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Age at diagnosis and distant metastasis in breast cancer – A surprising inverse relationship

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Abstract ***Introduction:*** Predictors for site of distant metastasis and impact on survival in breast cancer are incompletely understood.
Methods: Clinico-pathological risk factors for site of distant metastasis and survival were analysed in patients with invasive breast cancer treated between 1986 and 2006.
Results: Of 3553 patients, with median follow-up 6.32 years, 825 (23%) developed distant metastasis. The site of metastasis was bone in 196/825 (24%), viscera in 540/825 (65%) and unknown in 89 (11%). Larger primary invasive tumour size, higher tumour grade and axillary nodal positivity increased risk of metastasis to all sites. Lobular carcinoma was more likely to first metastasise to bone compared to invasive ductal carcinoma (NST). Oestrogen receptor (ER) negative, progesterone receptor (PgR) negative and/or Human epidermal growth factor (HER2) positive tumours were more likely to metastasise to viscera. A striking relationship between increasing age at diagnosis and a reduction in risk of distant metastasis to bone and viscera was observed. Median time to death from onset of metastatic disease was 1.52 (Interquartile range (IQR) 0.7–2.9) years for patients with bone metastasis and 0.7 (IQR 0.2–1.5) years for visceral metastasis. On multivariate analysis, despite the decrease in risk of distant metastasis with increasing age, there was an elevated hazard for death in patients >50 years at diagnosis of metastasis if they developed bone metastasis, with a similar trend observed in the >70 years age group if they developed visceral metastasis.
Conclusion: These findings indicate that there are biological mechanisms underlying the impact of age on the development of distant metastasis and subsequent death. This may have important implications in the treatment of breast cancer.

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1. Introduction

Metastatic events occur with temporal and organ site predilection patterns that are typical for primary cancers arising in different organ sites. The long latency period between presentation of the primary carcinoma and subsequent development of metastases of certain tumour types suggests that disseminated cells interact with the microenvironment of a particular organ in complex ways over a long period. Paget [1] proposed the 'seed and soil' hypothesis to describe the variation in organ susceptibility to metastasis over 100 years ago. Despite this, little is known about predictors for metastatic spread, organ susceptibility to metastasis and subsequent outcome for most tumours.

Metastatic progression in breast cancer is hypothesised to be mediated by both host and tumour factors, including different classes of metastasis genes [2–5]. However, few investigators have systematically registered the sequence of clinical events for large breast cancer patient cohorts and hence published evidence is sparse concerning patient, tumour and treatment determinants for the pattern of metastasis and outcomes in invasive breast cancer.

The aim of this study was to determine predictors of distant metastatic spread to bone and viscera, and to examine factors that influence subsequent clinical outcome in a large cohort of patients treated with curative intent for breast cancer.

2. Patients and methods

The source population of the study was 4014 consecutive patients treated for primary operable invasive breast cancer at Guy's Hospital, London, between January 1st 1986 and December 30th 2006, with data on patient demographics, tumour characteristics and treatments prospectively entered into a database. The study data are a result of systematic registration of clinical events over decades in a large cohort of patients treated at one institution over a period during which therapies have changed and improved. Nevertheless, stage and treatment information were available, and are included, in the analyses. Follow-up data, including the metastatic site, were prospectively recorded.

Patients were excluded from analysis if there was no documented evidence of curative surgery being undertaken or if they attended for less than 3 months of follow-up. A study cohort of 3553 patients remained available for analysis. At follow-up, the date and the site of recurrence were prospectively recorded. We utilised the prospective registration of the first site of distant relapse and these sites of first distant metastatic disease were divided into two groups: bone or viscera. We defined predilection to bone metastasis as a first event of bone metastasis and no visceral metastasis detected within 90 days. Predilection to visceral metastasis was defined as a first metastasis to viscera only or to a combination of viscera and bone metastases within a 90-day period.

Baseline demographic features, tumour characteristics and treatment parameters were compared in the two metastatic site groups. For oestrogen receptor (ER) and progesterone receptor (PgR), the cut-off for positivity has varied according to the assay and scoring method used at the time of assessment. Where the dextran-coated charcoal (DCC) ligand binding assay was used, cut-off was 20 fmol/mg protein, where the Abbott enzyme immunoassay (EIA) was used the cut-off was 15 fmol/mg protein and with immunohistochemistry (IHC), we used either the Quick score divided as 0–3 versus 4–7 and the Allred score 0–2 versus 3–8. HER2 positivity was established using IHC and evaluated using the well established UK HER2 testing guidelines. Very few equivocal cases during this period (score of 2+) were re-analysed using Fluorescence *in situ* hybridisation (FISH), but a cut-off of 0–1 versus 2–3 was used.

Distant metastasis free interval (DMFI) was defined as time between surgery and the diagnosis of the first event of distant metastasis. We estimated the cause-specific hazard for each metastatic site group, treating other sites of distant metastasis as right-censored and censoring for death without an event. Cox univariate analysis was used to compare each cause-specific hazard among risk factors to investigate further the metastatic pattern profile by site and within categories of each risk factor. Cox multivariate analysis was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of independent risk factors associated with each metastatic site group. The cumulative incidence of first metastatic event was estimated and plotted, considering death without metastases as a competing risk and censoring for end of follow-up [6].

Overall survival after presentation with distant metastasis was calculated based on the time interval between the first metastatic event and time to death or last follow-up. Analysis of overall survival after development of metastases was performed using Cox regression. Both univariate and multivariate analyses were used to investigate the relationships between risk factors and survival after development of metastases and the results are presented as HR and 95% CI. All statistical analyses were performed using the statistical program package R (http://www.R-project.org) [7].

3. Results

Of 3553 patients, 825 (23%) developed distant metastasis. The first site of metastasis was bone in 196/825 (24%), viscera in 540/825 (65%) and unknown in 89 (11%) of patients. Of the 540 women with visceral metastases, 114 had visceral plus bone metastases

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