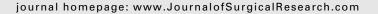


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Menopausal status does not predict Oncotype DX recurrence score



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ABSTRACT

Background: Adjuvant treatment for early stage, estrogen receptor (ER) positive invasive breast cancer has been based on prognosticators such as menopausal status. The recurrence score (RS) from the 21-gene assay Oncotype DX (ODX) is predictive of a 10-y distant recurrence in this population but is rarely applied to premenopausal patients. The relationship between menopausal status and RS was evaluated.

Materials and methods: An institutional review board-approved retrospective review was conducted of invasive breast cancer patients with known RS. ODX eligibility was based on National Comprehensive Cancer Network guidelines or physician discretion. Perimenopausal women were classified as premenopausal for statistical analyses. Comparisons of menopausal status and RS were made using general linear regression model and the exact Wilcoxon rank-sum test.

Results: Menopausal status was available for 575 patients (142 premenopausal, 433 postmenopausal). Median age was 46 y for premenopausal and 62 y for postmenopausal. Median invasive tumor size was 1.5 cm for both cohorts. Mastectomy rate was higher in the premenopausal group (54.8%) than postmenopausal (42%; P=0.0001). Premenopausal women had a higher local-regional recurrence rate (2.8% versus 0%; P=0.0384) but distant recurrence and overall survival were not statistically different (P=0.6808). Median ER H-score was lower in premenopausal (H-score = 270) than postmenopausal women (H-score = 280; P<0.0001). Median RS was 16 for both premenopausal (range, 0–54) and postmenopausal (range, 0–63) women. Menopausal status as a categorical variable was not predictive of RS (P-value = 0.6780).

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Conclusions: Menopausal status has limited predictive power for distant recurrence. Therefore, menopausal status alone should not preclude performance of ODX in ER-positive, early stage breast cancer.

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1. Introduction

As the most common cancer in adult women, surpassed only by skin cancer, breast cancer affects approximately 1 million women worldwide on an annual basis [1]. With an estimated 40,000 deaths in 2014 in the United States alone [2], breast cancer is far from being eradicated. Known for its heterogeneous nature, this disease requires a tailored plan of treatment to provide optimal therapeutic care. Many factors are taken into consideration when determining prognosis. Tumor size, hormone receptor status, lymph node status, and overexpression of HER2/NEU are used as indicators to predict local-regional and distant recurrence probabilities [3,4]. Thus treatment of cancer continues to rely primarily on histopathologic and immunohistochemical characteristics of the primary tumor [4]. This limited insight may result in overtreatment of many breast cancer patients and is a driving force in the exploration of the molecular mechanisms underlying these neoplastic processes and their metastatic potential.

To better guide the approach of personalized treatments in breast cancer, attempts have been made to identify molecular signatures to gain a better understanding of the biology of each tumor. The ultimate goals of these innovations are to improve tumor genotyping and to optimize breast cancer treatment in hopes of improving overall survival while minimizing morbidity of therapy. Some of these modalities have been validated through multiple retrospective studies [5–7] and are currently being used in the treatment of primary breast cancer. One such method of assessing a tumor's genotype is Oncotype DX (ODX), a 21-gene assay that estimates the risk of recurrence in estrogen receptor (ER) positive, node-negative invasive breast cancer patients receiving antihormonal therapy [8]. This assay is performed on formalinfixed, paraffin-embedded tumor specimens and classifies patients into one of three risk categories for distant recurrence—low, intermediate, and high. The ODX correlates these findings to a 10-y distant recurrence risk and generates a recurrence score (RS) as a quantifiable risk estimate.

Studies suggest that premenopausal women present with more advanced breast cancer likely due to a combination of unique biological and clinical factors separating this patient population as a unique clinical entity [9,10]. Clinical factors contributing to the more advanced stage and larger tumor sizes observed in this younger patient population include increased breast density, lack of mammographic screening, higher proportions of triple-negative or HER2/NEU-positive cancers, and high grade disease. However, despite the preponderance of advanced disease in this young population, not all breast cancers in premenopausal women are inherently biologically aggressive [11,12]. Most breast cancers in the United States, even in the premenopausal population, are hormone receptor positive and many are diagnosed at stage I or stage II disease.

This early stage diagnosis is likely a result of increased breast cancer awareness in the general US population. Limited information exists regarding optimal treatment for early stage breast cancer patients, whether premenopausal or postmenopausal. This is in part because of use of age as a surrogate for reporting menopause status, such that women under 50 are labeled as premenopausal, and in part because of paucity of young women included historically in breast cancer clinical trials. Currently, the treatment and management of premenopausal breast cancer patients is more aggressive than that of their older counterparts. Special consideration is frequently given to their young age, health status, and presumed longevity, contributing to the frequency with which adjuvant chemotherapy is recommended to premenopausal breast cancer patients [7,13]. Given that ODX is a strong predictive tool of recurrence, as well as an indicator of responsiveness to chemotherapy [7], this tool has the potential to greatly impact the special population of premenopausal breast cancer.

Despite difficulty in estimating the exact underutilization of ODX in the premenopausal population, due to reasons such as variable menopausal status documentation, there is reasonable speculation that the ODX is not reaching its full potential as a tool for treatment planning, especially in the premenopausal population. For example, in 2008, the National Comprehensive Cancer Network (NCCN) incorporated a recommendation to use the ODX assay for adjuvant treatment planning of early stage, node-negative, ER-positive breast cancer. Yet, when the NCCN queried its 2009 breast cancer database (of which our institution was a participating site) in 2010, only 22% of patients eligible for ODX had the assay performed [14]. Although this study did not specifically address menopause status, it would be hard to imagine that premenopausal women had a disproportionally higher rate of ODX usage. Given the rampant underutilization of the ODX in general, our study aimed to support the validity of this test, especially in this given population.

2. Methods

This is a retrospective study of a prospective clinical ODX database. All patients received surgical intervention by fellowship-trained surgical oncologists at a single tertiary cancer center in accordance with NCCN and institutional guidelines. Institutional review board approval was obtained before this investigation.

A retrospective chart review of invasive breast cancer patients with known ODX RSs was performed. All patients received an ODX test for subsequent adjuvant systemic treatment planning. An ODX was primarily performed on definitive surgical resection specimens between 2003 and 2012. The tumor biology of each breast was classified separately in the few patients with synchronous or metachronous

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