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ABOUT COVER

Peer Reviewer of *World Journal of Clinical Oncology*, Arkadeep Dhali, MBBS, MPH, FRSPH, Academic Clinical Fellow, Academic Unit of Gastroenterology, Sheffield Teaching Hospitals, Sheffield, United Kingdom. arkadipdhali@gmail.com

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LETTER TO THE EDITOR

Bridging the gap: Predicting brain metastasis in breast cancer

Daniela Gonsalves, Raquel Ciérvide, Felipe Couñago

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Daniela Gonsalves, Felipe Couñago, Department of Radiation Oncology, GenesisCare Madrid, Madrid 28043, Spain

Daniela Gonsalves, Felipe Couñago, Facultad de Medicina Salud y Deporte, Universidad Europea de Madrid, Madrid 28670, Spain

Raquel Ciérvide, Department of Radiation Oncology, HM Hospitales, Madrid 28050, Spain

Corresponding author: Felipe Couñago, PhD, Director, Department of Radiation Oncology, GenesisCare Madrid, Modesto La Fuente, Madrid 28010, Spain. fcounago@gmail.com

Abstract

Chen *et al* explored clinicopathological features and prognostic factors, revealing advanced tumor stage, lung metastases, HER-2 overexpression, and triple-negative status as key contributors. Recent research connects astrocytes' role in brain metastasis with signaling pathways and the impact of Trastuzumab on HER-2 tumor survival. Factors such as positive HER2 status, lack of estrogen receptor expression, and liver metastasis are identified as additional risk factors. The routine use of magnetic resonance imaging, insights into gene mutations associated with metastasis, and the role of radiotherapy, including prophylaxis possibilities, is controversial in clinical practice. Understanding these risk factors in a multidisciplinary collaboration is precise for local treatments and targeted therapies, particularly for HER2+ tumors, impacting directly on longer survival.

Key Words: Brain metastases; Breast cancer; Clinicopathological features; High-risk factors

Core Tip: Based on an institutional analysis of risk factors to develop brain metastases in a setting of breast cancer patients, we have conducted a brief review of the literature on the known risk factors as well as the various strategies that could contribute to improving disease control and survival prospects for these patients.

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TO THE EDITOR

We have read with great interest the institutional analysis by Chen *et al*[1] entitled "Analysis of clinicopathological features and prognostic factors of breast cancer brain metastasis" and we would like to express our congratulations to the authors for their research, which is highly relevant to the oncology community.

The authors conducted an analysis of clinical and pathological characteristics in 68 breast cancer (BC) patients with brain metastases. These patients were compared in a 1:2 ratio with another 136 breast cancer patients who did not develop brain metastases, and this comparison was based on age and the site of disease onset. The study involved a retrospective examination, an evaluation of risk factors, and an identification of prognostic markers related to brain metastases.

They shared their institutional discoveries with the readers, determining that an advanced tumor stage at diagnosis (hazard ratio: 5.58, 95%CI: 1.99-15.68), the presence of lung metastasis (HR: 24.18, 95%CI: 6.40-91.43), HER-2 overexpression ($P < 0.001$), and the triple-negative status ($P < 0.005$) increased the likelihood of developing brain metastases. With a special interest in lung metastasis resulting as the only statistically significant risk factor in multivariate analysis associated with increasing the risk for breast cancer brain metastasis (BM) (BCBM) (HR: 24.18,95%CI: 6.40-91.43). Regarding survival time, they showed that the presence of neurological symptoms (HR: 1.923, 95%CI: 1.005-3.680), the occurrence of bone metastasis (HR: 2.011, 95%CI: 1.056-3.831), and molecular type independently contribute to influencing the prognosis of BM[1].

Although the blood-brain barrier acts as a significant protector against tumor cells, infections, and external agents, recent studies, such as the one by Priego *et al*[2], suggest that astrocytes, which constitute approximately 50% of the cells in the brain, participate in the development of brain metastases through signaling pathways such as STAT3, PI3K-Akt, and Her2-Her3. This involvement facilitates tumor cells in crossing the barrier and creating favorable microenvironments for their development[2,3].

Since the introduction of Trastuzumab in 1990, the survival of patients with HER-2 tumors has significantly increased, allowing them more time to develop brain metastasis[4].

Despite the relatively small sample size of the analysis, their results align with the existing body of literature on this subject since numerous prognostic factors have been identified as being linked to an increased risk of recurrence and developing BM, such as III-IV stage at initial diagnosis, presence of nodal infiltration, size of initial tumor and histological differentiation[5].

As highlighted by the authors, the risk and prognosis vary depending on the BC subtype. According to existing literature, patients who are HER2-positive and those with triple-negative BC, exhibit higher rates of brain metastases, approximately 20%-50% and 25%-46% respectively, will eventually develop brain metastasis[6].

Furthermore, positive HER2 status and lack of estrogen receptor expression (ER-), were identified as risk factors for the development of cerebral metastasis[7].

Some other risk factors for the development of BM have been identified, such as liver metastasis[8].

Although authors didn't find a statistical association with age and the risk of developing brain metastasis, literature remains controversial regarding this issue[9].

Another clinical factor contributing to the development of brain metastases is the resistance to endocrine therapy observed in breast cancer patients with ER+. It is recognized that, initially, fifteen to twenty percent of ER+ breast cancer patients exhibit resistance, and an additional 30%-40% develop resistance to endocrine treatment over time[10]. Endocrine resistance was not evaluated as a factor in this analysis. However, it could certainly be interesting to explore in future studies.

A recent German multicenter registry of brain metastases of breast cancer published in 2023, analyzed a total of 2889 patients, showing long-term survival factors in BCBM such as performance status, younger age, HER2-positive subtype, oligo BM and visceral metastases[11].

Hence, individuals displaying these clinical features might be more suitable for prolonged local and systemic treatments. Remarkably recognizing factors linked to prolonged survival holds significance in enhancing treatment strategies.

The authors also suggest that early diagnosis and early treatment could potentially enhance the prognosis of high-risk patients. This alignment with the literature stems from the observation that early detection of BM (within the first 6 months of metastatic disease diagnosis) and the presence of asymptomatic BM are linked to longer overall survival[12].

However, there is still controversy in routine use of magnetic resonance imaging in the follow up of breast patients. European Association of Neuro-Oncology (EANO) guidelines indicate that screening for BM should be considered for metastatic BC patients with HER2-positive and triple-negative breast cancer with a level IV (EANO) and IV B (European Society for Medical Oncology)[13]. Although this approach would increase the detection rate of asymptomatic BM, practical implementation in routine follow-up is constrained by health economic considerations.

In addition, and regarding early diagnosis, recent reviews have identified 268 genes in 431 evaluated studies, with 8% of these mutations being associated with the onset of metastasis. Surprisingly, 68% of these genes are targets for future drugs[14]. An in line with this article, a meta-analysis published in 2023 identified six genes exhibiting high prevalence of mutations in BM, due to their potential role in the cerebral metastatic process and resistance to first-line anticancer drugs: ESR1, ERBB2, EGFR, PTEN, BRCA2, and NOTCH1[15].

Regarding the role of radiotherapy in brain metastases, its efficacy is not in question due to the scientific evidence in its favor. However, there is a possibility of extending its role to prophylaxis, similar to what is done in small cell lung carcinoma. Hashem *et al*[16] randomly assigned 62 high-risk breast cancer patients to prophylactic cranial irradiation (PCI) with 24 *Gy* in 10 fractions over 2 wk, comparing them with an observation group. Neurocognitive function (NCF) was assessed at baseline and every 6 months using the Mini-Mental State Exam. No patient in the PCI group developed

brain metastases, compared to 6.4% in the non-prophylaxis group. NCF was similar in both arms[17]. Canney *et al*[18] also published a prospective randomized clinical trial testing the role of prophylactic cranial radiotherapy based on 30 *Gy* in 10 fractions in metastatic breast cancer patients treated with Trastuzumab. Results showed that the cumulative incidence of BM at 2 years in the PCI arm was 21%, compared to 32.4% in the non-PCI arm. However, no significant differences in NCF were reported.

No less important is the role of the multidisciplinary collaboration of different specialists, better and quicker access to precise local treatments like cerebral radiosurgery compared to whole-brain radiotherapy, as well as more equitable access to the latest targeted therapies, especially in patients with HER2+ tumors, would likely have a favorable impact on their prognosis.

To conclude, all efforts that enable to understand the risk factors that help predict the occurrence of brain metastases, as well as to identify which patients with metastases survive longer, will have a direct impact on personalizing and better tailoring treatments for each patient.

FOOTNOTES

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Country/Territory of origin: Spain

ORCID number: Raquel Ciérvide 0000-0003-0130-878X; Felipe Couñago 0000-0001-7233-0234.

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