Use of the 21-gene Oncotype DX® Breast Recurrence Score® assay in the neoadjuvant treatment setting

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Background

- The 21-gene Recurrence Score (RS) assay is used to determine prognosis and select post-operative adjuvant hormone and/or chemotherapy in HR-positive, HER2-negative breast cancer [1,2]. Its use in neoadjuvant therapy is less established.
- Eleven percent of all commercially submitted RS assays are performed on core biopsy tissue samples. Overall success rates on core biopsy submissions exceed 97% [3].
- Response to neoadjuvant therapy can predict favorable outcome, render inoperable tumors operable, and improve eligibility for breast-conserving surgery [4].
- Thus, the ability to select pre-operative therapy and to identify patients more likely to achieve pathological or clinical response to neoadjuvant therapy is of clinical interest.

Objective

- To summarize published and presented evidence for use of the RS assay in the neoadjuvant setting

Methods

- Published and presented studies of the RS assay used in patients undergoing neoadjuvant therapy were reviewed.
- Study findings were summarized descriptively, by type of neoadjuvant therapy received (chemotherapy [NACT] or hormonal therapy [NAHT]) and by study endpoint used to measure response.

Results

Table 1. List of Studies Included

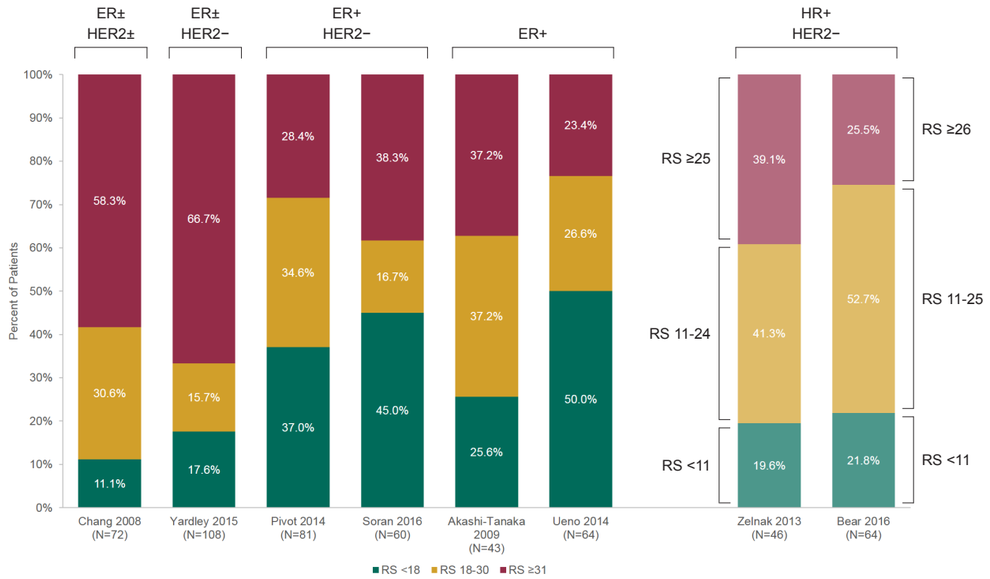
Study	Patients	NAT received	Endpoint(s)
NACT Studies			
Gianni 2005 [5]	89 (ER±)	DOX/PAC × 3 cycles → PAC × 12 cycles	% pCR (pathology review of surgical sample)
Chang 2008 [6]	72 (ER±, HER2±)	DOC × 4 cycles	% cCR (RECIST criteria)
Pivot 2014 [7]	81 (ER+, HER2−)	CT (NOS)	RS distribution by pCR (yes vs no)
Yardley 2015 [8]	108 evaluable (ER±, HER2−) (168 enrolled)	IXA/CYC × 3 to 6 cycles	% pCR (RECIST criteria)
Soran 2016 [9]	60 (ER+, HER2−)	DOX/CYC/TAX × 24 weeks	% tumor response[a], % cPR, % pCR
NAHT studies			
Akashi-Tanaka 2009 [10]	43 (ER+, PR+)	ANA or TAM × 4 months	% clinical response (WHO criteria)
Ueno 2014 [11]	64 (ER+)	EXE × 24 weeks	% clinical response (RECIST criteria)
NACT vs NAHT studies			
Zelnak 2013 [12]	46 (ER+ and/or PR+, HER2−)	RS <11: EXE RS 11-24: EXE vs DOC/CYC × 6 cycles RS ≥25: DOC/CYC × 6 cycles	% pCR in breast and axilla at surgery
Bear 2016 [13]	64 (HR+, HER2−)	RS <11: HT (NOS) RS 11-25: HT (NOS) vs CT (NOS) RS ≥26: CT (NOS)	% cPR, % cCR, % clinical response, % pCR in breast and axilla, % successful BCS

[a] Percentage tumor size reduction was based on pre-therapy size (largest dimension) and detailed pathology evaluation of the resection specimen. The pre-therapy tumor size was abstracted from clinical charts by MRI, ultrasound, mammogram, physical examination maximum dimension (unidimensional measurement). The post-therapy tumor size was defined as the product of: maximum dimension of tumor-bed (or area of fibrosis) × percentage cellularity (compared with pre-therapy biopsy) of the tumor-bed (or area of fibrosis) by microscopic exam.

ANA, anastrozole; BCS, breast-conserving surgery; cCR, clinical complete response; cPR, clinical partial response; CYC, cyclophosphamide; CT, chemotherapy; DOC, docetaxel; DOX, doxorubicin; ER, estrogen receptor; HR, hormone receptor; HT, hormonal therapy; IXA, ixabepilone; NOS, not otherwise specified; PAC, paclitaxel; pCR, pathologic complete response; PR, progesterone receptor; TAM, tamoxifen; TAX, taxane

Results

Figure 1. RS Group Distribution



- The Gianni study did not report distribution of RS results.
- The large proportions of patients with RS ≥31 in the Chang and Yardley studies most likely reflected the high numbers of ER− and/or HER2+ patients in those studies.
  - 45% of patients in the Yardley study had triple-negative disease.

Table 2. Response to Neoadjuvant Therapy, by RS Group

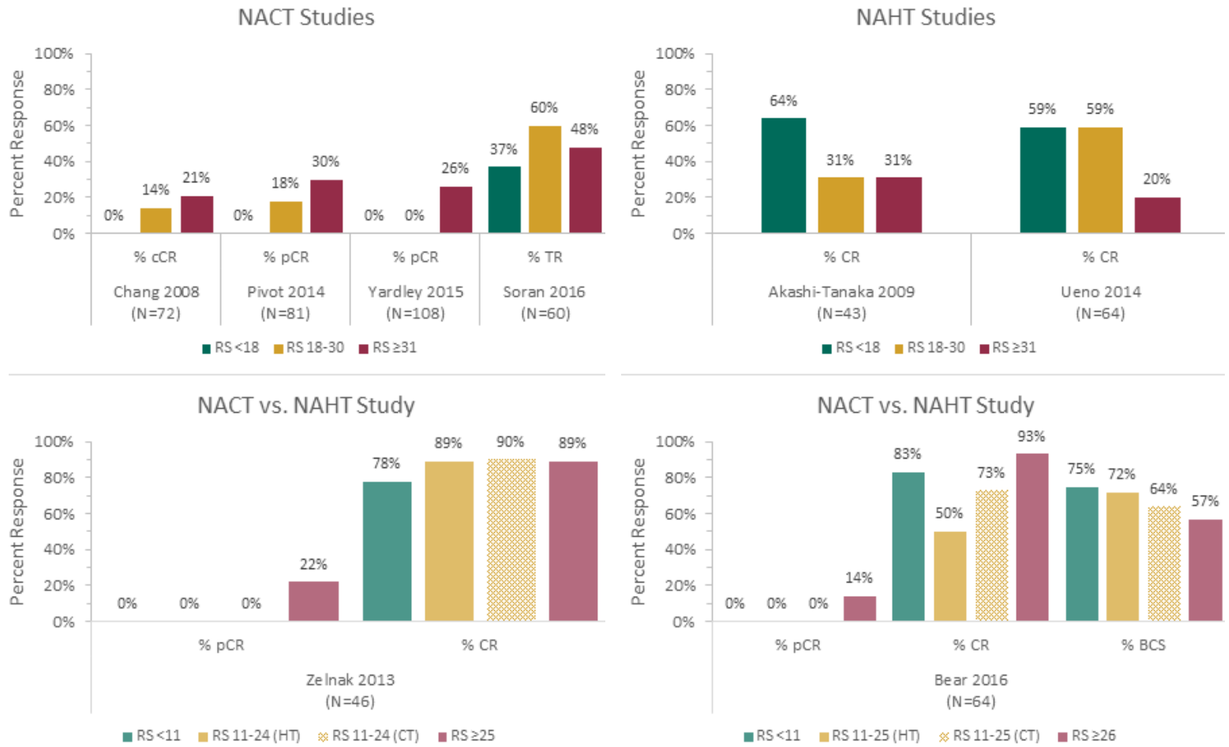
			Response to neoadjuvant therapy				
Study	**N**	**Endpoint(s)**	**RS <18**	**RS 18-30**		**RS ≥31**	**P value**
NACT Studies							
Gianni 2005	89	% pCR	Continuous RS results correlated positively with probability of pCR				.005[a]
Chang 2008	72	% cCR	Odds of clinical response increased 5-fold with higher RS results (per 50 units)				.008[a]
Pivot 2014	81	% pCR	0%	18%		30%	.02[b]
Yardley 2015	108	% pCR	0%	0%		26%	.002[c]
Soran 2016	60	% tumor response	37%	60%		48%	.43[d]
NAHT studies							
Akashi-Tanaka 2009	43	% clinical response	64%	31%		31%	.11[d]
Ueno 2014	64	% clinical response	59%	59%		20%	.015[b]
NACT vs NAHT studies							
			RS <11	RS 11-24 (HT)	RS 11-24 (CT)	RS ≥25	
Zelnak 2013	46	% pCR	0%	0%	0%	22%	—
			RS <11	RS 11-24 (HT)	RS 11-24 (CT)	RS ≥26	
Bear 2016	64	% clinical response (cCR + cPR)	83%	50%	73%	93%	.049[b]
		% pCR (breast and axilla)	0%	0%	0%	14%	NS
		% successful BCS	75%	72%	64%	57%	NS

[a] Likelihood-ratio test; [b] Fisher's exact test; [c] Mantel-Haenszel chi-square; [d] Trend test.

BCS, breast-conserving surgery; cCR, clinical complete response; cPR, clinical partial response; CT, chemotherapy; HT, hormonal therapy; NS, not significant; pCR, pathologic complete response.

Results

Figure 2. Response to Neoadjuvant Therapy, by RS Group



- Patients with high RS results tend to experience pCR or cCR with NACT.
- Patients with low RS results tend to experience CR with NAHT.
- Soran et al reported a trend toward better tumor response with higher RS results (p=0.06); however, according to authors, nonsignificant results may have been related to underpowered sample size (less than half of planned 130 evaluable patients were available for RS analysis). Additionally, 9 of 69 patients with ER+, HER2− (by IHC) tumors were excluded after the RS assay found HER2+ status by RT-PCR.

Conclusions

- Neoadjuvant studies of the 21-gene RS assay are consistent with adjuvant studies in that RS results correlate with observed benefits from CT and HT.
- Findings suggest that lower RS results are associated with greater clinical responses from NAHT, while higher RS results are associated with greater clinical and pathologic responses from NACT.
- The RS assay performed on pre-therapy core biopsies in patients with ER+ locally advanced breast tumors may help guide treatment decision options for NACT vs NAHT or primary surgery to maximize opportunities to achieve successful breast conserving surgery outcomes.
- Further investigations of the clinical utility of the RS assay in this setting are warranted.

References

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