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.

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and data collection. Ye Zhang: management of patients and data collection. Dainan Zhang: management of patients and data collection. Shanshan Chen: management of patients and data collection. Ruigang Cai: management of patients and data collection. Jiayu Wang: management of patients and data collection. Yang Luo: management of patients and data collection. Ying Fan: management of patients and data collection. Peng Yuan: management of patients and data collection. Pin Zhang: management of patients and data collection. Qing Li: management of patients and data collection. Fei Ma: study design and supervision. Binghe Xu: study design and supervision. All authors have read and approved this manuscript, and agree to its submittal to this journal.

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, and 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 %10 positive tumor cells with nuclear staining by IHC and then ≥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-, 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-, 407(19.5%) patients had triple negative breast cancer (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 (36 months), 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 = 1.83; 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
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: 12–125.3 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

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**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) | 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-Histology | 24 (26.7%) | 760 (38.1%) | |
| **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** | | | |
| I | 1 (1.1%) | 22 (1.1%) | 0.47 |
| II | 25 (27.8%) | 411 (20.6%) | |
| III | 20 (22.2%) | 231 (11.6%) | |
| **Stage** | | | |
| 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** | | | <0.0001 |
| HR+/HER2- | 27 (30.0%) | 1072 (53.7%) | |
| HER2 positive | 42 (46.7%) | 539 (27.0%) | |
| TNBC | 21 (23.3%) | 386 (19.3%) | |
| **Breast surgery** | | | 0.20 |
| Breast conservation | 8 (8.9%) | 153 (7.7%) | |
| Mastectomy | 75 (83.3%) | 1763 (88.3%) | |
| None | 7 (7.8%) | 81 (4.1%) | |
| **Anthracycline** | | | |
| Yes | 58 (64.4%) | 1226 (61.4%) | 0.69 |
| No | 28 (31.1%) | 540 (27.0%) | |
| **Taxane** | | | |
| Yes | 53 (58.9%) | 1062 (54.2%) | 0.98 |
| No | 33 (36.7%) | 677 (33.9%) | |
| **Adjuvant radiation** | | | |
| Yes | 50 (55.6%) | 852 (42.7%) | 0.09 |
| No | 39 (43.3%) | 964 (48.3%) | |
| **Previous anti-HER2 therapy** | | | <0.0001 |
| Yes | 16 | 65 | |
| No | 20 | 402 | |
| **Bone metastases** | | | 0.37 |
| Yes | 29 (32.2%) | 737 (36.9%) | |
| No | 61 (67.8%) | 1260 (63.1%) | |
| **Liver metastases** | | | 0.29 |
| Yes | 17 (18.9%) | 474 (23.7%) | |
| No | 73 (81.1%) | 1523 (76.3%) | |
| **Lung metastases** | | | 0.75 |
| Yes | 34 (37.8%) | 721 (36.1%) | |
| No | 56 (62.2%) | 1276 (63.9%) | |
| **All three sites** | | | 0.001 |
| Yes | 9 (10.0%) | 68 (3.4%) | |
| 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.

* Some of histological grades, clinical stage and treatment information at local hospitals were missing.
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+, 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 BM at MBC diagnosis [10]. This study was limited to patients in the United States, and the results might not be 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,
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 meta-
static 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 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%)                                    |
| Taxane                                   | 48 (53.3%)                                    |
| Capecitabine                             | 32 (35.6%)                                    |
| Vinorelbinea                             | 5 (5.6%)                                      |
| Gemcitabine                              | 4 (4.4%)                                      |
| Bevacizumab                              | 2 (2.2%)                                      |
| 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    | 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.

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**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.
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 is 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+ (27.7 months), 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, 21 months, 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.

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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.

References

[1] Zheng RS, Sun KX, Zhang SW, Zeng HM, Zou XN, Chen R, et al. [Report of cancer epidemiology in China, 2015]. Zhonghua Zongliu Zazhi 2019;41(1):19–28.
[2] Martin AM, Cagney DN, Catalano PJ, Warren LE, Bellon JR, Punglia RS, et al. Brain metastases in newly diagnosed breast cancer: a population-based study. JAMA Oncol 2017;3(8):1069–77.
[3] Lin NJ, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol 2004;22(17):3608–17.
[4] Cardoso F, Senkus E, Costa A, Papadopoulo E, Aapro M, Andre F, et al. 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4) dagger. Ann Oncol 2018;29(8):1634–57.
[5] Ramakrishna N, Temin S, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32(19):2100–8.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in Oncology. Breast cancer. 2020 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf].

[6] Jin J, Gao Y, Zhang J, Wang L, Wang C, Cao J, et al. Incidence, pattern and prognosis of brain metastases in patients with metastatic triple negative breast cancer. BMC Cancer 2018;18(1):446.
[7] Xiao W, Li X, Yang A, Chen B, Zheng S, Zhang C, et al. Analysis of prognostic factors affecting the brain metastases free survival and survival after brain metastases in breast cancer. Front Oncol 2020;10:431.
[8] Wolff AC, Hammond ME, Schwartz JN, Hagerty RL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/Collaborative of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007;25(1):118–45.
[9] Brufsky AM, Mayer M, Rugio HS, Kaufman PA, Tan-Chiu E, Tripathy D, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Canc Res 2011;17(14):4634–43.
[10] Pestalozzi BC, Zahirsh D, Price RN, Holmberg SB, Lindner J, Collins J, et al. Identifying breast cancer patients at risk for central nervous system (CNS) metastases in trials of the international breast cancer study group (IBCSG). Ann Oncol 2006;17(6):935–44.
[11] Dawood S, Lei X, Litton JK, Buchholz TA, Horigayni GN, Gonzalez-Angulo AM. Incidence of brain metastases as a first site of recurrence among women with triple receptor-negative breast cancer. Cancer 2012;118(19):4652–9.
[12] Tonyali O, Coskun U, Yukoel S, Inanis M, Bal G, Akinan T, et al. Risk factors for brain metastasis as a first site of disease recurrence in patients with HER2 positive early stage breast cancer treated with adjuvant trastuzumab. Breast 2016;25:22–6.
[13] Miller KD, Weathers T, Haney LG, Timmerman R, Dicker M, Shen J, et al. Occult central nervous system involvement in patients with metastatic breast cancer: prevalence, predictive factors and impact on overall survival. Ann Oncol 2003;14(7):1072–7.
[14] Murphy RK, Loe S, Oksnes A, Paplomata E, Hamilton E, Huritz SA, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med 2020;382(7):397–609.
[15] Min Yan LB, Hu Xichun, Zhang Qingyuan, Ouyang Quchang, Feng Jifeng, Yin Yongmee, et al. Pyrotinib plus capecitabine for human epidermal growth factor receptor 2-positive metastatic breast cancer after trastuzumab and taxanes (PHENIX): a randomized, double-blind, placebo-controlled phase 3 study. Translational Breast Cancer Research 2020;1(31).
[16] Bachet T, Romieu G, Campone M, Diersas V, Cropet C, Dalenc F, et al. Lapatinin plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol 2013;14(13):94–71.
[17] Montemero F, Delaforge S, Barrios CH, Wuerstle R, Antron A, Brain E, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIb clinical trial. J. Ann Oncol 2020;31(10):1150–8.
[18] Zhuang Q, Wong RX, Lian WX, Li YQ, Wong FV. Validation of Modified Breast Gradated Prognostic Assessment for breast cancer patients with brain metastases: extra-cranial disease progression is an independent risk factor. Ann Palliat Med 2019;8(4):390–400.
[19] Ahn HK, Lee S, Park YH, Sohn JH, Jo JC, Ahn JH, et al. Prediction of outcomes for patients with brain parenchymal metastases from breast cancer (BC): a new BC-specific prognostic model and a nomogram. Neuro Oncol 2012;14(8):1105–13.
[20] Sprenduto PW, Mesko S, Li J, Cagney D, Aizer A, Lin NU, et al. Beyond an updated graded prognostic assessment (breast GPA): a prognostic index and trends in treatment and survival in breast cancer brain metastases from 1985 to today. Int J Radiat Oncol Biol Phys 2020;107(2):334–43.
[21] Ou D, Cao L, Xu C, Kirova Y, Chen JY. Upfront brain radiotherapy may improve survival for unfavorable prognostic breast cancer brain metastasis patients with Breast-GPA 0-2.0. Breast J 2019;25(6):1134–42.
[22] Nieder C, Dehike D, Hinz M, Gross AL. The challenge of durable brain control in patients with brain-only metastases from breast cancer. SpringerPlus 2015;4:585.
[23] Loh D, Hagg F, Edwards P, MacColl J, Brogna C, Bhangoo R, et al. Two-year experience of multi-disciplinary team (MDT) outcomes for brain metastases in a tertiary neuro-oncology centre. Br J Neurosurg 2018;32(1):53–60.
[24] McKee MJ, Keith K, Deal AM, Garrett AL, Wheelis AA, Green RL, et al. A multidisciplinary breast cancer brain metastases clinic: the university of North Carolina experience. Oncol 2016;21(1):16–20.