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Original Research

Intrinsic and extrinsic flaws of the nomogram predicting bone-only metastasis in women with early breast cancer: An external validation study

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Abstract ***Background:*** The recently developed MDACC nomogram purports to predict the risk of bone-only metastasis in women with early breast carcinoma based on five clinical and pathological characteristics. We set out to externally validate and assess its robustness using a tertiary breast cancer centre database.
Methods: All consecutive women treated for early breast cancer in our centre between January 1989 and December 2013 and who had all the nomogram variables documented were eligible for analysis.
Results: We identified 1255 eligible women for external validation analysis. The median follow-up was 54 months (range: 1–312) and time to initial metastasis 20 months (range: 1–80). The correspondence between the actual bone-only metastasis and the nomogram predictions implied poor calibration of the nomogram in the validation cohort, be it in the whole cohort or when stratified by breast cancer subtype.
Conclusion: This external validation study of the MDACC nomogram showed limitations in its generalizability to a new and independent European patient population.
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1. Introduction

Bone is the most common site of metastatic recurrence in breast cancer and is a major cause of morbidity and of altered quality of life. Sherry *et al.* [1,2] reported that metastatic breast cancer confined to the skeletal system is highly responsive to treatment and associated with prolonged survival giving rise to the concept of bone-only metastasis (BOM) as a first site of relapse. BOM implies bone metastasis without evidence of other organ involvement and has been estimated to occur in 17–37% of women with breast cancer [3–5].

Women at high risk of BOM could benefit from selective bone-targeted therapy which has low toxicity and prolonged response [6,7]. In this specific setting, a nomogram-based predictive model could improve medical management by helping in the decision-making process at an individual level [8]. Delpech *et al.*[9] recently developed in the MDACC cohort, a nomogram to predict the probability of BOM in patients with early breast cancer. The nomogram includes five independent criteria; woman's age, tumour classification, lymph node status, lymphovascular space invasion and hormone receptor status. However, although it has been internally and externally validated, the concordance index in the training and the validation set emerged as fair at 0.69 and 0.73 respectively, raising the issue of its widespread use.

The aim of the present study, therefore, was to evaluate Delpech *et al.*'s [9] BOM nomogram in a large independent cohort in France to assess whether it was robust enough to support widespread use.

2. Material and methods

2.1. Patients

Data of all women with stage I–III breast cancer at diagnosis referred to our institution between January 1989 and December 2013 were abstracted from our prospectively maintained database. Extracted data included patient demographics, clinical tumour stage as determined at presentation before any treatment initiation, axillary lymph node status, hormone receptor status and the presence or not of lymphovascular space invasion. To be included for this validation analysis, the women had to have all the nomogram variables documented.

Oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status were determined by immunohistochemistry (IHC). For ER and PR, cases with 10% or more positive staining were considered positive. Hormone receptors were considered positive when ER or PR was positive. For HER2, women with 3+ staining by IHC or those with 2+ IHC staining and amplification by *in situ* hybridisation were considered positive. The grade was defined according to the modified Scarff–Bloom–Richardson system.

Four molecular subtypes were defined according to pathological criteria [10]. The following definitions were used: triple negative (ER and PR-negative/HER2-negative), HER2-positive (ER and PR-negative/HER2-positive), luminal A (ER and/or PR positive/HER2-negative/ki67 $< 14\%$), luminal B (ER and/or PR positive/HER2-negative/Ki67 $> 14\%$ or HER2-positive and ER or PR positive whatever the Ki67).

2.2. Methods

Women received neoadjuvant and/or adjuvant systemic therapy (endocrine therapy or chemotherapy) according to their TNM classification and standard-of-care recommendations.

As in the MDACC cohort, BOM was defined as the group of women with bone-only disease. Time to isolate bone metastasis was calculated from the date of breast cancer diagnosis to the date of BOM. BOM was diagnosed by the use of bone scans and/or positron emission tomography scans/positron emission tomography–CT scans. As needed, confirmatory studies were conducted using plain X-ray films, CT scans and MRI as well as biopsy of a suspicious solitary bone lesion. Overall survival was measured from the date of diagnosis of breast cancer to the date of death from any cause. Women who were alive at last follow-up were censored. Women with metastasis other than bone (with or without bone metastasis) at the first recurrence were also censored.

2.3. Statistical analysis

The discrimination (i.e. ability to differentiate between women with BOM and those without) and calibration accuracy of the nomogram were assessed [11]. It is measured using the receiver operating characteristic curve and summarised by the area under the curve (AUC). It is generally accepted that an AUC of 1.0 indicates perfect accuracy, an AUC of 0.7–0.8 indicates satisfactory discrimination, values >0.8 represent good discrimination whereas an AUC of 0.5 indicates no relationship [12,13]. Calibration is the agreement between the frequency of observed outcome and the predicted probabilities and was studied using graphical representations of the relationship between the two calibration curves. The grouped proportions of BOM versus the mean predicted probabilities were represented at 3, 5, 7 and 10 years. In addition, women were clustered according to their molecular subtype (Luminal A, Luminal B, triple negative and HER2) to evaluate the performance of the nomogram.

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