

Invasive Carcinoma of the Breast

Morphology · Molecular phenotypes · Clinicopathologic integration

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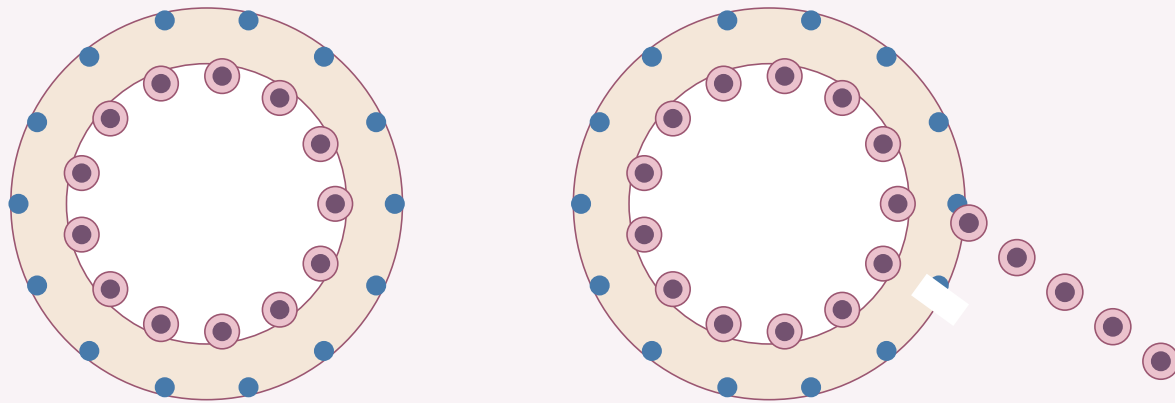
Learning objectives

- Distinguish stromal invasion from in situ breast carcinoma.
- Relate histologic type and grade to breast cancer biology.
- Interpret ER, PR, HER2, stage and major prognostic variables.
- Connect morphologic patterns with clinical presentation and diagnostic pitfalls.

What defines invasive breast carcinoma?

- Malignant epithelial cells extend beyond the basement membrane into breast stroma.
- Invasion permits access to lymphovascular routes and distant dissemination.
- Invasion status, histologic type, grade and anatomic extent are distinct diagnostic outputs.

In situ disease versus stromal invasion



IN SITU

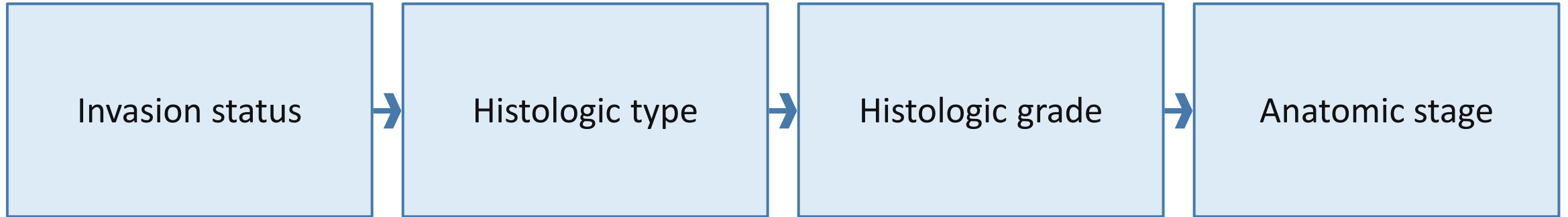
INVASIVE

Schematic — not a histologic specimen

Morphologic interpretation

- In situ: Atypical epithelial cells remain enclosed by the myoepithelial–basement membrane interface.
- Invasive: Malignant cells breach that boundary and enter surrounding stroma.

Four complementary dimensions of a diagnosis



Biomarkers and molecular alterations further refine prognosis and therapy selection.

Pathology classification has two distinct axes

Morphologic axis

- In situ versus invasive
- No special type versus defined special histologic type
- Nottingham grade and extent

Biologic axis

- ER and PR nuclear expression
- HER2 protein / gene status
- Selective genomic or gene-expression assays

Three major routine clinical groups

Luminal

- ER-positive / HER2-negative
- Usually endocrine-responsive
- Variable grade and proliferation

HER2-positive

- HER2 overexpression or amplification
- Targetable ERBB2 pathway
- ER may be positive or negative

Triple-negative

- ER-negative / PR-negative / HER2-negative
- Biologically heterogeneous
- Often high-grade and proliferative

Molecular subtyping is more granular

- Expression profiling describes luminal A, luminal B, HER2-enriched, basal-like, normal-like and claudin-low groups.
- These intrinsic classes correlate imperfectly with ER/HER2 clinical assays.
- Expression signatures can add prognostic or predictive information in selected settings.

Global burden context

- Breast cancer became the most commonly diagnosed cancer worldwide in 2020.
- The chapter reports approximately 2.3 million new cases worldwide in that year.
- Earlier detection and more effective adjuvant treatment have improved outcomes, unequally across settings.

Age is linked to subtype distribution

- Breast cancer is uncommon before age 25 and incidence rises with age.
- ER-positive luminal tumors continue to rise in incidence at older ages.
- HER2-positive and triple-negative tumors contribute a larger fraction of cancers in younger patients.

How invasive tumors first come to attention

Screen-detected

- Often relatively small
- Usually nonpalpable
- More commonly luminal

Symptom-detected

- Palpable irregular mass
- May show skin or nipple change
- More common with rapidly growing subtypes

Detection and clinical correlation

- Mammography can detect a density, architectural distortion or calcifications; None is cancer-specific.
- Ultrasonography, tomosynthesis and MRI may clarify lesions occult on conventional views.
- A negative screening image does not exclude an invasive tumor when clinical suspicion remains.

Clinical manifestations of local invasion

- Desmoplastic stromal growth can produce a hard, irregular breast mass.
- Skin tethering causes dimpling; Central tumors may retract the nipple.
- Advanced local spread can involve the dermis or chest wall.

Breast carcinoma risk is multifactorial

Constitutional

- Increasing age
- Inherited susceptibility and family history
- Prior breast carcinoma

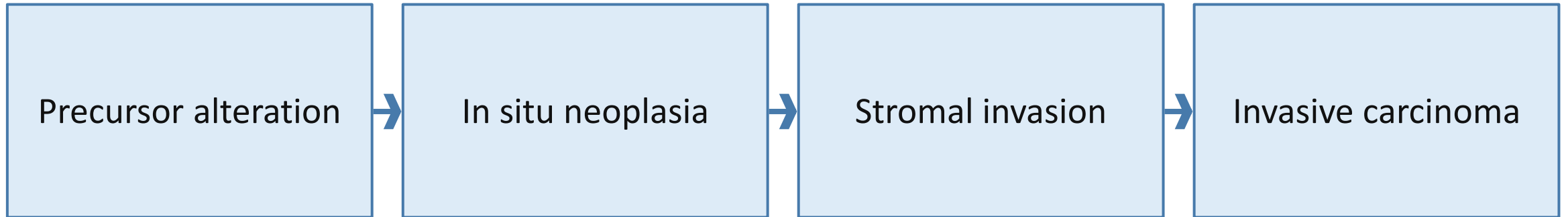
Hormonal / exposure

- Cumulative estrogen exposure
- Reproductive history and exogenous hormones
- Postmenopausal obesity and physical inactivity

Estrogen exposure and luminal cancer

- Estrogen stimulates epithelial proliferation and influences gene transcription.
- Repeated cell cycling creates opportunities for the acquisition and fixation of mutations.
- Estrogen signaling can also promote growth of an established ER-positive neoplastic clone.

Two broad evolutionary pathways



Low-grade and high-grade cancers often follow distinct evolutionary trajectories; They are not absolutely isolated.

Low-grade versus high-grade routes

Low-grade neoplasia

- Columnar cell lesion → atypia
- Low-grade DCIS / classic LCIS
- Typically luminal, ER-positive

High-grade neoplasia

- Early precursor incompletely defined
- High-grade DCIS
- More genomic instability; Several clinical phenotypes

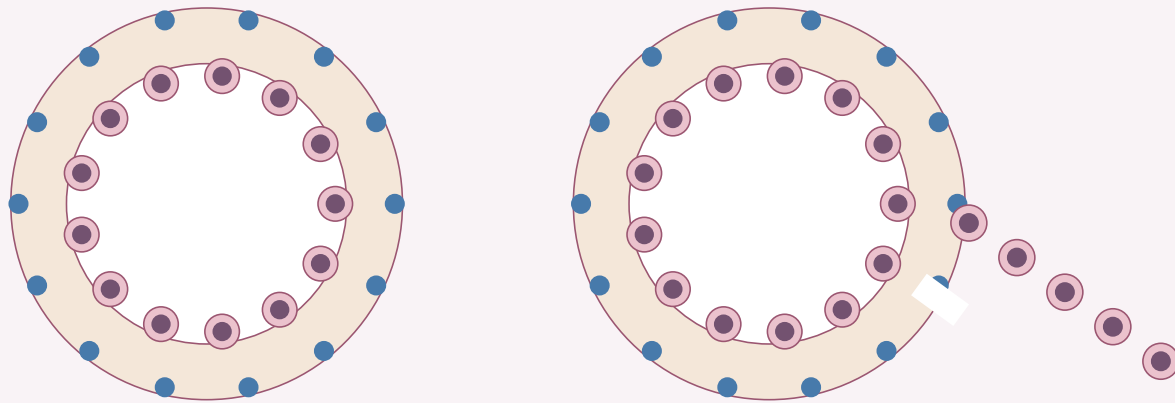
Characteristic alterations in low-grade evolution

- Gain of chromosome 1q and loss of 16q are characteristic genomic changes.
- PIK3CA activation is encountered in the luminal pathway.
- Many lesions remain indolent; Progression requires additional biologic events.

Characteristic alterations in high-grade evolution

- High-grade tumors more often show TP53 mutations and complex chromosomal changes.
- HER2 amplification and DNA repair defects define biologically important subsets.
- High-grade DCIS is a recognized precursor, but earlier steps are less clearly characterized.

The invasive transition: Epithelial–stromal interface



IN SITU

INVASIVE

Schematic — not a histologic specimen

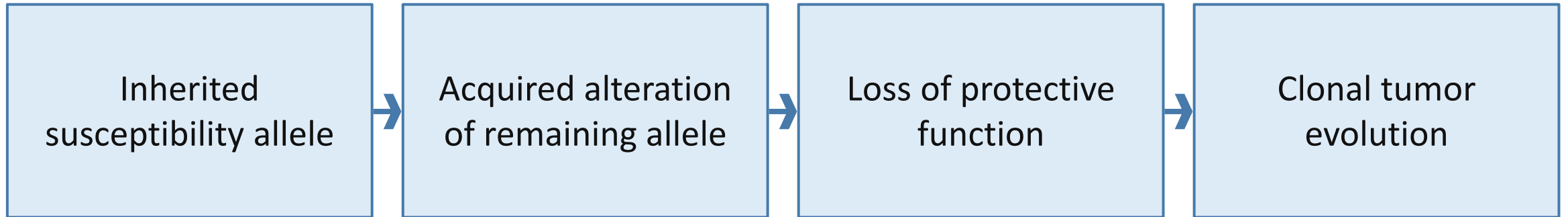
Morphologic interpretation

- In situ precursors may contain many of the same driver alterations as invasive carcinomas.
- Breakdown of the myoepithelial–basement membrane interface and microenvironmental changes may facilitate invasion.

Tumor microenvironment is an active participant

- Cancer-associated fibroblasts can remodel extracellular matrix and facilitate invasion.
- Myoepithelial–stromal interactions contribute to basement membrane integrity.
- Tumor and immune cell signaling can help establish an immunosuppressive microenvironment.

Genetic predisposition: The two-hit principle



This tumor-suppressor model is important for BRCA-associated breast cancer.

BRCA1 and BRCA2: Repair pathway biology

- BRCA1 and BRCA2 help maintain genomic integrity through homologous recombination repair.
- Inactivation favors accumulation of DNA damage and genomic instability.
- BRCA1-associated breast carcinomas are commonly triple-negative; BRCA2-associated cancers are often ER-positive.

Selected susceptibility genes and associated patterns

BRCA1 / BRCA2

- Homologous recombination repair
- BRCA1: Often TNBC
- BRCA2: Often luminal

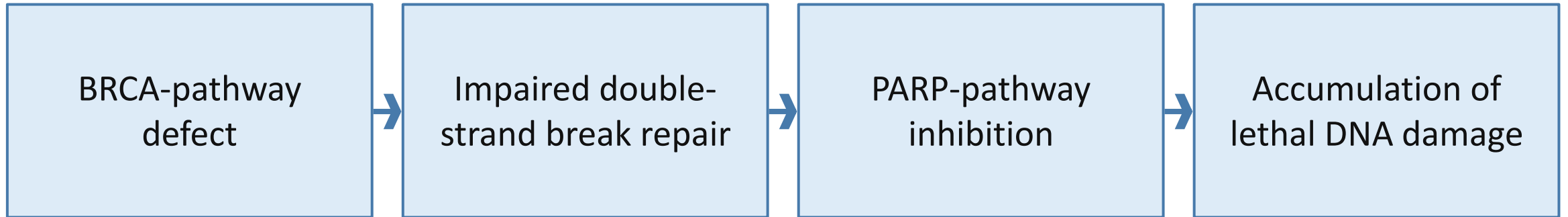
TP53 / PTEN

- Cell growth and genome control
- Li–Fraumeni / Cowden syndromes
- Distinct cancer spectra

CDH1 / PALB2

- Adhesion / DNA repair
- CDH1: Lobular type
- PALB2: Luminal or TNBC

Synthetic lethality in homologous recombination deficiency



A biologic rationale for PARP inhibitor sensitivity in selected hereditary-associated cancers.

Luminal carcinoma: Defining biology

- ER-positive / HER2-negative tumors represent the largest routine clinical group.
- Estrogen-regulated transcription is central to their tumor biology.
- They span low-grade, slowly proliferating tumors to more aggressive proliferative cancers.

Luminal A–like phenotype

- Strong ER-driven gene-expression program; Usually PR-positive.
- Lower proliferation and better glandular differentiation are typical.
- PIK3CA mutations, 1q gain and 16q loss are recurring associations.

Luminal B–like phenotype

- Stronger proliferation-associated expression than luminal A.
- Often lower ER/PR protein levels and greater genomic complexity.
- May be less differentiated and more clinically aggressive than luminal A.

Luminal A versus luminal B: Conceptual distinction

Luminal A

- Dominant estrogen-response signature
- Low proliferation
- Generally lower grade

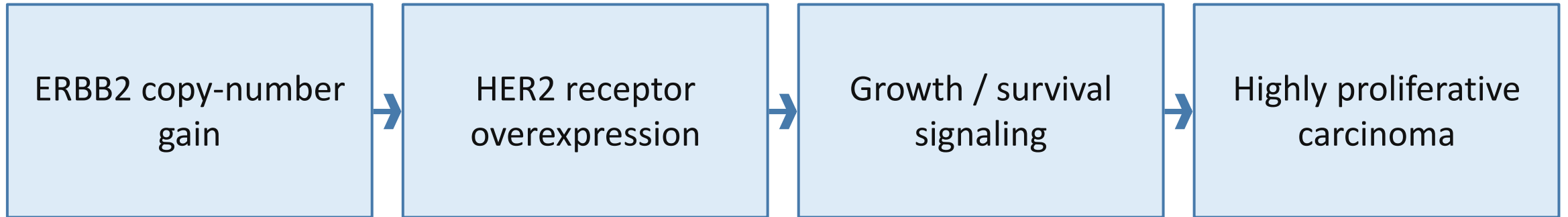
Luminal B

- Enhanced proliferation signature
- Higher proliferation
- Often higher grade

HER2-positive carcinoma: Defining event

- HER2 (ERBB2) is a receptor tyrosine kinase encoded on chromosome 17q.
- HER2 amplification is the major cause of HER2 protein overexpression.
- Downstream signaling includes pathways favoring proliferation and cell survival.

HER2 signaling links genotype to phenotype



Pathway diagram is conceptual; Individual signaling steps are simplified.

Two complementary ways to assess HER2

Immunohistochemistry

- Protein overexpression at cell membrane
- Assesses expression in tumor cells
- Requires appropriate scoring and controls

In situ hybridization

- HER2 gene copy-number changes
- Assesses gene amplification
- Interpreted with laboratory-validated criteria

Triple-negative breast carcinoma is heterogeneous

- Triple-negative is a clinical immunophenotype, not a single molecular entity.
- Many tumors have a basal-like gene-expression signature.
- High-grade cancers often show marked genomic instability and proliferative activity.

Homologous recombination defects in TNBC

- BRCA1/BRCA2 dysfunction and related repair deficiencies are biologically important.
- Genomic copy-number alterations and rearrangements can be extensive.
- The degree and mechanism of repair deficiency differ between individual tumors.

Clinical phenotypes are not intrinsic subtypes

Routine surrogate classification

- ER / PR immunohistochemistry
- HER2 immunohistochemistry or ISH
- Available in standard workflows

Intrinsic expression classes

- Genome-wide expression patterns
- More complex biological taxonomy
- Not routinely required for all diagnoses

Role of multigene expression assays

- Selected mRNA signatures contribute prognostic information beyond basic morphology.
- Many signatures emphasize proliferation-associated genes.
- Clinical utility is context-dependent, particularly within certain ER-positive cancers.

Invasive carcinoma of no special type (NST)

- NST is the predominant morphologic category of invasive breast cancer.
- It encompasses tumors without defining features of a special histologic type.
- Architecture, cytologic atypia, immune infiltration and desmoplasia vary widely.

NST: Irregular invasive nests in a stromal reaction



Morphologic interpretation

- Irregular malignant epithelial glands and nests dissect into fibrous stroma.
- A desmoplastic reaction can account for firmness and spiculated margins.

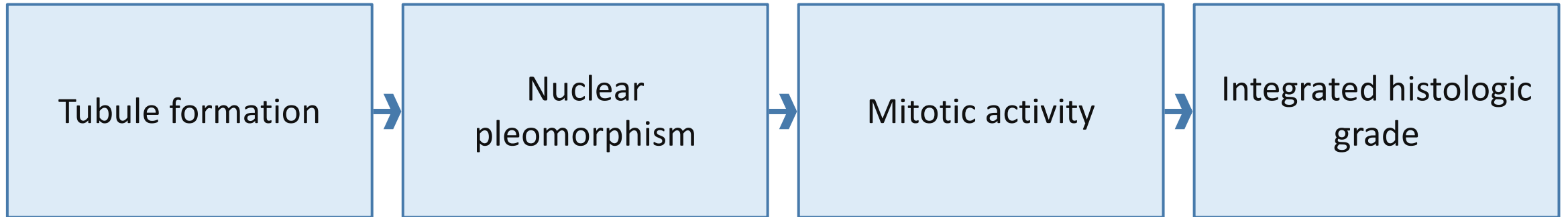
Gross appearance of NST carcinoma

- A firm, irregular mass with radiodense or spiculated margins is typical.
- Cut surfaces may appear pale or chalky-white when desmoplasia is prominent.
- Some cancers are deceptively circumscribed or diffuse with little stromal reaction.

NST may not form a discrete mass

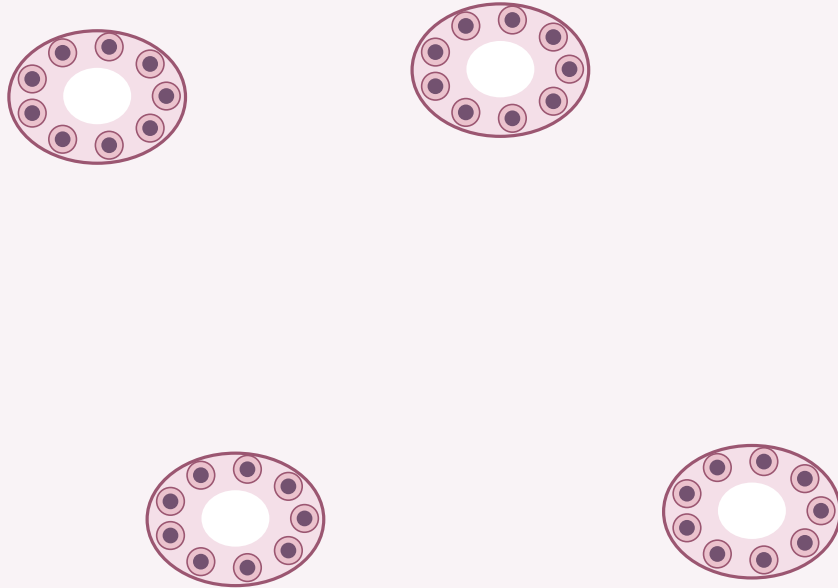
- Scattered cells or tiny neoplastic glands may infiltrate otherwise normal fibrofatty tissue.
- Some high-grade carcinomas grow as cellular sheets with relatively little desmoplasia.
- Morphology and clinical imaging must be correlated rather than assumed concordant.

Nottingham histologic grade is multidimensional



Grade reflects differentiation and proliferation; It is not interchangeable with stage.

Grade 1: Well differentiated



Schematic — not a histologic specimen

Morphologic interpretation

- Predominantly gland-forming architecture with relatively uniform nuclei.
- Low proliferative activity and infrequent mitoses.

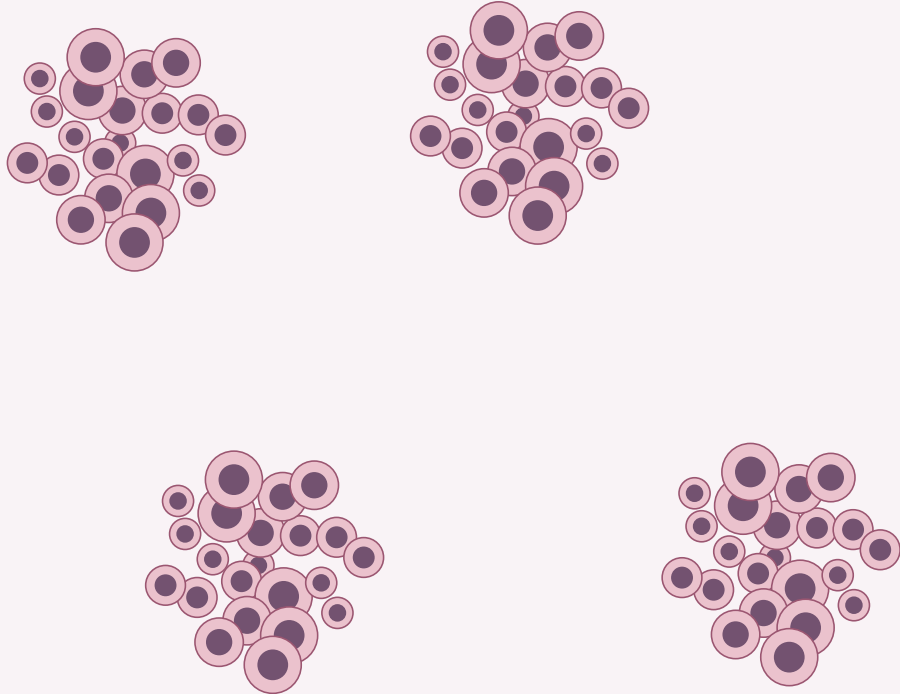
Grade 2: Intermediate differentiation



Morphologic interpretation

- Mixture of glandular structures and solid or infiltrative groups.
- Greater nuclear variation and mitotic activity than grade 1.

Grade 3: Poorly differentiated



Schematic — not a histologic specimen

Morphologic interpretation

- Ragged solid nests or sheets with little gland formation.
- Marked nuclear pleomorphism, high proliferation and possible necrosis.

Grade and stage answer different questions

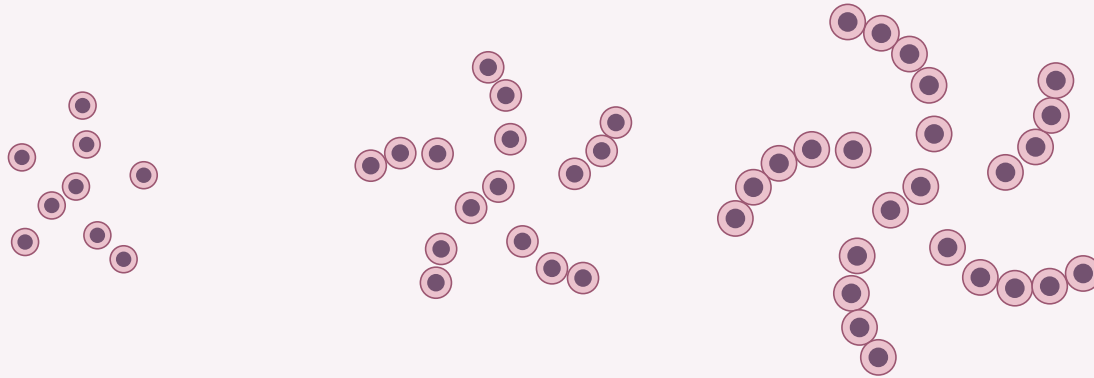
Histologic grade

- How differentiated and proliferative is the carcinoma?
- Tubules, nuclei, mitoses
- Biologic aggressiveness

Anatomic stage

- How far has carcinoma spread?
- Tumor extent, nodes, metastasis
- Disease burden

Morphologic spectrum of invasive carcinoma



Tubules

Mixed nests

Solid sheets

Schematic — not a histologic specimen

Morphologic interpretation

- Invasive breast carcinomas range from well-formed infiltrative tubules to poorly differentiated cellular sheets.
- The diagnostic category must integrate invasion, defining subtype features and grading.

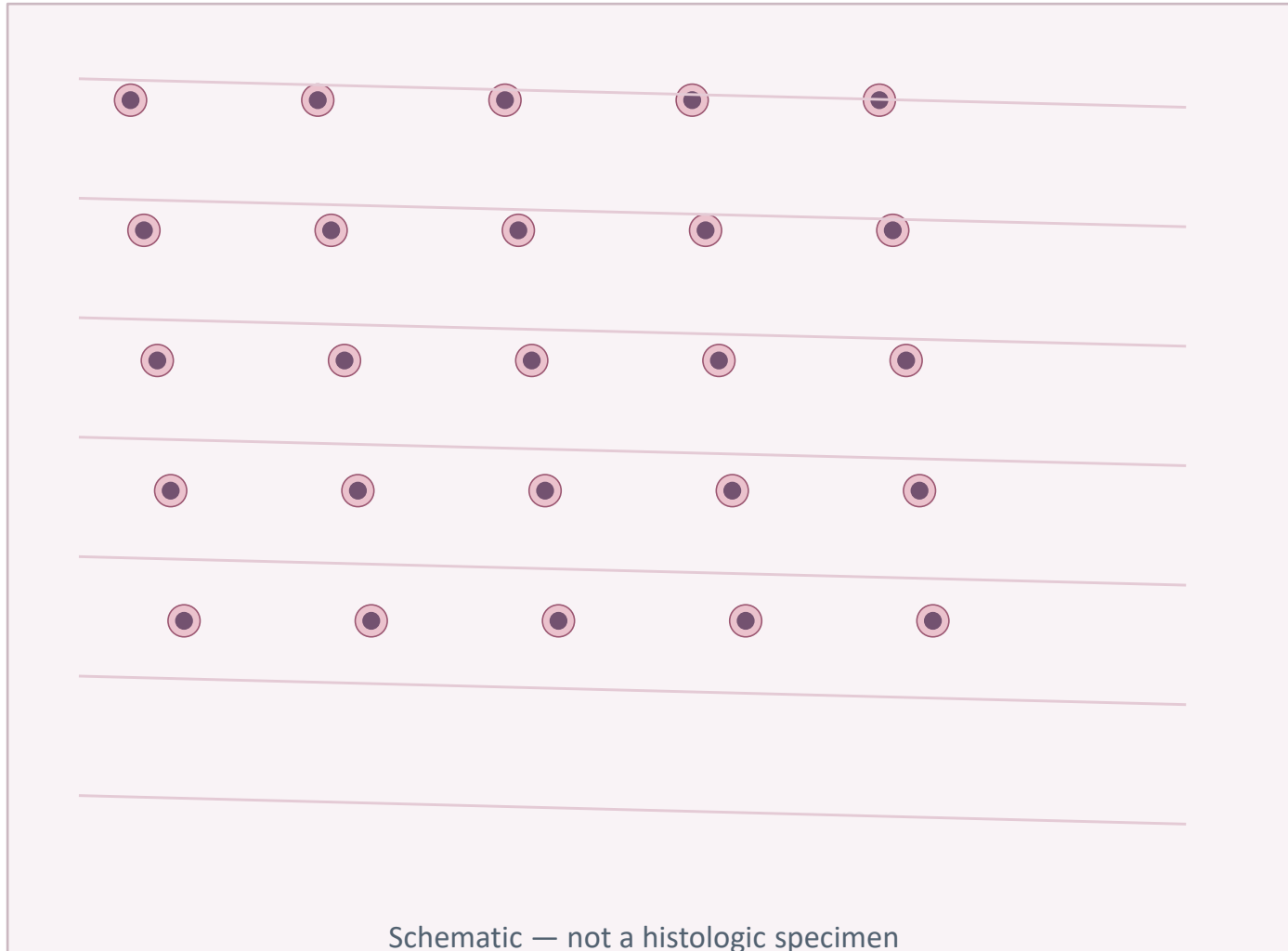
Why special histologic types matter

- Defined architectural or cytologic patterns can correlate with distinct genomic alterations.
- Some subtypes have characteristic biomarker profiles and clinical behavior.
- Recognizing a special subtype can materially change differential diagnosis and prognostic interpretation.

Invasive lobular carcinoma: The adhesion defect

- Loss of E-cadherin expression is typical and relates to reduced cell–cell cohesion.
- Dyscohesive tumor cells often infiltrate singly or in linear cords.
- Infiltration may induce little desmoplasia and can be difficult to detect radiologically.

Lobular carcinoma: Single-file invasion



Morphologic interpretation

- Dyscohesive cells form narrow linear cords within stroma.
- Intracytoplasmic mucin may produce signet-ring morphology.

NST versus invasive lobular carcinoma

NST carcinoma

- Irregular glands and cohesive nests
- Common desmoplasia
- Heterogeneous biomarker patterns

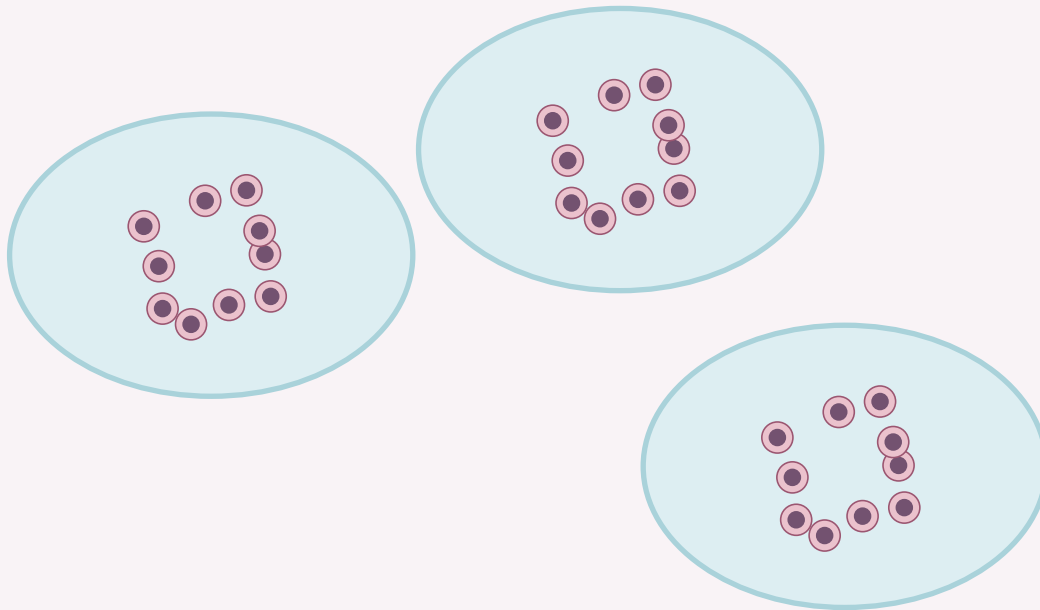
Lobular carcinoma

- Single cells / linear cords
- Often subtle desmoplasia
- Common loss of E-cadherin; Usually luminal

Lobular carcinoma: Dissemination patterns

- Invasive lobular carcinoma may involve peritoneum, retroperitoneum and gastrointestinal tract.
- Additional reported sites include leptomeninges, ovaries and uterus.
- Such distributions can complicate identification of the breast primary.

Mucinous carcinoma: Extracellular mucin pools

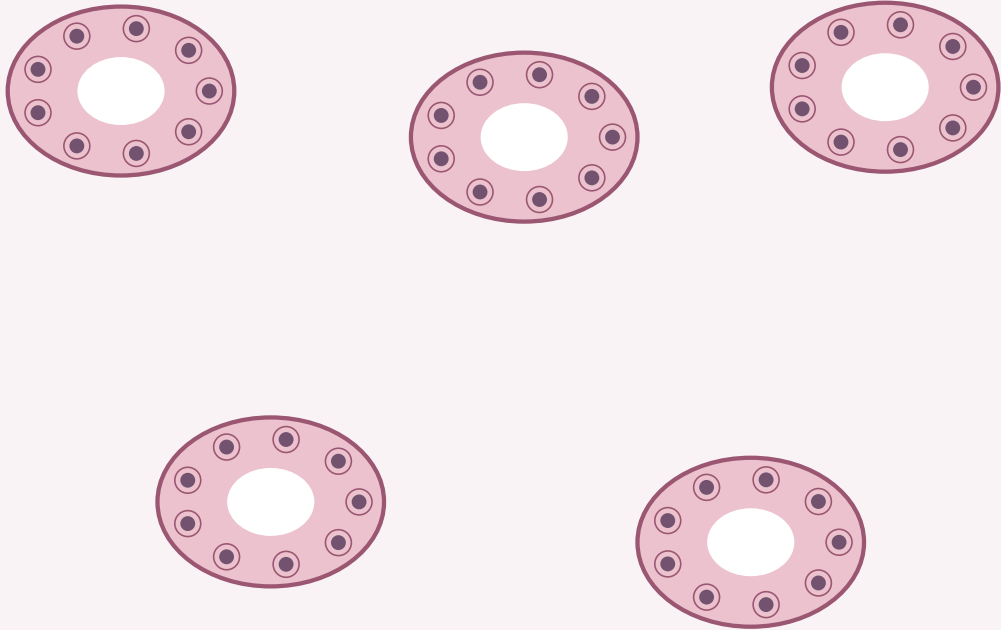


Schematic — not a histologic specimen

Morphologic interpretation

- Rounded nests or clusters of malignant cells reside in large pools of extracellular mucin.
- Grossly, the tumor may be soft, gelatinous or rubbery.

Tubular carcinoma: Highly gland-forming invasion



Schematic — not a histologic specimen

Morphologic interpretation

- Small well-formed infiltrating tubules are the central morphologic feature.
- Can resemble benign sclerosing lesions; Evidence of invasion is critical.

Cribriform and papillary invasive carcinomas

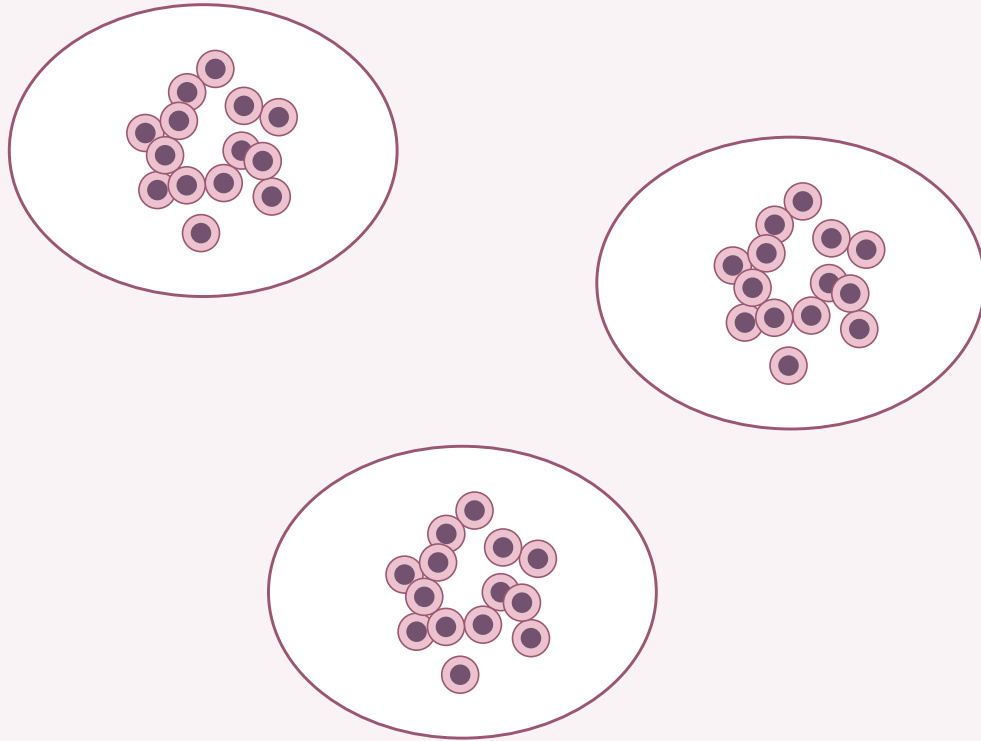
Cribriform carcinoma

- Invasive nests with sieve-like lumina
- Architecture is the defining feature
- Typically associated with the luminal group

Papillary carcinoma

- True fronds with fibrovascular cores
- Distinct from micropapillary spaces
- Requires careful invasive versus in situ assessment

Micropapillary carcinoma: No true fibrovascular cores



Schematic — not a histologic specimen

Morphologic interpretation

- Tumor cell clusters appear to float in lacunae or intercellular fluid spaces.
- The structures mimic papillae but lack genuine fibrovascular cores.

Apocrine carcinoma morphology

- Tumor cells have abundant eosinophilic, sometimes granular cytoplasm.
- Large nuclei and prominent nucleoli contribute to the cytologic appearance.
- HER2 overexpression is more common in this special morphologic pattern.

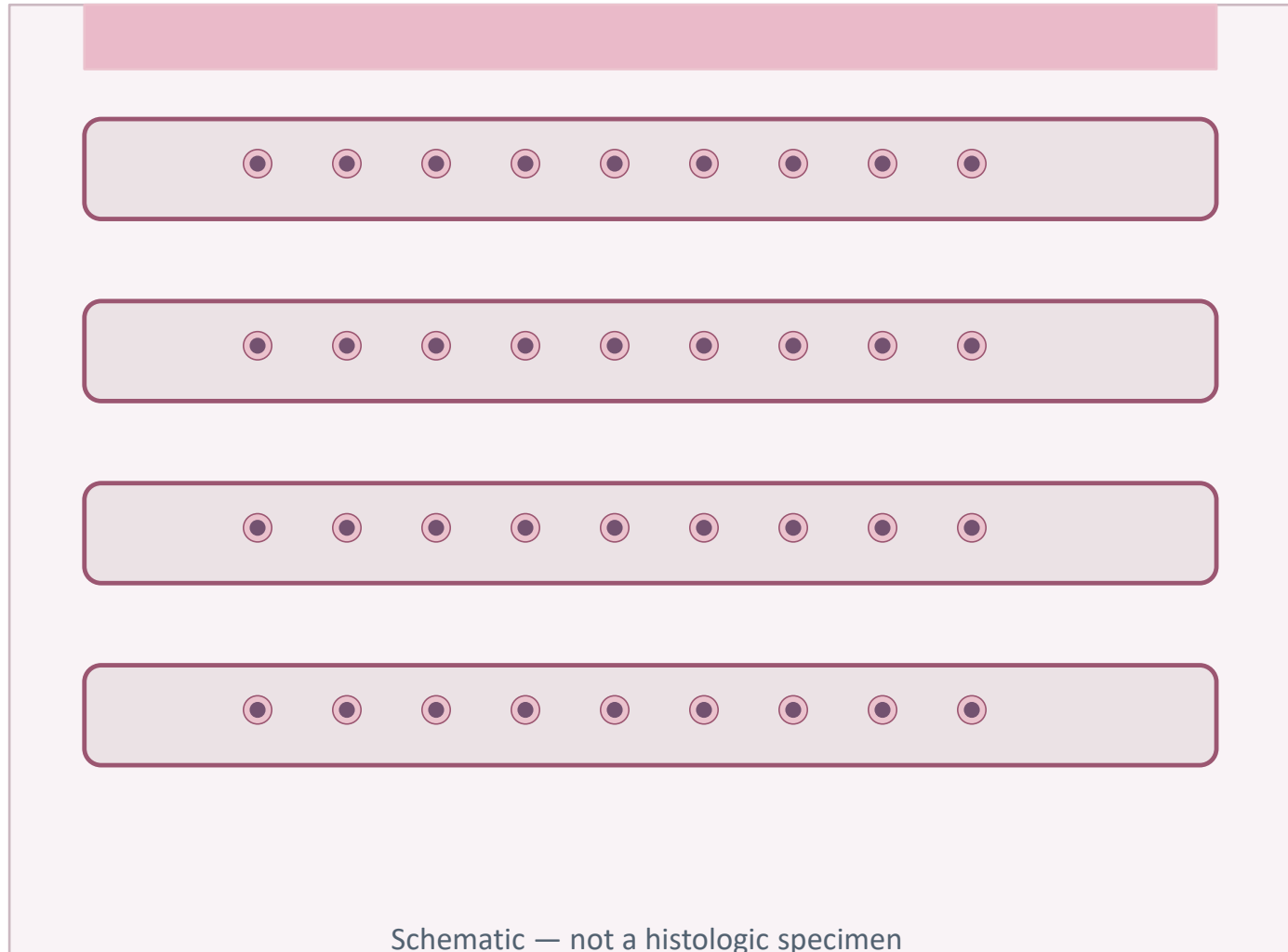
Metaplastic carcinoma is a broad TNBC-associated group

- Neoplastic cells may show squamous or mesenchymal differentiation.
- Spindle, chondroid or osseous components can complicate recognition as carcinoma.
- Many metaplastic tumors behave aggressively, although some low-grade forms are indolent.

Salivary gland-like breast carcinomas

- Adenoid cystic, secretory and mucoepidermoid carcinomas are uncommon examples.
- These tumors resemble counterparts occurring in salivary glands.
- Some triple-negative special types have favorable behavior despite absent routine receptors.

Inflammatory carcinoma: Clinical, not histologic subtype



Morphologic interpretation

- Extensive dermal lymphovascular tumor emboli impair skin lymphatic drainage.
- Rapidly developing erythema, swelling and peau d'orange result.

Inflammatory carcinoma: Diagnostic pitfall

- Erythema and swelling can mimic a breast infection.
- The designation refers to a clinical presentation rather than inflammatory histology.
- The associated carcinoma is commonly high-grade and diffusely infiltrative.

Occult primary carcinoma is possible

- Nodal or distant metastasis occasionally precedes detection of a breast lesion.
- Small primary cancers may be concealed by dense breast tissue or lack desmoplasia.
- Targeted ultrasound or MRI may identify a previously occult lesion.

Biology and extent jointly determine outcome

- Molecular or histologic phenotype modifies natural history.
- Tumor size, nodal status and metastatic spread capture anatomic extent.
- Histologic grade, biomarkers and lymphovascular invasion add information.

Prognostic versus predictive biomarkers

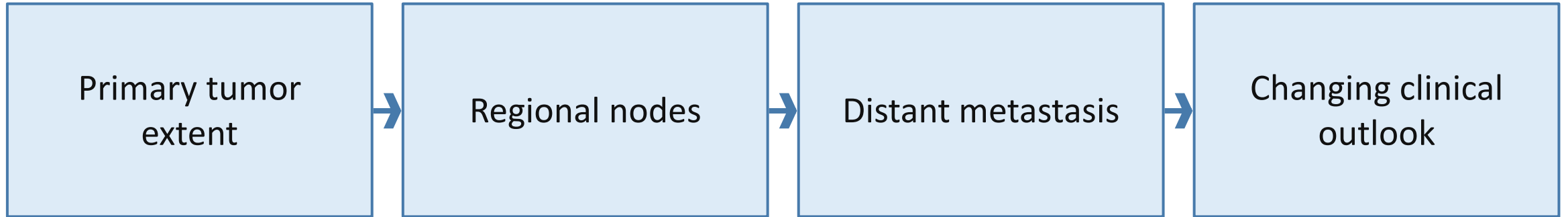
Prognostic

- Associated with likely disease outcome
- Example: Tumor size, nodal burden
- Can inform counseling and risk

Predictive

- Associated with benefit from a specific treatment
- Example: ER for endocrine therapy
- Can guide treatment selection

Anatomic progression and prognostic significance

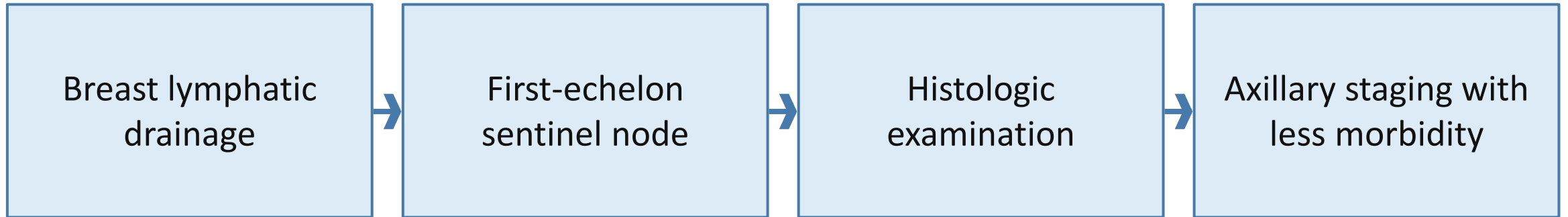


Distant metastasis is the strongest adverse prognostic element framework.

Regional lymph nodes: Powerful prognostic variable

- In the absence of distant spread, pathologic axillary nodal status is highly informative.
- Physical examination alone can miss small deposits or misclassify reactive nodes.
- Number and extent of involved nodes matter, not only presence or absence.

Why sentinel lymph node evaluation works

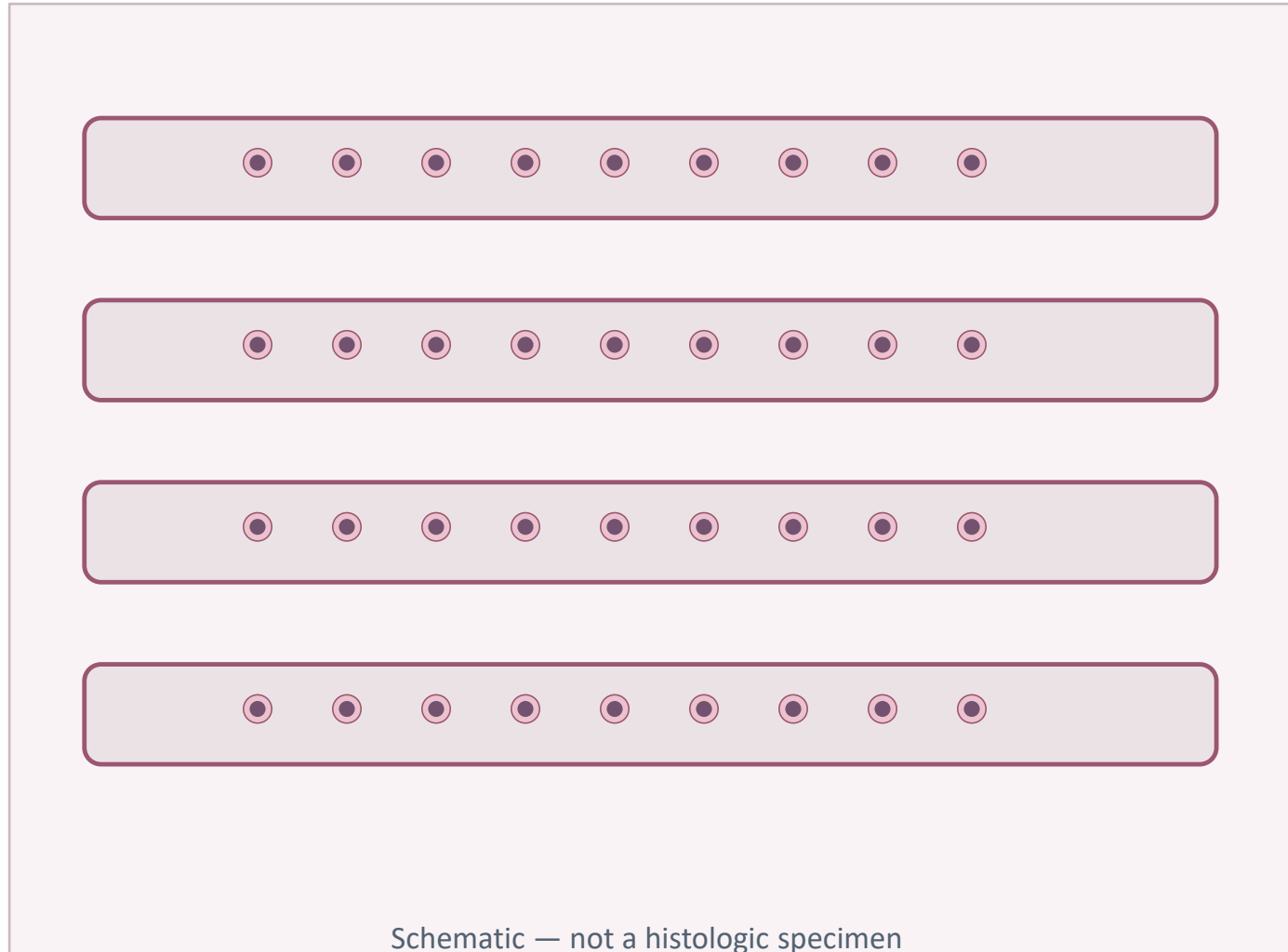


A negative sentinel node lowers the probability of additional regional nodal involvement.

Tumor size and locally advanced disease

- Increasing invasive tumor size carries progressively greater risk.
- Skin or chest-wall involvement represents advanced local extension.
- Larger cancers may be harder to control locally irrespective of molecular subtype.

Lymphovascular invasion: Tumor within a vessel



Morphologic interpretation

- True vascular-space invasion represents access to dissemination routes.
- It is associated with recurrence risk and poorer outcomes in relevant clinical settings.

Histologic type and grade modify prognosis

- Higher histologic grade is generally associated with worse outcome within stage groups.
- Tubular and cribriform subtypes are associated with favorable clinical behavior.
- Metaplastic carcinoma encompasses subtypes with substantially different prognoses.

ER and PR: Separate but related readouts

Estrogen receptor

- Nuclear ER expression predicts endocrine responsiveness
- Both prognostic and predictive
- Intensity and extent carry additional context

Progesterone receptor

- Often coexpressed in ER-positive tumors
- Low PR can associate with worse outcome
- Reflects aspects of hormone-response biology

HER2 is prognostic and predictive

- HER2 positivity is associated with biologically aggressive behavior without effective targeted treatment.
- HER2-directed therapies exploit receptor overexpression or amplification.
- Biomarker assessment must use validated methods and appropriate interpretation.

Genomic profiling in selected ER-positive cancers

- Proliferation-weighted multigene assays can further stratify prognosis.
- Their major clinical value is identifying selected endocrine-responsive cases unlikely to benefit from chemotherapy.
- A gene-expression assay does not replace histologic diagnosis and basic receptor assessment.

Neoadjuvant response has subtype-specific meaning

- Pretreatment systemic therapy permits direct assessment of tumor response.
- Pathologic complete response is an important prognostic correlate in TNBC and HER2-positive cancers.
- The relationship between pathologic response and prognosis is less uniform in luminal cancers.

Tumor-infiltrating lymphocytes

- TILs include lymphocytes and plasma cells in and around tumor-associated stroma.
- A brisk infiltrate can reflect an active host antitumor response.
- TIL prominence is linked to better neoadjuvant response and prognosis in TNBC and HER2-positive tumors.

ESR1 mutations and endocrine resistance

- ESR1 encodes the estrogen receptor.
- Acquired activating alterations can promote ligand-independent ER signaling.
- The chapter highlights testing in ER-positive/HER2-negative metastatic disease at endocrine progression.

Selected predictive molecular alterations

Alteration / biomarker	Pathologic context	Associated therapeutic strategy
BRCA1 or BRCA2 germline variant	Homologous recombination deficiency	PARP inhibitor sensitivity
PIK3CA mutation	ER-positive / HER2-negative cancer	PI3K pathway inhibition
NTRK fusion	Selected secretory carcinomas	NTRK-targeted inhibition
PD-L1 expression	Selected immunotherapy contexts	Checkpoint therapy selection

Staging: Anatomy versus prognostic integration

Anatomic TNM

- Primary tumor extent (T)
- Regional nodal burden (N)
- Distant metastasis (M)

AJCC 8th prognostic stage

- T, N and M
- Histologic grade
- ER, PR and HER2 (plus select assay data)

Treatment strategy follows biology and extent

- Local control usually involves surgery and, in selected settings, radiation.
- Systemic treatment addresses potential or documented distant disease.
- Subtype, stage and tumor responsiveness determine the role and timing of systemic therapies.

Application: Infiltrative glands in a hard mass

Core biopsy shows irregular malignant glands and nests infiltrating a fibrotic stroma. No defining special-type morphology is identified.

Invasive carcinoma of no special type.

Stromal invasion establishes carcinoma; Desmoplasia and disordered glands support the NST morphologic pattern.

Application: Subtle infiltrative single cells

A poorly defined breast lesion shows rows of isolated, dyscohesive carcinoma cells with loss of E-cadherin expression.

Invasive lobular carcinoma.

The single-file invasive pattern and cell-adhesion phenotype strongly favor lobular carcinoma.

Application: Rapidly swollen erythematous breast

The skin is diffusely thickened with peau d'orange. Tumor emboli are seen in dermal lymphovascular spaces.

Inflammatory breast carcinoma (clinical presentation).

Dermal lymphatic obstruction explains the skin findings; This is not a distinct underlying histologic tumor type.

Final synthesis: Integrate four reports

Morphology

- Is invasion present?
- What histologic type?
- What Nottingham grade?

Biology

- What are ER, PR and HER2 results?
- Are selected additional assays indicated?
- Does phenotype alter treatment?

Extent

- What is invasive tumor size?
- Are nodes involved?
- Is there distant spread?

Core take-home concepts

- Invasive carcinoma is defined by stromal invasion—not by a specific cytologic appearance.
- Clinical receptor groups and intrinsic expression subtypes are related but nonidentical.
- Histologic type, grade, biomarkers and stage provide complementary information.
- Accurate morphology and biologic interpretation require clinical–radiologic correlation.

Source and figure provenance

Primary textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 23, The Breast, pp. 954–966.

Source handling

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