Pediatric solid tumors

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	Neuroblastoma	Nephroblastoma (Wilm's tumor)
Features	– Embryonal tumor arising from neuroblasts, unpredictable behavior. – Most common intra-abdominal malignancy in children. (5-10% of all childhood cancers). – Age of onset: (prognosis is better in younger children) 30% in infancy **50% 1-4 years** 5% 10-14 years – Slight male predominance.	– Highly malignant renal tumor, derived from embryonic tissue, reasonable progress due to successful multimodal therapy. – The most common pediatric renal tumor. And second most common intra-abdominal malignancy. (10% of all pediatric malignancies). – Median age of onset: 3.5 years (good prognosis in older children) – M:F ratios = 0.9:1 unilateral, 0.6:1 bilateral – Solitary 88%, multicentric 12% – Unilateral 93%, bilateral 7% (synchronous 85%, metachronous 15%)
Sites of origin	- Adrenal medulla 50% - Abdominal sympathetic ganglia 25% - Posterior mediastinum 20% - Pelvis 3% - Neck 3%	Arises from fetal undifferentiated metanephric blastema tissue
Pathology	– **Grossly:** soft with areas of hemorrhage and necrosis (mature areas tend to be firm). – **Histologically:** sheets of dark blue round cells with scanty cytoplasm, ir in a delicate vascular stroma. – Ring of neuroblasts around a neurofibrillary core (rosette formation) differentiates it from other blue, round cell tumors – Spreads with local encasement of major vessels, may metastasize to lymph nodes, bones, bone marrow, liver, and skin. – Secondary spread is usually associated with large primaries (except stage 4S)	– Favorable histology (90%): tubular epithelial, blastemal, and stromal elements. – Unfavorable histology (10%): anaplasia (focal or diffuse nuclear enlargement)
Clinical features	– Palpable abdominal mass – Child is sick, lethargic with fatigue, bone pain, weight loss, fever, sweating, and anemia. (check rare features in appendix)	– Asymptomatic abdominal mass 80% – Abdominal pain 20% – Hematuria 20% (check rare features in appendix)
Investigations	– ↑ vanillylmandelic acid (VMA) and homovanillic acid (HVA) in urine. – ↑ ferritin – ↑ LDH – ↑ neuron specific enolase (NSE) – AXR: we see tumor calcification in 50% of cases, and this is specific to neuroblastoma compared to nephroblastoma. – US: solid vs. cystic // renal vein and caval involvement – CT/MRI: to see anatomy, metastases, and intraspinal extension (dumb-bell tumor) – Radio isotopes (MIBG scan) – Biopsy to confirm dx (percutaneous or open)	– β-FGF – Renin – Erythropoietin – Cytogenetic studies – US – CT/ MRI (for staging, extension into renal vein and cava 40%) – Bone and brain scan, to identify mets – ECG (right atrial involvement) – Arteriography (preoperative embolization in large tumors, solitary kidney, bilateral tumors, or tumor in a horseshoe kidney) – DMSA (bilateral WT to assess individual renal function).

Management (Mx)	1. Tumor biopsy (to assess MYCN status → direct Mx plan) 2. Surgical resection alone: **low risk groups**: stage 1, stage 2 (<1 y/o), stage 4s absence of Image defined risk factor (IDRF) preresection 3. Neoadjuvant chemotherapy, then surgery +/- radiotherapy for residuals **intermediate risk group** intraspinal extension, apical thoracic tumors 4. Neoadjuvant chemotherapy, then surgery, then adjuvant chemotherapy +/- radiotherapy **high risk groups**	1. Neoadjuvant chemotherapy, then surgery to downstage the tumor and decrease operative morbidity 2. Surgery, then adjuvant chemotherapy
Surgery	Aim of surgery: to achieve complete resection Aim of second-look procedure: to achieve as complete a debulking as possible. Role of laparoscopy & thoracoscopy: diagnostic, biopsy taking, +/- excision of small tumors	– Nephrectomy: including perinephric fascia and regional lymph nodes. – Partial nephrectomy: a. bilateral WT b. Contralateral pre-existing abnormality of kidney c. WT in single kidney d. WT with nephroblastomatosis – Venous extension (venotomy). – Hepatic or pulmonary metastatectomies .

1. Neuroblastoma

Shimada system classification:

1. Favorable prognosis: infants, low MKI, stroma-rich, well differentiated, or intermixed differentiation.
2. Unfavorable prognosis

*Classification depends on:

1. Mitosis karyorrhexis index (MKI)
2. Age of child
3. Degree of differentiation (towards ganglioneuroma)
4. Stroma-rich or stroma-poor

International neuroblastoma staging system (INSS):

- Stage 1: completely resectable localized tumor
- Stage 2: incompletely resected tumor and/ or presence of +ve ipsilateral nodes
- Stage 3: primary tumor crossing the midline. Unilateral tumor with =ve contralateral; nodes, midline tumor with bilateral =ve nodes.
- Stage 4: tumor with spread to other organs; bones or lymph nodes
- Stage 4s: infants, skin, liver, and bone marrow

Stage 4s neuroblastoma:

- 30% of infantile neuroblastoma
- Spontaneous regression is possible
- >80% survive without any specific treatment

Features:

- Hepatosplenomegaly: may cause respiratory failure, can be treated with low dose radiotherapy or cyclophosphamide
- Subcutaneous nodules: 'blueberry muffin' spots
- Positive bone marrow

The international neuroblastoma risk group (INRG): It defines risk group by:

1. Pretreatment grade
2. Post-surgery INSS staging
3. Age (infants: better prognosis for all stages, e.g. 5-year SR in stage 4 is 75%)
4. Tumor biology, histology, and MYCN status

Risk groups and predicted 3-year survival rate

- Low risk: >90%
- Intermediate risk: 70-90%
- High risk: <30%

New treatments:

- I^{131} labeled MIBG
- New chemotherapy agents
- Immunologic therapy (monoclonal antibodies, cytokine therapies and vaccines)
- Antiangiogenic factors
- Other experimental agents (tyrosine kinase inhibitors, direct targeting of MYCN amplified cells.)

2. Nephroblastoma (Wilm's tumor):

Clinical patterns:

1. Sporadic >90%
2. Association with congenital anomalies (5%, GU anomalies)
3. Syndromic (<1%, overgrowth phenotypic syndromes, as BWS. Nonovergrowth phenotypic syndromes (as WAGR & Denys-Drash syndrome)

Histological risk stratification:

1. Low-risk: mesoblastic nephromas, cystic partially differentiated WT, completely necrotic WT.
2. Intermediated-risk: nephroblastoma (epithelial, stromal, mixed type), regressive typ (>2/3 necrotic), focal anaplasia.
3. High-risk: nephroblastoma (blastemal type and diffuse anaplasia).

Staging:

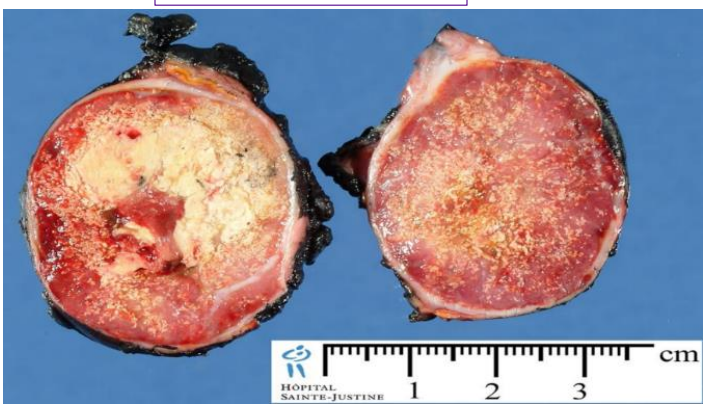
WT has been divided into five stages (with some national differences)
Stage I – confined to kidney and completely excised
Stage II – extending beyond kidney but completely resected
Stage III – incompletely resected, +ve abdominal lymph nodes, peritoneal spread, rupture (pre or intraoperative), open biopsy
Stage IV – distant metastasis (lungs, liver, bone, or brain)
Stage V – bilateral synchronous

Prognosis:

- Stage 1-3: SR>90%
- Stage 4: SR ~70
- Most important prognostic factors: stage, tumor histology, age at diagnosis, recurrence.

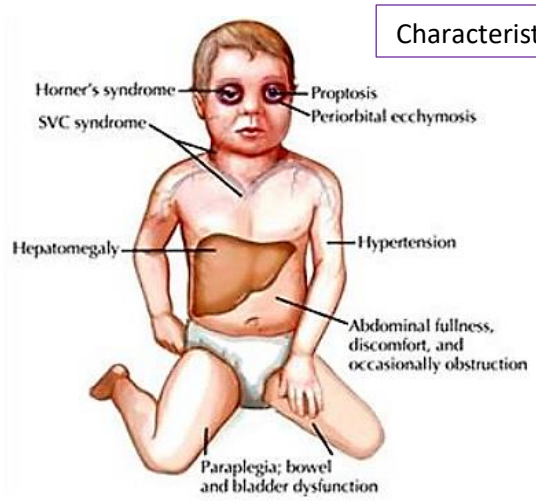
Appendix

Neuroblastoma tumor



Blueberry muffin spots → subcutaneous nodules of stage 4S neuroblastoma

Characteristic features of neuroblastoma patients



- Unusual But Characteristic Features
  - Periorbital ecchymosis or proptosis (racoon eyes) retro-orbital secondaries
  - Horner's syndrome[1] apical thoracic tumors
  - Progressive cerebellar ataxia and trunk opsomyoclonus
  - Dancing eye syndrome
  - Progressive paraplegia extradural cord compression
  - Hypertension (~25%) catecholamine production or renal artery compression
  - Skin nodules stage 4S disease
  - Diarrhea (VIP) release

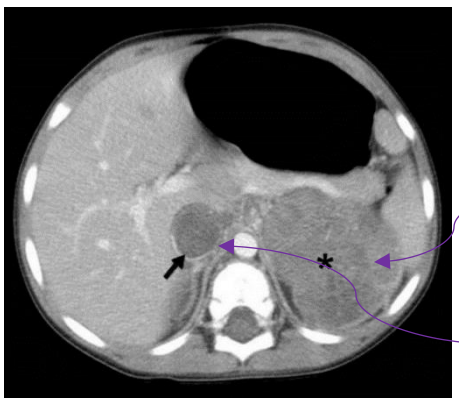
1. miosis, ptosis, and hemifacial anhidrosis

Cytogenetics and prognostic factors in neuroblastoma patients:

- MYCN gene amplification (poor prognosis)
- DNA ploidy (poor prognosis)
- Multidrug resistance-associated protein (MRP) (poor prognosis)
- Ch 17q gain, Ch 1p deletion
- Expression of the H-*ras* oncogene (low-stage disease)
- CD44 expression (good prognosis)
- TRKA expression (good prognosis)

Rare features of nephroblastoma:

- ✓UTI
- ✓Fever (from tumor necrosis)
- ✓Hypertension and anemia
- ✓Varicocele
- ✓Acute abdomen with tumor hemorrhage or rupture



Left WT

Invasion of the inferior vena cava through the left renal vein. We still can resect the tumor and do venotomy.