European Journal of Cancer 102 (2018) 1–9

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Treatment and outcomes of patients in the Brain Metastases in Breast Cancer Network Registry

I. Witzel [a,*], E. Laakmann [a], R. Weide [b], T. Neunhöffer [c], T.-J. Park-Simon [d], M. Schmidt [e], P.A. Fasching [f], T. Hesse [g], A. Polasik [h], S. Mohrmann [i], F. Würschmidt [j], C. Schem [k,l], C. Bechtner [m], R. Würstlein [n], T. Fehm [o], V. Möbus [p], N. Burchardi [q], S. Loibl [q], V. Müller [a]

[a] *University Medical Center Hamburg-Eppendorf, Department of Gynecology, Hamburg, Germany*
[b] *Oncological Outpatient Department, Koblenz, Germany*
[c] *HELIOS Dr. Horst Schmidt Clinic Wiesbaden, Wiesbaden, Germany*
[d] *Hannover Medical School, Department of Gynecology, Hannover, Germany*
[e] *Department of Gynecology, University Medical Center of the Johannes Gutenberg University Mainz, Germany*
[f] *Department of Gynecology and Obstetrics, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany*
[g] *Agaplesion Diakonie Clinic Rotenburg, Department of Gynecology, Rotenburg, Germany*
[h] *Department of Gynecology and Obstetrics, University Medical Center Ulm, Germany*
[i] *Duesseldorf University Hospital, Department of Gynecology, Duesseldorf, Germany*
[j] *Radiologische Allianz Hamburg, Hamburg, Germany*
[k] *University Medical Center-UKSH, Department of Gynecology, Kiel, Germany*
[l] *Mammazentrum, Krankenhaus Jerusalem, Hamburg, Germany*
[m] *Frauenklinik, Memmingen Hospital, Germany*
[n] *Department of Gynecology and Obstetrics, Ludwig-Maximilian-University Munich, Germany*
[o] *Translational Research Board of the Gynecological Oncology Working Group (AGO-Trafo), Germany*
[p] *Breast Study Group of the Gynecological Oncology Working Group (AGO-B), Germany*
[q] *German Breast Group GmbH, Neu-Isenburg, Germany*

Received 2 July 2018; accepted 3 July 2018
Available online 9 August 2018

* *Corresponding author*: Department of Gynecology, Breast Center, University Medical Center Hamburg, Martinistraße 52, 20246 Hamburg, Germany.

E-mail addresses: iwitzel@uke.de (I. Witzel), e.laakmann@uke.de (E. Laakmann), weide@onkologie-koblenz.de (R. Weide), Tanja.Neunhoeffer@helios-gesundheit.de (T. Neunhöffer), Park-Simon.tjoung-won@mh-hannover.de (T.-J. Park-Simon), marcus.schmidt@unimedizin-mainz.de (M. Schmidt), Peter.Fasching@uk-erlangen.de (P.A. Fasching), Hesse@diako-online.de (T. Hesse), arkadius.polasik@uniklinik-ulm.de (A. Polasik), svjetlana.mohrmann@med.uni-duesseldorf.de (S. Mohrmann), florian.wuerschmidt@radiologische-allianz.de (F. Würschmidt), schem@mammazentrum.eu (C. Schem), christina.bechtner@klinikum-memmingen.de (C. Bechtner), Rachel.Wuerstlein@med.uni-muenchen.de (R. Würstlein), tanja.fehm@med.uni-duesseldorf.de (T. Fehm), Volker.Moebus@KlinikumFrankfurt.de (V. Möbus), Nicole.Burchardi@gbg.de (N. Burchardi), sibylle.loibl@gbg.de (S. Loibl), vmueller@uke.de (V. Müller).

https://doi.org/10.1016/j.ejca.2018.07.004

KEYWORDS
Brain metastases;
Breast cancer;
Survival;
Diagnostic procedures

Abstract ***Background:*** Brain metastases (BMs) have a major impact on life expectancy and quality of life for many breast cancer patients. Knowledge about treatment patterns and outcomes is limited.
Methods: We analysed clinical data of 1712 patients diagnosed with BMs from breast cancer between January 2000 and December 2016 at 80 institutions.
Results: Median age at diagnosis of BMs was 56 years (22–90 years). About 47.8% (n = 732) of patients had HER2-positive, 21.4% (n = 328) had triple-negative and 30.8% (n = 471) had hormone receptor (HR)–positive, HER2-negative (luminal-like) primary tumours. The proportion of patients with HER2-positive BMs decreased comparing the years 2000–2009 with 2010–2015 (51%–44%), whereas the percentage of patients with luminal-like tumours increased (28%–34%; p = 0.0331). Patients with BMs in the posterior fossa were more often HER2 positive (n = 169/314, 53.8%) than those diagnosed with triple-negative (n = 65/314, 20.7%) or luminal-like primary breast cancer (n = 80/314, 25.5%), (p < 0.0001). Median overall survival (OS) time after development of BMs for the overall cohort was 7.4 months (95% confidence interval [CI]: 6.7–8.0 months). One-year survival rate was 37.7% (95% CI: 35.2–40.1). Patients with HER2-positive tumours had the longest median OS of 11.6 months (95% CI: 10.0–13.4) compared with 5.9 months (95% CI: 5.0–7.2) for patients with luminal-like and 4.6 months (95% CI: 3.9–5.4) for patients with triple-negative tumours. Patients with HER2-positive tumours who received anti-HER2 treatment had longer median OS than those without (17.1 months versus 7.2 months, p < 0.0001).
Conclusions: Prognosis of patients after developing BMs varies significantly according to the subtype. The outcome in this cohort is similarly poor in triple-negative and HR-positive/HER2-negative patients. Our results underline the high medical need for improvement of treatment and prevention strategies for BMs in breast cancer patients.

1. Introduction

About 30% of patients with metastatic breast cancer develop brain metastases (BMs), despite systemic therapies [1]. BMs are associated not only with a very unfavourable prognosis compared with other metastatic sites but also with severe neurological symptoms including cognitive and motoric impairments. In almost all patients, this results in a severe reduction of quality of life [2]. After lung cancer, breast cancer is the second most common primary cancer of patients with BMs. The incidence of BMs is higher than that of primary brain tumours.

Improvements in systemic therapy with better control of extracranial disease probably explain in part the rising incidence of BMs in breast cancer patients during the last years. This also reflects insufficient control of cerebral tumour spread and growth by current treatment strategies. Moreover, detection rates of asymptomatic BMs have increased with improved imaging techniques by contrast-enhanced magnetic resonance imaging (MRI) as a standard approach for the diagnosis of BMs.

Several risk factors for the development of BMs after breast cancer diagnosis have been identified. Younger age, poorly differentiated primary tumours, negative hormone receptor (HR) status and axillary node–positive breast cancer have been associated with increased BM risk. Patients with HER2-positive and triple-negative breast cancer have a higher risk of developing BMs than patients with luminal tumours [3,4]. In patients with metastatic HER2-positive or triple-negative disease, prevalence of BMs as high as 30–40% has been described [3–5].

Most current reports on BMs lack detailed data about treatment patterns. Furthermore, sample sizes of published studies are limited, and analyses with regard to characteristics of BMs in specific subgroups are scarce. To improve knowledge about this clinically important cohort, we initiated the registry ‘Brain Metastases in Breast Cancer Network Germany’ (BMBC, German Breast Group [GBG] 79).

2. Material and methods

We retrospectively identified patients diagnosed with BMs between January 2000 and December 2016 at 80 participating institutions in Germany. The presence of BMs was defined based on appropriate imaging and/or histological findings since the year 2000. Patients were excluded if they had a history of other malignant diseases, no histological verification of the diagnosis of breast cancer or a history of a neurologic disease.

The project is a collaborative study of the University Medical Center Hamburg-Eppendorf, the German

Breast Group (GBG), the German Gynecological Oncology Working Group-Breast (AGO-B) and the Working Group Translational Research (AGO-Trafo). Data were captured in a web-based remote data entry system, which were also used for clinical trials (MedCodes). The BMBC registry was approved by all local ethics committees. Patients still under treatment at the institution gave their informed consent. Of the 80 participating study sites that contributed patients for this analysis, 16 (20%) were in a university setting, 53 (66%) were non-university clinical institutions and 11 (14%) were in outpatient practice setting. All participating study sites were either located in departments of gynaecology, or oncology. Patients were documented from the patient records, and plausibility and completeness were checked by the GBG study team. Overall, we analysed the data set of 1712 patients.

2.1. Definition of subtypes

A tumour was considered to be HER2 positive if immunohistochemistry yielded a score of 3+ or if fluorescence in situ hybridisation showed amplification of the *HER2* gene. A patient was considered to have HR-positive disease if the study site considered the tumour to be HR positive. Based on immunohistochemical staining findings of the primary tumour, we defined breast cancer subtypes as follows: 'luminal like': HR-positive and HER2-negative tumours; 'HER2 positive': all HER2-positive tumours; 'triple negative': HR-negative and HER2-negative tumours.

2.2. Statistical analysis

Associations between clinicopathologic characteristics and treatment were evaluated using Fisher's exact and chi-square test for categorical variables. Differences in continuous variables between subgroups were investigated using Wilcoxon–Mann–Whitney test or Kruskal-Wallis test. Brain metastases–free interval (BMFI) was calculated as the time interval (months) from histological confirmation of breast cancer to the date of the first BM. Overall survival (OS) was defined as the time interval (months) from the diagnosis of BMs until death. Time-to-event curves were estimated using the Kaplan–Meier method and compared between subgroups with a two-sided log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to assess the effects of treatment and other predictive factors.

All reported p-values are two-sided, and the significance level was set to 0.05. No adjustment for multiple testing was performed. The results are to be considered explorative. The analyses were performed using SAS Enterprise Guide, 4.3, (SAS 9.02; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics, diagnostic procedures and systemic therapy

In this analysis, 1712 patients were included (Table 1). Median age at diagnosis of BMs was 56 years (22–90 years). About 47.8% (n = 732) of patients had HER2-positive, 21.4% (n = 328) had triple-negative and 30.8% (n = 471) had luminal-like primary tumours.

In 343 patients (20.0%), BMs were the first manifestation of metastatic disease without extracranial disease. With computed tomography, 30.8% of patients (n = 528) were diagnosed for BMs and with MRI (combination of procedures was possible), 73.8% of patients (n = 1264) were diagnosed for BMs; 15.6% of patients (n = 267) had no clinical symptoms of BMs at diagnosis. Regarding the number of BMs, 30% of patients (n = 458) had one, 26.8% (n = 408) had two or three and 43.2% (n = 659) had four or more BMs. The most frequent manifestations of extracranial disease were bone metastases (45%), followed by lung (37%) and liver metastases (36%). The majority of patients received chemotherapy during the course of their further disease (74.8%, n = 666), 27.9% of patients (n = 248) received endocrine treatment and 53.6% (n = 477) received targeted therapy.

3.2. Localisation of BMs

Localisations of BMs were the anterior fossa (31.1%), followed by the posterior fossa (22.7%) or both (30.6%) and leptomeningeal disease (8.6%; Table 1). Patients with BMs in the posterior fossa more often had HER2-positive (n = 169/314, 54%) than triple-negative (n = 65/314, 21%) or luminal-like primary breast cancer (n = 80/314, 26%), ($p < 0.0001$). Patients with leptomeningeal disease more often had luminal-like (66/111, 60%) than triple-negative (28/111, 25%) or less frequent HER2-positive tumours (17/111, 15%; $p < 0.0001$) (Table 2). In addition, patients with leptomeningeal disease more often had lobular histology than ductal histology ($p < 0.001$, data not shown). No correlation between the number of BMs and subtype was observed, but HER2-positive patients had a larger maximum size of the largest metastasis than other subtypes (HER2 positive median 23 mm compared with 18 or 19 mm, $p < 0.0001$, Supplement Table 1).

3.3. Treatment of BMs

In 91% of patients (1554/1712), at least one local treatment for BMs was documented (Fig. 1). In 438 patients (28%), surgery was the first treatment for BMs. Ten percent of those patients (35/342) received further stereotactic radiotherapy, 75% (256/342) received whole-brain radiotherapy and 9% (30/342) received both.

Table 1
Patients' characteristics (n = 1712).

Parameter	Category	Overall
Age at diagnosis of breast cancer (years)	Median (range)	51 (20–87)
Age at diagnosis of BMs (years)	Median (range)	56 (22–90)
Tumour subtype (primary breast cancer)	TNBC	328 (21.4)
	Luminal like	471 (30.8)
	HER2 positive	732 (47.8)
	Missing	181
Tumour subtype of BMs	TNBC	59 (17.6)
	Luminal like	63 (18.8)
	HER2 positive	214 (63.7)
	Missing	1376
Histologic subtype of primary tumour	Ductal	1243 (73.2)
	Lobular	126 (7.4)
	Others	330 (19.4)
	Missing	13
Diagnostic method	Only clinical	58 (3.5)
	Only CT	301 (18.0)
	Only MRI	961 (57.5)
	Clinical and CT	49 (2.9)
	Clinical and MRI	125 (7.5)
	CT and MRI	141 (8.4)
	Clinical and CT and MRI	37 (2.2)
	Missing	40
Localisation of BMs	Only anterior fossa	482 (31.1)
	Only posterior fossa	352 (22.7)
	Only meninges	133 (8.6)
	Anterior/posterior fossa	475 (30.6)
	Anterior fossa/meninges	35 (2.3)
	Posterior fossa/meninges	31 (2.0)
	All	42 (2.7)
	Missing	162
Number of BMs	1	458 (30.0)
	2–3	408 (26.8)
	≥4	659 (43.2)
	Missing	187
ECOG (Karnofsky status) at diagnosis of BMs	0 (100%)	101 (14.5)
	1 (80–90%)	313 (45.0)
	2 (60–70%)	197 (28.3)
	3 (40–50%)	64 (9.2)
	4 (10–30%)	20 (2.9)
	Missing	1017
BMs without extracranial metastases at time of BM diagnosis	No	1369 (80.0)
	Yes	343 (20.0)
Localisation of extracranial disease		
	Bone metastases	779 (45.5)
	Liver metastases	616 (36.0)
	Lung metastases	637 (37.2)
	Skin metastases	102 (6.0)
Asymptomatic BMs	No	1445 (84.4)
	Yes	267 (15.6)
Systemic treatment after the diagnosis of BMs (combination possible)		
Chemotherapy		1163 (50.1)
	Anthracycline	110 (4.7)
	Taxane based	256 (11.0)
	Taxane and anthracycline	23 (0.99)
	Others	774 (33.3)
Endocrine treatment		324 (14.0)
	Tamoxifen	58 (2.5)
	Aromatase inhibitor	165 (7.1)
	GnRH analogues	28 (1.2)
	Others	73 (3.1)
Targeted therapy		836 (36.0)
	Trastuzumab	267 (11.5)
	Trastuzumab and pertuzumab	35 (1.5)
	Lapatinib	177 (7.6)

Table 1 (*continued*)

Parameter	Category	Overall
	T-DM 1	70 (3.0)
	Bevacizumab others	58 (2.5) 229 (27.3)

BMs, brain metastases; TNBC, triple-negative breast cancer; MRI, magnetic resonance imaging; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; GnRH, gonadotropin-releasing hormone.

Table 2
Tumour subtypes and localisation of BM.

Localisation of BM	Anterior fossa (n = 413)	Posterior fossa (n = 314)	Leptomeningeal disease (cytologically confirmed) (n = 111)	Multiple locations (n = 513)	P-value
Subtype	N (%)	N (%)	N (%)	N (%)	<0.0001
TNBC	79 (19.1)	65 (20.7)	28 (25.2)	123 (24.0)	
HER2 positive	199 (48.2)	169 (53.8)	17 (15.3)	235 (45.8)	
Luminal like	135 (32.7)	80 (25.5)	66 (59.5)	155 (30.2)	

BMs, brain metastases; TNBC, triple-negative breast cancer.

Thousand patients (64%) received only radiotherapy. Stereotactic radiotherapy was applied in 7% (73/980), whole-brain radiotherapy in 89% (873/980) and both in 3% (34/980) of patients. An association between the number of metastases and treatment was observed. Patients with one BM (n = 394) received more often surgery with or without radiotherapy (256/394, 64%) than patients with four and more BMs (n = 565) who received more often only radiotherapy (513/565, 91%; $p < 0.0001$), while this difference was not significant for patients with two or three BMs (data not shown).

3.4. Survival analysis

Median BMFI from diagnosis of primary breast cancer to the diagnosis of BMs for the entire patient group was 35.0 months (95% confidence interval [CI]: 33.0–37.4 months). In univariate analysis, patients with triple-negative tumours had the shortest BMFI with 21.0 months (95% CI 18.5–23.7) compared with HER2-positive tumours (32.4 months, 95% CI: 29.6–36.1) and luminal-like tumours (43.4 months, 95% CI: 38.4–50.1; $p < 0.0001$; Table 3).

Median OS after development of BMs for the entire cohort was 7.4 months (95% CI: 6.7–8.0 months). One-year survival rate was 37.7% (95% CI: 35.2–40.1), and 3-year survival rate was 9.6% (95% CI: 8.0–11.3). Regarding subtypes, patients with HER2-positive tumours had the longest median OS with 11.6 months (95% CI: 10.0–13.4) compared with 5.9 months (95% CI: 5.0–7.2) for patients with luminal-like and 4.6 months (95% CI: 3.9–5.4) for patients with triple-negative tumours (Fig. 2 and Table 3). HER2-positive patients had a significantly lower risk of death compared

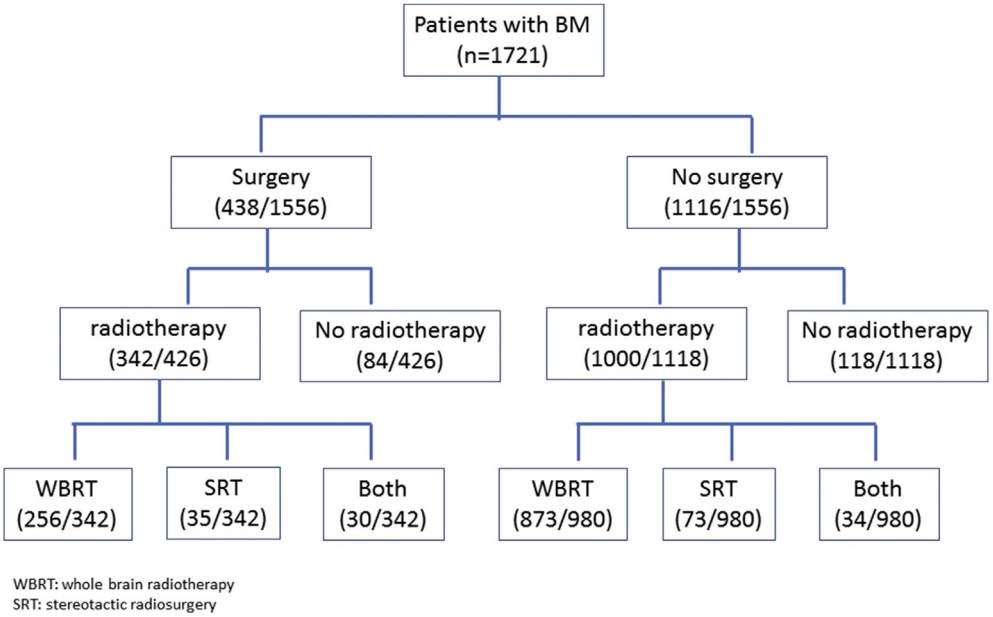

Fig. 1. Local treatment after the diagnosis of BMs. BMs, brain metastases; WBRT, whole-brain radiotherapy; SRT, stereotactic radiotherapy.

Table 3
Brain metastases–free interval (BMFI) and overall survival (OS) for subtypes and the whole cohort.

Survival	TNBC	HER2 positive	Luminal like	All
BMFI	21.0 (18.5–23.7)	32.4 (29.6–36.1)	43.4 (38.4–50.1)	35.0 (33.0–37.4)
Median survival (months, 95% CI)				
BMFI at 12 months (%, 95% CI)	76.5 (71.3–80.8)	85.3 (82.3–87.8)	84.7 (81.0, 87.8)	84.1 (82.1–85.8)
BMFI at 36 months (%, 95% CI)	27.5 (22.6–32.5)	46.5 (42.6–50.3)	56.9 (52.2–61.4)	48.9 (46.4–51.4)
OS	4.6 (3.9–5.4)	11.6 (10.0–13.4)	5.9 (5.0–7.2)	7.4 (6.7–8.0)
Median survival (months, 95% CI)				
OS at 12 months (%, 95% CI)	21.0 (16.5–26.0)	49.5 (45.3–53.4)	33.0 (28.5–37.5)	37.7 (35.2–40.1)
OS at 36 months (%, 95% CI)	2.5 (1.0–5.1)	16.1 (13.0–19.6)	6.7 (4.4–9.7)	9.6 (8.0–11.3)

TNBC, triple-negative breast cancer; CI, confidence interval.

with patients with other subtypes (hazard ratio = 0.493, 95% CI: 0.426–0.572; $p < 0.0001$). Patients with HER2-positive tumours receiving anti-HER2 treatment after the diagnosis of BMs had longer median OS of 17.1 months (95% CI: 14.4–19.5) versus 7.2 months without treatment (95% CI: 5.8–8.7; $p < 0.0001$).

Regarding localisation of BMs, patients with leptomeningeal disease had the shortest survival (median survival 3.9 months, 95% CI 3.0–5.0) compared with parenchymal metastases (anterior fossa: 8.6 months, 95% CI 7.1–10.9, posterior fossa 11.6 months, 95% CI 8.9–13.6; $p < 0.0001$).

Patients with no evidence of extracranial disease showed a longer OS than patients with extracranial metastases (median 10.8 months, 95% CI: 9.1–12.7, versus 6.7 months, 95% CI: 6.0–7.4; $p < 0.0001$). In addition, the number of BMs was associated with OS. Patients with singular BM had the longest median survival of 11.2 months (95% CI: 9.2–14.0) compared with 7.7 months (95% CI: 6.2–9.8) for patients with two or three BMs and 5.7 months (95% CI: 4.9–6.7) for patients with four or more BMs ($p < 0.0001$). Patients diagnosed with asymptomatic BMs showed a longer median survival of 11.9 months (95% CI: 9.1–13.6) versus 6.7 months (95% CI: 6.0–7.4) ($p < 0.0001$). Also, application of systemic treatment after the diagnosis of BMs was associated with better survival (13.0 months [95% CI: 11.4–14.1] versus 3.4 months [95% CI: 3.1–3.8], $p < 0.0001$).

In multivariate analysis, younger age at first diagnosis of BMs, triple-negative subtype of the primary tumour, four or more BMs and low performance status (Eastern Cooperative Oncology Group ≥ 2) remained predictors of shorter OS (Supplement Table 2).

3.5. Treatment and outcomes in different time periods

To detect potential changes in the diagnosis and treatment of BMs over time, we analysed the data of patients who were diagnosed with BMs until the end of 2015 and analysed two different time periods (time period 1: diagnosis between 2000 and 2009, time period 2:

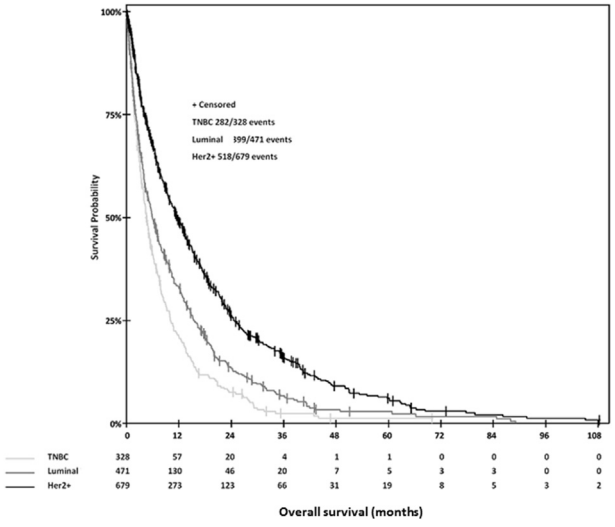

Fig. 2. Overall survival in months after the diagnosis of BMs for subgroups of patients. TNBC, triple-negative breast cancer.

Table 4
Subtype, diagnosis, treatment of BMs and survival in two different time periods.

Parameter	Year of diagnosis		p-value
	2000–2009	2010–2015	
	N (%)	N (%)	
	N = 507	N = 893	
Subtype			
TNBC	105 (20.7)	198 (22.2)	
Luminal like	144 (28.4)	303 (33.9)	
HER2 positive	258 (50.9)	392 (43.9)	0.0331
	N = 623	N = 967	
Diagnostic method			
Clinical	32 (5.1)	26 (2.7)	0.0027
CT	150 (24.1)	183 (18.9)	
MRI	382 (61.3)	649 (67.1)	
CT and MRI	59 (9.5)	109 (11.3)	
	N = 552	N = 817	
First treatment			
Surgery only	36 (6.5)	55 (6.7)	0.7093
Surgery and radiotherapy	125 (22.6)	200 (24.5)	
Radiotherapy only	391 (70.8)	562 (68.8)	
	Months (95% CI)	Months (95% CI)	
Median overall survival	7.6 (6.5–9.2)	5.8 (5.0–6.5)	<0.0001

TNBC, triple-negative breast cancer; CI, confidence interval; TNBC, triple-negative breast cancer; CI, confidence interval.

diagnosis between 2010 and 2015; Table 4). We found a decrease in patients with HER2-positive BMs (51%–44%) and an increase in patients with luminal-like primary tumours (28%–34%; p = 0.0331) in our sample. Since 2010, patients were more often diagnosed with MRI (61–67%, p = 0.027). First-documented local treatment for BMs did not change between the two time periods. Also, the proportion of patients with no evidence of extracranial disease did not change (18% in 2000–2009 versus 20% in 2010–2015, p = 0.2923). Interestingly, the median survival time in the overall cohort decreased between the two time periods with a median survival of 7.6 months in 2000–2009 versus 5.8 months in 2010–2015 ($p < 0.0001$).

4. Discussion

In this large cohort of breast cancer patients with BMs, we could show that the subtype of the primary tumour influences the localisation of BMs and has a high impact on prognosis.

It might seem surprising that despite improved local and systemic treatment for metastatic breast cancer, survival rates of patients with BMs did not improve during the last years but in contrast, seem to have slightly decreased. One explanation could be a better control of extracranial disease which has led to longer survival so patients develop BMs as a sign of more advanced disease. In addition, when comparing two time intervals, we could show that the proportion of HER2-positive patients has decreased, whereas the proportion of luminal-like patients has increased. This is in line with other studies that describe increasing survival rates for patients with HER2-positive primary breast cancer [6] and prolonged time between initial breast cancer diagnosis and diagnosis of BMs [7]. In our study, HER2-positive patients with BMs had a better prognosis compared with other subtypes, and therefore, the decrease of HER2-positive BMs over the time might have influenced the survival rates for the whole cohort. The decrease in survival time might also be explained by the increase in luminal patients who metastasised more frequently into the leptomeninges and, thus, had an impaired prognosis. Therefore, one could hypothesise that improvements in the adjuvant treatment of breast cancer have led to a time-dependent change of the proportion of BM patients with different subtypes of the primary tumour.

Survival rates after BMs differ depending on prognostic factors, tumour subtype, performance status and treatment [2]. We observed that the subtype of the primary tumour has high impact on survival rates. As for other metastatic settings, patients with a triple-negative tumour had the worst prognosis. In a retrospective analysis of 740 patients with BMs at the time of initial breast cancer diagnosis between 2010 and 2013, triple-negative subtype was associated with a median survival time of 6 months compared with 22 months for patients with HER2-positive subtype [8]. In the retrospective study by Niikura *et al.* with 1256 patients diagnosed with BMs and treated in 24 Japanese institutions, an impact of subtype on survival was also observed with a median survival of 4.9 months for patients with triple-negative subtype [9].

In our cohort, patients with asymptomatic BMs and a lower number of BMs had longer survival rates, but this survival benefit could be a result of an earlier diagnosis. From this, it cannot be concluded that early detection by screening of BMs is beneficial for all patients. However, intensive effort should be given in the attempt to set up a prospective trial evaluating BM screening in a subgroup of patients with breast cancer and a high risk of developing BMs.

The high long-term risk of BMs in the HER2 subtype has been described by several groups [10]. Recently, more evidence on different localisation patterns in the brain depending on subtypes was published. In a small cohort, HR-negative/HER2-positive breast cancer patients with BMs were more likely to present with occipital metastases [11]. Laakmann *et al.* have published results on brain imaging of 400 breast cancer patients with BMs, of whom 102 had HER2-positive primary tumours, and observed also a correlation between HER2 positivity and metastases in the posterior fossa [12]. Here, we could confirm this finding in 314 patients with HER2-positive breast cancer in the BMBC registry. In contrast to others, we could not observe an association between the number of BMs and subtype. However, we found that HER2 positivity was associated with a larger diameter of the largest metastasis in the brain. Arvold *et al.* described that triple-negative and luminal-like tumours were associated with larger sizes of the BM in a cohort of 1434 primary breast cancer patients, but only 24 patients developed BMs [13]. In addition, we observed that luminal-like tumours metastasised more frequently into the leptomeninges. This was also described in a case series of patients with leptomeningeal disease [14]. In our cohort, we could confirm that invasive lobular subtype was more frequently associated with leptomeningeal disease [14,15]. The high proportion of patients with leptomeningeal disease in the group of patients with luminal tumours might also explain the short OS for luminal-like patients with BMs in our cohort.

Whole-brain radiotherapy (WBRT) in comparison to stereotactic radiotherapy is not associated with improved survival in patients with a limited number of BMs but is associated with negative neurocognitive effects [16–18]. As a consequence, stereotactic radiotherapy without WBRT for patients with a limited number of BMs, mostly defined as up to four lesions, is currently the preferred treatment strategy [19,20]. However, in our data set, the majority of patients received WBRT. Only a minority of patients (less than 10%) received stereotactic radiotherapy, which is lower than in other published

cohorts [21]. This could be explained by the fact that most of the data were collected retrospectively and that patients were treated before guidelines changed. There is increasing evidence that WBRT has negative impact on survival. In a Swedish cohort of 241 breast cancer patients with BMs treated with WBRT in a single institution between 1999 and 2012, median survival time was 2.9 months (2.0 months for triple-negative, 3.5–3.9 months for luminal and 4.1 months for HER2-positive patients) [22]. Authors explain short survival rates with the inclusion of patients who might have been judged unfit under different conditions. In a Dutch trial of 1962 breast cancer patients with BMs treated in 15 different institutions with WBRT, median survival was also only 3.7 months [23]. This is in line with our data showing lower survival rates in a real-world setting compared with other trials with a WBRT rate of 70% (1193/1721 patients).

A potential limitation of our study is that data were not documented prospectively, providing a risk of bias. As patients with HER2-positive breast cancer with BMs have a better prognosis, there may be a documentation bias leading to a higher registration of these patients compared with other subgroups with poorer survival. In addition, in Germany, one could expect 2000 breast cancer patients with BMs yearly. Therefore, the study only represents data of a limited number of patients with BMs in this study period, which may bias the results. Despite the large size of the cohort, the number of patients in subgroups such as HER2-positive patients with current treatment strategies still remains relatively low. However, either it would take several years to set up a prospective registry or a pooled analysis of multinational data would be required.

5. Conclusions

Taken together, we present data of the largest cohort of breast cancer patients with BMs described so far. Results indicate a time-dependent change of BMs. The multicenter setting is likely to be representative also for other European countries.

Ethical approval and consent to participate

The study received ethical approval from the Ethics Committee Hessen, Germany (FF 42/2013). All participating sites received approval of the local ethics committee. Patients still under treatment at the institution gave their informed consent.

Funding

The trial was a collaborative effort of 80 participating study sites and was supported by institutional resources.

Conflict of interest statement

All authors declare that they have no conflict of interest.

Acknowledgements

The authors thank Birgit Raasch from the German Breast Group for her support. They thank Christoph Heiss and Gabriele Kaltenecker for including patients in the registry.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.07.004.

References

[1] Tabouret E, Chinot O, Metellus P, Tallet A, Viens P, Goncalves A. Recent trends in epidemiology of brain metastases: an overview. Anticancer Res 2012;32:4655–62.
[2] Quigley MR, Fukui O, Chew B, Bhatia S, Karlovits S. The shifting landscape of metastatic breast cancer to the CNS. Neurosurg Rev 2013;36:377–82.
[3] Yau T, Swanton C, Chua S, Sue A, Walsh G, Rostom A, et al. Incidence, pattern and timing of brain metastases among patients with advanced breast cancer treated with trastuzumab. Acta Oncol 2006;45:196–201.
[4] Witzel I, Kantelhardt EJ, Milde-Langosch K, Ihnen M, Zeitz J, Harbeck N, et al. Management of patients with brain metastases receiving trastuzumab treatment for metastatic breast cancer. Onkologie 2011;34:304–8.
[5] Kaplan MA, Isikdogan A, Koca D, Kucukoner M, Gumusay O, Yildiz R, et al. Biological subtypes and survival outcomes in breast cancer patients with brain metastases (study of the Anatolian Society of Medical Oncology). Oncology 2012;83:141–50.
[6] Guiu S, Arnould L, Bonnetain F, Dalban C, Favier L, Desmoulins I, et al. Pathological response and survival after neoadjuvant therapy for breast cancer: a 30-year study. Breast 2013;22:301–8.
[7] Mounsey LA, Deal AM, Keith KC, Benbow JM, Shachar SS, Zagar T, et al. Changing natural history of HER2-positive breast cancer metastatic to the brain in the era of new targeted therapies. Clin Breast Cancer 2017;18(1):29–37.
[8] Leone JP, Leone J, Zwenger AO, Iturbe J, Leone BA, Vallejo CT. Prognostic factors and survival according to tumour subtype in women presenting with breast cancer brain metastases at initial diagnosis. Eur J Cancer 2017;74:17–25.
[9] Niikura N, Hayashi N, Masuda N, Takashima S, Nakamura R, Watanabe K, et al. Treatment outcomes and prognostic factors for patients with brain metastases from breast cancer of each subtype: a multicenter retrospective analysis. Breast Cancer Res Treat 2014;147:103–12.
[10] Lim YJ, Lee SW, Choi N, Kwon J, Eom KY, Kang E, et al. Failure patterns according to molecular subtype in patients with invasive breast cancer following postoperative adjuvant radiotherapy: long-term outcomes in contemporary clinical practice. Breast Cancer Res Treat 2017;163:555–63.
[11] Lekanidi K, Evans AL, Shah J, Jaspan T, Baker L, Evans AJ. Pattern of brain metastatic disease according to HER-2 and ER

receptor status in breast cancer patients. Clin Radiol 2013;68:1070–3.
[12] Laakmann E, Witzel I, Scriba V, Grzyska U, Zu Eulenburg C, Burchardi N, et al. Radiological patterns of brain metastases in breast cancer patients: a subproject of the German Brain Metastases in Breast Cancer (BMBC) Registry. Int J Mol Sci 2016;17.
[13] Arvold ND, Oh KS, Niemierko A, Taghian AG, Lin NU, Abi-Raad RF, et al. Brain metastases after breast-conserving therapy and systemic therapy: incidence and characteristics by biologic subtype. Breast Cancer Res Treat 2012;136:153–60.
[14] Le Rhun E, Taillibert S, Zairi F, Devos P, Pierret MF, Dubois F, et al. Clinicopathological features of breast cancers predict the development of leptomeningeal metastases: a case-control study. J Neurooncol 2011;105:309–15.
[15] Morikawa A, Jordan L, Rozner R, Patil S, Boire A, Pentsova E, et al. Characteristics and outcomes of patients with breast cancer with leptomeningeal metastasis. Clin Breast Cancer 2017;17:23–8.
[16] Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA 2016;316:401–9.
[17] Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. J Clin Oncol 2013;31:65–72.
[18] Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011;29:134–41.
[19] Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2012;2:210–25.
[20] Brown PD, Ahluwalia MS, Khan OH, Asher AL, Wefel JS, Gondi V. Whole-brain radiotherapy for brain metastases: evolution or revolution? J Clin Oncol 2018;36:483–91.
[21] Mix M, Elmarzouky R, O'Connor T, Plunkett R, Prasad D. Clinical outcomes in patients with brain metastases from breast cancer treated with single-session radiosurgery or whole brain radiotherapy. J Neurosurg 2016;125:26–30.
[22] Frisk G, Tinge B, Ekberg S, Eloranta S, Backlund LM, Lidbrink E, et al. Survival and level of care among breast cancer patients with brain metastases treated with whole brain radiotherapy. Breast Cancer Res Treat 2017;166:887–96.
[23] Jeene PM, de Vries KC, van Nes JGH, Kwakman JJM, Wester G, Rozema T, et al. Survival after whole brain radiotherapy for brain metastases from lung cancer and breast cancer is poor in 6325 Dutch patients treated between 2000 and 2014. Acta Oncol 2018;57:637–43.