Precision Medicine and Imaging

Clinical Cancer Research

21-Gene Recurrence Score Assay Predicts Benefit of Post-Mastectomy Radiotherapy in T1-2 N1 Breast Cancer

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Abstract

Purpose: Post-mastectomy radiotherapy (PMRT) yields improvements in both locoregional control and overall survival (OS) for women with T1-2 N1 breast cancer. The value of PMRT in this population has been questioned given advances in systemic therapy. The 21-gene recurrence score (RS) assay was evaluated as a predictor of OS among women with T1-2 N1 breast cancer who received or did not receive PMRT.

Experimental Design: An observational cohort study was performed on women with T1-2 N1 estrogen receptor–positive breast cancer from the National Cancer Database (NCDB) and, as a validation cohort, from the surveillance, epidemiology, and end results (SEER) registry who underwent mastectomy and were evaluated for RS. Multivariable parametric accelerated failure time models were used to estimate associations of RS and PMRT with OS using propensity score-adjusted matched cohorts.

Results: In both the NCDB ($N = 7{,}332$) and SEER ($N = 3{,}087$) cohorts, there was a significant interaction of RS and PMRT with OS ($P = 0.009$ and $P = 0.03$, respectively). PMRT was associated with longer OS in women with a low RS [NCDB: time ratio (TR) = 1.70; 95% CI (confidence interval), 1.30–2.22; $P < 0.001$; SEER: TR = 1.85; 95% CI, 1.33–2.57; $P < 0.001$], but not in women with an intermediate RS (NCDB: TR = 0.89; 95% CI, 0.69–1.14; $P = 0.35$; SEER: TR = 0.84; 95% CI, 0.62–1.14; $P = 0.26$), or a high RS (NCDB: TR = 1.10; 95% CI, 0.91–1.34; $P = 0.33$; SEER: TR = 0.79; 95% CI, 0.50–1.23; $P = 0.28$).

Conclusions: Longer survival associated with PMRT was limited to women with a low RS. PMRT may confer the greatest OS benefit for patients at the lowest risk of distant recurrence. These results caution against omission of PMRT among women with low RS. *Clin Cancer Res; 24(16); 3878–87. ©2018 AACR.*

Introduction

Post-mastectomy radiotherapy (PMRT) for women with T1–2 breast cancer and one to three positive axillary nodes (N1) remains controversial. Although PMRT has been demonstrated in multiple randomized trials to reduce the risk of locoregional recurrence (LRR) and breast cancer mortality in women with limited nodal disease, given advances in adjuvant systemic therapy it is thought that for a subset of low-risk women the potential late toxicity of PMRT may be greater than its absolute benefit on LRR (1–4). Current national guidelines recommend PMRT primarily for "high-risk" women under the assumption that those with the greatest risk of LRR will derive the greatest survival benefit from adjuvant locoregional therapy (5).

There is considerable interest in identifying prognostic factors alongside standard clinicopathologic variables that are potentially predictive of benefit for adjuvant therapy in early-stage breast cancer. The 21-gene recurrence score (RS) assay (Genomic Health) is calculated on the basis of the RNA expression levels of 21 genes and has been validated in T1-2 N1 breast cancer to be prognostic of LRR, disease-free survival, and overall survival (OS; refs. 6–10). Other gene profiling assays have demonstrated similar correlations (11–13). More recently, the 21-gene RS has been shown in retrospective analyses to be predictive of survival benefit for adjuvant chemotherapy in women with T1-2 N1 cancer with a high RS, while those with a low RS did not derive a significant benefit (6). By extension, it is hypothesized that PMRT may provide the greatest benefit for LRR, and therefore survival, in women with a high RS (10).

Potentially confounding this hypothesis, the 21-gene RS is also strongly prognostic for distant recurrence, a competing risk to LRR (8, 9). Women with a higher RS are more likely to harbor occult systemic disease and therefore potentially less likely to derive a survival benefit from locoregional treatment. To test this concept, women with T1-2 N1 estrogen receptor (ER)–positive breast cancer who underwent mastectomy were identified from the National Cancer Database (NCDB) and, as a validation cohort, from the surveillance, epidemiology, and end results (SEER) registry. Survival analyses were performed to examine the

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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doi: 10.1158/1078-0432.CCR-17-3169

Translational Relevance

The American Society of Clinical Oncology focused guideline update (2017) concluded that post-mastectomy radiotherapy (PMRT) may be potentially omitted for women with T1–2 N1 breast cancer at a low risk of locoregional recurrence. The 21-gene recurrence score (RS) assay has been presented previously as a potential means of identifying patients with a low risk of locoregional recurrence for whom PMRT could be omitted. In this analysis of two large national cancer databases, patients with a low RS derived a greater survival benefit from PMRT than those with an intermediate or high RS. This may be due to a low competing risk of subclinical micrometastatic disease at diagnosis resulting in improved translation of locoregional control to a survival benefit. These results caution against omission of PMRT for women with node-positive disease on the basis of a low-risk RS, and strongly suggest the need for prospective validation prior to widespread adoption.

associations and interactions of the 21-gene RS and use of PMRT with OS in these cohorts.

Materials and Methods

Women with pathologic T1-2 ER-positive breast cancer with one to three positive nodes (including micrometastatic nodal disease) that underwent mastectomy and were evaluated using the RS in the 2004–2014 NCDB and the 2004–2014 SEER 18 registry were included (Fig. 1). The NCDB is a nationwide, facility-based comprehensive clinical surveillance resource oncology dataset established by the Commission on Cancer of the American College of Surgeons and the American Cancer Society in 1989 that captures 70% of all newly diagnosed malignancies (14). The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals. Deidentified data from the National Cancer Institute SEER registry, including radiation and chemotherapy variables, were linked to 21-gene Oncotype DX breast RS assay results from the Genomic Health Clinical Laboratory (2004–2014) by Information Management Services. The deidentified linked dataset was provided to the investigators after SEER approval of a custom data request (15). All investigators with access to the dataset signed a Data-Use Agreement prior to receiving access. Local institutional review board approval and informed consent were not required for these analyses of deidentified data from the NCDB and SEER registry.

Exclusion criteria were receipt of neoadjuvant chemotherapy, no adjuvant antiendocrine therapy, unknown radiation status, radiation to primary sites other than the breast/chest wall, radiation to a documented dose <45 Gy, or follow-up time <2 months. Predictor variables of interest were RS and PMRT. RS was defined as "low-risk" (score <18), "intermediate-risk"(18–30), or "high-risk" (>30; ref. 16). Covariates were included in the creation of the matched cohorts and to adjust for potential confounding during regression analyses (Supplementary Methods).

Statistical analyses

Baseline characteristics between patient groups were compared using the Fisher exact test for categorical data, the Mann–Whitney *U* test for nonnormally distributed numeric or ordinal data, or the *t* test or ANOVA for normally distributed data. Five years restricted mean survival times for OS and 5-year OS proportions were estimated using the Kaplan–Meier method and compared with the log-rank test. Survival curves were plotted as unadjusted Kaplan–Meier estimates.

Multivariable parametric accelerated failure time (AFT) models using the generalized gamma distribution were used to evaluate the association of RS and PMRT with OS. This model was chosen in place of the Cox proportional hazards (PHs) model due to the presence of significant non-PH between women within each RS subgroup based on use of PMRT when the Cox model was used for the multivariable analyses (17). When the PH assumption is found to be violated using the Cox model, the AFT model for multivariable analyses provides better goodness-of-fit to the observed data and therefore more robust statistical inference (18–21). The AFT model estimates the time ratio (TR), which describes the multiplicative factor by which the time-to-event is related between two groups. A TR >1 describes longer survival. Covariates utilized in analyses were selected *a priori* based on clinical knowledge and availability and are described in detail in Supplementary Methods. The prespecified statistical plan was to determine if there was a significant interaction between RS and PMRT and, if so, to perform the subset analyses of PMRT effect within each RS group. The interaction between RS and PMRT was tested using the likelihood ratio test based on the fitted model.

To reduce potential confounding, nearest neighbor propensity score-matching was performed for each RS subgroup using available variables as described in detail in the Supplementary Methods to generate well-balanced matched cohorts based on the receipt of PMRT for both the NCDB and SEER cohorts. Baseline characteristics of the generated matched cohorts are presented in Supplementary Tables S1 and S2 (22). Propensity score-matched and inverse probability-weighted cohort analyses were performed to reduce treatment-assignment biases related to measured covariates (22). Analyses of RS subsets were performed both for all patients as well as for the matched patient cohorts within each RS risk group. A composite variable was made combining RS and PMRT to calculate TR estimates relative to a single reference level (low RS/no PMRT). All statistical tests were two-tailed with an alpha of 0.05 used as the cutoff for statistical significance.

A series of separate sensitivity analyses were performed on a subgroup of patients whose receipt of chemotherapy was consistent with their RS score, as well as a subgroup of patients with Her2-negative disease. To test the robustness of the observed results, sensitivity of TR estimates to a possible unmeasured confounder was explored (23, 24). Statistical analyses were performed in Rstudio v1.0.143 using MatchIt, survival, flexsurv, Hmisc, and rms packages (19, 25–30).

Results

Cohorts

The NCDB and SEER began reporting 21-gene RS assay results in 2005 and 2004, respectively. A documented RS was identified in 11.1% (11,181/65, 873) and 9.5% (3,752/32, 551) of eligible women, respectively, within the NCDB and SEER registry. The majority of cases within the NCDB (98.6%) and SEER (74.7%) were coded in 2010 or after. Of the identified cases, 53.3% ($N = 3,907$) and 58.6% ($N = 1,803$) had a low-risk RS

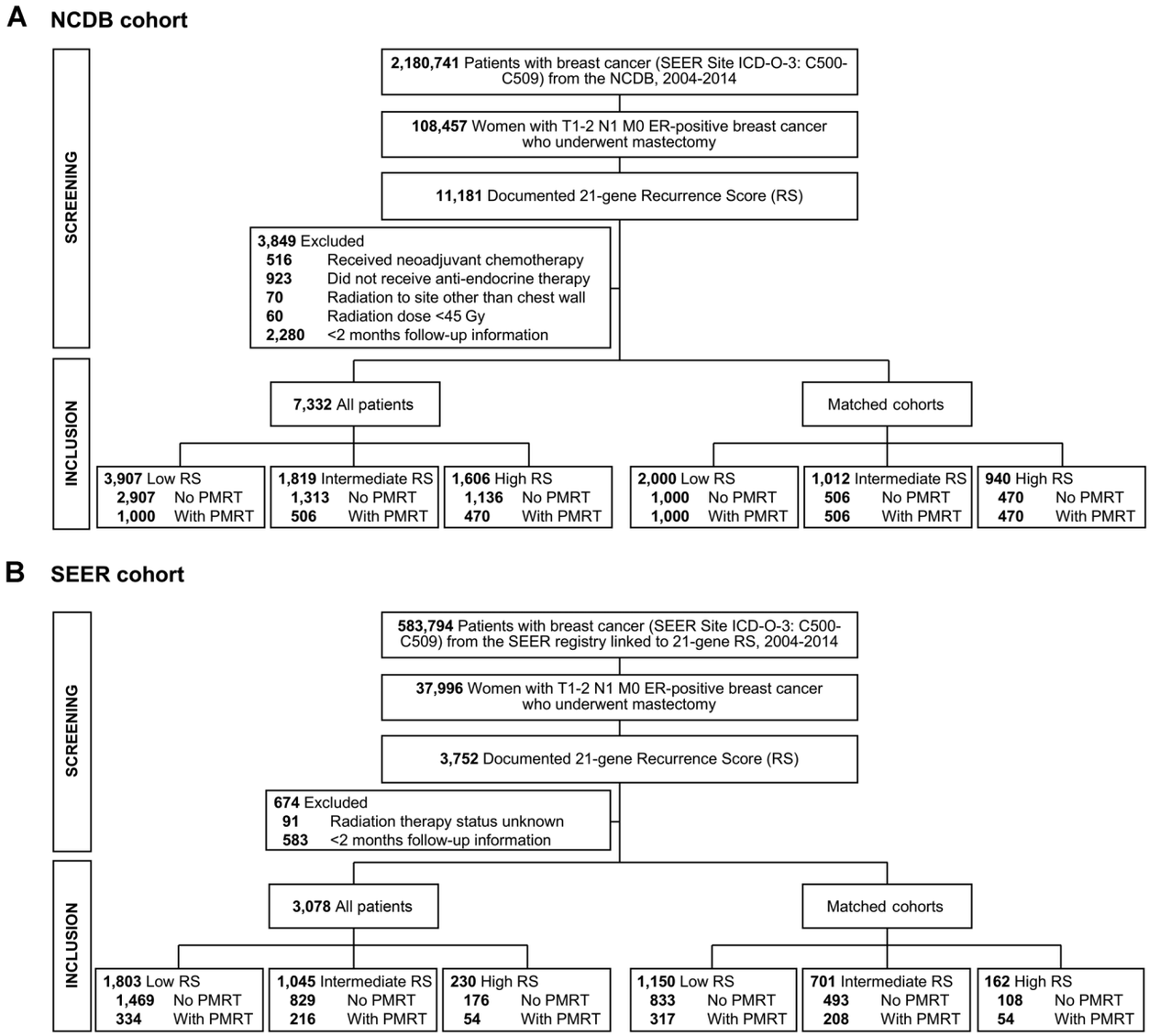

Figure 1.

CONSORT diagram of cohort selection within the NCDB (**A**) and SEER registry (**B**). PUF, participant user files; T1-2, tumor stage, including tumors between 0.1 cm–5 cm; N1mi-1, nodal stage, including micrometastatic nodal disease and one to three axillary lymph nodes; M, metastasis stage; RS, 21-gene RS assay risk group. ER, estrogen receptor; PMRT, post-mastectomy radiotherapy.

within the NCDB and SEER cohorts, respectively (Fig. 1). The median RS was 12 for the low-risk group (IQR = 8–15), 21 for the intermediate-risk group (IQR = 19–25), and 38 for the high-risk group (IQR = 33–45).

Clinicopathologic and demographic characteristics of women within each RS subgroup compared by receipt of PMRT are shown for both cohorts (Tables 1 and 2). Omission of PMRT among women in the NCDB cohort due to documented contraindication or refusal was not associated with RS (Kruskal–Wallis, $P = 0.21$), increased age (one-way ANOVA, $P = 0.43$), or higher comorbidity scores (Kruskal–Wallis, $P = 0.28$). Clinicopathologic and treatment characteristics of women within each RS subgroup compared by receipt of PMRT were well balanced for all matched cohorts (Supplementary Tables S1 and S2).

Kaplan–Meier estimates and multivariable survival analyses

Unadjusted survival curves, estimates of 5-year survival probabilities, and restricted mean survival times are shown for both cohorts (Fig. 2, Supplementary Tables S3 and S4). In univariate analyses of the unadjusted cohorts, low-risk women who received PMRT had significantly longer 5-year OS compared with low-risk women who did not receive PMRT as well as intermediate risk and high-risk women regardless of receipt of PMRT in both the NCDB and the SEER cohorts ($P < 0.001$ for both cohorts; Supplementary Tables S3 and S4).

In multivariable analysis of all patients within the NCDB cohort, receipt of PMRT was not significantly associated with OS when examined independently (TR = 1.12, 95% CI = 0.93–1.35, $P = 0.21$), but there was a significant interaction of RS and PMRT

Table 1. Characteristics of patients from the NCDB cohort grouped by 21-gene RS assay risk group

	Low-risk				Intermediate-risk				High-risk			
Variable	**No PMRT (*N* = 2,907)**	**PMRT (*N* = 1,000)**	***P***	**SMD**	**No PMRT (*N* = 1,303)**	**PMRT (*N* = 506)**	***P***	**SMD**	**No PMRT (*N* = 1,136)**	**PMRT (*N* = 470)**	***P***	**SMD**
Age (years)	60 [50–68]	58 [49–65]	<0.001	0.19	59 [51–67]	56 [48–66]	<0.001	0.22	61 [52–68]	58 [49–67]	0.001	0.18
Follow-up (months)	34 [24–46]	33 [24–46]	0.80	0.01	36 [24–49]	34 [24–45]	0.05	0.10	37 [26–48]	36 [25–47]	0.50	0.03
Tumor stage												
pT1	1,667 (57.3)	473 (47.3)	<0.001	0.20	659 (50.2)	197 (38.9)	<0.001	0.23	595 (52.4)	180 (38.3)	<0.001	0.27
pT2	1,240 (42.7)	527 (52.7)			654 (49.8)	309 (61.1)			541 (47.6)	290 (61.7)		
Nodal stage												
pN1mi	1,079 (37.1)	160 (16.0)	<0.001	0.49	428 (32.6)	103 (20.4)	<0.001	0.28	363 (32.0)	95 (20.2)	<0.001	0.27
pN1	1,828 (62.9)	840 (84.0)			885 (67.4)	403 (79.6)			773 (68.0)	375 (79.8)		
Grade												
1	822 (28.3)	244 (24.4)	0.02		249 (19.0)	77 (15.2)	0.21		237 (20.9)	81 (17.2)	0.009	
2	1,715 (59.0)	597 (59.7)		0.11	712 (54.2)	291 (57.5)		0.11	567 (49.9)	234 (49.8)		0.19
3	220 (7.6)	92 (9.2)			282 (21.5)	105 (20.8)			270 (23.8)	141 (30.0)		
Unknown	150 (5.2)	67 (6.7)			70 (5.3)	33 (6.5)			62 (5.5)	14 (3.0)		
LVI												
Negative	1,782 (61.3)	544 (54.4)	<0.001	0.15	702 (53.5)	245 (48.4)	0.06	0.13	639 (56.2)	222 (47.2)	0.001	0.21
Positive	736 (25.3)	319 (31.9)			420 (32.0)	192 (37.9)			326 (28.7)	180 (38.3)		
Unknown	389 (13.4)	137 (13.7)			191 (14.5)	69 (13.6)			171 (15.1)	68 (14.5)		
Histology												
IDC	2,023 (69.6)	660 (66.0)	0.16		965 (73.5)	356 (70.4)	0.13		854 (75.2)	346 (73.6)	0.27	
ILC	433 (14.9)	174 (17.4)		0.08	166 (12.6)	76 (15.0)		0.13	135 (11.9)	49 (10.4)		0.11
IDC/ILC	393 (13.5)	143 (14.3)			151 (11.5)	68 (13.4)			111 (9.8)	61 (13.0)		
Other	58 (2.0)	23 (2.3)			31 (2.4)	6 (1.2)			36 (3.2)	14 (3.0)		
PR status												
PR+	2,838 (97.6)	970 (97.0)	0.29	0.04	1,143 (87.1)	455 (89.9)	0.11	0.09	992 (87.3)	399 (84.9)	0.20	0.07
PR-	69 (2.4)	30 (3.0)			170 (12.9)	51 (10.1)			144 (12.7)	71 (15.1)		
Her2 status												
Her2-	2,841 (97.7)	978 (97.8)	0.36	0.06	1,255 (95.6)	492 (97.2)	0.30	0.09	1,039 (91.5)	435 (92.6)	0.44	0.08
Her2+	36 (1.2)	8 (0.8)			31 (2.4)	7 (1.4)			53 (4.7)	23 (4.9)		
Unknown	30 (1.0)	14 (1.4)			27 (2.1)	7 (1.4)			44 (3.9)	12 (2.6)		
Chemotherapy												
No	2,338 (80.4)	632 (63.2)	<0.001	0.40	615 (46.8)	148 (29.2)	<0.001	0.37	620 (54.6)	170 (36.2)	<0.001	0.38
Yes	518 (17.8)	347 (34.7)			689 (52.5)	353 (69.8)			487 (42.9)	288 (61.3)		
Unknown	51 (1.8)	21 (2.1)			9 (0.7)	5 (1.0)			29 (2.6)	12 (2.6)		
Race												
White	2,568 (88.3)	880 (88.0)	0.95		1,161 (88.4)	433 (85.6)	0.22		991 (87.2)	395 (84.0)	0.02	
Black	200 (6.9)	74 (7.4)		0.02	93 (7.1)	50 (9.9)		0.11	100 (8.8)	39 (8.3)		0.16
Asian/PI	78 (2.7)	26 (2.6)			33 (2.5)	11 (2.2)			25 (2.2)	17 (3.6)		
Other/Unknown	61 (2.1)	20 (2.0)			26 (2.0)	12 (2.4)			20 (1.8)	19 (4.0)		
Hispanic												
No	2,680 (92.2)	930 (93.0)	0.39	0.05	1,216 (92.6)	471 (93.1)	0.84	0.03	1,043 (91.8)	428 (91.1)	0.59	0.05
Yes	122 (4.2)	43 (4.3)			45 (3.4)	18 (3.6)			48 (4.2)	25 (5.3)		
Unknown	105 (3.6)	27 (2.7)			52 (4.0)	17 (3.4)			45 (4.0)	17 (3.6)		
Insurance status												
Private	1,722 (59.2)	648 (64.8)	<0.001		781 (59.5)	326 (64.4)	0.32		629 (55.4)	280 (59.6)	0.23	
Medicare	940 (32.3)	256 (25.6)		0.17	409 (31.2)	133 (26.3)		0.11	401 (35.3)	145 (30.9)		0.14
Medicaid	171 (5.9)	71 (7.1)			77 (5.9)	29 (5.7)			69 (6.1)	35 (7.4)		
None	53 (1.8)	13 (1.3)			30 (2.3)	13 (2.6)			25 (2.2)	8 (1.7)		
Unknown	21 (0.7)	12 (1.2)			16 (1.2)	5 (1.0)			12 (1.1)	2 (0.4)		
Comorbidity score												
0	2,376 (81.7)	828 (82.8)	0.75	0.03	1,097 (83.5)	436 (86.2)	0.37	0.08	903 (79.5)	378 (80.4)	0.89	0.03
1	431 (14.8)	139 (13.9)			180 (13.7)	57 (11.3)			185 (16.3)	72 (15.3)		
2	100 (3.4)	33 (3.3)			36 (2.7)	13 (2.6)			48 (4.2)	20 (4.3)		
Prior cancer												
No	2,100 (72.2)	760 (76.0)	0.02	0.09	979 (74.6)	393 (77.7)	0.18	0.07	833 (73.3)	376 (80.0)	0.005	0.16
Yes	807 (27.8)	240 (24.0)			334 (25.4)	113 (22.3)			303 (26.7)	94 (20.0)		
Facility type												
Academic	1,017 (35.0)	326 (32.6)	0.11		467 (35.6)	180 (35.6)	0.92		386 (34.0)	138 (29.4)	0.26	
Community	221 (7.6)	83 (8.3)		0.10	103 (7.8)	38 (7.5)		0.05	104 (9.2)	52 (11.1)		0.12
Comprehensive	1,279 (44.0)	480 (48.0)			594 (45.2)	229 (45.3)			520 (45.8)	217 (46.2)		
Integrated	370 (12.7)	105 (10.5)			137 (10.4)	52 (10.3)			112 (9.9)	55 (11.7)		
Unknown	20 (0.7)	6 (0.6)			12 (0.9)	7 (1.4)			14 (1.2)	8 (1.7)		
Income quartile												
Top	1,187 (40.8)	401 (40.1)	0.98		498 (37.9)	190 (37.5)	0.87		412 (36.3)	171 (36.4)	0.93	
2nd	771 (26.5)	271 (27.1)		0.02	360 (27.4)	148 (29.2)		0.04	310 (27.3)	134 (28.5)		0.04
3rd	601 (20.7)	207 (20.7)			279 (21.2)	104 (20.6)			224 (19.7)	92 (19.6)		
Bottom	348 (12.0)	121 (12.1)			176 (13.4)	64 (12.6)			190 (16.7)	73 (15.5)		

(Continued on the following page)

Table 1. Characteristics of patients from the NCDB cohort grouped by 21-gene RS assay risk group (Cont'd)

	Low-risk				Intermediate-risk				High-risk			
Variable	No PMRT ($N = 2,907$)	PMRT ($N = 1,000$)	*P*	SMD	No PMRT ($N = 1,303$)	PMRT ($N = 506$)	*P*	SMD	No PMRT ($N = 1,136$)	PMRT ($N = 470$)	*P*	SMD
Education quartile												
Top	940 (32.3)	348 (34.8)	0.20		422 (32.1)	168 (33.2)	0.60		320 (28.2)	132 (28.1)	0.20	
2nd	1,031 (35.5)	339 (33.9)		0.08	427 (32.5)	164 (32.4)		0.07	368 (32.4)	171 (36.4)		0.12
3rd	630 (21.7)	195 (19.5)			277 (21.1)	94 (18.6)			282 (24.8)	115 (24.5)		
Bottom	306 (10.5)	118 (11.8)			187 (14.2)	80 (15.8)			166 (14.6)	52 (11.1)		
Year												
2010 and before	536 (18.4)	145 (14.5)	0.01		301 (22.9)	74 (14.6)	0.001		237 (20.9)	86 (18.3)	0.57	
2011	604 (20.8)	226 (22.6)		0.12	311 (23.7)	129 (25.5)		0.21	291 (25.6)	117 (24.9)		0.08
2012	856 (29.4)	282 (28.2)			321 (24.4)	139 (27.5)			299 (26.3)	127 (27.0)		
2013	911 (31.3)	347 (34.7)			380 (28.9)	164 (32.4)			309 (27.2)	140 (29.8)		

NOTE: Data are presented as count (percentage) or median (interquartile range) with significance determined by Fisher exact test or Kruskal–Wallis test; 1mi: 1 (microscopic); grade 1: well differentiated, grade 2: moderately differentiated, grade 3: poorly differentiated/undifferentiated; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; PR: progesterone receptor; and Her2: Her2/Neu receptor.

with OS ($P = 0.009$). Age, grade 3 disease, higher tumor stage (pT2), absence of PR expression, Medicaid/none insurance status, higher comorbidity score, and history of prior cancer were also significantly associated with decreased OS in this model (Supplementary Table S3). In analyses of propensity-score–matched cohorts for each RS subgroup, women with low RS who received PMRT had significantly longer OS compared with women with low RS who did not receive PMRT (5-year OS: 96.8% vs. 94.9%; TR = 1.70, 95% CI = 1.30–2.22, $P < 0.001$; Table 3). PMRT was not associated with longer OS in women with intermediate RS (5-year OS: 94.4% vs. 93.6%; TR = 0.89, 95% CI = 0.69–1.14, $P = 0.35$) or high RS (5-year OS: 92.2% versus 91.9%; TR = 1.10, 95% CI = 0.91–1.34, $P = 0.33$; Table 3). Unadjusted survival curves of the matched cohorts of the NCDB cohort are presented in Fig. 2.

In multivariable analysis of all patients within the SEER cohort, receipt of PMRT did not independently impact OS (TR = 1.11, 95% CI = 0.83–1.47, $P = 0.48$), but there was a significant interaction of RS and PMRT with OS ($P = 0.03$). Age, Medicaid/none insurance status, and history of prior cancer were also significantly associated with decreased OS in this model (Supplementary Table S4). In subset analyses, women with low RS who received PMRT had significantly longer OS compared with women with low RS who did not receive PMRT (5-year OS: 97.4% vs. 94.2%; TR = 1.85, 95% CI = 1.33–2.57, $P < 0.001$; Table 3). PMRT was not associated with longer OS in women with intermediate RS (5-year OS: 91.7% vs. 90.4%; TR = 0.84, 95% CI = 0.62–1.14, $P = 0.26$), or high RS (5-year OS: 77.0% vs. 87.8%; TR = 0.79, 95% CI = 0.50–1.23, $P = 0.28$; Table 3). Unadjusted survival curves of the matched cohorts of the SEER cohort are presented in Fig. 2.

Sensitivity analyses were performed in a subgroup of patients within the NCDB cohort whose receipt of *chemotherapy* was consistent with their RS. In this subgroup, women with low RS did not receive chemotherapy, while women with high RS did receive chemotherapy; women with intermediate RS who both received or did not receive chemotherapy were included. Results of this analysis were consistent with those of the overall cohort: women with low RS who received PMRT had significantly longer OS compared with women with low RS who did not receive PMRT (TR = 1.84; 95% CI = 1.15–2.97, $P = 0.01$), while PMRT was not associated with longer OS in women with intermediate RS (TR = 0.88, 95% CI = 0.62–1.14, $P = 0.44$) or high RS (TR = 1.64, 95% CI = 0.82–3.30, $P = 0.16$). Results were similarly consistent in a subgroup of analysis of only women within the NCDB cohort with Her2-negative disease: women with low RS who received PMRT had significantly longer OS compared to women with low RS who did not receive PMRT (TR = 1.80; 95% CI = 1.18–2.74, $P = 0.007$), while PMRT was not associated with longer OS in women with intermediate RS (TR = 0.86, 95% CI = 0.60–1.21, $P = 0.38$) or high RS (TR = 1.04, 95% CI = 0.81–1.35, $P = 0.74$). Due to the small number of women with Her2-positive disease, it was not possible to perform a separate analysis for women with Her2-positive disease.

TR estimates for decreased OS associated with low RS and omission of PMRT within the NCDB cohort were very robust to reasonable assumptions about possible unmeasured confounding. For example, in order for the observed effect of PMRT to be rendered nonsignificant, there would need to be a moderately imbalanced (prevalence of 70% vs. 30%) unmeasured confounder that demonstrated an association with OS with a TR ≥ 3 (Supplementary Table S3).

Discussion

In this analysis of a large cohort of women from the NCDB with T1–2 N1 ER-positive breast cancer who underwent mastectomy, the 21-gene RS assay predicted benefit of PMRT for OS. This finding was validated in a separate cohort using the SEER registry. In both cohorts, women with low RS who received PMRT had significantly longer OS compared with women with low RS who did not receive PMRT. The survival advantage seen among women with low RS who received PMRT was approximately 2% to 3% at 5 years. In the matched cohort analysis of the low RS subgroup of the NCDB cohort, 29 of 1,000 women who did not receive PMRT had died, while only nine of 1,000 women died who did receive PMRT. Receipt of PMRT was not associated with longer OS among women with intermediate or high RS. The use of robust statistical analyses and the consistency across two datasets and sensitivity analyses adds to the strength of this finding. The 21-gene RS assay may therefore be useful as a predictive marker for potential OS benefit from PMRT in women with T1–2 N1 ER-positive breast cancer.

The value of PMRT in patients with T1–2 N1 breast cancer remains a topic of great clinical relevance and controversy. Until recently, it had been assumed that the absolute reduction in LRR achieved by PMRT would be proportional to its benefit in OS. The 2005 Early Breast Cancer Trialists Collaborative Group (EBCTCG)

Table 2. Characteristics of patients from the SEER cohort grouped by 21-gene RS assay risk group

	Low-risk				Intermediate-risk				High-risk			
Variable	**No PMRT (*N* = 1,469)**	**PMRT (*N* = 334)**	***P***	**SMD**	**No PMRT (*N* = 829)**	**PMRT (*N* = 216)**	***P***	**SMD**	**No PMRT (*N* = 176)**	**PMRT (*N* = 54)**	***P***	**SMD**
Age (years)	58 [49–66]	57 [48–66]	0.52	0.05	57 [49–66]	56 [48–65]	0.06	0.16	56 [47–66]	53 [44–62]	0.06	0.25
Follow-up (months)	37 [23–57]	36 [23–52]	0.15	0.10	39 [24–58]	33 [20–49]	0.001	0.24	42 [27–59]	32 [19–55]	0.05	0.23
Tumor stage												
pT1	923 (62.8)	161 (48.2)	<0.001	0.30	486 (58.6)	95 (44.0)	<0.001	0.30	87 (49.4)	23 (42.6)	0.47	0.14
pT2	546 (37.2)	173 (51.8)			343 (41.4)	121 (56.0)			89 (50.6)	31 (57.4)		
Nodal stage												
pN1mi	632 (43.0)	93 (27.8)	<0.001	0.32	345 (41.6)	58 (26.9)	<0.001	0.32	60 (34.1)	16 (29.6)	0.66	0.10
pN1	837 (57.0)	241 (72.2)			484 (58.4)	158 (73.1)			116 (65.9)	38 (70.4)		
Grade												
1	488 (33.2)	87 (26.0)	0.009		162 (19.5)	25 (11.6)	0.04		8 (4.5)	1 (1.9)	0.43	
2	825 (56.2)	201 (60.2)		0.21	464 (56.0)	129 (59.7)		0.23	67 (38.1)	25 (46.3)		0.30
3	111 (7.6)	39 (11.7)			188 (22.7)	56 (25.9)			97 (55.1)	28 (51.9)		
Unknown	45 (3.1)	7 (2.1)			15 (1.8)	6 (2.8)			4 (2.3)	0 (0.0)		
Histology												
IDC	1,090 (74.2)	228 (68.3)	0.16		653 (78.8)	154 (71.3)	0.08		159 (90.3)	44 (81.5)	0.06	
ILC	224 (15.2)	62 (18.6)		0.14	105 (12.7)	41 (19.0)		0.19	9 (5.1)	3 (5.6)		0.34
IDC/ILC	125 (8.5)	34 (10.2)			61 (7.4)	17 (7.9)			3 (1.7)	5 (9.3)		
Other	30 (2.0)	10 (3.0)			10 (1.2)	4 (1.9)			5 (2.8)	2 (3.7)		
PR status												
PR+	1,421 (96.7)	317 (94.9)	0.14	0.09	725 (87.5)	190 (88.0)	0.91	0.02	131 (74.4)	41 (75.9)	1.00	0.04
PR-	48 (3.3)	17 (5.1)			104 (12.5)	26 (12.0)			45 (25.6)	13 (24.1)		
Her2 status												
Her2-	1,056 (71.9)	271 (81.1)	<0.001	0.25	584 (70.4)	167 (77.3)	0.04	0.20	106 (60.2)	35 (64.8)	0.20	0.35
Her2+	19 (1.3)	7 (2.1)			10 (1.2)	5 (2.3)			10 (5.7)	0 (0.0)		
Unknown	394 (26.8)	56 (16.8)			235 (28.3)	44 (20.4)			60 (34.1)	19 (35.2)		
Chemotherapy												
No/Unknown	1,136 (77.3)	212 (63.5)	<0.001	0.31	447 (53.9)	72 (33.3)	<0.001	0.42	49 (27.8)	3 (5.6)	<0.001	0.63
Yes	333 (22.7)	122 (36.5)			382 (46.1)	144 (66.7)			127 (72.2)	51 (94.4)		
Race												
White	1,232 (83.9)	279 (83.5)	0.59		699 (84.3)	178 (82.4)	0.17		146 (83.0)	45 (83.3)	0.96	
Black	105 (7.1)	29 (8.7)		0.10	58 (7.0)	24 (11.1)		0.16	15 (8.5)	4 (7.4)		0.12
Asian/PI	119 (8.1)	25 (7.5)			68 (8.2)	13 (6.0)			14 (8.0)	5 (9.3)		
Other/Unknown	13 (0.9)	1 (0.3)			4 (0.5)	1 (0.5)			1 (0.6)	0 (0.0)		
Hispanic												
No	1,319 (89.8)	309 (92.5)	0.51	0.07	762 (91.9)	193 (89.4)	0.29	0.09	160 (90.9)	50 (92.6)	0.91	0.06
Yes	150 (10.2)	25 (7.5)			67 (8.1)	23 (10.6)			16 (9.1)	4 (7.4)		
Insurance status												
Insured	1,271 (86.5)	286 (85.6)	0.61		700 (84.4))	191 (88.4)	0.47		139 (79.0)	48 (90.6)	0.40	
Medicaid	127 (8.6)	32 (9.6)		0.09	69 (8.3)	14 (6.5)		0.14	19 (10.8)	3 (5.7)		0.29
None	25 (1.7)	3 (0.9)			25 (3.0)	3 (1.4)			3 (1.7)	1 (1.9)		
Unknown	46 (3.1)	13 (3.9)			35 (4.2)	8 (3.7)			15 (18.5)	2 (3.7)		
Prior cancer												
No	1,355 (92.2)	307 (91.9)	0.85	0.01	762 (91.9)	202 (93.5)	0.48	0.06	165 (93.8)	50 (92.6)	0.76	0.05
Yes	114 (7.8)	27 (8.1)			67 (8.1)	14 (6.5)			11 (6.2)	4 (7.4)		
Socioeconomic tertile												
Top	318 (21.6)	76 (22.8)	0.95		189 (22.8)	56 (25.9)	0.16		41 (23.3)	11 (20.4)	0.77	
Middle	490 (33.4)	107 (32.0)		0.04	239 (28.8)	74 (34.3)		0.17	61 (34.7)	16 (29.6)		0.17
Bottom	637 (43.4)	146 (43.7)			386 (46.6)	83 (38.4)			72 (40.9)	26 (48.1)		
Unknown	24 (1.6)	5 (1.5)			15 (1.8)	3 (1.4)			2 (1.1)	1 (1.9)		
Year												
2010 and before	585 (39.8)	107 (32.0)	0.03		349 (42.1)	65 (30.1)	0.004		80 (45.5)	20 (37.0)	0.11	
2011	235 (16.0)	71 (21.3)		0.18	138 (16.6)	37 (17.1)		0.28	32 (18.2)	5 (9.3)	0.39	
2012	331 (22.5)	77 (23.1)			169 (20.4)	48 (22.2)			32 (18.2)	13 (24.1)		
2013	318 (21.6)	79 (23.7)			173 (20.9)	66 (30.6)			32 (18.2)	16 (29.6)		

NOTE: Data are presented as count (percentage) or median (interquartile range) with significance determined by Fisher exact test or Kruskal-Wallis test; 1mi: 1 (microscopic); grade 1: well differentiated, grade 2: moderately differentiated, grade 3: poorly differentiated/undifferentiated; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; PR: progesterone receptor; and Her2: Her2/Neu receptor.

meta-analysis posited that for every four LRRs prevented at 5 years, one death from breast cancer would be prevented at 15 years (1). More recently, the 2014 EBCTCG meta-analysis demonstrated that PMRT reduced the 10-year risk of any recurrence by 10.6% and the 20-year risk of breast cancer–specific death by 8.1% (3). Consensus statements that incorporate more modern data suggest that there has been a reduction in absolute benefit of PMRT attributable to improvements in other modalities, namely systemic therapy; more recent series have reported rates of 10-year LRR following mastectomy and without PMRT to range between 4% and 10% (5). The steadily improving rates of LRR have led many to question whether the long-term risks associated with PMRT may outweigh its potential absolute benefits in women with one to three positive nodes (4, 5, 10).

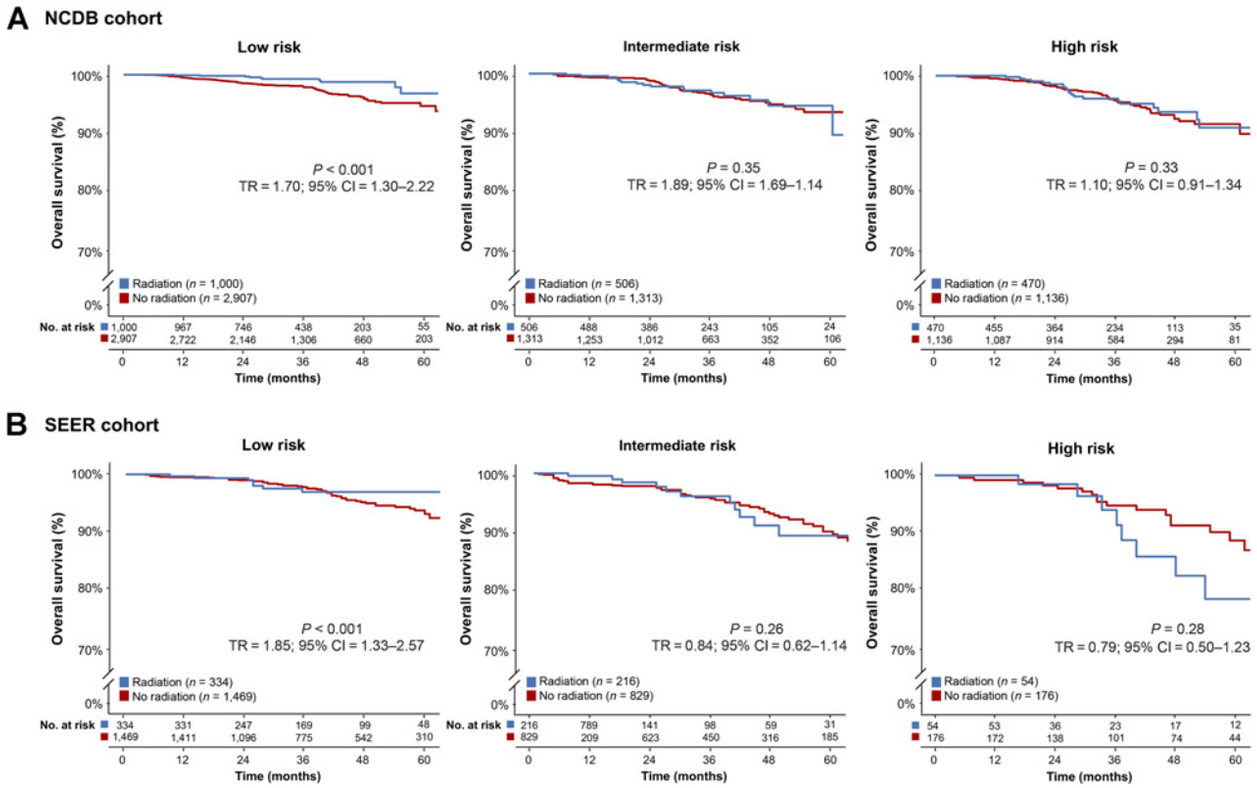

Figure 2.

Survival curves for the NCDB and SEER cohorts. Unadjusted survival curves based on Kaplan–Meier estimates of overall survival for women with low-, intermediate-, and high-risk 21-gene RS assay groups diagnosed with T1-2 N1 ER-positive breast cancer treated with (blue) or without (red) post-mastectomy radiotherapy from the NCDB (**A**) and SEER cohorts (**B**). Significance determined by Wald test of multivariable analyses of matched cohorts. Statistical results represent analyses of matched cohorts for each RS subgroup.

The American Society of Clinical Oncology (ASCO) focused guideline update (2017) concluded that PMRT may be potentially omitted for patients with a low risk of LRR (5). Running counter to this line of thinking, however, is the understanding that adjuvant locoregional therapy will necessarily confer the greatest survival benefit to patients at the lowest risk of harboring subclinical micrometastatic disease. Patients with a low RS are at the lost risk of future distant metastasis. Sterilization of potential residual disease may therefore be of the greatest clinical utility to patients within this subgroup. This point is most elegantly demonstrated by the subgroup analysis of the DBCG 82 b&c trials in which patients within the low-risk subgroup experienced the smallest absolute reduction in LRR following PMRT, but the largest benefit in OS (31). In contrast, patients within the high-risk group achieved a large absolute reduction in LRR following PMRT, but demonstrated no OS benefit. It is hypothesized that this may be potentially due to the competing risk of distant disease recurrence ultimately negating any survival benefit from a locoregional treatment. Another potential contributor to this effect may be that radiosensitivity differs between biologic subtypes; tumors with lower risk of LRR may derive a larger relative benefit in OS due to greater radiosensitivity. The potential translation of a small absolute benefit in LRR to a surprisingly large downstream benefit is similarly exhibited in both the MA-20 and EORTC 22922 trials, in which the improvement in distant disease-free survival exceeded the reduction in LRR (32, 33).

The 21-gene RS assay has been validated as an independent prognosticator of LRR, distant recurrence, and OS in women with node-positive ER-positive breast cancer (6–10). Furthermore, RS has been shown to predict benefit to adjuvant systemic chemotherapy for women with node-negative cancer, and is endorsed by the ASCO 2016 Focused Guideline Update to be used in decision making regarding systemic treatment (34–36). Consistent with this, a retrospective analysis of the Southwest Oncology Group (SWOG)-8814 demonstrated that women with one to three positive nodes and low RS may not derive a significant benefit to adjuvant chemotherapy; the RxPONDER trial is currently accruing patients for prospective validation of this finding (NCT01272037; ref. 6). Similarly, it has been hypothesized that the 21-gene RS assay may be prognostic for LRR and therefore predicts the value of PMRT. Mamounas and colleagues (10) recently demonstrated that RS has independent prognostic value for assessing risk of LRR in node-positive patients and may be useful in identifying patients with a low risk of LRR for whom PMRT could be omitted.

The argument posited in the analysis by Mamounas and colleagues is logical. It is also reasonable, however, to surmise the opposite: patients with high RS who are at the highest risk for subclinical micrometastatic disease may not derive a survival

Table 3. Kaplan–Meier estimates and parametric accelerated failure time models for overall survival from the NCDB and SEER cohorts

	Kaplan–Meier estimates				Multivariable AFT analysis			
					All patients		Matched cohorts	
Variable	*N* at risk (*N* events)	Restricted mean OS (mo; 95% CI)	5y OS (95% CI)	Log-rank *P*	TR (95% CI)	*P*	TR (95% CI)	*P*
NCDB cohort								
Low-risk								
No PMRT	2,907 (79)	91.3 (88.4–94.1)	94.9 (93.6–96.2)		1.00 (reference)		1.00 (reference)	
PMRT	1,000 (9)	94.7 (93.5–96.0)	96.8 (93.9–99.7)		1.72 (1.14–2.58)	0.009	1.70 (1.30–2.22)	<0.001
Intermediate-risk								
No PMRT	1,313 (45)	91.3 (88.8–93.8)	93.6 (91.4–95.8)	<0.001	1.00 (reference)		1.00 (reference)	
PMRT	506 (17)	91.0 (87.3–94.8)	94.4 (91.3–97.6)		0.85 (0.60–1.20)	0.35	0.89 (0.69–1.14)	0.35
High-risk								
No PMRT	1,136 (51)	90.8 (89.1–92.6)	91.9 (89.5–94.4)		1.00 (reference)		1.00 (reference)	
PMRT	470 (19)	89.3 (83.8–94.4)	92.2 (87.9–96.7)		1.09 (0.83–1.43)	0.54	1.10 (0.91–1.34)	0.33
SEER cohort								
Low-risk								
No PMRT	1,469 (56)	111.3 (108.8–113.9)	94.2 (92.4–96.0)		1.00 (reference)		1.00 (reference)	
PMRT	334 (6)	117.1 (115.1–119.0)	97.4 (95.3–99.5)		1.65 (1.03–2.64)	0.04	1.85 (1.33–2.57)	<0.001
Intermediate-risk								
No PMRT	829 (53)	106.8 (103.6–110.0)	90.4 (87.5–93.4)	<0.001	1.00 (reference)		1.00 (reference)	
PMRT	216 (11)	107.7 (101.3–114.1)	91.7 (86.3–97.4)		0.84 (0.52–1.37)	0.49	0.84 (0.62–1.14)	0.26
High-risk								
No PMRT	176 (16)	100.4 (92.1–108.8)	87.8 (81.0–95.3)		1.00 (reference)		1.00 (reference)	
PMRT	54 (6)	99.5 (86.4–112.5)	77.0 (61.6–96.2)		0.49 (0.23–1.03)	0.06	0.79 (0.50–1.23)	0.28

NOTE: AFT models for the matched cohorts were covariate-adjusted and inverse probability-weighted using propensity-weighted matched cohorts. Significance determined by log-rank test or Wald test. AFT, accelerated failure time.

benefit from a locoregional treatment due to a competing risk of distant failure. Our results are consistent with the latter hypothesis: women with a low RS had longer OS associated with receipt of PMRT, while women with intermediate or high RS did not. Survival benefit may therefore not be proportional to the absolute reduction of LRR in this patient population. Instead, the translation from LRR benefit to survival benefit appears to be heterogeneous and varies between subpopulations on the basis of distant recurrence risk and/or intrinsic radiosensitivity.

The current analyses are most critically limited by cohort size, particularly for the high-risk subset within the SEER cohort, which had very few high-risk patients who received PMRT. Although the size of cohorts used is large compared with many other studies evaluating RS, a relatively small proportion of eligible patients underwent testing for RS. Given that the 21-gene RS is not routinely ordered for women with node-positive disease, the majority of patients who were otherwise eligible for this analysis were not evaluated for RS. This may be due to a range of factors, including type of treatment facility, physician specialty, and other physician-related characteristics (37). Survival estimates of the selected cohorts, however, were reflective of those calculated for all eligible T1–2 N1 women within the NCDB and SEER registry, and were also consistent with recently published studies of this patient population (38). Cohort size precluded subset analyses by race, which may be relevant given that among women with node-negative disease, non-Hispanic black women have higher RS compared with non-Hispanic white women (39).

Interestingly, a larger proportion than expected of women with high RS within the NCDB cohort did not receive chemotherapy (49.2%; $N = 790/1{,}606$), while 22.1% ($N = 865/3{,}907$) of patients with low RS did receive chemotherapy. To address this, a sensitivity analysis was performed on the subgroup of patients within the NCDB cohort whose chemotherapy status was consistent with their reported RS; these results were very similar to those of the overall cohort. In addition, although the sensitivity of the SEER registry for recording receipt of chemotherapy and radiotherapy is moderate to high, there may be patients who are incorrectly categorized as not having received either or both treatments (40). Lastly, the short median follow-up times, necessarily limited by the availability of RS in the databases, may have precluded finding survival advantages that may appear later in time. Indeed, it was surprising to find such an obvious survival advantage so early in the low RS subsets. It should also be noted that although the NCDB and SEER registry are created independently and sampled for inclusion differently, there are likely shared patients between these two datasets that would make the two cohorts not entirely unique. The NCDB reports approximately 70% to 75% of cases within the United States, while the SEER registry reports approximately 28% of cases (41). As a result, the majority of patients within the NCDB cohort are likely not represented in the SEER cohort (42).

Given that the NCDB and SEER do not provide data regarding LRR and are subject to notable limitations, the current findings require prospective validation. The Canadian Tailor RT trial (MA.39), to begin accrual in mid-2018, will randomize women with T1–2 N1 disease and documented low RS who underwent BCS or mastectomy to either regional radiation or no regional radiation, with breast cancer recurrence-free interval as the primary objective. This trial should provide clarity regarding the value of RS as a predictor of the value of radiotherapy in women with T1–2 N1 breast cancer.

In conclusion, the current analyses provide initial evidence that survival benefit of PMRT in women with T1–2 N1 breast ER-positive breast cancer may be more pronounced in, or even limited to, women with low-risk RS. These data are remarkable for consistent validation with robust statistical analysis across two large cohorts. These results support and extend the findings from subgroup analyses of seminal trials which demonstrated that PMRT conferred the greatest improvement in survival to patients within the most favorable prognostic group (31). Although

women with high RS may experience the greatest absolute reduction of LRR, women with low RS may derive the greatest survival benefit from PMRT due to a low competing risk of subclinical micrometastatic disease at diagnosis. These results caution against omission of PMRT for women with node-positive disease on the basis of a low-risk 21-gene RS alone and strongly suggest the need for prospective validation of this strategy prior to widespread adoption.

Disclosure of Potential Conflicts of Interest

M. Kocherginsky is listed as a co-inventor on a patent issued "Methods and compositions related to glucocorticoid receptor (GR) antagonists and breast cancer," which has been licensed to Corcept Therapeutics by The University of Chicago. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The NCDB and SEER have not verified and are not responsible for the statistical validity of the data analysis or conclusions.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.R. Goodman, B.-L.L. Seagle
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.R. Goodman, B.-L.L. Seagle, M. Kocherginsky, E.D. Donnelly
Writing, review, and/or revision of the manuscript: C.R. Goodman, B.-L.L. Seagle, M. Kocherginsky, E.D. Donnelly, J.B. Strauss
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.R. Goodman
Study supervision: S. Shahabi

Acknowledgments

We acknowledge the NCDB and SEER for collecting the data used in these analyses. The NCDB and SEER and their participating hospitals are the source of the data.

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Received October 25, 2017; revised March 8, 2018; accepted April 18, 2018; published first April 23, 2018.

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