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ORIGINAL ARTICLE

# Brain metastases as late breast cancer relapse. Single institution experience and review of the literature

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## Summary

***Purpose:*** *Approximately 40% of HER2-positive breast cancer patients will develop brain metastases, usually during the first 2-3 years following initial diagnosis and up to 2 years after overt metastatic spread. However, there are no data about brain metastases development as a late disease relapse. In addition, there are no data whether the high incidence of brain metastases is maintained in patients with HER2 overexpression even in late brain metastases. The aim of this paper was to determine the incidence of brain metastases and the HER2 status in patients who developed late relapse, at least 5 years after the initial diagnosis.*

***Patients and methods:*** *Among 384 consecutive breast cancer patients with late relapse, only 8 developed brain metastases. Archival pathological specimens of the primary tumors of those 8 patients were tested by immunohistochemistry (IHC) for HER2 status.*

***Results:*** *The incidence of late brain metastases was 2% (8/384). None of these patients had HER2 3+ primary breast cancer.*

***Conclusion:*** *This study shows that the risk for brain metastases in HER2 3+ breast cancer patients is very low or might be even absent as a late relapse. Absence of late brain metastases in HER2 3+ breast cancer might be attributed to specific biological characteristics of HER2 3+ carcinomas to develop brain metastases mostly in the early course of metastatic disease.*

**Key words:** brain metastases, breast cancer, HER2 3+, late relapse

## Introduction

Development of brain metastases in breast cancer is a relatively frequent complication of metastatic disease, with incidence of symptomatic metastatic lesions ranging from 10-20% [1,2].

The true incidence is probably much higher, because many patients die from metastases in other organ sites before central nervous system (CNS) symptoms develop [3]. In one autopsy study with 1,044 breast cancer patients 309 cases (29.6%) had brain metastases. Brain as the only metastatic site was seen only in 3 (0.97%) cases, and 86% had metastases to 6 or more organ sites other than CNS [4].

HER2 overexpression, negative steroid receptor status, presence of lung metastases, and young patient age are recognized factors contributing to higher incidence of brain metastases [5-7].

HER2 overexpression is often referred to as the most important factor, characterizing aggressive tumor type, with more potential to develop metastases in all visceral organs, and especially to the brain. Approximately 40% of HER2-positive breast cancer patients develop brain metastases, usually during first 2-3 years following initial diagnosis and up to 2 years after overt metastatic spread.

However, there are no data about brain metastases development as a late relapse. In addition, there are no data whether the high incidence of brain metastases is maintained in patients with HER2 overexpression even in late brain metastases.

Therefore, the aim of this paper was to determine

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the incidence of brain metastases and the HER2 status in patients who developed late CNS disease.

Late relapse is defined as development of any metastases or contralateral breast cancer, at a minimum of 5 years after initial diagnosis.

## Patients and methods

Hospital medical records of breast cancer patients with late relapses were retrospectively reviewed.

Only patients who developed any metastases or contralateral breast cancer after being disease-free for at least 5 years were included in this analysis.

Three hundred and eighty-four consecutive patients with late disease relapse (more than 5 years) were identified. Brain lesions in those with late brain disease were identified by brain CT scan. Archival pathological specimens of the primary tumors of patients with late brain relapse were tested by IHC (Herceptest ® DAKO) for HER2 status.

Analysed were also age at the primary diagnosis, histology and size of the primary tumor, nodal, and steroid receptor status, time interval to brain metastases development and presence of other metastatic sites. Survival and treatment were out of the scope of this paper.

## Results

The centralized organization of cancer care allowed us to capture most recurrences during the standardized patients' follow-up.

Among 384 patients with late relapse (median follow-up 9 years, range 5-34) only 8 (2%) patients developed brain metastases. Seven of them had multiple and one had a solitary metastasis.

IHC HER2 testing of the primary breast cancer revealed that none of the patients with brain metastases had HER2 3+ primary breast cancer.

The median age at the time of initial breast cancer diagnosis was 42 years (range 39-63).

The median time from initial breast cancer diagnosis to brain metastases development was 8.5 years (range 6-21).

Seven patients had brain metastases as a first metastatic site, and only one had lung metastases developed 4 months before brain metastases.

Histology of the primary tumor was predominantly ductal (7/8). Three patients had primary tumor ≥2 cm, 4 had primary tumor <2 cm, one patient underwent radical radiation therapy, therefore the size of her primary tumor, as well as nodal status were not assessed.

Three out of 8 patients had negative steroid receptors, and among them 2 had triple negative breast cancer. Two patients had 4 or more lymph nodes involved at the time of initial diagnosis.

Results are presented in Table 1.

## Discussion

It is generally accepted that brain metastases develop in aggressive breast cancers. Median time from breast cancer diagnosis to brain metastases development is approximately 34 months, and 16 months after the development of metastasis in other sites [8].

In the last few years, HER2 overexpression became one of the most notorious predictive factors for brain metastases. According to the literature, brain metastases develop in up to 42% of breast cancer patients with HER2 overexpression, but mostly during early metastatic spread [5-7].

**Table 1.** Characteristics of the patients and of primary breast cancer with late brain metastases

| *No.* | *Age (years)* | *Histology* | *Tumor size (T)* | *Nodal status* | *ER (score)* | *PGR (score)* | *DFS (months)* | *HER2 status* | *Metastatic sites before BM* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 42 | lobular | 2 | 1/11 | 0 | 0 | 144 | 2+ | none |
| 2 | 39 | ductal | 1 | 0/16 | 0 | 0 | 252 | 0+ | none |
| 3 | 43 | ductal | 1 | 0/6 | 5 | 6 | 120 | 0+ | none |
| 4 | 41 | ductal | 2 | 4/14 | 8 | 8 | 192 | 0+ | none |
| 5 | 58 | ductal | 1 | 9/10 | 3 | 2 | 72 | 1+ | none |
| 6 | 63 | ductal | NA | NA | 8 | 8 | 84 | 0+ | none |
| 7 | 49 | ductal | 2 | 1/11 | 8 | 0 | 72 | 1+ | lungs |
| 8 | 48 | ductal | 1 | 1/10 | 0 | 0 | 84 | 0+ | none |

ER: estrogen receptors, PGR: progesterone receptors, DFS: disease-free survival, BM: brain metastasis, NA: non applicable

Whether the risk for brain metastases remains that high, even in late relapses, has not been specifically addressed.

Reviewing the literature, we have been able to find only one study about late breast cancer relapse in the brain. The authors defined late relapse as relapse after at least 10 years. Eleven patients were identified and the median time to brain metastases was 16 years (range 11-30) [9]. However, the incidence of late brain metastases was not determined and the HER2 status was not assessed.

In one study, the incidence of brain metastases was prospectively monitored among 215 patients with breast cancer. Following the diagnosis of the first relapse, 31 patients developed brain metastases after a median of 13 months. The highest incidence was recorded in patients with short disease-free interval (<24 months, p=0.008), lung metastases as first relapse (p=0.0001), absence of bone metastases at first relapse (p=0.008) and negative hormone receptors status (p=0.0002). The 2-year incidence of brain metastases was 6 vs. 37% in patients with positive and negative hormone receptors status (p= 0.0001) and 24 vs. 7% in patients with and without lungs metastases (p= 0.0001) [10]. However, HER2 status in this study was not determined, and it is unknown how many patient developed brain metastases as a late relapse.

In a recently published study, more than 600 early breast cancer patients were followed prospectively until brain metastases development [11]. After a median follow-up of 45 months, brain metastases were registered in statistically significantly higher percentage in patients with HER2 overexpressing breast cancer (9.0 vs. 1.9%) with similar incidence as a first-site relapse (30 vs. 29%). The authors discussed several explanations for higher brain metastases risk in HER2 positive breast cancer. The basic conclusion was that limited drug delivery through the blood-brain barrier and trend to prolonged survival in metastatic stage was the most logical explanation. The authors also stated that the potential role of chemokine-mediated chemotaxis in breast cancer with tropism for brain cannot be underestimated.

Actually, there are data that the chemokine receptor CXCR4 and its ligand SDF-1 alpha (stromal-cell-derived factor-1 alpha) are expressed in organs that are frequent sites of breast cancer metastasis [12]. It has also been proved that CXCR4 expression is associated with HER2 overexpression/ amplification [13] and that expression of SDF-1 can increase the vascular permeability and penetration of HER2 overexpressing breast cancer cells through human blood-brain barrier [14].

Several other molecular characteristics that could enhance the development of brain metastases in HER2 positive breast cancers were also analysed.

Vascular endothelial growth factor (VEGF) was quantitatively measured in tumor cytosol from 362 consecutive patients with breast cancer and compared with disease-free interval and relapse sites. Patients whose primary breast cancers had highest levels of VEGF had also the highest incidence of brain metastases [15].

In another experimental study, expression of mRNA from several metastases suppressor genes (MSG), particularly in Maspin (serpin B5) was compared within breast cancer primaries, brain metastases and breast cancer cell lines. Using RT-PCR it was confirmed that MSG Maspin is reduced in brain metastases as compared with its expression in primary breast cancers and in bone metastases [16].

Some other breast cancer characteristics have also been analyzed as potential predictive factors for brain metastases development.

No relationship between primary tumor size and nodal status and development of brain metastases has been confirmed in some earlier studies [17,18]. However, in a recently published study [11], tumor size larger than 2 cm and at least one positive lymph node were predictive for brain metastases if accompanied with HER2 overexpression.

Patients with late relapse represent a very selected subgroup of breast cancer that has not been extensively studied, especially regarding HER2 status and brain metastases.

To the best of our knowledge, this is the first report of breast cancer brain metastases developed as a late relapse, with a focus to HER2 status of the primary tumor.

In our analysis the overall incidence of brain metastases was 2% among 384 patients with any late relapse.

The results of the HER2 testing in the subgroup of patients with brain metastases was quite unexpected because none of the patients had HER2-overexpressing primary breast cancer.

According to this result it seems that the risk for late brain metastases in HER2 3+ breast cancer is very low or might be even absent.

Only one (12.5%) of the patients had previously confirmed lungs metastases, while all the others actually had brain metastases as a first-documented late relapse site.

Breast cancer is a very heterogeneous disease, with quite unpredictable definite outcome, even among patients with similar age, initial stage, steroid receptor and HER2 status, and treatment as well.

Even though many studies explored various as-

pects of brain metastases, it is obvious that we still do not know why some patients develop brain metastases even many years after primary breast cancer was "cured", and some never do so even if breast cancer had notorious characteristics for brain metastases development like HER2 overexpression.

The absence of HER2-overexpressing primary breast carcinoma in our patients with late relapse in the brain could be a consequence of sample bias, but this is highly unlikely since the centralized organization of cancer care in our institution allow us to register most, if not all, recurrences.

A more intriguing hypothesis is that the absence of late brain metastases in HER2 3+ breast cancer could be attributed to specific biological characteristics of HER2 3+ carcinomas to develop brain metastases mostly in the early course of metastatic disease.

This is a hypothesis that should be explored in depth with a higher number of patients and with more sophisticated molecular analysis of the primary breast cancer.

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