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Mediastinal Tumors: Diagnosis and Treatment

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Abstract. Mediastinal tumors are uncommon and often asymptomatic if benign. Tumors have a predilection for arising in one of three mediastinal compartments; anterior, middle, or posterior. If symptoms are present, they are usually compressive in origin. Computed tomography is almost always the imaging modality of choice. Benign-appearing lesions are usually resected for cure. Malignant-appearing lesions usually require biopsy by the least invasive route appropriate for the suspected tumor type.

Mediastinal tumors are uncommon and represent far fewer than 1% of all cancers when reported by site of origin [1–3]. The three imaginary mediastinal compartments [anterior, middle (or visceral), posterior] are useful for locating and suggesting common diagnostic possibilities when a mediastinal mass is present. Each mediastinal tumor has a predilection for one of the mediastinal compartments, although encroachment into an adjacent space is common (Table 1). Thymomas are the most common mediastinal tumors in adults and are the most common tumor of the anterior mediastinum [1].

Clinical Factors

About one-third of mediastinal tumors produce symptoms. Pressure symptoms are the most common and may include cough, dyspnea, and central chest pain. Compression of vital structures may occur and cause the superior vena caval (SVC) syndrome, dyspnea, stridor, or dysphagia. Direct invasion of vital structures may occur, leading to chest or back pain, hoarseness, Horner syndrome, or diaphragmatic paralysis. An abnormal chest radiograph is the most common presentation of a benign mediastinal mass. Most mediastinal masses in adults are benign. Not surprisingly, malignant mediastinal tumors are more often symptomatic than benign tumors.

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Diagnostic Investigations

Computed tomography (CT) is the examination of choice for virtually all suspected mediastinal tumors [4, 5]. CT reliably distinguishes cystic, fatty, vascular, and soft tissue masses. The soft tissue component of the mass can be further defined in terms of the homogeneity of the lesion, the presence or absence of calcification, and whether there is enhancement with contrast. Abutment, encasement, or invasion of adjacent structures may be demonstrated. Pleural metastases, pleural effusions, and pulmonary lesions may also be documented.

Magnetic resonance imaging (MRI) is not routinely used to investigate mediastinal tumors, but it can be helpful [4, 5]. The resolution is less than that of CT, the scanning time is significantly longer, and the examination is more expensive. However, it can provide coronal and sagittal cuts if desired; and it identifies vascular structures, cysts, and nerves with precision. Cystic lesions that are homogeneous and of relatively high density on CT can be reliably diagnosed by MRI (i.e., bronchogenic cysts). Neurogenic tumor involvement of the intervertebral foramen or with intraspinal extension can be assessed by MRI. Vascular structures or mediastinal tumors that are highly vascular (paraganglioma, goiter, hemangioma, Castleman's disease) are readily demonstrated by MRI.

Iodine 131-metaiodobenzylguanidine (MIBG) radiopharmaceutical scanning has proven to be helpful for demonstrating and localizing occult paragangliomas [6]. Serum tumor markers are extraordinarily helpful for diagnosing mediastinal nonseminomatous germ cell tumors. All young adult men who present with an anterior mediastinal mass should have their b -human chorionic gonadotropin (b-hCG) and a-fetoprotein (AFP) levels measured. About 90% of patients with nonseminomatous elements have an elevation of at least one marker [7].

A variety of techniques are available to obtain tissue to ascertain the diagnosis of mediastinal tumors. Needle biopsy is appropriate for tumors that appear malignant by CT, such as thymic carcinoma, seminomas, and nonseminomatous germ cell tumors. Needle biopsy does not usually provide enough diagnostic material to allow diagnosis of a lymphoma. Mediastinoscopy allows access to tumors in the paratracheal and subcarinal areas of the middle mediastinum. Anterior mediastinotomy (Chamberlain

Table 1. Common mediastinal tumor locations.

Anterior third	Middle	Posterior
Endocrine		
Substernal thyroid	Lymphoma	Neurogenic tumor
Parathyroid adenoma	Castleman's disease	Paraganglioma
Thymic tumors	Paraganglioma	
Thymoma		
Thymic carcinoma		
Thymolipoma		
Lymphomas		
Germ cell tumors		
Teratoma		
Seminoma		
Nonseminomatous		
Mesenchymal tumors		

procedure) is usually the procedure of choice when an anterior mediastinal lymphoma is suspected. Enough tissue can be obtained to allow marker studies, flow cytometry, and other studies the pathologist requires. Clinically benign anterior mediastinal tumors that appear resectable should usually undergo excision without preliminary biopsy, usually through a median sternotomy. Biopsy of a clinically resectable thymoma is contraindicated for fear of local or pleural implantation of tumor cells.

Endocrine Tumors

Substernal Goiter

Substernal extension of a goiter is reported to occur in 1% to 15% of thyroidectomies [8]. Most of these goiters are benign multimodular lesions [8]. Most are asymptomatic and are discovered during incidental chest radiography. Symptoms include local fullness, choking, stridor, or dysphagia. Virtually all of the patients are euthyroid. The diagnosis can be readily confirmed by chest CT. All symptomatic substernal goiters should be removed. Management of an asymptomatic substernal goiter is somewhat controversial, with most surgeons favoring removal in otherwise fit, relatively young patients. The approach is always cervical, as the blood supply remains tethered in the neck. A partial upper sternal split is only rarely required. Complications are rare after surgery.

Parathyroid Tumors

Parathyroid tumors are usually located on the posterior capsule of the thyroid but may be in other ectopic positions. The mediastinum is the most frequent location for ectopic parathyroid tumors, with approximately 20% of parathyroid tumors located in the mediastinum [9]. Most mediastinal parathyroid tumors (80%) are in the anterior mediastinum, although some (20%) are in the upper posterior mediastinum [9]. Most mediastinal parathyroids are present in the upper portions of the thymus gland and are supplied by the inferior thyroid artery. Because of the usually small size of parathyroid tumors, imaging studies are often not helpful. Most mediastinal parathyroid adenomas (90%) can be removed via a cervical approach alone [9].

Thymic Tumors

Thymomas are rare neoplasms but are the most common tumor of the anterior mediastinum. The average age at presentation is 55 years [10]. Thymomas are rare in children. Males and females are equally affected. About one-half of the patients are asymptomatic. Many patients have vague chest pain, dyspnea, or cough as presenting symptoms. Some patients have constitutional symptoms such as fever, weight loss, and fatigue. About 30% to 50% of patients with thymoma have myasthenia gravis, whereas about 15% of patients with myasthenia gravis have thymoma [10]. Previously, the presence of myasthenia gravis was thought to be a poor prognostic factor, but recent reports indicate that myasthenia gravis is associated with a slightly more favorable outcome after resection [11], most likely due to earlier diagnosis in myasthenia patients. About 5% of patients with thymoma have red blood cell aplasia, whereas about one-half of patients with red blood cell aplasia have thymomas [10]. Thymoma removal has improved the hematologic situation in some patients. Hypogammaglobulinemia has rarely (1–10%) been associated with thymomas [10]. Thymoma removal has not been beneficial in reversing the syndrome. Most thymomas are located in the anterior mediastinum, although they have been reported in the neck, lung, and pericardium.

Computed tomography usually demonstrates a rounded or lobulated soft tissue mass in the anterior mediastinum abutting the ascending aorta. Calcification, cystic areas, or areas of hemorrhage occasionally occur. Lymphadenopathy is not usually present; if it is, it should lead to the possible diagnosis of lymphoma. The presence of vascular invasion, encasement, pericardial invasion, droplet pleural metastasis, or metastatic deposits suggest an invasive thymoma.

The traditional classification of thymomas is based primarily on the relative admixture of thymic epithelial cells and lymphocytes. Four histologic subgroups have been identified: (1) lymphocytic (two-thirds of cells are lymphoid); (2) mixed lymphoepithelial (one-third to two-thirds of cells are lymphoid); (3) epithelial (two-thirds of cells are epithelial); and (4) spindled (two-thirds of cells are epithelial and spindled). Although many reports suggest an improved survival with spindle cell tumors and a worse prognosis for epithelial variants, histology was not thought to be an independent prognostic factor. However, a recent multivariant analysis of prognostic factors in 118 patients confirmed that the histologic type (spindle cell best, epithelial cell worst) was an independent ($p = 0.004$) predictor of long-term survival [12].

More recently, Marino and Muller-Hermelink [13] and Kirchner and Muller-Hermelink [14] reported a new classification of thymomas based on relating thymoma epithelial cells to the normal differentiation of thymic cells into medullary and cortical types. Their current classification of thymic epithelial tumors (thymoma and thymic carcinoma) includes six subtypes: medullary, mixed, predominantly cortical, cortical, well differentiated carcinoma, and high grade carcinoma. When originally proposed, the histology did correlate with stage, but it was not clear if histology was independent of stage for predicting survival. Controversy ensued between the two histologic classifications, and both are in use today. Implementation of the Muller-Hermelink classification has not been easy for some pathologists, which has limited its usefulness. Recently, three centers reported that the Muller-Hermelink classification independently predicts survival

Table 2. Masaoka staging system for thymomas.

Stage	Criteria
I	Macroscopically completely encapsulated with no microscopic extracapsular invasion
IIa	Macroscopic invasion into mediastinal fat or pleura
IIb	Microscopic invasion through the capsule
III	Invasion into adjacent structures (pericardium, great vessels, lung)
IVa	Pleural or pericardial metastases
IVb	Lymphogenous or hematogenous metastases

[15–17]. Medullary and mixed tumors are benign tumors with little chance of recurrence, with obvious implications about the advisability of postoperative adjuvant therapy.

Thymomas are usually diagnosed clinically, based largely on the CT scan appearance. Surgical excision then provides the precise histology and staging information necessary for a decision about postoperative adjuvant treatment. This approach has arisen because of the long-held dictum shunning preoperative biopsy for fear of local implantation of thymoma cells. The natural history of thymoma certainly illustrates the tendency for local mediastinal recurrence and pleural "droplet" recurrence presumably due to mediastinal pleural invasion after resection. Local recurrences have been noted in the surgical incision used to remove a thymoma completely, and we have had a local recurrence at a limited anterior mediastinotomy site used for preoperative biopsy. Accordingly, for straightforward "encapsulated" tumors judged to be completely resectable, an excisional approach seems reasonable. In patients with atypical features or "invasive" tumors thought to be candidates for induction therapy, preoperative biopsy is appropriate. The standard approach is a limited anterior mediastinotomy (Chamberlain approach) on the side over which the tumor projects. Mediastinoscopy is rarely useful, as this approach gains access to the middle compartment, rather than the anterior mediastinum. Fine-needle aspiration (FNA) biopsy has not been useful in our experience but has been reported to be beneficial by others [18]. Caution must be applied, however, as misdiagnoses have occurred, especially when differentiating lymphoma from thymoma. Perhaps utilization of the new core biopsy system in conjunction with immunohistochemical staging will improve the diagnostic accuracy of FNA. The most common tumors one must include in the differential diagnosis of an anterior mediastinal tumor are lymphomas and germ cell tumors.

The staging system proposed by Masaoka has been widely adopted [19] (Table 2). Stage is an independent predictor of recurrence and long-term survival [12, 15]. Some tumors can be staged accurately preoperatively (obvious vascular invasion or pleural implants); the Masaoka staging system is for the postsurgical patient, as invasion of the capsule is reliably diagnosed only by pathologic examination.

All patients who have potentially resectable lesions should undergo operative exploration and resection of their thymoma. Patients with myasthenia gravis should be in excellent physiologic condition, with plasmapheresis used liberally if necessary. Removal of a thymoma by video-assisted thoracic surgery (VATS) techniques has been reported as a technical feat, but no long-term follow-up is available. Removal by VATS is ill-advised, as it compromises the operation by an incomplete thymectomy and a non-en-bloc approach to a tumor known for its capability for local implantation.

When the preoperative CT scan suggests that the tumor is unresectable, large, or significantly invasive, biopsy alone is appropriate to obtain a diagnosis of thymoma. Preoperative adjuvant radiation therapy has been utilized in the past in these cases to increase the possibility of a complete resection and to minimize mediastinal or transpleural seeding of the tumor [20]. Doses of 30 to 45 Gy have been used for this approach. Complete responses have rarely been recorded. Treatment has been nonrandomized and reports anecdotal in nature, so the value of this approach is difficult to determine. Nonetheless, it is rational, and some tumors have become resectable after preoperative radiation therapy alone. Induction chemotherapy followed by surgery with postoperative chemoradiotherapy has been reported to achieve complete responses and facilitate complete resections [21]. Medium-term survival appears to be better than that of historical controls.

Radiation therapy has traditionally been used postoperatively for all invasive thymomas, although its benefit has never been tested in a randomized trial. The use of radiation therapy after incomplete resection is standard and can lead to long-term survival [11]. A dose-response curve has not been formulated in thymomas, but generally 40 to 50 Gy is given in the adjuvant setting and 50 to 60 Gy when treating gross disease.

Mediastinal Lymphomas

The mediastinum is commonly involved by malignant lymphomas [22]. Most mediastinal lymphomas occur in the anterior or middle mediastinal compartments. They usually arise from mediastinal lymph nodes but may arise from the thymus gland or other mediastinal structures. About 50% of Hodgkin's disease and 20% of non-Hodgkin's lymphomas present as mediastinal lymphomas. The size of the mass dictates whether symptoms are present. Bulky mediastinal disease usually causes compression symptoms. Patients commonly have chest pain or heaviness and cough. Dyspnea may result from large airway compression, lung compression, pleural effusion, or pericardial effusion. Due to the right-sided predominance of paratracheal lymph nodes, SVC syndrome is relatively common (20–60% of patients), especially in those with non-Hodgkin's lymphoma [23].

Patients with middle mediastinal lymphoma usually present with a CT scan showing pathologic lymphadenopathy. The differential diagnosis usually involves lymphoma, sarcoidosis, lung cancer, and granulomatous disease. Mediastinoscopy is usually possible and reliably provides a tissue diagnosis with minimal morbidity. Patients who present with anterior mediastinal lymphomas are more difficult to approach because the diagnostic possibilities are more varied. The differential diagnosis usually includes germ cell tumors and thymomas. Small, benign-appearing lesions usually should be resected for both diagnosis and therapy. Large, infiltrative-appearing lesions should be biopsied (by FNA if a germ cell tumor or invasive thymoma is suspected and by anterior mediastinotomy if a lymphoma is suspected). A frozen section should be obtained to make sure diagnostic tissue is present, and the surgeon should ascertain whether the pathologist has enough tissue to do the necessary studies. Some patients with large mediastinal lymphomas present with severe compression symptoms (SVC syndrome or airway compression) that force an urgent diagnosis. Treatment should *not* precede a tissue diag-

nosis despite a tentative clinical diagnosis. Radiation therapy prior to biopsy can greatly hinder the ability to make an accurate diagnosis. SVC syndrome is almost never a true emergency; and any necessary diagnostic biopsy procedure, including mediastinoscopy, can be done safely. Airway compression can be more problematic and potentially life-threatening. FNA or anterior mediastinotomy can be done in a semiupright position under local anesthesia. Rarely, short-term intubation and ventilation are needed for control of the airway until after the biopsy is done and therapy is instituted.

Therapy for lymphomas is beyond the scope of this review. Reviews are available, but therapy is constantly evolving and varies among centers [24, 25]. Clearly lymphomas are sensitive to both radiotherapy and chemotherapy. Patients with limited Hodgkin's disease are generally treated with radiotherapy if the tumor mass is small and no B symptoms (fever, sweats, weight loss) are present. Bulky Hodgkin's disease or non-Hodgkin's lymphoma are usually treated with chemotherapy first (to limit the size of the eventual radiation field) followed by radiation therapy. Cure rates approach 90% for patients with small-volume, asymptomatic Hodgkin's disease but diminish as the volume of tumor or the presence of B symptoms occur. Patients with large-cell non-Hodgkin's lymphoma have a low survival rate, which approaches 30% to 50% at 5 years [25].

Germ Cell Tumors

Germ cell tumors occur in the anterior mediastinum and are commonly grouped into teratomas (benign germ cell tumors), seminomas, and nonseminomatous germ cell tumors. Teratomas are equally distributed between men and women, and the average age at presentation is 30 years [26]. Most patients are asymptomatic, reflecting a benign status. Compression symptoms may occur. Cough productive of hair or sebaceous material is rare but pathognomic of cyst rupture into the tracheobronchial tree. CT is usually highly suggestive, with a well demarcated cystic lesion, often with calcification, fat, teeth, or bone. Curative treatment is by surgical excision, usually by a median sternotomy.

Seminomas

Mediastinal seminomas occur usually in men in their third decade [27]. Most patients are symptomatic, with pain, cough, or dyspnea. Serum tumor markers (b-hCG and AFP) should be measured to rule out an occult nonseminomatous component in the tumor. CT usually shows an anterior mediastinal mass that is relatively homogeneous with pushing or infiltrative borders. Small, benign-appearing tumors should be excised and followed by radiation therapy. Large, infiltrative seminomas should be biopsied and referred for definitive chemotherapy or radiotherapy. Seminomas are highly radiosensitive. In the past moderate-size tumors were treated with radiation alone, with cure rates reported from 50% to almost 100% [27]. Advanced tumors are treated with cisplatin-based chemotherapy with excellent results. Controversy currently exists about treating less advanced tumors with chemotherapy rather than radiotherapy.

Nonseminomatous Germ Cell Tumors

Nonseminomatous germ cell tumors of the mediastinum represent a rare subset of both mediastinal tumors and germ cell cancers [7]. Almost all of these patients are young men (average age 30 years). Histologic types seen include teratocarcinoma and embryonal cell, yolk sac, and choriocarcinoma. Symptoms are almost always present and are of short duration because of rapid tumor growth. Chest pain, dyspnea, fever, and cough are common. CT usually shows a large, inhomogeneous mass with areas of necrosis and hemorrhage. Compression and invasion of mediastinal structures are common. Measurement of serum b-hCG and AFP are indispensable for the diagnosis and management of these tumors. About 90% of these patients have elevation of one or both of these markers [7]. FNA is the preferred approach for obtaining a tissue diagnosis.

Cisplatin-based chemotherapy has dramatically improved the survival of patients with germ cell cancer. Survival rates are related to the volume of disease at presentation. The serum tumor markers act as indicators for viable germ cell cancer, allowing the oncologist to monitor the response to chemotherapy. If the serum tumor markers and CT scan return to normal after therapy, the patient is closely followed. If the markers normalize but a mass remains on CT, the residual mass is excised. Usually a benign teratoma or necrotic tumor is present in a residual marker-negative mass. If the markers remain elevated after chemotherapy, further chemotherapy is instituted. The 5-year survival approaches 50% in patients with mediastinal nonseminomatous germ cell tumors treated with intensive cisplatin regimens [7].

Paragangliomas

Paragangliomas are rare, arising from the paraganglia in the region of the cardiac plexus (middle mediastinum) or along the aorticosympathetic chain in the costovertebral sulcus (posterior mediastinum) [28, 29]. Histologically identical to pheochromocytoma, they may be functional or not as well as benign or malignant. Functional tumors present as extraadrenal pheochromocytomas with catecholamine excess. Nonfunctional tumors are either asymptomatic or present with compression or invasion of local structures. Urinary catecholamine levels are elevated with functional tumors. CT shows a solid lesion in the middle or posterior mediastinum. The radiopharmaceutical ^{131}I-metaiodobenzylguanidine (MIBG) has facilitated localization of intrathoracic pheochromocytomas [6, 29].

Functional tumors require preoperative pharmacologic blockade with a- and b-blockers to prevent intraoperative hypertensive crises. Posterior tumors are resected through a posterolateral thoracotomy, and middle mediastinal tumors are resected by a median sternotomy, usually with cardiopulmonary bypass. Benign tumors are cured by excision. Malignant tumors usually require postoperative adjuvant radiation therapy.

Neurogenic Tumors

Neurogenic tumors are common tumors of nerve sheath or autonomic nervous system origin [30]. In adults most of these tumors are benign. More than 90% are in the posterior mediastinum in the costovertebral gutter. Other sites include the thoracic inlet (brachial plexus origin) and the vagus and phrenic nerves. Patients

with von Recklinghausen's neurofibromatosis have an increased incidence of mediastinal neurogenic tumors.

Neurilemomas (schwannomas) and neurofibromas are of nerve sheath origin and represent about 60% of all mediastinal neurogenic tumors. Almost all of these tumors are benign. About 40% of mediastinal neurogenic tumors are derived from the autonomic nervous system. These tumors include ganglioneuroma, ganglioneuroblastoma, and neuroblastoma. Ganglioneuromas are benign, whereas the latter two tumors are malignant. Neuroblastomas present almost entirely during childhood. Most neurogenic tumors are asymptomatic. If symptoms occur, malignancy should be suspected. A plain chest radiograph is almost diagnostic, with the lateral view showing a rounded mass arising in the costovertebral sulcus. CT scans confirm a rounded, well demarcated, solid lesion. Rarely, enlargement of the intervertebral foramina occurs with intraspinal extension of the tumor. This situation requires preoperative identification; and a joint thoracic surgery and neurosurgical approach is required for safe removal of these tumors [31]. Accordingly, any enlargement of the foramina requires that MRI be performed to assess the spinal cord, as it allows precise identification of the limits of the tumor.

Treatment is by excision, and preoperative biopsy is usually unwarranted. Posterolateral thoracotomy or VATS may be utilized for the surgical approach. Benign lesions are cured by excision.

Castleman's Disease

Castleman's disease, also known as giant lymph node hyperplasia, was first described in 1956 as causing a benign lymphoid mass in the chest [32]. Although the disease can present anywhere lymph nodes are found, 70% of the cases are in the chest. Most are located along the tracheobronchial tree or hilum of the lung in the middle mediastinum, but they can also occur in the anterior or posterior compartments. Close to 90% are the hyaline-vascular variant, the classic type described by Castleman in 1956, which usually appears as an asymptomatic enhancing mediastinal mass on CT characterized histologically by small hyaline-vascular follicles. The rare plasma cell variant consists of large hyperplastic lymphoid follicles with surrounding zones of plasma cells. Systemic symptoms (fever, fatigue, anemia, arthralgias, elevated erythrocyte sedimentation rate) may be associated with this disease. The plasma cell variant may progress to a lymphoproliferative disorder. Most patients are young, with an average age of 30 years [33].

Resection is routinely performed to clarify the diagnosis. Resection is usually curative, but follow-up is appropriate, as local recurrences have been noted and the plasma cell variant may have late malignant potential [33].

Mesenchymal Tumors

About 6% of all mediastinal tumors are mesenchymal in origin and arise most commonly from the anterior mediastinum [2]. These tumors are rare and so are not commonly reported in detail. Lipomas, hemangiopericytomas, lymphangiomas, and hemangiomas have all been reported [3, 34]. Excision is usually both diagnostic and curative. Primary sarcomas of the mediastinum are rare and have been reviewed elsewhere [35]. About one-half can be completely resected, which is the most important factor determining long-term survival. Despite resection, the local recurrence rate was 64%, and the overall survival at 5 years was 32%. Adjuvant therapy with irradiation, chemotherapy, or both seems necessary to enhance survival.

Résumé

Les tumeurs médiastinales sont rares et souvent asymptomatiques lorsqu'elles sont bénignes. Les tumeurs se développent dans un des compartiments médiastinaux, antérieur, moyen ou postérieur. Si des symptômes sont présents, ils sont généralement compressifs. La tomodensitométrie est presque toujours la modalité diagnostique de choix. Les lésions ayant une allure bénigne sont généralement réséquées avec guérison. Les lésions d'allure maligne nécessitent une biopsie par la route la moins traumatisante, adaptée au type de tumeur soupçonnée.

Resumen

Los tumores mediastinales benignos son poco comunes y frecuentemente asintomáticos. Tienen predilección por originarse en uno de los tres compartimentos mediastinales: anterior, medio o posterior. Cuando hay sintomatología, ésta es usualmente originada en compresión. En casi todos los casos la tomografía computadorizada es la modalidad imagenológica de primera escogencia. Las lesiones de apariencia benigna usualmente se resecan con intención curativa; las de apariencia maligna generalmente requieren biopsia por el método menos invasor y más apropiado para cada tipo de lesión sospechosa.

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