Do Tumor Characteristics Predict Changes in Breast Cancer Biomarkers Following Neoadjuvant Chemotherapy?

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Background:

• Neoadjuvant chemotherapy (NAC) prior to surgical excision is associated with decreased tumor size and improved surgical outcomes in the treatment of breast cancer in a subset of patients.

• Previous studies have reported changes in biomarker status following NAC; however, there has been little investigation of factors that may correlate with these biomarker discordances or a lack thereof.

• Our aim was to evaluate the relationship between tumor characteristics and biomarker status stability post-NAC.

Design:

• A retrospective search was performed to identify cases from 2012-2015 with invasive breast carcinoma diagnosed via biopsy that were subsequently treated with NAC and surgical resection.

• Biomarker studies for each needle core biopsy included estrogen receptor (ER) immunohistochemistry (IHC), progesterone receptor (PR) IHC, and both HER2 IHC and HER2 fluorescence in situ hybridization (FISH).

• Cases in which biomarker testing was performed on both the pre-NAC biopsy and post-NAC excision specimen were reviewed to identify discordances in biomarker status upon repeat testing.

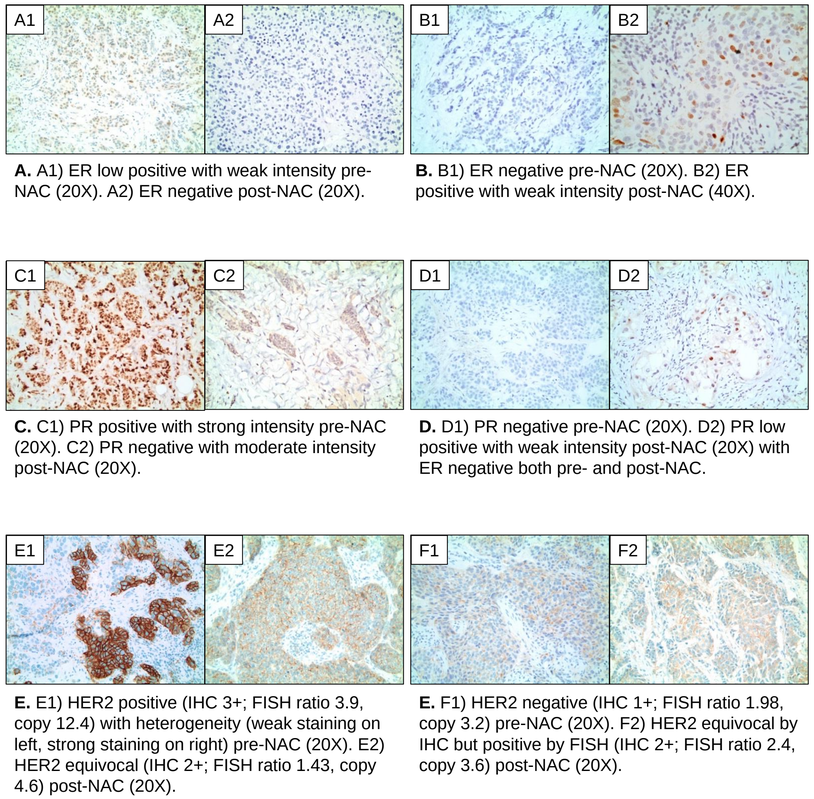
• Tumor characteristics in the biopsy and excision were assessed for correlation with biomarker stability.

• Unequal variances 2 tailed 2 sample T test was performed to compare mean age. A $\chi 2$ test was performed to compare tumor grade, triple positivity and negativity at biopsy, and tumor size and node status at resection.

Table 1. Tumor characteristics of cases with repeat biomarker testing.

		Biopsy				Resection	
Biomarker Repeated	Age (y)	Median grade	ER Negative	PR Negative	HER2 Negative	≥ypT1a	≥ypN1mi
ER (n = 75)	51.8	3	47%	60%	77%	92%	55%
PR (n = 73)	52.0	3	48%	60%	79%	93%	53%
HER2 (n = 77)	52.2	3	51%	60%	84%	94%	56%

Figure 1. Photomicrographs of biomarkers pre- and post-NAC.



A. A1) ER low positive with weak intensity pre-NAC (20X). A2) ER negative post-NAC (20X).

B. B1) ER negative pre-NAC (20X). B2) ER positive with weak intensity post-NAC (40X).

C. C1) PR positive with strong intensity pre-NAC (20X). C2) PR negative with moderate intensity post-NAC (20X).

D. D1) PR negative pre-NAC (20X). D2) PR low positive with weak intensity post-NAC (20X) with ER negative both pre- and post-NAC.

E. E1) HER2 positive (IHC 3+; FISH ratio 3.9, copy 12.4) with heterogeneity (weak staining on left, strong staining on right) pre-NAC (20X). E2) HER2 equivocal (IHC 2+; FISH ratio 1.43, copy 4.6) post-NAC (20X).

E. F1) HER2 negative (IHC 1+; FISH ratio 1.98, copy 3.2) pre-NAC (20X). F2) HER2 equivocal by IHC but positive by FISH (IHC 2+; FISH ratio 2.4, copy 3.6) post-NAC (20X).

Table 2. Biomarker status of pre-NAC biopsy cases.

Pre-NAC Biomarker Status	% (n)
ER+/PR+/HER2-	27% (22)
ER+/PR-/HER2-	10% (8)
ER-/PR-/HER2+	5% (4)
ER+/HER2+	13% (11)
ER-/PR-/HER2-	42% (35)
Other	4% (3)

Table 3. Changes in ER, PR, and HER2 status pre-NAC vs post-NAC.

	Pre-NAC Biopsy	Post-NAC Resection	% (n)	Biopsy Median Tumor Grade
ER	+	+	48% (36)	3
	+	-	5% (4)	2.5
	-	+	3% (2)	3
	-	-	44% (33)	3
PR	+	+	26% (19)	2
	+	-	12% (9)	2
	-	+	5% (4)	2.5
	-	-	55% (40)	3
	not tested	-	1% (1)	2
HER2	+	+	8% (6)	3
	+	equivocal	3% (2)	3
	+	-	4% (3)	2
	equivocal	-	1% (1)	3
	-	equivocal	4% (3)	3
	-	+	1% (1)	3
	-	-	79% (61)	3

Table 4. Impact of tumor characteristics on biomarker status changes.

		Biopsy			Resection	
	Age (y)	Median Grade	Triple Positive	Triple Negative	≥ypT1a	≥ypN1mi
No biomarker change	52.2	3	50%	91%*	93%	58%
Biomarker change	52.8	3	50%	9%	92%	50%

* Statistically significant ($p < 0.01$)

Results:

• 83 NAC treated breast resections had repeat testing of at least 1 biomarker (**Table 1, Table 2**).

• 30% (n = 25) demonstrated changes in pre-NAC biopsy vs post-NAC resection biomarker status. 16% (4/25) of those cases had changes in the status of 2 biomarkers.

• The rate of biomarker discordance was 8% (6/75) for ER, 18% (13/73) for PR, and 13% (10/77) for HER2 (**Table 3, Figure 1**).

• Retesting for ER:
  • 5% changed from positive to negative.
  • 3% changed from negative to positive.

• Retesting for PR:
  • 12% changed from positive to negative.
  • 5% changed from negative to positive.

• Retesting for HER2:
  • 3% changed from positive to equivocal.
  • 4% changed from positive to negative.
  • 1% changed from equivocal to negative.
  • 4% changed from negative to equivocal.
  • 1% changed from negative to positive.

• Tumors that did not demonstrate any changes in biomarker status were more likely to be triple negative prior to NAC (triple negative with no changes, 91% vs not triple negative, 58%, $p < 0.01$) (**Table 4**).

• There was no impact of age, grade, tumor triple positivity on biopsy, or tumor size or node status at resection on biomarker concordance or discordance post-NAC (**Table 4**).

Conclusion:

• Triple negativity on biopsy correlated with stable biomarker status post-NAC.

• Other tumor characteristics did not predict biomarker stability.