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Original Article

Bone metastases in GEP-NET: response and long-term outcome after PRRT from a follow-up analysis

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Abstract: Bone metastases of gastroenteropancreatic neuroendocrine tumors (GEP NET) can be associated with pain and a poor prognosis. Peptide receptor radionuclide therapy (PRRT) has been shown to be effective against this tumor manifestation. This study represents an update of the therapeutic assessment of PRRT with ^{177}Lu-octreotate in GEP NET patients with bone metastases focusing on potential predictors for impaired outcome and overall survival. We retrospectively analyzed a consecutive subgroup of n=68 patients with bone metastases (BM) of GEP NET treated with ^{177}Lu-octreotate (4 intended cycles at 3 monthly intervals; mean activity per cycle, 8.1 GBq). Baseline characteristics, including age, performance status, tumor origin, tumor load, plasma chromogranin A (CgA), and neuron-specific enolase (NSE) were analyzed regarding the impact on tumor regression (modified M.D. Anderson criteria) and survival of the patients. Survival analyses were performed using Kaplan–Meier curves, log-rank test at a significance level of $p < 0.05$, and Cox proportional hazards model for uni- and multivariate analyses. Median follow-up was 48 months. The observed response of BMs consisted of complete remission in 2 (2.9%), partial remission in 23 (33.8%), minor response in 8 (11.8%), stable disease in 26 (38.2%), and progressive disease in 8 (13.2%) patients. Median time-to-progression (TTP) of BMs and overall survival (OS) were 35 mo (95% CI: 25-45) and 51 mo (95% CI: 38-64), respectively. Patients with responding BMs survived significantly longer than other patients (median 56 mo vs. 39 mo, p=0.034). NSE >15 ng/ml (p=0.002) and Ki67 index >10% (p=0.008) were associated with shorter overall survival. BM of GEP NET are effectively controlled by PRRT with a long median progression-free survival of approx. 3 years. Non-regression of BM, high proliferation rate and increased plasma NSE at baseline are predictive of shorter survival. However, this study confirms that poor patient condition (Karnofsky-Index ≤70%) and multifocality of BM (>10 lesions) do not affect outcome efficacy, further encouraging the use of PRRT in advanced bone metastatic disease.

Keywords: Bone metastases, gastroenteropancreatic neuroendocrine tumors (GEP NET), peptide receptor radionuclide therapy (PRRT)

Introduction

Neuroendocrine tumors of the gastroenteropancreatic system (GEP NET) comprise a mostly slow growing but challenging group of malignant neoplasms. Bone metastases (BMs) are present in 8%-19% of metastatic GEP NETs and are associated with a poorer prognosis [1-6]. They occur predominantly in patients with liver metastases, are frequently multiple and may cause several clinical complications including bone pain, pathologic fractures, and decreased bone marrow function [4, 7, 8]. The presence of bone metastases is a contraindication for extended surgical resection and patients may benefit more from systemic therapeutic approaches [2].

Expression of somatostatin receptors by neuroendocrine tumors (NET) has been exploited for diagnostic and therapeutic purposes [9, 10]. Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogues is a successful systemic treatment modality in patients with inoperable, metastatic GEP NET producing outstanding overall response and survival [11, 12]. Bone marrow suppression, along with nephrotoxicity, is regarded one of the

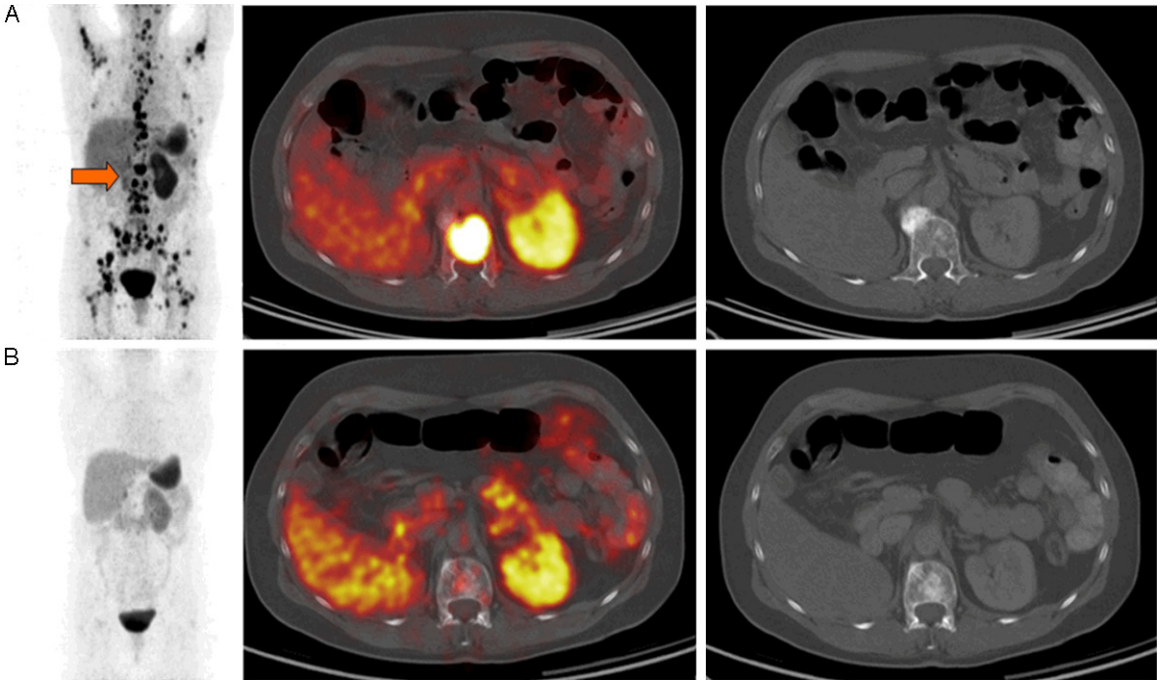

Figure 1. Near-complete remission illustrated by ^{68}Ga-DOTATOC PET/CT before (A) and 3 mo after (B) PRRT in a patient with bone metastases of a renal neuroendocrine tumor. From left to right: Maximum-intensity-projection PET images (coronal view), fused PET-CT and unfused CT images (selected lesion indicated by arrow).

most serious side effects of PRRT [13-16] and a higher frequency of hematotoxicity has been observed in the presence of BM [17]. This is explained by the proximity of BM to hematologically active bone marrow resulting in the delivery of myelotoxic radiation. 90Y and ^{177}Lu are the two most frequently used radionuclides for this purpose. Due to the lower energy characteristics and the shorter tissue penetration of the emitted beta particles from ^{177}Lu, treatment with ^{177}Lu-labeled peptides yields a higher absorbed dose to the tumors with about equal doses to potentially dose-limiting organs, including bone marrow [18]. Thus, treatment with ^{177}Lu-based radionuclides is considered to be safer especially in patients with bone metastatic GEP-NETs. There are only limited data regarding the particular efficacy of PRRT on BMs. In a preliminary report we assessed the therapeutic effect of treatment with [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate (^{177}Lu-octreotate) on bone metastases of GEP NET [19]. In this study, we represent the updated results in a larger patient cohort with a considerably longer follow up duration permitting a more accurate assessment of potential predicting factors for impaired outcome and overall survival.

Materials and methods

Patients

68 consecutive patients (39 men, 29 women; age range, 40-88 y; mean age 63) with well-differentiated neuroendocrine tumors and bone metastases were included into the retrospective analysis. 23 patients had pancreatic NET and 45 patients had non-pancreatic GEP-NET. The diagnosis of bone metastases was based on the imaging findings including CT/MRI, receptor imaging (111In DTPA-octreotide or PET/CT ^{68}Ga-DOTATOC) and bone scintigraphy. Apart from the bone metastases, metastatic sites included the liver in 66 (97.1%), the lymph nodes in 43 (63.2%), and other organs in 31 (45.5%) patients. Previous treatments were comprised of surgery (n=35), biotherapy (n=30), chemotherapy (n=18), and locoregional treatment (n=2).

PRRT

Inclusion criteria for PRRT were histologically confirmed, unresectable, metastatic GEP-NET, sufficient tumor uptake, i.e. ≥ liver uptake on

Table 1. Response of bone metastases to PRRT according to various baseline characteristics. Regression = complete, partial or minor response (CR, PR or MR)

Variable	*N*	Regression (%)	*p*
Total	68	33 (48.5%)	
Tumor type			
P-NET	23	14 (60.8%)	0.201
other GEP NET	45	19 (42.2%)	
Performance status			
KPS ≤70	18	10 (55%)	0.586
KPS >70	50	23 (46%)	
CgA			0.025
≤600 ng/ml	36	22 (61.1%)	
>600 ng/ml	32	11 (34.3%)	
NSE			0.799
≤15 ng/ml	23	12 (52.2%)	
>15 ng/ml	45	21 (46%)	
Ki67 index			0.786
≤10%	50	25 (50%)	
>10%	18	8 (44%)	
Number of lesions			0.635
Few (≤10)	37	19 (51.3%)	
multiple	31	14 (45.2%)	

P-NET, pancreatic NET; KPS, Karnofsky performance score; CgA, chromogranin A; NSE, neuron-specific enolase.

baseline receptor imaging, a glomerular filtration rate of >30 ml/min/1.73 m^2, WBC count ≥3000/mm^3, haemoglobin ≥10 g/dl and platelets ≥100000/mm^3. Patients gave their signed informed consent for the scientific analysis of their data and the local ethics committee approved the study. PRRT was performed with a mean of 8.1±0.76 GBq ^{177}Lu-octreotate per treatment cycle and aimed at four courses and standard intervals of 3 months (10-14 weeks). Amino acids were co-administered to reduce the absorbed dose to the kidneys. The ^{177}Lu (IDB Holland, Baarle-Nassau, Netherlands) had a specific activity in the approximate range of 100-160 GBq/μmol at the time of administration. The peptide labeling [20, 21] was performed such that an apparent specific activity of about 54 GBq/μmol (ratio of activity to the total amount of peptide) was obtained.

Assessment of outcome and toxicity

Hematological parameters were determined prior to each treatment course, in 2-4 weeks intervals between the courses, 8-12 weeks after the last course of PRRT and in 3 monthly intervals in the further follow-up. Toxicity was recorded using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Patients were restaged 3 months after termination of PRRT using CT or MRI according to the baseline. Functional imaging was also added consisting of somatostatin receptor scintigraphy (111In-DTPA-octreotide [OctreoScan]) or somatostatin receptor PET-CT (^{68}Ga-DOTA-TOC), and bone scintigraphy. Follow-up imaging was performed at 6-monthly intervals after the first restaging. Due to the fact that bone metastatic disease is considered nonmeasurable in conventional imaging response criteria (response evaluation criteria in solid tumors (RECIST), SWOG) [22, 23], Response of BMs was determined in this study according to functional M.D. Anderson criteria [24] and modified for the purpose of assessment in NET. Complete remission (CR) was defined as complete resolution of all bone lesions in functional imaging; partial remission (PR) as complete disappearance of one or more bone lesions, together with substantial decrease in tracer uptake in the remaining lesions; minor remission (MR) as substantial decrease in tracer uptake in the bone lesions without complete resolution of any lesion; stable disease (SD) as no significant change in functional imaging; and progressive disease (PD) as the appearance of new bone lesions.

Statistical analysis

The baseline characteristics of the study population were analyzed regarding the associated tumor response. For this purpose, the Fisher exact test was applied after dichotomizing for each factor and the resulting response: regression (CR, PR, or MR) versus non-regression (stable disease or PD). The underlying event for calculation of time to progression (TTP) of bone metastases was documentation of progressive BMs. TTP was censored at the time of commencement of another significant treatment, such as chemotherapy but not somatostatin analogue medication. Survival analysis was performed using the Kaplan–Meier curve method. The log-rank test was carried out with a significance level of P less than 0.05. Univariate regression analysis by Cox proportional hazards model was performed for each baseline factor. Multivariate analysis (stepwise model by

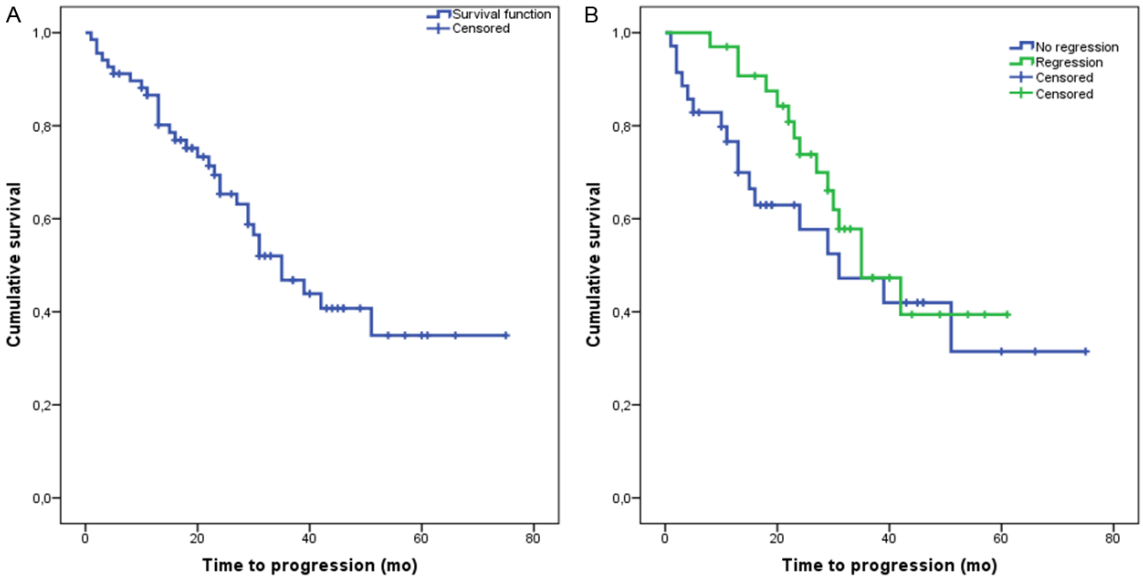

Figure 2. Median time to progression of BM was 35 months in the entire cohort (95% CI, 25-45; A) and patients with regressive bone metastases showed a trend toward a longer TTP (p=0.255; B).

backward elimination) was performed with those variables contributing to a shorter overall survival in the univariate model. All tests were performed with a significance level of $p < 0.05$. The statistical software package SPSS (version 20; SPSS Inc., Chicago/IL, USA) was used to analyze the data.

Results

232 PRRT courses were performed in 68 patients with bone metastatic GEP NET. The median cumulative activity of ^{177}Lu-octreotate was 29.1 GBq (15-37, 95%-CI) and the median follow up was 48 months (39-54, 95%-CI). Significant but reversible hematotoxicity (grade III/IV) was observed after at least one of the administrations in 7 patients (10.2%). Mean time to complete blood count recovery after termination of PRRT was 12 months (range 5-19). No other relevant toxicities or treatment related death was observed. Of the 19 patients with metastatic bone pain, 8 (42%) experienced complete and 11 (58%) partial resolution of symptoms within 3-9 weeks after commencement of treatment.

The observed treatment response of BM consisted of CR in 2 (2.9%), PR in 23 (33.8%), MR in 8 (11.8%), SD in 26 (38.2%), and PD in 9 (13.2%) patients. **Figure 1** gives an example of a patient with PR. Looking at the different baseline characteristics with regard to treatment response of BMs (**Table 1**), CgA >600 ng/mL was the only variable associated with an increased rate of treatment failure, i.e. progression despite treatment (p=0.006) and a decreased rate of regression (CR, PR, or MR; p=0.025). Time to progression of BM was 35 months (95% CI, 25-45; **Figure 2A**) and patients with responding bone metastases exhibited a minor trend toward a longer TTP (p=0.255; **Figure 2B**). Pancreatic origin (p=0.013), CgA >600 ng/mL (p=0.004) and Ki67 index >10% (p=0.038) were the contributing baseline characteristics for early progression of bone metastases.

The median overall survival from start of PRRT was 51 months (95% CI 38-64; **Figure 3A**). Assessment of the prognostic value of response in bone metastases showed that responders (56 mo, 95% CI 46-66) had significantly longer OS (p=0.034) than non-responders (39 mo, 95% CI 22-56). **Figure 3B** gives the respective Kaplan Meier curves of the patients stratified by the response status. The baseline variables contributing to overall survival in the univariate analysis were NSE >15 ng/ml (p=0.001) and Ki67 index >10% (p=0.005). As given in **Table 2** both variables remained significant on multivariate analysis with cox proportional-hazards model: NSE >15 ng/ml; HR 4.0 (95%-CI, 1.6-9.9), p=0.002 and Ki67 index >10%; HR 2.7 (95%-CI, 1.3-5.7), p=0.008 (**Figure 4A**, **4B**).

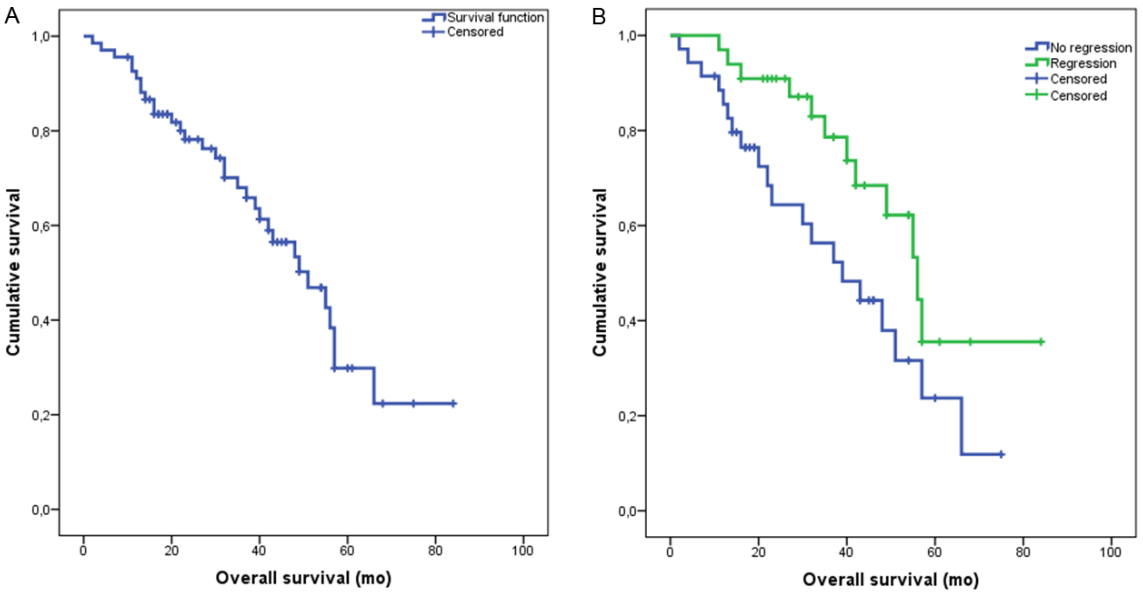

Figure 3. Median overall survival was 51 months (38-64, 95%-CI; **A**) and patients with regressive bone metastases showed a significantly longer OS (56 vs 39 mo; p=0.034; **B**).

Table 2. Uni- and multivariate analyses for potential factors associated with OS of patients with bone metastases

Variable	OS (95% CI)	Univariate analyses		Multivariate analysis	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Total	51 (38-46)				
Age					
≤65 y	57 (28-86)		0.402		
>65 y	49 (44-54)				
Tumor type					
P-NET	48 (29-67)		0.207		
other GEP NET	57 (36-78)				
Performance status					
KPS ≤70	49 (33-65)		0.066		
KPS >70	55 (35-75)				
CgA					
≤600 ng/ml	51 (38-64)		0.178		
>600 ng/ml	49 (31-67)				
NSE					
≤15 ng/ml	57 (48-66)	3.9 (1.6-9.4)	0.001	4.0 (1.6-9.9)	0.002
>15 ng/ml	40 (33-47)				
Ki67 index					
≤10%	55 (45-65)	2.7 (1.3-5.7)	0.005	2.7 (1.3-5.7)	0.008
>10%	30 (12-48)				
Number of lesions					
few (≤10)	51 (42-60)		0.451		
multiple	43 (26-57)				

OS is given as the median and in months. P-NET, pancreatic NET; KPS, Karnofsky performance score; CgA, chromogranin A; NSE, neuron-specific enolase.

Discussion

Regression of bone metastases (complete, partial or minor remission) was frequently observed in our cohort (n=33; 48.5%) and patients with responding bone metastases had a weak trend towards longer TTP (P=0.255, **Figure 2B**). More importantly regression of bone metastases was significantly assocated with improved OS (p=0.034, **Figure 3-B**).

Median time to progression of approximately 3 years (35 mo) confirms the efficacy of PRRT with ^{177}Lu-octreotate for controlling the BMs of GEP-

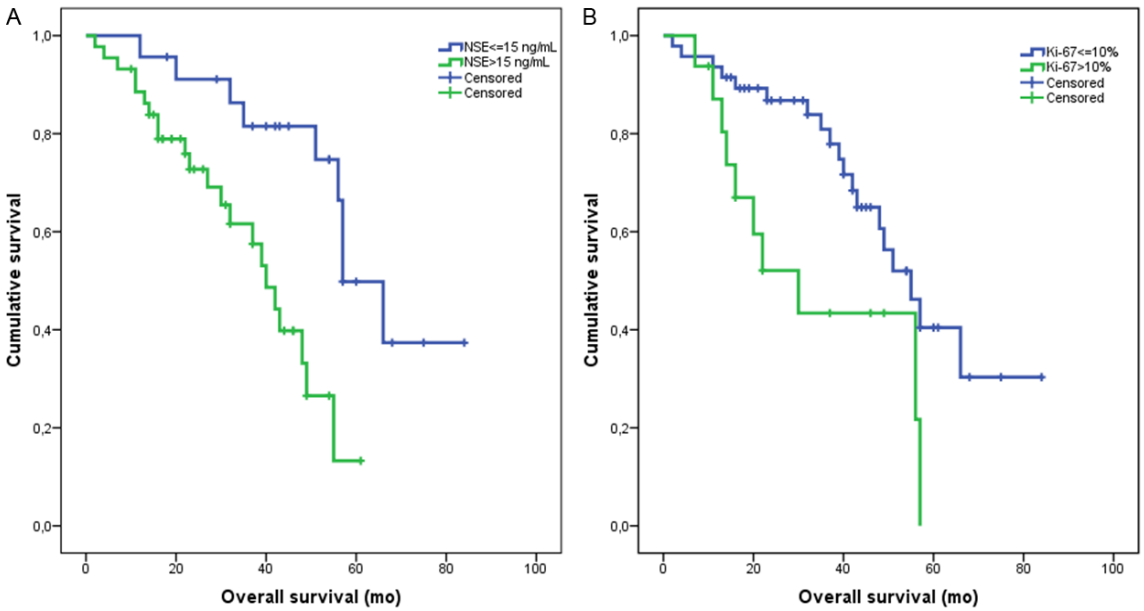

Figure 4. Overall survival stratified by the pre-treatment NSE level (A) and tumor proliferation index (B).

NETs over a long period of time. Consistent with our previous report Chromogranin A >600 ng/mL and Ki-67 index >10% were associated with a shorter time to progression. However, in contrast to our previous report on a smaller cohort (n=42), time to progression of bone metastases from P-NET is significantly shorter than that of nonpancreatic NET in the present cohort. This observation corresponds to the known fact of shorter progression-free survival of patients with P-NET despite a more pronounced initial response to PRRT [25, 26].

In our previous report [19] patients with responding bone metastases did not reach median OS during follow up. Longer observation time of the present study allowed a more accurate assessment of OS and contributing factors. In agreement with few existing data on this subgroup of patients [26], we confirmed an encouraging median OS of 51 mo in our patient cohort. Furthermore, patients with responding BMs were identified to have prolonged OS compared to non-responders (56 vs. 39 mo; p=0.034).

Ki-67 index is an important prognostic factor of survival in GEP NET [6, 27, 28]. In our study we observed that despite the similar treatment response of bone metastases in patients with Ki-67 >10% and Ki-67 ≤10%, an earlier progression can be expected in tumors with higher proliferation rates (p=0.038). Moreover, patients with higher Ki67 indices (>10%) face shorter survival compared to patients with lower indices (p=0.008, **Figure 4**). The other contributing factor to impaired overall survival in our study was baseline NSE >15 ng/mL (p=0.002; **Figure 4**). This negative impact of elevated plasma NSE level on outcome has been also indicated in other studies [29-31], our results confirm this prognostic relevance for patients with bone metastatic NET undergoing PRRT.

Significant hematotoxicity following ^{177}Lu-octreotate has been reported in 3.6% of administrations and 9.5% of 504 patients with advanced GEP-NET [26]. In our study, 7 patients (10.2%) showed significant hematotoxicity after at least one of the administrations. However, treatment-induced myelosuppression was reversible in our patient cohort and peripheral blood counts returned to baseline ranges within up to 22 months. These results may indicate the safety of PRRT in GEP NET patients with bone metastases.

In correspondence to our previous study, treatment with PRRT led to a complete (42%) or partial (58%) resolution of bone pain in symptomatic patients within 3-9 weeks after the first therapy cycle. This is particularly encouraging considering the impact of bone pain on quality of life and increased morbidity rates of patients with bone metastatic GEP-NET.

The main limitations of the study are the small population size, which limits statistical analyses and the retrospective nature of the study that will inevitably impact on the strength of conclusions.

Conclusion

In conclusion, this study confirms that bone metastases of well-differentiated gastroenteropancreatic NET are very effectively controlled by peptide receptor radionuclide therapy, leading to long overall survival as well as alleviation of pain – if present. Non-regression of BM, high proliferation rate and increased plasma NSE at baseline may be predictive of shorter survival. However, treatment efficacy – i.e. response, long-term inhibition of progression, and overall survival – seems not clearly affected by multifocality of bone lesions or reduced patient condition. As stated in our previous work, this may encourage the use of PRRT in advanced bone metastatic disease.

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