Modern Pathology (2021) 34:77–84
https://doi.org/10.1038/s41379-020-0620-2

ARTICLE

Magee Equations™ and response to neoadjuvant chemotherapy in ER+/HER2-negative breast cancer: a multi-institutional study

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Received: 20 May 2020 / Accepted: 29 June 2020 / Published online: 13 July 2020

Abstract

Magee Equations™ (ME) are multivariable models that can estimate onco*type* DX® recurrence score. One of the equations, Magee Equation 3 (ME3) which utilizes only semi-quantitative receptor results has been shown to provide chemopredictive value in the neoadjuvant setting in a single institutional study. This multi-institutional study (seven institutions contributed cases) was undertaken to examine the validity of ME3 in predicting response to neoadjuvant chemotherapy in estrogen receptor positive, HER2-negative breast cancers. Stage IV cases were excluded. The primary endpoint was the pathologic complete response (pCR) rate in different categories of ME3 scores calculated based on receptor results in the pre-therapy core biopsy. A total of 166 cases met the inclusion criteria. The patient age ranged from 24 to 83 years (median 53 years). The average pre-therapy tumor size was 3.9 cm, and axillary lymph nodes were confirmed positive by pre-therapy core biopsy in 85 of 166 cases (51%). The pCR rate according to ME3 scores was 0% (0 of 64) in ME3 < 18, 0% (0 of 46) in ME3 18–25, 14% (3 of 21) in ME3 > 25 to <31, and 40% (14 of 35) in ME3 score 31 or higher (p value: <0.0001). There were no distant recurrences and no deaths in the 17 patients with pCR. In the remaining 149 cases with residual disease, ME3 score of >25 was significantly associated with shorter distant recurrence-free survival and showed a trend for shorter breast cancer-specific survival. The results of this multi-institutional study are similar to previously published data from a single institution (PMID: 28548119) and confirm the chemo-predictive value of ME3 in the neoadjuvant setting. In addition, ME3 may provide prognostic information in patients with residual disease which should be further evaluated.

Introduction

Breast cancer is treated with multimodality therapy including surgery, radiation, and systemic therapy. Systemic therapy can be in the form of hormonal therapy (offered to almost all patients with hormone receptor-positive tumors) and/or chemotherapy. The latter is offered to patients with hormone receptor-negative tumors and a subset of patients with hormone receptor-positive tumors. Clinical trials have shown that the timing of chemotherapy, whether given after surgery (adjuvant) or prior to surgery (neoadjuvant), does not affect survival [1]. Consequently, the use of neoadjuvant chemotherapy increased significantly in the past decade. It is no longer reserved for unresectable tumors and is frequently used in early-stage breast cancer. However, the decision to use chemotherapy in estrogen receptor-positive tumors is complicated. Although systemic therapy decisions can be judiciously made using data in pathology reports, medical oncologists frequently use

Findings presented in part at the United States and Canadian Academy of Pathology, February 29-March 5, 2020.

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multigene assays for making systemic therapy decisions in the adjuvant setting. Similar principles are applied in the neoadjuvant setting; but due to limited tissue availability, limited time to make decisions, and insurance issues, neoadjuvant chemotherapy decisions are often made without molecular testing.

It has been previously shown that multivariable models known as Magee Equations (MEs) may be used in lieu of molecular testing [2–4]. MEs are multivariable models that were developed to estimate the onco*type* DX® recurrence score. These equations were first published as a "proof of principle" and later modified and validated on an independent dataset [3, 4]. The three new equations (commonly known as MEs) can be calculated using a free online calculator (https://path.upmc.edu/onlineTools/mageeequations.html). ME1 utilizes tumors size, Nottingham score, estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 data. ME2 utilizes similar data as ME1 except for Ki-67. ME3 utilizes only ER, PR, HER2, and Ki-67 semi-quantitative results for the calculation. The last equation (ME3) is easier to use in the neoadjuvant setting as pathologic tumor size and Nottingham scores are generally not available or reliable at the time of pre-therapy core biopsy. In a neoadjuvant study from Magee, pathologic complete response (pCR) was mainly seen in patients with ME3 score of 31 or higher (36% pCR rate) [2]. The pCR rate was 4% in cases with ME3 score 18 to <31 and 0% in cases with ME3 score <18. Although this was a large retrospective study, it was limited to one institution and doubts remained regarding the applicability of MEs outside of Magee-Womens Hospital.

The current study was designed to determine if ME3 is predictive of response to neoadjuvant chemotherapy in ER positive, HER2-negative tumors when the equation is used outside of Magee-Womens Hospital.

Methods

This multi-institutional study was undertaken to examine the validity of ME3 in predicting response to neoadjuvant chemotherapy in ER+, HER2-negative (including HER2 immunohistochemical 2+ cases with 4 to <6 HER2 copies per cell by in-situ hybridization) breast cancers. The study was limited to stage I–III cases diagnosed in the year 2010 to 2014 for homogeneity of treatment and to facilitate comparison to the original Magee study from the same time period [2]. The following patients were excluded: patients treated with neoadjuvant hormonal therapy alone, patients who had undergone excision biopsy of the tumor before chemotherapy (not true neoadjuvant cases), HER2 positive cases, triple-negative cases, and stage IV or metastatic (M1) disease at presentation. Several institutions were contacted for participation in the multi-institutional study by one author (RB). After their desire to participate, each institution got Institutional Board Approval at their institutions. Magee-Womens Hospital remained the data coordinating center. Data use agreements were signed between Magee and all other institutions. The data obtained at each institution was securely transferred to Magee for compilation and analysis. The primary endpoint was the pCR rate in different categories of ME3 scores calculated based on receptor results in the pre-therapy core biopsy. Therefore, the minimal criteria for case inclusion were the availability of semi-quantitative receptor results on the pre-therapy core biopsy specimen and information regarding pCR on the resection specimen. Pathologic complete response was defined as the absence of invasive carcinoma in the breast surgical resection specimen and the absence of carcinoma in regional lymph nodes and a lack of tumor in lymphovascular spaces. The presence of residual ductal carcinoma in-situ was allowed. The secondary goals were to examine pCR rate with respect to other MEs (Equations 1 and 2) and tumor grade based on available data. Since MEs 1 and 2 require tumor size and Nottingham score in addition to semi-quantitative receptor results for calculation, ME1 and ME2 scores were not available on all cases. For cases with residual disease, residual cancer burden (RCB) score/category (whenever available) was correlated with ME3 scores.

Univariable analysis was performed using the Fisher's exact test to compare the differences in percentages between groups and *t* test to compare means. A p value <0.05 was considered significant. Kaplan–Meier survival curves for recurrence-free survival, distant recurrence-free survival, overall survival, and breast cancer-specific survival in patients with the residual disease were analyzed with respect to ME3 cut-off value of 25 and the p values were obtained using Gehan–Breslow–Wilcoxon test (GraphPad Prism software, version 8.3.0, San Diego, CA).

Results

Seven institutions were able to contribute cases. A total of 166 cases met the inclusion criteria. The patient age ranged from 24 to 83 years (median 53 years) with 75 patients (45%) aged 50 years or younger. The average pre-therapy tumor size was 3.9 cm, and axillary lymph nodes were confirmed positive by pre-therapy core biopsy in 85 of 166 cases (51%) indicating the inclusion of locally advanced cases in this cohort. Of the 166 cases, 137 (83%) were ductal, 23 (14%) lobular, 6 (3%) mixed, and other subtypes. The pre-therapy tumor grade was grade I in 20 (12%), grade II in 89 (54%), and grade III in 57 cases (34%). Exact neoadjuvant regimen and number of cycles slightly varied but most patients (145 of 166 or 83%) received the standard

Table 1 Pathologic complete response (pCR) rates with respect to MEs and grade.

Variables	Pathologic complete response	*P* value
Magee Equation 3 (ME3)		
ME3 < 18	0/64 (0%)	Reference
ME3 18–25	0/46 (0%)	1.000
ME3 >25 to <31	3/21 (14%)	0.0135
ME3 31 or higher	14/35 (40%)	<0.0001
Magee Equation 2 (ME2)		
ME2 < 18	0/45 (0%)	Reference
ME2 18–25	2/58 (3%)	0.5031
ME2 > 25 to <31	1/22 (5%)	0.3284
ME2 31 or higher	13/34 (38%)	<0.0001
Magee Equation 1 (ME1)		
ME1 < 18	0/43 (0%)	Reference
ME1 18–25	0/41 (0%)	1.000
ME1 > 25 to <31	2/35 (6%)	0.1981
ME1 31 or higher	14/40 (35%)	<0.0001
Nottingham grade		
Grade I	1/20 (5%)	Reference
Grade II	3/89 (3%)	0.5611
Grade III	13/57 (23%)	0.0982; I and II v/s III: 0.0002

Total cases: 166; ME1 and ME2 available on 159 cases.

"ACT" regimen (Adriamycin, Cyclophosphamide, Taxane). Since these were all ER+ cases, post-surgery endocrine therapy was administered-tamoxifen only in 48 cases (29%), non-tamoxifen therapy or tamoxifen plus an aromatase inhibitor in 102 cases (61%). The type of endocrine therapy was unknown in 16 cases (10%)

The pCR was seen only in tumors with ME3 scores >25, with the highest pCR rate in tumors with ME3 score 31 or higher (Table 1). The pCR rate was not different in patients 50 years and younger ($n = 75$) when determined by ME3 scores (0% pCR in scores <18, 0% in 18–25, 11% in >25 to <31, and 27% in 31 or higher; p value: 0.0092). Other MEs (ME1 and ME2) were also evaluated in 159 of 166 cases which showed similar results as ME3 (Table 1). Pre-therapy tumor Nottingham grade was also predictive of chemotherapy response (pCR in grade I: 1/20 [5%]; grade II: 3/89 [3%]; grade III: 13/57 [23%]; p value I and II versus III: 0.0002); however, of all the equations and the tumor grade, the separation of categories was best seen with ME3 (Table 1).

As expected, the individual components of Magee Equation 3 were significantly different between cases that showed pCR and cases with residual disease. The average ER H-score was 227 for cases without pCR and 52 for cases with pCR (p value <0.0001). The average PR H-score was 125 for cases without pCR and 13 for cases with pCR (p value <0.0001). The mean Ki-67 labeling index was 27% for cases without pCR and 68% for cases with pCR (p value <0.0001). Although most cases with pCR had high proliferation index, it is important to note that many cases with high proliferation index failed to achieve pCR. The cases with highest likelihood for achieving pCR had high proliferation index coupled with lower ER and PR H-scores (i.e. high ME3 score).

Table 2 Magee Equation 3 (ME3) versus Nottingham Grade as predictor of pathologic complete response (pCR).

Categorization by	Subdivision by	*N*	pCR *N* (%)	*P* value
Magee Equation 3 scores	Nottingham grade			
High (score > 25)	I/II	21	4 (19%)	0.2313
	III	35	13 (37%)	
Low (score ≤ 25)	I/II	88	0 (0%)	NA
	III	22	0 (0%)	
Nottingham grade	Magee Equation 3 scores			
I/II	High (score > 25)	21	4 (19%)	0.0020
	Low (score ≤ 25)	88	0 (0%)	
III	High (score > 25)	35	13 (37%)	0.0064
	Low (score ≤ 25)	22	0 (0%)	

pCR Pathologic complete response, *NA* not applicable.

Due to the significant association of pre-therapy Nottingham grade 3 with pCR, we analyzed if Nottingham grade provides additional information beyond what is provided by ME3 alone and vice versa. When cases were categorized by ME3 categories, further division by Nottingham grade did not show significantly different pCR rates (Table 2). However; when cases were categorized according to Nottingham grade, further divisions into ME3 categories showed significantly different pCR rates (Table 2).

There were no distant recurrences and no deaths in the 17 patients with pCR. Only one of 17 pCR patients experienced local recurrence. In the remaining 149 cases with residual disease, there were 43 (29%) recurrences, of which 6 were loco-regional only and 37 were distant or both distant and local. The average time to recurrence was 35 months. Of the 149 patients with residual disease, 23 died (15%). ME3 score of >25 was significantly associated with shorter recurrence-free survival (p value: 0.0274) shorter distant recurrence-free survival (p value: 0.0179) and showed a trend for shorter overall survival (p value: 0.0672) and shorter breast cancer-specific survival (p value: 0.0574) (Fig. 1).

RCB class was available in 112 cases, of which 17 were RCB-0 (pCR), 2 RCB-I (minimal residual disease), 68 RCB-II and 28 RCB-III. As mentioned there were no distant

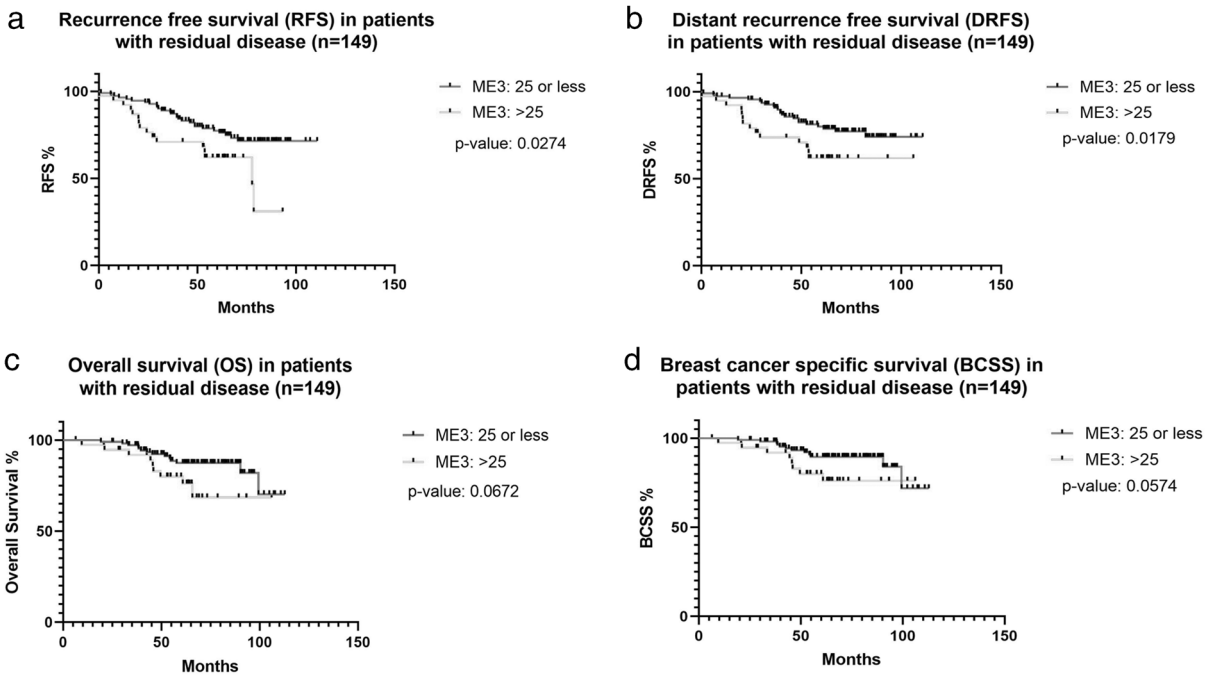

Fig. 1 Kaplan–Meier survival curves in patients with residual disease after therapy ($N = 149$) with respect to Magee Equation 3 (ME3) scores ($N = 110$ for ME3 ≤ 25 and $N = 39$ for ME3 > 25). a Recurrence free survival (RFS) in patients with residual disease ($n = 149$). **b** Distant recurrence free survival (DRFS) in patients with residual disease ($n = 149$). **c** Overall survival (OS) in patients with residual disease ($n = 149$). **d** Breast cancer-specific survival (BCSS) in patients with residual disease ($n = 149$).

recurrences and no deaths in 17 pCR cases. The two patients with RCB-I also did not experience distant recurrence or death. Although recurrences and deaths were higher in RCB-III compared to RCB-II, differences in survival (RFS, DRFS, OS, BCSS) did not reach statistical significance. ME3 (using score cut-off of 25) did not separate cases with better or worse survival within the RCB-II class. However, within RCB-III class, patients with low ME3 scores (25 or less) had significantly better survival compared to patients with a high ME3 score (>25) (Fig. 2). Since RCB class is strongly influenced by the post-therapy nodal status (which was available in 144 of 149 cases with the residual disease), we also examined the relationship between ME3 scores and post-therapy nodal status in determining prognosis. The lowest recurrence and deaths were seen in patients with negative post-therapy nodes and ME3 score ≤25 and the highest recurrence and death in patients with positive nodal status and ME3 score >25 (Table 3).

Discussion

The last two decades have seen a meteoric rise of gene expression based assays in clinical use for breast cancer management. Developed as prognostic assays, these are now frequently used as predictive assays, especially in the management of ER+/HER2-negative breast cancer [5–11]. One of the most commonly used commercial assays is onco*type* DX® which is frequently used in the adjuvant setting in ER+/HER2-negative, lymph node-negative cases to make chemotherapy decisions [9, 12]. Recently, a prospective clinical trial, TAILORx (**T**rial **A**ssigning Individua**L**ized **O**ptions for **T**reatment) showed that there is a lack of chemotherapy benefit in patients with recurrence score 11–25 [13]. However, oncotype and other similar assays are expensive and subject to inconsistent reimbursement in the pre-operative setting, and may result a delay in initiating care due to extended turnaround times. Moreover, the molecular assays may be unavailable/unaffordable in resource-poor locations and are sometimes subject to inaccurate results due to sub-optimal microdissection. A readily available alternative to such multigene assays is MEs (an example is shown in Fig. 3), a multivariable model that utilizes routinely reported histopathologic and immunohistochemical data from pathology reports to estimate the onco*type* DX® score [3, 4]. This concept was first published in 2008 and further improvised and validated in 2013 [3, 4]. Recently, an algorithmic approach called Magee Decision Algorithm™ has been described that can be used to safely forgo onco*type* DX® testing [14, 15]. A prior single-institution study showed strong predictive value of ME3 in the neoadjuvant setting as a standalone test [2].

The purpose of the current study was to evaluate the predictive value of ME3 outside of Magee-Womens

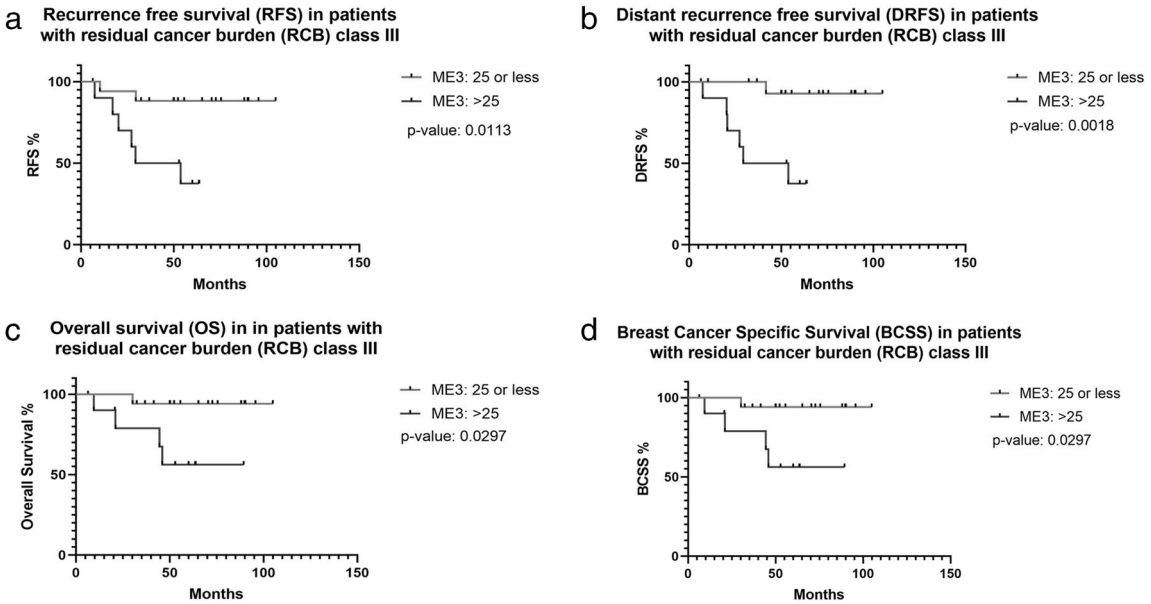

Fig. 2 Kaplan–Meier survival curves in patients with residual cancer burden (RCB) class III ($N = 28$) sub-divided according to Magee Equation 3 (ME3) scores ($N = 17$ for ME3 ≤ 25 and $N = 11$ for ME3 > 25). **a** Recurrence free survival (RFS) in patients with residual cancer burden (RCB) class III. **b** Distant recurrence free survival (DRFS) in patients with residual cancer burden (RCB) class III. **c** Overall survival (OS) in patients with residual cancer burden (RCB) class III. **d** Breast cancer-specific survival (BCSS) in patients with residual cancer burden (RCB) class III.

Table 3 Association of post-therapy lymph node status and Magee Equation 3 (ME3) scores with recurrence and death in patients with residual disease ($n = 149$).

Nodal status and ME3	*N*	Recurrence	Death
Node negative	57	12 (21%)	7 (12%)
ME3 < 25	42	8 (19%)	5 (12%)
ME3 > 25	15	4 (27%)	2 (13%)
Node positive	87	28 (32%)	13 (15%)
ME3 < 25	64	17 (27%)	7 (11%)
ME3 > 25	23	11 (48%)	6 (26%)

Post-therapy lymph node status unknown/unclear on five cases.

Hospital. ME3 utilizes results available in standard core biopsy pathology reports, including semi-quantitative results for ER, PR, HER2, and Ki-67, to determine chemotherapy effectiveness. Seven different institutions participated in this study. Stringent inclusion/exclusion criteria allowed this multi-institutional study results to be compared to the prior Magee study. Pathologic complete response rate after standard neoadjuvant chemotherapy in this ER+/HER2-negative cohort was limited to tumors with pre-therapy ME3 scores >25. The highest pCR rate was seen in tumors with ME3 scores 31 or higher. These results are remarkable and very similar to the previous single-institution Magee study [2]. These results are also concordant with the small number of prior studies of oncotype and other molecular assays in the neoadjuvant setting. Yardley et al. studied the pCR rate after neoadjuvant treatment with ixabepilone and cyclophosphamide with respect to the onco*type* DX® recurrence score [16]. Of the 60 ER+/HER2-negative cases, pCR was identified in 17% (4 of 24 cases) of the patients with high-risk recurrence scores and 0% (0 of 36 cases) in patients with low/intermediate-risk scores [16]. In an older study, Gianni et al. studied 89 patients neoadjuvantly treated with paclitaxel and doxorubicin and reported a pCR rate of 12% (11 cases) [17]. The pCR rate in ER-negative patients was 23% and in the ER+ patients was 8%. Although response according to recurrence score categories was not reported, pCR was associated with higher expression of proliferation-related genes, and lower expression of ER-related genes, i.e, the genes that determine the likelihood of high recurrence score [17]. In phase II NEONAB trial (neoadjuvant treatment with epirubicin, cyclophosphamide, and nab-paclitaxel), Murphy et al. reported pCR in 3 of 10 (30%) high-risk (score > 25) oncotype cases [18]. In the largest study to date, Pease et al. reported the pCR rate on 989 cases with onco*type* DX® scores from the National Cancer Database. Pathologic complete response was identified in 2.2% (5/227) within the low-risk category (scores < 18); 1.6% (7/450) in the intermediate category (score 18–30); and 9.6% (30/312) within the high-risk category (scores 31 or higher) [19]. For MammaPrint® assay, pCR has been reported in 2–3% of MammaPrint low risk and 11–13% in MammaPrint high risk [20, 21]. The similar BluePrint® assay has been reported to show a pCR rate of 6–7% for luminal A tumors compared to 9–10% for luminal B [22, 23].

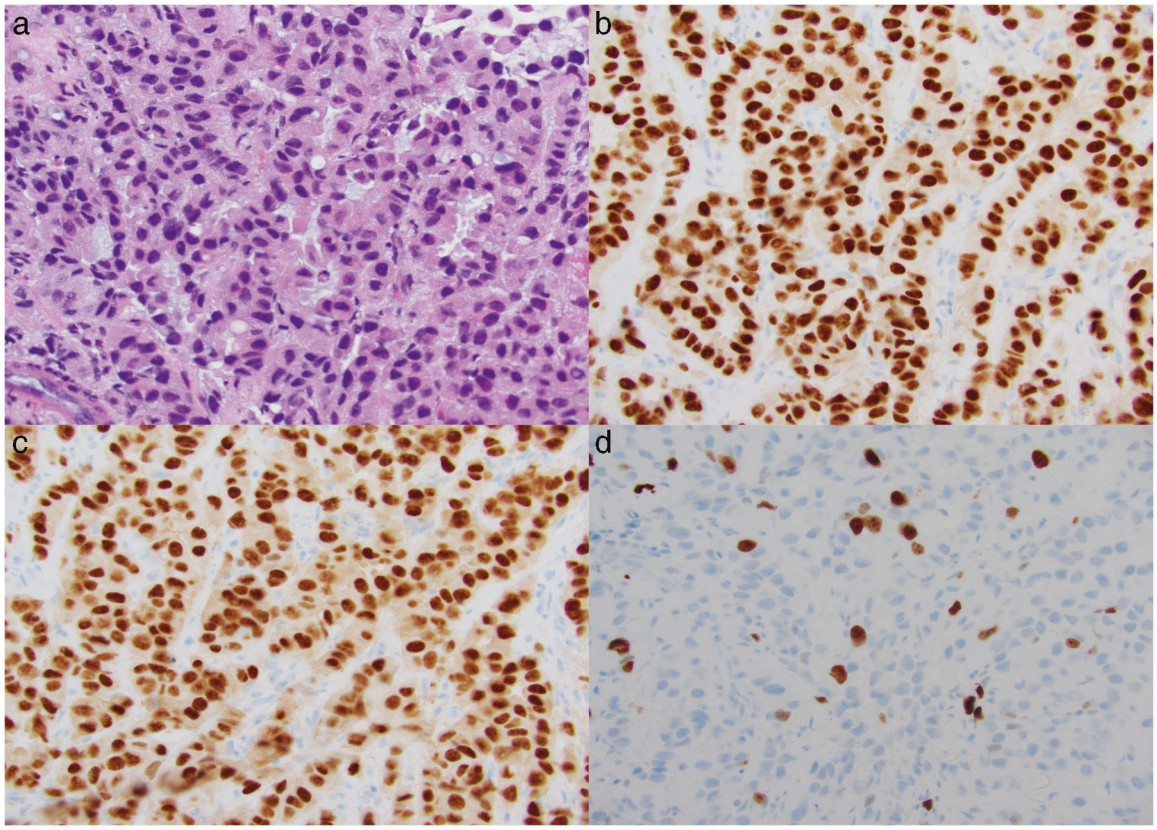

Fig. 3 Example of an invasive breast carcinoma with receptor results for consideration of neoadjuvant chemotherapy. It is difficult to determine if this grade II invasive breast carcinoma would benefit from chemotherapy based on H&E section alone (**a**). However, strong reactivity for estrogen receptor (**b**, H-score of 300), strong reactivity for progesterone receptor (**c**, H-score of 280), HER2-negative (not shown), and relatively low Ki-67 labeling index (**d**, index of 10%) results in Magee Equation 3 (ME3) score of 11.5, suggesting lack of significant benefit from chemotherapy and almost no chance of pathologic complete response (pCR) if chemotherapy is given in the neoadjuvant setting.

Buechler et al. developed a novel "EarlyR" gene risk signature using expression pattern of five genes (*ESPL1*, *SPAG5*, *MKI67*, *PLK1,* and *PGR*) and reported pCR rate of 10% in the low-intermediate risk group, and 24% in the high-risk group in a cohort of 659 patients [24]. Our current study results are most similar to what has been reported for IHC4 score (another immunohistochemistry based model) in ER+/HER2-negative tumors where Sheri et al. reported pCR + RCB1 rate of 35% in the highest quartile of IHC4 and no pCR in the lower half of IHC4 [25]. It is clear from the available data that the results reported in the current study and the prior Magee study are either equivalent or superior to previously published studies regarding expensive genomic assays.

Apart from the strong predictive power of ME3 in the current study and prior Magee study, there appears to be a modest prognostic value of pre-therapy ME3 scores [2]. As shown in the current study, the patients with residual disease and high ME3 scores had worse recurrence-free survival and showed a trend for worse overall and breast cancer-specific survival. In the neoadjuvant setting, RCB score/class is a strong factor in determining prognosis after neoadjuvant chemotherapy [26, 27]. We wanted to study the impact of ME3 on each RCB class; however, RCB data were not available on all cases. In cases where RCB class was available, we analyzed if ME3 scores could further provide prognostic information. ME3 did not provide prognostic information within RCB class II, but within RCB-III, patients with ME3 scores 25 or less had significantly improved survival compared to patients with ME3 scores >25 (Fig. 2). However, due to the limited number of cases with available data for analysis, these findings should be evaluated and confirmed in other larger studies.

Our results confirm the chemo-predictive value of ME3 in the neoadjuvant setting. However, our study does have some limitations/concerns. Although multi-institutional, the study is still retrospective, which is subject to bias and heterogeneity in treatment. A large prospective multi-institutional study with more homogeneity could further help validate the use of ME3 in routine practice. A small number of cases resulted in pCR (17 of 166 or 10%), which

could also be considered a limitation, but this number is in accordance with prior studies and confirms that pCR in ER+/HER2-negative breast cancers is an uncommon event [2, 19, 24, 25]. Another limitation or concern raised regarding MEs or similar models that require semi-quantitative results is with respect to standardization and reproducibility [28, 29]. The performance and reporting of immunohistochemical assays can show some degree of inter-observer and/or inter-laboratory variability that can impact Magee Equation scores. Pre-analytical factors can interfere with accurate immunohistochemical scoring, and therefore it is important to adhere to the good laboratory practices of tissue handling and fixation [30–32]. There is limited data on the assessment of inter-observer variability with respect to semi-quantitative scoring, though such variability appears to be limited [33, 34]. Reports on the clinical usefulness of MEs from various institutions also suggest more widespread applicability of MEs [35–45]. The multi-institutional nature of the current study is important in this regard and allays some of the concern about the reproducibility of MEs.

In summary, ME3 is a simple, fast, robust, and reliable tool to select ER+/HER2-negative patients who will benefit the most from neoadjuvant chemotherapy. A prospective multi-institutional validation may be warranted for more widespread adoption by breast cancer care providers.

Disclosures

DJD is an independent contractor breast pathologist at PreludeDx (Laguna Hills, CA). AMB is an advisor to Myriad Genetics (Salt Lake City, UT), Biotheranostics Inc. (San Diego, CA), and Agendia (Irvine, CA). Dr. RPH has been a consultant for Bristol Myers Squibb (New York, NY) from 2016–2018. RB is an ad hoc advisor to Eli Lilly & Company (Indianapolis, IN).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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