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ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms

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Introduction

Gastric neuroendocrine neoplasms (g-NENs) represent the most frequent digestive NENs and are increasingly recognized due to expanding indications of upper gastrointestinal endoscopy. Often silent and benign, g-NENs may however be aggressive when sporadic and may sometimes mimic the course of gastric adenocarcinoma. Duodenal neuroendocrine neoplasms (d-NENs) may be sporadic or associated with multiple endocrine neoplasia type 1 (MEN-1) and present with a functional syndrome (i.e. gastrinoma with Zollinger-Ellison syndrome).

Since the last ENETS guidelines [1], new data have become available, especially focusing on g-NENs, while few changes have been reported concerning d-NENs over the last three years.

For an alphabetical list of all other Vienna Consensus Conference participants, see Appendix.

Epidemiology

New epidemiological data come from a study performed in Argentina [2], showing that g-NENs and d-NENs represent 6.9 and 2.0% of all digestive NENs, respectively. These data are similar to the SEER data, where g-NENs were found to represent 8.7% of all enteric NENs [3], and quite similar to a recent prospective Austrian study by Niederle et al. [4], where g-NENs represented 5.6% of all digestive NENs. The proportions of g-NENs with respect to the overall NEN rates do vary, however; g-NENs represented 23% of all NENs in the Austrian study compared to 6% in the SEER data, 5% in a Canadian study (Ontario) and 7.4% in a Taiwanese study [4–7]. These differences underline the need for multicenter prospective studies with long-term analysis to better describe the European epidemiology of these tumors.

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Table 1. Classification of g-NENs

	Type 1	Type 2	Type 3
Proportion among g-NENs, %	70–80	5–6	14–25
Tumor characteristics	Often small (<1–2 cm), multiple in 65% of cases, polypoid in 78% of cases	Often small (<1–2 cm) and multiple, polypoid	Unique, often large (>2 cm) polypoid and ulcerated
Associated conditions	Atrophic body gastritis	Gastrinoma/MEN-1	None
Pathology	G1–G2 NET	G1–G2 NET	G3 NEC
Serum gastrin levels	↑	↑	Normal
Gastric pH	↑↑	↓↓	Normal
Metastases, %	2–5	10–30	50–100
Tumor-related deaths, %	0	<10	25–30

Clinical and Histological Features

Well-differentiated g-NENs may be divided into three types (table 1): type 1 and 2 are ECLomas, due to chronic hypergastrinemia, associated with chronic atrophic gastritis (CAG) and Zollinger-Ellison syndrome, respectively. Type 3 g-NENs are rare and sporadic and are not a consequence of an underlying gastric mucosal abnormality; they are mostly single large lesions with a high metastatic potential and with a high grade (often G3 NEC) [8, 9]. Some issues remain open with respect to the above definitions, as well-differentiated g-NENs with a range of grades (G1–G3) not associated with CAG have been described [10–12], and thus a further distinction among type 3 g-NENs may be appropriate. Mixed gastric neoplasms as endocrine/exocrine have also been described; 68 cases have been reported in the literature so far, but no data about the patients' survival rate are available [13].

Prognosis and Survival

The overall outcome in type 1 g-NENs is universally excellent; when managed by endoscopic surveillance and lesion resection for larger lesions, recurrence-free survival of approximately 24 months can be achieved with a 100% survival rate. Data on metastatic rates for types 2 and 3 g-NENs have not significantly changed since the last ENETS guidelines [1, 14]. Similarly, no new data regarding d-NENs survival rates have been reported.

Diagnosis and Tumor Staging

Upper gastrointestinal endoscopy with careful appraisal of the tumor(s) and background gastric mucosa is still the gold standard in diagnosing g- and d-NENs. Endoscopic ultrasonography also plays a pivotal role in locoregional evaluation, but the cut-off in terms of size when defining the indication for this examination in type 1 NENs needs to be investigated. Conventional imaging techniques such as CT scan and MRI are of very limited value for small type 1 and 2 tumors of the stomach and duodenum in terms of cost/benefit ratio, while they are needed for disease staging in advanced neoplasms and in type 3 NENs. Data concerning the application of somatostatin receptor imaging (either using somatostatin receptor scintigraphy or ^{68}Ga-PET-DOTANOC) in these patients are scanty. These examinations are rarely useful for type 1 g-NENs that are invariably small and indolent, but they can be useful in type 2 and 3 g-NENs as part of the overall staging and perhaps choosing therapy [15–17]. Larger cohort studies with long-term follow-up are needed to evaluate the clinical usefulness of these tests both in g- and in d-NENs.

Treatment

In patients with type 1 g-NENs (fig. 1), conservative management strategies are to be preferred over surgery. Previously, the ENETS guidelines recommended surveillance after 1–2 years and resection for lesions ≥1 cm or those threatening the deep muscularis propria to avoid

metastatic spread. Some investigators have advocated resecting all visible lesions using biopsy forceps for small lesions and endoscopic mucosal resection (EMR) for lesions >5 mm [18, 19]; however, there are no randomized data comparing an aggressive endoscopic approach (resecting all visible tumors) to more selective endoscopic therapy (resecting only larger lesions). The overall metastatic risk is low in type 1 g-NENs and has been directly correlated with tumor size (10 mm appearing to be the cut-off) [20]. Therefore, the minimal approach should be to resect tumors ≥10 mm. Resection should be performed by experienced endoscopists in gastric tumors using either EMR or endoscopic submucosal dissection (ESD); the latter has the benefit of an en bloc resection for complete histological appraisal and has been shown effective in a total of 96 patients [21–24]. Nonetheless, EMR and ESD do carry risks of bleeding and perforation. A randomized trial comparing a less aggressive therapy to more aggressive endoscopic therapies is needed. It is also important to carefully analyze the non-involved adjacent gastric mucosa for dysplasia in a background of CAG, and mapping biopsies are recommended. For patients with type 1 tumors that are predicted T2 or with positive margins, local excision or partial gastrectomy should be discussed; surgical antrectomy to suppress hypergastrinemia and limit ECL growth is still debated [1] but rarely practiced as completeness of antrectomy remains speculative.

Somatostatin analogues (SSAs) have been used in limited series in patients with type 1 g-NENs; they do lead to regression of tumors but this has not been compared to surveillance strategies and as such cannot be recommended in early disease. SSAs might be useful to treat patients with multiple small lesions that are hard to eradicate endoscopically [25], but RCTs comparing their efficacy to endoscopic management are needed to confirm this hypothesis. Their use can be an option for patients with metastatic disease, proven SSTR2 expression and a low Ki-67 index. The gastrin receptor antagonist netazepide has been shown to have anti-proliferative properties in g-NENs in non-controlled studies [26, 27]. Again, its use cannot be universally recommended and needs to be tested in RCTs.

For type 2 g-NENs, treatment is usually dictated by the possible presence of duodenal or pancreatic NENs as part of MEN-1, and local or limited excision can be recommended, but this should be patient tailored at multidisciplinary NET centers of excellence. Netazepide is also being tested in a trial enrolling patients with type 2 neoplasms [NCT01322542].

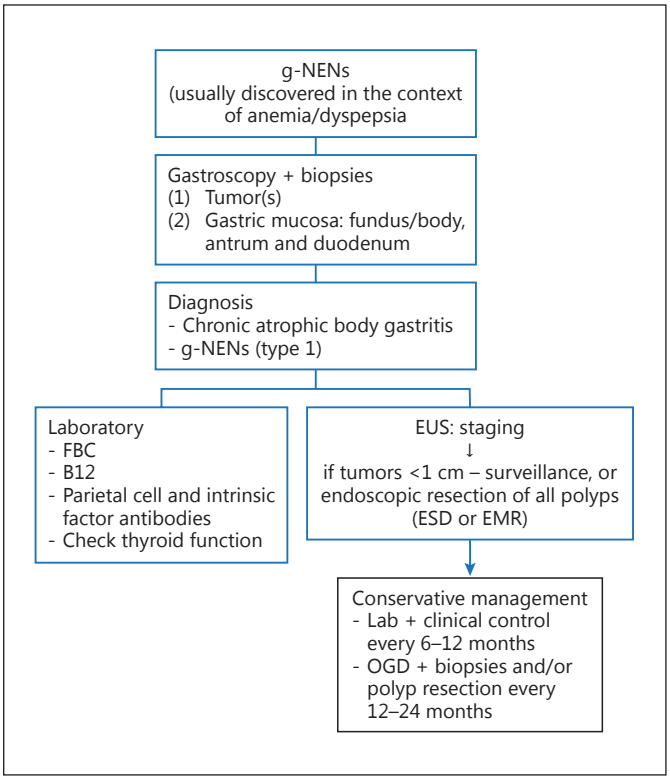

Fig. 1. Algorithm for type 1 g-NEN management. EUS = Endoscopic ultrasonography; FBC = full blood count; OGD = oesophageal gastroduodenal endoscopy.

In patients with type 3 g-NENs, while endoscopic management for small lesions has been proposed [1, 28], surgical treatment remains the recommended option and follows the strategy employed for gastric adenocarcinomas (partial or total gastrectomy with lymph node dissection). Systemic therapies are required for inoperable or stage 4 disease.

For d-NENs, endoscopic management has been proven to be safe and effective for lesions ≤10 mm in size, confined to the submucosal layer, without lymph node or distant metastasis (fig. 2). In a series of 38 patients diagnosed over a 5-year period, no recurrence was observed at a mean follow-up of 17 months, and ESD achieved a higher rate of radical excision than EMR [24]. Surgery should be performed for suspected T2 tumors or in those with positive margins after resection (local excision and antrectomy or total gastrectomy depending on tumor-histological features and invasion).

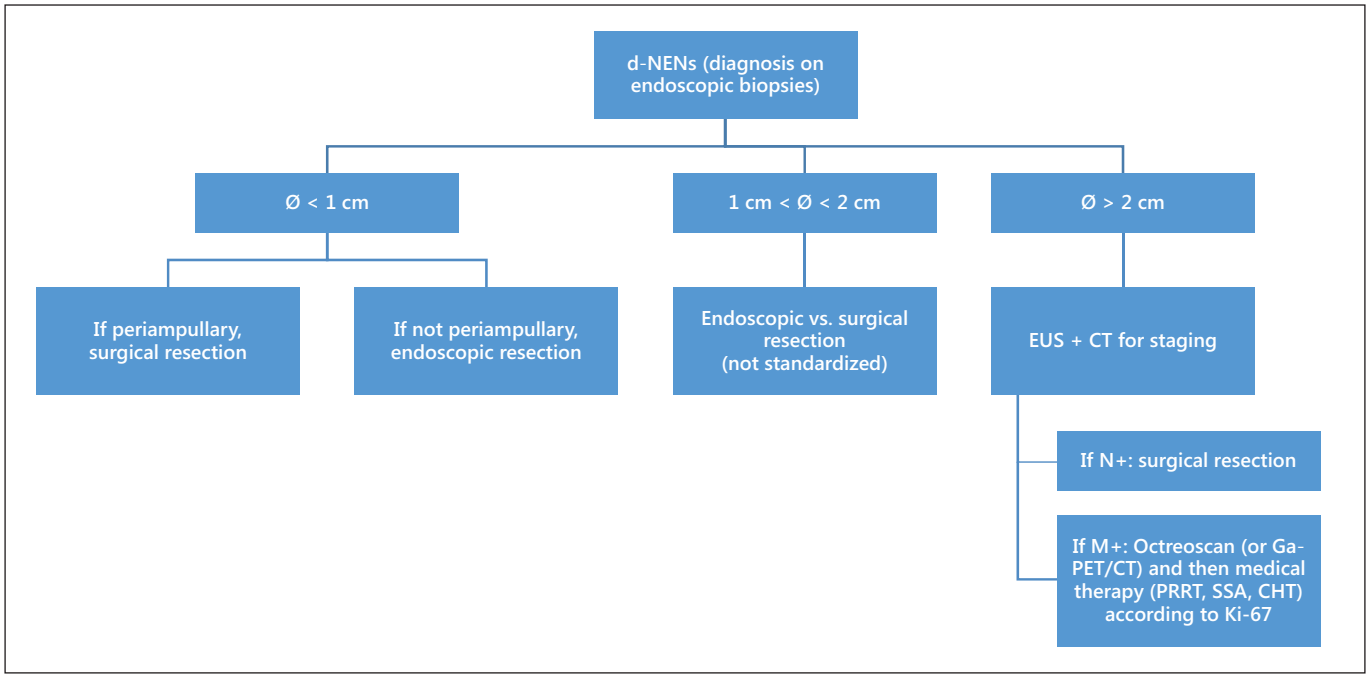

Fig. 2. Algorithm for d-NENs. EUS = Endoscopic ultrasonography; N+ = positive lymph nodes; M+ = positive for metastasis; CHT = chemotherapy.

Follow-Up

Endoscopic follow-up is recommended for patients with g- and d-NENs following excision, but the correct timing has never been defined. It is recommended that patients undergo endoscopy at least every 2 years. For type 1 g-NENs, an approach based on tumor recurrence has been proposed, but it has never been validated in prospective trials. Patients with CAG also require careful surveillance for apparition of intestinal metaplasia and dysplasia using modern endoscopic equipment [29, 30].

Please also refer to the ENETS consensus guideline updates for other gastroenteropancreatic neuroendocrine tumors [31–36, this issue].

Appendix

All Other Vienna Consensus Conference Participants

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