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Rupesh Kotecha
Baptist Health Medical Group; Miami Cancer Institute, rupeshk@baptisthealth.net

Raees Tonse
Miami Cancer Institute, Mohammed.Tonse@baptisthealth.net

Muni Rubens
Miami Cancer Institute, MuniR@baptisthealth.net

Michael McDermott
Baptist Hospital of Miami; Miami Neuroscience Institute, mwmcd@baptisthealth.net

Yazmin Odia
Baptist Health Medical Group; Miami Cancer Institute, yazmino@baptisthealth.net

See next page for additional authors

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Authors

Rupesh Kotecha, Raees Tonse, Muni Rubens, Michael McDermott, Yazmin Odia, Haley Appel, and Minesh Mehta

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Systematic review and meta-analysis of breast cancer brain metastasis and primary tumor receptor expression discordance

Rupesh Kotecha, Raees Tonse, Muni Rubens, Michael W. McDermott, Yazmin Odia, Haley Appel, and Minesh P. Mehta

Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida, USA (R.K., R.T., H.A., M.P.M.); Herbert Wertheim College of Medicine, Florida International University, Miami, Florida, USA (R.K., M.W.M., Y.O., M.P.M.); Office of Clinical Research, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida, USA (M.R.); Miami Neuroscience Institute, Baptist Health South Florida, Miami, Florida, USA (M.W.M., Y.O.); Department of Neuro-Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida, USA (Y.O.)

Corresponding Author: Rupesh Kotecha, MD, Office 1R203, Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, FL 33176, USA (rupeshk@baptisthealth.net).

Abstract

Background. Change in hormone receptor (estrogen [ER] and progesterone [PR]) and/or human epidermal growth factor receptor type 2 (HER2) status during the evolutionary course of metastatic breast cancer and the effect of tumor classification subtype switching remain understudied and underappreciated in brain metastasis patients.

Methods. Using preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, a systematic review of series published prior to April 2020 obtained from the Medline database of biopsied or resected breast cancer brain metastasis (BCBM) was performed. Weighted random effects models were used to calculate pooled estimates.

Results. 15 full-text articles were included with receptor expression analyses on 1373 patients who underwent biopsy or resection of at least one intracranial lesion to compare to the primary tumor. Primary tumor receptor expression immunophenotypes were 45.0% ER+, 41.0% ER–, 31.0% PR+, 51.0% PR–, 35% HER2+, and 47.0% HER2–. Corresponding BCBM immunophenotypes were 19.0% ER+, 31.0% ER–, 13.0% PR+, 40.0% PR–, 21.0% HER2+, and 26.0% HER2–. On primary/BCBM comparison, 540 patients (42.6%) exhibited discordance in any receptor with 17.0% (95% CI: 13.0%–23.0%) discordant on ER, 23.0% (95% CI: 18.0%–30.0%) discordant on PR, and 12.0% (95% CI: 8.0%–16.0%) discordant on HER2 status. The most common receptor conversions found in BCBM were ER loss 11.0% (95% CI: 8.0%–16.0%), PR loss 15.0% (95% CI: 11.0%–21.0%), and HER2 gain 9.0% (95% CI: 7.0%–11.0%).

Conclusions. BCBM exhibits significant receptor expression discordance in comparison to primary tumors in approximately 40% of patients. Classification patterns need to be analyzed to determine factors predictive of BCBM/primary tumor discordance. Overall, tumor subtype switching and its effect on clinical management remains underappreciated.

Key Points

- 40% of brain metastasis exhibit receptor discordance from primary tumors.
- Approximately 12% had discordance in HER2 between the primary and brain metastasis.
- ER loss, PR loss, and HER2 gain were the most common conversions observed.

Importance of the Study

Management guidelines for relapsed or metastatic breast cancer, newly diagnosed or progressing on systemic therapy, support the reassessment of hormone receptor and HER2 expression during the disease course of breast cancer. However, given the challenges in routinely obtaining intracranial tissue, patients with brain metastasis are underrepresented or excluded entirely from series evaluating subtype switching. These findings, combined with the recent revelation that extracranial metastatic sites may not be reliable genomic surrogates for intracranial metastatic disease, underscore the need for a systematic analysis of receptor expression discordance rates specifically among breast cancer brain metastasis compared to paired primary tumor immunophenotypes.

Advances in the management of locally-advanced and metastatic breast cancer, increased central nervous system (CNS) screening, and improved access to MRI have collectively contributed to an increase in the detection and diagnosis of breast cancer brain metastases (BCBM).[1,2] The incidence, prognosis, and management of BCBM differs based on hormone receptor expression status (estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor type 2 (HER2). Importantly, treatment paradigms for patients with metastatic breast cancer consist of cytotoxic chemotherapy, hormone therapy, and targeted therapy, all of which depend on the receptor expression profile of the patient's disease.

Large series of matched primary tumor and metastatic site tissue samples have demonstrated that receptor expression profiles can change during a disease course, due to biological changes in the tumor, as a result of selective pressure of systemic therapy, or because metastatic lesions at a specific location might result from clones with a molecular pattern for homing and successfully growing in those particular organs.[3,4] However, given the challenges in routinely obtaining intracranial tissue, patients with BCBM were underrepresented[5] or excluded entirely from these series.[6] These findings, combined with the recent revelation that extracranial metastatic sites may not be reliable genomic surrogates for intracranial metastatic disease,[7] underscore the need for a systematic analysis of receptor expression discordance rates specifically among BCBM compared to primary tumor immunophenotypes.

Methods

Selection of Articles

This systematic review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria.[8] Initial article selection was performed by searching the MEDLINE (PubMed) and Cochrane electronic bibliographic databases. To ensure a comprehensive initial search strategy, generic keywords were used in the initial article screen: "breast cancer" and "brain metastasis" combined with "estrogen receptor/ER," "progesterone receptor/PR," "HER2/neu," and "receptor conversion/dis- or concordance." Full text articles published in the English language were considered, and no publishing date restrictions were used through April 2020.

The initial query identified 3141 articles that were subsequently screened by a thorough review of the article titles, abstracts, and manuscripts, as necessary. Specific inclusion criteria included: retrospective or prospective case series of >10 adult patients, original full-text research articles directly describing ER, PR, or HER2 statuses in primary breast tumors compared with BCBM, and receptor conversion or discordance. Exclusion criteria included: nonclinical reports, expert opinion, commentary or review studies which did not provide unique data on >10 patients; abstract only publications; and studies on receptor comparisons to extracranial metastasis only (ie, lung, liver, or bone). The search strategy used for this report and the methodology for study inclusion is illustrated in Supplementary Figure 1.

Outcome measures and statistical analysis

The hormonal subtypes data included the techniques used to define a positive ER, PR, and HER2 status. The individual receptor statuses at the initial diagnosis of the primary tumor and BCBM were recorded. The receptor discordance data included the BCBM to primary tumor discordances by individual receptor expression and overall tumor subtype. Gain or loss of each individual receptor, also termed receptor "conversion," was also recorded. The primary outcomes consisted of the incidence of individual receptor expression, overall tumor subtypes, and individual receptor discordances among primary tumors and BCBM. R Studio (version 1.1.423, Boston, Massachusetts) was used for statistical analyses and R package "metafor" (version 2.0–0)[9] was used for meta-analyses, tests for heterogeneity, and analysis of publication bias. Study variances for overall estimates were calculated using the DerSimonian-Laird method.[10,11] Weighted random effects models were used to calculate pooled estimates for each of the outcome variables. Given the types of studies included in this meta-analysis, spanning numerous years in a number of different populations and varied geographic locations, the random effects model was considered superior to the fixed effects model when calculating pooled estimates.[12,13] Since some studies had missing data, we conducted a sensitivity analysis by excluding studies with missing data. We compared the ER, PR, and HER2 discordance rates between

studies with and without missing data to see assess for potential statistically significant differences in the pooled estimates. I^2 statistic was used for identifying heterogeneity: I^2 of 0%, 25%, 50%, and 75% were interpreted as absent, low, moderate, and high heterogeneity, respectively.[14] Funnel plots and the Egger test (P value < .05 indicating presence of bias) were used for identification of publication bias.

Results

The initial search strategy used for this study yielded 201 unique reports, that were further reviewed based on the strict inclusion criteria. Detailed individual study review revealed that a majority of reports (n = 92, 46% of evaluated studies) only described receptor comparisons among extra-cranial metastasis (or included <10 patients with brain metastasis), resulting in 15 reports that met all inclusion and exclusion criteria for this meta-analysis (Supplementary Figure 1). There was no presence of publication bias detected across the included reports regarding the primary tumor receptor immunophenotype, the BCBM receptor immunophenotype, or discordances in ER, PR, or HER2 status (P > .05). A majority of studies (n = 9, 60%) represented single-institution reports and 6 studies (40%) were multi-institutional collaborations. All were retrospective in nature.

Key patient characteristics, demographics, and treatment information were not uniformly or consistently reported across the literature (Supplementary Table 1). In total, 1368 patients were included in this meta-analysis and the median number of patients in each study was 41 (range: 18–316 patients). The median age was 52 years (range: 40–56 years). The median time between primary tumor diagnosis and development of BCBM was 33 months (11 studies, range 2–46 months). Ten studies included information on systemic therapy prior to BCBM diagnosis, of which 38% (n = 370 patients) received hormonal therapy and 31% (n = 301 patients) received HER2-directed therapy.

Details regarding ER, PR, and HER2 positivity cutoffs, proportions at initial diagnosis and at time of brain metastasis are presented in Table 1. The ER/PR positive threshold varied across the included studies: >1% of cells staining positive was used in 6 studies; >10% by immunohistochemistry (IHC) in 8 studies, and an Allred score of >3 in 1 study. The HER2 positive cutoff methodology used was 3+ overexpression by IHC or 2+ with fluorescence in-situ hybridization (FISH) in 13 studies, and >30% IHC in 2 studies. Since only one study reported the total number of hormone positive or negative cases and 6 studies reported subtype grouping (with 2 studies having missing information in these sections), all random effects meta-analyses were performed by individual receptor expression only. Weighted pooled estimates of the tumor receptor expression immunophenotypes from the primary tumors were 45.0% ER+ (95% CI: 35.0–55.0%), 41.0% ER– (95% CI: 32.0–50.0%), 31.0% PR+ (95% CI: 22.0–43.0%), 51.0% PR– (95% CI: 40.0–62.0%), 35.0% HER2+ (95% CI: 27.0–44.0%), and 47.0% HER2– (95% CI: 39.0–56.0%) (Figure 1). Weighted pooled estimates of the paired receptor expression immunophenotypes from the corresponding BCBM were 19.0% ER+ (95% CI: 10.0–33.0%), 31.0% ER– (95% CI: 18.0–47.0%), 13.0% PR+ (95% CI: 8.0–19.0%), 40.0% PR– (95% CI: 24.0–58.0%), 21.0% HER2+ (95% CI: 12.0–34.0%), and 26.0% HER2– (95% CI: 15.0–41.0%) (Figure 2). Sensitivity analysis showed that there was no significant difference in pooled estimates of ER discordance rates between studies without any missing data and studies with incomplete data (0.15 [95% CI: 0.10–0.23] versus 0.17 [95% CI: 0.13–0.23]). Similarly, estimates of PR discordance rates (0.17 [95% CI: 0.12–0.26] versus 0.23 [95% CI: 0.18–0.30]) and HER2 discordance rates (0.05 [95% CI: 0.05–0.14] versus 0.12 [95% CI: 0.08–0.16]) between studies without any missing data and studies with incomplete data did not show significant differences in pooled estimates.

When compared to the primary tumor receptor expression immunophenotypes, 540 patients (42.6%) exhibited discordance in any receptor status (Table 2). When evaluated by each receptor individually, 17.0% (95% CI: 13.0%–23.0%) were discordant for ER status, 23.0% (95% CI: 18.0%–30.0%) discordant for PR status, and 12.0% (95% CI: 8.0%–16.0%) discordant for HER2 status (Figure 3). ER conversions found in BCBM compared to primary tumors were ER gain in 6.0% (95% CI: 4.0–9.0%) and ER loss in 11.0% (95% CI: 8.0–16.0%). Similarly, PR gain occurred in 6.0% (95% CI: 4.0–10.0%) and PR loss in 15.0% (95% CI: 11.0–21.0%). HER2 gain occurred in 9.0% (95% CI: 7.0–11.0%) and HER2 loss in 3.0% (95% CI: 3.0–5.0%) (Figure 4).

Discussion

Management guidelines for relapsed or metastatic breast cancer support the reassessment of hormone receptor and HER2 expression during the disease course of breast cancer.[30] Historically, this practice originated from case series of patients with ER+ disease who developed recurrent disease despite hormonal therapy and, on re-biopsy, were determined to exhibit ER-receptor conversion.[31] These discoveries have been bolstered by recent large retrospective and prospective studies; however, the application of these findings to a brain metastasis population has remained relatively understudied until recently. Most commonly, patients are treated based on the primary tumor immunophenotype, or the most recent biopsy from a metastatic site, assuming no change had occurred in the brain metastasis. The present meta-analysis provides key insights into the tumor biology of BCBM and offers important implications for clinical practice and clinical trial design, by suggesting that receptor discordance is in fact very common, >40%.

The breast cancer subtype has been correlated with the incidence, kinetics, and prognosis of BCBM patients.[32] One of the most commonly utilized tools used in clinical practice and trial stratification, the diagnosis-specific Graded Prognostic Assessment, uses tumor subtype (in addition to performance status and age), to estimate survival after diagnosis of BCBM.[33] The most recent iteration defined 5 criteria for estimating prognosis, with subtype continuing to be an important variable for prognosis estimation.[34] Incorporation of receptor expression status at the time of brain metastasis development may lead to further refinements of current

Table 1. Estrogen, Progesterone, and HER2 Receptor Statuses at Initial Diagnosis of the Primary Tumor and in the Brain Metastasis

Author	*N*	ER/PR Positive Cutoff	HER2 Positive Cutoff	ER+	ER–	PR+	PR–	HR+	HR–	HER2+	HER2–	HR+/ HER2+	HR+/ HER2–	HR-/ HER2+	HR-/ HER2–
Gaedcke et al., 2007[15]	23	>10% IHC	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				11	12	6	17	NA	NA	14	30	NA	NA	NA	NA
				Brain metastasis								Brain metastasis			
				29	56	15	70	NA	NA	29	56	NA	NA	NA	NA
Yonemori et al., 2008[16]	24	>10% IHC	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				25	4	27	2	NA	NA	18	11	NA	NA	NA	NA
				Brain metastasis								Brain metastasis			
				1	19	1	22	NA	NA	7	14	NA	NA	NA	NA
Broom et al., 2009[17]	100	>10% IHC	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				73	24	60	35	NA	NA	7	41	NA	NA	NA	NA
				Brain metastasis								Brain metastasis			
				52	12	26	36	NA	NA	6	34	NA	NA	NA	NA
Hoefnagel et al., 2010[18]	44	>10% IHC	>6 HER2 copies/ tumor cell nucleus	Initial diagnosis								Initial diagnosis			
				NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
				Brain metastasis								Brain metastasis			
				NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Omoto et al., 2010[19]	21	>10% IHC	>30% IHC	Initial diagnosis								Initial diagnosis			
				9	12	6	15	NA	NA	7	14	NA	NA	NA	NA
				Brain metastasis								Brain metastasis			
				9	12	4	17	NA	NA	9	12	NA	NA	NA	NA
Shao et al., 2011[20]	18	>1% of cells stained positive	>30% IHC	Initial diagnosis								Initial diagnosis			
				10	8	6	12	NA	NA	6	12	NA	NA	NA	6
				Brain metastasis								Brain metastasis			
				9	9	6	12	NA	NA	7	11	NA	NA	NA	NA
Brogi et al., 2011[21]	209	>10% IHC	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				11	43	6	48	NA	NA	25	30	NA	NA	NA	NA
				Brain metastasis								Brain metastasis			
				4	27	1	30	NA	NA	18	20	NA	NA	NA	NA
Duchnowska et al., 2012[22]	120	>1% of cells stained positive	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				51	69	40	78	NA	NA	51	62	NA	NA	NA	NA
				Brain metastasis								Brain metastasis			
				29	56	18	67	NA	NA	51	51	NA	NA	NA	NA

Table 1. Continued

Author	*N*	ER/PR Positive Cutoff	HER2 Positive Cutoff	ER+	ER–	PR+	PR–	HR+	HR–	HER2+	HER2–	HR+/ HER2+	HR+/ HER2–	HR-/ HER2+	HR-/ HER2–
Bachmann et al., 2013[23]	32	>10% IHC	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				12	12	13	11	NA	NA	11	13	NA	NA	NA	NA
				Brain metastasis								Brain metastasis			
				5	17	2	20	NA	NA	12	10	NA	NA	NA	NA
Shen et al., 2015[24]	140	>1% of cells stained positive	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				58	76	51	82	NA	NA	56	72	26	34	29	37
				Brain metastasis								Brain metastasis			
				10	15	9	18	NA	NA	16	19	NA	NA	NA	NA
Thomson et al., 2016[25]	41	Allred score of >3	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				15	NA	6	NA	NA	NA	NA	NA	NA	NA	NA	NA
				Brain metastasis								Brain metastasis			
				18	NA	7	NA	NA	NA	NA	NA	NA	NA	NA	NA
Timmer et al., 2017[26]	24	>1% of cells stained positive	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				10	14	10	14	NA	NA	10	14	NA	NA	NA	5
				Brain metastasis								Brain metastasis			
				3	21	4	20	NA	NA	15	8	NA	NA	NA	NA
Jung et al., 2018[27]	37	>1% of cells stained positive	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				16	21	13	24	NA	NA	19	18	3	13	16	5
				Brain metastasis								Brain metastasis			
				10	9	10	3	NA	NA	10	6	NA	NA	NA	NA
Sperduto et al., 2020[28]	316	>1% of cells stained positive	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				140	108	54	180	118	120	133	151	68	88	75	85
				Brain metastasis								Brain metastasis			
				30	38	30	52	40	38	22	10	84	74	71	87
Hulsbergen et al., 2020[29]	219	>10% IHC	3+ overexpression IHC or 2+ with FISH	Initial diagnosis								Initial diagnosis			
				117	102	79	135	114	NA	96	114	53	61	42	53
				Brain metastasis								Brain metastasis			
				NA	NA	NA	NA	NA	NA	NA	NA	40	47	64	55

BM, brain metastasis; ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor type 2; HR, hormonal receptor; IHC, immunohistochemistry; NA, not available; PR, progesterone receptor.

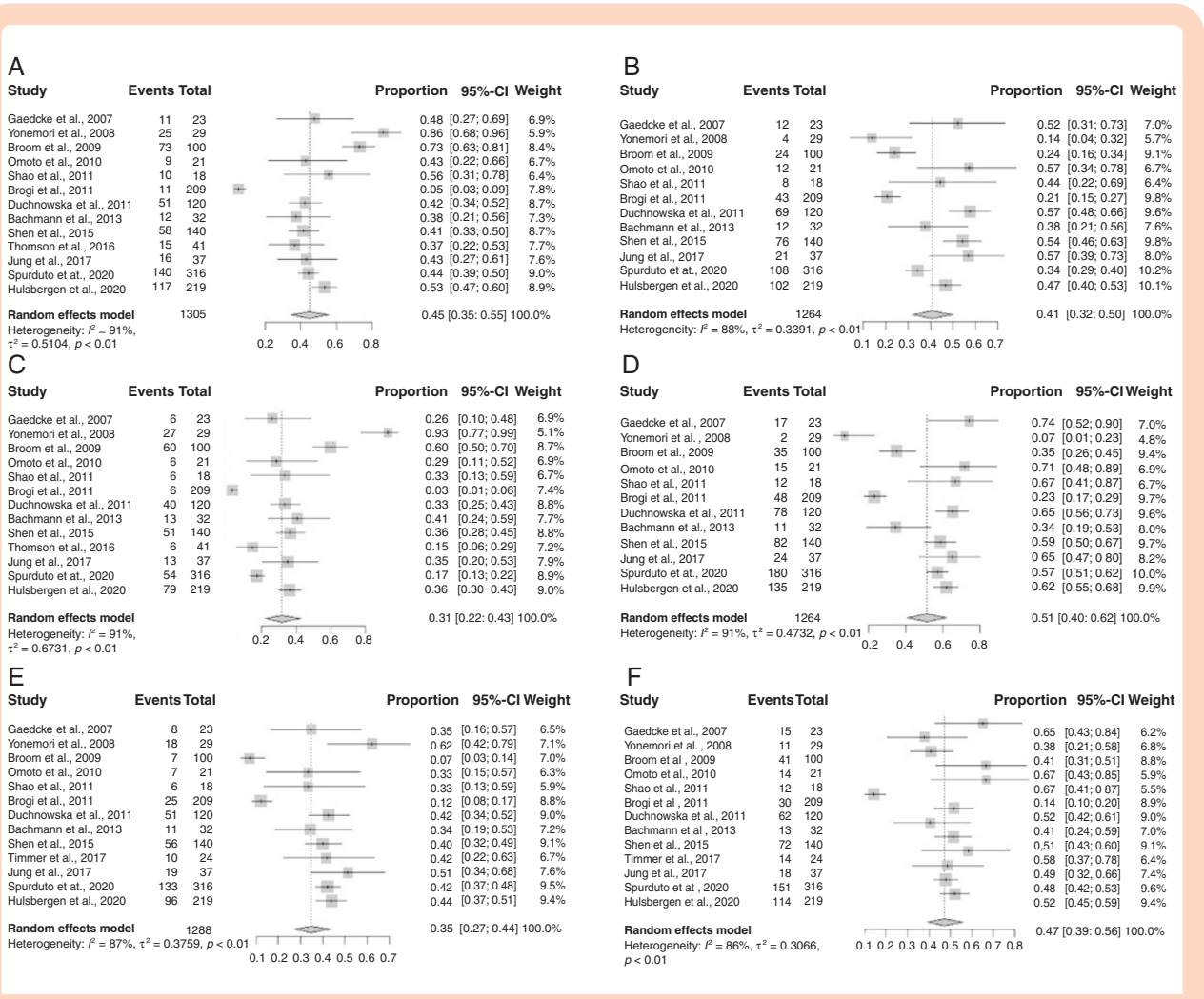

Figure 1. Forest plots of primary tumor receptor expression profiles for each receptor expression subtype: (A) ER+; (B) ER–; (C) PR+; (D) PR–; (E) HER2+; (F) HER2–. Squares indicate the proportions from individual studies and horizontal lines indicate the 95% confidence interval. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using the random effects model. Diamond indicates the pooled proportion with 95% confidence interval.

prognostic estimates. However, to-date, the influence of receptor expression conversion at the time of disease relapse or development of metastatic disease on survival remains controversial. For example, one large retrospective analysis failed to demonstrate any difference in survival in patients exhibiting receptor discordances,[35] while a prospective study demonstrated significant differences in survival in patients exhibiting receptor conversion.[36]The studies included in this BCBM meta-analysis also yielded conflicting results in this regard. Therefore, updated analysis and comparison of prognostic estimates specific to BCBM patients using primary tumor subtype (as is classically used) and tumor subtype of the brain metastasis, is clearly warranted.

The most common receptor discordances between primary tumors and BCBM were PR status (23%) and ER status (17%). The most common receptor conversions in BCBM compared to paired primary tumors were PR loss in 15% and ER loss in 11%. Whether these conversions occur as result of changes in tumor biology to a more malignant phenotype with increased potential for metastatic disease spread to the brain or from selective pressure of systemic therapy is controversial. Conversion to hormone receptor negative status has been associated with upregulation of growth factor expression, a more aggressive disease course, and reduced survival.[17] Moreover, genomic sequencing of small subsets of BCBM and paired primary tumor samples have revealed multiple shared mutations as well as *de novo* mutations, suggesting that BCBM arises from a minority of cells present in the original tumor.[37] On the other hand, selective pressure of hormonal therapies can also result in the development of dominant metastatic clones that lack the hormone receptors of the original primary tumor.[38] To some degree, both processes are likely at play. To provide further etiological insight, large-scale, massively-paralleled DNA sequencing studies are needed to screen the entire genomes of primary tumors, extracranial metastases, and intracranial metastases at initial diagnosis and throughout the disease course.

One of the key actionable findings from the present study was the gain of HER2 observed in approximately

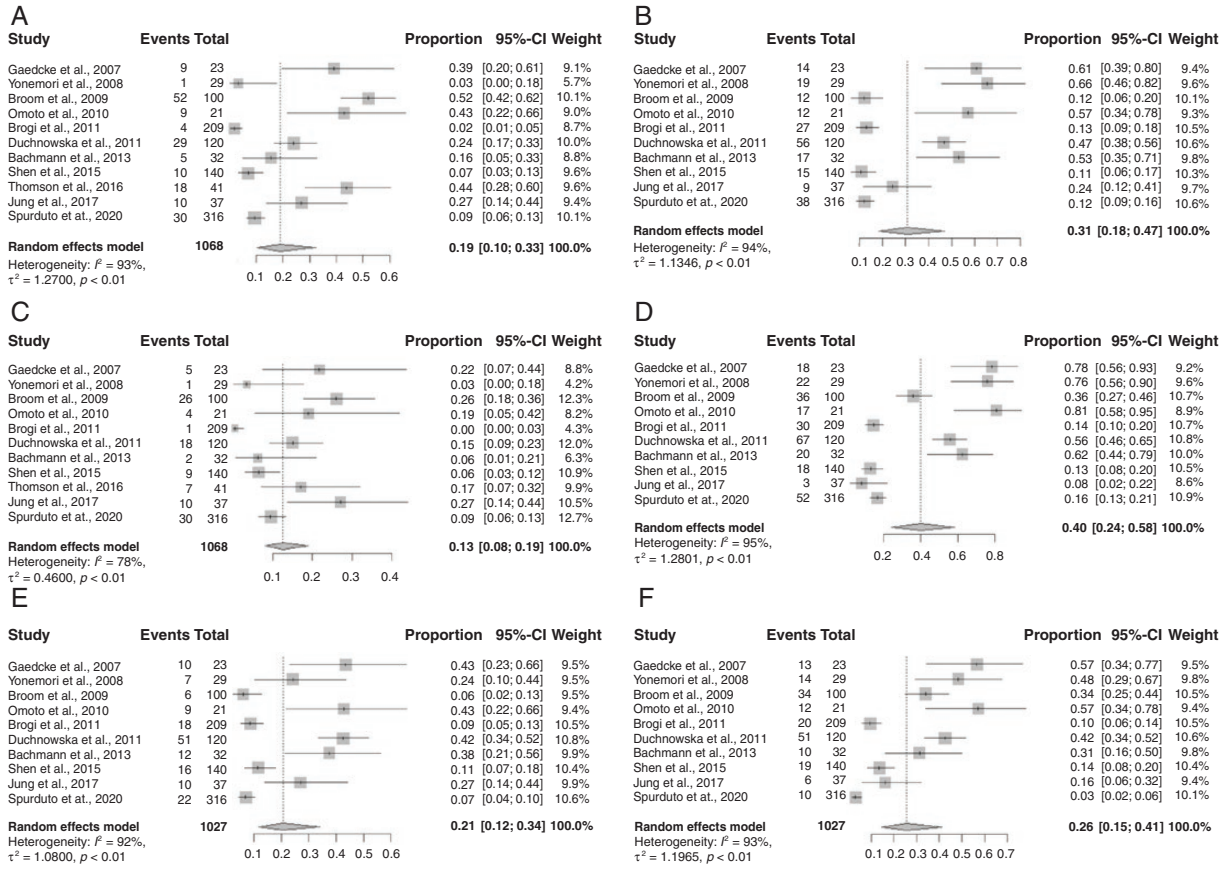

Figure 2. Forest plots of breast cancer brain metastasis tumor receptor expression profiles for each receptor expression subtype: (A) ER+; (B) ER–; (C) PR+; (D) PR–; (E) HER2+; (F) HER2–. Squares indicate the proportions from individual studies and horizontal lines indicate the 95% confidence interval. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using the random effects model. Diamond indicates the pooled proportion with 95% confidence interval.

10% of BCBM. This observation differs from the largest series of comparisons between primary tumors and extracranial metastases which have demonstrated discordance in ER and PR status in up to 40% of patients, but relatively unchanged levels of HER2 expression in metastatic sites, whether synchronous or metachronous.[5,39] Smaller series of extracranial metastases which focused on HER2 conversions verified by IHC and FISH have, in fact, revealed an opposite trend: HER2 loss in extracranial metastatic sites.[17] The effect of tumor discordance on the selection of systemic therapy is difficult to assess from retrospective studies. However, a prospective cohort of 40 patients with metastatic breast cancer who underwent biopsy of a metastatic site for the purpose of treatment modification demonstrated a 20% rate of change in the treatment plan, the most common of which was treatment with HER2 directed therapy or enrollment on a clinical trial with a novel anti-HER2 agent.[6] For HER2– breast cancer patients with brain metastasis whose BCBM-specific HER2 status is unestablished, HER2-targeted therapy would obviously not be selected. The data from this study suggest that perhaps up to 10% of these patients could have been found to be HER2+ and could potentially have benefitted from a change in the therapeutic regimen.[28] Given the increasing availability of HER-2 directed therapeutic options for patients with BCBM with intracranial response rates of 50–66%,[40–43] as well as the evidence of the importance of timing these agents with SRS,[44] tumor receptor expression analysis is recommended to be performed on all biopsied or resected BCBM, with specific inclusion of retesting HER2. Whether this practice change translates into an actual survival benefit could only be determined by a large randomized prospective trial.

A number of factors are hypothesized to correlate with receptor expression discordance, including age, tumor grade, number and location of sites of metastatic disease, the interval between primary tumor diagnosis and development of the intracranial metastatic disease, and use of systemic therapy. However, consistent observations of key factors correlated with tumor subtype switching in BCBM were not observed in any of the series in this meta-analysis. Yet, it is important to note the considerable variability in time to development of brain metastasis from primary diagnoses across series ranging from months to years, depending on the series. Therefore, the influence of timing and associated systemic therapy

Table 2. Estrogen, Progesterone, and HER2 Receptor Discordances and Gain/loss in Brain Metastases Compared to Paired Primary Tumors

Author and Year	*N*	Breast/Brain ER Discordance	BM ER Gain	BM ER Loss	Breast/Brain PR Discordance	BM PR Gain	BM PR Loss	Breast/Brain HER2 Discordance	BM HER2 Gain	BM HER2 Loss
Gaedcke et al., 2007[15]	23	6	2	4	5	2	3	3	2	1
Yonemori et al., 2008[16]	24	4	2	2	1	0	1	3	1	2
Broom et al., 2009[17]	100	11	5	6	22	NA	22	1	NA	1
Hoefnagel et al., 2010[18]	44	6	NA	NA	16	NA	NA	1	NA	NA
Omoto et al., 2010[19]	21	4	2	2	4	1	3	4	3	1
Shao et al., 2011[20]	18	1	0	1	8	4	4	1	1	0
Brogi et al., 2011[21]	209	6	2	4	8	4	4	2	NA	2
Duchnowska et al., 2012[22]	120	35	19	22	34	11	23	17	10	7
Bachmann et al., 2013[23]	32	7	0	7	9	0	9	4	3	1
Shen et al., 2015[24]	35	10	5	5	7	3	4	1	1	0
Thomson et al., 2016[25]	41	3	3	0	1	1	NA	6	5	1
Timmer et al., 2017[26]	24	9	1	8	6	0	6	7	6	1
Jung et al., 2018[27]	37	2	1	1	8	6	2	5	2	3
Sperduto et al., 2020[28]	316	68	30	38	82	30	52	32	22	10
Hulsbergen et al., 2020[29]	219	36	4	32	53	6	47	31	16	5

BM, brain metastasis; ER, estrogen receptor; HER2, human epidermal growth factor receptor type 2; NA—not available; PR, progesterone receptor.

interventions on subtype switching remains prone to retrospective selection bias. To date, no model has been developed with enough diagnostic accuracy to predict the BCBM immunophenotype based on patient characteristics and treatment details alone. Adding to this complexity, a small series of rapid autopsies on 10 patients with metastatic breast cancer, 5 of whom had brain metastases, not only demonstrated extensive heterogeneity between the primary breast tumor and metastatic sites but also among distinct metastatic sites when compared to each other.[45] Whole-exome sequencing studies have also supported the principle that extracranial metastatic sites may not be reliable genetic surrogates for brain metastasis.[7] Given the challenges in routinely obtaining intracranial tissue for patient management, the development of minimally invasive approaches of analyzing the biology and tumor immunophenotype are clearly needed. To this end, advanced imaging studies and radiomics research aimed at noninvasively predicting tumor immunophenotype are needed.[46,47]

Clinical trial enrollment criteria for brain metastasis patients cannot mandate re-biopsy of intracranial disease. Mandatory tumor biopsy, with an estimated 5–10% risk of procedure-related complication, for correlative studies and selection of novel cancer-directed therapies in clinical trials, was found to be acceptable to only 22% of patients, 1% of oncologists, and 1% of academic medical center IRBs in a recent survey.[48] However, the implications to clinical trial design and the reported outcomes of these studies can be severely affected without considering subtype switching. Brain metastasis trials are often powered to show small differences, and eligibility criteria are based on the tumor immunophenotype, generally determined from the primary tumor.[17] A 40% discordance rate between the primary tumor and BCBM, as observed in this meta-analysis, may lead to (1) underpowered studies given the unknown true BCBM immunophenotype in each of the study cohorts and/or (2) suboptimal treatment in the absence of hormone and HER2 receptor expression information from the BCBM. From this study, the most common conversions were PR loss (15%), ER loss (11%), and HER2 gain (9%), which may lead to the inclusion or exclusion of hormonal agents or HER2-directed therapies into tested therapeutic combinations. Taken together, one

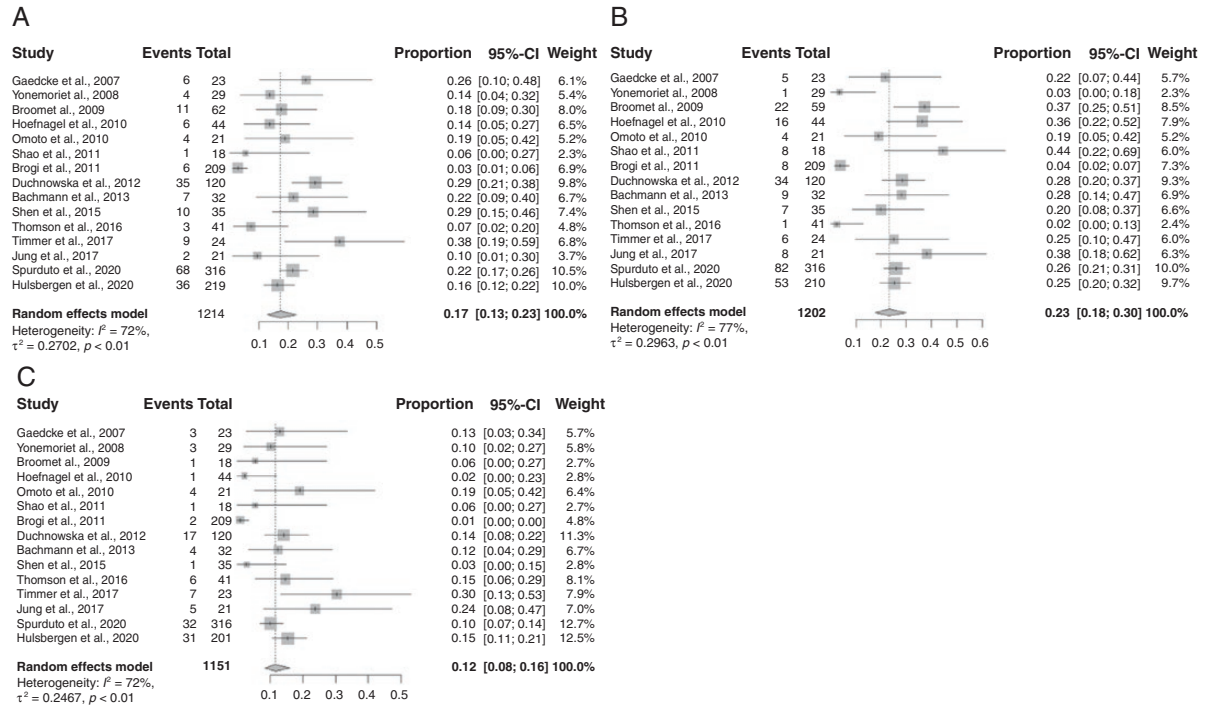

Figure 3. Forest plots of discordances for each receptor expression subtype in the brain metastasis compared to the primary tumor: (A) ER status; (B) PR status; (C) HER2 status. Squares indicate the proportions from individual studies and horizontal lines indicate the 95% confidence interval. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using the random effects model. Diamond indicates the pooled proportion with 95% confidence interval.

could consider biopsy in patients who are to be enrolled onto clinical trials where no local therapy (such as radiation therapy) would be offered, with a trial of targeted systemic therapy alone. Moreover, a biopsy can be considered for patients with multiply recurrent brain metastasis in the setting of targeted therapy to determine mechanisms of resistance or in those with discordant responses between extracranial and intracranial sites. Highly sensitive and targeted methods of evaluating the immunophenotype of cerebrospinal fluid cell-free DNA, such as next-generation sequencing and digital PCR,[49] should be integrated in future trials of BCBM to promote minimally invasive efforts at guiding precision therapy.

Although there was no publication bias detected in this meta-analysis, there is a potential for selection bias for higher proportions of metastatic-prone immunophenotypes in each of the individual series in this BCBM-specific meta-analysis. Patients undergo biopsy or resection of brain metastasis for a specific and finite number of reasons: (1) to confirm a diagnosis of cancer (ie, in patients with suspicion of another pathological abnormality or atypical presentation of disease), (2) to confirm a diagnosis of metastatic cancer spread (ie, presence of a solitary metastasis or prolonged interval from the primary tumor), or (3) to aid in tumor control or improve tumor-related symptomatology (ie, large brain metastasis or in those with tumor-related symptoms expected to benefit from resection).[5,6] This inherent selection bias may result in a cohort of BCBM at higher risk for subtype switching being reported in the literature, and consequently, in this meta-analysis. A comparison of patient, tumor, and treatment-related characteristics between patients who undergo biopsy or resection for BCBM and those diagnosed radiographically may provide more information on the impact of this selection bias.

There are several limitations to the present study. Given the study periods and retrospective nature of the data collection, it is possible that technical differences in tumor sample analysis or variations in staining methodology over time contributed to a reporting of "pseudo-discordance" between the primary tumor and BCBM.[17] However, given that intracranial metastasis, unlike commonly biopsied osseous sites, do not have to pre-treated with agents that may alter receptor expression rates,[50] we consider receptor conversion in BCBM to reflect true biological events. Although each study reported strict definitions for ER, PR, and HER2 status, these likely remain at risk for inter-laboratory differences (ie, initial diagnosis at one center and relapsed diagnosis at a different center).[51] Moreover, 3 different definitions of ER/PR status were considered "ER positive" for this study, as were the 3 different definitions for "HER2 positive." Each of these definitions is consistent with the clinical practice guidelines.[52] However, it is possible that the percent discordances would vary across studies based on these different positive thresholds,[53] especially when considered with the possibility of heterogeneity of receptor expression in the sampled tumors. Finally, known technical limitations with

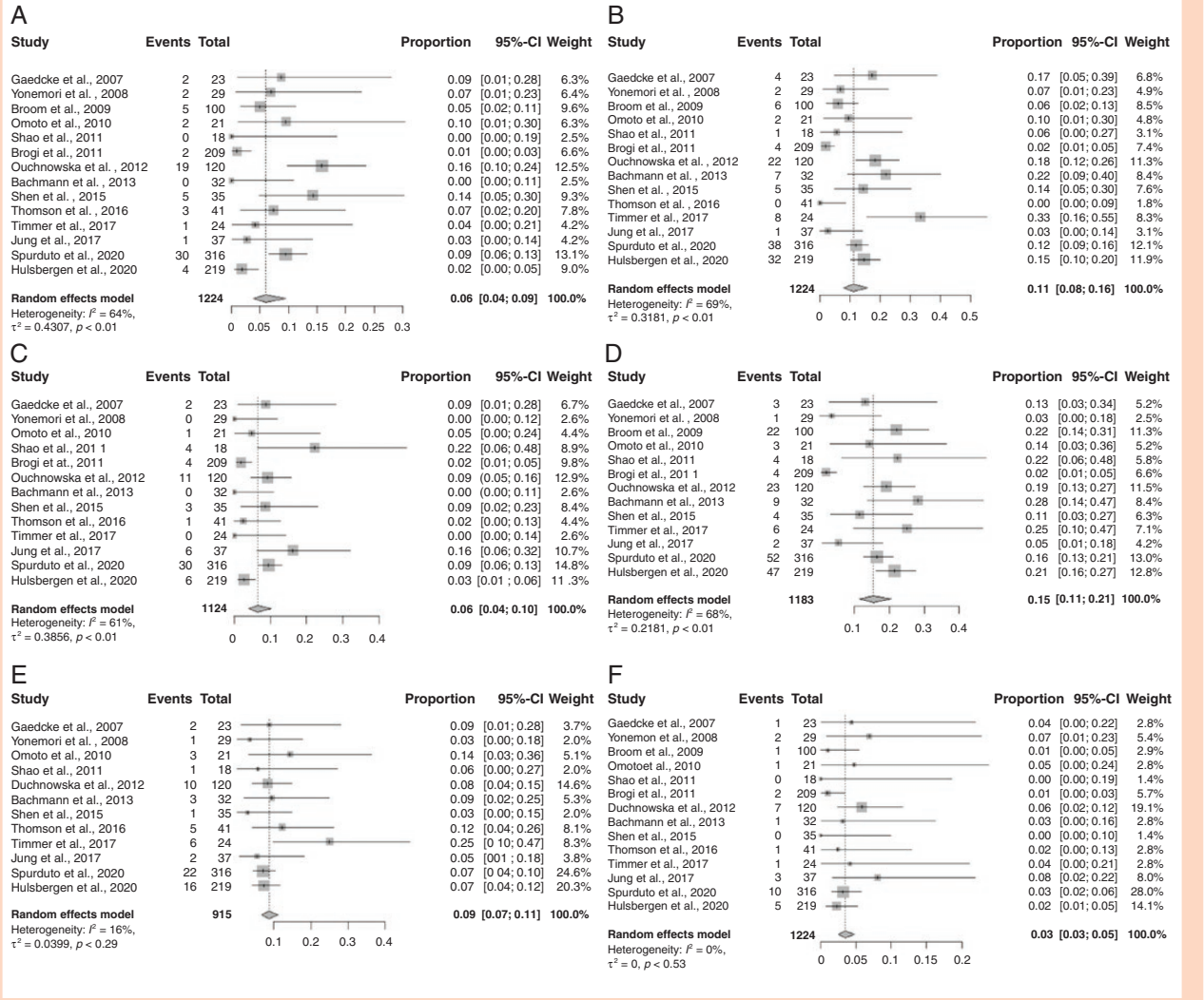

Figure 4. Forest plots of receptor conversions for each receptor expression subtype in the brain metastasis compared to the primary tumor: (A) ER gain; (B) ER loss; (C) PR gain; (D) PR loss; (E) HER2 gain; (F) HER2 loss. Squares indicate the proportions from individual studies and horizontal lines indicate the 95% confidence interval. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using the random effects model. Diamond indicates the pooled proportion with 95% confidence interval.

current testing methodologies (ie, different lengths of antigen retrieval and tissue fixation across institutions[54] or the subjectivity associated with the immunostaining approaches used across centers), are known errors in the determination of receptor expression status.[55] Together, these findings, in weighted summation, may lead to individual study variances, but given the methodology of the meta-analysis, the overall conclusions from this study would likely be reasonably consistent.

Conclusion

This meta-analysis of BCBM compared with paired primary tumors in over 1300 patients with metastatic breast cancer demonstrated a high-rate (40%) of receptor expression discordance. These findings could help to better refine our current prognostic models, treatment paradigms, clinical trial design, and stratification criteria. Most intriguingly, a proportion of patients may be eligible for an increasing selection of emerging CNS-active targeted therapies, while others may be able to discontinue ineffective therapies, and therefore be spared treatment-related toxicities. Further analysis of receptor conversion dynamics, studied in a prospective manner with sensitive and standardized profiling tests, is clearly needed in the modern era of precision medicine.

Supplementary Data

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

Keywords

breast cancer | discordance | estrogen receptor | HER2 | progesterone receptor

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