Original Article

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Financial De-Escalation in T1 Breast Cancers With the Low Magee Equation: An Experience From A Single Institution Without Genomic Testing

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ABSTRACT

Objective: The Oncotype Dx® assay is a validated tool for determining prognosis and predicting benefit from adjuvant systemic chemotherapy in patients with node-negative, early-stage hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER-2)-negative breast cancer. However, genomic testing could incur additional costs, impacting both the patient and the health system. This study aims to explore a subset of patients with a Magee equation score ≤18 who may safely forgo Oncotype Dx® testing.

Materials and Methods: Single institution retrospective analysis of postmenopausal patients with *de novo*, unifocal breast carcinoma that is node negative, Nottingham grade 1, T1, HR positive (>1%), and HER-2 negative. Magee equation 2 (ME2) (https://path.upmc.edu/onlineTools/mageeequations.html) scores were calculated for each patient. The correlation coefficient between Oncotype Dx® and ME2 was determined.

Results: Oncotype Dx® recurrence score, treatment, and outcomes were analyzed in 126 post-menopausal women diagnosed between 2015 and 2020. The mean tumor size was 1.09 cm, and the mean Oncotype DX® score was 12. The average ME2 score was 13.6. The correlation coefficient between Oncotype and ME2 score was statistically significant (r = 0.3442; p<0.0001). At a median follow-up of 5.03 years, there were no local or distant recurrences or breast cancer-related deaths reported in this patient cohort.

Conclusion: This study suggests that omitting the Oncotype Dx® assay may be feasible in postmenopausal women with early breast cancer and an ME2 score ≤18. Using comparable tools, such as ME2, may reduce financial toxicity in this population and overall costs to the system. Larger study recommended.

Keywords: Breast cancer; cost-effectiveness; hormone receptor-positive; Magee equations (TM); Oncotype Dx

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Key Points

- In this retrospective study of 126 postmenopausal women with grade 1, estrogen receptor-positive, human epidermal growth factor receptor-2-negative, node-negative breast cancer, all patients had low-risk Oncotype DX® recurrence scores (<26).
- Magee equation 2 (ME2) scores correlated significantly with Oncotype DX® results (r = 0.34, p<0.0001).
- Findings support the use of ME2 as a cost-effective alternative to Oncotype DX® testing in this low-risk population.

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Introduction

Adjuvant systemic treatment decisions for early-stage, hormone receptor-positive, node-negative breast cancer (BC) have historically been based on clinicopathologic features such as tumor size, tumor grade, axillary lymph node involvement, and hormone receptor status (1). These factors provide prognostic information regarding the risk of BC (1). Most recently, the incorporation of genomic testing, such as the Oncotype DX® 21-gene recurrence score (RS) assay (Genomic Health, Redwood City, CA), has helped guide treatment recommendations by providing predictive information regarding the potential benefit of adjuvant chemotherapy (2). The prospective Trial Assigning Individualized Options for Treatment (TAILORx) demonstrated that postmenopausal women (aged 50 years and older) with hormone receptor-positive, HER2-negative, axillary node-negative BC, and a 21-gene assay score of 25 or lower may safely omit chemotherapy (3).

Economic models have demonstrated the cost-saving benefits of gene expression assays, such as Oncotype DX®, in early-stage BC because they can help identify patients with low genomic risk who may forgo chemotherapy (1). Consequently, Oncotype DX® has become widely used and is frequently requested by providers to assist in adjuvant treatment decision-making. However, the validation and cost-effectiveness analyses of Oncotype DX® have largely been conducted in patient populations with varying clinicopathologic features and age groups (4, 5). Given that certain postmenopausal women with low-risk clinicopathologic features, such as grade 1 tumors, already achieve an excellent five-year survival rate of nearly 99% with endocrine therapy alone, it remains uncertain whether genomic testing is truly necessary for this subset of patients.

Additionally, both internal and external studies have demonstrated that alternative testing methods, such as the Magee equations (ME), can serve as a cost-effective substitute for the Oncotype DX® RS. The ME are mathematical formulas developed to estimate the Oncotype DX® RS using histopathologic features—including tumor grade, mitotic score, and hormone receptor intensity—and to identify patients who may not require genomic testing (6).

There are three ME: ME1 incorporates the Nottingham score, tumor size, and results for estrogen receptor (ER), progesteron receptor (PR), human epidermal growth factor receptor-2 (HER-2), and Ki-67; ME2 excludes Ki-67; and ME3 uses only ER, PR, HER-2, and Ki-67. A prospective validation study found that patients with an ME score below 25 and a mitotic score of 1 did not require Oncotype DX® testing, resulting in an estimated cost savings of $280,000 per 100 clinical requests (7). Therefore, this study aims to identify a subset of patients who may not require Oncotype DX® testing and to evaluate the potential use of the ME within our institutional cohort.

Materials and Methods

This was a single-institution retrospective analysis of postmenopausal patients with early-stage, ER-positive, HER-2-negative, lymph-node-negative BC whose tumors were classified as Nottingham Histologic Overall grade 1. Only patients with primary breast tumors measuring between 5 mm and 20 mm (American Joint Committee on Cancer 7th edition anatomic stage T1b–T1c) and who had an available Oncotype DX® score were included. Patient data were obtained from the University of Pittsburgh Medical Center Cancer Registry. Postmenopausal status was defined in women as those aged 50 years or older, consistent with the criteria used in the TAILORx study (3). Tumor grading was determined by our pathology department using the Nottingham Histologic score.

Clinicopathologic data obtained included tumor size, lymph node status, hormone receptor staining intensity, Nottingham Histologic score, and Ki-67. Patient demographics and clinical outcomes, including current disease status, were also recorded.

The ME was calculated for each patient using ME2 based on pathology report data, including ER/PR percentage, staining intensity, Nottingham score, and tumor size. In our study, not all patients had an available Ki-67 percentage; therefore, only ME2 was used (https://path.upmc.edu/onlineTools/mageeequations.html). A correlation coefficient was then calculated between the Oncotype DX® RSe and the ME2 score for each patient. This retrospective study was approved by the UPMC Central PA Region Institutional Review Board (approval date: 29.06.2022; decision no: 22E025).

Statistical Analysis

Continuous variables, such as follow-up duration (in days), were reported as the median and interquartile range. The linear correlation between the ME2 score and Oncotype DX® RS was assessed using the Pearson correlation coefficient (r). A p-value of <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 126 postmenopausal women seen between 2015 and 2020 met our selection criteria and were included in the analysis. The mean age was 64.4 years (range: 51–85 years). The median tumor size was 1.09 cm (range: 0.2–2 cm). Patient demographics and tumor characteristics are summarized in Table 1.

The majority of patients underwent partial mastectomies (n=109; 87%), and sentinel lymph node biopsy (SLNB) was performed in 120 patients (95%). After a shared discussion with their surgeons, six patients (age range 71–78; RS range 7–18; ME2 range 7.76–13.84) did not undergo SLNB, in accordance with the American Society of Breast Surgeons' Choosing Wisely Campaign.

Thirty-five patients (28%) did not undergo adjuvant radiotherapy. Of those, 17 patients underwent a total mastectomy; therefore, radiation was not indicated. Eighteen patients underwent partial mastectomies but declined adjuvant radiation. Of those, twelve patients were aged 70–85 years (RS range 3–22; ME2 range 5.42–17.61). Six patients (age range 51–69; RS 11–21; ME2 range 11.12–18.41) declined radiation after it was recommended. Adjuvant endocrine therapy was recommended to all the patients. However, 17% of the patients (*n* = 21; age range 55–78; RS 0–25; ME2, 7.86–24.01) either declined endocrine therapy after discussion or discontinued it due to side effects.

The median follow-up period was 5.03 years (range, 3.88–6.82 years), and no local or distant recurrences or BC-related deaths were observed in this patient cohort. The average Oncotype DX® RS was 12.4 [range: 0–25, standard deviation (SD) = 0.41] and no patients had scores greater than 25. The average ME2 score was 13.6 (range: 5.42–24.01, SD: 4.1), and no patients had an ME2 score above 25. Oncotype DX® RS was <18 in 106 (84%) patients, and ME2 was <18 in 114 (90%) patients. A correlation coefficient of 0.3442 was calculated between the Oncotype DX® RS and ME2 scores, with a statistically significant *p*-value of <0.0001 (Figure 1).

Table 1. Patients' clinic-pathologic characteristics, treatment, and recurrence scores

	Tumor ≤5 mm, T1a (*n* = 4) (%)	Tumor >5 -≤10 mm, T1b (*n* = 64) (%)	Tumor >10-≤20 mm, T1c (*n* = 58) (%)	Recurrence score ≤18 (%)	ME2 score ≤18 (%)
Age (years)	64.3	64.5	64.2		
(Average, range)	(58-69)	(53-78)	(51-85)		
Tumor size average (mm)	5	7.9	14.5		
(± standard)	0	0.16	0.31		
(Range)	(5 to 5)	(5 to 11)	(10 to 20)		
Estrogen receptor status					
Positive	4 (100)	64 (100)	58 (100)		
ER H score average	293	281	278		
Progesterone receptor status					
Positive	4 (100)	61 (96)	56 (97)		
Negative (<1%)	0 (0)	3 (4)	2 (3)		
PR H score average	105	196	278		
Histologic features					
Presence of LVI	0	1 (1)	0		
Presence of PNI	0	0	5 (8)		
Partial mastectomy	4 (100)	53 (83)	52 (90)	92 (84)	99 (87)
Mastectomy	0 (0)	11 (17)	6 (10)	17 (16)	15 (13)
Sentinel lymph node biopsy					
Yes	4 (100)	59 (92)	57 (98)	100 (94)	108 (95)
Omitted	0 (0)	5 (8)	1 (2)	6 (6)	6 (5)
Radiation					
Whole breast	4 (100)	39 (61)	44 (76)	74 (70)	78 (68)
Partial breast	0 (0)	3 (5)	1 (2)	4 (4)	3 (3)
Omitted	0 (0)	22 (34)	13 (22)	28 (26)	33 (29)
Endocrine therapy					
Yes	3 (75)	48 (75)	54 (93)	93 (88)	99 (87)
Omitted	1 (25)	16 (25)	4 (7)	13 (12)	15 (13)

ME2: Magee equation 2; LVI: Lymphovascular invasion; PNI: Perineural invasion; ER: Estrogen receptor; PR: Progesteron receptor

Discussion and Conclusion

Treatment decisions for early-stage, hormone receptor-positive, node-negative BCs have largely relied on the Oncotype DX® RS assay. However, our results suggest that the ME2 may serve as an effective alternative for grade 1 tumors, in which the average Oncotype DX® RS was 12 and the highest RS score in our cohort remained below 26. Our findings demonstrated a statistically significant correlation between a low Oncotype DX® RS and the ME2, although the magnitude of the correlation was modest.

Previous studies have validated the relationship between the ME and the Oncotype DX® RS assay. The original ME was first tested in 2006 in 42 cases with available Oncotype DX® RS results and found to correlate with tumor nuclear grade, mitotic activity, HER2 status, ER, and PR scores (6). Subsequent studies, conducted between 2004 and 2009, further refined the ME using additional cases and ultimately validated their predictive accuracy (6). While the Oncotype DX® RS assay remains a valuable tool for guiding adjuvant chemotherapy decisions, its high cost and overlap with the ME may limit its role in treatment decisions for low-grade BC (8). As our study demonstrates, ME may allow clinicians to omit Oncotype DX® testing, providing a more cost-effective approach to treatment decision-making for grade 1 tumors.

According to Bhargava et al. (7), Oncotype DX® RS testing can be omitted when ME scores are below 18 or above 31. For scores between 18 and 25, testing can be avoided if the mitotic score is 1 because the expected RS would be less than 25. In our cohort, all patients had a mitotic score of 1, and none had an RS above 25, further supporting the omission of Oncotype DX® testing in these patients. The correlation coefficient between Oncotype DX and ME was $r = 0.3442$ ($p<0.0001$), indicating statistical significance.

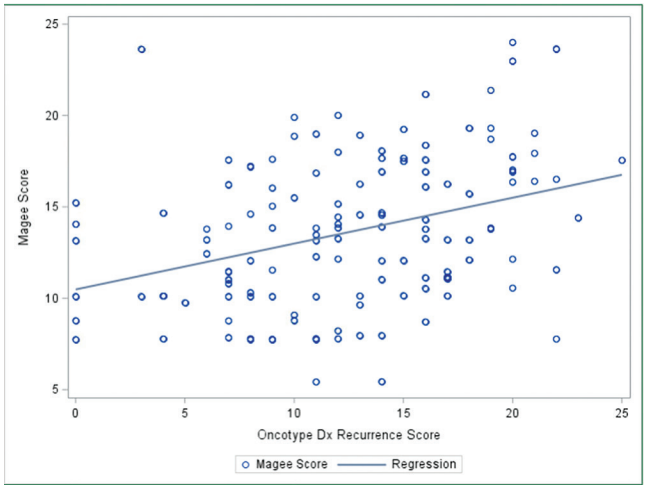

Figure 1. Correlation between Magee equation 2 and Oncotype DX® recurrence score. The Pearson correlation coefficient (r = 0.34; p<0.001) demonstrates a statistically significant but modest positive association

Given these findings, Oncotype DX® RS testing may be selectively deferred in this low-risk patient population based on the ME2 score, resulting in potential cost savings. An average cost of approximately $4,600 per Oncotype DX® RS test represents a substantial financial burden when broadly applied. Therefore, eliminating unnecessary testing could provide a substantial economic benefit. In our patient cohort, the potential cost savings to the health system would be $579,600 if only ME2 scores were used. Additionally, a cost analysis by Reed et al. (9) found that patients who did not undergo Oncotype DX® RS testing had lifetime medical costs $2,692 lower than those who did. Recent budget-impact analyses have similarly shown that Oncotype DX® RS testing is associated with significant health-system costs, with an incremental budget impact of $261,067 for node-negative disease and $56,143 for node-positive disease over 5 years, despite cost offsets from reduced recurrence and chemotherapy use (10). Therefore, an additional $338,192 may be saved in lifetime medical costs for our patient cohort.

Study Limitations

Our study has several limitations. First, given the subjectiveness of histologic grading, there may be a limitation of concordance and interrater reliability amongst various pathologists reviewing pathology samples. Second, most patients lacked Ki-67 data, limiting us to using ME2 to calculate the Magee score. Third, two patients in our cohort were treated in early 2015, before the publication of the TAILORX trial results. If evaluated today, they might not be recommended for chemotherapy. In addition, although Pearson correlation was used to evaluate the association between ME2 and Oncotype DX RS, more comprehensive approaches such as regression or agreement analyses should be applied in larger, multicenter studies to further validate this relationship. Furthermore, because late recurrences may occur in hormone receptor-positive BC, our median follow-up may underestimate long-term recurrence rates.

Several studies have evaluated the omission of radiotherapy in selected patients with low-risk early-stage BC. In a recent prospective IDEA trial, postmenopausal women aged 50–69 years with T1N0, ER(+), PR(+), HER-2(-) BC and Oncotype DX RS ≤18 who underwent partial mastectomy followed by endocrine therapy without radiation were evaluated. At 5 years, recurrence-free survival was 99% (95% confidence interval, 96 to 100) (11). In our study, approximately 10% of patients who underwent partial mastectomy declined radiation. None of these patients developed local or systemic recurrence at the time of follow-up. The role of ME2 in predicting benefit from radiation and endocrine therapy should be explored in future studies.

Our findings suggest that Oncotype DX® RS testing may be omitted in selected postmenopausal women with low-grade, ER-positive, HER2-negative, node-negative BC. Instead, the ME may provide a cost-effective and equally reliable alternative for guiding chemotherapy decisions in this patient population.

Ethics

Ethics Committee Approval: This retrospective study was approved by the UPMC Central PA Region Institutional Review Board (approval date: 29.06.2022; decision no: 22E025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.B, K.L., Y.W., A.S.; Concept: K.B, K.L., Y.W., A.S.; Design: K.B, K.L., Y.W., A.S.; Data Collection or Processing: F.S., B.D., C.E.L., M.S., K.L.; Analysis or Interpretation: F.S., B.D., K.B, C.E.L., M.S., K.L., Y.W., A.S.; Literature Search: C.E.L., M.S., K.L., Y.W., A.S.; Writing: F.S., B.D., K.B, C.E.L., M.S., K.L., Y.W., A.S.

Conflict of Interest: Atilla Soran MD is section editor in European Journal of Breast Health. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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