Journal of Medical and Medical Specialities
Volume 1, Issue 2, June 2025; pp: 80-84
eISSN: 2455-2879 DOI: 10.65129/medical.v1i2.34

RESEARCH ARTICLE

A Retrospective Study of Assessing the Risk Factors for Brain Metastasis in Patients with Breast Cancer

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Abstract

Breast cancer is the most common malignancy among women worldwide and remains a leading cause of cancer-related mortality. Brain metastases represent a devastating complication associated with neurological decline and poor prognosis. Breast cancer is the second most common cause of brain metastases after lung cancer, and incidence has been rising partly due to improved systemic therapies that prolong survival but inadequately penetrate the blood-brain barrier. Approximately 10-30% of patients with advanced breast cancer develop brain metastasis during their disease course. This retrospective study aims to identify clinical and pathological predictors of brain metastasis in breast cancer and to develop a risk prediction model, thereby facilitating early detection and guiding individualised management strategies.

Keywords: Brain Metastasis, Breast Cancer, Metastatic Breast Cancer

1. Introduction

Breast cancer is the most common cancer among women globally and continues to be a major contributor to cancer-related deaths. Metastasis to the brain is regarded as one of the most serious complications, often resulting in neurological deterioration, restricted therapeutic options and unfavourable survival outcomes[1,2]. Following lung cancer, breast cancer represents the second most common cause of brain metastases and is the solid malignancy most frequently linked to leptomeningeal involvement[3]. In recent years, the occurrence of brain metastases has increased, a trend attributed to systemic therapies that effectively control extracranial disease but have limited ability to cross the blood-brain barrier[4].

This retrospective study aims to identify clinicopathological risk factors associated with brain metastases in breast cancer patients to improve early detection and guide risk-adapted management strategies.

2. Aim and Objectives

To assess the risk factors for brain metastasis in patients with breast cancer and to generate a brain metastasis prediction model from variables obtained at carcinoma breast cancer diagnosis.

3. Review of Literature

Brain metastases develop in approximately 10-30 % of patients with advanced breast cancer during the course of illness[3]. Owing to its biological heterogeneity, the likelihood of Central Nervous System (CNS) involvement differs across breast cancer subtypes. Patients often develop gradually worsening neurological and motor problems, which may manifest as headaches, nausea, personality alterations, seizures, paralysis or difficulties with memory and cognition[5]. Brain metastasis is generally regarded as a later manifestation of breast cancer, usually appearing 2 to 3 years after the initial diagnosis and often following

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Article Received on: 15 Feb 2025 Revised on: 20 Apr 2025 Accepted on: 18 June 2025

spread to the lungs, liver or bones[3,6]. However, direct dissemination to the brain is also observed, as the brain's distinctive microenvironment may act as a protective niche for tumour cells[7]. Notably, the incidence of breast cancer brain metastasis has been rising in recent decades, largely due to improved detection with MRI and prolonged survival among patients with metastatic disease[8].

Multiple studies have shown that larger primary tumour size is an important risk factor for the development of brain metastases in breast cancer. In a cohort of over 2,000 patients, increased tumour size significantly predicted later brain involvement, with a hazard ratio of 3.6[9]. A systematic review of nearly 100 studies by Koniali *et al.*[10] confirmed this association across different populations. The presence of a large primary lesion and significant nodal burden further enhances the probability of hematogenous spread to the brain[3]. In HER2-positive disease, tumours exceeding 2 cm were at especially high risk with a hazard ratio of 4.94[11]. The advanced stage at diagnosis similarly correlates with brain relapse, underscoring the prognostic value of tumour size. Patients with high-grade tumours (Grade III) have a markedly elevated risk of developing brain metastases[12].

The highest rates are observed in HER2-positive and Triple Negative Breast Cancers (TNBC)[12]. Although HER2-positive tumours were historically regarded as highly aggressive, the introduction of trastuzumab and subsequent HER2-directed agents has significantly improved systemic outcomes. Because many of these therapies have limited ability to cross the blood-brain barrier, patients often experience an increased incidence of brain metastases despite better control of extracranial disease[13]. Similarly, TNBC, defined by the absence of Estrogen Receptor (ER), progesterone receptor (PR) and HER2 expression, exhibits a strong tendency for CNS dissemination. This subtype frequently spreads early and aggressively to visceral organs, including the brain, often within a short period after initial diagnosis[14,15].

Patients diagnosed before the age of 40 are more likely to exhibit aggressive molecular subtypes such as HER2-positive and TNBC, both strongly linked to central nervous system metastases. Tumours in this age group also tend to be of higher grade, and the extended survival achieved with modern systemic therapies increases the cumulative probability of CNS involvement over time[1,12]. In contrast, the incidence of brain metastases is relatively lower among patients above 60 years. This population is more often associated with luminal breast cancer subtypes, which display a reduced tendency for CNS dissemination. Moreover, the generally shorter survival of older patients decreases the time available for brain metastases to develop[16].

4. Materials and Methods

Study Type: Retrospective observational study.
Study Setting: Department of Radiation Oncology, Tirunelveli.
Study Period: Medical records from the period of January 2022 to December 2023.
Methodology: Records of the carcinoma breast with brain metastasis patients were obtained from the Department of Radiation Oncology, Government Tirunelveli Medical College and Hospital, Tirunelveli were analysed.
Inclusion criteria: Patients with brain metastases from primary breast cancer.
Exclusion criteria: Patients with brain metastases from non-breast primary cancers.

5. Results (Including Observations)

A total of 28 patients were included in this study. With respect to age distribution, 3 (12%) were younger than 40 years, while 25 (88%) were older than 40 years (Table 1, Figure 1). The mean age was 50.7 years, ranging from 32 to 76 years. Among them, 1 patient (4%) was male and 27 patients (96%) were female (Table 2, Figure 2).

Histological grading revealed that Grade II tumours were the most common (n=19, 68%), followed by Grade III (n=8, 29%), while only one patient (n=1, 3%) had Grade I disease (Table 3, Figure 3). Regarding molecular subtype, TNBC was seen in eight patients (n=8, 28%), and HER2-enriched tumours were identified in seven patients (n=7, 25%) (Table 4, Figure 4).

Table 1. Age distribution

Characteristics	No. of patients	Percentage (%)
Age <40 years	3	12
Age >40 years	25	88

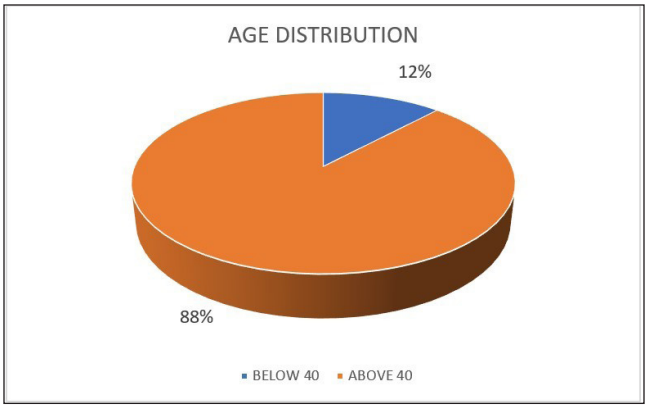

Figure 1. Age distribution.

Table 2. Gender distribution

Characteristics	No. of patients	Percentage (%)
Male	1	4
Female	27	96

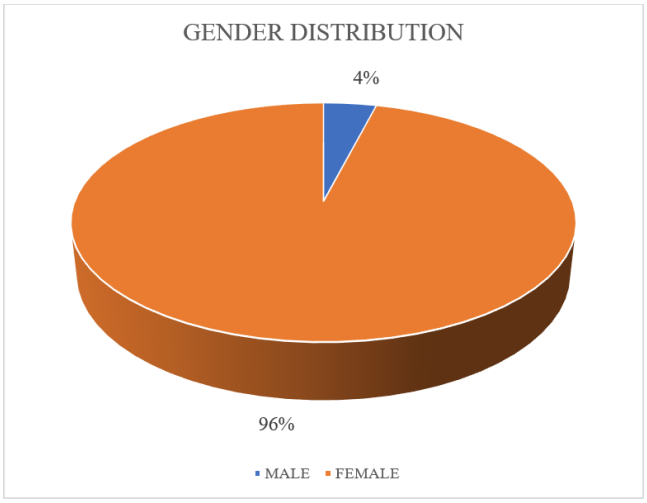

Figure 2. Gender distribution.

Table 3. Tumour grading

Characteristics	No. of patients	Percentage (%)
Grade I	1	3
Grade II	19	68
Grade III	8	29

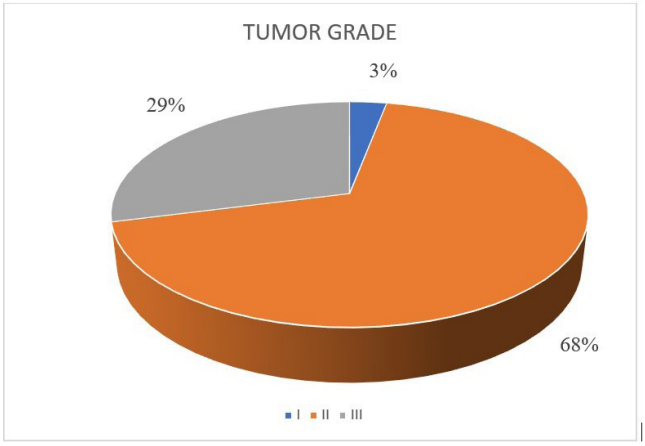

Chart 3. Tumour grading.

Table 4. Molecular type

Characteristics	No. of patients	Percentage (%)
TNBC	8	28
HER2 Enriched	7	25

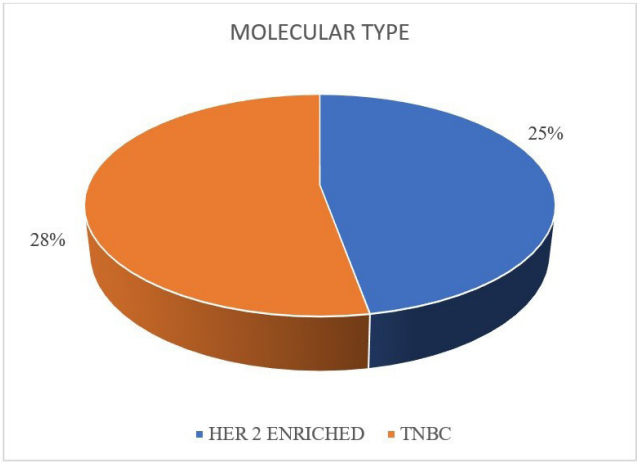

Chart 4. Molecular type.

Table 5. Tumour staging

Characteristics	No. of patients	Percentage (%)
T1	2	7
T2	4	14
T3	3	11

With respect to tumour size, the majority presented with T4 disease (n=19, 68%), whereas smaller proportions had T1 (n=2, 7%), T2 (n=4, 14%) and T3 (n=3, 11%) tumours (Table 5, Figure 5). Nodal involvement showed a similar trend, with most patients in the N2 stage (n=15, 54%), followed by N0 (n=7, 25%), N1 (n=3, 10%) and N3 (n=3, 11%) (Table 6, Figure 6).

Collectively, these findings highlight that the majority of patients presented with advanced primary tumours (T4), significant nodal disease (N2), triple negative breast cancer and HER2-enriched subtypes showing a higher propensity for brain metastasis.

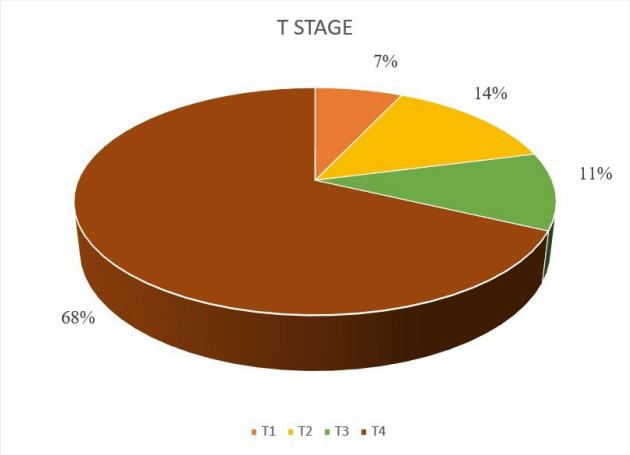

Chart 5. Tumour stage.

Table 6. Nodal staging

Characteristics	No. of patients	Percentage (%)
N0	7	25
N1	3	10
N2	15	54
N3	3	11

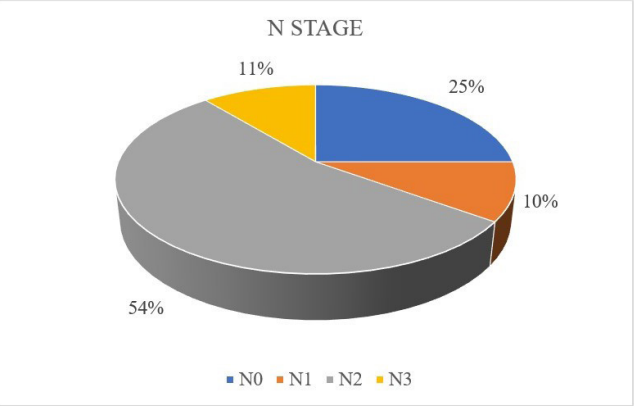

Chart 6. Nodal stage.

6. Discussion

In this retrospective study of 28 patients with breast cancer and brain metastases, we observed that the majority of patients presented with advanced primary tumours (T4) and significant nodal disease (N2). Furthermore, TNBC and HER2-enriched subtypes were found to be more frequently associated with brain metastases, consistent with previously published evidence.

Our findings align with prior studies demonstrating that an advanced stage at diagnosis is a strong predictor of CNS involvement. Larger primary tumours and higher nodal burden facilitate hematogenous dissemination, increasing the risk of brain metastasis. In our cohort, nearly 68% of patients presented with T4 disease and 54% with N2 nodal involvement, underscoring the link between tumour burden and subsequent CNS relapse. This trend has also been reported by Koniali *et al.*[10] and others, who identified tumour size and nodal positivity as significant predictors of brain metastasis.

Histological grade also appeared relevant in our series, with 97% of patients presenting with Grade II or Grade III tumours. High-grade tumours are biologically aggressive, proliferate rapidly and have a higher likelihood of CNS dissemination. Several studies have similarly reported that Grade III breast cancers, particularly those lacking hormone receptor expression, carry a significantly increased risk of brain metastasis.

The molecular subtype distribution in our cohort further reinforces the existing literature. TNBC (28%) and HER2-enriched tumours (25%) were overrepresented among patients with brain metastasis. These subtypes are well established to have a strong predilection for CNS involvement. While HER2-directed systemic therapies have markedly improved extracranial disease control, their limited penetration across the blood-brain barrier leaves the brain as a sanctuary site for metastatic spread. Consequently, brain metastasis has become an increasingly recognised clinical challenge in HER2-positive patients. Similarly, TNBC is characterised by aggressive biology and early visceral spread, including to the CNS, often within a short interval from the initial diagnosis. These findings underscore the importance of early surveillance and risk-adapted strategies for patients with these high-risk subtypes.

Age also played a role in the distribution of brain metastases. In our study, younger patients (<40 years) accounted for 12% of cases, consistent with reports that younger women more frequently present with aggressive molecular subtypes such as TNBC and HER2-positive disease. Although the proportion was smaller than in older patients, the aggressive biology in this age group may explain the predisposition to CNS spread. In contrast, luminal subtypes are more common in older patients, tend to have a lower risk of brain metastases and a longer latency period before CNS involvement.

7. Summary and Conclusion

Our results suggest that advanced tumour stage, high nodal burden, higher grade and aggressive molecular subtypes TNBC and HER2-enriched) are key risk factors for brain metastasis in breast cancer. These findings highlight the need for closer monitoring of such high-risk patients, possibly through early neuroimaging in selected cases or incorporation of CNS-penetrating therapies where available.

8. Limitations

The retrospective design and relatively small sample size may limit the generalizability of our findings. Additionally, treatment-related variables such as systemic therapy received, duration of disease-free survival, and time to CNS relapse were not included in the present analysis. Larger prospective studies are warranted to validate these observations and to refine predictive models for brain metastasis in breast cancer.

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