The Academic
International Journal of Multidisciplinary Research

An Online Peer Reviewed / Refereed Journal
Volume 3 | Issue 8 | August 2025
ISSN: 2583-973X (Online)
Website: www.theacademic.in

Breast Carcinoma: A Histopathological Approach

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DOI : https://doi.org/10.5281/zenodo.17136403

ARTICLE DETAILS

Research Paper

Accepted: 23-08-2025

Published: 10-09-2025

Keywords:

Breast carcinoma, histopathology, Nottingham grading, immunohistochemistry, WHO classification, molecular subtyping, digital pathology

ABSTRACT

Breast carcinoma is the most frequently diagnosed malignancy in women and the leading cause of cancer-related mortality worldwide. Histopathology remains the cornerstone for diagnosis, prognosis, and therapeutic stratification, despite rapid advances in imaging and molecular diagnostics. Accurate evaluation begins with meticulous specimen handling and gross examination, followed by detailed microscopic assessment. The histopathological spectrum includes invasive carcinoma of no special type, invasive lobular carcinoma, and several distinct morphological subtypes such as tubular, mucinous, medullary, and metaplastic carcinoma. Grading using the Nottingham system remains the most widely accepted method for assessing differentiation and predicting outcomes. Equally significant are precursor lesions such as ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), which serve as markers for early intervention. Immunohistochemistry (IHC) is indispensable in modern breast pathology, enabling evaluation of hormone receptors (ER, PR), HER2 status, Ki-67 proliferative index, and lineage markers such as E-cadherin. Integration of histopathology with molecular subtyping stratifies tumors into luminal A, luminal B, HER2-enriched, and triple-negative groups, ensuring personalized therapy. This paper highlights the histopathological approach to breast carcinoma, emphasizing specimen handling, microscopic morphology, grading,

immunohistochemistry, and diagnostic challenges. Future directions include digital pathology, artificial intelligence, and molecular diagnostics, which promise to refine the accuracy and predictive power of histopathological assessment.

1. Introduction

Breast carcinoma is a heterogeneous group of malignant tumors arising from epithelial cells of the breast ducts or lobules. Globally, it accounts for approximately 24.5% of all cancers in women and is responsible for 15.5% of cancer-related deaths. The disease burden is increasing, particularly in low- and middle-income countries, due to urbanization, delayed childbearing, lifestyle changes, and limited screening programs.

Histopathology continues to play a pivotal role in the diagnosis of breast carcinoma. While imaging modalities such as mammography, ultrasonography, and MRI assist in detection, definitive diagnosis relies on histological confirmation obtained from core needle biopsy or surgical specimens. Histopathology not only provides a morphological diagnosis but also offers critical prognostic information, including tumor grade, lymphovascular invasion, and nodal status. Moreover, advances in immunohistochemistry and molecular profiling have made histopathology central to precision oncology.

This paper provides an in-depth discussion of the histopathological approach to breast carcinoma, emphasizing diagnostic workflow, morphological classification, immunohistochemical evaluation, and integration with molecular subtypes.

2. Specimen Handling and Gross Examination

Proper specimen handling is essential to preserve tissue architecture and molecular integrity. Pathologists frequently encounter the following specimen types:

- **Core needle biopsy:** Provides tissue cores for diagnosis and biomarker testing.
- **Excision biopsy:** Used for smaller lesions requiring complete removal.
- **Lumpectomy:** Wide local excision with margins, often performed in breast-conserving surgery.
- **Mastectomy:** Total removal of breast tissue, indicated in large or multifocal tumors.

- **Axillary lymph node specimens:** For nodal staging, obtained via sentinel lymph node biopsy (SLNB) or axillary dissection.

Gross Examination involves:

- Measuring **tumor size** (largest dimension is critical for staging).
- Assessing **tumor location** relative to nipple and margins.
- Checking for **necrosis, hemorrhage, or calcification.**
- **Inking of margins** in lumpectomy specimens to evaluate adequacy of excision.
- Sampling representative sections: tumor center, periphery, adjacent normal tissue, margins, and associated structures (skin, nipple, muscle).

Gross examination is the foundation upon which microscopic interpretation and accurate staging depend.

3. Histopathological Classification

Table 1. WHO Classification of Invasive Breast Carcinoma (2020)

Major Types	Features
Invasive carcinoma of no special type (NST)	Most common (70–80%); variable morphology, desmoplastic stroma
Invasive lobular carcinoma (ILC)	Small, uniform, discohesive cells in single-file pattern; loss of E-cadherin
Tubular carcinoma	Well-formed small tubules; favorable prognosis
Mucinous carcinoma	Tumor cells floating in mucin pools; indolent course
Medullary carcinoma (rare)	Syncytial growth, circumscribed border, prominent lymphoplasmacytic infiltrate
Micropapillary carcinoma	Aggressive, frequent lymphovascular invasion
Apocrine carcinoma	Cells with abundant eosinophilic cytoplasm and prominent nucleoli
Metaplastic carcinoma	Squamous/spindle differentiation; poor prognosis
Papillary carcinoma	Arborizing papillary structures, often with fibrovascular cores
Adenoid cystic carcinoma	Rare; cribriform architecture with dual cell population

4. Morphological Features of Major Subtypes

- **Invasive ductal carcinoma (NST):** Irregular nests, cords, or sheets of pleomorphic epithelial cells infiltrating fibrous stroma with frequent desmoplasia.
- **Invasive lobular carcinoma:** Small, uniform, discohesive cells arranged in linear ("single-file") patterns; classic "targetoid" periductal pattern; E-cadherin loss.
- **Tubular carcinoma:** Predominantly small, well-formed tubules with open lumina, lined by a single epithelial layer; excellent prognosis.
- **Mucinous carcinoma:** Abundant extracellular mucin pools containing clusters of floating tumor cells.
- **Medullary carcinoma:** Syncytial growth (>75%), pushing borders, dense lymphoplasmacytic infiltrate; relatively favorable prognosis despite high grade.
- **Metaplastic carcinoma:** Exhibits epithelial–mesenchymal transition; squamous, spindle, or heterologous elements; aggressive clinical behavior.

5. Grading of Invasive Carcinoma

The **Nottingham Histological Score (Elston–Ellis modification of Bloom–Richardson system)** is the standard for grading invasive carcinoma.

Table 2. Nottingham Grading System

Feature	Score 1	Score 2	Score 3
Tubule formation	>75% tumor forms tubules	10–75%	<10%
Nuclear pleomorphism	Small, regular nuclei	Moderate variability	Marked pleomorphism
Mitotic count	Low	Intermediate	High

Grade I (3–5): Well-differentiated

Grade II (6–7): Moderately differentiated

Grade III (8–9): Poorly differentiated

Grading correlates strongly with prognosis and therapeutic decisions.

6. In Situ Lesions: Precursors to Carcinoma

- **Ductal carcinoma in situ (DCIS):** Malignant epithelial proliferation confined within ducts; patterns include comedo, cribriform, micropapillary, papillary, and solid. Necrosis and calcifications are common.
- **Lobular carcinoma in situ (LCIS):** Dyscohesive, monotonous cells filling and expanding lobules; often bilateral and multifocal; E-cadherin negative.

Recognizing these precursor lesions is vital, as they represent opportunities for early detection and preventive management.

7. Immunohistochemistry (IHC) in Breast Carcinoma

IHC is integral to histopathological evaluation.

Table 3. Key IHC Markers in Breast Carcinoma

Marker	Role
ER & PR	Predict endocrine therapy response
HER2/neu	Identifies candidates for trastuzumab, pertuzumab
Ki-67	Proliferation index; prognostic marker
E-cadherin	Differentiates ductal vs lobular carcinoma
p63, calponin, SMA	Myoepithelial markers to distinguish invasive vs in situ lesions
CK5/6, EGFR	Basal markers; often positive in triple-negative breast cancers

8. Molecular Classification and Histopathology Integration

Gene expression studies divide breast cancers into four intrinsic molecular subtypes:

1. **Luminal A:** ER+, HER2-, low Ki-67; best prognosis.
2. **Luminal B:** ER+, HER2±, high Ki-67; intermediate prognosis.
3. **HER2-enriched:** HER2+, ER-/PR-; aggressive but responsive to anti-HER2 therapy.
4. **Triple-negative/basal-like:** ER-, PR-, HER2-; poor prognosis, limited targeted therapy.

Histopathology combined with IHC serves as a practical surrogate for molecular testing in routine practice.

9. Lymph Node Evaluation

Lymph node status remains a critical prognostic factor.

- **Sentinel lymph node biopsy (SLNB):** Preferred over full dissection to reduce morbidity.
- **Micrometastases (<2 mm) and isolated tumor cells:** Detected using H&E or IHC.
- Nodal staging is incorporated into **AJCC TNM classification** and influences adjuvant therapy.

10. Diagnostic Pitfalls in Histopathology

- Distinguishing invasive carcinoma from DCIS with desmoplastic reaction.
- Confusion between tubular carcinoma and sclerosing adenosis.
- Metaplastic carcinoma vs primary breast sarcoma.
- Misdiagnosis of lobular carcinoma due to subtle morphology.

Close correlation with IHC and clinical findings is often necessary.

11. Pathology Reporting Standards

International guidelines (e.g., CAP, RCP) recommend structured pathology reports covering:

- Tumor type and grade.
- Tumor size and extent.
- Lymphovascular invasion.
- Margin status.
- Nodal status.
- ER, PR, HER2, Ki-67 results.

Standardized reporting ensures consistency, reproducibility, and clinical utility.

12. Future Directions in Histopathological Approach

- **Digital pathology and AI:** Automated image analysis for grading and biomarker quantification.

- **Molecular diagnostics:** Next-generation sequencing (NGS) for identifying actionable mutations.
- **Liquid biopsy:** Detecting circulating tumor DNA for monitoring recurrence.
- **Radiopathology integration:** Correlating histology with imaging features for precision diagnosis.

13. Conclusion

Histopathology continues to be the gold standard in diagnosing and managing breast carcinoma. It provides essential insights into morphology, grading, staging, and biomarker expression. Immunohistochemistry has transformed the field, enabling integration of molecular biology into routine practice. Despite emerging technologies, the histopathological approach remains indispensable, offering a comprehensive evaluation that underpins personalized treatment. The future lies in harmonizing morphology with digital tools, molecular profiling, and artificial intelligence to enhance diagnostic precision and improve patient outcomes.

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