Does the 21-gene recurrence score have clinical utility in HR+/HER2+ breast cancer?

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A B S T R A C T

The 21-gene recurrence score assay has been validated as a predictive biomarker in early-stage HR+ and HER2-breast cancer. It is not indicated for use in HER2+ disease based on national guidelines. In this study, we assessed the value of 21-gene recurrence score (RS), or OncotypeDX (ODX), testing in HR+/HER2+ breast cancer.

We used the National Cancer Database to identify patients with stages I-II, HR+/HER2+ breast cancer who received multi-gene testing with ODX. We then explored the prognostic and predictive value of this biomarker through various forms of survival modeling.

ODX testing was performed in n = 5,280 patients. N = 2,678 patients (50.7%) had a RS < 26, while n = 2,602 (49.3%) had a RS ≥ 26. In Kaplan-Meier survival modeling for patients with recurrence scores < 26, there was no significant difference in overall survival (p = 0.445) between patients receiving different systemic treatment regimens. However, when recurrence scores were ≥ 26, there was a statistically-significant difference in overall survival between systemic treatment regimens (p < 0.001). 5-year overall survival was highest (97.4%) for patients receiving triple therapy (anti-HER2 with chemotherapy and endocrine therapy), followed by those receiving dual therapy with endocrine and anti-HER2 (96.7%), and endocrine with chemotherapy (94.9%). Patients receiving endocrine therapy alone exhibited the lowest 5-year overall survival (88.5%).

Results: Analysis from this large national cancer registry suggests that multigene testing may have predictive value in treatment selection for patients with early-stage, HR+/HER2+ breast cancer. Prospective trials are warranted to identify subgroups of patients with HR+/HER2+ breast cancer who can be spared anti-HER2 treatments and cytotoxic chemotherapy.

1. Introduction

Breast cancer is the most common cancer in women worldwide, and its incidence is increasing at an estimated rate of 3% annually [1]. It is second only to lung cancer as the largest cancer-related cause of death in developed countries [2]. Despite this, outcomes in breast cancer have improved over time due to a combined impact of population-level screening facilitating stage migration, and the evolution of efficacious, including more recently, targeted therapies [3].

Historically, the crux of therapeutic decision-making in breast cancer was largely based on the unique molecular biology of each tumor, specifically the expression of three receptors on the surface of neoplastic cells: the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor 2 (HER2) receptor. Primary tumors that are ER+/PR-, also known as hormone receptor-positive (HR+) neoplasms, can be treated with endocrine therapies with or without chemotherapy. Endocrine therapies include selective estrogen receptor modulators (SERMs), such as tamoxifen, that directly modulate these hormonal receptors. Alternatively, aromatase inhibitors decrease the natural conversion of androgens to estrogens in the body – effectively ‘starving’ neoplastic cells of the hormones that would otherwise stimulate their growth. HER2 is one of four transmembrane growth factors that comprise the epidermal growth factor receptor (EGFR) family [4]. Tumors that overexpress HER2 constitute around one fifth of breast cancers. These tumors have been previously known to portend poorer natural prognosis, due to the accelerated growth and greater metastatic potential of these tumors [5]. However, with the implementation of HER2-targeted therapy, such as the monoclonal antibody trastuzumab, survival outcomes for patients with HER2+ breast cancer have improved in comparison to other tumor subtypes such as triple-negative breast cancer (TNBC) [6].

The last decade has seen a new era in cancer clinical practice, trending towards treatment de-escalation in favor of less toxic regimens, without compromising survival outcomes. Key clinical and pathologic
features of disease, such as extent of lymph node invasion and tumor grade, are considered in the decision to recommend chemotherapy to patients with high-risk disease. Additionally, genomic assays were validated to identify patients with early-stage, HR+/HER2-breast cancer that are unlikely to benefit from the addition of chemotherapy to endocrine therapy. The large, randomized TAILORx trial was the first to provide evidence for the prognostic and predictive value of the 21-gene OncotypeDX assay [7], which has since been incorporated into treatment practice guidelines such as the National Comprehensive Cancer Network (NCCN) guidelines [8]. The OncotypeDX genomic test provides a risk-of-recurrence score ranging from 0 to 100. For patients receiving a score ≥26, NCCN guidelines for adjuvant systemic therapy in early-stage HR+/HER2-breast cancer recommend the addition of chemotherapy to endocrine therapy. Other panels, including the 70-gene MammaPrint assay, have also been shown to have value in HR+/HER2-breast cancer [9].

OncotypeDX testing, however, is not recommended for HR+/HER2-breast cancer [8] and these tumors were excluded from the multigene assay trials for early HR+ breast cancers. However, one large retrospective analysis using the Surveillance, Epidemiology, and End Results (SEER) database found that in an analysis of clinical practice in the decade following the introduction of OncotypeDX in the USA, approximately 4.7% of ER+/HER2+ patients underwent OncotypeDX testing [10,11]. In this study, we used a large national registry to assess the predictive value of OncotypeDX for response to chemotherapy and anti-HER2 therapy for patients with early-stage HR+/HER2+ breast cancer, as well as the prognostic implication of OncotypeDX in this population.

2. Materials and methods

2.1. Patient data

Data was accessed from the National Cancer Database (NCDB) for patients in the United States diagnosed with early-stage (AJCC clinical staging I-II), HR+/HER2+ breast cancer between 2004 and 2017, based on a Participant User File (PUF) award granted to the principal investigator, Z.N. This database is supported jointly by the Commission on Cancer (CoC) and the American College of Surgeons (ACS), and the information it contains is collected with high fidelity from over 1,500 medical institutions [21]. HER2-positivity was determined via immuno-histochemistry (IHC) or fluorescence in situ hybridization (FISH). We identified a subgroup within this cohort that have undergone testing with OncotypeDX. This was an opportunity to conduct an analysis in this patient population.

2.2. Statistical analysis

Data analysis was conducted using SPSS version 28.0 (IBM Corp, Armonk, NY). Descriptive univariate statistics were performed to describe the patient sociodemographic, clinical, and pathologic characteristics of this cohort of patients with AJCC clinical stage I-II HR+/HER2+ breast cancer with OncotypeDX scoring.

We explored the prognostic and predictive value of OncotypeDX using two forms of survival modeling. First, we performed Cox regression modeling to confirm whether the prognostic significance of OncotypeDX was independent of other important confounders of survival, including: age, race, Charlson/Deyo comorbidity index, nodal status and systemic treatment regimen. Treatment approach was categorized as following: a. endocrine therapy alone, b. endocrine therapy + anti-HER2 targeted treatment, c. endocrine therapy + chemotherapy and d. endocrine therapy + anti-HER2 + chemotherapy.

Subsequently, used Kaplan-Meier modeling to further investigate the potential predictive utility of 21-gene recurrence scoring in early-stage, HR+/HER2+ breast cancer. Stratifying by treatment approach, we explored overall survival in one Kaplan-Meier model for patients with RS < 26 and another for those ≥26. Finally, we controlled for age: replicating these stratified Kaplan-Meier survival models in one subgroup of patients younger than 50 as well as the other subgroup of patients older than 50.

3. Results

Of the n = 101,852 patients with early-stage, HR+/HER2+ breast cancer available in this national registry, n = 5,280 (5.2%) underwent OncotypeDX testing. A total of n = 5,280 patients with AJCC clinical stages I-II, HR+/HER2+ breast cancer, as well as OncotypeDX data, were included in this analysis (Table 1). This cohort was almost evenly-split by the results of this genomic panel; with one group of n = 2,678 (50.7%) patients prognosticated to have a low risk of recurrence (RS < 26), and another group of n = 2,602 (49.3%) patients prognosticated to have a high risk of disease recurrence (RS ≥ 26). The majority of patients that underwent OncotypeDX testing were White (n = 4,484, 84.9%) with private insurance (n = 3,060, 56.0%). Additionally, almost all patients that underwent OncotypeDX testing in this cohort had node-negative disease (n = 4,947, 93.7%). Using chi-squared testing, a statistically-significant association between 21-gene recurrence score testing and systemic therapy regimen used (p < 0.001) was noted. Among the group who received endocrine therapy alone, 82.8% of patients who had low-risk scoring. On the other hand, in those that received chemotherapy and anti-HER2 therapy, followed by endocrine therapy, 60.4% had a high-risk recurrence score.

Multivariable Cox regression survival analysis indicated that after controlling for the impact of age, race, insurance status, Charlson/Deyo comorbidity scoring, nodal status and treatment approach, OncotypeDX scoring was a statistically-significant prognosticator of overall survival (OS). In this context of stages I-II, HR+/HER2+ breast cancer, patients with a recurrence score greater than or equal to 26 exhibited inferior overall survival compared to those with a score less than 26 (HR 1.87, 95% CI 1.13–3.09, p = 0.015) (Table 2). In additional analyses using Kaplan-Meier models (Fig. 1), one controlling for patients with OncotypeDX scores less than 26 and the other for those with scores greater than or equal to 26, the following was identified: in those with low risk scores, there was no statistically-significant difference in overall survival when stratifying by treatment approach (i.e. endocrine therapy alone, endocrine and anti-HER2 therapy, chemotherapy and endocrine therapy, and chemotherapy with anti-HER2 therapy and endocrine therapy), as exhibited by survival curves that overlap and a log-rank p-value of 0.445 (Fig. 1). Conversely, in the model of those with high risk scores, we found a significant difference in overall survival by treatment approach (log-rank p-value <0.001): i.e. those receiving endocrine therapy alone exhibited inferior overall survival (5-year OS 88.5%), while those receiving anti-HER2 therapy with endocrine therapy (5-year OS 96.7%) or chemotherapy (5-year OS 94.9%), or both (5-year OS 97.4%), had comparable survival curves. After controlling for age, we found a statistically-significant difference in overall survival in patients at least 50 years old receiving various forms of systemic therapy when 21-gene recurrence scoring was high (p < 0.028), but not when it was low (p = 0.375). There was no statistically-significant difference in patients younger than 50 (p > 0.05), however, this may be due to the limited sample size of this population.

4. Discussion

This real-world analysis based on a large national registry suggests that OncotypeDX may have prognostic as well as predictive value in stages I-II, HR+/HER2+ breast cancer. Patients with high risk scores based on OncotypeDX who received endocrine therapy alone and who received neither HER2-targeted treatment nor chemotherapy had a significantly inferior overall survival. This analysis found that patients with recurrence risk scores ≥26 had equivalent overall survival regardless of the treatment approach. This finding warrants further
evaluation in future prospective trials to identify potential subgroups of patients with HR+/HER2+ disease with low OncotypeDX scores who could benefit from treatment de-escalation. Prediction analysis of microarray 50, or PAM50, is a genomic test measuring the expression of 50 genes and can identify various intrinsic subtypes of breast cancer. In HER2+ disease, it has shown prognostic [12] and predictive value, particularly to predict pathologic complete response after neoadjuvant anthracycline-taxane-based chemotherapy [13,14]. Research is ongoing to validate the clinical utility of PAM50, and other prognostic models that incorporate PAM50—such as HER2DX—in HER2+ breast cancer [15]. While there remains a paucity of validated biomarkers to detect low-risk patients in this context of early-stage, HR+/HER2+ breast cancer, this study shows that 21-gene recurrence score testing may be another promising surrogate to evaluate.

National Comprehensive Cancer Network guidelines do not recommend the use of genomic panels for HR+/HER2+ breast cancer due to the availability of HER2-targeted therapies for these patients and the lack of prospective trials validating the use of OncotypeDX in patients with HER2+ disease [8]. Interestingly, out of the n = 101,852 patients with early-stage, HR+/HER2+ breast cancer, n = 5,280 (5.2%) underwent OncotypeDX testing for unclear reasons. This is consistent with other published data outlining the occasional use of genomic panels in this context [10]. This may open further opportunities for exploratory and research purposes, as in this analysis. In addition, the significant association identified in this study between the results of OncotypeDX testing (high versus low risk of disease recurrence) and the systemic treatment approach selected—i.e. greater use of chemo-endocrine therapy, or chemo-endocrine therapy with anti-HER2 therapy, versus endocrine therapy alone when recurrence scoring was ≥ 26—indicates that genomic testing may have informed clinical decision-making for these patients, but this could not be confirmed.

A potential additional benefit to considering the exploration of OncotypeDX further in clinical practice to de-escalate chemotherapy is the possibility of determining a subgroup of HR+/HER2+ patients who might not benefit from receiving anti-HER2 therapy. While there are concerns about the anti-HER2 treatment use in patients with cardiac comorbidities due to cardiotoxic effects of anti-HER2 treatments, including patients with cardiomyopathy (ischemic, inherited, or otherwise), or those older than 65 with risk factors for heart failure, other dose-limiting toxicities include acute liver injury and cytopenias [16]. Historically, patients with cardiac risk factors or dysfunction have been excluded from, or under-represented in, trials studying HER2-targeted treatments [17]. The SAFE-HEaRT study is one of few prospective trials providing safety data of these therapies in patients with breast cancer and pre-existing systolic dysfunction [18]. Data from this study suggests potential utility in genomic testing when anti-HER2 drugs are indicated to allow clinicians to identify patients likely to benefit from anti-HER2 therapy with chemotherapy and endocrine therapy, versus endocrine therapy alone. As of now, temporarily withholding or ceasing HER2-targeted therapy is recommended in clinical practice if significant decreases in left ventricular ejection fraction are detected during treatment with HER2-targeted drugs [17]. It is not clear how often patients need cardiovascular screening, or how to risk-stratify those who cannot receive HER2-targeted drugs. Cardio-oncology, a rapidly-growing domain of research and clinical practice, could contribute significantly to optimizing care in these challenging situations.

In summary, endocrine and anti-HER2 therapies represent a great success story in the practice of targeted therapy for breast cancer. The
hormone and epidermal growth factor receptors (ER/PR and HER2 respectively) are high-reliability biomarkers that drove this outcome. Numerous other biomarkers, including the presence of PIK3CA mutations [19], tumor-infiltrating lymphocytes [20], or the expression of PD-L1 [21,22], have been explored in the context of HER2+ disease, with predominantly mixed or inconclusive data to support changes in clinical practice. Other biomarkers used in the early-stage, HER2-setting may prove to also have value in HER2+ disease, and should be validated through prospective clinical trials, as the major limitation of this study is its retrospective nature. Another limitation of this study pertains to the dramatic evolution of breast cancer systemic treatment options over recent years and the lack of granular detail in National Cancer Database regarding specific agents used. As one example, updated analysis of data from the monarchE trial corroborated the value of Ki-67 (a marker of proliferation) scores $\geq20\%$ as predictive of the benefit of the CDK inhibitor abemaciclib in the adjuvant setting for patients with high-risk of recurrence [23]. Abemaciclib has since been FDA-approved for use in this setting [24].

21-gene recurrence score testing may add prognostic and predictive value to guide treatment decisions in HR+/HER2+ breast cancer. Future research is needed to confirm the promising data from this analysis.

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There are no sources of funding to declare.

Ethical approval statement

This study was approved by the Cleveland Clinic institutional review board.

Declaration of competing interest

The authors declare no competing financial or non-financial interests.

APPENDICES.

Table 1

Sociodemographic, clinical, and pathologic characteristics of this cohort of patients with AJCC clinical staging I-II, HR+/HER2+ breast cancer and OncotypeDX data.

| Variable                        | OncotypeDX (n = 5,280) |
|---------------------------------|------------------------|
|                                 | Low RS (<26) | High RS ($\geq$26) |
| **Age**                        |             |                     |
| $<50$                           | 549 (20.5%) | 571 (21.9%)         |
| $50-70$                         | 1,659 (61.9%) | 1,536 (59.0%) |
| $>70$                           | 470 (17.8%) | 495 (19.0%)         |
| **Sex**                        |             |                     |
| Male                            | 31 (1.2%) | 35 (1.4%)           |
| Female                          | 2,647 (98.8%) | 2,567 (98.7%) |
| **Race**                       |             |                     |
| White                           | 2,297 (87.5%) | 2,187 (86.1%) |
| Black                           | 252 (9.6%) | 254 (10.0%)         |
| Asian                           | 77 (2.9%) | 99 (3.9%)           |
| **Charlson/Deyo comorbidity index** |             |                     |
| 0                               | 2,283 (85.3%) | 2,217 (85.2%) |
| 1                               | 324 (12.1%) | 312 (12.0%)         |
| 2                               | 55 (2.1%) | 55 (2.1%)           |
| 3                               | 16 (0.6%) | 18 (0.7%)           |
| **Nodal status**                |             |                     |
| Node-negative                   | 2,521 (94.6%) | 2,426 (93.6%) |
| Node-positive                   | 145 (5.4%) | 167 (6.4%)          |
| **Grade**                      |             |                     |
| I                               | 519 (19.4%) | 146 (5.6%)          |
| II                              | 1,470 (54.9%) | 1,104 (42.4%) |
| III                             | 574 (21.4%) | 1,241 (47.7%)      |
| **Histology**                   |             |                     |
| Ductal                          | 2,159 (80.6%) | 2,319 (89.1%) |
| Lobular                         | 416 (15.5%) | 204 (7.8%)          |
| Other                           | 103 (3.8%) | 79 (3.0%)           |
| **Insurance status**           |             |                     |
| Uninsured                       | 39 (1.5%) | 23 (0.9%)           |
| Private insurance               | 1,539 (58.2%) | 1,521 (59.0%) |
| Medicare                        | 167 (6.3%) | 147 (5.7%)          |
| Medicaid                        | 900 (34.0%) | 888 (34.4%)         |
| **Treatment approach**         |             |                     |
| Endocrine therapy alone         | 1,227 (45.8%) | 254 (9.8%)       |
| Endocrine therapy + anti-HER2   | 45 (1.7%) | 46 (1.8%)           |
| Endocrine therapy + chemotherapy| 435 (16.2%) | 940 (36.1%)       |
| Endocrine therapy + anti-HER2 + chemotherapy | 568 (21.2%) | 865 (33.2%) |

* For n = 226 cases, data on tumor grade was missing from the NCDB.

* For n = 900 cases, data on treatment approach missing from the NCDB.
Table 2
Multivariate Cox regression models for factors associated with overall survival in AJCC clinical stage I-II, HR+/HER2+ breast cancer.

| Variable | Early-stage, HR+/HER2+ breast cancer (n = 3,846)* |
|----------|-------------------------------------------------|
|          | No. (%) | HR | 95% CI | p-value |
| Oncotype DX score | | | | |
| <26 (ref) | 1,981 (51.5%) | 1 | – | 0.018 |
| ≥26 | 1,865 (48.5%) | 1.49 | 1.07–2.07 | |
| Age | | | | |
| <50 (ref) | 2,373 (61.7%) | 2.29 | 1.28–4.12 | 0.005 |
| 50–70 | 671 (17.4%) | 8.38 | 4.62–15.20 | <0.001 |
| >70 | 3,348 (87.1%) | 1 | – | 0.025 |
| Race | | | | |
| White (ref) | 363 (9.4%) | 1.61 | 1.08–2.40 | 0.021 |
| Black | 135 (3.5%) | 0.40 | 0.10–1.61 | 0.198 |
| Asian | | | | |
| Charlson/Deyo comorbidity index | | | | |
| 0 (ref) | 3,276 (85.2%) | 1 | – | <0.001 |
| 1 | 476 (12.4%) | 2.09 | 1.50–2.92 | <0.001 |
| 2 | 80 (2.1%) | 2.30 | 1.20–4.40 | 0.012 |
| 3 | 14 (0.36%) | 6.43 | 2.00–20.65 | 0.002 |
| Nodal status | | | | |
| Node-negative (ref) | 217 (5.6%) | 2.46 | 1.56–3.90 | |
| Node-positive | | | | |
| Systemic therapy | | | | |
| Endocrine therapy alone (ref) | 1,304 (33.9%) | 1 | – | 0.016 |
| Endocrine therapy + anti-HER2 | 75 (2.0%) | 0.21 | 0.03–1.48 | 0.177 |
| Endocrine therapy + chemotherapy | 1,295 (33.7%) | 0.78 | 0.55–1.11 | 0.163 |
| Endocrine therapy + anti-HER2 + chemotherapy | 1,172 (30.5%) | 0.47 | 0.29–0.79 | 0.004 |

* n = 3,846 patients were included in the multivariable analysis after excluding n = 900 cases for which treatment approach was unknown and n = 534 patients for which survival data was not yet documented in the NCDB.

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