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Association of Chemotherapy With Survival in Elderly Patients With Multiple Comorbidities and Estrogen Receptor–Positive, Node-Positive Breast Cancer

Nina Tamirisa, MD; Heather Lin, PhD; Yu Shen, PhD; Simona F. Shaitelman, MD, EdM; Meghan Sri Karuturi, MD; Sharon H. Giordano, MD, MPH; Gildy Babiera, MD; Isabelle Bedrosian, MD

IMPORTANCE Breast cancer risk and comorbidities increase with age. Data are lacking on the association of adjuvant chemotherapy with survival in elderly patients with multiple comorbidities and node-positive breast cancer.

OBJECTIVE To examine the association of chemotherapy with survival in elderly patients with multiple comorbidities and estrogen receptor–positive, node-positive breast cancer.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included patients in the US National Cancer Database who were 70 years or older; had a Charlson/Deyo comorbidity score of 2 or 3; had estrogen receptor–positive, *ERBB2* (formerly *HER2* or *HER2/neu*)–negative breast cancer; and underwent surgery for pathologic node–positive breast cancer from January 1, 2010, to December 31, 2014. Propensity scores were used to match patients receiving adjuvant chemotherapy with those not receiving adjuvant chemotherapy based on age, comorbidity score, facility type, facility location, pathologic T and N stage, and receipt of adjuvant endocrine and radiation therapy. Data analysis was performed from December 13, 2018, to April 28, 2020.

EXPOSURES Chemotherapy.

MAIN OUTCOMES AND MEASURES The association of adjuvant chemotherapy with overall survival was estimated using a double robust Cox proportional hazards regression model.

RESULTS Of a total of 2 445 870 patients in the data set, 1592 patients (mean [SD] age, 77.5 [5.5] years; 1543 [96.9%] female) met the inclusion criteria and were included in the initial nonmatched analysis. Of these patients, 350 (22.0%) received chemotherapy and 1242 (78.0%) did not. Compared with patients who did not receive chemotherapy, patients who received chemotherapy were younger (mean age, 74 vs 78 years; $P < .001$), had larger primary tumors (pT3/T4 tumors: 72 [20.6%] vs 182 [14.7%]; $P = .005$), and had higher pathologic nodal burden (75 [21.4%] vs 81 [6.5%] with stage pN3 disease and 182 [52.0%] vs 936 [75.4%] with stage pN1 disease; $P < .001$). More patients who received chemotherapy also received other adjuvant treatments, including endocrine therapy (309 [88.3%] vs 1025 [82.5%]; $P = .01$) and radiation therapy (236 [67.4%] vs 540 [43.5%]; $P < .001$). In the matched cohort, with a median follow-up of 43.1 months (95% CI, 39.6-46.5 months), no statistically significant difference was found in median overall survival between the chemotherapy and no chemotherapy groups (78.9 months [95% CI, 78.9 months to not reached] vs 62.7 months [95% CI, 56.2 months to not reached]; $P = .13$). After adjustment for potential confounding factors, receipt of chemotherapy was associated with improved survival (hazard ratio, 0.67; 95% CI, 0.48-0.93; $P = .02$).

CONCLUSIONS AND RELEVANCE This cohort study found that in node-positive, estrogen receptor–positive elderly patients with breast cancer and multiple comorbidities, receipt of chemotherapy was associated with improved overall survival. Despite attempts to adjust for selection bias, these findings suggest that physicians carefully selected patients likely to derive treatment benefit from adjuvant chemotherapy based on certain unmeasured variables. A standardized, multidisciplinary approach to care may be associated with long-term treatment outcomes in this subset of the population.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Nina Tamirisa, MD, Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1400 Pressler St, Unit 1434, Houston, TX 77030 (ntamirisa@mdanderson.org).

Breast cancer risk and the incidence of comorbidities increase with age. Treatment of elderly patients with significant comorbidities is challenging. Efforts are made to provide comprehensive treatment to these patients while minimizing the effect on quality of life and avoiding a compromise of functional status for patients with an already limited life expectancy. A retrospective review[1] of 4 randomized clinical trials in women with lymph node–positive breast cancer concluded that older and younger women derived similar reductions in breast cancer mortality and recurrence from regimens that contain more aggressive chemotherapy. However, only 2% of the patients in that study[1] were older than 70 years, and the authors cautioned against application of these findings in older patients. The current National Comprehensive Cancer Network guidelines for breast cancer in elderly patients state, "For women greater than 70 years of age…there are insufficient data to make definitive chemotherapy recommendations…treatment should be individualized in this age group, with consideration given to comorbid conditions."[2(pp 42-43)]

To minimize age-related bias, tools have been developed to assess surgical risk and risks associated with chemotherapy to provide tailored treatments to patients while preserving quality of life.[3-6] In 2012, the International Society of Geriatric Oncology and European Society of Breast Cancer Specialists recommended a comprehensive geriatric assessment to identify specific patient factors associated with a higher risk of treatment-related complications.[6] In this functionally heterogeneous subset of the population, there is often a debate across disciplines on the least toxic form of therapy for patients with multiple comorbidities. Prior studies[7,8] have found decreased rates of multimodal therapy among older patients with breast cancer. Because older patients with multiple comorbidities are often excluded from clinical trial participation, data are lacking on the survival benefit associated with adjuvant chemotherapy.

In light of the increasing aging population and lack of a standardized approach for older patients with breast cancer, it is essential to study the association of cancer treatment with survival in this subset of the population. The aim of this study was to examine the association of adjuvant chemotherapy with survival in elderly patients with multiple comorbidities who have undergone breast and axillary surgery and have estrogen receptor–positive, pathologic node-positive invasive breast cancer.

Key Points

Question Is receipt of adjuvant chemotherapy associated with survival in elderly patients with multiple comorbidities and node-positive, estrogen receptor–positive breast cancer?

Findings In this retrospective cohort study of 1592 elderly patients with multiple comorbidities and estrogen receptor–positive, node-positive breast cancer from the US National Cancer Database, after adjusting for confounding factors in a matched cohort, receipt of chemotherapy was associated with an overall survival benefit.

Meaning Adjuvant chemotherapy may be associated with improved survival outcomes in elderly patients with breast cancer.

Methods

Patient Population

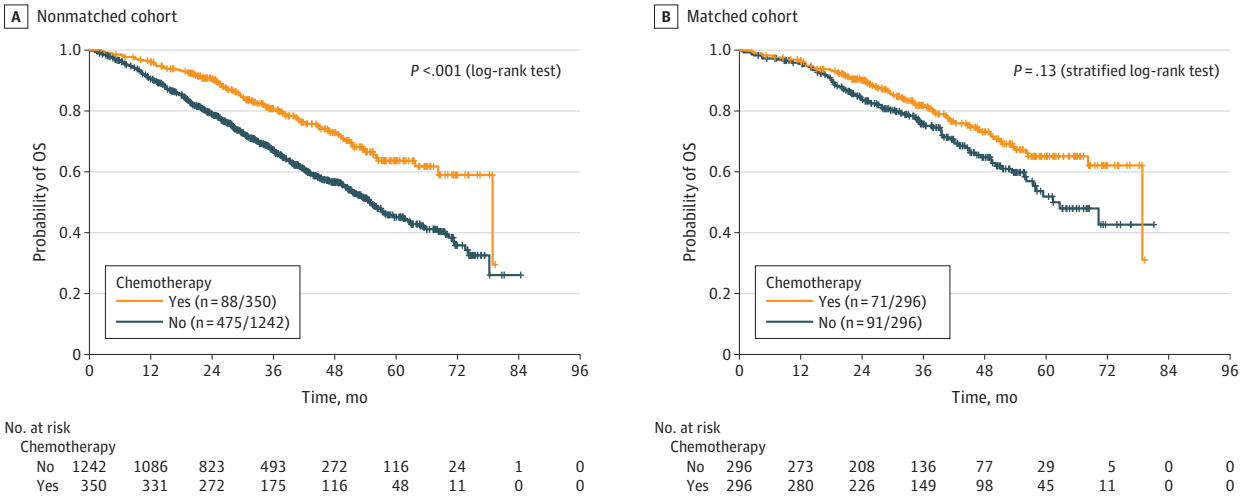
This retrospective cohort study used data from the US National Cancer Database (NCDB), a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB is a hospital-based registry that captures approximately 70% of newly diagnosed cancer cases in the US and Puerto Rico and includes data from more than 1500 commission-accredited cancer programs. Originating in 1989, the NCDB now contains approximately 34 million records. Data registries contain patient characteristics, cancer stage, tumor histologic characteristics, type of treatment administered, and survival outcomes. The institutional review board of The University of Texas MD Anderson Cancer Center deemed analysis of the NCDB Participant User File to be exempt from review.

Patients 70 years or older who underwent breast and axillary surgery and had estrogen receptor–positive, *ERBB2* (formerly *HER2* or *HER2/neu*)–negative and pT1 to 4/pN1 to 3 invasive breast cancer from January 1, 2010, to December 31, 2014, were selected from the NCDB. Patients were included if they had a Charlson/Deyo comorbidity score of 2 or 3, and those with a comorbidity score of 0 or 1 were excluded. The Charlson/Deyo score is a weighted score derived from the sum of scores for comorbid conditions. For example, a score of 2 could include a patient with chronic pulmonary disease and congestive heart failure. In our study, patients with a score of 2 or 3 were considered to have severe comorbidities that require medical management affecting general health and potentially limit life expectancy. Race/ethnicity as defined by the NCDB was included in the analysis to make the results more generalizable to the US population. Patients were excluded if they received a diagnosis of stage M1 disease. Patients who underwent neoadjuvant therapy (chemotherapy, radiation therapy, or endocrine therapy), who underwent a breast surgery other than lumpectomy or mastectomy, who did not have axillary surgery, and with missing or unknown surgery or adjuvant treatment data were excluded. Patients with missing hormone receptor status and those with *ERBB2*-positive disease were excluded. The start date of 2010 was the first year that data on *ERBB2* status was captured in the NCDB. Patients who received a diagnosis in 2015 were excluded because no survival data for such patients were included in the database. Lastly, patients with pathologic node-negative disease were excluded.

Statistical Analysis

To reduce the influence of treatment selection bias on the estimation of the association of treatment with overall survival (OS) using observational data, we conducted propensity score–matched analyses.[9-11] The propensity score was the conditional probability of receiving chemotherapy given a set of observed covariates (eMethods in the Supplement).

Figure. Kaplan-Meier Curves for Overall Survival (OS) Among Patients Who Did and Did Not Receive Chemotherapy



In the matching analyses, we included the following covariates in the multivariate logistic regression model to create the propensity scores: age at diagnosis, Charlson/Deyo score (2 or 3), facility type, geographic location (metropolitan, urban, rural, or unknown), pathologic T stage, pathologic N stage, endocrine therapy, and radiation therapy. For each match, we identified 1:1 matched doublets using a 5- to 1-digit greedy match algorithm.[12]

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Overall survival was measured from the time of diagnosis to the time of death and, for patients who did not die, was censored at the time of last contact. The distribution of OS was estimated by the Kaplan-Meier method.[13] For the nonmatched cohorts, the log-rank test was performed to test the difference in survival between groups.[14] Regression analyses of survival data based on the Cox proportional hazards regression model were conducted for OS in a multivariate setting.[15] For the matched cohort, a stratified log-rank test with the matched pairs as strata were fitted to evaluate the difference in OS between the treatment groups. We also adjusted for the matching factors using double robust estimation under the Cox proportional hazards regression model.[16] Data analysis was performed from December 13, 2018, to April 28, 2020. All tests were 2-sided. $P < .05$ was considered statistically significant. All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc) and S-plus software, version 8.04 (Tibco Software Inc).

Results

Patient Characteristics

Of a total of 2 445 870 patients in the data set, 1592 patients (mean [SD] age, 77.5 [5.5] years; 1543 [96.9%] female) met the inclusion criteria and were included in the initial nonmatched analysis. Of these, 350 (22.0%) received chemotherapy and 1242 (78.0%) did not. Compared with patients who did not receive chemotherapy, node-positive patients who received chemotherapy were younger (mean age, 74 vs 78 years; $P < .001$), had higher-grade disease (grade 3: 116 [33.1%] vs 302 [24.3%]; $P = .002$), had larger primary tumors (pT3/T4 tumors: 72 [20.6%] in the chemotherapy group vs 182 [14.7%] nonchemotherapy group; $P = .005$), and had a higher degree of nodal burden (75 [21.4%] vs 81 [6.5%] with stage pN3 disease in the chemotherapy group and 182 [52.0%] vs 936 [75.4%] with stage pN1 disease in the nonchemotherapy group; $P < .001$) (eTable in the Supplement). More patients who received chemotherapy were treated with radiation therapy (236 [67.4%] vs 540 [43.5%]; $P < .001$) and endocrine therapy (309 [88.3%] vs 1025 [82.5%]; $P = .01$) compared with patients who did not receive chemotherapy. No difference was found in the type of primary breast surgery performed (lumpectomy or mastectomy) between patients who did and did not receive chemotherapy, and most patients in both groups underwent mastectomy.

OS Outcomes

Median follow-up was 41.4 months (95% CI, 39.7-43.7 months) in the nonmatched cohort. Median OS for the entire group was 59.5 months (95% CI, 55.0-65.6 months): 78.9 months for the patients who received chemotherapy (95% CI, 68.2 months to not reached) and 54.9 months (95% CI, 51.3-58.0 months) for

Table 1. Absolute Standardized Difference Between the Groups That Did and Did Not Receive Chemotherapy in the Propensity Score–Matched Analysis Before and After Matching[a]

Variable	Nonmatched cohort	Matched cohort
Age, mean (SD), y	77.5 (5.5)	74.2 (3.5)
Charlson/Deyo comorbidity score, mean (SD)	2.2 (0.4)	2.2 (0.4)
Treatment facility	5.1	8.6
Home location	9.1	10.2
Pathologic stage		
T	22.8	8.5
N	58.3	9.1
Therapy		
Endocrine	16.4	10.0
Radiation	49.6	2.8

[a] Data are presented as the standardized difference defined as the absolute difference in sample means divided by an estimate of the pooled SD of the variable unless otherwise indicated. A difference of less than 10% represents well-matched cohorts.

the patients who did not receive chemotherapy ($P < .001$) (**Figure**).

Propensity Score–Matched Analysis and Outcomes

A total of 592 patients were included in the matched analysis. The absolute standardized difference between groups for all variables was less than 10.25% (**Table 1**), representing a well-matched cohort. In the matched cohort, the median follow-up was 43.1 months (95% CI, 39.6-46.5 months). The median OS in the chemotherapy group was 78.9 months (95% CI, 78.9 months to not reached), and the median OS in the nonchemotherapy group was 62.7 months (95% CI, 56.2 months to not reached); this difference was not statistically significant ($P = .13$) (Figure).

Multivariate Analysis

After adjustment for other risk factors in the matched cohort (**Table 2**), a benefit in OS was seen in the chemotherapy group compared with the nonchemotherapy group (hazard ratio [HR], 0.67; 95% CI, 0.48-0.93; $P = .02$). Factors significantly associated with worse OS in the matched cohort were a Charlson/Deyo score of 3 vs 2 (HR, 1.94; 95% CI, 1.34-2.79; $P < .001$), a higher pathologic T stage (pT4 vs pT1: HR, 3.51; 95% CI, 1.86-6.62; $P < .001$), and a higher pathologic N stage (pN3 vs pN1: HR, 1.71; 95% CI, 1.09-2.69; $P = .04$). Factors associated with an improved OS in the matched cohort were receipt of endocrine therapy (HR, 0.47; 95% CI, 0.31-0.72; $P < .001$) and, similar to receipt of chemotherapy, receipt of radiation therapy (HR, 0.61; 95% CI, 0.43-0.87; $P = .006$).

Table 2. Comparison of Overall Survival by Chemotherapy Status in the Multivariate Analysis in the Matched Cohort

Variable	HR (95% CI)	*P* value
Age	1.03 (0.99-1.07)	.09
Charlson/Deyo comorbidity score		
2	1 [Reference]	<.001
3	1.94 (1.34-2.79)	
Home location		
Metropolitan	1 [Reference]	.44
Unknown	1.61 (0.55-4.69)	
Rural	2.10 (0.74-5.96)	
Urban	1.13 (0.73-1.76)	
Treatment facility		
Academic or research program	1 [Reference]	.17
Comprehensive community program	1.51 (0.96-2.38)	
Community cancer program	1.24 (0.75-2.06)	
Pathologic T stage (pT)		
T1	1 [Reference]	<.001
T2	2.30 (1.49-3.55)	
T3	2.30 (1.30-4.05)	
T4	3.51 (1.86-6.62)	
Pathologic N stage (pN)		
N1	1 [Reference]	.04
N2	1.43 (0.97-2.11)	
N3	1.71 (1.09-2.69)	
Adjuvant chemotherapy		
No	1 [Reference]	.02
Yes	0.67 (0.48-0.93)	
Adjuvant endocrine therapy		
No	1 [Reference]	<.001
Yes	0.47 (0.31-0.72)	
Adjuvant radiation therapy		
No	1 [Reference]	.006
Yes	0.61 (0.43-0.87)	

Abbreviation: HR, hazard ratio.

Discussion

Increasing age is associated with a higher incidence of comorbidities and an elevated risk of breast cancer.[17] Although management decisions should not be based on age alone, the National Comprehensive Cancer Network guidelines recommend that treatment of patients with breast cancer who are 70 years or older should be tailored to account for comorbid conditions.[2] However, this population is often excluded from clinical trial participation, and few data exist on the association of treatment with survival in elderly patients with multiple comorbidities. In this contemporary analysis of elderly patients with estrogen receptor–positive, pathologic node-positive breast cancer, 22.0% were treated with chemotherapy. This finding is comparable to those of a study by Giordano et al[18] that evaluated adjuvant chemotherapy outcomes in patients older than 65 years, in which rates of chemotherapy increased over time to 16.3% by 1999.

To our knowledge, this was the first retrospective study to evaluate adjuvant chemotherapy outcomes in elderly patients with breast cancer and comorbidities. We evaluated only patients with estrogen receptor–positive, pathologic node-positive disease because most breast cancer in women older than 70 years is estrogen receptor positive, and a clinical question in these patients is the added value of chemotherapy. We

found that patients who received chemotherapy were younger and had a higher degree of nodal burden and a higher stage of disease. In a study on adjuvant chemotherapy in patients older than 66 years using the Surveillance, Epidemiology and End Results cancer registries, Elkin et al[19] found a survival benefit in patients who received chemotherapy that occurred mostly in those with lymph node–positive disease; however, this finding was among hormone receptor–negative patients only.[19] In a cohort analysis of Dutch and Belgian postmenopausal, hormone receptor–positive patients with breast cancer, breast cancer mortality was higher and rates of chemotherapy were lower in patients older than 70 years compared with patients younger than 70 years, but this finding was statistically significant only in patients without comorbidities in both groups.[17]

In our study, in analysis adjusted for matching factors, receipt of chemotherapy was associated with improved OS. This finding is consistent with findings from a prospective study by Owusu et al[20] that evaluated treatment patterns in older patients with breast cancer. That study found that in women older than 75 years, who were also more likely to have a Charlson Comorbidity Index score of 2 or higher, receipt of guideline-concordant care was associated with a reduced proportional increase in age-related breast cancer–specific mortality hazard by 25%.[20] In a single-institution study by Ibrahim et al[21] that evaluated adjuvant chemotherapy in elderly patients with breast cancer, most of whom had hormone receptor–positive and node-positive cancer, disease-free survival and OS were similar between patients 65 years or older and younger than 65 years. In addition, adjuvant chemotherapy was well tolerated in elderly patients with good performance status and cardiac function.[21] Of note, all patients included in our study underwent breast and axillary surgery despite multiple comorbidities; however, only a subset of these patients was treated with adjuvant chemotherapy, suggesting that other nonstandardized factors were used in clinical decision-making. This finding is supported by findings from a multicenter prospective study by Okonji et al[22] that evaluated rates of adjuvant therapy in elderly patients with stage I to III breast cancer who were deemed to be fit for treatment by a comprehensive geriatric assessment. Although all women 70 years or older underwent surgery, only 51% of those with high-risk disease received adjuvant chemotherapy.[22]

Increased life expectancy in the context of effectively managed comorbidities is an important aspect of adjuvant chemotherapy decisions in older patients with breast cancer. Prior studies[23,24] have investigated the association of age and comorbidity with breast cancer–specific survival and OS. In a retrospective review[25] of toxicity data from randomized clinical trials of chemotherapy for pathologic node-positive breast cancer, healthy older patients experienced more toxic effects from treatment compared with their younger counterparts, which did not translate to increased mortality.[25] These findings have led to the guideline recommendations of administering adjuvant chemotherapy to older patients based on comorbidity instead of chronologic age alone.[2,6] However, several studies[7,20,26,27] have found age-related disparities with respect to receipt of guideline-concordant care in elderly patients with breast cancer, resulting in undertreatment. Although the effect on prognosis is controversial, these findings reflect the lack of a standardized assessment of comorbidities required for optimal multidisciplinary treatment of the older, deconditioned patients with breast cancer. Our study found that carefully selected patients within this subset of the population may benefit from additional adjuvant treatment, highlighting the importance of accurately estimating life expectancy in patients with multiple comorbidities. In addition, genomic tests, such as Oncotype DX, may help to better capture tumor biology and refine patient selection for chemotherapy among those with node-positive disease. Future studies should focus on integrating geriatricians into multidisciplinary breast cancer care to optimize outcomes in less well-studied older patients with multiple comorbidities and node-positive breast cancer.

Limitations

This study has limitations, including those inherent to large database analyses. The NCDB does not provide breast cancer–specific survival data, and OS might not be an appropriate surrogate in elderly patients with breast cancer with increased life expectancy rates. However, for this study, in evaluating breast cancer treatments in the context of competing comorbidities, OS was a useful primary outcome measure. In addition, the Charlson/Deyo comorbidity score is limited in its ability to accurately reflect the true health status of patients and has been found in a previous study[28] to underestimate comorbidity in patients with breast cancer because of coding inaccuracies and underreporting of comorbid conditions by CoC-accredited programs. Although we used a propensity score–matched analysis in an attempt to minimize selection bias, it is likely that additional unmeasured variables contributed to our findings. In addition, although we found that patients undergoing chemotherapy had higher-grade disease, the estrogen receptor and progesterone receptor percentages and Ki67 data are not included in the NCDB, and we did not have all the information needed to construct luminal A vs luminal B subtypes. We hypothesize that the benefit of chemotherapy would have been greater in the luminal B subset of patients who were recommended to undergo chemotherapy based on clinicopathologic features that we could not capture. The NCDB does not provide data on exact type and length of adjuvant systemic therapy. A previous study[29] found that nonadherence with adjuvant endocrine treatment was associated with decreased disease-free survival.[29] In patients who were not deemed to be fit for chemotherapy, it is possible that they received suboptimal treatment with endocrine therapy, which would further widen the gap in survival between the chemotherapy and nonchemotherapy groups. With regard to chemotherapy, it is unlikely that these patients received the standard anthracycline and taxane regimen at full doses. Knowledge of the chemotherapy regimens and potential dose reductions could serve as a surrogate for a physician's perception of a patient's general health status. Although we were unable to obtain this information from the NCDB data, use of any chemotherapy in older patients with multiple comorbidities indicates that these patients may still derive benefit. This assumption underscores the need for prospective clinical trials to develop individualized adjuvant treatments for patients with complex dis-

ease. Furthermore, we found that patients selected to undergo surgery and chemotherapy were also more likely to undergo radiation therapy and endocrine therapy, resulting in treatment bias. Although we included only patients with reported comorbidity scores of 2 or 3 and propensity score matching reduces such bias, these limitations may have skewed the population to a healthier cohort who could tolerate treatment associated with improved survival outcomes. Therefore, the results of this study should be interpreted with caution.

Conclusions

In this study of estrogen receptor–positive, pathologic node-positive elderly patients with breast cancer and multiple comorbidities, receipt of adjuvant chemotherapy was associated with improved OS. Patients who received chemotherapy were younger and more likely to receive other adjuvant treatments, suggesting that physicians carefully selected patients likely to derive treatment benefit from adjuvant chemotherapy despite multiple comorbidities based on certain unmeasured variables. In addition, estrogen receptor–positive breast cancer is a heterogeneous disease, and survival benefit from chemotherapy may be associated with differences in luminal subtype. Prospective clinical trials would inform the development of standardized tools to account for life expectancy, tolerance to treatment, and clinicopathologic tumor features for patients who might benefit from systemic therapy to optimize care in this underrepresented group of patients.

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Author Affiliations: Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston (Tamirisa, Bedrosian); Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston (Lin, Shen); Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston (Shaitelman); Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston (Sri Karuturi, Giordano); Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston (Giordano); MD Anderson Physician Network, The University of Texas MD Anderson Cancer Center, Houston (Babiera).

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Concept and design: Tamirisa, Shen, Shaitelman, Giordano, Babiera, Bedrosian.
Acquisition, analysis, or interpretation of data: Tamirisa, Lin, Shen, Shaitelman, Sri Karuturi, Babiera, Bedrosian.
Drafting of the manuscript: Tamirisa, Lin, Shaitelman.
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