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STANDARDS

ENETS standardized (synoptic) reporting for endoscopy in neuroendocrine tumors

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Abstract

Despite efforts from various endoscopy societies, reporting in the field of endoscopy remains extremely heterogeneous. Harmonisation of clinical practice in endoscopy has been highlighted by application of many clinical practice guidelines and standards pertaining to the endoscopic procedures and reporting are underlined. The aim of the proposed "standardised reporting" is to (1) facilitate recognition of gastrointestinal neuroendocrine neoplasms (NEN) on initial endoscopy, (2) to enable interdisciplinary decision making for treatment by a multidisciplinary team, (3) to provide a basis for a standardised endoscopic follow-up which allows detection of recurrence or progression reliably, (4) to make endoscopic reports on NEN comparable between different units, and (5) to allow research collaboration between NEN centres in terms of consistency of their endoscopic data. The ultimate goal is to improve disease management, patient outcome and reduce the diagnostic burden on the side of the patient by ensuring the highest possible diagnostic accuracy and validity of endoscopic exams and possibly interventions.

*See the Members of the Advisory Board of the European Neuroendocrine Tumor Society (ENETS) are listed in the Appendix.

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KEYWORDS
endoscopy, neuroendocrine neoplasms, standardised reporting

1 | INTRODUCTION

1.1 | Standards in endoscopy

Despite efforts from various endoscopy societies reporting in the field of endoscopy remains extremely heterogeneous.[1–5] Quality standards in upper and lower gastrointestinal endoscopy have however been pushed forward by several societies recognising that adopting standards in reporting and documentation aims towards optimising the improved recognition and diagnosis of gastrointestinal disease and thereby improving patient outcomes.[1,3] Standardising measures for upper gastrointestinal (UGI) performance has been more challenging than for colonoscopy where several performance indices (inspection time, adenoma detection rate, and interval cancers, etc) have been identified over the last decade.[1,2,6] The European Society of Gastrointestinal Endoscopy (ESGE) in association with the American Society for Gastrointestinal Endoscopy (ASGE) elaborated a joint initiative as part of a working group for the World Congresses of Gastroenterology and Digestive Endoscopy with a major aim to devise a "minimal" list of terms that could be included within any computer system used to record the results of a gastrointestinal endoscopic examination.[3–5] It was felt that the lists should not be exhaustive but instead provide a minimal common language and a standardised reporting system among endoscopists worldwide. The system should be adaptable to various software vendors to facilitate common structure and language. Harmonisation of clinical practice in endoscopy has been highlighted by application of many clinical practice guidelines and standards pertaining to the endoscopic procedures and reporting are also underlined.[3] Minimal standard terminology (MST) for digestive endoscopy – including gastroscopy, colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP) - were prospectively validated in a large study (GASTER project) showing that MST appeared adequate to cover a large part of routine endoscopy reports, and could thus be used as a tool for standardization of endoscopic reports in clinical practice.[7] These authors argue that everyday practice could be significantly improved by the use of a structured and standardised terminology for the production of endoscopic reports.

The aim of the proposed “standardised reporting” is to (1) facilitate recognition of gastrointestinal NEN on initial endoscopy, (2) to enable interdisciplinary decision making for treatment by a multidisciplinary team MDT, (3) to provide a basis for a standardised endoscopic follow-up which allows detection of recurrence or progression reliably, (4) to make endoscopic reports on NEN comparable between different units, and (5) to allow research collaboration between NEN centres in terms of consistency of their endoscopic data. The ultimate goal is to improve disease management, patient outcome and reduce the diagnostic burden on the side of the patient by ensuring the highest possible diagnostic accuracy and validity of endoscopic exams and possibly interventions.

1.2 | Gastrointestinal neuroendocrine neoplasms

Neuroendocrine neoplasms (NEN) are rare epithelial neoplasms with an increasing incidence also probably associated with the increased use of diagnostic gastrointestinal (GI) endoscopy.[8] NENs arise mainly from the GI tract, representing about 80% of all NENs. Their behaviour and management varies according to different sites affected. The term NEN is preferred to the formerly used term - neuroendocrine tumour (NET) - as it encompasses both well-differentiated neuroendocrine tumours (NET) and poorly differentiated neuroendocrine carcinomas (NEC). The biological behaviour is often very different between NET and NEC and gastroenterologists need to be aware of these differences. It is recommended that once discovered, NEN in general should be discussed at NEN-related multidisciplinary tumour boards (MDT). Features common to GIT NEN are that they usually affect both the mucosa and submucosa and the endoscopist needs to be alerted to this in terms of both staging and management. Several important differences in primaries from each GIT site are indicated in Table 1. Pathological classification should be performed in accordance with the Union for International Cancer Control (UICC) and European Neuroendocrine Tumor Society (ENETS) staging and grading systems.[9–11] Asymptomatic NEN are frequently discovered incidentally when performing endoscopy or investigations for other reasons (this especially applies to the stomach, duodenum, pancreas and rectum). Expanding use of endoscopy especially as part of screening for upper and lower GIT neoplasms has increased the number of incidentally discovered GIT NEN and endoscopists need to be particularly aware of their presence and challenges.[12,13] Frequently, the first biopsy is performed without the beforehand knowledge of a NEN. Instead of modifying the initial endoscopy protocol, we advise repeating the endoscopy and follow the recommendations detailed in this study. Other NEN are diagnosed due to functional symptoms from overexpression and/or uncontrolled secretion of peptides or hormones causing a specific set of symptoms (or clinical syndrome, e.g., Zollinger-Ellison-syndrome of gastrinomas, or carcinoid syndrome). Expertise in NEN is always required prior to making treatment decisions. Most general gastroenterologists are not experts in GIT NEN, and the use of a standardised reporting structure should prove helpful in initial work-up and indeed subsequently surveillance when clinically relevant.

2 | METHODS

In 2018, members of the scientific advisory board of ENETS were invited to initiate a working group to provide standardised reporting

TABLE 1 General classification of neuroendocrine neoplasms of the gastrointestinal tract

GIT Site	Pathology	Frequency/incidence	Endoscopy	Outcome
Oesophageal[31–36]	Mostly high-grade neuroendocrine carcinomas (NEC), 90% small cell[a], 10% large cell High mitotic index and Ki-67	Rare (0.3%–3.8% of all oesophageal carcinomas)	Flat or exophytic lesion, ± central ulceration Mid to lower 1/3 Can be multiple nodes (>50%)	Survival: 52% at 3 years (median survival 44.9 months)
Gastric[8,11,16,17,37–43]		0.3–0.45 /100 000; Increased over 15-fold past four decades; Overall APC, 6.3%		
Gastric type 1 (histamine-producing enterochromaffin-like (ECL) cell tumours; hypergastrinaemia in autoimmune gastritis with CAG); male/female ratio (1/2.5)	Majority well differentiated, low mitotic index and grade, low Ki-67 (mostly <10%); Background gastric atrophy, ECL hyperplasia also in background, also look for intestinal metaplasia and dysplasia in background mucosa	70%–80% of all gastric NENs	Small, multiple polyps or nodules (<1–2 cm); flat, sessile, macular, ulcerated when large; associated features of atrophy[b]	Slow growing, metastatic rate 3 to 7%; 5 year DSS 98%–100%
Gastric type 2 (hypergastrinaemia in ZES and MEN-1)	Majority well differentiated, low to intermediate mitotic index and Ki-67 (mostly <10%)	6% of gastric NENs	Like type 1 but thickened gastric folds (due to ZES) and often signs of high acid related mucosal damage; duodenal NENs associated (in ZES & MEN-1)	10%–30% rate of metastasis; no accurate survival data
Gastric Type 3 (sporadic)	Well differentiated (G1–G2 or G3); Poorly differentiated NEC (G3)	15–20% of gastric NENs	Solitary, mostly antrum, sessile, normal background gastric mucosa	Metastatic rate, 70% Survival rate: median OS <12 months for metastatic and high grade; no accurate data on well-differentiated
Duodenal (gastrinomas, gangliocytic paraganglioma [GCPG], NF duodenal NENS)[26,27,44–52]	Varied pathology; mostly well differentiated; ampullary periampullary more aggressive (poorly differentiated or higher grades)	Gastrinomas, 48%; GCPG, 30%–40% NF NENs 10%–20%)	Gastrinomas, duodenal bulb (often occult even if nodal metastasis present), D1 (single; if multiple, suspect MEN-1); GCPG, sessile single ampulla, peri-ampullary ±ulceration; NF lesions (often small sessile nodules 1–2 cm)	Gastrinomas, often metastatic (60%); GCPG (nodal metastasis, 30%); NF (varied)
Small intestine Majority enterochromaffin cell (EC) cells with serotonin production (carcinoid syndrome); nonfunctional also occur[53,54]	Well differentiated. Small lesions can have metastases (node often larger than primary)	26% of all gastrointestinal well-differentiated NEN	Usually <2 cm; >70% in ileum with distal ileum most common; up to 30% multiple along small intestine; small sessile or submucosal-like terminal ileal lesion	Lymph node metastasis 36%–39% Distant metastasis 64% Survival rate
Colorectal[8,14,30,53,55-59] Colonic - EC origin	Colonic - well to poorly differentiated, moderate to high mitotic index and Ki-67	Colon incidence 0.2/100.000 (SEER data)	Right and transverse more common	Metastases >50%

(Continues)

TABLE 1 (Continued)

GIT Site	Pathology	Frequency/incidence	Endoscopy	Outcome
Rectal - L cell (GLP), pancreatic polypeptide (PP)/ peptide tyrosine (PYY) cells	Rectal - mostly well differentiated; low to intermediate mitotic index and Ki-67 (mostly <20%); occasionally higher grades; (Ki-67 >20%); Chromogranin A often absent	Rectal incidence 1.04 / 100 000 (increasing in incidence up to 9-fold in recent SEER data)	Mid to lower rectum, size usually <2 cm; varied morphology (sessile, submucosal-like, umbilicated, polypoid); Different pit pattern from adenomas or hyperplastic polyps at WLE or electronic chromoendoscopy	

Abbreviations: CAG, chronic atrophic gastritis; ECL, enterochromaffin-like cells (high gastrin result in ECL cell hyperplasia and ultimately in clustering of ECL cells into tumorlets [small ECLomas]) and eventually the development of type 1 g-NETs; MEN-1, Multiple endocrine - type 1; NF, nonfunctional; ZES, Zollinger Ellison syndrome.

[a]Tumor is also known in the literature as small cell carcinoma of the oesophagus.

[b]Gastric aspirate to check for pH useful to confirm achlorhydria.

on endoscopy for digestive NEN for initial assessment and follow-up. The group consisted of a mixed panel of gastroenterologist-NEN specialists ($n = 5$) as well as at least one pathologist, radiologist, oncologist and nuclear medicine specialist. The group considered to focus their attention on the relevant commonly encountered GIT NEN (gastric, duodenal, and rectal) primaries. Oesophageal NEN were not included as they are universally high grade and often locally advanced. Similarly small intestinal NEN were also excluded as they are rarely identified on endoscopy and management is invariably surgical.

The group made reference to previously used endoscopic lexicons[3,7] to help elaborate a common pathway to be used in standardised reporting templates for the three primary sites discussed. These templates were first presented during the annual advisory board (AB) meeting in June 2018. During this meeting, a breakout session was organised in which ENETS advisory board members representing different medical specialties deliberated on the various specific aspects of endoscopy reports and conveyed their results to the board conference attendees. All of the individual items selected were discussed in detail and the group arrived at a minimal endoscopic standardised reporting system for the three primary NEN sites. Based on discussions within the breakout subcommittee, refined templates were presented to obtain feedback, using a sequential process, firstly from the breakout group members and secondly from the larger group of entire advisory board members. The group worked iteratively, with consensus agreement to define each of the data elements and refine the structure of the report. Through this iterative process, a standardised endoscopic reporting system was developed for gastric, duodenal, and rectal NENs; one template for initial report and one for follow up purposes. For each of the templates, pull-down menus were created for distribution and testing at ENETS Centers of Excellence (CoEs).

2.1 | Gastric neuroendocrine neoplasia

Gastric neuroendocrine neoplasias (gNEN) may arise anywhere in the stomach but are most frequently found in the corpus. As in all NEN, if the proliferative capacity (WHO grade) as assessed by Ki-67-index is ≤20%, these NENs are termed neuroendocrine tumors (grade 1 or 2 *NET*) with better tumour cellular differentiation and better prognosis.[14,15] Grade 3 NENs (Ki67>20%) are either well or poorly differentiated[16]; both tend to behave aggressively, especially the poorly differentiated NECs.

Type 1 and type 2 gastric NENs result from hypergastrinaemia. Type 1 occurs in the setting of gastric atrophy, most commonly caused by autoimmune gastritis where hypochlorhydria leads to chronic gastrin elevation and ECL hyperplasia. High gastrin levels in Type 2 comes from Zollinger-Ellison in MEN-1 patients.[16–18] Gastric atrophy associated with chronic *H. pylori*-infection may also be a factor in some cases.[19–21] Both type 1 and type 2 gNEN typically arise as multiple gastric polyps (See Case Study 1 and Figure 1) or

subepithelial lesions (SEL), type 2 being quite rare while type 1 is by far the most frequent gNEN.[16–18]

Type 3 gastric NEN includes either well-differentiated grade 1 or 2 NET (this is independent from gastrin secretion) and well-differentiated grade 3 NET, or poorly differentiated (always grade 3) NEC[17]

Well-differentiated NENs often appear as rounded elevated lesions with a darker (reddish) colour and some degree of endoscopically recognizable vascularity as compared to the surrounding mucosa. Frequently, they are firm to the touch with the biopsy forceps as is typical for neoplastic subepithelial lesions (SEL). It is important to biopsy both the tumor and the adjacent non-involved gastric mucosa (both antrum and body) in order to make the tumor diagnosis but also check for the presence of chronic atrophic gastritis. (see Case Study 1 and Figure 1). The presence of multiple small (<1 cm) gastric NENs is a strong indicator of type 1 or 2 gNEN. Type 3 gNEN are invariably single and are typically larger than 1cm lesions, occurring in normal gastric mucosa. Gastric NEC can resemble ordinary gastric adenocarcinoma, as polypoid and/or ulcerated large masses (see Case Study 2 and Figure 2).

The information to be noted during endoscopic examination for standardised reporting includes:

2.2 | Characterization of gastric neoplastic lesions

a. Anatomical localization (fundus, corpus, antrum, prepyloric region, pylorus)
b. Location on the greater or lesser curvature; on the anterior or posterior wall.
c. The appearance of the lesion (round, nodular, polypoid, sessile, pedunculated, tumor mass, ulcerated, haemorrhagic); if chromoendoscopy is used, it should be noted
d. The size in mm - use an open biopsy forceps (usually 4 mm wide; please refer to your specific endoscopy equipment) for measurement.
e. The number of lesions has to be noted – If greater than 10 give a range estimate but define marker lesions precisely
f. The shape of the lesion - use the Paris classification[22]
   Ip pedunculated
   Is sessile
   IIa flat elevated
   IIb completely flat
   IIc central depression
   III ulcerated

2.3 | Characterization of surrounding gastric mucosa

a. Mucosal appearance (erythematous, oedematous, granular, nodular, atrophic)
b. Vascular translucency
c. Distribution of mucosal appearance (localised, patchy, diffuse)

After visual characterization (see Case Studies and Figures 1 and 2), a histological specimen must be obtained. If the initial mucosal specimen is not diagnostic due to subepithelial localization, additional biopsy may need to be performed either by the "mucosa incision-assisted biopsy" technique, or eventually by endoscopic ultrasound fine needle biopsy (EUS-FNB). Biopsies (at least six) of the surrounding gastric mucosa assessing for atrophic gastritis and ECL cell hyperplasia should be taken and at least two biopsies from the antrum which aids in differentiating corpus atrophic gastritis. The endoscopist should request specific histopathology criteria of NEN from the pathologist (including tumor differentiation, WHO-grade, Ki-67%-count, tissue and vascular invasion, presence of mucosal atrophy, neuroendocrine cell hyperplasia in the surrounding mucosa).

Further treatment decisions may require EUS-characterization of the primary lesion as well as lymph node status and even cross-sectional imaging or somatostatin receptor imaging for (potential) distant metastases. However, metastases are extremely rare in type 1 and rare in type 2 gNEN, in which case metastasis may be related to the primary gastrinoma in type 2 gNEN[9–11,18,23]; please refer to guidelines for further management detail.[24,25]

2.4 | Duodenal neuroendocrine neoplasia

Duodenal NEN (dNEN) are in 90% of cases lesions <2 cm in diameter.[26] gNEN, can be of all grades, although grades 1 or 2

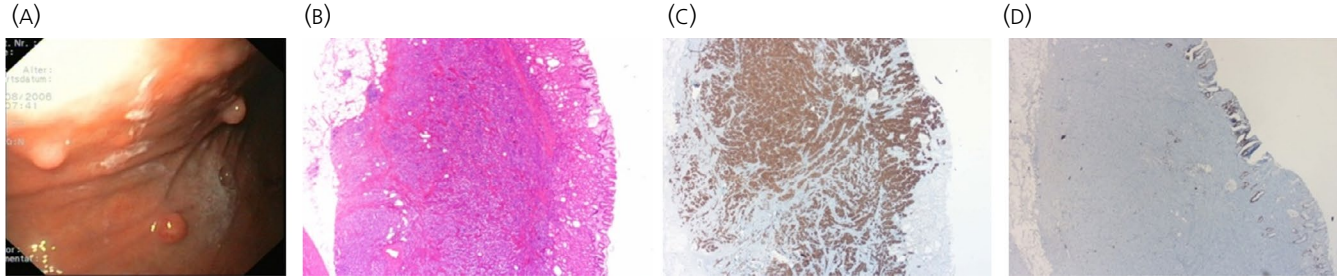

FIGURE 1 Gastric NET type 1 - refers to Case Study 1. (A) Initial endoscopy, (B) HE-stain after EMR, (C) chromogranin A- and (D) Ki67-immunohistochemistry

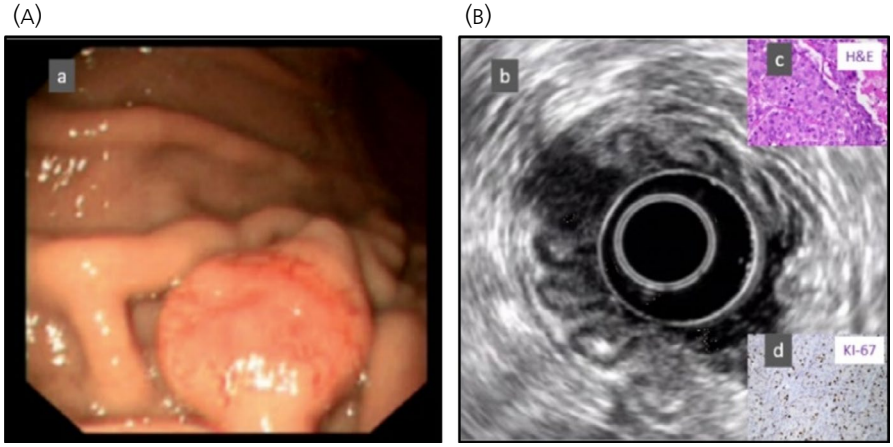

FIGURE 2 Sessile polyp corresponding to a gastric NET type 3 - refers to Case Study 2. (A) Sessile polyp (type 1s) in the mid body of stomach (corpus) measuring 2 cm and as can be seen in a background of normal gastric rugae (absence of atrophy); (B) At EUS lesion is seen to just about touch the muscularis propria and is deemed uT2 (no nodes were found). Standard biopsies with H&E (insert c) confirm NET nature with a high Ki-67 (30%) in insert d

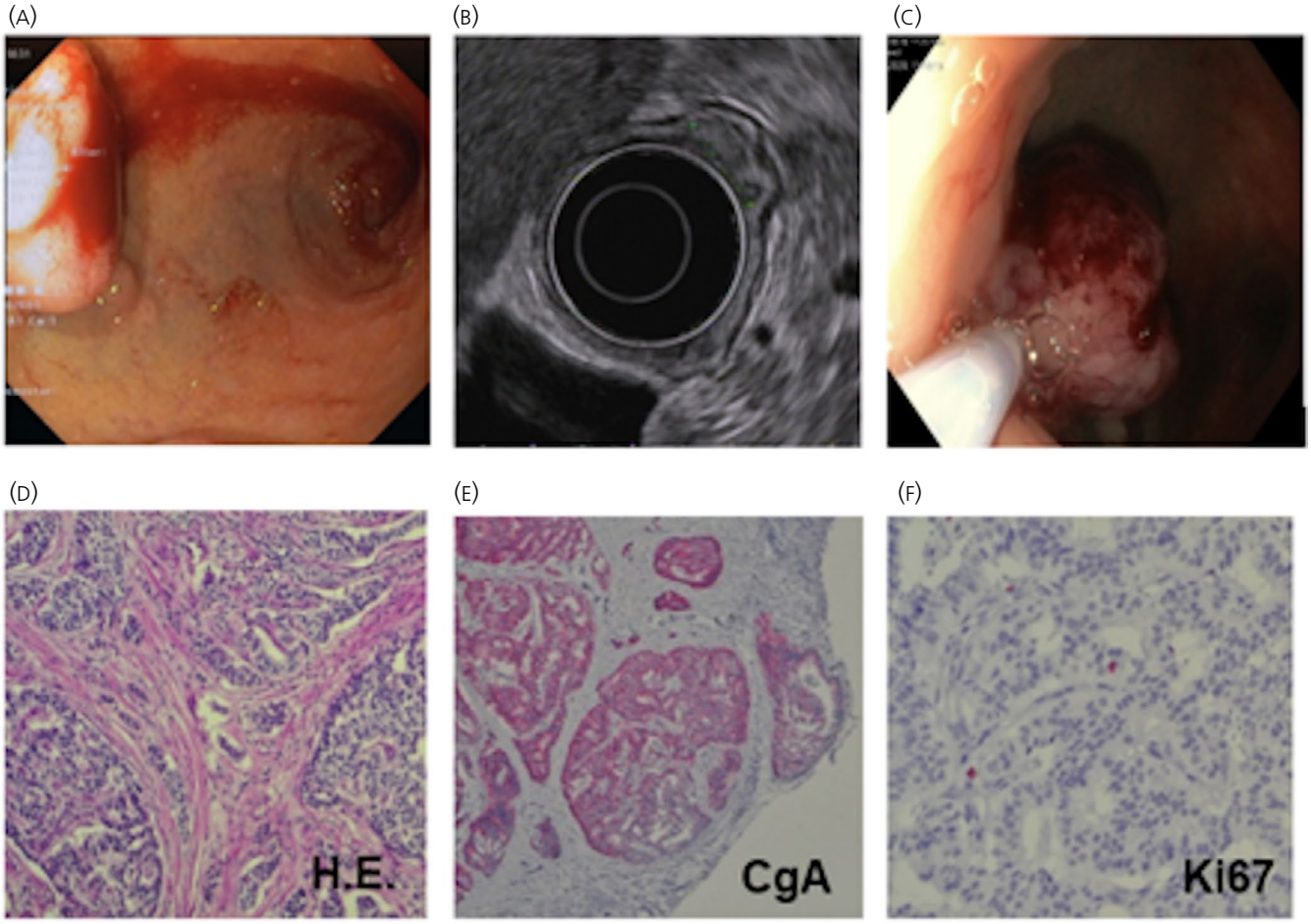

FIGURE 3 Duodenal NEN - refers to Case Study 3. (A) initial endoscopy, (B) at EUS of the polyp prior to resection, (C) at resection of the index polyp; histopathology by (D) HE-stain and (E) chromogranin A- and (F) Ki67-immunohistochemistry

are by far more frequently encountered than grade 3. dNEN are usually sporadic lesions. Although rare gastrinomas typically arise in the duodenum and may occur in the context of the hereditary multiple endocrine neoplasia syndrome type 1 (MEN-1).[27] Somatostatinomas, although exceedingly rare, are more commonly found in the pancreas than duodenum and can be associated with Neurofibromatosis type 1. dNEN usually appear as rounded lesions, often with a lighter (yellow) or darker (red) colour as compared to the surrounding mucosa. They appear firm to the touch with the biopsy forceps.

The information to be noted during the endoscopic examination for standardised reporting is:

a. Anatomical localization (proximal bulbar, distal bulb, proximal part of the *genus superius*, distal part of the *genu superius*, periampullary region, D3, D4).

b. Location on anterior or posterior wall.
c. The appearance of the lesion (round, nodular, polypoid, ulcerated, haemorrhagic).
d. The size in mm - use an open biopsy forceps for measurement.
e. The shape of the lesion - use the Paris classification[22]
   Ip pedunculated
   Is sessile
   IIa flat elevated
   IIb completely flat
   IIc central depression
   III ulcerated

After visual characterization (see Case study 3 and Figure 3), a histological specimen must be obtained. If the initial mucosal specimen is not diagnostic due to subepithelial localization additional biopsy must be performed either by the "mucosa incision-assisted biopsy" technique, or eventually by EUS-FNB. The endoscopist should request specific histopathology criteria of NEN from the pathologist (including differentiation, WHO-grade, Ki-67%-count, tissue and vascular invasion, any associated adjacent features in the surrounding mucosa). EUS could be performed to better assess the T stage and look for lymph nodes.

2.5 | Colonic neuroendocrine neoplasia

Colonic NEN (cNEN) are very rare. In the US, among 700,759 invasive colon cancers diagnosed between 2004 and 2014, there were 7967 NEN (1.13%). Staging was 0–1 in 34.1%, local procedure was performed in only 6.6% of cases, confirming previous reports that colon NEN are often higher grade tumors, and may be associated with advanced disease.[28] Other authors reported that tumour size and T stage predicted lymph node metastases: Tm and tumors <10 mm were linked with a 4% risk of lymph node invasion. Thus, if lesions are either ≥10 mm, or Tsm or more, a complete work-up including thoracoabdominal CT and somatostatin receptor imaging (SRI)[29] should be performed.

As for dNENs, cNEN usually appear as rounded lesions, often with a lighter (yellow) or darker (red) colour as compared to the surrounding mucosa. They appear firm to the touch with the biopsy forceps.

The information to be noted during the endoscopic examination for standardised reporting is:

a. Anatomical localization (sigmoid flexure, left colon, splenic flexure, transverse colon, hepatic flexure, right colon, caecum).
b. The appearance of the lesion (round, nodular, polypoid, ulcerated, haemorrhagic).
c. The size in mm - use an open biopsy forceps for measurement.
d. The shape of the lesion - use the Paris classification[22]
   Ip pedunculated
   Is sessile
   IIa flat elevated
   IIb completely flat
   IIc central depression
   III ulcerated

After visual characterization, a histological specimen must be obtained. If the initial mucosal specimen is not diagnostic due to subepithelial localization additional biopsy must be performed either by the "mucosa incision-assisted biopsy" technique, or eventually by EUS-FNB. The endoscopist should request specific histopathology criteria of NEN from the pathologist (including differentiation, WHO-grade, Ki67%-count, tissue and vascular invasion).

2.6 | Rectal neuroendocrine neoplasia

The identification of rectal NEN (rNEN) during the initial endoscopy is of paramount importance, as unfortunately, small rNEN (mostly <5 mm) are often mistaken for hyperplastic lesions and resected with cold snare polypectomy, leading to incomplete resection. Risk factors for metastasis are a size >15 mm, atypical endoscopic appearance (depression, ulceration), suspicious lymph nodes on EUS and or pelvic magnetic resonance imaging MRI, invasion of the muscularis propria, histological grade 2, and lymphovascular invasion.[15,30] Among these, size and endoscopic appearance are readily assessable by the endoscopist (see Case Study 4 and Figure 4).

The information to be noted during the endoscopic examination for standardised reporting is:

a. Anatomical localization – distance from the anal verge

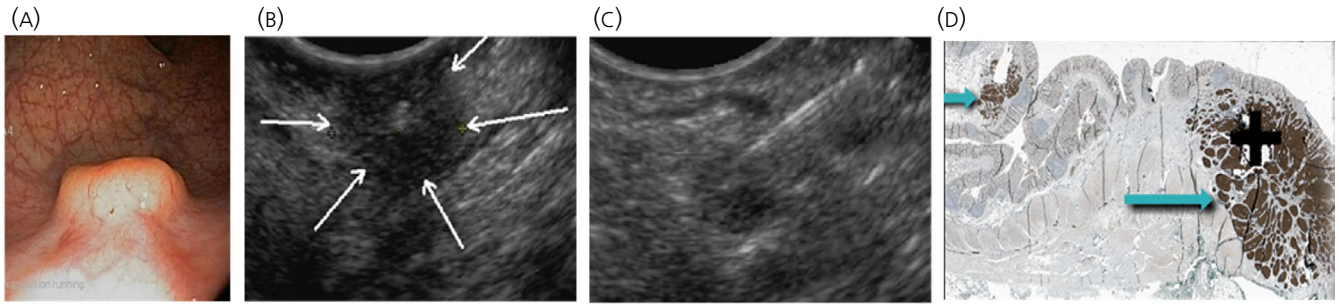

FIGURE 4 Rectal NEN - refers to Case Study 4. Rectal NEN at (A) initial endoscopy, (B) at EUS of the SEL prior to resection, (C) FNA of the lymph node, (D) histopathology of the TME surgical resection of the polyp (note that two lesions were found) by chromogranin A

b. Location on the anterior or posterior wall.
c. The appearance of the lesion (round, nodular, polypoid, ulcerated, haemorrhagic)
d. The size in mm - use an open biopsy forceps for measurement.
e. The shape of the lesion - use the Paris classification[22]
   Ip pedunculated
   Is sessile
   IIa flat elevated
   IIb completely flat
   IIc central depression
   III ulcerated

After careful endoscopic examination, anorectal EUS or pelvic MRI is recommended for lesions ≥10 mm. Biopsy is paramount; if the initial mucosal specimen is not diagnostic due to subepithelial localization additional biopsy must be performed either by the "mucosa incision-assisted biopsy" technique, or eventually by EUS-FNB. However, a diagnostic or effectively even therapeutic endoscopic mucosal resection (with or without cap) in lesions <10 mm should be considered. If >10 mm biopsy as aforementioned and consecutive endoscopic submucosal dissection (ESD) or surgical resection such as transanal total mesorectal excision (TME; see Case Study 4 and Figure 4) may be considered by a MDT. The endoscopist should in any case request specific histopathology criteria of NEN from the pathologist (including differentiation, WHO-grade, Ki-67%-count, tissue and vascular invasion, and any abnormalities in the surrounding mucosa).

3 | DISCUSSION

Despite numerous efforts to improve information regarding endoscopy recording systems,[1–5] to date no standardization of the process or terminology is readily employed. However, most joint efforts to standardise endoscopic terminology have focused on the characterization of the most frequent usually epithelial lesions with the GIT.[5] In contrast many NEN of the GIT in fact appear as subepithelial lesions (SEL) with a pathophysiology different from that of adenomatous or hyperplastic lesions because of their cellular and functional relation to the cells of the diffuse endocrine system of the GIT. A systematic endoscopic classification of GIT-NEN has therefore not yet been attempted and is presented here as the result of an interdisciplinary and multinational discussion and consensus process initiated by the ENETS. The suggested standardised reporting comprises NEN of the most frequently and endoscopically readily accessible location that is, gastric, duodenal and colorectal NEN. The criteria for reporting have been adopted from the minimal standard terminology MST as proposed by the World Congress of Gastroenterology and Digestive Endoscopy and have been tailored to fit the specific endoscopic, clinical, and pathophysiological requirements as specific for NEN in the respective locations.[3,7] Broad use of the suggested "standardised reporting" and additional validation studies will be future tasks to prove the validity of this first ever published endoscopic reporting system for GIT-NEN.

This article is part of a special issue on standised (synoptic) reporting of neuroendocrine tumours (see editorial[60] and articles[61-64]).

AUTHOR CONTRIBUTIONS

Ivan Borbath: Conceptualization; Data curation; Formal analysis; Methodology; Validation; Writing – original draft; Writing – review & editing. **Ulrich-Frank Pape:** Conceptualization; Data curation; Formal analysis; Methodology; Validation; Writing – original draft; Writing – review & editing. **Pierre H. Deprez:** Conceptualization; Methodology; Writing – original draft. **Detlef Klaus Bartsch:** Conceptualization; Visualization. **Martyn Caplin:** Conceptualization; Visualization; Writing – review & editing. **Massimo Falconi:** Conceptualization; Visualization. **Rocio Garcia-Carbonero:** Conceptualization; Visualization; Writing – review & editing. **Simona Grozinsky-Glasberg:** Conceptualization; Visualization; Writing – review & editing. **Robert T Jensen:** Conceptualization; Visualization. **Rudolf Arnold:** Conceptualization. **Philippe Ruszniewski:** Conceptualization; Visualization; Writing – review & editing. **C. Toumpanakis:** Conceptualization; Visualization; Writing – review & editing. **Juan Valle:** Conceptualization; Visualization; Writing – review & editing. **Dermot O'Toole:** Conceptualization; Formal analysis; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing.

CONFLICT OF INTEREST

The authors report no conflict of interest related to the article.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing not applicable – No new data generated.

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