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Review

Definition of High-Risk Early Hormone-Positive HER2−Negative Breast Cancer: A Consensus Review

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Simple Summary: Breast cancer is one of the major causes of cancer-related morbidity and mortality in women worldwide. Despite recent improvements in adjuvant treatment of hormone receptor-positive/HER2−negative breast cancer, estimating the risk of relapse of breast cancer on an individual basis is still challenging. The IRIDE (high risk definition in breast cancer) working group was established with the aim of reviewing evidence from the literature to synthesize the current relevant features that predict hormone-positive/HER2−negative early breast cancer relapse. This work may guide clinicians in the practical management of hormone-positive/HER2−negative early breast cancers.

Abstract: Breast cancer is one of the major causes of cancer-related morbidity and mortality in women worldwide. During the past three decades, several improvements in the adjuvant treatment of hormone receptor-positive/HER2−negative breast cancer have been achieved with the introduction of optimized adjuvant chemotherapy and endocrine treatment. However, estimating the risk of relapse of breast cancer on an individual basis is still challenging. The IRIDE (hIGh Risk DEfinition in breast cancer) working group was established with the aim of reviewing evidence from the literature to synthesize the current relevant features that predict hormone-positive/HER2−negative early breast cancer relapse. A panel of experts in breast cancer was involved in identifying clinical, pathological, morphological, and genetic factors. A RAND consensus method was used to define the relevance of each risk factor. Among the 21 features included, 12 were considered relevant risk factors for relapse. For each of these, we provided a consensus statement and relevant comments on the supporting scientific evidence. This work may guide clinicians in the practical management of hormone-positive/HER2−negative early breast cancers.

Keywords: breast cancer; hormone receptors; adjuvant; endocrine therapy; chemotherapy; risk of relapse; genomic signature; ctDNA; TNM; consensus

1. Introduction

Breast cancer (BC) is one of the major causes of cancer-related morbidity and mortality in women worldwide [1].

BC is generally subdivided into four distinct subtypes according to the expression of hormone receptors (HR; estrogen receptor (ER) and progesterone receptor (PgR)) and human epidermal growth factor receptor-2 (HER2): HR+/HER2−, HR+/HER2+, HR/HER2+ and triple-negative BC. HR+/HER2− BC represents the most common subtype, accounting for around 70% of all BC cases. Moreover, the majority (more than 90%) of HR+/HER2− BC primary diagnoses occur in non-metastatic stages (stages I–III) [2].

During the past three decades, several improvements in the adjuvant treatment of HR+/HER2− BC have been achieved with the introduction of optimized chemotherapy regimens (e.g., sequential anthracycline and taxane-based chemotherapy and dose-dense regimens) and optimized adjuvant endocrine treatment (e.g., aromatase inhibitors, extended endocrine therapy, and, more recently, ovarian suppression for the treatment of premenopausal patients) [3–6]. Moreover, novel targeted agents, such as cyclin-dependent kinase 4 and 6 (CDK4 and 6) inhibitors or poly(ADP-ribose) polymerase (PARP) inhibitors for germline *BRCA*-mutated patients, might become available in the near future for patients at high risk of recurrence despite the standard adjuvant treatment [7,8].

In this context, adequately estimating the risk of BC relapse on an individual basis is essential. On one hand, unmet needs and the potential for the implementation of new treatments exist for those at higher risk of recurrence, whereas on the other hand, there is a significant risk of overtreatment for patients at a lower risk of relapse.

A multitude of putative prognostic factors associated with risk of relapse (distant and loco-regional) have been described in HR+/HER2− BC; however, the level of evidence and the relevance of each of these factors varies significantly. In addition to the canonical well-consolidated prognostic factors, such as nodal involvement and tumor size, for several novel molecular prognostic factors, such as gene-expression signatures, consistent data