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CNS metastases after breast cancer

# Incidence and relapse risk of intracranial metastases within the perihippocampal region in 314 patients with breast cancer

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ABSTRACT

*Purpose:* The safe prerequisite of hippocampal-sparing whole brain radiotherapy (HS-WBRT) for patients with breast cancer is unclear. This study investigated the risk and relapse of perihippocampal (PH) metastases in breast cancer.

*Methods:* Consecutive breast cancer patients with brain metastasis (BM) were reviewed. Metastases and hippocampi were contoured in cranial magnetic resonance imaging (MRI). The closest distance from metastasis to hippocampus was calculated. Clinical and radiographic variables were correlated with PH (in or within 5 mm around the hippocampus) metastasis. The risk of post-treatment PH recurrence was estimated.

*Results:* Three hundred and fourteen patients with 1678 metastases exhibited a median breast cancer-specific overall survival (OS) and OS after BM (BMOS) of 75.4 and 14.3 months, respectively. Hippocampal metastases were identified in 1.2% of metastases and 4.1% of patients. PH lesions comprised 3.5% of lesions in 11.1% of patients. The number and aggregated volume of BM were associated with PH disease probability (univariate). Only the number of BM significantly correlated with PH disease in the multivariate analysis. The patients with PH lesions exhibited more non-oligometastatic disease, increased tumor volume, and poor BMOS. One hundred and eleven patients without original PH lesions developed intracranial progression post-treatment. The risks of PH metastasis recurrence were 4.6% for WBRT and 6.8% for sub-therapeutic irradiation in the PH region. The increase in the absolute risk of PH recurrence with hippocampal-sparing irradiation was approximately 2%.

*Conclusions:* These novel findings indicate that BM from breast cancer exhibits low risks of metastases and relapse within the hippocampal avoidance region. Non-oligometastatic disease is associated with PH metastasis. Thus, HS-WBRT is considered safe and suitable for breast cancer.



Breast cancer is the most common malignancy in women and is associated with a high mortality worldwide. Approximately 10–30% of patients with breast cancer who received standard systemic treatment (which include chemo, radiation, and endocrine therapy, if appropriate) developed brain metastasis (BM), which is the principle cause of death [1]. Whole-brain radiotherapy (WBRT) is used as a standard treatment for patients with BM, which relieves BM-related symptoms and prolongs survival [2–4]. However, WBRT may impair neural stem and progenitor cells, which are located in the subgranular zone of the adult hippocampus; these impairments are associated with declines in short-term memory and recall [5–7]. Recent clinical evidence indicates that approximately one-third of patients treated with WBRT exhibited deterioration in neurocognitive function [8–10].

Based on evidence that radiation-induced damage to the hippocampus plays a considerable role in neurocognitive decline after cranial irradiation, hippocampal-sparing whole brain radiation therapy (HS-WBRT) has been proposed in several clinical trials [11–13]. The safe preconditions of the HS-WBRT are the low incidences of hippocampal metastasis and relapse to avoid increasing the risks of tumor instability or recurrence. Studies have reported low rates (8.0–8.6%) of incidence of perihippocampal (PH) metastasis in predominantly lung cancer patients, whereas the rate was approximately 0–6.3% in breast cancer patients [14–18]. Therefore, the assessment of the incidence of PH metastasis is necessary in a

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large sample of breast cancer patients, in whom BM is an important concern.

In this study, 314 patients with BM from breast cancer were retrospectively analyzed from a large cohort of breast cancer patients to comprehensively investigate the characteristics of PH metastasis. We hypothesized that HS-WBRT is appropriate and does not increase PH disease recurrence. The aims of this study are as follows: (a) identify the incidence of hippocampal and PH metastases, (b) investigate the relationship between clinical and radiographic variables and the risk of PH disease, and (c) estimate the risk of PH disease relapse after a sub-therapeutic irradiation dose to the PH region.

## Methods

### *Patients and study design*

Three hundred and seventy-eight female patients with BM from breast cancer were reviewed from consecutive cases that had undergone treatment at our hospital from January 2008 to October 2014. Three hundred and fourteen eligible patients with integrated clinical, radiographic, and follow-up data were selected. Appendix Fig. S1 illustrates the patient distribution and study design. This retrospective study was approved by local Human Investigation Committee. All patients provided written informed consent to have their medical records used for research purposes.

The inclusion criteria included advanced breast cancer with BM (with or without leptomeningeal disease) confirmed by gadolinium contrast-enhanced magnetic resonance imaging (MRI), with or without clinical symptoms and pathology, and without a history of BM treatment. Furthermore, radiographic materials (including MRI examination) for the response assessment of brain lesions were obtained from the baseline and subsequent follow-up. The response was evaluated by RECIST (Response Evaluation Criteria in Solid Tumor) criteria. The clinical variables included age at diagnosis, age at BM, tumor staging, local lymph node staging, clinical staging according to the 7th edition of the American Joint Committee on Cancer (AJCC), the status of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), first sites of metastasis and prognosis. The classification of biological subtypes was based on the 2011 St. Gallen International Expert Consensus [19].

### *Treatment and radiographic data*

First-line treatment data for BM, which included the modality of treatment, radiation target region, and dose, were collected for the response analysis. Axial images from pre-treatment and post-contrast MRIs with gadolinium contrast-enhanced T1-weighted sequence were imported to the Eclipse treatment planning system (version 7.3, Varian Medical Systems, Palo Alto, CA, USA). Each metastasis and hippocampus was contoured according to a published hippocampal contouring atlas developed by the Radiation Therapy Oncology Group (RTOG) [20]. The PH region was defined as a 5 mm three-dimensional margin surrounding the hippocampi, which comprised the hippocampus-sparing (HS) region. The closest distance from the border of a mass to the hippocampal margin was calculated. Appendix Fig. S2 delineates the PH distance and typical metastases. For patients without PH metastases at diagnosis who developed intracranial failure after treatment, the subsequent MRI images with these previously defined standards were imported for delineation to estimate the risk of PH relapse (Appendix Fig. S1).

### *Statistical analysis*

Events for the calculation of disease-free survival (DFS) included local–regional relapse and distant recurrences. The disease-specific overall survival (OS) analysis was calculated from the diagnosis of breast cancer to the date of breast cancer-related deaths or last follow-up. Breast cancer-specific overall survival after brain metastasis (BMOS) was calculated from the diagnosis of the BM to the date of breast cancer-related deaths (203 events) or the last follow-up. The patients who did not die were censored at the last follow-up date. The progression-free survival (PFS) of the first-line local treatment was calculated from the date of treatment to the date of confirmed intracranial failure or last contact date. Intracranial failure included existing lesion progression and/or the development of a new parenchymal lesion. For the patients who did not have a confirmed recurrence but had died, the PFS was calculated from the date of treatment to the date of death. The final data analyses were based on information received until April 1, 2015. At this time, 298 patients had follow-up information, and there were 209 deaths.

All calculations and statistical tests were performed using IBM SPSS 21.0 software (SPSS, Inc., Chicago, IL, USA). A binary logistic regression model was used to determine the relationship between clinical and radiographic variables and PH metastasis. According to the Kaplan–Meier method, the survival curves were compared using the log-rank test. The hazard ratios (HRs) with 95% CIs were calculated with a Cox proportional hazards model. All significance tests were two tailed with a significant $p$ value of <0.05.

## Results

The clinical characteristics and outcomes of the 314 eligible patients are listed in Table 1. Consistent with Asian breast cancer [21], the patients were predominantly premenopausal women (<50 years old) (72.3%), stage I–II (74.2%), hormone receptor (HR)-positive (58.6%), and luminal subtype (49.4%). The median follow-up was 61.5 months. The median BMOS and breast cancer-specific OS were 14.3 and 75.4 months, respectively. The median intracranial PFS after first-line local treatment was 10.6 months.

A total of 1678 metastases were analyzed with a mean of 5.3 metastases per patient (range 1–109). The brain lesion characteristics are shown in Table 2. Of note, meningeal metastasis without a parenchyma lesion occurred in 29 (9.2%) patients, which was not calculated for the tumor number, size, and distance to the hippocampus because of lack of a well-defined border of the meningeal lesion. Most patients (50.9%) were oligometastatic (1–3 metastases), with a relatively high metastasis incidence identified in the cerebellum (46.8% of the patients and 30.6% of all BM). The median aggregated volume of the parenchyma lesion was 4.6 (0.003–103.02) $cm^3$.

The incidence of hippocampal involvement was analyzed according to the closest distance between the border of the metastasis and hippocampus. BM was identified inside the hippocampal structures in 20 (1.2%) metastases and 13 (4.1%) patients. Thirty-eight (2.3%) lesions were located within 5 mm around the hippocampus in 28 (8.9%) patients. Overall, the PH lesions accounted for 3.5% of the total metastatic lesions in 11.1% of the patients. The rates of PH metastasis were increased when the hippocampal margin was expanded to 20 mm, as shown in Table 2.

Logistic regression analyses for PH metastasis were performed with the following variables: age at BM, nodal status, clinical stage, status of HR and HER-2, subtype, aggregated BM volume, number of BM, and concurrent meningeal lesions. Univariate analysis indicated that the number and aggregated volume of BM were associated with PH disease (Table 3). In the multivariate analysis, the number of BM was the only significant factor (4–9 *vs* 1–3, OR = 3.45, 95% CI 1.12–10.63, $p = 0.031$; $\geqslant 10$ *vs* 1–3, OR = 10.50, 95% CI 3.56–31.01, $p < 0.001$), and the risk of PH disease increased with an increase in the BM number.