Treatment and outcomes in patients with central nervous system metastases from breast cancer in the real-life ESME MBC cohort

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Short running title: Brain metastases in breast cancer patients

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Abstract

Aim

The aims of the present study were to describe treatment patterns and survival outcomes in patients with central nervous system metastases (CNSM) selected among MBC patients included in a retrospective study from the Epidemio-Strategy and Medical Economic (ESME) metastatic breast cancer (MBC) cohort.

Methods

Neurological progression-free survival (NPFS) and overall survival (OS) were estimated using the Kaplan Meier method. Significant contributors to NPFS were determined using a multivariate Cox proportional hazards model.

Results

After a median follow-up of 42.8 months, of 16 701 patients included in the ESME MBC database, CNSM were diagnosed in 24.6% of patients. The most frequent treatments after CNSM diagnosis were whole brain radiotherapy (WBRT) (45.2%) and systemic treatment (59.3%). Median OS and NPFS were 7.9 months (95% CI: 7.2-8.4) and 5.5 months (95% CI: 5.2-5.8), respectively. In multivariate analysis, age >70 (vs <50; HR=1.40; 95% CI: 1.24-1.57), triple-negative tumours (vs HER2-/HR+; HR=1.87; 95% CI: 1.71-2.06), HER2+/HR- tumours (vs HER2-/HR+; HR=1.14; 95% CI: 1.02-1.27), ≥3 metastatic sites (vs <3; HR=1.32; 95% CI: 1.21-1.43) and ≥3 previous treatment lines (vs <3; HR=1.75; 95% CI: 1.56-1.96) were detrimental for NPFS. A time interval between selection and CNSM diagnosis superior to 18 months (vs <9 months; HR=0.88; 95% CI: 0.78-0.98) was associated with longer NPFS.

Conclusions

This study describes current treatment patterns of MBC patients in a "real life" setting. Despite advances in SRT, most patient still received WBRT. More research is warranted to identify patient subsets for tailored treatment strategies.

Introduction

An estimated 20% of patients with cancer will develop brain metastases. Among metastatic breast cancer (MBC) patients, 30-50% with will develop metastases of the central nervous system (CNSM) during the course of the disease [1]. This incidence is expected to increase with advances in systemic therapies and prolonged survivals, as well as more effective neuroimaging techniques for the detection of metastatic disease [2]. It has been shown that CNSM from breast cancer (BC) are more common in young women, those presenting advanced disease or a higher nuclear grade, triple-negative and human epidermal growth factor receptor 2 (HER2) amplified tumour subtypes [2,3].

CNSM are not only associated with a poor prognosis – one out of two patients with CNSM is expected to die from central nervous system disease progression - but also with neurological impairment [4]. They have become a major limitation of life expectancy and quality of life in many patients and the development of management strategies for CNSM constitutes an important clinical challenge.

For patients with a limited number of CNSM and reasonable performance status, surgery or stereotactic radiation therapy (SRT) is the standard of care [5]. For patients with multiple metastases, current practice is to administer whole-brain radiotherapy (WBRT), but it has been proven to cause important neurocognitive toxicities [6,7]. Recent studies have assessed systemic treatment in this setting, before or after WBRT [1,5,8].

There is currently paucity of data regarding treatment patterns in BC patients with CNSM, as well as on neurological disease behaviour based on tumour biology [9,10]. In view of the growing burden of MBC, real-life data is necessary to address the clinical challenges related.

In 2014, Unicancer, the French network of 18 comprehensive cancer centres, launched the Epidemiological Strategy and Medical Economics (ESME) programme with the aim of collecting and centralising real-life patient data with a focus in areas including MBC [11]. The database includes information on patient characteristics and management strategies, as well as outcomes. Darlix *et al* recently submitted the kinetics of CNSM occurrence and subsequent prognosis according to the molecular subtype [12]. We undertook this analysis to describe treatment patterns in patients with CNSM from BC making use of the high-quality, real-life data from the ESME-MBC cohort. The analysis also aimed at estimating neurological progression free survival (NPFS), overall survival (OS) and to assess factors associated with NPFS in real-life conditions.

Methods

Study design

This was a retrospective study of MBC patients with CNSMs from the ESME-MBC cohort. The ESME-MBC database was authorised by the French data protection authority (authorisation no. 1704113) in compliance with the French regulations. The database is managed by R&D Unicancer in accordance with Good Pharmacoepidemiology Practices and Good Epidemiology Practices [11]. The study was approved by an independent ethics committee. No informed consent was required.

Study population

The ESME MBC cohort (NCT03275311) included adult male and female patients starting treatment (partial or complete) for a MBC in one of the 18 French comprehensive cancer centres from 1-Jan-2008 to 31-Dec-2014 [11]. The present analysis focused on patients from the ESME cohort diagnosed with CNSMs either at the time of MBC diagnosis or during the course of the disease. CNSMs included both brain metastases (BM) and leptomeningeal metastases but the difference was not specified in the case report form.

Data collection

Data were collected from the ESME MBC Data platform, a real-life database using a retrospective collection of data from patient's electronic medical records, inpatient hospitalisation records and pharmacy records [11]. The cut-off date for the present analysis was 15-Jan-2016.

Objectives

The main objective of this study was to describe treatment patterns in patients with CNSM from BC in the ESME MBC cohort. The study also aimed at estimating OS, NPFS and to assess factors associated with NPFS. Analyses were performed for the population with CNSM overall and for two sub-cohorts: patients with CNSM treated by WBRT and patients with CNSM treated by SRT.

Statistical methods

Categorical variables were reported as frequency and percentage, while continuous variables were reported as mean, standard deviation (SD), median and range values.

The median follow-up was calculated using the reverse Kaplan-Meier method. NPFS was defined as the time interval (months) between the CNSM diagnosis and the date of first progression of CNSM or death, whichever occurred first. OS was defined as the time interval (months) between the date of

CNSM diagnosis and the date of death, regardless of cause. Patients without events were censored at the cut-off date of the analysis (15-Jan-2016). The Kaplan-Meier method was used to determine NPFS and OS, presented as median with the 95% confidence interval (CI) and survival rates in percentages, with 95% CIs. Survival estimations were compared with the log-rank test. The Cox proportional hazards model with a backward regression procedure was used to determine significant contributors to NPFS. Variables were included in the multivariate analysis only if significant on univariate analysis ($p<0.020$). Hazard ratios (HR) with their 95% CIs were calculated to display risk changes. All p-values reported were two-sided, and the significance level was set at 5%. Statistical analysis was performed using the SAS® software (version 9.4).

Results

Patients

After a median follow-up of 42.8 months (95% CI: 42.1-43.7), of the 16 701 patients included in the ESME MBC database, CNSM were diagnosed in 4118 patients (24.6%) (1200 patients [7.2%] at diagnosis of metastatic disease and 2918 [17.5%] during follow-up). Among them, 85 patients were diagnosed with CNSM after the cut-off date for the analysis (15-Jan-2016), therefore 4033 patients with CNSM were included in the analysis population .

The mean (SD) age at CNSM diagnosis was 57.8 (12.6) years (Table 1). Among CNSM patients with known immunohistochemistry (N=3564), breast cancer subtypes were the following: 45.0% (N=1599) HER2-/HR+, 25.6% (N=906) triple-negative, 15.0% (N=540) HER2+/HR- and 14.4% (N=519) HER2+/HR+. Phenotype switching between the primary and the surgical specimens in patients that had undergone an operation (N=94) was observed most frequently among patients with a primary HER2+/HR+ tumour (Supplementary Table 1). In total, 38.4% of CNSM patients had ≥3 metastasis sites. The most frequent metastatic sites other than CNSM were bone (59.4%) followed by the liver (42.7%) and the lung parenchyma (39.2%).

Diagnosis

CNSM were diagnosed based on the occurrence of symptoms in 70.7% of patients, and through systematic imaging examination in 29.3% of patients (Table 1).

Treatments

In the first 3 months after CNSM diagnosis, patients received at least one of the following treatments: surgical resection of CNSM (2.3%), SRT (10.5%), WBRT (45.2%), systemic treatment (59.3%) and

best supportive care only (16.2%). The most frequent association was WBRT and systemic treatment (31.4% of patients). Over a third of patients (33.1%) received systemic treatment only (Supplementary Table 2). The type of systemic treatment according to the treatment line is presented in Supplementary Table 3.

Figure 1 presents the first treatment patterns depending on the year of CNSM diagnosis. WBRT and systemic treatment were the most common approaches, regardless of the year. The use of surgical resection and SRT as first treatment after CNSM diagnosis increased slightly over time (p<0.0001).

Survival analysis

Median follow-up of patients with CNSM was 30.0 months (95% CI: 28.0-32.0). The median OS was 7.9 months (95% CI: 7.2-8.4) and median NPFS was 5.5 months (95% CI: 5.2-5.8). The 6- and 12-month NPFS rates were 47.1% (95% CI: 45.8%-48.7%) and 26.2% (95% CI: 24.9%-27.8%), respectively.

Median NPFS for HER2-/HR+ was 5.3 months (95% CI: 4.9-5.7), for HER2+/HR- 6.9 months (95% CI: 6.4-7.7), for HER2+/HR+ 8.8 months (95% CI: 8.0-10.0) and for triple-negative 3.7 months (95% CI: 3.4-4.1) (Table 3).

In multivariate analysis (Table 2), age >70 (vs <50; HR=1.40; 95% CI: 1.24-1.57; p<0.0001), triple-negative tumours (vs HER2-/HR+ subtype; HR=1.87; 95% CI: 1. 71-2.06; p<0.0001), HER2+/HR- tumours (vs HER2-/HR+ subtype; HR=1.14; 95% CI: 1.02-1.27; p=0.0262); ≥3 metastatic sites (vs <3; HR=1.32; 95% CI: 1.21-1.43; p<0.0001), ≥3 previous treatment lines (vs <3; HR=1.75; 95% CI: 1.56-1.96; p<0.0001), year of management 2011-2014 (vs 2008-2010; HR=1.08; 95% CI: 1.00-1.17; p=0.0428) were detrimental for NPFS. Systematic examination (vs symptoms; HR=0.85; 95% CI: 0.78-0.92; p<0.0001), interval between selection and CNSM diagnosis superior to 18 months (vs < 9 months; HR=0.88; 95% CI: 0.78-0.98; p=0.0221) were associated with longer NPFS.

Patients with a disease stage eligible for surgery had the highest survival probability, followed by those with an indication for SRT, for systemic and for WBRT; those with an indication for supportive care had the lowest survival probability (log-rank test: p<0.0001) (Figure 2).

Patients treated with WBRT

Median OS for patients with CNSM treated with WBRT was 8.0 months (95% CI: 7.2-9.1).

Median NPFS was 5.9 (95% CI: 5.5-6.4) months. NPFS rate after WBRT was 49.6% (95% CI: 46.9%–52.3%) at 6 months and 24.6% (95% CI: 22.2%-27.1%) at 12 months.

In multivariate analysis, patients >70 of age (vs patients <50 years HR=1.59; 95% CI: 1.32-1.92; p<0.0001), patients with triple-negative tumours (vs HER2-/HR+; HR=1.71; 95% CI: 1.46-2.00; p<0.0001), patients with ≥3 metastatic sites (vs <3; HR=1.46; 95% CI: 1.27-1.66; p<0.0001), and with ≥3 previous treatment lines (vs <3; HR=1.44; 95% CI: 1.23-1.70; p<0.0001) had an increased risk of neurological progression (Table 3).

Patients treated with SRT

Median OS for patients with CNSM treated with SRT was 12.8 months (95% CI: 10.8-16.0).

Median NPFS was 7.2 months (95% CI: 6.2-8.5). The 6- and 12-month NPFS rate after SRT were 57.1% (95% CI: 50.9-62.9) and 31.9% (95% CI: 26.2-37.8), respectively.

Multivariate analysis (Table 4) revealed that, after treatment with SRT, NPFS was significantly shorter in patients with triple-negative breast cancer (vs HER2-/HR+ patients; HR=2.88; 95% CI: 2.09-4.12; p<0.0001) and in those having received ≥3 treatment lines (vs <3; HR=2.82; 95% CI: 1.99-3.97; p<0.0001) was associated with improved NPFS.

Discussion

This is, to our knowledge, the largest real-life database providing information on treatment patterns and outcomes in MBC patients with CNSM. The impact of the year of MBC diagnosis on OS for this cohort has already been published [13]. There is, however, paucity of data regarding the neurological evolution of the disease and the factors associated with the risk of neurological progression in this population. In this analysis, we found that NPFS was associated with age, time interval between inclusion and CNSM diagnosis, tumour biology, number of treatment lines, number of metastatic sites and the first treatment type after diagnosis of CNSM.

The distribution of molecular subtypes of BC in this population was consistent with previous reports [14-16].

Median NPFS was the shortest for triple-negative tumours (3.7 months). Our results also showed that NPFS is molecular subtype-dependant regardless of treatment. These data confirm results observed by Arslan *et al* in a small series of patients treated by WBRT, which found median brain-specific

progression-free survival to be 9.1 (95% CI: 3.7-14.5), 8.2 (95% CI: 4.7-11.7), 7.1 (95% CI: 6.2-8.1) and 3.6 (95% CI: 1.2-6) months in HER2-/HR+, HER2+/HR-, HER2+/HR+ and triple-negative subgroups, respectively (p=0.014) [17]. Frisk *et al* evaluated survival outcomes in a retrospective series of 241 patients with late stage cancer and BM receiving WBRT [18]. Triple-negative tumours were associated with short overall survival: 2.0 months; HR=1.87; 95% CI: 1.23-2.84 versus Luminal A tumours. In the ESME MBC cohort, median OS for patients with triple-negative tumours was 4.4 months (95% CI: 4-4.8) [12]. Given the delayed effect of radiotherapy, the known rapid onset of BM in triple-negative tumours and the poor prognosis in these patients, this raises the question of whether all patients with triple-negative tumours should be treated with WBRT. Specific prognostic factors, such as the ones reported here, could help select patients suitable for aggressive treatment.

CNSMs have historically been managed using local treatments, mostly WBRT and more recently SRT. In this study, almost half of the patients received WBRT. As reported by Rostami *et al.* [2] in their literature review, local treatments involved WBRT (52%), SRT (20%) and surgical resection (14%). In the SysHERs prospective, observational registry of 977 patients with HER2-positive MBC enrolled from 2012-2016, of the 299 patients with CNSMs, 61.2% received WBRT [14]. Similarly, in the German registry of 1721 patients, 51% of patients received WBRT and 4% SRT [16]. The rate of WBRT use, including that in our series, seem high considering that they are contemporary studies and the recent technological advances allowing SRT or surgery in cases of localised brain disease. While the studies on the USA- and Germany-based registries did not analyse the change in treatment patterns over time, our analysis revealed that the use of WBRT decreased and surgery increased slightly over the study period.

Due to the lack of data on the beneficial effects, the NCCN and ESMO guidelines do not recommend brain screening among BC patients, including HER2+ and triple-negative patients for whom BM are common [5, 19]. This is in contrast to patients with stage III or IV non-small cell lung cancer, small cell lung cancer any stage and melanoma stage IV, for whom MRI screening of the brain is recommended [20]. This has been shown to have an implication on the type of treatment since the size and number of BM at diagnosis determine management. Cagney *et al* compared the presentation, management and outcome of breast cancer patients with BM and NSCLC patients with BM [20]. Breast cancer patients were more often symptomatic (75.9% *vs* 60.5%; p<0.001). BC patients had more and larger BM when diagnosed and therefore received WBRT more often (59.9% of patients compared with

42.9% of NSCLC patients). This did not have an impact on neurological recurrence or treatment-based outcomes. In Cagney *et al*'s study, neurological death was, however, more common among BC patients (HR=1.54; 95% CI: 1.10-2.17; p=0.01). In our study, over two thirds of patients were diagnosed due to symptoms. Even if not recommended by guidelines, screening could be of interest for MBC patients, due to the high incidence of CNSM. Diagnosing CNS earlier could lead to a reduction in WBRT use in some patients. For example, ESMO guidelines state that because patients with HER2-positive MBC and BM can live for several years, consideration of long-term toxicity is important and less toxic local therapy options (e.g. SRT) should be favoured to WBRT, when available and appropriate (e.g. with a limited number of BM) [19]. Brain monitoring for high risk of BM occurrence in MBC is currently being evaluated in a clinical trial [17].

The strengths of this study include the large, geographically diverse population including patients from 18 centres and with all types of BC, the details of the real-life care delivered and the relatively long follow-up. This database is reflective and provides data generalizable to women with MBC. The present analysis also provided access to the largest amount of data on neurological disease behaviour from patients with CNSM over time.

This retrospective study has several limitations. No conclusions can be drawn from treatment comparison due to differences in the populations. Other limitations from the study are inherent to the observational nature of the study. The complete background information of patients might be missing and lead to bias. Also, the number, the type (brain *vs* leptomeningeal) and location of CNSMs was not recorded, so no association between these factors and the treatment received could be explored. The impact of performance status and of associations of different treatments on survival was not included in the multivariate models. Last, a bias of anticipation of diagnosis cannot be excluded: while NPFS seems to be longer after systematic diagnosis in multivariate analysis, this could be due to the earlier detection of the metastases and not due to a different course of the disease.

In conclusion, this study describes current treatment patterns of MBC patients in a "real life" setting. Despite advances in SRT, most patient still received WBRT. More research is warranted to identify patient subsets for tailored treatment strategies.

Conflicts of interest:

Anthony Goncalves declare non-financial support (travel, meeting registration and accommodation) from Roche, Novartis, Pfizer, Astra Zeneca, MSD, Boheringer, Celgene.

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The other authors have no conflict of interest to declare.

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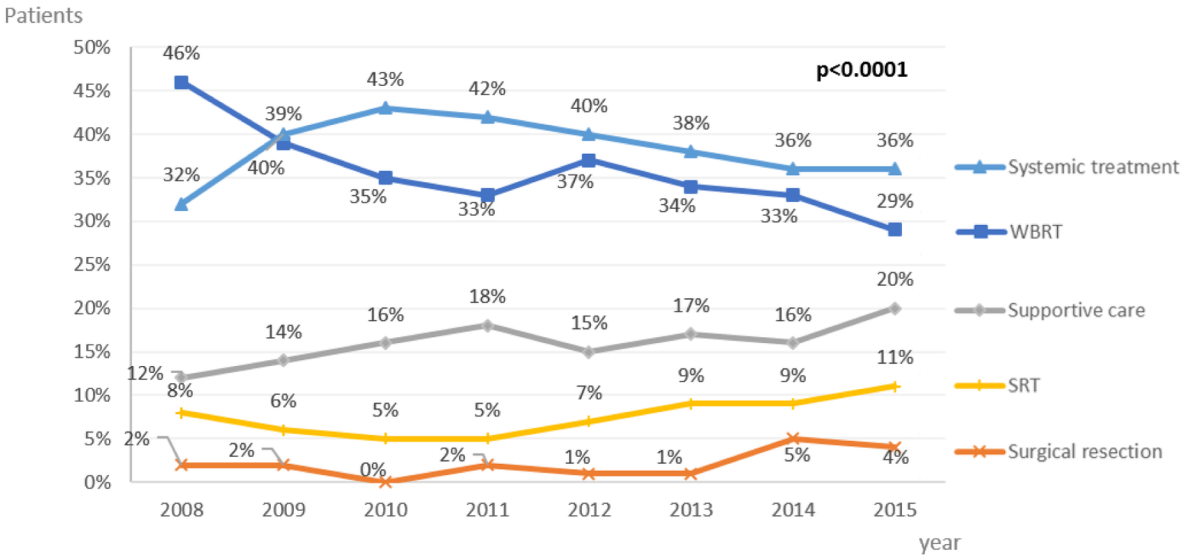
Figure captions

Figure 1. Type of first CNSM treatment depending on the year of CNSM diagnosis

Figure 2. Kaplan Meier curve for N-PFS stratified by first treatment post CNSM diagnosis.



WBRT: whole brain radiation therapy; SRT= stereotactic radiation therapy

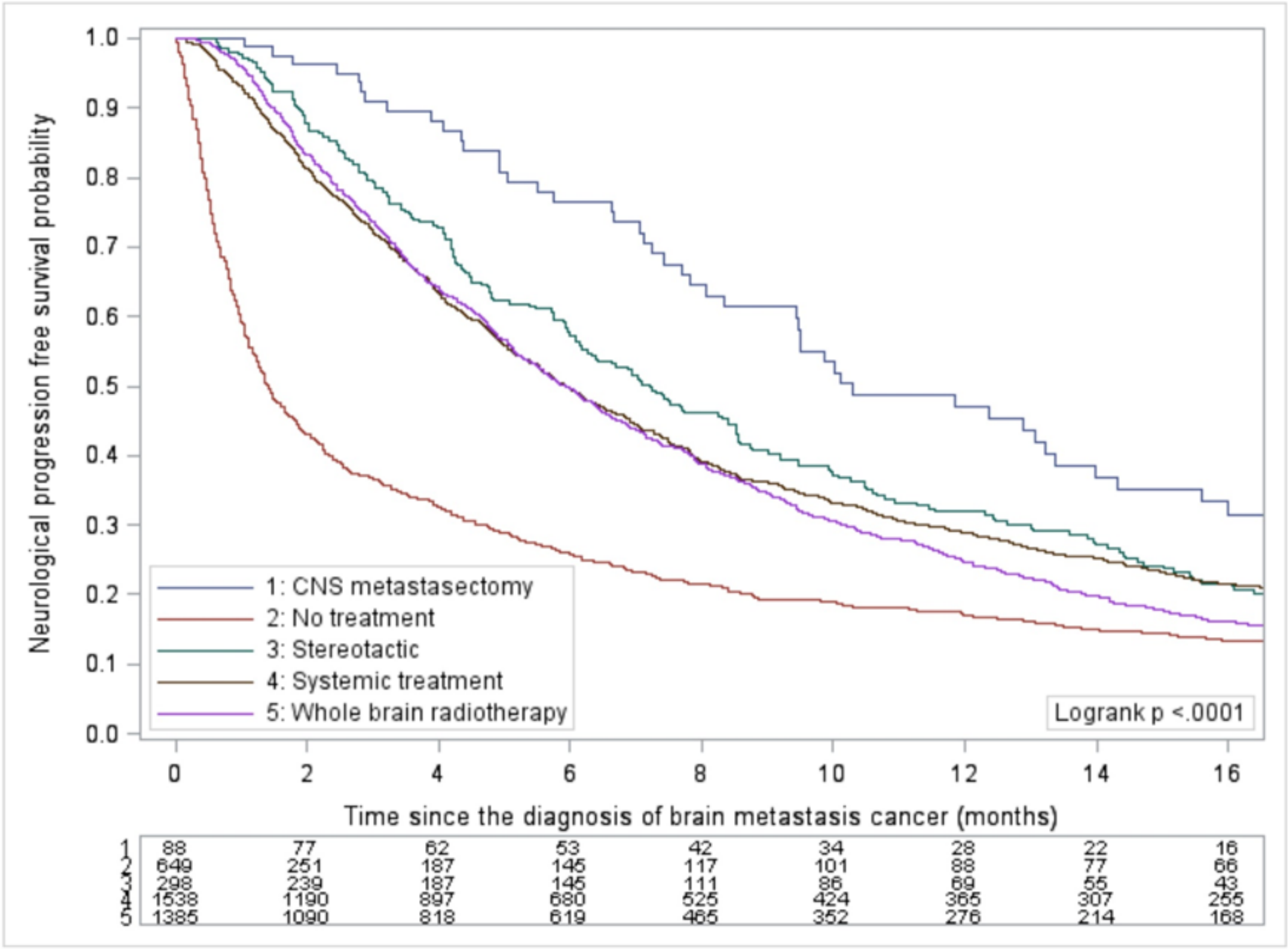

Neurological progression free survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
1: CNS metastasectomy
2: No treatment
3: Stereotactic
4: Systemic treatment
5: Whole brain radiotherapy
Logrank p <.0001
0
2
4
6
8
10
12
14
16
Time since the diagnosis of brain metastasis cancer (months)
1 88 77 62 53 42 34 28 22 16
2 649 251 187 145 117 101 88 77 66
3 298 239 187 145 111 86 69 55 43
4 1538 1190 897 680 525 424 365 307 255
5 1385 1090 818 619 465 352 276 214 168

Table 1. Baseline characteristics of patients with CNSM.

Characteristics	Patients CNSM (N=4033)
Mean (SD) age at diagnosis of CNSM, years	57.8 (12.6)
Gender, n (%)	
Male	26 (0.6)
Female	4007 (99.4)
CNSM diagnosed, n (%)	
At initial diagnosis of MBC	1059 (26.3)
During follow-up	2974 (73.7)
Mode of diagnosis, n (%)	
Systematic examination	1140 (29.3)
Symptoms	2745 (70.7)
Missing	148
Visceral extracranial metastases, n (%)	2707 (67.1)
Non-visceral metastases, n (%)	2980 (73.9)
Metastatic sites, n (%)	
CNSM only	615 (16.7)
CNSM and others	3358 (83.3)
If others, localisation, n (%)	
Bone	2394 (59.4)
Lung parenchyma	1580 (39.2)
Pleura	606 (15.0)
Skin	503 (12.5)
Liver	1724 (42.7)
Other	688 (17.1)
Number of metastatic sites, n (%)	
<3	2484 (61.6)
≥3	1549 (38.4)
Immunological status, n (%)	
Triple-negative	950 (25.6)
HER2+/HR-	557 (15.0)
HER2+/HR+	534 (14.4)
HER2-/HR+	1667 (45.0)
Missing	325
Inclusion period (in the ESME cohort), n (%)	
2008-2010	1932 (47.9)
2011-2014	2100 (52.1)
Missing	1

Table 2. Univariate and multivariate analyses (Cox regression) of factors associated with NPFS.

	Univariate			Multivariate		
Factors	**HR (95% CI)**	**Median NPFS (95% CI)**	**P value**	**HR**	**95% CI**	**P value**
Age						
<50	1.00 (=ref)	6.4 (6.0-7.1)	<.0001	1.00 (=ref)		
[50-70]	1.08 (1.00-1.17)	5.4 (5.0-5.8)		1.06	0.98-1.16	0.1452
>70	1.31 (1.18-1.46)	4.0 (3.5-4.6)		1.40	1.24-1.57	**<0.0001**
Interval between MBC diagnosis and CNSM diagnosis (months):						
<9	1.00 (=ref)	6.1 (5.7-6.6)	<.0001	1.00 (=ref)		
[9-18]	1.29 (1.18-1.41)	4.8 (4.3-5.7)		1.07	0.96-1.19	0.2009
>18	1.25 (1.15-1.35)	4.8 (4.5-5.2)		0.88	0.78-0.98	**0.0221**
Global molecular subtype status						
HER2-/ HR+	1.00 (=ref)	5.3 (4.9-5.7)	<.0001	1.00 (=ref)		
HER2+/HR+	0.93 (0.84-1.04)	6.9 (6.4-7.7)		0.86	0.77-0.96	**0.0094**
HER2+/HR-	0.80 (0.71-0.89)	8.8 (8.0-10.0)		1.14	1.02-1.27	**0.0262**
Triple-negative	1.60 (1.47-1.75)	3.7 (3.4-4.1)		1.87	1.71-2.06	**<0.0001**
Number of treatment lines						
<3	1.00 (=ref)	6.3 (6.0-6.7)	0.0012	1.00 (=ref)		
≥3	1.62 (1.50-1.76)	3.8 (3.4-4.1)		1.75	1.56-1.96	**<0.0001**
Number of metastatic sites						
<3	1.00 (=ref)	7.4 (6.9-7.9)	<.0001	1.00 (=ref)		
≥3	1.41 (1.31-1.51)	4.7 (4.3-4.9)		1.32	1.21-1.43	**<0.0001**
Year of management			0.8458			
2008-2010	1.00 (=ref)	5.2 (4.9-5.6)		1.00 (=ref)		
2011-2014	0.99 (0.93-1.06)	5.8 (5.4-6.2)		1.08	1.00-1.17	**0.0428**
1st treatment post diagnosis of CNSM						
No treatment	1.00 (=ref)	1.4 (1.2-1.7)	<.0001	1.00 (=ref)		
Systemic treatment	0.56 (0.51-0.62)	5.9 (5.5-6.4)		0.54	0.49-0.61	**<0.0001**
SRT	0.49 (0.42-0.57)	7.2 (6.2-8.5)		0.49	0.41-0.58	**<0.0001**
WBRT	0.60 (0.54-0.67)	5.9 (5.5-6.4)		0.58	0.51-0.64	**<0.0001**
Resection	0.34 (0.26-0.45)	10.3 (9.4-14.3)		0.39	0.29-0.53	**<0.0001**
Mode of diagnosis						
Symptoms	1.00 (=ref)	5.3 (5.0-5.7)	<.0001	1.00 (=ref)		
Systematic examination	0.82 (0.76-0.88)	6.1 (5.6-6.8)		0.85	0.78-0.92	**<0.0001**

NS= non significant; HR= hazard ratio

Table 3. Univariate and multivariate analysis (Cox regression) of factors associated with NPFS – patients treated with WBRT

	Univariate			Multivariate		
Factors	**HR (95% CI)**	**Median (95% CI)**	**P value**	**HR (95% CI)**	**Median (95% CI)**	**P value**
Age						
<50	1.00 (=ref)	7.4 (6.4-8.1)	<0.0001*	1.00 (=ref)		
[50-70]	1.10 (0.96-1.25)	6.0 (5.5-6.6)		1.08	0.94-1.24	0.2563
>70	1.51 (1.27 – 1.80)	3.7 (3.3-4.7)		1.59	1.32-1.92	**<0.0001**
Interval between selection and CNSM diagnosis (months):						
<9	1.00 (=ref)	6.3 (5.7-6.9)	0.0064*	1.00 (=ref)		
[9-18]	1.16 (1.00-1.35)	6.0 (4.7-7.3)		NS	NS	NS
>18	1.23 (1.07-1.42)	5.2 (4.7-6.1)		NS	NS	NS
Molecular subtype						
HER2-/HR+	1.00 (=ref)	5.7 (5.2-6.8)	<0.0001*	1.00 (=ref)		
HER2+/HR-	0.96 (0.81-1.14)	6.4 (5.7-7.4)		1.09	0.91-1.29	0.3531
HER2+/HR+	0.84 (0.70-1.00)	7.9 (6.2-9.8)		0.93	0.77-1.13	0.4691
Triple-negative	1.42 (1.22-1.65)	4.6 (3.8-5.1)		1.71	1.46-1.99	**<0.0001**
Number of metastatic sites						
<3		7.3 (6.5-8.1)	<0.0001*			
≥ 3	1.45 (1.29-1.63)	5.2 (4.7-5.7)		1.46	1.27-1.66	**<0.0001**
Number of treatment lines						
<3	1.00 (=ref)	6.4 (6.0-7.1)	0.0059*	1.00 (=ref)		
≥ 3	1.51 (1.31-1.75)	4.6 (4.0-5.2)		1.44	1.23-1.70	**<0.0001**
Year of management initiation						
2008 - 2010	1.00 (=ref)	5.7 (5.1-6.3)	0.1119			
2011 - 2014	0.91 (0.81-1.02)	6.2 (5.6-7.2)		NS	NS	NS
Mode of diagnosis						
Symptoms	1.00 (=ref)	5.9 (5.5-6.4)	0.0594			
Systematic examination	0.88 (0.77-1.01)	6.1 (5.1-7.7)		NS	NS	NS

Table 4. Univariate and multivariate analysis (Cox regression) of factors associated with N-PFS – patients treated with SRT

	Univariate			Multivariate		
Factors	**HR (95% CI)**	**Median (95% CI)**	**P value**	**HR**	**95% CI**	**P value**
Age						
<50	1.00 (=ref)	8.2 (6.0-12.3)	0.0847			
[50-70]	1.20 (0.87-1.64)	7.3 (6.1-9.0)		NS	NS	NS
>70	1.61 (1.05-2.45)	6.1 (3.3-8.8)		NS	NS	NS
Delay between selection and CNMS diagnosis (months):						
<9	1.00 (=ref)	7.1 (6.2-8.7)	0.0064*			
[9-18]	1.13 (0.78-1.65)	6.4 (4.2-14.2)		NS	NS	NS
>18	1.09 (0.81-1.47)	7.4 (5.7-10.1)		NS	NS	NS
Molecular subtype						
HER2-/HR+	1.00 (=ref)	8.5 (7.2-12.6)	<0.0001*	1.00 (=ref)		
HER2+/HR -	1.02 (0.68-1.52)	8.7 (6.9-16.1)		1.13	0.75-1.69	0.5666
HER2+/HR +	1.12 (0.74-1.71)	10.6 (8.5-15.0)		1.06	0.69-1.62	0.7977
Triple-negative	2.32 (1.64-3.27)	4.5 (4.1-6.2)		2.88	2.09-4.12	**<0.0001**
Number of metastatic sites						
<3	1.00 (=ref)	7.5 (6.3-9.9)	0.4081	NS	NS	NS
≥ 3	1.12 (0.86-1.46)	6.4 (4.8-8.5)				
Number of treatment lines						
<3	1.00 (=ref)	8.4 (7.1-10.1)	0.8353	1.00 (=ref)		
≥ 3	2.03 (1.49-2.76)	4.2 (3.5-6.0)		2.81	1.99-3.97	**<0.0001**
Year of management initiation						
2008 - 2010	1.00 (=ref)	5.9 (4.7-7.1)	0.1841	NS	NS	NS
2011 - 2014	0.83 (0.64-1.09)	8.5 (7.2-10.0)				
Mode of diagnosis						
Symptoms	1.00 (=ref)	7.2 (6.1-8.5)	0.1598	NS	NS	NS
Systematic examination	0.81 (0.61-1.09)	6.6 (5.7-13.0)				