Original Article

# Investigation of Prevalence, Survival, and Molecular Type of Breast Cancer Patients with Brain Metastases

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## Abstract

**Background:** This study aims to investigate the factors associated with breast cancer brain metastasis (BCBM) in individuals suffering from breast cancer (BC).

**Materials and Methods:** This cross-sectional study conducted on 200 patients with metastatic breast cancer (MBC) including 52 brain and 148 other organ metastases. The demographic, medical, clinical, laboratory, and therapeutic approach characteristics were compared between the groups.

**Results:** Headache (61.5%), weakness and lethargy (26.9%), dizziness (15.4%), blurred vision/blindness (15.4%), and convulsions (15.4%) were the major initial symptoms of BCBM. Radiotherapy (71.2%), injectable (34.6%), and oral chemotherapy (26.9%) were the major applied therapeutic strategies to manage brain metastasis (BM). The overall survival of the patients from cancer diagnosis to death accounted for 33 months (95%CI: 27.52–38.47), while this period after BM diagnosis was limited to 6 months (95%CI: 5.15–6.84). The rate of hormone therapy was remarkably higher among the metastasis in other organs than the brain ($P$ value = 0.005), while targeted therapy was performed in higher rates for BM ($P$ value = 0.001). The evaluation of BC-related tumor markers revealed that human epidermal growth factor 2 (HER2) ($P$ value < 0.001) positivity was remarkably higher among BCBM, while positive estrogen receptor (ER) ($P$ value = 0.004) and progesterone receptor (PR) ($P$ value = 0.013) were statistically more in the other group.

**Conclusion:** Based on the findings of this study, the BC patients with BM had a remarkable short survival, had a higher rate of perineural invasion, and were mostly positive for HER2. Radiotherapy, chemotherapy, and surgery were the most common approaches to these patients.

**Keywords:** Brain neoplasms, breast neoplasms, registries, tumor biomarkers

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## Introduction

Breast cancer (BC) is the most prevalent and the second cancer-related cause of death in the female population accounting for more than 2.7 million new diagnosed cases in 2020. Moreover, 42170 deaths have occurred in 2020 equaling 30% of all newly diagnosed cancer cases and 15% of all deaths associated with malignancies.[1] In spite of all the developments occurred in recent years to screen, diagnose, and treat the BC individuals, its recurrence and devastating consequences, such as distant metastasis, remained a challenging issue. Bone, lung, liver, and brain are the most distant areas that can potentially get involved with brain metastasis (BM).[2]

Metastasis originating from BC is the second most common cause of BM among solid malignancies. BM accounts for 10–30% of all metastatic breast cancers (MBC) leading to poor prognosis and unfavorable outcomes, such as cognitive

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impairment, sensory dysfunction, and seriously impaired quality of life.[3-5]

It has been proposed that BM occurs following a cascade of events occurring to let a breast cancerous cell seed in the brain. Accordingly, the cancer cells landing in breast parenchyma must undergo epithelial-to-mesenchymal transition (EMT) in advance to the entrance into the bloodstream. Afterward, they should survive from the hematological diffusion in the way of brain where it is supposed to be implanted and another transition from mesenchymal to epithelial cells occurs. It is noteworthy that the cancerous cells must deal with several fundamental adaptations to cross the blood-brain barrier (BBB). Afterward, the cells initiate to proliferate perivascularly and begin neoangiogenesis until the creation of a brain tumor barrier.[4]

Despite the variety of the modes applied to manage BM, including surgical approaches, radiotherapy, and chemotherapy, the presence of BBB as an obstacle to achieve the ultimate outcomes has hindered response to the treatments. Therefore, with this condition, the breast cancer brain metastasis (BCBM) individuals would not significantly benefit from the current solo or combined therapies.[6,7]

Accordingly, several steps are required to tackle the issue of incidence of BM in BC patients, anticipating the risk of facing BM among BC subjects in order to precisely screen the individuals who are at increased risk for BM and strategies that are required to be applied in order to manage BM in these cases. This study has been derived from the registry of BC in Isfahan, center of Iran, aiming to investigate the factors associated with BM in individuals suffering from BC.

## Materials and Methods

### Study population

This cross-sectional study was conducted on 200 patients with MBC, including 52 individuals with brain and 148 ones with other organ metastases, admitted at the Seyed-o-Shohada Hospital affiliated with the Isfahan University of Medical Sciences from April 2019 to December 2021. These data were gathered out of 3200 patients diagnosed with BC.

The study protocol was designed based on the tenets of the Helsinki Declaration and proposed to the Ethics Committee of Isfahan University of Medical Sciences where it was approved via code number "IR.ARI.MUI.REC.1401.278." Considering that the Seyed-o-Shohada Hospital is an educational center, the probable use of the medical data for scientific research was explained to the patients/their legal guardians, and they were reassured regarding the confidentiality of the personal information and signed written consent for participation in the study.

All the BC patients whose BM was documented in the medical data of the hospital were included. Any flaw in the medical data was considered the exclusion criteria.

Due to the census design of the study, all the patients who met the study criteria entered into the investigation through convenience sampling.

### Data collection

The patients who were primarily diagnosed with BC based on the core needle biopsy (CNB) taken from the breast masses entered into the registry,[8] given that the patients' demographic, medical, and clinical characteristics, including age, past medical diseases, drug history, the type and molecular study of BC, and the applied chemotherapy, were recorded.

Besides, chest X-ray and abdominopelvic computed tomography (CT) were performed for the patients in the primary visits in order to investigate the probable involvement of the other regions of body.

In the clinical assessments, the number and locations of metastasis, tumor morphology, tumor TNM staging, and the biopsies taken from the mass and lymph nodes derived from the fine needle aspiration (FNA) or CNB were gathered. Besides that, the available performed imaging, including abdominopelvic, thoracic, and brain CT scans, brain magnetic resonance imaging (MRI), whole body scan, and positron emission tomography (PET) scan, was recruited.

The therapeutic approach was divided into two groups of curative versus palliative care. Moreover, the applied treatments were subgrouped as chemotherapy, hormone therapy, surgery, radiotherapy, targeted therapy, and adjuvant therapy. The latter was categorized as chemotherapy, radiotherapy, and hormone therapy. The duration and protocols of adjuvant therapies were retrieved. The etiology of cessation or failure to apply each regimen was recorded, as well.

The related data to extralesional involvement included the number of involved lymph nodes, perineural invasions, lymphovascular invasion (LVI), and breast ulcer or inflammatory cancer. Furthermore, the BC markers, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2), chromogenic *in situ* hybridization (CISH), fluorescence *in situ* hybridization (FISH), and Ki-67, were entered into the study checklist, if applicable.

The primary symptoms associated with BM, including headache, dizziness, weakness and lethargy, paralysis, nausea and vomiting, blurred vision/blindness, convulsions, imbalance, cognition/memory impairment, numbness, sleepiness or restlessness, distractions, slurred speech, and neck pain, were entered into the checklist. The other assessed variables included the therapeutic approach taken to manage BM (radiotherapy, surgery, and chemotherapy), the mortality rate, and the interval between the cancer diagnosis and death and BM diagnosis and death.

### Statistical analysis

The obtained data were entered into the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 23. Descriptive data were presented in mean,

standard deviation, percentages, and absolute numbers. For analytic data, Chi-square test, *t*-test, Fisher's exact test, and Spearman-Pearson correlation test were utilized. Cox regression analysis was applied to determine the factors associated with the overall survival of the patients with BM. Besides that, the Kaplan-Meier survival curve was depicted to evaluate the longevity of the BC patients with BM. *P* value of less than 0.05 was considered a significant level.

## Results

In this study, 200 patients with MBC among whom 52 (26%) ones had BM and 148 (74%) patients had metastases in other organs, including 90 (60.8%) bone, 33 (22.3%) liver, 53 (35.8%) lung, and 30 (20.3%) other metastases, were evaluated [Table 1]. The mean age of the studied population was 47.18 ± 12.5 years (ranged 18 to 86 years). Among all the studied patients, one patient (in the BM group) had a previous history of BC and also a previous history of chest and neck radiotherapy.

Table 2 compares the demographic and clinical characteristics of the patients in advance to the treatment initiation. Given that, the two groups were similar in terms of age (*P* value = 0.474), tumor grade at the time of diagnosis (*P* value = 0.379), the performance of tumoral open biopsy (*P* value = 0.740), lymph node FNA (*P* value = 0.217), and CNB (*P* value = 0.145) as well as the imaging modalities taken at the time of diagnosis, including abdominopelvic (*P* value = 0.232), thoracic (*P* value = 0.732), and brain (*P* value = 0.380) CT scan, whole body bone scan (*P* value = 0.697), and PET scan (*P* value = 0.142). However, the patients' tumor morphology and the performance of brain MRI significantly differed between the study groups (*P* value < 0.05).

The detailed information about the applied approach to manage the MBC patients in two groups of brain or other organ metastases is shown in Table 3. Based on this table, the rate of hormone therapy was remarkably higher among the individuals with metastasis in other organs than the brain (*P* value = 0.005).

**Table 1: Frequency of metastases in patients**

| Organ metastases | Brain metastases *n*=52 | Metastasis to the other organs *n*=148 |
|---|---|---|
| | *n* (%) | |
| Bone | 16 (30.8) | 90 (60.8) |
| Liver | 13 (25) | 33 (22.3) |
| Lung | 13 (25) | 53 (35.8) |
| Brain | 52 (100) | 0 (0) |
| Other metastases | 4 (7.7) | 30 (20.3) |
| The number of metastasized organs | | |
| 1 | 25 (48.1) | 100 (67.6) |
| 2 | 13 (25) | 39 (26.4) |
| 3 | 9 (17.3) | 3 (5.4) |
| 4 | 5 (9.6) | 1 (0.7) |

Contrarily, targeted therapy was performed in higher rates among those with BM (*P* value = 0.001). The other approaches were similar between the groups (*P* value > 0.05).

The tumor characteristics are presented in Table 4. Perineural invasion was statistically more among those with BM (*P* value = 0.021), while the other parameters, including LVI, breast ulcer, the tumor stage based on T and N, and the diagnosis of inflammatory BC, did not differ (*P* value > 0.05). The evaluation of BC-related tumor markers revealed significantly differed rates of ER (*P* value = 0.004), PR (*P* value = 0.013), and HER2 (*P* value < 0.001) positivity among the two groups. Other variables were not statistically different (*P* value > 0.05).

Headache (61.5%) followed by weakness and lethargy (26.9%), dizziness (15.4%), blurred vision/blindness (15.4%), and convulsions (15.4%) were the major initial symptoms associated with BM in the studied patients. Radiotherapy (71.2%), injectable (34.6%), and oral chemotherapy (26.9%) were the most common applied therapeutic strategies to manage BM, respectively. The majority of the patients died (96.2%). The overall survival of the patients from cancer diagnosis to death accounted for 33 months (95%CI: 27.52–38.47), while this period after BM diagnosis was limited to 6 months (95%CI: 5.15–6.84) [Table 5]. Figures 1 and 2 depict the interval between BC diagnosis and death as well as the interval between BM and death, respectively.

## Discussion

That BM originating from BC is a significant issue with discouraging outcomes regardless of all the efforts made to manage this condition. Accordingly, it is tried to provide a thorough view of BM and then compare the medical and clinical characteristics of the cases suffering from BM versus those who had metastasis to the other organs. In our study, patients with BC who were not metastatic from the beginning were included in this issue, and based on clinical symptoms and diagnostic procedures, they were diagnosed with metastasis.

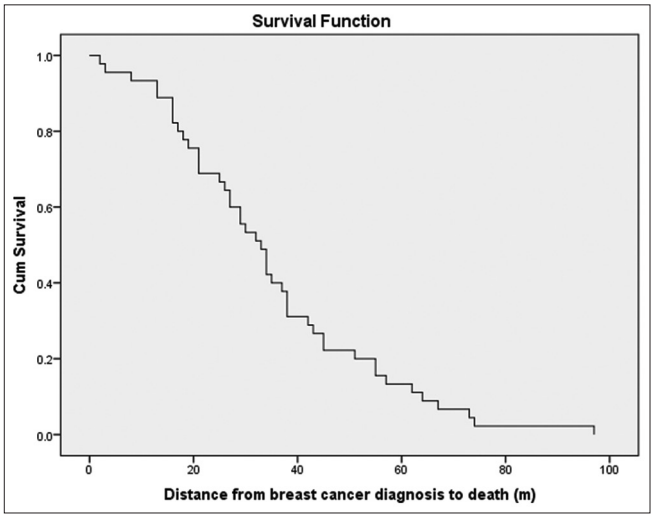


**Figure 1:** Distance from breast cancer diagnosis to death

**Table 2: Demographic and clinical characteristics of studied patients**

| Variables | | Brain metastases | No brain metastases | *P* |
|---|---|---|---|---|
| **Risk factors** | | | | |
| Age. mean±SD | | 45.41±11.57 | 48.05±13.07 | 0.474 |
| Morphology of the excisional biopsy* | Carcinoma (not otherwise specified) | 2 (3.8) | 2 (1.4) | 0.047* |
| | Ductal carcinoma in situ (not otherwise specified) | 3 (5.8) | 0 (0) | |
| N (%) | Infiltrating ductal carcinoma | 44 (84.6) | 124 (83.8) | |
| | Infiltrating micropapillary carcinoma | 0 (0) | 1 (0.7) | |
| | Lobular carcinoma in situ | 1 (1.9) | 0 (0) | |
| | Infiltrating lobular carcinoma | 1 (1.9) | 10 (6.8) | |
| | Infiltrating carcinoma with ductal and lobular feature (mixed type carcinoma) | 0 (0) | 2 (1.4) | |
| | Infiltrating cribriform carcinoma | 0 (0) | 3 (2) | |
| | Infiltrating lobular mixed with other types of carcinoma | 0 (0) | 2 (1.4) | |
| | Unknown | 1 (1.9) | 4 (2.7) | |
| Tumor grade | 1 | 1 (2) | 6 (4.2) | 0.379 |
| N (%) | 2 | 22 (43.1) | 66 (45.8) | |
| | 3 | 16 (31.4) | 43 (29.9) | |
| | 4 | 4 (7.8) | 3 (2.1) | |
| | Grade not determined | 8 (15.7) | 26 (18.1) | |
| **Diagnostic biopsy before treatment** | | | | |
| Open biopsy | Yes | 0 (0) | 1 (0.7) | 0.740 |
| N (%) | No | 52 (100) | 147 (99.3) | |
| Lymph node biopsy (FNA) | Yes | 2 (3.8) | 4 (2.7) | 0.217 |
| N (%) | No | 49 (94.2) | 144 (97.3) | |
| | Unknown | 1 (1.9) | 0 (0) | |
| Lymph node biopsy (CNB) | Yes | 13 (25) | 23 (15.5) | 0.145 |
| N (%) | No | 39 (75) | 125 (84.5) | |
| Breast tumor biopsy (CNB) | Yes | 40 (76.9) | 115 (77.7) | 0.145 |
| N (%) | No | 12 (23.1) | 33 (22.3) | |
| Morphology of CNB* | Ductal carcinoma in situ (not otherwise specified) | 1 (1.9) | 0 (0) | 0.018* |
| N (%) | Infiltrating ductal carcinoma (not otherwise specified) | 3 (5.8) | 35 (23.6) | |
| | Infiltrating lobular carcinoma (not otherwise specified) | 0 (0) | 2 (1.4) | |
| | Infiltrating carcinoma with ductal and lobular feature (mixed type carcinoma) | 0 (0) | 1 (0.7) | |
| **Diagnostic imaging before treatment** | | | | |
| Abdominopelvic CT scan | Yes | 40 (76.9) | 104 (70.3) | 0.232 |
| N (%) | No | 12 (23.1) | 44 (29.7) | |
| Brain CT scan | Yes | 3 (5.8) | 4 (2.7) | 0.380 |
| N (%) | No | 49 (94.2) | 144 (97.3) | |
| Thoracic CT scan | Yes | 40 (83.3) | 111 (79.3) | 0.732 |
| N (%) | No | 8 (16.7) | 28 (20.7) | |
| Brain MRI | Yes | 14 (35.9) | 11 (8.5) | <0.001* |
| N (%) | No | 25 (64.1) | 118 (91.5) | |
| Whole body bone scan | Yes | 37 (71.2) | 104 (70.3) | 0.697 |
| N (%) | No | 15 (28.8) | 44 (29.7) | |
| PET scan | Yes | 1 (1.9) | 0 (0) | 0.142 |
| N (%) | No | 51 (98.1) | 148 (100) | |

*Based on ICDO codes

The diagnosis of metastasis was at least 1 year after adjuvant treatment (primary treatment) of BC.

Headache was the most common complaint of the patients with brain tumor metastasis (BTM) followed by weakness and lethargy, dizziness, blurred vision/blindness, and convulsions. The majority of studies in the literature have presented the aforementioned symptoms as the main presentations of BM in the patients with MBC.[3,9] However, due to lacking any screening strategy for BM in BC, the authors have alarmed to cautiously consider any new-onset symptoms compatible with

**Table 3: Summary of treatments performed for breast cancer in patients**

| Treatment | | Brain metastases | No brain metastases | *P* |
|---|---|---|---|---|
| | | N (%)/mean±SD | | |
| Treatment objective | Curative | 46 (91.8) | 119 (82.6) | 0.165 |
| | Palliative | 4 (8.2) | 25 (17.4) | |
| Chemotherapy | Yes | 45 (88.2) | 117 (81.2) | 0.352 |
| | No | 6 (11.8) | 23 (16) | |
| | Unknown | 0 (0) | 4 (2.8) | |
| Reason for not doing chemotherapy | 10^ | 1 (16.7) | 12 (52.2) | 0.484 |
| | 40^ | 1 (16.7) | 2 (8.7) | |
| | 998^ | 1 (16.7) | 2 (8.7) | |
| | 999^ | 3 (50) | 7 (30.4) | |
| Hormonotherapy | Yes | 16 (31.4) | 83 (57.6) | 0.005* |
| | No | 33 (64.7) | 58 (40.3) | |
| | Unknown | 2 (3.9) | 3 (2.1) | |
| Reason for not doing hormone therapy | 10^ | 29 (90.6) | 45 (77.6) | 0.165 |
| | 999^ | 4 (9.4) | 13 (22.4) | |
| Surgery | Yes | 46 (90.2) | 120 (83.3) | 0.347 |
| | No | 5 (9.8) | 20 (13.9) | |
| | Unknown | 0 (0) | 4 (2.8) | |
| Reason for not doing surgery | 10^ | 3 (60) | 16 (80) | 0.564 |
| | 20^ | 1 (20) | 1 (5) | |
| | 40^ | 0 (0) | 1 (5) | |
| | 998^ | 0 (0) | 1 (5) | |
| | 999^ | 1 (20) | 1 (5) | |
| Radiotherapy | Yes | 41 (80.4) | 101 (70.1) | 0.286 |
| | No | 9 (17.6) | 34 (23.6) | |
| | Unknown | 1 (2) | 9 (6.2) | |
| Reason for not doing radiotherapy | 10^ | 2 (22.2) | 19 (55.9) | 0.131 |
| | 30^ | 0 (0) | 1 (2.9) | |
| | 40^ | 1 (11.1) | 0 (0) | |
| | 998^ | 1 (11.1) | 4 (11.8) | |
| | 999^ | 5 (55.6) | 10 (29.4) | |
| Targeted therapy | Yes | 24 (47.1) | 29 (20.1) | 0.001* |
| | No | 26 (51) | 113 (78.5) | |
| | Unknown | 1 (2) | 2 (1.4) | |
| Reason for not doing targeted therapy | 10* | 21 (80.8) | 101 (89.4) | 0.085 |
| | 40^ | 1 (3.8) | 0 (0) | |
| | 999^ | 4 (15.4) | 12 (10.6) | |
| Response to neoadjuvant therapy | Complete response | 1 (4) | 0 (0) | 0.221 |
| | Partial response | 0 (0) | 1 (1.4) | |
| | Response noted but no mention if it was complete or partial | 8 (32) | 12 (16.9) | |
| | No response | 0 (0) | 2 (2.8) | |
| | Not applicable, neoadjuvant therapy not given | 16 (64) | 54 (76.1) | |
| | Unknown OR no information OR not documented in patient record | 0 (0) | 2 (2.8) | |
| **Adjuvant treatment** | | | | |
| Duration of adjuvant chemotherapy (month) | | 4.58±1.89 | 3.75±2.39 | 0.089 |
| Chemotherapy protocol | AC | 4 (10.5) | 5 (5.7) | 0.843 |
| | AC followed by docetaxel | 10 (26.3) | 25 (28.7) | |
| | AC followed by paclitaxel | 5 (13.2) | 17 (19.5) | |
| | EC followed by paclitaxel | 3 (7.9) | 6 (6.9) | |
| | TAC | 5 (13.2) | 10 (11.5) | |
| | FAC | 0 (0) | 1 (1.1) | |
| | Paclitaxel and adriamycin | 0 (0) | 1 (1.1) | |
| | Docetaxel | 2 (5.3) | 1 (1.1) | |
| | Paclitaxel | 0 (0) | 1 (1.1) | |

*Contd...*

**Table 3: Contd...**

| | Treatment | Brain metastases | No brain metastases | *P* |
|---|---|---|---|---|
| | | N (%)/mean±SD | | |
| | EC | 0 (0) | 4 (4.5) | |
| | Other | 2 (5.3) | 5 (5.7) | |
| | Docetaxel + cyclophosphamide | 0 (0) | 1 (1.1) | |
| | Paclitaxel + carboplatin | 1 (2.6) | 2 (2.3) | |
| | Unknown | 6 (15.8) | 8 (9.2) | |
| Change/stop in chemotherapy regimen | Yes | 0 (0) | 1 (1.2) | 0.247 |
| | No | 34 (97.1) | 82 (98.8) | |
| | Unknown | 1 (2.9) | 0 (0) | |
| Duration of adjuvant radiotherapy (month) | | 0.67±2.69 | 0.72±1.27 | 0.887 |
| Change in the radiotherapy protocol | Yes | 4 (11.4) | 4 (4.8) | 0.339 |
| | No | 30 (85.7) | 78 (94) | |
| | Unknown | 1 (2.9) | 1 (1.2) | |
| Hormone therapy regiment | None | 1 (5.9) | 0 (0) | 0.235 |
| | Tamoxifen | 11 (64.7) | 45 (62.5) | |
| | Letrozole | 4 (23.5) | 21 (29.2) | |
| | Exemestane | 0 (0) | 4 (5.6) | |
| | Other | 1 (5.9) | 1 (1.4) | |
| | Unknown | 0 (0) | 1 (1.4) | |
| Target therapy regimen | Trastuzumab (herceptin) | 24 (100) | 23 (95.8) | 0.312 |
| | Unknown | 0 (0) | 1 (4.2) | |

10^ Not part of the planned course of therapy. 20^ Was not recommended/administered because it was contraindicated due to patient risk factors. 30^ Was not administered because the patient died before planned or recommended therapy. 40^ Was not administered because of patient refuse. 998^ Was recommended, but it is unknown if it was administered. 999^ Unknown whether it was recommended. FNA: fine needle aspiration, CNB: core needle biopsy, AC: doxorubicin/cyclophosphamide, FAC: fluorouracil/doxorubicin/cyclophosphamide, TAC: docetaxel/doxorubicin/cyclophosphamide, EC: epirubicin/cyclophosphamide

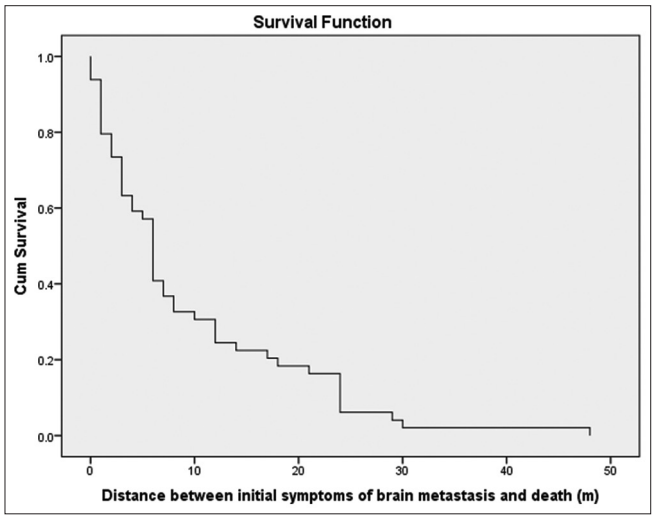


**Figure 2:** Distance between initial symptoms of brain metastasis and death

the involvement of the central nervous system (CNS) as the probable incidence of BM.[9] They continued that symptomatic BM was an independent predictor of devastating outcomes and poor prognosis with short overall survival.[10] Furthermore, the incidence of the symptoms associated with BM probably equals to debilitating outcomes which imposes significant burden on the patients with limited therapeutic strategies.[11,12]

Radiotherapy played the most crucial role in approaching to BM, whereas injectable and oral chemotherapy ranked the second and third, respectively. With the development of perspectives toward BM management in MBC, local strategies, such as radiotherapy and surgery, have attracted the attentions[13]; however, gene sequencing has provided a positive view regarding target therapy to invade the cells responsible for BM only.[9] Nevertheless, local radiotherapy affecting the involved area only has advantages, such as being less invasive and enabling to retain cognitive function.[14] Radiotherapy has been suggested following injectable chemotherapy, as well. Minniti *et al*.[15] have presented that multifraction (3 × 9 Gy) stereotactic radiotherapy after surgery led to 12-month local control of the MBC. Moreover, the systemic treatments, including oral and injectable agents, have led to remarkable control of CNS diseases and improved patients' survival; albeit the presence of BBB significantly impairs the efficacy of anticancerous drugs.[13]

In agreement with the studies in the literature, BM was accompanied by devastating outcomes in this study as more than 95% of the patients died. Although the mean period of the patients' longevity from BC diagnosis was 33 months, they survived for a limited period of 6 months after BM diagnosis. Similarly, Bailleux and colleagues published a review article in which they presented the overall survival of about 8 months after BM diagnosis in the evaluated individuals.[4] The reported median longevity of the patients in the study of Darlix *et al*.[16] was 7.1 months. However, all the researchers have insisted on the significance of the factors, including type of the BC,

**Table 4: Tumor characteristics**

| Variable | | Brain metastases | No brain metastases | *P* |
|---|---|---|---|---|
| | | *n* (%)/mean±SD | | |
| Exact number of nodes positive | | 7.41±5.51 | 7.81±6.71 | 0.749 |
| Perineural invasion | Yes | 20 (47.6) | 38 (33.3) | 0.021* |
| | No | 11 (26.2) | 58 (50.9) | |
| | Unknown | 11 (26.2) | 18 (15.8) | |
| Lymphovascular invasion (LVI) | Yes | 31 (70.5) | 73 (61.9) | 0.445 |
| | No | 9 (20.5) | 36 (30.5) | |
| | Unknown | 4 (9.1) | 9 (7.6) | |
| Breast ulcer | Positive | 0 (0) | 3 (1.8) | 0.570 |
| | Negative | 52 (100) | 145 (98.2) | |
| Inflammatory breast cancer | Positive | 1 (2) | 3 (1.8) | 0.246 |
| | Negative | 51 (98) | 145 (98.2) | |
| T extension (T stage) | TX | 6 (11.8) | 22 (15.3) | 0.200 |
| | T0 | 1 (2) | 0 (0) | |
| | T1 | 8 (15.7) | 7 (4.9) | |
| | T1 (mi) | 1 (2) | 0 (0) | |
| | T1a | 0 (0) | 1 (0.7) | |
| | T1b | 0 (0) | 1 (0.7) | |
| | T1c | 0 (0) | 4 (2.8) | |
| | T2 | 24 (47.1) | 74 (51.4) | |
| | T3 | 8 (15.7) | 27 (18.8) | |
| | T4 | 2 (3.9) | 5 (3.5) | |
| | T4a | 1 (2) | 2 (1.4) | |
| | T4d | 0 (0) | 1 (0.7) | |
| N stage | NX | 6 (11.8) | 26 (18.1) | 0.223 |
| | N0 | 7 (13.7) | 26 (18.1) | |
| | N1 | 11 (21.6) | 21 (14.6) | |
| | N1a | 0 (0) | 4 (2.8) | |
| | N1c | 0 (0) | 1 (0.7) | |
| | N2 | 10 (19.6) | 33 (22.9) | |
| | N2a | 3 (5.9) | 2 (1.4) | |
| | N2b | 0 (0) | 3 (2.1) | |
| | N3 | 12 (23.5) | 24 (16.7) | |
| | N3a | 0 (0) | 3 (2.1) | |
| | N3c | 2 (3.9) | 1 (0.7) | |
| **Tumor markers** | | | | |
| Estrogen receptor | Positive/elevated | 17 (34.7) | 78 (62.9) | 0.004* |
| | Negative/normal: within normal limits | 30 (61.2) | 43 (34.7) | |
| | Not done | 1 (2) | 0 (0) | |
| | Unknown or no information or not documented | 1 (2) | 3 (2.4) | |
| Progesterone receptor | Positive/elevated | 16 (32.7) | 71 (57.3) | 0.013* |
| | Negative/normal: within normal limits | 31 (63.3) | 50 (40.3) | |
| | Not done | 1 (2) | 0 (0) | |
| | Unknown or no information or not documented | 1 (2) | 3 (2.4) | |
| HER2 lab value | Score 0 | 15 (31.9) | 73 (60.8) | <0.001* |
| | Score of 1+ | 3 (6.4) | 11 (9.2) | |
| | Score of 2+ | 7 (14.9) | 17 (14.2) | |
| | Score of 3+ | 22 (46.8) | 19 (15.8) | |
| The result of ER, PR, and HER2 receptors | ER-negative, PR-negative, HER2-negative (triple-negative) | 2 (4.3) | 5 (4.2) | 0.017* |
| | ER-negative, PR-negative, HER2-positive | 2 (4.3) | 5 (4.2) | |
| | ER-negative, PR-positive, HER2-negative | 10 (2.7) | 58 (48.7) | |
| | ER-negative, PR-positive, HER2-positive | 4 (8.7) | 11 (9.2) | |
| | ER-positive, PR-negative, HER2-negative | 8 (17.4) | 21 (17.6) | |

*Contd...*

**Table 4: Contd...**

| Variable | | Brain metastases | No brain metastases | *P* |
|---|---|---|---|---|
| | | *n* (%)/mean±SD | | |
| | ER-positive, PR-negative, HER2-positive | 17 (37) | 15 (12.6) | |
| | ER-positive, PR-positive, HER2-positive | 2 (4.3) | 2 (1.6) | |
| | One or more tests not performed, one or more tests unknown if performed, one or more tests with unknown or borderline results | 1 (2.2) | 2 (1.6) | |
| CISH test interpretation | Positive/elevated | 0 (0) | 1 (0.8) | 0.489 |
| | Negative/normal: within normal limits | 1 (2.2) | 1 (0.8) | |
| | Not applicable | 26 (57.8) | 85 (70.2) | |
| | Ordered but not recorded | 0 (0) | 2 (1.6) | |
| | Not done | 16 (35.6) | 28 (23.1) | |
| | Unknown OR no information OR not documented | 2 (4.4) | 4 (3.3) | |
| FISH test interpretation | Positive/elevated | 1 (2.2) | 5 (4.1) | 0.517 |
| | Negative/normal: within normal limits | 3 (6.7) | 7 (5.8) | |
| | Not applicable | 26 (57.8) | 84 (69.4) | |
| | Not ordered and not performed | 13 (28.9) | 22 (18.2) | |
| | Unknown OR no information OR not documented in patient record | 2 (4.4) | 3 (2.5) | |
| Ki67 value category | Not evaluated | 10 (21.3) | 15 (12.2) | 0.063 |
| | <10% | 2 (4.3) | 7 (5.7) | |
| | 10-20% | 9 (19.1) | 41 (33.3) | |
| | >20% | 19 (40.4) | 54 (43.9) | |
| | Unknown | 7 (14.9) | 6 (4.9) | |

hormone receptors, and HER2 positivity as the determinants of survival among the BMBC. Accordingly, the worst condition was for triple-negative BC followed by HER2-positive' hormone receptor-negative and then hormone receptor-positive individuals.[17]

The extension and nodal involvement were similar in both studied group metastasis to brain or other organs, while perineural invasion was more prominent among the individuals with BM. It is well-documented that perineural invasion is a predictor of poor prognosis among the patients with distant metastasis in BC.[18] However, the association of perineural invasion with BM has not been studied thoroughly. It is not surprising to find this invasive characteristic among the patients with BM considering the invasive behavior of the tumors metastasizing to the brain. Nevertheless, Wu *et al*.[19] did not find any association between the incidence of BM and perineural invasion. Further investigations in this area are strongly recommended.

Those tumors that invaded the brain were mostly HER2-positive, while ER-PR positivity was mostly noted among the lesions metastasizing to the other organs. The association of BM in BC with HER-2 positivity is to the extent that up to 50% of HER-2-positive women with advanced cancers might have distant metastasis to the brain.[20-22] Moreover, despite the poor overall survival of the patients with BM, the studies in the literature have estimated longer survival of even up to 18 months for the HER2-positive individuals.[16-23]

The therapeutic approach to BCBM is one of the most challenging issues with unsatisfactory responses in this state. Considering what aforementioned, radiotherapy played the most critical role in the treatment of our patients followed by chemotherapy and surgery. In fact, BBB is the most significant limitation in the chemotherapeutic approach to BCBM due to the limitations in the penetration of the drugs. Nevertheless, the metastasis to the brain can impair the barrier and lead to the creation of the blood-tumor barrier (BTB).[4] Given that, it has been raised that some agents, such as trastuzumab, $^{14}$C-paclitaxel, $^{14}$C-doxorubicin, and $^{14}$C-lapatinib can penetrate into the BTB and concentrate there.[24-27] Therefore, chemotherapy might be influential in BM, as well.

Recent advancements in the introduction of new agents, particularly those targeting HER2, have opened new windows for the management of BCBM. Although we applied trastuzumab only in our patients, further investigations have shown promising outcomes. Trastuzumab is a monoclonal antibody with a large molecular weight that makes it difficult to cross the BBB, and normal intravenous administration might not be as effective as expected; however, the data about this agent are controversial.[28,29] Some recommend for intrathecal injection of trastuzumab for patients with leptomeningeal disease.[30] Accordingly, recent investigations have shown that applying agents affecting HER2 with better intracranial penetration, such as tucatinib, neratinib, trastuzumab deruxtecan, and trastuzumab emtansine could substantially exert intracranial efficacy against HER2-positive BC.[31-34] Data for these drugs alone or in combination with other medications were encouraging but limited.[32,33,35-37] Inaccessibility to these drugs in Iran has restricted our ability to use them. Therefore, further investigations are strongly recommended.

We found the tumors that metastasized to other organs than brain were morphologically different from those that invaded

**Table 5: Symptoms, treatments, and outcomes in patients with brain metastasis**

| | *n** | % |
|---|---|---|
| **Early brain symptoms** | | |
| Headache | 32 | 61.5 |
| Weakness and lethargy | 14 | 26.9 |
| Dizziness | 8 | 15.4 |
| Blurred vision/blindness | 8 | 15.4 |
| Convulsions | 8 | 15.4 |
| Nausea and vomiting | 6 | 11.5 |
| Numbness | 4 | 7.7 |
| Paralyzed | 2 | 3.8 |
| Balance disorder | 2 | 3.8 |
| Forgetfulness/memory impairment | 2 | 3.8 |
| Sleepy and restless | 1 | 1.9 |
| Distractions | 1 | 1.9 |
| Slurred speech | 1 | 1.9 |
| Neck pain | 2 | 3.8 |
| None | 1 | 1.9 |
| **Treatments for brain metastases** | | |
| Radiotherapy | 37 | 71.2 |
| Injectable chemotherapy | 18 | 34.6 |
| Oral chemotherapy | 14 | 26.9 |
| Surgery | 10 | 19.2 |
| **Outcomes** | | |
| Mortality | 50 | 96.2 |
| | **Median (std error)** | **95% CI** |
| Survival of patients since breast cancer diagnosis [month] | 33 (2.79) | 27.52, 38.47 |
| Survival of patients since initial symptoms of brain metastasis [month] | 6 (0.43) | 5.15, 6.84 |

*Only the number of positive cases is mentioned

brain. Given that, infiltrating ductal carcinoma pathology was predominantly more in MBC affecting other organs than the brain. Further studies in the literature mostly have not divided the tumors in such details. Besides, they mostly emphasized on the tumor markers rather than the pathologies of breast tumor. Nevertheless, Zimmerman and colleagues presented that invasive lobular carcinoma subtypes dominantly metastasized to organs, such as the gastrointestinal and gynecologic tracts, while the rate of BM was greater in those with invasive ductal carcinoma. Moreover, invasive lobular carcinoma was accompanied by poor outcomes.[38] These findings were confirmed in other studies representing higher rate of BM in patients with BCBM whose cancer pathology was invasive ductal carcinoma.[39,40] However, the individuals with invasive lobular carcinoma and BC had worse outcomes compared with counterparts who had invasive ductal carcinoma.[40]

The treatment of most patients with MBC is palliative. All treatments for these patients, including chemotherapy, radiotherapy, and surgery, are considered palliative treatment. Our goal of palliative treatments is to pain relief, reduce side effects, and ameliorate the patients' life expectancy.

Other applied therapeutic approaches and the reasons for what they have not been used were not different between the studied groups. The duration of adjuvant therapy did not statistically differ between the groups; however, it was longer among those with metastases other than BM. Besides that, the applied adjuvant treatments, including the regimens of hormone therapy, target therapy, and radiotherapy, were similar between those who were diagnosed with BCM regardless of the involved organ.

### Limitations

The cross-sectional design of the study is the most prominent limitation, whereas the conduction of further investigations with cohort design and long-term follow-up of the patients can lead to more thorough knowledge in this issue.

## Conclusion

Based on the findings of this study, the BC patients with BM had a remarkable short survival, had a higher rate of perineural invasion, and were mostly positive for HER2. Radiotherapy, chemotherapy, and surgery were the most common approaches to these patients. However, there is no screening protocol for early BM diagnosis, and it can be recommended to perform screening brain imaging for the patients with perineural invasions and HER2-positive individuals.

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### Conflicts of interest

There are no conflicts of interest.

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