

# Esophageal Tumors

Major histologic types • Barrett-associated adenocarcinoma • clinical significance

A source-grounded pathology lecture

**Dr Abu Suraih Sakhri**

MBBS, MD (Pathology)

[www.abusuraihsakhri.com](http://www.abusuraihsakhri.com)

## Learning outcomes

- Classify major esophageal neoplasms by histologic lineage
- Relate Barrett metaplasia and dysplasia to adenocarcinoma
- Recognize essential gross and microscopic features
- Connect invasion, symptoms and survival to disease extent

# The major tumor families

## Esophageal neoplasms

```
graph TD; A[Esophageal neoplasms] --> B[Epithelial: Adenocarcinoma / SCC]; A --> C[Mesenchymal: Leiomyoma]; A --> D[Other rare malignancies];
```

**Epithelial: Adenocarcinoma /  
SCC**

**Mesenchymal: Leiomyoma**

**Other rare malignancies**

- Nearly all esophageal cancers are adenocarcinoma or squamous cell carcinoma

# Histologic lineage matters

## Adenocarcinoma

## Squamous cell carcinoma

- Adenocarcinoma is gland-forming, often mucin-producing
- Squamous cell carcinoma recapitulates squamous differentiation
- A tumor's location and precursor lesion help support its origin

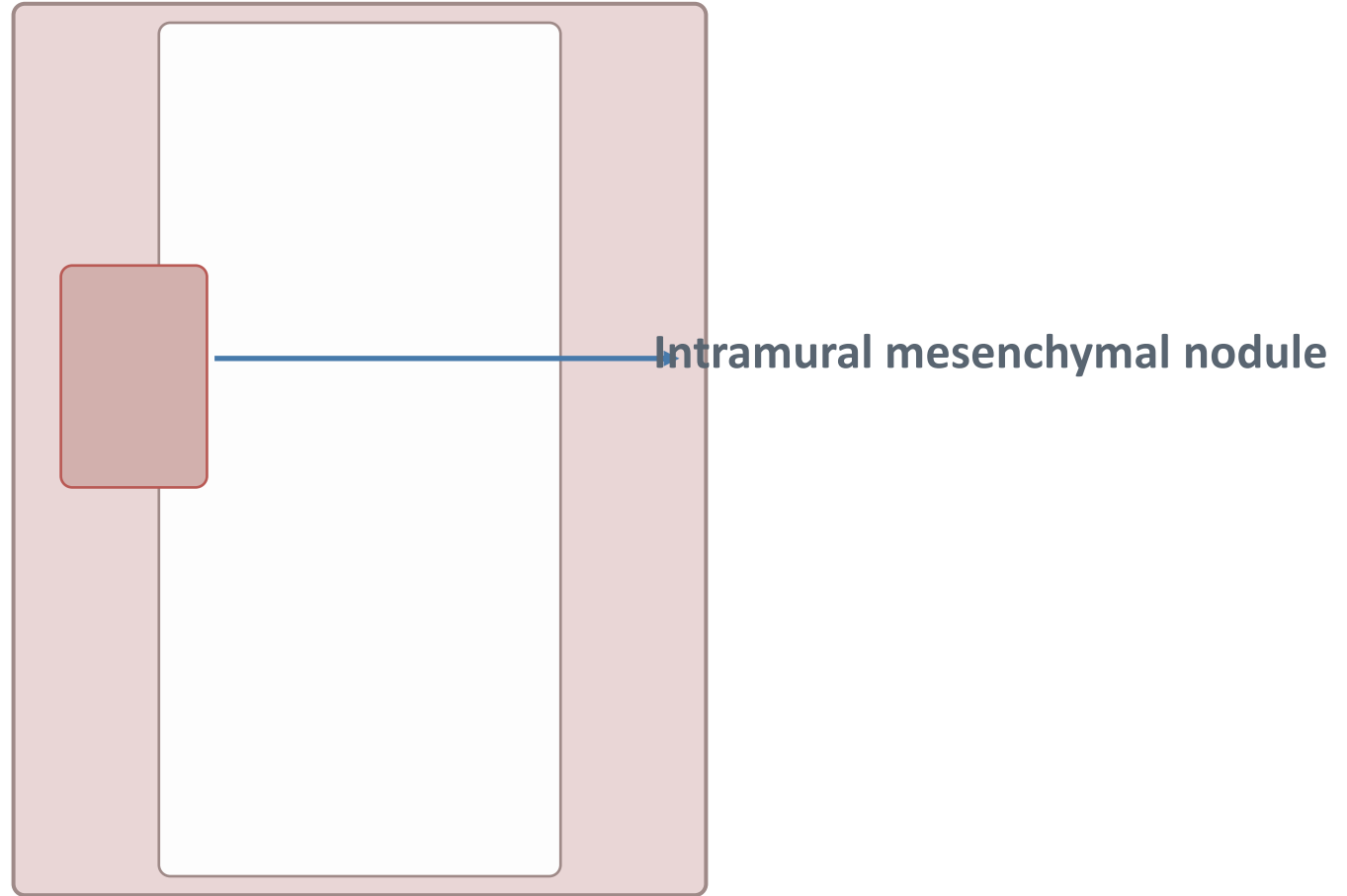
## A worldwide histologic shift

- Squamous cell carcinoma remains more common globally
- Adenocarcinoma has risen markedly in the United States and other Western countries
- Different risk patterns underlie the geographic contrast

**SCC worldwide  
EAC rising in West**

# Leiomyoma: The leading benign tumor

Most benign esophageal tumors are mesenchymal

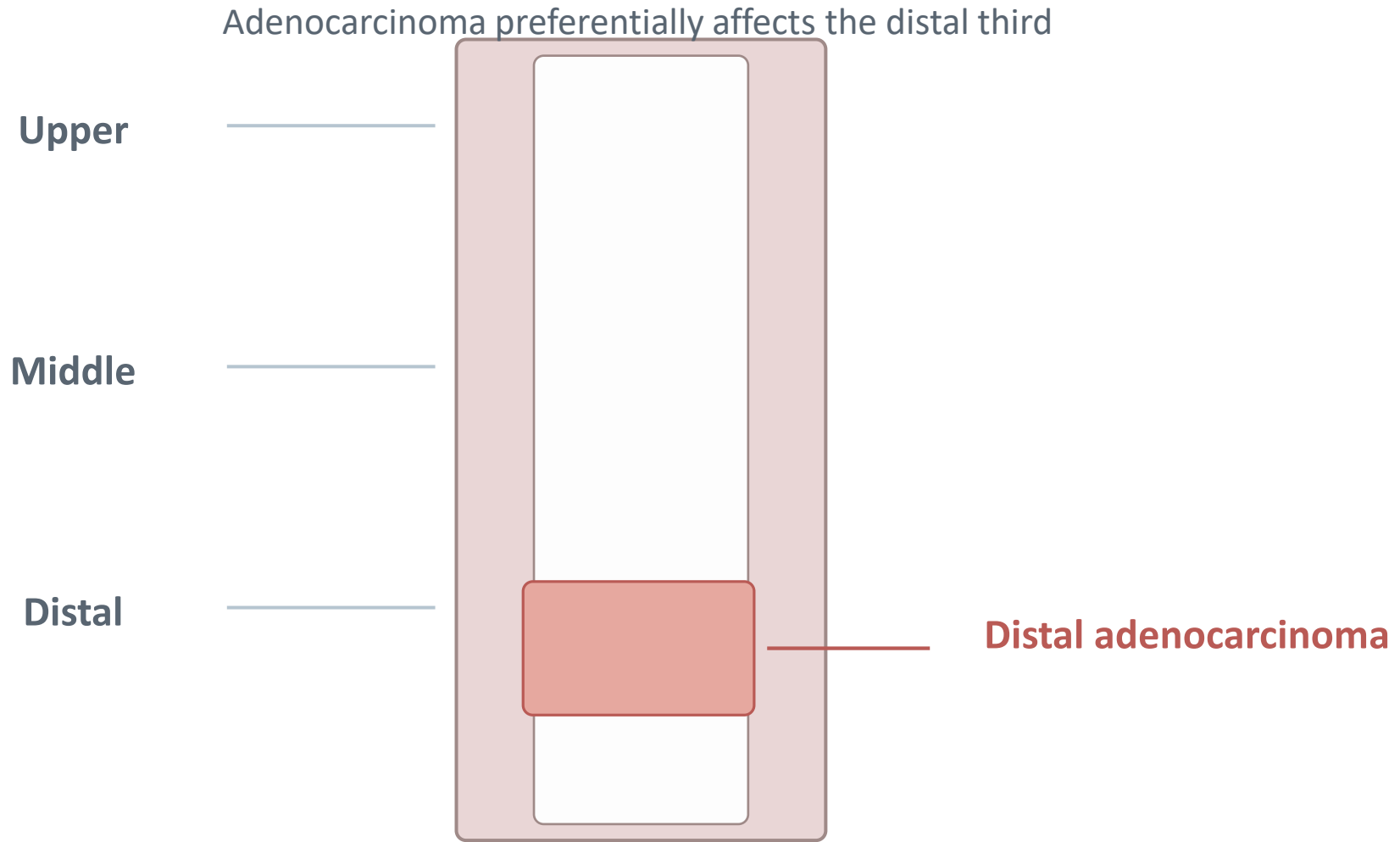


Schematic esophageal wall

## **Uncommon malignant lineages**

- Unusual forms of adenocarcinoma and undifferentiated carcinoma
- Neuroendocrine carcinoma and melanoma
- Lymphoma and sarcoma
- Robbins mentions these but does not detail them in this section

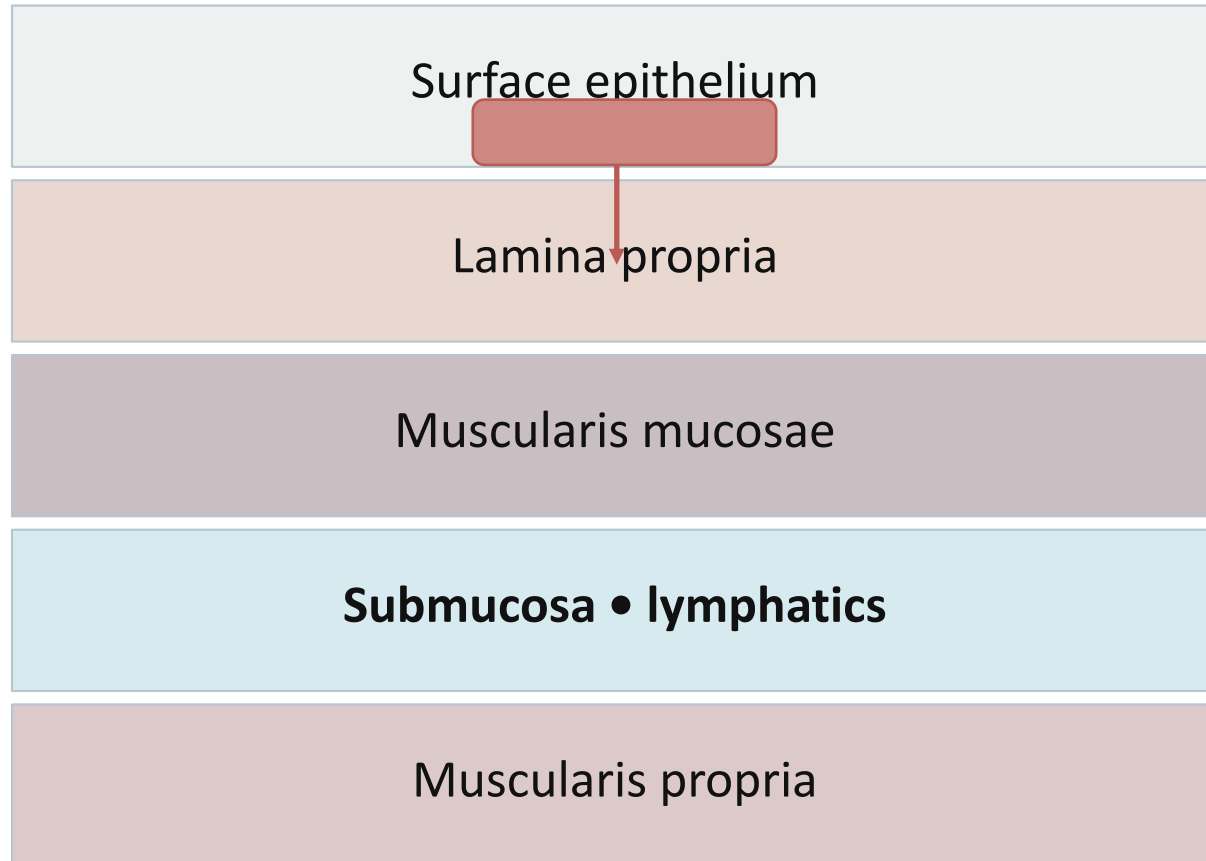
# Anatomic location is informative



Schematic; Tumor locations vary

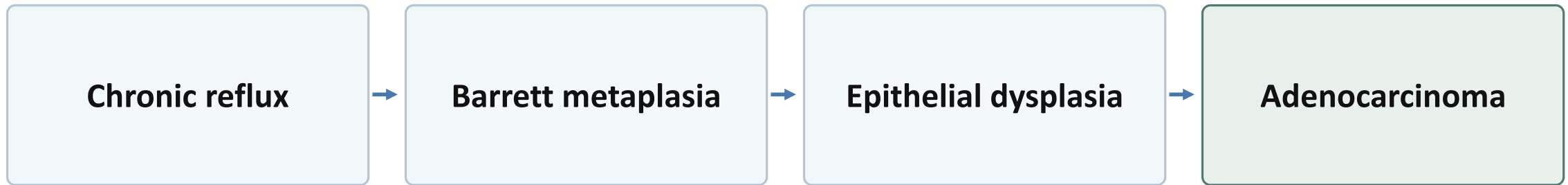
# Symptoms often reflect advanced disease

Difficulty or pain on swallowing may appear late



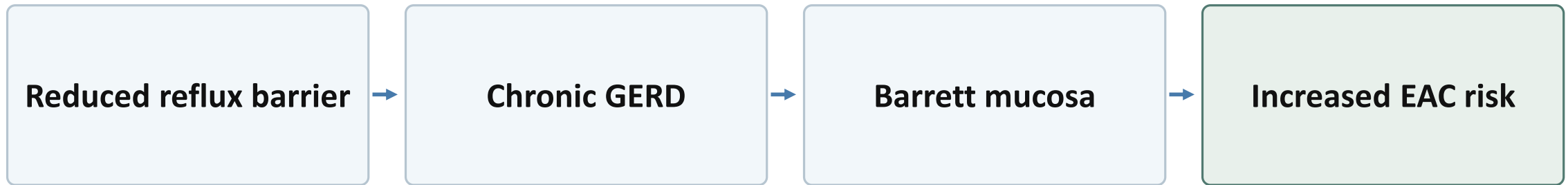
Illustrative path of increasing depth

# Adenocarcinoma commonly follows Barrett esophagus



**Schematic sequence — conceptual progression, not an inevitable patient course**  
Long-standing gastroesophageal reflux disease is a key background

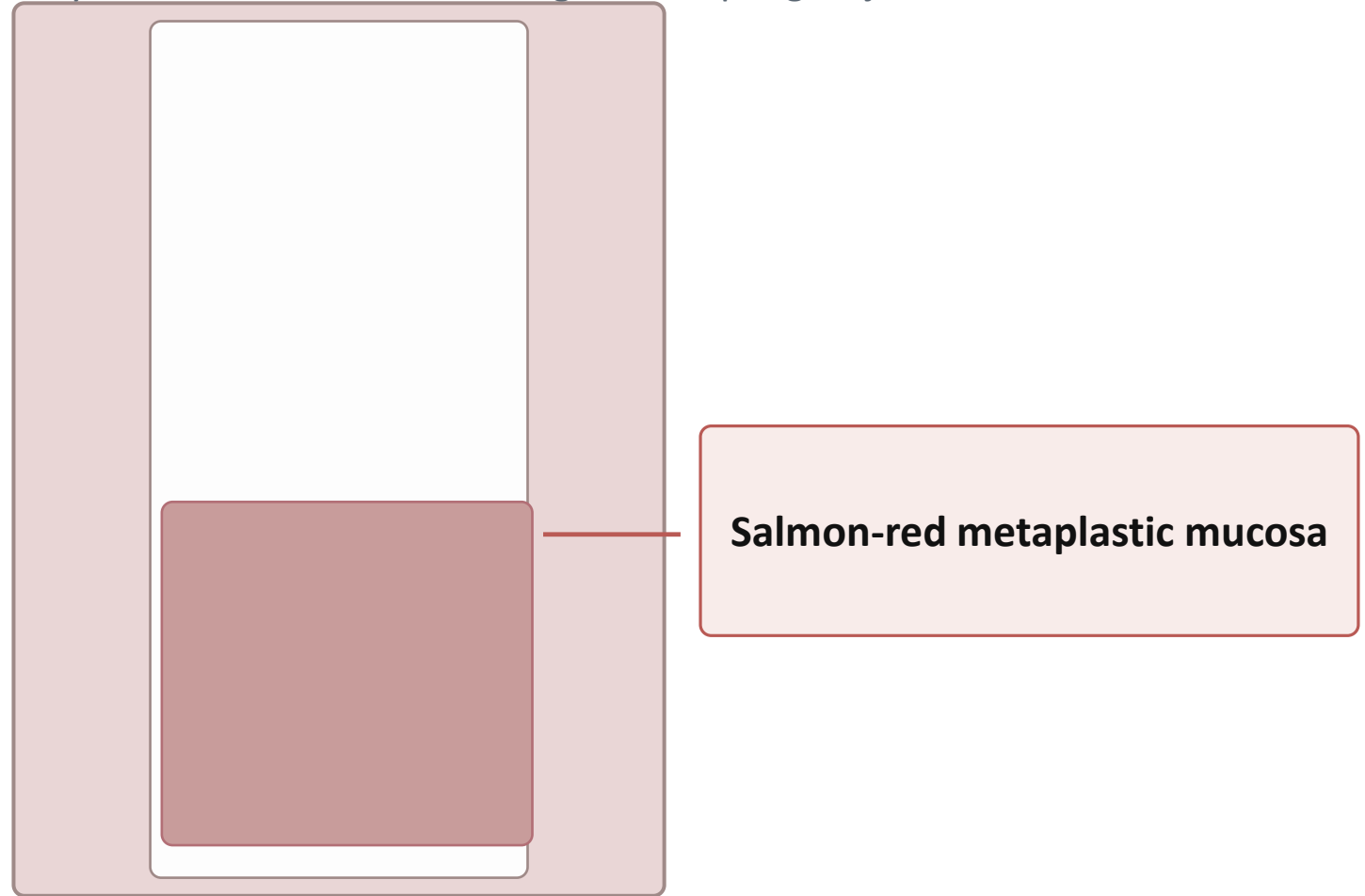
# Why reflux increases cancer risk



**Schematic sequence — conceptual progression, not an inevitable patient course**  
The textbook links increased adenocarcinoma rates to GERD and Barrett esophagus

# Barrett mucosa: Endoscopic appearance

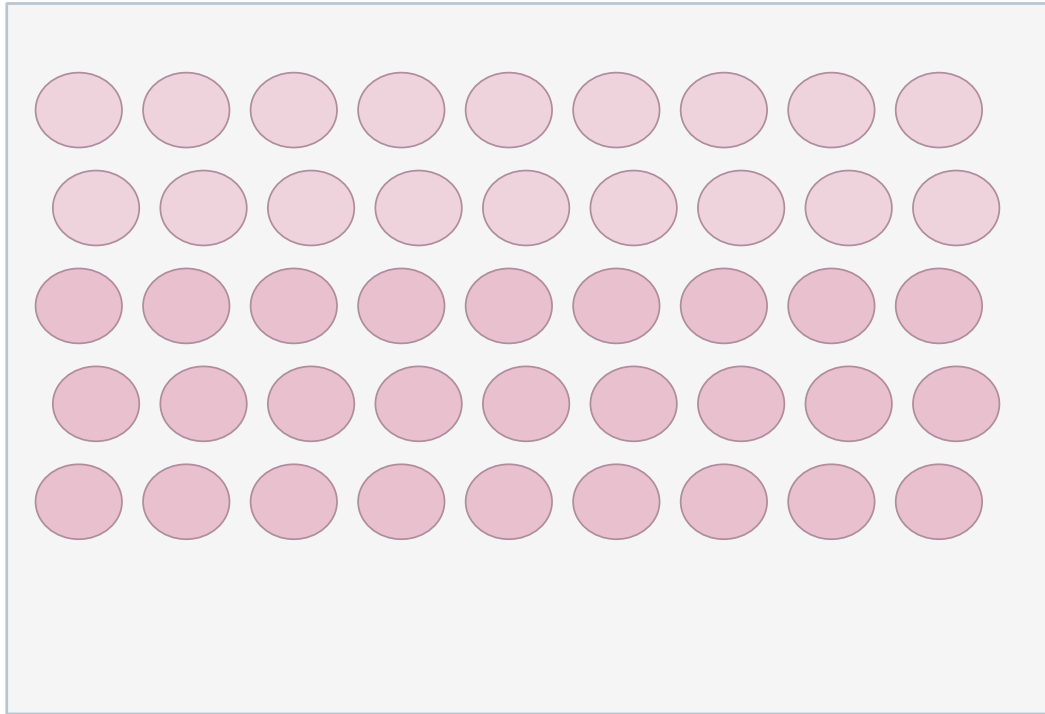
Tongues of red, velvety mucosa extend above the gastroesophageal junction



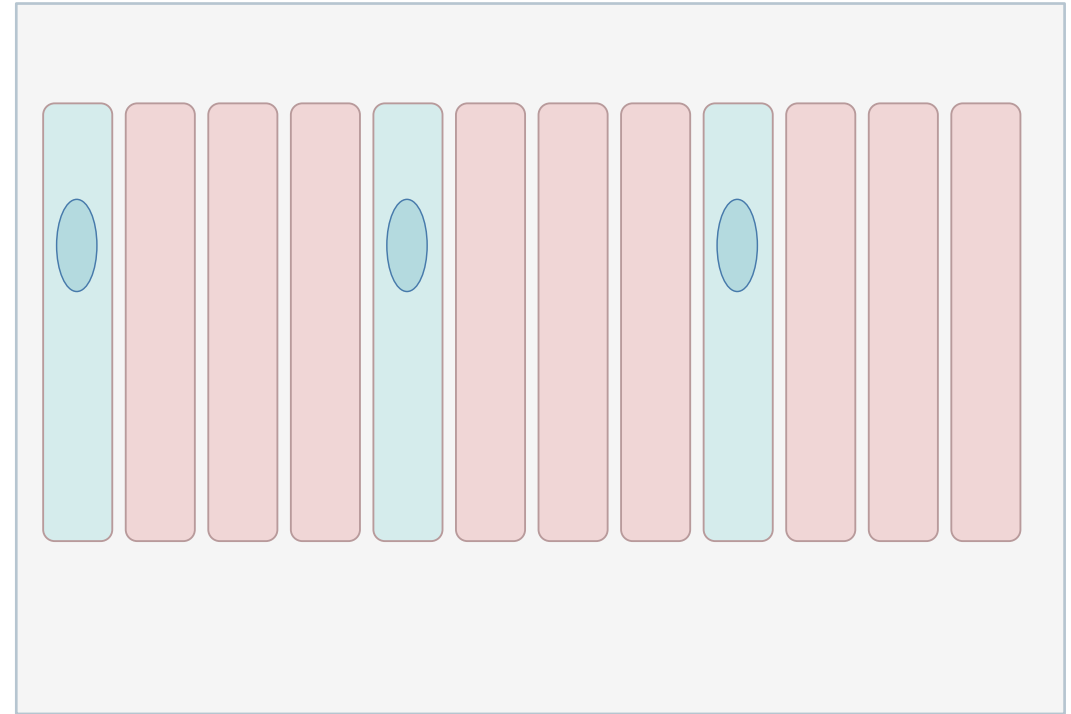
Original schematic, not endoscopic evidence

# The squamous–columnar transition

Normal esophagus is lined by stratified squamous epithelium



**Stratified squamous epithelium**

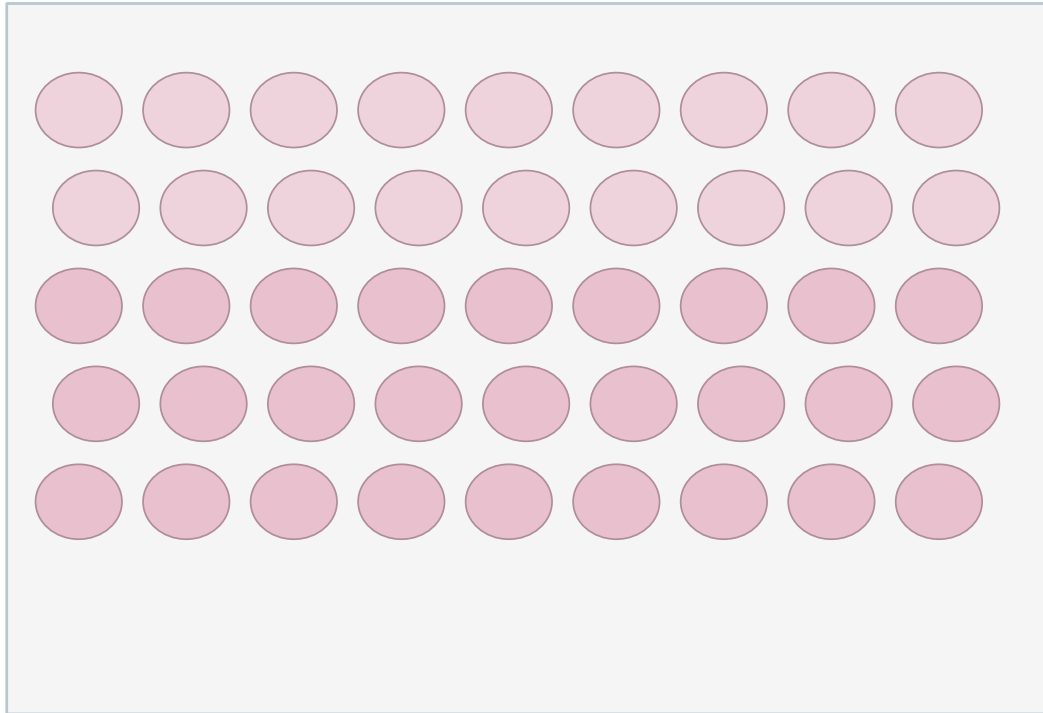


**Intestinalized columnar epithelium**

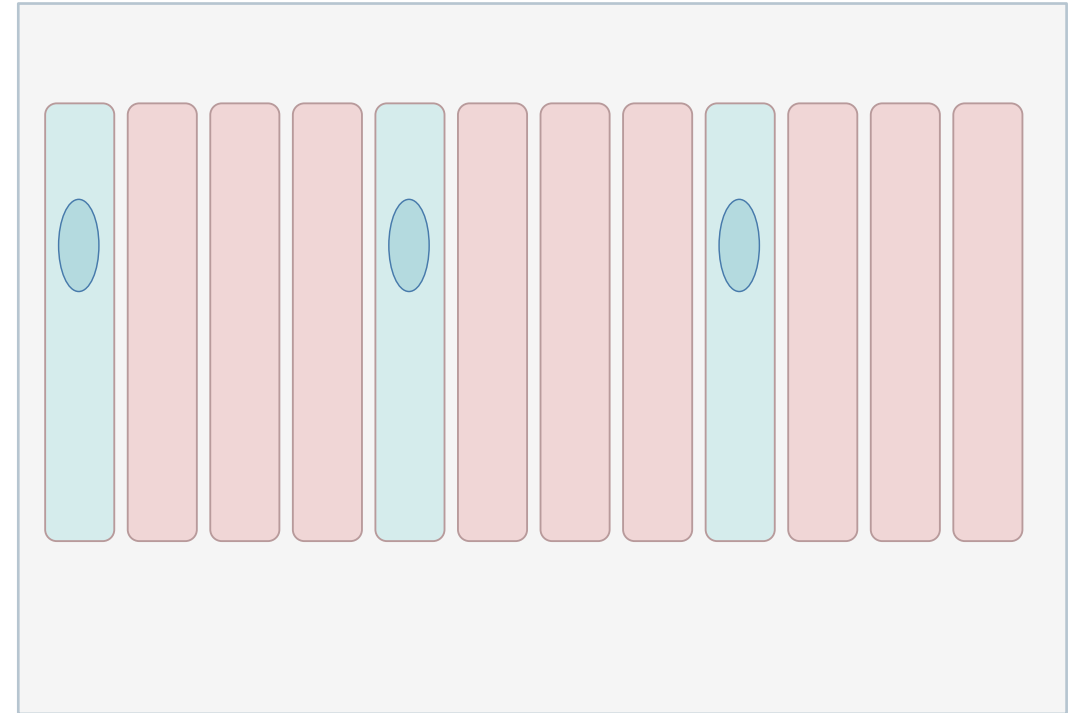
Schematic — not a photomicrograph

# Goblet cells identify intestinal metaplasia

Goblet cells contain conspicuous mucin vacuoles



**Stratified squamous epithelium**

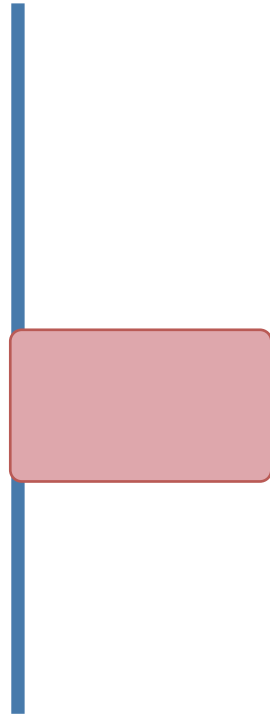


**Intestinalized columnar epithelium**

Schematic — not a photomicrograph

# Short- and long-segment Barrett esophagus

Long-segment disease extends  $\geq 3$  cm above the junction



Short segment  $< 3$  cm



Long segment  $\geq 3$  cm

Conceptual comparison; Not drawn to scale

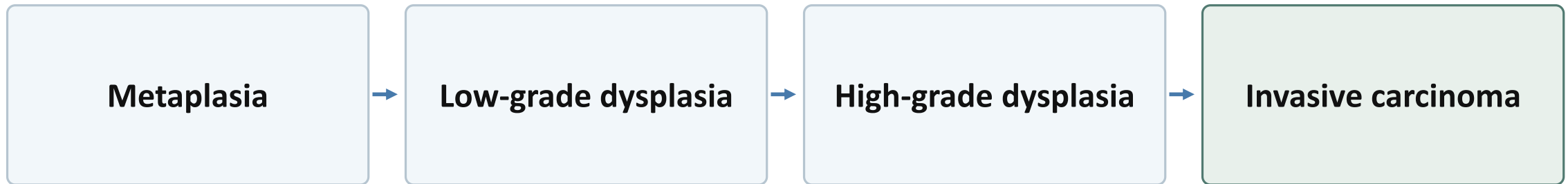
# Cancer risk is not inevitable

## Associated precursor

## Not inevitable cancer

- Most esophageal adenocarcinomas arise with Barrett esophagus
- Most people with Barrett esophagus never develop esophageal tumors
- Metaplasia must not be equated with carcinoma

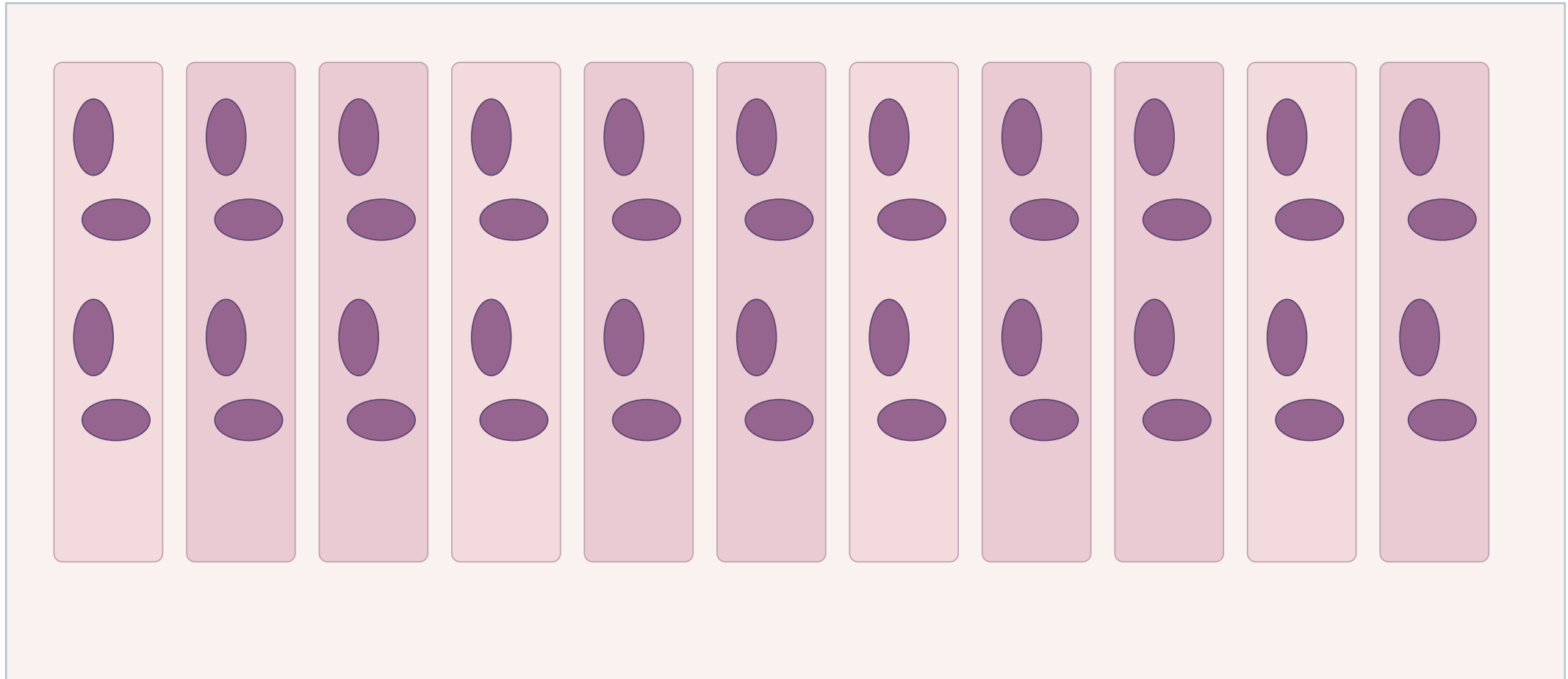
# Dysplasia is a preinvasive change



Schematic sequence — conceptual progression, not an inevitable patient course  
Barrett dysplasia arises in metaplastic epithelium

# Shared cytologic features of dysplasia

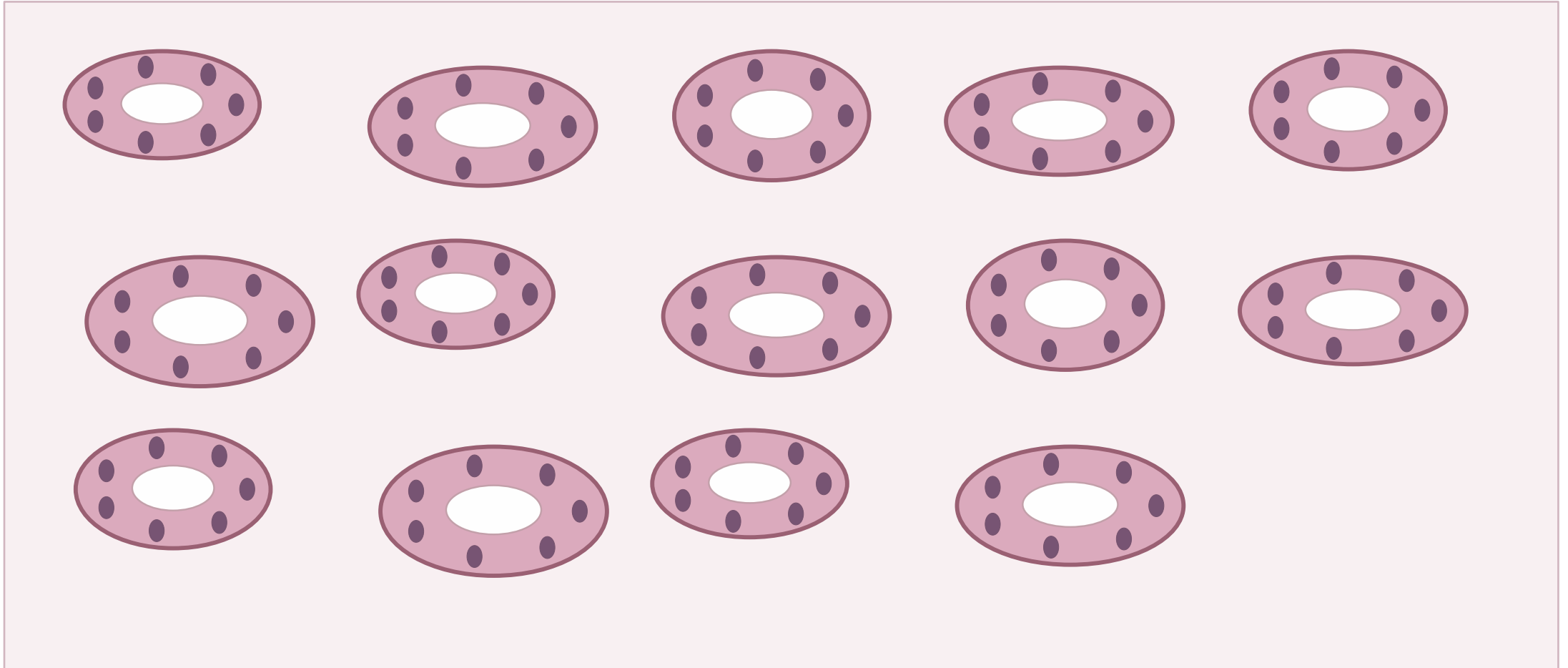
Nuclear hyperchromasia and atypical mitotic activity



Schematic — crowded atypical nuclei extend toward the surface

# Dysplastic glands lose regular architecture

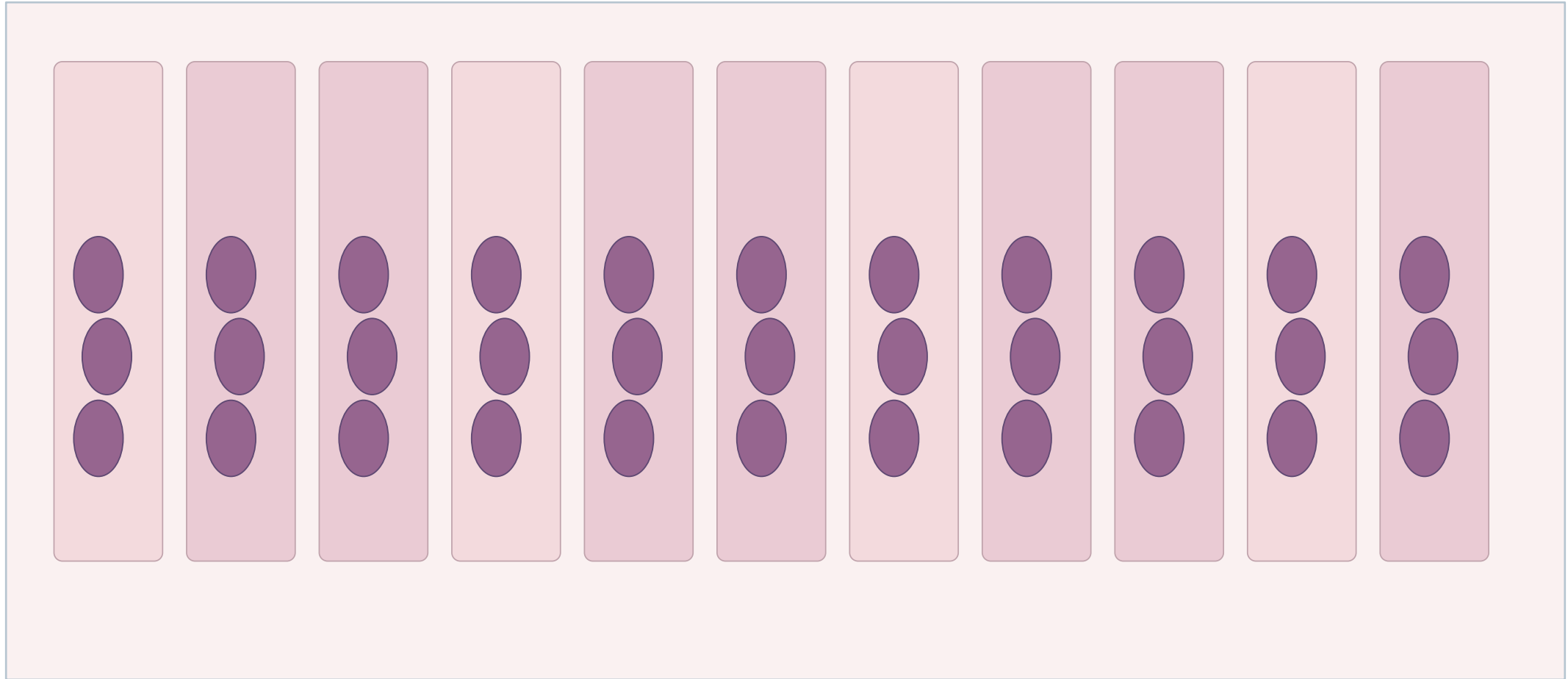
Irregular gland shapes and budding



Schematic — crowding and irregular gland outlines

# Low-grade dysplasia: Characteristic pattern

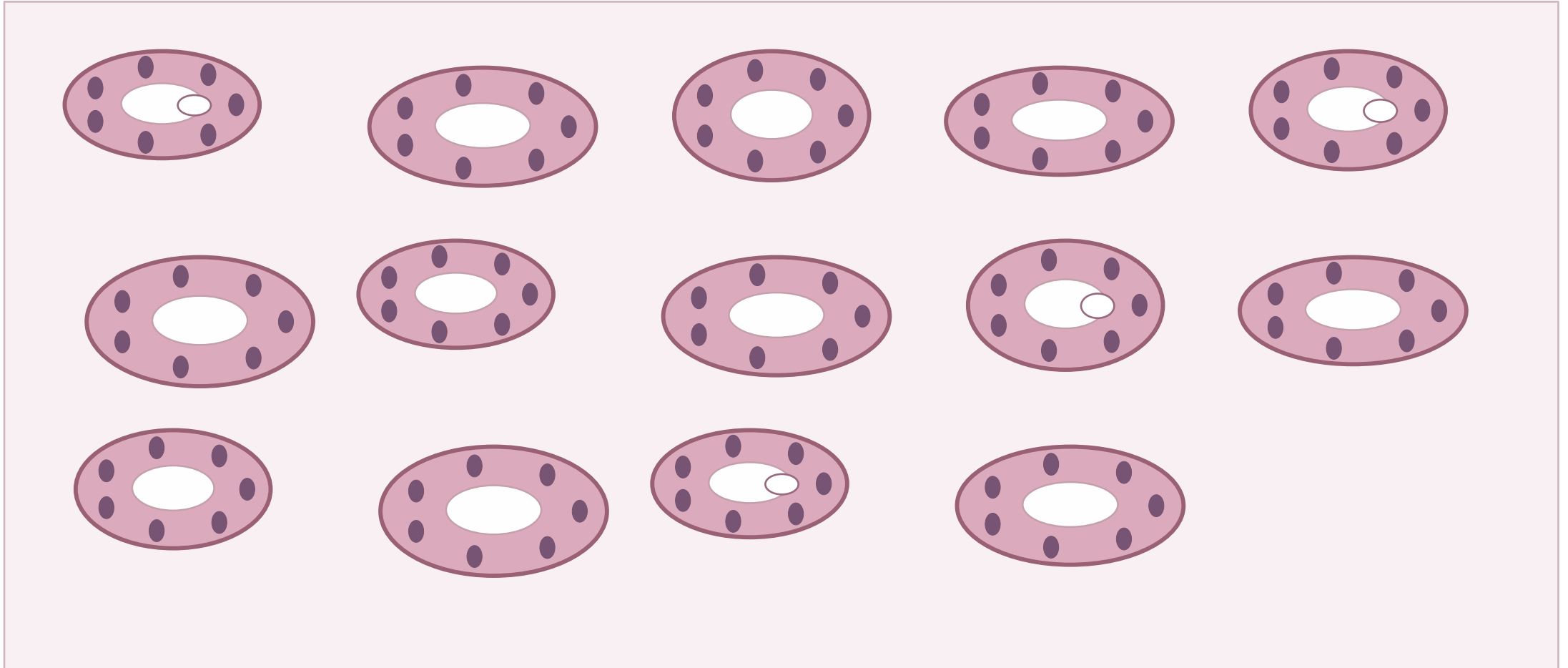
Elongated, stratified hyperchromatic nuclei



Schematic — elongated, stratified nuclei within columnar glands

# High-grade dysplasia: Greater disorder

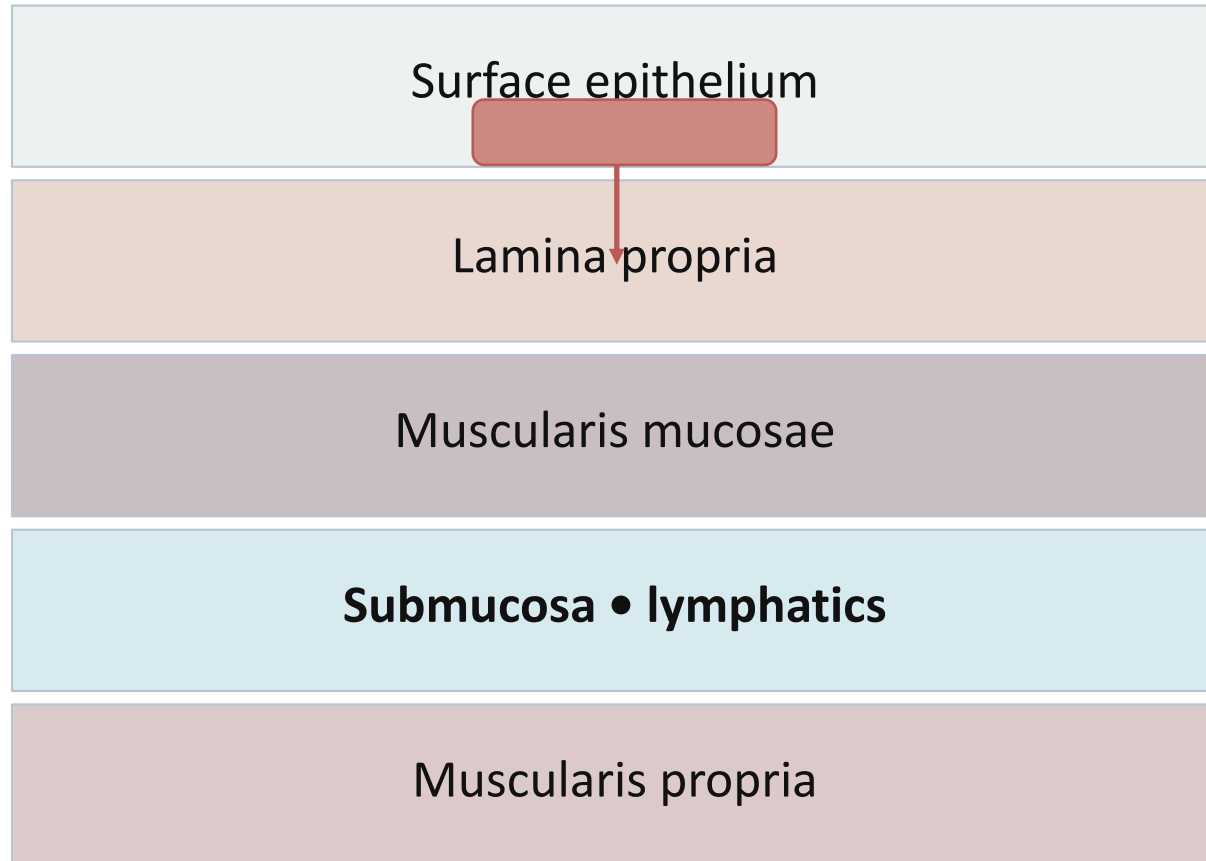
More severe cytologic and architectural abnormalities



Schematic — severe gland crowding and cribriform complexity

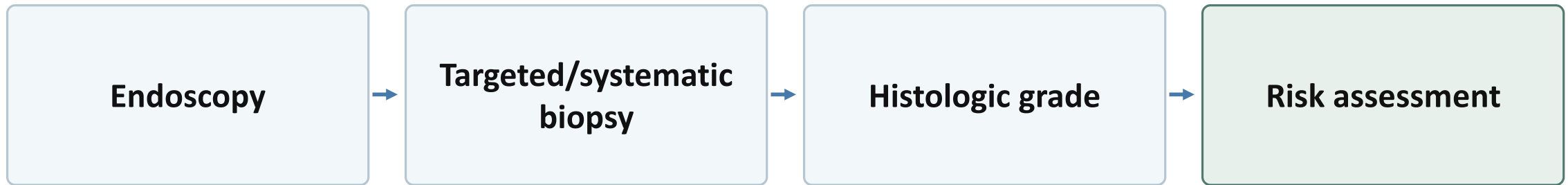
# When is carcinoma invasive?

Dysplasia remains intraepithelial



Illustrative path of increasing depth

# Dysplasia and surveillance



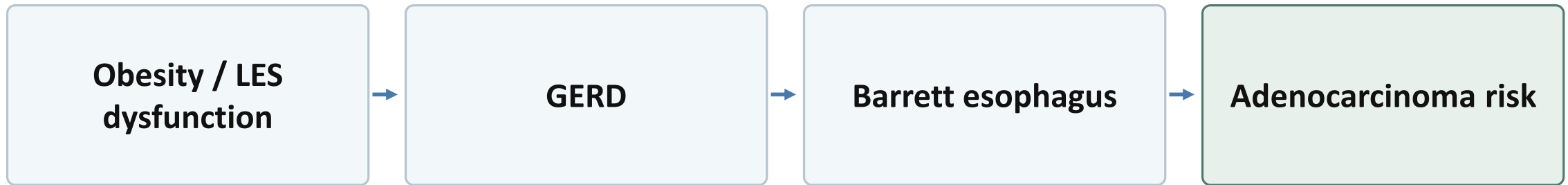
Schematic sequence — conceptual progression, not an inevitable patient course  
Barrett esophagus is identified by endoscopy with biopsy

## Endoscopic treatment is stage-dependent

- The text discusses radiofrequency ablation and endoscopic mucosal resection for dysplasia
- Selected superficial carcinoma may also be treated endoscopically
- Management depends on extent, comorbidity and specialist assessment

**Endoscopy**  
**Biopsy**  
**Ablation / resection**

# The dominant risk pathway



**Schematic sequence — conceptual progression, not an inevitable patient course**  
Chronic GERD and Barrett esophagus are central to adenocarcinoma risk

## **Additional exposure associations**

Tobacco use

**Tobacco use**

**Dietary nitrosamines**

**Radiation exposure**

# **Dietary patterns linked to lower risk**

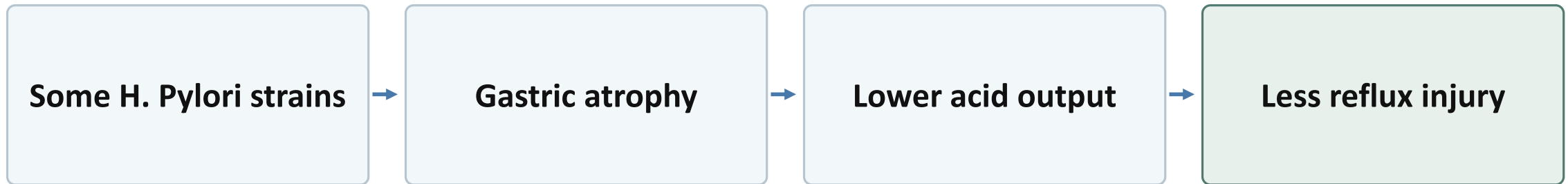
Fresh fruits and vegetables

**Fresh fruits and vegetables**

**Whole grains and dietary fiber**

**Vitamins C and B6, and folate**

# Helicobacter pylori: Inverse association



**Schematic sequence — conceptual progression, not an inevitable patient course**  
Some H. Pylori serotypes correlate with lower adenocarcinoma risk

# Alcohol distinguishes carcinoma subtypes

**Adenocarcinoma: Alcohol not a risk association**

**Squamous carcinoma: Alcohol + tobacco synergy**

- Alcohol is not associated with increased adenocarcinoma risk
- Alcohol and tobacco synergize in squamous cell carcinoma
- Risk-factor patterns must not be transferred from one histotype to the other

# Sex and ancestral distribution

Adenocarcinoma about seven-fold more common in males

**7×**

Male predominance reported

Figures are reported; Not a current population estimate

## Marked geographic heterogeneity

| Higher                        | Lower           |
|-------------------------------|-----------------|
| United States; United Kingdom | Korea; Thailand |
| Canada; Australia             | Japan; Ecuador  |
| Netherlands; Brazil           | —               |

# Adenocarcinoma incidence rose in the West

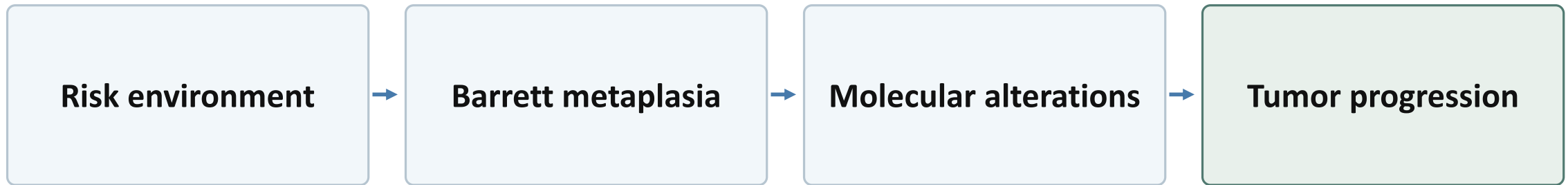
The text describes a pronounced increase since 1970

**<5% → >60%**

U.S. Proportion of esophageal cancers; Historical comparison

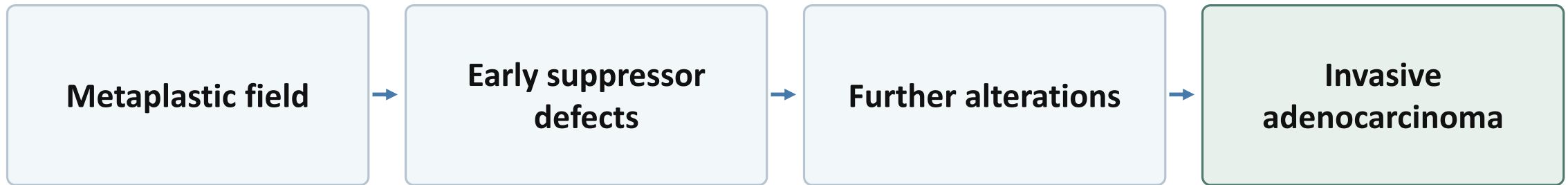
Figures are reported; Not a current population estimate

## **Risk factors should be synthesized**



**Schematic sequence — conceptual progression, not an inevitable patient course**  
Exposure: Reflux, tobacco, radiation, dietary associations

# Neoplastic progression accumulates alterations



Schematic sequence — conceptual progression, not an inevitable patient course  
A stepwise genetic and epigenetic process

# **Chromosomal instability is characteristic**

Adenocarcinomas often show multiple chromosomal abnormalities

**Chromosomal instability**

**TP53**

**CDKN2A**

# **TP53: Early tumor-suppressor alteration**

TP53 abnormalities can be detected early in neoplastic evolution

**TP53**

**Early change**

**Tumor-suppressor pathway**

# **CDKN2A products restrain neoplasia**

CDKN2A is another early-affected suppressor locus

**CDKN2A**

**P16 / ARF**

**Early inactivation**

# Genetic loss and epigenetic silencing

## Allelic loss

## Promoter hypermethylation

- Allelic loss removes functional tumor-suppressor material
- Hypermethylation can silence expression without changing sequence
- Both mechanisms are described at CDKN2A in the source

# Oncogene amplification can accompany progression

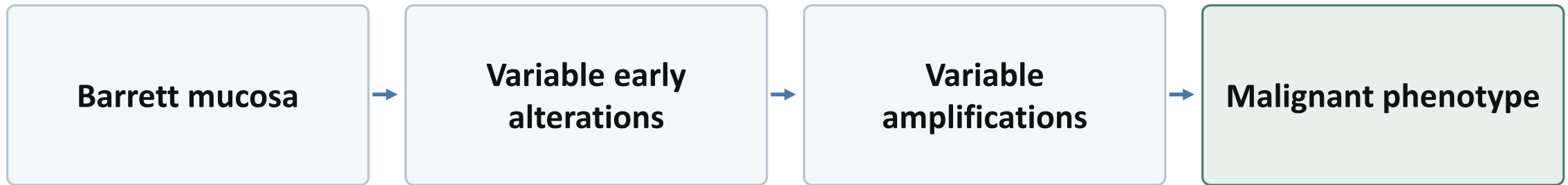
ERBB2, VEGFA and EGFR

**ERBB2 • EGFR**

**VEGFA • KRAS**

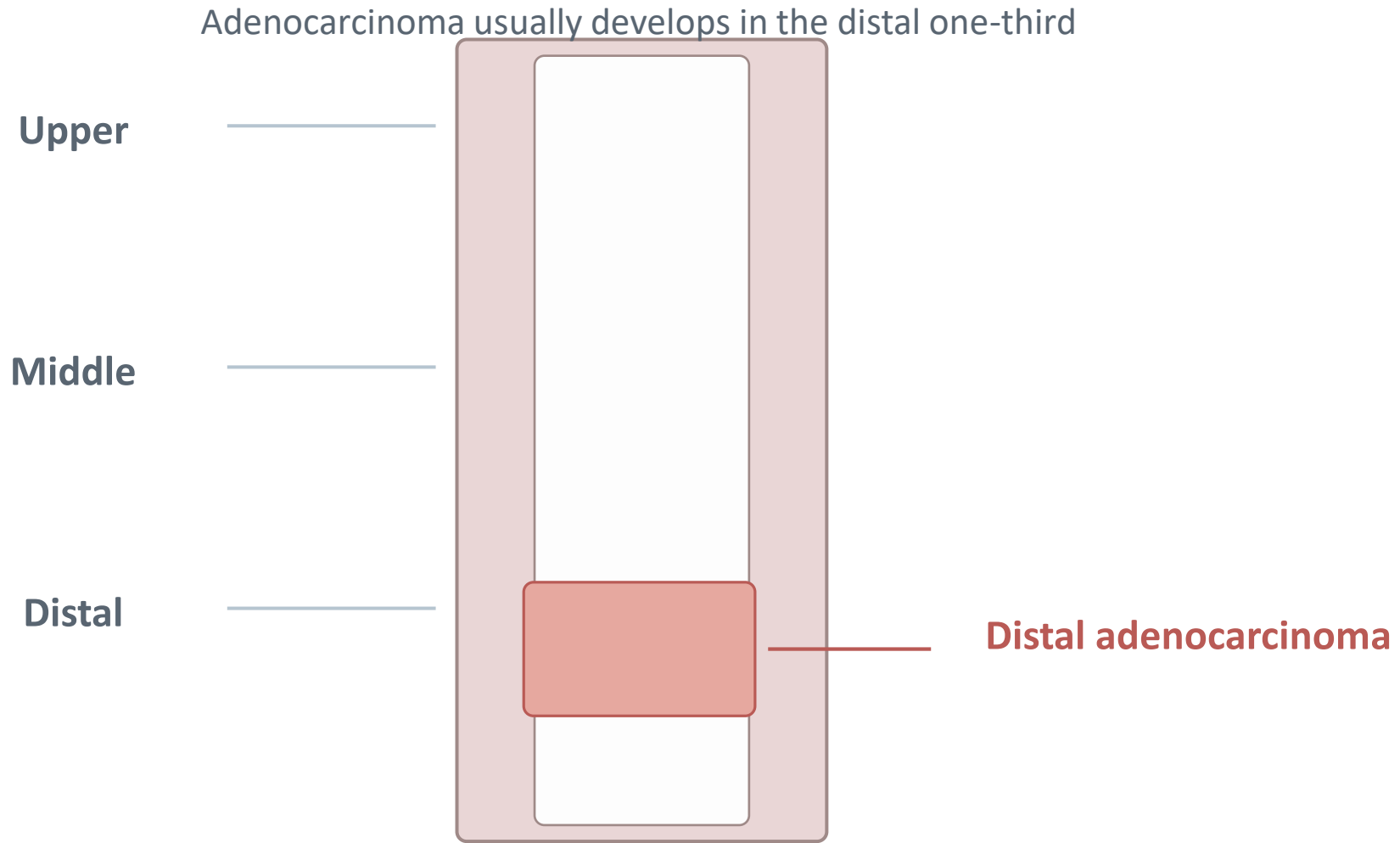
**CCND1 • CDK6**

# No single obligatory molecular sequence



**Schematic sequence — conceptual progression, not an inevitable patient course**  
Chromosomal instability can yield heterogeneous combinations of changes

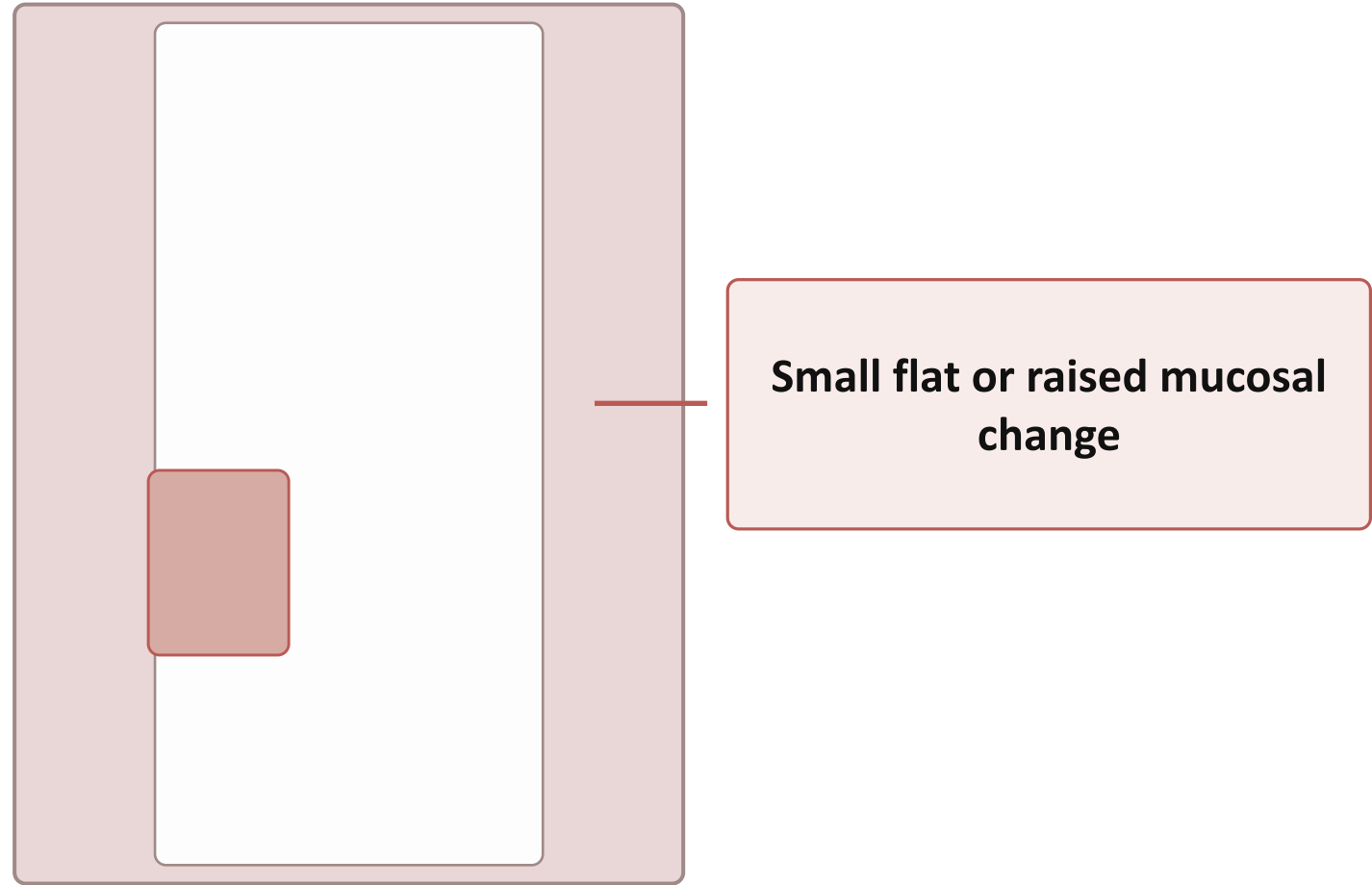
# Distal esophagus is the typical site



Schematic; Tumor locations vary

# Early gross lesions may be subtle

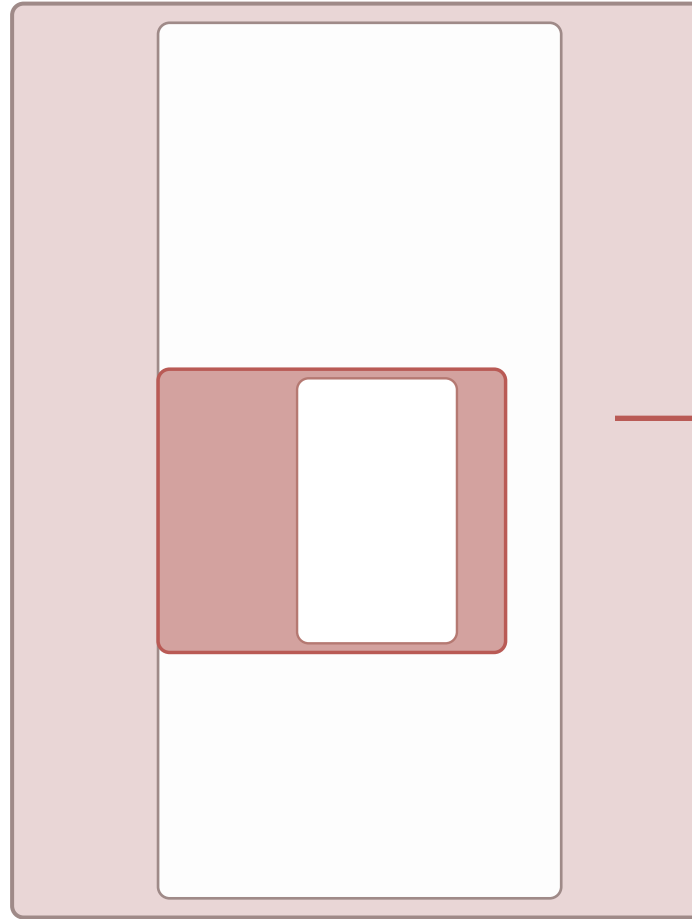
Initial lesions may appear as flat mucosal patches



Conceptual gross morphology schematic

# Advanced gross growth patterns

Some tumors form large, protruding masses



**Luminal encroachment / wall infiltration**

Conceptual gross morphology schematic

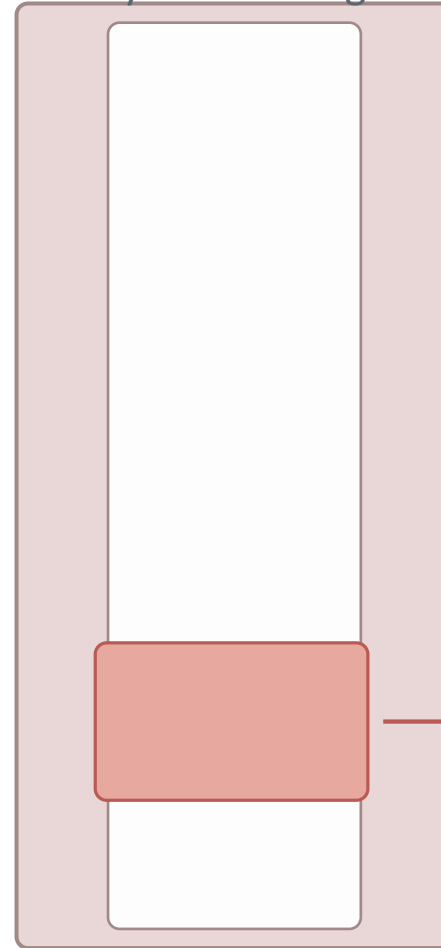
# Esophagogastric junction: An origin problem

Advanced distal esophageal tumors may be indistinguishable from gastric cardia primaries

Upper

Middle

Distal

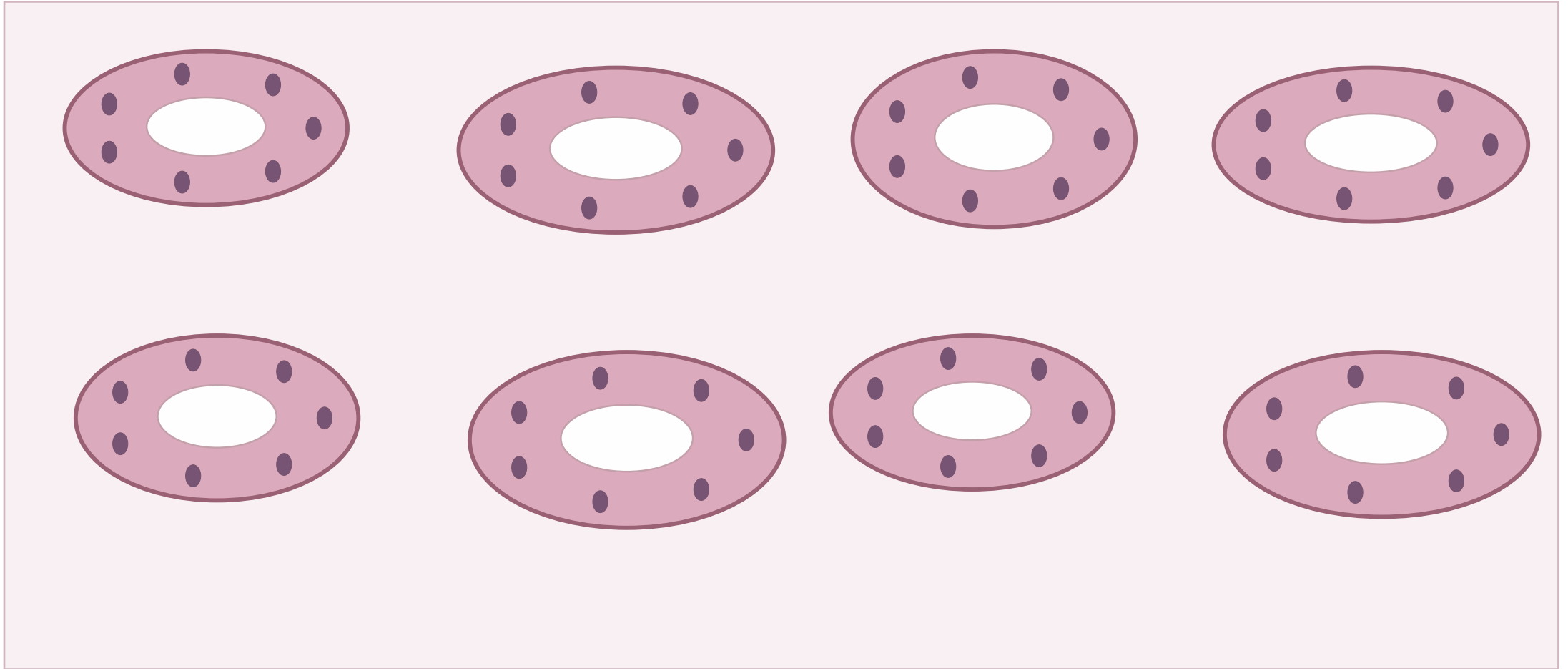


Distal adenocarcinoma

Schematic; Tumor locations vary

# Gland formation identifies conventional adenocarcinoma

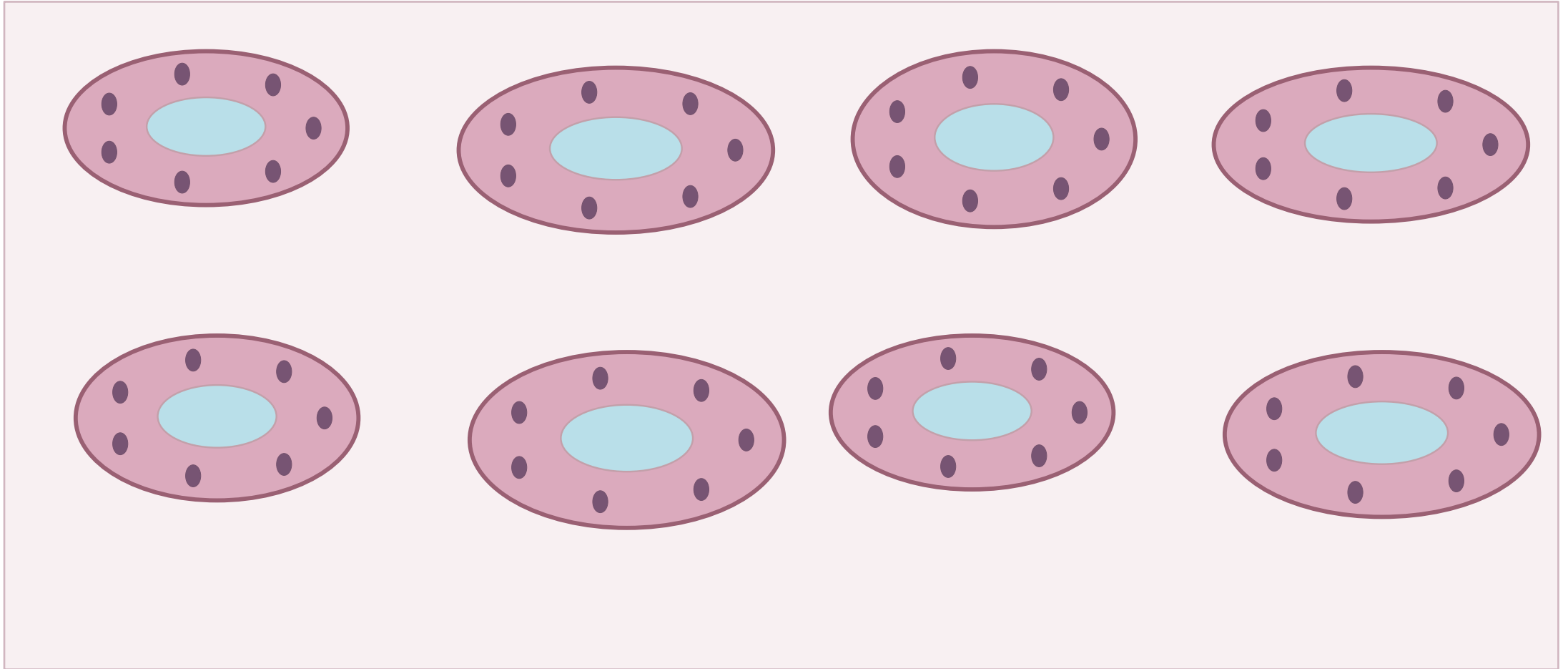
Typical tumors show irregular malignant glands



Schematic — variably sized atypical glands with lumens

# Tumor mucin is a characteristic product

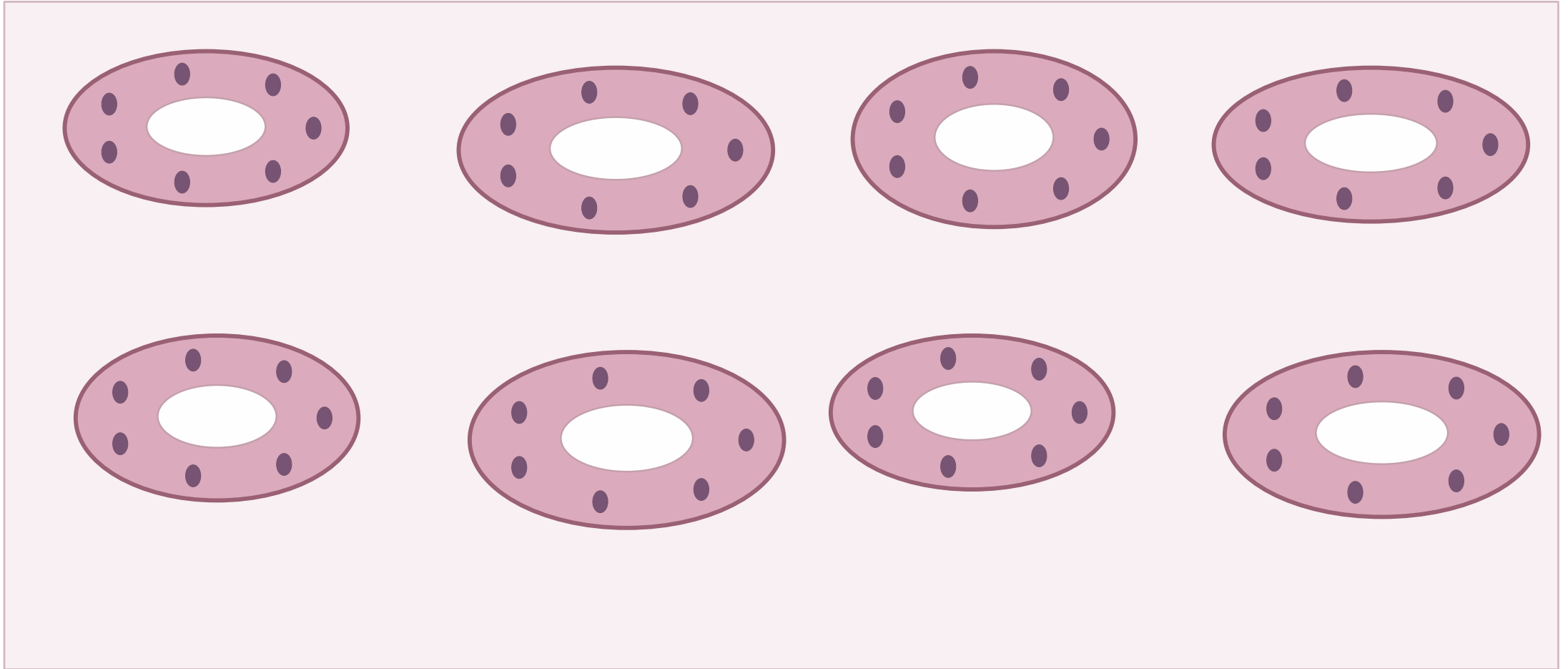
Most conventional tumors are mucin-producing



Schematic — blue luminal material represents tumor mucin

# Intestinal-type morphology predominates

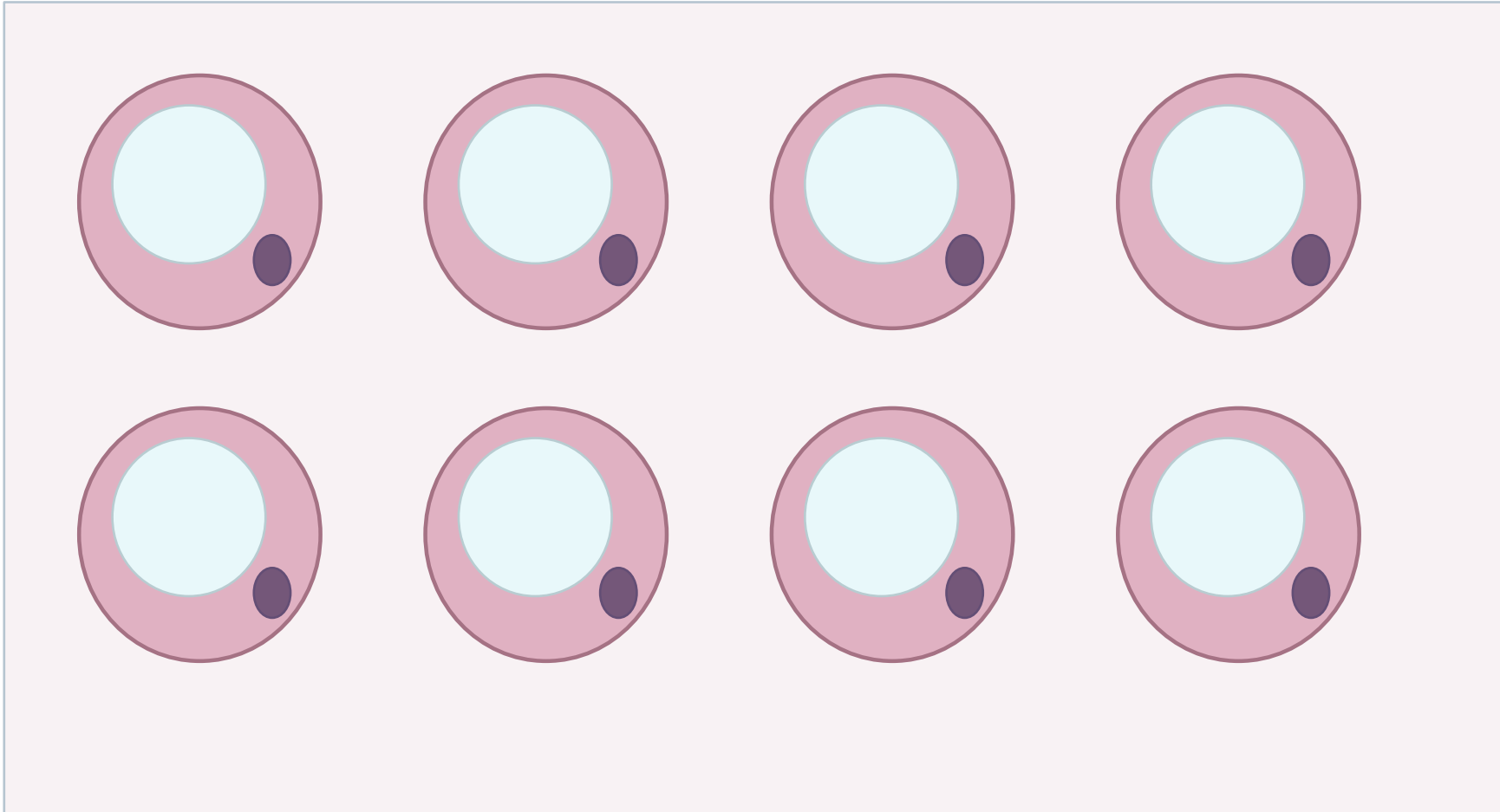
Typical adenocarcinoma has intestinal-type gland formation



Schematic — variably sized atypical glands with lumens

# Signet-ring cells are a less common pattern

Some tumors infiltrate diffusely as signet-ring cells



Schematic signet-ring cells: Mucin vacuole displaces nucleus

## Poorly differentiated patterns also occur

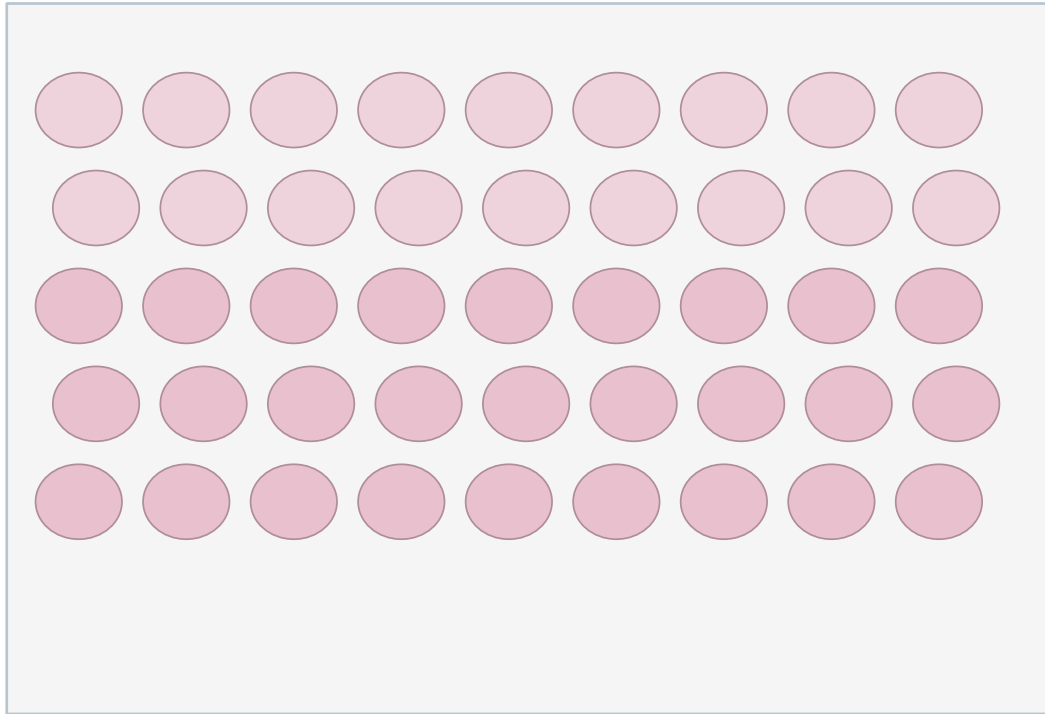
### Conventional glands

### Poorly differentiated cells

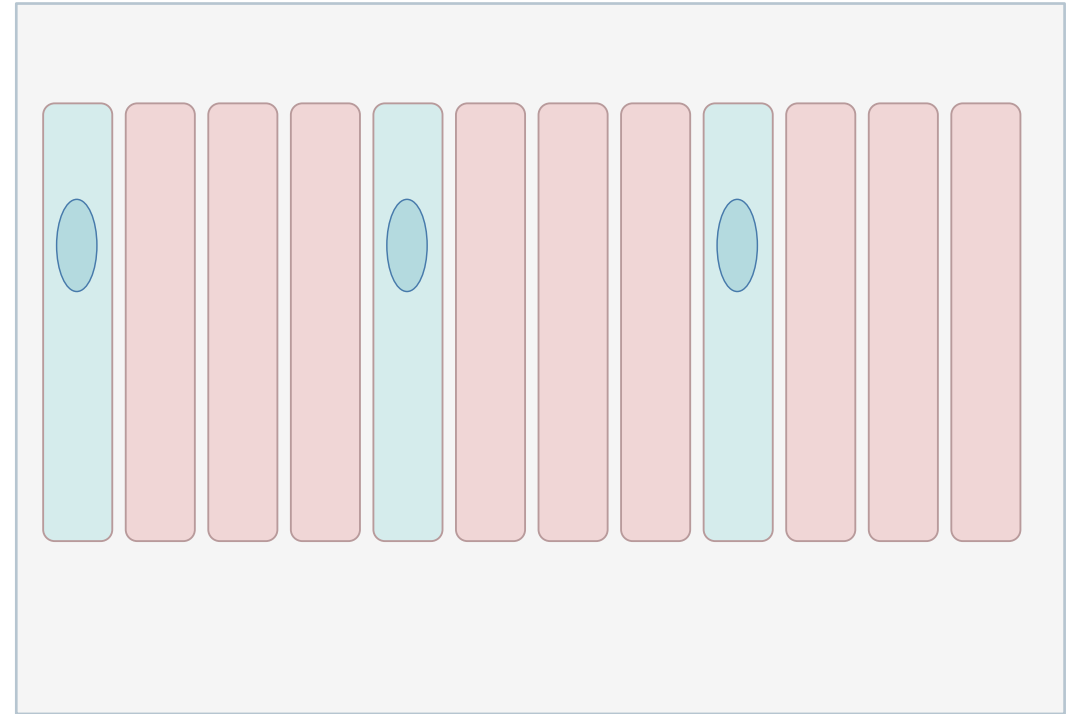
- Rare tumors consist of small poorly differentiated cells
- The text compares this appearance to small cell carcinoma of lung
- Atypical morphology requires careful classification

# Residual Barrett mucosa helps localize origin

Barrett metaplasia often borders an esophageal adenocarcinoma



**Stratified squamous epithelium**

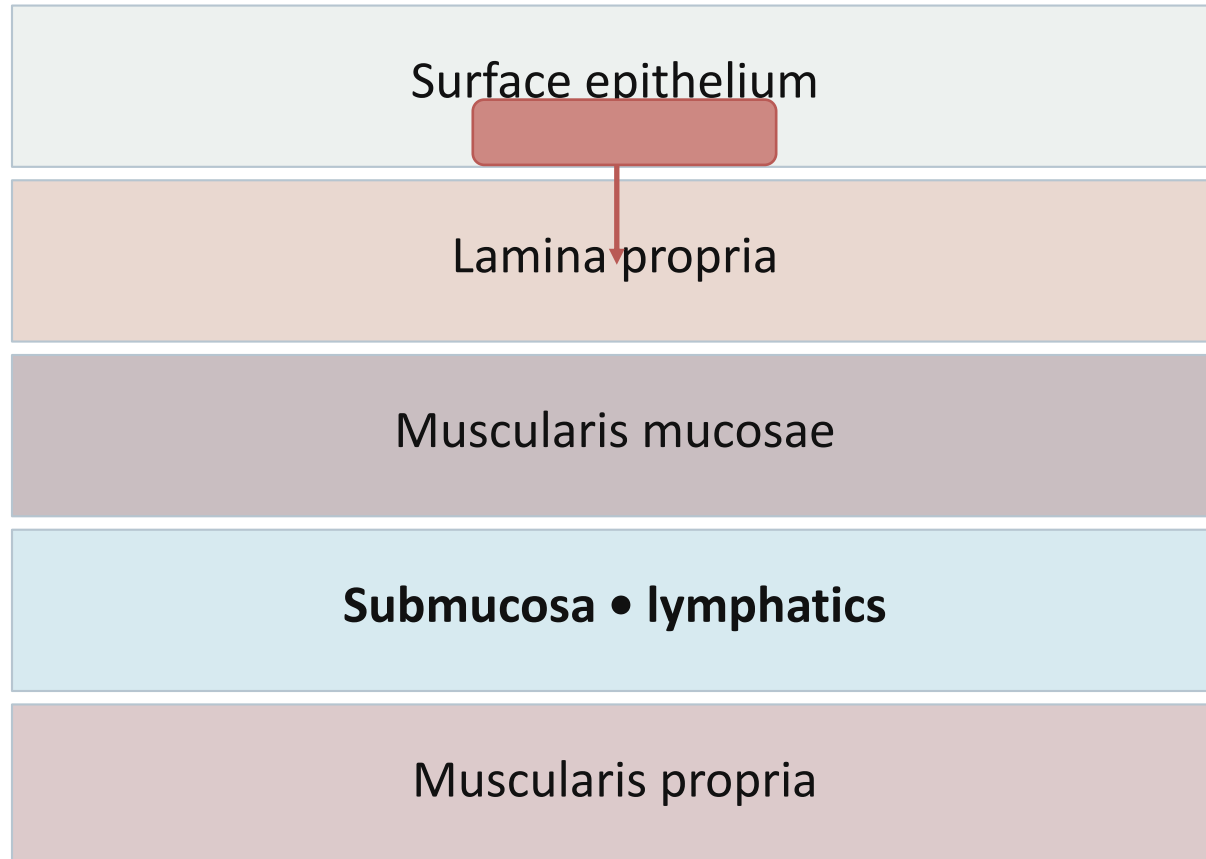


**Intestinalized columnar epithelium**

Schematic — not a photomicrograph

# Dysplasia and invasive glands: Conceptual contrast

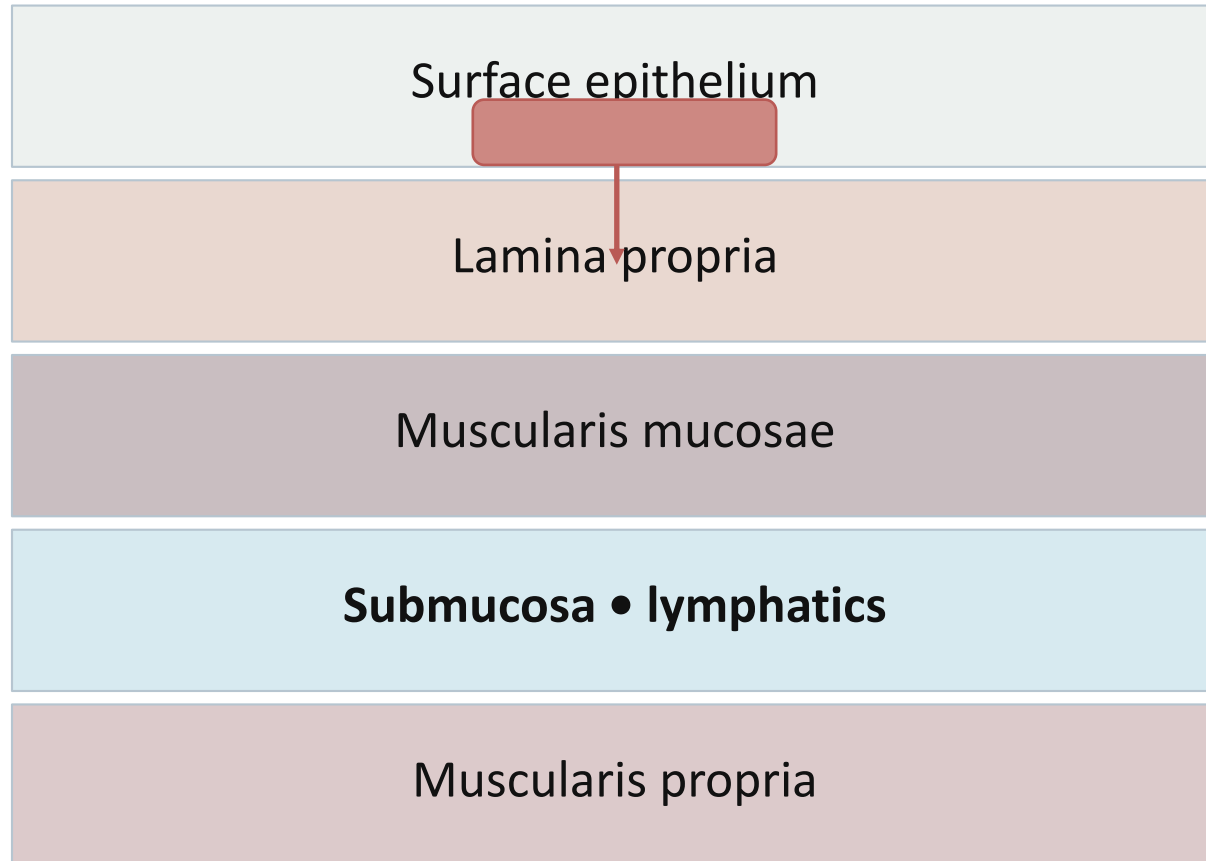
Dysplasia: Abnormal epithelium remains confined to epithelial compartments



Illustrative path of increasing depth

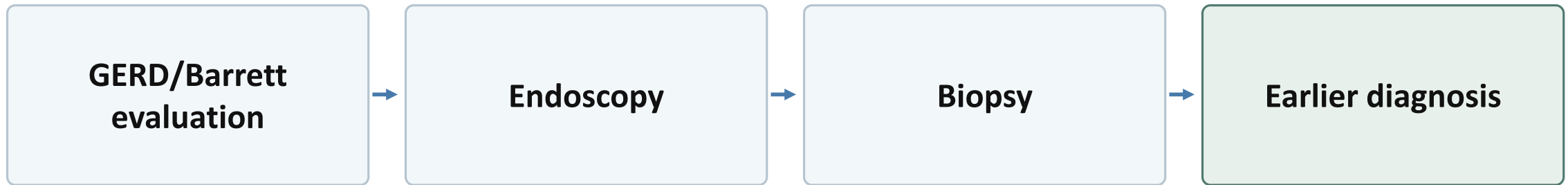
# Superficial versus advanced invasion

Carcinoma restricted to mucosa or submucosa has a substantially better reported outcome



Illustrative path of increasing depth

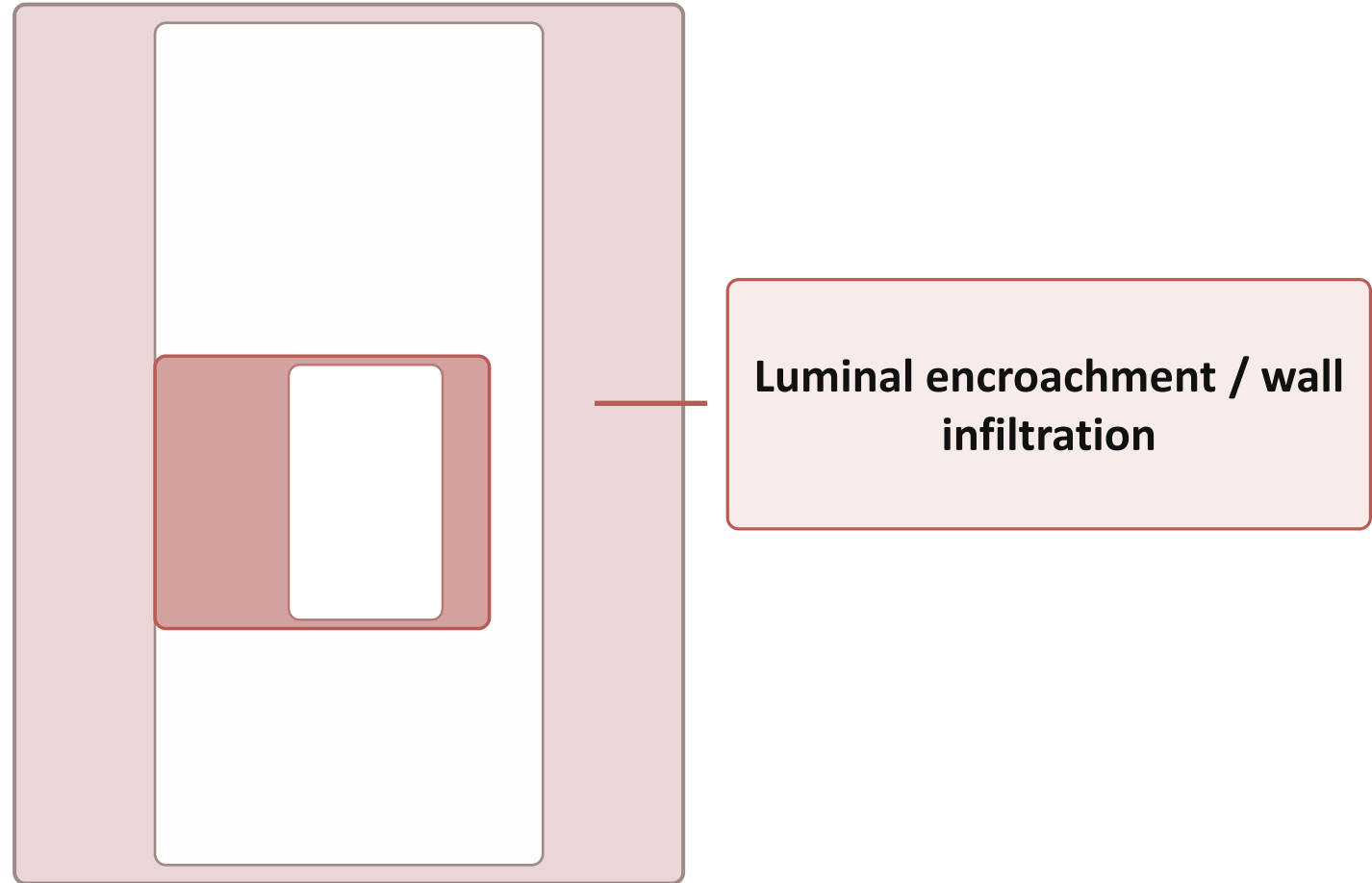
## Early lesions may be found incidentally



Schematic sequence — conceptual progression, not an inevitable patient course  
Evaluation for GERD may identify unsuspected neoplasia

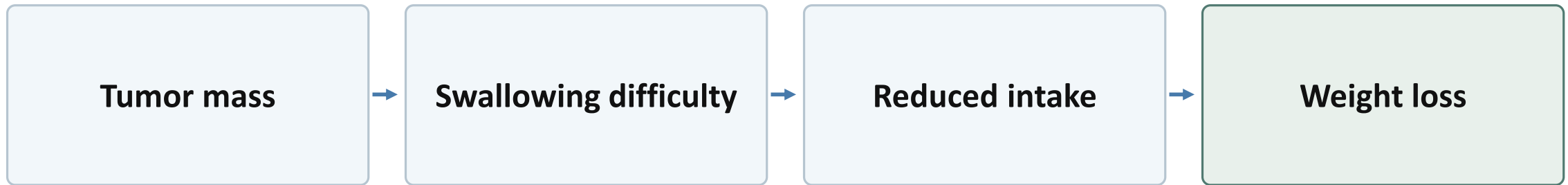
# Progressive dysphagia reflects narrowing

Tumor growth and infiltrative wall thickening impair bolus transit



Conceptual gross morphology schematic

# Weight loss is multifactorial



Schematic sequence — conceptual progression, not an inevitable patient course  
Impaired swallowing reduces effective oral intake

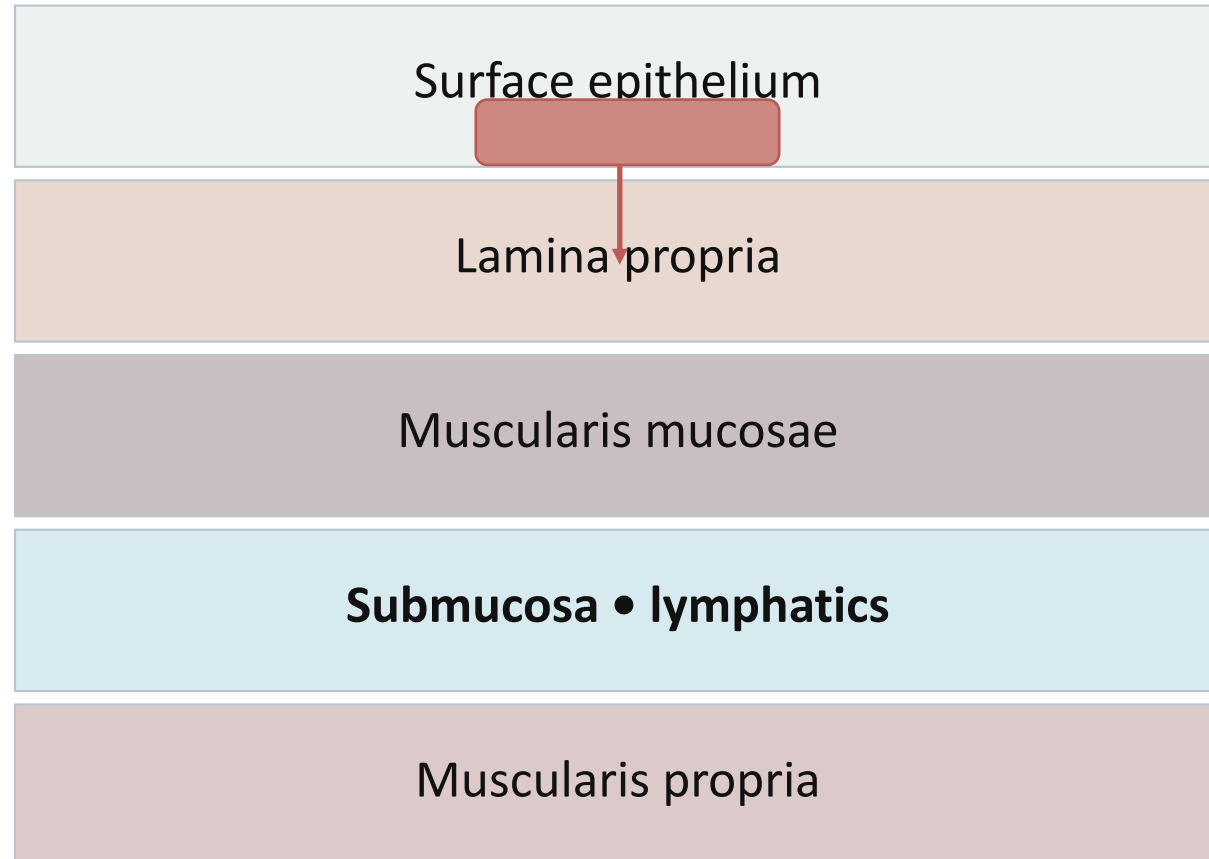
## Bleeding and chest symptoms

- Hematemesis can accompany tumor ulceration
- Chest pain or vomiting may occur
- These symptoms are nonspecific; Tissue diagnosis is necessary

**Dysphagia**  
**Weight loss**  
**Bleeding**  
**Chest symptoms**

# Submucosal lymphatics explain early spread

By symptomatic presentation, tumor frequently reaches submucosal lymphatics



Illustrative path of increasing depth

# Extent at diagnosis strongly changes survival

Typical 5-year survival <25% for symptomatic adenocarcinoma

**~80% vs <25%**

Five-year survival: Superficial vs commonly symptomatic EAC (Robbins)

Figures are reported; Not a current population estimate

## A different pathway: Squamous carcinoma

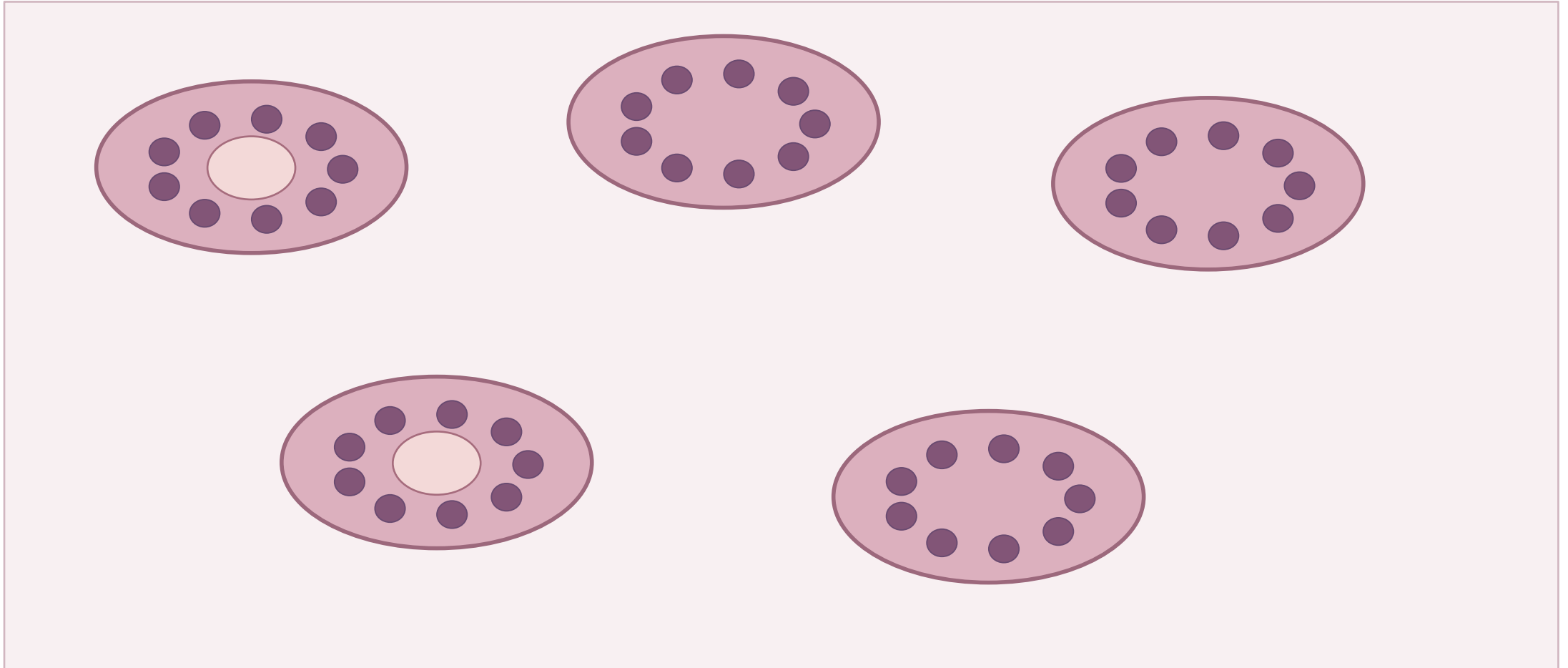
**Barrett → adenocarcinoma**

**Squamous dysplasia → SCC**

- Squamous carcinoma typically begins as squamous dysplasia
- It is most common in the proximal and middle esophagus
- Alcohol, tobacco and other injury exposures are major associations

# Squamous carcinoma: Key morphology

Gray-white plaques can precede a larger tumor



Schematic — epithelial nests and central keratinization

# Adenocarcinoma versus squamous carcinoma

| Feature      | Adenocarcinoma          | Squamous cell carcinoma  |
|--------------|-------------------------|--------------------------|
| Typical site | Distal third            | Middle / proximal        |
| Precursor    | Barrett dysplasia       | Squamous dysplasia       |
| Morphology   | Malignant glands; Mucin | Malignant squamous nests |
| Association  | GERD; Barrett           | Alcohol; Tobacco         |

## Case: Barrett surveillance biopsy

- A patient with long-standing reflux has Barrett epithelium on biopsy
- Glands show stratified hyperchromatic nuclei but no stromal infiltration
- Interpretation: Dysplasia, not automatically invasive adenocarcinoma

## Case: A distal obstructing tumor

- Progressive dysphagia and weight loss accompany a distal esophageal mass
- Biopsy shows atypical, infiltrative mucin-producing glands
- Most consistent major histotype: Adenocarcinoma

# Pattern recognition: Glands versus nests

## Malignant glands

## Squamous nests

- Irregular glandular lumens favor adenocarcinoma
- Squamous nests with differentiation favor squamous cell carcinoma
- Correlate histology with mucosal precursor and anatomic site

## **Five clinicopathologic conclusions**

- Adenocarcinoma and squamous carcinoma dominate esophageal cancer
- Barrett dysplasia is the principal precursor of adenocarcinoma
- Chromosomal instability accompanies neoplastic evolution
- Distal location and malignant mucin-producing glands favor adenocarcinoma
- Early depth-limited disease has a much better reported prognosis

## **Diagnostic integration at sign-out**

- Determine the site: distal esophagus, esophagogastric junction or other level
- Identify lineage: malignant gland formation versus squamous differentiation
- Assess adjacent precursor tissue: Barrett metaplasia or squamous dysplasia
- Describe invasion depth and potential lymphatic access