

Neuroblastic Tumors

Neuroblastoma • Ganglioneuroblastoma • Ganglioneuroma

Morphology, clinical behavior, staging, and prognostic biology

Dr Abu Suraih Sakhri

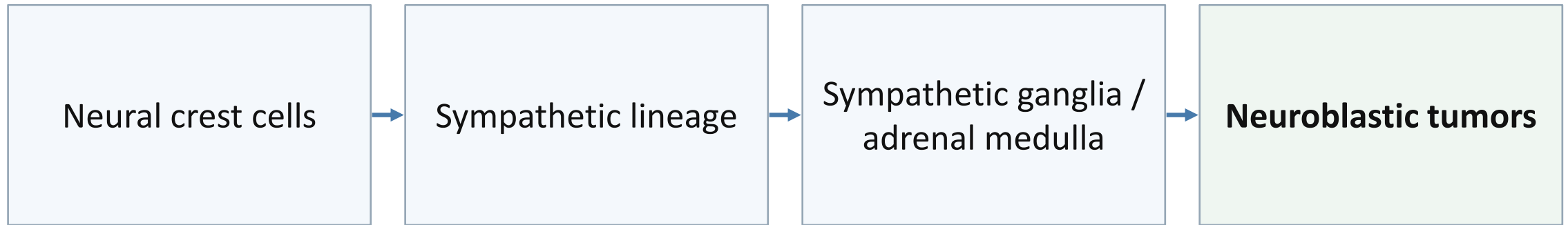
MBBS, MD (Pathology)

www.abusuraisakhri.com

Learning objectives

- Trace the neural crest origin and differentiation spectrum of neuroblastic tumors.
- Recognize classic neuroblastoma morphology, neuropil, and Homer–Wright pseudorosettes.
- Apply INRGSS staging and identify image-defined risk factors.
- Relate age, MYCN, ploidy, histology, and chromosome alterations to risk.

A shared embryologic origin



The tumor family reflects neoplasia of primitive neural crest–derived sympathetic cells.

The neuroblastic tumor spectrum

Neuroblastoma

Predominantly undifferentiated primitive neuroblasts.

Ganglioneuroblastoma

Neuroblasts admixed with maturing ganglion cells.

Ganglioneuroma

Mature ganglion cells and abundant Schwannian stroma.

Differentiation and schwannian stroma are important biologic distinctions.

Neuroblastoma in pediatric oncology

- Most common extracranial solid tumor of childhood.
- Most frequently diagnosed malignancy in infancy.
- Prevalence approximately 1 in 7,000 live births.
- Approximately 700 new diagnoses annually in the United States (textbook estimate).

Age distribution at diagnosis

- Median age at diagnosis: Approximately 18 months.
- About 40% of cases are diagnosed during infancy.
- Age is a major prognostic variable, not merely an epidemiologic descriptor.
- Younger patients often have more favorable outcomes with comparable disease burden.

Sporadic versus familial neuroblastoma

Sporadic

Great majority of cases;
Lesions may contain
acquired oncogenic
mutations.

Familial

Approximately 1%–2%;
May involve both adrenal
glands or multiple
autonomic sites.

Molecular link

Germline activating ALK
alterations are an
important hereditary
mechanism.

Bilateral or multifocal disease should raise consideration of hereditary predisposition.

ALK pathway: Inherited and acquired activation

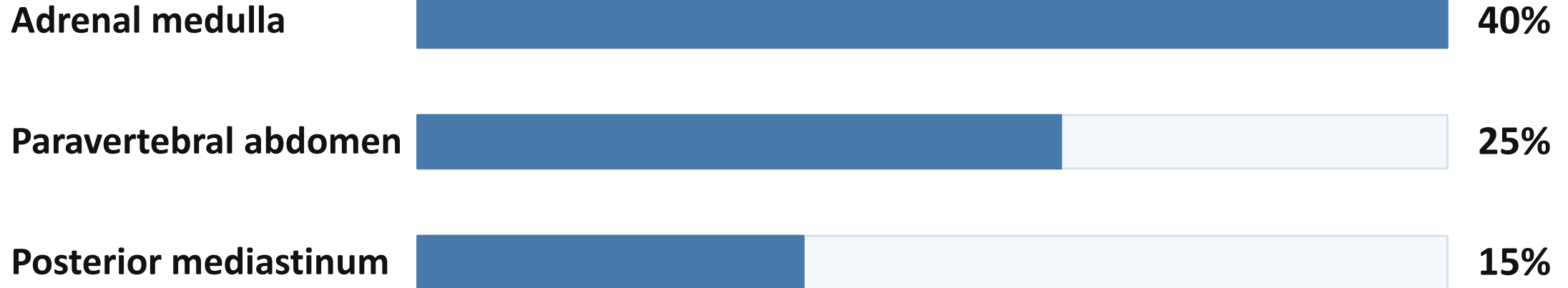


The same proto-oncogene is implicated in familial susceptibility and a subset of sporadic tumors.

ALK mutations in sporadic disease

- Somatic gain-of-function ALK mutations are present in approximately 10% of sporadic neuroblastomas.
- A somatic driver is not equivalent to a hereditary predisposition allele.
- ALK status also creates a molecular rationale for targeted-therapy research.
- A mutation must be interpreted within the broader neuroblastoma risk profile.

Frequent primary tumor locations



The sympathetic chain also permits primaries in neck and pelvis.

Locations reflect sympathetic anatomy

- Adrenal-medullary tumors are particularly common.
- Extra-adrenal tumors arise along paravertebral sympathetic chains.
- Posterior mediastinal primaries may present differently from abdominal tumors.
- Pelvic and cervical primaries are possible but less common.

Minute lesions and clinically overt tumors

Anatomic finding

- “In situ” lesions may be very small and clinically silent.
- Reported far more frequently than overt clinical tumors.
- May leave only fibrosis or calcification after regression.

Biologic implication

- Incidental microscopic lesions do not inevitably progress.
- Spontaneous involution is a distinctive feature of neuroblastic biology.
- The neoplastic designation of some in situ foci has been questioned.

Spontaneous regression: Observed morphologic sequence

Minute neuroblastic focus



Spontaneous involution



Fibrosis and/or calcification

Spontaneous regression is well documented; Its molecular basis is not fully established.

Gross growth patterns

- Some lesions are sharply delimited by a fibrous pseudocapsule.
- Other tumors infiltrate adjacent soft tissues and organs.
- The apparent boundary is not a substitute for assessing local invasion.
- Growth configuration has direct relevance to surgical and imaging assessment.

Gross specimen: What to look for

Cut surface

Soft, gray–tan tumor parenchyma.

Large lesions

Necrosis, cystic softening, and hemorrhage may occur.

Additional finding

Punctate intratumoral calcification may be palpable.

These observations should be sought in a real gross specimen when available.

Invasive relationships in abdominal primaries

- Neuroblastoma may invade kidney, renal vein, or inferior vena cava.
- The tumor can envelop the aorta rather than simply displace it.
- Encasement of major vessels is relevant to pretreatment imaging risk factors.
- Local invasion and distant metastasis are distinct patterns of spread.

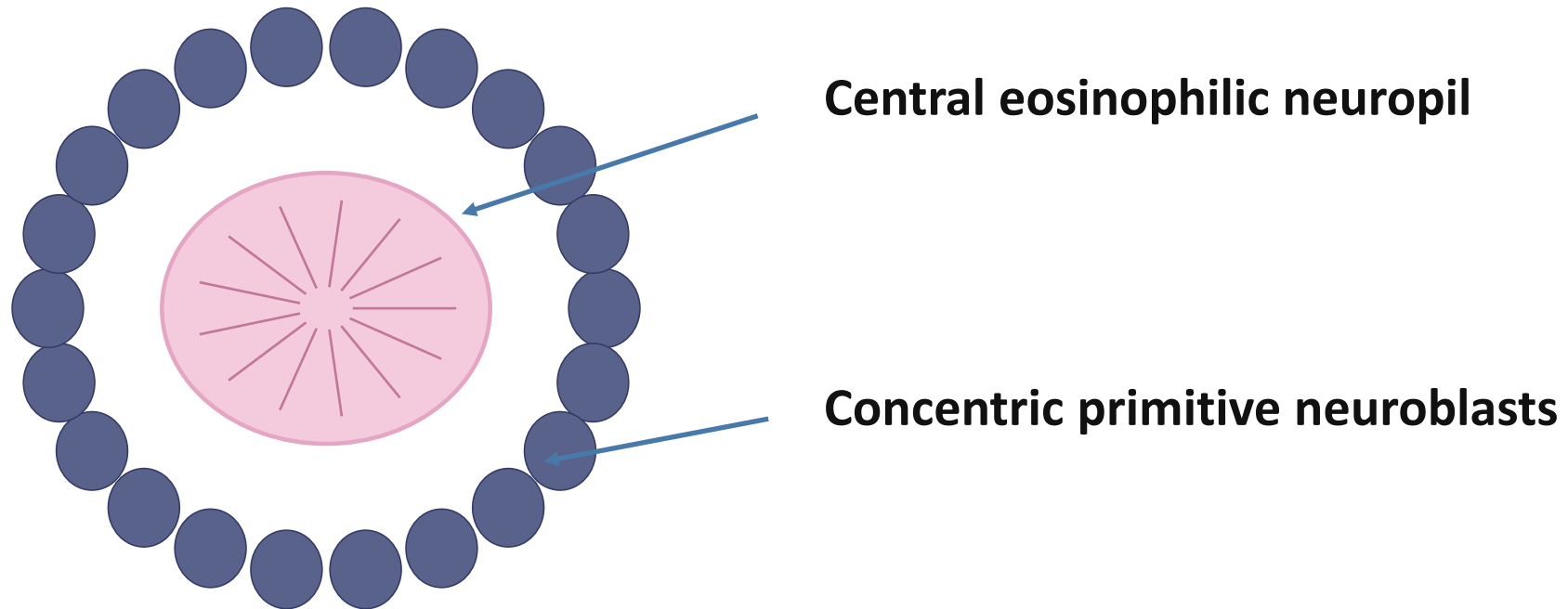
Classic microscopic appearance

- Sheets of small, primitive-appearing neuroblasts.
- Dark nuclei, scant cytoplasm, and poorly defined cell borders.
- Mitotic activity, karyorrhexis, and pleomorphism may be conspicuous.
- The tumor enters the differential diagnosis of small round blue cell neoplasms.

Neuropil: A clue to neuroblastic differentiation

- Background often contains faintly eosinophilic fibrillary material.
- This neuropil corresponds to neuritic processes of primitive neuroblasts.
- Neuropil provides architectural context when tumor cells themselves look undifferentiated.
- Distinguish true neuropil from a nonspecific pale tumor background.

Homer–Wright pseudorosette: Architecture



Schematic — not a histologic specimen

Reading a Homer–Wright pseudorosette

- Tumor cells form a roughly concentric arrangement.
- The central zone is filled with neuropil, not a true lumen.
- Rosettes are characteristic but not universally present.
- Interpret rosette formation together with cytology and neural markers.

Small round blue cell tumor: Diagnostic reasoning

Morphologic problem

- A primitive neuroblast population may resemble other childhood small round cell tumors.
- A blue-cell appearance alone does not specify lineage.
- Necrosis and mitoses do not uniquely establish neuroblastoma.

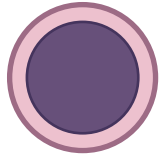
Source-supported resolution

- Search for neuropil and characteristic pseudorosettes.
- Use neural-lineage immunohistochemistry within a panel.
- Integrate site, patient age, imaging, and biochemical findings.

Immunophenotypic support

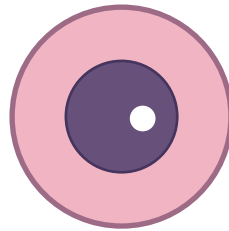
- PHOX2B: Useful transcription-factor marker for neuroblastic lineage.
- Neuron-specific enolase (NSE): Can also show positive immunoreactivity.
- Marker positivity must be interpreted in morphologic and clinical context.
- A diagnosis should not rest on one nonspecific stain.

Cytologic maturation: From neuroblast to ganglion cell



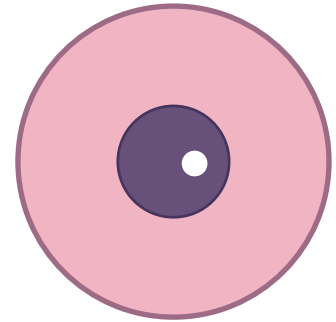
Primitive neuroblast

Dark nucleus; Minimal cytoplasm



Ganglion-like cell

Increased cytoplasm; Vesicular nucleus



Mature ganglion cell

Prominent nucleolus; Abundant cytoplasm

Schematic differentiation spectrum — not diagnostic histology

Ganglioneuroblastoma: The mixed phenotype

- Primitive neuroblasts are admixed with cells displaying ganglionic maturation.
- Maturing ganglion-like cells have more cytoplasm, vesicular nuclei, and nucleoli.
- The degree of differentiation may vary within a tumor.
- Maturation may occur spontaneously or after therapy.

Ganglioneuroma: Mature neural phenotype

- Predominance of cells resembling mature ganglion cells.
- No residual primitive neuroblast population in fully mature lesions, as.
- Prominent Schwannian stromal component.
- Typically clinically indolent compared with neuroblastoma.

Histologic clues across the spectrum

Neuroblastoma

Primitive small cells;
Fibrillary neuropil;
Pseudorosettes may be evident.

Ganglioneuroblastoma

Mixture of primitive neuroblasts and differentiating ganglion-like cells.

Ganglioneuroma

Ganglion cells with abundant cytoplasm embedded in Schwannian stroma.

This is an original teaching comparison, not a substitute for diagnostic microscopy.

Schwannian stroma: A prognostic clue

- Neuroblastic maturation is often accompanied by increasing Schwann cells.
- Presence of Schwannian stroma is linked to a more favorable outcome.
- Document stromal characteristics as part of morphologic assessment.
- Schwann cells are not simply interchangeable with neural tumor cells.

What is the origin of Schwann cells?

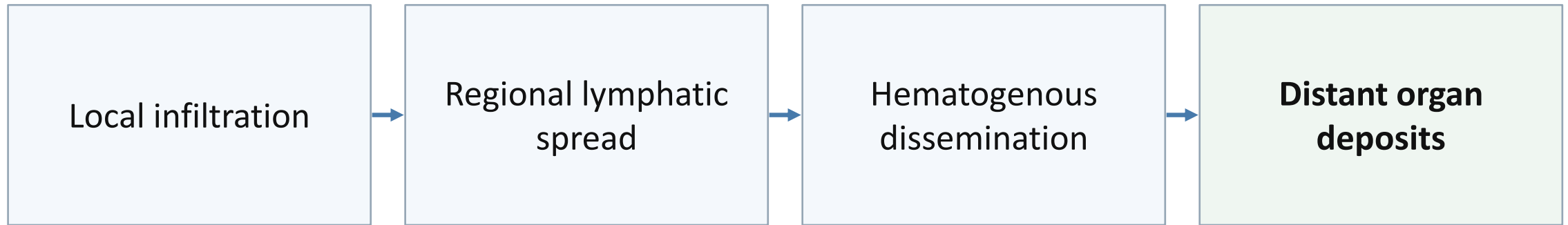
Reactive hypothesis

- One interpretation: Stromal Schwann cells are recruited non-neoplastic cells.
- The presence of stroma could reflect tumor-associated differentiation signals.

Clonal hypothesis

- Microdissection studies have identified shared genetic alterations with neuroblasts in some cases.
- At least a subset of Schwann cells may belong to the neoplastic clone.

Dissemination from a primary tumor



Metastatic spread may develop early and may involve multiple organ systems.

Common metastatic destinations

Bone and marrow

Bone pain and marrow involvement can dominate the presentation.

Liver

An important metastatic site, including in infants with stage MS.

Other sites

Lung, lymph nodes, and periorbital tissues may be involved.

Patterns of spread explain many clinical signs more directly than primary-tumor size.

Clinical presentation in very young children

- Large abdominal mass is a typical initial finding.
- Fever and weight loss may accompany the tumor.
- Infants can sometimes present with widespread yet biologically favorable disease.
- Clinical presentation alone cannot assign prognostic risk.

Clinical presentation in older children

- Metastatic symptoms may bring the disease to attention.
- Bone pain is a prominent manifestation of skeletal involvement.
- Respiratory or gastrointestinal complaints may accompany disseminated disease.
- The site and biological behavior of metastases must be assessed.

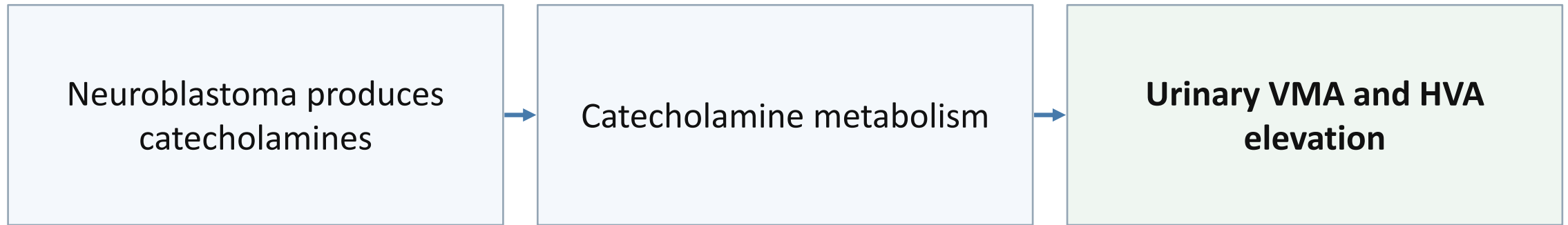
Periorbital metastases: A recognizable pattern

- Spread to periorbital tissues may cause proptosis.
- Associated ecchymoses can occur around the eyes.
- These findings indicate metastatic involvement rather than primary orbital origin.
- The clinical picture must be integrated with imaging and pathology.

Cutaneous metastases in neonates

- Disseminated neuroblastoma may produce multiple skin nodules.
- Deep blue discoloration is a characteristic clinical description.
- Metastatic skin involvement is included in the stage MS pattern when age and distribution meet criteria.
- Extent of spread must be staged precisely; Skin lesions alone do not define risk.

Catecholamine metabolism as a diagnostic signal



Catecholamine-related laboratory findings support evaluation of suspected neuroblastoma.

VMA and HVA: Clinical interpretation

- Approximately 90% of neuroblastomas produce catecholamines (textbook estimate).
- Urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) are useful metabolites.
- Biochemical evidence supports the diagnosis but does not establish stage or histologic subtype.
- Always interpret laboratory results alongside tumor imaging and tissue assessment.

Neuroblastoma versus pheochromocytoma

Neuroblastoma

- Neuroblastoma commonly synthesizes catecholamines.
- Catecholamine metabolites are useful diagnostic markers.
- Clinical hypertension is relatively infrequent.

Pheochromocytoma

- Pheochromocytoma is also catecholamine-producing.
- Hypertension is a more prominent feature in comparison.
- The clinical distinction cannot be made from catecholamine excess alone.

Clinical effects of ganglioneuroma

- May remain asymptomatic until discovered incidentally.
- Mass effect and compression are principal causes of symptoms.
- Clinical behavior differs from that of poorly differentiated neuroblastoma.
- Location remains relevant because compression can affect adjacent structures.

Why neuroblastoma prognosis is heterogeneous

- Spontaneous regression can occur in selected tumors.
- Other lesions behave aggressively despite multimodal therapy.
- Clinical stage, age, morphology, and genetics interact.
- Risk groups are constructed from multiple independent attributes.

From INSS to INRGSS

Historical INSS framework

- Earlier INSS stage was partly dependent on surgical resection.
- Extent of surgery can complicate pretreatment risk comparison.

Pretreatment INRGSS framework

- INRGSS uses imaging features before therapy.
- Image-defined risk factors (IDRFs) distinguish localized stages.
- Pretreatment staging helps communicate anatomic risk.

INRGSS: Four stage categories

L1

Localized tumor
confined to one body
compartment; No
image-defined risk
factors.

L2

Locoregional disease
with one or more
image-defined risk
factors.

M

Distant metastatic
disease except cases
qualifying as MS.

MS

Age <18 months;
Metastases limited to
skin, liver, and/or
marrow.

Stage is an anatomic descriptor, not by itself a complete biological risk group.

Stage L1: Localized, without an IDRF

- Disease is confined to one body compartment.
- The specified image-defined risk factors are absent.
- L1 describes pretreatment imaging rather than completeness of resection.
- Absent IDRFs generally simplifies anatomic surgical assessment.

Stage L2: Locoregional, with an IDRF

- One or more recognized imaging-defined risk factors are present.
- Vascular encasement, organ infiltration, or intraspinal extension may contribute.
- L2 is not synonymous with distant metastasis.
- L2 is distinguished from L1 by pretreatment imaging anatomy.

Stage M: Distant metastatic disease

- Distant metastasis is the defining feature.
- Patients who meet the special MS criteria are excluded from M.
- Organ involvement should be recorded explicitly.
- Stage M enters prognosis together with age, MYCN, histology, and ploidy.

Stage MS: A distinctive infant presentation

- Children must be younger than 18 months.
- Metastatic deposits are confined to skin, liver, and/or bone marrow.
- The age and metastatic distribution restrictions are both required.
- A subset may undergo spontaneous tumor regression.

IDRFs: A structured imaging concept

Vascular

Encasement of named critical arteries or veins.

Airway / neural

Airway compression;
Brachial plexus or spinal canal relationships.

Organ / compartment

Infiltration of organs or extension across specified compartments.

Risk is determined by defined radiologic relationships, not merely primary-tumor diameter.

Image-defined risk factors: Neck and thorax

- Neck: Encasement of carotid or vertebral artery or internal jugular vein; Skull-base extension.
- Cervicothoracic junction: Brachial plexus roots or subclavian vessels may be encased.
- Tracheal compression is an IDRF at relevant levels.
- Thorax: Aortic involvement or major-bronchus compression are examples.

Image-defined risk factors: Abdominal region

- Encasement of the aorta or inferior vena cava.
- Involvement of celiac-axis origin or superior mesenteric arterial branches.
- Invasion of one or both renal pedicles.
- Porta hepatis or hepatoduodenal ligament infiltration.

Image-defined risk factors: Pelvis and spine

- Encasement of iliac vessels and pelvic extension across the sciatic notch.
- Intraspinal extension is relevant when more than one-third of the canal is invaded.
- Loss of visible perimedullary leptomeningeal spaces is another criterion.
- An abnormal spinal-cord signal also qualifies under the textbook table.

IDRFs versus findings to record

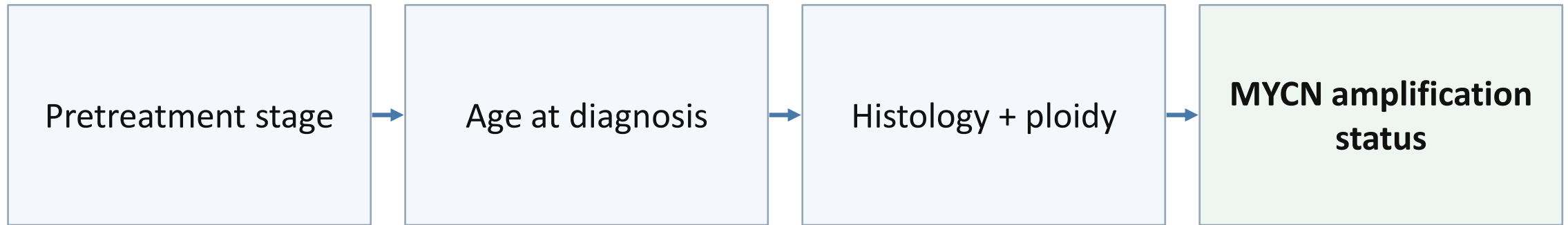
Image-defined risk factors

- Vascular encasement in designated anatomical regions.
- Named adjacent-organ infiltration.
- Qualifying intraspinal tumor extension.

Recorded; Not classified as IDRFs

- Multifocal primary tumors.
- Pleural effusion with or without malignant cells.
- Ascites with or without malignant cells.

Risk assignment: Multiple dimensions



A biologically high-risk tumor can emerge even when stage alone looks favorable.

Age 18 months: A prognostic threshold

- 18 months as a clinically important prognostic divider.
- Younger patients typically have a more favorable outcome.
- Age effects are interpreted together with metastatic burden and tumor biology.
- The age criterion for stage MS and age-related prognostic tendencies are related but distinct.

Why stage MS is biologically unusual

- Distant disease may coexist with favorable clinical behavior in eligible infants.
- Tumors can regress spontaneously without parallel behavior in most older patients.
- The biological mechanism underlying this regression is unresolved.
- The favorable pattern must not be generalized to all metastatic neuroblastomas.

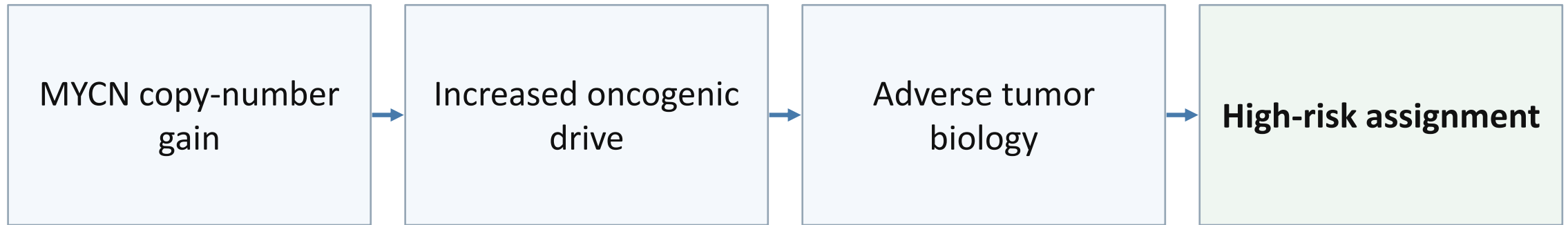
Histologic prognostic features

- Schwannian stromal development signals greater differentiation.
- Ganglion-cell maturation is generally associated with favorable behavior.
- Mitotic and karyorrhectic activity provide measures of tumor proliferation and cell turnover.
- Morphologic features are integrated with age-based classification.

Mitosis–karyorrhexis index (MKI)

- MKI counts mitotic and karyorrhectic tumor cells in a sample of 5,000 tumor cells.
- High MKI reflects brisk proliferation and nuclear breakdown.
- Higher MKI with less favorable histologic prognosis.
- Interpret thresholds only in the correct age-linked histologic grading framework.

MYCN amplification: Why it matters



Amplification may override otherwise favorable age, stage, or histology.

MYCN: Source-derived molecular facts

- MYCN locus is located on chromosome 2p24.
- Amplification occurs in approximately 20% of primary tumors.
- The alteration is frequent in advanced-stage disease.
- MYCN amplification is a central genetic criterion in clinical risk stratification.

MYCN amplification: Cytogenetic forms

Native locus

MYCN maps to distal chromosome 2p (2p24).

Double minutes

Amplified DNA may appear as extrachromosomal double-minute elements.

HSR

Amplification may be present as homogeneously staining regions on other chromosomes.

The site of gene origin is distinct from the cytogenetic position of amplified copies.

MYCN and otherwise favorable disease

- MYCN amplification can occur despite localized disease or younger patient age.
- The presence of amplification changes expected clinical risk substantially.
- Risk assessment should not infer favorable biology from stage alone.
- MYCN assessment is fundamental to a complete neuroblastoma evaluation.

DNA content and chromosomal architecture

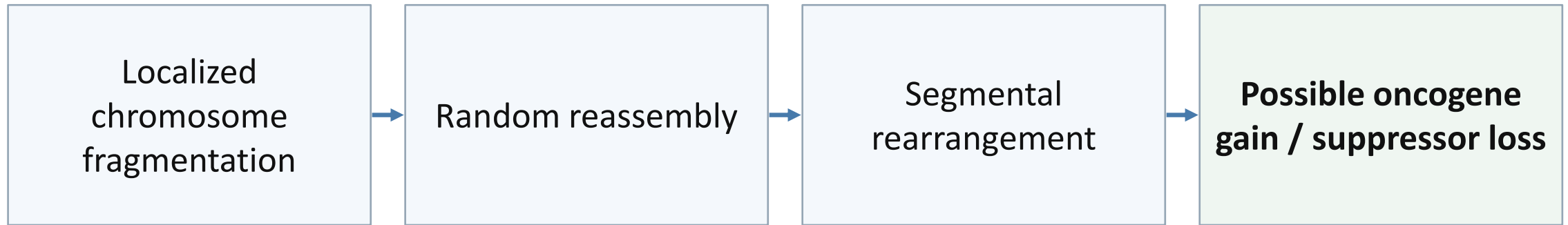
Whole-chromosome gain

- Hyperdiploidy with whole-chromosome gains.
- Tends to be more favorable in young children.
- May reflect errors in chromosomal segregation.

Segmental chromosomal instability

- Near-diploid tumors with multiple segmental aberrations.
- Complex genomic changes are linked to more aggressive behavior.
- Chromothripsis is one possible form of segmental genomic damage.

Chromothripsis: A catastrophic rearrangement



In some neuroblastomas, chromothripsis contributes to complex copy-number changes.

Chromosome 1p36 loss

- Hemizygous deletion of distal chromosome 1p36 occurs in a subset of primary tumors.
- Approximately 25%–35% of primaries with 1p loss.
- Correlates with MYCN amplification and advanced-stage disease.
- Associated with increased risk of relapse.

Chromosome 11q loss

- Another relatively common segmental chromosomal deletion.
- Associated with adverse prognosis.
- Unlike 1p loss, it does not correlate closely with MYCN amplification.
- Distinct genomic alterations can mark distinct adverse biological pathways.

Additional biology highlighted

Variable	Favorable association	Unfavorable association
TRK receptor expression	TRKA present	TRKB present
Schwannian stroma	Greater differentiation	Poor stromal development
Chromosome 1p	Loss absent	Loss present
Chromosome 11q	Loss absent	Loss present
DNA content	Hyperdiploid gains	Near-diploid / segmental changes

Neuritogenesis and altered differentiation

- Neuritogenesis is part of neuronal differentiation and includes neurite outgrowth.
- ATRX, ARID1A, ARID1B, and NTRK-family genes as altered in subsets.
- Alterations can involve chromatin regulation or neurotrophin signaling.
- The clinical prognostic significance of these changes continues to be investigated.

Investigational differentiation therapy

- Retinoids are discussed as an adjunct strategy to promote neuroblastoma differentiation.
- Retinoic-acid signaling participates in embryonic cell maturation.
- The pathology rationale is to shift tumor cells toward a more differentiated state.
- The source presents this as a therapeutic strategy, not a universal cure.

ALK-directed therapy: Biologic rationale

- Activating ALK alterations create a defined therapeutic target.
- Clinical evaluation of small-molecule ALK inhibitors.
- Molecularly selected therapy is not interchangeable with unselected treatment.
- No regimen, response rate, or current guideline recommendation is inferred here.

Integrated neuroblastoma prognostic framework

Dimension	Favorable pattern	Unfavorable pattern
Age	Younger than 18 months	Older age
Stage	L1; Selected MS	M; Risk-defining L2 findings
Histology	Schwannian stroma / maturation	Primitive, high-turnover pattern
MYCN	Not amplified	Amplified
Ploidy	Hyperdiploid whole gains	Segmental aberrations / near-diploid

Case discussion: Infant with unusual dissemination

A 10-month-old infant has an abdominal sympathetic-chain primary and deposits limited to the skin and liver.

Questions

- Which INRGSS stage should be considered?
- What makes the expected clinical behavior potentially unusual?

Discussion: The distribution meets the anatomic pattern of stage MS if all formal conditions are satisfied; Spontaneous regression is possible.

Case discussion: Molecular override

An infant has localized neuroblastoma with otherwise favorable features. Molecular testing demonstrates MYCN amplification.

Questions

- Which feature changes risk most importantly?
- Why is early age not sufficient reassurance?

Discussion: MYCN amplification is adverse and can override an otherwise favorable clinical profile.

Case discussion: An imaging-defined risk factor

A 3-year-old child has a locoregional abdominal neuroblastoma encasing the superior mesenteric artery at its origin, without distant disease.

Questions

- Would a localized label alone justify stage L1?
- Which feature places the primary in L2?

Discussion: Specified vascular encasement is an IDRF, supporting locoregional stage L2.

Case discussion: A differentiated tumor

A paravertebral mass contains mature ganglion-like cells and numerous spindle-shaped Schwann cells, without primitive neuroblasts.

Questions

- Which tumor category best fits these features?
- What symptoms may arise despite mature morphology?

Discussion: Ganglioneuroma; Symptoms may result from compression or mass effect.

Integrated diagnostic approach

- Recognize the clinical syndrome and locate the primary tumor by imaging.
- Characterize pretreatment anatomy and determine presence or absence of IDRFs.
- Use morphology, neuropil, and neuroblastic immunophenotype to establish lineage.
- Assess catecholamine metabolites and tumor biology for diagnostic and risk context.
- Combine stage, age, histology, MYCN, and ploidy rather than interpreting one variable alone.

Essential clinicopathologic synthesis

- Neuroblastic tumors derive from sympathetic neural crest lineage.
- Neuropil and Homer–Wright pseudorosettes are characteristic neuroblastoma clues.
- Maturation toward ganglion cells and Schwannian stroma is generally favorable.
- INRGSS is pretreatment, imaging-based; Age and molecular features refine risk.
- MYCN amplification remains a major adverse prognostic indicator.

References and image-source limitations

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Chapter 10, pp. 434–437.
- Source staging table: Monclair T, Brodeur GM, Ambros PF, et al. J Clin Oncol. 2009;27:298 (as cited by Robbins).
- Histologic morphology in this presentation is conveyed through original editable schematics, not photomicrographs.
- Original chapter PDF and copyright-cleared embedded photomicrographs were unavailable for this build.