

Olfactory Neuroblastoma

Morphology, diagnostic reasoning and clinicopathologic correlation

Head and neck pathology

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Learning outcomes

- Localize the typical anatomic origin and connect site to presenting symptoms.
- Recognize characteristic lobular small-round-cell morphology and neurofibrillary stroma.
- Construct a defensible immunohistochemical and differential-diagnostic approach.
- Distinguish tumor grade from anatomic extent and interpret outcome variability.

Site / symptoms

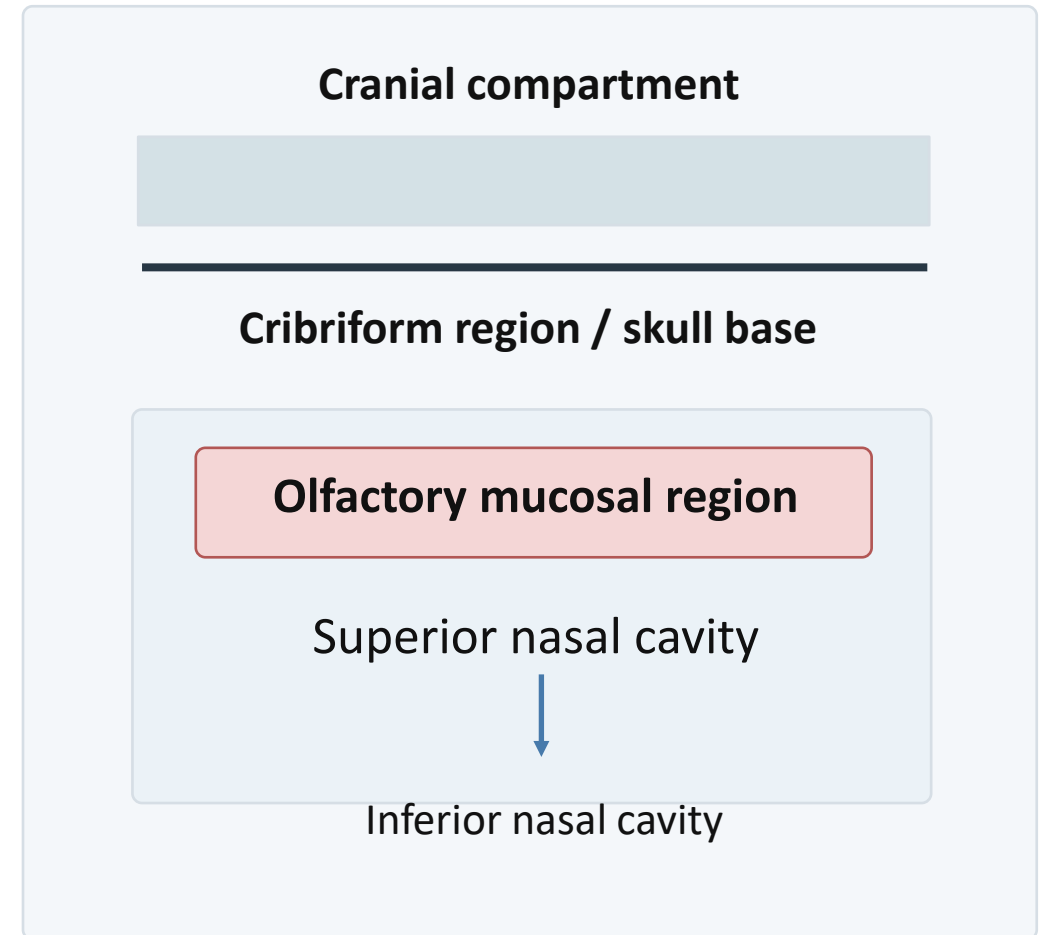
Morphologic pattern

IHC and mimics

Grade / stage / outcome

A sinonasal neuroectodermal neoplasm

- Olfactory neuroblastoma is a malignant neoplasm associated with specialized olfactory mucosa.
- Robbins locates its origin particularly near the superior nasal cavity and cribriform plate.
- Neural and neuroendocrine differentiation informs its microscopic and immunophenotypic profile.



Terminology: Two names, one entity

- Olfactory neuroblastoma and esthesioneuroblastoma are alternative names for the same lesion.
- The term describes its olfactory-region association and primitive neural phenotype.
- Do not assume a tumor is olfactory neuroblastoma from the name “neuroblastoma” alone.

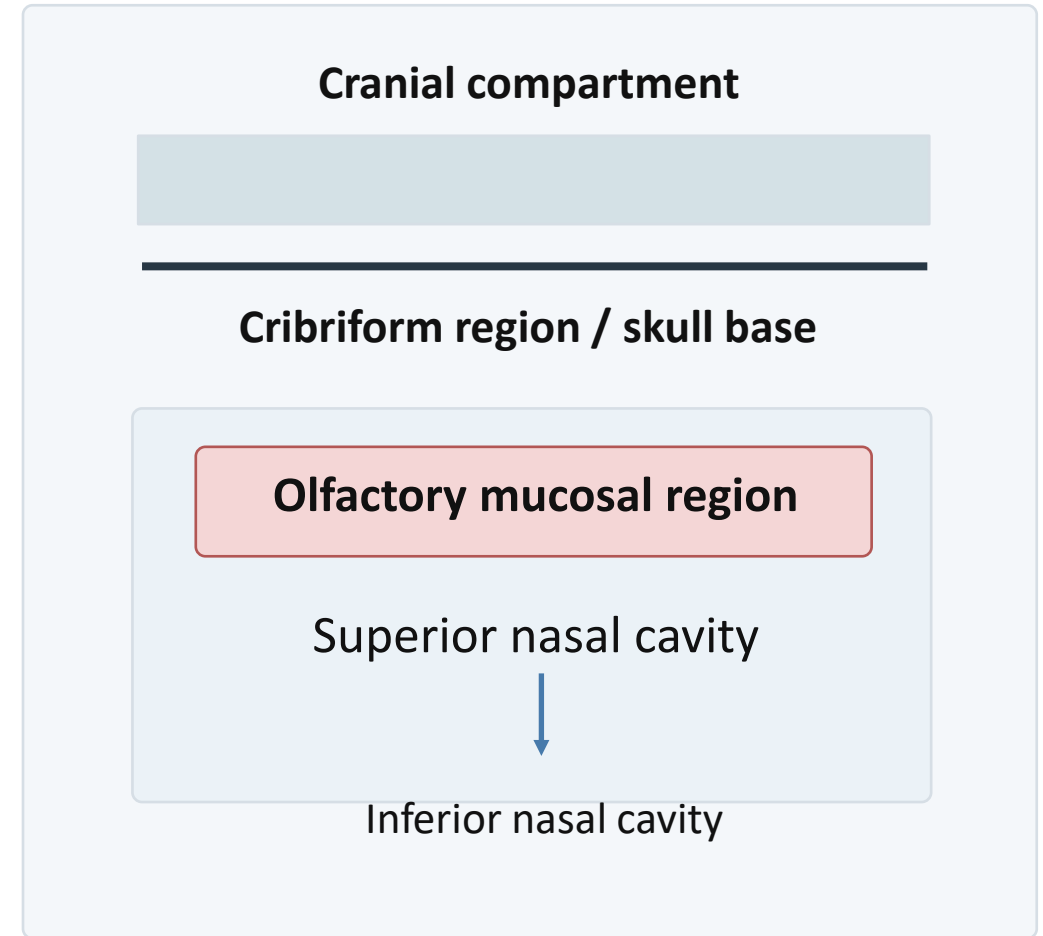
Olfactory neuroblastoma

=

Esthesioneuroblastoma

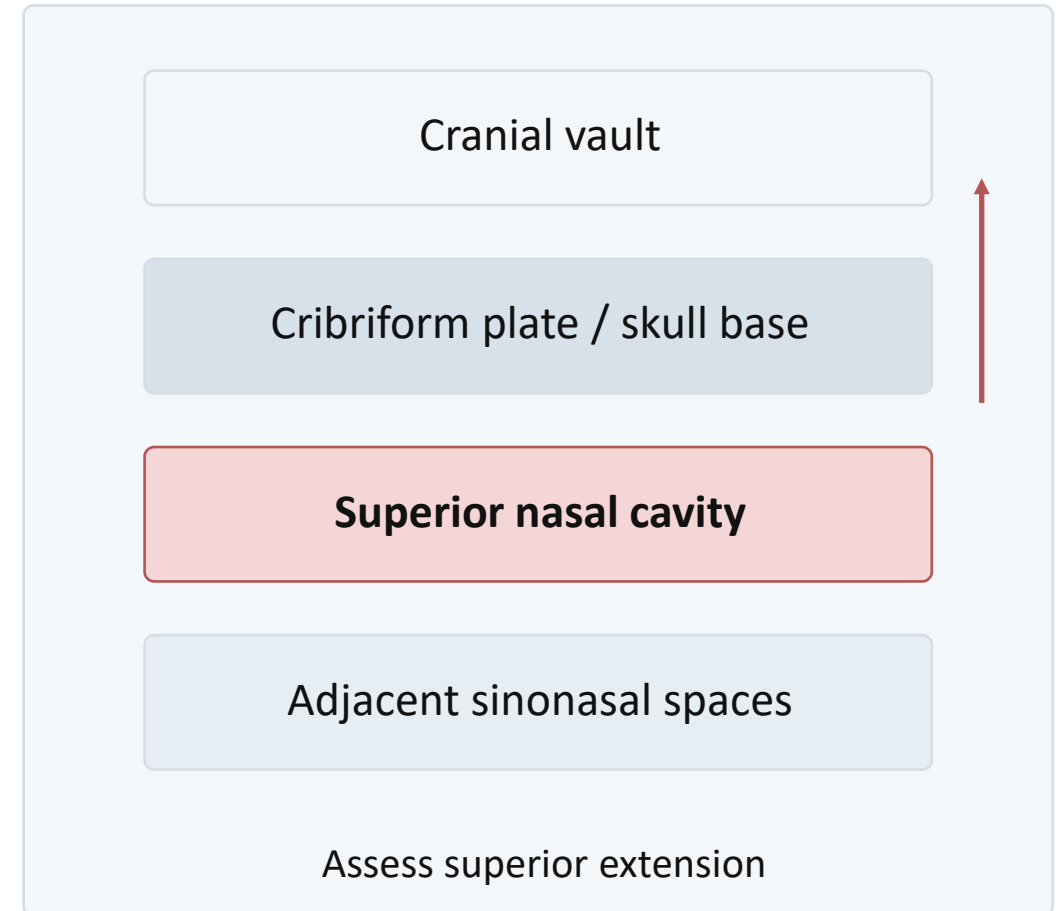
Olfactory mucosa is the site of origin

- The source identifies neuroectodermal olfactory cells within the nasal mucosa.
- Its superior location explains why the cribriform plate must be considered.
- Anatomic localization is an input to diagnosis; Histology and IHC must still agree.



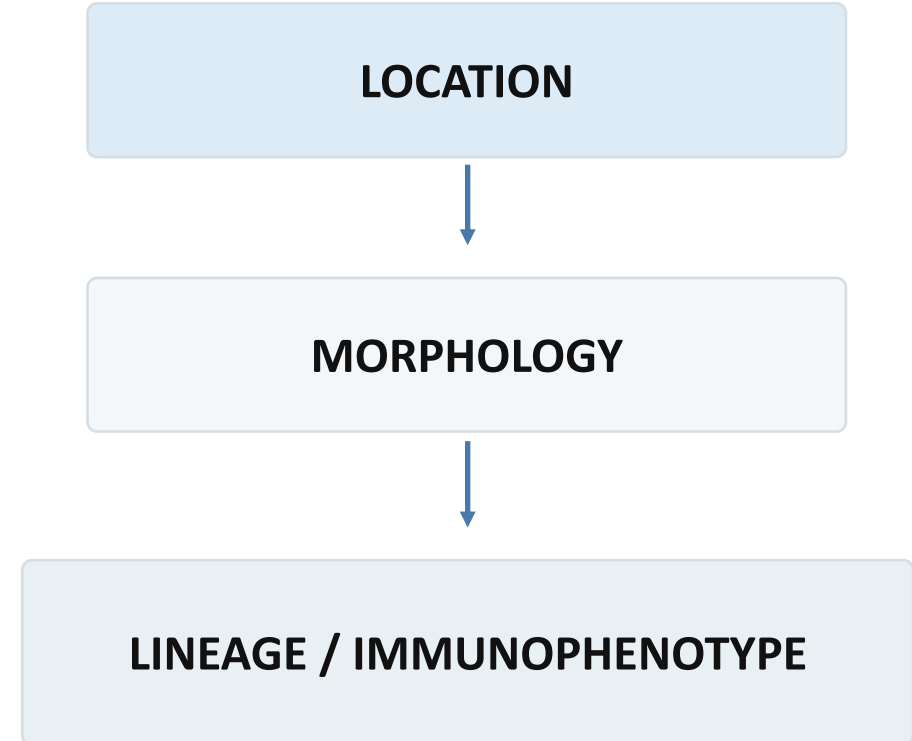
Why the cribriform plate matters

- It forms the superior boundary of the nasal cavity near the olfactory region.
- Tumor proximity creates a potential route for skull-base and intracranial extension.
- Assessment of local extent therefore requires more than inspection of the nasal lumen.



Anatomic diagnosis starts with location

- A superior nasal cavity lesion is anatomically compatible with olfactory neuroblastoma.
- Site is a clue, not a substitute for determining differentiation and lineage.
- The diagnostic record should preserve the mass location and its relationship to the skull base.

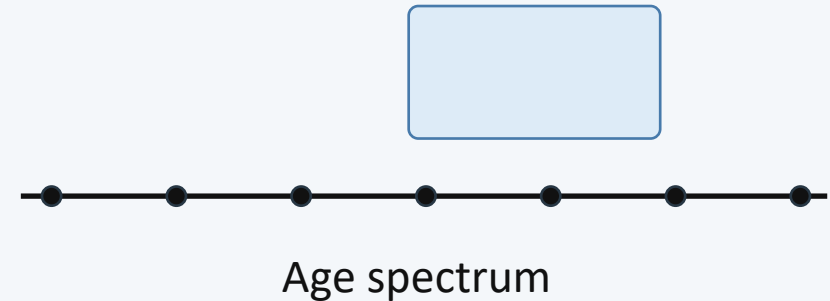


Age distribution is broad

- Cases can occur at any age.
- A peak during the fifth and sixth decades.
- Patient age alone cannot establish or exclude the diagnosis.

Can occur at any age

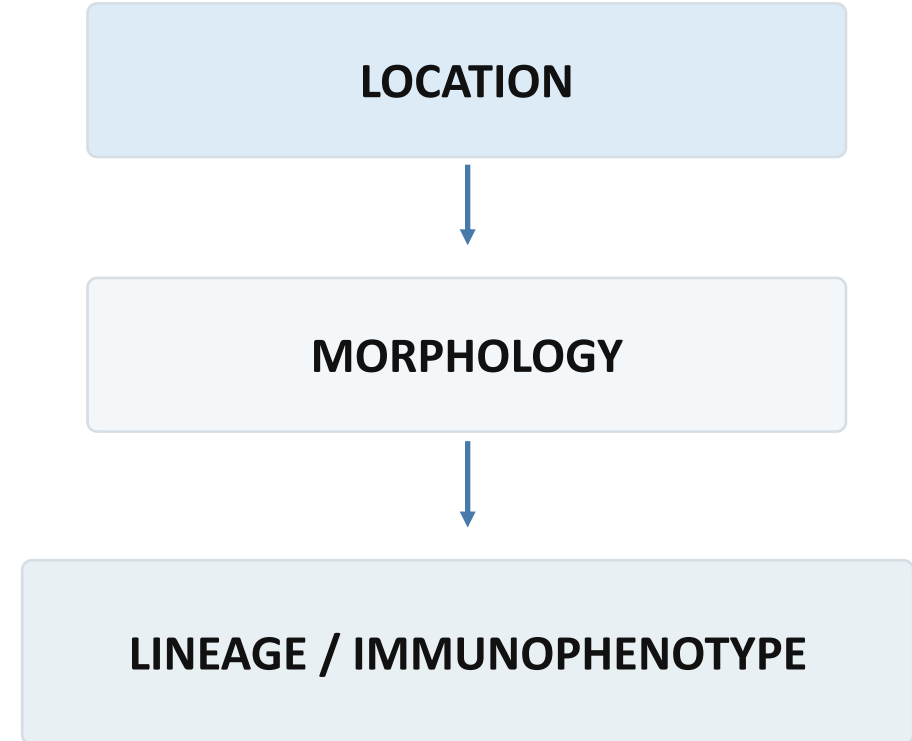
Peak: 5th–6th decades



Qualitative distribution — no incidence histogram

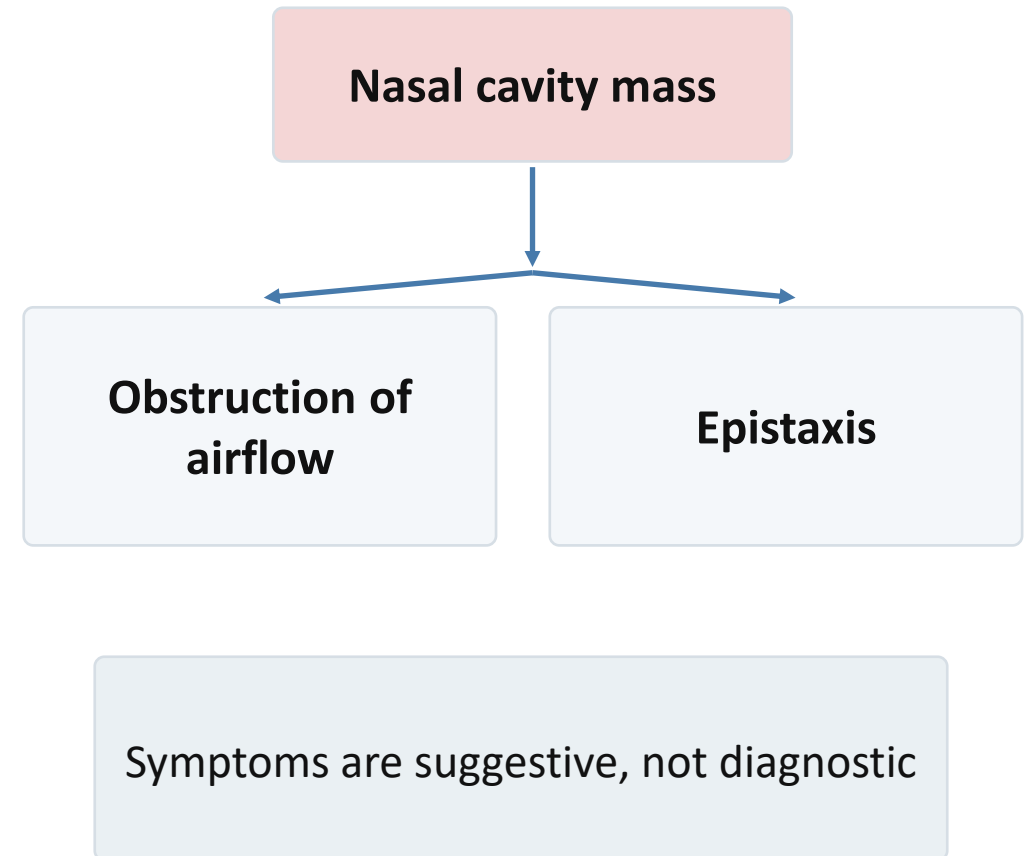
Epidemiology: An interpretive caution

- A typical age range is useful for clinical suspicion, not a deterministic cutoff.
- An unusual patient age should broaden the differential rather than end the workup.
- The relevant diagnostic evidence remains location, morphology and differentiation.



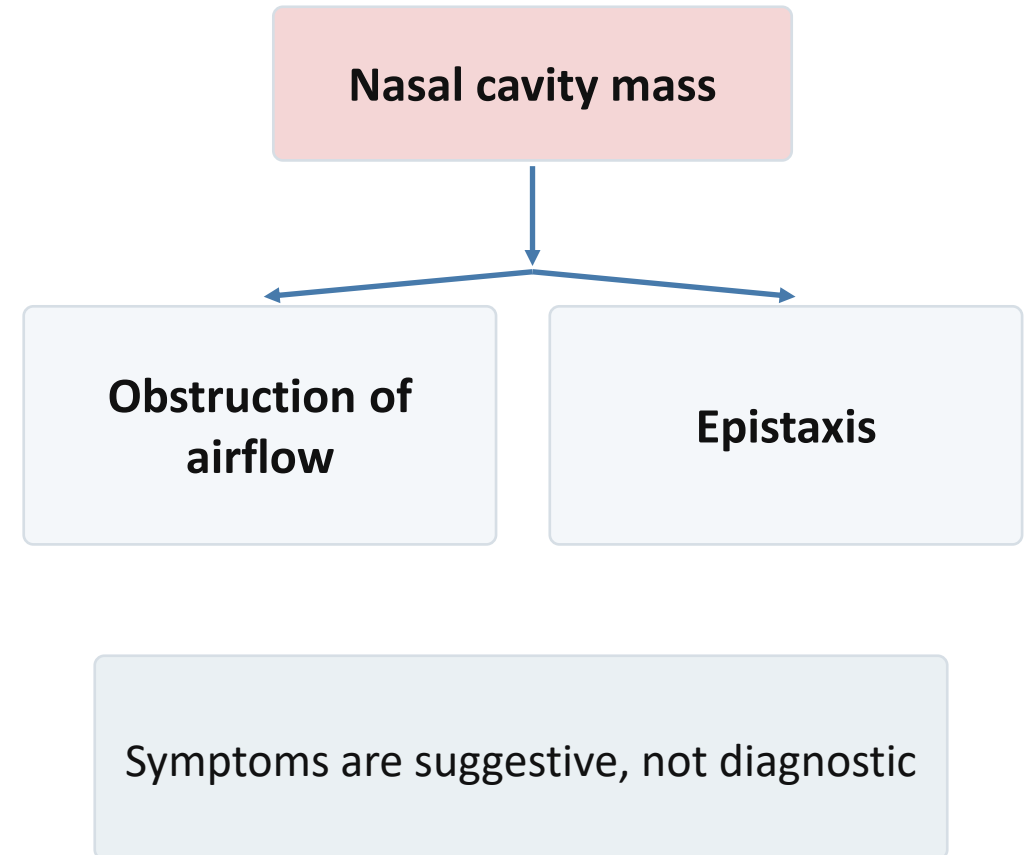
Two common presenting symptoms

- Nasal obstruction is a typical presentation.
- Epistaxis is another typical presentation.
- Neither symptom is specific to this tumor; Each requires contextual evaluation.



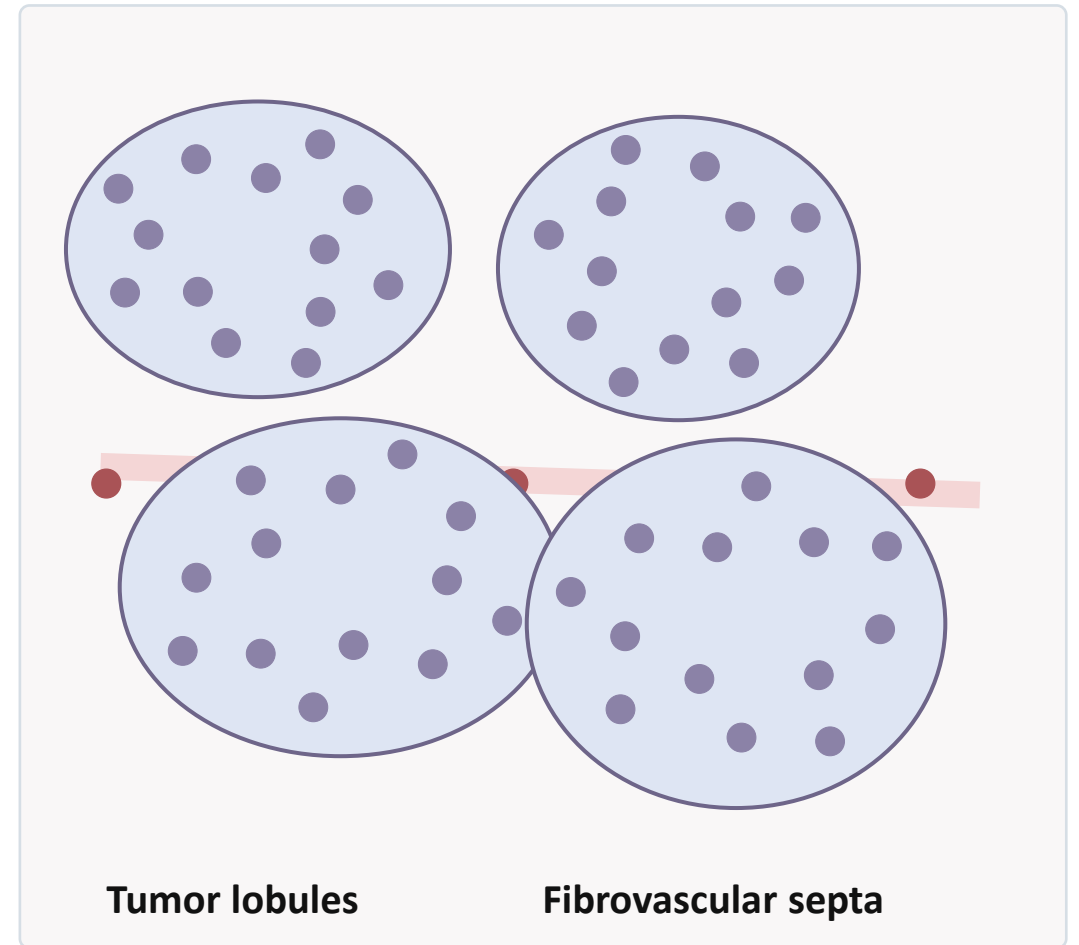
Obstruction reflects local tumor mass

- A space-occupying lesion in the nasal cavity narrows the airway.
- The obstruction can resemble symptoms caused by non-neoplastic sinonasal lesions.
- Anatomic examination and tissue sampling are needed to resolve the cause.



Epistaxis reflects a vascular environment

- Fibrovascular stroma within the tumor.
- A nasal mass with bleeding may therefore be consistent with this phenotype.
- Epistaxis is not uniquely diagnostic: Other vascular and epithelial lesions can bleed.



Schematic cellular architecture — not a micrograph

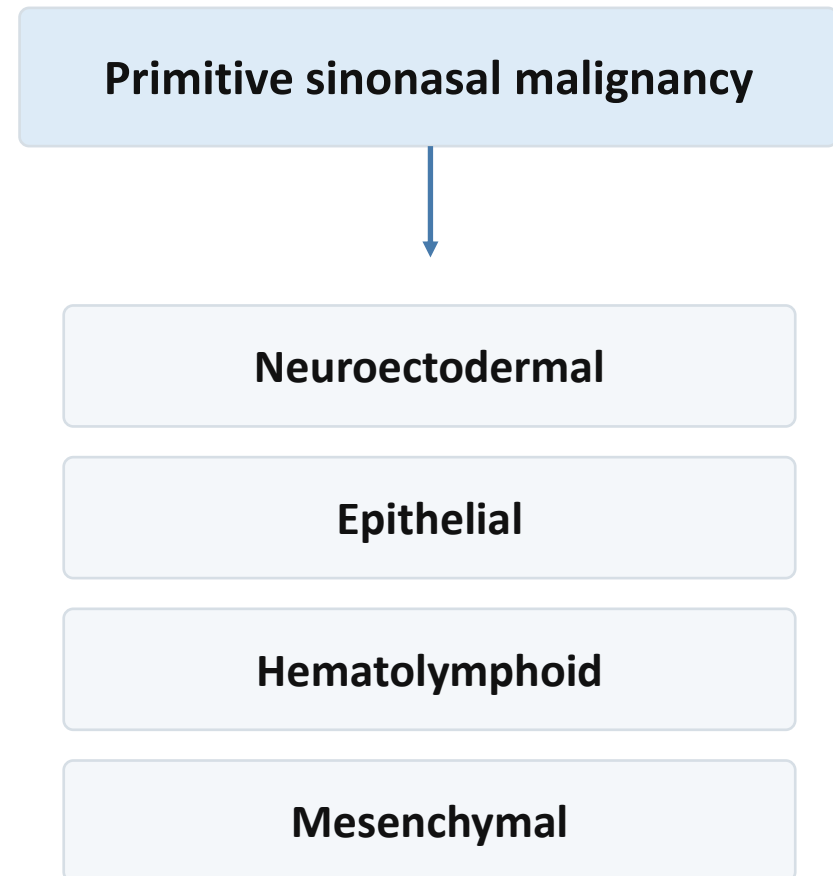
Opening clinical problem

An adult has persistent unilateral nasal obstruction and episodic epistaxis. Imaging demonstrates an upper nasal cavity mass.

Which features would support olfactory neuroblastoma, and what competing tumors must be excluded?

Initial diagnostic question: What lineage?

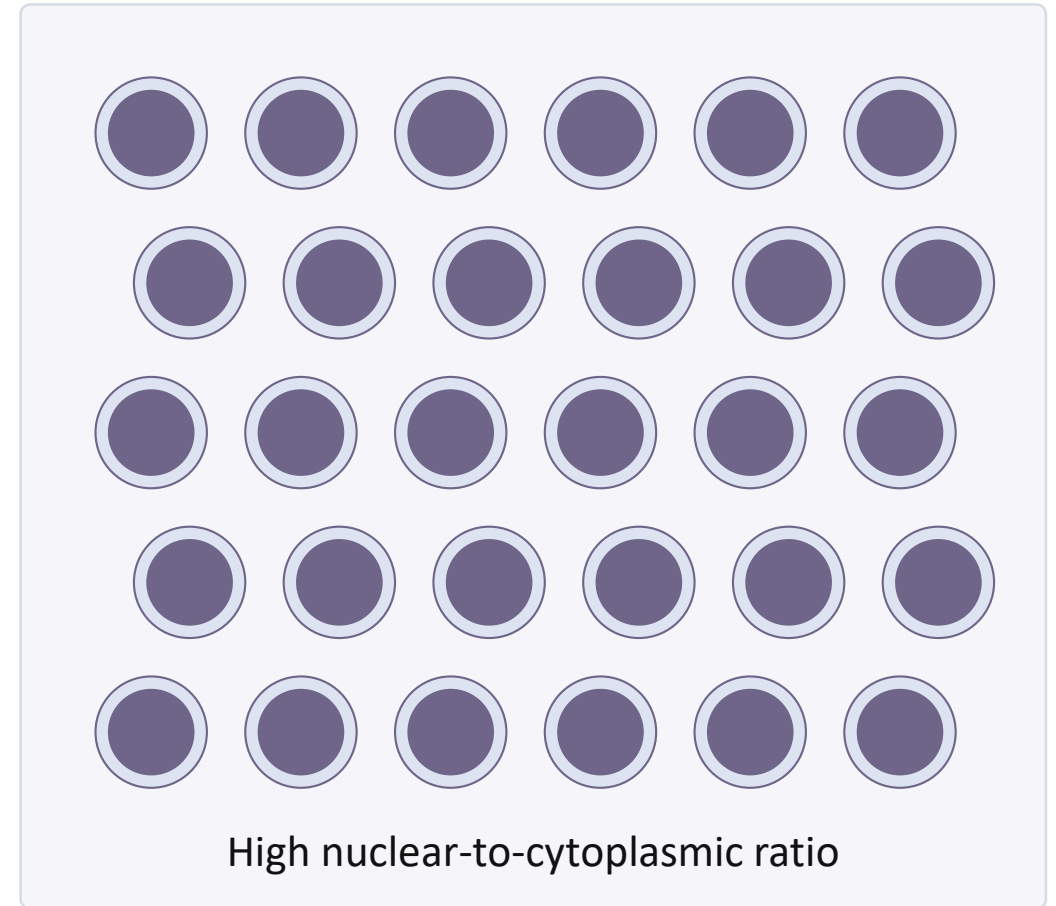
- Establish whether the sampled lesion is neuroectodermal, epithelial, hematolymphoid or mesenchymal.
- Avoid final classification based on symptoms and a small round blue cell morphology alone.
- Use anatomy, architecture and a targeted immunohistochemical panel together.



Work from morphology to lineage-specific evidence

The small-round-blue-cell family

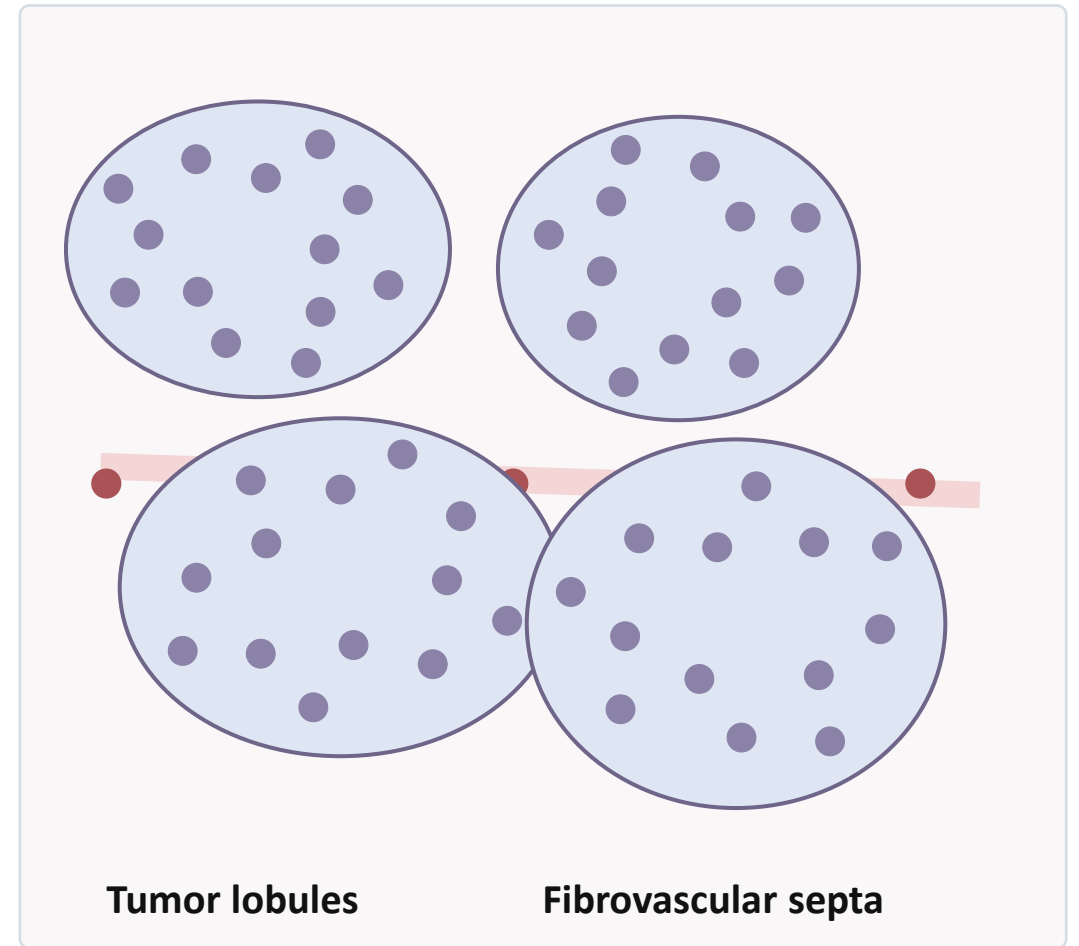
- Olfactory neuroblastoma in the small round blue cell category.
- Morphologic mimics listed include lymphoma, small cell carcinoma, Ewing sarcoma and rhabdomyosarcoma.
- Shared cytologic resemblance creates a diagnostic problem, not a unified lineage.



Stylized small round cells — not histologic evidence

Architecture is more informative than color

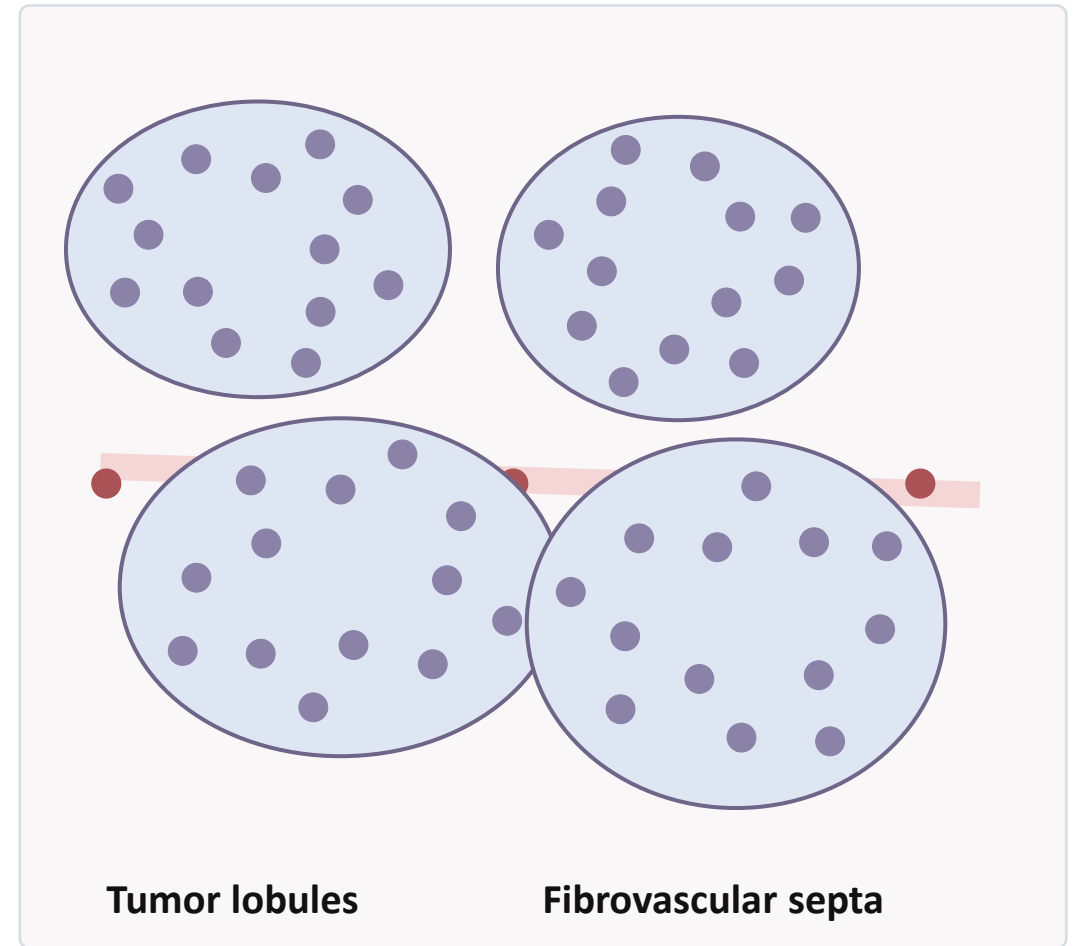
- A low-power survey looks for well-circumscribed nests and lobules.
- These groups are separated by fibrovascular stroma.
- Pattern recognition at low magnification precedes cytologic refinement.



Schematic cellular architecture — not a micrograph

Typical nests and lobules

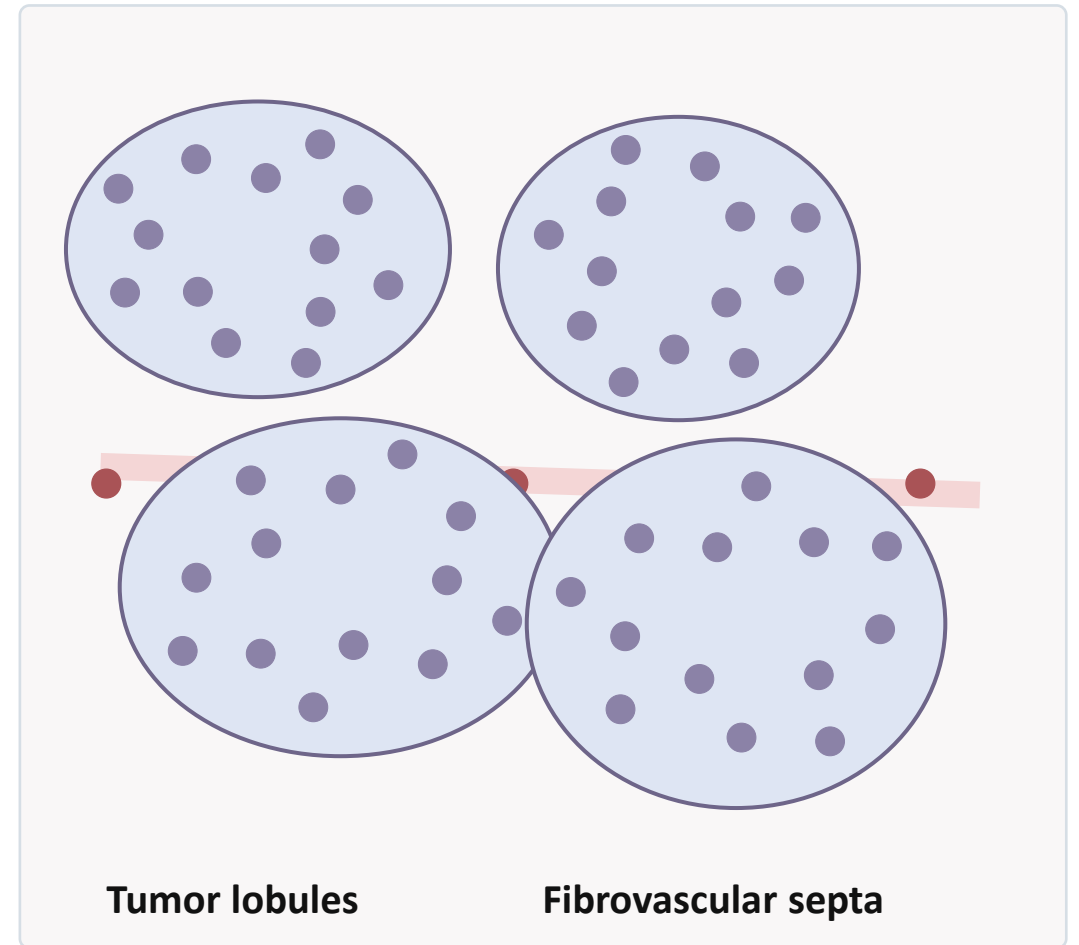
- The neoplastic cells form discrete cohesive appearing aggregates.
- Stromal septa delineate boundaries between lobules.
- Atypical or high-grade examples may lose portions of this organized pattern.



Schematic cellular architecture — not a micrograph

Fibrovascular stroma defines the spaces

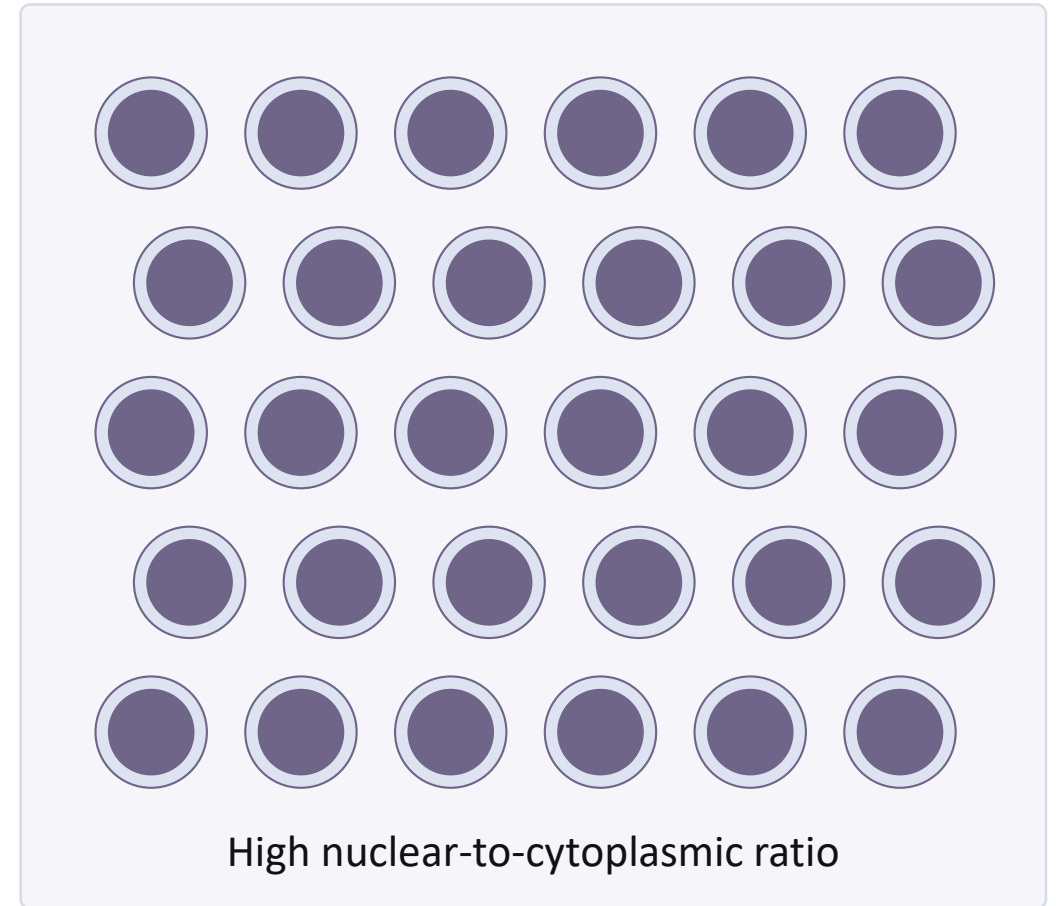
- Connective tissue separates tumor nests rather than forming a diffuse cellular sheet.
- Vascular channels may be evident within intervening stroma.
- Assess both neoplastic cell islands and their intervening background.



Schematic cellular architecture — not a micrograph

Nuclear appearance in typical tumors

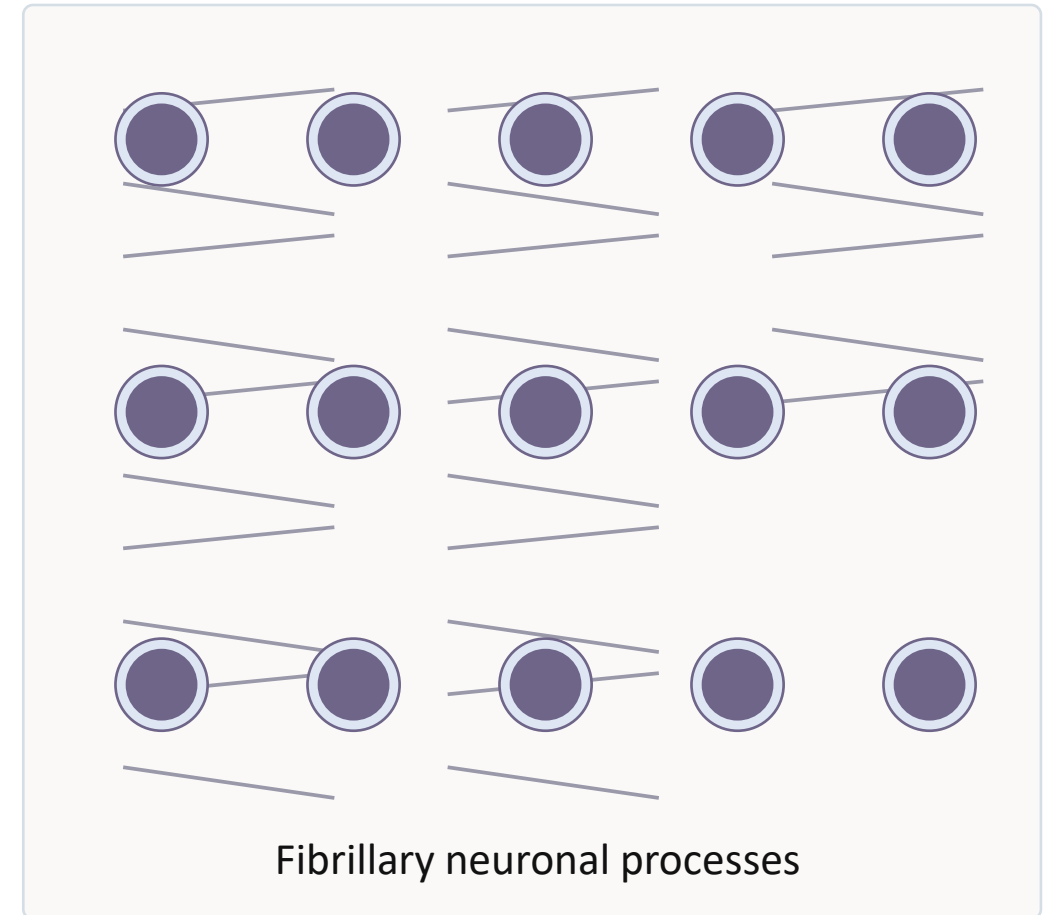
- Tumor cells are relatively monotonous and small at conventional H&E review.
- The blue-cell appearance principally reflects densely staining nuclei.
- Low-grade examples often have relatively uniform, stippled nuclear chromatin.



Stylized small round cells — not histologic evidence

Neurofibrillary stroma is diagnostically valuable

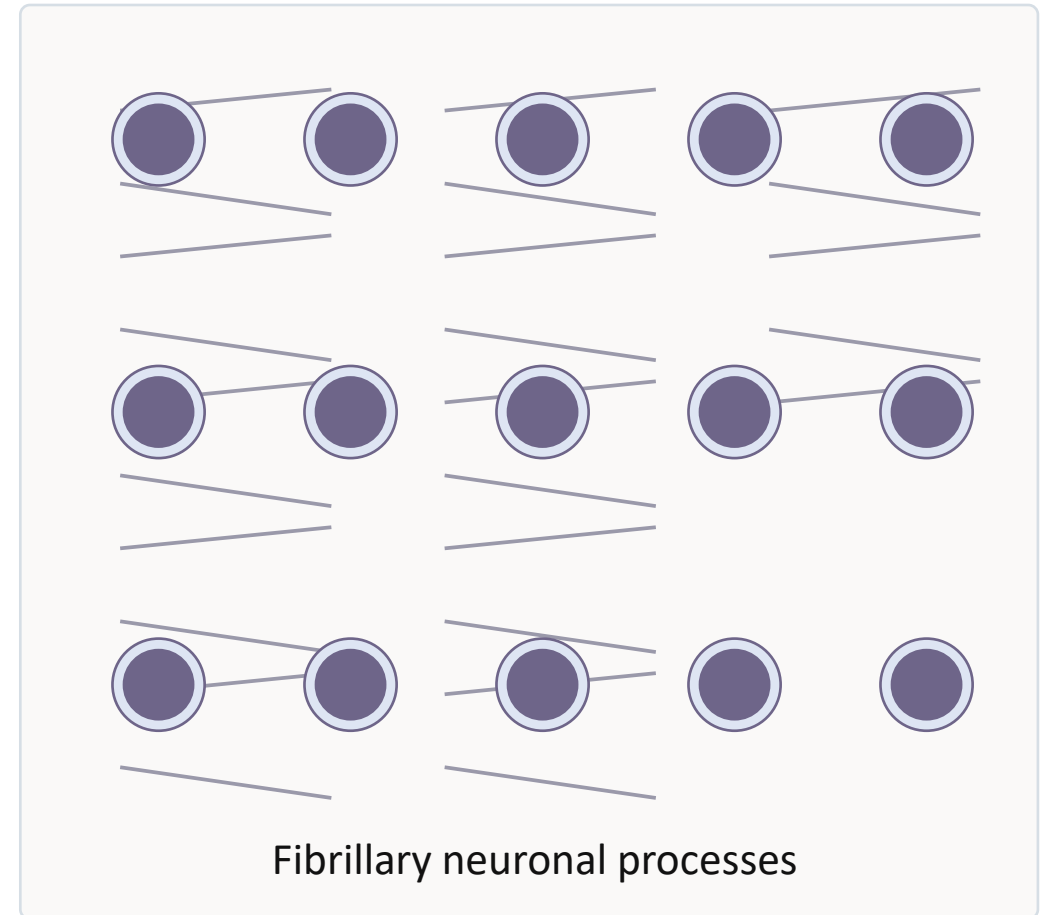
- The fibrillary background represents tangled neuronal cell processes.
- It differs conceptually from ordinary connective-tissue septa.
- Its presence adds evidence of neural differentiation beyond cell shape alone.



Neurofibrillary matrix schematic — not H&E

Reading the fibrillary matrix

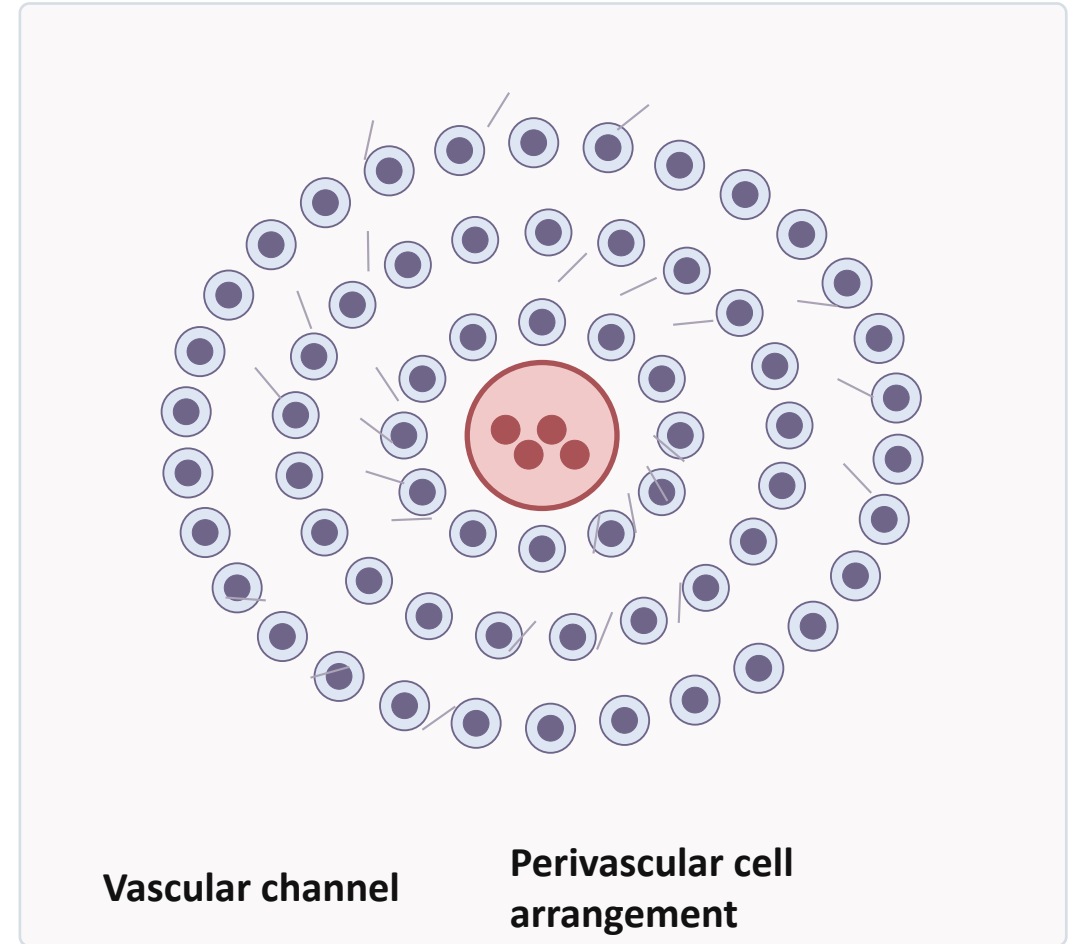
- Search for delicate fibrillary material between or around tumor cells.
- Distinguish this background from pale fibrovascular septa and processing artifacts.
- High-grade lesions may have less recognizable neuropil, increasing diagnostic difficulty.



Neurofibrillary matrix schematic — not H&E

Source figure: A verbal reconstruction

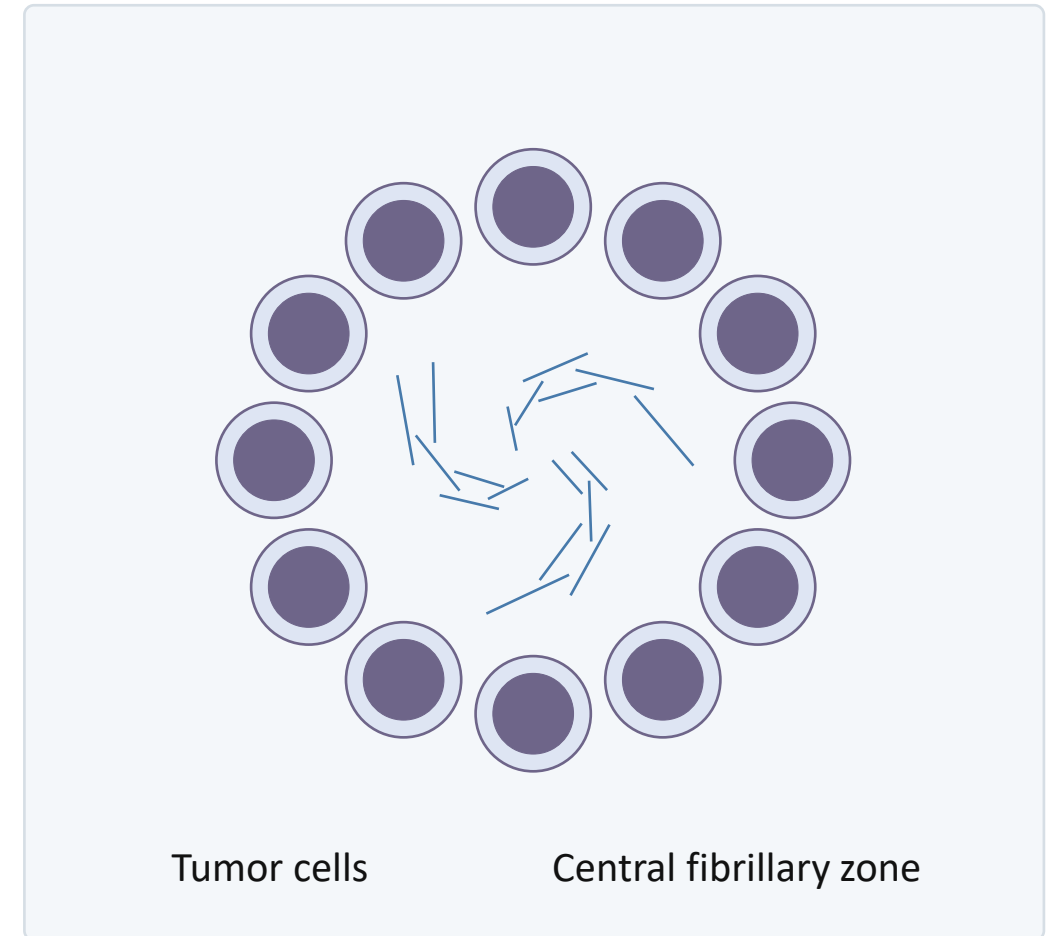
- Robbins Figure 16.13 describes small monotonous round cells.
- An eosinophilic fibrillary stroma surrounds the cells.
- The cells appear to swirl around a blood-filled vascular channel.



Original schema of textual figure description — not H&E

Rosettes: An additional histologic clue

- Some tumors form neuroblastic rosette-like arrangements.
- A pseudorosette can organize tumor cells around a fibrillary central zone.
- Rosettes support a neuroblastic pattern but are not exclusive to this entity.



Rosette/pseudorosette concept — not a micrograph

Recognizing atypical morphology

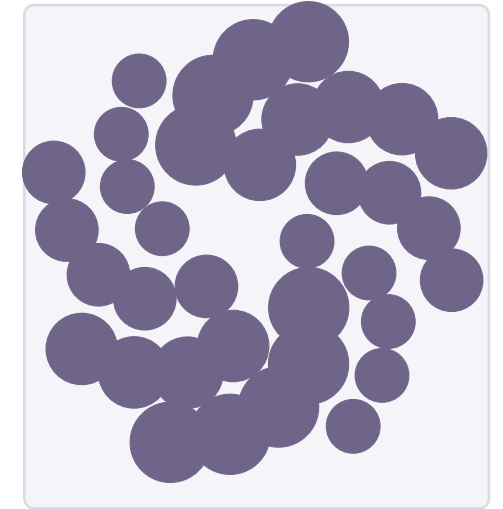
- The classic lobular/neurofibrillary phenotype is easiest to recognize in lower-grade areas.
- Atypia, necrosis and increased mitoses complicate high-grade interpretation.
- A small biopsy may not represent the highest-grade component of a heterogeneous tumor.

**Lower-grade
appearance**



More lobular/neuropil

**Higher-grade
appearance**

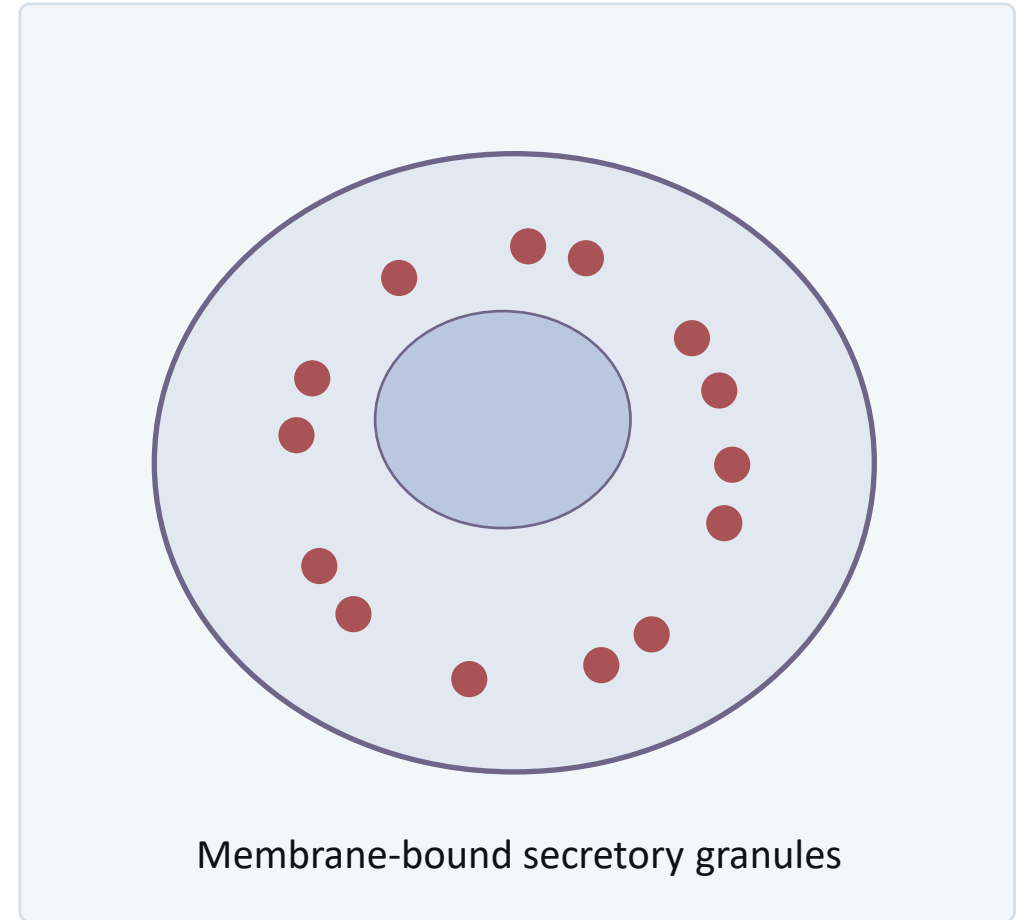


More atypia/necrosis

Qualitative contrast only — not grading specimens

Ultrastructure supports secretory differentiation

- Membrane-bound secretory granules on electron microscopy.
- Such granules are consistent with neuroendocrine differentiation.
- Modern diagnosis generally integrates morphology and IHC; Ultrastructure is corroborative.



Cell ultrastructure schematic — not electron microscopy

Four markers emphasized

- Synaptophysin and chromogranin demonstrate neuroendocrine-associated proteins.
- INSM1 and CD56 provide additional evidence of neuroendocrine differentiation.
- Positive staining is interpreted alongside architecture, site and exclusion of mimics.

Synaptophysin

Chromogranin

INSM1

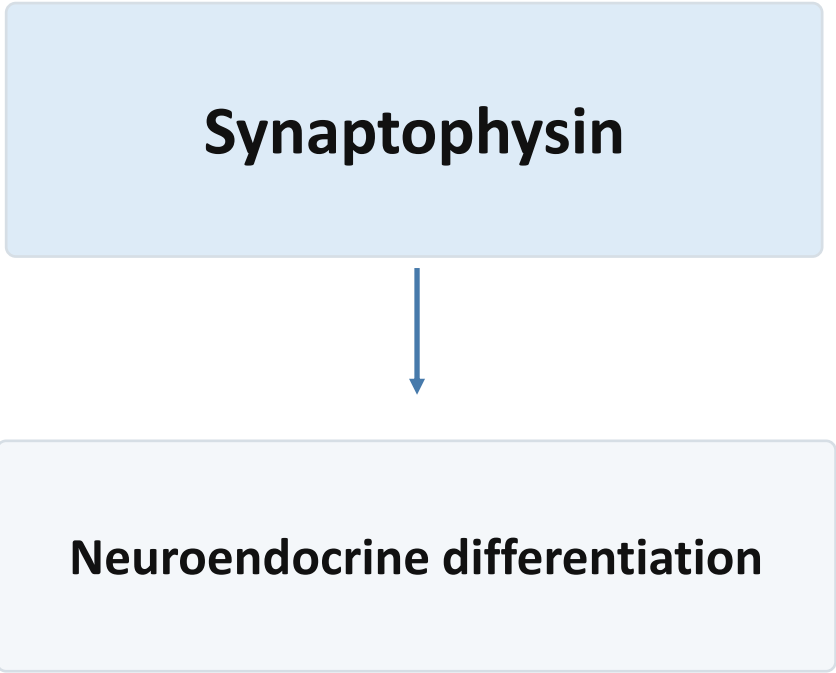
CD56

Markers describe differentiation, not unique tumor identity

Synaptophysin: Vesicle-associated marker

- Synaptophysin is a commonly positive neuroendocrine marker in olfactory neuroblastoma.
- Its staining provides evidence of differentiation, not a tumor-specific fingerprint.
- Other neuroendocrine neoplasms can express synaptophysin.

Synaptophysin



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graph TD; A[Synaptophysin] --> B[Neuroendocrine differentiation];
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Neuroendocrine differentiation

Interpret within a lineage-specific panel

Chromogranin: Secretory granule association

- Chromogranin is included among positive markers.
- Expression complements synaptophysin in assessing neuroendocrine phenotype.
- Staining must be evaluated in a panel rather than treated as independently diagnostic.

Chromogranin

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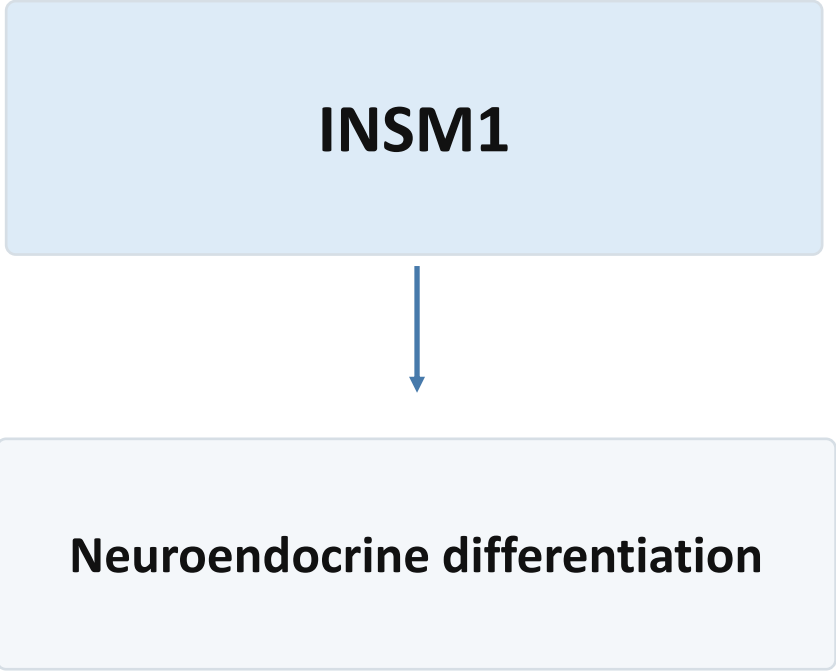
Neuroendocrine differentiation

Interpret within a lineage-specific panel

INSM1: Nuclear neuroendocrine marker

- INSM1 is explicitly named marker set.
- A nuclear staining pattern offers information complementary to cytoplasmic markers.
- Neuroendocrine lineage confirmation does not alone distinguish ONB from carcinoma.

INSM1



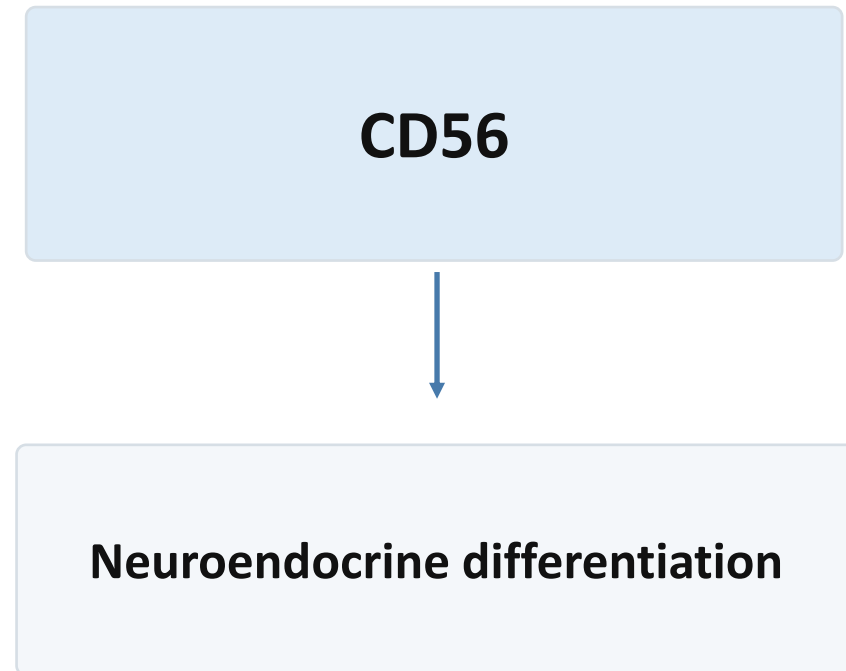
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Neuroendocrine differentiation

Interpret within a lineage-specific panel

CD56: Useful but not a stand-alone test

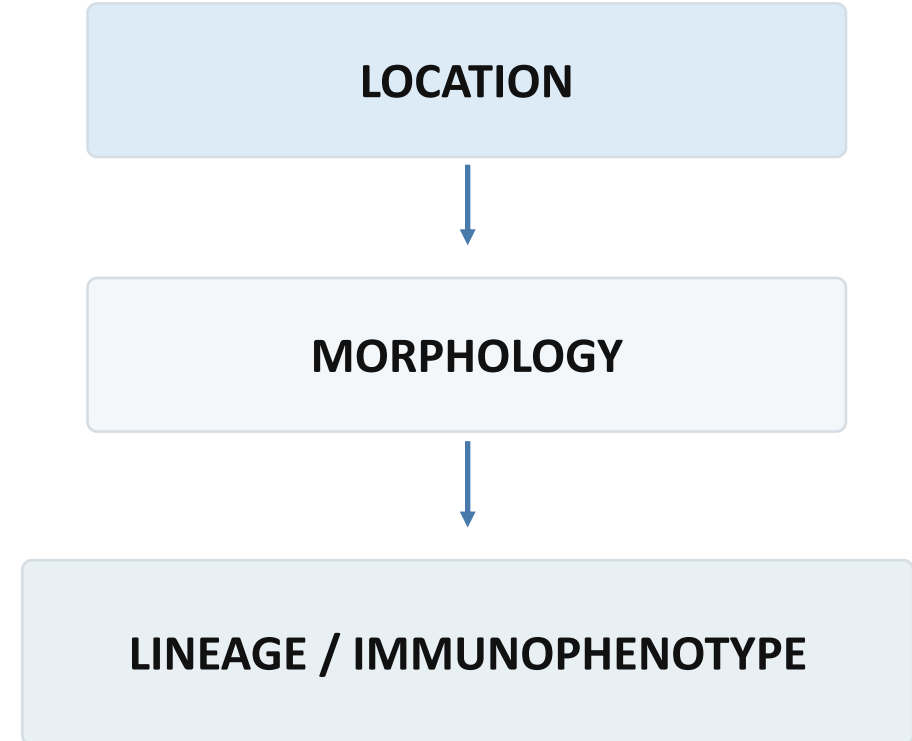
- CD56 is part of the textbook-supported immunophenotype.
- Because CD56 is not tumor specific, interpretation requires other markers and morphology.
- A single positive CD56 result cannot establish olfactory neuroblastoma.



Interpret within a lineage-specific panel

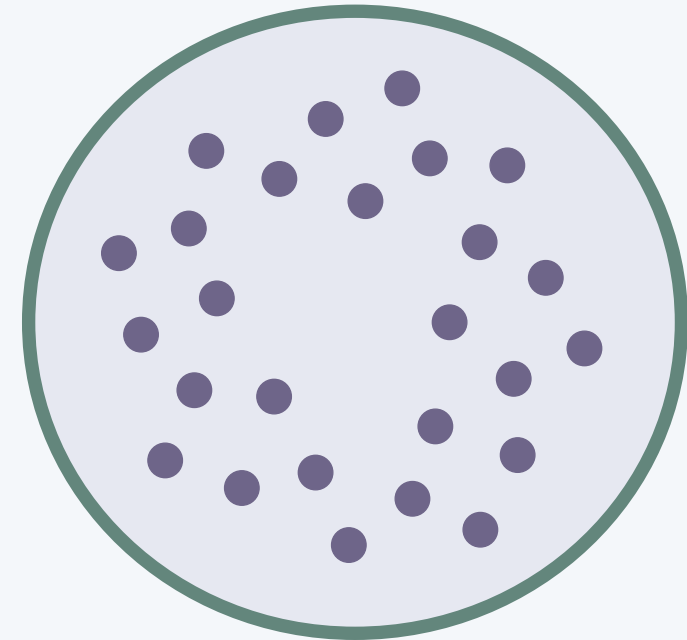
Neuroendocrine positivity is a phenotype

- A positive panel supports neuroendocrine differentiation.
- Phenotypic overlap with small cell neuroendocrine carcinoma remains possible.
- Therefore, resolve epithelial lineage, architecture and anatomic context as well.



Peripheral S100 sustentacular pattern

- S100-positive sustentacular cells can outline tumor nests, especially in lower-grade lesions.
- The peripheral pattern is different from diffuse staining of the tumor-cell population.
- This is useful supplementary diagnostic evidence, not among the primary four diagnostic markers.



S100-positive peripheral sustentacular rim

S100 staining-pattern schematic — not IHC specimen

Cytokeratin: A nuanced discriminator

- Olfactory neuroblastoma is usually non-epithelial in immunophenotype.
- Focal keratin expression may occur, so isolated focal positivity does not automatically exclude it.
- Strong diffuse epithelial staining should prompt scrutiny for a carcinoma mimic.

Shared small-cell appearance

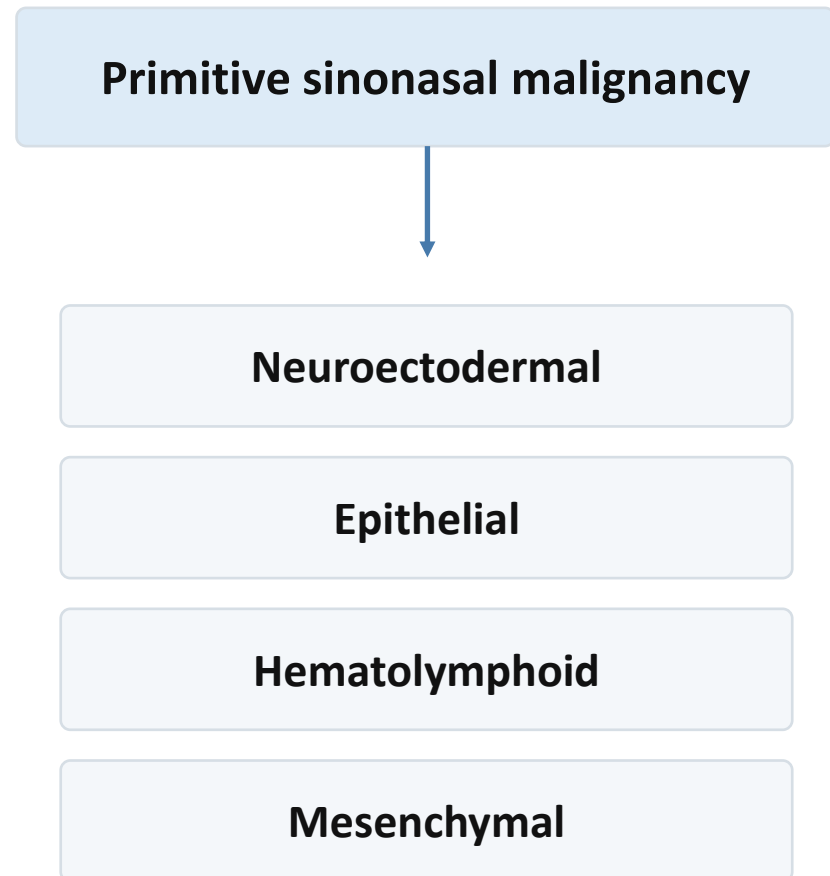


Resolve by phenotype + architecture

One stain ≠ one diagnosis

Exclusion markers prevent anchoring

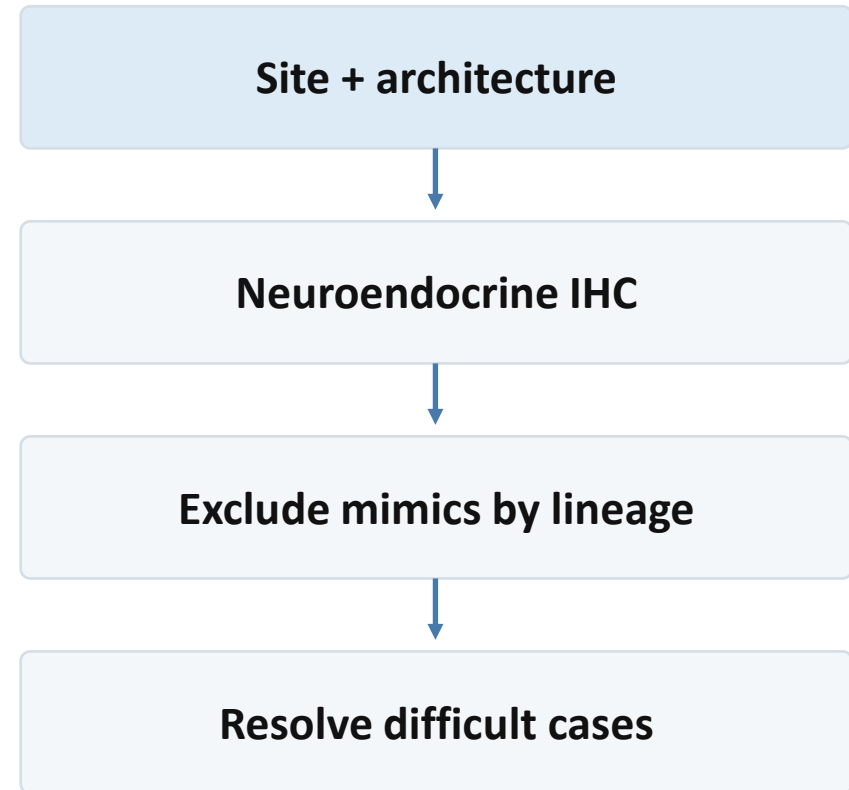
- CD45 supports a hematolymphoid differential when positive in tumor cells.
- Myogenin and desmin can direct attention toward skeletal muscle differentiation.
- CD99/NKX2.2, interpreted with morphology and molecular studies, can aid Ewing workup.



Work from morphology to lineage-specific evidence

A staged IHC workup

- First integrate tumor location, architecture and routine morphology.
- Then evaluate neuroendocrine, epithelial, lymphoid and muscle-lineage markers.
- Reserve molecular confirmation for cases where the phenotype suggests a specific genetically defined mimic.



Differential: Lymphoma

- Lymphoma is one of the textbook-listed small-round-cell mimics.
- Consider lymphoid lineage when cells lack characteristic lobular/neuropil architecture.
- CD45 and appropriate subtype markers are more informative than nuclear size alone.

Shared small-cell appearance



Resolve by phenotype + architecture

One stain ≠ one diagnosis

Differential: Small cell carcinoma

- Both tumors can express neuroendocrine markers, so positivity alone is insufficient.
- An epithelial keratin phenotype and different growth architecture favor carcinoma.
- Correlate immunophenotype with location and morphology.

Shared small-cell appearance



Resolve by phenotype + architecture

One stain ≠ one diagnosis

Differential: Ewing sarcoma

- Ewing sarcoma belongs to the textbook-listed small-round-blue-cell differential.
- CD99/NKX2.2 can raise suspicion but require contextual interpretation.
- Appropriate molecular investigation can establish a characteristic Ewing-family rearrangement.

Shared small-cell appearance



Resolve by phenotype + architecture

One stain ≠ one diagnosis

Differential: Rhabdomyosarcoma

- Rhabdomyosarcoma is another textbook-listed morphologic mimic.
- Skeletal muscle-lineage markers redirect the differential away from a neural tumor.
- Lineage evidence is decisive when primitive cytology overlaps.

Shared small-cell appearance



Resolve by phenotype + architecture

One stain ≠ one diagnosis

Adjacent sinonasal entity: NUT carcinoma

- NUT carcinoma follows ONB as a separate entity Chapter 16.
- Its poorly differentiated appearance can complicate sinonasal differential diagnosis.
- NUT nuclear immunohistochemistry and fusion testing are entity-directed ancillary studies.

Shared small-cell appearance



Resolve by phenotype + architecture

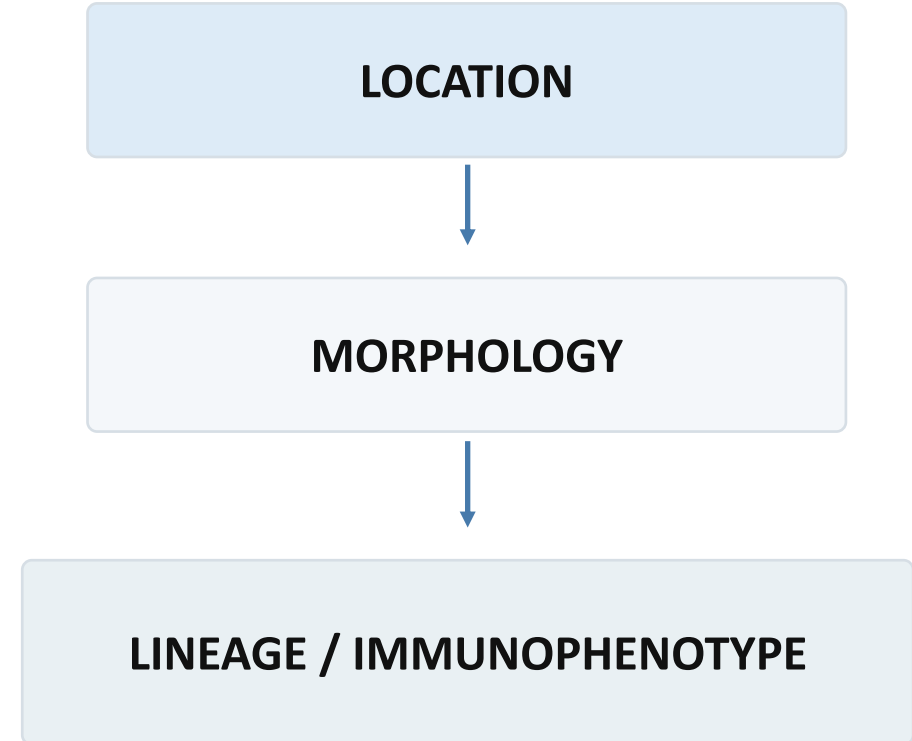
One stain ≠ one diagnosis

Compact differential-diagnostic matrix

Entity	Useful discriminators
Olfactory neuroblastoma	Lobules; Neuropil; NE markers; Peripheral S100 cells
Small cell carcinoma	Neuroendocrine markers with epithelial keratin phenotype
Lymphoma	CD45 and lineage-specific hematolymphoid markers
Rhabdomyosarcoma	Desmin / nuclear myogenin support muscle lineage
Ewing sarcoma	CD99 / NKX2.2; Confirm with suitable molecular studies

Avoid interpreting one stain in isolation

- A neuroendocrine-positive, keratin-positive lesion has more than one plausible classification.
- A strong sustentacular pattern is helpful only in compatible morphologic context.
- Integrate multiple concordant findings and investigate discordance.



Low-grade morphology: Recognizable organization

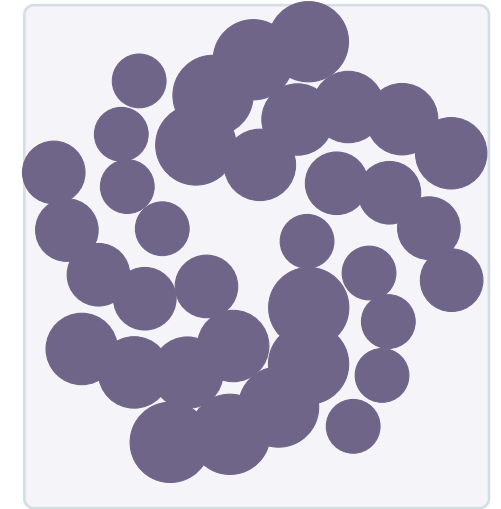
- Well-delineated lobules and conspicuous neuropil favor a lower-grade appearance.
- Uniform nuclei and limited atypia contribute to histologic assessment.
- Grade assignment requires systematic review, not one isolated feature.

**Lower-grade
appearance**



More lobular/neuropil

**Higher-grade
appearance**



More atypia/necrosis

Qualitative contrast only — not grading specimens

High-grade morphology: Diagnostic difficulty

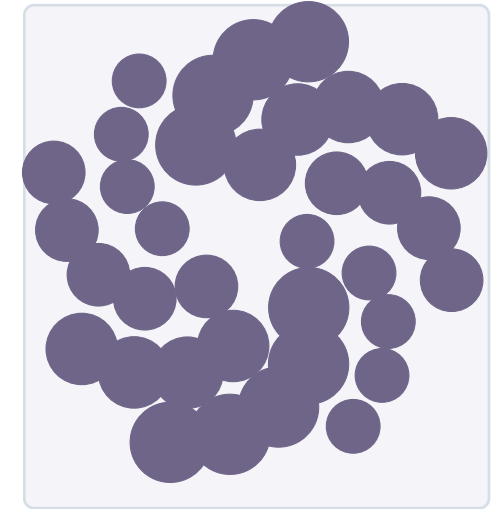
- Marked atypia, necrosis and mitotic activity can obscure typical features.
- Growth may appear more diffuse as lobularity and neuropil become less conspicuous.
- High-grade examples warrant a particularly broad sinonasal malignancy differential.

**Lower-grade
appearance**



More lobular/neuropil

**Higher-grade
appearance**



More atypia/necrosis

Qualitative contrast only — not grading specimens

Hyams grading: A composite assessment

- The Hyams system evaluates several histologic characteristics together.
- Features include architecture, neurofibrillary matrix, cytologic atypia, mitoses and necrosis.
- Four original grades are often considered as lower grade (I–II) versus higher grade (III–IV).

Architecture

Neuropil / rosettes

Atypia / mitoses

Necrosis

Grade and stage answer different questions

- Grade: What aggressive features are visible under the microscope?
- Stage: How far has the tumor extended anatomically?
- Both dimensions matter when interpreting treatment strategy and prognosis.

HISTOLOGIC GRADE

Cytology · Mitotic activity · Necrosis ·
Architecture

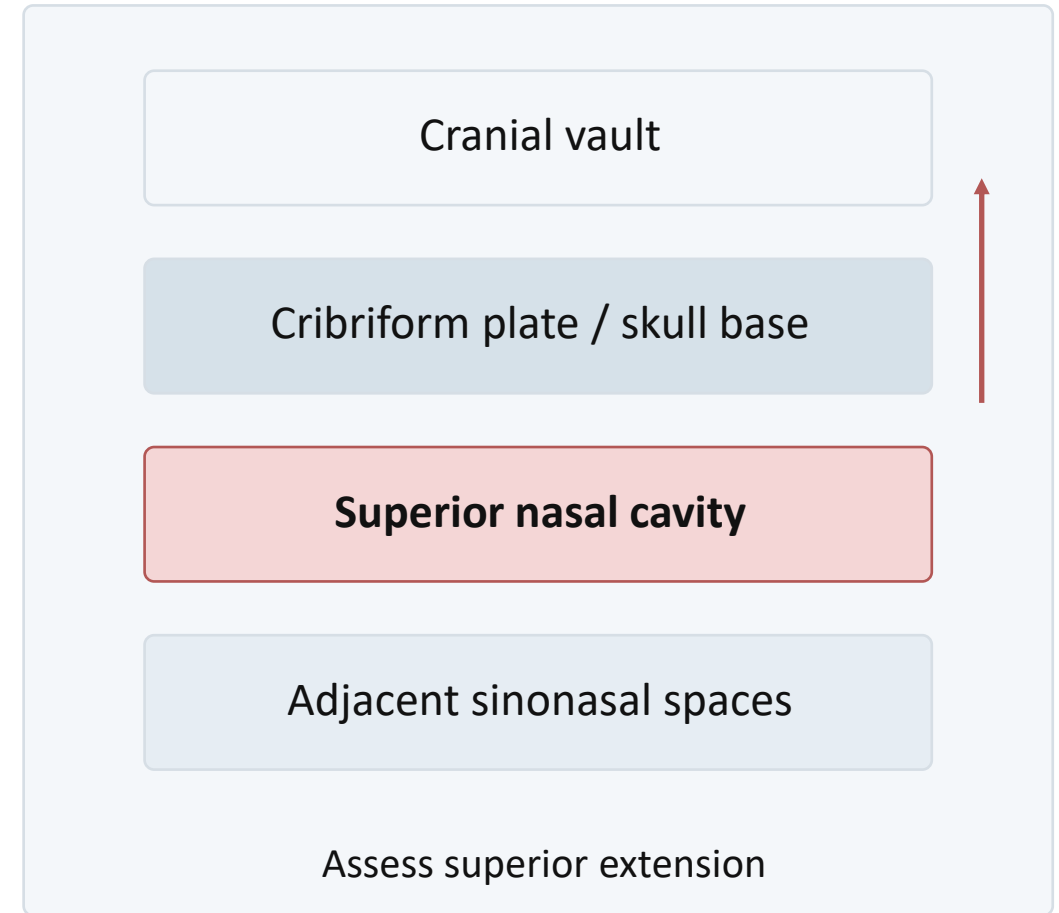


ANATOMIC EXTENT

Local spread · Skull-base involvement · Other
sites

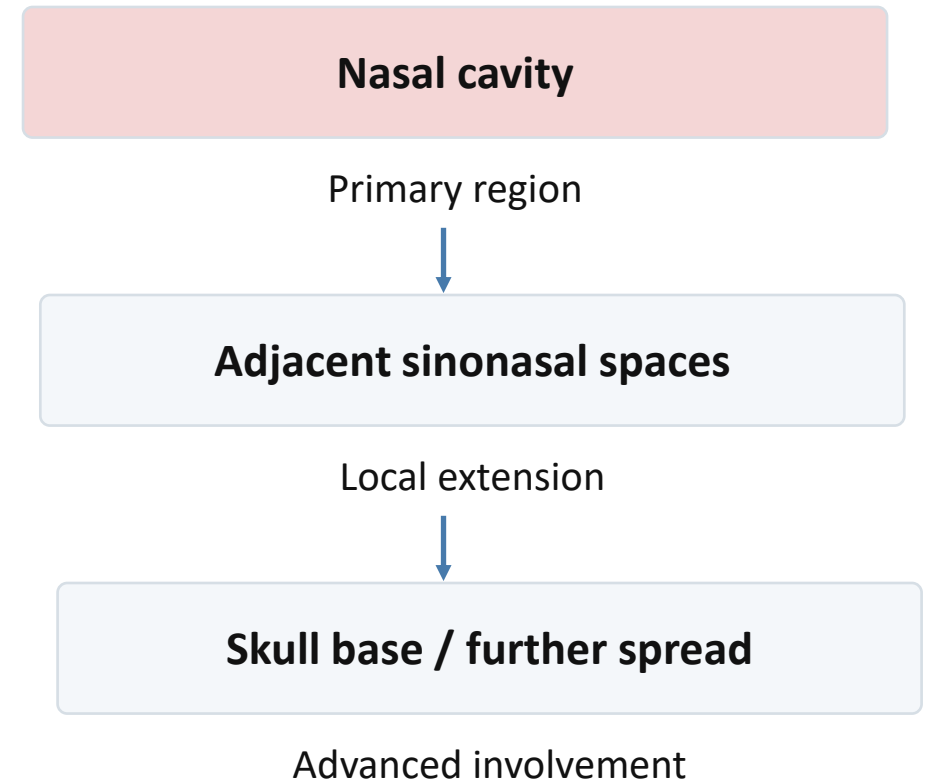
Anatomical spread is clinically central

- The lesion starts near the superior nasal cavity and cribriform region.
- The skull base, adjacent sinuses and intracranial compartment are relevant to mapping extent.
- Extent assessment cannot be inferred reliably from a small biopsy alone.



Clinical stage systems are not histologic grades

- Modified Kadish and Dulguerov schemes are used to describe clinical extent.
- Both incorporate local spread; Detailed categorization depends on the specified system.
- Use a named and dated staging scheme in reports rather than an ambiguous “stage”.



Conceptual progression only; Not a formal stage table

Imaging complements pathologic diagnosis

- Pathology establishes lineage and histologic grade in sampled tissue.
- Cross-sectional imaging delineates lesion extent and skull-base relationships.
- Multidisciplinary correlation is required before definitive local treatment planning.

PATHOLOGY

Lineage / grade

IMAGING

Extent / skull base

MULTIDISCIPLINARY

Treatment synthesis

Report elements that answer clinical questions

- Specify the histopathologic diagnosis and recognizable morphological grade features.
- Document the pattern and breadth of immunohistochemical findings.
- Correlate with site, imaging and surgical margin status where material permits.

Anatomic site

Architecture + differentiation

Histologic grade

Extent / margin correlation

Genetics are heterogeneous

- Chromosomal gains and losses vary between cases.
- This heterogeneity argues against a single uniform genomic alteration.
- Molecular findings should not replace the morphologic and phenotypic diagnostic framework.

Genomic heterogeneity

Chromosomal gain

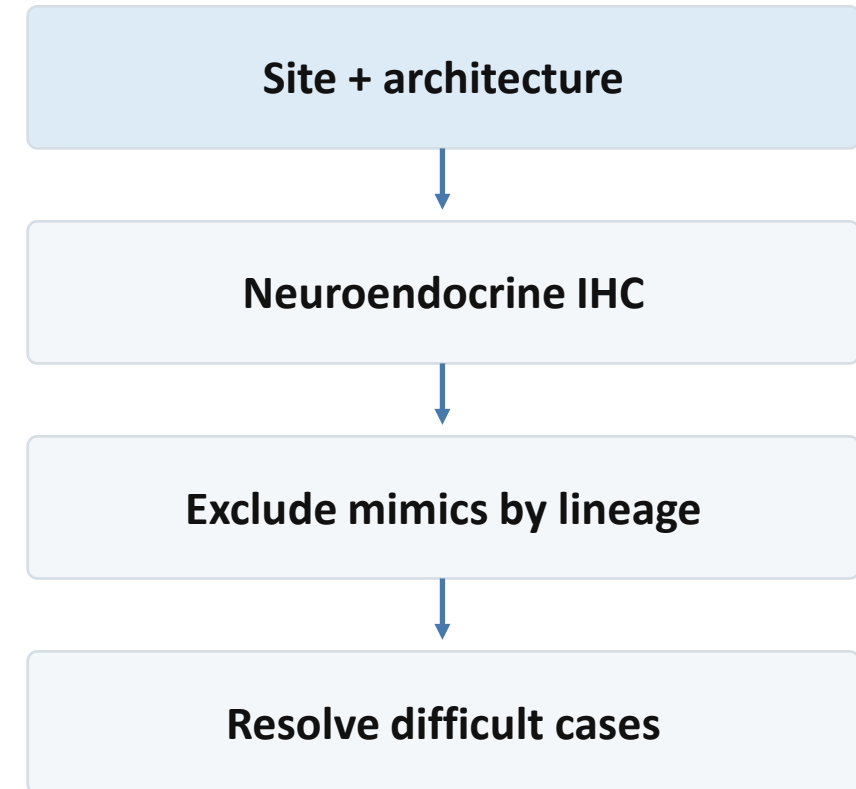
Chromosomal loss

Variable combinations

Conceptual categories — no invented karyotype or cohort data

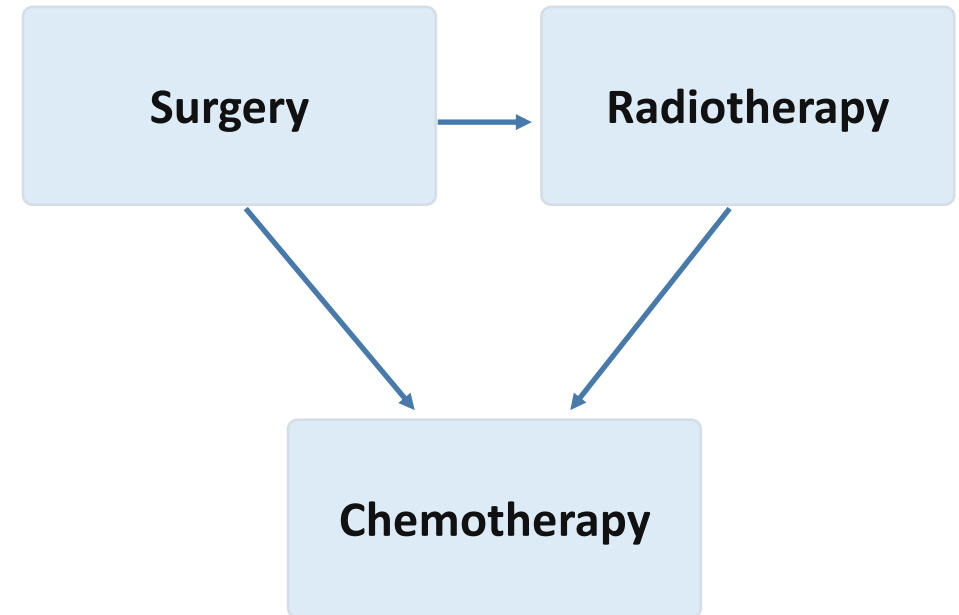
A molecular result needs a question

- Molecular tests may help resolve genetically defined differential diagnoses.
- Do not order a broad panel without a morphology-driven diagnostic hypothesis.
- No unique, universally required molecular signature for ONB is stated.



Treatment is typically multimodal

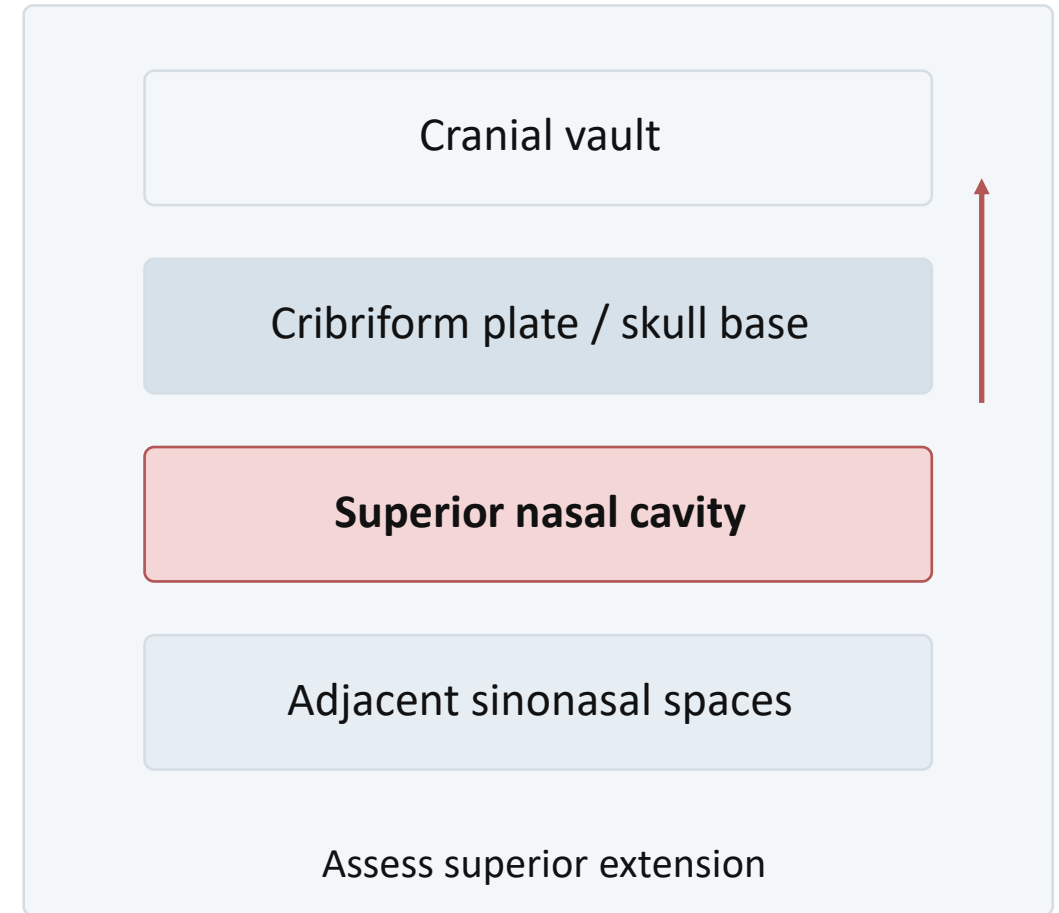
- Combinations of surgery, radiotherapy and chemotherapy.
- Stage and grade influence treatment selection and expected outcome.
- There is no single uniform modality appropriate for all disease extents.



Combined according to clinical context

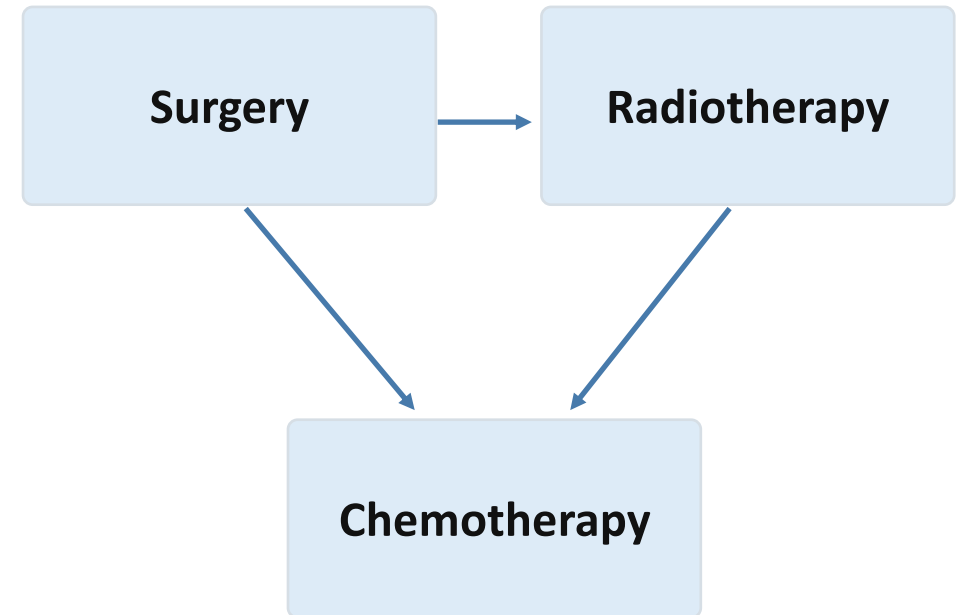
Surgical therapy: Local control

- Resection targets local tumor removal when anatomically feasible.
- The proximity to the skull base makes complete extent assessment important.
- Surgical planning requires clinical and imaging information beyond microscopic diagnosis.



Radiotherapy: A complementary modality

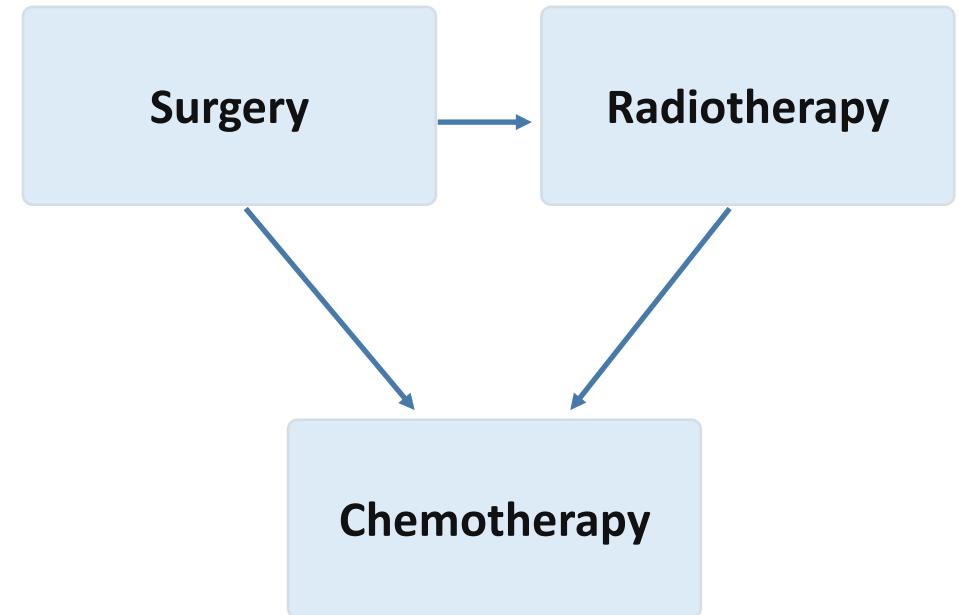
- Radiotherapy is included's treatment combinations.
- Use may depend on resection status, disease extent and multidisciplinary decisions.
- Treatment decisions should not be inferred from a limited histologic section.



Combined according to clinical context

Chemotherapy: Context-dependent use

- Chemotherapy is one possible component of multimodal treatment.
- Its role varies with stage, grade and clinical treatment strategy.
- A pathology lecture cannot substitute for current tumor-board planning.



Combined according to clinical context

Outcome spans a broad range

- Five-year survival rates ranging from 40% to 90%.
- The source explicitly qualifies this range by tumor stage, grade and combined therapy.
- It is not a patient-specific probability or a uniform contemporary benchmark.

Five-year survival

40%–90%

Across differing stage, grade and treatment contexts

Source-reported range; Not a patient-level estimate

Why a single survival number misleads

- A localized lower-grade lesion and an advanced higher-grade lesion are not equivalent.
- Study era, treatment strategy and case mix influence reported estimates.
- When presenting a prognosis, identify cohort, endpoint and risk context.

HISTOLOGIC GRADE

Cytology · Mitotic activity · Necrosis ·
Architecture

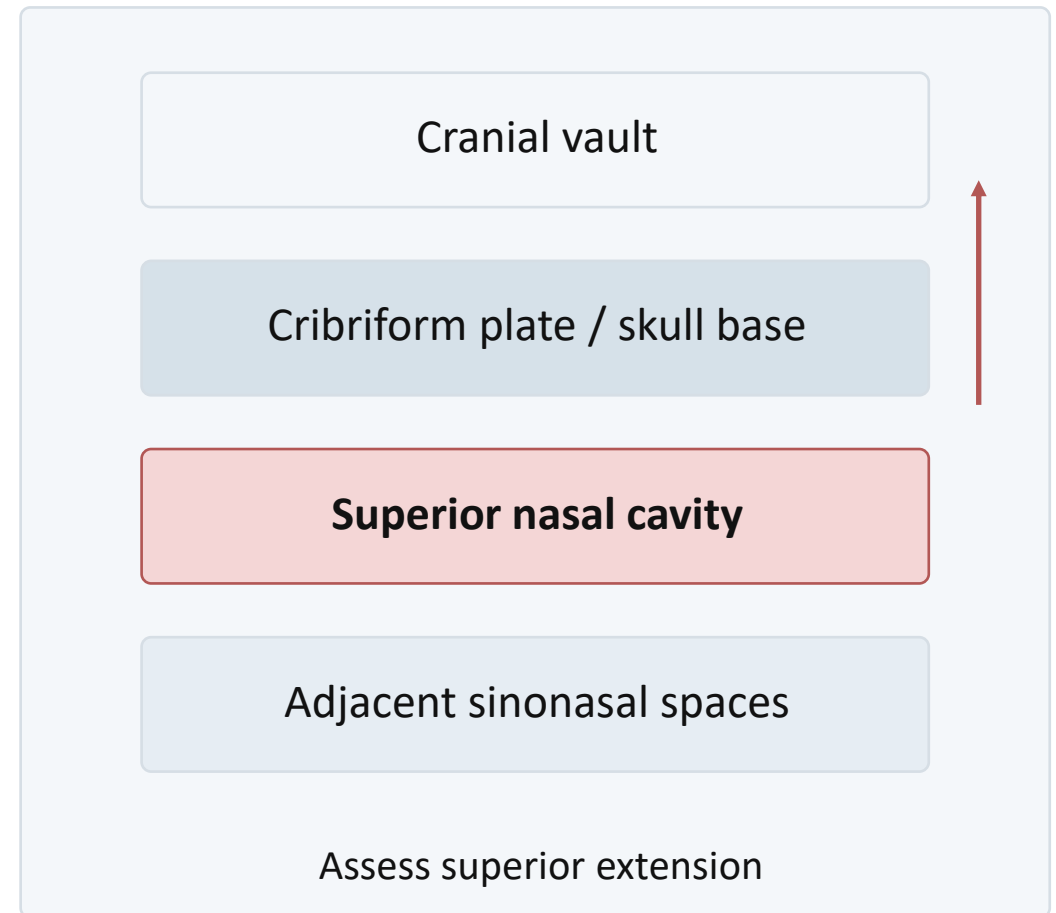


ANATOMIC EXTENT

Local spread · Skull-base involvement · Other
sites

Follow-up needs a long-term perspective

- Disease control and surveillance are distinct from initial pathologic classification.
- Local recurrence or distant spread may change clinical management.
- Interval and modality of surveillance require local specialist protocols.



Case 1: Classic low-power morphology

A superior nasal cavity tumor shows sharply defined lobules of uniform small blue cells, separated by fibrovascular septa. Delicate neuropil is conspicuous.

Which additional evidence most directly supports olfactory neuroblastoma?

Case 1: Diagnostic synthesis

- Synaptophysin, chromogranin and INSM1 positivity support neuroendocrine differentiation.
- A peripheral S100 sustentacular pattern would strengthen this interpretation.
- The final diagnosis still requires exclusion of epithelial and other small-round-cell mimics.

Synaptophysin

Chromogranin

INSM1

CD56

Markers describe differentiation, not unique tumor identity

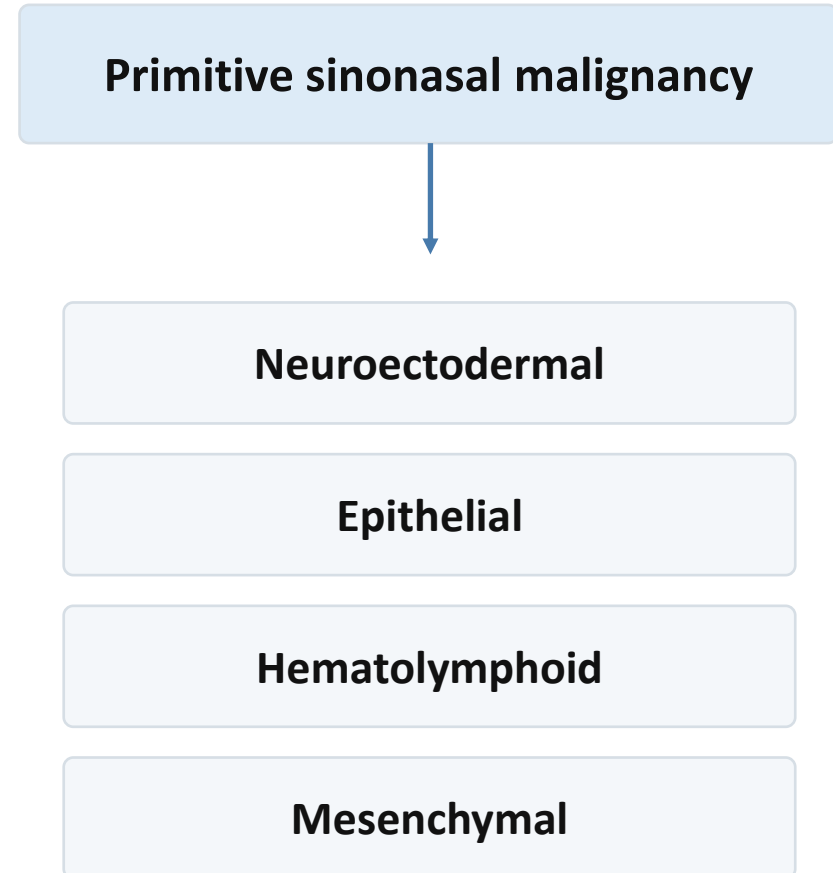
Case 2: The high-grade pitfall

A sinonasal biopsy contains a diffuse small-cell malignancy with brisk mitoses, necrosis and strong synaptophysin staining. No classic lobules are evident.

Why is “olfactory neuroblastoma” not yet a secure final diagnosis?

Case 2: Resolving uncertainty

- High-grade ONB can lose recognizable lobularity and neuropil.
- Small cell neuroendocrine carcinoma may share neuroendocrine positivity.
- Assess keratins, other lineage markers and the full clinical/imaging context before classification.



Work from morphology to lineage-specific evidence

Case 3: Prognosis and communication

Two confirmed ONBs have different anatomic extents and histologic grades. A team asks for one universal five-year survival percentage.

How should the pathologist communicate the evidence without false precision?

Case 3: Evidence-based response

- Describe histologic grade and documented anatomic extent separately.
- Explain that an overall 40–90% five-year survival range across varied cases.
- Avoid assigning a personalized prognosis without stage, grade and relevant cohort data.

Five-year survival

40%–90%

Across differing stage, grade and treatment contexts

Source-reported range; Not a patient-level estimate

Integrated diagnostic synthesis

- Site: Superior nasal cavity / olfactory mucosal region.
- Morphology: Circumscribed nests, fibrovascular septa and neurofibrillary background.
- Phenotype: Multiple neuroendocrine markers; Targeted exclusion of mimics.
- Clinicopathology: Histologic grade, extent and treatment context together matter.

Superior nasal site

Lobular + fibrillary H&E

Neuroendocrine IHC panel

Exclude competing lineages

Selected reading and source provenance

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- Treatment evaluation review. 2024. PMID: 38762332.