90 THYMOMAS AND THYMIC TUMORS

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The thymus, a key immune system organ, can be the site of many different benign and malignant tumors (Table 90.1). According to Rosai and Levine,[1] it should be emphasized that the term "thymoma" is restricted to neoplasms of the thymic epithelial cells. A detailed historical review of the thymus gland and thymomas has been published by Givel.[2] The first description of a thymic tumor is credited to Sir Astley Paston Cooper, a surgeon from London, in 1832. The British microscopist Arthur Hill Hassall described in 1849 the corpuscles unique to the thymus. The first association between myasthenia gravis (MG) and thymoma was discovered by the German neurologist Hermann Oppenheim, in 1899. The first thymectomy for MG was performed in 1911 by Ernst Ferdinand Sauerbruch in Zurich, Switzerland. The thymus showed hyperplasia but no tumor, and myasthenia improved markedly after surgery. Alfred Blalock at Vanderbilt University in Nashville pioneered the surgical technique of total thymectomy in 1936 (case published in 1939) and advocated it for the treatment of MG.

EPIDEMIOLOGY AND ETIOLOGY

Thymomas are usually slowly growing tumors with about equal incidence in men and women; they occur through a wide age range, with a peak in the 40s and 50s.[3–5] Thymomas are rare, and more aggressive, in children.

There are currently no known etiologic factors for thymomas. Among 23 patients with thymoma, Cohen and colleagues noted that 2 had received radiation for an enlarged thymus in childhood, 17 and 28 years before the diagnosis of thymoma, respectively.[6] In the past, that practice was based on the belief that such physiologic enlargement of the thymus in some infants could cause sudden death (status thymicolymphaticus).[1] Such radiation has been shown to lead to an increased incidence of cancer, particularly of the thyroid and breast.[1,7] The role of Epstein-Barr virus (EBV) in the etiology of a subtype of thymic carcinoma, the lymphoepithelioma variety, has now been documented, as discussed below.

ANATOMIC PATHOGENESIS

Embryology and Anatomy The thymus is embryonically derived from the endodermal epithelium of the third pharyngeal pouches (which also give rise to the lower pair of parathyroid glands) and, less constantly, the fourth ones as well.[1,5] The right and left thymic anlagen migrate downward into the anterosuperior mediastinum, joining together without complete fusion to form a bilobate organ.[1] Although most thymic tumors are located in the anterosuperior mediastinum, variations in migration account for the findings of gross or microscopic thymic tissue anywhere between the hyoid bone superiorly and the diaphragm inferiorly.[8] Wide exposure of the mediastinum and even the neck is therefore necessary, if surgical removal of the entire thymus is indicated, as in patients with thymoma or those with myasthenia gravis (with or without associated thymoma).[8] The absolute weight of the thymus reaches its peak in the pubertal years (mean, 34 ± 15 g between age 10 and 15 years) and then gradually decreases, although this age-related involution normally is never complete.[1]

Histologically, the normal thymus shows distinctive lobules with a sharp demarcation between the cortex, rich in lymphocytes, and the medulla rich in epithelial cells and characteristic Hassall's corpuscles, formed by concentric layers of mature epithelial cells.

The thymus plays a critical role in the maturation of bone marrow–derived lymphocytes into T cells and, as such, in cell-mediated immunity. It has a rich blood supply but no afferent lymphatics. Efferent lymphatics apparently originate from perivascular spaces and drain into the mediastinal and lower cervical nodes.[1]

Table 90.1. Thymic Tumors

Tumors of the thymic epithelium	Germ cell tumors
Thymomas (encapsulated or invasive)	Seminomas
Thymic carcinomas	Teratomas
Lymphoid tumors	Carcinomas
Hodgkin's disease	Others
Other lymphomas	Thymolipoma
Neuroendocrine tumors	Thymic cysts
Thymic carcinoids	Metastases
Oat cell carcinoma	

Pathology of Thymomas Distinctive features reminiscent of the normal thymus make the pathologic diagnosis of thymoma easy in most cases. A fibrous capsule surrounds the tumor and sends thick, fibrous septa, dividing the tumor into well-demarcated lobules.[1,9–11] Microscopically, there is a distinctive dual cell population, including lymphocytes (small with dark nuclei) and epithelial cells (larger and lighter) (Plate19, Fig. 90.1). Quantitatively, the lymphocyte–depithelial cell ratio varies widely (average about 2).[12] Even though there is a continuum among the extremes, thymomas are often classified according to the relative ratio of cells between predominantly lymphocytic, mixed epithelial–lymphocytic, and predominantly epithelial. In 4% of cases only epithelial cells are seen.[1] Since thymomas are defined as neoplasms of thymic epithelial cells, pure lymphocytic tumors are not thymomas and should raise the possibility of lymphoma. The epithelial cells represent the neoplastic component of thymomas.[1] They appear cytologically bland; mitosis and cellular atypia are rare. They are typically round or oval, but sometimes have a spindle-shaped nucleus, which may represent the predominant cell in about 5 to 12% of thymomas, justifying the term "spindle cell thymoma," which tends to grow more slowly and to be associated with red cell hypoplasia or hypogammaglobulinemia rather than MG.[1,9] The lymphocytes are not considered neoplastic and, as in the normal thymus, are constituted mainly of T cells in various stages of maturation. They often exhibit mitotic figures. A higher percentage of epithelial cells has been reported to have a negative prognostic influence, as seen in cases with recurrent tumor or more advanced stage.[12–14]

There are no reliable histologic features of "malignancy" for thymomas. The malignant behavior of a thymoma is indicated by microscopic or macroscopic invasion of the tumor capsule or of surrounding organs or by the presence of metastasis. Therefore, it is the gross examination of the tumor at surgery which is critical in suspecting or establishing the malignant nature of a thymoma. About 30 to 40% of thymomas are invasive. On the other hand, a well-encapsulated thymoma may, on occasion, recur years after surgical resection. This leads some to suspect that all thymomas are potentially malignant and should be treated as such.[5] Since the term "malignant" can also cause confusion with thymic carcinomas, where the epithelial cells appear cytologically malignant (see below), it is best to avoid it and divide thymomas into encapsulated and invasive ones.

It was recently postulated that thymomas may be further subdivided into those with cortical, medullary, and mixed differentiation, reflecting the anatomy of the normal thymus.[15] Cortical thymomas contain large epithelial cells with vesicular chromatin and prominent nucleoli, whereas medullary thymomas show oval to spindle-shaped epithelial cells with dispersed chromatin and inconspicuous nucleoli.[16] Mixed thymomas contain both cortical and medullary components. Medullary and mixed thymomas appear to follow a more benign course than cortical ones. They show a lower incidence of invasiveness, lower incidence of MG, lower recurrence rate, and better survival, even when capsular invasion is present.[16,17] This classification has also been correlated with the size of epithelial cell nuclei using morphometric analysis.[17] Cortical thymomas have larger epithelial cell nuclei than do medullary ones. The prognostic value of nuclear DNA content measured by flow cytometry is controversial.[18] Although the percentage of cells in the S-phase does not appear to have any prognostic significance, some studies have found that aneuploidy correlates with poorer survival.[18]

Other histologic features of thymomas include, in order of frequency,[1] typical perivascular spaces (56%), foci of foamy macrophages (27%), pseudorosette formations of epithelial cells (20%), gland-like structures (20%), Hassall's corpuscles (16%), areas of cystic degeneration which vary in size to produce occasionally cystic thymomas (16%), lymphoid follicles with germinal centers (8%), and a variable number of hemorrhagic, necrotic, and/or calcified areas. Occasionally, scattered macrophages among the lymphocytic component can mimic a "starry-sky" appearance, not to be confused with Burkitt's lymphoma. Myoid cells, so designated because their cytoplasm contains cross-striations identical to those of skeletal muscle fibers, have also been identified in rare cases.[1] Normal thymic tissue can be found in almost half the cases at the periphery of the tumor.

It is in rare cases that special stains may be helpful when the diagnosis is difficult, as in the distinction among thymoma and lymphoma, seminoma, carcinoid, hemangiopericytoma, and sarcoma, or when only a limited amount of tissue is available, such as from needle biopsy or fine-needle aspiration. Epithelial cells in thymomas, even the spindled ones, stain positively with keratin and epithelial membrane antigen (EMA) and negatively with markers for lymphocytes, such as common leukocyte antigen.[10,11] This pattern rules out a lymphoma or a mesenchymal tumor. The lymphocytes show a predominance of OKT 6 (CD1a) and terminal deoxy-nucleotidyltransferase (TdT)-positive cells, as well as Leu-7 (CD 57)- and/or HLA-DR–positive cells.

Finally, electron microscopy can reveal characteristic features of epithelial cells, such as desmosomes, tonofilaments, elongated cell processes, and lack of dense core granules.[1] Few studies have addressed the genetic changes of thymomas. On the one hand, alterations of p53 were found in 2 of 17 cases of "benign" thymomas versus 11 of 18 cases of "malignant" thymomas and 7 of 9 cases of thymic carcinomas.[19] On the other hand, p53 protein expression was seen in only 1 of 17 thymomas versus 14 of 19 cases of thymic carcinomas in another study.[20] An inverse correlation between p53 and bcl-2 protein expression has been described in thymomas.[21]

CLINICAL FEATURES

Tumor-related Findings Most tumor-related symptoms are vague (cough, dyspnea, chest pain) or secondary to local and regional mediastinal spread (pleural effusion, superior vena caval syndrome, or pericardial effusion) and, therefore, often indicate invasiveness. Occasionally, thymomas may present as diffuse pleural tumors and simulate malignant mesothelioma.[22] About half of thymomas occur in asymptomatic persons and are discovered fortuitously on a chest radiograph, which shows a retrosternal mass in the anterosuperior mediastinum forming a bulge in the cardiovascular silhouette. The tumor may be best seen on oblique and lateral views. Computed tomography (CT) is invaluable for detecting small thymomas and assessing possible invasion of surrounding structures, such as the mediastinum, pleura, and pericardium. It can show calcifications in or at the periphery of the tumor in about 20% of cases,[5] although they bear no relation to invasiveness. The presence of a fat plane all around the tumor is a good sign of noninvasiveness, but, conversely, fibrous adherence to surrounding structures may simulate invasion.[23] CT can also help differentiate thymomas from vascular structures and tumors, such as aneurysms, particularly when intravenous contrast is used.[23] Thymomas show increased T_1- and T_2-weighted image signal intensity by magnetic resonance imaging (MRI), but the role of that technique in detecting possible capsular invasion as well as vascular invasion as compared with CT, needs further study.[23] The use of positron emission tomography (PET) with 18-fluorodeoxyglucose has been evaluated to distinguish malignant from benign mediastinal tumors.[24] Thymic carcinomas and invasive thymomas show high uptake, whereas noninvasive thymomas show low uptake. It should be emphasized, however, that surgical exploration and pathologic evaluation remain the most reliable means to assess invasiveness of thymomas.

Table 90.2. Thymomas: Associated Disorders

Myasthenia gravis	Leukemias
Red cell aplasia	Lymphomas
Hypogammaglobulinemia	Kaposi's sarcoma
Collagen diseases	Eaton-Lambert syndrome
Sjogren's syndrome	Nephrotic syndrome
Pemphigus	Endocrine disorders
Cancer (nonthymic)	

Adapted from Marchevsky and Kaneko.[10]

ASSOCIATED PARANEOPLASTIC SYNDROMES

There is a remarkable number of paraneoplastic syndromes associated with thymoma that are mostly related to autoimmune mechanisms. They are dominated by three characteristic entities (Table 90.2).

Myasthenia Gravis MG occurs in about a third to a half of patients with thymoma, and about one-tenth of patients who have MG have a thymoma.[1,25] Such patients are usually older than those with MG without thymoma, although the clinical signs of MG are similar in both groups. Few features distinguish the histologic appearance of thymomas in patients with MG; predominantly spindle cell thymomas are rare in this group, and the surrounding thymic tissue reveals the presence of lymphoid follicles with germinal centers in about 50% of the cases (versus only 5 to 8% in thymomas without MG).[1] MG is an autoimmune disorder characterized by the presence of antibodies to the acetylcholine receptors of the neuromuscular junction. Such serum antibodies are found in 90% of patients with generalized MG.[23] The triggering mechanisms are unknown. Myoid cells in the normal thymus raise the possibility of in situ sensitization.[26] Serum striational antibodies directed against elements of the sarcomere, such as titin, have also been detected in 80% of patients with MG and thymoma and in 25% of patients with thymoma but without MG.[23] Total thymectomy rather than thymomectomy is indicated in patients with MG, even in the absence of a thymoma (see Surgery below).

Red Cell Hypoplasia Also called pure red cell aplasia (PRCA), red cell hypoplasia is an autoimmune disorder characterized by an acquired anemia with markedly decreased blood reticulocytes and a virtual absence of erythroblasts in the bone marrow.[1,27] There are often changes (increase or decrease) also in white blood cell and/or platelet counts. PRCA is seen in about 5% of patients with thymoma, but 50% of patients with PRCA have a thymoma, which is of the spindle-cell type in two-thirds.[1] PRCA generally occurs in patients older than 40 years who have thymoma, and the incidence of local invasion is not different from other thymomas. The bone marrow is usually quite cellular, and erythropoietin levels are typically high.[27] An immunoglobulin G (IgG) inhibitor of erythroblastic growth has been described in the serum of some patients.[27] Thymectomy produces remission of the anemia in about 30% of cases.[27] Corticosteroids and immunosuppressive agents are also effective. Recently, a prolonged complete remission (with tumor regression) has been described in one case with the combination of octreotide and prednisone.[28]

Hypogammaglobulinemia First reported by Good in 1954,[29] this acquired syndrome results in extreme susceptibility to recurrent, and often serious, infections.[30] It occurs in about 5 to 10% of patients with thymoma, and a thymoma is found in 10% of patients with acquired hypogammaglobulinemia.[1,5] There is a decrease in all major immunoglobulins, particularly IgG and IgA, and decreased eosinophils in the blood and bone marrow. A combined deficit in cell-mediated immunity can also be seen. Almost a third of patients have PRCA, too. Like those with PRCA, the age group is somewhat older (> 40 years), and the thymoma is of the spindle-cell type in 75% of cases.[1] The pathogenesis is obscure. There is a lack of pre–B cells, B cells, and plasma cells in the bone marrow, with decreased peripheral B cells.[30] Thymectomy does not result in any improvement; palliative treatment with immunoglobulins is indicated.[30]

A large number of other paraneoplastic syndromes or associated disorders have been described in patients with thymoma (see Table 90.2). It is noteworthy that Cushing's syndrome with ectopic adrenocorticotropin (ACTH) production is a typical feature of thymic carcinoids, not thymomas.[1,31]

DIAGNOSIS

The diagnosis of an anterior mediastinal mass is guided by the clinical suspicion of its etiology. Invasive incisional biopsy techniques, with mediastinoscopy or mediastinotomy for thymoma, carry the risk of violating the tumor capsule and disseminating tumor cells.[32] If typical paraneoplastic syndromes, such as myasthenia gravis, are present, surgical approach with resection of the tumor en bloc, frozen sections, and definitive surgery (total thymectomy) is justified, whenever technically possible. Otherwise, percutaneous fine-needle aspiration or core biopsy under fluoroscopic or CT guidance is generally considered safe and effective. Combined with special stains and electron microscopy, if necessary, it has a sensitivity of 80% and specificity of greater than 90%.[5] It is of prime importance, however, to establish a firm pathologic diagnosis, in view of the many other tumor types which may require specific therapies, as discussed below.

DIFFERENTIAL DIAGNOSIS

Extrathymic Tumors Although thymic neoplasms are by far the most common tumors of the anterosuperior mediastinum, other mass lesions in that location include thyroid or parathyroid tumors, nonthymic lymphomas, aneurysms, myxomas, lipomas, paragangliomas, and bronchogenic cysts.[1,5] Hemangiopericytoma and giant lymph node hyperplasia (Castleman's disease) can resemble thymoma.[1]

Other Thymic Tumors The major differential diagnostic step is to assess the exact nature of a thymic tumor (see Table 90.1).

Thymic Carcinoma. Thymic carcinoma is differentiated from thymoma by the fact that the epithelial cells appear cytologically malignant.[9,11,33] These are rare tumors; only 16 cases were seen at the Mayo Clinic in 75 years.[11] Several subtypes have been identified. Lymphoepithelioma-like carcinoma bears a strong histologic resemblance to nasopharyngeal carcinoma associated with EBV.[9,33] Indeed, we reported in 1985 the first case of such a thymic carcinoma associated with EBV.[34] That 19-year-old male patient had a serologic profile similar to that of patients with EBV-associated pharyngeal carcinoma, with elevated antibody titers to the viral capsid antigen (VCA) (IgG and IgA anti-VCA), to the diffuse components of the early antigen (IgG anti-D), and to EBV nuclear antigen (EBNA). Moreover, an average of 49 EBV genomes per tumor cell was detected by hybridization techniques. Another such case was reported in 1988 in a 30-year-old woman.[35] The embryologic origin of the thymus from the primitive pharynx further reinforces a possible unified theory about the pathogenesis of lymphoepithelioma-like carcinomas of the pharynx and the thymus.[34] Since then, other investigators have demonstrated the presence of EBV genomes in cases of lymphoepithelioma-like thymic carcinoma, but the role of EBV in other thymic tumors (thymomas and other types of thymic carcinomas) is not established.[36–38]

Other types of thymic carcinomas include keratinizing squamous carcinoma, basaloid squamous carcinoma, clear cell carcinoma, sarcomatoid carcinoma, and mucoepidermoid carcinoma.[11] A unique, and apparently distinctive, chromosome abnormality involving translocation of fragments of chromosome 15 and 19 has been reported in thymic carcinoma.[39] Primary, small cell (oat-cell) carcinoma of the thymus has also been described, and it is histologically similar to the lung variety, which should be excluded as a possible primary neoplasm with thymic metastasis.[31]

The overall 5-year survival of 60 cases of thymic carcinoma was 33.3%.[40] Patients with low-grade histology did much better than those with high-grade histology.

Lymphomas. Lymphomas are, with thymomas, the most common tumors of the thymus. Hodgkin's disease is, as a rule, of the nodular sclerosis type, and it was formerly considered to be a granulomatous thymoma.[4,31] It is frequently confined to the thymus. Although any lymphoma, including Burkitt's lymphoma, may arise in the thymus, the lymphoblastic type in children typically involves the mediastinum in a third of cases and is of T-cell origin.[41] More recently, the occurrence of B-cell lymphomas of the mediastinum with sclerosis and an aggressive course, mainly in young adults, has been emphasized.[41] It is of prime importance to differentiate a lymphoma from a thymoma, in view of the different therapeutic approaches. Special stains and electron microscopy may be necessary in difficult cases.

Germ Cell Tumors. The thymus is a classic site of extragonadal primary germ cell tumors. This may be explained by the proximity of the urogenital ridge to the primitive pharynx in the embryo.[1,4,31] The most common ones are seminomas (sometimes difficult to differentiate from thymoma), and teratomas (mature or immature). Almost every type of germ cell tumor, however, has been reported in the thymus, either in a pure or mixed form, including embryonal carcinomas, yolk sac tumors, teratocarcinomas, and choriocarcinomas. Most of these tumors occur in men in their 20s or 30s, although mature teratomas occur with equal frequency in males and females.[31] Testicular examination (by palpation and sonography) fails to reveal a tumor, confirming an extragonadal origin.[4,5] It is of prime importance to recognize germ cell tumors of the thymus and to distinguish them from thymomas because of the therapeutic implications. A liberal practice of obtaining serum markers, including alpha-fetoprotein (AFP) and beta-human chorionic gonadotrophin (β-hCG) may help identify a germ cell tumor in patients otherwise diagnosed as having undifferentiated carcinoma of the mediastinum.[42,43] Tissue staining for such markers should also be performed and can be positive even when serum levels are normal. Germ cell tumors are highly responsive to radiotherapy (seminomas) or chemotherapy, although the overall results and long-term survival are usually inferior to those of corresponding testicular primaries.[31]

Thymic Carcinoid Tumors. Thymic carcinoids were distinguished from thymomas in 1972.[1,31] They are often aggressive tumors, and extrathoracic metastases are present in 30 to 40% of cases at diagnosis.[31] Cushing's syndrome with ectopic ACTH production in a patient with a thymic tumor should raise this possibility, since it occurs in 30% of patients with thymic carcinoid but not in patients with thymoma.[1,31] Other paraneoplastic syndromes, such as osteoarthropathy and Eaton-Lambert syndrome, and an association with multiple endocrine neoplasia (type I or type II) have been described.[31] Carcinoid syndrome has not been reported. The microscopic appearance reveals complex organoid patterns, with typical areas of necrosis and calcifications. Special stains show positive argyrophil and negative argentaffin reactions characteristic of foregut neuroendocrine tumors.[31] They may also stain positively for neuron-specific enolase and chromogranin. Characteristic dense neurosecretory-type granules are seen by electron microscopy.

Other thymic tumors include thymolipomas, which may become quite large, thymic cysts, and metastases to the thymus.

STAGING

Although there is no standardized staging system for thymoma, the one proposed by Masaoka and colleagues is commonly employed (Table 90.3).[13] Most metastases are intrathoracic (pleura, pericardium) and may represent direct implants from the primary. Extrathoracic and embolic metastases were so rare that only 12 cases were collected from the literature in 1971.[44] In more recent series, however, extrathoracic metastases to the bone, liver, lymph nodes, and other organs have been seen in up to 30 to 45% of some series, probably as a result of referral selection,[44] longer survival, or better imaging techniques.

Table 90.3. Staging of Thymomas

Stage	Extent of Disease	No. Cases 5 Years	No. Cases 10 Years	Survival
I	Totally encapsulated	37	96%	67%
II	Microscopic or macroscopic capsular invasion into surrounding fat or mediastinal pleura	13	86%	60%
III	Invasion of surrounding organs (pericardium, lung, great vessels)	32	70%	58%
IV	(a) pleural or pericardial implants (b) embolic metastasis	11	50%	0%

Adapted from Masaoka et al.[13]

THERAPY

Surgery Since there are no reliable histologic criteria for the malignant nature of thymomas, all such tumors should be considered potentially malignant. Total thymectomy (rather than thymomectomy) is the procedure of choice, even for stage I encapsulated tumors.[4,5] It is also the procedure indicated for patients with MG, with or without thymoma. The usual approach is by median sternotomy, although additional thoracic or cervical incisions may be necessary, and some surgeons advocate maximal thymectomy with exploration of all the possible areas where ectopic thymic tissue might be found.[8] There is a need for the surgeon to carefully explore the mediastinum for evidence of local invasion, which is the most reliable indication of malignancy and the most important prognostic factor. The tumor capsule should not be breached. Systematic microscopic examination is necessary to search for capsular invasion and to distinguish it from simple adhesions. Following total thymectomy, the recurrence rate is usually low (about 2%) for stage I encapsulated thymomas.[1] Recently, video-thoracoscopic approaches have been performed for well-encapsulated small thymomas,[45] but the long-term results are unknown.

In patients with thymoma and MG, remission of MG occurs in about 10 to 30% following thymectomy, often after a delay of up to 2 years or more, as compared with a remission rate of about 40 to 80% after thymectomy for MG without a thymoma.[1,4,5,46,47] An additional fraction of patients show improvement of MG. Early thymectomy (within 1 year) after onset of MG is associated with a higher percentage of less invasive thymomas.[48] Recurrence, and even first occurrence, of MG after apparent total thymectomy has been observed and could be related to tumor regrowth or persistent ectopic thymic tissue.[5] In the past, MG was a poor prognostic sign in patients with thymoma. Most recent surgical series, however, do not show a significant difference in survival for patients with thymoma, with or without MG.[3,4,13,14,49] Such a change is attributed to better surgical and anesthesia techniques, which have largely prevented postoperative deaths from MG.

Local invasion is seen in about 30 to 40% of thymomas at surgery,[3,13,14,49] but the slow-growing nature of the tumor and the rarity of distant metastases justify attempts at radical surgery. Identification of the phrenic, recurrent laryngeal and vagus nerves is of major importance.[8] Extended resections—including one lung, one phrenic nerve, pericardium, or even resection and repair of great vessels, such as the innominate vein or superior vena cava—have been performed. They should be undertaken only if they lead to complete tumor resection. Radiotherapy is indicated in cases of invasive thymoma (see below). With modern techniques of peri- and postsurgical care, surgical mortality is low (0 to 5%), even in patients with myasthenia gravis.[13,46,49]

In four large series with a total of 744 patients,[3,13,14,49] the 5- and 10-year survival rates were 75 to 85% and 63 to 80%, respectively, for patients with noninvasive thymomas. Survival figures for patients with invasive thymomas were 50 to 67% at 5 years and 30 to 53% at 10 years. Whereas invasiveness is the major prognostic factor in patients with thymoma, most series also report a better prognosis for spindle-cell thymomas and those with a higher lymphocyte–epithelial cell ratio.[13,14,49] Local recurrences and/or metastases (often intrathoracic) may also be amenable to surgical resection.

Radiotherapy Thymomas are radiosensitive, and the efficacy of radiotherapy (RT) has been emphasized in many reports. Following surgical biopsy, or partial excision, survival of more than 10 years after RT has been seen.[44] The argument that it is the lymphocytic component rather than the epithelial one which is sensitive to RT is not shared by most authors.[44]

The role of RT is best discussed according to stage. For stage I disease following total surgical resection, postoperative RT is not indicated in view of the very low relapse rates. For stage II and III disease, the use of postoperative RT is recommended even after total surgical resection.[4,5,13,14,50] In a review of the literature, as well as their own experience, Curran and colleagues reported a 28% intrathoracic relapse rate after complete surgical resection without RT, as opposed to 5% when postoperative RT was given.[51] The latter figure may be an underestimation, however, since others have reported no such differences in favor of RT after complete surgical resection.[6] The irradiated volume should include the mediastinum with adjacent areas and probably the supraclavicular areas, which are possible sites of relapse.[44] The total dose is usually about 45 Gy, with appropriate protection of the spinal cord, although doses of 50 Gy and higher have been used.[44,51] Radiation pneumonitis, mediastinitis, pericarditis, coronary artery fibrosis, and hypothyroidism are potential complications.

RT is also given to patients with residual disease, following biopsy only or incomplete surgical resection for stage III disease. In 20 such cases, Curran and colleagues observed four mediastinal recurrences and five others outside the mediastinum, whereas no local relapse was seen when radiotherapy was given after total surgical resection for stage II or III.[51] Tumor debulking by surgery prior to RT in patients with stage III or IV disease does not appear beneficial.[52] The 5-year survival for such patients was 45% overall, including 61% for stage III and 23% for stage IV after RT. Collaboration between the surgeon and the radiotherapist is essential to delineate areas of tumor involvement by radiopaque clips and to plan the treatment. Figure 90.2 shows a proposed algorithm for the management of thymoma, according to stage.

Chemotherapy Thymomas are also relatively chemosensitive. As experience with chemotherapy is increasing, good response rates and sometimes dramatic tumor regressions have been observed.[53]

Single Agents. The rarity of thymomas precludes knowledge of the efficacy of many agents.[44,54] The two most commonly used and most active single agents are cisplatin and corticosteroid therapy (Table 90.4). In the literature, of 28 patients treated with cisplatin at various doses (up to 130 mg/m^2), there were 3 complete and 6 partial responses, for a response rate of 32%. A rather low dose of cisplatin (50 mg/m^2 every 3 weeks) was used in 21 of these patients as part of an Eastern Cooperative Oncology Group trial.[55] Only two partial responses were seen, raising the possibility of a dose–response relationship. The occurrence of complete responses and the long duration of some responses (over 20 months) further indicate that cisplatin is an effective agent.

Corticosteroid therapy, either as ACTH or glucocorticoids, has been known to be effective in inducing tumor regression in patients with invasive or metastatic thymoma. The thymolytic effects of these

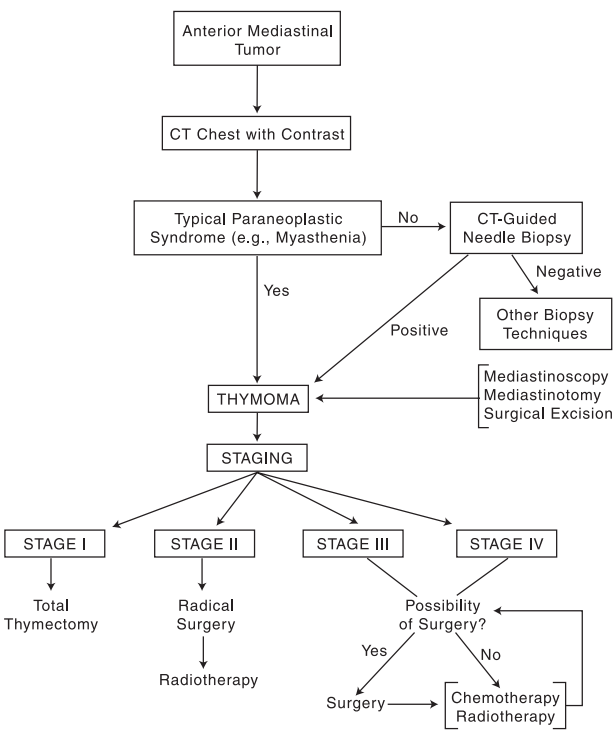

Figure 90.2. Algorithm for the work-up and management of thymoma.

Table 90.4. Single Agents in Thymoma

Agent	Patients (no.)	CR	PR	Resp dur (mo)	Surv (mo)	Ref. no.
Cisplatin	—	1	—	1	13	64
	1	1	—	10+	—	65
	1	—	1	4	13	66
	1	—	1	1	—	67
	1	1	—	20+	—	68
	1	1*	—	24	24+	69
	1	—	1	1	—	70
	21	0	2	—	—	56
Total	28	3	6			
Steroids†	12	2	8	—	—	71
	1	—	1	23	—	59
Ifosfamide	13	5	1	66+	—	60
Maytansine	4	0	2	1.5, 4.5	—	44
Doxorubicin	3	0	2	—	—	71
Vincristine	2	0	0	—	—	71
Chlorambucil	2	0	0	—	71	—
Nitrogen Mustard	1	0	0	—	—	71

CR = complete response; PR = partial response; resp dur = duration of response; surv = survival; RT, radiotherapy.

* with RT.

† ACTH or corticosteroids.

drugs, especially for cortical lymphocytes, has been reported even in relatively corticosteroid-resistant species, such as human.[44] The relative role of this lympholytic effect versus a direct oncolytic effect on the neoplastic epithelial cells of thymomas remains to be determined. It is of note, however, that glucocorticoid receptors have been found in the cytosol of human thymoma cells,[56] including those with pure epithelial histology,[57] suggesting a possible direct antineoplastic effect. In 13 reported patients, there have been 2 complete and 9 partial responses or improvement from steroid therapy (see Table 90.4). Some of these responses were long-lived (23–36 months) or could be re-induced by resumption of higher daily doses after relapse.[58]

The efficacy of other single agents is largely anecdotal. Ifosfamide with mesna produced a high response rate, which deserves confirmation. Ifosfamide at a dose of 1.5 g/m^2 daily for 5 days every 3 weeks with mesna has now been evaluated in 13 patients, with 5 complete responses (38%) with a median duration of response of 66+ months, and 1 partial one.[59] Doxorubicin has produced regressions of short duration in 2 of 3 patients.

Combination Chemotherapy. Various regimens of combination chemotherapy have been reported in small numbers of patients.[44,54] The overall cumulative response rate for cisplatin-containing regimens is 72%, with 26% complete responses (Table 90.5), not much different from regimens without cisplatin (65% response with 35% complete responses) (Table 90.6). In the absence of prospective randomized trials, there is no basis to recommend one regimen over another.

These results are highly encouraging, since many patients experienced prolonged responses. Patients with thymoma and severe MG that is resistant to conventional medical therapy can sometimes benefit dramatically from chemotherapy for the relief of myasthenia symptoms. Some patients requiring ventilatory support have been weaned from the respirator just a few days after receiving chemotherapy.[60] Thymic carcinomas also can respond to cisplatin combinations, such as BAPP[34] or a cisplatin-bleomycin-etoposide combination.[61]

An algorithm applicable to the management of the vast majority of patients with thymoma is shown in Figure 90.2. The effectiveness of chemotherapy in thymoma may lead to preoperative use in patients with large or extensively invasive thymomas.[44] The management of such patients requires a combined-modality approach with chemotherapy, surgery, and radiotherapy in the most appropriate sequence, according to the individual case. In patients with unresectable thymoma, treatment

Table 90.5. Combination Chemotherapy with Cisplatin in Thymoma

Regimen	Patients (no.)	Response: Type	Response: Duration (mo)	Ref. no.
BAPP	9*	1CR, 5PR*	6 - 37+	44, 72
CAP	1	1CR	12+	73
	29	3CR		
		12PR	med.11.8	74
	23	5CR		
		11PR		75
CAP ± prednisone	6*	2CR		
		3PR	4 - 49+	76
	13	3CR		
		8PR		77
AP	1	1PR	6	66
	1	1PR	3	78
	2	2CR	4+, 12+	79
EP	16	5CR		
		4PR	med.41	70
PVB	5	2CR	48+, 72+	80
		2PR	3,9	
ADOC	32	15CR		
		14PR	med. 11	81
VIP	14	6PR		82
Total	152	39CR or 26%		
		70PR or 46%		

BAPP = bleomycin, doxorubicin, cisplatin, prednisone; CAP = cyclophosphamide, doxorubicin, cisplatin; AP = doxorubicin, cisplatin; EP = etoposide, cisplatin; PVB = cisplatin, vinblastine, bleomycin; ADOC = doxorubicin, cisplatin, vincristine, cyclophosphamide; VIP = etoposide, ifosfamide, cisplatin; CR = complete response; PR = partial response.

*Includes one patient with thymic carcinoma.

Table 90.6. Combination Chemotherapy without Cisplatin in Thymoma

Regimen	Patients (no.)	Response: Type	Response: Duration (mo)	Ref. no.
MVPV	2	2PR	0.8, 3	83
ACVB	1	1PR	2	83
COPP	5	4PR*		84
DC	1	1CR	13	85
VCC ± prednisone	9	4CR	31–62	86
		1PR	2	
CAV	4†°	1CR	12+	60
		3PR	4–9	
CHOP	1	1CR	12	87
CHOP ± bleomycin	13	5CR		88
COP ± procarbazine	6	3CR		88
		1PR		
PCb	1	1PR		89
Total	43	15CR or 35%		
		13PR or 30%		

MVPV = nitrogen mustard, vincristine, procarbazine, vinblastine; ACVB = doxorubicin; CCNU = vincristine, bleomycin; COPP = cyclophosphamide, vincristine, prednisone, procarbazine; DC = doxorubicin, cyclophosphamide; VCC = vincristine, cyclophosphamide, CCNU; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CAV = cyclophosphamide, doxorubicin, vincristine; COP = cyclophosphamide, vincristine, prednisone; PCb = paclitaxel and carboplatin; CR = complete response; PR = partial response.

*Two patients in CR for 33 and 34 months after radiotherapy added.

† A fifth patient without measurable tumor had complete remission of myasthenia gravis following chemotherapy.

with radiotherapy, chemotherapy or both can induce tumor regression and allow surgical resection of residual disease, if any. Using this approach, complete tumor eradication was achieved in 5 of 8 patients in one study,[62] and in 11 of 16 patients in another.[63] Thus, the treatment was successful in two-thirds of the patients. Excellent long-term results are within reach, and it seems justified to add invasive thymoma to the list of neoplasms that are curable even at an advanced stage.

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