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Symptom Management for Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: ASCO Guideline

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ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

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PURPOSE To develop a clinical practice guideline and recommendations for symptom management of patients with well-differentiated grade 1 to grade 3 metastatic gastroenteropancreatic neuroendocrine tumors.

METHODS ASCO convened an Expert Panel to develop a clinical practice guideline by reviewing the literature for relevant guidelines, systematic reviews, randomized controlled trials (RCTs), and observational studies to develop recommendations for clinical practice.

RESULTS The literature review identified eight guidelines, 19 systematic reviews, and three RCTs that informed the development of guideline recommendations.

RECOMMENDATIONS Recommendations are included for carcinoid syndrome, carcinoid heart disease and carcinoid crisis, and functional pancreatic neuroendocrine tumor syndromes. Recommendations are provided for surgical management, liver-directed therapy, and systemic therapy options, as well as palliative care. Limited guidance is provided for sequencing of interventions.

Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

Neuroendocrine neoplasms (NENs) include poorly differentiated neuroendocrine carcinomas, well-differentiated neuroendocrine tumors (NETs), and mixed neuroendocrine non-NENs.[1] The focus of this guideline is on grade 1 (G1) to grade 3 (G3) well-differentiated NETs, which account for approximately 80%-90% of NENs.[2] Historically, NETs were considered rare, but incidence and prevalence rates have been increasing in recent decades because of improvement in diagnosis, more NETs being incidentally diagnosed, stage migration, and longer survival.[3] In the

TARGET POPULATION AND AUDIENCE

Target Population

Patients with well-differentiated grade 1 (G1)-grade 3 (G3) metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) with symptoms from hormone excess or tumor bulk.

Target Audience

Medical oncologists, surgical oncologists, endocrinologists, nuclear medicine specialists, and other health care professionals who are involved in the care and treatment of patients with metastatic well-differentiated G1-G3 metastatic GEP-NETs.

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United States, the age-adjusted incidence of NETs per 100,000 persons rose from 4.90 in 2000 to 8.19 in 2018.[4] As these tumors grow and metastasize, there is more potential for patients to experience symptoms related to secretion of hormones, which can cause a wide range of symptoms, depending on the type of hormone that is secreted. In a study of data gathered between 2000 and 2011, 32.4% of 2,211 patients with small bowel NETs had symptoms of carcinoid syndrome.[5] Approximately 10%-20% of patients with pancreatic NETs (panNETs)[6] are reported to have one of several clinical syndromes as a result of hormone excess. These statistics may underestimate the prevalence of functional NETs that are associated with clinical symptoms related to hormone secretion because many patients experience nonspecific symptoms for several years before diagnosis, and these symptoms may be attributed to other causes. The focus of this guideline is on management of symptoms related to metastatic NETs that arise in the GI tract and pancreas (gastroenteropancreatic neuroendocrine tumors [GEP-NETs]). This clinical practice guideline is intended to raise awareness of NETs and treatment options in the oncology community. It includes options for surgical management, medical management, liver-directed therapy, and other interventions for metastatic functioning GEP-NETs. The main outcomes of interest are reduction in symptoms, reduction in adverse events with treatment, and overall improvement, stabilization, or lengthened time to deterioration of quality of life. A previously published ASCO guideline includes recommendations for systemic therapy for tumor control of metastatic well-differentiated GEP-NETs, which can also positively affect symptom management.[7]

GUIDELINE QUESTIONS

This clinical practice guideline addresses the question: What are the recommended treatment options for management of symptoms of functional GEP-NETs, including carcinoid syndrome, carcinoid heart disease, and functional panNETs?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included patient representatives, a community oncologist, and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only).

The recommendations were developed by using a systematic review of evidence identified through online searches for existing guidelines from organizations such as the North American Neuroendocrine Tumor Society (NANETS), the European Neuroendocrine Tumor Society (ENETS), a search of PubMed (January 1, 2005-June 1, 2024), and the Cochrane Database of Systematic Reviews, for existing guidelines, systematic reviews, and randomized controlled trials (RCTs). Articles were selected for inclusion in the systematic review based on the following criteria:

- Population: Patients with well-differentiated G1-G3 GEP-NETs who are experiencing symptoms, including those associated primarily with small bowel NETs (carcinoid syndrome, carcinoid heart disease, carcinoid crisis) and with panNET syndromes—insulinoma, vasoactive intestinal peptide (VIP)–secreting tumors (VIPomas), gastrinoma, glucagonoma, somatostatinoma, and other rare functional panNET syndromes.
- Interventions and Comparisons:
  - Small bowel tumors: Somatostatin analogs (SSAs), telotristat ethyl, surgery, liver-directed therapy (embolization), systemic therapy options, including chemotherapy and peptide receptor radionuclide therapy (PRRT), and others.
  - panNETs: SSAs, surgery, liver-directed therapy, systemic therapy options such as PRRT, chemotherapy, targeted therapy, and options to treat symptoms specific to each panNET syndrome.
- Outcomes: Symptom management and symptom control outcomes, quality of life reported on validated scales, toxicity, and adverse events.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language.

One full-panel meeting was held, and members were asked to provide ongoing input on the guideline development protocol, quality and assessment of the evidence, generation of recommendations, draft content, and review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the Expert Panel cochairs and corresponded with the panel via e-mail to coordinate the process to completion. Ratings for strength of the recommendations and evidence quality are provided with each recommendation and defined in Appendix Table A2. The

quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[8,9] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel cochairs and reviewed by the full Expert Panel. For some recommendations, good practice statements were made; this occurred when high-quality indirect evidence was available, but the Expert Panel did not consider it a good use of resources to conduct a formal systematic review. All funding for the administration of the project was provided by ASCO.

Guideline Review and Approval

The draft recommendations were released to the public for open comment from September 6, 2024, through September 20, 2024. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree" were offered with the option to provide comments. There were eight respondents in total, of whom 100% were medical or surgical oncologists. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. For the most part, the respondents agreed with the recommendations, with suggestions for changes to a minority of the recommendations. There was one disagreement with including ondansetron as a recommended treatment option, because of the low level of evidence. Suggested modifications included less specificity in the cardiac surgery recommendations (ie, recommended referring to a cardiac surgeon for this), as well as some minor wording and strength of evidence suggestions. Caution in patients who had Whipple procedures for locoregional treatments was suggested and incorporated.

The draft was submitted to two external reviewers for comment, and they agreed that the guideline would be useful in practice. Comments were reviewed by the Expert Panel and integrated into the manuscript. In addition, a guideline implementability review was conducted. Based on this review, revisions were made to the draft to clarify recommended actions for clinical practice.

All changes were incorporated into the final manuscript before ASCO Evidence-Based Medicine Committee (EBMC) review and approval. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC before submission to an ASCO journal for editorial review and consideration for publication.

Data Analysis

Hazard ratios and odds ratios were extracted where available for time-to-event data; for other dichotomous outcomes, relative risk was extracted where available or calculated using reported events and population totals in the treatment and control groups, using Review Manager 5.3.

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

RESULTS

Because of the relatively broad topic scope, and to avoid duplication of effort, this guideline draws on relevant existing guidelines when possible, such as those from ENETS,[10,11] NANETS,[12,13] the National Comprehensive Cancer Network,[14] and the European Society for Medical Oncology.[2] These six guidelines as well as five systematic or narrative reviews,[15-18,21] four expert statements,[19,20,22,23] and six publications from three RCTs[24-29] identified through the literature search provided evidence to support the recommendations. Where necessary, other literature was cited according to consensus of the Expert Panel.[30-75] For topics for which RCTs exist, data table are provided in the Data Supplement (Data Supplement 1, Tables S1-S4, online only). Data Supplement 2 includes tables of source documents for ASCO guideline recommendations, including those which were adapted with permission from other sources.

RECOMMENDATIONS

All recommendations are available in Tables 1-4. Algorithms outlining treatment options for patients with carcinoid syndrome and panNETs are available in Figures 1 and 2, respectively.

CARCINOID SYNDROME

Carcinoid syndrome is the most common hormonal complication associated with NENs and is much more commonly diagnosed in patients with intestinal NETs than in patients with panNETs.[5,6] Symptoms arising from elevated levels of serotonin and other active amines and peptides include flushing, diarrhea, bronchospasm, and, in advanced NETs, carcinoid heart disease, which can lead to right heart failure because of regurgitation and stenosis of the right-sided heart valves.[10] Carcinoid crisis is rare and involves the sudden onset of hemodynamic instability because of massive release of vasoactive substances and may occur after an abdominal procedure.[47] SSAs are the most frequently used first-line therapy for functional NETs and have also demonstrated efficacy with respect to tumor control. SSAs are synthetic analogs of somatostatin that bind to somatostatin receptors (SSTRs) on NETs and inhibit hormonal secretion. In a

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TABLE 1. Summary of Recommendations for Carcinoid Syndrome and Carcinoid Heart Disease

Topic	Recommendation
General note. The following recommendations (strong or conditional) and terminology (Data Supplement) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible	
Differential Diagnosis of Diarrhea	1.1. Although diagnostic topics are outside the scope of this guideline, the Expert Panel notes the importance of accurately determining the cause of diarrhea prior to treatment. Possible causes of diarrhea can be multifactorial and include short bowel syndrome postsurgery, intestinal ischemia due to mesenteric fibrosis or lymph node metastases, and pancreatic exocrine insufficiency causing steatorrhea. These reasons should be ruled out before therapy with SSAs is initiated.[23,30,31] Long-acting SSAs have also been associated with diarrhea following long-term use, typically secondary to pancreatic exocrine insufficiency.[32] Further information on this topic is provided in a flow diagram outlining the differential diagnosis of diarrhea.[23] (Data Supplement, Fig S1). (Good Practice Statement)
Carcinoid Syndrome	1.2. For patients with symptoms of carcinoid syndrome (ie, flushing and/or diarrhea), therapy with a long-acting SSA should be offered as first-line therapy, following exclusion of other causes of diarrhea. (Evidence quality: High; Strength of recommendation: Strong)
	Qualifying statements for Recommendation 1.2 • Due to body habitus, some patients may experience breakthrough carcinoid symptoms as a result of suboptimal absorption of octreotide LAR, which is delivered intramuscularly. In this scenario, symptoms may be better managed with subcutaneous administration of lanreotide LAR. • If using depot octreotide LAR, overlap with subcutaneous octreotide is often required within the first few weeks to control symptoms while drug levels are rising.
	1.3. For patients with symptoms of carcinoid syndrome, if liver metastases are resectable, surgery may be discussed either first or in conjunction with SSAs. See qualifying statements to Recommendation 5.3 for additional information related to resection of liver metastases. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying statement for Recommendation 1.3: The decision regarding surgery should take into account effectiveness of treatment with SSAs, performance status, potential for improvement in symptoms, overall survival, and goals of care.
Refractory Carcinoid Syndrome	*Note:* Refractory carcinoid syndrome refers to persistent symptoms of diarrhea or flushing or symptom related to tumor-related hormone excess despite stable dose of SSA. Following exclusion of other causes of diarrhea and treatment with SSAs according to Recommendation 1.1, strategies that lead to cytoreduction are preferred. In general, if the patient has resectable disease, surgery should be initiated early, either first or in conjunction with the SSAs (Recommendation 1.2). For patients with diarrhea that is uncontrolled by SSAs, the interventions outlined subsequently may be utilized depending on patient characteristics and preferences. As there is no strong evidence for sequencing of interventions, patient preferences and cost may be considered when choosing between therapy options. Treatment delivery should be at centers that treat a high volume of patients with NETs, particularly for challenging clinical situations, or high-volume NET centers should be consulted for advice, although therapy may be delivered in the community.
	2.1. For patients with refractory carcinoid syndrome, options include dose escalation or increased injection frequency of the current long-acting SSA, or administration of a subcutaneous short-acting SSA (in addition to the long-acting SSA).[33] (Evidence quality: Low; Strength of recommendation: Conditional)
	Qualifying statements for Recommendation 2.1 • Examples of strategies when symptoms are not well-controlled include increasing frequency of octreotide LAR from the standard 30 mg once every 4 weeks to 30 mg once every 3 weeks,[33] or once every 2 weeks; increasing octreotide LAR dose to 40 mg or 60 mg once every 4 weeks,[34] or increasing the frequency of lanreotide autogel from 120 mg once every 4 weeks to 120 mg once every 2 or 3 weeks. • Based on limited evidence, the use of an increased dose of SSAs appears to improve symptoms with little increased risk of toxicity,[35] although there has been little study of the rate of adverse events with increased doses of SSAs. • Patients with poorly controlled carcinoid syndrome diarrhea and normal serotonin and/or HIAA levels should be assessed for other causes of diarrhea such as pancreatic exocrine insufficiency and malabsorptive diarrhea due to treatment with SSAs and bile acid diarrhea associated with short-gut syndrome related to surgical factors (Data Supplement, Fig S1). These two causes of diarrhea may be treated with pancreatic enzymes and bile acid sequestrants, respectively. • Given the need to administer short-acting SSAs 2-3 times per day, which may be challenging for patients, short-acting SSAs should ideally be used only in short-term scenarios.
	2.2. Nonspecific antidiarrheal medications such as loperamide or diphenoxylate may be offered in addition to SSAs[18] if the main symptom of refractory carcinoid syndrome is diarrhea, taking into account the risk of adverse events. (Evidence quality: Low; Strength of recommendation: Conditional)
	Note for Recommendation 2.2: When considering optimal antidiarrheal use, note that loperamide is approximately 3 times more potent milligram for milligram than diphenoxylate.[36,37]
	2.3. Telotristat ethyl may be offered to patients with refractory carcinoid syndrome and diarrhea that is inadequately controlled by SSAs.[21] (Evidence quality: Moderate; Strength of recommendation: Conditional)
	Qualifying statements for Recommendation 2.3 • SSAs should be continued during telotristat ethyl therapy. • As mentioned previously, other common causes of diarrhea should be ruled out prior to commencement of therapy with telotristat ethyl.[23,30,31]
	2.4. Everolimus has been tested in the setting of tumor control, but not symptom control,[38] therefore, this intervention is not a preferred therapy to offer to patients for symptom management of carcinoid syndrome. (Evidence Quality: Low; Strength of recommendation: Conditional)
	2.5. In the setting of uncontrolled carcinoid syndrome, locoregional therapies, including hepatic resection and intra-arterial therapies such as TAE, TACE, or bland embolization should be offered to patients.[16] (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying statements for Recommendation 2.5 • A patient-tailored approach is recommended when discussing any liver-directed therapy for patients who have undergone a prior Whipple procedure or who have a biliary stent. • Frequency of TAE or TACE should be determined based on disease burden and clinical response. • Drug-eluting embolics are not indicated for chemoembolization in the NET population.[14] • The most common side effects of these interventions are fever, abdominal pain, nausea, and vomiting, although the safety profile is relatively favorable compared to other interventions.[39]
	2.6. Another option, TARE (also known as SIRT), particularly when the entire liver volume is treated, can lead to late RECHT in 10%-20% of patients surviving more than 2 years,[14] therefore, caution should be used when considering radioembolization of the entire liver. (Good Practice Statement)
	2.7. PRRT is usually relevant in the setting of tumor growth but may be offered for control of symptoms of persistent refractory carcinoid syndrome, following attempts to control symptoms with previously recommended therapy options, such as with dose escalation of SSAs, liver-directed therapy, or telotristat ethyl. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	Qualifying statement for Recommendation 2.7: Continuation of SSAs in patients with carcinoid syndrome following PRRT is recommended.

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TABLE 1. Summary of Recommendations for Carcinoid Syndrome and Carcinoid Heart Disease (continued)

Topic	Recommendation
Carcinoid Crisis	3.1. Clinicians should be prepared to recognize and respond to carcinoid crisis intraoperatively with treatment as needed, for example, with vasopressors (eg, vasopressin or phenylephrine) for low blood pressure, antihypertensives for high blood pressure, and beta blockers for tachycardia. These interventions may be used in conjunction with octreotide. (Evidence quality: Moderate; Strength of recommendation: Strong)
	3.2. Although evidence is lacking, prophylactic administration of SSAs may be recommended for patients with NETs, especially those with functional symptoms undergoing surgery or other invasive procedures (eg, TAE or TACE), to prevent hemodynamic instability associated with carcinoid crisis, given the low risk associated with this therapy. (Evidence quality: Very Low; Strength of recommendation: Conditional)
Carcinoid Heart Disease	*Note:* Surgical interventions (rather than medical) are the main treatment for carcinoid heart disease.
	General Recommendation
	4.1. A multidisciplinary team approach including NET specialist oncologists, cardiologists, surgeons, anesthetists, endocrinologists, registered dieticians, palliative care specialists, and other specialties as needed is recommended along with treatment in the setting of a higher-volume NET specialty center. (Good Practice Statement)
	Screening for Carcinoid Heart Disease
	4.2. In patients with no evidence of carcinoid heart disease on the initial echocardiogram, repeat echocardiogram should be performed every 1-2 years, if there is a change in clinical status, or in the setting of a rising B-type natriuretic peptide (BNP) level. (Good Practice Statement)
	Note for Recommendation 4.2: Median levels of BNP are significantly higher in patients with CHD than in patients without CHD. BNP should be assessed at baseline and follow-up appointments for patients with carcinoid syndrome and/or high 5-HIAA with symptoms suggestive of carcinoid heart disease or right ventricular failure.
	Surgical Recommendations for Carcinoid Heart Disease
	4.3. Patients with carcinoid heart disease should be referred to cardiology at the first sign of valve involvement, prior to referral for surgery. (Good Practice Statement)
	4.4. Patients with carcinoid heart disease and severe valve regurgitation should be referred for valve surgery when they develop symptoms or evidence of right ventricular dysfunction according to echocardiography.[19] (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying statement for Recommendation 4.4: It is important to discuss disease activity and overall prognosis of the patient and the availability of systemic therapy options when considering open heart surgery for valve replacement, as this surgery may not be appropriate for patients with advanced and progressive metastatic NETs who have little or no remaining therapeutic options.
	4.5. Patent foramen ovale should be closed at the time of valve surgery.[19] (Evidence quality: Moderate; Strength of recommendation: Strong)
	4.6. Biological valve prostheses are the preferred option to offer to patients.[19] Choice of valve for repair should be at the discretion of the cardiac surgeon. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Non-Surgical Recommendations for Carcinoid Heart Disease
	4.7. Most patients with evidence of carcinoid heart disease who are not referred for operative intervention should generally have annual cardiology evaluation and echocardiography, with timing tailored to the individual patient. (Good Practice Statement)
	4.8. In patients with symptomatic right heart failure, standard treatments, including loop and/or thiazide diuretics, aldosterone antagonist therapy, and cautious fluid and salt restriction are recommended to improve symptoms.[10] (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying statement for Recommendation 4.8: These interventions must be used cautiously due to their potential to reduce cardiac output and subsequently worsen symptoms.[10]

NOTE. The strength of the recommendation is defined as follows, Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional/Weak: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; BNP, B-type natriuretic peptide; CHD, carcinoid heart disease: LAR, long-acting repeatable; NET, neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; RECHT, radioembolization-induced chronic hepatic toxicity; SIRT, selective internal radiation therapy; SSA, somatostatin analog; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization.

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systematic review of retrospective nonrandomized studies by Hofland et al,[21] SSAs were associated with reductions in diarrhea, flushing, and overall experience of symptoms by 65%, 72%, and 66% for octreotide and 65%, 69%, and 65% for lanreotide, respectively. There is a substantial potential for symptom reduction with SSAs and few associated adverse events. Gallstones are one potential long-term toxicity, and prophylactic cholecystectomy can be considered in patients undergoing abdominal surgery for other reasons.[48] Steatorrhea because of pancreatic exocrine insufficiency is also common and should be anticipated in patients on SSAs and after major pancreatic resections, and treatment should be offered if symptoms are troublesome. The Expert Panel agreed that most patients would choose this therapy as there are significant benefits and few adverse effects associated with SSAs. Resection of liver tumors in the setting of carcinoid syndrome is also recommended as debulking has been shown to have benefits in terms of symptom palliation.[40]

REFRACTORY CARCINOID SYNDROME

The SSAs octreotide and lanreotide produce a reduction in symptoms in approximately 50% of patients; however, there is a need for additional treatment options when patients are refractory, that is, their disease progresses or is no longer responding to first-line treatment with SSAs.[49] Other causes of

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TABLE 2. Summary of Recommendations for Symptom Management of Functioning Pancreatic NETs

Topic	Recommendation
General note. The following recommendations (strong or conditional) and terminology (Data Supplement) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible.	
Sequencing of Therapies	5.1. As there is no strong evidence for sequencing of interventions, patient preference and cost should be considered when choosing between therapy options. In some SSTR-positive patients starting SSAs, liver cytoreduction may be considered at the same time rather than sequentially, or debulking with surgery or embolization may be offered after failure of SSA as the next line of therapy in eligible patients. For patients with syndromic and symptomatic panNETs, upfront resection of primaries and metastases is very reasonable and may have profound symptomatic benefit.[40] (Good Practice Statement)
Chemotherapy, Targeted Therapy, or PRRT	5.2. Chemotherapy, targeted therapy, or PRRT may be offered to patients for symptom management in functioning panNETs. Chemotherapy is generally reserved for patients with bulky and/or progressive and/or high-grade disease. (Evidence quality: Low; Strength of recommendation: Conditional)
Surgery for NET Hepatic Metastases	5.3. Surgery (hepatic resection) may be offered to patients with resectable liver metastases, taking into account performance status, potential for improvement in symptoms and overall survival, and goals of care. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying statements for Recommendation 5.3 • Resection is recommended for patients with functioning tumors when ≥70% of visible disease can be debulked and the remaining liver function is adequate.[11] Outcomes are improved with more extensive debulking.[40,41] • Although surgery is effective for providing symptomatic relief, the majority of patients will experience disease progression following therapy.[42] • Parenchymal-sparing procedures of the liver are recommended where feasible to preserve functional hepatic parenchyma.[11,13]
Embolization for NET Hepatic Metastases	5.4. When surgery of liver hepatic metastases is not feasible, intra-arterial therapies, including TAE, TACE, or bland embolization, may be offered to patients. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	Qualifying statement for Recommendation 5.4: See qualifying statements for Recommendation 2.5
Thermal Ablation	5.5. Thermal ablation may be offered to patients with unresectable GEP-NET hepatic metastases, alone or in combination with surgery, when lesions are limited in size and number, and single lesions are rapidly growing. (Evidence quality: Low; Strength of recommendation: Conditional)
	Qualifying statement for Recommendation 5.5: Ablation is associated with more favorable outcomes when tumors are ≤3 cm.
Recommendations for Symptom Management of Specific Functioning Pancreatic NET Syndromes	6.1. A multidisciplinary approach is strongly recommended for treatment of patients with NET syndromes, involving an endocrinologist experienced in this area when possible. (Good Practice Statement)
	Note for Recommendation 6.1: For recommendations related to tumor cytoreduction strategies for panNET syndromes, please see Recommendations 5.3 and 5.4.
	Insulinoma
	6.2. Patient counseling (and counseling of family and friends, when appropriate) should be offered regarding the symptoms of hypoglycemia, including precipitating factors such as exercise and prolonged length of time between meals.[12,43] (Good Practice Statement)
	6.3. To control the symptoms of hypoglycemia, carbohydrate-rich meals and administration of simple carbohydrates (eg, cornstarch) at regular intervals depending on the hypoglycemia pattern are recommended.[12] (Good Practice Statement)
	6.4. If patients with insulinoma do not respond to dietary changes and supportive medication, SSAs may be added to the treatment plan, as an alternative to surgical resection or embolization, taking into account disease burden.[44] (Evidence quality: Low; Strength of recommendation: Conditional)
	Qualifying statements for Recommendation 6.4 • SSAs should only be considered for insulinoma patients who are SSTR-positive and must be used with caution and close monitoring due to the risk for worsening of hypoglycemia. Short-acting SSAs should be initiated, then once a glucose stimulating effect is observed, the patient can be started on longer-acting SSAs.[44] • Diazoxide may be offered as a bridging therapy, although there is no high-quality evidence for this intervention.[45]

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TABLE 2. Summary of Recommendations for Symptom Management of Functioning Pancreatic NETs (continued)

Topic	Recommendation
	6.5. Additional recommended measures may be offered to patients, including wearing a medic alert bracelet, continuous glucose monitoring, and stocking of glucagon for emergency situations. (Good Practice Statement)
	6.6. When insulinoma cases are refractory to SSAs, everolimus may be offered to patients.[44] (Evidence quality: Low; Strength of recommendation: Conditional)
	Gastrinoma (Zollinger-Ellison Syndrome)
	6.7. High-dose PPIs should be offered to patients for control of gastric acid secretion associated with Zollinger Ellison Syndrome.[11,12] (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying statements for Recommendation 6.7 • The PPI recommendation is for long-acting PPIs such as omeprazole (60 mg once per day) or equivalent dose of other PPI.[11] • Twice-daily therapy is recommended to protect against acute absorption problems.[12] Monitoring of vitamin B12, hypomagnesemia, and risk of bone fractures is suggested.[11]
	6.8. In addition to PPIs, SSAs should be offered to patients with gastrinoma. (Evidence quality: Low; Strength of recommendation: Conditional)
	Glucagonoma Syndrome
	6.9. The use of SSAs should be offered as first-line treatment for symptom control in patients who have glucagonoma.[12] (Evidence quality: Moderate; Strength of recommendation: Strong)
	VIPoma
	6.10. Intravenous fluids and electrolytes should be offered to patients with VIPoma and severe dehydration.[11] (Evidence quality: Moderate; Strength of recommendation: Strong)
	6.11. SSAs should be offered as first-line treatment of diarrhea associated with VIPoma. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Note for Recommendation 6.11: If using depot octreotide LAR, patients often need overlap with subcutaneous octreotide with the first few weeks to control symptoms while drug levels are rising.
	6.12. Corticosteroids may be offered for patients with refractory diarrhea following treatment with SSAs. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	Other functional pancreatic NETs syndromes (ACTHoma, somatostatinoma, PTHrP-producing NETs)
	6.13. A multidisciplinary approach is strongly recommended for treatment of patients with rare NET syndromes, involving an endocrinologist at a center with NETs expertise. (Good Practice Statement)

NOTE. The strength of the recommendation is defined as follows, Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention; Conditional/Weak: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

Abbreviations: ACTH, adrenocorticotropic hormone; GEP-NET, gastroenteropancreatic NET; LAR, long-acting repeatable; NET, neuroendocrine tumor; panNET, pancreatic neuroendocrine tumor; PPI, proton pump inhibitor; PRRT, peptide receptor radionuclide therapy; PTHrP, parathyroid hormone-related protein; SSA, somatostatin analog; SSTR, somatostatin receptor; TACE, transarterial chemoembolization; TAE, transarterial embolization; VIPoma, vasoactive intestinal peptide–secreting tumor.

TABLE 3. Summary of Recommendations for Resection of the Primary Tumor to Treat or Potentially Prevent Symptoms Related to the Primary Tumor

Topic	Recommendation
General note. The following recommendations (strong or conditional) and terminology (Data Supplement) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible.	
Palliative Resection of the Primary Tumor	7.1. Assessment for possible surgery for patients with metastatic small bowel NETs should be carried out by a surgeon who is experienced in the management of NETs.[46] (Good Practice Statement)
	7.2. For patients with small bowel NETs and metastatic disease, resection of the primary tumor may be recommended, taking into consideration factors such as the patient's performance status, tumor burden, and weighing the risk of surgical morbidity and mortality in the context of frequent long-term survival among patients with metastatic NETs.[15] (Evidence quality: Very low; Strength of recommendation: Conditional)

NOTE. The strength of the recommendation is defined as follows: Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional/Weak: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.
Abbreviation: NET, neuroendocrine tumor.

TABLE 4. Summary of Good Practice Statements for Palliative and/or End-of-Life Care

Topic	Recommendation
General note. The following statements and terminology (Data Supplement) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible.	
Palliative and/or end-of-life care	8.1. Many of the interventions recommended previously in this guideline for refractory carcinoid syndrome, carcinoid heart disease, and specific panNET syndromes can be considered in the context of palliative care, and many other measures considered for palliation toward end of life in other cancers are also applicable to NETs. (Good Practice Statement)
	8.2. Continued use of short- and long-acting SSAs should be offered for symptom palliation in patients with small bowel NETs including for patient who are not candidates for tumor-directed therapy for reasons such as performance status, medical comorbidities, or toxicity.[22] (Good Practice Statement)
	8.3. Patients may be offered symptom palliation strategies such as[22]: • Placement of percutaneous catheters to provide relief from fluid accumulation • Surgical resection, bypass, or diversion (ostomy formation) or endoscopic stenting • Biliary stenting for common bile duct obstruction to address symptoms of jaundice • Superior mesenteric vein stenting for intestinal ischemia and venous stasis of the intestine • Percutaneous J-stents for obstructive uropathy causing hydronephrosis from mesenteric fibrosis • For patients requiring para- or thoracentesis more than once a month, expert consultation should be obtained for a Denver shunt or tunneled catheter (Good Practice Statement)

Abbreviations: NET, neuroendocrine tumor; panNET, pancreatic neuroendocrine tumor; SSA, somatostatin analog.

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diarrhea should be explored and treated. The presence of refractory diarrhea in the absence of elevated blood or urine 5-HIAA should raise concerns for other diarrhea etiologies than carcinoid syndrome diarrhea, especially bile acid diarrhea. The management of bile acid diarrhea is reviewed elsewhere.[50] A figure outlining the differential diagnosis of diarrhea is included in the Data Supplement (Fig S1). [23] The options for refractory patients are outlined in Table 1 and include escalation of dosing of SSAs, telotristat ethyl, and PRRT. There is no clear recommendation currently for sequencing of treatment, but adverse events profile and feasibility are some considerations when choosing treatments beyond the first-line setting.

Dose Escalation of SSAs

The current recommended dose of long-acting octreotide is 30 mg once every 4 weeks to control diarrhea and flushing associated with carcinoid syndrome or VIPoma, after a consensus decision by a panel of experts.[51] Broder et al[33] conducted a systematic review on the topic of dose escalation of SSAs. The search covered the years 1998-2012 and included eight conference abstracts and nine full-text articles of any study design, with only one RCT among these. The only prospective comparative study looked at octreotide long-acting repeatable 30 mg once every 3 weeks *v* historical controls receiving 30 mg once every 4 weeks. Forty percent reported normalization, and 60% reported control of symptoms (flushing, diarrhea, and bronchospasm) with the higher dose. These data and other noncomparative and retrospective trials included in the review lend support for the strategy of increasing the SSA dose for patients with refractory carcinoid syndrome.[51] Based on limited evidence, the use of an increased dose of SSAs appears to improve symptoms with minimal increased risk of toxicity although there has been little study on the rate of adverse events with increased doses of SSAs.

Telotristat Ethyl (TELESTAR, TELECAST)

Carcinoid syndrome diarrhea is caused by excess secretion of serotonin from metastatic NETs. Telotristat ethyl is a

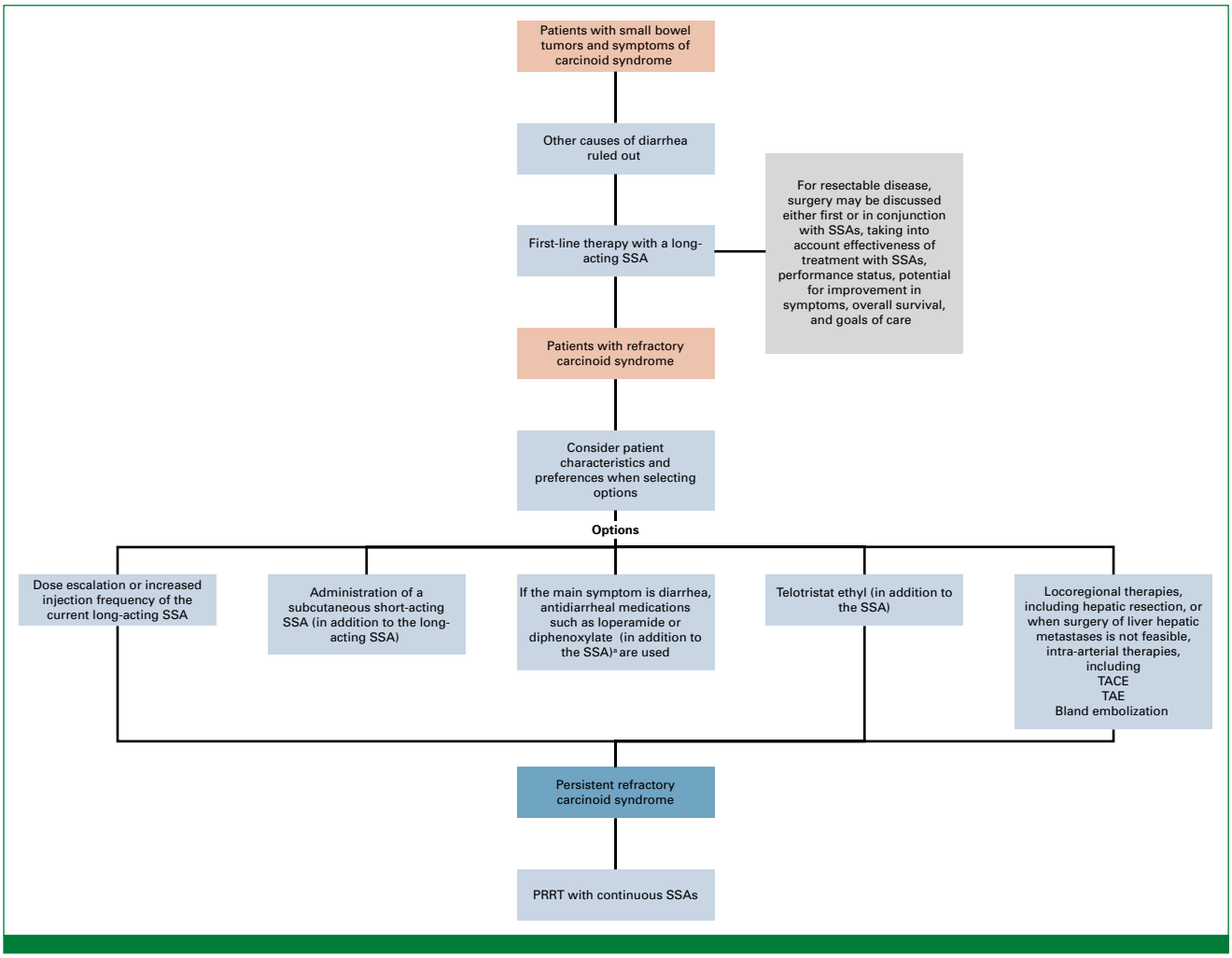

FIG 1. Symptom management of carcinoid syndrome. [a]When considering optimal antidiarrheal use, note that loperamide is approximately three times more potent milligram for milligram than diphenoxylate. PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analog; TACE, transarterial chemoembolization; TAE, transarterial embolization.

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tryptophan hydroxylase inhibitor, which is the rate-limiting enzyme in the biosynthesis of serotonin.[27] This treatment may be an option for patients with diarrhea from refractory carcinoid syndrome, based on two RCTs. In the 135-patient phase III TELESTAR trial, conducted with patients who were experiencing at least four bowel movements (BMs) per day while on SSAs, durable response was defined as a BM frequency reduction of at least 30% from baseline for at least 50% of the time.[29] Among patients with a durable response, there was a meaningful improvement in global health status, diarrhea, and pain during the 12-week double-blind treatment period.[28] There was also a modest reduction in daily BMs averaged over the 12-week double-blind treatment period.[29] Patients in these trials continued with SSAs during telotristat ethyl therapy (Data Supplement, Tables S1-S2). In the 76-patient TELECAST RCT, the safety and efficacy of telotristat ethyl for patients with symptoms of carcinoid syndrome and fewer than four BMs per day were assessed.[27] Durable responses were experienced among 40% of patients in both the telotristat ethyl 250 mg once per day group and the telotristat ethyl 500 mg once per day group, whereas no patients in the placebo group experienced a durable response. There was also a nonsignificant increase in treatment-emergent adverse events among patients treated with telotristat ethyl versus placebo in the TELECAST trial (Data Supplement, Table S3).

Peptide Receptor Radionuclide Therapy (NETTER-1)

When metastatic small bowel NETs are refractory to treatment with SSAs, another option for inoperable patients is targeted therapy with radiolabeled SSAs, called PRRT, administered once every 8 weeks for a total of four doses given intravenously. Patients in the NETTER-1 phase III trial of PRRT had metastatic tumors with SSTRs present on all target lesions and had disease progression after up to 3 years of treatment with SSAs.[24] PRRT resulted in a significant delay in deterioration of several outcomes including global health

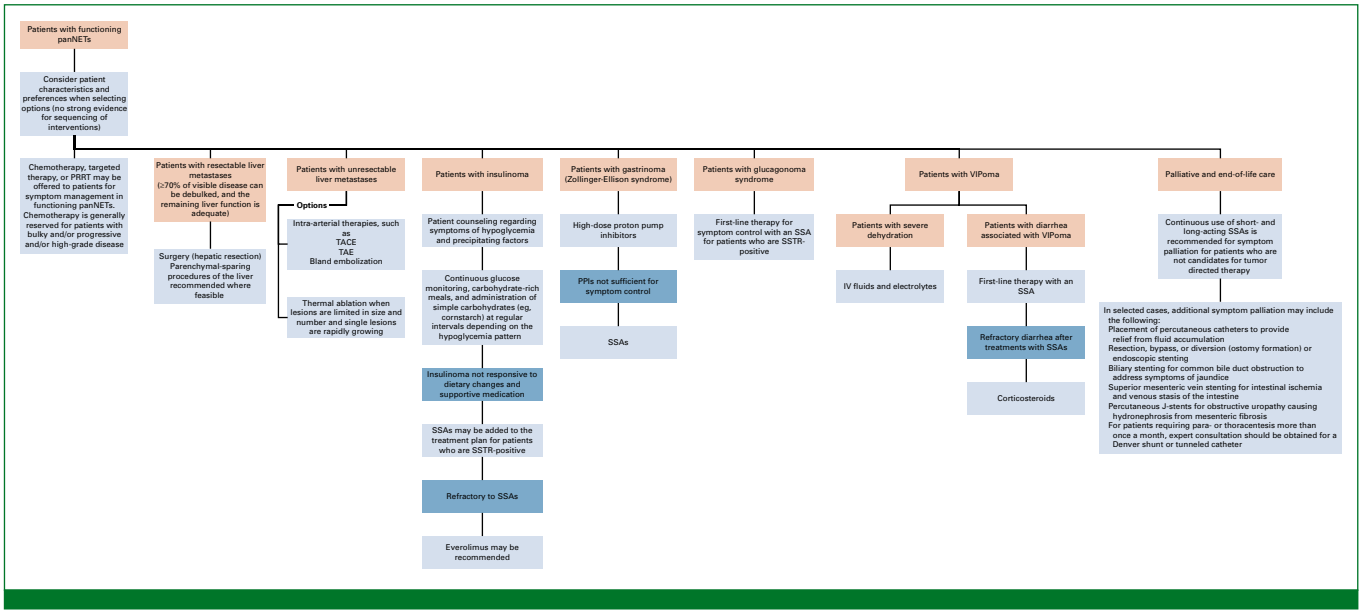

FIG 2. Symptom management of functioning pancreatic NETs. IV, intravenous; NET, neuroendocrine tumor; pan, pancreatic; PPI, proton pump inhibitor; PRRT, peptide receptor radionuclide therapy; SIRT, selective internal radiation therapy; SSA, somatostatin analog; SSTR, somatostatin receptor; TACE, transarterial chemoembolization; TAE, transarterial embolization.

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status, role functioning, physical functioning, and diarrhea. For patients with advanced progressive NETs, PRRT was associated with a median 22.7-month increase in time to deterioration in global health status. There was also a greater reduction in number of days with abdominal pain, diarrhea, and flushing for the PRRT group compared with the SSA group (Data Supplement, Table S4).[25,26] There was a significantly greater incidence of adverse events in the PRRT group (9.9% with PRRT *v* 1% with SSA). Initial nausea and vomiting in the PRRT group were attributable to amino acid infusions coadministered with ^{177}Lu-DOTATATE PRRT for the purposes of protecting the kidneys and resolved when these infusions were completed. A systematic review found that treatment-related myeloid neoplasia occurred in 2.6% of patients treated with PRRT[52]. Transient grade 3 or grade 4 neutropenia, thrombocytopenia, and lymphopenia were reported in 1%, 2%, and 9% of patients, respectively, in the PRRT group of the NETTER-1 trial.[24]

MESENTERIC FIBROSIS

Mesenteric lymph node metastases can secrete growth factors and vasopeptides that lead to mesenteric fibrosis in the surrounding tissue of the mesentery.[22,53] This condition occurs in up to 50% of patients with small intestine NETs,[22] usually arising in the terminal ileum, and can occur in patients with small tumors <1 cm.[53] There is no preventive therapy for mesenteric fibrosis.[44] Surgical resection, when possible, is the main treatment for relief of symptoms related to mesenteric fibrosis.[53] Recommendations for mesenteric fibrosis are not specifically included in this guideline as the Expert Panel considered this to be out of scope; rather, it is recommended that therapy options for patients with mesenteric fibrosis be discussed in the setting of a multidisciplinary team.

CARCINOID CRISIS

Hemodynamic instability and other symptoms of carcinoid crisis can occur in patients with small bowel NETs when there is an acute release of vasoactive hormones in response to stressors during invasive procedures such as small bowel NET resection and debulking of hepatic metastases. Hormonal crisis may also occur after PRRT.[2] Carcinoid crisis is a serious condition that can result in organ dysfunction, which can lead to circulatory collapse.[13,47] There is a significant variation in the reported incidence of carcinoid crisis,[54] and there is very little available evidence for its prevention or treatment.[55] Perioperative octreotide is often used as prophylaxis at various doses and timeframes. A systematic review and meta-analysis of perioperative management of carcinoid crisis among patients undergoing an operation, with a focus on the role of preoperative octreotide, did not show a benefit of this intervention for preventing carcinoid crisis.[54] Despite this lack of evidence, prophylactic SSAs are recommended as an option because of the low risk associated with them. However, more research is needed to develop an evidence-based strategy for carcinoid crisis.[47] As noted in the ENETS guidelines, anesthetists and others should be prepared to recognize and respond to carcinoid crisis intraoperatively. Several examples of intraoperative treatment options, such as vasopressors[56] and antihypertensives, are included in Table 1. Vasopressin and phenylephrine are the most recommended vasopressors when treating carcinoid crisis although emerging data

suggest that β-adrenergic vasopressors may be used if needed.[57]

CARCINOID HEART DISEASE

Carcinoid heart disease is likely caused in part by chronically elevated levels of circulating serotonin associated with GI NETs. This involves the development of plaque-like fibrous endocardial thickening of mostly the right heart valves.[19] Carcinoid heart disease is an independent negative prognostic factor for patients with NETs that secrete serotonin. The recommendations for carcinoid heart disease contained in Table 1 draw on recommendations previously published by a multidisciplinary consensus panel in 2017[19] and the ENET guidance document for carcinoid syndrome and carcinoid heart disease.[10] Biological valves are recommended as the preferred option for patients. Note that bioprosthetic valves may develop fibrosis because of exposure to serotonin.

ACUTE SYMPTOM MANAGEMENT OF FUNCTIONING panNETs

Patients with functioning panNETs have elevated hormone levels and display the symptoms associated with a clinical syndrome. There are five main types of functioning panNETs, including insulinoma, gastrinoma, somatostatinoma, glucagonoma, and VIPoma (Table 2). Other syndromes, including those caused by growth hormone-releasing hormone (GHRHoma) and adrenocorticotropic hormone (ACTHoma), and hypercalcemia caused by excess parathyroid hormone–related protein secretion, are more rarely diagnosed. The priority for functioning panNETs is to control the hormone excess state as soon as possible,[6] even before diagnosis and staging. A summary of the syndromes associated with functioning panNETs, responsible hormonal factors, signs and symptoms, and the prevalence among functioning panNETs is included in Appendix Table A3. Interventions for acute symptom control are outlined in subsequent sections and in Table 2. The evidence base for functioning panNETs comprises lower-quality data with case reports, case series, and retrospective studies. Reduction of tumor bulk is an important intervention that can reduce the symptoms of hormonal syndromes, and these interventions are covered within the section on *Surgery and Liver-directed Therapy for NET Liver Metastases* (*NETLMs*).

Insulinoma

Insulinoma is the most common type of functional NET. Tumors with insulin-secreting cells lead to patients experiencing symptoms of hypoglycemia and recovery to normal glucose levels with glucose administration. Localized insulinomas are cured with surgery or definitive endoscopic management and have a lower incidence of metastases even if very symptomatic. Strategies to reduce metastatic tumor bulk are often prioritized for patients with insulinoma to improve quality of life (see *Surgery and Liver-directed Therapy for NETLMs*). Urgent symptom control of hypoglycemia associated with the secretion of insulin and/or proinsulin is also required.[58] Patients should be counseled about the increased risk of hypoglycemia with exercise and infrequent meals.[12] Carbohydrate-rich meals, continuous glucose monitoring, and carbohydrates (eg, cornstarch) are recommended. SSAs prevent hypoglycemia in 40%-60% of patients,[45] but should only be used in SSTR-positive patients because they can cause paradoxical hypoglycemia.[12] PRRT can effectively control hypoglycemia secondary to insulinoma and may be considered early on in the management if the hypoglycemia is refractory to SSA therapy.[59] Everolimus has been reported to effectively control hypoglycemia, but prospective trials are lacking. Pasireotide is the SSA associated with the highest rate of hyperglycemia and may therefore be considered in refractory malignant insulinoma, although data are limited,[12] and this option is not available in the United States.

Gastrinoma (Zollinger-Ellison Syndrome)

Gastrinomas are most frequently located in the duodenum (70%) or pancreas (25%). After insulinomas, gastrinomas are the second most common functioning panNET, comprising 15% of all panNETs, and are the most common type of functional NET found in the duodenum. Gastrinoma is the name for the functioning NET, whereas Zollinger-Ellison Syndrome (ZES) is the name for the associated syndrome. ZES is associated with gastric acid hypersecretion, resulting in hyperchlorhydria and severe acid-related peptic disease, abdominal pain, and diarrhea. It is often misdiagnosed as irritable bowel syndrome.[60] Diagnosis is challenging because use of proton pump inhibitors (PPIs) can improve symptoms and delay a diagnosis of NETs and because the symptoms are nonspecific.[60] Surgical resection is only successful for <50% of patients with gastrinoma in the long term.[61] SSAs have been recommended for these tumors for their antiproliferative effects.[62] The PPI recommendation is for long-acting PPIs such as omeprazole (60 mg once per day) or equivalent dose of lansoprazole, esomeprazole, pantoprazole, rabeprazole, and dexlansoprazole, once or twice a day.[11] Twice-daily therapy is recommended to protect against acute absorption problems.[12] PPIs cause prolonged inhibition of gastric acid secretion (>3-4 days) and are highly effective for inhibiting gastric acid secretion for patients with ZES and other conditions.[61] Monitoring of vitamin B12 levels is suggested because of the potential for malabsorption because of hypochlorhydria.[11,63]

Glucagonoma Syndrome

Glucagonoma syndrome (hyperglucagonemia) arises from glucagon hypersecretion by NETs in the alpha cells of the islets in the pancreas. Most cases (87%) occur in the tail or body of the pancreas.[64] Patients with glucagonoma may develop a rash known as necrolytic migratory erythema (NME) and other symptoms such as diabetes mellitus, depression, diarrhea, and deep vein thrombosis. Awareness of the condition is important to facilitate prompt treatment.[65] This rash can be resolved by surgical removal of the

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glucagonoma, but surgery is not always possible for 50% to 90% of well-differentiated glucagonomas that have already metastasized at the time of diagnosis.[64] Stabilization of glucagon levels with SSAs can result in prompt improvement in NME.[12,66] Everolimus can increase patients' glucose levels, and therefore, if this medication is being considered for tumor control in patients with glucagonoma syndrome, caution should be used and patients' glucose levels should be monitored.[11] In a study of PRRT in 34 patients with metastatic functioning G1-G2 panNETs, five of the seven patients with uncontrolled symptoms of glucagonoma experienced a symptomatic response, including decrease in skin lesions or increase in weight, and none of these patients experienced a hormonal crisis.[59]

VIPoma

VIPomas secrete VIP. The symptoms associated with this syndrome include profuse watery diarrhea, decreased potassium levels, and the absence of hydrochloric acid in gastric secretions. Sixty to eighty percent of patients with VIPomas present with metastases, and diagnosis may be delayed because of the nonspecificity of symptoms. For patients with symptomatic VIPoma, immediate patient stabilization is recommended, including rehydration, balancing electrolytes and pH, and decreasing BMs.[67] SSAs can improve symptoms by decreasing VIP plasma levels. For highly symptomatic patients, tumor debulking is recommended, preferably with surgery, but frail patients may undergo alternative therapies such as PRRT, embolization, and antisecretory therapy. Targeted therapy has shown results in terms of symptom improvement in a small number of patients who were SSTR-negative.[67]

SURGERY AND LIVER-DIRECTED THERAPY FOR NETLMs

The liver is the most common site of NET metastases. Metastatic disease is present in up to 40%-45% of patients with small bowel, large bowel, or panNETs.[16] Surgery can be used to reduce the symptom burden of NETLMs, but many patients are not candidates for surgical resection. NETLMs derive the majority of their blood supply from the hepatic artery, whereas normal liver parenchyma derives its blood supply from the portal vein.[68] Therefore, intra-arterial therapies that are delivered through the hepatic artery can be used to treat the tumor without affecting the liver itself. Surgery and intra-arterial interventions are described in subsequent sections.

Surgery of NETLMs

Surgical management of liver metastases for survival benefit and symptom control is widely recommended[2,10,13]; however, there are no RCTs comparing surgery with other interventions for functional NETs. For patients with well-differentiated NETs, when liver metastases are completely resectable and there is no extrahepatic disease, 5-year survival is approximately 60%-80% after complete resection.[69] In a systematic review of 29 studies by Saxena et al,[42] which included a mix of GI and panNETs, there was a high rate of symptomatic relief across the 17 studies reporting that outcome (median, 95%; range, 50%-100%) and the median rate of 5-year symptom-free survival was 37% (range, 15%-46%). The authors noted the heterogeneity of included studies in terms of treatment practices, disease subtypes, and patient selection. Median surgical morbidity and mortality rates were 23% (range, 3%-45%) and <1% (range, 0%-9%), respectively. Surgery may be followed by other liver-directed therapies, which are discussed subsequently.

Liver-Directed Therapy for NETLMs

Debulking of liver metastases can be performed in approximately 10% of cases because of tumor location and burden of disease. For patients who are not surgical candidates, interventions that affect the blood supply of the liver, including transarterial chemoembolization, transarterial radioembolization (with Y90 or also called selective internal radiation therapy), and bland embolization, may be considered.[68] These embolization techniques deliver agents intravascularly via a selective catheter.[69] There have been no published prospective comparative studies of these interventions with each other or with other therapies, so it is not possible to say which type of embolization is preferred. The most common side effects of these interventions are fever, abdominal pain, nausea, and vomiting. The Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver (RETNET) RCT is currently underway to study the optimal mode of embolotherapy.[70] In RETNET, the drug-eluting bead arm was closed early because of severe adverse events.[71] Thermal ablation can be considered for small liver oligometastases. This intervention can be used repeatedly and has a low side effect profile[72]; however, the evidence base for this intervention is also very sparse; a systematic review of thermal ablation included only 127 patients in the assessment of symptoms, and all these patients were part of retrospective cohorts.[72] Within this guideline, thermal ablation is recommended for patients with unresectable GEP-NET hepatic metastases, alone or in combination with surgery, when lesions are limited in size and numbers or single lesions are rapidly growing. Thermal ablation is associated with more favorable outcomes when tumors are ≤3 cm. Stereotactic body radiation therapy (SBRT) is another liver-directed treatment option that is sometimes used for patients with NETs, with an evidence base of retrospective data.[73,74] A recent report showed a profound and durable response in malignant insulinoma after SBRT to liver metastases refractory to hepatic artery embolization.[75] Histotripsy is an emerging treatment option for liver metastases although there is a lack of prospective data supporting this intervention.[17]

OTHER PALLIATIVE INTERVENTIONS

Patients with NETs might have metastatic disease with a significant symptom burden and require referral to palliative care, despite prolonged survival compared with patients

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with advanced-stage cancer in other tumor types. Palliative interventions are intended to improve quality of life while treating and managing the disease.[76] Some palliative interventions may be considered for quality-of-life improvement even when active treatment of NET is no longer pursued. Patients with NETs may experience symptoms that are not often seen in other cancers and will have unique palliative needs. Many of the interventions discussed previously are appropriate for palliative care of patients with NETs. Some additional specific good practice statements in the Palliative and/or end-of-life care topic (Table 4) are drawn from a white paper on practical considerations for palliative care in this patient population.[22]

Patients with small bowel NETs may be experiencing the symptoms of carcinoid syndrome and symptoms associated with the tumor burden and mesenteric and retroperitoneal fibrosis. With prolonged overall survival, these symptoms can be debilitating and significantly affect quality of life. Debate is ongoing regarding the role of palliative-intent surgery in the primary tumor and regional lymph nodes.[46] For patients undergoing primary surgery of small bowel NETs, the 30-day mortality is below 2% and the morbidity is lower than 20%. Resection of primary small bowel NETs in selected patients with metastatic disease may be considered when feasible to relieve existing symptoms and avoid future symptoms and for its potential survival advantage.

DISCUSSION

This guideline covers recommended treatment options for management of GEP-NET symptoms, including those from hormone excess and symptoms of tumor bulk. The overarching intention of the guideline is to raise awareness of GEP-NETs and to improve understanding of treatment options within the wider oncology community as the incidence and prevalence of GEP-NETs are increasing. This guideline draws on existing guidelines and provides a resource for treatment options for both gastroenteric NETs and panNETs. This guideline is a companion to the 2023 ASCO guideline on tumor control in the well-differentiated GEP-NET population. There is some overlap across these two ASCO guidelines as symptom progression may also be a sign of tumor progression and several interventions are recommended in both guidelines. In general, the evidence base for this guideline consisted of lower-quality evidence as the RCT evidence from three trials was limited to PRRT and telotristat ethyl. More research is needed to identify effective therapies and to define best practices in terms of treatment sequencing although this will continue to be a challenge given the relative rarity of GEP-NETs. We will continue to update this guideline and the related ASCO guideline on tumor control of GEP-NETs with new developments, such as the CABINET trial of cabozantinib for tumor control.[77]

PATIENT AND CLINICIAN COMMUNICATION

Trust is a foundational element in the relationship between doctors and their patients, especially in oncology, where it holds even greater significance. For individuals diagnosed with rare cancers, the uniqueness of their condition can shape how they view and experience trust in their health care clinicians. When trust is lacking, it can lead to poorer outcomes in cancer screening, treatment follow-through, and overall well-being. Patients with NETs often cite the subtle and uncommon nature of their illness and the limited expertise in local medical settings as factors that hinder communication and trust with their doctors. High levels of anxiety have been detected in patients with NETs.[78] To improve care of patients with NETs, focus on enhancing patient-clinician communication to build stronger trust is recommended. For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[79]

HEALTH EQUITY CONSIDERATIONS

Social determinants of health, defined by the World Health Organization as the conditions in which an individual is born, grows, lives, works, and ages, can impact the implementation and outcomes associated with ASCO's expert recommendations on best practices for prevention, screening, palliative and supportive care, and disease management for many patients with cancer.[80] A feature of NETs is the relatively nonspecific symptom profile, which can lead to misdiagnosis and prolonged time to diagnosis. A Canadian study found that the mean number of physician visits leading to an NET diagnosis ranged from 18.1 to 20.1 depending on patients' socioeconomic status. Similarly, the average number of outpatient visits among older adults with NETs in the year before diagnosis was 22, underscoring the need for adequate and accessible health care to facilitate the timely determination of a diagnosis. The relative rarity of NETs means that many practitioners working outside of high-volume NET centers will not be readily familiar with the symptoms of NETs. In this guideline, as well as a previous ASCO guideline on tumor control in NETs,[7] specialist multidisciplinary care in a higher-volume NET center is advised; however, this may not be feasible for patients in rural or remote locations. Furthermore, the resources and expertise to deliver some of the modalities used to treat NETs, such as PRRT, may not be widely available. With the incidence of NETs rising globally, and current prevalence of approximately 35 per 100,000, the challenge of meeting the needs of this population will increase and improved awareness and access to care will be needed. The goal of this guideline is to raise awareness of the symptoms of NETs, leading to more timely diagnoses and referrals to higher-volume centers.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[81,82] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[83,84]

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Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which might have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[85]

With the prolonged survival associated with NETs, there may be a significant cost associated with ongoing long-term use of SSAs. In a global survey, 50% of patients with NETs reported moderate to substantial negative effects on their finances and increased time (52%) and money (51%) spent on travel required to attend medical appointments.[86] The costs of treatment of NETs is highest during the prolonged period after diagnosis, compared with patients with colon cancer, who had higher relative costs during the diagnosis and postdiagnosis phases.[87] The white paper referenced in this guideline for palliative care interventions calls attention to the limited coverage of recommended treatments while patients are in hospice and calls on drug companies to consider accommodations for patients who need medications such as SSAs during hospice care.[22] In addition, as noted in a previous ASCO guideline on tumor control of NETs,[7] a cost-effectiveness analysis of NETs found significant gaps in the literature on resource use, cost, economics, and budget impacts and the authors call for more research in this area.[88]

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, slide sets, and clinical tools and resources, visit www.asco.org/gastrointestinal-cancer-guidelines. The Data Supplement for this guideline includes additional data tables. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

RELATED ASCO GUIDELINES

- Palliative Care for Patients with Cancer[89] (http://ascopubs.org/doi/10.1200/JCO.24.00542)
- Patient-Clinician Communication[79] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Systemic Therapy for Tumor Control in Metastatic Well-differentiated Gastroenteropancreatic Neuroendocrine Tumors[7] (http://ascopubs.org/doi/10.1200/JCO.23.01529)

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[90] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.[91-94] With the acknowledgment that ASCO guidelines may impact the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data based on gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.org, is available at www.asco.org/gastrointestinal-cancer-guidelines.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Symptom Management for Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: ASCO Guideline

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

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TABLE A1. Symptom Management for Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumor Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Kimberly Perez, MD (co-chair)	Dana-Farber Cancer Institute, Boston, MA	Medical Oncology
Jaydira Del Rivero, MD (co-chair)	Center for Cancer Research, National Cancer Institute, Bethesda, MD	Medical Oncology, Endocrinology
Junaid Arshad, MD	University of Arizona Cancer Center, Tucson, AZ	Medical Oncology
Sandip Basu, MBBS	Bhabha Atomic Research Centre, Tata Memorial Hospital Parel, Mumbai, India	Nuclear Medicine
Emily K. Bergsland, MD	University of California, San Francisco, San Francisco, CA	Medical Oncology
Jennifer A. Chan, MD, MPH	Dana-Farber Cancer Institute, Boston, MA	Medical Oncology
Chandrikha Chandrasekharan, MBBS	University of Iowa, Iowa City, IA	Medical Oncology
Callisia N. Clarke, MD, MS	Medical College of Wisconsin, Milwaukee, WI	Surgical Oncology
Heidi M. Connolly, MD	Mayo Clinic School of Medicine, Rochester, MN	Cardiology
Aman Chauhan, MD	University of Miami Health System, Miami, FL	Medical Oncology
Arvind N. Dasari, MD	MD Anderson Cancer Center, Houston, TX	Medical Oncology
Alexandra Gangi, MD	Cedars-Sinai Medical Center, Los Angeles, CA	Surgical Oncology
Erin Grady, MD	Stanford Medicine, Palo Alto, CA	Nuclear Medicine
Thorvardur R. Halfdanarson, MD	Mayo Clinic School of Medicine, Rochester, MN	Medical Oncology
Julie Hallet, MD, MSc	Sunnybrook Health Sciences Centre, Toronto, Canada	Surgical Oncology
James R. Howe, MD	University of Iowa, Iowa City, IA	Surgical Oncology
Jana Ivanidze, MD, PhD	Weill Cornell Medicine, New York, NY	Nuclear Medicine
Eva Tiensuu Janson, MD, PhD	Uppsala University Department of Medical Sciences, Uppsala, Sweden	Endocrinology
Pamela L. Kunz, MD	Yale School of Medicine, North Haven, CT	Medical Oncology
Mark A. Lewis, MD	Intermountain Healthcare, Murray, UT	Patient Representative
Josh Mailman, MBA	NorCal CarciNET Community, Oakland, CA	Patient Representative
Erik S. Mittra, MD, PhD	Oregon Health and Science University, Portland, OR	Nuclear Medicine
Nitya P. Raj, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical Oncology
Simron Singh, MD, MPH	Sunnybrook Health Sciences Centre, Toronto, Canada	Medical Oncology
Heloisa P. Soares, MD, PhD	Huntsman Cancer Center, University of Utah, Salt Lake City, UT	Medical Oncology
Michael C. Soulen, MD	Penn Medicine, Philadelphia, PA	Interventional Radiology
Jonathan R. Strosberg, MD	Moffitt Cancer Center, Tampa, FL	Medical Oncology
Namrata Vijayvergia, MD	Fox Chase Cancer Center, Philadelphia, PA	Medical Oncology
Sarah B. White, MD, MS	Medical College of Wisconsin, Milwaukee, WI	Interventional Radiology
Erin B. Kennedy, MHSc	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

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TABLE A2. Evidence Quality and Recommendation Rating Definitions

Term	Definition
Evidence quality	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Conditional/weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not
Good practice statement	Good practice statements represent the consensus of the Expert Panel and are used when high-quality indirect evidence is available, but it would not be a good use of the Expert Panel's resources to conduct a formal systematic review

NOTE. GRADE Handbook, Schünemann et al.[95]

TABLE A3. Symptoms, Signs, and Incidence of Functional panNETs

Syndrome Name	Responsible Hormonal Factors	Signs and Symptoms	Percentage in Functional panNETs
Insulinoma	Insulin	Hypoglycemic episodes	35%-40%
Zollinger-Ellison syndrome	Gastrin	Refractory peptic stomach and duodenum ulcer, diarrhea	16%-30%
Glucagonoma	Glucagon	Dermatitis with migratory necrotic erythema, diarrhea, deep vein thrombosis	<10%
VIPoma	Vasoactive intestinal peptide	Profuse watery diarrhea, hypokalemia	<10%
Somatostatinoma	Somatostatin	Subtle symptoms including diabetes mellitus, biliary stone, steatorrhea, weight loss	<5%

NOTE. Reprinted with permission from: Li et al,[96] Clin Endosc, Table 3, pp 539.
Abbreviations: panNET, pancreatic neuroendocrine tumor; VIPoma, vasoactive intestinal peptide–secreting tumor.

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