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Incidence of bone metastases and survival after a diagnosis of bone metastases in breast cancer patients

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ABSTRACT

Background: Bone is the most common metastatic site associated with breast cancer. Using a database of women with breast cancer treated at Guy's Hospital, London 1976–2006 and followed until end 2010, we determined incidence of and survival after bone metastases. *Methods*: We calculated cumulative incidence of bone metastases considering death without prior bone metastases as a competing risk. Risk of bone metastases was modelled through Cox-regression. Survival after bone metastases diagnosis was calculated using Kaplan–Meier methodology. *Results*: Of the 7064 women, 589 (22%) developed bone metastases during 8.4 years (mean). Incidence of bone metastases was significantly higher in younger women, tumour size >5 cm, higher tumour grade, lobular carcinoma and ≥four positive nodes, but was not affected by hormone receptor status. Median survival after bone metastases diagnosis was 2.3 years in women with bone-only metastases compared with <1 year in women with visceral and bone metastases. There was a trend for decreased survival for patients who developed visceral metastases early, and proportionately fewer patients in this group. *Interpretation*: Incidence of bone metastases has decreased but bone metastases remain a highly relevant clinical problem due to the large number of patients being diagnosed with breast cancer.

1. Introduction

In the United Kingdom (UK), 48,417 women were diagnosed with breast cancer in 2009 [1]. Outcomes continue to improve, with current UK age-standardised relative survival rates for breast cancer being 85% at 5 years and 77% at 10 years [2]. Bone is the most common metastatic site for breast cancer and most women who die from their disease have bone metastases at time of death [3].

The burden of bone metastases for patients is considerable and often endured over several years. Bone pain (requiring radiation or surgery) and fractures are common consequences of bone metastases [4]. Bone metastases may occur independently or with visceral metastases, with best survival reported in patients with bone-only metastases [4,5]. Median survival for bone-only metastases has been reported to be as high as 72 months in one study [5], but can be substantially less [3,5–8], and only 20–30% of patients with breast cancer are expected to achieve 5 year survival post diagnosis of bone metastases.

Many studies have not been able to accurately describe the epidemiology of bone metastases. Accurate estimates of the number of patients at risk of bone metastases and the impact on subsequent survival are vital for healthcare services and resource planning. Understanding the epidemiology of bone metastases also allows for accurate design and stratification of clinical trials directed at the populations most at risk. Furthermore, better understanding the burden of bone metastases is important when considering the health economic implications of treatments designed to prevent or treat bone metastases.

Using a database containing detailed information for over 7000 women with breast cancer treated at Guy's Hospital, London, UK, we analysed factors influencing incidence of bone metastases and survival post bone metastasis diagnosis. Guy's Hospital, part of Guys and St Thomas's National Health Service (NHS) Trust, is a

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teaching hospital and specialist cancer centre that accepts local patient referrals and referrals from outside the immediate London region. However, the majority of patients treated at Guy's Hospital live locally in South East London.

2. Methods

We studied a cohort of 7064 female patients diagnosed and treated 1975–2006 for breast cancer at Guy's Hospital, London, UK and followed up until end 2010. All data was prospectively collected for each breast cancer patient since 1975 and is fully computerised in the Guy's & St Thomas Research Tissue & Data Bank, that holds data and tissue according to the Human Tissue Act and ethical permit (REC No 07/H0804/131). Data each time the patient attended hospital for an inpatient or outpatient appointment or at disease recurrence were recorded. The database contains clinical information on initial diagnosis of breast cancer including age, histopathological type (ductal, lobular, other), size and location of tumour (left versus right breast), clinical grade and stage, receptor status (progesterone receptor [PR], oestrogen receptor [ER] and Human Epidermal Growth Factor Receptor 2 [HER2]), number of positive lymph nodes, surgical and (neo)adjuvant treatments, the site of metastases (including visceral or bone), treatment received, date of recurrence or disease progression and date of death. Note the "other" category for histological type includes the following carcinoma types: adenocystic, low-grade adenosquamous, medullary, mucinous, papillary, metaplastic, micropapillary, and mixed.

We included women diagnosed with invasive breast cancer stage I–III, and women with an initial diagnosis of stage IV disease with visceral metastases but no bone metastases (as they were at risk for later development of bone metastases). For analysis purposes, we grouped stage at diagnosis into three groups based on the International Union Against Cancer (UICC) stages: 1, 2–3 and 4. We excluded males, patients with pre-invasive only disease, death certificate only patients (patients whose cancer diagnosis was only known through a death certificate without any previous clinical or histopathological breast cancer diagnosis at Guy's hospital or at the Thames Cancer Registry) and patients not initially diagnosed at Guy's Hospital. Only women with a complete clinical history recorded were included.

We classified women with bone metastases into three groups:

(i) Women who developed bone metastases and no visceral metastases within six months, "Bone-only" (Group 1).
(ii) Women who developed both bone metastases and visceral metastases within a six month period from the time of first metastasis, "Bone and Visceral" (Group 2).
(iii) Patients with visceral metastases and subsequently diagnosed with bone metastases later than a six month period after the diagnosis of first metastasis "Early Visceral" (Group 3).

A six month window of time between diagnosis of bone and visceral metastases was chosen to differentiate between women who developed simultaneous metastases at both visceral and bone sites and women who developed metastases at both sites with some time in between.

2.1. Statistical methods

For time to bone metastases analysis, start date was date of first diagnosis of breast cancer and end date was date of diagnosis of bone metastases, death, loss to follow up or last clinical appointment, whichever occurred first. To calculate cumulative incidence, diagnosis of bone metastases was considered the event of interest, death without prior bone metastases was considered as a competing risk, and we censored for all other events [9]. We plotted cumulative incidence graphs using the above statistical methods by year of diagnosis of breast cancer for all patients (n = 7064) and by stage at diagnosis of breast cancer for all patients excluding those who presented with metastatic disease (n = 6835).

Gray's test was used to test for equalities between cumulative incidence plots by year of diagnosis and initial stage of breast cancer [10]. Where we censored for death, risk of bone metastases was modelled through Cox-regression for univariate and multivariate analysis. Incidence rate of bone metastases was calculated as ratio between number of events and time of follow up and reported per 1000 person years.

For survival analysis, start date was date of diagnosis of bone metastases and end date was date of death, loss to follow up or last clinical appointment, or end of study period (31 December 2010), whichever came first. Survival after diagnosis of bone metastases was estimated using the Kaplan–Meier method.

Complete case analysis and analysis with missing data introduced as categories was performed separately. Results from both methods were compared. In case of similar results we judged that analysis using imputed data would not change our results as was shown in a related study at Guy's hospital reported in a thesis based on the same dataset (personal communication to the authors) [11].

HER-2 status was judged to have too many missing values to justify it as a covariate in the analyses, and the missing pattern was closely related to the date of diagnosis, with decreasing number of missing values over time. Similarly, there was insufficient detail in treatment information recorded in the clinical database for use in the analysis as records of radiotherapy, chemotherapy, hormone therapy was listed as yes:no.

3. Results

Of 7064 women diagnosed with breast cancer included in this study, 1589 (22%) developed bone metastases by end of study follow-up (31 December 2010). Mean follow up was 8.4 years per patient (total 59,191 person years of follow up for the entire cohort). Of 1589 women diagnosed with bone metastases, 535 (33.7%) were in Group 1, 871 (54.8%) in Group 2 and 183 women (11.5%) in Group 3 (Table 1). Among women diagnosed with bone metastases within 10 years of initial breast cancer diagnosis, 25% were diagnosed within 9 months, 50% within 2 years and 75% within 4 years.

Compared with all women in the cohort, those diagnosed with bone metastases were on average younger, with 29.6% of patients with breast cancer diagnosed under age of 40 years developing bone metastases versus 23.0% in the 40–49 year age group, 25.1% in the 50–59 year age group, 21.7% in the 60–69 year age group and 15.3% in those over 70 years (Table 2). In the multivariate analysis, the hazard ratio (HR) of developing bone metastases was highest in women diagnosed with breast cancer under age 40 years and lowest in women diagnosed $\geq$70 years (HR 0.54, 95% confidence interval [CI] 0.45–0.64) (Table 2).

When analysing risk of developing bone metastases by clinical characteristics at breast cancer diagnosis, risk was highest for women whose breast cancer size was >5 cm in diameter. In the multivariate analysis, the HR of risk of developing bone metastases was 3.31 (2.73–4.01) in patients with tumour size >5 cm diameter versus tumour size <2 cm. Women with higher grade tumours were also more likely to develop bone metastases: in the multivariate analysis, HR of developing bone metastases was 1.23 (1.08–1.40) when comparing tumours of grade 3 to those of grade 1 and 2. There