XXI GISMO

LE NUOVE FRONTIERE DELLE MALATTIE METABOLICHE DELL'OSSO

UDINE

14 - 15 novembre 2025

www.gismo.net

Salute ossea nei tumori neuroendocrini

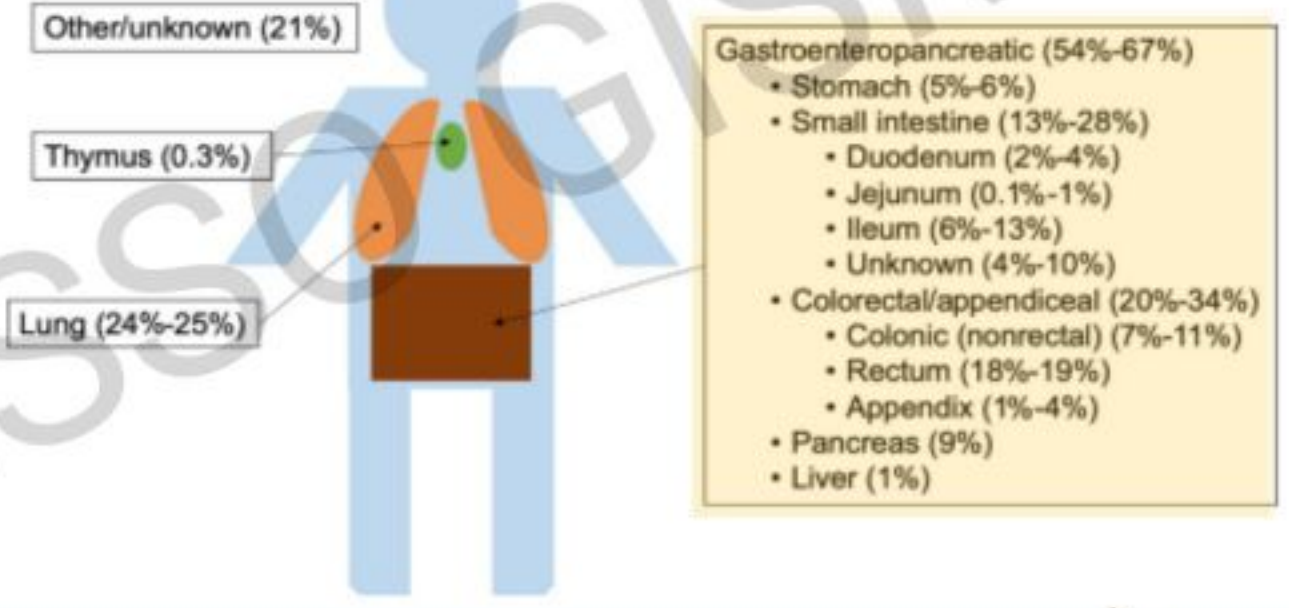
Dr. Alessandro Brunetti

SOC, Endocrinologia

Presidio Ospedaliero S. M. M, Udine

Introduction

Neuroendocrine neoplasms (NENs) are an uncommon, heterogeneous group of tumors arising from cells of neuroendocrine origin, which can be found at multiple sites throughout the body.



Fernandes et al. Gastroenterol Clin N Am 2022

Introduction

Cell differentiation (**grading**) and tumor stage at diagnosis (**staging**) are major prognostic factors in NENs.

GRADING

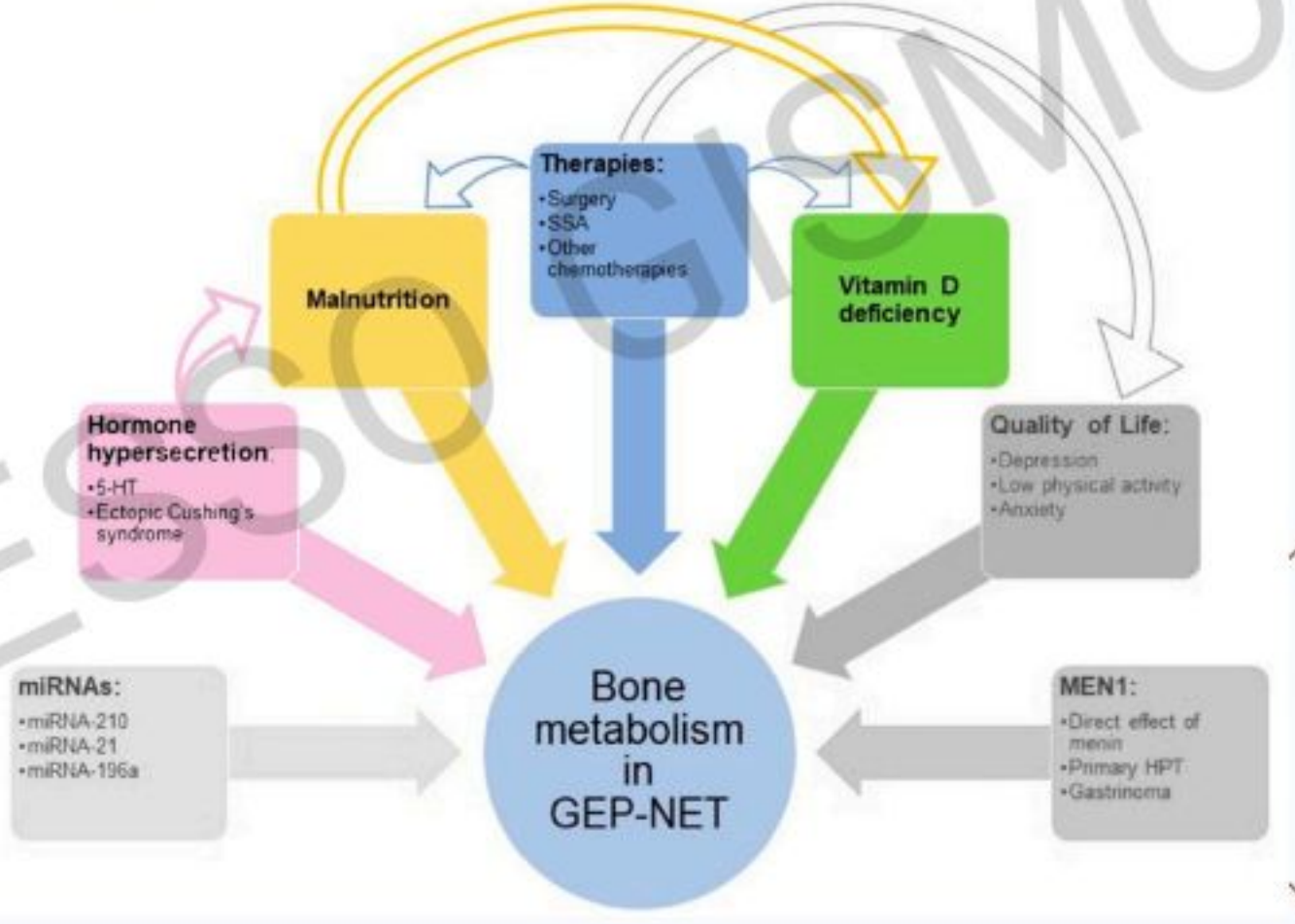
Classification	Differentiation	Grade	Mitotic Rate (Mitoses/ 2 mm^2 or Mitoses/ 10HPFs)	Ki-67 Index
Grade 1 NET (G1)	Well differentiated	Low	<2	<3%
Grade 2 NET (G2)	Well differentiated	Intermediate	2–20	3%–20%
Grade 3 NET (G3)	Well differentiated	High	>20	>20%
NEC	Poorly differentiated	High	>20	>20%

STAGING

AJCC Stage	Stage grouping	Stage description*
I	T1 N0 M0	The tumor is less than 2 centimeters (cm) across and is still just in the pancreas (T1). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
II	T2 N0 M0	The tumor is at least 2 cm across but no more than 4 cm across, and it is still just in the pancreas (T2). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
	OR	
	T3 N0 M0	The tumor is more than 4 cm across and is still just in the pancreas, OR the tumor has grown into the duodenum (the first part of the small intestine) or the common bile duct (T3). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
III	T4 N0 M0	The tumor has grown into nearby organs (such as the stomach, spleen, colon, or adrenal gland) or it has grown into nearby large blood vessels (T4). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0).
	OR	
	Any T N1 M0	The tumor can be any size and might or might not have grown outside of the pancreas (any T). It has spread to nearby lymph nodes (N1), but not to distant parts of the body (M0).
IV	Any T Any N M1	The tumor can be any size and might or might not have grown outside of the pancreas (any T). It might or might not have spread to nearby lymph nodes (any N). The cancer has spread to distant parts of the body (M1).

Introduction

Patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are exposed to multiple risk factors for bone fragility.



Altieri B. et al Nutrients 2020

Hypovitaminosis D in GEP-NET

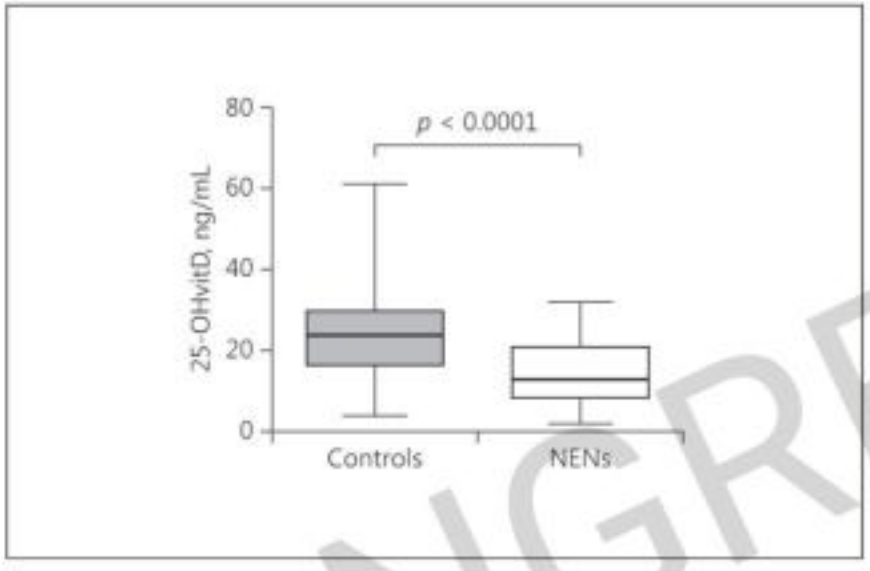


Fig. 1. Circulating 25-OHvitD values in NEN patients compared to controls (median 12.9 vs. 23.9 ng/mL, $p < 0.0001$).

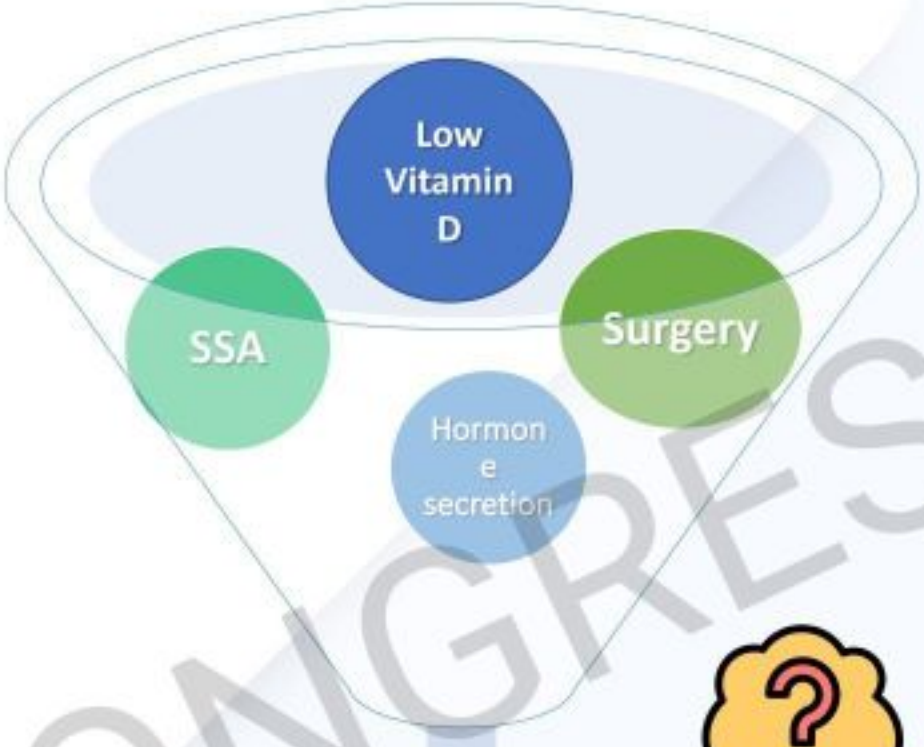
138 GEP-NET vs over **1200** controls

GEP-NET group

Median 25-OHvitD levels : 12.9 ng/mL [2-30]
68% had 25-OHvitD <20 ng/ml
33% had 25-OHvitD <10 ng/ml

Massironi et al. Neuroendocrinology 2017

Introduction



Only few studies investigated bone fragility in GEP-NETs.

Bone fragility

Introduction

90 GEP-NETs vs **50** controls

Increased risk of osteopenia/osteoporosis in NET group vs controls
OR: 3.17 [95%CI 1.16–7.8], p < 0.001

No data about fragility fractures

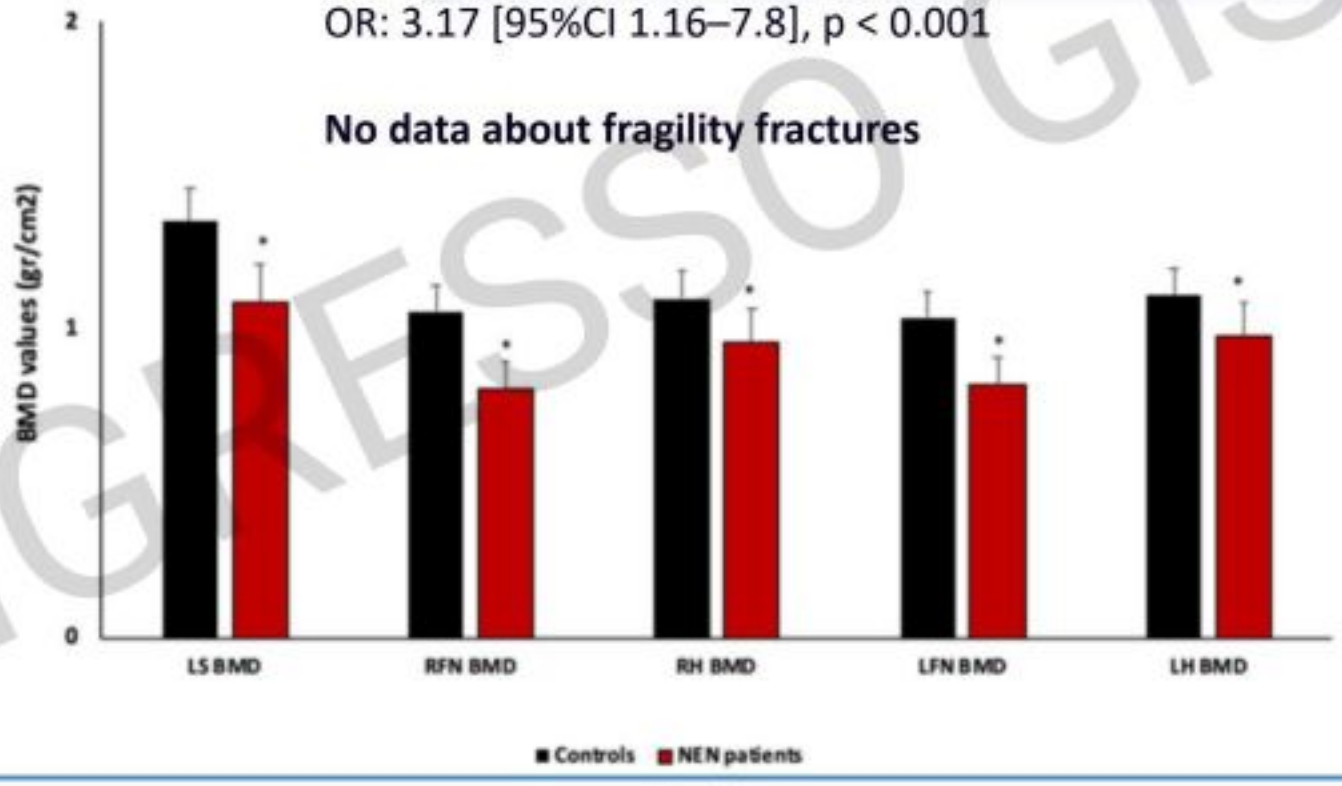


Fig. 1 Comparisons of bone mineral density measurements at the lumbar spine and total hip between patients with gastroenteropancreatic neuroendocrine tumors and healthy controls. Values are depicted as mean ± S.E.M. NET neuroendocrine tumor, BMD bone mineral density, LS lumbar spine, RFN right femoral neck, RH right total hip, LFN left femoral neck, LH left total hip. *$p < 0.001$, comparisons performed between NET patients and controls

Atkypis et al. Endocrine 2025

Study design

Type of study: Retrospective study including 291 patients with GEP-NET admitted in the last year (July 1st, 2022, to July 1st, 2023) in our two hospitals.

Aim: Investigate prevalence and risk factors for fragility fractures in patients with low-grading (G1-G2) GEP-NET in comparison to general population.

Inclusion criteria: Age > 18 years, diagnosis of well-differentiated GEP-NET.
Exclusion criteria: NET G3 or neuroendocrine carcinomas.

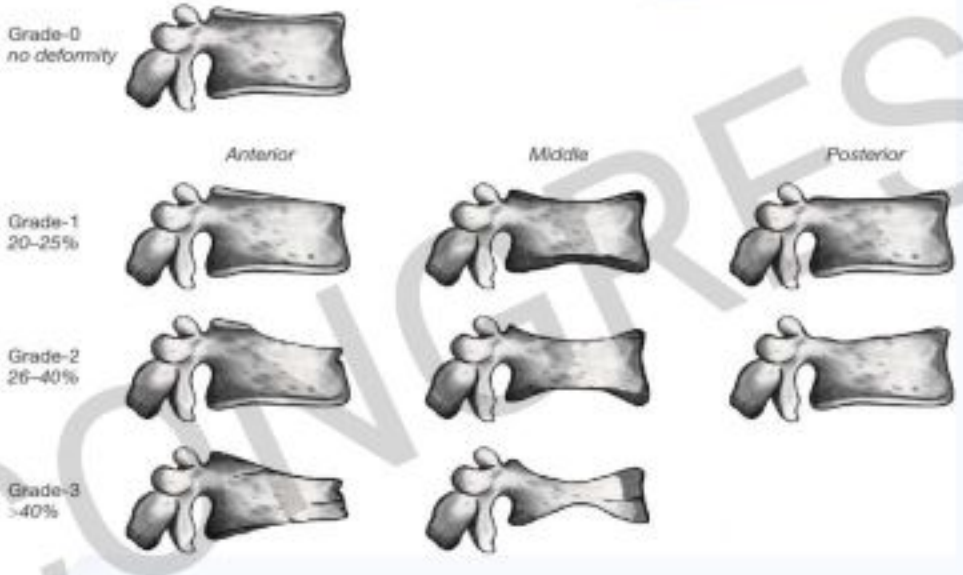
Study design

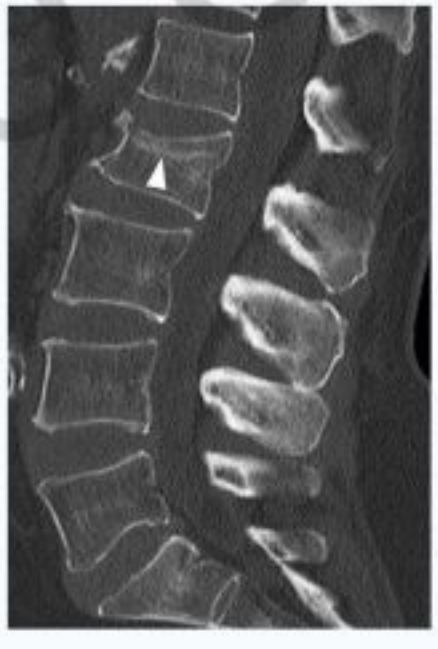
Methods

Reports about clinical fractures, disease grading, staging and hormonal secretion, treatments were retrospectively collected from patients' clinical charts from time of diagnosis to the last follow-up visit.

We revised chest and abdomen **CT or MRI** performed both at diagnosis and during follow up to investigate **vertebral morphometric fractures**, classified according to **Genant semi-quantitative classification.**

Genant classification





Study design

Selection of the control group

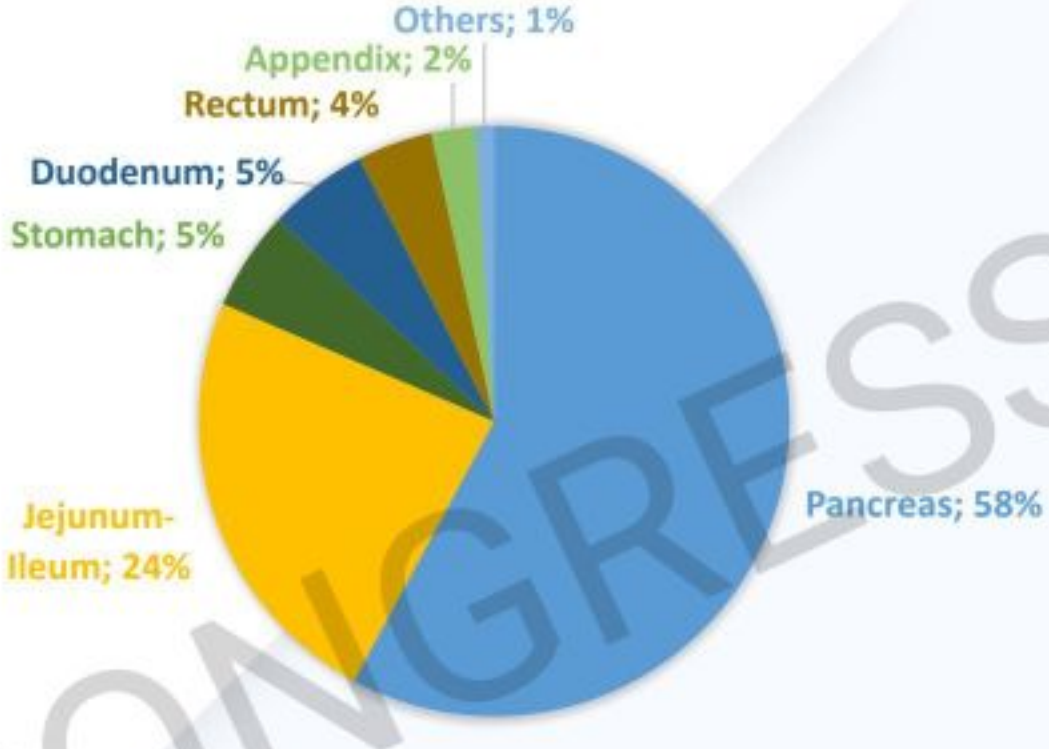
The control group included patients from "Siena Osteoporosis" (SiOP) study. This study included **1149 patients** (174 men and 975 women) randomly selected from general practitioners from Central-Northern Italy among **men above 50 years old and post-menopausal women**.

In collaboration with University of Siena, these patients underwent a comprehensive assessment of bone health including: **collection of previous clinical fractures, comorbidities, medications; bone densitometry and blood tests**. Morphometric vertebral fractures were investigated through vertebral fractures assessment (VFA) of bone densitometry and retrospective evaluation of any previous dorsal and lumbar spine imaging (X-ray, CT and MRI) available through electronic medical records (EMR). Vertebral fractures were classified according to Genant's classification.

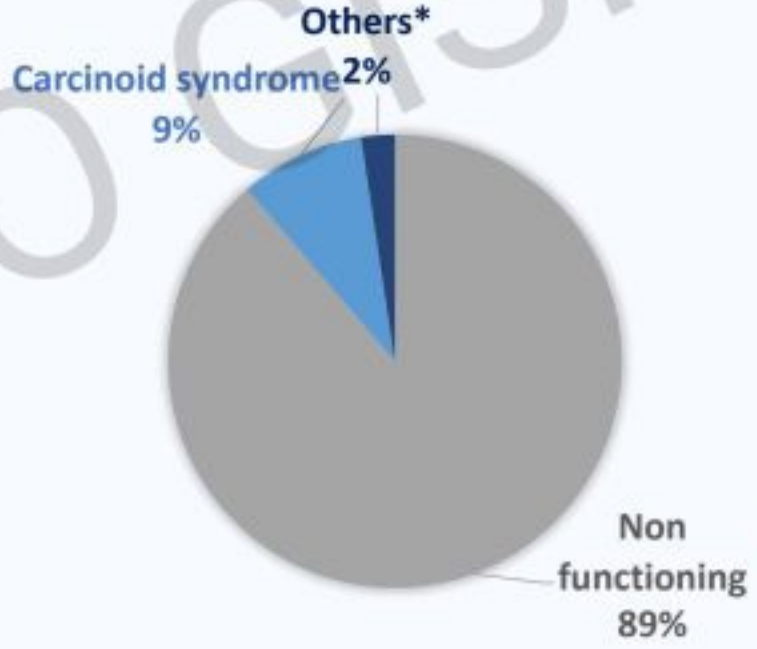
After exclusion of patients with comorbidities impacting on bone health* (BoneCom), **1010 subjects** were included in the control group (146 men and 864 women).

Results

PRIMARY SITE LOCALIZATION



HORMONAL SECRETION

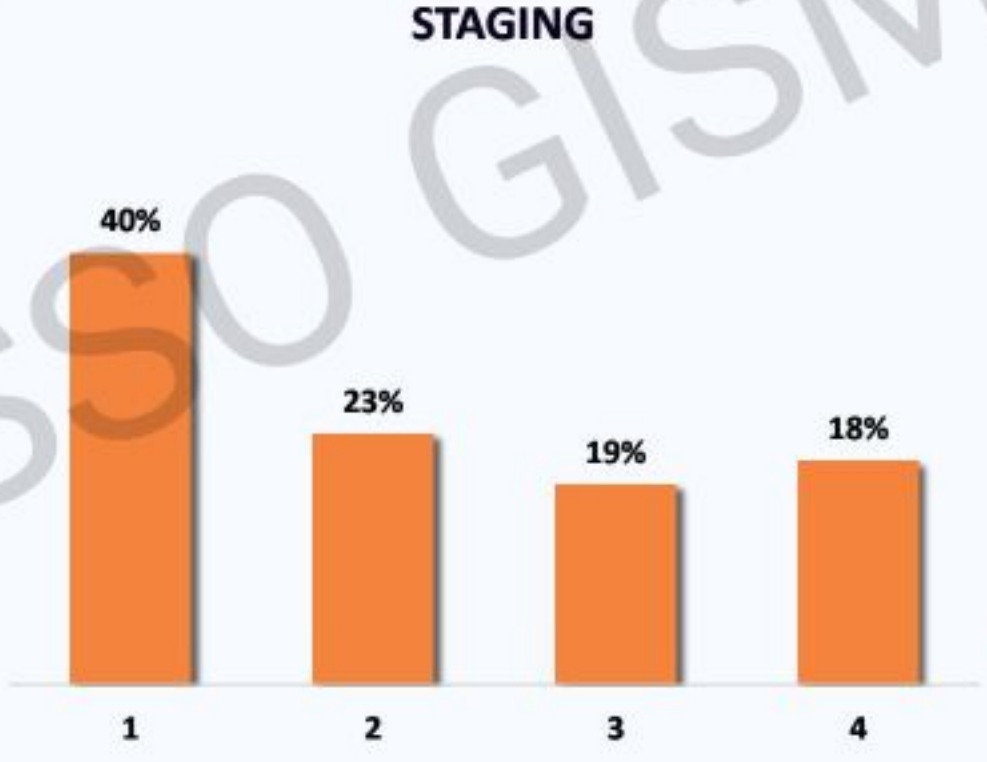


4 insulinoma, 2 Ectopic ACTH secretion, 1 somatostatin secretion

Results

Results

9 patients (3%) presented with bone metastases

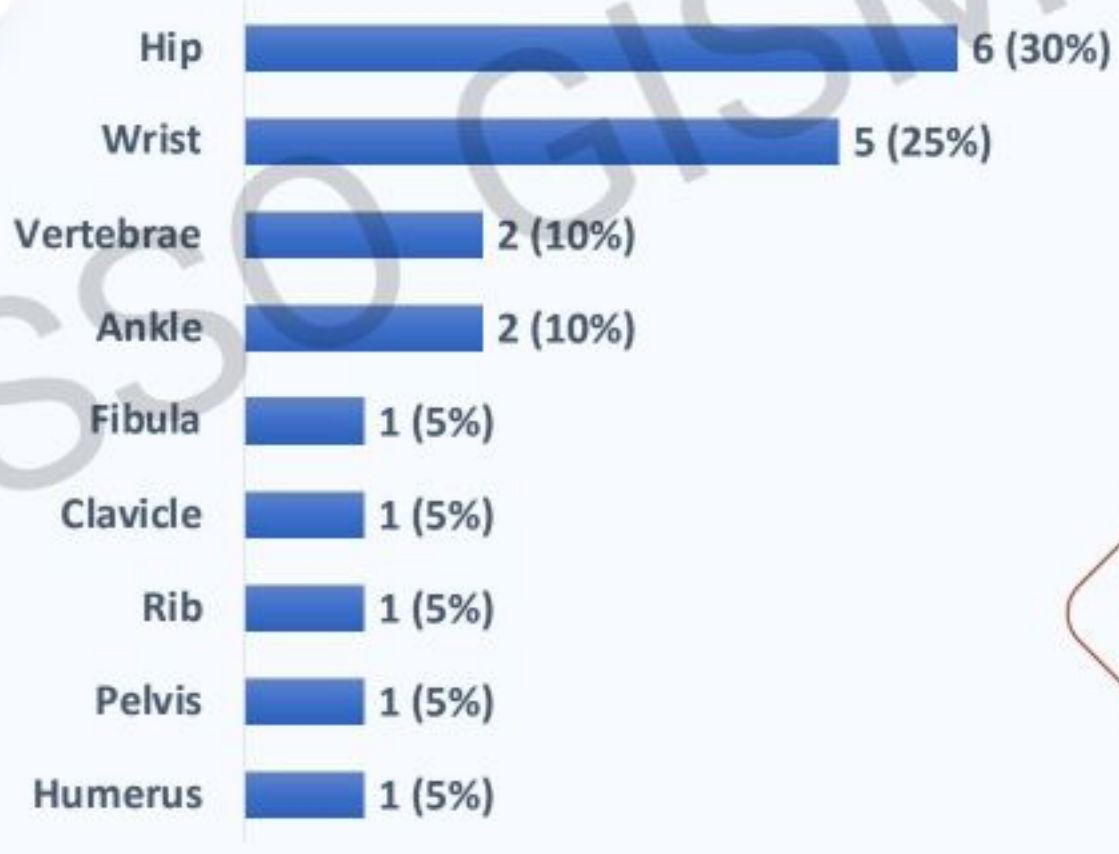


Results

CLINICAL FRAGILITY FRACTURES

20 patients reported a clinical fragility fracture at diagnosis

DISTRIBUTION OF CLINICAL FRACTURES



Results

CLINICAL FRAGILITY FRACTURES

20 patients reported a clinical fragility fracture at diagnosis

MORPHOMETRIC FRAGILITY FRACTURES

29 patients had at least one morphometric vertebral fracture at diagnosis after CT/MRI imaging revision

At least one fracture at any site was observed in **45 patients** (15.5%)

Results

	Fractured, *n* = 38 (14%)	Non-fractured, *n* = 233 (86%)	*p*
Mean age	71.1 ± 8.8 y	59.2 ± 13.1 y	<.001
Sex	15 women (40%)	113 women (49%)	
	23 men (60%)	120 men (51%)	.38
BMI	27.2 ± 5.1 kg/m^2	25.6 ± 4.1 kg/m^2	.04
Primary site			
Pancreas	26 (68%)	129 (55%)	
Jejunum-ileum	8 (21%)	57 (25%)	.33
Others	4 (11%)	47 (20%)	
Grading			
G1	25 (66%)	158 (68%)	.89
G2	13 (34%)	75 (32%)	
Staging			
I	16 (42%)	96 (41%)	
II	7 (18%)	56 (24%)	.84
III	9 (24%)	44 (19%)	
IV	6 (16%)	37 (16%)	

Results

	Fractured, *n* = 38 (14%)	Non-fractured, *n* = 233 (86%)	*p*
Carcinoid syndrome	1 (3%)	21 (9%)	.33
BoneCom[b]	18 (47%)	61 (26%)	.01
Active smoking	7 (18%)	47 (20%)	.88
History of chronic glucocorticoid therapy	2 (5%)	5 (2%)	.24

	Fractured, *n* = 38 (14%)	Non-fractured, *n* = 233 (86%)	*p*
Median 25(OH)vitamin D (ng/mL)	15.5 (7.5–31.2)	26.0 (14.2–30.8)	.18
25(OH)vitamin D <20 ng/mL (% of patients)	63%	35%	.05
25(OH)vitamin D <10 ng/mL (% of patients)	37%	12%	.02
Secondary hyperparathyroidism (% of patients)	45%	22%	.04

At multivariate analysis, **severe vitamin D deficiency** maintained a **significant association with the presence of fractures at diagnosis (OR 5.9 IC95[1.2; 27.8], p = .03)**, along with age (p = .01)

Results

NETs vs controls

The prevalence of fractures in the control group was compared to that of the subgroup of NET patients who fulfilled the same inclusion criteria (**age > 50 years and post-menopausal status**).

	GEP-NET (men >50 years and post-menopausal women), *n* = 200	Healthy controls, *N* = 1010	*p*
Age (years)	66.6 ± 8.8 years	66.1 ± 6.5 years	.46
BMI (kg/m^2)	26.5 ± 4.2	25.5 ± 4.0	<.01
Sex	90 women (45%)	864 women (85.5%)	<.001
	110 men (55%)	146 men (14.5%)	
BoneCom[a]	53 (27%)	0 (0%)	<.001
Fractures (any site)	36 (18.0%)	83 (8.2%)	<.001
Vertebral	25 (12.5%)	78 (7.7%)	.04
Hip	5 (2.5%)	1 (0.1%)	.001
Other sites	10 (5.0%)	4 (0.4%)	<.001

Results

NETs vs controls

A subgroup analysis including only patients without BoneCom, confirmed a higher prevalence of fractures in NETs compared to healthy controls.

	NET > 50y & post-menopause (without Bonecom) n=147	Control group N=1010	p
Age	65.9 ± 8.8 y	66.1 ± 6.5 y	0.56
BMI	25.7 ± 3.9	25.5 ± 4.0	0.51
Total Fractures (any site)	29 (18.0%)	83 (8.2%)	**<0.001**
Vertebral	21 (13.0%)	78 (7.7%)	**0.03**
Hip	4 (2.5%)	1 (0.1%)	**<0.001**
Other sites	8 (5.0%)	4 (0.4%)	**<0.001**

Results

NETs vs controls

At multivariate analysis including age, BMI, sex, BoneCom, **the diagnosis of GEP-NET resulted an independent risk factor for the presence of fractures (OR 2.0 IC95% [1.1–3.6], p = 0.02**), along with age ($p < 0.01$) and BMI ($p = 0.03$), while there was no association with sex ($p = 0.74$) or BoneCom ($p = 0.24$).

Results

NETs vs controls

	NET > 50y & post-menopause n=200	Control group n=1010	p
Median 25OHvitD (ng/mL)	24.1 [13.5-30.8]	20.4 [12.8-31.7]	0.73
25OHvitD <10 ng/mL	19.4%	15.6%	0.39
25OHvitD <20 ng/mL	45.3%	49.1%	0.55
25OHvitD <30 ng/mL	70.1%	73.2%	0.78
Secondary Hyperparathyroidism	**29.7%**	**1.6%**	**<0.001**

Secondary Hyperparathyoidism was significantly associated with fractures only in the GEP-NETs group (p = 0.04), but not in the control group.

Results

247 patients (85%)

performed at least one complete clinical and radiological follow-up

82% of patients with hypovitD started supplementation

Only 11 patients with fractures at diagnosis (24%) started an **anti-resorptive therapy***

10% of patients developed a new fracture

(either clinical or morphometric)

Median follow-up time 49 months [IQR 24-83]

Results

Risk factors for new fractures during follow-up
BONE STATUS AT DIAGNOSIS

- Presence of a fracture at time of diagnosis was strongly associated to development of new fractures during follow up. Odds ratio: **2.9** [IC95% 1.2 ; 7.1] p=0.02.

Results

Risk factors for new fractures during follow-up
NET TREATMENTS

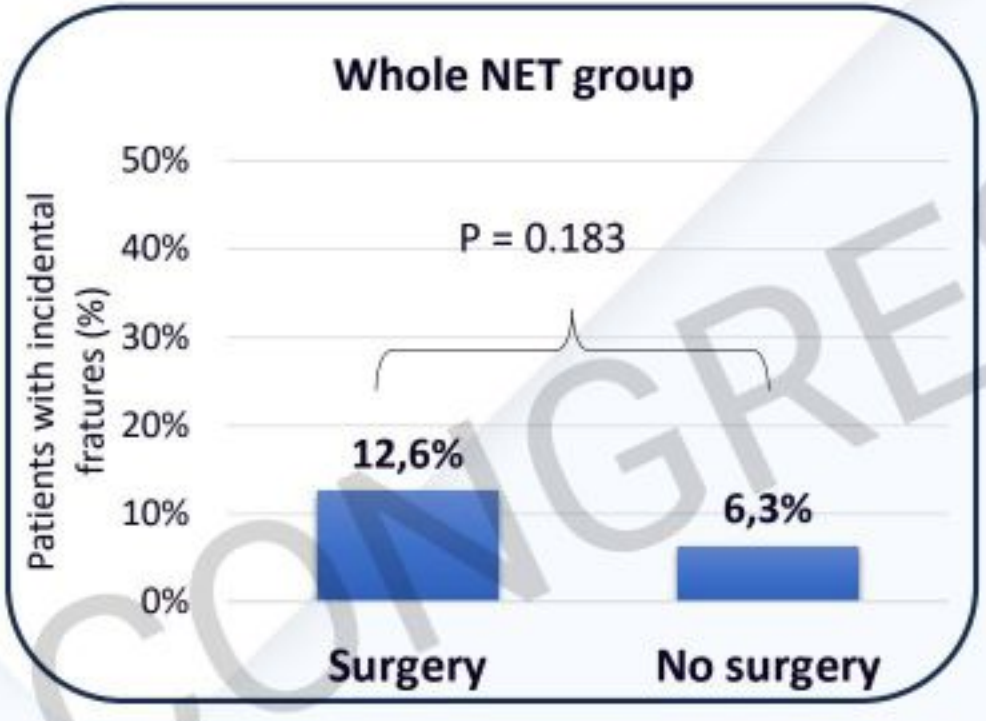
Treatment (local)	Number (%)
Surgery	**167 (67.6)**
Radiofrequency ablation	9 (3.6)

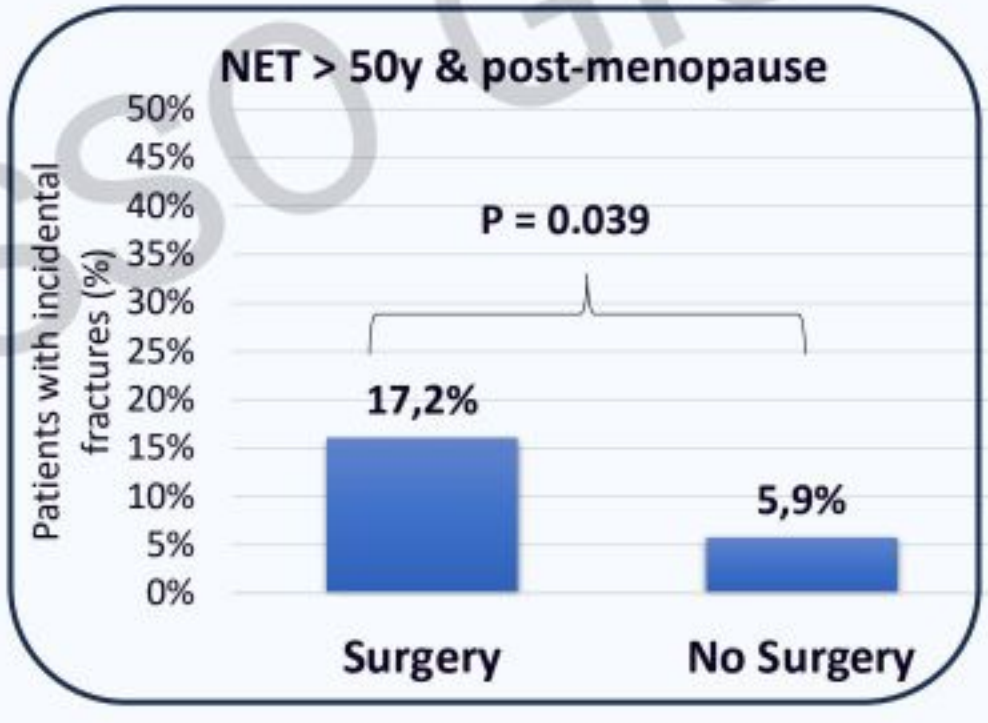
Treatment (systemic)	Number (%)
Somatostatin analogues (SSA)	91 (36.8)
Peptide Receptor Radionuclide Therapy (PRRT)	28 (11.3)
Chemotherapy (Various schemes)	10 (4.0)
Everolimus	8 (3.2)
Sunitinib	1 (0.4)

Results

Risk factors for new fractures during follow-up: NET treatments

- We found a trend towards to a higher risk of fractures in patients who underwent surgery compared to those who did not. **This result was significant in men age>50 years old and post-menopausal women.** Odds ratio: **3.3** [IC95% 1.1 ; 10.2] p=0.04.





Conclusions

Patients with GEP-NETs present an increased prevalence of fragility fractures compared to general population. These fractures remain **often underdiagnosed and/or undertreated**.

Hypovitaminosis D and secondary hyperparathyroidism are frequent in GEP-NETs, suggesting and impaired calcium metabolism.

Surgery may represent a risk factor for bone fragility in GEP-NETs. Particular attention to bone health should be paid in patients above 50 years old and post-menopausal women.

THANK YOU!