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ORIGINAL ARTICLE

The prognosis and management of neuroendocrine neoplasms-related metastatic bone disease: lessons from clinical practice

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Abstract

Purpose To study the evolution and optimal management of metastatic bone disease (mBD) in patients with neuroendocrine neoplasms (NENs).

Methods Seventy-four patients were recruited from four NEN centers in this observational multicenter study.

Results Pancreas and small bowel were the most common primaries (30 and 27%, respectively). Almost all gastrointestinal (GI)-NENs were grades 1 and 2, whereas bronchopulmonary-thymic were atypical carcinoids. Thirty-two (43%) patients had synchronous metastatic bone disease (mBD) and three patients reported bone-specific symptoms; metachronous mBD developed at a median of 35 (range: 4–395) months. Thirty-six (86%) of patients with metachronous mBD had stage IV disease at diagnosis. Somatostatin receptor functional imaging and computed tomography were the modalities mostly used for mBD identification. Fifty-two patients received assessable bone-related therapy (bisphosphonates, denosumab, local radiotherapy, and radionuclide treatment). Improvement in mBD was seen in 5, stable disease in 22, and deterioration in 25 patients. The presence of synchronous mBD and the negative outcome of bone-related therapy negatively affected overall survival (OS). In the multivariate analysis, the stronger predictor of OS was the outcome of bone-related therapy (HR: 4.753; 95% CI: 1.589–14.213). Bisphosphonates therapy was the mostly used bone-specific treatment but its monthly administration did not affect OS. At last follow-up, 39 patients were alive with OS 50 (14–463) months.

Conclusions Early investigation for mBD offers a prognostic marker of patients with NENs, since synchronous mBD has a negative impact on survival. The outcome of bone-related therapy affects OS but the monthly administration of bisphosphonates did not show a benefit over less intense schemes.

Keywords Neuroendocrine neoplasms · Metastatic bone disease · Bisphosphonates · Denosumab

Introduction

Neuroendocrine neoplasms (NENs) are rare tumors with heterogeneous biological behavior, more commonly having a slow progression. Metastatic bone disease (mBD) has been reported to have a prevalence of 7–18% in patients

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with NENs [1–4] and it is most commonly seen in patients with advanced disease, as a surrogate marker of aggressive tumor behavior [5]. However, mBD is a common finding among autopsy series [6]. It has been suggested that multiple imaging studies such as whole-body bone scintigraphy (WBS), ^{68}Gallium-DOTA-conjugated peptide-positron emission tomography/computed tomography (Ga-PET/CT), somatostatin receptor scintigraphy (SRS), or ^{18}fluorodeoxyglucose-positron emission tomography (FDG-PET) may be necessary to detect asymptomatic mBD; though the clinical significance of this finding is yet to be defined [7, 8].

The development of mBD has been considered as a marker of disseminated disease and thus being associated with a limited prognosis in cancer patients [9]. However, the natural history of NEN may not corroborate the above conception as it has been suggested that mBD may be dormant. Bisphosphonates are osteoclast inhibitors approved to treat mBD in solid tumors while reducing the complications [10]. Furthermore, bisphosphonates may also improve disease-free survival and overall survival (OS) in some solid tumors and hematological malignancies [11, 12]. Recently, the RANKL (receptor activator of nuclear factor-κβ ligand) inhibitor denosumab, another bone-specific drug, has been used to treat mBD in other solid tumors [12]. Currently, there are no guidelines regarding the use of these agents in patients with mBD from NENs, since prospective studies are lacking.

Therefore, we undertook a retrospective observational study to attempt the assessment of the natural history of patients with synchronous or metachronous mBD with NENs, as well as to present current modalities of treatment of these patients among centers of excellence.

Patients and methods

Patients were recruited from four European Neuroendocrine Tumor Society (ENETS) Centers of Excellence of Greece, Israel, and two of United Kingdom (UK) (London/UK and Coventry/UK). The study was approved independently by each institutional ethics committee (Scientific Committee of 'Laiko' University Hospital (1456/10-12-2012); Hadassah Ethical Committee (0072–16), Gastroenterology Clinical Audit Project Register (Gastro-013), Institutional Audit Department in UHCW (118/2017), respectively). Patients, after consent, were enrolled in a NEN database. Data were recruited from the specific electronic patients-registries as per ENETS requirements.

Data collection was done through the review of medical notes (to exclude other malignancies), as well as review of biochemical, radiological, and histopathological a findings. Tumor details, such as proliferation index (Ki-67, %), site of the primary and of metastases, grading of gastrointestinal (GI)-NENs, and morphological differentiation as typical, atypical, or well differentiated in bronchopulmonary-thymic versus small-cell neuroendocrine carcinoma (NEC) or large-cell NEC, the extent of the disease (staging), and the functional status of NENs, were recorded. The use of different therapeutic modalities along with long-term outcome was also analyzed. Surgical treatment included the intention to remove the primary neoplasm and/or the metastatic foci, while the systemic treatment included somatostatin analogs, molecular targeted treatment, variable chemotherapeutical schemes, peptide receptor radionuclide therapy (PRRT), external beam radiation therapy (EBRT), local therapies including transarterial (chemo)embolization (TACE or TAE, respectively) and radiofrequency ablation (RFA) used from each center. Since the majority of unknown primary origin (UPO) NENs is considered to develop from the intestine, these neoplasms were regarded as originating from the GI system [13]. Bronchopulmonary–thymic NENs were considered an independent group for comparison purposes. The mBD was defined as synchronous when its presence was documented within 3 months from the diagnosis of the primary NEN, and metachronous when its presence was found at a later stage [14]. The extent of mBD was classified as either axial mBD, defined when metastases were involving the vertebrae, pelvis, skull, and ribs, or appendicular when involving bones in the extremities [15]. Low-volume skeletal disease was considered when less than 5 metastatic bone foci were documented and high-volume skeletal disease when more or equal to 5 metastatic bone foci were documented [16]. Functional status was defined by the presence of diarrhea and/or flushing or along with a distinct hormonal hyper-secretory syndrome.

The imaging modalities used to diagnose mBD depended on the preference and availability of each center and included: conventional X-ray, magnetic resonance imaging (MRI), computed tomography (CT), WBS SPECT (single photon emission computed tomography)/CT, SRI with either 111 In-pentetreotide (^{111}In-Octreoscan) (Octreoscan ®) or Tectrotyde, Ga-PET/CT, and FDG-PET/CT. In a few instances where a conclusive diagnosis could not be made from imaging, a bone biopsy was performed. The extent of liver disease was also assessed by a specialized radiologist according to each center's practice and was characterized as diffuse or focal pattern; in two centers (Greece, Coventry/UK), a quantitative value was also given as 'percent of liver involvement' that estimated metastatic volume as percent of total liver volume [17].

The different treatment modalities across centers were also recorded and that included bone-related therapies, i.e., bone-specific (bisphosphonates, denosumab) and bone-targeted therapies (EBRT and PRRT) or non-bone-related systemic therapy and surgery. The outcome of bone-related

therapy was assessable when patients received at least two doses of the drug and they were re-assessed by at least one imaging study. Since current guidelines do not address specifically the treatment of mBD in patients with NENs, the decision to treat mBD was based on individual cases and as part of a single-center study. Hence, most patients received 4–5 mg zolendronic acid intravenous (IV) infusion yearly (or in 6-month time in case of high-volume mBD or progression), alendronate 70 mg per os once per week, or other bisphosphonates. In all four institutions, denosumab was recently introduced in patients with NENs and given twice yearly in cases of renal dysfunction or failure/ intolerance/side effects of bisphosphonates; in complicated cases (symptomatic or with multiple involvement), denosumab was given as off-label treatment or after a multidisciplinary team decision on a monthly basis (recently its prescription has been approved considering NENs as solid tumors).

The Neuroendocrine Tumor Unit at Hadassah-Hebrew University Medical Center followed an individualized protocol with monthly IV administration of 4 mg zolendronic acid infusions lasting 2 years for high-volume skeletal disease ($n = 3$) and every 3 months lasting 2 years for low-volume skeletal metastases, or pamidronate when the above was not approved. Moreover, a subset of patients ($n = 16$) from Greece prospectively received monthly 4 mg zolendronic acid intravenously for 2 consecutive years, followed by 3 monthly maintenance infusions for 1 year and daily oral calcium and vitamin D supplementation. The monthly administration of bisphosphonates group ($n = 19$) was compared with the group of other protocols of bisphosphonate administration.

Statistical analysis

Values are presented as median value and range since continuous variables were not normally distributed. The normality of distribution was assessed by applying the non-parametric Kolmogorov–Smirnov test. Comparisons between different subgroups were made by Mann–Whitney U test for the age, Ki-67, number of metastases in addition to mBD, and the number of mBD foci. The significance of the contingency between categorical variables was examined by the chi-square test or with Fisher's exact test when appropriate; kappa statistic was used to define the agreement between the different imaging modalities. The OS was analyzed using Kaplan–Meier analysis with the time point of NEN diagnosis set as baseline. To calculate the mBD-related survival (BS), the time point of mBD diagnosis was set as baseline. Log-rank test (Mantel–Cox) and multivariable Cox-regression analysis were used to determine whether there was a difference between patients with synchronous and metachronous mBD in survival correcting for the impact of age, gender, Ki-67, outcome of bone-specific/targeted treatment, origin of primary, percent of liver involvement by metastases, and type of treatment (primary, additional, bone-related). A stepwise backward method was used to determine the stronger independent predictor(s) of mortality. Statistical significance in the results was accepted at a p value < 0.05 and 95% confidence intervals (95% CIs) were given for survival estimates. Analysis was performed using SPSS (version 22.0; PASW SPSS, Inc., Chicago, IL, USA).

Results

Seventy-four patients with NENs and mBD were recruited from the four centers (Greece: 19, Israel:13, London: 23, and Coventry: 19); the median time interval of the recruitment was 6 years (range: 5–9) from 2011 to 2018. Seventy-three patients, of which 37 were males, with a median age of 62 (20–87) years and sporadic disease, and one had a pancreatic NEN in the context of multiple endocrine neoplasia (MEN) type 1. The median time from NEN diagnosis to the identification of mBD was 5 months (0–395) (Table 1).

Survival data

Thirty-five (47%) patients had died with median OS of 62 (19–80) months (Table 1). In univariate analysis, median OS was shorter in synchronous versus metachronous mBD (51.7 months 95% CI: 30.96–72.45 vs. 116.40 months 95% CI: 60.26–172.54; log-rank $p < 0.001$) (Fig. 1) and in patients with deteriorated vs. improved/stable response on bone-related therapy (72.07 months 95% CI: 56.10–88.03 vs. 210.40 months 95% CI: 56.04–364.76; log-rank $p < 0.001$). Multivariate analysis revealed that the stronger predictor of OS was the outcome of bone-related therapy (hazard ratio (HR): 4.753; 95% CI: 1.589–14.213) (Tables 2 and 3). Percent of liver involvement at the time of NEN diagnosis predicted mortality (HR: 1.034; 95% CI: 1.007–1.063, $p = 0.014$) independently from the presence of synchronous or metachronous disease but was not introduced in the multivariate analysis since it was only assessed in 23 patients.

Moreover, the outcome of bone-related therapy had a significant role on BS since patients with deteriorated response on bone-related therapy had a shorter median BS vs. patients with improved/stable mBD (40.77 months 95% CI: 37.57–43.96 vs. 72.00 months 95% CI: 22.60–121.40; log-rank $p = 0.001$). However, BS did not differ between patients with synchronous versus metachronous mBD (48.70 months 95% CI: 28.09–69.31 vs. 67.37 months 95% CI: 43.69–91.05; log-rank $p = 0.2$) (Table 3, Fig. 1). Multivariate analysis revealed that the stronger predictors for BS

Table 1 Characteristic features of the total population and the subgroups with synchronous versus metachronous metastatic bone disease (mBD), with gastrointestinal (and unknown primary origin) (GI) versus bronchopulmonary and thymic neuroendocrine neoplasms (NENs), and the NENs under monthly versus non-monthly biphosphonate administration

Values (median, range)	Total population ($n = 74$)	Synchronous mBD ($n = 32$)	Metachronous mBD ($n = 42$)	GI-NENs (and UPO) ($n = 61$)	Bronchopulmonary and thymic NENs ($n = 13$)	Bisphosphonate monthly ($n = 19$)	Bisphosphonate other schemes ($n = 18$)
Age (years)	62 (19–87)	62 (34–78)	61 (19–87)	58 (19–82)	67 (20–87)	60 (19–82)	59 (20–87)
Males/females	37/37	15/17	22/ 20	28/33	9/4	12/7	9/9
Alive/deceased	39/ 35	16 /16	23/ 19	34/27	5/8	7/12	9/9
Synchronous/ metachronous mBD	32/ 42	32/0	0/ 42	29/32	3/10	7/12	9/9
Latent time to mBD manifestation (months)	5 (0–395)	0 (0–3)	35 (4–395)	4 (0–180)	72 (0–395)	5 (0–137)	7 (0–395)
Bone-related survival (months)	34 (0–189)	32 (0–166)	37 (3–189)	33 (0–188.6)	37 (9–68)	46 (20–189)	32 (3–185)
Overall survival (months)	52 (0–462)	32 (0–167)	72 (25–463)	51 (0–321)	82 (20–463)	74 (20–321)	49 (18–463)
Ki-67 (%)	5 (4–60)	**10 (9–60)***	**4 (4–31)**	**5 (4–60)****	**10 (4–31)**	7 (1–31)	10 (1–20)
Low/high-volume mBD	23/49	8/24	15/25	21/39	2/10	3/15	2/16
Number of mBD	6 (1–19)	6 (1–19)	5 (1–14)	6 (1–19)	7 (4–19)	**10 (2–19)**	**6 (2–13)*****
Number of metastases in addition to mBD	2 (0–5)	2 (0–4)	2 (0–5)	2 (0–5)	2 (1–4)	2 (0–3)	2 (1–4)

The time point of NEN diagnosis or mBD documentation was set as baseline for overall survival (OS) and mBD-related survival (BS) calculation, respectively

$P < 0.05$: *versus NENs with metachronous mBD; **versus broncopulmonary and thymic NENs; ***versus NENs on monthly bisphosphonate administration

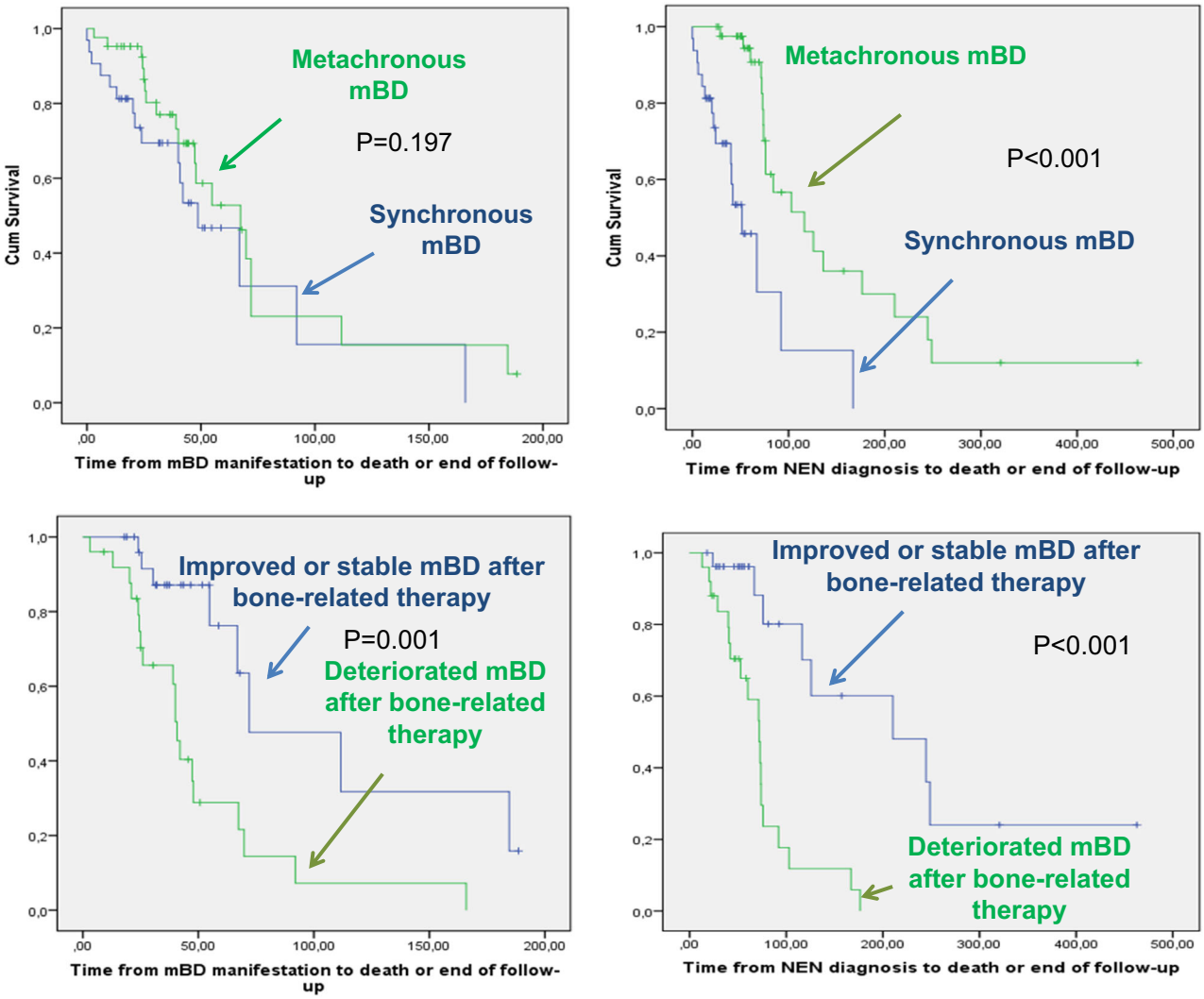


Fig. 1 Survival curves of the total population for the synchronous and the metachronous metastatic bone disease (mBD) and for the outcome of bone-related therapy (improved or stable versus deteriorated mBD). Overall survival (OS) was analyzed using Kaplan–Meier analysis with the time point of neuroendocrine neoplasm (NEN) diagnosis set as baseline. To calculate the mBD-related survival (BS) the time point of mBD diagnosis was set as baseline

were the age of diagnosis (HR: 1.050; 95% CI: 1.006–1.096) and the outcome of bone-related therapy (HR: 4.13; 95% CI: 1.45–1.74) (Table 3).

Site of origin

The most common primary site was the pancreas ($n = 22$, 30%), followed by small bowel ($n = 20$, 27%), UPO ($n = 12$, 16%), and the lung ($n = 11$, 15%) (Table 2). The majority of patients had grade 2 disease ($n = 32$, 59%), followed by grade 1 ($n = 17$, 32%) while grade 3 ($n = 5$, 9%: in 4 with Ki-67 20–55% and one with Ki-67 > 55%) for GI-NENs; 10 bronchopulmonary-thymic NENs had atypical carcinoid (well differentiated). GI-NENs had lower Ki-67 values compared to bronchopulmonary-thymic NENs (5% (range: 4–60) versus 10% (range: 4–31), $p = 0.014$). The liver was the most prevalent concomitant metastatic site of disease in this cohort of patients and was found in 60 patients, followed by lymph nodes in 43, lung in 10, and other sites (Table 2).

Twenty patients (27%) had hormonal hypersecretion-related symptoms. Pain was the most prevalent complaint in 19 (25.7%) patients. No symptoms were reported from 11 (14.9%) patients (Fig. 2).

Metastatic bone disease

The characteristics of bone-related metastases as well as the other metastatic sites are presented in Table 2. Only 7 (10%) patients had a single bone metastatic deposit, while the remaining had a median of 6 (range 2–19) metastatic deposits. Low-volume mBD was seen in 23 (32%) patients

Table 2 Site of primary, metastatic foci and metastatic bone disease (mBD) extension in the total population studied and in the subgroups with synchronous and metachronous mBD

N/median (range)	Total ($N = 74$, %)	Synchronous mBD ($N = 32$, %)	Metachronous mBD ($N = 42$, %)
Pancreas	22 (30%)	12 (29%)	10 (24%)
Small bowel	20 (27%)	5 (16%)	15 (36%)
Unknown origin	12 (16%)	9 (28%)	3 (7%)
Lung	11 (15%)	2 (6%)	9 (21%)
Large bowel	6 (8%)	3 (9%)	3 (7%)
Thymus	2 (3%)	1 (3%)	1 (2%)
Breast	1 (1%)	(–)	1 (2%)
Other metastatic sites			
Liver	60 (81%)	27 (84%)	33 (79%)
Focal/diffuse liver metastases pattern	23/22	10/12	13/10
Percent liver involvement (%)[a]	30 (5–90)	30 (5–80)	35 (5–90)
Lymph nodes	43 (58%)	18 (56%)	25 (60%)
Lung	10 (14%)	6 (19%)	4 (10%)
(Retro)Peritoneal/omental/ pelvic implantation	7 (9.5%)	3 (9%)	3 (8%)
Adrenal gland	5 (7%)	3 (9%)	2 (5%)
Pancreas	3 (4%)	2 (6%)	1 (2%)
Mediastinum	2 (3%)	1 (3%)	1 (2%)
Orbital brain	2 (3%)	1 (3%)	0
Ovaries and uterus	2 (3%)	1 (3%)	1 (2%)
Spleen	2 (3%)	2 (6%)	0
Other	1 (1%)*	1 (3%)**	1 (2%)***
Bone metastases	$N = 72$[b]	$N = 32$	$N = 40$
Axial, appendicular, or both	28 (39%), 1 (1%), 43 (60%)	11 (34%), 1 (3%), 20 (63%)	17 (43%), 0, 23 (58%)
Metastatic bone foci: multiple/ unique	65/7	29/3	36/4
Spine (total: cervical, dorsal, lumbar, sacrum)	61 (85%: 10%, 60%, 58%, 38%)	25 (78%: 9%, 63%, 59%, 41%)	36 (90%: 10%, 58%, 58%, 35%)
Pelvis	33 (60%)	23 (72%)	20 (50%)
Ribs	33 (45.8%)	16 (50%)	17 (43%)
Sternum	24 (33%)	11 (34%)	13 (33%)
Skull	17 (24%)	10 (31%)	7 (18%)
Clavicle	6 (8%)	3 (9.4%)	3 (8%)
Orbit	3 (4%)	2 (6%)	1 (3%)
Mandible	3 (4%)	2 (6%)	1 (3%)
Bone marrow	3 (4%)	2 (6%)	1 (3%)
Femur	37 (51%)	19 (59%)	18 (45%)
Humerus	18 (25%)	9 (28%)	9 (23%)
Scapula	16 (23%)	8 (25%)	8 (20%)
Forearm	5 (7%)	2 (6%)	3 (8%)
Tibia	1 (1%)	0	1 (3%)

Others: *breast, brain, heart, parotid gland; **brain; and ***parotid gland, heart

[a]Assessed in 23 patients (13 with synchronous and 10 with metachronous) mBD

[b]Missing data for two patients

as opposed to high-volume mBD that was seen in 49 (68%) patients. Axial mBD was found in 32% of patients, appendicular in 2% of patients, and both were involved in 66% (Table 2).

Table 3 For overall survival (OS), time point of NEN diagnosis was set as baseline, and to calculate the mBD-related survival (BS), the time point of mBD diagnosis was set as baseline

Covariates	*P* value	HR	95% CI for HR	
			Lower	Upper
Time point set at the time of NEN diagnosis to death/end of follow-up for overall survival				
Improved/stable (0) vs. deteriorated mBD after bone-related therapy	0.005	4.753	1.589	14.213
Time point set at mBD manifestation to death/end of follow-up for mBD-related survival				
Age at NEN diagnosis	0.025	1.050	1.006	1.096
Improved/stable (0) vs. deteriorated mBD after bone-related therapy	0.008	4.132	1.454	1.742

Multivariable Cox-regression analysis was used to determine the stronger predictor for OS and BS

NEN neuroendocrine neoplasm, *GI-NENs* gastrointestinal neuroendocrine neoplasms, *mBD* metastatic bone disease, *HR* hazard ratio, *CI* confidence interval

Thirty-two (43.2%) patients had synchronous mBD while the median period from diagnosis to mBD development in the metachronous was 35 (4–395) months (Table 1). The number of metastatic bone deposits, the number of different liver foci, and the extent (%) of liver involvement did not differ between patients with NENs and synchronous or metachronous mBD. Thirty-six (86%) of patients with metachronous mBD had stage IV disease. The six patients with a stage other than IV at diagnosis had: one atypical thymic NEN stage I, three stage II, one small bowel NEN of grade 1, and two bronchopulmonary, one of grade 1 and one of grade 2, and two small bowel NENs of grade 1. Ki-67 was higher in patients with synchronous mBD ($p = 0.007$), displaying a median value of 10% (9–60%) compared to 4% (4–31%) of Ki-67 seen in metachronous mBD ($p = 0.007$) (Tables 1 and 2).

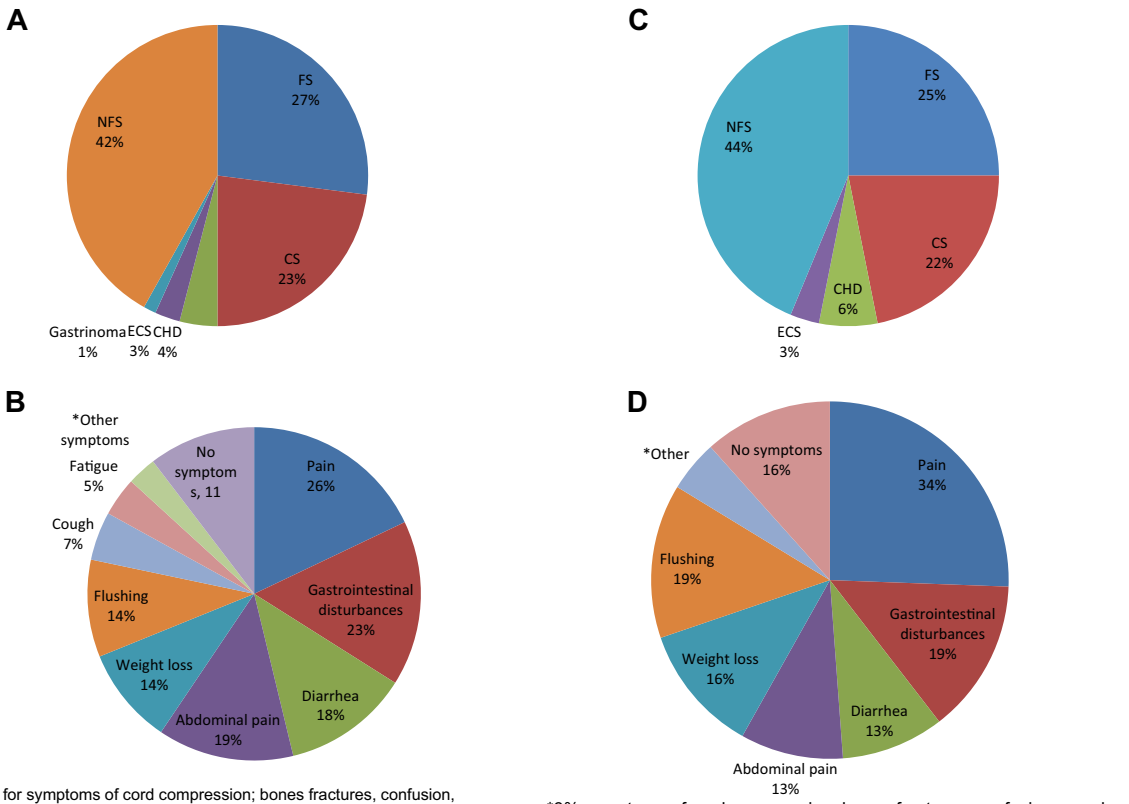
Of the 32 patients with synchronous mBD, only 3 had symptoms attributed to mBD that led to NEN diagnosis: one complained of pain in the femur bone, one had pain with concomitant fractures in the ribs, and the third patient had sought medical help because of cord suppression symptoms.

The comparison of the combined findings of CT/MRI had a substantial agreement with the combined findings of SRS/Ga-PET (kappa value = 0.65). Concordance was seen in 39 (59%) cases (in 32 cases findings were positive in both modalities and in 7 cases findings were negative in both modalities). Of the discordant cases, in 9 (14%) patients, NEN disease was detected by anatomical but not by functional imaging as opposed to 18 (27%) who had positive functional imaging and negative anatomical imaging. No conclusion could be driven for the agreement of the other different imaging modalities used in this specific study. In 32 patients with synchronous mBD, the anatomical imaging methods used that identified mBD was CT that was positive in 68% and MRI in 62%. Radionuclide imaging that identified mBD was: WBS was positive in all the patients submitted in this imaging study, SRS in 86%, Ga-PET in 77%, or if these latter were considered as a unique imaging study for somatostatin receptor detection in 86% (Table 4). Imaging modalities used to identify metachronous mBD was CT in 42% and MRI in 59%. Radionuclide imaging that identified metachronous mBD was WBS in 86%, SRS in 54%, Ga-PET in 79%, or if these latter were considered as a unique imaging study in 68% (Table 4). The radionuclide imaging had higher performance to detect any extent of NEN disease, since in patients with synchronous mBD SRS was positive for any metastatic foci in 96%, Ga-PET in 100% (and similarly for FDG-PET in 100%), and in patients with metachronous mBD SRS was positive for any metastatic foci in 86% and Ga-PET in 95% (and FDG-PET in 80%). The number of the investigations used to detect mBD did not differ between patients with synchronous or metachronous mBD. The diagnostic ability of both CT and bone-specific SRS was statistically higher for synchronous compared to metachronous disease ($p = 0.049$ and $p = 0.020$, respectively).

Therapeutic modalities used in NEN patients with mBD

The registered first-line treatment and the additional treatment modalities for NENs are shown on Table 5. Bone-related therapy included biphosphonates in 41 (72%) and denosumab in 13 (23%); EBRT was administered in 13 (23%) and PRRT in 34 (60%) (Table 5). The bone-related therapy was assessable in 52 patients resulting in an improvement in 5 (10%), stable disease in 22 (42%), and deterioration in 25 (44%) patients. The rate of patients who received biphosphonate treatment and PRRT did not differ between living (17 out of 41 (42%) and 24 out of 41 (58%), respectively) and dead (15 out of 34 (44%) and 19 out of 34 (56%), respectively) patients. However, 78% (10 out of 13) of living patients had taken denosumab compared to only 22% (3 out of 13) of deceased patients ($p = 0.025$); on the other hand, 15% (2 out of 13) of living patients had EBRT compared to 85% (11 out of 13) of deceased patients ($p = 0.01$) (Table 5).

No difference was seen in the subgroup receiving monthly biphosphonate treatment and the subgroup receiving other biphosphonate schemes; the group receiving monthly biphosphonate treatment had higher number of mBD foci compared to the group receiving other biphosphonate schemes (10 (2–19) versus 6 (2–13), $p = 0.014$) (Table 1).



*1% for symptoms of cord compression; bones fractures, confusion, hypertensive crisis, central obesity; 3% broncospasm, hemoptysis, anemia, fever, hyperglycemia; 4% symptoms of bowel perforation and/or obstruction, neurological symptoms, headaches, pedal edema.

*3% symptoms of cord compression; bones fractures, confusion, cough, broncospasm, anemia, pedal oedema. hypertensive crisis, central obesity; 6% fatigue, neurological symptoms, headaches, hyperglycemia

Fig. 2 Clinical features of the total population studied during first-diagnosis of neuroendocrine neoplasms. **A** Functional and hormonal syndromes in the total population (74 patients). **B** Symptoms in the total population (74 patients). **C**: Functional and hormonal syndromes in the population with synchronous metastatic bone disease (mBD) (32 patients). **D** Symptoms in the population with synchronous mBD (32 patients). CHD carcinoid heart disease, CS carcinoid syndrome, ECS ectopic Cushing's syndrome, FS functional syndrome

Secondary malignancies

Twelve (16%) patients had a secondary malignancy. Four patients had breast cancer, two had differentiated thyroid cancer, and one patient had each one of the following: ovarian cancer, colon adenocarcinoma, myelodysplastic syndrome, multiple myeloma, squamous cell carcinoma, melanoma, and prostate NENs. One patient besides the pancreatic NEN presented with a somatomammotroph pituitary adenoma, lung atypical carcinoid, and parathyroid hyperplasia, in the context of MEN1. The differential diagnosis for the source of mBD origin was performed accordingly by the protocols of each Center of Excellence as appropriate.

Discussion

Our data have shown that patients with synchronous mBD had a more aggressive disease, and that the outcome of bone-related therapy independently predicted mortality, as assessed by both OS and BS. Monthly administration of bisphosphonates did not show an advantage over less intensive schemes of bisphosphonate administration.

To the best of our knowledge, there are no study data to address the possible different natural history of metachronous mBD compared to synchronous mBD in NENs. The mBD is mostly encountered in patients with aggressive disease, either because it is more likely to be screened in this subset of patients, or because of symptoms that may indicate mBD presence [5, 13, 18]. Published data are mostly referred to the initial presence of mBD, defining the synchronous mBD. Our data support that synchronous mBD indicates a more aggressive behavior with a worse OS along with higher values of Ki-67 compared to a better OS of metachronous disease along with lower Ki-67 [18]. It is important to note that the extent of investigations was similar in the metachronous and synchronous mBD, implying that a diagnosis of metachronous disease was unlikely related to less intense follow-up. The parameter that mostly affected mortality independently from the timing of mBD documentation was the age at initial diagnosis, and the percent of liver involvement by metastatic disease, well-known parameters of aggressive neoplastic diseases

Table 4 Imaging modalities used in the total population studied and in the subgroups with synchronous and metachronous metastatic bone disease (mBD)

Imaging modality, +ve/total patients	Total population $N = 74$ (%)		Synchronous mBD $N = 32$ (%)		Metachronous mBD $N = 42$ (%)	
	mBD-imaging		mBD		mBD	
CT	36/67 (54)		**21/31 (68)**		**15/36 (42)***	
MRI	21/35 (60)		8/13 (62)		13/22 (59)	
X-rays	3/3 (100)		2/2 (100)		1/1 (100)	
WBS	21/23 (91)		9/9 (100)		12/14 (86)	
SRS	38/57 (67)	*53/70 (76)*	**19/22 (86)**	*25/29 (86)*	**19/35 (54)***	*28/41 (68)*
Ga-PET/CT	25/32(78)		10/13 (77)		15/19 (79)	
F-FDG PET/CT	14/23 (61)	10/13 (77)			4/10 (40)	
Bone biopsy	4/5 (80)	3/3 (100)			1/2 (50)	

CT computed tomography, *FDG* ^{18}fluorodeoxyglucose, *mBD* metastatic bone disease, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *SRS* somatostatin receptor scintigraphy, *WBS* whole-body bone scan scintigraphy, *F-DOPA* fluoro-18-L-Dihydroxyphenylalanine, *Ga-PET/CT* ^{68}Gallium-DOTA-conjugated peptide-PET/CT

*$P < 0.05$ compared to synchronous mBD

Table 5 First-line and additional treatment modalities (surgical and systemic treatments) of patients with neuroendocrine neoplasms (NENs)

Treatment modalities	1st-line treatment	additional treatment	Bone-related treatment
Somatostatin analogs	39 (53%)	24 (32%)	
Surgical treatment	23 (31%)	7 (10%)	
Chemotherapy	15 (20%)	11 (15%)	
Peptide receptor radionuclide therapy (PRRT)	10 (14%)	25 (34%)	34 (60%)
Molecular targeted treatment (MTT)	12 (16%)[a]	10 (14%)[b]	
Electron beam radiation therapy (EBRT)	5 (7%)	4 (5%)	13 (23%)
Bevacizumab	1 (1%)	2 (3%)	
Interferon	1 (1%)	1	
Local treatment (RFA, TACE, TAE)	7 (10%) (3/3/1)	4 (1/2/1)	
Selective internal radiation therapy (SIRT)		1 (1%)	
Telotristat		1	
Bisphosphonates			41 (72%)
Denosumab			13 (23%)

Bone-related treatment was assessable in 52 NEN patients who received bone-specific (biphosphonates, denosumab) or bone-targeted treatment (PRRT, EBRT)

RFA radiofrequency ablation, *TACE* transarterial chemoembolization, *TAE* transarterial embolization with lipiodol

[a]Everolimus/ sunitinib = 10:2; [b]everolimus/ sunitinib = 9:1

[14, 18, 19]. An additional factor that affected survival independently from the timing of mBD documentation was the outcome of bone-related therapy, implying the need of treating these patients. This latter factor proved to be an independent predictor for OS and also for BS together with age at diagnosis (Table 3). More aggressive behavior of GI-NENs despite their lower Ki-67 values was not confirmed by a reduced OS (Tables 1 and 3).

The present study provided evidence on other features of mBD such as the anatomical distribution of primary tumors being represented mainly by pancreas and small bowel, confirming recently published data [12], as opposed to older studies reporting a higher prevalence for so-called (according to the previous terminology) 'foregut and hindgut' primaries [1, 7, 15, 20]. Moreover, in older studies, the presence of mBD was further investigated when clinical symptoms suggestive for mBD occurred [1]. In the present study, bone pain, fracture, or cord compression was the 'warning' symptom that guided the patients to seek medical care in 9% of patients with synchronous mBD, as opposed to higher rates in earlier studies [14, 15]. This discrepancy with the older study results may reflect an earlier diagnosis by using whole-body imaging modalities in our study, as well as the inclusion of other pathologies such as

pheochromocytomas and paragangliomas by the older studies [14, 15].

The recent introduction of PET-CT with ^{68}Ga-DOTA-conjugated peptides in diagnosis and follow-up of NENs is considered superior to SRS, showing higher sensitivity, spatial resolution, identification of more lesions, less radiation, and a shorter investigation time [21, 22]. A recent study comparing two-time periods before and after the introduction of ^{68}Ga-PET showed an increase in mBD detection because of improved use of appropriate methodology and the introduction of new techniques [15]. In another study, ^{68}Ga-PET had a sensitivity of 97% and a specificity of 92% when assessed in 51 patients and compared with CT imaging (sensitivity 58% and specificity 100%) [23]. However, MRI was also reported to have a high sensitivity for mBD [1, 24, 25] and was considered as the most sensitive imaging modality for the detection of NENs with mBD [24]. In our study, anatomical imaging such as MRI and/or CT substantially agreed as was shown by the high kappa value (0.65) with the findings of functional imaging, SRS, and/or ^{68}Ga-PET. However, a lower resolution was seen by all functional imaging to detect mBD compared to their ability to detect the neoplastic disease in other sites. Moreover, no agreement was seen between the somatostatin receptor detection by SRS and/or Ga-PET and WBS, as was also reported by others previously [26–28]. These data support current guidelines, suggesting the combination of different imaging modalities to facilitate mBD diagnosis [1, 21]. Indeed, the extent of mBD has to be clearly defined since the number of mBD was positively correlated to Ki-67.

In solid tumors, the documentation of mBD is followed by bone-targeted therapies. Considering that bone destruction is the main skeletal-related event associated with mBD, anti-resorptive drugs are the currently accepted first-line therapy [12]. Bisphosphonates and the anti-RANKL antibody denosumab are approved bone-targeting therapies for various other malignancies, but their potential role in NENs has not been studied in detail previously. In our study, the comparison of a monthly scheduled treatment of bisphosphonates, suggested in patients with solid tumors, did not show any impact on OS or on BS when compared to other schemes of bisphosphonate administration. However, the bone-related (bone-specific or bone-targeted) therapies affected survival independently from the type of treatment and the frequency of dosing. In line with this, PRRT has been recently established as an important therapeutic option for patients with mBD; in the present study, the number of patients treated by PRRT was too small to allow safe conclusions [21, 29–31]. Moreover, almost all patients with denosumab treatment were alive, but this may be related to the relatively recent introduction of denosumab as a therapeutic modality in these patients. EBRT can be considered for patients with mBD, especially if they are experiencing pain, or in a prophylactic setting to avoid fractures [10]. Finally, no other systemic treatment individually, either primary or additional, had a significant impact on survival or on mBD outcomes. Systemic therapies, such as administration of mammalian target of rapamycin (mTOR) inhibitors, have been recently used alone or in combination with bone-related therapies with good results in other type of solid tumors, but a similar effect was not possible to be shown by the present data [12, 32].

In our study, a multicenter setting was necessary to reach a meaningful number of patients to be studied, However, such an approach also has inherent limitations related to differences in methods (therapeutic or diagnostic) and protocols used. Moreover, despite the multicenter setting, the number of diagnosed NENs patients with mBD was relatively small. Finally, the current available data did not allow us making solid recommendations about the use and frequency of administration of zoledronic acid or denosumab in NENs.

Conclusions

Our study highlights the need to diagnose mBD early, particularly in patients with known metastatic disease in other organs, as its presence affects prognosis. Both anatomical imaging and functional imaging for somatostatin receptor detection have a complementary role in the mBD documentation. A worse outcome is expected when mBD is identified early. The diagnosis of mBD should be followed by bisphosphonate or denosumab treatment (both currently unlicensed for NENs) to improve survival independently from their dosing, at least for bisphosphonate administration. Additional factors to affect survival were the older age of patients at diagnosis, and the higher percent of liver involvement. Given that mBD aggravates the natural history of other solid tumors, larger multicenter studies in patients with NENs may better characterize the more advantageous treatment among the various modalities, particularly in the era of novel emerging bone-specific treatments.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Formal consent was given by all participants.

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