Ann Surg Oncol (2019) 26:3152–3158
https://doi.org/10.1245/s10434-019-07553-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Is Routine Recurrence Score Testing in Patients Older than 70 Years of Age Warranted? An Evaluation of the National Cancer Database After TAILORx

Rachel M. Lee, MD[1], Jeffrey M. Switchenko, PhD[2], Tran B. Ho, DO[1], Cletus A. Arciero, MD[1], Manali A. Bhave, MD[3], and Preeti D. Subhedar, MD[1]

[1]Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, GA; [2]Winship Cancer Institute, Biostatistics and Bioinformatics Shared Resource, Emory University, Atlanta, GA; [3]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA

ABSTRACT

Background. Recurrence score (RS) testing in early-stage, ER-positive breast cancer is used to predict the benefit of adjuvant chemotherapy for disease recurrence and overall survival. TAILORx results decreased the ambiguity of "intermediate risk" RS by creating a binary classification system. We aimed to determine how women $\geq$ 70 years with intermediate RS were redistributed post-TAILORx and to identify predictors of low RS.

Methods. Patients $\geq$ 70 years with early-stage, node-negative, ER-positive breast cancers in the National Cancer Database(2006–2014) were included. "Pre-TAILORx" RS were classified as low (0–17), intermediate (18–30), and high (> 30). "Post-TAILORx" RS were classified as low (0–25) and high (> 25).

Results. In total, 14,925 women were included. Average age was 74 years. 60% (n = 9009) had low pre-TAILORx RS, 31% (n = 4635) intermediate, and 9% (n = 1281) high. Of 4635 patients with intermediate RS, 72% (n = 3660) were reclassified to low RS. Only 12% (n = 1783) of patients received chemotherapy. Of patients with pre-TAILORx intermediate RS who received chemotherapy, 55% (n = 417) would have been spared chemotherapy by being reclassified with low RS post-TAILORx. The strongest predictor of post-TAILORx low RS was tumor grade; 95% of well-differentiated had low RS, compared with 56% of poorly/undifferentiated tumors ($p < 0.001$). Smaller tumor size also was associated with low RS. Age was not associated with RS.

Conclusions. With post-TAILORx RS criteria, the vast majority of patients $\geq$ 70 years can be classified as low-risk and unlikely to benefit from chemotherapy. Given that the elderly have greater rates of chemotherapy-associated complications, reconsideration of routine RS testing in patients $\geq$ 70 years is warranted. Tumor grade and size also may inform the decision to omit RS testing.

In 1989, the National Surgical Adjuvant Breast and Bowel Project (NSABP) published results from a randomized clinical trial (B-14) investigating the use of adjuvant endocrine therapy for women < 70 years of age with early-stage, estrogen receptor (ER)-positive, node-negative breast cancers. Compared with placebo, tamoxifen resulted in improved recurrence-free survival (RFS).[1] Subsequently, B-20 was initiated to investigate the use of adjuvant chemotherapy in addition to tamoxifen for early-stage, ER-positive, node-negative cancers. This study found an advantage in both RFS and overall survival (OS) in patients who received chemotherapy in addition to tamoxifen. Interestingly, these advantages were the greatest in younger women, specifically those < 50 years of age.[2]

Long-term findings showed that the vast majority of patients do not experience a disease recurrence in 10 years, even without chemotherapy; 10-year RFS in women treated with tamoxifen alone was found to be 78% in patients enrolled in B-14 and 79% of patients enrolled in B-20. Long-term results from B-20 again demonstrated greater

First Received: 21 April 2019;
Published Online: 24 July 2019

P. D. Subhedar, MD
e-mail: preeti.subhedar@emory.edu

benefit of adjuvant chemotherapy in younger women; a progressive reduction in recurrence was seen with increasing age at surgery in patients treated with tamoxifen but not chemotherapy.[3] Given these relatively low risks of recurrence, a 21-gene assay was developed and used to create a classification system to identify women at high risk of recurrence and thus most likely to benefit from chemotherapy. These recurrence score (RS) risk categories (low: RS < 18, intermediate: 18–30, high: > 30) were used to guide adjuvant treatment decisions. However, best practices for women with intermediate scores remained unclear, with systemic treatments prescribed using a combination of patient and tumor characteristics, and physician preference, rather than evidence-based, objective tools.[4] The TAILORx study sought to determine the benefit of chemotherapy in these intermediate RS patients, randomizing patients with a RS of 11–25 to receive a combination of chemotherapy followed by endocrine therapy or endocrine therapy alone.[5] These adjuvant therapy regimens resulted in similar disease-free survival (DFS), RFS, and OS.[5] Application of these results decreased the ambiguity of an "intermediate risk" RS by stratifying scores into a binary classification system (low: 0–25, high: > 25).[5] However, the benefit of chemotherapy in elderly women and best practices for this age group remains unknown.

The uncertain benefit of chemotherapy in elderly patients is multifactorial, including the decreased benefit seen in elderly patients receiving chemotherapy in B-20, the heterogeneity in the health and functional status of older patients, and the increased risks in overtreatment with chemotherapy in elderly patients.[2,3,6] Thus, it is critically important in this age group to accurately risk stratify women based on risk of recurrence.

Our goals were to (1) determine how women ≥ 70 years of age with intermediate recurrence scores were redistributed using post-TAILORx criteria, (2) to determine the rates of adjuvant chemotherapy utilization in these patients, and (3) to identify predictors of low RS, based on TAILORx criteria using a large national database.

METHODS

National Cancer Database

The National Cancer Database (NCDB) is a collaboration between the American College of Surgeons Commission on Cancer and the American Cancer Society.[7] Data are sourced from more than 1500 Commission on Cancer accredited hospitals across the United States. The NCDB was queried for adult patients ≥ 70 years of age with T1 or T2, N0, ER-positive, HER2-negative breast cancer from 2006 to 2014. Patients with missing RS were excluded. RS was defined as "pre-TAILORx" (low: 0–17, intermediate: 18–30, high: > 30) and "post-TAILORx" (low: 0–25, high > 25).

Statistical Analysis

Statistical analysis was conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC) and SAS macros or software developed at the Biostatistics and Bioinformatics Department at Winship Cancer Institute.[8] Statistical significance was predefined as two-tailed $p < 0.05$. Descriptive statistics for each variable were reported. The percentage of patients with low RS via both pre- and post-TAILORx criteria, intermediate RS via pre-TAILORx and low RS via post-TAILORx criteria, intermediate RS via pre-TAILORx and high RS via post-TAILORx criteria, and high RS via both pre- and post-TAILORx criteria were calculated. The univariate association between each covariate and study outcomes (receipt of chemotherapy and low or high post-TAILORx RS) was assessed using the Chi squared test. The multivariable association between age, tumor size, and tumor grade and low RS was assessed using logistic regression and reported as odds ratios (OR) with corresponding 95% confidence intervals (CI).

RESULTS

Patient Characteristics

A total of 14,925 women ≥ 70 years of age with T1-T2, N0, ER-positive, HER2-negative breast cancer were included. Mean age was 74 years. Seventy-six percent ($n = 11{,}355$) and 26% ($n = 3750$) of women had T1 tumors and well differentiated histology, respectively. Twelve percent of women ($n = 1783$) received chemotherapy. Sixty percent ($n = 9009$) had a low RS based on pre-TAILORx criteria, 31% ($n = 4635$) intermediate RS, and 9% ($n = 1281$) high RS. Of women initially classified with intermediate RS, 79% and 21% were reclassified to low and high RS, respectively (Table 1).

Receipt of Chemotherapy

Using pre-TAILORx criteria, 2% ($n = 200$) of patients with low RS, 17% ($n = 753$) with intermediate RS and 65% ($n = 830$) with high RS received chemotherapy ($p < 0.001$). Using post-TAILORx criteria, 5% ($n = 617$) of patients with a low RS received chemotherapy compared with 52% ($n = 1166$) with high RS ($p < 0.001$). Of the patients with intermediate RS before TAILORx who received chemotherapy, 55% ($n = 417$) would have been

TABLE 1 Baseline demographic and clinicopathologic data

Variable	*N* (%)
Age	
70–74	9295 (62.3)
75–79	4253 (28.5)
≥ 80	1377 (9.2)
Age (mean ± SD)	74.1 ± 3.7
Charlson-Deyo Score	
0	11,532 (77.3)
1+	3393 (22.7)
AJCC Clinical T	
1	2619 (17.5)
1A	515 (3.5)
1B	2864 (19.2)
1C	5342 (35.8)
2	3570 (24.0)
AJCC Clinical N	
0	14,925 (100)
ER+	14,925 (100)
HER2−	14,925 (100)
Tumor size	
≤ 1 cm	3086 (20.7)
1–2 cm	7324 (49.1)
> 2 cm	4506 (30.2)
Tumor grade	
Well differentiated	3750 (26.4)
Moderately differentiated	8045 (56.6)
Poorly differentiated/undifferentiated	2410 (17.0)
Lymphovascular invasion (present)	1974 (15.0)
Recurrence score (pre-TAILORx)	
Low (0–17)	9009 (60.4)
Intermediate (18–30)	4635 (31.1)
High (> 30)	1281 (8.6)
Recurrence score (post-TAILORx)	
Low (0–25)	12,669 (84.9)
High (> 25)	2256 (15.1)
Recurrence score (pre/post-TAILORx)	
Low/low	9009 (60.4)
Intermediate/low	3660 (24.5)
Intermediate/high	975 (6.5)
High/high	1281 (8.6)
Received chemotherapy	1783 (12.2)

spared chemotherapy by being reclassified with low RS after TAILORx (Table 2).

Predictors of Low-Risk Recurrence Score

On univariate analysis, age, T stage, tumor size, tumor grade, and lymphovascular invasion were associated with post-TAILORx low RS. Specifically, younger age, T1 tumors, well differentiated tumors, smaller tumor size, and absence of lymphovascular invasion were more likely to be associated with a low RS (Tables 3 and 4). On multivariable analysis, higher tumor grade (moderately differentiated vs well differentiated: OR 0.43, 95% CI 0.36–0.51; poorly differentiated vs well differentiated: OR 0.07, 95% CI 0.06–0.09, all $p < 0.001$) and T2 tumors (T2 vs T1: OR 0.83, 95% CI 0.71–0.96, $p = 0.015$) were significantly less likely to be associated with a low RS, while increasing age and lymphovascular invasion were not associated with RS (Table 4).

DISCUSSION

Since the development of the 21-gene RS assay in 2004, RS testing has been adopted to guide adjuvant therapy decisions. Partin and colleagues found a threefold increase in the percentage of patients receiving RS testing in the first 5 years after development, with 50% of patients receiving RS testing in 2009.[9] Since that time, RS testing has become incorporated into practice guidelines, with the American Society of Clinical Oncology and the National Comprehensive Cancer Network including RS testing in their guidelines in 2007 and 2008, respectively.[10,11] The RS now forms the backbone of the prognostic staging groups presented in the 8th edition of the AJCC Cancer Staging manual, highlighting the importance of disease biology in staging and treatment decision making.[12]

After B-20 showed benefit of chemotherapy in addition to tamoxifen, the majority of women with ER+, node-negative breast cancer were recommended to receive adjuvant chemotherapy, mostly based on T stage.[2] The development of the 21-gene RS allowed for a more nuanced understanding of tumor biology and potential benefit from chemotherapy.[4] Paik and colleagues demonstrated that patients included in B-20 did not benefit equally from chemotherapy when stratified by RS; patients with high RS benefited greatly from chemotherapy, whereas patients with low RS did not. Patients with intermediate RS did not appear to benefit from chemotherapy; however, the uncertainty in the relative risk estimate did not definitively exclude a clinically relevant benefit for these patients.[13] Thus, a large degree of uncertainty in treating these patients remained, until TAILORx allowed for a binary classification system, reclassifying 69% of women enrolled in the study from intermediate to low risk of distant recurrence.[5] Given that the majority of women are classified as low risk and unlikely to benefit from chemotherapy, the question arises as to whether recurrence score testing is mandated in all women with early stage, ER+, node-negative breast cancer.

TABLE 2 Receipt of chemotherapy by recurrence score

	Chemotherapy		*P* value
	Yes *N* (%)	No *N* (%)	
Recurrence score (pre-TAILORx)			
Low (0–17)	200 (2.3)	8593 (97.7)	< **0.001**
Intermediate (18–30)	753 (16.6)	3775 (83.4)	
High (> 30)	830 (65.3)	441 (34.7)	
Recurrence score (post-TAILORx)			
Low (0–25)	617 (5.0)	11,746 (95.0)	< **0.001**
High (> 25)	1166 (52.3)	1063 (47.7)	
Recurrence score (pre/post-TAILORx)			
Low/low	200 (2.3)	8593 (97.7)	< **0.001**
Intermediate/low	417 (11.7)	3153 (88.3)	
Intermediate/high	336 (35.1)	622 (64.9)	
High/high	830 (65.3)	441 (34.7)	

Bold values indicate statistical significance ($p < 0.05$)

TABLE 3 Differences in clinicopathologic variables by recurrence score (Post-TAILORx)

	Recurrence score		*P* value
	Low (0–25) *N* (%)	High (> 25) *N* (%)	
Age			
70–74	7938 (85.4)	1357 (14.6)	**0.003**
75–79	3603 (84.7)	650 (15.3)	
≥ 80	1128 (81.9)	249 (18.1)	
Tumor size			
≤ 1 cm	2721 (88.2)	365 (11.8)	< **0.001**
1–2 cm	6302 (86.1)	1022 (13.9)	
> 2 cm	3638 (80.7)	868 (19.3)	
Tumor grade			
Well differentiated	3559 (94.9)	191 (5.1)	< **0.001**
Moderately differentiated	7124 (88.6)	921 (11.4)	
Poorly differentiated/undifferentiated	1347 (55.9)	1063 (44.1)	
Lymphovascular invasion			< **0.001**
Present	1557 (78.9)	417 (21.1)	
Not present	9598 (85.8)	1582 (14.2)	

Bold values indicate statistical significance ($p < 0.05$)

Although increasing age is the primary risk factor for breast cancer, multiple studies have shown breast cancers in elderly women to have more indolent, lower risk features compared with tumors in younger women, which likely explains why younger women have been shown to derive greater benefit from chemotherapy; low-risk tumors rarely require chemotherapy due to low rates of recurrence.[2,14,15] A study using data from the San Antonio Breast Cancer Database and the Surveillance, Epidemiology, and End Results Database found that tumors in elderly women were more likely to have normal p53 expression and lower proliferative indices compared with tumors in younger women.[14] Gennari and colleagues, in a single-institution study of 2999 women, found that breast cancer in elderly women is also more likely to be estrogen receptor expressing, less likely to be HER2 overexpressing, and less likely to have peritumoral vascular invasion compared with breast cancer in younger women.[15] Similarly to these studies, we found that the majority of elderly women in our cohort also had indolent tumors, as reflected by well or moderate differentiation.

Although elderly women are a heterogeneous group in terms of health status, on the whole elderly cohorts have higher rates of comorbid conditions. In elderly women with

TABLE 4 Multivariable association with low recurrence score (Post-TAILORx)

Covariate	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age				
70–74	Reference	–	Reference	–
75–79	0.95 (0.86–1.05)	0.298	0.96 (0.86–1.08)	0.534
≥ 80	0.77 (0.67–0.90)	< **0.001**	0.84 (0.71–1.00)	0.053
Charlson-Deyo Score				
0	Reference	–	Reference	–
1+	0.95 (0.86–1.06)	0.379	1.04 (0.92–1.18)	0.512
AJCC Clinical T Stage				
1	Reference	–	Reference	–
2	0.61 (0.56–0.68)	< **0.001**	0.83 (0.71–0.96)	**0.015**
Tumor size				
≤ 1 cm	Reference	–	Reference	–
1–2 cm	0.83 (0.73–0.94)	**0.004**	1.04 (0.90–1.21)	0.607
> 2 cm	0.56 (0.49–0.64)	< **0.001**	0.93 (0.77–1.12)	0.439
Tumor grade				
Well differentiated	Reference	–	Reference	–
Moderately differentiated	0.42 (0.35–0.49)	< **0.001**	0.43 (0.36–0.51)	< **0.001**
Poorly differentiated/undifferentiated	0.07 (0.06–0.08)	< **0.001**	0.07 (0.06–0.09)	< **0.001**
Lymphovascular invasion	0.63 (0.55–0.69)	< **0.001**	0.96 (0.84–1.10)	0.565

Bold values indicate statistical significance ($p < 0.05$)

breast cancer, comorbid conditions have been shown to impact overall survival to a much greater degree than breast cancer. After 12 years of follow-up in a study of women ≥ 70 with early-stage, ER+ breast cancer, Hughes and colleagues found that only 3% of patients had died due to breast cancer, whereas 49% died due to other causes.[16] These findings were mirrored in recent data published from Japan in which OS was significantly worse with increasing age, however breast cancer specific survival (BCSS) was not, indicating comorbidities are contributing to mortality at a greater rate than breast cancer recurrence in elderly women.[17] This is especially important to keep in mind when considering adjuvant therapies that can be associated with significant complications. Given the heterogeneity in the health status of older patients and increased rates of comorbidities, treatment decisions must be individualized in order to deliver the best possible care to this population.

Receipt of chemotherapy in the elderly can be associated with significant complications, morbidity, hospitalization, and decreases in cognitive and functional status. The extent of these complications varies with the overall health of the individual and with her comorbidities. Adjuvant chemotherapy in breast cancer has been associated with a threefold risk of acute kidney injury, and, emphasizing the interaction of comorbidities with chemotherapy, elderly patients with diabetes have been shown to have significantly increased odds of hospitalization for any chemotherapy toxicity, for infection or fever, and for neutropenia or anemia.[18,19] Adjuvant chemotherapy leads to hospitalization rates from 13 to 24% in elderly women, contributing to significant declines in functional status and quality of life in 30–60% of patients.[6,20,21] The goals and wishes of the patients themselves in this unique population are important to consider when making adjuvant treatment decisions, where independent living and preservation of mental faculties may be a higher priority than modest recurrence gains.

The concept of tailoring adjuvant therapy in elderly patients with early breast cancer is not new. In the CALGB 9343 study, Hughes and colleagues studied the effect of adjuvant radiation combined with endocrine therapy compared to endocrine therapy alone in women ≥ 70 years. Radiation provided a small, yet significant benefit in locoregional recurrence (LRR).[16] However, this benefit did not translate into a benefit in OS or distant DFS, leading to the conclusion that adjuvant radiation may be omitted after breast conservation surgery (BCS) in elderly women ≥ 70.[16] Similarly, in the PRIME II study, Kunkler and colleages considered omission of adjuvant radiation after BCS in women ≥ 65 years old with low risk tumors. Radiation was associated with a modest reduction in LRR at 5 years; however, there were no differences in regional

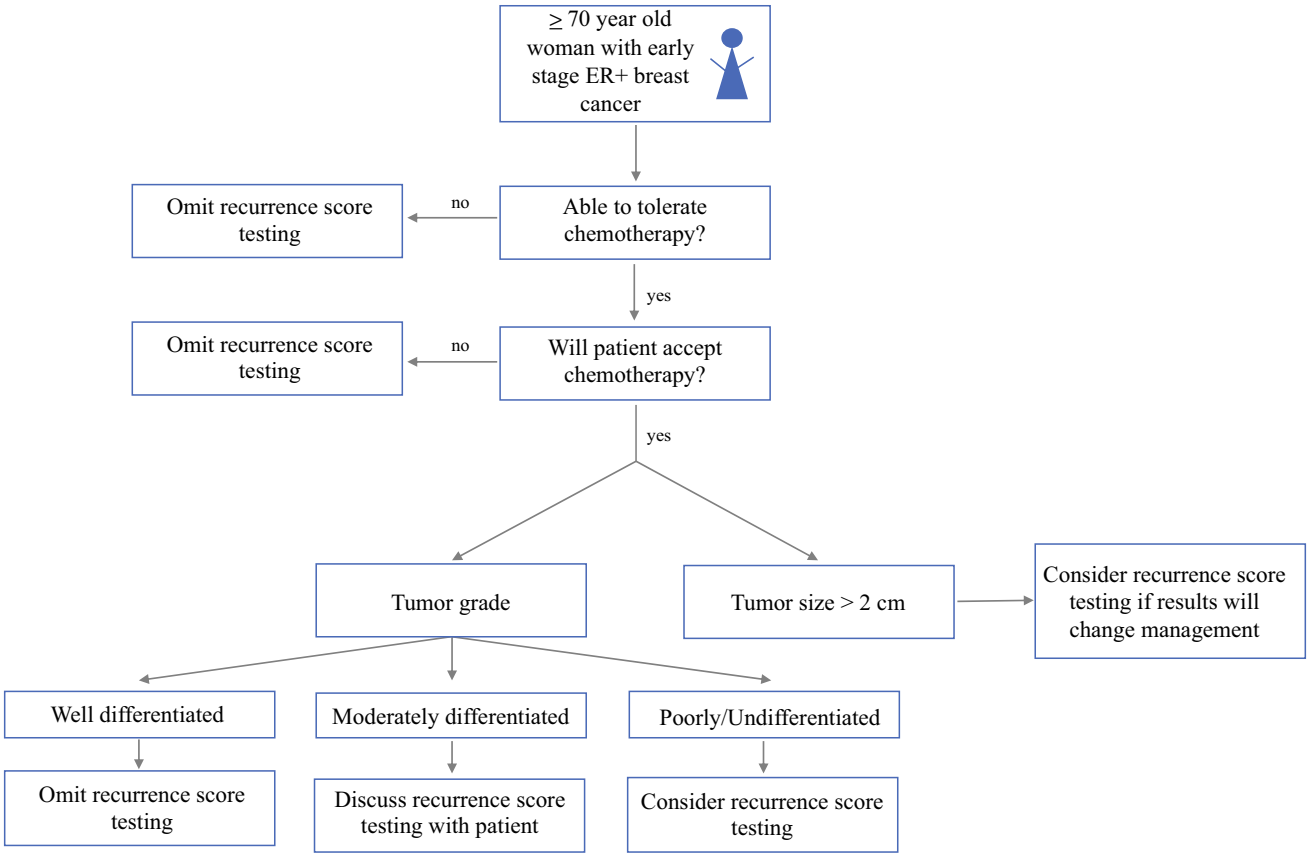

FIG. 1 Proposed algorithm for considering recurrence score testing in elderly women with early-stage, ER+ breast cancer

recurrence, distant metastases, contralateral breast cancer, new breast cancers, or OS between those who did and did not receive radiation.[22] Given low LRR rates, the authors concluded that radiation had no effect on long-term outcomes, and omission in select patients was warranted.[22]

We advocate for a personalized approach to recurrence score testing in the elderly population (Fig. 1). The initial consideration for RS testing should be whether a patient is functional enough to tolerate systemic therapy, followed closely by whether or not they would accept said therapy if offered, and these questions are to be decided by detailed discussion and consideration with the patient as the definition of "tolerate" is likely to vary amongst individuals. As we demonstrated, tumor grade is the strongest predictor of low RS. Patients with poorly differentiated tumors should be tested, if they are functionally able to tolerate chemotherapy and would be interested in receiving it, as they are significantly more likely than patients with well-differentiated tumors to have high RS. Our results suggest that 95% of elderly patients with well-differentiated tumors have low RS, and thus testing in this cohort is not a cost-effective measure. Patients with moderately differentiated tumors may be electively tested after thorough consideration and discussion with their physician, keeping in mind that 89% will have low RS. Finally, larger tumors can be considered for testing, regardless of grade, provided that the results would change management.

Recurrence score testing is an important adjunct in the personalization of breast cancer treatment. It highlights the importance of tumor biology over standard clinicopathologic measures to guide the receipt of systemic therapy. We advocate for the nuanced use of this test, particularly for elderly patients, to enhance resource utilization in an already overburdened healthcare system.

This study has several limitations. Use of a retrospective database naturally is prone to selection bias; however, the NCDB is a large dataset with a comprehensive representation of the national population. Patients without RS data were excluded from analysis, thus excluding patients who were not considered for chemotherapy creating additional risk of selection bias. Only 7% of patients in the NCDB had recurrence score data. The exclusion of patients without recurrence score data likely accounts for the high overall performance status of the patients in our study as likely patients who would not tolerate chemotherapy or would not accept it were not tested.

With updated TAILORx data, the majority of women with early stage, node-negative, ER-positive, HER2-negative cancers have a low risk for recurrence. This is particularly true in elderly women with more favorable tumor biology, perhaps making this group of patients an "ultra-low risk" cohort. Mortality in this age group is largely due to comorbidities, rather than breast cancer recurrence, and frequently patients in this age group are unwilling to receive chemotherapy. Given that these women have a greater rate of chemotherapy associated complications, and considering increased healthcare costs associated with testing, reconsideration of routine RS testing in patients $\geq$ 70, especially in those with well-differentiated tumors is warranted. We propose that the decision to use recurrence score testing be individualized in this elderly cohort. In addition to taking into account functional status and ability to tolerate chemotherapy, tumor grade and size also may better inform the decision to use RS, especially in elderly patients with well-differentiated tumors or those who can be considered as being "ultra-low" risk.

ACKNOWLEDGMENTS Research reported in this publication was supported in part by the Biostatistics and Bioinformatics Shared Resource of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

DISCLOSURE None.

REFERENCES

1. Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med.* 1989;320(8):479–84.
2. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. *J Natl Cancer Inst.* 1997;89(22):1673–82.
3. Fisher B, Jeong JH, Bryant J, et al. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. *Lancet.* 2004;364(9437):858–68.
4. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* 2004;351(27):2817–26.
5. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med.* 2018;379(2):111–21.
6. Muss HB. Adjuvant chemotherapy in older women with breast cancer: who and what? *J Clin Oncol.* 2014;32(19):1996–2000.
7. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol.* 2008;15(3):683–90.
8. Nickleach D, Liu Y, A S. SAS (R) macros to conduct common biostatistical analyses and generate reports. *SESUG 2013: The Proceeding of the SouthEast SAS User Group.* 2013.
9. Partin JF, Mamounas EP. Impact of the 21-gene recurrence score assay compared with standard clinicopathologic guidelines in adjuvant therapy selection for node-negative, estrogen receptor-positive breast cancer. *Ann Surg Oncol.* 2011;18(12):3399–406.
10. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol.* 2007;25(33):5287–312.
11. *National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology Breast Cancer (Version 2.2008)* http://www.nccn.org/professionals/physician_gls/f/guidelines.asp.
12. Hortobagyi G, Connolly J, D'Orsi C, et al. Breast. In: Amin M, ed. *AJCC Cancer Staging Manual Eighth Edition*. Chicago, IL: Springer; 2017:589–628.
13. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol.* 2006;24(23):3726–34.
14. Diab S, Elledge R, Clark G. Tumor characteristics and clinical outcome of elderly women with breast cancer. *J Natl Cancer Inst.* 2000;92(7):550–6.
15. Gennari R, Curigliano G, Rotmensz N, et al. Breast carcinoma in elderly women: features of disease presentation, choice of local and systemic treatments compared with younger postmenopasual patients. *Cancer.* 2004;101(6):1302–10.
16. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol.* 2013;31(19):2382–7.
17. Takuwa H, Tsuji W, Yotsumoto F. Overall survival of elderly patients with breast cancer is not related to breast-cancer specific survival: A single institution experience in Japan. *Breast Dis.* 2018;37(4):177–83.
18. Li S, Liu J, Virnig BA, Collins AJ. Association between adjuvant chemotherapy and risk of acute kidney injury in elderly women diagnosed with early-stage breast cancer. *Breast Cancer Res Treat.* 2017;161(3):515–24.
19. Srokowski TP, Fang S, Hortobagyi GN, Giordano SH. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. *J Clin Oncol.* 2009;27(13):2170–6.
20. Barcenas CH, Niu J, Zhang N, et al. Risk of hospitalization according to chemotherapy regimen in early-stage breast cancer. *J Clin Oncol.* 2014;32(19):2010–7.
21. Hoogerduijn JG, Buurman BM, Korevaar JC, Grobbee DE, de Rooij SE, Schuurmans MJ. The prediction of functional decline in older hospitalised patients. *Age Ageing.* 2012;41(3):381-7.
22. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, investigators PI. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol.* 2015;16(3):266–73.