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Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database

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Abstract

Purpose The Oncotype DX® Breast Recurrence Score™ (RS) assay is validated to predict breast cancer (BC) recurrence and adjuvant chemotherapy benefit in select patients with lymph node-positive (LN+), hormone receptor-positive (HR+), HER2-negative BC. We assessed 5-year BC-specific survival (BCSS) in LN+ patients with RS results in SEER databases.

Methods In this population-based study, BC cases in SEER registries (diagnosed 2004–2013) were linked to RS results from assays performed by Genomic Health (2004–2014). The primary analysis included only patients (diagnosed 2004–2012) with LN+ (including micrometastases), HR+ (per SEER), and HER2-negative (per RT-PCR) primary invasive BC ($N = 6768$). BCSS, assessed by RS category and number of positive lymph nodes, was calculated using the actuarial method.

Results The proportion of patients with RS results and LN+ disease ($N = 8782$) increased over time between 2004 and 2013, and decreased with increasing lymph node involvement from micrometastases to ≥4 lymph nodes. Five-year BCSS outcomes for those with RS < 18 ranged from 98.9% (95% CI 97.4–99.6) for those with micrometastases to 92.8% (95% CI 73.4–98.2) for those

with ≥4 lymph nodes. Similar patterns were found for patients with RS 18–30 and RS ≥ 31. RS group was strongly predictive of BCSS among patients with micrometastases or up to three positive lymph nodes ($p < 0.001$).

Conclusions Overall, 5-year BCSS is excellent for patients with RS < 18 and micrometastases, one or two positive lymph nodes, and worsens with additionally involved lymph nodes. Further analyses should account for treatment variables, and longitudinal updates will be important to better characterize utilization of Oncotype DX testing and long-term survival outcomes.

Abbreviations

1LN	One positive lymph node
1–3LN	One to three positive lymph nodes
2LN	Two positive lymph nodes
2–3LN	Two to three positive lymph nodes
3LN	Three positive lymph nodes
≥4LN	Four or more positive lymph nodes
ANOVA	Analysis of variance
BC	Breast cancer
BCSS	Breast cancer-specific survival
CI	Confidence interval
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HR+	Hormone receptor-positive (ER-positive, PR-positive, or both)
LN+	Lymph node-positive
N1mi	Micrometastases
PR	Progesterone receptor

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RS	Recurrence Score®
RT-PCR	Reverse transcription-polymerase chain reaction
RxPONDER	Treatment (Rx) for positive node, endocrine-responsive breast cancer
SD	Standard deviation
SEER	Surveillance, epidemiology, and end results
SES	Socioeconomic status

Background

The 21-gene Oncotype DX® Breast Recurrence Score™ (RS) assay (Genomic Health, Inc., Redwood City, CA, USA) aids in adjuvant chemotherapy decision-making for those with early-stage hormone receptor-positive (HR+), HER2-negative breast cancer. The assay was initially validated to predict recurrence risk and chemotherapy benefit among those with lymph node-negative disease [1, 2]. In this context, the RS assay provides additional information to the chemotherapy decision-making process, and has been shown to impact chemotherapy recommendations [3–6], reduce overall chemotherapy overuse [7], and be cost-effective [8].

Following its commercial availability in 2004, the test became covered by insurers beginning in 2006 and has been incorporated into current clinical guidelines beginning in 2007 for use among those with lymph node-negative disease [9]. Retrospective evidence accrued thereafter suggested that the test is also predictive among select patients with minimal lymph node involvement (1–3 positive nodes) [10, 11]. RS results in select lymph node-positive (LN+) patients have been validated to be prognostic for 10-year distant recurrence and breast cancer-specific survival (BCSS) [10, 11] and predictive of chemotherapy benefit in prospectively designed studies of archival tissue [10]. As a result, the 2015 National Comprehensive Cancer Network Clinical Practice Guidelines in Breast Cancer have incorporated Oncotype DX testing into clinical guidelines for LN+ patients, specifically noting that Oncotype DX testing can be considered for patients with 1–3 involved ipsilateral axillary lymph nodes [12].

Currently, the RxPONDER trial is underway to evaluate the use of the 21-gene assay for breast cancer patients with 1–3 positive lymph nodes (HR+, HER2-negative), by randomizing research participants with a RS ≤ 25 to receive hormonal therapy alone or hormonal therapy with adjuvant chemotherapy [13]. Awaiting results from RxPONDER, limited information remains available about outcomes of contemporary patients with LN+ disease who were treated based on RS results. As such, the primary objective of this study was to assess 5-year BCSS among those with LN+ breast cancer who have oncotype DX RS results.

Methods

Data source

The National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) breast cancer cases (diagnosed 2004–2012) were linked to 21-gene Oncotype DX Breast Recurrence Score assay results from the Genomic Health Clinical Laboratory (2004–2013) by Information Management Services (IMS, Inc.; Calverton, MD, USA). IMS released the de-identified, linked dataset to the study team for analyses following SEER approval.

Study population

The study population included men and women with estrogen receptor (ER)- and/or progesterone receptor (PR)-positive invasive breast cancer as defined by the SEER-reported ER and PR (positive or borderline) immunohistochemistry results. We include men because treatment guidelines for male breast cancer are similar to those for female breast cancer, and evidence indicates that the distribution of Recurrence Score results among men is similar to that among women [14]. We excluded those (1) with distant metastases, (2) affected by Hurricane Katrina (incident cases in Louisiana from July to December 2005), (3) with breast cancer diagnosis over the age of 99, (4) with zero years of survival time, (5) with autopsy data only, and (6) without a state death certificate. The cohort was stratified by lymph node status: lymph node-negative (N0, including isolated tumor cells), micrometastases only (N1mi), 1 positive lymph node (1LN), 2 positive lymph nodes (2LN), 3 positive lymph nodes (3LN), or 4–90 positive lymph nodes (≥4LN). We examined uptake of the 21-gene assay from 2004 to 2013 using these inclusion/exclusion criteria ($n = 352,468$).

For the remaining analyses, we further restricted the study population. We included only those who had a 21-gene assay Recurrence Score result within 12 months following breast cancer diagnosis among those diagnosed between 2004 and 2012. Furthermore, we excluded patients with HER2-positive disease. HER2 status was determined by the RT-PCR single-gene HER2 scores (≤11.5 = HER2-negative) performed by Genomic Health, Inc., as HER2 status was unavailable in SEER prior to 2010.

Measures

Uptake was defined as the proportion of patients in the study cohort who had a 21-gene assay ordered within 12 months following breast cancer diagnosis.

BCSS was calculated using cause of death data reported by the SEER registries, which link with state death certificates and the National Center for Health Statistics' National Death Index [15]. These analyses utilized a variable derived by the SEER program that uses a mapping to dichotomize causes of death as breast cancer-specific or other-cause specific [16]. In the estimates of BCSS, follow-up is censored at the time of other-cause deaths or last known follow-up. In the estimates of other-cause survival, follow-up is censored at the time of breast cancer-specific death or last known follow-up. Overall survival was estimated by including all deaths as events regardless of cause.

Statistical analyses

For the 21-gene assay uptake evaluation, the proportion tested was calculated among those with HR+, non-metastatic, invasive breast cancer as the denominator. The proportions were calculated and plotted by year of breast cancer diagnosis (from 2004 to 2013). Descriptive statistics of the analytic sample were tested using ANOVA and Chi square to compare sample characteristics by number of positive lymph nodes. The survival analysis used the actuarial method using SAS version 9.4 (SAS Institute Inc.; Cary, NC) and was stratified by 21-gene assay RS cutpoints (RS < 18, RS 18–30 or RS ≥ 31) and by number of positive lymph nodes. A two-degrees-of-freedom log-rank test was used to determine if there was evidence of differences across the three categorical RS groups. Survival curves are presented through 5 years, but all observed events and follow-up were included for statistical testing purposes. Confidence intervals were computed using the log–log transformation. As a sensitivity analysis, we also examined BCSS by 21-gene assay RS cutpoints that correspond to those used in the RxPONDER trial (RS < 11, RS 11–25, RS ≥ 26) [13].

Exploratory analysis

Chemotherapy use among those with RS results was examined as an exploratory aim. Chemotherapy was assessed using SEER-reported data from 2004 to 2012. The proportion of those for whom the registries reported chemotherapy use (versus those reported as no or unknown) was plotted by the standard RS cutpoints (low < 18, intermediate 18–30 or high ≥ 31) and by continuous RS value (0–100). This aim was exploratory, as chemotherapy is under-reported in SEER [17], and as such the results must be interpreted with caution.

Results

Of the 352,468 HR+ and non-metastatic breast cancer cases, 74,207 patients had a 21-gene breast cancer assay ordered (Supplemental Fig. 1). Overall, the uptake of the 21-gene breast cancer assay increased over time (Fig. 1), with lower uptake among patients with greater lymph node involvement. For example, during 2004–2013, only 1.6% of those with ≥4LN received the 21-gene breast cancer assay compared with 21.6% of those with micrometastases. Uptake of the 21-gene breast cancer assay increased from 0.7% in 2004 to 44.4% in 2013 among those with micrometastases.

Patient characteristics of those with LN+ disease diagnosed between 2004 and 2012 who received a Recurrence Score result (n = 6768) varied by lymph node involvement. More specifically, patients with greater lymph node involvement tended to be older, to have tumors that were larger and higher in grade, to have higher mean RS results, and to live within a lower socioeconomic status (SES) area, compared with those with lower lymph node involvement (Table 1). There were no significant differences across lymph node status by race, year of diagnosis, or ER/PR status.
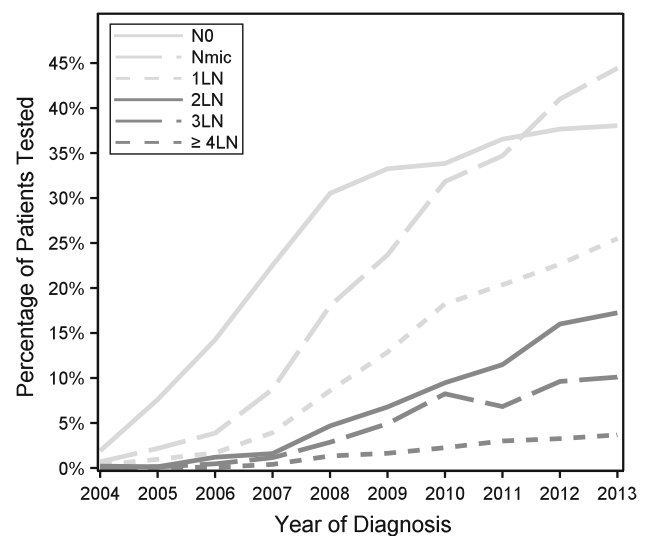

Fig. 1 The proportion of individuals receiving Recurrence Score testing who had HR+, non-metastatic breast cancer, by year and number of positive lymph nodes. *N0* lymph node-negative, *N1mi* micrometastases only, *1LN* 1 positive lymph node, *2LN* 2 positive lymph nodes, *3LN* 3 positive lymph nodes, *≥4LN* 4, or more positive lymph nodes

Table 1 Descriptive statistics for patients with HR+, non-metastatic breast cancer who had Oncotype DX Recurrence Score results, by number of positive lymph nodes, 2004–2012 ($n = 6768$)

Proportions/mean (SD)[a]	# Positive lymph nodes					p
	Micrometastases N = 2820	1 N = 2620	2 N = 771	3 N = 272	4+ N = 285	
Age						<0.001
20–29 years	0.3	0.4	0.9	1.4	0.0	
30–39 years	4.1	2.6	3.1	3.0	3.9	
40–49 years	19.9	16.6	15.1	22.8	16.5	
50–59 years	31.7	27.5	26.5	22.1	28.0	
60–69 years	30.1	31.4	31.0	24.2	27.0	
70–79 years	12.7	18.7	20.8	23.1	15.1	
80+ years	1.1	3.0	3.1	4.0	9.5	
Race						0.22
White	84.9	84.2	87.2	84.2	84.6	
Asian/Pacific Islander	7.1	6.0	6.1	6.6	4.6	
Black	7.0	8.6	6.4	8.5	10.2	
American Indian/Alaska Native	0.6	0.6	0.1	0.4	0.7	
Unknown	0.5	0.6	0.3	0.4	0.0	
SES (Yost quintile)						<0.01
1 (lowest)	9.4	12.3	10.6	12.1	13.7	
2	15.4	14.5	16.1	17.3	18.6	
3	18.5	17.0	23.1	17.3	20.0	
4	23.4	24.0	20.2	24.3	20.4	
5 (highest)	31.7	30.8	28.0	27.6	25.6	
Unknown[b]	1.6	1.2	1.9	1.5	1.8	
Year of diagnosis						0.05
2004	0.2	0.3	0.3	0.0	0.0	
2005	1.2	0.8	0.3	0.4	1.1	
2006	2.1	1.5	2.3	0.7	0.7	
2007	5.2	4.0	3.1	3.3	3.5	
2008	10.2	8.8	8.7	7.7	10.5	
2009	13.9	13.5	13.5	14.3	14.7	
2010	19.1	19.7	17.8	24.6	17.9	
2011	22.0	24.1	22.8	20.6	24.6	
2012	26.1	27.1	31.3	28.3	27.0	
Tumor size						<0.001
<1 cm	14.8	12.1	8.6	5.1	3.9	
1–1.9 cm	51.0	47.1	39.0	33.1	22.8	
2–2.9 cm	21.8	25.0	30.1	35.3	28.4	
3–3.9 cm	7.5	8.9	10.6	13.6	16.5	
4+ cm	4.6	6.5	11.0	12.1	27.4	
Unknown	0.3	0.4	0.6	0.7	1.1	
Grade						<0.01
I	27.6	29.2	25.2	23.5	19.3	
II	54.7	53.1	55.8	51.8	55.1	
III/IV	15.2	15.5	16.6	22.8	23.5	
Unknown	2.4	2.2	2.5	1.8	2.1	
ER-positive[c]	99.8	99.9	99.9	100.0	99.6	0.81
PR-positive[c]	91.3	91.8	91.4	91.1	88.7	0.54
Mean (SD) RS result	17.0 (8.3)	17.0 (8.6)	16.7 (8.0)	18.8 (10.2)	20.0 (10.3)	<0.001

Table 1 continued

Proportions/mean (SD)[a]	# Positive lymph nodes					p
	Micrometastases N = 2820	1 N = 2620	2 N = 771	3 N = 272	4+ N = 285	
RS group						<0.001
Low	58.3	59.1	59.4	51.1	45.3	
Intermediate	35.4	34.1	34.8	38.2	41.1	
High	6.3	6.8	5.8	10.7	13.7	

ER estrogen receptor, *PR* progesterone receptor, *RS* Recurrence Score, *SD* standard deviation, *SES* socioeconomic status

[a] All ANOVA (for continuous dependent variables) and Chi square (for binary/categorical variables)

[b] Unknown for reasons of: unable to calculate, unable to track in SEER, or no match in census

[c] Includes patients with positive/borderline hormone receptor status, as described in the Methods section
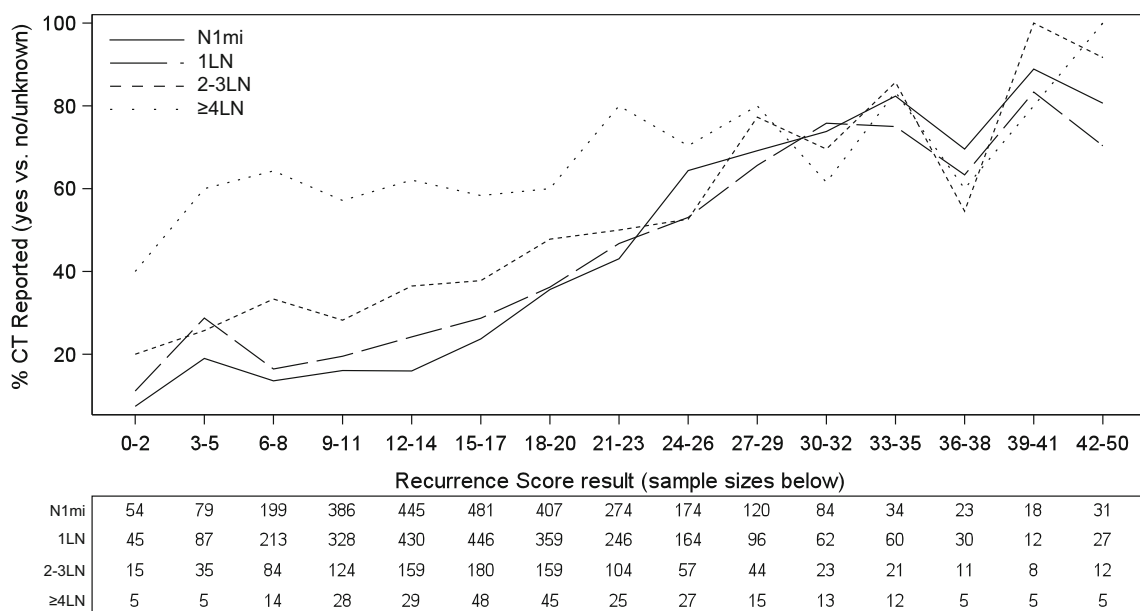

	0-2	3-5	6-8	9-11	12-14	15-17	18-20	21-23	24-26	27-29	30-32	33-35	36-38	39-41	42-50
N1mi	54	79	199	386	445	481	407	274	174	120	84	34	23	18	31
1LN	45	87	213	328	430	446	359	246	164	96	62	60	30	12	27
2-3LN	15	35	84	124	159	180	159	104	57	44	23	21	11	8	12
≥4LN	5	5	14	28	29	48	45	25	27	15	13	12	5	5	5

Fig. 2 Chemotherapy use reported as "yes" versus "no/unknown," by Recurrence Score results and number of positive lymph nodes. Overall chemotherapy use was reported as "yes" in 32.1% with N1mi, 34.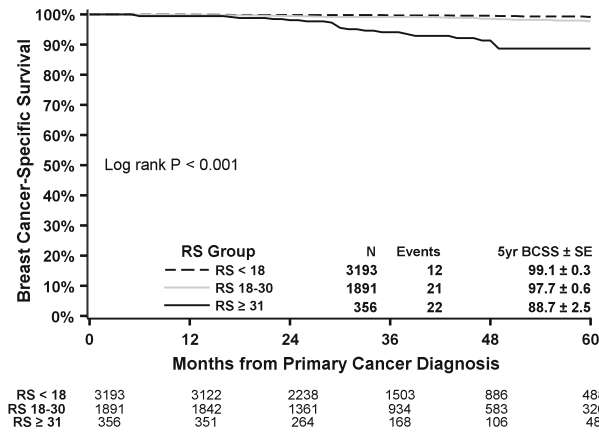6% with 1LN, and 43.9% with 2–3LN. For comparative purposes, chemotherapy use reported for lymph node-negative patients (N = 49,681), by Recurrence Score results, are shown in Supplemental Fig. 2

Table 2 Five-year breast cancer-specific survival in patients with lymph node-positive HR+ invasive breast cancer and Recurrence Score results in the SEER database; N = 6768
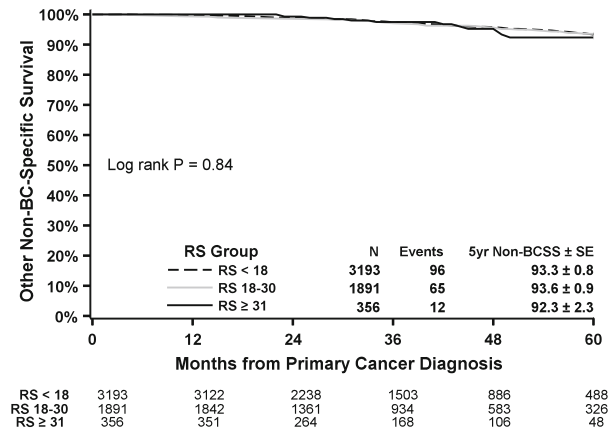
# of positive lymph nodes	RS < 18 (N = 3919)		RS 18–30 (N = 2380)		RS ≥ 31 (N = 469)	
	N (%CT)[a]	5-year BCSS (95% CI)	N	5-year BCSS (95% CI)	N	5-year BCSS (95% CI)
Micrometastases	1644 (18%)	98.9 (97.4–99.6)	998 (47%)	99.1 (97.9–99.6)	178 (79%)	84 (74.1–90.4)
1	1549 (23%)	99.4 (98.4–99.8)	893 (47%)	95.9 (92.6–97.7)	178 (73%)	93.3 (85.2–97.0)
2	458 (31%)	97.1 (91.3–99.0)	268 (52%)	97.8 (91.4–99.4)	45 (82%)	87.0 (54.4–96.9)
3	139 (41%)	95.1 (87.0–98.2)	104 (54%)	87.2 (65.2–95.7)	29 (83%)	89.8 (63.5–97.5)
≥4	129 (59%)	92.8 (73.5–98.2)	117 (69%)	83.9 (69.5–91.9)	39 (77%)	65.4 (40.9–81.8)

[a] Percentage of patients with chemotherapy reported by the registries as "yes" versus "no/unknown." Among patients younger than 70 years, percentages were typically 1–10 percentage points higher than those in the overall cohort. Chemotherapy use was more than 10 percentage points higher for patients with three positive LN and RS 18–30, and for patients with ≥4 positive LN and RS < 18
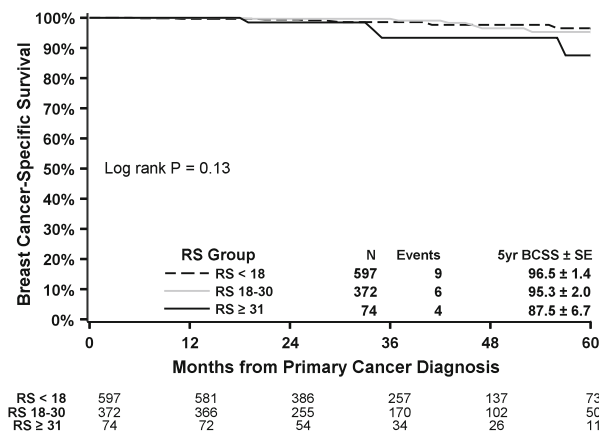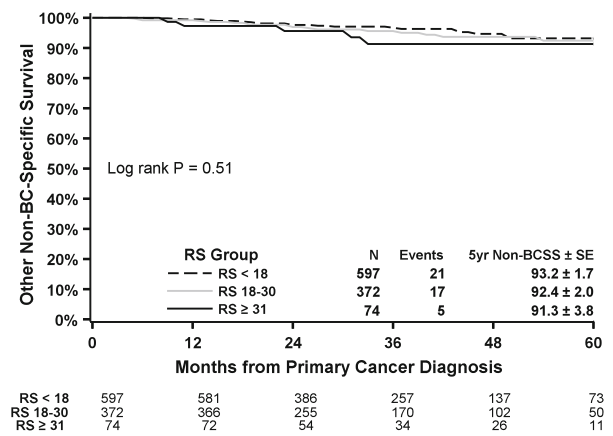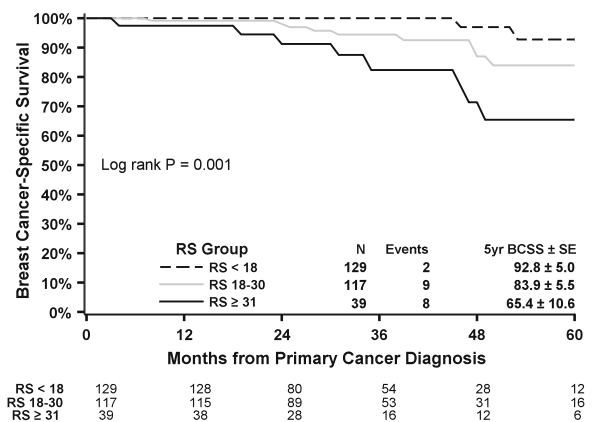
(a) 5-year BCSS; N1mi and 1LN

RS Group	N	Events	5yr BCSS ± SE
RS < 18	3193	12	99.1 ± 0.3
RS 18-30	1891	21	97.7 ± 0.6
RS ≥ 31	356	22	88.7 ± 2.5

Log rank P < 0.001

RS < 18	3193	3122	2238	1503	886	488
RS 18-30	1891	1842	1361	934	583	326
RS ≥ 31	356	351	264	168	106	48

(b) 5-year non-BCSS; N1mi and 1LN

RS Group	N	Events	5yr Non-BCSS ± SE
RS < 18	3193	96	93.3 ± 0.8
RS 18-30	1891	65	93.6 ± 0.9
RS ≥ 31	356	12	92.3 ± 2.3

Log rank P = 0.84

RS < 18	3193	3122	2238	1503	886	488
RS 18-30	1891	1842	1361	934	583	326
RS ≥ 31	356	351	264	168	106	48

(c) 5-year BCSS; 2-3LN

RS Group	N	Events	5yr BCSS ± SE
RS < 18	597	9	96.5 ± 1.4
RS 18-30	372	6	95.3 ± 2.0
RS ≥ 31	74	4	87.5 ± 6.7

Log rank P = 0.13

RS < 18	597	581	386	257	137	73
RS 18-30	372	366	255	170	102	50
RS ≥ 31	74	72	54	34	26	11

(d) 5-year non-BCSS; 2-3LN

RS Group	N	Events	5yr Non-BCSS ± SE
RS < 18	597	21	93.2 ± 1.7
RS 18-30	372	17	92.4 ± 2.0
RS ≥ 31	74	5	91.3 ± 3.8

Log rank P = 0.51

RS < 18	597	581	386	257	137	73
RS 18-30	372	366	255	170	102	50
RS ≥ 31	74	72	54	34	26	11

(e) 5-year BCSS; ≥4LN

RS Group	N	Events	5yr BCSS ± SE
RS < 18	129	2	92.8 ± 5.0
RS 18-30	117	9	83.9 ± 5.5
RS ≥ 31	39	8	65.4 ± 10.6

Log rank P = 0.001

RS < 18	129	128	80	54	28	12
RS 18-30	117	115	89	53	31	16
RS ≥ 31	39	38	28	16	12	6

(f) 5-year non-BCSS; ≥4LN

RS Group	N	Events	5yr Non-BCSS ± SE
RS < 18	129	1	99.1 ± 0.9
RS 18-30	117	6	92.3 ± 3.2
RS ≥ 31	39	4	85.7 ± 6.8

Log rank P = 0.03

RS < 18	129	128	80	54	28	12
RS 18-30	117	115	89	53	31	16
RS ≥ 31	39	38	28	16	12	6

Fig. 3 Five-year breast cancer-specific survival (**a**, **c**, **e**) and other-cause (non-breast cancer-specific) survival (**b**, **d**, **f**), by Recurrence Score group among patients with micrometastases and 1 positive lymph node (N1mi, 1LN; N = 5440; **a**, **b**), patients with 2–3 positive lymph nodes (2–3LN; N = 1043; **c**, **d**), and patients with ≥4 positive lymph nodes (≥4LN; N = 285; **e**, **f**). For comparative purposes,

5-year BCSS and other-cause (non-BCSS) among patients with micrometastases up to three positive lymph nodes, by Recurrence Score group, are shown in Supplemental Fig. 3. Also, 5-year overall survival, by Recurrence Score group and number of positive lymph nodes, is shown in Supplemental Fig. 4

Chemotherapy reported as "yes" increased as lymph node involvement and RS value increased (Fig. 2). For example, among those with RS < 18, the registries

reported 19% of patients with micrometastases as "yes" for chemotherapy use, compared with 56% of those with ≥4LN. Among those with ≥4LN, the proportion for whom

the registries reported as "yes" for chemotherapy use increased from 56% among those with low RS results (RS < 18) to 77% among those with high RS results (RS ≥ 31). Reported chemotherapy was also modestly higher for patients with larger tumors or poorly differentiated tumors; however, age was the only variable with an effect of comparable magnitude to nodal status or RS results.

Five-year BCSS outcomes for those with RS < 18 ranged from 98.9% (95% CI 97.4–99.6) in those with micrometastases to 92.8% (95% CI 73.4–98.2) among those with ≥4LN. Similar patterns of worsening BCSS with increasing number of positive lymph nodes were found for those with RS results 18–30 and ≥31 (Table 2). The RS result was strongly predictive of BCSS among the group with micrometastases or 1–3LN, and the group with micrometastases or 1LN (both $p < 0.001$; Fig. 3). RS results were not significantly associated with other non-BCSS (Fig. 3). In a multivariable Cox model adjusting for grade, tumor size, age, and race, both the number of positive lymph nodes and the RS category remained strongly associated with BCSS ($p < 0.001$) (Supplemental Table 1).

Discussion

Overall, 5-year BCSS is high in patients with RS < 18, particularly among those with micrometasteses and fewer positive lymph nodes. Five-year survival worsened both as the number of involved lymph nodes increased, and as RS result increased. Not all patients with LN+ disease had aggressive disease. Patients with RS < 18 had good survival and a low proportion for whom the registries reported as "yes" for chemotherapy use, suggesting that the addition of chemotherapy to adjuvant treatment in this RS group may have relatively little impact on BCSS. Furthermore, our findings support evidence that those with LN+ disease who receive 21-gene assay testing tend to be older and to have lower grade, smaller tumors, compared with those who do not receive such testing [18], and that rates of test uptake have increased over time among LN+ patients [19].

Future analyses that account for treatment are warranted; in particular, a comparison of survival among those who did and did not receive chemotherapy is of interest. Longitudinal data updates through the SEER and Genomic Health Clinical Laboratory linkage will allow for better characterization of how the 21-gene breast cancer assay is used, as well as survival outcomes among LN+ patients. Studying health services use of the 21-gene breast cancer assay and associated health outcomes in LN+ patients are

particularly important, as our findings indicate increasing uptake of the assay.

Limitations

This study has several limitations. First, follow-up time has been relatively short to date; as such, additional analyses with longer follow-up are warranted. Of note, most chemotherapy benefit, if any, is observed in the first 5 years, and 5-year BCSS predicts 10- and 15-year BCSS [4]. Thus, study findings are informative for the decision to treat with chemotherapy and for longer-term survival outcomes. Second, future studies should incorporate treatment data into survival analyses; specifically, to examine survival by chemotherapy use and to account for surgery and/or radiation therapy. Chemotherapy use is known to be under-reported to SEER, and therefore such analyses were suboptimal in this study. Moreover, estimates of chemotherapy use should be interpreted with caution, as they likely under-report chemotherapy uptake. Third, the SEER registries do not collect information on distant recurrence, and this outcome could not be evaluated. Finally, we were unable to restrict the 21-gene assay uptake analyses by HER2-negative status in Fig. 1, as SEER did not begin collecting HER2 data until 2010. This may have led to an underestimate of 21-gene assay uptake prior to 2010 and to challenges to the comparison of survival between tested and untested patients.

Conclusions

This SEER study adds to the current understanding of survival outcomes among LN+ patients who receive the 21-gene breast cancer assay RS results. Our findings demonstrate high survival outcomes among those with low RS results, and lesser lymph node involvement. Future studies should continue to examine longer-term survival outcomes and incorporate treatment variables into analyses.

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