Turkish Journal of Thoracic and Cardiovascular Surgery 2024;32(Suppl 1):S98-S107

REVIEW / DERLEME

Pediatric mediastinal tumors

Çocukluk çağı mediasten tümörleri

Ömer Soysal[1], Fatma Betül Çakır[2]

Author Affiliations:
[1]Department of Thoracic Surgery, Bezmialem Vakıf University Faculty of Medicine, Istanbul, Türkiye
[2]Department of Pediatrics, Pediatric Hematology Oncology, Bezmialem Vakıf University Faculty of Medicine, Istanbul, Türkiye

ABSTRACT

Mediastinal tumors are the most common thoracic tumor in the pediatric population. They include a spectrum of tumors, and most are malignant. These lesions can be anatomically and radiologically classified by means of compartments; anterior, middle, and posterior. Symptoms, signs, localization of the tumor, age of the child, and tumor markers are key points of diagnosis. Surgical approaches are typically needed for diagnosis, but sometimes tru-cut needle biopsies may be sufficient. Mediastinoscopy, mediastinotomy, and video-assisted thoracoscopic surgery may be used in the diagnostic workup of mediastinal tumors in children as they are used in adults. Frequently, diagnosis and treatment are both established by means of surgery. Surgery remains the mainstay of treatment of most benign and malignant nonlymphoid tumors. Combined modality of treatment incorporating chemotherapy and radiotherapy is often required in malignant tumors and is associated with high survival rates in these patients.

Keywords: Mediastinum, pediatric, tumor.

ÖZ

Mediastinal tümörler, çocukluk yaş grubunda en sık görülen torasik tümörlerdir. Çok fazla çeşit tümör bulunur ve çoğu maligndir. Anatomik ve radyolojik olarak kompartmanlara ayrılarak sınıflandırılabilir; ön, orta ve arka. Semptomlar, bulgular, tümör lokalizasyonu, çocuğun yaşı ve tümör belirteçleri tanıda anahtar noktalardır. Tanı için sıklıkla cerrahi işlemlere gerek duyulur, fakat bazen "tru-cut" biyopsi de yeterli olabilmektedir. Çocukta mediyastinoskopi, mediyastinotomi ve video yardımlı torakoskopik cerrahi, tanıda erişkinde olduğu gibi kullanılabilir. Çoğu zaman, cerrahi ile tanı ve tedavi aynı anda yapılır. Benign tümörlerde ve non-lenfoid olanlar dışındaki malign tümörlerde cerrahi, tedavinin temel taşı olmaya devam etmektedir. Malign tümörlerde tedaviye sıklıkla kemoterapi ve radyoterapi eklenmesi gerekir ve bu uygulama yüksek sağkalım oranları ile ilişkilidir.

Anahtar sözcükler: Mediyastinal, pediatrik, tümör.

Most thoracic tumors in childhood are found in the mediastinum. Pediatric mediastinal tumors can be either malignant or benign. Unlike in adults, symptoms in pediatric mediastinal tumors emerge earlier due to both the higher frequency of malignant tumors and the smaller size of the mediastinum.

The localization of mediastinal tumors contributes to the diagnosis. In the anterior mediastinum, lymphomas, thymic tumors, and teratomas; in the middle mediastinum, cystic lesions and lymphomas; and in the posterior mediastinum, neurogenic tumors should primarily be considered in the diagnostic algorithm due to their specific localizations. As with other tumors, the diagnosis of mediastinal tumors should be definitively established through histopathological examination. Since the mediastinum is a relatively challenging region to access, surgical procedures are often required for biopsy in the presence of a mediastinal tumor. Sometimes, surgical procedures that combine diagnosis and treatment are employed.

Pediatric mediastinal tumors are not common. In one study, out of 110,284 malignant tumors, 22 (0.02%) cases were reported as pediatric mediastinal tumors.[1] In a study from Türkiye, 31 pediatric mediastinal tumors

Corresponding author: Ömer Soysal.
E-mail: dromersoysal@gmail.com

Doi: 10.5606/tgkdc.dergisi.2024.25799

Received: November 30, 2023
Accepted: December 11, 2023
Published online: February 05, 2024

Cite this article as: Soysal Ö, Çakır FB. Pediatric mediastinal tumors. Turk Gogus Kalp Dama 2024;32(Suppl 1):S98-S107. doi: 10.5606/tgkdc.dergisi.2024.25799.

were identified over 16 years, with approximately two cases reported annually.[2]

ANATOMY OF THE MEDIASTINUM AND ITS RELATIONSHIP WITH TUMORS

The mediastinum is the region located between the two lungs, limited superiorly by the thoracic outlet, inferiorly by the diaphragm, anteriorly by the posterior surface of the sternum, and posteriorly by the anterior surfaces of the vertebrae. It is examined by dividing it into three regions. The anterior mediastinum is the region between the sternum and the pericardium and major vessels. In this area, the thymus, lymph nodes, internal mammary vessels, adipose tissue, and connective tissue are present. Tumors commonly found in the anterior mediastinum include lymphomas, thymic tumors, germ cell tumors (GCTs), lymphangiomas, ectopic thyroid, and parathyroid. The posterior mediastinum includes the area between the posterior surface of the heart and the vertebral column, comprising the descending aorta, esophagus, azygos vein, lymph nodes, intercostal vessels and nerves, thoracic duct, sympathetic chain, vagus nerve, and connective and adipose tissues. This region is also known as the paravertebral sulcus. Neurogenic tumors are almost always observed in the posterior mediastinum, with lymphomas occasionally present. The middle mediastinum, situated between the anterior and posterior mediastinum, is a region containing vital organs and structures, including the pericardium, heart, main arteries of the heart (ascending aorta, aortic arch, and branches), vena cava and their branches, phrenic nerves, trachea, main bronchi, vagus nerve, and lymph nodes. Also referred to as the visceral mediastinum, lymphomas are common tumors in this region, and cysts, which will be discussed in another section, may also occur here.

Localization and the relationship of tumors can be disrupted as the tumor grows and advances into adjacent mediastinal regions. For instance, a GCT originating from the anterior mediastinum can extend to the vertebra, or a non-Hodgkin lymphoma (NHL) can encompass the entire mediastinum. This occurrence is more common in children and larger tumors and should be kept in mind.

LESIONS MIMICKING MEDIASTINAL TUMORS

Intrathoracic goiter

Intrathoracic goiter, also known as substernal goiter or plunging goiter, is rare in childhood and can manifest in three forms: *(i)* cervical goiter with a small substernal extension (82%), *(ii)* partial intrathoracic, with a significant portion in the mediastinum (15%), and *(iii)* complete intrathoracic, where the entire goiter is in the thorax, with no cervical involvement (3%). Typically situated between the brachiocephalic veins and the sternum, it can extend behind the trachea or even the esophagus. It may exert pressure on the trachea, and the presence of hoarseness should raise suspicion of malignancy. Vascular supply usually comes from the inferior thyroid artery. In cases of ectopic mediastinal thyroid, the vasculature originates within the mediastinum. Surgical excision, with cervical thyroid incision, is sufficient in 98% of cases, with sternotomy or thoracotomy rarely required.[3] Chest surgeons should be prepared for possible intraoperative complications and consider the need for sternotomy or thoracotomy, given that 5.4% of 19,662 goiters were substernal (cervicomediastinal) in one study.[4] Of these, 6.5% required manubriotomy. Symptoms, malignancy rates, surgical morbidity, and recurrence paralysis were found to be higher in cervicomediastinal goiters compared to cervical goiter cases.[4]

Cervicomediastinal cystic hygroma

Cervical cystic hygroma is a lymphangioma, a congenital anomaly typically identified at birth or in the early infant period. It represents a malformation of the jugular lymphatics. Extension into the mediastinum is observed in 3% of cases, making it a rare occurrence. Surgical intervention is the primary treatment modality.[5]

Vertebral chordoma

Vertebral chordoma originates from the ectopic embryonic remnants of the primitive notochord and is rare. It is a malignant tumor. Extensive resection and spinal reconstruction are necessary.

Paravertebral abscess

Paravertebral abscess, also known as Pott's abscess, cold abscess, or tuberculosis abscess is common in our country but relatively rare in children. Among 26 children presenting with persistent back pain, Pott's abscess was identified in two cases.[6] Drainage by means of thoracotomy is sufficient for treatment.

Others

Anterior meningocele, extramedullary hematopoietic tissue, vascular lesions, esophageal lesions, lung tumors, and lesions originating below the diaphragm (hiatal hernia, Morgagni hernia, or pancreatic pseudocyst)[3] can mimic mediastinal tumors.

CLINICAL PRESENTATION: SYMPTOMS AND FINDINGS IN MEDIASTINAL TUMORS

In adults, one-third of mediastinal tumors are symptomatic, while in children, two-thirds exhibit symptoms. Approximately 75-85% of malignant tumors are symptomatic, whereas 33-46% of benign tumors present with symptoms.[7] Symptoms and findings in mediastinal tumors generally arise due to the pressure exerted by the tumor on surrounding structures. Additionally, if a mediastinal tumor causes symptoms, it is typically malignant. The higher incidence of symptoms in children with mediastinal tumors compared to adults is attributed to the more frequent occurrence of malignant tumors, the smaller size of the mediastinum, and the smaller diameter of the trachea and vessels, making them more susceptible to compression.

Airways, being small and delicate in children, manifest more prominently than in adults. Symptoms include dyspnea, tachypnea, stridor, respiratory distress, and hemoptysis. Pressure on the esophagus can lead to dysphagia, and manifestations such as superior vena cava syndrome, Horner's syndrome, diaphragmatic paralysis due to phrenic nerve compression or invasion, hoarseness due to recurrent nerve involvement, and effusion symptoms and signs with pleura and pericardium invasion may occur.

Symptoms and signs related to the metastatic region, such as headaches, bone pain, and abdominal pain, may be observed. Common paraneoplastic syndromes in children are myasthenia gravis, hypertension, and hypocalcemia.

NONINVASIVE DIAGNOSIS METHODS

Physical examination may reveal signs of lung infection or pleural fluid. There is no pathognomonic physical examination finding. Diagnosis is typically confirmed through investigations and a biopsy obtained by an invasive method. A lateral chest X-ray is crucial in demonstrating which mediastinal region the tumor is located. Esophagography is appropriate for patients with dysphagia symptoms.

The most important radiological method in the diagnosis of mediastinal masses is computed tomography (CT), which should be performed with contrast. The characteristics of the tissues inside the tumor, invasion of the surroundings, whether it is solid/cystic, and the specific mediastinal region are evaluated in axial, coronal, and sagittal sections. Biopsy is often performed under CT guidance.

Magnetic resonance imaging may provide better visualization of vascular invasion, cardiac invasion, and surrounding bone tissue invasions. It is less commonly used with the development of three-dimensional spiral CT and CT angiography.

Echocardiography is useful in evaluating mediastinal tumors adjacent to the heart, detecting pericardial fluid, and identifying myocardial invasion.

Nuclear medicine studies

Iodine-131 thyroid scintigraphy can show mediastinal thyroid. Technetium-99m MIBI (methoxyisobutylisonitrile) scintigraphy can identify ectopic mediastinal parathyroid adenomas. Octreotide can reveal neuroendocrine tumors. Iodine-131-MIBG (metaiodobenzylguanidine) can show pheochromocytomas. Gallium scintigraphy can recognize malignant lesions but is less commonly used with the introduction of positron emission tomography.

Positron emission tomography, a nuclear medicine technique, is used for distinguishing between malignant and benign tumors, assessing the extent of lymphomas, detecting distant metastases, and determining the response to treatment.

Tumor markers

Tumor markers are biological products indicating the presence of a tumor. They are often not specific for diagnosis but are used for screening, supporting diagnosis, monitoring treatment response, and detecting recurrences. Table 1 shows mediastinal tumors and related tumor markers (Table 1).[8]

INVASIVE DIAGNOSIS METHODS

The cornerstone of diagnosing mediastinal tumors is the histopathological diagnosis obtained through biopsy. Biopsy from the mediastinum can be relatively challenging due to the difficulty in accessing this region, and the abundant vascular structures increase the risk of the biopsy procedure. Biopsy of a mediastinal tumor is typically performed through a surgical procedure under general anesthesia. Therefore, it should be done by a thoracic surgeon. In cases where surgical removal of the tumor is considered necessary for treatment, diagnosis and treatment can be planned together in the same session.

Transthoracic fine-needle aspiration biopsy

Transthoracic fine-needle aspiration biopsy (TFNAB), widely accepted and highly diagnostic in lung lesions and many other organ tumors, is performed under the guidance of CT or ultrasound.

Table 1. Tumor markers in mediastinal tumors

Tumors	Tumor marker
Nonseminomatous germ cell tumor (especially endodermal sinus, Yolk sac tumor)	AFP
Nonseminomatous germ cell tumor (especially choriocarcinoma)	Beta HCG
Seminoma	PLAP
Neuroendocrine tumor (thymic, pheochromocytoma, neuroblastoma, ganglioneuroblastoma)	NSE, chromogranin, synaptophysin
Parathyroid adenoma	PTH
Pheochromocytoma, neuroblastoma, ganglioneuroblastoma	Catecholamines, VMA, HVA

AFP: Alpha-fetoprotein; Beta HCG: Human Chorionic Gonadotropin; PLAP: Placental alkaline phosphatase; NSE: Neuron-specific enolase; PTH: Parathormone; VMA: Vanillylmandelic acid; HVA: Homovanillic acid.

In a study of 157 cases with mediastinal tumors, a definitive diagnosis was achieved in 82% of the cases.[9] Among these, 29.6% were primary mediastinal tumors, and 56.2% were metastatic tumors, with a histopathological confirmation of TFNAB diagnosis in 78% of the cases. Tru-cut biopsy may be preferred instead of TFNAB, particularly in lymphomas.

Mediastinotomy

Also known as anterior mediastinotomy or the Chamberlain procedure, mediastinotomy provides access only to the anterior mediastinal region. Depending on the location of the mediastinal tumor, biopsies are conducted by entering the anterior mediastinum through the excision of the second or third left or right costal cartilage. This approach offers advantages such as manual examination and palpation of the lesion, direct observation for biopsy, and the ability to obtain larger biopsy specimens. The insertion of a mediastinoscope through the opened window allows for the visualization of deeper regions, combining the use of mediastinotomy and mediastinoscopy. In lung cancer staging, it is utilized for the biopsy of mediastinal lymph nodes 5 and 6 on the left side. In a study involving 95 cases of mediastinal lymphoma, the cases were categorized into four groups: anterior mediastinal, mediastinotomy in 22 cases; middle mediastinal, mediastinoscopy in 19 cases; two other groups of 27 patients, each with both anterior and middle mediastinum localization who randomly underwent anterior mediastinotomy or mediastinoscopy. For cases where a diagnosis could not be established, other methods were used to diagnose lymphoma. As a result, the diagnostic accuracy for mediastinal lymphoma was reported as 80.4% with mediastinoscopy and 95.9% with mediastinotomy, and the authors noted the significance of this difference.[10] Mediastinotomy may be accomplished by using mediastinoscopy via the second or third intercostal space without rib resection in appropriate cases. This surgical approach is called anterior mediastinoscopy in our center.

Mediastinoscopy

Mediastinoscopy is performed through a tracheostomy skin incision, reaching the trachea and providing access to the anterior, bilateral, subcarinal, and peribronchial regions. While commonly used in the sampling of mediastinal lymph nodes for lung cancer staging, it is also frequently employed in the diagnosis of tumors around the trachea and the middle mediastinum. Its use may pose challenges in small children.

Video-assisted thoracoscopic surgery

Through the pleural cavity, all mediastinal regions can be easily accessed with thoracoscopy. The decision for a video-assisted thoracoscopic surgery (VATS) biopsy should be carefully made by radiologically evaluating the location of the mediastinal tumor and its anatomical relationship with vital structures, such as major vessels, the heart, and the esophagus. In the absence of the use of mediastinoscopy and mediastinotomy for reaching posterior mediastinal tumors, VATS becomes the sole invasive option. In some cases, complete removal of the tumor with VATS is possible, making it a procedure where diagnosis and treatment are simultaneously planned.[11] Robotic surgery may also be used instead of VATS, but it should be reserved only for treatment.

Endobronchial and esophageal ultrasound with TFNAB

Cytological examination through aspiration can be performed on mediastinal tumors using endobronchial or esophageal ultrasound guidance.

Despite reported high sensitivity and specificity, these techniques have not become widely used.[12] There is currently a lack of significant studies related to children.

Thoracotomy

In cases where a diagnosis cannot be established through other methods, thoracotomy may be necessary for the diagnosis of mediastinal tumors. This indicates the difficulty in diagnosing mediastinal tumors. The use of thoracotomy for diagnosing mediastinal tumors has significantly decreased with the utilization of VATS. Sternotomy is almost never required for the diagnosis of mediastinal tumors.

Dealing with mediastinal tumors, irrespective of age, demands the expertise of thoracic surgeons. Particularly in the case of pediatric mediastinal tumors, the involvement of thoracic surgeons becomes indispensable. Unlike certain malignancies that might be primarily addressed through chemotherapy, mediastinal tumors often require some form of thoracic surgery for effective diagnosis, treatment, and management. The unique challenges posed by mediastinal tumors underscore the crucial role of thoracic surgery in providing optimal care for patients of all ages.

THYMIC TUMORS

Thymoma

Thymic tumors are predominantly located in the anterior mediastinum, with 95% of cases arising in this region. They are rare in children. Thymomas have epithelial and lymphocytic forms, with a distribution of 22% lymphocytic, 27% epithelial, and 50% mixed-type thymoma. Histopathologically, thymomas consist of cells that appear benign, but 30-40% exhibit invasive characteristics, termed malignant or invasive thymoma. Noninvasive thymomas have a capsule and are labeled benign. Benign thymomas report local recurrence in 2-12% and capsule invasion in 17%. These findings imply the malignant potential of encapsulated thymomas, emphasizing the consideration of all thymomas as malignant, necessitating extensive and complete resection with postoperative radiotherapy for local control. Thymomas typically do not show distant metastasis, with a reported 3% occurrence in a series of 283 cases of invasive and noninvasive thymomas. Masaoka staging is the preferred method for thymoma staging (Table 2).

As an expression of autoimmunity, 40% of thymoma cases present with one and 30% with two paraneoplastic syndromes. Paraneoplastic syndromes associated with thymomas include myasthenia gravis, found in 30% of cases (10% of myasthenia gravis patients have thymomas), and "pure red cell aplasia," observed in 5% of thymomas. Additionally, immune deficiencies, systematic lupus erythematosus, and nonthymic cancers are among other paraneoplastic syndromes.

Biopsy is crucial for diagnosis, and screening for myasthenia gravis is recommended. Distant metastasis screening is unnecessary. Alpha-fetoprotein and beta-human chorionic gonadotropin are considered for differential diagnosis. Surgical excision forms the basis of treatment, with median sternotomy being the preferred surgical approach. Thoracotomy or VATS may be considered in suitable cases. Postoperative radiotherapy is recommended in almost all cases, except for very small Stage I thymomas. Stages III and IV necessitate multimodal treatment involving chemotherapy, followed by surgery and postoperative radiotherapy. Local recurrences should be considered for reresection. The prognosis for thymomas is generally favorable, with five-year survival rates of 95-97% for Stage I, 60-70% for Stage II-III, and 40% for Stage IVA-B.[13]

Thymic carcinoma

Thymic carcinoma is rare and comprises squamous, basaloid, and mucoepidermoid types, which have a low malignant potential. Anaplastic and sarcomatoid types have an aggressive course, and treatment is similar to lung cancer. Neoadjuvant chemotherapy, followed by surgery with radiotherapy is the treatment approach in totally unresectable tumors.[14]

Neuroendocrine thymic tumors

Neuroendocrine thymic tumors include thymic carcinoid and thymic small-cell cancer forms, resembling neuroendocrine tumors of the lung. They can have an aggressive course.

Table 2. Masaoka staging in thymoma

Stage	Characteristics
I	Encapsulated, no invasion of capsule
IIA	Invasion (+): Fat tissue or pleura
IIB	Invasion (+): Capsule
III	Invasion (+): Pericardium, vessels, lung
IVA	Pleural, pericardial dissemination
IVB	Distant metastasis

Thymic hyperplasia

Thymic hyperplasia denotes the enlargement of the thymus, characterized by lymphoid and follicular growth. It may occur in conjunction with autoimmune diseases. In some cases, immunosuppression develops after disease or tumor treatments, leading to thymic atrophy. When treatment is discontinued, hyperplasia may occur with "rebound" growth. Massive thymic hyperplasia is a distinct form, often idiopathic. Thymus is hyperplastic in the infant, and it has typical appearances in the chest X-ray. It gradually shrinks in size when periodical X-rays are obtained. It is rarely symptomatic; if it leads to symptoms, malignity of the lesion should be ruled out (neuroblastoma).

Thymolipoma

Thymolipoma is fundamentally a mesenchymal tumor, characterized by benign thymic tumors containing fatty tissue. They can reach significant sizes.

GERM CELL TUMORS

Approximately 2-3% of childhood cancers and 20% of mediastinal masses are GCTs.[15,16] These tumors form along the migration path of primitive germ cells originating from the yolk sac endoderm to develop the gonads. Thoracic GCTs are localized in the anterior mediastinum, with rare exceptions. Infants and young children may experience severe respiratory symptoms, including cough, dyspnea, orthopnea, and superior vena cava syndrome due to airway compression. Adolescents are generally asymptomatic. Histologically, mature and immature teratomas are the most common, with teratomas being the most frequent tumor in newborns and common in the first five years of life. In adolescents and adults with Klinefelter syndrome, mediastinal GCTs are prevalent.[15]

Table 3. Staging in extragonadal germ cell tumors

Stage	Characteristics
I	Complete resection (including coccyx in the sacrococcygeal region), negative surgical margins, tumor markers positive or negative, no lymph node involvement
II	Microscopic residue, negative lymph nodes, tumor markers positive or negative
III	Macroscopic residue or biopsy only, positive or negative lymph nodes, tumor markers positive or negative
IV	Distant organ spread

Teratomas typically contain elements from all three germ layers-endoderm, mesoderm, and ectoderm. They are often encapsulated and cystic, and mature teratomas may contain structures, such as bone, cartilage, teeth, hair, brain, hematopoietic, and intestinal components. Other types reported include endodermal sinus tumor, germinoma, and embryonal carcinoma. In these cases, tumor markers such as alpha-fetoprotein and beta-human chorionic gonadotropin should be assessed. Imaging, including anteroposterior and lateral chest X-rays, is crucial. Computed tomography confirms the tumor's anterior mediastinal location. Definitive diagnosis relies on histopathological examination. The treatment plan is tailored to the tumor's histology, localization, and stage (Table 3).[15-17]

For benign tumors like teratomas, surgical excision alone is usually sufficient, with a 95% survival rate for mature lesions. However, undetected malignant foci may lead to relapse. Prognosis for immature teratomas depends on the amount of immature teratoma present, the presence of residual tumors, and the presence of malignancy not pathologically detected. The BEP chemotherapy containing bleomycin, VP-16, and cisplatin is recommended for immature teratomas with malignancy. However, tumors without malignancy may be chemotherapy-resistant. In malignant GCTs, complete surgical removal is crucial for local control. However, due to the tumors' vascularity and size, complete excision may not always be possible. In such cases, BEP chemotherapy following biopsy is administered to shrink the tumor and allow for secondary surgery.[15-17] For germinomas with residual disease after chemotherapy, radiation therapy is included in the treatment. The prognosis, although generally unfavorable, ranges from 57 to 88% for event-free survival.[15,16]

LYMPHOMAS

Lymphomas are a heterogeneous group of malignancies resulting from the malignant proliferation of immune system cells, constituting about 25% of childhood cancers. Approximately 60% of lymphomas are NHLs, with NHL most commonly manifesting between 7-10 years of age and showing mediastinal involvement in 20-30% of cases.[18,19] Superior vena cava syndrome is frequently associated with primary disease in the anterior mediastinum. Hodgkin lymphoma (HL), NHL, and T-cell leukemia are the most common cancers causing superior vena cava syndrome. Symptoms include swelling of neck veins, facial and neck edema, dyspnea, orthopnea, confusion, and syncope. Emergency treatment involves reducing

Table 4. "St. Jude Staging System for Childhood NHL (Non-Hodgkin Lymphomas)

Stage	Characteristics
I	Single tumor (extranodal) or single lymph node involvement (nodal), not in the mediastinum or abdomen
II	Single tumor with regional lymph node involvement, two or more lymph nodes on the same side of the diaphragm, two tumors on the same side of the diaphragm (extranodal), or surgically removed primary gastrointestinal system tumor
III	Two tumors on both sides of the diaphragm (extranodal), two or more lymph nodes on both sides of the diaphragm, all primary intrathoracic tumors (mediastinal, pleural, thymic), widespread primary intraabdominal disease, or any paraspinal and epidural tumors independent of tumor localization
IV	Involvement of the central nervous system or bone marrow at diagnosis (blast rate <25%) in any of the above tumors

the mass with steroid therapy, followed by prompt tissue biopsy once the patient stabilizes. Mediastinal lymphomas rapidly metastasize to the bone marrow, transforming into lymphoblastic leukemia. Diagnosis can be confirmed through bone marrow aspiration. Additionally, pleural and pericardial involvement may lead to fluid accumulation, allowing for a rapid diagnosis without the need for tissue confirmation in this group of patients with generally poor overall condition.

Primary treatment for NHL is chemotherapy, with the intensity varying based on stage and disease type (Table 4). Using protocols from American, German, and French sources, long-term survival rates of 80-90% for localized disease and 60-80% for widespread disease are achieved.[18,19] However, the prognosis is not favorable in cases of relapsed disease.

In HL, mediastinal involvement is detected in 60% of cases. Intrathoracic disease is present in 60% of patients, primarily affecting the anterosuperior, paratracheal, and tracheobronchial lymph node groups. Mediastinal involvement is common in adolescents with the nodular sclerosing type.[20,21] Pulmonary parenchymal involvement and pleural effusion are rare in HL. Pericardial effusion can be detected by echocardiography in patients with large masses. Computed tomography is crucial for staging (Table 5) and detecting parenchymal involvement. Diagnosis is confirmed through excisional biopsy of a pathologically enlarged lymph node. Aspiration of lymph nodes can yield misleading results. If there are no peripheral lymph nodes, image-guided percutaneous needle biopsy, mediastinoscopy, or open biopsy may be performed. Treatment for HL varies in chemotherapy courses based on stage and

Table 5. Ann Arbor staging classification for Hodgkin lymphoma

Stage	Characteristics
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) (I) or involvement of a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or limited involvement of an extralymphatic organ or site and lymph nodes on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III) and involvement of the spleen (IIIS) or limited involvement of an extralymphatic organ or site (IIIE), or both (IIISE)
	Involvement of splenic hilar, celiac, or portal nodes with or without involvement of paraaortic, iliac, or mesenteric nodes
IV	Widespread or advanced disease with or without lymph node involvement of an extralymphatic organ or tissue
	A, Asymptomatic
	B, Presence of one or more of the following symptoms: unexplained weight loss of more than 10% in six months, unexplained fever above 38°C, and night sweats
	X, Bulky disease, defined as nodal mass ≥10 cm, or mediastinal mass width greater than one-third of the chest at the level of T5-T6
	E, Limited involvement of an extralymphatic organ

tumor response. Consolidation radiotherapy follows chemotherapy for some cases. The five-year disease-free survival rate with chemoradiotherapy in HL is around 95-98% in early stages and approximately 80% in advanced stages.[20,21]

NEUROBLASTOMA

Adrenal medulla, sympathetic ganglia, and other sympathetic neurons originate from primitive neural crest cells. Neuroblastoma is the most common malignant tumor in infancy, with a median age of 22 months. About 36% of cases are diagnosed before the age of one, 55% before the age of two, and 79% before the age of four. It is one of the small round blue cell tumors of childhood. The histopathology is classified as "favorable-good" or "unfavorable-bad" based on patient age, stroma presence, degree of differentiation, and mitosis-karyorrhexis index, using the prognostic classification developed by Shimada et al.[22] Determining the biological character of the tumor is also important for assessing the risk group. The MYCN oncogene amplification is the most important indicator of poor prognosis. The amplification of copy numbers 10 and above is significantly associated with advanced-stage disease, rapid tumor growth, high risk of relapse, and poor prognosis.

It often presents with an abdominal mass. Thoracic tumors, usually detected incidentally in chest X-rays due to infection symptoms, may cause Horner's syndrome (unilateral ptosis, miosis, and anhidrosis) when located in the upper thorax or cervical area. Large thoracic tumors can lead to superior vena cava syndrome. Urinary catecholamine metabolites (vanillylmandelic acid and homovanillic acid) are important in the diagnosis. Neurospecific enolase, ferritin, and elevated lactate dehydrogenase can also be detected. Thoracic CT shows the location, size, invasion into adjacent tissues, and invasion of bones (ribs and vertebrae). Posterior mediastinal masses can enter the spinal canal through the neural foramina, causing the compression of the spinal cord. This is an emergency, and if there are signs of spinal cord compression (back pain, extremity weakness, and decreased or loss of sensation), contrast-enhanced magnetic resonance imaging of the spinal axis should be performed. The definite diagnosis is made through histopathological and immunohistochemical examination. The presence of neuroblastoma cell clusters and rosette formation in bone marrow aspiration, along with an increase in catecholamine metabolites in urine (vanillylmandelic acid), can establish a diagnosis without tissue biopsy.[23,24]

Bone scans and skeletal surveys are useful for detecting bone metastases. Iodine-131-MIBG scintigraphy is important in diagnosis, staging, and response assessment to treatment. Staging is performed using the International Staging System, which is used worldwide (Table 6).[22] In this staging system, in addition to the factors mentioned in Table 6, resectability of the lesion is another criterion. However, essential staging could be done after surgery. Recently, another international neuroblastoma risk group staging system has become more popular. In this staging system, radiological evidence obtained from magnetic resonance imaging or CT is used as the risk stratification. For instance, image-defined risk factor is defined with a mass lesion when surrounded by major vessels. The possibility of resectability, age of the patient, and the morphological and molecular genetic features of the tumor are taken into account

Table 6. International Neuroblastoma Staging System (INSS)

Stage	Characteristics
1	Tumor confined to the organ of origin, with complete macroscopic resection. Microscopic residual tumor may or may not be present. No involvement of ipsilateral and contralateral lymph nodes.
2a	Unilateral tumor with incomplete macroscopic resection. No involvement of ipsilateral and contralateral lymph nodes.
2b	Unilateral tumor with complete or incomplete macroscopic resection. Involvement of ipsilateral regional lymph nodes, but no contralateral lymph node involvement.
3	Tumor crossing the midline ± regional lymph node involvement. Unilateral tumor with contralateral lymph node involvement. Midline tumor with bilateral lymph node involvement.
4	Widespread disease with distant metastases (distant lymph nodes, bone marrow, bone, liver, or other organs).
4S	Localized primary tumor like Stage I and II. Age <365 days. Presence of tumor cells in liver, skin, or bone marrow (<10% tumor cells).

during staging. Localized tumors along with different risk factors are classified as L1 or L2; metastatic tumors are classified as M or MS.[25]

Stage 4S is a very good prognosis group, characterized by localized tumors and only liver, skin, or bone marrow involvement (<10%) in cases under one year old.

Treatment is determined based on risk groups: low, intermediate, and high risk. In the low-risk group, surgery should be performed during diagnosis if it is possible to safely remove at least 90% of the tumor; otherwise, biopsy alone is sufficient. The tumor should be reduced with chemotherapy before surgery, and then surgical removal should be performed. In this group, where only surgery is performed, a cure rate of 85% is reported, and a five-year overall survival rate of 92% is determined. In the intermediate-risk group, where more intensive chemotherapy is given before secondary surgery, the four-year overall survival rate is reported to be 89% in well-differentiated histology, while it drops to the 73% range in cases with poorly differentiated histology. In the high-risk group, which includes older children with Stage 4 disease, intensive chemotherapy is followed by autologous stem cell transplantation. Radiation therapy is applied after surgery if there is live tumor presence. The prognosis is poor in the high-risk group, with a five-year overall survival rate of 38-31%, depending on the treatment approach.[26] In patients with high risk of recurrence, immunotherapy is included in addition to aforementioned treatment modalities. Radioactive marked MIBG treatment is another option in those patients.[27]

In conclusion, mediastinal tumors in children present with symptoms of compression on surrounding organs and structures. There is a wide range of tumors. Radiology, specifically thoracic CT, plays a significant role in diagnosis, but invasive surgical methods are often required for histopathological diagnosis. In children, mediastinoscopy, mediastinotomy, and VATS can be used for diagnosis, similar to adults. Surgical excision is curative for benign tumors, but in many cases, appropriate chemotherapy and radiotherapy are necessary based on the diagnosis.

Acknowledgement: I would like to express my gratitude to Levent Faruk Soysal for his valuable contributions to both the writing and formatting of this chapter.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Temes R, Allen N, Chavez T, Crowell R, Key C, Wernly J. Primary mediastinal malignancies in children: Report of 22 patients and comparison to 197 adults. Oncologist 2000;5:179-84. doi: 10.1634/theoncologist.5-3-179.
2. Bostancı K, Toker A, Alpagut U, Dayıoğlu E, Yılmazbayhan E, Çamcı E, et al. Pediatrik mediastinal kitlelere yaklaşım. Istanbul Tip Fak Mecmuasi 1998;61:252-6.
3. Shields TW. Lesions masquerading as primary mediastinal tumors and cysts. In: LoCicero III J, Feins RH, Colson YL, Rocco G, editors. Shields' General thoracic surgery. Vol 2, 8th ed. Philadelphia: Wolters Kluwer; 2019. p. 2082-95.
4. Testini M, Gurrado A, Avenia N, Bellantone R, Biondi A, Brazzarola P, et al. Does mediastinal extension of the goiter increase morbidity of total thyroidectomy? A multicenter study of 19,662 patients. Ann Surg Oncol 2011;18:2251-9. doi: 10.1245/s10434-011-1596-4.
5. Singh S, Baboo ML, Pathak IC. Cystic lymphangioma in children: Report of 32 cases including lesions atrrare sites. Surgery 1971;69:947-51.
6. Bezer M, Erol B, Kocaoğlu B, Aydin N, Güven O. Çocuk ve adölesanlarda görülen sırt ve bel ağrıları. Acta Orthop Traumatol Turc 2004;38:136-44.
7. Takeda S, Miyoshi S, Akashi A, Ohta M, Minami M, Okumura M, 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. doi: 10.1002/jso.10231.
8. Robinson PG. Mediastinal tumor markers. In: LoCicero III J, Feins RH, Colson YL, Rocco G, editors. Shields' General thoracic surgery. Vol 2, 8th ed. Philadelphia: Wolters Kluwer; 2019. p. 1974-99.
9. Assaad MW, Pantanowitz L, Otis CN. Diagnostic accuracy of image-guided percutaneous fine needle aspiration biopsy of the mediastinum. Diagn Cytopathol 2007;35:705-9. doi: 10.1002/dc.20738.
10. Elia S, Cecere C, Giampaglia F, Ferrante G. Mediastinoscopy vs. anterior mediastinotomy in the diagnosis of mediastinal lymphoma: A randomized trial. Eur J Cardiothorac Surg 1992;6:361-5. doi: 10.1016/1010-7940(92)90173-u.
11. Matsumura Y. Thoracoscopic surgery of mediastinal tumor. Kyobu Geka 2010;63(8 Suppl):724-9.
12. Vilmann P, Puri R. The complete "medical" mediastinoscopy (EUS-FNA + EBUS-TBNA). Minerva Med 2007;98:331-8.
13. Shields TW. Thymic tumors. In: LoCicero III J, Feins RH, Colson YL, Rocco G, editors. General thoracic surgery. Vol 2, 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. p. 2323-62.

14. Thymoma and Thymic Carcinoma Treatment (PDQ®)–Health Professional Version. Available at: https://www.cancer.gov/types/thymoma/hp/thymoma-treatment-pdq. [Accessed: 26.11.2023].
15. Olson TA, Schneider DT, Perlman EJ. Germ cell tumors In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 6th ed. Philadelphia: Lippincott Raven; 2011. p. 1045-67.
16. Olson TA. Germ cell tumors. In: Lanzkowsky P, editor. Manual pediatric hematology and oncology. 5th ed. San Diego: Elsevier; 2011. p. 776-795.
17. Schneider DT, Calaminus G, Koch S, Teske C, Schmidt P, Haas RJ, et al. Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer 2004;42:169-75. doi: 10.1002/pbc.10321.
18. Gross TG, Perkins SL. Malignant non-hodgkin lymphomas in children. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 6th ed. Philadelphia: Lippincott-Raven; 2011. p. 663-82.
19. Cairo MS, Hochberg J. Non-Hodgkin Lymphoma In: Lanzkowsky P, editor. Manual pediatric hematology and oncology. 5th ed. San Diego: Elsevier; 2011. p. 624-46.
20. Metzger M, Krasin MJ, Hudson M, Onciu M. Hodgkin lymphoma. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 6th ed. Philadelphia: Lippincott-Raven; 2011. p. 638-62.
21. Friedman D. Hodgkin lymphoma. In: Lanzkowsky P, editor. Manual pediatric hematology and oncology. 5th ed. San Diego: Elsevier; 2011. p. 599-623.
22. Shimada H, Ambros IM, Dehner LP, Hata J, Joshi VV, Roald B, et al. The international neuroblastoma pathology classification (the Shimada system). Cancer 1999;86:364-72.
23. Brodeur GM, Hogarty MD, Mosse YP, Maris JM. Neuroblastoma. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. Philadelphia: Lippincott-Raven; 2011. p. 886-922.
24. Bagatell R, Park JR. Neuroblastoma. In: Lanzkowsky P, editor. Manual pediatric hematology and oncology. 5th ed. San Diego: Elsevier; 2011. p. 671-94.
25. Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, et al. The international neuroblastoma risk group (INRG) staging system: An INRG task force report. J Clin Oncol 2009;27:298-303. doi: 10.1200/JCO.2008.16.6876.
26. Türk Pediatrik Onkoloji Grubu (TPOG) Nöroblastom-2009 Tedavi Protokolü TPOG-NB-2009. İzmir; 2009. Erişim adresi: https://www.gpoh.de/kinderkrebsinfo/content/hastalklar/baka_solid_tuemoer/pohneuroblpatinfo120120611/pohneuroblpatinfokurz120120611/index_tur.html [Erişim tarihi: 26.11.2023]