JBUON 2016; 21(6): 1425-1432
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Receptor discordance rate and its effects on survival in primary and recurrent breast cancer patients

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Summary

Purpose: *The receptor status of breast cancer plays a critical role in clinical practice. During the metastatic process, a change in the biological characteristics of the tumor can be seen. This study aimed to investigate the hormone receptor and HER2 status changes between primary and recurrent breast cancers and their effect on survival.*

Methods: *Eighty-six breast cancer patients with biopsy-proven local recurrences or distant metastases during the follow-up period were included in the study. Patients with metastatic disease at the time of first diagnosis or with history of previous neoadjuvant chemotherapy were excluded.*

Results: *Forty-three of the 86 patients (50%) had changes in at least one of the estrogen receptor (ER), progesterone receptor (PR), or HER2. ER, PR and HER2 discordance rates were 12.7, 38.3, and 15.1%, respectively, and PR discordance was significantly higher (p=0.000). Among all molecular subtypes, the triple negative breast cancer (TNBC) subtype showed the least change. When the effect of chemotherapy on receptor change was analyzed, PR discordance was significantly higher in the group who received chemotherapy (p=0.029). Analysis of the hormonotherapy effects on receptor discordance revealed results similar to those of chemotherapy. Only the PR discordance was significantly greater in the group that received hormonotherapy (p=0.000). None of the three receptor discordances or loss of any receptor were related to survival. Primary tumor TNBC subtype and disease-free-interval (DFI) shorter than 5 years were found as independent prognostic factors that negatively affected overall survival (OS).*

Conclusion: *This study showed that during recurrent disease there was 50% discordance in the expression of ER, PR, and HER2. The receptor showing the greatest discordance and influence from the systemic treatment was PR. A significant relationship between receptor discordance and survival could not be demonstrated in our study.*

Key words: *breast cancer, discordance, metastasis, receptor*

Introduction

Hormone receptor and epidermal growth factor (EGF) status evaluated by immunohistochemistry have become the most important predictive markers in breast cancer. In addition to their pre-

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Received: 28/03/2016; Accepted: 21/04/2016

dictive importance, the receptor status of a tumor plays a critical role in daily clinical practice. Only those patients who express hormone receptors benefit from adjuvant tamoxifen or aromatase inhibitor treatment [1]. Similarly, the benefit of anti-HER2 monoclonal antibody trastuzumab is limited to patients with HER2 overexpression or amplification [2].

During the metastatic process, a change in the biological characteristics of the recurrent tumor is possible due to various mechanisms including genetic shift during the evolution of metastasis [3], intratumoral heterogeneity leading to a more aggressive phenotype than the primary tumor, or selection of resistant clones following adjuvant treatment [4,5]. This phenomenon has highlighted the need to define the molecular phenotype of the recurrent tumor in order to provide more effective treatment options.

The primary aim of this retrospective study was to investigate the hormone receptors' and HER2 status changes between primary and recurrent or metastatic tumors. The secondary aim was to identify the predictive factors associated with the changes in receptor status and to determine the prognostic effect of the discordance in the biological phenotype.

Methods

The study was carried out after the institutional review board approved a retrospective analysis of 1412 patients who received breast cancer treatment in Istanbul Florence Nightingale Oncology Center between 1994 and 2014. Eighty-six patients who had biopsy-proven local recurrences or distant metastases during their follow-up were included in the study. Patients with metastatic disease at the time of first diagnosis or with history of previous neoadjuvant chemotherapy were excluded.

The patient files were retrospectively analyzed. The pathology specimens were evaluated by pathologists experienced in breast pathology. ER and PR levels were detected with immunohistochemical methods. Immunohistochemically, the antibodies used for ER were Novocastra, ER, clone 6F11 (Leica Microsystems, Wetzlar, Germany), Neomarkers, ER, clone SP1 (Thermo Scientific, USA), Biocare, cloneER and 6F11(Biocare, CA, USA). Antibodies used for PR were Novocastra, clone PR (Leica Microsystems, Wetzlar, Germany), Thermoscientific, PR (Thermo Scientific, USA), Biocare, PR, clone SP2 (Biocare, CA,USA).

As stated in the ASCO-CAP Guideline recommendations, intranuclear staining greater than 1% was accepted as ER and PR positivity. Three patients lacked HER2 receptor information in their original pathology reports. Their tissue blocks could be re-assessed and HER2 receptor was immunohistochemically analyzed again. HER2 expression was assessed with the antibodies Dako, clone CB11 (Dako, Glostrup, Denmark), Thermoscientific, and HER2/c-erbB-2/neu Ab-17 (Thermo Scientific, USA). Patients whose HER2 results were ++ i.e. equivocal and who did not have *in situ* hybridization (ISH) results in their charts were excluded from the study. Data on hormone and HER2 receptor status in the primary, recurrent and metastatic tumor, number of lymph nodes removed and involved, multifocality-multicentricity, histological grade, history of previous chemotherapy, presence of metastatic disease, and DFI and OS were recorded.

Statistics

Lowest, highest, frequency and rate values were used for descriptive statistics of the data. Qualitative data were analyzed with the chi-square test or with the Fisher's test when the conditions for chi-square were not met. Correlation analysis was performed with Pearson and Spearman correlation methods. Single variable analysis of the survival-related prognostic factors was performed with Kaplan Meier method and log rank test. Cox univariate and multivariate regression analysis was performed for determining the independent prognostic factors, and a model was constructed to include standard prognostic factors, including the histological type, single or multiple focality of the primary tumor, tumor diameter, lymph node involvement, stage of the primary tumor, histological grade, local or systemic recurrence, receptor status and molecular subtypes of the primary and recurrent tumors. The McNemar test was used in repeated measurements. A two-sided p value <0.05 was considered as statistically significant. The analyses were performed with SPSS 22.0 software.

Results

Eighty-six patients were included in the study. Their median age was 44 years (range 25-66). Median follow-up was 70 months (range 8-243). Fifty-four patients (62.8%) had systemic metastasis, and 32 (37.2%) had local-regional recurrence. Median time from surgery to disease recurrence (DFI) was 43 months (range 4-242). Five-year OS survival was 87.7% and 10-year survival 73.4%.

Forty-three of the 86 patients (50%) had changes in at least one of the ER, PR, or HER2 receptors. Analysis of the clinical factors including age, histopathological type, grade, multifocality, tumor diameter, presence of lymph node metastasis, number of involved lymph nodes, and the type of adjuvant systemic treatment showed no relation to the receptor discordance between the primary and recurrent tumor (Table 1).

Besides these standard factors, there was no difference with respect to receptor mismatch between metastasis and local-regional recurrence. Also, the relationship between the duration of DFI and receptor change was not significant (Table 1).

ER discordance rate between primary and recurrent disease was 12.7% (11 patients). Among 64 (74.4%) patients who were ER-positive in the primary tumor, 8 (9%) turned negative in recurrent tumors. Among 22 (25.6%) patients who were ER-negative in the primary tumor, 3 (13%) turned ER-positive in recurrent tumor. The difference in the ER status between the primary and recurrent tumors was not statistically significant (p=0.227) (Table 2).

PR discordance rate between primary and recurrent disease was calculated as 38.3% (33 patients). Among 59 (68%) patients who were PR-positive in primary tumors, 31 (52.5%) became PR-negative in recurrent disease. Among 27 (31.4%) patients who were PR-negative in primary disease, 2 (7%) became PR-positive in recurrent tumor. The PR discordance between primary and recurrent disease was statistically significant (p=0.000) (Table 2).

Table 1. Receptor discordance and standard prognostic factors

Standard factors	*All patients (N=86)*		*Patients with receptor discordance (N=43;50%)*		*Patients without receptor discordance (N=43;50%)*		
	N	%	*N*	%	*N*	%	x^2, *p*
Age, years							0.716
≤40	32	37.2	17	40.5	15	34.1	
>40	54	62.8	25	59.5	29	65.9	
Surgery							1.000
Breast conserving	53	61.6	27	62.8	26	60.5	
Mastectomy	33	38.4	16	37.8	17	39.3	
Histological type							0.258
Ductal	71	82.6	37	88.1	34	77.3	
Others	15	17.4	5	11.9	10	22.7	
Tumor focality							0.802
Unifocal	65	75.6	32	74.4	33	76.7	
Multifocal or multicentric	21	24.4	11	25.6	10	23.3	
Tumor size (mm)							1.000
<25	50	58.1	24	57.1	26	59.1	
≥25	36	41.9	18	42.9	18	40.9	
T stage							0.494
I	37	43.0	16	38.1	21	47.7	
II-III	49	57.0	26	61.9	23	52.3	
N stage							0.133
N0	41	47.7	24	55.8	17	39.5	
N+	45	52.3	19	44.2	26	60.5	
Stage at diagnosis							0.215
I	21	24.4	12	28.6	9	20.5	
II	39	45.3	21	50.0	18	40.9	
III	26	30.2	9	21.4	17	38.6	
Histological grade							0.658
I-II	38	46.3	20	48.8	18	43.9	
III	44	53.7	21	51.2	23	56.1	
Type of chemotherapy							0.947
Anthracycline only	34	47.2	14	45.2	20	48.8	
Anthracycline +Taxane	38	52.8	17	54.8	21	51.2	
Recurrence							0.615
Local-Regional	32	37.2	14	33.3	18	40.9	
Systemic	54	62.8	28	66.7	26	59.1	
Disease free interval (years)		0.645					
≤ 5	58	67.4	30	69.8	28	65.1	
> 5	28	32.6	13	30.2	15	34.9	

Table 2. Receptor discordance

	Recurrent tumor					
	ER change		*PR change*		*HER2 change*	
	+	-	+	-	+	-
Primary tumor						
+, N (%)	56 (65.1)	8 (9.3)	28 (32.6)	31 (36)	11 (12.8)	5 (5.8)
-, N (%)	3 (3.5)	19 (22.1)	2 (2.3)	25 (29.1)	8 (9.3)	63 (72)
Total change	11 (12.7)		33* (38.3)		13 (13.9)	

*Mc Nemar test p=0.000

Table 3. Molecular subtype discordance

		Recurrent tumor				
		Luminal A N (%)	*Luminal B N (%)*	*HER2 positive N (%)*	*TNBC N (%)*	*Total N (%)*
Primary tumor	Luminal A	8	17	0	1	26
		(30.8)	(65.4)	(0.0)	(3.8)	(100.0)
	Luminal B	2	30	3	6	41
		(4.9)	(73.2)	(7.3)	(14.6)	(100.0)
	HER2 positive	0	1	2	1	4
		(0.0)	(25.0)	(50.0)	(25.0)	(100.0)
	TNBC	0	1	1	13	15
		(0.0)	(6.7)	(6.7)	(86.7)	(100.0)
Total	10	49	6	21	86	
	(11.6)	(57.0)	(7.0)	(24.4)	(100.0)	

TNBC: triple negative breast cancer

Table 4. Chemotherapy effects on receptor discordance

		Chemotherapy(+)		*Chemotherapy (-)*		
		N	*%*	*N*	*%*	x^2, *p*
ER	Discordance	65	90	11	79	0.316
	Concordance	7	10	3	21	
PR	Discordance	48	67	5	36	0.029
	Concordance	24	33	9	64	
HER2	Discordance	63	88	10	71	0.125
	Concordance	9	13	4	29	
Any	Discordance	41	57	3	21	0.015
	Concordance	31	43	11	79	

Table 5. Chemotherapy effects on receptor loss

		Chemotherapy(+)		*Chemotherapy (-)*		
		N	*%*	*N*	*%*	x^2, *p*
ER	Loss	6	6	2	2	0.611
	Others	66	76	12	13	
PR	Loss	22	25	9	10	0.016
	Others	50	58	9	10	
HER2	Loss	3	3	2	2	0.185
	Others	69	80	12	12	

HER2 discordance was observed in 13 (15.1%) patients. In 5 (31.2%) of the 16 patients who showed HER2 positivity in the primary tumor, HER2 turned negative during the recurrent period. In 8 (11.4%) of the 70 patients who were HER2 negative in primary disease, HER2 turned positive in the recurrent disease. The changes in HER2 were not statistically significant (p=0.581) (Table 2).

The classification of patients according to the biological phenotypes of the initial tumor as Luminal A, Luminal B, HER2 positive (HER2+), and TNBC, revealed that the least change was observed in the triple negative group (Table 3).

When the effect of chemotherapy on receptor change was analyzed, there were no significant differences were noticed in ER and HER2 changes of primary/recurrent tumors between the patients who received chemotherapy vs those who did not. However, the PR discordance was significantly higher in the group who received chemotherapy (p=0.029) (Table 4). Also PR loss was significant in the chemotherapy group while there was no significant difference of ER and HER2 loss between the two groups (p=0.016) (Table 5).

Analysis of the hormonotherapy effects on receptor change revealed results similar to those of chemotherapy. There were no significant differences in the ER and HER2 changes between patients who received hormonotherapy vs those who did not. On the other hand, the discordance in PR was significantly greater in the group that received hormonotherapy (p=0.000) (Table 6). Also, PR loss was significantly higher in the same group of patients (p=0.000). However, when patients with positive hormone receptor (ER and/or PR) in the primary tumors were analyzed separately, the significance of PR discordance and loss disappeared.

According to the results of the study, the discordance in receptors between primary and recurrent tumors did not have an effect on OS. Similarly, the change of the hormone receptors or HER2 from positive to negative did not have a significant effect on OS. Also, in univariate analysis, the length of survival decreased with ER and PR negativity in the primary tumor, with ER negativity in the recurrent tumor and with DFI shorter than 5 years (p<0.05). When the molecular subtypes were included in the analysis, primary TNBC tu-

Table 6. Hormonotherapy effects on receptor discordance

		Hormonotherapy(+)		*Hormonotherapy(-)*		
		N	*%*	*N*	*%*	x^2, *p*
ER	Discordance	57	89	19	86	0.783
	Concordance	7	11	3	14	
PR	Discordance	32	50	21	95	0.000
	Concordance	32	50	1	5	
HER2	Discordance	55	86	18	82	0.642
	Concordance	9	14	4	18	
Any	Discordance	27	42	17	77	0.005
	Concordance	37	58	5	23	

Table 7. Survival analysis

	Univariate analysis				*Multivariate analysis*			
		95.0% CI				*95.0% CI*		
	HR	*Lower*	*Upper*	*p value**	*HR*	*Lower*	*Upper*	*p value**
Primary tumor ER negativity	0.176	0.060	0.515	0.001				
Recurrent tumor ER negativity	0.274	0.097	0.778	0.015				
Primary tumor PR negativity	0.154	0.049	0.485	0.001				
Primary tumor triple negative	15.315	4.366	53.727	0.000	10.123	2.723	37.633	0.001
Disease free interval	0.196	0.057	0.675	0.010	0.198	0.043	0.921	0.039

*Cox regression

mor had the most significant negative effect on OS. In multivariate analysis, TNBC of the primary tumor and DFI shorter than 5 years were found as independent prognostic factors that negatively affected survival (Table 7).

Discussion

Molecular studies in recent years have shown that in residual micrometastatic disease, the proliferation of resistant clones after adjuvant systemic treatment may lead to alteration of the tumor phenotype. Advances in interventional radiologic techniques and more straightforward techniques for sampling metastatic lesions have changed the approach to metastatic disease. Obtaining biopsies from metastatic lesions and planning the treatment according to the characteristics of the tumor is the contemporary approach described in treatment guidelines [6-10].

In our study, 43 of the 86 patients (50%) demonstrated a change in at least one of the ER, PR or HER2 between primary and recurrent breast cancer. ER, PR, and HER2 discordances were seen in 12.7, 38.3 and 15.1% of the patients, respectively. The changes were mostly from positive to negative. The PR discordance carried a statistical significance, whereas the changes in other receptors did not. Other studies also showed that the discordances in ER, PR, and HER2 between the primary and recurrent tumors were between 42–59%, with the PR showing the greatest (29–33.8%) discordance rate. The hormone receptor discordances in recurrent disease are mostly in the form of receptor loss, a common finding of other studies as well [11-13]. These findings of receptor changes from positive to negative, may have resulted from the emergence of a more aggressive molecular phenotype by clonal selection or genomic evolution during the process of metastasis or local recurrence [14]. In our study, the triple negative group had the least amount of change among all the molecular subtypes, a finding that supports the hypothesis discussed above. However, the heterogeneity of the techniques used in the assessment of primary and recurrent disease and the variability of the evaluator may be responsible for that difference. Similar technical problems are also present in other studies. Although the heterogeneity of technique constitutes a weakness in our study, we believe that the presence of a different change for each receptor and the changes being mostly from positive to negative, cannot be explained solely by the heterogeneity of the technique.

In the present study, there were no significant relationships between the receptor changes in the primary and recurrent tumors vs the standard prognostic factors, including the patient age, tumor size, its histopathological type, grade, unifocality or multifocality, the number of lymph node metastases, and the disease stage. These findings are similar to those of other studies [11-13].

Yang et al. [13] retrospectively studied the receptor changes of local-regional and metastatic disease in 133 patients, and found that ER and HER2 did not show a significant difference, whereas PR change was significantly greater in metastatic disease. Aurelio et al.[15] performed a metaanalysis involving 48 studies and 4200 patients, and found that when local recurrences and metastatic lesions were compared, ER and HER2 changes did not reach statistical significance and the PR change was significantly more common in metastatic disease (26 vs 41%). Guarneri et al. [16] analyzed 77 patients with metastatic breast cancer, and found no significant difference between the metastatic site and the changes in ER, PR, and HER2. In our study, there was no significant difference between metastatic disease and local-regional recurrence in regards with ER, PR and HER2 discordance.

A relationship between time and receptor discordance might be expected in the metastatic process. Indeed, Nishimura et al. [11] found that in patients with a DFI of 5 years or longer, the ER receptor change was significantly greater. In contrast, the study by Gong et al. [17] from MD Anderson Cancer Center investigated 227 patients and found no relationship between ER change and DFI. Our study similarly revealed no significant correlation between the DFI and receptor change.

Previous studies that investigated the effects of systemic treatment on receptor change have reported conflicting results. When the heterogeneous nature of breast cancer is considered, elimination of the sensitive clones by chemotherapy and hormonotherapy and selection of resistant clones, constitute the basis of micrometastatic disease, a phenomenon accepted by numerous researchers [18-20]. Similarly, Karlson et al. [21] showed a significant relationship between hormonotherapy and chemotherapy and the loss of ER expression. In another similar study by Bogina et al. [22] although patients who received chemotherapy and hormonotherapy had no changes in ER, they showed loss of PR expression. In contrast, Li et al. [23] could not show a significant relationship between systemic treatment and receptor change. The changes in ER or HER2 were not sig-

nificantly affected by chemotherapy or hormonotherapy in our study. However, 48 (67%) patients who underwent chemotherapy and 32(50%) who underwent hormonotherapy showed PR changes, which were statistically significant (p=0.029 and p=0.000, respectively). In the present study, during the course of recurrent disease after systemic treatment, a more aggressive molecular phenotype was seen to emerge together with PR expression loss. In our opinion, determining the molecular mechanisms that underlie this genomic evolution, which eventually results in PR loss, may provide significant information for preventing micrometastatic disease.

In a study analyzing the effects of primary and recurrent disease receptor discordances on survival, Karlson et al. [21] found that hormone receptor loss negatively affected survival. Similarly, Matsumoto et al. [24] found that in recurrent tumors survival was better in those where the hormone receptors had turned positive. In another study by Yang et al. [13] the loss of HER2 expression in addition to hormone receptor discordance had a negative effect on overall survival. Despite all these findings, there are other studies that have yielded results similar to ours in showing no significant relationship between receptor change and survival [12,25]. Univariate analysis of our data showed that the triple negativity or ER negativity of the primary tumor had negative effects on survival. Multivariate analysis showed that only the triple negative subtype of primary tumor and DFI shorter than 5 years were related to survival as independent prognostic factors. The patient populations in previous studies with reported relationships between receptor change and survival were larger. One of the most significant weaknesses of our study is the small patient sample, which may account for the failure to statistically show the survival difference. In addition, the lack of analysis of the heterogeneity of the systemic treatments applied after recurrence, and the irregular distribution of the standard prognostic factors caused by the retrospective nature of the study may have played roles in the failure to show an effect on survival. Also the tumor specimens were evaluated by more than one pathologist, which could lead to problems in quality control and therefore negatively affected the reliability of the data. Finally, biopsies performed in recurrent disease may not represent the molecular discordances in the whole tumor; therefore, their diagnostic value may be limited. This is a potential problem that may affect all the studies performed.

This study showed that during recurrent disease there was 50% discordance in the expressions of ER,PR and HER2. The receptor showing the greatest discordance and influence from the systemic treatment was PR. Although no significant relationship between receptor discordance and survival could be demonstrated, demonstration of the mechanisms that underlie the basis of PR expression loss during the genomic evolution in metastasis may constitute a significant step in the prevention of metastatic disease.

Conflict of interests

The authors declare no confict of interests.

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