Local and Systemic Therapy in Breast Cancer Patients with Central Nervous System Metastases

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Abstract

Purpose As survival of patients with central nervous system (CNS) metastases from breast cancer is poor and incidence rates are increasing, there is a growing need for better treatment strategies. In the current study, the efficacy of local and systemic therapies was analyzed in breast cancer patients with CNS metastases.

Methods Medical records from patients with breast cancer and brain and/or leptomeningeal metastases treated at a tertiary referral center and a teaching hospital between 2010 and 2020 were retrospectively studied. Main outcomes of interest were overall survival and CNS progression free survival. Analyses were performed for the different systemic and local therapies for CNS metastases, and subgroups based on breast cancer subtypes and brain metastases vs leptomeningeal metastases were tested.

Results We identified 155 patients, 44 HER2-positive, 68 hormone receptor positive/HER2-negative and 43 triple negative. Median overall survival was 5.9 months for all 155 analyzed patients. Survival differed significantly between breast cancer subtypes (HER2-positive 22.8 months, hormone receptor positive/HER2-negative 2.4 months, triple negative 4.2 months, P<0.001). Patients receiving a combination of local and systemic therapy demonstrated prolonged median overall survival (18.5 months) as compared to local therapy only (5.7 months) or systemic therapy only (4.3 months, P<0.001). No significant difference in overall survival was observed between different systemic treatment regimens.

Conclusion Breast cancer patients with CNS metastases show longest median overall survival when the subtype is HER2-positive and when they are treated with both local and systemic therapy.

Introduction

Central nervous system (CNS) metastases cause significant morbidity and mortality in breast cancer (BC) patients. As life expectancy for advanced BC patients is improving, the frequency of CNS metastases, including brain (BM) and leptomeningeal metastases (LM), increases.[1] This longer life expectancy is considered to be partly due to the introduction of new systemic treatments (e.g., anti-HER2 therapy) with a better control of systemic disease.[2, 3]

10-30% of BC patients will develop CNS metastases.[4, 5] These rates differ among the three BC biological subtypes: human epidermal growth factor receptor 2 (HER2) positive, hormone receptor (HR) positive and triple negative (TN). HER2 amplification or overexpression has shown to be a significant risk factor for metastatic disease.[2, 4] Over the past decades, the introduction of HER2-targeted therapies has contributed to better control of systemic disease and prolonged survival.[4] However, along with these improved outcomes, the incidence of CNS metastases in HER2 positive BC has increased up to 30-55% and occurs particularly in patients with controlled extracranial disease.[2, 4, 6, 7] Among the three BC subtypes, HER2-positive patients with CNS metastases have demonstrated longest median overall survival in the range of 18 to 38 months.[8, 9] 24-45% of TN BC patients will develop CNS metastases.[4, 5, 10] In contrast to HER2-positive patients, CNS metastases in TN patients frequently occur with concurrent new or progressive extracranial metastases. Moreover, the time of onset between first extracranial metastases and CNS metastases is short.[7, 11] Prognosis among TN patients with CNS involvement is poor, with survival rates of only 4-7 months.[4, 12] HR-positive tumors, which account for the majority of BC, tend to have less CNS involvement (5%).[12, 13]

For treatment of BM, local and systemic options are available. Local treatment options involve surgical resection, whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS). Surgical resection is only considered in a small percentage of patients with a single BM, large in tumor size and, in a for neurosurgery accessible location.[14] In patients with up to ten BM with small tumor sizes, SRS is recommended.[15] With increasing experience with SRS over the past years, the use of WBRT has decreased.

Regarding systemic therapy for breast cancer brain metastases (BCBM), few clinical trials have been conducted, and BCBM patients have frequently been excluded from clinical trials in metastatic BC.[16] Systemic therapy includes chemotherapy, targeted therapy, endocrine therapy, and immunotherapy. The role of systemic therapy has been considered to be limited because of poor permeability of the blood-brain barrier (BBB) for these agents.[17] However, advanced BM are associated with (some) disruption of the BBB and radiotherapy may also increase BBB permeability and enhance CNS penetrance of systemic agents.[18] In addition, clinical studies have shown response of BCBM to several systemic agents.[17–19] Agents which have previously shown efficacy in the treatment of BM in HER2-positive patients are T-DM1, capecitabine combined with lapatinib, and docetaxel combined with trastuzumab and pertuzumab.[20–26] A recent trial in HER2-positive BCBM patients demonstrated a significantly longer progression free survival (PFS)

and overall survival (OS) by adding tucatinib to trastuzumab and capecitabine in HER2-positive BCBM patients.[27] Another new promising agent, trastuzumab-deruxtecan, is currently being investigated in HER2-positive BCBM patients in the TUXEDO-1 trial.[28] Apart from HER2-positive BC, there is no clinical evidence of effective systemic therapy for BM of the other BC subtypes, although case reports have described activity of many different systemic therapies for both HR-positive and TN BC patients.[29, 30]

LM represents a minority of the patients with CNS metastases (10-25%).[31–33] Development of LM occurs frequently in the context of progressive systemic disease and median OS is poor.[34] Treatment options for LM include WBRT, intrathecal therapy and systemic therapy.[35] Although retrospective series have suggested some efficacy of systemic therapy, very few prospective trials showed treatment efficacy in patients with LM.[34, 36, 37]

As incidence rates of CNS metastases are increasing and survival remains poor, there is a need for better treatment strategies. Although over the past decades new agents have been added to the wide range of systemic therapeutics, optimal systemic treatment strategies in the management of CNS metastases from BC remain unclear. Recently, two published retrospective studies have described the effect of local and systemic therapeutic options in 873 and 730 BCBM patients.[38, 39] In the current retrospective study the efficacy of various systemic treatment regimens and local therapies (surgery and radiotherapy) was analyzed in 155 BC patients with CNS metastases in two clinical centers in The Netherlands.

Methods

Patient selection and data collection

Data were collected from 302 BC patients with BM and/or LM, treated at the Netherlands Cancer Institute - Antoni van Leeuwenhoek (NKI-AvL), Amsterdam between 2010 and 2020, and the St Antonius Hospital, Utrecht/Nieuwegein between 2015 and 2020. Data of all patients with BC and BM and/or LM were extracted from electronic medical records and manually imported into a pre-designed database. Eligibility criteria for study inclusion were BC patients diagnosed with BM, based on neuroimaging, and/or LM based on neuroimaging and cerebrospinal fluid (CSF) cytology. Patients were excluded when the primary tumor was not BC or the origin of the primary tumor was unknown. Patients with insufficient data on administered therapies were also excluded. Patients treated with oral capecitabine at the NKI-AvL have not been analyzed as they were included in another retrospective study (data unpublished).

Information retrieved from medical records included patient demographics, date of BC diagnosis, BC biological subtype at first BC diagnosis (HER2-positive, HR-positive/HER2-negative or TN), distant metastases before diagnosis of CNS metastases, systemic treatment and RT for BC before CNS metastases, date of CNS metastases (BM and/or LM), number of BM, BM and LM symptoms at time of diagnosis, ECOG/WHO score at time of diagnosis of CNS metastases, extracranial disease at time of CNS diagnosis, local treatment for CNS metastases (radiotherapy, surgical resection), start and duration of systemic treatments after diagnosis of CNS metastases, clinical and radiological response to treatment, date of CNS progression, date of extracranial progression, date of last follow-up, date of death and cause of death.

The study was approved by the institutional review boards of both institutions.

Study outcomes

Main outcomes of interest were OS and CNS-PFS. OS was measured from diagnosis of CNS metastases until death or last follow-up. CNS-PFS was measured from diagnosis of CNS metastases until progression of CNS metastases, based on MRI or clinical symptoms. Secondary outcomes were radiological response of CNS metastases and concurrent clinical response after therapy, and overall PFS. Overall PFS was measured from diagnosis of CNS metastases until first intracranial or extracranial progression.

To analyze differences between systemic therapy, patients were divided based on the first line systemic treatment after diagnosis of CNS metastases. A distinction was made between newly started chemotherapy, newly started other therapy (including targeted therapy, endocrine therapy, or immunotherapy), continuation with systemic therapy as administered before diagnosis of CNS metastases, and no systemic therapy. Secondly, treatment efficacy in patients treated with local and/or systemic treatments within two months after diagnosis of CNS metastases was analyzed. Comparison of OS and CNS-PFS were made between local treatment only (including surgery and RT), systemic treatment only, combination of both local and systemic treatment, and no treatment. Thirdly, patients were compared based on BC subtype. BC subtypes were defined based on histological subtype of first BC diagnosis and were

categorized in three groups: HER2-positive, HR-positive/HER2-negative and TN. Finally, outcomes of patients with BM vs LM were compared. LM also included patients with simultaneous BM and LM at first diagnosis of CNS metastases.

Statistical analyses

Patient characteristics and treatment results after diagnosis of CNS metastases are presented for continuous variables as mean and standard deviation (SD) (normal distribution) or median and interquartile range (IQR) (no normal distribution). Categorical variables are presented as a number with percentage. Descriptive statistics for comparison of continuous variables between two groups was assessed with the independent T-test (or Wilcoxon test when data were not normally distributed) and for more than two groups with the one-way ANOVA test (or the Kruskal-Wallis test). For comparison between categorical variables the chi-square test was used (and Fisher-Freeman-Halton Exact test when cohort sizes were small, <5). OS and PFS were estimated by the Kaplan-Meier method, presented as median and 95% confidence interval (CI), and results among groups were compared using the log-rank test. SPSS (version 27.0) was used for the statistical analyses. A p-value <0.05 was considered statistically significant.

Results

Patient selection

A total of 302 patients with BC and BM and/or LM treated at the at the NKI-AvL, Amsterdam and the St Antonius Hospital, Utrecht/Nieuwegein were consecutively included in the study. 147 patients were excluded based on previously defined exclusion criteria and 155 patients were analyzed (Figure 1).

Baseline characteristics

Baseline characteristics are presented in Table 1. 66.5% of the patients were treated at the National Cancer Institute – Antoni van Leeuwenhoek hospital, and 33.5% at the Sint Antonius Hospital. All patients were female. Mean age at diagnosis of BC was 49 years (SD 11.2). Most frequent previous metastatic sites were bone (53.5%, n=83), lymph nodes (50.3%, n=78), lung (38.7%, n=60) and liver (36.1%, n=56). Mean age at diagnosis of CNS metastases was 55 years (SD 11.6) and CNS metastases occurred at a mean of 81 months (SD 70.6) after BC diagnosis. At first diagnosis of CNS metastases, there were 97 patients (62.6%) with only BM, 34 (21.9%) with only LM and 24 (15.5%) with both BM and LM. Among the 121 BM patients, 47.9% (n=58) had >4 BM, 33.1% (n=40) had single BM and 19.0% (n=23) had 2-4 BM. At diagnosis of CNS metastases, an MRI brain was performed in 152 patients (98.1%), an MRI spine in 19 patients (12.3%) and a lumbar puncture was performed in 31 patients (20%). Among patients with LM a lumbar puncture was performed in 23 patients (39.7%). BM were symptomatic in 90.1% (n=109), with symptoms of headache in 44.1% (n=48) and focal neurologic deficit in 48.6% (n=53). 56 patients (96.6%) with LM were symptomatic: 79.3% (n=46) had cerebral symptoms, 24.1% (n=14) had cranial nerve symptoms, and 6.9% (n=4) had spinal symptoms. At diagnosis of CNS metastases, 60 patients (38.7%) had progression of already existing extracranial metastases and 15 (9.7%) had new extracranial metastases; in 54 (34.8%) extracranial metastases were stable and 26 patients (16.8%) showed no extracranial disease.

Table 1
Baseline characteristics

	Patients (n=155)
Hospital	103 (66.5)
- NKI-AvL	52 (33.5)
- SAZ	
Female	155 (100)
Age in years at BC diagnosis, mean (SD)	49 (11.2)
Hormonal status	94 (60.6)
- ER positive	68 (43.9)
- PR positive	44 (28.4)
- HER2 positive	
BC subtype	68 (43.9)
- HR-positive/HER2-negative	44 (28.4)
- HER2-positive	43 (27.7)
- TN	
Previous metastatic sites	83 (53.5)
- Bone	78 (50.3)
- Lymph node	60 (38.7)
- Lung	56 (36.1)
- Liver	36 (23.2)
- Other	
Previous systemic therapy for BC	151 (97.4)
- Chemotherapy	145 (93.5)
- Endocrine therapy	89 (57.4)
- Targeted therapy	72 (46.5)
HER2	45 (29)
VEGF	8 (5.2)
PARP	6 (3.9)
Other TKI	20 (12.9)
- Immunotherapy	9 (5.8)
Previous RT for (metastatic) BC	110 (71)
Duration between diagnosis of BC and CNS metastases in months, median (IQR)	64.5 (84.9)

Data are presented as n (%), unless otherwise specified.

NKI-AvL=Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital. SAZ=Sint Antonius hospital. BC=breast cancer. SD=standard deviation. ER=estrogen receptor. PR=progesterone receptor. HER2=human epidermal growth factor receptor 2. TN=triple negative. VEGF=vascular endothelial growth factor. PARP=poly(ADP-ribose) polymerase. TKI=tyrosine kinase inhibitor. RT=radiotherapy. CNS=central nervous system. BM=brain metastases. LM=leptomeningeal metastases. MRI=magnetic resonance imaging. LP=lumbar puncture. ECOG=Eastern Cooperative Oncology Group. WHO=World Health Organization.

	Patients (n=155)
Type of CNS metastases	97 (62.6)
- Only BM	34 (21.9)
- Only LM	24 (15.5)
- BM and LM	
BM at first CNS diagnosis	121 (78.1)
- Single	40 (33.1)
- 2-4	23 (19)
- >4	58 (47.9)
LM at first CNS diagnosis	58 (37.4)
Diagnostics at first diagnosis of CNS metastasis	152 (98.1)
- MRI brain	19 (12.3)
- MRI spine	31 (20)
- LP	17 (54.8)
Positive CSF cytology	
ECOG/WHO performance score	27 (19.0)
- 0	66 (46.5)
- 1	32 (22.5)
- 2	15 (10.6)
- 3	2 (1.4)
- 4	13
- Missing	
Symptomatic BM	109 (90.1)
- Headache	48 (44.1)
- Focal neurologic deficit	53 (48.6)
- Epilepsy	18 (16.5)
- Cognitive symptoms	11 (10)
Symptomatic LM	56 (96.6)
- Cerebral symptoms	46 (79.3)
- Cranial nerve symptoms	14 (24.1)
- Spinal symptoms	4 (6.9)

Data are presented as n (%), unless otherwise specified.

NKI-AvL=Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital. SAZ=Sint Antonius hospital. BC=breast cancer. SD=standard deviation. ER=estrogen receptor. PR=progesterone receptor. HER2=human epidermal growth factor receptor 2. TN=triple negative. VEGF=vascular endothelial growth factor. PARP=poly(ADP-ribose) polymerase. TKI=tyrosine kinase inhibitor. RT=radiotherapy. CNS=central nervous system. BM=brain metastases. LM=leptomeningeal metastases. MRI=magnetic resonance imaging. LP=lumbar puncture. ECOG=Eastern Cooperative Oncology Group. WHO=World Health Organization.

	Patients (n=155)
Extracranial metastases at time of CNS metastases diagnosis	26 (16.8)
- No extracranial metastases	15 (9.7)
- New extracranial metastases	54 (34.8)
- Stable extracranial metastases	60 (38.7)
- Progression of extracranial metastases	

Data are presented as n (%), unless otherwise specified.

NKI-AvL=Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital. SAZ=Sint Antonius hospital. BC=breast cancer. SD=standard deviation. ER=estrogen receptor. PR=progesterone receptor. HER2=human epidermal growth factor receptor 2. TN=triple negative. VEGF=vascular endothelial growth factor. PARP=poly(ADP-ribose) polymerase. TKI=tyrosine kinase inhibitor. RT=radiotherapy. CNS=central nervous system. BM=brain metastases. LM=leptomeningeal metastases. MRI=magnetic resonance imaging. LP=lumbar puncture. ECOG=Eastern Cooperative Oncology Group. WHO=World Health Organization.

Treatment results

Treatment results for all patients are shown in Table 2. 20% (n=31) of the patients received no local or systemic therapy for CNS metastases of BC. 98 patients (63.2%) received local therapy, of which 2 patients (1.3%) underwent resection only, 22 (14.2%) resection followed by RT and 74 (47.4) RT only. 89 (57.4%) patients received systemic therapy. Median OS for all patients was 5.9 months (95% CI, 4.2-7.7 months). In the majority of patients the cause of death was progressive CNS disease (n=69, 64.5%). In patients who received local or systemic therapy, CNS-PFS was 3.1 months (95% CI, 1.1-5.1 months), and overall PFS was 3.5 months (95% CI, 2.2-4.7 months).

Table 2
– Treatment results after diagnosis of CNS metastases for all patients

	Patients (n=155)
Systemic therapy	89 (57.4)
Local therapy	2 (1.3)
Resection only	22 (14.2)
Resection followed by RT	74 (47.7)
RT only	57 (36.8)
No local therapy	
RT	42 (27.1)
SRS	54 (34.8)
WBRT	59 (38.1)
No RT	
Treatment	31 (20)
No therapy	35 (22.6)
Local therapy only (RT/resection)	26 (16.8)
Systemic therapy only	63 (40.6)
Local and systemic therapy	
First systemic therapy after diagnosis of CNS metastases	66 (42.6)
No systemic therapy	38 (24.5)
Chemotherapy	9 (5.8)
Other systemic therapy	42 (27.1)
Continuation therapy	
OS in all patients, median (95% CI)	5.9 (4.2-7.7)
Overall PFS after therapy, median (95% CI)	3.5 (2.2-4.7)
CNS-PFS after therapy, median (95% CI)	3.1 (1.1-5.1)
Cause of death	69 (64.5)
Progressive CNS metastases	21 (19.6)
Progressive systemic metastases	17 (15.9)
Other	20
Missing	
Data are presented as n (%), unless otherwise specified.	
RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. CNS=central nervous system. OS=overall survival. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. 95% CI=95% confidence interval.	

Systemic therapy

Table 3 shows the results of the analysis of the different systemic therapy regimens. Comparisons were made between newly started chemotherapy (n=38), newly started other systemic therapy (n=9) (mainly endocrine therapy), continuation of systemic therapy (n=42) and no systemic therapy (n=66). In the group of patients that continued their systemic therapy after diagnosis of CNS metastases, 18 patients (42.7%) received chemotherapy, 12 patients (28.6%) endocrine therapy, 9 patients (21.4%) HER2-targeted therapy and 3

patients (7.2%) another form of systemic therapy, like immunotherapy or tyrosine kinase inhibitor (TKI). When systemic therapy was continued, patients underwent significantly more frequent RT as compared to patients with newly started chemotherapy (P<0.001) and no systemic therapy (P=0.001). Significantly more intracranial progression was observed when other systemic therapy, mainly endocrine therapy, was started (P=0.017), compared to newly started chemotherapy and continuation of therapy. Clinical response and extracranial response did not differ significantly between the systemic therapy subgroups (P=0.763, P=0.063, respectively). No significant difference in PFS, CNS-PFS and OS was observed between different systemic treatment regimens (P=0.348, P=0.252, P=0.186, respectively) (Figure 2). Separate chemotherapeutic agents could not be compared as groups were too small.

Table 3
Analysis for first systemic treatment after diagnosis of CNS metastases

	Newly started chemotherapy (n=38)	Newly started other systemic therapy (n=9)	Continuation therapy (n=42)	No systemic therapy (n=66)	P-value
RT	5 (13.2)	3 (33.3)	19 (45.2)	15 (22.7)	<0.001
SRS	13 (34.2)	3 (33.3)	18 (42.9)		
WBRT	20 (52.6)	3 (33.3)	5 (11.9)	20 (30.3)	
No RT				31 (47.0)	
Resection BM	2 (5.3)	1 (11.1)	8 (19.0)	13 (19.7)	0.215
Chemotherapy	8 (21.1)	4 (44.4)	8 (19.0)		<0.001
Paclitaxel/docetaxel/vinorelbine/eribulin	4 (10.5)	4 (44.4)	3 (7.1)		
T-DM1	13 (34.2)	1 (11.1)	1 (2.4)		
Gemcitabine/capecitabine/fluorouracil/methotrexate	10 (26.3)	0	3 (7.1)		
Chlorambucil/thiotepa/cyclophosphamide/carboplatin/mitomycine C	1 (2.6)	0	3 (7.1)		
Doxorubicin/epirubicin	2 (5.3)		0		
Experimental chemotherapy			6 (14.3)		
Other therapy			6 (14.3)		
Anti-estrogens			4 (9.5)		
Aromatase inhibitors			5 (11.9)		
Trastuzumab monotherapy			3 (7.2)		
Trastuzumab/pertuzumab					
Other (immunotherapy, TKI)					

*In both chemotherapy and continuation therapy groups, one patient received combination therapy with two agents.

Data are presented as n (%), unless otherwise specified.

RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. T-DM1=trastuzumab-emtansine. TKI=tyrosine kinase inhibitor. CNS=central nervous system. FUMRI=follow-up magnetic resonance imaging. LM=leptomeningeal metastases. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. OS=overall survival. SD=standard deviation. 95% CI=95% confidence interval.

	Newly started chemotherapy (n=38)	Newly started other systemic therapy (n=9)	Continuation therapy (n=42)	No systemic therapy (n=66)	P-value
Combination therapy with above mentioned chemotherapy/other therapy*	25 (65.8)	7 (77.8)	32 (74.4)		0.154
Monotherapy	3 (7.9)	0	0		
Capecitabine/gemcitabine/fluorouracil/methotrexate	0	0	1 (2.3)		
Doxorubicin/epirubicin	4 (10.5)	1 (11.1)	1 (2.3)		
Pertuzumab/trastuzumab	2 (5.3)	0	3 (7.0)		
Trastuzumab	3 (7.9)	1 (11.1)	1 (2.3)		
Other TKI (palbociclib, lapatinib, bevacizumab)	0	0	5 (11.6)		
Endocrine therapy	1 (2.6)	0	0		
Immunotherapy					
Months between diagnosis of CNS metastases till FUMRI, mean (SD)	3.5 (1.8)	2.9 (1.2)	3.4 (1.2)	6.5 (5.2)	0.002
Clinical response	4 (13.3)	0	6 (16.7)	4 (19.0)	0.763
Better	13 (43.3)	4 (80.0)	17 (47.2)	7 (33.3)	
Stable	13 (43.3)	1 (20.0)	13 (36.1)	10 (47.6)	
Worse	8	4	6		
Missing				14	

*In both chemotherapy and continuation therapy groups, one patient received combination therapy with two agents.

Data are presented as n (%), unless otherwise specified.

RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. T-DM1=trastuzumab-emtansine. TKI=tyrosine kinase inhibitor. CNS=central nervous system. FUMRI=follow-up magnetic resonance imaging. LM=leptomeningeal metastases. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. OS=overall survival. SD=standard deviation. 95% CI=95% confidence interval.

	Newly started chemotherapy (n=38)	Newly started other systemic therapy (n=9)	Continuation therapy (n=42)	No systemic therapy (n=66)	P-value
Radiological response BM/LM	0	0	0	1 (6.7)	0.017
Complete response	9 (36.0)	0	10 (37.0)	7 (46.7)	
Partial response	10 (40.0)	1 (20.0)	14 (51.9)	2 (13.3)	
Stable disease	6 (24.0)	4 (80.0)	3 (11.1)	5 (33.3)	
Progressive disease	13	4	15	20	
Missing					
Radiological response of extracranial disease	0	0	0	0	0.063
Complete response	7 (26.9)	1 (33.3)	3 (9.7)	0	
Partial response	12 (46.2)	1 (33.3)	20 (64.5)	5 (38.5)	
Stable disease	7 (26.9)	1 (33.3)	8 (25.8)	8 (61.5)	
Progressive disease	12	6	11	22	
Missing					
Overall PFS after therapy, median months (95% CI)	3.3 (1.8-4.8)	2.1 (0-4.2)	5.2 (3.8-6.5)	2.0 (1.0-3.0)	0.278
CNS-PFS, median months (95% CI)	2.6 (1.0-4.2)	2.1 (1.6-2.6)	6.5 (4.5-8.6)	1.7 (0-3.9)	0.465
OS, median months (95%CI)	6.9 (4.8-8.9)	6.5 (0-14.1)	17.8 (12.4-23.2)	1.5 (0.6-2.3)	<0.001
Cause of death	17 (63.0)	3 (50.0)	14 (56.0)	35 (71.4)	0.302
Progressive CNS metastases	8 (29.6)	2 (33.3)	5 (20.0)	6 (12.2)	
Progressive systemic metastases	2 (7.4)	1 (16.7)	6 (24.0)	8 (16.3)	
Other	5	2	4	9	
Missing					
*In both chemotherapy and continuation therapy groups, one patient received combination therapy with two agents.					
Data are presented as n (%), unless otherwise specified.					
RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. T-DM1=trastuzumab-emtansine. TKI=tyrosine kinase inhibitor. CNS=central nervous system. FUMRI=follow-up magnetic resonance imaging. LM=leptomeningeal metastases. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. OS=overall survival. SD=standard deviation. 95% CI=95% confidence interval.					

Local and/or systemic therapy

Results of analysis between local and/or systemic treatment are presented in Table 4. Outcomes were compared between no therapy (n=31), local therapy only (resection and/or RT) (n=35), systemic therapy only (newly started or continued) (n=26), and local plus systemic therapy (n=63). Patients who did not receive therapy after diagnosis of CNS metastases more often had a poor performance score at diagnosis of CNS metastases (ECOG/WHO score of 3 or 4) (P<0.001). ECOG/WHO performance scores did not differ significantly between the patient groups treated with local therapy, systemic therapy, or a combination of both (P=0.632). Systemic therapy only was associated with significantly more intracranial progression, compared to local therapy only or combination of local and systemic therapy (P<0.001). Both median overall PFS and CNS-PFS were longer when local and systemic therapy were combined, compared with systemic therapy only and local therapy only (5.5 vs 2.0 and 2.0 months P<0.001 and 6.6 vs 1.7 and 1.8 months,

P=0.001, respectively). Patients receiving both local and systemic therapy also had a longer median OS (18.5 months), compared with the other three subgroups (local therapy only: 5.7 months, systemic therapy only: 4.3 months, no therapy: 0.5 months, P<0.001) (Figure 3).

Table 4
– Analysis for local and/or systemic treatment

	No therapy (n=31)	Local therapy only (n=23)	Only systemic therapy (n=23)	Systemic plus local therapy (n=78)	P-value
ECOG/WHO performance score	16 (59.3)	29 (93.5)	22 (91.7)	58 (96.7)	<0.001
0-2	11 (40.7)	2 (6.5)	2 (8.3)	2 (3.3)	
>2	4	4	2	3	
Missing					
RT	0	15 (42.9)	0	27 (42.9)	<0.001
SRS	0	20 (57.1)	0	34 (54.0)	
WBRT	31 (100)	0	26 (100)	2 (3.2)	
No RT					
BM resection	0	13 (37.1)	0	11 (17.5)	<0.001
Systemic therapy			17 (65.4)	28 (44.4)	0.034
Chemotherapy			5 (19.2)	5 (7.9)	
Chemo + targeted therapy			0	1 (1.6)	
Chemo + immunotherapy			4 (15.4)	10 (15.9)	
Endocrine therapy			0	9 (14.3)	
Endocrine + targeted therapy			0	9 (14.3)	
Targeted therapy			0	1 (1.6)	
Immunotherapy					
Months between CNS diagnosis till FUMRI, mean (SD)		6.5 (5.2)	2.4 (0.8)	3.8 (1.5)	<0.001
Clinical response		4 (19.0)	2 (11.1)	8 (15.1)	0.592
Better		7 (33.3)	7 (38.9)	27 (50.9)	
Stable		10 (47.6)	9 (50.0)	18 (34.0)	
Worse		14	8	10	
Missing					
Radiological response BM/LM		1 (6.7)	0	0	<0.001
Complete response		7 (46.7)	1 (6.3)	18 (43.9)	
Partial response		2 (13.3)	5 (31.3)	20 (48.8)	
Stable disease		5 (33.3)	10 (62.5)	3 (7.3)	
Progressive disease		20	10	22	
Missing					

Data are presented as n (%), unless otherwise specified.

ECOG=Eastern Cooperative Oncology Group. WHO=World Health Organization. RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. CNS=central nervous system. FUMRI= follow-up magnetic resonance imaging. SD=stable disease. LM=leptomeningeal metastases. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. OS=overall survival. 95% CI=95% confidence interval. SD=standard deviation.

	No therapy (n=31)	Local therapy only (n=23)	Only systemic therapy (n=23)	Systemic plus local therapy (n=78)	P-value
Radiological response of extracranial disease		0	0	0	0.072
Complete response		0	1 (6.7)	10 (22.2)	
Partial response		5 (38.5)	10 (66.7)	23 (51.1)	
Stable disease		8 (61.5)	4 (26.7)	12 (26.7)	
Progressive disease		22	11	18	
Missing					
Overall PFS after therapy, median months (95% CI)		2.0 (1.0-3.0)	2.0 (1.6-2.4)	5.5 (4.0-7.0)	<0.001
CNS-PFS, median months (95% CI)		1.7 (0-3.9)	1.8 (1.2-2.4)	6.6 (5.1-8.1)	0.001
OS, median months (95% CI)	0.5 (0.4-0.6)	5.7 (0-13.6)	4.3 (1.4-7.2)	18.5 (13.8-23.1)	<0.001
Cause of death	20 (76.9)	15 (62.5)	15 (71.4)	19 (51.4)	0.222
Progressive CNS metastases	4 (15.4)	2 (8.7)	4 (19.0)	11 (29.7)	
Progressive systemic metastases	2 (7.7)	6 (26.1)	2 (9.5)	7 (18.9)	
Other	4	5	2	9	
Missing					
Data are presented as n (%), unless otherwise specified.					
ECOG=Eastern Cooperative Oncology Group. WHO=World Health Organization. RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. CNS=central nervous system. FUMRI= follow-up magnetic resonance imaging. SD=stable disease. LM=leptomeningeal metastases. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. OS=overall survival. 95% CI=95% confidence interval. SD=standard deviation.					

BC subtypes

Results for subgroup analysis between BC subtypes, TN (n=43), HR-positive/HER2-negative (n=68) and HER2-positive (n=44), are listed in Table 5. Among HR-positive patients mean time from BC diagnosis to diagnosis of CNS metastases was 112.3 months, which was significantly longer than in TN patients and HER2-positive patients (46.5 months and 66.0 months, respectively, P<0.001). HER2-positive patients received significantly more systemic therapy (P<0.001). Resection was significantly less performed in HR-positive BM (P<0.001). Overall PFS and CNS-PFS were not significantly different among three BC subtypes (overall PFS: TN 2.8 months, HR-positive 2.3 months, HER2-positive 5.2 months, P=0.264; CNS-PFS: TN 2.4 months, HR-positive 1.7 months, HER2-positive 4.7 months, P=0.460). Median OS was significantly longer among HER2-positive patients (22.8 months vs TN 4.2 months and HR+ 2.4 months, P<0.001) (Figure 4). Median OS did not differ significantly between HR-positive and TN patients.

Table 5
– Subgroup analysis for breast cancer subtypes

	TN (n=43)	HR+/HER2- (n=68)	HER2+ (n=44)	P-value
Months between BC diagnosis to diagnosis of CNS metastases, mean (SD)	46.5 (39.8)	112.3 (83.3)	66.0 (50.3)	<0.001
RT	13 (30.2)	11 (16.2)	18 (40.9)	0.053
SRS	15 (34.9)	25 (36.8)	14 (31.8)	
WBRT	15 (34.9)	32 (47.1)	12 (27.3)	
No RT				
Resection	9 (20.9)	2 (2.9)	13 (29.5)	<0.001
Systemic therapy	18 (41.8)	36 (52.9)	35 (79.5)	<0.001
First systemic therapy after diagnosis of CNS metastases	12 (27.9)	12 (17.6)	4 (9.1)	<0.001
Chemotherapy	0	0	9 (20.5)	
Chemotherapy + targeted therapy	1 (2.3)	0	0	
Chemotherapy + immunotherapy	0	6 (8.8)	0	
Endocrine therapy	0	1 (1.5)	1 (2.3)	
Endocrine therapy + targeted therapy	0	0	1 (2.3)	
Targeted therapy	5 (11.6)	17 (25.0)	20 (45.5)	
Continuation	25 (58.1)	32 (47.1)	9 (20.5)	
No systemic therapy				
Duration first systemic therapy in days (SD)	109 (136)	116 (119)	179 (218)	0.461
Months between diagnosis of CNS metastasis until FUMRI, mean (SD)	4.0 (2.7)	2.7 (0.9)	4.7 (3.4)	0.069
Clinical response	4 (14.8)	3 (10.3)	7 (19.4)	0.195
Better	10 (37.0)	11 (37.9)	20 (55.6)	
Stable	13 (48.1)	15 (51.7)	9 (25.0)	
Worse	9	16	7	
Missing				
Radiological response BM/LM	1 (4.8)	0	0	0.441
Complete response	8 (38.1)	4 (25.0)	14 (40.0)	
Partial response	5 (23.8)	8 (50.0)	14 (40.0)	
Stable disease	7 (33.3)	4 (25.0)	7 (20.0)	
Progressive disease	15	29	8	
Missing				

Data are presented as n (%), unless otherwise specified.

TN=triple negative. HER2+=human epidermal growth factor receptor 2 positive. HR+=hormone receptor positive. BC=breast cancer. CNS=central nervous system. RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. FUMRI= follow-up magnetic resonance imaging. LM=leptomeningeal metastases. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. OS=overall survival. 95% CI=95% confidence interval. SD=standard deviation.

	TN (n=43)	HR+/HER2- (n=68)	HER2+ (n=44)	P-value
Radiological response of extracranial disease	0	0	0	0.550
Complete response	2 (10.0)	4 (16.0)	5 (17.9)	
Partial response	10 (50.0)	11 (44.0)	17 (60.7)	
Stable disease	8 (40.0)	10 (40.0)	6 (21.4)	
Progressive disease	16	14	15	
Missing				
Overall PFS after therapy, median months (95% CI)	2.8 (1.4-4.2)	2.3 (1.6-3.1)	5.2 (3.5-6.8)	0.264
CNS-PFS, median months (95% CI)	2.4 (0-5.3)	1.7 (0.8-2.7)	4.7 (2.2-7.2)	0.460
OS, median months (95% CI)	4.2 (0.9-7.5)	2.4 (0.6-4.3)	22.8 (11.0-34.6)	<0.001
Cause of death	20 (64.5)	36 (66.7)	13 (59.1)	0.886
Progressive CNS metastases	7 (22.6)	10 (18.5)	4 (18.2)	
Progressive systemic metastases	4 (12.9)	8 (14.8)	5 (22.7)	
Other	8	7	5	
Missing				
Data are presented as n (%), unless otherwise specified.				
TN=triple negative. HER2+=human epidermal growth factor receptor 2 positive. HR+=hormone receptor positive. BC=breast cancer. CNS=central nervous system. RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. FUMRI= follow-up magnetic resonance imaging. LM=leptomeningeal metastases. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. OS=overall survival. 95% CI=95% confidence interval. SD=standard deviation.				

BM vs LM

Results for BM and LM are shown in Table 6. LM were significantly more present in HR-positive/HER2-negative patients, while BM occurred more in HER2-positive patients (P=0.001). LM patients received less local and systemic treatment (P<0.001). Median OS in BM patients was significantly longer than in LM patients (15.9 vs 1.5 months, P<0.001) and LM patients died more often because of progressive CNS metastases (P=0.023) (Figure 5).

Table 6
– Subgroup analysis for only BM vs LM patients

	Only BM (97)	LM (58)	P-value
BC subtype	27 (27.8)	16 (27.6)	0.001
TN	33 (34.0)	35 (60.0)	
HR+/HER2-	37 (38.1)	7 (12.1)	
HER2+			
RT	40 (41.2)	2 (3.4)	<0.001
SRS	35 (36.1)	19 (32.8)	
WBRT	22 (22.7)	37 (63.8)	
No RT			
Resection	24 (24.7)	0	<0.001
Systemic therapy	21 (21.6)	17 (29.3)	0.081
Chemotherapy	6 (6.2)	3 (5.2)	
Other systemic therapy	33 (34.0)	9 (15.5)	
Continuation therapy	37 (38.1)	29 (50.0)	
No systemic therapy			
Local/systemic therapy	28 (28.9)	7 (12.1)	<0.001
Local therapy	49 (50.5)	24 (24.1)	
Systemic + local therapy	11 (11.3)	15 (25.9)	
Systemic therapy	9 (9.3)	22 (37.9)	
No therapy			
Months between CNS metastases and FUMRI, mean (SD)	4.5 (3.2)	2.9 (1.6)	0.038
Clinical response	12 (17.1)	2 (9.1)	0.115
Better	34 (48.6)	7 (31.8)	
Stable	24 (34.3)	13 (59.1)	
Worse	18	14	
Missing			

Data are presented as n (%), unless otherwise specified.

BC=breast cancer. TN=triple negative. HR+=hormone receptor positive. HER2-=human epidermal growth factor receptor 2 negative. HER2+=human epidermal growth factor receptor 2 positive. CNS=central nervous system. RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. FUMRI= follow-up magnetic resonance imaging. LM=leptomeningeal metastases. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. OS=overall survival. 95% CI=95% confidence interval. SD=standard deviation.

+ Other systemic therapy included endocrine therapy (n=8, 88.8%) and anti-HER2 therapy (n=2, 22.2%)

* Continuation therapy refers to patients who continued with systemic therapy as before diagnosis of CNS metastases and included 18 patients (42.7%) with chemotherapy, 12 patients (28.6%) with endocrine therapy, 9 patients (21.4%) with HER2-targeted therapy and 3 patients (7.2%) with another form of systemic therapy.

	Only BM (97)	LM (58)	P-value
Radiological response BM/LM	1 (1.9)	0	0.674
Complete response	21 (39.6)	5 (26.3)	
Partial response	19 (35.8)	8 (42.1)	
Stable disease	12 (22.6)	6 (31.6)	
Progressive disease	35	17	
Missing			
Radiological response of extracranial disease	0	0	0.887
Complete response	9 (15.8)	2 (12.5)	
Partial response	30 (52.6)	8 (50.0)	
Stable disease	18 (31.6)	6 (37.5)	
Progressive disease	31	20	
Missing			
Overall PFS after therapy, median months (95% CI)	4.3 (3.4-5.3)	2.0 (1.6-2.4))	0.007
CNS-PFS, median months (95% CI)	4.7 (2.8-6.6)	1.8 (1.1-2.5)	0.045
OS, median months (95% CI)	15.9 (9.9-22.0)	1.5 (0.5-2.5)	<0.001

Data are presented as n (%), unless otherwise specified.

BC=breast cancer. TN=triple negative. HR+=hormone receptor positive. HER2-=human epidermal growth factor receptor 2 negative. HER2+=human epidermal growth factor receptor 2 positive. CNS=central nervous system. RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. FUMRI= follow-up magnetic resonance imaging. LM=leptomeningeal metastases. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. OS=overall survival. 95% CI=95% confidence interval. SD=standard deviation.

+ Other systemic therapy included endocrine therapy (n=8, 88.8%) and anti-HER2 therapy (n=2, 22.2%)

* Continuation therapy refers to patients who continued with systemic therapy as before diagnosis of CNS metastases and included 18 patients (42.7%) with chemotherapy, 12 patients (28.6%) with endocrine therapy, 9 patients (21.4%) with HER2-targeted therapy and 3 patients (7.2%) with another form of systemic therapy.

	Only BM (97)	LM (58)	P-value
Cause of death	32 (53.3)	37 (78.7)	0.023
Progressive CNS metastases	15 (25.0)	6 (12.8)	
Progressive systemic metastases	13 (21.7)	4 (8.5)	
Other	14	6	
Missing			
Data are presented as n (%), unless otherwise specified.			
BC=breast cancer. TN=triple negative. HR+=hormone receptor positive. HER2-=human epidermal growth factor receptor 2 negative. HER2+=human epidermal growth factor receptor 2 positive. CNS=central nervous system. RT=radiotherapy. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. BM=brain metastases. FUMRI= follow-up magnetic resonance imaging. LM=leptomeningeal metastases. PFS=progression free survival. CNS-PFS=central nervous system progression free survival. OS=overall survival. 95% CI=95% confidence interval. SD=standard deviation.			
+ Other systemic therapy included endocrine therapy (n=8, 88.8%) and anti-HER2 therapy (n=2, 22.2%)			
* Continuation therapy refers to patients who continued with systemic therapy as before diagnosis of CNS metastases and included 18 patients (42.7%) with chemotherapy, 12 patients (28.6%) with endocrine therapy, 9 patients (21.4%) with HER2-targeted therapy and 3 patients (7.2%) with another form of systemic therapy.			

Discussion

This retrospective cohort study gives an overview of administered treatments among BC patients with CNS metastases treated at a comprehensive cancer center and a teaching hospital in The Netherlands from 2010-2020. Our results show a significantly longer (P<0.001) median overall survival for HER2-positive patients of 22.8 months, as compared to HR-positive/HER2-negative or TN patients (2.4 and 4.2 months, respectively). Likewise, a significantly longer (P<0.001) median survival was observed in patients after treatment of CNS metastases with local and systemic treatment (18.5 months) compared to local therapy only (5.7 months) or systemic therapy only (4.3 months).

Median overall survival (OS) for BCBM (no LM) patients in our study was 15.9 months which is in line with the reported median OS of 15.0 months in the study by Kim et al. published in 2020.[39] Gao et al. reported a shorter median OS (9.1 months, 95% CI 8.2-10.0) based on a retrospective cohort from 1999 to 2012 with 873 BCBM patients, possibly because of less effective systemic treatments in that time period.[38] In our study, OS for all patients, including patients with LM, was 5.9 months, which is in line with an OS of 5.0 months that was reported in another observational study in BC patients with CNS metastases from the Netherlands between 2004 and 2010.[40] In the present study LM was detected in an unusual high percentage of patients, namely 37%, comprising 22% with ‘pure’ LM and 15% with both BM and LM. In the former Dutch study only 12% of the patients had LM. This difference may be attributed to a longer survival due to better systemic treatments and improvement of diagnostic modalities for LM (MRI).

This study demonstrated a substantial longer median OS of 22.8 months in HER2-positive patients, compared with 2.4 months in HR-positive/HER2-negative and 4.2 months in TN patients. Prolonged survival among HER2-positive patients has previously been described by other studies and is probably attributed to effective HER2-targeted therapies.[41] OS between TN patients and HR-positive/HER2-negative patients did not differ significantly in this study, although positive HR status has been previously stated as a positive prognostic factor for prolonged survival in BCBM.[39, 42] There are three possible explanations for this finding. At first, receptor status of CNS metastases does not always correspond with the receptor status of primary BC.[43, 44] Hulsbergen et al. found that this so called receptor discordance occurs predominantly (37.5%) in HR-positive BC.[44] This indicates that a substantial part of HR-positive CNS metastases could in fact have been HR-negative. Secondly, CNS metastases from HR-positive BC occur at a later stage of disease when tumors have developed resistance of hormonal therapy, as suggested by the longer time between primary BC diagnosis and diagnosis of CNS metastases in HR-positive patients (112.3 vs TN 46.5 and HER2+ 66.0 months, P<0.001). This has previously been described in other studies.[41, 45] Thirdly, our study showed an overrepresentation of 60% HR-positive patients in patients with LM. A systematic review also reported highest LM incidence in HR-positive BC patients of 48.1% (range 35.3-58%).[46] This substantial percentage of HR-positive BC in the LM subgroup may have caused worse overall outcomes for HR-positive patients, since most other studies only included BM patients.

We found longer median OS after treatment with a combination of local and systemic therapy, compared with local or systemic therapy only. This finding may partially be explained by confounding by indication since therapy is usually withheld from patients with poor prognostic factors. In this respect, it should be noted that performance scores between the groups were similar, which suggests combining local and systemic therapy for CNS metastases may be the best treatment. Previous studies have also described beneficial effects of the combination of local and systemic therapy in BCBM patients. In a retrospective cohort comprising 873 patients from the MD Anderson Cancer Center from 1999 to 2012, Gao et al. reported an improvement of median OS with 7.2 months (9.7 vs 2.3 months) by local therapy, compared to no therapy, and an improvement of the median OS with 9.8 months (12.2 vs 2.4 months) by systemic chemotherapy, compared to no systemic therapy.[38] Two retrospective studies have previously described the additional value of systemic therapy after local therapy in BCBM patients with controlled extracranial disease.[47, 48] A large study by Niwinska concluded that systemic therapy prolonged OS in BCBM patients when BM were the first site of metastatic recurrence.[48] Hulsbergen et al. only found prolonged OS with systemic therapy in ER-positive BC patients, but no effect of HER2-directed therapy in HER2-positive patients, after resection of a single BM.[47]

We did not find statistically significant differences between systemic therapy subgroups, comparing patients that received chemotherapy with patients that were treated with other systemic therapies (endocrine therapy and HER2-targeted therapy). The previous study by Gao et al. compared capecitabine with other chemotherapy and found no statistically superior effect on OS and CNS-PFS.[38]

Conclusion And Recommendation

In patients with BC and CNS metastases, longer median OS is observed in HER2-positive patients, whereas HR-positive/HER2-negative patients, in contrast with previous studies, had an equally poor prognosis as TN patients. Patients with only BM showed longer median OS than patients with LM. The combination of local and systemic treatment is associated with longer PFS and OS. For further research we recommend larger study populations of systemic treatment subgroups to evaluate OS and PFS between the various systemic therapy regimens to further clarify optimal systemic treatment for patients with BC and CNS metastases.

Abbreviations

CNS
Central Nervous System
BC
Breast cancer
BM
Brain metastases
BCBM
Breast cancer brain metastases
CI

Confidence interval
IQR
Interquartile range
LM
Leptomeningeal metastases
HER2
Human epidermal growth factor receptor 2
HR
Hormone receptor
TN
Triple negative
RT
Radiotherapy
WBRT
Whole brain radiotherapy
SRS
Stereotactic radiosurgery
BBB
Blood-brain barrier
NKI-AvL
Netherlands Cancer Institute – Antoni van Leeuwenhoek
MRI
Magnetic resonance imaging
CSF
Cerebrospinal fluid
OS
Overall survival
PFS
Progression free survival
SD
Standard deviation

Declarations

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Conflict of interest GSS reports institutional research support from AstraZeneca, Merck, Novartis, Roche and Seagen and advisory roles for Biovica and Seagen. The other authors declare that they have no competing interests.

Data availability The datasets generated and analyzed during the current study are available via the corresponding author on reasonable request.

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Figures

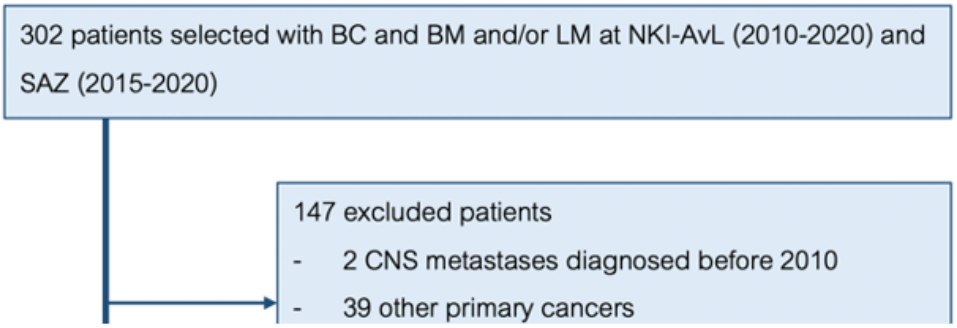

Figure 1

Flowchart of study

Figure 2

Kaplan Meier curves for median overall survival in months by systemic therapy after diagnosis of CNS metastases

+ Other systemic therapy included endocrine therapy (n=8, 88.8%) and anti-HER2 therapy (n=2, 22.2%)

* Continuation therapy refers to patients who continued with systemic therapy as before diagnosis of CNS metastases and included 18 patients (42.7%) with chemotherapy, 12 patients (28.6%) with endocrine therapy, 9 patients (21.4%) with HER2-targeted therapy and 3 patients (7.2%) with another form of systemic therapy.

Figure 3

Kaplan Meier curves for overall survival in months by local and/or systemic therapy

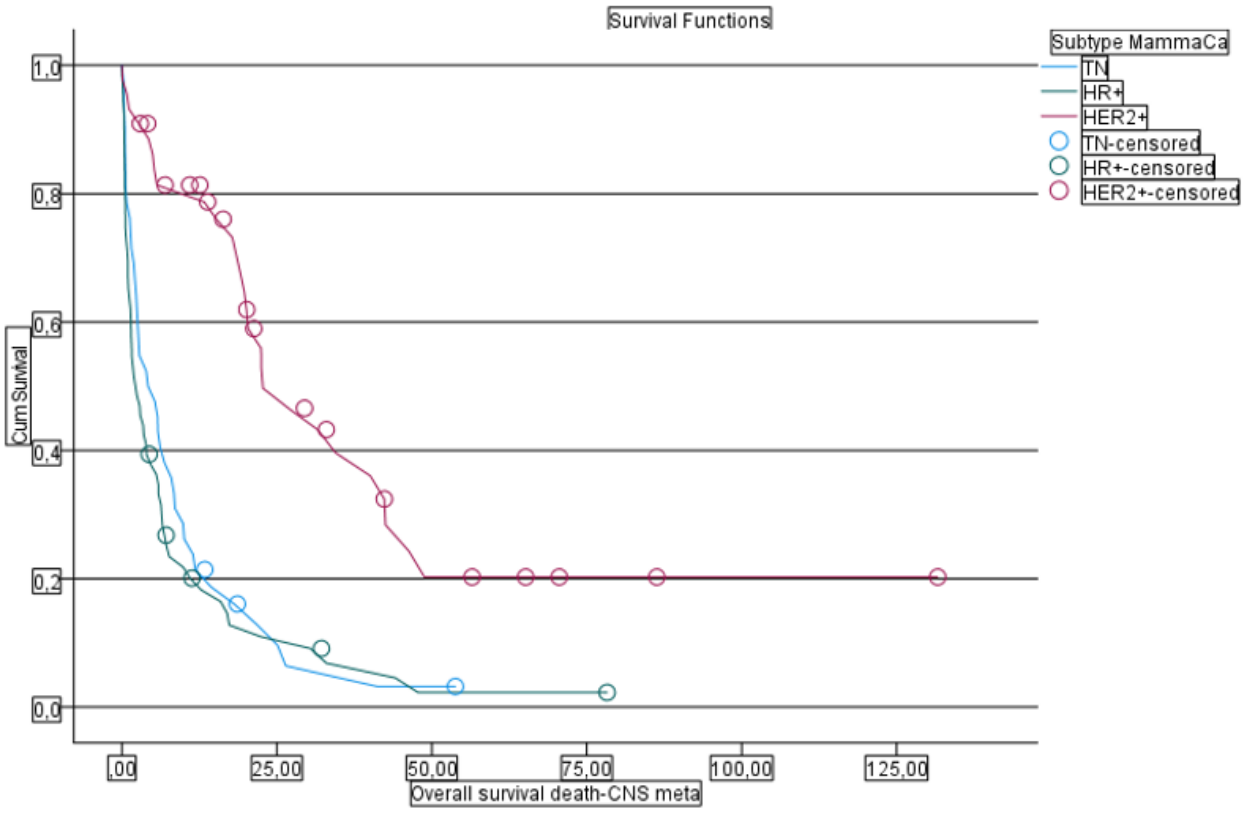

Figure 4

Kaplan Meier curves for overall survival in months by breast cancer subtype

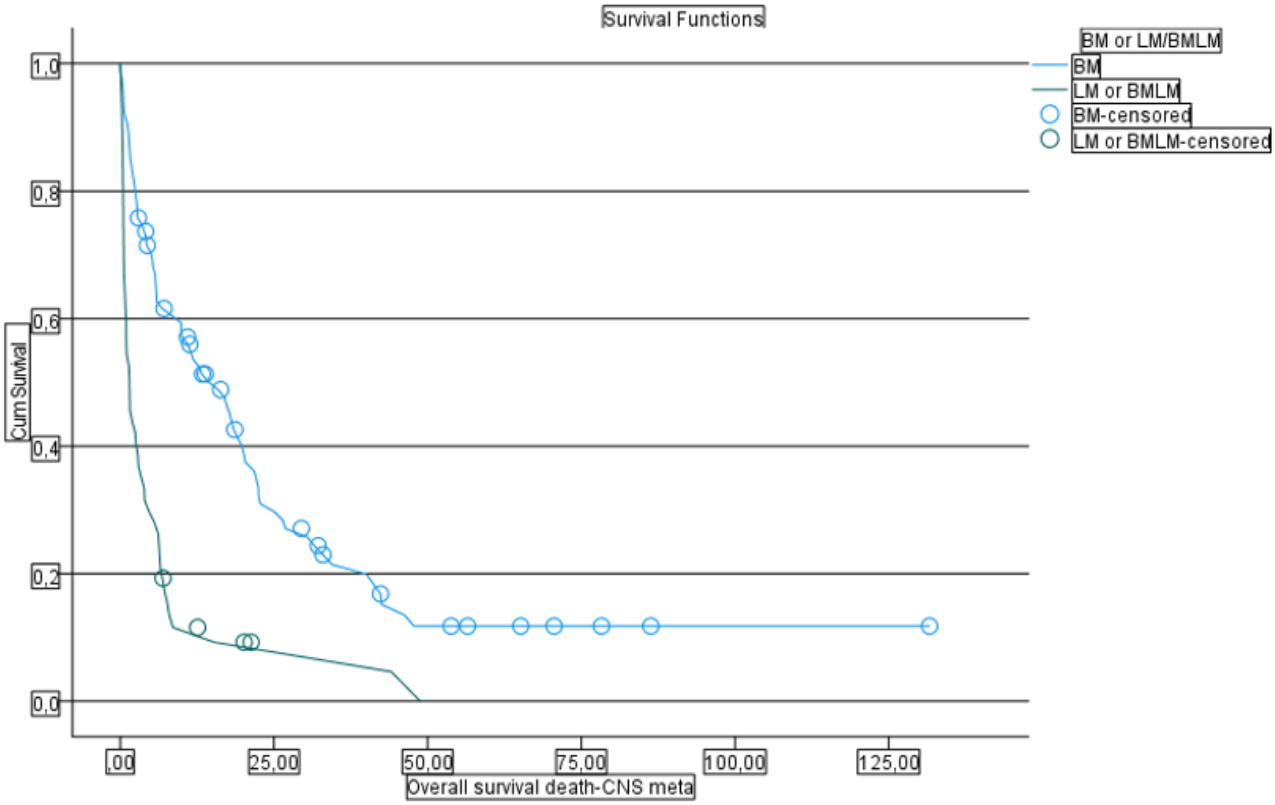

Figure 5

Kaplan Meier curves for overall survival in months for patients with brain metastases and leptomeningeal metastases with or without brain metastases patients