Variations in measured ER, PR, and HER2 status in synchronous and asynchronous paired breast cancer (BC) tumors

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Abstract

Background: That tumor heterogeneity exists and evolves over time is well appreciated but how often to biopsy patients' metastatic BC is not well established.

Methods: Immunohistochemical (IHC) and *in situ* hybridization (ISH) analysis of estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), and HER2 in 337 cases with >1 asynchronous primary/metastatic BC molecular profiles and in 40 cases with >1 synchronous molecular profiles was performed at a single institution. We evaluated differences in ER, PR and HER2 status in same or contralateral breast, and in primary vs. locally recurrent or metastatic BC's.

Results: We identified a change in ER or HER2 status in 8 (31%) synchronous BCs and in 55 (16%) primary/recurrent BCs, including in biopsies of distinct tumor foci within the same breast or metastatic organ site.
Of the 8 synchronous bilateral primary BC's, 4 (50%) had discordant ER results (ER, PR, and HER2 negative [TN] vs. ER+); 5 of 18 (28%) with two or more metastatic foci tested within the same organ had discordant ER results; 23% of BCs with biopsies of different organ sites had discordant ER results.
Of the 55 paired primary/metastatic BCs, 15% of the discordant findings were in cases with biopsies from two different metastatic sites, 19% were in cases with one metastatic and one primary or local recurrent biopsy, and 23% were from 2 primary biopsies or from primary and locally recurrent disease. Discordance was bidirectional from either TN to ER+ or ER+ to TN, and independent of discordance in HER2.

Conclusions: Standard systemic treatment of BC relies on reliable assessment by IHC analysis of ER, PR, and HER2. Within a patient, ER and HER2 status are not always concordant between lesions within the same breast, between bilateral BCs, and between distinct foci in a metastatic organ site. Patients are at risk of not being treated for the most clinically important foci of BC if the biopsy(s) obtained are not representative of the more aggressive areas of disease. Profiling should be performed on multiple BC samples both at diagnosis and at each time of recurrence/progression in the cancer continuum, to more accurately reflect the tumor profile at the time of treatment.

Patient ER, PR, HER2 Status

Table 1A. 337 patients with >1 asynchronous molecular profile (tissue from primary or metastatic).

ER, PR, HER2 Status	Status at First Profile	Status at Last Profile
TN	132	136
HR+/HER2-	148	143
HR+/HER2+	24	14
HR-/HER2+	23	25
Not available	8	15
HR?/HER2-	2	3
HR?/HER2+	0	1

Table 1B. 40 patients with >1 synchronous molecular profile (tissue from primary or metastatic).

ER, PR, HER2 Status Tissue A	ER, PR, HER2 Status Tissue B	#
HR+/HER2-	TN	11
	HR+/HER2-	23
HR+/HER2+	HR-/HER2+	1
HR-/HER2+	HR-/HER2+	1
TN	TN	4

Figure 1. Comparison of ER, PR, HER2 concordance between case samples profiled synchronously or asynchronously

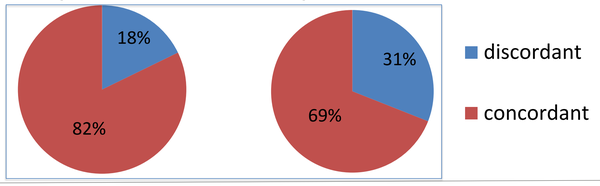

Figure 2. Comparison frequency and type of change in status between profiles. Status at first profile **A-D** vs. status at 2nd profile (designated by color as shown to right).

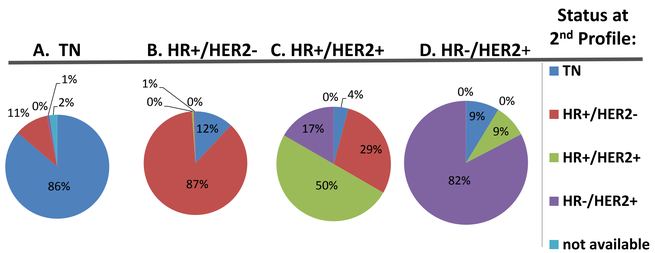

Table 2. Analysis of 13 synchronous profiles obtained from same organ or same breast. Seven cases had a difference in HR status in the two tissues tested and represented here. Of the 6 cases with no change between tissues, 4 were HR+/HER2- (3 were also AR+) and 2 were TN (one each AR+ or AR-).

nd = not documented; nt = not tested

Patient	Age	Subtype; AR status	Synchronous: Same breast or same met site	Primary or Met	Available Clinical Details
1	56	HR+/HER2-; AR+	Breast, right	M	Tissue tested is from diagnosis; has since metastasized.
		HR+/HER2-; AR-	Breast, right same block	M	
6	61	HR+/HER2-; nt	Breast, right	M	6 cm high-grade infiltrating ductal carcinoma is present associated with ulceration of the skin
		TN; AR+	Breast, right	M	
7	55	TN; AR-	Breast, left	M	Infiltrating mammary carcinoma with neuroendocrine features
		HR+/HER2-; AR+	Breast, left	M	
8	53	HR+/HER2-; AR+	Breast, right	nd	Two separate (10:00 and 6:00) foci of moderately differentiated invasive ductal carcinoma, 1.4 cm and 1.0 cm. in greatest dimension
		TN; AR+	Breast, right	nd	
9	38	HR+/HER2-; AR+	Breast, right	M	Infiltrating carcinoma with mixed ductal and lobular features, high grade (grade 3)
		TN; AR-	Breast, right	M	
10	57	HR+/HER2-; AR+	Upper-outer quadrant, right breast	nd	Lower outer and additional lower outer, biopsy: Poorly differentiated invasive ductal carcinoma
		TN; AR+	Lower-outer quadrant, right breast	nd	
13	51	HR+/HER2+; AR+	CNS	M	Left frontal (ER-) and left parietal (ER+) tumors excised
		HR-/HER2+; AR+	CNS	M	

HR and HER2 expression was determined by IHC, data not shown

Table 3. Association of ER/PR changes with AR change.
295 cases with results for ER, PR, and AR were evaluated.

NC = no change
↑=HR goes from negative to positive
↓= HR goes from positive to negative

ER/PR	AR	# of cases
↑	↑	4
↑	NC	7
↑	↓	4
NC	↑	24
NC	NC	205
NC	↓	24
↓	↑	3
↓	NC	18
↓	↓	6

Case Report

44 year-old patient initially diagnosed with well to moderately differentiated adenocarcinoma of breast; ER+, PR+ and received treatments. 4 years later HER2 was tested and was negative. 11 years after initial diagnosis patient presented with a cough. Evaluation revealed multiple bilateral pulmonary nodules, liver metastases, and bone metastases. LDH was normal and CA 15-3 was substantially elevated at 1004.9. Biopsy of the right middle lobe and pleura revealed grade 2 adenocarcinoma compatible with her known infiltrating ductal carcinoma, but now ER+, PR-, HER2+ (FISH-). By yr. 13, the patient was found to have grade 3, poorly differentiated metastatic adenocarcinoma of the breast with florid overexpression of HER2. Patient was given Herceptin, with a fairly prolonged period of disease control, now at 21 years post diagnosis.

Conclusions

- Within a patient, ER and HER2 status are not always concordant between lesions within the same breast, between bilateral BCs, and between distinct foci in a metastatic organ site.
- Patients are at risk of not being treated for the most clinically important foci of BC if the biopsy(s) obtained are not representative of the more aggressive areas of disease.
- Profiling should be performed on multiple BC samples both at diagnosis and at each time of recurrence/progression in the cancer continuum, to more accurately reflect the tumor profile at the time of treatment.
- Changes in androgen receptor are not dependent upon estrogen or progesterone changes.

References

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