Adjuvant Chemotherapy in Premenopausal Patients With Hormone-Positive Breast Cancer With a Recurrence Score of 16-25: A Retrospective Analysis Using the National Cancer Database

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ABSTRACT

PURPOSE Results from the TAILORx trial revealed that the use of adjuvant chemotherapy along with endocrine therapy had no survival advantage in patients with estrogen receptor (ER)–positive, human epidermal growth factor receptor 2–negative (HER2–), node-negative (N0) breast cancer (BC) with an intermediate (11-25) 21-gene recurrence score (RS) in the overall population. However, in patients under age 50 years, adjuvant chemotherapy demonstrated a progression-free survival benefit when the RS ranged from 16-25. We studied this cohort with the population-based national database.

METHODS The 2010-2018 National Cancer Database was used to include patients with BC age 18-50 years, N0, M0, RS 16-25, ER+/progesterone receptor±, and HER2–. Patients were divided into two groups on the basis of adjuvant chemotherapy use, and the survival between them was compared.

RESULTS Adjuvant chemotherapy use was noted in 4,808/15,792 (30.45%) patients. Median RS was 18 and 21 in patients without and with adjuvant chemotherapy, respectively. Factors associated with adjuvant chemotherapy use were higher T stage, poor and moderately differentiated tumors, age <40 years, care at an academic center, Caucasian race, patients undergoing mastectomy, regional lymph node surgery, and radiation therapy. Kaplan-Meier survival at 10 years was better with adjuvant chemotherapy (96.2% *v* 91.6%). Patients without adjuvant chemotherapy had more adverse outcomes (hazard ratio [HR], 1.683 [95% CI, 1.392 to 2.036]; $P < .0001$). Subgroup analysis showed that the benefit was significant in patients with RS scores 21-25 (HR, 1.953 [95% CI, 1.295 to 2.945]), ductal histology (HR, 1.521 [95% CI, 1.092 to 2.118]), Caucasian race (HR, 1.655 [95% CI, 1.180 to 2.322]), and 41-50 years age group (HR, 1.732 [95% CI, 1.244 to 2.411]).

CONCLUSION Our study showed an overall survival benefit for adjuvant chemotherapy use in patients with ER-positive, N0 premenopausal BC patients, age less than 50 years, with an intermediate RS score, particularly 21-25.

INTRODUCTION

Several gene expression profiling tests are currently available for use in patients with breast cancer (BC). These include Oncotype DX recurrence score (RS), Prosigna (PAM 50), EndoPredict, and MammaPrint. Among these, the Oncotype DX is the most widely used test.[1] The RS is a validated tool to guide physicians on the need for adjuvant chemotherapy in patients with hormone receptor–positive and human epidermal growth factor receptor 2–negative (HER2–), early-stage BC.[2] The Trial Assigning Individualized Options for Treatment (TAILORx) was a prospective trial designed to analyze the utility of adjuvant chemotherapy in patients with intermediate RSs of 11-25. It was a prospective study that involved ≥10,000 women. Patients were hormone receptor–positive, HER2–, and had an age range of 18-75 years. On the basis of the RS, patients were stratified into four groups (≤10, 11-25 and ≥26). The ≤10 group received endocrine therapy (ET) alone, while the ≥26 received both adjuvant chemotherapy and ET. Patients in the mid-range RS group of 11-25 were randomly assigned to receive either ET alone or chemo-ET (adjuvant chemotherapy + ET).

CONTEXT

Key Objective

Our aim was to see if addition of adjuvant chemotherapy to endocrine therapy (ET) had any survival advantage in patients with hormone receptor–positive, early-stage, node-negative, premenopausal breast cancer (BC) with an intermediate recurrence score (RS) of 16-25. Although clinical trials such as the TAILORx showed that there was merit to adding chemotherapy in this group, real-world data were lacking, which we tried to provide with our analysis.

Knowledge Generated

We found that chemotherapy use along with ET after surgery in the above-mentioned cohort of young patients with node-negative BC did lead to a better overall survival compared with ET alone. This adds merit to the findings of prospective studies such as the TAILORx.

Relevance

With our results, physicians have additional evidence to recommend adjuvant chemotherapy to this cohort of premenopausal patients, particularly those with ductal histology and a RS of 21-25.

Although ET alone was noninferior to adjuvant chemotherapy + ET in the overall cohort, in young women age ≤50 years, lower risk of distant recurrence was noted with adjuvant chemotherapy + ET when the RS was above 15. When the original study was published in 2018, no difference in overall survival (OS) was seen, but a longer follow up was to follow.[3]

Despite these findings, experts remain divided on adjuvant chemotherapy use for premenopausal patients RS-16-25. Particularly, it is believed that patients who are clinically low risk with small- and low-grade tumors will not benefit from adjuvant chemotherapy.[4] To better understand this aspect in young, premenopausal patients, we performed an analysis using an established national database, the National Cancer Database (NCDB).[5] Our aim was to see if adjuvant chemotherapy had any survival benefit in young patients having similar characteristics to those of the TAILORx cohort.

METHODS

Data Source

The NCDB is a conglomeration of information consisting of patient demographic, pathologic, and clinic characteristics from Commission on Cancer–accredited facilities in the United States. It is managed by the American College of Surgeons, who reviewed our proposal and provided access to the database.[6] The study was reviewed by the SUNY Upstate Institutional Review Board (IRB) and was provided an exempt status.

Patient Selection

Our cohort comprised patients diagnosed between 2010 and 2018, as RS and HER2 data were available only from 2010 onwards. Patients with BC age 50 years and younger were included and stratified into 18-40 years and 40-50 years (any age >40 years, but ≤50 years was included in this group). The study utilized the ICD-O-3 Site Codes for breast cancer (C500-C506, C508-C509) to ensure inclusion of patients specifically diagnosed with BC. Only female patients with T1-T4 and N0 staging were included in the analysis. Ductal carcinoma in situ or stage IV patients were excluded. The NCDB included American Joint Committee on Cancer (AJCC) Staging Manual eighth edition and previous editions for staging; we preferably used the eighth edition when available. Only HR+ (estrogen receptor [ER] and/or progesterone receptor [PR] + and HER2-) patients were included. Oncotype DX RSs were identified and only those patients with a RS of 16-25 were included. We used both collaborative stage site-specific factors and site-specific data items defined in the NCDB data dictionary as needed for ER/PR/HER2 status and Rx score.[8] Dates of definitive surgery and chemotherapy start dates were identified and used to ascertain patients who received adjuvant chemotherapy. This was done by ensuring that chemotherapy start dates were after definitive surgery. Patients who received neoadjuvant chemotherapy were excluded. Patients were divided into two cohorts on the basis of whether they received adjuvant chemotherapy (Chemo+) or not (Chemo−) and survival outcomes were compared.

Statistical Analysis

Demographic and clinical characteristics of patients who received adjuvant chemotherapy versus those that did not receive adjuvant chemotherapy were summarized by frequencies and proportions, and chi square tests were performed to assess the association. Multivariate logistic regression analysis was used to evaluate the impact of each characteristic on the likelihood of receiving adjuvant chemotherapy, including grade, analytic stage, Charlson Deyo Comorbidity Score (CDCC) total score, ER/PR, surgery type

(regional lymph node [RLN]), insurance, race, radiation (Y/N), age, facility type, hormone used, surgery site, AJCC pathologic T stage, Rx score, and histology. After backward selection, factors that were left in the model other than the study group include race, insurance, grade, CDCC total score, surgery type (RLN), hormone used, AJCC pathologic T stage, and Rx score. Survival data were summarized and presented by Kaplan-Meier curves. The survival rates at 5 and 10 years were provided with the 95% CIs calculated after log-log transformation. The impact of adjuvant chemotherapy on OS was assessed by fitting a variety of Cox's proportional hazards regression models: univariate model with only the adjuvant chemotherapy group; multivariate models with all factors as in the logistic regression that may relate to receiving adjuvant chemotherapy treatment; same multivariate models but with a backward selection procedure; and propensity score (PS) weighted Cox model with the weighted derived from the logistic regression above. Exploratory subgroup analyses were also performed to assess whether the effect of adjuvant chemotherapy use on survival differed by subgroups. Separate multivariate Cox models were fitted within each subgroup where all other related factors were included, other than the one defining the subgroup. All statistical analyses were performed using SAS 9.4 (Cary, NC) and a two-sided $P < .05$ was considered statistically significant.

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. The SUNY Upstate IRB has reviewed the project and has determined this project does not meet the definition of human subject research under the purview of the IRB according to federal regulations. IRB No. 1778292.

Consent to Participate

Not applicable. Data were obtained from the NCDB PUF file. It is a Health Insurance Portability and Accountability Act–complaint data file where patient information is deidentified.

RESULTS

A total of 15,792 patients met our inclusion criteria. Of these, 4,808 (30.45%) received adjuvant chemotherapy, while 10,984 (69.55%) did not receive adjuvant chemotherapy. Table 1 shows the distribution of patients on the basis of adjuvant chemotherapy use (Chemo+ or Chemo–). Most of the patients had T1 (Chemo+: 69.72%, Chemo–: 80.64%) and stage I disease (Chemo+: 69.8%, Chemo–: 80.55%). Chemo+ group had relatively more T2 patients (Chemo+: 28.33%, Chemo–:18.62%). Both cohorts predominantly comprised patients age 40-50 years (Chemo+: 74.27%, Chemo–:83.15%). Chemo+ cohort had a median age of 44 years (20-49 years), while Chemo– had a median age of 45 years (18-49 years). Patients were relatively healthy as >90% in both cohorts had a CDCC of 0. On analyzing the demographics of both groups, it was noted that both groups predominantly belonged to the Caucasian race (>90%), had an annual income of ≥$48,000 US dollars (>70%), and had private insurance (around 85%) as shown in Table 1. Most patients who received adjuvant chemotherapy started them between 61 and 90 days (41.78%) or >90 days (42.72%). Again, as shown in Table 1, distribution for radiation therapy (RT) and type of surgery (mastectomy *v* breast conserving surgery) was similar between the two groups. 97.52% received multiagent chemotherapy. The median RS score was 21 for Chemo+ and 18 for Chemo–.

Table 2 represents the odds ratio estimate of the likelihood of receiving adjuvant chemotherapy. Factors that reached significance for adjuvant chemotherapy use includes age 18-40 years, poor and moderately differentiated tumors, T2, T3, and T4 compared with T1, mastectomy, RLN surgery, RT use, hormonal therapy use, Rx score 21-25, and ductal histology.

Overall Kaplan-Meier (KM) survival estimate at 10 years was 96.2% (94.8%-97.3%) with adjuvant chemotherapy use and 91.6% (88%-94.2%) without it. This is shown in Table 3, and the curves are represented in Figure 1. Multivariate and PS weighted models showed that the Chemo+ group had better overall outcomes after adjustment of other factors. PS score–adjusted hazard ratio (HR) estimates showed that Chemo– had 66% higher chance of mortality than Chemo+ (HR, 1.664 [95% CI, 1.387 to 1.995]; $P < .0001$; Table 3). Forest plot for the subgroup analysis of the HR estimates for adjuvant chemotherapy benefit using the multivariate model is shown in Figure 2. Survival benefit with adjuvant chemotherapy use was seen in patients with Rx score of 21-25 (HR, 1.953 [95% CI, 1.295 to 2.945]), ductal histology (HR, 1.521 [95% CI, 1.092 to 2.118]), Caucasian race (HR, 1.655 [95% CI, 1.180 to 2.322]), and 41-50 years age group (HR, 1.732 [95% CI, 1.244 to 2.411]). Other factors that showed significance include T1 (HR, 1.610 [95% CI, 1.107 to 2.340]) and G2 disease (HR, 1.766 [95% CI, 1.140 to 2.736]).

DISCUSSION

The results from our analysis of NCDB, a large, national hospital–based database, led us to hypothesize that for patients with early-stage, node-negative, hormone receptor–positive BC with Rx scores of 16-25, adjuvant chemotherapy may offer an OS advantage. Although the KM survival curves showed a modest survival benefit of 4.6% at 10 years, the adjusted HR estimates confirmed that omitting adjuvant chemotherapy led to a 66% higher mortality rate. The survival curves at 5 years were very similar between the two groups but showed separation near the 10-year mark. Subgroup analysis showed a significant mortality benefit

TABLE 1. Demographic, Pathologic, and Clinical Characteristics of the Study Population and Their Distribution on the Basis of Adjuvant Chemotherapy Use

	Adjuvant Chemotherapy Used, No. (%)	Adjuvant Chemotherapy Not Used, No. (%)	
Variable	4,808 (30.45)	10,984 (69.55)	*P*
Age, years			.002[a]
18-40	1,237 (25.73)	1,851 (16.85)	
41-50	3,571 (74.27)	9,133 (83.15)	
Race			.002[a]
Caucasian	3,975 (82.67)	9,111 (82.95)	
African American	408 (8.49)	906 (8.25)	
Other races	425 (8.84)	967 (8.80)	
Pathologic T			.002[a]
T1	3,352 (69.72)	8,857 (80.64)	
T2	1,362 (28.33)	2,045 (18.62)	
T3	88 (1.83)	77 (0.70)	
T4	6 (0.12)	5 (0.05)	
Disease stage			.002[a]
Stage I	3,356 (69.80)	8,848 (80.55)	
Stage II	1,445 (30.05)	2,130 (19.39)	
Stage III	7 (0.15)	6 (0.05)	
Charlson-Deyo score			.002[a]
0	4,373 (90.95)	10,121 (92.14)	
1	396 (8.24)	776 (7.06)	
2	31 (0.64)	63 (0.57)	
≥3	8 (0.17)	24 (0.22)	
ER/PR receptor status			.002[a]
ER-positive, PR-positive	4,618 (96.09)	10,653 (97.05)	
ER-positive, PR-negative	186 (3.87)	314 (2.86)	
ER-negative, PR-positive	2 (0.04)	10 (0.09)	
Tumor grade			.002[a]
Well differentiated	817 (16.99)	3,220 (29.32)	
Moderately differentiated, moderately well differentiated, and intermediate differentiation	2,670 (55.53)	6,128 (55.79)	
Poorly differentiated	1,148 (23.88)	1,249 (11.37)	
Undifferentiated, anaplastic	4 (0.08)	1 (0.01)	
Cell type not determined, not stated not applicable, unknown primaries	169 (3.51)	386 (3.51)	
% who completed high school degree in 2012			.002[a]
≥21%	466 (11.02)	1,045 (10.95)	
13.0%-20.9%	797 (18.85)	1,821 (19.07)	
7.0%-12.9%	1,407 (33.29)	3,170 (33.20)	
<7.0%	1,557 (36.83)	3,511 (36.78)	
Regional lymph node surgery			.002[a]
No RLN surgery	25 (0.52)	94 (0.86)	
RLN surgery done	4,781 (99.44)	10,888 (99.13)	
Unknown if there was any RLN surgery	2 (0.04)	2 (0.02)	
RT			.002[a]
No RT received	2,076 (43.18)	4,470 (40.70)	
RT received	2,732 (56.82)	6,514 (59.30)	
Type of facility			.002[a]
Community cancer program	1,542 (32.07)	4,038 (36.76)	
Academic/research program	1,504 (31.28)	3,453 (31.44)	

(continued on following page)

TABLE 1. Demographic, Pathologic, and Clinical Characteristics of the Study Population and Their Distribution on the Basis of Adjuvant Chemotherapy Use (continued)

	Adjuvant Chemotherapy Used, No. (%)	Adjuvant Chemotherapy Not Used, No. (%)	
Variable	4,808 (30.45)	10,984 (69.55)	*P*
Integrated network cancer program	781 (16.24)	2,166 (19.72)	
Data not available	981 (20.40)	1,327 (12.08)	
Hormonal therapy			.002[a]
Hormonal therapy was used	4,522 (94.05)	10,162 (92.52)	
Not used	210 (4.37)	685 (6.24)	
Unknown	76 (1.58)	137 (1.25)	
Annual income in 2012, US dollars			.002[a]
<$48,000	1,108 (26.22)	2,533 (26.54)	
≥$48,000	3,118 (73.78)	7,012 (73.46)	
Type of insurance			.002[a]
Not insured	96 (2.00)	184 (1.68)	
Private insurance	4,105 (85.38)	9,439 (85.93)	
Government	553 (11.50)	1,247 (11.35)	
Unknown	54 (1.12)	114 (1.04)	
Type of surgery			.002[a]
Partial mastectomy	2,620 (54.49)	6,518 (59.35)	
Mastectomy	2,188 (45.51)	4,462 (40.63)	
Surgery, not otherwise specified	0	3 (0.03)	
Histology			<.001[b]
Ductal	3,779 (78.60)	8,323 (75.77)	
Lobular	407 (8.47)	1,132 (10.31)	
Others	622 (12.94)	1,529 (13.92)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; RT, radiation therapy.
[a]Fisher's exact test (used when <five individuals in a category).
[b]*P* < .05.

with adjuvant chemotherapy use in patients with Rx scores of 21-25 (HR of 1.953 suggesting almost a doubling of survival benefit) and in those with ductal histology. Our findings support those of the TAILORx trial[3] and emphasize the need for further research in this subset of patients with ER+ BC.

Invasive lobular histology constitutes 15% of all BC and is the second most common subtype.[9] The response to both neoadjuvant and adjuvant chemotherapy has been relatively lackluster in this subtype compared with the more common ductal variant.[10] A previous NCDB analysis showed that lobular histology was less often treated with chemotherapy than ductal (17.3% *v* 24.6%),[11] which is in line with our odds ratio estimates, where lobular histology had a lower chance of getting adjuvant chemotherapy (0.832, 0.729-0.950; Table 2). NCDB started recording RS since 2010 and with each advancing year, the proportion of patients who had information on RS progressively increased, reaching 44% in 2016.[11] When the RS score was designed, the intention was to provide a score from 0 to 100 that correlated with distant recurrence. A high score was meant to indicate a higher risk.[12] From the subgroup analysis of the HR estimates in our study that compared Chemo− versus Chemo+, while adjuvant chemotherapy led to lower mortality overall, only ductal histology (HR, 1.521 [95% CI, 1.092 to 2.118]) retained this advantage, and the significance was not seen in lobular histology (HR, 1.350 [95% CI, 0.505 to 3.614]). However, due to the limited sample size and the wide CI, a definitive conclusion cannot be drawn.

Other studies have used the NCDB to study the utility of RS in young patients.[13,14] Nash et al[13] queried a similar question using the NCDB but had key differences compared with our study. That study only included invasive ductal carcinoma, whereas our study included all BC histologies. The Nash study specifically analyzed patients between age 40 and 50 years and included both N0 and N1 patients, as opposed to our analysis where we included all patients younger than 50 years and only used the N0 population. In contrast to our results where patients age 41-50 years and ductal histology did have OS benefit with adjuvant chemotherapy use, the Nash cohort included patients age 40-50 years, N0, and RS 16-25 who did not have any OS benefit. This could be due to

TABLE 2. Estimated ORs and 95% CIs of Receiving Adjuvant Chemotherapy From Multivariate Logistic Regression

OR Estimates and Wald CI		
OR Comparison	Estimate	95% CI
Age, years: 41-50 *v* 18-40	0.815	0.690 to 0.964
Type of facility: academic/research program *v* community cancer program	1.076	0.981 to 1.179
Type of facility: integrated network cancer program *v* community cancer program	0.902	0.809 to 1.006
Race: African American *v* Caucasian	0.873	0.762 to 1
Race: other races *v* Caucasian	0.897	0.786 to 1.023
Insurance: private insurance *v* not insured	0.852	0.648 to 1.119
Insurance: government *v* not insured	0.806	0.602 to 1.080
Charlson-Deyo score: 1 *v* 0	1.153	1.004 to 1.324
Charlson-Deyo score: 2 *v* 0	1.168	0.733 to 1.863
Charlson-Deyo score: ≥3 *v* 0	0.694	0.290 to 1.659
Grade: moderately differentiated, moderately well differentiated, intermediate differentiation *v* well differentiated, differentiated	1.495	1.359 to 1.644
Grade: poorly differentiated *v* well differentiated	2.547	2.258 to 2.873
T stage: T2 *v* T1	1.927	1.010 to 3.677
T stage: T3 *v* T1	3.361	1.620 to 6.976
T stage: T4 *v* T1	2.263	0.058 to 88.754
Stage II *v* stage I	0.858	0.449 to 1.637
Stage III *v* stage I	1.401	0.045 to 43.275
Type of surgery: mastectomy *v* partial mastectomy	1.459	1.225 to 1.739
RLN surgery *v* no RLN surgery	1.701	1.054 to 2.745
Radiation received *v* no radiation received	1.420	1.193 to 1.692
ER+/PR− *v* ER+/PR+	1.120	0.915 to 1.370
ER−/PR+ *v* ER+/PR+	0.665	0.140 to 3.163
Hormonal therapy: not used *v* used	0.647	0.544 to 0.771
Rx score 21-25 *v* 16-20	4.351	4.035 to 4.691
Histology lobular *v* ductal	0.832	0.729 to 0.950

Abbreviations: ER, estrogen receptor; OR, odds ratio; PR, progesterone receptor; RLN, regional lymph node.

the differences detailed above as well as the subtle differences in biostatistical techniques between the studies. Although Nash used the Cox proportional model, our study applied the PS method in addition to the Cox model and included more factors in the models.[13] PS methods have become more popular to balance patient characteristics between groups by assigning a weight to each subject proportional to the likelihood of the subject receiving the treatment.[15] Although the PS methods allow us to resemble the measures of effect commonly reported in randomized clinical trials, the methods can only consider observed confounders and effect modifiers, and do not address any unknown and/or unobserved factors. Moreover, the Nash et al[13] study's abstract mentions that patients between 2010 and 2017 were included, which is different from ours, where patients up until 2018 were used. Ibraheem et al used the NCDB 2010-2014 NCDB cohort to study the utility of adjuvant chemotherapy on the basis of RS subgroups. Patients were from all age groups and were not exclusively premenopausal. Marginally significant 5-year risk reduction was observed in the RS 18-25 group (HR, 0.79 [95% CI, 0.62 to 1]).[14] Adjuvant chemotherapy utilization trends were evaluated by Reyes et al using the 2010-2015 NCDB cohort. Patients younger than 50 years with RS of 16-25 were more likely to receive chemotherapy if they had a moderate tumor grade.[16]

In the TAILORx trial, among patients age 50 years or younger, a breakdown of the number of patients in the ET alone and ET+ adjuvant chemotherapy groups on the basis of the Rx score has been provided.[17] In this study, 454 patients with Rx between 16 and 20 received ET alone and, of these, 65 (14.31%) had an adverse event such as ipsilateral/contralateral local or distant recurrence, second primary cancer, or death. Four hundred and sixty-nine patients received ET+ adjuvant chemotherapy, of whom 38 (8.1%) had an adverse event. Among those with an Rx of 21-25, 246 received ET alone and 41 (16.67%) of them had an adverse event, while 246 received ET+ adjuvant chemotherapy, of whom 26 (10.57%) had an adverse event. From the subgroup analysis for invasive disease-free survival (DFS), for patients age 50 years or younger, the outcome was worse for ET alone when compared with ET+ adjuvant chemotherapy in both Rx score groups (Rx, 16-20, HR, 1.9 [95% CI, 1.27 to 2.84]; Rx, 21-25, HR, 1.7 [95% CI, 1.03 to 2.8]). For distant recurrence-free interval, significance was noted for Rx of 21-25 (HR, 2.19 [95% CI, 1.06 to 4.55]) but not with Rx of 16-20. With regards to relapse-free interval, Rx 21-25 showed significance (HR, 2.17 [95% CI, 1.2 to 3.92]) and 16-20 did not reach significance.[3,17] An updated analysis with the 12-year event rates presented at the San Antonio Breast Cancer Symposium 2022 confirmed the findings of the original publication. The updated analysis recorded more events than the primary analysis and noted that late recurrence exceeded the earlier recurrence rate.[18] It also showed the incorporation of clinical risk and noted that women age 50 years and younger with an RS of 16-25 and high clinical risk derived some benefits with adjuvant chemotherapy use, which remained at the 12-year mark.[18] This highlights the importance of tools such as the RSClin score in clinical practice. The tool can be used to determine an individualized absolute benefit from adjuvant

TABLE 3. Survival Outcomes

(A) KM Survival Estimates (%)

Time Frame	Chemo+	Chemo−	All Subjects
5 years	99 (98.6-99.3)	98.7 (98.4-99.0)	98.8 (98.6-99.0)
10 years	96.2 (94.8-97.3)	91.6 (88.0-94.2)	93.4 (91.2-95.1)

(B) HR (Chemo− *v* Chemo+)

Model	HR (95% Wald CI)	*P*
Univariate Cox model	1.305 (0.986 to 1.726)	.0627
Multivariate Cox model with all factors[a]	1.698 (1.260 to 2.289)	.0005
Multivariate Cox model with backward selection procedure[b]	1.748 (1.299 to 2.352)	.0002
PS weighted Cox model	1.664 (1.387 to 1.995)	<.0001

NOTE. (A) KM survival estimates with 95% Cis overall and by treatment groups (adjuvant chemotherapy use: Chemo+, no adjuvant chemotherapy use: Chemo−). (B) HR (Chemo− *v* Chemo+) from univariate, multivariate, and PS weighted Cox models.
Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; PS, propensity score.
[a]Other than the study group, the multivariate Cox model included grade, analytic stage, CDCC total score, ER/PR, surgery type (regional lymph node), insurance, race, radiation (Y/N), age, facility type, hormone used, surgery site, AJCC pathological T stage, RS score and histology.
[b]After backward selection, the following factors are left in the model other than the study group: race, insurance, grade, CDCC total score, surgery type (regional lymph node), hormone used, AJCC pathological T stage, and RS score.

chemotherapy, as it incorporates factors such as tumor grade, size, and age, in addition to the RS score.[19,20] Although the nature of our study, a retrospective database analysis, is completely different from TAILORx, which is a prospective clinical trial, our findings add flavor to these results by showing an OS advantage.

Hormone receptor–positive BC is a highly heterogenous disease. Several factors such as tumor grade, ER and PR expression level, Ki-67 index, and genomic characteristics play an important role in determining therapeutic outcome. The advent of RNA-based genomic assays and the improved understanding of the interplay between ER expression,

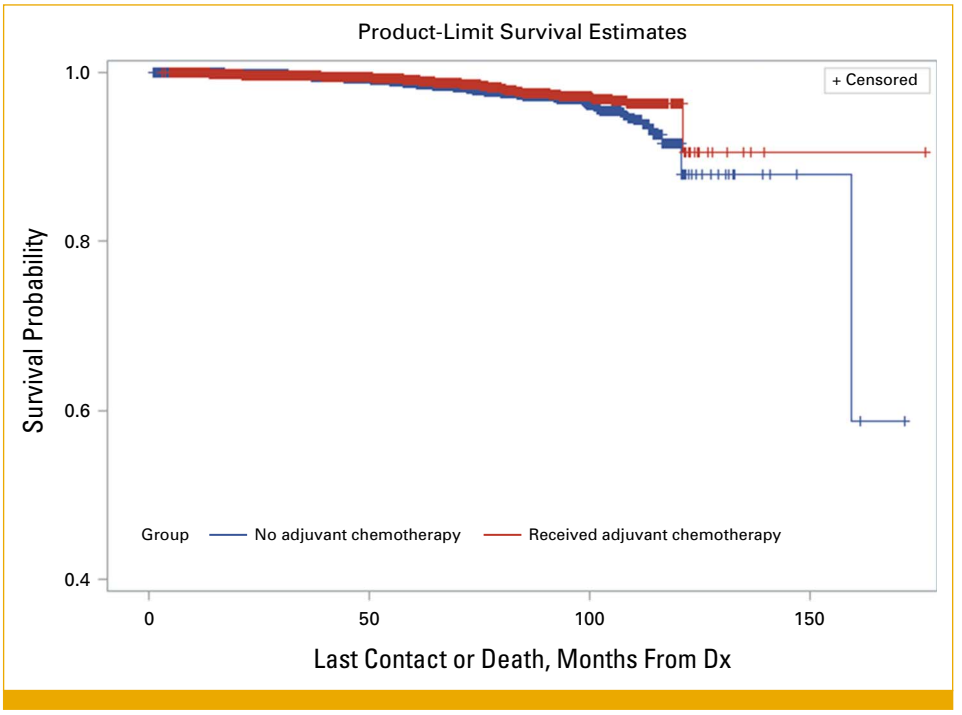

FIG 1. KM survival estimate curve comparing survival of Chemo+ and Chemo− groups. Chemo, adjuvant chemotherapy; KM, Kaplan-Meier.

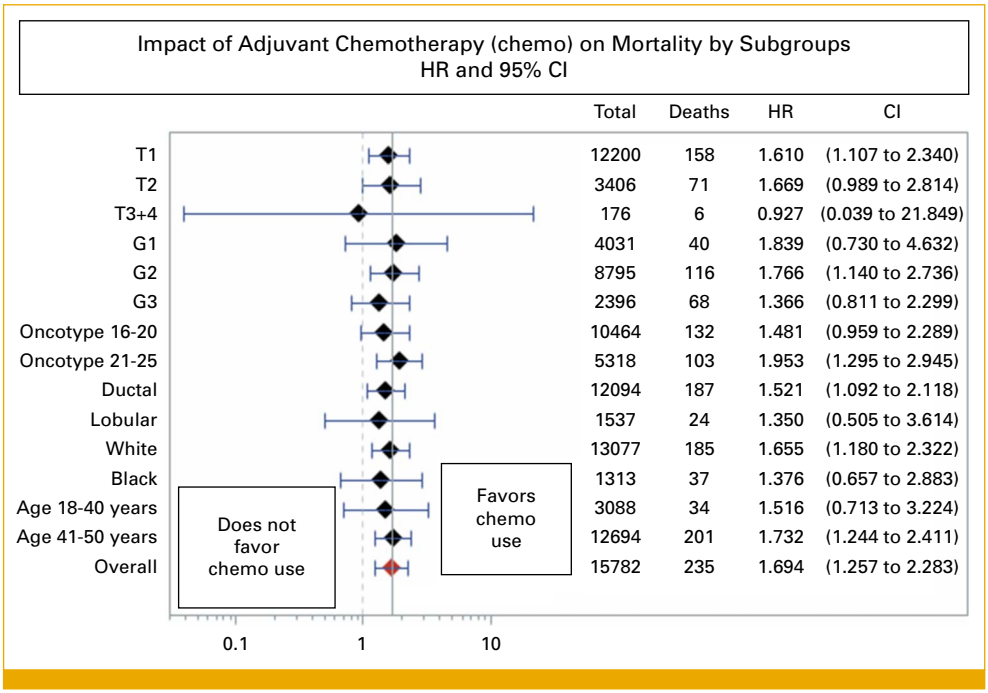

FIG 2. Forest plot of the subgroup HR mortality analysis for Chemo− versus Chemo+. Chemo, adjuvant chemotherapy; HR, hazard ratio.

tumor grade, and proliferation have created a space for the use of genomic assays in clinical practice, aiding physicians as they determine the need for chemotherapy for a particular patient.[21] The MammaPrint uses a set of 70 genes to classify patients as low or high risk for distant metastasis and OS.[22] The prospective MINDACT trial stratified patients into cohorts on the basis of both clinical and genomic risks. No adjuvant chemotherapy was given when both were low, while adjuvant chemotherapy was given when both were high. Patients with discordant clinical and genomic risk were stratified to receive either ET alone or ET+ adjuvant chemotherapy. The 5-year distant metastasis-free survival was 94.7% for patients with high clinical but low genomic risk, thereby identifying a cohort where adjuvant chemotherapy can be skipped.[23] In the updated analysis, it was reported that in the same group (high clinical and low genomic risk), women aged 50 years and younger had a higher metastasis-free survival benefit (5% *v* 0.2%) compared with women older than 50 years with adjuvant chemotherapy.[23] The Oncotype Dx RS uses 16 cancer-associated genes and five reference genes to provide a score ranging from 0 to 100.[12] Besides TAILORx, the adjuvant chemotherapy conundrum in patients with an intermediate RS exists even in the node-positive setting. The phase III RxPONDER trial evaluated patients with hormone receptor–positive BC with 1-3 positive nodes and a RS of ≤25. No additional advantage of adding adjuvant chemotherapy to ET was noted in this trial. However, in a subgroup of premenopausal patients 50 years and younger, DFS and relapse-free survival were significantly better.[24] The West German Study Group Plan B trial confirmed that N0 patients with an RS ≤11 can safely omit adjuvant chemotherapy.[25] Adjuvant chemotherapy in young patients with an RS of 16-25 could have a benefit, but it remains uncertain if the benefit is due to the direct cytotoxic effects of chemotherapy or due to ovarian suppression and menopause induction caused by adjuvant chemotherapy.[26] The ongoing NRG-BR009 prospective trial will answer this question.

Limitations of our study include its retrospective nature and the confounding that may arise from it despite PS weighted matching. Although 97.52% of our cohort received multi-agent chemotherapy, the specific agents used as a part of the regime are not available in NCDB. Furthermore, the number of cycles, details on compliance, dose modifications, and other specific treatment-related information are also unavailable.[27]

To conclude, our results, by demonstrating OS benefit, supplement the findings of the TAILORx study and support the use of adjuvant chemotherapy in patients with node-negative, hormone receptor–positive, young premenopausal BC, particularly with an RS score of 21-25 and ductal histology. Our study also contributes evidence suggesting that lobular histology may not derive significant benefit from adjuvant chemotherapy, although this conclusion is based on a small sample size. Future clinical trials looking into this cohort may help to better understand this question.

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DISCLAIMER

The authors have no relevant financial or non-financial interests to disclose. The National Cancer Database (NCDB) is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data used in the study are derived from a de-identified NCDB Participant User File (PUF) 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 investigators.

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DATA SHARING STATEMENT

The data sets analyzed during the current study are not publicly available as they were provided by the American College of Surgeons. They are available through an application process to investigators in Commission on Cancer–accredited cancer programs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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