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Current Trends in Clinical and Experimental Breast Cancer Pathology

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Breast cancer is not a single disease entity. It is a group of complex, heterogeneous malignant neoplasms occurring in the breast. This heterogeneity is reflected by diverse clinical outcomes and therapeutic responses, and has been further proven at the molecular level [1,2]. Over the past several decades, accumulating studies have led to the identification of many prognostic and predictive biomarkers, which have played essential roles in the current clinical management of patients with breast cancer. Meanwhile, there has been increasing demanding for therapy tailored to each individual patient–targeted therapy–so that the individual is not over- or undertreated. As a result, many studies now focus on both the traditional clinicopathologic factors and molecular prognostic/predictive biomarkers. These validated prognostic/predictive factors have been incorporated into the routine management of breast cancer.

Accurate evaluation of each breast cancer is the first step toward optimal management. Almost as important as the diagnosis of breast cancer itself, other features revealed by pathologic evaluation (histologic type, histologic grade, pathologic stage including tumor size and regional node status, lymph vascular invasion, and extent of associated in situ component) are essential prognostic elements which will ultimately determine the clinical outcome of the disease. Therefore, these features are now designated as "scientifically validated data elements" specified by the College of American Pathologists (CAP) protocols (Table 1), and mandated in surgical pathology cancer reports as a new standard for the American College of Surgeons Commission on Cancer (ACS-CoC). This mandate has drastically changed the way we report breast cancer, from a one paragraph diagnosis several decades ago to the several pages-long synoptic report of today which incorporates the breast cancer checklist recommended by the CAP in its cancer protocols [3]. This improvement in breast cancer reporting has become one of the key elements in optimizing patient care.

In addition to these histologic elements, testing for three traditional predictive biomarkers has been employed in our daily practice for nearly two decades; these include immunohistochemical staining for Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2/neu, and (in some cases) in situ hybridization for HER2/neu gene amplification. Due to their significant impact in selecting the appropriate targeted therapy, i.e. hormonal therapy if ER/PR is positive or HER2 targeted therapy if the HER2/neu protein is over expressed or its gene is amplified, the CAP has issued requirements for proper breast tissue processing and guidelines for the interpretation of these tests [4,5].

Due to specific hormonal or HER2 targeted therapy, breast cancer survival has been significantly improved. However, not all patients respond equally well to these treatments. As breast cancer often harbors complex genetic and epigenetic abnormalities involving multiple genes and genetic pathways, targeting a single gene or pathway may not be effective. Therefore, there is an increasing need to further stratify breast cancers into different molecular subgroups based on arrays of multiple genes. The advancement of genetic technology has enabled the identification of several molecular subtypes, which have helped to stratify patients into therapeutic responders and non-responders (e.g., luminal A and B subtypes are both hormone receptor positive, but only the luminal A type responds well to hormonal therapy only, and luminal B type requires additional chemotherapy). Molecular classification has also helped to identify new molecular targets for therapy, particularly in triple negative (ER/PR-, HER2-) breast cancers [6].

Technological advances have tremendously expanded our knowledge of breast cancer biology. Multi-gene prognostic and predictive biomarker tests have evolved to become part of breast cancer diagnosis and treatment (Table 2). Clinical trials (NCT00433589 and NCT00310180) for individualized therapy based on these tests are underway [7]. Tailored targeted therapy will be the near future for breast cancers.

In summary, the future of breast cancer pathology will be a combination of detailed and accurate histologic evaluation, plus sophisticated molecular biomarker testing, to ensure that patients are not over- or undertreated, but instead receive the most optimal targeted therapy for their disease.

Breast specimen (primary tumor)	**Axillary lymph nodes**
Organ site	Total number of lymph nodes identified
Procedure	Total number of positive lymph nodes
Histologic type	Largest dimension of the largest tumor deposit
Histologic grade	Presence of extranodal extension
Number of foci of invasive carcinoma	
Size of invasive carcinoma	
Lymphovascular invasion	
Margin status	
Presence and extent of ductal carcinoma in situ	
Skin, nipple, or skeletal muscle involvement, if available for assessment	
Total number of lymphnodes identified	
Total number of positive lymph nodes	
Largest dimension of the largest tumor deposit	
Presence of extranodal extension	

Table 1: Scientifically validated data elements for invasive breast cancer pathology report.

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	MammaPrint	PAM 50 (Breast bioclassifiers)	MapQuant Dx/simplified	Oncotype DX	Breast Cancer Index (HoxB13:IL17BR/MGI)
Analysis	Microarray	qRT-PCR	Microarray/qRT-PCR	qRT-PCR	qRT-PCR
Provider	Agendia (Amsterdam, Netherlands)	NanoString Technologies (Seattle, WA, USA)	Ipsogen (Marseille, France)	Genomic Health (Redwood City, CA, USA)	bioTheranostics (San Diego, CA, USA)
Assay	70-gene signature	50-gene signature	97-gene signature or 8-gene PCR	21-gene recurrence score	Two-gene HOXB13:IL17R/ 5-gene molecular grade index
Tissue type	Fresh or Frozen	FFPE	Fresh or Frozen or FFPE	FFPE	FFPE
Clinical indications	• 0- 3 node positive • < 5cm • All ages • ER+ or ER-	• Stage I-III • All ages • ER+ or ER-	• ER+ • Histologic grade 2	• ER+ • 0-3 node positive • Treated with tamoxifen • Post menopausal, treated with aromatase inhibitors (AI)	• ER+ • Node negative • All ages
Prognostic/ predictive value	• Prognostic for early distant recurrence within first 5 year after diagnosis • Predictive for chemoresponse in poor prognostic group	• Prognostic based on assigned intrinsic molecular subtypes • • Predictive for tamoxifen benefit in luminal cancers	• Prognostic in ER+ tumors • Predictive for chemoresponse in high GGI tumor	• Prognostic for distant recurrence in 10 years • Predictive for chemoresponse in high recurrence score group	• Prognostic in ER+ tumors • Predictive for tamoxifen response in low risk group

Table 2: Commercially available prognostic/predictive multigene tests for invasive breast cancers.

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