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Original Research

Prognostic factors and survival according to tumour subtype in women presenting with breast cancer brain metastases at initial diagnosis

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Progesterone receptor;
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Abstract ***Background:*** The presence of brain metastases at the time of initial breast cancer diagnosis (BMIBCD) is uncommon. Hence, the prognostic assessment and management of these patients is very challenging. The aim of this study was to analyse the influence of tumour subtype compared with other prognostic factors in the survival of patients with BMIBCD.
Methods: We evaluated women with BMIBCD, reported to Surveillance, Epidemiology and End Results program from 2010 to 2013. Patients with other primary malignancy were excluded. Univariate and multivariate analyses were performed to determine the effects of each variable on overall survival (OS).
Results: We included 740 patients. Median OS for the whole population was 10 months, and 20.7% of patients were alive at 36 months. Tumour subtype distribution was: 46.6% hormone receptor (HR)+/HER2−, 17% HR+/HER2+, 14.1% HR−/HER2+ and 22.3% triple-negative. Univariate analysis showed that the presence of liver metastases, lung metastases and triple-negative patients (median OS 6 months) had worse prognosis. The HR+/HER2+ subtype had the longest OS with a median of 22 months. In multivariate analysis, older age (hazard ratio 1.8), lobular histology (hazard ratio 2.08), triple-negative subtype (hazard ratio 2.25), liver metastases (hazard ratio 1.6) and unmarried patients (hazard ratio 1.39) had significantly shorter OS.

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Conclusions: Although the prognosis of patients with BMIBCD is generally poor, 20.7% were still alive 3 years after the diagnosis. There were substantial differences in OS according to tumour subtype. In addition to tumour subtype, other independent predictors of OS are age at diagnosis, marital status, histology and liver metastases.
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1. Introduction

Breast cancer represents the second most frequent cause of brain metastases after lung cancer, with metastases occurring in 10–16% of the patients [1]. The incidence of brain metastases seem to have increased in recent years, this is likely due to prolonged survival of patients receiving more efficient treatments and the availability of better imaging techniques that lead to increased detection of this event [2].

Brain metastases in breast cancer patients represent a catastrophic event that portends a poor prognosis, with a median survival that ranges from 2 months to 25.3 months despite the treatment [3–6]. In addition, brain metastases are a major cause of morbidity, associated with progressive neurologic deficits that result in a reduced quality of life [7].

Previous studies have identified the subgroups of patients with triple-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer as having an increased risk for the development of brain metastases [8–11], with up to half of patients with HER2-positive metastatic breast cancer experiencing brain metastases over time [12]. Tumour subtypes are also an important factor for the median time interval from primary diagnosis to the development of brain metastases; a recent large study showed shorter intervals for triple-negative and HER2-positive patients, and longer periods for oestrogen receptor positive tumours [13].

Brain metastases generally occur as a late event in the natural course of breast cancer. Most of them will be detected after a median of 32 months from the initial cancer diagnosis [3]. Therefore, the analysis of prognostic factors and survival of this patient population can be confounded by the potential changes that cancer cells might develop at the time of distant relapse, as well as potential changes related to treatment exposure. The presence of brain metastases at initial diagnosis of breast cancer is less common. There is a lack of data about patient characteristics and prognostic factors in this unique group of patients, which makes the prognostic assessment and management very challenging.

The aim of this study was to analyse the influence of tumour subtype compared with other prognostic factors in the survival of patients who present with brain metastases at the time of initial diagnosis of stage IV breast cancer.

2. Materials and methods

2.1. Data source and study design

We obtained data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, using the 18 registry (1973–2013) database [14]. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28% of the US population. The SEER Program registries routinely collect data on patient demographics, primary tumour site, tumour morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. More recently, SEER started collecting sites of metastasis at initial diagnosis since 2010, because of this, we used that year as the starting point for our study.

We extracted all cases of women with brain metastases at the time of initial diagnosis of microscopically confirmed stage IV breast cancer, diagnosed between 2010 and 2013. We selected women with only one primary malignancy in their lifetime.

Study variables included age at diagnosis, race, year of diagnosis, histology, tumour grade, tumour subtype, type of breast surgery, radiation therapy, laterality, marital status, site of metastases, survival months and vital status. Four tumour grades were collapsed into 3 grades, with grade 4 merged with grade 3 tumours. Histology codes were grouped according to frequency into five categories using the WHO classification (ductal, lobular, mixed ductal and lobular, mucinous and other carcinoma). Tumour stage was registered according to the American Joint Committee on Cancer Staging System seventh edition. Tumour subtypes were classified according to the breast subtype variable as: hormone receptor (HR)-positive/HER2-negative, HR-positive/HER2-positive, HR-negative/HER2-positive and triple-negative. The variables metastasis at diagnosis to bone, liver and lung were used to define other sites of metastases.

The University of Iowa Institutional Review Board exempted this study from review because patients cannot be identified. This study was approved by Scientific and Ethical Committee of GOCS.

2.2. Statistical analysis

Descriptive statistics, including frequencies, medians and proportions, were used to evaluate characteristics of

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