

Neuroblastic Tumors

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Tumors of primordial (embryonal) **neural crest cells** (pluripotent sympathetic cells - ultimately populate **sympathetic chain** and **adrenal medulla**):

1. **PHEOCHROMOCYTOMA** – if in adrenals
2. Sympathoblastomas (s. neurocristopathies) - spectrum of maturation and dedifferentiation:
 - 1) **GANGLIONEUROMA** - **benign**, composed entirely of **well-differentiated ganglia cells**.
 - 2) **GANGLIONEUROBLASTOMA** - moderately differentiated: contains $\geq 50\%$ mature cells (if $< 50\%$, some investigators use term *MATURING NEUROBLASTOMA*).
 - 3) **NEUROBLASTOMA** - **malignant**, consists predominantly of **postganglionic sympathetic undifferentiated neuroblasts**.
 - *NEUROBLASTOMAS* may show spontaneous or induced differentiation to *GANGLIONEUROBLASTOMA* or *GANGLIONEUROMA*.

NEUROBLASTOMA

- highly undifferentiated embryonal malignancy arising from **postganglionic sympathetic neuroblasts**.

- first described by Virchow in 1864.

EPIDEMIOLOGY

Typically occurs in **INFANTS & YOUNG CHILDREN**:

- most common malignancy during **infancy!** (30-50% of all neoplastic cases in neonates)
- 7.8-10% of **childhood** cancers - 4th most common malignancy of childhood (after leukemias, CNS tumors, lymphomas); 15% of deaths from cancer in pediatric population!
- most common **intra-abdominal** malignancy of infancy.
- most common **extracranial solid** tumor in children < 5 yrs.
- PREVALENCE ≈ 1 case per 7-10,000 live births.
- INCIDENCE 0.1-1 case per 8000-10,000 children (8.0-8.7 per million per year in children < 15 yrs).
- **Japan** has highest incidence! (result of neonatal screening - detected tumors that normally would have not been discovered and would have regressed spontaneously; \rightarrow neonatal screening has been abandoned in Japan since it was shown not to significantly improve mortality or morbidity!!!).
- **age at diagnosis**: 36-40% children < 1 year, 35% children 1-2 years, 25% children > 2 years (**95-97% are diagnosed by age 10 yrs**).
 - Median age at diagnosis - 22 months.
 - Rare after age 10 years!
 - Have been diagnosed in utero (at 19 weeks' gestational age)
- **male-to-female** ratio = 1.2-1.3 : 1

GENETICS

- 1-2% cases are **familial** (median age at diagnosis – only 9 months); associated with number of disorders (Hirschsprung disease, fetal alcohol syndrome, DiGeorge syndrome, neurofibromatosis type 1, Beckwith-Wiedemann syndrome).
- 20% cases are inherited through **AUTOSOMAL DOMINANT** pattern.
- **1p deletion** is found in 70-80% neuroblastomas.
- **N-myc oncogene amplification** (occurs in 20-25% cases; located on distal 2p, linked to 1p deletion and 17q gain) = aggressive behavior (high metastatic potential).
 - Oncogene amplifications cytogenetically are seen as **double-minute chromatin bodies** or as **homogeneously staining regions**.

PATHOLOGY

- some neuroblastomas weight > 1 kg.
- neural malignant **poorly differentiated SMALL, BLUE, ROUND cell tumor** (uniform cells resemble primitive neuroblasts - dense hyperchromatic nuclei and scant cytoplasm).
 - Small, blue, round cell tumors of childhood:
 - 1) neuroblastoma
 - 2) primitive neuroectodermal tumors (incl. medulloblastoma)
 - 3) non-Hodgkin lymphoma
 - 4) Ewing sarcoma
 - 5) undifferentiated soft tissue sarcoma (rhabdomyosarcoma).
- diagnostic **Homer-Wright rosettes** (observed in 15-50% patients); also present in PNETs (incl. medulloblastoma) see p. Onc18 >>>!!!!
- **electron microscopy** can be useful - ultrastructural features (e.g. neurofilaments, neurotubules, synaptic vessels, dense core granules) are diagnostic for neuroblastoma!

- **maintenance of dedifferentiated state** involves failure in ligand-receptor pathways; one of most studied and most popular pathways is nerve growth factor (NGF) and its receptor (NGFR).
- **spontaneous regression** of microscopic clusters of neuroblastoma cells (*NEUROBLASTOMA IN SITU*) is common!!!

Documented spontaneous rate of resolution!!! (surgical capsule can be violated, leaving residual tumor, and good outcome still might be achieved)

½ neuroblastomas that reach size that would be detectable by screening actually regress without specific therapy, whereas equivalent number are detected clinically

LOCATION

- anywhere along sympathetic nervous system (during 5th week of embryogenesis, primitive sympathetic neuroblasts invaginate → migrate along entire sympathetic chain from neural crest to site where adrenal anlage eventuates):

- 60-70% in **abdominal retroperitoneum** (35-40% **adrenal medulla**, 25-30% paraspinal ganglia)
- 15-20% posterior mediastinum (sympathetic trunk, aortic body)
- 5% pelvic (organ of Zuckerkandl)
- 3-5% cervical (carotid body)
- 2% intracranial (e.g. olfactory bulb & olfactory mucosa - so called *ESTHESIONEUROBLASTOMAS*)
- 1% primary tumor cannot be found.

- infants - more frequently thoracic and cervical tumors; older children - abdominal tumors.
- locations of METASTASES: bone* (60%), regional lymph nodes (35-45%), orbit (20%), liver (15%), intracranial areas (14%), lung (10%), skin.

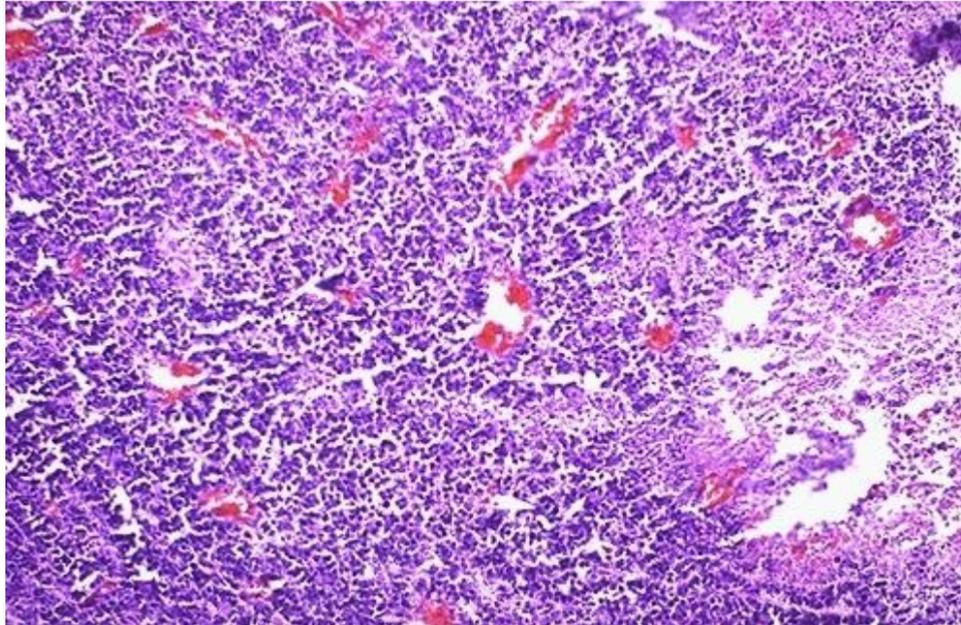
*often metaphyseal and symmetrical

Neuroblastoma of right adrenal in neonate - neoplasm (*white arrow*) is displacing liver to left:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

Neuroblastoma (one of "small round blue cell" tumors) - areas of necrosis and calcification:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

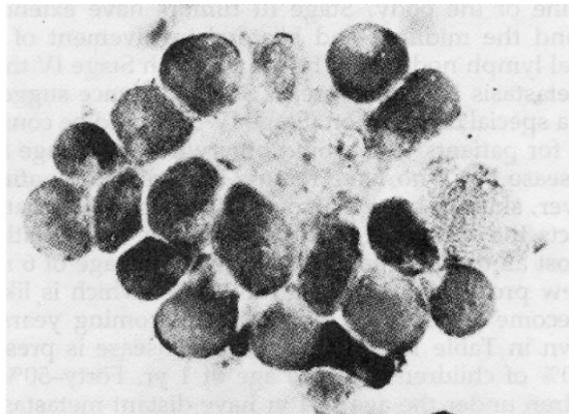


Figure 15-9 Neuroblastoma cells aspirated from the bone marrow. Clumps of cells often contain 3 or more cells without evidence of rosette formation. Rosettes of cells surrounding an inner mass of fibrillary material are characteristic of neuroblastoma.

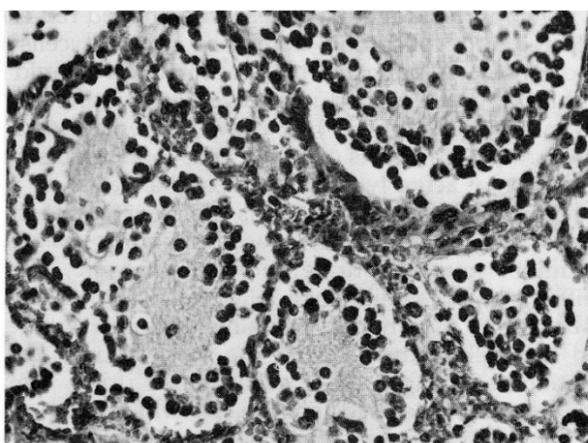


Figure 15-7 The diagnostic criteria of neuroblastoma: poorly formed compartments of cells with relatively uniform, round, dark nuclei, which surround an acellular, fibrillar central area.

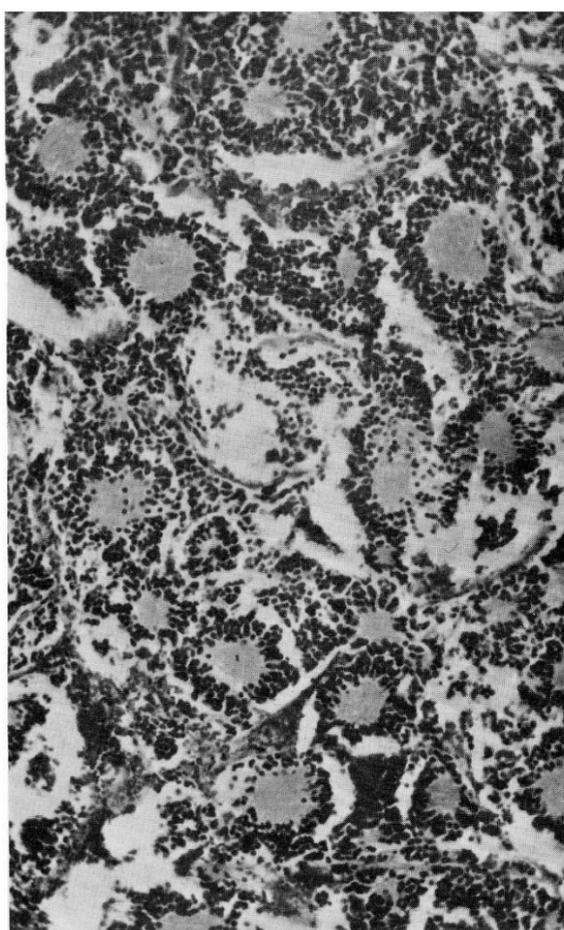
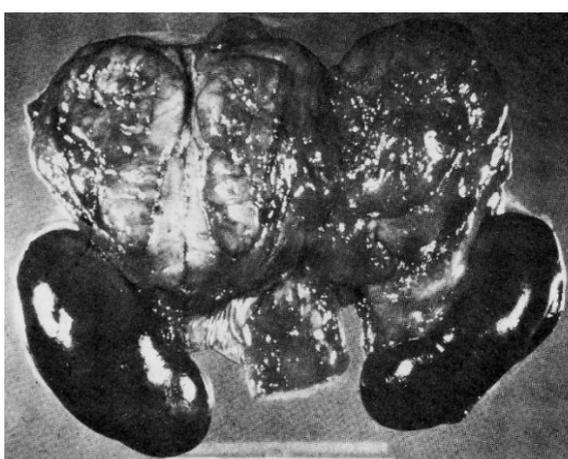


Figure 26–53. Neuroblastoma of adrenal, clearly demonstrating numerous rosettes.



Bilateral adrenal neuroblastomas that dwarf kidneys.

CLINICAL FEATURES

- children with *localized disease* are **asymptomatic**.
- children with *disseminated disease* are generally **sick**.

Great mimicker - myriad clinical presentations related to:

1. **Site of primary tumor**

- 45-54% patients have palpable fixed, large, nontender, irregular, firm ABDOMINAL TUMOR that crosses midline*
*vs. Wilms' tumor - smooth mobile flank mass that does not cross midline
- **adrenal tumor** → *abdominal complaints* (abdominal pain, anorexia, emesis, weight loss).
- **organ of Zuckerkandl tumor** → *bladder and bowel compression*.
- neuroblastoma in **paraspinal ganglia** may invade through neural foramina (*“dumbbell” tumor*) → *spinal cord compression* (7-15% patients).
H: emergency chemotherapy (laminectomy reserved for patients who do not respond!)
- **cervical region or high thoracic tumor** → *compression of sympathetic ganglia* (e.g. Horner syndrome) or *superior vena cava syndrome*.
- **posterior mediastinum neuroblastoma** may be asymptomatic (or *mild airway obstruction*, chronic cough).

2. **Metastatic disease** – present in 50-66% patients.

- *constitutional symptoms* - general malaise, anorexia, failure to thrive, weight loss, anemia, irritability, fever.
- **HUTCHINSON syndrome** - widespread metastasis to **bone**: bone *pain* → *limping* and pathologic fractures (can simulate osteomyelitis).
- **bone marrow** metastases → *bone marrow failure*.
- **PEPPER syndrome** (occurs only in infants) - overwhelming metastatic neuroblastoma of **liver** → intra-abdominal pressure↑ → *respiratory compromise*; associated with stage 4S; spontaneous regression (few infants may die of massive hepatomegaly, respiratory failure, and overwhelming sepsis).
- **“blueberry muffin” babies** - infants with random **subcutaneous** metastases - nontender, bluish subcutaneous nodules; when provoked, nodules become intensely red and subsequently blanch for several minutes thereafter (secondary response to release of vasoconstrictive tumor by-products).
- rarely, metastases to **orbits** → *periorbital ecchymosis* (“racoon eyes”)*, **proptosis**.
*can mimic child abuse

3. **Metabolically active by-products**

- 89-95% neuroblastomas (esp. differentiated tumors with good prognosis) produce **catecholamines**, but patients rarely have symptoms related to catecholamine secretion.
N.B. *hypertension* (≈ 10% patients) is caused by renal artery or vein compression, not catecholamine excess!
- 7% neuroblastomas (esp. differentiated tumors with good prognosis) secrete **VIP** → *paraneoplastic VERNER-MORRISON syndrome*: intractable secretory diarrhea; resolves with complete tumor removal.

2-4% patients have **OPSOCLONUS - MYOCLONUS paraneoplastic syndrome**, s. **MYOCLONIC encephalopathy** (*antineural antibodies* against tumor that cross-react with neural cells in cerebellum or elsewhere in brain): *opsoclonus, myoclonus, truncal ataxia*.

- indicator of good long-term prognosis for survival.
- neurology can progress and be devastating despite successful treatment of tumor!!!

FETAL NEUROBLASTOMA

- can be detected on obstetric ultrasound as early as 19 weeks.
- typically adrenal gland (90%).
- placental metastases → fetal hydrops.
- catecholamine secretion → preeclampsia.

DIAGNOSIS

N.B. neonatal screening has no benefit on mortality and morbidity!!!

LABORATORY TESTS

1. **ESR**↑
2. **Liver function tests** (liver metastases)
3. **CBC** (bone marrow metastases)
4. **Metabolic catecholamine by-products**↑
 - in urine (90-95%): **homovanillic acid (HVA)↑**, **vanillylmandelic acid (VMA)↑**; **low VMA-to-HVA ratio** is poor prognosis (poorly differentiated tumor - lost final enzymatic pathway that converts HVA to VMA).
 - Screening - **LaBrosse VMA spot test** (highly inaccurate).
 - Confirmation - **high-performance liquid chromatography** on 24-hour urine.
 - levels must be > 3.0 SD above mean for age.
 - normalizing urinary VMA and HVA excretion to milligrams of creatinine in sample makes timed collection unnecessary, and avoids most false-negatives.
 - serum: **dopamine or norepinephrine**↑.
 - tumor cells lack enzyme that converts norepinephrine to epinephrine (but norepinephrine does not reach detectable serum levels - 1) catabolized within tumor; 2) tyrosine hydrolase is subject to negative feedback loop by norepinephrine).
5. **Tumor markers**: **neuron-specific enolase (NSE)***, **ferritin**, lactic dehydrogenase (LDH), chromogranin A, neuropeptide Y.

*elevated in 96% metastatic neuroblastomas.

IMAGING

These imagings are necessary for all infants and children with abdominal mass!

Plain radiographs:

- **abdomen** – flank mass, finely stippled calcifications (30%).
- **chest** – posterior mediastinal mass, splaying of ribs and rib erosion, pleural effusions and pleural nodules.
- **long bones** – irregular lucencies or lytic lesions in metaphysis or submetaphyseal bone; tumor infarction → sclerotic lesions; periosteal reaction is common.
- **skull** – widening of cranial sutures secondary to dural metastasis; classic *hair-on-end* appearance (albeit unusual in neuroblastoma) can be seen.
- **spine** – widening of neuroforamina, vertebral body scalloping, erosion of pedicles, scoliosis.

Sonogram (small tumors have been detected on prenatal ultrasound!) - inhomogeneous mass with focal brightly echogenic areas (calcifications).

Excretory urograms (were widely used in past) - adrenal neuroblastomas typically displace ipsilateral kidney laterally and downward → classic “*drooping-lily*” sign.

CT / MRI - tumor extent, regional lymph nodes, vessel invasion, distant metastatic disease;

- CT - stippled calcifications (80-90%), lobulated heterogeneous appearance on contrast-enhanced CT (areas of low attenuation - necrosis and hemorrhage).
- MRI: neuroblastomas are hypointense on T1 and hyperintense on T2; inhomogeneous enhancement.
- **spinal MRI** – determining cord compression (alternative – **CT myelography**).
- **head CT** – only if clinically indicated; enhancing dural metastases can simulate meningitis.

Scintigraphy:

- **metaiodobenzylguanidine (MIBG)** - sensitive and specific compound taken up by catecholaminergic cells.
- **¹¹¹In pentetreotide** (somatostatin analog) is as sensitive as MIBG.
- if MIBG scintigraphy negative* → bone scintigraphy using **⁹⁹Tc diphosphonate** and **skeletal bone survey**.
- **I¹²³ iobenguane** - structure similar to norepinephrine - taken up by norepinephrine transporter in adrenergic nerve terminals and stored in presynaptic storage vesicles in adrenergically innervated tissues (adrenal medulla, salivary glands, heart, liver, spleen and lungs as well as tumors derived from neural crest).
 - *30% neuroblastomas may not take up MIBG (though 90-95% secrete catecholamines); 50% recurrent neuroblastomas do not take up MIBG even if they took up MIBG before therapy

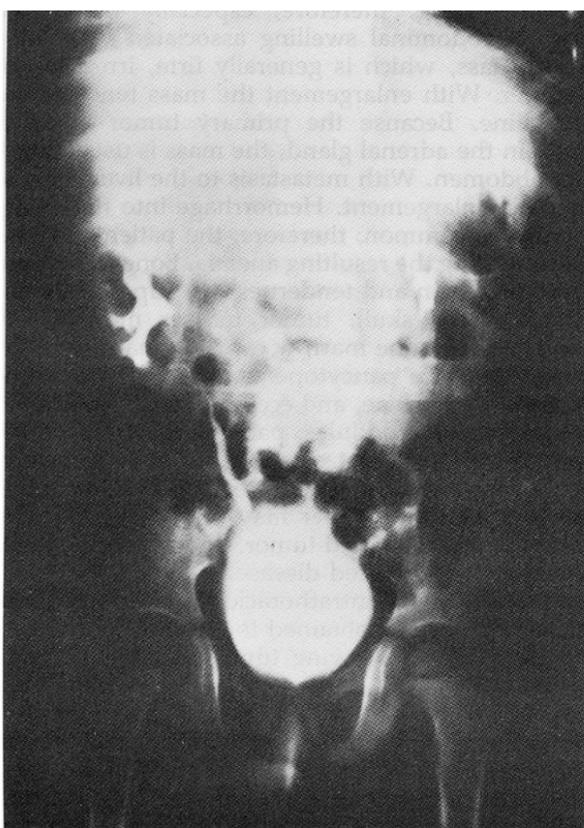
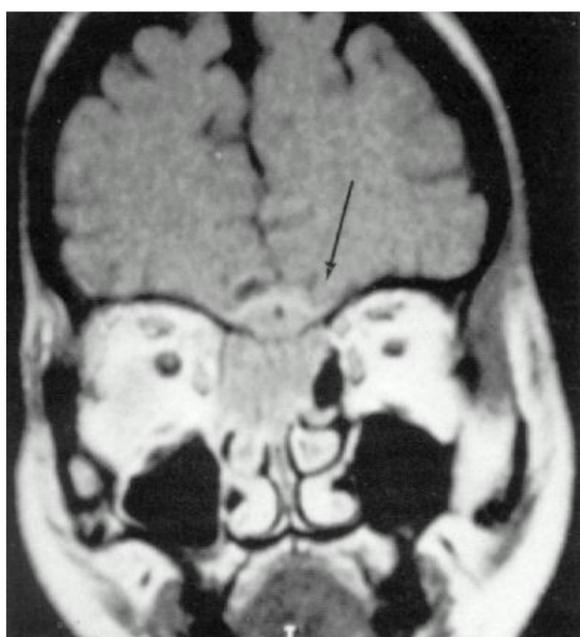


Figure 15-8 The intravenous pyelogram of a patient with a neuroblastoma arising in the right adrenal gland. The kidney is shown as displaced by the tumor mass downward and to the right.

Esthesioneuroblastoma (MRI) in ethmoid sinus with intradural extension (*arrow*):



BIOPSY

- sine qua non of diagnostic evaluation:

- 1) H & E stain
- 2) IMMUNOHISTOCHEMISTRIES - neuroblastoma stains with monoclonal Ab recognizing neurofilaments, synaptophysin, and neuron-specific enolase (NSE).
- 3) BIOLOGIC STUDIES of tumor tissue sample assign risk category (particularly important in nonmetastatic disease); e.g. test *N-myc* oncogene copy number + chromosome studies.
- 4) ELECTRON MICROSCOPY - dense core, membrane-bound neurosecretory granules, microfilaments, parallel arrays of microtubules within neuropil.

Option is to sample **bone marrow** (frequent metastatic site) - 2 **aspirates** and 2 **biopsies*** (1 from each posterior iliac crest); only single study positive for tumor is required to document bone marrow involvement, but all four studies are required if findings are negative.

*might become obsolete because immunocytology of aspirates may offer single best source of diagnostic information

DIAGNOSTIC CRITERIA

- require histopathologic diagnosis:

- a) unequivocal pathologic diagnosis made from tumor tissue by light microscopy ± immunohistology, electron microscopy, or urine / serum catecholamines↑.
 - b) bone marrow (aspirate or trephine biopsy) contains unequivocal tumor cells (e.g. syncytia or immunocytologically positive clumps of cells) + urine (or serum) catecholamines↑.
- genetic features characteristic of neuroblastoma (1p deletion, *N-myc* amplification) support diagnosis.

STAGING

Extent of disease	Infants	Older children
localized tumors	39-40%	19-20%
regional lymph node spread	18%	13%
disseminated disease	7-25%	68-80%

INTERNATIONAL NEUROBLASTOMA STAGING SYSTEM (INSS)

Stage 1 - complete gross excision (with or without microscopic residual disease); ipsilateral and contralateral lymph nodes are microscopically negative (nodes attached to and removed with primary tumor may test positive).

Stage 2A - incomplete gross excision; ipsilateral and contralateral lymph nodes are microscopically negative.

Stage 2B - complete or incomplete gross excision; ipsilateral nonadherent lymph nodes are positive; contralateral lymph nodes test negative microscopically.

Stage 3 - tumor crosses midline: *midline is defined as vertebral column*

- a) unresectable unilateral tumor infiltrating* across midline (with or without regional lymph node involvement).
- b) localized unilateral tumor with positive contralateral regional lymph node.
- c) midline tumor with bilateral extension by infiltration* (unresectable) or by lymph node involvement.

*vs. pedunculated tumor that hangs over midline

Stage 4 - distant metastases to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S).

Stage 4S (limited to infants < 1 yr!) - localized primary tumor (as defined for stages 1-2B), with dissemination limited to skin, liver, and/or bone marrow.

- 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 or cortical bone involvement is stage 4.
- MIBG scan (if performed) should be negative for disease in bone marrow.
- significantly better prognosis (than with stage 4); spontaneous regression is common; 5-yr survival ≈ 70-75%.

EVANS STAGING SYSTEM

Stage 1 - tumor confined to organ of origin.

Stage 2 - tumor extends beyond organ of origin but does not cross midline; ipsilateral regional lymph nodes may be involved.

Stage 3 - tumor extends beyond midline.

Stage 4 - distant metastases

Stage 4s - localized tumor in infants that does not cross midline, with metastatic disease confined to liver, skin, and bone marrow (no evidence of cortical bone involvement!).

SHIMADA HISTOPATHOLOGIC CLASSIFICATION

- (1) age
- (2) presence or absence of Schwannian stromal development (stroma-rich, stroma-poor)
- (3) nodular pattern
- (4) degree of neuroblast differentiation
- (5) mitosis-karyorrhexis index (MKI) - index of cellular proliferation (number of karyorrhectic cells per number of cells scanned)

Favorable histology group:

- a) any age, stroma-rich tumors without nodular pattern

- b) age < 18 months, stroma-poor tumors, MKI < 200/5000.
- c) age < 60 months, stroma-poor tumors, MKI < 100/5000, well-differentiated neuroblasts.

Unfavorable histology group:

- a) any age, stroma-rich tumors, nodular pattern.
- b) any age, stroma-poor tumors, MKI > 200/5000.
- c) age > 18 months, stroma-poor tumors, undifferentiated neuroblasts, MKI > 100/5000.
- d) age > 18 months, stroma-poor tumors, differentiated neuroblasts, MKI 100-200/5000.
- e) age > 60 months, stroma-poor tumors, differentiated neuroblasts, MKI < 100/5000.

JOSHI HISTOPATHOLOGIC CLASSIFICATION

Joshi et al attempted to simplify Shimada classification using presence of **calcification** and **mitotic rate**:

Good prognosis (grade 1) - low mitotic rate (≤ 10 mitoses/10 high-power fields) and calcification.

Intermediate prognosis (grade 2) - low mitotic rate or calcification.

Poor prognosis (grade 3) - high mitotic rate and no calcification.

Criteria for Risk Assignment:

INSS Stage	Age (years)	MYCN Status	Shimada Histology	DNA Ploidy	Risk Group
1	0-21	Any	Any	Any	Low
2A/2B	< 1	Any	Any	Any	Low
	≥ 1-21	Nonamplified	Any	-	Low
	≥ 1-21	Amplified	Favorable	-	Low
	≥ 1-21	Amplified	Unfavorable	-	High
3	< 1	Nonamplified	Any	Any	Intermediate
	< 1	Amplified	Any		High
	≥ 1-21	Nonamplified	Favorable		Intermediate
	≥ 1-21	Nonamplified	Unfavorable		High
	≥ 1-21	Amplified	Any		High
4	< 1	Nonamplified	Any	Any	Intermediate
	< 1	Amplified			High
	≥ 1-21	Any			High
4S	< 1	Nonamplified	Favorable	>1	Low
		Nonamplified	Any	=1	Intermediate
		Nonamplified	Unfavorable	Any	Intermediate
		Amplified	Any	Any	High

Low = survival > 90%
 Intermediate = survival 30-50%.
 High = survival < 20%.

Feature	Type 1	Type 2	Type 3
MYCN gene	Normal	Normal	Amplified
Karyotype/ploidy	Hyperdiploid or Triploid	Near-diploid or Near-tetraploid	Near-diploid or Near-tetraploid
1p loss of heterozygosity	-	±	+
TRK-A expression	High	Variable (low)	Low or absent
Age	Usually ≤ 1 yr	Usually > 1 yr	Usually 1-5 yr
INSS stage	Usually 1, 2, 4S	Usually 3, 4	Usually 3, 4
3-y survival	≈ 95%	25-50%	≈ 5%

DIFFERENTIAL

- 1) lymphoma / leukemia
- 2) hepatoblastoma
- 3) rhabdomyosarcoma
- 4) Ewing's sarcoma
- 5) renal cell carcinoma
- 6) Wilms tumor (nephroblastoma)
- 7) adrenal hemorrhage

Stains	Neuroblastoma	Lymphoma	Ewing's sarcoma	Rhabdomyosarcoma	Primitive neuroectodermal tumor
Neurofilament	+	-	±	-	-
Synaptophysin	+	-	-	-	-
Neuron-specific enolase (NSE)	+	-	.*	.*	+
β ₂ -microglobulin	-	-	-	-	+
Leukocyte common antigen (T-200 protein)	-	+	-	-	-
Vimentin	-	±	+	+	+
Myoglobin	-	-	-	+	-
Myosin	-	-	-	+	-
Actin	-	-	-	+	-
Desmin	-	-	-	+	-

*extraosseous Ewing's sarcoma, variants of Ewing's sarcoma and rhabdomyosarcoma stain for NSE.

TREATMENT

SURGERY

- manages only **low-stages (stages 1-2)**.

Surgery is contraindicated for **high-stage neuroblastoma!**

- **PREOPERATIVELY** - general bowel preparation and 3rd-generation cephalosporin.
- **NEUROBLASTOMA** does not require specific anesthetic protocol (vs. **PHEOCHROMOCYTOMA**).
- **incision** - midline transperitoneal; alternatives - upper transverse abdominal incision, chevron incision.
- neuroblastoma invades tunica adventitia of large blood vessels (but rarely invades into lumen) - obtain distal and proximal control of major blood vessels (most common surgical complication is vascular injury!)

- if renal hilum is involved → nephrectomy.
- if tumor cannot be removed primarily → **wedge biopsy** for histopathology, immunohistochemistry, and genetic studies.
Avoidance of surgical risk is particularly important in infants who have substantially better survival!
Complications are lower for delayed or second-look procedures, after tumor shrinkage by chemotherapy.
- to complete protocol, **regional lymph nodes are evaluated + liver biopsy**.
- send tumor for BIOLOGIC STUDIES.
- POSTOPERATIVELY - if *residual disease* is present → second-look surgery (chemotherapy has no advantage).

CHEMOTHERAPY

Multiple-agent chemotherapy is backbone of multimodality treatment (routine for **advanced stages**).

Common chemotherapeutic agents:

- 1) **CISPLATIN, CARBOPLATIN***
- 2) **DOXORUBICIN***
- 3) **CYCLOPHOSPHAMIDE*, IFOSFAMIDE**
- 4) epipodophyllotoxins (**TENIPOSIDE** and **ETOPOSIDE***)
- 5) **TOPOTECAN**

*most active drugs against neuroblastoma

- most active drug pairs (combining non-cell cycle-specific agents with cell cycle-dependent drugs): **CYCLOPHOSPHAMIDE + DOXORUBICIN; CISPLATIN + TENIPOSIDE**.
- high-dose **IFOSFAMIDE, CARBOPLATIN** and **ETOPOSIDE** (HD-ICE) is effective treatment for refractory or relapsed neuroblastoma - retrospective study from Memorial Sloan-Kettering Cancer Center.
- *large number of nonproliferating tumor cells* – poor chemosensitivity!
- may result in ↓size of primary tumor and metastases, occasional bone marrow sterilization, rare transformation of neuroblastoma into benign ganglioneuroma.
- emergency chemotherapy is first choice for **spinal cord compression!**
- autologous **bone marrow transplant** or peripheral blood **stem cell rescue** allow high-dose treatment.

DINUTUXIMAB (Unituxin, United Therapeutics Corporation) - FDA approved in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA), for pediatric patients with high-risk neuroblastoma who achieve at least partial response to prior first-line multiagent, multimodality therapy.

Other Medical Treatments

- symptomatic treatments:

1. **ACTH** - fairly efficacious (some patients are resistant).
2. Plasmapheresis & **IVIG**

Supplemental nutrition often is required during therapy!

OPSOCLONUS-MYOCLONUS syndrome – may be treated:

- a) **ACTH** or corticosteroids.
- b) **IVIG**.
- c) multimodal chemotherapy.

RADIOTHERAPY

- limited yet well-defined role; indicated for:

- 1) regional **lymph node** metastases with sequential **CYCLOPHOSPHAMIDE**
 - 2) stage 4 infants with **Pepper syndrome** (to control respiratory compromise)
 - 3) **total-body irradiation** (TBI) with autologous bone marrow transplantation (ABMT).
- in vitro neuroblastoma is radiosensitive, but clinical trials have been inconsistent and inconclusive.

COOPERATIVE GROUP RISK-RELATED TREATMENT STRATEGIES

LOW-RISK GROUP

- **surgical excision** alone (even residual microscopic disease does not affect survival significantly) → **observation**.

- recurrent disease → **chemotherapy**; radiation is reserved for those who fail to chemotherapy.

INTERMEDIATE-RISK GROUP

- **surgery, chemotherapy** (adjuvant or neoadjuvant).

- second-look **surgery** post-chemotherapy is used to attempt complete resection.
- residual disease postchemotherapy and surgery → **radiotherapy**.

HIGH-RISK GROUP

- **surgery, multiagent chemotherapy** (adjuvant or neoadjuvant) ± **radiation therapy** (e.g. for residual disease) → consolidation with high-dose **chemotherapy** (with peripheral blood **stem cell rescue**).

- risk of relapse after consolidation may be decreased with **13-CIS-RETINOIC ACID** (induces neuroblast differentiation an death).

RESPONSE TO TREATMENT

- evaluations are recommended:

- 1) at end of induction (usually 3-4 months)
- 2) at end of treatment (usually 8-12 months)
- 3) before and after surgical procedures
- 4) before bone marrow transplantation
- 5) as indicated clinically.

Response	Primary	Metastases	Markers
COMPLETE RESPONSE	No tumor	No tumor (chest, abdomen, liver, bone, bone marrow, nodes, etc.)	HVA/VMA normal
VERY GOOD PARTIAL RESPONSE	Reduction > 90% but < 100% improved	No tumor (as above except bone); no new bone lesions	HVA/VMA decreased > 90%

Response	Primary	Metastases	Markers
PARTIAL RESPONSE	Reduction 50-90%	No new lesions; 50-90% reduction measurable sites; 0-1 bone marrow samples with tumor; no new bone lesions	HVA/VMA decreased 50-90%
MIXED RESPONSE	No new lesions; > 50% reduction of any measurable lesion (primary or metastases) with < 50% reduction in any other; < 25% increase in any existing lesion*		
NO RESPONSE	No new lesions; < 50% reduction but < 25% increase in any existing lesion*		
PROGRESSIVE DISEASE	Any new lesion; increase of any measurable lesion by > 25%; previous negative marrow positive for tumor		

*quantitative assessment does not apply to marrow disease

- **COMPLETE RESPONSE** in metastatic sites and **PARTIAL RESPONSE** in primary tumor are considered **PARTIAL RESPONSE** overall.

PROGNOSIS

Most recurrences occur during first 2 years following treatment.

Overall 5-year survival rate - 55% (83% for infants, 40% for children > 5 yrs)

AGE is most significant prognosticator – **INFANTS (< 1 YR)** have better prognosis compared with older children:

- 40% infants have localized neuroblastoma (vs. only 20% children > 1 yr).
- only 7-25% infants have disseminated neuroblastoma (vs. 68-80% children > 1 yr).
- several reports have described adults with neuroblastoma - course of disease is more indolent than in children!

Prognosis of disseminated neuroblastoma:

INFANTS - favorable outcomes with combined chemotherapy and surgery.

children > 1 year - very poor survival despite intensive multimodal therapy.

Other prognosis indicators:

- 1) **stage** at diagnosis; survival :
 - stage 1 – 90%
 - stage 2 – 80%
 - stage 3 – 60%
 - stage 4 – 10%
 - stage 4S – 70-75%
- 2) tumor **N-myc amplification** (> 10 copies) - poor prognosis (except for infants)
- 3) tumor **1p deletion** - poor prognosis
- 4) serum **neuron-specific enolase (NSE)**↑ (> 100 ng/mL) - poor prognosis
- 5) serum **ferritin**↑ (> 142 ng/mL) - poor prognosis*.
- 6) serum **LDH**↑ (> 1500 µg/mL) - poor prognosis*.
- 7) **hyperdiploid tumor DNA** (DNA index > 1) (only for infants) - favorable prognosis (good response to **CYCLOPHOSPHAMIDE** and **DOXORUBICIN**)

*marker of rapid tumor growth or large tumor burden

- worst location of primary tumor - **adrenal gland**.
- worst location of metastases - **bones**.

GANGLIONEUROMA (s. GANGLIOMA)

- composed of **mature (fully differentiated) ganglion cells**, Schwann cells, and neuritic processes (neuropil) - completely benign counterpart of *NEUROBLASTOMA*.

N.B. histopathologic features may vary within single tumor - *multiple sections* (particularly from regions with different gross appearance) should be examined!

- usually occurs in **adults**.
- if occurs in **CNS**, it is called **GANGLIOCYTOMA (s. CENTRAL GANGLIONEUROMA)**; if in **CNS** and **glial component** is also present – **GANGLIOGLIOMA**. see p. Onc22 >>

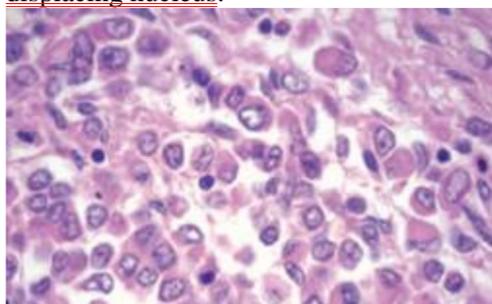
ATYPICAL TERATOID/RHABDOID TUMOUR (WHO GRADE IV)

AT/RT + Bilateral renal malignant rhabdoid tumors

“Nasty CP angle tumor in kids”

“CP angle tumor in ≤ 3 yo kid is AT/RT until proven otherwise”

- **age < 3 yrs**
- **inactivation of INI1/hSNF5 gene** (22q) in 100% cases (SMARC mutation).
- Ki-67/MIB-1 labelling indices > 50%, focally **up to 100%**
- **rhabdoid cells** - vesicular chromatin, prominent nucleoli, eosinophilic globular cytoplasmic inclusions displacing nucleus:



Rhabdoid = rod-shaped

- can stain for anything (muscle markers, etc).
- 4 : 3 = supratentorial : infratentorial

BIBLIOGRAPHY for ch. “Neuro-Oncology” → follow this [LINK >>](#)