Sponsored by ENETS

Neuroendocrine Tumours Histopathology Reporting Guide

ICCR

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

TUMOUR SITE (Note 1)

- ◯ Not specified
- ◯ Pancreas
  - ◯ Pancreatic tail
  - ◯ Pancreatic body
  - ◯ Pancreatic head
- ◯ Stomach
  - ◯ Cardia
  - ◯ Fundus
  - ◯ Corpus
  - ◯ Antrum
  - ◯ Pylorus
- ◯ Duodenum
  - ◯ Pars I
  - ◯ Pars II
  - ◯ Pars III
  - ◯ Pars IV
  - ◯ Ampulla of Vater
  - ◯ Minor ampulla
- ◯ Jejunum
- ◯ Ileum
- ◯ Small intestine not otherwise specified (NOS)
- ◯ Appendix
  - ◯ Tip of appendix
  - ◯ Body of appendix
  - ◯ Base of appendix
- ◯ Colon
  - ◯ Caecum
  - ◯ Ascending colon
  - ◯ Transverse colon
  - ◯ Descending colon
  - ◯ Sigmoid colon
- ◯ Rectum
  - Distance to linea dentata ____ mm
- ◯ Unknown primary site
- ◯ Other, *specify*

CLINICAL INFORMATION (Note 2)

- ◯ Information not provided
- ◯ Information provided

Known hormonal syndrome

- ◯ Information not provided
- ◯ No
- ◯ Yes, *specify*

Known hereditary syndrome

- ◯ Information not provided
- ◯ No
- ◯ Yes, *specify*

Pre-operative biochemical and imaging data, *specify*

Previous therapy, *specify*

Other clinical information, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 3)

- ◯ Not specified
- ☐ Biopsy
- ☐ Appendectomy
- ☐ Ileocecal resection
- ☐ Right hemicolectomy
- ☐ Endoscopic polypectomy
- ☐ Pancreaticoduodenectomy
- ☐ Duodenal segmental resection
- ☐ Ileo-colectomy
- ☐ Ileal resection
- ☐ Jejunal resection
- ☐ Resection of small intestine NOS
- ☐ Whipple pancreatoduodenectomy (PD)
- ☐ Pylorus preserving pancreaticoduodenectomy
- ☐ Distal pancreatectomy
- ☐ Total pancreatectomy
- ☐ Pancreatic segmental resection
- ☐ Enucleation
- ☐ Partial gastrectomy
- ☐ Total gastrectomy
- ☐ Antrectomy
- ☐ Polypectomy
- ☐ Other, *specify*

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TUMOUR FOCALITY (Note 4)

- ◯ Unifocal
- ◯ Multifocal
  - Specify number of tumours in specimen ◯ >1 OR [ ]
- ◯ Cannot be assessed (e.g., unknown primary), *specify*
  - [ ]

TUMOUR DIMENSIONS (Note 5)

Maximum tumour dimension (largest tumour)

[ ] mm

Additional dimensions (largest tumour)

[ ] mm x [ ] mm

Dimensions of additional smaller tumour foci

[ ] mm x [ ] mm x [ ] mm

- ◯ Cannot be assessed, *specify*
  - [ ]

BLOCK IDENTIFICATION KEY (Note 6)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

CLINICAL-PATHOLOGICAL TYPE (Note 7)

(Applicable to stomach only)

- ◯ Cannot be determined
- ◯ Type I (associated with autoimmune chronic atrophic gastritis)
- ◯ Type II (associated with gastrinoma in MEN1 patients)
- ◯ Type III (arising in normal mucosa)
- ◯ Type IV (associated with *ATP4A* mutation)
- ◯ Type V (associated with longstanding PPI therapy)

Non-neoplastic stomach

NE-CELL HYPERPLASIA

- ◯ Absent
- ◯ Linear
- ◯ Micronodular

OXYNTIC GLANDS

- ◯ Normal
- ◯ Atrophic
- ◯ Hyperplastic

INTESTINAL METAPLASIA

- ◯ Absent
- ◯ Present

HISTOLOGICAL TUMOUR GRADE (Note 8)

- ◯ Cannot be assessed
- ◯ Grade 1
- ◯ Grade 2
- ◯ Grade 3

MITOTIC COUNT (Note 9)

[ ] /mm²

- ◯ Cannot be assessed

TUMOUR NECROSIS (Note 10)

- ◯ Not identified
- ◯ Present
  - ◯ Punctate
  - ◯ Geographic

If you are reporting unknown primary site skip to MARGIN STATUS on page 3.

EXTENT OF INVASION (Note 11)

Pancreas

- ◯ Cannot be assessed
- ◯ Confined to the pancreas
- ◯ Serosal invasion
- ◯ Tumour invades into peripancreatic soft tissues
- ◯ Tumour infiltrates into duodenum
- ◯ Tumour infiltrates into portal vein
- ◯ Tumour invades other organ(s), *specify*
  - [ ]

Stomach

- ◯ Cannot be assessed
- ◯ Tumour infiltrates mucosa
- ◯ Tumour infiltrates submucosa
- ◯ Tumour infiltrates muscularis propria
- ◯ Tumour infiltrates subserosa
- ◯ Tumour perforates serosa
- ◯ Tumour invades other organ(s), *specify*
  - [ ]

Duodenum and ampulla

- ◯ Cannot be assessed
- ◯ Duodenum
  - ◯ Tumour infiltrates mucosa
  - ◯ Tumour infiltrates submucosa
  - ◯ Tumour infiltrates muscularis propria
  - ◯ Tumour infiltrates the pancreas
  - ◯ Tumour infiltrates peripancreatic adipose tissue
  - ◯ Tumour infiltrates the visceral peritoneum (serosa)
  - ◯ Tumour invades other organ(s), *specify*
    - [ ]
- ◯ Ampulla
  - ◯ Within the sphincter of Oddi
  - ◯ Tumour infiltrates into duodenal submucosa
  - ◯ Tumour infiltrates into duodenal muscularis propria
  - ◯ Tumour infiltrates the pancreas
  - ◯ Tumour infiltrates peripancreatic soft tissues
  - ◯ Tumour perforates serosa
  - ◯ Tumour invades other organ(s), *specify*
    - [ ]

EXTENT OF INVASION (Note 11) **continued**

Jejunum and ileum

- ◯ Cannot be assessed
- ◯ Tumour infiltrates mucosa
- ◯ Tumour infiltrates submucosa
- ◯ Tumour infiltrates muscularis propria
- ◯ Tumour infiltrates subserosa
- ◯ Tumour perforates serosa

Appendix

- ◯ Cannot be assessed
- ◯ Tumour infiltrates mucosa and submucosa
- ◯ Tumour infiltrates muscularis propria
- ◯ Tumour infiltrates subserosa
- ◯ Tumour infiltrates mesoappendix
- ◯ Tumour perforates serosa
- ◯ Tumour invades other organ(s), *specify*

Colon and rectum

- ◯ Cannot be assessed
- ◯ Tumour infiltrates mucosa
- ◯ Tumour infiltrates submucosa
- ◯ Tumour infiltrates muscularis propria
- ◯ Tumour infiltrates pericolic/perirectal adipose tissue
- ◯ Tumour perforates serosa
- ◯ Tumour invades other organ(s), *specify*

LYMPHATIC AND/OR VASCULAR INVASION (Note 12)
(Not applicable to unknown primary site)

Lymphatic invasion

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present

Venous invasion

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present

PERINEURAL INVASION (Note 13)
(Not applicable to unknown primary site)

- ◯ Not identified
- ◯ Present

MARGIN STATUS (Note 14)

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour from closest margin ____ mm
  - Specify margin
- ◯ Involved
  - Specify margin

LYMPH NODE STATUS (Note 15)
(Not applicable to unknown primary site)

Number of lymph nodes examined

- ◯ Not involved
- ◯ Involved
  - Number of involved lymph nodes
  - Location of involved lymph nodes, *specify*

MESENTERIC MASS(ES) (Note 16)
(Applicable to ileum and jejunum only)

- ◯ Absent
- ◯ Present
  - Size of largest ____ mm

ANCILLARY STUDIES (Note 17)

Synaptophysin

- ◯ Not performed
- ◯ Performed
  - ◯ Positive
    - ____ % of positive tumour cells
  - ◯ Negative

AND

Chromogranin-A

- ◯ Not performed
- ◯ Performed
  - ◯ Positive
    - ____ % of positive tumour cells
  - ◯ Negative

OR

INSM1

- ◯ Not performed
- ◯ Performed
  - ◯ Positive
    - ____ % of positive tumour cells
  - ◯ Negative

AND

Ki-67 proliferation index

- ◯ Not performed
- ◯ Performed
  - ____ %

ANCILLARY STUDIES (Note 17) **continued**

Somatostatin receptor 2 (SSTR2)

- ◯ Positive (at least 10% of tumour cells with membranous positivity)
  - ____ % of positive tumour cells
- ◯ Negative

Hormone expression (select all apply)

- ☐ Gastrin
- ☐ Somatostatin
- ☐ Other, *specify*

Transcription factor expression
(*Applicable to unknown primary site only*)

- ◯ Not performed
- ◯ Performed
  - ◯ Positive, *specify*
  - ◯ Negative, *specify*

DAXX
(Applicable to pancreas only)

- ◯ Retention of nuclear staining
- ◯ Loss of nuclear staining

Molecular test performed

- ◯ Wild type
- ◯ Mutant

ATRX
(Applicable to pancreas only)

- ◯ Retention of nuclear staining
- ◯ Loss of nuclear staining

Molecular test performed

- ◯ Wild type
- ◯ Mutant

Other, *record test(s), methodology and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 18)

- ◯ Not applicable
- ◯ Not identified
- ◯ Present (M1), *specify site(s)*

PATHOLOGICAL STAGING (UICC TNM 9th edition)[a] (Note 19)

TNM Descriptors (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ y - post-therapy
- ☐ r - recurrent

PANCREAS

Primary tumour[b] (pT)

- ◯ TX[c] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T1 Tumour limited to pancreas[d] 2 cm or less in greatest dimension
- ◯ T2 Tumour limited to pancreas[d] but more than 2 cm but less than or equal to 4 cm in greatest dimension
- ◯ T3 Tumour limited to pancreas[d] more than 4 cm in greatest dimension or invading duodenum or bile duct
- ◯ T4 Tumour invades adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (coeliac axis or the superior mesenteric artery)

Regional lymph nodes (pN)

- ◯ NX[c] Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

STOMACH

Primary tumour[b] (pT)

- ◯ TX[c] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T1 Tumour invades mucosa or submucosa and 1 cm or less in greatest dimension
- ◯ T2 Tumour invades muscularis propria or is more than 1 cm in greatest dimension
- ◯ T3 Tumour invades subserosa
- ◯ T4 Tumour perforates visceral peritoneum (serosa) or invades other organs or adjacent structures

Regional lymph nodes (pN)

- ◯ NX[c] Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

[a] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 9th Edition, eds by James Brierley, Meredith Giuliani, Brian O'Sullivan, Brian Rous, Elizabeth Van Eycken. 2025, Publisher Wiley (incorporating any errata published up until 18 July 2026).*

[b] *For any T, add (m) for multiple tumours.*

[c] *TX and NX should be used only if absolutely necessary.*

[d] *Invasion of adjacent peripancreatic adipose tissue is accepted but invasion of adjacent organs is excluded.*

PATHOLOGICAL STAGING (Note 19) **continued**

DUODENUM

Primary tumour[b] (pT)

- ◯ TX[c] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T1 *Duodenal:* Tumour invades mucosa or submucosa and 1 cm or less in greatest dimension
  Ampullary: Tumour 1 cm or less in greatest dimension and confined within the sphincter of Oddi
- ◯ T2 *Duodenal:* Tumour invades muscularis propria or is more than 1 cm in greatest dimension
  Ampullary: Tumour invades through sphincter into duodenal submucosa or muscularis propria, or more than 1 cm in greatest dimension
- ◯ T3 Tumour invades the pancreas or peripancreatic adipose tissue
- ◯ T4 Tumour perforates visceral peritoneum (serosa) or invades other organs

Regional lymph nodes (pN)

- ◯ NX[c] Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

JEJUNUM/ILEUM

Primary tumour[b] (pT)

- ◯ TX[c] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T1 Tumour invades mucosa or submucosa and 1 cm or less in greatest dimension
- ◯ T2 Tumour invades muscularis propria or is greater than 1 cm in greatest dimension
- ◯ T3 Tumour invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
- ◯ T4 Tumour perforates visceral peritoneum (serosa) or invades other organs or adjacent structures

Regional lymph nodes (pN)

- ◯ NX[c] Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Less than 12 regional lymph node metastasis without mesenteric mass(es) greater than 2 cm in size
- ◯ N2 12 or more regional nodes and/or mesenteric mass(es) greater than 2 cm in maximum dimension

[b] *For any T, add (m) for multiple tumours.*

[c] *TX and NX should be used only if absolutely necessary.*

APPENDIX

Primary tumour[e] (pT)

- ◯ TX[c] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T1 Tumour 2 cm or less in greatest dimension
- ◯ T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension
- ◯ T3 Tumour more than 4 cm or with subserosal invasion or involvement of the mesoappendix
- ◯ T4 Tumour perforates peritoneum or invades other adjacent organs or structures, other than direct mural extension to adjacent subserosa, e.g., abdominal wall and skeletal muscles[f]

Regional lymph nodes (pN)

- ◯ NX[c] Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

[e] *Poorly differentiated neuroendocrine carcinomas, mixed adenoneuroendocrine carcinomas and goblet cell adenocarcinoma, are excluded and should be classified according to criteria for classifying carcinomas.*

[f] *Tumour that is adherent to other organs or structures, macroscopically, is classified as T4. However, if no tumour is present in the adhesion, microscopically, the tumour should be classified as pT1-3 as appropriate.*

COLON AND RECTUM

Primary tumour[b] (pT)

- ◯ TX[c] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T1 Tumour invades lamina propria or submucosa or is less than or equal to 2 cm in greatest dimension
  - ◯ T1a Tumour less than or equal to 1 cm in greatest dimension
  - ◯ T1b Tumour more than 1 cm but less than or equal to 2 cm in greatest dimension
- ◯ T2 Tumour invades muscularis propria or is greater than 2 cm in greatest dimension
- ◯ T3 Tumour invades subserosa, or non-peritonealised pericolic or peri-rectal tissues
- ◯ T4 Tumour perforates the visceral peritoneum or invades other organs

Regional lymph nodes (pN)

- ◯ NX[c] Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence(1)). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system, e.g., Pathological TNM staging, would normally be included as a CORE element.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of DAC.

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Scope

The dataset has been developed for the pathology reporting of well differentiated neuroendocrine tumours (NETs), including pancreas, luminal gut and unknown primary site. Neuroendocrine carcinoma (NEC) are excluded from this dataset; respective ICCR datasets for carcinomas should be used.(2)

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Note 1 – Tumour site (Core and Non-core)

Neuroendocrine tumours (NETs) can occur in the entire gastro-entero-pancreatic system. While they share a common neuroendocrine phenotype by expression of neuroendocrine markers and transcription factors,(3) there are organ specific features regarding hormone/amine production, risk of metastasis and staging.

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Note 2 – Clinical information (Core and Non-core)

The majority of NETs manifest with non-specific symptoms and are found incidentally by endoscopic procedures or imaging. Hormonal syndromes occur in fewer than 30% of patients. The main clinical syndromes related to functional NETs are carcinoid syndrome (related to serotonin and/or other amines hypersecretion), Zollinger-Ellison syndrome (ZES) (related to gastrin hypersecretion) and insulinoma syndrome; other rarer hormonal syndromes are watery diarrhoea, hypokalaemia, achlorhydria (WDHA) (related to vasoactive intestinal peptide (VIP) hypersecretion), glucagonoma syndrome, and Cushing syndrome (related to ectopic adrenocorticotropic hormone (ACTH) secretion). When functional tumours produce hormones that are normally secreted from the organ in which they arise, this is called eutopic hormone production(4) (e.g., serotonin-production in the small intestine, gastrin production in the duodenum or stomach and insulin production in the pancreas). Ectopic hormone production is much rarer and most frequently occurs in pancreatic NETs (PanNETs), which may produce ACTH, calcitonin and other non-pancreatic hormones.(5, 6)

It should be noted that the sole identification of hormone expression in neoplastic cells (by immunohistochemistry) is not diagnostic of a functional tumour, which is defined by elevated circulating hormone levels along with specific symptoms indicative of a hormonal syndrome. When hormone expression is detected by immunohistochemistry, in the absence of a clinical hormone excess-related syndrome, NETs are defined as non-functioning and hormone production may be acknowledged in the pathology report (e.g., somatostatin-expressing PanNET, serotonin-expressing PanNET, calcitonin-expressing PanNET, etc.).

Pancreatic, duodenal and gastric NETs may arise in the setting of a familial multiple endocrine neoplasia syndrome (MEN1, MEN4). PanNETs may also arise in neurofibromatosis type 1 (NF1), von Hippel-Lindau (VHL) and tuberous sclerosis complex (TSC) syndromes. Multiple primary tumours and association with other endocrine or non-endocrine manifestations are indicators of a possible inherited predisposition; in this context, an accurate family history and a genetic counselling are advisable.

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Note 3 – Operative procedure (Core)

Depending on the location, grade and stage, operative procedures for NET include endoscopic resections or oncological surgical resection including regional lymph nodes dissection.(7-10)

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Note 4 – Tumour focality (Core)

The majority of NETs are unifocal. Multifocality can occur in the following scenarios: occurrence in one organ; multifocal tumours of the pancreas, sometimes in association with microtumours (<5 millimetres (mm)) in familial syndromes such as MEN1,(11) MEN4,(12) MEN5,(13) VHL syndrome,(14) and NF1. In the stomach, multifocality of histamine-producing entero-chromaffin like cells (ECL-cells) NET is associated with hypergastrinaemia(15) in the setting of either chronic atrophic gastritis or ZES, or proton pump inhibitor (PPI) therapy. Multifocal duodenal tumours are a feature of MEN-1 syndrome, usually presenting as ZES. Jejunoileal NETs are multifocal in up to 30%,(16) rarely in association with familial inheritance but most frequently without any known reasons.

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Note 5 – Tumour dimensions (Core and Non-core)

The tumour dimension is recorded in millimeters in three dimensions. The largest tumour dimension is a prognostic factor in most sites, but not for jejunoileal NETs (core). The dimensions of additional tumours in the presence of multifocality is recorded in three dimensions (non-core).

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Note 6 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important when further internal or external review arises. The reviewer needs to have unequivocal description of the origin of each block in order to provide an informed expert opinion. If this information is not included in the final pathology report, it should be available on the laboratory information system and relayed to the reviewing pathologist. It is highly encouraged to have a digital image (photograph) of the specimen and record of the key of the tumour blocks.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.

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Note 7 – Clinical-pathological type (Core) (Applicable to stomach only)

Gastric NETs are a heterogeneous group of malignant proliferations including different entities showing a specific topographic distribution within the gastric mucosa: histamine-producing ECL-cells NETs are exclusively located in the oxyntic mucosa, gastrin producing G-cell NETs typically arise in the antro-pyloric region, and serotonin producing EC-cell and somatostatin-producing D-cell NETs can be observed in both antral and oxyntic mucosa.(17)

ECL-cell NETs represent more than 90% of gastric NETs and they are separated into five prognostically different subtypes based on the morphology of peritumoral oxyntic mucosa, the presence of antral G-cell hyperplasia, the presence of hypergastrinaemia, the setting of MEN1 syndrome, the presence of hypo/achlorhydria, the presence of anti-parietal cells and/or intrinsic factor autoantibodies, the presence of megaloblastic anaemia, the mutational status of *ATP4A* gene, and long-standing treatment with PPIs.(18) Type 1 ECL-cell NETs are related to autoimmune atrophic gastritis. Type 2 arise in the context of MEN1 syndrome in patients with duodenal or, more rarely, pancreatic gastrinoma. Type 3 are not related to any pathologic condition. Type 4 are associated with mutations in the *ATP4A* gene. Type 5 arise in patients treated for a long time with PPI therapy. Except for type 3 ECL-cell NETs, these are associated with hypergastrinaemia and show excellent prognosis. In detail, the 5-year survival for type 1 and type 5 NETs is approximately 100%, and it is 60-90% for type 2 NETs (and depending on the gastrinoma), compared to 55-80% for type 3 NETs.(19, 20)

For all these reasons, the exact subtyping of histamine-producing ECL-cell gastric NETs is mandatory to identify different prognostic categories that need different therapeutic strategies ranging from a ‘wait and see’ approach (small intramucosal type 1 ECL-cell NETs), to endoscopic resection for larger hypergastrinaemia-associated gastric NETs to gastric resection (for type 3 NETs).

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Note 8 – Histological tumour grade (Core)

Tumour grade of NET is not based on the morphology of tumour cells, but on tumour cell proliferation evaluated using both mitotic count/2 mm^2 and Ki-67 expression detected in at least 500 tumour cells in a 'hot spot area'. Since its introduction by the European Neuroendocrine Tumor Society (ENETS) in 2006,(21) tumour grade has been demonstrated to impact outcomes significantly(22) with only rare exceptions including type 1 gastric NETs and appendiceal NETs.(20, 23) Tumour grade currently includes three categories in agreement with the 6th edition World Health Organization (WHO) Classification of Digestive Tumours, 2026 (refer to Table 1).(24)

Table 1: Criteria for grading neuroendocrine tumours.(24)

Grading		
Grade	**Mitotic count 2 mm^2**	**Ki-67 proliferation index**
G1	<2	<3%
G2	2-20	3%-20%
G3	>20	>20%

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Note 9 – Mitotic count (Core)

The mitotic count, also known as mitotic index, should be reported in every NET since it is an essential parameter used, together with the Ki-67 proliferation index, to assess tumour grade. Mitotic count should be evaluated in a 2 mm^2 area showing the highest mitotic activity. Since in several NETs, mitoses may be very rare or even absent, from a practical point of view the cell count should start in the field containing a mitotic figure (if present). As the area of high power fields (HPFs) is variable among different microscopes, the use of mitotic count per HPF is discouraged.

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Note 10 – Tumour necrosis (Core)

Tumour necrosis is frequently observed in NECs, where it is generally abundant with a typical 'geographic chart' pattern. In NETs necrosis is rare, and generally focal or punctate (small foci of necrosis within tumour nests or necrosis of single cells). It is worth noting that only true tumour necrosis characterised by degenerating cytoplasm, karyorrhectic nuclear debris and abrupt transition to viable cells needs to be considered. True tumour necrosis must be differentiated from ischemic (infarct-like) necrosis, which is associated with granulation tissue, extravasated blood, hemosiderin deposition, and a gradual transition to more viable areas. Although some studies have demonstrated adverse prognostic significance,(25, 26) necrosis is not currently formally included in the grading system of digestive NETs, unlike in certain non-digestive NETs such as lung NET/carcinoids and medullary thyroid carcinomas.

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Note 11 – Extent of invasion (Core)

Surgical resection specimens should be carefully evaluated, macroscopically and microscopically, to assess tumour extension and invasion, which is the basis for pT-staging according to the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC).(27, 28) For gastrointestinal NETs, the depth of infiltration of the wall is the cornerstone of pT assessment, while for appendiceal NETs it should be combined with tumour size. It is worth noting that in hypergastrinaemia-associated ECL-cell gastric NETs (type1, type 2, type 4, and type 5) the depth of infiltration is more relevant than tumour grade in determining biological aggressiveness(25) and, for this reason, its ultrasound-endoscopic evaluation is strongly recommended for the correct management of patients.(19, 20)

For panNETs, particular attention should be paid to the evaluation of bile duct and duodenal wall invasion since it increases stage pT2, based on tumour size, to pT3 in cases not invading other adjacent organs (i.e., stomach, spleen, etc.) or large vessels. Microscopic invasion of peripancreatic adipose tissue should be searched for and reported, but it does not influence pT stage.(27, 28)

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Note 12 – Lymphatic and/or vascular invasion (Core) (Not applicable to unknown primary site)

The association of both vascular and lymphatic invasion with the development of lymph node and distant metastases and with prognosis is well known in digestive neuroendocrine tumours, and it has been confirmed in different studies.(29-33) The assessment of vascular and lymphatic invasion should be accurate and, in difficult cases, confirmed by immunostaining using endothelial markers (CD31, CD34, and podoplanin/D2-40). This appears particularly important in specific sites such as the jejunum-ileum, where fixation artifacts determine retraction spaces between tumour nests and fibro-muscular stroma mimicking vascular or lymphatic invasion.

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Note 13 – Perineural invasion (Core) (Not applicable to unknown primary site)

Perineural invasion in digestive NETs is commonly observed, especially in more aggressive ones.(29, 34) Its prognostic role has been demonstrated in large series in multivariate analyses.(29, 35) In difficult cases, immunostaining for S100 may help the identification of perineural invasion.

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Note 14 – Margin status (Core)

The margin status of resected NETs has been proven to have a prognostic impact. Indeed, positive margins (R1) in resected PanNETs have been demonstrated to be associated with a worse recurrence-free survival in large series.(36) In another recent investigation including 904 patients, R1 status showed a prognostic trend but did not appear significant in multivariate analysis.(29) R1 margin status has also been considered a parameter of high risk of recurrence for endoscopically resected rectal NETs.(31)

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Note 15 – Lymph node status (Core and Non-core) (Not applicable to unknown primary site)

Lymph node status is part of the TNM staging reporting system. The prognostic role of lymph node metastasis has been demonstrated for gastric, intestinal, and PanNETs,(25, 37, 38) while it is still under debate for appendiceal NETs(23, 39) since recent findings seem to suggest that lymph node dissemination is not prognostically relevant in NETs of the appendix, especially for those of 10-20 mm in size.(23, 40) Recent evidence indicates that the number of lymph nodes evaluated may have a prognostic impact,(25, 38, 41) consequently the accurate identification and reporting of positive lymph nodes is core. In addition, for jejunoileal NETs the assessment of mesenteric tumour deposits including their size needs to be performed, as it is clinically relevant and determines the pN stage (pN2 if nodal metastasis/tumour deposit is larger than 20 mm).(41)

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Note 16 – Mesenteric mass(es) (Core) (Applicable to ileum and jejunum only)

Mesenteric lymph node metastases of serotonin-producing jejunoileal NET may lead to a strong local mesenteric reactive fibrosis leading to an ill-defined mesenteric mass (if >20 mm in maximal dimension). The fibrosis may involve mesenteric vessels and induce bowel ischaemia or small or large bowel obstruction.(42) Presence of a mesenteric mass is independently associated with decreased survival rate(43) and classified as pN2 if >20 mm. Mesenteric tumour deposits <20 mm have recently also been associated with increased risk of metastasis.(44).

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Note 17 – Ancillary studies (Core and Non-core)

For confirming a NET, expression of two neuroendocrine markers is required. Most well differentiated NET express synaptophysin diffusely and strongly as well as chromogranin A. A minority, especially L-cell NET of the rectum, do not express chromogranin.

INSM1 is a very specific and sensitive second general neuroendocrine marker.(45) The use of CD56 as neuroendocrine marker is discouraged because of lack of specificity. Staining for cytokeratins (e.g., cytokeratin (CK)18) should be used if any doubt of epithelial origin exists; this will allow distinction from paragangliomas.

Ki-67 staining is needed for grading of NETs.(46, 47) As this is a linear variable with higher rate implying a poor prognosis, the exact Ki-67 proliferation index is critical for clinical management. Prognosis depends on the highest Ki-67 proliferation index; therefore, the analysis is done in hot spots, counting >500 tumour cells. Ki-67 may vary between metachronous and synchronous metastases and should therefore be repeated at each recurrence.(48)

Immunohistochemical detection of membranous somatostatin receptor 2 (SSTR2) shows a correlation with SSTR-DOTA-PET CT positivity if present in >10% tumour cells.(49)

Immunohistochemical positivity for peptide/aminic hormones indicates the production of a hormone and is not equivalent to the secretion and presence of a clinical syndrome. Therefore, these immunostains are used to confirm the origin of a clinical syndrome in a resected tumour, especially in the setting of multiple primary tumours in MEN1 patients.

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Note 18 – Histologically confirmed distant metastases (Core)

Tumour classifiable as distant metastatic disease may sometimes be present within the primary tumour resection specimen, for example a peritoneal deposit that is discontinuous from the primary mass. Metastatic deposits in 'non-regional' lymph nodes are usually submitted separately by the surgeon, but may be present within a surgical specimen. Note: Pathologists can only base assessment of distant metastatic disease on submitted specimens and therefore should not use the terms 'pM0' or 'pMX'.

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Note 19 – Pathological staging (Core)

Staging data must be assessed according to the 9th editions of the UICC/AJCC Cancer Staging Manuals.(27, 28)

Reporting of pathological staging categories (pT, pN, pM) is based on the evidence available to the pathologist at the time of reporting. pM is only recorded in the presence of histologically confirmed metastases. As indicated in UICC/AJCC TNM9,(27, 28) the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

Staging for NEC, which is not included in this protocol, is performed according to the non-neuroendocrine carcinoma staging system of the respective organs.(27, 28)

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