

SINONASAL PAPILLOMA

Morphology · Molecular pathogenesis · Diagnostic interpretation

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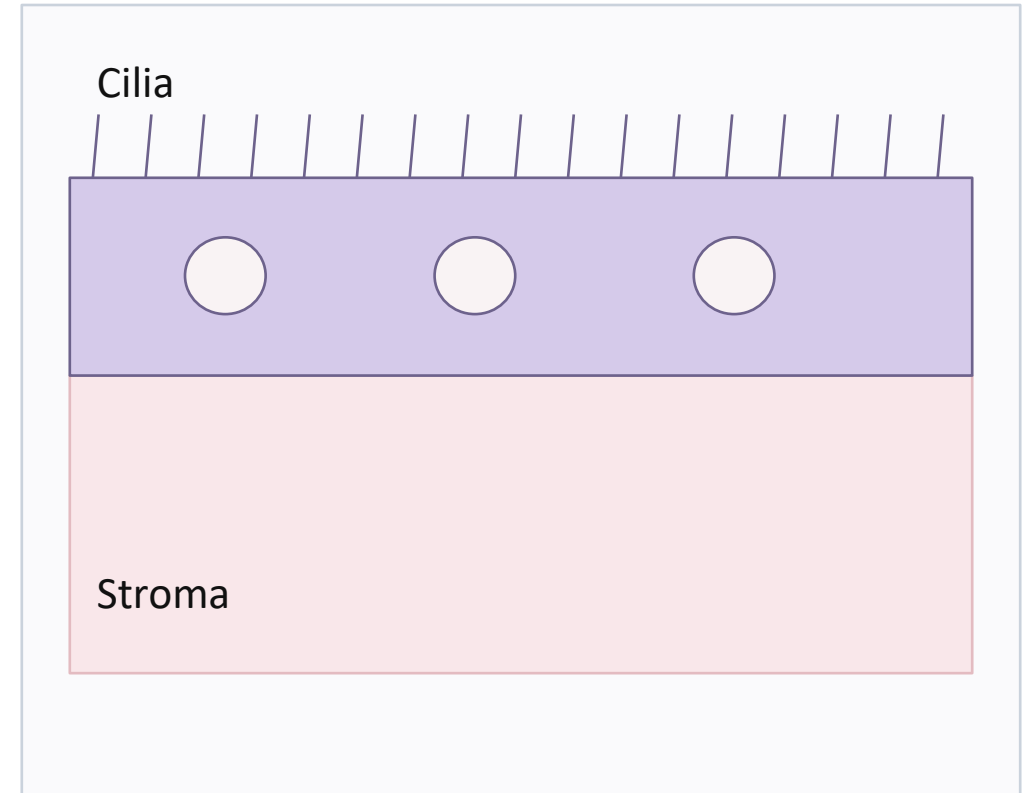
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Learning goals

- Define sinonasal (Schneiderian) papilloma and identify its three variants.
- Explain inverted, exophytic, and oncocytic epithelial growth patterns.
- Integrate histology with EGFR, KRAS, and low-risk HPV associations.
- Recognize recurrence risk, carcinoma red flags, and diagnostic mimics.

Primary site: Schneiderian respiratory mucosa

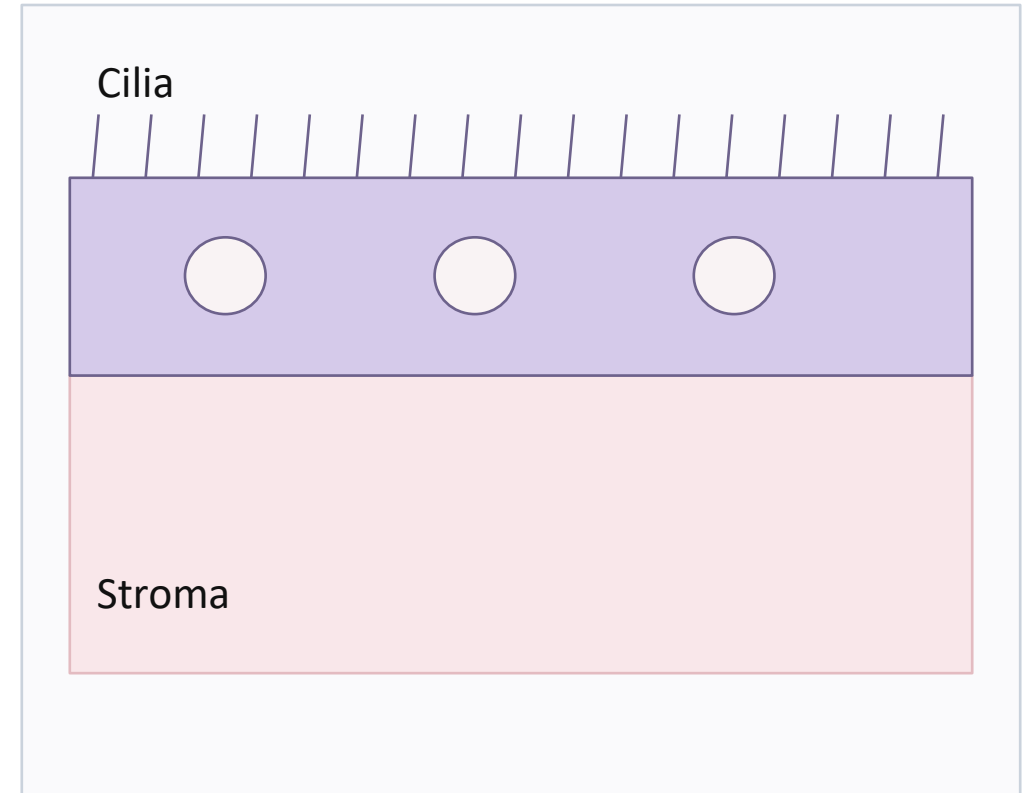
- Origin: Mucosa lining the nasal cavity and paranasal sinuses.
- A true epithelial neoplasm rather than a nonspecific inflammatory polyp.
- Anatomic location and architectural pattern are fundamental diagnostic clues.



Schematic — not a histologic specimen

Respiratory epithelium provides the substrate

- Normal sinonasal lining contains ciliated respiratory-type cells and mucocytes.
- Papilloma epithelium may display respiratory, transitional, or squamous differentiation.
- Background inflammation can coexist without defining the neoplasm.



Schematic — not a histologic specimen

Sinonasal tumors form a diverse differential

- Benign papilloma, inflammatory polyp, and respiratory epithelial hamartoma may appear polypoid.
- Malignant epithelial lesions can also produce unilateral sinonasal masses.
- Histologic architecture—not the word “polyp”—determines classification.

Three recognized papilloma types

Inverted

Downward epithelial
lobules

Oncocytic

Granular columnar lining

Exophytic

Outward fibrovascular
fronds

Current nomenclature

- Sinonasal papilloma is often called Schneiderian papilloma.
- WHO 5th edition (2022) retains inverted, oncocytic, and exophytic entities.
- “Cylindrical-cell” and “fungiform” are historical descriptive synonyms for oncocytic and exophytic forms.

Demographic pattern

- Robbins: Most common in men aged 30–60 years.
- Age and sex support clinical context but are not diagnostic criteria.
- Interpret the epidemiologic statement at the group level; Subtype distributions differ.

Benign does not imply clinically trivial

- Non-invasive epithelial histology can coexist with significant local expansion.
- An incompletely excised inverted papilloma may recur.

- Inverted and oncocytic lesions require attention to associated dysplasia or carcinoma.

Clinical presentation: Obstruction and bleeding

- Unilateral nasal obstruction is a common presenting clue, particularly in inverted lesions.
- Epistaxis, rhinorrhea, or recurrent sinus symptoms may occur.
- Symptoms overlap with benign inflammatory disease: Tissue diagnosis is needed.

A unilateral nasal mass warrants evaluation

- Papilloma and carcinoma can mimic an inflammatory polyp on examination.
- History, endoscopy, and imaging identify attachment and extent.
- Biopsy should be interpreted with imaging and adequate sampling.

Typical location of inverted papilloma

- Frequently arises from the lateral nasal wall with extension to adjacent sinuses.
- Site of attachment helps interpret focal hyperostosis on CT.

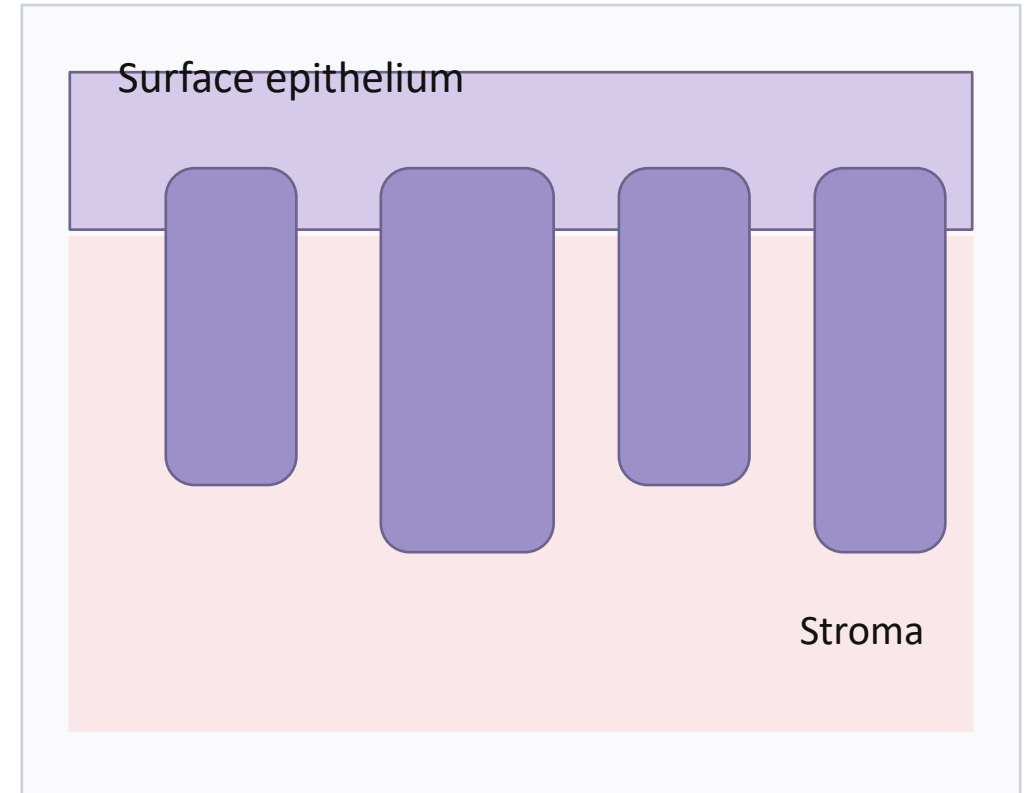
- Septal origin is more characteristic of the exophytic subtype.

The significance of local extension

- Inverted papilloma can expand within nasal cavity and paranasal sinuses.
- Possible extension to orbit or cranial vault.
- Extent is an anatomic behavior; It is not itself histologic proof of carcinoma.

Inverted papilloma: Defining architecture

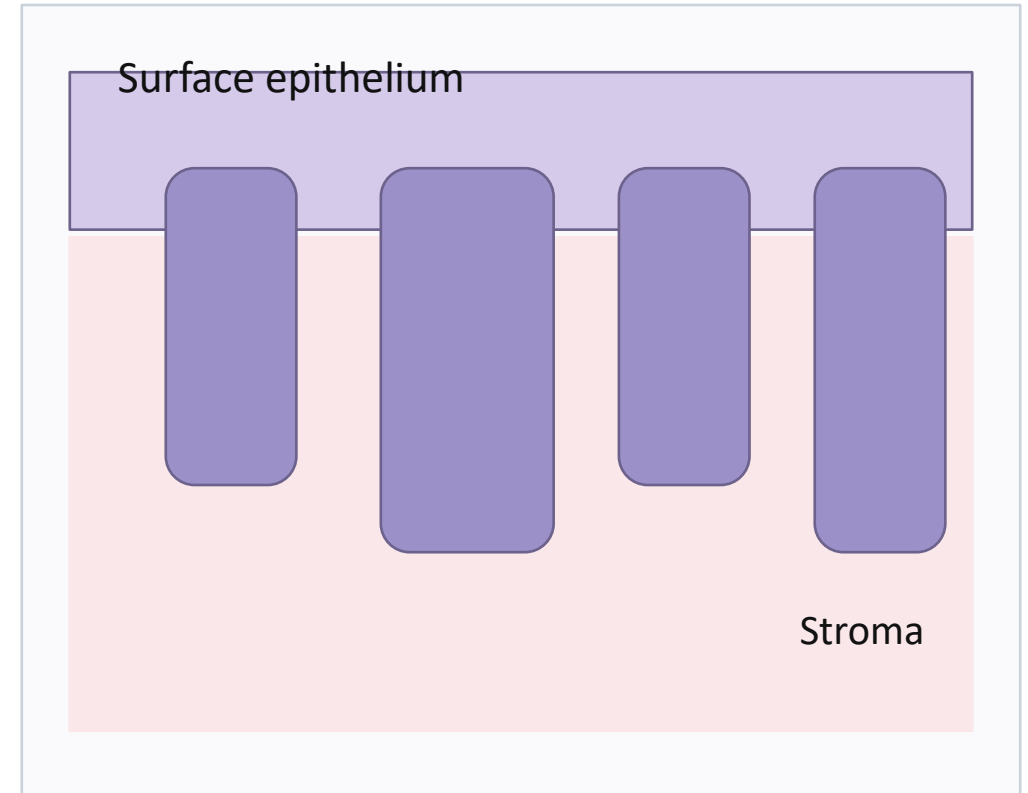
- Broad, bulbous lobules of neoplastic epithelium project downward.
- Epithelial islands sit within stroma while retaining a basement membrane.
- An endophytic growth configuration explains the term “inverted”.



Schematic — not a histologic specimen

A native schematic of endophytic growth

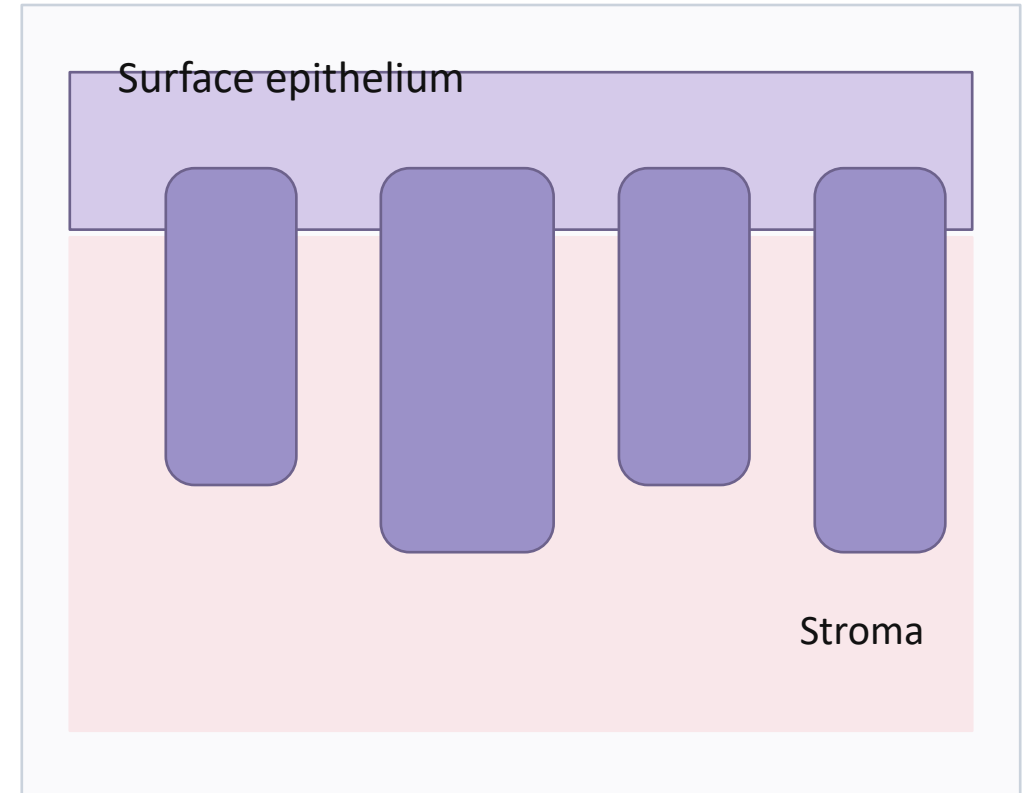
- Observe the direction from surface epithelium toward submucosal stroma.
- Broad interconnected epithelial lobules create a pushing contour.
- Distinguish this configuration from irregular destructive stromal invasion.



Schematic — not a histologic specimen

Pushing growth is not synonymous with invasion

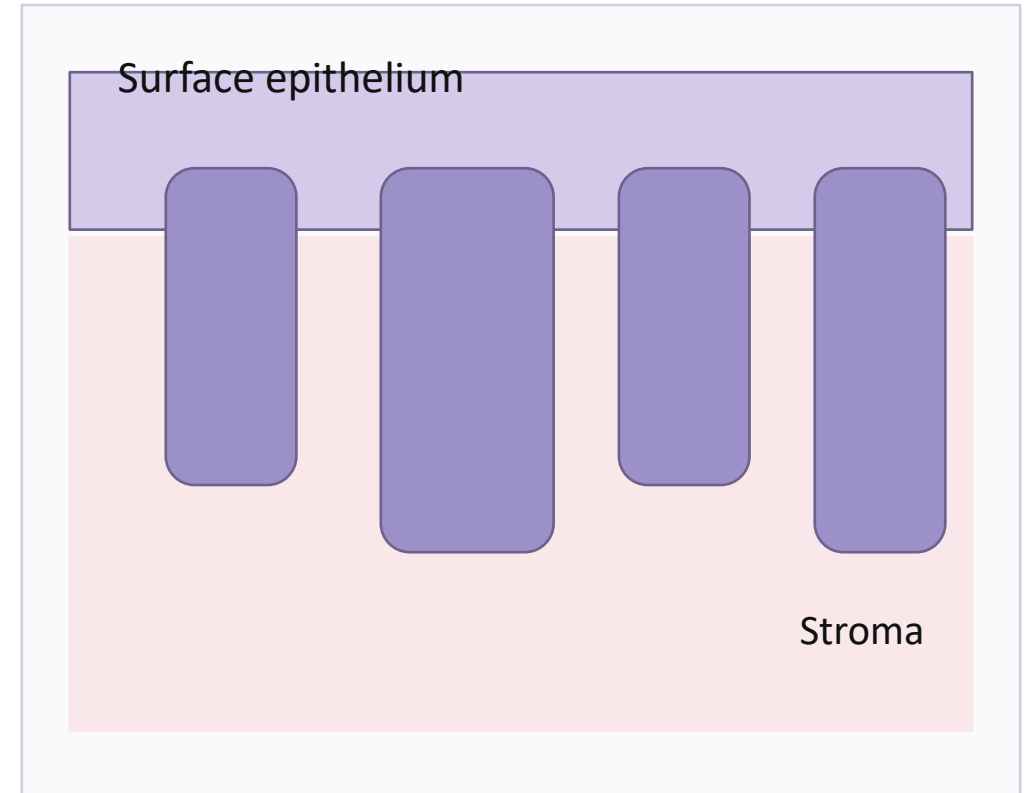
- A benign inverted papilloma can contain extensive epithelial downgrowth.
- Intact basement-membrane relationships and orderly maturation favor benignity.
- Irregular infiltrative nests and desmoplasia require assessment for carcinoma.



Schematic — not a histologic specimen

Low-power histology: What to locate first

- Find the surface epithelium and identify its relation to subjacent stroma.
- Look for broad tongues, ribbons, or nests of thickened epithelium.
- Assess whether the deep border is circumscribed or destructive.



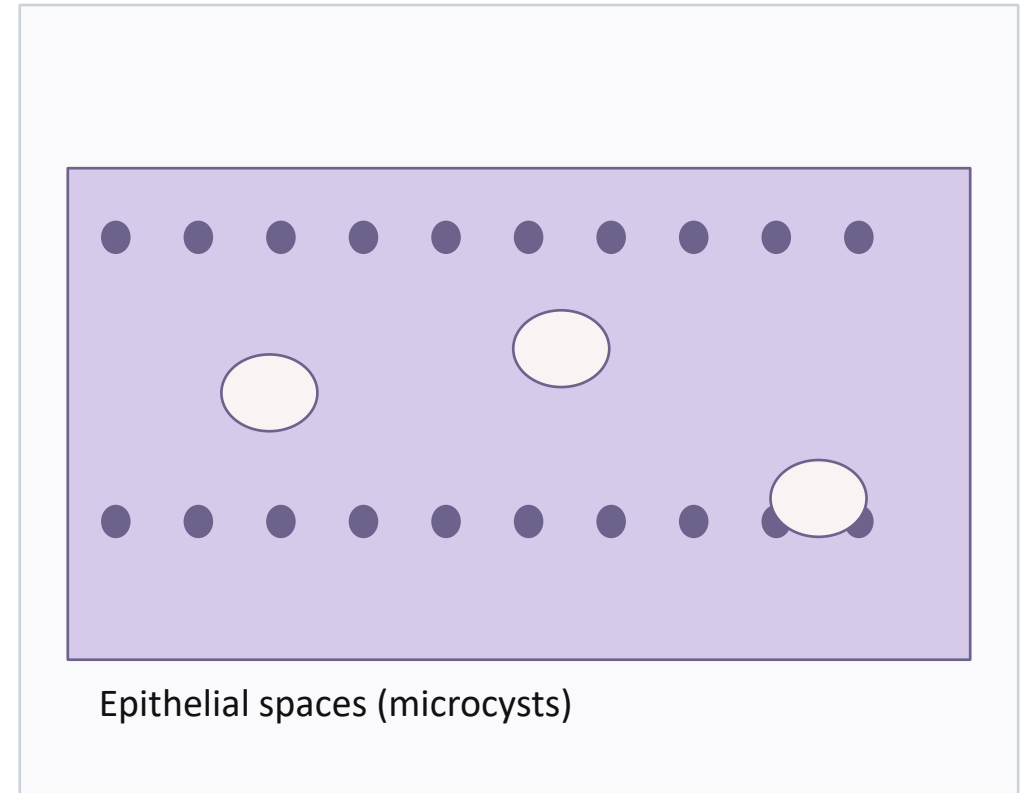
Schematic — not a histologic specimen

Inverted papilloma: Epithelial differentiation

- Nonkeratinizing squamous and transitional-type cells commonly predominate.
- Respiratory-type columnar or ciliated elements may remain.
- Different epithelial appearances can occur within one lesion.

Mucocytes and intraepithelial microcysts

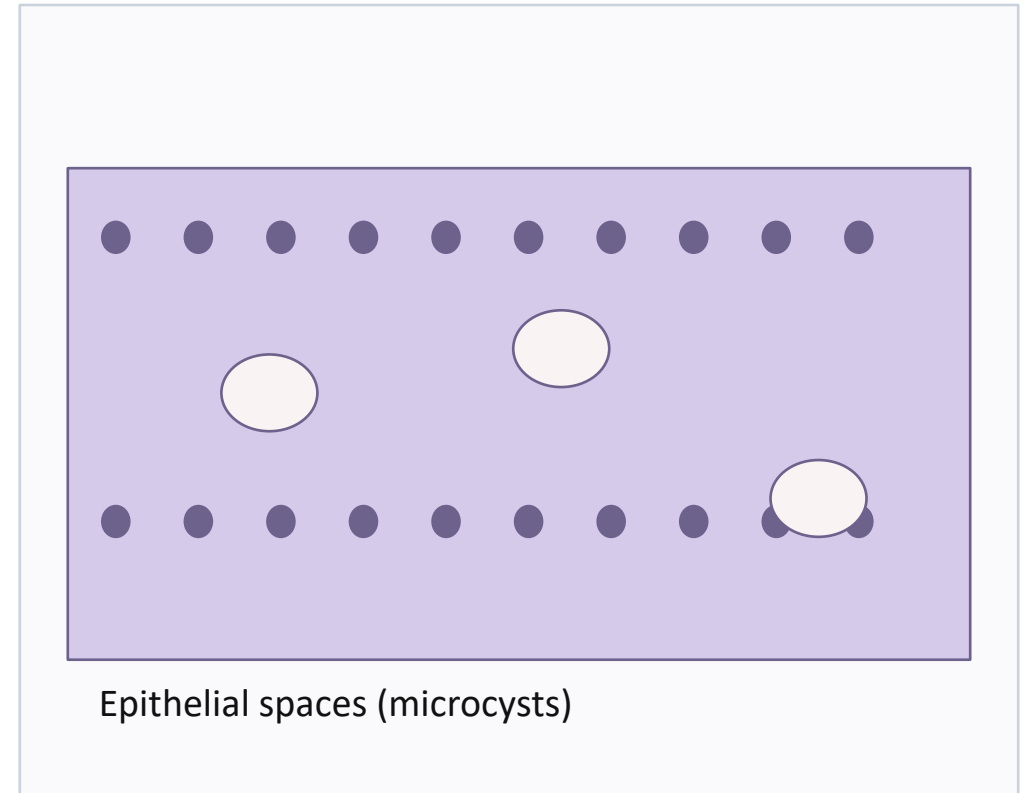
- Goblet-type mucocytes may occur within the papillomatous epithelium.
- Entrapped mucin may create intraepithelial microcystic spaces.
- These findings support context, but are not unique to the inverted type.



Schematic — not a histologic specimen

Neutrophils can enter papilloma epithelium

- Transepithelial neutrophils and microabscesses are recognized findings.
- Inflammatory cells do not automatically signify epithelial invasion.
- Interpret them together with the overall architecture and cytology.



Schematic — not a histologic specimen

Stroma and secondary inflammation

- Stroma may be fibrous, edematous, or chronically inflamed.
- Obstruction from the neoplasm can produce secondary polypoid inflammatory change.
- The accompanying stroma should not obscure the epithelial tumor.

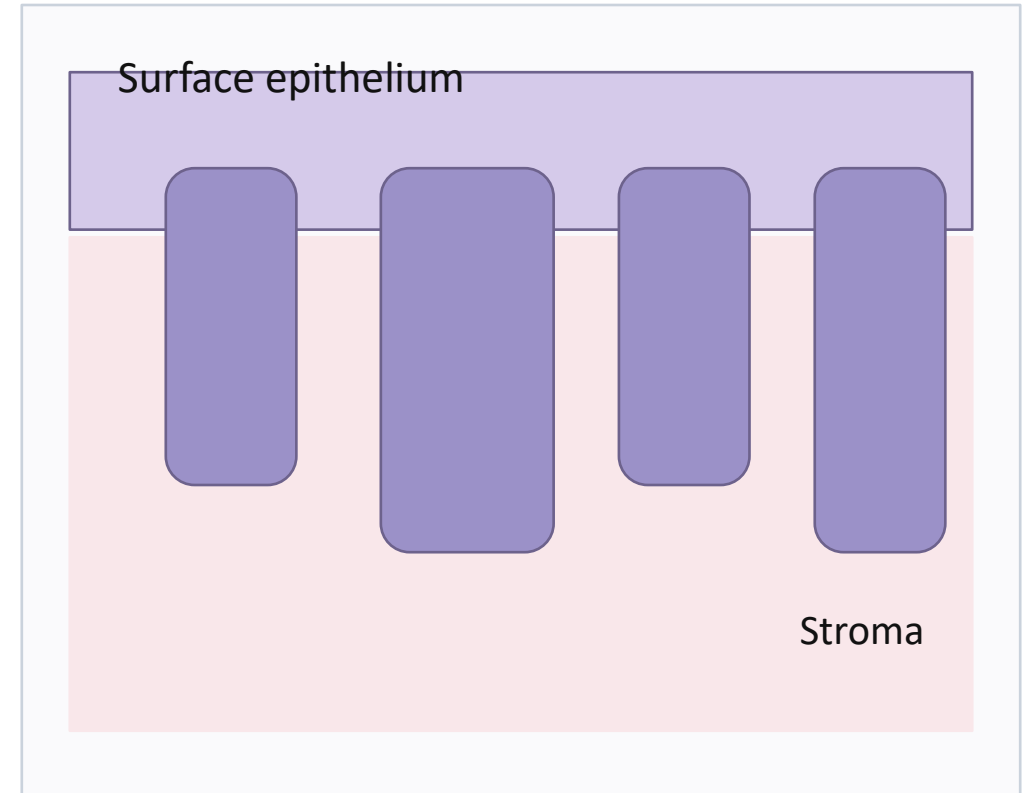
Atypia: Architectural context is essential

- Mild nuclear variation can be seen in otherwise benign epithelium.
- Marked dysplasia, atypical mitoses, necrosis, or infiltrative growth are concerning.
- A superficial fragment may not show the deepest tumor interface.

Exophytic versus inverted architecture

- Exophytic: Outward-growing finger-like projections with fibrovascular cores.
- Inverted: Thick epithelium forms broad downward lobules into stroma.
- Some papillomas have mixed surface and inward growth; Classify by the defining component.

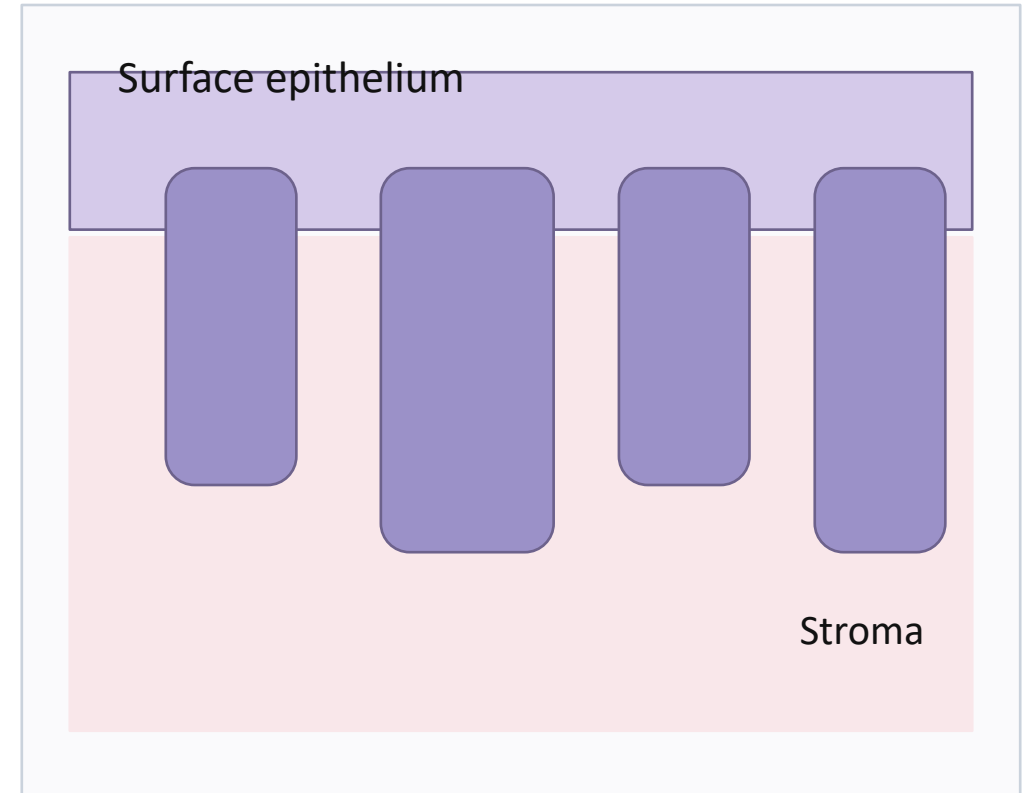
Inverted = downward



Schematic — not a histologic specimen

Morphology exercise: Downward islands

- A biopsy shows bland squamous/transitional cells in downward stromal nests.
- Basement-membrane relationships remain smooth and cohesive.
- Interpretation: Inverted sinonasal papilloma, if representative.



Schematic — not a histologic specimen

EGFR in inverted papilloma

- Robbins: Most inverted papillomas have EGFR gene mutations.
- WHO 2022 review reports somatic EGFR alterations in approximately 90% of inverted cases in reviewed series.

- This molecular association reinforces a neoplastic, subtype-specific pathogenesis.

The HPV nuance in inverted papilloma

- HPV DNA in a subset lacking EGFR mutations, often HPV 6 or 11.
- WHO 2022 highlights low-risk HPV transcripts in some tumors but generally no active high-risk E6/E7 signal.
- DNA detection alone is not synonymous with a transcriptionally active driver.

Two alternative molecular patterns

Subtype-specific biology and progression

Pathway A: Somatic
EGFR-altered inverted
papilloma.

Pathway B: Less common
low-risk HPV-associated
inverted papilloma.

An individual tumor is
not assumed to have
both drivers; Most
reports describe mutual
exclusivity.

Illustrative conceptual grouping — not a quantitative model

Molecular testing: Avoid overinterpretation

- EGFR status can clarify biologic classification in a difficult case.
- Neither EGFR mutation nor HPV DNA alone demonstrates invasive carcinoma.
- Histology and sampling remain decisive for malignant transformation.

Gross appearance of inverted papilloma

- Often described as a pink-gray, lobulated, polypoid sinonasal mass.
- Broad attachment and a folded surface may suggest the lesion endoscopically.
- Gross examination should document size, attachment, and sampling of abnormal regions.

Imaging: Complementary diagnostic value

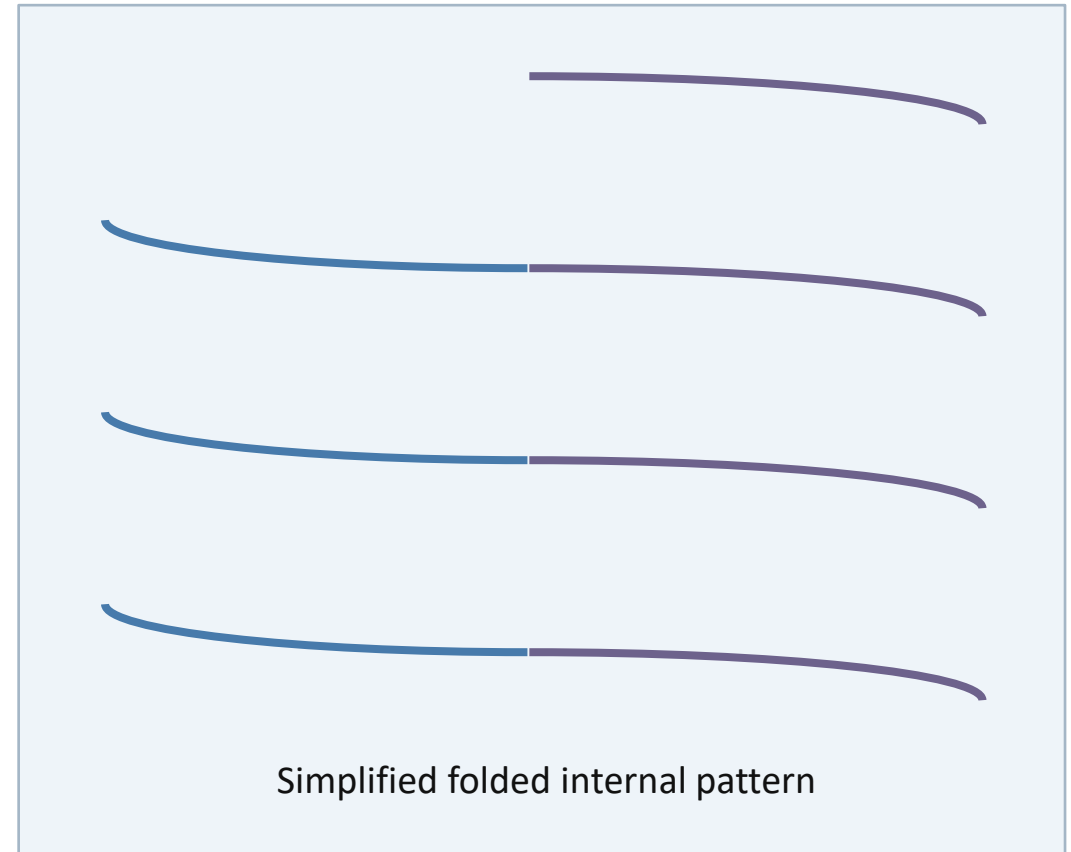
- CT maps bony anatomy and may show focal osteitis or hyperostosis.
- MRI more clearly depicts soft-tissue extent and internal signal pattern.
- Imaging supports localization; Histopathology makes the definitive diagnosis.

Focal hyperostosis may identify attachment

- On CT, focal bony thickening near a lesion may mark its origin.
- This clue can guide the surgical assessment of the attachment site.
- Hyperostosis must not be confused with unequivocal invasive bony destruction.

MRI: Cerebriform architecture

- WHO review notes a convoluted cerebriform pattern on T2 and post-contrast T1 MRI.
- The pattern can support inverted papilloma when concordant with location.
- It is suggestive rather than pathognomonic.



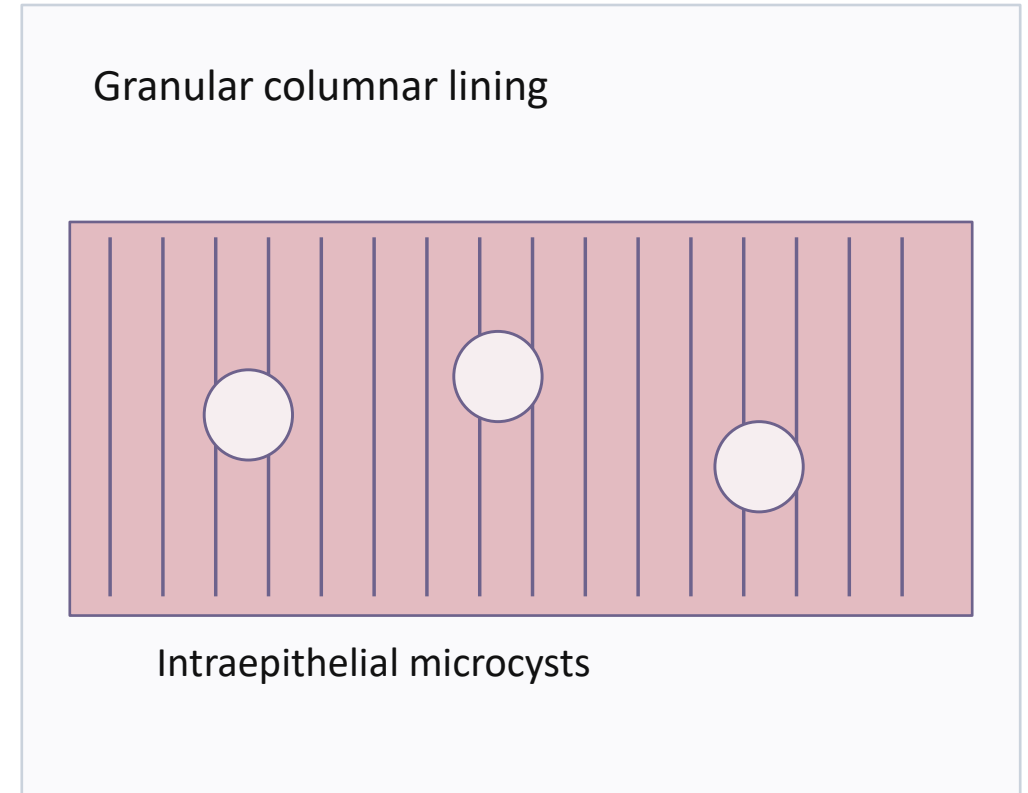
Schematic — not a histologic specimen

Expansion, erosion, and malignant concern

- Locally expansive benign papilloma may affect adjacent anatomy.
- Destructive invasion, loss of expected tumor architecture, or a suspicious focal region warrants carcinoma exclusion.
- Final categorization requires tissue correlation rather than imaging alone.

Oncocytic papilloma: A distinct lineage

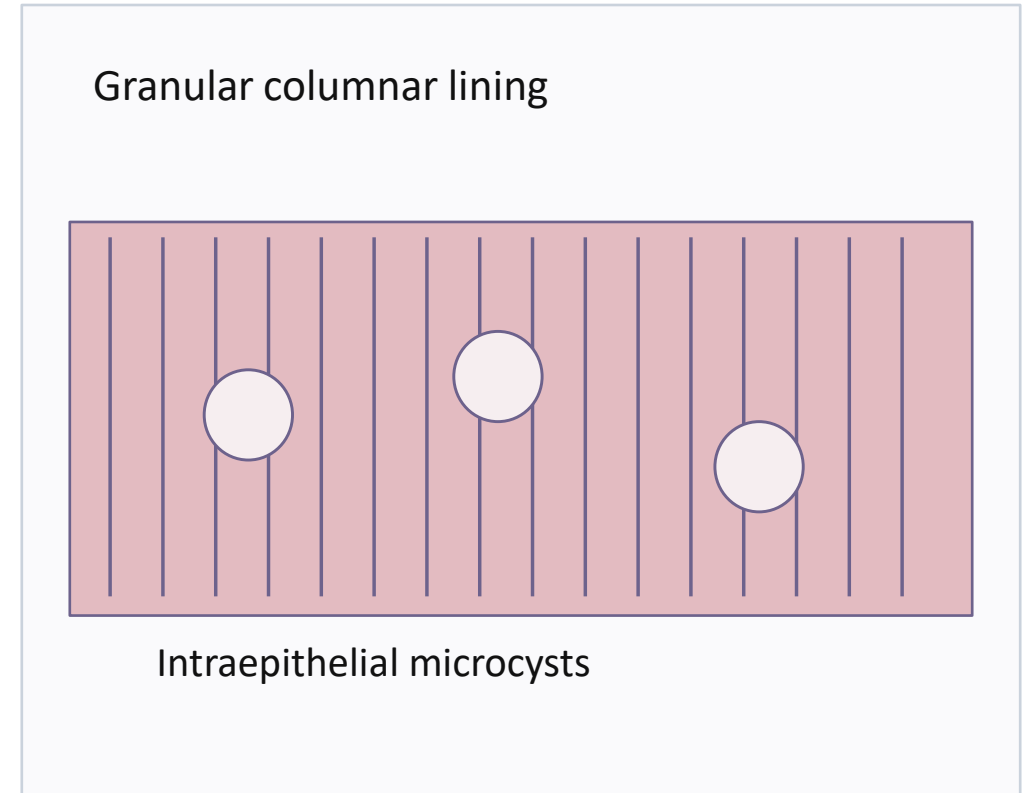
- Oncocytic sinonasal papilloma is a separate WHO-recognized subtype.
- It may have both outward and inward epithelial growth.
- Its defining feature is the character of the lining epithelium.



Schematic — not a histologic specimen

Oncocytic epithelium: Cytologic identity

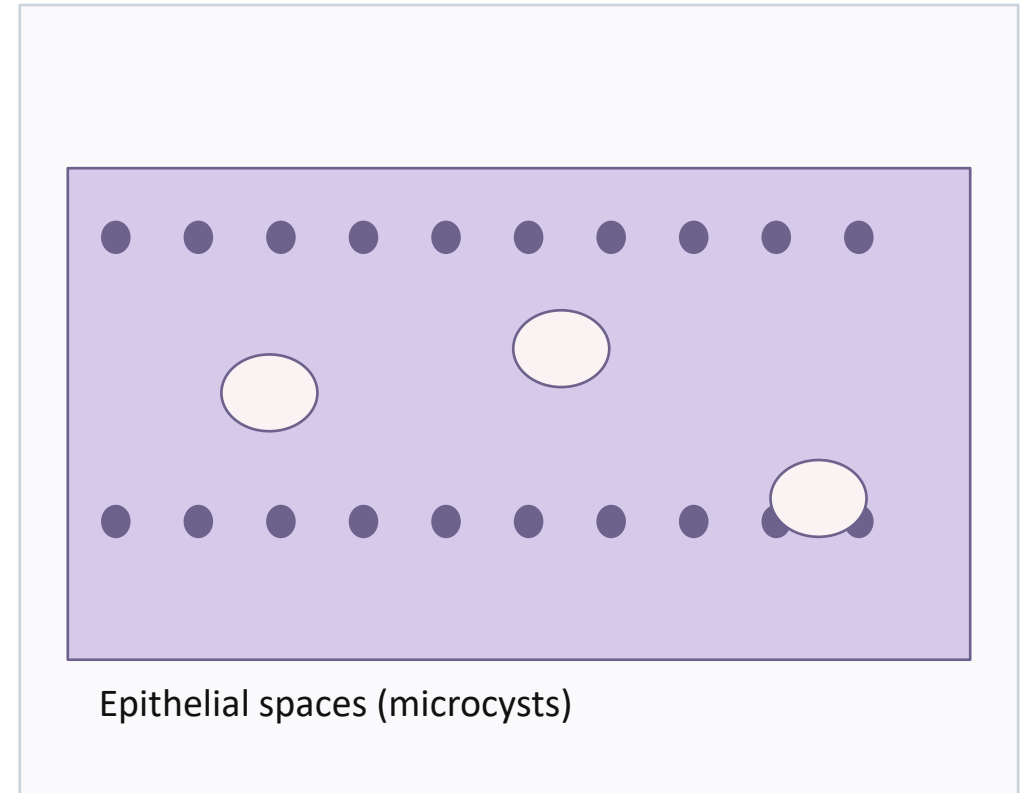
- Tall columnar epithelial cells contain abundant granular eosinophilic cytoplasm.
- Rounded nuclei tend to be relatively uniform in benign regions.
- The granular cytoplasm distinguishes oncocytic from non-oncocytic papilloma.



Schematic — not a histologic specimen

Oncocytic microcystic change

- Intraepithelial mucin-containing microcysts are common.
- Mixed exophytic and endophytic architecture may be present.
- Both the cell type and the architectural organization are needed for typing.



Epithelial spaces (microcysts)

Schematic — not a histologic specimen

KRAS is the characteristic oncocytic driver

- WHO 2022 describes recurrent hotspot KRAS mutations in oncocytic papilloma.
- HPV infection is not regarded as an etiologic driver of this subtype.

- This provides a biologic contrast with EGFR-altered inverted papilloma.

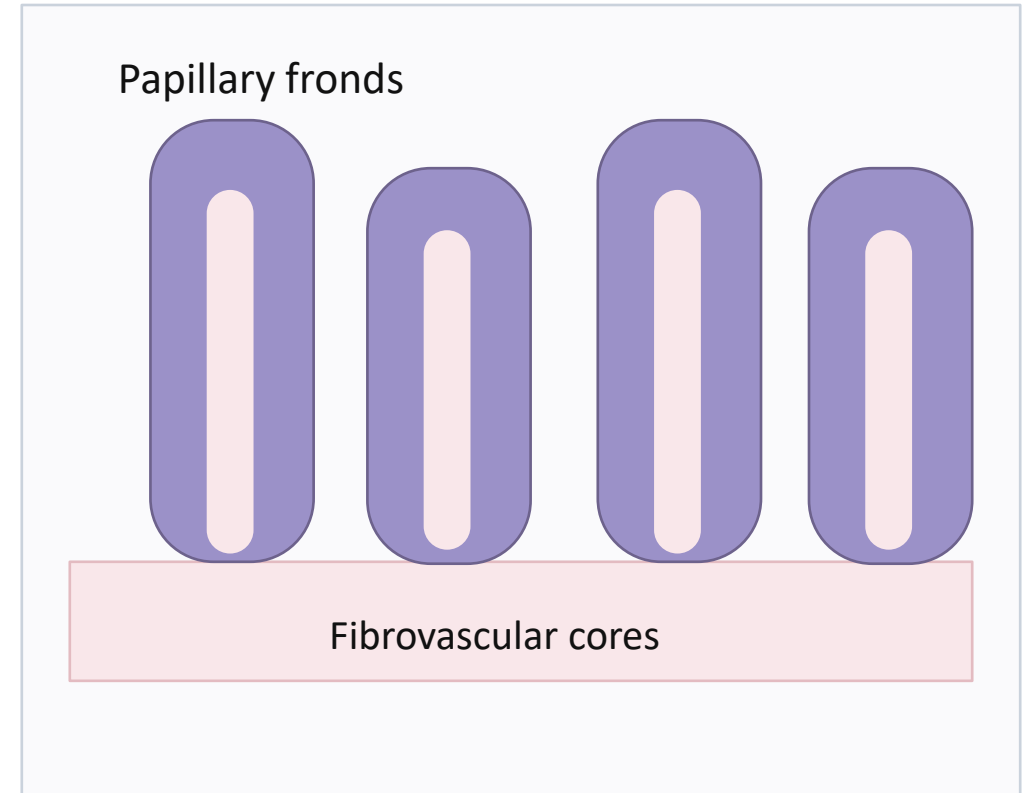
Oncocytic versus inverted papilloma

- Both can show endophytic components and intraepithelial microcysts.
- Oncocytic: Diffuse granular eosinophilic columnar cells; Often KRAS-altered.

- Inverted: Typically transitional/squamous thickening; Often EGFR-altered.

Exophytic papilloma: Papillary surface growth

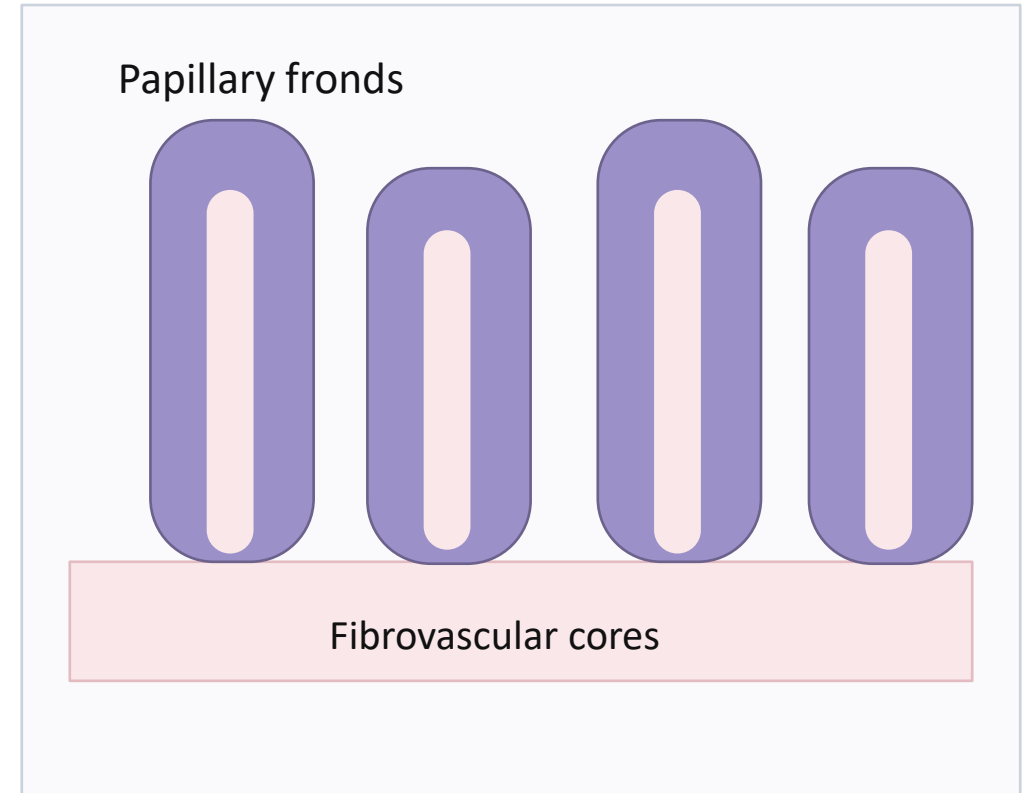
- Also termed fungiform or septal papilloma.
- Outward epithelial projections are supported by fibrovascular cores.
- The lesion lacks the dominant deep broad epithelial ingrowth of inverted papilloma.



Schematic — not a histologic specimen

Exophytic histology: Fibrovascular cores

- Finger-like fronds are lined by stratified squamous or transitional-type epithelium.
- Each frond encloses a connective tissue and vascular core.
- Superficial HPV-related change may be visible, but need not be present.



Schematic — not a histologic specimen

Low-risk HPV predominates in exophytic lesions

- WHO 2022 identifies HPV types 6 and 11 in many exophytic papillomas.
- This association differs from HPV-negative, KRAS-altered oncocytic tumors.

- Low-risk HPV in papilloma does not imply the biology of an HPV-driven carcinoma.

Exophytic tumors favor the anterior septum

- Typical origin is the anterior/lower nasal septum.
- This location provides a useful correlation with the outward-growing architecture.
- Anatomic distribution supports, but does not replace, histologic classification.

Three types: Morphological discrimination

Variant	Dominant histology	Frequent location / nuance
Inverted	Broad downward epithelial lobules	Lateral nasal wall / sinuses
Oncocytic	Granular eosinophilic columnar cells	Mixed growth; Microcysts
Exophytic	Fronds with fibrovascular cores	Often anterior nasal septum

Three types: Molecular discrimination

Variant	Predominant association	Important caveat
Inverted	EGFR mutation	Occasional low-risk HPV subset
Oncocytic	KRAS hotspot mutation	HPV generally not etiologic
Exophytic	Low-risk HPV 6/11	Active high-risk HPV not typical

P16 and HPV: A Diagnostic consideration:

- Immunohistochemical p16 expression is not proof of transcriptionally active HPV in these lesions.
- High-risk viral oncogenic activity is a different question from low-risk HPV DNA detection.
- Use targeted tests only for a defined diagnostic problem.

Classification is primarily histologic

- Anatomic location, low-power growth pattern, and epithelial phenotype usually establish type.
- Special stains or IHC have no universal diagnostic role in routine sinonasal papilloma.
- Molecular tests may support selected difficult cases, not replace morphology.

Inflammatory polyp: The major mimic

- Inflammatory polyps typically have edematous stroma and a relatively thin epithelial covering.
- Papilloma features prominent true epithelial proliferation with type-specific architecture.

- The distinction matters because papillomas require attention to complete removal and follow-up.

Respiratory epithelial adenomatoid hamartoma

- REAH typically shows a glandular/adenomatoid proliferation of respiratory epithelium.
- Thick hyalinized basement-membrane material around gland-like structures may help recognition.
- Broad squamous/transitional epithelial islands favor inverted papilloma instead.

Exophytic papilloma versus common squamous papilloma

- True Schneiderian lesions arise within respiratory sinonasal mucosa.
- A keratinizing vestibular squamous papilloma arises from skin-type lining.
- Location and epithelial maturation help avoid conflating two sites.

When oncocytic papilloma mimics a glandular tumor

- Prominent columnar cells and cysts can create a gland-like impression.
- The orderly papillomatous epithelium and absence of destructive infiltrative growth favor benign papilloma.
- Unequivocal atypia or destructive growth demands exclusion of adenocarcinoma or another carcinoma.

Carcinoma-associated warning signs

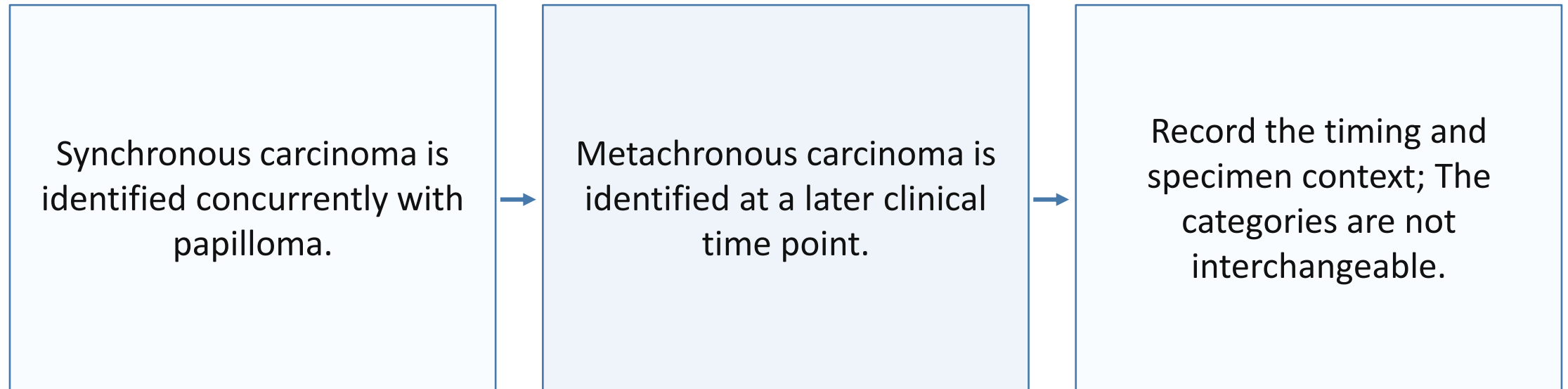
- Conspicuous cytologic atypia or abnormal maturation.
- Atypical mitoses, comedo-like necrosis, or destructive stromal nests.
- An abrupt transition from benign papilloma to malignant epithelium.
- Suspicious focal change should trigger adequate additional sampling.

Dysplasia is not the same as invasion

- Dysplasia refers to abnormal epithelial maturation and cytology within the epithelial compartment.
- Invasive carcinoma requires destructive extension beyond normal epithelial boundaries.

- A small or superficial specimen may establish atypia without resolving stromal invasion.

Carcinoma can be synchronous or metachronous



Diagnostic or mechanistic sequence (schematic)

Interpreting malignant transformation risk

- Robbins gives malignant transformation in up to 5% of cases in its sinonasal papilloma discussion.
- Published estimates vary by histologic subtype and study design; Avoid treating one number as universal.
- Exophytic carcinoma is especially rare; Inverted and oncocytic types require greater vigilance.

Additional progression-associated alterations

Subtype-specific biology and progression

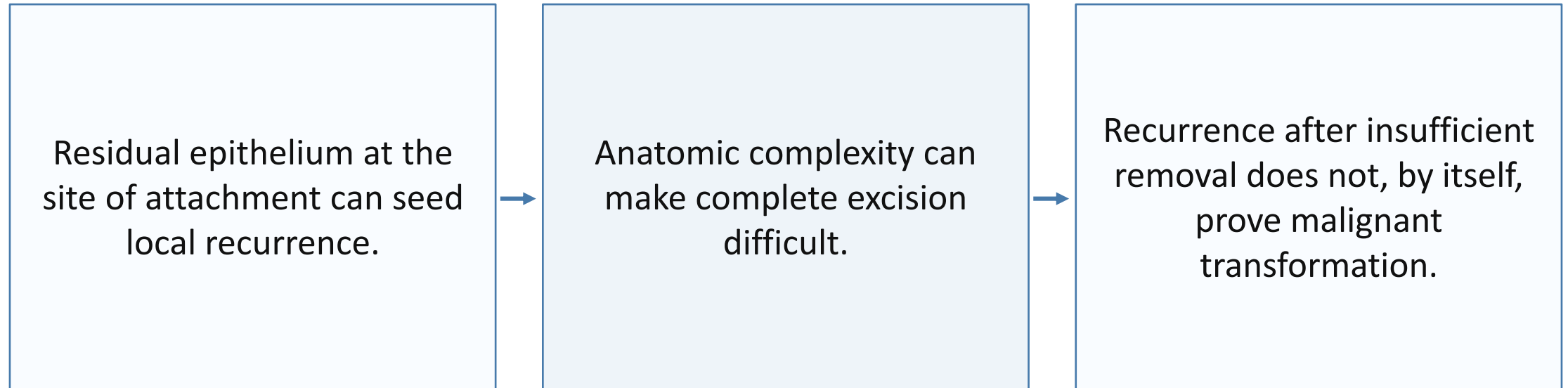
WHO 2022 describes TP53 and/or CDKN2A alterations with carcinoma progression in inverted/oncocytic lesions.

These associations are not stand-alone clinical screening thresholds.

Structural histology remains the basis for identifying carcinoma.

Illustrative conceptual grouping — not a quantitative model

Why inverted papilloma recurs



Diagnostic or mechanistic sequence (schematic)

Why attachment-oriented excision matters

- Surgical management aims to remove the lesion and address its attachment.
- Imaging and endoscopy inform the surgical map.
- Separate margin and specimen orientation information help clinicopathologic assessment.

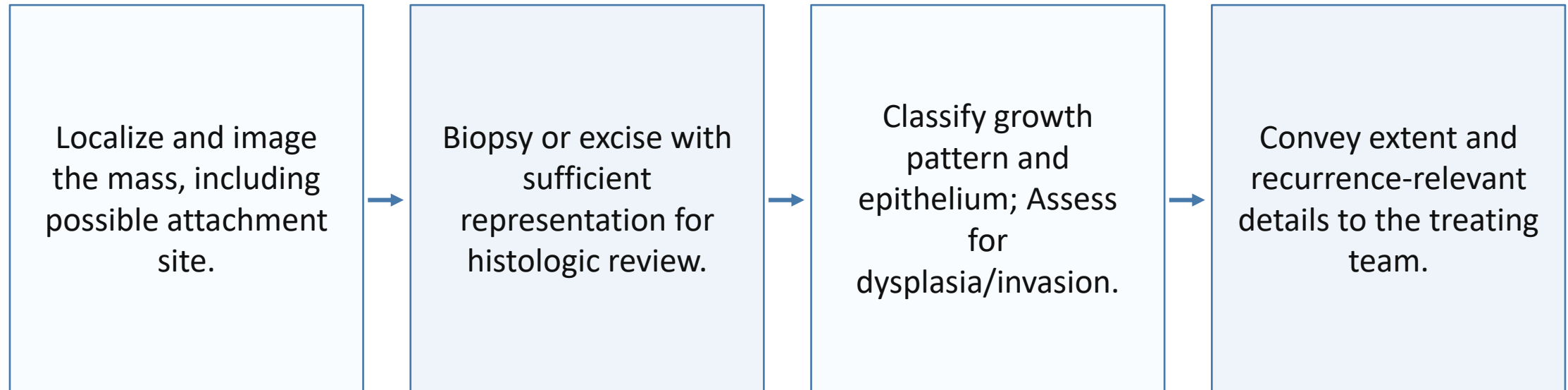
Follow-up is a pathology-informed decision

- Recurrence surveillance is important after treatment, especially for inverted papilloma.
- New symptoms or a concerning focal mass may require reassessment and sampling.
- Intensity and duration of surveillance are clinical decisions informed by site, treatment, and findings.

Structured pathology report essentials

- Specify variant and specimen/site when available.
- Describe epithelial atypia, dysplasia, or associated carcinoma explicitly.
- Comment on margins only when their assessment is technically meaningful.
- Correlate fragmented samples with operative localization.

Diagnostic workflow for a sinonasal mass



Diagnostic or mechanistic sequence (schematic)

Case 1: Endophytic nasal mass

- A middle-aged patient has a unilateral lateral-wall polypoid mass.
- Biopsy shows thick bland epithelial lobules pushing downward into stroma.
- Question: Which subtype and which common gene association?

Discussion answer (see speaker notes)

Case 2: Papillary septal lesion

- An anterior-septal lesion is composed of outward fronds with fibrovascular cores.
- The epithelium resembles stratified transitional/squamous lining.
- Question: Subtype and relevant viral association?

Discussion answer (see speaker notes)

Case 3: Granular eosinophilic lining

- A nasal lesion has mixed endophytic and exophytic growth and numerous epithelial microcysts.
- The lining is composed of tall cells with granular eosinophilic cytoplasm.
- Question: Subtype and characteristic molecular alteration?

Discussion answer (see speaker notes)

Common diagnostic errors to avoid

- Calling every sinonasal “polyp” an inflammatory lesion.
- Mistaking benign endophytic lobules for destructive carcinoma.
- Assuming oncocytic and exophytic papillomas share the EGFR driver.
- Equating HPV DNA detection with transcriptionally active high-risk HPV.

Integrated take-home distinctions

Variant	Dominant histology	Frequent location / nuance
Inverted	Broad downward epithelial lobules	Lateral nasal wall / sinuses
Oncocytic	Granular eosinophilic columnar cells	Mixed growth; Microcysts
Exophytic	Fronds with fibrovascular cores	Often anterior nasal septum

Knowledge check

- Which histologic boundary prevents benign endophytic growth being called invasion?
- Which molecular alteration is most characteristic of oncocytic papilloma?
- Why is p16 staining alone insufficient to infer active high-risk HPV?
- How can CT hyperostosis help management of inverted papilloma?

Discussion answer (see speaker notes)

Selected references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Ch 16, p 673 (2026).
- WHO Classification of Head and Neck Tumours. 5th ed. (2022); Thompson et al., Head Neck Pathol 2022.
- “OSPs and ESPs and ISPs, Oh My!” Head Neck Pathol 2017; PMCID: PMC5550400.
- “Sine Qua Non: Sinonasal Inverted Papilloma.” Head Neck Pathol 2021; PMCID: PMC8385096.