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# Chapter 45

# Mediastinum and Trachea

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## INTRODUCTION

Primary mediastinal tumors are rare and most commonly arise from thymic, neurogenic, lymphatic, germinal, and mesenchymal tissues. Secondary mediastinal tumors, which are far more common than primary tumors, most frequently represent mediastinal lymphatic involvement from lymphoma or metastasis of the lung or infra-diaphragmatic organs such as gastric cancer, pancreatic cancer, testicular cancer, and gastroesophageal adenocarcinoma. Lymphomas, the most common tumor in the middle mediastinum (341), as well as tumors of lung, esophagus, heart, and great vessels are discussed in detail in other chapters.

Approximately two third of primary tumors are histologically benign, and surgical resection is often curative (23). Clinically, most patients with asymptomatic mediastinal tumors have benign lesions whereas most symptomatic patients have malignant disease (81). Symptomatology is related usually to pressure or invasion of the structures within the mediastinum causing substernal chest pain, dyspnea, cough, and dysphagia (33,81).

### Anatomy

The mediastinum is located in the central portion of the thoracic cavity. It is roughly trapezoidal in shape bounded anatomically by the sternum and attached muscles anteriorly, the thoracic vertebral column and adjacent ribs posteriorly, the lungs and parietal pleurae laterally, the diaphragm inferiorly, and the thoracic outlet at the level of first thoracic vertebral body and the manubrium superiorly (256). Various recommendations for dividing the mediastinum into different compartments have been proposed (43,112,342); a practical and clinically relevant division defines three compartments in the mediastinum: anterior (anterosuperior), middle, and posterior (Fig. 1). There are no physical anatomical barriers or fascial planes that separate these compartments, and considerable overlap may exist.

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 thymus occupies the superior anterior mediastinum. It includes lymph nodes and vessels. The middle mediastinum is defined as the space occupied by the heart, pericardium, proximal great vessels, and central airways. It includes the ascending and transverse aortic arch, brachiocephalic vein, innominate artery, vena cavae, main and proximal right pulmonary arteries, pulmonary veins, trachea, mainstem bronchi, and lymph nodes. The posterior mediastinum includes the paravertebral gutters and is bounded by the heart and great vessels anteriorly, the thoracic inlet superiorly, the diaphragm inferiorly, and the chest wall posteriorly. The anatomic structures normally found in the different mediastinal compartments and the tumors arising from those structures are listed in Table 1 and Table 2 respectively.

The thymus gland is an irregular, lobulated lymphoepithelial organ lying in the anterior mediastinum. Embryologically, the thymus derives from the endoderm of the lower portion of the third pharyngeal pouch. By week 8 of fetal development, the primitive thymus descends into the mediastinum to become a bilobed glandular structure. The blood supply is from the internal mammary arteries and venous drainage is into the innominate and internal thoracic veins. The thymus is composed primarily of an epithelial stroma as well as abundant

lymphocytes in various stages of maturation. It is considered a lymphatic organ having function in the cellular immune process by providing a unique environment for maturation of T lymphocytes. Its lymphatics drain into lower cervical nodes, internal mammary nodes, and hilar nodes. It slowly involutes during adulthood and is largely replaced by adipose tissue (374).

Incidence of Primary Mediastinal Tumors

Primary mediastinal neoplasms are relatively rare. Some studies suggest that the frequency and the prevalence of primary malignant mediastinal lesions have recently been increasing (4,16,66,81); however, the exact incidence is unknown. Table 3 shows the relative incidence and distribution of primary mediastinal tumors. These tumors are most commonly found in the 3rd through 5th decade of life but may be found in all age groups and in all compartments of the mediastinum (81). In the adult population, over 50% of mediastinal neoplasms occur in the anterosuperior mediastinum, approximately, 20% in the middle mediastinum, and 26% in the posterior mediastinum (81,382). In the pediatric population, 26%-43% of the neoplasms occur in the anterosuperior mediastinum, 11%-18% in the middle mediastinum, and 40%-63% in the posterior mediastinum (16, 134,136). The differences in distribution between adults and children are attributed to the higher incidence of thymic tumors and lymphomas in adults and of neurogenic tumors in the pediatric population.

In adults, thymic neoplasms predominate in the anterosuperior mediastinum, followed in frequency by lymphomas, germ cell tumors, and carcinoma (342). Bronchial, enteric, pericardial cysts, tumors of connective tissue and vascular origin, aberrant parathyroid tumors, and thyroid neoplasms are also found in this compartment. Although lymphomas are the most common tumors in the mediastinum overall, among the primary tumors, thymomas are more common in the anterior mediastinum (342,382). This is probably due to the fact that lymphomas rarely present as an isolated single anterior mediastinal mass as most thymomas usually do. In the middle mediastinum, cystic lesions are most common, followed by lymphomas, mesenchymal tumors, and carcinoma (341). In the posterior mediastinum, neurogenic tumors are most common, followed by cysts, mesenchymal tumors, and endocrine neoplasms (81,341,66). Most neurogenic tumors (80%) are located in the posterior mediastinum, and 50% of mediastinal lymphomas are in the middle mediastinum (146).

In pediatric patients, neurogenic tumors predominate, followed by thymic tumors, lymphomas, and germ cell tumors. Cystic lesions account for 16% of the adult mediastinal masses and 24% of the pediatric masses. The differences of the relative frequency of these mediastinal tumors are illustrated in Table 4 (16). The relative incidence of benign and malignant primary mediastinal tumors and cysts are shown in Table 5.

THYMIC TUMORS

The vast majority of thymic tumors are thymomas, ninety percent of which are found in the anterosuperior mediastinum; other variants are found in the middle and posterior mediastinum or neck. (252). Thymomas are epithelial tumors associated with an exuberant lymphoid component composed of immature

cortical thymocytes. Although lymphomas, carcinoid tumors, and germ cell tumors may all arise within the thymus, only thymomas, thymic carcinomas, and thymolipomas arise from true thymic elements.

## Thymomas

### Epidemiology

The true incidence of thymoma is unknown. The Surveillance, Epidemiology and End Results (SEER) reported a thymoma incidence of 0.13 per 100,000 (258). Although thymoma is a relatively rare neoplasm, it is the most common tumor of the anterior mediastinum, representing approximately 30% of anterior mediastinal lesions (16,66,71,81,252,354) and 20% of all mediastinal tumors in adults (126,207,342,382). Thymomas are less common in children, accounting for approximately 15% of anterior mediastinal masses (252). Most patients with thymoma are adults between the ages of 40 and 60 years, with an average age of 48 years, a median age of 52 years, and an equal overall gender ratio (22,25,82,203,227,315).

There is a reported association between the Epstein-Barr virus and thymoma and lymphoepithelioma of the thymus. The diseases are more frequent in far-Eastern countries (87,235,352). Childhood thymus irradiation has been linked to the development of thymic tumors (163), and familial cases have also been reported suggesting a possible relationship with cytogenetic abnormalities (193,228,383).

### Natural History

Thymoma is characterized by an indolent growth pattern with a tendency toward local invasion. It is frequently associated with a variety of systemic diseases, most notably myasthenia gravis, which occurs in approximately 30-40% of thymoma patients (195). Furthermore, unlike other mediastinal tumors its prognosis appears to be more closely related to the invasive characteristics seen at operation rather than to the histological appearance. The predominant pattern of spread of thymomas is by direct invasion into adjacent organs. Indeed, the degree of encapsulation and the invasion of adjacent tissues define malignancy for these tumors rather than the histologic appearance of the tumor cells (68). Overall, approximately 50% (39% to 64%) of cases reported in surgical series are noninvasive (22,24,25,75,81,114,175,202,203,218,257,315,386).

Thymomas may metastasize as implants on pleural surfaces or pulmonary nodules, but they rarely metastasize via a vascular route to extrathoracic areas (207). The most frequent area of dissemination is into the pleural cavity with resultant pleural plaques, diaphragmatic masses, and malignant pleural effusions. Pericardial effusions have also been reported. All cases of effusion have revealed positive cytologic findings. In advanced cases, invasion into the superior vena cava, brachiocephalic vein, lung, and pericardium may be observed (5). Superior vena cava syndrome as a presenting symptom is not uncommon. Distant metastases, although rare, have been reported to liver, lung, and bone (166).

Thymoma is frequently associated with a variety of paraneoplastic syndromes, the most common being myasthenia gravis, but other diseases, including benign cytopenia, overt malignancy, hypogammaglobulinemia, and polymyositis, have also been reported (91,336).

Myasthenia gravis is an autoimmune disease characterized by the presence of antiacetylcholine receptor antibodies, which cause an acetylcholine receptor deficiency at the motor end plate; it is characterized by rapid exhaustion of voluntary muscular contractions with a slow return to the normal state. The most common clinical feature is neuromuscular fatigue; ocular muscles are involved in 90% of patients. Next in frequency of involvement are facial and pharyngeal muscles, progressing to fatigue of proximal limb girdle muscles and respiratory suppression (90,372). Patients with thymoma and myasthenia gravis may have an increased operative mortality since most surgical deaths can be attributed to myasthenia gravis crisis (219). However, the overall long-term prognosis does not appear to be adversely affected by the presence of myasthenia gravis (218,219). Death in patients with thymoma and myasthenia gravis is commonly due to complications of myasthenia gravis, whereas in patients without myasthenia gravis, death often is attributed to local progression of tumor (219).

Of patients with myasthenia gravis, approximately 25% have a normal-sized thymus and 75% have thymic abnormalities. Of these, 15% are associated with thymoma, and the remaining 60% have thymic lymphoid hyperplasia (306). Recurrence of thymoma may be higher in those without myasthenia gravis than those with myasthenia gravis (240). Interestingly, approximately 15% of patients with thymoma may develop a second malignancy such as Kaposi's sarcoma, chemodectoma, multiple myeloma, acute leukemia, or various other carcinomas (lung, colon, etc.) (221).

Clinical Presentation

The typical symptoms and signs of thymoma resemble those of patients with mediastinal masses as illustrated in Table 6. Approximately 30% to 40% of thymomas are asymptomatic, and in these patients, the tumor is usually an incidental finding on chest x-ray examination (202,203,207). Clinical symptoms may vary greatly. Patients often present with symptoms of ocular muscle weakness, ptosis, dysphagia, and fatigue, 5% with red cell aplasia, and 5% with hypogammaglobulinemia (53,150,172,306,385). On the other hand, only about 10-15% of patients with myasthenia gravis have thymoma, either benign or malignant (91,219,245). Symptoms frequently the result of impingement on surrounding mediastinal structures include cough, chest pain, dyspnea, hoarseness, superior vena cava syndrome, and symptoms related to tumor hemorrhage (279). Dysphagia, fever, weight loss, and anorexia may also be present.

Other signs and symptoms can be attributed to a wide variety systemic disorders that may occur in 5-10% of patients with thymoma. Souadjian and associates reviewed over 500 cases of thymoma and noted that 71% were associated with a systemic disease (336). These include erythroid and neutrophil hypoplasia, pancytopenia, Cushing's syndrome, DiGeorge syndrome, carcinoid syndrome, Lambert-Eaton syndrome, pernicious anemia, nephrotic syndrome, SIADH, Whipple's disease, lupus erythematosis, pemphigus, myotonic

dystrophy scleroderma, polymyositis, polyneuritis, myocarditis polyarthropathy, myotonic dystrophy, Sjogren's syndrome, Addison's disease, panhypopituitarism, sarcoidosis, hypogammaglobulinemia, ulcerative colitis, rheumatoid arthritis, Hashimoto's thyroiditis, hyperthyroidism, hyperparathyroidism, and thyroid carcinoma (53,68,200,221,252,385). Other miscellaneous diseases include hypertrophic osteoarthropathy and chronic mucocutaneous candidiasis (221). Table 7 shows some of paraneoplastic syndromes that may be associated with thymoma and other mediastinal tumors.

Diagnostic Workup for Mediastinal Tumors

Patients with mediastinal tumors may manifest systemic symptoms secondary to hormone production (Table 8). However, an extensive work-up concerning extrathoracic sites should not be applied routinely in the absence of symptoms. The diagnostic workup for mediastinal tumors is outlined in Table 9. Diagnostic work-up of a patient with a mediastinal mass begins with a thorough history and physical examination. Particular focus should be given to detect subtle physical findings that may suggest the presence of myasthenia gravis. Routine screening blood work and chemistries should be obtained as they may give clues to the presence of associated syndromes. Serum alpha-feto-protein (AFP) and beta-human chorionic gonadotropin (ß-HCG) levels should be obtained in young adult males, as they are most certainly elevated in the presence of non-seminomatous germ cell tumors (329). Chest x-rays often demonstrate a mass in the anterior mediastinum in 45-80% of the patients (Fig. 2) and are useful in comparison with older films to detect growth and chronological changes. Other advanced imaging studies such as computed tomography (CT) are the most valuable radiologic techniques in the evaluation and clinical staging of mediastinal tumors (21,205,314,315). The size, contour, tissue density, and homogeneity of a mediastinal lesion can be defined, as well as its relation to or invasion of other mediastinal structures (Fig. 2). CT is well suited for staging of many of these tumors and is helpful as a baseline for monitoring response to treatment with irradiation or chemotherapy. It is also imperative for planning radiation therapy portals. Magnetic resonance imaging (MRI) has not been shown to yield more information than the CT scan (49). MRI, however, has the advantage of demonstrating musculoskeletal anatomy and differentiating the neurovascular structures of the mediastinum, particularly useful in patients with allergies to contrast or renal insufficiency (49,194,355). The role of positron emission tomography (PET) scan has not been established, but early data suggests its ability to distinguish thymoma from thymic hyperplasia and the association of high uptake of fluorodeoxyglucose with the degree of tumor invasiveness (186,210).

Although a preoperative biopsy of an anterior mediastinal mass can aid in its diagnosis, a planned operation of a resectable anterior mediastinal mass may be appropriate without a preoperative biopsy when a thorough clinical and radiographic evaluation of peripheral lymph nodes is negative and tissue diagnosis is obtained at thoracotomy. Most patients presenting with a mediastinal mass, however, need a histologic diagnosis before instituting definitive therapy. CT- or US-guided fine-needle aspiration biopsy of the mass may be performed to establish the diagnosis preoperatively (327). Such procedures may have a diagnostic sensitivity and

specificity of 87-90% and 88-100%, respectively in detecting thoracic neoplasms (248). Sometimes, when larger tumor samples are required to distinguish between lymphoma and lymphoid predominant thymoma, core needle biopsy usually provides sufficient specimens with an overall sensitivity of 96% and specificity of 100% (248). Bronchoscopy, video-assisted thoracic surgery, mediastinoscopy, or anterior thoracoscopy may help yield the diagnosis prior to resection, especially if enlarged lymph nodes are present (63,85,329). The potential risk of breaching the capsule leading to spillage of tumor cells during biopsy has been debated and is unsettled (244,330).

Pathologic Classification

Controversies regarding the classification and terminology of thymic tumors still exist. A malignant thymoma, for example, may be defined as an invasive or metastatic thymoma by some clinicians or a thymic carcinoma by others (182,183). However, tumors with true malignant cytologic characteristics are considered thymic carcinomas rather than thymoma, whereas malignant thymoma refers to invasive thymoma as defined either macroscopically or microscopically that retain typically "bland" cytologic characteristics of thymic epithelial cells admixed with mature lymphocytes. The term invasive thymoma should be used instead of malignant thymoma to denote its behavior of capsular invasion. Grossly, they are lobulated, firm, irregularly shaped, tan-pink to gray tumors that may contain cystic spaces, calcification, or hemorrhage. They may be neatly encapsulated, adherent to surrounding structures, or invasive. Nodal and hematogenous metastases may occur but are rare (207).

Among the classifications of thymomas that have been proposed, the more widely accepted histologic classification is that proposed by Marino and Muller-Hermelink that classifies thymoma into cortical, mixed and medullary types (223). According to their data, cortical thymomas have a more aggressive course than medullary thymomas and are more likely to be associated with myasthenia gravis. Likewise, those tumors that are mixed tend to show an intermediate behavior and have an intermediate prognosis (300). The 10-year survival rates are approximately 100% for medullary, 76% for mixed and 45% for cortical and well-differentiated thymomas (149,283,300,350,370).

Although degree of tumor invasiveness is strongly related to stage and prognosis of thymoma, in a recent series by Quintanilla-Martinez and colleagues (291), the histologic classification of Marino and Muller-Hermelink (223) seems to support the prognostic significance of histology, independent of tumor stage. In their study, none of the medullary and mixed thymomas recurred even though 30% had capsular invasion. Organoid and cortical thymomas showed intermediate invasiveness and low but significant risk of late relapse, even with minimal invasion (291). Thymic carcinomas, regardless of histology, were always invasive and carried a significant risk of relapse and death, even in stage II patients (291).

The classification of Rosai and Levine (302) divides thymomas into three types depending on the predominant architecture of the tumor: lymphocytic, epithelial, or mixed (lymphoepithelial). Some authors have

suggested a fourth group, spindle cell type, but this is often considered a variant of the epithelial type (203). In general, most series report no consistent correlation between the histopathology of thymomas and their malignant potential (302,315) and no correlation between histopathologic subtype of thymomas and the associated systemic syndromes.

A more recent conceptual approach to the classification of thymic lesions was proposed, based on level of differentiation, dividing thymic lesions into thymoma (well differentiated), atypical thymoma (moderately differentiated), and thymic carcinoma (poorly different differentiated) (344). However, like other thymic classification systems, classification by degree of differentiation can be misleading (182). Further studies will be needed. Currently, among the different classification schemes the traditional grouping based on invasiveness, cell type, and epithelial cell architecture appears to be accepted by most clinicians (143,182,345).

Staging

Bergh and associates introduced the first clinical staging system for thymoma in 1978 (24). Their staging system was subsequently modified and refined by Masaoka and associates in 1981 (227) and is the most widely used. It is based on pathologic findings at time of surgery (Table 10). Another clinically useful staging system is the French Groupe d'Etudes des Tumeurs Thymiques (GETT) classification, which is illustrated in Table 11 (118). The GETT system correlates with the Masaoka system prognostically (72,118).

Prognostic Factors

The two most important prognostic factors that affect treatment outcome for thymoma are invasiveness (stage) and completeness of surgical resection of the tumor (22,25,24,47,82,203,227,364). Invasiveness is commonly used as the basis for designation as benign or malignant. Five- and 10-year survival rates for a well-encapsulated thymoma without invasion are over 90%. Ten-year survival rates for invasive thymomas range from 27% to 69% (24,75,227,278,364,386). The approximate 5-year survival rates according to Masaoka stage are 93% for stage I, 86% for stage II, 70% for stage III and 50% for stage IV (227,381).

Numerous authors have reported on the long-term prognostic significance of the extent of resection (33,119,296,353,381,387), tumor size (>10 cm), and the presence of symptoms (33,207,284). Patients with complete or radical excision have significantly improved survival over those with subtotal resection or biopsy only (227,288). Although almost all noninvasive thymomas can be totally resected, the ability to achieve a complete resection in invasive cases is relatively low (58% to 73%) (218,227,257). Some studies also suggest that histologic type (medullary vs. cortical vs. mixed) is an important prognostic indicator (119,196,254) whereas other studies do not (22,202,284).

Patients with autoimmune diseases such as red cell aplasia, hypogammaglobulinemia and lupus erythematosus appear to have a poorer prognosis (33,181,219). Contrary to older series that report a poor prognosis in the setting of myasthenia gravis (22,25,386), several modern series have failed to confirm this

observation (196,227,233,254,257,278,284,364,387). In fact, myasthenia gravis may even confer a survival advantage because it may lead to earlier discovery of a small thymoma (33,181,303,371). Age also appears to be a prognostic factor. Thymomas in children appear to have a more malignant course than those in adults (379). Fortunately, malignant thymomas in children are extremely rare (56).

## General Management

### Surgery

Depending on the stage and thus resectability, complete surgical resection alone is the most effective therapy of a thymoma (Table 12). Complete en-bloc surgical resection remains the treatment of choice for all thymomas regardless of invasiveness, except in rare advanced cases with extensive intrathoracic or extrathoracic metastasis. Operation for thymoma carries a low morbidity and mortality, especially in patients with early stage thymoma; most surgical deaths can be attributed to myasthenia gravis crisis (219). If an encapsulated thymoma without associated myasthenia gravis can be removed without disturbing the integrity of the capsule, recurrence is very rare (22). For encapsulated, noninvasive thymomas, survival is excellent (114,218).

Successful surgical treatment of locally invasive thymoma is dependent on completeness of resection (396). An aggressive surgical approach to invasive tumors should be taken to remove as much of the lesion as possible at the time of surgery. However, resection of an involved phrenic nerve is controversial. However, if both nerves were involved, most surgeons would agree that both phrenic nerves should be left intact. Although somewhat debatable, in those cases, in which a complete resection is not possible, a debulking operation should be considered since good long-term results can still be achieved when such surgery is followed by postoperative radiation therapy (47,219). Others found no obvious survival advantage of debulking procedures over biopsy alone (72,219,246,257). The surgeons should delineate the extent of the tumor, specify the areas of invasion, and identify the areas of positive or questionable margins and residual disease with metallic clips to assist future radiation therapy planning.

### Recurrent Thymoma

Experience in the management of recurrent thymomas is lacking because of its rarity. Although patients with encapsulated thymomas are mostly cured by complete excision, delayed recurrence has been reported in up to 12% and as late as 32 years after initial surgery (14,218,245,254,320). As a result, patients with thymoma need to be followed life-long. Most recurrent thymomas often remain indolent and are confined to the thorax, thus facilitating reoperation. Treatment for recurrent thymomas is usually surgery and radiation therapy (177,297,311). Patients undergoing surgery for local recurrence seem to have similar five-year survivals when compared with patients with no recurrence (33). Other studies of reoperation for recurrent thymoma show acceptable short and long-term results (177,297). Of the 28 patients undergoing reoperation for recurrent thymoma, Regnard and colleagues reported that 19 of them were able to undergo a complete resection (297).

The five and ten year actuarial survival rates after reoperation were 51% and 43% respectively, and for those with complete resection, the rates were 64% and 53%. Hence patients who develop locally recurrent thymoma should be considered for surgery. In unresectable cases, preoperative chemotherapy or radiation therapy may facilitate surgical resection (177,311,365).

Results of Surgery

For noninvasive stage I disease, results of surgery alone may result an approximately 90% 5-year survival and 80% 10-year survival (219,257,385). The frequency of local recurrence is only about 0-5% for encapsulated thymomas. However, for stage II and III, results of surgery alone for invasive thymomas are generally poorer with recurrence rates of 10% to 47% (33,219,240,296). In one study, overall five-year prognosis of completely resected invasive vs. non-invasive thymoma was 67% vs. 85% (218). In a series reported by Fujimura and associates (114), 10-year survival rates for invasive and noninvasive thymomas were 49.4% and 74.3%, respectively. Similar results were reported by Maggi and colleagues (218).

Radiation Therapy

Encapsulated, non-invasive thymomas (stage I) do not require postoperative radiation therapy after complete resection because recurrence is approximately 1.5% (219). However, post-operative irradiation is indicated in patients with invasive thymoma even after complete resection, as the recurrence of completely resected invasive thymoma may approach 30% with a median time for local recurrence of 3.8 years (33). Completely resected invasive thymomas carry a poorer prognosis than noninvasive tumors (25,47,282,354). In general, five-year survival rates range from 53% to 70% (75,227,257). Survival rates continue to fall with long-term follow-up, and 10-year survival rates may be considerably poorer (278). The role of postoperative irradiation for invasive thymomas has never been tested in a prospective fashion. However, numerous retrospective studies have reported improvements in local tumor control and survival (75,227,233,257,288,364).

Radiation therapy is an effective adjuvant therapy for invasive thymomas (stage II) as these tumors are usually radioresponsive. In many series, patients with gross fibrous adhesions of the tumor to the pleura at the time of surgery or microscopic invasion of the pleura on histology (stage II) are at increased risk for recurrence. Haniuda and colleagues (142) found that patients with fibrous adhesion to the mediastinal pleura without microscopic invasion benefited the most from postoperative radiation therapy. The recurrence rates, with and without adhesion to the mediastinal pleura, were 36.4% vs. 0%, respectively.

In a study by Monden and colleagues (240), there was a 29% recurrence rate for patients with resected stage II thymoma who did not undergo adjuvant radiation therapy, as compared with an 8% recurrence rate with postoperative irradiation. Although postoperative radiation therapy has been shown to be effective at decreasing local recurrence in completely resected invasive thymoma, it does not appear to decrease the incidence of subsequent pleural dissemination that may occur in these patients whose pleurae are usually outside of radiation

fields and not treated. This may be a reflection of the natural pattern of spread of this disease with pleural dissemination occurring even before, during, or after the time of surgery. Unfortunately, extended irradiation to include the entire pleura significantly increases the normal tissue complications and thus is not routinely employed.

For stage III disease, the evidence supporting the use of postoperative radiation therapy is even more apparent. Urgesi and colleagues (364) reported no in-field recurrences in a study of 33 patients with completely resected stage III thymoma given post-operative irradiation. All three recurrences occurred out-of-field. For locally advanced, large, invasive thymomas that are unresectable or marginally resectable, preoperative radiation therapy has been advocated to render it resectable (22,271,326,378). Several studies on limited numbers of patients who received preoperative radiotherapy for extensive disease note a decrease in tumor burden at the time of surgery with response rates as high as 80% and describe a theoretical decrease in the potential for tumor seeding during surgery (72,75,219). These series report that preoperative irradiation facilitated total or subtotal resection of the invasive thymoma mass by reducing the tumor volume (271).

Primary radiation therapy alone as the definitive treatment has been advocated in non-surgical candidates or patients with unresectable advanced disease (stage III-IV). Arakawa and associates reported on twelve patients who presented with unresectable tumors and were treated with primary radiation therapy, and seven patients were alive from 1 year 8 months to 5 years 1 month (10). Ciernik and associates (62) reported similar outcomes when comparing radiation alone to tumor debulking and adjuvant radiation therapy in 31 patients with stage III and IV unresectable disease. A 5-year survival of 87% was reported in a small group of patients with IVA disease treated with radiation therapy alone (153). Jackson and associates (157) reported an overall survival of 53% at 5 years and 44% at 10 years for patients with advanced thymoma receiving radiation following biopsy only or incomplete resection. Urgesi and associates (365) reported on the use of radiotherapy alone in 21 patients with intrathoracic recurrences of thymoma. The seven-year survival of 70% was similar for those treated with radiation alone and for those treated with surgery and adjuvant therapy. However, the retrospective nature of these studies, small number of patients, differing amounts of clinical disease, and variations in radiation doses and techniques are likely confounding variables that relate to the results in the literature. The role of preoperative and primary radiation therapy has generally fallen out of favor. With the high response rates of chemotherapy, most patients with advanced disease will be treated with a combined modality approach.

Chemotherapy

Although most chemotherapeutic trials involving thymoma are small and the exact role of chemotherapy in the treatment of patients with invasive thymoma is not well defined (357), a number of studies have reported reasonable results with various systemic agents, either alone or in combination. Platinum-based regimens have commonly been used over the past decade. Response rates range between 24 and 100% (145). In a recent study,

thirteen patients with stage III and IV disease were treated with single agent ifosfamide (148). Five patients had a complete response and one had a partial response with an estimated 5-year survival of 57%. There are numerous case reports or small series reporting antineoplastic activity for both multiple and single agents, including steroids, and for combination chemotherapy (35,48,54,79,95,103,109,110, 122,127,150,158, 211,216,273,328). In general, chemotherapy is reserved for locally advanced or metastatic disease. However, there are only a few prospective clinical trials conducted in thymic malignancies. The most promising use of chemotherapy is combination chemotherapy given neoadjuvantly to convert initially marginally resectable or unresectable disease into potentially resectable disease. There are no reported prospective randomized trials comparing different chemotherapeutic agents (47,354). In a recent review of the literature, response rates of over 50% have been found consistently with the application of combination chemotherapy (145). Some of the commonly employed active drugs in combination chemotherapy are cisplatinum, doxorubicin, and cyclophosphamide with reported overall responses in excess of 50% (212,213). In a study by Forniasiero and colleagues, 37 patients with stage III or IV thymoma were treated with cisplatinum, doxorubicin, vincristine, and cyclophosphamide (109). The overall response rate was 91.8%, of which 43% were complete responses. Loehrer and associates studied 23 patients with localized but unresectable thymomas (212). These patients were treated with combination chemotherapy consisting of cisplatinum, doxorubicin, and cyclophosphamide followed by radiotherapy. The overall objective response rate was 70% with 5 complete responders. The estimated 5-year disease survival was 54% and a median survival of 93 months. Multivariate analysis demonstrated that chemotherapy was associated with an improvement in overall survival for patients with stage III and IV disease.

Combined modality

Most patients with locally advanced or metastatic thymoma can be effectively treated with combined modality consisting of radiation therapy, chemotherapy, and surgery with acceptable results (47,53,331,354). In a study by Macchiarini and colleagues (216), all seven patients with stage III invasive thymoma treated with neoadjuvant cisplatinum, epirubicin and etoposide were able to undergo surgical resection. Four were complete and three were incomplete resections. It has also been shown that neoadjuvant chemotherapy, and then surgery, followed by additional chemotherapy and irradiation may improve the survival of the patients with locally advanced thymoma (369). Shin and colleagues reported that nine out of eleven patients with unresectable stage III and IV thymoma were able to undergo complete resection after induction chemotherapy consisting of cyclophosphamide, doxorubicin and cisplatinum (331). All nine patients were given additional postoperative radiotherapy and chemotherapy. Out of these patients, seven continued to be disease-free at a median follow-up of 43 months.

Table 13 shows the results of combination chemotherapy with and without surgery and radiation in patients with mostly advanced thymoma. Most received cisplatinum-based regimens. The overall response rate was approximately 60%. However, in these series only some of the patients underwent surgical resection, which

raises the issue of selection bias. Furthermore, postoperative radiation therapy was not routinely given in all series. All patients who achieved a pathologic complete response had received cisplatinum-containing regimens.

These encouraging results are being evaluated in a prospective intergroup study that treats previously untreated patients with unresectable thymomas limited to the mediastinum with cisplatinum-doxorubicin-cyclophosphamide (PAC) chemotherapy plus irradiation (212). The impact of multimodality therapy on survival for these patients still needs to be evaluated. The role of chemotherapy as an adjuvant therapy after resection has not been established. However, it has been reported in conjunction with radiation therapy in unresectable surgical cases, including patients with advanced and recurrent disease (114,125,212,213,233).

Management of Myasthenia Gravis

The surgical approach for myasthenia gravis has been removal of the thymus; complete remission rates vary from 7 to 63% (32). However, thymectomy is not always successful in reversing the neurologic symptoms seen in patients with thymoma compared to those with other thymic abnormalities (27,32,91,226). In one study, thymectomy resulted in major improvement of myasthenia gravis in 40% of 75 patients with thymomas and in 62% of 161 patients without thymomas (104). Similar results have been reported by Jaretzki and colleagues (161). Braitman and colleagues (36) analyzed the results of surgery in 33 patients with thymic tumors, 17 of whom had associated myasthenia gravis. Response of myasthenia gravis to removal of the thymic tumor was good to excellent in 44% of the patients, with an average follow-up of 5.5 years.

Patients with thymoma have a higher acetylcholine receptor activity and titers of anti-striated muscles antibodies in approximately 80-90% of patients with thymoma and myasthenia gravis (388). Administration of an anticholinesterase such as pyridostigmine bromide and immunosuppressive medication may alleviate the associated symptoms. Schulz and Schwab (324) reported 17% improvement with no treatment or with medication alone and 65% improvement with surgery. For patients who have failed anticholinesterase therapy and other modalities, adrenal corticosteroids have been suggested (90).

The results of thymic irradiation for myasthenia gravis have been similar to those of surgery (285). In a report from Massachusetts General Hospital (324), 45 patients diagnosed with myasthenia gravis were treated with thymic irradiation only. Among the 10 patients who had associated thymic tumors, the improvement rate was 60%. In the remaining 35 patients with no thymic tumor, a 54% improvement rate was seen. A total of 27 patients in this series were treated by thymectomy followed by thymic irradiation; the overall improvement rate was 66%. Again, no significant difference in results was found between patients harboring an associated tumor and those having no tumor. The dose of irradiation to the thymic area in these studies ranged from 15 to 30 Gy with conventional fractionation.

Currier and associates (76) reported on 28 patients with progressive myasthenia gravis without thymoma who received treatment of 30 Gy to the anterior mediastinum. The follow-up was from 5 to 18 years. Of 24 patients with generalized myasthenia in this series, 20 patients had an improved median survival time of 1.5

years. In the other 4 patients, who had ocular myasthenia gravis only, the course of disease was not altered by radiation treatment. Older patients had longer remissions than younger patients.

Radiation Therapy Techniques

Reported radiation doses have ranged from 30 to 60 Gray (Gy) given in 1.8 or 2.0 Gy per fraction daily. The recommended postoperative radiation dose after gross total resection for malignant thymoma is 45-50 Gy in 1.8-2.0 Gy daily fractions. For microscopically positive resection margins and grossly positive margins, higher radiation doses of 54 Gy and 60 Gy, respectively, administered in 1.8 to 2.0 Gy of daily dose fractions are appropriate. Although one retrospective study did not find any relationship between radiation dose and local control (12), others have noted that radiation dose was a significant prognostic factor for local control (231,246). It is difficult to prove a consistent improvement in local tumor control with higher doses in part due to the rarity of this tumor and prospective clinical trials. However, excellent local tumor control has been reported with doses higher than 40 Gy and increased local recurrences have been reported with doses lower than 40 Gy. When resection is impossible, doses of 60 Gy or more to gross disease may be required for adequate tumor control, but not without higher associated risks of complications such as pericarditis or radiation myelitis (222). Dose to the spinal cord should be limited to 45 Gy using oblique mediastinal fields.

Treatment fields and dose fractionation should be carefully planned and arranged to minimize complications such as pulmonary fibrosis, pericarditis, and myelitis. The typical volume treated should include the entire thymus or tumor bed, mediastinum and part of the involved adjacent lung if there is parenchymal involvement or as delineated by CT scan or surgical clips, plus a margin of at least 2 cm to account for daily variability during treatment and allow coverage of areas of possible microscopic disease (Fig. 3). In general, inclusion of the non-involved supraclavicular fossa is unnecessary and has not shown consistent therapeutic benefits (311). Treatment portals may include single anterior field, opposed anterior-posterior fields with differential weighting (1:1, 2:1, or 3:1), wedge pair, and multi-field arrangements. Modern CT simulation with customized treatment planning can yield optimized isodose distribution and avoid geographic misses (Fig. 3). Conformal therapy with three-dimensional treatment (3D-CRT) planning, as described in detail in chapter 44 (lung), may further minimize dose heterogeneity and radiation toxicity to adjacent non-involved structures while allowing higher doses to be delivered to the tumor.

Results of Radiation Therapy

There are no large prospective randomized phase 3 clinical trials to evaluate the primary endpoint of efficacy of primary or adjuvant radiation therapy in patients with thymoma. Until recently, radiation therapy was used primarily for patients with advanced disease, especially in patients with stage III and IVA disease. Often, inadequate equipment or dose resulted in less than optimal results (197). Of 23 patients treated with irradiation as the main therapy, 8 had complete regression, 10 had partial regression, and 5 had no regression (22). Six of the

eight patients with complete regression, 5/10 of the patients with partial regression, and only 1/5 of the patients with no regression received tumor doses of 40 Gy or more.

With megavoltage radiation therapy, control of malignant thymomas is satisfactory. In a report by Marks and colleagues (224), tumor was controlled in all nine cases treated with megavoltage irradiation with doses of 35 to 48 Gy. The average follow-up was 5.5 years (minimum, 30 months). Ariaratnam and associates (11) observed tumor control in 8 of 11 patients with malignant thymoma with minimum follow-up of 2 years. Three patients died, two of whom had received only 30 Gy in 3 weeks to the mediastinum. Overall, radiation as a monotherapy may result in approximately 65% local control and a 5-year survival rate of 40-50% (180).

Postoperative radiation therapy has resulted in improved survival of patients with invasive thymomas, after both complete and incomplete resections (47,354). In a study of 141 patients with thymoma, Nakahara and associates (257) reported a 5-year survival rate of 91.5% for patients with stage II and 87.8% for patients with stage III disease who were treated with postoperative irradiation.

Curran and co-workers (75) reported a retrospective study of patients with stage II or III thymoma. Twenty-six percent (20/78) of the patients who had not received post-operative radiation therapy developed local recurrences compared with 5% (2/43) of similar patients who had received postoperative radiation therapy. There was no significant difference in relapse rate or survival between those patients undergoing biopsy and radiation therapy versus subtotal resection and radiation therapy. They reported a 5-year actuarial mediastinal relapse of 53% for patients with stages II and III disease treated with total resection alone. But no relapses were noted in patients who received postoperative irradiation after total resection. Monden and associates (240) reported that in stage II patients the rates of thoracic recurrence were 29% for patients treated by surgery alone and 8% for patients treated by surgery and postoperative irradiation. In cases with complete radical surgery and postoperative irradiation, Urgesi and colleagues (364) observed that 15% of patients relapsed in the chest, but only 6.8% of recurrences were within the irradiation field.

The benefit of postoperative radiation therapy after subtotal resection or biopsy alone of thymoma is clear. In this group of patients if no postoperative irradiation is given, there is a 100% local recurrence rate; in irradiated patients, this falls to 20% (75). Patients undergoing radical surgery with complete resection prior to adjuvant radiation therapy often have substantially better local control and five year survival compared to those undergoing biopsy alone or limited surgery with minimal tumor resection (72,219,246,257). A summary of the results of select radiation therapy series is given in Table 14, and the overall prognoses according to stage are given in Table 15a and 15b.

Other Thymic Tumors

Both thymic carcinoma and thymolipomas are much less common than thymomas. They commonly occur in the anterosuperior mediastinum. Similar to thymoma, thymic carcinoma is thought to arise from thymic epithelium but is far more malignant with dismal prognosis than thymoma (223,384) whereas thymolipoma is a

benign thymic neoplasm containing a mixture of fat and hyperplastic thymic tissue and cured after surgical removal.

The majority of thymic carcinomas are undifferentiated, lacking the histologic features of a normal thymus; the remaining may be adenocarcinomatous, sarcomatous, squamous, basoloid, mucoepidermoid, or lymphoepithelial-like histologically. Most variants of thymic carcinoma are highly lethal with frequent metastases to regional lymph nodes, bone, liver, and lung (290,346). Approximately 80% of patients with thymic carcinoma may have radiographic evidence of invasion into adjacent structures in the mediastinum, and 40% may have evidence of mediastinal lymphadenopathy at presentation (89,190). Proper management requires an aggressive multi-modality approach, including the use of cisplatinum-based chemotherapy often coupled with radiotherapy or surgery. The prognosis corresponds with tumor grade and stage. Five-year survival rates for those patients with high stage and grade neoplasms range approximately 15 to 20% whereas patients with low grade, localized disease may have five-year survivals of 80 to 90% (346,349).

Primary thymic carcinoid tumors are exceedingly rare. They arise from the neuroendocrine cells within the thymus and not the thymic epithelium. Few cases (no more than 100 cases) have been reported in the literature (96). Like other carcinoids commonly in the gastrointestinal and respiratory tracts, they are malignant neuroendocrine neoplasms with the potential for aggressive local, regional, and distant spread. They affect males more frequently than females with a male to female ratio of 9:1. Clinical symptoms at presentation resemble those with mediastinal masses (94). In addition, Cushing syndrome, multiple endocrine neoplasia I and II, and inappropriate secretion of antidiuretic hormone (SIADH) are sometimes seen in patients with thymic carcinoids (96). However, carcinoid syndrome has not been reported in patients with primary thymic carcinoid tumor in the literature (94). Approximately 20-30% of patients may have extrathoracic metastases at presentation. The prognosis is generally poor despite aggressive surgical resection with frequent local recurrence and metastases (96). In one study, local or distant metastatic spread developed in all patients (100%) even after complete resection (28). The role of adjuvant therapy is unclear but may improve the outcome in select patients (83,96). A 5-year survival of 31% has been reported (83).

## MALIGNANT MEDIASTINAL GERM CELL TUMORS

### Epidemiology

Approximately, 50 to 70% of primary extragonadal germ cell tumors occur in the mediastinum (188,262). However, primary malignant mediastinal germ cell tumors are exceedingly rare and account for 1-2% of all germ cell tumors (73,215), 5% to 13% of malignant mediastinal tumors (73,81) and about 1-3.5% of all mediastinal neoplasms (81). The disease is more common in Caucasian males. Of 150 patients with mediastinal germ cell tumors reported in seven series, 127 (84%) were males and 24 (16%) were females (73,169,171,225,312,380). Pure seminomas are most common in the third decade of life, followed by the fourth and second decades. Nonseminomatous germ cell tumors (pure or mixed histology) occur in young adults, the

majority being in the 15 to 35-year age group. In the adult population, men and women have an equal incidence of benign germ cell tumors; approximately 90% of malignant extragonadal germ cell tumors are found in men (261). In the pediatric population, the incidence of benign and malignant mediastinal germ cell tumors is similar in both males and females.

Approximately 20% of patients with nonseminomatous germ cell tumors have Klinefelter's syndrome (86). Mediastinal germ cell tumors have also been associated with other systemic diseases, including systemic mast cell disease, acute myeloid leukemia, and malignant histiocytosis (55,265).

Natural History

Extragonadal germ cell tumors occur along the body's midline from the pineal gland in the cranium, through the mediastinum, to the retroperitoneum and presacral areas. This corresponds to the embryologic urogenital ridge, which extends from C-6 to L-4. The origin of these extragonadal germ cell tumors remains controversial. Several theories have been proposed as to their development (52,113,138,318). It is presumed that extragonadal germ cell tumors arise from germ cells that have abnormally migrated along the urogenital ridge during embryonic development (215,261). These tumors are the result of malignant transformation of these germinal elements, displaced to extragonadal sites without there ever having been a gonadal primary tumor (262). These tumors are generally not metastasis from occult gonadal primaries; primary testicular tumors that metastasize to the anterior mediastinum are uncommon (261,262). Retroperitoneal germ cell tumors, however, have been more frequently associated with a gonadal primary than their mediastinal or pineal counterparts.

The mediastinum is the most common site for the development of extragonadal germ cell tumors. The majority of mediastinal germ cell tumors are located in the anterosuperior mediastinum accounting for approximately 10 to 23% of all primary anterior mediastinal tumors (81,241,382). In a review by Martini and colleagues (225), the tumor was located in the anterior mediastinum in all 30 of the reported patients.

Despite the fact that mediastinal germ cell tumors have the same morphologic and histologic appearance as germinal tumors of the testes, germ cell tumors of extragonadal origin have a poorer prognosis with much more aggressive biological behavior than their gonadal counterparts (8,93,168). Primary germ cell tumors of the mediastinum are commonly divided histologically into seminomas and nonseminomas. Unlike the nonseminomatous germ cell tumors, pure seminomas are very responsive to both radiation therapy and chemotherapy with cure rates of over 60-80% for localized disease despite their mediastinal location (108). Among the nonseminomatous germ cell tumors, 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 (261). 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. Surgical resection is often curative.

On the other hand, malignant nonseminomatous germ cell tumors are generally more aggressive with a tendency to metastasize. Long-term disease-free survival varies from 13% to 58% (266,395). Approximately

85% of these tumors occur in men with a mean age of 29 years (261). 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, and almost 90% of patients are symptomatic. They appear on CT scan as large inhomogeneous masses containing areas of hemorrhage and necrosis. Elevated levels of beta-HCG are seen in 30% to 50% of patients, and AFP is detected in 60% to 80%. One study reported the ratio of metastatic germ cell tumors in the chest to primary mediastinal germ cell tumors as 47:1.4 (225). However, the metastases occurred through out the chest. If anterior mediastinal metastases are present, middle and posterior mediastinal lymph nodes, as well as retroperitoneal nodes, are frequently involved (215). Rather and associates (292) described fibrotic scars in the testes after detailed histologic examination of patients with disseminated germ cell tumors. However, Luna and Tamariz (215) found evidence of a scar or occult tumor in the testes in only 2 of 20 cases of mediastinal germ cell tumors.

A number of unusual malignant processes are associated with nonseminomatous germ cell tumors; associated hematologic malignancies include acute myeloid leukemia, acute nonlymphocytic leukemia, acute megakaryocytic leukemia, erythroleukemia, myelodysplastic syndrome, and malignant histiocytosis (140,261,264,265). In one study, 9% of the 34 patients with mediastinal nonseminomatous germ cell tumors developed hematologic neoplasia while none of the 654 patients with testicular counterparts developed such malignancies (264). Less frequently, solid tumors such as embryonal rhabdomyosarcoma, small cell undifferentiated carcinoma, neuroblastoma, and adenocarcinoma have also been described (262). Similarly, Klinefelter's syndrome has been recognized in patients with mediastinal germ cell tumors, but not in patients with testicular germ cell tumors (77,263,362). In one study, up to 20% of the patients with mediastinal germ cell tumors were found to have the karyotypic pattern of Klinefelter's syndrome, 47,XXY (261), which is characterized clinically by hypogonadism, azospermia, and elevated gonadotropin levels.

Clinical Presentation

As with most patients having mediastinal tumors, local symptoms are usually caused by tumor compression or invasion of adjacent structures (Table 16). Of patients with malignant germ cell tumors, 90% to 100% have clinical symptoms (179); chest pain, dyspnea, cough, and fever are the most common symptoms (204). Patients with mediastinal germ cell tumors may be entirely asymptomatic, particularly when the tumor is a teratoma or seminoma (225,274). In approximately 25% to 30% of patients, the first sign of disease was an abnormality on routine chest x-ray examination (274). Anterior mediastinal tumors, because of their location, produce substernal pressure and pain radiating to the neck and the arms in 30% to 60% of patients (81,312). The tumors impinge on the venous system, producing superior vena cava syndrome in 10% of patients (73). Seminoma tends to grow slowly to a relatively large size tumor (>30 cm) before causing symptoms. Approximately 60% of patients with mediastinal seminoma may have metastases to intrathoracic structures (e.g. lungs) and extrathoracic sites (e.g. bones) (159,179), whereas 85-95% of patients with nonseminomatous germ

cell tumors have metastases at the time of diagnosis (139,156,214,332). Embryonal cell carcinoma, teratocarcinoma, and choriocarcinoma are more aggressively infiltrating neoplasms. They produce constitutional symptoms including weakness, weight loss, and fever, and substernal pleuritic pain. They are occasionally associated with dyspnea, cough, and hemoptysis more commonly than seminoma. Patients with choriocarcinoma have a high risk of hemorrhage and approximately 40% may have gynecomastia (67,106,225,274,332).

Diagnostic Workup

Mediastinal germ cell tumors are most often detected on chest x-rays with almost all masses noted in the anterosuperior mediastinum. Three percent to 8% of tumors arise within the posterior mediastinum (261). As with evaluation of other mediastinal tumors, CT is the radiologic method of choice (31,205). The chest CT scan frequently shows a large anterior mediastinal mass, often with a homogeneous appearance in case of seminoma, and with multiple areas of hemorrhage and necrosis in nonseminomatous germ cell tumors (205); cystic areas and calcification within the tumor may be seen. Abdominal imaging should also be performed to assess other common sites of metastasis including liver and retroperitoneal lymph nodes. Careful examination of the testes should be performed. If testes abnormalities are present, appropriate radiologic examinations should be obtained for a testicular or retroperitoneal neoplasm (ultrasonography, CT, and possibly lymphangiography). Similarly, retroperitoneal adenopathy suggests a testicular primary and also warrants testicular ultrasound. There is no need to perform blind orchiectomy or testicular biopsy in patients with normal physical examinations and unremarkable ultrasound findings (261,262).

Germ cell tumors may elaborate two proteins that are useful in the diagnosis and follow-up of mediastinal germ cell tumors. The ß-subunit of human chorionic gonadotropin (ß-HCG) is found in elevated levels in the serum of 60% of patients with nonseminomatous germ cell tumors and 7%-10% of patients with pure seminomas (81,159,169,339). When elevated in patients with pure seminoma, ß-HCG levels are usually less than 100ng/ml. All patients with choriocarcinoma have elevated urinary and serum ß-HCG levels. The a-fetoprotein (AFP), an a1-globulin, is produced in the liver, yolk sac, and gastrointestinal tract of the fetus. Approximately 70% of the patients with nonseminomatous germ cell tumors have elevated levels of AFP, which often correlates with the presence of embryonal or yolk sac components (44,81). More than 90% of patients with germ cell tumors have elevated levels of one or both of these markers (162). Patients with benign teratomas are serum tumor marker-negative, and elevations of HCG and AFP suggest a malignant component to the tumor. Similarly, very high level of ß-HCG or any elevation of AFP in patients with seminoma indicates the presence of nonseminomatous elements. Nonseminomatous tumors are often positive for AFP and HCG, with AFP being detected in 60% to 80% of these tumors and HCG in 30% to 50% (204,261).

Although less specific, serum lactate dehydrogenase (LDH) is elevated in the majority of patients with mediastinal seminomatous and nonseminomatous germ cell tumors (20,156,159). Serum measurements of these biomarkers are helpful in monitoring the response of the tumor to therapy and also can be used to detect

recurrences (97,162); therefore, the determination of pretreatment and posttreatment baseline levels is essential. These biomarkers have been studied extensively with testicular tumors; several reports indicate that they are of similar value in extragonadal germ cell tumors (44,81,97).

The diagnosis of nonseminomatous germ cell tumors may be made without tissue biopsy (123). In many centers, the presence of an anterior mediastinal mass in a young male with elevated serum tumor markers is adequate to initiate treatment (Table 17). However, patients with false positivity of ß-HCG levels have been reported and the diagnosis and treatment of choriocarcinoma should include a simple urine test for HCG (69,309). If a tissue diagnosis is deemed necessary, fine-needle-guided aspiration with cytologic staining for tumor markers is the least invasive and may be used for confirmation. Some of these tumors (e.g., seminomas) are very difficult to differentiate from other anterior mediastinal tumors such as lymphomas, small cell tumors, and thymomas; definitive diagnosis often requires open biopsy (123).

Pathologic Classification

Conventionally, mediastinal germ cell tumors can be broadly classified as benign or malignant. The benign tumors include mature teratomas, which 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 (261).

The malignant germ cell tumors are divided into seminoma (or dysgerminoma) and non-seminomatous tumors (225). The latter include embryonal carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and immature teratomas. In a 30-year review of 98 consecutive patients with germ cell tumors, 46% were found to have mature teratomas, 8% immature teratomas, 16% pure seminomas, and 24% malignant nonseminomatous germ cell tumors (93). A more recent review of 229 cases of malignant mediastinal germ cell tumors by the Armed Forces Institute of Pathology (AFIP) shows that 52% were pure seminoma, 20% teratocarcinoma, 17% yolk sac tumor, 5% mixed germ cell tumor, 3% embryonal carcinoma, and 3% choriocarcinoma (242).

Staging

Although there is no single widely accepted staging system for mediastinal germ cell tumors, Moran and associates have recently proposed a simple clinical staging scheme that may be helpful in categorizing patients and defining their treatment and prognosis (Table 18) (241,242).

Prognostic Factors

The most important prognostic factor in anterior mediastinal extragonadal germinal tumors is histologic type. Mature teratomas and seminomas are highly curable and carry a substantially better prognosis than immature teratomas and nonseminomatous germ cell tumors.

Several series report almost 100% cure rates with pure seminomas localized to the mediastinum and treated with either surgery plus postoperative radiation therapy or radiation therapy alone (73,171,317).

However, other series report 5-year survival rates of only 50% to 81% (93,179). Poorer prognosis is associated with extrathoracic involvement, age greater than 35 years, superior vena cava syndrome, lymphadenopathy, fever, hilar disease on chest x-ray, and incomplete resection (45,93,179).

Patients with malignant nonseminomatous tumors have a much poorer prognosis than either pure extragonadal seminoma or their gonadal nonseminomatous counterparts, with survival rates ranging from 0% in the prechemotherapy era to approximately 43% with cisplatinum-based chemotherapy (73,93,140). Eighty-five percent to 95% of these patients have obvious distant metastases at the time of diagnosis. Common metastatic sites include lung, pleura, lymph nodes, liver, and, less commonly, bone (140,394). Normalizing serum tumor markers in response to chemotherapy are a significant favorable prognostic factor. Long-term disease-free survival varies from 13% to 58% in the literature (266,395).

## General Management

### Seminomas

Although seminomas grow slowly to a large size and metastasize later than their nonseminomatous counterparts, synchronous metastases to the lungs and other intrathoracic structures may be seen up to 60% to 70% of patients (141,159,179). Seminomas are very sensitive to both radiation therapy and chemotherapy and all patients with mediastinal seminoma should be treated with curative intent.

Radical resection has a limited role in the definitive treatment of seminoma (123,261). In general, complete radical resection may be considered in selected patients if technically feasible. Postoperative radiation therapy is often required by most patients even after complete surgical resection. Some advocate surgical resection followed by radiation therapy in patients with small, asymptomatic seminomas; however, surgical debulking of large tumors has not been shown to be of consistent benefit in improving local tumor control (140,141).

Patients with localized mediastinal seminoma without evidence of metastatic disease can be managed with radiation therapy alone, with long-term survivals of 60% to 80% even though less favorable, bulkier tumors are referred for radiation (123,261). In comparison to chemotherapy, radiation therapy is generally more tolerable, far less toxic, and has a high salvage rate with systemic chemotherapy following a failure (141). A review of recommendations for radiation therapy treatment in extragonadal seminoma was recently reported by Hainsworth and Greco (140,141). Doses of 40-50 Gy are commonly used. Although doses as low as 20 Gy have been curative, some investigators report higher rates of local recurrence with doses less than 45 Gy (141). Radiation treatment portals should include a shaped mediastinal field and both supraclavicular areas and not necessarily the retroperitoneum (45,141,152). In cases of bulky, extensive, locally invasive disease, larger irradiation portals may be required. Such large fields may result in excessive irradiation of surrounding normal lung and mediastinal organs unless careful treatment planning and modern radiotherapy equipments are used.

Additionally, for 20% to 40% of patients in whom local tumor control is achieved, treatment can be expected to fail at distant sites (261).

Although systemic multiagent chemotherapy is highly effective, in most reported series, chemotherapy was reserved for locally advanced seminomas, failures of surgery and irradiation, or metastatic disease at presentation. Most series have been using cisplatinum-based combination chemotherapy with good results. Over twenty years ago, the Indiana group first reported a 63% complete response rate with median duration of 18 months in 19 patients with disseminated seminoma treated with cisplatinum-based chemotherapy (98). Minimum follow-up was 1 year, and four patients were in complete remission for longer than 2 years. Roth and co-workers (308) treated 26 patients with disseminated seminoma; 14 survived for a median of 26.6 months. Lemarie and coworkers (204) reported that 12 of 13 patients treated experienced complete remission, with two recurrences after treatment. Cisplatinum-based combination therapy achieved a complete response in 3 of 5 patients treated by Giaccione (121). A recent collective review of 73 patients was undertaken by Hainsworth and Greco (140). All underwent chemotherapy with cisplatinum and various combinations of cyclophosphamide, vinblastine, bleomycin, or etoposide. Some patients also received radiation therapy. Complete responses to treatment were noted in 90% of the patients, and 88% were long-term disease-free survivors. With encouraging results, chemotherapy has been used as initial therapy in many series. In a non-randomized study from Memorial comparing initial therapies, 5 of 9 patients treated with initial radiation therapy remained disease free compared with 10 of 11 patients receiving initial chemotherapy (159).

Residual radiographic abnormalities after completing chemotherapy are not uncommon for patients with bulky mediastinal seminoma. The management of patients with residual radiographic abnormalities is still controversial. Studies have shown that these residual masses represent dense scirrhous reaction or necrotic tumors, rather than residual viable seminoma, in approximately 80% to 90% of patients (249,261,289,323). Residual teratomas are also rare. Others have shown a 25% incidence of residual viable seminoma in these patients treated with chemotherapy followed by resection of residual masses (323). Based on experience with bulky retroperitoneal involvement with seminoma from testicular primaries, most residual masses > 3cm in diameter harbored residual viable seminoma and all residual seminoma was found in masses > 3 cm. The authors recommended biopsy or resection of the residual masses if they were 3 cm or greater (147,49,323). Others recommend close follow up of these patients with early intervention if the mass enlarges on chest x-ray or CT scan, reserving radiotherapy or further chemotherapy for those patients who subsequently develop progressive disease (140,141,261,323).

Nonseminomatous Germ Cell Neoplasms

Local treatment with surgery or radiation therapy alone is inadequate for germ cell tumors with nonseminomatous histologies, which include choriocarcinoma, embryonal carcinoma, teratocarcinoma, endodermal sinus (yolk sac) tumors, and malignant teratoma. These tumors usually 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. Because of their great propensity for distant metastasis, the primary treatment for nonseminomatous malignant tumors is intensive cisplatinum-based combination chemotherapy, which often includes etoposide, bleomycin and/or ifosfamide, and radical resection if residual mass present (140,375,394). Patients with mediastinal nonseminomatous germ cell tumors (NSGCT) do not respond as well to chemotherapy as those with other extragonadal or testicular presentations to chemotherapy. They usually have bulky disease at presentation, relapse more frequently, and have a worse survival rate; complete remission rates of 50% to 70% are achieved in most series using modern chemotherapy regimens, however **(**93,121,141,204,261). The potential long-term disease free survival is approximately 40% (140). After 4 courses of chemotherapy, patients should then be restaged with serum tumor markers and CT scan of the chest and abdomen. Patients with negative tumor markers and negative CT scans following initial chemotherapy require no further treatment. Persistent elevation of serum tumor markers requires salvage chemotherapy (140). Patients who are serum tumor marker-negative but have radiographic evidence of residual disease are commonly seen. These patients should undergo surgical resection of residual disease 4 to 6 weeks after completion of chemotherapy (123,140,375). Complete resection should be attempted, as it can be associated with prolonged survival (375). Patients found to have residual viable germ cell tumor undergo two additional cycles of chemotherapy. Nichols 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 approximating 50% (261). Equivalent results are obtained in all histologic subtypes.

Reynolds and colleagues (298) reported an objective response of 53% (10 of 19 patients) in mediastinal germ cell tumors treated with combination chemotherapy; 2 patients had complete remission of disease. In a series of 32 patients with primary NSGCT treated with surgery and combination chemotherapy, 4 survived with relapse, although follow-up was short (179). Dulmet and co-workers (93) reported median survival times of 4.5 and 38.5 months in patients with mediastinal NSGCT treated without and with cisplatinum-based chemotherapy, respectively. However, Toner and associates (358) compared 50 patients with poor prognosis extragonadal nonseminomatous germ cell tumors with 99 patients with poor risk testicular primary site. They noted a worse outcome for patients with mediastinal NSGCT treated with aggressive cisplatinum- or carboplatinum-based chemotherapy, with an overall complete response rate of 38% and a very poor event-free median survival time of only 10 months. In a relatively large collective review of 175 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 39% were long-term disease-free survivors (140).

Patients with residual radiographic masses following treatment with normalization of tumor markers are frequently found to have either benign teratomas or necrotic non-viable tumors. Surgical resection of residual masses may prevent subsequent local regrowth or malignant degeneration of these tumors. If viable malignant

tumor cells are completely resected, two additional courses of cisplatinum-based chemotherapy may reduce the risk of relapse (111).

Approximately, 20% of the patients after completion of chemotherapy will relapse, usually within the first 24 months after the last course of chemotherapy. These patients have a very poor prognosis. The treatment of recurrent disease is difficult; standard salvage chemotherapy has not proven consistently beneficial, and few patients achieve remission. Motzer and associates report a 23% complete response rate using high-dose carboplatinum, etoposide, and cyclophosphamide, combined with autologous bone marrow transplantation, in cisplatinum-refractory germ cell tumors (250). Saxman and colleagues (316) reported only 7% long-term disease-free survival after salvage chemotherapy, including autologous bone marrow transplantation, for relapsed extragonadal NSGCT; 58% of patients had mediastinal primary tumors, confirming the need for new approaches in this disease.

Nonseminomatous germ cell tumors are sensitive to radiation. But the role of radiation therapy in NSGCT has not been defined and the optimal dose and fields of radiation therapy have not been established. In addition to palliation, because of the poor resectability rate and high incidence of residual masses after chemotherapy, radiation therapy has been used for this group of patients to improve local tumor control. However, depending on the amount of bone marrow treated, irradiation given before chemotherapy may adversely affects the patient's ability to tolerate full cytotoxic doses. Newlands and co-workers (260) noted a decreased survival rate among patients receiving radiation therapy compared with those not receiving irradiation for this reason (56% versus 82%, respectively). Kersh and associates (171) reported on 14 patients with NSGCT and noted that none achieved local control with radiation doses of 47.5 Gy or less. They believed that objections to the use of radiation therapy are no longer warranted because of the more limited fields and smaller amounts of marrow irradiation with modern techniques, and they suggested use of doses closer to those required for epithelial tumors. If radiation therapy is contemplated, however, its administration should probably be after maximal response to chemotherapy. If there is no evidence of metastatic disease, high doses of 60 Gy or more appear to be necessary to achieve better local control.

The treatment of benign mediastinal teratoma is complete surgical resection, which results in excellent long-term cure rates (93). In general, irradiation and chemotherapy play no role in the management of this tumor and limited published data shows no tumor response to either radiation therapy or chemotherapy (394). However, some investigators have suggested that the preservation of vital structures may be more important than the completeness of resection because incomplete resection of benign teratomas has not resulted in subsequent evidence of tumor recurrence (206). In general, resection of mature teratomas results in prolonged survival with no significant chance of recurrence (93,206). However, malignant transformation of the teratoma can occur and is often refractory to cisplatinum-based chemotherapy with a very poor prognosis (8,179). Immature teratomas are potentially malignant tumors. Their prognosis is influenced by the anatomic site of the tumor, patient age, and the immature fraction of the tumor (93). In patients younger than 15 years, immature teratomas behave

similarly to their mature counterparts. In patients 15 years of age and older, they may behave as highly malignant tumors. One recent study suggests that a combination cisplatinum, vinblastine sulfate, and bleomycin sulfate regimen may result in improved long-term survival in these patients (93).

Radiation Therapy Techniques

There are variations in the radiation doses and treatment techniques to treat mediastinal seminomas (19,45,64,108,152,363). A review of the literature indicates that doses ranging from 20 to 60 Gy have been used. Based on experience with testicular seminoma, some have suggested similar lower radiation doses may be adequate. However, Bush and colleagues (45) recommended higher doses because of the frequently bulky nature and, despite similar histology, also the difference in radiosensitivity of mediastinal seminomas. They noted no local failures with doses greater than 47 Gy. Others reported a 91% local tumor control rate with doses of 30 to 50 Gy (171). The one patient in their series with a local failure received 45 Gy and was declared not to be a geographic miss. Cox (73) analyzed the dose-time relationship in irradiation of germ cell tumors. Based on his data from Walter Reed and Massachusetts General Hospitals, he suggested that 30 Gy given in 15 fractions over 3 weeks is adequate. However, Kersh and colleagues (171) suggested doses of 30 to 45 Gy for control of local and regional disease and Bagshaw and colleagues (19) recommended 40 to 50 Gy in 4 to 4.5 weeks to the mediastinum and the supraclavicular lymph nodes. With regard to volume, the entire mediastinum should be treated. Uematsu and colleagues (363) found four of six patients treated with involved-field irradiation had marginal relapses, while none of the three patients treated with whole mediastinal irradiation relapsed, suggesting the efficacy of the whole mediastinal irradiation. Others recommended inclusion of lower cervical, infraclavicular, high abdominal, and para-aortic lymph nodes to cover sites of metastatic spread with minimal additional morbidity (45,97,152,317). In summary, 30 Gy in 15 fractions over 3 weeks may be adequate for small volume disease. For gross tumors, 40 Gy (1.8 to 2 Gy daily, 5 days a week) to the large field encompassing the mediastinum and both supraclavicular areas, followed by an additional 10 Gy with reduced portals to the gross tumor volume (visible on CT scan) is appropriate. 3-D conformal irradiation should be utilized to deliver the high dose portion. As functional imaging becomes better to delineate the true biological target volume (BTV), the treatment portal may exclude more uninvolved normal tissue in selected cases.

Results of Radiation Therapy

Data on mediastinal seminoma treated with primary radiation therapy are generally good. Local tumor control of 89% to 100% and long-term survivals of 50% to 80% have been reported in patients with localized mediastinal seminoma without evidence of metastatic disease treated with irradiation alone (15,45,73,144,261,363). A report on 13 patients who were treated with definitive megavoltage radiation therapy and had 5-year follow-up noted the actuarial 10-year survival rate to be 69%, and the relapse-free survival rate was 54% (45). Schantz and colleagues (317) found no recurrences in a subgroup of 11 patients who received

primary radiotherapy. Treatment results of mediastinal seminoma are shown in Table 19. Long-term survival rates ranged from 50% to 100%. Some of these results were in the prechemotherapy era when salvage therapy was less effective, although even metastatic disease has been reported to be cured with multiple courses of radiation therapy (317). Local control also is excellent and usually exceeds 90% (73,171,173,174).

For mediastinal NSGCT, results of combinations of chemotherapy, surgery, and radiation therapy are relatively poor in comparison to their testicular counterparts, with complete response rates of 38% to 81% and long-term survival rates of only 10% to 50% (140,169,171,204,358,395). In a multi-institutional retrospective review by Kersh and associates (171), no patient with mediastinal NSGCT had local control despite radiation doses of 30 to 47.5 Gy. A recent prospective SWOG study of 41 eligible patients with extragonadal germ cell tumors, who were treated with combination chemotherapy followed by surgical resection when appropriate, showed that the overall complete response rate for those with nonseminomatous extragonadal germ cell tumors was 77% (42).

In the 30 to 50 Gy range used for seminoma, late effects such as secondary malignancies, may be expected to be similar to those of patients with Hodgkin's disease treated with mediastinal irradiation (230,373). Side effects of chemotherapy for mediastinal NSGCT and relapsed seminoma may be significant (267,338). Significant neutropenia and thrombocytopenia occur with both standard and high-dose regimens (77% and 76%, respectively) (267). Nonhematologic toxicities include gastrointestinal sequelae (nausea, vomiting and esophagitis), severe hearing loss, disabling tinnitus, peripheral neuropathy, salt-losing nephropathy, deep venous thrombosis, and pulmonary embolus. Sepsis and death from treatment have been reported in up to 4% of patients (267).

## TRACHEAL TUMORS

The trachea is a long fibrocartilaginous tube whose connections are the larynx superiorly and the mainstem bronchi inferiorly. The esophagus, thyroid, parathyroids, and trachea are derived from the same outpouching of the embryonic foregut; the lungs arise from terminal tracheal buds. This embryology dictates the blood supply of the trachea: inferior thyroidal arteries supply the superior trachea while branches of the bronchial arteries (with contributions from the supreme intercostal, internal thoracic, innominate, and subclavian arteries) supply the inferior portion. These arteries course into the trachea from side-to-side. The average adult trachea is 11-12 cm in length and 2.0 cm (females) to 2.3 cm (males) in diameter. In cross-section, the organ is usually “C” or “U” shaped (239). The upper border lies around the 6th or 7th cervical vertebra; the lower border around the 4th (full expiration) or 6th (full inspiration) thoracic vertebra. There are approximately 2 cartilaginous rings per cm (155).

### Epidemiology

Primary tracheal tumors are rare; the incidence of primary laryngeal and lung cancer is likely 75 and 180 times greater, respectively (276). The estimated U.S. incidence is 0.1 to 0.2 per 100 000, and over 90% are

malignant (280). Adenoid cystic carcinoma (formerly known as cylindroma) is often mentioned as the most common tracheal neoplasm, yet it appears the most common histology worldwide is actually squamous cell carcinoma (60-90%) (208,398). Males are more commonly affected than females if the histology is squamous (2-3:1). Male to female ratio seems equal regarding adenoid cystic carcinoma (232). With squamous cell variants, the usual presenting age is the sixth decade of life; adenoid cystic carcinomas appear to present at a younger age. Other various histologies found in primary tracheal neoplasms include carcinoid, carcinosarcoma, granular cell tumor, hemangioma, chondroma, and chondrosarcoma (281). Neurogenic tumors of the trachea have been described (356). Data as to the contributing factors for the development of these neoplasms is non-existent. Many assume, however, that tobacco use leads to squamous cell carcinoma of the trachea just as it does to other squamous cell carcinomas of the upper aerodigestive tract. It is unclear though why lung and laryngeal/pharyngeal neoplasms are so remarkably more common given that the trachea obviously facilitates passage of inhaled carcinogens between these two sites.

Other primary sites can metastasize to the trachea or invade it directly (lung and esophageal cancers being the most likely culprits here), but the majority of tracheal neoplasms are primary in nature (280). This section will focus on the presentation and management of primary tracheal neoplasms alone.

Natural History and Presenting Symptoms

The clinical presentation of these tumors is varied. For adenoid cystic carcinoma especially, asthma is the first diagnosis and these patients are treated as such for months until the "refractory" COPD is evaluated further with bronchoscopy (after numerous normal chest X-rays) (398). Hempotysis is far more common in squamous cell carcinoma, thus bringing these patients to diagnosis sooner. Dysphagia is sometimes seen and has been noted to be ominous; interestingly, however, tracheoesophageal fistula is seldom mentioned as a presenting comorbidity for primary tracheal neoplasms.

Adenoid cystic carcinomas are diagnosed often with synchronous metastases (20-40%) (208,281). The survival course is relatively prolonged, however, even in the face of distant metastases; in one series median survival for these patients was 37 months (232). The median survival for all from time of diagnosis is probably 5 years (398). These lesions have an indolent course yet are not easily locally controlled. When tumor spread occurs, it is almost always distant rather than to locoregional lymph nodes. Failure after treatment is usually local, and recurrences 10 or more years after treatment are not uncommon.

In contrast to adenoid cystic carcinoma, squamous cell carcinoma (the most common tumor of the trachea) has a more aggressive course. Median survival times range from 6-12 months and are quite dependent on whether or not the primary lesion is resected (208,295,398). These tumors spread to local lymph nodes (approximately 30% at presentation) and 10-20% will have distant metastases at presentation.

For other pathologic variants, the clinical course and natural history are variable. Adenocarcinoma and sarcomas behave poorly. Histologies such as granular cell tumor, carcinoid, lymphoma, leiomyoma, and small cell

carcinoma have a variable prognosis yet seem to behave better than the squamous carcinomas, adenocarcinomas, or sarcomas.

Staging and Prognostic Factors

No universally accepted system for staging tracheal neoplasms has been adopted. A staging system proposed by Licht et al (208) seemed not to have any predictable prognostic value (patients with positive nodes fared better than those without). Studies examining the lymph node question have found no statistically significant adverse prognostic association (131,208,295,398). Size and location of tumor seem to be important prognostically: this feature probably represents the extent of surgical resection necessary to remove the tumor and those carinal resection patients have heightened postoperative mortality (131). Acute respiratory compromise or distant metastases at presentation—regardless of histology—are predictors of poor outcome (398). As mentioned earlier, adenoid cystic carcinoma (and probably lymphoma) has a better prognosis than any other histologic variants.

Management and Work-up

Eventually all of these patients need a bronchoscopy. In some cases of acute respiratory compromise, rigid bronchoscopy is indicated so that a "coring out" of the tracheal neoplasm can be accomplished along with the biopsy (133). In a series from Boston, of 56 patients rigidly bronchoscoped airway improvement was seen in 90% and easily controlled bleeding present in 5% (229). An esophagoscopy should be done in all patients to rule out esophageal invasion. CT scan of the chest is indicated to help evaluate the full extent of tumor and aid in determining the presence of pathologically involved lymph nodes. Given the significant rate of synchronous metastases with primary tracheal neoplasms (and that most of these are to the lungs), a chest CT scan is important for staging purposes as well.

Treatment and Results

It is clear that patients who can be resected have better prognosis than those who can not, prompting the recommendation of surgical resection for most tracheal primary tumors. Resection rates vary widely, from around 75% at Massachusetts General Hospital under Grillo's supervision to 7% for all patients treated in Denmark from 1978-95 (131,208). Perhaps too many patients are deemed "unresectable" at the time of diagnosis due simply to tumor location (trachea) and/or institutional surgical inexperience with handling such lesions. For example, some recommend tracheal resection for select patients with adenoid cystic carcinoma with low-burden pulmonary metastases (the pulmonary metastases can behave indolently) yet many would consider a patient such as this unresectable (232). Surely a selection bias is present at centers with low (and high) resectability rates, but unduly low resection rates can not be explained by selection biases alone: surgical therapy nihilism might be thwarting more appropriate treatment for some patients (208).

From the radiation oncologist's perspective, what is important to keep in mind is that the thoracic surgeon pays utmost attention to maintaining the integrity of the tracheal repair—rightfully sometimes at the expense of obtaining adequate surgical margins (yet a tracheal prosthesis is an option in certain circumstances). Advances in thoracic surgical procedures—full mobilization of the right hilar ligament, detachment/implantation of the left hilum, mobilization of the cervical trachea, carinal resection techniques, intrapericardial dissection techniques—do not always mean a negative or solely microscopically positive margin can always be obtained (129,130,397). Furthermore (especially with adenoid cystic carcinoma), submucosal or perineural spread of tumor make negative resection margins less likely.

Resection techniques have been described in the literature. Most of these patients will receive a median sternotomy and cervical collar excision. Primary anastomosis is the reconstruction of choice, yet a minority will require some form of artificial tracheal prosthesis (232). Those with extensive subglottic or high tracheal disease may require cervical exenteration and a mediastinal tracheostomy (132).

If resection is attempted, absolute indications for adjuvant radiation therapy (RT) are unclear. A reasonable argument can be made that all resected patients (regardless of tumor burden, margin status, histology, or nodal status) need irradiation. It is the policy at the Massachusetts General Hospital that almost all patients with tracheal primary tumors receive postoperative irradiation (due to the low number of resected patients who did not receive post-op RT no retrospective comparison has been done). Regnand et al (295) found that 31 patients who had a complete resection with adjuvant radiation therapy had a better 5-year survival than 27 patients without postoperative RT did (74% vs. 53%, p=NS). The M.D. Anderson group noted that resection plus RT patients had a median survival of 61 months versus 16 months for those who received surgery alone (resection status unknown) (59). The Regnand study showed that post-op RT was even more effective for incompletely resected patients (5-year survival, 45% vs. 0%, $p<0.05$) (295). Representative data for patients undergoing resection are presented in Table 20. Preoperative RT has been attempted for some patients, yet the most compelling evidence for adjuvant RT comes from postoperative cases. For patients who have a tracheal prosthesis reconstruction (which is rare), postoperative RT seems risky; there are no clear indications in the literature as to the outcome of these patients post-irradiation or if doses have been tempered in this setting.

Retrospective data exists supporting the use of external beam radiation therapy (EBRT) alone. The best results with the most patient numbers have come from studies where doses greater than 60 Gy have been given. There seems to be a dose-response relationship for tracheal neoplasms. Chow et al (59) caution against doses higher than 60 Gy, as 3/6 patients with doses >60 Gy in this study had severe complications requiring surgical intervention (tracheoesophageal fistula, esophageal stricture, and severe tracheal crusting); none of the patients treated with doses <60 Gy (0/6) had late side effects. Increased dose also led to more complications in the another study (128). Fuwa et al (115) (whose group developed an endoluminal-centering catheter) report one treatment related death for a patient one year after therapy (113 Gy total dose); median cumulative dose for the group (EBRT + LDR Ir-192) was 91 Gy. Schraube and colleagues report an excellent median survival time (31

months) for the squamous cell carcinoma patients they treated using EBRT and an intraluminal HDR boost (322). Data summarizing select radiotherapy-alone experiences in primary tracheal neoplasms are given in Table 21.

Combined chemoradiotherapy (without resection) has been tried at some institutions (mostly for lymphomas, small cell carcinomas, or squamous cell carcinomas), but the utility of combined modality treatment is uncertain at best. The few patients presented in the literature with squamous cell carcinoma have fared poorly; those with small cell carcinoma or lymphoma have had relatively prolonged survival (13-67 months) (208,398).

Radiotherapy Techniques

For resected patients, 4-6 weeks of healing time should be allowed before beginning postoperative radiation therapy. Modern CT-based, 3-D conformal radiotherapy or intensity-modulated radiotherapy should theoretically allow higher, safer doses to be given to the trachea. All patients with this tumor—in either the postoperative or definitive setting—should be treated with 3-D conformal techniques. Because local tumor control has such a profound effect on quality of life and probably prolongation of survival in this patient population, we also recommend 3-D conformal techniques (along with doses in the 60 Gy range if possible) be used on intermediate to good performance status patients referred for palliation. Doses to less than 40 Gy have yielded abysmal partial tumor control rates; higher doses necessitate precise planning. For postoperative cases, experiences seem to indicate that doses of 50-60 Gy should be employed. Doses of >60 Gy have yielded the best results but with some indication of increased complications in definitive cases. An intraluminal boost technique after EBRT may decrease late side effects (115,220,322). In patients with extensive mediastinal and/or tracheal replacement by tumor, esophageal involvement (even in light of a normal EGD) may be a possibility; tracheoesophageal fistula after radical doses of radiation would be of concern here. For the emergent airway case, thoracic surgery intervention (with rigid bronchoscopy) should be sought instead of urgent radiotherapy.

Respect for nearby dose limiting structures (spinal cord, lung, heart, and esophagus) will dictate the radiation therapy plan. The preoperative tumor volume should be covered with adequate margin (1-2 cm), and a greater superior/inferior extent of volume may need to be in the field with adenoid cystic carcinoma given its submucosal-spreading/perineural-invading behavior. (Even so, adenoid cystic carcinomas notoriously recur at the anastomosis.)

The role of elective nodal irradiation for tracheal carcinoma is uncertain. As mentioned earlier, nodal status has not been found to be of clear prognostic significance; even cervical adenopathy was not associated with poorer outcome in a Japanese series (131,208,398). No series clearly outline what nodal regions were or were not treated. Given the low proclivity for adenoid cystic carcinomas to spread to lymph nodes, elimination of elective nodal irradiation is certainly reasonable for this variant. In addition, long-term, ten-plus-years survivors of adenoid cystic carcinoma are not unusual: the late effects of 45-50 Gy to the entire mediastinum and supraclavicular region (to cover the trachea and nodes) for these patients have to be factored into their

management. With most studies showing death occurring in the setting of a local recurrence (regardless of the histology), it would seem engaging in elective nodal irradiation would do little to change survival rates. Yet if mediastinal or cervical nodes are discovered at surgery or by CT, radiation therapy to these regions is likely warranted and must be considered.

## MEDIASTINAL MESENCHYMAL TUMORS

### Epidemiology

True mediastinal mesenchymal lesions (MMLs) are rare. Retrospective analyses show mesenchymal tumors comprise 2-8% of all mediastinal lesions; this places the estimated U.S. incidence at approximately 0.1 to 0.2 per million (81,82,376). Almost three-fourths will be of lipomatous, lymphangitic, or vascular origin. The remainder is somewhat equally divided among the other histologic variants. (For a complete list of tumor pathologies making up the mediastinal mesenchymal spectrum, refer to Table 22.) There has not been shown to be any clear gender predilection for MMLs. Age at presentation is dependent upon the pathologic variant (217,275).

### Clinical Presentation and Work-up

MMLs can occur in any of the three main compartments of the mediastinum, but the anterosuperior mediastinum seems least commonly involved (351). The outcome for these tumors is variable: patients with malignant-behaving lesions have been shown to have shorter survival times than those with benign-behaving lesions (approximately half of all MMLs are malignant at presentation) (217,275). For mediastinally-located tumors in general, malignancy is more frequently encountered in the pediatric population (252).

MMLs are often silent until reaching quite a large size. Presenting symptoms can vary widely, yet chest pain and dyspnea are the most commonly mentioned complaints in symptomatic patients. Proportionally more patients are symptomatic with malignant MMLs than those with benign tumors (80% malignant patients symptomatic vs. 44% benign patients symptomatic in the Duke series) (81).

The size and location of the tumor must be adequately illustrated first via either CT scan or MRI of the chest. Other radiographic studies (such as PET or SPECT scan) will not yield as much useful information. The histopathology of the lesion must be identified. This can be accomplished via mediastinoscopic biopsy, FNA (usually CT-guided), or bronchoscopic or esophagoscopic sampling (154). The resectability of the lesion can then be properly ascertained. After the diagnostic workup is complete, staging via AJCC recommendations for soft tissue tumors can be applied, but in actual practice this is seldom done owing to the rarity of these lesions.

### Tumors of Adipose Tissue

Mediastinal lipomas are the most common mediastinal mesenchymal lesion; they comprise only 1-5% of all lipomas (an extremity being the most common anatomic locale) (7,29,78,146,252). They can occur singly or multiply in the mediastinum and can simulate cardiomegaly or pleural effusion on chest X-ray. They are

usually well circumscribed and encapsulated but can grow to be quite large: lesions greater than 20 cm and 4 kg in size have been described (170). Surgery is almost always curative for these patients, and they are rarely seen intrathoracically (367,377).

In contrast, liposarcoma consists of immature fat cells as well yet is malignant. Prognosis may be related to the presence or absence of psuedoencapsulation: the few patients with well-circumscribed lesions in a review by Standerfer et al (337) had survivals of 3 to 17 years, whereas patients with non-encapsulated tumors all died within 2 years. Liposarcoma outcome also hinges greatly on the grade of the lesion (400). Optimal treatment probably consists of surgery and postoperative radiation therapy even completely resected, negative-margin cases. In Standerfer's review, 2 patients received postoperative RT: one remained disease-free, while rapid tumor growth and ensuing death 2 months later occurred in the other (337). Well-differentiated tumors have little propensity for distant metastases yet still have a tendency towards local recurrence (20-30%) (178,400).

Tumors of Lymph Tissue

Tumors arising from the vascular or lymphatic components of the mediastinum make up the bulk of the remaining MMLs (275). Pathologically, lymphangiomas and hemangiomas will look identical under the microscope (hence there being some debate about the true cell of origin) and can only be differentiated by the presence of red blood cells or chyle within tumor lumen (377). The pure mediastinal lymphangioma is rare, however: over 90% will have some degree of cervical extension (343). Lymphangiomatosis is usually seen in children and is characterized by widespread lymphangiomas; mediastinal or pulmonary involvement carries a poor prognosis (377). Lymphangiomyomatosis (formerly known as lymphangiopericytoma) is a very rare condition seen only in females of reproductive age characterized by the proliferation of smooth muscle and lymphatic tissue in mediastinal lymph nodes, lung, or retroperitoneum; the disease may in fact be a form of tuberous sclerosis (74,160,366). Lymphangiosarcoma is a malignant variant of lymphangioma. Whether or not there occurs malignant transformation of lymphangioma into lymphangiosarcoma for MMLs is unknown (60). Treatment for all MMLs of lymph tissue involves surgery when possible. The role for postoperative irradiation is unclear given previous unimpressive results (in fact, malignant transformation of benign lymphangioma into malignant lymphangiosarcoma after RT has been described.) (82,176) However, when these tumors are unresectable and/or causing significant symptoms, palliative treatment can be considered. Chemotherapy may play a role in unresectable lymphangiosarcoma (37). Johnson et al (165) describe a young patient with surgically refractory chylothorax and lymphangioma who had prompt resolution after 20 Gy in 10 fractions of mediastinal irradiation. Based upon their experience, Kandil et al (167) recommend radiation therapy for large, unresectable lymphangiomas and cite a local control of 100% (n=3). The addition of radiation therapy for symptomatic lymphangiomyomatosis has been effective, as well, yet progesterone therapy should be attempted first (234,392).

Tumors of Vascular Tissue

The vascular or endothelially-derived MMLs consist of the hemangiomas, hemangioendotheliomas, and hemangiopericytomas. These tumors can behave indolently, but hemangiopericytomas have a high rate of metastasis (approximately 50% at presentation) (236). Hemangiomas may be capillary or cavernous. The cavernous hemangiomas (also known as angiomyomas or hamartomatous hemangiomas) are distinguished from capillary hemangiomas by the presence of smooth muscle. The biological behavior is similar for the two, however (275). Hemangiomas and hemangioendotheliomas are well circumscribed, but the hemangioendotheliomas contain cytoplasmic Weibel-Palade bodies (characteristic of endothelial cells) and are not encapsulated (377).

Hemangiopericytomas arise from the capillary contractile pericytes of Zimmerman (325). They can behave non-aggressively, but distant metastases years after local resection can occur. Retrospective reviews indicate that lesions with high mitotic rates or increased proliferative indices are at increased risk for both distant metastases and local recurrences (107,236). However, isolated reports exist of long-term survivors after radiotherapeutic palliation (and subsequent disappearance) of metastatic lesions (92).

Surgery is the mainstay of therapy and is generally curative. When subtotal excision occurs, there is no evidence for postoperative radiation therapy for hemangiomas or hemangioendotheliomas (65) and it should be considered, however, for incompletely resected hemangiopericytomas or for completely resected high-grade lesions.

### Miscellaneous MMLs

Various other MMLs have been encountered, albeit very rarely. Extramedullary hematopoesis (usually in the setting of thalassemia) occurring within the mediastinum has been described. These patients seem to have been well-served by combinations of irradiation (usually 20 Gy in 10-20 fractions) and erythropoetin (necessary to stimulate marrow erythropoesis once the chest source for precursor red blood cells has been ablated) (61,124). The remainder of the miscellaneous MMLs falls into the skeletal/muscle/connective tissue categories, and most seem to arise in the posterior mediastinum. It would appear from the very few patients presented in the literature that the routine treatment has been surgical excision and postoperative radiation therapy (272,275,347,348); no meaningful discussions of doses used or volumes treated have been given. Approximately half of the patients survive long-term after surgery and postoperative radiation therapy; all others usually succumb to distant metastases.

## MEDIASTINAL NEUROGENIC TUMORS

### Epidemiology

The posterior mediastinum is the site of most neurogenic tumors of the thorax, which arise from peripheral nerves, sympathetic ganglia, or the mediastinal chemoreceptors. They comprise 20-40% of all mediastinal neoplasms, are the most common cause of a posterior mediastinal mass, and account for 75-90% of

all posterior mediastinal neoplasms (16,57,81,359). Their estimated incidence is 0.5 per million in adults (81). Neuroblastoma is the most aggressive of the mediastinal neurogenic tumors (MNTs) and occurs far more commonly in children than in adults. It is the most common extracranial malignant solid tumor of childhood involving one per 10 000 live births with an approximately 1 per 100 000 U.S. incidence (101,102). Children less than 5 years old account for 90% of all neuroblastomas; half occur in children less than 2 years old (377). Approximately 20% of the neuroblastomas will occur in the posterior mediastinal region; as such, neuroblastoma of the mediastinum is the most common tumor of this anatomic locale, and children suffer malignant MNTs at a higher incidence than adults (26,80,84,191). However, thoracic neuroblastoma portends a more favorable outcome than abdominal neuroblastoma. Neuroblastoma is somewhat more common in males and Caucasians (approximately 1.2-1.3:1 ratio). For MNTs in general, however, there is no clear gender predilection (209,293). Benign schwannomas and neurofibromas comprise the majority of MNTs in adults, while neuroblastoma and neurofibromatosis (in the setting of von Recklinghausen's disease) make up the majority of the pediatric lesions. Table 23 lists all commonly encountered MNTs.

Natural History and General Management

The natural history and management of these tumors are varied. Due to the relatively higher incidence of malignancy in the pediatric population, prognosis for this age group is somewhat poorer than that for adults. The most common presentation is not that of a symptomatic patient but rather of a suspicious mass on routine chest X-ray (117,293). When patients are symptomatic, lesions are usually sizable or metabolically active. Compression causing pain and nerve dysfunction or systemic complaints are then not uncommon. A roëntgenographic clue as to the malignancy of these tumors is that benign lesions usually appear circumscribed and spherical on imaging exams while more aggressive pathologies appear elongated with tapering edges (304). The clinical outcome of MNTs is dependent upon the age of the patient, which is closely related to the histology of the lesion (135). The very young (neuroblastoma patients less than 1 year of age) with mediastinal lesions do almost uniformly well with long-term survivors the rule (313). Long-term survivors occur 60-80% of the time in pediatric (older than 1 year) MNT patient, with histology greatly affecting outcome here (34,313). Patients with von Recklinghausen's disease (neurofibromatosis type I, NF-1) account for 5-10% of all MNTs. They have increased incidences of malignant nerve sheath tumors and hence poorer prognoses overall (277). Adults have a good outlook: with most MNTs being benign for this cohort, local control and long-term survivors number in the 90-plus percent range (9). This can decrease to 30-50% when malignant lesions are encountered, however (393).

Management for patients with MNTs entails multimodality, multidisciplinary approach. After routine chemistries (including assessment of urine or serum catecholamines in the patient with idiopathic hypertension) and chest X-rays have been obtained, CT scan of the lesion should then be performed. If by CT there is any equivocality about intraspinal extension of tumor, an MRI of the area should be performed (294). The intraspinal, so-called "dumbbell" tumor is encountered in approximately 10% of all these patients (6). The

presence or absence of this lesion, occurring when tumor contents invade through the intervertebral foramina into the spinal canal (with the "blobs" of tissue intrathoracically and intraspinally constituting the two ends of the dumbbell), must be determined preoperatively so that the proper surgical procedure can be planned. Any of the histologic variants can present in this manner. Akwari et al (6) were early champions of the combined (rather than two-stage) neurosurgical/thoracic surgery approach to these patients. They summarized their experience on 706 patients and found dumbbell tumors in 69. Finding significant rates of paraplegia (usually permanent) in the patients who had thoracic tumor removed in one sitting and spinal tumor at another, they strongly advised against this. Other thoracic surgeons have found similar results and made the similar suggestion (399). Dumbbell tumors, once resected, do not appear to behave any more poorly than non-dumbbell tumors.

In the past most patients with MNTs received thoracotomies, yet thoracoscopic resections can be achieved easily and quickly for most patients with MNTs with shorter hospital stays (209). Resection rates vary. The benign lesions seem to have a very high resectability rate at presentation, approximately 90-95% (209,299,401). For malignant lesions, gross total resection is achievable for 55-80% of all cases (185,299,393). Once surgery is complete, adjuvant treatment with radiation and/or polychemotherapy can be delivered but is not necessary for benign lesions totally resected. Radiochemotherapy alone can be attempted with some success for unresectable malignant lesions.

Schwannomas

Schwannomas (neurilemomas) are the most common MNTs in adults. They are usually well encapsulated; intimate nerve association is usually seen at the time of surgery. Compared with non-mediastinal schwannomas, they can reach a very large size (377). Histologically, pathologists have classically described Antoni A (hypercellular, compact areas with Verocay bodies) or Antoni B areas (hypocellular areas); immunohistochemical analysis reveals S-100 positivity and helps to differentiate these tumors from other malignancies that look similar under the microscope (305). Melanocytic schwannomas are uncommonly encountered and behave no more aggressively than their non-pigmented counterparts. The degree of Antoni A or B patterns within the tumor will determine CT appearance and enhancement but, when large, schwannomas will usually demonstrate central hemorrhage (201). Resection can be completed for almost all patients and long-term local control ranges from 90-100% (9,209,277,360). When resection is incomplete, there exists no evidence for adjuvant radiotherapy. However, if tumor regrowth occurs (rare) after excision and reoperation is necessary, postoperative radiation therapy may be considered.

Neurofibromas

Neurofibroma occurs as a soft, non-encapsulated tumor. Isolated neurofibroma can be easily resected and almost never recurs. Malignant transformation of an isolated neurofibroma is rare. Multiple neurofibromas occur in NF-1. Patients with 6 or more café-au-lait spots 1.5 cm or more in diameter are diagnosed as having NF-1; a plexiform (long, thick, "bag of worms" mass) neurofibroma is pathognomonic for NF-1. Long-standing

neurofibromatosis almost always induces a malignant peripheral nerve sheath tumor, and malignant peripheral nerve sheath tumors are more aggressive in NF-1 (221). Surgical intervention in NF-1 is often necessary in the pediatric population, especially when malignant transformation occurs; all rapidly-growing lesions in patients with NF-1 should be biopsied and aggressive treatment instituted if a malignant lesion is found (259).

Malignant Peripheral Nerve Sheath Tumors

Malignant schwannomas (neurofibrosarcomas), or more properly malignant peripheral nerve sheath tumors (MPNSTs), can occur in the mediastinum and are the most common malignant tumors of this location in adults. Their morphologic manifestation is usually that of a fusiform mass 5 cm or greater in diameter. Histologically they may appear low grade or anaplastically malignant, yet the usual clinical course is that of aggression (221). Most patients present symptomatically, with systemic manifestations such as the Leser-Trelat sign (the sudden or eruptive appearance or increase in size of multiple seborrhea keratoses) occurring occasionally (335). Preexisting NF-1 may account for 10-25% of all patients, and a history of prior irradiation plays a definite role, as well (30,88,393,340). Radiographically, bony destruction is a not uncommon finding (201). Distant metastases can be seen in up to 30% at the time of presentation (340).

Best analysis thus far of prognostic factors and treatment outcomes incorporating radiation therapy for MPNSTs comes from Wong et al (393). Their series included 134 patients treated at the Mayo Clinic between 1975 and 1993. Of these, 25 patients had mediastinal MPNSTs. Male to female ratio was 1.6:1. Eight percent had distant metastases at the time of initial presentation. A gross total resection was achieved in 83% of the patients; chest tumors had the second-highest likelihood of positive margins. (In contrast, Kruger et al (185) noted a 55% gross total resection rate for mediastinally located MPNSTs). A variety of radiation therapy techniques were used; 54% received adjuvant RT, most getting a mean dose of 51 Gy postoperatively (intraoperative radiotherapy and brachytherapy were employed for 12% and 10% respectively). Overall survival and local tumor tumor control (LC) was 42% and 50% at 10 years, which appears somewhat better than the isolated other, small-patient-number retrospective reviews. Having a lesion in a non-extremity site vs. extremity site tended toward poorer 5-yr survival in univariate analysis (43% vs 70%, p=0.006). Patients with negative margins had a 67% 5-yr LC rate vs. 23% for those with positive resection margins (p=0.003). In multivariate analyses of local tumor control, only surgical margin, radiation dose (60 Gy or more), or use of IORT/brachytherapy were found to be of statistical significance. With doses greater than 60 Gy, 73% 5-yr LC was achieved (vs. 50% without); for patients receiving IORT/brachytherapy, an 88% 5-yr LC was seen (vs. 51% without). For risk of distant relapse, only histology (perineural) and grade were found to be of significance in multivariate analyses. The radiation technique usually entailed the primary site with 3-5 cm of margin (smaller margins in the non-extremity sites); no attempt was made to cover nodal drainage sites. Analysis of margin size on local tumor control or survival was not attempted.

When MPNSTs are unresectable, chemoradiation may be attempted. The most active chemotherapeutic agent seems to be doxorubicin (40). However, given the quite poor outcomes of positive-margin surgery (and adjuvant RT) versus that of negative-margin surgery when tumor can be resected, every effort should be made to afford the patient an operation when possible.

Other tumors of probable nerve sheath origin, including the melanocytic malignant schwannoma and Askin's tumor, behave quite aggressively with similar tendencies towards local recurrence and distant metastases. The Askin's tumor is a relatively recently described disease entity and shares some ultrastructural and chromosomal similarities with Ewing's sarcoma and neuroblastoma; most clinicians feel it to be a Ewing's sarcoma variant, however (13,116). A report from Miser et al (238) indicated success with very aggressive therapy (induction chemotherapy with local control via surgery/XRT followed by bone marrow transplantation) above what had been previously reported. Historically, median survival for Askin's tumor is in the range of 6-8 months, yet the few patients presented as having undergone intensive treatment seem to fare better than this (approximately 50% 4-year overall survival and >70% local control) (18).

The granular cell tumor arises from a cell of unknown true origin (yet probably arises from the Schwann cell). The lesion usually behaves indolently and rarely metastasizes. Surgical resection is curative (377).

Tumors of Autonomic Ganglia and Paraganglia

Ganglioneuromas occur most commonly in children with few cases beyond the third or fourth decade of life. Of all the MNTs, these are the least likely to present in a dumbbell configuration (221). Aggressive neuroblastomas can occasionally mature into benign ganglioneuromas (237). As compared to neuroblastoma, ganglioneuromas present at an older age (79 mos vs. 16 mos in one study), have much lower rates of N-myc amplification, and may occur more commonly in thoracic or non-adrenal sites (120). Ganglioneuromas may demonstrate lymph node "metastases"; these may not be metastases at all but rather nearby nests of matured neuroblastoma (305). The presence of lymph nodes does not affect outcome, making it difficult to stage these tumors with ganglioneuroblastoma or neuroblastoma. Treatment is surgical excision, which seems to be curative even in cases of macroscopic residual disease (120). Most will survive long-term.

The ganglioneuroblastomas represent the "next step up" in malignancy within this subgroup of MNTs, yet its prognosis is still more favorable overall than that of neuroblastoma (187). These lesions can occur intraspinally and are more common in children less than three years of age. They may occasionally secrete vasoactive substances (10-15% of the time), and urinary analysis for catecholamines should be done for any of the autonomic ganglia-derived tumors. (When elevation is noted a CT scan of the abdomen should be done to rule out metastatic neuroblastoma from the adrenals.) (2) There does not seem to be any tendency for ganglioneuroblastoma to occur at a less advanced stage, with a differing age presentation, or with a more favorable histology than neuroblastoma, but survival is significantly better (60-70% vs 30-40% 5-year) (2,187). Thoracic ganglioneuroblastomas may behave even better yet. Neuroblastoma is discussed more in-depth in

chapter 80. Treatment based on stage for ganglioneuroblastoma and neuroblastoma is similar. A new system for staging neuroblastomas and ganglioneuroblastomas was proposed in 1996 by Kushner et al (191) to help guide therapy, and this has been expounded upon by International Neuroblastoma Staging System working committee. A staging schema that can be applied to mediastinal ganglioneuroblastoma and neuroblastoma is included in the chapter (50,191).

Mediastinal neuroblastoma seems to have a biology different from that of abdominal neuroblastoma (a significantly much less incidence of N-myc amplification occurs in these tumors than abdominal neuroblastoma), and 5-year survivals are higher even after corrections for age and stage are made (3,247,319,333,368). Treatment for neuroblastoma varies by stage, and the use of radiation therapy in the treatment of neuroblastoma has undergone change as knowledge of the disease process has grown. Little evidence exists for irradiation in limited disease (stage I or IIA), which has been adequately surgically removed. With better and more effective chemotherapeutic agents, what once used to be the standard of care (chemoradiotherapy) in regionally advanced disease (stages IIB-III) is now perhaps chemotherapy alone with radiation therapy held in reserve for select cases. Yet recent articles seems to suggest a benefit to trimodality therapy for select subsets (stage IV or high-risk stage III patients) (391). One report, containing one patient with a mediastinal neuroblastoma, showed benefit to IORT for high-risk patients (137). Hyperfractionation may prove useful, as well (192). For advanced mediastinal disease that is either recurrent or grossly residual after chemotherapy, doses in the range of 30 Gy have been employed in relatively small fraction sizes, usually 1.5 Gy (51). Radiation therapy can be effective in palliation, and low-dose XRT (4.5 Gy in 3 fractions) may be necessary in the occasional infant with stage IV-S disease and respiratory compromise due to extensive mediastinal or abdominal involvement (268). Consideration of total dose for any radiotherapeutic regimen must be carefully thought out, however, in case total body irradiation for bone marrow transplant occurs later on in the patient's course and because of the late effects of irradiation in children.

In the setting of a mediastinal dumbbell tumor compressing the spinal cord, patients can be adequately served without RT. This is especially desirable for very young patients. In a series by De Benardi et al (41) involving 26 patients with intraspinal neuroblastomas (18 of which had mediastinal tumors), 3 received EBRT as a component of their treatment with the rest being managed by chemotherapy and/or laminectomy alone. Functional outcome was lower in patients who had laminectomies yet there was a significant reversal of neurological deficits for patients; 12 total had resolution (9 with laminectomies and 3 with chemotherapy). Two case reports from Sweden indicate spontaneous regression of mediastinal, intraspinal neuroblastoma 2 weeks after the thoracic portion was debulked (189). With laminectomy and/or chemotherapy, a similar-type experience (without radiotherapy) was seen in an Institute Gustave-Roussy review (287). A primary medical (rather than surgical) approach is now being investigated for intraspinal neuroblastoma patients to evaluate the utility of chemotherapy alone for these patients. As such, radiotherapy for the infant or young child with a dumbbell ganglioneuroblastoma or neuroblastoma causing spinal cord compression is not routinely advised.

Paraganglioma (chemodectoma, “mediastinal pheochromocytoma”) MNTs have been described. Surgery is the usual management. These lesions can behave somewhat unpredictably, and lesions with no propensity for local aggressiveness or distant metastases seem to look exactly the same microscopically as malignant tumors (243). Management always begins with surgery if possible, with pre- and intraoperative cardiovascular maintenance being of the utmost import for functioning, endocrinologically active paragangliomas (290). There may exist certain instances of tumor location making resection unpalatable. In these cases, radical radiotherapy has been attempted. Experience with mediastinal paragangliomas is limited, but head and neck experience indicates that 70-80% long-term local control may be obtained with doses in the 45-50 Gy range (289). Surgical experiences with mediastinal paragangliomas indicate an approximate 70% long-term survivorship. For advanced or metastatic cases, the disease may show platinum-based chemotherapy sensitivity (270).

## SEQUELAE OF TREATMENT OF MEDIASTINAL TUMORS

The spinal cord, lung, esophagus, and heart are the dose-limiting normal structures in the thorax. Early (acute) sequelae of thoracic irradiation include fatigue, dysphagia, cough, chest tightness, and mild skin reaction. However, late sequelae of irradiation for thymoma are unusual. Reported sequelae include radiation pneumonitis, pericarditis, and, rarely, myelitis (285). Exposure of normal lung to ionizing radiation has had two well-recognized adverse sequelae: pneumonitis and pulmonary fibrosis (251). Clinical pneumonitis occurs in about 10% of cases treated for lung cancer and is less frequent for patients with mediastinal tumors. The influence of treatment factors related to pneumonitis remains unclear, but dose, volume, and fractionation have all been implicated (46,251,301,310).

Radiation myelitis is a dreaded complication of exceeding the dose threshold for the spinal cord. In general, a dose of 45 Gy at standard fractionation (1.8-2 Gy) to no more than 10 cm of the spinal cord is safe, although some suggest that the cervical cord can receive doses of 54-55 Gy, without serious neurologic sequelae (1,199,222,286). A report from Kyoto noted no instances of thoracic radiation myelopathy following a dose of 50.4 Gy given via a hyperfractionated (1.2 Gy B.I.D.) approach (164). In the study reported by Marks and colleagues (224), one patient died of myelitis; tumor dose was stated to be 40 Gy, but the spinal cord dose to a 20-cm segment was 43.4 Gy because of the technique used. One portal was treated each day.

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TABLES

Table 1. Structures within the mediastinum

| Anterior Mediastinum | Middle Mediastinum | Posterior Mediastinum |
|---|---|---|
| Thymus gland | Pericardium | Sympathetic chain ganglia |
| Internal mammary vein | Heart and proximal great vessels | Vagus nerve |
| Superior vena cava | Innominate artery and vein | Thoracic duct |
| Aortic arch, great vessels | Pulmonary vessels | Descending thoracic aorta |
| Lymph nodes, lymphatics | Phrenic nerves | Esophagus |
| Adipose tissue | Trachea, mainstem bronchi | Azygous/hemiazygous veins |
| Thyroid, Parathyroid (if displaced) | Lung hila | Lymph nodes |
| | Lymph nodes | Adipose tissue |
| | Adipose tissue | |

Table 2. Distribution and classification of primary masses of the mediastinum

| Anterior (anterosuperior) | Middle | Posterior |
|---|---|---|
| Thymic tumors | Lymphomas | Lymphomas |
| Thymomas | Cysts | Neurogenic tumors |
| Thymic carcinomas | Bronchogenic | Peripheral nerves |
| Thymic cysts | Foregut, | Malignant peripheral nerve sheath tumors |
| Carcinoids | Pericardial, | Schwannomas |
| Thymolipomas | Thoracic duct | Neurosarcomas |
| Lymphomas | Meningoceles | Sympathetic ganglia |
| Hodgkin's disease | Mesenchymal tumors | Ganglioneuroblastomas |
| Non-Hodgkin's lymphomas | Tracheal tumors | Ganglioneuromas |
| Undifferentiated | Carcinomas | Neuroblastomas |
| Germ cell tumors | Cardiac and pericardial tumors | Paraganglia |
| Seminomas | Hernias | Paragangliomas |
| Non-seminomas | Hiatal | Mesenchymal tumors |
| Embryonal carcinomas | Morgagni | Endocrine tumors |
| Choriocarcinomas | Vascular tumors | Esophageal tumors and cysts |
| Mixed germ cell tumors | Ascending aortic | Hiatal hernias |
| Teratomas (Dermoid cysts) | Transverse arch | Lateral thoracic meningoceles |
| Endocrine tumors | Descending aortic | |
| Parathyroid adenomas | Great vessels | |
| Thyroid tumors | Lymphadenopathy | |
| Mesenchymal tumors | Inflammatory | |
| Amyloid tumors | Granulomatous | |
| Castleman's disease | Sarcoidosis | |
| Chordomas | | |
| Extramedullary hematopoesis | | |
| Fibromas, fibrosarcomas, malignant fibrous histiocytoma | | |
| Hemangiomas, hemangioendotheliomas, hemangiopericytomas | | |
| Intrathoracic meningioma | | |
| Lipomas, liposarcomas | | |
| Leiomyomas, leiomyosarcomas, leiomyoblastomas | | |
| Lymphangiomas, lymphangiosarcoma, lymphangiomyomatosis | | |
| Mesotheliomas | | |
| Mesenchymomas | | |
| Myxomas | | |
| Rhabdomyosarcomas, rhabdomyomas | | |
| Xanthogranulomas | | |
| Morgagni Hernias | | |

Table 3. Relative incidence of primary mediastinal tumors

| Tumor Type | Davis et al. (81) 1986 (n=400) | Incident (%) | Total 1952-1986 (n=2,399) | Total Incidence (%) |
|---|---|---|---|---|
| Thymic | 67 | 17 | 458 | 19.7 |
| Thymoma | 57 | | | |
| Other | 10 | | | |
| Neurogenic | 57 | 14 | 496 | 20.7 |
| Ganglioneuroma | 16 | | | |
| Neurofibroma | 15 | | | |
| Neurilemoma | 12 | | | |
| Paraganglioma | 1 | | | |
| Ganglioneuroblastoma | 5 | | | |
| Neuroblastoma | 4 | | | |
| Neurosarcoma | 4 | | | |
| Lymphoma | 62 | 16 | 301 | 12.5 |
| Non-Hodgkin's | 39 | | | |
| Hodgkin's | 23 | | | |
| Germ cell tumor | 42 | 11 | 239 | 10 |
| Teratoma | 31 | | | |
| Seminoma | 7 | | | |
| Embryonal carcinoma | 4 | | | |
| Carcinoma (primary) | 34 | 9 | 111 | 4.6 |
| Mesenchymal | 24 | 6 | 143 | 6 |
| Benign | 17 | | | |
| Malignant | 7 | | | |
| Endocrine | 12 | 3 | 154 | 6.4 |
| Thyroid | 9 | | | |
| Parathyroid | 3 | | | |
| Cyst | 99 | 25 | | |
| Bronchogenic | 39 | | 151 | 6.3 |
| Pericardial | 36 | | 144 | 6 |
| Enteric | 11 | | 55 | 2.3 |
| Other | 13 | | 89 | 3.7 |
| Other | 3 | 1 | 58 | 2.4 |

Modified from Davis RD, et al. Primary cysts and neoplasms of the mediastinum: recent changes in clinical presentation, methods of diagnosis, management, and results. Ann Thorac Surg 1987;44:229-37 (81)

Table 4. Relative frequency of primary mediastinal tumors in adults and children

| Tumor | Incidence (%) Adults (n=163) | Children (n=47) |
|---|---|---|
| Thymic | 31 | 28 |
| Neurogenic | 15 | 47 |
| Lymphoma | 26 | 9 |
| Germ cell | 15 | 9 |
| Vascular | 1 | 6 |
| Miscellaneous | 13 | 2 |

Modified from Azarow et al. Primary mediastinal masses. A comparison of adult and pediatric populations. J Thorac Cardiovasc Surg 1993;106(1):67-72 (16).

Table 5. Relative incidence of benign and malignant mediastinal tumors and cysts

| Type of tumor | Benign (%) | Malignant (%) |
|---|---|---|
| Thymoma | 31 (54) | 26 (46) |
| Thymic cysts/hyperplasia | 10 (100) | — |
| Neurogenic tumors | 44 (77) | 13 (23) |
| Lymphomas | — | 62 (100) |
| Germ cell neoplasms | 21 (50) | 21 (50) |
| Carcinomas | — | 34 (100) |
| Mesenchymal tumors | 17 (71) | 7 (29) |
| Endocrine tumors | 8 (67) | 4 (33) |
| Cysts | 99 (100) | — |
| Total | 230 (58) | 167 (42) |

Modified from Davis RD et al. Primary cysts and neoplasms of the mediastinum: recent changes in clinical presentation, methods of diagnosis, management, and results. Ann Thorac Surg 1987;44:229-37 (81).

Table 6. Symptoms and signs of mediastinal tumors

| Symptom | Davis et al. (81) (n=400) | Whooley et al. (382) (n=124) | Conkle et al. (70) (n=43) | Bacha et al. (17) (n=89) |
|---|---|---|---|---|
| Chest pain | 30% | 30% | 33% | 19% |
| Dyspnea | 16% | 19% | 42% | 15% |
| Cough | 16% | 23% | 65% | |
| Fatigue | 6% | 7% | | |
| Dysphagia | 4% | | 16% | |
| Hemoptysis | | 4% | | |
| Hoarseness | | 2% | 16% | |
| No symptoms | 38% | 31% | 9% | 17% |
| Sign | | | | |
| Normal exam | | 63% | 33% | |
| Weight loss | 8% | 6% | 40% | 5% |
| Fever | 20% | 10% | 23% | 5% |
| Wheezing, stridor (cyanosis) | | 10% | 9% | |
| Superior vena cava syndrome | 6% | 10% | 23% | 16% |
| Vocal cord paralysis | | | | 3% |
| Horner's | | 2% | 7% | |
| Pericardial effusion | | | | 2% |
| Myasthenia gravis | 7% | 3% | | 12% |
| Others | | 9% | | 9% |

Table 7. Paraneoplastic syndromes associated with mediastinal neoplasms

| Tumor | Syndrome |
|---|---|
| Thymoma | Acute Pericarditis, Addison's Disease, Agranulocytosis, Alopecia Acreata, Cushing's Syndrome, Hemolytic Anemia, Hypogammaglobulinemia, Limbic Encephalopathy, Myasthenia Gravis, Myocarditis, Nephrotic Syndrome, Panhypopituitarism, Pernicious Anemia, Polymyositis, Pure Red Cell Aplasia (Diamond-Blackfan Anemia), Rheumatoid Arthritis, Sarcoidosis, Scleroderma, Sensorimotor Radiculopathy, Stiff-Person's 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 |
| Schwannoma | Peptic Ulcer |
| Malignant peripheral nerve sheath tumor | Leser-Trelat sign |

Modified from Cameron et al. Neoplasms of the Mediastinum. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*, 6th ed. Philadelphia: Lippincott-Raven Publishers, 2000;1019-36 (47).

Table 8. Systemic Manifestations of Hormone Production by Mediastinal Neoplasms

| Symptoms | Hormone | Tumor |
|---|---|---|
| Hypertension | Catecholamines | Paraganglioma<br>Neuroblastoma<br>Ganglioneuroma |
| Hypercalcemia | Parathyroid Hormone | Parathyroid Adenoma |
| Thyrotoxicosis | Thyroxine | Thyroid |
| Cushing's Syndrome | ACTH | Carcinoid Tumor |
| Gynecomastia | HCG | Germ Cell Tumor |
| Hypoglycemia | ? Insulin | Mesenchymal Tumors |
| Diarrhea | VIP | Ganglioneuroma,<br>Neuroblastoma,<br>Neurofibroma |

Modified from Cameron et al. Neoplasms of the Mediastinum. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology,* 6th ed. Philadelphia: Lippincott-Raven Publishers, 2000;1019-36 (47).

Table 9. Diagnostic workup for mediastinal tumors.

| |
|---|
| **General** |
| History and Physical examination, to include a thorough examination of the testes especially for male patients with mediastinal germ cell tumors |
| **Radiographic Studies** |
| Standard |
| Chest Radiographs |
| Computed Tomography Scan |
| Complementary |
| Magnetic Resonance Imaging |
| Barium Swallow |
| Fluoroscopy |
| Arteriography |
| Iodine-131 Scan |
| Gallium Scan |
| Ultrasonography of Testes (In Mediastinal Germ Cell Tumors) |
| Lymphangiography (In Mediastinal Germ Cell Tumors) |
| Positron Emission Tomography Scan |
| **Laboratory Studies** |
| Complete Blood Cell Count, Blood Chemistries, Urinalysis |
| Germ Cell Tumors: Alpha-Fetoprotein, Beta-Human Chorionic Gonadotropin, Carcinoembryonic Antigen |
| Thymoma: Radioimmunoassay for Acetylcholine Receptors |
| **Special Tests and Procedures** |
| CT-guided or ultrasound-guided biopsy |
| Mediastinoscopy |
| Anterior mediastinotomy with biopsy |
| Bronchoscopy |
| Esophagoscopy |
| Biopsy of palpable supraclavicular lymph nodes |
| Thoracotomy |

Table 10. Masaoka Staging System for thymoma

| Stage | Description |
|---|---|
| I | Macroscopically completely encapsulated with no microscopic detectable capsular invasion |
| II | Macroscopic invasion into surrounding mediastinal fatty tissue or mediastinal pleura or microscopic invasion in the capsule |
| III | Macroscopic invasion into surrounding organs or intrathoracic metastases or both (pericardium, great vessels, lung) |
| IVA | Pleural or pericardial implants/dissemination |
| IVB | Lymphagenous or hematogenous metastases |

Adapted from Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485 (227).

Table 11. Thymoma staging system of GETT

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

Adapted from Gamondes JP, Balawi A, Greenland T, et al. Seventeen years of surgical treatment of thymoma: factors influencing survival. Europ J cardiothorac Surg 1991;5:124-131 (118).

Table 12. General treatment of thymoma by stage of disease

| Stage | Surgery | Radiation Therapy | Chemotherapy |
|---|---|---|---|
| I | Complete resection | None | None |
| II | Complete resection | 45-60 Gy Postop | None |
| III | Complete or incomplete resection | 50-60 Gy | Cisplatinum-based combination |
| IV | Incomplete resection | 50-60+ Gy | Cisplatinum-based combination |

Modified from Cameron et al. Neoplasms of the Mediastinum. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology,* 6th ed. Philadelphia: Lippincott-Raven Publishers, 2000;1019-36 (47).

Table 13. Results of combination chemotherapy with and without radiation therapy or surgery for invasive thymoma

| Study | No. of Patients | Chemotherapy Regimen | Surgery | Radiation | PR/CR | Path CR | Survival |
|---|---|---|---|---|---|---|---|
| Dy et al. (95) 1988 | 4 | Cisplatinum Vinblastine Bleomycin Prednisone | 1 | 3 | 2 CR 2 PR | 1/1 | 3/4 |
| Estrada et al. (100) 1991 | 5 | Doxorubicin Ifosfamide Cisplatinum | 0 | | 1 CR 2 PR | 0 | |
| Evans et al. (103) 1980 | 4 | Cyclophosphamide Vincristine Prednisone Procarbazine | 1 | 4 | 4 PR | 0 | 4/5 |
| Fornasiero et al. (109) 1991 | 37 | Doxorubicin Cisplatinum Vincristine Cyclophosphamide | 10/16 | | 16 CR 18 PR | 7/10 | 15 months median |
| Giaccone et al. (122) 1996 | 16 | Cisplatinum Etoposide | | | 5CR 4 PR | | 4.3 years median |
| Loehrer et al. (211) 2001 | 28* | Cisplatinum Etoposide Ifosfamide | | | 9 PR | | 32 months median; 70% 2 YS |
| Loehrer et al. (213) 1994 | 30 | Cisplatinum Cyclophosphamide Doxorubicin | | Some prechemo | 3 CR 12 PR | | 38 months median; 32% 5 YS |
| Macchiarini et al. (216) 1991 | 7 | Cisplatinum Epirubicin Etoposide | 4 Complete resections 3 Incomplete resections | Postop | 7 PR | 2/7 | 80% 2 YS |
| Oshita et al. (273) 1995 | 14* | Cisplatinum Cyclophosphamide Doxorubicin Etoposide | 2 | 7 | 6PR | | 14.7 months median |
| Simpson WJ (334) 1989 | 8 | Cyclophosphamide Vincristine Procarbazine Prednisone | 2 | | 4 PR | | |

PR, partial response; CR, complete response; Path CR, pathologic complete response.
*****Included thymic carcinoma

Table 14. Results of radiation therapy in invasive thymomas

| Authors | No. of patients | Regimen | Radiation dose (Gy) | Local control (%) | 5-Y survival rate (%) |
|---|---|---|---|---|---|
| Akaogi et al. (5) 1996 | 12 | Preop/Postop | 18.3/42.3 | 75% complete resection | 66(III) (overall survival) |
| Curran et al. (75) 1988 | 25 | Postop | 32–60 | 84 | 86 (II)<br>69 (III) |
| Haniuda et al. (142) | 70 | Postop | 40-50 | 100 (IIp1)*<br>70 (III) | 74 (II)<br>69 (III) |
| Hug et al. (151) 1990 | 27 | Preop/Postop | 40 (median) | 89 | 92 (II)<br>62 (III) |
| Jackson et al. (157) 1991 | 28 | Postop (Bx Or Subtotal) | 32-60 | 61 | 57(III) |
| Kersh et al. (172) 1985 | 10 | Postop | 46–52 | 60 | 57 |
| Krueger et al. (184) 1988 | 12 | postop | 30–56 | 67 | 57(III) |
| Latz et al. (198) 1997 | 43 | Postop; some Chemotherapy | 50 (median) | 81% | 90(II)<br>67(III)<br>30(IV) |
| Mornex et al. (246) 1995 | 58 | Preop and Postop; Chemotherapy | 30-70<br>50 (median) | 14(IIIa)<br>41(IIIb) | 64(IIIa)<br>39(IIIb) |
| Myojin et al. (255) 2000 | 32 | Pre/Postop | 40/45-60 | 63 | 71(III) |
| Nakahara et al. (257) 1988 | 141 | Postop | 30–50 | — | 91.5 (II)<br>87.8 (III) |
| Nordstrom D. (269) 1979 | 20 | Postop | 40–50 | 55 | 50 |
| Pollack et al. (288) 1992 | 36 | Postop; Primary RT (22 pts) | 50 Gy (median) | 59 (overall) | 74(I)<br>71(II)<br>50(III)<br>29(IV) |
| Urgesi et al. (364) 1990 | 59 | Pre and postop | 39.6–60 | 85–90 | 78 (III) |

*Fibrous adhesion to the mediastinal pleura without microscopic invasion

Table 15A. Five-year survival (%) according to Masaoka staging system

| Stage | Masaoka et al. (227) (n=96) | Elert (99) (n=102) | Quintanilla-Martinez (291) (n=116) | Schneider (321) (n=82) |
|---|---|---|---|---|
| I | 93 | 83 | 100 | 100 |
| II | 86 | 90 | 100 | 95 |
| III | 70 | 46 | 70 | 56 |
| IV | 50 | - | 75 | 11 |

Table 15B. Ten-year survival (%) according to Masaoka staging system

| Stage | Wilkins et al (385) (n=85) | Regnard et al (296) (n=307) | Quintanilla-Martinez (291) (n=116) | Schneider (321) (n=82) |
|---|---|---|---|---|
| I | 78 | 80 | 100 | 91 |
| II | 74 | 78 | 100 | 88 |
| III | 20 | 47 | 60 | 47 |
| IV | -- | 30 | 0 | 11 |

Table 16. Presenting symptoms in patients with mediastinal germ cell tumors

| Symptoms | Walsh et al. (375) % (n=20) | Kiffer et al. (173) % (n=18) |
|---|---|---|
| Chest Pain | 50 | 55* |
| Cough | 45 | 22 |
| Dyspnea | 45 | 61 |
| Constitutional | 45 | 22 |
| Fever | 35 | 5 |
| Shoulder Pain | 30 | 55* |
| Hemoptysis | 20 | - |
| Night Sweat | 15 | 5 |
| SVC Syndrome | 10 | 17 |
| Neck Mass (nodes) | 10 | 17 |

*Chest pain is combined with shoulder pain.

Table 17. General pattern of tumor markers in germ cell tumors

| Germ Cell Tumor | AFP | ß-HCG (occasional) |
|---|---|---|
| Seminoma | - | - (+) |
| Choriocarcinoma | - | + |
| Yolk sac tumor | + | - (+) |
| Embryonal | + | - (+) |
| Teratoma | - | - |
| Mixed germ tumor | +/- | +/- |

Data from Davis et al. (81), Moran et al. (241), Wood DE (394), and Toner et al. (358).

Table 18. Clinical staging of mediastinal germ cell tumors

| Stage | Description |
|---|---|
| I | Well-circumscribed without invasion of adjacent structures |
| II | Micro or macroscopic invasion of adjacent structures |
| III | Presence of metastases |
| IIIA | Intrathoracic metastases |
| IIIB | Extrathoracic metastases |

Adapted from Moran CA, Suster S. Primary germ cell tumors of the mediastinum: I. Analysis of 322 cases with special emphasis on teratomatous lesions and a proposal for histopathologic classification and clinical staging. Cancer 1977;80:861-90 (242).

Table 19. Treatment results of mediastinal seminoma

| Study | No. of patients | Primary treatment (no. of pts) | Local control (%) | Survival (>24 months) (%) |
|---|---|---|---|---|
| Bush et al. (45) | 13 | RT | - | 54 RFS (10 yrs) |
| Cox JD (73) | 6 | RT | 100 | 66 |
| Dulmet et al. (93) | 16 | S (4);RT (12) | - | 81 |
| Kersh et al. (171) | 13 | S (1);RT (12) | 92 | 100 |
| Kiffer et al. (173) | 6 | RT | 100 | 67 RFS |
| Kiffer et al. (174) | 4 | C (1);RT (3) | 100 | 50 RFS |
| Knapp et al. (179) | 22 | S (1);RT (21) | - | 50 RFS |
| Martini et al. (225) | 10 | S (2);RT+/-C(8) | - | 40 |
| Schantz et al. (317) | 16 | S (5);RT (11) | - | 81 |

C, chemotherapy alone; S, surgery alone; RT, radiation therapy (+/- surgery); RFS, relapse free survival.

Table 20. Resection with adjuvant treatment for primary tracheal carcinoma.

| Series | Histology | Treatment | Local control | Survival |
|---|---|---|---|---|
| Grillo and Mathisen (131) | SCC (n=70) | Surgery ? XRT* | | 34 mos median |
| | ACC (n=80) | XRT alone | | 10 mos median |
| | | Surgery ? XRT* | | 118 mos median |
| | | XRT alone | | 28 mos median |
| Licht et al. (208) | | Surgery alone (n=6) | | 48% 5y |
| | | XRT alone (n=35) | | 7% 5y overall |
| | | >60 Gy (n=11) | | 60% 1y |
| | | <60 Gy (n=24) | | 24% 2y |
| | | Laser/cautery ? XRT (n=24) | | <11% 1y |
| | | | | 28% 5y |
| | | XRT + chemo (n=2) | | 0% 5y |
| Chow et al. (59) | | Surgery alone (n=5) | 1/5 | 16 mos median |
| | | XRT alone (n=12) | 3/4 | 26 mos median |
| | | >60 Gy | 1/8 | |
| | | <60 Gy | | |
| | | Surgery + XRT (n=5) | 0/1 | 61 mos median |
| | | 47.5 Gy | 4/4 | |
| | | >50 Gy | | |
| Regnand et al. (295) | | CR + XRT (n=31) | | 74% 5y |
| | | CR (n=27) | | 53% 5y (p=NS) |
| | | IR + XRT (n=15) | | 47% 5y |
| | | IR (n=6) | | 0% 5y (p<0.05) |
| Maziak et al. (232) | ACC (n=35) | CR ? XRT (n=14)* | | 9.8y mean |
| | | IR + XRT (n=15) | | 7.5y mean |
| | | XRT alone (n=6) | | 6.2y mean |

*The minority received surgery alone; SCC, squamous cell carcinoma; ACC, adenoid cystic carcinoma; XRT, radiotherapy; CR, complete resection; IR, incomplete resection; NS, not significant.

Table 21. Retrospective series examining radiotherapy alone for primary tracheal carcinoma.

| Series | Histology | Treatment | Local control | Survival |
|---|---|---|---|---|
| Schraube et al. (322) | SCC (n=11) | 46-60 Gy EBRT + 15-20 Gy HDR | 6/11 | 31 mos median |
| Cheung (58) | SCC (n=20)<br>ACC (n=4) | 40-60 Gy<br>40-60 Gy | | 5 mos median<br>1y median |
| Fields et al. (105) | SCC (n=17)<br>ACC (n=1) | >60 Gy<br>40-60 Gy<br><40 Gy<br>>60Gy | 5/6<br>1/7<br>0/4<br>1/1 | 25% 5y (n=18) |
| Rostom and Morgan (307) | SCC (n=28)<br>ACC (n=3) | 60-70 Gy<br><60 Gy<br>50-70Gy | 16/24<br>0/4 | 11% 4y<br>67% 4y |
| Makarewicz and Mross (220) | | 60 Gy EBRT +<br>6-12 Gy HDR (n=8)<br>40-60 Gy EBRT (n=3)<br><40 Gy (n=12) | 6/8<br>1/3<br>0/12 | 9.5 mos median (n=23) |
| Fuwa et al. (115) | | EBRT + LDR (n=4)<br>(80-128 Gy)* | 3/4 | 75% 3y |

*One treatment related death at 9 mos. post-XRT in a patient receiving 60 Gy EBRT + 53 Gy LDR Ir-192; SCC, squamous cell carcinoma; ACC, adenoid cystic carcinoma; HDR, high dose rate brachytherapy; LDR, low dose rate brachytherapy; EBRT, external beam radiotherapy.

Table 22**.** Mesenchymal mediastinal tumors (tumors with malignant tendencies underlined).

| | |
|---|---|
| Tumors of lymph vessels: | Tumors of fibroconnective tissue: |
| ? lymphangioma (lymphangiomatosis) | ? fibroma (fibromatosis) |
| ? lymphangiomyomatosis | ? fibrosarcoma |
| ? lymphangiosarcoma | ? malignant fibrous histiocytoma |
| Tumors of blood vessel origin: | |
| ? hemangioma | Other miscellaneous tumors: |
| ? hemangioendothelioma | ? benign mesenchymoma |
| ? hemangiopericytoma | ? malignant mesenchymoma |
| | ? myxoma |
| Tumors of fat tissue: | ? fibrous mesothelioma |
| ? lipoma | ? chordoma |
| ? lipoblastoma (lipoblastomatosis) | ? histiocytosis X |
| ? liposarcoma | ? amyloid tumor |
| | ? extramedullary hematopoesis |
| Tumors of muscle/skeletal tissue: | ? intrathoracic meningioma |
| ? chondrosarcoma | ? giant lymph node hyperplasia (Castleman's disease) |
| ? leiomyoma | |
| ? leiomyosarcoma | |
| ? osteogenic sarcoma | ? xanthogranuloma |
| ? rhabdomyoma | |
| ? rhabdomyosarcoma | |

Table 23. Neurogenic tumors of the mediastinum.

| TUMORS OF PERIPHERAL NERVES: | |
|---|---|
| BENIGN | MALIGNANT |
| schwannoma (neurilemoma)[‡] | malignant peripheral nerve sheath tumor (MPNST) aka malignant schwannoma[?] |
| melanotic schwannoma[‡] | |
| neurofibroma[‡] | neurogenic sarcoma |
| neurofibromatosis[‡] | neurofibrosarcoma |
| pigmented neuroectodermal tumor | malignant melanocytic schwannoma |
| granular cell tumor[†] | malignant peripheral neuroectodermal tumor (Askin's tumor) |
| **TUMORS OF AUTONOMIC GANGLIA:** | |
| BENIGN | MALIGNANT |
| ganglioneuroma | neuroblastoma |
| | ganglioneuroblastoma |
| **TUMORS OF PARAGANGLIA:** | |
| BENIGN or MALIGNANT | |
| paraganglioma (aka mediastinal pheochromocytoma, chemodectoma) | |

[‡] Any of these tumors may dedifferentiate into a MPNST; [?] falling out of favor, mostly because ultrastructural studies fail to indicate the presence of Schwann cells in some instances (361); [†] a tumor of probable but not proven Schwann cell origin (377).

FIGURE LEGENDS

Figure 1. Anatomy of the mediastinum.

Figure 2. A and B. Anterior-posterior and lateral chest radiographs of a patient with thymoma in the anterior mediastinum. C. Chest CT of the same patient. (Courtesy of Dr. Michael G. Beat)

Figure 3. Multi-field arrangement used in a patient with thymoma in the anterior mediastinum. A. Anterior-posterior field. B. Left lateral field. C. Right anterior oblique field. D and E. Isodose distributions. (Courtesy of Dr. Keith E. Eyre)