



## Clinical features, treatment, and prognosis of 16 breast cancer patients with ocular metastases

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### ABSTRACT

The incidence of ocular metastases in patients with disseminated breast cancer is increasing. This study aimed to investigate the clinical features, treatment, and prognosis of breast cancer patients with ocular metastases. For this purpose, a total of 16 patients were diagnosed with ocular metastases. Demographic, treatment, and other clinical data were obtained from patients' charts. The estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) statuses of the patients were obtained from the histopathologic reports. Demographic features were analyzed through descriptive statistics, and the Kaplan–Meier method was used for survival analysis. The results showed that among the 16 patients (median age: 41 years), 10 had ER-positive, 8 had PR-positive, and 3 had HER2-positive disease. The choroid was the most commonly involved structure (n = 8). Nine (56%) patients had blurred vision. Treatments for these patients included systemic therapy (six patients), radiotherapy (three patients), and combined therapy (seven patients). The median time from the diagnosis of breast cancer to the diagnosis of ocular metastasis was 52.9 months, and the median time from the diagnosis of metastatic breast cancer at any other site to the diagnosis of ocular metastasis was 21.3 months. The median overall survival (OS) was 136.5 months (95% confidence interval, 40.6–232.4 months), and the median survival duration after ocular metastasis was 32.4 months (95% confidence interval, 20.1–44.7 months). The OS of patients with unilateral eye involvement and bilateral eye involvement did not differ significantly (P = 0.573), nor did the OS of those diagnosed before 2000 and in 2000 or later (P = 0.409). In general, a breast cancer patient with ocular metastasis can have a good prognosis after therapy. However, large-scale clinical studies are needed to confirm our findings.

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### Introduction

Breast cancer is the most common malignancy in women with increasing incidence worldwide (1). In 2015, it has been reported that breast cancer accounts for approximately 15% of all new cancers in women in China (2). About 3%–8% of patients with newly diagnosed breast cancer have distant metastases at initial presentation (3). Moreover, about 20% of women with a history of early breast cancer will ultimately develop metastasis. Metastatic breast cancer is deemed an incurable disease with a poor prognosis (2–3 years of median overall survival) (4).

Lung, liver, bone, and brain are common sites of tumor metastasis, which are easily diagnosed because of some obvious symptoms and progress in detection methods. The breast is the most common site of origin of ocular metastatic tumors in women. In 49% of patients with ocular metastatic disease, the primary tumor origin is the breast (5). Presently, breast cancer ocular metastatic disease is discovered with increasing frequency due to enhanced survival and more accurate radiological examination tools (6).

In contrast to metastatic disease in other organs, ocular metastasis is usually asymptomatic (7). In

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previous trials, the incidence, clinical features, and survival of ocular metastases in patients with breast cancer were not similar (8). The reported incidence varied widely from 0.2% to 37% (9-11) and the reported median survival ranged from 5 to 26 months (12, 13). The varied incidence might be explained by the asymptomatic presentation of ocular metastasis as well as the lack of routine ocular examination for breast cancer patients. Therefore, recognition of ocular manifestation of metastatic disease and early treatment of metastases are essential for maximizing the life quality of these patients.

The incidence and survival of ocular metastasis may be affected by geographical areas or the particular ethnicity of the patients. Nevertheless, the reported data were limited, especially in Chinese patients. Therefore, this study aimed to assess the clinical features, management, and prognosis of breast cancer patients with ocular metastases in our hospital.

## Materials and methods

### Patients

We reviewed the medical records of all patients with a histologic diagnosis of breast cancer in our institution between January 1978 and December 2018. A total of 16 patients were diagnosed with ocular metastases, the diagnosis of which was based on the clinical findings and eye magnetic resonance imaging (MRI) or computed tomography (CT) in 14 patients (88%) (Figure 1) and fine-needle aspiration biopsy in 2 patients (13%) (Figure 2).

The following data were extracted from the clinical charts of all 16 patients: age, clinical disease stage, menopause status, pathological disease subtype, metastasis location, the clinical manifestation of metastasis, diagnosis method for metastasis, time from initial diagnosis of breast cancer to ocular metastasis, treatment modality, location and timing of other organ metastasis, and survival duration. The estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) statuses of breast cancer patients were obtained from the formal histopathologic reports. In brief, receptor positivity (+) is defined as positive nuclear staining equal to or more than 1% for ER and PR, and an immunohistochemistry score of 3+ or 2+ plus amplification ratio of  $\geq 2.0$  for HER2 (13, 14).

### Statistical analysis

The responses to therapy were assessed using Response Evaluation Criteria in Solid Tumors version 1.1. (RECIST 1.1). Additionally, the overall survival duration and survival duration after eye metastasis were assessed. The overall survival duration was defined as the time from the date of diagnosis of primary breast cancer to the date of death or last follow-up. The survival duration after eye metastasis was the time from the date of diagnosis of ocular metastasis to the date of death or last follow-up. Descriptive statistics were used to analyze demographic data, and the Kaplan–Meier method was applied to analyze the survival duration. All analyses were performed using statistical software PASW statistics 18.

## Results and discussion

### Patient characteristics

The median age at diagnosis was 41 years (range, 25–55 years) with 81% of patients younger than 50 years. Most of the patients ( $n = 13$ ; 81%) were in the premenopausal stage. Among these patients with the primary tumor, 12 (75%) had invasive ductal carcinoma and 2 (13%) had mucinous carcinoma. Additionally, 50% of the patients had stage III or IV at the time of diagnosis.

Ocular metastases were first detected in four patients. The other 12 patients were simultaneously diagnosed with ocular metastases and other organ metastases. In one patient, ocular metastasis symptoms led to the diagnosis of breast cancer. Ten (63%) patients were ER-positive, 8 (50%) were PR-positive, and 3 (6%) were HER2-positive. Since the Ki-67 status in some patients was unknown, the subtype of breast cancer was not determined.

The symptoms of ocular metastasis included blurred vision (nine patients), hemianopsia (three patients), shadows in the visual field (two patients), proptosis (two patients), metamorphopsia (one patient), palpebral edema (one patient), and ocular pain (one patient). The affected ocular sites included choroid (8 patients; 50%), orbit (4 patients; 25%), and other structures (4 patients; 25%). Two patients had bilateral ocular metastases.

The median time from breast cancer diagnosis to ocular metastasis was 52.9 months (range, 0–366.3 months), and the median time from metastasis to any

site to ocular metastasis was 21.3 months (range, 2.0–204.3 months).

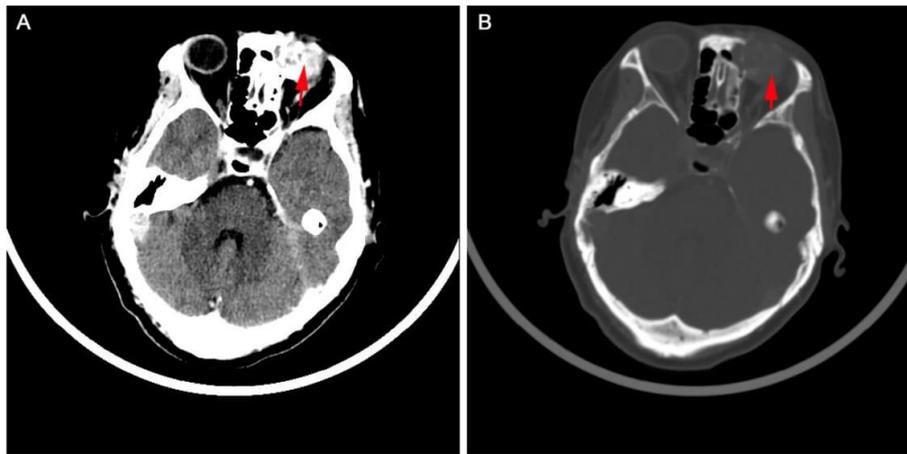
### Treatment

Among the 16 patients, 6 received systemic therapy alone including chemotherapy and/or hormonal therapy, 3 received radiotherapy alone for their ocular metastases, and 7 received combined therapy, 1 of whom received chemotherapy followed by ablation therapy and hormonal therapy. Finally, two patients exhibited partial response, six had stable disease, four had progressive disease, and four showed unknown response according to RECIST version 1.1.

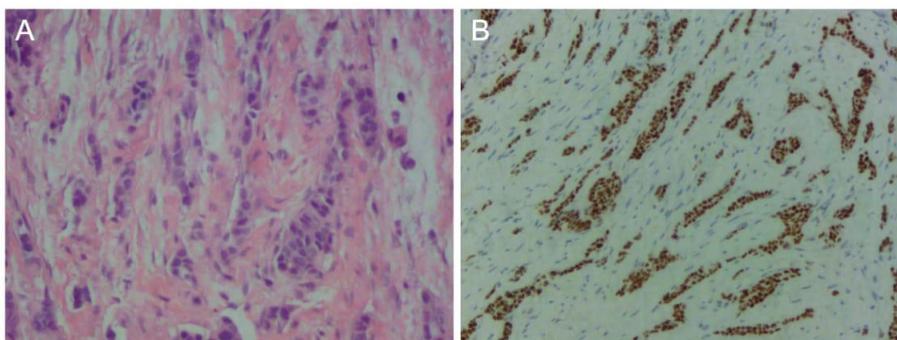
### Survival analysis

The median overall survival was 136.5 months (95% confidence interval, 40.6–232.4 months) (Figure

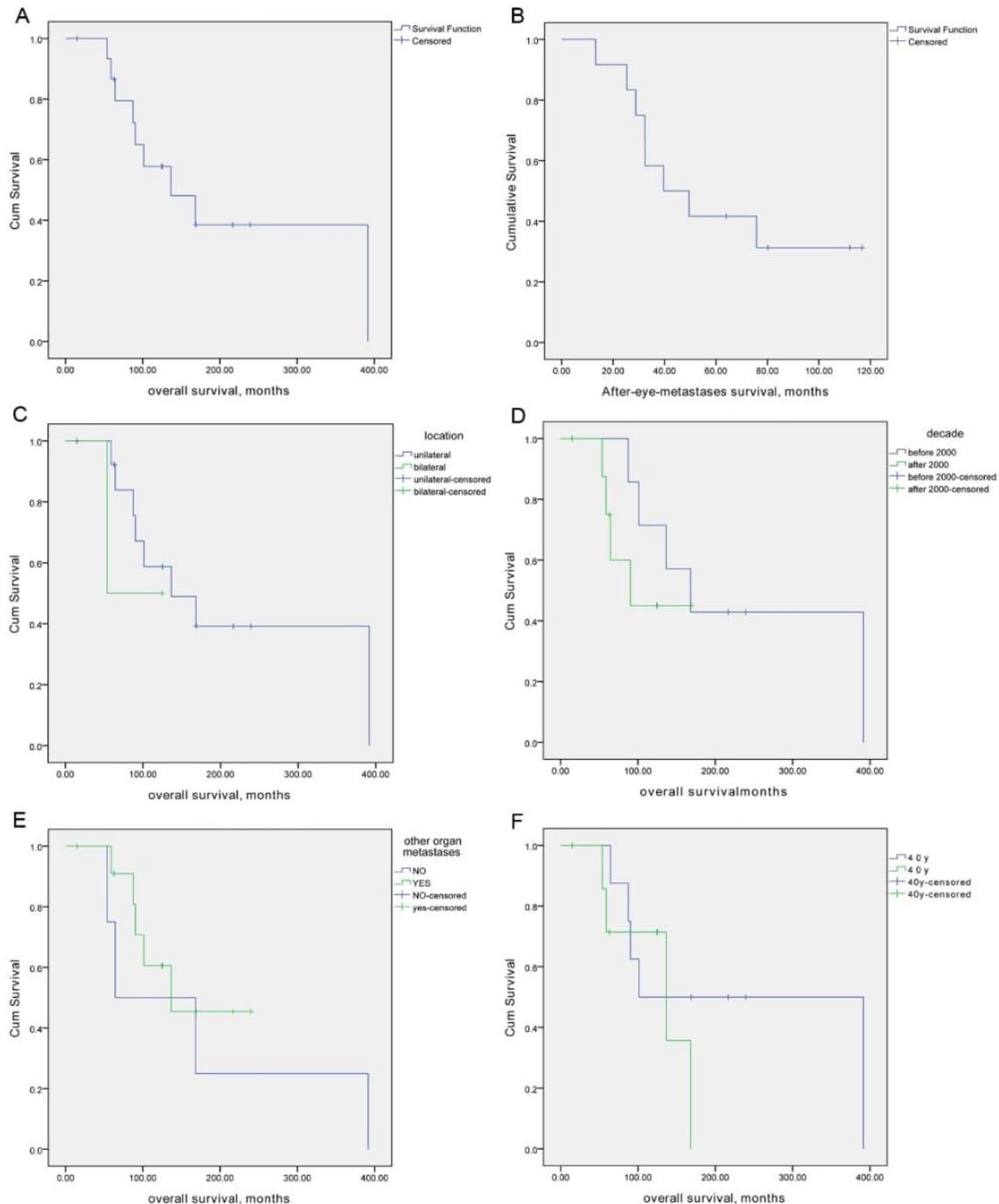
3A). The median survival duration after eye metastasis was 32.4 months (95% confidence interval, 20.1–44.7 months) (Figure 3B). There was no significant difference in overall survival between patients with unilateral eye involvement and those with bilateral eye involvement ( $P = 0.573$ ) (Figure 3C). Additionally, the overall survival of patients diagnosed with ocular metastasis before 2000, in 2000, and after 2000 was not considered significant ( $P = 0.409$ ) (Figure 3D). There was also no significant difference in overall survival between patients aged  $\leq 40$  years and those aged  $>40$  years at diagnosis ( $P = 0.445$ ) (Figure 3E). Furthermore, the overall survival of patients with ocular metastasis only and those with both ocular metastasis and other organ metastasis was not considered significant ( $P = 0.446$ ) (Figure 3F).



**Figure 1.** Computed tomography of a 53-year-old woman reveals orbital metastasis, which was the initial manifestation of breast cancer. (A) The arrow indicates the bone destruction of the orbital wall; (B) The arrow indicates the soft tissue of tumor.



**Figure 2.** Fine-needle aspiration biopsy pathological images. (A) Hematoxylin-and-eosin-stained breast cancer ocular metastasis (200 $\times$ ); (B) Immunohistochemical staining reveals estrogen receptor positivity (200 $\times$ ).



**Figure 3.** Overall survival analysis. (A)Kaplan–Meier estimates of the overall survival of 16 patients with breast cancer ocular metastases; (B) Kaplan–Meier estimates of the median survival duration after eye metastasis of 16 breast cancer patients; (C) Overall survival of patients with breast cancer ocular metastasis with unilateral eye involvement vs. bilateral eye involvement ( $P = 0.573$ ); (D)Overall survival of patients diagnosed with breast cancer ocular metastasis before 2000 vs. after 2000 ( $P=0.409$ ); (E)Overall survival of patients with age of  $\leq 40$  years vs.  $> 40$  years at diagnosis ( $P = 0.445$ ); (F) Overall survival of patients with breast cancer ocular metastasis alone vs. patients with both breast cancer metastasis and other organ metastasis ( $P = 0.446$ ).

Breast cancer is an important health problem in women and the most common tumor that can metastasize to the eyes (15). Although ocular metastasis as the primary presentation of breast cancer is rare, it is an important diagnosis to consider (16).

The incidence and survival rate of ocular metastasis may differ depending on the geographical area or race. However, data regarding this matter are limited, especially in Chinese patients. Therefore, this study aimed to assess the clinical features, management, and

prognosis of breast cancer patients with ocular metastases.

The incidence of ocular metastasis in autopsy studies is higher since the occult microscopic disease can be detected. An autopsy study by Bloch and Gartner (11) reported that ocular metastasis occurred in 37% of patients who died of breast cancer. However, asymptomatic presentation of ocular metastasis and the lack of routine ocular screening for all breast cancer patients made it difficult to detect ocular metastasis in clinical practice. Wiegel et al. (17) reported that 5% of patients with disseminated breast cancer had asymptomatic choroidal metastases. Tamura (9) found that 0.2% of patients who underwent surgery for breast cancer were diagnosed with ocular metastases during follow-up. As a retrospective study, we could not obtain the actual incidence rate of ocular metastasis, but the rate was estimated to be lower than 0.2% as more than 1,500 breast cancer patients received treatments in our hospital every year.

Studies have reported that patients with breast cancer ocular metastases have a poor prognosis, with median survival time ranging from 5 to 26 months (13, 14, 18). Nevertheless, we found that the breast cancer patients with ocular metastases had prolonged survival, with a median overall survival duration of 136.5 months (95% confidence interval, 40.6–232.4 months). In our study, most patients had ER- or PR-positive disease and received combined treatment, which may contribute to their prolonged overall survival.

In the United States, the median age of patients at diagnosis is 64 years. In China, the median age of patients at diagnosis is 48–50 years, with 62.9% of women diagnosed with breast cancer at the premenopausal stage (19). Our results showed that the median age at diagnosis was 41 years, and 81% of patients were at the premenopausal stage. Among these patients who represented an unusually young group, 10 (63%) were ER-positive, 8 (50%) were PR positive, and 3 (6%) were HER2 positive. Raffaele et al. (20) have consistently reported that the occurrence of choroid metastases in breast cancer patients is associated with the ER (100%) and PR (88.8%) expression in the primary tumor and with the luminal B molecular subtype (100%). This finding suggests that the receptor expression status and molecular

subtype of the primary tumor may have an influence on the metastasis of tumor to the choroid. However, their study has a major limitation, i.e., the receptor status in the intraocular lesion was not directly analyzed. Instead, only the receptor status in the primary tumor was analyzed. In our study, only two ocular metastatic tissues were obtained by fine-needle aspiration biopsy, which was a similar limitation of our study.

It has been reported that most ocular metastases occur in the choroid (56.25%–85%) and orbit (16.7–34.3%) (15, 21-23). In our study, 50% of the ocular metastases occurred in the choroid, which may be explained by the high vascularity of the choroid and microenvironmental factors such as the interactions between adhesion molecules on the surfaces of the cancer cells and ligand sites (24, 25).

Symptoms vary depending on the affected sites in the ocular region. In our study, patients with choroid metastases showed blurred vision, hemianopsia, shadows in the visual field, and metamorphopsia, while those with orbital metastases showed proptosis, palpebral edema, and ocular pain, which were similar to symptoms reported in previous studies (21, 22). Therefore, breast cancer patients who exhibit the above symptoms should undergo an ophthalmological examination including slit-lamp biomicroscopy. However, some patients with asymptomatic ocular metastases cannot be timely diagnosed (17). Hence, it is important to discuss the different methods of screening breast cancer patients for ocular examination.

Breast cancer patients with lung and brain metastases had a higher risk of asymptomatic metastases to the choroid (20). Our results revealed that 12 breast cancer patients had metastases to the eyes and other organs simultaneously, of which 4 were diagnosed to have lung and brain metastases prior to the occurrence of ocular metastases. This finding suggests that ocular screening should be considered when breast cancer patients have multiple metastases. Slit-lamp biomicroscopy, fluorescein angiography, fundus autofluorescence, and optical coherence tomography are useful for the diagnosis of choroidal metastases (26, 27). Additionally, tomographic imaging techniques such as CT or MRI should be performed as well. MRI was proven to be

superior to CT in difficult diagnostic situations. The pattern of tissue involvement as revealed by these imaging studies may suggest primary neoplasm. Orbital metastasis from breast cancer tends to be diffuse and irregular, often growing along with the rectus muscles and fascial planes (13). Unlike breast cancer metastases, choroidal melanoma demonstrates high signal intensity on T1-weighted images (28). Recently, Solav et al. (29) reported that positron emission tomography–CT could help identify breast cancer choroidal metastases. In our study, all 16 patients underwent CT or MRI examinations. Due to the long timespan, the defects of earlier diagnosis technologies may have missed some cases of ocular metastases.

Treatment for patients with ocular metastases is mainly local and palliative. Local treatments include external beam radiotherapy, proton beam radiotherapy, laser radiotherapy, photodynamic radiotherapy, and enucleation (30-33). Radiotherapy appears to be safe and effective. Breast cancer patients with choroidal metastases treated with 40 Gy of radiation given in 20 fractions had an objective response rate (comprising complete and partial responses) of 43% (14). The recommended total radiation dose for ocular metastases is 26–46 Gy (34), and the incidence rate of injury increases from 0% in patients receiving  $\leq 30$  Gy to 100% in patients receiving  $\geq 57$  Gy (35). Some studies have suggested using external beam radiotherapy in 10–25 fractions with a median dose of 2 Gy per fraction. Since most breast cancer patients with ocular metastases have metastases at other locations, these patients often receive combination therapy including chemotherapy, endocrine therapy, targeted therapy, and immunotherapy. Our results showed that 44% of patients underwent combined therapy with a response rate of 50%, which suggested that combination therapy may be recommended for ocular metastasis in breast cancer.

There were several limitations in this study. Due to the small patient population, we could not analyze the effects of different treatments on survival. Additionally, the ocular metastases in this study were mainly diagnosed by ocular screening. Thus, patients with breast cancer should undergo timely ophthalmological examinations in order to achieve long-term survival after active treatment. Given the

small sample size of our study, a large-scale of prospective trials are needed to confirm our results.

## Conclusion

In conclusion, ocular screening should be considered when breast cancer patients have multiple metastases. Most patients in our study had ER- or PR-positive disease. Combination therapy may contribute to prolonging overall survival for breast cancer patients with ocular metastases.

## Acknowledgments

None.

## Interest conflict

The authors declare no conflict of interest.

## Abbreviations

MRI: Magnetic Resonance Imaging; CT: computed tomography; ER: estrogen receptor; PR: progesterone receptor ; HER-2: human epidermal growth factor receptor 2; RECIST: **R**esponse **E**valuation **C**riteria in **S**olid **T**umors

## Ethical approval

All procedures performed in studies were in accordance with the ethical standards of the Hospital review board and the national research committee and with the 1964 Helsinki declaration and its later amendments.

## Informed consent

Informed consent was obtained from all individual participants included in the study.

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