Original article

Incidence, risk factors and survival of patients with brain metastases at initial metastatic breast cancer diagnosis in China

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ABSTRACT

Purpose: To characterize the incidence, risk factors and survival of patients with brain metastases at initial diagnosis of metastatic breast cancer (MBC) in China.
Methods: The China National Cancer Center database was used to identify 2087 MBC patients diagnosed between 2003 and 2015. Clinicopathological features, treatment and survival information were extracted. Multivariable logistic and Cox regression were performed to determine factors predictive of brain metastases at MBC diagnosis and survival, respectively.
Results: Brain metastases occurred in ninety patients (4.3%) at MBC diagnosis, and in 27 patients (2.5%), 42 patients (7.2%) and 21 patients (5.2%) with hormone receptor positive, human epidermal growth factor receptor 2 negative (HR + HER2-), HER2-positive and triple negative breast cancer (TNBC), respectively. HER2-positive subtype (OR = 2.38; 95% CI 1.40—4.04; p < 0.0001), TNBC subtype (OR = 1.89; 95% CI 1.02—3.51; p = 0.005), and metastases to all three sites of bone, liver and lungs (OR = 3.23; 95% CI 1.52—6.87; p = 0.002) were shown to increase the risk of BM at MBC diagnosis. Median survival after BM was 23.7 months. First-line tyrosine kinase inhibitors (TKI) improved survival compared to trastuzumab-based regimen (44.9 vs 35.4 months, p = 0.09). Factors that independently decreased BM death risk were ECOG<2, brain metastases only and multidisciplinary treatment.
Conclusion: HER2-positive and TNBC subtypes have a higher incidence of BM at initial MBC diagnosis. Brain screening might be considered in patients with HER2-positive disease at MBC diagnosis, and further prospective randomized study is warranted.

Authors' contributions

Yiqun Li: manuscript writing, data collection and analysis. Qiao Li: manuscript writing, data collection and analysis. Hongnan Mo: management of patients and data collection. Xiuwen Guan: management of patients and data collection. Shaoyan Lin: management of patients and data collection. Zijing Wang: management of patients and data collection. Yimeng Chen: management of patients

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Introduction

Breast cancer is the most frequently diagnosed cancer and the fifth leading cause of cancer death in female population in China [1]. Brain metastases (BM), constituting 7.56% of all metastatic sites, represent an important cause of morbidity and mortality among patients with breast cancer [2]. With the improvement in imaging and development in systemic therapy, the incidence of BM in metastatic breast cancer (MBC) patients is reported to increase to 30% [3]. The mortality rate within 1 year was about 80%.

However, while the incidence of BM is increasing, current breast cancer guidelines do not recommend routine screening for BM, due to the lack of proven benefit on prognosis [4—6]. Thus, most brain metastases are detected based on neurologic symptoms, and active strategies such as surgery or whole-brain radiotherapy (WBRT) are often needed.

Currently, robust studies focusing on brain metastases at initial MBC diagnosis in China are lacking. Small retrospective studies involving patients with BM at any period of metastatic setting have yielded varying results [7,8]. In this study, we aimed to characterize the incidence of BM at MBC diagnosis, using the China National Cancer Center database. We also sought to identify risk factors associated with BM at MBC diagnosis, as well as to describe the treatment, survival and prognosis of these patients.

Materials and methods

Patients

Medical records of breast cancer patients treated at the China National Cancer Center were retrospectively reviewed. The China National Cancer Center database was used to identify metastatic breast cancer patients diagnosed between January 1, 2003 to December 31, 2015, covering a time span of 12 years. Patients were included if they met the following criteria [1]: histologically confirmed breast cancer with reliable estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) status, reviewed and reported by two independent breast cancer pathologists from the pathology department of the China National Cancer Center. ER/PgR positivity were defined as $\geq$ 10% positive tumor cells with nuclear staining by IHC and then $\geq$1% after April 2010, according to the new College of American Pathologists guidelines. HER2 status was assessed by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH). HER2 positivity was defined as IHC scoring 3+ or FISH amplified based on the ASCO guidelines [9]. [2] Recurrent or metastatic breast cancers. We excluded patients who were with more than one primary cancer except excised basal cell skin carcinoma and cervical carcinoma in situ in the past five years. Demographics of patients, clinical and pathological features, first site of disease recurrence, imaging results, treatment and survival information were extracted.

Brain metastases were defined as those with either metastases in the brain parenchyma and/or with metastases in the leptomeninges. Multidisciplinary treatment was defined as receiving systemic therapy combined with radiotherapy or surgery. Survival after BM was defined as the time from diagnosis of first brain metastases to date of death from any cause or last follow-up. Overall survival (OS) was defined as the time from initial metastatic diagnosis to the date of death from any cause or last follow-up.

Statistical analysis

Clinical and pathological features of patients were summarized and stratified by whether or not BM was developed at MBC diagnosis and compared across groups using chi square test. Multivariable logistic regression model was utilized to determine factors that could predict for the development of BM at initial MBC diagnosis. First-line treatment regimens were compared between patients with BM and without BM at MBC diagnosis using chi square test. Survival analyses after BM were estimated using the Kaplan—Meier method and compared between groups using the log-rank test. Prognostic factors associated with OS were analyzed using Cox regression model with 95% confidence interval (95%C.I.). All statistical analyses were performed using SPSS 23.0 software (SPSS Inc., Chicago, IL, USA).

Results

Patient and tumor characteristics

We identified 2087 metastatic breast cancer patients diagnosed between January 1, 2003 to December 31, 2015, and brain metastases occurred in ninety patients at initial diagnosis of MBC. Patient demographics and tumor characteristics stratified by brain metastases at MBC diagnosis are summarized in Table 1. Median age at diagnosis of MBC was 49 years for the whole cohort (range: 20—83 years), with 1768(84.7%) patients <60 years and 1303(62.4%) patients being pre-menopausal. One thousand and ninety-nine (52.7%) patients were HR + HER2-, 581 patients (27.8%)were HER2-positive, and 407(19.5%)patients had triple negative breast cancer (TNBC). One thousand two hundred and eighty-four (61.5%) patients received anthracyclines and 1135 (54.4%) patients received taxanes during neoadjuvant or adjuvant treatment. Among HER2-positive patients, 77 patients were stage IV at initial diagnosis, of the rest 504 patients who relapsed after previous treatment, 81(16.1%) received anti-HER2 therapy. The incidence proportion of brain metastases at MBC diagnosis was 4.3% for the whole cohort, 2.5%, 7.2% and 5.2% for HR + HER2-,HER2-positive and TNBC, respectively. The pattern of metastatic seeding between de-novo metastatic breast cancer patients (9.4%) and recurrent breast cancer patients with non-metastatic primary diagnosis (90.6%) were also analyzed (Supplementary Table 1). A higher frequency of bone and liver metastases were found in the de-novo metastatic breast cancer group. The frequency of brain metastases was not statistically different between the two groups.

The median time from diagnosis of initial breast cancer to brain metastases was 19.6 months (range: 0—181 months) with HR + HER2-subtype being the longest (36months), followed by HER2-positive (14.6 months), and TNBC (11.8 months) subtypes. On multivariable logistic analysis, patients with HER2-positive subtype (OR = 2.38; 95% CI 1.40—4.04; p < 0.0001), TNBC subtype (OR = 1.89; 95% CI 1.02—3.51; p = 0.005), and metastases to all three sites of bone, liver and lungs (OR = 3.23; 95% CI 1.52—6.87; p = 0.002) were shown to be at an increased risk of developing BM at diagnosis of MBC. Age<60, stage II or III disease were not

Table 1
Patient and tumor characteristics stratified by brain metastases at diagnosis of metastatic breast cancer.

	Brain Metastases at MBC diagnosis (n = 90)	No Brain Metastases at MBC diagnosis (n = 1997)	
	No.(%)	No.(%)	P value
Age (median)	49	49	
Age			
<60	79 (87.8%)	1689 (84.6%)	0.41
≥60	11 (12.2%)	308 (15.4%)	
Menopausal Status			
Pre-	66 (73.3%)	1237 (61.9%)	**0.03**
Post-	24 (26.7%)	760 (38.1%)	
Histology			
Invasive ductal	82 (91.1%)	1810 (90.6%)	0.96
Invasive lobular	3 (3.3%)	79 (4.0%)	
Other	5 (5.6%)	108 (5.4%)	
Nuclear Grade[a]			
I	1 (1.1%)	22 (1.1%)	0.47
II	25 (27.8%)	411 (20.6%)	
III	20 (22.2%)	231 (11.6%)	
Stage[a]			
I	7 (7.8%)	170 (8.5%)	0.19
II	27 (30.0%)	643 (32.2%)	
III	32 (35.6%)	486 (24.3%)	
IV	13 (14.4%)	178 (8.9%)	
Molecular Subtypes			
HR + HER2-	27 (30.0%)	1072 (53.7%)	**<0.0001**
HER2 positive	42 (46.7%)	539 (27.0%)	
TNBC	21 (23.3%)	386 (19.3%)	
Breast surgery			
Breast conservation	8 (8.9%)	153 (7.7%)	0.20
Mastectomy	75 (83.3%)	1763 (88.3%)	
None	7 (7.8%)	81 (4.1%)	
Anthracycline[a]			
Yes	58 (64.4%)	1226 (61.4%)	0.69
No	28 (31.1%)	540 (27.0%)	
Taxane[a]			
Yes	53 (58.9%)	1082 (54.2%)	0.98
No	33 (36.7%)	677 (33.9%)	
Adjuvant radiation[a]			
Yes	50 (55.6%)	852 (42.7%)	0.09
No	39 (43.3%)	964 (48.3%)	
Previous anti-HER2 therapy			
Yes	16	65	**<0.0001**
No	20	402	
Bone metastases			
Yes	29 (32.2%)	737 (36.9%)	0.37
No	61 (67.8%)	1260 (63.1%)	
Liver metastases			
Yes	17 (18.9%)	474 (23.7%)	0.29
No	73 (81.1%)	1523 (76.3%)	
Lung metastases			
Yes	34 (37.8%)	721 (36.1%)	0.75
No	56 (62.2%)	1276 (63.9%)	
All three sites			
Yes	9 (10.0%)	68 (3.4%)	**0.001**
No	81 (90.0%)	1929 (96.6%)	

MBC = metastatic breast cancer; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple negative breast cancer.
Bold values indicate statistically significant results.
Factors that associated with brain metastases at MBC diagnosis.
[a] Some of histological grades, clinical stage and treatment information at local hospitals were missing.

independent factors associated with risk of developing BM. Significant results are presented in Table 2.

Treatment

Ninety patients developed BM at MBC diagnosis. The tumor characteristics and treatment are summarized in Table 3. Systemic therapy and local therapy was administered in 83 (92.2%) patients and 81(90%) patients, respectively. Four patients received systemic therapy without local treatment and five patients received only local treatment. Two patients received best supportive of care. The first-line systemic therapy regimens received in patients with or

without BM at MBC diagnosis are detailed in Table 4. In the subgroup of HER2-positive patients, anti-HER2 tyrosine kinase inhibitors (lapatinib and pyrotinib)-based regimen were more frequently used in first-line setting compared to the non-BM group (44.0% vs 8.5%, p < 0.0001).

Survival and prognosis

Median follow-up time after the diagnosis of BM was 36.1 months (range: 1.2–125.3 months). At the time of this analyses, 61 (67.8%) of the 90 patients with brain metastases had died and 1- and 2-year OS rate was 78.7% and 48.1%, respectively. Median

Table 2
Multivariable logistic regression for the presence of brain metastases at diagnosis of metastatic breast cancer.

	OR	95%CI	P value
Molecular Subtypes			
HER2 positive vs. HR + HER2-	2.38	1.40–4.04	**<0.0001**
TNBC vs. HR + HER2-	1.89	1.02–3.51	**0.005**
Extracranial metastatic sites to liver, lung and bone (number of sites 3 vs < 3)	3.23	1.52–6.87	**0.002**

OR = odds ratio; HER2 = human epidermal growth factor receptor 2; TNBC = triple negative breast cancer.
Only significant results were presented (p < 0.05).

Table 3
Tumor characteristics and treatment of patients with brain metastases at metastatic breast cancer diagnosis.

	Total (n = 90) No.(%)
ECOG	
0–1	72 (80.0%)
≥2	18 (20.0%)
Symptoms of BM	
Asymptomatic	32 (35.6%)
Symptomatic	54 (60.0%)
Setting of identification	
Symptomatic diagnosis	54 (60.0%)
Occasional in imaging	36 (40.0%)
Number of BMs	
1–2	47 (52.2%)
≥3	36 (40.0%)
Maximum diameter of BM	
<3 cm	46 (51.1%)
≥3 cm	19 (21.1%)
Metastatic site of BM	
Cerebrum	64 (71.1%)
Cerebellum	31 (34.4%)
Midbrain	3 (3.3%)
Brain stem	7 (7.8%)
Leptomeninges	7 (7.8%)
Pachymeninges + leptomeninges	2 (2.2%)
Brain metastases only	29 (32.2%)
De novo BM	13 (14.4%)
GPA score	
≤2	20 (22.2%)
>2	57 (63.3%)
Treatment for brain metastases[a]	
WBRT	43 (47.8%)
SRS	24 (26.7%)
WBRT + SRS	5 (5.6%)
Surgery	21 (23.3%)
Systemic therapy	83 (92.2%)
Multidisciplinary treatment[b]	79 (87.8%)

ECOG = Eastern Cooperative Oncology Group performance status; BM = brain metastases; GPA = graded prognostic assessment; WBRT = whole-brain radiotherapy; SRS = stereotactic radiosurgery.
[a] Two patients received best supportive of care.
[b] Multidisciplinary treatment: systemic therapy combined with radiotherapy or surgery.

survival from the occurrence of BM was 23.7 months (95% CI 15.9–31.5 months). Median OS of different molecular subtypes following BM was 30.9 months (95% CI 25.8–36.0 months),27.7 months (95% CI 8.0–47.4 months), 18.0 months (95% CI 13.4–22.6 months) and 16.9 months (95% CI 13.4–20.5 months) for HR + HER2-,HR + HER2+,HR-HER2+ and TNBC, respectively. Compared with patients without BM, patients with BM at MBC diagnosis had a significantly shorter OS (44.6 months vs 23.7 months, p < 0.0001) (Fig. 1). There were no significant survival differences between patients with different types of brain metastases (Supplementary Figs. 1 and 2). Patients receiving multidisciplinary treatment survived significantly longer than those who received only one treatment strategy (26.8 vs 13.8 months, p = 0.004)(Fig. 2). In HER2-positive subgroup, patients receiving

first-line tyrosine kinase inhibitors (TKI) survived longer than patients receiving trastuzumab-based regimens, although the difference was not statistically significant (44.9 vs 35.4 months, p = 0.09). Table 5 summarizes the prognostic factors associated with survival after diagnosis of BM. Multidisciplinary treatment (HR: 0.30, 95% CI: 0.12–0.76, p = 0.01), brain metastases only (HR: 0.51, 95% CI: 0.28–0.95, p = 0.035), and Eastern Cooperative Oncology Group (ECOG) < 2 (HR:0.52, 95%CI:0.27–0.99,p = 0.047) were identified to be independent prognostic factors that decreased BM death risk.

Discussion

We presented, to our knowledge, the first and largest study that focused on patients with BM at initial MBC diagnosis in China. We found that HER2-positive and TNBC subtypes were at higher risk of developing BM at MBC diagnosis with an incidence proportion of 7.2% and 5.2%, respectively, and that patients with metastases to all three sites of bone, liver and lung were associated with higher odds of having BM at MBC diagnosis. Moreover, we reported for the first time, the survival outcomes by molecular subtypes in patients with BM at MBC diagnosis in China. The median survival following BM diagnosis was 23.7 months, ranging from 16.9 months in TNBC patients to 30.9 months in HR + HER2-breast cancer patients. Patients with metastases limited to the brain, receiving multidisciplinary treatment and with better performance status were independently associated with improved overall survival.

In patients with early stage breast cancer, the incidence of BM as a first site of recurrence has been looked at by several studies. The documented overall 2-year incidence has been reported as 0.5% for HR + HER2-, 1.1% for HER2-positive and 3.7% for TNBC. However, these studies focused on early stage patients, and the incidence proportion of BM among MBC patients could not be addressed. A few studies reported the proportion of BM at initial MBC diagnosis in different molecular subtypes. In the largest prospectively followed cohort of 1012 HER2-positive MBC patients, the registHER study reported a 7% of BMat MBC diagnosis [10]. This study was limited to patients in the United States, and the results might not be that generalizable to China. Jin et al. reported a proportion of 7.4% of BM at MBC diagnosis among 430 metastatic TNBC patients in China [7], but this study included only TNBC patients. Our study described the incidence of BM at initial MBC diagnosis across different molecular subtypes based on the largest sample size in China. Of note, due to the lack of recommendation of brain screening, the majority of patients were diagnosed after neurologic symptoms in our study, and the true incidence of BM in patients at MBC diagnosis was likely underestimated.

Several studies have tried to identify risk factors that were predictive of the development of BM [11,12], however, most of the previous experience focused on early stage breast cancer patients. Pestalozzi et al. evaluated data from 9524 women who were randomized into the International Breast Cancer Study Group clinical trials between 1978 and 1999. Risk factors predictive of BM as first recurrence included HER2-positive, estrogen receptor-negative,

Table 4
First-line systemic treatment regimens in patients with or without brain metastases at metastatic breast cancer diagnosis.

	Brain Metastases at MBC diagnosis (n = 90)	No Brain Metastases at MBC diagnosis (n = 1997)
	No.(%)	No.(%)
Chemotherapy		
Anthracycline	11 (12.2%)	407 (20.4%)
Taxane	48 (53.3%)	1085 (54.3%)
Capecitabine	32 (35.6%)	645 (32.3%)
Vinorelbine[a]	5 (5.6%)	341 (17.1%)
Gemcitabine	4 (4.4%)	174 (8.7%)
Bevacizumab	2 (2.2%)	28 (1.4%)
HER2-targeted therapy		
Trastuzumab + other therapies without lapatinib	10 (11.1%)	191 (9.6%)
Lapatinib + other therapies without trastuzumab	11 (12.2%)	13 (0.7%)
Trastuzumab + lapatinib + other therapies	3 (3.3%)	1 (0.1%)
Trastuzumab only	1 (1.1%)	1 (0.1%)
Trastuzumab + lapatinib only	0 (0.0%)	0 (0.0%)
Pyrotinib	0 (0.0%)	5 (0.3%)
Trastuzumab-based regimen	14 (15.6%)	193 (9.7%)
TKI-based regimen without trastuzumab[a]	11 (12.2%)	18 (0.9%)
No anti-HER2 therapy	17 (18.9%)	328 (16.4%)

MBC = metastatic breast cancer; HER2 = human epidermal growth factor receptor 2; TKI = tyrosine kinase inhibitors.
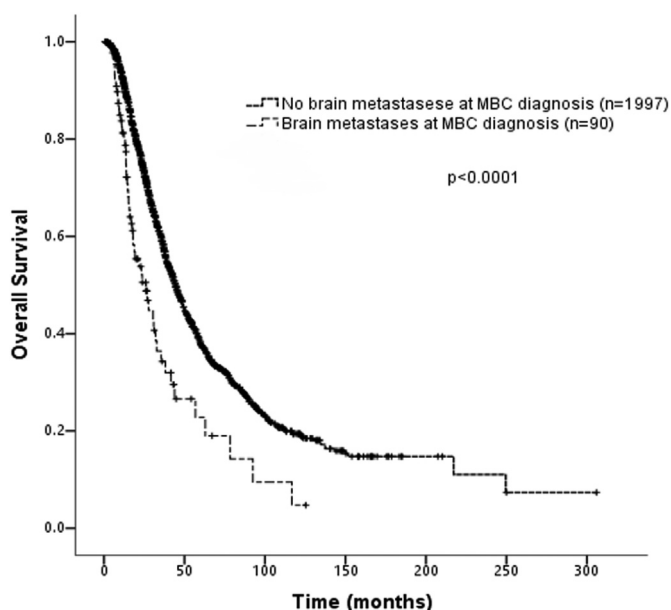 [a] p<0.05.

Fig. 1. Overall survival in patients with or without brain metastases at initial metastatic breast cancer (MBC) diagnosis.

Fig. 2. Overall survival following brain metastases stratified by multidisciplinary treatment.

node-positive and <35 years old [11], other factors such as stage 3 and larger tumor size have also been reported [7,13]. In the metastatic setting, only one study from the United States focused on patients with BM and newly diagnosed MBC, and HER2-positivity and TNBC were found to be associated with significantly greater odds of developing BM. Our study confirmed the association between tumor subtypes and BM development at MBC diagnosis in the Chinese population, and added on to previous work by finding that the extent of extracranial metastases was also suggestive of BM development. The risk of BM is significantly higher if two or more extracranial sites are involved [2].

Routine brain screening of brain metastases in asymptomatic patients was not recommended for breast cancer patients currently, due to the lack of survival advantage in retrospective studies [14]. However, with the rapid development of brain imaging and systemic therapy in breast cancer, these studies might need to
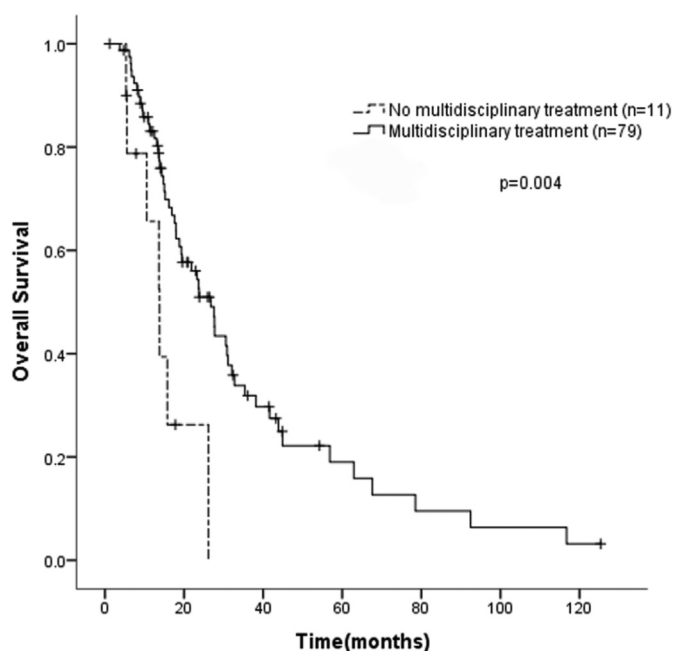
be interpreted with careful consideration. If BM is identified early, patients are typically in better performance status, have more available systemic therapy regimens and amenable to potentially less toxic approaches, such as SRS. Since HR + HER2-subtype has a low tendency to metastasize to the brain and TNBC has a poor prognosis regardless of BM, the benefit of brain screening is limited. On the contrary, HER2-positive subtype might be a good candidate for brain screening. The treatment landscape of systemic therapy in HER2-positive breast cancer brain metastases has changed dramatically in recent years. Novel anti-HER2 drugs have shown significant intracranial anti-tumor effect. In HER2CLIMB trial, tucatinib, in combination with trastuzumab and capecitabine, showed a significant 68% reduction in 1-year central nervous system (CNS) progression-free survival (PFS) compared with patients receiving placebo, with a respective CNS PFS duration of 9.9 months

Table 5
Univariate and multivariate survival analysis following brain metastases at metastatic breast cancer diagnosis.

Factor	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (<60/≥60)	0.51	0.23—1.14	0.10			
ECOG (<2/≥2)	0.53	0.29—0.98	**0.04**	0.52	0.27—0.99	**0.047**
HER2 positive/HR + HER2-	1.09	0.62—1.92	0.76			
TNBC/HR + HER2-	2.02	0.95—4.31	0.07			
De novo BM (Yes/No)	0.41	0.16—1.06	0.07			
Symptoms of BM (Yes/No)	1.15	0.66—2.01	0.62			
Number of BMs (>3/≤3)	1.13	0.66—1.95	0.66			
Leptomeningeal involvement (Yes/No)	1.14	0.51—2.55	0.74			
Brain only (Yes/No)	0.60	0.34—1.05	0.07	0.51	0.28—0.95	**0.035**
Local treatment (Yes/No)	0.41	0.17—0.95	**0.04**			
Systemic treatment (Yes/No)	0.35	0.12—0.98	**0.045**			
Multidisciplinary treatment[a](Yes/No)	0.32	0.14—0.73	**0.007**	0.30	0.12—0.76	**0.01**

ECOG = Eastern Cooperative Oncology Group performance status; BM = brain metastases; HER2 = human epidermal growth factor receptor 2; TNBC = triple negative breast cancer.
Bold values indicate statistically significant results.
[a] Multidisciplinary treatment: systemic therapy combined with radiotherapy or surgery.

versus 4.2 months (HR = 0.32; 95%CI:0.22—0.48; p < 0.0001) [15]. Other TKIs such as lapatinib and pyrotinib have also demonstrated brain activity [16,17], and new opportunities for antibody-conjugates are emerging [18]. In the current study, for HER2-positive subtype, approximately half of the clinicians chose to give TKI instead of anti-HER2 antibodies when BM was developed at MBC diagnosis, and the survival of TKI-based regimen appeared to be longer (44.9 vs 35.4 months, p = 0.09). Good control of both extracranial and intracranial lesions and extended survival could be expected in HER2-positive patients with BM in the near future. Whether routine screening of the brain should be performed in patients with initial MBC diagnosis is unknown at this time, however, we believe that it might be reasonable to carry out brain screening in HER2-positive patients who have the highest frequency of BM at MBC diagnosis and have more available systemic therapy regimens for both extra-and intra-cranial lesions. Further investigation of this clinical scenario are needed in the future.

In the current study, median survival following BM diagnosis was 23.7 months, with HR + HER2-being the most favorable subtype (30.9 months), followed by HR + HER2+ (27.7months), HR-HER2+(18.0 months) and TNBC(16.9 months). In a large retrospective study focusing on de novo stage IV patients with BM, a median survival of 14 months, 21months, 10 months and 6 months for HR + HER2-,HR + HER2+, HR-HER2+ and TNBC was reported [2]. The registHER study reported a median OS of 20.3 months for HER2-positive patients following BM at MBC diagnosis, and the survival for TNBC patients with BM at MBC diagnosis has been reported as 17.3 months [7,10], which were similar to our reports. The reason that HR + HER2+ subtype in our study did not show a survival benefit over HR + HER2-subtype as in other studies might be due to the limited use of anti-HER2 drugs in China where trastuzumab entered the market in 2002, and was not covered by health insurance until 2017. In fact, 40.5% of HER2-positive patients with BM did not receive anti-HER2 therapy in our study. Patients with no brain metastases at initial MBC diagnosis survived significantly longer than patients with brain involvement (44.6 vs 23.7 months, p < 0.0001). Notably, we found that even the median survival of TNBC subtype has reached more than 1.5 years after brain metastases at MBC diagnosis. The prolonged survival of BM patients support the importance of initial treatment strategies selection in managing brain events, avoiding long-term neurotoxic effects, as well as controlling extracranial diseases.

Brain metastases only, receiving multidisciplinary treatment, and ECOG<2 were factors associated with improved survival in the current study. Extracranial metastases have been shown to indicate poor prognosis in several studies and is updated as a strong independent prognostic factor within the breast graded prognostic assessment (GPA) [19—21]. Receiving chemotherapy, surgery or local treatment have individually been described as independent prognostic factors in breast cancer patients following BM diagnosis. However, previous prognostic studies mainly focused on BM that were developed during any period of MBC. Dawood et al. analyzed the survival of TNBC patients with BM as first recurrence, but did not find statistically significant independent prognostic factors in univariate analyses(12). Martin et al. also reported the factors that affect survival in patients with de novo BM, but failed to provide information on treatment due to the limitations of the Surveillance, Epidemiology, and End Results (SEER) database. We reported that when patients developed BM at initial diagnosis of MBC, multidisciplinary treatment including systemic therapy plus surgery or radiotherapy could prolong survival. Previous studies demonstrated that combining chemotherapy with radiotherapy, or active treatment involving surgery or SRS and chemotherapy were independently associated with better survival after BM diagnosis [22,23]. Multidisciplinary clinic experience have been described in some centers and might serve as a model that can be adapted in China to provide coordinated care for patients with such a challenging and complex disease [24,25].

Our study have several limitations. First, this was a single institution study, and some referral bias might exist. Second, the majority of patients were symptomatic at BM diagnosis because routine brain screening is not recommended. Therefore, the actual incidence of BM was likely to be underestimated. Third, the molecular subtypes were diagnosed on the primary tumor. Re-biopsy of metastatic lesions was not performed in the majority of cases, and the discordance of molecular subtypes could not be ruled out.

Conclusion

Our study provides insight into the incidence of brain metastases at initial metastatic breast cancer diagnosis in China. Brain screening might be considered in patients with HER2-positive disease at initial MBC diagnosis, and further prospective randomized trial is warranted. A coordinated care involving multidisciplinary treatment will become increasingly important in the coming years, with the rapid development of systemic therapy and extended survival of these patients.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.11.021.

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Ethics approval

The study was reviewed and approved by the Institutional Review Board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. The informed consent of the participants was exempted under the full review process of the ethics committee.

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