BREAST CANCER

Hormone Receptors

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Tumor Markers

- **Tumor markers are substances that can be found in abnormal amounts in the blood, urine and tissues of some patients with cancer .Markers are needed to predict cancer progression and the risk of late recurrence .A small number of single biomarkers, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), Ki67 have been used for several years to predict the prognosis of breast cancer and guide effectiveness of therapy.**
- **Hormone receptor status is a key parameter in the molecular classification of breast cancer .Molecular profiles indicate that breast cancer can be classified into five intrinsic subtypes on the basis of gene expression patterns : luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) overexpressing, basal like, and unclassified.**
- **Expression of estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) and proliferation marker Ki-67,alone can be used to differentiate between these subtypes in clinical settings.**

Classification of molecular subtypes and correlation with biomarker staining on immunohistochemistry

Molecular Subtype	ER		PR	HER 2
LuminalA	positive	and / or	positive	Negative
Luminal B	positive	and /or	positive or negative	Negative
Luminal B	positive	and or	positive or negative	positive
HER2	Negative		Negative	positive
Triple negative or basal-like	Negative		Negative	Negative

- **Through molecular analysis of breast cancers with gene expression profiling, both Perou and colleagues and Sorlie and colleagues showed that breast cancer could be subclassified into different subtypes. Broadly, these subtypes include luminal ER-positive (luminal A and luminal B), HER2 enriched, and basal-like (Table 1).**
- **Gene expression profiling can be costly, time-consuming, and, depending on the platform, may require a fresh tumor biopsy sample that has not been fixed in formalin.**
- **Accordingly, (ASCO), the National Comprehensive Cancer Network (NCCN), have issued guidelines and recommendations supporting the implementation of molecular analysis as useful for risk stratification and for treatment planning**
- **Luminal A and B tumors are ER+, whereas HER2 overexpressing is hormone receptor negative but HER2 overexpressing (ER−/PR −/HER2+). Both basal-like and unclassified tumors have atriple-negative phenotype (ER−/PR−/HER2−**

Estrogen receptor

- The sex steroid hormone estrogen is important in both men and women for a variety of physiologic processes. Estrogen affects growth, differentiation, and function of tissues of the reproductive system, including the mammary glands, uterus, vagina, and ovaries in females, and the testis, epididymis and prostate in males. The hormone estrogen is involved both in the development of the mammary gland, as well as the pathogenesis and progression of breast cancer in both pre- and post-menopausal women

****All of the effects of estrogens are mediated through their binding to nuclear proteins called estrogen receptors(ER), transcription factors that regulate expression of estrogen-responsive genes .In premenopausal women, the main source of estrogens is the ovaries, whereas in postmenopausal women, estrogen production takes place elsewhere such as in: adipose tissue, skin, and muscle

Although circulating estrogen concentrations are very low after menopause, peripheral tissues can generate concentrations that are sufficient to stimulate tumor growth. Approximately 80% of breast cancers diagnosed in postmenopausal women are estrogen receptor (ER) and/or progesterone receptor (PR) positive. In this population, the major source of estrogen is the peripheral synthesis of estrone (E1) and estradiol (E2) by the enzyme aromatase

- Moreover, ER is one of the most important prognostic biomarkers in breast cancer. ER belongs to a group of nuclear hormone receptors that act as transcription factors. There are 2 isoforms: ERa (the clinically measured isoform) and ERb. Patients whose tumors are ER-positive benefit from endocrine therapy targeting ER (such as tamoxifen and aromatase inhibitors), and treatment can reduce local and distant recurrence and mortality.
- However, ER-positive breast cancers do not respond as well to cytotoxic chemotherapy and are less likely to achieve a pathologic complete response (pCR) when compared with patients with ER-negative breast cancer who receive neoadjuvant chemotherapy.

Progesterone receptor

- **PR also manifests as 2 major isoforms (PR-A and PR-B) and plays a role in downstream ER signaling. It is likely that PR acts as a driver for the development of breast cancer that may be most impactful in postmenopausal women.**
- **. The ER is thought to regulate PR expression, and the presence of PR expression is considered indicative of a functional estrogen-ER axis. In most cases, PR expression correlates with ER expression, and from a practical standpoint, robust PR expression in the absence of ER may necessitate repeat testing.**
- **The presence of PR expression carries prognostic significance in early breast cancer with ER-positive and PR-positive cases having the best outcome. Additionally, PR expression correlates with tumor responsiveness to endocrine therapy even when PR expression is low**
- **(ie, _1% of tumor cell nuclei). However, in the setting of an ER-positive breast cancer, PR assessment may not add significant predictive information.**
- **That being said, breast cancers that are both ER-positive and PR-positive may derive greater benefit from endocrine therapy than ER-positive/PR-**

- **Currently, the evaluation of ER and PR receptor expression is standard practice and most often performed using immunohistochemistry. ER and PR immunoexpression manifests as nuclear staining, and heterogeneous ("physiologic") expression is typically observed in normal breast ductal epithelium. Up to 80% of breast cancers are ER-positive and 55% to 65% are positive for PR expression.**
- **ASCO and the College of American Pathologists (CAP) have provided recommendations regarding ER/PR measurement and reporting**
- **Most pathology laboratories use immunohistochemical methods to determine ER and PR status. Testing is often performed on biopsy material before surgery, as there is excellent agreement in hormone receptor expression between biopsy and resection specimens. This enables clinicians, oncologists, surgeons, and patients to possess vital prognostic and therapeutic information before establishing a treatment plan.**

Androgen receptor

- **Another hormone receptor currently being studied in breast cancer research is the androgen receptor (AR). Like ER and PR, immunohistochemical AR expression is nuclear and usually strong and diffuse when present (ie, present in >80% of tumor cell nuclei). Expression is seen in most ER-positive breast cancers, as well as subsets of triple-negative breast cancer (TNBC) and HER2-positive carcinomas.**
- **In the spectrum of TNBCs, tumors with robust AR expression often manifest as apocrine carcinoma ("carcinoma with apocrine differentiation"), a ductal tumor in which the invasive cells exhibit extensive apocrine cell change (>90% of tumor cells exhibiting apocrine features). Most pathologists view AR immunoexpression in 1% of tumor cell nuclei as AR-positive.**
- **Molecular studies using RNA expression profiling have revealed several potentially clinically relevant breast cancer subtypes. One of these is known as the molecular apocrine group, defined as tumors that are ER-negative but AR-positive. These tumors often exhibit an expression profile that overlaps with luminal, basal-like, and occasionally HER2-positive groups.**

Human epidermal growth factor receptor2

- **HER2 (erbB-2) is a transmembrane tyrosine kinase receptor that regulates cell growth, proliferation, and survival through several different signaling pathways, HER2 gene amplification is observed in 15% to 30% of breast cancers and is a strong prognostic biomarker for an aggressive clinical course.**
- **Immunohistochemistry for HER2 protein overexpression has been developed, and testing for this protein is standard for invasive breast carcinomas whether primary or metastatic**
- **Overexpression of the HER2 protein typically occurs secondary to HER2/neu gene amplification**
- **Patients with HER2-positive tumors have a poor prognosis,**
- **they have sensitivity to certain cytotoxic agents such as doxorubicin, resistance**
- **to hormonal agents and a susceptibility to metastasize to brain and other organs**

Ki67 (cellular marker for proliferation)

- **Ki-67 is a nuclear proliferation marker expressed in all phases of the cell cycle except G0**
- **In general, breast cancers expressing high levels of Ki67 correlate with worse outcomes**

Ki67 was considered as a prognostic factor; in literature review high index labeled Ki67 is considered an unfavorable factor that influences tumor progression and is associated with poorer prognosis.

- **In 2009, the St Gallen Consensus stratified tumors according to the Ki67 value**
- **as low (less than 15%),**
- **intermediate (16%–30%),**
- **and highly proliferative (greater than 30%),**
- **to help identify patients who could potentially benefit from treatment with chemotherapy or endocrine therapy.**
- **. The implementation of Ki67 has been complex, as some studies have used 10%, 14%, or 20% cutpoints for treatment recommendations.**

Four Major Subtypes of Breast Cancer Used Clinically (Trop *et al.*, 2014)

Subtype	Standard Immunochemical Results and Cancer Grade	Overall 5-year Survival Rate (%)*	Frequency (%)	Comments
Luminal A	ER+ PR+ HER2–, usually low grade	90	50–55	Best prognosis, low Ki-67 levels
Luminal B	ER+ PR+ HER2–, usually intermediate to high grade	40	15	Generally more proliferative (high Ki-67 levels) with less marked hormonal receptor expression than luminal A tumors, approximately 30% are HER2-positive
HER2-enriched	ER– PR– HER2+, usually mid to high grade	31	15	Prognosis much improved since trastuzumab, 30%–40% of tumors also express ERs and PRs
Basal-like	ER– PR– HER2–, high grade	0	10–20	Often synonymous with triple negative

Note.—ER+ = tumor expresses ERs, ER– = tumor does not express ERs, PR+ = tumor expresses PRs, PR– = tumor does not express PRs, HER2+ = tumor overexpresses HER2/neu, HER2– = tumor does not overexpress HER2/neu.

- **Accordingly, Cheang and colleagues defined a Ki67 cutoff to distinguish luminal A and B subtypes using immunohistochemistry.**

This work

- **defined the luminal A subtype as ER-positive and/or PR-positive, HER2-negative,**
- **and Ki67 low (ie, a Ki67 index of <14%), and the luminal B subtype as ER-positive**
- **and/or PR-positive, HER2-negative, and Ki67 high (ie, a Ki67 index of _14%) and**
- **showed that stratification using the immunohistochemical panel of 4 biomarkers**
- **(ie, ER, PR, HER2, and Ki67) was statistically significant**

- **Most pathology laboratories use immunohistochemical methods to determine ER and PR status. Testing is often performed on biopsy material before surgery, as there is excellent agreement in hormone receptor expression between biopsy and resection specimens.**
- **This enables clinicians, oncologists, surgeons, and patients to possess vital prognostic and therapeutic information before establishing a treatment plan. However, there is institutional variability in the manner by which ER and PR immunoexpression is evaluated.**
- **At some centers, pathologists use digital image analysis (DIA) in which slides are scanned and converted into high-resolution computer images so that quantitative immunohistochemistry can be performed.**
- **DIA is being used with greater frequency owing to established intraobserver and interobserver variability in scoring results by pathologists.**
- **Finally, repeat testing of ER and PR on excision specimens in cases in which prior core biopsy showed weak or equivocal expression is also undertaken at some institutions.**