Marino and Müller-Hermelink4 divides tumors into cortical (organoid), mixed, and medullary types.

Histologic type and classification of thymoma have fascinated pathologists for years and have stimulated a large number of articles in the pathology literature, each of which attempts to show that its system accurately reflects prognosis. On critical review,5 many of these studies have small numbers of patients and come to conflicting conclusions. Additionally, they may not be reproducible enough to have clinical relevance. Thus, there is probably little need for the practical clinician to be concerned with such esoterica. Dawson and colleagues6 found very low intraobserver and interobserver agreement in classifying thymomas and concluded that surgical stage has the best prognostic value.

Invasiveness remains the single most consistent factor for predicting outcome. However, as noted by Dawson et

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Areas of Controversy in the Management of Thymoma

Several areas in the management of thymoma have produced contradictory points of view. We will explore answers to the following questions: How do the various systems of histologic typing and pathologic differentiation fit into the clinical management of patients with thymoma? What should be the extent of the definitive surgery? Does debulking have any benefit? Should radiation therapy be given to patients with minimally invasive tumors? Does the presence of myasthenia gravis affect the prognosis of thymoma? Does minimally invasive surgery (thoracoscopy) have a place in the management of thymoma? How should recurrence be treated? Does chemotherapy have any utility in the treatment of thymoma2
Table 1—Criteria of Clinical Stages*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Macroscopically—completely encapsulated</td>
</tr>
<tr>
<td>II</td>
<td>Microscopically—no capsular invasion</td>
</tr>
<tr>
<td>III</td>
<td>Macroscopic invasion into neighboring organ (ie, pericardium, great vessels, or lung)</td>
</tr>
<tr>
<td>IV A</td>
<td>Pleural or pericardial dissemination</td>
</tr>
<tr>
<td>IV B</td>
<td>Lymphogenous or hematogenous metastasis</td>
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*Reprinted from Masaoka et al1 (with permission of Wiley-Liss Inc, a subsidiary of John Wiley & Sons Inc).

al,6 invasion as determined by the surgeon must be supplemented by histologic search by pathologist for evidence of capsular invasion of microscopic foci within mediastinal fat.

Extent of Surgery

All agree that complete resection should be performed in patients with malignant thymoma whenever possible. In the case of stage I and II disease, this is generally achieved without great difficulty. Stage III and IV disease provides a greater challenge. Patients whose tumor can be resected completely along with the structures it is invading appear to derive the greatest benefit. Parts of the innominate vein, superior vena cava, right atrium, pericardium, lung, and diaphragm can generally be safely sacrificed with or without reconstruction as appropriate. In the case of stage IV disease with pleural dissemination, a complete parietal pleurectomy may grossly eradicate tumor. Yagi et al7 report excellent long-term survival with extended resection in patients with stage III and IV disease. Their overall 5- and 10-year survival rates were 77% and 59%, respectively. Ten of 12 patients who underwent resection of the superior vena cava or innominate vein survived long term without evidence of recurrence. Nakahara and coworkers8 have shown that the survival rate in patients with stage III disease undergoing complete resection was comparable to that of patients with stage I and II disease.

There is great controversy regarding the value of incomplete resection. Many authors believe that incomplete resection has no survival or recurrence value over biopsy alone.9,10 Other authors, including Mornex et al,12 found that survival was better after partial resection than after biopsy (5-year survival, 64% vs 39%, respectively; p<0.02). Local relapse was observed in 16% of patients after partial resection and in 45% after biopsy (p<0.05). Nakahara et al10 also found a significant difference in survival between patients undergoing subtotal resection and those having biopsy only (p<0.01). In the report by Yagi and associates,7 patients with stage II disease who had complete resection fared significantly better than those who had incomplete resection. A report from M.D. Anderson Cancer Center 13 showed that 5-year disease-free survival rates by extent of surgery were 74% for total resection, 60% for subtotal resection, and only 20% biopsy alone (p=0.001).

Complete resection is always the treatment of choice in patients with malignant thymoma, and incomplete resection may have some advantage over biopsy alone.

Adjuvant Radiation Therapy

No one disputes the value of adjuvant radiation therapy in completely or incompletely resected stage III or IV thymomas. Data from Turin, Italy,14 confirm that a debulking operation followed by postoperative radiotherapy achieves high survival rates. The utility of this approach is more questionable in patients with stage II disease who have had a thorough surgical resection. Since thymoma is slow to recur, short-term follow-up will not represent relapse rates accurately. Also, the surgeon’s opinion of whether the tumor is invasive is not always reliable. In 122 cases reviewed at Massachusetts General Hospital,15 28.5% of cases (20/70) said by the surgeon to be encapsulated actually showed microscopic evidence of true capsular invasion; a number of these patients subsequently experienced local recurrence. In another report from the same institution,16 22% of patients (5/23) with stage II disease developed recurrence, leading the authors to recommend postoperative radiation for all patients with stage II and III thymoma. Maggi et al14 noted a similar recurrence rate of 12.5% in stage II disease.

Curran and colleagues11 modified the Masaoka staging system to include in stage I those tumors penetrating into but not through the capsule. Disease did not recur in patients with stage I disease treated with surgery alone, including seven patients with adhesions between the thymoma and adjacent structures with no tumor invasion through the capsule. Of 21 patients with stage II and III disease who did not receive radiation therapy after total resection, 8 had recurrence in the mediastinum. No relapses were noted among five patients who received adjuvant radiation.

Wang and colleagues17 found that patients undergoing surgery and postoperative radiation therapy obtained significant improvement in cumulative survival rates compared with those undergoing surgery alone (67% vs 24%, p<0.001). However, the series from Memorial Sloan-Kettering Cancer Center8 seemed to show that radiation in stage II and III disease did not confer any recurrence or survival advantage. However, tumor size was an independent predictor of survival, which induced these authors to conclude that patients whose tumors are >5 cm or those who have radiographic evidence of tumor invasiveness should be considered for neoadjuvant protocols that include chemotherapy. This approach has not been tested or proved.

The preponderance of evidence indicates that all thymomas except completely encapsulated stage I tumors should be treated with postoperative adjuvant radiation therapy in hope of reducing the incidence of local relapse.
Prognosis With Myasthenia

A seminal report from Massachusetts General Hospital in 1966 stated that myasthenia gravis adversely affected survival of thymoma patients.\textsuperscript{15} The difference in 10-year survival rates between patients with and without myasthenia was striking: 32\% and 67\%, respectively. This discrepancy was due mostly to deaths from myasthenic crisis. A more recent Massachusetts General Hospital series\textsuperscript{16} concluded that the presence of myasthenia gravis should no longer be considered an adverse factor in survival.

Several other reports support this conclusion and even indicate that tumor-free survival may be greater in myasthenic patients. Crucitti et al\textsuperscript{19} found that myasthenia patients with Osserman's classification I and II had higher rates of 5-year survival than did those with Osserman III and IV classifications (the severity of the myasthenia influenced the survival rate). In 61 patients with malignant thymoma, Wang et al\textsuperscript{17} found the resectability rate to be 70\% in myasthenic patients but only 47\% in patients without myasthenia gravis. Most patients did not have a complete thymectomy. Patients with myasthenia gravis also had a significantly higher survival rate vs those without myasthenia gravis (93\% vs 39\% at 5 years, respectively, p<0.001). Nakahara and associates\textsuperscript{8} reported death by tumor in 5 of 81 patients with myasthenia gravis and in 18 of 61 patients without.

In a 52-patient cohort (25 with myasthenia gravis and 27 without), the group from Toronto General Hospital\textsuperscript{20} reported that the presence of myasthenia gravis did not adversely affect long-term prognosis and may even have improved it as patients with myasthenia gravis often have their thymoma discovered at an earlier stage or even incidentally at the time of thymectomy. Maggi and associates\textsuperscript{14} also found that survival rates were higher in the presence of myasthenia gravis (p<0.05). However, other autoimmune diseases like pure red cell aplasia, hypogammaglobulinemia, and lupus had an important negative prognostic impact. This latter observation has been confirmed in a large series from Memorial Sloan-Kettering Cancer Center.\textsuperscript{19} Patients with thymoma and myasthenia gravis had a 5-year survival rate of 84\%, which did not differ from that of patients without myasthenia (74\%). However, patients with red cell aplasia, hypogammaglobulinemia, or lupus had decreased survival.

Early experience with thymoma in the face of myasthenia gravis included a significant death rate from myasthenic crisis. This rarely occurs anymore, and myasthenia can no longer be considered an adverse prognostic factor in thymoma. It may even confer a survival advantage, but this may be due to the preponderance of early-stage tumors discovered incidentally in myasthenic patients. Conversely, other associated autoimmune diseases confer a survival disadvantage.

Minimally Invasive Surgery

Landreneau and associates\textsuperscript{21} published a case report of a patient with a stage I thymoma resected by video thoracoscopy. The stage was determined at frozen section. The authors stated that they would have converted to sternotomy or formal thoracotomy if invasive thymoma had been determined on frozen section. The entire thymus was not removed. An invited commentary by Dr. Peter Pairolero cautioned that this was an untested approach that might compromise treatment. A subsequent letter to the editor\textsuperscript{22} described thoracoscopic total thymectomy, which might be more acceptable.

Roviaro et al\textsuperscript{23} operated on six patients with thymoma by video thoracoscopy. However, they did not describe the extent of resection or size or stage of tumor, and no long-term follow-up data are available.

Kaiser\textsuperscript{24} reported on 12 thymectomies performed using video thoracoscopy, 8 for thymoma. Later in his series, he advocated supplementing the thoracoscopic procedure with a transcervical dissection. He emphasized that any minimally invasive procedure should not be a compromise but concluded that his approach is a reasonable alternative to a transsternal thymectomy. Michael Mack recently showed a series of photographs of thymus glands removed using video thoracoscopy (General Thoracic Surgical Club; La Quinta, Calif; March 1995); the photographs confirmed that the entire thymus gland can be resected by experienced surgeons. However, it remains to be seen whether this procedure will prove to be adequate and comparable to standard thymectomy in the long run.

Treatment of Recurrence

When a thymoma recurs, perhaps many years after the initial resection, what should be the primary mode of therapy? Consultation with a surgeon is certainly in order, for if the tumor can be re-resected, the patient will gain a distinct advantage. Blumberg and associates\textsuperscript{9} from Memorial Sloan-Kettering, recently reported that surgical resection of recurrent thymoma was associated with a 5-year survival rate of 85\%, compared with 45\% for those not resected (p=0.001). In a personal series of 23 reoperations for thymoma, Kirschner\textsuperscript{25} reported long-term survival in several groups of patients, including those who had not had a complete thymectomy at their first operation, those whose tumors recurred despite complete prior thymectomy, and those who had unresectable tumor treated by chemotherapy and/or radiation prior to reoperation.

Surgery remains a mainstay of treatment for thymoma, even recurrent disease. Radiation therapy is also applied if not used previously.

Utility of Chemotherapy

A few reports in the literature detail single-institution success with chemotherapy for thymoma in small groups of patients. Wang et al\textsuperscript{17} found the mean survival time for 10 patients who received a variety of chemotherapeutic agents to be 2.5 years, and the response rate was 60\%. Weide et al\textsuperscript{26} reported three significant responses among five patients with thymic carcinoma treated with cisplatin-based chemotherapy. Fornasiero and colleagues\textsuperscript{27,28} noted success and some long-term survivors with a regimen of cisplatin/vincristine/doxorubicin/cyclophosphamide for unresectable or incompletely resected invasive thymoma. Using the same regimen in 16 patients with unresectable
(stages III and IV) thymomas, they reported a 100% response rate (complete or partial) and a complete resection rate of 68%.\textsuperscript{20}

Park et al\textsuperscript{13} observed a significant response rate to cisplatin with or without prednisone (6/17 complete responses, 5/17 partial responses, for an overall response rate of 64%). The responders had a much longer median survival time. These authors now recommend preoperative induction chemotherapy, surgical resection, postoperative radiotherapy, consolidative chemotherapy after radiotherapy.

The Eastern Cooperative Oncology Group published a report of the first American cooperative group effort to study chemotherapy in invasive thymoma.\textsuperscript{30} Twenty-four patients received up to eight courses of weekly cisplatin, 50 mg/m\textsuperscript{2}. Only two patients exhibited a partial response, and 50% had disease progression during therapy. The authors concluded that cisplatin given at this dose was ineffective in producing regression of recurrent or metastatic thymoma.

An intergroup trial published in 1994\textsuperscript{31} gave results on 30 patients treated with up to eight courses of cisplatin/doxorubicin/cyclophosphamide. The overall response rate was 50% (three complete and 12 partial responses), and toxic reactions were mild. Median survival was 37.7 months. This trial demonstrated that high objective response rates and prolonged survival can be achieved in patients with advanced thymoma.

Studying thymoma even in a multi-institutional setting is difficult because of its variability in clinical presentation and the rarity of advanced disease. Nevertheless, many of the studies mentioned hold promise that thymoma may be a chemoresponsive tumor in the proper setting, and further investigation is warranted. Currently, a phase II intergroup study in North America (Eastern Cooperative Oncology Group E1C93, Southwest Oncology Group 9949, Cancer and Leukemia Group B 9590) will study patients with extensive disease, including those with metastasis and those who have had prior radiotherapy. Patients are scheduled to receive four courses of etoposide/ifosfamide/cisplatin. Complete responders will be observed on follow-up, whereas resection will be attempted in partial responders. Patients with no tumor in the resected specimen will be observed, whereas those with residual tumor will receive two additional courses of the same chemotherapy. This study may shed additional light on the utility of chemotherapy in treating patients with extensive thymoma.

**CONCLUSIONS**

Invasiveness remains the single most consistent factor in predicting the outcome of patients with malignant thymoma. Invasion as determined by the surgeon must be supplemented by histologic search by the pathologist for evidence of capsular invasion of microscopic loci within mediastinal fat. The practical clinician need not be concerned with the various methods of classifying the cellular characteristics of thymoma, as they have little impact on patient treatment.

Surgery is the treatment of choice for thymoma whenever a complete resection can be accomplished. Incomplete resection may have some advantage over biopsy alone. The preponderance of evidence indicates that all thymomas except completely encapsulated stage I tumors should be treated with postoperative adjuvant radiation therapy in the hope of reducing the incidence of local relapse.

Early experience with thymoma in the face of myasthenia gravis included a significant death rate from myasthenic crisis. This rarely occurs anymore, and myasthenia can no longer be considered an adverse prognostic factor in thymoma. It may even confer a survival advantage, but this may be due to the preponderance of early-stage tumors discovered incidentally in myasthenic patients. Other associated autoimmune diseases confer a survival disadvantage.

Many years of investigation are needed before minimally invasive thoracoscopic approaches can be considered to be equivalent to standard thymectomy.

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**REFERENCES**

References:
