Brain Metastasis is Associated with Tumor Size, Nodal Status, and c-erbB-2 Expression in Invasive Breast Carcinoma

A metástase cerebral está associada com tamanho tumoral, status nodal e expressão de c-erbB-2 no carcinoma invasivo de mama

Eduardo Cambruzzi[1,2,3,4,5] Natália Brandelli Zandoná[3] José Nathan Andrade Müller da Silva[3] Gabriella Bezerra Cortês Nascimento[3] Mateus Scarabelot Medeiros[3]

[1] Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil
[2] Departament of Pathology, Hospital Santa Rita, Complexo Hospitalar Santa Casa, Porto Alegre, RS, Brazil
[3] Grupo Hospitalar Conceição, Porto Alegre, RS, Brazil
[4] Instituto de Cardiologia, Fundação Universitária de Cardiologia, Porto Alegre, RS, Brazil
[5] Universidade do Vale do Rio dos Sino – UNISINOS, São Leopoldo, RS, Brasil

Address for correspondence Eduardo Cambruzzi, PhD, Departament of Pathology, Hospital Santa Rita, Complexo Hospitalar Santa Casa de Porto Alegre, Rua Sarmento Leite 187, 2° andar, 90050-170, Porto Alegre, RS, Brazil (e-mail: dudacambruzzi@yahoo.com.br).

Arq Bras Neurocir 2023;42(2):e121–e126.

Abstract

Introduction According to the World Health Organization (WHO) classification, invasive breast carcinoma (IBC) of no special type (IBC-NST) is the second most common primary site of central nervous system metastases, affecting 15% to 30% of patients. Brain metastasis originating from IBC is associated with patient age, tumor size, and axillary lymph node status. Loss of expression of hormone receptors and c-erbB-2 amplification are frequent findings in patients who develop brain metastasis. Radiological studies of the central nervous system are carried out only in patients presenting with neurological signs or symptoms during the clinical follow-up.

Objective To evaluate the associations of clinical and pathological findings with brain metastasis in breast cancer.

Materials and Methods The sample comprised 73 patients with breast cancer who underwent mastectomy with lymph node resection. The following variables were evaluated: tumor size, histological grade, nodal state, expression of estrogen and progesterone receptors and c-erbB-2, and presence of brain metastasis.

Results The histopathological findings associated with brain metastasis in patients with IBC were tumor size ($p = 0.03$), presence of nodal metastasis ($p = 0.045$), and c-erbB-2 expression ($p = 0.012$).

Conclusion The assessment of specific pathological findings in breast carcinoma can help identify risk factors and/or clinical parameters associated with the development of brain metastasis.

Keywords
- central nervous system
- carcinoma
- breast
- tumor metastasis
- pathology
- prognosis

received
July 30, 2022
accepted
January 24, 2023

DOI https://doi.org/10.1055/s-0043-1769779.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Introdução O carcinoma invasivo de mama (CIM) de tipo não especial, segundo a classificação da Organização Mundial de Saúde, é o segundo sítio primário mais comum de metástases do sistema nervoso central, afetando de 15% a 30% das pacientes. A metástase cerebral originada de CIM está associada à idade do paciente, tamanho do tumor, estado nodal axilar e perfil imuno-histoquímico do local primário. A perda da expressão dos receptores hormonais e a amplificação do c-erbB-2 são achados frequentes em pacientes que desenvolvem metástase cerebral. Estudos radiológicos do sistema nervoso central são realizados apenas em pacientes que apresentam sinais ou sintomas neurológicos durante o acompanhamento clínico.

Objetivo Este estudo teve como objetivo avaliar associações de achados clínicos e patológicos com metástase cerebral em IBC. Método: A amostra foi composta por 73 pacientes com CIM submetidas à mastectomia e ressecção nodal axilar. Foram avaliadas as seguintes variáveis: tamanho do tumor, grau histológico, estado nodal, expressão de receptores de estrogênio e progesterona e c-erbB-2 e presença de metástase cerebral tratada por ressecção cirúrgica.

Resultados Os achados histopatológicos associados à metástase cerebral em pacientes com IBC foram tamanho do tumor ($p = 0,03$), presença de metástase nodal ($p = 0,045$) e expressão de c-erbB-2 ($p = 0,012$).

Conclusão A avaliação de achados patológicos específicos no IBC pode ajudar a identificar fatores de risco e/ou parâmetros clínicos associados ao desenvolvimento de metástase cerebral.

Palavras-chave

- sistema nervoso central
- carcinoma
- seios
- metástase tumoral
- patologia
- prognóstico

Introduction

According to the World Health Organization (WHO) classification, invasive breast carcinoma (IBC) of no special type (IBC-NST) is a heterogeneous malignant neoplasm characterized by extensive histopathological, genetic, and immunohistochemical alterations.[1–4] It represents the second most common primary site of central nervous system (CNS) metastases, affecting 15% to 30% of the patients. The occurrence of brain metastasis in patients with IBC is associated with age, tumor size, axillary lymph node status, and immunohistochemical profile of the primary tumor site.[2,4–6] Loss of expression of hormone receptors and amplification of human epidermal growth factor receptor-2 (HER-2) are frequent findings in patients who develop brain metastasis. Radiological examination of the CNS is carried out only in patients presenting with neurological signs or symptoms during the clinical follow-up.[1,3,4,6,7]

In the present study, the authors investigated anatomopathological variables that could be associated to the development of CNS metastasis in patients with IBC-NST.

Materials and Methods

The present cross-sectional study analyzed 73 cases of IBC-NST registered at the Pathology Laboratory of Hospital Nossa Senhora da Conceição, in the city of Porto Alegre, Southern Brazil, between May 2003 and April 2020. Specimens from total mastectomy with axillary lymph node resection were fixed in 10% buffered formalin, embedded in paraffin, stained with hematoxylin and eosin, and analyzed for estrogen receptor, progesterone receptor, c-erbB-2 (HER2), and Ki-67 expression using an automated immunohistochemical method (Ventana HE 600 System, Roche Diagnostics, Basel, Switzerland). The WHO histopathological criteria for IBC were used for tumor diagnosis and to determine the histological grades. The cases of IBC were graded according to the Nottingham classification system, which categorizes tumors into three stages of differentiation (1 to 3) according to patterns of tubule formation, nuclear pleomorphism, and mitotic index. The tumor-node-metastasis (TNM) system of tumor classification was used for clinical and pathological staging.

All patients with IBC and brain metastasis underwent surgical resection or tissue biopsy due to neurological signs and/or deficits. Patients with brain metastasis had positive immunoexpression for cytokeratin 7 (CK7), epithelial membrane antigen (EMA), mammaglobin, gross cystic disease fluid protein 15 (GCDFP-15), and T-cell specific transcription factor GATA-3, as well as negative immunoexpression for cytokeratin 20 (CK20), intestinal transcription factor CDX-2, thyroid transcription factor 1 (TTF-1), napsin, paired box transcription factor 8 (PAX-8), renal cell carcinoma-associated antigen (RCC), and carbohydrate antigen 19-9 (CA19-9).

The exclusion criteria were as follows: men with IBC, history of breast cancer, patients with breast cancer who had only undergone biopsy or breast sectorectomy, patients without immunohistochemical evaluation of the primary site or without histopathological evaluation of the metastatic brain lesion, other histological types of breast neoplasms, brain metastases associated with other primary sites, previous therapies for the current breast carcinoma (chemotherapy,

radiotherapy and/or hormonal therapy), and patients without clinical follow-up for at least 24 months.

The analyzed variables were patient age, tumor size (primary lesion), tumor grade, multifocality/multicentricity (primary lesion), presence of nodal or brain metastases, presence of intraductal lesions, expression for estrogen receptors, progesterone receptors, c-erbB-2, and Ki-67 (primary lesion), topography of brain metastases, size of and number of metastatic brain lesions, disease-free survival time, and clinical outcome (death, progression, or tumor recurrence in the breast parenchyma).

Quantitative variables were expressed as mean and standard deviation or median and interquartile range values. Categorical variables were reported as absolute and relative frequencies. The Student *t*-test was used to compare means between groups. The Mann–Whitney test was used for variables with skewed distribution. Comparisons regarding proportions were performed using the Pearson Chi-squared test and the Fisher exact test. Poisson regression was used to control confounding factors. Variables significant at $p < 0.2$ in the bivariate model were included in the multivariate model. The significance level was set at $p \leq 0.05$. The analyses were performed using the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, US) software, version 20.0.

Results

The mean age of the 73 patients in the sample was of 50.42 (± 7.565) years. The mean tumor size was of 2.48 (± 1.224) cm, with a mean of 18.6 (± 3.257) lymph nodes isolated in each specimen. Patients in the group without brain metastasis ($n = 51$) were predominantly classified as T1 (n = 20; 39.2%) N1 (n = 16; 50%) in the TNM staging system. Patients that developed brain metastasis ($n = 22$) were predominantly classified as T2 (n = 14; 63.6%) N2 (n = 7; 50%) according to the TNM. ►**Tables 1**, **2**, and the ►**Appendix** show the results of the present study. The histopathological findings associated with the presence of brain metastasis in patients with IBC were tumor size ($p = 0.03$), presence of nodal metastasis ($p = 0.045$), and c-erbB-2 expression ($p = 0.012$). The median time between the anatomopathological diagnosis of the primary tumor and the diagnosis of brain metastasis was of 29.5 months. The mean age did not differ between patients with and without brain metastasis. Triple-negative breast cancers were more frequent in the brain-metastasis group, with 4 cases among the 22 analyzed (19.04%). The prevalence of triple-negative tumors was of 8% ($n = 4$) among patients who did not have brain metastasis.

The brain-metastasis group had a survival probability of 11% after 120 months, whereas the group without brain

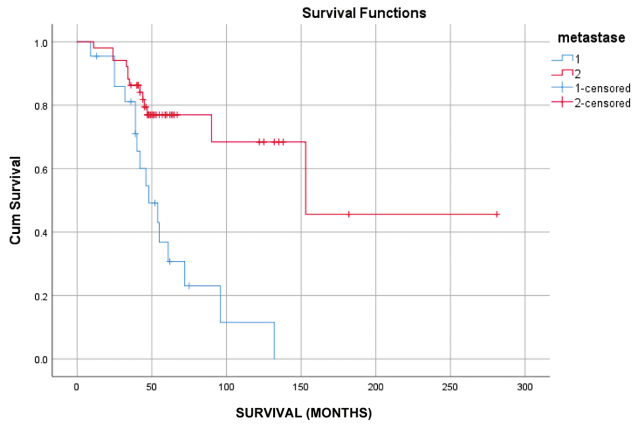

Fig. 1 Survival index associated to brain metastases in invasive breast carcinoma.

Table 1 Invasive breast cancer and central nervous system metastasis: relationships regarding age, histologic grade, and lymph node metastasis

Variable	Group without brain metastasis ($n = 51$)	Group with brain metastasis ($n = 22$)	*p*-value
Age, years	51.71 ± 12.727	49.32 ± 13.891	0.478
Histologic grade, *n* (%)			
1	5 (9.8%)	0 (0%)	0.308
2	26 (51%)	13 (59.1%)	
3	20 (39.2%)	9 (40.9%)	
Lymph node metastasis, *n* (%)			
Yes	32 (62.7%)	8 (36.4%)	0.045
No	19 (37.3%)	14 (63.6%)	
Size			
T1	20 (39.2%)	3 (13.6%)	0.03
T2	16 (31.4%)	14 (63.6%)	
T3	15 (29.4%)	5 (22.7%)	

Table 2 Invasive breast cancer and central nervous system metastasis: comparison of hormone receptor and HER-2 expression between groups

Variable	Group without brain metastasis ($n = 51$)	Group with brain metastasis ($n = 22$)	*p*-value
Estrogen receptors			
Negative	13 (25%)	11 (50%)	0.058
Positive	38 (75%)	11 (50%)	
Progesterone receptors			
Negative	18 (35.3%)	13 (59.1%)	0.074
Positive	33 (64.7%)	9 (40.9%)	
Human epidermal growth factor receptor-2 (HER-2)			
Negative	40 (78.4%)	10 (45.5%)	0.012
Positive	11 (21.6%)	12 (54.5%)	
Luminal A	11 (21.6%)	2 (9.1%)	0.019
Luminal B	19 (37.3%)	4 (18.2%)	

(*Continued*)

metastasis had a 68% chance of survival. The mean time until the presentation of brain metastasis was of 50 months after mastectomy (►**Fig. 1**). At this time, the relative risk of death was 3.8 times higher in the brain-metastasis group.

Discussion

The incidence of brain metastasis associated with IBC has increased in recent years. Although early detection of the primary lesion and different modalities of clinico-surgical treatment have consistently contributed to an increase in disease-free survival time, some patients manifest an aggressive biological course and develop brain, liver, or bone metastases.[1–3,5] In general, most chemotherapeutic agents, hormone therapies, and/or other target therapies present regular or poor effectiveness in patients with brain metastasis because these agents do not efficiently penetrate the blood–brain barrier. Important advances were obtained with the introduction of trastuzumab for the control of systemic diseases, but with little effect in patients with brain metastasis.[2,3,5,6,8,9] Currently, surgical resection, radiotherapy, and/or stereotactic radiosurgery are the most effective therapeutic measures for severe or acute neurological conditions, particularly in patients with neurological complaints.[2–4,6,9,10] The determination of anatomopathological factors capable of predicting the risk of brain metastasis in IBC patients may contribute to the increase in survival rates and identification of possible molecular pathways for pharmacological control. The current survival time of patients with brain metastasis ranges from 3 to 8 months.[1,2,4,5,7,9–11]

In general, young age, low disease-free interval, visceral metastasis, positive immunoexpression for c-erbB-2, and high number of metastatic sites are associated with the development of brain metastasis in IBC.[2,3,5,6,8,12–14] We found a higher ($p = 0.004$) incidence of brain metastasis in patients with positive expression for c-erbB-2. Brufsky et al.[5] found a cumulative incidence of brain metastasis of 31% over a 2-year period. Montagna et al.,[9] in a cohort of patients with newly diagnosed c-erbB-2-positive IBC, detected the presence of brain metastasis through computed tomography (CT) in about 6% of the patients at the time of initial diagnosis of the primary lesion, and in 40% of the sample at a median follow-up of 35.3 months.

Pellerino et al.[10] reported the presence of brain metastasis in 8% to 15% of advanced luminal A IBC cases, 11% of luminal B IBC cases, 11% to 48% of HER-2-positive carcinoma cases, and 25% to 46% of triple-negative cases. Yan et al.[15] analyzed 295 subjects with IBC using CT or magnetic resonance imaging (MRI) and detected brain metastasis in 49 patients (17%) in an interval of 6 months. In their study,[15] molecular subtype was associated with brain metastasis development over 12 months: 3.3% of the cases were luminal A, 14% were luminal B, 38% were c-erbB-2-positive, and 18% were triple-negative. The low incidence of brain metastasis as the first site of disease spread in patients with IBC (0.1% to 3.2% per year of follow-up) is considered by some authors a relevant factor for not conducting routine radiological investigation, even in patients with c-erbB-2 expression, triple-negative carcinomas, and locally advanced tumors. The patients in the current study had a median time of 29.5 months between diagnosis of the primary tumor and diagnosis of brain metastasis. Niwińska et al.[8] identified asymptomatic brain metastasis in 11 out of 32 women (34%) with c-erbB-2-positive IBC 3 to 84 months after the initial diagnosis (median of 15 months) using a single MRI scan.

For patients with c-erbB-2-positive IBC who developed regional or distant metastases and/or patients with triple-negative IBC, the 1-year cumulative incidence of brain metastasis ranges from 10% to 30%, which may support the need for radiological screening even in asymptomatic cases.[1,2,5,8,9,15,16] Because of the significant morbidity and mortality rates associated with brain metastasis in IBC, it is suggested that routine radiological assessments be carried out in high-risk populations.[2,5,8,9,16–18] According to Kuksis et al.,[13] clinical trials, such as the MRI Screening Versus SYMptom-directed Surveillance for Brain Metastases Among Patients with Triple Negative or HER2$^+$ MBC (SYMPToM, NCT03881605), are currently underway to investigate the potential risks and benefits of early detection and intervention of brain metastasis.

In recent years, there has been an increasing emphasis on molecular prognostic tests to the detriment of traditional clinical and pathological methods. Nevertheless, the number of regional lymph nodes affected by metastasis, the histological grade, and tumor size remain essential for prognosis and therapeutic decision-making.[3,5,9,14–16,19–21] According to Carter et al.,[22] the probability of developing metastasis increases with increasing tumor size. Patients with T1 tumors had a 100% 5-year overall survival, whereas patients with T2 and T3 had 89% and 86% survival rates respectively. Fung et al.[23] argued that tumor size (≤ 2 cm versus > 2 cm) and lymph node status are independent prognostic factors for local recurrence, regional recurrence, metastasis, breast cancer-specific survival, and overall survival. The authors[23] found differences ($p = 0.003$) in tumor size in groups with and without brain metastasis: 86.3% of patients with brain metastasis and 60.8% of patients without brain metastasis had a tumor ≤ 2 cm.

In the current study, we found a median overall survival of 52 months for patients with brain metastasis and primary tumor showing positivity for estrogen and progesterone receptors, of 44 months for patients with brain metastasis and primary tumor positive for c-erbB-2, and of 36.5 months for patients with brain metastasis and triple-negative carcinoma. Conceptually, CNS parenchymal metastases are of hematogenous origin.[14,16,18,24–27] Secondary CNS involvement usually occurs in advanced stages of the disease, and multiple metastases are observed in more than 50% of the cases. In most patients, metastasis to the lungs, liver, or bone precedes metastasis to the CNS.[6,14,20,24–26,28,29] In the current study, the presence of nodal metastasis was more common in patients without brain involvement (62.7%) than in patients with brain metastasis (36.4%; $p = 0.04$). This finding might be related to the hematogenous origin of metastases. Brain metastasis was observed in up to 30% of women with IBC who progressed to death. Similar rates of brain metastasis have been reported[2,4,5,9,15,25] in women

who underwent chemotherapy with epirubicin, docetaxel, and paclitaxel for visceral metastasis.

The development of brain metastasis in IBC is triggered by tumor clones, with PI3K mutations found in 40% to 70% of patients. Therefore, inhibition of the PI3K/AKT/mTOR pathway is a promising therapeutic strategy. However, most of the current agents targeting tumor lesions fail to penetrate the blood–brain barrier.[1,12,20,24,28]

Conclusion

Anatomopathological variables such as tumor size, c-erbB-2 expression, and triple-negative subtype can predict the presence of brain metastasis in patients with IBC. New mutations and/or genetic alterations have been studied to predict prognosis and improve the efficiency of the therapy for cases brain metastasis, including drugs that can successfully overcome the blood–brain barrier.

Authors' Contributions

EC: work design, scientific review, and writing of the manuscript MSM: work design and scientific review; and NBZ, JNAMS, and GBCN: data collection.

Ethics Declaration Statement

Approval was obtained from the Ethics Committee of Hospital Nossa Senhora da Conceição, Porto Alegre, RS, Brazil. The procedures used in the present study adhere to the tenets of the Declaration of Helsinki.

Funding

The authors declare they have received no funding pertaining to the present study.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Eberst L, Bailleux C, Bachelot T. Prevention of brain metastases in human epidermal growth factor receptor 2-positive breast cancer. Curr Opin Oncol 2020;32(06):555–560
2 Tham YL, Sexton K, Kramer R, Hilsenbeck S, Elledge R. Primary breast cancer phenotypes associated with propensity for central nervous system metastases. Cancer 2006;107(04):696–704
3 Allison M. Martin, BS Daniel N. Cagney, MD Paul J. Catalano, Sc et al. Brain Metastasis in Newly diagnosed breast cancer: a Population-based Study. JAMA Oncol. 2017;3(08):1069–1077. doi:10.1001/jamaoncol.2017.0001
4 Komorowski AS, Warner E, MacKay HJ, Sahgal A, Pritchard KI, Jerzak KJ. Incidence of brain metastases in nonmetastatic and metastatic breast cancer: is there a role for screening? Clin Breast Cancer 2020;20(01):e54–e64
5 Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res 2011;17(14):4834–4843
6 Graesslin O, Abdulkarim BS, Coutant C, et al. Nomogram to predict subsequent brain metastasis in patients with metastatic breast cancer. J Clin Oncol 2010;28(12):2032–2037
7 Minisini AM, Moroso S, Gerratana L, et al. Risk factors and survival outcomes in patients with brain metastases from breast cancer. Clin Exp Metastasis 2013;30(08):951–956
8 Niwińska A, Tacikowska M, Pieńkowski T. Occult brain metastases in HER2-positive breast cancer patients: frequency and response to radiotherapy. Acta Oncol 2007;46(07):1027–1029
9 Montagna E, Cancello G, D'Agostino D, et al. Central nervous system metastases in a cohort of metastatic breast cancer patients treated with trastuzumab. Cancer Chemother Pharmacol 2009;63(02):275–280
10 Pellerino A, Internò V, Mo F, Franchino F, Soffietti R, Rudà R Management of brain and leptomeningeal metastases from breast cancer. Int J Mol Sci 2020;21(22):8534
11 Babak MV, Zalutsky MR, Balyasnikova IV. Heterogeneity and vascular permeability of breast cancer brain metastases. Cancer Lett 2020;489:174–181
12 Ippen FM, Grosch JK, Subramanian M, et al. Targeting the PI3-K/Akt/mTOR pathway with the pan-Akt inhibitor GDC-0068 in PIK3CA-mutant breast cancer brain metastases. Neuro-oncol 2019;21(11):1401–1411
13 Kuksis M, Gao Y, Tran W, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. Neuro-oncol 2021;23(06):894–904
14 Pedrosa RMSM, Mustafa DA, Soffietti R, Kros JM. Breast cancer brain metastasis: molecular mechanisms and directions for treatment. Neuro-oncol 2018;20(11):1439–1449
15 Yan M, Lü HM, Liu ZZ, et al. High risk factors of brain metastases in 295 patients with advanced breast cancer. Chin Med J (Engl) 2013;126(07):1269–1275
16 Atahan IL, Ozyigit G, Yildiz F, et al. Percent positive axillary involvement predicts for the development of brain metastasis in high-risk patients with nonmetastatic breast cancer receiving postmastectomy radiotherapy. Breast J 2008;14(03):245–249
17 Altundag K, Bondy ML, Mirza NQ, et al. Clinicopathologic characteristics and prognostic factors in 420 metastatic breast cancer patients with central nervous system metastasis. Cancer 2007;110(12):2640–2647
18 Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol 2004;22(17):3608–3617
19 Evans AJ, James JJ, Cornford EJ, et al. Brain metastases from breast cancer: identification of a high-risk group. Clin Oncol (R Coll Radiol) 2004;16(05):345–349
20 Liu Y, He M, Zuo WJ, Hao S, Wang ZH, Shao ZM. Tumor size still impacts prognosis in breast cancer with extensive nodal involvement. Front Oncol 2021;11:585613
21 Nicolini A, Ferrari P, Duffy MJ. Prognostic and predictive biomarkers in breast cancer: Past, present and future. Semin Cancer Biol 2018;52(Pt 1):56–73
22 Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1989;63(01):181–187
23 Fung F, Cornacchi SD, Vanniyasingam T, et al. Predictors of 5-year local, regional, and distant recurrent events in a population-based cohort of breast cancer patients. Am J Surg 2017;213(02):418–425
24 Watanabe J, Mitsuya K, Nakamoto S, et al. Leptomeningeal Metastasis in ER + HER2- Advanced Breast Cancer Patients: A Review of the Cases in a Single Institute Over a 15-year Period. Breast Cancer Res Treat 2021;189(01):225–236
25 Galanti D, Inno A, La Vecchia M, et al. Current treatment options for HER2-positive breast cancer patients with brain metastases. Crit Rev Oncol Hematol 2021;161:103329
26 Hall WA, Djalilian HR, Nussbaum ES, Cho KH. Long-term survival with metastatic cancer to the brain. Med Oncol 2000;17(04):279–286
27 Kaplan A, Li MJ, Malani R. Treatments on the Horizon: Breast Cancer Patients with Central Nervous System Metastases. Curr Oncol Rep 2022;24(03):343–350. Doi: 10.1007/s11912-022-01206-2
28 Ben-Zion Berliner M, Yerushalmi R, Lavie I, et al. Central nervous system metastases in breast cancer: the impact of age on patterns of development and outcome. Breast Cancer Res Treat 2021;185(02):423–432
29 Koniali L, Hadjisavvas A, Constantinidou A, et al. Risk factors for breast cancer brain metastases: a systematic review. Oncotarget 2020;11(06):650–669

Appendix: Clinico-pathologic data from patients with invasive breast cancer and central nervous system metastasis

Case	Age	Tumor size/stage	Nodal status	ER	PR	HER-2	Ki-67	Metastasis topography	Metastasis size	Number of metastases
1	40	2.5 cm/T2	N2a	−	−	+	40%	Right frontal lobe	3.3 × 3.2 cm	1
2	55	2.0 cm/T1	N0	+	−	+	20%	Right cerebellar hemisphere	5.1 × 2.8 cm	1
3	70	2.5 cm/T2	N0	+	+	−	50%	Left cerebellar hemisphere	4.8 × 2.6 cm	1
4	53	6.0 cm/T3	N0	−	−	+	20%	Temporal lobe	2.5 × 2.3 cm	1
5	30	2.0 cm/T1	N1a	+	+	+	40%	Left occipital lobe	5.2 × 4.0 cm	1
6	45	3.5 cm/T2	N0	+	+	+	40%	Left cerebellar hemisphere	3.2 × 2.3 cm	1
7	59	2.5 cm/T2	N0	+	+	−	30%	Left frontotemporal region	4.5 × 3.7 cm	1
8	62	6.0 cm/T3	N2b	+	+	+	20%	Left frontal lobe	3.9 × 3.2 cm	1
9	31	2.0 cm/T1	N0	−	−	+	30%	Right frontal lobe	4.4 × 2.5 cm	1
10	53	3.0 cm/T2	N0	−	−	+	40%	Left frontal lobe	3.0 × 2.5 cm	1
11	73	4.0 cm/T2	N0	+	−	−	30%	Left cerebellar hemisphere	3.0 × 2.0 cm	1
12	68	3.0cm/T2	N0	−	−	+	70%	Right cerebellar hemisphere and left frontal lobe	2.2 × 1.5 cm and 1.9 × .8 cm	2
13	38	4.0 cm/T2	N1c	+	+	+	80%	Left cerebellar hemisphere	3.8 × 2.7 cm	1
14	60	2.5 cm/T2	N1a	−	−	+	30%	Right cerebellar hemisphere	4.2 × 3.0 cm	1
15	64	6.0 cm/T3	N2a	+	+	−	10%	Occipital lobe and left cerebellar hemisphere	5.4 × 3.4 cm, 2.7 × 2.0 cm, and 0.4 × 0.4 cm	3
16	50	4.0 cm/T2	N0	−	−	−	20%	Left cerebellar hemisphere	2.4 × 2.0 cm	1
17	38	7.5 cm/T3	N0	−	−	+	40%	Left and right cerebellar hemispheres	2.2 × 1.6 cm and 0.6 × 0.5 cm	2
18	43	3.5 cm/T2	N0	+	+	−	10%	Left cerebellar hemisphere, right cerebellar hemisphere, and left frontal lobe	5.5 × 4.8 cm, 3.2 × 1.8 cm, and 1.8 × 1.0 cm	3
19	33	4.5 cm/T2	N0	−	−	−	40%	Right cerebellar hemisphere, left cerebellar hemisphere, and occipital lobe	3.4 × 3.3 cm, 2.0 × 1.2 cm, and 0.7 × 0.7 cm	3
20	31	4.0 cm/T2	N0	−	−	−	60%	Left frontal lobe	2.0 × 1.3 cm	1
21	58	2.0 cm/T1	N1a	−	−	−	70%	Right posterior fossa	4.0 × 2.5 cm	1
22	31	2.0 cm/T1	N0	−	−	+	30%	Right frontal lobe	4.4 × 2.5 cm	1

Abbreviations: ER, estrogen receptor; HER-2, human epidermal growth factor receptor-2; PR, progesterone receptor.

