



Time interval between the diagnosis of breast cancer and brain metastases impacts prognosis after metastasis surgery

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Abstract

Purpose Breast cancer (BC) is the most frequently diagnosed tumor entity in women. Occurring at different time intervals (TI) after BC diagnosis, brain metastases (BM) are associated with poor prognosis. We aimed to identify the risk factors related to and the clinical impact of timing on overall survival (OS) after BM surgery.

Methods We included 93 female patients who underwent BC BM surgery in our institution (2008–2019). Various clinical, radiographic, and histopathologic markers were analyzed with respect to TI and OS.

Results The median TI was 45.0 months (range: 9–334.0 months). Fifteen individuals (16.1%) showed late occurrence of BM (TI ≥ 10 years), which was independently related to invasive lobular BC [adjusted odds ratio (aOR) 9.49, 95% confidence interval (CI) 1.47–61.39, $p=0.018$] and adjuvant breast radiation (aOR 0.12, 95% CI 0.02–0.67, $p=0.016$). Shorter TI (< 5 years, aOR 4.28, 95% CI 1.46–12.53, $p=0.008$) was independently associated with postoperative survival and independently associated with the Union for International Cancer Control stage (UICC) III–IV of BC (aOR 4.82, 95% CI 1.10–21.17, $p=0.037$), midline brain shift in preoperative imaging (aOR 10.35, 95% CI 1.09–98.33, $p=0.042$) and identical estrogen receptor status in BM (aOR 4.56, 95% CI 1.35–15.40, $p=0.015$).

Conclusions Several factors seem to influence the period between BC and BM. Occurrence of BM within five years is independently associated with poorer prognosis after BM surgery. Patients with invasive lobular BC and without adjuvant breast radiation are more likely to develop BM after a long progression-free survival necessitating more prolonged cancer aftercare of these individuals.

Keywords Breast cancer · Brain metastasis · Time interval · Brain metastasis surgery · Invasive lobular breast cancer

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Abbreviations

aOR	Adjusted odds ratios
aHR	Adjusted hazard ratios
AUC	Areas under the curve
BC	Breast cancer
BM	Brain metastases
CI	Confidence interval
ER	Estrogen receptor
G	Grade of cancer cells
HER2	Human epidermal growth factor receptor 2
IQR	Interquartile ranges
KPS	Karnofsky Performance Status
MRI	Magnetic resonance imaging
OS	Overall survival
PR	Progesterone receptor
ROC	Receiver operating characteristic
RS	Receptor status

T N M stage	T: Tumor size, N: Lymph nodes, M: distant metastasis
TI	Time interval
UICC	Union for international cancer control

Introduction

Breast cancer (BC) is one of the most frequent cancer entities in women with increasing rates of brain metastasis (BM). [1, 2] Multimodal treatment concepts for BC include the surgical and (neo-) adjuvant options with radiation, conventional chemotherapy, endocrine therapy, target therapy like anti-human epidermal growth factor 2 (HER2), as well as the treatment of distant metastases. [3]

The prevalence of BM varies between 15 and 50% depending on the presence of different tumor features. [4–6] Along with synchronous occurrence, BM might also develop in the further course of disease. The time interval (TI) for the occurrence of BM after BC diagnosis may range between several months and many years. [1, 5, 7–9] BC subtype [basal and HER2 receptor status (RS)], the initial Union for International Cancer Control (UICC) stage III–IV of BC and BC adjuvant therapy with Trastuzumab were reported to influence the TI of BC BM [5, 6, 10–12].

As the prognosis after BM occurrence is generally poor, the proper and timely management of BM is essential for outcome improvement of affected individuals [8] In this context, the knowledge on the risk factors impacting the timing of metachronous BM might be helpful in timely identification of BM and optimization of the frequency and duration of follow-up care. In particular, as the late occurrence of BM over 10 years after BC diagnosis without BC recurrence and/or extracranial metastases is sporadic, standard BC aftercare does not include routine BM screening after this TI [13, 14]. Previous studies have already shown that the time interval until brain metastasis is relevant for survival after radiosurgery, especially in breast cancer patients [15–17]. Finally, the possible impact of TI on the overall survival (OS) after BM surgery is also controversial, as both significant and nonsignificant associations were previously reported [1, 5, 7, 8, 18].

Therefore, we aimed to identify the predictors associated with TI of BC BM occurrence, as well as to elucidate the impact of TI on OS after BM surgery in a large monocentric series of individuals with metachronous BC BM.

Material and methods

This study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee of the University Hospital Essen (local registration number: 17-7855-BO).

Patient population

All female patients (age ≥ 18 years) who underwent BC BM surgery between January 2008 and December 2019 in a single institution were included. The selection process of individuals for BC BM surgery within the institutional interdisciplinary neuro-oncologic tumor board was reported previously [19, 20]. Patients with synchronous cerebral metastases were excluded from the study.

Data management

The following patient and tumor characteristics were collected from the electronic health records: patients' previous medical history (documented comorbidities) and specific laboratory parameters at admission to assess the presence of anemia (hemoglobin), renal function (creatinine), and inflammatory status (white blood cells); BC-related variables: time of BC diagnosis, the type of surgical and (neo-) adjuvant treatment, histopathological features (invasive ductal, invasive lobular), tumor stage, and RS; BM-related variables: time of BM diagnosis, preoperative Karnofsky performance status (KPS) scale, number (singular vs. multiple) and location of BM, RS, and radiographic features in the preoperative magnetic resonance imaging (MRI) as reported previously [20]. In addition, all available follow-up data after BM surgery was recorded to assess the patients' OS.

A gross total resection was performed in 92 operated metastases. The extent of resection was assessed by postoperative CT imaging and surgical report.

Not all patients underwent adjuvant radiation at our university hospital in Essen, some were treated at other centers, which could not always send a report to us. In summary, 19.4% (n = 18) received whole-brain irradiation, 58.1% (n = 54) received stereotactic irradiation, and in 1.1% (n = 1) it is unclear which radiation was performed. In total, 8 cases (8.6%) were not treated with adjuvant radiation. In 12 cases (12.9%) it is unclear whether and how they were adjuvant radiated.

Of 30 patients with multiple metastases, in 23 of cases (76.7%) one metastasis was removed. In 4 patients (13.3%), two metastases were removed. A maximum of 3 metastases were removed only in 3 cases (3.3%) (see supplementary table E1).

The RS evaluation at our neuropathology department was described elsewhere [19]. In short, immunoreactivity defines estrogen receptor, progesterone receptor, and HER2 positive status. With immunohistochemistry, positive HER2 status is described as HER2 3+ (DAKO score) or HER2+ with HER2 gene amplification detected by

fluorescence in situ hybridization. Positive receptor status exists with greater than 1% positive staining of tumor cell nuclei.

Study endpoints and statistical analysis

The evaluation of the impact of TI on postoperative survival after BM surgery was *the primary endpoint* of the present study. First, the outcome-relevant cutoff for TI was identified using the receiver operating characteristic (ROC) curve (see supplementary Figure E1). After the subsequent dichotomization, the impact of TI on OS was analyzed using the Kaplan–Meier survival plots and log-rank test. In addition, univariate Cox regression analysis was performed between all recorded BC and BM characteristics with OS after BM surgery. Finally, the associations with P-value < 0.1 were included in the multivariate Cox regression analysis.

As *secondary study endpoints*, the associations between the previously defined outcome-relevant TI with BC and BM characteristics were analyzed to identify the predictive factors. In addition, we evaluated the BC and BM parameters associated with the late occurrence of BM, defined as TI ≥ 10 years without other distant metastases or BC recurrence. First, univariate analysis using the Chi-square (χ^2 test) or Fisher exact test, as appropriate, was performed. Then, the associations with the P value < 0.1 were included

in the multivariable binary logistic regression analysis for the identification of independent associations.

Data were analyzed using SPSS (version 28, SPSS Inc., IBM, Chicago, IL, USA) statistical software. The variables were reported in median values and interquartile ranges (IQR) between 25 and 75%, or as the number of cases (with percentage), as appropriate. The significance level for the p value was set at ≤ 0.05.

Results

We included 93 female patients with metachronous BM in the final cohort. The median age at the time of BC diagnosis was 52.0 years (IQR 45.5–62.5). The median TI from initial BC diagnosis to BM was 45.0 months (IQR 23.0–100.0) with minimum and maximum TI of 9 and 334 months respectively (Fig. 1). Median OS after BM surgery was 16.0 months (IQR 7.0–33.0). The patients' characteristics are summarized in Table 1.

Evaluation of the impact of TI on postoperative survival after BM surgery

Using the ROC curve analysis (Supplementary Fig. E2), TI < 5 years was identified as clinically relevant cutoff for

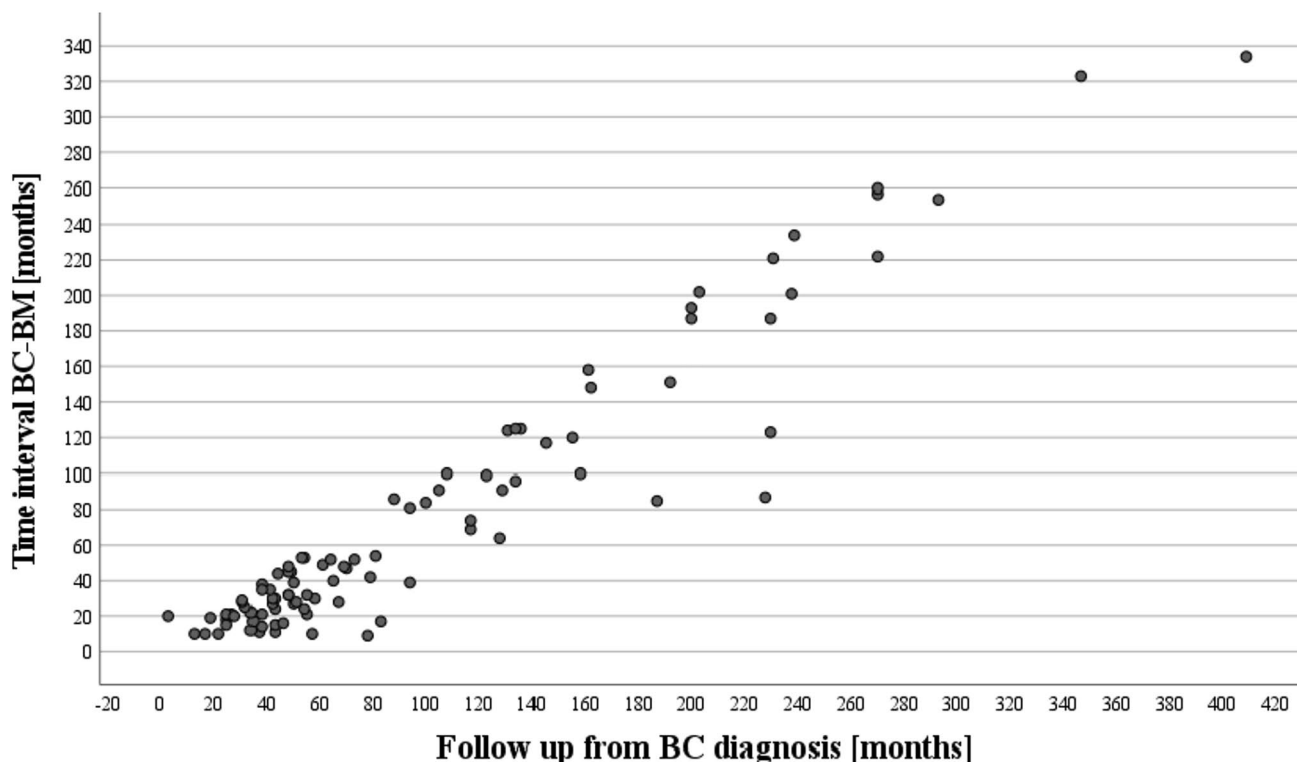


Fig. 1 Scatter plot of the TI distribution in the cohort. BC breast cancer, BM brain metastasis, TI time interval

Table 1 Baseline characteristics of BCBM patients

Parameter	Median (IQR) or No. (%)
Number of patients	93 (100%)
Interval BC to BM (months)	45.0 (23.0–100.0)
BC characteristics	
Age at BC diagnosis (years)	52.0 (45.5–62.5)
Surgical treatment of BC	
Mastectomy / BPS	43 (46.2%)/50 (53.8%)
Systemic treatment of BC	
(Neo-) adjuvant Trastuzumab therapy	25 (26.9%)
Adjuvant BC radiation	62 (66.7%)
Adjuvant Tamoxifen therapy	11 (11.8%)
Histopathology of BC	
Invasive ductal	52 (55.9%)
Invasive lobular	10 (10.8%)
TNM stage	
Initial T stage > T2	20 (21.5%)
Initial N stage ≥ N1	32 (34.4%)
Initial M stage M1	12 (12.9%)
G stage ≥ G2	49 (52.7%)
UICC stage	
I–II	41 (44.1%)
III–IV	25 (26.9%)
BC subtypes	
Basal (= triple-negative)	19 (20.4%)
LumA (HER2-ER + PR +)	29 (31.2%)
LumB (= triple positive)	10 (10.8%)
HER2 (HER2 + ER-PR-)	21 (22.6%)
Clinical characteristics at BM diagnosis	
Age at BM diagnosis [years]	60.0 (51.5–69.0)
Preoperative seizures	2 (2.2%)
Preoperative KPS score (= 90%)	57 (61.3%)
Preoperative laboratory values	
WBC ($\geq 10/nl$)	39 (41.9%)
Hemoglobin (< 12 g/dl)	15 (16.1%)
Creatinine (> 1.1 mg/dl)	1 (1.1%)
Pre-existing conditions	
Arterial hypertension	40 (43.0%)
Diabetes mellitus	6 (6.5%)
Hyperuricemia	2 (2.2%)
BM characteristics	
Preoperative MRI	
Tumor necrosis	46 (49.5%)
Edema > 10 mm	67 (72.0%)
Midline shift	13 (14.0%)
Singular/multiple BM	63 (67.7%)/30 (32.3%)
Supratentorial/infratentorial BM	59 (63.4%)/34 (36.6%)
BM receptor status	
HER2 status positive/negative	36 (38.7%)/57 (61.3%)
ER status positive/negative	45 (48.4%)/48 (51.6%)
PR status positive/negative	20 (21.5%)/73 (78.5%)
Identic/converted HER2	70 (75.3%)/9 (9.7%)
Identic/converted ER	58 (62.4%)/21 (22.6%)

Table 1 (continued)

Parameter	Median (IQR) or No. (%)
Identic/converted PR	54 (58.1%)/25 (26.9%)
Adjuvant brain radiation	73 (90.1%)
Adjuvant systemic therapy after brain radiation	30 (32.3%)

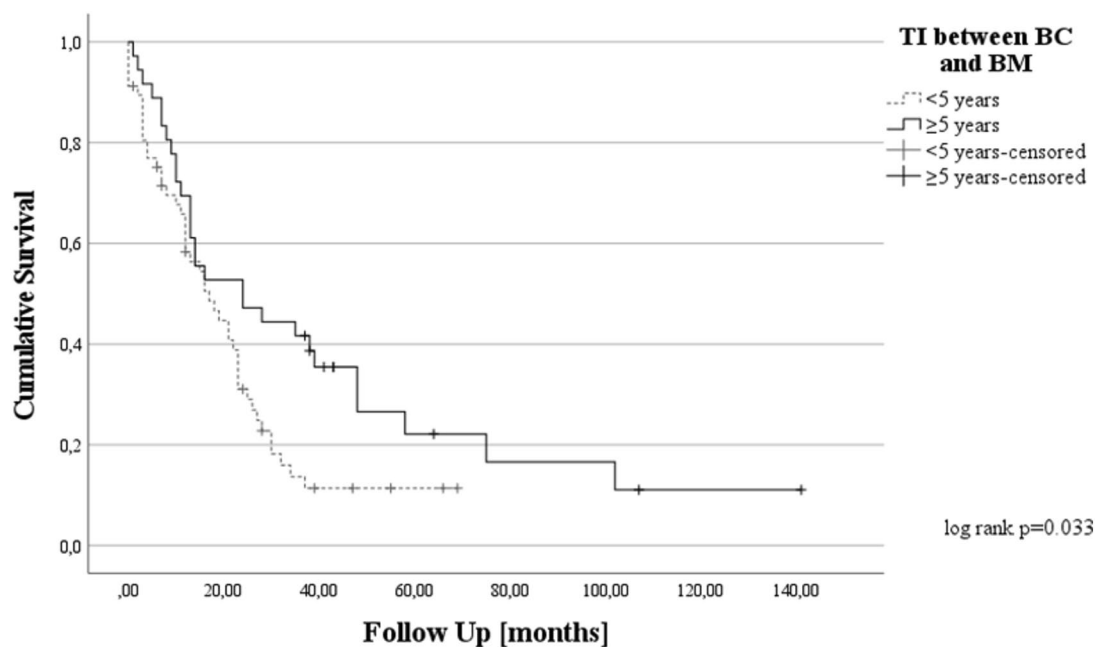
No number of cases, *IQR* interquartile ranges 25%–75%, *BC* breast cancer, *BM* brain metastasis, *HER2* human epidermal growth factor receptor 2, *ER* estrogen receptor, *PR* progesterone receptor, *preop* preoperative, *T* tumor size, *N* lymph nodes, *M* distant metastasis, *G* grade of cancer cells, *BPS* breast-preserving surgery, *KPS* Karnofsky Performance Score, *WBC* white blood cells, *UICC* Union for international cancer control, *MRI* magnetic resonance imaging

the prediction of OS after BM surgery. Kaplan–Meier survival plot (Fig. 2) showed significant survival differences depending on the above-mentioned TI cutoff.

In the univariate Cox regression analysis, TI < 5 years (p = 0.037) was significantly associated with OS. Moreover, the following parameters were also selected for further evaluation upon the results of univariate analysis (see Supplementary Table E2): age at BC diagnosis ≥ 65 years (p = 0.007), Trastuzumab treatment (p < 0.001), initial N

stage N0 (p = 0.027), initial higher G stage (p = 0.077), preoperative KPS < 90% (p = 0.026), preoperative seizure (p = 0.004), tumor necrosis in preoperative MRI (p = 0.037), preoperative leukocytosis (p = 0.073), negative HER2 RS in BM (p = 0.047) and adjuvant brain radiation (p = 0.012).

In the multivariate analysis (see Supplementary Table E3), TI < 5 years [adjusted hazard ratio (aHR) 4.28, 95% confidence interval (CI) 1.46–12.53, p = 0.008], age at BC diagnosis ≥ 65 years (aHR 7.87, 95% CI 1.98–31.33,



No. At risk								
< 5 years	57	23	4	2				
≥ 5 years	36	19	11	5	3	3	1	1

Fig. 2 Kaplan Meier curve illustrating the impact of time interval (< 5 years) on OS after BC BM surgery. *BC* breast cancer, *BM* brain metastasis, *TI* time interval, *OS* overall survival., *No* number

$p=0.003$), initial higher BC G stage (per grade increase: aHR 91.89, 95% CI 3.17–2668.18, $p=0.009$), BC treatment with Trastuzumab (aHR 0.06, 95% CI 0.01–0.34, $p=0.001$), tumor necrosis in preoperative MRI (aHR 5.15, 95% CI 1.33–19.86, $p=0.017$) and adjuvant brain radiation (aHR 0.09, 95% CI 0.01–0.69, $p=0.020$) were confirmed as independent predictors of postoperative survival after BM surgery.

Parameters associated with TI

(a) BC characteristics as predictors of outcome-relevant TI (<5 years)

The following BC characteristics were related to shorter TI in univariate analysis (see Supplementary Tables E4): age at BC diagnosis ≥ 65 years (84.2% vs. 55.4%, $p=0.033$), invasive ductal BC (71.2% vs. 30.0%, $p=0.026$), BC T stage $> T2$ (80.0% vs. 47.7%, $p=0.028$), HER2 RS and basal BC subtype (72.5% vs. 51.3%, $p=0.066$), the BC subtypes are shown in supplementary figure E3) and UICC stage III–IV (72.0% vs. 48.8%, $p=0.077$).

The final multivariate analysis, including all above-mentioned parameters showed UICC stage III–IV (adjusted odds ratio [aOR] 4.82, 95% CI 1.10–21.17, $p=0.037$) as the only independent predictor of TI <5 years (see Table 2).

(b) Association between TI <5 years and BM characteristics

First, the univariate analysis (see supplementary table E4) detected the following BM features associated with short TI: identical ER status (69.0% vs. 42.9%, $p=0.041$), edema ≥ 10 mm (67.2% vs. 35.3%, $p=0.025$) and midline shift in the preoperative MRI (92.3% vs. 54.9%, $p=0.013$). Of them, midline shift (aOR 10.35, 95% CI 1.09–98.33, $p=0.042$) and identical ER status (aOR 4.56, 95% CI 1.35–15.40, $p=0.015$) remained independently associated with TI <5 years in the multivariate analysis (see Table 2).

(c) Late occurrence of BM (TI ≥ 10 years)

In our cohort, 15 (16.1%) patients developed BM 10 years or later after BC diagnosis as first distant metastasis. The univariate analysis (supplementary table E5) identified the association between invasive lobular BC (40.0% vs. 9.6%, $p=0.031$) and adjuvant breast radiation (40% vs. 71.8%, $p=0.033$) with TI ≥ 10 years (see also Supplementary Table E6 for a detailed comparison of cohort characteristics). In the multivariate analysis, this association remained significant for invasive lobular BC subtype (aOR 9.49, 95% CI 1.47–61.39, $p=0.0018$) and adjuvant breast radiation (aOR 0.12, 95% CI 0.02–0.67, $p=0.016$, see supplementary table E5).

Table 2 Multivariate analysis (binary regression analysis) of predictors of shorter time interval BC-BM (<5 years)

Parameter	p-value	aOR	95% CI
BC-related characteristics			
Invasive ductal BC subtype	0.311	2.71	0.39–18.59
UICC III–IV	0.037	4.82	1.10–21.17
HER2 and basal BC subtype	0.127	3.00	0.73–12.25
T stage $> T2$	0.681	1.41	0.28–7.09
Age at BC ≥ 65 years	0.224	3.21	0.49–21.01
BM-related characteristics			
Edema ≥ 10 mm	0.098	2.84	0.83–9.76
Midline shift	0.042	10.35	1.09–98.33
Identical ER status	0.015	4.56	1.35–15.40

Bold indicates significant results

BC breast cancer, BM brain metastasis, TI time interval, HER2 human epidermal growth factor receptor 2, ER estrogen receptor, T tumor size, G grade of cancer cells, UICC Union for international cancer control, aOR adjusted odds ratio, CI confidence interval, HER2 subtype: HER2 positive, ER negative, PR negative, basal subtype: triple-negative

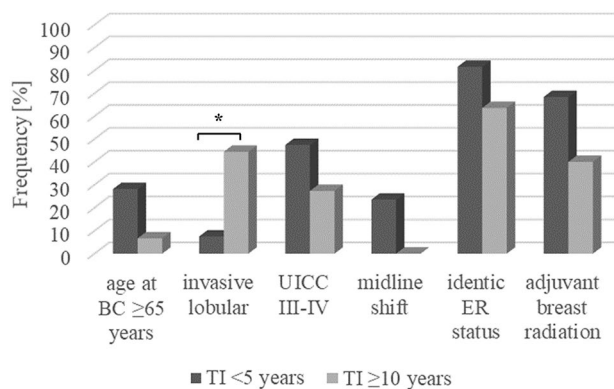


Fig. 3 Major differences in BC- and BM-related characteristics between individuals with short (<5 years) and long (≥ 10 years) TI. BC breast cancer, BM brain metastasis, TI time interval, ER estrogen receptor, UICC Union for international cancer control, * $p < 0.05$

Finally, Fig. 3 summarizes the basic differences in the BC/BM characteristics between the individuals with short (<5 years) and long (≥ 10 years) TI for the occurrence of metachronous BC BM. Additionally, Kaplan Meier curves for the illustration of TI from first BC to BM diagnosis stratified by several parameters are demonstrated in Supplementary Figure E4.

Discussion

The optimization of diagnostic and treatment strategies on BM improves the prognosis of patients with BC. Metachronous BM might occur at different TI after BC diagnosis, depending on the histological characteristics, initial tumor stadium and BC treatment modalities. Individuals with BM occurring within five years after BC diagnosis show poorer prognosis after BM surgery than their counterparts with later development of BM.

Impact of TI on OS after BM surgery

There are several acknowledged prognostic markers for post-operative survival after BC BM surgery like the preoperative KPS, BC subtype, age, number of BM and extracranial metastases. [2, 5, 21] As to the possible impact of BM timing on the postoperative course, there are several publications addressing this association, but with conflicting results [1, 5, 7, 8, 18]. Several reasons might underlie this discrepancy such as the differences in baseline characteristics and used TI cutoffs. According to the survival trends in the present cohort, we defined 5 years as the outcome-relevant TI cutoff. Of note, a previous study has already investigated the impact of the 5-year TI on OS in a heterogeneous cohort of BC BM patients, but could not show significant associations [8].

Along with TI, patients' age and G tumor stage, BC treatment with Trastuzumab, presence of necrosis in BM, and adjuvant brain radiation were independently associated with OS after BM surgery. Except for TI, which remains the contrary discussed survival predictor, other significant results of our study are in line with current evidence in the literature. So, higher age [2, 6] and tumor subtype [2], Trastuzumab therapy [1, 22], brain radiation [18], and tumor necrosis [20] are acknowledged survival predictors for BC BM patients undergoing surgery. Moreover, the relevance of these factors has also been shown for survival prognosis and treatment response of different cancer types, particularly with regard to patients' age and adjuvant therapy [18]. In addition, the association of tumor necrosis in MRI with poor tumor control after Gamma Knife radiosurgery of lung cancer BM has also been reported [20, 23].

Shorter TI (< 5 years)—predictors and associations with BC & BM characteristics

For a better understanding of the pathophysiological background of the eventual association between the TI and post-operative survival after BC BM surgery, the evaluation of the link between TI and other patient and tumor characteristics is essential. Accordingly, we analyzed different BC

and BM-related characteristics as potential predictors of TI. Consistently with the findings from earlier studies, [5, 6, 8, 10] we could show that the patients' age, tumor subtype, and stage of initial BC, as well as RS in BM were linked with TI in our univariate analysis. Of BC-related characteristics, only higher tumor stage (UICC III–IV) showed independent associations with shorter TI. The clinical relevance of the initial tumor stage for BM timing [6, 10] and survival prognosis of BC patients in whole [24] was already reported previously. Therefore, the initial BC stage might be the critical factor conditioning the survival effect of TI on the prognosis after BM surgery.

As to the BM-related characteristics, along with radiographic presentation (midline shift on preoperative MRI), an identical ER status in BM was also independently associated with shorter TI in our cohort. The probable link between TI and RS in BC and BM, as well as receptor conversion was also previously reported [9, 25]. BC as heterogeneous tumor entity with different tumor cell characteristics and the antihormonal as well as the target therapies could affect complex interactions which result in loss or gain of RS [26]. Several studies described the conversion of RS in distant metastases under adjuvant treatment of BC [9, 27, 28]. In particular, the adjuvant Tamoxifen treatment for ER positive BC might cross the blood–brain barrier and influence the ER status in BM [29].

The positive ER status plays an important role in tumor cell differentiation and is related to better prognosis for BC patients [30]. A recent study showed a trend to a shorter disease-free time and poorer prognosis in individuals with identical negative ER status [31]. In addition, an identical ER status was described as poor survival predictor for operated BCBM patients [32]. Our findings confirm the close relationship between the RS in BC and BM with disease progression and prognosis. Further studies are necessary to understand the complex cellular pathways behind the changes in RS, timing of BM and survival prognosis in individuals with BC.

Late occurrence BM (≥ 10 years): frequency and predictors

Standard tumor aftercare for BC patients does not usually include routine screening for BM. Brain MRI is indicated in individuals with neurological symptoms, initial tumor stage IV, or triple-negative BC [33–35]. In addition, BM in BC patients as a first distant metastasis after more than 10 years is very rare [13, 14, 36]. Generally, BC patients with a stable disease without distant metastases and/or BC recurrence after 10 years are not closely followed up, especially with regard to distant metastases [37, 38].

In this context, the analysis of the rate and risk factors of late occurrence of BC BM (≥ 10 years) is of particular clinical interest. In our cohort, late BM were common

(16.1%) in BC patients. We identified the invasive lobular BC subtype and adjuvant breast radiation as significant predictors of TI ≥ 10 years. Interestingly, invasive ductal subtype of BC showed associations with the risk of early BM occurrence (< 5 years) in our univariate analysis. The possible link between histopathological features of BC and further disease course has already been discussed previously. So, longer disease-free survival after the diagnosis of invasive lobular BC was reported already in a publication from 1994 [39]. However, recent studies could not identify survival differences between invasive lobular and ductal BC subtypes [40, 41]. The observed differences in the timing of BM might be related to the biological features of the BC subtypes. In particular, the invasive ductal BC might be prone to an earlier occurrence of distant metastasis due to their increased collective epithelial invasion, which is triggered by E-cadherin expression [42, 43]. In turn, the invasive lobular BC is characterized by higher rate of cell individualization resulting in slower development of distant metastasis [42, 43]. Our findings support the impact of BC subtype on the timing of BM.

Finally, there was an association between adjuvant breast radiation and late BM occurrence in the present study. The background of this link might be related to the effect of initial surgical strategy of BC treatment. So, individuals with late BM showed a higher proportion of mastectomy, after which radiation was not given. In case of breast-conserving surgery, residual tumor cells might sprout into the vascular and lymph nodal system and influence the risk and timing of distant metastases [44, 45]. This aspect might have led in the case of the late metastasized patients, most of whom were treated with mastectomy, to the presence of fewer residual tumor cells and thus the occurrence of distant metastases and thus brain metastases at a later time. The adjuvant radiation could promote the molecular changes in the residual tumor burden with the possibility of development of aggressiveness and resistance of BC [46, 47]. This circumstance might explain that in our group of late BM occurrence, the lack of breast irradiation resulted in fewer molecular changes and contributed to less early aggressiveness of BC. The irradiation of tumor cells increases the growth capacity and the transformation process. In this way, the tumorigenic effect is supported by the radiation [48]. It has been also reported that irradiation leads to greater heterogeneity of cells in breast tissue [49]. Although the exact role of residual tumor cells in the aggressiveness of BC BM is unknown [50], the described pathophysiological processes after initial BC treatment might condition the effect of adjuvant breast radiation on the timing of BM.

In summary, the reported predictors of TI between BC and BM underline the importance of an adjusted follow-up strategy, not limited to 10 years, depending on initial tumor and patient characteristics and previous BC treatment.

Limitations

The major limitations of this study were the retrospective and monocentric design as well as the incompleteness of patient and follow-up data. Moreover, our analyses were related to the specific group of BC patients with BM who received surgical therapy for BM that limits the generalizability of our study results to non-surgically treated BC BM patients. Finally, the relatively small sample size has limited the statistical power of the study results.

Conclusion

TI between BC and BM diagnosis impacts the survival prognosis after BM surgery. Individuals with BM occurring within 5 years after BC diagnosis are more likely to present with midline shift in preoperative MRI, identical ER status in BM, and show poorer OS. The initial BC tumor stage UICC III–IV was related to the risk of shorter TI (< 5 years). Moreover, later occurrence of BM (≥ 10 years) without any other distant metastases was common (16.1%) in our surgical cohort. This circumstance underlines the need for an individualized follow-up strategy of BC patients, not limited to 10 years. Especially, the patients with invasive lobular BC type and without initial adjuvant breast radiation were prone to later onset of first distant metastases in brain. Further comparative studies with larger data samples and inclusion of different BC subpopulations are needed for the confirmation of the presented study results.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11060-022-04043-2>.

Author contributions Conceptualization: AM and RJ; Methodology: AM, RJ; Formal Analysis: AM, RJ; Supervision: RJ; Writing—Original Draft Preparation: AM; Writing—Review and Editing: RJ, TFD, ANS, MDO, DP, YA, RK, PD, KHW, JH, CP, AI and US All authors have read and agreed to the published version of the manuscript.

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Data availability The data presented in the study are available on request from the corresponding author. All data are not publicly available due to ethical restrictions.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee of University Hospital Essen (local registration number: 17-7855-BO, 05.05.2020).

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