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Survival analysis of patients with breast cancer and secondary brain metastasis: a retrospective cohort

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ABSTRACT

Introduction: The presence of brain metastases secondary to primary breast cancer implies a worse prognosis for those affected. Therefore, the aim of this study was to determine the median survival after the diagnosis of brain metastasis in patients with breast carcinoma in a center in northeastern Brazil. **Methods:** The medical records of 345 patients diagnosed with breast cancer, treated between 1998 and July 2018, were analyzed. Those with brain metastasis along with their treatment performed and survival were identified. **Results:** Nine (2.6%) patients had brain metastasis; the mean age was 56.8 years. The mean survival time determined by the Kaplan-Meier method was 23.8 months (95%CI 6.9–40.8). Seven patients (78%) died from the disease and two were lost to follow-up (22%); invasive carcinoma of no special type was the most frequent (78%). Molecular classification by immunohistochemistry was possible in seven patients: five luminal B subtype cases, one luminal A case and one triple-negative case; luminal B subtype was associated with longer survival: 23.3 months (95%CI 3.0–43.6). As for the initial clinical staging, according to the TNM Classification of Malignant Tumors, there was one IA case, one IIA case, three IIB cases and two IIIB cases. Three patients underwent modified radical mastectomy, and six underwent conservative treatment (quadrantectomy); there was no statistical difference in survival between the different forms of treatment (p=0.771). **Conclusion:** The median survival after diagnosis of brain metastasis from breast cancer was 23.80 months.

KEYWORDS: breast neoplasms; brain neoplasms; conservative treatment; survival rate; immunohistochemistry.

INTRODUCTION

Breast cancer is the most prevalent type of cancer in Brazil and worldwide[1]. Despite the advances that have made, mainly in the areas of prevention and treatment, breast cancer remains the main cause of cancer mortality in Brazil among women, with a mortality rate adjusted by the world population of 14.23 deaths/100,000 women, in 2019, according to Brazil's National Cancer Institute (INCA)[2].

The progression of primary breast cancer to metastatic forms, especially those with cerebral involvement, is an impacting factor for the increase in morbidity and mortality of this disease[3]. Breast cancer is the second type of cancer with the highest risk to develop brain metastases[4]. In these cases, in general, the prognosis is poor and quality of life and life expectancy of patients is substantially reduced. This negative impact on life varies according to the affected location of the central nervous system and the number of metastases at the time of diagnosis. As an example of this, according to a retrospective North American cohort study, approximately 80% of the 420 patients who presented with tumor spread to the brain or another region of the central nervous system died within the first year of follow-up[5]. Another aggravating factor is the fact that the diagnosis is not always made in a timely manner, due to the absence of clinical manifestations of these lesions until death[6].

In Piauí, the estimates for breast cancer for the 2020/2021 biennium are 590 new cases[7]. Despite this number of cases,

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there are not many studies in the literature on the incidence of brain metastasis and analysis of survival time in this population. Accordingly, the main objective of the present study was to evaluate the median survival after the diagnosis of brain metastasis in a retrospective cohort of patients from an oncology clinic in Teresina, Piauí, Brazil.

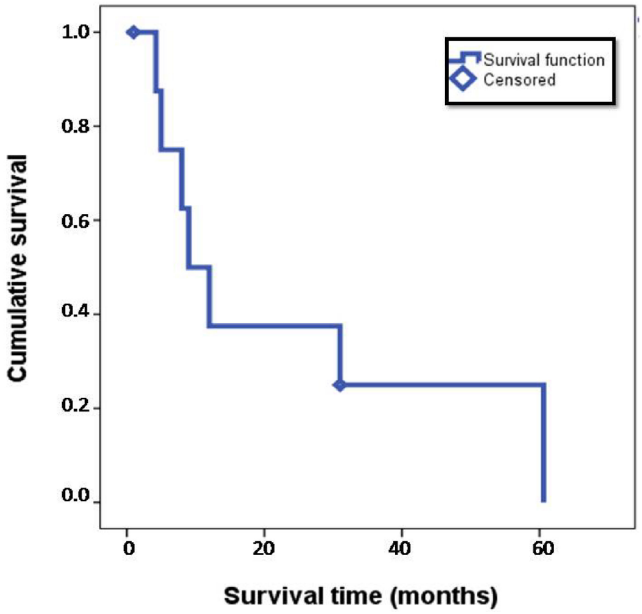
METHODS

The present study was conducted according to the STROBE statement for cross-sectional studies[8]. We analyzed the medical records of a cohort of 345 patients diagnosed with primary breast cancer, treated between January 1998 and June 2018, at a private clinic in Teresina, Piauí. The sample space had a 95% confidence level considering the female population of Piauí as 1,600,000 (according to the 2010 IBGE census), with a margin of error of 5.28%.

Those who had brain metastasis (12 cases) were identified. Three cases were excluded from the study because despite the presence of neurological symptoms, the diagnosis of tumor spread was only possible post mortem, which would compromise the determination of survival time; in addition, these cases did not have enough data regarding primary breast cancer to allow the assessment of prognostic factors. In the end, nine cases remained for descriptive analysis of variables and determination of survival rate and mean and median survival time using the Kaplan-Meier method. Median survival is understood as the time required for 50% of the sample to reach the outcome (death due to metastasis). To determine the statistical significance and confidence intervals of the influence of possible prognostic factors on survival (histological type, molecular subtype, tumor size, degree of differentiation and treatment), the log rank test was used by means of the IBM SPSS Statistics software 20. The study was approved by the Research Ethics Committee of UFPI – CAAE: 94518518.9.0000.5214. Substantiated approval :2.948.415.

RESULTS

Nine (2.6%) of the 345 patients had brain metastasis. The survival function determined using the Kaplan-Meier method is shown in Figure 1. The mean survival time was 23.80 months (95%CI 6.854–40.759), with a maximum value of 60.6 months and a minimum of 1 month (Figure 1); the median survival time was 9 months (95%CI 3.5–14.5); the 3-year overall survival found was 11.11%. The mean and median ages at diagnosis were respectively 56.8 and 50 years; the mean time between the diagnosis of breast cancer and the onset of brain metastasis was 36.9 months (range between 6 and 58 months). Seven patients (78%) died from the disease and two were lost to follow-up (22.22%), which were censored during the analysis.



Source: Prepared by the authors on the basis of study of online medical charts.

Figure 1. Survival curve of women diagnosed with brain metastasis secondary to primary breast cancer, treated at a private center in Piaui.

Invasive carcinoma of no special type was the histological type in nine cases; there was one case of papillary carcinoma (Table 1). Regarding the degree of differentiation, five cases had grade 2, two grade 3, and one grade 1. The average size of the largest dimension of the tumors in the analyzed cases was 1.96 cm (the largest with 3.5 cm and the smallest with 1 cm). There was no statistical difference in the risk of larger tumors progressing to metastasis. The presence of an undifferentiated histological grade had a median survival of 8.5 months (95%CI 7.5–9.5). There was no statistical increase in survival when comparing grades 2 and 3 (p=0.654).

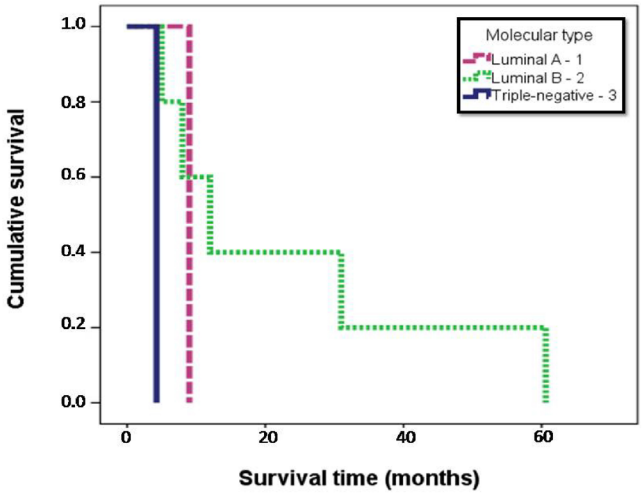
Molecular classification was possible in seven patients: five luminal B subtype, one luminal A case and one triple-negative case; patients with the luminal B subtype had a longer median survival – 23.3 months (95%CI 3.0–43.6; p=0.044<0.05). The triple-negative case had a lower median survival (4.25 months) (Figure 2). There was no study of germline mutations in hereditary breast cancer susceptibility genes in any of the cases.

As for clinical staging, there was one case of IA, one IIA, three IIB and two IIIB. Three (33%) of the patients underwent modified radical mastectomy, and six underwent conservative treatment (quadrantectomy). Three patients received neoadjuvant chemotherapy and five underwent adjuvant chemotherapy; in addition to these, three patients (30%) also used hormone therapy (tamoxifen). There was no statistical difference in survival when comparing the different treatments. (p=0.771).

Table 1. Characteristics of cases of primary breast cancer that developed brain metastasis.

Histological type	Histological grade	Molecular subtype	Treatment	Survival (months)
ICNST	3	Luminal B	neo CT+Sur+RT	60.60
ICNST	3	Luminal B	neo CT+Sur+RT	8.00
ICNST	3	Luminal A	Sur	9.00
ICNST	2	Luminal B	Sur+RT+CT+TMX	12.00
ICNST	1	NI	Sur+RT+CT+TMX	1.00
ICNST	2	Luminal B	Sur+RT+CT	5.00
ICNST	2	Triple-negative	Sur+RT+CT	4.25
ICNST	2	Luminal B	Sur+RT+CT	31.00
PC	NI	NI	NI	31.00

ICNST: invasive carcinoma of no special type; PC: papillary carcinoma; neo CT: neoadjuvant chemotherapy; CT: adjuvant chemotherapy; Sur: surgical procedure; RT: adjuvant radiotherapy; TMX: tamoxifen.
Source: Prepared by the authors on the basis of study of online medical charts.



Source: Prepared by the authors on the basis of study of online medical charts.

Figure 2. Survival curve of women diagnosed with brain metastasis secondary to primary breast cancer, according to molecular subtype.

DISCUSSION

In the present study, the median survival of patients with brain metastasis was 23.8 months (95%CI 6.9–40.8). We identified luminal B subtype as associated with a better outcome, with a median survival of 23.3 months (95%CI 3.0–43.6; p=0.044). The presence of an undifferentiated histological grade led to a worse prognosis, with a mean survival of 8.5 months (95%CI 7.5–9.5); however, there was no significant difference in survival when comparing grades 2 and 3 (p=0.654).

The mean time between the diagnosis of breast cancer and the onset of brain metastasis was 36.9 months (range between 6 and 58 months). Among the patients analyzed, seven (78%) died from the disease and two were lost to follow-up (22%), the latter being censored during the analysis. Survival time ranged from 1 – 60.6 months (Figure 2).

A Chinese study, published in 2019, using the Surveillance, Epidemiology, and End Results Database, analyzed the survival of 18,322 American patients diagnosed with metastatic breast cancer. Patients with brain metastasis had a worse prognosis when compared to those whose cancer progressed to metastases to other organs; they had a lower breast cancer-specific survival rate and lower overall survival; p<0.001, for both)[9]. This was observed in our cohort: the median survival found after the Kaplan-Meier analysis in our cohort was 9 months (95%CI 3.5–14.5 months), similar to the median value found in the US population (8 months for patients with brain metastasis with 95%CI 5.7–10.4 months)[9].

On the other hand, the overall 3-year survival rate found was 11%; lower than that found in the survival analysis of the US population, 19.90%[9]. An important limitation for this was our small number of cases of patients who developed brain metastasis in the present series.

Nine (2.6%) of the patients had brain metastasis in the present study; the mean age was 56.9 years, while the median age was 50 years. This number was similar to the median age of 56 years found in a European multicenter study that evaluated 668 patients with brain metastasis secondary to primary breast cancer. Furthermore, according to the literature, survival tends to decrease in patients with advancing age (over 40 years), when compared to younger patients (under 40 years)[10]. Only one patient in our sample was younger than 40 (31 years old).

Growing evidence indicates that the occurrence of distant metastases differs according to the histological subtype of primary breast cancer. According to the World Health Organization (WHO), there are 21 histological types of breast cancer, divided into non-invasive carcinomas, which include carcinomas in situ and Paget's disease, and invasive carcinomas, such as invasive

carcinoma of no special type (invasive ductal carcinoma) and other rarer types[11].

According to the literature, the most common histological type is invasive carcinoma of no special type[11]; this was also the most frequent type in patients who developed brain metastasis in the sample of the present study (88.89% of cases), as can be seen in Table 1. However, there was no statistically significant increase in risk in our sample, demonstrating that invasive carcinoma of no special type is most associated with brain metastasis (relative risk (RR) 3.75; 90%CI 0.35–18.56). However, this finding is in agreement with a multinational and multicenter cohort study, whose sample space involved 2,473 patients with primary breast cancer and brain metastasis. Invasive carcinoma of no special type was diagnosed in about 80% of these patients[12].

Among the invasive cancers of no special type, it is possible to see in Table 1 that three belonged to the most undifferentiated form, with one case being grade 1 (least undifferentiated) representing 11% of cases, and five grade 2 (56%). In one of the cases, it was not possible to assess the degree of tumor differentiation. When considering the degree of differentiation as a prognostic factor, there was no statistically significant difference in survival, when we compared the survival curves for grades 2 and 3 (p=0.654). Grade 3 patients had a median survival of 8.5 months (95%CI 7.5–9.5). The literature, in turn, points out that the more undifferentiated the tumor, the worse the prognosis tends to be, and therefore, the longer survival is usually found in patients diagnosed with grade 1 and 2 cancer; however, the small number of cases in our study severely limits this analysis[13]. Even with this good prognostic correlation, some cases of more differentiated histological grade may develop metastases, with the invasive ductal subtype being more commonly associated with this type of tumor dissemination[14].

Among the patients, there was also one case of papillary carcinoma with an unknown degree of differentiation, as shown in Table 1. Papillary carcinomas tend to have a better prognosis compared to invasive carcinoma of the no special type, and this patient had a 31-month survival rate[15].

Regarding size, the mean of the largest dimension of the tumors was 1.96 cm (ranging from 1 – 3.5 cm); there was no statistical difference in the association between a larger size of the primary tumor and the probability of progressing to brain metastasis. This limitation is possibly due to the small number of patients in our series. According to Wang et al. (2019), the size of the primary tumor is one of the variables with the worst prognosis for survival (hazard ratio HR>1, p<0.001), especially those with T4 classification[9].

Furthermore, the literature suggests that the survival time for patients with brain metastases differs significantly between the molecular subtypes of breast cancer. These are classified according to the presence or absence of estrogen (ER) and progesterone (PR) receptors or human epidermoid growth factor receptor 2 (HER2) in luminal A (ER+ and/or PR+ and HER2-), luminal B (ER+ and/or PR+ and HER2+), triple-negative (ER-, PR-, HER2-) and enriched or overexpressed HER2 (ER-, RP-, HER2+)[13]. Breast cancer subtypes with high expression of the HER2 marker and triple-negative (TN) are more prone to brain metastasis during the course of the disease, with triple-negative being associated with lower survival[15]. There is evidence that approximately 30% of primary breast cancers with HER2+ and about 50% of triple-negative cases progress with central nervous system invasion[16]. In the present study, molecular classification was possible in seven patients: luminal B subtype was the most prevalent (five cases); there was one luminal A case and one triple-negative case. There was a longer median survival (23.32 months) in those patients who had luminal B subtype (95%CI 3.01–43.63) and thereby a better outcome (Figure 2).

This result was consistent with that obtained by a retrospective French study that analyzed 4,118 patients with brain tumors secondary to breast cancer: the overall survival for HER2+/HR+ (luminal B) tumors was the highest (18.9 months; HR=0.57, 95%CI 0.50–0.64; p<0.0001)[17] when compared to the other molecular subtypes. Although the triple-negative subtype had a lower mean survival (4.25 months), accurate statistical analysis was not possible, because of the limiting factor of having only one patient with this characteristic in our series. Also, according to Darlix[17], patients with triple-negative tumors (HER2-/HR-) had a worse outcome, with an overall survival of 4.4 months (HR=1.55, 95%CI 1.42–1.69; p<0.0001)[17].

Another limitation of the present study was the fact that none of the nine cases (100%) included genetic tests, such as testing for the BRCA-1 gene. Nonetheless, five of them (55%) had an indication for genetic studies according to the NCCN (National Comprehensive Cancer Network), because primary breast cancer was diagnosed before the age of 50[18]. Furthermore, one of these five was within another criterion, as it met the triple-negative molecular classification. A French cohort study showed that positivity for BRCA-1 is associated with the development of high-grade tumors, as well as with a high rate of mitosis[19]. For a better approach, the American Society of Breast Surgeons, considering the results of a prospective multicenter study of genetic testing, currently recommends performing multigene panels in all breast cancer patients[20]. In addition, there are associations in the literature between this alteration and evolution with triple-negative tumors[21].

Regarding clinical staging (TNM) at the time of diagnosis, there was one case of IA, one IIA case, 3 IIB cases and two IIIB cases. The more advanced the stage at diagnosis, the worse the patient's prognosis tends to be. Patients diagnosed at stage 4, for example, have a median survival of 2 – 3 years[9]. It is important to emphasize, however, that in the estimation of survival, the TNM classification must be evaluated together with other individual factors. Its use for prognosis disregards variables such as

genetic, pathological (cell replication rate or tumor subtype) or treatment differences[22].

The factors are directly related to the therapeutic management of the patient. The spread of metastatic breast cancer makes treatment difficult, where the cancer is considered incurable and with a poor prognosis. The final objective of the treatment is therefore palliative to improve the patients' symptoms and delay the spread of the tumor[23]. In this cohort, 33% of the patients underwent modified radical mastectomy, and six underwent conservative treatment (quadrantectomy); three patients received neoadjuvant chemotherapy, five underwent adjuvant chemotherapy, while three patients (30%) also used hormone therapy (tamoxifen).

For patients with metastasis, the decision to treat with systemic chemotherapy or hormone therapy depends on a few factors: tumor location and extent, the presence of hormone receptors, age, menopausal profile, and disease-free period[23].

Primary tumor resection can increase patient survival when performed at early stages, and it also impacts disease recurrence[24]. In the management of metastatic tumors, however, evidence shows that aggressive local therapy does not lead to additional benefits to patient survival. However, in certain circumstances, surgical resection of the primary tumor of stage IV breast cancer works as palliative care in the control of ulcerations, bleeding and infections, and therefore, it should be considered in a multidisciplinary approach[23]. In the present study, all patients were operated on (100%), and adjuvant or neoadjuvant treatment was individualized. However, there was no statistically significant difference in survival when comparing the different forms of treatment (p=0.771).

An alternative for the treatment of brain metastasis is stereotactic surgery by radiotherapy. This type of intervention is indicated when the patient has less than four foci of brain metastasis. However, the prognosis is still guarded. In a cohort study with 50 patients, the median survival found after this approach was 33 months[25].

CONCLUSION

The median survival after diagnosis of brain metastasis from breast cancer was 23.8 months. The luminal B subtype was associated with a better outcome, with a mean survival of 23.3 months

AUTHORS' CONTRIBUTIONS

SCV: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. FECSF: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft. GMA: Investigation, Data curation, Methodology, Writing – original draft, Visualization. LLSB: Investigation, Data curation, Formal Analysis, Writing – original draft, validation. MACN: Investigation, Data curation, Formal analysis, Visualization, Writing – original draft.

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