

Recurrence score and quantitative ER expression to predict in late distant recurrence risk in ER+ BC after 5 years of tamoxifen.

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Background: Identification of molecular determinants predicting late recurrence (>5 yrs) in stage I and II breast cancer has become clinically important in light of data demonstrating a benefit for ten yrs of tamoxifen administration. Since the 21-gene Recurrence Score (RS) is commonly utilized in early stage BC, we wished to determine its utility in predicting distant recurrences beyond five yrs as a function of quantitative ER expression. **Methods:** The 21-gene RS was assessed in 1,065 chemo and tam-treated, ER+, node-positive pts from NSABP B-28 and 668 tam-treated, ER+, node-negative pts from NSABP B-14. Cox PH models, KM estimates and log rank statistics were used to assess the association of the RS with risk of DR by quantitative ER expression, using the 21-gene assay, in pts event-free after 5 yrs. We established an ER cut-point (high vs low) in B-28, and tested the cut-point in B-14, formally evaluating the interaction of RS and ER. **Results:** Median follow-up was 11.2 yrs (B-28) and 14.5 yrs (B-14). 832 B-28 pts and 564 B-14 pts were DR-free after 5 yrs. A reference normalized ER cut-point of 9.1 C_T was established in B-28 based on the association of the RS with DR after 5 yrs. Of the event-free pts at 5 yrs, 68% in B-28 and 88% in B-14 had ER>9.1. In B-28 the RS result was strongly associated with DR after 5 yrs in the higher ER expressing pts (log rank P=0.001), but not in the lower ER expressing pts (log rank P=0.87). It was confirmed in the B-14 data that RS was associated with DR after 5 yrs in higher ER pts (Table) but not in the lower ER pts (interaction P=0.03). **Conclusions:** For late recurrences (beyond 5 yrs), the RS is strongly prognostic in pts with higher quantitative ER expression (>9.1). The findings suggest that extending tamoxifen beyond 5 yrs may be most beneficial in pts with high (and intermediate) RS with higher quantitative ER expression and of limited benefit in pts with a low RS (>50% of population under study).

%DR KM estimate (95% CI)

RS risk group	N (%) pts	5 to 10 yrs %	5 to 15 yrs %
Low	289 (58%)	4.7 (2.8 - 8.0)	6.8 (4.4 - 10.6)
Intermediate	111 (22%)	4.1 (1.6 - 10.6)	11.2 (6.2 - 19.9)
High	97 (20%)	12.6 (7.4 - 21.2)	16.4 (10.2 - 25.7)

Log rank $P=0.01$

DR Risk after 5 yrs in B-14 by RS risk group for pts with ER>9.1 C_T.