CHAPTER **32**

Neoplasms of the Mediastinum

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Tumors involving the mediastinum may be primary or secondary in nature. Primary neoplasms can originate from any mediastinal organ or tissue but most commonly arise from thymic, neurogenic, lymphatic, germinal, and mesenchymal tissues. All primary mediastinal neoplasms, except those of thymic origin, also occur elsewhere in the body and are discussed in other chapters. Secondary (metastatic) mediastinal tumors are more common than primary neoplasms and most frequently represent lymphatic involvement from primary tumors of the lung or infradiaphragmatic organs, such as pancreatic, gastroesophageal, and testicular cancer. This chapter provides an overview of primary mediastinal neoplasms. Specific tumors are covered in detail, including thymic, primary mediastinal germ cell, mesenchymal, cardiac, and neurogenic tumors. Esophageal cancer and lymphomas are covered elsewhere, in Chapter 33.2 (Cancer of the Esophagus) and Chapter 45 (Lymphomas), respectively.

Anatomy

The mediastinum occupies the central portion of the thoracic cavity. It is bounded by the pleural cavities laterally, by the thoracic inlet superiorly, by the diaphragm inferiorly, by the sternum anteriorly, and by the chest wall posteriorly. The mediastinum can be divided into three clinically relevant compartments: anterior, middle, and posterior (Fig. 32-1*A*).[1] The anterior mediastinum lies posterior to the sternum and anterior to the pericardium and great vessels, extending from the thoracic inlet to the diaphragm. The

middle mediastinum is defined as the space occupied by the heart, pericardium, proximal great vessels, and central airways. The posterior mediastinum is bounded by the heart and great vessels anteriorly, the thoracic inlet superiorly, the diaphragm inferiorly, and the chest wall of the back posteriorly, and it includes the paravertebral gutters. Table 32-1 lists the major anatomic structures within each of the compartments. A thorough understanding of each area's contents helps define the diagnostic possibilities. Other divisions have been proposed, dividing the mediastinum into three or four compartments (Fig. 32-1*B*,*C*). Heitzman even proposed seven anatomic regions.[1] Although the exact scheme that should be used is still debated, these other schemes have limited clinical utility.

Incidence and Pathology

Mediastinal neoplasms are uncommon tumors that can occur at any age but are most common in the third through the fifth decades of life.[2–4] Table 32-2 reviews the classification of mediastinal neoplasms. The incidence of primary mediastinal tumors was documented in a review of 1900 patients (Table 32-3).[2] Additionally, 439 patients (18% of all mediastinal masses) were found to have cystic lesions. The distribution of primary mediastinal neoplasms is shown in Table 32-4. Thymic neoplasms predominate in the anterior mediastinum, followed in frequency by lymphomas, germ cell tumors, and carcinoma. Bronchial, enteric, and pericardial cysts are the most common masses in the middle mediastinum, followed by lymphomas, mesenchymal tumors, and carcinoma.[5] In the posterior mediastinum, neurogenic tumors and esophageal cancers are most common, followed by enteric cysts, mesenchymal tumors, and endocrine neoplasms.[2–4]

The incidence of mediastinal tumors in each anatomic compartment also varies with age. In adults, 54% of mediastinal neoplasms occur in the anterior, 20% in the middle, and 26% in the posterior mediastinum.[2] In pediatric populations, 43%, 18%, and 40% of neoplasms occur in the anterior, middle,

and posterior mediastinum, respectively.[4,6] A higher incidence of thymic tumors and lymphomas in adults and neurogenic tumors in children account for these differences. Azarow[4] compared mediastinal masses in 195 adult and 62 pediatric patients (Table 32-5). Cysts were not included but accounted for 16% to 18% of adult and 24% of pediatric mediastinal masses.[4] Therefore, age as well as location establishes the probable diagnosis.[2–4,6–9]

Diagnostic Considerations

A meticulous history and physical examination, along with a variety of imaging, serologic, and invasive tests (Table 32-6), often can confirm the suspected diagnosis. With improved imaging, biopsy, and pathologic techniques, the majority of patients no longer require open surgical biopsy before planning definitive therapy.

Symptoms and Signs

Approximately 40% of mediastinal masses are asymptomatic and discovered incidentally on a routine chest radiograph.[2,3] The remaining 60% of cases have symptoms related to compression or direct invasion of surrounding mediastinal structures or to paraneoplastic syndromes. Asymptomatic patients are more likely to have benign lesions, whereas symptomatic patients more often harbor malignancies.[2–4,7,8] Davis found that 85% of patients with a malignancy were symptomatic, but only 46% of patients with benign neoplasms had identifiable complaints. Symptoms and signs of mediastinal neoplasms are shown in Table 32-7. The most commonly described symptoms are chest pain, cough, and dyspnea.[2,3,8] Superior vena cava syndrome, Horner's syndrome, hoarseness, and neurologic deficits more commonly occur with malignancies.[10] Systemic syndromes associated with mediastinal neoplasms are shown in Tables 32-8 and 32-9.

Radiographic Imaging Studies

Radiographic imaging studies initially localize mediastinal neoplasms. The posteroanterior and lateral chest radiographs define the location, size, density, and calcification of a mass, limiting the diagnostic possibilities.[11] After these results, an intravenous contrast-enhanced computed tomography (CT) scan can further assess the nature (cystic vs. solid) of the lesion and detect fat and calcium.[12–17] The relationship to surrounding structures and blood vessels also can be determined, and in some instances the invasiveness of tumors can be predicted.[18]~~.~~

Magnetic resonance imaging (MRI) is used less frequently than CT.[19~~8~~–21~~0~~] Its advantages include multiplanar imaging and absence of ionizing radiation.[12] MRI scans are superior to CT in defining vascular involvement and in distinguishing recurrent tumor from radiation fibrosis.[20,22] However, patient claustrophobia, time, and expense limit the use of MRI scanning. Other imaging modalities that may be useful include transthoracic sonography,~~ and~~ transesophageal echocardiography, and transesophageal ultrasouns.[2~~1~~3,~~22~~-25]

Although t~~T~~he use ~~utility~~ of positron emission tomography is well established for the assessment of mediastinal lymph nodes in lung cancer and lymphoma, the utility of PET in the evaluation of primary mediastinal neoplasms~~masses~~ has not ~~fully~~ been fully defined~~ is yet to be determined~~. ~~, but it~~ There is some evidence that PET may help clarify the nature of such masses and the presence of neoplasm in residual mediastinal tissue after therapy.[~~23~~26]

Serology and Chemistry

Some mediastinal neoplasms release substances into the serum that can be measured by specific radioimmunoassays. These substances may be used to confirm a diagnosis, evaluate response to therapy, and monitor for tumor recurrence. ? -Fetoprotein (AFP), human chorionic gonadotropin-? (? -

HCG), and lactate dehydrogenase are elaborated by some germ cell tumors and should be obtained in male patients with anterior mediastinal masses.[1] Also, adrenocorticotropic hormone, thyroid hormone, and parathormone may help differentiate certain mediastinal tumors (see Table 32-9).

Invasive Diagnostic Tests

The determination of the histologic diagnosis of mediastinal masses often is essential for implementation of appropriate treatment. Previously, most patients underwent surgical procedures to establish the diagnosis of mediastinal neoplasms; however, improvements in less invasive diagnostic and immunohistochemical techniques and in electron microscopy have greatly improved the ability to differentiate the cell types in mediastinal neoplasms.[24–31] CT-guided percutaneous needle biopsy, using either fine-needle aspiration techniques and cytologic assessment or larger-core needle biopsy and histologic evaluation, now are standard in the initial evaluation of most mediastinal masses.[32–35] Although fine-needle specimens are usually adequate to distinguish carcinomatous lesions, core biopsies are recommended to distinguish most other mediastinal neoplasms, especially lymphoma and thymoma.[26–28] Most series report diagnostic yields for percutaneous needle biopsy of 72% to 100%, and, most recently, that figure is in excess of 90%.[25–27,29–32] Complications include simple pneumothorax (25%), pneumothorax requiring chest tube placement (5%), and hemoptysis (7% to 15%).[29,32] In some circumstances, fine needle aspiration of posterior and middle mediastinal tumors can be performed endoscopically using transesophageal ultrasonography.[25]

Surgical procedures are still occasionally required in the diagnosis of mediastinal tumors.[24,27,30] Mediastinoscopy is a relatively simple procedure, accomplished under general anesthesia. It provides access to the middle and a limited portion of the upper posterior mediastinum and has a diagnostic accuracy of more than 90%.[33,36,37] Anterior parasternal mediastinotomy (Chamberlain procedure) yields

a diagnosis in 95% of anterior mediastinal masses.[36,37] and, if necessary, can be accomplished under local anesthesia.[38] Thoracoscopy requires general anesthesia but is minimally invasive and provides a diagnostic accuracy of nearly 100% in most areas of the mediastinum.[37] Thoracoscopy should be reserved, however, for biopsies that cannot be obtained with mediastinoscopy or parasternal mediastinotomy. Thoracotomy is almost never necessary for diagnosis and should be reserved for rare circumstances.

Thymic Neoplasms

The thymus is an incompletely understood lymphatic organ functioning in T-lymphocyte maturation. It is composed of an epithelial stroma and lymphocytes. Although lymphomas, carcinoid tumors, and germ cell tumors all may arise within the thymus, only thymomas, thymic carcinomas, and thymolipomas arise from true thymic elements. Epithelial thymic neoplasms have been classified into three proposed categories: (1) thymomas, well-differentiated neoplasms; (2) atypical thymomas, moderately differentiated neoplasms; and (3) thymic carcinomas, poorly differentiated neoplasms. This classification is based on features of glandular differentiation; however, further validation of this system is needed.[39–41]

Thymic Anatomy and Physiology

The thymus develops from a paired epithelial anlage in the ventral portion of the third pharyngeal pouch. It is closely associated with the developing parathyroid glands.[42] The stroma of the thymus consists of epithelial cells, which are likely derived from both ectodermal and endodermal components.[43] During weeks 7 and 8 of development, the thymus elongates and descends caudally and ventromedially into the anterior mediastinum. By week 12, a separate cortex and medulla become evident, and mesenchymal septae develop perivascular spaces that contain blood vessels. Lymphoid cells arrive from the liver and

bone marrow during week 9 and are separated from the perivascular space by a flat layer of epithelial cells that create the blood–thymus barrier. Maturation and differentiation occurs in this antigen-free environment. By the fourth fetal month, lymphocytes circulate to peripheral lymphoid tissue.[39 43]

Six subtypes of epithelial cells have been identified in mature thymus.[3 43 9] Four exist primarily in the cortical region and two in the medullary region. Type 6 cells form Hassall's corpuscles that are characteristic of thymus. These cells have an ectodermal origin and are displaced into the thymic medulla, where they hypertrophy and form tonofilaments, finally appearing as concentric cells without nuclei.[3 42,43 8,39]

At maturity, the thymus gland is an irregular, lobulated organ. It attains its greatest relative weight at birth, but its absolute weight increases to 30 to 40 g by puberty. During adulthood, it slowly involutes and is replaced by adipose tissue.[3 43 9] Ectopic thymic tissue has been found to be widely distributed throughout the mediastinum and neck, particularly the aortopulmonary window and retrocarinal area, and often is indistinguishable from mediastinal fat.[40 4,41 5] This ectopic tissue is the likely explanation for thymomas outside the anterior mediastinum and possibly for failure of thymectomy in some cases to improve myasthenia gravis.[40 4–42 6]

Thymoma

Thymic neoplasms, mostly thymomas, constitute 30% of anterior mediastinal masses in adults.[2–4,8,43 7,44 8] Thymomas are less common in children, accounting for only 15% of anterior mediastinal masses.[8] Thymomas exhibit no gender predilection and occur most often in the fifth and sixth decades of life.[45 9] Nearly one-half of these tumors are asymptomatic and are discovered only on routine radiographs. In symptomatic patients, 40% have myasthenia gravis[35 9] (diplopia, ptosis, dysphagia, fatigue, etc.),

whereas others complain of chest pain and symptoms of hemorrhage or compression of mediastinal structures.[~~45~~9]

Pathology and Classification

Ninety percent of thymomas occur in the anterior mediastinum, and the remainder are located in the neck or other areas of the mediastinum. Grossly, they are lobulated, firm, tan-pink to gray tumors that may contain cystic spaces, calcification, or hemorrhage. They may be encapsulated, adherent to surrounding structures, or frankly invasive.[50~~46~~] Microscopically, thymomas arise from thymic epithelial cells, although lymphocytes may predominate histologically.[~~4~~51~~7~~] True thymomas contain cytologically bland cells and should be distinguished from thymic carcinomas, which have malignant cytologic characteristics. Confusion exists because of previous "benign" or "malignant" designations. Currently, the terms *noninvasive* and *invasive* are used. Noninvasive thymomas have an intact capsule, are movable, and are easily resected, although they can be adherent to adjacent organs. In contrast, invasive thymomas involve surrounding structures and can be difficult to remove without *en bloc* resection of adjacent structures. Despite this difficulty, their cytologic appearance remains benign.[~~46~~50] Metastatic disease does occur and is most commonly seen as pleural implants and pulmonary nodules. Metastases to extrathoracic sites are rare.[~~4~~50~~6~~]

Originally in 1976 Rosai and Levine proposed that thymomas be divided into three types depending on the predominant architecture of the tumor: lymphocytic, epithelial, or mixed (lymphoepithelial); however, there has been little direct correlation between this classification system and prognosis.[52] In 1985, Marino and Muller-Hermelink[~~48~~53] proposed a histologic classification system determined by the thymic site of origin—that is, tumors arising from epithelial cells of the cortex are termed *cortical thymomas*, those arising from the medullary areas are called *medullary thymomas*,

and those with features of both are termed *mixed thymomas*. Spindle-shaped cells predominate in the medullary area and likely correspond to spindle cell thymomas of the traditional classification system. Likewise, the cortex contains predominantly round to oval epithelial cells; thus, cortical thymomas probably correspond to the traditional epithelial thymoma.[~~49~~54] The Muller-Hermelink classification was later revised and further divided into medullary, mixed, predominantly cortical, and cortical thymomas. Well-differentiated and high-grade thymic carcinoma were also described.[5~~0~~5] Medullary and mixed thymomas were considered benign with no risk of recurrence, even with capsular invasion. Predominantly cortical and cortical thymomas exhibited intermediate invasiveness and a low but definite risk of late relapse, regardless of their invasiveness. Well- differentiated thymic carcinomas were always invasive, with a high risk of relapse and death.[5~~1~~6] Some support this revision, claiming that it better correlates pathology with prognosis.[5~~1~~6–5~~3~~8] Others believe that it has no distinct clinicopathologic advantage over the traditional system.[~~4~~54~~9~~,5~~0~~5,5~~4~~9–~~5~~61] This issue has been re- examined,[~~5~~62,63~~7,58~~] and the World Health Organization Committee on the Classification of Thymic Tumors adopted a new classification system for thymic neoplasms based on cytologic similarities between certain normal thymic epithelial cells and neoplastic cells, which is of prognostic significance (Table 32-10).[~~59~~64]

In 1981, Masaoka et al.[6~~0~~5] developed a staging system based on the previous work of Bergh et al.[6~~1~~6] The four stages are shown in Table 32-11. The Masaoka stage II classification assesses both microscopic invasion (occult in 28%) and gross—tumor adherence as determined by surgical findings.[~~49,~~54,59,67~~2~~] Staging was found to correlate with prognosis, with 5-year survival rates 96% for stage I, 86% for stage II, 69% for stage III, and 50% for stage IV.[6~~0~~5] The Groupe d'Etudes des Tumeurs Thymiques (GETT) staging system is surgery-based and demonstrates 90% concordance with the Masaoka system (Table 32-12).[6~~3~~8,6~~4~~9] Interestingly, the expression of genes c-JUN and AL050002

recently were found using microarray technology and real-time RT-PCR to correlate with Masaoka stage and prognosis; in addition, AL050002 expression was found also to correlate with the WHO tumor classification system.[70]

Associated Systemic Syndromes

A wide variety of systemic disorders are associated with 71% of thymomas.[65][71] The symptoms of these associated disorders often lead to the original discovery of the mediastinal tumor. Autoimmune diseases (systemic lupus erythematosus, polymyositis, myocarditis, Sjögren's syndrome, ulcerative colitis, Hashimoto's thyroiditis, rheumatoid arthritis, sarcoidosis, and scleroderma) and endocrine disorders (hyperthyroidism, hyperparathyroidism, Addison's disease, and panhypopituitarism) are most common.[6][72][6]

Blood disorders, such as red cell aplasia, hypogammaglobulinemia, T-cell deficiency syndrome, erythrocytosis, pancytopenia, megakaryocytopenia, T-cell lymphocytosis, and pernicious anemia, also have been noted.[66][72] Other than myasthenia, neuromuscular syndromes include myotonic dystrophy, myositis, and Eaton-Lambert syndrome.[66][72] Miscellaneous diseases include hypertrophic osteoarthropathy, nephrotic syndrome, minimal change nephropathy, pemphigus, and chronic mucocutaneous candidiasis.[66][72] Nearly 15% of patients with thymoma develop a second malignancy, such as Kaposi's sarcoma, chemodectoma, multiple myeloma, acute leukemia, and various carcinomas (e.g., lung, colon).[66][72]

myasthenia gravis

Myasthenia gravis is the most common autoimmune disorder, occurring in 30% to 50% of patients with thymomas. Younger women and older men usually are affected, with a female to male ratio of 2:1. Myasthenia is a disorder of neuromuscular transmission. Symptoms begin insidiously and result from the

production of antibodies to the postsynaptic nicotinic acetylcholine receptor at the myoneural junction. Ocular symptoms are the most frequent initial complaint, eventually progressing to generalized weakness in 80%. The role of the thymus in myasthenia remains unclear, but autosensitization of T lymphocytes to acetylcholine receptor proteins or an unknown action of thymic hormones remain possibilities.[5~~2~~7,~~6~~73]

Pathologic changes in the thymus are noted in approximately 70% of patients with myasthenia gravis. Lymphoid hyperplasia, characterized by the proliferation of germinal centers in the medullary and cortical areas, is most commonly seen. Thymomas are identified in only about 15% of patients with myasthenia.

The treatment of myasthenia gravis involves the use of anticholinesterase-mimetic agents [i.e., pyridostigmine bromide (Mestinon)]. In severe cases, plasmapheresis may be required to remove high antibody titers. Thymectomy has become an increasingly accepted procedure in the treatment of myasthenia, although the indications, timing, and surgical approach remain controversial.[4~~2~~6] Some improvement in myasthenic symptoms almost always occurs after thymectomy, but complete remission rates vary from 7% to 63%.[4~~2~~6] Patients with myasthenia gravis and thymomas do not respond as well to thymectomy as those without thymomas. Overall survival for myasthenia patients also is lower for patients with thymomas, but no differences were noted based on the extent of invasion present.[~~6~~74~~8~~]

red cell aplasia

Pure red cell aplasia is considered an autoimmune disorder and is found in approximately 5% of patients with thymomas. Of patients with red cell aplasia, 30% to 50% have associated thymomas.[~~6~~75~~9~~] Ninety-six percent of the patients affected are older than 40 years of age. Examination of the bone marrow reveals an absence of erythroid precursors and, in 30%, an associated decrease in platelet and leukocyte numbers. Thymectomy has produced remission in 38% of patients. Octreotide and

prednisone were effective in one patient with recurrent disease.[70,76] The pathologic basis of these responses is poorly understood.[69,75]

hypogammaglobulinemia

Hypogammaglobulinemia is seen in 5% to 10% of patients with thymoma, and 10% of patients with hypogammaglobulinemia have been shown to have thymoma. Defects in both cellular and humoral immunity have been described, and many patients also have red cell hypoplasia. Thymectomy has not proven beneficial in this disorder.

Treatment

Thymomas are slow-growing neoplasms that should be considered potentially malignant. Surgery, radiation, and chemotherapy all may play a role in their management.

surgery

Complete surgical resection is the mainstay of therapy for thymomas and is the most important predictor of long-term survival.[71–77-83] Although median sternotomy with a vertical or submammary incision is most commonly used, bilateral anterolateral thoracotomies with transverse sternotomy, or "clam- shell procedure," is preferred with advanced or laterally displaced tumors.[45,9,71,72,76,82] Video-assisted thoracoscopy also has been reported, but long-term results remain unproven.[78,4] Because of concern about tumor seeding, biopsy procedures are not routinely performed.[72,8] During surgery, a careful assessment of areas of possible invasion and adherence should be made by the surgeon, who is the best judge of tumor invasiveness.[67,72] Extended total thymectomy, including all tissue anterior to the pericardium from the diaphragm to the neck and laterally from phrenic nerve to phrenic nerve, is recommended in all cases. Complete surgical resection is associated with an 82% overall 7-year survival rate, whereas survival with incomplete resection is 71% and with biopsy is only 26%.[71,7]

Survival after complete tumor resection has been similar in patients with noninvasive and invasive thymomas in several studies.[6~~0~~5,7~~2~~8,~~74~~80,~~75~~81,85~~79~~] Patients with myasthenia gravis and thymoma were studied by Crucitti et al.,[8~~4~~6] who reported a 78% 10-year survival rate and a 3% recurrence rate with 4.8% (1.7% since 1980) operative mortality after extended thymectomy. Aggressive resection, including lung, phrenic nerve, pericardium, pleural implants, and pulmonary metastases, is occasionally helpful.[6~~0~~5,7~~1~~7,~~79~~84]

The role of debulking or subtotal resection in stage III and IV disease remains controversial. Several studies have documented 5-year survival rates from 60% to 75% after subtotal resection and 24% to 40% after biopsy alone.[6~~0~~5,7~~1~~7,~~76~~82,83~~77~~,85~~79~~] More recent studies, however, suggest no survival advantage to debulking followed by radiation when compared to radiation alone.[8~~0~~7,8~~1~~8] None of these studies take into account the potential additive role of systemic therapy upon survival. The use of surgery in recurrent disease remains to be defined. Maggi et al.[7~~1~~7] reported a 71% 5-year survival rate in 12 surgery patients and a 41% survival rate in 11 patients treated with radiation and chemotherapy alone. Prolonged tumor-free survival also was reported by Kirschner[8~~2~~9] in 23 patients. Urgesi et al.,[~~83~~90] however, noted a 74% 5-year survival rate in 11 patients undergoing surgery and radiation, compared with 65% in ten patients treated with radiation alone (not statistically different).[~~83~~90]

radiation therapy

Thymomas are radiosensitive tumors and, consequently, radiation has been used to treat all tumor stages as well as recurrent disease.[4~~3~~7,4~~5~~9,7~~1~~7,7~~2~~8,~~74~~80,~~76~~82,~~78~~37,~~78~~59,8~~1~~8,~~89~~15] In stage I thymomas, adjuvant radiotherapy has been administered but has not improved on the excellent results with surgery alone (more than 80% 10-year survival rate).[7~~1~~7,78~~2~~,~~78~~04,~~78~~37,~~78~~59] In stage II and III invasive disease, adjuvant radiation can decrease recurrence rates after complete surgical resection from 28% to

5%.[4~~3~~7,~~7~~82~~6~~,~~8~~92~~6~~,~~8~~93~~7~~] In addition, Pollack et al.[~~7~~82~~6~~] reported an increase in 5-year disease- free survival for stage II to IVa from 18% to 62% with the addition of adjuvant radiation. Others have documented similar results.[7~~2~~8,~~79~~85] Stage II patients with cortical tumors[~~8~~94~~8~~–96~~0~~] and microscopic invasion of pleura or pericardium are most likely to benefit from postoperative radiation.[97~~1~~,9~~2~~8] More recently, investigators have questioned the role of additional radiation following complete resection (negative surgical margins) of Stage II and III disease. In a review of 1320 patients with thymoma and thymic carcinoma, postoperative radiotherapy did not improve the recurrence rates or the overall survival { Kondo K, Monden Y: Therapy for Thymic Epithelial Tumors: A Clinical Study of 1,320 Patients from Japan. Ann Thorac Surg 2003; 76:878-85}. Preoperative radiotherapy for extensive tumors has been reported in limited studies that suggest a decreased tumor burden and potential for tumor seeding at the time of surgery.[7~~1~~7,~~7~~83~~7~~,~~86~~92]

Radiation therapy has proven beneficial in the treatment of extensive disease.[~~7~~82~~6~~,~~7~~83~~7~~,8~~0~~7,8~~1~~8,~~8~~91~~5~~,~~8~~92~~6~~,9~~3~~9] Radiotherapy after incomplete surgical resection produces local control rates of 35% to 74% and 5-year survival rates ranging from 50% to 70% for stage III and 20% to 50% for stage IVa tumors.[7~~2~~8,~~7~~83~~7~~,8~~0~~7,~~8~~90~~3~~,~~8~~91~~5~~,~~8~~92~~6~~] In addition, Ciernik et al.[8~~0~~7] and others[8~~1~~8,~~83~~90] have reported similar survival rates (87% 5-year and 70% 7-year) in patients treated with radiation alone compared with partial surgical resection and adjuvant radiation in small numbers of stage III and IV patients and patients with intrathoracic recurrences. Large variations in the amount of tumor treated and radiation delivered as well as data on systemic therapy, however, make interpretation of these results difficult.[6~~4~~9,~~7~~82~~6~~,~~7~~83~~7~~,~~8~~87~~0~~,~~8~~91~~5~~,~~9~~100~~4~~]

Radiation therapy is delivered in doses ranging from 30 to 60 Gy in 1.8 or 2.0 cGy fractions over 3 to 6 weeks.[4~~3~~7,7~~1~~7,7~~3~~9,~~7~~82~~6~~,~~77~~83,~~7~~85~~9~~,~~85~~91,~~8~~92~~6~~,~~94~~100–~~9~~102~~6~~] No improvement in local control has been

shown with doses exceeding 60 Gy[80,93]; however, completely resected and microscopic residual disease can be well controlled with only 40 to 45 Gy.[77,83,80,93,85,91] Treatment portals have included single anterior field, unequally weighted (2:1 or 3:2) opposed anterior-posterior fields, wedge- pair, and multifield arrangements.[43,47,9,103,7] The gross tumor volume is defined by visible tumor or surgical clips seen on a treatment- planning CT scan. Areas of possible microscopic disease and a small border to account for daily variability and respiratory motion are added to define the clinical and planning target volumes. Gating techniques to minimize respiratory variation and intensity-modulated radiation therapy are new techniques that can minimize the dose heterogeneity, increase total dose and fraction size, and minimize toxicity.[9,104,8–10,06] Prophylactic supraclavicular and hemithorax fields have been used but are not warranted because of increased risks of pulmonary fibrosis, pericarditis, and myelitis.[43,47,77,83,80,93,81,8,101,107,102,108]

chemotherapy

Chemotherapy has been used with increasing frequency in the treatment of invasive thymomas. Both single-agent and combination therapy have demonstrated activity in the adjuvant and neoadjuvant settings. Doxorubicin, cisplatin, ifosfamide, corticosteroids, and cyclophosphamide all have been used as single-agent therapy.[103,109,104-110] The most active agents are cisplatin, ifosfamide, and corticosteroids; however, only cisplatin, and ifosfamide and octreotide have undergone phase II testing.[43,47,104,110,105,11] Cisplatin, at doses of 100 mg/m^2, has produced complete responses lasting up to 30 months, but lower doses (50 mg/m^2) have associated response rates of only 11%.[103,109,104-110] Ifosfamide (with mesna) at a single dose of 7.5 g/m^2 or as a continuous infusion of 1.5 g/m^2/d for 5 days every 3 weeks has resulted in 50% complete and 57% overall response rates. Duration of complete remission ranged from 6 to 66 months.[105,111] Varying regimens of corticosteroids have shown effectiveness in the treatment of all histologic subtypes of thymoma (with and without myasthenia), with a 77% overall response rate in limited numbers of patients.[103,109,106-112] Corticosteroids also have been effective for patients unsuccessful with chemotherapy[109,103]; however, the actual impact may only be on the lymphocytic and not the malignant epithelial component of the tumor. Palmieri et al reported a complete response with octreotide and prednisone in a patient with pure red cell aplasia and chemotherapy resistant thymoma. { Palmieri g, Lastoria S, Colao A et al: Successful treatment of a patient with a thymoma and pure red-cell aplasia with octreotide and Prednisone. NEJM 1997; 336:263-4.} A subsequent ECOG trial evaluated octreotide alone for 2 cycles and if no response added prednisone in patients with octreotide postitive radioisotope scans. Two complete and 10 partial responses were noted in 38 evaluable patients. Only 4 (10.5%) of the patients responded to the octreotide alone. {Loehrer PJ, Wang W, Johnson DH, Ettinger DS:Octreotide

Alone or With Prednisone in Patients with Advanced Thymoma and Thymic Carcinoma: An Eastern Cooperative Oncology Group Phase II Trial J Clin Oncol (Accepted for publication)}

Combination chemotherapy regimens have shown higher response rates and have been used in both adjuvant and neoadjuvant settings in the treatment of advanced invasive, metastatic, and recurrent thymoma. Cisplatin-containing regimens appear to be the most active. Fornasiero et al.[107-113] reported a 43% complete and 91.8% overall response rate with a median survival of 15 months in 37 previously untreated patients with stage III or IV invasive thymoma treated with monthly (median, 5 months) cisplatin, 50 mg/m^2 on day 1; doxorubicin, 40 mg/m^2 on day 1; vincristine, 0.6 mg/m^2 on day 3; and cyclophosphamide, 700 mg/m^2 on day 4. Loehrer et al.[108-114] documented 10% complete and 50% overall response rates with a median survival of 37.7 months in 29 patients with metastatic or locally progressive recurrent thymoma treated with cisplatin, 50 mg/m^2; doxorubicin, 50 mg/m^2; and cyclophosphamide, 500 mg/m^2, given every 3 weeks for a maximum of 8 cycles after radiotherapy. Park et al.[109-115] retrospectively described 35% complete and 64% overall response rates with a median survival of 67 months in responding and 17 months in nonresponding patients in 17 patients with invasive stage II and IV thymoma initially treated after relapse with cyclophosphamide, doxorubicin, and cisplatin, with or without prednisone. The European Organization for Research and Treatment of Cancer noted 31% complete and 56% overall response rates with a median survival of 4.3 years in a small study of 16 patients with advanced thymoma treated with cisplatin and etoposide.[110-116] The addition of ifosfamide to cisplatin and etoposide had a lower than anticipated response rate (approximately nine partial responses in 28(32%) evaluable patients) 32% and a median survival time of 2.5 years) in patients with thymoma and thymic carcinoma.[111117] {Loehrer PJ, Jiroutek M, Green M, Aisner J, Thomas CR, Livingston R, Johnson DH: Combined Etoposide, Ifosfamide, and Cisplatin in the

Treatment of Patients with Advanced Thymoma and Thymic Carcinoma: An Intergroup Trial. Cancer 91:2010-2015, 2001. }

combined nodality approaches

The use of neoadjuvant chemotherapy as part of a multimodality approach to stage III and IV thymoma was reviewed by Tomiak and Evans.[103–109] Six combined reports document 31% complete and 89% overall response rates in 61 total patients treated with a variety of neoadjuvant chemotherapy regimens (80% cisplatin- based). Twenty-two patients (36%) underwent surgery, with 11 (18%) achieving a complete resection (all treated with cisplatin). Nineteen patients were treated with radiotherapy, but only five patients had disease-free survivals exceeding 5 years.[103-109] Rea et al.[112-118] reported 43% complete and 100% overall response rates with median and 3-year survival rates of 66 months and 70%, respectively, in 16 stage III and IVa patients treated initially with cisplatin, doxorubicin, vincristine, and cyclophosphamide, followed by surgery. At surgery, 69% were completely resected and the other 31% received postoperative radiation. Macchiarini et al.[113-119] reported similar findings. Twenty-five percent complete and 92% overall response rates with a remarkable 83% 7-year disease-free survival rate were reported in 12 patients at the M. D. Anderson Cancer Center who received cisplatin, doxorubicin, cyclophosphamide, and prednisone induction chemotherapy followed by surgical resection (80% complete) and adjuvant radiotherapy for locally advanced (unresectable) thymoma.[114-120] The degree of chemotherapy-induced tumor necrosis correlated with Ki-67 expression.

A multiinstitutional prospective trial demonstrated a 22% complete and 70% overall response rate with a median survival of 93 months and a Kaplan-Meier 5-year failure-free survival rate of 54.3% in 23 patients with stage III (22/23) unresectable thymoma (GETT stage IIIA/IIIB) stage IV (1/23) thymoma, and thymic carcinoma (2/23) treated with 2 to 4 cycles of cisplatin, doxorubicin, and

cyclophosphamide chemotherapy and sequential radiation therapy (54 Gy).[115121,116-122] Just more than 25% had myasthenia gravis. Although these results compare favorably to those obtained with neoadjuvant therapy followed by surgical resection and radiation, further confirmation is needed.

Results of Treatment

Five- and 10-year survival rates for stage I, III, and IV tumors are reported to be 89% to 95% and 78% to 90%,[671,7804,117-123] 70% to 80% and 21% to 80%,[6571,7480,117-123] and 50% to 60% and 30% to 40%,[6065,6571,7480,117-123] respectively. Disease-free survival rates of 74%, 71%, 50%, and 29% also have been reported for stage I, II, III, and IV disease, respectively.[7177] Although Maggi et al.[7177] reported a 10% overall recurrence rate in 241 patients, less than 5% of noninvasive thymomas and 20% of invasive thymomas were noted to recur.[65-71] Although myasthenia gravis was once considered an adverse prognostic factor, this is no longer the case because of improvements in perioperative care. Currently, myasthenia actually may lead to improved survival owing to earlier detection of thymomas.[6571, 84,118124,119125]

Thymic Carcinoma

Thymic carcinoma is a rare aggressive thymic neoplasm that has a poor prognosis. Like thymoma, it is an epithelial tumor, but cytologically it exhibits malignant features. Extensive local invasion and distant metastases are common. Approximately 150 cases have been reported.[120126-125-131] Suster and Rosai[120] Rosai[126] reported the largest single series, which included 60 patients ranging in age from 10 to 76 years and with a slight male predominance. Nearly 70% of patients had symptoms of cough, chest pain, or superior vena cava syndrome. Myasthenia and other thymoma-associated syndromes are rare.[120126]

The histologic classification of thymic carcinoma was proposed by Levine and Rosai[126]-Rosai[132] and revised by Suster and Rosai.[120-126] The tumors are classified broadly as low or high grade. Low-

grade tumors include squamous cell carcinoma, mucoepidermoid carcinoma, and basaloid carcinoma. High- grade neoplasms include lymphoepithelioma-like carcinoma and small cell, undifferentiated, sarcomatoid, and clear cell carcinomas.[120,126,122,128,123,129,127–134] The classification of thymic carcinoma has prognostic significance, with low-grade tumors following a favorable clinical course (median survival rates of 25.4 months to more than 6.6 years) because of a low incidence of local recurrence and metastasis, and high-grade malignancies exhibiting an aggressive clinical course (median survival of only 11.3 to 15.0 months).[120,126–122–128] Although the Masaoka thymoma staging system[120] system[126,122,128,124,130] and a proposed tumor-node-metastasis classification system[125]-system[131] have been used in staging thymic carcinoma, their utility is unproven. The histologic grade remains the best prognostic indicator.

The optimal treatment of thymic carcinoma remains undefined, but currently a multimodality approach, including surgical resection, postoperative radiation, and chemotherapy, is recommended. Initial surgical resection followed by radiation has been used in most studies.[4,5,7,111,117,120,126,122,128–125,131] Complete resection should be attempted, but usually is not possible.[122,128,133] One analysis noted a 9.5-month median survival after resection and postoperative electron beam radiation therapy,[111–117] with a trend toward improved survival in other studies.[122,128,123,129,126] Chemotherapy with cisplatin-based regimens similar to those used with thymomas have produced variable responses in small numbers of patients.[120,126,122,128–124–130] Combinations of cisplatin, doxorubicin, cyclophosphamide, and vincristine also have generated partial responses, as has the combination of 5-fluorouracil and leukovorin.[124–130] { Koizumi T, Takabayashi Y, Yamagishi S: Chemotherapy for advanced thymic carcinoma: clinical response to cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC Chemotherapy). Am J Clin Oncol 25:266-68, 2002; Lucchi M, Mussi A, Ambrogi M et al : Thymic Carcinoma: a report of 13 cases. EJSO 27:636-40; 2001; Kitami A, Suzuki T, Kamio Y and Suzuki S: Chemotherapy of

thymic carcinoma: Analysis of seve cases and review of the literature. Jpn J Clin Oncol 31: 601-04, 2001}. Use of neoadjuvant chemotherapy has been reported in a small number of patients but considered appropriate in selected patients with unresectable disease with the intention to down size the tumor for possible complete resection.[124][130]

The prognosis of thymic carcinoma is poor because of early metastatic involvement of pleura; lung; mediastinal, cervical, and axillary lymph nodes; bone; and liver.[120]-[126] The overall survival rate at 5 years is approximately 35%.[120][126,][122]–[128] Improved survival has been correlated with encapsulated tumors, lobular growth pattern, low mitotic activity, early stage tumors, and low histologic grade, and complete surgical resection.[120][126,133]

Thymic Carcinoid

Thymic carcinoid tumors are rare, with fewer than 125 200 reported cases.[128][135] [131]–[138] {Teh BT, Zedenius J, Kytoia S et al: Thymic Carcinoids in Multiple Endocrine Neoplasia Type 1. Ann Surgery 228:99-105, 1998}They occur predominantly in males[129]-males[136] and originate from normal thymic Kulchitsky's cells, which are part of the amine precursor uptake and decarboxylation (APUD) group. Most have the ability to manufacture peptides, amines, kinins, and prostaglandins. They are aggressive tumors that invade locally and commonly metastasize to regional lymph nodes. Metastases occur in 70% of patients within 8 years of initial diagnosis.[131][138]

The gross appearance of thymic carcinoids is similar to that of thymomas, but they are rarely are encapsulated. Microscopically, the tumors exhibit a ribbon-like growth pattern with rosette formation in a fibrovascular stroma. The cells are small, round, or oval with eosinophilic cytoplasm and uniformly round nuclei.[129]-[136] Immunohistochemical studies reveal argyrophilic cells that stain with cytokeratin and neuronal-specific enolase. Electron microscopy reveals the presence of secretory granules.[130]-[137] Thymic

carcinoids, like other foregut carcinoids, are associated with Cushing's syndrome, multiple endocrine neoplasia and, rarely, the carcinoid syndrome.[129][136][132][139]

The diagnosis of thymic carcinoid often requires open surgical biopsy. Complete surgical resection is recommended, although recurrence is common.[129][136][131][138] The effectiveness of adjuvant therapy is unproven, but most reports advocate adjuvant radiotherapy for incompletely resected tumors.[129][136][131][138] Chemotherapy rarely has been used in cases of metastatic or recurrent disease.[129][136][131][138]

Although a 5-year survival rate of 60% has been reported with complete surgical resection,[130][137] local recurrences are common and distant metastases occur in approximately 30% of patients.[129][136] The long-term prognosis is generally poor.

Thymolipoma

Thymolipomas are rare benign neoplasms composed of mature adipose and thymic tissue, and they account for 1% to 5% of thymic neoplasms.[133][140] These tumors are also known as *lipothymomas*, *mediastinal lipomas with thymic remnants*, and *thymolipomatous hamartomas*.[133][140,134][141] In a review of 27 patients, Rosado-de-Christenson et al.[134][141] noted an equal gender distribution and a mean age of 27 years. Approximately 50% of patients presented with symptoms of vague chest pain, dyspnea, and tachypnea. Others have reported, in adults only, an association with myasthenia gravis, red cell aplasia, hypogammaglobulinemia, lichen planus, and Graves' disease.[133][140,135][142]

Thymolipomas are soft, lobulated, encapsulated tumors that originate in the anterior mediastinum. They often attain a large size before becoming symptomatic. They frequently conform to the shape of the cardiac and mediastinal structures and are found in the anterior inferior mediastinum "draped along the diaphragm" and connected to the thymus by a small pedicle.[134][141] Microscopically,

the tumors are composed of thymic tissue, often with calcified Hassall's corpuscles, and more than 50% adipose tissue.[134–141] Histologically, thymolipomas do not appear malignant, and malignant transformation does not occur.[134–141] Treatment involves complete resection. Long-term follow-up is not available, but recurrences have not been reported.

Germ Cell Tumors

The vast majority of germ cell tumors arise within gonadal tissue, but the mediastinum is the most common site for the development of extragonadal germ cell tumors. They are most commonly seen in the anterior mediastinum and account for 10% to 15% of all primary mediastinal tumors.[2] These tumors have generated considerable interest because of their uncertain histogenesis.

Etiology

Extragonadal germ cell tumors are found along the body's midline from the cranium (pineal gland) to the presacral area. This line corresponds to the embryologic urogenital ridge. It is presumed that these tumors arise from malignant transformation of germ cells that have abnormally migrated during embryonic development.[136,137,143–144] Mediastinal germ cell neoplasms account for only 2% to 5% of all germinal tumors, but they constitute 50% to 70% of all extragonadal tumors.[137,138,144,145]

Classification

Mediastinal germ cell tumors are broadly classified as benign or malignant. Benign tumors include mature teratomas and mature teratomas with an immature component of less than 50%. Malignant germ cell tumors are divided into seminomas (dysgerminomas) and nonseminomatous tumors. Nonseminomatous tumors include embryonal carcinomas, choriocarcinomas, yolk sac tumors, and immature teratomas.[139–146] Seminomas may exist in a pure form, but any elevation of AFP indicates the presence of an element of a nonseminomatous tumor. In addition, mediastinal germ cell tumors have a

propensity to develop a component of non–germ cell malignancy (e.g., rhabdomyosarcoma, adenocarcinoma, permeative neuroectodermal tumor), which can become the predominant histology.

Incidence and Clinical Presentation

In adults, benign germ cell tumors have no gender predilection, but 90% of malignant germ cell tumors occur in men.[136][143] In the pediatric population, both benign and malignant extragonadal germ cell tumors occur with equal gender distribution. Mediastinal germ cell tumors are most commonly diagnosed in the third decade of life, but patients as old as 60 years of age have been reported. The incidence of these neoplasms is equal in all races. Many patients with benign tumors, including 50% of teratomas, are asymptomatic; however, 90% to 100% of patients with malignant tumors have symptoms of chest pain, dyspnea, cough, fever, or other findings related to compression or invasion of surrounding mediastinal structures.[140][147],[141][148]

Diagnosis

Mediastinal germ cell tumors are most often detected on the basis of standard chest radiographs. More than 95% of the chest films are abnormal, with almost all masses noted in the anterior mediastinum. Three percent to 8% of tumors arise within the posterior mediastinum.[136]–[143] Chest CT scans demonstrate the extent of disease, relationship to surrounding structures, and presence of cystic areas and calcification within the tumor.[16] Abdominal imaging should be performed to assess for possible liver metastases. Although careful examination of the testes, including a testicular ultrasound, should always be performed, an isolated tumor mass in the anterior mediastinum without retroperitoneal involvement is not consistent with a testicular primary tumor. It is not necessary to perform blind orchiectomy or testicular biopsy in patients with normal physical examinations and unremarkable ultrasound

findings.[137][144] Recently, mediastinal sonography imaging patterns have been suggested as a means to improve the diagnostic accuracy of mediastinal teratomas.[149]

Determination of serum tumor markers is important in the diagnosis and follow-up of mediastinal germ cell tumors. Immunoassays for ?-HCG and AFP should be obtained in all patients possessing mediastinal masses suspicious for germ cell tumors. Elevations of ?-HCG and AFP confirm a malignant component to the tumor. AFP or ?-HCG, or both, are elevated in 80% to 85% of nonseminomatous germ cell tumors, with AFP being detected in 60% to 80% of these tumors and ?-HCG in 30% to 50%.[140]-[147] Patients with benign teratomas have normal markers, and patients with pure seminoma may have low levels of ?-HCG, but AFP is not detected.

Teratomas

Benign teratomas are the most common mediastinal germ cell tumor, accounting for 70% of the mediastinal germ cell tumors in children and 60% of those in adults.[136]-[143] They can be seen in any age group but most commonly occur in adults from 20 to 40 years of age. There is no gender predilection.

Teratomas may be solid or cystic in appearance and are often referred to as *dermoid cysts* if unilocular. Teratomas contain elements from all three germ cell layers, with a predominance of the ectodermal component in most tumors, including skin, hair, sweat glands, sebaceous glands, and teeth. Mesoderm is represented by fat, smooth muscle, bone, and cartilage. Respiratory and intestinal epithelium are often seen as the endodermal component. The majority of mediastinal teratomas are composed of mature ectodermal, mesodermal, and endodermal elements and exhibit a benign course. Immature teratomas phenotypically may appear as a malignancy derived from these ectodermal, mesodermal, and endodermal elements. These latter tumors behave aggressively and generally are not responsive to systemic therapy.

Treatment of "benign" mediastinal teratoma includes complete surgical resection, which results in excellent long-term cure rates. Radiotherapy and chemotherapy play no role in the management of this tumor. The tumor may be adherent to surrounding structures, necessitating resection of pericardium, pleura, or lung. Complete resection of teratomas should be the goal of treatment. Resection of mature teratomas has been shown to result in prolonged survival with little chance of recurrence.[~~139~~146,~~142~~ 150] Immature teratomas are potentially malignant tumors; their prognosis is influenced by the anatomic site of the tumor, patient age, and the fraction of the tumor that is immature.[~~139~~-146] In patients younger than 15 years, immature teratomas behave similarly to their mature counterparts. In older patients, they may behave as highly malignant tumors. Currently, a trial of cisplatin-based combination chemotherapy (up to 4 cycles of cisplatin, etoposide, and ~~bleomycin~~Bleomycin (BEP) or etoposide~~vinblastine~~, ifosfamide, and cisplatin(VIP), if responding) is frequently administered before attempted surgical resection.[~~139~~146] {Hinton S, Catalano P, Einhorn LH, Nichols CR, Crawford ED, Vogelzang N, Trump D, Loehrer PJ: Cisplatin, Etoposide and Either Bleomycin or Ifosfamide in the Treatment of Disseminated Germ Cell Tumors. Final Analysis of an Intergroup Trial. Cancer 97(8):1869-1875, 2003.}

Seminoma

Primary pure mediastinal seminoma accounts for approximately 35% of malignant mediastinal germ cell tumors; it is principally seen in men aged 20 to 40 years.[~~143~~-151] Seminomas grow slowly and metastasize later than their nonseminomatous counterparts, and they may have reached a large size by the time of diagnosis. Symptoms are usually related to compression or even invasion of surrounding mediastinal structures. Twenty percent to 30% of mediastinal seminomas are asymptomatic when discovered,[~~143~~ 151] but metastases are present in 60% to 70% of patients. Pulmonary and other intrathoracic metastases are most commonly seen. Extrathoracic metastases usually involve bone.[~~143~~151]

The treatment of mediastinal seminoma has evolved since the early 1970s. Definitive conclusions regarding treatment are difficult, because several potentially curative treatment modalities exist. Seminomas are extremely radiosensitive tumors, and for many years, high-dose mediastinal radiation has been used as initial therapy, resulting in long-term survival rates of 60% to 80%.[~~144~~–152] A review of recommendations for radiation therapy treatment in extragonadal seminoma was reported by Hainsworth and Greco.[~~143~~–151] Thirty-five to 40 Gy are the most commonly used radiation doses. Doses as low as 20 Gy have been reported to be curative, but most reports note a significant local recurrence rate with doses of less than 45 Gy.[~~143~~–151] Radiation portals should include a shaped mediastinal field and both supraclavicular areas.[~~143~~151]

Mediastinal seminoma often presents as bulky, extensive, and locally invasive disease, requiring large radiotherapy portals. These portals result in excessive irradiation of surrounding normal lung, heart, and other mediastinal structures. Additionally, for 20% to 40% of patients in whom local control is achieved, treatment can be expected to fail at distant sites.[~~136~~143,~~143~~151]

Chemotherapy was previously used only in advanced gonadal seminoma, but encouraging results and the above- mentioned problems with radiotherapy have led to broadened indications; chemotherapy is now being used as initial therapy in many patients with bulky tumors. Pure mediastinal seminoma falls into the intermediate-risk category of the new International Staging System for Germ Cell Tumors. Even patients with visceral metastases fall into this intermediate category and, as such, have a prognosis with cisplatin-based combination chemotherapy exceeding 75% for 5-year survival. Standard systemic therapy consists of cisplatin-based combination chemotherapy. Lemarie and ~~coworkers[140]~~ coworkers[147] reported that 12 of 13 patients treated experienced complete remission, with two recurrences after treatment. ~~Cisplatin-based combination therapy achieved a complete response in~~

~~three of five patients treated by Giaccione~~Bokemeyer reported an international analysis of 51 patients with mediastinal seminoma.[~~145~~-153] In this study, patients were treated with chemotherapy (38 = 74.5%), chemotherapy and radiation (10 = 19.6%), or radiation alone (3 = 5.9%). Chemotherapy was primarily cisplatin-based (45 = 94%) but included carboplatin (3 = 6%) which had an inferior objective response rate (80% versus 93%). The progression-free survival and overall survival were 77% and 88%, respectively but patients with extrathoracic metastases (6 = 11.8%) had a worse prognosis. A collective review of 52 patients was undertaken by Hainsworth and Greco.[~~143~~-151] Fourteen patients had received prior radiation therapy, but all underwent chemotherapy with cisplatin and various combinations of cyclophosphamide, vinblastine, bleomycin, or etoposide. Complete responses to treatment were noted in 85% of patients, and 83% were long-term disease-free survivors.[~~143~~-151] Although ~~chemotherapy appears to be a superior modality in these small series,~~ radiotherapy is less toxic, chemotherapy appears to be superior, and ~~and the high salvage rate with chemotherapy after radiotherapy failure makes selection difficult. T~~therefore, ~~the recommended treatment is~~ cisplatin-based combination chemotherapy currently is recommended ~~either with or without~~ but supradiaphragmatic radiation is considered for patients with small volume and localized disease~~ or 4 cycles of cisplatin-based combination chemotherapy~~.

The management of patients with residual radiographic abnormalities after chemotherapy is controversial. Studies have shown that the residual mass is a dense scirrhous reaction in 85% to 90% of patients, and the presence of viable seminoma is rare. Others have shown a 25% incidence of residual viable seminoma in these patients treated with chemotherapy followed by resection of residual masses larger than 3 cm.[~~146~~-154] Close observation without surgery is recommended for residual masses after chemotherapy unless the mass enlarges.[~~147~~154,~~148~~-155] Evaluation with PET scans have had mixed results,

but if performed should be done 4-6 weeks after chemotherapy administration. ~~s not proven helpful and~~ ~~e~~~~E~~Empiric radiation therapy is not recommended.[~~143~~151,156] {Bob:There is an abstract from asco this year that I will find as a reference for you}

Despite a recent report of 76.9% long-term survival utilizing primary surgical resection followed by adjuvant therapy,[157] ~~M~~most authors believe that surgery does not play a role in the definitive treatment of seminoma.[~~144~~-152] In addition, surgical debulking of large tumors has not been shown to be of benefit in improving local control or survival.[~~143~~151]

All patients with mediastinal seminoma should be treated with curative intent. Isolated mediastinal seminoma with minimal disease and without evidence of metastatic disease is most often managed with radiotherapy alone, with an excellent prognosis and long-term survival. Locally advanced and bulky disease ~~may~~ should be treated initially with cisplatin-based combination chemotherapy, usually 4 cycles of cisplatin and etoposide, with radiotherapy, and followed by salvage chemotherapy (vinblastine, ifosfamide, and cisplatin) in the event of recurrence.[~~149~~-158] Patients with distant metastases should undergo cisplatin-based combination chemotherapy as initial treatment.

Nonseminomatous Germ Cell Tumors

Nonseminomatous germ cell tumors include choriocarcinoma, embryonal carcinoma, teratoma, and endodermal sinus (yolk sac) tumors. They may occur in pure form, but in approximately one-third of cases, multiple cell types are present. Other malignant components, including adenocarcinomas, squamous cell carcinomas, and sarcomas, may be present or even represent the predominant tissue type, as usually occurs in immature teratomas.

Nearly 85% of nonseminomatous germ cell tumors occur in men, with a mean age of 29 years.[~~136~~-143] Karyotypic analyses have been performed on a number of these patients, and the 47,XXY

pattern of Klinefelter's syndrome has been found in up to 20% of patients.[136–143] Mediastinal nonseminomatous germ cell tumors are most commonly found in the anterior mediastinum and appear grossly as lobulated masses with a thin capsule. They are frequently invasive at the time of diagnosis, with almost 90% of patients exhibiting symptoms. They appear on CT scans as large inhomogeneous masses containing areas of hemorrhage and necrosis. Elevated levels of ?-HCG are seen in 30% to 50% of patients, and AFP is detected in 60% to 80%.

These Primary mediastinal nonseminomatous germ cell tumors carry a poorer prognosis than either pure extragonadal seminoma or their gonadal nonseminomatous counterparts, and all patients with primary mediastinal nonseminomatous germ cell tumors fall into the poor risk category of the new International Germ Cell Consensus Classification.[150–159] Eighty-five percent to 95% of patients have obvious distant metastases at the time of diagnosis. Common metastatic sites include lung, pleura, lymph nodes, liver, and, less commonly, bone.[143151]

A number of non–germ cell malignant processes have been found in association with nonseminomatous germ cell tumors. One of the most interesting is that found in association with acute megakaryocytic leukemia. Other hematologic malignancies, such as acute myeloid leukemia, acute nonlymphocytic leukemia, erythroleukemia, myelodysplastic syndrome, malignant histiocytosis, and thrombocytosis, have all been reported. These malignancies may antedate the discovery of the germ cell tumor or occur synchronously. Solid tumors, such as embryonal rhabdomyosarcoma, small cell undifferentiated carcinoma, neuroblastoma, and adenocarcinoma have been described and occur more frequently in primary mediastinal tumors compared to gonadal germ cell neoplasms.[137144]

The diagnosis of nonseminomatous germ cell tumors can often be made without tissue biopsy.[144 152] In many centers, the presence of an anterior mediastinal mass in a young male with elevated serum

tumor markers (AFP and ?-HCG) is adequate to initiate treatment. If a tissue diagnosis is deemed necessary, fine-needle guided aspiration with cytologic staining for tumor markers may be used for confirmation. An anterior mediastinotomy provides the best exposure for open biopsy if necessary.[~~144~~152]

Treatment of nonseminomatous germ cell tumors incorporates cisplatin-based chemotherapy, which has markedly improved the prognosis in these patients. In the past, long-term survival after treatment of nonseminomatous germ cell tumors was very rare; today, however, overall complete remission rates of 40% to 50% are obtained in most series.[~~139~~146,~~140~~147,~~143~~151,~~145~~153] Treatment is initiated with cisplatin-containing combination chemotherapy, which often includes etoposide and bleomycin. Treatment should be administered every 3 weeks for 4 courses; patients should then be restaged with serum tumor markers and CT scans of the chest and abdomen.[~~143~~–151] In a collective review of 158 patients undergoing a variety of combination chemotherapeutic regimens for the initial treatment of nonseminomatous germ cell tumors, complete responses were noted in 54% of patients, and 42% were long-term disease-free survivors.[~~143~~151] In an international review of 287 patients, responses were noted in 178 (64%) and the progression-free and overall survival were 44% and 45%, respectively.[153]

Patients with negative tumor markers and no radiographic evidence of residual disease after initial chemotherapy require no further treatment. Persistent elevation of serum tumor markers, particularly if they begin to rise again, usually requires salvage chemotherapy.[~~143~~-151] Patients with normal serum tumor markers but radiographic evidence of residual masses after induction chemotherapy should undergo surgical resection 4 to 6 weeks after completion of chemotherapy.[~~143~~151,~~144~~–152] Complete resection should be attempted, because debulking procedures provide no benefit. Patients found to have residual viable germ cell tumor undergo 2 additional cycles of chemotherapy. Patients with immature teratoma or non–germ cell malignancies can simply be observed after complete resection.

~~Nichols[136]~~ Nichols[143] reports complete remissions in 18 of 31 patients using this regimen, and other series report complete remission rates of 50% to 70%, with long-term survival rates approximating 50%.~~[136]~~[143] Equivalent results are obtained in all histologic subtypes.

The treatment of recurrent disease is difficult, because patients with relapsing mediastinal nonseminomatous germ cell tumors do extraordinarily poorly with salvage therapy, such as vinblastine, ifosfamide, and ~~cisplatin[151]~~cisplatin[160]; optimal therapy has not been determined. Standard salvage chemotherapy has not proven beneficial with only 9 of 79 patients (8%) becoming disease-free in one study[153] and few patients ever achieve~~e~~ing durable remissions. High-dose chemotherapy with stem cell rescue is effective in only a few selected patients.~~[152]~~[161,~~[153]~~[162] Occasionally, surgical resection of residual disease despite persistently elevated tumor markers can be beneficial.[163] Most patients are candidates for experimental phase I trials.

Mesenchymal Tumors

Mediastinal mesenchymal tumors, or soft tissue tumors, originate from the connective tissue elements of the mediastinum. Smooth and striated muscle, lymphatic tissue, fat, and vascular tissue all give rise to a variety of neoplasms, which may be benign or malignant. Most of these tumors also occur in other parts of the body and are discussed in detail elsewhere in the chapter on soft tissue sarcomas.

Mesenchymal tumors account for approximately 6% of primary mediastinal neoplasms.[2] They are less common in the mediastinum than in other locations. Approximately 55% are malignant, and there is no gender predilection.[10,~~154~~[164] In general, treatment of malignant mesenchymal tumors involves combination therapy, including surgical resection, radiation therapy, and chemotherapy. Benign tumors should be ~~completely~~ excised completely, after which little chance of recurrence remains.

Lipomas are the most common mesenchymal tumor of the mediastinum, representing 2% of all mediastinal neoplasms.[8] Benign lipomas are most often located in the anterior mediastinum. They may grow to large size without symptoms. Treatment is complete resection, and although local recurrence is possible, it is unusual. Malignant liposarcoma is more commonly found in the posterior mediastinum.

Fibromas are encapsulated asymptomatic tumors that may grow to a very large size. Fibrosarcomas often are symptomatic malignancies associated with hypoglycemia. Fibromas are cured with complete surgical excision, but fibrosarcomas are usually unresectable and respond poorly to radiation and chemotherapy.[10] Leiomyomas, leiomyosarcomas, rhabdomyomas, rhabdomyosarcomas, synovial cell sarcomas, mesotheliomas, and xanthogranulomas also occasionally occur in the mediastinum.[8,~~154~~164]

Vascular tumors of the mediastinum include hemangiomas, hemangioendotheliomas, and benign and malignant hemangiopericytomas.[8,~~154~~-164] Ten percent to 30% of all vascular tumors are malignant.[10] Mediastinal hemangiomas represent 0.5% of all mediastinal neoplasms but are the most common vascular tumor.[~~155~~-165] They may be cavernous or capillary and are often associated with hemangiomas in other areas of the body.[~~155~~165,~~156~~-166] Sixty percent occur in the anterior mediastinum, and 25% occur posteriorly.[10] Diagnosis is best accomplished by CT scan or MRI, in which phleboliths may be seen in 30% of these tumors. Angiography is important in identifying and embolizing major feeding vessels before surgery.[~~156~~-166] Total excision is considered the treatment of choice; however, large, incompletely resected hemangiomas usually do not recur.[~~155~~165]

Lymphangiomas, also known as *cystic hygromas*, often extend into the anterior mediastinum from the cervical area. Seventeen percent are located exclusively in the mediastinum. They tend to enlarge as patients grow, particularly during puberty. Treatment involves surgical resection, but this is

often difficult because of adherence to surrounding structures. Response to radiation is variable.[10] Other lymphatic soft tissue tumors include lymphangiosarcoma and lymphangiopericytoma.

Neurogenic Tumors

Thoracic neurogenic tumors occur most commonly in the posterior mediastinum but occasionally are found in the anterior mediastinum and elsewhere. They compose between 19% and 39% of all mediastinal ~~tumors[157]~~tumors[167,~~158~~–168] and 75% of posterior mediastinal tumors.[~~159~~–169] They originate from peripheral nerves (nerves of the brachial plexus and intercostal nerves), autonomic sympathetic ganglia and, rarely, from the vagus nerve.[~~160~~-170] Neurogenic tumors in the anterior mediastinum originate in chemoreceptor paragangliomas.

Whereas neurogenic tumors in infants and children are frequently malignant and often present with metastatic disease,[~~161~~–171] in adults the majority of these tumors are benign. They occur without gender predilection at any age but are more likely in young adults. Often asymptomatic, they are solitary (except in neurofibromatosis) and found on a routine chest x-ray. Benign tumors can attain a considerable size. They frequently arise in the paravertebral sulcus from the posterior roots of the spinal nerves at the zone of transition between the central and peripheral myelin.[~~162~~-172] They also may arise on the posterior portion of the spinal nerve root in the spinal canal and grow through the intervertebral foramen into the paravertebral area, giving rise to the appearance of a dumbbell- or hourglass- shaped tumor. These tumors must be recognized to plan an appropriate operation in conjunction with a neurosurgeon. Depending on their size and location, lesions may cause spinal cord compression, pain, paresthesias, Horner's syndrome, and muscle atrophy. Superior vena cava syndrome, dyspnea, cough, and bony erosions, which wrongly suggest a malignant process, also have been described.

Neurilemoma (Schwannoma)

Neurilemoma (schwannoma) is the most common tumor in the paravertebral sulcus. Arising from the intercostal nerve sheath, the tumor is encapsulated, white or yellowish pink in color, with calcifications and cystic degeneration. Histologically, it is composed of uniform slender biphasic fusiform cells with elongated, twisted nuclei that have a tendency to align in a regimented or palisaded appearance.[163–173] The tumor may contain large blood vessels and may be a source of considerable blood loss during surgical removal. Schwannoma may be further differentiated into melanotic, adenomatous, or psammomatous tumors (Fig. 32-2).[163173]

Neurofibroma

Neurofibromas are most often benign and asymptomatic. However, they can have an intradural as well as an extradural component and may cause symptoms of cord compression. They are not encapsulated and may have a plexiform appearance.[164–174] Microscopically, neurofibromas have a heterogeneous cell population, but Schwann cell differentiation is not always present.[157–167] Neurogenic tumors can be differentiated from leiomyomas, meningiomas, and fibrous histiocytomas by the immunohistochemical identification of S-100 protein. Solitary neurofibromas are cured by surgical excision.

Neurofibromas can occur as multiple lesions in von Recklinghausen's disease.[165–175] Neurofibromatosis is inherited as an autosomal dominant trait affecting both genders equally; however, approximately one-half of the cases are sporadic.[166176,167–177] The clinical features vary and include hyperpigmented café au lait skin spots, skin and subcutaneous multiple neurofibromas (hamartomas), scoliosis, bowing of long bones, disorders of sexual development, and multiple neurogenic tumors and malignancies, such as malignant schwannomas.[168178,169–179] Mediastinal neurofibromas may be multiple and appear as long plexiform masses. Histologically, they consist of large nerve fibers mixed with

connective tissue stroma containing Schwann cells and fibroblasts. Surgical intervention is justified for lesions located in the spinal canal that cause spinal cord or nerve root compression. The prognosis generally is poor.[170][180]

Malignant Schwannoma

Malignant schwannomas are the malignant counterparts of neurilemmomas and neurofibromas. Ultrastructural studies, however, cannot always document Schwann cells in these tumors derived from nerve sheaths, and therefore the terms *malignant nerve sheath tumor*, *neurogenic sarcoma*, and *neurofibrosarcoma* are sometimes used.[170]–[180] Malignant nerve sheath tumors commonly are large. They are painful and may cause superior vena cava obstruction; Horner's syndrome; dyspnea; dysphagia; hoarseness; and invasion of the lung, bones, and aorta, depending on their location and size.

The diagnostic criteria for malignant nerve sheath tumors are controversial.[166]–[176] Origin from a major nerve, presence of Schwann cells and S-100 protein, the diagnosis of neurofibromatosis, and nuclear palisading are important features. Histologic findings include hypercellularity, pleomorphic dense nuclei, multiple and abnormal mitoses, and invasion of the surrounding structures.[160]–[170] The malignant nerve sheath tumors are usually large (often larger than 5 cm in diameter), partially encapsulated, soft, and gray, with hemorrhage and necrosis. Histologically, they are composed of spindle cells with comma- shaped, irregular nuclei. Neural and perineural invasion, mature cartilage, bone, striated muscle, squamous differentiation, and mucin-secreting glands also may be seen.[171][181],[172][182]

Clinically, these tumors are aggressive, locally invasive, and highly metastatic. They often recur after resection, leading to a 75% 5-year survival rate. Patients with neurofibromatosis and a malignant nerve sheath tumor have a 15% to 30% 5-year survival rate. Combination chemotherapy is recommended in stage III and IV disease (Fig. 32-3).

Tumors of Sympathetic Ganglia

Mediastinal ganglioneuromas are found in the posterior mediastinum along the sympathetic chain in children older than 4 years and in adults in the third and fourth decades of life. Occasionally, a neuroblastoma may mature into a benign ganglioneuroma.[173][183–175–185] The tumor usually is asymptomatic, but sometimes presents with Horner's syndrome and, rarely, with diarrhea caused by production of vasoactive intestinal polypeptide. Ganglioneuromas have a smooth contour and contain areas of stippled calcification. They may resemble other benign neurogenic tumors, causing rib erosions.[176–186] Microscopically, spindle cell proliferation is seen that appears identical to that in a neurofibroma, except that ganglioneuromas exhibit the presence of large ganglion cells.[160–170] Ganglioneuromas are benign tumors, although regional lymph nodes may contain islands of tumor cells attributed to matured neuroblasts.[166-176] They require complete excision.

Neuroblastomas

Although neuroblastomas can be found in any location in which embryonic neuroblasts migrated from the neural crest, they usually originate in the adrenal glands and along nerve plexuses. In the chest, they occur along the sympathetic trunk in the paravertebral sulcus. This tumor is the most common malignancy of early childhood, occurring most commonly in the first 2 years of life. Patients with mediastinal neuroblastomas usually are symptomatic and frequently have metastatic disease.[177,178-187,188] Symptoms are related to local compression (Horner's syndrome and heterochromia of the iris) or to systemic release of vasoactive peptides, such as catecholamines, vanillylmandelic acid, homovanillic acid, and 3-methoxy-4-hydroxyphenylglycol. Encephalopathy, myasthenia, and Cushing's syndrome may be present.[179–189] Radiographically, a mass is seen in the posterior mediastinum with stippled calcifications, skeletal erosion, and occasional extension into the spinal canal.

Pathology reveals lobulated gray or red tumors with hemorrhagic areas. Microscopically, small cells with scant cytoplasm and polygonal nuclei exhibit various degrees of differentiation. Intracytoplasmic neurofilaments and neurosecretory granules and extracellular material seen on electron microscopy distinguish neuroblastoma from other childhood tumors, such as lymphoma, Ewing's sarcoma, and rhabdomyosarcoma.[~~160~~170]

Neuroblastomas are highly aggressive tumors. Survival depends on the age of the patient, the stage of disease, the location of the tumor, and histologic differentiation. The prognosis is better in patients younger than 1 year of age and in patients with limited, well-differentiated tumors. Neuroblastomas may regress spontaneously or undergo maturation into ganglioneuromas. Ganglioneuroblastomas have a better prognosis than neuroblastomas.[~~180~~–190] The staging system for neuroblastoma shown in Table 32-13 was developed to help guide therapy. Treatment for stage I and II disease is simple surgical resection, although adjuvant postoperative radiotherapy is recommended for stage II tumors. For stage III and IV, a combination of chemotherapy and radiation is advised.

Granular Cell Tumor

Granular cell tumors (granular cell myoblastomas) are considered benign. They are found in the posterior mediastinum and are derived from Schwann cells. They are soft, gray, and poorly circumscribed tumors consisting of uniform polygonal cells either in nests or strands with eosinophilic granular cytoplasm and a stroma of fibrous connective tissue.[~~181~~-191] Resection is always curative.

Diagnosis

Although posterior mediastinal neoplasms are predominately neurogenic, other tumors also must be considered in the differential diagnosis. Goiters, esophageal leiomyomas, solitary fibrous tumors, and bronchial/esophageal duplication cysts all have been reported. Once identified, the nature of these

lesions, their relationship to other structures, and the presence of distant metastases can be determined by CT scans. MRI scans can define vascular involvement and provide multiplanar views that are valuable in assessing tumor extension into paravertebral foramina. An iodine 131 nuclear scan may be helpful if a goiter is suspected.

Histologic diagnosis is not necessary before surgery. However, if surgical resection is not contemplated, a definitive diagnosis is required for further treatment planning. This diagnosis generally requires a generous biopsy obtained by an open surgical procedure or a CT-guided core-needle biopsy.

Management

If no contraindication is present, resection of all neurogenic tumors is advised. Neurogenic tumors grow and can cause life- threatening symptoms, depending on their size and location. Therefore, observation of neurogenic tumors may be justified only with a stable, asymptomatic, benign tumor in an otherwise poor surgical candidate. The standard approach uses a posterolateral thoracotomy incision, removing the tumor with normal tissue margins. More recently, thorascopic resection of small- to moderate-size tumors has been reported.[192] In dumbbell tumors, the intraspinal component should be removed first. The mortality rate for surgical resection is less than 1%. Complications include Horner's syndrome and chylothorax. Surgery on tumors with spinal canal involvement may be complicated by direct spinal cord trauma, ischemia from spinal artery injury and, rarely, an epidural hematoma with spinal cord compression.

Primary Cardiac Malignancies

The vast majority of tumors involving the heart and pericardium are metastatic.[~~182~~193,~~183~~ [194] In addition, most primary cardiac tumors are benign myxomas, 75% to 80% of which arise from the left atrium.

Other benign primary cardiac neoplasms include rhabdomyoma, fibroma, lipoma, hemangioma, teratoma, and fibroelastoma. Primary malignant cardiac tumors make up one-fourth of all primary cardiac neoplasms and most commonly originate from the atria.[184][195],[185]–[196] Most are some variant of sarcomas,[186]–[197] including angiosarcoma,[187]–[198] rhabdomyosarcoma, leiomyosarcoma,[188]–[199] fibrosarcoma,[189]–[200] lymphoma, malignant fibrous histiocytoma,[190]–[201] and mesothelioma of the pericardium.[191]–[202] Pheochromocytomas also occur as primary cardiac neoplasms.

A high index of suspicion is imperative in establishing a diagnosis, because the presenting symptoms often mimic other nonneoplastic cardiac pathology. Whole body gallium scans,[192]–[203] echocardiography, CT, and MRI all may serve to localize a primary cardiac neoplasm. With the advent of EKG gating, MRI has taken the forefront in imaging of cardiac lesions.[204] Up to 80% of primary cardiac malignancies present with systemic metastases[193]–metastases[205] and have clinical evidence of right heart failure, and many develop tamponade. Surgical resection is required for cure; however, negative margins usually are not possible.[194][206]

Chemotherapy and external-beam radiation can be administered after surgery, although a report of 15 cases treated at the Institut Gustave-Roussy does not support the routine use of adjuvant chemotherapy for primary cardiac sarcomas.[190]–[201] There has been a report of a patient receiving neoadjuvant (induction) chemotherapy, which resulted in a response and subsequent surgical resection.[195][207]

New surgical techniques, including orthotopic and autotransplantation, may be beneficial in carefully selected patients.[196][208],[197]–[209] With the advent of “gating” technology and sophisticated treatment planning, more accurate targeting with electron beam radiation therapy may be possible,

similar to stereotactic radiosurgery of the brain. At times, a pericardial window may be required to palliate symptoms of pericardial tamponade. Currently, long-term survival is rare.[~~198~~210,~~199~~211]

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FIGURE 32-1.

Mediastinal compartments.

FIGURE 32-2.

Schwannoma in the paravertebral area in the apex of the left chest.

FIGURE 32-3.

A: Malignant neurofibroma, initially considered to be nonresectable, in a 34-year-old man. **B:** The tumor was resected after a combination of chemotherapy and radiation therapy.

TABLE 32-1.

Anatomic Structures within the Mediastinum

ANTERIOR MEDIASTINUM
Thymus gland
Internal mammary artery and vein
Lymph nodes
Parathyroid (rarely, if ectopic)
Thyroid (rarely, if ectopic)
MIDDLE MEDIASTINUM
Heart and pericardium

Ascending and transverse aortic arch

Superior and inferior vena cavae

Innominate artery and vein

Main and right pulmonary artery

Pulmonary veins

Trachea and mainstem bronchi

Phrenic nerves

Lymph nodes

POSTERIOR MEDIASTINUM

Esophagus

Descending aorta

Sympathetic chains

Vagus nerves

Azygous and hemiazygous veins

Thoracic duct

Lymph nodes

TABLE 32-2.

Classification of Mediastinal Tumors

NEUROGENIC

Arising from peripheral

nerves

Neurofibroma

Neurilemoma (schwannoma)

Neurosarcoma

Arising from sympathetic

ganglion

Ganglioneuroblastoma

Ganglioneuroma

Neuroblastoma

Arising from

paraganglionic tissue

Pheochromocytoma

Chemodectoma

(paraganglioma)

GERM CELL

Seminoma

Nonseminomatous

Pure embryonal cell

Mixed embryonal cell

__With seminomatous

elements

__With trophoblastic

elements

__With teratoid elements

__With endodermal sinus

elements

Teratoma, benign

HERNIAS

Hiatal

Morgagni

CYSTS

Pericardial

Bronchogenic

Enteric

Thymic

Thoracic duct

Meningoceles

THYMIC

Thymoma

Carcinoid

Thymolipoma

Thymic carcinoma

Ascending aortic

Transverse arch

Descending aortic

Great vessels

MESENCHYMAL

TUMORS

Fibroma, fibrosarcoma

Lipoma, liposarcoma

Myxoma

Mesothelioma

Leiomyoma, leiomyosarcoma

Rhabdomyosarcoma

Xanthogranuloma

Mesenchymoma

Hemangioma

Hemangioendothelioma

Hemangiopericytoma

Lymphangioma

Lymphangiopericytoma

Lymphangiomyoma

LYMPHADENOPATHY

Inflammatory

Granulomatous

Sarcoid

LYMPHOMA

Hodgkin's disease

Histiocytic lymphoma

Undifferentiated

ENDOCRINE

Thyroid

Parathyroid

ANEURYSMS

Ascending aortic

Transverse arch

Descending aortic

Great vessels

MESENCHYMAL

TUMORS

Fibroma, fibrosarcoma

Lipoma, liposarcoma

Myxoma

Mesothelioma

Leiomyoma,

leiomyosarcoma

Rhabdomyosarcoma

Xanthogranuloma

Mesenchymoma

Hemangioma

Hemangioendothelioma

Hemangiopericytoma

Lymphangioma

Lymphangiopericytoma

Lymphangiomyoma

LYMPHADENOPAT

HY

Inflammatory

Granulomatous

Sarcoid

LYMPHOMA

Hodgkin's disease

Histiocytic lymphoma

Undifferentiated

ENDOCRINE

Thyroid

Parathyroid

TABLE 32-3.

Relative Frequency of Primary Mediastinal Tumors

Tumor	*Incidence (%)*
Neurogenic	25.3
Thymoma	23.3
Lymphoma	15.3
Germ cell neoplasm	12.2
Endocrine tumor	7.8
Mesenchymal tumor	7.3
Primary carcinoma	5.7
Other	2.9

(Adapted from ref. 2, with permission.)

TABLE 32-4.

Distribution of Primary Mediastinal Masses by Anatomic Location

ANTEROSUPERIOR MEDIASTINUM

Thymic neoplasms

Lymphomas

Germ cell tumors

Carcinoma

Cysts

Mesenchymal tumors

Endocrine tumors

Morgagni hernias

MIDDLE MEDIASTINUM

Cysts

Lymphomas

Mesenchymal tumors

Carcinoma

Hiatal hernia

Sarcoidosis

POSTERIOR MEDIASTINUM

Neurogenic tumors

Cysts

Mesenchymal tumors

Endocrine tumors

Esophageal masses

Hiatal hernia

Aortic aneurysms

TABLE 32-5.

Relative Frequency of Primary Mediastinal Tumors in Adults and Children

Tumor	*Incidence (%)*	
	Adults	Children
Thymic	31	28
Neurogenic	15	47
Lymphoma	26	9
Germ cell	15	9
Vascular	1	6
Miscellaneous	13	2

(Adapted from ref. 4, with permission.)

TABLE 32-6.

Diagnostic Evaluation of Mediastinal Masses

HISTORY AND PHYSICAL EXAMINATION

RADIOGRAPHY

_Standard chest radiography

_Computed tomographic scanning

_Barium swallow

_Radioisotope scanning

_Angiography

_Myelography

_Ultrasonography

_Magnetic resonance imaging

ENDOSCOPY

SEROLOGY

NEEDLE BIOPSY PROCEDURES

_Computed tomography guided

_Ultrasound guided

SURGICAL PROCEDURES

_Mediastinoscopy

_Mediastinotomy

_Thoracotomy

TABLE 32-7.

Symptoms and Signs of Mediastinal Masses

SYMPTOM
Chest pain
Dyspnea
Cough
Fatigue
Dysphagia
Night sweats
Hemoptysis
Hoarseness
SIGN
Weight loss
Fever
Adenopathy
Wheezing, stridor
Superior vena cava syndrome
Vocal cord paralysis
Neurofibromatosis
Neurologic abnormalities
Pericardial tamponade

Arrhythmias

TABLE 32-8.

Systemic Syndromes Associated with Mediastinal Neoplasms

Tumor	*Syndrome*
Thymoma	Acute pericarditis, Addison's disease, agranulo cytosis, alopecia areata, Cushing's syndrome, hemolytic anemia, hypogammaglobulinemia, limbic encephalopathy, myasthenia gravis, myocarditis, nephrotic syndrome, panhypopi tuitarism, pernicious anemia, polymyositis, pure red cell aplasia, rheumatoid arthritis, sar coidosis, scleroderma, sensorimotor radicu lopathy, Stiff-person syndrome, thyroiditis, ulcerative colitis

Hodgkin's disease	Alcohol-induced pain, Pel-Ebstein fever
Neurofibroma	von Recklinghausen's disease, osteoarthritis
Thymic carcinoid	Multiple endocrine neoplasia
Neuroblastoma	Opsomyoclonus, erythrocyte abnormalities
Neurilemoma	Peptic ulcer

TABLE 32-9

Systemic Manifestations of Hormone Production by Mediastinal Neoplasms

Symptoms	*Hormone*	*Tumor*
Hypertension	Catecholamines	Pheochromocytoma, chemodectoma, neuroblastoma, ganglioneuroma
Hypercalcemia	Parathyroid hormone	Parathyroid adenoma
Thyrotoxicosis	Thyroxine	Thyroid
Cushing's	ACTH	Carcinoid tumor

syndrome		
Gynecomastia	HCG	Germ cell tumor
Hypoglycemia	? Insulin	Mesenchymal tumors
Diarrhea	VIP	Ganglioneuroma, neuroblastoma, neurofibroma

ACTH, adrenocorticotropic hormone; HCG, human chorionic gonadotropin; VIP, vasoactive intestinal polypeptide.

TABLE 32-10.

World Health Organization Staging System for Thymic Epithelial Tumors

Tumor Type	***Cells***	***Clinicopathologic Classification***	***Histologic Terminology***
A	**Spindle or oval**	**Benign thymoma**	**Medullary**
B	**Epithelioid or dendritic**	**Category I malignant thymoma**	**Cortical; organoid**
__B1			**Lymphocyte-rich; predominately cortical**
__B2			**Cortical**

__B3		**Well-differentiated thymic carcinoma**
AB	**Benign thymoma**	**Mixed**
C	**Category II malignant thymoma**	**Nonorganotypic; thymic carcinoma, epidermoid keratinizing and nonkeratinizing carcinoma, lymphoepithelioma-like carcinoma, sarcomatoid carcinoma, clear cell carcinoma, basaloid carci noma, mucoepidermoid carcinoma, undifferentiated carcinoma**

TABLE 32-11.

Thymoma Staging System of Masaoka

Stage	*Description*
I	Macroscopically completely encapsulated and microscopically no capsular invasion
II	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
	Microscopic invasion into capsule
III	Macroscopic invasion into neighboring organs (pericardium, great vessels, lung)
IVa	Pleural or pericardial dissemination

IVb	Lymphogenous or hematogenous metastasis

(From ref. 60, with permission.)

TABLE 32-12.

Thymoma Staging System of Groupe d'Etudes des Tumeurs Thymiques

Stage	*Description*
I	
__Ia	Encapsulated tumor, totally resected
__Ib	Macroscopically encapsulated tumor, totally resected, but the surgeon suspects mediastinal adhesions and potential capsular invasion
II	Invasive tumor, totally resected
III	
__IIIa	Invasive tumor, subtotally resected
__IIIb	Invasive tumor, biopsy
IV	
__IVa	Supraclavicular metastasis or distant pleural implant
__IVb	Distant metastases

(From ref. 63, with permission.)

TABLE 32-13.

Staging System for Neuroblastoma

Stage	*Description*
I	Tumor is limited to site of origin.
II	Tumor extends beyond site of origin, or when limited to site of origin, has metastatic regional lymph nodes present on same side.
III	Tumor extends to contralateral side.
IV	Metastases are present beyond regional lymph nodes.