Research Article

Incidence, consequences and treatment of bone metastases in breast cancer patients—Experience from a single cancer centre

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ABSTRACT

Background: There is a paucity of literature about the benefits of bone-targeted agents for breast cancer patients with bone metastases treated in the non-trial setting. We explored the incidence, consequences, and treatment of bone metastases at a single cancer centre.
Methods: Electronic records of metastatic breast cancer patients were reviewed and pertinent information was extracted.
Results: Of 264 metastatic breast cancer patients, 195 (73%) developed bone metastases. Of these patients, 176 were eligible for analysis. Median age at bone metastases diagnosis was 56.9 years (IQR 48–67) and initial presentation of bone metastases included asymptomatic radiological findings (58%), bone pain (40%), or a SRE (12.5%). Most patients (88%) received a bone-targeted agent, starting a median of 1.5 months (IQR 0.8–3.30) after bone metastasis diagnosis. 62% of patients had ≥ 1 SRE. The median time from bone metastasis diagnosis to first SRE was 1.8 months (IQR 0.20–8.43 months). Median number of SREs per patient was 1.5 (IQR 0–3). Overall, 26.8% of all SREs were clinically asymptomatic. Within the entire cohort, 51% required opioids and 20% were hospitalized due to either an SRE or bone pain.
Conclusions: Despite extensive use of bone-targeted agents, the incidence of SREs remains high. Nearly half of SREs occur prior to starting a bone-targeted agent. Use of opioids and hospitalizations secondary to bone metastases remain common. More effective treatment options are clearly needed.

1. Introduction

Despite advances in the treatment of early stage breast cancer, bone remains the most common site of distant metastasis [1]. The consequences of bone metastases include reduced survival, morbidity, pain and reduced quality of life [2]. While the care of these patients is multidisciplinary, possibly the most attention in recent decades has been given to the role of bone-targeted agents (BTAs) such as bisphosphonates and denosumab. Clinical trials of BTAs have shown statistically significant reductions in the incidence of, and time to, skeletal related events (SREs) (defined as need for surgery or radiotherapy to bone, pathological fractures, spinal cord compression, hypercalcemia) and reduced bone pain in patients with bone metastases from breast cancer [3–7] (Table 1). As a result of these trials, BTAs have become a standard of care, with

treatment starting at the time of bone metastasis diagnosis until evidence of a substantial decrease in performance status [8,9].

With the widespread use of BTAs there is a growing body of data that suggests that their benefits in routine clinical practice are more modest than that observed in randomised trials [10–14] (Table 2). We therefore decided to evaluate the incidence, consequences, and management of bone metastases in an unselected cohort of breast cancer patients at a large Canadian cancer centre. In addition, we assessed less commonly reported clinical outcomes of importance to patients and the health care system, such as the use of opioids and the need for hospitalization due to skeletal complications.

2. Methods

2.1. Data collection

Registry information was available for all patients seen with a diagnosis of breast cancer at The Ottawa Hospital Cancer Center between January 2008 and June 2012. Electronic charts were

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screened manually (IK, PM, TN) to identify eligible patients. Eligibility criteria included: radiologically and/or pathologically confirmed bone metastases, breast cancer as the only diagnosed

malignancy, and complete electronic chart data (i.e., radiologic imaging, serum calcium levels, reports of radiation/surgical procedures, and clinic dictations). Data collected included demographic

Table 1
Overview of SREs on BTA in randomised trials.

Reference	Study	Patients with bone disease only (%)	Radiologic screening	Outcomes on BTAs	Overall survival
Hortobagyi [3]	Pamidronate 90 mg IV vs. placebo	62 (pam) 60 (placebo)	Radiographic surveys of the skeleton were performed before entry into the study and after 3, 6, and 12 cycles of treatment	Median time to SRE—13 months Proportion of SREs—46%	14.8 vs. 14.2 months, no difference
Theriault [4]	Pamidronate 90 mg IV vs. placebo	66 (pam) 72 (placebo)	Radiologic bone survey within 1 month before entry and then at cycle 3, 6, 12, 18, 24 or at last visit if came off prematurely	Delay in 1st SRE-10.4 months SRE rate—56%	23.2 vs. 23.5 months, $p=0.685$
Conte [26]	Pamidronate 45 mg IV vs. control	55 (overall)	Bone survey on study entry, then at 3 and 6 month	Delay in 1st SRE—13.1 months	pam-592 control—642 days, no difference
Hultborn [33]	Pamidronate 60 mg vs. control	54 (pam) 57 (placebo	Bone scan and directed X-ray at study entry, then every 6 months	SRE-free survival 11.8 months	n/a
Body [6]	Ibandronate 2 mg or 6 mg vs. placebo	66 (6 mg) 69 (2 mg) 67 (placebo)	Not specified	SMR-1.19 for 6 mg median time to 1st SRE 50 weeks	8 patients died in IBA, 15 in placebo
Kohno [5]	Zoledronic acid 4 mg IV vs. placebo	Not specified	Radiologic bone survey on study entry, then at 3, 6, 9, 13 months, bone scan on study entry and at 6 and 13 months	Proportion of patients with SREs—30% SRE rate ratio at 1 year—0.61 Time to 1st SRE not reached	n/a
Rosen [21]	Zoledronic acid 4 mg IV vs. pamidronate 90 mg IV	Not specified	Radiologic bone survey on study entry, then at 3, 6, 9, 13 months, bone scan on study entry and at 6 and 13 months	Time to 1st SRE Zoledronic acid—356 days Pam—376 days SMR Zoledronic acid—1.04 Pam—1.39	More than 2 years, no difference between arms
Stopek [28]	Zoledronic acid 4 mg IV vs. denosumab 120 mg SC	Not specified	Skeletal surveys or any of radiological assessment (X-ray, CT, MRI) every 12 weeks	Time to 1st SRE Zoledronic acid—26.4 months Denosumab-not reached SMR Zoledronic acid—0.58 Denosumab—0.45	No difference between treatment groups

Table 2
Overview of retrospective data of SREs on bone-targeted agents.

Reference	Study	N	Proportion of patients with only bone disease (%)	Frequency of radiologic assessment	Outcomes	Overall survival
Trinkaus [11]	Retrospective study SREs on pamidronate	87	35	N/a	Time to 1st on pamidronate SRE—267 days Proportion of patients with SRE—38%	N/a
Liauw [14]	Retrospective study SREs on IV bisphosphonates	110	58	N/a	Time to 1st SRE—365 days Proportion of patients with SREs—30%	818 Days from start of bisphosphonates
Murphy [34]	Retrospective study SREs on IV bisphosphonates	62	N/a	N/a	Proportion of patients with SREs—zoledronic acid—75% Pam—62%	N/a
Young [12]	Retrospective study SREs on zoledronic acid	11	7.2 at diagnosis	N/a	Proportion of patients with SREs—42.3%	1.9–1.6 years, median 1.5 years
Crawford [35]	Retrospective study SREs on IV bisphosphonates	181			Proportion of patients with SREs—30%	
Ding [13]	Retrospective study SREs on bisphosphonates 181 patients		37	N/a	Proportion of patients with SREs—34.8%	Median 64 months (range 57–70)
Current study	Retrospective study Patients diagnosed with bone metastases	177	20.4	Q 3–5 months in 54% of patients	Time to 1st SRE on BTA—8.3 months Proportion of patients with SRE on BTA—48%	Median 40.0 months (IQR 22.3–93.3 months)

information, primary tumor features, time from primary diagnosis to development of bone metastases, presentation and distribution of bone metastases, presence of non-bone metastatic disease, incidence of SREs (defined as; pathologic fractures, need for radiation or surgical interventions to bone, spinal cord compression, and hypercalcemia of malignancy), time to SRE from the first date of BTA treatment, opioid treatment for bone pain control, and hospitalizations secondary to bone complications (SREs and pain control).

In order to assess the proportion of patients with first SRE prior to and after initiation of a BTA, SREs were considered to have occurred before BTA treatment if the therapy was administered as a consequence of the development of an SRE or if the SRE had occurred within 1 month of starting the BTA [11,14]. Treatment data collected included time of initiation of BTA treatment from the time of diagnosis of bone metastases, type of BTA, reasons for discontinuation of BTA treatment, and, when applicable, why BTAs were not commenced. Information on current and previous chemotherapy and hormonal treatments was also collected. The study was approved by the local institutional Research Ethics Board.

2.2. Statistical methods

Patient demographic variables were summarized using proportions for dichotomous measures, and means (with standard deviations) or medians (with interquartile range) for continuous measures. Binary outcomes of interest (including types of BTA administered, reasons for discontinuation/avoidance of BTAs, administration of multiple BTAs, the occurrence of SREs before/after BTA administration and individual types of SREs observed) were summarized using proportions and associated 95% confidence intervals. Kaplan–Meier analyses were performed to estimate the median time and associated interquartile range for all time-to-event outcome measures of interest; where clinical subgroups of patients were of interest, log rank tests were performed to make these comparisons. A multivariable logistic regression analysis to explore predictive variables of SRE occurrence was also conducted and considered six covariates: age at time of diagnosis (tertiles defined by; < 50 years, 50–60 years, and > 60 years), hormone receptor status (HER2 positive vs. ER or PR positive and HER2 negative, vs. triple negative), number of bone metastases (0–4 vs. 5 or more), duration of bone metastases (< 2 years vs. 2 years or more), timing of BTA initiation from bone metastasis diagnosis (≤ 3 months vs. > 3 months vs. no BTA use), and timing of BTA administration (before any SREs vs. other). All data analyses were performed using SAS software (version 9.2, Cary, North Carolina).

3. Results

3.1. Overview of cohort characteristics

Of 2096 charts screened, 264 patients had metastatic disease. Of these patients, 195/264 (73%) had bone metastases. Nineteen of these 195 patients were excluded from further analysis, due to diagnosis of second primary tumor ($n=11$) and loss to follow up ($n=8$). Data from 176 patients were therefore included for further analysis. Median duration of patient follow up, as measured from time of primary diagnosis to date of last visit, was 51.6 months (0.47–472.1 months). At the time of study analysis 99/176 (56%) patients were dead.

Baseline characteristics of the patients are summarized in Table 3. Median age was 56.9 years (IQR 47.5–67.0), 85.2% were hormone receptor positive, 18.8% were HER2 positive, and 5.7% were triple negative. At the time of initial breast cancer diagnosis, 21 (11.9%) were stage I, 38 (21.6%) stage II, 39 (22.2%) stage III and 74 (42.1%) stage IV. Stage was unknown for 3 (1.7%) patients, and 1

(0.6%) patient had ductal carcinoma in situ at primary diagnosis. In the course of their disease, from diagnosis of metastatic disease to last follow up or death, 60 (34.1%) also had soft tissue involvement, 123 (69.8%) visceral metastases, and 39 (22.5%) brain metastases. Bone only metastases throughout the course of disease until last follow up or death were observed in 36 women (20.4%). Median time from primary breast cancer diagnosis to development of bone metastases was 23.1 months (IQR 0.85–71.2 months). Of the patients analyzed, 31% presented with bone metastases at initial breast cancer diagnosis. The most frequent locations of bone metastases were the thoracic spine (83.5%) and lumbar spine (78.4%) (Fig. 1). Initial diagnosis of bone metastases was most commonly a result of asymptomatic radiological findings (58%), followed by pain (40.3%), and an SRE (12.5%). Most patients who presented with an SRE also had bone pain at the same time (86%).

For management of their metastatic disease, the majority of patients received hormonal therapy (76.7%) or chemotherapy (67.6%). Over the study period, patients had a median 1 line of endocrine therapy (range 0–5) and 1 line of chemotherapy (range 0–7). Radiologic assessments of metastatic disease (including one of following: bone scan, X-ray, CT scan, MRI) were performed every 3–5 months in 54% of patients.

3.2. Bone-targeted agent use

Overall, 88% percent of patients received a BTA. The most commonly used BTA across all lines of therapy was pamidronate (85.8%) as standard of care and funding across most of Canada. This was followed by zoledronic acid (13.1%), clodronate (8.0%) and denosumab (2.8%). Median time from diagnosis of bone metastases to BTA initiation was 1.5 months (IQR 0.8–3.30) and the median time on BTA therapy was 22.0 months (IQR 5.2–37.1). Treatment was eventually discontinued in 95 patients (61.2%) due to: deterioration and/or death ($n=64$, 41.2%), progressive bone metastases ($n=2$, 1.2%), side effects ($n=8$, 5.1%), progressive disease ($n=2$, 1.2%), patient's ($n=2$, 1.2%) and physician's preference ($n=3$, 1.9%). Treatment was discontinued in one patient due to contraindication and reason was unknown in 15 patients (9.6%).

With respect to side effects as the reason for drug discontinuation, pamidronate was discontinued due to elevated creatinine levels ($n=7$) and chronic heart failure exacerbation ($n=1$). Three patients discontinued clodronate due to gastro-intestinal intolerance and one patient for non-specified poor tolerability. One patient (0.6%) was diagnosed with osteonecrosis of the jaw (after 3 years of pamidronate).

Thirty six patients (23.2%) were switched to another BTA, 26 of them due to progression of bone metastases on prior BTA, 5 due to side effects of prior BTA, 5 based on physician's preference and 1 due to lack of funding. The most commonly prescribed agent in the second line setting was zoledronic acid (57.1%). In those 21 patients who never started a BTA, the reasons included: physician choice (18/176=10.2%) and patient refusal (3/176=1.7%).

3.3. Consequences of bone metastases

A Kaplan–Meier curve for survival of patients with bone metastases is shown in Fig. 2. The median overall survival from diagnosis of metastatic disease was 40.0 months (IQR 22.3–93.3 months). 62% of patients diagnosed with bone metastases had ≥ 1 SRE, with a median time from BM diagnosis to first SRE of 1.8 months (IQR 0.20–8.43 months). Among 155 patients receiving BTAs, 50 (32.4%) never experienced an SRE, 75 patients (48.4%) had their first SRE prior to initiation of BTA treatment, and 29 (18.8%) had their first SRE after BTA treatment initiation (Fig. 3). Over the entire course of the study, 74/155 patients (48%) experienced at least one new SRE after initiation of BTA.

Table 3
Baseline patient and disease characteristics.

Characteristic	Patients on BTAs (n=155)	Patients not on BTAs (n=21)	All patients (n=176)
Age at primary breast cancer, years (mean, SD)	56.2	61.8	56.9 (13.3)
BC stage at primary diagnosis			
I	20 (12.9%)	1 (4.7%)	21 (11.9%)
II	32 (20.6%)	6 (28.5%)	38 (21.6%)
III	33 (21.2%)	6 (28.5%)	39 (22.2%)
IV	67 (43.2%)	7 (33.3%)	74 (42.1%)
Unknown	2 (1.2%)	1 (4.7%)	3 (1.7%)
DCIS	1 (0.6%)	0 (0%)	1 (0.6%)
Subtype of primary BC			
Invasive ductal	122 (78.7%)	17 (81%)	139 (79%)
Invasive lobular	21 (13.5%)	2 (9.5%)	23 (13.1%)
Invasive other	10 (6.4%)	2 (9.5%)	12 (6.8%)
Missing	2 (1.2%)	0 (0%)	2 (1.1%)
Inflammatory breast cancer	10 (6.5%)	4 (19%)	14 (7.9%)
ER status			
Negative	18 (11.6%)	7 (33.3%)	25 (14.2%)
Positive	137 (88.4%)	13 (62%)	150 (85.2%)
Unknown	0 (0%)	1 (4.7%)	1 (0.6%)
PR status			
Negative	38 (24.6%)	10 (47.6%)	48 (27.3%)
Positive	116 (74.8%)	10 (47.6%)	126 (71.6%)
Unknown	1 (0.6%)	1 (4.7%)	2 (1.1%)
HER2 status			
Negative	120 (77.4)	13 (61.9%)	133 (75.6%)
Positive	29 (18.7%)	4 (19%)	33 (18.8%)
Unknown	6 (3.8%)	4 (19%)	10 (5.7%)
Grade			
1	14 (9%)	3 (14.2%)	17 (9.7%)
2	74 (47.7%)	5 (23.8%)	79 (44.9%)
3	36 (23.2%)	5 (23.8%)	41 (23.3%)
Unknown	31 (20%)	8 (38%)	39 (22.2%)

SD—standard deviation, BC—breast cancer, ER—estrogen receptor, PR—progesterone receptor, BTA—bone targeted agent.
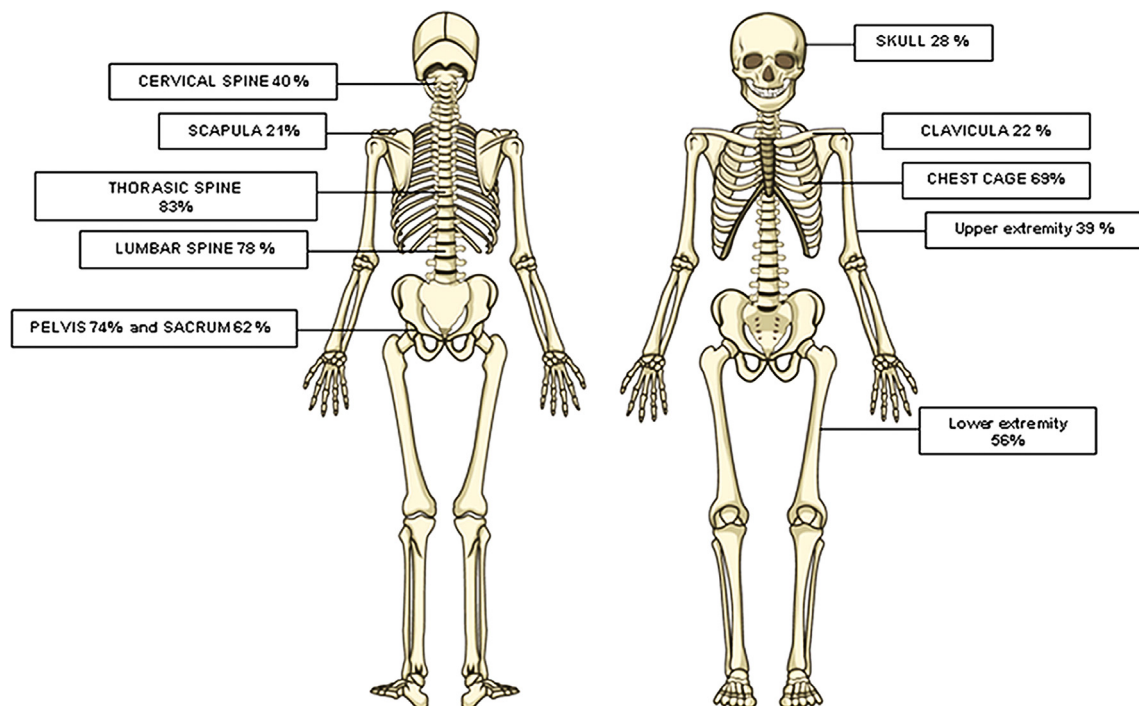

Fig. 1. Bone metastases distribution.

The median time from the first dose of BTA to the first SRE following the initiation of treatment was 8.3 months (IQR 0.9–29.7 months). Of 435 identified SREs, the most frequent were: radiotherapy (68.1%), fractures (17.2%), surgery (6.2%), hypercalcemia (4.8%) and spinal cord compression (3.7%). The most common sites of SRE occurrence were the thoracic (25.4%) and lumbar spine (16.2%).
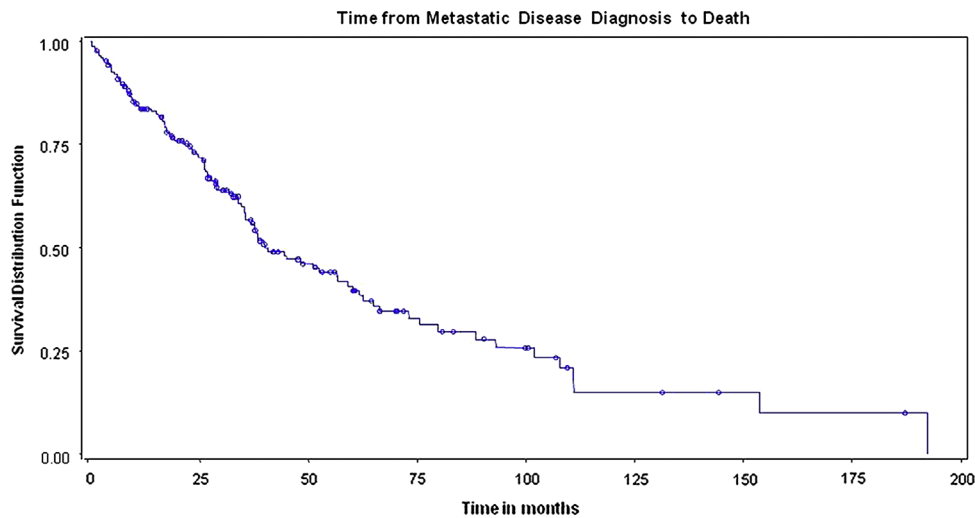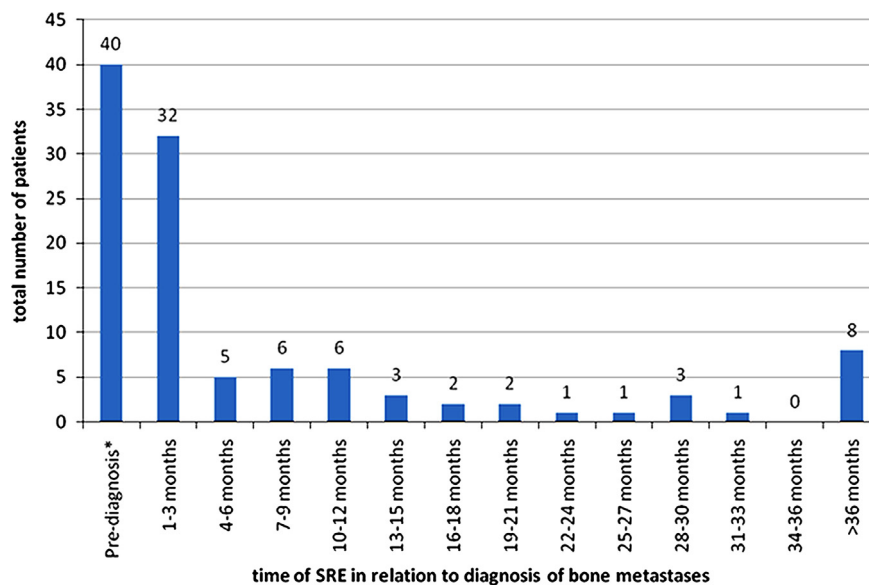
Fig. 2. Kaplan–Meier curve for survival of patients from time of diagnosis of bone metastases.

* pre-diagnosis includes SREs occurring within 30 days of diagnosis of bone metastases

Fig. 3. Time to first SRE from diagnosis of bone metastases (*n*=110 patients).

Overall, 26.8% of all SREs were clinically asymptomatic i.e., asymptomatic fractures that were usually detected on radiology and the radiotherapy was given for prevention of further fractures.

A higher proportion of patients had fractures and hypercalcemia and spinal cord compression as their 1st SRE prior to start of BTAs, whereas more patients underwent surgery after BTA initiation (Table 5).

3.4. Predictive factors for SREs

Of the patients who had an SRE before commencing a BTA, 62/75 (82.7%) went on to have further SREs after starting a BTA. Contrarily, of the patients who did not have an SRE before commencing a BTA, 25/80 (31.2%) went on to have at least one more1 SRE (OR 10.3, 95% CI 4.8–22.1) after starting BTA.

In a multivariable analysis, there was no increased risk of an SRE in patients aged 50–60 years (OR 0.71, 95% CI 0.31–1.62) or > 60 years (OR 1.10, 95% CI 0.49–2.48) when compared to those < 50 years. Patients with bone metastases for 2 years or longer had a higher risk to develop SREs than those who did not (OR 2.63,

95% CI 1.36–5.09). Patients with 5 or more bone metastases were more likely to have an SRE than those with 4 or fewer (OR 2.04, 95% CI 1.02–4.10). With regard to bone only disease as risk factor for SREs vs. bone and visceral and/or brain metastases the odd ratio was 1.55, suggesting there may be a higher incidence of SRE in patients with bone only disease, however, the confidence interval was wide (95% CI 0.71–3.39). There was no significant difference in incidence of SREs between patients with hormone receptor positive and hormone receptor negative disease, however, number of patients was relatively small. Type of lesion (lytic vs. sclerotic) and rate of bone turnover as determined by collagen breakdown markers or bone formation markers were previously reported as important predictors of SREs [10]. However, pure lytic vs. sclerotic disease is rarely seen these days when bone-targeted agents are so widely used. The vast majority of patients have mixed metastases. There was no consistency in the study around the use of plain films for baseline lytic vs. sclerotic assessment across all sites of bone metastases and therefore this data was not collected. In addition, data on alkaline phosphatase had not been collected due to lack of consistency in timing and

Table 4
Patient characteristics at time of bone metastases diagnosis.

Patient characteristic	Patients on BTAs ($n=155$)	Patients not on BTAs ($n=21$)	All patients ($n=176$)
Bone only metastases, n (%)	33 (21.3%)	3 (14.2%)	36 (20.4 %)
Solitary bone metastases, n (%)	8 (5.2%)	1 (4.7%)	9 (5.1%)
Metastasis sites in addition to bone			
Visceral, n (%)	105 (68%)	18 (81%)	123 (69.8%)
Brain, n (%)	33 (21.3%)	6 (28.6%)	39 (22.5%)
Soft tissue and lymph nodes, n (%)	51 (33%)	9 (42.8%)	60 (34.1%)
Presentation of BM			
Asymptomatic, presented at staging investigations, n (%)	86 (55.5%)	16 (76.2%)	102 (58%)
Pain, n (%)	66 (42.6%)	5 (23.8%)	71 (40.3%)
SRE, n (%)	21 (13.5%)	1 (4.7%)	22 (12.5%)
Bone metastases at breast cancer, Dx	49 (31.6%)	5 (23.8%)	24 (31%)
Number of lines of systemic treatment chemotherapy (median, minimum, maximum)	1(0–7)	1(0–4)	1 (0–7)
Number of lines of hormonal therapy (median, minimum, maximum)	1(0–5)	0 (0–4)	1 (0–5)
SRE prior to BP use, n (%)	75	N/A	75 of 154 (48.7%)
Frequency of radiologic assessment			
Q 1–2 months	17 (11%)	4 (19%)	21 (11.9%)
Q 3–5 months	93 (60%)	3 (14.2%)	96 (54.5%)
Q 6–9 months	34 (21.9%)	4 (19%)	38 (21.6%)
Q 10–12 months	6 (3.8%)	3 (14.2%)	9 (5.1%)
More than 12 months	2 (1.2%)	0 (0%)	2 (1.1%)
Once	2 (1.2%)	7 (33%)	9 (5.1%)
Missing	1 (0.6%)	0 (0%)	1 (0.6%)

Table 5
Nature of 1st SRE in patients who had ≥ 1 SRE depending on whether the first SRE occurred prior or after initiation of bone-targeted therapy.

SRE	Prior to initiation of BTA, n (%)	After initiation of BTA, n (%)
No. of patients	75 of155	74 of 155
Radiotherapy to bone	63(40.6%)	69 (44.5%)
Fractures	32 (21%)	21 (13.5%)
Spinal cord compression	7 (4.5)	7 (4.5%)
Surgery to bone	9 (6%)	11 (7%)
Hypercalcemia	12 (8%)	6 (4%)

BTA=bone targeted agent, SRE=skeletal related event.

laboratory of blood tests among patients that reflects differences in physicians practice and is one of known limitations of retrospective study.

Most of the patients who did not receive a BTA, had predominantly visceral (18/21=81%) or brain metastases (6/21=28.6%), higher proportion of ER (33%vs.11%) and PR (47%vs.24%) negative tumors compared to group of patients on BTAs, and remaining three patients from this group had low burden metastatic disease with single bone or soft tissue metastases (Table 4). In this group 6 (27%) patients experienced at least one SRE. Within the entire cohort of patients with bone metastases, 51% required opioids to control associated pain, and 20% were hospitalized due to an SRE or bone pain.

4. Discussion

The impact of bone metastases from breast cancer on patients' survival, quality of life, mobility and functional independence are well recognized. However, despite the multidisciplinary nature of care of these patients, in recent decades the focus of randomised trials has been predominantly on the benefits of BTAs on SREs. The purpose of the current paper was deliberately broad and designed to assess the consequences of the occurrence of bone metastases in patients treated outside of the clinical trial setting. We also wished to informally compare our findings and other retrospective

and clinical trial datasets. We also attempted to evaluate potential predictive for identifying patients at different risk for developing SREs [15–17].

As an overview of the cohort characteristics it is interesting simple observation that despite advances in adjuvant therapy that the proportion of patients with bone metastases remains the same (70%) as originally reported over 30 years ago [1]. As with other series, patients with bone metastases appear to have a favorable survival with a median overall survival from diagnosis of metastatic disease of 40.0 months (IQR 22.3–93.3 months) [13,18–20]. In our current series, most patients with bone metastases received a BTA starting soon after being diagnosed with bone metastases (median 1.5 months (IQR 0.8–3.30)). Patients were continued IV bisphosphonates every 3–4 weeks in most cases until significant deterioration or death, as per treatment guidelines [8].

It is of note that the incidence of SREs in patients who received a BTAs in our study was 62% with the majority of first SRE (75/155, 48.4%) occurred either before commencing a BTA or within 1 month of starting a BTA. The incidence of SREs prior to bone-targeted therapy is in keeping with the literature [3,21]. This likely reflects the imaging that is performed when the patient is being worked up for her new symptoms and therefore the suspicion of bone recurrence is being raised. For example, in our series 40% of patients had significant pain at the time of diagnosis of bone metastases, and it is therefore not surprising that palliative radiotherapy (an SRE) was offered in order to achieve pain relief. Indeed, in our study the most frequent SRE was radiotherapy with pain and prevention of fraction or spinal cord compression as indication for treatment.

However, it should be noted that large proportion of patients develop at least one SRE after BTAs initiation (74/155, 48%) appearing to be in keeping with the results of randomised BTA trials [3–6]. Indeed, for those patients who had not had an SRE prior to commencing a BTA, their risk of subsequent SREs was much lower than that observed in patients who had had an SRE prior to starting therapy and may therefore identify a potential lower risk patient population for alternative treatment strategies [22–25]. It is of interest that the majority of SRE in this study occurred within first 3 months of starting BTAs, similar observations have been observed before [3,4] where differences in incidence of SREs between pamidronate and placebo became significant after 3–6 months of treatment. This likely reflects the time needed for bone physiology to be modified to reduce SREs such as fractures.

In our current series, we saw that 26.8% of SREs were asymptomatic, and thus likely found as a result of routine bone imaging. This is of note, as most prospective trials of BTAs do not report how SREs were identified (i.e., symptomatic vs. asymptomatic radiologic findings). In contrast, retrospective studies (Table 2) are mostly focused on symptomatic SREs, as reflected by the lower incidence of SREs reported, generally around 30% [11–14]. A similarly low incidence of SREs was recently observed in the ZOOM trial, where patients only underwent imaging at the discretion of the treating physician [22]. Indeed, the proportion of clinically significant fractures was lower in our study (17.2%) than in large randomised bisphosphonate trials (25–45%) [4,21,26], while the proportion of patients receiving radiation to bone was higher (68% vs. 10–40%). These frequencies were more in keeping with other retrospective series [11,14].

Comparison of the benefits of BTAs between real world and clinical trial populations is important, for a number of reasons. Firstly, the frequency of radiological investigations is likely significantly less for patients treated in routine clinical practice compared to those entered on a clinical trial [27]. Individuals in the randomized studies underwent skeletal imaging every 12 weeks [4,21,28], and the SREs reported in these trials thus represents the composite of both symptomatic and asymptomatic radiological changes. In our current series bone imaging was performed every 3–5 months as part of systemic assessment of metastatic disease in a 54% of patients, once in 6 months and less frequent in 30%. 12% of patients had some imaging more frequently than every 3 months, mostly as part of follow up with CT scan for rapidly progressive visceral disease. In addition, clinical trial patients usually have a better performance status due to restrictive inclusion criteria; moreover, most of the patients enrolled in BTA trials have metastatic disease confined to skeleton only (55–70%), while in our study a significant proportion of BTA-treated bone metastatic patients also had visceral metastases (68%, 105/155). Again this is comparable with the most of retrospective trials (Table 2). Also of interest is the relatively low incidence of reported ONJ seen in the current series 0.6% again consistent with the literature [29].

As with other series, we have shown that multiple bone metastases, presence bone metastases for more than two years, and occurrence of previous SREs are associated with a risk of further SREs [10,12,30]. Several trials have investigated predictive factors for developing SREs among women with bone metastases secondary to breast cancer on bisphosphonate treatment. Baseline patients characteristics from randomized prospective trials investigating the efficacy of pamidronate in this group found increased SREs risk with presence of more than two osteolytic lesions, high pain scores, and history of prior radiation therapy [30]. Another retrospective analysis of a large prospective trial comparing zoledronic acid to pamidronate in women with bone metastases secondary to breast cancer found that age older than 60, Brief Pain Inventory score higher than 3, prior SREs and predominant lytic bone lesions put patients at an increased higher risk for subsequent SREs [10]. One retrospective study showed increased incidence of SREs in patients with pre-existing osteoporosis [11].

Clearly there are limitations to the current study. These include the single centre, retrospective nature of the study as well as its relatively small sample size compared with the randomised data. However, the duration of follow up is considerably longer than these trials (Table 1).

In conclusion, despite our increased understanding of the biology of metastatic bone disease [31,32] bone remains the most common site of breast cancer recurrence. Despite extensive use of BTAs the incidence of SREs remains high as does the use of opioid analgesics and hospitalizations secondary to bone metastases. Thus despite significant advances in the care of these patients there is a need for more effective treatment options and more individualized approach for these patients.

Conflict of interest statement

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