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Pediatric Solid Tumors

The International Classification of Childhood Cancer, Third Edition (ICCC-3)*

I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases

II. Lymphomas and reticuloendothelial neoplasms

III. CNS and miscellaneous intracranial and intraspinal neoplasms

IV. **Neuroblastoma** and other peripheral nervous cell tumors

V. Retinoblastoma

VI. **Renal tumors**

VII. Hepatic tumors

VIII. Malignant bone tumors

IX. Soft tissue and other extraosseous sarcomas

X. Germ cell tumors, trophoblastic tumors, and neoplasms of gonads

XI. Other malignant epithelial neoplasms and malignant melanomas

XII. Other and unspecified malignant neoplasms

* E. Steliarova-Foucher, C. Stiller, B. Lacour, and P. Kaatsch, "International Classification of Childhood Cancer, third edition," *Cancer*, vol. 103, no. 7, pp. 1457–1467, 2005.

Neuroblastoma

Mysterious embryonal tumor | Arising from neuroblasts | Unpredictable behavior

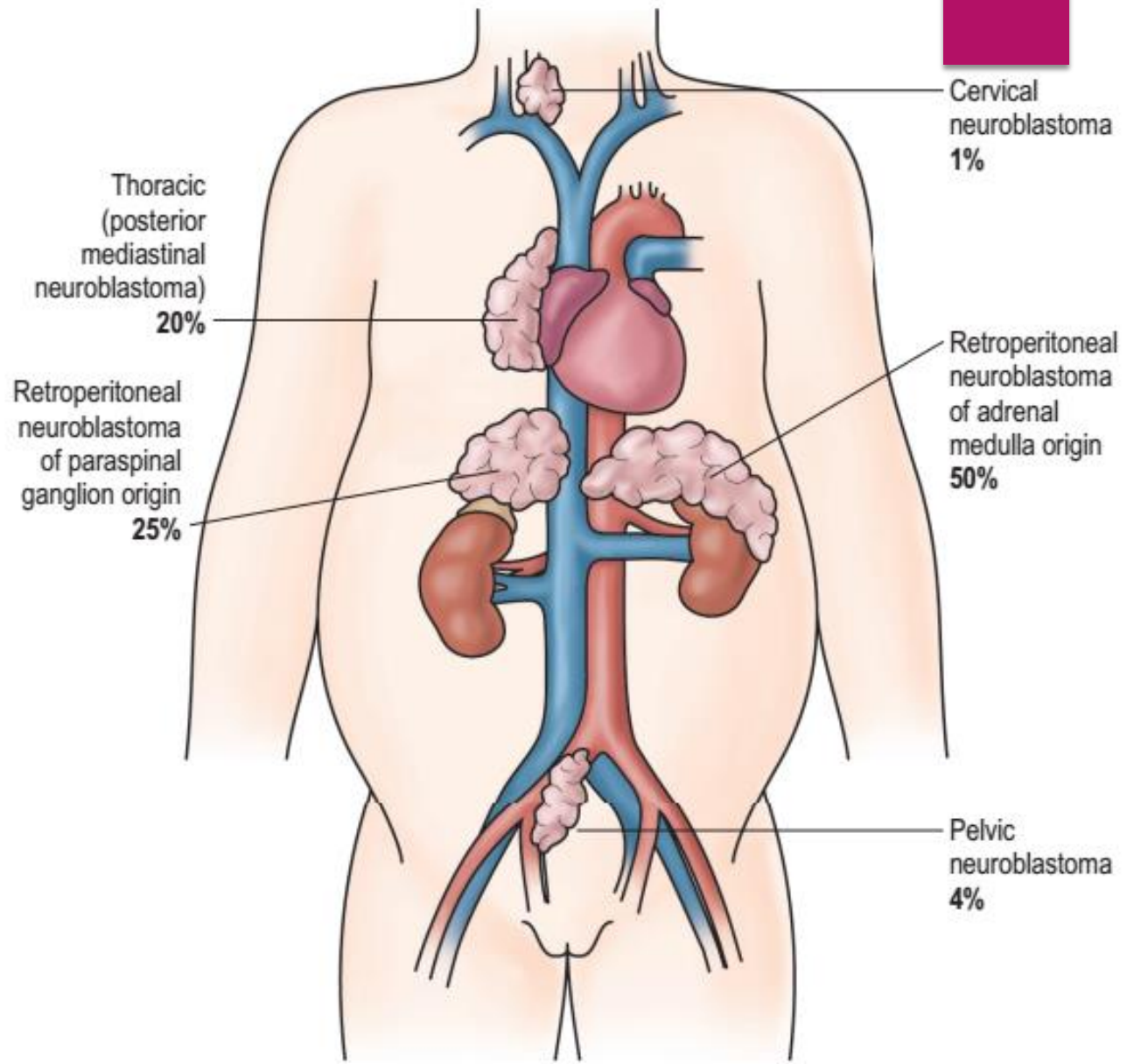
Neuroblastoma

- 5–10% of all childhood cancers
- Age of onset
  - Infancy ~30%
  - **1–4 years ~50%**
  - 10–14 years ~5%
- M> F (slight)

Neuroblastoma

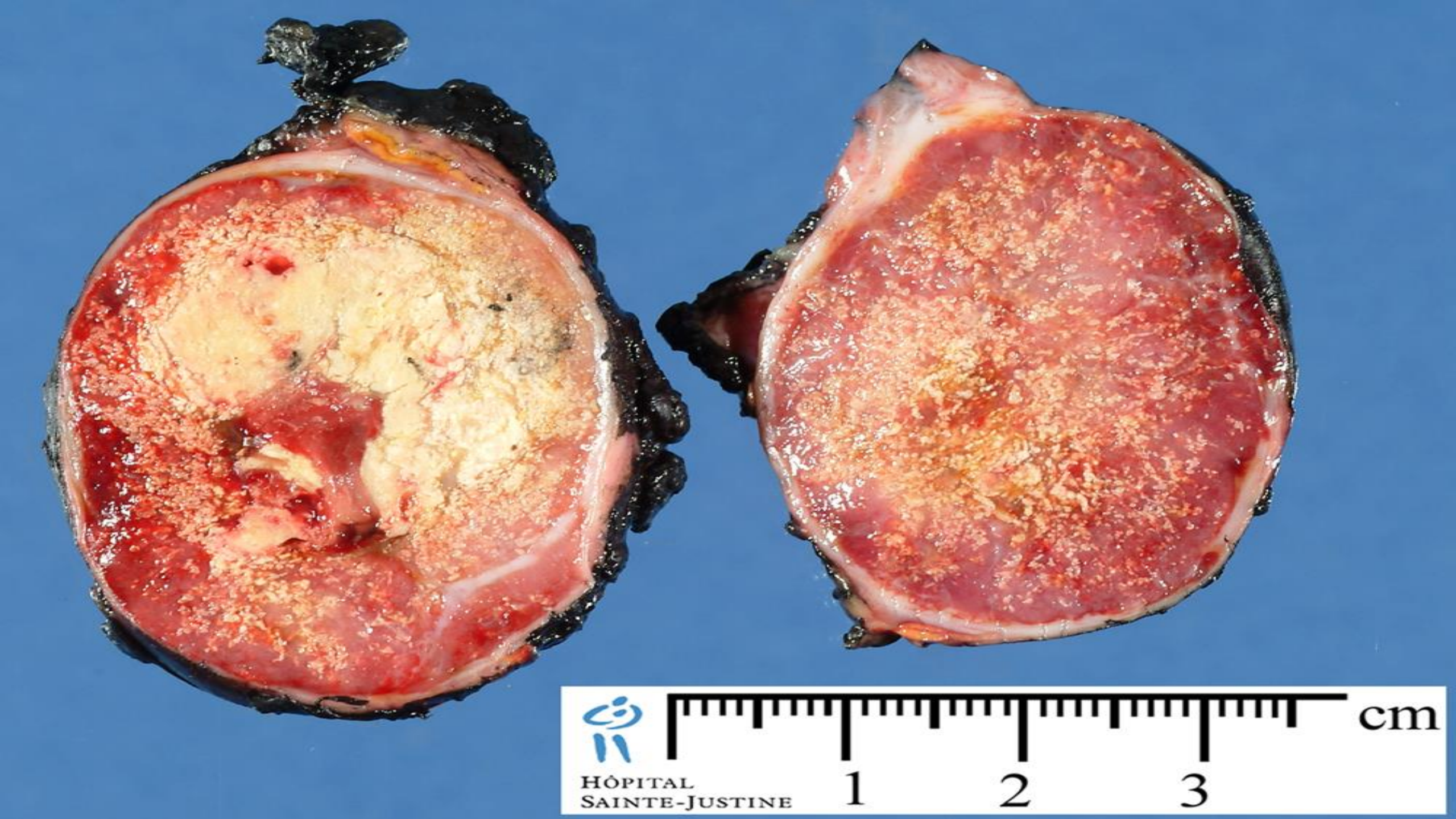
- Sites of Origin
  - **Adrenal medulla (~50%)**
  - Abdominal sympathetic ganglia (~25%)
  - Posterior mediastinum (~20%)
  - Pelvis (~3%)
  - Neck (~3%)

Primary sites for neuroblastoma



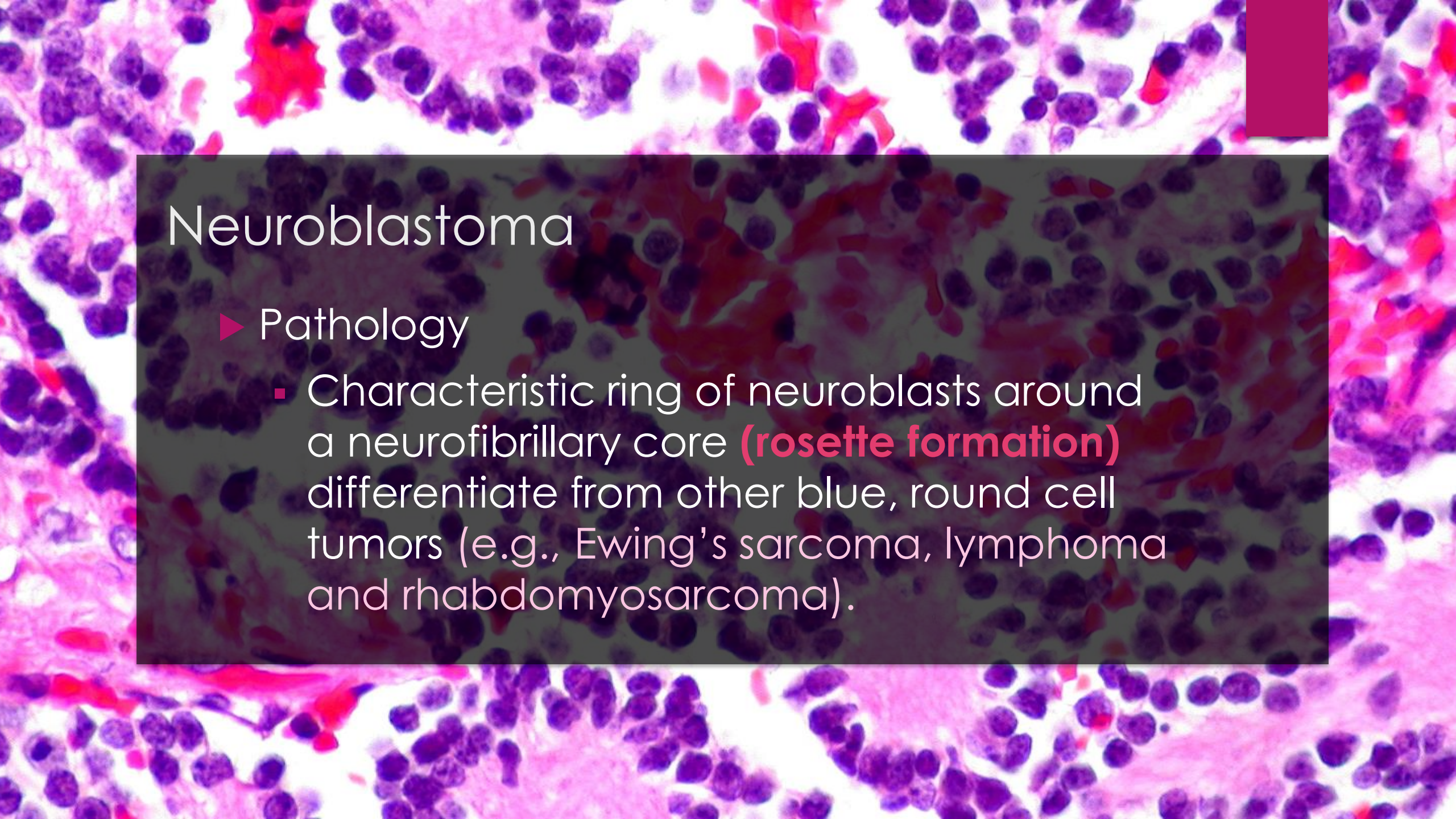
Neuroblastoma

- Pathology
  - Tumor appears as **soft** with areas of **hemorrhage** and **necrosis**.
  - More mature areas tend to be firm.


HÔPITAL
SAINTE-JUSTINE
1
2
3
cm

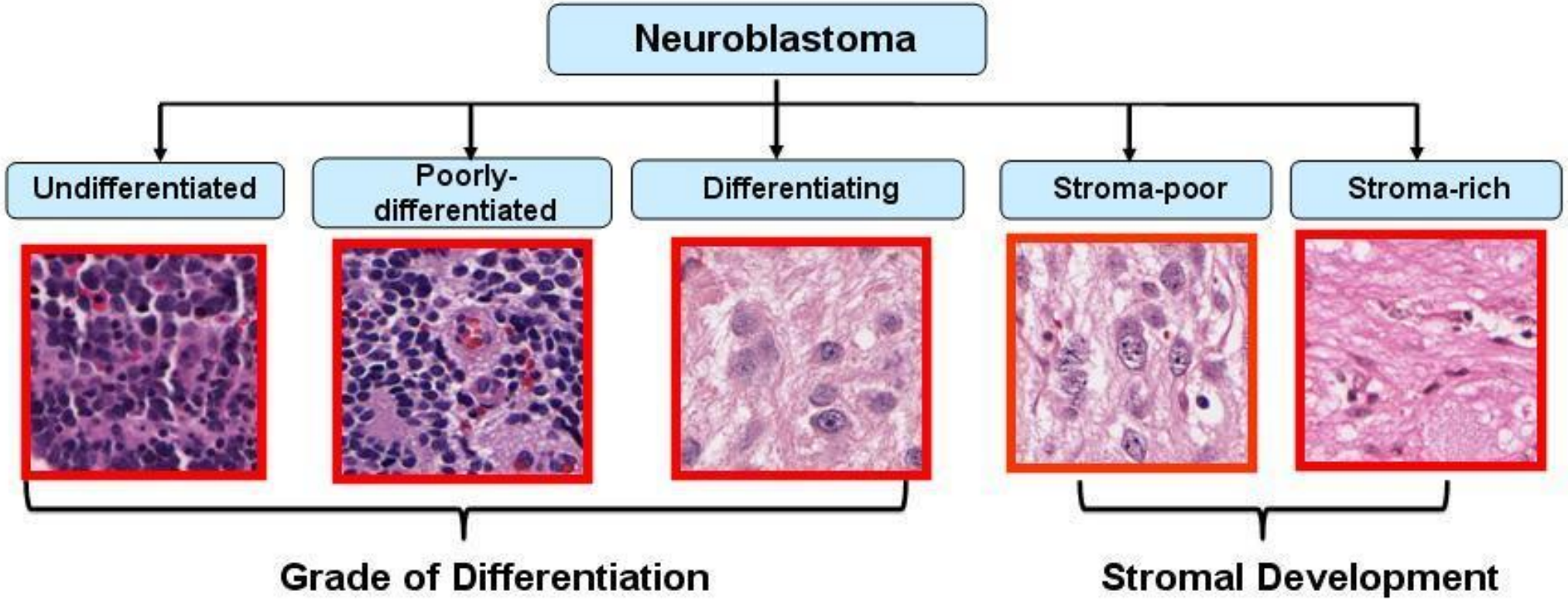
Neuroblastoma

- Pathology
  - Histological appearance is as sheets of **dark blue round cells** with scanty cytoplasm, embedded in a delicate vascular stroma.



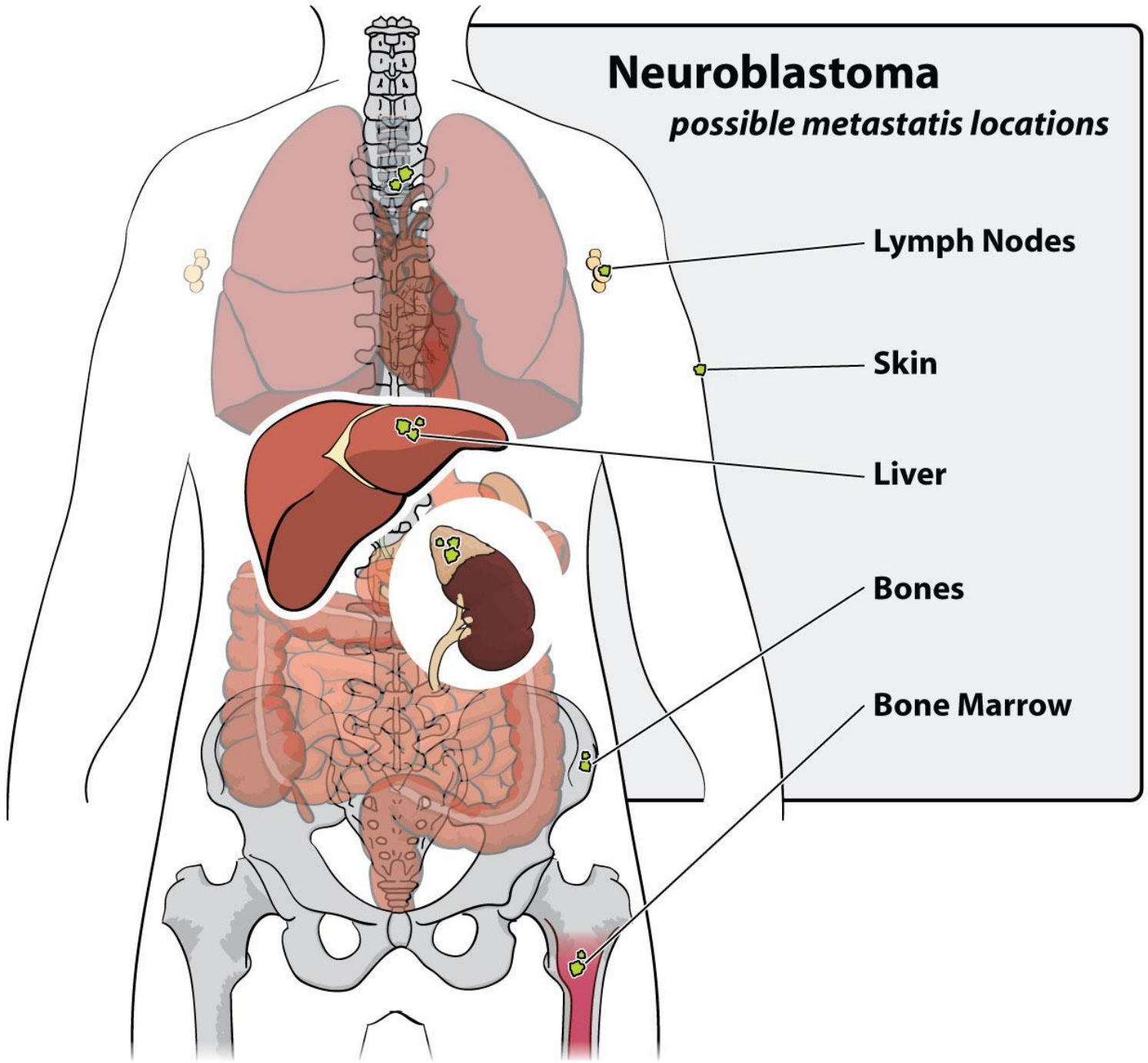
Neuroblastoma

- Pathology
  - Characteristic ring of neuroblasts around a neurofibrillary core **(rosette formation)** differentiate from other blue, round cell tumors (e.g., Ewing's sarcoma, lymphoma and rhabdomyosarcoma).


Neuroblastoma
Undifferentiated
Poorly-differentiated
Differentiating
Stroma-poor
Stroma-rich
Grade of Differentiation
Stromal Development

Neuroblastoma

- Pathology
  - Tends to spread with **local extension** and **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 tumors).


Neuroblastoma
possible metastatis locations
Lymph Nodes
Skin
Liver
Bones
Bone Marrow

Neuroblastoma

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

Neuroblastoma

- Shimada System Classification
  - Favorable prognosis:

    infants | low MKI | stroma-rich | well differentiated or intermixed differentiation

The International NB Pathology Classification (the Shimada System)

International Neuroblastoma Pathology Classification		Prognostic Group
NEUROBLASTOMA	SCHWANNIAN STROMA POOR	
<1.5 years	Poorly differentiated or differentiating, and low or intermediate MKI tumor	Favorable
1.5–5 years	Differentiating and low MKI tumor	
<1.5 years	(a) Undifferentiated tumor or (b) high MKI tumor	Unfavorable
1.5–5 years	(a) Undifferentiated or poorly differentiated tumor, or (b) intermediate or high MKI tumor	
≥5 years	All tumors	
Ganglioneuroblastoma, intermixed	Schwannian stroma rich	Favorable
Ganglioneuroblastoma, nodular	Composite schwannian stroma rich/stroma-dominant and stroma poor	Unfavorable or favorable (based on nodule histology)
Ganglioneuroma	Schwannian stroma-dominant	Favorable
Maturing		
Mature		

Neuroblastoma

- Cytogenetics and Prognostic Factors
  - 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)

Neuroblastoma

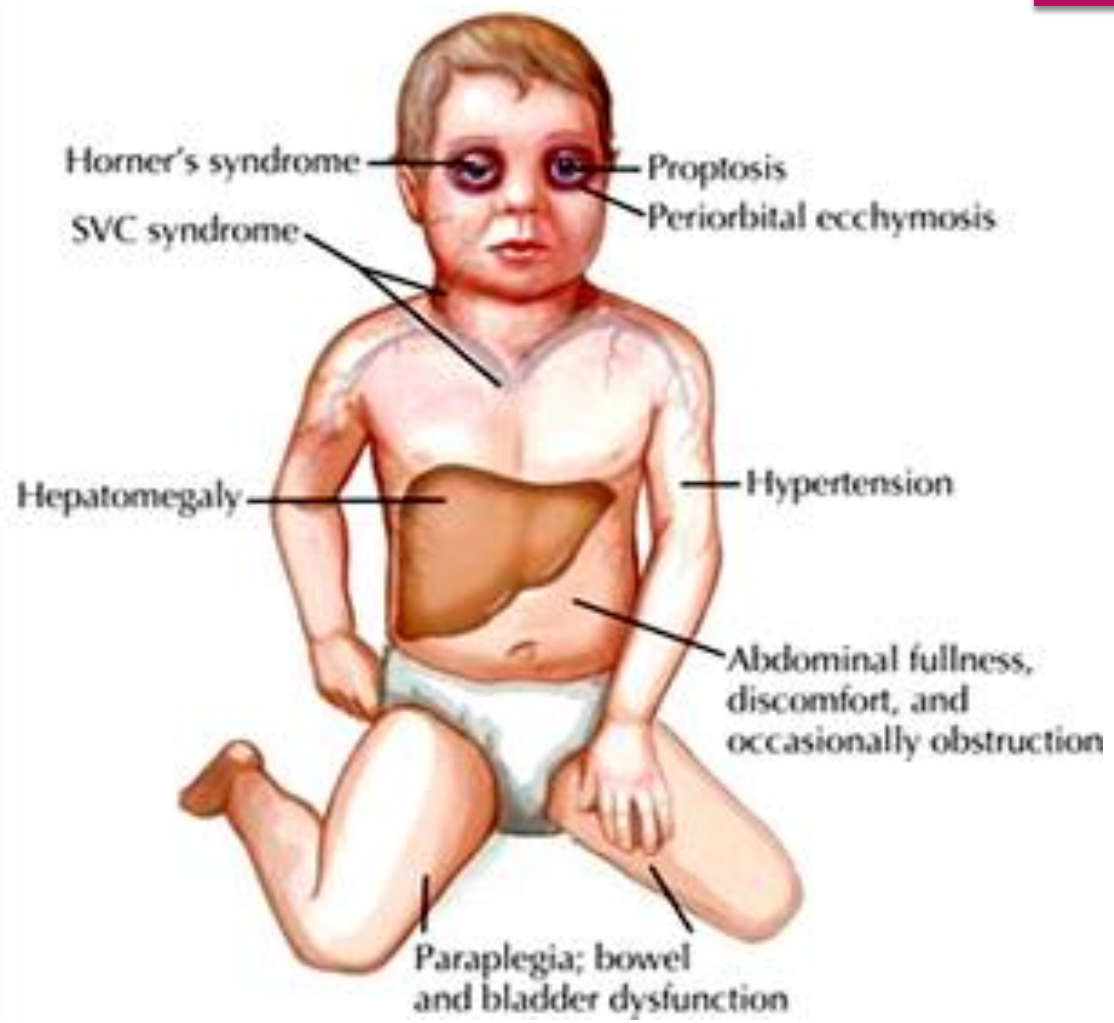
- Clinical Features
  - Palpable abdominal mass
  - Children often appear sick, lethargic with fatigue
  - Bone pain
  - Weight loss
  - Fever, sweating and anemia

Neuroblastoma

- 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

Characteristic Features



Neuroblastoma

- Investigations
  - ↑↑ Vanillylmandelic acid (VMA) and homovanillic acid (HVA) in urine urinary metabolites of catecholamines
  - ↑ ferritin
  - ↑ lactate dehydrogenase (LDH)
  - ↑ Neuron specific enolase (NSE)

Neuroblastoma

- Investigations
  - AXR tumor calcification (~50%)
  - US solid vs. cystic | renal vein and caval involvement
  - CT/MRI scans anatomy of tumor | metastases | intraspinal extension ("dumb-bell" tumor)
  - Radio-isotopes MIBG[1] scan

1. meta-iodobenzylguanidine

Neuroblastoma

- Investigations
  - Biopsy percutaneous or open
  - Bone marrow

Neuroblastoma

- International Neuroblastoma Staging System (INSS)
  - **Stage 1** completely resectable localized tumor
  - **Stage 2** incompletely resected tumor and/ or presence of +ve I/L nodes
  - **Stage 3** primary tumor crossing the midline | unilateral tumor with +ve C/L nodes | midline tumor with bilateral +ve nodes
  - **Stage 4** tumor with spread to other organs, bone or lymph nodes
    - **Stage 4S** infants | skin, liver and bone marrow

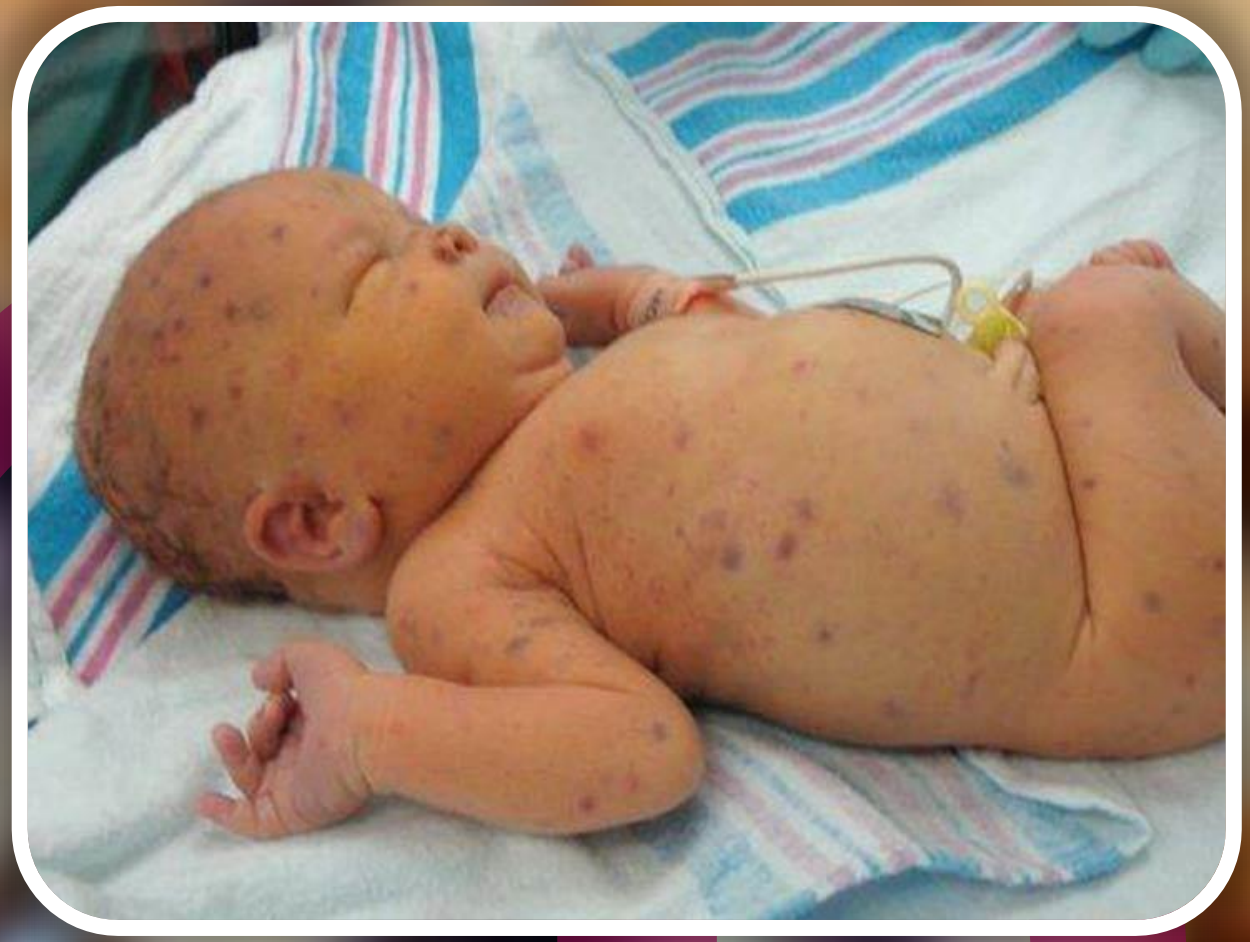
I/L: ipsilateral
C/L: contralateral

International neuroblastoma staging system (INSS) 1989

Stage 1	Localized tumor with complete gross excision, ±microscopic residual disease; representative I/L nodes –ve for tumor microscopically (nodes attached to and removed with the primary tumor may be +ve)
Stage 2A	Localized tumor with incomplete gross excision; representative I/L no adherent lymph nodes negative for tumor microscopically
Stage 2B	Localized tumor±complete gross excision, with I/L nonadherent lymph nodes +ve for tumor. Enlarged contralateral lymph nodes must be negative microscopically
Stage 3	Unresectable unilateral tumor infiltrating across the midline, ±regional node involvement; or localized unilateral tumor with C/L regional node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by node involvement
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S)
Stage 4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants <1 year). Marrow involvement should be minimal (i.e., <10% of total nucleated cells identified as malignant by bone biopsy or by bone marrow aspirate). More extensive bone marrow involvement would be considered to be stage IV disease. The results of the MIBG scan (if performed) should be –ve for disease in the bone marrow

Neuroblastoma

- **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' spot)
    - ✓ Positive bone marrow



Neuroblastoma

- The International Neuroblastoma Risk Group (INRG)
  - It defines risk group by:
    - ✓ pretreatment grade
    - ✓ postsurgery INSS staging
    - ✓ age (Infants → better prognosis for all stages → e.g. 5YSR in stage 4 is ~75%)
    - ✓ tumor biology, histology and MYCN status

Risk Groups

Patients are assigned into one of three groups	(Predicted 3 year survival rates)
Low risk	>90%
Intermediate risk	70–90%
High risk	<30%

Neuroblastoma

- Management
  - **Tumor biopsy** (to assess MYCN status → direct Mx plan)
  - **Surgical resection alone**
    - ✓ low risk group: stage 1 | stage 2 (<1yr old) | stage 4S
    - ✓ absence of IDRF preresection

IDRF: image defined risk factors

Neuroblastoma

- Management
  - **Neoadjuvant chemotherapy → Surgery**

    +/- radiotherapy (for residuals)

    - ✓ Intermediate risk group
    - ✓ Intraspinal extension | apical thoracic tumors

Neuroblastoma

- Management
  - **Neoadjuvant chemotherapy → Surgery → Adjuvant chemotherapy** +/- radiotherapy
    - ✓ High risk group

Neuroblastoma

- Surgery
  - Aim of surgery: to achieve complete resection
  - Aim of second-look procedure: to achieve as complete a debulking as possible
  - Possible role for laparoscopic and thoracoscopic surgery: diagnostic, biopsy taking, +/- excision of smaller tumors

Neuroblastoma

- 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)

Nephroblastoma
Wilms' Tumor

Highly malignant renal tumor | Derived from embryonic tissue |
Reasonable prognosis due to successful multimodal therapy

Wilms' Tumor

- The most common pediatric renal tumor
- The second most common intra-abdominal malignancy (after neuroblastoma)
- ~10% of all pediatric malignancies

Wilms' Tumor

- Median age of onset: 3.5 years
- M:F ratio = 0.9:1 (unilateral) | 0.6:1 (bilateral)
- Solitary 88% | multicentric 12%
- Unilateral 93% | bilateral 7% (synchronous 85% | metachronous 15%)

Wilms' Tumor

- Clinical Patterns
  - **Sporadic (>90%)**
  - Association with congenital anomalies (~5% | GU anomalies)
  - Familial/hereditary (1–2% | multiple | bilateral | earlier age of onset)
  - Syndromic (<1% | Overgrowth phenotypic syndromes (as BWS) | Nonovergrowth phenotypic syndromes (as WAGR & Denys–Drash syndrome))

BWS: Beckwith–Wiedemann Syndrome | WAGR: Wilms' Aniridia GU anomalies/Gonadoblastoma Retardation Syndrome

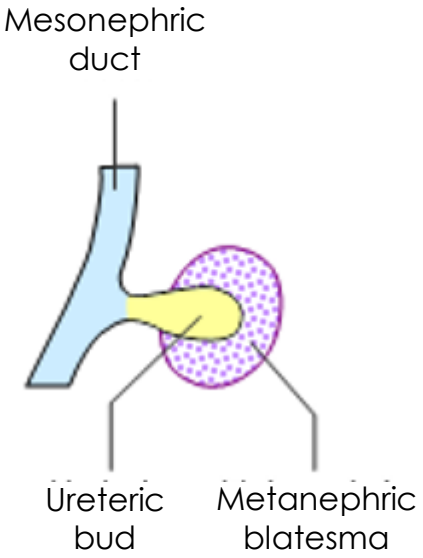
Wilms' Tumor

- Pathology
  - Arises from fetal undifferentiated metanephric blastema tissue
  - Favorable histology (90%)

tubular epithelial, blastemal, and stromal elements

  - Unfavorable histology (10%)

anaplasia (focal or diffuse nuclear enlargement)



Wilms' Tumor

- Clinical Features
  - Usual presentation is a small child with:
    - ✓**an asymptomatic abdominal mass (80%)**
    - ✓abdominal pain (~20%)
    - ✓hematuria (~20%)

Wilms' Tumor

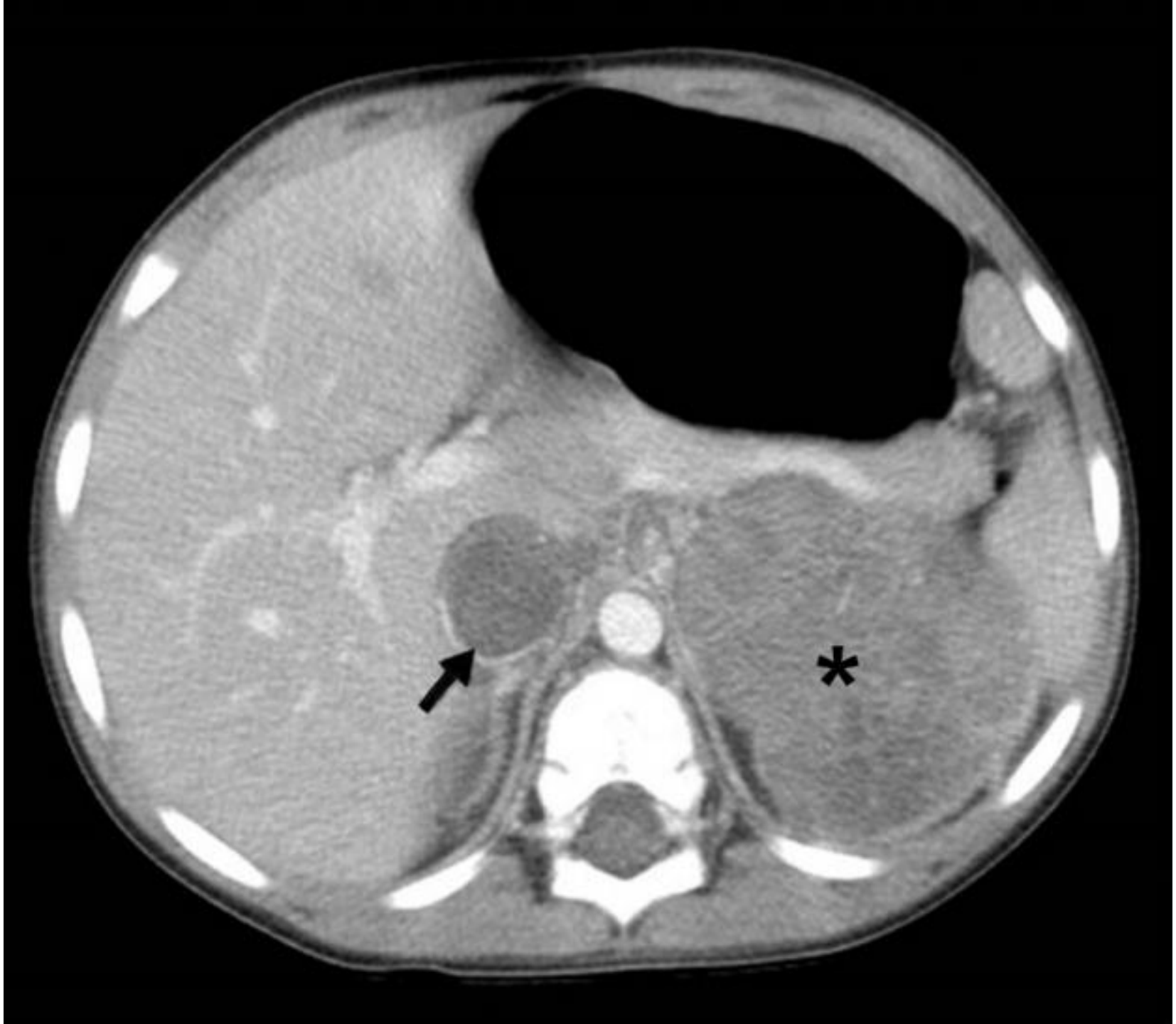
- Clinical Features
  - Rarer features include:
    - ✓UTI
    - ✓Fever (from tumor necrosis)
    - ✓Hypertension and anemia
    - ✓Varicocele
    - ✓Acute abdomen with tumor hemorrhage or rupture

Wilms' Tumor

- Investigations
  - βFGF
  - Renin
  - Erythropoietin
  - Cytogenetics studies

Wilms' Tumor

- Investigations
  - US
  - CT Scan/MRI staging, extension into renal veins and cava (~40%)
  - Bone and brain scan to identify mets
  - Echocardiogram 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



Staging of WT

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

Wilms' Tumor

- Histological Risk Stratification
  - Low-risk: Mesoblastic nephromas | cystic partially differentiated WT | completely necrotic WT
  - Intermediate-risk: Nephroblastoma (epithelial, stromal, mixed type) | regressive type (>2/3 necrotic) | focal anaplasia
  - High-risk: Nephroblastoma (blastemal type and diffuse anaplasia)

Wilms' Tumor

- Management options:
  - Neoadjuvant chemotherapy → Surgery
    - ✓ downstage the tumor
    - ✓ ↓ operative morbidity
  - Surgery → adjuvant chemotherapy

Wilms' Tumor

- Surgery
  - **Nephrectomy** including perinephric fascia and regional lymph nodes
  - **Partial Nephrectomy**:
    - ✓ Bilateral WT
    - ✓ Contralateral pre-existing abnormality of kidney
    - ✓ WT in single kidney
    - ✓ WT with nephroblastomatosis
  - Venous extension venotomy & removal
  - Hepatic or pulmonary metastatectomies

Wilms' Tumor

- Prognosis
  - Stage I–III : SR >90%
  - Stage IV : SR ~70%

  - Most important prognostic factors:
    - ✓ Stage (low vs high)
    - ✓ Tumor histology (favorable vs unfavorable)
    - ✓ Age at diagnosis (↓ survival in infants)
    - ✓ Recurrence

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