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Mini Review

ER negative PR positive breast cancer: Revisiting a rare and controversial molecular subtype

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Abstract

Estrogen receptor-negative/progesterone receptor-positive (ER-/PR+) breast carcinoma is a rare and controversial subtype that challenges conventional understanding of hormone receptor biology in breast cancer. Traditionally, the expression of progesterone receptors is considered a downstream effect of estrogen receptor activity, making the presence of PR in the absence of ER biologically puzzling. This discordant profile accounts for a small percentage of breast cancers and has raised questions regarding its reproducibility, prognostic significance, and therapeutic implications. Several studies have questioned the validity of the ER-/PR+ phenotype suggesting it may result from technical artifacts in immunohistochemical testing or heterogeneous tumor sampling. Nonetheless, when consistently identified, ER-/PR+ tumors have been observed to exhibit more aggressive clinicopathologic features than ER+ cancers, such as higher grade and increased proliferation rates. Despite this, they tend to have a better prognosis and overall survival compared to ER-/PR- tumors, suggesting some degree of hormone sensitivity.

Therapeutic management of ER-/PR+ tumors remains a subject of debate. While some clinicians consider them hormone receptor-positive and advocate for endocrine therapy, others are cautious due to the absence of ER expression, which is traditionally viewed as the primary target of such treatments. As a result, treatment strategies often vary, underscoring the need for further research and standardized guidelines.

In conclusion, ER-/PR+ breast carcinoma represents a biologically intriguing and clinically challenging subtype. Clarifying its molecular mechanisms, improving diagnostic accuracy and establishing evidence-based treatment approaches are essential for optimizing outcomes in this uncommon subtype of breast carcinoma.

Keywords: Invasive breast carcinoma, Molecular subtype, ER-/PR+ subtype

Introduction

Breast cancer is the most common cancer in females and as per GLOBOCAN 2022, worldwide the age-standardized rate incidence of this cancer is 46.8 and mortality of 12.7 per 100,000 [1]. Molecular markers play a critical role in its classification, prognosis, and treatment. Among these markers, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2 neu) are essential for guiding therapeutic decisions and predicting disease outcomes. These biomarkers help classify breast cancer into different subtypes, each with distinct biological behavior and treatment strategies. Immunohistochemical (IHC) analysis of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2 neu) expression along with Ki-67 proliferation index is widely used to categorize breast cancer into distinct subtypes [2,3]. These subtypes include Luminal A, Luminal B, HER2-enriched, and

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Triple-Negative Breast Cancer (TNBC) which exhibit different biological behaviors and therapeutic responses [4,5]. ER and PR are steroid hormone receptors that regulate breast cancer growth by responding to estrogen and progesterone signaling. Cancers that express these receptors (ER-positive and/or PR-positive) are typically more responsive to hormone-based therapies, such as tamoxifen and aromatase inhibitors, which block or reduce estrogen stimulation. In contrast, HER2 neu is a transmembrane tyrosine kinase receptor involved in cell growth and proliferation. HER2-positive breast cancers tend to be more aggressive but respond well to targeted therapies like trastuzumab (Herceptin) and pertuzumab. Thus, understanding the role of these molecular markers is essential for optimizing breast cancer management and improving patient survival.

Immunohistochemical expression of ER, PR, HER2 neu, and Ki67 provides breast carcinoma subtypes which include ER+/PR+ or ER+/PR- or ER-/PR-. However, another subtype ER-/PR+ is a controversial subtype which is not well recognized and poorly understood entity. Dou *et al.* conducted a systematic analysis of the clinicopathological features of the ER-/PR+ breast cancer phenotype and its response to chemotherapy in affected patients. They concluded that patients with the ER-/PR+ phenotype tend to exhibit more aggressive tumor biology and may derive considerable benefit from chemotherapy. Greater focus should be placed on this subgroup to enable more personalized treatment strategies which could improve breast cancer management and potentially reveal new therapeutic targets and clinical approaches [6]. As such, accurate identification and reporting of this phenotype are essential for understanding its clinical behavior, guiding treatment strategies, and informing future research into its underlying biology and prevalence across diverse populations.

Incidence

The reported prevalence of the ER-/PR+ breast cancer subtype varies among different cohorts. It is a rare subtype with incidence varying from 1–4%. In the study conducted by Delvallée J *et al.* involving 2,071 patients with invasive carcinoma, 1.2% were found to be ER-negative and PR-positive [7]. Beltjens F *et al.* observed ER-/PR+ breast cancer subtype constituting 0.3% of all breast cancers diagnosed in their institution between 2000 and 2014 [8]. Another study observed a rate of 2.3% in a case series of 5,374 consecutive breast cancers associated with higher histological grade and younger age group [9]. In contrast, Fan *et al.* observed that patients with ER-/PR+ tumors were more frequently aged 55 years or older (31.2% vs. 24.9%) and more likely to be postmenopausal (51.5% vs. 41.1%) than those with ER-positive disease [10].

Controversy About ER-/PR+ Molecular Subtype

The ER-negative/progesterone receptor-positive (ER-/PR+) breast cancer subtype remains a contentious entity in the field of oncology. Critics have suggested that technical artifacts such as pre-analytical variables or limitations in immunohistochemistry sensitivity may account for a proportion of these cases. However, accumulating evidence suggests that a subset of ER-/PR+ tumors may represent a true molecular phenotype possibly driven by alternative signaling pathways. Foley *et al.* conducted reappraisal of previously diagnosed cases of ER-/PR+ breast cancer phenotype and observed that on repeat immunohistochemistry none of the cases were confirmed as ER-/PR+ [11]. They concluded that this subtype may be attributed to technical artifact. Similar findings have also been observed by other studies who question whether the ER-/PR+ profile reflects a genuine molecular subtype necessitating individualized management or is simply an artifact of immunohistochemical assessment [12,13]. The American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) recommend that cases showing ER-/PR+ expression on immunohistochemistry should undergo repeat staining to rule out potential technical artifacts or errors in interpretation [14].

On the other hand, some studies have suggested that ER-/PR+ subtype may represent a distinct and biologically meaningful category within breast cancer classification [6,10]. Chandra *et al.* reported two cases of this subtype with both cases showing neuroendocrinal differentiation and high proliferative index [15]. Beltjens *et al.* suggest that ER-/PR+ breast cancers, though exceedingly rare, constitute a genuine tumor subtype. Accurate diagnosis is essential as these tumors exhibit distinct biological characteristics that may influence their therapeutic responsiveness and clinical trajectory [8]. Notably, the potential role of SUZ12 in the pathogenesis of these tumors represents a compelling avenue for future research with the possibility of informing the development of novel therapeutic strategies over time. Dembinski *et al.* suggested that hormone blocking in ER+/PR- tumor patients may be associated with increased survival and this benefit may last for years after completion of the course [16]. Similar therapy may be explored for ER-/PR+ breast cancer patients. Yu *et al.* suggested ER-low positive subtype for tumors with ER 1%–10% expression that accounts for 3% to 9% of all patients and is likely to have unique molecular features. These tumors are believed to have possibly less effective response to endocrine therapy compared to tumors with high ER expression [17].

Survival and Prognosis

ER-/PR+ breast cancers are said to be associated with more unfavorable clinical outcomes and exhibit more aggressive biological behavior compared to ER+ tumors. Specifically, ER-/PR+ cases were more likely to present with advanced stage, higher tumor grade, increased CK5/6 positivity, elevated HER2 expression and higher levels of Ki67 proliferation index [10,15]. It has also been observed that patients with ER-/PR+ tumors face a greater risk of mortality, locoregional recurrence (LRR), and distant recurrence (DR), even following endocrine therapy [10]. It has also been suggested that hat ER-/PR+ breast cancers may have more aggressive features than ER+ cancers but they are associated with better overall survival compared to ER-/PR- tumors [7]. Gamrani *et al.* observed that ER-/PR+ group statistically correlated with high risk of recurrence and death between the double-negative and double-positive hormone receptor along with low disease free survival in ER-/PR+/HER2- patients [18]. However, studies with follow ups are further required for definite knowledge about survival and prognosis of this subtype.

Further Suggestions

Further molecular and genomic characterization is warranted to clarify the nature of this receptor profile, determine its clinical relevance, and establish standardized diagnostic criteria to distinguish true ER-/PR+ tumors from false positives arising from technical variability. Further investigation using larger patient cohorts is necessary to more comprehensively define their molecular and clinical profiles.

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