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Brain metastases from breast cancer

Joana Santos [a], Joana Arantes [b], Eduarda Carneiro [c], Diana Ferreira [c], Susana Maria Silva [a,d,e], Susana Palma de Sousa [f], Mavilde Arantes [a,c,d,e,*]

[a] Faculty of Medicine of the University of Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal
[b] Psychology School, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal
[c] Division of Neuroradiology, Department of Radiology, Portuguese Institute of Oncology, R. Dr. António Bernardino de Almeida 865, 4200-072 Porto, Portugal
[d] Unit of Anatomy, Department of Biomedicine, Faculty of Medicine of the University of Porto, 4200-319 Porto, Portugal
[e] Center for Health Technology and Services Research (CINTESIS), Rua Dr. Plácido Da Costa, s/n, 4200-450 Porto, Portugal
[f] Department of Medical Oncology, Portuguese Institute of Oncology, R. Dr. António Bernardino de Almeida 865, 4200-072 Porto, Portugal

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ABSTRACT

Background: Breast cancer (BC) is one of the commonest causes of brain metastases (BM): approximately 10–16 % of patients diagnosed with metastatic breast cancer will eventually develop BM during the course of their disease, however, certain subtypes have a higher risk of this event. The aim of this analysis was therefore to evaluate the prognosis and the pattern and imaging features of BM according to different BC subtypes.
Patients and methods: We retrospectively reviewed the case records of patients with breast cancer and evidence of brain metastases from the database of IPO Porto between 2014–2018. The data obtained were statistically analysed.
Results: We analysed 147 patients with BM from BC. The triple-negative subtype had the shortest overall survival (OS) after BM, besides a short period of time between BC and BM. HER2 overexpressing tumors had the longest OS. The estrogen-receptor positive group had the greatest interval between initial BC diagnosis and diagnosis of BM. Larger lesions showed a heterogeneous contrast enhancement and were heterogeneous pn T2WI sequences; a hyposignal on T2*WI was also associated with larger lesions. Triple-negative BC tended to have more heterogeneous lesions on T1WI. We noticed that the hippocampus is rarely affected by metastatic lesions.
Conclusions: Based on the BC subtype it is possible to make a prediction about the prognosis of the disease and some imaging features of the BM, but not about their pattern of distribution. These data support further research concerning prevention, early detection, and treatment of BM from BC.

1. Introduction

Breast cancer is a heterogeneous and a complex disease [1]. It can be clustered into different biological subtypes according to expression of specific biomarkers, such as estrogen receptor (ER), progesterone receptor (PR) and the overexpression of human epidermal growth factor receptor 2 (HER2), which can be defined by immunohistochemical (IHC) markers or gene expression profiles [2]. The subtype triple-negative is defined by the absence of expression of hormonal receptors, particularly PR and ER, and lack of overexpression of HER2 [3].

Breast cancer is the second most common cause of metastatic brain disease with significant impact on patients' quality of life and survival [4]. The risk of developing brain metastases has been reported to range from 10 to 16 % among living, advanced breast cancer patients and as high as 30 % in autopsy series [5]. The brain is the first site of metastases from breast cancer in 12 % of patients [6]. Even if all breast cancer

Abbreviations: ADC, apparent diffusion coefficient; BBB, blood-brain barrier; BC, breast cancer; BG, basal ganglia; BM, brain metastases; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; CTCs, circulating tumor cells; DWI, diffusion-weighted images; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemical; IMRT, intensity modulated radiotherapy; IPO, Portuguese Institute of Oncology; MRI, magnetic resonance imaging; OS, overall Survival; PR, progesterone receptor; RANO-BM, Response Assessment in Neuro-Oncology - Brain Metastases; SD, standard deviation; SPSS, Statistical Package for Social Sciences; SRS, stereotactic radiosurgery; T1WI, T1-weighted images; T2WI, T2-weighted images; T2*WI, T2*-weighted images; TN, triple-negative; VS, versus; WBRT, whole brain radiotherapy.

* Corresponding author at: Unit of Anatomy, Department of Biomedicine, Faculty of Medicine of the University of Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal.
E-mail address: mavildearantes@med.up.pt (M. Arantes).

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patients are at risk for brain metastases, some factors that increase this risk have already been identified, as younger patients, poorly differentiated tumors (high grade) and certain breast cancer subtypes such as ER-negative, triple-negative and HER2 overexpressing tumors [7].

Magnetic resonance imaging (MRI) is widely used in diagnosing brain metastases and differentiating them from other intracranial tumors [8]. The Response Assessment in Neuro-Oncology - Brain Metastases (RANO-BM) criteria established minimum requirements for brain imaging. They suggest that the imaging should be made only on 1.5 T and 3 T MR scanners. A standard study should be performed that includes 3D T1-weighted images (T1WI) acquisition pre-contrast (MPRAGE, 3D IR FSPGR T1WI), diffusion weighted imaging (DWI), 2D FLAIR, T2WI-TSE and 3D T1WI acquisition after intravenous injection of contrast agents (MPRAGE, 3D IR FSPGR T1WI). To point out that DWI - usually with two diffusion b-values of 0 and 1000 s/mm^2 - is acquired in order to provide, among other features, information about tumor cellularity through measurement of the apparent diffusion coefficient (ADC) [9]. In addition to these sequences some centers also use the T2*WI to depict hemorrhage, calcification and iron deposition in the lesions. Brain metastases from breast cancer can differ in number, size and location; some studies have already found an association between some molecular subtypes of breast cancer and the pattern of brain metastases. Tomasevic et al. [10] demonstrate that HER2-positive patients were more likely to metastasize into the cerebellum. Lekanidi et al. [11] showed that ER-negative HER2-positive patients were more likely to present with a superior number of lesions, more brain stem or occipital metastases, and hydrocephalus. Niwinska et al. [12] showed that patients with a triple-negative tumor-subtype had a higher probability to metastasize to the leptomeninges. Laakmann et al. [13] showed that patients with positive ER, PR or HER2 status had a significantly lower number of brain metastases at diagnosis; that patients with a HER2-positive tumor developed cerebellar metastases more frequently compared with HER2-negative patients; whereas patients with triple-negative primary tumors had leptomeningeal disease more often.

Several local treatments for brain metastases, such as radiotherapy or surgical resection, are now available [14]. Radiotherapy options include whole brain radiotherapy (WBRT) typically given at doses of 3–4 Gy per fraction over 5–10 treatments sessions; stereotactic radiosurgery (SRS) which precisely delivers high doses of radiation to the tumor—in a single or a few fractions—with the intent of tumor ablation; and a combination of SRS and WBRT [15]. Surgery is reserved for selected patients with tumors amenable to surgical resection, usually for patients presenting with a solitary, large, symptomatic brain metastasis or when pathological diagnosis is needed. In addition, systemic treatment is also being increasingly used to treat brain metastases, especially with new targeted agents and immunotherapy drugs.

Although a relationship between the molecular subtypes of breast cancer and the pattern of brain metastases has been identified, little is known about the imaging features of brain metastases depending on different biological subtypes of breast cancer. The aim of this analysis was therefore to evaluate the pattern and imaging features of brain metastases in different breast cancer subtypes, to assess median time from breast cancer to brain metastases and to evaluate the overall survival according to hormonal receptor as well as HER2 status and according to the implemented therapeutic strategies. The data can provide a background for the prediction of the pattern and imaging features of brain metastases in breast cancer patients and support further research concerning prevention, early detection, and treatment of brain metastases from breast cancer.

2. Patients and methods

2.1. Patient population

After obtaining local Institutional Review Board approval, and in compliance with the Helsinki Declaration, we retrospectively reviewed the clinical data of patients with brain metastases from breast cancer registered at Portuguese Institute of Oncology (IPO) of Porto database between January 1st, 2014 and December 31st, 2018. Patients with known brain metastases were included in the study if a MRI of the brain was available to be reviewed (some patients had only computed tomography studies of the brain) and biological status of the primary tumor was known.

2.2. Clinical analysis

From patients with brain metastases from breast cancer, we determined their demographics, namely age. We also registered the timing of breast and brain disease, the implemented therapy and reviewed the recorded histologies of the primary breast cancer and brain metastases when available, in order to determine the biological subtypes. The time to diagnosis of brain metastases was defined as the number of months between the diagnosis of breast cancer and the appearance of brain metastases. Overall Survival (OS) in months after brain metastases detection (from the date of diagnosis of brain metastases to the date of death or last follow-up for survivors) was calculated.

2.3. Image analysis

For patients with brain metastases from breast cancer, the images from the initial MRI of the brain demonstrating brain metastases were reviewed by three board-certified attending neuroradiologists (M.A, E. C., D.F.) who were blinded to the receptor status and breast cancer therapy mode. Separately and for each patient, the three neuroradiologists documented the location, number and size of any brain metastases, the presence of hydrocephalus and if the lesion was located at the hippocampus or at a distance of less than 5 mm from it. Lesions were also classified according to the signal intensity on T1WI, T2WI, DWI, T2*WI and postcontrast T1WI images.

2.4. Statistical analysis

All the data collected in our study were exported to an Excel spreadsheet. The analyses were then conducted with Statistical Package for Social Sciences (SPSS, v. 21), and included: i) Pearson correlations, to examine the associations between the different variables in our study; ii) t-tests for independent means; iii) one-way ANOVAs; and iv) chi-square tests. A criterion of $p < .05$ was used for significance tests.

3. Results

3.1. Patients' characteristics

Our sample comprised a total of 147 patients with breast cancer and brain metastases. The mean age of the participants at the time of breast cancer diagnosis was 48.36 years ($SD = 11.58$; range: 30−91) and of brain metastases diagnosis was 53.41 years ($SD = 11.29$; range: 32−92). The mean time to the development of brain metastases from first diagnosis of breast cancer was 62.20 months ($SD = 60.53$; range: 0−287). During the follow-up period, 81.20 % of patients ($n = 115$) died. Median overall survival after brain metastases diagnosis was 14.23 months (range: 1–60 months).

3.2. Molecular subtype of lesions

Regarding the primary tumors, 64.62 % were ER-positive (n = 95), 46.94 % (n = 69) were PR-positive, 43.55 % (n = 64) were HER2-positive, and 14.96 % (n = 22) were triple-negative. A pathological report of brain metastases was available for 28 patients who received surgical resection of their brain metastases. From those, 53.57 % were ER-positive (n = 15), 32.14 % (n = 9) were PR-positive, 46.43 % (n = 13) were HER2-positive, and 32.14 % (n = 9) were triple-negative.

3.3. Metastases' characteristics

Most patients (83 %) had only parenchymal brain metastases. A total of 8.2 % of the patients had parenchymal and leptomeningeal disease simultaneously. 8.8 % percent of the patients had leptomeningeal metastases as the only localization.

Regarding the number of brain metastases, 33.33 % ($n = 46$) of the patients had one brain metastasis, 7.25 % ($n = 10$) had two brain metastases, 10.14 % ($n = 14$) had three brain metastases, and 49,28 % ($n = 68$) had four or more brain metastases.

A detailed summary of patients' and metastases' characteristics and therapies is listed in Table 1. To point out that one patient did not have the T2*WI and DWI sequences available for analysis.

3.4. Time between breast cancer diagnosis and brain metastases

In regard to time between initial breast cancer diagnosis and diagnosis of brain metastases, a *t*-test for independent means showed that patients with a ER-positive breast cancer reported a longer interval between initial breast cancer diagnosis and diagnosis of brain metastases versus negative ER (76.01 versus 36.98 months; $p < .001$). Patients with a PR-positive primary tumor reported a longer period of time between breast cancer diagnosis and diagnosis of brain metastases versus negative PR (78.94 versus 47.40 months; $p = .001$). Whereas, patients with a triple-negative breast cancer reported a shorter interval between breast cancer diagnosis and diagnosis of brain metastases versus non triple-negative primary tumor (37.41 versus 66.57 months; $p = .008$) (Fig. 1).

Besides, patients that had ER-positive brain metastases had a prolonged time between initial breast cancer diagnosis and diagnosis of brain metastases (88.47 versus 31.69 months; $p = 0.019$). Patients with triple-negative brain metastases reported a shorter period of time between initial breast cancer diagnosis and diagnosis of brain metastases than patients with non triple-negative brain metastases (21.67 versus 81.26 months; $p < .001$) (Fig. 1).

Time between breast cancer and brain metastases was greater in patients treated with chemotherapy when compared with patients who did not undergo this type of treatment (64.67 vs 4.33 months; $p < .001$). Additionally, patients that received endocrine therapy before the diagnosis of brain metastases reported a longer interval between initial breast cancer diagnosis and diagnosis of brain metastases than those who did not have hormonal treatment (82.94 vs 32.13 months; $p < .001$) (Fig.1).

3.5. Overall survival (OS)

In terms of overall survival, we found that patients with overexpression of HER2 breast cancer tended to survive a longer period of time after the diagnosis of brain metastases than patients without overexpression of HER2 (18.06 vs 11.57 months; $p < .01$). On the other hand, patients with triple-negative primary tumor had a shorter OS than other patients (6.88 vs 15.41 months; $p < .001$). As well as patients with triple-negative brain metastases, which tended to survive fewer months than other patients (8.40 vs 27.22 months; $p < .05$) (Fig. 2). We also found that overall survival was shorter for patients whose metastases showed restricted diffusion (7.58 vs 16.03 months; $p < .0.01$).

3.6. Involvement of the hippocampus

The hippocampus was not frequently involved in the metastatic process (89.8 % vs 10.2 %). Conversely, individuals that had hippocampal metastases or metastases located at a distance of less than 5 mm from the hippocampus showed a higher number of parenchymal brain metastases when compared with other patients (35.79 versus 9.19; $p < .05$).

Table 1
Detailed summary of patients' and lesions' characteristics and therapies.

Patients' or Lesions' Characteristics		Median or Number	Range or Percent
Age at diagnosis of BC in years		48.36 (median)	30–91 (range)
Age at diagnosis of BM in years		53.41 (median)	32–92 (range)
Time to BM from first diagnosis of BC in months		62.20 (median)	0–287 (range)
Overall Survival in months		14.23 (median)	1–60 (range)
Estrogen-receptor BC	Positive	95	64.6%
	Negative	52	35.4%
Progesterone-receptor BC	Positive	69	46.9%
	Negative	78	53.1%
HER2-overexpression BC	Yes	64	43.5%
	No	83	56.5%
Triple-negative BC	Yes	22	15.0%
	No	125	85.0%
Estrogen-receptor BM	Positive	15	53.6%
	Negative	13	46.4%
Progesterone-receptor BM	Positive	9	32.1%
	Negative	19	67.9%
HER2-overexpression BM	Yes	13	46.43 %
	No	15	53.57 %
Triple-negative BM	Yes	9	32.14 %
	No	19	67.86%
Chemotherapy before BM diagnosis	Yes	141	95.9%
	No	6	4.1%
Endocrine therapy before BM diagnosis	Yes	87	59.2%
	No	60	40.8%
HER2-targeted therapy before BM diagnosis	Yes	60	93.75%
	No	4	6.25%
Location of intracranial metastases	Parenchymal	122	83.0%
	Leptomeningeal	13	8.8 %
	Both	12	8.2 %
Location of parenchymal metastases	Supratentorial	45	33.58%
	Infratentorial	15	11.19%
	Both	74	55.22%
Supratentorial metastases	Lobes	89	74.79%
	BG + Hypotalamus	3	2.52%
	Lobes + BG	2	22.69%
Infratentorial metastases	Cerebellum	66	74.2%
	Brainstem	7	7.9%
	Both	16	18%
Number of BM	1	46	33.33 %
	2	10	7.25 %
	3	14	10.14 %
	≥ 4	59	42.75%
Size of the largest lesion	1–10mm	21	15.67%
	11–20mm	37	27.61%
	21–30mm	32	23.88%
	31–40mm	24	17.90%
	≥ 41 mm	20	14.92%
Hippocampal metastases or <5 mm	Yes	15	10.2 %
	No	132	89.8 %
Hydrocephalus	Yes	3	2.0%
	No	144	98.0%
Signal of lesion on T1WI	Isointense	66	44.89%
	Hypointense	19	12.92%
	Heterogeneous	51	34.69%
	Hyperintense	11	7.48%
Signal of lesion on T2WI	Isointense	22	14.96 %
	Hypointense	9	6.12%
	Heterogeneous	101	68.70%
	Hyperintense	15	10.2 %
Signal of lesion on T2*WI	Hypointense	49	33.33 %
	Isointense	97	65.98%
	Without info	1	0.68%

(continued on next page)

Table 1 (*continued*)

Patients' or Lesions' Characteristics		Median or Number	Range or Percent
Restricted diffusion on DWI	No	111	75.5%
	Yes	35	23.8%
	Without info	1	0.7%
Contrast enhancement	Heterogeneous	104	70.7%
	Homogeneous	36	24.5%
	Hetero w/ Ring	7	4.8%

Abbreviations: BC, breast cancer; BG, basal ganglia; BM, brain metastases; HER2, Human epidermal growth factor receptor 2; DWI, diffusion weighted imaging; Hetero w/ Ring, heterogeneous with ring-shaped contrast enhancement; Info, information; T1WI, T1 weighted image; T2WI, T2 weighted image; T2*WI, T2* weighted image.

3.7. Hydrocephalus

Patients with hydrocephalus (Fig. 3) reported their largest lesion as being bigger than those without hydrocephalus (47.00 mm vs 25.22 mm; $p = .005$).

3.8. Imaging features

Next we investigated whether there were any differences between patients with distinct contrast enhancements. One-way ANOVAs showed significant effect of size of the largest lesion, $F = 11.375$, $p < .001$. Post-hoc Bonferroni tests showed that there was a significant difference between individuals, when contrast enhancement is homogeneous the lesion is usually smaller than when the contrast is heterogeneous and ring-shaped (Fig. 4) (15.42mm vs 32.71mm; $p = 0.004$). When contrast enhancement is heterogeneous the lesion is usually larger than when the contrast is homogeneous (27.87 mm vs 15.42 mm; $p < .001$).

Concerning signal intensity of lesion on T1WI, results showed a significant effect of size of the largest lesion, $F = 8.338$, $p < .001$. Post-hoc Bonferroni tests showed that there was a significant difference between lesions, isointense lesions are smaller than heterogeneous lesions (20.49mm vs 31.18mm; $p < .001$). T1WI isointense lesions are smaller than hyperintense lesions (20.49 vs 32.91 mm; $p < .001$). T1WI hypointense lesions are smaller than heterogeneous lesions (21.53mm vs 31.18mm; $p = .039$). Besides, results showed that there was a significant association between triple-negative primary tumor and the sign of lesion on T1WI, $X^2 = 22.403$, $p < .001$. Post-hoc tests showed that patients with triple-negative primary tumor tended to have more heterogeneous

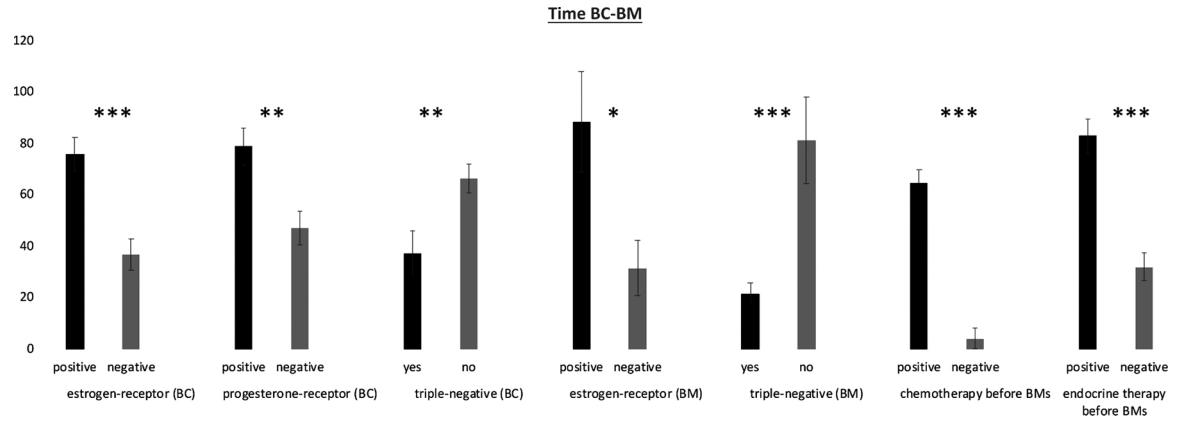

Fig. 1. Time from breast cancer to brain metastases in months, according to different subtypes.
Abbreviations: BC, breast cancer; BM, brain metastases. * $p < .05$; ** $p < .01$; *** $p < .001$.

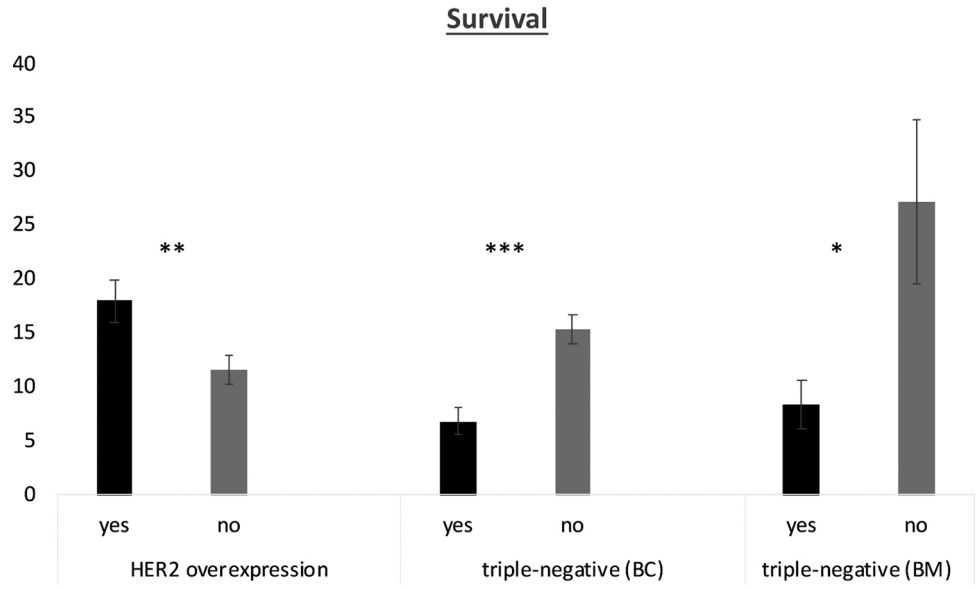

Fig. 2. Overall Survival in months, according to different subtypes.
Abbreviations: BM, brain metastases; HER-2, Human epidermal growth factor receptor 2. * $p < .05$; ** $p < .01$; *** $p < .001$.

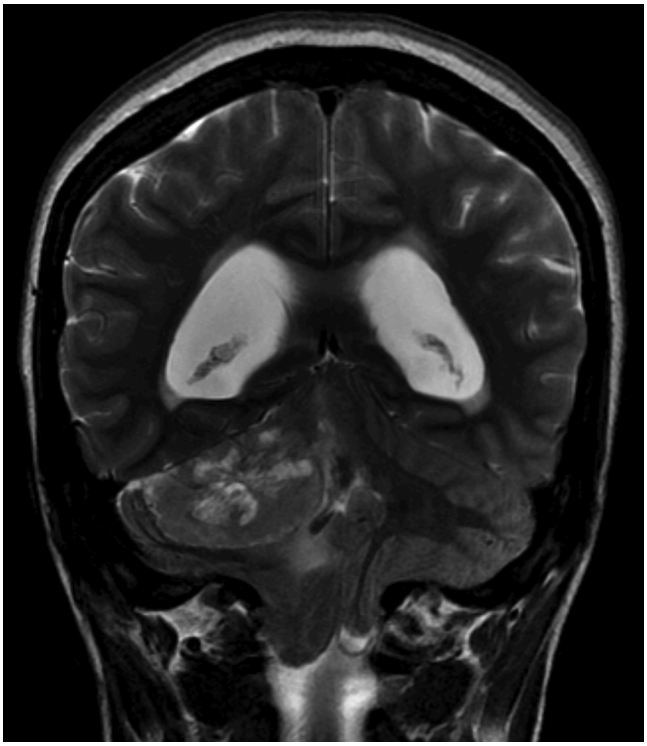

Fig. 3. Brain MRI. T2WI revealed a large cerebellar mass causing obstructive hydrocephalus.

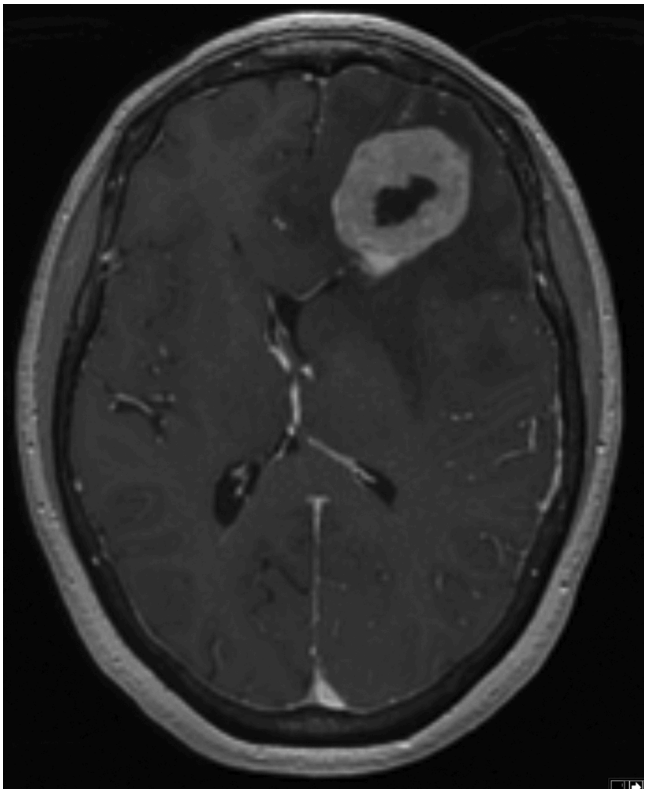

Fig. 4. Brain MRI. Postcontrast T1WI revelead a large left frontal mass with ring-shaped contrast enhancement due to central necrosis.

lesions on T1WI compared with non-triple-negative breast cancer patients, $p < .001$.

Concerning signal intensity of lesion on T2WI, results showed a significant effect of size of the largest lesion, $F = 6.871$, $p < .001$. Post-hoc Bonferroni tests showed that there was a significant difference between lesions, isointense metastatic lesions are smaller than heterogeneous lesions (20.49mm vs 31.18mm; $p = .001$).

A *t*-test for independent means showed that when the lesion had hyposignal on T2*WI (Fig. 5), the lesion's size was bigger than when it did not have hyposignal (30.93 mm vs 23.07 mm; $p = .001$).

A one-way ANOVA on location of metastases, when it comes to supratentorial or infratentorial position, showed a significant effect of size of the largest lesion, $F = 4.407$, $p < .05$. Post-hoc Bonferroni tests showed that there was a significant difference between individuals; patients with supratentorial lesions have larger lesions than patients with supratentorial and infratentorial lesions (29.87mm vs 22.72mm; $p = 0.014$). Results also showed a significant effect of number of brain metastases, $F = 14.912$, $p < .001$. Post-hoc Bonferroni tests showed that patients with simultaneous supratentorial and infratentorial lesions had more metastases than patients who had only supratentorial lesions ($n = 20.63$ vs $n = 2.27$; $p < .\ 0.001$).

Pearson's correlation coefficient showed that the number of brain metastases was significantly negatively correlated with the size of the largest lesion, showing that participants with a higher number of brain metastases (Fig. 6) reported a smaller lesion size ($r = -0.173$; $p = 0.046$).

We did not find any statistically significative association between location of metastases and breast cancer subtype.

4. Discussion

In this large cohort of breast cancer patients with brain metastases, we were able to show that the subtype of the primary tumor has a high impact on patients' prognosis and influences the timing of development of brain metastases as well as some imaging features.

Previous studies showed that many patients develop brain metastases as a manifestation of late-stage and advanced disease, often when other metastases have already been established in a variety of distant sites from the primary tumor6. In our study brain metastases were

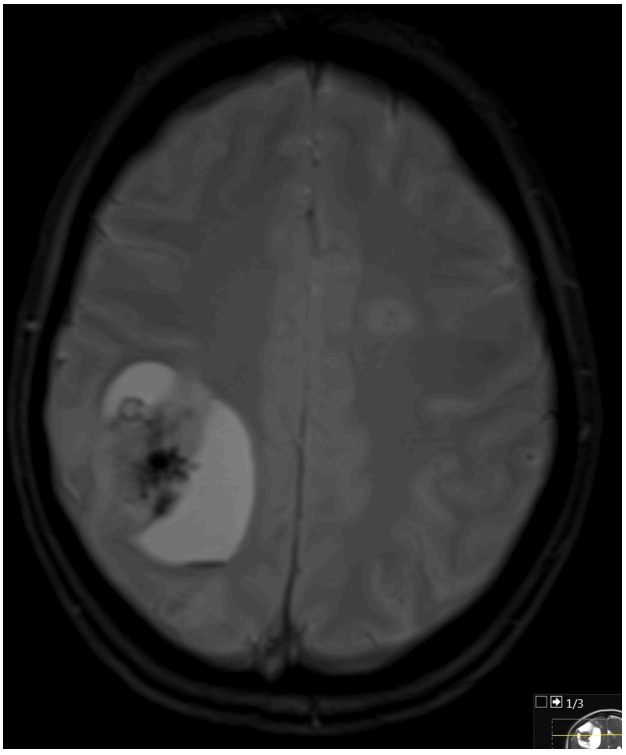

Fig. 5. Brain MRI. T2*WI image showed a large heterogeneous right frontoparietal mass with a central area of hyposignal.

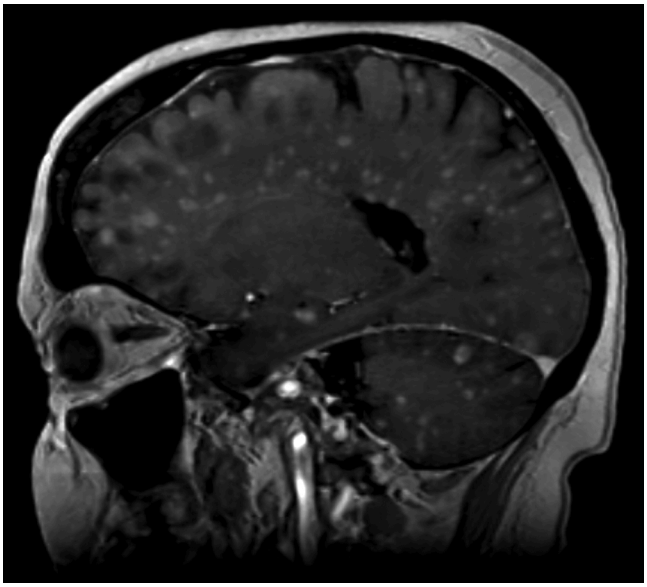

Fig. 6. Brain MRI. Postcontrast T1WI reported "miliary" metastasis of the brain. The patient had innumerable smaller nodular enhancing lesions involving both cerebral and both cerebellar hemispheres, the basal ganglia, and the brainstem.

found, in average, five years after the diagnosis of breast cancer. Median time to the development of brain metastases from first diagnosis of breast cancer was higher for patients with positive ER and PR and lower for patients with triple-negative primary tumors, which is in accordance with what is described in the literature [16,17]. Patients that had positive ER in brain metastases had a prolonged time between initial breast cancer diagnosis and diagnosis of brain metastases (88.47 vs 31.69 months). Since patients with estrogen and/or progesterone positive receptor disease received hormonal therapy, it is understandable that these groups of patients achieved a longer period between the diagnosis of breast cancer and the appearance of brain metastases. Our analysis also indicates that the time between breast cancer and brain metastases is higher in patients treated with chemotherapy or endocrine therapy before the diagnosis of brain metastases compared with patients without these therapies. Probably these therapies have the ability to reduce circulating tumor cells (CTCs) in the bloodstream, which are implicated as harbingers of metastases. CTCs were recognized in the 1800s [18]. These cells are thought to be a subpopulation detached from the primary or metastatic tumor sites and reflect the heterogeneous characteristics of their source [19]. Adjuvant therapies reach this microscopic form of disease and contain the spreading to other organs, reducing the incidence of metastases. Besides, patients that received endocrine therapy had to have a ER and/or PR-positive breast cancer, which is on itself a factor in favor of a longer interval between breast cancer and brain metastases. However, some patients did not receive chemotherapy before the diagnosis of brain metastases because there was no time, as the disease presented itself with neurological symptoms, making the breast cancer and brain metastases diagnosis simultaneous.

Patients with triple-negative breast cancer as well as triple-negative brain metastases reported a shorter period of time between initial breast cancer diagnosis and diagnosis of brain metastases, 37.41 vs 66.57 and 21.67 vs 81.26 months, respectively. Many studies have already documented that triple-negative patients have a higher risk of developing brain metastases than patients with ER or PR positive disease [20,21]. We postulated that the subtype of the lesion may be related to a propensity to reach and cross the blood-brain barrier (BBB) and to invade the brain. Metastases is a continuous and multi-step biological process, in which a subpopulation of cancer cells with highly invasive and metastatic potential depart from their original locations, degrade the extracellular matrix, intravasate into the blood or lymphatic vessels, survive in the circulation, and extravasate to and colonize new terrain in the target organs [22]. When it comes to the central nervous system (CNS), the metastatic process has one more step, which is the crossing of the BBB. But once the cells overcome this step, they can interact with the resident cells, such as astrocytes, and take advantage of oncogenic signals to keep on proliferating [23]. We believe that triple-negative cells may have an advantage in this complex process. In line with our hypothesis, Hohensee I et al. identified two separate pathways (EGFR/PTEN) among triple-negative patients, both leading to a significantly increased risk of brain metastasis [24]. Furthermore, Sirkisoon SR et al. showed that TGLI1 activation is associated with a shortened time to develop breast cancer brain metastasis and enriched in triple-negative breast cancers [25].

It is important to notice that no definitive conclusion regarding the metastatic potential and tumoral aggressiveness of different subtypes can be inferred from the obtained findings. For example, it is likely that, because of the unique behavior of ER-positive tumors, this cancer subtype was less prone to metastasize to the brain (resulting in longer time between diagnosis of the initial disease and diagnosis of brain metastasis). However, as the majority of patients in this cohort received chemotherapy and hormonal therapy, another very plausible explanation would be that such therapies (which tend to have better response in the ER-positive subtype) rather than the histological subtype per se were responsible for such findings. The same rationale applies for the findings of differences in time to development of brain metastasis between PR positive and negative tumors as well as triple-negative and non-triple negative tumors.

Patients with brain metastases from breast cancer have been historically linked to a bad prognosis. In a large study with data from patients diagnosed with brain metastases from breast cancer, collected between 1994 and 2004, the median survival time after the discovery of brain metastases was as short as 6,8 months [26]. However, due to advanced neuroimaging techniques as well as local and systemic treatment enhancements for metastatic breast cancer, the prognosis of most patients with brain metastases has improved [27]. Our study corroborates this statement, with patients achieving in average an overall survival of 1423 months after brain metastases diagnosis, more than double the previous records. We highlight that the patients with triple-negative primary tumor had the lowest overall survival, as reported in the literature [28]. We hypothesized that this could be in part explained by its naturally more aggressive phenotype, as well as due to the fact that treatment options are largely limited for patients with this type of breast cancer, since there is no specific target to direct specific therapeutic strategies. Conversely, our study showed that HER2-positive patients with brain metastases had a better prognosis compared with other subtypes. This is in line with other studies that describe increasing survival rates for patients with HER2-positive breast cancer [29]. These results can be justified by the recent therapeutic agents, such as trastuzumab and lapatinib, that specifically target cells with HER2 gene amplification that overexpress this receptor [30,31].

A few previous studies from brain tumors have demonstrated a relationship between DWI and patient's prognosis. More specifically, some authors report that patients whose brain metastases have restricted diffusion showed shorter overall survival [32]. We also found that survival after brain metastasis diagnosis was shorter for patients whose metastases showed restricted diffusion (bright on DWI and hypointense on ADC images). DWI is a short, non-contrast sequence that measures the ability of water molecules to freely diffuse within tissue [33]. Early investigations into DWI demonstrated that densely packed tumor cells with a high nuclear-to-cytoplasmic ratio could reduce water molecule motion [34]. Although exists a correlation between diffusion and tumor cellular density, Barajas et al. found that, unlike DWI, increased tumor cell density was not a statistically significant predictor of clinical outcome. Their results suggest that DWI has a capacity to summate additional unidentified prognostic biologic features of tumor

aggressiveness beyond cell density [35]. Zamecnik reported that besides cellularity, DWI of tumor can be affected by several others factors, such as extracelular matrix, tortuosity and vascularity [36]. In fact, the overproduction of certain components of the extracelular matrix, mainly of tenascin, changes extracelular space structure, hindering the diffusion of neuroactive substances or even molecules of drugs into the neoplastic tissue. The presence of tenascin in the extracelular space of the neoplasm correlates significantly with increased malignancy and poor clinical outcome of the disease. By other hand, it is possible that some degree of restricted diffusion also mean that the core of the tumor is not well-vascularized, suggesting a quite aggressive and fast-growing lesion. In fact, with increasing tumor size, the center of metastatic tumors exhibits decreasing blood flow, favoring ischemic. The hypoxia in necrotic core regions could also explain the limited efficacy of some therapies that target proliferating cells, decreasing overall survival [37].

Hydrocephalus is an abnormal accumulation of cerebrospinal fluid (CSF) within cavities in the brain called ventricles and occurs when there is an imbalance between the amount of CSF that is produced and the rate at which it is absorbed. Metastatic disease in periventricular brain tissue can obstruct the flow of CSF produced in the ventricles to the subarachnoid space where it is normally absorbed by arachnoid granulations. This typically causes an obstructive or non-communicating hydrocephalus [38]. Obviously, larger metastatic lesions are more likely to cause obstruction and our study corroborated this hypothesis by finding that hydrocephalus was present when the largest metastatic lesion had a bigger size.

Brain metastases can be solitary or multiple and our study showed that the greater the number of parenchymal metastases, the lower the size of the larger lesion. We believe that these findings may be closely related to the inherent biological behavior of different pathological subtypes of breast cancer cells, regarding the seeding and growth stages of metastasis. It seems quite likely that there may some tumor subtypes which tend to present a higher potential of developing multiple brain metastasis which, however, tend not to grow past a certain size. Tumor cell growth in the brain microenvironment is the result of genetic predisposition and cellular adaptation mechanisms, and is largely dependent on cross-talk between tumor cells and brain-resident cells [39]. As triple-negative and HER2+ breast cancers exhibit the characteristics of high malignancy and rapid growth, it is easy to metastasize and tend to be associated with extensive brain metastases [40]. Patients with supratentorial lesions have larger lesions than patients with simultaneous supratentorial and infratentorial lesions, but these last patients have more metastases than the first group. This is consistent with what we supposed, the number relates to the size, the higher the number the smaller the size.

The imaging characteristics of the lesions vary according to their size. Our study showed that hyposignal on T2*WI was associated with larger-sized lesions. We also observed that heterogeneous contrast enhancement metastatic lesions were larger than homogeneous lesions, that T1WI isointense or hypointense metastatic lesions were smaller than heterogeneous or hyperintense lesions and that T2WI isointense metastatic lesions were smaller than heterogeneous lesions. In fact, larger lesions tend to be cystic necrotic (have a thin/thick dense wall with central necrosis) [41], so contrast enhancement is more heterogeneous, often ring-shaped, and signal intensity on T1WI and T2WI sequences is also heterogenous. Besides, larger lesions are more likely to bleed, presenting hyposignal in T2*WI and hypersignal in T1WI. This occurs because tumor cells have a high metabolic rate which demands a large blood supply. In order to survive and proliferate, these cells emit signals to promote angiogenesis. Despite this ingenious mechanism, these new vessels are more fragile with a higher tendency to bleed and grow in a centripetal manner, leaving the central region of the mass more vulnerable to ischemia and necrosis, this is especially relevant in larger lesions [42]. Our study also revealed that patients who have triple-negative primary tumor tend to have more heterogeneous metastatic lesions at T1WI, reflecting the high metabolism of their tumor cells, in the context of high tumor aggression.

We also found, like in some other papers, that the hippocampus is not frequently involved in the metastatic process [43,44], which favors the use of hippocampal-sparing WBRT. In fact, preclinical and clinical studies have shown that radiation-induced injury to the hippocampus correlates with neurocognitive decline following WBRT [45]. Radiation-induced cognitive deficits may result, at least in part, from a radiation injury to the neuronal stem cells in the subgranular zone of the hippocampus, that are responsible for maintaining neurogenesis, and preserving memory functions [46]. Hippocampal-sparing WBRT uses intensity modulated radiotherapy (IMRT) to conformally reduce the radiation dose to the hippocampus, and thus preserving neurocognitive functions, while applying the usual higher dose to the rest of the brain [47].

Considering the retrospective nature of our study, we encountered some obstacles challenging to overcome, those stand as limitations of our work, such as: one patient did not have all the MRI sequences available and we did not have the information regarding hormonal receptor and HER2 status of the brain metastases on all the patients. Additionally, some patients had a short follow up time after developing brain metastases, for instance, patients from the year 2018 had only a 1 year follow up time, which could influence and underestimate the median overall survival as it was 14.23 months.

5. Conclusion

Based on the breast cancer subtype it is possible to make a prediction about the patients' prognosis. Besides, based on some imaging features, it is possible to predict the molecular subtype of certain brain metastasis, which can influence the complex decision-making regarding the best therapeutic alternatives (either surgery, radiation, chemotherapy or hormonal therapy). However, when it comes to the pattern of the brain metastases, we did not find a strong association in regard to the biological subtype of breast cancer. This data supports the need for further research concerning prevention, early detection, and treatment of the brain metastases of breast cancer.

Declaration of Competing Interest

The authors have stated that they have no conflict of interests.

CRediT authorship contribution statement

Joana Santos: Investigation, Formal analysis, Data curation, Writing - original draft. **Joana Arantes:** Methodology, Software, Validation, Investigation. **Eduarda Carneiro:** Visualization, Investigation. **Diana Ferreira:** Visualization, Investigation. **Susana Maria Silva:** Visualization, Investigation. **Susana Palma de Sousa:** Visualization, Investigation. **Mavilde Arantes:** Conceptualization, Methodology, Investigation, Supervision, Writing - review & editing, Project administration.

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