Breast cancer-specific survival in patients with node-positive breast cancer treated based on the 21-gene assay in clinical practice

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Background

- The 21-gene Oncotype DX Breast Recurrence Score® (RS) assay was shown in SWOG 8814 to predict chemotherapy (CT) benefit for patients with node-positive (N+) breast cancer and RS ≥31, but not RS <18 [1]. RS results were prognostic for distant recurrence in 306 patients with N+ breast cancer in the ATAC study [2].
- In the SWOG and ATAC studies, patients with ≥4N+ had much worse outcomes than patients with 1-3N+ [1,2].
- Based on SWOG and ATAC studies, the 21-gene assay has been widely used in clinical practice for N+ breast cancer since 2008, primarily in patients with limited nodal involvement [3-5]. In addition, the RxPONDER trial, a phase 3 study in which patients with 1-3N+ breast cancer and RS ≤25 are randomized to hormonal therapy with or without CT [6], was initiated in 2011 and is anticipated in the future to provide important information on chemotherapy benefit.
- Recently, three new studies in >7,500 contemporary patients with N+ breast cancer treated based on RS results were reported:
  - The prospective phase 3 PlanB trial reported favorable 5-year outcomes for patients with N+ breast cancer who had RS <12 and were treated without CT [7,8].
  - The Surveillance, Epidemiology, and End Results program (SEER; US) and the Clalit Health Services registry (CHS; Israel) showed that those with RS <18 had low 5-year rates of distant recurrence and/or breast cancer-specific mortality [3-5,9,10].
- Here, as we did previously for SEER patients with node-negative breast cancer [11], we characterize breast cancer-specific survival (BCSS) in N+ breast cancer by reported CT use in RS groups defined by both the standard (18 and 31) and TAILORx/RxPONDER (11 and 25) cutpoints [6,12].

Primary Objective

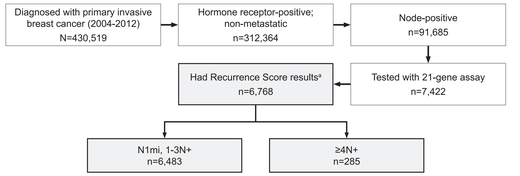
- To determine BCSS of SEER patients with hormone receptor-positive (HR+), HER2-negative, N+ (micrometastases, 1-3N+) invasive breast cancer, by RS group (RS <11, RS 11-17, RS 18-25, RS 26-30, and RS ≥31) and by reported CT use

Methods

- RS results were provided electronically to SEER by Genomic Health as mandated by registry operations [3].
- Patients with RS results were eligible if they had N+, HR+ (by SEER and RT-PCR), HER2-negative (by RT-PCR only; HER2 status not available in SEER prior to 2010) invasive breast cancer, diagnosed between January 2004 and December 2012.
  - Excluded were those with N0 disease, prior invasive tumors, or concurrent multiple tumors.
- SEER demographics, tumor characteristics, reported CT use, and BCSS were available through 2013.
  - Under-reporting of CT use to SEER is well-known [13].
- BCSS was defined according to pre-existing robust methodology [14]. Actuarial estimates of BCSS by reported CT use were computed through five years with 95% confidence intervals (CI) using standard cutpoints of 18 and 31, and TAILORx cutpoints of 11 and 25. The log-rank test was used to compare across RS groups.

Results

Figure 1. Eligible SEER Patients With N+, HR+, HER2-negative Breast Cancer



a. The cohort that met eligibility requirements, was tested, and had RS results excludes 654 patients (9% of 7,422 patients) for the following reasons: HER2-positive breast cancer based on 21-gene assay HER2 single-gene result (2%), inadequate tissue sample (2%), multiple tumors (2%), and test cancellation (3%). Median follow-up was 34 months.

Results

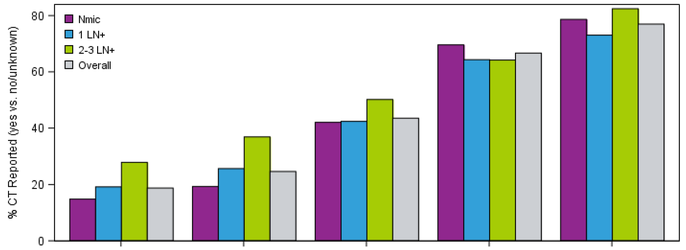
Table 1. Distribution of Patient and Tumor Characteristics by RS Group and Reported CT Use

		RS <11 (N=1,312; 20%)		RS 11-17 (N=2,478; 38%)		RS 18-25 (N=1,831; 28%)		RS 26-30 (N=432; 7%)		RS ≥31 (N=430; 7%)	
CT use		'No/Unk'	'Yes'	'No/Unk'	'Yes'	'No/Unk'	'Yes'	'No/Unk'	'Yes'	'No/Unk'	'Yes'
No. per group		1066	246	1869	609	1034	797	144	288	99	331
Age at diagnosis, y	<40	1%	7%	2%	7%	2%	6%	0%	7%	3%	7%
	40 to 49	13%	24%	17%	33%	13%	24%	11%	19%	9%	19%
	50 to 59	25%	33%	26%	32%	28%	34%	29%	35%	32%	34%
	60 to 69	35%	28%	33%	22%	32%	28%	24%	28%	30%	26%
	70 to 79	23%	9%	19%	6%	21%	8%	31%	11%	22%	12%
	≥80	3%	0%	3%	<1%	4%	<1%	5%	1%	3%	1%
Tumor size[a], mm	≤5	3%	2%	2%	3%	3%	3%	3%	2%	3%	2%
	>5 to 10	16%	13%	17%	11%	15%	14%	12%	12%	7%	6%
	>10 to 20	51%	45%	50%	46%	50%	47%	43%	44%	44%	40%
	>20 to 40	25%	30%	26%	32%	27%	30%	34%	36%	40%	46%
	>40	4%	10%	4%	7%	5%	6%	8%	5%	5%	5%
Grade[a,b]	Low	37%	27%	36%	31%	26%	24%	13%	11%	5%	4%
	Intermediate	55%	65%	55%	59%	59%	56%	58%	51%	33%	44%
	High	8%	9%	10%	11%	14%	20%	29%	38%	61%	52%

a. Among patients with nonmissing information. b. Low grade=well differentiated; intermediate grade=moderately differentiated; high grade=poorly differentiated, undifferentiated, or anaplastic.
CT use, chemotherapy use reported to SEER as 'yes' or 'no/unknown'; RS, Recurrence Score.

- Although reported CT use increased across the higher RS groups, reported CT use within each RS group was higher for patients <50 years and lower for patients ≥60 years.
- Within each RS group, grade had little impact on reported CT use.
- Within each RS group, reported CT use was slightly higher for larger tumors >20 mm than for smaller tumors.
- RS-tested patients were generally treated with CT according to the RS results.

Figure 2. Reported CT Use* by RS Group and Extent of Nodal Involvement

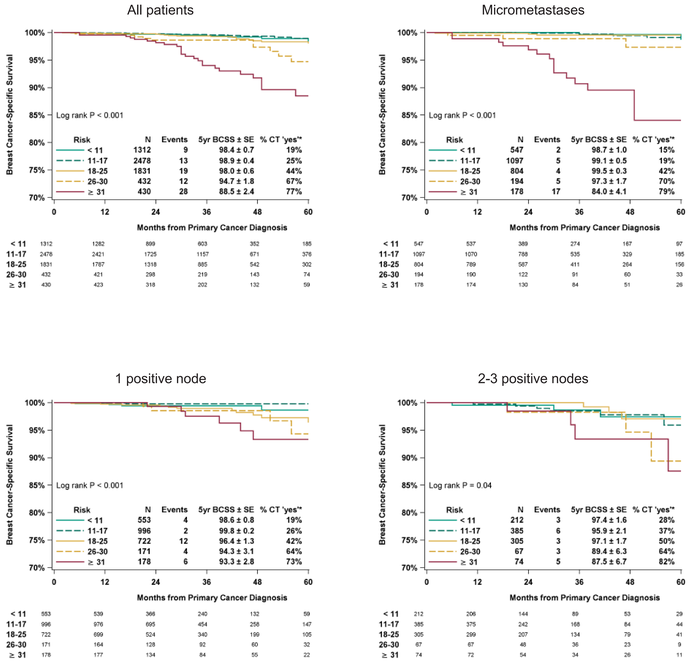


	< 11	11-17	18-25	26-30	≥ 31
Nmic	547	1097	804	194	178
1 LN+	553	996	722	171	178
2-3 LN+	212	385	305	67	74
Overall	1312	2478	1831	432	430

*Includes patients with CT use reported as 'yes' and 'no/unknown.' CT use is known to be under-reported in the SEER registries.

- Reported CT use increased with increasing RS result
- For RS <18, reported CT use also increased with increasing nodal involvement.

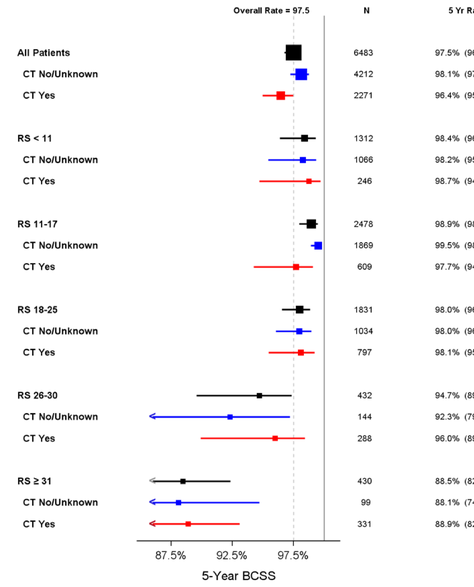
Figure 3. 5-year BCSS by RS Group and Extent of Nodal Involvement*



*Includes patients with CT use reported as 'yes' and 'no/unknown.' CT use is known to be under-reported in the SEER registries.

- 5-year BCSS was lower with increasing RS results for all N+ patients.
- The association between BCSS and RS group was statistically significant (p<0.001).
- Similar results were observed for patient grouped by extent of nodal involvement.

Figure 4. 5-year BCSS by RS Group and Reported CT Use*



- 5-year BCSS was >98% in the 2935 patients with RS <18 and CT use reported as no/unknown
- With regard to outcomes by reported CT use:
  - 5-year BCSS rates were similar for patients with CT use reported as 'yes' 'no/unknown' for RS groups <11, 11-17, and 18-25
  - 5-year BCSS rate appeared lower for patients with CT use reported as 'yes' and RS 26-30
  - Results should be interpreted with caution, as patients were not randomized to CT treatment

Conclusions

- Patients in real-world clinical practice with RS <11 or RS 11-17 and limited nodal involvement had favorable 5-year BCSS, even with limited CT use.
- This supports the use of hormonal therapy alone among patients with RS <18 and up to 3 positive nodes.
- Patients with RS 18-25 also had favorable 5-year BCSS, with or without CT use, highlighting the importance of the randomized results of RxPONDER.

For more information about SEER, visit http://seer.cancer.gov/.
For more information about the Surveillance Research Program, visit http://surveillance.cancer.gov/

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The authors thank John Bennett for biostatistical and graphics support and Anna Lau for editorial and layout support.

Presented at: 40th Annual San Antonio Breast Cancer Symposium; December 5-9, 2017; San Antonio, TX. Poster P6-13-03.

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