Clinical Study on Prognostic Factors and Nursing of Breast Cancer with Brain Metastases

Ying Zhou1, Kefang Zhong1, Fang Zhou*2

ABSTRACT
This paper aims to explore the clinical features and prognostic factors of breast cancer patients with brain metastases. To this end, the influencing factors such as clinical pathological data and therapeutic measures etc. on the prognosis of patients with BCBM treated in hospitals were retrospectively analyzed, and the proportional hazard model was established to make multivariate analysis. The results show that the disease-free survival time, whether with visceral metastasis, KPS score, whether with meningeal metastasis, brain metastasis number are significantly correlated to the survival time of patients with breast cancer brain metastasis (BCBM). Therefore, the disease-free survival time, whether with or without visceral metastasis, KPS score, the presence of meningeal metastasis, and the number of brain metastatic lesions are independent influencing factors on prognosis of patients with BCBM.

Key Words: Breast Cancer (BC), Brain Metastases (BM), Prognostic Factors, Nursing

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Introduction
Breast cancer is the most common malignant tumor in women. There are approximately 1.4 million new cases of breast cancer each year in the world, accounting for 22.9% of all women with malignant tumors; 460,000 women died of breast cancer, accounting for 13.7% of all women with malignant tumors. In 2013, there were 235,000 new cases of breast cancer in the United States, and 41,000 patients died of breast cancer (Posner, 1977). In China, the incidence of breast cancer has been rising rapidly in recent decades, and leapt to the top of women's malignant tumors; According to statistics, the annual incidence of breast cancer in China is 169,000, and about 45,000 died. The cause of breast cancer is not yet fully understood. The study found that the incidence of breast cancer has a certain degree of regularity, and women with high risk factors for breast cancer are prone to develop breast cancer. The so-called high-risk factors refers to various ones associated with the incidence of breast cancer, and the hazards that most breast cancer patients have are known as high-risk factors of breast cancer (Wroński et al., 1998). According to the China Cancer Registry Annual Report, the age-specific incidence rate of female breast cancer at the age of 0 to 24 years is relatively low, and it gradually increases after 25 years of age, reaches the peak in the 50 to 54-year-old group, and gradually declines after the age of 55 (Bilen et al., 2006). Family history of breast cancer is one risk factor for breast cancer. The family history means that someone in the first-degree relatives (mother, daughter, and sister) has the breast cancer. Although a series of progress have been made in the early diagnosis
and adjuvant treatment of breast cancer, 40 to 50% of patients will still have recurrence and metastases, while 20 to 40% of patients with advanced breast cancer will have brain metastases.

The presence of brain metastases in breast cancer patients means that the tumor has spread widely and often has a very poor prognosis. According to reports in the literature, the median time from diagnosis of breast cancer to the occurrence of brain metastases is 24-36 months; after diagnosis of brain metastases, the average survival time of patients varies from 2 to 14 months, and the 1-year survival rate is 20% (Brookmeyer et al., 2007). The current interventions for brain metastases from breast cancer often include surgery, radiation therapy, systemic chemotherapy, and targeted therapy. Radiation therapy includes whole brain radiation therapy and stereotactic radiosurgery techniques, both of which have their own characteristics and advantages. Because most chemotherapeutic drugs are difficult to pass through the blood-brain barrier, chemotherapy is generally not preferred unless the patient is accompanied by other visceral metastases. The treatment of BCBM should follow the principle of individualization, multidisciplinary comprehensive treatment, emphasis on both partial and total body, simultaneous improvement of quality of life and survival rate.

Although the survival time has prolonged after various treatments of BCBM, it is still a bottleneck in improving the quality of life of patients and prolonging survival (Nieder et al., 1998). Not only the treatment of brain metastases affects the patient’s prognosis, but other factors (such as age, general condition, pathological type, primary tumor control, presence or absence of extracranial organ metastasis, number and size of brain metastases, etc.) have also a deep influence on the patient survival. At present, there are no unified opinions on the influencing factors on the prognosis of patients.

There has been no uniform understanding of the influencing factors on the prognosis of BCBM, and different people have their own fixed characteristics. What’s more, there is also a lack of BCBM-related large-sample domestic studies. All these result in no universally acceptable prognostic evaluation system and treatment model in the industry. Therefore, the analysis of the clinical features and prognostic factors of brain metastases in breast cancer is of great significance in judging the prognosis of patients and establishing a reasonable treatment plan. The main purpose of this paper is to retrospectively analyze various factors affecting the prognosis of BCBM as well as the effects of different treatment methods on brain metastases, so as to provide the basis for clinical treatment decisions.

**Methods**

The medical records of breast cancer patients with brain metastases treated in our hospital from January 2000 to August 2013 were selected for retrospective analysis. The diagnosis of brain metastases in this study was made by experienced imaging and clinicians based on the clinical symptoms and imaging examination results (CT or MRI). The primary observation index includes: survival time after brain metastases. The secondary observation indexes include: age, clinical stage, lymph node metastasis status, ER, PR, HER2, brain metastasis appearance time, KPS score, brain metastasis symptom, number of brain metastases, extracranial metastases, brain metastases size, systemic treatment Intracranial tumor treatment (WBRT, SRS, or surgery), and time of death.

The classification of patients was based on the immunohistochemical results expressed by ER, PR and HER2 in the primary lesions. ER and PR immunohistochemistry results were determined: Before 2011, positive receptors were 10% of immunohistochemically positive cells. After 2011, according to the latest issued guide by American Society of Clinical Oncology and American College of Pathologists, the receptor positive criteria was 1% of immunohistochemical staining positive cells. HER2 results were determined: Those with "0 or +" immunohistochemical staining were judged as negative, those with "+++" were judged as positive, and those with "++" were verified by fluorescent immunohistochemical hybridization (FISH). Based on the expression of ER, PR and HER2 in primary lesions, the breast cancer is classified into 4 types: Luminal A (ER+ and/or PR+, HER2), Luminal B (ER+ and/or PR 10, HER2+), HER2 (HER2+, ER-, PR-) and triple-negative (ER-, PR-, HER2-) (Fenner et al., 2002).

The patient’s survival information was obtained through outpatient and telephone follow-up. The follow-up deadline was November 30, 2013, and the median follow-up time was 54.9 months. Overall survival was defined as the time from diagnosis of breast cancer to death due to...
various causes or follow-up termination. Survival time after brain metastases is defined as the time from the diagnosis of brain metastasis to death from various causes or follow-up termination. Disease-free survival time is defined as the time from first surgery to recurrence of disease.

Results and discussion
Of the 342 patients, 218 (63.7%) died, 76 (22.2%) survived, and 48 (14.1%) were lost to follow-up. Among the 218 dead patients, 132 were able to identify the cause of death. Analysis of the causes of death showed that 44.7% (59/132) of patients died of intracranial progression and 55.3% (73/132) of patients died of extracranial progression. The median age of brain metastases confirmed in the whole group was 47.8 years (25.3 to 79.9 years), and the median time from the first recurrence of breast cancer to the occurrence of brain metastases was 14.1 months (0 to 123.5 months). The median survival time after the brain metastases transfer was 14.3 months (0.0 to 86.2 months); the 1-year survival rate was 56.5%, the 2-year survival rate was 31.0%, and the 3-year survival rate was 16.5% (Figure 1 and Table 1).

Table 1. Overall characteristics of 342 patients with breast cancer brain metastasis

<table>
<thead>
<tr>
<th>Basic Features</th>
<th>Median value</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis</td>
<td>43.5</td>
<td>2.2-75.7</td>
</tr>
<tr>
<td>DFS</td>
<td>22.9</td>
<td>0-272.9</td>
</tr>
<tr>
<td>TTBMB</td>
<td>21.7</td>
<td>0-231.8</td>
</tr>
<tr>
<td>BMOS</td>
<td>14.3</td>
<td>0.0-86.2</td>
</tr>
<tr>
<td>OS</td>
<td>72.2</td>
<td>2.0-272.9</td>
</tr>
</tbody>
</table>

Table 2 shows that there were 305 cases (89.2%) 1 in the whole group of patients with the brain metastasis age <60 years old (89.2%), >60 years old, 37 cases (10.8%); for TNM staging: up to 201 cases in stage II (60.0%), 44 cases of stage I (13.1%), 56 cases of stage III (16.7%), 34 cases of stage IV (10.1%). There were 97 cases of Luminal A (31.3%), 66 cases (21.3%) Luminal B; 75 cases (24.2%) of HER2 positive cases, and 72 cases (23.2%) of triple negative types. Among them, 119 cases of HER2 positive patients were treated with anti-HER2 therapy (86.2%). In Brain metastases, the KPS scores were >70 points in 250 cases (77.4%), <70 points in 73 cases (22.6%). There were 99 cases (34.4%) of extracranial lesions, and 189 cases (65.6%) of extracranial lesions; 99 cases (31.6%) of brain metastases, and 214 cases (68.4%) of brain metastases; 55 cases of meningeal metastases (17.9%) and 253 cases (82.1%) of brain parenchymal metastases; 254 cases (74.3%) of visceral metastases with liver and lung; 223 cases (72.6%) of symptomatic brain metastases.

Table 2. Univariate analysis of clinical characteristics of 342 cases of brain metastases from breast cancer

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>n</th>
<th>Median survival time after brain metastasis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>305</td>
<td>14.0</td>
<td>0.739</td>
</tr>
<tr>
<td>≥60</td>
<td>37</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>44</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>201</td>
<td>15.2</td>
<td>0.432</td>
</tr>
<tr>
<td>III</td>
<td>56</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>34</td>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>

After brain metastases, 228 patients (86.0%) received whole-brain radiotherapy and 121 (43.6%) received stereotactic radiotherapy (SRS). 133 cases (48.2%) were treated with WBRT alone, 40 cases (14.5%) with SRS alone, 6 cases (2.2%) with surgery alone, 75 cases (27.2%) with WBRT + SRS, 16 cases (5.8%) with WBRT + surgery, 2 cases (0.7%) with surgery + SRS, and 4 cases (1.4%) with WBRT + SRS + surgery. In the whole group, the treatment with WBRT+SRS was longer than WBRT alone (21.1 vs 11.6 months, P=0.001) (Kocher et al., 1995). For the patients >3 with brain metastasis, the survival time with WBRT+SRS and WBRT alone was 38.8 (18.8 vs 8.9 months, P=0.005). WBRT+SRS and SRS alone had a survival time of (18.8 vs 18.2 months, P=0.042). 211 patients (70.8%) received radiochemotherapy, 55 (18.5%) received only chemotherapy, and 32 (10.7%) received radiotherapy alone. The median survival time of radiotherapy + chemotherapy vs. radiotherapy vs. chemotherapy was 17.7 vs12.7 vs 10.1 months (P=0.005) (Fig.2-5).

By combining clinical expertise and univariate analysis results, the clinically relevant indicators such as molecular type, KPS score,
visceral metastasis, meningeal metastasis, brain metastasis number, disease-free survival time, and maximum lesion diameter were included in the Cox proportional hazards model. Also, the multivariate analysis was performed using stepwise regression. The results showed that the disease-free survival time, whether or not accompanied with visceral metastasis, KPS score, meningeal metastasis, and number of brain metastatic lesions were independent factors affecting the prognosis of breast cancer metastasis (Table 3).

![Figure 2. Effect of DFS on Lifetime](image1)

![Figure 3. Effect of visceral metastasis on survival time](image2)

![Figure 4. Effect of KPS score on survival time](image3)

According to statistics, the RR ratio (risk ratio, relative risk ratio), i.e., \( \text{Exp}(B) \), is inversely proportional to the survival time, and the RR value >1 hints as a risk factor, and the greater the RR value, the more significant the impact of the corresponding factors on the reduction of survival; whereas the RR value <1 means the protection factor, and the smaller the RR value, the more significant the impact of the corresponding factors on the improvement of survival. In this study, disease-free survival time is long, and the high KPS score is the prognosis protection factor, while the visceral metastases, meningeal metastases, and multiple brain metastases are prognostic risk factors (Lin et al., 2004).

**Conclusion and prospect**

Disease-free survival time, whether with visceral metastasis, KPS score, whether with meningeal metastasis, number of brain metastatic lesions are independent factors in the prognosis of BCBM patients. Besides, the curative effect of WBRT+SRS is superior to WBRT alone in patients with multifocal brain metastases, and SRS can be used in place of WBRT+SRS in patients with less metastatic metastases.

Through analysis of the clinical features and survival of 342 patients with BCBM, this paper identified the clinical pathological characteristics of patients with brain metastases, found the factors to predict the prognosis of...
patients, and compared the effect of different treatment methods on survival time, so as to provide a clinical basis for the prognosis evaluation and treatment method selection of patients with brain metastases. However, there also exist some deficiencies with this study as follows: First, by retrospective analysis, the case selection bias of this study is inevitable, and then some patients’ information is missing. Second, because of the large time span of the study subjects, some patients’ contact information was changed, so follow-up was lost, which reduces the effectiveness of the results. Third, the sample size needs to be further expanded, especially when the patients are divided into different subgroups according to different treatment methods, which leads to too small sample size and further reduce the reliability of the results.

References