Title
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Permalink
https://escholarship.org/uc/item/7921n55c

Journal
Neuro-oncology advances, 3(1)

ISSN
2632-2498

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Publication Date
2021-01-16

DOI
10.1093/noajnl/vdab010

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

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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.
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 breast cancer brain metastasis compared to paired primary tumor immunophenotypes.

**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.

**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)\(^8\) 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.\(^9,10\) 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.\(^11,12\) 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

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**Methods**

**Selection of Articles**

This systematic review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria.\(^13\) 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 (i.e., lung, liver, or bone). The search strategy used for this report and the methodology for study inclusion is illustrated in Supplementary Figure 1.
results 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. 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. 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. 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. The most recent iteration defined 5 criteria for estimating prognosis, with subtype continuing to be an important variable for prognosis estimation. Incorporation of receptor expression status at the time of brain metastasis development may lead to further refinements of current
| 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   | 23   | >10% IHC               | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 11  | 12  | 6   | 17  | NA   | NA   | 14      | 30      | NA       | NA       | NA       |          |
|                        |      |                        |                      | Brain metastasis | 29  | 56  | 15  | 70  | NA   | NA   | 29      | 56      | NA       | NA       | NA       |          |
| Yonemori et al., 2008  | 24   | >10% IHC               | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 25  | 4   | 27  | 2   | NA   | NA   | 18      | 11      | NA       | NA       | NA       |          |
|                        |      |                        |                      | Brain metastasis | 1   | 19  | 1   | 22  | NA   | NA   | 7       | 14      | NA       | NA       | NA       |          |
| Broom et al., 2009     | 100  | >10% IHC               | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 73  | 24  | 60  | 35  | NA   | NA   | 7       | 41      | NA       | NA       | NA       |          |
|                        |      |                        |                      | Brain metastasis | 52  | 12  | 26  | 36  | NA   | NA   | 6       | 34      | NA       | NA       | NA       |          |
| Hoefnagel et al., 2010 | 44   | >10% IHC               | >6 HER2 copies/ tumor cell nucleus | Initial diagnosis | NA  | NA  | NA  | NA  | NA   | NA   | NA      | NA      | NA       | NA       | NA       |          |
|                        |      |                        |                      | Brain metastasis | NA  | NA  | NA  | NA  | NA   | NA   | NA      | NA      | NA       | NA       | NA       |          |
| Omoto et al., 2010     | 21   | >10% IHC               | >30% IHC             | Initial diagnosis | 9   | 12  | 6   | 15  | NA   | NA   | 7       | 14      | NA       | NA       | NA       |          |
|                        |      |                        |                      | Brain metastasis | 9   | 12  | 4   | 17  | NA   | NA   | 9       | 12      | NA       | NA       | NA       |          |
| Shao et al., 2011      | 18   | >1% of cells stained positive | >30% IHC             | Initial diagnosis | 10  | 8   | 6   | 12  | NA   | NA   | 6       | 12      | NA       | NA       | NA       | 6        |
|                        |      |                        |                      | Brain metastasis | 9   | 9   | 6   | 12  | NA   | NA   | 7       | 11      | NA       | NA       | NA       |          |
| Brogi et al., 2011     | 209  | >10% IHC               | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 11  | 43  | 6   | 48  | NA   | NA   | 25      | 30      | NA       | NA       | NA       |          |
|                        |      |                        |                      | Brain metastasis | 4   | 27  | 1   | 30  | NA   | NA   | 18      | 20      | NA       | NA       | NA       |          |
| Duchnowska et al., 2012| 120  | >1% of cells stained positive | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 51  | 69  | 40  | 78  | NA   | NA   | 51      | 62      | NA       | NA       | NA       |          |
|                        |      |                        |                      | Brain metastasis | 29  | 56  | 18  | 67  | NA   | NA   | 51      | 51      | NA       | NA       | NA       |          |
| Author                     | N  | ER/PR Positive Cutoff | HER2 Positive Cutoff | ER+  | ER−  | PR+  | PR−  | HR+  | HR−  | HER2+ | HER2− | HER2+/HER2− | HR+/HER2− |
|----------------------------|----|-----------------------|----------------------|------|------|------|------|------|------|-------|-------|-------------|------------|
| Bachmann et al., 2013      | 32 | >10% IHC              | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 12 | 12 | NA  | NA  | 11 | 13 | NA  | NA  | NA           | NA         |
|                           |    |                       | Brain metastasis     | 5   | 17  | 2   | 20  | NA  | NA  | 12 | 10 | NA           | NA         |
| Shen et al., 2015          | 140| >1% of cells stained positive | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 58 | 76 | 51  | 82  | NA  | NA  | 56 | 72 | 26  | 34  | 29 | 37 |
|                           |    |                       | Brain metastasis     | 10  | 15  | 9   | 18  | NA  | NA  | 16 | 19 | NA           | NA         |
| Thomson et al., 2016       | 41 | Allred score of >3    | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 15 | NA | 6    | NA  | NA  | NA  | NA  | NA | NA           | NA         |
|                           |    |                       | Brain metastasis     | 18  | NA  | 7   | NA  | NA  | NA  | NA  | NA | NA           | NA         |
| Timmer et al., 2017        | 24 | >1% of cells stained positive | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 10 | 14 | 10   | 14  | NA  | NA  | 10 | 14 | NA           | NA         |
|                           |    |                       | Brain metastasis     | 3   | 21  | 4   | 20  | NA  | NA  | 15 | 8  | NA           | NA         |
| Jung et al., 2018          | 37 | >1% of cells stained positive | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 16 | 21 | 13   | 24  | NA  | NA  | 19 | 18 | 3            | 13         |
|                           |    |                       | Brain metastasis     | 10  | 9   | 10  | 3   | NA  | NA  | 10 | 6  | NA           | NA         |
| Sperduto et al., 2020      | 316| >1% of cells stained positive | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 140| 108| 54   | 180 | 118 | 120 | 133 | 151 | 68 | 88           |
|                           |    |                       | Brain metastasis     | 30  | 38  | 30  | 52  | 40  | 38  | 22  | 10 | 84           | 74         |
| Hulsbergen et al., 2020    | 219| >10% IHC              | 3+ overexpression IHC or 2+ with FISH | Initial diagnosis | 117| 102| 79   | 135 | 114 | NA  | 96 | 114 | 53 | 61           |
|                           |    |                       | Brain metastasis     | NA  | NA  | NA  | NA  | NA  | NA  | NA  | NA | 40 | 47           | 64         |

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.
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, while a prospective study demonstrated significant differences in survival in patients exhibiting receptor conversion. 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 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. 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. 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. To some degree, both processes are likely.
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 metatstatic sites, whether synchronous or metachronous.5,38 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.37 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%,30−43 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...
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.

Whole-exome sequencing studies have also supported the principle that extracranial metastatic sites may not be reliable genetic surrogates for brain metastasis. 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.

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. 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. 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

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      | 23 | 6                          | 2          | 4          | 5                           | 2          | 3          | 3                              | 2            | 1            |
| Yonemori et al., 2008     | 24 | 4                          | 2          | 2          | 1                           | 0          | 1          | 3                              | 1            | 2            |
| Broom et al., 2009        | 100| 11                         | 5          | 6          | 22                          | NA         | 22         | 1                              | NA           | 1            |
| Hoefnagel et al., 2010    | 44 | 6                          | NA         | NA         | 16                          | NA         | NA         | 1                              | NA           | NA           |
| Omoto et al., 2010        | 21 | 4                          | 2          | 2          | 4                           | 1          | 3          | 4                              | 3            | 1            |
| Shao et al., 2011         | 18 | 1                          | 0          | 1          | 8                           | 4          | 4          | 1                              | 1            | 0            |
| Brogi et al., 2011        | 209| 6                          | 2          | 4          | 8                           | 4          | 4          | 2                              | NA           | 2            |
| Duchnowska et al., 2012   | 120| 35                         | 19         | 22         | 34                          | 11         | 23         | 17                             | 10           | 7            |
| Bachmann et al., 2013     | 32 | 7                          | 0          | 7          | 9                           | 0          | 9          | 4                              | 3            | 1            |
| Shen et al., 2015         | 35 | 10                         | 5          | 5          | 7                           | 3          | 4          | 1                              | 1            | 0            |
| Thomson et al., 2016      | 41 | 3                          | 3          | 0          | 1                           | 1          | NA         | 6                              | 5            | 1            |
| Timmer et al., 2017       | 24 | 9                          | 1          | 8          | 6                           | 0          | 6          | 7                              | 6            | 1            |
| Jung et al., 2018         | 37 | 2                          | 1          | 1          | 8                           | 6          | 2          | 5                              | 2            | 3            |
| Sperduto et al., 2020     | 316| 68                         | 30         | 38         | 82                          | 30         | 52         | 32                             | 22           | 10           |
| Hulsbergen et al., 2020   | 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.
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, 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). 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. However, given that intracranial metastasis, unlike commonly biopsied osseous sites, do not have to be treated with agents that may alter receptor expression rates, 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).

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. However, it is possible that the percent discordances would vary across studies based on these different positive thresholds, especially when considered with the possibility of heterogeneity of receptor expression in the sampled tumors. Finally, known technical limitations with

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.
### A: Meta-analysis of breast cancer receptor discordance

| Study               | Events | Proportion | 95% CI Weight |
|---------------------|--------|------------|---------------|
| Gaedcke et al., 2007 | 4      | 0.09       | [0.01; 0.28]  |
| Yamori et al., 2008  | 3      | 0.07       | [0.01; 0.29]  |
| Broom et al., 2009   | 1      | 0.05       | [0.02; 0.11]  |
| Orona et al., 2010   | 1      | 0.10       | [0.03; 0.30]  |
| Shao et al., 2011    | 0      | 0.00       | [0.00; 0.19]  |
| Brogi et al., 2011   | 1      | 0.11       | [0.02; 0.21]  |
| Ouchnouksa et al., 2012 | 120 | 0.16       | [0.10; 0.24]  |
| Bachmann et al., 2013 | 55  | 0.00       | [0.00; 0.11]  |
| Shen et al., 2015    | 3      | 0.14       | [0.02; 0.20]  |
| Thomson et al., 2016 | 1      | 0.04       | [0.00; 0.14]  |
| Timmer et al., 2017  | 1      | 0.03       | [0.00; 0.14]  |
| Jung et al., 2017    | 30      | 0.09       | [0.00; 0.13]  |
| Sparkbo et al., 2020 | 4      | 0.00       | [0.00; 0.05]  |
| Hulsbergen et al., 2020 | 219 | 0.02       | [0.00; 0.14]  |

### C: Meta-analysis of BCBM compared with paired primary tumors

| Study               | Events | Proportion | 95% CI Weight |
|---------------------|--------|------------|---------------|
| Gaedcke et al., 2007 | 4      | 0.09       | [0.01; 0.28]  |
| Yamori et al., 2008  | 3      | 0.07       | [0.01; 0.29]  |
| Omoto et al., 2010   | 1      | 0.05       | [0.02; 0.11]  |
| Shao et al., 2011    | 0      | 0.10       | [0.03; 0.30]  |
| Brogi et al., 2011   | 0      | 0.00       | [0.00; 0.19]  |
| Ouchnouksa et al., 2012 | 120 | 0.16       | [0.10; 0.24]  |
| Bachmann et al., 2013 | 55  | 0.00       | [0.00; 0.11]  |
| Shen et al., 2015    | 3      | 0.14       | [0.02; 0.20]  |
| Thomson et al., 2016 | 1      | 0.04       | [0.00; 0.14]  |
| Timmer et al., 2017  | 1      | 0.03       | [0.00; 0.14]  |
| Jung et al., 2017    | 30      | 0.09       | [0.00; 0.13]  |
| Sparkbo et al., 2020 | 4      | 0.00       | [0.00; 0.05]  |
| Hulsbergen et al., 2020 | 219 | 0.02       | [0.00; 0.14]  |

### Supplementary Data

Supplementary data are available at *Neuro-Oncology Advances* online.
Key words
breast cancer | discordance | estrogen receptor | HER2 | progesterone receptor

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments
This article was presented in Society for Neuro-Oncology Virtual Conference on Brain Metastases, August 14, 2020, held in association with the AANS/CNS Section on Tumors.

Conflict of interest statement. R.K.: Honorarium from Elsevier, Elekta AB, Accuray Inc, Novocure Inc. Research support from Novocure Inc. and Medtronic Inc. R.T.: None. M.R.: None. H.A.: None. M.W.M.: Consulting for Stryker. Y.O.: Advisory Board for Novocure Inc. and Abbvie Inc. Research support from Novocure Inc. and BMS. M.P.M.: Consulting for Karyopharm, Tocagen, Astra-Zeneca, Blue Earth Diagnostics, Celgene, Abbvie. Board of Directors: Oncoceutics.

Authorship Statement
Conception and Design: R.K., M.P.M. Analysis: R.K., R.T., M.R. Critical Review of Manuscript: R.K., R.T., M.R., H.A., M.W.M., Y.O., M.P.M.

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