Table 2 Clinical response and breast-conserving surgery according to categorical baseline Recurrence Score

RS risk group	Clinical response		
	Proportion (response rate)[a] (%)	Odds ratio (95 % CI)	*P* value
Low (RS <18)	19/32 (59.4)	1	n/a
Intermediate (RS 18–30)	10/17 (58.8)	0.977 (0.296, 3.233)	0.970
High (RS ≥31)	3/15 (20.0)	0.171 (0.040, 0.728)	0.017
RS risk group	Breast-conserving surgery		
	Proportion (BCS rate) (%)	Odds ratio (95 % CI)	*P* value
Low (RS <18)	29/32 (90.6)	1	n/a
Intermediate (RS 18–30)	13/17 (76.5)	0.336 (0.066, 1.722)	0.19
High (RS ≥31)	7/15 (46.7)	0.091 (0.019, 0.432)	0.003

Data are presented as the number of patients with the percentage in parenthesis

CI confidence interval, *BCS* breast-conserving surgery, *n/a* not available

[a] Primary analysis: $P = 0.015$ by Fisher's exact test for comparison of clinical response rates between the low and high RS groups

Table 3 Continuous baseline Recurrence Score and estrogen receptor by reverse transcriptase-PCR and Ki-67 by immunohistochemistry and clinical response and breast-conserving surgery

Endpoint/analysis	Continuous marker					
	RS (50 units)		ER by RT-PCR (log2 increase)		Ki-67 by IHC (%)	
	Odds ratio (95 % CI)	*P* value	Odds ratio (95 % CI)	*P* value	Odds ratio (95 % CI)	*P* value
Clinical response/unadjusted	0.205 (0.044, 0.946)	0.042	1.436 (0.963, 2.141)	0.076	0.981 (0.948, 1.015)	0.273
BCS/unadjusted	0.055 (0.009, 0.323)	0.001	1.786 (1.150, 2.774)	0.001	0.957 (0.921, 0.994)	0.024
BCS/covariate-adjusted[a]	0.016 (<0.001, 0.259)	0.004	1.881 (1.090, 3.245)	0.023	0.953 (0.907, 1.002)	0.060

RT reverse transcriptase

[a] Adjusted for tumor size and PgR Allred score, which were significantly associated with BCS in the univariable analyses

(range 32–73) while three of five PD patients had an intermediate Ki-67 LI (Fig. 1a).

No statistically significant difference was observed between baseline and post-treatment RS values ($P = 0.484$). A scatterplot is shown in Fig. 1b. The Spearman correlation analysis showed a high correlation (correlation coefficient 0.745, 95 % CI 0.592–0.846).

Discussion

In this study, we demonstrated the predictive value of the RS results for response to neoadjuvant endocrine therapy. Among our patient cohort, those with low scores showed a better response to neoadjuvant endocrine therapy than those with high scores. Since patients with high RS results have been shown to benefit from chemotherapy, the 21-gene assay may provide additional information that could facilitate the selection of neoadjuvant treatment with endocrine therapy for cancer patients with a low RS and chemotherapy for those with a high RS.

ER Allred scores have been reported to correlate with response rates to neoadjuvant letrozole or tamoxifen. The P024 trial of neoadjuvant letrozole or tamoxifen showed that tumors with low ER Allred scores still responded to letrozole [23]. Conversely, some tumors with higher ER levels did not respond to endocrine therapy [23, 24]. Gene expression-based profiles categorize HR+, HER2− breast cancers into two subtypes: luminal-A and -B [25]. However, the classification, which is based on PAM50, has been reported not to relate to clinical response or the likelihood of BCS after neoadjuvant AI treatment [7].

In our study, the RS was the only predictive factor for clinical responses to neoadjuvant endocrine therapy and the most potent predictive factor for BCS in the covariate-adjusted analysis. These results are consistent with those from other studies which suggest that a low RS can predict benefit from endocrine therapy [22, 24]. The study by Kim et al. [24] compared the outcomes of the tamoxifen and

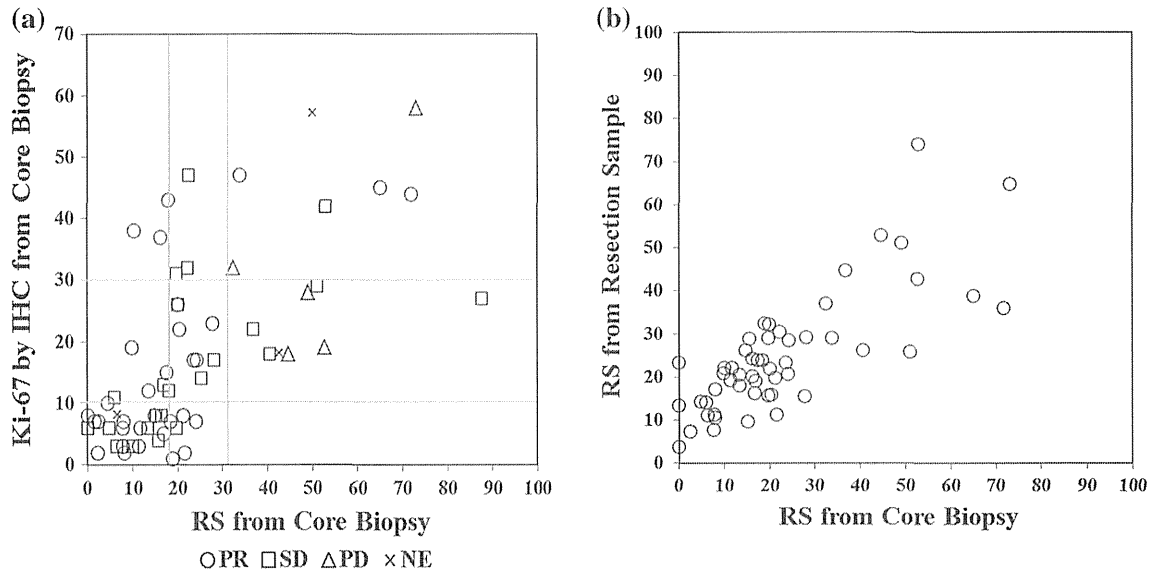

Fig. 1 **a** Scatterplot of the baseline Recurrence score (*RS*) and baseline Ki-67, with the Spearman correlation coefficient. The Spearman correlation coefficient between the baseline RS and baseline Ki-67 was 0.672 [95 % confidence interval (CI) 0.506–0.785]. None of five patients with tumor progression was in the low or intermediate RS groups. **b** Scatterplot of the baseline RS and post-treatment RS, with the Spearman correlation coefficient. The baseline RS was highly correlated with RS in the post-treatment samples (Spearman correlation coefficient 0.745, 95 % CI 0.592–0.846). *PR* Partial response, *SD* stable disease, *PD* progressive disease, *NE* Not evaluable

placebo arms of the NSABP B14 trial and demonstrated that higher levels of quantitative ER expression, as determined by RT-PCR, correlated with a greater benefit from adjuvant tamoxifen, as measured by distant recurrence.

Our results indicate that the values of the RS before and after endocrine therapy were highly correlated. Since a number of studies have suggested that post-treatment biomarkers such as Ki-67 LI and ER have better prognostic values than pre-treatment biomarkers, post-treatment biomarkers are receiving increasing interest in clinical trials as a tool for patient stratification [26–28]. Dowsett et al. [26] reported the results of an unplanned, exploratory investigation of the relationship between post-treatment Ki-67 (2 weeks) and recurrence-free survival (RFS) using archived tumors from the IMPACT study. Their results indicate that post-treatment Ki-67, larger baseline tumor size and post-treatment ER level are significantly correlated with DFS. Ellis et al. [27] analyzed the ability of post-treatment Ki-67 and other factors (tumor size, grade, nodal status, and post-treatment ER expression) to predict RFS and breast cancer-specific survival using archived tumors from the P024 study. Another interesting study (ACOSOG Z1031, Cohort B) has been conducted to determine whether patients with a high Ki-67 value after 2 weeks of neoadjuvant AI treatment show a higher than expected pathogenic CR rate to neoadjuvant chemotherapy than would be typically observed for those patients with unselected ER-rich tumors. The results will tell us whether an assessment of Ki-67 2 weeks after neoadjuvant AI treatment will be useful for the identification of a chemotherapy-sensitive subgroup of ER+ tumors. However, even if this is the case, intervention of a 2-week AI treatment and re-biopsy are necessary. Although further investigations are needed, the comparative stability of the RS would improve the overall decision-making process regarding the complete treatment before the initiation of treatment.

The main limitation of this was its small sample size. The availability of tumor samples from the parent study was limited and recovery of mRNA was not uniformly adequate. Further investigation in larger prospective studies would better define candidates for neoadjuvant endocrine therapy. Another limitation was the absence of any assessment of lymph node response. Although nodal response is clinically relevant, one of the major purposes of neoadjuvant endocrine therapy is improvement in surgical outcome. That said, however, the clinical response at the primary site and the BCS rate are also of clinical importance for the assessment of the effect of neoadjuvant endocrine therapy.

In conclusion, this study showed that RS results have predictive value for the clinical response to neoadjuvant exemestane therapy. The 21-gene assay would appear to be a promising tool for providing useful information to guide the clinician in choosing neoadjuvant treatment for systemic therapy, with neoadjuvant endocrine treatment for patients with low RS disease and neoadjuvant chemotherapy treatment for patients with high RS disease.

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Conflict of interest The authors declare that they have no conflict of interest.

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