

Discordance of the estrogen receptor and HER-2/neu in breast cancer from primary lesion to first and second metastatic site

Elyse E Lower¹
Shagufta Khan²
Diane Kennedy¹
Robert P Baughman¹

¹Department of Medicine,
²Department of Pathology, University
of Cincinnati Medical Center,
Cincinnati, OH, USA

Background: Hormone receptor and HER-2/neu discordance between the primary lesion and first metastasis has been reported. This study was performed to determine further biomarker discordance rates between the first and subsequent metastatic breast cancer lesions.

Methods: We performed a retrospective review of paired biomarkers from primary breast cancers compared to first reported and subsequent metastases from 103 patients with breast cancer. The estrogen receptor (ER), progesterone receptor (PR), and HER-2/neu status were reported at all three time points. In addition, hormone, cytotoxic, and targeted treatments were recorded for primary and metastatic disease, and survival was determined.

Results: Between the primary and first metastases, discordance rates for ER, PR, and HER-2/neu were 15.8%, 33.7%, and 14.3%, respectively. There was discordance between the first and second metastases for the ER receptor in 18.8%, PR receptor in 19.8%, and HER-2/neu in 10.7%. Overall, there was discordance between the primary tumor and either the first or second metastases for ER in 27.7%, PR receptor in 40.7%, and HER-2/neu in 19.6% of cases. Discordance of either ER or PR affected survival, with worse survival experienced by those patients with all three hormone receptors remaining negative, and intermediate survival reported for those with discordant tumors (ER $\chi^2=14.27$, $p=0.0008$; PR $\chi^2=11.31$, $p=0.0035$). There was no difference in survival for patients whose HER-2/neu tumors were discordant.

Conclusion: This study demonstrated that continued metastatic disease evolution may be associated with different tumor biology and that studies of metastatic lesions appear warranted, especially if targeted therapy is an option.

Keywords: breast cancer, estrogen receptor, progesterone receptor, survival, HER-2/neu, tumor discordance

Background

Patients with hormone-dependent metastatic breast cancer often experience a lengthy disease process that can extend for years, includes multiple sites of metastasis, and requires multiple systemic treatments. Documented discordance between primary and metastatic breast cancer is reported for both hormone receptors and HER-2/neu, with the rates of discordance ranging between 6% and 48%.¹⁻⁴ Re-biopsy of subsequent metastasis may be important if biomarkers continue to change; however, data are lacking with regard to the possible discordance between first and subsequent metastasis, as it has not been systematically studied. Traditionally, targeted systemic treatment for early-stage disease as well as metastatic breast cancer has been based on the biomarkers identified on primary lesions. However, today, with a growing body

Correspondence: Elyse E Lower
1001 Holmes Building, 200 Albert Sabin
Way, Cincinnati, OH 45267, USA
Email lowere@ucmail.uc.edu

of data suggesting that discordance occurs both for hormone receptors and HER-2/neu, treatment recommendations may change based upon the prevalence of hormone receptors and HER-2/neu in metastatic disease.⁵

If treatment recommendations are based upon metastatic tumor analysis, retrospective studies suggest that targeted therapy changes could be needed in 20% of patients.

Although the etiology of primary metastatic discordance can include tumor sampling, processing, and analysis as well as intrinsic tumor heterogeneity,⁵ the actual cause of discordance can be quite elusive. To date, discordance between estrogen receptors (ER) and HER-2/neu has analyzed primary and metastatic tissue from patients with breast cancer. Little data exist regarding biomarker changes during the evolution of metastatic breast cancer. The purpose of this study is to evaluate ER and HER-2/neu biomarker changes between the primary lesion, first metastasis, and subsequent metastatic disease. In addition, the study focused on which patients may be at higher risk for changes in receptor status with subsequent sites for metastasis.

Methods

Using an established database, we conducted a retrospective chart review of the reported ER and HER-2/neu status in paired primary and subsequent metastatic invasive breast cancers between 2005 and 2014. Pathology reports were reviewed to document histology, ER and progesterone receptor (PR), and HER-2/neu status from paired samples for primary tumors and first and subsequent metastases. Not all three biomarkers were available for all reports. For all patients, demographic information was available including patient age, initial tumor stage, as well as dates of primary, first metastasis, and subsequent metastatic diagnoses. ER and PR analysis was performed using the standard immunohistochemistry of the respective pathology department. HER-2/neu analysis was performed using either standard immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH). Because the reporting of hormone receptor and HER-2/neu status had changed over time, the biomarker interpretation was considered positive or negative based on the standard criteria at the time of the evaluation. The protocol was reviewed by the University of Cincinnati Institutional Review Board and we have received a waiver for obtaining patient consent to review their medical data. Patient confidentiality was maintained throughout the study as each patient was given a unique identifier and the information was stored in a password-protected file. This study was approved by the University of Cincinnati Institutional Review Board.

Comparisons were made between groups using chi-square analysis, and the overall survival from the time of initial diagnosis to the first metastasis and subsequent metastasis were calculated using Kaplan–Meier analysis. Using chi-square analysis, rates of concordance and discordance were compared between the primary lesion and the first metastasis as well as subsequent metastasis and the frequency of discordance between the different tissues.

Results

Hormone receptors and/or HER-2/neu results were available from a total of 103 patients with metastatic breast cancer. Patient demographics are summarized in Table 1, which characterizes age at diagnosis, stage at diagnosis, and median time to the first metastasis as well as median time between the first and second metastases.

Table 2 summarizes the receptor status of the primary lesion and first and second metastases when available. Not all patients had adequate stains performed for all three tumors. Patients with concordant tumors had either negative receptors for the primary lesion as well as the first and second

Table 1 Demographics of patients studied

Feature	
Patients studied, n	103
Age, years	48 (26–80)*
Time until first metastases, days	1225 (7–8115)*
Time between first and second metastases, days	581 (23–4769)*
Tumor stage at diagnosis	
One	27
Two	31
Three	5

Note: *Median (range).

Table 2 Discordance between paired primary lesion and first and second metastases

Primary/first/second metastases	ER	PR	HER-2
Neg/neg/neg	23	33	37
Neg/neg/pos	4	3	3
Neg/pos/neg	1	3	2
Neg/pos/pos	2	6	2
Pos/neg/neg	7	12	3
Pos/neg/pos	6	8	1
Pos/pos/neg	8	3	0
Pos/pos/pos	50	18	8
Total cases studied	101	86	56
Discordance primary and first	15.8%	33.7%	14.3%
Discordance first vs second	18.8%	19.8%	10.7%
Discordance primary second	20.8%	30.2%	14.3%
Overall discordance	27.7%	40.7%	19.6%

Abbreviations: ER, estrogen receptor; Neg, negative; Pos, positive; PR, progesterone receptor.

metastases (neg/neg/neg) or positive staining for receptors in the primary lesion as well as the first and second metastases (pos/pos/pos). When we compared the primary tumor to the first metastases, there was concordance between the ER, PR, and HER-2/neu analysis in the majority of cases. However, there was discordance for ER in 15.8%, PR in 33.7%, and HER-2/neu in 14.3% of cases.

Furthermore, we calculated the rate of discordance between the paired first and second metastases. Again, the majority of tumors were concordant. There was discordance between the paired first and second metastasis for the ER receptor in 18.8% of cases, for the PR receptor in 19.8% of cases, and for HER-2/neu in 10.7% of cases. There were similar discordance rates between the paired primary lesion and second metastasis: ER receptor in 20.8% of cases, PR receptor in 30.2%, and for HER-2/neu in 14.3% of cases.

Overall, there was discordance between the primary tumor and either the first or second metastases in a significant number of cases. For the ER receptor, it was in 27.7% of cases, for the PR receptor it was in 40.7% of cases, and for HER-2/neu it was in 19.6% of cases. This would include cases where the primary tumor was positive, the first metastasis was negative, and the second metastases remained positive or vice versa.

We then calculated the survival of patients from initial diagnosis for three scenarios: primary tumor negative and both the first and second metastases were also negative; primary tumor positive and both the first and second metastases were positive; and discordance between the primary lesion and either the first and/or the second metastases. Figure 1 shows the survival curve based on the ER status. There was a significant difference in survival, with the best survival noted in patients with biomarkers positive at all three time points. Worse survival was witnessed for patients with all three tumors negative for biomarkers, and intermediate survival for those with discordant tumors (chi-square=14.27, $p=0.0008$). Figure 2 shows the survival curve based on the PR status. Again, there was a significant difference between the survival curves (chi-square=11.31, $p=0.0035$). In this case, patients with tumors negative for PR at all three time points experienced a worse survival probability, whereas survival was similar for the other two situations. In contrast to hormone receptor discordance, there was no difference in survival for the three HER-2/neu concordant or discordant groups (Figure 3, chi-square=4.66, $p=0.972$).

Discussion

Because most targeted treatment decisions are recommended on the basis of biomarkers for hormone receptors and HER-2/neu,

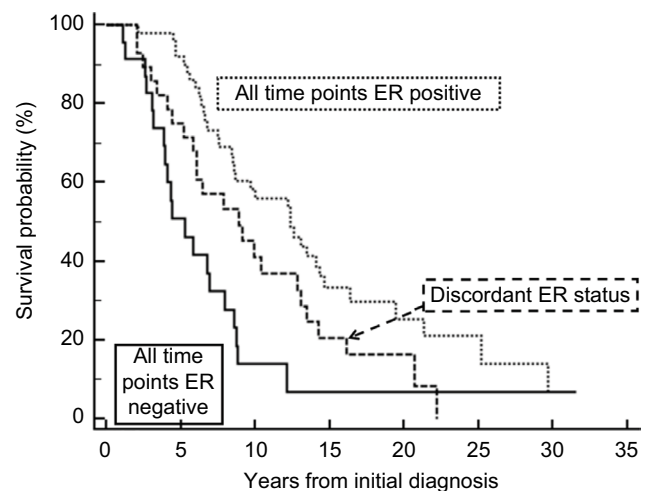


Figure 1 Survival curve based on the estrogen receptor (ER) status. There was a significant difference in survival, with the best survival noted in patients with biomarkers positive at all three time points. Worse survival was witnessed for those patients with all three parameters negative, and intermediate survival for those with discordant tumors (chi-square =14.27, $p=0.0008$).

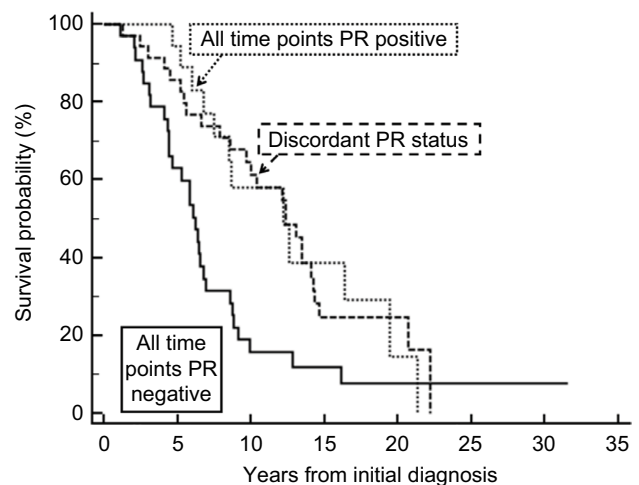


Figure 2 Survival curve based on the progesterone receptor (PR) status. Again there was a significant difference between the survival curves (chi-square =11.31, $p=0.0035$). In this case, patients with tumors negative for PR at all three time points experienced a worse survival probability, whereas survival was similar for the other two situations.

a change in biomarkers could have a dramatic impact on systemic treatment recommendations.⁵⁻⁷ Certainly, patients whose primary hormone receptor or HER-2/neu tumor biomarkers are negative and subsequent tumors are rendered positive provide great opportunity for additional targeted systemic management with hormone manipulation or HER-2/neu-targeted treatments. We and others have previously shown a substantial discordance rate between primary tumor and metastatic disease, with studies reporting hormone receptor discordance rates between 30% and 40% and HER-2/neu discordance rates between 10% and 30%.^{1,3,4,8-10} Although the American College of Pathologists recommends biomarker analysis on primary and metastatic

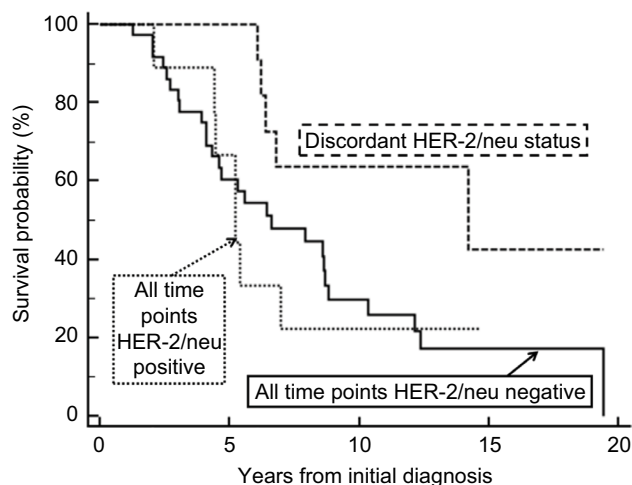


Figure 3 Demonstrates the survival curves for the three scenarios based on HER-2/neu status. In contrast to hormone receptor discordance, there was no difference in survival for the three HER-2/neu concordant or discordant groups (chi-square=4.66, $p=0.972$).

breast cancers,¹³ to the authors' knowledge this is the first report which analyzes the continued biomarker discordance of primary breast cancer with paired specimens of first and subsequent metastases. Our current study examined the markers on paired samples from subsequent sites of metastasis. We demonstrated overall discordance rates between 20% and 40%. In particular, we found discordance between the first and second metastases of approximately 20% for ER and PR receptors and 11% for HER-2/neu.

The lack of standardized pre-analytic and analytic variables previously may have accounted for some of these discrepancies between primary and metastatic lesions, as immunohistochemical analysis is dependent upon the timely placement of the specimen in fixative as well as specimen handling and the total fixation time. Adherence to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines should improve antigen retrieval and provide for more accurate IHC analysis of breast cancer specimens.^{11,12} Additionally, the interpretation of hormone receptor positivity has changed throughout the years.¹² The current cutoff point for receptor positivity can be very low (>1%); therefore, minor differences in antibody sensitivity can alter hormone receptor status. Current ASCO CAP guidelines require the hormone receptor status to be reported as positive or negative based upon a semiquantitative score of both the number of invasive tumor cells staining positively and the intensity of the stain. This system should better predict responses to hormone therapy and be easier and more cost-effective. Identifying the HER-2/neu-driven tumor has been vexing. Current guidelines define a breast tumor as HER-2/neu positive using either IHC or FISH.¹¹ Recent

changes in FISH positivity have modified the cutoff point to take into account both the HER-2/neu signal to chromosome 17 ratio as well as the gene copy number. Many systems still use HER-2/neu analysis by immunohistochemistry, wherein a score of 3+ is considered positive and 2+ score necessitates subsequent reflex testing.¹³ Currently, approximately 15–20% of all invasive ductal cancers will be considered HER-2/neu driven, using either a 3+ IHC score or FISH amplification. Most studies suggest that HER-2/neu concordance rates between IHC and FISH are approximately 90–96%.^{11,13} Unfortunately, inaccurate interpretation of HER-2/neu can result in false negatives which could deny patients HER-2/neu-targeted treatment, which can improve response rates and overall survival.

Etiology of primary and metastatic discordance can also involve tumor sampling as well as intrinsic tumor heterogeneity. Heterogeneous tumor clones with different hormone receptor and HER-2/neu biomarkers can occur as the result of host environmental changes or treatment consequences.¹⁴ In particular, tumors from patients who previously received adjuvant hormone or HER-2/neu-targeted treatment may develop receptor downregulation or resistance. Discordance between primary and metastatic breast cancer has been suggested for many years; however, most studies were retrospective, with only a few prospective studies now reporting biomarker discordance rates.^{8,9}

Only a few studies discuss the clinical importance of such discordance.¹⁵ The chance of discordance between the primary metastatic tumors for both hormone receptors approximates 20–30%. We previously reported that ER discordance was associated with changes in survival.⁴ Other investigators have also noted discordance affecting survival. Better survival was demonstrated in patients with either primary or metastatic disease ER positivity compared to those with ER-negative disease.^{14,16,17} However, survival advantage was not significant in all studies,¹⁸ which may reflect on study size or duration of follow-up.

Many patients with metastatic breast cancer witness prolonged survival which can be associated with the development of multiple sites of metastasis with differing biology. This study reveals the impact of tumor discordance which could occur during the evolution of metastasis. We studied hormone receptor and HER-2/neu discordance in primary, first, and second metastatic disease, and we noted the best survival was experienced by patients whose tumors remained ER positive at all three time points whereas significantly worse survival was found in those patients whose tumors remained ER negative at all three time points. Patients with

ER discordance between either the first or second metastases demonstrated intermediate survival. The finding was similar for the PR as well.

In our current study, discordance between HER-2/neu receptors failed to impact survival. This result is similar to findings from previous studies which compared primary and first metastatic disease sites.^{3,14} Although most studies do not report discordance rates for HER-2/neu-negative primary and metastatic tumors, some studies have noted a worse prognosis for those patients whose tumors lose HER-2/neu positivity over time.^{17–20} Additionally, there are cases in which a patient's primary tumor was HER-2/neu negative but the metastasis was considered HER-2/neu positive.²¹ In only approximately 7% of 800 cases was discordance reported for primary HER-2/neu negativity seen to change to metastatic HER-2/neu positivity.¹⁹ In our current study, seven of 44 patients (16%) with HER-2/neu negative primary tumors had either their first or second metastases recorded as HER-2/neu positive. Although HER-2/neu-positive breast cancer is associated with aggressiveness and impaired survival, treatment with HER-2/neu-targeted therapies including trastuzumab is quite effective in neutralizing the impact of HER-2/neu on survival.

Large studies report primary HER-2/neu-positive tumors with discordant metastatic disease in 24–64% of patients.^{16,17,19} However, bias may cloud these retrospective studies due to a tendency to repeat HER-2/neu testing only in patients considered likely to have discordant tumors.²¹ In our study of unselected cases, only four of 12 (33%) patients whose primary tumors were HER-2/neu positive experienced HER-2/neu negativity in either the first or second metastases.

As with ER discordance, the etiology of HER-2/neu change is probably multifactorial and includes pre-analytical as well as analytical factors.^{5,22} Tumor heterogeneity makes tissue sampling very problematic. Small case series suggest that HER-2/neu discordance occurs in some patients who have received neoadjuvant trastuzumab for HER-2/neu-positive primary cancers.

Current systemic treatment recommendations are based on primary tumor assessment, prior adjuvant treatments, time to relapse, and sites of metastasis. A wide range of systemic treatments are available for patients whose tumors are hormone receptor positive and/or HER-2/neu positive. Fifty percent improvement in survival has been identified in patients who have received adjuvant HER-2/neu-targeted trastuzumab.²³ Obviously, a false-negative biomarker interpretation could deny a patient a potentially life-saving treatment. Likewise, patients whose tumors are not truly hormone receptor positive or HER-2/neu driven should be spared the toxicity and cost of inappropriate therapy. Newer guidelines

suggest serial HER-2/neu evaluation to more precisely offer anti-HER-2/neu treatment in the metastatic setting.

This study confirms the previously reported discordance rates of approximately 25% between primary and metastatic breast cancer for hormone receptors and HER-2/neu. This discordance was noted for both the primary tumor and first metastasis as well as subsequent metastatic disease. Patients whose primary lesions are ER negative and whose metastatic lesion is ER positive could benefit from adjuvant hormone therapy. Likewise, changes in HER-2/neu can effect treatments. This study points out that one should consider reevaluating tumor biomarkers whenever a new metastatic lesion occurs. For example, it may help direct therapy for a patient whose previous tumor was ER positive but is no longer responsive to hormone therapy. Further studies will be needed to determine the potential role of routine repeat testing of tumor biomarker status for new metastatic lesions.

Conclusion

This study demonstrated that continued metastatic disease evolution may be associated with different tumor biology. Changes in tumor markers between first and second metastases can occur in up to 20% of cases. Therefore, studies of additional metastatic lesions appear warranted, especially if targeted therapy is an option.

Author contributions

EEL designed the study. DK was responsible for data collection and entry. EEL and RPB performed data analysis and manuscript preparation. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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