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Estrogen/progesterone receptor and HER2 discordance between primary tumor and brain metastases in breast cancer and its effect on treatment and survival

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Abstract

Background. Breast cancer treatment is based on estrogen receptors (ERs), progesterone receptors (PRs), and human epidermal growth factor receptor 2 (HER2). At the time of metastasis, receptor status can be discordant from that at initial diagnosis. The purpose of this study was to determine the incidence of discordance and its effect on survival and subsequent treatment in patients with breast cancer brain metastases (BCBM).

Methods. A retrospective database of 316 patients who underwent craniotomy for BCBM between 2006 and 2017 was created. Discordance was considered present if the ER, PR, or HER2 status differed between the primary tumor and the BCBM.

Results. The overall receptor discordance rate was 132/316 (42%), and the subtype discordance rate was 100/316 (32%). Hormone receptors (HR, either ER or PR) were gained in 40/160 (25%) patients with HR-negative primary tumors. HER2 was gained in 22/173 (13%) patients with HER2-negative primary tumors. Subsequent treatment was not adjusted for most patients who gained receptors—nonetheless, median survival (MS) improved but did not reach statistical significance (HR, 17–28 mo, $P = 0.12$; HER2, 15–19 mo, $P = 0.39$). MS for patients who lost receptors was worse (HR, 27–18 mo, $P = 0.02$; HER2, 30–18 mo, $P = 0.08$).

Conclusions. Receptor discordance between primary tumor and BCBM is common, adversely affects survival if receptors are lost, and represents a missed opportunity for use of effective treatments if receptors are gained. Receptor analysis of BCBM is indicated when clinically appropriate. Treatment should be adjusted accordingly.

Key Points

1. Receptor discordance alters subtype in 32% of BCBM patients.
2. The frequency of receptor gain for HR and HER2 was 25% and 13%, respectively.
3. If receptors are lost, survival suffers. If receptors are gained, consider targeted treatment.

Importance of the Study

This study is important because BCBM are a common clinical problem and this study demonstrates that ER, PR, and HER2 discordance between the primary tumor and BM is also common. Survival is worse if receptors are lost, and gain of receptors represents an often missed opportunity to implement receptor-targeted therapies. When clinically appropriate, biopsy/resection of BCBM for receptor analysis should be considered.

Breast cancer (BC) is the second most common cancer worldwide and the most common cancer in women. Globally, over 2 million patients receive this diagnosis annually and over 600000 die from the disease.[1] In the United States alone, in 2019 an estimated 268600 new patients will be diagnosed and approximately 41760 deaths will occur from the disease.[2] Tumor subtype, governed by receptor expression or lack thereof, is a key prognostic factor for recurrence and survival.[3] There are 3 established immunohistochemical biomarkers: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). These can be combined into 4 main subtypes: hormone receptor (HR)–positive/HER2-negative; HR-positive/HER2-positive (triple positive); HR-negative/HER2-positive, and HR-negative/HER2-negative (triple negative).[4] Initial treatment is predicated upon subtype at the time of initial diagnosis.[5] At the time of recurrence, the subtype can be discordant (receptor expression changing from that established at initial diagnosis).[6]

Studies focused on comparison of receptor status between primary tumor versus metachronous extracranial metastases have reported receptor discordance rates for ER, PR, and HER2 of 10–56%, 25–49%, and 3–16%, respectively.[7–12] Based on these data, current guidelines of the American Society of Clinical Oncology advise offering biopsy where feasible to patients with recurrence to evaluate receptor status.[13]

BC is the second most common cause of brain metastases (BM). About half of BCBM occur in HER2-positive patients, followed by triple negative and then HR (ER or PR)-positive patients.[14] There is limited literature on the incidence of subtype discordance and conflicting literature regarding the impact of discordance on subsequent treatment and survival.[15–22] The purpose of this study is to determine the incidence of subtype discordance and the impact of discordance on subsequent therapy and survival in patients with BCBM, and represents the largest effort in the literature to date on this subject.

Methods

Our multinational (n = 3), multi-institutional (n = 18) consortium created an institutional review board–approved retrospective database of 2473 evaluable patients with newly diagnosed BCBM treated between January 1, 2006 and December 31, 2017 using Research Electronic Data Capture (REDCap) software hosted at the University of Minnesota. All patients had newly diagnosed BM, which we arbitrarily defined as those receiving treatment within 2 months of the diagnosis of BCBM. Patients with recurrent BCBM and those with leptomeningeal metastases were excluded. Of these 2473 patients, 521 underwent craniotomy for resection of the BCBM. In 2019, each institution updated its REDCap data with receptor status of the resected BCBM. Receptor analysis was available in 316/521 (61%) patients. ER/PR was defined as positive if >1% of cells stained positive and HER2 was defined as positive if 3+ stained positive or if fluorescent in situ hybridization (FISH) was >2.0. Discordance was considered present if ER or PR or HER2 status differed between the primary tumor and the BCBM. The overall receptor discordance rate was defined as the number of patients who had any receptor (ER, PR, or HER2) differ in the BM compared with the receptors in the primary tumor. The subtype discordance rate was defined as the number of patients who had their tumor subtype (triple positive, triple negative, ER or PR positive and HER2 negative, ER and PR negative and HER2 positive) differ in the BM compared with the tumor subtype in the primary tumor. The type of hormonal therapy and HER2-targeted therapy and the dates the patient received those therapies were collected. The criterion for receiving a given treatment was receipt of one or more doses of that treatment.

Median survival (MS) was calculated in months from date of BCBM diagnosis using the Kaplan–Meier method. Survival curves were compared using standard log-rank tests, and time from primary diagnosis to BM was compared using Wilcoxon rank-sum tests.

Results

Patient characteristics are shown in Table 1. The majority of patients (59%) had solitary BM. The tumor subtypes of both the primary tumor and BM were roughly evenly distributed

Table 1 Patient characteristics

	Overall ($N = 316$)
Median age, y, at BM diagnosis (dx) (Q1, Q3)	54 (46, 62)
Female	312 (99%)
Ethnicity	
Not Hispanic or Latino	284 (90%)
Hispanic or Latino	17 (5%)
Unknown/not reported	15 (5%)
Race	
White	231 (73%)
Black or African American	33 (10%)
Asian	13 (4%)
American Indian/Alaska Native	2 (1%)
More than one race	2 (1%)
Unknown/not reported	35 (11%)
Number of BM at initial BM dx	
1	187 (59%)
2	57 (18%)
3	23 (7%)
4	11 (3%)
5	15 (5%)
6	5 (2%)
7	5 (2%)
>7	13 (3%)
Extracranial metastases at BM dx	187 (59%)
KPS at BM dx	
<70	16 (5%)
70	42 (13%)
80	82 (26%)
90	98 (31%)
100	29 (9%)
Unknown	49 (16%)
Subtype of primary tumor	
HR-positive/HER2-negative	88 (28%)
HR-positive/HER2-positive	68 (22%)
HR-negative/HER2-positive	75 (24%)
Triple negative	85 (27%)
Subtype of BM	
HR-positive/HER2-negative	74 (23%)
Triple positive	84 (27%)
HR-negative/HER2-positive	71 (22%)
Triple negative	87 (28%)
Complete receptor concordance	
ER, PR, and HER2 concordant	184 (58%)
ER, PR, or HER2 discordant	132 (42%)
ER concordance Concordant negative	140 (44%)
Concordant positive	108 (34%)
Primary-negative, BM-positive	30 (9%)
Primary-positive, BM-negative	38 (12%)
PR concordance	
Concordant negative	180 (57%)
Concordant positive	54 (17%)
Primary-negative, BM-positive	30 (9%)
Primary-positive, BM-negative	52 (16%)
Hormone receptor concordance (ER and PR)	
Concordant negative	120 (38%)
Concordant positive	118 (37%)
Primary-negative, BM-positive	40 (13%)
Primary-positive, BM-negative	38 (12%)
HER2 concordance	
Concordant negative	151 (48%)
Concordant positive	133 (42%)
Primary-negative, BM-positive	22 (7%)
Primary-positive, BM-negative	10 (3%)

across the 4 subtypes. The receptor discordance rate (change in at least 1 of the 3 receptors) was 132/316 (42%). The overall rate of subtype discordance (receptor discordance leading to change in subtype classification) was 100/316 (32%). Table 1 also shows that the HR (ER or PR) gain occurred in 40 of 160 patients (25%) with HR-negative primary tumors, and HER2 was gained in 22 of 173 patients (13%) with HER2-negative primary tumors. The HR was lost in 38 of 156 patients (24%) with HR-positive primary tumors and HER2 was lost in 10 of 143 patients (7%) with HER2-positive primary tumors. Fig. 1 shows the Kaplan–Meier curves comparing MS for patients with concordant versus discordant HR: the MS for HR-positive patients with concordant BM (27 mo) was significantly longer than that for patients who had HR-positive primary tumors and discordant HR-negative BM (18 mo) ($P = 0.02$). The MS for HR-negative patients with concordant brain metastases (17 mo) was shorter than that for patients who had HR-negative primary tumors and discordant HR-positive brain metastases (28 mo), but the difference did not reach statistical significance ($P = 0.12$).

Fig. 2 shows that the Kaplan–Meier curves comparing MS for HER2-positive patients with concordant BM (30 mo) was longer than that for patients with HER2-positive primary tumors and discordant HER2-negative BM (18 mo), but the difference did not reach statistical significance ($P = 0.08$). The MS for patients with HER2-negative primary tumors and concordant BM (15 mo) was shorter than that for patients with HER2-negative primary tumors and discordant HER2-positive brain metastases (19 mo), but the difference did not reach statistical significance ($P = 0.39$).

Table 2 shows survival by primary tumor subtype and BM subtype. MS for patients whose primary tumor was HR-positive/HER2-negative ($n = 88$) and who were concordant in their BCBM ($n = 55$) was 18 months, in contrast to 33 months for the 14 discordant patients who gained

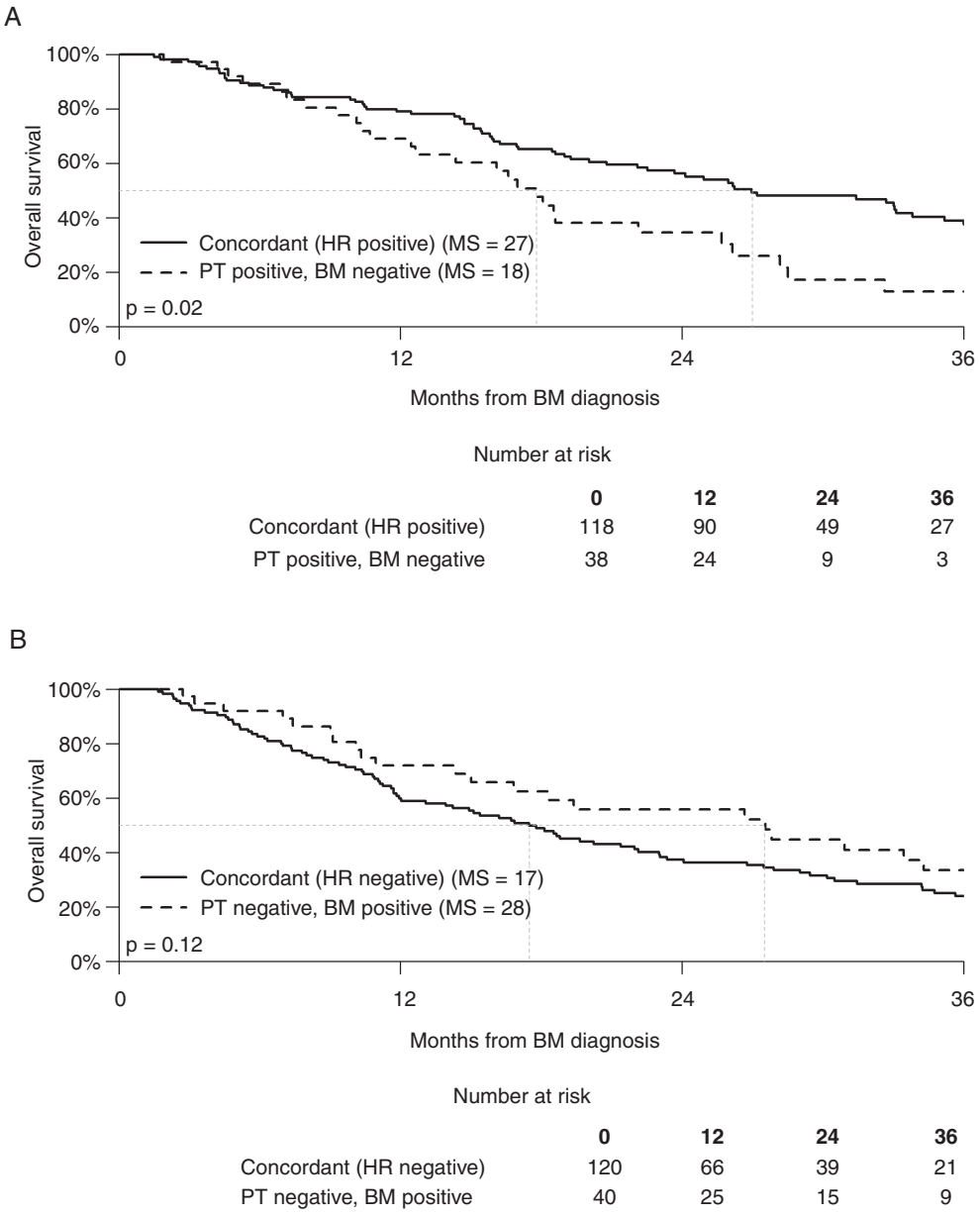

Fig. 1 PT: primary tumor.

HER2 expression, becoming HR-positive/HER2-positive. MS for patients whose primary tumor was HR-positive/HER2-positive ($n = 68$) and were concordant in their BCBM ($n = 47$) was 40 months, but only 18 months in the 18 discordant patients who lost ER/PR expression but maintained HER2 expression. MS for patients whose primary tumor was HR-negative/HER2-positive ($n = 75$) and who were concordant in their BCBM ($n = 50$) was 24 months compared with 33 months for discordant patients who gained ER/PR expression ($n = 18$), becoming HR-positive/HER2-positive. MS for patients whose primary tumor was triple negative ($n = 85$) and who were concordant in their BCBM ($n = 64$) was 11 months compared with 15 months for discordant patients who gained ER/PR expression ($n = 14$), becoming HR-positive/HER2-negative.

The time from primary diagnosis to BM was analyzed. There was no significant difference in this time between patients with concordant versus discordant receptor status.

Table 3 shows the subsequent treatment for discordant patients. Among the 40 patients whose ER or PR status changed from negative to positive, 33 (82%) did not receive hormonal therapy after the diagnosis of BCBM, and 15/22 (68%) patients whose HER2 status changed from negative to positive did not receive HER2-targeted therapy after diagnosis of BCBM.

Table 4 shows a comparison of ER, PR, and HER2 discordance rates between the primary breast tumor and BM

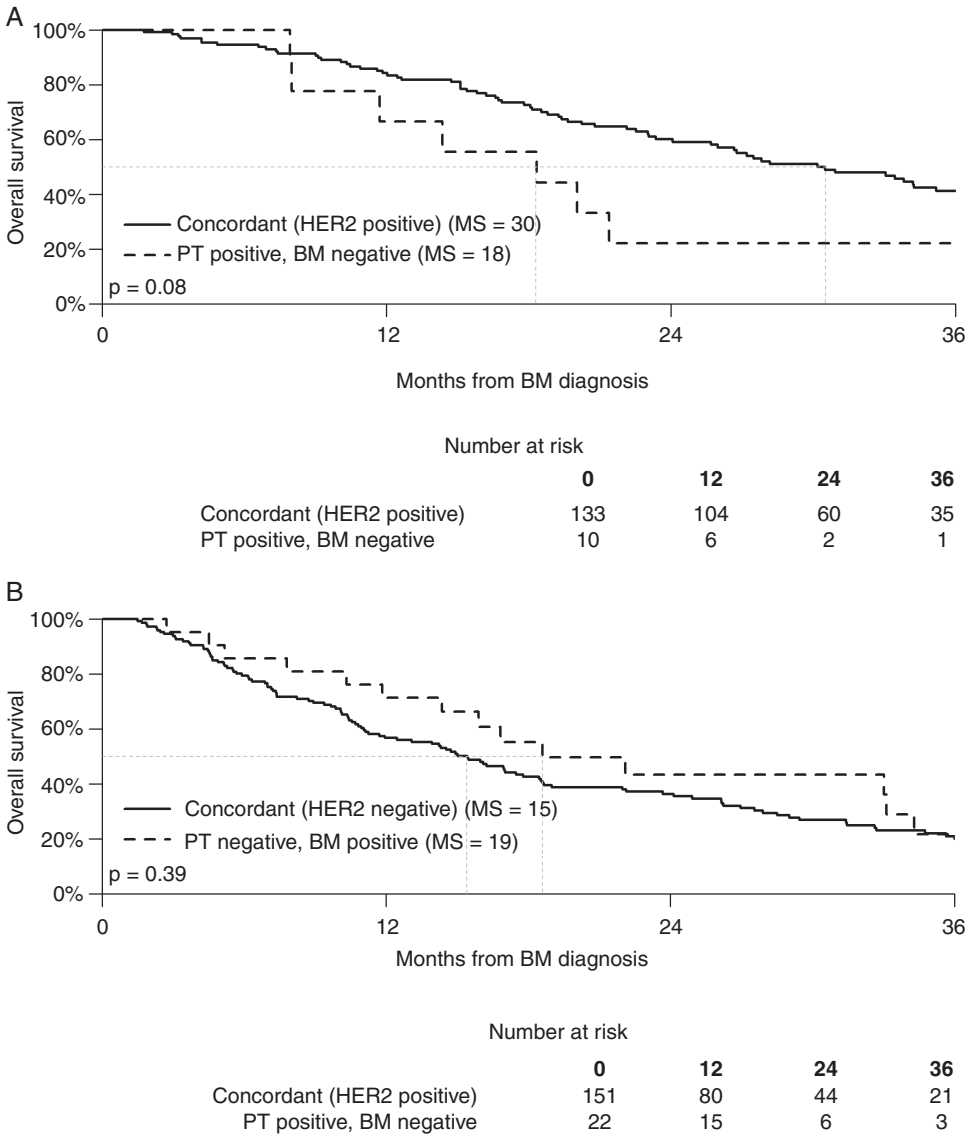

Fig. 2 PT: primary tumor.

in our data with 8 published studies. Supplementary Table 1 shows survival by era and primary treatment for BCBM patients. Supplementary Table 2 shows a list of the clinical data obtained in our REDCap database. Supplementary Figure 1 shows a diagram from the Consolidated Standards of Reporting Trials (CONSORT) for our study.

Discussion

Survival and our ability to predict survival for BCBM patients are improving.[23–25] Receptor discordance between the primary tumor and the BM may impact survival. This study represents the single largest series to investigate the incidence of receptor discordance in this patient population. Furthermore, this work both shows the prognostic relevance to receptor discordance and highlights the often missed opportunity to implement effective targeted therapies when receptors are gained.

Discordance Rates

Two independent meta-analyses have investigated receptor discordance between the primary breast cancer and metastases.[7,26] Aurilio reviewed 48 articles published between 1983 and 2011 from which ER, PR, and HER2 discordance was analyzed in 4200, 2739, and 2987 tumors, respectively.[7] The discordance rates for ER, PR, and HER2 receptors were 20%, 33%, and 8%, respectively. Schrijver reviewed 39 articles published between 1986 and 2016 from which ER, PR, and HER2 discordance was analyzed in 1948, 1730, and 2440 tumors, respectively.[26] They reported

Table 2 Discordance rate and survival by initial tumor subtype

Primary Subtype	*N* (% of total)	Metastasis Subtype	*N* (% of primary subtype)	MS, months
HRpos/HER2neg	88 (28)	Concordant	55 (62)	18
		HRpos/HER2pos	14 (16)	33
		HRneg/HER2pos	1 (1)	NA
		Triple negative	18 (20)	17
HRpos/HER2pos2HER	68 (22)	Concordant	47 (69)	40
		HRpos/HER2neg	2 (3)	NA
		HRneg/HER2pos	18 (26)	18
		Triple negative	1 (1)	NA
HRneg/HER2pos	75 (24)	Concordant	50 (67)	24
		HRpos/HER2neg	3 (4)	NA
		HRpos/HER2pos	18 (24)	33
		Triple negative	4 (5)	NA
Triple negative	85 (27)	Concordant	64 (75)	11
		HRpos/HER2neg	14 (6)	15
		HRpos/HER2pos	5 (6)	NA
		HRnegHER2pos	2 (2)	NA
Overall	316	Concordant	216 (68)	22
		Discordant	100 (32)	20

HR considered positive if either ER or PR was positive.

Table 3 Timing of targeted treatment by concordance status

	Concordant Negative, (*N* = 120)	Concordant Positive (*N* = 118)	Primary – BM + (*N* = 40)	Primary + BM - (*N* = =38)
Hormonal therapy				
Before BM only	4 (3%)	29 (25%)	3 (8%)	9 (24%)
After BM only	1 (1%)	8 (7%)	1 (2%)	1 (3%)
Both before and after BM	1 (1%)	33 (28%)	2 (5%)	8 (21%)
No hormonal therapy	113 (94%)	44 (37%)	33 (82%)	17 (45%)
Timing not reported	1 (1%)	4 (3%)	1 (2%)	3 (8%)
	Concordant Negative (*N* = 151)	Concordant Positive (*N* = 133)	Primary – BM+ (*N* = 22)	Primary + BM– (*N* = 10)
HER2 therapy				
Before BM only	7 (5%)	21 (16%)	1 (5%)	3 (30%)
After BM only	6 (4%)	7 (5%)	3 (14%)	1 (10%)
Both before and after BM	4 (3%)	62 (47%)	3 (14%)	1 (10%)
No HER2 therapy	133 (88%)	37 (28%)	15 (68%)	5 (50%)
Timing not reported	1 (1%)	6 (5%)	0 (0%)	0 (0%)

the direction of change (positive-to-negative or negative-to-positive) and metastasis location-specific differences. The positive-to-negative conversion rates for ER, PR, and HER2 were 22.5%, 49.4%, and 21.3%, respectively. The negative-to-positive conversion rates for ER, PR, and HER2 were 21.5%, 15.9%, and 9.5%, respectively. Furthermore, Schrijver found that ER discordance was more common in brain (20.8%) and bone (29.3%) than in liver (14.3%) metastases. PR discordance was more common in bone (42.7%) and liver (47.0%) than in brain (23.3%) metastases. There was no significant difference in HER2 discordance between brain, bone, and liver metastases. Both meta-analyses concluded that large prospective studies are needed to determine the impact of receptor discordance on treatment and survival. Meanwhile, reassessing receptor status in metastases was strongly encouraged.

The data that are focused on receptor discordance specifically in BC patients with BM are much more

Table 4 Comparison of ER, PR, and HER2 discordance rates between primary breast tumor and BM

Author	Year	Discordance Rate		
		ER (%)	PR (%)	HER2 (%)
Yonemori	2008	4/24 (17)	1/24 (4)	3/24 (13)
Hoefnagel	2012	6/44 (14)	16/44 (36)	1/44 (2)
Omoto	2010	4/21 (19)	4/21 (19)	4/21 (19)
Brogi	2011	6/37 (16)	8/37 (22)	2/40 (5)
Duchnowski	2012	35/120 (29)	34/119 (29)	17/119 (14)
Bachmann	2013	7/22 (32)	9/24 (38)	4/24 (17)
Shen	2015	10/35 (29)	7/34 (21)	1/36 (3)
Thomson	2016	3/41 (7.3)	1/41 (2)	6/41 (15)
Pooled rates		75/344 (21)	80/344 (23)	41/344 (12)
Current study	2020	68/316 (22)	82/316 (26)	32/316 (10)

limited. The combined sample size of the 8 retrospective reports in the Schrijver meta-analysis which included BM was 344.[9,15,17,18,20,22,27,28] Our sample ($n = 316$ in this single report) is comparable in size and the discordance rates are also similar. See Tables 1 and 4. Regarding the direction of conversion, our data showed that lower positive-to-negative conversion rates for ER, PR, and HER2 were 38/316 (12%), 52/316 (16%), and 10/316 (10%), respectively, compared with the pooled all-site data in the Schrijver meta-analysis detailed above. The negative-to-positive conversion rates for ER, PR, and HER2 were 30/316 (9%), 30/316 (9%), and 22/316 (7%) and were also lower than the pooled all-site data in the Schrijver meta-analysis.

Effect of Discordance on Survival

One prospective study analyzed the effect of discordance on survival and found no significant association between overall survival and discordance (median overall survival was 27.6 and 30.2 mo in the concordant and discordant groups, respectively); however, that study included all sites of metastases, not just BM.[29] In contrast, one retrospective series of patients who underwent craniotomies for BCBM between 2002 and 2014 reported 21/37 had receptor data available and 11/21 had conversion of at least one receptor from positive to negative.[11] In that study, MS for patients with concordant receptor status versus discordant (change from positive to negative) was 31 and 19 months ($P = 0.18$), respectively. Our results were similar, in that MS for patients with concordant receptor status versus discordant (change from positive to negative) was 27 versus 18 months ($P = 0.02$) for ER/PR and 30 versus 18 months ($P = 0.08$) for HER2.

Effect of Discordance Discovery on Treatment

A few small retrospective studies have identified a change in management in 12–20% of patients when there was a gain in receptor status.[30–32] Our results were similar in that only 18% of patients who gained estrogen or progesterone receptors (change from negative to positive) and only 32% of patients who gained HER2 received the indicated targeted therapy.

Physicians involved in the care of patients with BCBM need to be cognizant of the possibility of discordance, and when craniotomy is not clinically appropriate, we should develop other strategies to assess receptor status of BCBM (eg, liquid biopsy in either blood or even CSF) to help provide much-needed information to more effectively treat our patients. If an extracranial metastasis has been previously biopsied, a craniotomy is not indicated unless otherwise necessary for relief of mass effect.

Possible Explanations for Discordance

The many possible explanations for receptor discordance in BC include: (i) inaccuracy of the immunohistochemical staining varies[33]; (ii) different sampling methods (fine needle aspiration vs core biopsy vs surgical resection of the tumor) may contribute to discrepant receptor results[6]; (iii) intratumor and intertumor heterogeneity are more commonly seen with improved sequencing technology[34]; (iv) clonal genome evolution can cause discordance[14,35–37]; (v) newly acquired biological characteristics in the tumor microenvironment facilitate metastases[38]; and (vi) treatment can alter receptor status, as discussed below.

Effect of Treatment on Discordance

Intervening treatment between primary and metastasis may also explain loss of receptor expression either through a direct effect[16,17,20] or via clonal expression. For example, selective eradication of ER/PR positive cells by hormonal therapy could select for a population of ER/PR negative cells that could later metastasize.[39] Timmer et al reported that among 7 ER-positive patients treated with antihormonal therapy, the BM they developed were ER negative in all, and 5 of the 7 exhibited a negative conversion of the PR, whereas in patients without anti-estrogen treatment, only 1 of 10 had an ER conversion.[21] Neoadjuvant chemotherapy can result in a significant reduction in the expression of ER and Ki-67 index,[40] but the same group reported no significant change in PR or HER2.[41] To our knowledge, no study has reported, as ours does, the percent of patients who

actually had treatment added or omitted after discordance was discovered.

Limitations

Limitations of this study include the retrospective nature of the database, although there is no reason to believe that selection bias, inherent in all retrospective studies, would influence concordance/discordance status. Secondly, although this is the largest analysis of the concordance/discordance status of BC metastases ever reported ($N = 316$), some of the discordant subsets are relatively small (Table 1). Thirdly, no central review of pathology was performed, as it was not feasible in a retrospective study with 18 institutions spanning 3 countries. Fourth, retrospective data cannot be used to quantify the impact of a change in systemic therapy after diagnosis of BCBM on survival.

Conclusions

Receptor and subtype discordance between primary breast cancers and brain metastases is common. When discordance was found, subsequent treatment was not adjusted for most patients who gained receptors, nonetheless MS improved but did not reach statistical significance. Receptor gain thus represents an often missed opportunity to implement potentially effective therapies in discordant BC patients who gain ERs/PRs or HER2. This is important because survival for these patients is much improved than in the past. In contrast, loss of receptor adversely affects survival and should influence decisions regarding the relative merits of continuing receptor-targeted treatments. We recommend biopsy/resection and subtype analysis on brain metastasis tissue whenever feasible and clinically appropriate. If discordance is found, change of treatment should be considered.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

breast cancer | brain metastases | estrogen/progesterone/HER2 receptor discordance

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Conflict of interest statement. The authors have no conflict of interest related to this work.

Authorship statement. All authors contributed to data collection, analysis, and writing of the manuscript. The design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication was solely the responsibility of the authors and does not necessarily represent the official views of the funders/sponsors (National Center for Research Resources or the NIH).

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