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

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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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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