Title: Identification of areas for improvement in the management of bone metastases in patients with neuroendocrine neoplasms

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Short Title

Bone metastases in NENs

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1. Abstract

Background: There is no global consensus on the optimal management of bone metastases (BMs) in neuroendocrine neoplasms (NENs).

Objectives: To review current management and outcomes of patients with BMs in NENs, in order to identify areas for improvement.

Methods: A retrospective study of all patients with NENs, except Grade 3 (G3) lung NENs (April 2002-March 2018) was conducted. Baseline characteristics, nature of BMs, treatment received and overall survival (OS) were evaluated. Statistical analyses were performed using SPSS v23.0/STATA v12.

Results: Of 1212 patients, 85 (7%) had BMs; median age 58 years. The majority had a gastro-entero-pancreatic primary (49%, n=42) followed by lung (25%, n=21), unknown primary (20%, n=17), and "others" (6%, n=5). Two-thirds (n=57) had G1-2 neuroendocrine tumours, and 41% (n=35) had functional tumours. Overall, 28% (n=24) presented with synchronous BMs at first NEN diagnosis, and 55% (n=47) developed BMs at the same time as other distant metastases. For the subpopulation of patients in whom BMs developed metachronously to other distant metastases (45%, n=38), median time to development of BMs was 14.0 months. BMs were 'widespread' in 61% (n=52). Although only 22% (n=19) reported symptoms at initial diagnosis of BMs, most (78%) developed symptoms at some time during the follow-up period (pain/hypercalcaemia 64%, skeletal-related events 20%). BMs were mainly managed with analgesia (44%, n=37). Radiotherapy and bisphosphonates were used in 34% (n=29) and 22% (n=19), respectively. Surgery was rarely performed (2%, n=2). Median OS from identification of BMs was 31.0 months, and 18.9 months from development of BMs-related symptoms.

Conclusions: In this cohort study, most patients with BMs developed symptoms. The utility of radiotherapy and/or bisphosphonates should be prospectively and systematically explored further for its potential impact on patients' quality of life and survival outcomes.

2. Introduction

Neuroendocrine neoplasms (NENs) are relatively rare, although the incidence has been steadily increasing over the past few decades (1, 2). An improved understanding of the natural history and molecular characteristics of the various NEN subgroups has been made possible through better awareness, leading to earlier diagnosis, and via important advances in technology platforms. For instance, in utilising whole genome sequencing, Scarpa *et al.* characterised the somatic mutations leading to pathogenesis of pancreatic NENs, providing potential targets for further translational research into therapeutic interventions (3). In parallel, there has also been a significant increase in the repertoire of therapeutic agents available, resulting in meaningful improvements in both the quality of life and survival outcomes in NENs. As such, patients with metastatic NENs are now surviving longer and are more likely to experience disease-related complications associated with this.

It is well established that NENs, in particular moderate to high grade NENs, have the ability to spread to distant sites, including bone (4, 5). Nevertheless, bone metastases (BMs) in NENs are expected to be uncommon events, with several retrospective series reporting an incidence from 12% to as high as 25% in certain subtypes of NENs (5-8). Some studies have reported that more than half of patients with NENs with BMs were symptomatic, and that skeletal-related events (SREs) occurred in around 21% (7, 8). Currently, there remains no standardised guidelines for the diagnosis and management of BMs in NENs. Indeed, treatment strategies are often contemporaneously extrapolated from evidence derived in other tumour groups. In the United Kingdom (UK), bisphosphonates are broadly endorsed for symptom control in patients with BMs, although the registration trials considered did not include an adequate number of patients with NENs for conclusive recommendations (9-11). Anecdotally, external beam radiotherapy has also been routinely used to relieve pain from BMs. These treatment recommendations and caveats are also reflected in the most recent European Society for Medical Oncology (ESMO) guidelines on bone health in patients with cancer (12).

This study reports the clinical outcomes and treatment received in a large cohort of patients with BMs managed at a tertiary referral centre for NENs. The aim of this study was to assess the current clinical practice in order to identify areas for improvement and direct the focus of future clinical research.

3. Materials and Methods

Study Design

A retrospective study of patients with NENs diagnosed with BMs in a European Neuroendocrine Tumour Society (ENETS) Centre of Excellence in the United Kingdom was performed. Clinical and radiological data were collected from consecutive patients diagnosed with NENs from April 2002 to March 2018. Detailed review of electronic and/or paper medical case notes was conducted. Data on baseline patient characteristics at time of diagnosis of BMs, blood biochemistry results, specific details related to the nature and management of BMs, and patients' disease and overall survival outcomes were collected.

Diagnosis of BMs was based on radiological findings reported in computed tomography (CT), ^{68}Gallium-positron emission tomography (^{68}Ga-PET), ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET), and/or magnetic resonance imaging (MRI) scan reports, as appropriate. Patients attended scans either as part of their scheduled imaging surveillance appointments, or at the discretion of the treating clinician, if symptomatic. BMs were defined as 'oligometastases' if there were less than a total of 5 lesions; otherwise, they were described as 'widespread' or 'multiple'. BMs were considered 'symptomatic' if patients presented with any or a combination of the following: pain, pathological fractures, hypercalcaemia and metastatic spinal cord compression. In this study, 'skeletal-related events (SREs)' were defined as presence of pathological fractures and/or metastatic spinal cord compression (MSCC).

Patient Selection

Patients with small cell lung cancer and large cell lung cancer were excluded. Any other patients with NENs were eligible. Patients with a synchronous cancer diagnosis were excluded if BMs were considered to be more likely secondary to the other malignancy than to a NEN. Patients with high grade NENs were eligible, except if the primary site was lung.

Objectives and End-points

The aim of this study was to retrospectively analyse the outcomes and complications of BMs in patients diagnosed with advanced NENs, to enable identification of areas in clinical practice which could benefit from future clinical research in this patient population. Frequency of events and time-to-events were calculated, with the objective of informing future research in this setting.

The main outcomes evaluated included: 1) time to BMs (defined as time from diagnosis of metastatic NEN to detection of BMs [unless presented synchronously (defined as BMs identified at the same time as the diagnosis of a NEN) or if the BMs were identified within one month of diagnosis of primary)]), 2) time to SREs (time from diagnosis of BM to incidence of SRE), and 3) overall survival (OS) (time from diagnosis of BMs to death or last follow-up, if the patient was alive at the end of the follow-up period).

Statistical Analysis

Statistical analysis was performed using SPSS v25.0 and STATA v12. Demographic and clinical characteristics were organised in tables of frequency for categorical variables, and by calculation of median and interquartile range (IQR), mean ± standard deviation (SD) or proportion in percentage (%) for continuous variables. We used χ^2 and Student's t-test analyses to test categorical and continuous variables, respectively. Data were last updated on 15 July 2018. Median OS and survival analyses were performed by the Kaplan-Meier method, log-rank test and Cox regression. Factors predictive of development of SREs were identified using binary logistic regression. Univariate and

multivariate analyses (Cox and binary logistic regression) were performed as appropriate; variables significant in univariate analysis were included in the multivariate model. For the estimation of median time-to-SREs, due to death and SREs being competing events, the analysis was done using the Kaplan Meier method, but limited to those patients who had developed SRE/symptoms during the follow up period. Results were considered to be statistically significant if p was <0.05 (two-sided).

4. Results

Patient Characteristics

Of 1212 individual patients diagnosed with NENs between April 2002 and March 2018, a total of 85 patients (7.0%) had BMs and were included in this retrospective study (**Figure 1**). **Table 1** summarises the baseline characteristics of eligible patients. Half of the patients (49.4%) had gastroenteropancreatic (GEP) primaries, followed by bronchial (24.7%) tumours. Most patients had grade 1 (29.4%) or grade 2 (37.6%), non-functional (58.8%) tumours, and had metastatic disease at the time of initial presentation with a NEN (63.5%). A minority of patients (28.2% of the whole population, n=24) presented at this time with synchronous BMs.

Characteristics of Bone Metastases and BM-related Symptoms

At the time of development of metastatic disease, 47 patients (55.3%) had BMs (so called synchronous BMs). Within the subpopulation of patients (n=38, 44.7%) who were diagnosed with BMs as 'late events' (metachronous BMs), the time to development of BMs was 14.0 months (95% CI 3.1 – 24.9) (**Figure 2**). At the time of diagnosis of BMs, all patients had metastases in other distant organs; median number of other extraskeletal organ sites involved was 2 (range 2-3), with the majority of patients having liver metastases (n=74, 87.1%) (**Table 2**).

The characteristics of BMs are summarised in **Table 2**. The most frequent pattern of BMs was 'widespread' (n=52, 61.2%). Although only 22.4% (n=19) reported symptoms at their initial diagnosis of BMs, most (77.6%) developed symptoms at some time during the follow-up period (pain 61.2%,

hypercalcaemia 3.5%, skeletal-related events 20%). **Table 3** summarises the frequency of these events and time-to-event for those cases in which the symptoms appeared metachronously to BMs. **Figure 2** provides an overview of distribution of synchronous and metachronous events and time-to-event in the case of metachronous presentation. The development of pain was an early event following the diagnosis of BMs (time-to development of 2.8 months (95% CI 1.9-7.6)). A significant number of SREs were metachronous (44.4% with pathological fractures and 66.7% with MSCC), with a median time-to-event of 7.7 months (95% CI 0.3-14.9) and 14.2 months (95% CI 0.3-118.9) for pathological fractures and MSCC, respectively.

Factors Predictive of Increased Risk of Symptoms or Skeletal Related Events

No clinically significant factors were identified as predictors of higher risk of development of symptoms or SREs (**Supplementary Material 1**). Although an association between SREs and poorer performance status was identified (OR 2.44 (95% CI 1.02-5.84); p-value 0.045), the deterioration in performance status was likely to be an effect of the SRE rather than vice versa. Patients with SREs were also more likely to report pain (OR 7.98 (95% CI 2.11-30.15); p-value 0.002), as expected.

Management of Bone Metastases

Details for the clinical management of BMs are provided in **Table 4**. BMs were mainly managed with analgesia (n=37, 43.5%). Radiotherapy and bone modifying agents (BMAs) (zolendronic acid and denosumab) were used in 29 patients (34.1%; 36.5% when analysis limited to patients with BM-related pain) and 19 patients (22.4%; 28.8% when analysis limited to patients with 'widespread' BMs), respectively. Surgery was performed in 2% of patients.

Overall Outcomes of Patients with Bone Metastases

The mean duration of follow-up in the whole cohort was 30.9 months (95% CI 24.7 – 37.1) from diagnosis of metastatic disease (any non-bone distant metastases), and 20.2 months (95% CI 15.2 – 25.2) from diagnosis of BMs. There was a total of 58 deaths (68.2%) at the time of last follow-

up. Median OS from the identification of BMs was 31.0 months (95%-CI 19.6-42.4) and 18.9 months (95%-CI 8.7-29.1) from time of development of BM-related symptoms (**Figure 2**). The development of SREs did not impact on OS (p-value 0.449) (**Table 5**). On multivariate Cox regression, older age (p-value 0.016) and poorer performance status (p-value 0.018) were independent factors associated with shorter OS (**Table 5**).

5. Discussion

In recent years, there have been tremendous improvements in diagnostic imaging modalities and an increased repertoire of both pharmacological and non-pharmacological interventions available for patients with NENs. However, knowledge regarding BMs, their natural behaviour, and potential interventions remain scarce.

The findings from this study suggest that there could be an important role for future clinical trials to improve the clinical outcomes and quality of life in this population of patients. Based on these observations, such studies should focus on the prevention of SREs (predominantly primary prophylaxis), particularly utilising interventions in the form of bone-modifying agents (BMAs). This is supported by the following: 1) Despite BMs being relatively rare in NENs, most patients with BMs are expected to become symptomatic at some point during follow-up; 2) Almost half of the patients who developed pathological fractures and two-thirds of patients with MSCC developed such complications metachronously to the initial identification of BMs (with a time-to-event ranging between 7-14 months), thus, providing a window of opportunity for potential interventions; 3) In more than half of the patients, BMs were detected at the same time as the diagnosis of other distant metastases, and were usually widespread in pattern, therefore suggesting a possible intrinsic aggressive nature of the disease in this subpopulation of patients; 4) Prolonged OS, both measured from time of BM diagnosis and from time of symptom-development, allows adequate time for an intervention to be feasible and clinically meaningful.

Analgesia with paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) or opioids was sufficient to control pain in most patients. Patients were treated with radiotherapy on selected occasions where pain was refractory to pharmacological intervention. There is evidence that palliative radiotherapy can be effective in symptom control of BMs, and more importantly in improving patients' quality of life (13). Therefore, this should remain the mainstay of symptom control, particularly when there is a localised source for which the pain could be treated. The benefits of BMAs in this setting remains unclear, although current clinical guidelines permit the use of bisphosphonates and denosumab for patients with almost any solid tumours as a preventative measure against complications of BMs (9, 12). In selected patients with good performance status and in whom disease-related prognosis is favourable; surgery should remain an option particularly if the anticipated gain in quality of life is considered significant (12, 14). In the metastatic setting, surgery is predominantly indicated for the treatment or prevention of pathological fractures, or neurological deficit (or risk of) secondary to spinal cord compromise (15).

Of all the symptoms explored in this series, we identified SREs (defined as pathological fractures and MSCC in this study) to be the key BM-related complications in need of prioritisation in future clinical trials. Due to low incidence of hypercalcemia and the good response of pain to analgesia, interventional studies for these symptoms may not be warranted in this setting. On the contrary, the prevention of SREs in patients with known BMs is an unexplored area in NENs, and currently most clinicians tend to extrapolate data from other more prevalent solid malignancies.

The most common indication for prescribing a BMA in this patient population was in patients with widespread BMs in whom a SRE had already occurred (secondary prophylaxis). Whilst it is logical to use BMAs in patients with widespread BMs in NENs as secondary prevention for future SRE, there is no clear data identifying which target population are most at risk, and who would benefit most from such interventions. Based on current evidence, patients with asymptomatic, but widespread BMs, should receive BMAs as primary phosphylaxis if they have rapidly progressive

disease (grade 3 tumours/disease progression). Otherwise the use of BMAs should be individualised and carefully considered as they are not without risks. However, there is no clinical trial evidence clearly stating the benefits of BMAs for patients with NENs, and this can only be extrapolated from other studies in solid tumours. Experience in the use of BMAs comes from studies in advanced breast and prostate cancers. Indeed, in a recent meta-analysis of 6 large randomised-controlled trials, including a variety of solid tumours, both bisphosphonates and denosumab prolong time to SREs, with overall superiority in the latter (16). Clinical trials clarifying the role of BMAs as primary prevention of SREs in patients with BMs specifically from NEN are therefore required.

The current findings suggest that the rate of BMs in patients with NENs is 7%, which appears to be lower than previously reported (6-8). An explanation could be an underdiagnosis of BMs, considering most patients were followed-up using cross-sectional CT imaging, which has limited sensitivity in detecting BMs (17). It is expected that the recent introduction of more advanced ^{68}Gallium PET-CT scanning as a standard of care for patients with NENs will lead to earlier detection of BMs, which are at their asymptomatic phase. The impact of this on patients outcome should be explored in the future.

The OS in patients who develop BMs was over 2.5 years, which is inferior to the OS of 4 years that was reported in the recent cohort studied by Scharf *et al.* (8). Whilst there was no major difference in the proportion of patients receiving radiotherapy and surgery in both cohorts, more than two-thirds of their patients received BMAs compared to 22.4% in the current study (8). Additionally, patients who did not receive BMAs in their analysis had shorter OS, although this was not statistically significant (49.0 vs 37.4 months, p-value=0.39) (8). Similarly, however, patients who were asymptomatic of their BMs had more favourable survival outcomes compared to those who reported symptoms. The main factors associated with poorer OS in the current cohort were older age and poorer performance status, both of which are difficult to disentangle in terms of their cause-

effect with BMs. Together, this provides further impetus for a study to prospectively study the quality of life and OS outcomes of BMAs in this cohort of patients.

Despite screening a large cohort of patients over a period of more than 16 years, this remains a retrospective study with limitations. The imaging modality used as surveillance was part of standard of care and hence not intentionally performed to detect BMs. This may result in an underestimation of the incidence of BMs in patients diagnosed with NENs in the earlier years of this cohort study, or a delay in the eventual diagnosis resulting in lag time bias when analysing survival outcomes. In addition, the number of events (especially SRE) was small, impacting on limited power and wide 95% CI for time-to-event estimations. Imaging performed for identification of bone metastases also varied across patients, and therefore, outcome data could not be compared to patients without bone metastases and have not been not included in the study.

6. Conclusion

Currently, whether better screening of BMs or possible interventions (primary and/or secondary prophylaxis of SREs) may improve overall outcomes in patients with NENs is unknown, and should be explored further. The results from this study would favour future clinical research, focussing on the prevention of SREs in patients with BMs, particularly with interventions in the form of BMAs.

7. Appendix

Not applicable.

8. Statements

8.1. Acknowledgements

KHJL is currently funded by the Welcome Imperial 4i clinical research fellowship. JB received funding from the ENETS Centre of Excellence Fellowship Grant Award. AL received funding from The Christie Charity.

8.2. Statement of Ethics

External ethics approval was not required for this analysis as it was categorised as a retrospective audit. This study was registered at the Christie Hospital as audit number 18/2173.

8.3. Disclosure Statement

Authors have no conflicts of interest to declare with regards to this manuscript. KHJL is currently funded by the Wellcome Trust 4i clinical PhD fellowship at Imperial College London. JWV reports personal fees from Ipsen, personal fees from Novartis, personal fees from AstraZeneca, personal fees from Merck, personal fees from Delcath, personal fees from Agios, personal fees from Pfizer, personal fees from PCI Biotech, personal fees from Incyte, personal fees from Keocyt, personal fees from QED, personal fees from Pieris Pharmaceuticals, personal fees from Genoscience Pharma, personal fees from Mundipharma EDO, personal fees from Wren Laboratories, personal fees from Nucana, and personal fees from Imaging Equipment Limited outside the submitted work; and Travel Grants from Celgene and Nucana. MMN has received research grant support from Servier, Ipsen and NuCana. She has received travel and accommodation support from Bayer and Ipsen and speaker honoraria from Pfizer, Ipsen and NuCana. She has served on advisory boards for Celgene, Ipsen, Sirtex and Baxalta; all outside the scope of this

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8.4. Funding Sources

No financial support was received in relation to this study.

8.5. Author Contributions

KHJL, HR, and AL were responsible for the study concept, planning, design and drafting of the manuscript and carried out the statistical analysis. AL supervised the study. All authors contributed to the acquisition, analysis or interpretation of data and critical revision of the manuscript.

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10. Figure and Table Legends

- **Figure 1**. **CONSORT diagram.** A total of 85 eligible patients were included in the final analysis for this study. NET: neuroendocrine tumour, NEC: neuroendocrine carcinoma; IT: informatics; SCLC: small cell lung cancer; LCLC: large cell lung cancer; n: number of patients; G: grade.

- **Figure 2. Overview of patients' journey: from initial diagnosis to death. Percentage of synchronous/metachronous events and time-to-events are provided.** MSCC: metastatic spinal cord compression; NEN: neuroendocrine neoplasm; BMs: bone metastases; SREs: skeletal-related events; CI: confidence interval; Pts: patients; n: absolute number; %: percentage. Percentages of synchronous/metachronous symptoms/SRE are calculated using the total number of patients developing the corresponding event as a denominator.

- **Table 1. Baseline characteristics of patient cohort at time of diagnosis of bone metastases (BMs) (n=85).**

- **Table 2. Clinical characteristics of bone metastases (BMs) (n=85).**

- **Table 3. Summary of frequency and time-to-event of BM-related symptoms and SRE.** Percentages are calculated both for the whole population (n=85), and also for the population of patients who developed a specific event. Due to death and SREs being competing events, the analysis was performed by limiting the analysis to those patients who had developed the symptoms/SRE within the follow-up period (Kaplan-Meier). SREs: skeletal-related events; CI: confidence interval; MSCC: metastatic spinal cord compression.

- **Table 4. Detailed summary of management of bone metastases (BMs) (n=85).** Data presented as proportion (percentage, %). BMs: bone metastases; Pts : patients; MSCC: metastatic spinal cord compresion. SREs: skeletal-related events; fracture: pathological fracture.

- **Table 5. Univariate and multivariate Cox regression analyses of factors associated with overall survival (OS).** *(*factors with p-value <0.10 (arbitrary) included for multivariate analyses)*

Figure 1

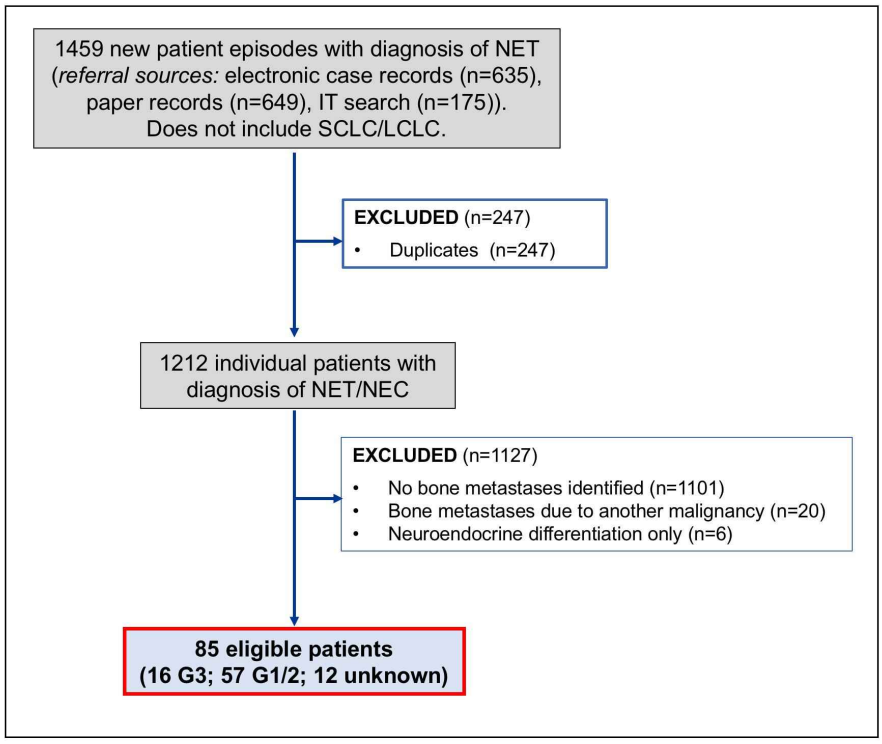
1459 new patient episodes with diagnosis of NET (*referral sources:* electronic case records (n=635), paper records (n=649), IT search (n=175)). Does not include SCLC/LCLC.
EXCLUDED (n=247)
• Duplicates (n=247)
1212 individual patients with diagnosis of NET/NEC
EXCLUDED (n=1127)
• No bone metastases identified (n=1101)
• Bone metastases due to another malignancy (n=20)
• Neuroendocrine differentiation only (n=6)
85 eligible patients (16 G3; 57 G1/2; 12 unknown)

Figure 2

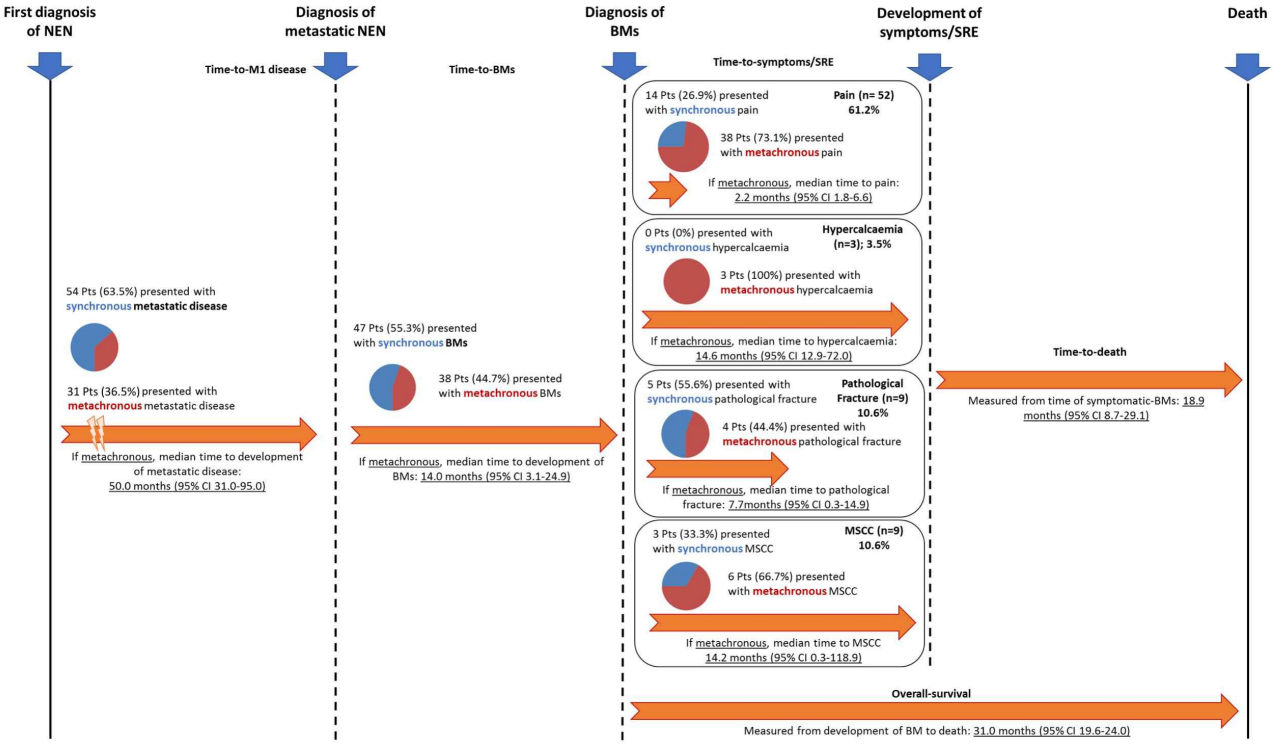
First diagnosis of NEN
Diagnosis of metastatic NEN
Diagnosis of BMs
Development of symptoms/SRE
Death
Time-to-M1 disease
Time-to-BMs
Time-to-symptoms/SRE
54 Pts (63.5%) presented with synchronous metastatic disease
31 Pts (36.5%) presented with metachronous metastatic disease
If metachronous, median time to development of metastatic disease: 50.0 months (95% CI 31.0-95.0)
47 Pts (55.3%) presented with synchronous BMs
38 Pts (44.7%) presented with metachronous BMs
If metachronous, median time to development of BMs: 14.0 months (95% CI 3.1-24.9)
14 Pts (26.9%) presented with synchronous pain
Pain (n= 52) 61.2%
38 Pts (73.1%) presented with metachronous pain
If metachronous, median time to pain: 2.2 months (95% CI 1.8-6.6)
0 Pts (0%) presented with synchronous hypercalcaemia
Hypercalcaemia (n=3); 3.5%
3 Pts (100%) presented with metachronous hypercalcaemia
If metachronous, median time to hypercalcaemia: 14.6 months (95% CI 12.9-72.0)
5 Pts (55.6%) presented with synchronous pathological fracture
Pathological Fracture (n=9) 10.6%
4 Pts (44.4%) presented with metachronous pathological fracture
If metachronous, median time to pathological fracture: 7.7months (95% CI 0.3-14.9)
3 Pts (33.3%) presented with synchronous MSCC
MSCC (n=9) 10.6%
6 Pts (66.7%) presented with metachronous MSCC
If metachronous, median time to MSCC 14.2 months (95% CI 0.3-118.9)
Time-to-death
Measured from time of symptomatic-BMs: 18.9 months (95% CI 8.7-29.1)
Overall-survival
Measured from development of BM to death: 31.0 months (95% CI 19.6-24.0)

Table 1

Characteristics	Proportion, n (%)
Gender	
Male	48 (56.5%)
Female	37 (43.5%)
Median age (years)	58.0 (47.5;67.5)
Adult comorbidity evaluation (ACE-27)	
No comorbidities	38 (44.7%)
Mild	34 (40.0%)
Moderate	13 (15.3%)
Severe	0
ECOG performance status at time of diagnosis of bone metastases	
0	20 (23.5%)
1	49 (57.6%)
2	7 (8.2%)
3	6 (7.1%)
4	1 (1.2%)
Unknown	2 (2.4%)
Primary site	
Bronchial	21 (24.7%)
Gastroenteropancreatic (GEP)	42 (49.4%)
Others	5 (5.9%)
Unknown	17 (20.0%)
Grade	
1	25 (29.4%)
2	32 (37.6%)
3	16 (18.8%)
Unknown	12 (14.1%)
Differentiation	
Well-differentiated	46 (54.1%)
Moderately differentiated	2 (2.4%)
Poorly-differentiated	11 (12.9%)
Unknown	26 (30.6%)
Ki-67	
≤2%	22 (25.9%)
3-20%	34 (40.0%)
>20%	16 (18.8%)
Unknown	13 (15.3%)
Hormone production	

Functional	35 (41.2%)
Non-functional	50 (58.8%)
Metastatic (any) disease at initial diagnosis	
Yes (synchronous)	54 (63.5%)
No (metachronous)	31 (36.5)
Presence of bone metastases at initial diagnosis	
Yes (synchronous)	24 (28.2%)
No (metachronous)	61 (71.8%)

Data presented as proportion (percentage, %) and median (interquartile range, IQR). ECOG, Eastern Cooperative Oncology

Table 2

Characteristics	Proportion, n (%)
Bone metastases present at diagnosis of metastatic NEN	
Yes (synchronous)	47 (55.3%)
No (metachronous)	38 (44.7%)
Other distant metastases present at time of diagnosis of bone metastases	
Yes	85 (100%)
No	0
Site of other distant metastases present	
Liver	74 (87.1%)
Lung	16 (18.8%)
Lymph nodes	63 (74.1%)
Mesentery	14 (16.5%)
Peritoneum	4 (4.7%)
Others	17 (20.0%)
Nature of bone metastases	
Oligometastases	28 (32.9%)
Multiple/Widespread metastases	52 (61.2%)
Not specified	5 (5.9%)
Clinical presentation of bone metastases	
Asymptomatic	66 (77.6%)
Symptomatic	19 (22.4%)
Median Alkaline phosphatase (ALP), iU/L	113 (85;226) *Normal range 30-130*
Median serum Chromogranin A, ng/mL	486 (132;1059) *Normal range 0-91*
Incidence of skeletal-related events	
Any	17* (20.0%)
Pathological fracture/collapse	9 (10.6%)
Metastatic spinal cord compression	9 (10.6%)
Other symptoms of bone metastases	
Pain	52 (61.2%)
Hypercalcaemia	3 (3.5%)

Data presented as proportion (percentage, %) and median (interquartile range, IQR);
*one patient had both, pathological fracture and metastatic spinal cord compression.

Table 3

Events	Frequency of events	Synchronous (frequency of events)	Metachronous	
			Frequency of events	Time-to-event if metachronous Median (95% CI) (months)
Any symptoms/SRE	66/85 (77.6%)	19/85 (22.4%) 19/66 (28.8%)	47/85 (55.3%) 47/66 (71.2%)	2.8 (1.9-7.6)
Any symptom (pain/hypercalcaemia)	66/85 (77.6%)	19/85 (22.4%) 19/66 (28.8%)	47/85 (55.3%) 47/66 (71.2%)	2.3 (1.8-7.2)
Pain	52/85 (61.2%)	14/85 (16.5%) 14/52 (26.9%)	38/85 (44.7%) 38/52 (73.1%)	2.2 (1.8-6.6)
Hypercalcaemia	3/85 (3.5%)	0/85 (0%) 0/3 (0%)	3/85 (3.5%) 3/3 (100%)	14.6 (12.9-72.0)
SRE (pathological fracture+/- MSCC)	17/85 (20.0%)	8/85 (9.4%) 8/17 (47.1%)	10/85 (11.8%) 10/17 (58.8%)	8.2 (0.4-39.7)
Pathological fracture	9/85 (10.6%)	5/85 (5.9%) 5/9 (55.6%)	4/85 (4.7%) 4/9 (44.4%)	7.7 (0.3-14.9)
MSCC	9/85 (10.6%)	3/85 (3.5%) 3/9 (33.3%)	6/85 (7.1%) 6/9 (66.7%)	14.2 (0.3-118.9)

Table 4

	Frequency (%)
Management of bone metastases	
Analgesia	37 (43.5%)
Radiotherapy	29 (34.1%)
Surgery (bone-targeted)	2 (2.4%)
Bone modifying agents	19 (22.4%)
Detailed treatment received	
Use of bisphosphonates	
Yes (all pts)	19/85: 22.4%
Yes (pts with widespread BMs)	15/52: 28.8%
Yes (pts with oligometastatic BMs)	4/28: 14.3%
Yes (pts with widespread BMs and any symptoms/SRE)	14/43: 32.6%
Yes (pts with widespread BMs and pain/hypercalcaemia)	10/36: 27.8%
Yes (pts with widespread BMs and fracture/MSCC)	5/9: 55.6%
Yes (pts with widespread BMs and pain)	10/36: 27.8%
Yes (pts with any symptoms/SRE)	17/66: 25.8%
Yes (pts with pain/hypercalcaemia)	11/54: 20.4%
Yes (pts with pain)	11/52: 21.2%
Yes (pts with fracture/MSCC)	7/17: 41.2%
Use of radiotherapy	
Yes (all pts)	29/85: 34.1%
Yes (pts with any symptoms/SRE)	27/66: 40.9%
Yes (pts with pain/hypercalcaemia)	20/54: 37.0%
Yes (pts with pain)	19/52: 36.5%
Yes (pts with fracture/MSCC)	9/17: 52.9%
Bone modifying agents used	
Zoledronic acid	12 (14.1%)
Denosumab	7 (8.2%)

Table 5

Variables	Univariate				Multivariate			
	Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI		p-value
		Lower	Upper			Lower	Upper	
Age	**1.049**	**1.023**	**1.076**	**<0.001**	**1.035**	**1.006**	**1.065**	**0.016**
Adult comorbidity evaluation (ACE-27)	1.286	0.868	1.904	0.210				
ECOG performance status at time of diagnosis of bone metastases	**1.861**	**1.321**	**2.623**	**<0.001**	**1.608**	**1.085**	**2.384**	**0.018**
Tumour grade	**1.787**	**1.136**	**2.812**	**0.012**	1.419	0.908	2.217	0.124
Functional status	1.339	0.783	2.288	0.286				
Extent of bone metastases	1.326	0.749	2.347	0.332				
Skeletal-related events (SREs)	**1.808**	**0.982**	**3.333**	**0.057**	1.672	0.773	3.610	0.191
Number of distant metastases (organ sites)	1.011	0.808	1.265	0.923				
Symptomatic of bone metastases	1.087	0.644	1.837	0.755				

ECOG, Eastern Cooperative Oncology Group.

Supplementary Material

Supplementary Material 1: Factors predictive of increased risk of symptoms/SRE

Table A.1 Binary logistic regression of factors associated with **skeletal-related events** – univariate analysis (n=17/85)

Variables	Odds Ratio	95% CI		p-value
		Lower	Upper	
Male gender	0.469	0.149	1.476	0.195
Age	1.022	0.980	1.065	0.315
Adult comorbidity evaluation (ACE-27)	1.152	0.554	2.396	0.705
ECOG Performance status at time of diagnosis of bone metastases	1.429	0.784	2.603	0.243
Tumour grade	1.560	0.689	3.531	0.286
Functional tumour	1.363	0.452	4.115	0.582
Extent of bone metastases	1.911	0.642	5.685	0.244
Bone metastases at initial diagnosis of metastatic disease	4.949	1.303	18.800	0.019
Number of distant metastases (organ sites)	0.659	0.387	1.121	0.124
Alkaline Phosphatase	0.998	0.993	1.003	0.379

ECOG, Eastern Cooperative Oncology Group; Extent of bone metastasis: oligometastases versus widespread metastases.

Table A.2 Binary logistic regression of factors associated with **skeletal-related events** – multivariate analysis (n=17/85) *(*factors with p-value <0.25 (arbitrary) included for analysis)*

Variables	Odds Ratio	95% CI		p-value
		Lower	Upper	
Male gender	0.223	0.040	1.242	0.087
ECOG Performance status at time of diagnosis of bone	**2.442**	**1.021**	**5.840**	**0.045**

metastases				
Extent of bone metastases	2.348	0.348	1.243	0.197
Bone metastases at initial diagnosis of metastatic disease	0.383	0.089	1.643	0.196
Number of distant metastases (organ sites)	0.658	0.348	1.243	0.197

ECOG, Eastern Cooperative Oncology Group; Extent of bone metastasis: oligometastases versus widespread metastases.

Table B.1 Binary logistic regression of factors associated with **pain** – univariate analysis (n=52/85)

Variables	Odds Ratio	95% CI		p-value
		Lower	Upper	
Male gender	0.880	0.365	2.119	0.776
Age	1.009	0.976	1.042	0.608
Adult comorbidity evaluation (ACE-27)	0.849	0.463	1.557	0.597
ECOG Performance status at time of diagnosis of bone metastases	0.690	0.407	1.170	0.169
Tumour grade	0.686	0.361	1.304	0.250
Functional tumour	0.470	0.187	1.179	0.107
Extent of bone metastases	0.444	0.173	1.145	0.093
Bone metastases at initial diagnosis of metastatic disease	0.952	0.396	2.287	0.912
Number of distant metastases (organ sites)	1.031	0.704	1.509	0.875
Skeletal-related events (SRE)	7.800	2.266	26.849	0.001
Alkaline Phosphatase	1.000	0.997	1.003	0.953

ECOG, Eastern Cooperative Oncology Group. Extent of bone metastasis: oligometastases versus widespread metastases.

Table B.2 Binary logistic regression of factors associated with **pain** – multivariate analysis (n=52/85) *(*factors with p-value <0.25 (arbitrary) included for analysis)*

Variables	Odds Ratio	95% CI		p-value
		Lower	Upper	
ECOG Performance status at time of diagnosis of bone metastases	0.937	0.469	1.870	0.853
Functional Status	0.400	0.133	1.202	0.103
Extent of bone metastases	0.443	0.145	1.290	0.133
Skeletal-related events (SREs)	**7.975**	**2.109**	**30.152**	**0.002**

ECOG, Eastern Cooperative Oncology Group; Extent of bone metastasis: oligometastases versus widespread metastases.

Table C.1 Binary logistic regression of factors associated with **MSCC** – univariate analysis (n=9/85)

Variables	Odds Ratio	95% CI		p-value
		Lower	Upper	
Male gender	0.335	0.065	1.717	0.189
Age	0.999	0.949	1.052	0.968
Adult comorbidity evaluation (ACE-27)	0.706	0.252	1.978	0.508
ECOG Performance status at time of diagnosis of bone metastases	1.363	0.629	2.952	0.433
Tumour grade	0.686	0.361	1.304	0.250
Functional status	1.917	0.476	7.718	0.360
Extent of bone metastases	0.638	0.157	2.598	0.531
Bone metastases at initial diagnosis of metastatic disease	0.317	0.062	1.628	0.169
Number of distant metastases (organ sites)	0.689	0.347	1.367	0.286
ALP	0.997	0.989	1.005	0.430

ECOG, Eastern Cooperative Oncology Group; Extent of bone metastasis: oligometastases versus widespread metastases. MSCC, metastatic spinal cord compression, ALP, alkaline phosphatase.

Table C.2 Binary logistic regression of factors associated with **MSCC** – multivariate analysis (n=9/85) *(*factors with p-value <0.25 (arbitrary) included for analysis)*

Variables	Odds Ratio	95% CI		p-value
		Lower	Upper	
Male gender	2.720	0.522	14.179	0.235
Bone metastases at initial diagnosis of metastatic disease	0.347	0.067	1.804	0.208