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Bone metastases from neuroendocrine neoplasms: Results of an Italian nationwide survey of natural history and management

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Abstract

Bone metastases (BMs) were reported in <15% of cases of neuroendocrine neoplasms (NENs). Their clinical behavior is various and clinical management is still undefined. This study aimed to describe the clinical practical management and survival outcome of neuroendocrine neoplasm patients with BMs. This is a retrospective, observational, multicenter, nationwide study, in which clinical-pathological characteristics, diagnostic tools, skeletal-related events (SREs), bone targeted agents (BTAs) and their correlation with clinical outcome were collected. Data from 320 patients from 18 Italian centers diagnosed with bone metastases during 2000–2013 were captured. Most patients had a well/moderately differentiated NEN, with synchronous distant metastases, mostly hepatic, the majority of which originated from a gastroenteropancreatic primary site. Bone was the first metastatic site in 41% of patients. After a median follow-up of 27 months 122 patients died. The median overall survival (OS) was 62 months. In 22% of patients ($n = 72$), SREs were observed, and 31% of patients received a BTA. At multivariable analysis of factors associated with OS after the development of BMs, primary lung site, Ki-67 ≥55% versus ≤20%, >10 BMs, mixed pattern (osteoblastic/osteolytic) versus osteoblastic, prior lung metastases and SREs were found to be significant poor prognosis factors. At

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multivariable analysis Ki-67 ≥55% versus ≤20% remains significantly associated with the development of SREs. Our study represents a real-life nationwide scenario of a large series of NEN patients with BMs handled at dedicated centers. Several hypotheses generated by this study are warranted to be tested in future homogeneous studies, including objective criteria for the use of BTAs.

KEYWORDS
bone metastases, neuroendocrine neoplasms, skeletal related events

1 | INTRODUCTION

Neuroendocrine neoplasms (NENs) are rare and heterogeneous malignancies originating from cells of the diffuse neuroendocrine system. They are specifically named neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs), when they are well (W) or poorly differentiated (PD), respectively.[1] Lung NENs were classified based on mitosis and necrosis into small cell lung cancer (SCLC), large cell neuroendocrine carcinoma (LCNEC), atypical carcinoid (AC), and typical carcinoid (TC).[2] The former two categories are equivalent to NECs whereas the latter two correspond to NETs.

At diagnosis NENs show distant metastases in around 50% of cases, mainly when they display advanced grades[3] and in the liver.[4] In some small monocentric studies a higher prevalence has been reported.[5] Bone metastases (BMs) have been reported in less than 15% of NENs.[6–8] In the largest epidemiological series from the Swedish Cancer Registry, 25.1% of 7334 NEN patients had distant metastases and 4.1% of these latter had BMs, small intestine resulting in the most frequent primary site for BMs.[9] However, autoptic series led to suppose that BMs from NETs could be underestimated, resulting in 10-fold more frequent than in living patients.[7,10] Over the last decades somatostatin receptor (SSTR)-related imaging (SRI) has been improving the diagnostic power for BMs, especially with the introduction of [^{68}Ga]Ga-DOTA-peptide-PET/CT.[11–13] Some reports remarked the predominant role of MRI for the first diagnosis of BMs.[5] Others suggested a diagnostic role of some circulating markers, such as CA125, CY18, and B2M, in pancreatic NET patients.[14] While clear general recommendations were reported in the main guidelines about BMs management in cancer patients[15] specific recommendations for BMs from NENs are sporadic.[7,16,17] Therefore, the clinical approach to handle BMs in NEN patients is still debated. This is probably because evidence is poorer than for frequent cancers like breast and prostate and/or because the clinical behavior of the different types of NENs is various. However, everyday clinical experience suggests that BMs and skeletal-related events (SREs) are not so rare in NENs, and they could impact patients' performance status, quality of life (QoL) and prognosis. Moreover, bone targeted agents (BTAs), such as bisphosphonates and denosumab, have been reported to reduce significantly the risk of SREs in BM patients from prostate, breast, lung and other primary malignancies.[18–20] Unfortunately, no clear data are available in this regard for NEN patients.

The rarity of the disease and the extreme variability of diagnostic and therapeutic approaches account for uncertainties of the best management in this specific population. Therefore, we performed a real-life nationwide analysis among several Italian centers dealing with NEN patients to describe clinical features and clinical management. This retrospective observational analysis could allow a better understanding of the natural history of BMs in NEN patients and could help in answering some of the outstanding questions on the management. Furthermore, it could provide new hypotheses to be addressed in future prospective studies.

2 | OBJECTIVES

The main objectives of the study were: (a) to describe the natural history, diagnostic and treatment approach of BMs in NEN patients in a real-life context, and (b) to correlate some parameters, particularly SREs, with overall survival (OS).

3 | PATIENTS AND METHODS

This is an observational, retrospective, multicenter nationwide study. All procedures were performed in accordance with relevant laws and institutional guidelines and were approved by the appropriate institutional committee. The protocol was approved with the no. R229/15-IEO 238 by the IRB, of the European Institute of Oncology (IEO), IRCCS, in Milan, which was the coordinating center, in February 2015. Each patient signed an informed consent. Eighteen Italian centers adhered to the study protocol and shared their series. Clinical records of patients with a histological diagnosis of NEN who developed BMs during their disease between 2000 and 2013 were retrospectively reviewed.

The diagnosis of BMs had to be defined with radiological and/or histological techniques. Synchronous or metachronous BMs were eligible. All types of NENs were allowed. We distinguished well/moderately from poorly differentiated NENs, based on tumor morphology, in other words NETs from NECs. The former comprised several definitions, including typical carcinoid, atypical carcinoid, carcinoid not otherwise specified, pheochromocytoma/paraganglioma, whereas the latter included definitions such as carcinoma, large cell carcinoma or small cell carcinoma. Several parameters were collected

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including timing of BMs (synchronous/metachronous), extra-bone metastases, radiological aspect of BMs, number of BMs, site of BMs, first imaging to diagnose BMs, further imaging (morphological and/or functional), SREs (type, timing), bone targeted agents (BTAs, including bisphosphonates and denosumab) bone palliative radiotherapy, bone surgery, follow-up. Skeletal-related events included: pathological fractures, spinal cord compression, hypercalcemia, orthopedic surgery, not considering bone-related pain.

4 | STATISTICAL ANALYSIS

Differences in the distribution of patients and tumors' characteristics according to the site of primary tumor were assessed using Fisher's exact test. Time to SRE was defined as the time from the date of diagnosis of BM to the date of first notification of an SRE. Overall survival was defined as the interval from the date of diagnosis of BM to the date of last contact with the patient. The curves of SRE survival and OS were drawn using the Kaplan–Meier method and the difference in survival between groups was assessed using the log-rank test. Univariable and multivariable Cox proportional hazards regression models were used to assess the association between the various characteristics and the risk of SRE or death. All models were fitted on all patients using the missing-indicator method to account for missing values. Development of SRE and use of bisphosphonate or denosumab were included as time-dependent covariables in the COX regression models. Data analyses were carried out with the SAS software version 9.4 (Cary, NC). All statistical tests were two-sided and p values <.05 were considered statistically significant.

5 | RESULTS

Data from 320 patients from 18 Italian centers were collected. The median age was 61 years (range: 13–86), males (63%) were prevailing. Well-moderately differentiated NENs constituted 82% of the series

TABLE 1 Clinicopathological characteristics of patients with NEN according to primary site.

	All ($n = 320$)	GEP ($n = 151$)	Lung $N = (117)$	Other[a] ($n = 52$)
Age				
Median [range]	61 [13–86]	61 [25–86]	61 [19–84]	60 [13–82]
Sex				
Male	200 (62.5)	85 (56.3)	89 (76.1)	26 (50.0)
Female	120 (37.5)	66 (43.7)	28 (23.9)	26 (50.0)
Tumor grade				
NET	255 (81.7)	130 (88.4)	87 (75.7)	38 (76.0)
NEC	57 (18.3)	17 (11.6)	28 (24.3)	12 (24.0)
Missing	8	4	2	2
Ki-67				
≤20	209 (77.7)	112 (86.2)	66 (68.8)	31 (72.1)
>20 to <55	37 (13.8)	13 (10.0)	19 (19.8)	5 (11.6)
≥55	23 (8.6)	5 (3.8)	11 (11.5)	7 (16.3)
Missing	51	21	21	9
BMs aspect				
Osteoblastic	173 (64.3)	86 (65.2)	64 (67.4)	23 (54.8)
Osteolytic	63 (23.4)	30 (22.7)	20 (21.1)	13 (30.9)
Mixed	33 (12.3)	16 (12.1)	11 (11.6)	6 (14.3)
Missing	51	19	22	10
BMs timing				
Metachronous				
Bone first	32 (10.0)	8 (5.3)	17 (14.5)	7 (13.5)
Other first	56 (17.5)	22 (14.6)	29 (24.8)	5 (9.6)
Synchronous (Metastatic)				
Bone first	99 (30.9)	34 (22.5)	43 (36.8)	22 (42.3)
Other first	133 (41.6)	87 (57.6)	28 (23.9)	18 (34.6)

Abbreviations: BMs, bone metastases; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.
[a]Other includes: Occult ($n = 24$), paraganglioma–pheochromocytoma ($n = 13$), Head and Neck ($n = 4$), mediastinum ($n = 1$), ovary ($n = 1$), presacral mass ($n = 1$), urogenital ($n = 8$).

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and 78% of NENs had Ki-67 ≤20%. The most frequent NEN primary site was the GEP tract (47%), followed by lung (37%).

Two hundred and thirty-two patients (73%) had synchronous distant metastases, mainly in the liver. The bone was the first metastatic site in 41% of patients, mostly synchronous, and the only one in 4%. Most BMs were osteoblastic. Further details are reported in Table 1.

One hundred and twenty-seven out of 320 patients (40%) underwent an SRS (bone-positive in 80% of cases) and 161/320 (50%) a [^{68}Ga]Ga-PET/CT-DOTA-peptide (bone-positive in 90%). An SRI was the first imaging to make a diagnosis of BMs (37% of cases), a CT scan in 35%, and an MRI in only 8% of cases. Information about a bone biopsy was present in 16% of patients, and it was positive in half of cases (Table 2). The spine was the most frequent site of BMs (78%), and the majority (64%) were osteoblastic in all primary sites except "other." The liver was the most common metastatic site (77%) (Table 3).

TABLE 2 Diagnostic tools for BMs.

	All ($n = 320$)	GEP ($n = 151$)	Lung $N = (117)$	Par-pheo ($n = 13$)	Other[a] ($n = 15$)	Occult ($n = 24$)
Bone scintigraphy						
Negative	14 (13.6)	8 (17.4)	5 (11.6)	1 (50.0)	0 (0.0)	0 (0.0)
Positive	89 (86.4)	38 (82.6)	38 (88.4)	1 (50.0)	4 (100.0)	8 (100.0)
Unknown	217	105	74	11	11	16
SRS						
Negative	25 (19.7)	13 (22.8)	9 (18.4)	0 (0.0)	1 (14.3)	2 (18.2)
Positive	102 (80.3)	44 (77.2)	40 (81.6)	3 (100.0)	6 (85.7)	9 (81.8)
Unknown	193	94	71	10	8	13
^{68}Ga-PET/CT						
Negative	15 (9.7)	6 (6.5)	4 (9.3)	0 (0.0)	0 (0.0)	2 (13.3)
Positive	149 (90.3)	86 (93.5)	39 (90.7)	5 (100.0)	6 (100.0)	13 (86.7)
Unknown	156	59	71	8	9	9
^{18}FDG-PET/CTPET						
Negative	47 (29.9)	31 (73.1)	10 (17.5)	0 (0.0)	0 (0.0)	4 (33.3)
Positive	110 (70.1)	41 (56.9)	47 (82.5)	8 (100.0)	6 (100.0)	8 (66.7)
Unknown	163	79	60	5	9	12
CT-scan						
Negative	55 (18.7)	37 (25.3)	10 (10.0)	1 (8.3)	1 (7.1)	5 (23.8)
Positive	239 (81.3)	109 (74.7)	90 (90.0)	11 (91.7)	13 (92.9)	16 (76.2)
Unknown	26	5	17	1	1	3
MRI						
Negative	12 (10.3)	8 (14.0)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Positive	105 (89.7)	49 (86.0)	35 (97.2)	8 (100.0)	10 (100.0)	3 (100.0)
Unknown	203	44	81	5	5	21
Biopsy						
Negative	23 (45.1)	8 (47.1)	15 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)
Positive	28 (54.9)	9 (52.9)	10 (40.0)	4 (100.0)	3 (100.0)	2 (100.0)
Unknown	269	134	92	9	12	22
Bone Radiotherapy						
No	248 (77.5)	121 (80.1)	87 (74.4)	9 (69.2)	9 (60.0)	22 (91.7)
Yes	72 (22.5)	30 (19.9)	30 (25.6)	4 (30.8)	6 (40.0)	2 (8.3)
Bone surgery						
No	309 (96.6)	147 (97.4)	112 (95.7)	13 (100.0)	14 (93.3)	23 (95.8)
Yes	11 (3.4)	4 (2.6)	5 (4.3)	0 (0.0)	1 (6.7)	1 (4.2)

Abbreviations: ^{18}FDG-PET, ^{18}F-FDG-PET/CT; ^{68}GaPET, ^{68}Ga-PET/CT-DOTA-peptide; CT, computed tomography; GEP, gastroenteropancreatic; MRI, magnetic resonance imaging; Par/Pheo, paraganglioma/pheochromocytoma; SRS, somatostatin receptor scintigraphy.

[a]Other includes: Head & Neck ($n = 4$), mediastinum ($n = 1$), ovary ($n = 1$), pre-sacral mass ($n = 1$), urogenital ($n = 8$).

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TABLE 3 BMs characteristics.

	All ($n = 320$)	GEP ($n = 151$)	Lung $N = (117)$	Par-Pheo ($n = 13$)	Other[a] ($n = 15$)	Occult ($n = 24$)	*p*-value
BMs site[b]							
Spine	248 (77.5)	111 (73.5)	92 (78.6)	10 (76.9)	12 (80.0)	23 (95.8)	.19
Pelvis	203 (63.4)	87 (57.6)	79 (67.5)	9 (69.2)	11 (73.3)	17 (70.8)	.35
Ribs	154 (48.1)	71 (47.0)	59 (50.4)	5 (38.5)	5 (33.3)	14 (58.3)	.54
Skull	48 (15.0)	27 (17.9)	12 (10.3)	2 (15.4)	4 (26.7)	3 (12.5)	.31
Limbs	129 (40.3)	50 (33.1)	51 (43.6)	4 (30.8)	10 (66.7)	14 (58.3)	.02
Number of BMs							
<5	138 (43.3)	80 (53.0)	43 (36.8)	5 (38.5)	4 (26.7)	6 (26.1)	
5–10	68 (21.3)	26 (17.2)	31 (26.5)	4 (30.8)	2 (13.3)	5 (21.7)	
>10	113 (35.4)	45 (29.8)	43 (36.8)	4 (30.8)	9 (60.0)	12 (52.2)	.035
BMs features							
Osteoblastic	173 (64.3)	86 (65.2)	64 (67.4)	6 (54.5)	4 (30.8)	13 (72.2)	
Osteolytic	63 (23.4)	30 (22.7)	20 (21.1)	3 (27.3)	7 (53.8)	3 (16.7)	
Mixed	33 (12.3)	16 (12.1)	11 (11.6)	2 (18.2)	2 (15.4)	2 (11.1)	.34
Other NEN metastatic sites[b]							
Liver	247 (77.2)	135 (89.4)	77 (65.8)	4 (30.8)	9 (60.0)	22 (91.7)	<.0001
Lung	55 (17.2)	13 (8.6)	31 (26.5)	4 (30.8)	2 (13.3)	5 (20.8)	.002
Lymph-node	156 (48.8)	74 (49.0)	54 (46.2)	8 (61.5)	7 (46.7)	13 (54.2)	.83
Peritoneum	32 (10.0)	24 (15.9)	3 (2.6)	0 (0.0)	0 (0.0)	5 (20.8)	.0007
CNS	5 (1.6)	1 (0.7)	3 (2.6)	0 (0.0)	1 (6.7)	0 (0.0)	.32
Soft tissue	17 (5.3)	2 (1.3)	14 (12.0)	1 (7.7)	0 (0.0)	0 (0.0)	.002
Other sites	57 (17.8)	17 (11.3)	34 (29.1)	2 (15.4)	1 (6.7)	3 (12.5)	.003
Number of major metastatic sites							
1–2	137 (42.8)	66 (43.7)	47 (40.2)	8 (61.5)	8 (53.3)	8 (33.3)	
3	122 (38.1)	59 (39.1)	43 (36.8)	3 (23.1)	6 (40.0)	9 (37.5)	
4 or more	61 (19.1)	26 (17.2)	25 (21.4)	2 (15.4)	1 (6.7)	7 (29.2)	.63

Note: Numbers do not add-up due to some missing values.

Abbreviations: BMs, bone metastases; GEP, gastroenteropancreatic; Par/Pheo, paraganglioma/pheochromocytoma.

[a]Other includes: Head and Neck ($n = 4$), mediastinum ($n = 1$), ovary ($n = 1$), pre-sacral mass ($n = 1$), and urogenital ($n = 8$).

[b]Patients may have involvement in more than 1 metastatic site.

With a median follow-up of 27 months (interquartile range IQR: 12–46 months) the median OS of the whole series of patients was 62 months (95% CI 45–74); 122 patients (38%) had died (Figure 1). Patients with Ki-67 ≥55% had the worst OS ($p < .0001$), as well as those with lung primary ($p = .002$) and those with mixed (osteoblastic/osteolytic) pattern ($p = .11$) (Figure 2).

Skeletal related events (excluding bone-related pain) occurred in 72 (23%) patients. The frequency was lower in GEP NETs (25%) than in lung NETs (36%) and it was higher in NECs (40%) than in NETs (31%). Bone-related pain occurred in 33% of our entire series. BMs were painful in 19% of osteoblastic, 24% of mixed, and 13% of osteolytic, by showing SREs in 36% of osteoblastic, 37% of mixed, and 37% of lytic, respectively.

Bisphosphonates or denosumab were administered to 31% of patients (28% of osteoblastic and 42% of mixed/osteolytic), in 51%

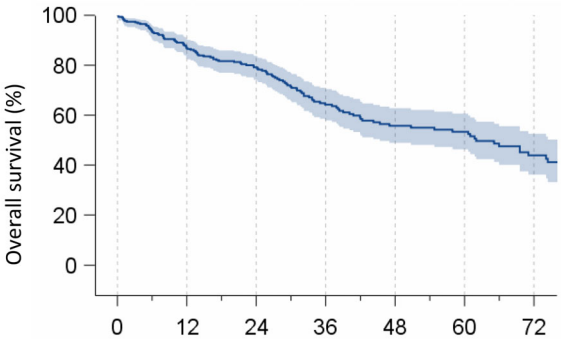

FIGURE 1 Overall survival after the development of BMs.

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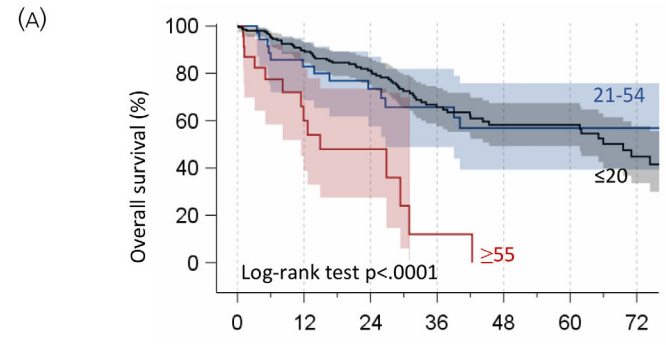
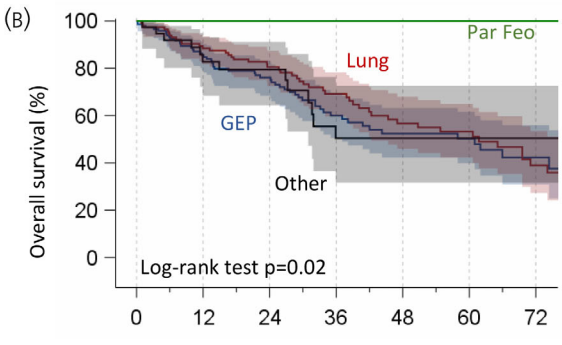
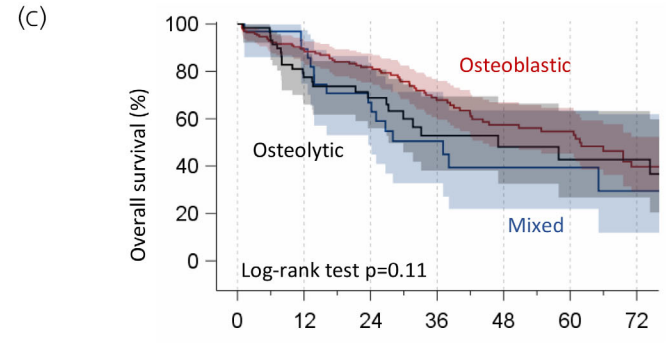


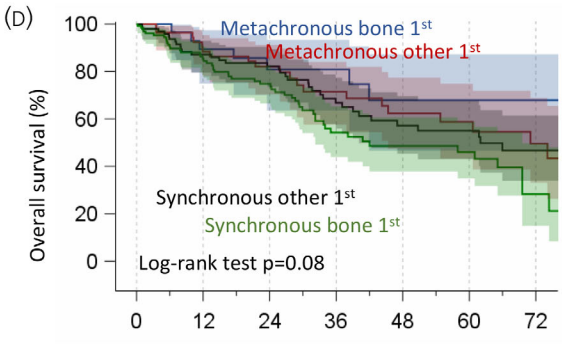
Number at risk	Time since bone metastasis (months)						
Ki-67 ≤20	206	159	114	62	40	35	15
Ki-67 21-54	37	29	21	15	11	8	7
Ki-67 ≥55	23	10	4	1	-	-	-
Overall survival							
Ki-67 ≤20	100%	90%	81%	66%	58	58%	48%
Ki-67 21-54	100%	83%	73%	66%	57%	57%	57%
Ki-67 ≥55	100%	60%	48%	12%	-	-	-



Number at risk	Time since bone metastasis (months)						
GEP	147	107	77	43	27	24	10
Lung	117	94	72	48	34	25	15
Par Feo	12	11	8	7	6	6	5
Other	39	27	21	10	9	6	5
Overall survival							
GEP	100%	86%	76%	60%	52%	50%	42%
Lung	100%	88%	81%	69%	57%	53%	39%
Par Feo	100%	100%	100%	100%	100%	100%	100%
Other	100%	83%	79%	50%	50%	50%	50%



Number at risk	Time since bone metastasis (months)						
Osteoblastic	170	132	101	66	44	36	17
Osteolytic	61	43	27	14	10	8	7
Mixed	33	24	17	9	6	5	3
Overall survival							
Osteoblastic	100%	89%	82%	69%	57%	55%	42%
Osteolytic	100%	78%	69%	53%	48%	43%	43%
Mixed	100%	89%	67%	51%	39%	39%	30%



Number at risk	Time since bone metastasis (months)						
Meta bone 1st	32	25	17	13	10	9	8
Meta other 1st	54	44	34	25	19	14	10
Synch bone 1st	99	75	61	38	27	21	13
Synch other 1st	130	95	66	32	20	17	4
Overall survival							
Meta bone 1st	100%	89%	81%	81%	68%	68%	68%
Meta other 1st	100%	88%	82%	71%	62%	59%	50%
Synch bone 1st	100%	87%	83%	67%	57%	55%	47%
Synch other 1st	100%	85%	75%	54%	49%	46%	28%

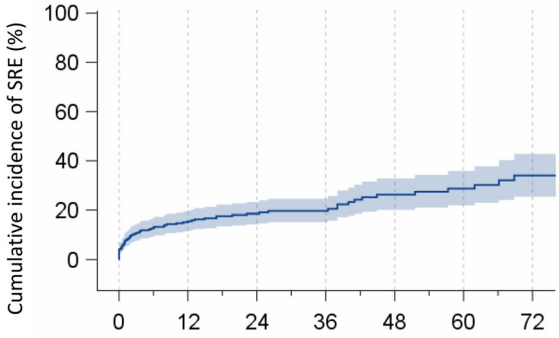
FIGURE 2 Overall survival after the development of BMs according to Ki-67 (A), tumor site (B), BM features (C) and clinical presentation (D).

TABLE 4 BTAs/SREs (not considering bone-related pain).

Subgroup	N (%)
Not treated no SRE	181 (56.9)
Not treated with SRE	37 (11.6)
Treated with no SRE	65 (20.4)
Treated before SRE	15 (4.7)
Treated after SRE	20 (6.3)

Abbreviations: BTAs, bone targeted agents; SREs, skeletal-related events.

of them without any SRE, in 21% earlier than SRE, and in 28% later than SRE (Table 4). Forty (56%) of the 72 SREs occurred within 6 months of the onset of BMs (Figure 3). In addition to BTAs about 20% of patients underwent bone radiotherapy and less than 5% underwent bone surgery (Table 5).



Number at risk	Time since bone metastasis (months)						
All	315	213	158	93	66	52	28
Cumul. Inc.	0%	16%	19%	20%	26%	29%	34%

FIGURE 3 Skeletal related events (SRE) after the development of BMs (not considering bone-related pain).

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TABLE 5 BMs treatment other than BTAs.

	All ($n = 320$)	GEP ($n = 151$)	Lung $N = (117)$	Par-Pheo ($n = 13$)	Other[a] ($n = 15$)	Occult ($n = 24$)
Bone radiotherapy						
No	248 (77.5)	121 (80.1)	87 (74.4)	9 (69.2)	9 (60.0)	22 (91.7)
Yes	72 (22.5)	30 (19.9)	30 (25.6)	4 (30.8)	6 (40.0)	2 (8.3)
Bone surgery						
No	309 (96.6)	147 (97.4)	112 (95.7)	13 (100.0)	14 (93.3)	23 (95.8)
Yes	11 (3.4)	4 (2.6)	5 (4.3)	0 (0.0)	1 (6.7)	1 (4.2)

Abbreviations: BMs, bone metastases; BTAs, bone targeted agents; GEP, gastroenteropancreatic; Par/Pheo, paraganglioma/pheochromocytoma.
[a]Other includes: Head and Neck ($n = 4$), mediastinum ($n = 1$), ovary ($n = 1$), pre-sacral mass ($n = 1$), urogenital ($n = 8$).

At the univariable and multivariable analysis of factors associated with OS after the development of BM the lung primary site, Ki-67 ≥55% versus ≤20%, >10 BMs, mixed pattern (osteoblastic/osteolytic) versus osteoblastic, prior lung metastases appeared as significant poor prognosis factors. Similarly, SREs significantly impacted OS (Table 6). At the univariable and multivariable analysis of factors associated with SREs after the development of BMs Ki-67 ≥55% versus ≤20% and other-first versus bone-first metastatic site were significant (Table 7).

All the analyses considered SREs without the bone-related pain. Considering also bone-related pain as SRE the HR for SRE during FUP is 2.99 (2.07–4.31) at univariable analysis and 2.71 (1.82–4.05) at multivariable analysis (data not shown).

6 | DISCUSSION

This study represents one of the largest cohorts of patients with BMs in NENs, surpassing the predominantly single-center series reported in the current literature.[5,6,21–25] The observed 23% incidence of SREs is somewhat lower than the rates reported in other rare cancers, including adrenocortical carcinoma[26] and sarcoma[27] and it is relatively consistent with what was reported in the single-center series of BMs in NENs considering the high heterogeneity of the various study populations.[5,6,21–24] Noteworthy the definition of SRE varies across studies, and bone-related pain can be misleading in this regard. In our study bone-related pain occurred in 33% of cases, aligning closely with the literature. Notably, we excluded bone-related pain from the SREs calculation.[5] This also implies that the majority of our NEN patients with BM were asymptomatic, a finding consistent with literature reports.[6,8,28] This clinical condition should be well considered since it highlights the relevance of the instrumental diagnosis of BM. To this regard SRI seems to have the major role, although up to 30% of BM can be diagnosed with an [^{18}F]F-DOPA-PET/CT in midgut NETs.[29,30]

The 2010 European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines on NEN-related BMs recommended bone scintigraphy and SRS, together with morphological imaging, for the detection of BMs in NENs.[7] In our cohort, <10% of patients underwent bone scintigraphy, suggesting a preference for SRI. Nowadays SRS has been overcome by [^{68}Ga]Ga-PET/CT-DOTA-peptide for metastatic NETs and consequently BMs diagnosis.[12,16,31] Since [^{68}Ga]Ga-PET/CT-DOTA-peptide was introduced into clinical practice in the mid-2000s,[32] it was performed in only a proportion of our patients, whereas another proportion underwent SRS. The accuracy of SRI has been reported superior to morphological imaging (magnetic resonance imaging, MRI, or computed tomography, CT-scan) for detecting BMs[13,33] and also to bone scintigraphy.[11] Furthermore SRI can anticipate the radiological and clinical appearance of BM.[16] In our study, the majority of BMs were osteoblastic, which is consistent with literature reports.[21–23]

Our evidence of GEP as a NEN primary site of BM is in line with what was reported in a large Swedish registry series (47% and 59%, respectively). However, we identified the pancreas as the most common primary site unlike the Swedish study where it was the small bowel.[9] We are aware that this is biased by the fact that ours is not a registry of population as was the Swedish; therefore it includes data arbitrarily reported for the specific study and not regularly registered.

In our series BMs were almost always associated with liver metastases, consistent with other reports.[9] In our 13 patients with BMs alone there was not a propensity for a specific site.

One third of our patients received BTAs, almost all bisphosphonates, 28% of them only after an SRE occurrence. This is lower than that reported in an Italian survey on BMs in patients with sarcomas, where in 60% of them BTAs were given at BM diagnosis even prolonging the time to SRE. In that study bone-related pain was not included in the SREs.[27] More in line with ours was the experience reported for BMs from adrenocortical carcinoma, with around 30% of patients receiving BTAs.[26] Since 2010 ENETS generically recommended the use of bisphosphonates in patients with BMs from NENs, but specific criteria were not defined, and this can account for the two-thirds of our patients who did not receive any BTAs. In accordance with ESMO guidelines Zoledronate or Denosumab is recommended in patients with BMs from breast cancer or prostate cancer whether they are symptomatic or not[15] and in patients with advanced lung cancer, renal cancer and other solid tumors with a life expectancy of at least 3 months and clinically significant BMs. Unfortunately, data about BMs in NENs are lacking as well as specific studies with BTAs

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TABLE 6 Univariable and multivariable analysis of factors associated with overall survival after the development of BMs.

		Univariable analysis		Multivariable analysis[a]		Multivariable analysis[b]	
Variable	**Comparison groups**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Age	Per 10-year	1.16 (1.01–1.33)	.03	1.13 (0.97–1.32)	.13	1.05 (0.90–1.22)	.52
Sex	Male vs. female	1.46 (0.98–2.18)	.07	1.14 (0.74–1.74)	.55	1.48 (0.96–2.28)	.08
Primary tumor site	GEP vs. lung	1.07 (0.73–1.57)	.74	1.32 (0.87–2.01)	.19	1.47 (0.96–2.24)	.07
	Par-Pheo vs. lung	No deaths	.002[c]	—		—	
	Other vs. lung	0.90 (0.36–2.27)	.83	0.56 (0.21–1.52)	.25	0.72 (0.27–1.89)	.50
	Occult vs. lung	1.02 (0.48–2.15)	.96	0.96 (0.45–2.08)	.92	1.26 (0.58–2.75)	.56
Tumor grade	NEC vs. NET	2.46 (1.61–3.74)	<.0001	—		—	
Ki-67	21–54 vs. ≤20	0.95 (0.52–1.72)	.86	1.10 (0.58–2.08)	.78	1.17 (0.61–2.22)	.64
	≥55 vs. ≤20	4.87 (2.69–8.81)	<.0001	5.09 (2.69–9.62)	<.0001	4.07 (2.12–7.81)	<.0001
Stage at diagnosis	Loc.adv. vs. localized	1.47 (0.60–3.61)	.40				
	Metast. vs. localized	1.51 (0.96–2.37)	.08				
Bone metastatic	Spine	1.65 (1.00–2.73)	.05				
Site[a]	Pelvis	1.33 (0.87–2.04)	.19				
	Ribs	0.83 (0.57–1.22)	.35				
	Skull	0.87 (0.52–1.46)	.60				
	Limbs	1.39 (0.95–2.01)	.09				
No. of bone mets	5–10 vs. <5	1.38 (0.85–2.23)	.19	1.43 (0.87–2.36)	.16		
	>10 vs. <5	1.55 (1.02–2.37)	.044	1.65 (1.05–2.57)	.03		
Aspect	Osteolytic vs. osteoblastic	1.44 (0.91–2.29)	.12	1.58 (0.98–2.55)	.06	1.22 (0.76–1.96)	.41
	Mixed vs. osteoblastic	1.73 (1.01–2.97)	.046	2.04 (1.17–3.58)	.01	1.89 (1.08–3.30)	.03
Sequence	Other first vs. bone first	1.39 (0.96–2.02)	.08				
Prior metast. site	Liver	1.13 (0.55–2.36)	.74				
	Lung	2.79 (1.56–4.97)	.0005	2.72 (1.58–4.68)	.0003	2.66 (1.55–4.57)	.0004
	Lymph-node	1.53 (0.93–2.50)	.09				
	Peritoneum	1.07 (0.53–2.13)	.86				
	SNC	0.19 (0.02–1.74)	.14				
	Soft tissue	1.38 (0.49–3.84)	.54				
	Other site	1.37 (0.70–2.67)	.36				
SRE during Fup[d]	Yes vs. no	2.60 (1.73–3.89)	<.0001			2.27 (1.46–3.52)	.0003
Bisphosfonate[d]	Yes vs. no	2.81 (1.94–4.08)	<.0001			2.25 (1.50–3.39)	<.0001

Note: Hazard ratios (HRs) and 95% confidence intervals (CI) obtained from Cox proportional Hazards regression models.
Abbreviations: BMs, bone metastases; GEP, gastroenteropancreatic; Par/Pheo, paraganglioma/pheochromocytoma; SREs, skeletal-related events.
The shaded cells indicate significant associations (p <.05).
[a]The first multivariable model includes only variables defined at baseline.
[b]The second multivariable model includes time-dependent covariables (SRE and bisphosphonate).
[c]The p-value based on the log-rank test.
[d]Set as a time-dependent covariables.

in NENs. In our study it seems that the decision about BTAs was made case-by-case and not as real preventive therapy like in breast and prostate cancers. This is similar to what was reported in other BM NENs series, with BTA use varying from 22% to 50%.[5,6,14,21–24] Probably bone resorption markers could help to identify patients with particular risk of SREs to be early treated with BTAs even why some NET patients could be at a higher risk of fractures compared with the general population regardless of BMs as it has been recently reported for GEP NET patients.[34]

We are aware of the several limitations of our study, starting from its retrospective design and dated dataset. Due to this the manuscript mixes various WHO classifications terminology. However re-classifying all the tumors included in this study into NET grade 1–3 and NEC per 2022 WHO was not possible. The heterogeneity of the diagnostic approach to BM, with different imaging modalities and timing, together with the heterogeneity of the population included advises to be very careful in the interpretation of the results due to the high risk of biases. The use of [^{68}Ga]Ga-PET/CT-DOTA-peptide in only a proportion of our patients

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TABLE 7 Univariable and multivariable analysis of factors associated with skeletal-related events after the development of bone metastasis (not considering bone-related pain).

		Univariable analysis		Multivariable analysis	
Variable	**Comparison groups**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Age	Per 10-year	1.00 (0.85–1.18)	.99		
Sex	Male vs. female	0.72 (0.45–1.15)	.17		
Primary tumor site	Lung vs. GEP	1.02 (0.61–1.71)	.94		
	Par-Pheo vs. GEP	0.98 (0.33–2.86)	.96		
	Other vs. GEP	1.83 (0.76–4.43)	.18		
	Occult vs. GEP	0.59 (0.19–1.95)	.39		
Tumor grade	NEC vs. NET	1.90 (1.09–3.29)	.02		
Ki-67	21–54 vs. ≤20	0.96 (0.45–2.05)	.92	1.06 (0.49–2.32)	.88
	≥55 vs. ≤20	2.74 (1.27–5.88)	.01	2.36 (1.10–5.08)	.03
Stage at diagnosis	Loc.adv. vs. localized	0.44 (0.10–1.87)	.26		
	Metast. vs. localized	0.77 (0.46–1.27)	.30		
Bone metastatic	Spine	0.93 (0.54–1.61)	.80		
Site[a]	Pelvis	1.62 (0.95–2.77)	.08		
	Ribs	0.78 (0.48–1.26)	.31		
	Skull	0.99 (0.52–1.91)	.98		
	Limbs	0.87 (0.54–1.41)	.56		
No. of bone mets	5–10 vs. <5	1.08 (0.59–1.98)	.80		
	>10 vs. <5	1.13 (0.66–1.92)	.66		
Aspect	Osteolytic vs. osteoblastic	1.83 (1.07–3.12)	.03	1.71 (1.00–2.93)	.05
	Mixed vs. osteoblastic	1.32 (0.61–2.84)	.48	1.60 (0.73–3.52)	.24
Sequence	Other first vs. bone first	0.54 (0.33–0.86)	.01	0.24 (0.32–0.87)	.02
Prior metast. site	Liver	0.91 (0.32–2.58)	.91		
	Lung	1.37 (0.49–3.77)	.55		
	Lymph node	1.95 (0.89–4.27)	.09		
	Peritoneum	0.52 (0.15–1.85)	.31		
	SNC	3.36 (0.75–15.1)	.11		
	Soft tissue	3.72 (0.94–14.7)	.06		
	Other site	0.58 (0.17–1.91)	.37		

Abbreviations: BMs, bone metastases; GEP, gastroenteropancreatic; Par/Pheo, paraganglioma/pheochromocytoma; SREs, skeletal-related events.
The shaded cells indicate significant associations (p <.05).
[a]Patients may have involvement in more than 1 metastatic site.

could have underestimated BM frequency; of course, our results should not be interpreted in terms of prevalence of BMs as it was a spontaneous data collection. No central review of the imaging was performed.

Other limitations include the lack of collected data about the activity of the anti-cancer therapies, which are sometimes controversial in BMs especially for PRRT. We did not report information about the time to SRE in patients on BTAs versus those without BTAs since it would have been strongly biased and misleading due to the type of study. Furthermore, we did not report further details about BTAs schedules and duration. Again we are aware of the lack of a pathological centralized review of NEN diagnosis and, finally, the explorative and hypothesis-generating rather than conclusive nature of the statistical analyses. Finally some time-related aspects could have had a role in the global prognosis of the study population, considering that EMA approved everolimus in NET for the first time in 2011 (only pancreatic), Sunitinib in pancreatic NET in 2009, Lutathera in GEP NET in 2017, Denosumab in bone metastases of solid cancers in 2010. Potential strengths of our study are the high number of patients and the real-life scenario at NET-dedicated centers in a country-based context.

7 | CONCLUSION

Our study is one of the largest series of patients with BMs of NENs and it represents a real-life analysis of their clinical management at Italian centers dealing with NEN patients. Although no conclusive

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results can be drawn, it generated several hypotheses that are warranted to be investigated with future specifically designed homogeneous studies. Particularly studies focused on primary prevention of SREs with BTAs are needed in NEN patients with BMs. To this aim in Italy a retrospective/prospective observational study has been approved by the IRB of the European Institute of Oncology in January 2021; this is the "Bone Metastases in neurOendocrine NEoplasms: naTural History, Prognostic Impact and Therapeutic Approach" (MONET trial) (ClinicalTrials.gov Identifier: NCT04720391) and it is ongoing. This study will involve all the Italian centers affiliated to the Italian society of NET (ItaNET).

AUTHOR CONTRIBUTIONS

Nicola Fazio: Conceptualization; investigation; writing – original draft; data curation; supervision; writing – review and editing. **Patrick Maisonneuve:** Software; data curation; writing – review and editing; formal analysis. **A. M. Frezza:** Conceptualization; data curation; writing – review and editing. **N. Ranallo:** Conceptualization; data curation; writing – review and editing. **T. Ibrahim:** Writing – review and editing. **Anna La Salvia:** Investigation; writing – review and editing. **Maria Pia Brizzi:** Writing – review and editing. **C. De Divitiis:** Investigation; writing – review and editing. **S. Tafuto:** Writing – review and editing. **Sara Pusceddu:** Writing – review and editing. **R. Marconcini:** Investigation; writing – review and editing. **Mauro Cives:** Investigation; writing – review and editing. **C. Ferrari:** Investigation; writing – review and editing. **Davide Campana:** Investigation; writing – review and editing. **D. De Lisi:** Investigation; writing – review and editing. **D. Santini:** Writing – review and editing. **Antongiulio Faggiano:** Writing – review and editing. **Roberta Modica:** Investigation; writing – review and editing. **S. Massironi:** Investigation; writing – review and editing. **A. Bianchi:** Investigation; writing – review and editing. **F. Panzuto:** Writing – review and editing. **L. Antonuzzo:** Writing – review and editing. **E. Pellegrini:** Investigation; writing – review and editing. **Vito Amoroso:** Investigation; writing – review and editing. **Ivana Puliafito:** Investigation; writing – review and editing. **Elettra Merola:** Investigation; writing – review and editing. **N. Silvestris:** Writing – review and editing. **Chiara Maria Grana:** Writing – review and editing. **Francesca Spada:** Investigation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All the authors declared to have no competing interests to declare in relation to this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol*. 2022;33:115-154.
2. Galateau-Salle F, Churg A, Roggli V, Travis WD. The 2015 World Health Organization classification of tumors of the pleura: advances since the 2004 classification. *J Thorac Oncol*. 2016;11:142-154.
3. Yao JC, Hassan M, Phan A, et al. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26:3063-3072.
4. Bhosale P, Shah A, Wei W, et al. Carcinoid tumours: predicting the location of the primary neoplasm based on the sites of metastases. *Eur Radiol*. 2013;23:400-407.
5. Scharf M, Petry V, Daniel H, Rinke A, Gress TM. Bone metastases in patients with neuroendocrine neoplasm: frequency and clinical, therapeutic, and prognostic relevance. *Neuroendocrinology*. 2018;106:30-37.
6. Van Loon K, Zhang L, Keiser J, et al. Bone metastases and skeletal-related events from neuroendocrine tumors. *Endocr Connect*. 2015;4:9-17.
7. Kos-Kudla B, O'Toole D, Falconi M, et al. ENETS consensus guidelines for the management of bone and lung metastases from neuroendocrine tumors. *Neuroendocrinology*. 2010;91:341-350.
8. Garcia-Torralba E, Spada F, Lim KHJ, et al. Knowns and unknowns of bone metastases in patients with neuroendocrine neoplasms: a systematic review and meta-analysis. *Cancer Treat Rev*. 2021;94:102168.
9. Riihimaki M, Hemminki A, Sundquist K, et al. The epidemiology of metastases in neuroendocrine tumors. *Int J Cancer*. 2016;139:2679-2686.
10. Ross EM, Roberts WC. The carcinoid syndrome: comparison of 21 necropsy subjects with carcinoid heart disease to 15 necropsy subjects without carcinoid heart disease. *Am J Med*. 1985;79:339-354.
11. Putzer D, Gabriel M, Henninger B, et al. Bone metastases in patients with neuroendocrine tumor: ^{68}Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. *J Nucl Med*. 2009;50:1214-1221.
12. Etchebehere EC, de Oliveira Santos A, Gumz B, et al. ^{68}Ga-DOTATATE PET/CT, 99mTc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: a prospective trial. *J Nucl Med*. 2014;55:1598-1604.
13. Albanus DR, Apitzsch J, Erdem Z, et al. Clinical value of (6)(8)Ga-DOTATATE-PET/CT compared to stand-alone contrast enhanced CT for the detection of extra-hepatic metastases in patients with neuroendocrine tumours (NET). *Eur J Radiol*. 2015;84:1866-1872.
14. Rosiek V, Janas K, Witkowska M, Kos-Kudla B. Role of selected circulating tumor biomarkers in patients with skeletal metastatic pancreatic neuroendocrine neoplasms. *J Clin Med*. 2023;12(14):4687.
15. Coleman R, Hadji P, Body JJ, et al. Bone health in cancer: ESMO clinical practice guidelines. *Ann Oncol*. 2020;31:1650-1663.
16. Sundin A, Arnold R, Baudin E, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine & hybrid imaging. *Neuroendocrinology*. 2017;105:212-244.
17. Riechelmann RP, Weschenfelder RF, Costa FP, et al. Guidelines for the management of neuroendocrine tumours by the Brazilian gastrointestinal tumour group. *Ecancermedicalscience*. 2017;11:716.
18. Sousa S, Clezardin P. Bone-targeted therapies in cancer-induced bone disease. *Calcif Tissue Int*. 2018;102:227-250.
19. LeVasseur N, Clemons M, Hutton B, Shorr R, Jacobs C. Bone-targeted therapy use in patients with bone metastases from lung cancer: a systematic review of randomized controlled trials. *Cancer Treat Rev*. 2016;50:183-193.
20. Saad F, Shore N, Van Poppel H, et al. Impact of bone-targeted therapies in chemotherapy-naive metastatic castration-resistant prostate cancer patients treated with abiraterone acetate: post hoc analysis of study COU-AA-302. *Eur Urol*. 2015;68:570-577.
21. Lim KHJ, Raja H, D'Arienzo P, et al. Identification of areas for improvement in the management of bone metastases in patients with neuroendocrine neoplasms. *Neuroendocrinology*. 2020;110:688-696.
22. Scopel M, De Carlo E, Bergamo F, et al. Bone metastases from neuroendocrine tumors: clinical and biological considerations. *Endocr Connect*. 2022;11:11.
23. Kavecansky J, Wei L, Caronia L, Ramirez MT, Bloomston M, Shah MH. Bone metastases in well-to-moderately differentiated neuroendocrine tumors: a single institutional review from the Ohio State University Medical Center. *Pancreas*. 2015;44:198-203.
24. Mathew A, Fendler WP, Theysohn J, Herrmann K, Führer D, Lahner H. Bone metastases in patients with pancreatic NETs: prevalence and prognosis. *Horm Metab Res*. 2023;55:827-834.
25. Lavezzi E, Jaafar S, Chiardi I, et al. Clinical presentation of bone metastases in neuroendocrine tumors: a retrospective cohort study. *Endocr Relat Cancer*. 2025;32(9):e250147.
26. Berruti A, Libe R, Lagana M, et al. Morbidity and mortality of bone metastases in advanced adrenocortical carcinoma: a multicenter retrospective study. *Eur J Endocrinol*. 2019;180:311-320.
27. Vincenzi B, Frezza AM, Schiavon G, et al. Bone metastases in soft tissue sarcoma: a survey of natural history, prognostic value and treatment options. *Clin Sarcoma Res*. 2013;3:6.
28. Wedin M, Janson ET, Wallin G, Sundin A, Daskalakis K. Impact on symptoms and survival of bone metastases in patients with small-intestinal neuroendocrine tumours. *J Neuroendocrinol*. 2025;37:e70073.
29. Lelievre M, Triumbari EKA, Brixi H, et al. Bone metastases in midgut neuroendocrine tumors: imaging characteristics, distribution, and risk factors. *Endocrine*. 2022;78:380-386.
30. Deleval N, Pesque L, Dieudonne A, et al. Prognostic impact of bone metastases detected by (18)F-DOPA PET in patients with metastatic midgut neuroendocrine tumors. *Eur Radiol*. 2021;31:4166-4174.
31. Ambrosini V, Nanni C, Zompatori M, et al. (68)Ga-DOTA-NOC PET/-CT in comparison with CT for the detection of bone metastasis in patients with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2010;37:722-727.
32. Al-Nahhas A, Win Z, Szyszko T, et al. Gallium-68 PET: a new frontier in receptor cancer imaging. *Anticancer Res*. 2007;27:4087-4094.

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33. Jha A, Patel M, Ling A, et al. Diagnostic performance of [(68)Ga] DOTATATE PET/CT, [(18)F]FDG PET/CT, MRI of the spine, and whole-body diagnostic CT and MRI in the detection of spinal bone metastases associated with pheochromocytoma and paraganglioma. *Eur Radiol*. 2024;34:6488-6498.
34. Brunetti A, Cellini M, Lavezzi E, et al. Fragility fractures in well-differentiated gastroenteropancreatic neuroendocrine tumors: results from a multicentered retrospective study. *J Neuroendocrinol*. 2025;37:e70053.

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