Cancer Treatment Reviews 47 (2016) 32–45

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Diagnosis and management of gastrointestinal neuroendocrine tumors: An evidence-based Canadian consensus

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ARTICLE INFO

Article history:
Received 6 May 2016
Accepted 7 May 2016

Keywords:
Neuroendocrine tumors
Gastrointestinal neoplasms
Carcinoid tumor
Malignant carcinoid syndrome
Disease management
Canadian consensus

ABSTRACT

The majority of neuroendocrine tumors originate in the digestive system and incidence is increasing within Canada and globally. Due to rapidly evolving evidence related to diagnosis and clinical management, updated guidance on the diagnosis and treatment of gastrointestinal neuroendocrine tumors (GI-NETs) are of clinical importance. Well-differentiated GI-NETs may exhibit indolent clinical behavior and are often metastatic at diagnosis. Some NET patients will develop secretory disease requiring symptom control to optimize quality of life and clinical outcomes. Optimal management of GI-NETs is in a multidisciplinary environment and is multimodal, requiring collaboration between medical, surgical, imaging and pathology specialties. Clinical application of advances in pathological classification and diagnostic technologies, along with evolving surgical, radiotherapeutic and medical therapies are critical to the advancement of patient care. We performed a systematic literature search to update our last set of published guidelines (2010) and identified new level 1 evidence for novel therapies, including telotristat etiprate (TELESTAR), lanreotide (CLARINET), everolimus (RADIANT-2; RADIANT-4) and peptide receptor radionuclide therapy (PRRT; NETTER-1). Integrating these data with the clinical knowledge of 16 multi-disciplinary experts, we devised consensus recommendations to guide state of the art clinical management of GI-NETs.

Introduction

Neuroendocrine cancers have more than doubled in incidence in the last 15 years in Canada [1] and are the second most prevalent cancer of the gastrointestinal (GI) tract. Most neuroendocrine tumors (NETs) present as, or progress to, metastatic disease with an average survival of ~3 years [1]. This is in contrast to the commonly perceived notion of NETs as slow-growing malignancies that often do not need treatment. A recent study showed that NETs

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http://dx.doi.org/10.1016/j.ctrv.2016.05.003
0305-7372/

also placed a considerable burden on patient lives (Singh et al. J Gastrointest Oncol, *in press*). Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasias arising from a variety of anatomic sites, with approximately 50% being of GI origin [1–6]. They are characterized by generally indolent but highly variable clinical behavior with tumor morphology, mitotic count and Ki-67 index being key parameters in the evaluation of each case. Although most GI-NETs are clinically non-secretory some patients present with, or develop, secretory syndromes resulting in complex symptomatologies [7]. The heterogeneity of NETs, as well as the variable clinical manifestations and disease course require multidisciplinary treatment for optimal outcomes. The complexity of care dictates the need for evidence-based guidelines integrating the most up to date clinical data.

Since the publication of the 2010 Canadian GI-NET consensus statement [8] and other international guidelines [9–11], there have been numerous advances in the diagnosis and management of GI-NETs. These include improved imaging modalities and large randomized phase III trials of systemic therapies [12–16]. We sought to update the GI-NETs Canadian consensus statement by incorporating the latest data to develop a comprehensive and practical evidence-based guide for the diagnosis and management of this disease. While this consensus statement discusses the presentation and treatment of common clinical symptoms of excessive hormone secretion, it is not exhaustive. A separate guideline was developed for pancreatic NETs [17] due to the unique biology and increasing data specific to the disease. Herein, we discuss only non-pancreatic NETs of the GI tract.

Methods

Published and presented literature was searched for original clinical studies and meta-analyses addressing the diagnosis and management of GI-NETs using the MEDLINE database (since 2005) and relevant conference databases (since 2013; Fig. 1). Search queries included the following terms: (neuroendocrine OR carcinoid) AND GI [defined as gastroenteropancreatic OR small bowel OR small intestin* OR large bowel OR large intestin* OR appendi* OR rect* OR hepatic OR liver OR gastrointestin* OR gastric OR stomach OR midgut OR foregut] and supplemented with a bibliographic review of recent reviews and guidelines (Fig. 1). Records were vetted to identify studies on imaging, diagnosis or treatment of GI-NETs.

Search findings were presented and discussed by a multidisciplinary panel of experts, including medical oncologists, surgeons, nuclear medicine physicians, interventional radiologists, endocrinologists, and pathologists at a consensus meeting held on November 5, 2015. A total of 8 lead experts prepared data summaries and, based on the best available data, minimal consensus statements were debated and final versions were endorsed through a consensus vote. The NCCN-based consensus process (Table 1) was used to assign categories of consensus for the recommendations provided, reflective of both the level of data and level of consensus. All consensus statements are Category 2A (C2A) unless otherwise indicated (Table 2).

Epidemiology

GI-NETs are uncommon, but increasing in incidence in Canada and globally [1,18,19]. Data from the Ontario Cancer Registry indicates that the incidence of NETs among adult patients in Ontario, Canada increased from 2.48 to 5.86 per 100,000 per year from 1994 to 2009, with metastatic disease documented in 20.8% at presentation and developing subsequent to diagnosis in an additional 38% [1]. Incidence was observed to increase significantly after the age of 50, peaking in those $\geqslant$71 years of age.

Diagnosis and classification

Diagnosis, classification and staging of GI-NETs involve assessment of clinical symptoms, hormone levels, expert histological review and specific imaging techniques [2,20,21].

Clinical assessment

NET symptoms may have secretory and/or non-secretory origins. Because serotonin produced by midgut GI-NETs is inactivated in the liver, the carcinoid syndrome usually occurs when serotonin secretion bypasses hepatic metabolism and reaches the systemic circulation [20,22,23], usually in the context of hepatic metastases, and may result in diffuse flushing, secretory diarrhea, and dyspnea. Other less frequent secretory syndromes can arise due to gastrinomas (diarrhea with or without peptic ulcerations), ghrelinomas (anorexia, weight loss), VIPomas (watery diarrhea, hypokalemia, acidosis), somatostatinomas (diabetes, diarrhea, steatorrhea, cholelithiasis), and neurotensinomas (edema, hypotension, cyanosis and flushing), all of which can originate from extrapancreatic locations. For non-secretory small intestinal NETs, symptomatology may arise from local–regional disease or hepatic bulk. Local–regional disease can result in episodic abdominal pain with or without obstructive symptoms due to mesenteric fibrosis or intestinal ischemia, constitutional symptoms due to lymphadenopathy and/or ascites, as well as symptomatic anemia or nutritional deficiencies due to intestinal blood loss or malabsorption. Bulky hepatic metastases can lead to progressive nausea, early satiety, pain and/or impaired liver function.

All patients should have a comprehensive functional inquiry at initial diagnosis and throughout the disease course, aiming to elucidate symptoms potentially related to a secretory syndrome and/or bulky disease. Biochemical work-up of newly-diagnosed patients should follow clinical symptomatologies with appropriate laboratory investigations to either confirm or rule out peptide hypersecretion. A 24-h urinary 5-HIAA analysis should be performed for all patients with a small intestinal primary NET, as well as those with symptoms suggestive of the carcinoid syndrome (Table 2). Chronic elevations of circulating serotonin can lead to carcinoid heart disease which is characterized primarily by right side valvular dysfunction, potentially leading to heart failure and death [7,22,24,25]. An echocardiogram is therefore recommended at diagnosis and annually for patients with biochemical evidence of serotonin excess with referral to cardiology and/or cardiac surgery as appropriate.

Pathology

Histology is always necessary to establish a NET diagnosis and core biopsies are preferred to fine needle aspiration (FNA) to optimize available material for analysis. Once histology is suggestive, confirmation of suspected GI-NETs begins with immunohistochemical (IHC) staining for low molecular weight keratins, and chromogranin, with synaptophysin staining also being supportive of the diagnosis (Fig. 2). Assessment of Ki-67 index should be performed in all cases, and within regions of highest mitotic density, given intratumoral heterogeneity and the importance of reporting disease with high proliferative capacity [26]. Automated Ki-67 labeling index (LI) methodologies are preferred over manual counts (x/1000 cells in hot spots) as they are more accurate and reproducible; however, manual counting of nuclear labeling hot spots on a printed image remains an option [27–29].

In cases where the primary NET site is unknown or the tumor is keratin negative, further IHC for common transcription factors (TTF-1, CDX-2, PDX-1, or ISL-1) and PSAP is recommended to

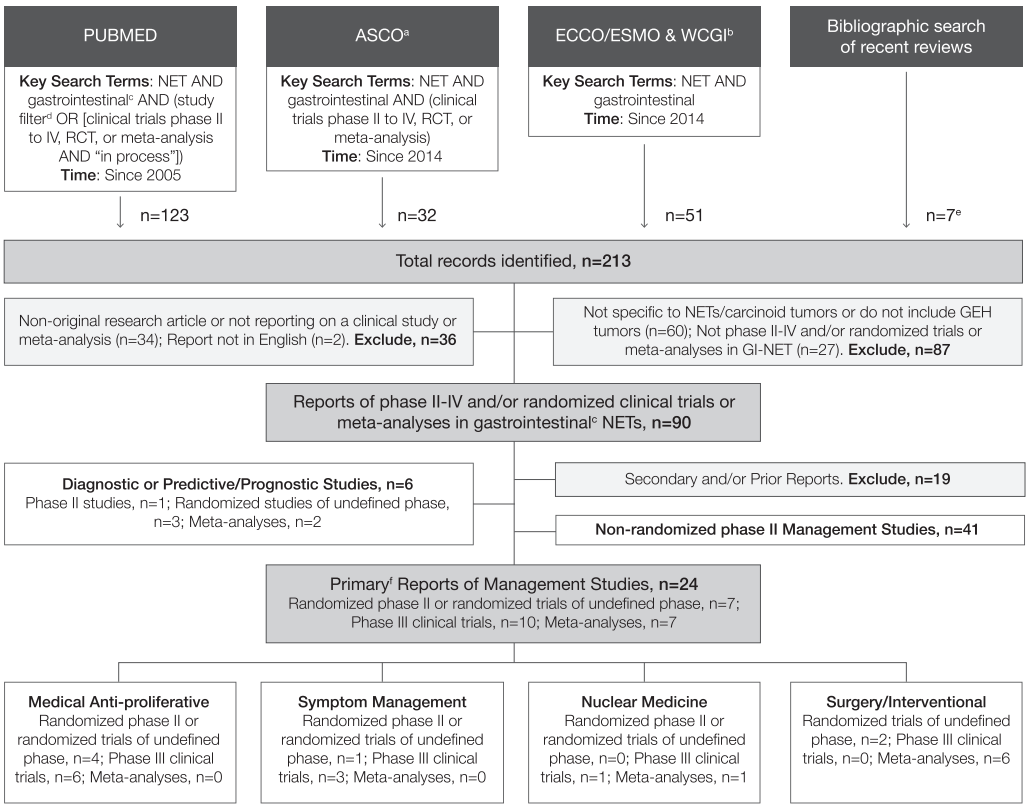

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses diagram. [a]JCO database; [b]ECCO18/ESMO2015: EJC database, ESMO2014 & WCGI2014/2015: Annals of Oncology database; [c]Does not include pancreatic; [d]Includes clinical trials phase II to IV, RCT, and meta-analysis; [e]Primary reports of eligible studies that were not identified through database search; [f]Most current reports of the primary endpoint analysis. ASCO, American Society of Clinical Oncology; CT, clinical trial; ECCO, European Cancer Congress; ESMO, European Society of Medical Oncology; EJC, European Journal of Cancer; GEH, gastroenterohepatic; NET neuroendocrine tumor; RCT, randomized controlled trial.

Table 1
NCCN-based consensus process.

Description	Supporting evidence	Level of consensus
Category 1 – Uniform consensus based on high-level evidence that the recommendation appropriate		
Based upon high-level evidence, there is uniform consensus that the intervention is appropriate	At least one convincing level I study OR at least two convincing and consistent level II studies OR at least three convincing and consistent level III studies	Uniform consensus: ⩾85% agreement
Category 2A – Uniform consensus based on lower-level evidence including clinical experience that the recommendation appropriate		
Based upon lower-level evidence, there is uniform consensus that the intervention is appropriate	At least one convincing level II study OR at least two convincing and consistent level III studies	Uniform consensus: ⩾85% agreement
Category 2B – Non-uniform consensus, but no major disagreement, based on lower level evidence including clinical experience that the recommendation appropriate		
Based upon lower-level evidence, there is consensus that the intervention is appropriate	At least one convincing level III study OR at least two convincing and consistent level IV studies	Consensus: ⩾50% but <85% agreement
Category 3 – Major disagreement that the recommendation is appropriate		
Based upon any level of evidence, a consensus on appropriate evidence cannot be reached	Level I–IV studies that are conflicting or inadequate to form a consensus	No consensus: <50% agreement

Note: All other recommendations are category 2A unless otherwise specified.

further focus the diagnosis and site of origin (Fig. 2) [30–34]. If the tumor is TTF-1 positive, IHC for calcitonin and CEA will distinguish thyroid MTC from lung NETs. If CDX-2 is positive, staining for serotonin indicates an intestinal enterochromaffin (EC) cell NET, which may also be positive for VMAT-1 and VMAT-2. IHC for gastrin (G cells), VMAT-2 (histamine-producing ECL cells) and other gastric/duodenal hormones may help to further clarify gastroduodenal NET origin. Likely pancreatic origin is suggested by ISL-1/PDX-1 positivity which is accompanied by positive IHC for pancreatic hormones. Positive PSAP staining suggests a rectal NET, and IHC for GLP-1/PP/PYY will distinguish L-cell from non-L-cell rectal NETs [35]. For tumors that are transcription factor and keratin-negative, a positive stain for tyrosine hydroxylase indicates a paraganglioma [36].

Once the primary site is known, the 2010 World Health Organization (WHO) Classification System for Ki-67 labeling index, mitotic count and differentiation should be applied to ensure consistency in nomenclature (G1–G3, NET, or NEC) [37], along with the 7th edition of AJCC Staging System to ensure staging consistency [38]. Use of the College of American Pathologist's minimum data set for NETs reporting is recommended for all resection specimens (Table 2) [39] and secondary review of specimens by a subspecialty expert should be considered to optimize reporting consistency.

Table 2
Minimal consensus statements for the diagnosis and management of GI-NETs.

Indication	Minimal consensus statements (category of consensus[a])
Diagnosis and classification	
Clinical assessment	• *NET symptoms may have secretory and/or non-secretory origins* • *All patients should have a comprehensive functional inquiry at initial diagnosis throughout the disease course and aiming to elucidate symptoms potentially related to a secretory syndrome and/or bulky disease* • *Biochemical work-up of newly-diagnosed patients should follow clinical symptomatologies with appropriate laboratory investigations to either confirm or rule out peptide hypersecretion* • *A 24-h urinary 5-HIAA analysis should be performed for all patients with a small intestinal primary NET and those with symptoms suggestive of carcinoid syndrome*
For secretory disease	The carcinoid syndrome typically arises in the context of hepatic metastases • Usually occurs when serotonin secretion bypasses hepatic metabolism and reaches the systemic circulation • May result in diffuse flushing, secretory diarrhea, and dyspnea Other less frequent secretory syndromes can originate from extrapancreatic locations and arise due to • Gastrinomas (diarrhea with or without peptic ulcerations) • Ghrelinomas (anorexia, weight loss) • VIPomas (watery diarrhea, hypokalemia, acidosis) • Somatostatinomas (diabetes, diarrhea, steatorrhea, cholelithiasis) • Neurotensinomas (edema, hypotension, cyanosis and flushing) An echocardiogram is recommended at diagnosis and annually for patients with biochemical evidence of serotonin excess, with referral to cardiology and/or cardiac surgery as appropriate
For non-secretory small intestinal NETs	For non-secretory small intestinal NETs, symptomatology may arise from local–regional disease or hepatic bulk Local–regional disease can result in episodic abdominal pain with or without • Obstructive symptoms due to mesenteric fibrosis or intestinal ischemia • Constitutional symptoms due to lymphadenopathy and/or ascites • Symptomatic anemia or nutritional deficiencies due to intestinal blood loss or malabsorption Bulky hepatic metastases can lead to progressive nausea, early satiety, pain and/or impaired liver function
Pathology	• *Histology is always necessary to establish a NET diagnosis and core biopsies are preferred to fine needle aspiration (FNA) to optimize available material for analysis* • *Use of the College of American Pathologist's minimum data set for NETs reporting[b] is recommended for all resection specimens and secondary review of specimens by a subspecialty expert should be considered to optimize reporting consistency* • *Re-biopsy is recommended for patients with newly diagnosed metastatic disease in the context of a previously resected primary tumor at time of disease recurrence*
All suspected GI-NETs	Confirmation of suspected GI-NETs begins with immunohistochemical (IHC) staining for chromogranin, low molecular weight keratins, and Ki-67 index; synaptophysin staining may also be performed Ki-67 index assessment • Should be performed in regions of highest mitotic density due to intratumoral heterogeneity and the importance of reporting disease with high proliferative capacity • Automated Ki-67 labeling index (LI) methodologies are preferred over manual counts (x/1000 cells in hot spots) as they are more accurate and reproducible; however, manual counting of nuclear labeling hot spots on a printed image remains an option
NET with known primary site	The 2010 WHO Classification System for Ki-67 labeling index, mitotic count and differentiation should be applied to ensure consistency in nomenclature (G1-G3, NET, or NEC) Use of the 7th edition of AJCC Staging System should be considered to ensure staging consistency
Primary site unknown or keratin negative	Immunohistochemistry for common transcription factors (TTF-1, CDX-2, PDX-1, or ISL-1) and PSAP is recommended to further focus the diagnosis and site of origin • If TTF-1 positive, IHC for calcitonin and CEA will distinguish thyroid MTC from lung NETs • If CDX-2 positive, staining for serotonin indicates an intestinal enterochromaffin (EC) cell NET, which may also be positive for VMAT-1 and VMAT-2 • IHC for gastrin (G cells), VMAT-2 (histamine-producing ECL cells) and other gastric/duodenal hormones may help to further clarify gastroduodenal NET origin • ISL-1/PDX-1 positivity suggests pancreatic origin, which is accompanied by positive IHC for pancreatic hormones • Positive PSAP staining suggests a rectal NET, and IHC for GLP-1/PP/PYY will distinguish L-cell from non-L-cell rectal NETs • If transcription factor and keratin negative, a positive stain for tyrosine hydroxylase indicates a paraganglioma
Imaging	*Both cross-sectional and functional imaging are important in the diagnosis and ongoing management of patients with GI-NETs*
All GI-NETs	For liver assessment, multiphasic CT or contrast enhanced MRI are options, with the latter preferred for those patients being considered for hepatic-ablative or debulking therapies ^{68}Ga somatostatin receptor PET/CT is the preferred functional imaging modality, if available ^{111}In pentetreotide SRS with SPECT/CT continues to be a reasonable functional imaging option Other imaging modalities that may be helpful in determining the origin of the primary tumor site include endoscopy, endoscopic ultrasonography (EUS) and CT or MR enterography/enteroclysis

(*continued on next page*)

Table 2 (*continued*)

Indication	Minimal consensus statements (category of consensus[a])
Disease management	
Treatment individualization, with input from a dedicated multi-disciplinary team and consideration of all options at different points along the disease trajectory, is important to optimize outcomes *Consideration of disease extent and location, tumor grade, pace of disease progression, performance status, symptomatologies, comorbidities and patient preference should all be considered and re-evaluated at each treatment decision point*	
Cytoreductive therapy for early disease	
Patients with secretory disease should be evaluated for possible pre-treatment with an SSA to prevent potential carcinoid crises	
	Disease subtype defined by clinical and pathologic features should be considered when developing a surgical plan
Gastric tumor	Whenever possible • Apply minimally invasive techniques • Preserve gastric volume and function
Small bowel tumor	Evaluate for multifocality Goal of surgery should be complete resection of the primary tumor(s) and the associated lymphatic drainage field
Appendiceal tumor	Right hemicolectomy for • Appendiceal NETs $\geqslant$ 2 cm • Appendiceal NETs < 2 cm with adverse prognostic factors[c]
Rectal tumor	Low risk tumors[d] should be treated with minimally invasive techniques that aim to preserve anal sphincter and function Higher risk tumors should be treated with total mesorectal excision
Residual disease or positive margins post primary resection	Definitive resection (including consideration of gastrointestinal function) should be considered when technically feasible
Cytoreductive therapy for metastatic or unresectable disease	
Patients with secretory disease should be evaluated for possible pre-treatment with an SSA to prevent potential carcinoid crises	
Synchronous primary and metastatic disease	Primary and regional nodal resection should be considered when feasible, to prevent future gastrointestinal complications related to mesenteric fibrosis and ischemia
Liver metastases	Resection of liver metastases with the goal of preserving liver parenchyma and both left and right inflow and outflow vascular patency, where possible, may be an option for appropriately selected patients Image-guided ablation is an option, either alone for limited disease (tumors ideally < 3 cm), or in combination with surgical resection
Hepatic disease when cytoreductive surgical/ablative procedures are not indicated[e]	Hepatic-arterial therapies are treatment options • Bland embolization • Chemoembolization • Radioembolization
Peritoneal metastases	Surgical strategies to reduce peritoneal disease bulk may be warranted, while synchronous resection of peritoneal disease with hepatic metastectomy is an option for select patients
Abdominal disease (liver, peritoneal) in the setting of extra-abdominal metastases (bone, lung, etc.)	Cytoreduction should be carefully considered for selected patients after appropriate multidisciplinary consultation and where the need for symptom control warrants an attempt at surgical debulking
Potential cholelithiasis secondary to long term SSA therapy and/or potential complications of future liver-directed therapy	Prophylactic cholecystectomy should be considered as part of any abdominal surgical procedure
Cases of Grade 1 primary NET, hepatic only metastases and no disease progression over a minimum 12-month period	Liver transplantation may be an option
Systemic therapy for metastatic or unresectable disease	
In principle, secretory and non-secretory NETs should be treated similarly, while multi-disciplinary teams should consider patient and disease characteristics, therapeutic ratios, treatment availability and cost when developing individualized treatment plans	
Non-progressive disease	For GI-NETs without evidence of carcinoid syndrome, initiation of SSA treatment or expectant management are both appropriate therapeutic options

Indication	Minimal consensus statements (category of consensus[a])
Progressive disease – treatment naive	Single agent SSAs (octreotide LAR 30 mg, i.m. q4w or lanreotide autogel 120 mg, s.c. q4w; C1)
Progressive disease on SSA therapy	Single agent use of everolimus (10 mg/day; C1)
SSR-positive disease via In-111 Octreotide or Ga-68 DOTA-TATE imaging (for PRRT)	Everolimus in combination with SSAs is an additional option Peptide receptor radionuclide therapy (PRRT) • ^{177}Lu DOTA-TATE should be considered for mid-gut NETs (C1) • ^{177}Lu DOTA-TATE is an option for other GI-NETs • If ^{177}Lu DOTA-TATE is unavailable, ^{90}Y-DOTA-octreotide is an option Patients receiving PRRT, particularly ^{90}Y-DOTA-octreotide, are at risk of kidney toxicity and amino-acid protection to reduce toxicity is required
Symptom control	
• *Supportive treatments for carcinoid syndrome-related diarrhea may include bile salt sequesters such as Questran, anti-diarrheal agents, and pancreatic enzyme replacement* • *Management of symptoms due to hepatic bulk or loco-regional disease may include pain control with narcotics, anti-nauseants, prokinetics (e.g., domperidone, maxeran), proton pump inhibitors or H2 blockers and corticosteroids* • *Psychosocial support and expert nursing care should be provided at all times throughout the disease course and referral to reputable informational websites and/or patient support groups should be encouraged*	
Systemic therapy	
Primary symptoms	Initial SSA therapy • Octreotide LAR 20–30 mg i.m., q4w • Lanreotide 120 mg deep s.c., q4wFor immediate symptom control • Short-acting octreotide 150–500 s.c., TID should be initiated and continued for two weeks after the first dose of long-acting SSA
Symptoms refractory to SSAs	• Telotristat etiprate – awaiting approval (C1) • Interferon alpha 3–5 million units s.c., three times per week, with careful attention to toxicity management • SSA dose escalation: octreotide LAR up to 60 mg q2-4w or lanreotide up to 180 mg q3w
Loco-regional therapy	
Patients who remain symptomatic in spite of SSA therapy may be considered for cytoreductive surgery and hepatic directed therapies following the same principles outlined in the Disease Management *section*	
Metastatic neuroendocrine disease with symptomatic bone and brain metastasis	External beam radiotherapy is an option
Monitoring and follow-up	
• *Regular clinical, biochemical and radiologic follow-up should be performed throughout the disease course, although optimal timing has not been defined* • *Ongoing surveillance for patients undergoing expectant management or active treatment should include cross-sectional anatomical imaging with optimal imaging protocols*	
Curative-intent surgical therapy	Regular surveillance anatomical and functional imaging, depending on which techniques were deemed useful at baseline
Metastatic disease	Assessment intervals should be individualized based on patient and disease-related factors, tumor characteristics, therapy, and goals of care For young patients (<age 40) with hepatic-only disease, MRI may be considered to minimize cumulative radiation exposure
Patients with carcinoid syndrome and risk of carcinoid heart disease	Annual echocardiography is recommended

Abbreviations: GI-NET, gastrointestinal neuroendocrine tumor; NET, neuroendocrine tumor; SSA, somatostatin analogue; SSR, somatostatin receptor; VIP, vasoactive intestinal polypeptide.

[a]Categories (C) of consensus are defined as: C1 (uniform consensus based on high-level evidence that the recommendation is appropriate); C2A (uniform consensus based on lower-level evidence, including clinical experience, that the recommendation is appropriate); C2B (non-uniform consensus, but no major disagreement, based on lower-level evidence, including clinical experience, that the recommendation is appropriate); C3 (major disagreement that the recommendation is appropriate. All recommendations in this statement are category C2A unless otherwise indicated.

[b]CAP.org; follow links for Resources & Publications; Cancer Protocols.

[c]Risk factors in consideration for right hemicolectomy after appendectomy for appendiceal NETs < 2 cm include (1) disease at base of appendix or positive luminal margin, (2) positive node in mesoappendix, (3) lymphovascular invasion of mesoappendix, (4) ENETs grade 2-3 disease.

[d]Characterized by tumor size < 1 cm, with well-differentiated morphology, a low KI-67 index and no evidence of nodal metastases on MRI.

[d]e.g., disease extent and/or location precludes surgical intervention or secretory symptoms are difficult to control with medical therapy alone.

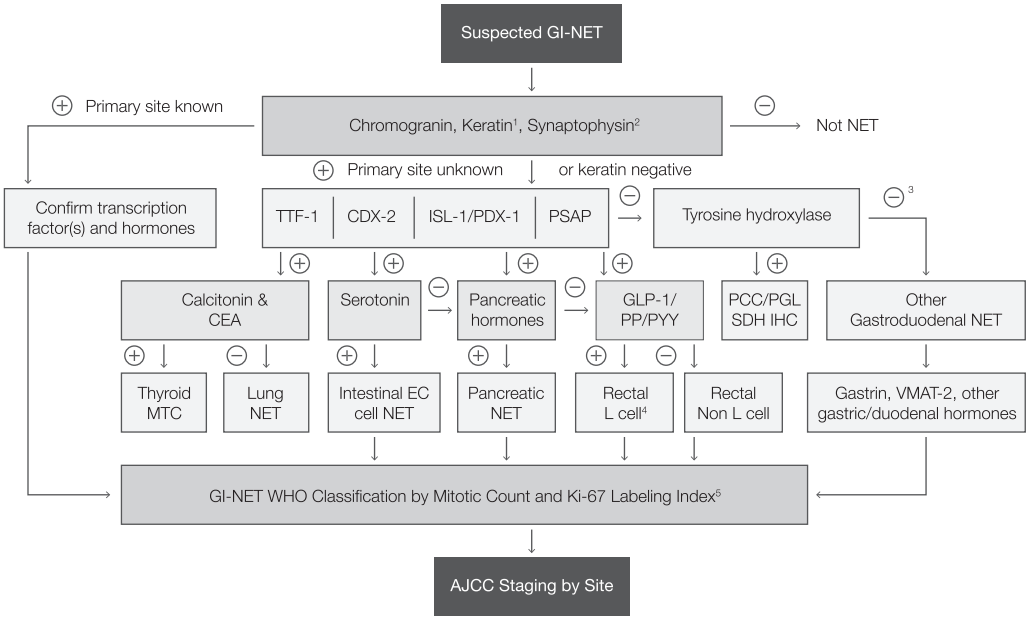

Fig. 2. Differential diagnosis of suspected non-pancreatic GI-NET. +, positive; –, negative; [1]Pan-keratin (e.g., AE1/AE3) or low molecular weight keratin (e.g., Cam 5.2); [2]Optional; [3]Some paragangliomas, especially non-functioning tumors of parasympathetic type in the head and neck, can be negative for tyrosine hydroxylase; [4]Rare proximal GI tract NETs can display L cell phenotype; [5]Ki67 labeling index can be performed as manual count of 1000 cells in hot spots but automated counts are more accurate and reproducible. Note that rare NETs are not detailed in this schematic. AJCC, American Joint Committee on Cancer; CDX-2, caudal type homeobox 2; CEA, carcinoembryonic antigen; EC, enterochromaffin; GI-NET, gastrointestinal neuroendocrine tumor; GLP-1, glucagon-like peptide-1; IHC, immunohistochemistry; ISL-1, Islet-1; MTC, medullary thyroid cancer; NET, neuroendocrine tumor; PCC, pheochromocytoma; PDX-1, pancreatic duodenal homeobox 1; PGL, paraganglioma; PP, pancreatic polypeptide; PSAP, prostate-specific acid phosphatase; PYY, peptide YY; SDH, succinate dehydrogenase; TTF-1, thyroid transcription factor-1; VMAT-1 or 2, vesicular monoamine transporter-1 or 2.

Studies have described significant and potentially clinically relevant discordance in pathological characteristics between primary tumors and metachronous metastases [40,41]. As such, re-biopsy is recommended for patients with newly diagnosed metastatic disease in the context of a previously resected primary tumor at time of disease recurrence.

Grade 3 neuroendocrine carcinomas (NECs) can include both well and poorly differentiated disease [42]. Well-differentiated NECs typically have a Ki-67 index ranging between 20% and 55%, whereas poorly differentiated large cell or small cell NECs usually have a Ki-67 index >55% [42–44]. This distinction is of clinical significance, since well-differentiated Grade 3 NECs are not as biologically or clinically aggressive as poorly differentiated NECs and are generally unresponsive to platinum-based chemotherapy [45,46]. Prospective randomized trials are underway to evaluate optimal therapy for G3 neuroendocrine neoplasms.

Imaging

Both cross-sectional and functional imaging are important in the diagnosis and ongoing management of patients with GI-NETs [47]. For liver assessment, multiphasic computed tomography (CT) or contrast enhanced magnetic resonance imaging (MRI) are options, with the latter preferred for those patients being considered for hepatic-ablative or debulking therapies given its greater sensitivity and specificity [48,49]. ^{111}In pentetreotide (Octreoscan™) imaging continues to be an important diagnostic test and serves to identify patients who may be candidates for octreotide-based peptide receptor radiotherapy (PRRT) [47]. A recent meta-analysis assessing the diagnostic performance of ^{68}Ga somatostatin receptor positron emission tomography (PET) and PET/CT has demonstrated high sensitivity (93%; 95% CI: 91–95%) and specificity (91%; 95% CI: 82–97%) for NETs, with evolving evidence that it may also aid in guiding therapy and have prognostic value [50]. ^{68}Ga somatostatin receptor PET/CT is the preferred functional imaging modality but access is limited in North America, therefore ^{111}In pentetreotide SRS with single-photon emission computerized tomography (SPECT)/CT continues to be a reasonable option as both a diagnostic and clinical management tool [51,52]. Other imaging modalities that may be helpful in determining the origin of the primary tumor site include endoscopy, endoscopic ultrasonography (EUS) and CT or magnetic resonance (MR) enterography/enteroclysis [47,53–56].

Disease management

Therapeutic interventions to be considered include surgical, loco-regional, pharmacological and nuclear systemic therapies. Treatment individualization, with input from a dedicated multidisciplinary team and consideration of all options at different points along the disease trajectory, is important to optimize outcomes. Consideration of disease extent and location, tumor grade, pace of disease progression, performance status, symptomatologies, comorbidities and patient preference should all be considered and re-evaluated at each treatment decision point.

Cytoreductive therapies

Prior to any loco-regional therapy, patients with secretory disease should be evaluated for possible pre-treatment with a somatostatin analogue (SSA) to prevent potential carcinoid crises.

Early disease

For primary gastric NETs, disease subtype defined by clinical and pathologic features should be considered when developing a surgical plan [10]. Whenever possible, minimally invasive techniques that preserve gastric volume and function should be applied [57]. Small bowel NETs should be evaluated for multifocality and

Table 3
Phase III randomized controlled trials examining systemic therapy for well to moderately differentiated unresectable or metastatic GI-NETs.

Trial	Eligibility criteria	Intervention	*n*	Median PFS (months)	⩾10% Difference any grade AEs[a] (%)	⩾5% Difference grade 3/4 AEs[b] (%)
PROMID (Rinke, 2009)	Treatment-naïve, midgut NETs, secretory/non-secretory	Octreotide LAR 30 mg i.m., q4w	42	14.3 (TTP) HR = 0.34 95% CI: 0.20–0.59 $p = 0.000072$	NA	Serious AES Any (26 vs 23) Hematopoietic system (12 vs 2) Fatigue and fever (19 vs 5)
		Placebo i.m., q4w	43	6.0 (TTP)		
CLARINET (Caplin, 2014)	Previous treatment permitted, enteropancreatic NETs, non-secretory,[1] SSR+	Lanreotide autogel 120 mg s.c., q4w	101	NR HR = 0.47 95% CI: 0.30–0.73 $p < 0.001$	Diarrhea (26 vs 9) Abdominal pain (14 vs 2)	Any serious AE (25 vs 31)
		Placebo s.c., q4w	103	18.0		
RADIANT-2 (Pavel, 2011)	Previous treatment permitted, multiple disease sites,[2], low or intermediate grade, history of secretory symptoms	Everolimus 10 mg/day p.o. + Octreotide LAR 30 mg i.m., q4w	216	16.4 HR = 0.77 95% CI: 0.59–1.00 $p = 0.026$[3]	Stomatitis (62 vs 14) Rash (37 vs 12) Diarrhea (27 vs 16) Infection (20 vs 6)	Stomatitis (7 vs 0) Thrombocytopenia (5 vs 0)
		Placebo + Octreotide LAR 30 mg i.m., q4w	213	11.3	Dysgeusia (17 vs 3) Anemia (15 vs 5) Decreased weight (15 vs 3) Thrombocytopenia (14 vs 0) Peripheral edema (13 vs 3) Hyperglycemia (12 vs 2) Dyspnoea (12 vs 1) Pulmonary events (12 vs 0)	
RADIANT-4 (Yao, 2016)	Advanced (prior treatment & treatment-naïve) lung or GI NETs, non-secretory	Everolimus 10 mg/day p.o.	205	11.0[4] HR = 0.48 95% CI: 0.35–0.67 $p < 0.00001$	Stomatitis (63 vs 19) Diarrhea (31 vs 16) Infections (29 vs 4) Rash (27 vs 8) Peripheral edema (26 vs 4)	Stomatitis (9 vs 0) Diarrhea (7 vs 2) Infections (7 vs 0)
		Placebo	97	3.9[4]	Anemia (16 vs 2) Decreased appetite (16 vs 6) Asthenia (16 vs 5) Non-infections pneumonitis (16 vs 1) Dysgeusia (15 vs 4) Cough (13 vs 3)	
NETTER-1 (Strosberg, 2015)	NETs progressing on Octreotide LAR (30 mg), midgut NETs, secretory/non-secretory, SSR+	7.4 GBq ^{177}Lu-Dotatate, q8w + Octreotide LAR 30 mg i.m., q4w	116	NR HR = 0.209 95% CI: 0.129–0.388 $p < 0.0001$	Any AE related to treatment (86 vs 31)	Any serious AE related to treatment (9 vs 1)
		Octreotide LAR 60 mg i.m., q4w	113	8.4		

Abbreviations: AE, adverse event; GI, gastrointestinal; NA, not available; NET, neuroendocrine tumor; NR, not reached; PFS, progression-free survival; SSR+, somatostatin receptor-positive; TTP, time to progression.

[a] All reported adverse events of all grades with at least 10% difference in frequency; experimental versus control arm, respectively.

[b] All reported grade 3 or 4 adverse events with at least 5% difference in frequency; experimental versus control arm, respectively.

[1] Includes gastrinomas that had been adequately controlled by means of proton-pump inhibitors for 4 months or longer.

[2] Small intestine, lung, colon, pancreas, liver, other.

[3] Analysis by central review; adjusted for two interim analyses, the pre-specified boundary at final analysis was $p \leqslant 0.0246$; Investigator review: Median PFS 12.0 vs 8.6, HR 0.78 (95% CI: 0.62–0.98, $p = 0.018$; everolimus + octreotide LAR vs placebo + octreotide LAR, respectively).

[4] Analysis by central review.

the goal of surgery should be complete resection of the primary tumor(s) and the associated lymphatic drainage field [10,58]. For appendiceal NETs, a right hemicolectomy is recommended for tumors ⩾2 cm and should be considered for smaller tumors with adverse prognostic factors including (i) disease at base of appendix or positive luminal margin, (ii) positive node in mesoappendix, (iii) lymphovascular invasion of mesoappendix, and (iv) ENETs grade 2–3 disease [10,58]. Low-risk rectal NETs, characterized by tumor size <1 cm, with well-differentiated morphology, a low Ki-67 index and no evidence of nodal metastases on MRI should be treated with minimally invasive techniques that aim to preserve anal sphincter and function, while higher risk tumors should be treated with total mesorectal excision [59]. When technically feasible, definitive resection (including consideration of gastrointestinal function) should be considered for residual disease or positive margins following incomplete primary resection.

Metastatic or unresectable disease

Surgery. Surgery plays an integral role in the management of GI-NETs even in the presence of metastatic disease [60–62]. Retrospective analyses have observed that liver-directed cytoreductive surgery can be associated with long survival times (median 125 months; overall 5- and 10-year survival of 74%, and 51%, respectively) [63], with the greatest benefit seen among those with low-volume or symptomatic high-volume disease [64]. Resection of liver metastases with the goal of preserving liver parenchyma and both left and right inflow and outflow vascular patency, where possible, may be an option for appropriately selected patients (Table 2). For synchronous primary and metastatic disease, primary and regional nodal resection should be considered when feasible, to prevent future gastrointestinal complications related to mesenteric fibrosis and ischemia. Surgical strategies to reduce peritoneal disease bulk may be warranted, while synchronous resection of peritoneal disease with hepatic metastectomy is an option for select patients (Table 2). Cytoreduction of abdominal disease (liver, peritoneal) in the setting of extra-abdominal metastases (bone, lung, etc.) should be carefully considered for selected patients after appropriate multidisciplinary consultation and where the need for symptom control warrants an attempt at surgical debulking (Table 2).

In cases where long term SSA therapy (risk of cholelithiasis) and/or liver-directed therapy (risk of gallbladder ischemia) are anticipated, prophylactic cholecystectomy should be considered as part of any abdominal surgical procedure. Finally, in cases of a resected Grade 1 primary GI-NET with hepatic only metastases and no disease progression over a minimum 12-month period, liver transplantation may be an option [21].

Ablative therapy. Liver-directed ablation either alone or in combination with surgical resection can be considered for appropriately selected patients [63,65]. Image-guided ablation is an option, either alone for limited disease (tumors ideally <3 cm), or in combination with surgical resection (Table 2).

Hepatic artery embolization. Hepatic-arterial therapy with bland or chemoembolization techniques is a well-established therapy when disease extent and/or location precludes surgical intervention or where secretory symptoms are difficult to control with medical therapy alone [66–68]. Yttrium-90 (^{90}Y) radioembolization employing glass or resin beads is a new option for hepatic-directed therapy. A prospective, multicenter phase II study evaluated the safety and dose reproducibility of ^{90}Y (glass) radioembolization in the treatment of patients with diverse liver metastases, including a relatively large cohort of patients with NETs [69] and a recent meta-analysis demonstrated an objective response rate of 50% and disease control rate of 86% [70]. Currently available data does not suggest an optimal embolization technique but all options could be considered for disease and/or symptom control (Table 2).

Systemic therapy for metastatic or unresectable disease

In principle, secretory and non-secretory NETs should be treated similarly, while multi-disciplinary teams should consider patient and disease characteristics, therapeutic ratios, treatment availability and cost when developing individualized treatment plans (Table 2). Progression free survival (PFS) has been considered an appropriate endpoint in clinical trials of NET therapies due to the extended survival periods, crossover design of recent studies and confounding effects of multiple therapies that prevent overall survival (OS) determination [71,72]. A recent meta-analysis has confirmed the use of PFS as a surrogate for OS [72,73]. Therefore, we consider PFS the primary endpoint of assessment when reviewing and recommending treatment options.

Somatostatin analogues (SSAs)

Recent data have confirmed the anti-proliferative activity of SSAs in well and moderately differentiated NETs [13,74]. The phase III PROMID trial compared octreotide LAR (30 mg) to placebo in treatment-naïve patients with midgut NETs. Time to tumor progression favored octreotide LAR with a net benefit of 8.3 months (14.3 vs 6.0 months; HR = 0.34, 95% CI: 0.20–0.59; $p = 0.000072$; Table 3) [74] with no difference in OS (84.7 vs 83.7 months; HR = 0.83, 95% CI: 0.47–1.46; $p = 0.51$) [75]. The phase III CLARINET trial compared lanreotide autogel (120 mg) to placebo in primarily treatment-naïve patients with enteropancreatic NETs and Ki-67 index <10% [13]. Median PFS (not yet reached vs 18.0 months, HR = 0.47, 95% CI: 0.30–0.73; $p < 0.001$) was significantly improved in the lanreotide arm (Table 3), with estimated PFS rates at 24 months of 65.1% and 33.0% in the lanreotide and placebo groups respectively [13]. Adverse event (AE) profiles were favorable in both trials and consistent with previously reported SSA AEs (Table 3).

Targeted therapies and biologics

Everolimus is an oral mammalian target of rapamycin (mTOR)-inhibitor which has been evaluated in multiple phase III trials of patients with advanced NETs of both GI and non-GI origin. Most recently, RADIANT-4 compared everolimus (10 mg/day) to placebo in a patient population with non-secretory lung or GI-NETs with prior SSA (53%) or chemotherapy (26%) permitted. Everolimus resulted in a net PFS benefit of 7.1 months compared to placebo (11.0 vs 3.9 months, HR = 0.48, 95% CI: 0.35–0.67; $p < 0.00001$; Table 3) [16]. The earlier RADIANT-2 trial assessed the addition of everolimus (10 mg/day) versus placebo to octreotide LAR (30 mg) in heavily pre-treated patients (prior SSA, 78%; biologics or immunotherapy, 38% or chemotherapy 46%) with metastatic, secretory, non-pancreatic NETs [14]. Everolimus resulted in a non-significant net PFS improvement of 5.1 months compared to placebo (16.4 vs 11.3 months, $p = 0.026$; Table 3). The AEs associated with everolimus alone or in combination with octreotide were consistent with the known safety profiles of these drugs (Table 3). In contrast to NETs of pancreatic origin, there is no data available supporting the use of sunitinib in GI-NETs of non-pancreatic origin. A phase II trial of pazopanib for GI-NETs demonstrated clinical activity but also substantial toxicity [76] and the addition of interferon or bevacizumab to SSAs (phase III) did not improve PFS outcomes and added toxicity compared to SSAs alone [77].

For non-progressive small bowel and other GI-NETs without evidence of carcinoid syndrome, initiation of SSAs or expectant management are both appropriate initial therapeutic options (Tables 2 and 3) [13,74]. For treatment-naïve progressive disease,

Table 4
Types of symptoms and associated approaches to symptom control for GI-NETs.

	Secretory symptoms	**Non-secretory symptoms**	
	Carcinoid syndrome *(diffuse flushing, secretory diarrhea)*	**Hepatic bulk** *(nausea, early satiety, pain)*	**Loco-regional disease** *(abdominal pain and/or obstructive symptoms due to mesenteric fibrosis or intestinal ischemia, lymphadenopathyand/or ascites)*
Systemic therapy	*Primary treatment* • Octreotide LAR 20–30 mg i.m., q4w • Lanreotide 120 mg deep s.c., q4w *Immediate symptom control* • Short-acting octreotide 150–500 s.c., TID, initiated and continued for two weeks after the first dose of long-acting SSA *Prevention or treatment of carcinoid crisis* • Octreotide 500 μg s.c. bolus then 50–100 μg/hour i.v. titrated to symptom and blood pressure control *Symptoms refractory to SSAs* • Telotristat etiprate - awaiting approval • Interferon alpha 3–5 million units s.c., three times per week* • SSA dose escalation, octreotide LAR up to 60 mg q2-4w or lanreotide up to 180 mg q3w	NA	*Primary treatment* • Octreotide LAR 20–30 mg i.m., q4w • Lanreotide 120 mg deep s.c., q4w
Surgery	• Cytoreduction of dominant hepatic disease with preservation of liver parenchyma and both left and right inflow and outflow vascular patency with goal of amelioration of secretory symptoms • Consideration of cardiology assessment and cardiac valvular surgery for carcinoid heart disease	• Cytoreduction of hepatic disease with preservation of liver parenchyma and both left and right inflow and outflow vascular patency with goal of significant debulking	• Definitive resection with consideration of residual gastrointestinal function should be considered when technically feasible
Hepatic-directed therapy	*Limited disease* • Image-guided ablation (RFA, microwave ablation) alone*Extensive disease* • Ablative therapy as an adjunct to surgery • Hepatic-arterial therapy (bland embolization, chemoembolization or radioembolization)	*Extensive disease* • Ablative therapy as an adjunct to surgery • Hepatic-arterial therapy (bland embolization, chemoembolization or radioembolization)	NA
Supportive care	*For diarrhea* • Questran • Lomotil • Pancreatic enzyme replacement • Immodium • Psychosocial support and expert nursing care	*For pain, nausea, obstructive symptoms, anorexia-cachexia syndrome, ascites* • Pain control with narcotics • Anti-nauseants • Prokinetics (e.g., domperidone, maxeran) • Proton pump inhibitors or H2 blockers • Low dose dexamethasone for anorexia-cachexia syndrome • Diuretics for ascites • Psychosocial support and expert nursing care	

Abbreviations: NA, not applicable; RFA, radiofrequency ablation; i.m., intramuscular; s.c., subcutaneous; TID, three times daily.
* With careful attention to toxicity management.

single agent SSAs (octreotide LAR 30 mg, i.m. q4w or lanreotide autogel 120 mg, s.c. q4w; Category 1 [C1]) should be considered. For patients with disease progression on SSA therapy, single agent everolimus (10 mg/day) should be considered (C1) and everolimus in combination with SSAs is an additional option (Table 3) [13,14,74,78]. There is currently no level 1 evidence informing an optimal second-line treatment strategy for disease progression on first-line therapy. Use of biologics other than everolimus should be limited to the clinical trial setting (C1; Table 2).

Peptide receptor radionuclide therapy (PRRT)

PRRT has been used for over two decades in the treatment of NETs and next generation PRRT employs ^{90}Y or ^{177}Lu labeled high-affinity SSAs (octreotide or octreotate) and more stable chelators (e.g., DOTA) [79]. The safety and efficacy of PRRT for both secretory and non-secretory GI-NETs is supported by phase I and II data [80–85], while use of ^{177}Lu-DOTA-TATE (^{177}Lu) in mid-gut, SSR-positive NETS is supported by the phase III NETTER-1 trial [15]. This trial compared ^{177}Lu delivered concurrently with standard dose (30 mg) octreotide to high dose (60 mg) octreotide LAR for patients with disease progression on standard dose octreotide. At the time of analysis, both median PFS (not yet reached vs 8.4 months, HR = 0.209; 95% CI: 0.129–0.388; $p < 0.0001$) and OS (22 vs 13 months; $p < 0.0186$) were significantly improved for patients on the ^{177}Lu arm (Table 3)[15]. PRRT with ^{177}Lu should be considered in patients with well-differentiated, SSR-positive midgut NETs with Ki-67 index $\leqslant$20% who have progressed on standard dose SSA therapy regardless of secretory status (C1) [15], and is an option for other GI-NETs. If ^{177}Lu is unavailable, use of ^{90}Y-DOTA-octreotide is also an option, although not assessed in the above trial. SSR-positivity should be established based on either ^{68}Ga-DOTA-TATE or ^{111}In pentetreotide imaging. Patients receiving PRRT, particularly ^{90}Y-DOTA-octreotide, are at risk of kidney toxicity and amino-acid protection to reduce toxicity is required (Table 2) [82,83]. The extent to which internal dosimetry can optimize therapeutic PRRT responses while limiting renal and myelotoxicities deserves further evaluation.

Symptom control

Systemic therapy

SSAs represent the first line of therapy in the management of symptomatic secretory NETs. Both short acting sub-cutaneous and long-acting octreotide (LAR) provide significant benefit in control of diarrhea and flushing associated with the carcinoid syndrome [74,86,87]. The phase III placebo-controlled ELECT trial observed a lower mean percent of days of octreotide rescue medication required by patients treated with lanreotide (overall, 34% vs 49%; $p = 0.02$) [88]. Initial therapy with SSAs, either octreotide LAR 20–30 mg i.m. q4w or lanreotide 120 mg deep s.c. q4w, is therefore an option for patients with symptomatic carcinoid syndrome (Tables 2–4) [74,87]. For patients requiring immediate symptom control, short acting octreotide 150–500 μg s.c. TID should be initiated and continued for two weeks after the first dose of long-acting SSA.

For patients with refractory diarrhea, it is important to consider causes other than tumor progression or refractory disease such as bile salt and/or fat malabsorption, intestinal hypermotility, short bowel syndrome post resection or transient viral illnesses. The TELESTAR trial compared different doses of the tyrosine hydroxylase inhibitor telotristat etiprate to placebo in patients with disease-related diarrhea not adequately controlled on SSAs. A significant reduction in frequency of bowel movements favoring the treatment arm was observed (29%, 250 mg TID; 35%, 500 mg TID; $p < 0.001$ for both doses) [12]. The response to treatment was durable in 44% and 42% of patients receiving telotristat etiprate at doses of 250 mg TID ($p = 0.011$) and 500 mg TID ($p = 0.020$), respectively, compared to 20% of those receiving placebo. Telotristat etiprate has not yet been approved for use in Canada. Other options for progressive or refractory symptoms due to carcinoid syndrome include interferon alpha 3–5 million units s.c. 3 times per week, with careful attention to toxicity management [89–91], and SSA dose escalation with octreotide LAR up to 60 mg q2-4w or lanreotide up to 180 mg q3w (Tables 2 and 4) [92,93]. Administration of pancreatic enzymes may be necessary to avoid progressive steatorrhea due to pancreatic insufficiency secondary to SSA dose escalation.

Loco-regional therapy

Patients who remain symptomatic in spite of SSA therapy may be considered for cytoreductive surgery and hepatic directed therapies (Table 4). Cytoreductive surgery should follow the same principles outlined in the *Disease Management* section of this manuscript (see also Table 2). A recent systematic review and meta-analysis of radiofrequency ablation (RFA) observed symptom improvement following RFA alone or after RFA in combination with surgery. Among patients presenting with symptoms, 92% reported improvement with a median duration of 14–27 months [94].

The role of external beam radiation in the management of patients with metastatic neuroendocrine disease is generally limited to the palliation of symptomatic bone and brain metastases (Table 2). Stereotactic body radiation therapy (SBRT) continues to evolve and may have a future role in local–regional disease management.

Supportive care

Ongoing supportive care complements all therapeutic modalities in the management of GI-NET symptomatologies. Supportive treatments for carcinoid syndrome-related diarrhea may include bile salt sequesters such as Questran, anti-diarrheal agents, and pancreatic enzyme replacement (Table 4). Management of symptoms due to hepatic bulk or loco-regional disease may include pain control with narcotics, anti-nauseants, prokinetics (e.g., domperidone, maxeran), proton pump inhibitors or H2 blockers and corticosteroids. Psychosocial support and expert nursing care should be provided at all times throughout the disease course and referral to reputable informational websites and/or patient support groups should be encouraged.

Monitoring and Follow-up

Regular clinical, biochemical and radiologic follow-up should be performed throughout the disease course, although optimal timing has not been defined (Table 2) [8].

In cases of curative-intent surgical therapy, consideration should be given to regular surveillance anatomical and functional imaging, depending on which techniques were deemed useful at baseline [8]. For patients with metastatic disease, assessment intervals should be individualized based on patient and disease-related factors, tumor characteristics, therapy, and goals of care. For young patients (<age 40) with hepatic-only disease, MRI may be considered to minimize cumulative radiation exposure. For patients with carcinoid syndrome and who therefore are at risk of developing carcinoid heart disease, annual echocardiography is recommended [8].

Ongoing surveillance for patients undergoing expectant management or active treatment should include cross-sectional anatomical imaging with optimal imaging protocols.

Summary

A multi-disciplinary approach, involving experienced and collaborative health care teams leads to optimal diagnostic, disease management and symptom control strategies for GI-NET patients. Clinical review at disease presentation and at each clinical decision point by multi-disciplinary expert care teams is essential to ensure all potential treatment and supportive care options are considered. The potential benefit of specific therapies change throughout the disease process and an iterative evaluation of options is important for each patient. Keeping abreast of new data and emerging diagnostic and treatment modalities for patients with GI-NETs is important to optimize delivery of state of the art care.

Funding

This work was supported by the Susan Leslie Fund for Neuroendocrine Tumors.

Disclosures

Simron Singh has received research funding, honorarium and acted as a consultant for Novartis, and received honorarium and acted as a consultant for Ipsen.

Sylvia Asa serves on the Medical Advisory Board of Leica Aperio.

Chris Dey has nothing to disclose.

Hagen Kennecke has received research support from Hoffman La Roche, honoraria from Ipsen, Novartis, Amgen, and Celgene, and travel funding form Amgen.

Calvin Law has served on advisory boards and received honoraria and from Novartis Oncology, Ipsen Canada and Amgen Canada.

David Laidley has nothing to disclose.

Timothy Asmis has received research funding, fellowship funding and has acted as a consultant for Novartis, and has acted as a consultant for Ipsen.

David Chan has received honoraria from Ipsen.

Shereen Ezzat has received honoraria from Ipsen, Novartis, and Pfizer.

Rachel Goodwin has received consultant honoraria from Novartis and Ipsen.

Ozgur Mete has nothing to disclose.

Janice Pasieka has nothing to disclose.

Juan Rivera has received consulting fees from Novartis, Pfizer and Ipsen.

Ralph Wong Has received consultant honoraria from Novartis and Ipsen.

Eva Segelov has received travel subsidies from Ipsen and sits on Advisory Board for Ipsen Australia.

Daniel Rayson has received meeting honoraria from Novartis and has served as an advisor for Lexicon and Ipsen.

Acknowledgements

We thank Deanna McLeod and Loretta Collins of Kaleidoscope Strategic for research and editorial assistance.

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