Bone metastases (BM) are still the main cause of morbidity in cancer patients because of skeletal-related events (SREs) that reduce quality of life. They have also led to increased social and healthcare costs. At present, data available on BM are insufficient. This was a multicentre prospective observational study of patients with BM from breast cancer (BC) with at least 6 months' follow-up. Information on patients at the first diagnosis of BM, including demographics and characteristics of the primary tumor and BM. Data were periodically updated by participating centres and reviewed by the coordinator centre. From October 2014 to July 2019, 618 patients with BM from solid tumors were enrolled and 220 were eligible for the present study. Median age was 62 years (range 26–86). Median follow-up was 34 months (range 6–149). At the time of enrolment, 109 (50%) had only BM (BOM) and 109 (50%) had concomitant visceral lesions and BM (BVM). Median time-to-first BM was 47 months (range 0–312) in BOM and 78.6 months in BVM patients. Disease-free interval differed on the basis of BC molecular subtype and stage. Ninety-eight BM patients had at least one SRE. Zoledronate was used in 69.1% of cases and denosumab in 28.3%. First-line treatment was hormone-based (50.7%), chemotherapy-based (38.7%) or chemotherapy-+ hormone therapy-based (9.7%). Median progression-free and overall survival were 15.1 months (95% CI 12.6–18.4) and 66.8 months (95% CI 52.1–79.2), respectively. Our prospective study could substantially help to better understand the natural history of BM from BC.

Breast cancer (BC) is the most common malignancy and a major cause of morbidity and mortality among women. The mortality rate has decreased thanks to improved diagnostic procedures, screening and more advanced treatments. However, the rate of recurrence in distant organs is still fairly high, ranging from 20 to 30%1,2.

Bone is the most common site of metastasis in BC and significantly impacts patient survival3–5.

Bone metastases (BMs) represent an important clinical-epidemiological issue in oncology because their diagnosis and treatment are often necessarily handled by several specialists, resulting in fragmented patient information6. For these reasons, great efforts have been made to develop a new scientific and clinical branch of medicine, i.e. Osteoncology7.

The major problem faced by BM patients is the risk of skeletal complications defined as skeletal-related events (SREs) all of which are highly detrimental to quality of life and survival8,9.
There is still limited information available on BM clinical presentation, the difference in disease response between bone and visceral sites, and the difference in prognosis between solitary, oligometastatic and multiple sites or axial and trunk bone metastases\(^{10}\). A clearer understanding of their natural evolution would thus help us to identify new strategies capable of reducing both BM incidence and morbidity.

The risk of SREs in BC patients with BM has been the focus of numerous studies\(^ {41-13}\). However, their findings are of limited value because of their poor generalizability with respect to current clinical practice. In the retrospective studies, authors usually considered a lengthy time period during which available therapies and clinical practice may have changed substantially. In the prospective studies, patients were followed for a short period (24 months) and data were extrapolated from a BC database rather than from a database dedicated to BM. Furthermore, in recent years, new therapeutic options have become available. There has also been growing interest in BM since dedicated multidisciplinary groups began to emerge\(^ {44}\).

The main aims of this prospective multicenter study were to evaluate the evolution of skeletal disease in BC patients, assess the impact of BM on disease outcome, examine the role of a number of clinical-pathological parameters in predicting survival, and further our understanding of the natural history of patients with BM from BC.

**Materials and methods**

This was a multicentre prospective observational study of patients with BM from BC with at least 6 months follow-up, enrolled into the prospective Italian Bone Metastases Data Base (BMDB). The study was approved by the Local Ethics Committee of each participating centre and carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. List of participating centers was provided in Supplementary Table 1. Written informed consent was obtained from all patients. Information on data source is provided in Appendix 1.

**Data extraction and measure definition.** The evolution of skeletal disease in BC patients was evaluated by extracting data from the BMDB for patients who had a first diagnosis of BC with a synchronous (within 2 months) or metachronous diagnosis of bone metastasis and were followed up for at least 6 months after the BM diagnosis.

Time to event outcomes were defined as follows: disease-free interval (DFI) was the time from primary BC disease to the appearance of the first metastasis (bone or visceral), and bone disease-free interval (bDFI) was the time between diagnosis of primary BC and first diagnosis of BM. Overall survival (OS) was calculated as the time from the date of the diagnosis of primary BC to the date of death. OS from metastatic disease (metOS) was calculated as the time from the diagnosis of metastasis (either bone or visceral) to death. Progression-free survival (PFS) was the time between the date of the first diagnosis of bone metastasis and date of the first documented evidence of disease progression (bone or visceral) and death. Bone PFS (bPFS) was the time between the date of the first diagnosis of BM and first progression to bone and death. Time-to-first SRE was the time between the first diagnosis of BM and the first SRE event. Patients without events of interest were censored at the date of the last follow-up visit.

**Statistical analysis.** Descriptive statistics are used to summarize baseline patient characteristics, BC characteristics and treatment patterns. Continuous variables are presented using median and range or interquartile range. The Wilcoxon rank-sum test was used for continuous variables, together with the chi-squared test or Fisher's exact test, as appropriate. McNemar's test was used in cases of paired data. Time-to-event measures were analysed using the Kaplan–Meier method, and the nonparametric log-rank test was used to evaluate the role of stratification factor. We used the Cox proportional hazards regression model to estimate hazard ratios (HRs) and relative 95% confidence intervals (CI) of potential clinical prognostic factors for time-to-event outcomes.

All statistical analyses were performed using STATA/MP 15.0 for Windows (StataCorp LLP, College Station, TX, USA).

**Results**

**Patient characteristics.** From October 1st 2014 to June 30th 2018, 618 patients with BM from any solid tumor were registered in the Italian BMDB. Three hundred and nine had BC as the primary site of disease and 220/309 with at least 6 months' follow up were included in the present analysis (Fig. 1). Median age was 62 (range 26–85) years.

At the time of the first diagnosis of BM, 152 (92.1%) patients showed a good ECOG PS (0–1). Forty-nine (22.3%) patients were diagnosed with BM synchronous to the primary tumor, while metachronous BM were found in 171 patients.

Bone-only metastases (BOM) were found in 109 (50.0%) patients, while the remaining 109 had concomitant visceral and BM (BVM). Histological and biological characteristics of the primary BC are shown in Tables 1 and 2. Luminal A and B tumors were more frequently associated with BOM, whereas basal-like or HER2-enriched BC subtypes more often showed BVM (p = 0.012). A higher, albeit not significant, Ki-67 value was observed for patients with BVM (p = 0.074). The majority of patients had T0–T2 (n = 159, 85%) and node-positive tumors (n = 138, 74.6%) at diagnosis (Table 3), the former associated with a higher rate of metachronous BM than synchronous BM (83.2% and 16.8%, respectively) (p < 0.001) (Table 4). Patients with N0 primary tumors had a higher incidence of metachronous BM than synchronous (95.8% and 4.2%, respectively) (p = 0.001). No difference between BOM or BVM according to node status (node negative vs. node positive tumors) was observed. Both node-negative and node-positive patients showed a high rate of metachronous BM (95.8% and 75.5%, respectively), even if in node-negative patients there is a significantly higher proportion of patients with metachronous BM.
Bone biopsy was performed in 58 (26.4%) cases. The median time from primary disease diagnosis to the appearance of BM in this subgroup was 79 months (95%CI: 65.0–118.1).

**Time to event outcomes.** Disease-free interval. Disease-free interval was calculated excluding patients with synchronous disease at bone (n = 49) and visceral (n = 2). The disease-free interval (DFI) differed slightly according to molecular subtype. The univariate hazard ratio (HR) for visceral or bone metastasis was higher in luminal B tumors (1.66, 95% confidence interval [CI] 1.1–2.5) (p = 0.023), basal-like tumors (3.92, 95% CI 1.6–9.7) (p = 0.003), and HER2-enriched tumors (1.28, 95% CI 0.7–2.4) (p = 0.442).

DFI for patients with stage I disease at diagnosis of primary BC was longer than that for stage III patients (median 67.2 months, 95% CI 53.1–96.1, vs. 58.1 months, 95% CI 41.9–73.4), with a univariate HR of 1.84 (95% CI 1.1–3.0) (p = 0.015) for the stage III group, and 0.98 (95% CI 0.6–1.5) (p = 0.931) for the stage II group. Older patients had a higher risk of metastasis (HR 1.91, 95% CI 1.4–2.7), as did those with larger tumors at diagnosis (HR: 3.7, 95% CI 1.9–7.1). Multivariate analysis confirmed these data for patients with basal-like and larger tumors (Table 5).

Bone disease-free interval. For this analysis, were excluded all patients with synchronous bone metastasis (n = 49). Median time to BM appearance was 78.2 months (95% confidence interval [CI] 63.6–87.9) for all patients.

Median bone disease-free interval (bDFI) was 63.5 months (95% CI 47.9–83.3) for the BM-only group at diagnosis and 86.6 months (95% CI 66.5–99.6) for those with visceral metastases. Median bDFI was 78.5 months (95% CI 63.6–87.9) in T0–T2 patients and 18.6 months (95% CI 57.0–79.0) for the node-positive subgroup (log rank test p = 0.032) (Fig. 2a,b). bDFI was significantly higher (p < 0.001) in patients aged <55 years at diagnosis than in those ≥55 years, (median 89.6 [95% CI 61.1–118.2] vs. 65.0 [95% CI 51.1–86.0] months) (Supplementary Fig. 1). Multivariate analyses confirmed a higher risk for patients with basal-like and larger tumors (Table 5).

**Overall survival.** Median follow-up was 46 months (range: 6–117) on 220 evaluable patients.

Seventy-four deaths were observed during follow-up. Median OS was 217.5 months (95% CI 172.5–340.1).

Molecular profile subtypes were an independent prognostic factor. Median OS (mOS) in patients with luminal A tumors was not-reached and 128.1 months (95% CI 108.0–182.6) for those with luminal B tumors, 101.2 months (95% CI 17.1–not estimable) for patients with basal-like BC, and 274.5 months (95% CI 70.3–not estimable) for those HER2-enriched BC (p = 0.010). Patients aged ≥55 years and those with stage IV disease...
Patients (n=220)  

| Median age, years (range) | 62 (26–85) |
|--------------------------|------------|
| Age at diagnosis of primary BM, years | |
| < 65 | 133 (60.5) |
| 65 | 87 (69.5) |
| ECOG PS at diagnosis of primary BM | |
| 0–1 | 152 (92.1) |
| ≥ 2 | 13 (7.9) |
| Unknown | 55 |
| Histology | |
| Ductal carcinoma | 166 (75.5) |
| Lobular carcinoma | 29 (13.0) |
| Mixed ductal and lobular carcinoma | 11 (5.0) |
| Adenocarcinoma, NOS | 9 (4.0) |
| Signet ring cell carcinoma | 1 (0.5) |
| Other | 4 (2.0) |
| pT at primary diagnosis of BC | |
| T0–T2 | 159 (85.0) |
| T3–T4 | 28 (15.0) |
| Tx | 31 |
| pN at primary diagnosis of BC | |
| N0 | 47 (25.4) |
| N+ | 138 (74.6) |
| Nx | 33 |
| Stage at diagnosis of primary disease | |
| I | 28 (14.1) |
| II | 68 (34.3) |
| III | 42 (21.2) |
| IV | 60 (30.3) |
| Unknown | 22 |
| BC molecular subtype | |
| Luminal A | 35 (18.8) |
| Luminal B | 118 (63.4) |
| Basal-like | 8 (4.3) |
| HER+ | 25 (13.4) |
| Unknown | 34 |
| Grading | |
| G1 | 6 (3.7) |
| G2 | 85 (52.5) |
| G3 | 71 (43.8) |
| Unknown | 58 |
| Bone metastasis | |
| Synchronous | 49 (22.3) |
| Metachronous | 171 (77.7) |
| BOM | 109 (40.0) |
| BVM | 109 (40.0) |

Table 1. Patient characteristics at baseline and at onset of BM. BM bone metastasis, ECOG PS Eastern Cooperative Oncology Group Performance Status, NOS not otherwise specified, BC breast cancer, pT primary tumour, pN pathological lymph node, Nx unknown lymph node stage, G grade, BOM bone-only metastasis, BVM visceral and bone metastasis.

at diagnosis had a shorter mOS (128.1 months [95% CI 101.2–182.6] and 65.3 months [95% CI 41.0–80.9], respectively) than the groups diagnosed at a younger age (< 55 years) and with lower-stage disease (Supplementary Fig. 2a,b). Patients with pain at the first diagnosis of bone metastases had an mOS of 143.8 months (95% CI 98.0–247.5) with respect to 257.4 months (95% CI 135.1–not estimable) for those with no pain.
Bone metastases represent a common complication of cancer, their incidence reaching around 65% in BC. There are still aspects of bone metastatic disease that need to be further investigated. As reported in previous studies, our case series showed a majority of lytic bone metastases. The nature (lytic or not) of BM would not appear to impact patient outcome. Small BC tumors (T0–T2) were associated with adverse events. Patients treated with zoledronic acid or pamidronate had a similar HR for SREs with respect to untreated patients (HR 1.32, 95% CI 0.74–2.38), while those taking denosumab had a HR of 0.20 (95% CI 0.04–0.87), indicating a reduced risk of SRE (Supplementary Fig. 4). Supplementary data are reported in Appendix 2.

### Table 2: Biomarker characteristics at diagnosis of primary BC and at onset of BM.

| BC characteristics | At diagnosis | At the onset of bone metastasis |
|--------------------|--------------|--------------------------------|
|                    | Positive (%) | Negative (%) | NA | Positive (%) | Negative (%) | NA |
| ER                 | 183 (89.7)   | 21 (10.3)    | 16 | 48 (88.9)    | 6 (11.1)     | 166 |
| PgR                | 144 (70.6)   | 60 (29.4)    | 16 | 24 (45.3)    | 29 (54.7)    | 167 |
| Ki-67              | <15%         | ≥ 15%        | NA | <15%         | ≥ 15%        | NA |
| HER2 (IHC or FISH) | 145 (79.7)   | 37 (20.3)    | 38 | 29 (65.9)    | 15 (34.1)    | 176 |

**Discussion**

Bone metastases represent a common complication of cancer, their incidence reaching around 65% in BC. There are still aspects of bone metastatic disease that need to be further investigated.

As reported in previous studies, our case series showed a majority of lytic bone metastases. The nature (lytic or not) of BM would not appear to impact patient outcome. Small BC tumors (T0–T2) were associated with adverse events. Patients treated with zoledronic acid or pamidronate had a similar HR for SREs with respect to untreated patients (HR 1.32, 95% CI 0.74–2.38), while those taking denosumab had a HR of 0.20 (95% CI 0.04–0.87), indicating a reduced risk of SRE (Supplementary Fig. 4). Supplementary data are reported in Appendix 2.
mOS from the time of diagnosis of metastatic disease and primary BC in patients < 55 years and < 65 years, respectively.

Our data are also consistent with previous literature reporting that luminal BC subtype confers an independent survival benefit regardless of tumor receptor status. The initial stage of disease at BC diagnosis represented an important prognostic factor for survival and is consistent with the literature on this topic. Some preclinical and clinical studies have reported promising results for concurrent ENDO + CH in postmenopausal patients with metastatic hormone-positive BC. In line with these findings, our patients undergoing the ENDO + CH combination showed a slight benefit in terms of mPFS with respect to those treated with ENDO + CH ± BIO. These fascinating suggestions warrant further exploration and validation prospective clinical trials.

Table 3. Baseline patient characteristics in relation to presence of visceral metastases. BC breast cancer, BOM bone-only metastasis, BVM visceral and bone metastasis, pT primary tumour, pN pathological lymph node, ER oestrogen receptor, PgR progesterone receptor, IHC immunohistochemistry, FISH fluorescence in situ hybridisation.
Previous studies have shown a better prognosis for BOM patients than for those with BVM. However, in our study BOM and BVM groups had a similar mOS which may be attributable to a conditioning effect of the molecular BC subtype and also to new treatments available.

A recently published study on BOM reported no correlation between bone pain and survival. Our results are in line with these findings in both BOM and BVM groups. BM localization proved to have a prognostic value in our case series, an appendicular site negatively impacting mOS more than axial or mixed localizations. In a retrospective study conducted by Parkes et al., BOM patients with axial localisation had a mOS from the diagnosis of distant disease of 5.62 years compared to 6.78 years for those with appendicular BM and 4.58 years the appendicular + axial BM group. A possible explanation for this could be the higher incidence of axial bone metastases in luminal BC.

Another interesting finding of our study was that patients with single or oligo- metastases had a better prognosis than those with multiple bone lesions. Although there is already evidence of this for the former, interest in oligo-metastatic disease has recently come to the fore because of its challenging management.

It has been seen that changes in BC cell biology occur between primary tumors and metastases. In our study a significant difference in PgR expression was observed between primary BC and metastatic bone lesions.

### Table 4. Baseline patient characteristics in relation to synchronous or metachronous metastases. BM bone metastasis, pT primary tumour, pN pathological lymph node, ER oestrogen receptor, PgR progesterone receptor, IHC immunohistochemistry, FISH fluorescence in situ hybridisation.
Clinicians should take this into account in cases of disease recurrence more than 5 years after the primary diagnosis.

Age was found to have a significant impact on OS. This is in line with retrospective works published on BC and BM patients in which age was found to be an independent prognostic factor. Age at diagnosis of primary BC, years

| Overall DFI | bDFI |
|------------|------|
| **DFI**    | **HR from univariate Cox regression model (95%CI)** | **HR from multivariate Cox regression model (95%CI)** | **DFI**    | **HR from univariate Cox regression model (95%CI)** | **HR from multivariate Cox regression model (95%CI)** |
| All cases  | 75.7 (63.5–87.3) | – | – | 78.2 (63.6–87.9) | – |
| Age at diagnosis of primary BC, years |
| < 55       | 82.1 (65.4–112.9) | 1.00 | 1.00 | 89.6 (65.4–114.8) | 1.00 |
| ≥ 55       | 65.0 (48.1–81.5)  | 1.91 (1.4–2.7) | 1.48 (0.9–2.2) | 65.0 (51.1–86.0) | 1.89 (1.4–2.6) |

**BC molecular subtypes**

- Luminal A: 101.9 (57.0–125.7) 1.00 1.00 101.9 (57.0–125.7) 1.00 1.00
- Luminal B: 63.5 (48.6–75.7) 1.66 (1.1–2.5) 1.46 (0.9–2.4) 63.6 (52.7–78.5) 1.54 (0.9–2.4) 1.27 (0.8–2.0)
- Basal-like: 30.0 (13.4–NE) 3.92 (1.6–9.7) 3.94 (1.4–11.0) 30.0 (21.6–66.1) 4.29 (1.8–10.1) 3.82 (1.4–10.6)
- HER2+: 53.1 (30.9–100.1) 1.28 (0.7–2.4) 1.44 (0.7–2.9) 53.1 (47.9–100.2) 1.17 (0.6–2.2) 1.22 (0.6–2.5)

**Stage at diagnosis**

- I: 67.2 (53.1–96.1) 1.00 1.00 82.2 (53.6–125.7) 1.00 1.00
- II: 83.3 (66.5–99.2) 0.98 (0.6–1.5) 1.09 (0.5–2.3) 83.2 (66.5–101.9) 1.07 (0.7–1.7) 1.16 (0.6–2.4)
- III: 58.1 (41.9–73.4) 1.84 (1.1–3.0) 1.35 (0.5–3.2) 60.9 (41.9–75.6) 2.1 (1.3–3.5) 1.55 (0.7–3.7)
- IV: – – – – – –

**pT at primary diagnosis of BC**

- T0–T2: 76.7 (61.0–87.3) 1.00 1.00 78.5 (63.6–87.9) 1.00 1.00
- T3–T4: 20.6 (3.3–65.4) 3.7 (1.9–7.1) 3.24 (1.5–7.1) 18.6 (3.3–57.0) 4.5 (2.4–8.2) 3.02 (1.4–6.6)

**pN at primary diagnosis of BC**

- N0: 83.3 (56.1–101.9) 1.00 1.00 89.6 (61.1–118.2) 1.00 1.00
- N+: 66.3 (56.3–80.0) 1.36 (0.9–1.9) 0.91 (0.5–1.7) 66.5 (57.0–79.0) 1.47 (1.0–2.1) 0.97 (0.5–1.8)

Table 5. Median DFI and independent risk factors for metastasis. *DFI* disease-free interval, *bDFI* bone disease-free interval, *HR* hazard ratio, *BC* breast cancer, *NE* not evaluable from statistical software, *pT* primary tumour, *pN* pathological lymph node.

**Clinicians should take this into account in cases of disease recurrence more than 5 years after the primary diagnosis.**

Age was found to have a significant impact on OS. This is in line with retrospective works published on BC and BM patients in which age was found to be an independent prognostic factor.

Finally, our data confirm the protective effect of denosumab in preventing SREs, which leveled off over time. Albeit with an incidence reducing over time.

One of the limitations of our study is the patient sample even though it's consistent with other studies in which patients were followed prospectively in a dedicated database on BM and not extrapolated from large registries. Another limit is the lack of information available on specific treatments, a result of opting not to enter a large amount of data into the database. To overcome this we grouped treatments into specific categories.

In contrast, the strengths of our study are its collection of prospective data on BM and their clinical evolution and the fact that it constitutes a national representative study population for this disease setting.
In conclusion, the Italian BMDB represents an invaluable tool to better understand the natural history of bone metastases from breast cancer and improve their management. The Italian BMDB continues to enroll patients also in other solid tumors to increase the case series and give more answer to clinician questions.

**Data availability**
The datasets gathered and analyzed during the current study are available from the corresponding author on reasonable request.
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**Competing interests**
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**Additional information**

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