

Bone Metastases in Patients with Pancreatic NETs: Prevalence and Prognosis

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ABSTRACT

The clinical relevance of bone metastases (BM) in advanced pancreatic neuroendocrine tumors (PanNETs) is poorly described. We analyzed 314 consecutive PanNET patients treated at the European Neuroendocrine Tumour Society (ENETS) Center Essen between 2009 and 2021 in terms of the occurrence and clinical and prognostic impact of BM using hybrid imaging with ⁶⁸Ga-DOTATOC PET/CT. According to UICC staging, 171/314 (54.5%) patients had stage IV PanNETs. BM was diagnosed in 62/171 (36.3%) patients. Initially, 35% of BMs were visible by pathological tracer uptake only. Skeletal-related events (SREs) were detected in 11 of the 62 patients (17.7%). Patients with antiresorptive therapy had a significantly lower rate of SRE (2/36, 5.6%) than individuals without bone-specific therapy (9/26, 34.6%) (odds ratio 9.0, $p=0.0054$, Fisher's exact test). The median overall survival (OS) was 82 months (53.6–110.4, 95% CI) in the stage IV PanNET cohort. The median OS was significantly lower for patients with BM (63 months; 49.9–76.0, 95% CI) than for patients with distant metastases other than BM (116 months; 87.6–144.3, 95% CI) ($p=0.016$, log-rank test). BM occurs in more than one-third of advanced PanNETs and is associated with an unfavorable prognosis. One in five patients experiences a persistent quality-of-life-lowering SRE. Antiresorptive therapy is associated with a more favorable risk of SREs and should be offered to all patients with BM in PanNETs.

Introduction

Pancreatic neuroendocrine tumors (PanNETs) are rare neoplasms with an increasing annual incidence of 0.48/100 000 [1]. Surgical removal is the only curative therapy. At presentation, a majority of patients have unresectable disease due to local extension or metastases. Hence, only palliative therapy can be offered [2]. The clinical course of differentiated PanNETs is variable. Grading and staging play a pivotal role in NET prognosis and management. Accord-

ing to the 2017 classification of the World Health Organization (WHO), well-differentiated PanNETs are classified as G1, G2, or G3 tumors, depending on the Ki-67 proliferation marker. The presence of distant metastases of any site corresponds to stage IV, whereas stages I to III are characterized by increasing locoregional manifestation, with (IIIb) or without lymphonodular metastases (I–IIIa) [3]. The presence of other factors influencing survival is likely, but these are poorly understood.

In general, PanNETs can metastasize to any organ, with the liver being most commonly affected [4]. In contrast to soft tissue metastases, bone metastases (BM) are particularly challenging because their detection depends on the type of imaging used. Combining ^{68}Ga -DOTATOC positron emission tomography (PET) with concurrent contrast-enhanced X-ray computed tomography (ceCT) is considered the gold standard for the detection of BM with a sensitivity of 100% and a specificity of 89% [5]. In contrast, ceCT alone, which is frequently used in neuroendocrine tumor (NET) imaging, has a poor sensitivity of 47% with a specificity of 49% [5, 6].

To date, the incidence of BM in PanNETs is not well defined. Previous reports came from highly diverse NET cohorts and imaging methods. For example, a recent analysis of 14 685 gastrointestinal neuroendocrine neoplasm (GI-NEN) patients enrolled in the US Surveillance, Epidemiology, and End Results (SEER) database between 1973 and 2015 found a BM rate of 5.7% in stage IV patients, but detection methods were not disclosed [7]. Similarly, in the Spanish national NET database, a BM rate of 5.2% in gastro-entero-pancreatic (GEP)-NEN in general and of 4.3% in PanNET in particular was reported [8]. In contrast, in institutional series from academic centers, BM rates in NET patients as high as 26.0% were observed, with varying degrees of tumor differentiation, different primary tumor localizations and imaging detection methods reported in each study [9–11]. To date, all studies have suffered from a lack of standardization in terms of tumor characteristics, NET primary location, grading, staging, clinical course and imaging modality. As a result, there is a lack of information about the true prevalence of BMs in PanNETs and uncertainty regarding their potential relevance for NET prognosis and treatment.

We therefore aimed (1) to determine the true prevalence of BM in a histologically defined group of differentiated PanNETs using ^{68}Ga -DOTATOC PET/CT as the gold standard for BM imaging; (2) to investigate the influence of BM on the course of the disease; and (3) to identify clinical complications arising from PanNET BM.

Patients and Methods

Patients were identified from our prospective NET database at the European Neuroendocrine Tumour Society (ENETS) Center of Excellence, Department of Endocrinology, Diabetes and Metabolism, University Hospital Essen. Eligible patients included those with histologically confirmed differentiated PanNETs who were treated at our department between January 2009 and January 2021. All patients underwent contrast-enhanced ^{68}Ga -DOTATOC PET/CT at initial presentation and at subsequent follow-up. Patients with incomplete data were excluded from further analysis. To ensure consistency, scheduling of visits as well as indication for therapies was determined according to ENETS guidelines by an experienced, multidisciplinary tumor board (MTB). All staging was performed in-house at our center. The presence of BM was divided into BM with morphological evidence, pathological tracer uptake only or morphological evidence combined with pathological tracer uptake. Skeletal-related events (SREs) were defined as the presence of pathological fractures, bone surgery, bone radiation and/or metastatic spinal cord compression.

Data were reported as the number of patients (percentage of the group) for the categorical data and the median (95% confidence

interval (CI)) for quantitative variables unless otherwise stated. SREs and antiresorptive therapy were compared using Fisher's exact test. Overall survival (OS) was computed as the time from initial diagnosis to death from any cause. Patients who were still alive were censored at the last visit. OS was estimated using the Kaplan–Meier method and compared with the results from the log-rank test. A Cox proportional hazards model was used to calculate hazard ratios and to assess independent predictors of OS. The tests were two-tailed, and results at $p < 0.05$ were interpreted as statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 26.0 software program (IBM Corporation, Armonk, NY, USA).

Written informed patient consent and approval for data collection and analysis were obtained upon admission to our institution. The study was approved by the local ethics committee (18–8367-BO).

Results

Patient characteristics

Based on our prospective NEN database, 314 consecutive patients with histologically confirmed differentiated PanNETs who were treated between January 2009 and January 2021 were identified. Of these, 149 patients (47%) were females, and 165 (53%) were males. The median age of subjects at the initial diagnosis of PanNET was 54 years (14–85 years, range). The Ki67 index was available for 287 patients. Among these, 98 patients (31%) had grade 1 tumors, 161 (51%) had grade 2 tumors and 28 (9%) had differentiated grade 3 tumors according to the World Health Organization (WHO) 2017 criteria [3]. The median follow-up time of this basic cohort was 44 months (39–49, 95% CI).

All further evaluations refer to the group of stage IV patients. According to the UICC staging, 171 of 314 subjects (55%) had distant metastasized (stage IV) PanNETs (▶ **Table 1**). Of all stage IV patients, 35 patients (21%) had G1-NETs, 104 (61%) had G2 tumors and 24 (14%) had differentiated G3 tumors. Differentiated PanNETs were diagnosed in 8 patients (5%) without the availability of a Ki-67 index. The median age at PanNET diagnosis was 56 years (14–81 years, range). The median disease duration from initial PanNET diagnosis to first ^{68}Ga -DOTATOC PET/CT was 6 months (3–15 months, 95% CI). Nine patients (5%) had hereditary tumors (multiple endocrine neoplasia type 1). Twenty patients (12%) had functioning PanNETs (9 insulinomas, 9 gastrinomas and 2 VIPomas). The median follow-up of the stage IV cohort was 47 months (40.0–55.0, 95% CI) (▶ **Table 1**).

Manifestation of bone metastases

BM manifested in 62 of the 171 stage IV patients (36.3%) (▶ **Table 2**). In 49 patients, BMs were detected on initial ^{68}Ga -DOTATOC PET/CT. An additional 13 patients developed BM during follow-up. The median interval between the initial diagnosis of PanNET and the first detection of BM was 21.5 months (9.0–35.0, 95% CI). Ten patients (16.1%) had synchronous osseous metastasis at the time of PanNET diagnosis, and BM occurred in another 14 patients (22.6%) within the first year after diagnosis. The longest interval between PanNET diagnosis and manifestation of bone metastases was 20.2

► **Table 1** Patient characteristics of the stage IV PanNET cohort (n = 171).

Stage IV PanNET cohort	n (%)
No. of patients	171 (100)
Sex	
Male	86 (50.3)
Female	85 (49.7)
Age at PanNET diagnosis (years)	56 (14–81, range)
Median duration from PanNET diagnosis to initial ⁶⁸ Ga-DOTATOC- PET/CT (months)	6.0 (3.0–15.0, 95% CI)
Median follow-up (months)	47.0 (40.0–55.0, 95% CI)
PanNET tumor grade (WHO 2017)	
G1	35 (20.5)
G2	104 (60.8)
G3	24 (14.0)
unknown	8 (4.7)
Functioning PanNET	20 (11.7)
<i>Insulinoma</i>	9
<i>Gastrinoma</i>	9
<i>VIPoma</i>	2
Hereditary tumor syndrome – Multiple endocrine neoplasia type 1	10 (5.9)

Age, disease duration and follow-up are given as median, categorical parameters as absolute and relative frequencies.

years in a patient with multiple endocrine neoplasia type 1 (MEN1) (► **Table 2**).

BM occurred at each grading according to WHO criteria: G1 (10/35; 28.6%), G2 (39/104; 37.5%), and G3 PanNET (9/24; 37.5%). Neither the proliferation marker Ki-67 nor the intrapancreatic location of the primary tumor (pancreatic head, body, or tail) was associated with the occurrence of BM (► **Fig. 1**).

Seventeen patients (17/49, 35%) presented initially solely with tracer uptake of BM on ⁶⁸Ga-DOTATOC PET, without morphological correlate on the corresponding ceCT (► **Fig. 2**). In 9 of those cases (9/17, 53%), BM became morphologically evident on ceCT during follow-up. The median time from pathologic tracer uptake to visualization of a morphologic correlate on ceCT was 8 months (4–13 months, range).

At the last follow-up, BM was visible by both tracer uptake and morphology in 50 patients (50/62, 81%). Ten patients (10/62, 16%) merely showed pathological tracer uptake of BM. In two cases (2/62, 3%), BM were morphologically visible without tracer accumulation. Forty-four patients (71%) showed multifocal manifestations, and 18 (29%) showed unifocal manifestations of BM. The most common sites were the spine (37/62, 60%) and pelvis (21/62, 34%).

► **Table 2** Comparison of metastatic patients with and without BM.

Stage IV PanNET cohort	Patients with BM, n (%)	Patients without BM, n (%)
No. of patients (%)	62 (100)	109 (100)
Sex		
Male	32 (51.6)	54 (49.5)
Female	30 (48.4)	55 (50.5)
Age at PanNET diagnosis (years)	57 (17–81, range)	55 (14–79, range)
Time between PanNET diagnosis and initial detection of BM (months)	21.5 (9–35, 95% CI)	–
Time between PanNET diagnosis and first ⁶⁸ Ga-DOTATOC- PET/CT (months)	15.5 (5–27, 95% CI)	4 (3–13, 95% CI)
Median follow-up (months)	44 (31–67, 95% CI)	48 (40–56, 95% CI)
PanNET tumor grade (WHO 2017)		
G1	10 (16.1)	25 (22.9)
G2	39 (62.9)	65 (59.6)
G3	9 (14.5)	15 (13.8)
unknown	4 (6.5)	4 (3.7)
Functioning PanNET	7 (11.3)	13 (11.9)
<i>Insulinoma</i>	5	4
<i>Gastrinoma</i>	2	7
<i>VIPoma</i>	0	2
Hereditary tumor syndrome – Multiple endocrine neoplasia type 1	3 (4.8)	7 (6.4)

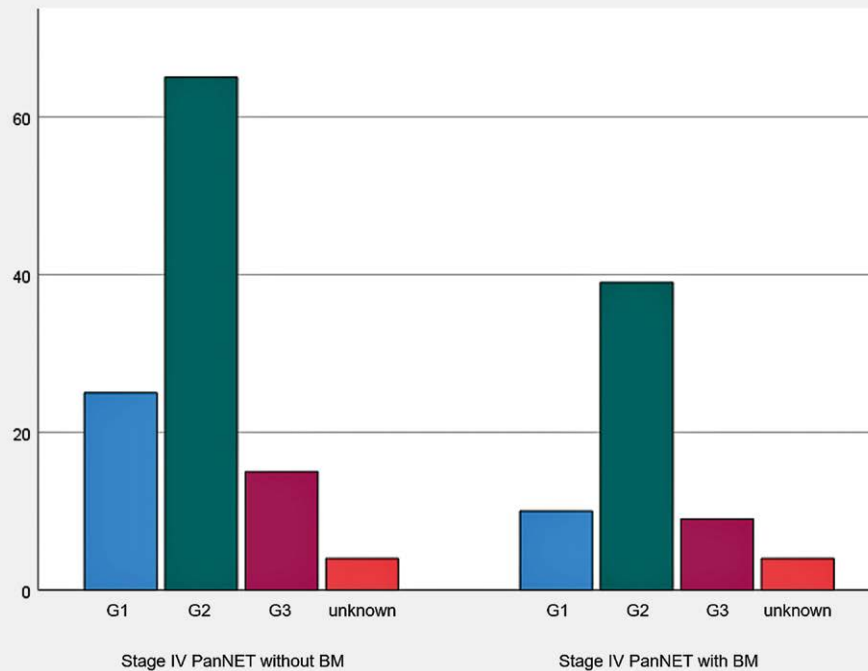
Age, disease duration and follow-up are given as median, categorical parameters as absolute and relative frequencies.

Morphology of BM, skeletal-related events and therapy

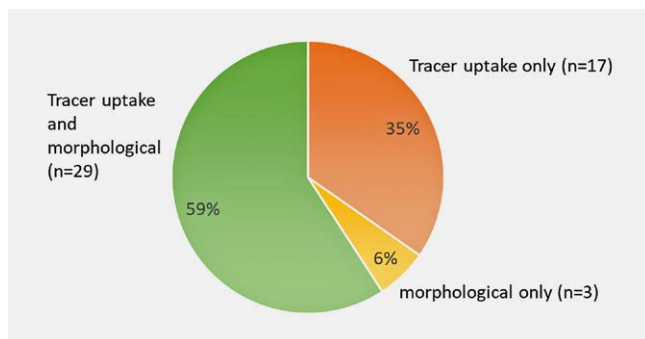
The morphology of BM was available for 32 patients. Twenty-three patients showed osteoblastic metastases (23/32, 72%), while 5 had osteolytic metastases (5/32, 16%). In 4 cases, the morphology was mixed (4/32, 13%).

Skeletal-related events (SREs) were detected in 11 of the 62 patients (18%), including pathological fractures, bone surgery, spinal cord compression and bone radiation. There was a trend toward shorter survival in patients with an SRE (41 months, 0.0–85.1, 95% CI) versus patients with BM but without an SRE (67 months, 52.7–81.3, 95% CI). However, this difference did not reach statistical significance (p = 0.185, log-rank test).

Thirty-six patients received antiresorptive therapy, that is, bisphosphonates or denosumab. Among these, 2 patients (2/36, 6%) experienced an SRE. In contrast, 26 patients did not receive bone-specific therapy. In this group, 9 SREs (9/26, 35%) occurred (odds ratio 9.0, p = 0.0054, Fisher's exact test) (► **Fig. 3**).



► **Fig. 1** Grading of PanNET in patients with and without BM.



► **Fig. 2** Presentation of BM on initial ^{68}Ga -DOTATOC PET/CT (n = 49).

Overall survival (OS)

The median OS of the stage IV PanNET cohort was 82.0 months (53.6–110.4 months, 95% CI). The median OS was significantly longer at 116.0 months (87.7–144.4 months, 95% CI) in patients with distant metastases other than BM compared with 63.0 months (50.0–76.1 months, 95% CI) in patients with BM ($p = 0.016$, log-rank test) (► **Fig. 4**). The median OS was 121.0 months (79.7–162.3; 95% CI) in G1 PanNET patients, 103.0 months (68.8–137.2; 95% CI) in G2 PanNET patients and 59.0 months (34.6–83.4; 95% CI) in G3 PanNET patients ($p = 0.003$, log-rank test). Mortality was increased 1.8-fold when comparing the risk in G1 vs. G2 NET and G2 vs. G3 NET. At the same time, mortality risk was increased by 1.65 in patients with BM compared to those with distant metastases other than BM. Interestingly, the time of BM manifestation had

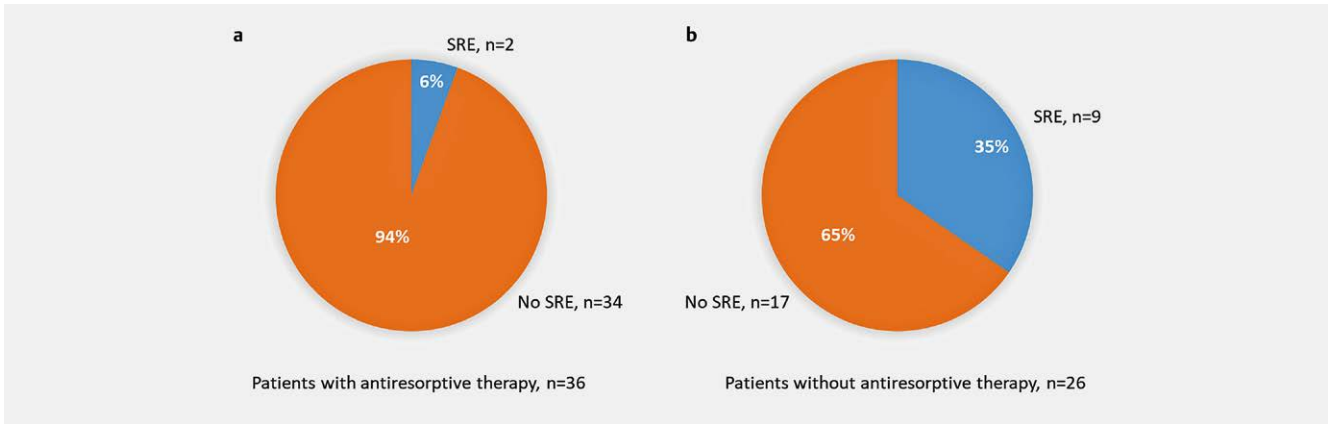
no impact on mortality risk. Multivariate analysis confirmed these results.

Discussion

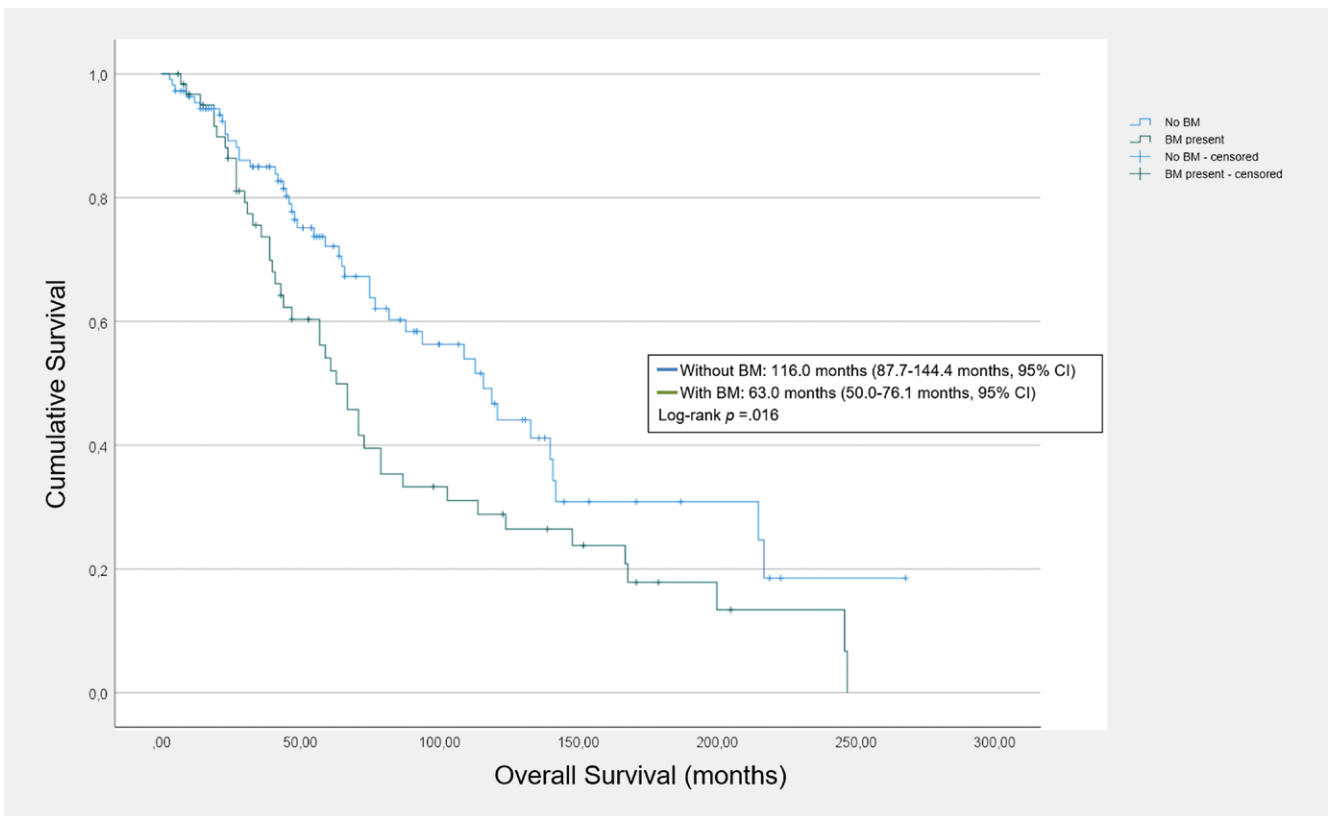
Historically, BMs have been considered to be rare in patients with NETs, with conflicting or lacking data on individual primary locations [9–11]. In this study, we investigated 171 stage IV PanNET patients from a cohort of 314 consecutive PanNET patients treated with regular hybrid imaging at a single-center institution.

Occurrence of BM

BM has been reported in 3.6–26.0% of NEN patients using heterogeneous examination methods and in different primary tumor localizations (► **Table 3**). The highest prevalence to date was reported by Scharf et al. [9], who also included 92 PanNET patients. However, a proportion of poorly differentiated NENs and the multitude of screening techniques with different sensitivities limit this study (► **Table 3**). Therefore, the authors concluded that their study, like others, may underestimate the true prevalence of BM in NET [9]. In fact, we demonstrate a significantly higher frequency of BM. In total, 36.3% of stage IV PanNET patients showed BM at the time of the last follow-up. We consider this to be due to several reasons. The focus on advanced NETs results in an increased prevalence of metastases. However, the 26% prevalence reported by Scharf et al. [9] also referred to a stage IV cohort; therefore, additional causes are likely. The exclusive testing of pancreatic NETs, which may have a higher incidence of BM than other NETs, is an option. Previous studies that employed scintigraphy or conventional imaging demonstrated a lower BM prevalence. In contrast, the exclusive use of superior SSTR-based multi-phase contrast-enhanced hybrid im-



► **Fig. 3** Proportion of skeletal-related events (SRE) in PanNET patients with and without antiresorptive therapy.



► **Fig. 4** Median overall survival in PanNET patients with BM and distant metastases other than bone (n = 171).

aging at initial diagnosis and follow-up may reflect the real prevalence of BM more accurately. Thus, known restrictions can be eliminated; selection bias in terms of availability of methods or correlation of health status with a specific imaging technique can be excluded. At the same time, our approach is independent of the distribution of different disease stages in the cohort.

Interestingly, the majority of patients with bone metastases developed them within the first two years after PanNET diagnosis. Together with the shorter survival of these patients, this indicates that PanNET with BM is a more aggressive subentity of PanNET rather than a stochastic coincidence in the course of the disease. In 35%

of cases, BM was initially confirmed solely by tracer uptake. After a median of 8 months, morphological lesions were visible in the majority of these patients. This underlines the importance of hybrid imaging not only at initial diagnosis but also during follow-up. A more aggressive course is thus detected earlier.

In addition to stage, grading based on the Ki-67 proliferation marker is a second independent prognostic parameter for survival [3]. In line with previous data [9], the occurrence of BM was not dependent on grading in our study (► **Fig. 1**). Interestingly, the hazard ratio for death from any cause increases almost as significantly in the presence of BM as with higher grading. The presence of BM

► **Table 3** Frequency of bone metastases (BM) in neuroendocrine neoplasia (NEN) patients, reported in the literature.

Entity	Cohort Size, n	Stage	Sample	BM Frequency	Imaging	Origin	Year	Reference
GEP NEN, CUP NEN, Other	668	I–IV	random, 87 centers	6.4%	CT, SRS, MRI	France	2009	Lombard-Bohas et al. [13]
GEP NEN, CUP NEN	837	I–IV	random, 46 centers	5.4%	CT, MRI, SRS	Spain	2010	Garcia-Carbonero et al. [14]
GEP NEN, Other NEN, Paraganglioma	691	I–IV	random, 2 centers	11.9%	X-ray, CT, MRI, bone scintigraphy, MIBG scan, PET scan	US	2015	Van Loon et al. [11]
GEP NEN, Other NEN, Pulmonary NEN	341	I–IV	retrospective institutional database	11.7%	CT, SRS, X-ray, MRI, bone scintigraphy	US	2015	Kavecansky et al. [10]
GEP NEN, Other NEN, Pulmonary NEN	7.334	I–IV	Swedish Cancer Registry	3.6%	not defined	Sweden	2016	Riihimäki et al. [4]
GEP NEN, CUP NEN, Pulmonary NEN	327 (677 all stages)	IV	institutional database	26.0%	MRI, DOTATOC PET/CT, SRS, CT, bone scintigraphy, other PET/CT, X-ray	Germany	2017	Scharf et al. [9]
Differentiated PanNET	171 (314 all stages)	IV	prospective institutional registry, consecutive patients	36.3%	⁶⁸ Ga-DOTATOC PET/CT	Germany	2022	Current study

GEP: GastroEnteropancreatic; CUP: Cancer of Unknown Primary; CT: Computed tomography; SRS: Somatostatin receptor scintigraphy; MRI: Magnetic resonance imaging; MIBG: ¹³¹I/123I-Metaiodobenzylguanidine; PET: Positron emission tomography.

is almost as strong an influence on OS as grading and should be considered an independent risk factor for OS in PanNETs. In addition, we investigated the influence of intrapancreatic localization of the primary tumor on the presence of BM, following evidence that localization in the pancreatic tail is associated with a more favorable clinical course [12]. For the occurrence of BM, there was no correlation with the intrapancreatic location of the primary tumor.

One-third of patients with BM presented only by tracer uptake in the first scan, not morphologically. This rate halved to 16% at the end of the study. False-positive results may have occurred since tracer accumulation represents the expression of somatostatin receptors rather than malignancy per se. However, in the majority of cases, a morphological correlate appeared in ceCT after a median of 8 months. Thus, a high specificity can be assumed. Published data indicate a specificity of 89–92% with a sensitivity of 97–100% for ^{68}Ga -DOTATOC PET/CT in NET bone metastases [5].

SRE, therapy, and morphology of BM

Until now, the frequency of SRE in differentiated PanNETs has not been elucidated. In a sample of NENs of different primaries, a high rate of 59% was reported for bone-specific symptoms in BM patients [11]. However, this result cannot simply be transferred. Only twelve PanNETs were involved and different entities, such as high-grade NEC, pheochromocytoma and NEN of unknown primary, were also included. Other limitations apply to the results of Scharf et al. [9]. The rate of SRE was reported as “nearly half of the patients” [9]. However, the number of PanNET patients examined in this work was low as well; in addition, symptoms could have triggered the need for imaging; therefore, overreporting seems likely. In contrast, the SRE ratio in our study was significantly lower in 18% of BM patients. In addition to the first-time analysis of SRE in differentiated PanNETs, we attribute the lower rate to the structured use of hybrid imaging, which maps even asymptomatic BMs sensitively. At the same time, the likelihood of SRE – one in five patients with BM – is clinically highly relevant. We defined SRE as a composite endpoint consisting of pathologic fracture, spinal cord compression, or radiation or surgery to bone. Each of these events can have a lasting impact on a patient’s quality of life.

It must be emphasized that the rate of SREs was not evenly distributed among BM patients. In subjects treated with antiresorptive therapy, the probability of SRE was significantly lower at 6% (2/36) than in those not treated with bone-specific therapy (9/26, 35%; $p=0.0054$, Fisher’s exact test). The use of antiresorptive therapy in PanNETs is thus associated with a lower rate of SRE. The type of therapy – bisphosphonates or denosumab – did not influence the outcome. Of course, it must be considered that the patients were not randomized prospectively. Nevertheless, we consider the result significant. Although we cannot exclude that more advanced patients were more likely to be treated with antiresorptive therapy, they still suffered less SRE.

The majority of our patients had osteoblastic BM. Given the limited number of patients, morphology had no influence on the occurrence of SRE. Antiresorptive therapy was similarly distributed in osteoblastic and osteolytic metastases. Patients who initially showed tracer uptake only virtually always had osteoblastic BM, suggesting that osteoblastic metastases are more likely not to become morphologically evident.

Overall survival (OS)

OS between stage IV PanNET patients with and without BM differed significantly between 63 and 116 months. A significant shortening of OS in patients with BM compared with stage IV patients without BM was also reported in two of three published studies. Congruent with our findings, both reported a near halving of OS, Kavecansky et al. [10] from 98 to 52 months and Scharf et al. [9] from 100.8 to 49.0 months. The approximately one-year longer OS of our cohort in both groups can be attributed to the biologic behavior of differentiated PanNETs, as the two aforementioned studies included numerous other NETs (► **Table 3**). In addition, improved therapies are also possible, as our cohort is approximately 10 years more recent than the two mentioned. Van Loon et al. [11] showed a shortened OS in patients with BM, but the difference was not significant (62.1 vs. 75.4 months), most likely due to the heterogeneous group of different primary sites.

It must be noted that the patients who initially showed only tracer uptake in bone had an OS as limited as the patients with morphologically visible BM. Thus, the structured use of SSTR-based hybrid imaging allows early identification of a clinically vulnerable subgroup of PanNETs and should be used routinely.

Conclusion

Bone metastases in advanced PanNETs are not only common but also significant. The presence of BM diminishes OS similar to higher tumor grade. One in five patients experiences an SRE that persistently lowers the quality of life. Regarding this, antiresorptive therapy is associated with a more favorable risk and should be offered to all patients with BM in PanNETs.

Conflict of Interest

The author declare that they have no conflict of interest.

References

- [1] Dasari A, Shen C, Halperin D et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 2017; 3: 1335–1342
- [2] 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
- [3] Lloyd RVOR, Klöppel G, Rosai J. WHO classification of tumours of endocrine organs. IARC Press; 2017
- [4] Riihimäki M, Hemminki A, Sundquist K et al. The epidemiology of metastases in neuroendocrine tumors. *Int J Cancer* 2016; 139: 2679–2686
- [5] 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
- [6] Sadowski SM, Neychev V, Millo C et al. Prospective study of ^{68}Ga -DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary Sites. *J Clin Oncol* 2016; 34: 588–596

- [7] Zheng Z, Chen C, Jiang L et al. Incidence and risk factors of gastrointestinal neuroendocrine neoplasm metastasis in liver, lung, bone, and brain: A population-based study. *Cancer Med* 2019; 8: 7288–7298
- [8] Nunez-Valdovinos B, Carmona-Bayonas A, Jimenez-Fonseca P et al. Neuroendocrine tumor heterogeneity adds uncertainty to the world health organization 2010 classification: real-world data from the Spanish tumor registry (R-GETNE). *Oncologist* 2018; 23: 422–432
- [9] Scharf M, Petry V, Daniel H et al. Bone metastases in patients with neuroendocrine neoplasm: frequency and clinical, therapeutic, and prognostic relevance. *Neuroendocrinology* 2018; 106: 30–37
- [10] Kavecansky J, Wei L, Caronia L et al. 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
- [11] Van Loon K, Zhang L, Keiser J et al. Bone metastases and skeletal-related events from neuroendocrine tumors. *Endocr Connect* 2015; 4: 9–17
- [12] Reher D, Fehrenbach U, Kayser A et al. Localization defines streptozotocin/5-FU response in primary pancreatic neuroendocrine tumours. *Neuroendocrinology* 2022; 112: 595–605
- [13] Lombard-Bohas C, Mitry E, O'Toole D et al. Thirteen-month registration of patients with gastroenteropancreatic endocrine tumours in France. *Neuroendocrinology* 2009; 89: 217–222
- [14] Garcia-Carbonero R, Capdevila J, Crespo-Herrero G et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). *Ann Oncol* 2010; 21: 1794–1803