

Esophageal squamous cell carcinoma

Pathogenesis • morphology • spread • clinical consequences

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Learning outcomes

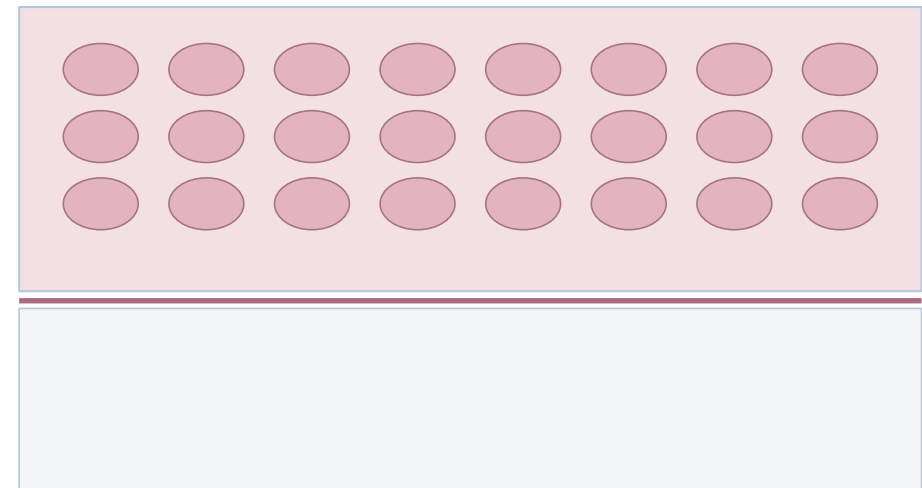
By the end of this lecture, learners should be able to:

- Relate epidemiologic exposures to carcinogenesis in the squamous-lined esophagus.
- Trace squamous dysplasia to invasive growth and interpret characteristic gross and microscopic findings.
- Predict local complications and lymph-node spread from anatomy.
- Explain why stage at diagnosis strongly determines prognosis.

Esophageal epithelium and tumor origin

- The esophagus is lined by stratified squamous epithelium.
- Squamous cell carcinoma arises from this mucosal epithelial compartment.
- A precursor squamous dysplastic lesion precedes invasive cancer.

Stratified squamous epithelium



Supporting tissue

Mucosal architecture — simplified schematic

The two predominant esophageal cancer types

Feature	Squamous cell carcinoma	Adenocarcinoma
Origin	Squamous lining	Gland-forming tumor
Common site	Middle/proximal portions	Distal esophagus
Typical background	Squamous dysplasia	Barrett esophagus
Morphologic cue	Malignant squamous nests	Malignant glands / mucin

Global distribution is highly uneven

Up to 180-fold

Up to 180-fold

- Incidence varies markedly both between countries and within countries.
- Variation of up to 180-fold.
- Risk is concentrated in several lower-resource communities.

High-incidence regions

- Regions listed by Robbins include Iran, central China, Hong Kong, Brazil, and South Africa.
- Risk varies within countries, not solely across national borders.
- Geographic clustering motivates inquiry into local exposures.

Iran

Central China

Hong Kong

Brazil

South Africa

Examples listed, not a ranking

Age and sex patterns

Patterns depend on local disease burden.

- The disease occurs predominantly in adults older than 45 years.
- Male predominance is described in low-risk regions.
- In high-risk regions, this male predominance may disappear.

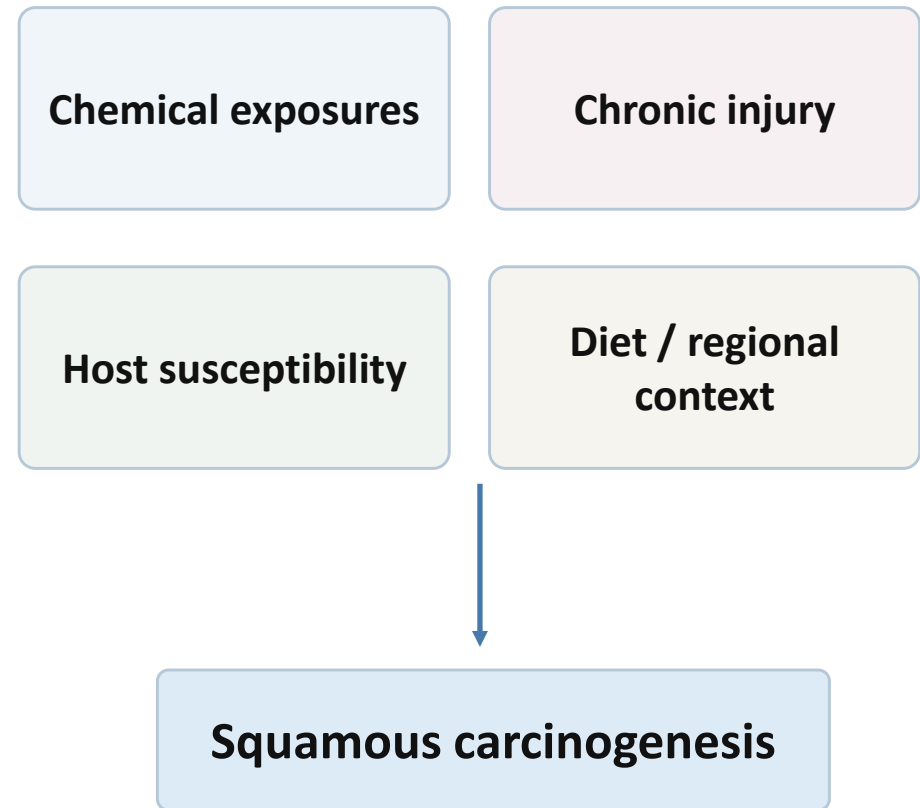
Population disparities require careful interpretation

Exposure and context matter.

- A large incidence disparity between Americans of African descent and Northern European descent.
- Known risk exposures only partially explain that disparity.
- Population-level differences should not be misconstrued as an inherent individual biologic risk.

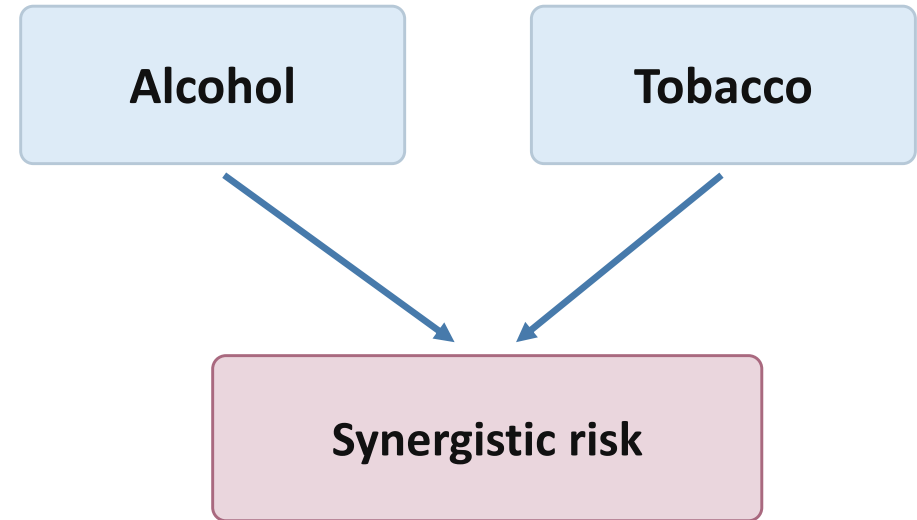
Risk factors: An integrated framework

- Carcinogenic exposure, repeated mucosal damage, inherited susceptibility, and dietary context all contribute.
- Multiple risk factors may coexist in one individual.
- Associations do not establish that all pathways are equivalent.



Alcohol and tobacco act synergistically

- Alcohol and tobacco are major associated exposures in Europe and the United States.
- Combined exposure increases risk more than either in isolation (synergy).
- Their importance varies with the geographic population.



Combined exposure is more than an additive association

Why exposures differ between regions

Etiologic heterogeneity is central to epidemiology.

- Substantial incidence occurs where alcohol and tobacco exposure is uncommon.
- Additional suspected exposures include nutrition-related factors and environmental mutagens.
- No single exposure model explains worldwide disease distribution.

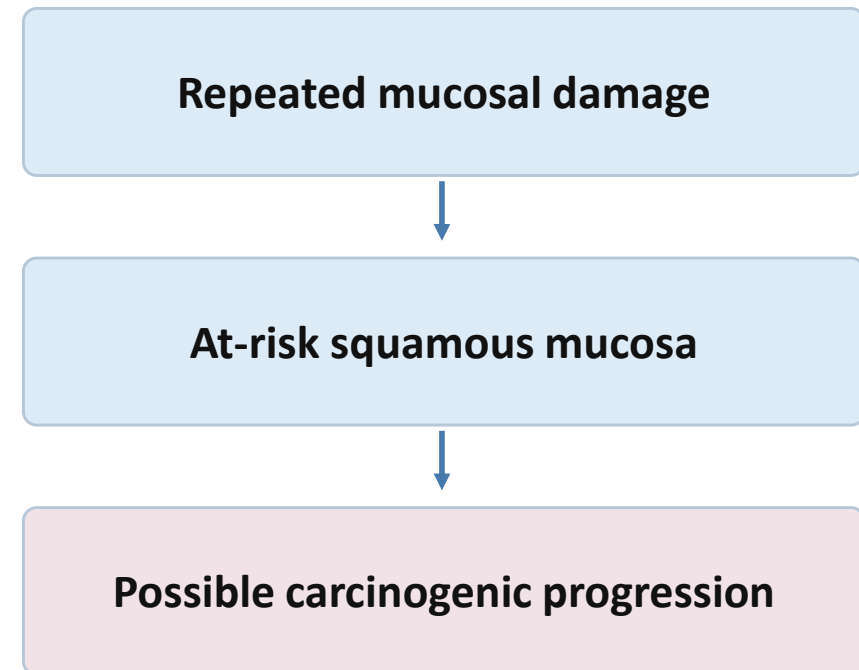
Nutrition-related risk context

Diet may modify background susceptibility.

- Diets deficient in fruits or vegetables are associated with esophageal SCC.
- Broader nutritional deficiencies are suspected to contribute in high-risk settings.
- These are risk associations; The source does not assign a single molecular mechanism.

Repeated thermal injury

- Frequent consumption of very hot beverages is an associated risk factor.
- Repeated mucosal injury as a plausible contributor.
- Thermal injury is not established as the sole cause of regional clusters.



Conceptual sequence; Precise mechanism is not established

Food and environmental mutagens

Chemical mutagen exposure is one proposed route.

- Suspected exposures include polycyclic hydrocarbons and nitrosamines.
- Other mutagenic compounds may occur in fungus-contaminated foods.
- Associations in high-risk populations require cautious interpretation.

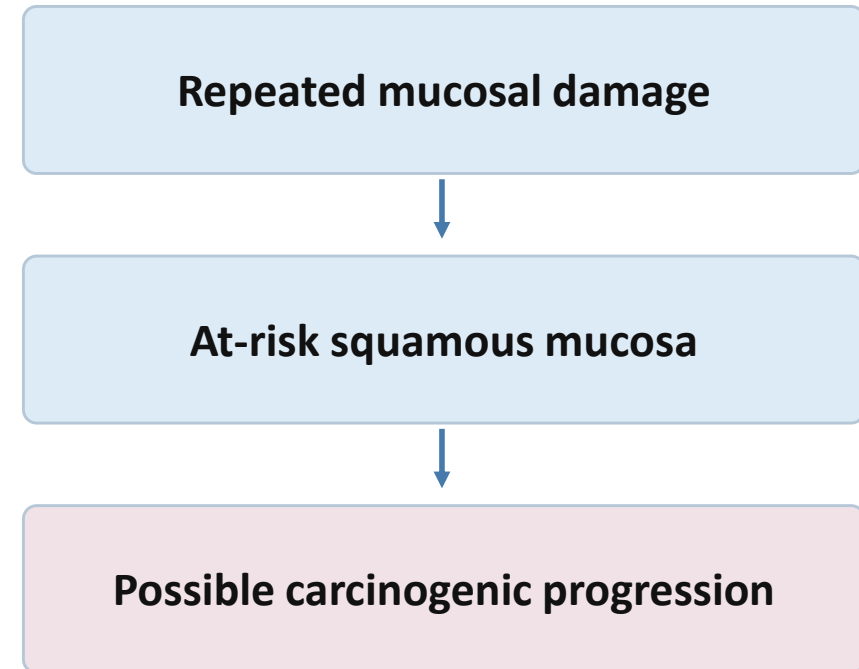
Acetaldehyde-associated high-risk setting

An example of a geographically specific exposure.

- A high-incidence pocket in western Kenya.
- Consumption of mursik, a traditional fermented milk containing acetaldehyde, has been linked to this setting.
- This is a site-specific epidemiologic association—not a universal cause of esophageal SCC.

Caustic esophageal injury

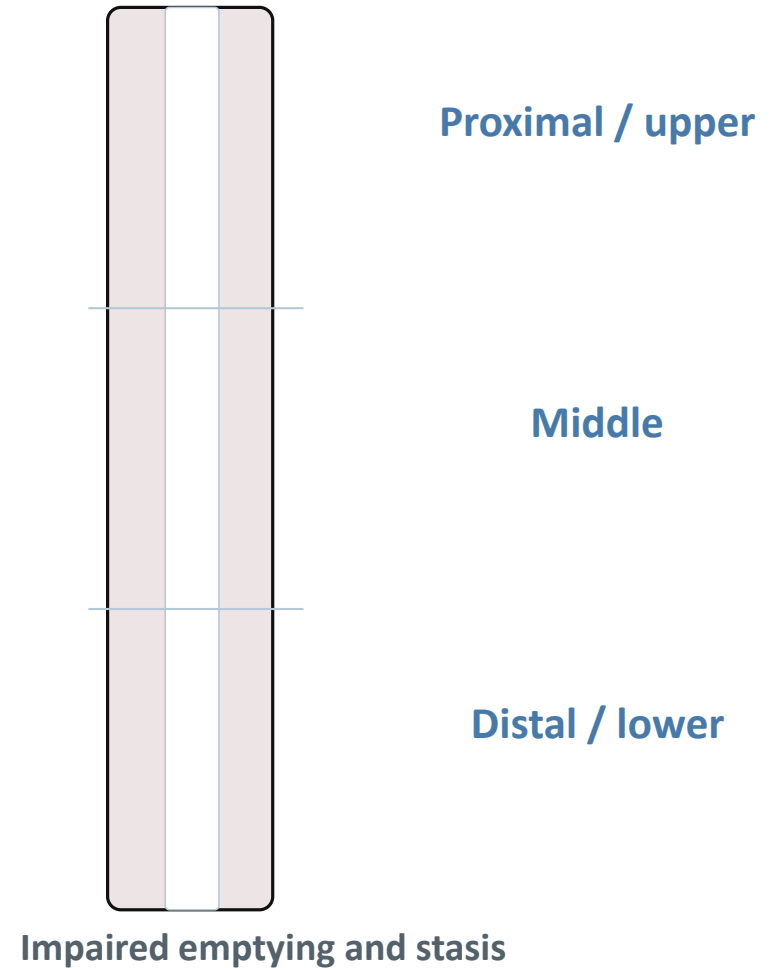
- Previous caustic injury is an established clinical risk factor.
- A history of severe esophageal injury may define an at-risk clinical context.
- Not every patient with caustic injury develops carcinoma.



Conceptual sequence; Precise mechanism is not established

Achalasia as a predisposing condition

- Achalasia is associated with increased esophageal cancer risk.
- It produces impaired esophageal emptying and stasis in the source chapter.
- Its inclusion highlights a clinical condition rather than a direct chemical carcinogen.



Plummer–Vinson syndrome

Recognize the named association.

- Plummer–Vinson syndrome is listed as a risk factor for esophageal SCC.
- Its relevance is identifying an associated clinical syndrome.
- The provided SCC section does not quantify attributable risk or specify surveillance protocols.

Tylosis: Inherited susceptibility

- Tylosis is a rare autosomal dominant disorder.
- It is marked by hyperkeratosis of palms and soles.
- It is strongly associated with esophageal squamous cell carcinoma.

Autosomal dominant tylosis



Palmar / plantar hyperkeratosis

Esophageal SCC association

Inherited clinical association; Not a risk prediction model

Remote mediastinal radiation

Exposure history may precede symptoms by years.

- Prior radiation to the mediastinum predisposes to esophageal carcinoma.
- Most associated cases occur at least five years after exposure.
- A remote treatment history is relevant during risk assessment.

Human papillomavirus: Uncertain contribution

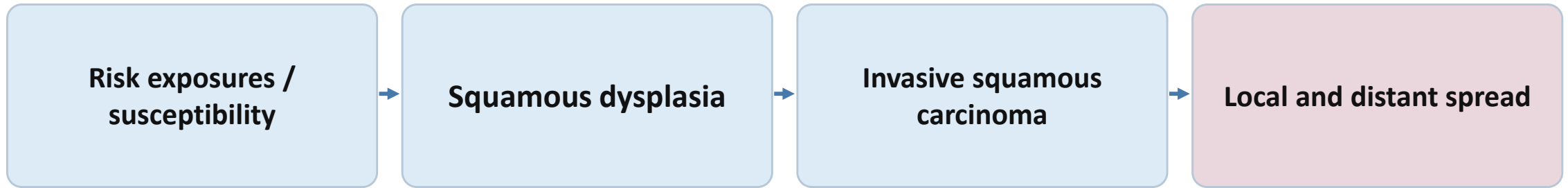
Suspected association ≠ confirmed etiologic driver.

- Robbins suggests HPV infection might contribute in certain high-risk regions.
- The language is explicitly tentative and geographically qualified.
- Do not treat HPV as an established universal cause of esophageal SCC.

Etiology: Synthesis of evidence strength

Association in Robbins	Interpretation	Examples
Prominent	Established risk association	Alcohol; tobacco
Recognized clinical risk	Predisposing condition	Achalasia; caustic injury; tylosis
Suspected contribution	Unresolved etiologic weight	Food mutagens; thermal injury
Possible / uncertain	Do not generalize	HPV in high-risk regions

Carcinogenesis is a multistep process

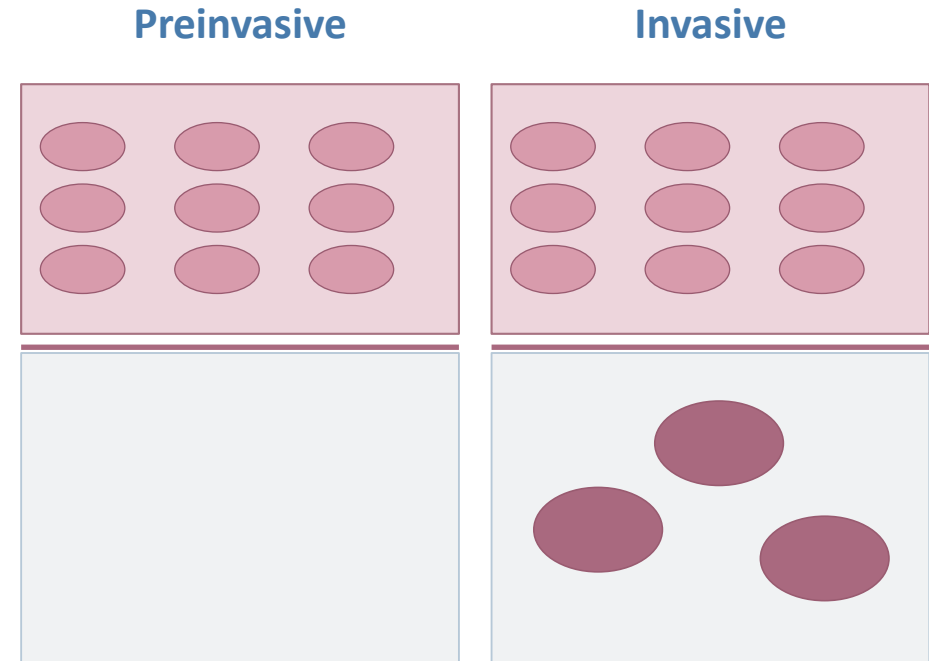


Schematic sequence

- Neoplastic precursor lesions arise within squamous mucosa.
- Invasion permits extension beyond the epithelial compartment.

Squamous dysplasia: Preinvasive precursor

- Robbins calls the in situ precursor “squamous dysplasia.”
- Comparable lesions may be termed intraepithelial neoplasia or carcinoma in situ at other sites.
- The critical transition is progression from epithelial atypia to invasive growth.



Epithelial boundary (horizontal line); Invasion shown at right

In situ disease versus invasion

In situ / squamous dysplasia

Atypical neoplastic epithelial cells

Preinvasive compartment

No invasion shown in schematic

Invasive squamous carcinoma

Malignant cells extend beneath epithelium

Infiltration into supporting tissues

Capacity for local extension and nodal spread

Conceptual comparison — not a histologic micrograph

Molecular heterogeneity: Three subtypes

- Three molecular genetic subtypes.
- Two subtypes are chromosomally unstable.
- A rarer third subtype is described as chromosomally stable.

Subtype 1

Nrf2-pathway overlap

Subtype 2

Immune infiltration

Subtype 3

SMARCA4; PIK3CA / PTEN

Biological categories described

Molecular subtype 1: Oxidative-stress signaling

A distinctive mutational signature, not a temporal cascade.

- This molecular subgroup overlaps in mutation patterns with head-and-neck squamous cell carcinoma.
- Altered genes include components of the Nrf2 pathway.
- The Nrf2 pathway regulates cellular responses to oxidative stress.

Molecular subtype 2: Immune-associated pattern

A distinct tumor-associated immune phenotype.

- Lacks the Nrf2-pathway mutations used to characterize subtype 1.
- Displays pronounced immune-cell infiltration.
- Increased executioner caspase-7 cleavage is described.

Subtypes 1 and 2 share cell-cycle alterations

- Both are chromosomally unstable.
- Mutations or amplifications affect genes associated with cell differentiation and cell-cycle control.
- The shared genomic theme does not erase differences between subtypes.

Differentiation control

Cell-cycle regulation

Chromosomal instability

Shared findings in molecular subtypes 1 and 2

Subtype 3: A rare stable-genome subtype

Chromatin regulation and PI3K-pathway genes feature in this subtype.

- An uncommon chromosomally stable subtype.
- It carries missense mutations of SMARCA4.
- Either PIK3CA or PTEN mutation is also described.

Molecular subtype comparison

Characteristic	Subtype 1	Subtype 2	Subtype 3
Chromosomal state	Unstable	Unstable	Stable
Distinctive features	Nrf2-pathway lesions	Immune infiltration; caspase-7 cleavage	SMARCA4 and PIK3CA/PTEN
Shared / caveat	Cell-cycle abnormalities	Cell-cycle abnormalities	Uncommon subgroup

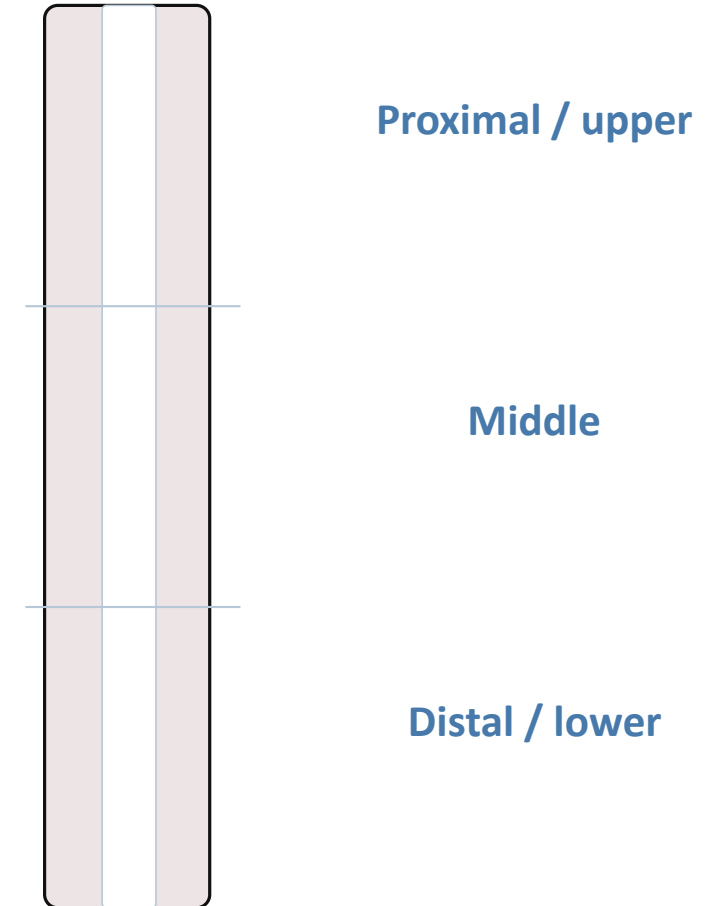
Molecular classifications: Proper use

Subtype ≠ validated clinical treatment guide.

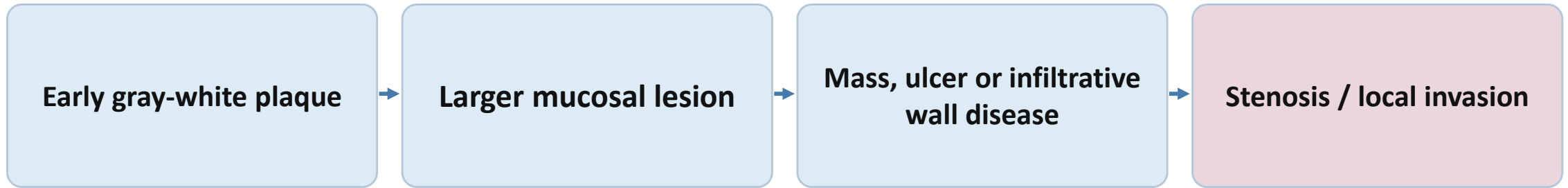
- The Robbins discussion is biological taxonomy, not a treatment decision algorithm.
- No assay thresholds or routine molecular testing indications are provided in the source.
- Avoid inventing predictive biomarkers or clinical actionability from descriptive genomics.

Anatomical distribution of esophageal SCC

- SCC primarily occurs in the proximal esophagus.
- Approximately half develop in the middle third.
- This contrasts with the distal predominance of adenocarcinoma.



Gross lesion evolution

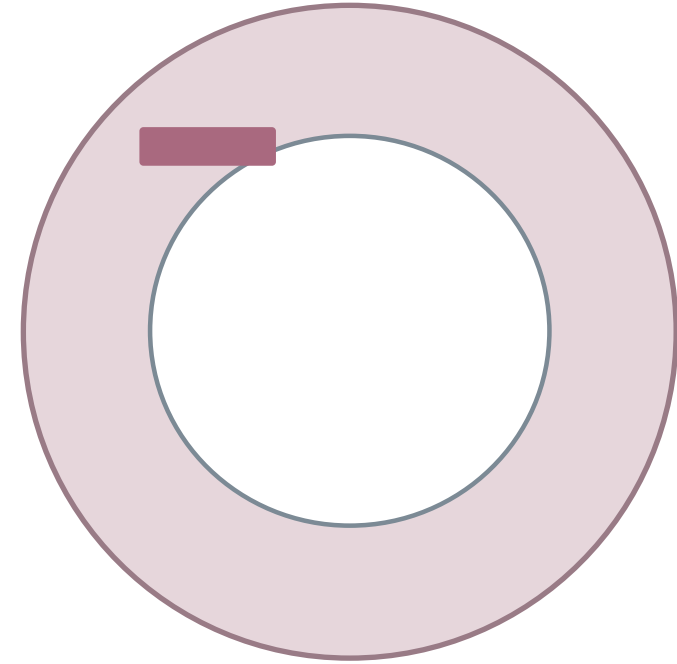


Schematic sequence

- Growth can occur over months to years.
- Macroscopic pattern depends on how tumor expands.

Earliest gross appearance

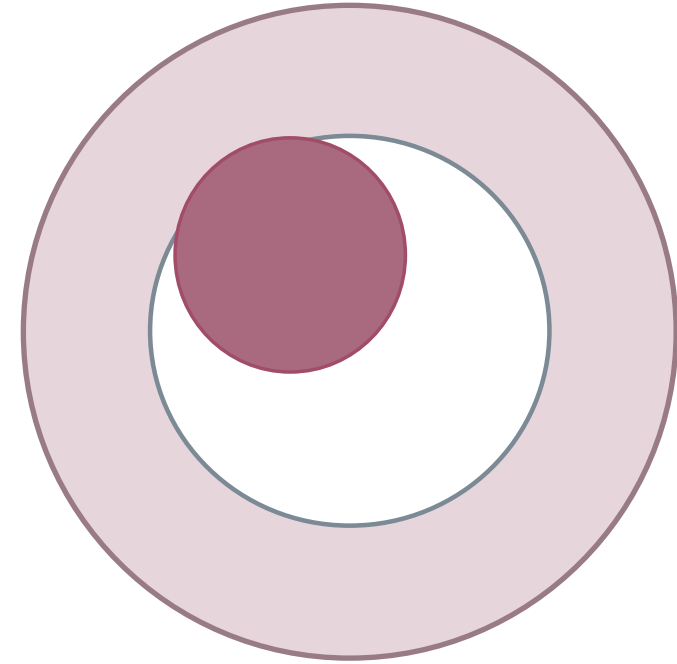
- Initial lesions can appear as small, gray-white plaque-like thickenings.
- Their subtle appearance contrasts with large symptomatic tumors.
- Early recognition matters because superficial disease has better outcomes.



Early gray-white mucosal plaque

Exophytic growth causes obstruction

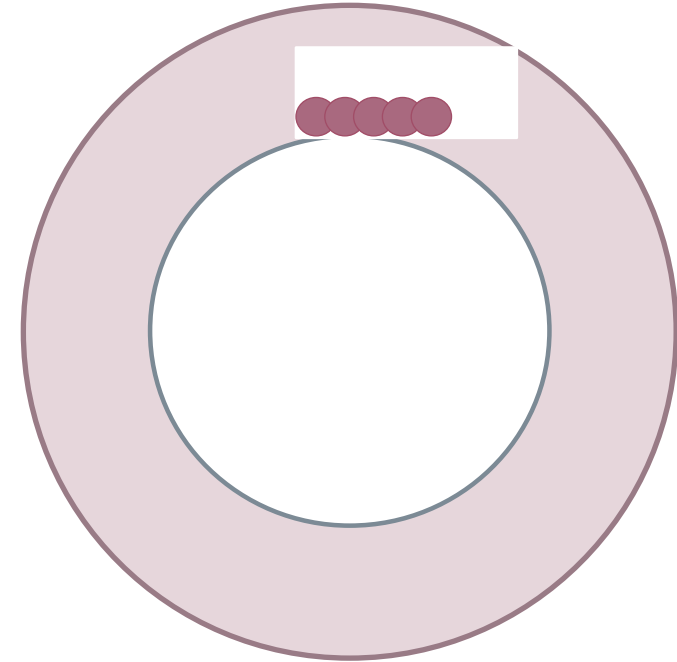
- Polypoid or exophytic tumors project toward the lumen.
- Progressive encroachment physically impedes bolus passage.
- Larger lesions contribute to dysphagia and luminal obstruction.



Mass projects inward and narrows lumen

Ulcerated growth: Surface destruction

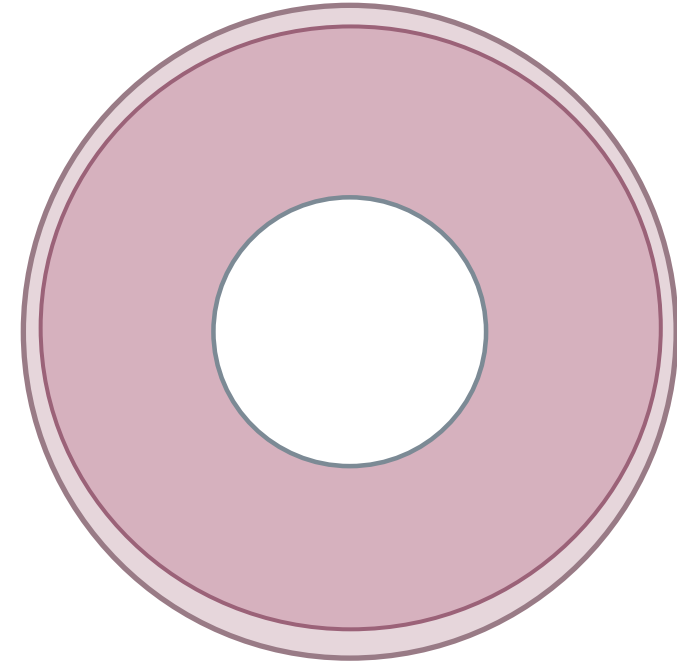
- Some tumors form an ulcerated mucosal surface.
- Tumor ulceration may be accompanied by hemorrhage and sepsis.
- Bleeding can contribute to iron-deficiency symptoms.



Ulcerated tumor disrupts mucosal surface

Diffuse infiltrative growth: A rigid wall

- Infiltrative tumors spread within the wall rather than predominantly into the lumen.
- Wall thickening and rigidity progressively narrow the passage.
- This morphology can produce a stricture-like presentation.



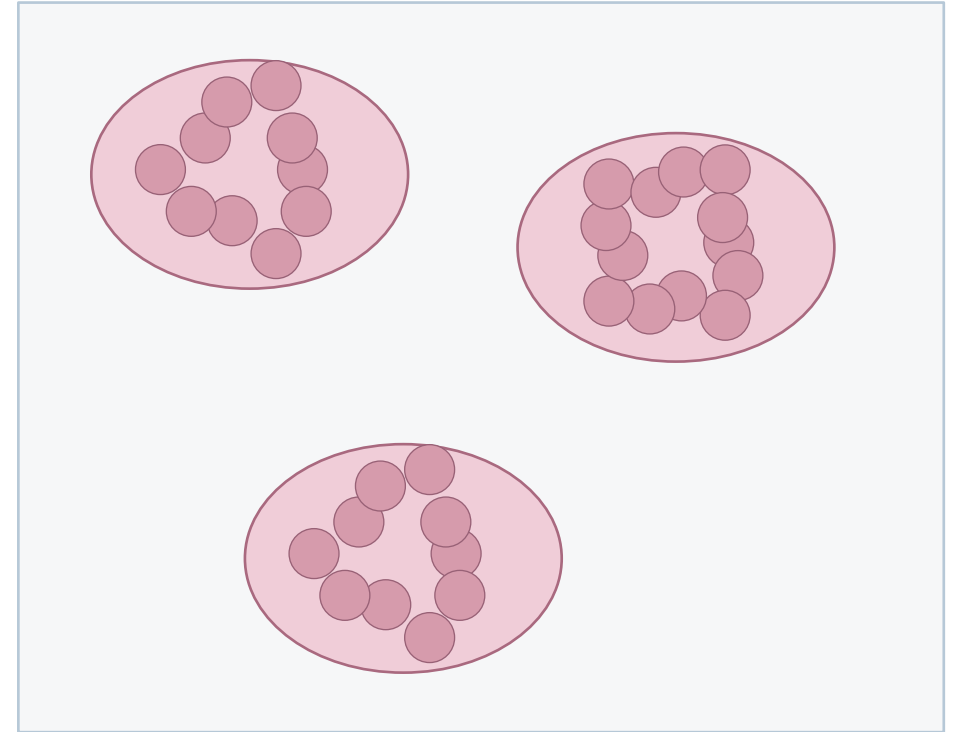
Wall infiltration and rigid stenosis

Growth-pattern comparison

Pattern	Principal growth direction	Clinical effect
Exophytic	Into the lumen	Mechanical obstruction
Ulcerating	Mucosal destruction	Bleeding / ulcer-related sepsis
Infiltrating	Within the wall	Rigid narrowing and extension

Squamous differentiation on microscopy

- Nests of malignant cells that partially resemble normal squamous epithelium.
- Most lesions are moderately to well differentiated.
- Cytologic squamous identity does not indicate early stage.



Schematic tumor nests; NOT a clinical histology image

Tumor nests versus normal epithelium

Normal squamous architecture

Organized stratified epithelial sheet

Compartmentalized surface lining

Native tissue boundaries maintained

Invasive SCC architecture

Disorganized malignant cell nests

Tumor islands within supporting tissue

Tissue architecture disrupted

Conceptual comparison — not a histologic micrograph

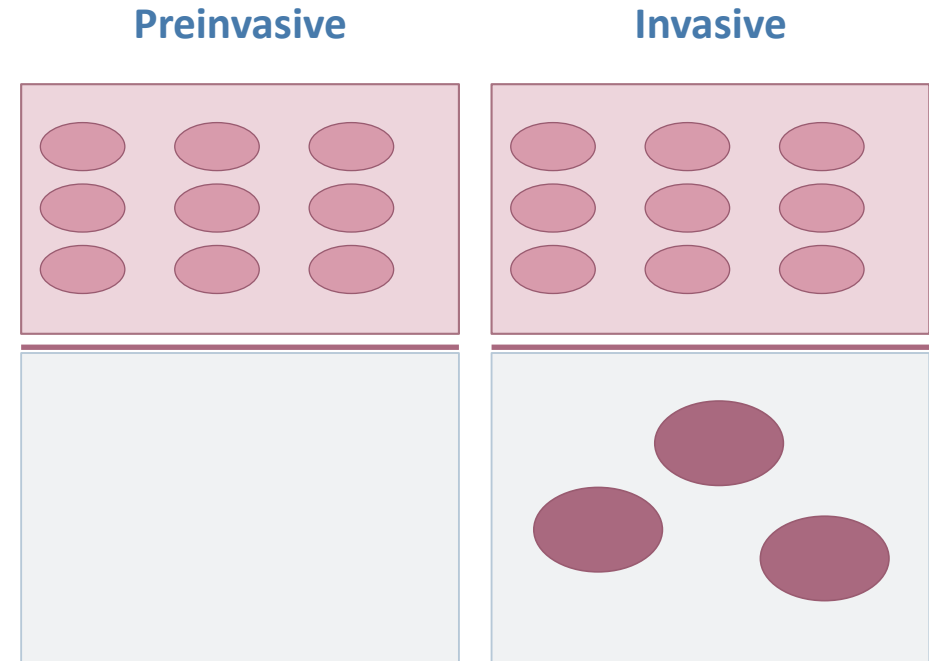
Histologic differentiation and clinical stage

A well-differentiated carcinoma can still be advanced.

- Moderate-to-well differentiated morphology is common.
- Symptomatic lesions are generally already large and invasive at diagnosis.
- Differentiation and anatomic extent are different descriptive axes.

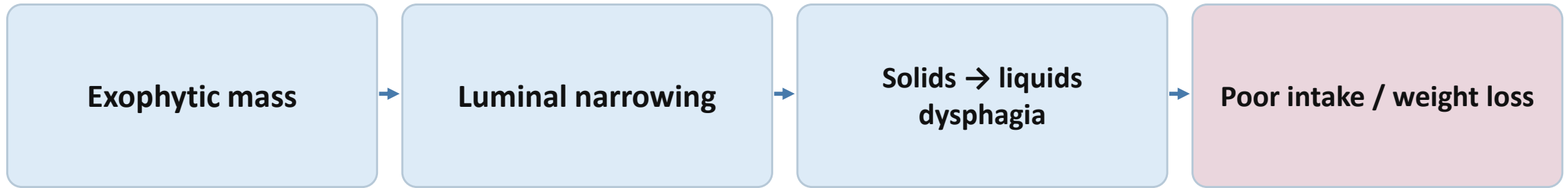
The critical pathologic question: Invasion

- Preinvasive squamous dysplasia remains restricted to the epithelial compartment.
- Invasive carcinoma infiltrates deeper tissue.
- Anatomic depth and spread must be assessed separately from squamous differentiation.



Epithelial boundary (horizontal line); Invasion shown at right

Morphology predicts clinical effects

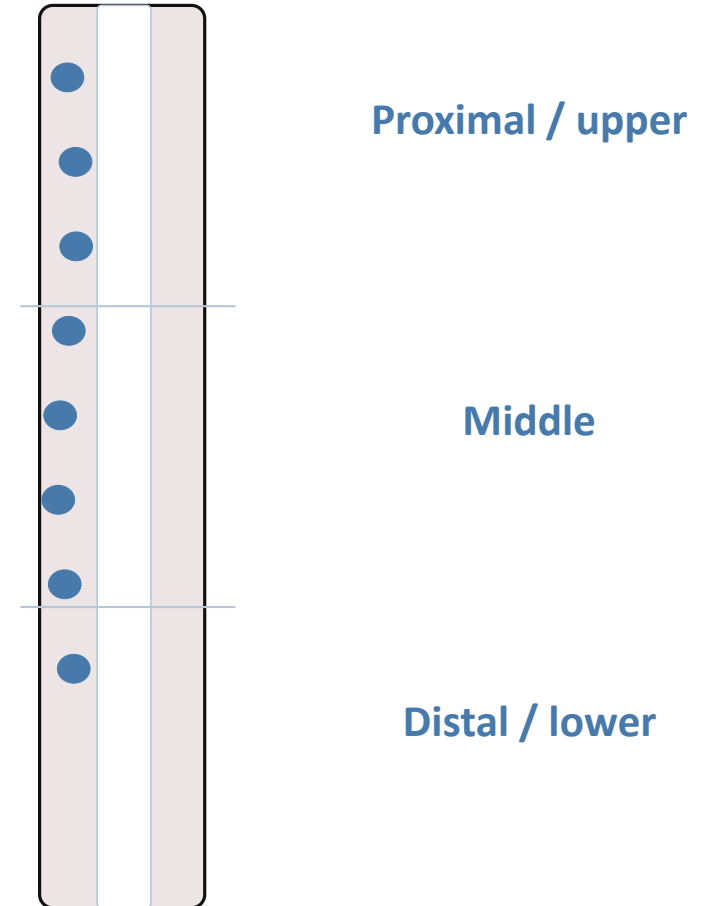


Schematic sequence

- Mechanical obstruction links visible growth pattern to symptoms.
- More than one gross pattern may coexist in advanced disease.

The esophageal lymphatic network

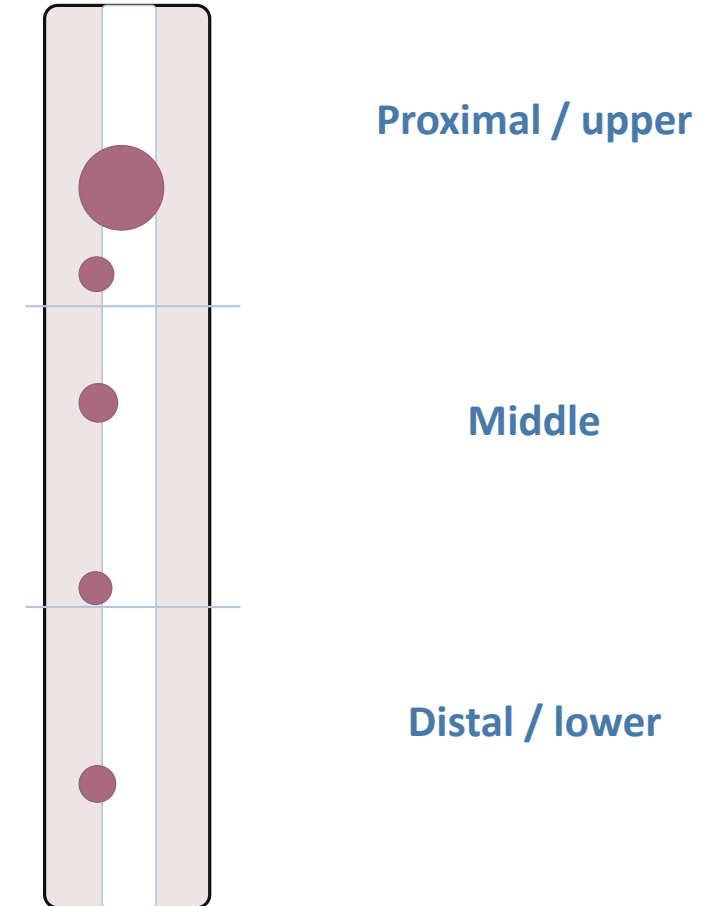
- Esophageal lymphatic channels are rich.
- They facilitate circumferential and longitudinal tumor spread.
- They also provide routes to regional lymph nodes.



Longitudinal channels permit wall spread and metastasis

Intramural satellite tumor nodules

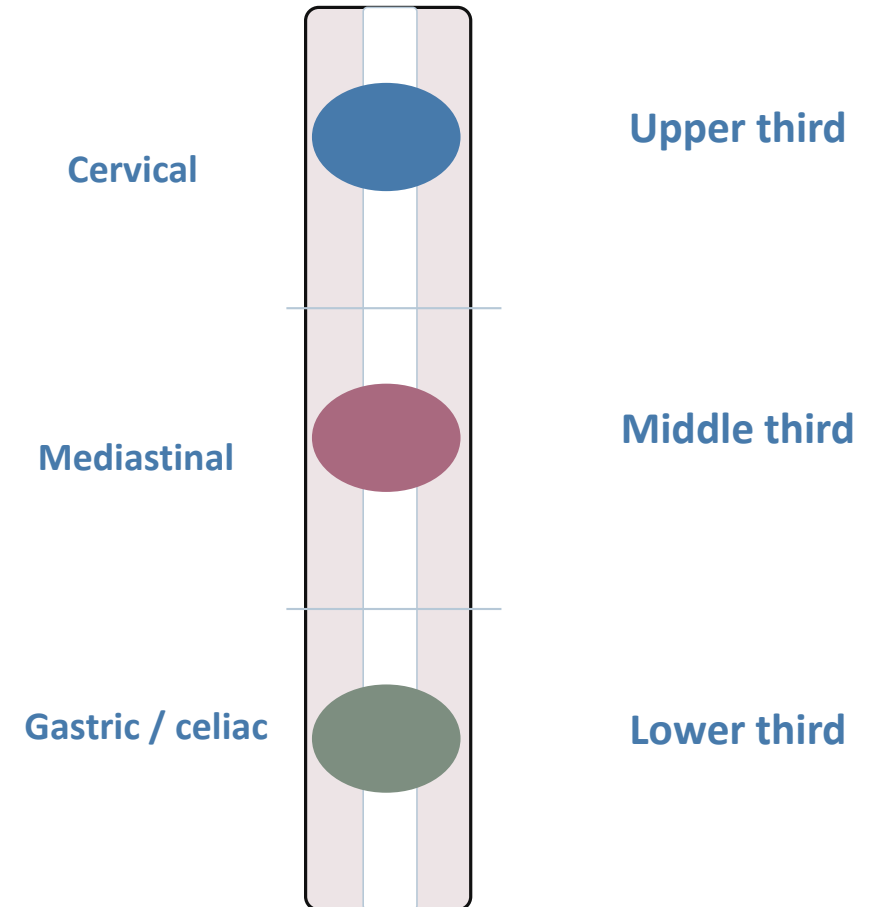
- Tumor foci may occur within the wall several centimeters from the main mass.
- Satellite nodules reflect noncontiguous-looking intramural spread.
- Their existence complicates assumptions based only on visible tumor length.



Separate intramural tumor foci can be distant from main mass

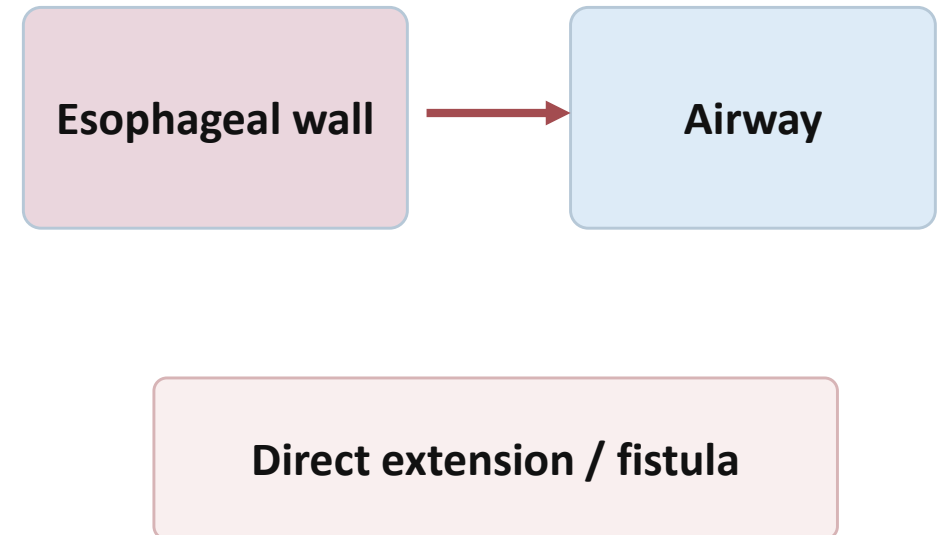
Regional nodes depend on tumor level

- Upper third: Predominantly cervical lymph nodes.
- Middle third: Mediastinal, paratracheal and tracheobronchial nodes.
- Lower third: Gastric and celiac nodes.



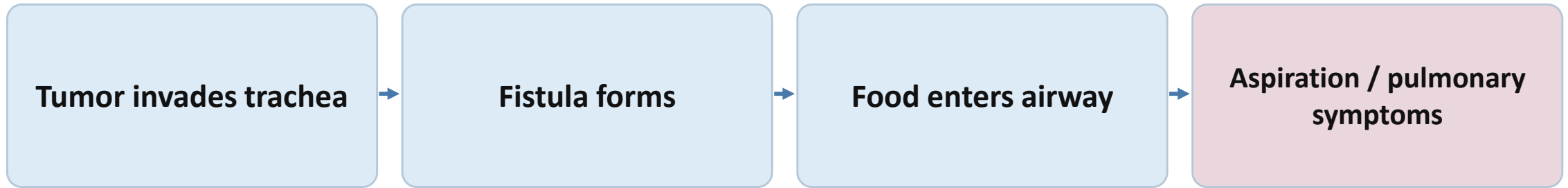
Direct invasion of the respiratory tree

- Tumor can extend into adjacent tracheobronchial structures.
- Associated consequences include pneumonia.
- Communication with the airway can produce a tracheoesophageal fistula.



Conceptual adjacency; Not anatomical scale

Tracheoesophageal fistula and aspiration

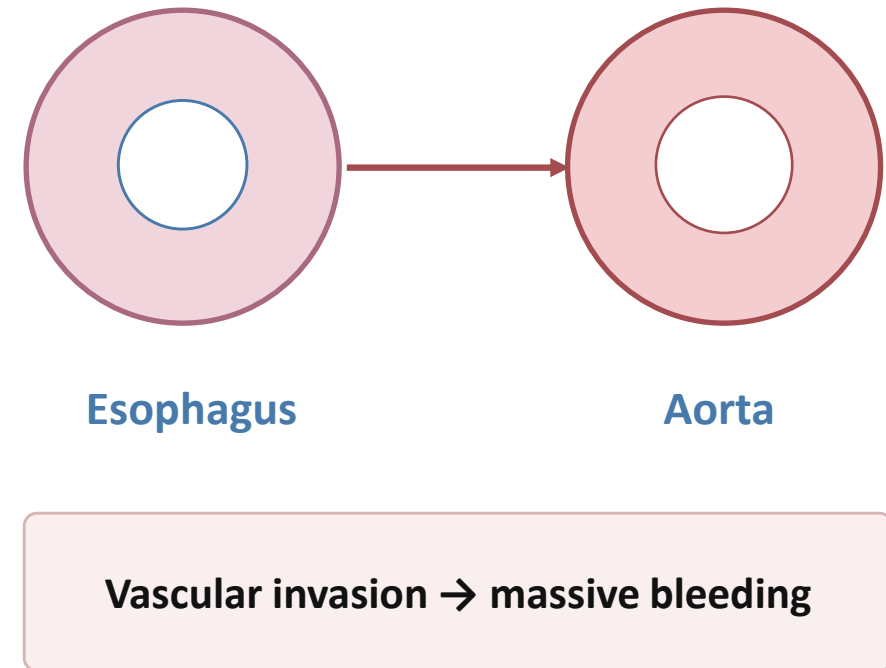


Schematic sequence

- Aspiration may occasionally be the initial clinical presentation.
- A new respiratory complication may signal advanced local extension.

Aortic invasion: Catastrophic hemorrhage

- Esophageal SCC can invade the adjacent aorta.
- Vascular erosion may cause sudden, massive blood loss.
- This is a high-severity complication of advanced local disease.



Mediastinal and pericardial extension

Anatomical proximity determines local hazards.

- Local growth can involve mediastinal structures.
- Robbins also lists extension toward the pericardium.
- The anatomic neighborhood makes a locally advanced lesion dangerous even without distant metastasis.

Three major routes of disease extension

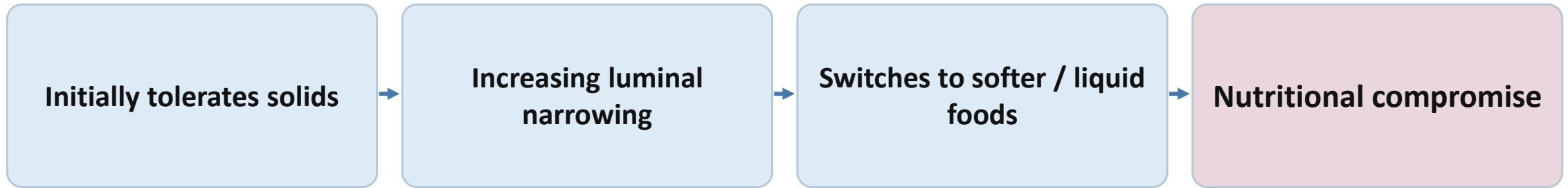
Route	Tissue direction	Consequence
Luminal	Encroaches on food passage	Dysphagia / obstruction
Contiguous	Invades neighboring organs	Airway disease; aortic hemorrhage
Lymphatic	Along wall and into nodes	Satellites; nodal metastases

Clinical onset is often insidious

Late recognition is a central diagnostic challenge.

- Symptoms can develop gradually as the passage narrows.
- Patients may adapt their diet before describing overt obstruction.
- The disease can be anatomically advanced when it first becomes clinically apparent.

Progressive dysphagia has a mechanism



Schematic sequence

- A change in food texture may reveal evolving obstruction.
- A history of progressive swallowing difficulty warrants evaluation.

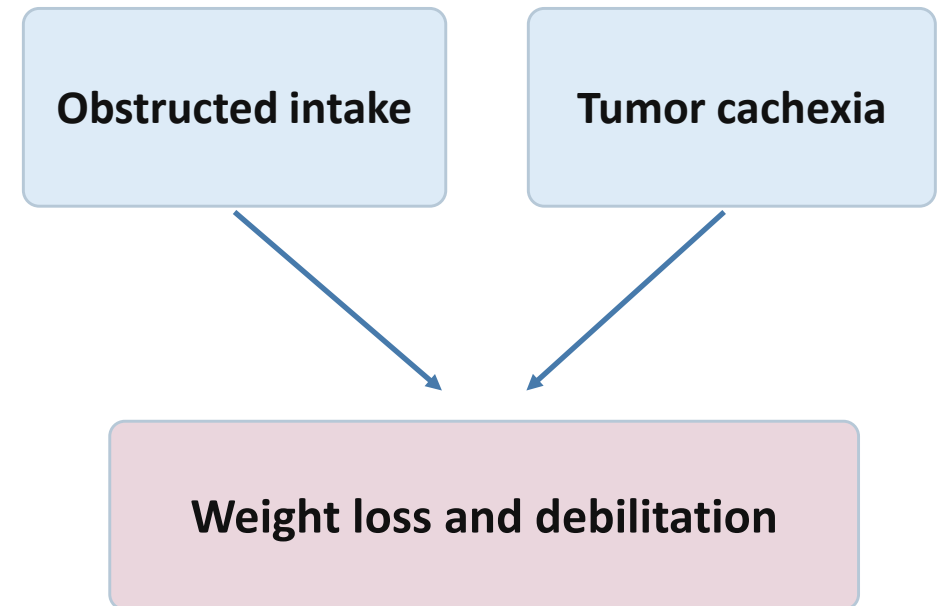
Odynophagia and obstruction

Pain and impaired bolus transit are distinct symptoms.

- Odynophagia means pain on swallowing.
- Dysphagia and odynophagia may coexist in esophageal SCC.
- Tumor enlargement can eventually cause marked obstruction.

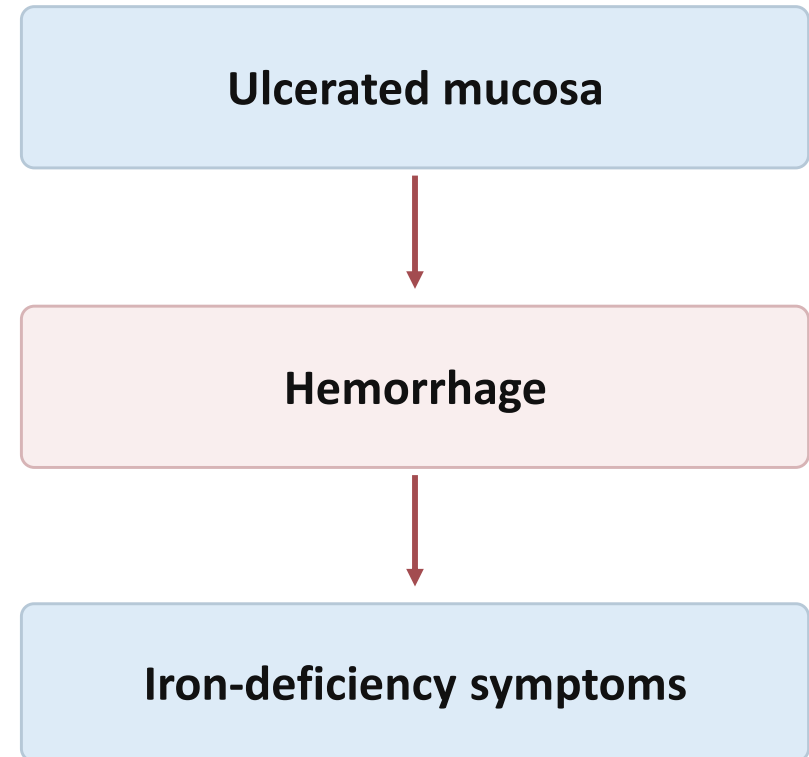
Weight loss and debilitation

- Mechanical dysphagia reduces nutritional intake.
- Tumor cachexia contributes independently to weight loss.
- Progressive debilitation in advanced disease.



Hemorrhage and iron deficiency

- Tumor ulceration may cause bleeding.
- Chronic blood loss can produce symptoms of iron deficiency.
- Sepsis may also complicate an ulcerated tumor.



An atypical respiratory presentation

An older adult develops cough during meals and recurrent chest symptoms, with only modest previously recognized dysphagia.

What local anatomic complication best explains this presentation?

- Think about abnormal communication between esophagus and airway.
- Aspiration via tumor-associated tracheoesophageal fistula as an occasional first manifestation.

Endoscopic detection changes stage at diagnosis

Earlier detection shifts the extent of disease found.

- Increasing use of endoscopic screening has led to earlier detection in some settings.
- Recognition of superficial lesions is clinically important.
- Robbins does not prescribe a universal screening program or eligibility criteria.

Superficial versus advanced disease

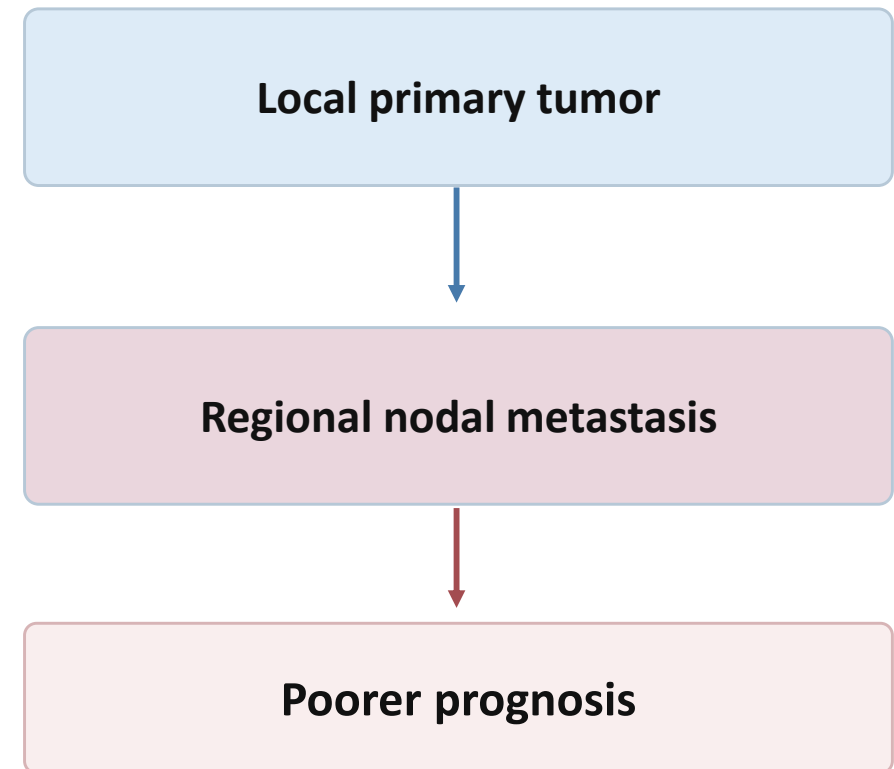
75% at 5 years

75% at 5 years

- Approximately 75% 5-year survival for superficial lesions.
- Survival is much lower in patients with advanced tumors.
- Outcome comparisons are stage-dependent, not an effect estimate for a screening intervention.

Regional nodal metastasis worsens prognosis

- Lymph-node involvement is associated with poor outcome.
- Spread reflects progression beyond the primary tumor.
- Nodal status adds information beyond gross luminal size.



Overall outcome remains unfavorable

Below 20% at 5 years

Below 20% at 5 years

- Overall 5-year survival below 20% in the United States.
- The figure varies with tumor stage and demographic strata.
- It is a textbook cohort-level estimate, not an individual survival prediction.

Clinical profile: An integrated pattern

Finding	Pathologic explanation	Clinical implication
Progressive dysphagia	Luminal obstruction / rigidity	Often insidious
Weight loss	Poor intake + cachexia	Debilitation
Hemorrhage	Ulceration	Iron-deficiency symptoms
Aspiration	Tracheoesophageal fistula	Airway involvement

SCC versus adenocarcinoma: Avoid category error

Dimension	Esophageal SCC	Esophageal adenocarcinoma
Typical location	Middle / proximal	Distal
Important antecedent	Squamous dysplasia	Barrett esophagus
Histology	Squamous nests	Gland-forming / mucinous
Risk pattern	Tobacco, alcohol + other risks	GERD / Barrett context

Case synthesis: Progressive obstruction

A 62-year-old adult reports gradually worsening swallowing difficulty, initially for solids, now also for liquids, with marked weight loss.

Apply morphology, anatomy, and symptoms together.

- What gross growth patterns could explain the obstruction?
- Which symptoms support a clinically advanced lesion?
- Why should nodal evaluation consider the tumor level?

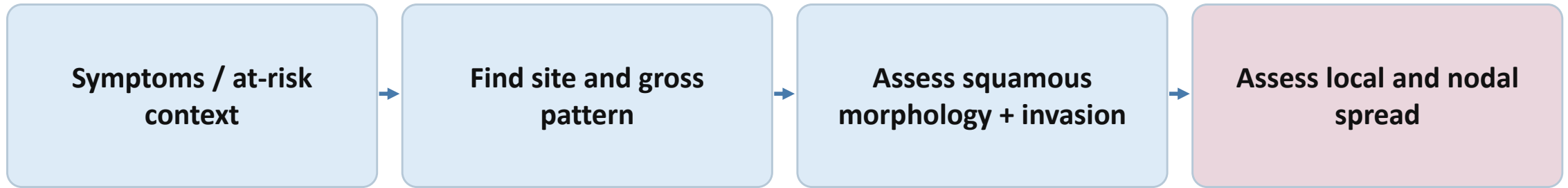
Case synthesis: Microscopic diagnosis

A biopsy shows malignant nests partially recapitulating squamous epithelium in an esophageal lesion.

Explain your reasoning in three steps.

- Which carcinoma histotype is favored?
- How does invasion differ from squamous dysplasia?
- Why does a differentiated appearance not establish favorable stage?

Integrated diagnostic reasoning



Schematic sequence

- An organ-based interpretation combines risk, tumor architecture, and anatomic extension.
- Stage and spread are central to clinicopathologic prognosis.

Key concepts: One-slide synthesis

Anatomic extent is as important as epithelial phenotype.

- Etiology is geographically heterogeneous; Tobacco and alcohol are prominent but not exclusive risks.
- The neoplasm progresses through squamous dysplasia to invasion and forms plaque-like, exophytic, ulcerated, or infiltrative lesions.
- Lymphatic and contiguous spread explain severe complications and nodal involvement.
- Superficial diagnosis carries markedly better outcome than advanced symptomatic disease.

Selected reference and evidence boundaries

Primary teaching source and limitations

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Primary section: esophageal squamous cell carcinoma; comparator discussions: adenocarcinoma, Barrett esophagus, and achalasia.
- Molecular subtypes and reported survival estimates should be interpreted in the context of the cited textbook edition.
- Current staging, screening policy, and management recommendations require consultation of separate authoritative guidelines.