JBUON 2017; 22(2): 365-376
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Comparative study of receptor discordance between primary and corresponding metastatic lesions in breast cancer

Gokmen U Erdem[1], Kadri Altundag[2], Nuriye Y Ozdemir[1], Suleyman Sahin[3], Nebi S Demirci[1], Fatih Karatas[3], Yakup Bozkaya[1], Aydin Aytekin[4], Vildan Tasdemir[2], Alma C Aslan[2], Ali R Sever[5], Nurullah Zengin[1]

[1]Ankara Numune Training and Research Hospital, Department of Medical Oncology, Ankara; [2]Hacettepe University Cancer Institute, Department of Medical Oncology, Ankara; [3]Diskapi Training and Research Hospital, Department of Medical Oncology, Ankara; [4]Gazi University Faculty of Medicine, Department of Medical Oncology,Ankara; [5]Hacettepe University Faculty of Medicine, Department of Radiology, Ankara, Turkey

Summary

Purpose: *It is well–known that tumor phenotype may change during the progression of breast cancer (BC). The purpose in this study was to compare the discordance in estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) between primary and recurrent/metastatic lesions (RML) and also to evaluate the prognostic significance of change in tumor phenotype on survival in patients with metastatic BC.*

Methods: *The medical records of 6638 patients with BC from two breast centers treated between 1992 and 2015 were retrospectively analyzed. Of the 6638 patients, 549 cases in whom recurrence was histologically proven by biopsy or by surgical resection were enrolled into this study.*

Results: *Our presentation 13.5% of the patients had metastatic disease. Biopsy on recurrence was obtained from distant metastasis sites in 250 (63.6%) patients or from locoregional soft tissues/lymph-nodes in 143 (36.4%). Receptor discordance in ER, PgR and HER2 expressions between primary and RML were 27.2% (p=0.32), 38.6% (p<0.001) and 14.4% (p=0.007), respectively. Subsequent gain of ER and PgR showed significantly higher overall survival (OS) and post-recurrence survival (PRS) compared to the corresponding concordant-negative patients (119 vs 57 months, p=0.001 and 56 vs 31 months, p=0.03 for ER, 148 vs 58 months, p=0.003 and 64 vs 31 months, p=0.01 for PgR, respectively), hormone receptor (HR) loss was associated with worse OS. Similarly, HER2-loss cases experienced poorer PRS and OS outcomes, compared with those having stable HER2 expression (median 26 vs 60 months, p=0.009 for PRS and median 60 vs 111 months, p=0.06 for OS, respectively).*

Conclusion: *This study confirmed the receptor discordance in ER/PgR and HER2 receptor expressions between primary and RML in patients with metastatic BC. As the loss of receptor expression is the most responsible factor for the discordance, treatments of recurrent/metastatic tumors should be individualized on the basis of molecular and genomic properties.*

Key words: *breast cancer, discordance, HER-2, hormone receptor, metastatic, primary*

Introduction

BC is the most common cancer in women and second most leading cause of cancer-related deaths worldwide. Despite efficient treatment strategies, approximately 20-30% of the patients with early BC will develop recurrences [1]. The choice of hormone or HER2 targeted therapy in BC depends on the positivity of ER, PgR or HER2 overexpression [1-3]. Such HR and HER2 status is not only important in determining the response to specific therapies but also helps in providing prognostic information.

Correspondence to: Kadri Altundag, MD. Hacettepe University Cancer Institute,Department of Medical Oncology, 06100 Ankara, Turkey.
Tel: +90 312 3052939, Fax: +90 312 3242009, E-mail: altundag66@yahoo.com
Received: 14/08/2016; Accepted: 02/09/2016

Metastatic relapse in BC is usually diagnosed using biological, radiological and clinical findings. In most cases, a new histological confirmation of metastatic relapse is not required, and biological properties of the primary tumor define the treatment planning. The discordance rates regarding the positivity of HR [4-24] (range: 6.4-54%) and overexpression of HER2 [4-6, 8-10, 14, 15, 17-19, 21-29] (range: 0-33%) between primary and metastatic lesions in BC have been debated for over 30 years without any established consensus. It has been estimated that the repeated biopsies in cases of newly formed metastatic lesions may lead to a change in the treatment decision in 12.1- 20.0% of the cases [4, 8, 19, 30, 31]. Therefore, it is highly important to know the frequency of receptor discordance between primary and RML, which has a direct influence in decision-making for determining the optimal treatment. Currently, tissue confirmation of recurrent BC lesions is recommended in international guidelines [32,33].

This retrospective, two large-centered study aimed to compare the rate of receptor discordance for ER, PgR and HER2 between primary and RML, and also to evaluate the prognostic impact of the change in tumor phenotype.

Methods

The medical records of 6638 patients with BC from two large centers treated between 1992 and 2015 were retrospectively analyzed. Of the 6638 patients, 549 in whom recurrence or progression were histologically proven by biopsy or by surgical resection were enrolled into this study. Exclusion criteria were as follows: male BC patients (n=6), patients with bilateral BC (n=35), presence of a second non-breast primary tumor (n=15), ductal carcinoma in situ (n=3), unknown receptor status for the primary or metastatic lesions (n= 82), and patients who underwent fine-needle aspiration biopsy (n=15). The remaining 393 patients were evaluated in terms of demographic characteristics, tumor location, TNM stage, histopathological characteristics, sites of systemic metastasis, receptor discordance, date of metastasis, treatments in adjuvant and advanced setting and site of biopsy.

Recurrent and/or metastatic lesion was defined as any local/regional recurrence or distant metastasis. Tissue samples were in general obtained through image-guided core biopsy. Tumor samples provided by other methods including therapeutic metastasectomy or local excision were also examined. Immunohistochemical (IHC) analysis of tissues was performed by using standard techniques and reported by pathologists, as in routine clinical care. Different antibodies and IHC kits were used in different time periods, but all were standardized and optimized during their use. All patients who gained a new tumor phenotype in RML were treated with targeted-agent therapy according to the new receptor pattern.

ER and PgR nuclear staining with ≥ 1% was accepted as ER and/or PgR-positive by IHC evaluation in all biopsy specimens. The evaluation of HER2 status was performed by using the standard scoring system of 0 to 3+, according to the membrane staining [34]. Tumors scoring 2+ in IHC were analyzed by fluorescence in situ hybridization (FISH). Tumors were considered as HER2-positive in cases of either IHC 3+ score or FISH amplified, and were considered as negative in case of either IHC 0 and 1+ score or non-FISH amplified. IHC subtypes were classified as luminal-like (ER+ and/or PgR+, and HER2-), luminal/HER2-like (ER+ and/or PgR+, and HER2+), HER2-like (ER-, PgR-, and HER2+), or triple negative (TN) (ER-, PgR-, and HER2-). The final status of the patients was determined by adult deaths notification in the hospital recording system or according to their final follow-update.

Table 1. Biopsy sites of RML and distribution of HR and HER2 discordance according to biopsy sites

Biopsy sites	*Change in HR status*		*Total*	*Change in HER-2 status*		*Total*
	Discordant	*Concordant*		*Discordant*	*Concordant*	
Locoregional disease (n=79)	17	61	78	7	65	72
Lymphadenopathy (n=76)	20	54	74	9	59	68
Liver (n=70)	13	56	69	14	53	67
Lung (n=57)	16	40	56	7	37	44
Bone (n=40)	8	32	40	4	29	33
Brain (n=29)	4	24	28	2	27	29
Skin (n=22)	8	13	21	5	14	19
Ovary (n=15)	3	12	15	2	10	12
Other* (n=5)	1	4	5	0	3	3
Total (n=393)	90	296	386	50	297	347

HR: hormone receptors, RML: recurrent/metastatic lesions *Four gastric, one bladder metastasis

Table 2. Patients and tumor characteristics at primary diagnosis and recurrence

Characteristics	*n*	*%*
Patients with primary and corresponding recurrent breast cancer samples	393	100
Median age at diagnosis, years (range)	45.7 (20-92)	
Menopausal status		
Premenopausal	252	64.1
Postmenopausal	141	35.9
Clinical stage at diagnosis		
I	39	9.9
II	124	31.6
III	157	39.9
IV	53	13.5
Unknown (non-metastatic)	20	5.1
Nodal status		
Positive	267	67.9
Negative	110	28.0
Unknown	16	4.1
Grade		
I	30	7.6
II	146	37.2
III	155	39.4
Unknown	62	15.8
Primary tumor histology		
Invasive ductal	324	82.4
Invasive lobular	24	6.1
Mix	29	7.4
Other	16	4.1
Type of tumor resection		
Modified radical mastectomy	301	76.6
Breast conserving surgery	75	19.1
No	17	4.3
Biopsy sites of RML		
Locoregional disease	143	36.4
Distant metastasis	250	63.6
ER status of the primary tumor		
Positive	250	63.6
Negative	141	35.9
Unknown	2	0.5
PgR status of the primary tumor		
Positive	260	66.2
Negative	129	32.8
Unknown	4	1.0
HER-2 status of the primary tumor		
Positive	75	19.1
Negative	297	75.6
Unknown	21	5.3
ER status of the RML		
Positive	238	60.6
Negative	150	38.2
Unknown	5	1.3
PgR status of the RML		
Positive	189	48.1
Negative	196	49.9
Unknown	8	2.0
HER-2 status of the RML		
Positive	98	24.9
Negative	266	67.7
Unknown	29	7.4
Radiotherapy		
Adjuvant	246	62.6
Palliative	16	4.1
No	131	33.3
Hormonal therapy		
Adjuvant	231	58.8
Palliative	90	22.9
No	72	18.3
Transtuzumab		
Adjuvant	41	10.4
Palliative	66	16.8
No	286	72.8

ER: estrogen receptor, PgR: progesterone receptor, RML: recurrent / metastatic lesions

Statistics

Statistical Package for Social Sciences software, version 18.0 for Windows (SPSS, Inc, Chicago, IL, USA) was used for all statistical analyses. P values less than 0.05 were considered as statistically significant. For descriptive analysis, categorical variables were defined as frequency and distributions with percentages, and quantitative variables were presented as median, minimum and maximum values. Statistical differences between groups were determined by using chi-square test. The prevalence of ER, PgR and HER2 immunoreactive cells in primary tumors and RML was compared by using McNemar's test.

Survival analysis was performed according to Kaplan-Meier method. Log-rank statistics was used to compare the subgroups. OS was defined as the time between the date of diagnosis and the date of death or the date of last follow-up of the patient. DFS was defined as the time from the date of BC diagnosis to the date of first loco-regional or distant recurrence. PRS was calculated from the date of relapse to the date of death or to the date of last follow up.

Results

The median age of the patients at diagnosis was 45.7 years (range: 20-92). In 13.5% of the patients (n=53) there was metastatic disease at presentation. Of these 53 patients, 10 underwent a synchronous biopsy of both primary and metastatic lesions. When analyzing the whole population (n=393) according to their recurrences and biopsy sites, 250 (63.6%) biopsies were obtained from distant metastases and 143 (36.4%) from locoregional recurrences (soft tissues or lymph nodes). Of the latter 143 patients, 52 had synchronous local as well as distant metastasis, however the biopsy was taken from the local recurrence site since such an approach was regarded as less invasive (Table 1).

The patient characteristics included in the study and the receptor status of the primary and RML are displayed in Table 2. ER, PgR and HER2 expressions in both primary and RML were determined in 386, 381 and 347 patients, respectively. Expression rates of ER, PgR and HER2 for primary vs RML were 63.9 vs 61.3, 66.8 vs 49.1% and 20.2 vs 26.9%, respectively (McNemar's test, p=0.32, p<0.001 and p=0.007, respectively).

The discordance rates of single-receptor measurements are summarized in Table 3. Discordance in ER, PgR and HER2 was present in 105 (27.2%), 147 (38.6%) and 50 (14.4%) patients, respectively. While the number of patients with gain of ER expression was observed to be more than those showing loss of ER (33.8 vs 23.5%), the gain of PgR was detected to be much less than loss of PgR (31.2 vs 42.2%).

In clinical practice, ER and/or PgR positivity

Table 3. Changes in tumor phenotype, HER2, ER, PgR and HR between the primary tumor and the recurrence

Tumor phenotypes	*Locoregional recurrence* n (%)	*Distant metastasis* n (%)	*All patients* n (%)	*p value*
Tumor phenotype				
Concordant	85 (66.4)	139 (65.3)	224/341 (65.7)	0.82
Discordant	43 (33.6)	74 (34.7)	117/341 (34.3)	
Triple-negative recurrent tumor	17 (13.3)	22 (10.3)	39/117 (33.3)	
HER2 status				
Concordant	114 (88.4)	183 (83.9)	297/347 (85.6)	0.25
Discordant	15 (11.6)	35 (16.1)	50/347 (14.4)	
Loss	5 (18.5)	10 (21.3)	15/74 (20.3)	0.77
Gain	10 (9.8)	25 (14.6)	35/273 (12.8)	0.25
ER status				
Concordant	106 (75.2)	175 (71.4)	281/386 (72.8)	0.42
Discordant	35 (24.8)	70 (28.6)	105/386 (27.2)	
Loss	19 (24.7)	39 (22.9)	58/247 (23.5)	0.76
Gain	16 (25.0)	31 (41.3)	47/139 (33.8)	0.04
PgR status				
Concordant	93 (66.4)	141 (58.5)	234/381 (61.4)	0.12
Discordant	47 (33.6)	100 (41.5)	147/381 (38.6)	
Loss	34 (39.1)	74 (43.8)	108/256 (42.2)	0.47
Gain	13 (24.5)	26 (36.1)	39/125 (31.2)	0.16
HR status				
Concordant	105 (74.5)	191 (78.0)	296/386 (76.7)	0.43
Discordant	36 (25.5)	54 (22.0)	90/386 (23.3)	
Loss	21 (21.9)	33 (17.0)	54/290 (18.6)	0.31
Gain	15 (33.3)	21 (41.2)	36/96 (37.5)	0.42

ER: estrogen receptor, PgR: progesterone receptor, HR: hormone receptors

Table 4. Discordance in subtypes between primary tumor and RML

Subtypes	*Recurrent lesion (%)*				
	Luminal-like *n (%)*	*Luminal/HER2-like* *n (%)*	*HER2-like* *n (%)*	*Triple negative* *n (%)*	*Discordance rate* *n (%)*
Luminal-like	152 (71.4)	23 (10.8)	5 (2.3)	33 (15.5)	61/213 (28.6)
Luminal/HER2-like	8 (18.6)	23 (53.5)	10 (23.3)	2 (4.7)	20/43 (46.5)
HER2-like	0	5 (17.9)	19 (67.9)	4 (14.3)	9/28 (32.1)
Triple negative	20 (35.1)	3 (5.3)	4(7.0)	30 (52.6)	27/57 (47.3)
Total	180	54	38	69	117/341 (34.3)

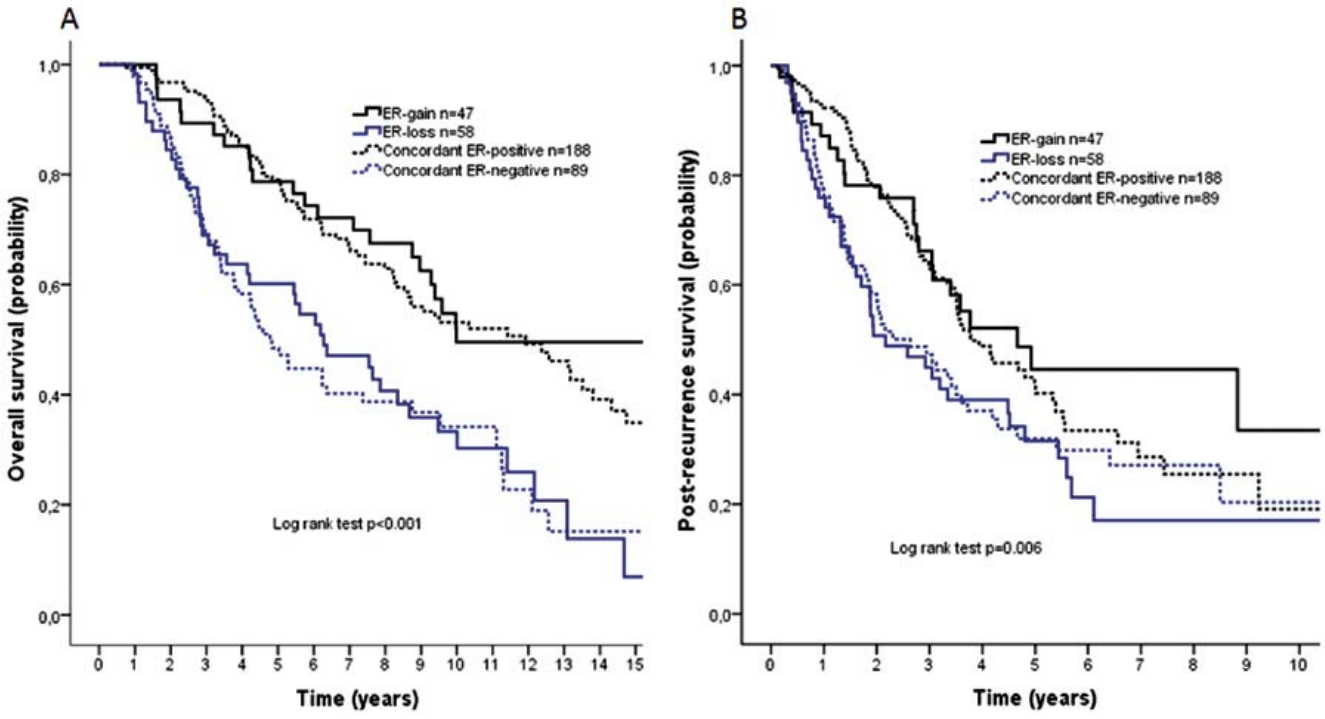

Figure 1. Survival by ER-receptor discordance and concordance: **(A)** overall survival; **(B)** post-recurrence survival.

is generally used in the decision-making of hormonal treatment. On the basis of these findings, we also assessed the receptor changes in hormone-positive cases. Among 386 patients with known hormone receptor status, 90 (23.3%) exhibited a receptor discordance (McNemar's test, p=0.07). Of the 90 patients, 16 (17.7%) showed only ER, 21 (23.3%) only PgR, and 53 (58.8%) both ER and PgR discordance. The change in hormonal status from negative to positive was observed rather commonly (37.5% vs 18.6%).

Thirty-one (88.5%) of 35 patients who gained HER2 positivity received targeted therapy in recurrence. Considering the discordant results in HR and HER2 expression between primary and corresponding RML, according to metastatic sites as locoregional or distant, no statistical significance was found between the groups. The gain of ER was more common in distant metastatic sites (Table 3).

At a median follow up time of 74.8 months (range: 3.8-358.4), 54.2 % of patients (n=213) have died. The median time from diagnosis to recurrence biopsy was 39.9 months (range 0.5-321). Median OS, DFS and PRS durations for the whole population were 105 months (95% CI 90.1-120.0), 39.4 months (95% CI 34.9-43.9) and 42.2 months (95% CI 35.5-49.0), respectively.

Discordance in tumor phenotype

Patients were categorized into 4 subgroups as luminal-like (HR-positive/HER2-negative), HER2/luminal-like (HR positive/HER2 positive), HER2-like (HR negative/HER2 positive) and triple negative (TN) (HR-negative/HER2-negative), according to the HER2 and HR expression. Among 341 patients, 117 (34%) presented with a change in tumor phenotype during progression. The highest rate of discordance was noticed in TN and luminal/HER2-like group (Table 4).

Prognostic impact of single-receptor discordance

When comparing the ER-discordant cases with ER-concordant ones, there was no distinctive

Table 5. Evaluation of OS and PRS according to tumor phenotype, HER2, ER, PgR and HR between locoregional and distant metastatic sites

	Locoregional recurrence (n=92)		*Distant metastasis (n=301)*		*All patients (n=393)*	
	*OS**	*PRS**	*OS**	*PRS**	*OS**	*PRS**
Tumor phenotype						
Concordant	NR	NR	83	36	104	43
Discordant	176	89	85	27	98	40
HER2 status						
Concordant	NR	NR	84	36	103	41
Discordant	176	89	72	26	104	40
HER2 Loss	60	37	54.	19	60	26
HER2 Positive	88	55	111	60 p=0.009	111 p=0.06	60 p=0.009
HER2 Gain	176	89	104	32	119	45
HER2 Negative	NR	NR	83.6	33.6	104	40
ER status						
Concordant	251	89	89	40	105	42
Discordant	176	73	91	32	105	38
ER Loss	104	68	65	22	75	26
ER Positive	251 p=0.001	89 p=0.07	104 p=0.001	42 p=0.008	143 p<0.001	45 p=0.01
ER Gain	242	141	115	43	119	56
ER Negative	88 p=0.05	43 p=0.08	53 p=0.001	24 p=0.06	57 p=0.001	31 p=0.03
PgR status						
Concordant	176	73	75	36	114	42
Discordant	242	89	99	38	104	42
PR Loss	89	251	90	32	94	36
PR Positive	NR	NR	115 p=0.01	42 p=0.08	143 p=0.003	48 p=0.04
PR Gain	141	242	119	59	148	64
PR Negative	68	133	53 p=0.002	25 p=0.01	58 p=0.003	31 p=0.01
HR status						
Concordant	251	89	98	40	112	42
Discordant	242	141	76	25	91	36

ER: estrogen receptor, PgR: progesterone receptor, HR: hormone receptors, PRS: post-recurrence survival, OS: overall survival, NR: not reached *Months

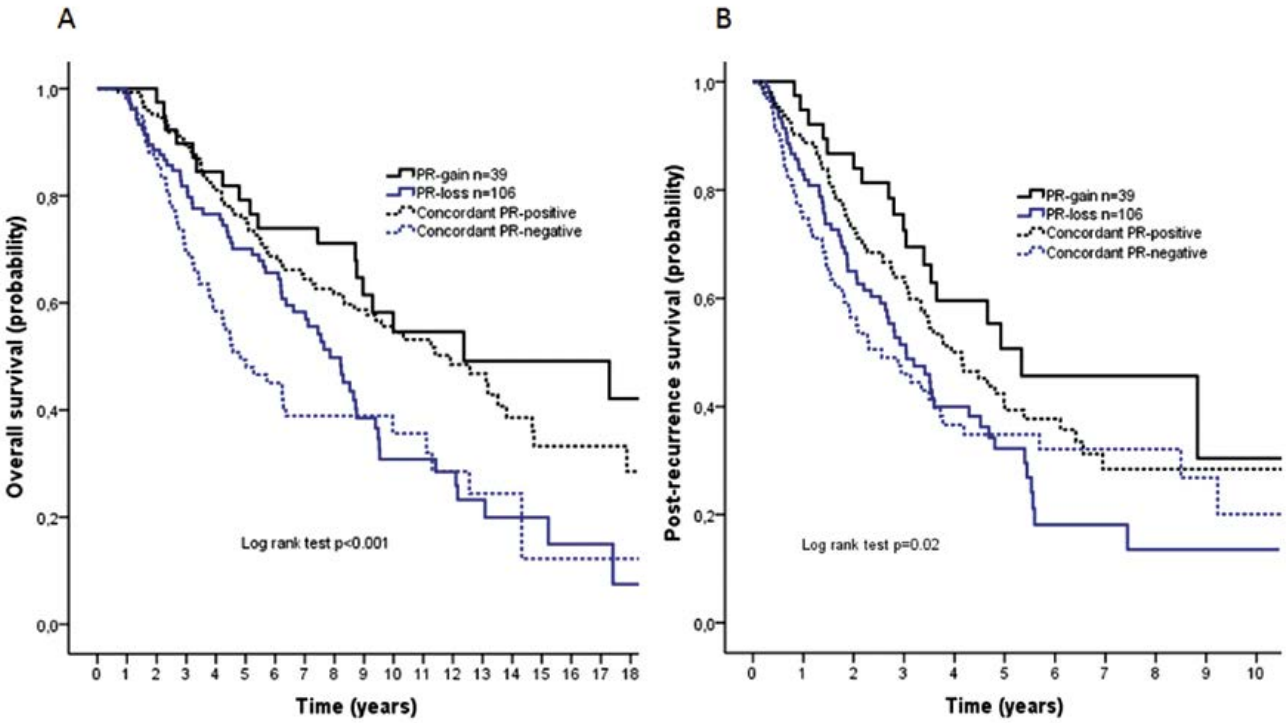

Figure 2. Survival by PR-receptor discordance and concordance: **(A)** overall survival; **(B)** post-recurrence survival.

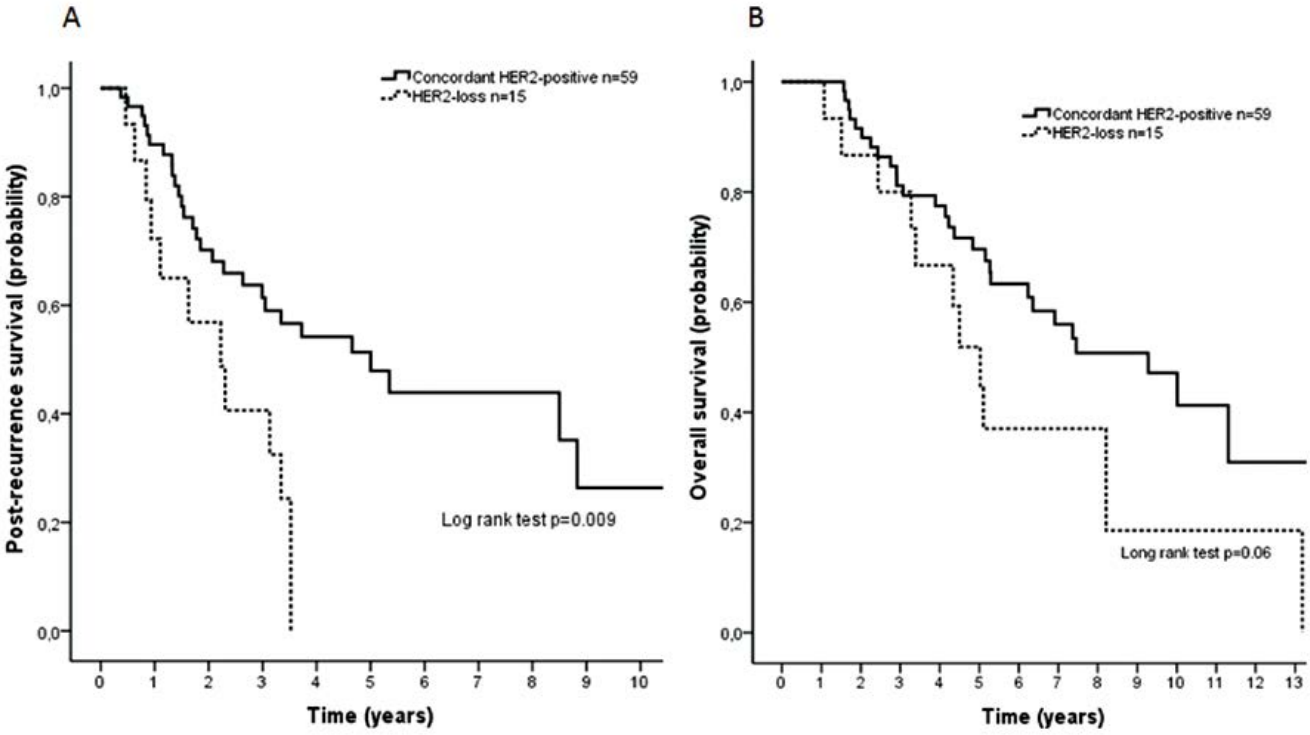

Figure 3. Survival by HER2-loss: **(A)** post-recurrence survival; **(B)** overall survival.

difference in OS between the groups (for median OS, 105 vs 105 months, p=0.67; for median PRS, 38 vs 42 months, p=0.53). Median OS was 75 months for the patients with ER-loss and 143 months for the respective concordant ER-positive groups (p<0.001), indicating a significant difference in terms of PRS (26 vs 45 months, p=0.01). On the other hand, patients with gain of ER had favorable survival outcomes in OS and PRS, as compared with respective ER-negative concordant patients (median OS 119 vs 57 months, p=0.001 and median PRS 56 vs 31 months, p=0.03) (Figure 1 and Table 5).

Comparing the PgR discordant cases with the respective concordant ones, no significant difference was observed in OS and PRS (median OS 104 vs 114 months, p=0.77 and median PRS 42 vs 42 months, p=0.85). While PgR-loss cases had poorer OS and PRS durations compared to PgR-positive concordant cases (median OS 94 vs 143 months, p=0.003 and median PRS 36 vs 48 months, p=0.04), patients with gain of PgR showed better survival outcomes, as compared with PgR-negative concordant cases (median OS 148 vs 58 months, p=0.003 and median PRS 64 vs 31 months, p=0.01) (Figure 2 and Table 5). This significant survival difference was evident in distant metastasis sites.

In the comparison of HR discordant cases with HR concordant ones, PRS and OS did not differ between the groups (p=0.20 and p=0.12, respectively). HR-loss cases had poorer OS and PRS durations compared to those with the respective HR-positive concordant cases. (median OS 65 vs 120 months, p<0.001 and median PRS 23 vs 44 months, p=0.001). By contrast, patients with gain of HR had better OS (median 207 vs 58 months, p=0.01) and a trend toward higher PRS (median 59 vs 35 months, p=0.09), as compared with the respective HR-negative concordant cases.

No significant difference in OS and PRS was observed according to the overall HER2 discordance (p=0.45 for OS and p=0.40 for PRS). HER2-loss cases experienced poorer PRS (median 26 vs 60 months, p=0.009) and a trend toward decreased OS (median 60 vs 111 months, p=0.06), compared to the respective HER2-positive concordant cases (Figure 3 and Table 5). However, when stratifying the HER2-loss cases according to the metastatic sites as local regional and distant, this significance was evident only in distant, metastatic sites. Patients with gain of HER2 expression did not exhibit any OS and PRS difference from the respective HER2-negative concordant cases (median OS 119 vs 104 months, p=0.85 and median PRS 45 vs 40 months, p=0.63) (Table 5).

Prognostic impact of discordance in tumor phenotype

There was no significant OS and PRS difference between the discordant and concordant tumor phenotypes (median OS 98 vs 104 months, p=0.19 and median PRS 40 vs 43 months, p=0.34).

The cases with a change in tumor phenotype to TN group had worse OS and PRS durations,

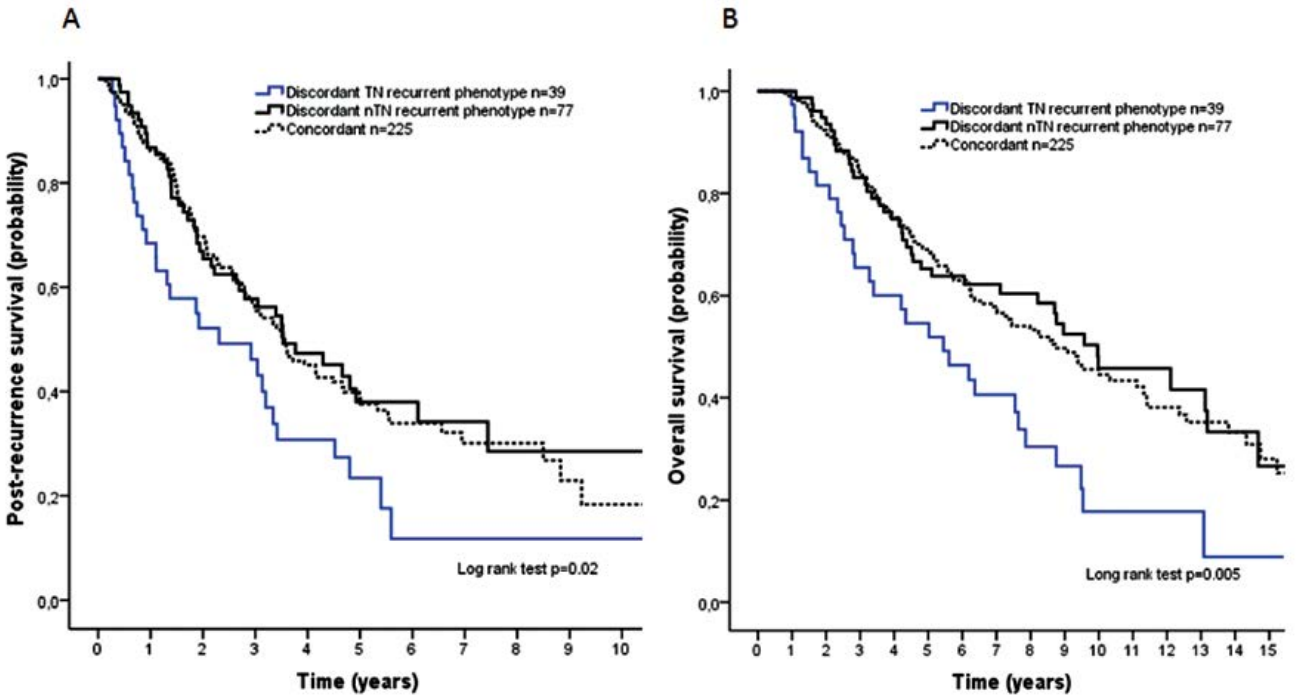

Figure 4. Survival curves for the concordant group, the discordant group with non-triple-negative phenotype at recurrence (nTN) and the discordant group with triple-negative phenotype at recurrence (TN). **(A)** post-recurrence survival; **(B)** overall survival.

compared to those with respective concordant tumor phenotypes or other discordant tumor phenotypes (median OS 64 vs 104 vs 119 months, p=0.005 and median PRS 28 vs 43 vs 42 months, p=0.02) (Figure 4).

Discussion

The receptor differences between primary and metastatic BC is an important clinical issue that may be affected from several factors such as intratumoral heterogeneity, genetic instability of tumor cells, local and systemic therapies, time to metastasis, sites of metastasis, receptor staining techniques, analytical variability regarding the receptor evaluation and the clonal selection of tumor cells [35].

In the present study, ER, PgR and HER2 discordance has been evaluated among 393 patients with metastatic BC. The most common biopsied sites were locoregional recurrence and liver metastasis, as a part of routine standard of care. Compatible with the previous literature reports, in our study discordance rates in ER, PgR and HER2 expressions between primary and RML were 27.2% (p=0.32) [12,13,15,16,20,21], 38.6% (p<0.001) [5,7,9,10,13-16,24] and 14.4% (p=0.007) [8-10,14,15,18,28,36], respectively. Receptor discordance rates in ER and PgR were much greater when compared to those in HER2. Similarly, Lindstrom et al. found receptor discordance rates to be 32.4% (p<0.001), 40.7% (p<0.001), and 14.5% (p=0.44) in ER (459 patients), PgR (430 patients), and HER2 (104 patients) between primary and RML, respectively. In accordance with the literature, no significant difference was observed in ER, PgR and HER2 discordance between distant metastasis and locoregional recurrence [13,16,18,30].

The rates of ER-loss and PgR-loss (23.5 and 42.2%) in our study were in concordance with the results (24 and 46%) of a meta-analysis performed by Aurilio et al. [5] in 2014. Besides, gain of ER and PgR (33.8 and 31.2%) in our study was compatible with previous studies [15,20,30] and higher than those (14 and 15%) reported in this meta-analysis. Moreover, we showed that PgR was the receptor that had the highest discordance rates, and we also confirmed the findings of other retrospective and prospective studies [4,5,9,10,16,19,31] by obtaining that PgR-loss was the main change in our study. Additionally, the rates of loss and gain of HER2 (20.3%) [4,9,21,29,37] and 12.8% [9,10,18,22,28,38] in the present study were consistent with some previous studies and greater than those reported in the aforementioned meta-analysis (13 and 5%). HER2-loss in our study was greater than gain of HER2, as shown in this meta-analysis. The possible reasons of increased HER2 discordance rates in our study that differs from the above mentioned study may partly be

due to technical differences or the effect of prior trastuzumab therapy.

It is well-known that higher response rates have been reported in patients with HR-positive BC [39,40]. In our study, a great proportion (75.2%) of the study population had HR positivity in the primary tumor, and discordance in HR was 23.3% in these patients. Gain of HR (37.5%) was higher than HR-loss (18.6%), suggesting that patients with initially HR-negative primary tumor had a higher likelihood of having HR-positive disease in metastasis or recurrence. This finding does not support the theory that the dedifferentiation during tumor progression leads to a more aggressive disease phenotype [41]. If no biopsy would have been performed in case of disease progression or relapse, possible available hormonal treatments for that specific patient might have been omitted.

The prognostic impact of receptor discordance between primary and RML in BC is controversial [14,15,21,31,42,43]. However, our findings regarding the receptor discordance rates between primary and the corresponding recurrent BC showed a significant prognostic effect. The cases with gain of ER [15,16] and PgR in the discordant group experienced a favorable OS and PRS outcomes, compared with the concordant group. Lower [16] et al. showed that ER-loss in metastatic disease was associated with worse survival rates, while cases with gain of ER had better outcomes, suggesting that ER status in metastatic disease was an important predictor of survival. As compatible with the literature, patients with loss of ER [9,15-17,24], PgR [6,15,31,44] and HER2 [24,37] expression in our study experienced worse survival rates, compared with the respective concordant group. In addition, HER2- and/or HR-loss cases and the change in tumor phenotype to TN group exhibited decreased survival compared to the respective concordant cases, indicating similar findings to previous works [9,14]. Despite the numerous available studies that showed a significant association between HR-loss and adverse prognosis [6,9,15-17,24,31,37], studies aiming at evaluating the correlation between gain of HR and favorable survival have remained limited [15,16,45]. Moreover, in some studies, detrimental effect of discordance could not be shown [31,43].

Dieci et al. [9] reported that a negative change in HR and HER2 expression resulted in worse OS and PRS. In the same context, they also emphasized that patients with concordant receptor status had significantly better PRS and OS rates, suggesting an important role of HER2 and/or HR change in the treatment of patients with metastatic BC. Based on these findings, in HER2-positive disease, the addition of trastuzumab therapy to patients who were not previously treated with anti-HER2 agents has provided better outcomes [27]. Today, it is highly important to note that there are no available supportive data to discontinue the targeted therapy if HER2 expression is not present in recurrences, suggesting that an adverse prognosis related to HER2-loss could not be attributed to anti-HER2 discontinuation. By contrast, a gain in the expression of HR and/or HER2 will possibly enable new treatment options to be administered.

Resistance to endocrine [46] and HER2-targeted therapy [47,48] may be due to the loss of receptor expression, expression of truncated receptor isoforms or post-translational modifications of the receptors. Loss of ER and/or HER2 expression evaluated through IHC methods may reflect one of the mechanisms of this resistance. As for the patients with gain of HR, favorable outcomes may be attributed to the slow-growing nature of the hormone-positive BC.

Similar to previous studies, in the adjuvant treatment of primary and the corresponding RML, the rate of ER- [15,49] and PgR-loss [6,49] was higher in patients treated with HT, while gain of HR [15] was quite common in those not receiving HT. However, during the adjuvant treatment, the other studies could not show any significant relation in ER and PgR discordance between the primary and RML [13,31]. Additionally, a recent study [43] has reported that ER discordance was correlated with the prior anthracycline exposure, while the switch in PgR was more associated with the biopsy specimens obtained from liver metastasis.

The results regarding the discordance rates in different studies are not always comparable due to the various definitions of concordance [14,31] and ER/PgR positivity (1%) [24,31] and 10% [9,16,43]). Unlike the previous studies, we accepted the cases presenting with the same HR and HER2 status in the primary and corresponding RML as "concordant''.

One limitation of our study is its retrospective nature, as in most of the previous studies. Also it is possible that technical variations in the receptor assessments in IHC analysis and inter-observer bias might partly affect our results. Besides, the influence of adjuvant chemotherapy on discordance rates between primary and RML

could not be evaluated due to missing data. Another limitation of the study was that the analysis of the patients was conducted in two different hospitals, reflecting that different laboratory techniques such as various antibodies might be used in different time periods. However, all the antibodies were standardized and optimized when used. Accordingly, due to these limitations, we can not reach a definite conclusion with respect to the prognostic value of discordance in recurrent BC. However, our findings show that re-biopsies in the recurrent lesions are proper along with their ability to indicate a switch in the receptor status in 14-38% of the whole population. Thus, re-biopsies and re-assessments should optimally be considered in order to make the correct treatment decision in recurrent BC.

In the large proportion of patients with metastatic BC, discordance in ER and PgR has been reported in different sites of metastasis, leading to a change in the hormonal treatment in 11-15% of the cases [50]. These findings point out that multiple biopsies are required from various metastatic sites, with an attempt to render the hormonotherapy optimal, and to re-assess the receptor status.

On the other hand, there were also several strengths of our work : it had a large sample size including primary and corresponding RML; all the specimens, including inconclusive samples, benign diseases and cases with secondary malignancies have been accurately recorded; the factors associated with discordance in HR were evaluated; cytology samples were excluded from the study design; all the samples of relapse lesions were obtained by core biopsy or by surgical resection at both centers, providing a complete histological evaluation.

Conclusion

Intratumoral heterogeneity along with natural biologic drift or the existence of small undetected subclones within the primary tumors and corresponding metastatic lesions might play an important role in detecting receptor discordance. Overall, receptor discordance seems to be more dependent on a multifactorial process rather than a single mechanism. If there was a reproducible and 100% accurate method for determining the ER, PgR and HER2 receptor status, the degree and the frequency of the changes in the receptor status would be known. The differences in fixation methods, antibody selection and use of different threshold values may have an important effect on the immunohistochemical results. Thus, receptor discordance and its prognostic impact should be evaluated by using prospective studies. Nowadays, we know that loss of receptor expression is the responsible factor in most discordant cases. Accordingly, the treatments should be individualized on the basis of the molecular and genomic features of the tumor. We expect that future clinical trials will include more metastatic tissue in order to achieve a successful assessment of molecular differences, not only at the receptor level but also at the DNA, RNA, protein and functional pathway levels.

Conflict of interests

The authors declare no confict of interests.

References

1. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.
2. Cobleigh MA, Vogel CL, Tripathy D et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639-2648.
3. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783-792.
4. Amir E, Ooi WS, Simmons C et al. Discordance between receptor status in primary and metastatic breast cancer: an exploratory study of bone and bone marrow biopsies. Clin Oncol 2008;20:763-768.
5. Aurilio G, Disalvatore D, Pruneri G et al. A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. Eur J Cancer 2014;50:277-289.
6. Bogina G, Bortesi L, Marconi M et al. Comparison of hormonal receptor and HER-2 status between breast

primary tumours and relapsing tumours: clinical implications of progesterone receptor loss. Virchows Archiv 2011;459:1-10.

7. Broom RJ, Tang PA, Simmons C et al. Changes in estrogen receptor, progesterone receptor and Her-2/neu status with time: discordance rates between primary and metastatic breast cancer. Anticancer Res 2009;29:1557-1562.
8. Curigliano G, Bagnardi V, Viale G et al. Should liver metastases of breast cancer be biopsied to improve treatment choice? Ann Oncol 2011;22:2227-2233.
9. Dieci MV, Barbieri E, Piacentini F et al. Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-institution analysis. Ann Oncol 2013;24:101-108.
10. Guarneri V, Giovannelli S, Ficarra G et al. Comparison of HER-2 and hormone receptor expression in primary breast cancers and asynchronous paired metastases: impact on patient management. Oncologist 2008;13:838-844.
11. Holdaway I, Bowditch J. Variation in receptor status between primary and metastatic breast cancer. Cancer 1983;52:479-485.
12. Kuukasjarvi T, Kononen J, Helin H, Holli K, Isola J. Loss of estrogen receptor in recurrent breast cancer is associated with poor response to endocrine therapy. J Clin Oncol 1996;14:2584-2589.
13. Li BD, Byskosh A, Molteni A, Duda RB. Estrogen and progesterone receptor concordance between primary and recurrent breast cancer. J Surg Oncol 1994;57:71-77.
14. Liedtke C, Broglio K, Moulder S et al. Prognostic impact of discordance between triple-receptor measurements in primary and recurrent breast cancer. Ann Oncol 2009;20:1953-1958.
15. Lindstrom LS, Karlsson E, Wilking UM et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol 2012;30:2601-2608.
16. Lower EE, Glass EL, Bradley DA, Blau R, Heffelfinger S. Impact of metastatic estrogen receptor and progesterone receptor status on survival. Breast Cancer Res Treat 2005;90:65-70.
17. MacFarlane R, Speers C, Masoudi H, Chia S. Molecular changes in the primary breast cancer versus the relapsed/metastatic lesion from a large population-based database and tissue microarray series. ASCO Annu Meet Proceed 2008, p 1000.
18. Sari E, Guler G, Hayran M, Gullu I, Altundag K, Ozisik Y. Comparative study of the immunohistochemical detection of hormone receptor status and HER-2 expression in primary and paired recurrent/metastatic lesions of patients with breast cancer. Med Oncol 2011;28:57-63.
19. Simmons C, Miller N, Geddie W et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Ann Oncol 2009: mdp028.
20. Spataro V, Price K, Goldhirsch A et al. Sequential estrogen receptor determinations from primary breast cancer and at relapse: prognostic and therapeutic relevance. The International Breast Cancer Study Group (formerly Ludwig Group). Ann Oncol 1992;3:733-740.
21. Wilking U, Skoog L, Elmberger G, Wilking N, Bergh J. HER2 gene amplification (HER2) and hormone receptor expression (ER/PR) in early (EBC) and metastatic breast cancer (MBC) in the same patients. ASCO Annu Meet Proceed 2007, p 1023.
22. Wu JM, Fackler MJ, Halushka MK et al. Heterogeneity of breast cancer metastases: comparison of therapeutic target expression and promoter methylation between primary tumors and their multifocal metastases. Clin Cancer Res 2008;14:1938-1946.
23. Karagoz Ozen DS, Ozturk MA, Aydin O, Turna ZH, Ilvan S and Ozguroglu M. Receptor expression discrepancy between primary and metastatic breast cancer lesions. Oncol Res Treat 2014;37:622-626.
24. Yang YF, Liao YY, Yang M, Peng NF, Xie SR, Xie YF. Discordances in ER, PR and HER2 receptors between primary and recurrent/metastatic lesions and their impact on survival in breast cancer patients. Med Oncol 2014;31:214.
25. Gancberg D, Di Leo A, Cardoso F et al. Comparison of HER-2 status between primary breast cancer and corresponding distant metastatic sites. Ann Oncol 2002;13:1036-1043.
26. Gong Y, Booser DJ, Sneige N. Comparison of HER-2 status determined by fluorescence in situ hybridization in primary and metastatic breast carcinoma. Cancer 2005;103:1763-1769.
27. Lower EE, Glass E, Blau R, Harman S. HER-2/neu expression in primary and metastatic breast cancer. Breast Cancer Res Treat 2009;113:301-306.
28. Santinelli A, Pisa E, Stramazzotti, Fabris G. HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer J Cancer 2008;122:999-1004.
29. Tapia C, Savic S, Wagner U et al. HER2 gene status in primary breast cancers and matched distant metastases. Breast Cancer Res 2007;9:R31.
30. Thompson AM, Jordan LB, Quinlan P et al. Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the Breast Recurrence In Tissues Study (BRITS). Breast Cancer Res 2010;12:R92.
31. Amir E, Miller N, Geddie W et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol 2012;30:587-592.
32. Network NCC. NCCN clinical practice guidelines in oncology: breast cancer. Version 2.2015. Updated March 11, 2015. 2015.
33. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E and EGW Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;(23 Suppl 7):vii11-9.
34. Wolff AC, Hammond ME, Schwartz JN et al. American Society of Clinical Oncology/College of American

Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007;25:118-145.

35. Arslan C, Sari E, Aksoy S, Altundag K. Variation in hormone receptor and HER-2 status between primary and metastatic breast cancer: review of the literature. Expert Opin Ther Targets 2011;15:21-30.
36. Edgerton SM, Moore D, 2nd, Merkel D, Thor AD. erbB-2 (HER-2) and breast cancer progression. Appl immunohistochem Molec Morphol 2003;11:214-221.
37. Niikura N, Liu J, Hayashi N et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. J Clin Oncol 2012;30:593-599.
38. Zidan J, Dashkovsky I, Stayerman C, Basher W, Cozacov C, Hadary A. Comparison of HER-2 overexpression in primary breast cancer and metastatic sites and its effect on biological targeting therapy of metastatic disease. Bri J Cancer 2005;93:552-556.
39. Osborne CK, Yochmowitz MG, Knight WA, 3rd, McGuire WL. The value of estrogen and progesterone receptors in the treatment of breast cancer. Cancer 1980;46:2884-2888.
40. Raemaekers JM, Beex LV, Pieters GF, Smals AG, Benraad TJ, Kloppenborg PW. Progesterone receptor activity and the response to the first endocrine therapy in advanced breast cancer. Eur J Cancer Clin Oncol 1987;23:443-448.
41. Kuukasjarvi T, Karhu R, Tanner M et al. Genetic heterogeneity and clonal evolution underlying development of asynchronous metastasis in human breast cancer. Cancer Res 1997;57:1597-1604.
42. Botteri E, Disalvatore D, Curigliano G et al. Biopsy of liver metastasis for women with breast cancer: impact on survival. Breast 2012;21:284-288.
43. Curtit E, Nerich V, Mansi L et al. Discordances in estrogen receptor status, progesterone receptor status, and HER2 status between primary breast cancer and metastasis. Oncologist 2013;18:667-674.
44. Balleine RL, Earl MJ, Greenberg ML, Clarke CL. Absence of progesterone receptor associated with secondary breast cancer in postmenopausal women. Bri J Cancer 1999;79:1564-1571.
45. Matsumoto A, Jinno H, Murata T et al. Prognostic implications of receptor discordance between primary and recurrent breast cancer. J Clin Oncol 2015;20:701-708.
46. Musgrove EA, Sutherland RL. Biological determinants of endocrine resistance in breast cancer. Nat Rev Cancer 2009;9:631-643.
47. Mukohara T. Mechanisms of resistance to anti-human epidermal growth factor receptor 2 agents in breast cancer. Cancer Sci 2011;102:1-8.
48. Pohlmann PR, Mayer IA, Mernaugh R. Resistance to Trastuzumab in Breast Cancer. Clin Cancer Res 2009;15:7479-7491.
49. Idirisinghe PK, Thike AA, Cheok PY et al. Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Pathologic correlations and clinical significance. Am J Clinical Pathol 2010;133:416-429.
50. Hoefnagel LD, van der Groep P, van de Vijver MJ et al. Discordance in ERalpha, PR and HER2 receptor status across different distant breast cancer metastases within the same patient. Ann Oncol 2013;24:3017-3023.