Stability Of Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) in Residual Invasive Tumor after Neoadjuvant Therapy in Inflammatory Breast Cancer

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Background

Current guidelines do not mandate routine evaluation of ER, PR, and HER2 in residual tumor after neoadjuvant therapy (NAT), including chemotherapy, targeted therapy, and immune checkpoint inhibitors, in breast cancer.. There are no studies that evaluated the stability of these biomarkers in inflammatory breast cancer (IBC). We examined expression of ER, PR, and HER2 by immunohistochemistry (IHC) in residual tumor after NAT in IBC and compared the values with baseline values to determine changes in biomarker status.

Methods

We included 81 IBC patients with residual tumor in radical mastectomy specimens after NAT. IHC analysis was performed on routinely processed tissue sections of the residual invasive breast tumor using antibodies against ER (6F11, Leica), PR (16, Leica), and HER2 (4B5, Roche/Ventana). The American Society of Clinical Oncology/College of American Pathologists criteria for scoring ER/PR/HER2 were followed. Expression of ER/PR in ≥ 1% of tumor cells was regarded as the cut off to categorize the invasive tumor as ER or PR positive; 1-10% positive staining of any intensity was regarded as low positive and >10% as positive for ER or PR. The invasive tumor was scored as HER2 0 including no incomplete membrane staining in any invasive tumor cell; HER2 Ultralow with <10% of tumor cells with faint barely perceptible incomplete membrane staining in tumor cells; HER2 Low with incomplete membrane staining in >10% of tumor cells which is faint or barely perceptible; HER2 2+ including complete membranous staining in >10% of tumor cells of moderate intensity; HER 2 3+ including complete membranous staining in >10% of tumor cells of strong intensity. The associations between expression of ER, PR, and HER2 (positive vs. not) at baseline in the breast core biopsy specimen obtained as standard of care and in residual tumor in the mastectomy specimen was measured with the kappa statistic and 95% confidence intervals (CIs), using the weighted kappa for the combination of ER/PR and HER2.

Results

Of the 81 patients in the study, 68 (84%) had invasive ductal tumors, and 13 (16%) had other tumor types (mixed ductal and lobular, lobular, micropapillary, mucinous, and metaplastic). The clinical and pathological features of the inflammatory breast cancer patients included in the study is summarized in Table 1. The IHC findings at baseline and after NAT and alterations in invasive tumor subtypes are summarized in Table 2.

Results

Alterations in ER, PR, ER/PR, and HER2 status occurred in 10%, 22%, 12%, and 12%, respectively, of IBC patients treated with NAT. The ER/PR+/HER2- status was stable after NAT; ER/PR+/HER2+ status decreased significantly and triple negative status increased significantly in the residual tumor after NAT; ER/PR-/HER2+ status decreased from 9% to 6% respectively. After NAT, 15 patients had low and 14 had ultralow HER2 expression (29/81, 36%).

Table 1. Clinical and pathological features of the inflammatory breast cancer patients included in the study.

	N (%)
Total Patients	81
Age at Dx, Median (IQR)	50.0 (40.0, 57.0)
Feature of Carcinoma	
Ductal	68 (84.0%)
Lobular	1 (1.2%)
Metaplastic/Sarcomatoid	1 (1.2%)
Micropapillary	2 (2.5%)
Mixed Ductal and Lobular	8 (9.9%)
Mixed Ductal and Metaplastic Carcinoma	1 (1.2%)
Clinical Stage	
IIIA	1 (1.2%)
IIIB	35 (43.2%)
IIIC	23 (28.4%)
IIIX	4 (4.9%)
IV	18 (22.2%)
Pathologic Tumor Stage (ypT)	
T1mic	2 (2.5%)
Tis	1 (1.2%)
T1	11 (13.6%)
T2	16 (19.8%)
T3	32 (39.5%)
T4b	2 (2.5%)
T4d	17 (21.0%)

Table 2. Results of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) in the baseline core biopsy and residual tumor after completion of neoadjuvant therapy.

	Baseline n/%	After NAT n/%	Kappa (95% CI)
ER+	47/81 (58)	41/81 (51)	0.80 (0.67-0.93)
PR+	41/81 (56)	25/81 (31)	0.56 (0.39-0.72)
ER/PR+	50/81 (62)	42/81 (52)	0.75 (0.61, 0.89)
HER2+	18/81 (22)	8/81 (10)	0.55 (0.32-0.79)
ER/PR/HER2 status			0.69 (0.56, 0.82)

Results

Table 3. Alterations in the genomic types of inflammatory breast cancer in the baseline primary tumor and in the residual tumor after completion of neoadjuvant systemic therapy.

	Baseline n/%	After NAT n/%
ER/PR+/HER2+	11/81 (14)	3/81 (4)
ER/PR+/HER2-	39/81 (48)	39/81 (48)
ER/PR-/HER2+	7/81 (9)	5/81 (6)
ER/PR-/HER2-	24/81 (30)	34/81 (42)

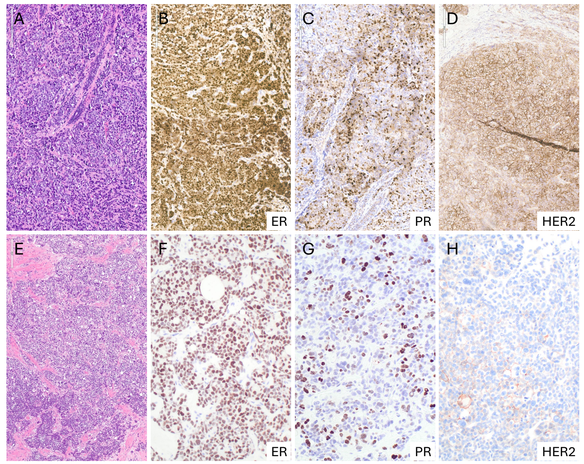


Figure 1. Illustration of a case of inflammatory breast cancer showing hematoxylin and eosin (H&E) stained tissue section, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) immunostain's in baseline core biopsy (1 A,B,C,D) and residual tumor in mastectomy after neoadjuvant therapy (1 E,F,G,H). Note that the invasive tumor is positive for ER,PR in the baseline core biopsy while the status of HER2 changed from 3+ in core biopsy (1D) to 1+ (1H) in the residual tumor.

Conclusions

- Alterations in ER/PR/HER2 status occurred in 22% that resulted in a change in invasive tumor subtype in 22% of IBC patients.
- Low levels of HER2 expression (HER2 low and ultralow) in 36% of IBC patients may provide options for targeted therapy.
- Evaluation of ER/PR/HER2 status in residual tumor after NAT in IBC may be considered to determine the altered expression of biomarkers, which has implications for prognosis and response to adjuvant therapy.

Results

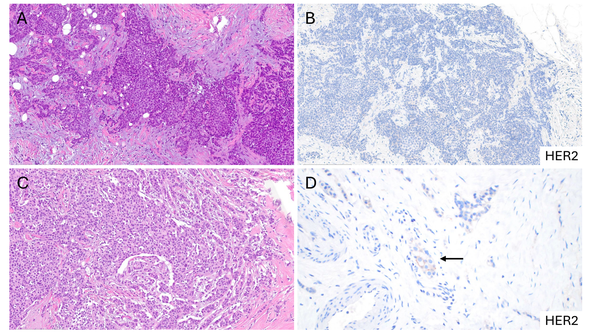


Figure 2. Illustration of a case of inflammatory breast carcinoma showing hematoxylin and eosin (H&E) stained tissue and human epidermal growth factor receptor 2 (HER2) immunostain in baseline core biopsy (2A,B) and residual tumor after neoadjuvant therapy (2C,D). Note the invasive tumor in baseline biopsy is HER2 0 without any membrane staining while the residual tumor shows HER2 0 Ultralow (arrow).

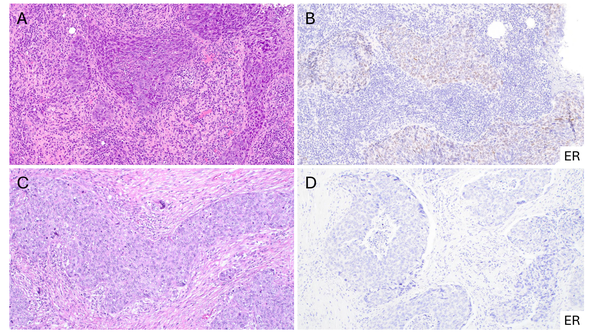


Figure 3. Illustration of a case of inflammatory breast cancer showing hematoxylin and eosin stained tissue and estrogen receptor (ER) immunostain of baseline core biopsy (3A,B) and residual tumor after neoadjuvant therapy (3C,D). Note that the invasive tumor is positive for ER with weak to moderate intensity while the residual tumor is entirely negative.

References

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