Management of Neuroendocrine Tumors: A Meeting of Experts from Latin America


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ommendations were made based upon the collective experience of the authors. The panel recommendations were provided in light of the recognition that the appropriate management of patients with NETs of the gastrointestinal tract and pancreas requires close collaboration between specialists in multiple fields, including pathology, endocrinology, radiology/nuclear medicine, surgery, medical oncology and radiation oncology. In addition, the meeting was held with the underlying philosophy that it is often difficult to provide universal recommendations for adoption in Latin America, given the diversity of medical scenarios that are likely to be found in this world region. For this reason, some of the recommendations are provided in a broad sense, with their implementation calling for the consideration of the issues of local feasibility and affordability.

Classification of NETs

Although NETs of the gastrointestinal tract and pancreas comprise only about 2% of all malignancies, they include a number of different tumors derived from cells of the diffuse neuroendocrine system [2]. Such cells display the capacity to produce and store biogenic amines and peptides. Although different NETs are categorized together, their clinical behavior may be strikingly divergent in terms of molecular features, symptoms and outcome [3]. As a result of this heterogeneity, several classification schemes have been proposed in the last decades. The recent World Health Organization (WHO) classification now indicates five subtypes (Table 1): well-differentiated endocrine tumor, well-differentiated endocrine carcinoma, poorly differentiated endocrine carcinoma, mixed exocrine and endocrine carcinomas, and tumor-like lesions [4]. The differentiation between tumor types in the WHO classification is based on histomorphology, tumor size and the presence of local invasion and/or metastases. In the WHO classification, the term ‘carcinoid’ was retained to refer to gastrointestinal NETs that are well differentiated NETs [3]. Although this new classification of NETs is a step forward, the former classification of carcinoids into foregut, midgut and hindgut is still useful, and it will probably take some time before the new classification is widely accepted [2].

Despite the rational basis for predicting prognosis provided by the WHO classification, there is no reliable means of predicting the clinical course of patients with NETs of the gastrointestinal tract and pancreas [3]. Thus, clinicians are still left with the challenge of translating the morphologic and biologic information provided by the classification systems into clinically useful categories. Furthermore, the tumor-node-metastasis (TNM) system has not been validated for use in the overall classification of NETs of the gastrointestinal tract and pancreas. Recently, the European Neuroendocrine Tumour Society (ENETS) has proposed a TNM classification for NETs of the stomach, duodenum, and pancreas [5]. It is hoped that the WHO classification, coupled with anatomical staging systems such as TNM, and possibly incorporating molecular features [3] of NETs will provide clinicians with effective means of classification and prognostication of patients with these tumors. According to the panel, although pathologists vary significantly in their reporting of NETs, the WHO classification system should be encouraged as a useful tool in Latin-American countries. In addition, the use of the TNM classification, recently proposed by the ENETS, is also considered valuable.

### Table 1. WHO classification of NETs of the gastrointestinal tract and pancreas

<table>
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<tr>
<th>Tumor subtype</th>
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<tr>
<td>Well-differentiated endocrine tumor</td>
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<tr>
<td>Well-differentiated endocrine carcinoma</td>
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<tr>
<td>Poorly differentiated endocrine carcinoma</td>
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<tr>
<td>Mixed exocrine and endocrine carcinomas</td>
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<td>Tumor-like lesions</td>
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Diagnostic Pathology in NETs

The pathologist plays a prominent role in the management of patients with NETs. However, the pathology report may only be as good as the material and information provided by the clinician to the pathologist. Therefore, enough tissue should be obtained for analysis, along with information regarding the clinical scenario. Fine-needle aspiration biopsy is considered insufficient in most instances to provide meaningful information about the tumor. Core biopsy should be favored over fine-needle aspiration whenever possible. In some cases, a repeat biopsy is indicated, for example when there is a change in the clinical course of the disease [1]. Clinicians and organizations in Latin-American countries may find it interesting, on a local or national level, to prepare explicit instructions for the handling of clinical specimens by surgeons and health care staff. The panel considered that
macroscopic description of the tumor should be followed by light microscopic examination and immunohistochemical staining (Table 2). Other techniques, such as electron microscopy, immunofluorescent hybridization and molecular testing, should be considered when possible, but might not be widely available in Latin America. In addition, clinicians and investigators may find it useful to identify local or national referral centers for diagnosis of NETs in Latin America, such as the Argentum and GETNE working groups in Argentina and Brazil, respectively.

Among the immunohistochemical markers for NETs, chromogranin A and synaptophysin are important in delineating the neuroendocrine nature of gastrointestinal and pancreatic tumors [6], and staining for these two markers should be an integral part of pathologic evaluation. Staining for other markers, such as gastrin and glucagon, should be considered in selected patients when the clinical scenario warrants it. Immunohistochemical staining for Ki-67 is also considered an essential component of the diagnostic algorithm in NETs [7, 8]. A cutoff point of 2% has been suggested as an indication of aggressiveness [1, 7]. The panel recommends that Ki-67 staining be reported by the pathologist as a continuous variable (i.e., percent staining). Given the role of Ki-67 in terms of predicting prognosis, the ENETS has proposed a working formulation for the grading of digestive NETs based on mitotic count and on Ki-67 staining [5].

Imaging Workup

Even though close to 75% of the patients are diagnosed with localized disease, preoperative staging is important in order to identify all sites of disease and optimize treatment strategies. In some cases of NETs of the gastrointestinal tract and pancreas, the primary tumor is not found because of its small size and paucity of symptoms. Special imaging techniques should be used to identify suspected tumors, especially in the duodenum, pancreas and ileum, using dynamic computed tomography (CT) scan and magnetic resonance imaging (MRI). Endoscopic ultrasound and capsule endoscopy increase the identification of unsuspected lesions by conventional radiology, but are available only in referral centers. Colonscopy is performed to diagnose suspected colonic and rectal tumors. The use of nuclear medicine techniques to complement tumor staging should be considered in all patients prior to treatment initiation. Somatostatin receptor scintigraphy (SRS), also known as Octreoscan, is available in many Latin-American countries and uses Indium-111 radiolabeled octreotide ([111In-DPTA]-octreotide) to identify tumors that express mainly type 2 somatostatin receptors on the cell surface. A positive result on Octreoscan can be used to select patients for treatment with somatostatin analogues, including peptide-receptor radionuclide therapy. Unfortunately, the sensitivity with this method varies according to tumor type and size. Meta-iodobenzylguanidine (MIBG) is another available method recommended for catecholamine-producing tumors such as pheochromocytoma and paragangliomas [6]. MIBG is less sensitive then Octreoscan for detecting other NETs. The use of 2-[18F]-2-deoxy-D-glucose positron emission tomography may have some benefit only in poorly differentiated NETs [7]. Currently, serotonin and levodopa labeled with carbon-11 are being used with higher sensitivity in NETs [8]. The use of PET-CT with gallium 68 as a radiotracer, available only in some European countries, seems to be more sensitive in detecting unsuspected metastasis and does not depend on tumor receptor expression [9].

Surgical Approach to Patients with NETs

Surgery is the mainstay of treatment for patients with potentially curable NETs of the gastrointestinal tract and pancreas [2, 10–13]. However, adequate selection of patients is paramount in order to optimize treatment re-
colon and rectum are frequently metastatic upon diagnosis of small- and large-cell neuroendocrine carcinomas of the pancreas: (1) somatostatin analogues play a cytostatic role in indolent tumors; (2) interferon-α is commonly used notwithstanding its still undefined benefits; (3) chemotherapy regimens may play a role against some types of NETs, and (4) there is an urgent need for novel therapies.

Systemic Treatment of Patients with NETs

General Principles
The panel recommends a practical approach to patients with NETs of the gastrointestinal tract and pancreas that takes into account the clinical nature of the disease. Patients with well-differentiated tumors or islet-cell carcinomas may be categorized as having indolent disease, unless proven otherwise. Similarly, patients with poorly differentiated, anaplastic, and small-cell carcinomas, or with atypical carcinomas, may be approached initially as having aggressive disease. Several systemic modalities are currently available for the treatment of patients with indolent and aggressive NETs of the gastrointestinal tract and pancreas. Although no individual drug is sufficiently active and devoid of toxicity, the panel suggests the following general conclusions regarding systemic therapy of NETs of the gastrointestinal tract and pancreas: (1) somatostatin analogues play a cytostatic role in indolent tumors; (2) interferon-α is commonly used notwithstanding its still undefined benefits; (3) chemotherapy regimens may play a role against some types of NETs, and (4) there is an urgent need for novel therapies.

Somatostatin Analogues
High-affinity somatostatin receptors are found in approximately 90% of NETs [2]. The currently available somatostatin analogues include regular octreotide as well as long-acting formulations, such as long-acting release octreotide and lanreotide. In addition, the radiolabeled somatostatin analogue [111In-DPTA0]-octreotide (Octreoscan) is available in some major Latin-American centers. Novel analogues are under development and should be available in the future, including pasireotide (SOM230) and the radioactive analogue [177Lu-DOTA0,Tyr3]-octreotate [26]. The binding affinity to somatostatin receptors varies according to the somatostatin analogues [27], and some patients who become resistant to one agent may on occasion respond to another. In addition, dose escalation and temporary treatment interruption, with institution of interferon-α, may help circumvent resistance [2].

Somatostatin analogues play an important role in the treatment of patients with indolent tumors, especially carcinoids (well-differentiated endocrine carcinomas of
the small bowel, in the WHO classification). In these tumors, somatostatin analogues may induce symptomatic, biochemical and objective responses. The former two types of responses occur in nearly two thirds of patients, while objective responses are seen in approximately 10% of cases [2]. Therefore, patients with symptomatic tumors, and those whose metastatic disease progresses even without a clinical syndrome, are candidates for therapy with somatostatin analogues. In addition, the perioperative use of somatostatin analogues is critical in the prevention of ‘carcinoid crisis’. Currently, controversial indications for somatostatin analogues include their use after debulking procedures, the adjuvant treatment with octreotide in patients who have no evidence of residual disease, and use in the asymptomatic patient at the time of diagnosis of metastatic disease.

Despite the low response rates to somatostatin analogues, most patients with indolent tumors achieve disease stabilization during treatment [28–36]. While all currently available agents seem to be similarly effective, patient convenience should be taken into account when choosing treatment. Table 3 shows the typical schedules and mode of administration of somatostatin analogues for the treatment of NETs of the gastrointestinal tract and pancreas.

One of the limiting factors of treatment with interferon-α is toxicity, such as severe flu-like symptoms, mild depression and autoimmune phenomena [1, 2]. Therefore, the panel considers treatment with interferon-α an alternative in cases where somatostatin analogues are not available, not tolerable, or not effective. As a general rule, doses should be titrated individually according to tolerance and laboratory parameters such as the leukocyte count [2].

### Chemotherapy

Chemotherapy has an established role in the treatment of patients with several types of NETs of the gastrointestinal tract and pancreas. However, most of the current studies suffer from the limited number of patients and variable criteria for response assessment [2]. Concerning NETs of the gastrointestinal tract and pancreas, there is currently more enthusiasm with islet-cell carcinomas [41] and small-cell carcinomas [42], although patients with poorly differentiated or anaplastic carcinomas, and with atypical carcinoids, may also benefit from chemotherapy. In addition, despite the efficacy of somatostatin analogues in carcinoid tumors, the prognosis of patients with progressive, unresectable metastases is dismal, and palliative chemotherapy may be considered in these cases. Active chemotherapeutic agents include dacarbazine, doxorubicin, etoposide, fluorouracil, ifosfamide, irinotecan, platinum compounds, streptozocin, taxanes, and temozolomide. Various combinations have been investigated along the years, and the doublet fluorouracil/streptozocin has demonstrated good results in a contemporary randomized trial [43]. Moreover, the triplet fluorouracil/streptozocin/doxorubicin is active in islet-cell carcinoma [41]. However, streptozocin is not available in all Latin-American countries, and alternative regimes, such as fluorouracil/doxorubicin, or fluorouracil/epirubicin/dacarbazine [44], will need to be considered in individual cases. Finally, novel chemotherapy

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<th>Table 3.</th>
<th>Typical schedules and mode of administration of somatostatin analogues</th>
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<tr>
<td>Somatostatin analogue</td>
<td>Injection</td>
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<tr>
<td>Octreotide</td>
<td>SC</td>
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<tr>
<td>Octreotide LAR</td>
<td>IM</td>
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<tr>
<td>Lanreotide SR</td>
<td>IM</td>
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<tr>
<td>Lanreotide autogel</td>
<td>deep SC</td>
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IM = Intramuscular; LAR = long-acting release; SR = slow release; SC = subcutaneous; TID = three times a day.
regimens, such as oral temozolomide and thalidomide [45], or oral capecitabine and intravenous oxaliplatin [46], seem to be active options in some cases.

**Novel Therapies**

Given the genetic abnormalities found in NETs of the gastrointestinal tract and pancreas, several targeted agents are currently undergoing investigation in clinical trials [47]. Among these agents, the tyrosine-kinase inhibitors AMG 106, gefitinib, GW786034, imatinib, sorafenib and sunitinib, the mammalian target of rapamycin inhibitors everolimus (RAD001) and temsirolimus, and the antibody bevacizumab, are the ones with more encouraging early results so far.

**Treatment Algorithms for NETs**

One of the goals of gathering the Latin-American panel was to initiate the process of developing treatment algorithms for NETs of the gastrointestinal tract and pancreas, on the assumptions that the rarity of these tumors, the fact that only a few centers are dedicated to their management, and that new developments in diagnosis and treatment need to be rapidly disseminated in order to ensure adequate patient management. Although international guidelines are currently available [1, 48, 49], it is hoped that locally developed treatment algorithms should help expedite treatment decisions based on the best available evidence and the specific resources that are likely to be found in Latin-American countries. The panel therefore plans to develop disease- and organ-specific guidelines, a model of which is shown in figure 1.

**Follow-Up of Patients with NETs**

Follow-up of patients with NETs of the gastrointestinal tract and pancreas aims at detecting disease recurrence and second tumors, and may also help in the assessment of functional symptoms and the various medical aspects involved in the treatment of such patients. Despite the fact that evidence-based data on the optimal surveillance strategies are lacking, as a general rule, follow-up tests may include imaging studies, gastrointestinal endoscopies and serum or urinary markers such as chromogranin A and 5-hydroxyindoleacetic acid, all coupled with the clinical assessment. The panel suggests follow-up strategies for some of the specific clinical situations, as discussed in the following paragraphs.

In well-differentiated gastric tumors, surveillance with upper endoscopy should be performed every 2 years in type 1, or every year in type 2 lesions, and mucosal resection should be attempted in lesions measuring >10 mm. In patients with chronic atrophic gastritis, biopsies on flat mucosa should be done to rule out adenocarcinoma. In type 3 tumors resected with curative intent, imaging and chromogranin A should be performed every 6 months for the first 2 years and yearly for the next 3 years. In well-differentiated metastatic disease, follow-up with CT scan or MRI should be done every 3 months.

In well-differentiated, asymptomatic duodenal carcino ma resected with curative intent, the minimal suggested strategy includes upper endoscopy, CT scan and chromogranin A at 6, 24 and 36 months. In patients with metastatic disease, CT scan and chromogranin A should be done every 3–4 months, as dictated by the clinical scenario, and SRS, when available, should be performed every 12 months. Patients with gastrinoma and the multiple endocrine neoplasia type 1 (MEN-1)/Zollinger-Ellison syndrome (ZES) should be seen every 6–12 months, after control of the medical problems related to MEN-1. Typical patients with ZES should be seen yearly with tumor assessment (CT scan and/or SRS), and fasting gastrin determination.

Patients with benign or borderline asymptomatic pancreatic NETs should be followed every 12 months with CT scans (or ultrasound) and serum chromogranin A. Pancreatic tumors of uncertain behavior should be followed every 12 months with CT scans or MRI, and biochemical markers. When available, SRS is recommended at 6 months after surgery. Patients with malignant, asymptomatic pancreatic carcinoma require follow-up every 3–6 months with CT scans or MRI, and serum chromogranin A, according to the clinical scenario. In cases of insulinoma, the first follow-up after pancreatic

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![Fig. 1. Sample treatment algorithm, in this case showing the suggested management for sporadic (type III) gastric carcinoids.](image-url)
surgery for a well-differentiated tumor should take place at 3 months, followed by reassessments every 6 months for 3 years. In rare cases of symptomatic pancreatic tumors, such as VIPoma, glucagonoma, somatostatinoma, etc., the suggested follow-up includes assessment every 3–6 months in metastatic disease and yearly in patients with no metastases, using specific markers coupled with CT scan and SRS.

In poorly-differentiated NETs of the stomach, duodenum and pancreas, patients should be closely followed every 3 months with CT scans or MRI, and with biochemical markers that were positive at diagnosis. In mid-gut tumors (lower jejunum and ileum), clinical examination, ultrasound, CT scans or MRI, SRS, and chromogranin A are suggested every 4–6 months for patients with localized disease. In advanced disease, in addition to the same procedures, echocardiography once a year is considered mandatory to rule out right-sided valvular heart disease. Also, clinicians should keep in mind the risk of second tumors, including NETs, adenocarcinomas of the gastrointestinal tract, and tumors of the lung, prostate, cervix uteri, etc.

Patients who have undergone an appendectomy for a carcinoid tumor <2 cm, located in the tip of the appendix, and with no evidence of serosal invasion or lymph node metastases need no follow-up. After hemicolectomy for carcinoids or goblet cell tumors, patients should be followed annually for 5 years. The suggested follow-up immediately after surgery for patients with rectal carcinoids depends on tumor size. In tumors <1 cm, no follow-up is recommended; for tumors measuring 1–2 cm, follow-up is suggested if there is angioinvasion, muscular invasion or an atypical histology; for tumors >2 cm, routine follow-up should include CT scan or MRI, and chromogranin A if positive at baseline. In the longer term, patients undergoing resection of a rectal carcinoid should be followed with endoscopic ultrasound and chromogranin A every 6 months until 3 years, and annually thereafter.

Finally, all patients with poorly differentiated carcinomas of the hindgut should be closely followed with CT scans every 3 months. In some instances, MRI might provide better imaging of the pelvis, and could be indicated in selected cases. Furthermore, positive biochemical markers at baseline should be followed. In metastatic disease, follow-up will vary according to symptoms and the type of treatment.

Conclusions

A final role of the panel was to determine whether a Latin-American Registry of patients with NETs of the gastrointestinal tract and pancreas is in order. Although data on NETs may originate from population-based tumor registries [50–52], no such mechanism is currently in operation in Latin America. On the other hand, previous experience of some of the panel members has shown that setting and maintaining a tumor registry is feasible. Therefore, a Latin-American Registry of patients with NETs of the gastrointestinal tract and pancreas is currently planned, and should provide valuable information regarding the epidemiology and patterns of care for these tumors in this part of the world.

References


23 Costa et al.