REVIEW ARTICLE

Thymoma: State of the Art

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Thymoma is the most common tumor of the anterior mediastinum. This tumor is associated with unique paraneoplastic syndromes, such as myasthenia gravis, hypogammaglobulinemia, and pure red cell aplasia. The rarity of this tumor, however, has somewhat obscured the optimal treatment for this disease. For the majority of patients who present with localized tumor, surgical extirpation remains the standard of choice. Adjuvant radiotherapy seems to improve local control and survival. In more advanced disease, systemic therapy has been demonstrated to produce a 50% to 80% objective response rate. These observations have led to the development of multimodality therapy for the treatment of patients with advanced thymoma. In this article, we will review the current perspectives on the management of early stage and advanced thymoma.

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THE THYMUS HAS BEEN an enigma to students of medicine up until only the last few decades.[1] This gland plays an integral role in the immune process via its complex microenvironment, along with providing an interaction between stromal epithelial cells and developing lymphocytes.[2,3] Thymoma is a tumor originating within the epithelial cells of the thymus. The major constituents of the epithelial cells have defined histologic subtypes of thymoma, which also contain admixtures of lymphocytes. Thymic carcinoma (for which there are various subsets) is also believed to be a tumor of the thymic epithelium, but it is associated with a paucity of other lymphocytes and often presents with more invasive or metastatic disease.[4,5] In more recent years, awareness has been raised regarding the clinical, biologic, and therapeutic aspects of thymoma, which is the focus of this update.

CLINICAL PRESENTATION

Thymomas usually present in the fourth and fifth decades of life, although cases have been reported within the first year and well into the ninth decade.[6,7] There is no clear sex predisposition. One third to one half of patients present with an asymptomatic anterior mediastinal mass on chest radiograph, one third present with local symptoms (eg, cough, chest pain, superior vena cava syndrome, and/or dysphagia), and one third of cases are detected during the evaluation of myasthenia gravis. Distant metastases are distinctly uncommon at initial presentation with this tumor. However, when present, the most common metastatic site is the pleura, with involvement of the kidney, bone, liver, and brain metastases infrequently seen.

In addition to myasthenia gravis (MG), which occurs in approximately 30% of patients with thymoma, a host of paraneoplastic syndromes have been seen in association with thymoma (Table 1). These other syndromes, which occur in less than 5% to 10% of patients, include pure red cell aplasia, hypogammaglobulinemia and a variety of other autoimmune disorders and vasculitides.[6-8] Interestingly, with the exception of well-differentiated thymic carcinoma, MG does not usually manifest in patients with thymic carcinoma.[9] Approximately 10% to 15% of patients with MG will have thymoma.[10] Most patients with MG and abnormalities of the thymus have a thymic hyperplasia without a thymoma, for which the clinical course is more favorable.[10-12]

DIAGNOSTIC WORK-UP

The diagnosis of thymoma is usually made clinically. Initial suspicions are based largely on the computed tomography (CT) scan appearance of an anterior mediastinal mass. The epicenter of the mass is usually where the normal thymus is found (just below the innominate vein and abutting the sternum but it may extend caudally to abut either cardiac border). Thymomas are of a soft tissue density but may have areas of calcification. Their contours are usually smooth or lobulated. Features suggestive of malignancy include vascular invasion, encasement, and pleural deposits.[13]

Surgical excision then provides the precise histology and staging information necessary to render a decision regarding

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Table 1. Paraneoplastic Syndromes Associated With Thymoma

Acute pericarditis
Addison's disease
Agranulocytosis
Alopecia areata
Cushing's syndrome
Hemolytic anemia
Hypogammaglobulinemia
Limbic encephalopathy
Myasthenia gravis
Myocarditis
Nephrotic syndrome
Panhypopituitarism
Pernicious anemia
Polymyositis
RBC aplasia
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sensorimotor radiculopathy
Stiff-persons' syndrome
Systemic lupus erythematosus
Thyroiditis
Ulcerative colitis

the appropriateness of postoperative (adjuvant) treatment. Small, encapsulated, ''typical'' thymomas are excised for diagnosis and treatment. Large, invasive, ''atypical'' thymomas are best managed by biopsy to learn the histology of the tumor and to assess its invasive potential. This approach has arisen because of the long-held dictum shunning preoperative biopsy for fear of local implantation of thymoma cells. The natural history of thymoma certainly illustrates the tendency for local mediastinal recurrence and pleural ''droplet'' recurrence presumably caused by mediastinal pleural invasion after resection. Local recurrences have been noted in the surgical incision used to completely remove a thymoma.[14] The Boston group had a local recurrence at a limited anterior mediastinotomy site used for preoperative biopsy.[7] Accordingly, for typical ''encapsulated'' tumors judged to be completely resectable, an excisional approach seems reasonable. In patients with atypical features or ''invasive'' tumors thought to be candidates for induction (neoadjuvant) therapy, preoperative biopsy is appropriate. The standard approach is a limited anterior mediastinotomy (Chamberlain approach) on the side over which the tumor projects. Mediastinoscopy is rarely useful, because this approach gains access to the middle compartment rather than the anterior mediastinum. Fine-needle aspiration biopsy has not been part of the Boston experience but has been reported to be beneficial by others.[14] Caution must be applied, however, because misdiagnoses have occurred, especially in differentiating lymphoma from thymoma.[15] Use of the new core biopsy system in conjunction with immunohistochemical staging is favored over fine-needle aspiration because of improved diagnostic accuracy. The most common tumors one must include in the differential diagnosis of an anterior mediastinal tumor are lymphomas and germ cell tumors.[13] Lymphomas usually have a characteristic CT appearance, including an ill-defined lobulated mass, often with associated regional or distant lymphadenopathy.[16] Flow cytometry is useful in distinguishing lymphoma from thymoma. Benign germ cell tumors are notable for the characteristic CT appearance of a sharply defined mass with cystic areas and mixed areas of calcification and fat.[17] Nonseminomatous germ cell tumors usually have a characteristic CT appearance with a large, poorly defined mass with zones of hemorrhage and necrosis.[18] Almost all of the patients have elevated serum tumor markers (beta human chorionic gonadotropin or alpha-fetoprotein), which are diagnostic of these tumors.

PATHOLOGY

The nomenclature for the histologic subclassification of thymic malignancies is under considerable discussion. Regardless of several proposed classifications, investigators do agree that the epithelial cell is a malignant component, or the cell of origin, of thymomas and thymic carcinomas. The lymphocytic, usually T-cell, component, which may vary in these subtypes, is considered benign. Although some subtypes of thymoma may have a lesser or greater frequency of malignant potential, the invasiveness of the tumor rather than the histologic architecture dominates the prognosis.[19-21]

Three of the most common classifications are listed in Table 2. Verley and Hallman[22] propose a classification based on tumor architecture, cellular differentiation, and predominant cell type. Lewis et al[23] describe a simpler classification by presenting thymoma based on the percentage of epithelial cells and lymphocytes. In both of these systems, thymoma with a predominance of epithelial cells was associated with a greater increased incidence of invasion and a subsequently worse prognosis.

More recently, Marino and Muller-Hermelink,[4] Kirchner and Muller-Hermelink,[24] and Kirschner[25] reported a new classification of thymomas based on relating thymoma epithelial cells to the normal differentiation of thymic cells into medullary and cortical types. Their current classification of thymic epithelial tumors (thymoma and thymic carcinoma) includes six subtypes: medullary, mixed, predominately cortical, cortical, well-differentiated carcinoma, and high-grade carcinoma. When originally proposed, histology did correlate with stage, but it was not clear whether histology was independent of stage in predicting survival. Controversy has ensued between the two histologic classifications and both are in use today. The implementation of the Muller-Hermelink classification has not been easy for some

Table 2. Clinicopathologic Correlates of Thymoma and Thymic Carcinoma

	No. of Patients	Subgroups (% of total)	Comment
Thymoma survival			10-year DFS (%)
Verley and Hollman[22]	200	Type I: spindle and oval cell (30)	75
		Type II: lymphocyte rich (30)	75
		Type III: differentiated epithelial rich (33)	50
		Type IV: undifferentiated epithelial rich (equivalent to thymic carcinoma) (7)	0
			15-year DFS (%)
Bernatz et al[19]	283	Predominantly lymphocytic (25)	90
		Mixed lymphoepithelial (43)	80
		Predominantly epithelial (25)	50
		Spindle cell (6)	100
			Subgroup with invasion
Muller-Hermelink et al[85]	58	Cortical (43)	67
		Mixed: predominantly cortical (8)	0
		Mixed: common (36)	0
		Medullary (5)	0
		Mixed: predominantly (8)	0
Thymic carcinoma			Median survival (mo)
Low grade	ND	Keratinizing squamous, basaloid squamous ,mucoepidermoid	25.4
High grade	ND	Lymphoepithelial-like, small cell, large cell anaplastic, clear cell, sarcomatoid	11.3

pathologists, which has limited its usefulness.[26] Earlier this decade, three centers reported that the Muller-Hermelink classification independently predicts survival.[27-29] Medullary and mixed tumors are benign tumors with little chance of recurrence, with obvious implications in the advisability of postoperative adjuvant therapy.

STAGING

The staging system proposed by Masaoka et al[30] has been widely adopted (Table 3). Stage is an independent predictor of recurrence and long-term survival.[27-29,31] Although some tumors can be accurately staged preoperatively (obvious vascular invasion or pleural implants), the Masaoka staging system is postsurgical, because invasion of the capsule is only reliably diagnosed by pathologic examination. Another less commonly used system is the Groupe d'Etudes des Tumeurs Thymiques (GETT) staging system, as described by the French Study Group on Thymic Tumours.[32] In this system, the predominant feature is the extent of surgical resection (Table 4). One retrospective comparison noted an 88% concordance between the Masaoka and GETT systems.[33]

Table 3. Masaoka Staging System of Thymomas

Stage I	Macroscopically completely encapsulated and microscopically no capsular invasion
Stage II	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura; microscopic invasion into capsule
Stage III	Macroscopic invasion into neighboring organs (ie, pericardium, great vessels, or lung)
Stage IVa	Pleural or pericardial dissemination
Stage IVb	Lymphogenous or hematogenous metastases

NOTE. Data adapted.[30]

ROLE OF SURGICAL TREATMENT

All patients whose tumors are potentially resectable should undergo operative exploration and resection of their thymoma. Under the guidance of a preoperative consultation by a clinical neurologist, patients with MG should be in excellent physiologic condition. The incision of choice is almost always a median sternotomy, which is quick and easy to make, provides excellent exposure to the anterior mediastinum and neck, and is relatively painless (compared with a posterolateral thoracotomy). Cervical approaches are not adequate and lead to a high recurrence rate. A posterolateral thoracotomy is occasionally useful for recurrences that involve the lung or pleura, but it is rarely the approach of choice for primary surgery because there is poor access to the neck and opposite side of the anterior mediastinum to facilitate a complete thymectomy, a cornerstone of the operation. Recurrences have been noted in the residual thymus after unilateral thoracotomy.[32,34] The removal of a thymoma by video-assisted thoracic surgery techniques has been reported as a technical feat, but no long-term follow-up

Table 4. GETT Staging System of Thymomas

Stage I	
Ia	Encapsulated tumor, totally resected
Ib	Macroscopically encapsulated tumor, totally resected, but the surgeon suspects mediastinal adhesions and potential capsular invasion
Stage II	Invasive tumor, totally resected
Stage III	
IIIa	Invasive tumor, subtotally resected
IIIb	Invasive tumor, biopsy
Stage IV	
IVa	Supraclavicular metastasis or distant pleural implant
IVb	Distant metastases

Data adapted.[32]

is available.[35] Removal by video-assisted thoracic surgery is ill advised because it compromises the operation by an incomplete thymectomy and a non–en bloc approach in a tumor known for its ability to locally implant.

After median sternotomy, both pleural envelopes should be opened widely by elevating each hemisternum and incising the parietal pleura lateral to the mediastinal reflection to facilitate complete removal of all possibly involved mediastinal pleura. An accurate assessment of the gross extent of the tumor and its invasiveness and an inspection of the total pleural (parietal and visceral) surface for droplet metastases can then be made. If the tumor is small, apparently noninvasive, and readily movable, a total thymectomy (including the cervical tongues) with contiguous removal of all mediastinal fat around the tumor is appropriate. If an invasive tumor is found, en bloc removal of affected pericardium, pleura, lung, phrenic nerve, innominate vein, or superior vena cava (SVC) is performed in addition to the total thymectomy. Long-term survival has been reported despite the necessity of resecting and replacing the SVC; hence, SVC involvement should not deter complete resection.[36,37] If only one phrenic nerve is involved, resection should generally be carried out. If both phrenic nerves are involved, neither should be resected and the area should be debulked only. Clips to assist the radiation oncologist in treatment planning should mark areas of close margins or residual disease. Pleural implants should be removed by extrapleural dissection, which can lead to long-term survival, although if multiple pleural implants are found preoperatively, systemic therapy before surgery is preferred. The issue of whether subtotal excision is superior to biopsy only in unresectable tumors is controversial and unresolved. Previous reports have suggested no difference in survival, whereas others suggest that subtotal excision is superior.[31,38] In general, if the surgeon is already committed, a partial resection should be performed with care taken to avoid maneuvers that could lead to excessive perioperative morbidity. Patients with locally advanced tumors would benefit from a multimodality evaluation by the thoracic surgeon, medical oncologist, and radiation oncologist, with consideration for preoperative therapy. For those with invasive or residual disease, postoperative therapy is warranted.

Death after thymoma resection in the perioperative period is now rare and should be less than 1%. Historically, the majority of deaths occurred in patients with MG from respiratory complications with poorly controlled myasthenia. Modern preoperative preparation, intensive care, and, in selected cases, plasmapheresis have essentially eliminated this risk. Age, sex, the disease-free interval, and the presence of MG are not consistent independent predictors of survival.[27,28,31] Some series report that large size epithelial variants (in the traditional histologic classification scheme), and the presence of autoimmune diseases (red cell aplasia, hypogammaglobulinemia, and lupus erythematosus) are significant poor prognostic factors.[27,31] Several large series have demonstrated convincingly that stage (early), resection status (complete), and the medullary variant (in the Marino and Muller-Hermelink classification scheme) are independent predictors of long-term survival.[27-29] Thymomas are notably indolent tumors, such that comparisons of 5-year survival figures (especially for stage I and II tumors) are misleading because of relapses 10 to 20 years after primary therapy.[39] Thus long-term follow-up of such patients should probably be performed for life. Isolated recurrences can be surgically resected and result in a prolonged disease-free survival. The results according to stage after resection are compiled in Table 5.[28,29,31]

ROLE OF RADIATION THERAPY FOR THYMOMA

Encapsulated Thymomas

All encapsulated thymomas, by definition, should be completely resectable, with the possible exception of the occasional rupture of a bulky tumor, at the time of surgery.[40] Masaoka stage I, and some stage II, lesions without evidence of tumor beyond the capsule may also be considered encapsulated thymomas. Careful pathologic review, in addition to surgical assessment of capsular invasion, is critical because pathologic upstaging occurs in some patients.[7] Although some oncologists have promoted routine postoperative external-beam radiotherapy (EBRT) for all patients with thymomas regardless of stage,[41] it is well recognized that the risk of failure after complete resection of encapsulated disease is considerably low. Most oncologists would

Table 5. Survival According to the Masaoka Staging System

First Author	Year	Masaoka Stage	Survival	
			5-Year (%)	10-Year (%)
Quintanilla-Martinez[28]	1994	I	100	100
		II	100	100
		III	70	60
		IV	75	0
Blumberg[31]	1995	I	95	86
		II	70	55
		III	50	—
		IV	100	—
Schneider[29]	1997	I	100	91
		II	95	88
		III	56	47
		IV	11	11

NOTE. Quintanilla-Martinez et al reported disease-free survival, whereas Blumberg et al and Schneider et al reported overall actuarial survival. Data adapted.[30]

concur that adjuvant therapy is not indicated for patients with encapsulated thymomas, in whom disease-specific survival rates approach 100%.[38,42,43] The intrathoracic failure rates are less than 5% after complete surgical resection alone in patients with encapsulated thymomas. For locoregional failures, aggressive radiotherapy and/or surgical resection can be incorporated into multimodal approaches for attempted salvage.

Completely Resected Invasive Disease

This heterogeneous category of patients includes those with Masaoka stages II, III, and IVa disease. The rate of complete resectability varies by stage (essentially 100% for stage II, 50% to 60% for stage III, and approaching 0% for stage IVa tumors), as well as surgical experience at the reporting institution.[38,41,43-47]

Most investigators recommend adjuvant radiotherapy after total surgical resection of invasive thymomas. Curran et al[43] strongly suggest the need for postoperative thoracic irradiation in such patients. In 21 patients with completely resected thymomas (18 stage II, and three stage III) who did not undergo postoperative irradiation, eight mediastinal failures were noted, for a crude local failure rate of 38%; the 5-year actuarial mediastinal relapse rate was 53%; and the 5-year relapse-free survival rate was 47%. In contrast, there were no failures among five patients (one stage II, and four stage III) who received adjuvant radiotherapy, and these patients had a 5-year relapse-free survival rate of 100%. When these data were pooled with that from seven other studies in which patients underwent complete resection of invasive stages II and III thymomas, the crude intrathoracic failure rate was 28% in patients who did not receive postoperative radiotherapy, versus a 5% failure rate in irradiated cases.[42-43]

Stage II

Although there is general consensus regarding the use of adjuvant radiotherapy in fully resected stage III disease, its role in invasive stage II thymoma (tumor extending through the capsule into mediastinal fat) is more widely debated.[42] In the experience of Curran et al,[43] one-third (six of 18) of patients undergoing complete resection of stage II tumors who did not receive EBRT eventually experienced recurrence in the mediastinum as the first site of relapse. The one patient with a stage II lesion who did receive postoperative EBRT did not experience recurrence.[43] Monden et al[48] reported a 29% (two of seven) recurrence rate for patients with resected stage II thymomas who did not undergo adjuvant EBRT, as compared with 8% (two of 25) in those who received postoperative EBRT. Other investigators have noted a low rate of recurrence in stage II disease and questioned the need for routine EBRT.[31,38,47]

Massachusetts General Hospital reported a 10% (three of 30 patients) relapse rate in stage II thymoma after complete tumor removal.[39] They emphasize the importance of adding histologic criteria to surgicopathologic staging in assessing prognosis for these patients because recurrences occurred in patients with more aggressive histologic profiles, such as cortical subtype.[39,49] Although the observations in the report may support limiting the use of adjunctive EBRT to patients with more ''histologically aggressive'' stage II tumors, it should be noted that approximately one third of the stage II patients received postoperative EBRT, making definitive conclusions difficult.[39]

Pescarmona et al[27] have presented a rather complex scheme of combined clinicopathologic staging, which advocates postoperative radiotherapy only for selected patients with stage II thymomas. The pathologic evaluation of a ''pleural factor'' has been suggested as a potentially useful guide to the selection of postoperative radiation in patients with completely resected stage II thymoma.[44] Patients with fibrous adhesions (p1/c1) or microscopic invasion to the mediastinal pleura or pericardium (p2/c2) are at increased risk for recurrence.[44] An update of these investigators noted a significantly lower relapse rate (0%) with mediastinal EBRT (40 to 50 Gy) compared with those who did not receive EBRT (36%) for resected p1/c1 lesions, indicating that selected patients with stage II thymoma may benefit from adjuvant therapy.[50]

Despite the varying opinions expressed by different investigators, pending further clinical validation of some of the aforementioned factors, postoperative EBRT should be strongly considered in all patients with completely resected stage II thymomas when tumor extension beyond the capsule is documented pathologically.[42]

Stage III

The usefulness of adjuvant radiotherapy after complete resection of stage III thymomas is supported by Urgesi et al,[47] who noted that in 33 such patients there were no in-field recurrences, although there were three out-of-field intrathoracic relapses. However, there was no surgery-only group for comparison. Arakawa et al[51] reported 15 patients with invasive thymomas (stages III and IV) who received postoperative EBRT (30 to 58.7 Gy in 1.8- to 2.0-Gy fractions) after total surgical extirpation. Only two tumor recurrences were noted, and all patients remained alive at last follow-up. Moreover, no significant radiation-induced morbidity was observed. Nakahara et al[41] noted a 95% 15-year survival rate in 35 patients with stage III thymoma whose tumors were completely resected and who were given routine postoperative radiation. On the other hand, the Memorial group failed

to observe any survival or relapse advantage at 5 years with EBRT.[31] These results are conflicting and are likely a function of selection bias, a common problem with comparing retrospective data sets. Overall, most data suggest that postoperative EBRT after complete surgical resection of stage III disease is beneficial.[42]

Unresectable or Locally Advanced Disease

In patients with Masaoka stage III and IVa thymoma, operative approaches range from biopsy alone to nearly complete tumor removal. Comparison between different series is challenging because of the varying amount of postoperative residual disease. The definition of what constitutes a subtotal resection has ranged from 10% to less than 100% of the initial disease volume.[40,43,45,52]

A review of the literature indicates that thymomas are moderately radiosensitive. Radical postoperative radiotherapy may control residual disease and provide long-term, disease-free survival in a subset of patients after incomplete resections. We have previously summarized selected clinical experiences for which approximate 5-year data are available and noted that approximately two thirds of patients with locally advanced disease were locally controlled, and slightly less than one half were still alive.[42] More recent series have reported data in actuarial terms, but they remain in close agreement with past studies documenting 5-year survival rates of approximately 40% to 50%.[22,38,41,45,47,53]

The amount of residual disease present after surgery will likely impact on local tumor control and survival.[42,54] Mornex et al[55] reported, in a study of 90 patients with stage III or IVa disease receiving a median dose of 50 Gy after a partial resection or biopsy, a complete remission in 78%, with approximately two thirds locally controlled at 8 years. Although the relapse rate was only 14% for those patients whose tumors were completely resected, the figure increases to 41% in those who underwent less extensive surgery, suggesting that doses higher than 50 Gy may be appropriate for the latter group. Another study treated 149 patients, who were staged postoperatively via the GETT classification (Table 4) of the French Study Group on Thymic Tumours[32] and received postoperative EBRT to a median dose of 50 Gy.[33] Investigators reported a 97% local control rate after a complete resection compared with 16% and 45% after subtotal resection and biopsy-only cases, respectively. The overall survival rate at 5 years was 80%, 64%, and 39% respectively, significantly favoring patients able to receive a more complete resection.

Jackson and Ball[40] reported 28 patients with incompletely resected thymoma. In 14 patients for whom gross tumor removal was possible, leaving only microscopic residual, local control was achieved in 13 (93%) of 14 and the 10-year overall actuarial survival rate was 62%. In comparison, 14 other patients had gross residual tumor, with a local control rate of four (29%) of 14 and a 10-year survival rate of 29%.[40] A Swiss group reported on 31 patients with partially resected tumors who received postoperative EBRT to 42 to 66 Gy.[56] The 10-year survival rates were 57% and 8% for stage III and IVa thymomas, respectively. The M.D. Anderson Cancer Center group reported an actuarial 5-year, disease-free survival rate of 60% after radiotherapy in subtotally resected thymomas (defined as removal of $>$ 50% but $<$ 100% of the tumor), as compared with 20% for patients who had tumor biopsies only ($<$ 50% of disease surgically removed).[45]

Other authors have also described better clinical outcomes with more aggressive tumor debulking in patients with incompletely resectable thymomas.[30,38,41,47] Yet additional investigations have not shown any consistent significant benefit with postoperative EBRT after an incomplete or subtotal resection.[57-59]

Given the limited experience of any single institution and the lack of prospective multicenter data, there is an expected selection bias in reports of better outcome with aggressive tumor debulking because patients with stage III or less bulky thymomas are more likely to have greater resectability than patients with stage IVa or more extensive tumors.[42]

Radiotherapy Dose, Fractionation, Treatment Planning, and Normal Tissue Toxicity Issues

A variety of dose and fractionation schemes have been reported in the literature.[42] Total doses of 40 to 50 Gy, in conventional fractionation of 1.8 to 2.0 Gy/d, have been used for adjuvant treatment of completely resected invasive thymomas.[31,33,43,50,51,55,60,61] For patients with gross residual disease after resection, doses greater than 60 Gy have been used.[56] It is challenging to define a clear dose-response relationship because of the paucity of cases.[33]

Local control, defined as failure to have a recurrence within the radiation port or within the thorax, was 81% and 74%, respectively, in one study of postoperative EBRT Gy.[61] In-field recurrences occurred after 48 Gy (stage II), 50 Gy, and 54 Gy (stage III). The M.D. Anderson Cancer Center group noted a 50% in-field local failure rate, all in stage III and IVa patients who had undergone varying degrees of surgical resection.[45] The local control rates after a complete resection have ranged between 65% to 85%.[33,40,45,47,51,60-63] It is likely that doses greater than 60 Gy may be required to address residual macroscopic disease.[55]

EBRT port arrangements have included a single anterior field, variably weighted (2:1 or 3:2) opposed anterior-posterior ports, wedged-pair techniques, and other multiple-field arrangements. Given present technical capabilities, at least two fields, treated daily, are recommended to provide

dose homogeneity and allow sparing of adjacent normal critical structures. Whereas most reports do not clearly describe the intended target or beam arrangements and most reporting institutions have taken multiple decades to accrue a publishable experience, an exception is the Eastern Cooperative Oncology Group–driven intergroup trial and the most recent M.D. Anderson Cancer Center data. These studies specifically attempted to treat the gross tumor volume, mediastinal nodal stations, and bilateral hilar nodes with 2-cm margins, to 54 Gy after neoadjuvant chemotherapy.[60,64] Other studies have targeted the whole mediastinum without hila, plus a 2-cm margin.[33]

CT is currently indispensable for adequate radiation treatment planning. Clips placed at the time of surgery, either denoting the extent of resection in completely removed thymomas or outlining regions of unresectable disease, are useful in guiding postoperative radiotherapy. A recommended target volume should include the gross tumor volume with a 1.5- to 2.0-cm margin when using traditional treatment planning arrangements with multiple beams, preferably with the assistance of three-dimensional conformal radiotherapy.[65,66] There is no demonstrable need to treat the mediastinal nodal basins prophylactically, because the pattern of failure within nodes has little similarity to that of lung cancer. For selected patients, this extended-field approach may be worthwhile, although we believe the potential risk may outweigh the benefits in most patients[33,45,53,67-70] because a higher normal tissue complication rate can be expected if large target volumes are used without any consistent proven benefit.[60,61,63,64,71,72]

ROLE OF CHEMOTHERAPY FOR THYMOMA

The role of chemotherapy in thymoma has been somewhat elusive. In large part this is secondary to a low incidence of this tumor and because most patients have resectable disease that is cured with surgery and/or radiation therapy. Approximately one third of patients with invasive thymoma, who later develop metastases, and all patients with stage IV disease will be potential candidates for systemic therapy.

In the 1960s and 1970s, several case reports in small series suggested that thymoma was a chemosensitive disease.[73] Only three prospective phase II trials have been published that evaluated single-agent therapy in thymoma. The first trial examined cisplatin (50 mg/m^2 every 3 weeks) in patients with advanced or recurrent thymoma.[74] In 21 assessable patients, two partial responses (10%) were noted. Patients in this study, it should be noted, were allowed to have prior chemotherapy.

Another trial from Indiana evaluated interleukin-2 in recurrent thymoma.[75] The basis of this trial was a case report, which documented a durable complete remission to interleukin-2 in a heavily pretreated patient with advanced thymoma.[76] Unfortunately, in the 14 patients treated on this phase II trial, no objective responses were confirmed.

Finally, in 1991, Harper and Addis[77] evaluated ifosfamide in patients with advanced thymoma. In 13 assessable patients, seven had an objective response with no relapses in the complete remissions at the time of publication.

Most recently an interesting case report was published in which a patient with red cell aplasia and heavily pretreated thymoma achieved a durable complete remission when treated with high-dose octreotide plus prednisone.[78] The authors (G. Palmieri, personal communication, 1998) have seen activity in other patients treated with this regimen. An Eatern Cooperative Oncology Group (E1C97) trial is evaluating octreotide alone, without initial prednisone, in patients with advanced thymoma. A number of other agents have yielded responses in selected patients, including paclitaxel, gallium nitrate, suramin, fluorouracil, and daily oral etoposide (P.J.Loehrer, personal communication, 1999).

COMBINATION CHEMOTHERAPY

Similar to the published experience with single-agent therapy, numerous small series and case reports have demonstrated varying results with combination chemotherapy in patients with advanced disease. Most noted was cisplatin-based or anthracycline-based chemotherapy. During the last 10 to 15 years, several phase II trials have evaluated different therapeutic strategies in patients with locally advanced and advanced thymoma. The Southeastern Cancer Study Group initiated one of the first prospective trials evaluating combination chemotherapy in 1983. This trial was designed to identify the activity of cisplatin, doxorubicin, and cyclophosphamide (PAC) in patients with unresectable or advanced thymoma. In those patients with limited disease (defined as that encompassable in a single radiotherapy portal), the trial design was to administer two to four cycles of PAC followed by radiotherapy. In patients with advanced disease (or patients with prior thoracic radiotherapy), patients received up to six cycles of PAC chemotherapy. In the group of patients with advanced disease, a 50% response rate (three complete and 12 partial responses) was noted in 30 assessable patients treated with the PAC chemotherapy.[79] The median survival time was 38 months and the 5-year survival rate was 32%. In patients with limited disease, PAC produced a 70% response rate before radiation therapy in 23 assessable patients, with an approximate 50% 5-year survival rate.[64]

Forniasiero et al,[80] who treated patients with stage III and IV disease, reported a similarly high response rate to combination chemotherapy with doxorubicin, cisplatin, vin-

cristine, and cyclophosphamide. Among 32 patients, a 47% complete and 90% overall response rate was observed. The median survival time, however, was only 15 months.

More recently, Giaccone et al[81] reported the results of a trial conducted by the European Organization for Research and Treatment of Cancer. Among 16 patients with recurrent or metastatic thymoma, five complete and four partial remissions were noted, with a median duration of response of 3.4 years and a median survival time of 4.3 years.

Based on these findings, an intergroup trial coordinated by the Eastern Cooperative Oncology Group evaluated ifosfamide, etoposide, and cisplatin in patients with recurrent and metastatic thymoma. The preliminary results suggest that the overall response rate is comparable to that in the previously conducted trials with PAC chemotherapy.[82]

CHEMORADIOTHERAPY

The concept of combined-modality therapy is attractive for patients with thymoma in whom the burden of tumor volume is located in the mediastinum. Macchiarini et al[83] were among the first to evaluate preoperative chemoradiotherapy in patients with potentially resectable disease. Seven patients with clinical stage III thymoma received three cycles of cisplatin, epirubicin, and etoposide before surgery. Four patients experienced complete remission, whereas the remaining three patients developed either microscopic disease (n = 2) or gross residual disease (n = 1).

A similar trial disease was also developed by Rea et al.[84] Sixteen patients with stage III and stage IVa disease were treated with a doxorubicin, cisplatin, vincristine, and cyclophosphamide regimen every 3 weeks for three to four cycles. After chemotherapy, surgery was performed, and if residual was present, postoperative radiation therapy was given. Patients with a complete remission received three additional cycles of chemotherapy. Results of this trial demonstrated seven complete and five partial responses and a projected 2-year survival rate of 80%.

A third study evaluated three cycles of cisplatin, doxorubicin, cyclophosphamide, and prednisone in 12 patients with stage III to IVa disease.[60] Four patients had almost no evidence of viable malignancy (defined as $\geq$ 80% tumor necrosis) at the time of surgery and five additional patients were able to undergo complete resection of tumor. Postoperative radiotherapy was administered to all patients and was followed by three additional cycles of consolidated chemotherapy. A median follow-up of 43 months revealed all 12 patients were alive, including two alive with disease.

Finally, the aforementioned intergroup trial studying PAC chemotherapy and radiation in 23 patients demonstrated a high response rate of around 70%. The progression-free and overall survival rates at 5 years were 54% and 52%, respectively.[64]

A prospective phase II trial evaluating high-dose chemotherapy with carboplatin and etoposide with stem-cell rescue is currently underway at Indiana University in patients with relapsed thymoma.

In conclusion, thymoma is a rare neoplasm with interesting biologic and therapeutic potential. Much is unknown regarding the genetic alteration that leads to the development of thymoma and the unique association with paraneoplastic syndromes. This remains a challenge for investigators. Prospective randomized trials conducted in the past 10 to 15 years have demonstrated that thymomas are tumors sensitive to chemotherapy. In patients without a pre-existing cardiomyopathy, a cisplatin/doxorubicin–based combination chemotherapy seems to produce the best overall response rate and survival. Second-line therapy can consist of a variety of single-agent or combination chemotherapeutic regimens, but entry onto clinical trials is preferred. Durable remissions are possible with multiple regimens, but permanent control in heavily pretreated patients is doubtful. The optimal coordination of chemotherapy, radiation therapy, and surgery has yet to be defined. Consequently, there is a need for prospective, rapid-accruing intergroup-driven trials to help identify the optimal therapy of this disease. Such trials are being planned by the American College of Surgeons/Oncology Group.

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