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Pathological Prognostic Factors and Classification of Breast Cancer

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Introduction

Breast cancer (BC) is a diverse collection of tumors that range greatly in terms of their molecular makeup, biological behavior, clinical presentation, and therapeutic response when it is categorized according to the disease's outward symptoms and indicators. Mid-18th century ideas for early surgical excision of the breast tumor before something reached the lymph node nodes resulted from the fact that cancer was a confined illness that developed in phases instead of a *de novo* systemic disease. Resulting in recommendations for doing an early surgical excision of the breast tumor before it had axillary lymph nodes were affected by the spread. Trastuzumab (Herceptin), the first specific anti-HER2 (human epidermal growth factor 2) medication, a drug used to treat metastatic BC, was approved [1]. Together with these adjustments, the pathologic diagnostic and prognostic categorization of BC significantly improved. It assessed hormone receptors, receptors for HER2, and extensive histomorphological data. With the discovery of intrinsic molecular subtypes and the creation of multigene signatures, the idea of molecular categorization of BC was established, marking a significant advancement in our understanding of BC. Despite the significance of well characterized morphological prognostic markers in BC, subsequent histological categorization is often determined by the kind and degree of differentiation at first diagnostic and verification of a basic breast tumor. staining slides with hematoxylin and eosin (HandE), taking gross observations into account and if required, enabling special staining, immunohistochemistry, and other molecular analyses the diagnosis of BC (Figure 1) is completed by the evaluation of prognostic indicators as well as other factors such tumor stage, vascular invasion, margin status, and the presence of concurrent and prior lesions [2]. Normal clinical care for breast cancer presently relies on the availability of trustworthy medical and pathological prognostic and predictive indicators to enable clinician and patient decision-making because there are an increasing number of potentially successful treatment options. Histological grade, which reflects the morphological evaluation of tumor biological features and has been shown to be able to produce significant information linked to the clinical behavior of BCs, is one of the best-established prognostic variables in BC. For instance, proof of lymph node metastases or vascular invasion establishes both the tumor's invasiveness and its prognostic relevance. Similar to this, the analysis of BCs molecular features, which is primarily done for prognosis purposes, may be useful for both diagnostic and prognostic purposes [3]. Modern medicine's advancement has resulted in the creation of cutting-edge therapeutic alternatives including hormonal, targeted, and chemotherapies. Treatment of triple negative BC and overcoming medication resistance are two ongoing therapeutic problems.

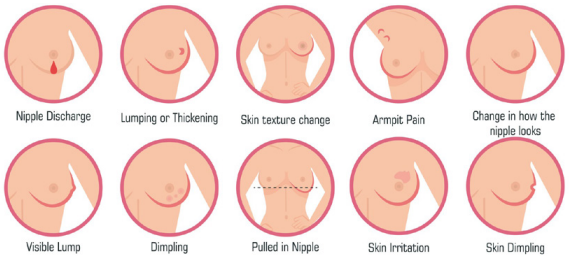

Figure 1: Examination of breast cancer [4].

Classification Based on Tumor Differentiation

The histomorphological categorization plays a crucial role in the diagnostic of BC and serves as the foundation for every other classification

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system, notwithstanding the clinical significance of BC staging (Table 1). This categorization method mainly depends on pathologists' findings and knowledge, who have little assistance from molecular testing. Differentiating essentially two ways situ and invasive disease, tumor type and grading, and separating original BCs from their imitators are just a few of the daily obstacles. The existence or disappearance of myoblasts at the epithelial-stromal interface, as well as the cytological and architectural characteristics of proliferating cells, malignant cells stroma, and other features, are used to make a histological diagnosis of BC [5]. In some circumstances, hand-stained slides, immunohistochemistry, and other molecular analyses are helpful. The Nottingham classification system is used to categories BCs based on mitotic count, nuclear pleomorphism, and the extent of tubule or gland development [6]. As with carcinoma of the invasive ductal of no specified type (IBC-NST), lobular, malignant tumors, and metaplastic carcinoma, most BCs exhibit a variety of histological characteristics while retaining certain characteristics of the tumor type. Tumor-specific traits, such as cytologic features, tumor growth pattern and shape, secretory activity, and mesenchymal features, help to identify the type of tumor that has developed [7]. Tumor-specific traits, such as cytologic features, cancer progression pattern and shape, stored in the posterior pituitary and stromal features, help to identify the type of tumor that has developed. To correctly diagnose and identify the main origin of the breast, the kind of tumor must be determined. Even while specific tumor forms are associated with particular clinical characteristics, each tumor type has a unique prognosis (Table 2) and prognostic value [8]. This is mostly because there are several histological kinds of BC and variations of the more prevalent types, including IBC-NST, lobular, and metaplastic carcinomas. Cancers that are HER2-positive and triple-negative are anticipated to have a poorer prognosis than tumors that are ER-positive at the same kind and stage. Despite the type of tumor, extremely small (5 mm) tumors frequently have a very good prognosis [9]. Certain tumor types, particularly lobular and processes to occur carcinomas, may react to therapy less favorably than IBC-NST. Tumor typing is a dynamic process; new entities are found, renamed, or combined with other tumor types. While some pathologist's categories some malignancies as "splits," distinct or independent organisms, others associate comparable characteristics with a more common and well-established tumor form and categories these cancers as "variants" of the original tumor type ("relapse"). On the reverse hand, clustering of these malignancies may be the consequence of the discovery that an uncommon tumor type shares epithelial characteristics with a more common malignant tumor and the lack of a distinct therapeutic advantage to specific identification. The identification of the basal-like/triple-negative genetic subtype led to the proposal of basal-like carcinoma as a separate tumor type. Further research revealed that certain basal-like tumors identified through genetic testing would not display the identical histological characteristics as these cancers and that they overlapped morphologically with a number of other rising IBC-NST tumors. It is common to think of ILC, which covers a variety of tumors with different histological features and clinical behaviour, as a single tumor type that is characterized by the collapse of the cell adhesion protein E-cadherin and the ensuing cell decohesion. The most common subtype and distinctive clinical feature is the classic variation, which frequently falls within Nottingham grade 2 [10]. The solid ILC variant has a unique growth pattern, demonstrates high levels of spindle cells, and occasionally behaves aggressively in the clinic. ILC variants that are alveolar or tubulo-lobular have a good prognosis, whereas those that are poorly differentiated have high-grade cytological traits and a poor prognosis [11]. Although pathologists and doctors sometimes combine these elements into a single tumor category, the term "metaplastic breast cancer" (MBC) refers to a broad group of tumors with distinct histological traits. Differentiation routes between MBC subtypes and adenocarcinomas are illustrated. The two most important pathways for differentiation in MBC are squamous and mesenchymal routes.

Table 1: Main classification systems of breast cancer.

Classifier	Variables
Presentation	• Detection (Screen-detected versus symptomatic). • Stage (Early stage, locally advanced, or metastatic). • Signs and symptoms (inflammatory BC, lump size, consistency, shape, and fixation, skin and nipple changes, axilla, laterality, and focality). • Menopausal status (premenopausal versus postmenopausal). • Others: gender, age, ethnic origin, family history.
Imaging	Mass shape, margin, depth, and site, breast composition, calcification, axillary findings, laterality.
Pathological	
Morphological classification (mainly diagnostic and prognostic)	
Tumor differentiation	
Tumor type	Several tumor types (currently at least 18 tumor types) are described and some types include multiple variants based on the combination of cytological, architecture features, and secretory activity and stromal features.
Tumor grade	Three grades based on the degree of differentiation and similarity to TDLUs.
Disease extent	
Tumor stage	Invasive tumor size, infiltration of other tissues, lymph node status, and assessment of lesions at distant sites.
Other factors	
	Lymphovascular invasion (present or absent), presence and extent of the *in situ* lesions (DCIS), stromal features such as TILs, Paget's disease, focality, bilaterality, and excision status.
Molecular classification (mainly predictive but can provide diagnostic and prognostic value)	
Single gene classifier	• Oestrogen receptor and HER2 are the most important classifiers to guide treatment decision with the addition of PDL1. • Other markers include progesterone receptor (PR), KI67 as prognostic markers. • Familial predisposition genes such as BRCA1, BRCA2, and PALB2.
Multiple gene classifier	Multigene prognostic signatures are composed of multiple genes assessed together to assess risk in certain BC groups mainly the luminal class.
Global gene expression and genomic classification	• Intrinsic molecular subtypes including, luminal, basal, and HER2 enriched. • Mutation signatures. • Integrated class classification based on a combination of transcriptomic and genomic (e.g., gene copy number) classification.
Therapy classification	• Systemic therapy naïve versus treated patients. • Neoadjuvant therapy treated versus adjuvant treated patients. • Type of therapy (hormone, cytotoxic, targeted, or immunotherapy). • Line of therapy (first-line therapy versus second- or third-line).

Table 2: Prognostic tumor type groups.

Prognostic groups	Types
Very indolent (excellent prognosis similar to locally infiltrative lesions with limited metastatic potential)	Pure low-grade adenosquamous carcinoma, pure fibromatosis like metaplastic carcinoma, pure low-grade mucoepidermoid, adenoid cystic and secretory carcinomas. Other special type tumors which include encapsulated and solid papillary carcinomas that lack myoepithelial cells but staged as *in situ* disease (pTis), and other lesions such as atypical adenomyoepithelioma and malignant adenomyoepithelioma *in situ*.
Excellent prognosis group (low metastatic potential. Mainly lymph node metastasis)	Pure tubular and invasive cribriform carcinoma of limited size (<3 cm).
Good prognosis group	Grade 1 invasive lobular, mucinous, invasive papillary and IBC-NST, and tubulolobular carcinoma.
Moderate prognosis group	Grade 2 IBC-NST, and invasive lobular carcinoma classical type.
Poor prognosis group	High grade IBC-NST, solid and other high-grade invasive lobular carcinoma, high-grade matrix producing and squamous cell metaplastic carcinomas.
Very poor prognosis group	High grade spindle cell metaplastic carcinoma, small cell carcinoma and high-grade triple-negative IBC-NST of large size.

Conclusion

BC is a diverse illness that may be categorized using a number of different approaches. They comprise morphological and molecular categories for therapeutic, imaging, and pathological conditions, each with various subclassification schemes [12-14]. The justification for other categorizations used to confirm the finding of malignancy, to characterize it as an invasive breast tumor, to provide information about tumor type and other crucial predictor variables is pathologic morphological diagnosis, and although both molecular and clinical classification methods are important in determining survival rate and predicting response to treatment decisions. The use of only one, cross, and global BC classifiers for gene expression, which provide varying degrees of prognostic information and serve as companion diagnosis for BC care, is becoming more and more popular. Although a tremendous amount of work has been put into creating and enhancing molecular diagnostic and prognostic testing for BC, it is continuously changing [15, 16]. A plethora of knowledge that might help identify novel treatment targets and enable more precise classification systems to estimate health outcomes and responses is continuously accumulating as the usage of sophisticated molecular methods rises.

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