

Original article

The androgen receptor as a surrogate marker for molecular apocrine breast cancer subtyping



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ABSTRACT

The Androgen Receptor (AR) is a potential prognostic marker and therapeutic target in breast cancer. We evaluated AR protein expression in high-risk breast cancer treated in the adjuvant setting. Tumors were subtyped into luminal (ER+/PgR±/AR±), molecular apocrine (MAC, [ER-/PgR-/AR+]) and hormone receptor negative carcinomas (HR-negative, [ER-/PgR-/AR-]). Subtyping was evaluated with respect to prognosis and to taxane therapy. High histologic grade ($p < 0.001$) and increased proliferation ($p = 0.001$) more often appeared in MAC and HR-negative than in luminal tumors. Patients with MAC had outcome comparable to the luminal group, while patients with HR-negative disease had increased risk for relapse and death. MAC outcome was favorable upon taxane-containing treatment; this remained significant upon multivariate analysis for overall survival (HR 0.31, 95%CI 0.13–0.74, interaction $p = 0.035$) and as a trend for time to relapse ($p = 0.15$). In conclusion, AR-related subtyping of breast cancer may be prognostic and serve for selecting optimal treatment combinations.

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Introduction

Even though androgens have successfully been applied in advanced breast cancer therapy [1], the role of AR in breast carcinogenesis is not as thoroughly investigated as is the Estrogen Receptor α (ER). However, emerging experimental and clinical data have reinstated AR as a potential target for the treatment of breast cancer, especially triple negative (TNBC) and advanced disease [2]. Currently, AR-targeting agents are tested at the clinical level with

promising results in the group of patients with hormone receptor negative, AR-positive disease [3].

AR is the prevalent sex steroid hormone receptor in primary breast cancer, expressed in up to 90% of ER-positive [4] and up to 55% of ER-negative tumors [5]. Following the originally identified intrinsic subtypes [6], AR-related gene expression profiles were identified for further classifying ER-negative tumors as molecular apocrine carcinomas (MAC) [7], AR-regulated class A [8], luminal androgen receptor (LAR) [9], and steroid hormone responsive (SR+) tumors [10]. Two of these phenotypes were also characterized by apocrine morphology [7,8], while most were of unfavorable prognosis [7,9,10].

Long before this relatively recent gene expression profiling classification, apocrine carcinomas of the breast have been

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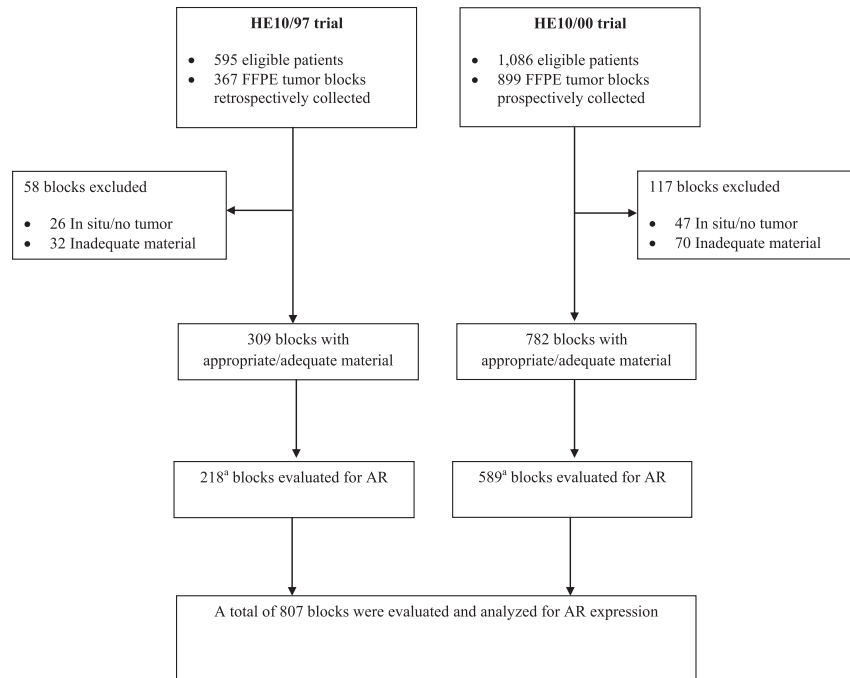


Fig. 1. REMARK flow chart. ^a: The smaller number of cases available for analysis in the present study is due to multiple processing of TMA blocks.

distinguished for their histologic features [11] while they are generally considered ER/PgR-negative, mostly AR-positive and frequently expressing HER2 with immunohistochemistry (IHC) [12–14]. A favorable impact of this phenotype on patient outcome has been shown upon the application of strict morphologic criteria [15]; however, features of apocrine differentiation are also observed in breast carcinomas other than apocrine [16]. Driven by the gene expression-based MAC classification, AR protein expression was used for breast carcinoma subtyping among histologically apocrine [12,13], HER2-positive [17–19] and ER-negative tumors [4,20]. However, the clinical behavior of these AR IHC-based subtypes is still uncertain.

In the present study, we investigated the expression of AR protein profiled with classic breast cancer markers (ER, PgR, HER2) in tumors from high-risk breast cancer patients from the HE 10/97 [21] and HE 10/00 [22] randomized phase III trials conducted by the Hellenic Cooperative Oncology Group (HeCOG). AR-related subtyping was evaluated with respect to prognosis, since all patients had received adjuvant chemotherapy, as well as with respect to responsiveness to taxanes-based treatment in the pre-trastuzumab era. The latter is of particular importance because it favors the evaluation of interactions between the markers studied and conventional chemotherapy in HER2 positive tumors without confounding effects from specific HER2 targeting.

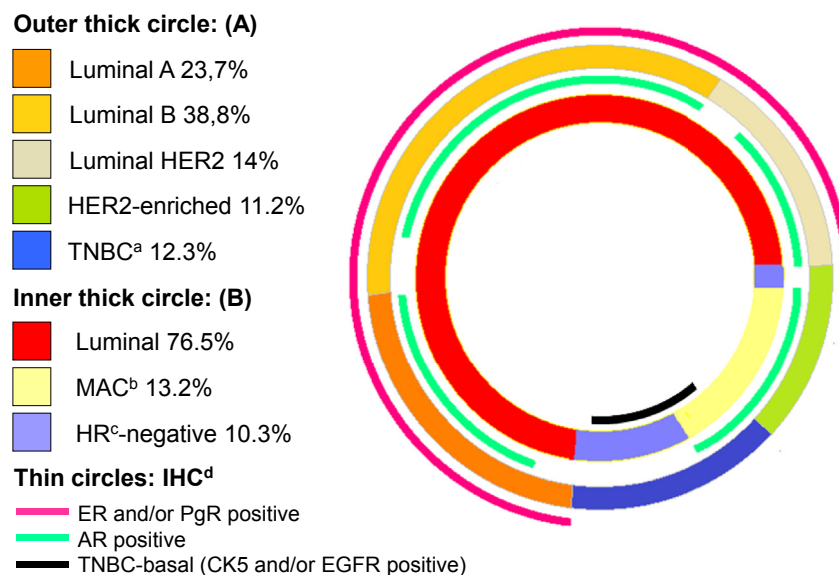


Fig. 2. Schematic representation of the relationship between breast cancer subtyping methods. A: Breast Cancer subtypes in Fountzilas et al. [25]. B: Subtypes in the present study. A considerable overlap is noted between the HER2-enriched and MAC subtypes. The latter also includes a proportion of TNBC. ^a: Triple Negative Breast Cancer, ^b: Molecular Apocrine Carcinoma, ^c: Hormone Receptor, ^d: Immunohistochemistry.

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