OncotypeDX Testing Does Not Benefit Patients with Grade 1, Estrogen and Progesterone Receptor Positive Breast Cancers: A TAILORx Validated Study

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Abstract

Background & Objectives: We previously described a predictive AAMC model that identifies patients (grade 1, hormone-positive) who would not benefit from OncotypeDX testing. The purpose of this study was to validate the AAMC model by assessing distant recurrence-free interval (DRFI) and invasive disease-free survival (IDFS) using TAILORx clinical trial data.

Materials & Methods: We retrospectively analyzed TAILORx trial data and categorized patients based on the AAMC model. AAMC low-risk patients are those with grade 1 and hormone-positive tumors. Kaplan–Meier curves examined DRFI and IDFS.

Results: Of the 9195 cases, 2246 (24.4%) were identified by AAMC as low-risk. Among these AAMC low-risk patients, 55.2% had Recurrence Score (RS) 0–15, 42.3% had RS 15–25, and 2.4% had RS > 25. The 10-year DRFI did not differ for those who received adjuvant chemotherapy versus those who did not (98% vs. 96%, log-rank p = 0.46). Similarly, IDFS was comparable between those who received adjuvant chemotherapy and those that did not (86% vs. 86%, log-rank p = 0.66). Only 2.4% of AAMC low-risk patients were categorized as high-risk (RS > 25). A sensitivity analysis of this discordant group, wherein those with RS > 25 were re-classified into the no-chemotherapy group and assumed to have experienced recurrences at the rate expected without chemotherapy, did not find any difference in DRFI between those who received adjuvant chemotherapy and those who did not (log-rank p = 0.16).

Conclusion: OncotypeDX testing does not benefit AAMC low-risk patients with hormone-positive grade 1 tumors. Based on these data, 1 in 4 TAILORx participants would not need OncotypeDX testing.

Key words: Oncotype DX, 21-gene genomic assay, Screening tool, Outcomes, Over-treatment, Breast cancer

1. Introduction

The 21-gene Recurrence Score (RS) assay (Oncotype DX Breast Recurrence Score®, Exact Sciences Corporation, Madison, WI) provides prognostic information and predicts chemotherapy benefits in early-stage breast cancer [1–4]. The National Comprehensive Cancer Network (NCCN) recommends Oncotype DX (ODX) testing in patients with >0.5 cm, hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) tumors, with 0–3 positive nodes [5].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B20 trial showed that ODX testing could identify patients who would benefit from adjuvant chemotherapy [2]. The Trial Assigning Individualized Options for Treatment (TAILORx) clinical trial refined the clinical usefulness of the ODX test by demonstrating that chemotherapy should be spared in patients older than 50 years with RS ≤ 25, as well as in patients younger than 50 years with RS ≤ 15 [6]. Some chemotherapy benefit was observed in patients younger than 50 years with RS 16 to 25 [7]. Chemotherapy was associated with a...
lower rate of distant recurrence in this patient population, but overall survival was similar compared to patients receiving endocrine therapy alone.

The use of ODX testing holds the promise of improved risk stratification, treatment selection, and clinical outcomes in early-stage breast cancer patients [8,9]. The incorporation of recurrence scores into clinical practice has been shown to be cost-effective, as it lowers the overall use of chemotherapy in early-stage breast cancer patients [10–13]. Yet, the indiscriminate use of these tests increases the overall cost of care within the healthcare system [13].

The Anne Arundel Medical Center (AAMC) model is a pathology-based predictive tool that identifies patients who are unlikely to benefit from ODX testing [14–16]. The AAMC model defines low-risk patients as those meeting all of the following three criteria: histologic grade 1, progesterone receptor (PR) > 3%, and estrogen receptor (ER) > 20% tumors. We previously showed that adjuvant chemotherapy does not improve breast cancer-specific survival (BCSS) or overall survival (OS) in AAMC low-risk patients [16]. The previous study was limited in that we were unable to evaluate distant recurrence-free interval (DRFI) or invasive disease-free survival (IDFS). This study aims to validate the AAMC low-risk categorization model using the TAILORx database to assess DRFI and IDFS.

2. Materials and methods

The TAILORx clinical trial was sponsored by the National Cancer Institute (NCI) and coordinated by the Eastern Cooperative Oncology Group (ECOG). The trial was approved by the NCI central institutional review board. This study was approved by the TAILORx study group and our institutional review board.

We retrospectively reviewed TAILORx trial data [6] and risk-stratified patients according to the AAMC model [14–16]. The AAMC risk model defines low-risk patients as those with grade 1, ER>20%, and PR>3% tumors [14–16]. Patients must meet all three criteria to be categorized as low risk, while all other tumors are not considered low-risk. Hormone receptor status in the TAILORx trial database is reported as a binary variable (i.e., positive or negative). Therefore, for the purposes of this analysis, we used a modified definition of AAMC low-risk. Patients had to meet these three criteria: histologic grade 1, ER-positive, and PR-positive.

Quantitative measures of hormone receptor status have been shown to be prognostic indicators of breast cancer [17]. The American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines acknowledge that data is limited on the overall benefit of endocrine therapy for patients with low level (1–10%) ER expression, and suggest that invasive cancers with low-ER expression levels are heterogenous in both behavior and biology, and often have gene expression profiles similar to ER-negative cancers [5,18]. Similar interpretation principles apply to low-PR (1–3%) expression tumors. Our previous work showed that PR<3% was associated with 5-year disease recurrence, and a few tumors with ER<20% had a high Oncotype score that would have justified Oncotype testing [14]. Therefore, our model defines AAMC low-risk as ER>20% and PR>3% tumors.

A total of 10,273 cases were identified in the TAILORx dataset. We excluded cases with missing tumor grade, missing hormone receptor information, and those with a DRFI interval of 0 days, leaving 9195 cases for our final analysis (Fig. 1). We categorized tumors based on RS scores, as defined by the results of the TAILORx study [6,7,19]. The RS low-risk group included tumors for which chemotherapy was not recommended (RS < 16 and age ≤50 years, or RS ≤ 25 and age >50 years). The RS intermediate-risk group comprises tumors for which chemotherapy demonstrated some benefit (RS 16–25 and age ≤50 years). The RS high-risk group represents those recommended for chemotherapy (RS > 25). Patient age and tumor characteristics (i.e., size, Nottingham histological grade, HR expression, and RS) were collected. The use of adjuvant chemotherapy was recorded.

Descriptive statistics were used to characterize patients in the AAMC low-risk group. Kaplan–Meier methods were used to assess DRFI and IDFS, comparing patients who received adjuvant chemotherapy to those who did not. The methodology and power of our statistical analysis were similar to that of the TAILORx trial. The log-rank test was used to test for statistical significance, defined as p-value <0.05.

3. Results

A total of 9195 cases were included in the final analysis, of which 2246 cases (24.4%) were identified as AAMC low-risk. Patient and tumor characteristics are described in Table 1. In AAMC low-risk patients, 55.2% had an RS of 0–15, 42.3% had an RS of 15–25, and 2.4% had an RS > 25 (Table 2).

The 9-year DRFI did not differ between AAMC low-risk patients who received adjuvant chemotherapy and those who did not (98% vs. 96%, log-rank p = 0.46)
Similarly, IDFS was comparable between those who received adjuvant chemotherapy and those who did not (86% vs. 86%, log-rank p = 0.66) (Fig. 2A). Restricting the analysis of AAMC low-risk patients to study participants who were randomly assigned to receive or not receive chemotherapy (RS 11–25) did not result in a significant difference in 9-year DRFI (97% vs. 95% in the 9-year DRFI, log-rank p = 0.07; Fig. 3A) or IDFS (86% vs. 86% in the 9-year IDFS, log-rank p = 0.80; Fig. 3B).

In the subgroup of patients ≤50 years with RS 16 to 25, the 9-year DRFI did not differ between AAMC low-risk patients who received adjuvant chemotherapy and those who did not (96% vs. 92%, log-rank p = 0.14) (Fig. 4A). Similarly, IDFS was comparable between those who received adjuvant chemotherapy and those who did not (87% vs. 83%, log-rank p = 0.39) (Fig. 4B).

Only 2.4% of AAMC low-risk patients were categorized as high-risk by OncotypeDX testing (RS > 25). Sensitivity analysis was performed since all patients in the small high-risk group received chemotherapy.

Table 1. Patient and tumor characteristics

<table>
<thead>
<tr>
<th>AAMC Model</th>
<th>Low-risk</th>
<th>Intermediate or high-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50 years</td>
<td>795</td>
<td>35%</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>1451</td>
<td>65%</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 cm</td>
<td>123</td>
<td>5%</td>
</tr>
<tr>
<td>1–2 cm</td>
<td>1619</td>
<td>72%</td>
</tr>
<tr>
<td>2–3 cm</td>
<td>415</td>
<td>18%</td>
</tr>
<tr>
<td>3–4 cm</td>
<td>65</td>
<td>3%</td>
</tr>
<tr>
<td>≥14 cm</td>
<td>23</td>
<td>1%</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2246</td>
<td>100%</td>
</tr>
<tr>
<td>Medium</td>
<td>1627</td>
<td>24%</td>
</tr>
<tr>
<td>High</td>
<td>1627</td>
<td>24%</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2246</td>
<td>100%</td>
</tr>
<tr>
<td>Negative</td>
<td>52</td>
<td>1%</td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2246</td>
<td>100%</td>
</tr>
<tr>
<td>Negative</td>
<td>926</td>
<td>13%</td>
</tr>
</tbody>
</table>

Table 2. Percent of TAILORx trial participants and treatment recommendations based on OncotypeDX

<table>
<thead>
<tr>
<th>OncotypeDX</th>
<th>Treatment recommendation based on TAILORx results</th>
<th>AAMC Model</th>
<th>Low-risk (n = 2246, 24.4%)</th>
<th>Not low-risk (n = 6949, 75.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS 0 to 15</td>
<td>No chemotherapy</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>RS 16 to 20, age ≤50</td>
<td>Chemotherapy and/or OFS/ET</td>
<td>1240</td>
<td>55.2%</td>
<td>2535</td>
</tr>
<tr>
<td>RS 21 to 25, age ≤50</td>
<td>Chemotherapy and/or OFS/ET</td>
<td>258</td>
<td>11.5%</td>
<td>604</td>
</tr>
<tr>
<td>RS 16 to 25, age &gt;50</td>
<td>No chemotherapy</td>
<td>93</td>
<td>4.1%</td>
<td>376</td>
</tr>
<tr>
<td>RS &gt; 25</td>
<td>Chemotherapy</td>
<td>600</td>
<td>26.7%</td>
<td>2171</td>
</tr>
<tr>
<td>Recurrence Score (RS); Ovarian function suppression (OFS); Endocrine therapy (ET)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(per TAILORx protocol). For this sensitivity analysis, all AAMC low-risk patients with RS > 25 were assumed to have not received chemotherapy. These patients were assigned an expected recurrence rate based on their RS and the assumption that they did not receive chemotherapy according to published literature [1]. Under these assumptions, there was still no difference in DRFI between the chemotherapy and no-chemotherapy groups (2% difference in 9-year DRFI, log-rank p = 0.16).
4. Discussion

We previously described a prognostic and predictive tool that identifies early-stage breast cancer patients who will not benefit from chemotherapy and whose ODX testing can be omitted [14–16]. Our model is based on pathologic data and does not increase the cost of care. We previously determined that adjuvant chemotherapy does not improve BCSS or OS in AAMC low-risk patients [16]. This current study builds on our previous work and demonstrates that ODX testing can be omitted in AAMC low-risk patients (grade 1, PR+, ER+); our findings show that adjuvant chemotherapy does not improve...
DRFI or IDFS in these patients. Based on these data, ODX testing could have been omitted for 1 in 4 patients in the TAILORx trial.

Breast cancer treatment costs influence treatment decisions, especially for patients from low-income households [20]. The majority of breast cancer patients report being fiscally unprepared and describe higher-than-expected treatment costs [20]. The annual adjusted out-of-pocket costs for breast cancer patients are estimated to be $2,700, rising even higher for prolonged treatment due to adverse events [21–24]. Financial toxicity of cancer treatments is now
recognized as a major adverse effect of cancer care and is associated with reduced quality of life, non-adherence to treatment regimens, and increased risk for early mortality [25–30]. Eliminating unnecessary genomic testing for early-stage breast cancer patients can reduce this financial burden.

Several tools to refine the use of ODX are described in the literature. The University of Tennessee model incorporates patient age, tumor size, grade, lymphovascular invasion (LVI), and ER/PR status [31,32]. The University of Pittsburgh Magee equations utilize a combination of tumor size, grade, ER/PR, HER2, Ki-67 and surrogate H scores [33–35]. In contrast, our model utilizes only tumor grade and ER/PR status, which can easily be obtained from pathologic data. Tumor grade and hormone receptor status have been shown to be the strongest predictors of ODX scores [31,32].

The strength of our model is illustrated by >97% of AAMC low-risk patients having RS < 25. A limitation of this study is that the small (2.4%) group of AAMC low-risk patients with RS > 25 all received adjuvant chemotherapy per TAILORx study protocol. This precludes an analysis of the benefit of adjuvant chemotherapy in this subgroup of patients. To address this limitation, we performed a sensitivity analysis in which we assumed that these patients experienced recurrences at rates expected without chemotherapy, using published RS-based event rates without chemotherapy [1]. Taking this into account, we found no difference in recurrence based on the use of adjuvant chemotherapy. Therefore, we feel confident in recommending that ODX testing can be omitted for all AAMC low-risk patients.

The TAILORx trial showed some chemotherapy benefit in the subgroup of patients ≤50 years with RS 16 to 25 for distant recurrence, but overall survival remained unchanged [7]. In our analysis of AAMC low-risk patients who are ≤50 years with RS 16 to 25, we did not find a significant difference in DRFI or IDFS for those who received adjuvant chemotherapy compared to those who did not. Similar to the TAILORx trial, our analysis is underpowered, given the small number of patients in this subgroup. Therefore, although we demonstrated that the AAMC low-risk patients overall do not benefit from chemotherapy, we cannot make definite conclusions regarding the safety of omitting ODX testing for the specific subset of patients ≤50 years of age.

5. Conclusion

The AAMC model is a validated pathology-based tool that identifies patients who would not benefit from ODX testing. OncotypeDX testing may be omitted in early-stage breast cancers that are AAMC low-risk (defined as grade 1 and ER+ and PR+), as adjuvant chemotherapy does not improve DRFI or IDFS in these patients. Our analysis was underpowered for the subset of patients ≤50 years of age, and we cannot make definite conclusions regarding the safety of omitting ODX testing in these patients. Based on these data, ODX testing could have been eliminated for 1 in 4 patients in the TAILORx trial. Incorporating the AAMC screening tool into clinical practice could decrease the frequency of indiscriminate ODX testing, resulting in substantial cost savings to the healthcare system.

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