Tumors of the Mediastinum and Chest Wall

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KEYWORDS

• Mediastinum • Mediastinal • Thymoma • Chest wall • Tumor

Tumors of the mediastinum and chest wall encompass a wide variety of histologies and may be primary, metastatic, or secondary to direct invasion from an adjacent cancer. Given the complex anatomy of the chest and proximity to vital structures, these lesions can be challenging to diagnose and treat. This review focuses on primary tumors.

MEDIASTINAL TUMORS

Mediastinal Anatomy

The mediastinum is bounded superiorly by the thoracic inlet and inferiorly by the diaphragm. For clinical purposes, the mediastinum has traditionally been divided into the anterior (or anterosuperior), middle, and posterior compartments (**Fig. 1**). There are no fascial planes between these divisions and they are in continuity with each other. Thus tumors can exist in more than 1 compartment. Nonetheless, these divisions are helpful in forming a differential diagnosis for a mediastinal mass (**Table 1**).

The anterior mediastinum lies between the sternum and the pericardium. It contains the thymus, lymph nodes, and loose connective tissue. The middle mediastinum contains the heart, the proximal great vessels, phrenic nerves, trachea, and main bronchi. The posterior mediastinum lies posterior to the pericardium and anterior to the thoracic vertebrae. It contains the esophagus, descending thoracic aorta, azygous vein, thoracic duct, and autonomic ganglia.[1] Although the heart, trachea, and esophagus lie within the mediastinum, tumors of these structures are outside the scope of this review.

ANTERIOR MEDIASTINUM

The anterior mediastinum is the most common site of primary mediastinal tumors. Anterior mediastinal masses are malignant in 59% of cases, compared with 29% for middle and 16% for posterior masses.[2] The most common primary masses in

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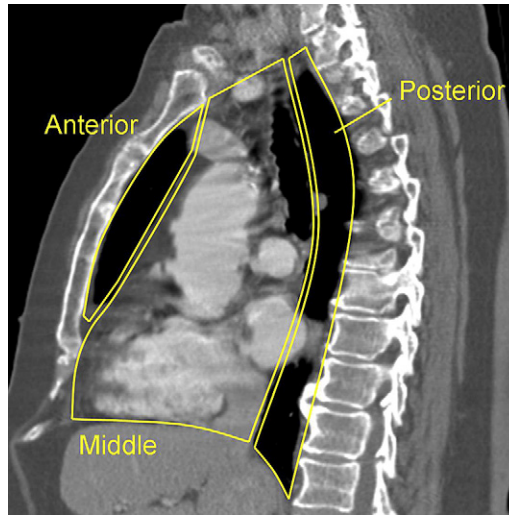

Fig. 1. A sagittal image from a computed tomography (CT) scan of the chest illustrating the anterior, medial, and posterior compartments of the mediastinum.

the anterior mediastinum are lymphomas, thymic neoplasms, germ cell tumors (GCTs), thyroid tissue, parathyroid adenomas, and cysts. Their presentations may range from an incidental finding on a radiograph to debilitating superior vena cava syndrome. Symptomatic patients are more likely to harbor malignancy. In a study of 400 patients with a primary mediastinal mass, 57% of symptomatic patients had a malignant lesion compared with only 17% of asymptomatic patients.[2] The most common symptoms were chest pain (30%), dyspnea (16%), fever/chills (20%), and cough (16%). Tumors in the anterior mediastinum are more likely to cause superior vena cava syndrome and phrenic nerve palsy.[3] The Pemberton sign is the development of facial plethora induced by raising both arms above the head. Although originally described for substernal goiter, the sign may be elicited when any mass obstructs venous outflow of the head and neck.[4]

Diagnostic Approach

A posterior-anterior (PA) and lateral chest radiograph is the initial diagnostic test that should be obtained for suspicion of any mediastinal mass. Whenever possible, the film

Table 1
Differential diagnosis for mediastinal masses

Anterior mediastinum	Thymic neoplasm Germ cell tumor Lymphoma Thyroid Parathyroid
Middle mediastinum	Lymphoma Granuloma Cyst: bronchogenic, esophageal, pericardial
Posterior mediastinum	Neurogenic Neurenteric cyst Esophageal

should be compared with previous chest films. A computed tomography (CT) scan of the chest should be next. The CT scan provides invaluable information regarding the morphology of the mass, its extent, and relation to surrounding structures. Magnetic resonance imaging (MRI) is helpful for evaluating cystic lesions.[5] Sestamibi should be used to help localize ectopic parathyroid tissue.[6] Positron emission tomography (PET) scans are also being used more frequently for the evaluation and staging of many mediastinal tumors, including thymic neoplasms.[7]

Alpha fetoprotein (AFP) and beta human chorionic gonadotropin (beta-hCG) levels should be checked in any male with an anterior mediastinal mass. Serum calcium level should also be considered if parathyroid adenoma is suspected.

For a solid mass, the surgeon is faced with the decision of whether to obtain a biopsy or proceed with resection. A small, well-encapsulated anterior mediastinal mass on CT scan may be resected without preoperative biopsy.[8] If the mass is large or if there is the suggestion of invasion of adjacent structures, biopsy is preferred so that appropriate neoadjuvant therapy may be given.[9] In addition, if there is lymphadenopathy or if the patient presents with B symptoms, the mass should be biopsied given a suspicion of lymphoma. Fine-needle aspiration (FNA) biopsy has an accuracy of 82% for the diagnosis of mediastinal masses.[10] FNA, however, does not reliably distinguish between thymoma and lymphoma, and does not usually provide enough tissue for flow cytometry. Core needle biopsy has greater diagnostic sensitivity and specificity for mediastinal tumors. In a series of 42 patients with anterior mediastinal masses, ultrasound-guided core needle biopsy provided adequate tissue for diagnosis in 100% of the cases.[11]

In the unusual case that adequate tissue cannot be obtained from needle biopsy, then mediastinoscopy, incisional biopsy, or thoracoscopic biopsy may be performed. Parasternal mediastinotomy offers good access for incisional biopsy of most anterior masses, but must be done carefully to avoid entering the pleural cavity and disseminating the tumor with drop metastases or chest wall implants.[8] Video-assisted thoracoscopy (VATS) may also be used for biopsy but also has a risk of pleural dissemination of tumor. In general, incisional biopsy of mediastinal masses should be avoided if possible, but if necessary should be performed by surgeons who are experienced in these procedures.

Thymic Neoplasms

Thymomas are the most common anterior mediastinal tumor in adults, comprising 20% of anterior mediastinal tumors.[1,12] They have a peak incidence in the fifth and sixth decades of life.[13] Thymomas have a wide range of presentations. Many are found incidentally on imaging done for another reason. When symptoms are present cough, substernal chest pain, and dyspnea are the most common. More advanced tumors may present with findings consistent with superior vena cava syndrome, phrenic nerve paralysis, pleural effusion, or airway obstruction.[14,15] Many paraneoplastic syndromes are also associated with thymomas, most commonly myasthenia gravis and red cell aplasia.[14,16] Paraneoplastic syndromes should be screened for in any patient with suspected thymoma because they have important anesthetic and perioperative implications. Myasthenia gravis occurs in 30% to 65% of patients with thymoma. Conversely, 75% of patients with myasthenia gravis have some thymic abnormality, but only 15% have thymomas.[16] Most patients with thymomatous myasthenia gravis (70%–100%) have improvement in their neurologic symptoms after thymectomy and between 30% and 70% may attain complete remission.[17,18]

The most commonly used staging system for thymoma is the modified Masaoka staging system, which has been shown to correlate well with survival (**Table 2**).[19,20]

Table 2
Five-year survival rates for Masaoka stage

Stage		5-Year Survival (%)
I	Completely encapsulated; no microscopic capsular invasion	93–100
II	Microscopic invasion into capsule or macroscopic invasion into surrounding fatty tissue or mediastinal pleura	86–95
III	Macroscopic invasion into adjacent organs	56–70
IV	Pleural or pericardial dissemination (IVa) Lymphatic or hematogenous spread (IVb)	11–50

Data from Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485; Schneider PM, Fellbaum C, Fink U, et al. Prognostic importance of histomorphologic subclassification for epithelial thymic tumors. Ann Surg Oncol 1997;4:46.

The World Health Organization (WHO) classification system for thymic neoplasms is less commonly used, but has also been shown to correlate with survival.[21,22] Invasive thymomas are often described as malignant thymomas, but they should not be confused with thymic carcinomas, which are a distinct histologic entity with more aggressive behavior.[23] Thymic carcinoids are included in the WHO classification with thymic carcinomas, but are biologically more similar to poorly differentiated neuroendocrine tumors. Like thymic carcinomas, they are aggressive tumors with potentially poor overall prognosis.[24] The mainstay of therapy is complete resection when possible.

On CT scan, the typical appearance of a thymoma is an encapsulated mass with smooth contours (**Figs. 2** and **3**). Thymic carcinomas are more heterogeneous with irregular borders and often show evidence of invasion into adjacent structures.[23] In addition, thymic carcinomas are more fluorodeoxyglucose-avid on PET.[7]

Complete surgical resection is the goal and leads to the best prognosis for patients with thymic tumors.[13] Median sternotomy, either partial or complete, has been the traditional approach, and provides excellent exposure to the tumor as well as potentially involved great vessels. Thoracoscopic resection has also been used, primarily for early stage tumors and myasthenia gravis.[25] A transcervical approach may also be used for early stage tumors less than 4 cm in size.[8] Regardless of the approach, the most important principle is removal of the entire tumor and thymus without spillage.

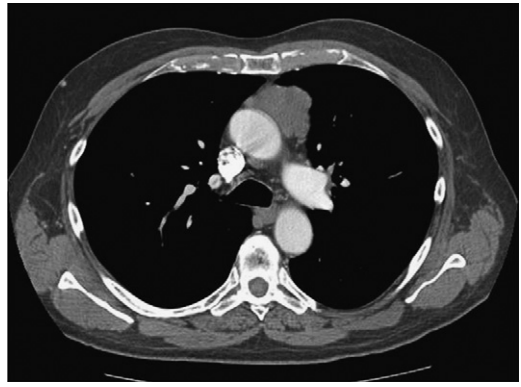

Fig. 2. CT scan of an early stage thymoma.

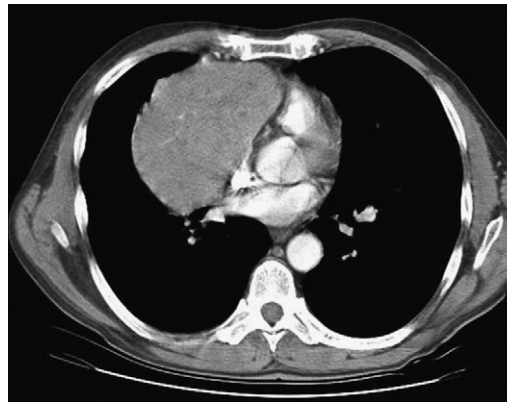

Fig. 3. CT scan of an invasive thymoma.

For Masaoka stage I tumors, complete surgical resection is sufficient therapy and overall 5-year survival is 90% to 100%[15,26] The role of adjuvant radiotherapy for stage II tumors is controversial. The overall survival of Masaoka stage II patients is more than 80%, so a survival advantage for radiation in this group has been difficult to demonstrate.[27,28] There is general agreement that radiation therapy should be considered for patients with stage II disease after incomplete resection. Tumors stage III or higher and tumors that are greater than 4 cm in largest dimension may be best served by multimodality therapy.[9,29] At our institution, we typically use induction chemotherapy followed by surgery and then radiotherapy for advanced stage thymomas and thymic carcinomas. In a study of 22 patients with advanced thymomas (11 stage III, 10 stage IVa, 1 stage IVb, no thymic carcinomas) undergoing this approach to therapy, 76% of patients were able to achieve complete surgical resection. With a median follow-up of 50 months, the overall 5-year survival rate was 95%.[9] Locally advanced tumors may require resection of the superior vena cava, the innominate vein, part of the aorta, the pericardium, or 1 phrenic nerve. Bilateral phrenic nerve division should be avoided. Even in cases with isolated pleural metastases (stage IVa), if a complete resection is possible, patients can achieve long-term survival. Local recurrence and limited pleural recurrence can also be treated surgically with good outcomes, provided that complete excision is technically possible.[30] Goals for surgical resection should emphasize an R0, complete resection. Debulking operations are associated with lower overall survival and consideration should be given to alternative therapies.[8]

Germ Cell Tumors

Primary mediastinal GCTs compose 15% of anterior mediastinal masses in adults.[31] They are believed to arise from primitive germ cells that fail to migrate during embryogenesis. Testicular GCTs are far more common, comprising 95% to 98% of all GCTs in men. Extragonadal GCTs are split roughly equally between retroperitoneal and mediastinal primaries.[32] Both testicular and retroperitoneal GCTs may metastasize to the mediastinum. Therefore, the diagnosis of a mediastinal GCT should trigger a search for an extrathoracic primary. Primary mediastinal GCTs have a peak age of incidence in the third decade of life.[3,31] Mediastinal GCTs are divided into 3 cell types: mature teratomas, seminomas, and nonseminomatous GCTs. Whereas mature teratomas occur with equal frequency between men and women, malignant GCTs are much more common in men (>90%).[1]

Teratoma

Mature mediastinal teratoma is the most common mediastinal GCT.[31] Teratomas contain tissue from at least 2 of the 3 primitive germ layers. Ectodermal tissues include skin, sweat glands, hair, and toothlike structures. Mesodermal tissues include fat, cartilage, bone, and smooth muscle. Endodermal tissues include respiratory and intestinal epithelium and pancreatic tissue. Mature teratomas are almost always benign. If a teratoma contains fetal tissue, it is considered immature.[33] Immature teratomas have greater malignant potential and may be better treated with neoadjuvant chemotherapy followed by surgery.[34]

Many patients with mature teratomas are asymptomatic. Cough, chest pain, or dyspnea may occur as a result of local growth of the mass. The expectoration of hair (trichoptysis) occurs in about 5% of patients and is pathognomonic for teratoma.[35,36] Chest radiograph typically demonstrates a well-circumscribed mass. Calcification is seen about a quarter of the time, from a calcified tumor wall, bone, teeth, or nonspecific tissues.[36] CT shows a well-circumscribed, heterogeneous mass with varying amounts of soft tissue, fat, fluid, and calcium.

With a CT scan suggestive of teratoma, surgical resection without biopsy can proceed if there is no evidence of invasion of other structures. Complete surgical resection is curative with low rates of recurrence.[31,35]

Seminoma

Seminomas compose 25% to 40% of primary malignant mediastinal GCTs. The peak incidence is in the third decade of life and greater than 90% occur in men.[31,35,37,38] Most patients are symptomatic at presentation. Substernal chest pain, dyspnea, and cough are the most common presenting symptoms. Gynecomastia and superior vena cava syndrome may also accompany seminomas. Because gonadal seminomas may metastasize to the mediastinum, all patients with mediastinal seminoma should undergo a thorough lymph node and gonadal examination. Approximately 10% of patients with seminoma may have an increased beta-hCG level, but never an increased AFP level.[3] On CT scan, they are large, lobulated, well-circumscribed masses with relatively homogeneous attenuation.[36] The histology is essentially the same as gonadal seminomas. If any other germ cell types are present, the tumor is classified as a mixed GCT and is treated like a nonseminomatous GCT.[39] Metastatic disease is common at the time of presentation.[32]

Seminomas are highly sensitive to both chemotherapy and radiation. Chemotherapy may result in better progression-free survival than radiation therapy and is used more often as primary therapy, with an overall 5-year survival greater than 80%.[40] Treatment of residual masses following chemotherapy is controversial. Observation, radiotherapy, and surgery are all reasonable options, but none has clearly been shown to be superior.[41]

Nonseminomatous GCTs

Nonseminomatous GCTs comprise a heterogeneous group of histologies that include yolk sac tumor, choriocarcinoma, embryonal carcinoma, and mixed GCTs. Like seminomas, they occur predominantly in men and have a peak incidence in the third and fourth decades of life.[42] In addition to local symptoms of chest pain, dyspnea, cough, and superior vena cava syndrome, nonseminomatous GCTs are more likely to present with systemic symptoms of fever, chills, and weight loss. Gynecomastia may accompany beta-hCG secreting tumors. Kleinfelter syndrome may be observed in 20% of patients.[3] Most patients have an increased AFP level and many have an increased beta-hCG level.[31] The combination of an anterior mediastinal mass in a young man

with an increased AFP level is so characteristic of a nonseminomatous GCT that some oncologists are willing to begin chemotherapy in this setting without a tissue diagnosis. Chemotherapy is the standard primary treatment, but fewer than half of patients have normalization of tumor markers following chemotherapy.[32] Whenever possible, complete surgical resection of residual tumor should be attempted after chemotherapy.[43,44] If viable tumor is identified in surgical specimens, additional chemotherapy is recommended. Nonseminomatous GCTs in the mediastinum carry a worse prognosis than retroperitoneal nonseminomatous GCTs. Even with multimodality therapy, the overall 5-year survival is only 40% to 60%.[32,45]

Thyroid

Substernal goiter is found in 3% to 20% of all operations for goiter.[46] Most are asymptomatic, but some patients may present with compression of the airway, dysphagia, hoarseness, or superior vena cava syndrome.[3] If a substernal goiter is suspected, iodinated contrast should be avoided because of the risk of iodine-induced hyperthyroidism and possible delay of radioiodine scanning. Radioactive iodine ablation has a low success rate for substernal goiter, therefore total thyroidectomy is the treatment of choice. The entire gland can be removed via a cervical approach in more than 95% of patients.[46] The surgery team should be aware of tracheomalacia associated with large goiters and the possibility of airway compromise (**Fig. 4**). Upwards of 10% of patients are not able to be extubated immediately postoperatively secondary to this effect. Informed surgical consent should contain a section on the possibility of tracheostomy.

Parathyroid

Ectopic parathyroid adenomas in the mediastinum are a common cause of failed operations for hyperparathyroidism. In 1 series of 285 patients with hyperparathyroidism, 20/53 (38%) of the reoperations had mediastinal parathyroid tumors. Eighty-one percent of the mediastinal parathyroids were in the anterior mediastinum and 19% were in the posterior mediastinum. Eighty-eight percent were removed via cervical incision.[47] Sestamibi scan is particularly helpful for identifying these ectopic adenomas.

Lymphoma

Most patients with mediastinal lymphoma have systemic disease and only 10% of patients have primary mediastinal lymphoma. The most common types of mediastinal lymphoma are Hodgkin disease, large B-cell lymphoma, and lymphoblastic lymphoma.[1,3,37] FNA is typically not sufficient for flow cytometry. Thus, the primary

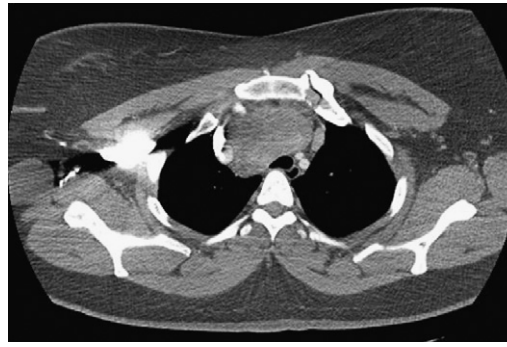

Fig. 4. CT scan of a large substernal goiter with tracheal compression.

role of the surgeon is for tissue diagnosis when core needle biopsy is not possible or is not sufficient for flow cytometry.

MIDDLE MEDIASTINUM

Lymphoma, granulomatous disease, mediastinal cysts, and tracheal tumors are the most common masses in the middle mediastinal. Aside from lymphoma, true tumors of the middle mediastinum are rare. Airway compression and dysphagia are the most common presenting symptoms.

Mediastinal Cysts

Mediastinal cysts are true cysts with fluid-filled, cell-lined sacs. They make up 12% to 25% of all mediastinal masses.[2,48,49] Although cysts may be found in any compartment of the mediastinum, they are most commonly found in the middle mediastinum. Most mediastinal cysts are asymptomatic in adults, but are more likely to be symptomatic in children.[49] A plain radiograph can often make the diagnosis, but CT scan should be obtained to better define the extent of the lesion. Cysts are usually distinguishable from solid tumors on CT scan.[5] CT typically demonstrates a round, well-demarcated, fluid-filled mass. The wall may or may not have calcifications. Some tumors (thymomas, GCTs) can undergo cystic degeneration and may be difficult to distinguish from a cyst. In addition, if a cyst contains nonserous fluid, it may appear solid on CT. In these cases, MRI may be helpful, demonstrating increased signal intensity on T2-weighted MRI.[5] Historically, surgeons have advocated resection of all bronchogenic cysts because up to 72% of these patients may become symptomatic or develop complications, at which time resection may be more difficult.[50] However, we have found that most asymptomatic cysts may be observed. Specific types of cysts are now described.

Enterogenous and bronchogenic cysts both develop as outgrowths from the primitive foregut in the fourth to eighth week of gestation.[51] Bronchogenic cysts compose 40% to 50% of mediastinal cysts.[48,49] They are lined by ciliated columnar epithelium and may contain bronchial glands and mucoid material. Cartilage is often found in the cyst wall. Forty percent of patients are symptomatic at presentation with chest pain, cough, and fever being the most common symptoms.[48] Most bronchogenic cysts are not in communication with the tracheobronchial tree and are homogeneous. However, if a communication or infection develops, an air-fluid level may be seen.[52] The diagnosis is often made radiologically. However, if a more definitive diagnosis is necessary, a needle aspiration by transbronchial, endoscopic, or percutaneous methods could be obtained.[53] Endobronchial ultrasound has also been reported for therapeutic aspiration and follow-up of a bronchogenic cyst.[54] Although rare, esophageal duplication cysts are the second most common enteric duplication cysts after ileal duplication cysts.[55] The cysts are lined by squamous or alimentary tract epithelium. They may contain gastric or pancreatic tissue. Symptoms are similar to bronchogenic cysts, but patients are more likely to present with dysphagia. Gastric mucosa may cause hemorrhage or perforation. The CT appearance is similar to bronchogenic cysts, but the wall may be thicker and more often calcified. Patients with possible esophageal duplication cysts should undergo barium swallow and endoscopy to determine communication with the lumen of the esophagus when symptomatic. Endoscopic ultrasound is accurate for the diagnosis of esophageal duplication cysts and is being used more frequently for their treatment. Endoscopic treatment via aspiration or resection of the cyst wall has been reported.[53,56]

Pericardial cysts are lined by mesothelium and are connected to the pericardium, although usually not in communication with the pericardial space. Most occur at the right cardiophrenic angle.[5] They are usually asymptomatic and present later in middle age, and are often found incidentally on echocardiography.[57] On CT, they are well circumscribed, round or teardrop shaped with homogeneous fluid. These cysts are usually observed if asymptomatic.

If there is a solid component or if the diagnosis is in doubt, mediastinal cysts may be aspirated. This often relieves any local symptoms as well. Depending on the location of the cyst, needle aspiration may be performed via a percutaneous, transbronchial, or transesophageal approach.[53,54] There is a chance of infecting a previously sterile cyst with aspiration, and most cysts can be removed thoracoscopically with low morbidity and minimal chance of recurrence.[58] Thus, in most cases, it may be more prudent to simply resect the cyst than risk infecting it with transbronchial or transesophageal aspiration.

POSTERIOR MEDIASTINUM

In the posterior mediastinum, neurogenic tumors and esophageal tumors are the most common masses.[2] Neuroenteric cysts are rare foregut malformations that contain both enteric and nerve tissue that are also found in the posterior mediastinum.[59] Neurogenic tumors constitute 75% of primary tumors in the posterior mediastinum.[2,60] Most arise from the spinal nerve roots or sympathetic chain and are located in the paravertebral sulcus. Most tumors in the posterior mediastinum are asymptomatic, but they may cause neuralgia or present with Horner syndrome from sympathetic ganglion involvement depending on location.[60,61] Neurogenic tumors are benign in 70% to 80% of cases.[2,60]

Neurogenic tumors have a characteristic appearance depending on their histology. MRI does not typically add much diagnostic information beyond CT, but may be of value in planning surgery, particularly for determining spinal cord involvement of neurogenic tumors.[62] *Meta*-Iodobenzylguanidine (MIBG) scans can help localize neuroblastomas and catecholamine-secreting paragangliomas.[63] Urine metanephrines and catecholamines should be measured in patients with paragangliomas who have symptoms or radiographic appearance suspicious for catecholamine-secreting tumor.

Nerve Sheath Tumors

Nerve sheath tumors compose 40% to 65% of neurogenic tumors in the chest.[1] Approximately 75% of these nerve sheath tumors are schwannomas (neurilemmomas) and 25% are neurofibromas. Whereas schwannomas are firm and encapsulated, neurofibromas are soft and nonencapsulated, although they may have a pseudocapsule; 10% to 30% of neurofibromas occur in association with neurofibromatosis. These are more likely to be multiple.[64] Malignant nerve sheath tumors are rare. They include malignant schwannomas, malignant neurofibromas, and neurogenic fibrosarcomas. Symptoms of pain and neurologic deficit are more common among malignant tumors. Approximately half of malignant nerve sheath tumors arise in the setting of neurofibromatosis.[65] Nerve sheath tumors may also grow outward and present as a chest wall mass.

On CT scan, nerve sheath tumors are typically round and well circumscribed. They grow into the intervertebral foramen and take on a dumbbell shape. MRI is helpful to evaluate intraspinal extension.[62] Nerve sheath tumors have increased signal intensity on T2-weighted MRI (**Fig. 5**). Traditionally, resection of all nerve sheath tumors has been recommended to exclude malignancy. However, the incidence of malignant

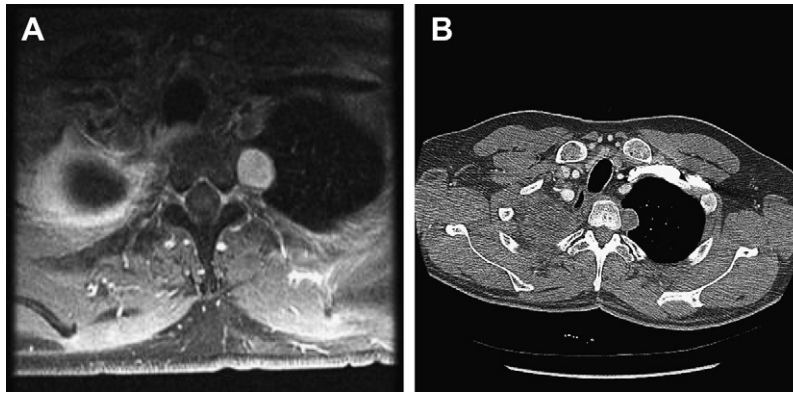

Fig. 5. MRI (*A*) and corresponding CT image (*B*) of an apical neurofibroma. The MRI shows increased signal intensity on a T2-weighted image.

nerve sheath tumor is so low that we recommend observation of small tumors without any high-risk features (symptoms, size >5 cm, previously irradiated field, evidence of invasion on CT or MRI).[65]

When necessary, benign nerve sheath tumors can be resected thoracoscopically in more than 90% of cases.[66,67] Dumbbell tumors may be removed with a combined open neurosurgical approach for the spinal component and a thoracosocpic approach for the thoracic component. Horner syndrome, sympathectomy, and paraplegia are possible complications, but all of these usually improve with time. A more radical resection, often including a chest wall resection, is the treatment of choice for malignant nerve sheath tumors. Adjuvant chemotherapy and radiation may also be of value in this setting.[65]

Ganglion Tumors

Autonomic ganglion tumors in the mediastinum usually occur in the sympathetic ganglia, but may occasionally occur in the parasympathetic ganglia. These tumors arise from nerve cells rather than the nerve sheaths.[63] They are primarily pediatric tumors, with two-thirds occurring in patients less than 20 years of age. Unlike nerve sheath tumors, most ganglion tumors are malignant.[61,68] On imaging, they are typically oblong-shaped, well-circumscribed, large masses that occur along the anterolateral border of the spine. On CT scan, they are more likely to have calcifications than nerve sheath tumors.[69]

Ganglioneuromas are the most common benign ganglion tumors in the mediastinum. They are well-differentiated tumors and most are asymptomatic.[70] They are treated by complete surgical resection.

Neuroblastomas are principally pediatric tumors. Most are diagnosed before 2 years age and the tumor is rare after the age of 10 years. Overall, it is the most common extracranial solid cancer in children, accounting for 6% to 10% of all childhood cancers and 15% of childhood cancer mortality in the United States.[71] Neuroblastomas are nonencapsulated and have small round cells on histology. They are associated with amplification of the *MYCN* oncogene. The tumors are highly aggressive and are frequently metastatic at presentation. Up to 30% of neuroblastomas arise in the mediastinum. In addition to local symptoms, patients may present with fatigue, weight loss, or fever. Neuroblastomas are sometimes associated with paraneoplastic syndromes, including severe diarrhea from vasoactive intestinal peptide and opsomyoclonus. On CT scan 80% of neuroblastomas show calcification. MIBG scanning is helpful for demonstrating

the extent of disease and identifying metastatic disease.[63] Complete surgical resection is the treatment of choice for early stage tumors. Although somewhat controversial, neoadjuvant therapy has been shown to increase the likelihood of complete excision for more advanced tumors.[71] Ganglioneuroblastomas are rare tumors that have features of both ganglioneuromas and neuroblastomas. They are staged similarly to neuroblastomas and prognosis depends on histology.[63]

CHEST WALL TUMORS

Tumors of the chest wall can be either primary or secondary. The secondary tumors are caused by either local invasion (from breast, lung, or pleural cancers) or distant metastases. Primary chest wall tumors are rare, but include a wide variety of benign and malignant histologies (**Table 3**). Among primary tumors of the chest wall, roughly half are benign and half are malignant.[72]

History

Chest wall resections were exceedingly rare until the twentieth century, when the development of anesthesia, asepsis, and positive pressure ventilation allowed chest

Table 3
Primary chest wall tumors

Soft Tissue	
Benign	Lipoma Elastofibroma Neurofibroma Lymphangioma Hemangioma Hamartoma
Desmoid	
Malignant	Malignant fibrous histiocytoma Liposarcoma Leiomyosarcoma Spindle cell sarcoma Angiosarcoma Synovial cell sarcoma Fibrosarcoma Rhabdomyosarcoma Undifferentiated sarcoma Lymphoma
Bone and Cartilage	
Benign	Fibrous dysplasia Enchondroma Osteochondroma Aneurysmal bone cyst Osteoid osteoma Osteoblastoma Eosinophilic granuloma Giant cell tumor
Malignant	Chondrosarcoma Osteosarcoma Ewing sarcoma Primitive neuroectodermal tumor Solitary plasmacytoma

wall resections to be performed safely. In 1887, Joseph O'Dwyer developed a steel apparatus that could be intubated into the larynx and attached to a bellows previously developed by George Fell to deliver positive pressure ventilation. A decade later, F.W. Parham reported using the device in a series of chest wall resections. The following passage from his address to the Southern Surgical Association in 1887 underscores the technical challenges posed by such operations:

> *I operated in the Charity Hospital … for a sarcoma of the thoracic wall requiring the resection of several inches of the third, fourth, and fifth ribs …. A rent of five inches was made, which permitted easily the thrusting of the whole hand into the pleural cavity. Suddenly was presented to our anxious view one of the most startling clinical pictures that the surgeon can ever be called upon to witness. At such a sight the stoutest heart will quaver.*

In Parham's review of the world literature at the time, he reported a perioperative mortality rate of 30%.[73] Since that time, advances in anesthesia and perioperative care have improved the mortality for thoracic surgery. In addition, the development of reconstructive techniques has helped decrease the long-term morbidity of chest wall resection. Today, surgery is the main therapy for most primary chest wall malignancies and postoperative mortality should approach zero. Advances in imaging and adjuvant therapy continue to improve the diagnosis and treatment of these rare tumors.

Chest Wall Anatomy

A thorough understanding of the structure and function of the chest wall is critical to the evaluation and treatment of chest wall tumors. The chest wall provides a semi-rigid cage that protects the thoracic viscera but allows for respiratory movement.[74] The bony frame is formed by the ribs, vertebral bodies, and sternum. Normally, there are 12 paired ribs on each side. The first 7 are referred to as true ribs, whereas the bottom 5 are referred to as false ribs. Anteriorly, the true ribs are attached to the costal cartilage of the sternum. The 8th to 10th ribs connect to the costal cartilage of the seventh rib. The bottom 2 ribs are unattached anteriorly and are referred to as floating ribs.

The structure of the chest wall facilitates respiratory mechanics, allowing effective ventilation. The curvature of the lower ribs causes a bucket handle type of movement with inspiration, allowing the ribs to move laterally and cephalad and helping the lower chest to expand in volume. The external intercostals contribute to the lateral and cephalad retraction of the ribs during inspiration, whereas the internal and innermost intercostals contribute expiratory force.

The muscles of the chest wall serve a variety of functions. The accessory muscles of respiration include the scalenes, trapezius, pectoralis minor, rhomboids, and serratus. The scapula and clavicle form the pectoral girdle, which connects the upper extremity to the axial skeleton. The rhomboids and trapezius retract the pectoral girdle, whereas the serratus anterior and pectoralis minor protract (push) the pectoral girdle. The supraspinatus, pectoralis major, latissimus dorsi, teres major, teres minor, subscapularis, and infraspinatus all aid in movement of the upper extremity. A thorough understanding of the blood supply of these muscles is critical for chest wall resections because they may be used for flap coverage and reconstruction.

General Approach to Chest Wall Tumors

Most tumors of the chest wall present either as an enlarging, asymptomatic mass or with pain. Bony and cartilaginous tumors are often identified incidentally on imaging. The presence of pain is more common with malignant lesions. Many tumors, particularly cartilaginous tumors, have a characteristic radiologic appearance.[75] If

a suspicious osseous lesion is seen on routine chest radiograph, a dedicated, lower voltage bone radiograph may better delineate the abnormality. CT scan is usually necessary to identify the extent of the lesion and aid in planning possible resection. MRI is helpful for determining disc space or neural involvement.[76] PET is not a routine part of the evaluation of chest wall tumors, but there are some data that PET may be more accurate than CT scan for determining the extent of large tumors.[77] The use of ultrasound to mark the edges of a tumor has also been shown to help in obtaining negative surgical margins.[78]

Historically, incisional biopsy has often been performed for diagnosis; however, at our institution, we have found that FNA or core needle biopsy is preferable and usually sufficient for diagnosis with a skilled cytopathologist.[79,80] The biopsy track should be within the planned excision site whenever possible. Therefore, biopsy is preferably performed at the treating center rather than the referring center. Excisional biopsy may be performed for benign-appearing tumors less than 2 cm involving only 1 rib. If malignancy is found, then a wider excision may be performed. For malignant or large tumors, a multidisciplinary approach is valuable for planning neoadjuvant therapy, reconstruction, and adjuvant therapy.

Soft Tissue Tumors

Benign

Deep chest wall lipomas can be difficult to distinguish from liposarcoma or other sarcomas by physical examination. On CT, lipomas are typically homogeneous and do not enhance with intravenous contrast, whereas liposarcomas have heterogeneous enhancement and tend to be larger. They both have high signal intensity on T2-weighted MRI.[81]

Elastofibromas are benign tumors that classically occur in the subscapular region. They have a female predominance with a peak incidence in the 40- to 70-year-old age range. These tumors have a characteristic layered appearance on CT and exhibit mild enhancement with intravenous contrast.[82] Local excision is curative.

Other benign lesions found in the soft tissue of the chest wall include neurofibroma, lymphangioma, and hamartoma.

Desmoid

Desmoid tumors are rare tumors that do not metastasize but can be difficult to treat because of their locally aggressive nature and propensity for local recurrence. They are often associated with familial adenomatous polyposis. Most desmoids tumors occur in the abdominal wall, but the chest wall and shoulder girdle are common sites for extra-abdominal disease.[83] The peak incidence is in the second and third decades of life. On CT and MRI, desmoid tumors have a variable nondescript appearance depending on the amount of collagen content, but generally have similar enhancement to muscle.[76]

Local control can be difficult, particularly in the chest. The recurrence rate for chest wall desmoids tumors is 25% to 75%.[83–85] Wide margins are critical because of the high incidence of microscopic positive margins. In a series of 53 patients with desmoids tumors of the chest wall, 7 (13%) had positive margins. The local recurrence rate was 89% for those with positive margins, compared with 18% for those with negative margins.[84] Chemotherapy using a doxorubicin-based regimen may be of benefit in the adjuvant setting. Antiestrogens, such as tamoxifen have also been used.[86] Radiation therapy is typically used for unresectable disease, for locally recurrent disease, or to treat positive margins, but its effectiveness remains uncertain.

Soft tissue sarcomas

Soft tissue sarcomas of the chest come in a wide range of histologies, including malignant fibrous histiocytoma (MFH), angiosarcoma, leiomyosarcoma, synovial cell sarcoma, spindle cell, liposarcoma, and undifferentiated sarcomas. These tumors can arise either de novo or in the setting of previous radiation therapy. On CT, they usually have a heterogeneous appearance with varying levels of enhancement with intravenous contrast.[87] Depending on the histology, sarcomas demonstrate varying degrees of calcification on CT scan.[88] The diagnosis cannot be made radiologically and therefore requires tissue for confirmation. Normally a core biopsy is sufficient.

The mainstay of therapy for soft tissue sarcomas is surgical resection with wide margins. A 2-cm margin is recommended for low-grade sarcomas, and a 4-cm margin with resection of a rib above and below the tumor is recommended for high-grade sarcomas.[79] Published series report 5-year survival rates with a wide range (50%–80%), reflecting the heterogeneity of these tumors.[79,89–92] Margin status, grade of tumor, and histology have all been shown to be associated with survival.[93,94] Because chest wall sarcomas are rare, the use of adjuvant therapies for these lesions has largely been extrapolated from experience with extremity sarcomas. For large tumors or if there is any question about the resectability of a tumor, a multidisciplinary approach with neoadjuvant therapy should be considered. If it can be done safely, reoperation should also be performed for local recurrences. Wouters and colleagues[95] reported a 5-year survival rate of 50% following reoperation for recurrent chest wall sarcoma without a significantly increased risk of perioperative complications.

Cartilage and Bone

Metastatic tumors of the bones and cartilage of the chest wall are far more common than primary tumors. Primary tumors are equally likely to be benign or malignant. Tumors arising in the sternum are more likely to be malignant.[76,96]

Benign Tumors

Fibrous dysplasia (FD) is the most common benign tumor of the ribs, accounting for 30% of benign chest wall tumors.[96] FD is not a true neoplasm, but is a tumor that occurs because of the failure of osteoblasts to undergo normal maturation. The marrow is instead replaced by immature bone and fibrous stroma. FD is slow growing and typically asymptomatic at presentation, although may present with pathologic fracture or local pain. In 75% of patients FD is monostotic, affecting 1 rib; in 25% it is polyostotic, affecting multiple ribs or other bones. Monostotic FD most commonly affects the second rib. When polyostotic FD is associated with café-au-lait macules and endocrine abnormalities, it is known as McCune-Albright syndrome.[97] The diagnosis of FD is usually made radiologically and these lesions do not require therapy unless symptomatic.

Osteochondroma and enchondroma are the next most common benign tumors of thoracic bones and cartilage, but each composes less than 10% of primary chest wall tumors.[96,98] They have a peak incidence in the second decade of life. Osteochondromas arise from the cortex of bone and are characterized by a cartilaginous covering. Fifteen percent of osteochondromas occur in the setting of multiple hereditary exostoses. In the chest, osteochondromas are most commonly found at the costochondral junction. The risk of malignant degeneration to chondrosarcoma is related to the thickness of the cartilaginous cap. Caps greater than 2 cm thick are suspicious for carcinoma.[81,96] Enchondromas are cartilaginous tumors that arise from the medullary cavity. They have a lobulated appearance with distinct borders. In the chest, enchondromas typically occur in the anterior portions of the ribs.

Aneurysmal bone cysts (ABCs) are osteolytic lesions with blood-filled cystic spaces. ABCs are often associated with abnormal bone. They are sometimes preceded by trauma or may be found in the setting of an underlying bone tumor such as osteoblastoma. In the chest, they are typically located in the lateral and posterior ribs. Surgery is the mainstay of treatment with cure rates of 70% to 90%.[99] ABCs do not metastasize, but radiation therapy is occasionally used for local control in the setting of locally aggressive or recurrent tumors.

Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X, can affect many different types of tissue, but commonly affects bone. Bony involvement can be monostotic or polyostotic.[100] Eosinophilic granuloma is a form of LCH that is isolated to the bone. Most forms of LCH are not treated surgically, but isolated eosinophilic granuloma can be treated with resection or curettage with good results. Most eosinophilic granulomas are monostotic and affect children less than 15 years of age. Solitary eosinophilic granulomas involve the ribs in 9% to 15% of patients. The destructive lytic appearance may resemble Ewing sarcoma, particularly if there is a significant soft tissue component. Osteoid osteoma is the most common benign bone tumor overall, accounting for 10% to 20% of benign bone tumors in the body.[101] However, it is rare in the ribs and accounts for only 1% of primary rib tumors. It is characterized by a nidus of osteoid tissue surrounded by a rim of reactive sclerotic bone. In the chest, it usually presents with pain, particularly at night. Most tumors occur in the posterior rib and have a characteristic appearance on bone scan, called the doubled density sign.[96] Osteoblastoma has many similarities to osteoid osteoma and was known formerly as giant osteoid osteoma. It is also rare in the ribs. Lesions are typically larger than osteoid osteoma and do not have a central nidus. Although osteoblastomas are benign, they may be locally aggressive with potential for local recurrence, thus resection of all affected bone is the preferred treatment.[102] Giant cell tumors occur rarely in the ribs, with a peak incidence in the third and fourth decades of life. Although considered benign, they can be locally aggressive. Wide local excision is recommended.[96,103]

Malignant

Chondrosarcoma

Chondrosarcoma is the most common primary malignant tumor of the chest wall. They most commonly occur along the costochondral junction. The age of presentation has 2 peaks: 1 in the second decade of life and the other in the fifth decade of life.[87] There is a slight male predominance.[88] Most patients present with a large mass, which may or may not be accompanied by pain. Depending on the degree of differentiation and invasion, tumors can have a wide range of appearance on imaging. CT demonstrates areas of calcification in the chondroid matrix (**Fig. 6**). Surgery with wide margins is the primary mode of treatment. Incomplete resection is associated with decreased survival. In 1 series of 106 patients with chest wall chondrosarcoma, patients who underwent surgery with wide margins had a 10-year survival rate of 92%, compared with 47% for incomplete resection. The local recurrence rates were 4% and 73%, respectively.[104] Radiation therapy has been shown to help with local control for recurrent or incompletely resected disease. Chemotherapy has not yet been shown to provide significant benefit, except possibly for mesenchymal or dedifferentiated subtypes.[105]

Osteosarcoma

Although osteosarcoma is the most common malignant bone tumor throughout the body, it is rare in the chest wall. Only 1% to 3% of osteosarcomas involve the chest wall.[106,107] The peak incidence is in the second decade of life. Like the other malignant

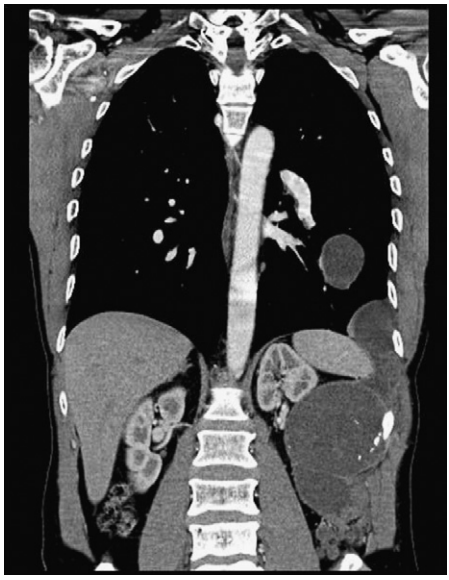

Fig. 6. CT scan of a chondrosarcoma originating from the 10th rib. Note the extensive intra-abdominal as well as intrathoracic component of the tumor.

bony tumors of the chest wall, most patients present with a painful mass. On CT, there is typically a large mass that is heterogeneous with areas of bony destruction (**Fig. 7**). Because of the poor results from single modality therapy for osteosarcomas of the chest wall, these tumors are typically treated with neoadjuvant chemotherapy followed by surgery. As with the other sarcomas, clear margins are associated with improved survival. Osteosarcomas are not very radiosensitive, but radiation therapy has been used for tumors with inadequate resection. The overall survival, even with neoadjuvant therapy, is 15% to 27% at 5 years compared with 65% to 75% for extremity osteosarcomas.[107]

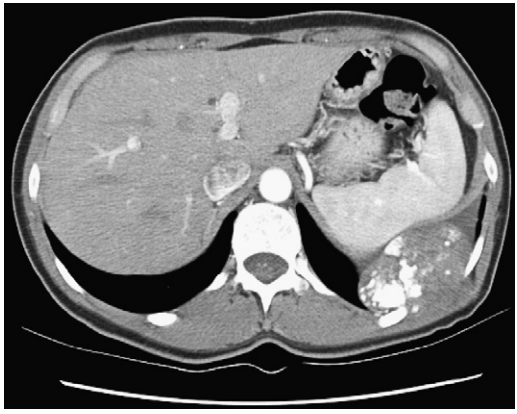

Fig. 7. Primary osteosarcoma of the chest wall.

Ewing sarcoma and primary neuroectodermal tumors

The Ewing sarcoma family of tumors includes Ewing sarcoma and primitive neuroectodermal tumor (PNET). These tumors harbor the same chromosomal translocation t(11;22) and are believed to arise from primitive cells of the neural crest.[108] PNETs that arise in the chest are also known as Askin tumors.[109] Ewing sarcoma/PNET tumors typically occur in the first 2 decades of life and are the most common tumor of the chest wall in children and young adults.[110] In the chest, Ewing sarcoma most commonly affects the ribs, but may arise in the paravertebral region or occasionally in the soft tissue. Most patients have pain as a presenting symptom. CT scan typically shows a large ill-defined tumor with cystic degeneration with soft tissue extension. Tumors usually have increased signal intensity on T1-weighted MRI and intermediate intensity on T2-weighted images.[87,109] However, larger tumors have heterogeneous intensity. Retrospective analysis from an intergroup study found that patients with Ewing sarcoma of the rib were more likely to undergo complete resection and avoid radiation therapy if chemotherapy was given before surgery.[111,112] Therefore, it is recommended that most patients with Ewing sarcoma undergo multimodality therapy. Radiation therapy has been shown to provide good local control when complete resection is not possible, but has significant cardiopulmonary toxicities in the chest and also has oncogenic potential in such a young patient population.[113] Five-year survival is greater than 60% with chemotherapy and surgery.[111]

Reconstruction of the Chest Wall

Reconstruction of the chest wall can be complex and often requires working with a plastic surgery team. The ideal reconstruction provides protection to the thoracic viscera and preserves respiratory mechanics with a good cosmetic outcome. For posterior rib defects, the scapula may provide adequate coverage and stabilization. For lateral and anterior defects greater than 5 cm in diameter, a synthetic material is used to provide a frame, which is covered by vascularized tissue. Polypropylene and polytetrafluoroethylene are the most commonly used synthetic meshes. In cases where rigidity is required, we typically use methyl methacrylate sandwiched between 2 pieces of Marlex mesh. This should then be covered with a vascularized tissue flap. A variety of pedicled and free muscle flaps have been described for chest wall reconstruction. Omental flaps may also be used, but require a laparotomy and may lead to hernia formation.[114]

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