# Clinicopathological characteristics and prognosis of breast cancer patients with isolated central nervous system metastases in the multicentre ESME database

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## Abstract

**Background:** As a result of progress in diagnosis and treatment, there is a growing prevalence of metastatic breast cancer (MBC) with isolated CNS metastases. This study describes the largest-to-date real-life cohort of this clinical setting and compares it to other clinical presentations.

**Methods:** We retrospectively analysed the French Epidemiological Strategy and Medical Economics (ESME) MBC database including patients who initiated treatment for MBC between 2008 and 2016. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method. Descriptive statistics and multivariate Cox model were used.

**Results:** Of 22,266 patients, 647 (2.9%) and 929 (4.2%) patients had isolated first-site CNS metastases or combined with extra-CNS metastases, with longer OS for the group with isolated CNS metastases (16.9 *versus* 13.9 months, adjusted HR = 1.69 (95% CI: 1.50–1.91), $p < 0.001$). Among the 541 (2.4%) patients with isolated CNS metastases and no intrathecal therapy (excluding leptomeningeal metastases), HER2+ cases were preponderant over TN or HR+ /HER2– cases (41.6% *versus* 26.1% *versus* 28.5%, respectively, $p < 0.01$). The treatment strategy consisted of a combination of local treatment and systemic therapy (49.2%), local treatment only (35.5%) or systemic therapy only (11.4%), or symptomatic therapy only (3.9%). Median PFS was 6.1 months (95% CI: 5.7–6.8). Median OS was 20.7 months (95% CI: 17.3–24.3), reaching 37.9 months (95% CI: 25.9–47.6) in the HR+ /HER2+ subgroup. Older age, TN subtype, MBC-free interval of 6–12 months, lower performance status, and WBRT were associated with poorer survival. Patients who received systemic therapy within 3 months from MBC diagnosis had longer OS (24.1 *versus* 16.1 months, $p = 0.031$), but this was not significant on multivariate analysis [HR = 1.0 (95% CI: 0.7–1.3), $p = 0.806$].

**Conclusions:** Patients with isolated CNS metastases at MBC diagnosis represent a distinct population for which the role of systemic therapy needs to be further investigated in prospective studies.

*Keywords:* breast cancer, CNS metastases, real-world data

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## Introduction

Breast cancer (BC) is the most commonly diagnosed tumour and the leading cause of cancer death in women, representing a growing health concern worldwide despite the therapeutic progress achieved in the past two decades.[1]

Central nervous system (CNS) metastases represent very poor outcomes, associating debilitating symptoms, impaired quality of life and poor survival,[2,3] and BC is the second most common primary tumour associated with CNS metastases.[2,4] Although routine screening for CNS metastases is not recommended in the absence of CNS symptoms, recent reviews have reported an incidence exceeding 20% in the overall metastatic BC (MBC) population,[2,5] reaching 30–40% in the presence of human epidermal growth factor receptor 2 overexpression (HER2+) or triple-negative BC (TNBC).[6] Some authors have also reported an increasing incidence of BC-related CNS metastases over the last two decades, likely due to progress in imaging techniques and systemic therapies for MBC.[7] Pharmacokinetic hypotheses such as poor diffusion of trastuzumab across the brain-blood barrier (BBB) could explain the high incidence of CNS metastases observed in HER2+ MBC patients, especially those with long-term control of extracranial disease.[8,9] Some papers have even reported a higher incidence of CNS metastases as the first site of recurrence after adjuvant trastuzumab therapy,[10] which could be due to the poor CNS diffusion of trastuzumab in the presence of a supposedly intact BBB that fails to effectively prevent growth of CNS micro-metastases, while more effectively controlling extracranial micro-metastatic disease.[2]

Patients with CNS metastases as the first and isolated metastases from BC are rare and have been reported in small retrospective series.[11–14] Most published studies, as well as current guidelines, refer to CNS metastases occurring at any time during the course of BC,[15,16] which is of limited value to draw conclusions about specific strategies, whether CNS metastases are isolated or combined with extracranial disease. However, several authors have stressed the potentially different clinicopathological characteristics and prognosis of isolated CNS metastases, requiring a different approach[11,12] compared to the more common situation in which extracranial disease is also present and drives the choice of systemic therapy.[5,17,18] Except for HER2+ disease, for which maintenance of targeted anti-HER2 systemic therapy is recommended whether or not CNS metastases are isolated, there is no strong recommendation for the use of additional systemic therapy for isolated CNS disease following local treatment.[16,19] Real-world data from large populations may contribute to a better understanding of the prognostic factors and management of this specific clinical entity of MBC with isolated CNS metastases.

## Materials and methods

### Study design

Based on the large Epidemiological Strategy and Medical Economics (ESME) MBC data platform, this study was designed to provide an in-depth analysis of the clinical features of patients with isolated CNS metastases as first metastatic site compared to patients with both CNS and extra-CNS metastases and patients with extra-CNS metastases only.

The ESME MBC database (NCT03275311) is a national multicentre retrospective observational programme that collects individual data from all consecutive patients, aged ≥18 years, who have initiated treatment for MBC at one of the 18 French Comprehensive Cancer Centres belonging to the UNICANCER network, as from 2008. Data are updated annually and include the main patient and tumour characteristics, outcome and treatment patterns.

In line with French regulations, the ESME MBC database has been approved by the French data protection authority (Registration ID 1704113 and authorization No. DE-2013-117). In compliance with the applicable European regulations, a complementary authorization was obtained on 14 October 2019 regarding the ESME research data warehouse. The present analysis was approved by an independent Ethics Committee (*Comité de Protection des Personnes Sud-Est II*-2015-79). No specific formal informed consent was required for this study, but all patients had approved the re-use of their electronically recorded data. The ESME Research Programme is managed by UNICANCER according to best practice guidelines, and the ESME Scientific Committee approved the present study.

### Study objectives

The primary objective was to describe the outcome of patients with isolated CNS as first metastatic site, using median overall survival (OS) and

progression-free survival (PFS) as primary end-points. Secondary objectives were (1) to describe and compare characteristics and outcomes of MBC cases according to the first site of metastases (isolated CNS metastases, both CNS and extra-CNS metastases, or no CNS metastases); (2) report local treatment and first-line systemic therapy modalities; and (3) report time to CNS progression (TTCNS) and time to extra-CNS progression (TTexCNS) in patients with isolated CNS metastases.

### Study population and data collected

All female patients available in the ESME MBC database (included in the database between 1 January 2008 and 31 December 2016) were included in the comparative analysis. This in-depth analysis was based on patients with isolated and exclusive intraparenchymal brain metastases (BM) at MBC diagnosis, excluding patients treated with intrathecal (IT) chemotherapy as a proxy for leptomeningeal metastases. Only local treatment and systemic therapy initiated during the first 3 months after the diagnosis of MBC with isolated CNS disease were documented. According to hormone receptor (HR) and HER2 statuses, tumours were classified into four subtypes: HR+ /HER2−, HR+ /HER2+, HR−/ HER2+, and triple-negative (TN).

### Statistical analysis

Clinicopathological characteristics and demographic data were assessed using descriptive statistics.

OS was defined as the time between the date of MBC diagnosis and the date of death from any cause, and PFS was defined as the time between the date of MBC diagnosis and the date of progression or death. TTCNS was defined as the time between the date of MBC diagnosis and the date of CNS progression or death, while TTexCNS was defined as the time between the date of MBC diagnosis and the date of extra-CNS progression or death. Patients not experiencing an event were censored at the date of last news in the centre. MBC diagnosis was based on imaging exams, and pathological confirmation was not mandatory. The time to MBC was defined as the time between the diagnosis of primary cancer and the diagnosis of MBC.

Survival distribution was estimated by the Kaplan–Meier method, reported as the median

and 95% confidence interval (CI) and compared between groups using the log-rank test. Univariate and multivariable Cox proportional hazards regression models were performed to assess significant prognostic factors for patients with isolated CNS metastases. Comparisons of survival hazard ratios (HR) between groups were reported with point estimates and 95% CI. For all tests, a two-sided $p$ value $<0.05$ was considered statistically significant. All statistical analyses were performed using R software, version 3.6.1.

Further details on the study population, data collection and statistical analysis are reported in Supplementary Materials and Methods.

## Results

### Patient characteristics according to the first metastatic site

Of 22,266 MBC female patients included in the ESME database between 2008 and 2016, 20,690 (92.9%) had only extra-CNS metastases, 929 (4.2%) had CNS and extra-CNS metastases, and 647 (2.9%) had isolated CNS metastases as first metastatic site (Figure 1). Among these 647 patients, 541 (2.4% of 22,266 patients) were considered to have exclusively intraparenchymal BM, after excluding 106 patients treated with IT chemotherapy, suggesting the presence of leptomeningeal metastases.

Some of the main patient characteristics according to the distribution of metastases are reported in Supplementary Table 1.

Patients with isolated CNS metastases more commonly had a HER2+ tumour compared to those with both CNS and extra-CNS metastases, or extra-CNS metastases only (37.1% *versus* 23.3% *versus* 17.2%, $p<0.001$), and less commonly had a HR+ /HER2− tumour (29.5% *versus* 42.6% *versus* 63.6%, $p<0.001$). The distribution of TNBC was not different between patients with isolated CNS metastases or CNS metastases together with extra-CNS metastases, but TNBC was more common in these patients compared to those with no CNS metastases (28.4% and 28.1% *versus* 12.3%, respectively, $p<0.001$). Higher rates of CNS metastases were observed in HER2+ and TN subtypes compared to HR+ /HER2− subtype (11.4% and 14.9% *versus* 4.3%, $p<0.001$) and this was also true for isolated CNS metastases (6% and 6.2% *versus* 1.4%, respectively, $p<0.001$).
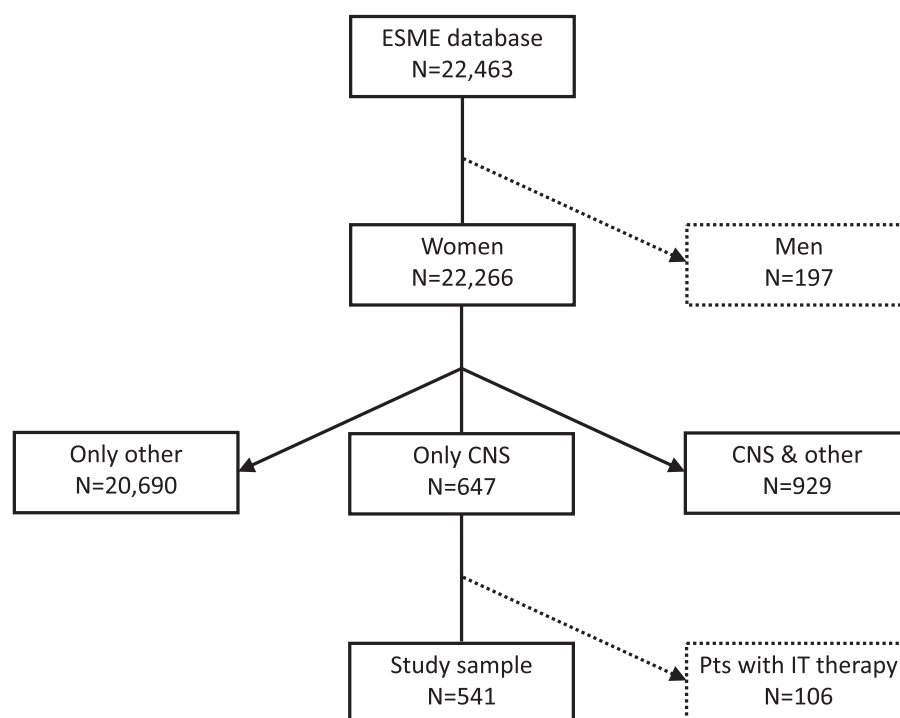
**Figure 1.** Flowchart of MBC patients in the ESME MBC cohort according to the first metastatic site.
CNS, central nervous system; ESME, Epidemiological Strategy and Medical Economics; IT, intrathecal; Pts, patients.

Patients with CNS metastases (isolated or combined with extra-CNS metastases) had more commonly received adjuvant or neoadjuvant chemotherapy (excluding patients with *de novo* MBC, 89.6% and 82.6% *versus* 69.2%), presented a histological grade III tumour (46.5% and 40.9% *versus* 28.0%), were young (median age at MBC diagnosis of 56 years and 56 years *versus* 61 years) and had a poor ECOG PS (PS = 2–4) compared with those with no CNS metastasis (15.9% and 21.3% *versus* 9.7%), all $p < 0.001$.

The shortest median time to MBC (estimated only for recurrent MBC) diagnosis was observed in patients with isolated CNS metastases compared to those with both CNS and extra-CNS metastases or those with extra-CNS metastases only [24.3 months (IQR 15.3–45.5) *versus* 39.3 months (IQR: 20.8–89.6) *versus* 71.1 months (IQR: 33.2–136), respectively, $p < 0.001$].

More patients with isolated CNS metastases did not receive any systemic therapy during the first 3 months following the diagnosis of MBC, as opposed to patients with both CNS and extra-CNS metastases or patients with extra-CNS metastases only (32.6% *versus* 9.4% *versus* 3.6%, respectively, $p < 0.0001$).

### Survival according to the first metastatic site

Patients with CNS metastases had a poorer survival than those without CNS metastases, irrespective of tumour subtype ($p < 0.001$, data not shown). Median OS ranged from 16.9 months (95% CI: 14.9–19.7) in patients with isolated CNS metastases, 13.9 months (95% CI: 12.1–16.0) in those with both CNS and extra-CNS metastases, and 41.7 months (95% CI: 40.9–42.4) in those with only extra-CNS metastases, $p < 0.001$ (Figure 2). In multivariable analysis, patients with both CNS and extra-CNS metastases had significantly poorer OS than those with isolated CNS metastases [HR = 1.69 (95% CI: 1.50–1.91), $p < 0.001$]. On the other hand, patients with only extra-CNS metastases had better OS than those with isolated CNS metastases [HR = 0.76 (95% CI: 0.69–0.84), $p < 0.001$; Supplementary Table 2].

### Characteristics of patients with isolated CNS metastases

Our main analysis was based on 541 patients with exclusive and isolated parenchymatous brain metastases, after the exclusion of 106 patients who received IT chemotherapy, in order to control for heterogeneity, as reflected by the very different
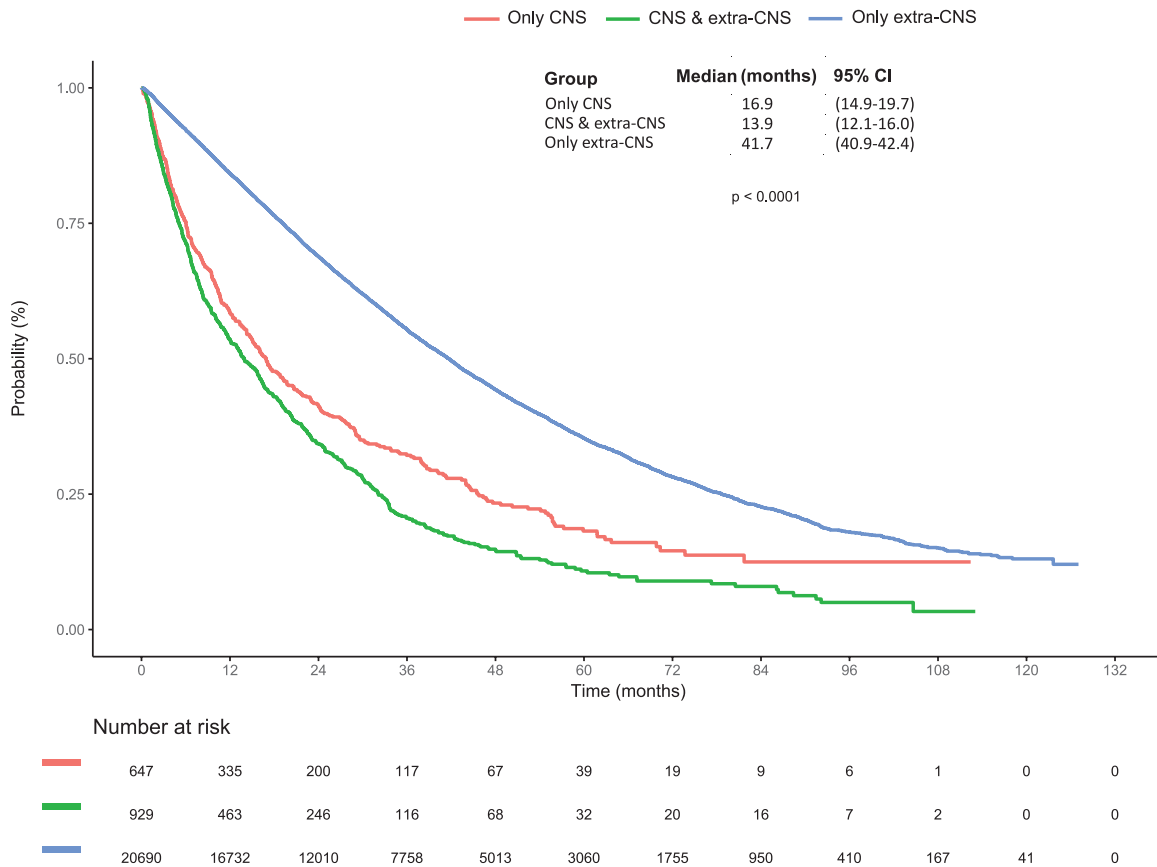
**Figure 2.** Kaplan–Meier curves for overall survival of patients according to the first site(s) of metastasis: only CNS metastases *versus* CNS and extra-CNS metastases *versus* only extra-CNS metastases (log-rank *p* < 0.0001).
CNS, central nervous system; OS, overall survival.

outcomes following adjustment for subtypes: median OS of 20.7 months (95% CI: 7.3–24.3) *versus* 7.4 months (95% CI: 4.9–9.7) depending on the use of IT therapy, respectively [HR = 1.99 (95% CI: 1.56–2.53), *p* < 0.001; data not shown]. Compared with patients with no IT therapy, those receiving IT therapy also more often had poor PS (2–4) (28.3% *versus* 13.5%), TNBC (40.6% *versus* 26.1%), HR+/HER2− subtype (34.9% *versus* 28.5%) or lobular histology (23.1% *versus* 10.4%) and less often had HER2+ disease (16% *versus* 41.4%), all *p* < 0.01 (data not shown).

In our population of interest (*N* = 541), the median age at MBC diagnosis was 57 years (IQR: 47–67) and the median time to MBC diagnosis (after excluding patients with *de novo* MBC) was 24.4 months (IQR: 16.3–45.5). *De novo* MBC (defined as MBC diagnosed within 6 months from primary cancer diagnosis) was diagnosed in

46 patients, while 492 patients had recurrent MBC. The majority of patients had HER2+ tumours (41.4%). Also, the majority of patients was symptomatic at MBC diagnosis (Table 1).

### Treatment characteristics of patients with isolated CNS metastases

In our main population (*N* = 541), 266 (49.2%) patients received both local treatment and first-line systemic therapy, 192 (35.5%) received local treatment only, 62 (11.4%) received systemic therapy only, and 21 (3.9%) received no specific treatment in the first 3 months after MBC diagnosis (Table 1).

Details on the modalities of local treatment and systemic therapy and the agents most commonly used in each subgroup are reported in Supplementary Tables 3 and 4.

**Table 1.** Patient characteristics in our population of interest.

| Characteristic | *N* = 541 | % |
|---|---|---|
| Tumour grade | | |
| Grade I/II | 204 | 37.7 |
| Grade III | 252 | 46.6 |
| NA | 85 | 15.7 |
| Histological type | | |
| Ductal | 410 | 75.8 |
| Lobular | 56 | 10.4 |
| Other | 64 | 11.8 |
| NA | 11 | 2.0 |
| (Neo-)adjuvant chemotherapy[a] | | |
| No | 55 | 10.2 |
| Yes | 437 | 80.8 |
| NA | 49 | 9.0 |
| Age at MBC diagnosis | | |
| <55 years | 236 | 43.6 |
| ≥55 years | 305 | 56.4 |
| Time to MBC diagnosis[b] | | |
| <6 months | 46 | 8.6 |
| 6–11 months | 75 | 13.9 |
| 12–23 months | 164 | 30.5 |
| 24–59 months | 155 | 28.8 |
| ≥60 months | 98 | 18.2 |
| NA | 3 | 0.6 |
| Symptoms at MBC diagnosis | | |
| Yes | 411 | 76 |
| No | 117 | 21.6 |
| NA | 13 | 2.4 |
| BC Subtype | | |
| HR+/HER2– | 154 | 28.5 |
| HR+/HER2+ | 117 | 21.6 |

*(Continued)*

**Table 1.** (Continued)

| Characteristic | *N* = 541 | % |
|---|---|---|
| HR–/HER2+ | 107 | 19.8 |
| TN | 141 | 26.1 |
| NA | 22 | 4.1 |
| Performance status | | |
| PS 0 | 65 | 12 |
| PS 1 | 81 | 15 |
| PS 2–4 | 73 | 13.5 |
| NA | 322 | 59.5 |
| Treatment strategy[c] | | |
| Local and systemic | 266 | 49.2 |
| Only local | 192 | 35.5 |
| Only systemic | 62 | 11.4 |
| No specific therapy | 21 | 3.9 |
| Surgical resection (+/-systemic therapy)[c]? | | |
| Surgical resection and systemic therapy | 46 | 8.5 |
| Surgical resection without systemic therapy | 42 | 7.8 |
| No surgical resection | 453 | 83.7 |

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; NA, not available; PS, performance status; TN, triple-negative.
[a]The category 'NA' included patients with *de novo* MBC.
[b]Defined as the time between the diagnosis of primary cancer and the diagnosis of MBC.
[c]Within the first 3 months after CNS metastases diagnosis.

Local treatment consisted of surgical resection in 88 patients (16.3%) either alone (*n* = 19) or followed by stereotactic radiosurgery (SRS; *n* = 34) or whole-brain radiotherapy (WBRT; *n* = 35), exclusive SRS in 94 patients (17.4%), or exclusive WBRT in 276 patients (51.0%), while 83 patients (15.3%) did not receive any local treatment.

Systemic therapy was administered within the first 3 months after MBC diagnosis in 328 patients (60.6%) and in 266 (58.1%) of the 458 patients with local treatment, with no significant difference according to the type of local treatment administered (*p* = 0.49). The prevalence of

| Outcome | Median (months) | 95% CI |
|---------|-----------------|--------|
| OS | 20.7 | (17.3-24.3) |
| PFS | 6.1 | (5.7-6.8) |
| TTCNS | 9.4 | (8.3-10.6) |
| TTexCNS | 9.4 | (7.2-10.6) |

**Number at risk**

| | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 |
|--|---|----|----|----|----|----|----|----|----|
| OS | 541 | 305 | 189 | 109 | 61 | 36 | 18 | 8 | 6 |
| PFS | 541 | 138 | 65 | 37 | 23 | 13 | 6 | 2 | 1 |
| TTCNS | 541 | 198 | 96 | 54 | 32 | 21 | 10 | 5 | 2 |
| TTexCNS | 541 | 210 | 120 | 66 | 40 | 25 | 13 | 5 | 5 |
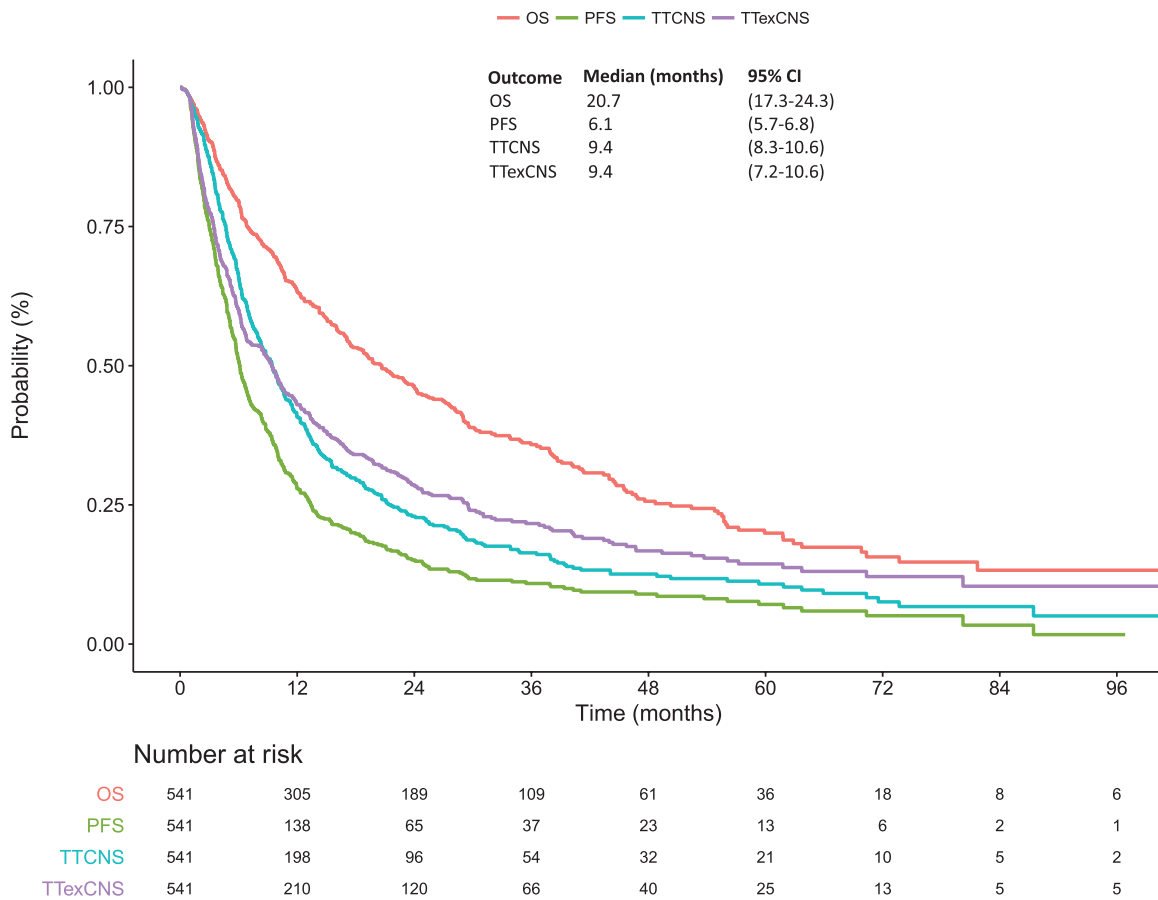
**Figure 3.** Kaplan–Meier curves for overall survival (OS), progression-free survival (PFS), time to CNS progression (TTCNS), and time to extra-CNS progression (TTexCNS) in our population of interest. CNS, central nervous system; MBC, metastatic breast cancer.

systemic therapy was associated with BC subtype: 74.7% of HR+ /HER2− cases, 82.9% of HR+ / HER2+ cases, 54.2% of HR−/HER2+ cases, and 31.9% of TNBC cases received systemic therapy ($p < 0.001$). The type of systemic therapy varied according to subtype: 50% of HR+ / HER2− BC patients received endocrine therapy (ET) alone while 22.7% received chemotherapy (either alone or in combination with ET or bevacizumab). The majority of patients with HER2+ tumours (50.4%) received anti-HER2 therapy either alone or in combination with chemotherapy or ET, while TNBC patients more commonly received chemotherapy alone (27.7%) or in combination with bevacizumab (4.3%).

### Survival of patients with isolated CNS metastases

With a median follow-up of 43.3 months (range: 0.8–112.4 months, 95% CI: 36.8–50.7) 352/541

patients have died. Median OS, PFS, TTCNS, and TTexCNS were 20.7 months (95% CI: 17.3–24.3), 6.1 months (95% CI: 5.7–6.8), 9.4 months (95% CI: 8.3–10.6), and 9.4 months (95% CI: 7.2–10.6), respectively (Figure 3). The first site of subsequent progression was CNS in 37.7% of patients and extra-CNS in 28.8% of patients, while 14.2% of patients did not experience progression. Prognostic factors associated with significantly poorer OS on multivariable analysis (Table 2) were age at MBC ≥55 years [HR = 1.8 (95% CI: 1.5–2.3), $p < 0.001$], TNBC subtype [HR = 1.5 (95% CI: 1.1–2.0), $p = 0.011$], time to metastatic disease from initial diagnosis of 6–12 months [HR = 2.0 (95% CI: 1.2–3.1), $p = 0.001$], and PS 2–4 (HR = 1.7 (95% CI: 1.1–2.8), $p = 0.001$). However, the presence of symptoms at MBC diagnosis *versus* none did not significantly influence OS [HR = 1.1 (95% CI: 0.9–1.4), $p = 0.436$] and PFS [HR = 1.1 (95% CI: 0.9–1.3), $p = 0.537$].

Outcomes differed across subtypes: OS decreased from 37.9 months (95% CI: 25.9–47.6) in HR+/HER2+ cases to 22.9 months (95% CI: 17.1–31.9) in HR+/HER2− cases, 19.2 months (95% CI: 14.3–28.9) in HR−/HER2+ cases, and 11.5 months (95% CI: 9.6–15.4) in the TNBC group ($p < 0.001$). A similar pattern was observed for PFS: 7.1 months (95% CI: 5.9–10.1), 6.8 months (95% CI: 5.7–9.4), 6.1 months (95% CI: 5.4–8.7), and 4.8 months (95% CI: 3.6–6.1), respectively, $p = 0.0033$ (Supplementary Figure 1). Between *de novo* and recurrent MBC, no significant difference in OS (19.2 months (95% CI: 12.7–37.8) *versus* 21.1 months (95% CI: 17.5–25.9), $p = 0.59$) or PFS (6.3 months (95% CI: 3.9–12.1) *versus* 6.1 months (95% CI: 5.7–6.9), $p = 0.31$) was noted (Supplementary Figure 2).

### Survival of patients with isolated CNS metastases, according to treatment

Compared with patients with no early systemic therapy, those who had received systemic therapy during the first 3 months after MBC diagnosis had longer median OS: 24.1 months (95% CI: 19.7–29) *versus* 16.1 months (95% CI: 11.7–21.6), HR = 0.8 (95% CI: 0.6–1.0), $p = 0.031$. This advantage was not confirmed by multivariable analysis after adjustment for local treatment and the previously identified prognostic factors [adjusted HR = 1.0 (95% CI: 0.7–1.3), $p = 0.806$]. Systemic therapy in the first 3 months did not influence PFS (median PFS 6.2 months *versus* 5.8 months) on univariate or multivariable analysis (Table 2, Supplementary Figure 3).

Among patients who received at least one treatment modality during the first 3 months after MBC diagnosis, the use of systemic therapy conferred an OS benefit compared with local treatment alone [24.3 months (95% CI: 18.9–30.2) *versus* 15.4 months (95% CI: 10.8–21.7), $p = 0.026$], similar to the exclusive use of systemic therapy [median OS of 21.2 months (95% CI: 16.0–35.0); Figure 4]. This advantage on univariate analysis [HR = 0.7 (95% CI: 0.6–0.9), $p = 0.009$] was no longer statistically significant on multivariable analysis [HR = 0.85 (95% CI: 0.6–1.1), $p = 0.26$] and was not observed for PFS ($p = 0.43$; data not shown).

In HR+/HER2− BC patients with local treatment, the use of either chemotherapy, ET alone or no systemic therapy was not associated with a statistically significant difference in terms of OS [27.5 months (95% CI: 7.1–NA) *versus* 23.3 months (95% CI: 16.0–44.6) *versus* 18.6 months (95% CI: 6.2–NA), $p = 0.68$] or PFS [6.2 months (95% CI: 5.1–11.9) *versus* 6.7 months (95% CI: 5.4–12.3) *versus* 5.7 months (95% CI: 3.7–23.2), $p = 0.58$; Supplementary Figure 4].

### Survival of patients with isolated CNS metastases according to local treatment

Patients treated with exclusive WBRT had a significantly poorer outcome compared to patients treated by surgical resection, SRS, or no local treatment (Supplementary Figure 5). This was consistent across BC subtypes (Supplementary Figure 6). On multivariable analysis, compared with WBRT as reference [median OS of 14.3 months (95% CI: 11.2–17.4), median PFS of 5.4 months (95% CI: 4.8–6.1)], surgical resection was associated with the best outcome [median OS: 59.9 months, adjusted HR = 0.4 (95% CI: 0.2–0.5), $p < 0.001$, median PFS: 8.3 months, adjusted HR = 0.6 (95% CI: 0.5–0.8), $p = 0.001$], followed by SRS [25.5 months (adjusted HR = 0.6 (95% CI: 0.4–0.8), $p < 0.001$] and 6.9 months [adjusted HR = 0.7 (95% CI: 0.5–0.9), $p = 0.001$, respectively]. No significant interaction was noted between WBRT and BC subtypes in the multivariable analysis ($p_{interaction} = 0.73$). Median OS and PFS were also longer in patients with no local treatment (21.2 and 7.4 months), but this difference was not statistically significant (Table 2, Supplementary Figure 5).

### Discussion
This is the largest study to extensively describe the clinical features of isolated CNS metastases as first site of metastatic disease, highlighting potential prognostic factors that could be useful in treatment decision-making.

Based on more than 20,000 cases of MBC observed over nearly a decade, we found 2.9% of cases of isolated CNS metastases and 4.17% of CNS metastases concurrent with other distant metastatic sites, as first sites of metastatic disease. The incidence of CNS metastases as first site of recurrence following management of early-stage BC per year of follow-up ranges from 0.1–0.2 to more than 3% in aggressive subtypes (HER2+, TNBC, or inflammatory BC) in the literature.[6,20–22] The rate of isolated CNS metastases among MBC patients is even more variable, ranging from 1.5% to 14%, depending on subtypes.[20–24] In the present

**Table 2.** Cox univariate and multivariable analysis for OS and PFS in patients with isolated CNS metastases who received or did not receive systemic therapy.

| Categories | N | Cox univariate analysis | | | | | | Cox multivariable analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OS | | | PFS | | | OS | | | PFS | | |
| | | HR | 95% CI | p value | HR | 95% CI | p value | HR | 95% CI | p value | HR | 95% CI | p value |
| Type of local treatment | | | | | | | | | | | | | |
| WBRT | 275 | 1 | | <0.001 | 1 | | 0.001 | 1 | | <0.001 | 1 | | 0.001 |
| Surgical resection | 88 | 0.3 | [0.2–0.5] | | 0.6 | [0.5–0.8] | | 0.4 | [0.2–0.5] | | 0.6 | [0.5–0.8] | |
| SRS | 93 | 0.7 | [0.5–0.9] | | 0.7 | [0.6–0.9] | | 0.6 | [0.4–0.8] | | 0.7 | [0.5–0.9] | |
| No local treatment | 82 | 0.8 | [0.6–1.0] | | 0.8 | [0.6–1.0] | | 0.7 | [0.5–1.0] | | 0.8 | [0.6–1.1] | |
| Systemic therapy | | | | | | | | | | | | | |
| No systemic therapy within the first 3 months | 212 | 1 | | 0.031 | 1 | | 0.201 | 1 | | 0.806 | 1 | | 0.957 |
| At least one systemic therapy | 326 | 0.8 | [0.6–1.0] | | 0.9 | [0.7–1.1] | | 1.0 | [0.7–1.3] | | 1.0 | [0.8–1.2] | |
| Age at MBC diagnosis | | | | | | | | | | | | | |
| <55 years | 236 | 1 | | <0.001 | 1 | | 0.041 | 1 | | <0.001 | 1 | | 0.048 |
| ≥55 years | 302 | 1.7 | [1.4–2.1] | | 1.2 | [1.0–1.5] | | 1.8 | [1.5–2.3] | | 1.2 | [1.0–1.5] | |
| Time to MBC | | | | | | | | | | | | | |
| <6 months | 46 | 1 | | <0.001 | 1 | | 0.03 | 1 | | 0.001 | 1 | | 0.033 |
| 6–12 months | 75 | 1.7 | [1.1–2.6] | | 1.7 | [1.1–2.6] | | 2.0 | [1.2–3.1] | | 1.9 | [1.2–2.9] | |
| 12–24 months | 164 | 0.9 | [0.6–1.3] | | 1.1 | [0.8–1.6] | | 1.0 | [0.7–1.5] | | 1.2 | [0.8–1.8] | |
| 24–60 months | 155 | 0.8 | [0.5–1.2] | | 1.1 | [0.8–1.6] | | 0.9 | [0.6–1.4] | | 1.3 | [0.9–1.8] | |
| ≥60 months | 98 | 0.8 | [0.5–1.2] | | 1.1 | [0.8–1.7] | | 0.8 | [0.5–1.3] | | 1.3 | [0.9–2.0] | |
| Symptoms at MBC diagnosis[a] | | | | | | | | | | | | | |
| No | 115 | 1 | | 0.436 | 1 | | 0.537 | Not included | | | | | |
| Yes | 410 | 1.1 | [0.9–1.4] | | 1.1 | [0.9–1.3] | | | | | | | |
| BC subtype | | | | | | | | | | | | | |
| HR+ /HER2– | 153 | 1 | | <0.001 | 1 | | 0.007 | 1 | | 0.011 | 1 | | 0.036 |

*(Continued)*

**Table 2.** (Continued)

| Categories | N | Cox univariate analysis | | | | | | Cox multivariable analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OS | | | PFS | | | OS | | | PFS | | |
| | | HR | 95% CI | p value | HR | 95% CI | p value | HR | 95% CI | p value | HR | 95% CI | p value |
| HR+/HER2+ | 116 | 0.8 | (0.6–1.0) | | 1.0 | (0.8–1.3) | | 0.8 | (0.6–1.1) | | 1.0 | (0.8–1.3) | |
| HR−/HER2+ | 107 | 1.1 | (0.8–1.5) | | 0.9 | (0.7–1.2) | | 0.9 | (0.7–1.3) | | 0.9 | (0.7–1.2) | |
| TN | 141 | 1.8 | (1.4–2.4) | | 1.5 | (1.1–1.9) | | 1.5 | (1.1–2.0) | | 1.4 | (1.0–1.9) | |
| NA | 21 | 0.9 | (0.5–1.8) | | 1.0 | (0.5–1.7) | | 0.9 | (0.4–1.7) | | 0.9 | (0.5–1.6) | |
| Performance status | | | | | | | | | | | | | |
| PS 0 | 64 | 1 | | < 0.001 | 1 | | 0.031 | 1 | | 0.001 | 1 | | 0.183 |
| PS 1 | 81 | 1.2 | (0.7–1.8) | | 1.3 | (0.9–1.9) | | 0.9 | (0.6–1.5) | | 1.2 | (0.8–1.7) | |
| PS 2–4 | 72 | 2.1 | (1.3–3.3) | | 1.8 | (1.2–2.5) | | 1.7 | (1.1–2.8) | | 1.5 | (1.0–2.2) | |
| PS NA | 321 | 1.8 | (1.3–2.6) | | 1.3 | (1.0–1.8) | | 1.6 | (1.1–2.2) | | 1.2 | (0.9–1.7) | |

CI, confidence interval; CNS, central nervous system; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR, hormone receptor; MBC, metastatic breast cancer; NA, not available; OS, overall survival; PFS, progression-free survival; PS, performance status; SRS, stereotactic radiosurgery; TN, triple-negative; WBRT, whole-brain radiotherapy.
[a]Not included in the multivariable analysis as it did not reach statistical significance in univariate analysis.
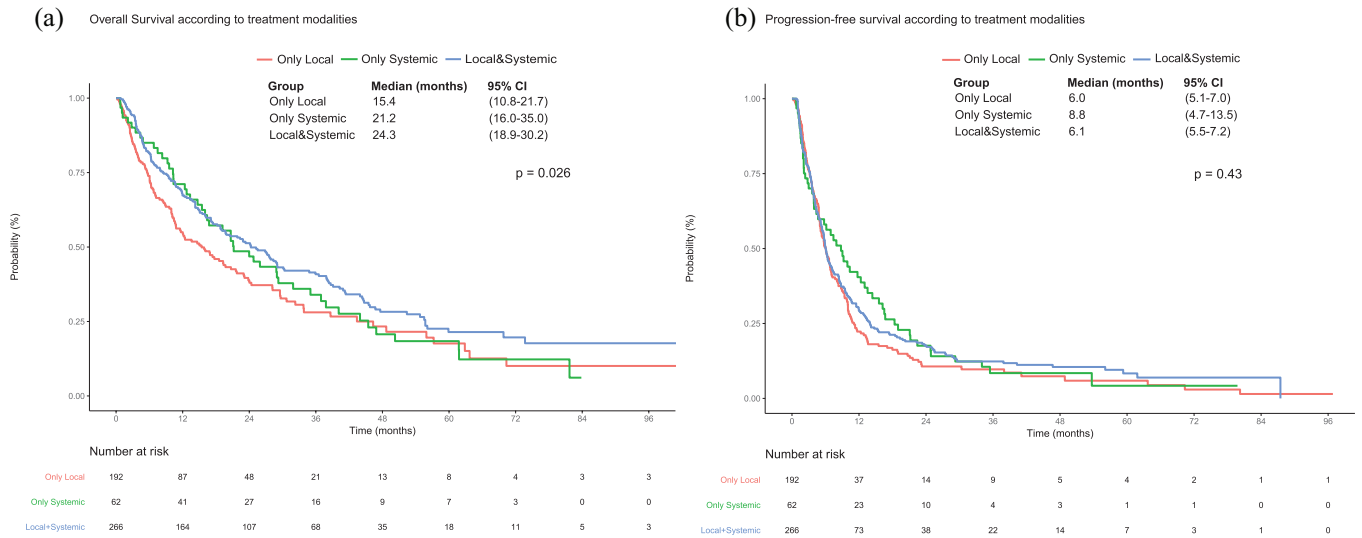
**Figure 4.** Kaplan–Meier curves for (a) overall survival and (b) progression-free survival in patients who received local treatment or systemic therapy in our population of interest, according to treatment modalities (local treatment only versus systemic therapy only versus local treatment and systemic therapy) (log-rank *p* = 0.026 and 0.43, respectively).
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

study, we confirm this variability with a higher propensity for CNS metastases among patients with HER2+ tumours or TNBC.

Risk factors for CNS metastases usually include ER−[21,22] and HER2+ [20,22] tumours, higher tumour grade,[22,25] larger size, and axillary node involvement.[20,22] However, isolated CNS relapse has rarely been reported in the literature, and many questions remain unanswered concerning the specific prognosis and management of isolated CNS metastases. Although several large population-based studies (such as those based on the Surveillance, Epidemiology, and End Results database) have highlighted the prognostic impact of brain metastases compared to isolated extracranial metastatic disease[3,26] or inversely the presence of extracranial metastases in addition to brain metastases,[18,26] these studies did not extensively describe patients with isolated CNS metastases as a distinct and specific population nor did they compare this population with the other two MBC presentations described here.

To the best of our knowledge, this is the first large-scale study comparing the three clinical settings of MBC patients with either isolated CNS metastases, both CNS and extra-CNS metastases, or only extra-CNS metastases. In our series, patients with CNS metastases (with or without extracranial metastases) presented distinct characteristics to those with only extracranial metastases, as

consistently reported in the literature (i.e. more commonly younger age, grade III, HER2+ tumours or TNBC, neoadjuvant or adjuvant chemotherapy, low PS and short time to MBC diagnosis). More importantly, they had significantly poorer survival, confirming the prognostic impact of the first metastatic site and the negative impact of CNS involvement.[3,23,24,26]

Interestingly, these patients also presented different characteristics depending on whether CNS metastases occurred alone or with concurrent extra-CNS disease: patients with isolated CNS metastases more often had HER2+ tumours, had less frequently received systemic therapy, had a shorter time to MBC diagnosis, and significantly better OS, suggesting a different clinical entity and stressing the need for further research.[12,25] We also confirm the negative prognostic impact of the presence of extracranial metastases in addition to CNS metastases, as already observed in the general MBC population and as supported in an updated breast-Graded Prognostic Assessment (GPA).[5,17,18,26]

In our study, the population with isolated CNS metastases had a better survival than that reported in other less strictly selected series (10.5 to 14 months),[11,13,25] likely reflecting the inclusion of patients with leptomeningeal metastases in some series or differences in management over time. For example, Sperduto *et al.*[17] reported an

improvement of OS in MBC patients with CNS metastases (alone or combined with extracranial metastases) from 11 months between 1985 and 2007 to 16–23 months in more recent cohorts. A limitation of our study was the fact that parenchymal and leptomeningeal metastases were not directly differentiated, so the use of intrathecal chemotherapy had to be used as a proxy for leptomeningeal disease. However, intrathecal chemotherapy is recommended by the current EANO-ESMO guidelines as part of the therapeutic approach for the grand majority of leptomeningeal metastases (LM)[27] and, despite the still existing heterogeneity in the use of different treatment modalities, intrathecal chemotherapy is reported as being commonly used in this setting.[28,29] Our results, showing significantly inferior outcomes for patients with CNS metastases treated with intrathecal chemotherapy *versus* those without intrathecal therapy, confirm that they represent two different subgroups of patients.

Of note, compared with other analyses conducted in the general ESME MBC population, patients included in this study had shorter survival,[30] although longer than that of all unselected patients with CNS metastases.[31] We also found a longer time to CNS progression than in other studies,[13] but subsequent progression more often occurred in the CNS, consistent with previous reports,[11,13,14] suggesting that, despite the potential for long-term survival, long CNS response is a rare phenomenon.

In the population with isolated CNS MBC, we confirm the impact of well-known prognostic factors for CNS metastases, such as BC subtype and age, now included in the modified or updated breast-GPA,[17,32] as well as time to MBC diagnosis. In our study, an interval of 6 to 12 months to MBC diagnosis was found prognostic for worse outcome than *de novo* MBC, in line with other studies that report worse survival in patients with 'early relapse' than in those with *de novo* MBC or with 'later relapse'.[30,33] HR+ /HER2+ BC patients had the longest survival. This result is in line with the prognosis of all HR+ /HER2+ MBC patients with brain metastasis in the ESME database, which was significantly better even than that of HR+ /HER2− patients.[31] Also, Sperduto *et al.*[17] reported significantly better prognosis for patients with 'luminal B' MBC with brain metastasis than all other subtypes. As reported in other studies,[5,13,18,31] TNBC was correlated with poorer outcome on multivariable analysis.

In our cohort, 84.7% of patients received local treatment, a considerably higher proportion than in the overall MBC population with CNS metastases in the ESME database and with higher rates of 'focal' treatment.[34] In agreement with previous studies,[13,17,35] surgical resection and SRS were associated with significantly longer survival compared to exclusive WBRT on multivariable analysis, irrespective of the use of systemic therapy. This outcome was probably in large part the expression of the impact on survival of the intracranial disease burden, that also influenced the choice of treatment, but an important limitation of our work is the missing data for the number and size of brain lesions for all patients and PS for nearly one-half of patients. Patients treated with WBRT, as a proxy for a high burden of intracranial disease, had poorer outcomes than the rest of patients consistently across all BC subtypes.

Despite growing evidence of the beneficial impact of systemic agents on the course of MBC with CNS involvement,[36] no systemic therapy has yet been specifically approved for the treatment of brain metastases.[16] In the literature, a significant proportion (50–67%) of BC patients receive systemic therapy as part of their first-line treatment strategy in the presence of isolated CNS metastases,[11,13,14] as found in our series. Despite the reported positive impact of systemic therapy on outcome, the addition of systemic therapy to the management of patients with isolated CNS metastases remains controversial and many confounding and limiting factors have been identified, such as small sample sizes, retrospective design, and patient selection.[11,13,14,37] Our study contributes to the previous literature by providing a detailed description of real-life patterns of care in a large cohort. Administration of systemic therapy was associated with prolonged OS only on univariate analysis. Interestingly, patients who did not receive local treatment also had a similar, relatively good outcome, suggesting that local treatment could be delayed when an effective systemic therapy is available, as previously reported in the case of WBRT, which has a deleterious effect on cognitive function.[38]

In the absence of specific recommendations, a large number of HR+ BC patients in our cohort received ET, possibly due in part to continuing adjuvant therapy. Although the literature is limited to case reports[39] and retrospective analyses,[40] ET has also been shown to have a good CNS distribution,[36,40] making it an attractive modality for

HR + BC patients with isolated CNS metastases[13,14] not exposed to prior lines of palliative ET, with a lower risk of endocrine resistance. As the impact of ET on survival has been shown to be not significantly different from that of chemotherapy, ET could represent a good alternative to chemotherapy with fewer side effects.

Finally, the lack of significant impact on multivariable analysis of early systemic therapy could be explained by several limitations: (1) most patients who did not undergo surgical resection for BM received systemic therapy according to the primary subtype, while subtype switching has been described between timepoints;[34,41] (2) the 3-month cut-off was arbitrarily defined and some patients may have started systemic therapy just after 3 months; (3) we could not assess whether the ET used for adjuvant therapy was continued following CNS relapse; (4) effective targeted agents such as CDK4/6 inhibitors, inhibitors of the PI3K/AKT/mTOR axis, pertuzumab or T-DM1 have been gradually introduced and may have mitigated or diluted the impact of first-line treatment on survival; and (5) these data are not randomized, with all the usual confounding factors, the use of real-world data is associated with a potential selection bias that may have influenced treatment strategies. These limitations support randomized studies designed to specifically address the value of adding systemic therapy for each subtype. Another important question to be addressed would be whether local treatment with significant toxicity can be delayed or avoided in certain cases, with the use of effective systemic therapies such as CDK4/6 inhibitors, newer generations of anti-HER2 agents, or other novel therapeutic agents already demonstrated to be active on CNS metastases or currently investigated in ongoing clinical trials.[36]

## Conclusion

The first metastatic site influences survival in MBC patients. Patients who initiate their metastatic disease with isolated CNS involvement represent a specific population, with a potential for better outcome than patients with both CNS and extra-CNS metastases. In the absence of specific guidelines, we found a great variety of real-life management strategies. Although patients who received systemic therapy in addition to local treatment had longer median survival, systemic therapy was not an independent prognostic factor

on multivariable analysis. Efforts should be pursued to further refine specific management. Inclusion of more patients with CNS metastases, even in the absence of extracranial disease, in prospective studies evaluating systemic therapies should therefore be encouraged.

## Author contributions

**Marcela Carausu:** Conceptualization; Writing – original draft.

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## Supplemental material

Supplemental material for this article is available online.

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