Phenotype Discordance between Primary Tumor and Metastasis Impacts Metastasis Site and Outcome: Results of WSG-DETECT-PriMet

Cornelia Kolberg-Liedtke^a Rachel Wuerstlein^{b, c} Oleg Gluz^{c, d} Florian Heitz^{e, f}
Muriel Freudenberger^c Elena Bensmann^g Andreas du Bois^{e, f} Ulrike Nitz^{c, d}
Enrico Pelz^h Matthias Warmⁱ Monika Ortmann^j Elena Sultova^k
Sara Y. Brucker^l Ronald E. Kates^c Tanja Fehm^m Nadia Harbeck^{b, c}

^aKlinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Essen, Essen, Germany; ^bBreast Center, Department of Gynecology and Obstetrics, University of Munich and CCCLMU, Munich, Germany; ^cWest German Study Group, Mönchengladbach, Germany; ^dEvangelical Hospital Bethesda, Breast Center Niederrhein, Mönchengladbach, Germany; ^eDepartment of Gynecology and Gynecologic Oncology, Kliniken Essen Mitte, Essen, Germany; ^fHorst-Schmidt-Klinik Wiesbaden, Wiesbaden, Germany; ^gAbteilung für Gynäkologie, Rotkreuzklinikum München, Munich, Germany; ^hInstitut für Pathologie, Viersen, Germany; ⁱBrustzentrum, Krankenhaus Köln-Holweide, Cologne, Germany; ^jInstitut für Pathologie, Universitätsklinikum Köln, Cologne, Germany; ^kInstitut für Pathologie, Ludwig-Maximilians-Universität München, Munich, Germany; ^lDépartement für Frauengesundheit, Universitätsklinikum Tübingen, Tübingen, Germany; ^mKlinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Düsseldorf, Düsseldorf, Germany

Keywords

Breast cancer · Metastases · Heterogeneity · Hormone receptors · HER2

Abstract

Introduction: Tumor biological factors of breast cancer (BC) such as hormone receptor (HR) status, HER2 status, and grade can differ in the metastatic cascade from primary to lymph node (LN) metastasis and to distant metastatic tissue. Systematic data regarding therapeutic consequences are yet limited. **Methods:** We conducted a prospectively planned, retrospective cohort study comparing BC phenotype in tissue from primary tumors (PTs), locoregional LN metastases, and disease recurrence (DR). HR and HER2 as well as tumor grade in PTs and DR were obtained by a database search. No centralized biomarker testing was performed. The impact of changes in tumor biological factors on post-recurrence survival (PRS) and overall survival was analyzed. **Results:** PriMet comprises 635 patients (LN tissue

in 142 patients). Discrepancies for HR or HER2 status between PT and DR were observed in 18.7 and 21.6% of cases, respectively. For HR status, positivity of PT and negativity of DR was seen more often (13.2%) than vice versa (5.5%). For HER2 status, negativity of the primary and positivity of DR was seen more often (14.9%) than vice versa (6.7%). Discordance was more often observed between PT and LN metastasis compared to LN versus DR. However, numbers were small. Compared to concordant non-triple-negative (TN) disease, concordant TN disease showed significantly inferior PRS. **Conclusion:** We demonstrate receptor discordance to occur relatively frequently between PT, LN metastasis, and DR and to impact patient prognosis. However, clinical consequences of receptor discordance need to be drawn with caution considering clinical aspects as well as tumor biology.

© 2020 The Author(s)

Published by S. Karger AG, Basel

C. Kolberg-Liedtke and R. Wuerstlein contributed equally.

Introduction

In metastatic breast cancer (BC), therapy concepts are based both on clinical considerations – such as site and severity of recurrence, time to progression, prior therapies – and on tumor biology [1, 2]. Advances in imaging, interventional methods, and pathology allow for a reliable determination of tumor biological factors in metastatic tissue. A substantial body of evidence has demonstrated that tumor biological factors such as hormone receptor (HR) status, HER2 status, and grade can differ in the metastatic cascade from primary to lymph node (LN) metastases and to distant metastatic tissue [3–8].

These alterations could impact outcome and treatment choice, but systematic data regarding these therapeutic consequences are yet limited. For example, Botteri et al. [9] showed significant benefit (in terms of post-recurrence survival [PRS]) in patients with gain of HER2-positive status who received trastuzumab compared to those not receiving trastuzumab.

In the case of HR status, gain of endocrine sensitivity would suggest that endocrine therapy could lead to benefit. Conversely, loss of endocrine sensitivity could indicate immediate need for chemotherapy, bypassing an endocrine alternative such as fulvestrant, aromatase inhibitors, or new combinations of endocrine-based targeted drug combinations.

National as well as international guidelines all recommend re-biopsy of suspected metastatic tissue [1, 10]. Most importantly, re-biopsy allows the physician to distinguish true BC metastasis from secondary malignancies or other diagnoses such as lesions of benign origin. Furthermore, guidelines also anticipate a potential improvement in predictive quality gained by matching the therapy concept to the metastatic rather than to the primary tissue. However, in view of methodological challenges, interdisciplinary requirements, and the complexity of the metastatic setting including aspects such as clonal heterogeneity, re-biopsies are not always performed in practice. Currently, re-biopsies tend to be performed in cases of negative primary receptors (either HR or HER2), with the hope of a gain in status for addition of a properly targeted therapy option. However, the loss of either hormone sensitivity or HER2 status could also have therapeutic consequences.

In addition to alterations in parameters such as HR status, HER2 status, or grade between PT and metastatic tissue, discordances of tumor biology in LN metastases could also impact outcome and affect optimal treatment choice. However, this aspect has been examined much less. In a recent publication, El Nemr Esmail et al. [11] found discordances in 60 paired samples between PTs and axillary node metastases in about half of samples regarding HR status and in about one-third regarding

HER2 amplification. However, no analysis regarding the prognostic impact of these discordances was performed.

Ultimately, quantification of the predictive impact of receptor information in metastatic tissue would require randomized controlled trials. However, in view of the complexity of a potential trial design in the metastatic setting, retrospective designs in this setting can provide considerable biological and clinical insight. The present paper presents the results of a multicenter analysis focusing on discordances in tumor biology during the course of disease (primary tumors [PTs], LN metastases and (local/distant) disease recurrence [DR]) and their impact on PRS in a large patient cohort.

Methods

Patient Characteristics

PriMet is a prospectively planned, retrospective multicenter cohort study comparing BC phenotype in tissue from PTs, locoregional LN metastases, and local DR (LDR)/distant DR (DDR). PriMet comprises 635 patients from the WSG and DETECT study groups (11 certified breast centers) whose BC was diagnosed between 1980 and 2010; follow-up data cover the period until mid-2012. Patients were included if they presented with unilateral BC with histologically confirmed subsequent/simultaneous local/regional or distant metastasis. Availability of estrogen receptor (ER), progesterone receptor (PR), and HER2 status was required.

Clinical data in PT and DR, including ER, PR, HER2, and grade, were obtained from a systematic chart review; in two centers, these factors were also measured in LN metastasis by central pathology. Overall, of the 635 patients, 592 were primary nonmetastatic (cM0) at first diagnosis.

All therapy decisions in the primary and metastatic setting were made locally based upon local interdisciplinary tumor board recommendations in accordance with current national guidelines (www.ago-online.de). Treatment heterogeneity may reflect possible changes in standard of care during the period of the study.

Tissue Sample and Biomarker Measurement

ER, PR, HER2, and tumor grade were determined in PT and DR according to national and international guidelines as well as German quality assurance and benchmarking programs for pathology in the respective certified pathology departments of the eleven participating centers valid at the time of analysis of each specimen. No centralized biomarker testing was performed. HR status was classified by ER and PR status, i.e., HR positivity was assigned to samples that showed either ER or PR positivity or both according to current guidelines; HR negativity was assigned if neither ER nor PR status was positive.

LN tissue immunohistochemistry (IHC) was available for 142 patients. IHC was performed at the time of PriMet analysis.

Statistics

PRS was defined as the interval between the time of recurrence and the time of termination (death or censoring). Recurrence-free survival (RFS) was defined as the interval between the time of diagnosis and DR. Overall survival was defined as the interval between the time of diagnosis and the time of termination (death or censoring).

The impact of changes in tumor biological factors on PRS was analyzed by survival analysis; hazard ratios were estimated by uni-

Table 1. Primary BC patients and tumor characteristics of the PriMet population

Characteristics	Category	n (valid %)
Age at first diagnosis, years	≤50	275 (46.5%)
	>50	317 (53.5%)
Nodal status (pN)	0	255 (44.3%)
	1	214 (37.2%)
	2	55 (9.6%)
	3	51 (8.9%)
	unknown	17 (–)
Tumor grade	1 or 2	352 (62.1%)
	3	215 (37.9%)
	unknown	25 (–)
ER status	positive	420 (72.3%)
	negative	161 (27.7%)
	unknown	11
PR status	positive	378 (65.2%)
	negative	202 (34.8%)
	unknown	12
HR status	positive	435 (74.9%)
	negative	146 (25.1%)
	unknown	11
HER2 status	positive	102 (22.6%)
	negative	350 (77.4%)
	unknown	140
TN status	TN	92 (16.1%)
	non-TN	479 (83.9%)
	unknown	21
(Neo)adjuvant chemotherapy	no	192 (32.4%)
	yes	400 (67.6%)
(Neo)adjuvant endocrine therapy (HR positivity in n = 427)	no	228 (38.5%)
	yes	364 (61.5%)
	unknown	8
(Neo)adjuvant HER2 targeted therapy (i.e., trastuzumab*) (HER2 positivity in n = 102)	no	554 (93.6%)
	yes	36 (6.4%)
	unknown	2

BC, breast cancer; ER, estrogen receptor; HR, hormone receptor; PR, progesterone receptor; TN, triple-negative. * Lapatinib was given in one case.

variate Cox proportional hazards (stepwise forward), and survival curves were estimated by the product-limit method (log-rank test).

Descriptive statistics were reported for the metastatic sequences. For each binary characteristic (referred to as “phenotype”) such as ER status measured in two kinds of tissue (e.g., PT and DR), a patient can experience one of four possible sequences, i.e., concordant positive and concordant negative, as well as both combinations of discordant status (i.e., positive status in PT and negative DR or vice versa). Each status combination was coded for each characteristic as a nominal variable with four classes. The reference category for reporting hazard ratios was generally the class with concordant positive status. In the case of grade, a binary variable grade 3 versus grade 1 or 2 was defined, and the reference category was concordant grade 3. An additional nominal variable was cod-

Table 2. Receptor discordance and concordance for HR and HER2 status

PT	LN	DR	HR status		HER2 status	
			<i>n</i>	%	<i>n</i>	%
<i>Cases without known status in LN</i>						
pos	–	pos	313	61.5	61	14.6
neg	–	neg	101	19.8	266	63.8
pos	–	neg	67	13.2	28	6.7
neg	–	pos	28	5.5	62	14.9
<i>Cases with known status in LN</i>						
pos	pos	pos	51	50.0	11	12.5
neg	neg	neg	21	20.6	55	62.5
pos	pos	neg	5	4.9	1	1.1
neg	neg	pos	3	2.9	6	6.8
pos	neg	neg	7	6.9	8	9.1
neg	pos	pos	4	3.9	5	5.7
pos	neg	pos	7	6.9	0	0.0
neg	pos	neg	4	3.9	2	2.3

DR, disease recurrence; HR, hormone receptor; LN, lymph node; PT, primary tumor.

ed to classify metastatic (recurrence) site as LN tissue, bone, local, or visceral (central nervous system, lung, liver, other); patients with primary metastasis were excluded from analysis or considered as a separate category.

The descriptive statistic “number needed to change therapy” was defined here in terms of discordant HER2 or HR status (or both) as measured in PT versus DR: it is the reciprocal of the discordant percentage.

SPSS was used for statistical analysis and estimation; 95% CIs are reported; all *p* values are two-sided.

Results

Patient Characteristics

Table 1 summarizes the demographics, histopathological characteristics, and (neo)adjuvant treatment of the cohort. Paired samples from PT and DR were analyzed in 635 patients, including 592 primary BC patients (93%) without evidence of metastatic disease; 43 patients (7%) presented with primary metastatic disease. Additionally, IHC results from LN tissue were available in 124 patients. PRS was available in 629 patients.

In cM0 patients, subsequent DDR was present in 317 cases (53.3%), while 275 patients (46.5%) presented with LDR only. The median follow-up in cM0 patients alive at the time of analysis was 101 months (range 11–372 months), the estimated median overall survival was 176 months, and the estimated median overall RFS was 48 months (DDR subgroup: 45 months; LDR subgroup: 50 months). The estimated median overall PRS was 59 months (DDR subgroup: 45 months; LDR subgroup: 127 months).

Fig. 1. PRS according to concordance/discordance in ER status (PT vs. DR) (**a**), PR status (PT vs. DR) (**b**), HR status (PT vs. DR) (**c**), HER2 status (PT vs. DR) (**d**), TN status (PT vs. DR) (**e**), and grade (PT vs. DR) (**f**). DR, disease recurrence; ER, estrogen receptor; HR, hormone receptor; PR, progesterone receptor; PRS, post-recurrence survival; PT, primary tumor; TN, triple-negative.

Concordance/Discordance in Receptor Status of PT, LN Metastasis, and DR

Table 2 summarizes the comparison of endocrine receptor status between PT and metastatic lesions. HR sta-

tus was available for PT and DR in 509 patients; among those, 101 patients also had known HR status in the LNs. HER status was available in 417 patients for PT and DR, among whom 88 had known HER2 status in the LNs.

Table 3. Receptor discordance in TN status between PT, LN, and DR

PT	LN	DR	TN status	
			<i>n</i>	%
<i>Cases without known status in LN</i>				
TN	–	TN	54	10.5
Non-TN	–	non-TN	381	74.4
TN	–	non-TN	31	6.1
Non-TN	–	TN	46	9.0
<i>Cases with known status in LN</i>				
TN	TN	TN	10	10.1
Non-TN	non-TN	non-TN	64	64.6
TN	TN	non-TN	2	2.0
Non-TN	non-TN	TN	5	5.1
TN	non-TN	non-TN	4	4.0
Non-TN	TN	TN	6	6.1
TN	non-TN	TN	2	2.0
Non-TN	TN	non-TN	6	6.1

DR, disease recurrence; LN, lymph node; PT, primary tumor; TN, triple-negative.

Briefly, discrepancies for HR or HER2 status between PT and metastasis were observed in 18.7 and 21.6% of cases, respectively. In case of discordance for HR status, positivity of the primary and negativity of the recurrence was seen more often (13.2%) than vice versa (5.5%). Regarding HER2 status, negativity of the primary and positivity of the recurrence was seen more often (14.9%) than vice versa (6.7%).

In cases in whom LN status was analyzed, HR status between PT and LN metastasis was observed in 10.8% of cases (positive/negative/negative and negative/positive/positive), while discordance between LN and DR was observed in 7.8% of cases (positive/positive/negative and negative/negative/positive). However, numbers were small. Similarly, HER2 status discordance between PT and LN metastasis was already present in 14.8% of cases (positive/negative/negative and negative/positive/positive), while discordance between LN metastasis and DR was observed in 7.9% of cases (positive/positive/negative and negative/negative/positive).

We specifically looked at triple-negative (TN) concordance/discordance status. The results are given in Table 3. Total discordance was noted in 77 cases (15.1%).

Impact of Phenotypes on PRS

Kaplan-Meier curves for concordances/discordances in ER, PR, HR, HER2, and TN status as well as grade are given in Figure 1a–f.

In brief, compared to patients with concordant HR-positive status, both patients with concordant HR-negative status and discordant HR status (PT-positive vs. DR-negative) demonstrated an inferior PRS (hazard ratio

2.01, $p < 0.001$ and hazard ratio 1.62, $p = 0.012$, respectively). Furthermore, compared to concordant non-TN disease, concordant TN disease showed significantly inferior PRS (hazard ratio 0.37, $p < 0.001$). In contrast, cases with discordant TN status only showed a trend towards decreased PRS (hazard ratio 0.57, $p = 0.115$ and hazard ratio 0.68, $p = 0.158$ for TN/non-TN and non-TN/TN, respectively).

The impact of phenotype discordance arising in LN tissue (as opposed to changes occurring first in DR) on PRS was not possible to assess due to the limited sample size with LN IHC results.

Impact of Metastatic Site on PRS

Among patients with DDR ($n = 341$), the association between metastatic site and PRS was analyzed (Fig. 2). Metastasis in bone only was associated with better PRS than primary or visceral metastasis ($p < 0.001$, online suppl. Table 1; see www.karger.com/doi/10.1159/000512416).

We analyzed the association between TN concordance/discordance and distribution of DR. Distributions are shown in Table 4.

Impact of Recurrence-Free Interval on PRS

The results of Kaplan-Meier analysis regarding the impact of RFS on PRS are given in Figure 3. As expected, PRS was highly dependent on time to DDR: in patients with first DDR within 18 months, the estimated median PRS was 29 months, in others 79 months.

Discussion

In the WSG-DETECT-PriMet cohort study, 653 patients were included to evaluate the rate of discordance in HR and HER2 status as well as the impact of discordance regarding receptor status on survival parameters.

In our analysis, a discordance rate for HR status and HER2 status between PT and DR was detected in 18.7 and 21.6%, respectively. Discordance in ER, PR, and HER2 status between primary and metastatic BC has been reported to occur frequently and vary significantly [12]. Based upon the results of a meta-analysis, rates of discordance for ER, PR, and HER2 status of approximately 20, 33, and 8%, respectively can be assumed [13]. In our analysis, the discordance rates for HR were within the reported range of the meta-analysis, whereas the discordance rates for HER2 were significantly higher. The latter can be attributed both to our multicenter setting and to the lack of central conformation of HER2 status (particularly in PT). Furthermore, HER2 receptor discordance has been reported to depend significantly on the method of detection, with IHC being less reliable (and therefore more commonly associated with discordance) compared

Fig. 2. Impact of metastatic site on PRS. PRS, post-recurrence survival.

Fig. 3. Impact of RFS on PRS. PRS, post-recurrence survival; RFS, recurrence-free survival.

Table 4. Distribution of metastatic sites according to TN status in PT and DR

	Non-TN/non-TN	TN/non-TN	Non-TN/TN	TN/TN
Primary metastatic disease	22 (84.6%)	1 (3.9%)	0 (0%)	3 (11.5%)
Visceral metastases	113 (77.9%)	11 (7.6%)	13 (9.0%)	8 (5.5%)
Bone-only disease	40 (83.3%)	1 (2.1%)	3 (6.3%)	4 (8.3%)
Lymph node/soft tissue	47 (74.6%)	3 (4.8%)	8 (12.7%)	5 (7.9%)
Local recurrence	168 (69.7%)	15 (6.2%)	22 (9.2%)	36 (14.9%)

Values are presented as *n* (%). DR, disease recurrence; PT, primary tumor; TN, triple-negative.

to in situ hybridization methods [3]. Of note, since neither HR status nor HER2 status have been validated centrally, these parameters were determined according to local standards at each time point. We emphasize that this as well as the fact that (inter)national guidelines may have been implemented with varying pace and rigor at each institution may be one potential source of bias regarding our results.

We further analyzed the direction of receptor discordance, i.e., whether discordance was observed to be negative/positive versus positive/negative. In case of HR expression, positive/negative discordance (13.2%) was more commonly observed compared to negative/positive discordance (5.5%). In contrast, regarding HER2 status, negative/positive discordance (14.9%) was observed more commonly compared to positive/negative discordance (6.7%). Although absolute numbers may vary, our results are supported by other research groups in that HR status has been reported to occur as positive/negative discordance more frequently compared to negative/positive discordance, whereas the opposite holds true for HER2 status [5]. Regarding HR expression, the observed discordance may very well be explained both by true loss of receptor expression due to exposure to (neo)adjuvant endocrine therapy as well as selection of more aggressive (i.e., HR-negative) subclones during disease progression. In contrast, selection of more aggressive subclones mirrored by a higher probability of HER2 expression may serve as one explanation for our observation regarding HER2 status discordance. However, due to the retrospective nature of our analysis, we cannot determine whether alterations of HR and/or HER2 status during the course of disease result in an increased probability of metastasis or whether a more aggressive disease type is associated with a higher probability of receptor discordance. However, most importantly, analytical parameters such as variation on ER/PR antibody sensitivity and cutoffs of ER/PR positivity need to be considered. However, if at least in some cases our observations may result from true biological phenomena, this would be of high clinical interest, particularly regarding HER2 status. Given that HER2 positivity is associated with an increase in thera-

peutic options, such as HER2-targeted antibodies or small molecules, “de novo” HER2 positivity may justify adjustment of the therapeutic plan. Consequently, re-biopsy of primarily HER2-negative cases may be one option in recurrent disease (whenever feasible and possible), given that among HER2-negative PTs, 23.3% (62/266) presented with HER2-positive status in case of recurrence.

In our analysis, we observed a significant effect of receptor discordance on PRS. For instance, compared to patients with concordant HR-positive status, both patients with concordant HR-negative status and discordant HR status (PT positive vs. DR negative) demonstrated an inferior PRS. With regard to TN disease, concordant TN disease showed significantly inferior PRS compared to concordant non-TN disease.

These results are in concordance with previous results. We previously analyzed a cohort of 789 patients with recurrent BC. In this analysis, patients were classified based on their primary and recurrent tumors as triple-negative BC (TNBC) or receptor-positive BC (i.e., expressing at least one receptor). We found that patients with concordant TNBC status had significantly better PRS (median 43.0 months, 95% CI 31.2–52 months) compared with patients who had discordant receptor results (median 15.6 months, 95% CI 11.6–30.5 months). Furthermore, patients who had concordant receptor-positive BC of both PT and recurrence had the most favorable PRS (median 45.1 months, 95% CI 37.1–53.9 months). In this analysis, the other two groups, i.e., concordant TNBC cases and cases with discordant receptor status, had significantly worse survival, which again is similar to our observations [3]. Similarly, Yang et al. [14] reported discordant status for ER or HER2 in BC to be clinically significant and to correlate with an adverse prognosis. Furthermore, Erdem et al. [15] analyzed 549 BC cases with histologically proven recurrences and demonstrated a significant impact of receptor discordance on prognosis: negative/positive discordance regarding ER and PR status was associated with significantly higher PRS compared to concordant negative status (56 vs. 31 months, $p = 0.03$ for ER, 64 vs. 31 months, $p = 0.01$ for PR, respectively). Similarly, positive/negative discordance regard-

ing HER2 status was associated with poorer PRS compared to concordant HER2 expression (median 26 vs. 60 months, $p = 0.009$).

More importantly, PriMet is one of the very few datasets that describe HR and HER2 receptor alterations between PT, LN metastasis, and DR in a large cohort of patients. In the cohort with available LN IHC results, we saw that discordance of HR status in either direction could already be observed in the LNs in about half of the cases. Regarding HER2 status, most discordances of HER2 expression resulting in HER2-negative DR were already observed in LN tissue, whereas HER2 receptor discordance resulting in HER2-positive DR was already observed in about half of LN samples. This observation suggests that receptor status in primary LN metastasis could give a hint of the possibility of a receptor switch in the metastatic setting. These data are in concordance with the results by Falck et al. [16]. The authors constructed tissue microarrays from archived tissue blocks of PTs ($n = 524$), synchronous LN metastases ($n = 147$), and asynchronous relapses ($n = 36$). They reported significant discordance between PTs and relapses, but not between PTs and synchronous metastatic LNs. Furthermore, prognostic information was reported to be obtained both by the molecular subtype classification in PTs and in nodal metastases. For instance, TN status was an adverse prognostic parameter both in PTs (hazard ratio 4.0, 95% CI 2.0–8.2, $p < 0.001$) and LN metastases (hazard ratio 3.5, 95% CI 1.3–9.7, $p = 0.02$). The authors concluded that in case of discordance in receptor status between PT and metastatic LN, prognosis seemed to be determined by the receptor status of the LN [16]. Given that we found receptor status discordance to occur frequently relatively early in the metastatic sequence (i.e., in synchronous LN metastasis), we conclude that the LN phenotype may have the potential to impact therapeutic patient management, and novel study concepts guiding therapy according to LN receptor status should be investigated. Before clinical consequences are employed (particularly given current efforts to deescalate axillary interventions [17]), however, one should acknowledge the limited sample size of our cohort. Furthermore, we cannot rule out that a significant number of patients undergoing axillary surgical staging in our cohort had received neoadjuvant/preoperative chemotherapy which could have potentially influenced the receptor status of the available axillary LN metastasis.

In our project, discordance in HR or HER2 status (or both) was found in 35% ($n = 398$) of patients initially free from primary metastasis and in 39% ($n = 214$) of those with primary distant metastasis. For patients with metastatic disease, a switch has clinically relevant therapy implications. The “number needed to change therapy” is approximately 2.8 patients tested per change in therapy indication (either endocrine or HER2-targeted therapy or

both). It represents an estimate of the ratio of tested patients to those with a therapy implication. Although evidence for this mostly stems from retrospective analyses, a few recent prospective studies have analyzed the impact of receptor discordance regarding disease management and survival [18].

However, before such therapeutic measures are taken, the biological cause of receptor discordance has to be determined. Three potential causes for receptor discordance seem plausible: (1) a true switch of receptor status during the course of the disease as a result of prior therapy, (2) clonal selection, or (3) inadequate testing/sampling [19]. Although technical issues on their own do not seem to explain the discrepancy in ER, PR, and HER2 (since it may be assumed that roughly the same discordance rates for ER, PR, and HER2 status should be observed), lack of perfect reproducibility in the determination of ER, PR, and HER2 status has been described in several prospective clinical trials based on comparison of local and central pathology results [20, 21].

In the latter case, poor survival outcomes of patients with discordant receptor may be caused both by false-negative results that could lead to withholding HR- or HER2-targeted therapy and by false-positive receptor results that may also contribute to an adverse outcome as they may lead to an initial period of ineffective therapy with targeted agents in patients who will not be able to benefit [3].

It has to be acknowledged that few studies have focused on treatment changes based on analysis of the receptor status of the metastasis [22]. However, biomarker evaluation of metastasis may result in treatment alteration in a significant number of cases. Furthermore, repeated re-biopsies of different locations may also result in some level of molecular biomarker discordance [23].

In conclusion, in PriMet, we demonstrate HR and HER2 receptor discordance to occur relatively frequently between PT, LN metastasis, and DR and to impact patient prognosis. However, due to the retrospective nature of our analysis, we cannot determine whether and to what extent a true biological finding, clonal selection, or lack of methodological validity have contributed to this phenomenon. Clinical consequences of receptor discordance (particularly within LN metastasis) need to be drawn with caution, considering clinical aspects as well as tumor biology.

Statement of Ethics

No ethics approval or specific consent was obtained given that the study was part of a quality insurance program. However, all institutions had received patients' consent for use of their data and tumor materials for scientific purposes.

Conflict of Interest Statement

C. Kolberg-Liedtke has received honoraria/travel support by Phaon Scientific, Novartis, Pfizer, Celgene, Roche, AstraZeneca, Lilly, HEXAL, Amgen, Eisai, and SonoScape and has received research funding by Roche, Novartis, and Pfizer (CKL). O. Gluz has received lecture/consultancy fees from Celgene, Roche, Genomic Health, Amgen, Pfizer, Novartis, Lilly, Nanostring, Eisai, and MSD, and assistance with travel costs from Celgene, Roche, and Daiichi-Sankyo. N. Harbeck has received honoraria for lectures and/or consulting from Agendia, Amgen, AstraZeneca, BMS, Celgene, Daiichi-Sankyo, Genomic Health, Lilly, MSD, Novartis, Odonate, Pierre Fabre, Pfizer, Roche, Sandoz/Hexal, and Seattle Genetics. R. Wuerstlein, M. Freudenberger, E. Bensmann, A. du Bois, U. Nitz, E. Pelz, M. Warm, M. Ortmann, E. Sultova, S.Y. Brucker, R.E. Kates, and T. Fehm state that they have no conflict of interest regarding the paper.

Funding Sources

The study did not receive any external financial support.

Author Contributions

C. Kolberg-Liedtke and R. Wuerstlein designed and planned the analysis, interpreted the data, and drafted and finalized the manuscript. O. Gluz planned the analysis, collected clinical data, and finalized the manuscript. F. Heitz analyzed the tissue microarray, interpreted the data, and assisted in writing the manuscript. F. Heitz, M. Freudenberger, E. Bensmann, A. du Bois, U. Nitz, E. Sultova, E. Pelz, M. Warm, S.Y. Brucker, R.E. Kates, T. Fehm, and N. Harbeck interpreted the data, recruited patients onto the dataset, and assisted in writing the manuscript. M. Ortmann provided pathological analyses and assisted in writing the manuscript. All authors read and approved the final manuscript.

References

- 1 Thill M, Liedtke C, Müller V, Janni W, Schmidt M; AGO Breast Committee. AGO Recommendations for the Diagnosis and Treatment of Patients with Advanced and Metastatic Breast Cancer: Update 2018. *Breast Care (Basel)*. 2018 Jul;13(3):209–15.
- 2 Liedtke C, Kolberg HC. Systemic Therapy of Advanced/Metastatic Breast Cancer – Current Evidence and Future Concepts. *Breast Care (Basel)*. 2016 Aug;11(4):275–81.
- 3 Liedtke C, Broglio K, Moulder S, Hsu L, Kau SW, Symmans WF, et al. Prognostic impact of discordance between triple-receptor measurements in primary and recurrent breast cancer. *Ann Oncol*. 2009 Dec;20(12):1953–8.
- 4 Simmons C, Miller N, Geddie W, Gianfelice D, Oldfield M, Dranitsaris G, et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? *Ann Oncol*. 2009 Sep;20(9):1499–504.
- 5 Thompson AM, Jordan LB, Quinlan P, Anderson E, Skene A, Dewar JA, et al.; Breast Recurrence in Tissues Study Group. 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(6):R92.
- 6 Amir E, Miller N, Geddie W, Freedman O, Kassam F, Simmons C, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. *J Clin Oncol*. 2012 Feb;30(6):587–92.
- 7 Dieci MV, Barbieri E, Piacentini F, Ficarra G, Bettelli S, Dominici M, et al. Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-institution analysis. *Ann Oncol*. 2013 Jan;24(1):101–8.
- 8 Heitz F, Barinoff J, du Bois O, Hils R, Fisseler-Eckhoff A, Harter P, et al. Differences in the receptor status between primary and recurrent breast cancer – the frequency of and the reasons for discordance. *Oncology*. 2013; 84(6):319–25.
- 9 Botteri E, Disalvatore D, Curigliano G, Brollo J, Bagnardi V, Viale G, et al. Biopsy of liver metastasis for women with breast cancer: impact on survival. *Breast*. 2012 Jun;21(3):284–8.
- 10 Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. *Ann Oncol*. 2018 Aug;29(8):1634–57.
- 11 El Nemr Esmail RS, El Farouk Abdel-Salam LO, Abd El Ellah MM. Could the Breast Prognostic Biomarker Status Change During Disease Progression? An Immunohistochemical Comparison between Primary Tumors and Synchronous Nodal Metastasis. *Asian Pac J Cancer Prev*. 2015;16(10):4317–21.
- 12 Vignot S, Besse B, André F, Spano JP, Soria JC. Discrepancies between primary tumor and metastasis: a literature review on clinically established biomarkers. *Crit Rev Oncol Hematol*. 2012 Dec;84(3):301–13.
- 13 Aurilio G, Monfardini L, Rizzo S, Sciandivasci A, Preda L, Bagnardi V, et al. Discordant hormone receptor and human epidermal growth factor receptor 2 status in bone metastases compared to primary breast cancer. *Acta Oncol*. 2013 Nov;52(8):1649–56.
- 14 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 Oct;31(10):214.
- 15 Erdem GU, Altundag K, Ozdemir NY, Sahin S, Demirci NS, Karatas F, et al. Comparative study of receptor discordance between primary and corresponding metastatic lesions in breast cancer. *J BUON*. 2017 Mar–Apr;22(2):365–76.
- 16 Falck AK, Bendahl PO, Chebil G, Olsson H, Fernö M, Rydén L. Biomarker expression and St Gallen molecular subtype classification in primary tumours, synchronous lymph node metastases and asynchronous relapses in primary breast cancer patients with 10 years' follow-up. *Breast Cancer Res Treat*. 2013 Jul; 140(1):93–104.
- 17 Yan M, Abdi MA, Falkson C. Axillary Management in Breast Cancer Patients: A Comprehensive Review of the Key Trials. *Clin Breast Cancer*. 2018 Dec;18(6):e1251–9.
- 18 Amir E, Clemons M, Purdie CA, Miller N, Quinlan P, Geddie W, et al. Tissue confirmation of disease recurrence in breast cancer patients: pooled analysis of multi-centre, multi-disciplinary prospective studies. *Cancer Treat Rev*. 2012 Oct;38(6):708–14.
- 19 Pusztai L, Viale G, Kelly CM, Hudis CA. Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. *Oncologist*. 2010;15(11):1164–8.
- 20 Viale G, Regan MM, Maiorano E, Mastropasqua MG, Dell'Orto P, Rasmussen BB, et al. Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG 1-98. *J Clin Oncol*. 2007 Sep;25(25):3846–52.
- 21 Perez EA, Suman VJ, Davidson NE, Martino S, Kaufman PA, Lingle WL, et al. HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 intergroup adjuvant trial. *J Clin Oncol*. 2006 Jul;24(19):3032–8.
- 22 Criscitiello C, André F, Thompson AM, De Laurentiis M, Esposito A, Gelao L, et al. Biopsy confirmation of metastatic sites in breast cancer patients: clinical impact and future perspectives. *Breast Cancer Res*. 2014;16(2):205.
- 23 Juric D, Castel P, Griffith M, Griffith OL, Won HH, Ellis H, et al. Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. *Nature*. 2015 Feb;518(7538):240–4.