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Why does Oncotype DX recurrence score reduce adjuvant chemotherapy use?

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Abstract

The Oncotype DX recurrence score (RS) reduces breast cancer adjuvant treatment utilization, but the reasons for this effect are not straightforward. We performed a retrospective chart review of 89 consecutive node-negative breast cancer patients for whom RS was ordered to facilitate adjuvant treatment decisions. By subtracting the relapse rate predicted by RS from that calculated using the Adjuvant! Online (AOL) web-based instrument, a “prognostic delta” (P) was determined, reflecting the difference between prognoses predicted by these two indices. Clinician interviews were conducted to evaluate the actual effect of RS on treatment decisions and its relation to P . Adjuvant chemotherapy use decreased from 61 to 26 % as a consequence of RS results ($p < 0.0001$). In multivariate analysis, RS was the only factor significantly associated with the final adjuvant treatment choice. Surprisingly, RS caused chemotherapy to be withheld even when P was negative (i.e., cases in which RS predicted a *less* favorable outcome than AOL). The prognostic and chemotherapy predictive utilities of the RS do not fully account for its effect in reducing adjuvant chemotherapy use. Further studies are required to more fully elucidate other factors that may be responsible for this effect, including the possibility of unintended influence.

Keywords

Breast cancer; Oncotype DX recurrence score; Adjuvant therapy; Treatment decision making; Breast cancer genetic signature

Introduction

Based on the notion that a tumor’s behavior can be predicted by assessing the expression of an array of its genes, the Oncotype DX recurrence score (RS) has been developed to facilitate adjuvant treatment decision making for patients with surgically resected breast

cancers [1, 2]. The RS has been reported to be an independent prognostic factor for recurrence of estrogen receptor positive (ER+), axillary lymph node negative (N0) breast cancers in several [1, 3–5] but not all [6] reported retrospective validation cohorts. High RS (>30) results are associated with worsened prognosis and have also been reported to predict for enhanced benefit from CMF or MF chemotherapy as compared with low RS (<18) [3]. The assay has been incorporated into both NCCN [7] and ASCO [8] treatment guidelines for patients with ER+, HER2 neu negative, N0 breast cancers measuring >0.5 cm.

Following its commercial introduction in January 2005, the RS has rapidly pervaded medical oncology practice, and is now being applied to the management of >60,000 early stage breast cancer patients annually [9]. A meta-analysis [10] of seven studies reporting on the use of RS in clinical practice indicates that this test is frequently responsible for changing adjuvant treatment decisions. Of all patients tested, 33 % had chemotherapy withheld on the basis of RS, whereas just 4 % received chemotherapy that would not otherwise have been administered on the basis of RS. Because of this net reduction in chemotherapy utilization, this assay has also been reported to be cost-effective despite its price in excess of \$4000 [11–13].

Consequently, it can be estimated that >20,000 early stage breast cancer patients who would have otherwise received adjuvant chemotherapy in 2011 had it withheld on the basis of their RS despite the absence, to date, of prospective data to support this change in management. Trial Assigning Individualized Options for Treatment (TAILORx) is a prospective study that randomly assigns adjuvant treatment candidates with scores in the 11–25 range to either receive hormonal therapy alone or hormonal therapy plus chemotherapy [14]. Limitations of TAILORx include the fact that it is unblinded, and that it presupposes a predictive value of RS in this range (as the use of RS itself is not a study variable).

Our experience with the RS in the first 89 consecutive N0 breast cancer patients for whom this test was ordered to facilitate adjuvant treatment decision making is herein reviewed. The primary purpose of this analysis is to better understand why the RS seems to discourage adjuvant chemotherapy utilization.

Patients and methods

Study design

The first 89 consecutive ER+, N0 breast cancer patients for whom Oncotype DX RS (Genomic Health Inc, Redwood City, CA) testing was ordered for the purpose of facilitating adjuvant treatment decisions in a single community medical oncology practice (Winthrop Oncology and Hematology PC, Mineola, NY) were identified retrospectively. Medical records were reviewed to determine RS results, tumor characteristics, patient demographics, comorbid illness, and ultimate breast cancer adjuvant treatment decisions. Extracted data for each patient was utilized to calculate 10-year recurrence rates predicted by the Adjuvant! Online (AOL) internet program [15].

Since RS reports prognosis in terms of 10-year distant only recurrence rates, we adjusted the relapse rates predicted by AOL to exclude local recurrences and contra-lateral breast events.

We incorporated a 10-year ipsilateral breast event rate of 3.5 % as reported in the original cohort used to validate RS [16]. Contralateral breast event rates were determined according to online instructions provided by AOL with division in half to account for an approximately 50 % reduction by tamoxifen [17].

Oncologists were individually interviewed to assess the factors influencing adjuvant treatment decisions for each patient. To enhance the reliability of physician responses, medical records were available at each interview. The Winthrop-University Hospital Institutional Review Board approved the design and conduct of this study.

Statistical analysis

The Chi-square test for trend or Fisher's Exact Test was used to determine the association of categorical variables, including the independent associations between RS prognostic category and each of the following: age, histology, tumor size, tumor grade, AOL, and immunohistochemical (IHC) staining for cytokeratin in sentinel lymph nodes. McNemar's test was used to compare rates of chemotherapy preference before and after results of RS were known. Multiple logistic regression was used to determine the independent association of RS and AOL with the ultimate decision of whether to administer chemotherapy. (Separate components of AOL were *not* examined individually in this analysis.)

Receiver operating characteristic (ROC) curves were used to determine the independent association of RS and AOL with the decision to administer chemotherapy. We determined whether there was a significant increase in the area under the ROC curve when AOL was added to RS, using the method of DeLong.

As our continuous data were non-normally distributed, comparison of continuous variables (as well as ordinal variables) across levels of RS was evaluated by the Kruskal-Wallis test (non-parametric analysis of variance). All calculations were performed using SAS 9.2 for Windows (SAS Institute, Cary, NC).

Results

Patient selection

We identified 89 unique ER+ N0 breast cancer patients for whom RS assays were obtained between July 2005 and June 2010. Eighteen of these patients were enrolled in the TAILORx clinical trial. After reviewing the charts and interviewing the treating physicians, it was evident that these patients, including the eight intermediate RS patients whose treatment was supposed to have been randomly assigned, made their decisions in a similar manner to non-protocol patients. For instance, three of the eight intermediate RS patients randomized to receive adjuvant chemotherapy rejected their treatment assignment while a fourth withdrew before randomization, but after receiving her RS of 11 and then deciding that she was unwilling to receive chemotherapy.

RS and traditional prognostic factors

RS results in relation to demographics and other prognostic indices are shown in Table 1. Both increasing tumor size and grade were associated with worsening RS prognostic

category. Prognostic category predicted by AOL was also significantly associated with that predicted by RS, but only after AOL relapse rates were adjusted to exclude local events and to incorporate tamoxifen effects. There was no significant relationship between RS prognostic category and patient age, tumor histology, or positivity of IHC staining for cytokeratin in sentinel lymph nodes.

We, like others [18–20] who have analyzed the use of RS in clinical practice, observed a significantly smaller proportion of RS's in the high-risk range than that which had been reported in validation cohorts ($p < 0.0001$; Fig. 1). Data from the validation cohort of Dowsett et al. [21, 22] reveal that high RS is seen in just 10 % of HER2-negative patients, but 57 % of HER2 overexpressing patients. The lower frequency of unfavorable RS results in clinical practice as compared with that seen in validation cohorts may well be accounted for by the exclusion of HER2 overexpressing patients in the commercial use of RS, but their inclusion in original validation studies.

Adjuvant treatment decisions

The decision to give chemotherapy was independently associated with both AOL ($p = 0.03$) and RS ($p < 0.0001$) prognosis (Fig. 2). However, in multivariate analysis, RS was the only significant predictor of the chemotherapy decision. In a model designed to predict chemotherapy utilization, there was no significant increase in the receiver operating characteristic (ROC) when AOL was added to RS (0.84 vs. 0.865, $p = 0.21$). This is consistent with the perception that RS was ordered for the express purpose of facilitating adjuvant treatment decisions, and once available, it drove decision making irrespective of other prognostic factors.

Adjuvant treatment choices *changed* on the basis of the RS for 45 % of patients. Among all patients, 39 % switched to omitting chemotherapy while only 4.5 % switched to receiving chemotherapy (Fig. 3). The change in preference for chemotherapy from 61 % before RS to 26 % after RS was highly significant by McNemar's test ($p < 0.0001$). Following RS, 11 % of patients chose not to receive chemotherapy despite their oncologist's recommendation for it. No patient in our cohort chose to receive chemotherapy against her doctor's recommendation.

In an attempt to identify the specific circumstances in which RS was most likely to alter adjuvant treatment decisions, we re-analyzed the information shown in Fig. 3 after subcategorizing patients on the basis of their predicted prognoses. Using the boundaries defined by RS, nine “prognostic quadrants” were generated by plotting each patient on the basis of both RS and AOL predicted relapse rates (Fig. 4).

As anticipated, patients with low RS (Quadrants G, H, and I) rarely received chemotherapy and those with high RS (Quadrants A, B, and C) always received chemotherapy, irrespective of their prognoses calculated by AOL. Interestingly, when patients had essentially the same favorable prognosis predicted by both AOL and RS (Quadrant G), their chemotherapy was frequently withheld on the basis of RS. Likewise patients with intermediate RS frequently had chemotherapy withheld on the basis of RS when it predicted similar (Quadrant E), or even worse (Quadrant D), prognoses than those predicted by AOL.

The prognostic delta: ($P = AOL_{RR} - RS_{RR}$)

We were surprised to find RS driving decisions to withhold chemotherapy even when it predicted a *less* favorable outcome than AOL. To further investigate this finding, we subtracted the relapse rate reported by RS (RS_{RR}) from that predicted by AOL (AOL_{RR}) for each patient. This difference, the “prognostic delta” (P), allowed us to quantify the degree by which the respective prognoses differed, and to consider changes in management as a function of this difference.

When AOL was fully modified to reflect the same 10-year distant relapse rate as that reported by RS, the prognoses predicted by each of these measures were similar for most patients (Fig. 5a). This difference in prognosis exceeded 10 % (i.e., $|P| > 10\%$) in just 17 % of patients. Importantly, RS did not consistently predict a more (or less) favorable prognosis than AOL as indicated by roughly equal numbers of positive (49 %) and negative (51 %) P values in this analysis. Many patients for whom RS predicted a worse outcome than AOL (indicated by *bars* to left of *dotted line*) are seen to have had chemotherapy withheld on the basis of their RS (*green shaded portion* of *bars*).

To explore the possibility that RS might be perceived to be more favorable than AOL because of the manner in which it is reported, we chose to reevaluate P with AOL not modified to reflect distant only recurrences (Fig. 5b) and also not modified to reflect either distant only recurrences or tamoxifen effect (Fig. 5c). Because these sequential modifications increase AOL relapse rates (and thereby P), RS appears increasingly more favorable than AOL as manifested by progressively increasing P . When viewed from this perspective, the effect of RS in decreasing chemotherapy utilization may also seem more understandable.

Discussion

Not surprisingly, when oncologists ordered the RS for the express purpose of facilitating adjuvant chemotherapy decisions in our cohort, it became the single most important factor driving that decision. Low-RS patients almost uniformly deferred chemotherapy while high-RS patients uniformly received it (Fig. 2). Based on the treating oncologist’s review of each patient’s medical record, this adjuvant treatment decision changed, as compared with what would have been done if the RS were not available, in 39 of our 89 cases (Fig. 3). Importantly, the overwhelming majority of patients who changed their treatment preference on the basis of RS chose to *not* receive chemotherapy. Prior reports have consistently described this same tendency [10, 23, 24] but it remains unclear *why* the RS should have this predominantly unidirectional effect of influencing doctors and patients to forgo adjuvant chemotherapy when they would otherwise have opted for it. Our analysis was undertaken to address this question.

First, we examined the possibility that chemotherapy use may have decreased because RS predicted a more favorable prognosis than that which would otherwise have been appreciated. We used the AOL calculator to estimate conventionally determined prognosis and generated a “ P ” to reflect the difference between it and that determined by RS. When AOL prognosis was calculated to the same 10-year distant only relapse rate as that reported

by RS, we found that RS prognosis varied little from that reported by AOL (Fig. 5a). In fact, chemotherapy was frequently withheld on the basis of RS even when it predicted for a *less* favorable prognosis than that calculated by AOL. We conclude that RS may decrease chemotherapy use on the basis of something other than a *real* improvement in predicted prognosis.

We hypothesized that the RS might often create the perception of an improved prognosis because it reports relapse rates incorporating tamoxifen effects and excluding local recurrences. We performed an exploratory analysis to examine this hypothesis by sequentially “backing out” these effects from the AOL calculation (Fig. 5b, c). When compared with relapse rates not “discounted” in this manner, RS obviously appears numerically more favorable (i.e., P increases). This change in perceived prognosis may represent an important “illusory factor” accounting for the tendency of RS to reduce chemotherapy utilization, especially if it also changes the perception of risk category (i.e., high to intermediate or intermediate to low). Because patients may be less apt to recognize the illusory nature of these differences than their doctors, it is noteworthy that 11 % of patients in our cohort chose not to receive adjuvant chemotherapy on the basis of their RS *against* their oncologists’ recommendations.

For low-RS patients, chemotherapy may have also been withheld because low RS has been reported to predict for lack of adjuvant chemotherapy benefits. If so, it may be important to recognize that this chemo-predictive utility of low RS is based on just one study [3] that used chemotherapy (CMF or MF) that has been shown to be inferior to current second- and third-generation regimens [25, 26] and further compromised by its concurrent administration with adjuvant tamoxifen [27]. Even so, that one study could not exclude an important chemotherapy benefit as it reported 95 % confidence intervals that included the possibility that chemotherapy might reduce recurrence risk by >50 % in low-RS patients. HER2 overexpressing patients, who are known to derive chemotherapy benefits, but rarely have low RS, were also included in that study, calling into question the independent predictive power of RS in a cohort of entirely HER2-negative patients. The fragility of RS’s predictive power is also highlighted by the observation that when the RS was combined with other prognostic factors to *improve* its prognostic precision, the “enhanced RS” was noted to *lose* its predictive utility [28].

Only seven of the 89 patients studied had high RS and all of them received adjuvant chemotherapy, including two whose treatment decisions were changed on the basis of their RS. High RS scores were observed far more frequently in validation cohorts where HER2 overexpressing patients had been uniformly included. Because HER2 is an important component of the RS calculation, our exclusion of HER2 overexpressing tumors represents the most likely explanation for this observed difference and may be seen as another reason why more patients did not choose to receive adjuvant chemotherapy on the basis of their RS.

The exclusion of HER2 overexpressing patients in our series is in keeping with current clinical guidelines for the use of the RS [7, 8], but raises concerns that the RS is now being applied to a population that differs from the one in which it was validated. HER2’s prognostic and predictive significance cannot be underestimated in determining the utility of

RS in validation cohorts [1, 3, 5, 21], especially because these cohorts predate the use of HER2-targeted therapies. Importantly, HER2 overexpressing ER+ tumors may be both *more* responsive to chemotherapy and *less* responsive to hormonal therapies because of the cross-talk between these two receptors [29–31]. In the validation study reported by Goldstein et al. [5], RS had no added prognostic utility over conventional prognostic factors when analysis was restricted to HER2-negative patients. Dowsett et al. [22] re-analyzed the HER2-negative subgroup from their validation cohort and reported that the RS had preserved prognostic utility when hazard ratios were determined by comparing RS's at 50 point increments. We are concerned that a 50-point increment has little practical significance and note that the difference between the highest and lowest RS's amongst the 89 patients studied here was 47 points.

Before adopting adjuvant cancer treatments, oncologists require validation in prospectively randomized studies, but somewhat ironically the RS has been broadly adopted to impact adjuvant treatment choices without prospective validation. TAILORx is a prospective study that has completed accrual, but cannot validate the RS because chemotherapy, rather than the use of the RS itself, is the study variable. Adjuvant chemotherapy will either be shown to be of some benefit or to be of no benefit for intermediate RS patients because those are the only two possible outcomes; but not because the RS will be shown to be an appropriate tool for selecting treatment. The interpretation of TAILORx will be further compromised by the unblinded protocol design which allows patients to reject their randomized treatment assignments in favor of personal preferences, as we observed in our limited experience with 18 TAILORx participants.

Our analysis is limited by this study's retrospective design and relatively small sample size. We took several steps to address these important limitations. First, we accounted for every oncotype test that was ordered in our practice through the specified study endpoint. Second, we confirmed that the observed impact of RS on adjuvant treatment decisions as well as patient demographics and RS subgroup proportions in our series were all consistent with that which has been previously described by others reporting on their experience with RS in clinical practice. Finally, both authors rigorously reviewed every patient medical record and made those records available to treating oncologists at the time of individual interviews when assessing their adjuvant treatment decisions. Despite these important efforts to limit study biases, we recognize that the hypotheses generated by our data should be subject to more robust prospective analyses.

At present, the question remains: "Why does the RS so frequently lead doctors and breast cancer patients to forgo adjuvant chemotherapy?" Somewhat surprisingly, in our experience, the answer to this question is *not* simply that the RS drives this change because it predicts a more favorable prognosis than that which would otherwise have been predicted by conventional prognostic factors. Instead, we suggest that the preponderance of low-RS results coupled with a reliance on the ability of low RS to predict against chemotherapy benefits may represent an important factor driving this decision. The exclusion of HER2+ patients from RS testing in current clinical practice accentuates this preponderance of low-RS results, but also raises questions as to the reliability of the chemo-predictive power of the RS in its current clinical application. Finally, we suggest that the relapse rate reported in

association with RS is numerically reduced in a manner that may not be fully appreciated by doctors and likely, even more so, by patients. Recognition of these and other factors affecting the application of RS is especially important given the current power and scope of the RS in the management of patients with breast cancer.

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Fig. 1.
Distribution of RS categories by cohort

Fig. 2.
Likelihood of receiving adjuvant chemotherapy according to RS category

Fig. 3.
Adjuvant treatment decisions following receipt of recurrence score results

Fig. 4.
 Adjuvant treatment decisions following RS results according to prognostic categories

Fig. 5.

Adjuvant treatment decisions as a function of $P\Delta$. Panels **a**, **b** & **c** differ by the terms in which AOL relapse rates are reported. **a** AOL calculated to 10-year distant only relapse rates after accounting for risk reduction attributable to tamoxifen therapy. **b** AOL calculated to 10-year *local and distant* relapse rates after accounting for risk reduction attributable to tamoxifen. **c** AOL calculated to 10-year *local and distant* relapse rates *without* accounting for risk reduction attributable to tamoxifen

Table 1

Conventional prognostic variables according to RS risk categories

	Low RS < 18 n = 51	Intermediate RS 18–30 n = 31	High RS > 30 n = 7
Age ($p = 0.14$)			
50	16	14	1
51–60	11	10	3
> 60	24	7	3
Histology ($p = 0.73$)			
Ductal	39	27	7
Lobular	8	3	0
Other	4	1	0
Tumor size ($p = 0.05$)			
1.0 cm	12	13	0
1.1–2.0 cm	27	14	3
2.1 cm	12	4	4
Tumor grade ^a ($p < 0.01$)			
1	19	8	0
2	29	17	2
3	1	5	5
Sentinel LN IHC ^b stain ($p = 0.99$)			
Not positive	45	27	7
Positive	6	4	0
AOL ^c ($p = 0.02$)			
Low	23	16	0
Intermediate	26	14	4
High	2	1	3

^aTumor grade was not specified for three patients^bCytokeratin staining by immunohistochemistry of sentinel lymph node^cAOL prognostic categories reflect the same 10 year, distant only relapse rates with tamoxifen effect as that defined by RS risk groups

Low risk <10 %, intermediate risk 10–20 %, high risk >20 %