

Brain metastases secondary to breast cancer: symptoms, prognosis and evolution

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ABSTRACT

Aims and background. Brain metastases confer a worse prognosis to breast cancer because they determine a severe increase in mortality. The aim of this study was to identify the early symptoms in patients with brain metastases after breast cancer treatment and to evaluate the median survival rate in women with single and operable brain lesions.

Patients and methods. We examined 43 patients with brain metastases secondary to breast cancer treated in the Oncological Institute Prof I Chiricuță, Cluj-Napoca, during the period 2000-2006.

Results. The median interval between the breast cancer diagnosis and detection of central nervous metastases was 21 months. The most frequent symptoms were headache, gait disturbance, nausea and vomiting. Patients with a single brain lesion had a median survival of 23 months compared to only 7 months in case of patients with multiple brain metastases.

Conclusions. The prognosis is worse in patients with solitary brain metastases secondary to breast cancer than in patients who present extracranial metastases. Among factors considered favorable in these patients are a single brain lesion, accessibility to surgery, and the absence of associated extracranial metastases.

Introduction

Every year, one million cases of breast cancer are diagnosed worldwide¹. As a complication of this disease, brain metastases worsen the prognosis, causing a severe increase in mortality. There has also been an increase in the frequency of brain metastases in the last few years, probably due to improvements in treatment of the primary tumor, which leads to an increase in survival²⁻⁵. Autopsy studies suggest that brain metastases occur in approximately 20% of patients with metastatic breast cancer, even if only 10-15% of cases are clinically diagnosed⁵⁻⁷.

Several studies have identified some favorable risk factors in these patients. As risk factors that may be associated with brain metastases are negative hormone receptor status (estrogen or progesterone), lung as the first site of relapse, infiltrating ductal carcinoma histology, and aggressive tumor behavior in young women⁶. A longer survival was reported in patients with solitary brain metastases, a brain tumor less than 4 cm in diameter, the absence of systemic metastases, a controlled primary tumor, or in those treated with chemotherapy, hormone therapy as adjuvant treatment for breast cancer and whole brain radiotherapy (WBRT) for brain metastases^{2,4,8-10}.

Patients and methods

A retrospective study was carried out on 43 patients diagnosed with brain metastases, hospitalized and treated in the Oncological Institute "Prof I Chiricuță" Cluj-Napoca, between 2000-2006 – representing 7.5% of metastatic breast cancer cases.

Key words: brain metastases, breast cancer, prognostic factors, whole brain radiotherapy.

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The median follow-up for these patients was 74 months. Diagnosis of brain metastases was made after the patients complained of various symptoms, according to the metastases location, and following a CT or MRI scan. In case of 3 patients, pathologic analysis confirmed the results of the stereotactic biopsy.

Patient characteristics

The most important characteristics of the patients (42 women and 1 man) are listed in Table 1. The primary tumor was located in the left breast in 19 cases, in 24 patients the first location was the right breast, and in 4 cases the lesion affected both breasts. At the moment of breast cancer diagnosis, 6 patients were stage II, 16 stage III, and 8 stage IV (graded according to UICC criteria). Modified radical mastectomy was performed in 44% of the breast cancer patients, and chemotherapy was administered in 35%. Hormonal receptor status was negative in 14 and positive in 8 patients. Receptor status was unknown in 21 patients.

Statistical analyses

Survival curves were determined by the Kaplan-Meier method and compared using Mantel-Cox statistics (log-rank test). All statistical analyses were performed using Prism 5.0 software (GraphPad, San Diego, CA, USA). Dif-

ferences were considered statistically significant when $P < 0.05$.

Results

The median age at the diagnosis of breast cancer and brain metastases was respectively 49 years (range, 28-65) and 50 years (range, 28-66), whereas the median interval between both diagnoses was 21 months (range, 5-122). The median survival after diagnosis of brain metastases was 10 months. Figure 1 presents the overall survival in 43 patients. Only 4 patients were still alive at last follow-up.

Twelve patients had single brain metastases and 31 had multiple brain lesions. Median survival for patients with single metastases was 23 months and for patients with multiple brain metastases, 7 months (Figure 2) (log-rank test, $P = 0.0015$).

Brain metastases were the first site of metastatic involvement in 26 cases (60%). In 25 cases (58%), they were

Table 1 - Characteristics of 43 patients with brain metastases from breast cancer

Characteristic	No.	%
Age (yr)		
≤50	25	58
>50	18	42
Treatment of BC		
Surgery	19	44
Radiotherapy	2	5
Chemotherapy	15	35
Unknown	7	16
Interval BC-BM (mo)		
<12	21	49
13-24	12	28
25-36	5	11
37-60	2	5
>60	3	7
No. of BM		
Single	12	28
Multiple	21	72
BM size (mm)		
≤ 40	22	51
> 40	8	19
NA	13	30
BM associated with extracranial lesions	18	42
Bone	10	
Liver	9	
Lung	7	
Pleurae	3	
Ovary	1	
Peritoneum	1	

BC, breast cancer; BM, brain metastases; NA, not assessed.

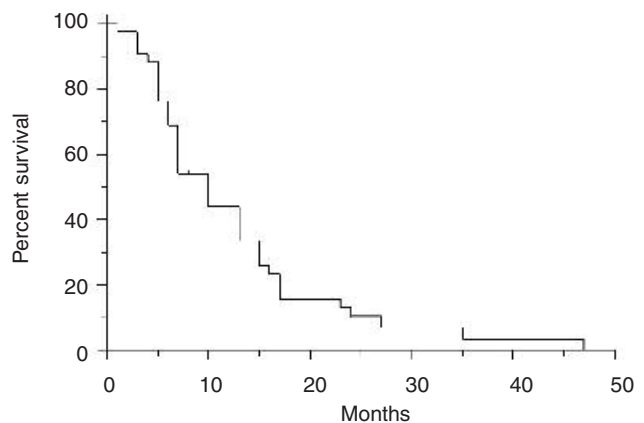


Figure 1 - Overall survival in 43 patients with brain metastases from breast cancer. Median survival was 10 months.

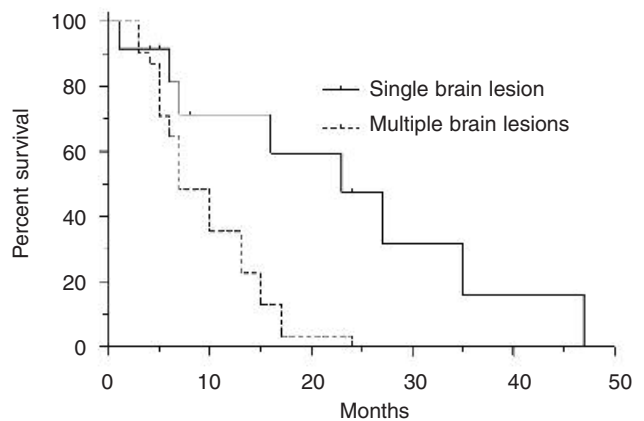


Figure 2 - Survival of patients with solitary (solid line, $n = 12$) or multiple (dashed line, $n = 31$) brain metastases ($P = 0.0015$).

the exclusive sites, and the median survival for these patients was 9 months. Most commonly, brain metastases occurred in association with bone (10 cases) or liver metastases (9 cases). These patients had a shorter survival (6 months) than patients with solitary brain metastases (9 months). In 16 cases, extracranial metastatic disease was discovered before the brain metastases.

One patient developed late brain metastases (they appeared 10 years after the diagnosis of breast cancer). The patient developed multiple brain metastases and survived 24 months after the diagnosis. The male patient had a worse prognosis because his extracranial metastases (liver and lung) were associated with brain injury.

As signs of complications of their disease, patients with brain metastases presented various symptoms (Table 2). The most common complaints were headache (20 cases), gait disturbances (19 cases), and nausea and vomiting (18 cases). Several symptoms developed within a few weeks and depended on the size, number and location of metastatic lesions. Patients with lesions in the cerebral hemispheres (27 cases) presented alterations in cognition, mental status and behavior. Lesions in the cerebellum (12 cases) produced gait disturbance and headache. There was also 1 case of a rare localization in the optic nerve. Eighteen patients who had edema also had nausea and vomiting and deficits in motor function, speech or vision.

Four different treatments as well as their concomitant combinations were applied in the therapy of the brain metastases: surgery, radiation, chemotherapy and hormone therapy. Only 2 patients (5%) had surgery alone and another 7 (16%) had surgery associated with radiotherapy. The median survival for patients subjected to surgery and radiation was 17 months, and 3 of those women are still alive. Systemic chemotherapy as the first line of treatment was applied in 3 cases and in association with radiation in 2 cases. The most frequently applied therapy for patients with multiple brain metastases was radiation alone – WBRT – 26 cases (60%). The median survival for patients who underwent whole brain irradiation was 7 months. WBRT was applied in a total dose

of 30, 20 or 18 Gy; only one patient received radiation to 12 Gy. For 3 cases, data on the treatment of brain metastases were not available. For the second line of treatment, dexamethasone was associated to chemotherapy or radiation in 31 patients (72%). The dosage depended on the symptoms and on signs of edema.

Discussion

The causes of brain metastases secondary to breast cancer are not well known, but there are some hypotheses. Carey *et al.*¹¹ formulated three hypotheses about brain metastases causality: first, the blood-brain barrier hypothesis, then metastatic longevity, and the possibility of a tropism of metastatic breast cancer involvement for the CNS.

Management of brain metastases is difficult because the patients have a poor prognosis^{3,12,13}. Untreated patients usually live only for several weeks, whereas different types of treatment can prolong life for a short period of time, compared to other patients with metastatic breast cancer but without brain involvement. Mu-Tai *et al.*⁴ studied 62 patients with brain metastases from breast cancer and reported a survival rate of 7.3 months. In another study on 30 cases of brain metastases from breast cancer, the median survival was 9 months¹⁴. Nevertheless, similar studies reported median survivals of 5, 6, 13.1 and 16.2 months^{3,7,15,16}.

Some authors consider that breast cancer is more common in younger, premenopausal patients, who tend to have more aggressive forms of malignancy than older patients^{2,4,9,17}. In our study, the group aged between 45 and 54 years had the highest incidence of brain metastases. The study of Nieder *et al.*¹⁸ reported a better survival for patients less than 50 years of age than for those over 50 years and age as a significant prognostic factor. Mu-Tai *et al.*⁴ reported a median survival for patients aged under 50 years and over 50 years of 10.2 and 4.3 months, respectively. We compared the two groups of patients, but the difference was not statistically significant (median, 8 vs 7 months).

Symptoms of brain metastases usually reported in previous studies are headache, nausea and vomiting, motor weakness, gait disturbance, mental status changes, seizures, speech, vision or neurologic deficit^{5,7,13,19}. In our study, most of the patients had headache, gait disturbance and nausea with vomiting. Tsukada *et al.*²⁰ identified 2 patients with ataxia, another 2 patients with aphasia, and 5 patients with an affected cranial nerve, whereas Wronski *et al.*¹⁶ had 15 patients who suffered from hemiparesis.

In our study, the presence of systemic disease at the time of brain metastases diagnosis reduced median survival from 9 to 6 months. Extracranial metastases decreased median survival (4 months) compared to patients without systemic metastases (16 months) in the

Table 2 - Neurologic symptoms and signs

Symptoms	No. of patients
Headache	20
Gait disturbance	19
Nausea and vomiting	18
Hemiparesis	16
Intracranial pressure	12
Visual disturbance, diplopia	8
Confusion, personality changes	8
Fatigue, weakness	7
Conscience disturbance	6
Speech deficit (dysarthria)	2
Seizures	1

study of Boogerd *et al.*⁶ Most frequently associated extracranial metastases were in the skeletal tissue, liver or pulmonary parenchyma^{9,11,15,19-26}.

In patients with brain metastases secondary to breast cancer, the survival rate depends even on the number of brain metastases. We found a significant difference in the survival of patients with single and of those with multiple brain lesions (23 *vs* 7 months). Mu-Tai *et al.*⁴ and Lederman *et al.*¹⁶ had similar results in their studies. However, the number of brain metastases did not significantly influence overall survival in the studies of Wronski *et al.*¹⁶ and Combs *et al.*¹³

Surgery is an important treatment in brain metastases, but its usefulness is limited. It is applicable to a very selective group of patients, with a single, surgically accessible metastasis, when favorable prognostic factors and systemic disease control are present^{5,27,28}. In our study, 9 of 12 patients with single metastases underwent surgery, and their median survival was 17 months. Due to the possibility of excision, patients with single metastases are considered a distinct subset of patients with a marked response to the treatment⁶. To support this theory, Nieder *et al.*²⁹ published a case report about a 51-year-old woman who developed a single brain metastasis found 11 months after the primary diagnosis; after surgery and WBRT, she had a disease-free survival of more than 10 years²⁹.

The remaining 3 patients with single metastases, but with systemic disease, received WBRT, like most patients with multiple brain metastases. Some authors consider that patients treated with whole brain irradiation have a high response rate and a transient palliation, but also a relatively short period of response^{5,15}. The benefit of WBRT for palliation can be limited, largely due to the presence of extracranial metastases^{15,30-34}.

Although breast cancer is a chemosensitive tumor, chemotherapy has not been used for decades in the treatment of brain metastases secondary to breast cancer, because until recently it was believed that drugs cannot pass the blood brain barrier^{5,15,20,24}. Recent experience suggests that progress in the treatment of brain metastases from breast carcinoma might be gained by the use of chemotherapy, based on the fact that brain metastases are at least as responsive as other metastatic sites to chemotherapeutic drugs^{5,35}. The advantage of using systemic chemotherapy in the treatment of brain metastases was simultaneous control of both intra- and extracranial metastases, which was reflected by improved survival. An improvement in quality of life and functional neurologic status were also noticed in most treated patients^{5,15}. Despite these encouraging results, the only treatment that is recommended for inoperable and multiple brain lesions from breast cancer is radiotherapy^{26,36}. In our study, 3 patient received chemotherapy as the first line of treatment and 2 patients had a combination of radiotherapy and chemotherapy. Six other patients received chemotherapy in the second

line of treatment and others received hormone therapy or corticosteroids.

Late brain metastases are known as metastases that appear at least 10 years after the breast cancer diagnosis. Our patient with late brain metastases developed multiple lesions that were treated with WBRT. The absence of extracranial metastases in this patient also contributed to a survival of 2 years after the brain metastases diagnosis. Piccirilli *et al.*³⁷ considered this kind of brain lesion as a rare event, but drew attention to the fact that in the presence of neurologic symptoms (and neuroradiological evidence of a cerebral neoplasm in 1 patient with a history of breast cancer), the presence of late brain metastases from the primary tumor can be suspected³⁷.

Conclusions

Any patient treated for breast cancer who presents signs such as headache, nausea, dizziness, vomiting or neurologic deficit should be suspected of developing brain metastases and would benefit from contrast computed tomography and/or magnetic resonance imaging study of the head to rule out possible brain lesions.

The present study suggests that medical behavior in patients with one brain lesion is different from that in patients with multiple brain metastases. Surgery with postoperative irradiation seems the most beneficial treatment for patients with a single brain lesion. WBRT was the therapy most often applied in cases of multiple brain metastases. An improvement was found following treatment with corticosteroids in patients with single and multiple metastases. The strategy of treatment for brain metastases is evolving and could include stereotactic radiosurgery or chemotherapy. However, it must be adapted and individualized for every patient, according to his needs and disease status.

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