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Breast Cancer

Comparison of HER-2 and Hormone Receptor Expression in Primary Breast Cancers and Asynchronous Paired Metastases: Impact on Patient Management

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Key Words. Breast cancer • HER-2 • Hormone receptors • Primary tumor • Metastasis biopsy

Disclosure: The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors, planners, independent peer reviewers, or staff managers.

ABSTRACT

Introduction. **The assessment of hormone receptors (HRs) and human epidermal growth factor receptor (HER)-2 is necessary to select patients who are candidates for hormonal and anti–HER-2 therapy. The evaluation of these parameters is generally carried out in primary tumors and it is not clear if reassessment in metastatic lesions might have an impact on patient management. The primary aim of this analysis was to compare HER-2 and HR status in primary tumors versus metastatic sites in breast cancer patients.**

Patients and Methods. **Seventy-five patients with available samples from primary tumors and paired metastases were included. HER-2 status was evaluated by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH); HR status was assessed by IHC.**

Results. **Nineteen percent of primary tumors were HER-2 positive; 77% were HR positive. Sites of biopsied or resected metastases were: locoregional soft tissues ($n = 30$), liver ($n = 20$), central nervous system ($n = 5$), bone ($n = 5$), pleura ($n = 4$), distant soft tissues ($n = 3$), abdomen (stomach, colon, peritoneum) ($n = 3$), bronchus ($n = 3$), and bone marrow ($n = 2$). For paired metastases, the HER-2 status was unchanged in 84% of cases; two patients changed from positive to negative, while 10 patients converted from negative to positive (agreement, 84%; $\kappa = 0.5681$). A change in HR status was observed in 16 cases (21%): nine cases from positive to negative and seven cases from negative to positive (agreement, 78.7%; $\kappa = 0.4158$).**

Conclusions. **Further studies are necessary to better define the level of discordance in HER-2 or HR status between primary tumors and paired metastases. However, a biopsy of metastatic disease can be recommended, if feasible with minimal invasiveness, because treatment options might change for a significant proportion of patients.** ***The Oncologist*** 2008;13: 838–844

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INTRODUCTION

Hormonal therapy and anti–human epidermal growth factor receptor (HER)-2 treatments represent the most successful examples of targeted therapy for breast cancer. For at least three decades, the expression of hormone receptors (HRs) has been recognized as the main determinant of the efficacy of endocrine manipulation. The last update of the Oxford meta-analysis has shown, in >30,000 patients, that the benefit of adjuvant tamoxifen is limited to patients with expression of HRs [1].

Similarly, in metastatic disease, the benefit of the anti–HER-2 monoclonal antibody trastuzumab is clearly limited to those patients with HER-2 overexpression or amplification [2], and adjuvant studies have been performed in this subset of patients only. The precise definition of the HR and HER-2 status is therefore critical for the selection of appropriate therapies. The evaluation of these predictive parameters is generally carried out in the primary tumor, and this assessment is taken into account to select treatment even in cases of metastases that occur several years later. Several reports have shown a lack of concordance in the expression of these predictive factors between primary tumors and metastatic sites [3–16]. However, these data are derived, in most cases, from relatively small retrospective series, because sampling of metastatic sites is not routinely performed in the majority of centers. In these series, the disagreement in HER-2 expression between primary tumors and distant metastases is in the range of 0%–34%.

Similarly, the expression of HRs has also shown a certain variability between primary tumors and recurrences [15–22].

The differences between primary tumors and metastases could be a result of genetic drift occurring during tumor progression [8] or intratumoral heterogeneity wherein the clone with the more aggressive phenotype starts the micrometastatic process from the beginning [23, 24]. Moreover, treatments might also interfere with this process, by selecting resistant clones. As a matter of fact, the question of whether or not it is appropriate to reassess HR and HER-2 expression in metastatic lesions also needs to be addressed in the light of new therapeutic options based on the molecular subtypes of breast cancer.

The aim of this study was to evaluate concordance in the expression of HER-2 and HRs between primary breast cancers and asynchronous paired metastases.

METHODS

Patient Selection

The archive of the pathology division of our institution was searched to identify all biopsies for metastases in patients with breast cancer performed in the period 2004–2007. Eighty-seven patients were identified, and 75 patients with available samples from primary tumors and who were followed in our department were considered for this analysis. Patients with stage IV disease at diagnosis were included only in cases when sampling of metastases was performed on metachronous lesions.

Study Aims

The primary aim of the present analysis was to compare the HER-2 status of primary tumors and paired asynchronous metastases in breast cancer patients. Secondary aims were to compare the expression of HRs in primary tumors and paired asynchronous metastases and to evaluate changes in HER-2 and HR expression according to the site of sampled metastases, the time between the primary diagnosis and metastasis biopsy, and prior therapies.

Pathology

All specimens from both primary tumors and metastatic site biopsies were analyzed at our department of pathology by a dedicated breast pathologist. HER-2 status was evaluated by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH). HR status was measured by IHC.

All cases were re-evaluated according to the initial procedure (either IHC or FISH). Retesting was done only if the original samples were not available or suitable for re-evaluation. Retesting was always done using the same assay used in the original report, and the same assay (either FISH or IHC) was always used in paired samples. Discordant cases were independently reviewed by another pathologist, blinded to the previous results.

IHC Staining

Tumor specimens were fixed in 10% neutral-buffered formalin for 20–28 hours before processing and embedding.

The antibodies used were: Novocastra clone CB11 (Novocastra Laboratories, Ltd., Newcastle upon Tyne, UK) for the evaluation of HER-2, Ventana Medical Systems clone 6F11 (Ventana Medical Systems, Inc., Tucson, AZ) for evaluation of the estrogen receptor (ER), and Ventana Medical Systems clone 1E2 (Ventana Medical Systems, Inc.) for evaluation of the progesterone receptor (PgR).

IHC staining was performed according to the avidin–biotin method, using tissue sections of 3-μm thickness. After deparaffinization in xylene and graded alcohols, epitope retrieval was performed with the Ventana CC1 reagent buffer (pH 8, Ventana Medical Systems, Inc.) at 98°C for 60 minutes. After epitope retrieval, endogenous peroxidase was blocked by 0.3% hydrogen peroxide for 15 minutes. Sections were incubated with primary antibody for 30 min-

utes at 37°C, then with the biotinylated secondary antibody for 20 minutes at 37°C, and then in avidin–biotin complex for a further 45 minutes. Diaminobenzidine tetrahydrochloride was used as the chromogen. For ER and PgR assessment, the following parameters were recorded: the presence or absence of an immunoreaction and the percentage of immunostained cells. The ER or PgR status was defined as positive in cases where there was IHC staining in ≥10% of cells.

The scoring of HER-2 by IHC was evaluated semiquantitatively according to the following categories: 0, no membrane staining; 1+, partial membrane staining in >10% of tumor cells; 2+, weak complete staining in >10% of tumor cells; 3+, complete staining of the membrane in >10% of tumor cells.

FISH analysis was performed using the PathVysion HER-2 DNA Probe Kit (Vysis Inc., Downers Grove, IL) consisting of two labeled DNA probes. The HER-2 probe, which spans the entire *her-2* gene (17q11.2-q12), was labeled in SpectrumOrange and the CEP 17 probe, which hybridizes to the α satellite DNA located at the centromere of chromosome 17p11.1-a11.1, was labeled in SpectrumGreen. Selected paraffin-embedded tissue sections of 3 μm, containing representative malignant cells, were deparaffinized in two 15-minute changes of xylene and dehydrated in two 5-minute changes of 100% alcohol followed by 5-minute changes of 95% alcohol. Air-dried tissue sections were treated with the Paraffin Pretreatment Kit (Vysis Inc). The slides were immersed for 20 minutes in 0.2 mol/l HCl, washed with wash buffer, incubated for 30 minutes at 80°C with pretreatment solution (NaSCN), washed with wash buffer, and finally treated in a protease I solution (0.5 mg/ml protease buffer; pH, 2) for 8–10 minutes at 37°C. Ten microliters of the hybridization probe was applied to the target area of the slide and immediately coverslipped. Denaturation and hybridization of DNA were performed using the metal block of a thermocycler (HyBrite; Vysis Inc.). The denaturation was performed at 83°C for 3 minutes and the hybridization was carried out overnight at 37°C. After hybridization, slides were placed, for 2 minutes, in prewarmed 73°C standard saline citrate/0.3% NP40 to remove excess of probes. The slides were air-dried in the dark for approximately 15 minutes, and then the 1,000 ng/ml DAPI/Antifade (4.6-diamidine-2-phenylindole; Vysis Inc.) counterstain was applied to the target area. For scoring, a Zeiss Axioscope fluorescence microscope equipped with a specially designed filter combination (Carl Zeiss Inc., Jena, Germany) was used: the *her-2* sequence was visualized with an orange filter, the chromosome 17 centromere sequence was visualized with a green filter, and the nuclei were identified with a DAPI filter. A triple bandpass filter (orange, green, and DAPI; Vysis Inc.) was also used. Hybridization signals were scored in at least 60 intact nonoverlapping nuclei and FISH analysis was performed by one observer using constant adjustment of the microscope focus because the signals were located on different focal plans. Overlapping nuclei were not scored. Representative images of each specimen were acquired with a high-performance charged-coupled device camera in monochromatic layers that were subsequently merged by the Quips PathVysion Software (Vysis Inc.).

The *her-2* gene status was scored as the ratio between HER-2 red signals and CEP17 green signals. A HER-2/CEP17 ratio >2 was interpreted as positive for gene amplification.

Overall, samples were considered positive for HER-2 in cases in which the IHC was 3+, or the IHC was 2+ and the FISH was amplified, or the FISH was amplified. In case of discordance between the IHC and FISH results, the HER-2 status was defined according to the FISH result.

Statistics

Agreement between the test results at different time points was measured by κ-statistics. Comparisons of percentages between groups were performed using the χ^2 test. The Mann-Whitney test was used to compare the follow-up data between groups. Continuous variables were compared using Student's *t*-test for paired data.

Results

Seventy-five metastatic breast cancer patients were included in this analysis. The patient characteristics are summarized in Table 1. For primary tumors, HER-2 was overexpressed and/or amplified in 14 cases (19%). HER-2 was assessed by IHC in 54 patients, with the following results: 0 in 19 cases (35%), 1+ in 22 cases (41%), 2+ in four cases (7%), and 3+ in nine cases (17%). Forty-three patients were evaluated by FISH: 35 cases (81%) showed no amplification and eight cases were amplified (19%).

ER and PgR expression levels were ≥10% in 73% and 58% of primary tumors, respectively. Overall, the ER and/or PgR status was positive in 77% of the cases.

Sites of biopsied or resected metastases were: locoregional soft tissues (n = 30), liver (n = 20), central nervous system (n = 5), bone (n = 5), pleura (n = 4), distant soft tissues (n = 3), abdomen (stomach, colon, peritoneum) (n = 3), bronchus (n = 3), and bone marrow (n = 2). The median time between the primary diagnosis and metastatic site biopsy was 53.2 months (range, 7.2–308 months).

The median times between the primary diagnosis and

Table 1. Patient characteristics

Characteristic	*n*	%
Evaluable patients	75	100
Median age at diagnosis, years (range)	53	(27–67)
Clinical stage at diagnosis		
I	19	25
IIA/IIB	26	35
IIIA/IIIB	13	17
IIIC/IV	17	33
Histologic type		
Ductal	60	80
Lobular	12	16
Other	3	4
Histologic grade		
1/2	25	34
3	38	50
NA	12	16
Overall HER-2 status		
Negative	61	81
Positive	14	19
HER-2 status by IHC[a]	54	100
0/1+	41	76
2+	4	7
3+	9	17
her-2 status by FISH[a]	43	100
Negative	35	81
Positive	8	19
Hormone receptor status		
ER positive	55	73.3
ER negative	20	26.7
ER and/or PgR positive	58	77.3
ER and PgR negative	17	22.7
Prior adjuvant chemotherapy	58	77
Prior adjuvant hormonal therapy	53	71

[a] Twenty-two cases with HER-2 assessment by both IHC and FISH (17 negative and five positive).
Abbreviations: ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER-2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NA, not available; PgR, progesterone receptor.

locoregional versus distant metastatic site biopsy were 42.8 months (range, 7.2–197.4 months) and 54.2 months (range, 7.4–308.2 months), respectively ($p = .144$).

For paired metastases, the HER-2 status was found to be unchanged in 63 cases (51 cases confirmed HER-2 negative, 12 cases confirmed HER-2 positive). A change in HER-2 status was observed in 12 cases (16%): two patients (2.7%) changed from positive to negative and 10 patients (13.3%) changed from negative to positive (agreement, 84.00%; $\kappa = 0.5681$).

In detail, the 12 cases with a change in *her-2* status were evaluated by FISH (eight cases), IHC (two cases), or both IHC and FISH (two cases).

With respect to the HR status, a change in ER status was observed in 17 cases (22%): eight patients (10%) changed from positive to negative and nine patients (12%) changed from negative to positive (agreement, 77.33%; $\kappa = 0.4111$). A change in PgR status was observed in 27 cases (36%): 21 patients (28%) changed from positive to negative and six patients (8%) changed from negative to positive (agreement, 63.51%; $\kappa = 0.298$).

Overall, when considering ER and/or PgR expression, a change in HR status was observed in 16 cases (21%): nine cases (12%) changed from positive to negative and seven cases (9%) changed from negative to positive (agreement, 78.67%; $\kappa = 0.4158$).

When considering HR expression as a continuous variable, no significant difference was observed in the expression of the ER (mean expression on primary tumor 46.8%, versus 48.3% on metastatic site biopsy; $p = .788$). A significant decrease was observed in the expression of the PgR (mean expression on primary tumor 29%, versus 19.3% on metastatic site biopsy; $p = .028$).

The median interval from the primary diagnosis to metastasis sampling was 53.2 months (range, 7.4–308.2 months) in patients with no change in HER-2 status versus 52.5 months (range, 7.2–113 months) in the 12 patients with a change in HER-2 expression ($p = .644$).

The median interval from the primary diagnosis to metastasis sampling was 53.9 months (range, 7.4–308.2 months) in patients with no change in HR status versus 46.6 months (range, 7.2–126.3 months) in the 16 patients with a change in HR status ($p = .442$).

No differences were observed when comparing patients with a change in HER-2 status and HR status with patients with no change with respect to site of biopsy (locoregional versus distant metastases) and prior therapies, as summarized in Table 2.

Among the 10 patients who changed from HER-2 negative to HER-2 positive, seven subsequently received trastuzumab (two of these patients received trastuzumab followed by lapatinib). The median duration of anti–HER-2 treatment in these patients treated after a change in HER-2 status was 26+ weeks (range, >2–108). Four patients were still on anti–HER-2 therapy at the time of this report.

Three of the seven patients who converted from a negative to positive HR status subsequently received hormonal therapy (median duration, 104 weeks; range, 48–128 weeks).

Table 2. Change in HER-2 and HR status by site of biopsy and prior therapies

	HER-2 status			HR status		
	No change	Change	*p*-value	No change	Change	*p*-value
Site of biopsy			.89			.730
Locoregional	25	5		23	7	
Distant	38	7		36	9	
Prior chemotherapy			.188			.563
Yes	54	12		52	14	
No	8	0		7	1	
Prior hormonal therapy			.222			.864
Yes	44	11		46	12	
No	19	1		13	3	
Prior trastuzumab			.28			.357
Yes	2	1		3	0	
No	61	11		56	16	

Abbreviations: HER-2, human epidermal growth factor receptor 2; HR, hormone receptor.

Discussion

The molecular classification of breast cancer represents the foundation of treatment selection for early and advanced disease. The more clinically useful classification recognizes three subtypes: HR positive (ER and/or PgR ≥10%), HER-2 positive (IHC 3+ and/or FISH amplified, irrespective of HR expression), and triple-negative tumors (ER, PgR, and HER-2 negative). Endocrine manipulation and anti–HER-2 agents represent the foundation of treatment in cases of HR-positive and HER-2–positive tumors, respectively, while, so far, chemotherapy is the only available option in triple-negative tumors.

Nowadays, these predictive parameters are evaluated at the time of diagnosis in primary tumors, and, even though the National Comprehensive Cancer Network guidelines recommend a biopsy of metastatic deposits when feasible [25], the practice of obtaining biopsies of metastatic lesions varies considerably across centers; therefore, the clinical management of the majority of patients is still based on the initial assessment.

However, the appropriateness of this approach in clinical practice can now be questioned for several reasons. First of all, several reports showing a lack of concordance in the expression of HER-2 and HRs between primary tumors and disease recurrence have been published, thus weakening the assumption that tumor phenotype is stable throughout disease progression. Moreover, new imaging and radiological techniques (e.g., ultrasound or computed tomography–guided biopsy) have improved our ability to easily and safely obtain tissue samples from metastatic sites. Finally, the increasing use in the adjuvant setting of targeted agents might exert selective pressure, possibly facilitating a modification in tumor phenotype.

In the present analysis, we observed a change in the expression of HER-2 from primary tumors to disease recurrences in 12 of the 75 evaluated patients (overall disagreement, 16%). Interestingly, in 10 patients, the HER-2 status changed from negative to positive, while in two cases only a loss in the expression of HER-2 was observed (one patient had received prior trastuzumab).

In the literature, the discordance in HER-2 expression between primary tumors and metastases, as measured by IHC and/or FISH, is in the range of 0%–33.2% [3–16]. In these reports, a change from negative to positive HER-2 expression as well as from positive to negative HER-2 expression has been described. In particular, the largest report included 382 cases, evaluated by IHC. In that analysis, a discordant HER-2 status was found in 127 patients (33.2%): 90 cases (23.6%) changed from positive to negative while 37 cases (9.6%) changed from negative to positive [14]. None of those patients received trastuzumab prior to metastasis sampling. That study showed the highest percentage of discordance compared with other similar studies. The authors acknowledge that a possible explanation might be the possible misclassification of the 33 IHC 2+ patients not confirmed by FISH. However, even when excluding these cases, the percentage of discordance remains >20%.

In our study, the expression of HRs showed disagreement in 21% of the cases: nine cases (12%) changed from positive to negative and seven cases (9%) changed from negative to positive. Moreover, the quantitative evaluation

of the PgR showed a significant decrease from primary tumors to metastases. Both these observations have been described in the literature [15–22]; however, the data are more scanty than in the studies performed on HER-2, in particular because in the older experiences the detection of HR was performed by ligand-binding assay, which is less reliable than IHC.

The mechanisms responsible for the change in the expression of HER-2 and HRs have yet to be completely understood. Possible explanations include genetic drift during tumor progression, intratumoral heterogeneity, and the selective pressure of therapies.

In our study, the change from a positive to negative HR status, as well as the decreased PgR expression, might reflect acquired resistance to hormonal therapy. In fact, virtually all the patients with HR expression in primary tumors received hormonal therapy prior to metastasis biopsy (as adjuvant therapy or for treatment of metastatic disease). Less clear is the mechanism that drives the change in the opposite direction, both for HR and HER-2 expression.

When comparing the subsets of patients who did or did not experience a change in HER-2 status or HR expression, no differences in terms of the site of biopsy, the interval from the primary diagnosis to the metastasis biopsy, and prior therapies were observed. Therefore, in our study population, neither the site of biopsy nor the time period seem to impact the probability of observing a change in the expression of these parameters. However, even though no differences were observed according to prior hormonal therapy or chemotherapy, it must be underlined that, overall, all the patients included in the present analysis received al least one anticancer therapy. Therefore, a role for treatment in the observed phenomenon cannot been excluded.

Our results, together with other previously reported series, might have relevant clinical implications in patient management. In our study, seven of 10 patients who changed from HER-2 negative to HER-2 positive subsequently received anti–HER-2 therapy (five patients, trastuzumab only; two patients, trastuzumab followed by lapatinib). In these patients, the median duration of anti–HER-2 treatment was 26+ weeks (range, >2–108), which is consistent with the expected time on treatment for HER-2–positive patients. The same considerations are valid for the three patients treated with hormonal therapy following evidence of a change from negative to positive HR expression (median duration of hormonal therapy, 104 weeks; range, 48–128 weeks).

In conclusion, our report confirms that, as already reported by others, the biological characteristics of breast cancer can vary between primary tumors and asynchronous metastatic sites. All the pathological determinations were performed at a single institution, thus minimizing the risk for error. Of interest, the long duration of the treatments decided on the basis of the molecular subtype defined by the metastatic site biopsy indicates that this procedure might also be appropriate when a discordance exists between the primary tumor and metastasis assessments.

The retrospective nature of this analysis and the relatively limited number of patients included do not allow us to draw any firm conclusion. It is, however, clear that a change in molecular subtype can occur over time and, in light of the efficacy of targeted agents, when feasible with minimal invasiveness, a biopsy of metastatic disease might increase treatment options for a significant proportion of patients.

Acknowledgments

Data were presented at the 19th International Congress on Anti-Cancer Treatments, Paris, February 5–8, 2008.

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Oncologist 2008;13;838-844; originally published online Jul 23, 2008;
DOI: 10.1634/theoncologist.2008-0048