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Prognostic impact of tumour burden in stage IV neuroendocrine neoplasia: A comparison between pancreatic and gastrointestinal localizations

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ABSTRACT

Background: Although prognosis of NENs is affected by several features including tumour burden, the specific role of this factor in pancreatic NENs (PanNENs) and gastrointestinal NENs (GI NENs) is not well established.
Aim: To compare the prognostic role of tumour burden in PanNENs and GI NENs.
Patients and methods: This study was a retrospective analysis of stage IV PanNENs and GI NENs. Tumours were classified based on liver tumour volume (<25% or >25%). Overall survival as assessed by Kaplan-Meier curves, and Cox proportional hazards method was used to perform risk factor analysis.
Results: The analysis included 300 patients, including 166 panNENs (55.3%) and 134 GI NENs (44.7%). A total of 158 patients (52.7%) had G2 tumours, 107 had G1 tumours (35.7%), and 35 had G3 tumours (11.6%). Tumour liver involvement >25% was observed in 187 patients (62.3%): 106 PanNENs (56.7%), and 81 GI NENs (43.3%) ($p = 0.551$). Bone metastases were present in 45 patients (15%): 22 PanNENs (13.2%) and 23 GI NENs (17.1%) ($p = 0.416$). Characteristics of the PanNENs, including: grading (G2 vs G1, HR = 3.7; G3 vs G1, HR = 16.40), liver involvement > 25% (HR = 3.09), and bone metastases (HR = 2.27) were independent predictors for poor survival, whereas the only significant risk factor in GI NENs was grading (G2 vs G1, HR = 4.36; G3 vs G1, HR = 8.60).
Conclusions: PanNENs and GI NENs have different risk profiles. Liver tumour volume and the presence of bone metastases significantly affect survival in patients with PanNENs but has no impact on the clinical outcomes of GI NENs.

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Background

The prognosis of gastro-entero-pancreatic neuroendocrine neoplasia (GEP-NENs) is affected by several factors, including primary tumour site, tumour grading, and staging. Since each factor may have a specific prognostic weight influencing the clinical outcome, it has been proposed to regard them as combined when assessing patient prognosis using risk scores [1–3].

In accordance with the European Neuroendocrine Tumours Society (ENETS) staging system, patients are included in the stage IV group when distant metastases are present, irrespective of their number, sites or specific extension [4,5]. However, it has been proposed to consider stage IV as a heterogenous group, since it may include patients with different metastatic extension and different prognosis [6].

Specifically, the proportion of metastatic tumour liver involvement has been shown to impact clinical outcome in terms of patient survival and probability to respond to antitumour medical treatments [3,7,8]. The presence of bone metastases is also considered a negative prognostic factor in NENs in general, and this has been recently confirmed in a large series of patients with GEP, bronchial, and unknown primary NENs [9].

As far as the primary tumour site is concerned, among GEP NENs, pancreatic NENs (PanNENs) are usually considered more aggressive compared with gastrointestinal NENs (GI NENs) due to their higher risk of progression and worse long-term survival [10,11]. Additionally, therapeutic approaches may vary depending on primary tumour site. In fact, recent phase 3 randomized controlled trials that were performed to investigate the efficacy of targeted agents or peptide receptor radionuclides as therapies for NENs have selected patients to be included according to the primary tumour site [12–14].

Although several studies have been performed to identify risk factors affecting clinical outcome in NENs, comparative data on the role of tumour burden between pancreatic and gastrointestinal localizations are scant.

The aim of this study was to compare the prognostic role of tumour burden, expressed as extension of liver metastases and presence of bone metastases, between PanNENs and GI NENs.

Patients and Methods

In this multicentre study, a retrospective analysis of institutional anonymized databases from four Italian ENETS Centres of Excellence (Rome, Milan INT, Bologna, Naples) was performed. All patients with a histologically proven diagnosis of stage IV GEP-NEN performed by a participant centre according to the ENETS staging system [4,5] were included. Minimal datasets required in the final analysis were as follows: demographic data; dates of initial NEN diagnosis and of stage IV evidence; Ki67 value to assess ENETS grading; radiological data to assess proportion of metastatic liver tumour involvement; data from diagnostic procedures used to stage disease according to the ENETS guidelines; and follow-up data, including treatments, tumour progression and patient survival. Patients with familial syndromes were excluded. The data were prospectively collected at the centres that managed patients, a uniform computerized datasheet was created, and data were analysed retrospectively.

Therapeutic approaches were not standardized, and thus different treatments were used at each centre. However, in accordance with the ENETS standard of care [15], the therapeutic approaches were always discussed within a multidisciplinary team at each ENETS Center of Excellence. Although no specific prospectively planned follow-up programme was shared by the participating centres, they all followed the ENETS standards of care for advanced GEP-NENs follow-up [15]. Somatostatin receptor expression was assessed by Octreoscan® or Gallium-68 PET/CT.

Based on data retrieved from available charts, gastrointestinal and pancreatic NENs were retrospectively classified according to the WHO 2010 [16] and WHO 2017 [17] classifications. Patients were arbitrarily classified into two different categories according to the proportion of metastatic liver involvement, as assessed by conventional radiological examinations by measuring hepatic tumour volume whether or not metastatic liver involvement was >25%. Liver involvement was assessed by evaluating initial radiological report or by eyes label two-dimensional evaluation of radiological images when needed.

This work has been carried out in accordance with the Declaration of Helsinki. Informed consent for data collection was obtained from all patients.

The primary endpoint was overall survival from diagnosed stage IV GEP NEN. As a secondary endpoint, progression-free survival from the time of stage IV diagnosis was also evaluated. The distribution of continuous variables was reported as the median and interquartile range (IQR; 25th–75th percentiles). A comparison between the subgroups was carried out using the Fisher's exact test or the chi-square test for noncontinuous variables, whereas the Mann–Whitney *U* test was used to compare the continuous variables, as appropriate. OS and PFS analyses were performed by using the Kaplan-Meier method, and results were compared by log-rank test. The cox proportional hazards method (univariate and multivariate analysis) was used to identify risk factors for patient death. All variables with significant results by univariate analysis ($p < 0.05$) were included in the multivariate model, which was constructed by the enter method. Receiver operating characteristic (ROC) analysis was performed to evaluate the ability of the multivariate model to discriminate between patients who died and patients who did not die during follow-up, and the area under the

Table 1
Patients' general features.

Feature	Total (n = 300)	PanNENs (n = 166)	GI NENs (n = 134)	p
Male gender	169 (56.3%)	93 (56%)	76 (56.7%)	0.907
Median age, yr (IQR)	58.5 (48–67)	55.5 (45–64)	61 (53–70)	0.0008
Stage IV at initial NEN diagnosis	233 (77.7%)	127 (76.5%)	106 (79.1%)	0.676
Functioning tumor	52 (17.3%)	18 (10.8%)	34 (25.4%)	0.001
SSTr positive[a]	263 (90.4%)	140 (87%)	123 (94.6%)	
WHO classification				
G1	107 (35.7%)	40 (24.1%)	67 (50%)	<0.0001
G2	158 (52.7%)	101 (60.8%)	57 (42.5%)	
G3	35 (11.6%)	25 (15.1%)	10 (7.5%)	
Median Ki67 (IQR)	5% (2%–10%)	6.5% (3%–15%)	2.5% (1%–5%)	<0.0001
Tumor liver involvement > 25%	187 (62.3%)	106 (63.9%)	81 (60.4%)	0.551

[a] Data available in 291 out of 300 patients (97%).

Table 2
Most frequent sites of distant extra-hepatic metastases in stage IV GEP NENs.

Metastatic site	Total (n = 300)	PanNENs (n = 166)	GI NENs (n = 134)	p
Extra-hepatic metastases	84 (28%)	34 (20.5%)	50 (37.3%)	0.001
Bone	45 (15%)	22 (13.2%)	23 (17.1%)	0.416
Distant lymphnodes[a]	28 (9.3%)	15 (9%)	13 (9.7%)	0.844
Lung	9 (3%)	4 (2.4%)	5 (3.7%)	0.520
Peritoneum	20 (6.7%)	2 (1,2%)	18 (13.4%)	<0.0001

[a] N2 according with ENETS staging system [4,5].

curve (AUC) was used to express the predictive ability. The statistical analysis was performed using a dedicated software programme (MedCalc 17, Belgium, www.medcalc.org).

Results

Patient population

A total of 429 patients with stage IV GEP-NEN were evaluated. Of these, 129 patients (30%) were excluded due to the lack of relevant data required by the minimal dataset criteria (Ki67 value, radiological data to assess tumour extension, accurate disease staging, follow-up data). Thus, a total of 300 patients, including 166 panNENs (55.3%) and 134 GI NENs (44.7%. Small intestine: 113 patients, 37.7%), were included in the final analysis (Table 1).

Compared to GI NENs, PanNENs had a higher median Ki67 value (6.5% vs 2.5%, $p < 0.0001$) and a higher proportion of high-grade tumours. In fact, among 166 PanNENs, 101 (60.8%) were G2 tumours, and 25 (15%) were G3 tumours, whereas the GI NENs group included 57 (42.5%) and 10 (7.4%) G2 and G3 tumours, respectively ($p < 0.0001$). As expected, a higher proportion of patients with GI NEN had a specific associated syndrome, with a functioning tumour diagnosed in 34 patients (25.4%, all with carcinoid syndrome) vs 10.8% (n = 18) of PanNENs ($p = 0.001$), including: insulinomas (n = 11), Zollinger-Ellison syndromes (n = 5), and ACTH secreting tumours (n = 2).

The proportion of tumour liver involvement was similar between PanNENs and GI NENs (Table 1). However, extra-hepatic metastases were more frequently observed in the latter group of patients ($p = 0.001$), mostly due to the higher number of GI NENs patients who had peritoneal tumour disease compared with PanNENs (18 patients, 13.4% and 2 patients, 1.2%; $p = 0.0008$). Bone metastases were observed in a similar proportion in the two groups, specifically in 22 PanNENs (13 females, 59%) and 23 GI NENs (17 females, 73.9%: $p = 0.558$). A slightly higher median age was observed in GI NENs with bone lesions compared with PanNENs (62 yr vs 54.5 yr, $p = 0.071$). Specific sites of distant metastases are detailed in Table 2.

As far as medical treatments are concerned, 263 patients (87.7%), including 144 PanNENs (86.7%) and 119 GI NENs (88.8%) received somatostatin analogues, 94 patients were treated with everolimus (78 PanNENs, 47% and 19 GI NENs, 14.2%), 90 patients (30%) received systemic chemotherapy (68 PanNENs, 41% and 22 GI NENs, 16.4%), 88 patients (29.3%) were treated with peptide receptor radionuclide therapy (47 PanNENs, 28.3% and 41 GI NENs, 30.6%), and 20 PanNENs were treated with sunitinib (12%). A total of 30 patients (10%) including 19 PanNENs (11.4%) and 11 GI NENs (8.2%) underwent hepatic arterial embolization.

Risk factors affecting patient survival

Risk factor multivariate analysis performed for the general

Table 3
Comparison of risk factors affecting survival between stage IV PanNENs and GI NENs.

	Overall						Pancreatic NENs						Gastrointestinal NENs					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis[a]			Univariate analysis			Multivariate analysis		
Variable	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p
Male gender	1.29	0.80–2.07	0.293				1.06	0.60–1.87	0.827				1.47	0.58–3.71	0.405			
Age	1.00	0.99–1.02	0.362				0.99	0.97–1.01	0.762				1.05	1.00–1.10	0.018	1.03	0.99–1.08	0.147
Functioning tumor	1.39	0.79–2.42	0.245				1.24	0.55–2.75	0.596				1.99	0.81–4.89	0.131			
SSTr positive	0.26	0.15–0.47	<0.0001	0.41	0.22–0.76	0.004	0.42	0.21–0.82	0.011	0.44	0.21–0.89	0.023	0.09	0.03–0.30	0.0001	0.25	0.05–1.21	0.08
WHO classification																		
G2 vs G1	3.02	1.60–5.71	0.0006	3.70	1.92–7.12	0.0001	2.28	1.04–4.97	0.037	3.70	1.92–7.12	0.016	4.23	1.34–13.39	0.013	4.36	1.35–14.00	0.013
G3 vs G1	17.88	8.39–38.08	<0.0001	16.40	7.19–37.36	0.0002	13.88	5.45–35.30	<0.0001	16.40	7.19–37.36	<0.0001	26.53	6.73–104.58	<0.0001	8.60	1.33–55.23	0.023
Liver involvement >25%	2.22	1.25–3.93	0.005	3.09	1.70–5.62	0.0002	2.07	1.03–4.16	0.038	3.09	1.70–5.62	0.005	1.99	0.72–5.51	0.181			
Extra-hepatic metastases	1.50	0.91–2.48	0.109				2.29	1.24–4.24	0.007				1.19	0.48–2.93	0.698			
Bone metastases	1.53	0.85–2.77	0.152				2.58	1.29–5.15	0.007	2.27	1.09–4.71	0.026	0.77	0.22–2.64	0.682			

[a] Variable "bone metastases" was selected for multivariate model instead of "extra-hepatic metastases" because of the higher predictive ability (AUC = 0.707 and AUC = 0.697, respectively).

population of stage IV GEP NENs showed that tumour grading (G2 vs G1: HR 3.70, p = 0.0001; G3 vs G1: HR 16.40, p = 0.0002) and the proportion of tumour liver involvement (>25% vs < 25%: HR 3.09, p = 0.0002) were significantly associated with poor clinical outcome, whereas somatostatin receptor expression was an independent protective factor associated with low risk of death (HR: 0.41, p = 0.004).

When risk factor analysis was performed according to the primary tumour site, different variables were associated with poor clinical outcome in PanNENs and GI NENs. In fact, tumour grading (G2 vs G1 HR 2.69, G3 vs G1 HR 19.00), tumour liver involvement > 25% (HR 2.90), and the presence of bone metastases (HR 2.27) were independent negative risk factors for increased risk of death in PanNENs. Somatostatin receptor expression was instead associated with better survival (HR 0.44) (Table 3). Conversely, grading was the only significant independent variable in the multivariate model performed in GI NENs and was a strong predictor for increased risk of death in these patients (Table 3).

Overall survival and progression-free survival

A total of 74 patients (24.7%) died of disease during follow-up, after a median interval of 25.5 months (IQR 14–71) from diagnosis of stage IV disease. Median survival was 131 months, and the 5-yr survival rate was 76.5%.

Compared with GI NENs, PanNENs showed worse clinical outcome, with a median survival of 204 months and 108 months, respectively (p = 0.012) (Fig. 1).

Survival was significantly different in both PanNENs and GI NENs after stratifying patients according to grading (Fig. 2). Both presence of bone metastases and tumour liver extension significantly affected survival in PanNENs, whereas these factors had an irrelevant impact on survival in GI NENs (Fig. 3 and Fig. 4).

Overall, the median PFS after diagnosis of stage IV disease was 24 months. Significantly longer median PFS was observed in GI NENs compared with PanNENs (32 months and 20 months, respectively, p = 0.005).

Discussion

The present study shows that tumour burden plays a different prognostic role in PanNENs compared with GI NENs. In fact, in the former group of patients, proportion of metastatic liver involvement >25% and presence of bone metastases were strong independent negative prognostic factors affecting patient survival. Conversely, in the GI group, these factors did not have any impact

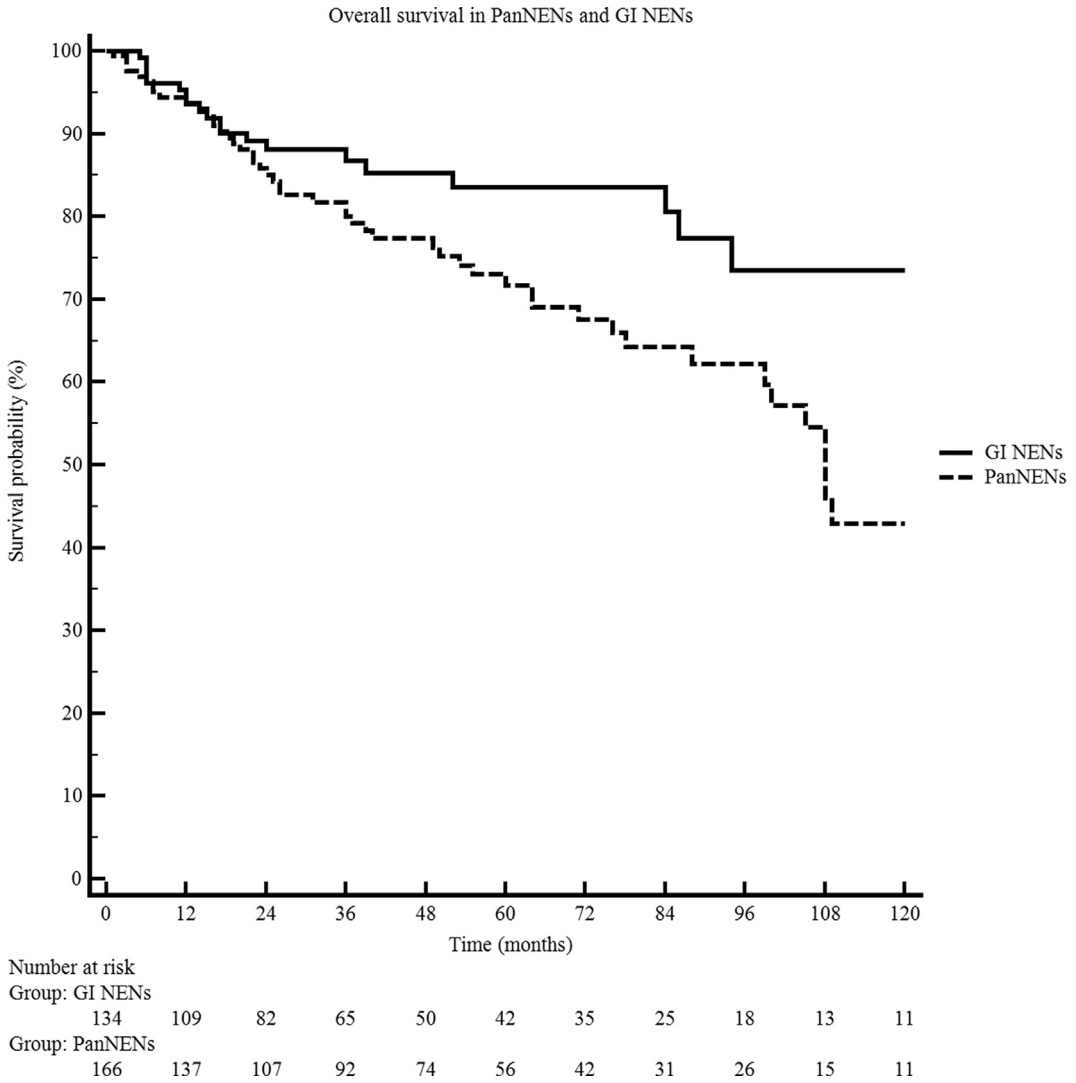

Fig. 1. Comparison between overall survival in PanNENs and GI NENs (p = 0.012).

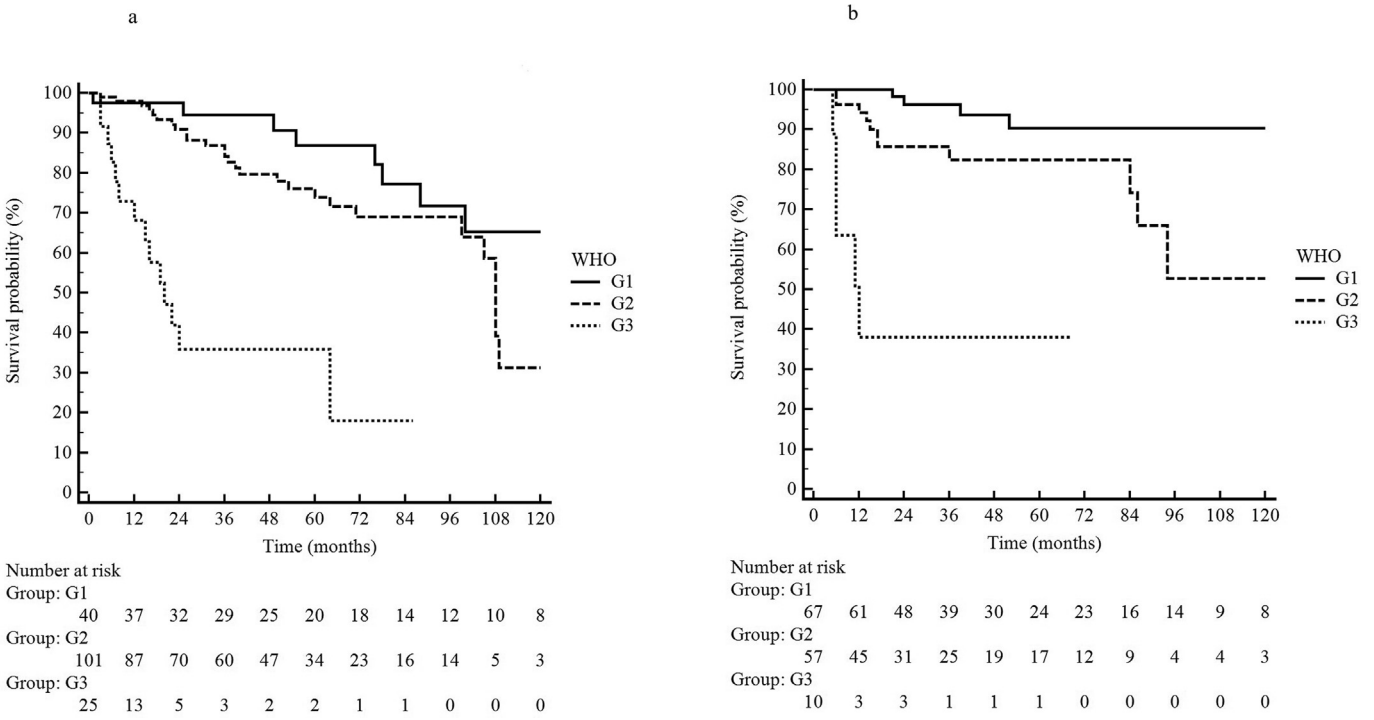

Fig. 2. Comparison between survival in PanNENs (2a) and GI NENs (2b) according with WHO classification [16,17]. Fig. 2a, $p < 0.0001$. Fig. 2b, $p < 0.0001$.

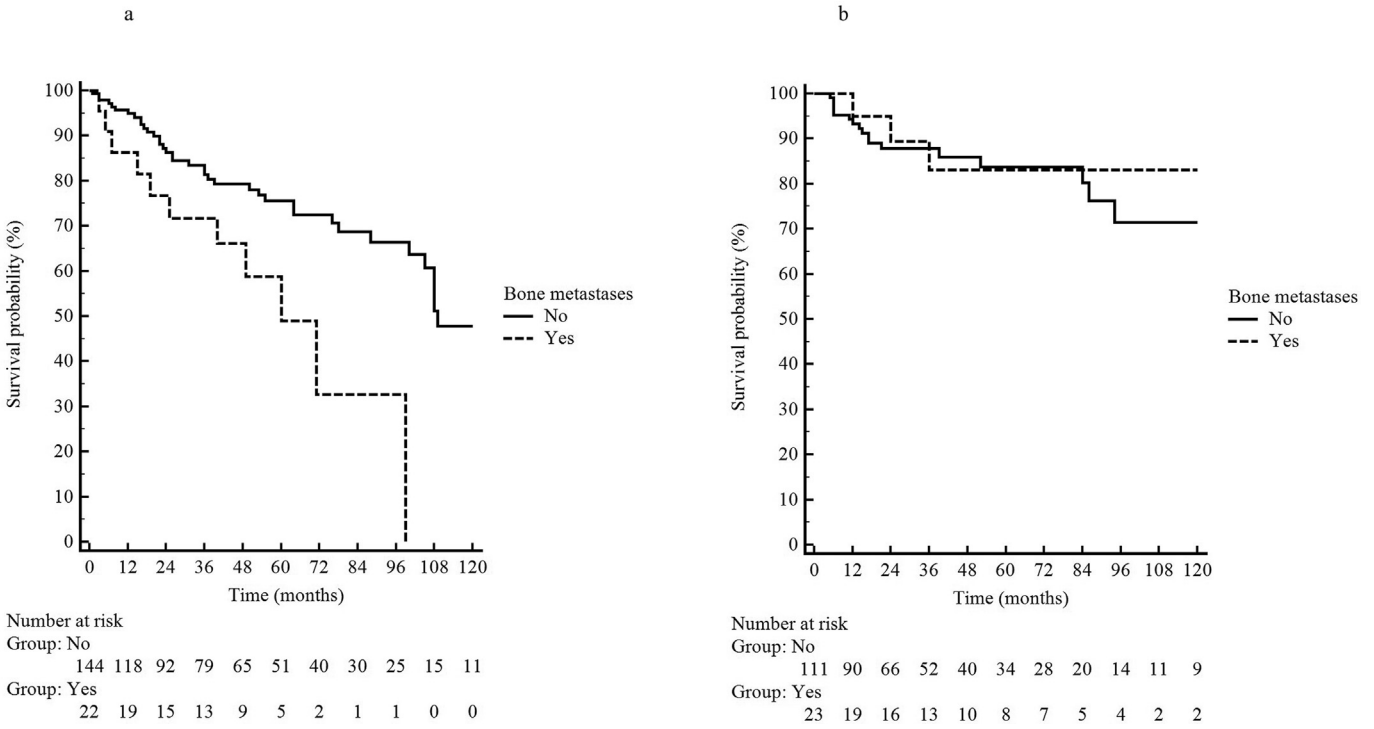

Fig. 3. Comparison between survival in PanNENs (3a) and GI NENs (3b) according with presence of bone metastases. Fig. 3a, $p = 0.005$. Fig. 3b, $p = 0.680$.

on clinical outcome.

Hepatic tumour volume is a relevant feature affecting both patient survival and response to medical antitumour treatments. It has been reported that the presence of multiple liver lesions, as well as a high proportion of tumour liver involvement and the specific metastatic liver dissemination, are associated with poor survival in populations including mixed types of GEP NENs [3,6,18,19]. Extension of hepatic tumour involvement has also been used as a parameter to predict response to somatostatin analogues [7,8]; however, its specific prognostic role with regard to primary tumour site has not been investigated.

In general, distant extra-hepatic metastases are related with

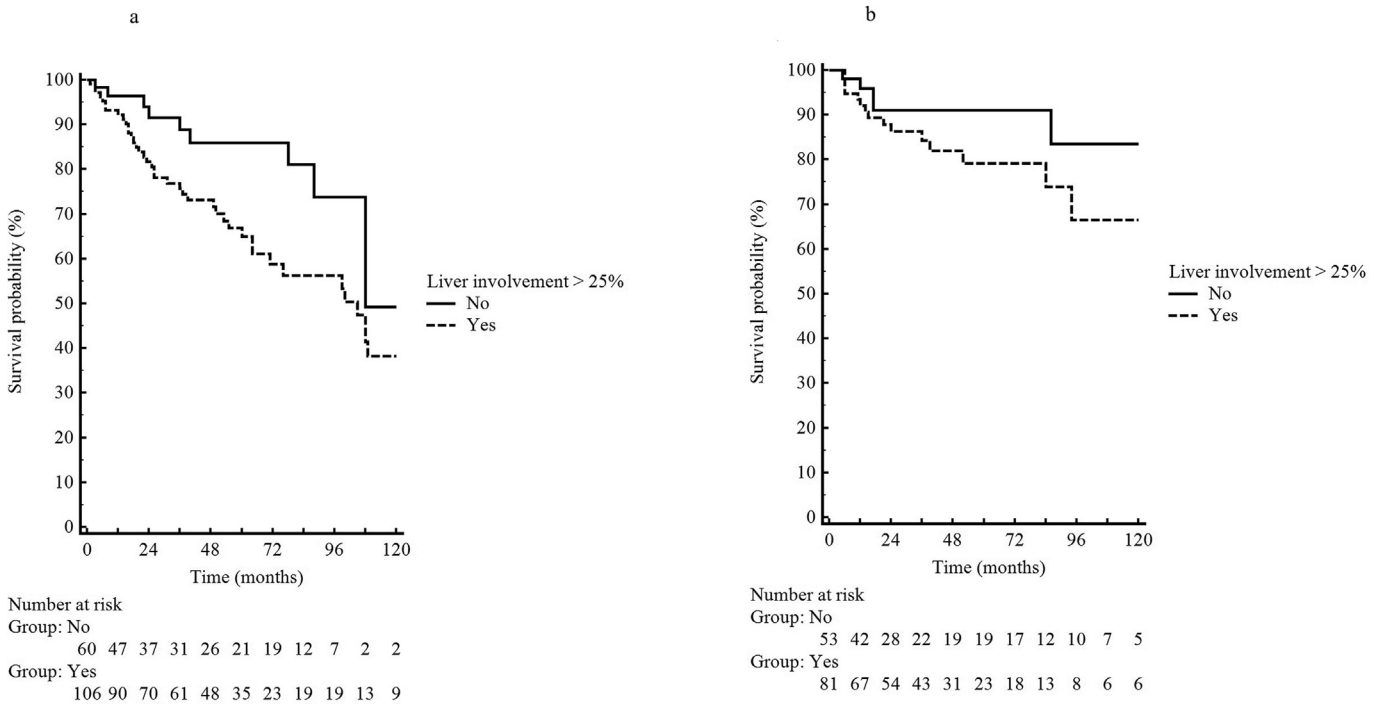

Fig. 4. Comparison between survival in PanNENs (4a) and GI NENs (4b) according with tumor liver volume. Fig. 4a, p = 0.034. Fig. 4b, p = 0.171.

poor patient survival, since they may be the result of a diffuse long-standing disease. Several papers have reported a worse clinical outcome in NEN patients with distant metastases [3,6,9,10,18]. The real incidence of distant extra-hepatic metastases in NENs is not completely known. It has been reported that they may be present in 2–5% of patients with metastatic GEP-NENs [20]. However, these data refer to a national cancer registry based on death certificates and hospital-based data from two nationwide Swedish registers and thus may not be reliable in the clinical scenario of referral to centres for NEN management.

Among different distant extra-hepatic sites, bones are usually reported to be the most frequent. These metastases have been shown to play a significant role in a mixed population of NENs [9]. The ability to detect bone metastases has increased since the introduction of 68-Gallium PET, which adds a significant diagnostic yield to conventional radiological procedures and may change NEN management in a significant proportion of patients [21,22]. However, the specific impact of bone metastases on patient survival according to the primary tumour site has not been analysed in depth. A similar affinity of NEN (PanNEN and GI NENs) to bone was observed in the present study, bone metastases being observed in 13.2% and 17.1%, respectively (p = 0.416). A possible impact of bone metastases on tumor biology might be the differences in bone metabolism in relationship with the gender and age of the patient. However, similar figures in terms of the gender distribution and the median age of the patients were observed between PanNENs and GI NENs with bone lesions. Another possible explanation might be found at a molecular level because of the high expression level of the C-X-C chemokine receptor type 4 in pancreatic cell lines, which has been proposed to be related to tumour potential for skeletal colonization [23]. Furthermore, a dysregulation of the Receptor Activator of Nuclear factor Kappa-B-/Ligand (RANK/RANKL)/osteoprotegerin (OPG) pathway might be involved in the development of bone metastases. An imbalance of this pathway with a high RANKL/OPG ratio has been found in well-differentiated NET patients with bone metastases compared to a matched population of NET patients without bone metastases, indicating the activation of bone resorption processes in the former [24]. However, further evidence is needed to make these hypotheses more solid. In this study, bone metastases had a different prognostic impact depending on primary site. In fact, 5-yr survival rates were 58.8% and 75.5% in PanNENs with or without bone metastases, respectively (p = 0.005) (Fig. 3a), whereas equal 5 yr survival rates were observed in GI NENs: 83.0% and 83.7% in GI NENs with or without bone metastases, respectively (p = 0.680) (Fig. 3b). This finding was further corroborated by multivariate analysis, which found different hazard ratios in pancreatic and GI NENs (Table 3), suggesting a different impact of bone metastases on patient survival depending on primary tumour site.

As expected, tumour grading was a strong independent risk factor for patient death in both PanNENs and GI NENs, with increasing risk of poor prognosis in G2 and G3 tumours compared with G1 (Table 3). Furthermore, a higher proportion of highly proliferating tumours was observed in PanNENs compared with GI NENs. These figures are in agreement with solid data available in the literature, which universally consider grading based on Ki67 value as the most powerful predictor for clinical outcome in NENs and which report that G3 NENs are mostly located in the pancreas [25].

As a major novel finding, this study shows that tumour burden plays a major role in PanNENs, whereas it has a weak impact on the clinical outcome of GI NENs.

However, this study has some limitations, mainly related to its design. Although data were collected by ENETS Centres of Excellence with experience in NENs management, they were analysed retrospectively. This may represent a limitation in terms of therapeutic approaches received by the patients and possibly by the different timing and method of follow-up programmes performed by each centre, although they were planned in accordance with the ENETS standard of care [15]. However, due to the rarity of GEP-NENs, the retrospective study design is a major inherited pitfall for the majority of studies on these diseases. An additional

limitation may be represented by the cut-off level of 25% regarding tumour liver involvement, which was arbitrarily defined; however, although not-standardized, this value has been used by other studies to stratify patients according to liver tumour volume [8,26].

In conclusion, this study suggests to separately manage GI NENs and PanNENs due to their different risk profiles and clinical behaviours: in the case of GI NENs, patient prognosis is mostly driven by grading expressed by the Ki67 value, whereas specific metastatic pattern and tumour burden seem not to play a significant additional prognostic role. In contrast, when faced with patients with PanNENs, the tumour burden should be carefully assessed, since patients with extensive liver involvement and/or the presence of bone tumour lesions have a significantly worse survival rate. In these patients, more aggressive therapeutic approaches and intensive follow-up programmes should be planned.

Declaration of competing interest

None declared.

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