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Original research

Adverse skeletal related events in patients with bone-metastatic pheochromocytoma/paraganglioma

Marta Laganà [a], Mouhammed Amir Habra [b], Hanna Remde [c], Madson Q. Almeida [d], Deborah Cosentini [a,*], Sara Pusceddu [e], Chiara Maria Grana [f], Eleonora P.M. Corssmit [g], Alberto Bongiovanni [h], Giuseppina De Filpo [i], Eugenie S. Lim [j], Manuel Zamparini [a], Salvatore Grisanti [a], Timo Deutschbein [c,k], Martin Fassnacht [c], Gustavo F.C. Fagundes [d], Maria Adelaide A. Pereira [d], Simone Oldani [e], Simone Rota [e], Natalie Prinzi [e], Camilo Jimenez [b], Alfredo Berruti [a]

[a] Medical Oncology Unit, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, ASST Spedali Civili, Brescia, Italy
[b] Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[c] Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital Wuerzburg, Wuerzburg, Germany
[d] Unidade de Adrenal, Laboratório de Endocrinologia Molecular e Celular LIM25, Divisão de Endocrinologia, Hospital das Clínicas & Instituto do Câncer do Estado de São Paulo (ICESP), Faculdade de Medicina, Universidade de São Paulo, Sao Paulo, Brazil
[e] Department of Medical Oncology, Fondazione IRCCS INT Istituto Nazionale Tumori Milano, Milan, Italy
[f] Division of Nuclear Medicine, IRCCS IEO European Institute of Oncology, Milano, Italy
[g] Division of Endocrinology, Department of Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands
[h] Osteoncology and Rare Tumors Center (CDO-TR), IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST "Dino Amadori"), Meldola, Italy
[i] Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy
[j] Department of Endocrinology, St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK
[k] Medicover Oldenburg MVZ, Oldenburg, Germany

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ABSTRACT

Metastatic pheochromocytomas and paragangliomas (PPGLs) are frequently associated with skeletal complications.

Primary objective: to describe the frequency of adverse skeletal related events (SREs) in PPGL patients with bone metastases (BMs). Secondary objectives: to 1) identify predictive and prognostic factors for SREs and 2) obtain information on the effectiveness of bone resorption inhibitors in reducing SRE risk and improving outcomes in term of survival and SREs time onset.

In this retrospective multicenter, multinational study, 294 PPGL patients were enrolled.

SREs occurred in 90 patients (31 %). Fifty-five patients (19 %) had bone fractures, 47 (16 %) had spinal cord compression, and 11 (4 %) had hypercalcemia. Twenty-two patients (7 %) had more than one SRE. Sixty-four patients (22 %) underwent surgery, and 136 (46 %) underwent radiotherapy. SREs occurred a median of 4.4 months after diagnosis of BM (range, 0–246.6 months). Independent factors associated with reduced risk of SREs in multivariable analysis were I-131-MIBG radionuclide therapy (hazard ratio [HR], 0.536 [95 % CI, 0.309–0.932]; $P = .027$) and absence of liver metastases (HR, 0.638 [95 % CI, 0.410–0.992]; $P = .046$). The median overall survival duration was 5.3 year. In multivariable analysis, age younger than 48 years at PPGL diagnosis (HR, 0.558 [95 % CI, 0.3877–0.806]; $P = .002$), absence of liver metastases (HR, 0.618 [95 % CI, 0.396–0.965]; $P = .034$), treatment with bisphosphonates or denosumab (HR, 0.598 [95 % CI, 0.405–0.884]; $P = .010$), and MIBG radionuclide therapy (HR, 0.444 [95 % CI, 0.274–0.718]; $P = .001$) were associated with a reduced risk of death.

SREs occur frequently and early in bone-metastatic PPGL patients but do not negatively impact survival. MIBG radionuclide therapy and treatment with bone resorption inhibitors are associated with favorable outcome.

* Corresponding author.
E-mail address: d.cosentini@unibs.it (D. Cosentini).

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1. Introduction

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors originating from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. The estimated incidence of PPGLs in Western countries is 2–8 per million people per year. [1,2] Metastatic disease occurs in 15–25 % of patients, with bone being the most frequent metastatic site, followed by the lymph nodes, lungs, and liver. [3] Metastases in patients with PPGLs usually are metachronous and arise after long latency following surgery for the primary tumor. A less frequent finding is PPGL that is already metastatic at initial diagnosis, which is associated with an unfavorable outcome. [1] Radionuclide therapy with I-131-MIBG or Y-90- or Lu-177-DOTA peptides, treatment with tyrosine kinase inhibitors, and chemotherapy with alkylating agents like the regimen of cyclophosphamide, vincristine, and dacarbazine and single-agent temozolomide are commonly employed for PPGL. [4,5] These treatments induce objective remission in a minority of patients with PPGLs, but whether they significantly change the natural history of these neoplasms is uncertain. The recent genetic classification of PPGLs into three clusters according to the molecular pathways involved in their development: pseudohypoxic, tyrosine kinase signaling and Wnt-β-catenin has paved the way for more effective pharmacological treatment strategies. [6].

The median survival duration for PPGL is 6–7 years from the time of diagnosis of metastatic disease. This relatively good prognosis is primarily a result of a usually indolent disease course. However, chronic catecholamine excess exposes patients to typical long-term complications such as cardiovascular complications. A retrospective single-center analysis of 91 patients with bone-metastatic PPGLs demonstrated that 70 % of them experienced adverse skeletal related events (SREs), defined as severe pain requiring radiotherapy or orthopedic surgery, spinal cord compression, pathological fracture, hypercalcemia or asymptomatic disease requiring intervention (either radiotherapy or surgery) because of an impending fracture or cord compression. Bone-metastatic cancers are treated using specific antineoplastic measures and drugs that prevent bone resorption, such as bisphosphonates and denosumab. [7] Randomized trials have demonstrated that bone resorption inhibitors are effective in preventing SREs in patients with bone metastases (BMs) of breast, prostate, or lung cancer. However, given the extreme rarity of bone-metastatic PPGLs, data on the efficacy of these drugs in patients with such neoplasms is lacking.

The purpose of the retrospective multicenter, multinational study described herein was to determine the prevalence of SREs in patients with bone-metastatic PPGLs. The secondary objectives were to evaluate factors that can predict SRE occurrence and have a prognostic impact and to assess the effectiveness of treatment with bone resorption inhibitors in these patients.

2. Patients and methods

2.1. Study design

This retrospective, observational, multicenter study included PPGL patients with BMs who underwent treatment and follow-up at 10 international referral centers. Data were collected from adult patients of all ages who received standard treatments in accordance with their treating physicians' and multidisciplinary tumor boards' practice. Only patients with histologically confirmed PPGL who had at least one BM during their disease course as identified via imaging (standard computed tomography, FDG-positron emission tomography/computed tomography, somatostatin receptor targeted positron emission tomography/computed tomography, I-131-MIBG scintigraphy, or magnetic resonance imaging of the skeleton) were included in the study. Patients with bone invasion by contiguity but not originating from bone itself were excluded.

Data collected at baseline and throughout the disease course consisted of age, sex, date of initial diagnosis of PPGL BM and true SREs (i.e., fracture, spinal cord compression, hypercalcemia), presence of a germline mutation, type of primary tumor treatment, surgery and/or radiotherapy for bone lesions, tumor stage at PPGL diagnosis, time from diagnosis to onset of BM (synchronous metastases were defined as bone lesions detected within 3 months after the initial diagnosis of the primary tumor), type of imaging used to assess BM development, BM appearance at imaging (lytic, sclerotic, or mixed), skeletal sites of BM, extra skeletal disease sites, hormonal status, hormonal hypersecretion symptoms at initial diagnosis of PPGL and BM, bone pain, type of SREs, time from BM diagnosis to onset of first SRE, and overall survival (OS) duration from diagnosis of BM. In the definition of SREs, true SREs were differentiated from radiotherapy and surgery, which are considered SREs but are actually treatments.

Data on the study patients were entered into the European Network for the Study of Adrenal Tumors registry, which was approved by the ethics boards of Comitato Etico Provinciale Provincia di Brescia c/o Spedali Civili, Comité de protection des personnes Ile de France IV, METC, Medical Ethical Review Committee, Máxima Medisch Centrum Veldhoven, and Ethical Committee of University of Würzburg. Also, registry entry for the patients was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board. Deidentified patient data were collected with either a waiver of consent or provision of written informed consent based on each site's regulations. Regular meetings with medical or clinical staff and a data registrar of each center were performed to address missing or inconsistent data. Regular meetings with medical or clinical staff and a data registrar of each center were performed to address missing or inconsistent data.

2.2. Statistical analysis

The primary endpoint was the frequency of SREs in this patient population. The secondary endpoints were the time to first SRE (defined as the interval from the date of initial diagnosis of BM to the first occurrence of a bone fracture, spinal cord compression, or hypercalcemia). Patients without SREs were censored at the last follow-up visit or death. OS duration was defined as the interval from the date of diagnosis of BM to the date of death or last known alive date.

Descriptive statistics were used for patient demographics, PPGL and BM characteristics, diagnosis, symptoms, imaging modality assessments, and treatments. Categorized variables were expressed as percentages.

Survival curves were created using the Kaplan-Meier method, and differences in terms of overall survival were compared using a log-rank test. A Cox proportional hazards regression model was employed to determine hazard ratios (HRs) and 95 % CIs in both univariable and multivariable analyses with the lowest risk group used as the reference group. The parameters associated with OS or time to SRE in the univariable analysis (at $P \leq .1$) were included in the multivariable analysis.

Patients with missing data were excluded from analyses if their files did not contain data for the required variables. All reported P values were two-sided, and P values less than.05 were considered significant.

SPSS statistical software (version 24.00) was used for statistical analysis. Owing to the absence of published data on clinical outcomes of bone-metastatic PPGL and the explorative nature of our study, a formal calculation of the sample size was not performed. However, a minimum of 100 patients was considered to be adequate power for statistical analyses.

3. Results

Our cohort consisted of 294 PPGL patients with BM (40 % female) at 10 major referral centers. The patients' demographic and baseline characteristics are presented in Table 1.

The median age at BM diagnosis was 48 years (range, 6–80 years). One hundred seventy-three patients (59 %) had paragangliomas, often originating in the abdomen or retroperitoneum (87 patients [30 %]),

whereas 121 patients (41 %) had pheochromocytomas. Physicians performed genetic testing in 109 cases, 80 of which (73 %) had SDHB gene mutations. At primary tumor diagnosis, 162 of 224 patients (72 %) with available data on, reported symptoms related to catecholamine hypersecretion, including tachycardia, hypertension, constipation, and headache. Physicians performed surgery for the primary tumor in 223 patients (76 %). Before diagnosis of BMs, 118 patients (40 %) had received chemotherapy, 75 (26 %) had received I-131-MIBG radionuclide therapy, and 66 (22 %) had received Y-90- or Lu-177-DOTA peptide receptor radionuclide therapy. The imaging techniques most frequently used to diagnose BMs were computed tomography in 175 patients (60 %) magnetic resonance imaging in 149 patients (51 %), FDG-positron emission tomography in 98 patients (33 %) and I-131-MIBG scintigraphy in 98 patients (33 %).

Table 1
Patient characteristics.

Characteristic	No. (%)
Median age at PPGL diagnosis years (range)	48 (6-80)
Paraganglioma	173 (59)
Pheochromocytoma	121 (41)
Sex	
Male	176 (60)
Female	118 (40)
Primary tumor site	
Adrenal	121 (41)
Head and neck	41 (14)
Abdomen and/or retroperitoneum	87 (30)
Pelvis (including bladder)	14 (5)
Chest	14 (5)
Other/missing	18 (6)
Mutations	
Germinal (overall	109 (37)
SDHB	80 (27)
Symptoms of catecholamine hypersecretion at primary tumor diagnosis (data available for 224 patients)	162 (72)
Only BMs	108 (37)
Liver metastases	95 (32)
Lung metastases	89 (30)
Lymph node metastases	47 (16)
BM timing	
Synchronous	96 (33)
Metachronous	198 (67)
Median time to development of metachronous BM from primary tumor diagnosis, years (range)	5.7 (0-48.0)
Number of BM Sites	
≥ 3 sites	152 (52)
Median number of sites (range)	2 (1-7)
BM appearance	
Lytic	125 (43)
Sclerotic	31 (11)
Mixed	42 (14)
Unknown	96 (33)
Treatment with bone resorption inhibitors	
Denosumab	28 (10)
Bisphosphonates	80 (27)
BM treatment	
Radiotherapy	136 (46)
Surgery	64 (22)
Radiotherapy and surgery	46 (16)
Sites of bone involvement	
Ribs/sternum	106 (36)
Spine	245 (83)
Pelvis	148 (50)
Skull	68 (23)
Lower or upper limb/scapula/clavicle	98 (33)
Symptoms of hormone hypersecretion at BM diagnosis (data available for 250 patients)	70 (28)
Imaging technique used to diagnose BMs	
CT	175 (60)
MRI	149 (51)
FDG-PET	98 (33)
68Ga-DOTA-peptide–PET	69 (23)
I-131-MIBG scintigraphy	98 (33)
Bone scintigraphy	56 (19)
Octreotide scan	22 (7)
Treatment of advanced PPGL	
Surgery	223 (76)
Chemotherapy	118 (40)
I-131-MIBG radionuclide therapy	75 (26)
DOTA PRRT	66 (22)
TKI	72 (24)

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PRRT, peptide receptor radionuclide treatment; TKI, tyrosine kinase inhibitor.

Metastatic disease was limited to bone in 108 patients (37 %), whereas 95 (32 %) and 89 (30 %) patients had concomitant metastases in the liver and lung, respectively. Ninety-six patients (33 %) had synchronous BMs, whereas 198 (67 %) experienced metachronous BM (median time from diagnosis, 5.7 years [range, 0–48.0 years]). Most bone lesions were lytic (125 patients [43 %]), and the spine was the most frequent site of bone involvement (245 patients [83 %]). Seventy (28 %) of 250 patients for whom data were available reported symptoms of hormone hypersecretion (e.g., hypertension, palpitation, constipation, flushing, diaphoresis).

After BM diagnosis, 108 patients (37 %) received bone resorption inhibitors: 80 (27 %) received bisphosphonates, and 28 (10 %) received denosumab. Two patients (<1 %) received both bisphosphonates and denosumab. Bisphosphonates and denosumab were prescribed according to what it is recommended in oncology guidelines. Commonly used therapies include denosumab 120 mg subcutaneous or zoledronic acid 4 mg intravenous every month. [7].

3.1. SREs

SREs occurred in 90 patients (31 %): 29 (10 %) with spinal cord compression, 34 (12 %) with pathological fractures, and 5 (2 %) with hypercalcemia. Sixteen patients (5 %) had both pathological fractures and spinal cord compression, 4 (1 %) had both hypercalcemia and pathological fractures, 1 (<1 %) had hypercalcemia and spinal cord compression, and 1 (<1 %) had all three SREs. One hundred thirty-six patients (46 %) underwent radiotherapy for BM, 64 (22 %) underwent surgery, and 46 (16 %) underwent both radiotherapy and surgery. Overall, 172 patients (59 %) had at least one SRE when considering both those with true SREs and those who received BM surgery or radiotherapy.

In comparing the patients at U.S. centers with those at European and Brazilian centers (Figure 1), we found that the proportions of patients who had SREs were similar (31 % and 30 %, respectively). Regarding the distribution of single SREs, pathological fractures were the most frequently observed SREs in the two groups (30 patients [24 %] in the United States vs. 25 patients [15 %] in Europe and Brazil), followed by spinal cord compression (25 [20 %] vs. 22 [13 %] patients) and hypercalcemia (0 vs. 11 [6 %] patients). Pain owing to BMs occurred in 144 patients (49 %), with it occurring more commonly in the U.S. group (69 patients [56 %]) than in the non-U.S. group (75 patients [44 %]). Physicians administered zoledronic acid to 44 (35 %) and 36 (21 %) patients in the U.S. and non-U.S. groups, respectively, whereas they administered denosumab to 24 patients (19 %) and 10 patients (6 %) in the U.S. and non-U.S. groups, respectively.

Concerning local bone treatment, physicians performed radiotherapy and surgery more often in the U.S. group (65 [52 %] and 35 [28 %] patients, respectively) than in the non-U.S. group (71 [42 %] and 29 [17 %] patients, respectively).

3.2. Time to SREs

eFigure 1 shows the cumulative proportion of SREs in our study cohort over time. The median time from BM diagnosis to first occurrence was 4.4 months (range, 0–246.6 months). eFigure 2 shows the distribution of SREs according to the time of onset after BM diagnosis (≤12 vs. >12 months), sixty-seven of the of SREs occurred within the first year of

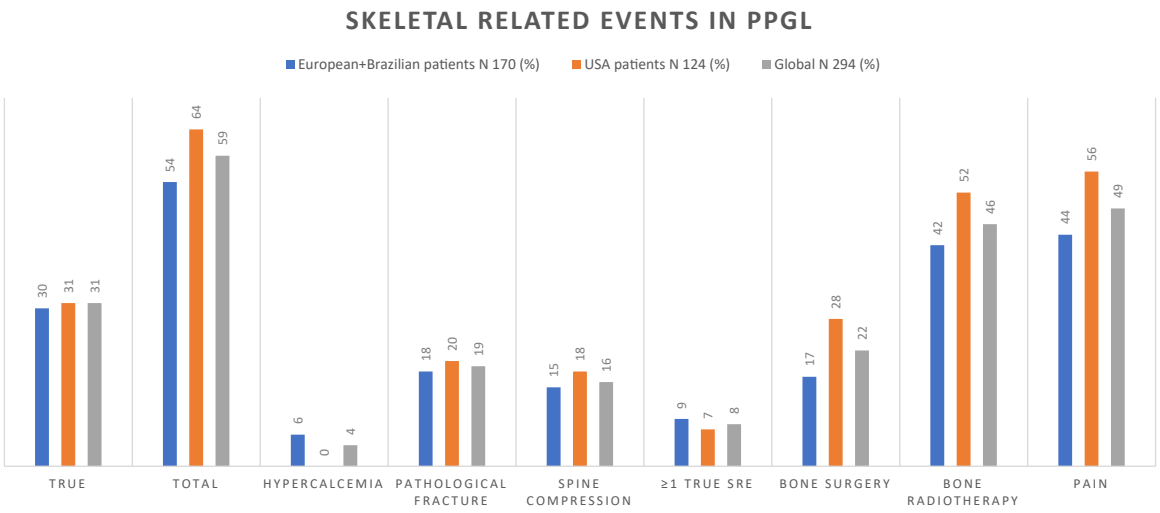

Fig. 1. Skeletal related events.

BM diagnosis: 36 of 55 patients (65 %) had pathological fractures, 30 of 47 (64 %) had spinal cord compression, and 7 of 11 (64 %) had hypercalcemia.

As shown in Table 2, factors associated with a reduced risk of SREs according to univariable Cox proportional hazards regression analysis were absence of liver metastases (HR, 0.639 [95 % CI, 0.411–0.995]; $P = .047$), I-131-MIBG radionuclide therapy (HR, 0.554 [95 % CI, 0.325–0.943]; $P = .030$), and sclerotic BM appearance (HR, 0.248 [95 % CI, 0.090–0.689]; $P = .007$). Absence of liver metastases (HR, 0.638 [95 % CI, 0.410–0.992]; $P = .046$) and MIBG radionuclide therapy (HR, 0.536 [95 % CI, 0.309–0.932]; $P = .027$) were independently associated with a reduced risk of SREs in multivariable analysis. We did not include patients with sclerotic BMs in the multivariable model because of missing data.

3.3. OS

At the last follow-up examination, 143 of 274 patients (49 %) were dead; thus, OS data were missing for 20 patients. The median OS duration from diagnosis of BM was 5.3 years (range, 0–30.6 years) (eFigure 3).

As shown in Table 3, in univariable analysis, the factors significantly associated with longer survival were absence of true SREs (HR, 0.808 [95 % CI, 0.573–1.140]; $P = .226$), metastatic disease confined to bone (HR, 0.679 [95 % CI, 0.480–0.960]; $P = .029$), treatment with denosumab or bisphosphonates (HR, 0.659 [95 % CI, 0.467–0.930]; $P = .018$), no chemotherapy (HR, 0.619 [95 % CI, 0.445–0.859]; $P = .004$), age of up to 48 years (HR, 0.589 [95 % CI, 0.423–0.820]; $P = .002$), germinal mutation (HR, 0.569 [95 % CI, 0.369–0.877]; $P = .011$), MIBG radionuclide therapy (HR, 0.551 [95 % CI, 0.360–0.845]; $P = .006$), and absence of hormone-associated symptoms (HR, 0.533 [95 % CI, 0.351–0.810]; $P = .003$). In contrast, primary pheochromocytoma (HR, 2.403 [95 % CI, 1.348–4.284]; $P = .007$) was correlated with shortened OS.

In multivariable analysis, absence of liver metastases (HR, 0.618 [95 % CI, 0.396–0.965]; $P = .034$), treatment with denosumab or bisphosphonates (HR, 0.598 [95 % CI, 0.405–0.884]; $P = .010$) (Figure 2), no chemotherapy (HR, 0.574 [95 % CI, 0.395–0.835]; $P = .001$), age of up to 48 years (HR, 0.558 [95 % CI, 0.387–0.806]; $P = .002$), MIBG radionuclide therapy (HR, 0.444 [95 % CI, 0.274–0.718]; $P = .001$), and primary pheochromocytoma (HR, 3.191 [95 % CI, 1.652–6.164]; $P = .001$) had an independent prognostic role (Table 3). We did not include patients with germinal mutation or symptoms associated with hormone hypersecretion in the multivariable

Table 2
Time to skeletal related events univariable and multivariable analysis.

Characteristic (Cox proportional hazards regression analysis)	*Univariable*			*Multivariable*		
	HR	*95 % CI*	*P*	*HR*	*95 % CI*	*P*
Female sex	0.898	0.583-1.382	.625			
Age ≤ 48 years	0.961	0.631-1.463	.851			
Primary tumor						
Paraganglioma (head and neck)	1.000					
Pheochromocytoma	1.240	0.664-2.318	.500			
Paraganglioma (not head and neck)	0.982	0.524-1.841	.955			
Germinal mutation	0.793	0.445-1.411	.429			
Absence of hormone-associated symptoms	0.829	0.511-1.347	.449			
Denosumab or bisphosphonates	0.796	0.516-1.228	.302			
PPGL treatment						
No chemotherapy	0.884	0.582-1.341	.117			
MIBG radionuclide therapy	0.554	0.325-0.943	.030	0.536	0.309-0.932	0.027
No PRRT	0.877	0.540-1.424	.595			
TKI	0.669	0.383-1.168	.669			
BM appearance						
Lytic	-		.027			
Sclerotic	0.248	0.090-0.689	.007	-	-	-
Mixed	0.837	0.470-1.491	.547			
≤ 1 BM site	0.868	0.530-1.423	.576			
Metastases						
Only BMs	0.903	0.587-1.390	.643			
Absence of liver metastases	0.639	0.411-0.995	.047	0.638	0.410-0.992	.046
Absence of lung metastases	0.745	0.475-1.167	.745			

Abbreviations: PRRT, peptide receptor radionuclide treatment; TKI, tyrosine kinase inhibitor.

Table 3
Overall Survival univariable and multivariable analysis.

Characteristic (Cox proportional hazards regression analysis)	*Univariable*			*Multivariable*		
	HR	*95 % CI*	*P*	*HR*	*95 % CI*	*P*
Female sex	0.805	0.571-1.137	.218			
Age ≤ 48 years	0.589	0.423-0.820	.002	0.558	0.387-0.806	.002
Primary tumor						
Paraganglioma (head and neck)	1.000			1.000		
Pheochromocytoma	2.403	1.348-4.284	.007	3.191	1.652-6.164	.001
Paraganglioma (not head and neck)	1.486	0.830-2.658	.182	2.174	1.139-4.149	.019
Germinal mutation	0.569	0.369-0.877	.011	-	-	-
Absence of hormone-associated symptoms	0.533	0.351-0.810	.003	-	-	-
BM treatment						
Radiotherapy	0.871	0.626-1.211	.412			
Surgery	0.783	0.526-1.167	.230			
Denosumab or bisphosphonates	0.659	0.467-0.930	.018	0.598	0.405-0.884	.010
Surgery or radiotherapy	0.833	0.599-1.158	.277			
PPGL treatment						
No chemotherapy	0.619	0.445-0.859	.004	0.574	0.395-0.835	.001
MIBG radionuclide therapy	0.551	0.360-0.845	.006	0.444	0.274-0.718	.001
PRRT	0.768	0.515-1.145	.195			
No TKI	0.925	0.642-1.333	.677			
BM Appearance						
Lytic	-	-	.310			
Sclerotic	0.823	0.509-1.331	.427			
Mixed	0.722	0.403-1.294	.274			
Metachronous BM	0.744	0.528-1.048	.090			
Number of BM sites (1 vs. >1)	0.693	0.464-1.034	.073			
Metastases						
Only BMs	0.679	0.480-0.960	.029	0.852	0.504-1.441	.551
Absence of liver metastases	0.551	0.390-0.780	.001	0.618	0.396-0.965	.034
Absence of lung metastases	0.683	0.478-0.978	.037	0.753	0.492-1.154	.193
True SREs						
Absence of true SREs	0.808	0.573-1.140	.226			
No pathological fracture	0.939	0.630-1.398	.759			
No spine compression	0.791	0.513-1.221	.290			
No hypercalcemia	0.738	0.360-1.512	.408			

Abbreviations: PRRT, peptide receptor radionuclide treatment; TKI, tyrosine kinase inhibitor.

model because of missing data.

4. Discussion

BMs and SREs are common in PPGL patients, resulting in significant morbidity and often requiring therapy. Although bone is the most common metastatic site in patients with PPGLs, researchers at only one institution (MD Anderson) have reported on the prevalence of SREs in PPGL patients to date. In this study, they observed pathological fractures and spinal cord compression in 27 % and 25 % of PPGL patients, respectively, while in our multicentric study the SRE prevalence rate was 31 % (19 % fractures and 16 % spinal cord compression), which is lower than that reported previously. [3] We confirmed this finding when considering data from the U.S. and non-U.S. centers separately. Across all tumor types, patients with breast cancer have the highest incidence of SREs and in prostate cancer, despite the osteosclerotic nature of bone metastases, SREs are still very common. [7] We had a greater percentage of patients with SREs than those in other retrospective multicenter series involving patients with bone-metastatic kidney cancer (24 %) [8] and colon cancer (18 %). [9] The proportion of patients with SREs in our study was comparable with those seen for lung cancer (28 %) [10] and head and neck cancer (27 %) [11] but lower than those observed for other endocrine cancers, such as adrenocortical cancer (47 %) [12] and thyroid cancer (43 %). [13] Worth mentioning is that the prognosis for metastatic PPGL in our study was generally favorable, with a median OS duration of 5 years. However, in patients with SREs, occurred within the first year in 65 % of cases, the median time to SRE occurrence of 4 months. Because SREs did not adversely affect the survival of our patients, most patients with SREs have experienced these complications for extended periods, resulting in significant declines in quality of life (e.g., owing to pain, specific treatments, or hospitalization). Among the factors predictive of SREs, the relationship between liver involvement and SRE occurrence suggests that patients with more aggressive disease were more likely to be affected by bone complications. A blastic radiological appearance had a positive effect on SREs in univariable analysis, but incomplete data did not allow for confirmation of this effect in multivariable analysis. These data do not align with previously reported data on blastic bone lesions in prostate cancer patients, which demonstrated similar frequency of SREs and lytic lesions. [14] Furthermore, administration of MIBG radionuclide therapy protected patients against SRE occurrence according to both univariable and multivariable analyses, proving the importance of this therapeutic strategy in PPGL patients. The lack of evidence of bone resorption inhibitors' preventive effects on SREs probably results from their frequent use after onset of SREs.

The OS rate for patients with bone-metastatic PPGL in our study was high, with a median OS duration of 5 years. Age of up to 48 years at PPGL diagnosis, absence of extra skeletal metastases, and primary head and neck disease all had a positive impact on prognosis. Of note is that the occurrence of SREs was not associated with a worse prognosis than was a lack of them, which contrasts with previous case studies of other cancers. With regard to the prognostic effect of therapy, chemotherapy, which is usually administered in patients with more aggressive disease, correlated with poor prognosis. Administration of MIBG radionuclide therapy and bone resorption inhibitors was associated with better prognosis. Given that the comparison was not randomized, we cannot rule out that the prognostic effect of MIBG radionuclide therapy is actually a result of MIBG-positive tumors being less aggressive than their MIBG-negative counterparts.

Regarding bone resorption inhibitors, post hoc analyses of randomized studies of their use in patients with castration-resistant prostate cancer [15] as well as a meta-analysis of studies in patients with metastatic castration-sensitive prostate cancer [16] revealed a correlation between use of these drugs and improved prognosis.

These observations are in line with the specific antineoplastic activity of these drugs, which should be confirmed. A prospective trial collecting PPGL patients treated with bone anti-resorptive drug started at bone metastasis diagnosis would be advantageous to strengthen our results in this rare disease.

5. Conclusions

This large retrospective study demonstrated that adverse SREs occur in one third of patients with PPGL and BMs. These data are reproducible as evidenced by the comparison between the cohorts from the U.S. and

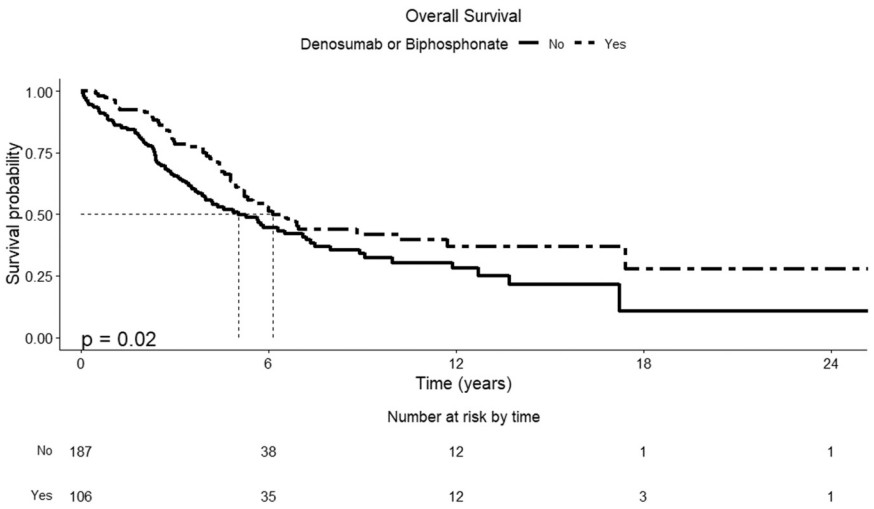

Fig. 2. Overall Survival according denosumab bisphosphonates treatment.

non-U.S. centers. Owing to the high survival rate for PPGL patients with BMs that we observed, SREs may have a negative impact on quality of life, as they occur in two thirds of cases in the first year BM diagnosis, and survival is not affected by their occurrence. MIBG radionuclide therapy and treatment with bone resorption inhibitors may be effective strategies for preventing skeletal complications of and improving prognosis for PPGL.

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Data Sharing Statement

Data sharing.

Supplementary Material

eFigure 1S Cumulative skeletal related events.
eFigure 2S Timing true skeletal related events.
eFigure 3S Overall Survival since bone metastases diagnosis.

CRediT authorship contribution statement

Natalie Prinzi: Writing – review & editing, Resources, Data curation. **Alberto Bongiovanni:** Data curation. **Giuseppina De Filpo:** Resources. **Simone Oldani:** Investigation, Data curation. **Chiara Maria Grana:** Writing – original draft, Validation, Data curation. **Simone Rota:** Resources, Data curation. **Eleonora P.M. Corssmit:** Writing – review & editing, Resources. **Gustavo Fagundes:** Writing – review & editing, Resources. **Deborah Cosentini:** Writing – review & editing, Resources, Data curation, Conceptualization. **Maria Adelaide Pereira:** Writing – review & editing, Data curation. **Sara Pusceddu:** Writing – review & editing, Validation, Resources. **Timo Deutschbein:** Writing – review & editing, Supervision, Data curation. **Hanna Remde:** Data curation. **Martin Fassnacht:** Writing – review & editing, Supervision, Conceptualization. **Madson Almeida:** Data curation, Validation. **Manuel Zamparini:** Methodology, Data curation. **Marta Lagana:** Writing – original draft, Resources, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Salvatore Grisanti:** Writing – review & editing, Supervision. **Mouhammed Amir Habra:** Writing – review & editing, Validation, Resources, Data curation, Conceptualization. **Camilo Jimenez:** Writing – review & editing, Validation, Supervision, Data curation, Conceptualization. **Alfredo Berruti:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Conceptualization. **Eugenie Kim:** Resources, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114122.

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