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ORIGINAL RESEARCH

Bone Metastases and Skeletal Complications: Information and Involvement of Patients with Cancer in the Treatment Pathway

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ABSTRACT

Introduction: Adequate information about patients with bone metastases could increase adherence to treatment and reduce or delay skeletal and dental complications. Limited data are available on patient awareness, the degree of information received, and adherence to specific treatment for bone metastases.

Methods: ROPI (Rete Oncologica Pazienti Italia) conducted an anonymous survey from 1 February to 31 August 2022 among patients with bone metastases from solid tumors to evaluate their level of information and adherence to specific treatments and dental evaluations. Questionnaires were administered by oncologists or nurses at participating cancer centers.

Results: Analysis of 351 questionnaires revealed that 75% of patients felt "fairly/well" informed about bone metastases and skeletal complications. The oncologists were the primary source of information. More than 80% of patients reported undergoing specific treatment

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for bone metastases (denosumab, 48%; zoledronic acid, 46%); 93% of patients received dental evaluations before starting therapy (with dental complications in only 0.3% of patients) and 78% received information about the importance of regular dental checkups. Vitamin D and calcium supplements were taken by 83% of patients. Among patients with skeletal complications (47% of patients), bone radiotherapy was the most frequent (94%).

Conclusions: Most patients stated that they had received information about bone metastases, skeletal complications, and specific treatments. This could increase awareness and adherence to treatment and potentially reduce or delay skeletal and/or dental complications improving patients' quality of life and survival.

Keywords: Bone metastases; Skeletal complications; Bisphosphonates; Denosumab; Patient information

Key Summary Points
Limited data are available on patient awareness, the degree of information received, and adherence to specific treatment for bone metastases.
Adequate information about patients with bone metastases could increase adherence to treatment and reduce or delay skeletal and dental complications.
The study evaluated the level of information received by patients with bone metastases from solid tumors.
Providing information on bone metastases and related complications could improve adherence to treatment, potentially reducing skeletal and dental complications, and enhancing quality of life and survival for patients.

INTRODUCTION

Bone metastases develop in 70% of patients with breast and prostate cancer and in more than 30% of patients with lung cancer [1]. The most frequent symptom is bone pain at the site of the metastasis. In addition, bone metastases are clinically important because they increase the risk of skeletal complications: bone fractures, bone marrow compression, hypercalcaemia, need for radiotherapy. Clinical studies have reported a 2-year cumulative incidence of skeletal events from bone metastases in 68% of patients with breast cancer [2] and in 49% of patients with prostate cancer [3]. In clinical practice in the USA, the incidence of skeletal complications at diagnosis of bone metastases (between January 1995 and December 2009) was 22.4% in 621 patients with breast cancer, 22.4% in 477 patients with lung cancer, and 10% in 721 patients with prostate cancer [4]. Despite the low percentage of patients starting bisphosphonate therapy, the incidence of skeletal events increased over the course of the disease, with overall incidence at 24 months of 62.6% in breast cancer, 58.7% in lung cancer, and 51.7% in prostate cancer [4].

Skeletal events occurring as complications of bone metastases in patients with solid tumors are associated with reduced survival [5, 6].

Pamidronate, zoledronate, and denosumab can reduce and delay the occurrence of skeletal events in breast cancer [7], prostate cancer [8–10] and lung cancer [11]; these drugs are available in clinical practice.

However, there are limited data on the information received by patients regarding bone metastases, skeletal complications, and available therapy for bone metastases. Patient education and engagement are crucial for effective participation in their therapeutic pathway, as informed patients are more likely to adhere to prescribed therapies and achieve better outcomes. To address this gap, the ENGAGE project was conducted by ROPI (Rete Oncologica Pazienti Italia—Oncology Patients Network Italy) with the objective of evaluating the degree of information received by patients with cancer about bone metastases, skeletal

complications, and specific therapy for bone metastases.

METHODS

ROPI is a network of oncology patient associations established to coordinate and represent associations and their needs to healthcare institutions, provide patients and caregivers with certified information, and train patients for their inclusion in institutional working groups.

ROPI distributed a questionnaire to Italian patients with cancer aged ≥ 18 years with bone metastases from solid tumors. The questionnaire consisted of 30 questions, to assess to what degree patients with cancer were informed about their bone metastases, skeletal complications, and treatment for bone metastases. This questionnaire was tested in 10 patients with bone metastases prior to distribution.

The questionnaires were delivered to the patients in either paper or digital form by oncologists or nurses at the cancer centers involved in this survey and were completed anonymously. The digital questionnaires were accessible to patients through the ROPI website, while the paper ones were distributed by hospital staff of the Italian cancer centers involved in the project.

The questionnaire (online supplementary material) comprising 30 questions was developed taking into account the following important topics:

1. Patient characteristics (age, primary tumor, cancer center)
2. Degree of information received on bone metastases and skeletal complications, and sources of information
3. Patient's involvement in the treatment pathway
4. Patient's attention to bone metastases and degree of concern about the presence of bone metastases
5. Treatment of bone metastases (drugs, duration)
6. Dental evaluations and supplementation with vitamin D and calcium
7. Any skeletal complications that have occurred
8. Pain at sites of bone metastases
9. Impact of the COVID-19 pandemic on the treatment of bone metastases

The study was approved on January 2022 by the Internal Review Board of IRCCS Sacro Cuore Don Calabria, Negrar di Valpolicella, Italy (approval protocol number 01-2022). The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

The objective of this study was to evaluate the degree of information received by patients with cancer about bone metastases, skeletal complications, and specific therapy for bone metastases.

Statistical Analysis

Descriptive statistical analyses were conducted using Microsoft® Excel® for Microsoft 365 MSO (Version 2302 Build 16.0.16130.20586). Within the questionnaire, there were multiple-choice questions or questions with open-text answers. When the responses to each question were analyzed, for multiple-choice questions, only the answers with one option selected were considered valid responses (unless the possibility of choosing multiple options was specified). The only open-text questions related to the hospital where the patients were treated.

Chi-square tests of independence were performed to compare information sources by age group for both bone metastases and skeletal complications.

A detailed analysis of the factors influencing dental checkups and vitamin D intake among patients with bone metastases was conducted using cross-tabulation, incorporating chi-square tests and Pearson correlation analyses to examine these relationships in depth.

RESULTS

From 1 February 2022 to 31 August 2022, 396 questionnaires were collected from patients

under treatment in 76 hospitals across Italy; 45 were excluded from the analysis because patients jointly declared the following: they were not receiving specific therapy for bone metastases and there were no bone metastases.

The analysis was performed on 351 (88.6%) questionnaires and showed that the majority of responding patients with cancer were being treated at eight cancer centers (IRCCS Istituto Tumori of Milan, ASST Papa Giovanni XXIII of Bergamo, IRCSS Sacro Cuore Don Calabria of Negrar, Molinette Hospital of Turin, Azienda Ospedaliera Santa Maria of Terni, Casa di Cura INI of Grottaferrata, IRCCS Policlinico A. Gemelli of Rome, and V. Fazi Hospital of Lecce).

The majority of responding patients were being treated at centers in Northern Italy (69%), followed by Central Italy (24%) and the South/Islands (7%).

Age of patients and distribution by cancer disease are summarized in Fig. 1.

About 50% of patients were ≥ 60 years of age, 47% were 40–59 years old, and only 4% were 18–39 years old. The primary cancer site was the breast (67%) followed by prostate (17%) and lung (7%). Overall, 63% of patients with breast cancer were over 40 years old of age.

About the degree of information that patients claimed to have received about bone metastases and related information sources (questions 5 and 7), the results showed that 75% (263/351) of

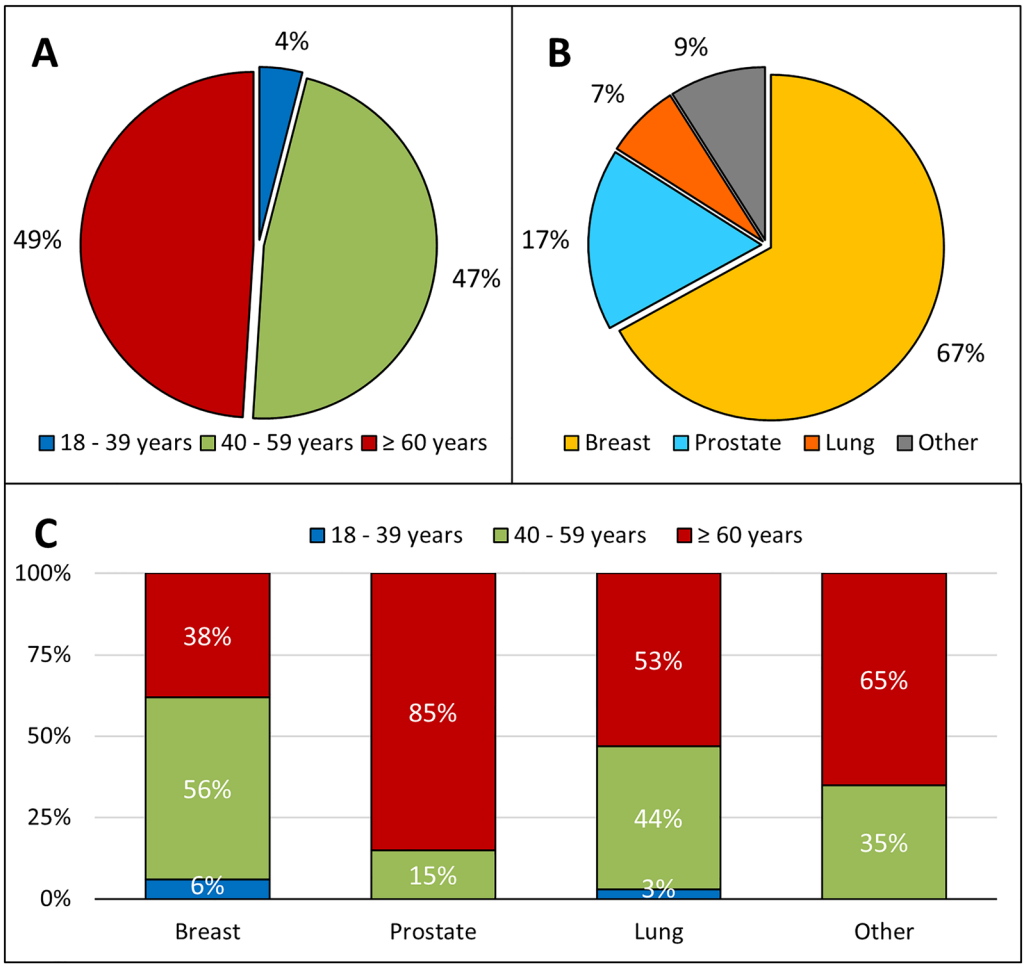

Fig. 1 Patient's characteristics. Distribution of 351 patients by age (**A**), by primary cancer site (**B**), and by the combination of age and primary cancer site (**C**)

patients stated that they were "fairly enough/a lot" informed about bone metastases and 82% (288/351) that they "fairly/well" understood the information they received.

Regarding information sources, the patients reported that information on bone metastases was mainly obtained from the oncologist (92%), followed by the general practitioner (32%), the internet (19%), family and friends (7%), magazines (4%), and social groups (1%), with difference between the various age groups (Table 1). The oncologist was the most frequent source of information for the age group ≥ 60 years (95%); the internet was used more frequently by the age group 18–39 years (67%).

A chi-square test of independence revealed that the choice of information sources about bone metastases varied significantly by age group ($p = 0.0044$). Younger patients tended to rely more on digital resources (e.g., internet) or peer networks, whereas older patients were more likely to seek information from oncologists and general practitioners.

Out of 351 patients with bone metastases, 72% stated that they received information about skeletal complications (question 8) and that the oncologist was the most frequent source of information (85%), followed by the internet (32%), general practitioner (17%), social groups (9%), family and friends (7%), and magazines (2%). The internet, on the other hand, was the information source predominantly used by young people (18–39 years) in comparison to older patients (≥ 60 years): 47% versus 20%, respectively (Table 2).

A chi-square test of independence indicated a statistically significant difference among age groups for the information sources about skeletal complications ($p = 0.0356$). Younger individuals were more likely to rely on digital platforms and peer networks, whereas older adults primarily consulted healthcare professionals.

Table 1 Sources of information about bone metastases in all patients and by age

Characteristic	*n*	Information source about bone metastases[a]					
		Oncologist	General practitioner	Internet	Family/friends	Magazines	Social groups
Overall	351	323 (92%)	112 (32%)	67 (19%)	25 (7%)	14 (4%)	4 (1%)
Age	349						
18–39 years	15	13 (87%)	1 (7%)	10 (67%)	3 (20%)	1 (7%)	0 (0%)
40–59 years	162	146 (90%)	26 (16%)	70 (43%)	15 (9%)	6 (4%)	5 (3%)
≥ 60 years	172	163 (95%)	38 (22%)	34 (20%)	9 (5%)	7 (4%)	0 (0%)

[a]Answers to question 6: "What were your sources of information?" (Supplementary material)

Table 2 Sources of information about skeletal complications in all patients and by age

Characteristic	*n*	Information source about skeletal complications[a]					
		Oncologist	General practitioner	Internet	Family / friends	Magazine	Social groups
Overall	351	298 (85%)	60 (17%)	112 (32%)	25 (7%)	7 (2%)	32 (9%)
Age	349						
18–39 years	15	12 (80%)	1 (7%)	7 (47%)	1 (7%)	0 (0%)	1 (7%)
40–59 years	162	134 (83%)	24 (15%)	71 (44%)	13 (8%)	3 (2%)	18 (11%)
≥ 60 years	172	151 (88%)	33 (19%)	34 (20%)	9 (5%)	3 (2%)	14 (8%)

[a]Answers to question 9: "What were your sources of information?" (Supplementary material)

About the patient's involvement in the care pathway (questions 10 and 11), the results showed that 89% (312/351) of patients said they would like to be involved in the care pathway and that 85% (299/351) said they would ask the doctor questions to better understand their disease and treatment management.

Regarding the degree of patient attention to the issue of bone metastases (question 12), 83% (284/342) of the patients answered that they were "quite a lot/much" attentive on a scale of 1 to 4 (1 = not at all; 2 = a little; 3 = quite a lot; 4 = much), with a mean response of 3.2 (IQR 3–4). The breast patients with cancer (mean 3.3) and the patients aged 40–59 years (mean 3.4) were the most attentive, on average, to bone metastases. In addition, 72% of patients answered that they were "fairly concerned/very worried/feeling anxious" on a scale of 1 to 5 (1 = quiet; 2 = slightly concerned; 3 = fairly concerned; 4 = very worried; 5 = feeling anxious), with a mean response of 3.1 (IQR 2–4). The breast patients with cancer (mean 3.4) and the younger (18–39 years) patients (mean 3.8) reported feeling more anxious.

About the type of therapy for bone metastases and its duration (questions 14–17), 82% (285/345) of patients responded that they were receiving specific therapy: 47% (134/285) zoledronic acid, 49% (140/285) denosumab, and 4% (11/285) other bisphosphonates. Drugs used for bone metastases in relation to age and tumor type are reported in Table 3.

More than 80% of patients (240/279; 86%) stated that they had started drug therapy for bone metastases within 2 years. Only a third of patients (107/300; 36%) knew the duration of therapy and 86% (92/107) of these patients stated that they would have to continue therapy for bone metastases for a maximum of 2 years.

Regarding dental checkups (before starting therapy for bone metastases and during therapy and vitamin D and calcium supplementation; questions 18–23), 93% of patients (293/316) had an X-ray orthopanoramic and a dental examination before starting therapy and 78% (262/334) had received information regarding periodic dental checkups during therapy for bone metastases. About periodic dental checkups during drug therapy for bone metastases, 72% (225/311) of patients stated that they had a periodic dental checkup; this percentage was higher in patients younger (92%), with breast cancer (77%) and in therapy with denosumab (85%) (Table 4). Sixty-nine percent (152/221) of the patients responded that they undergo periodic dental checkups every 3–6 months (question 22). Dental complications were reported by

Table 3 Distribution of patients by drugs used for bone metastases in relation to age and tumor type

Characteristic	*n*	Drugs		
		Zoledronic acid	Denosumab	Other bisphosphonates
Overall	285	134 (47%)	140 (49%)	11 (4%)
Age	285			
18–39 years	12	1 (8%)	10 (83%)	1 (8%)
40–59 years	137	58 (42%)	74 (54%)	5 (4%)
≥ 60 years	136	73 (54%)	53 (39%)	10 (7%)
Tumor type	267			
Breast	199	80 (40%)	109 (55%)	10 (5%)
Prostate	49	32 (65%)	15 (31%)	2 (4%)
Lung + other	19	8 (42%)	10 (53%)	1 (5%)

Table 4 Distribution of patients by periodic dental checkups in relation to age, tumor type, and drugs administered for bone metastases

Characteristic	*n*	Periodic dental checkups[a]	
		Yes	No
Overall	311	225 (72%)	86 (28%)
Age	311		
18–39 years	12	11 (92%)	1 (8%)
40–59 years	144	112 (78%)	32 (22%)
≥ 60 years	153	99 (65%)	54 (35%)
Tumor type	287		
Breast	189	146 (77%)	43 (23%)
Prostate	56	29 (52%)	27 (48%)
Lung	20	12 (60%)	8 (40%)
Other	22	15 (68%)	7 (32%)
Drug for bone metastases	261		
Zoledronic acid	130	81 (62%)	49 (38%)
Denosumab	123	105 (85%)	18 (15%)
Other bisphosphonates	8	6 (75%)	2 (25%)

[a]Answers to question 21: "If you are undergoing specific therapy for bone metastases, do you perform periodic dental checkups?" (Supplementary material)

only 0.3% of patients who had undergone basal dental evaluations before starting therapy for bone metastases.

During specific therapies for bone metastases, 83% of patients (267/320) reported taking oral supplementation with vitamin D and calcium during therapy for bone metastases (question 23).

Table 5 Distribution of patients by vitamin D and calcium supplementation in relation to age, tumor type, and drugs administered for bone metastases

Characteristic	*n*	Vitamin D and Ca supplementation[a]	
		Yes	No
Overall	320	267 (83%)	53 (17%)
Age	318		
18–39 years	12	11 (92%)	1 (8%)
40–59 years	148	127 (86%)	21 (14%)
≥ 60 years	158	126 (80%)	32 (20%)
Tumor type	315		
Breast	213	190 (89%)	23 (11%)
Prostate	57	38 (67%)	19 (33%)
Lung	21	15 (71%)	6 (29%)
Other	24	21 (88%)	3 (13%)
Drug for bone metastases	282		
Zoledronic acid	132	96 (73%)	36 (27%)
Denosumab	139	133 (96%)	6 (4%)
Other bisphosphonates	11	10 (91%)	1 (9%)

[a]Answers to question 23: "If you are undergoing treatment for bone metastases, do you also take vitamin D and calcium?" (Supplementary material)

Table 5 shows the percentage of patients who reported taking/not taking vitamin and calcium supplementation according to age, cancer, and type of drug administered for bone metastases.

When the various age groups were evaluated, vitamin D and calcium supplementation was taken by 92% of younger patients (18–39 years), 86% of patients aged 40–59 patients, and 80% of over-60 patients.

On the basis of the primary tumor, oral supplementation was taken more by patients with breast cancer (89%) followed by patients with lung cancer (71%) and patients with prostate cancer (67%). According to the type of therapy for bone metastases, vitamin D and calcium supplementation was prevalent in patients treated with denosumab (96%) in comparison to zoledronic acid (73%) (Table 5).

To investigate the association between information provision and adherence to dental checkups, between information sources and adherence to dental checkups, and between information sources and vitamin D intake to assess whether awareness plays a role in supplementation decisions, cross-tabulation analyses were performed.

The results showed that there was a strong association between receiving information on dental checkups during specific therapy for bone metastases (question 20) and actually undergoing those checkups (question 21) ($p < 0.001$). In contrast, the relationship between patients' adherence to dental checkups (question 21) and the sources of information about bone metastases (multiple-answer question 6) was not statistically significant ($p = 0.074$).

In addition, information sources (again derived from multiple-answer question 6) were not significantly associated with vitamin D intake (question 23) ($p = 0.155$).

Other correlation analyses were performed to investigate the relationships between four clinical and demographic factors (age group, tumor type, region, and macro region) and four key variables (bone metastases, dental controls, vitamin D intake, and information source). The results showed that age group was linked to both dental controls ($p = 0.006$) and information source ($p = 0.004$), suggesting that the adherence to dental checkups and the source of information about bone metastasis are directly linked to different age cohorts. Tumor type was also significantly related to dental controls ($p = 0.001$) and vitamin D intake ($p < 0.0001$), indicating that the specific tumor profiles might influence a patient's preventive behaviors and supplement use.

Geographic factors also play an important role. Region shows significant associations with all four variables: bone metastases ($p < 0.0001$), dental controls ($p < 0.0001$), vitamin D intake ($p < 0.0001$), and information source ($p = 0.011$). This points to substantial regional variations in clinical and behavioral outcomes. Likewise, macro region (North, Centre, South/Islands) correlates significantly with dental controls ($p = 0.001$), vitamin D intake ($p = 0.031$), and information source ($p = 0.001$), suggesting that broader geographic divisions may further shape patient behaviors and information-seeking patterns.

The seventh part of the questionnaire was related to skeletal complications (questions 24 and 25): 47% (159/336) of patients responded that they had skeletal complications. Radiotherapy to bone metastases was the most frequent skeletal-related event (149/159; 94%). Other reported skeletal complications were pathological fractures (37/159; 23%), bone surgery (17/159; 11%), spinal cord compression (10/159; 6%), and hypercalcaemia (3/159; 2%). About half of the patients (167/330; 51%) reported pain at the sites of bone metastases, 90% (208/231) of the respondents said they had reported this symptom to their doctor (questions 26 and 27), and 71% (184/261) of patients stated that they had experienced "quite/much benefit" from specific therapy for bone metastases on the pain symptom (question 28).

The last part of the questionnaire assessed the impact of the COVID-19 pandemic on the treatment pathway for bone metastases (questions 29 and 30), because in the years 2020–2021 many patients reported having difficulty starting or continuing hospital treatment. Out of 344 patients, 75% stated that it had no impact on their treatment pathway and 25% stated that it had an impact; the main problem encountered (49/87; 56%) was a delay in making one or more oncology visits, without compromising the course of the therapy.

Evaluating the impact of the COVID-19 pandemic on the treatment pathway of bone metastases according to the geographical area of the patients' cancer center of reference, the data showed a lower impact on the course of treatment reported by patients treated at oncological centers in Northern Italy (20%) compared to the

other geographical areas (36% in the Centre and 41% in South/Island of Italy).

For complete questionnaire answers, see online supplementary material.

DISCUSSION

From 1 February 2022 to 31 August 2022, we conducted a survey on patients with bone metastatic cancer treated or being treated in 76 hospitals across Italy, where standard practices of bone metastases therapy were based on Italian and international guidelines [12–15].

Analyses of 351 questionnaires showed that 75% of patients reported that they were "fairly/well informed" about their bone metastases, with a good understanding of the information reported by 83% of patients.

In addition, 72% of patients stated that they also received information on skeletal complications. The most frequent source of information for patients was the oncologist (92% for bone metastases and 85% for skeletal complications), followed by the general practitioner and the internet (Tables 1 and 2). The general practitioner was the most frequent source of information for older patients. According to the age of the patients, the internet was used more to retrieve information on bone metastases by young patients (18–39 years) than by patients over 60 (67% vs. 20%, respectively). In contrast, the general practitioner was consulted more frequently by patients aged ≥ 60 year in comparison to young patients (Tables 1 and 2). The choice of information sources both about bone metastases and about skeletal complications varied significantly by age group ($p = 0.0044$ and 0.0356, respectively): these findings emphasize the importance of tailoring information delivery to match the preferences of different age cohorts and the need to provide more communication channels (such as printed materials, digital platforms, and face-to-face consultations) to help ensure that patients of all ages receive relevant and accessible information.

In addition to cancer therapy, 82% of patients stated that they were on therapy for bone metastases: 47% with zoledronic acid, 49% with denosumab, and 4% with other bisphosphonates. These drug utilization rates reported by patients were similar to those reported by a real-world study conducted in the USA on 14,881 patients with bone metastases (diagnosed in 2012–2014) from breast (33%), prostate (26%), or lung (26%) cancer. Overall, 49% of these patients started therapy with denosumab and 51% with zoledronic acid [16]. Thus, our results showed that patient-reported data may also be important to know the utilization rate of specific drugs for bone metastases in clinical practice.

In our survey, 86% of patients who knew the duration of therapy for bone metastases stated that this therapy would not exceed 2 years. This result underlines the good knowledge of patients about the duration of their therapy for bone lesions. Nevertheless, in the literature, the optimal duration of bone metastases therapy has not been defined [12] but it is reasonable to interrupt therapy after 2 years for patients in remission for bone metastases [13, 14].

The survey results show that patients with bone metastases have:

1. A high awareness of their disease (85% of patients stated that they ask their doctor "fairly often/very often" questions to better understand their disease situation)
2. A high desire to be actively involved in the treatment process (89% of patients stated that they wanted to be "quite/very much" involved)
3. A high degree of attentiveness to bone disease (83%)
4. A high degree of concern (72% of patients reported being fairly concerned/very worried/anxious)

In addition, the results of this survey underline that correct information and full awareness of the disease situation by patients could facilitate patient adherence to therapy for bone metastases. Indeed, we report high adherence to:

1. Specific therapy for bone metastases (82% of patients stated that they were being treated with bisphosphonates or denosumab and 64.3% knew the duration of therapy)

2. Dental checkups before therapy (93%) and during specific therapy for bone disease (72%), as indicated by American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and Associazione Italiana di Oncologia Medica (AIOM) guidelines to avoid osteonecrosis of the jaw [12–15]
3. Supplementation with vitamin D and calcium (83%) [13, 15]

In this survey a difference was reported in the use of specific drugs for bone metastases according to age and type of cancer. Denosumab was more used in younger patients (in 83% of patients aged 18–39 years compared to 39% of patients ≥ 60 years), while zoledronic acid was used more in patients ≥ 60 years of age (54%). According to the type of cancer, denosumab was used in 55% of patients with metastatic breast cancer compared to 31% of patients with metastatic prostate cancer; zoledronic acid in 65% of patients with prostate cancer versus 40% of patients with breast cancer (Table 3).

In addition, although 72% of patients reported having periodic dental checkups during treatment for bone metastases, the percentage of patients with metastasis who reported receiving/not receiving periodic dental checkups was different in relation to patient age, cancer, and type of drug administered for bone metastases (Table 4). Dental complications were reported by only 0.3% of patients. The analysis of these data showed that periodic dental checkups were performed during therapy for bone metastases mainly in younger patients (92%), patients with breast cancer (77%), and patients on denosumab therapy (85%). In contrast, fewer periodic procedures were performed in patients ≥ 60 years of age (65%), patients with prostate cancer (52%), and patients on zoledronic acid therapy (62%).

Our analyses showed that the provision of information can significantly influence patient behavior regarding dental checkups during specific therapy for bone metastases. These results emphasize the importance of targeted communication strategies in promoting preventive care. By ensuring that patients are well informed, healthcare professionals can likely increase patient compliance with regular dental checkups, which in turn may mitigate dental complications related to bone metastases.

About half of the patients with bone metastases (159/336; 47%) had experienced skeletal complications: radiotherapy on bone metastases (94%), pathological fractures (23%), surgery (11%), spinal cord compression (6%), and hypercalcaemia (2%); 51% of them reported pain in the bone metastases requiring radiation therapy in over 90% of cases. About 90% of patients had started specific therapy for bone metastases less than 2 years earlier.

In clinical practice, in the absence of specific therapy for bone metastases, the 2-year cumulative incidence of skeletal-related events (SREs) observed in 47,052 patients with bone metastases from solid tumors (diagnosis between January 2008 and March 2015) was 52% [17]. In clinical trials, the 2-year cumulative incidence of skeletal events in the placebo arm was 49% in patients with prostate cancer [3] and 68% in patients with breast cancer [2].

Moreover, skeletal complications following bone metastases in patients with solid tumors are associated with poorer quality of life [18] and shorter survival [5, 6].

Since the goals of treatment for bone metastases are to reduce pain and morbidity and to improve quality of life and since bisphosphonates and denosumab can reduce the incidence of skeletal complications in patients with bone metastases from solid cancers and delay their occurrence [2, 3, 7, 9–11, 19], it is important to perform these therapies to improve patients' quality of life and survival, and to start these drugs early, as recommended by ESMO and AIOM guidelines [13, 15].

The impact of the COVID-19 pandemic on the treatment pathway of bone metastases was also investigated in our survey. This impact was modest and reported by only 25% of patients, with differences between geographical areas. The greatest difficulty reported by patients was the delay of one or more doctor's visits, without however compromising the course of treatment.

There are some biases in our descriptive analysis that should be acknowledged. One limitation is that not all patients answered every question in the questionnaire. However, the number of respondents for each question is fully reported

in the supplementary material. Another limitation is the lack of demographic data collection (sex/gender; race/ethnicity). In addition, we were unable to verify the actual degree of understanding that each patient had regarding the information provided. We also could not assess whether patients were able to accurately evaluate the correctness of the information they received. Furthermore, this survey was not designed to include data from patient records regarding the site of the lesion(s), the oncologic status of the patient (such as time from diagnosis, presence of other metastases), duration of treatment, and secondary surgery for pathological fractures. Additionally, no formal sample size calculation was conducted prior to the study. Finally, our survey did not specifically ask about the intervals at which zoledronic acid was administered. However, it is important to note that recent research, including three randomized controlled trials [20–22], one systematic review [23], and one real-world study [24], has demonstrated that administering zoledronic acid every 12 weeks is as effective as every 4 weeks in preventing SREs and time to the first SRE.

CONCLUSIONS

The survey results showed that the majority of patients reported that they received information on bone metastases, skeletal complications, and specific treatments for bone disease, mainly from the oncologist; 75% of patients stated that they were "fairly enough/ a lot" informed about bone metastases and 83% that they "fairly/well" understood the information they received.

Appropriate information could make patients more aware of the problem of bone metastases and increase adherence to specific therapy. This is very important because adequate therapy can reduce the incidence or delay the onset of related skeletal events, which negatively impact the quality of life and patient survival.

In addition, these results showed that more of 90% of patients had a dental checkup before starting bisphosphonates or denosumab, according to Italian and international guidelines.

This analysis also highlights that patient reports may coincide with the results of real-world studies. The results of this questionnaire showed that approximately half of patients with bone metastases from solid tumors were receiving denosumab and the other half were on zoledronate, with rates similar to those observed in clinical practice in the USA.

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Declarations

Conflict of Interest. Stefania Gori, Alessandra Fabi, Giuseppe Procopio, Mario Airoldi, Alberto Zambelli, Gaetano Lanzetta, Sergio Bracarda, Jennifer Foglietta, Silvana Leo, Anna Baggi, Jean Marie Franzini, Matteo Valerio, Matteo Verzè and Fabrizio Nicolis have nothing to disclose.

Ethical Approval. The study was approved on January 2022 by the Internal Review Board of IRCCS Sacro Cuore Don Calabria, Negrar di Valpolicella, Italy (approval protocol number 01-2022). The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

REFERENCES

1. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12:6243s–9s. https://doi.org/10.1158/1078-0432.CCR-06-0931.

2. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer. 2000;88:1082–90. https://doi.org/10.1002/(sici)1097-0142(20000301)88:5%3c1082::aid-cncr20%3e3.0.co;2-z.

3. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94:1458–68. https://doi.org/10.1093/jnci/94.19.1458.

4. Oster G, Lamerato L, Glass AG, et al. Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems. Support Care Cancer. 2013;21:3279–86. https://doi.org/10.1007/s00520-013-1887-3.

5. Nørgaard M, Jensen AØ, Jacobsen JB, et al. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). J Urol. 2010;184:162–7. https://doi.org/10.1016/j.juro.2010.03.034.

6. Yong M, Jensen AÖ, Jacobsen JB, et al. Survival in breast cancer patients with bone metastases and skeletal-related events: a population-based cohort study in Denmark (1999–2007). Breast Cancer Res Treat. 2011;129:495–503. https://doi.org/10.1007/s10549-011-1475-5.

7. Stopeck AT, Lipton A, Body J-J, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010;28:5132–9. https://doi.org/10.1200/JCO.2010.29.7101.

8. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet. 2012;379:39–46. https://doi.org/10.1016/S0140-6736(11)61226-9.

9. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377:813–22. https://doi.org/10.1016/S0140-6736(10)62344-6.

10. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst. 2004;96:879–82. https://doi.org/10.1093/jnci/djh141.

11. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol. 2011;29:1125–32. https://doi.org/10.1200/JCO.2010.31.3304.

12. Van Poznak C, Somerfield MR, Barlow WE, et al. Role of bone-modifying agents in metastatic breast cancer: an American Society of Clinical Oncology-Cancer Care Ontario focused guideline update. J Clin Oncol. 2017;35:3978–86. https://doi.org/10.1200/JCO.2017.75.4614.

13. Coleman R, Hadji P, Body J-J, et al. Bone health in cancer: ESMO clinical practice guidelines. Ann Oncol. 2020;31:1650–63. https://doi.org/10.1016/j.annonc.2020.07.019.

14. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32:1475–95. https://doi.org/10.1016/j.annonc.2021.09.019.

15. Linee Guida Metastasi ossee e Salute dell'osso. Edizione 2021. https://www.aiom.it/wp-content/uploads/2021/11/2021_LGAIOM_Metastasi_Ossee.pdf. Accessed 19 Aug 2024.

16. Qian Y, Bhowmik D, Kachru N, Hernandez RK. Longitudinal patterns of bone-targeted agent use among patients with solid tumors and bone metastases in the United States. Support Care Cancer. 2017;25:1845–51. https://doi.org/10.1007/s00520-017-3583-1.

17. Bhowmik D, Song X, Intorcia M, et al. Examination of burden of skeletal-related events in patients naive to denosumab and intravenous bisphosphonate therapy in bone metastases from solid tumors population. Curr Med Res Opin. 2019;35:513–23. https://doi.org/10.1080/03007995.2018.1532884.

18. Weinfurt KP, Castel LD, Li Y, et al. Health-related quality of life among patients with breast cancer receiving zoledronic acid or pamidronate disodium for metastatic bone lesions. Med Care. 2004;42:164–75. https://doi.org/10.1097/01.mlr.0000108746.69256.45.

19. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med. 1996;335:1785–91. https://doi.org/10.1056/NEJM199612123352401.

20. Amadori D, Aglietta M, Alessi B, et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. Lancet Oncol. 2013;14:663–70. https://doi.org/10.1016/s1470-2045(13)70174-8.

21. Hortobagyi GN, Van Poznak C, Graydon Harker W, et al. Continued treatment effect of zoledronic acid dosing every 12 vs 4 weeks in women with breast cancer metastatic to bone. The OPTIMIZE-2 randomized clinical trial. JAMA Oncol. 2017;3:906–12. https://doi.org/10.1001/jamaoncol.2016.6316.

22. Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: a randomized clinical trial. JAMA. 2017;317:48–58. https://doi.org/10.1001/jama.2016.19425.

23. Santini D, Galvano A, Pantano F, et al. How do skeletal morbidity rate and special toxicities affect 12-weeks versus 4-weeks schedule zoledronic acid efficacy? A systematic review and a meta-analysis of randomized trials. Crit Rev Oncol Hematol. 2019;142:68–75. https://doi.org/10.1016/j.critrevonc.2019.07.013.

24. Clemons M, Liu M, Stober C, et al. Two-year results of a randomised trial comparing 4- versus 12-weekly bone-targeted agent use in patients with bone metastases from breast or castration-resistant prostate cancer. J Bone Oncol. 2021;2(30): 100388. https://doi.org/10.1016/j.jbo.2021.100388.