Main Thoracic Tumors in Pediatric Age

21

Stefano Avanzini, Federico Palo,
Vittorio Guerriero, and Girolamo Mattioli

21.1 Introduction

Thoracic tumors in pediatric age mainly arise from the mediastinum. Tumors arising from the bone and cartilage of the chest wall are rare. Primary lung and bronchial tumors are exceptionally rare, while metastases are more frequent. Thoracic tumors are most commonly discovered incidentally on chest radiographs. Large thoracic masses can cause compression of adjacent structures. Patients may have airway compression or cardiovascular compromise (Fig. 21.1) [1]. The location of the mass, its effect on adjacent mediastinal organs, and its radiological internal characteristics (calcification, fat, water, and necrosis) can help in establishing a differential diagnosis and clinical planning [2].

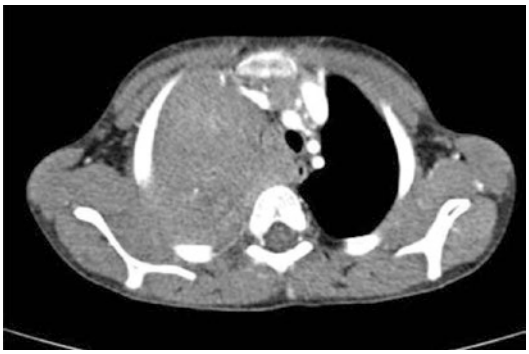

Fig. 21.1 Huge thoracic tumor with airway displacement

21.2 Classification

Classification of thoracic tumors is mainly related to the site of origin of the mass. They can be grossly divided into:

- Mediastinal tumors
  - Anterior mediastinum
  - Middle mediastinum
  - Posterior mediastinum
- Lung tumors
  - Primary
  - Secondary
- Chest wall tumors
  - Primary
  - Secondary
- Airways tumors

S. Avanzini (✉)
Pediatric Surgery, IRCCS Giannina Gaslini, Genoa, Italy
e-mail: stefanoavanzini@gaslini.org

F. Palo · G. Mattioli
Pediatric Surgery, IRCCS Giannina Gaslini Genoa, University of Genoa, DINOGMI, Genoa, Italy
e-mail: girolamomattioli@gaslini.org

V. Guerriero
Pediatric Surgery and Airway Team, IRCCS Giannina Gaslini, Genoa, Italy
e-mail: vittorioguerriero@gaslini.org

G. Mattioli et al. (eds.), *Pediatric Thoracic Surgery*, https://doi.org/10.1007/978-3-030-74668-1_21

21.2.1 Mediastinal Tumors

Mediastinal masses in children are a heterogeneous group of asymptomatic or potentially life-threatening congenital, infectious, or neoplastic lesions that present complex diagnostic and therapeutic dilemmas.

The mediastinum is located in the central portion of the thorax, between the two pleural cavities, the diaphragm and the thoracic inlet [3]. The classification of Fraser et al. [4] divides the mediastinum into the traditional anterior, middle, and posterior compartments based on the lateral chest radiograph. The anterior mediastinum is defined as the region posterior to the sternum and anterior to the heart and brachiocephalic vessels. It contains the thymus, fat tissue, and lymph nodes. The middle mediastinal compartment is located posterior to the anterior mediastinum and anterior to the posterior mediastinum. This space contains the heart and pericardium, the ascending and transverse aorta, the brachiocephalic vessels, the vena cava, the main pulmonary artery and veins, the trachea, bronchi, and lymph nodes. The posterior mediastinal compartment is located posterior to the heart and trachea and extends posteriorly to the thoracic vertebral margin and includes the costovertebral space. It contains the descending thoracic aorta, esophagus, azygos veins, autonomic ganglia and nerves, thoracic duct, lymph nodes, and fat [5]. Mediastinal masses are usually assigned to a single mediastinal compartment to limit the differential diagnosis. Because tumors arise from normal structures that may be located within multiple regions, a given mass can develop in any compartment.

21.2.1.1 Anterior Mediastinum

Several benign and malignant conditions may arise in the anterior mediastinum (see Box 21.1).

Box 21.1 Pediatric Anterior Mediastinal Masses. *Most Frequent Diseases

Pediatric anterior mediastinal masses	
Thymus	**Normal thymus***
	Thymic cyst
	Thymomegaly
	Thymoma
	Thymic hemorrhage
Adenopathy	**Infectious adenopathy***
	Lymphoma or leukemia*
	Sarcoidosis
	Castleman disease
	Rosai–Dorfman disease
Solid tumors	**Germ cell tumors***
	Thyroid or parathyroid tumors
	Hamartoma
	Vagus-phrenic nerve tumors
	Hemangioma
	Sternal tumors
Infections	Mediastinitis
	Sternal osteomyelitis or abscess
Vascular abnormalities	Vascular malformations
	Aneurysm
Other	Histiocytosis
	Morgagni's hernia
	Hematoma
	Extension of middle mediastinal mass

Thymus

Thymic disorders are rare in the pediatric population. Hyperplasia of the thymus is the most common process to involve the thymus gland in infants and children. The hyperplastic gland usually maintains the radiographic characteristics of the normal thymus. Thymic enlargement rarely causes neonatal respiratory distress but should be considered in the differential diagnosis of marked tachypnea in the neonatal period [6]. Thymomas account for up to 4% of pediatric mediastinal neoplasms [7, 8]. Thymoma is associated with four organ-specific autoimmune diseases: (1) myasthenia gravis (2) type 1 diabetes mellitus, (3) autoimmune hepatitis, and (4) Hashimoto's thyroiditis [7].

Lymphoma

Lymphomas are the third most common group of cancers in children and adolescents, accounting for approximately 13% of newly diagnosed cancers in this age group. Non-Hodgkin's lymphoma represents approximately 60% of these diagnoses, and Hodgkin's disease accounts for the remainder [9–12]. Lymphomas are the most com-

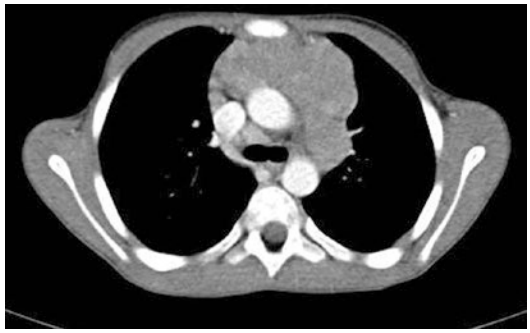

Fig. 21.2 Anterior mediastinal mass (lymphoma)

mon cause of masses in the pediatric mediastinum (Fig. 21.2). More than 50% of children with lymphoblastic lymphoma present with an anterior mediastinal mass, and more than one-third of all patients with non-Hodgkin's lymphoma have their primary sites in the mediastinum. Hodgkin's disease also frequently involves this anatomic compartment with approximately two-thirds of all pediatric cases manifesting mediastinal adenopathy [13]. Being radiological and clinical presentation similar in different lymphoma subtypes, biopsy (either image-guided needle biopsy or properly surgical) may be the only possibility to diagnose and classify the tumor and consequently address the appropriate chemotherapy.

Germ Cell Tumors

Germ cell tumors are the third most common neoplasm of the mediastinum after lymphoma and neurogenic tumors. Most often, they arise within the anterior mediastinum near the thymus gland. A small subset of germ cell tumors arises from other mediastinal compartments. Germ cell tumors account for 6–18% of mediastinal tumors and comprise only 1–3% of all germ cell tumors [14, 15]. Two theories have been proposed to explain the development of malignant nonseminomatous germ cell tumors (MNSGCT). One is that mediastinal germ cell tumors originate from germ cells that mismigrate during embryogenesis, and the other theory is that they originate from germ cells that are widely distributed during embryogenesis. Both theories could explain the central location of germ cell tumors in the mediastinum, retroperitoneum, sacrococcygeal area, and in the central nervous system [16, 17].

Teratomas are the most common mediastinal germ cell tumor and are divided into mature, immature, and mixed malignant types. Nonteratomatous tumors include seminoma, yolk sac tumor, embryonal carcinoma, choriocarcinoma, and mixed types. A malignant germ cell tumor is a complex tumor of varied histology with frequent coexistence of benign elements. Lesions often have incomplete regression with chemotherapy alone, and tumor resection may be undertaken at diagnosis or after primary chemotherapy [18].

The clinical picture is nonspecific. Germ cell tumors are large and produce respiratory distress caused by tracheobronchial compression. Most children have a subacute course that may span several weeks or longer. Germ cell tumors can be seen in patients with Klinefelter's syndrome and may present with precocious puberty [19].

With chest radiography, teratomas can be rounded or lobulated and can be large in size. Up to 26% of teratomas exhibit calcification [20]. On CT scan, teratomas are multilocular cystic tumors with a variable wall thickness [21]. The combination of fluid, soft tissue, calcium, and fat attenuation in the anterior mediastinal mass is highly specific for teratoma [5]. Seminoma generally presents as a bulky lobulated mass, which uncommonly invades adjacent structures but can metastasize to regional lymph nodes and bone [22–24]. Seminoma rarely calcifies. Nonseminomatous malignant germ cell tumors are radiographically large and irregular with extensive heterogeneous areas of low attenuation on CT caused by necrosis, hemorrhage, and cyst formation [23]. Germ cell tumors appear on MR imaging as masses of heterogeneous signal intensity. The most striking difference between mediastinal and gonadal nonseminomatous germ cell tumors concerns prognoses. Overall, 5-year survival in MNSGCT is about 40%, which is much lower than in gonadal non-seminomatous germ cell tumor and is a unique feature of MNSGCT [24, 25].

The current standard treatment in MNSGCT is chemotherapy combined with post-chemotherapy residual mass excision. In most cases, surgery is technically challenging. Adhesion and invasion of surrounding structures are usually found during exploration, and vascular involvement often makes complete excision impossible. Total resection includes en bloc resection of the primary

lesion and the complete excision of metastatic lesions. Given poor alternative options in this aggressive disease, surgery may also be offered even to patients with increasing post-chemotherapy markers if complete resection can be accomplished. Unfortunately, hope for cure remains feeble in this subset of patients and supports ongoing investigation of other salvage modalities for primary treatment failure [26].

After the introduction of cisplatin-based chemotherapy, followed by surgical resection, survival in cases of MNSGCT improved dramatically, and this multimodality treatment has become the standard treatment for MNSGCT [27, 28].

21.2.1.2 Middle Mediastinum

Benign and malignant conditions may arise in the middle mediastinum (sometimes extending from the anterior mediastinum), the majority and more relevant to the aim of this chapter being adenopathies (see Box 21.2).

Box 21.2 Pediatric Middle Mediastinal Masses. * Most Frequent Diseases

Pediatric middle mediastinal masses	
Adenopathy	**Infectious adenopathy (e.g., tuberculosis)*** **Metastatic disease*** **Lymphoma or leukemia*** Sarcoidosis Castleman disease Rosai-Dorfman disease
Solid tumors	Thyroid or parathyroid tumors Vagus-phrenic nerve tumors Cardiac tumors Hemangioma Hamartoma
Infections	Mediastinitis
Vascular abnormalities	Vascular malformations Vascular rings Aneurysm
Other	**Bronchopulmonary foregut malformations (i.e., esophageal duplication cyst, neuroenteric cyst)*** Histiocytosis Hematoma Diaphragmatic rupture Pancreatic pseudocyst Esophageal hernia Achalasia, chalasia Pericardiac cyst

Lymph node groups may be visible on chest radiography when they become enlarged. The etiology of lymph node enlargement is extensive. In fact, most middle mediastinal masses are caused by either adenopathy or bronchopulmonary foregut malformations. The most frequent causes of adenopathy are lymphoma; leukemia; tuberculosis; histoplasmosis; sarcoidosis; cystic fibrosis; infectious mononucleosis; Langerhans' cell histiocytosis; Castleman disease; and metastatic neoplasms, such as neuroblastoma in the young child and testicular carcinoma in the teenager that metastasize to mediastinal nodes [29].

21.2.1.3 Posterior Mediastinum

Of all pediatric mediastinal masses, 30–40% occur in the posterior mediastinum [5]. Most (85–90%) of these masses are of neurogenic origin [30]. CT and MR imaging are used to stage the extent of the disease, establishing a differential diagnosis list, and help in judging the efficacy of treatment (see Box 21.3).

Box 21.3 Pediatric Posterior Mediastinal Masses. *Most Frequent Diseases

Pediatric posterior mediastinal masses	
Ganglion cell tumors	**Peripheral neuroblastic tumors*** **• Neuroblastoma** **• Ganglioneuroblastoma** **• Ganglioneuroma**
Other nervous system tumors	Nerve sheath tumors (schwannoma, neurofibroma) Paraganglioma
Adenopathy	Metastases Infectious adenopathy Sarcoidosis Castleman disease Rosai-Dorfman disease
Solid tumors	Osseocartilaginous tumors Thoracic duct cyst Hemangioma
Infections	Mediastinitis Vertebral osteomyelitis Diskitis
Vascular abnormalities	Vascular malformations Aneurysm Dilated azygous system

Pediatric posterior mediastinal masses	
Other	Hematoma (secondary to fracture) Bochdaleck's congenital diaphragmatic hernia Extramedullary hematopoiesis Lateral meningocele Extension of normal thymus Histiocytosis

Neurogenic Tumors

Neurogenic tumors or ganglion cell tumors arise from the sympathetic chain ganglia. These lesions range from malignant masses (neuroblastoma) to benign tumors (ganglioneuroma). Ganglioneuroblastoma has components of both ganglioneuroma and neuroblastoma. All three histologic types are radiographically indistinguishable. Therefore, the appropriate differential diagnosis is partly determined by the patient's characteristics, blood and urine examinations, and mostly by biopsying the tumor.

Neuroblastoma is the most common extracranial solid tumor in children. It represents 10% of all childhood cancers and, because of its potentially highly aggressive nature, accounts for 15% of cancer deaths [31]. After the abdomen, the thorax is the second most common location of neuroblastoma (15%) followed by the neck (1–5%) and the pelvis (2–3%) [32, 33].

Age at presentation is one of the most important criteria when evaluating a patient with a posterior mediastinal mass. Neuroblastoma is a malignancy of young children and is diagnosed at a median age of less than 2 years old and greater than 95% by age 10. In younger patients (less than 5 years old), neuroblastoma is twice as common in boys as girls. As they get older, however, it affects both sexes equally. Fetal or congenital neuroblastoma may even be seen on prenatal ultrasonography. The median age of presentation of ganglioneuroblastoma is 5.5 years of age. Mature ganglioneuroma presents even later in childhood, most often after 10 years of age [31]. Furthermore, it is possible for the immature cells found in neuroblastoma and ganglioneuroblastoma to undergo a spontaneous maturation process and follow the benign course of ganglioneuroma [34].

Patients with thoracic neuroblastoma can be asymptomatic; masses are found incidentally on chest radiographs. When symptoms do occur, they can be related either to the primary tumor or to the metastatic disease. Local mass effect or intraspinal extension can lead to symptoms of respiratory distress or cord compression, respectively. Neuroblastoma can secrete catecholamines, such as vanillylmandelic acid and homovanillic acid. In such a scenario, high levels of these catabolites may be detected in the urine, thus allowing for a proper diagnosis [30, 31]. Finally, patients with a widely disseminated disease can present with constitutional symptoms, such as fever, weight loss, and bone pain.

With conventional radiographs of the thorax, ganglion cell tumors appear as paraspinal well-defined masses. Chest wall involvement and rib remodeling are uncommon but possible with neuroblastoma. Intraspinal extension includes widening of the intervertebral foramina or pedicle erosion. Because the skeletal system is the most common site of metastasis, an initial skeletal survey with a combination of conventional radiographs and bone scintigraphy, including iodine 123 m-iodobenzylguanidine (123I-MIBG), is an essential part of the evaluation for any patient with the diagnosis of neuroblastoma. CT and MR examination are routinely employed to assess thoracic neuroblastoma (Fig. 21.3). Contrast enhancement may highlight intratumoral areas of necrosis or hemorrhage.

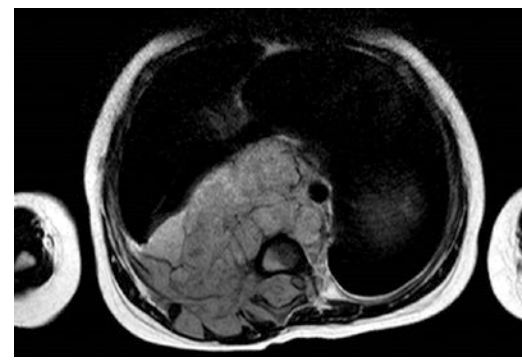

Fig. 21.3 Posterior mediastinal mass (neuroblastoma), with vascular encasement (aorta) and with spinal canal invasion

Calcification can be seen in up to 80% of patients with neuroblastoma [35]. Imaging provides information regarding the extent of tumor, regional invasion, metastatic adenopathy, and vascular encasement. The concept of "surgical risk factors" lately named "image-defined risk factors" (IDRFs) was introduced in 1994 and routinely applied since 2005 [36, 37]. The IDRFs and the INRGSS are designed for use at the time of diagnosis, but they may also be used at reassessments during treatment. The exact preoperative evaluation of IDRFs is mandatory to stage the patient and therefore plan the appropriate treatment (see staging). If one or more of these features have been documented, presurgical chemotherapy should be administered in order to shrink the tumor and enable safe tumor resection [38]. Thoracic IDRFs include:

- Cervicothoracic junction:
  - Tumor encasing brachial plexus roots
  - Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
  - Tumor compressing the trachea
- Thorax:
  - Tumor encasing the aorta and/or major branches
  - Tumor compressing the trachea and/or principal bronchi
  - Lower mediastinal tumor, infiltrating the costovertebral junction between T9 and T12

The primary tumor can also spread through the neural foramina and extend through it into the spinal canal creating a classic dumbbell. This appearance is seen in up to 28% of patients with thoracic neuroblastoma [31]. 123I- or 131I-MIBG, an analog to catecholamine precursors, can concentrate in neuroblastic cells. MIBG localizes in primary sites of neuroblastoma and in metastatic sites in 90–95% of patients [39–41]. MIBG scintigraphy should be performed in all newly diagnosed patients. MIBG findings can result in the detection of metastases that are not evident by other imaging studies. Determination of MIBG avidity can influence the choice of follow-up evaluation [42].

The role of PET is gaining importance in the management of patients with neuroblastoma. FDG-PET may offer advantages over MIBG scintigraphy in detecting small lesions or localizing the extent of the disease. In addition, PET can detect lesions in the liver, which are obscured in MIBG scintigraphy by normal MIBG uptake by the liver. PET cannot demonstrate lesions in the cranium because of normal brain avidity [34].

The staging of neuroblastoma and ganglioneuroblastoma is radiologically or surgically determined by the local extent of disease and locating the sites of metastatic involvement.

The International Neuroblastoma Risk Group (INRG) classification system was introduced in 2009 first alongside the International Neuroblastoma Staging System and then progressively gaining clinical relevance with the advantage to facilitate the comparison of risk-based clinical trials conducted in different regions of the world by defining homogenous pretreatment patient cohorts [43]. In the INGRSS, locoregional tumors are staged L1 or L2 based on the absence or presence of one or more IDRFs, respectively. Metastatic tumors are defined as stage M, except for stage MS, in which metastases are confined to the skin, liver, and/or bone marrow in children younger than 18 months of age.

Neuroblastoma prognosis varies tremendously based on the stage and biological features of the tumor. Treatment varies depending on the risk group and can range from surgery alone for localized tumors to aggressive multimodality treatment for MYCN-amplified tumors. Although surgery plays a role in the diagnosis and management of all stages of neuroblastoma, the importance of that role, especially the extent of resection, in high-risk neuroblastoma continues to evolve. In the past 5 years, there have been several advances in neuroblastoma surgery. Studies have demonstrated that patients with low-risk disease can be treated with surgery alone, and in a subset of patients who are neonatally diagnosed with adrenal tumors, surgery can be avoided in 80% [44–46]. In contrast to its pivotal role in localized disease, surgery has a somewhat controversial role in metastatic disease. However, given the high incidence of local relapses, the current indi-

cation in most treatment protocols is resection of the primary tumor after debulking at metastatic sites [46–48]. Since neuroblastoma has an elevated tropism for lymphatic vessels and lymph-node infiltration, surgical tumor resection should include exploration of locoregional lymph nodes, especially in abdominal and pelvic locations. In the case of paravertebral locations with spinal canal invasion through intervertebral foramina, laminectomy is indicated only in the presence of rapidly progressive neurological symptoms, as chemotherapy can rapidly reduce the volume of the tumor and relieve compression [49].

Nerve Sheath and Nerve Tumors

Nerve sheath tumors are either schwannomas or neurofibromas. Histologically, schwannomas are encapsulated without nerve fibers running through the tissue. Conversely, neurofibromas are unencapsulated with nerve fibers running through the tissue. These nerve sheath tumors are most commonly benign and asymptomatic and are rarely seen in less than 20 years of age [50]. They often arise from intercostals or sympathetic nerves and are more common in patients with neurofibromatosis type II. Schwannomas constitute 75% of nerve sheath tumors.

Malignant degeneration of these neurofibromas and schwannomas is rare in the pediatric population and involves less than 5% of nerve sheath tumors. Benign lesions can either be observed or resected; however, malignant lesions require complete surgical resection for cure. For malignant tumors, adjuvant chemotherapy and radiation do not seem to improve survival. Local recurrence is common, and the prognosis is poor [51].

Paragangliomas

Although most pediatric posterior mediastinal masses are of ganglion cell or nerve sheath or nerve origin, other nervous tissue tumors must be considered when formulating a complete differential diagnosis. Paragangliomas or extra-adrenal pheochromocytomas are rare tumors of chromaffin cells of the sympathetic nervous tissue that can be seen in the posterior mediastinum within the paravertebral sulcus. Patients with these lesions often present with signs of catecholamine excess. Less than 2% of these tumors are malignant [52]. Treatment consists of surgical resection; however, recurrence can occur, and close follow-up after excision is recommended.

Nonneurogenic Posterior Mediastinal Masses

Extramedullary hematopoiesis is often clinically asymptomatic; however, it may present as signs of spinal cord compression. Extramedullary hematopoiesis is seen in hematologic disorders, most commonly thalassemia. The actual pathogenesis of this disorder, however, is unknown. Bilateral paraspinal masses with smooth margins are the classic presentation on chest radiographs. The soft tissue mass may contain fat and is almost always seen within the lower thorax. These masses are either observed if clinically silent or maybe surgically resected.

Lipomatosis is a deposit of mature fat in the extrapleural and mediastinal spaces, commonly associated with long-term steroid administration [53]. On CT or MR imaging, the appearance is that of the normal subcutaneous fat.

Vascular masses, including hemangiomas (true neoplasms) and vascular malformations, can occur in the posterior mediastinum, although they rarely isolate to the posterior mediastinum. The CT or MR imaging appearance depends on the type of vascular malformation (cystic spaces, large blood vessels, fatty components) or stage of hemangioma. Hemangiomas densely enhance in the proliferative stage, with eventual fibrofatty replacement during involution.

The differential diagnosis of nonneurogenic posterior mediastinal masses also includes primary soft tissue malignancies, such as Ewing's sarcoma, germ cell tumor, and rhabdomyosarcoma. All these malignancies can arise in the paraspinal area and can dumbbell into the spinal canal [54, 55]. Adenopathy, both infectious and metastatic, is also a consideration.

21.2.2 Lung Primary and Secondary Tumors

Primary pulmonary tumors are rare in infants and children. The spectrum of pediatric lung tumors is quite different from that occurring in adults.

Most pulmonary neoplasms in children are malignant in nature, and metastatic lesions are far more common than primary malignancy. This latter group includes primary lung parenchymal tumors and airways tumors (see the following chapter).

21.2.2.1 Pleuropulmonary Blastoma

Pleuropulmonary blastoma (PPB) is a rare mesenchymal childhood malignant neoplasm. Three types are described based on morphology and increasing malignant behavior. Type I is purely cystic and mostly seen in younger children. Type I PPB resembles congenital pulmonary adenomatoid malformation (CPAM) clinically and radiologically and cannot be differentiated without histological examination (Fig. 21.4). Type II PPBs are mixed cystic and solid, while type III tumors are predominately solid. Both type I and II PPB occur in older children and often arise from preexisting cystic lesions. Some evidence suggest that type I tumors may evolve into the more malignant types II and III if untreated [56]. Cough, fever, and sometimes pain in the chest suggesting a respiratory infection are often the first symptoms. The chest radiographs may be interpreted as "pneumonia," delaying the diagnosis. Pneumothorax is another common presentation, especially in younger patients. Malignant potential increases with the solid component, and more than 20% of patients present with metastatic disease [57]. The tumor is usually located at the periphery of the lung, but it may also be located in extrapulmonary locations, such as the mediastinum, diaphragm, and/or pleura. Since most of the lung tumors are located peripherally, resection is usually possible by segmental or lobar resection. However, since the limit between the lesion and the normal parenchyma may be difficult to determine grossly and because of the high risk of local recurrence and metastatic spread, the surgical procedure of choice for parenchymal PPB is lobectomy. The use of multimodal neoadjuvant chemotherapy and radiation following surgical resection has shown promising results in a few patients with extensive disease and dissemination. Despite aggressive treatment protocols, the prognosis for patients with PPB is not good, with 5-year survival rates of 83% for type 1 and 42% for types 2 and 3. Furthermore, it appears that type II and III lesions have a tendency to recur, even at remote or contralateral sites, despite an apparently complete resection of the primary tumor [58]. It is not known whether the tumor can develop in preexisting benign congenital cystic lung disease or whether the cysts in these cases are type I PPB from the outset. The latter opinion has been favored recently, especially since PPB has been identified in fetuses and neonates [59].

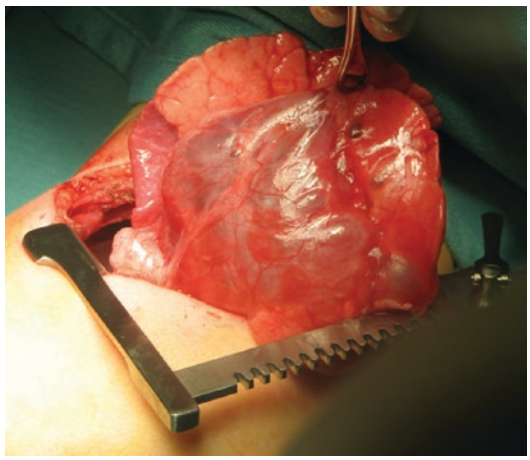

Fig. 21.4 Surgical resection of a macrocystic lung lesion (differential diagnosis should include PPB type I and macrocystic CPAM)

21.2.2.2 Secondary Lung Tumors

In recent decades, significant progress has been made in the treatment of pediatric solid tumors, with current overall survival rates of 75–90% in nonmetastatic tumors. Unfortunately, 10–30% of children with solid tumors present with metastases, and an additional 15–20% relapse at distant sites [60]. Advances in the treatment of metastatic disease, however, have not mirrored those of nonmetastatic solid malignancies, with overall survival ranging from 20% to 70%, depending primarily on histology [60]. As metastasis is a disseminated process, treatment depends on effective systemic therapy, but surgical resection can sometimes be therapeutic [61].

Computed tomography (CT) scan is nowadays the gold standard for the identification of pulmo-

nary nodules. However, the limitations of CT are still apparent in multiple pediatric solid tumors, including the fact that there are generally no findings pathognomonic for specific histologies, both neoplastic and non-neoplastic (Fig. 21.5). Although the high sensitivity of CT can be beneficial, its lack of specificity with respect to differentiating malignant from benign nodules can lead to false-positive interpretations, resulting in unnecessary anxiety, surgery, and/or overtreatment if a confirmatory biopsy is not performed [61]. Additional difficulties arise when trying to localize the CT-identified lesions for diagnostic or therapeutic resection, particularly if a minimally invasive approach, such as thoracoscopy, is planned. While superficial lesions can be seen intraoperatively on visual inspection and larger, firmer lesions can be palpated with instruments, many deeper, smaller, softer lesions can easily be missed, regardless of the surgical approach. Given that the goal of metastasectomy is resection with maximal preservation of normal lung tissue, lobectomies or segementectomies are not a solution to this problem. Multiple techniques have been used to overcome this problem, including preoperative marking with wires, coils, or dye, and localization with intraoperative ultrasound [62–64]. All these strategies are useful, but each has its drawbacks. Dyes spread along the pleura, coils, and wires can be inaccurately placed or dislodged, and the accuracy of ultrasound is limited by lesion depth and the amount of air in the lung. Despite the risk of dislodgement, most authors favor preoperative wire or coil placement when attempting to localize a difficult lesion in the lung.

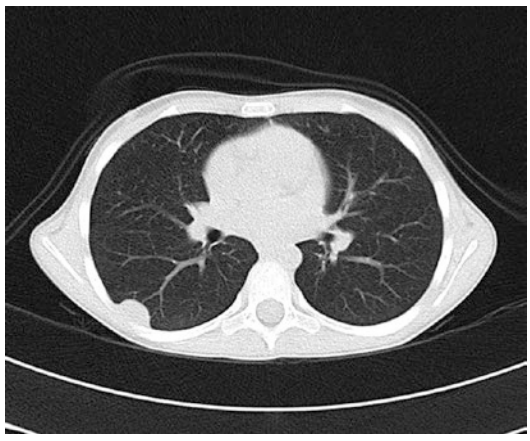

Fig. 21.5 Wilms tumor right lung metastasis

21.2.2.3 Osteosarcoma

Osteosarcoma is the most common pediatric bone tumor. Twenty percent of these patients present with metastasis at diagnosis, and another 22% eventually develop metastasis at some point. Pulmonary metastases comprise 85% of these metastases. While the overall survival of patients with osteosarcoma has improved to 75% in recent trials, survival for metastatic osteosarcoma is still only 17–34%. Many studies have found that complete surgical resection of primary and metastatic disease is essential for survival in osteosarcoma [61]. Good prognostic factors in metastatic osteosarcoma include diagnosis of metastasis after treatment rather than prior to or during chemotherapy, longer disease-free interval between treatment and relapse, fewer metastatic lesions, better histologic response to preoperative chemotherapy, and the ability to clear all metastatic disease surgically. Metastasectomy in osteosarcoma should be attempted whenever complete surgical resection of the primary and metastatic sites is possible. The presence of miliary disease and/or hilar node or pleural involvement can be considered relative contraindications, depending on the ability to resect all lesions and maintain adequate pulmonary function. The use of an open technique with exploration and palpation of both lungs has been supported by overwhelming evidence that complete resection of all detectable disease is necessary for survival, because of the finding that pre-operative CT misses up to a quarter of viable osteosarcoma metastases found by palpation, and by evidence that up to 60% of patients with unilateral CT lesions have contralateral metastases at exploration. Unfortunately, no studies to date have attempted to identify the ideal open approach from among the available options of a median sternotomy, transverse sternotomy, synchronous bilateral or staged bilateral thoracotomies using posterolateral muscle-sparing, vertical transaxillary, or lateral incisions. While sternotomy allows access to both lungs at

once, the posterior lung and left lower lobe are difficult to evaluate. Despite the exposure that thoracotomy provides, its use necessitates two incisions, and usually two separate surgeries, as it is better tolerated when staged [65].

21.2.2.4 Wilms Tumor

Approximately 10% of Wilms tumor patients present with pulmonary metastasis although they still have high overall survival rates [66]. Although burdened by a percentage of long-term sequelae and a significant risk of developing a second tumor, in the United States, these pulmonary nodules have traditionally been treated with whole-lung radiation with good outcomes [67]. In Europe, therapeutic metastasectomy has been used to avoid the long-term effects of lung radiation. The International Society of Pediatric Oncology (SIOP) protocol 93-01 allowed for pulmonary metastasectomy after initial chemotherapy. If complete remission is achieved by chemotherapy alone or with chemotherapy and surgery, patients continue on similar chemotherapy and did not receive lung radiation [68]. The recently closed Children's Oncology Group (COG) trial AREN0533 also eliminated lung radiation for patients who achieved complete remission of lung disease after 6 weeks of 3-drug chemotherapy and encouraged biopsy of lung nodules after initial chemotherapy to ensure that patients did not receive unnecessary lung radiation. Overall, the use of surgery in the diagnosis and treatment of pulmonary disease in Wilms tumor is increasing. The upcoming COG high-risk Wilms tumor trial will incorporate the use of metastasectomy to achieve pulmonary complete remission after initial chemotherapy, with the goal of obviating the need for lung radiation, as has been done in the SIOP protocol. With the current diagnostic role of surgery, minimally invasive techniques can be used when complete sampling of the lesions is possible.

21.2.2.5 Hepatoblastoma

Approximately 20% of patients with hepatoblastoma present with pulmonary metastases. Patients with metastases have a much lower survival rate (25–50%) compared to those without [69]. While early case reports showed the potential for cure following metastasectomy, initial chemotherapy trials also showed the possibility of complete resolution of lung metastases with chemotherapy alone. Two larger Japanese trials showed the importance of this combined approach and emphasized the use of metastasectomy for residual lung disease after chemotherapy [70, 71]. The strategy of combining chemotherapy and metastasectomy for the residual disease is still used in all major hepatoblastoma cooperative trials for patients with pulmonary metastatic disease at diagnosis. The resection of any residual disease in the lungs is of utmost importance before local control for PRETEXT III and IV patients who require liver transplantation due to the need for post-transplant immunosuppression. Contraindications to metastasectomy include an inability to achieve a complete resection while preserving adequate lung function and the presence of uncontrolled disease at the primary site. There is no contraindication to minimally invasive techniques if complete resection can be accomplished.

21.2.2.6 Neuroblastoma

Among patients with neuroblastoma, pulmonary metastasis at diagnosis is rare. The International Neuroblastoma Risk Group Study most recently reported an incidence of 3.6% [72]. However, all of these might be underestimates, as detailed lung imaging was not obtained in the majority of these patients. The likelihood of metastasis in general and lung metastases, in particular, is higher in patients older than 1 year and with MYCN amplification (denoting a higher risk group). Patients with lung metastases are much more likely to have metastases to the CNS and other locations. Regardless of the metastatic burden or location of metastases, surgery should be reserved for diagnosis only. Biopsy of the most easily accessed site, whether primary or metastatic, for initial diagnosis or recurrence is recommended.

21.2.2.7 Rhabdomyosarcoma

Overall survival for metastatic rhabdomyosarcoma (RMS) is poor. One early mixed-histology case series reported that patients with pulmonary

metastases from RMS are 35 times more likely to relapse in the lung than patients with lung metastases from other sarcomatous histologies [73], and other reports confirmed a dismal outcome [74]. The largest European study included 174 patients with metastatic RMS, 55% of whom had metastases to multiple organ systems. The unfavorable primary site, bone or bone marrow involvement, and age <1 or >10 years were independent, unfavorable risk factors. Patients with 0 or 1 of these factors had an overall survival of 47%, whereas overall survival was 9% for those with two or more risk factors [75]. A more recent COG report divided patients into groups, as the previous European trial did, and found that patients with 0 or 1 risk factor (age <1 or >10, unfavorable site, bone or bone marrow involvement) had 3-year event-free survival of 69%, which is an improvement over earlier trials. Unfortunately, patients with 2 or more risk factors, which constitute the majority of metastatic RMS patients, still only have a 3-year event-free survival of 20% [76]. Given the poor outcome and good response to chemotherapy and radiation, metastasectomy in rhabdomyosarcoma should only be performed for diagnosis, and minimally invasive techniques can be used when appropriate.

21.2.2.8 Non-Rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS)

This family of sarcomas includes alveolar soft part sarcoma, synovial sarcoma, chondrosarcoma, and malignant fibrous histiocytoma, among others. These tumors have a propensity to metastasize to the lung and are generally resistant to chemotherapy and radiation. The rarity of these tumors makes their study difficult. Based on resistance to other treatments, metastasectomy has been recommended for this family of tumors whenever complete resection of all diseases is possible [77]. CT is the modality of choice for the diagnosis of these lung lesions, and because of their consistency, these tumors may be difficult to palpate. Localization techniques described earlier may be advisable for deeper lesions regardless of open or minimally invasive approach.

21.2.2.9 Ewing Sarcoma

Ewing sarcoma is a chemo- and radiosensitive tumor, which makes the assessment of the utility of surgery more difficult. A recent Polish study, published in 2016, reviewed 38 patients with Ewing sarcoma and isolated lung metastases treated with modern multi-modal therapy from 2000–2014. Patients with a radiographic response to initial chemotherapy had improved event-free survival, but no effect of metastasectomy was observed [78]. Given the multitude of conflicting reports hampered by poorly controlled data, there is no reliable evidence that metastasectomy in Ewing sarcoma is of therapeutic benefit. However, with the 47% rate of negative biopsy in patients with small to moderate lung lesions, it can still play an important role in diagnosis, perhaps saving some patients from intensified therapy or lung radiation.

21.2.2.10 Adrenocortical Carcinoma

Adrenocortical carcinoma is a rare chemotherapy and radiation-resistant tumor. Although pediatric case series examining the effect of pulmonary metastasectomy do not exist, there is ample evidence in the adult literature that this procedure is beneficial and can enhance long-term survival [79]. Case reports confirm the ability of metastasectomy to produce long-term survival in the pediatric population [80, 81]. Pulmonary metastasectomy should be performed in any patient with metastatic adrenocortical carcinoma in who complete resection is possible. Although there is no contraindication to minimally invasive resection, there are ample data from adults that these tumors are at high risk of rupture during dissection and removal and that spillage can lead to implants and carcinomatosis. The implications of spillage are heightened as there is little useful treatment other than surgery, so the surgeon must make every attempt to dissect and remove the tumor intact.

21.2.3 Bronchial Tumors

Primary tracheobronchial tumors represent a heterogeneous group of rare tumors with an overall

incidence of 0.0049 per 100 thousand children (about 0.2% of all tumors in this age group) [82]. Because of nonspecific clinical presentations showing heterogeneous symptoms, diagnosis is often difficult, and the airway involvement can lead progressively to a bronchial or tracheal obstruction [83].

Due to the rarity of these tumors, oncological guidelines on preoperative workup, treatment, and follow-up are lacking. Surgical resection often seems to be the treatment of choice, while the endoscopic approach is recommended only in highly selected cases depending on tumor localization and histological type. Chemotherapy and radiotherapy are usually indicated only for the management of tumor relapse [83]. Tumor histology is the main factor determining the survival rate with a better survival reported for carcinoids and mucoepidermoid carcinoma. The better prognosis of these tumors is also related to the intraoperative findings of negative lymph nodes, and survival is higher when lymphadenectomy and a lesser extensive surgery are performed [84].

Symptoms are usually connected to the site and type of the tumor. Obstructive symptoms are prevailing in case of severe upper airway obstruction (>50% of the lumen) with stridor, wheezing, and dyspnea; cough is very common, expression of mucosal irritation or poor clearance with the accumulation of airway secretions distal to the stenosis; rarely, in case of mucosal ulceration, hemoptysis may be observed. Commonly, clinical presentations of primary tracheobronchial tumors are misdiagnosed as bronchitis, pneumonia, or asthma episodes. Complete or partial lung atelectasis is another frequent occurrence in these patients with bronchial localization. Neuroendocrine tumors as carcinoids can present with the paraneoplastic syndrome (hypotension, diarrhea, and vasomotor flushing in 10–30% of cases); other nonspecific symptoms comprise chest pain and weight loss [83].

Tracheobronchial tumors include both benign and malign lesions: In the first group, the most common histological types are represented by infantile hemangioma and squamous papilloma, while inflammatory pseudotumors, leiomyomas, granular cell tumor, juvenile xanthogranuloma, tracheal lipoblastoma, and laryngotracheal chondromas can occur more rarely. The second group includes carcinoid and mucoepidermoid carcinomas, and less frequently rhabdomyosarcoma, leiomyosarcoma, and adenoid cystic carcinoma [85].

Concerning malignant masses, bronchial carcinoid and mucoepidermoid carcinoma are the most common entities, with a generally good prognosis.

Carcinoid accounts for 80% of all malignant forms. Basing on the mitotic activity rate and the grade of tumor necrosis, they are classified as typical and atypical, with the latter one showing more aggressive behavior and a worse prognosis. Lymph node metastases are frequently described, while local recurrences and distant metastasis rarely occurred [85].

Mucoepidermoid carcinoma looks like an exophytic mass arising from the submucosal bronchial glands. According to cell type, pleomorphism, mitotic index, and the presence of cystic structures, they are classified into low, intermediate, and high-grade tumors. The most common in children is the low-grade type, mainly composed of mucous cells [85].

Rhabdomyosarcoma and leiomyosarcoma together with adenoid cystic carcinoma are the less frequent malignant lesions reported in the pediatric population. The former accounts for 5.8% of all pediatric endobronchial tumors with previous radiation therapy, genetic predisposition, and immunological factors as the main documented risk factors for its occurrence. Leiomyosarcoma is even more sporadic, making up 3.8% of all pediatric forms. Finally, adenoid cystic carcinoma is a very rare lesion in the pediatric population, with an aggressive attitude, because of frequent local relapse and local lymph nodes metastases [85].

A conventional chest X-ray is often performed in these patients, usually detecting nonspecific indirect signs of airway obstruction, as pulmonary collapse, opacity, or hyperinflation. The gold standard for radiological diagnosis is CT scan with intravenous contrast that provides the exact location of the tumor, the intra- and

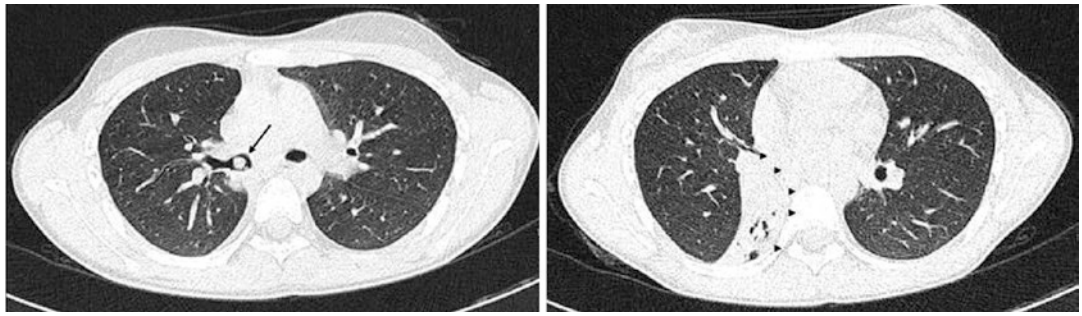

Fig. 21.6 Preoperative CT scan showing an intraluminal mass close to the bifurcation of the right main bronchus in the superior and lower lobar bronchi (*black arrow*) with subsequent atelectasis of the basal segments (*arrowheads*) (with permission from Avanzini S et al. Intraoperative bronchoscopy for bronchial carcinoid parenchymal-sparing resection: a pediatric case report.Pediatr Surg Int. 2012 Jan;28(1):75-8

extra-luminal extension, and the connection with the adjacent organs and vessels (Fig. 21.6). CT also allows 3D reconstruction with the possibility of measurement of the tracheal and bronchial lumen [83]. However, airway endoscopy is essential and commonly used to assess tumor location and obtain tissue sampling. Both flexible fiberoptic endoscopy and rigid bronchoscopy are useful and complementary techniques. Flexible endoscopy is particularly useful to explore the distal airways, and rigid bronchoscopy allows a better view and multiple biopsies or debulking of the tumor while maintaining the patient ventilated. In case of emergency during endoscopy, some procedures can be performed such as hemostasis, tumor debulking, and stenting.

Radical surgical resection of the mass with sparing of the normal lung tissue is the treatment of choice in most cases. Although pneumonectomy and lobectomy have been typically performed for bronchial tumors, parenchyma-sparing procedures, such as sleeve resections and bronchoplasty, are the main procedures performed recently. Moreover, lymph nodes sampling is strictly recommended in case of carcinoid and mucoepidermoid carcinoma because of their capability to metastasize.

Although several reports describe endoscopic resection of tracheobronchial tumors, this approach is still controversial compared to radical surgery. Several limitations and different surgical complications are reported during endoscopic treatment (bleeding, transmural injuries, fiber ruptures, and dislocations). Moreover, repeated procedures are often needed to remove completely the neoplastic mass exposing patients to many anesthesiologic procedures.

In the case of tumors located in the laryngeal and upper trachea region, an anterior transverse neck incision is indicated. During surgery, a temporary intraoperative tracheotomy could be performed. If cartilaginous tissue is not infiltrated, and a clear separation plane is evident, radical excision can be safely performed. Partial resection is mandatory in the case of larynx or tracheal infiltration. Laryngotracheal defect can be repaired by rib grafts. Otherwise, huge tumors require cricotracheal resection with end-to-end anastomosis.

21.2.4 Chest Wall Tumors

Chest wall tumors occur rarely in infants and children, accounting for only 1.8% of all solid childhood tumors. Chest wall neoplasms are primarily of mesenchymal origin and comprise a broad spectrum of benign and malignant lesions, arising from the skeletal or soft tissues of the chest wall. The majority are malignant in nature, with distinct behaviors and varying responses to chemotherapy and radiation. Benign tumors are less common in most series, although they may be underreported. Any growing chest wall mass in children should be evaluated promptly because of the high frequency of malignancy. Most

frequent malignant tumors include Ewing sarcoma, rhabdomyosarcoma, chondrosarcoma, osteosarcoma, and infantile fibrosarcoma [86]. The goals of chest wall resection and reconstruction include complete removal of the local tumor, restoration of adequate protection of the thoracic viscera, restoration of physiologic function providing for adequate lung and chest wall growth, and an acceptable chest wall appearance. Chest wall resection can be achieved via a standard thoracotomy incision, which should include the initial biopsy site. Serratus anterior or pectoralis muscles may need to be excised with appropriate margins. The extent of rib resection depends on the type of tumor. Incisions must be appropriately placed to allow preservation of overlying skin and, if possible, muscle flaps. In most cases, resection of one or multiple ribs is required. The resulting defect can either be closed primarily or may require chest wall reconstruction. Reconstruction of segments of the chest wall is performed to protect underlying structures, to obtain chest wall rigidity and fixation for effective respiratory effort, to prevent flail segments and reduce paradoxical movements, and prevent herniation. Small defects (those involving fewer than three ribs) can usually be covered primarily with muscle and skin; those greater than 5 cm often require chest wall reconstruction, as a large flail segment would otherwise result. Posterior defects of up to 10 cm in diameter can be tolerated as long as the scapula remains to provide stability. Generally, resection of ribs 1–4 posteriorly is well-tolerated, but if resection also involves the fifth and sixth ribs, additional support is necessary to prevent the scapula from becoming caught below the lower ribs. Resections that include the lower ribs can be reconstructed by reapproximating the diaphragm to the lowest remaining rib. This transforms a thoracic defect into an abdominal defect, which has less physiological consequences. However, this technique cannot be used if the resection extends above the fifth rib. Defects involving the sternum should be reconstructed to protect underlying structures and to prevent the paradoxical motion that occurs with the removal of the anterior costal attachments. Defects involving mid-thoracic segments can be reconstructed with a rib transposition, by disinserting the anterior portion of the rib below the defect from the sternum and fixing it back to the sternum or the remaining extremity of a resected rib in the middle of the defect. Prosthetic materials should be avoided whenever possible to decrease the risks of infection and complications related to radiation therapy. Several materials and techniques have been used to reconstruct large chest wall defects, including fascia lata, omental transplants, contralateral rib grafts, assorted muscle flaps, and prosthesis, including Gore-tex and other non-absorbable materials [87]. The major deterrence to the use of these prosthetic materials in the young infant or growing child is that they do not expand as the child grows and may result in more severe scoliosis than occurs if the defect is closed with living tissue. Prosthetic materials provide a rigid base for reconstructing chest wall defects, but the overlying soft tissue must also be replaced. The pectoralis major, latissimus dorsi, and rectus abdominus myocutaneous flaps and the greater omentum are all available for use [87].

21.3 Surgical Approaches in Pediatric Thoracic Tumors

21.3.1 Posterolateral Thoracotomy

The patient is placed in a full lateral decubitus position with appropriate pressure point padding. The skin incision is started at the level of the anterior axillary line over the fifth intercostal space. It is curved around the tip of the scapula and continued posteriorly along a line between the medial aspect of the scapula and the spine. It is carried upward to the level of T4. Anteriorly, the skin incision follows the rib outline (Fig. 21.7a). If an additional posterior extension is required, the anterior portion of the trapezius and rhomboid muscles can be divided. If an additional anterior extension is required, the skin incision is extended to the lateral edge of the sternum, and the serratus anterior and pectoralis major muscles are divided. The mammary vessels

are dissected and ligated in case a partial sternotomy is needed [88–90]. The thorax is then entered either in the intercostal space or with a partial rib resection with preservation of the periosteum, which is split on the midline. Dissection then begins with mobilization of the thymus and identification of the phrenic, vagus, and recurrent laryngeal nerves. The tumor is dissected piecemeal, in a cranial direction, and major vascular structures are controlled proximally and distally. For teratomas, an attempt to remove the whole tumor and prevent spillage of cells is optimal, although not always possible. When the thoracic duct can be identified, it is isolated, tied, and ligated. Meticulous dissection continues with frequent use of neural monitoring, and marginal biopsies are taken after tumor extraction. Once the tumor is completely removed and lymph nodes have been sampled (if necessary), a chest tube is placed one or two intercostal spaces below or above the thoracotomy (Fig. 21.7b). The ribs involved in the thoracotomy are approximated with pericostal interrupted absorbable sutures. If the rib was partially resected, the periosteum is now sutured on the midline to facilitate rib regrowth.

21.3.2 Thoracoscopy

Thoracoscopic surgery in pediatric oncology remains an evolving field that has grown over the past 30 years. Surgical intervention remains a standard principle underlying the multidisciplinary treatment of many childhood cancers, and the integration of minimally invasive surgery (MIS), including thoracoscopic approaches, requires validation for the efficacy of these surgical techniques and to expand the indications of MIS for the treatment of pediatric cancer. To date, the paucity of outcome data has limited the ability to create guidelines for the use of MIS in pediatric oncology. Many children with pulmonary or mediastinal masses may initially require

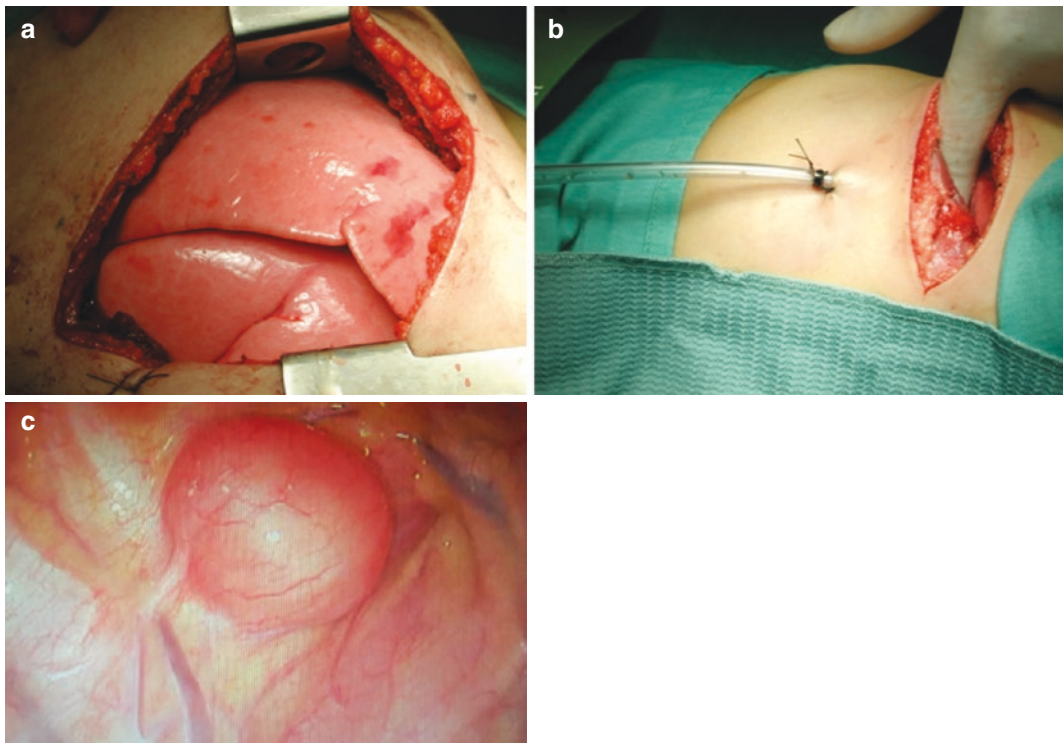

Fig. 21.7 (**a** and **b**) Posterior thoracotomy and chest drain insertion. (**c**) Thoracoscopic resection of a localized thoracic neuroblastoma.

tissue for pathologic diagnosis and in some circumstances tumor resection. Although percutaneous biopsies may be performed with the assistance of image-guided technology, situations remain in which a surgical biopsy is required either via the thoracoscopic or the open surgical technique [91]. A thoracoscopic approach is to be considered to limit long-term sequelae such as winged scapula and scoliosis in this special population. Pediatric surgeons have used thoracoscopy to diagnose and resect benign, malignant, or metastatic intrathoracic tumors [92]. However, tumor extirpation remains controversial and continues to be limited (Fig. 21.7c).

Theoretical advantages of using thoracoscopy include access to a wide area through limited incisions, better visualization of thoracic and mediastinal structures, and magnification of the local anatomy. Additionally, the use of thoracoscopy has led to a decreased intraoperative blood loss, decreased postoperative pain, reduced hospital length of stay, fewer chest tubes required and/or earlier removal, improved cosmetic result, faster return to normal activity, and reduced pulmonary adhesions [93–102].

Factors limiting the use of thoracoscopy in children with cancer are related to the surgeon, patient, pathology, and technology. Pediatric surgeons' experience with advanced thoracoscopic techniques may be limited. Although the ability to gain thoracoscopic experience has increased over time, the relatively low volume of pediatric oncologic cases encountered by general pediatric surgeons can negatively impact their decisions or confidence to use a thoracoscopic approach. Single-lung ventilation with double-lumen endotracheal tubes is unavailable for the smallest of patients, and, alternatively, bronchial blockers require highly skilled anesthesiologists for the fragile airway of small children [103]. Although thoracoscopy is feasible using only positive pressure carbon dioxide insufflation without single-lung ventilation, the resulting lung collapse is often suboptimal, thus hampering visualization of pulmonary nodules, decrease working space in the thorax, and increasing the risk of lung injury. The small working space within the thoracic cavity or mediastinum, the patient's ability to tolerate single-lung ventilation, and hemodynamic effects caused by pressure generated by pneumothorax are competing factors that make every case uniquely different.

Large masses can potentially impede safe accessibility and specimen delivery and contribute to the potential risk of intraoperative tumor spillage and port-site recurrence [104, 105]. Deep or subcentimeter pulmonary lesions are difficult to visualize, and because the tactile ability is lost in thoracoscopy, these pulmonary lesions may be missed [106]. Adhesions due to prior thoracotomy may limit the ability for a thoracoscopic approach. This is especially relevant in scenarios where multiple serial thoracic surgeries are expected over the course of the disease, such as with serial pulmonary metastasectomies for recurrent metastatic osteosarcoma.

Complications related to thoracoscopy are not different from those encountered in traditional open surgery. A direct comparison of percentages of complications in these different approaches is frequently biased by selection criteria, which generally favor the use of thoracoscopy in "easier" cases. [93, 94, 96, 105, 107–109]. Recurrence at the chest tube site has been reported after thoracoscopic resection of pulmonary metastasis from osteosarcoma [105], although this is extremely rare.

Inadequate equipment, insufficient training, and experience are considered contraindications to performing advanced thoracoscopy. Relative contraindications can be anatomical, such as difficult thoracic access due to large tumor size with consequently increased potential for tumor rupture or spill, and physiologic, such as abnormalities in cardiac output, difficulty tolerating single-lung ventilation or thoracic carbon dioxide insufflation, and coagulopathy [98].

With ultra-advanced technologies, rapidly improving thoracoscopic training, and adherence to the fundamental oncologic principles in surgical technique, pediatric surgeons from across the world can selectively customize treatments for thoracic and mediastinal tumors in neonates, infants, and children. However, significant oncologic concern remains whether malignant tumors can be safely removed in these

children, given the risk of potential iatrogenic tumor cell dissemination and metastasis. Appropriate patient selection and correct surgical indications for advanced surgical procedures in children with cancer are necessary to minimize the risk of surgical complications.

21.3.2.1 Surgeon and Patient

The safety threshold and the patient selection are important for consideration of any thoracoscopic approach. The surgeon's experience, patient size, detail regarding the potential pathology, location, and proximity to vital structures all impact the final decision of whether or not to pursue this minimally invasive approach.

21.3.2.2 Anesthesia

Thoracoscopic surgery requires the ability to create enough working space within the hemithorax to safely visualize and perform the operative procedure. Impediments that lead to difficulty with anesthesia in infants and young children include one-lung ventilation (OLV), carbon dioxide insufflation, hypothermia, and the effect of lateral decubitus positioning [110–114]. The smaller tracheal and bronchial diameters in children and infants may prohibit the use of double-lumen tubes or bronchial blockers because there is a lack of double-lumen tubes and commercially available bronchial blockers. OLV currently remains a technically difficult and demanding task on behalf of the anesthesia team.

Key safety considerations in the decision to adopt a thoracoscopic surgical approach are heavily influenced by the risk of cardiopulmonary collapse under anesthesia. In children with anterior mediastinal masses due to Hodgkin's or non-Hodgkin's lymphoma or less commonly neuroblastoma or germ cell tumors, the pros and cons of proceeding with an anesthetic need to be considered, especially in the presence of airway compression. General anesthesia should be avoided in patients with tracheal cross-sectional area or peak inspiratory flow rate less than 50% of predicted for age and sex, and those with less respiratory compromise can generally safely undergo general anesthesia [115]. Thoracic epidural anesthesia or bilevel positive airway pressure management has been used in children for open biopsies of anterior mediastinal masses [116, 117].

21.3.2.3 Localization and Biopsy

Thoracoscopic biopsy of intrathoracic lesions has been effectively used for mediastinal masses, most commonly neuroblastoma and lymphoma, and for pulmonary masses that are usually metastatic lesions or infiltrates. Approaches for localization include image-guided hook wire, methylene blue injection, and/or the utilization of endoscopic ultrasound [91].

Although these various preoperative localization techniques serve as adjunctive tools, several case series have been reported using thoracoscopic biopsy without preoperative localization with excellent results [118, 119]. Conversion to open thoracotomy ranged from 0% to 30% and was primarily due to limited visibility, adhesion, bleeding, decreased intraoperative oxygen saturations, and hypercarbia. Therefore, thoracoscopy was largely successful, and some patients were able to begin adjuvant therapy earlier [91].

21.3.2.4 Future Developments

Single-incision surgery allows chest surgery to be performed through a single access site that admits multiple working instruments. Experiences with pediatric single-incision thoracoscopic surgery for tumors are extremely rare [120].

Robotic surgery eliminates tremors and allows three-dimensional vision with a magnified view and the use of articulated instrumentation [103]. Mediastinal masses are proposed as “the golden indication” for robotic resection, and successful resection has been reported of malignant tumors such as neuroblastoma and mediastinal germ cell tumor, tumors of intermediate malignant potential, including ganglioneuroblastoma and lipoblastoma, and benign tumors, including ganglioneuromas and mature teratomas [103, 121]. Limitations such as robot costs compared with standard thoracoscopy are thought to be the single most limiting factor in the use of this technology. Additional factors are the limited hemithorax space in patients less than 2.5 kg, instrumentation size and availability, and learning curve [121].

21.3.3 Cervicothoracic Tumors

High thoracic tumors and tumors of the cervicothoracic junction are often not amenable to complete resection by either an isolated unilateral cervical or thoracic approach. Nonetheless, adequate surgical exposure of these tumors is essential to prevent injury to nearby nerves (brachial plexus, phrenic, vagus, recurrent laryngeal, and spinal accessory) and vascular structures (carotid, subclavian, and vertebral arteries, the thyrocervical trunk, and the subclavian and jugular veins), while assuring complete resection. Large mediastinal tumors that require access to both hemithoraces also present a challenge to complete resection with low postoperative morbidity. Series regarding pediatric bilateral anterior thoracotomy ("clamshell" approach) are found most often in the cardiothoracic literature. Isolated case reports have described excellent exposure for resection cervicothoracic junction tumors using a combined supraclavicular incision sternotomy-anterior thoracotomy ("trap-door" approach).

21.3.3.1 Transmanubrial Approach

The technique was described initially by Grunenwald and Spaggiari in 1997 [122]. The patient is placed in dorsal decubitus, with a roll placed under the shoulder. An L-shaped skin incision is made, the upper line corresponding to the anterior part of the sternomastoid muscle as far as the angle of manubrium and prolonged in an anterior thoracotomy at the level of the second rib. The sternal manubrium is exposed after dissecting the sternomastoid muscle (from the anterior part to the internal jugular vein), sparing the major pectoral muscles. The originality of this technique lies in the division of the superior lateral part of the manubrium and after the cartilage section of the first rib, with an L-shaped incision. After cutting the insertion of the anterior scalene muscle, an anterior flap is retracted progressively, preserving the sternoclavicular articulation and the insertion of the sternomastoid muscle, and offering a perfect plane of dissection for the subclavian vessels. Tumor dissection then begins, starting with the internal jugular vein and its junction with the brachiocephalic vein (Pirogoff confluence). Step by step, all the vascular and nervous structures are exposed (subclavian and jugular vein to the brachiocephalic vein, subclavian artery, phrenic and vagus nerve, and control of the carotid artery). In the posterior plane, dissection exposes the anterior part of the vertebral bodies from C3 to T4. Moreover, this dissection facilitates the removal of extradural intraspinal involvement and pleural extension. Ligation of the thoracic duct can be performed easily for left-sided tumors. Reconstruction of the manubrium is performed with resorbable sutures [88].

21.3.3.2 Trap-door Incision

The patient is placed in the dorsal recumbent position with a roll beneath the shoulders, the arm ipsilateral to the lesion outstretched, and the contralateral arm tucked at the side. General anesthesia is induced, using either a double-lumen endotracheal tube or a single lumen endotracheal tube with a bronchial blocker for intubation. The head is then rotated 30–45° away from the tumor. The patient is prepped from the ear to the umbilicus and a clear head and neck drape is used. A transverse incision is begun superior to the clavicle with a parallel course, or along the anterior border of the sternocleidomastoid with a descending course, to the mid-portion of the suprasternal notch, continued downward through the midline sternum to the fifth interspace, then laterally through the fifth interspace to the anterior-axillary line (Fig. 21.8). The pectoralis is divided close to its point of insertion, and the intercostal muscles are divided at the fifth interspace. The pleural space is entered and the internal mammary vessels are isolated, ligated, and divided. The retrosternal space is bluntly dissected, and a sternal saw is used to divide the sternum to the level of the fifth interspace, then laterally to the thoracotomy. Bleeding from the edge of the sternum is treated with bone wax. The sternal and a portion of the clavicular head of the sternocleidomastoid are divided close to their points of origin and marked with sutures for later approximation. The strap muscles are similarly divided. A retractor is then placed between the cut edges of the sternum allowing excellent

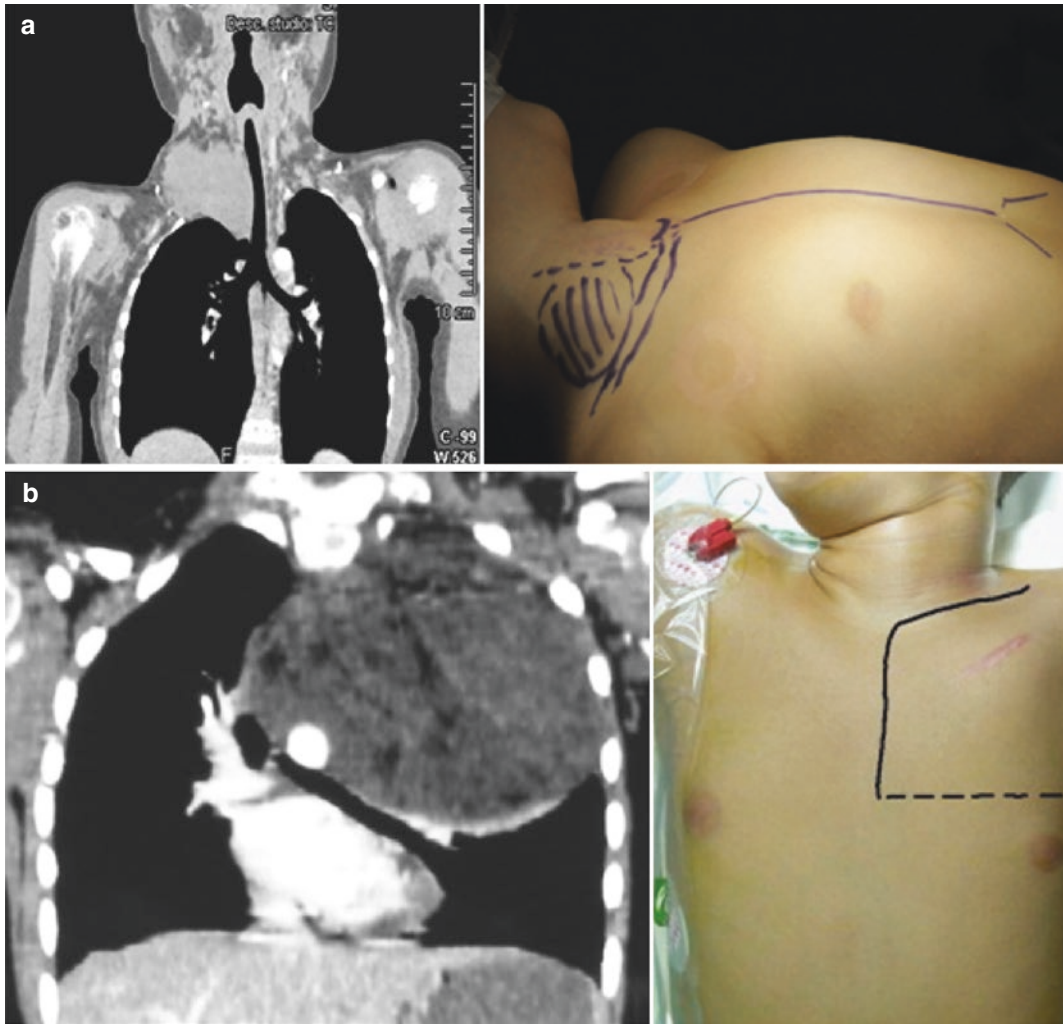

Fig. 21.8 (**a**) Right schwannoma tumor located at the right thoracic inlet, involving major cervical vessels and nerves. Anterior cervical transsternal approach was adopted. (**b**) Rhabdomyosarcoma located at the posterosuperior left mediastinum, determining compression and right-anterior displacement of the esophagus and trachea. The aorta is compressed and shifted medially, with slight anterior dislocation of left carotid and left subclavian artery: the left pulmonary artery and left principal bronchus appear compressed and inferiorly displaced; superiorly, the mass arrives in proximity to the left thyroid lobe. Trap-door approach was adopted. (with permission from De Corti F et al. The surgical approach for cervicothoracic masses in children. J Pediatr Surg.2012 Sep;47(9):1662-8)

exposure. At the end of the dissection, the sternum is reapproximated with 3–4 sternal wires or nonabsorbable sutures in small patients. The thoracotomy is closed as described above. The lungs are then inflated under direct vision, and the pericostal sutures and sternal wires are secured. The mobilized edges of the pectoralis flaps are closed over the sternal wires. Attention is then directed to the neck where the sternal and clavicular heads of the sternocleidomastoid muscle are reapproximated with the figure of eight sutures of heavy absorbable suture [90].

21.3.3.3 Sternotomy

The procedure consists of an anterior cervical transsternal approach as described by Ladas et al [123] and also previously adopted by Grosfeld et al [124]. The patient is placed in a

supine position, with the head extended and rotated contralaterally to the mass. The incision extends from the level of the thyroid cartilage downward along the anterior margin of the sternocleidomastoid muscle onto the manubrium and the upper sternum (Fig. 21.8). If required—in case of malignant infiltrating tumors—the incision may be prolonged caudally to perform a complete sternotomy. The clavicle is not resected. In instances of large-sized tumors, the sternocleidomastoid muscle may be divided to allow better exposure of the surgical field and reattached at the end of the operation. This approach offers a wide exposure of the cervical neurovascular structures, subclavian vessels, and brachial plexus. Vessels are identified and progressively isolated to guarantee immediate vascular control in case of bleeding during dissection of the mass. The tumor is progressively freed from the surrounding structures, making sure to preserve the roots of the brachial plexus (a nerve stimulator may be used) as much as possible. Once the tumor is removed, a laminar drain is placed in the surgical field along with a suction drain in the anterior mediastinum. A chest drain is not necessary unless the pleura is breached.

21.3.4 Thoraco-abdominal Tumors

21.3.4.1 Thoraco-phrenolaparotomy

The child is positioned on the homologous oblique lateral decubitus with the arm lifted and bent over the head, avoiding any outstretched position to reduce the risk of brachial plexus injuries. Then, the surgeon identifies the 10th rib and marks the skin. A single skin incision is made following the 10th rib, starting posteriorly from the inferior margin of the scapula proceeding obliquely downward on the lateral margin of the rectus abdominis muscle beyond the umbilical transverse line. The rib is exposed and partially resected with preservation of the periosteum as described above. Then, the parietal pleura is incised to get access into the chest cavity. This leads to the wide exposure of the lung, diaphragm, and thoracic parts of the tumor. Selective lung ventilation is not generally required.

Laparotomy is performed following the direction of the lateral margin of the rectus abdominal muscle. Blunt dissection of the peritoneum from the diaphragm proceeds till touching the abdominal part of the tumor.

The diaphragm is incised along the posterior peripheral margin close to its insertion on the lateral chest wall to avoid phrenic nerve lesions.

Once thoracotomy, laparotomy, and diaphragmatic incision are performed, intrathoracic and retroperitoneal spaces are both accessible and tumor complete resection can proceed following the usual steps.

A chest tube and a retroperitoneal suction drain are placed once the tumor is completely removed. The diaphragm is closed using interrupted non-absorbable sutures.

21.3.5 Bilateral Thoracic Tumors

21.3.5.1 Clamshell Incision

The patient is placed in the dorsal recumbent position with a roll behind the midportion of the chest. The arms are abducted to 90° at the shoulder and elbow. General anesthesia is induced with a double-lumen or single-lumen endotracheal tube capable of lung isolation, and the patient is prepped from the chin to the umbilicus and transversely to the bilateral posterior axillary lines. An anterior curvilinear incision is made along the fifth interspace bilaterally from each anterior-axillary line, connecting at the midline. The pleural space is entered and the mammary vessels are isolated, ligated, and divided. The retrosternal space is then bluntly dissected, and the sternum is divided transversely with a sternal saw. A retractor is placed, allowing for exposure of both pleural cavities, from the pulmonary hilum to the posterior aspect of the diaphragm. When the tumor dissection is complete and hemostasis is assured, bilateral chest tubes are placed and the sternum is either approximated with wires. Pericostal sutures are used to approximate the ribs.

21.4 Complications

21.4.1 Cardiopulmonary Complications

21.4.1.1 Atelectasis

Intraoperatively, adequate inflation of the lungs by positive pressure ventilation should be assured by looking at the lung at the time of closure or completion of thoracoscopy. After the operation, pain relief is critical to allowing the full opening of the lung. While some degree of atelectasis is a normal postoperative finding, it responds well to incentive spirometry, flutter valve, and other measures for a pulmonary toilet. How frequently atelectasis leads to pneumonia is unclear but not often. Family members can encourage the patient with these measures, and this helps them to realistically feel they are contributing to recovery.

21.4.1.2 Pneumonia

Postoperative pneumonia in children occurs in several settings, generally following atelectasis. Its incidence ranges between 9% and 21% according to different series. Gram-negative bacilli generally predominate, causing 86% of cases of pneumonia. Fungi caused 7%, and the remainder is related to gram-positive cocci (7%). With increasing antibiotic resistance recently reported in most centers, local susceptibility patterns must be followed.

21.4.1.3 Respiratory Distress Syndrome (RDS)

Respiratory distress syndrome (RDS) arises in children from the same pathophysiologic processes as in adults. Pulmonary edema occurring as a result of oncotic and hydrostatic pressure differences leads to fluid in the alveolar spaces. RDS in children is often complicated by infection of the edematous lung and may require prolonged ventilatory support and tracheostomy. Management remains controversial.

21.4.2 Complications of Chest Incision

Posterolateral thoracotomy complications noted in a series of 49 children [125] were: scoliosis, 31%; elevation of the shoulder 61%; winged scapula 77%; asymmetry of the thoracic wall due to atrophy of the serratus anterior 14%; deformity of the thoracic cage 18%; and asymmetry of the nipples 63%. A greater incidence of denervation problems was noted with more cephalad incisions. Most of the abnormalities were not functionally significant but caused the authors to recommend that incisions should be as low as possible, and should be performed after the first year of life if possible.

Median sternotomy in childhood has been followed by scoliosis in 34%. Median sternotomy is sometimes complicated by mediastinitis or sternal wound infections.

Thoracoscopy or VATS operations should minimize the incidence of neurologic and chest wall complications that confound surgeons obliged to use a posterolateral thoracotomy. However, the approach is not without difficulties. Preparations should be made for rapid thoracotomy in case of unexpected massive hemorrhage.

Scoliosis is a well-established complication of thoracotomy and/or chest wall resection. The severity of the curve is directly related to the number of ribs resected. Resection of the posterior segment of ribs produces more scoliosis than resection of the anterior segments. Similarly, resection of lower ribs produces a greater curve than resection of upper ribs [126]. Radiation can also affect the growth of the hemivertebrae on the radiated side. Scoliosis is often progressive until the child reaches full stature and therefore requires long-term follow-up. For these reasons, several authors recommend techniques sparing the serratus anterior and latissimus dorsi.

21.4.3 Complications of Pulmonary and Bronchial Resection

21.4.3.1 Pneumothorax

Pneumothorax or prolonged air leak from a thoracostomy tube following thoracic surgery may be a result of air leaking from the chest drainage device, air entering the chest along the chest tube as it passes through the chest wall, or leak from the lung. Air leak from a bronchial stump leak is more troublesome. This complication is

sufficiently infrequent in children that an incidence is hard to obtain. Air leak is often associated with debility, poor nutrition, infection, or malignancy, and reoperation on a high-risk patient.

21.4.3.2 Restrictive Pulmonary Function

Residual pulmonary function depends on the amount of lung parenchymal resection in case of pulmonary tumors and/or on the entity of chest wall resection and consequent scoliosis. The forced vital capacity (FVC), forced expiratory volume, and functional residual capacities (FRC) studied from 1 month to 10 years after surgery demonstrates minimal early reduction in the FRC and FVC. Progressive worsening over time may be noted, with all patients eventually demonstrating a certain degree of pulmonary restrictive disease.

21.4.4 Complications Involving the Pleural Space

21.4.4.1 Pleural Effusion

Pleural effusion following thoracotomy is more commonly an expected outcome of the operation rather than a complication and is usually managed adequately by placing chest drains at the time of surgery. Reaccumulation after drain removal might indicate premature removal but might also signal the development of pneumonia with effusion or hemorrhage.

21.4.5 Complications of Mediastinal Surgery

21.4.5.1 Chylothorax

Chylothorax occurs in a variety of mediastinal operations in 1–4% of cases. Chylothorax is initially managed by placing and leaving a chest tube. The median duration of drainage is generally 15 days. The great majority responds to treatment with dietary modification and/or octreotide. Surgical ligation of the thoracic duct was reported to decrease but not eliminate drainage. Recent reviews in the critical care medicine literature note that there is no consensus about the optimal route of administration, dose, duration of therapy, or strategy for discontinuation of therapy. Thoracic duct ligation has been successfully performed thoracoscopically [127].

21.4.5.2 Diaphragmatic Paralysis

Diaphragmatic paralysis can result from phrenic nerve injury by dissection, clamp, electrocautery, or ice used for cardioplegia. Phrenic nerve injury is a serious complication. Its frequency was reported to be 1.5%. Half of the patients may require plication of the diaphragm. Video-assisted plication can be performed generally through an abdominal approach [128].

21.4.5.3 Spinal Ischemia

Posterior mediastinal tumors may extend into the intervertebral foramina and may potentially compress the spinal cord. Moreover, resection of inferior posterior mediastinal tumors carries the possibility of injury to the artery of Adamkiewicz (AKA), typically located at the level of T9–T12. Disruption of the AKA may lead to anterior spinal cord ischemia and subsequent paraparesis or paraplegia. Some authors suggest to routinely perform a spinal angiography for all posterior mediastinal tumors with intraforaminal involvement located between the levels of T5–L1 in order to visualize the AKA for preoperative surgical planning [129].

21.4.5.4 Horner Syndrome

The classic triad of Horner syndrome, consisting of ipsilateral miosis, mild upper eyelid ptosis, and facial anhidrosis, is caused by interruption of at least one of the three neurons in the oculosympathetic pathway. Neuroblastoma is the most common neoplasm presenting with Horner syndrome and, indeed, an isolated Horner syndrome is the first presenting symptom of neuroblastoma in 2% of cases. Horner syndrome may obviously appear following resection of a tumor involving and/or located at the stellate ganglion [130].

References

1. Freud E, Ben-Ari J, Schonfeld T, et al. Mediastinal tumors in children: a single institution experience. Clin Pediatr. 2002;41:219–23.
2. Meza MP, Benson M, Slovis TL. Imaging of mediastinal masses in children. Radiol Clin North Am. 1993;31:583–604.
3. Wychulis AR, Payne WS, Clagett OT, et al. Surgical treatment of mediastinal tumors. J Thorac Cardiovasc Surg. 1971;62:379–92.
4. Fraser RS, Pare JAP, Fraser RG. The normal chest. In: Fraser RS, Pare JAP, Fraser RG, editors. Synopsis of diseases of the chest. 2nd ed. Philadelphia: WB Saunders; 1994. p. 1–116.
5. Strollo DC, Rosado de Christenson ML, Jett JR. Primary mediastinal tumors. Part 1: tumors of the anterior mediastinum. Chest. 1997;112:511–22.
6. Dimitriou G, Greenough A, Rafferty G, et al. Respiratory distress in a neonate with an enlarged thymus. Eur J Pediatr. 2000;159:237–8.
7. Kuleva SA, Kolygin BA. Malignant mediastinal neoplasms in children. Vestn Khir Im I I Grek. 2003;162:46–8.
8. Takeda S, Miyoshi S, Akashi A, et al. Clinical spectrum of primary mediastinal tumors: a comparison of adult and pediatric populations at a single Japanese institution. J Surg Oncol. 2003;83:24–30.
9. Sandlund JT, Downing JR, Crist WM. Medical progress: non-Hodgkin's lymphoma in childhood. N Engl J Med. 1996;334:1238–48.
10. Robison LL. General principles of the epidemiology of childhood cancer. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 2nd ed. Philadelphia: JB Lippincott; 1993. p. 3–10.
11. Magrath IT. Malignant non-Hodgkin's lymphomas in children. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 2nd ed. Philadelphia: JB Lippincott; 1993. p. 537–75.
12. Young JL Jr, Ries LG, Silverberg E, et al. Cancer incidence, survival, and mortality for children younger than age 15 years. Cancer. 1986;58:598–602.
13. Glick RD, La Quaglia MP. Lymphomas of the anterior mediastinum. Semin Pediatr Surg. 1999;8:69–77.
14. Billmire DF. Germ cell, mesenchymal, and thymic tumors of the mediastinum. Semin Pediatr Surg. 1999;8:85–91.
15. Nichols CR. Mediastinal germ cell tumors: clinical features and biologic correlates. Chest. 1991;99:472–9.
16. Bokemeyer C, Nichols CR, Droz JP, et al. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. J Clin Oncol. 2002;20:1864–73.
17. Kang CH, Kim YT, Jheon SH, Sung SW, Kim JH. Surgical treatment of malignant mediastinal nonseminomatous germ cell tumor. Ann Thorac Surg. 2008;85(2):379–84.
18. Billmire D, Vincour C, Rescorla F, et al. Malignant mediastinal germ cell tumors: an intergroup study. J Pediatr Surg. 2001;36:18–24.
19. Bebb GG, Grannis FW Jr, Paz IB, et al. Mediastinal germ cell tumor in a child with precocious puberty and Klinefelter syndrome. Ann Thorac Surg. 1998;66:547–8.
20. Lewis BD, Hurt RD, Payne WS, et al. Benign teratoma of the mediastinum. J Thorac Cardiovasc Surg. 1983;86:727–31.
21. Brown LR, Muhm JR, Aughenbaugh GL, et al. Computed tomography of benign mature teratomas of the mediastinum. J Thorac Imaging. 1987;2:66–71.
22. Aygun C, Slawson RG, Bajaj K, et al. Primary mediastinal seminoma. Urology. 1984;23:109–17.
23. Lee KS, Im JG, Han CH, et al. Malignant primary germ cell tumors of the mediastinum: CT features. AJR Am J Roentgenol. 1989;153:947–51.
24. Shin MS, Ho KJ. Computed tomography of primary mediastinal seminomas. J Comput Assist Tomogr. 1983;7:990–4.
25. Childs WJ, Goldstraw P, Nicholls JE, Dearnaley DP, Horwich A. Primary malignant mediastinal germ cell tumours: improved prognosis with platinum-based chemotherapy and surgery. Br J Cancer. 1993;67:1098–101.
26. Sarkaria IS, Bains MS, Sood S, Sima CS, Reuter VE, Flores RM, Motzer RJ, Bosl GJ, Rusch VW. Resection of primary mediastinal nonseminomatous germ cell tumors: a 28-year experience at memorial Sloan-Kettering cancer center. J Thorac Oncol. 2011;6(7):1236–41.
27. Vuky J, Bains M, Bacik J, et al. Role of postchemotherapy adjunctive surgery in the management of patients with nonseminoma arising from the mediastinum. J Clin Oncol. 2001;19:682–8.
28. Walsh GL, Taylor GD, Nesbitt JC, Amato RJ. Intensive chemotherapy and radical resections for primary nonseminomatous mediastinal germ cell tumors. Ann Thorac Surg. 2000;69:337–43.
29. Kuhn JP. Middle mediastinal masses. In: Kuhn JP, Slovis TL, Haller JO, editors. Caffey's pediatric diagnostic imaging. St. Louis: Mosby; 2004. p. 1160–240.
30. Frush DP. Pediatric mediastinal masses. Ann Acad Med Singap. 2003;32:525–35.
31. Lonergan GJ, Schwab CM, Suarez ES, et al. Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma: radiologic-pathologic correlation. Radiographics. 2002;22:911–34.
32. Hiorns MP, Owens CM. Radiology of neuroblastoma in children. Eur Radiol. 2001;11:2071–81.
33. Daldrup HE, Link TM, Wortler K, et al. MR imaging of thoracic tumors in pediatric patients. AJR Am J Roentgenol. 1998;170:1639–44.
34. Perel Y, Conway J, Kletzel M, et al. Clinical impact and prognostic value of metaiodobenzylguanidine imaging in children with metastatic neuroblastoma. Pediatr Hematol Oncol. 1999;21:13–8.

35. Sofka CM, Semelka RC, Kelekis NL, et al. Magnetic resonance imaging of neuroblastoma using current techniques. Magn Reson Imaging. 1999;17:193–8.
36. Cecchetto G, Mosseri V, De Bernardi B, et al. Surgical risk factors in primary surgery for localized neuroblastoma: The LNESG1 study of the European International Society of Pediatric Oncology Neuroblastoma Group. J Clin Oncol. 2005;23:8483–9.
37. Holmes K, Mosseri V, Cecchetto G, et al. Surgical risk factors (SRF) and outcome following primary surgery for localised neuroblastoma: Results of LNESG1. Pediatr Blood Cancer. 2007;49:433.
38. Monclair T, Mosseri V, Cecchetto G, De Bernardi B, Michon J, Holmes K. Influence of image-defined risk factors o n the outcome of patients with localised neuroblastoma: a report from the LNESG1 study of the European International Society of Paediatric Oncology Neuroblastoma Group. Pediatr Blood Cancer. 2015;62(9):1536–42.
39. Montalldo PG, Lanciotti M, Casalaro A, et al. Accumulation of m-iodobenzylguanidine by neuroblastoma cells results from independent uptake and storage mechanism. Cancer Res. 1991;51:4342–6.
40. Iavarone A, Lasorella A, Servidei T, et al. Uptake and storage of m-iodobenzylguanidine are frequent neuronal functions of human neuroblastoma cell line. Cancer Res. 1993;53:304–9.
41. Biasotti S, Garavanta A, Villavecchia GP, et al. False-negative metaiodobenzylguanidine scintigraphy at diagnosis of neuroblastoma. Med Pediatr Oncol. 2000;35:153–5.
42. Suc A, Lumbroso J, Rubie H, et al. Metastatic neuroblastoma in children older than one year: prognostic significance of the initial metaiodobenzylguanidine scan and proposal for a scoring system. Cancer. 1996;77:805–11.
43. Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, Kaneko M, London WB, Matthay KK, Nuchtern JG, von Schweinitz D, Simon T, Cohn SL, Pearson AD, INRG Task Force. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. J Clin Oncol. 2009;27(2):298–303.
44. Alvarado CS, London WB, Look AT, Brodeur GM, Altmiller DH, Thorner PS, Joshi VV, Rowe ST, Nash MB, Smith EI, Castleberry RP, Cohn SL. Natural history and biology of stage A neuroblastoma: a Pediatric Oncology Group Study. J Pediatr Hematol Oncol. 2000;197—205:22.
45. Perez CA, Matthay KK, Atkinson JB, Seeger RC, Shimada H, Haase GM, Stram DO, Gerbing RB, Lukens JN. Biologic variables in the outcome of stages I and II neuroblastoma treated with surgery as primary therapy: a children's cancer group study. J Clin Oncol. 2000;18:18–26.
46. Murphy JM, La Quaglia MP. Advances in the surgical treatment of neuroblastoma: a review. Eur J Pediatr Surg. 2014;24(6):450–6.
47. Simon T, Häberle B, Hero B, von Schweinitz D. F. BertholdRole of surgery in the treatment of patients with stage 4 neuroblastoma age 18 months or older at diagnosis. J Clin Oncol. 2013;31(6):752–8.
48. Yeung F, Chung PH, Tam PK, Wong KK. Is complete resection of high-risk stage IV neuroblastoma associated with better survival? J Pediatr Surg. 2015;50:2107–11.
49. De Bernardi B, Quaglietta L, Haupt R, Castellano A, Tirtei E, Luksch R, et al. Neuroblastoma with symptomatic epidural compression in the infant: the AIEOP experience. Pediatr Blood Cancer. 2014;61:1369–1375T.
50. Laurent F, Latrabe V, Lecesne R, et al. Mediastinal masses: diagnostic approach. Eur Radiol. 1998;8:1149–59.
51. Inci I, Turgut M. Neurogenic tumors of the mediastinum in childrens. Nerv Syst. 1999;15:372–6.
52. Hutchins K, Dickson D, Hameed M, et al. Sudden death in a child due to an intrathoracic paraganglioma. Am J Forensic Med Pathol. 1999;20:338–42.
53. Pungavkar S, Shah J, Patkar D, et al. Isolated symmetrical mediastinal lipomatosis. J Assoc Physicians India. 2001;49:1026–8.
54. Siebenrock K, Nascimento A, Rock M. Comparison of soft tissue Ewing's sarcoma and peripheral neuroectodermal tumor. Clin Orthop. 1996;329:288–99.
55. Cohen M. Tumors involving multiple tissues or organs. Imaging of children with cancer. St. Louis: Mosby; 1992. p. 342–58.
56. Priest JR, et al. Type I pleuropulmonary blastoma: A report from the International Pleuropulmonary Blastoma Registry. J Clin Oncol. 2006;24(27):4492–8.
57. Dehner LP. Pleuropulmonary blastoma is THE pulmonary blastoma of childhood. Semin Diagn Pathol. 1994;11(2):144–51.
58. Priest JR, et al. Cerebral metastasis and other central nervous system complications of pleuropulmonary blastoma. Pediatr Blood Cancer. 2007;49(3):266–73. https://doi.org/10.1002/pbc.20937. PMID: 16807914.
59. Hill DA, Dehner LP. A cautionary note about congenital cystic adenomatoid malformation (CCAM) type 4. Am J Surg Pathol. 2004;28(4):554–5. author reply 555
60. Fuchs J, Seitz G, Handgretinger R, Schafer J, Warmann SW. Surgical treatment of lung metastases in patients with embryonal pediatric solid tumors: an update. Semin Pediatr Surg. 2012;21:79–87.
61. Heaton TE, Davidoff AM. Surgical treatment of pulmonary metastases in pediatric solid tumors. Semin Pediatr Surg. 2016;25(5):311–7.
62. Parida L, Fernandez-Pineda I, Uffman J, Davidoff AM, Gold R, Rao BN. Thoracoscopic resection of computed tomography-localized lung nodules in children. J Pediatr Surg. 2013;48:750–6.
63. Partrick DA, Bensard DD, Teitelbaum DH, Geiger JD, Strouse P, Harned RK. Successful thoracoscopic lung biopsy in children utilizing preop-

erative CT-guided localization. J Pediatr Surg. 2002;37:970–3. discussion 970–973
64. Gow KW, Saad DF, Koontz C, Wulkan ML. Minimally invasive thoracoscopic ultrasound for localization of pulmonary nodules in children. J Pediatr Surg. 2008;43:2315–22.
65. Kayton ML. Pulmonary metastasectomy in pediatric patients. Thoracic Surg Clin. 2006;16:167–83.
66. Green DM, Breslow NE, Ii Y, et al. The role of surgical excision in the management of relapsed Wilms' tumor patients with pulmonary metastases: a report from the National Wilms' Tumor Study. J Pediatr Surg. 1991;26:728–33. [PubMed] [Google Scholar]
67. Bond JV, Martin EC. Pulmonary metastases in Wilms' tumour. Clin Radiol. 1976;27:191–5.
68. Verschuur A, Van Tinteren H, Graf N, Bergeron C, Sandstedt B, de Kraker J. Treatment of pulmonary metastases in children with stage IV nephroblastoma with risk-based use of pulmonary radiotherapy. J Clin Oncol. 2012;30:3533–9.
69. Meyers RL, Katzenstein HM, Krailo M, McGahren ED 3rd, Malogolowkin MH. Surgical resection of pulmonary metastatic lesions in children with hepatoblastoma. J Pediatr Surg. 2007;42:2050–6.
70. Uchiyama M, Iwafuchi M, Naito M, et al. A study of therapy for pediatric hepatoblastoma: prevention and treatment of pulmonary metastasis. Eur J Pediatr Surg. 1999;9:142–5.
71. Matsunaga T, Sasaki F, Ohira M, et al. Analysis of treatment outcome for children with recurrent or metastatic hepatoblastoma. Pediatr Surg Int. 2003;19:142–6.
72. Dubois SG, London WB, Zhang Y, et al. Lung metastases in neuroblastoma at initial diagnosis: a report from the International Neuroblastoma Risk Group (INRG) project. Pediatr Blood Cancer. 2008;51:589–92.
73. Temeck BK, Wexler LH, Steinberg SM, McClure LL, Horowitz M, Pass HI. Metastasectomy for sarcomatous pediatric histologies: results and prognostic factors. Ann Thorac Surg. 1995;59:1385–9. discussion 1390
74. Abel RM, Brown J, Moreland B, Parikh D. Pulmonary metastasectomy for pediatric solid tumors. Pediatr Surg Int. 2004;20:630–2.
75. Carli M, Colombatti R, Oberlin O, et al. European intergroup studies (MMT4-89 and MMT4-91) on childhood metastatic rhabdomyosarcoma: final results and analysis of prognostic factors. J Clin Oncol. 2004;22:4787–94.
76. Weigel BJ, Lyden E, Anderson JR, et al. Intensive multiagent therapy, including dose-compressed cycles of ifosfamide/etoposide and vincristine/doxorubicin/cyclophosphamide, irinotecan, and radiation, in patients with high-risk rhabdomyosarcoma: a report from the children's oncology group. J Clin Oncol. 2016;34:117–22.
77. Pappo AS, Rao BN, Jenkins JJ, et al. Metastatic nonrhabdomyosarcomatous soft-tissue sarcomas in children and adolescents: the St. Jude Children's Research Hospital experience. Med Pediatr Oncol. 1999;33:76–82.
78. Raciborska A, Bilska K, Rychlowska-Pruszynska M, et al. Management and follow-up of Ewing sarcoma patients with isolated lung metastases. J Pediatr Surg. 2016;51:1067–71.
79. Kwauk S, Burt M. Pulmonary metastases from adrenal cortical carcinoma: results of resection. J Surg Oncol. 1993;53:243–6.
80. De Leon DD, Lange BJ, Walterhouse D, Moshang T. Long-term (15 years) outcome in an infant with metastatic adrenocortical carcinoma. J Clin Endocrinol metab. 2002;87:4452–6.
81. Appelqvist P, Kostianinen S. Multiple thoracotomy combined with chemotherapy in metastatic adrenal cortical carcinoma: a case report and review of the literature. J Surg Oncol. 1983;24:1–4.
82. Pio L, Varela P, Eliott MJ, et al. Pediatric airway tumors: a report from the International Network of Pediatric Airway Teams (INPAT). Laryngoscope. 2020;130(4):E243–51. https://doi.org/10.1002/lary.28062. PMID: 31090942.
83. Varela P, Pio L, Torre M. Primary tracheobronchial tumors in children. Semin Pediatr Surg. 2016 Jun;25(3):150–5.
84. Rojas Y, Shi YX, Zhang W, et al. Primary malignant pulmonary tumors in children: a review of the national cancer data base. J Pediatr Surg. 2015;50(6):1004–8.
85. Varela P, Pio L, Brandigi E, et al. Tracheal and bronchial tumors. J Thorac Dis. 2016;8(12):3781–6.
86. Shamberger RC, Grier HE. Chest wall tumors in infants and children. Semin Pediatr Surg. 1994;3(4):267–76.
87. Chang RR, et al. Reconstruction of complex oncologic chest wall defects: A 10-year experience. Ann Plast Surg. 2004;52(5):471–9. discussion 479
88. Sauvat F, Brisse H, Magdeleinat P, et al. The transmanubrial approach: a new operative approach to cervicothoracic neuroblastoma in children. Surgery. 2006;139:109–14.
89. De Corti F, Avanzini S, Cecchetto G, Buffa P, Guida E, Zanon GF, Jasonni V. The surgical approach for cervicothoracic masses in children. J Pediatr Surg. 2012;47(9):1662–8.
90. Christison-Lagay ER, Darcy DG, Stanelle EJ, Dasilva S, Avila E, La Quaglia MP. "Trap-door" and "clamshell" surgical approaches for the management of pediatric tumors of the cervicothoracic junction and mediastinum. J Pediatr Surg. 2014;49(1):172–6. discussion 176-7.
91. Malkan AD, Loh AH, Fernandez-Pineda I, Sandoval JA. The role of thoracoscopic surgery in pediatric oncology. J Laparoendosc Adv Surg Tech A. 2014;24(11):819–26.
92. Gow KW, Chen MK, New Technology Committee, Barnhart D, Breuer C, Brown M, Calkins C, Ford H, Harmon C, Hebra A, Kane T, Keshen T, Kokoska ER, Lawlor D, Pearl R. American Pediatric Surgical Association New Technology Committee review on

video-assisted thoracoscopic surgery for childhood cancer. J Pediatr Surg. 2010;45:2227–33.
93. Malek MM, Mollen KP, Kane TD, Shah SR, Irwin C. Thoracic neuroblastoma: A retrospective review of our institutional experience with comparison of the thoracoscopic and open approaches to resection. J Pediatr Surg. 2010;45:1622–6.
94. Petty JK, Bensard DD, Partrick DA, Hendrickson RJ, Albano EA, Karrer FM. Resection of neurogenic tumors in children: Is thoracoscopy superior to thoracotomy? J Am Coll Surg. 2006;203:699–703.
95. Tanaka Y, Uchida H, Kawashima H, Sato K, Takazawa S, Masuko T, Deie K, Iwanaka T. Complete thoracoscopic versus video-assisted thoracoscopic resection of congenital lung lesions. J Laparoendosc Adv Surg Tech A. 2013;23:719–22.
96. Fraga JC, Aydogdu B, Aufieri R, Silva GV, Schopf L, Takamatu E, Brunetto A, Kiely E, Pierro A. Surgical treatment for pediatric mediastinal neurogenic tumors. Ann Thorac Surg. 2010;90:413–38.
97. Bratu I, Laberge JM, Flageole H, Bouchard S. Foregut duplications: Is there an advantage to thoracoscopic resection? J Pediatr Surg. 2005;40:138–41.
98. Fraga JC, Rothenberg S, Kiely E, Pierro A. Video-assisted thoracic surgery resection for pediatric mediastinal neurogenic tumors. J Pediatr Surg. 2012;47:1349–53.
99. Metzelder ML, Kuebler JF, Shimotakahara A, Glueer S, Grigull L, Ure BM. Role of diagnostic and ablative minimally invasive surgery for pediatric malignancies. Cancer. 2007;109:2343–8.
100. Shah RM, Spirn PW, Salazar AM, Steiner RM, Cohn HE, Solit RW, Wechsler RJ, Erdman S. Localization of peripheral pulmonary nodules for thoracoscopic excision: Value of CT-guided wire placement. AJR. 1993;161:279–83.
101. Gonfiotti A, Davini F, Vaggelli L, De Francisci A, Caldarella A, Gigli PM, Janni A. Thoracoscopic localization techniques for patients with solitary pulmonary nodule: Hookwire versus radio-guided surgery. Eur J Cardiothorac Surg. 2007;32:843–7.
102. Dingemann C, Ure B, Dingemann J. Thoracoscopic procedures in pediatric surgery: What is the evidence? Eur J Pediatr Surg. 2014;24:14–9.
103. Meehan JJ. Robotic surgery for pediatric tumors. Cancer J. 2013;19:183–8.
104. Hayes-Jordan AA, Daw NC, Furman WL, Hoffer FA, Shochat SJ. Tumor recurrence at thoracostomy tube insertion sites: A report of two pediatric cases. J Pediatr Surg. 2004;39:1565–7.
105. Sartorelli KH, Patrick D, Meagher DP. Port site recurrence after thoracoscopic resection of pulmonary metastasis owing to osteogenic sarcoma. J Pediatr Surg. 1996;31:1443–4.
106. Acer T, Karnak I, Ciftçi AO, Akçören Z, Tanyel FC, Senocak ME. The prognostic factors in children undergoing pulmonary metastatectomy. Turk J Pediatr. 2012;54:45–51.
107. Esposito C, Lima M, Mattioli G, Mastroianni L, Riccipetitoni G, Monguzzi G, Zanon G, Cecchetto G, Settimi A, Jasonni V, Italian Society of Videosurgery in Infancy. Thoracoscopic surgery in the management of pediatric malignancies: A multicentric survey of the Italian Society of Videosurgery in Infancy. Surg Endosc. 2007;21:1772–5.
108. Sandoval C, Stringel G. Video-assisted thoracoscopy for the diagnosis of mediastinal masses in children. JSLS. 1997;1:131–3.
109. DeCou JM, Schlatter MG, Mitchell DS, Abrams RS. Primary thoracoscopic gross total resection of neuroblastoma. J Laparoendosc Adv Surg Tech A. 2005;15:470–3.
110. Gentili A, Lima M, De Rose R, Pigna A, Codeluppi V, Baroncini S. Thoracoscopy in children: Anaesthesiological implications and case reports. Minerva Anestesiol. 2007;73:161–71.
111. Byon HJ, Lee JW, Kim JK, Kim JT, Kim YT, Kim HS, Lee SC, Kim CS. Anesthetic management of video-assisted thoracoscopic surgery (VATS) in pediatric patients: The issue of safety in infant and younger children. Korean J Anesthesiol. 2010;59:99–103.
112. Choudhry DK. Single-lung ventilation in pediatric anesthesia. Anesthesiol Clin N Am. 2005;23:693–708. ix
113. Hammer GB, Fitzmaurice BG, Brodsky JB. Methods for single-lung ventilation in pediatric patients. Anesth Analg. 1999;89:1426–9.
114. Cohen DE, McCloskey JJ, Motas D, Archer J, Flake AW. Fluoroscopic-assisted endobronchial intubation for single-lung ventilation in infants. Paediatr Anaesth. 2011;21:681–4.
115. Shamberger RC, Holzman RS, Griscom NT, Tarbell NJ, Weinstein HJ, Wohl ME. Prospective evaluation by computed tomography and pulmonary function tests of children with mediastinal masses. Surgery. 1995;118:468–71.
116. Bassanezi BS, Oliveira-Filho AG, Miranda ML, Soares L, Aguiar SS. Use of BiPAP for safe anesthesia in a child with a large anterior mediastinal mass. Paediatr Anaesth. 2011;21:985–7.
117. Soliman LM, Mossad EB. Thoracic epidural catheter in the management of a child with an anterior mediastinal mass: a case report and literature review. Paediatr Anaesth. 2006;16:200–5.
118. Spurbeck WW, Davidoff AM, Lobe TE, Rao BN, Schropp KP, Shochat SJ. Minimally invasive surgery in pediatric cancer patients. Ann Surg Oncol. 2004;11:340–3.
119. Rodgers BM, Moazam F, Talbert JL. Thoracoscopy in children. Ann Surg. 1979;189:176–80.
120. Prasad R, Arthur LG, Timmapuri SJ, Schwartz MZ, Fairbanks TJ, Mendelson KG, Thatch K, Moront ML. Early experience with single-incision thoracoscopic surgery in the pediatric population. J Laparoendosc Adv Surg Tech A. 2011;21:189–92.
121. Meehan JJ, Sandler AD. Robotic resection of mediastinal masses in children. J Laparoendosc Adv Surg Tech A. 2008;18:114–9.
122. Grunenwald D, Spaggiari L, Girard P, Baldeyrou P. Transmanubrial approach to the thoracic inlet. J

Thorac Cardiovasc Surg. 1997;113(5):958–9. author reply 960-1
123. Ladas G, Rhys-Evans PH, Goldstaw P. Anterior cervical-transsternal approach for resection of benign tumors at the thoracic inlet. Ann Thorac Surg. 1999;67:785–9.
124. Grosfeld JL, Weber TR, Vane DW. One-stage resection for massive cervicomediastinal hygroma. Surgery. 1982;92:693–6.
125. Bal S, Eishershari H, Celiker R, et al. Thoracic sequels after thoracotomies in children with congenital cardiac disease. Cardiol Young. 2003;13(3):264–7.
126. DeRosa GP. Progressive scoliosis following chest wall resection in children. Spine. 1985;10(7):618–22.
127. Pini Prato A, Bava GL, Dalmonte P, Vercellino N, Michelazzi A, Pio L. AvanziniS, Mattioli G. Sixteen years of experience with persistent chylothorax in children. Minerva Pediatr. 2017 Dec;69(6):476–80.
128. Hines MH. Video-assisted diaphragm plication in children. Ann Thorac Surg. 2003;76(1):234–6.
129. Nordin AB, Fallon SC, Jea A, Kim ES. The use of spinal angiography in the management of posterior mediastinal tumors: case series and review of the literature. J Pediatr Surg. 2013 Sep;48(9):1871–7.
130. Mahoney NR, Liu GT, Menacker SJ, Wilson MC, Hogarty MD, Maris JM. Pediatric horner syndrome: etiologies and roles of imaging and urine studies to detect neuroblastoma and other responsible mass lesions. Am J Ophthalmol. 2006;142(4):651–9.