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Peer Reviewer of *World Journal of Clinical Oncology*, Serghei Covantsev, BSc, MD, Doctor, Research Scientist, General Surgeon, Surgical Oncologist, Plastic Surgeon, Department of Research and Clinical Development & Department of Emergency Surgery №76, Botkin Hospital, Moscow 125284, Russia kovantsev.s.d@gmail.com

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EDITORIAL

Navigating breast cancer brain metastasis: Risk factors, prognostic indicators, and treatment perspectives

Jayalingappa Karthik, Amit Sehrawat, Mayank Kapoor, Deepak Sundriyal

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Jayalingappa Karthik, Amit Sehrawat, Mayank Kapoor, Deepak Sundriyal, Department of Medical Oncology Haematology, All India Institute of Medical Sciences Rishikesh, Rishikesh 249203, Uttarakhand, India

Corresponding author: Amit Sehrawat, MBBS, MD, DrNB, Associate Professor, Department of Medical Oncology Haematology, All India Institute of Medical Sciences Rishikesh, Virbhadra Road, Rishikesh 249203, India. dramitsehrawat@gmail.com

Abstract

In this editorial, we comment on the article by Chen *et al*. We specifically focus on the risk factors, prognostic factors, and management of brain metastasis (BM) in breast cancer (BC). BC is the second most common cancer to have BM after lung cancer. Independent risk factors for BM in BC are: HER-2 positive BC, triple-negative BC, and germline *BRCA* mutation. Other factors associated with BM are lung metastasis, age less than 40 years, and African and American ancestry. Even though risk factors associated with BM in BC are elucidated, there is a lack of data on predictive models for BM in BC. Few studies have been made to formulate predictive models or nomograms to address this issue, where age, grade of tumor, HER-2 receptor status, and number of metastatic sites (1 *vs* > 1) were predictive of BM in metastatic BC. However, none have been used in clinical practice. National Comprehensive Cancer Network recommends screening of BM in advanced BC only when the patient is symptomatic or suspicious of central nervous system symptoms; routine screening for BM in BC is not recommended in the guidelines. BM decreases the quality of life and will have a significant psychological impact. Further studies are required for designing validated nomograms or predictive models for BM in BC; these models can be used in the future to develop treatment approaches to prevent BM, which improves the quality of life and overall survival.

Key Words: Breast cancer; Brain metastasis; HER2 positive; Metastatic breast cancer; Risk factors, Predictive models

Core Tip: Breast cancer brain metastasis management faces many challenges. Key risk factors include HER-2 positivity, triple-negative subtype, and germline *BRCA* mutation. Limited predictive models emphasize the need for validated nomograms. Current guidelines recommend screening when symptomatic. Chen *et al* highlight HER-2 and triple-negative associations, impacting treatment strategies. Proactive research is crucial for preventive strategies, blood-brain barrier-penetrating therapies, and validated predictive models.

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INTRODUCTION

Breast cancer (BC) is one of the three most common cancers in women, apart from lung cancer and colorectal cancer. BC accounts for 30% of all cancer in women and is the leading cause of death in the age group between 20 to 59 years. At the same time, survival of BC is about 90%[1]. BC is the second most common cancer to metastasize to the brain after lung cancer; about 30%-50% of metastatic BC (MBC) develop brain metastasis (BM)[2]. The incidence of breast cancer brain metastasis (BCBM) has increased in recent times; reasons could be due to the increased survival rate of MBCs, the inability of some drugs to cross the brain barrier, the use of targeted agents to control systemic disease[3] and the use of newer imaging techniques to diagnose the central nervous system (CNS) metastasis.

BM significantly reduces the quality of life and overall survival (OS) and poses significant challenges in the treatment. Median OS of BCBM ranges around 4.5 to 13.8 months. Factors influencing the survival include patient age, Karnofsky performance status > 70, single BM, size of BM < 5 cm, and control of extracranial disease.

Considering the challenges in the management, poor quality of life, and poor OS with BCBM, there is a need for an hour to formulate a nomogram or identify the risk factors associated with BM and prevention of it. Future research should focus on systemic therapy, which can penetrate the blood-brain barrier and target metastatic lesions. In our discussion, we focus on elucidating risk factors associated with BM and prospects for managing BM in BC.

In the recent issue of *World Journal of Clinical Oncology*, Chen *et al*[4] published a retrospective analysis of clinicopathological features and prognostic factors of BCBM. The study involved 68 patients with BCBM, treated between 2000 and 2022; these BCBM patients were matched with BC patients without BM in the ratio of 1:2. Cohort consisted of 19.1% of luminal A subtype, 32.2% of luminal B subtype, 20.6% of HER-2 overexpressing subtype, 20.6% of triple-negative BC (TNBC) subtype. The median age of diagnosis of BC was 47 years. The median age from diagnosis of BM in BCBM was 50.5 years. The incidence of BM in the study population was 4.42%, and the prevalence of BM at the time of diagnosis was 0.089%. The cumulative incidence of BM in stage IV was 10.3%. The median time from diagnosis of BC to development of BM was 33.5 months (0-181). In multivariate analysis, stage III/IV tumor at initial diagnosis [hazard ratio (HR): 5.58, 95% confidence interval (CI): 1.99-15.68], lung metastasis (HR: 24.18, 95%CI: 6.40-91.43), and HER2-overexpressing and TNBC were significantly associated with BM and were more prone for BM in BCBM. The presence or absence of bone metastasis, molecular type, and presence or absence of neurological symptoms were significantly associated with the prognosis of patients with BCBM. These results were consistent with previous population-based studies regarding the incidence of BM in BC patients (5.1%) and molecular subtype association with BM in BC patients. In contrast, the cumulative incidence of BM after diagnosis of MBC was higher in previous studies A retrospective study by Darlix *et al* [5]. involving 16703 MBC from French epidemiological strategy and medical economics reported that 7.2% of the study population had BM at the time of diagnosis of MBC, and 24.6% of the study population developed BM during follow-up, median time 17 months for BM. Differences in these studies can be attributed to smaller sample size and inclusion of earlier stages of BC in Chen *et al*[4]. When considered among the early-stage BC, the incidence of BC was similar to previous studies. A study by Pestalozzi *et al*[6], aimed at identifying BC patients at risk of BM in the trial of an international BC study group, showed 10-year cumulative BM incidence was 5.2% and significantly associated with lymph node (> 4, 2.2%; $P < 0.01$), HER-2 expression (2.7%, $P < 0.01$), large tumor size (1.7%, $P < 0.01$) and ER-negative tumors (2.3%, $P < 0.01$) in univariate analysis. Similar observations were made in Chen *et al*[4] study.

The study highlighted the HER-2 overexpression in BCBM. In the study population, HER-2 overexpression was seen in 20.6%, which was similar to other previous studies, and it was statistically significant with BCBM in both univariate and multivariate analysis. HER-2 is an oncogene that encodes 185-kDa transmembrane glycoprotein receptor with intracellular tyrosine kinase activity and belongs to the epidermal growth factor receptors family. These receptors are involved in intracellular signal transduction pathways such as PI3K/Akt, Ras/MEK/ERK, and JAK/STAT, which control epithelial cell growth, angiogenesis, migration differentiation, and survival. In humans, HER-2 overexpression is seen in 25% of BCs; overexpression is mainly attributed to HER-2 gene amplification and HER-2 signaling pathways. HER-2 overexpression association with CNS metastasis in BC has been shown in both pre- and post-trastuzumab era, indicating biological predisposition of HER-2 positive BC for BM and increased survival of HER-2 positive BC with the use of trastuzumab. The study by Chen *et al*[4] was unique in that it included cohorts from the pre-trastuzumab and post-trastuzumab eras in China. Among 68 patients, 52.9% received HER-2 targeted therapy, and the median OS of the trastuzumab arm was 17 months, which was similar to the reported median OS in previous studies in the range of 13.1-

17.5 months[7-9] and the highest for capecitabine + tyrosine kinase inhibitor (TKI) arm of 54 months. However, the study did not highlight the secondary prevention of BM in patients receiving HER-2 targeted therapy without BM. Western studies have shown a longer median time to BCBM with trastuzumab (15 months *vs* 10 months, $P = 0.035$) and capecitabine + TKI[10,11]. These findings could have helped us understand the disease biology and design clinical trials to prevent BM.

TNBC accounts for 15% to 20 % of all BC diagnosed worldwide, more commonly seen in young age and older African American women[12-14]. TNBC is a highly aggressive variant lacking ER/PR and HER-2 expression. Due to the aggressive nature of the disease, distant metastasis is seen in the early stage of TNBC. Almost one-third of patients with TNBC will develop BM[15]. BM occurs early in the course of the disease compared to HR-positive and HER-2-positive BC [5,16]. Even early-stage BC treated with curative intent has distant recurrence within five years and is more prone to metastasis to the brain, liver, lungs, and other organs. In a retrospective study of 2448 patients involving stage I to stage III BC, the cumulative incidence rate of developing BM as the first site of recurrence at five years was 2.8%, 4.6%, and 9.6% among patients with stage I, II, and III disease, respectively ($P < 0.0001$)[17]. Similarly, the incidence of BM in TNBC at the time of diagnosis of MBC is around 14%. Recent studies have shown that the cumulative incidence rate of BM in TNBC after diagnosis of MBC continued to increase over the period[5,18,19]. Similar observations were made by Chen *et al*[4], where TNBC accounted for 20.6% with an incidence rate of 20%-30% and was significantly associated with BM in multivariate analysis[HR: 4.34 (1.55-12.11), $P = 0.005$] and had a shorter survival time of 8 months. Management of TNBC with BM poses a unique challenge as targeted therapy and hormonal therapy, which are used in HER2 and HR-positive subtypes, are ineffective, and only a few systemic chemotherapy agents can penetrate the intact blood-brain barrier. Considering the aggressive nature of the disease and challenges in the management of BM, OS, and prognosis are poor for TNBC when compared to HR-positive and HER-2-positive tumors[18,19].

Data are lacking in the secondary prevention of BM in MBC and routine screening for BM in MBC. As BM is associated with poor survival and poor quality of life, identifying the early metastatic brain lesion before the appearance of symptoms and managing it with its local therapy would improve the quality of life and survival; this approach showed significant differences in small cell lung cancer (SCLC) of the lung.

Data still need to be included, and only a few studies have been done in this regard to address occult BM. A study involving 155 screening imaging studies from four clinical trials conducted between 1998 and 2001 showed occult BM in 14.8% of patients. These clinical trials excluded established BM. Survival among patients with occult BM and symptomatic BM were similar. Clinical trials are ongoing to evaluate the role of periodic magnetic resonance imaging brain screening and its benefit in terms of quality of life and survival outcomes (NCT03881605, NCT04030507, NCT03617341).

The success of prophylactic cranial radiation (PCI) in SCLC, which prevented BM, was partly due to the high incidence of BM with no PCI intervention in SCLC (59%-67%).

However, in metastatic breast lesions, overall incidence is about 30%-50%, lowest for ER/PR subtype and highest for HER-2 positive and TNBC. Data are lacking on the benefits of PCI in MBC. Murine models and extrapolating these to computational models have shown promising results of the PCI role[20,21]. With recent advances in hippocampal sparing whole brain radiation therapy, which has shown a lesser incidence of neuropsychological adverse events, a newer approach is needed to prevent and treat HER-2/TNBC.

One such approach is identifying the high-risk individuals who will benefit from PCI in MBC. Predictive models are needed to determine the patients with MBC who will develop BM and benefit from PCI. Such an approach to formulating predictive models for identifying BM was used by Graesslin *et al*[22] in 2011, who made a nomogram to predict the risk of BM in MBC. The study involved 2136 patients of MBC, out of which 362 patients developed subsequent BM. In multivariate analysis, age, grade of the tumor, ER/PR negative and HER-2 positive status, a number of metastatic sites (1 *vs* > 1), and short disease-free survival were all independent factors associated with BM in MBC. Race, primary tumor size, and nodal stage were not significantly associated with BM in MBC. A nomogram was made using this data, and to test the accuracy and performance of the model, discrimination and calibration metrics were quantified. In the external validation set, discrimination was good, with an area under the curve (AUC) of 0.74 (95%CI: 0.70-0.79), and the calibration of the set showed no significant differences between the probabilities of observed and predicted probabilities of BM ($P = 1$). Genre *et al*[23] validated this predictive model by retrospective analysis and the study included 70 MBC patients. Multivariate analysis showed that risk factors associated with BM in MBC were HER-2+ status, TNBC subtype, and number of extracranial metastases. Validation cohort characteristics were similar in age, histological type, immunohistochemical subtypes, and number of brain metastases. Quantified discrimination and calibration were comparable with Graesslin's nomogram model [AUC of 0.695 (95%CI: 0.61-0.77) *vs* AUC of 0.74 (95%CI: 0.70-0.79)][22]. Such predictive models are required in the future to identify the high-risk individuals who are likely to develop BM and design the trail to evaluate the role of PCI or chemotherapy/targeted therapy/immunotherapy. Temozolomide has shown promising results in the secondary prevention of BM in the metastatic breast in HER-2 positive subtype cancer in the phase I trial, and further evaluation is ongoing in phase II[24-26].

CONCLUSION

Management of BCBM is a growing challenge; future research is needed to formulate predictive models for BM in BC, overcome the difficulties of drug transport through the blood-brain barrier, and early intervention of asymptomatic BM. Research focusing on these topics would significantly reduce BM's burden and improve survival and quality of life in BCBM.

FOOTNOTES

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Country of origin: India

ORCID number: Amit Sehrawat 0000-0001-7100-8999; Mayank Kapoor 0000-0002-7764-0044; Deepak Sundriyal 0000-0002-6378-7694.

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