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Original article

# Features of aggressive breast cancer

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ABSTRACT

*Background:* Aggressive breast cancer is a term commonly used in literature to describe breast cancer with a poor prognosis. Identifying and understanding the factors associated with aggressiveness could be helpful to the management of patients with breast cancer. Breast cancer is a heterogeneous disease, both clinically and biologically, which may be responsible for the wide range of survival durations for patients with metastatic disease.

*Aim:* The goal of this study was to identify the factors most often described in association with aggressive metastatic breast cancer (MBC).

*Methods:* A systematic review was performed by querying PubMed from January 1, 2012 to June 1, 2014 for "metastatic breast cancer" ("aggressive" or "poor prognosis" or "high risk"). The level of evidence to support each potential prognostic factor of aggressive MBC was also reviewed.

*Results:* The identified factors were grouped into 3 principle categories: clinical, biological, and patient related. Because patient-related factors may not be indicative of inherent cancer aggressiveness, this review focused only on clinical and biological factors. The factors with the highest levels of evidence to support associations with survival in metastatic breast cancer were visceral metastases, number of metastatic sites, disease-free interval, presence of CTCs, triple-negative disease, and tumour grade.

*Conclusion:* Identification of these factors and understanding their contribution to the aggressiveness of MBC and disease progression may lead to more personalized treatment in this patient population.



## Introduction

Breast cancer is the most prevalent cancer malignancy and the leading cause of cancer-related mortality in women in developed countries [1]. In 2014 in the United States, an estimated 232,670 women will be diagnosed with invasive breast cancer, and 40,000 will die from it [2]. In 2012 in Europe, there were an estimated 463,800 new breast cancer cases and 131,200 breast cancer–related deaths [3]. Approximately 5% of patients with breast cancer in the United States are diagnosed with metastatic disease at initial presentation [4]. Furthermore, a recent study found that approximately 10% of patients diagnosed with early-stage breast cancer developed metastatic disease within a mean follow-up of 5.7 years [5].

Breast cancer is a clinically and biologically heterogeneous disease, characterized by dysregulation of multiple cellular pathways [6] and different sensitivities to treatment [7–9], which may contribute to the wide range of survival durations for patients with metastatic disease. Some types of breast cancers are more aggressive than others. "Aggressive breast cancer" is not a standard term commonly used in the breast cancer literature. However, the ability to identify factors associated with aggressive breast cancer and to predict prognosis and treatment response has a considerable impact on patient management.

Studies in early-stage breast cancer have established numerous factors prognostic of efficacy outcomes, including axillary nodal status, tumour size, oestrogen receptor status, and histological grade, among others [10,11]. There have been relatively fewer reports on prognostic factors in metastatic breast cancer (MBC). This may in part be due to the inherent difficulty in separating whether a factor is a "pure" prognostic factor, a predictive factor for response to therapy, or both. However, prognostic factors could aid in selecting treatment for the individual patient and developing risk-adjusted treatment strategies.

Here we report a systematic literature review of breast cancer publications to identify potential prognostic factors of aggressive MBC and describe studies that evaluated them.

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## Methods

### *Identifying factors*

PubMed was queried from January 1, 2012 to June 1, 2014 for the following search terms: "metastatic breast cancer" ("aggressive" or "poor prognosis" or "high risk"). The abstracts of the resulting returns were reviewed for factors that were examined with respect to prognosis, and these factors were chosen for more detailed evaluation.

### *Evaluating factors*

Once aggressive disease factors were identified, PubMed was queried for each term specifically ("breast cancer" [prognostic OR predictive] [specific factor]), with no date ranges selected to allow a more robust analysis. If these criteria returned limited results for a given factor, then the search was further relaxed. In selecting studies to describe for the evaluation of factors, preference was given to prospective, randomized data in evaluating the prognostic ability of each factor. However, in many cases, retrospective analyses were the only studies available. Discussions were prioritized to include the most relevant, statistically rigorous (prospective and multivariate analysis where possible), and recent results possible.

## Results of systematic analysis

### *Identification of factors*

The most relevant prognostic factors associated with aggressive MBC were identified based on systematic search methods described earlier. This search returned a total of 141 results (135 in English). Three categories of factors were identified: clinical, biological, and patient-related (Table 1). Patient-related factors were not examined in detail. Other factors were excluded for further analysis for the following reasons: representation in only 1 report, relevance to early-stage breast cancer only, or difficulty evaluating the factor in other reports due to lack of uniformity in its definition.

### *Clinical features*

#### *Site of metastasis/recurrence*

Definitions of metastatic site may vary slightly from one study to the next. It may refer to simply the presence of a lesion in that site, the first distant recurrence after treatment for early-stage disease, or the dominant site of metastasis.

*Visceral metastases.* Visceral lesions are those confined to visceral organs, typically the liver or lung. Approximately 70% of patients enrolled in MBC trials have visceral metastases at baseline [12–14]. Multiple studies have suggested that the presence of visceral metastases is associated with worse overall survival [15–20]. A phase III trial (N = 739) in which patients with MBC were treated with doxorubicin, paclitaxel, or the combination of both demonstrated that patients with visceral-dominant metastases had worse overall survival than those with other dominant sites of metastasis [21]. Specifically, a multivariate analysis demonstrated that visceral-dominant metastases were significant, independent predictors of overall survival (hazard ratio [HR] 1.4; $P = 0.004$; Table 2). In another robust dataset, a meta-analysis (N = 1361) performed on 10 consecutive MBC trials conducted by the Hellenic Oncology Cooperative Group (HeCOG) from 1991 through 2006 found that the presence of visceral metastases significantly associated with a worse prognosis [17]. Most patients (79.5%) received taxanes as first-line treatment. Patients with visceral metastases made up 70% of the total population. The results of a Cox model that accounted for different treatments demonstrated a 44% higher risk of mortality for patients with visceral metastases vs those without (HR 1.44; 95% CI, 1.24–1.68; $P < 0.001$; Table 2).

*Brain metastases.* Based on case series, the incidence of clinically evident central nervous system metastases among women with

**Table 1**
Identification of potential prognostic factors for aggressive breast cancer.

| Factor | Represented in >1 publication? | Relevance for MBC | Selected for evaluation? |
|---|---|---|---|
| **Clinical** | | | |
| Site of metastasis | Yes | Yes | Yes |
| Number of metastatic sites | Yes | Yes | Yes |
| DFI | Yes | Yes | Yes |
| Prior therapy | Yes | Yes | No – less relevant to understand disease aggressiveness |
| Nodal status | Yes | No | No – less relevant to MBC |
| Response to prior therapy | No | Yes | No – low representation |
| Platelet-to-lymphocyte ratio | No | Yes | No – low representation |
| **Biological** | | | |
| ER/PR status | Yes | Yes | Yes |
| HER2 status | Yes | Yes | Yes |
| TNBC | Yes | Yes | Yes |
| Presence of CTCs | Yes | Yes | Yes |
| Tumour grade/differentiation | Yes | Yes | Yes |
| Tumour size | Yes | Yes | Yes |
| Molecular subtype | Yes | Yes | No – focus will be on clinical markers (e.g., ER/PR, HER2) |
| Inflammation | Yes | Yes | No – no standard marker of inflammation in these reports |
| Ki-67 | No | Yes | No – low representation |
| Histology (ductal vs lobular) | No | Yes | No – low representation |
| Concordance of receptor status between primary tumour and metastasis | No | Yes | No – low representation |
| **Patient-related** | | | |
| Age | Yes | Yes | No – less relevant to understand disease aggressiveness |
| Performance status | Yes | Yes | |
| Race | Yes | Yes | |

CTCs, circulating tumour cells; DFI, disease-free interval; ER, oestrogen receptor; HER2, human epidermal growth factor receptor-2; MBC, metastatic breast cancer; PR, progesterone receptor; TNBC, triple-negative breast cancer.

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