Common paediatric solid tumours

Introduction

The malignant solid tumors of children are histologically very diverse and a substantial proportion consists of characteristic entities that are rarely seen in adults.

They have been classified and categorized by International Classification of Childhood Cancers, (3rd ed.) into 12 groups which are further divided into subgroups and divisions.

1. Leukemias, myeloproliferative diseases, and myelodysplastic diseases
2. Lymphomas and reticuloendothelial neoplasms
3. CNS and miscellaneous intracranial and intraspinal neoplasms
4. Neuroblastoma and other peripheral nervous cell tumors
5. Retinoblastoma
6. Renal tumors
7. Hepatic tumors
8. Malignant bone tumors
9. Soft tissue and other extraosseous sarcomas
10. Germ cell tumors, trophoblastic tumors, and neoplasms of gonads
11. Other malignant epithelial neoplasms and malignant melanomas
12. Other and unspecified malignant neoplasms

Neuroblastoma

- One of the most common solid tumours of the infancy and childhood.

- Neoplasm of the neural crest origin.

- Clinical course variable-highly malignant tumour demonstrates unusual behaviour:
  - Spontaneous regression
  - Tumour maturation from a malignant to a benign histologic
  - Progressive disease

- Clinical incidence 1 in 7500-10000 children.
- 10% of all childhood tumours and 15% of all cancer deaths.
- Approx. 40% cases are diagnosed by 1year of age, 75% by 7 years and 98% by 10years.
- Slightly more common in boys than girls.(1.2:1).
- Most common intra-abdominal malignancy in newborns.
- Most frequently diagnosed malignancy in children less than 1 year of age.

- Embryonal nature of neuroblastoma- invade the placenta during the antenatal period.
  - Mothers of infants with congenital neuroblastoma occasionally experience flushing and hypertension
  - release of catecholamines from the fetal tumour in utero.

- Familial neuroblastoma: hereditary factors present:
  - Described in twins and family members
  - Median age for the occurrence of familial neuroblastoma is 9 months, in contrast to 18 months in the general population.
  - 20% of patients with familial neuroblastoma have bilateral or multifocal tumors.
  - Locus on chromosome 16p12-13

OTHER ASSOCIATED SYNDROMES

- Beckwith Weidmann syndrome
- Neurofibromatosis (von Recklinghausen disease)
- Hirschsprung's disease
- Central hypoventilation syndrome (ondine's curse)
- Fetal alcohol syndrome
- Offsprings of mothers taking phenytoin for seizure disorder (fetal hydantoin syndrome)

SITES

- Neuroblastoma may occur at any site where neural crest tissue is found in the embryo.
- Tumours may arise in the neck, posterior mediastinum, retroperitoneal (paraspinal) ganglia, adrenal medulla, and pelvic organ of Zuckerkandl.
- In 75% of cases, the tumour is located in the retroperitoneum
  - the adrenal medulla (50%)
  - the paraspinal ganglia(25%).
- In 20% of cases, the primary tumour is in the posterior mediastinum.
- Less than 5% of tumours occur in the neck or pelvis.
- Primary intracranial cerebral neuroblastoma also occurs.

CLINICAL PRESENTATION

- Neuroblastoma is a tumour with multiple clinical manifestations related to:
  - site of the primary tumour
  - Presence of metastases
  - production of certain metabolic tumour by-products.

SITE OF THE PRIMARY TUMOR: ABDOMEN

- Abdominal mass(50-70%)-hard, nodular, fixed and painful on palpation.

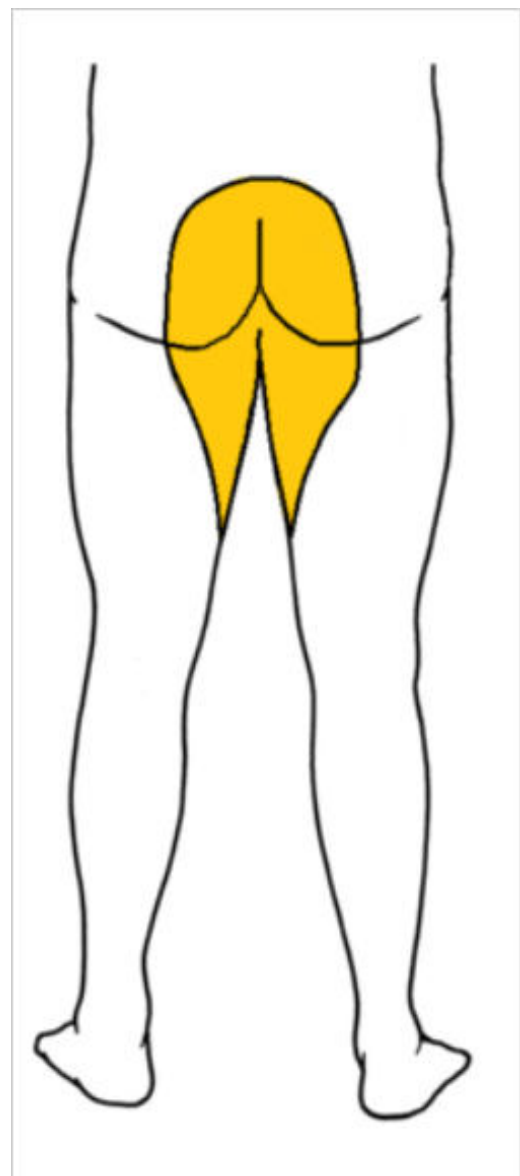
- Occasionally, large tumours can result in compression of venous and lymphatic drainage from the lower extremities, leading to scrotal and lower extremity oedema.

- Rarely, patients will experience renin-mediated hypertension because of compromise of renal vasculature.

- Hemoperitoneum caused by sudden spontaneous rupture of the neoplasm.

- Paraspinal tumours
  - may manifest with paraplegia related to tumour extension through an intervertebral foramen, resulting in a dumbbell- or hourglass-shaped lesion that may cause extradural compression of the spinal cord.

- Pelvic- may be palpable on rectal examination.
  - Cauda equina syndrome.
    - Severe back ache
    - Saddle anaesthesia-including the perineum, external genitalia and anus with numbness or "pins-and-needles" sensations of the groin and inner thighs which would contact a saddle when riding a horse.
    - Bladder and bowel dysfunction
    - Weakness of the muscles of the lower legs (often paraplegia)
    - Gait disturbance



UPPER MEDIASTINUM OR NECK

- Neoplasms arising in the upper mediastinum or neck may involve the stellate ganglion and cause Horner syndrome, which is characterized by
  - Ptosis
  - Miosis
  - Enophthalmos
  - Anhydrosis
  - heterochromia of the iris on the affected side.

MEDIASTINAL TUMOURS

- Respiratory distress because of the tumour's interference with lung expansion and dysphagia caused by extrinsic pressure on the oesophagus.
- May manifest with paraplegia.

METASTASIS

- Neuroblastoma may spread by direct extension into surrounding structures, lymphatic infiltration, or hematogenous metastases.

- Regional and distant lymph nodes, liver, bone marrow, and bone cortex are frequently involved.

- Patients with bone cortex metastases- ominous prognosis. Bone metastases occur in sites containing red marrow and involve the metaphyseal areas of long bones in addition to the skull, vertebral column, pelvis, ribs, and sternum.
  - Bone lesions may cause extreme pain and may be first identified when a child refuses to walk because of leg pain.

- Haematogenous metastases-brain, spinal cord, and heart.

- Brain metastases usually manifest in older children with headaches and seizures.

- Lung metastasis-result of direct extension to the lung from mediastinal lymph nodes or diffuse haematogenous spread, presenting with a radiographic pattern that may be confused with pulmonary oedema or interstitial pneumonia.

- Metastases to the bony orbit may produce proptosis or bilateral orbital ecchymosis—often referred to as “panda eyes” or “raccoon eyes”.

- Anemia is often related to bone marrow invasion by the tumor.

- Bleeding diathesis related to thrombocytopenia from extensive involvement of bone marrow and interference with hepatic production of clotting factors by liver metastases.

- Massive involvement of the liver with metastatic disease is particularly frequent in infants with stage 4S and may result in respiratory compromise (Pepper Syndrome).

- Multiple subcutaneous skin nodules- stage 4S
  - non-tender, bluish and mobile- called the "blueberry muffin sign"

PRODUCTION OF CERTAIN METABOLIC TUMOR BYPRODUCTS

- Excessive catecholamine production by the tumour may result in flushing, sweating, and irritability.
  - Hypertension(25% of cases)

- Acute cerebellar ataxia, characterized by opsomyoclonus and nystagmus ("dancing eye syndrome"):
  - seen more frequently (>60%) in patients with primary mediastinal tumours, in patients with stage I or II disease, and in infants younger than 1 year of age.
  - autoimmune phenomenon related to an antigen–antibody complex involving antibodies that cross-react with Purkinje cells in the cerebellum.
  - Poor school performance and learning deficits may occur as sequelae.
  - The survival rate for patients is 90%.
  - Persists even when the tumour is removed.

- Intractable diarrhea characterized by watery, explosive stools and hypokalemia. The diarrhea is related to the production of vasoactive intestinal polypeptide (VIP) by the tumour.
  - Often have somatostatin receptors and are differentiated, low-risk tumours.
  - Serum VIP levels can serve as a tumour marker
  - Tumour often does not secrete catecholamines.
  - somatostatin receptor expression is a favourable prognostic factor.

DIAGNOSIS: LABORATORY FINDINGS:

- ***Lactate Dehydrogenase:***
  - High serum levels of LDH- high proliferative activity or large tumour burden.
  - LDH level higher than 1500 IU/L-poor prognosis

- ***Ferritin:***
  - High levels of serum ferritin (>150 ng/mL)-reflect a large tumour burden or rapid tumour progression.
  - Elevated serum ferritin is often seen in advanced-stage neuroblastomas and indicates a poor prognosis.

- ***Neuron-Specific Enolase:***
  - Another useful prognostic marker of advanced-stage neuroblastoma-correlate with tumour burden.
  - The incidence of elevated NSE levels increases with stage.
  - A serum level of NSE >100 ng/mL - poor outcome.
- ***Catecholamine or their Metabolites:***
  - Neuroblastoma-secretion of catecholamine products, the metabolites of which can be detected in the urine of more than 90% of patients.
  - Urine specimen is of clinical value in diagnosing neuroblastoma and determining the response to therapy.
  - Urinary levels of vanillylmandelic acid (VMA) and homovanillic acid (HVA) can also be used as markers of tumour progression or relapse, and serve as a surrogate prognostic indicator.
  - 24-hour urine estimations for younger children.

Diagnostic Imaging

- ***Standard Radiographs:***
  - Chest radiography- presence of a posterior mediastinal mass.
  - Abdominal radiography is less often the modality by which a neuroblastoma is discovered- as a mass with fine calcification(50%).
  - Paraspinal widening is commonly found with celiac axis tumors.
- ***Ultrasonography:***
  - Most often used during the initial assessment of a suspected abdominal mass.
  - Sensitivity and accuracy are less than that of CT or MRI for diagnosing neuoblastoma.
- ***Computed Tomography :***
  - CT can demonstrate calcification in almost 85% of neuroblastomas
  - Intraspinal extension of the tumor can be determined on contrast-enhanced CT.
  - Overall, contrast-enhanced CT has been reported to be 82% accurate in defining neuroblastoma extent, with the accuracy increasing to nearly 97% when performed with a bone scan.

- ***Magnetic Resonance Imaging:***
  - MRI is the most useful and most sensitive imaging modality for the diagnosis and staging of neuroblastoma.
  - More accurate than CT for detection of stage 4 disease.
  - Sensitivity of MRI is 83%, and that of CT is 43%
  - Specificity of MRI is 97%, and that of CT is 88%.
  - Metastases to the bone and bone marrow, in particular, are better detected by MRI, as is intraspinal tumor extension.
  - When considering skeletal metastases alone, MRI and bone scan have been shown to be equivalent.
  - Encasement of major vessels can be better defined by MRI than CT, especially with the use of MR angiography.

Metaiodobenzylguanidine Imaging

- Metaiodobenzylguanidine (MIBG) is transported to and stored in the chromaffin cells in the same way as norepinephrine.
- Preferred imaging study for evaluating the bone and bone marrow involvement by neuroblastoma.
- Primary tumors and lymph node metastases are also detectable.
- Technetium-99m methylene diphosphonate(99mTc-MDP) bone scans is a second choice if MIBG imaging is not available or does not visualize known disease.

- **Bone Marrow Examination:**
  - Marrow biopsy is a routine method for detecting bone marrow involvement.
  - Both aspiration and trephine biopsy should be performed, although the latter has better diagnostic value.

STAGING

- In 1988, an international staging system was devised.
- This system takes into account:
  - tumor size and location relative to the midline
  - presence and degree of metastatic disease.
  - extent of surgical resection of the primary tumor in patients with nonmetastatic disease.

International Neuroblastoma Staging System

Stage	*Description*
I	Localized tumor confined to area of origin; complete excision, with or without microscopic residual disease; ipsilateral and contralateral lymph nodes negative (nodes attached to primary tumor and removed en bloc with it may be positive)
IIA	Unilateral tumor with incomplete gross excision; ipsilateral and contralateral lymph nodes negative
IIB	Unilateral tumor with complete or incomplete excision; positive ipsilateral, nonadherent regional lymph nodes; contralateral lymph nodes negative
III	Tumor infiltrating across the midline with or without lymph node involvement; or unilateral tumor with contralateral lymph node involvement; or midline tumor with bilateral lymph node involvement or bilateral infiltration (unresectable)
IV	Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver, or other organs
IV-S	Localized primary tumor as defined for stage I or II with dissemination limited to liver, skin, or bone marrow (limited to infants younger than 1 yr)

Pathology

- On histological examination, the immature neuroblasts appear as sheets of dark-blue nuclei with scanty cytoplasm set in a delicate vascular stroma.
- More differentiated areas show the presence of ganglion cells with a more abundant stroma.
- Rosette formation may be observed and is considered a sign of early tumor differentiation. The center of each rosette is formed by a tangle of fine nerve fibers.

MOLECULAR BIOLOGY

- **DNA Content:**
- The majority (55%) of primary neuroblastomas are triploid or 'near-triploid/hyperdiploid'

- Remainder (45%) are either 'near-diploid' or 'near-tetraploid'.

- Neuroblastomas that are near-diploid or near-tetraploid usually have frequently chromosome 1p deletion and *MYCN* amplification.

- Patients with near-triploid tumors typically have favourable clinical and biologic prognostic factors and excellent survival rates.

- **Amplification of *MYCN***
  - *MYCN* encodes a 64 kDa nuclear phosphoprotein that is located at chromosome 2p24).

- Approx. 25% of primary neuroblastomas in children have *MYCN* amplification

- *MYCN* amplification being present in 40% with advanced disease but only 5–10% with low-stage disease.

- Amplification of *MYCN* is associated with advanced stages of disease, rapid tumour progression, and poor outcome.

- **Chromosomal Changes:**
  - 1p deletions.
  - Deletion of the long arm of chromosome 11 (11q) is also common in neuroblastoma(40% of cases).
  - Unbalanced deletion of 11q is inversely related to *MYCN* amplification.

- **Other Molecular Abnormalities:**
  - Trk A appears to mediate differentiation of developing neurons or neuroblastoma.
  - High Trk A expression is associated with favorable tumor.

Treatment

- For stage 1 or 2 disease, surgery alone may be sufficient or associated with neoadjuvant and adjuvant chemotherapy.

- Initial chemotherapy is mandatory for children with stage 3 or 4 disease. Immediate surgery for those with locally advanced disease is markedly more difficult and unsatisfactory.

- In some children with stage 4S disease, no treatment is necessary and the disease resolves spontaneously.
  - Treatment is required in the face of relentless hepatomegaly causing respiratory compromise.

- Combination chemotherapy may include cyclophosphamide, vincristine, cisplatin, carboplatin, doxorubicin and etoposide, among others.

- Radiotherapy- Neuroblastoma is a radiosensitive tumour.
  - Radiotherapy is usually used in advanced stages or myeloablative therapies.

- Immunotherapy is also being used.

- The goal of resection is a complete dissection of the vasculature and should include the primary tumour site, in addition to all regional lymph nodes.

- Neuroblastoma often adheres to or surrounds the great vessels, and special care should be taken to identify and spare the blood supply to important visceral structures, such as the branches of the celiac axis and superior mesenteric artery.

- Because neuroblastoma may have a friable pseudocapsule, careful handling of the tumour during dissection is important to avoid tumor spill and haemorrhage.

Wilm’s tumour

Wilms' Tumour(Nephroblastoma)

- Max Wilms (1867–1918), Professor of Surgery in Heidelberg, described the tumour that still bears his name in 1899.
- Wilms tumour (WT, nephroblastoma) is the most common renal tumour of childhood and the second most common intra-abdominal malignancy after neuroblastoma.
- The risk of developing WT in the general population is 1:10,000.
- The incidence is slightly elevated for American and African blacks compared with whites and is significantly lower in Asians.
- The mean age at diagnosis is 36 months, with most children presenting between the ages of 12 and 48 months.
- Tumours tend to occur about 6 months later in girls than in boys.

- Tumours can be unilateral or bilateral.
- Bilateral Wilms(4-13%) is common in congenital syndromes.

- WAGR syndrome (WT, aniridia, genitourinary malformation, mental retardation) is a rare genetic syndrome associated with a chromosomal defect in 11p13.
  - Children with WAGR syndrome are at a 30% higher risk of developing WT than a normal child.

- Beckwith-Wiedemann syndrome (BWS) is a congenital disorder of growth regulation, affecting 1 in 14,000 children.
  - Children with BWS have visceromegaly, macroglossia, omphalocele, and hyperinsulinemic hypoglycemia at birth.
  - They also have an increased risk of tumor development.
  - The most common tumours associated are hepatoblastoma, WT and neuroblastoma.

- Denys-Drash syndrome (DDS) (nephropathy, renal failure, male pseudohermaphroditism, and WT) is also associated with an increased risk of WT.
  - Some investigators have recommended prophylactic nephrectomy in children with this syndrome once they develop renal failure
- Other syndromes are:
  - Hemihypertrophy
  - Pearlman syndrome

Molecular Genetics of Wilms Tumor

- Multiple mutated WT genes have been identified as well as areas of loss of genetic material and allelic uniqueness (loss of heterozygosity) that are important to tumor development.
- ***TP53***
  - *TP53* mutations in WT are almost exclusively found in tumors with anaplastic histology.
  - 75% of anaplastic WT have *p53* mutations.
  - *p53* mutations may be essential for anaplastic progression.
- ***CTNNB1***
  - *CTNNB1* mutations have been reported to occur in 15% of WT.

- ***WTX***
  - The *WTX* gene (also known as *AMER1* for adenomatous polyposis coli (APC) membrane recruitment 1) was found to be mutated in 29% WT.
  - It is the most common known gene mutation in WT.
  - It is located on X chromosome.

- ***WT1***
  - *WT1* gene was the first gene to be linked with WT development.
  - It is located at chromosome 11p13.

- ***WT2***
  - This second WT gene location was identified by linkage analysis in children with BWS.
  - It is located at 11p15.

- ***Loss of Heterozygosity***
  - LOH refers to loss of genetic material and allelic uniqueness.
  - Outcomes for patients with LOH at 1p and 16q were at least 10% worse than those without LOH.

- **DNA ploidy**
  - DNA index greater than 1.5 was strongly associated with anaplastic histology and predictive of poor outcome.

Clinical Presentation

- Most children with WT present with an asymptomatic abdominal mass, often discovered incidentally.
- Abdominal pain is second most common presentation.
- Gross hematuria (18.2% of patients) and microscopic hematuria (24.4%).
- 10% of children with WT have coagulopathy.
- 20% to 25% present with hypertension because of activation of the renin-angiotensin system.
- Fever, anorexia, and weight loss occur in 10%.
- Extension of tumour thrombus into the renal vein can obstruct the spermatic vein and result in a left varicocele.
- In rare cases, tumour extension into the atrium may produce cardiac malfunction.
- Tumour rupture and haemorrhage are also infrequent events that can present as an acute abdomen.

Diagnosis

- Ultrasonography (US) is a good screening examination of a mass to determine its site of origin and to assess for possible intravascular or ureteral extension.
  - About 4% of WT present with inferior vena cava (IVC) or atrial involvement and 11% with renal vein involvement.
- A computed tomography (CT) scan of the abdomen will confirm the renal origin of the mass and determine whether there are bilateral tumors.
- The common sites of metastatic spread are the lungs and the liver. Therefore, in addition to abdominal imaging, pulmonary imaging must be performed.

- Trucut needle biopsy under ultrasound guidance is confirmatory.
  - Helps to know favourable and unfavourable histology.

- DMSA
  - For planning of bilateral tumours.

Pathology

- WT are embryonal tumors containing components seen in normal developing kidneys.

- The classic WT consists of three elements:
  - blastemal, stromal, and epithelial tubules.

- Anaplastic tumours are aggressive and bear unfavourable histology.

Socie´te´ Internationale d'Oncologie Pe´diatrique (SIOP) Staging Systems

Stage	Criteria
1	The tumor is limited to the kidney or surrounded with a fibrous pseudocapsule, if outside the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface, and it is completely resected. The tumor may be protruding (bulging) into the pelvic system and dipping into the ureter, but it is not infiltrating the walls. The vessels of the renal sinus are not involved. Intrarenal vessels may be involved.
2	The tumor extends beyond the kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into the perirenal fat, but it is completely resected. The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma, but it is completely resected. The tumor infiltrates adjacent organs or vena cava, but it is completely resected. The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery.
3	There is incomplete excision of the tumor, which extends beyond resection margins (gross or microscopic tumor remains postoperatively). Any positive lymph nodes are involved. Tumor ruptures before or during surgery (irrespective of other criteria for staging). The tumor has penetrated the peritoneal surface. Tumor implants are found on the peritoneal surface. The tumor thrombi present at resection, margins of vessels or ureter are transected or removed piecemeal by surgeon.
4	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases are outside the abdominopelvic region.
5	Bilateral renal tumors present at diagnosis. Each side has to be substaged according to above classifications.

PROGNOSTIC FACTORS

- Histology: Most important prognostic factor.
- Stage: Higher the stage poor is prognosis. Second most important prognostic factor.
- Rapid response: This is a prognostic category being evaluated in patients who have stage IV disease that is based on lung metastasis alone. The goal in these patients is to avoid lung radiation. Response to therapy is also being assessed in bilateral disease.
- Loss of heterozygosity: LOH at both 1p and 16q are now used as determinants of therapy.

Chemotherapy

- Actinomycin- D is the major chemotherapeutic agent used.
- Other active chemotherapeutic agents are vincristine, doxorubicin, and cyclophosphamide.
- For children with favorable-histology stage I and II tumors without LOH, 18 weeks of vincristine and dactinomycin is recommended.
- For children with FH stage III and IV tumors without LOH, 24 weeks of vincristine, dactinomycin, and doxorubicin is recommended.
- For those patients who have positive LOH at both loci (1p and 17q), treatment will be intensified.

Surgery

- Routine preoperative chemotherapy is administered for 4-6 cycles and nephrectomy being carried out at five to six weeks.
- Immediate surgery is indicated in the following situations:
  - ruptured tumour at presentation (emergency)
  - largely cystic tumour (not possible to biopsy, relatively insensitive to chemotherapy)
  - doubt in diagnosis, despite needle biopsy
  - infants under six months of age (likelihood of mesoblastic nephroma, increased difficulties in chemotherapy).

- Approach is always through transperitoneal approach via a generous transverse upper abdominal supraumbilical incision.

- The renal artery should be ligated before the renal vein to avoid sequestration of blood within the tumour, congestion and rupture.

- Before dividing the renal vein, it should be inspected carefully and vascular clamps applied so that any tumour extension can be seen and extracted.

Intracaval extension

- If the extension is infrahepatic, it can be extracted safely by cavotomy alone.
- If intrahepatic or intra-atrial, the operation should be planned with a paediatric cardiac surgeon and cardiopulmonary bypass must be available.

Bilateral Wilms

- Two options:
  - Bilateral partial nephrectomy.
  - Most involved side total nephrectomy and partial nephrectomy on the other side.

OUTCOME

- *Stage I:* 90–95 per cent.
- *Stage II:* 80–90 per cent.
- *Stage III:* 80–85 per cent.
- *Stage IV:* 70–75 per cent.
- *Stage V:* 80–85 per cent.

Rhabdomyosarcoma

- Rhabdomyosarcoma is a soft tissue malignancy that accounts for approximately 4% of all pediatric malignancies.
- Derived from embryonic mesenchymal cells that can later differentiate into skeletal muscle.
- Incidence is 4.3 cases/million children, with approximately 350 new cases diagnosed annually.
- Bimodal peak incidence
  - Ages of 2 and 5 years and again from 15 to 19 years of age.
- Almost 50% are diagnosed before the age of 5 years.

- Most cases occur sporadically, with no recognizable risk factors.
- Occurs with increased frequency in patients with
  - neurofibromatosis type I
  - Li-Fraumeni syndrome
  - Beckwith-Wiedemann syndrome

Sites of Involvement

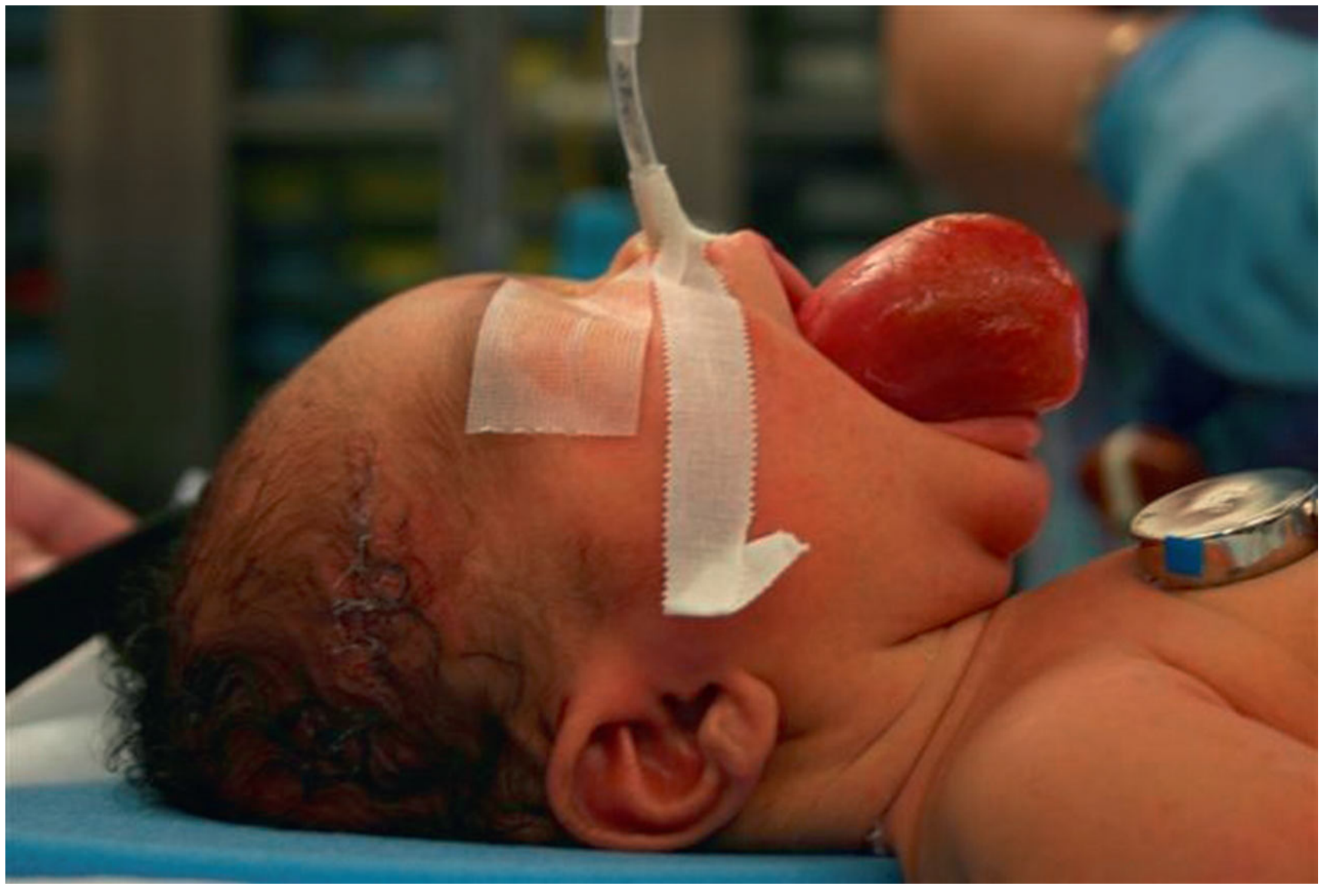
- Rhabdomyosarcoma can appear at any site in the body, including those that do not typically contain skeletal muscle.
- Most common sites in children are:
  - head and neck (35%)
  - Genitourinary tract (25%)
  - extremities (20%).
- Less common primary sites include the trunk, GI tract, intrathoracic, and perineal regions.
- Head and neck lesions tend to occur in the parameningeal region, orbits, and pharynx.
- Other specific sites include the bladder, prostate, vagina, uterus, liver, biliary tract, paraspinal region, and chest wall.

Pathology

- Pathologically classified into three types:
  - Embryonal
  - Alveolar
  - pleomorphic.
- Embryonal rhabdomyosarcoma is the most common type(2/3rd). Two subtypes of embryonal rhabdomyosarcoma—botryoides and spindle cell—appear to be associated with a better prognosis than others of similar histology.
- On examination of a sample, characteristic rhabdomyoblasts may be present.
- Immunohistochemical staining for muscle-specific proteins, such as myosin and actin, desmin, and myoglobin, can bolster the diagnosis.

Clinical Presentation

- Manifestations of rhabdomyosarcoma depend on its size, location, age of the patient, and presence of metastatic disease.
- The mass is typically asymptomatic, although most symptoms are related to compressive effects and can result in pain.
- Orbital tumors can produce proptosis, decreased visual acuity, and ophthalmoplegia.
- Those arising from parameningeal sites frequently produce headaches and nasal or sinus obstruction that can be accompanied by a mucopurulent or bloody discharge. Moreover, these tumors can invade intracranially to produce cranial nerve palsies.

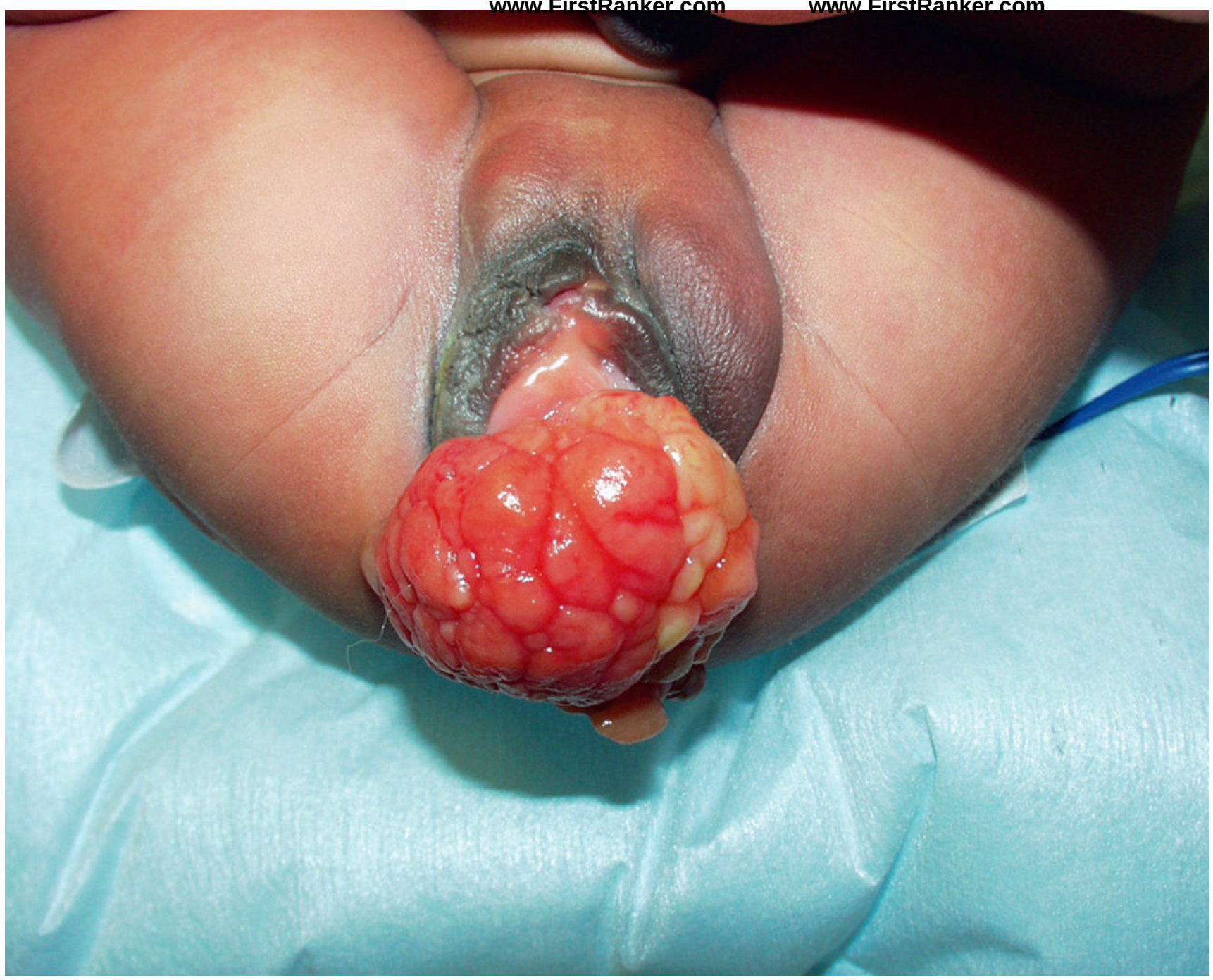


- For genitourinary rhabdomyosarcoma, paratesticular tumors may present as painless swelling in the scrotum, which may be confused with a hernia, hydrocele, or varicocele.

- Bladder tumors, commonly located at the base and trigone, result in hematuria and urinary obstruction.

- Prostate tumors can cause polyuria and constipation caused by compression of the bladder or bowel.

- Vaginal tumors in girls present with a protruding mass or vaginal bleeding and discharge.



- In the case of extremity rhabdomyosarcoma, distal involvement is more common than proximal, and the lower extremities are more commonly involved than the upper extremities.
  - These tumors present as a painless mass, and some children may develop a limp or disuse of the affected limb.
  - At the time of diagnosis, almost 50% of patients have regional lymph node metastasis.
- Retroperitoneal tumors can grow large, making them difficult to resect. Symptoms arise secondary to invasion of adjacent structures and the associated pain and distention are typical late features of disease.
- Biliary tract tumors comprise 0.8% of all rhabdomyosarcomas and, like other signs of biliary obstruction, patients present with jaundice, abdominal swelling, fever, and loss of appetite.

Diagnosis and Staging

- The patient should be thoroughly examined and diagnostic imaging and basic laboratory studies performed.
- With concern for parameningeal involvement, cerebrospinal fluid should also be evaluated.
- There are no specific serum tumor markers for diagnosis.
- Depending on tumor location, MRI or CT should be used to characterize the mass better and evaluate for adjacent structural invasion, vessel encasement, metastasis, and adenopathy.
- One of the most critical aspects of the diagnostic process is obtaining tissue for histologic confirmation, which is usually accomplished by an incisional or core needle biopsy.
- On confirmation, surgical resection can be completed, although it may necessitate preoperative chemotherapy for tumor shrinkage.
- It should also be noted that during preoperative planning, the biopsy site should also be excised because there can be local recurrence.
- Based on histologic variances, rhabdomyosarcoma subtypes are associated with prognosis.
- Botryoid (cluster of grapes) and spindle cell sarcomas are noted to have a favorable prognosis
- Embryonal and pleomorphic histologies have an intermediate prognosis
- Alveolar and undifferentiated histologies exhibit a poor prognosis.

- Pretreatment staging serves to stratify patients, determine the most appropriate treatment regimen, and compare outcomes.
- Because it relies on preoperative imaging, this is technically clinical staging, although it is still based on TNM criteria
- It should be stressed that intraoperative or pathologic results from resected samples should have no bearing on patient stage. This is reserved for what is known as *clinical grouping*, which consists of selection into a group depending on operative findings, pathology, margins, and node status.
- Taken together, clinical grouping and pretreatment staging have been shown to correlate with outcomes.

Staging for Rhabdomyosarcoma

- Group I: Localized disease that is completely resected, with no regional node involvement
- Group II
  - A: Localized, grossly resected tumor with microscopic residual disease but no regional nodal involvement
  - B: Locoregional disease with tumor-involved lymph nodes with complete resection and no residual disease
  - C: Locoregional disease with involved nodes, grossly resected, but with evidence of microscopic residual tumor at the primary site and/or histologic involvement of the most distal regional node (from the primary site)
- Group III: Localized, gross residual disease including incomplete resection, or biopsy only of the primary site
- Group IV: Distant metastatic disease present at time of diagnosis

- Low-risk patients have an estimated 3-year failure-free survival rate of 88%.

- Intermediate-risk patients have an estimated 3-year failure-free survival rate of 55% to 76%.

- High-risk patients have a 3-year failure-free survival rate less than 30%.

Treatment

- The main goal of therapy is to achieve cure or, if that is not feasible, at least to obtain local control.
- Multimodality approach, with a combination of surgery, chemotherapy, and radiation therapy. Equally important is the need to minimize the short- and long-term effects of therapy.
- Currently, all patients with rhabdomyosarcoma receive some combination chemotherapy because it improves progression-free and overall survival.
- The recommended regimen depends on the risk stratification,
  - low-risk patients subgroup A- vincristine and dactinomycin
  - low-risk subgroup B and higher, cyclophosphamide is added to above therapy.

- Radiation therapy has been found to be effective for the local control of rhabdomyosarcoma, especially in patients who have microscopic disease after resection.

- It has also been successfully used in patients in whom surgery could result in significant disfigurement, such as with head and neck lesions.

- As is the case with most surgical approaches, a complete resection with negative margins and nodal sampling is the mainstay of treatment.
- The specific operative guidelines depend on the location of the tumor.
- For head and neck tumors that are superficial and nonorbital, wide excision of the primary tumor with sampling of ipsilateral cervical lymph nodes is acceptable.
- Parameningeal lesions are particularly difficult to resect completely, given their degree of extension into critical structures. In these patients, and in patients with tumors that are considered unresectable, chemotherapy and radiation therapy are first-line treatment.

- For extremity lesions, it is important to achieve complete resection through wide local excision. Amputation is rarely necessary, except for distal tumors in the hand or foot that involve neurovascular structures.
- Given that trunk and extremity lesions have a high incidence of lymph node metastasis, sentinel lymph node mapping is being increasingly recommended.
- Reexcision may also be considered with evidence of minimal residual disease after initial resection.
- Patients with extremity tumors receive combination chemotherapy but, because of the high incidence of the alveolar histology, radiotherapy is also often used.

- The approach for patients with genitourinary tumors depends on which organ is affected.
  - Preservation of bladder function is the key in resection of tumors involving the bladder or prostate.
  - If this goal cannot be met, preoperative chemoradiation is usually recommended.
  - If residual disease remains despite this, more aggressive measures can be considered, including a partial cystectomy, prostatectomy, or anterior (rectum-sparing) exenteration.
- Patients with paratesticular rhabdomyosarcoma should undergo a radical inguinal orchiectomy with a retroperitoneal lymph node dissection in boys younger than 10 years because of the frequent prevalence of metastasis.
  - When the tumor is clearly fixed to scrotal skin, resection is required.
  - Chemotherapy is standard, whereas radiation therapy is indicated only with positive nodes.
- For patients with vaginal or vulvar rhabdomyosarcoma, vaginectomy and wide local excision, respectively, and multiagent chemotherapy are recommended.

Outcomes

- Approximately 15% of children present with metastatic disease and their prognosis remains poor.
- Approximately 30% of patients with rhabdomyosarcoma will relapse, and 50% to 95% of them will die as the disease progresses.
- Median survival from the first recurrence is 0.8 years, with an estimated 5-year survival rate of only 17%.
- Rhabdomyosarcoma is a curable disease in most children, with more than 60% surviving 5 years after diagnosis.
- Survival for children with this malignancy has improved secondary to a number of factors, including better imaging and pathologic classification, use of multiagent chemotherapy, and appropriate use of radiotherapy.