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Nutritional status and gastroenteropancreatic neuroendocrine neoplasms: lights and shadows with a clinical guide from the NIKE Group

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Abstract

Neuroendocrine neoplasms (NENs) originating in the gastroenteropancreatic (GEP) tract are rare tumors often associated with significant metabolic disturbances and nutritional challenges. This review explores the intricate relationship between nutritional status and the development, progression, and prognosis of GEP-NENs. Through an extensive literature search encompassing studies up to April 2024, we examined various factors, including obesity, malnutrition, metabolic syndrome and type 2 diabetes mellitus, and their roles in the development and progression of GEP-NENs. The review highlights the dual role of obesity, both as a risk factor and a potential prognostic indicator, drawing attention to the 'obesity paradox' observed in cancer research. Additionally, we discuss the impact of malnutrition on patient outcomes and emphasize the need for comprehensive nutritional assessments beyond BMI. This analysis highlights the importance of incorporating nutritional interventions into preventive and therapeutic strategies for GEP-NEN patients. Future research should further clarify these associations and develop personalized nutritional management protocols to improve patient prognosis and quality of life. Acronyms adopted in the text and tables: AOR: adjusted odd ratio, BIA: Bioelectrical Impedance Analysis, BMI: Body Mass Index, CI: confidence interval, CLARINET: Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumor, FLI: fatty liver index, GEP: gastroenteropancreatic, GLIM: global leadership into malnutrition, HR: hazard ratio, MS: metabolic syndrome, MUST: malabsorption universal screening tool, NEC: neuroendocrine carcinoma, NENs: Neuroendocrine neoplasms, NETs: Neuroendocrine tumors, NRS: Nutritional Risk Screening, OR: odd ratio, OS: overall survival, PFS: progression-free survival, RR: risk ratio, SGA: Subjective Global Assessment, T2DM: type 2 diabetes mellitus, VAI: visceral adiposity index, WD: well-differentiated,

Keywords Gastroenteropancreatic neuroendocrine neoplasm · Obesity · Malnutrition · BMI · Prognosis

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1 Introduction

Adequate nutrition is essential for overall health and the prevention of various diseases. Malnutrition, whether from undernutrition or overnutrition, can significantly increase the risk and progression of a wide range of health problems, including cancer. Many of these effects are likely mediated by the development of obesity and related comorbidities, such as metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM). Although the term 'malnutrition' technically encompasses both undernutrition and overnutrition, it is often used interchangeably with 'undernutrition,' as is done in this article. In cancer patients, malnutrition results from a combination of anorexia and metabolic disturbances induced by the tumor or its treatment, leading to cachexia. This can worsen prognosis, increase therapy toxicity, and reduce therapeutic response [1–3].

Neuroendocrine neoplasms (NENs) are rare tumors that primarily arise from the gastroenteropancreatic (GEP) tract [4]. In most patients with GEP-NENs, energy metabolism and nutritional status are disrupted due to the excessive production of several peptides, amines, and gastrointestinal hormones. These hormonal imbalances can lead to metabolic disorders and clinical syndromes, including diarrhea, steatorrhea, and malabsorption, which further contribute to nutritional deficiencies and metabolic disturbances. In addition, several studies have shown that obesity and related metabolic disorders may affect the development and progression of NENs [5]. However, the relationship between nutritional status and GEP-NENs remains highly controversial, similar to observations in other types of cancer where the 'obesity paradox' is debated [5]. This concept suggests that obesity may serve as both a risk factor and, paradoxically, a positive prognostic or predictive factor in cancer patients [6].

This paper provides a comprehensive overview on the role of nutritional status in both the development and progression of GEP-NENs, as well as its consequences resulting from the disease itself, with a focus on preventive and therapeutic approaches in clinical practice.

2 Materials and methods

A comprehensive literature search was conducted using online databases, including PubMed, ISI Web of Science and Scopus. The search was performed up to April 2024, by using a combination of keywords such as "nutrition", "malnutrition", "cachexia", "obesity", "Body Mass Index (BMI)", "metabolic syndrome", "diabetes", "neuroendocrine neoplasms" and "neuroendocrine tumors". In this review, we included articles that met the following criteria: English language and published in peer-reviewed journals. We excluded articles that were irrelevant to the topic, duplicates, or written in languages other than English.

3 Nutritional status as risk factor for the development of GEP-NENs

Obesity and its related comorbidities have been found to elevate the risk of developing GEP-NENs (Table 1).

In a meta-analysis, obesity, measured in terms of BMI, emerged as a risk factor for pancreatic NETs (adjusted summary effect of 1.37, 95% CI 0.25–7.69, $p < 0.001$), but not for those of the intestine and rectum [7]. However, it is important to consider that this analysis, by the authors' own admission, was based on conflicting results from three case-control studies [8–10]. In fact, an increased risk of 2–5 times for pancreatic NETs was associated with higher BMI in 2 studies, as described by Zhan et al. and Halfdanarson et al. [8, 9]. Conversely, a cross-sectional study highlighted a significant reduction in occurrence of pancreatic NETs among overweight and obese individuals compared to the control population [10]. When stratified by sex, the inverse association between overweight and obesity and pancreatic NETs was observed only in men. Interestingly, this study reported an inverse association of overweight and obesity with small bowel NETs in both men and women. Additionally, the inverse association between overweight and the risk of gastric NETs was found only in men [10]. Other studies have reported a direct association between high BMI and GEP-NENs. A study examining 124 patients with NETs of the small intestine reported a twofold increased risk for individuals with a BMI ≥ 35 compared to those with a BMI of 18.5 to < 25 kg/m² [11]. In this context, the authors suggested that pinpointing adjustable risk factors for NETs, such as weight control, might also reduce the risk of other types of cancer. Indeed, individuals with NETs of the small intestine face a threefold increased risk of developing colorectal cancer and a 60% higher risk of other malignancies [12, 13].

More recently, a retrospective case-control study (148 GEP-NENs and 210 controls) identified obesity as an independent risk factor for these neoplasms. The majority of GEP-NENs were classified as G1 and G2 NETs (91.9%). The prevalence of obesity was significantly higher among patients than controls (44.1% vs. 28.1%, $p = 0.002$), with a multivariate odds ratio of 1.88 (95% CI 1.18–2.99, $p = 0.007$). In a subanalysis dividing the cohort into two groups (pancreatic NENs: 75 patients, intestinal NENs: 73 patients), obesity was confirmed as a risk factor for both pancreatic and intestinal NENs [14].

Further evidence suggesting that obesity may be a risk factor for GEP-NETs comes from incidental findings during

Table 1 Summary of nutritional status parameters representing risk factors for GEP-NENs. For each nutritional and metabolic parameter, the type of NEN, the measure of association, or the frequency in the affected and control populations, and related references are reported. The p-value was not reported for all measures of association or frequencies due to its unavailability in the original references

Risk factor	Type of NEN	Measures of associations or frequence	Reference
BMI	Pancreatic NET	An increased risk in patients with higher BMI (OR 1.37, 95% CI 0.25–7.69, $p<0.001$)	[7]
	Insulinoma	An increased risk in patients with higher BMI (OR 5.31, 95% CI 3.51–8.04, $p<0.0001$)	[8]
	Pancreatic NET	An increased risk in patients with higher BMI (OR 1.65, 95% CI 1.11–2.45, $p=0.0126$)	[9]
	Pancreatic, small bowel and gastric NETs	Inverse association of overweight (AOR 0.4, 95% CI 0.2–0.7) and obesity (AOR 0.2, 95% CI 0.1–0.4) with the risk of pancreatic NET in men Inverse association of overweight (AOR 0.3, 95% CI 0.2–0.6) and obesity (AOR 0.3, 95% CI 0.1–0.4) with the risk of small bowel NET in both men and women Inverse association of overweight with the risk of gastric NET risk in men (AOR 0.7, 95% CI 0.1–0.4)	[10]
	NET of the small intestine	An increased risk in patients with BMI ≥ 35 (HR 1.95, 95% CI 1.06–3.58, P-trend = 0.025)	[11]
	Pancreatic and intestinal NENs	Obesity was associated with an increased risk of pancreatic NENs (OR 1.98, 95% CI 1.11–3.52, $p=0.020$) and intestinal NENs (OR 1.90, 95% CI 1.08–3.33, $p=0.026$)	[14]
	Gastric and duodenal NETs	Gastric and duodenal NETs resulted more frequent in obese patients (0.23–0.358%) than in the control population (0.001–0.002%)	[15, 16]
	Appendiceal NET	Appendiceal NET was more frequent in obese patients (1.4%) than in controls (0.001%)	[17]
Visceral obesity	GEP-NET	Waist circumference of > 80 cm for females and > 94 cm for males resulted as a risk factor (OR 2.5, 95% CI 1.4–4.6, $p=0.002$)	[18]
MS	Rectal NET	Higher prevalence in patients with MS (23.8%) than in controls (16.1%)	[19]
	GEP-NET	Increased risk when the number of individual MS components exceeded four (OR 3.40, 95% CI 1.17–9.86, $p=0.024$) or five (OR 5.15, 95% CI 1.15–23.01, $p=0.032$)	[18]
T2DM	Pancreatic NET	A recent diagnosis of T2DM emerged as an independent risk factor (OR 40.1, 95% CI 4.8–328.9, $p=0.0005$).	[20]
	Gastric NET	A long-term history (> 1 year) of T2DM was a significant risk factor (adjusted OR 5.6, 95% CI 2.1–14.5), particularly in women (adjusted OR 8.4, 95% CI 1.9–38.1) T2DM increased the risk among women with a positive family history of cancer (OR 52.2, 95% CI 5.5–491.5)	[10]
	Pancreatic NET	Higher occurrence of T2DM in patients than in controls (19% vs. 11%, $p<0.001$)	[9]
	Pancreatic NEN	An increased risk in patients with non-recent onset T2DM (OR 2.09, CI 1.27–3.46, $p=0.003$)	[21]
	Pancreatic NEN	An increased risk in patients with T2DM (OR 2.5, 95% CI 3.9–4.51, $p=0.002$)	[14]
	Pancreatic NEN	An increased risk in patients with T2DM (OR 3.01, 95% CI 1.15–7.89, $p=0.002$)	[22]
Malnutrition indices	GEP-NET	MUST ≥ 1 in 14% of outpatients with GEP-NET MUST-positive patients were more likely to have rectal ($p<0.017$) or unknown primary ($p<0.017$) NETs	[25]

AOR Adjusted Odd Ratio, *BMI* Body Mass Index, *CI* Confidence Interval, *GEP* Gastroenteropancreatic, *HR* Hazard Ratio, *MS* Metabolic Syndrome, *MUST* malabsorption universal screening tool, *NEC* Neuroendocrine Carcinoma, *NEN* Neuroendocrine Neoplasm, *NET* Neuroendocrine Tumor, *OR* Odd Ratio, *T2DM* Type 2 Diabetes Mellitus

routine endoscopic evaluations conducted prior to bariatric surgery [15]. Although additional clinical reports are needed to corroborate these findings, gastric and duodenal NETs appear to be more frequently observed in obese patients (0.23–0.358%) compared to the control population (0.001–0.002%) [15, 16]. In a retrospective analysis involving 588 patients who underwent bariatric surgery, 477 also had routine appendectomies. Among these, 7 were diagnosed with appendiceal NETs, representing 1.4% of the sample, which is significantly higher than the 0.001% prevalence in the general population [17]. These findings suggest that obesity may contribute to the development of intestinal NETs and highlight the importance of preoperative endoscopic evaluations in patients undergoing bariatric surgery [15].

Recently, Santos et al. reported that visceral obesity, characterized by a waist circumference greater than 80 cm for females and 94 cm for males, increased the risk of developing GEP-NETs by 2–3 times [18].

Several lines of evidence suggest that MS, as well as its individual components, may be risk factors for GEP-NETs. A cross-sectional study involving 57,819 Korean patients who had screening colonoscopy, including 101 diagnosed with rectal NETs, revealed that MS, fatty liver, high triglyceride levels (≥ 150 mg/dL), and insulin resistance (HOMA-IR ≥ 2.5) were more prevalent in patients with rectal NETs compared to unaffected individuals. Specifically, the prevalence of these conditions in both groups was as follows: 23.8% vs. 16.1% for MS ($p = 0.035$), 45.5% vs. 34.8% for fatty liver ($p = 0.024$), 31.7% vs. 22.1% for high triglyceride levels ($p = 0.021$), and 9.9% vs. 4.5% for insulin resistance ($p = 0.025$). However, it is important to note that these results were not statistically significant after performing a multivariate analysis [19]. In the study described above by Santos et al., involving 96 patients with GEP-NETs and an equal number of matched controls, MS and some of its individual components (dyslipidemia, visceral obesity, and increased fasting glucose) were found to be associated with these tumors. Furthermore, the risk was higher when the number of MS components exceeded four or five [18].

Numerous studies have recognized T2DM as an independent risk factor for GEP-NENs, particularly those occurring in the pancreas. The first evidence emerged in 2009 from a case-control study involving 162 pancreatic NETs and 648 controls, where a recent diagnosis of T2DM (within 12 months) was found to be a significant risk factor for pancreatic NETs. Notably, there were no differences in BMI between the cases and controls [20]. In the same year, Hassan et al. observed that a long-term history (> 1 year) of T2DM was a relevant risk factor for gastric NETs, particularly in women. Moreover, T2DM altered the risk of developing gastric NETs in women with a positive family history of cancer [10]. Subsequently, a case-control study involving 355 patients with pancreatic NETs and 602 controls reported that the incidence of T2DM was nearly twice as high in patients with pancreatic NETs compared to controls [9]. In a multinational European case–control study (201 cases and 603 controls), non-recent onset T2DM was associated with a doubled risk of developing pancreatic NENs [21]. In the retrospective case-control study described above by Feola et al., T2DM was reported as an independent risk factor for pancreatic NENs, but not for those localized in the intestine [14]. A case-control study conducted in 2022 on 184 patients with NENs (100 with pancreatic and 84 with lung NENs) and 248 controls revealed an association between T2DM and an increased risk of pancreatic NENs [22].

Regarding malnutrition, which has been reported in GEP-NEN patients with percentages ranging from 5 to 38% at the first visit or during follow-up [23, 24], a cross-sectional study described a correlation with the risk of developing these neoplasms [25]. Nutritional status was evaluated through the malabsorption universal screening tool (MUST), which considers not only BMI but also unplanned weight loss in the past 3–6 months, as well as the presence of acute illness or the absence of nutritional intake for 5 days or more. A MUST score ≥ 1, indicating a high risk of malnutrition, was found in 14% of outpatients with GEP-NETs. MUST-positive patients were more frequently diagnosed with rectal NETs or NETs of unknown primary origin. However, it was not possible to determine whether malnutrition is a cause or an effect of the tumor [25].

4 Nutritional status and tumor progression of GEP-NENs

Several studies evaluated the potential impact of nutritional status on GEP-NEN progression (Table 2).

BMI: Body Mass Index; CI: Confidence Interval; FLI: and fatty liver index; GEP: Gastroenteropancreatic; GLIM: global leadership into malnutrition; HR: Hazard Ratio; MS: Metabolic Syndrome; NEC: Neuroendocrine Carcinoma, NEN: Neuroendocrine Neoplasm; NET: Neuroendocrine Tumor; NRS: Nutritional Risk Screening; OR: Odd Ratio; OS: overall survival; PFS: progression free survival; RR: relative risk; SGA: Subjective Global Assessment; T2DM: Type 2 Diabetes Mellitus; VAI: visceral adiposity index;

Although Cherefant et al. found no correlation between BMI and the risk of distant metastasis or overall survival (OS) in patients with non-functioning pancreatic NETs [26], low values of BMI in GEP-NET patients have been correlated with a poor prognosis in many studies. The first evidence comes from a retrospective study of 67 patients with liver metastases from NETs, which found that an increasing BMI was associated with delayed time to progression [27]. In a later retrospective study of 324 patients with pancreatic

Table 2 Summary of nutritional status parameters potentially impacting GEP-NEN progression. For each nutritional and metabolic parameter, the type of NEN, the measure of association, or the frequency in the affected and control populations, and related references are reported. The p-value was not reported for all measures of association or frequencies due to its unavailability in the original references

Risk factor	Type of NEN	Measures of associations or frequence	Reference
BMI	Pancreatic NET	No correlation between BMI and the risk of distant metastasis or OS	[26]
	NET with liver metastases treated with transcatheter arterial chemoembolization	Increasing BMI was associated with delayed time to progression (HR 0.85, 95% CI 0.76–0.86, $p=0.01$)	[27]
	Pancreatic NET	BMI < 20 was associated with a poorer prognosis (HR 2.5, $p=0.005$)	[28]
	GEP-NET	Obesity was associated with lower inpatient mortality rates (OR 0.61, 95% CI 0.40–0.93, $p=0.02$) Malnutrition was associated with higher inpatient mortality (OR 1.95, 95% CI 1.55–2.45, $p<0.0005$) The incidence of inpatient hospital complications increased in malnourished individuals (15% vs. 10%, $p<0.0005$)	[29]
	GEP-NEN	A lower BMI was associated with worse OS (HR 0.97; 95% CI: 0.95–0.98) in the overall population, a finding that was confirmed in both NET and NEC subpopulations.	[30]
Visceral obesity	GEP-NET	Visceral obesity was associated with worse PFS (HR 1.03, 95% CI: 1.01–1.06)	[18]
Malnutrition indices	GEP-NEN	NRS (RR 1.75, 95% CI 1.06–2.89, $p=0.028$) and SGA (RR 5.34, 95% CI 1.78–15.96, $p=0.003$) were risk factors for poorer survival. The prevalence of malnutrition was higher in patients with G3 NEC than in those with G1/2 NET.	[32]
	GEP-NET	The presence of 2 or 3 GLIM criteria was associated with worse OS (HR 2.16, 95% CI 1.34–3.48, $p=0.002$) Weight loss was a risk factor for worse OS (HR 3.5, 95% CI 1.14–10.85, $p=0.03$)	[33]
MS	GEP-NET	VAI was higher in G2 (2.88 ± 1.99) than in G1 (1.89 ± 1.05) patients ($p=0.001$) FLI was higher in G2 (65.77 ± 26.27) than in G1 (42.93 ± 28.15) patients ($p<0.001$) Number of MS parameters was higher in G2 (3.00 ± 1.56) than in G1 (1.42 ± 1.12) patients ($p<0.001$) VAI was higher in progressive (3.12 ± 2.02) than in stable (1.66 ± 0.93) disease ($p<0.001$) FLI was higher in progressive (69.24 ± 31.58) than in stable (45.24 ± 27.22) disease ($p=0.006$) Number of MS parameters was higher in progressive (3.19 ± 1.78) than in stable (1.55 ± 1.27) disease ($p<0.001$) VAI was higher in metastatic (3.14 ± 2.17) than in non-metastatic (2.00 ± 1.20) disease ($p=0.001$) FLI was higher in metastatic (69.04 ± 26.62) than in non-metastatic (46.59 ± 28.42) disease ($p<0.001$) Number of MS parameters was higher in metastatic (3.00 ± 1.64) than in non-metastatic (1.74 ± 1.35) disease ($p<0.001$)	[34]
	GEP-NET	MS was associated with larger tumor size and higher Ki-67 proliferation index	[35]
	GEP-NET	MS was associated with grade G1 (OR 4.35, 95% CI 1.30–14.53, $p=0.018$) and disseminated disease (OR 4.52, 95%CI 1.44–14.15, $p=0.010$)	[36]

Table 2 (continued)

Risk factor	Type of NEN	Measures of associations or frequence	Reference
T2DM	GEP-NET	T2DM at baseline did not negatively affect PFS	[37]
	Pancreatic NET	A previous history of T2DM was associated with metastatic disease (OR 6.0, 95% CI: 1.2–28.7)	[20]
	Pancreatic NEN	T2DM was statistically more prevalent in patients with G3 NEC than with G1 or G2 NET (40.9% vs. 15.8%, $p=0.01$) Non-recent onset T2DM was associated with a more advanced stage (TNM III–IV vs. TNM I–II, 23.3% vs. 11.8%, $p=0.05$) and higher tumor grade (G3 vs. G1–2, 40.9% vs. 14.9%, $p=0.006$)	[21]
	Pancreatic NET	Patients with T2DM were at high risk for tumor metastasis (OR 2.81, 95% CI 1.54–5.12 $p=0.001$), nerve invasion (OR 2.43, 95% CI 1.10–5.37, $p=0.029$), and G3 (OR 4.97, 95% CI 1.46–16.88, $p=0.010$)	[38]

BMI Body Mass Index, *CI* Confidence Interval, *FLI* and fatty liver index, *GEP* Gastroenteropancreatic, *GLIM* global leadership into malnutrition, *HR* Hazard Ratio, *MS* Metabolic Syndrome, *NEC* Neuroendocrine Carcinoma, *NEN* Neuroendocrine Neoplasm, *NET* Neuroendocrine Tumor, *NRS* Nutritional Risk Screening, *OR* Odd Ratio, *OS* overall survival, *PFS* progression free survival, *RR* relative risk, *SGA* Subjective Global Assessment, *T2DM* Type 2 Diabetes Mellitus, *VAI* visceral adiposity index

NENs, those who were underweight at diagnosis (BMI < 20) had a worse prognosis. However, this finding did not remain significant in the multivariate analysis [28]. In a retrospective study on 22,096 patients with GEP-NETs who underwent surgery, obesity was linked to lower inpatient mortality rates, while malnutrition was associated with higher odds of inpatient mortality. Malnourished individuals experienced a higher incidence of inpatient hospital complications. It is important to note that in this study, individual BMI values of the patients were not available. A national database of patients categorized according to the International Classification of Diseases for obesity and malnutrition was used. Therefore, BMI was not considered as a continuous variable but as a categorical one [29]. In a recent retrospective study involving 1,010 patients with NENs (60% of them from GEP tract, 60.5% NETs and 39.5% NECs), a lower BMI was linked to poorer overall survival, regardless of tumor stage or histology [30].

All findings of these analyses align with the "obesity paradox" that have been previously reported for other solid tumors [6]. Nevertheless, the "obesity paradox" has been critically examined and questioned by the epidemiological community. Critics suggest that the perceived association between obesity and improved outcomes may be influenced by confounding factors, such as selection bias and the reliance on BMI alone to assess adiposity [31]. Indeed, BMI is an inadequate measure of body composition, because it provides only a rough estimate and fails to differentiate between lean and fat mass or to analyze their distribution. For example, in oncology, individuals classified as overweight based solely on BMI might actually be younger patients with higher muscle mass and more favorable pharmacokinetics, which could lead to better treatment outcomes and fewer adverse events [6].

In this context, some studies assessing the prognostic value of the nutritional status in GEP-NENs evaluated malnutrition using strategies that do not rely solely on BMI. For instance, in a cross-sectional study by Maasberg et al., two clinical scores, the Subjective Global Assessment (SGA) and the Nutritional Risk Screening (NRS), were combined with anthropometry, Bioelectrical Impedance Analysis (BIA), and serum surrogate parameters such as albumin to assess malnutrition in GEP-NEN patients. The authors demonstrated, through a multivariate analysis, that malnutrition could be an important risk factor for poorer survival in NEN patients, whether assessed using the NRS or the SGA. Furthermore, poorer nutritional status was associated with significantly reduced long-term outcomes and survival rates in patients with high-grade tumors, NEC, progressive disease, and those receiving chemotherapy [32].

In a recent study, which included 118 patients with GEP-NETs undergoing therapy with somatostatin analogues, malnutrition was evaluated by the global leadership into malnutrition (GLIM) criteria, that include weight loss, sarcopenia and BMI. The prevalence of malnutrition according to the GLIM criteria was higher (75%) than previously reported (5–38%) in patients with GEP-NETs [22, 23, 32]. Moreover, a multivariate analysis revealed that having 2 or 3 GLIM criteria was significantly associated with worse overall survival, with weight loss emerging as the strongest determinant among the GLIM criteria [33].

Considering these studies in their entirety, malnutrition appeared to be associated with a worse prognosis, whereas a high BMI was associated with a more favourable outcome. However, it is challenging to determine whether malnutrition

is a cause of poorer prognosis in GEP-NEN or a consequence of disease progression, particularly given the heterogeneity of both the examined cohorts and the analytical strategies employed.

Different observations have been made when obesity, particularly visceral obesity, was evaluated in the context of MS. Barrea et al. explored the relationship between visceral adiposity index (VAI) and fatty liver index (FLI), along with MS, and their correlation with the clinical severity of GEP-NETs. VAI serves as a marker of adipose tissue associated with MS and various metabolic disorders, such as T2DM. On the other hand, FLI is a useful algorithm for predicting the presence of non-alcoholic fatty liver disease, demonstrating high concordance with ultrasound liver imaging and histological criteria. Both values, together with MS presence, were significantly higher in G2 than in G1 patients, in patients with progressive disease compared to those with stable disease and in metastatic than in non-metastatic patients. In this context, it has been suggested that the adipokines secreted by a dysfunctional visceral adipose tissue may play a key role in the relationship between MS and tumor aggressiveness. Although these results should be interpreted with caution until appropriate cross-validation is conducted, clinical assessment of both cardio-metabolic indexes (VAI and FLI) may provide insights into potential mechanisms of tumor progression and guide tailored preventive and treatment strategies for patients with GEP-NETs [34]. In another study on GEP-NETs, visceral obesity was measured in terms of waist circumference and resulted a negative prognostic marker for progression-free survival (PFS), although it did not affect OS [18].

Other studies have explored the association between MS and GEP-NET prognosis. In a series of patients with non-functioning GEP-NETs, where overweight and obesity were common (40.6% and 28.1% of patients, respectively), MS was associated with greater tumor severity, as indicated by larger tumor size and a higher Ki-67 proliferation index [35]. In another cohort of patients with GEP-NETs, after adjusting for age and gender, the odds of having MS were significantly higher in patients with G1 grading and disseminated disease [36].

Several studies have investigated the interaction between T2DM and NETs independently of obesity. In a recent post-hoc analysis of the Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumor (CLARINET), data suggested that T2DM may not impact the prognosis of patients with advanced GEP-NETs. In particular, the presence of T2DM at baseline did not negatively affect PFS in the final multivariate model [37]. Conversely, two case-control studies reported that T2DM may increase the risk of metastasis in patients with pancreatic NETs. Capurso et al. [20] showed that patients diagnosed with metastatic disease were more likely to have a prior history of T2DM (17% vs. 3.7%, $p = 0.008$) and recent-onset T2DM (9.7% vs. 2.5%, $p = 0.09$) compared to those with non-metastatic disease. In a multivariate logistic regression model, a previous history of T2DM was associated with metastatic disease. Valente et al. [21] reported that T2DM was 2.5 times more prevalent in patients with pancreatic G3 NEC than in those with G1/G2 NET. Moreover, non-recent onset T2DM was associated with a later stage at diagnosis and higher tumor grading. In a recent study involving 299 patients with pancreatic NETs, logistic regression revealed a significantly higher risk of tumor metastasis, nerve invasion and G3 tumors among patients with T2DM [38].

5 Nutritional status, quality of life and treatment in patients with GEP-NENs

Several studies have investigated the relationship between the nutritional status of GEP-NEN patients, particularly malnutrition, and their quality of life. These factors mutually influence each other, acting as both causes and consequences. As observed in other neoplasms, malnutrition can impact the quality of life of cancer patients. Additionally, a decline in quality of life due to anxiety and depression following a cancer diagnosis, along with therapy-related side effects, can increase the likelihood of nutrition-related complications, such as malnutrition [32, 39, 40].

Although patients with GEP-NETs generally do not show significant weight loss or acute symptoms until the disease is advanced, they often experience compromised nutritional status, affecting their metabolic state, dietary patterns, and body composition. These issues are primarily related to the overproduction of gastrointestinal hormones, tumor mass effects, mesenteric tumor infiltration, medical treatment, and surgical procedures [41].

In a global survey examining the effects of a NET diagnosis, 71% of patients reported a substantial negative impact on their personal lives, including reduced energy levels and impaired ability to perform activities of daily living. Although the causative factor was not identified, more than half of the patients reported making dietary changes as a result of their tumor [42]. It is important to underline this aspect because dietary changes, such as the prolonged reduction in dietary intake and the food avoidance, can lead to dietary inadequacy and nutritional deficiencies, including malnutrition. Notably, reduced food intake is one of the two etiological criteria of the GLIM framework, alongside inflammation, thus contributing to an increased risk of malnutrition [43]. In another study the health-related-quality of life resulted lower in patients with GEP-NETs than in general population. While the lower percentage of malnourished patients at 6 months post-recruitment (13%) compared to baseline (29%) suggests that medical management may

improve nutritional status, 48% of enrolled patients experienced weight loss, with 20% losing more than 5% of their body weight. Additionally, 62% lost fat-free mass, with an average loss of 2.8 kg, indicating substantial changes in body composition. Despite these findings and dietary changes reported by 56% of patients at baseline and 53% at 6 months, only 21% consulted a dietitian at baseline and 18% at six months. The authors concluded that screening practices to detect excessive weight loss, changes in body composition, and nutritional issues in GEP-NET patients should be implemented to facilitate dietary intervention and potentially improve quality of life [44].

The progressive loss of fat-free mass observed in GEP-NET patients can lead to sarcopenia, a condition often experienced by cancer patients that results in reduced muscle function and strength, increased morbidity and mortality, thereby negatively impacting quality of life [45]. Notably, a high prevalence of sarcopenia at the time of diagnosis of metastatic GEP-NENs was associated with worse OS in patients with pancreatic NETs (HR 3.79, 95% CI 1.1–13.03, $p=0.035$), potentially affecting quality of life [46].

Body composition and nutritional status may impact the efficacy of antitumor treatments in many neoplasms [47–50]. To date, only a few studies have investigated their predictive potential in GEP-NETs, yielding conflicting results (Table 3).

In some studies, higher BMI resulted associated with reduced therapy efficacy or quality of life. For instance, a retrospective study of metastatic GEP-NEC ($n=19$) treated with cisplatin or cisplatin/etoposide, demonstrated that patients with BMI ≥ 25 had a higher risk of death and disease progression than those with a lower BMI [51]. At the same time, the beneficial effect of peptide receptor radionuclide therapy on health-related quality of life in patients with GEP-NETs was less evident in patients with overweight (BMI > 25), who showed less improvement in several domains (nausea/vomiting, pain, diarrhea, social functioning, and treatment-related symptoms) [52].

On the other hand, lower BMI has been reported as a predictor of poorer response to the therapy. In a study involving 30 patients with advanced NETs (70% from the GEP tract) treated with everolimus, the median PFS was

Table 3 Summary of nutritional status parameters that potentially predict the effect of the treatment strategies. For each nutritional and metabolic parameter, the type of NEN, the measure of association, or the frequency in the affected and control populations, and related references are reported. The p-value was not reported for all measures of association or frequencies due to its unavailability

Risk factor	Type of NEN	Measures of associations or frequence	Reference
BMI	Metastatic GEP-NEC treated with cisplatin or cisplatin/etoposide	A BMI ≥ 25 was associated with a higher risk of death (HR 5.00, 95% CI 1.00–24.91, $p=0.049$) and disease progression (HR 7.17, 95% CI 1.45–35.51, $p=0.016$)	[51]
	GEP-NET treated with peptide receptor radionuclide therapy	A BMI > 25 was associated with a less pronounced effect on health-related quality	[52]
	Metastatic NET treated with everolimus	Underweight patients showed a lower median PFS (mean PFS 3.2 months, 95% CI 0.9–6.7, $p=0.011$) compared to normal weight (mean PFS 10.1 months, 95% CI 3.7–28.4, $p=0.011$)	[53]
	NET with liver metastases treated with transcatheter arterial chemoembolization	Increasing BMI was associated with higher responsiveness (OR 1.3, 95% CI 1.04–1.63, $p=0.022$)	[27]
Lipidic profile	Advanced pancreatic NET treated with everolimus	High plasma triglyceride levels during the first 3 months of treatment were associated with an increased risk of disease progression (adjusted HR 3.08, 95% CI 1.15–8.21, $p=0.025$)	[54]
T2DM	Advanced non-functional GEP-NET treated with metformin	Longer PFS was found in metformin-treated patients compared to untreated ones (97.7 vs. 50.7 weeks, $p=0.002$)	[37]
	Advanced pancreatic NET treated with octreotide LAR and everolimus, as well as insulin or metformin in case of T2DM	PFS was longer in metformin- than in insulin-treated patients (36 vs. 17 months)	[57]
	Pancreatic NET treated with everolimus or somatostatin analogue, as well as with metformin	PFS was longer in patients who started metformin before or within three months of initiating everolimus or somatostatin analogue therapy, compared to patients who did not take metformin or those who started metformin more than three months after treatment initiation (43.7 vs. 23.3 months)	[58]

BMI Body Mass Index, *CI* Confidence Interval, *GEP* Gastroenteropancreatic, *HR* Hazard Ratio, *NEC* Neuroendocrine Carcinoma, *NEN* Neuroendocrine Neoplasm, *NET* Neuroendocrine Tumors, *OR* Odd Ratio, *PFS* Progression Free Survival, *T2DM* Type 2 Diabetes Mellitus

three times shorter in underweight patients compared to those with normal weight. One possible explanation is that patients with reduced muscle mass may have lower levels of mTORC1 receptors compared to those with higher muscle mass, resulting in less pronounced mTOR inhibition and a diminished therapeutic response to everolimus [53]. Marrache et al. found a BMI < 20 to be a predictor of poor response to transcatheter arterial chemoembolization in NET patients with liver metastases, whereas a higher BMI was significantly linked to a better response to the therapy [27].

Interestingly, preliminary studies have shown a potential role of metabolic profile in influencing the response to therapy in patients with GEP-NETs. Vernieri et al. reported that high plasma triglyceride levels during the first 3 months of treatment with everolimus increased the risk of disease progression in patients with advanced pancreatic NETs [54]. This highlights the importance of maintaining proper nutritional status and a healthy metabolic profile in these patients.

Emerging evidence suggests that T2DM therapy can modulate the response to anticancer treatment or exert a direct antitumor effect, highlighting the complex interplay between metabolic regulation and cancer progression. An intriguing finding from a post-hoc analysis of the CLARINET study, a clinical trial involving patients with advanced non-functional enteropancreatic NETs, showed that lanreotide significantly lowered the risk of disease progression or death compared to a placebo. The post hoc analysis reported that diabetic patients in the placebo group who were treated with metformin had twice the PFS compared to those who were untreated [37]. This confirmed the potential benefit of metformin on PFS, demonstrating its anti-tumor activity when used as a single-agent therapy in patients with less aggressive GEP-NETs. The mechanism by which metformin might provide these benefits could be related to the activation of AMPK and the subsequent inhibition of mTORC1, a critical component in the pathogenesis and progression of these tumors [55, 56]. This positive effect would be abrogated during therapy with somatostatin analogues therapy, considering that lanreotide alone was already effective in inhibiting the mTORC1 axis in patients with less aggressive disease. Indeed, in the subgroup of patients with T2DM randomized to receive lanreotide, metformin use was not significantly associated with an improvement in PFS ($p = 0.241$) [37]. Two studies by Pusceddu et al. evaluated the association between metformin and PFS in patients with advanced pancreatic NETs. In the first study, all patients were treated with octreotide LAR and everolimus until disease progression, with diabetic patients receiving either insulin or metformin. Patients treated with metformin had twice the PFS compared to those treated with insulin, indicating a beneficial impact of metformin on clinical outcomes. This beneficial effect of metformin on PFS appeared to remain consistent regardless of dosage, glycemic status, or additional antitumor therapies [57]. In another study, patients with pancreatic NETs who started metformin either before or within three months of initiating everolimus or somatostatin analogue therapy experienced longer PFS compared to those who started metformin after more than three months or did not use it at all [58].

Interestingly, some studies have hypothesized that antitumor therapy may contribute to malnutrition. In the previously mentioned study by Qureshi et al., patients with a positive MUST score, indicating malnutrition, were more likely to be treated with somatostatin analogues than those with a negative score (65% vs. 38%, $p = 0.021$) [25]. Moreover, Maasberg et al. found that malnutrition was highly frequent in a population of 203 patients with NENs undergoing chemotherapy [32]. However, further evidence is needed to verify the potential causative role of each specific anticancer treatment in malnutrition.

6 Nutritional intervention in patients with GEP-NENs and metabolic disorders

Dietary therapy is essential for both preventing and managing patients with GEP-NENs and metabolic disorders, including obesity, T2DM and MS [59]. As previously described, patients with GEP-NENs are at high risk of nutritional imbalances, which negatively impact outcomes, metabolic alterations, and the response to pharmacological therapy [40, 59]. In this scenario, the nutritional status of these patients is critically relevant, particularly in those with metabolic disorders [40, 59]. Of interest, protein-caloric malnutrition in GEP-NEN patients may result from tryptophan depletion, loss of appetite with reduced intake of food, and severe diarrhoea and/or flushing [24].

The assessment of nutritional status, including body composition through bioimpedance analysis, anthropometric evaluation, and dietary intake, should be incorporated into clinical practice for managing patients with GEP-NENs. This approach helps identify high-risk individuals with more aggressive tumors and metabolic disorders who may benefit significantly from targeted dietary interventions [60].

Although there are no specific guidelines for patients with GEP-NENs, it is generally recommended that cancer patients consume a diet low in simple carbohydrates and rapid-absorbing sugars, while including higher amounts of proteins and unsaturated fats (monounsaturated and polyunsaturated fatty acids) [61]. Likely, similar advice can be extended to GEP-NEN patients with metabolic disorders to reduce their cardio-metabolic risk [62]. Additionally, vitamin status has been studied in NENs, with vitamin D deficiency observed in roughly half of these patients [63–65]. Interestingly, supplementation with vitamin D

has been shown to have a positive influence on PFS in NEN patients [65].

In this context, every GEP-NEN patient should receive medical dietary therapy prescribed by an expert nutritionist. The goals of this therapy should include achieving and maintaining a normal body weight, optimizing blood pressure, lipid, and glycaemic levels, delaying or preventing metabolic complications, and controlling tumor-related symptoms [66]. It is important to underline the importance of a nutritionist expert in oncology, as meal planning must be personalized to the individual patient. There is no "one size fits all" dietary pattern in general, and this is particularly true for patients with GEP-NENs and metabolic complications [35]. Among the various eating patterns studied in NEN patients, the Mediterranean-style diet and the ketogenic diet are the most extensively researched [66–68].

The Mediterranean diet, which emphasizes extra virgin olive oil, whole grains, vegetables, fruits, and fish, may help improve lipid and glucose metabolism and reduce cardiometabolic risk [69–71]. In the context of cancer, there has been reported correlation between low adherence to the Mediterranean diet and cancer, suggesting that insufficient adherence to this diet could influence the aggressiveness of different cancer types [72]. Conversely, high adherence to the Mediterranean diet may benefit cancer outcomes due to its significant anti-inflammatory, antioxidant, and anti-aggregating properties [73]. The anti-tumoral beneficial effects of the Mediterranean dietary pattern can be attributed to different foods such as vegetables, fruits, cereals, fish, olive oil, and legumes. These foods are rich in antioxidants such as flavonoids, polyunsaturated fatty acids, vitamins A, C, and E, lycopene, carotenoids, and fibers, all of which support numerous cellular signalling pathways [42]. For these reasons, adopting a Mediterranean dietary pattern could be considered beneficial for patients with GEP-NENs, both with and without comorbidities. However, there are still limited scientific results regarding these aspects. In detail, only one case-control, cross-sectional study aimed to investigate adherence to the Mediterranean diet in GEP-NET patients. This study utilized a validated 14-item questionnaire to evaluate adherence to the Mediterranean diet [60]. Barrea et al. reported that patients with more aggressive GEP-NETs exhibited lower adherence to the Mediterranean diet compared to those with G1 tumors, localized disease, or stable disease. Interestingly, patients with low adherence to the Mediterranean diet demonstrated a higher incidence of metastases and disease progression. These findings suggest that a Mediterranean dietary pattern may be an effective strategy for reducing cancer aggressiveness in patients with GEP-NETs [60]. Finally, although the Mediterranean diet could be considered a useful dietary pattern in NEN patients, there is still a lack of comprehensive research on its specific impact on this type of tumor.

Very recently, the ketogenic diet has been suggested as a potentially effective dietary approach for managing GEP-NENs [66–68] and other types of tumors [74]. A ketogenic diet is characterized by high fat, low carbohydrate intake (less than 50 g per day), and sufficient protein [35]. The ketogenic diet seems to improve the effectiveness of standard treatments by targeting the altered metabolism of cancer cells, making it a promising candidate for adjuvant cancer therapy. Preclinical and clinical studies suggest that a ketogenic diet may offer antitumor benefits, potentially extending to the management of NENs [66–68]. In particular, the ketosis induced by a ketogenic diet likely creates a less favourable metabolic environment for tumor cell growth by inhibiting several pathways crucial for cancer cell survival [75]. Although this dietary pattern is well-tolerated and considered safe, additional research and randomized controlled trials are needed to clarify its efficacy and safety when combined with pharmacological treatments. It is essential that these medical dietary therapies will be assessed through prospective clinical trials.

7 Conclusions

The role of nutrition is paramount in cancer patients, especially those with GEP-NENs. Numerous studies have emphasized the significant impact of nutritional status and related comorbidities on the development, progression, and management of GEP-NENs, leading to various clinical consequences. While evidence suggests a potential increased risk of developing GEP-NENs in patients with obesity, metabolic disorders, and T2DM, further research is needed to fully understand this relationship and potential differences between NETs and NECs. Longitudinal studies and investigations into the molecular and biological mechanisms involved will be crucial. These efforts will aid in developing targeted prevention and treatment strategies.

Emerging data suggest that metabolic alterations may influence the behaviour and progression of GEP-NENs. While numerous studies have demonstrated a strong correlation between obesity and its associated comorbidities with the development and progression of aggressive tumors, there is also evidence suggesting a poorer prognosis in malnourished patients with GEP-NENs, thus introducing the concept of the "obesity paradox". However, establishing a cause-effect relationship between malnutrition and cancer outcomes is extremely difficult due to the complex interplay of factors involved. Cancer itself can lead to changes in metabolism, appetite, and nutrient absorption, contributing to malnutrition. Furthermore, cancer treatments can cause side effects such as nausea, vomiting, diarrhoea, malabsorption, and alterations in taste or smell, which can further exacerbate malnutrition. Future studies have the potential to

shed light on the complexities of this paradox and its implications for patient care and public health policy.

Regular nutritional assessment and therapy are crucial for optimizing the clinical outcomes of GEP-NEN patients. From a clinical practice perspective, screening for the risk of malnutrition or obesity should be conducted at diagnosis and at regular intervals during treatment by expert nutritionists or other trained health professionals using validated tools. It is imperative to move beyond simple BMI measurements and analyze the body composition of patients, as a normal or high BMI may not accurately reflect the distribution of body mass. Special attention should be given to patients with GEP-NEC, progressive disease, and those undergoing chemotherapy, as they are at the highest risk of malnutrition. Moreover, prospective longitudinal studies are needed to evaluate the impact of changes in nutritional status over time or during treatment, to assess the prevalence of malnutrition and obesity in GEP-NEN patients, and to determine the most appropriate methods of nutrition therapy. Nutritional plans should be integrated into the multidisciplinary treatment approach for these patients to enhance both quality of life and survival outcomes.

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References

1. Muscaritoli M, Corsaro E, Molfino A. Awareness of cancer-related malnutrition and its management: analysis of the results from a survey conducted among medical oncologists. Front Oncol. 2021;11: 682999. https://doi.org/10.3389/fonc.2021.682999.
2. Sadeghi M, Keshavarz-Fathi M, Baracos V, Arends J, Mahmoudi M, Rezaei N. Cancer cachexia: diagnosis, assessment, and treatment. Crit Rev Oncol Hematol. 2018;127:91–104. https://doi.org/10.1016/j.critrevonc.2018.05.006.
3. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12:489–95. https://doi.org/10.1016/S1470-2045(10)70218-7.
4. Modica R, Benevento E, Liccardi A, Cannavale G, Minotta R, Iasi DI, Colao G. Recent advances and future challenges in the diagnosis of neuroendocrine neoplasms. Minerva Endocrinol. 2024;49(2):158–74. https://doi.org/10.23736/S2724-6507.23.04140-4.
5. Lan X, Fazio N, Abdel-Rahman O. Exploring the relationship between obesity, metabolic syndrome and neuroendocrine neoplasms. Metabolites. 2022;12: 1150. https://doi.org/10.3390/metabo12111150.
6. Lennon H, Sperrin M, Badrick E, Renehan AG. The obesity paradox in cancer: a review. Curr Oncol Rep. 2016;18:56. https://doi.org/10.1007/s11912-016-0539-4.
7. Leoncini E, Carioli G, La Vecchia C, Boccia S, Rindi G. Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. Ann Oncol. 2016;27:68–81. https://doi.org/10.1093/annonc/mdv505.
8. Zhan H-X, Cong L, Zhao Y-P, Zhang T-P, Chen G. Risk factors for the occurrence of insulinoma: a case-control study. Hepatobiliary Pancreat Dis Int. 2013;12:324–8. https://doi.org/10.1016/S1499-3872(13)60051-X.
9. Halfdanarson TR, Bamlet WR, McWilliams RR, Hobday TJ, Burch PA, Rabe KG, et al. Risk factors for pancreatic neuroendocrine tumors: a clinic-based case-control study. Pancreas. 2014;43:1219–22. https://doi.org/10.1097/MPA.0000000000000234.
10. Hassan MM, Phan A, Li D, Dagohoy CG, Leary C, Yao JC. Risk factors associated with neuroendocrine tumors: a U.S.-based case-control study. Int J Cancer. 2008;123:867–73. https://doi.org/10.1002/ijc.23529.
11. Cross AJ, Hollenbeck AR, Park Y. A large prospective study of risk factors for adenocarcinomas and malignant carcinoid tumors of the small intestine. Cancer Causes Control. 2013;24:1737–46. https://doi.org/10.1007/s10552-013-0251-8.
12. Scélo G, Boffetta P, Hemminki K, Pukkala E, Olsen JH, Andersen A, et al. Associations between small intestine cancer and other primary cancers: an international population-based study. Int J Cancer. 2006;118:189–96. https://doi.org/10.1002/ijc.21284.
13. Babovic-Vuksanovic D, Constantinou CL, Rubin J, Rowland CM, Schaid DJ, Karnes PS. Familial occurrence of carcinoid tumors and association with other malignant neoplasms. Cancer Epidemiol Biomarkers Prev. 1999;8:715–9.
14. Feola T, Puliani G, Sesti F, Modica R, Centello R, Minotta R, et al. Risk factors for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs): a three-centric case–control study. J Endocrinol Invest. 2022;45:849–57. https://doi.org/10.1007/s40618-021-01715-0.
15. Mottin CC, Cruz RP, Gomes Thomé G, Padoin AV. Carcinoid tumors and morbid obesity. OBES SURG. 2009;19:247–9. https://doi.org/10.1007/s11695-008-9541-8.
16. Al-Harbi O, Shakir M, Al-Brahim N. Gastric carcinoid and obesity: association or coincidence? Report of two cases and literature

review. Case Rep Gastrointest Med. 2013;2013:1–4. https://doi.org/10.1155/2013/848075.
17. Crea N, Pata G, Di Betta E, Titi A, Mittempergher F. High incidence of appendix carcinoid tumors among candidates for bariatric surgery: diagnostic and therapeutic implications. Obes Surg. 2011;21:151–6. https://doi.org/10.1007/s11695-010-0112-4.
18. Santos A, Santos A, Castro C, Raposo L, Pereira S, Torres I, et al. Visceral obesity and metabolic syndrome are Associated with Well-differentiated gastroenteropancreatic neuroendocrine tumors. Cancers. 2018;10:293. https://doi.org/10.3390/jcm11206026.
19. Jung YS, Yun KE, Chang Y, Ryu S, Park JH, Kim HJ, et al. Risk factors associated with rectal neuroendocrine tumors: a cross-sectional study. Cancer Epidemiol Biomarkers Prev. 2014;23:1406–13. https://doi.org/10.1158/1055-9965.EPI-14-0132.
20. Capurso G, Falconi M, Panzuto F, Rinzivillo M, Boninsegna L, Bettini R, et al. Risk factors for sporadic pancreatic endocrine tumors: a case-control study of prospectively evaluated patients. Am J Gastroenterol. 2009;104:3034–41. https://doi.org/10.1038/ajg.2009.466.
21. Valente R, Hayes AJ, Haugvik S-P, Hedenström P, Siuka D, Korsæth E, et al. Risk and protective factors for the occurrence of sporadic pancreatic endocrine neoplasms. Endocrine-related Cancer. 2017;24:405–14. https://doi.org/10.1530/ERC-17-0040.
22. Giraldi L, Vecchioni A, Carioli G, Bilotta M, La Rosa S, Imperatori A, et al. Risk factors for pancreas and lung neuroendocrine neoplasms: a case-control study. Endocrine. 2021;71:233–41. https://doi.org/10.1007/s12020-020-02464-5.
23. Borre M, Dam GA, Knudsen AW, Grønbaek H. Nutritional status and nutritional risk in patients with neuroendocrine tumors. Scand J Gastroenterol. 2018;53:284–92. https://doi.org/10.1080/00365521.2018.1430848.
24. Clement DS, Tesselaar ME, van Leerdam ME, Srirajaskanthan R, Ramage JK. Nutritional and vitamin status in patients with neuroendocrine neoplasms. World J Gastroenterol. 2019;25:1171–84. https://doi.org/10.3748/wjg.v25.i10.1171.
25. Qureshi SA, Burch N, Druce M, Hattersley JG, Khan S, Gopalakrishnan K, et al. Screening for malnutrition in patients with gastro-entero-pancreatic neuroendocrine tumours: a cross-sectional study. BMJ Open. 2016;6:e010765. https://doi.org/10.1136/bmjopen-2015010765.
26. Cherenfant J, Stocker SJ, Gage MK, Du H, Thurow TA, Odeleye M, et al. Predicting aggressive behavior in nonfunctioning pancreatic neuroendocrine tumors. Surgery. 2013;154:785–93. https://doi.org/10.1016/j.surg.2013.07.004.
27. Marrache F, Vullierme MP, Roy C, El Assoued Y, Couvelard A, O'Toole D, et al. Arterial phase enhancement and body mass index are predictors of response to chemoembolisation for liver metastases of endocrine tumours. Br J Cancer. 2007;96:49–55. https://doi.org/10.1038/sj.bjc.6603526.
28. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. Clin Cancer Res. 2008;14:7798–803. https://doi.org/10.1158/1078-0432.CCR-08-0734.
29. Glazer E, Stanko K, Ong E, Guerrero M. Decreased Inpatient Mortality in obese patients with abdominal nets. Endocr Pract. 2014;1–20. https://doi.org/10.4158/EP14203.OR.
30. Abdel-Rahman O, Ghosh S, Morrish D. Impact of baseline body mass index on the outcomes of patients with neuroendocrine neoplasms. J Endocrinol Invest. 2022;45:1683–8. https://doi.org/10.1007/s40618-022-01805-7.
31. Lee DH, Giovannucci EL. The obesity paradox in cancer: epidemiologic insights and perspectives. Curr Nutr Rep. 2019;8:175–81. https://doi.org/10.1007/s13668-019-00280-6.
32. Maasberg S, Knappe-Drzikova B, Vonderbeck D, Jann H, Weylandt KH, Grieser C, et al. Malnutrition predicts clinical outcome in patients with neuroendocrine neoplasia. Neuroendocrinology. 2017;104:11–25. https://doi.org/10.1159/000442983.
33. Clement DSVM, van Leerdam ME, Tesselaar MET, Cananea E, Martin W, Weickert MO, et al. The global leadership into malnutrition criteria reveals a high percentage of malnutrition which influences overall survival in patients with gastroenteropancreatic neuroendocrine tumours. J Neuroendocrinol. 2024;36: e13376. https://doi.org/10.1111/jne.13376.
34. Barrea L, Muscogiuri G, Modica R, Altieri B, Pugliese G, Minotta R, et al. Cardio-metabolic indices and metabolic syndrome as predictors of clinical severity of gastroenteropancreatic neuroendocrine tumors. Front Endocrinol. 2021;12: 649496. https://doi.org/10.3389/fendo.2021.649496.
35. Gallo M, Muscogiuri G, Pizza G, Ruggeri RM, Barrea L, Faggiano A, et al. The management of neuroendocrine tumours: a nutritional viewpoint. Crit Rev Food Sci Nutr. 2019;59:1046–57. https://doi.org/10.1080/10408398.2017.1390729.
36. Santos, Castro, Antunes, Henrique, Cardoso, Monteiro. Disseminated well-differentiated gastro-entero-pancreatic tumors are Associated with metabolic syndrome. JCM. 2019;8:1479. https://doi.org/10.3390/jcm8091479.
37. Pusceddu S, Vernieri C, Di Maio M, Prinzi N, Torchio M, Corti F, et al. Impact of diabetes and metformin use on enteropancreatic neuroendocrine tumors: Post hoc analysis of the CLARINET Study. Cancers (Basel). 2022;14: 69. https://doi.org/10.3390/cancers14010069.
38. Fan Z, Gong Y, Huang Q, Yang C, Cheng H, Jin K, et al. Diabetes is associated with the metastasis of pancreatic neuroendocrine tumors. Pancreas. 2020;49:751. https://doi.org/10.1097/MPA.0000000000001564.
39. Laing E, Kiss N, Michael M, Gough K, Krishnasamy M. Investigating Nutrition-related complications and quality of life in patients with gastroenteropancreatic neuroendocrine tumors: protocol for a mixed-methods prospective study. JMIR Res Protoc. 2018;7: e11228. https://doi.org/10.2196/11228.
40. Altieri B, Barrea L, Modica R, Muscogiuri G, Savastano S, Colao A, et al. Nutrition and neuroendocrine tumors: an update of the literature. Rev Endocr Metab Disord. 2018;19:159–67. https://doi.org/10.1007/s11154-018-9466-z.
41. Go VLW, Srihari P, Kamerman Burns LA. Nutrition and gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am. 2010;39:827–37. https://doi.org/10.1016/j.ecl.2010.08.003.
42. Singh S, Granberg D, Wolin E, Warner R, Sissons M, Kolarova T, et al. Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the first global survey of patients with NETs. J Glob Oncol. 2017;3:43–53. https://doi.org/10.1200/JGO.2015.002980.
43. Jensen GL, Cederholm T, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. J Parenter Enter Nutr. 2019;43:32–40. https://doi.org/10.1002/jpen.1440.
44. Laing E, Gough K, Krishnasamy M, Michael M, Kiss N. Prevalence of malnutrition and nutrition-related complications in patients with gastroenteropancreatic neuroendocrine tumours. J Neuroendocrinol. 2022;34: e13116. https://doi.org/10.1111/jne.13116.
45. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019;393:2636–46. https://doi.org/10.1016/S0140-6736(19)31138-9.
46. Clement DSVM, van Leerdam ME, de Jong S, Weickert MO, Ramage JK, Tesselaar MET, et al. Prevalence of Sarcopenia and Impact on survival in patients with metastatic

gastroenteropancreatic neuroendocrine tumours. Cancers. 2023;15: 782. https://doi.org/10.3390/cancers15030782.
47. Ryan AM, Prado CM, Sullivan ES, Power DG, Daly LE. Effects of weight loss and sarcopenia on response to chemotherapy, quality of life, and survival. Nutrition. 2019;67–68:110539. https://doi.org/10.1016/j.nut.2019.06.020.
48. Baldessari C, Guaitoli G, Valoriani F, Bonacini R, Marcheselli R, Reverberi L, et al. Impact of body composition, nutritional and inflammatory status on outcome of non-small cell lung cancer patients treated with immunotherapy. Clin Nutr ESPEN. 2021;43:64–75. https://doi.org/10.1016/j.clnesp.2021.02.017.
49. Vandoni G, D'Amico F, Fabbrini M, Mariani L, Sieri S, Casirati A, et al. Gut microbiota, metabolome, and body composition signatures of response to therapy in patients with advanced melanoma. Int J Mol Sci. 2023;24:11611. https://doi.org/10.3390/ijms241411611.
50. Tenuta M, Gelibter A, Pandozzi C, Sirgiovanni G, Campolo F, Venneri MA, et al. Impact of sarcopenia and inflammation on patients with advanced Non-small Cell Lung Cancer (NCSCL) treated with Immune Checkpoint Inhibitors (ICIs): a prospective study. Cancers (Basel). 2021;13: 6355. https://doi.org/10.3390/cancers13246355.
51. Bongiovanni A, Riva N, Ricci M, Liverani C, La Manna F, De Vita A, et al. First-line chemotherapy in patients with metastatic gastroenteropancreatic neuroendocrine carcinoma. Onco Targets Ther. 2015;8:3613–9. https://doi.org/10.2147/OTT.S91971.
52. Edfeldt K, Hellman P, Granberg D, Lagergren P, Thiis-Evensen E, Sundin A, et al. Improved health-related quality of life during peptide receptor radionuclide therapy in patients with neuroendocrine tumours. J Neuroendocrinol. 2023;35: e13342. https://doi.org/10.1111/jne.13342.
53. Ranallo N, Iamurri AP, Foca F, Liverani C, De Vita A, Mercatali L, et al. Prognostic and predictive role of body composition in metastatic neuroendocrine tumor patients treated with everolimus: a real-world data analysis. Cancers (Basel). 2022;14:3231. https://doi.org/10.3390/cancers14133231.
54. Vernieri C, Pusceddu S, Fucà G, Indelicato P, Centonze G, Castagnoli L, et al. Impact of systemic and tumor lipid metabolism on everolimus efficacy in advanced pancreatic neuroendocrine tumors (pNETs). Int J Cancer. 2019;144:1704–12. https://doi.org/10.1002/ijc.32042.
55. Luengo A, Sullivan LB, Heiden MGV. Understanding the complex-I-ty of metformin action: limiting mitochondrial respiration to improve cancer therapy. BMC Biol. 2014;12:82. https://doi.org/10.1186/s12915-014-0082-4.
56. Pollak MN. Investigating metformin for cancer prevention and treatment: the end of the beginning. Cancer Discov. 2012;2:778–90. https://doi.org/10.1158/2159-8290.CD-12-0263.
57. Pusceddu S, Buzzoni R, Vernieri C, Concas L, Marceglia S, Giacomelli L, et al. Metformin with everolimus and octreotide in pancreatic neuroendocrine tumor patients with diabetes. Future Oncol. 2016;12:1251–60. https://doi.org/10.2217/fon-2015-0077.
58. Pusceddu S, Vernieri C, Maio MD, Marconcini R, Spada F, Massironi S, et al. Metformin use is associated with longer progression-free survival of patients with diabetes and pancreatic neuroendocrine tumors receiving everolimus and/or somatostatin analogues. Gastroenterology. 2018;155:479-e4897. https://doi.org/10.2217/fon-2015-0077.
59. Natalicchio A, Faggiano A, Zatelli MC, Argentiero A, D'Oronzo S, Marrano N, et al. Metabolic disorders and gastroenteropancreatic-neuroendocrine tumors (GEP-NETs): how do they influence each other? An Italian Association of Medical Oncology (AIOM)/ Italian Association of Medical Diabetologists (AMD)/ Italian Society of Endocrinology (SIE)/ Italian Society of Pharmacology (SIF) multidisciplinary consensus position paper. Crit Rev Oncol/Hematol. 2022;169:103572. https://doi.org/10.1016/j.critrevonc.2021.103572.
60. Barrea L, Altieri B, Muscogiuri G, Laudisio D, Annunziata G, Colao A, et al. Impact of nutritional status on gastroenteropancreatic neuroendocrine tumors (GEP-NET) aggressiveness. Nutrients. 2018;10: 1854. https://doi.org/10.3390/nu10121854.
61. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36:11–48. https://doi.org/10.1016/j.clnu.2016.07.015.
62. Ragni A, Retta F, Arvat E, Gallo M. Diabetes in cancer patients: risks, goals and management. Front Horm Res. 2021;54:103–14. https://doi.org/10.1159/000513807.
63. Albertelli M, Petolicchio C, Brasili S, Pogna A, Boschetti M, Luciano G, et al. Impact of vitamin D deficiency on tumor aggressiveness in neuroendocrine neoplasms. Nutrients. 2023;15: 3771. https://doi.org/10.3390/nu15173771.
64. Lind A, Wängberg B, Ellegård L. Vitamin D and vitamin B12 deficiencies are common in patients with midgut carcinoid (SI-NET). Eur J Clin Nutr. 2016;70:990–4. https://doi.org/10.1038/ejcn.2016.40.
65. Massironi S, Zilli A, Bernasconi S, Fanetti I, Cavalcoli F, Ciafardini C, et al. Impact of vitamin D on the clinical outcome of gastro-entero-pancreatic neuroendocrine neoplasms: report on a series from a single Institute. Neuroendocrinology. 2017;105:403–11. https://doi.org/10.1159/000456619.
66. Muscogiuri G, Barrea L, Cantone MC, Guarnotta V, Mazzilli R, Verde L, et al. Neuroendocrine tumors: a comprehensive review on nutritional approaches. Cancers (Basel). 2022;14: 4402. https://doi.org/10.3390/cancers14184402.
67. Barrea L, Verde L, Annunziata G, Camajani E, Caprio M, Sojat AS, et al. Role of Mediterranean diet in endocrine diseases: a joint overview by the endocrinologist and the nutritionist. J Endocrinol Invest. 2024;47:17–33. https://doi.org/10.1007/s40618-023-02169-2.
68. Muscogiuri G, Barrea L, Campolo F, Sbardella E, Sciammarella C, Tarsitano MG, et al. Ketogenic diet: a tool for the management of neuroendocrine neoplasms? Crit Rev Food Sci Nutr. 2022;62:1035–45. https://doi.org/10.1080/10408398.2020.1832955.
69. Karam G, Agarwal A, Sadeghirad B, Jalink M, Hitchcock CL, Ge L, et al. Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: systematic review and network meta-analysis. BMJ. 2023;380:e072003. https://doi.org/10.1136/bmj-2022-072003.
70. Muscogiuri G, Verde L, Sulu C, Katsiki N, Hassapidou M, Frias-Toral E, et al. Mediterranean diet and obesity-related disorders: what is the evidence? Curr Obes Rep. 2022;11:287–304. https://doi.org/10.1007/s13679-022-00481-1.
71. Rees K, Takeda A, Martin N, Ellis L, Wijesekara D, Vepa A, et al. Mediterranean-style diet for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2019;3:CD009825. https://doi.org/10.1002/14651858.CD009825.pub3.
72. Mentella MC, Scaldaferri F, Ricci C, Gasbarrini A, Miggiano GAD. Cancer and Mediterranean diet: a review. Nutrients. 2019;11: 2059. https://doi.org/10.3390/nu11092059.
73. Castro-Espin C, Agudo A. The role of diet in prognosis among cancer survivors: a systematic review and meta-analysis of dietary patterns and diet interventions. Nutrients. 2022;14: 348. https://doi.org/10.3390/nu14020348.
74. Barrea L, Caprio M, Tuccinardi D, Moriconi E, Di Renzo L, Muscogiuri G, et al. Could ketogenic diet starve cancer? Emerging evidence. Crit Rev Food Sci Nutr. 2022;62:1800–21. https://doi.org/10.1080/10408398.2020.1847030.

75. Muscogiuri G, Barrea L, Laudisio D, Pugliese G, Salzano C, Savastano S, et al. The management of very low-calorie ketogenic diet in obesity outpatient clinic: a practical guide. J Translational Med. 2019;17:356. https://doi.org/10.1186/s12967-019-2104-z.