

Squamous Cell Carcinoma

Head and neck pathology

Oral cavity and HPV-associated oropharyngeal disease

Morphology • molecular biology • clinical implications

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Learning objectives

- Separate HPV-associated from conventional HPV-negative head and neck SCC.
- Explain site-specific risk factors, precursor lesions, and molecular alterations.
- Recognize the morphologic patterns of keratinizing and nonkeratinizing SCC.
- Connect primary-site behavior, cervical nodal spread, and prognosis.

What is included in this lecture?

Within scope

- Oral cavity squamous cell carcinoma
- HPV-associated oropharyngeal SCC
- Head and neck SCC molecular biology and behavior

Outside this source unit

- Cutaneous SCC
- Esophageal or pulmonary SCC
- Detailed surgical staging algorithms

SCC dominates head and neck malignancy

~95%

Of head and neck cancers are
squamous cell carcinomas in
the Robbins text

- Most arise from mucosa lined by stratified squamous epithelium.
- The remaining head and neck cancers include many salivary gland tumors.
- The same histologic name encompasses biologically distinct etiologies.

Anatomic site changes disease biology

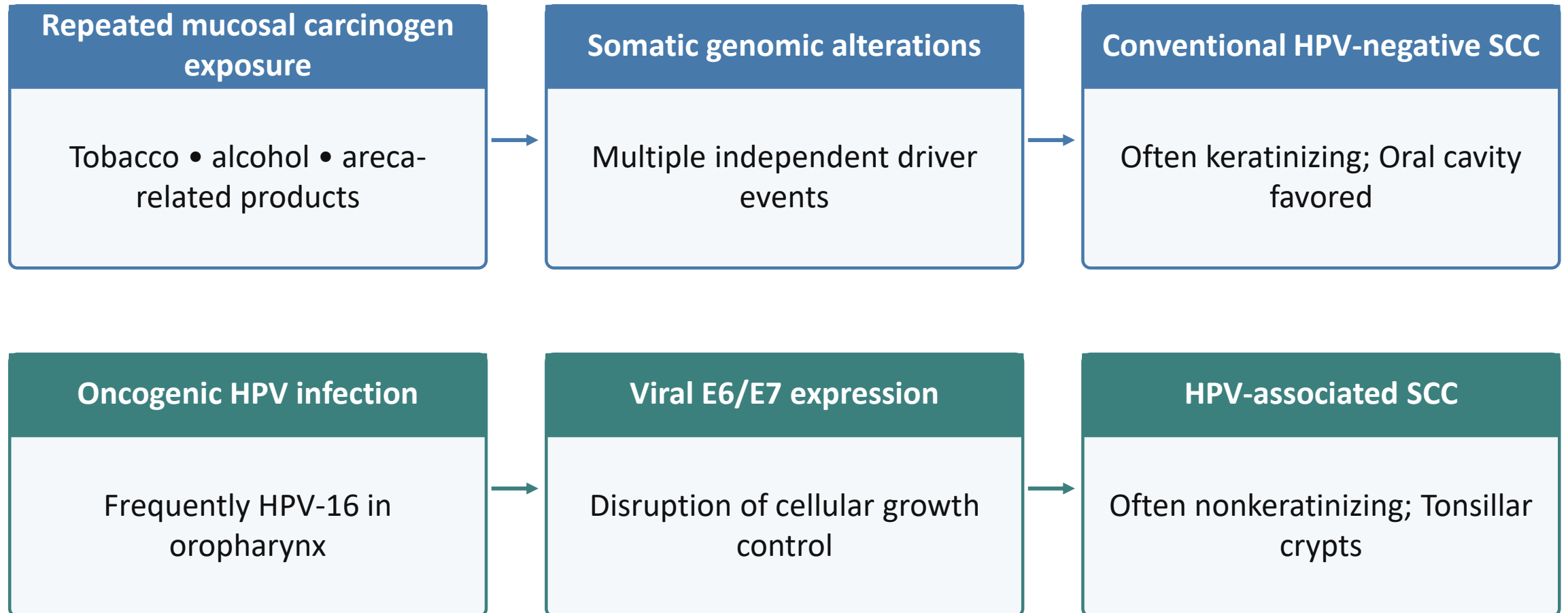
Oral cavity

- Ventral tongue and floor of mouth are frequent classic sites.
- Tobacco and alcohol remain major exposures.
- Keratinizing histology is typical.

Oropharynx

- Palatine tonsil and base of tongue are favored HPV-related sites.
- Occult mucosal primary may be very small.
- Nonkeratinizing histology is characteristic.

Two major etiopathogenic routes

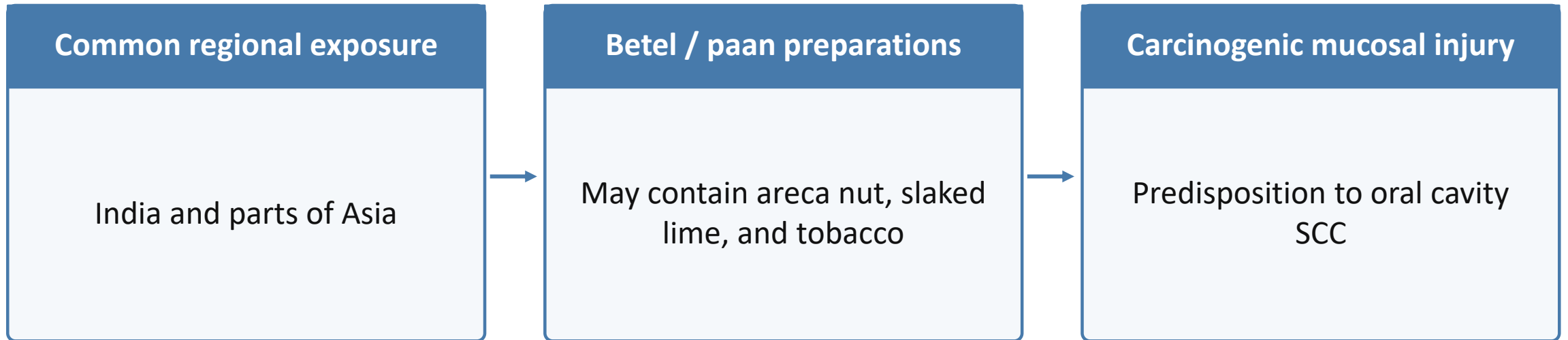


Two etiologic routes; Simplified teaching schematic

Classic exposures: Tobacco and alcohol

- The Robbins classic oral cavity SCC phenotype is linked to chronic smoked tobacco use and alcohol.
- Long-term carcinogen contact involves broad regions of upper aerodigestive mucosa.
- Multiple independent primaries are one clinical consequence of this exposure pattern.

Betel quid and paan: Regional risk



Conceptual sequence — schematic

Lower lip SCC: Distinctive exposures

- Sunlight (actinic radiation) predisposes to lower-lip SCC.
- Pipe smoking is also identified as an important lower-lip exposure.
- The specific mucosal site therefore helps interpret etiologic context.

Young adults with oral tongue SCC

- An increase in oral tongue SCC among some patients younger than 40 years.
- Some affected patients have no smoking history or established HPV association.
- The pathogenesis in this group remains unexplained in the supplied source.

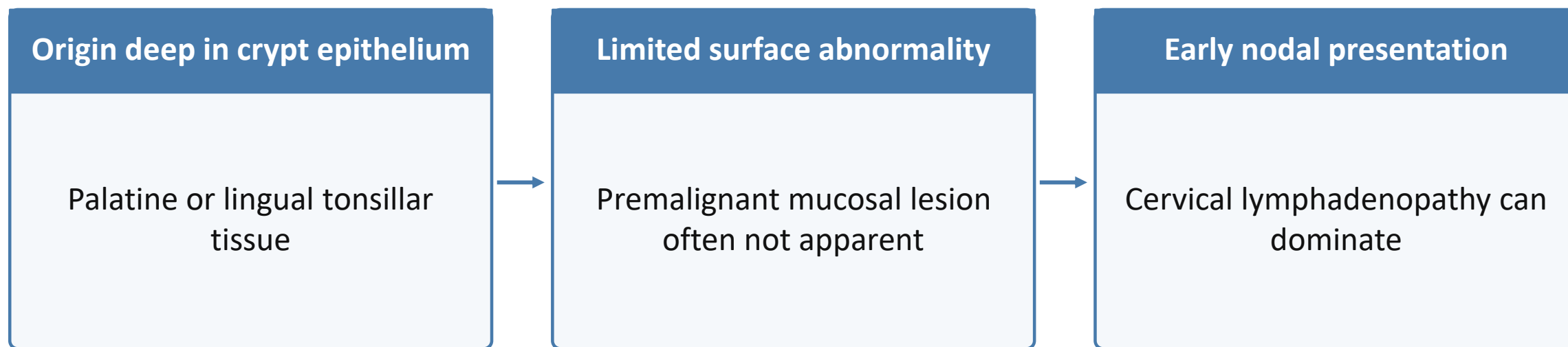
High-risk HPV drives oropharyngeal SCC

HPV-16

Prominent high-risk HPV type
associated with oropharyngeal
SCC

- Association is particularly strong for tonsillar and base-of-tongue primaries.
- HPV-related SCC is uncommon in the oral cavity compared with the oropharynx.
- Anatomic origin is essential when interpreting an HPV-associated tumor.

Why tonsillar crypt origin matters



Conceptual sequence — schematic

The screening challenge in oropharynx

- Tonsillar crypts and base of tongue are difficult to survey directly.
- A readily identifiable dysplastic mucosal precursor often is not present.
- The cervical screening analogy does not translate directly to this anatomy.

HPV association depends on subsites

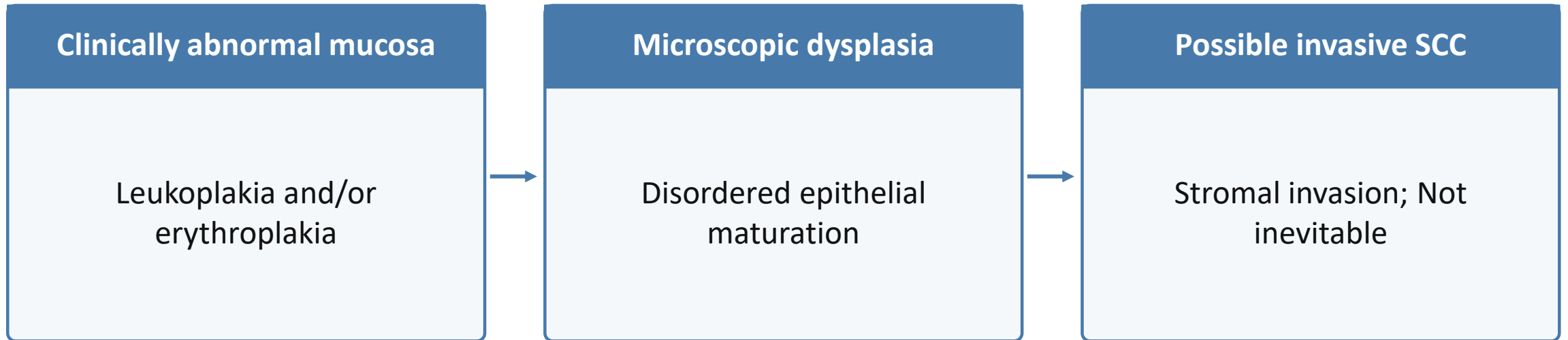
Oropharyngeal SCC

- A large fraction is oncogenic HPV-associated.
- Tonsillar crypt / base-of-tongue primaries predominate.
- P16 may serve as a useful HPV-associated marker.

Oral cavity SCC

- Most tumors are not HPV-driven in this source.
- Exposure-related keratinizing tumors are typical.
- Do not equate any oral SCC with HPV-associated disease.

Precursor lesions of classic SCC



Conceptual sequence — schematic

Leukoplakia: A clinical designation

- A persistent white patch or plaque not removable by scraping may be termed leukoplakia after excluding other causes.
- It describes appearance—not a specific histologic diagnosis.
- Biopsy establishes whether dysplasia or carcinoma is present.

Erythroplakia warrants concern

- Erythroplakia is a red, velvety mucosal lesion, sometimes eroded or depressed.
- Compared with leukoplakia, it more often contains severe dysplasia or carcinoma.
- Its red appearance may reflect epithelial abnormalities plus subjacent vascular inflammation.

White versus red mucosal lesions

Leukoplakia

- Clinically white plaque
- May range from hyperkeratosis to severe dysplasia
- Histology cannot be inferred from color alone

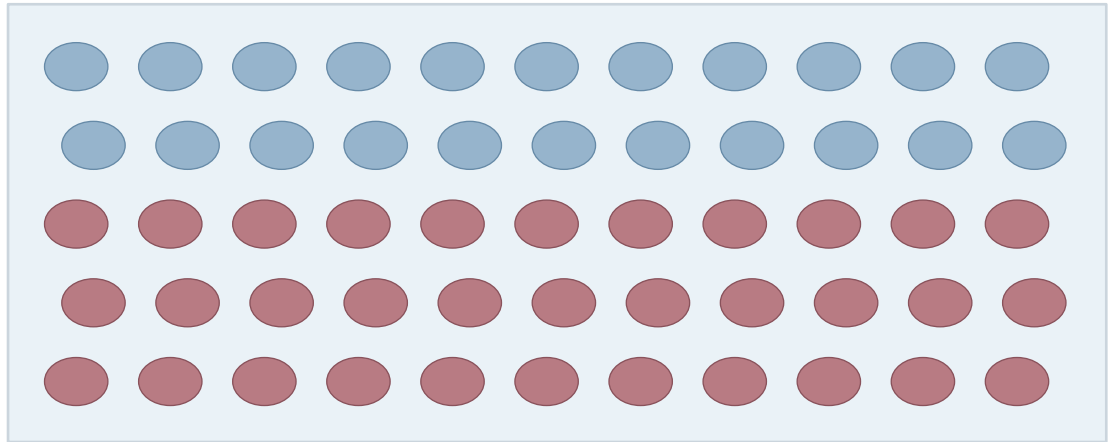
Erythroplakia

- Clinically red or velvety lesion
- Frequently severe dysplasia or carcinoma
- High-priority histologic evaluation

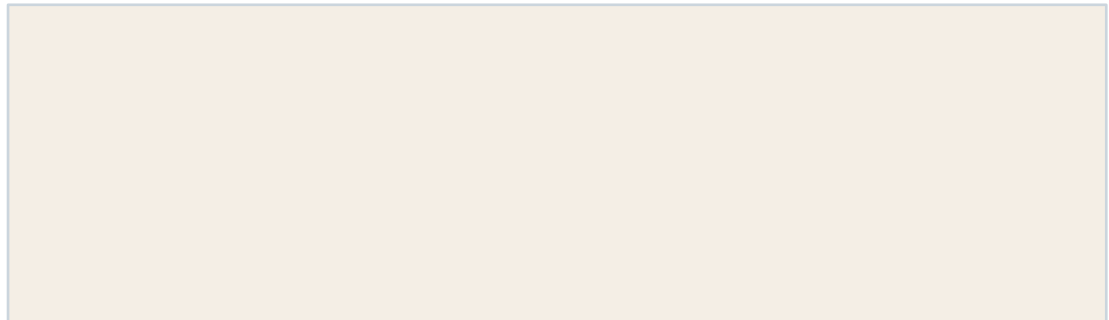
Dysplasia is the premalignant substrate

- Loss of orderly squamous maturation signifies epithelial dysplasia.
- Cytologic abnormalities and abnormal mitotic activity support the diagnosis.
- The basement membrane remains intact before invasion.

Epithelium



Intact basement membrane



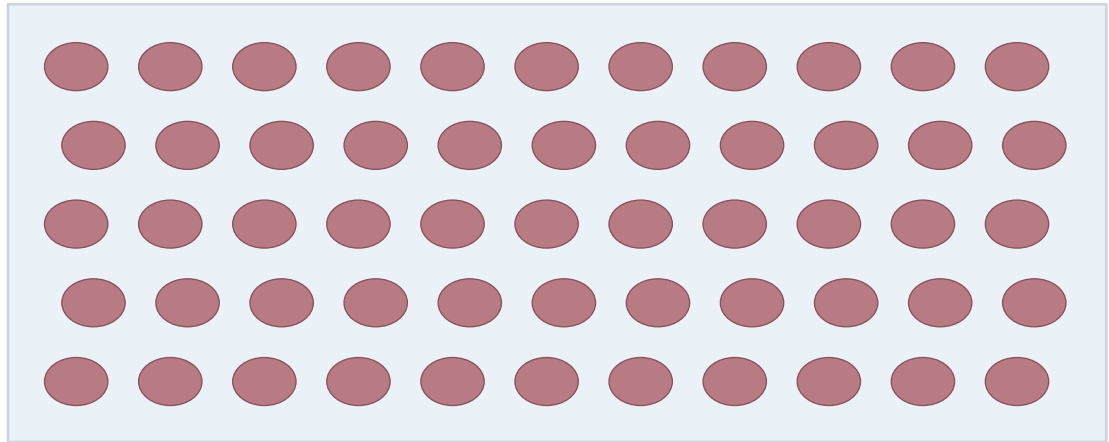
Connective tissue / stroma

Schematic — not a tissue specimen

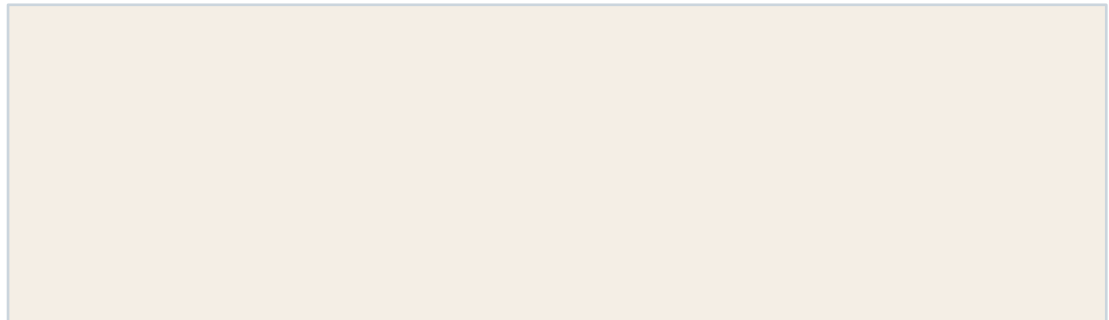
Carcinoma in situ: Full-thickness atypia

- Carcinoma in situ represents full-thickness epithelial dysplasia.
- Atypical epithelium is still confined above the basement membrane.
- It is not synonymous with stromal invasion.

Epithelium



Intact basement membrane



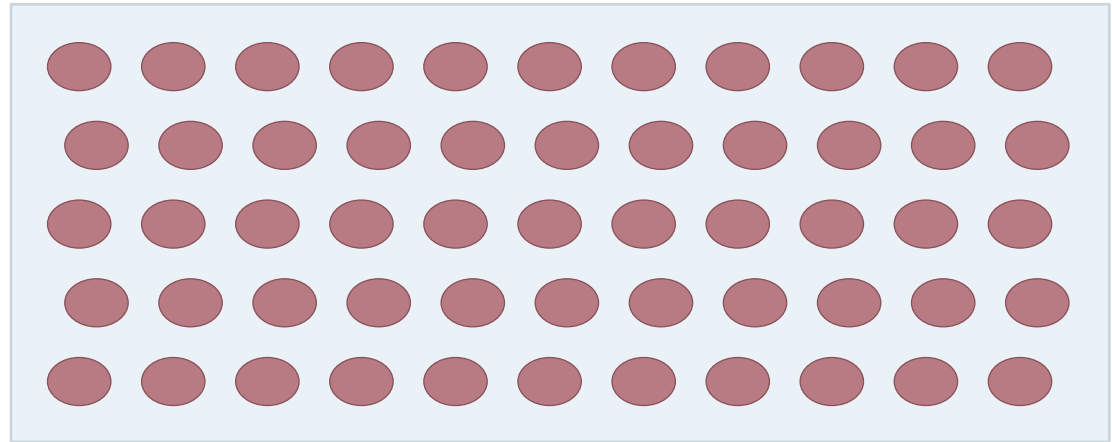
Connective tissue / stroma

Schematic — not a tissue specimen

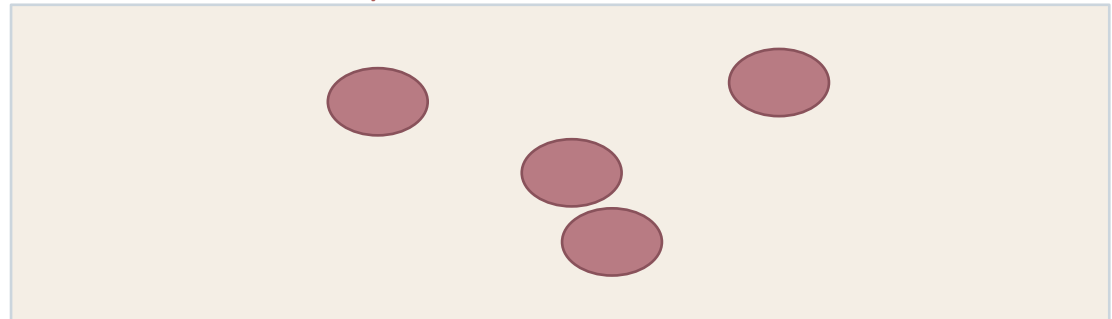
Invasion establishes carcinoma

- Malignant squamous cells penetrate into subepithelial connective tissue.
- Nests and islands extend beyond the surface epithelial compartment.
- Local infiltrative capacity underlies destructive growth and later spread.

Epithelium



Disrupted basement membrane



Connective tissue / stroma

Schematic — not a tissue specimen

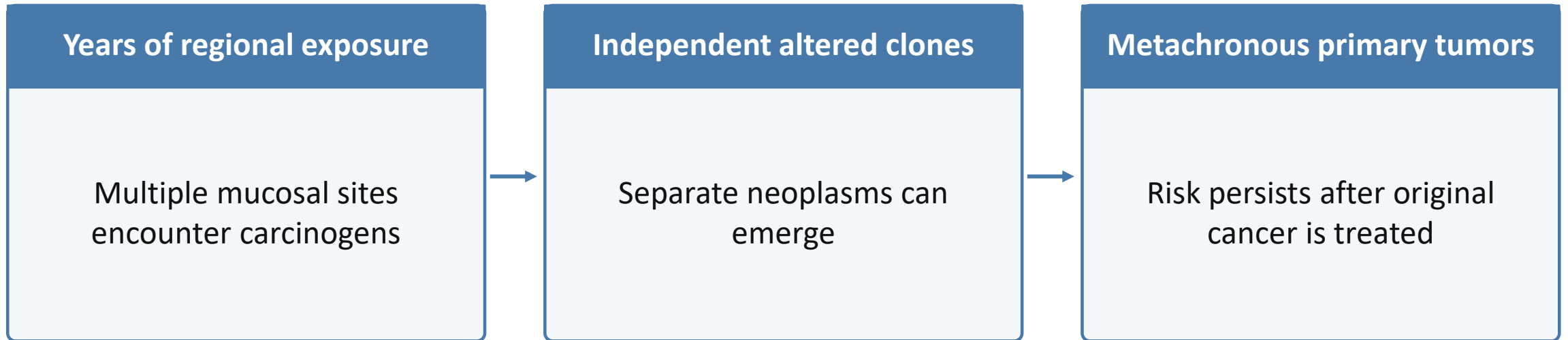
In situ disease need not precede invasion

- Classic head and neck SCC can invade without an observed full-thickness in situ phase.
- Therefore an identified precursor lesion does not establish a fixed linear timetable.
- This differs from the classic stepwise cervical SCC narrative.

Predicting transformation remains difficult

- Histologic dysplasia grading has meaningful interobserver variability.
- No single morphologic feature reliably predicts malignant transformation.
- Molecular criteria for more precise risk prediction remain a research need.

Field cancerization: The concept



Conceptual sequence — schematic

Field disease is not the same as spread

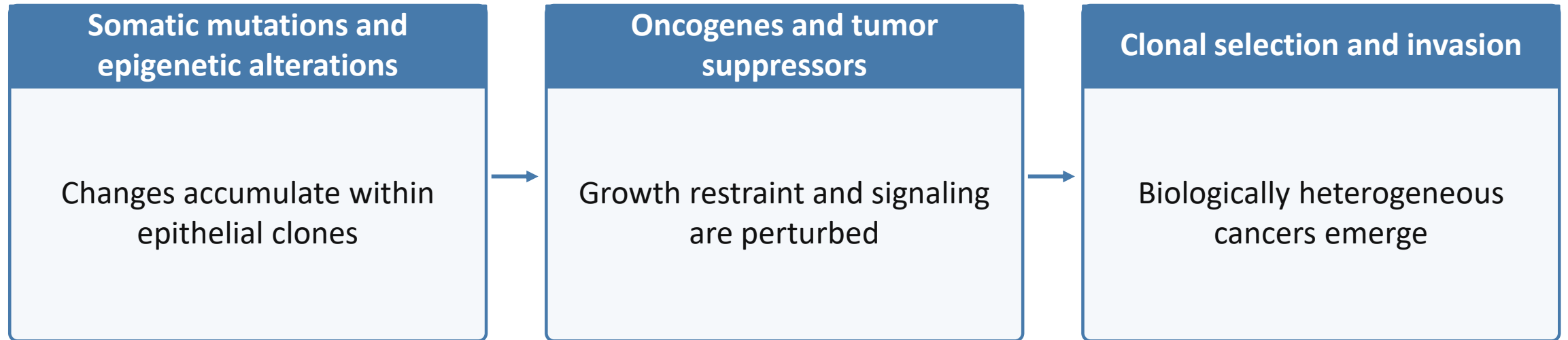
Independent second primary

- Arises separately in an exposed epithelial field
- May have a distinct origin and site
- Reflects multifocal carcinogenesis

Metastatic spread

- Arises from cells of an existing malignancy
- Nodal or distant deposits derive from primary tumor
- Reflects dissemination of one clone

Molecular transformation is multistep



Conceptual sequence — schematic

Sequencing uncovered SCC heterogeneity

- Large-scale exome studies, including TCGA, characterized head and neck SCC mutations.
- TP53, CDKN2A, and PIK3CA emerged as recurrent altered genes.
- Different tumors often harbor distinct driver combinations.

TP53: Frequent molecular alteration

TP53

Tumor-suppressor pathway

- Most frequently mutated gene described in the SCC sequencing summary.
- Mutation burden and pathway alteration differ by HPV status.
- Direct TP53 mutation is typically not the route used by HPV-driven tumors.

CDKN2A and PIK3CA: Recurring drivers

CDKN2A

- Cell-cycle regulatory locus
- Recurrent somatic alteration in conventional SCC
- Part of tumor-suppressor control of proliferation

PIK3CA

- Encodes a PI3K signaling component
- Recurrent alteration in head and neck SCC
- Highlights growth-signaling dysregulation

NOTCH1 and FAT1: Newly emphasized genes

NOTCH1

- Loss-of-function mutations identified in SCC sequencing.
- Downstream NOTCH pathway components can also be altered.

FAT1

- Tumor suppressor within the cadherin family.
- Loss-of-function events form part of the SCC landscape.

Not one mutation defines all SCC

- Beyond TP53, individual recurrent gene alterations occur at substantially variable frequencies.
- The genotype of one tumor may not represent another tumor from the same anatomic region.
- HPV status further separates mutational profiles.

HPV-negative SCC has more somatic mutations

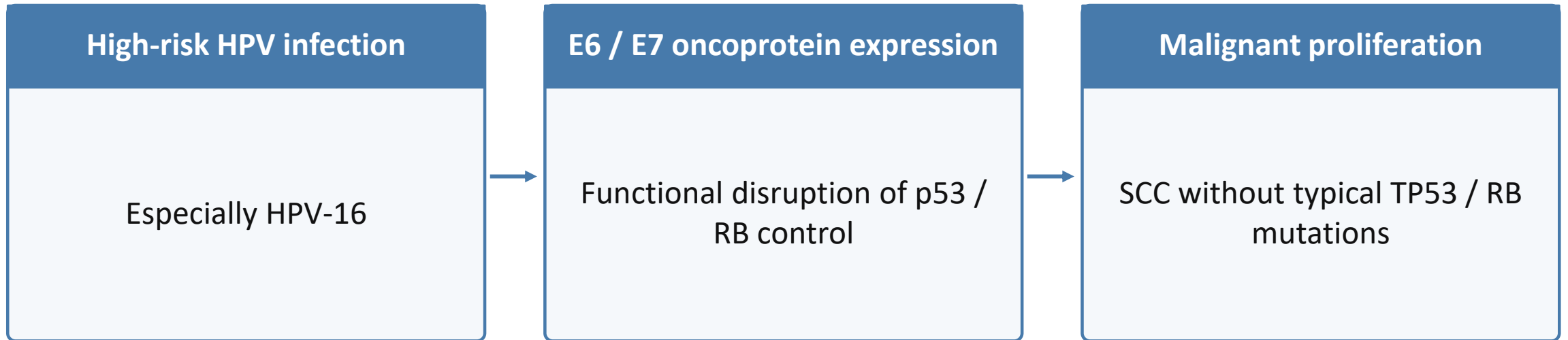
HPV-negative route

- Greater burden of acquired somatic mutations
- Common alteration of cellular tumor-suppressor genes
- Often linked with environmental carcinogen exposure

HPV-associated route

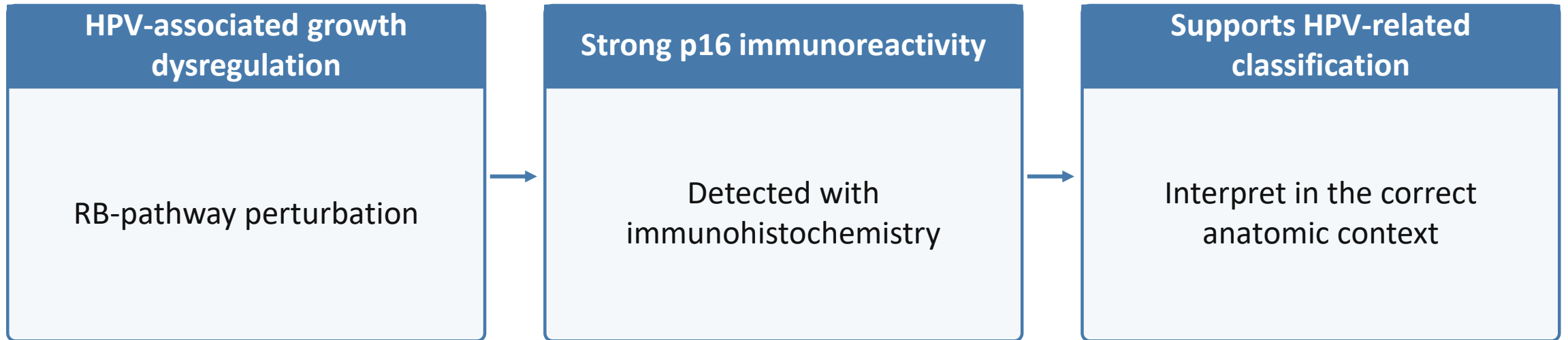
- Viral oncogenes contribute to cell-cycle dysregulation
- TP53 and RB mutation commonly unnecessary
- Lower somatic mutation burden in textbook comparison

Viral E6 and E7 change the route to cancer



Conceptual sequence — schematic

P16: Surrogate marker of HPV association



Conceptual sequence — schematic

HPV-specific confirmation is sometimes needed

P16 immunohistochemistry

- Assesses cellular protein expression
- Strong positivity correlates with HPV association
- Practical screening / surrogate technique

HPV-directed testing

- PCR detects viral nucleic acid
- In situ hybridization localizes relevant viral sequences
- May resolve selected diagnostically uncertain cases

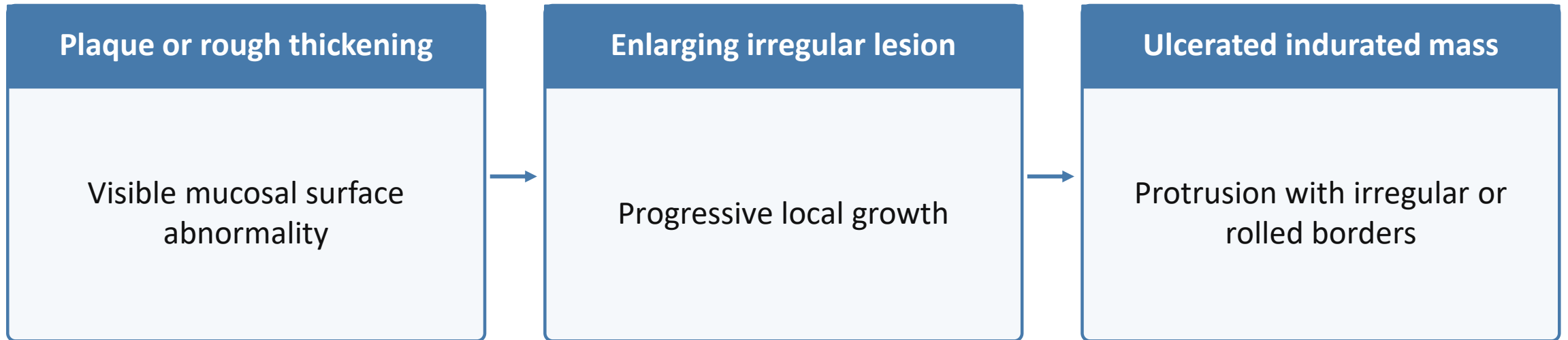
Do not confuse marker with mechanism

- P16 is a host-cell protein, not the viral genome itself.
- Positive p16 staining is supportive—not identical to direct HPV detection.
- Interpretation depends on morphology, site, and the clinical diagnostic question.

Early keratinizing SCC: Clinical appearance

- May begin as a raised, firm, pearly mucosal plaque.
- Other early lesions are rough, irregular, or verrucous thickenings.
- Pre-existing leukoplakic or erythroplakic mucosa may be present.

Progressive keratinizing SCC: Ulcerated mass



Conceptual sequence — schematic

Small oropharyngeal primary, large neck node

Primary lesion

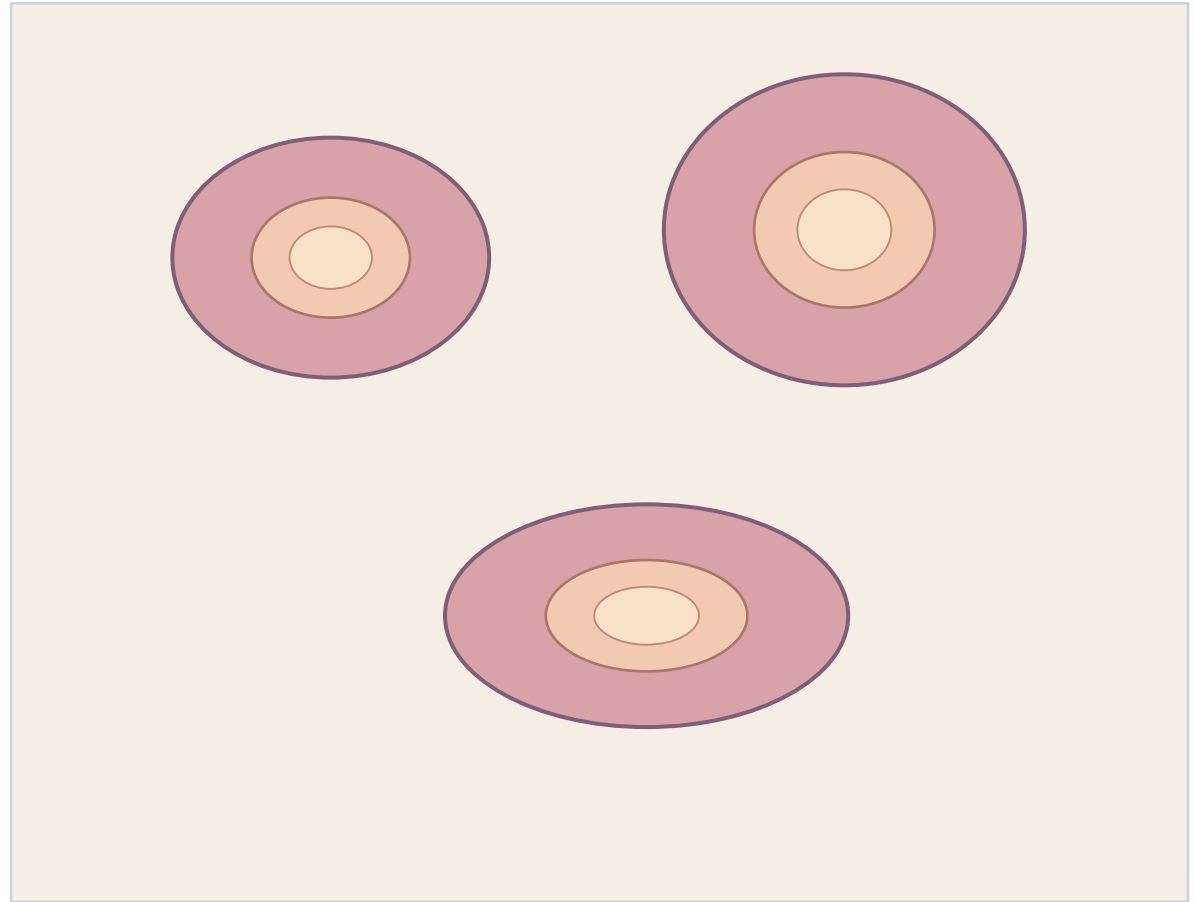
- Can be very small and deep in tonsillar crypts
- Little obvious surface mucosal alteration
- May evade early direct visualization

Regional disease

- Cervical lymphadenopathy may be prominent
- Metastatic disease can be presenting finding
- Nodal burden alone does not imply the classic HPV-negative biology

Keratinizing SCC: Invasive nests

- Malignant keratinocytes form islands and nests in stroma.
- The tumor may invade skeletal muscle beneath mucosa.
- Concentric keratin whorls demonstrate squamous maturation.

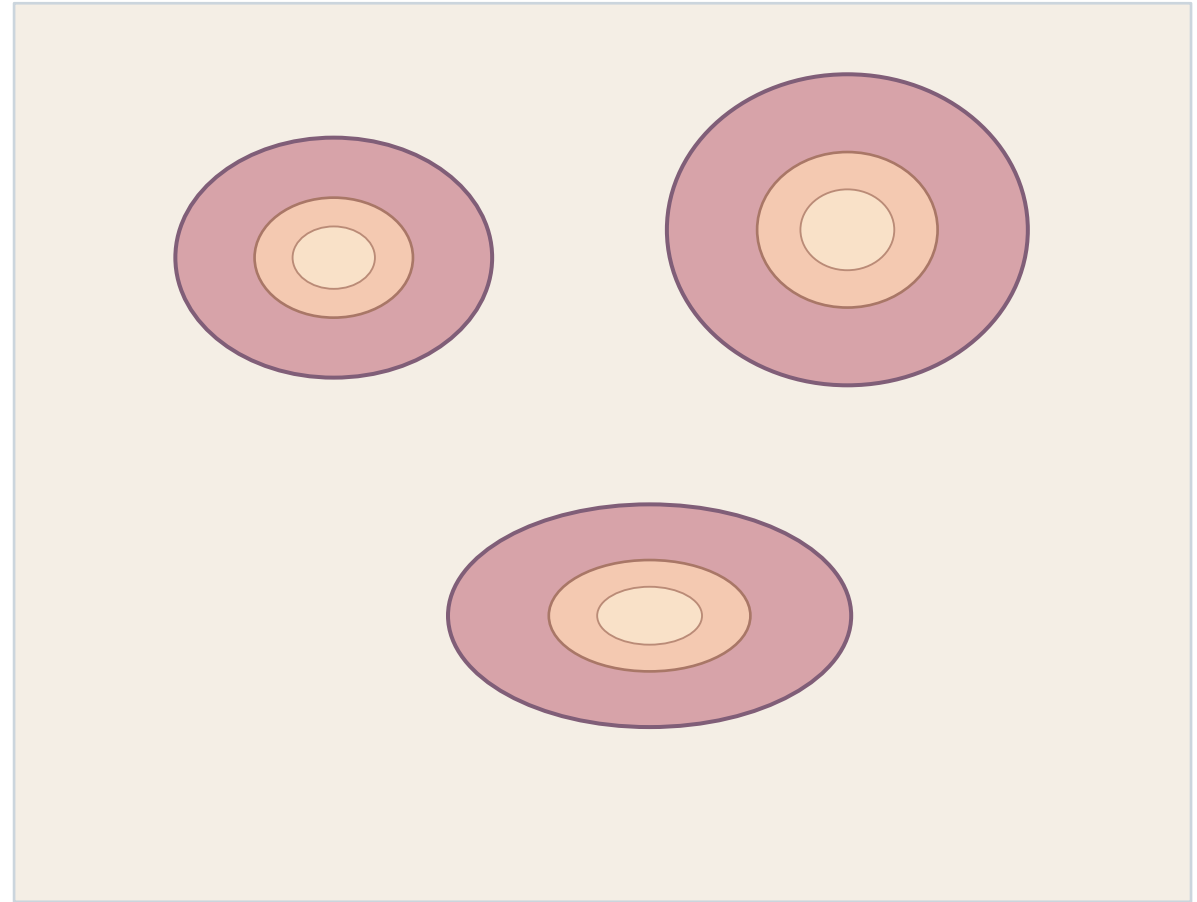


Invasive tumor nests with schematic keratinization

Schematic — not a histologic specimen

Keratin pearls indicate differentiation

- Concentric eosinophilic keratin accumulates within invasive tumor nests.
- Prominent keratinization supports a well-differentiated pattern.
- Keratinization alone does not determine aggressive behavior.



Invasive tumor nests with schematic keratinization

Schematic — not a histologic specimen

Differentiation varies widely

Well differentiated

- Recognizable squamous maturation
- Often conspicuous keratin formation
- Tumor nests resemble squamous differentiation

Poorly differentiated / anaplastic

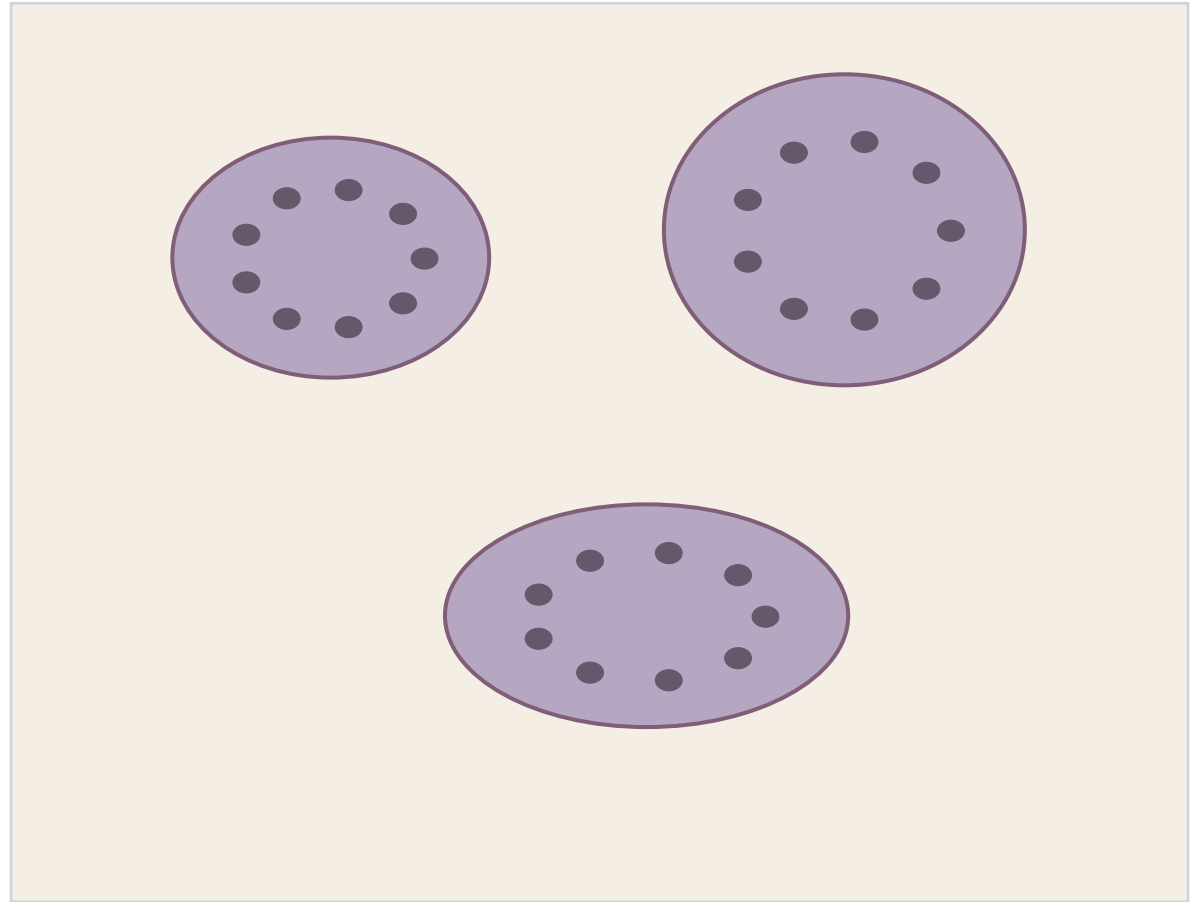
- Marked loss of keratinizing maturation
- More primitive-appearing malignant cells
- Occasional sarcomatoid morphology

Histologic keratinization is not prognosis

- The Robbins account states that degree of keratinization does not reliably correlate with growth behavior.
- Well-differentiated morphology must not be equated automatically with low clinical risk.
- Anatomic extent and etiologic class are important prognostic contexts.

HPV-associated SCC: Nonkeratinizing nests

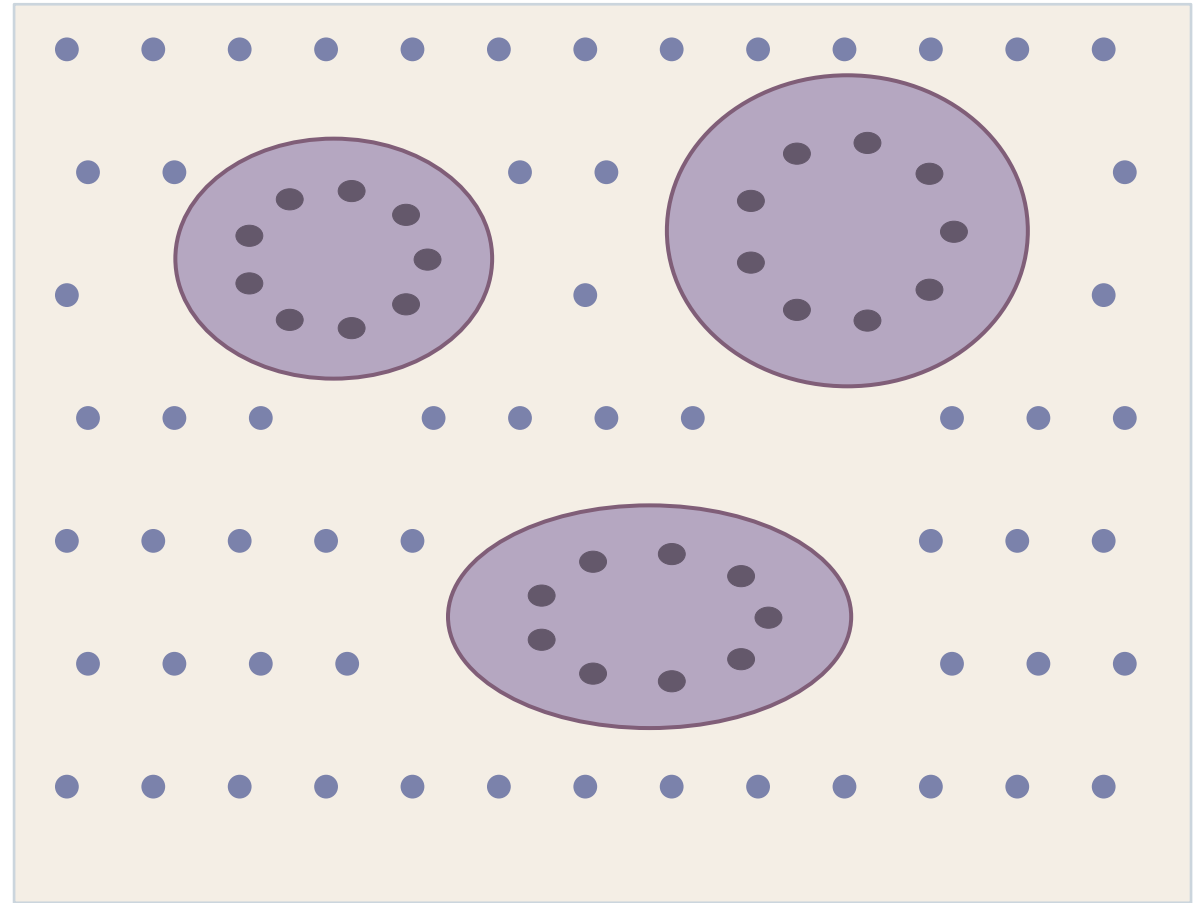
- Nests and lobules contain nonkeratinizing basaloid malignant cells.
- Keratin whorls are usually not the dominant pattern.
- Morphology reflects a distinct etiopathogenic class.



*Basaloid nonkeratinizing tumor nests
Schematic — not a histologic specimen*

Lymphoid background in HPV-related SCC

- Nonkeratinizing tumor nests may lie within sheets of lymphocytes.
- This setting mirrors lymphoid-rich tonsillar tissue.
- Anatomic origin plus morphology guides ancillary testing.



*Tumor nests within a lymphocyte-rich field
Schematic — not a histologic specimen*

Gross-to-microscopic correlation

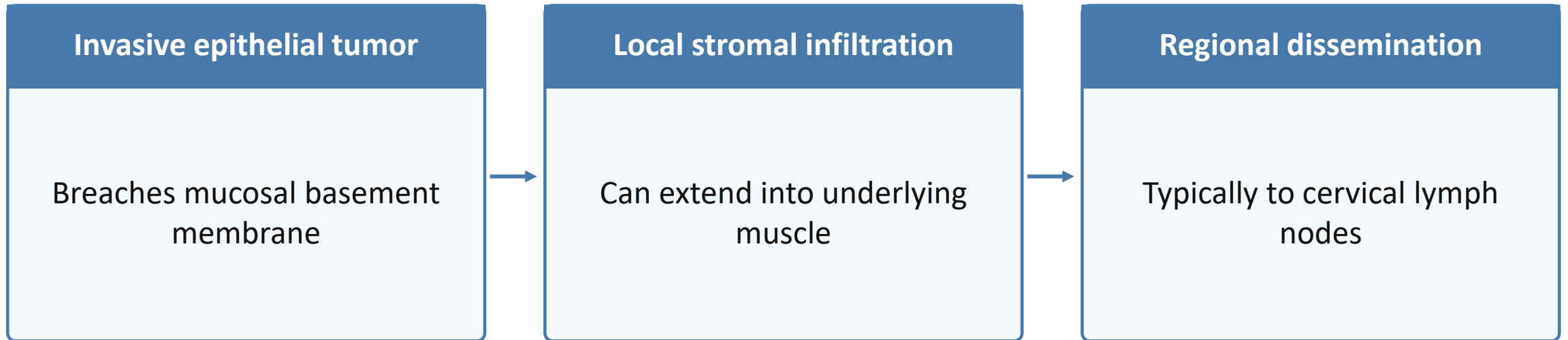
Conventional oral SCC

- Mucosal plaque → ulcerated / indurated mass
- Invasive keratinizing islands in connective tissue
- Visible surface dysplasia is often relevant

HPV-associated oropharyngeal SCC

- Occult / small crypt-associated primary
- Nonkeratinizing basaloid nests in lymphoid tissue
- Prominent cervical nodal disease is possible

SCC first infiltrates locally



Conceptual sequence — schematic

Regional lymph nodes are critical

- Cervical nodes are frequent first sites of metastatic spread.
- The route and pattern of extension depend on the primary anatomic site.
- HPV-associated tumors may show substantial nodal involvement with favorable relative outcomes.

Potential sites of distant spread

Mediastinal lymph nodes

Nodal dissemination beyond the neck

Lung

Distant metastatic site

Liver

Visceral metastatic site

Bone

Skeletal metastatic site

Why stage at presentation matters

~80% →
~20%

Textbook-reported 5-year
survival: Early to late classic
smoking/alcohol-related SCC

- These estimates describe the source text, not a current patient-specific prediction.
- Delayed detection contributes to the poor outlook in conventional SCC.
- Avoid substituting degree of keratinization for stage assessment.

HPV-associated status changes prognosis

HPV-associated oropharyngeal SCC

- Long-term outcomes are generally more favorable.
- Cervical nodal metastases can nevertheless be frequent.
- Low second-primary risk in the Robbins comparison.

Conventional HPV-negative SCC

- Classic prognosis worsens substantially with stage.
- Repeated carcinogen exposure increases field effects.
- Second primary malignancies are an important hazard.

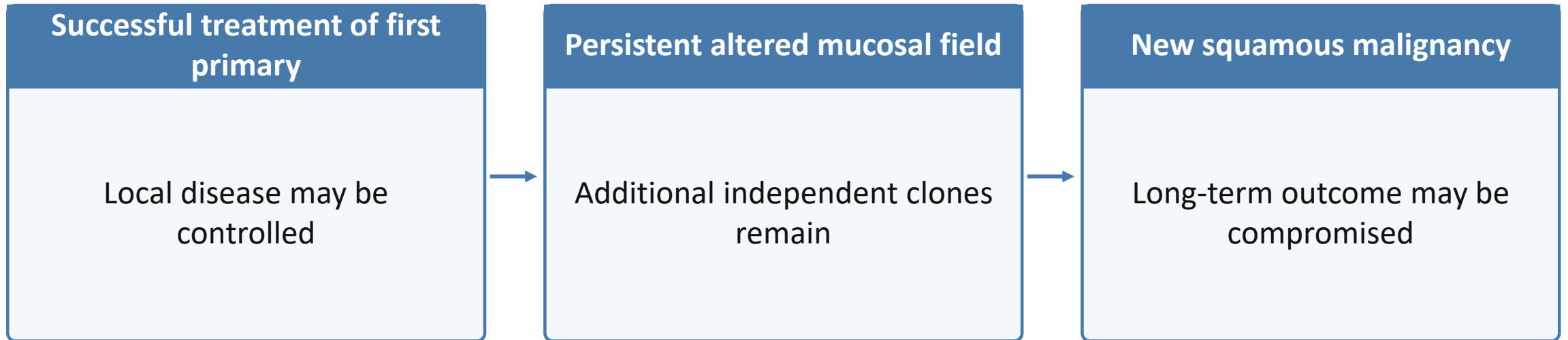
The second-primary problem

3–7%/year

Textbook-reported annual rate
of new primary tumors in
classical head and neck SCC

- Reflects persistent risk within a carcinogen-exposed mucosal field.
- A second primary is biologically distinct from metastasis.
- Surveillance must extend beyond the originally treated lesion.

Late consequences of field cancerization

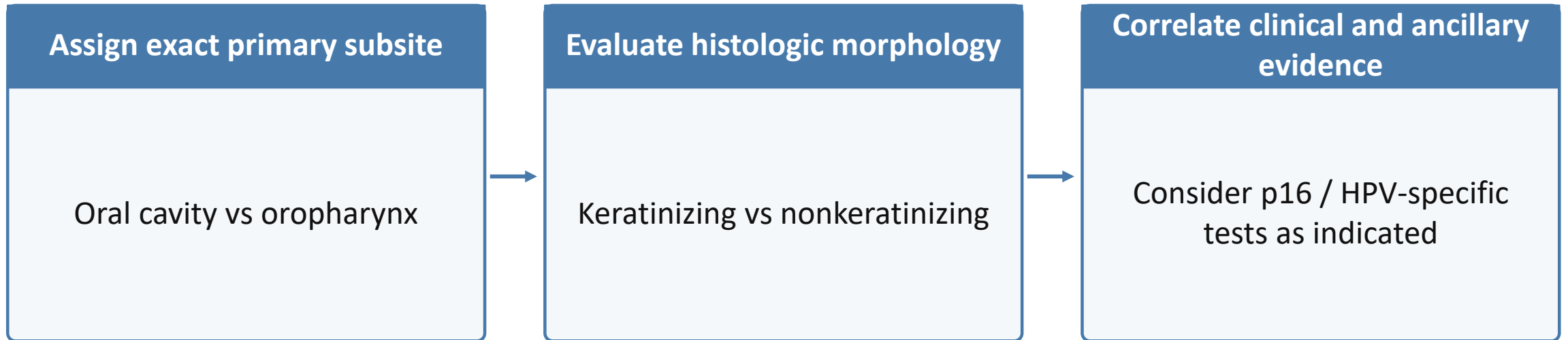


Conceptual sequence — schematic

HPV-associated versus conventional SCC

Dimension	HPV-associated	HPV-negative classic
Typical site	Oropharynx	Oral cavity
Usual phenotype	Nonkeratinizing	Keratinizing
Etiologic context	High-risk HPV	Tobacco and alcohol
Primary presentation	Small / occult primary	Often visible mucosal mass
Cervical nodes	May be bulky	Variable
Second primaries	Relatively low risk	Higher field-related risk
Overall prognosis	Generally better	Generally worse

Diagnostic reasoning begins with site



Conceptual sequence — schematic

Biopsy asks three distinct questions

Is it invasive?

Surface-confined atypia versus stromal infiltration

What morphology?

Keratinizing versus nonkeratinizing pattern

Which etiologic setting?

Site, exposure history, HPV-related evidence

Where has it spread?

Anatomic extent and cervical nodal disease

Case 1 — an ulcerated tongue lesion

A longstanding smoker has a firm ulcer with rolled margins on the ventral tongue. Biopsy shows invasive nests of atypical keratinizing cells.

Which etiopathogenic route and precursor context are most likely?

Clues for discussion

Anatomic site: Ventral tongue

Surface ulceration and induration

Keratinizing invasive nests

Case 1 — interpretation

- This pattern favors conventional HPV-negative oral cavity SCC.
- An exposure-related precursor field may include leukoplakia or erythroplakia.
- Clinical assessment must address local extension and cervical nodes.

Case 2 — a cervical neck mass

An adult presents with bulky cervical lymphadenopathy. A small palatine tonsillar lesion is found; The biopsy shows nonkeratinizing nests within lymphoid tissue and strong p16 staining.

Which SCC subgroup is supported, and why?

Clues for discussion

Small tonsillar primary

Nonkeratinizing, lymphoid-rich
histology

P16 strongly positive

Case 2 — interpretation

- An HPV-associated oropharyngeal SCC is strongly supported.
- Primary site, histology, and p16 are concordant.
- HPV-specific confirmation may be indicated in selected diagnostic circumstances.

Core diagnostic distinctions

Carcinoma in situ vs invasion

- Full-thickness atypia does not itself establish invasion.
- Malignant cells within stroma establish invasive SCC.

HPV marker vs direct HPV test

- P16 is a correlated cellular surrogate.
- PCR / ISH interrogate viral material more directly.

Summary: Four teaching conclusions

Etiology

Two dominant routes: Carcinogens and high-risk HPV

Morphology

Keratinizing oral SCC versus nonkeratinizing oropharyngeal SCC

Molecular

HPV-dependent changes differ from somatic-driver profiles

Outcome

Stage, HPV association, and field cancerization shape risk

Source and image interpretation notes

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 16, pp. 667–670.
- The primary source comprises extracted textbook text; original plate images were not supplied.
- All tissue illustrations in this deck are original editable SCHEMATICS, not clinical or histologic specimens.
- Textbook epidemiologic and survival estimates are identified as source-reported rather than current registry estimates.