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Original Article

Prognostic factors in patients with metastatic breast cancer at the time of diagnosis

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ABSTRACT

Approximately 90% of breast cancer mortality is due to metastases that are resistant to adjuvant therapies. Thus, assessment of factors associated with clinical outcomes in patients with advanced breast cancer is of significant importance. Despite the recent improvement in early detection, between 5 and 10% of breast cancer patients are diagnosed with metastasis at initial presentation or, rarely, before the primary breast cancer has been identified. These patients typically have poorer survival outcomes compared to those who develop distant metastasis subsequently. Yet, the prognostic relevance in these patients has not been intensively explored. In this study, we analyzed breast cancer patients with distant metastasis at the time of diagnosis between 1997 and 2010 ($n = 194$) to identify the clinicopathological factors significant for overall survival. By univariate analysis, race, estrogen receptor (ER) and progesterone receptor status were significantly associated with overall survival, while race and ER remained independent factors in multivariate analysis. Being Caucasian and overexpressing of ER both showed a significantly decreased hazard of death ($P = 0.015$ and 0.017, respectively). Reflecting these findings, the overall survival differed significantly between breast subtypes, with the luminal subtype and triple negative disease being associated with the longest and worst survival, respectively. Further, multi-organ involvement was associated with a worse prognosis than those with single organ metastasis, whereas no significant difference in survival was found between the different anatomic sites (bone, viscera and brain). Our findings suggest that it is predominantly the intrinsic nature of the tumor along with the genetic makeup of the patient that predicts the prognostic outcome in those patients with advanced disease at presentation.

Introduction

Breast cancer is the most common cancer among women in the United States and the second leading cause of cancer death. In 2010, there were over 1.6 million newly diagnosed breast cancer cases, and near half a million women died of breast cancer worldwide [1]. There is pronounced variation in breast cancer mortality across regions and countries, with about 40,000 annual breast cancer deaths among US women [2]. Approximately 5–10% of breast cancer patients are diagnosed with metastasis at initial presentation, and overall 20% will eventually develop metastasis [3]. The development of metastases dramatically worsens the prognosis. About 90% of breast cancer mortality is due to metastases that are resistant to adjuvant therapies [4].

Metastatic breast cancers represent a heterogeneous population with a diverse clinical course. Although the median survival ranges from 15 to 27 months in stage IV breast cancer despite more aggressive disease management and the more effective therapeutic agents in recent years [5–7], the overall survival rates vary significantly among patients. This highly unpredictable clinical behavior reflects the biologic heterogeneity of the disease. Thus, it is of significant importance to assess the clinicopathologic factors associated with clinical outcomes in this group of patients to select appropriate treatment strategies in the pursuit of individualized medicine.

The prognostic factors in patients with early-stage breast cancer have been extensively studied. To date, a number of factors with prognostic significance in early-stage breast cancer have been established, including age, race, tumor size, nodal status, histologic grade, estrogen receptor (ER), progesterone receptor (PR) and HER2 status, with the axillary nodal status being arguably the most significant prognostic indicator [8]. On the other hand, the prognostic factors in patients with stage IV breast cancer have been

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less intensively studied. The reported favorable prognostic factors in patients with advanced breast cancer include the hormonal receptor status of the primary tumor, bone and soft tissue only metastases, a small number of metastatic sites, a long relapse-free interval, and a good performance status [3,9–13]. However, these studies combined the patients with distant metastases at diagnosis with those developed metastases during follow-up. Studies solely focusing on the breast cancer metastasis at presentation are limited. Thus, this study was aimed to determine the significant clinicopathological factors predicting overall survival in that subset of patients with advanced breast cancer at diagnosis.

Materials and methods

After approval by the University of Alabama at Birmingham Institutional Review Board, the UAB Tumor Registry was searched to identify breast cancer cases with associated distant organ metastasis between 1997 and 2010. A total of 552 cases with associated distant (bone, visceral organs, brain) metastasis were identified. Of those, 206 patients had distant metastasis at the time of diagnosis. The patients' demographic data and the pathologic features of the primary tumor were recorded, including age, race, tumor size, tumor type, histologic grade, number of positive lymph nodes, ER, PR and HER2 status. The accuracy of the data was further validated for each patient using the electronic medical record and/or Surgical Pathology data base. Given that the receptor status of breast cancer is unarguably significant for prognosis, the cases with absence of any recorded receptor status were excluded, leading to 194 cases included in the study. All patients received systemic therapy (endocrine therapy, targeted therapy, cytotoxic chemotherapy, or their combination). All but 26 patients with positive hormonal receptors received endocrine therapy, based on physician and patient discussions. Twenty-four of 87 patients with HER2-positive disease received HER2-targeted therapy with Trastuzumab. All but 33 patients with receptor-positive disease received cytotoxic chemotherapy.

The ER and PR expression status was assessed by immunohistochemistry (IHC), and HER2 protein overexpression and/or gene amplification was evaluated by IHC or fluorescent/chromogenic *in situ* hybridization (FISH/CISH) as previously described [14,15]. ER and PR positivity was defined as $\geq$1% of tumor cell nuclei with immunoreactivity. HER2 positivity was defined as either a 3+ IHC score (uniform and intensity membrane staining of >30% of tumor cells) or a positive ISH result. An IHC core of 2+ or an equivocal FISH result for HER2 was repeated by performing a Ventana INFORM HER2 Dual ISH assay (Tucson, AZ, USA), which achieved either a positive or a negative result (http://www.ventana.com/product/1553?type=2013). When the receptor (ER, PR or HER2) status was reported to be unknown in the Tumor Registry and in the medical chart, the patient was coded as having unknown receptor status for that particular receptor.

Classification of breast cancer subtypes was based on the results of ER, PR and HER2 testing as previously described [16]. In brief, tumors were defined as luminal (ER+ and/or PR+), HER2 (ER−/PR−/HER2+), or triple-negative carcinoma (ER−/PR−/HER2−). Tumors with unknown ER and PR status were excluded from the subtype analysis due to the incapability for subtype classification. The luminal subtypes were subclassified into ER+ and/or PR+/HER2− and ER+ and/or PR+/HER2+. While some studies have defined them as luminal A and B, respectively, this definition for luminal B will misclassify a significant proportion of luminal B tumors as luminal A [17], thus the terminology of luminal A and B was not used in our study. Those with unknown HER2 status were not included in the survival analysis of luminal tumors. Although a subset of carcinomas with triple-negative phenotype represents basal-like carcinomas, this group was not further subclassified.

Statistical analysis

Overall survival (calculated from the date of diagnosis to the date of death from any cause or the follow-up cutoff) was estimated by the Kaplan–Meier method. Patients who survived or were lost to follow-up were considered censored in the analysis. The Log Rank test was utilized to compare groups. A P value <0.05 was considered statistically significant. The multivariate analysis was further modeled with logistic regression analysis. The Cox proportion hazard models were utilized to determine an association between the overall survival with all other tested factors. Statistical analysis was performed by utilizing SAS v9.1 software (http://www.sas.com).

Results

Clinicopathological characteristics

A total of 194 breast cancer patients with distant organ metastases at the time of diagnosis were included in the study. The mean and median follow-up time was 25.9 and 20.2 months, respectively. The clinicopathological characteristics of these patients are summarized in Table 1. In brief, the majority of the patients were Caucasian (72%). The mean age at diagnosis was 55 years (ranged 17–84 years), with a standard deviation of 12 years. At least half of the patients harbored poorly differentiated (Grade III) tumors. In 31 patients, metastatic breast cancer was diagnosed prior to the identification of the primary tumor and thus was ungraded. Sixty-four percent (121/190) of tumors with known hormonal receptor status were ER and/or PR positive (86 ER+/PR+, 29 ER+/PR−, 5 ER+/PR unknown, and 1 ER−/PR+). Thirty-one percent (54/172) of cases with known HER2 status were HER2 amplified/overexpressed.

With regard to organ distribution, approximately one-third (67/194) of the patients developed metastases in more than one organ system. Two-thirds (63/94) of patients with bone metastases were bone-only metastases. Eleven of 20 patients (55%) with brain metastases were brain-only metastases. Fifty-three of 104 patients (51%) with visceral organ involvement had an isolated visceral organ (liver, lung, or pleura) metastasis.

Factors significantly associated with overall survival

Univariate analyses for factors significantly associated with overall survival were performed utilizing the Log-Rank test. Among the factors analyzed, age at diagnosis, tumor type and size, and most surprisingly, the number of positive lymph nodes were not associated with an altered prognosis. Poor differentiation (grade III) showed a trend toward an unfavorable outcome when compared to non-high grade (grade I/II) tumors, but did not reach a statistically significant difference (median survival 896 *vs.* 542 days, $P = 0.08$). Interestingly, African American patients had a significantly increased hazard of death, indicating a poor prognosis. Not surprisingly, overexpression of ER and PR both showed a significant survival benefit (Table 2 and Fig. 1). Lack of HER2 overexpression/amplification showed a slightly increased survival (median survival 820 *vs.* 701 days, $P = 0.3$).

After adjustment for potential confounders in the Cox proportional hazards regression model for multivariate analysis, race and ER status remained independently associated with overall survival (Table 2).