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ORIGINAL ARTICLE

Clinical and Genomic Risk for Late Breast Cancer Recurrence and Survival

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Abstract

BACKGROUND The 21-gene recurrence score (RS) assay (Oncotype DX) is used to guide adjuvant chemotherapy use for patients with hormone receptor–positive, HER2 (human epidermal growth factor receptor 2)-negative, axillary node-negative breast cancer. Its role, however, in providing prognostic information for late distant recurrence when added to clinicopathologic prognostic factors is unknown.

METHODS A patient-specific meta-analysis including 10,004 women enrolled in three trials was updated using extended follow-up data from TAILORx, integrating the RS with histologic grade, tumor size, and age at surgery for the RSClin tool. Cox models integrating clinicopathologic factors and the RS were compared by using likelihood ratio (LR) tests. External validation of prognosis for distant recurrence in years 0 to 10 and 5 to 10 was performed in an independent cohort of 1098 women in a real-world registry.

RESULTS RSClin provided significantly more prognostic information than either the clinicopathologic factors (ΔLR chi-square, 86.2; P<0.001) or RS alone (ΔLR chi-square, 131.0; P<0.001). The model was prognostic in an independent cohort for distant recurrence by 10 years after diagnosis (standardized hazard ratio, 1.56; 95% confidence interval, 1.25 to 1.94), was associated with late distant recurrence risk between 5 and 10 years after diagnosis (standardized hazard ratio, 1.78; 95% confidence interval, 1.25 to 2.55), and approximated the observed 10-year distant recurrence risk (Lin concordance, 0.87) and 5- to 10-year distant recurrence risk (Lin concordance, 0.92).

CONCLUSIONS The 21-gene RS is prognostic for distant recurrence and overall survival in early breast cancer. A model integrating the 21-gene RS and clinicopathologic factors improved estimates of distant recurrence risk compared with either used individually

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and stratified late distant recurrence risk. (Funded by the National Cancer Institute, National Institutes of Health [U10CA180820, U10CA180794, UG1CA189859, U10CA180868, and U10CA180822] and others.)

Introduction

Distant recurrence after primary surgical treatment of localized breast cancer may occur more than 30 years after potentially curative surgery despite adjuvant systemic therapy, especially in estrogen receptor–positive breast cancer.[1] Although adjuvant systemic chemotherapy and endocrine therapy (ET) reduce recurrence risk, largely by reducing recurrences within the first 5 years,[2,3] more than one half of distant recurrences occur more than 5 years after initial surgery, often following completion of a 5-year or longer course of adjuvant antiestrogen ET.[4]

Clinicopathologic factors such as axillary node metastases, larger tumor size, and poor histologic grade are prognostic for both early and late recurrence.[4] Results of the 21-gene recurrence score (RS) assay, Oncotype DX, provide prognostic information for distant recurrence and predictive information for chemotherapy benefit in hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer,[5-12] as well as prognostic information regarding clinicopathologic factors.[13,14] To the best of our knowledge, however, its role in providing added prognostic information for late recurrence when integrated with clinicopathologic factors has not been previously evaluated.

TAILORx (Trial Assigning Individualized Options for Treatment) established the clinical utility of the 21-gene RS for guiding chemotherapy use in hormone receptor–positive, HER2-negative, axillary node–negative breast cancer, which is now recommended in practice guidelines.[15-17] The additional analysis reported here had three main objectives. The first objective was to provide an update regarding the patient-specific meta-analysis including 10,004 women with hormone receptor–positive, HER2-negative, axillary node–negative breast cancer, including TAILORx patients, used for development of the RSClin tool (a combination of the RS and clinical features of the breast cancer at the time of diagnosis); use of this tool at the time of diagnosis provides estimates of 10-year distant recurrence risk and absolute chemotherapy benefit.[14] The primary outcome of this analysis was the prognostic value of the full RSClin model compared with reduced models estimated using clinicopathologic factors alone and the RS alone. The secondary objective was to develop and validate a new tool, RSClin Late, that provides prognostic information for late distant recurrence beyond 5 years after completing a 5-year course of adjuvant ET without recurrence. The final objective was to provide an updated analysis of TAILORx with substantially longer follow-up and more recurrence events for confirming that the primary study objective of establishing noninferiority of ET compared with chemoendocrine therapy (CET) in the RS 11 to 25 group remains unchanged.

Methods

TAILORx UPDATE

Details regarding TAILORx have been previously described,[9,10,12,13] and are available in the protocol provided with the full text of this article at evidence.nejm.org. The "primary analysis" refers to the original prespecified analysis for the primary invasive disease–free survival end point, defined as recurrence of invasive disease, second primary cancer, or death. There were 836 events with full information in the RS 11 to 25 group after a median 7.5 years of follow-up. Although the TAILORx trial design did not prespecify additional event-driven or time-driven analyses beyond the primary analysis, it did prespecify continued follow-up of surviving patients up to 20 years after trial registration to allow additional post hoc analyses.

The same intention-to-treat population previously reported in the primary analysis of TAILORx was evaluated in the current study. Event-free rates were estimated by using the Kaplan–Meier method, and clinical outcomes according to RS treatment group for each clinical end point were compared by using the log-rank test. Hazard ratios were estimated by using partial likelihood analysis of the Cox proportional hazards model. Associations with clinical outcomes according to three post hoc subgroups (age, clinical risk, and self-reported race) were also examined in exploratory analyses. No multiplicity adjustments for exploratory end points were defined. Therefore, only point estimates and 95% confidence intervals (CIs) are provided. The CIs have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

RSClin TOOL UPDATE

The development and validation of the RSClin tool have all been previously reported in detail and are described in the Final Statistical Methods in the Supplementary Appendix.[14] The RSClin estimates of 10-year risk of distant recurrence, which are based on the 21-gene RS result, tumor grade, tumor size, and patient age at surgery, were updated to include the extended follow-up data and more events from TAILORx. Due to evidence of nonproportional hazards in the multivariable models, estimates were made using time-varying effects assuming piecewise constant hazard ratios for the years 0 to 5 after surgery and 5 or more years after surgery. The information provided by the updated RSClin model for distant recurrence prognosis was evaluated as the primary outcome of this analysis, using the likelihood ratio (LR) chi-square test statistic. As previously described,[14] external validation of distant recurrence risk estimation was performed in an independent cohort.[18]

DEVELOPMENT AND VALIDATION OF THE RSClin LATE TOOL

The risk of late distant recurrence (from years 5 to 10) in patients who survive free of distant recurrence after 5 years of ET alone after surgery was estimated by using the patient-specific meta-analysis methods described for RSClin (including age at surgery, tumor size, tumor grade, and RS). Further details are provided in the Planned Statistical Methods for the Update of RSClin in the Supplementary Appendix and externally validated in an independent cohort (Planned Analysis Methods for Validation in the Supplementary Appendix).[18]

Results

ADDITIONAL FOLLOW-UP AND EVENTS IN TAILORx UPDATE

The updated TAILORx analysis was performed after a median follow-up of 11.0 and 10.4 years in the randomized and overall populations, respectively. The updated analysis included more events than the primary analysis for the overall population, including invasive disease–free survival events (1819 vs. 1210), distant recurrence (561 vs. 384), locoregional recurrence with or without distant recurrence (764 vs. 543), and death (910 vs. 499). For the randomized groups for patients with an RS of 11 to 25, there were also more events for invasive disease–free survival (1295 vs. 836), distant recurrence (375 vs. 250), locoregional and/or distant recurrence (528 vs. 367), and death (660 vs. 343) compared with the original primary analysis.

When evaluating 12-year event rates in all groups of the intention-to-treat population (Fig. 1), the RS provided prognostic information for all clinical outcomes, including invasive disease–free survival, freedom from disease recurrence at a distant site, freedom from disease recurrence at a distant or locoregional site, and overall survival. For patients in group A (i.e., those whose RS results were 0 to 10 and were treated with ET alone), distant and overall recurrence-free interval rates were 93.2% (95% CI, 90.0% to 95.3%) and 91.4% (95% CI, 88.1% to 93.8%), respectively. For patients whose RS results were 11 to 25 and who were randomly assigned to receive ET alone (group B) or CET (group C), there was a less than 1% difference for all end points when comparing ET with CET at 12 years. As shown in Figure 1, these outcomes were driven largely by worse outcomes for the 1389 patients in group D (i.e., those with RS results of 26 to 100 assigned to CET); distant and overall recurrence-free interval rates were 84.8% (95% CI, 78.0% to 89.7%) and 80.9% (95% CI, 72.4% to 87.0%), respectively.

RS 11 TO 25 GROUPS IN THE TAILORx UPDATE

With longer follow-up and more events in the updated analysis, the primary trial conclusions remained unchanged for the ET-alone group compared with CET in patients with an RS of 11 to 25 for the primary end point of invasive disease–free survival (hazard ratio, 1.09; 95% CI, 0.94 to 1.24) and the secondary end point of freedom from disease recurrence at a distant site (hazard ratio, 1.11; 95% CI, 0.90 to 1.36). There were also no changes in the other prespecified end points, including freedom from disease recurrence at a distant or locoregional site (hazard ratio, 1.15; 95% CI, 0.96 to 1.36) or overall survival (hazard ratio, 1.06; 95% CI, 0.91 to 1.24).

Event rates (and standard errors) are shown in Table 1 for the two treatment groups in patients with an RS of 11 to 25, including the entire population and according to age (women $\leq$50 years of age and women >50 years of age at registration). Five-, 10-, and 12-year event rates were nearly identical between randomized treatment groups in the entire population for all four end points. Although the estimated 12-year recurrence rate was approximately 10% among patients with an RS of 11 to 25, late recurrence beyond 5 years was 7.1%, and earlier recurrence occurred

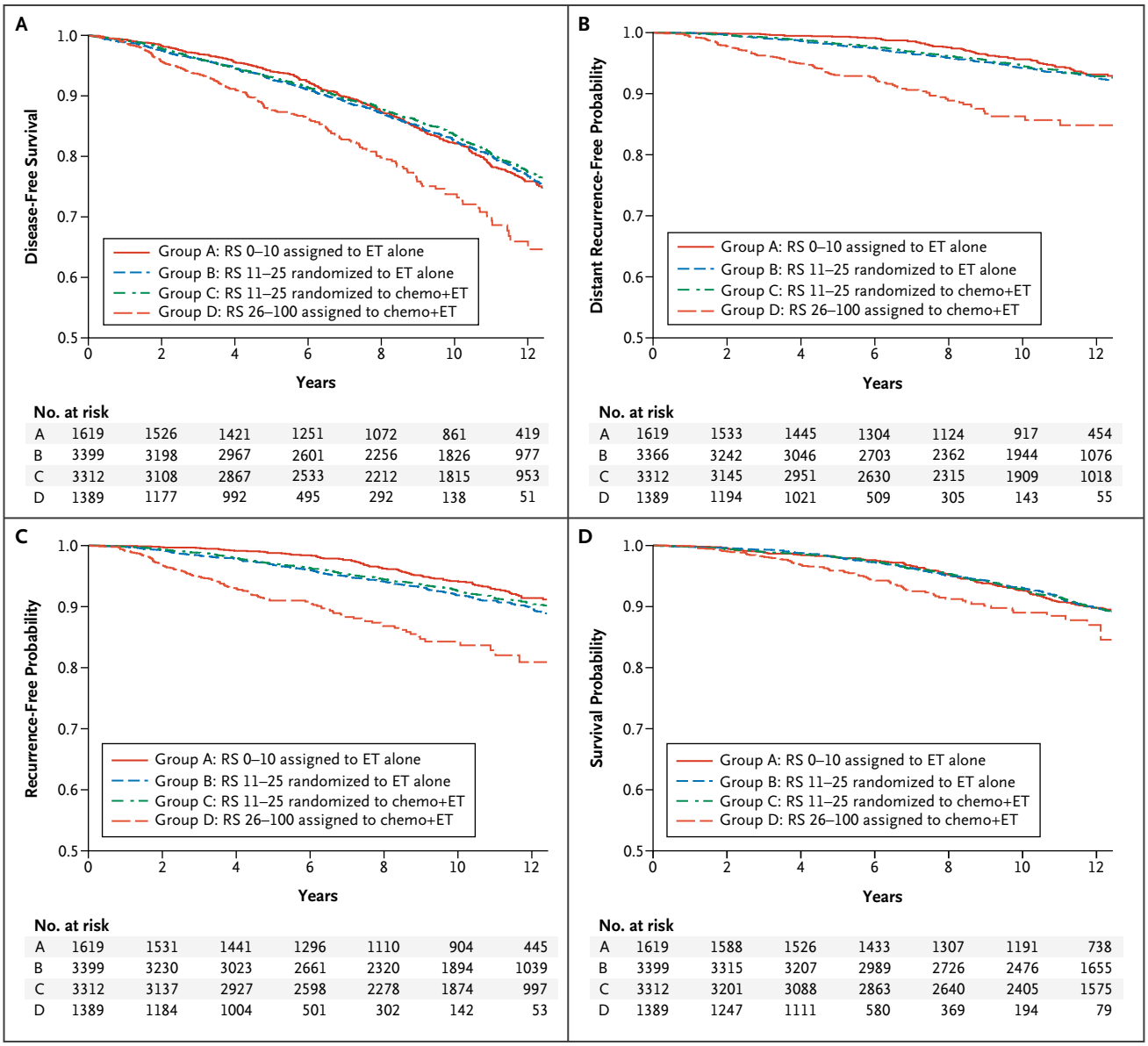

Figure 1. Kaplan–Meier Estimates for Clinical End Points for the Four Study Groups in the TAILORx Trial Using an Intention-to-Treat Analysis.

Study groups are as follows: patients with a recurrence score (RS) of 0 to 10 and assigned to receive endocrine therapy (ET) alone (group A), an RS of 11 to 25 and randomly assigned to receive ET alone (group B), an RS of 11 to 25 and randomly assigned to receive chemotherapy plus ET (chemo+ET; group C), and an RS of 26 to 100 assigned to receive chemo+ET (group D). Disease-free survival probability (Panel A), distant recurrence-free probability (Panel B), recurrence-free probability (Panel C), and survival probability (Panel D) are shown.

in 3.1% of the trial populations. The rate of nonrecurrence events, estimated by evaluating the difference between the invasive disease–free survival and freedom-from-recurrence end point, was about 13% at 12 years (about 1% per year).

CLINICAL OUTCOMES ACCORDING TO AGE, CLINICAL RISK, AND RACE IN THE TAILORx UPDATE

For women 50 years of age or younger, as shown in Table 1, there were differences comparing the CET group versus the ET-alone group at 12 years for invasive disease–free survival

Table 1. Five-, 10-, and 12-Year Event Rates for Patients with a 21-Gene RS of 11 to 25 in the Entire TAILORx Trial Population and Stratified According to Age (≤50 Years and >50 Years).*

		Entire Population (N=6711)				≤50 Years of Age (N=2216)				>50 Years of Age (N=4495)			
		Endocrine Therapy Alone (n=3399)		Chemoendocrine Therapy (n=3312)		Endocrine Therapy Alone (n=1139)		Chemoendocrine Therapy (n=1077)		Endocrine Therapy Alone (n=2260)		Chemoendocrine Therapy (n=2235)	
End Point	**Years**	**Rate**	**SE**	**Rate**	**SE**	**Rate**	**SE**	**Rate**	**SE**	**Rate**	**SE**	**Rate**	**SE**
Invasive disease–free survival	5	92.8	0.5	93.1	0.5	92.0	0.8	94.0	0.8	93.2	0.5	92.7	0.6
	10	82.6	0.7	83.6	0.7	82.3	1.3	87.9	1.1	82.8	0.9	81.6	0.9
	12	76.8	0.9	77.4	0.9	78.7	1.4	83.9	1.4	75.9	1.1	74.5	1.1
Freedom from recurrence at a distant site	5	98.0	0.3	98.2	0.2	97.3	0.5	98.2	0.4	98.3	0.3	98.2	0.3
	10	94.2	0.5	94.5	0.4	93.5	0.8	95.0	0.8	94.6	0.5	94.2	0.6
	12	92.6	0.5	92.8	0.5	92.5	0.9	93.8	0.9	92.7	0.7	92.4	0.7
Freedom from recurrence at a distant or locoregional site	5	96.9	0.3	97.0	0.3	95.2	0.7	96.5	0.6	97.7	0.3	97.2	0.4
	10	91.9	0.5	92.6	0.5	89.4	1.0	92.7	0.9	93.1	0.6	92.5	0.6
	12	89.6	0.6	90.5	0.6	87.7	1.1	91.1	1.0	90.6	0.8	90.2	0.8
Overall survival	5	98.0	0.2	98.1	0.2	98.8	0.3	99.1	0.3	97.7	0.3	97.6	0.3
	10	93.1	0.5	92.9	0.5	94.1	0.8	95.9	0.7	92.6	0.6	91.4	0.6
	12	89.8	0.6	89.8	0.6	92.4	0.9	94.5	0.8	88.5	0.7	87.6	0.8

* No multiplicity adjustments for exploratory end points were defined. Therefore, only point estimates and standard errors (SEs) are provided. Estimates have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. RS denotes recurrence score.

(83.9% [95% CI, 79.0% to 87.8%] vs. 78.7% [95% CI, 73.7% to 82.9%]), freedom from disease recurrence at a distant site (93.8% [95% CI, 91.7% to 95.3%] vs. 92.5% [95% CI, 90.5% to 94.1%]), freedom from recurrence at a distant or locoregional site (91.1% [95% CI, 87.3% to 93.9%] vs. 87.7% [95% CI, 83.6% to 90.8%]), and overall survival (94.5% [95% CI, 91.5% to 96.5%] vs. 92.4% [95% CI, 89.2% to 94.8%]), respectively. When invasive disease–free survival and freedom from recurrence at a distant site were further stratified according to RS (Fig. 2A), differences emerged in the RS 16 to 20 range. When further stratified according to clinical risk (Fig. 2B) in the RS 16 to 25 range, there was evidence of chemotherapy benefit for RS 21 to 25 irrespective of clinical risk, and the RS 16 to 20 range and high clinical risk.

Information on race, ethnicity, and representativeness of the TAILORx study population is presented in Table S11 in the Supplementary Appendix. In multivariable models adjusting for age, tumor size, grade, RS, and insurance status in the entire TAILORx population, Black race was associated with a risk of recurrence (hazard ratio, 1.57; 95% CI, 1.11 to 2.22) and death (hazard ratio, 2.00; 95% CI, 1.32 to 3.02) compared with White race within 5 years; similar findings were not observed after 5 years (hazard ratio for recurrence, 0.83 [95% CI, 0.56 to 1.23]; hazard ratio for death, 0.98 [95% CI, 0.73 to 1.31]).

RSClin PATIENT-SPECIFIC META-ANALYSIS UPDATE

Derivation of the analysis data sets for all studies used in the patient-specific meta-analysis calculations and characteristics of the analysis populations are shown in Figure S1 and Table S1, respectively. In multivariate Cox regression analyses of B-14, TAILORx groups A and B (ET alone and RS 0 to 25) and TAILORx groups C and D (CET and RS 11 to 100), the associations of RS, tumor grade, tumor size, and patient age at surgery with distant recurrence were broadly consistent across studies (Table S2). LR tests were used to quantify performance of the RSClin model versus a reduced model with clinicopathologic factors alone (tumor grade, tumor size, and age) and versus a reduced model with RS result alone (Table S4). As with the original

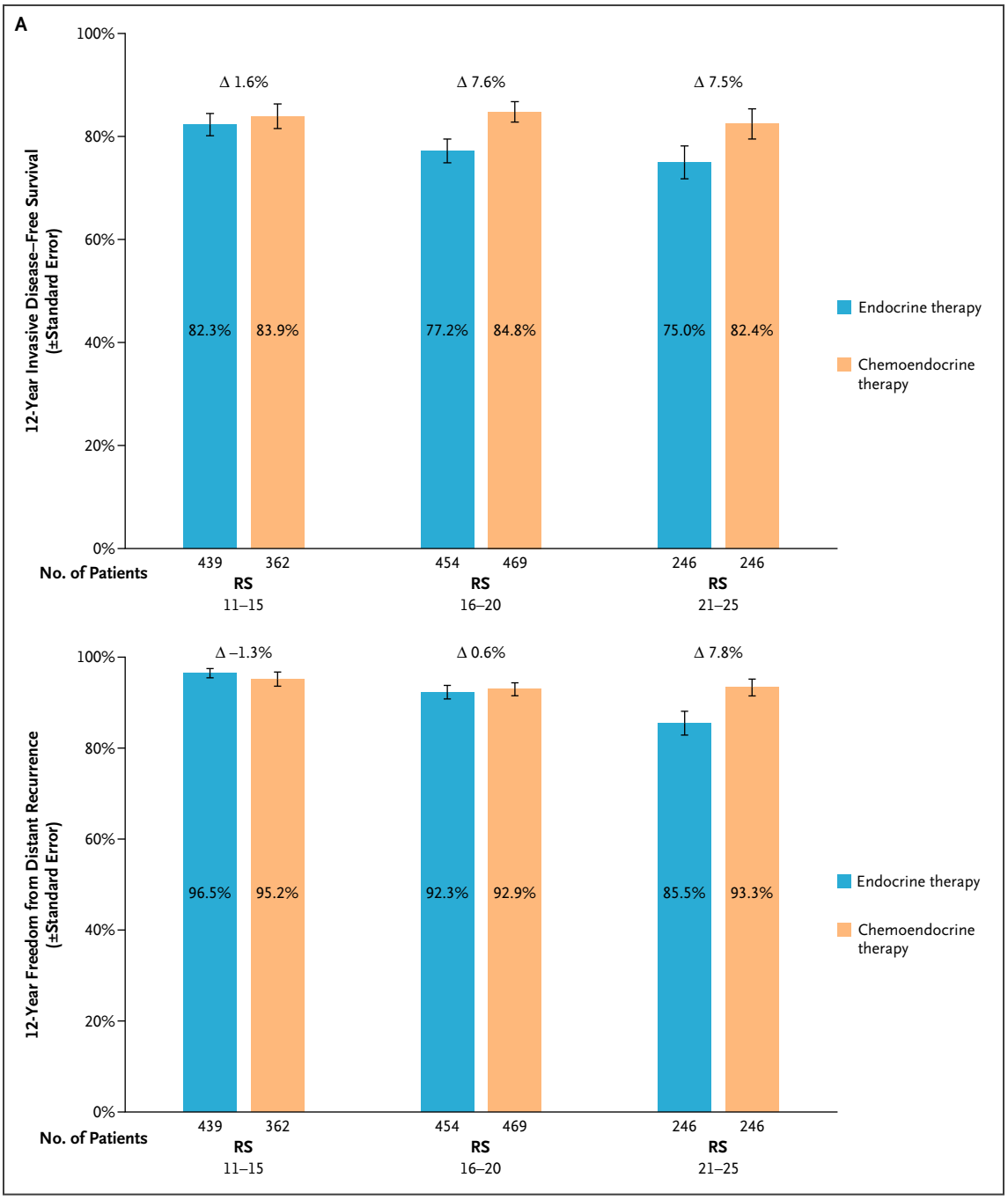

Figure 2. Effect of RS and Clinical Risk on Clinical End Points and Chemotherapy Benefit for Patients ≤50 Years.

Twelve-year Kaplan–Meier estimates for invasive disease–free survival and freedom from recurrence at a distant site for patients 50 years of age or younger with a recurrence score (RS) of 11 to 25 randomly assigned to receive chemoendocrine therapy or endocrine therapy alone stratified according to RS (Panel A) or 12-year freedom from recurrence at a distant site stratified according to RS (11 to 15, 16 to 20, and 21 to 25) and clinical risk category (high vs. low) (Panel B). No multiplicity adjustments for exploratory end points were defined. Therefore, only point estimates and 95% confidence intervals are provided. Estimates have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

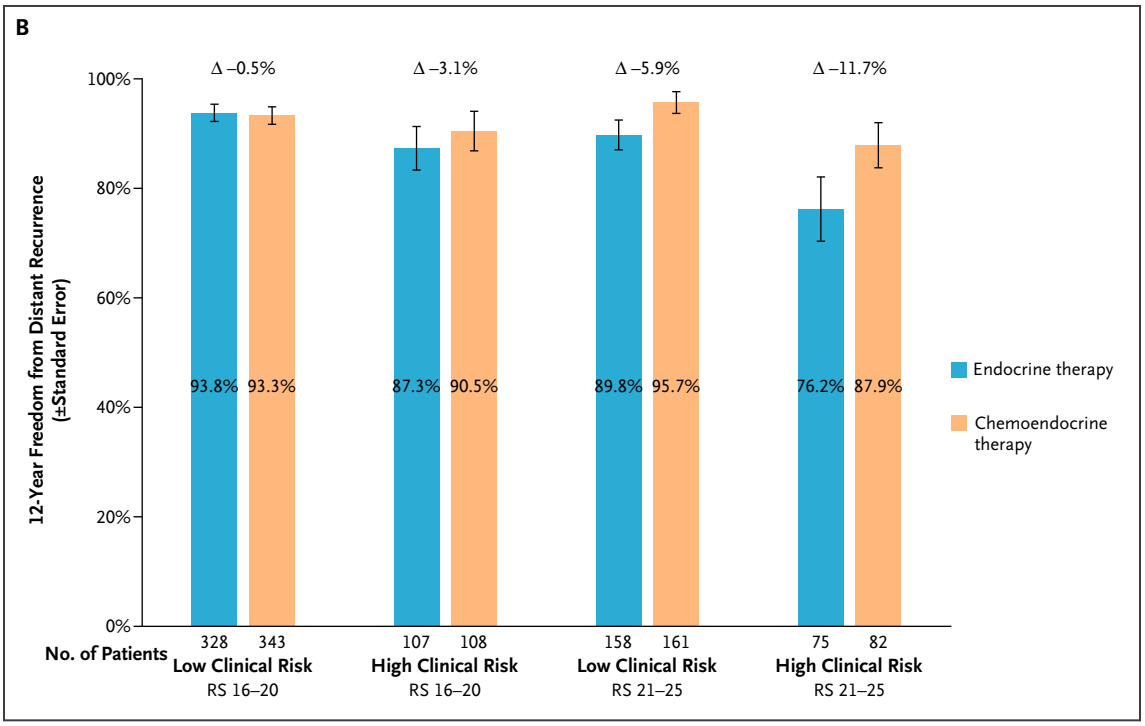

Figure 2. Continued.

data set, a comparison of LR tests using the updated data set with longer follow-up and more events found that the RSClin model provides significantly improved estimates of risk versus the model with tumor grade, tumor size, and age (ΔLR chi-square test, 86.2; P<0.001) and the model with RS result alone (ΔLR chi-square test, 131.0; P<0.001).

RSClin AND 10-YEAR DISTANT RECURRENCE UPDATE

Multivariable proportional hazards regression models for the covariate hazard ratios at 0 to 5 years after surgery versus after 5 years are given in Tables S5 to S7. In patients treated with ET alone who had an RS of 0 to 25, the RS was associated with distant recurrence in years 0 to 5 (hazard ratio, 5.87 for RS 25 vs. RS 10; 95% CI, 2.88 to 11.96) and after year 5 (hazard ratio, 1.73; 95% CI, 1.06 to 2.83). For those treated with CET who had an RS of 11 to 100, the RS was associated with distant recurrence in years 0 to 5 (hazard ratio, 3.32; 95% CI, 1.95 to 5.65) and after year 5 (hazard ratio, 2.52; 95% CI, 1.43 to 4.44). Patient-specific adjustment for the effect of chemotherapy using NSABP B-20 (B-20 study of the National Surgical Adjuvant Breast and Bowel Project) (overall estimates are provided in Table S3) also showed an association between the RS and distant recurrence in years 0 to 5 (hazard ratio, 3.03; 95% CI, 2.04 to 4.49) and after year 5 (hazard ratio, 1.98; 95% CI, 1.02 to 3.86) (Table S8). Since patients in TAILORx were not randomized to different endocrine therapies, we verified that the relationship of the RSClin covariates with the risk of distant recurrence does not depend on which ET was used (tamoxifen or an aromatase inhibitor) (Table S9).

The updated RSClin model 10-year distant recurrence risk estimates accounted for the different hazard ratios in years 0 to 5 and after year 5 using time-varying covariate effects having piecewise constant hazard ratios for years 0 to 5 and after year 5. (Comparisons of risk estimates using time-varying and time-invariant effects are shown in Fig S2.) Compared with the original RSClin 10-year distant recurrence risk estimates, the updated risk estimates are somewhat reduced for very high RS values (Figs. S3 and S4). The inclusion of the extended follow-up data from TAILORx increased the precision of the risk estimates relative to the original RSClin estimates, particularly for patients with midrange (i.e., 11 to 25) RS values. The estimates for absolute chemotherapy benefit were slightly reduced in the updated RSClin model compared with the original RSClin model (Fig. S5).

RSClin AND LATE RECURRENCE AFTER YEAR 5

The RS result was prognostic in the TAILORx cohort for late recurrence after 5 years in those with an *ESR1* ribonucleic acid (RNA) score of 9.1 or lower (27.2%) and in those with a score of 9.2 or higher (72.8%); there was no interaction between the RS and the *ESR1* RNA score (Table S10). Therefore, late distant recurrence risk was estimated using all patients who survived 5 years after surgery without a distant recurrence, regardless of *ESR1* RNA score. Risk estimates accounted for whether patients had received ET alone or CET in the first 5 years after surgery. Late distant recurrence risk estimates illustrating the independent prognostic information provided by the RS for patients who received ET alone in the first 5 years are shown in Figure 3 for various

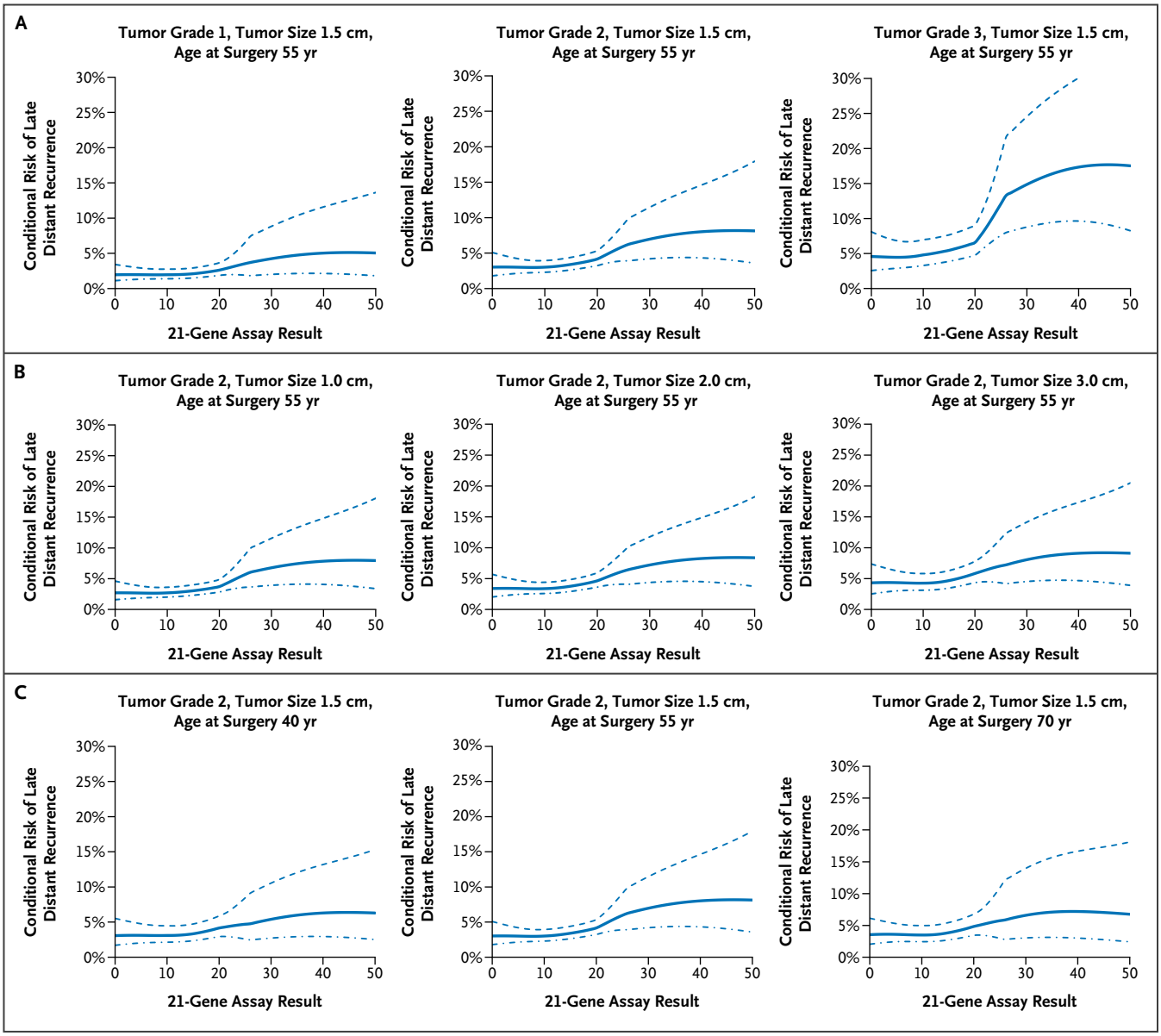

Figure 3. RSClin Estimates.

Estimates using RSClin (a combination of the recurrence score and clinical features of the breast cancer at the time of diagnosis) of distant recurrence risk in years 5 to 10 for patients who received adjuvant endocrine therapy alone conditional on surviving 5 years without distant recurrence. Typical clinical scenarios are provided stratified according to grade (low, intermediate, or high) in a 55-year-old patient with a 1.5-cm tumor (Panel A), tumor size (1.0, 2.0, or 3.0 cm) in a 55-year-old patient with an intermediate-grade tumor (Panel B), and age (40, 55, or 70 years) in a patient with a 1.5-cm intermediate-grade tumor (Panel C). No multiplicity adjustments for exploratory end points were defined. Therefore, only point estimates and 95% confidence intervals are provided. Estimates have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

tumor grades, tumor sizes, and the age of the patient at the time of surgery. Risk estimates for patients who received CET in years 0 to 5 had too much variability for RS values outside the 11 to 25 range to be clinically useful.

EXTERNAL VALIDATION OF RSClin FOR DISTANT RECURRENCE

External validation of RSClin prognosis for distant recurrence in the 10 years after surgery used data from 1098 evaluable patients with node-negative disease in the Clalit Health Registry, of whom 876 received ET alone and 222 received chemotherapy guided by use of the 21-gene assay in addition to ET. The updated RSClin risk estimate was prognostic for distant recurrence (standardized hazard ratio, 1.56; 95% CI, 1.25 to 1.94), and the estimated risk closely approximated the observed 10-year risk (Lin concordance, 0.87; 95% CI, 0.29 to 0.98) (Fig. 4A).

The new RSClin risk estimates for late distant recurrence in patients who received ET alone were validated in the 850 Clalit Health Registry patients who received ET alone and survived 5 years after surgery without a distant recurrence. The risk estimate was prognostic for distant recurrence after 5 years in these patients (standardized hazard ratio, 1.78; 95% CI, 1.25 to 2.55) and closely approximated the observed risk (Lin concordance, 0.92; 95% CI, 0.12 to 0.99) (Fig. 4B).

Discussion

With follow-up beyond 10 years and more recurrence events, this updated analysis of TAILORx is consistent with the primary trial conclusions, showing similarity between the ET-alone group compared with CET for the primary end point of invasive disease–free survival. We believe it provides additional prognostic and predictive evidence supporting current guidelines recommending the 21-gene RS for guiding adjuvant chemotherapy use.[15,16]

By combining predictive information for chemotherapy benefit provided by the 21-gene RS with prognostic information for distant recurrence supplied by both the RS and clinicopathologic factors at diagnosis, the updated RSClin

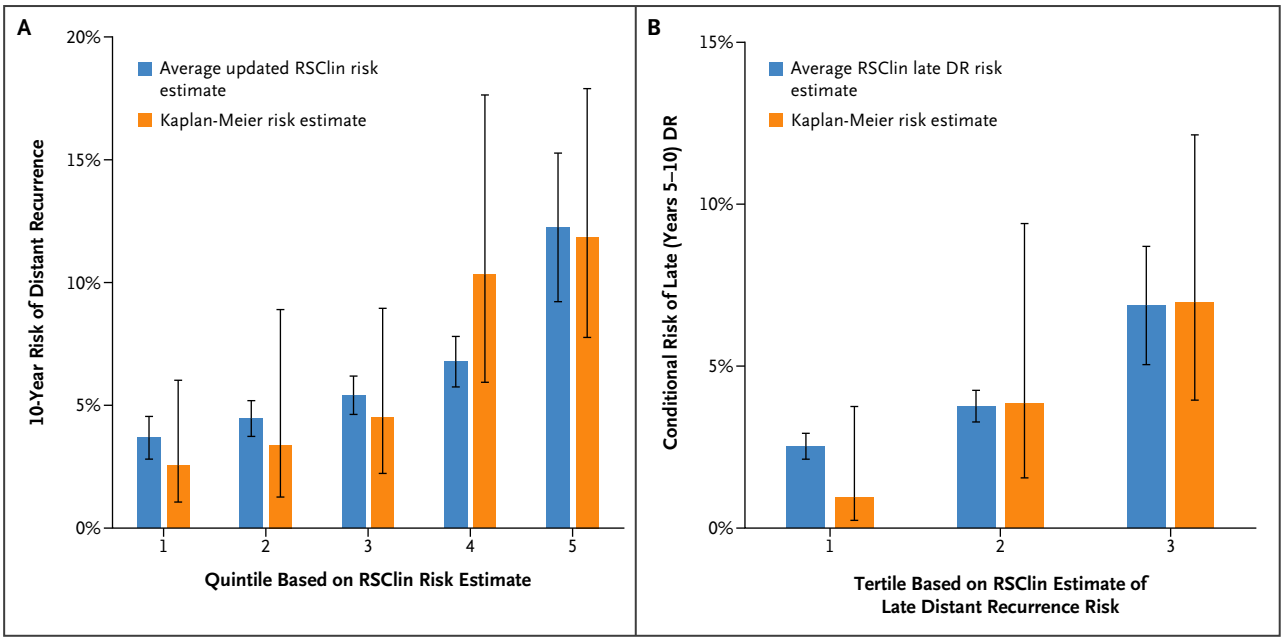

Figure 4. RSClin External Validation.

External validation of RSClin (a combination of the recurrence score and clinical features of the breast cancer at the time of diagnosis) in the real-world Clalit Health Registry including 1098 patients with estrogen receptor–positive, HER2 (human epidermal growth factor receptor 2)-negative, axillary node–negative breast cancer who had a 21-gene recurrence score (RS) assay performed as a component of standard care. This included the RSClin model used at diagnosis (Panel A) and for patients treated with endocrine therapy alone without distant recurrence (DR) at 5 years (Panel B). No multiplicity adjustments for exploratory end points were defined. Therefore, only point estimates and 95% confidence intervals are provided. Estimates have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

educational tool provides improved estimates of distant recurrence risk at 10 years compared with either feature used individually in patients with hormone receptor–positive, HER2-negative, axillary node–negative breast cancer, as well as refined estimates of chemotherapy benefit. We think that RSClin may be especially informative in patients 50 years of age or younger who derive some chemotherapy benefit in the RS 16 to 25 range, and those with larger or high-grade tumors and smaller or low-grade tumors in which the prognostic information provided by clinicopathologic features adds to the prognostic and predictive information provided by the RS.

RSClin Late, a new tool for late recurrence developed and validated in this analysis, provides prognostic information for late recurrence for the majority of patients who remain without evidence of disease recurrence after a 5-year course of ET, including women 50 years of age or younger. The RSClin estimates of late distant recurrence risk were not adjusted for the 20% who continued ET beyond 5 years, which may have induced a small downward bias. In addition, risk estimates for late recurrence were restricted to patients who received ET alone due to the high variability in estimates for RS values outside of the 11 to 25 range. Although RSClin Late does not provide predictive information for the benefit of continuing adjuvant ET beyond 5 years, this decision is informed largely by the ensuing recurrence risk, which the tool does provide, plus other factors such as prior treatment tolerance and menopausal status.[19] There are other options for assessing late recurrence risk, including the CTS5 (Clinical Treatment Score post-5 years) tool[20] and the homeobox protein Hox-B13/interleukin-17 receptor B gene expression assay.[21-23]

Despite the inclusion of approximately 10,000 patients in the development of the RSClin tool, a limitation of the model is that it was developed in patients who met the inclusion criteria for the associated trials, which may limit external generalizability. However, external validation results suggest that the model is well calibrated for real-world patients. The RSClin tool has also been validated for clinical outcomes in an independent data set including 122,680 patients with node-negative breast cancer derived from the National Cancer Database in the United States.[24] Decision aides have been shown to be effective tools for enhancing patient knowledge and making more informed decisions regarding local and systemic therapy in early breast cancer and other health care settings.[25,26]

Disclosures

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