The Royal College of Pathologists
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Standards and datasets for reporting cancers

Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract

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Comments	This document replaces the third edition of the *Dataset for neuroendocrine tumours of the gastrointestinal tract including pancreas* published in 2012. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 2 to 30 May 2019. Responses and authors' comments are available to view following final publication of this dataset. **Dr Brian Rous** **Clinical Lead for Guideline Review (Cellular Pathology)**

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Foreword

The cancer datasets published by the Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items (see appendices C–Q) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult on this document:

- Association for Coloproctology of Great Britain and Ireland (www.acpgbi.org.uk)
- British Society of Gastroenterology (www.bsg.org.uk)
- UK Endocrine Pathology Society (www.ukeps.com)
- UK and Ireland Neuroendocrine Tumour Society (www.ukinets.org).

Evidence for the revised dataset was obtained from updates to international tumour grading, staging and classification systems. All publications have widespread national and/or international peer acceptance and reflect the current accepted professional standards and practice in neuroendocrine tumour (NET) diagnosis.

Evidence for the revised dataset was also obtained by electronically searching medical literature databases for relevant research evidence, systematic reviews and national or international publications on NETs up to March 2018. The level of evidence (Appendix Q) for the recommendations has been summarised. Most of the supporting evidence is at least grade C or meets the GPP (good practice point) criteria. No major conflicts in the evidence have been identified and any minor discrepancies between evidence have been resolved by expert consensus. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in Appendix R.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset.

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the author of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be

placed on the College website for two weeks for members' attention. If members do not object to the changes, the changes will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Clinical Effectiveness department, Working Group on Cancer Services and Lay Governance Group and placed on the College website for consultation with the membership from 2 to 30 May 2019. All comments received from the Working Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review (Cellular Pathology).

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness department and are available on request. The authors have declared no conflicts of interest.

1 Introduction

This document is an update to the third edition, published in 2012.

Careful and accurate pathology reporting of gastroenteropancreatic neuroendocrine neoplasm (GEP-NEN) resection specimens is important because pathology reports are used to:[1]

- make or confirm the diagnosis
- inform prognosis
- plan the treatment of individual patients
- audit pathology services
- evaluate the quality of other clinical services, notably radiology, surgery and oncology
- collect accurate data for cancer registration and epidemiology
- facilitate high-quality research
- plan service delivery.

1.1 Target users and health benefits of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists, clinical scientists/biomedical scientists with an extended role in histopathology dissection[1] and, on their behalf, the suppliers of IT products to laboratories. The secondary users are clinicians, surgeons, radiologists, oncologists, cancer registries and the National Cancer Registration and Analysis Service (NCRAS). Standardised cancer reporting and multidisciplinary team (MDT) working reduce the risk of histological misdiagnosis and help ensure clinicians have all the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer-specific data also provides information for healthcare providers and epidemiologists, and facilitates international benchmarking and research.

1.2 Changes since the previous edition: tumour classification

Since the previous edition, three new WHO classifications have been published: the fourth edition of the WHO classification of neuroendocrine tumours of the digestive system in 2010,[2] the fourth edition of the WHO classification of pancreatic neuroendocrine neoplasms (PanNENs) in 2017[3] and the fifth edition of the WHO classification of tumours of the digestive system in 2019.[4]

Based on new evidence, we recommend the use of the WHO 2017 classification for PanNENs[3] and the WHO 2019 classification for neuroendocrine neoplasms of the gastrointestinal (GI) tract and hepatopancreatobiliary organs,[4] along with the updated SNOMED codes (Appendix B).

The classification and nomenclature of neuroendocrine neoplasms (NENs) is complex, can be confusing and has undergone major changes over the last three decades, as illustrated by the evolution in classification of GEP-NENs by the WHO.

The first WHO classification of GEP-NENs was proposed in 1980 and used the term 'carcinoid' to describe most GI-NENs, excluding the pancreatic islet cell tumour and small cell carcinoma.

The WHO classification that appeared in 2000 for NENs of the GI tract[5] and in 2004, for NENs of the pancreas,[6] followed a new approach that attempted to predict the biological behaviour of GEP-NENs. The WHO 2000/2004 classification introduced the terms 'neuroendocrine tumour' and 'neuroendocrine carcinoma' to stratify the old term 'carcinoid' into three different groups of NENs: well-differentiated endocrine tumours with benign or uncertain behaviour; well-differentiated endocrine carcinomas of low-grade malignancy; and poorly differentiated endocrine carcinomas of high-grade malignancy. It aimed to separate benign from malignant disease, introducing the concepts of benign NETs, NETs of unknown behaviour and malignant neuroendocrine carcinoma. Assessment for malignant behaviour was based on a mixture of morphological (tumour grading, angioinvasion and perineural invasion) and staging (depth of tumour invasion, presence of lymph node and distant metastases) criteria.[7] Although this stratification was an important step forward, the characterisation of different prognostic groups was impracticable owing to the combination of staging, grading and tumour typing. Some of the criteria were only applicable in resection specimens.

In the second half of 2010, a revised version of the WHO classification of GEP-NENs appeared.[2] This new classification introduced several changes. The most important change was based on the assumption that all GEP-NENs, and in particular PanNENs, are malignant tumours (all, except for gangliocytic paraganglioma and pancreatic neuroendocrine microadenomas, which are classified as benign tumours, and L-cell-type [glucagon-like peptide and peptide YY-producing] NETs and tubular carcinoids, which are classified as uncertain malignancies).[2] The WHO 2010 classification also introduced a stricter separation between well-differentiated neoplasms (defined as NETs) and poorly differentiated neuroendocrine carcinomas (defined as NECs). This separation implies fundamentally different treatment modalities. As a further step to orientate clinical decision, the WHO adopted the European Neuroendocrine Tumour Society (ENETS) three-tier grading system (G1–G3), subdividing the NETs into G1 and G2 and reserving the G3 category for NEC only. As per the WHO 2010 classification, NETs are, by definition, either grade G1 or G2 and NECs are, by definition, always grade G3. There is no 'well-differentiated neuroendocrine carcinoma' in the WHO 2010 classification.

Following the introduction of such a strict classification system, histopathologists have faced diagnostic dilemmas, in daily practice, when some NENs, especially of pancreatic origin, presented with histological features of well-differentiated NETs and a mitotic count still within the G2 range, but were found to have a Ki-67 proliferation index higher than 20%. In the WHO 2010 classification, these NENs do not fit any category. They have generally been reported as G3, even though they have typical morphology of well-differentiated NETs, and G3 NEC was reserved for poorly differentiated tumours.

Accumulating evidence strongly suggests that the G3 category of PanNENs (Ki-67 >20%) is a heterogeneous group and actually includes two different entities that differ profoundly in their biology, prognosis and molecular genetics:[8–11] well-differentiated NET with an elevated proliferative rate; and poorly differentiated NEC with small cell or large cell morphology. Supporting this concept, it was shown by Yachida *et al*[8] in 2012 that pancreatic small cell carcinoma and large cell NEC are genetically related entities and that the genetic changes

frequently seen in these poorly differentiated carcinomas, such as inactivation of the TP53 and the Rb/p16 pathways, are rarely observed in well-differentiated pancreatic NETs (PanNETs). Conversely, inactivating mutations in *DAXX* and *ATRX* and mutations in *MEN1* are exclusively found in well-differentiated PanNETs. In 2015, Basturk *et al*[11] found that high-grade well-differentiated PanNETs are characterised by a much lower average Ki-67 index (40% vs 70%), and that their outcome is not as poor as that of poorly differentiated NEC (two- and five-year survival rates of 74.9% and 29.1% vs 22.5% and 16.1%, respectively). Furthermore, the mitotic rate of well-differentiated G3 NETs appears to be mostly in the G2 range. The Nordic NEC study[10] found that not all patients with WHO 2010 classification G3 NEC benefit from the platinum-based chemotherapies typically used for poorly differentiated NECs such as small cell carcinoma. G3 tumours with a Ki-67 index <55% were less responsive than G3 NECs with a Ki-67 index >55%, although the latter group experienced early recurrence with shorter ultimate survival rates than the group with a Ki-67 in the 20–55% range.

In 2017, based on this new evidence, the WHO classification specifically improved the grading system of the PanNEN group by applying a three-tier grade system and introducing the NET G3 category[3] (see Table 1). This new pancreatic NET G3 category was subsequently formally adopted in 2019 in the fifth edition of the WHO classification of the digestive system for tumours arising throughout the entire GI tract and in the hepatopancreatobiliary organs.[4]

[Level of evidence B/C – histopathological tumour differentiation and tumour grading are important for clinical management and prognosis.]

1.3 Validation of decision to retain or revise data collected

The document remains largely unchanged in relation to staging.

The guidance and reporting forms in the following pages are based on the ENETS staging system (2006/2007).[12,13] The ENETS staging system is applied to all NENs to include both well-differentiated and poorly differentiated NENs.

The eighth edition of the Union for International Cancer Control (UICC) tumour-node-metastasis (TNM) classification (2017)[14] of GEP-NENs widely adopted the ENETS TNM classification. The two systems are now comparable for stomach, duodenum, jejunum, ileum, colon, rectum and pancreas, but not for the appendix. Minor differences include the N status for the jejunum and ileum, which is subdivided by UICC TNM 8 into N1 when there are fewer than 12 regional lymph nodes metastases without a mesenteric mass greater than 2 cm and N2 when there are 12 or more regional lymph nodes and/or a mesenteric mass that is greater than 2 cm in maximum dimension. Differences are still present for the T stage of the appendiceal NENs.

The rationale for recommending the ENETS TNM staging systems[12,13] throughout this dataset (as opposed to the UICC TNM 8 system)[14] is the same as the previous dataset (third edition).

[Level of evidence C – the prognostic validity of the TNM system as proposed by ENETS has been established.]

1.4 Key pathology data

The optimal management of patients with GEP-NENs involves multiple specialists. The diagnosis and management of NENs is best achieved within the MDT environment. The key pathology data that facilitate accurate decision-making by all members of the management team include the following:

- tumour differentiation:
  - for all pathology reports, the diagnosis must indicate whether the NEN is well- or poorly differentiated (see section 5.4.2). Without reference to differentiation, the pathology report is inadequate for prognosis or treatment
- tumour grade and proliferative index (see section 5.4.5):
  - the grading, in addition to staging, is the most important predictor of prognosis. For all pathology reports, the NENs must be graded according to the WHO 2019 classification for GI-NENs[4] and WHO 2017/2019 classification for PanNENs.[3,4] Even though the grading of a NEN in biopsy material may not always be reliable owing to small size sample or error sampling, the information on proliferation with Ki-67 and mitotic count might be relevant for clinicians and should be included in the final pathological report of biopsies.
- tumour stage (see Appendix A):
  - for resected specimens, all NENs must be staged according to the ENETS TNM system[12,13]
- status of margins:
  - for resected NENs, the adequacy of surgical resection should be reported (see section 7.1)
- other prognostic features:
  - the report should include findings of other pathological prognostic features, such as necrosis[12,13,15] or vascular invasion.[6,12,13,16]

2 Clinical information required on specimen request form

The nature of the resection and the site of the tumour should be specified on the specimen request form. A diagram of the surgical procedure is important in complex specimens.

It is also desirable for the pathologist to be told:[17,18]

- the type of tumour, if known (with details of the previous biopsy)
- the preoperative stage of the tumour
- specific hormone production, particularly in the case of pancreatic NETs, as this may prompt immunohistochemical search for the specific hormone production, if the site of production is in doubt; non-specific neuroendocrine marker levels such as serum chromogranins A and B, and urinary 5-hydroxyindoleacetic acid.

[Level of evidence GPP – these data are required for accurate staging and cancer registration.]

3 Preparation of specimens before dissection

Where possible, resection specimens should be received fresh, unopened and unincised, as soon as possible after resection. If submitted outside laboratory hours, they can be refrigerated at 4°C overnight without risk of appreciable autolysis, but if there is likely to be a longer delay before handling, they should be placed unopened in a large volume of formalin-based fixative. Specimen handling of the stomach, pancreas, duodenum, proximal jejunum and colorectum are as for carcinomas of these respective organs.[1,19–24] For distal jejunum and ileum, opening and fixation are as for colon.[19]

4 Specimen handling and block selection

The intact surgical specimen is first inspected to locate the tumour and the presence of any macroscopically obvious perforation through the tumour is recorded. For colorectal tumours, the non-peritonealised circumferential margin, previously known as the radial margin, in the vicinity of the tumour is then inked or painted with a suitable marker to enable subsequent identification of margin involvement. This margin represents the 'bare' area in the connective tissue, at the surgical plane of excision, which is not covered by a serosal surface.

The following blocks of tissue are recommended as minimum sampling:

- blocks of the tumour to show:
  - the deepest tumour penetration into or through the organ wall
  - involvement of a serosal surface, noting whether that is via direct local spread or metastasis
  - vascular invasion, if suspected
  - involvement of any adjacent organs
- a block to show the closest approximation of the tumour to any non-peritonealised resection margin, e.g. mesentery or pancreatic parenchyma (either in continuity with the main tumour mass or a separate extramural deposit or tumour in a lymph node, whichever is closest)
- appropriate blocks to show the closest approximation of the tumour to the proximal or distal margin (including stapling device doughnuts, if appropriate), if that distance has any likelihood of being <30 mm (see sections 5.2.1e and 5.4.7a)
- a block of tumour and the adjacent mucosa
- a block of normal-appearing background mucosa (to include the antral and corpus mucosa in the case of gastric NENs)
- all lymph nodes identified, embedding the whole node
- sampling of any other macroscopic abnormalities
- sampling of any additional organs in the resection.

Serosal involvement is best identified in blocks that are taken from areas that are dulled, fibrotic or haemorrhagic and is particularly prone to occur where the peritoneum is reflected at an acute angle from the bowel surface on to the adjacent mesentery or in deep crevices or clefts between fat lobules. It is very important to emphasise that all of the lymph nodes that can be found in a specimen are examined histologically. NENs may be incidental findings in initially less thoroughly sampled specimens, e.g. the finding of an NEN at the tip of an appendix. Under these circumstances, the specimen should have its sampling upgraded to that which would have been done if the existence of the tumour had been known. For example, in the appendix, the appendicular and mesoappendicular resection margins would be blocked, any lymph nodes would be sampled, and the serosal surface would be re-inspected and sampled where abnormal.

[Level of evidence C – evidence for block selection is extrapolated from the need to provide microscopic confirmation or evaluation of prognostic and predictive factors.]

5 Core data items

5.1 Macroscopic core data items

Macroscopic core items to be reported are:

- type of specimen and specimen dimensions
- organs/tissues included
- site of tumour
- tumour perforation
- whether solitary or multiple
- maximum tumour dimension
- resection margins (end margins and non-peritonealised margins), measurement confirmed histologically (rectal tumours only)
- relation of the tumour to the peritoneal reflection (rectal tumours only)
- distance of the tumour from the dentate line (for abdominoperineal excisions only)
- whether a named vessel has been identified and its identity.

[Level of evidence D – whether a named vessel is identified should be reported to assist quality assurance of surgery.]

5.2 Explanatory notes on macroscopic assessment

Measurements made on the gross specimen are recorded in millimetres. They are confirmed or amended, where appropriate, by subsequent microscopy.

5.2.1 Data recorded for all gastrointestinal and pancreatic NETs

a) Site of tumour: this will usually be stated on the request form. However, if examination of the specimen suggests that the stated site is incorrect, this should be queried with the surgeon and corrected if necessary.

b) Multiple tumours: it is not uncommon to find multiple NENs, especially in cases where tumourigenesis occurs in a background of neuroendocrine cell hyperplasia[25] that may or may not have an inherited basis.[26,27] The presence of multiple tumours should be recorded. Whether or not two (or more) reporting proformas are used will depend on the clinical background, the macroscopic appearances and the discretion and judgement of the pathologist. When a single proforma is used, the data recorded should relate to the most prognostically adverse lesion identified.

c) Maximum tumour dimension: this is best measured after slicing. If multiple tumours are present, state dimensions of the largest one (unless separate forms are being used for each tumour) and the range of the tumour size. Measurements relating to the tumour, made on the gross specimen, are recorded in millimetres. They are confirmed or amended, where appropriate, by subsequent microscopy.

d) Presence of tumour perforation: perforation is defined as a macroscopically visible defect through the tumour, such that the bowel lumen is in communication with the external surface of the intact resection specimen. Perforation of the proximal bowel as a result of a distal obstructing tumour does not count as tumour perforation.

e) Distance of tumour to the nearer cut end: this is the measurement from the nearer cut end of the specimen, and not the non-peritonealised or circumferential margin. This margin is unlikely to be involved by well-differentiated NETs that are >30 mm away macroscopically, but it should be sampled for microscopic examination if subsequent histology shows the

tumour to be high grade (G3), either well differentiated or poorly differentiated, to have an exceptionally infiltrative growth pattern or extensive vascular or perineural invasion, or to be a mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) with a signet ring cell component.

5.2.2 Data recorded for rectal NETs only

a) Relationship to the peritoneal reflection: the peritoneal reflection is identified from the exterior surface of the anterior aspect of the rectum. Tumours are classified as being entirely above, entirely below or astride this landmark.

b) Distance from dentate line: this measurement is only made for low rectal tumours in abdominoperineal excision of rectum specimens to give an idea of the location of the tumour in relation to the internal sphincter.

5.3 Microscopic core data items

Microscopic core items to be reported are:

- histological tumour type (including pure NENs and MiNEN/mixed tumours – see sections 5.4.1, 5.4.2 and 5.4.3 and Table 1)
- histological differentiation (well or poorly differentiated – see section 5.4.2)
- expression of pancytokeratins and general neuroendocrine immunohistochemical markers (see section 5.4.4)
- specific hormone immunostaining, if considered clinically essential (e.g. to find the relevant tumour causing a clinical syndrome, see section 5.4.4)
- histological grade (including the mitotic rate and/or proliferation index with Ki-67 – see section 5.4.5)
- maximum extent of local invasion (pT stage). This may not be assessable in small gastric and rectal endoscopic mucosal resection.
- serosal involvement
- margin involvement
- lymph node status (number present, number involved)
- lymphovascular invasion
- perineural invasion
- tumour deposits (see section 5.4.8b)
- histologically confirmed distant metastases and site (see sections 5.4.8b and 7.2.3)
- background abnormalities, e.g. enterochromaffin-like (ECL)-cell or G-cell hyperplasia[25] in stomach with autoimmune chronic gastritis, as these inform the WHO classification of ECL-cell gastric carcinoid tumours[2,4]
- WHO 2019 classification for GI-NENs (see Table 1), WHO classification for gastric ECL-cell tumours (see Table 2) and WHO 2017 classification for PanNENs (see Table 1)
- ENETS TNM stage (see section 7.2)
- completeness of resection (R stage) (see section 7.1)
- SNOMED CT (see section 11).

5.4 Explanatory notes on microscopic assessment

5.4.1 Nomenclature

The terminology used to classify NENs has undergone major changes in recent years.

One semantic issue relates to the use of the term 'endocrine' versus 'neuroendocrine'.[16] The WHO 2010 classification of GEP-NENs has officially adopted the term 'neuroendocrine' to indicate the expression of neural markers in neoplastic cells with otherwise exquisite endocrine properties and phenotype.[2]

Another debated terminological issue relates to the use of the term 'tumour' instead of 'neoplasm'. The WHO 2010 classification accepted both terms: 'neuroendocrine tumour' can be used synonymously with 'neuroendocrine neoplasm' for differentiated neoplasms, with epithelial and neuroendocrine differentiation, in the gastroenteropancreatic system.

The term 'carcinoid tumour' has become archaic in the gastroenteropancreatic tract and it should be avoided as a primary diagnostic term at these sites.

According to the WHO 2019 classification of GI-NENs[4] (see Table 1):

- NET is a well-differentiated epithelial neoplasm with morphological and immunohistochemical features of neuroendocrine differentiation
- NETs can be low-grade (G1), intermediate-grade (G2) or high-grade (G3) tumours
- NEC is a poorly differentiated epithelial neoplasm with morphological and immunohistochemical features of neuroendocrine differentiation
- NEC is, by definition, high grade (for this reason, the WHO 2019 classification proposed not to assign a grade to NECs, whereas previously all NECs were graded G3)
- NEC is not defined by local vascular invasion or metastasis, but by tumour histology and grading (G3, mitoses >20 per 2 mm^2 and/or Ki-67 >20%)
- there is no 'well-differentiated neuroendocrine carcinoma' category
- the term 'NEN' encompasses all well-differentiated and poorly differentiated tumours of the neuroendocrine cells
- MiNEN is a mixed epithelial neoplasm in which a neuroendocrine component is combined with a non-neuroendocrine component, each of which is morphologically and immunohistochemically recognisable as a discrete component and constitutes ≥30% of the neoplasm.

According to the WHO 2017 classification of PanNENs[3] (see Table 1):

- NETs can be G1, G2 or G3
- MiNEN replaces the WHO 2010 classification term MANEC for mixed tumours, recognising that the non-neuroendocrine component does not have to be an adenocarcinoma (e.g. it can be a squamous cell carcinoma, acinar cell carcinoma, etc.).

Table 1: Comparison of the WHO 2019 GI-NEN classification, the WHO 2017 PanNEN classification and the WHO 2010 GEP-NEN classification.

WHO 2019 GI-NEN classification	WHO 2017 PanNEN classification	WHO 2010 GEP-NEN classification
Well-differentiated NETs: • NET G1 • NET G2 • NET G3	Well-differentiated NETs: • NET G1 • NET G2 • NET G3	Well-differentiated NETs: • NET G1 • NET G2
Poorly differentiated NECs: • NEC (large cell or small cell NEC)	Poorly differentiated NECs: • NEC G3 (large cell or small cell NEC)	Poorly differentiated NECs: • NEC G3 (large cell or small cell NEC)
MiNEN	MiNEN	MANEC
Abolished, but recognised in gastric NENs	Abolished preneoplastic category because PanNEN precursor changes have not been clearly identified in association with sporadic neoplasms[3]	Hyperplastic and preneoplastic lesions[25,28]

GI-NEN: Gastrointestinal neuroendocrine neoplasm; MANEC: Mixed adenoneuroendocrine carcinoma; MiNEN: Mixed neuroendocrine-non-neuroendocrine neoplasm; NEC: Neuroendocrine carcinoma; NET: Neuroendocrine tumour; PanNEN: Pancreatic neuroendocrine neoplasm; GEP-NEN: gastroenteropancreatic neuroendocrine neoplasm.

5.4.2 Tumour type and differentiation

The WHO 2017 classification[3] is recommended for PanNENs, whereas the WHO 2019 classification[4] is recommended for GI-NENs (see Table 1).

There is another important terminological issue to clarify, regarding the difference between 'tumour differentiation' and 'tumour grade'. The concept of differentiation is linked to the grade of the tumours, but there are subtle differences between the concepts of differentiation and grade. Differentiation refers to the extent to which the neoplastic cells resemble their non-neoplastic counterparts. Grade, on the other hand, refers to the inherent biologic aggressiveness of the tumour. Low-grade NETs are relatively indolent, high-grade NETs are extremely aggressive and intermediate NETs have less a predictable, moderately aggressive course.[16]

[Level of evidence C – differentiation and grading are important for prognosis.]

GEP-NENs comprise a heterogeneous group of neoplasms. While some clinical and pathologic features of these tumours are unique to the site of origin, other characteristics are shared, regardless of the site.

Regardless of the site there are three major tumour types:

- well-differentiated NETs, classified by the WHO 2019 for GI-NENs (see Table 1) and WHO 2017 for PanNENs
- poorly differentiated NECs, classified by the WHO 2019 for GI-NENs and the WHO 2017 for PanNENs (see Table 1)
- MiNENs, classified by the WHO 2019 for GI-NENs (see Table 1) and the WHO 2017 for PanNENs (see Table 1).

Regardless of the site, well-differentiated NEN cells have a similar cytological appearance:

- small- to medium-sized cells with a round/oval shape and eosinophilic, lightly granular, cytoplasm

- the nuclei are usually centrally placed, fairly uniform, with a finely dispersed, slightly coarse, 'stippled' ('salt and pepper') chromatin pattern
- nucleoli are usually inconspicuous or absent
- the growth pattern is organoid (nested, trabecular, insular, acinar, pseudoglandular), with rare tumour necrosis
- the proliferative activity is usually low/intermediate, rarely high.

Regardless of the site, poorly differentiated NEC cells resemble small cell or large cell NEC of the lung:

- small cell NECs are composed of small- to medium-sized cells, with scant cytoplasm and round to ovoid, hyperchromatic nuclei with coarse chromatin and inconspicuous nucleoli. Nuclear moulding may be present.
- large cell NECs are composed of medium-sized to large cells, with highly atypical, vesicular nuclei and prominent nucleoli
- the growth pattern is solid/diffuse, with frequent areas of necrosis
- the proliferative activity is always high with mitotic counts usually in the range of 30 to 145 (median: 65) per ten high power fields (HPFs) and a Ki-67 index of 50–100%.

Terminology, definition and diagnostic criteria for mixed tumours are as follows:

- the term MiNEN replaces the previous term MANEC
- MiNENs may have a non-endocrine component other than adenocarcinoma (e.g. squamous cell carcinoma, acinar cell carcinoma)
- to qualify as MiNEN, each component must comprise at least ~30% of the entire tumour
- usually both components are high grade (G3), but occasionally one of the two or both components may belong to the G1/G2 category. When the components are morphologically distinguishable, they should be individually graded, using the respective grading systems for each.

5.4.3 Organ-specific characteristics

Gastric NENs

At least five neuroendocrine cell types have been described in the human gastric mucosa: histamine-producing ECL-cells, serotonin-producing enterochromaffin-cells (EC-cells), gastrin-producing G-cells, somatostatin-producing D-cells and ghrelin-producing X/A-like cells, but most gastric NENs are composed of ECL-cells.

There are three distinct types of ECL-cell NETs.[4] Examination of the background non-neoplastic mucosa is essential to discriminate the three forms of ECL-cell NETs. Use of immunohistochemistry for synaptophysin or chromogranin (if available) and gastrin (if available) is recommended for identification of early hyperplastic ECL-cell proliferations. ECL-cells are the main neuroendocrine cells of the stomach, comprising approximately 70% of the gastric neuroendocrine cells. They are located in the body/fundic glands. They are positive for neuroendocrine markers and negative for gastrin, since they secrete histamine rather than gastrin like antral G-cells. Gastrin immunostain helps to establish that the chromogranin-positive cells are not G-cells but ECL-cells, which is useful when identifying the site of the biopsy as gastric body/fundus, particularly when the latter is affected by autoimmune chronic atrophic gastritis and the oxyntic glands are entirely replaced by metaplastic antral-like and intestinal type glands.

Histologically, the benign/preneoplastic gastric neuroendocrine proliferations are classified as:

- ECL-cell hyperplasia:[25]
  - simple (diffuse), defined as an increased number (more than two times greater than normal values) of endocrine cells, otherwise retaining their normal distribution
  - linear or chain forming, defined as linear sequences of at least five cells along the basement membrane and at least two chains per millimetre length of mucosa
  - micronodular, defined as clusters of five or more cells (size 30–150 μm), either within glands or the deep aspect of the lamina propria, and at least one micronodule per millimetre length of mucosa
  - adenomatoid, defined as at least five adjacent micronodules with intervening basal membrane in the lamina propria
- ECL-cell dysplasia, defined as large confluent micronodules of ECL-cells lying deep in the mucosa, ranging from 150 to 500 μm in size.

Table 2: Pathological/clinical features of gastric NENs.[4,29]

Features	Type		
	I	II	III
Histology	ECL-cell WD-NET	ECL-cell WD-NET	ECL-cell WD-NET
Grading	G1 G2 (rare) G3 (exceptional)	G1 G2 (rare)	G1 (rare) G2 G3 (rare)
Background mucosa	CAG + ECL-cell hyperplasia[26] +/− antral G-cell hyperplasia	Hyperplasia of parietal cells + ECL-cell hyperplasia[26]	Normal
Location	Fundus/corpus	Fundus/corpus	Anywhere
Number of tumours	Multifocal	Multifocal	Solitary
Serum gastrin level	Secondary hypergastrinaemia (resulting from achlorhydria)	Primary hypergastrinaemia (resulting from gastrin-secreting tumours)	No hypergastrinaemia
Pathogenetic mechanism	Autoimmune gastritis	ZES, MEN I	Undetermined
Clinical course	Indolent, regress spontaneously, endoscopic removal often adequate	Somatostatin analogues effective	Aggressive behaviour

CAG: Chronic atrophic gastritis; ECL: Enterochromaffin-like; MEN I: Multiple endocrine neoplasia syndrome, type I; WD-NET: Well-differentiated neuroendocrine tumour; ZES: Zollinger–Ellison syndrome.

Duodenal NENs[29]

A significant proportion of gastrin-producing well-differentiated NETs occur in the gastrinoma triangle of the duodenum. A third are associated with Zollinger–Ellison syndrome; these patients are typically younger, and the tumours have more indolent behaviour compared with those seen in other cases. Despite being small or occult, one third of duodenal gastrinomas have lymph node metastases. Some syndromic gastrinomas appear as primaries within peripancreatic lymph nodes, although undetected minute duodenal primaries with large nodal metastases likely account for some of these cases.

Ampullary NENs
Ampullary NENs can be very glandular and mistaken for an adenocarcinoma, particularly when they entrap ampullary ductules. They characteristically contain psammoma bodies. These NENs are often called somatostatinomas, not because patients have somatostatin-related symptoms, but because tumour cells typically stain positive for somatostatin immunohistochemically.[29]

Small bowel NENs
The distal small bowel is the most common site of clinically relevant well-differentiated NETs,[29] with most small bowel NENs being derived from the serotonin-producing EC-cells. These are well known for manifesting with a mesenteric mass, leading to buckling or tethering of the bowel. Microscopically, they typically show a nested growth pattern with characteristic peripheral cytoplasmic granularity and palisading. Rosette formation can be seen, especially at the periphery of the nests. Artifactual clefting around the nests is common, potentially leading to misdiagnosis as lymphovascular invasion. Small bowel NENs are those most associated with the classic carcinoid syndrome of diarrhoea, flushing and right heart fibrosis. Even small tumours have a strong tendency to metastasise to local lymph nodes and the liver.[2]

Appendiceal NENs
The tip of the appendix is the preferred site of appendiceal NENs. Most tumours are detected incidentally during appendicectomies for acute appendicitis. More than 95% of appendiceal well-differentiated NETs are smaller than 2 cm in diameter. Appendicectomy is considered curative for non-angioinvasive well-differentiated NETs <2 cm, confined to appendix with <3 mm deep invasion of the subserosa/mesoappendix and clear resection. Right-sided hemicolectomy is justified only in those rare tumours measuring 1–2 cm, but with positive or unclear margins or with deep mesoappendiceal invasion (>3 mm; ENETS stage T3), higher proliferation rate (G2), appendiceal base location and/or vascular invasion. Tumours with a diameter >2 cm should be treated by right-sided hemicolectomy.[30] The invasion into the subserosa/mesoappendix has been shown to have a higher rate of vascular (V1) or lymphatic vessel involvement (L1) than in cases without. Furthermore, an invasion depth of >3 mm has been suggested to reflect the aggressiveness of the disease.[13,30] The ENETS TNM staging system recognised the prognostic significance of the depth of invasion of the subserosa/mesoappendix, for this reason it is important to measure the depth of invasion beyond the muscularis propria, distinguishing a minimal invasion up to 3 mm (pT2) from an extensive invasion with a depth of >3 mm (pT3). The previous UICC TNM (7) was based on size only, whereas the latest UICC TNM (8) also recognises the importance of the invasion of the subserosa/mesoappendix for T stage, although without measuring the depth of invasion.

Although the spectrum of appendiceal goblet cell tumours has been included within the 2010 WHO classification of NENs of the appendix, these tumours are associated with a less favourable clinical outcome compared with stage-matched ordinary NENs; however, they have a more favourable disease-specific survival rate as compared with conventional appendiceal adenocarcinomas. According to the latest WHO 2019 classification of tumours of the digestive system,[4] the goblet cell tumours (previously called “goblet cell carcinoids”) have been renamed goblet cell adenocarcinoma, a tumour that must demonstrate at least a component of classic low-grade goblet cell adenocarcinoma. Staining for chromogranin and synaptophysin highlights variable numbers of endocrine cells, but these stains are not required for diagnosis. Goblet cell adenocarcinoma is graded by using a three-tiered system[31] based on the proportion of the tumour that consists of low-grade and high-grade pattern (see Table 3), thus Ki-67 and mitotic count are not used in the grading of these tumours. The staging of appendiceal goblet cell adenocarcinoma is identical to that of appendiceal adenocarcinoma UICC TNM 8.[4,31]

Table 3: Three-tiered grading system for goblet cell adenocarcinoma.[4,31]

Grade	Tubular or clustered growth (low-grade pattern)	Loss of tubular or clustered growth (any combination of high-grade patterns)
1	>75%	<25%
2	50–75%	25–50%
3	<50%	>50%

Hindgut/colorectal NENs

Rectal NENs are more common than colonic NENs. Macroscopically, rectal NENs present as a solitary sessile or semi-pedunculated polyp with intact overlying epithelium. Histologically, rectal well-differentiated NETs show a characteristic trabecular pattern. Immunohistochemically, rectal NENs are usually positive for prostatic acid phosphatase and synaptophysin and negative for chromogranin A. Well-differentiated NETs are uncommon in the large bowel, the majority of which are detected in the caecum. Histologically, colonic well-differentiated NENs proliferate with a nodular, trabecular or mixed pattern. NECs are more common in the colon, especially the right colon, than in the rectum. Large cell carcinoma is the most common colorectal NEC.[2,29]

PanNENs

PanNENs constitute less than 5% of pancreatic tumours. Almost half are functional and show serologic activity attributable to one of the six hormones that are produced by the islet cells (i.e. insulin, glucagon, gastrin, somatostatin, vasoactive intestinal polypeptide or pancreatic polypeptide),[29] along with other less common tumours producing serotonin[32] (resembling midgut/small bowel EC-cell NETs), adrenocorticotropic hormone, growth hormone-releasing hormone, parathyroid hormone-related protein and cholecystokinin.[4] The suffix 'oma' following the name of a hormone (e.g. gastrinoma, insulinoma, glucagonoma, etc.) should not be used in the pathology reports, as the functional terms are clinical terminology indicating a precise clinical syndrome related to excessive production of that hormone and are not histopathological diagnostic categories. For cases in which the production of a specific hormone has been demonstrated in the majority of the neoplastic cells, it is acceptable to supplement the diagnosis of PanNET to reflect the corresponding cell type (e.g. 'α cell/glucagon-producing NET', 'β cell/insulin-producing NET', 'G-cell/gastrin-producing NET').[2] Although there are prognostic implications to some of the functional categories (e.g. insulinomas are generally very indolent), the biologic behaviour of most functioning NETs is still defined by the grade and stage of the tumour. Pancreatic well-differentiated NETs appear to have more morphologic versatility than GI well-differentiated NETs. Along with the lipid-rich, clear cell, pleomorphic, oncocytic, rhabdoid and other variants, which are more commonly seen in PanNETs, some PanNETs exhibit a pattern very similar to that of paragangliomas.[29]

5.4.4 Use of immunohistochemistry

The histological diagnosis of NENs is based on morphological criteria and is confirmed by immunohistochemical staining. The immunohistochemistry must be adequately controlled and quality assured, for example through laboratory membership of an immunohistochemistry national external quality assessment scheme (NEQAS).

All GEP-NENs are epithelial tumours and this should be confirmed using pancytokeratins, such as CAM5.2, MNF-116 or AE1/3, to exclude a potential non-epithelial NEN[33] (paraganglioma, Ewing sarcoma, primitive neuroectodermal tumours, etc.).

The neuroendocrine signature of a cell is defined by the expression of general and specific neuroendocrine markers. General neuroendocrine markers are observed in all cell types and include chromogranin A (staining of components of neurosecretory granules), synaptophysin (staining synaptic vesicles), neuron-specific enolase (NSE), protein gene product 9.5 (PGP9.5) and neural cell adhesion molecule (N-CAM or CD56). Chromogranin A is the most specific,

whereas synaptophysin is very sensitive but less specific, with a variety of mimics showing potential expression of this marker. CD56 is even less specific (it should not be used as a sole marker of neuroendocrine differentiation). Therefore, only synaptophysin and chromogranin A are recommended for use in routine practice. The use of other markers, such as CD56/N-CAM, Leu7, PGP9.5 and NSE, is discouraged owing to their low specificity.[29,33,34]

It should be noted that:

- in poorly differentiated NECs, only synaptophysin may be detected. The rate of chromogranin A positivity is reduced.[33,34]
- in large cell NECs, positivity for synaptophysin is mandatory[33]
- care must be taken when using CD56 alone in the diagnosis of NENs, particularly NECs. Poorly differentiated carcinoma from any site can express positivity for CD56. Isolated positivity for CD56 only, in the absence of expression for at least another neuroendocrine marker (preferably synaptophysin, as chromogranin A can be absent or focal in NECs), is not sufficient for a diagnosis of an NEC. Since it is good and safe practice to always have positive expression of at least two neuroendocrine markers to confirm the neuroendocrine nature of a morphologically suspected NEN, CD56 can be used in diagnostic practice as an additional marker, especially when chromagranin A or synaptophysin expression is absent or questionable.

  [Level of evidence – GPP.]
- rectal/hindgut NENs are often negative for chromogranin A[34] and can express prostatic acid phosphatase; this presents a potential diagnostic pitfall for tumours arising in male patients.[35]

Specific neuroendocrine markers include peptide hormones and bioamines (e.g. gastrin, serotonin, insulin, glucagon, pancreatic polypeptide, somatostatin, etc.). Routine immunohistochemical staining for these markers is not recommended, but is optional in selected cases, since functional NENs are not defined by immunohistochemical expression, but rather by clinical symptoms and serology.[36] Limited peptide immunohistochemistry can be performed (e.g. for insulin or gastrin) if there is a clinical indication to demonstrate the production of a specific peptide in a functional tumour.[36]

Regarding site-specific immunomarkers, most GI-NENs express CDX2. In particular, diffuse positivity for both serotonin and CDX2 is a characteristic feature of an EC NEN of midgut origin. However, some PanNENs also express CDX2,[37] although the staining pattern is usually weak and patchy compared with the strong and diffuse staining observed in midgut well-differentiated NETs.[32] Several transcription factor proteins, such as PDX1, ISL-1 and PAX8, have been reported to be pancreas-specific.[38] Positivity for thyroid transcription factor-1 (TTF-1) in a well-differentiated NET favours a primary site from either the head and neck (specifically medullary thyroid carcinoma) or the thorax (specifically pulmonary carcinoid). However, TTF-1 is not helpful in indicating the site of origin in cases of high-grade NECs, such as small cell carcinoma, as poorly differentiated NECs, regardless of the site, may express this marker.[39]

BCL2 overexpression, loss of RB expression and abnormal p53 expression (either total loss or overexpression) were more commonly seen in poorly differentiated NECs, whereas expression of these proteins was reported in only a few well-differentiated NETs. Therefore, BCL2, RB and p53 immunohistochemical staining can be useful in some settings for discriminating well-differentiated NETs (particularly G3 well-differentiated NETs) from poorly differentiated NECs.[8,40]

Although somatostatin receptor functioning imaging is widely used in the clinical setting for planning treatment with somatostatin analogues, immunohistochemical staining for the

somatostatin receptor is not recommended for routine practice. However, it could be indicated, if available, in the absence of in vivo somatostatin imaging studies.[34]

5.4.5 Tumour grade

Grading is performed on the basis of proliferative activity, according to the WHO 2017 classification[3] for PanNENs (see Table 4) and the WHO 2019 classification[4] for GI-NENs (see Table 4). Mitotic count is reliable when there is a large volume of tumour to evaluate (e.g. surgical resection), while the Ki-67 index is more reliable when the sample size is limited (e.g. biopsy). If the grade differs when classifying according to mitotic count compared with the Ki-67 index, it is suggested that the higher grade should be assumed.[2,3,4]

Table 4 (whose categories have the accumulated evidence on their prognostic value) was based around 0.2 mm^2 HPFs for assessment of mitotic count. Pathologists should determine the diameter of their own microscope's HPF with the exact objective, eyepieces and other lenses that they prefer to use, and calculate the area of that field to enable adjustment to be made to their counts. For example, if a microscope has an HPF of 0.22 mm^2 (10% larger than 0.2 mm^2), then the count will be 10% higher and needs to be multiplied by 100/110 to achieve the count that would have been made if the field had only been 0.2 mm^2 in area. In practice, ×40 HPFs on a modern microscope with wide-field optics can considerably exceed 0.2 mm^2, therefore it is necessary to check and adjust accordingly.

Table 4: Grading system for PanNENs[3] and GI-NENs.[4]

Grade	Mitotic count (10 HPFs)*	Ki-67 index (%)**
G1	<2	<3***
G2	2–20	3–20
G3	>20	>20

*10 HPF = 2 mm^2 based on each HPF being 0.2 mm^2 with at least 50 consecutive fields evaluated in areas of highest mitotic density (hot spots).

**Ki-67 proliferation index is based on the evaluation of ≥500 tumour cells in the areas of highest nuclear labelling (so-called hot spots). For assessing Ki-67, casual visual estimation (eyeballing) is not recommended; manual counting using printed images is advocated.

***<3 replaces ≤2 in the 2010 WHO classification to include decimal numbers between 2 and 3.

HPF: High power field.

The Ki-67 index should be assessed on regions of most intense and highest nuclear labelling using a validated antibody (i.e. MIB1 antibody).

The new recommendations for reporting Ki-67, according to the WHO 2017 classification of PanNENs and the WHO 2019 classification of GI-NENs are:

- the Ki-67 is based on the evaluation of ≥500 cells
- round up or down to the nearest whole number
- manual counting using camera-captured, printed images is recommended instead of casual visual estimation or eyeballing.

5.4.6 Local invasion

The structures invaded, with relevant maximum depth measurements, should be recorded where they underpin the pT stage (Appendix A), as in the proformas. The pT stage thresholds vary depending on tumour site.

5.4.7 Resection margins

a) Doughnuts: it is not necessary to examine doughnuts from stapling devices histologically if the tumour does not reach the end margin of the main resection specimen. If doughnuts

are not sectioned or if no doughnuts are submitted for examination, this item should be recorded as 'Not applicable'.

b) Margin (cut end): cut ends are examined histologically when the main tumour is within 30 mm of one or both of these or in other rare cases described in section 5.2.1e. The presence or absence of tumour should be recorded. If margins are not examined histologically, the proforma item should be recorded as 'Not applicable'.

c) Non-peritonealised ('circumferential') resection margin and/or mesenteric margin: if this surgically transected margin is positive in a resection specimen, it should be highlighted in the pathology report and brought to the attention of the MDT. The minimum distance between the tumour and the non-peritonealised margin in millimetres should also be recorded from the histological slides. It is not known what distance constitutes adequate clearance for NENs. The serosa is not a resection margin (see section 7.1), but any serosal involvement should be reported.

5.4.8 Metastatic spread

a) Lymph nodes: all lymph nodes that have been identified in the specimen should be examined histologically. Multiple or serial sections from lymph node blocks are not recommended for routine reporting, neither is the use of immunohistochemistry or molecular techniques, because there is insufficient evidence about the prognostic significance of tumour deposits identified in this way. Any tumour involvement of a lymph node, no matter how small, is regarded as significant, but extracapsular invasion is not recorded specifically. Lymph nodes are distinguished from extramural lymphoid aggregates by the presence of a peripheral sinus.

[Level of evidence B – nodal status predict prognosis.]

b) Tumour deposits: controversy persists around the distinction between tumour deposits and lymph nodes and their prognostic significance. The recently revised UICC TNM 8 clarified this issue for colorectal carcinomas, defining tumour deposits (satellites) as discrete macroscopic or microscopic nodules of cancer in the perivisceral adipose tissue's lymph drainage area of a primary carcinoma, which are discontinuous from the primary and do not show histological evidence of residual lymph node or identifiable vascular or neural structures. Furthermore, according to the UICC TNM 8 definition, the presence of tumour deposits does not change the primary tumour T category, but changes the node status (N) to N1c if all regional lymph nodes are negative, implying that the number of tumour deposits should not be added to the total number of positive lymph nodes and the N1c status should only be used in cases without any positive lymph nodes. Regarding NENs, only two studies, from the same group, have attempted to determine the appropriate classification of tumour deposits in patients with small intestine NETs.[41,42] Gonzalez *et al*[41] defined mesenteric tumour deposits (MTDs) as discrete mesenteric tumour nodules >1 mm with an irregular growth profile, differentiating them from lesions that could be similar but clearly resulting from extranodal extension or direct contiguous spread by the primary lesion. The deposits were significantly associated with lymphovascular invasion ($p=0.001$), pT3 or pT4 disease ($p=0.001$), nodal metastases ($p=0.040$) and liver metastases ($p<0.001$) at time of surgery. The authors concluded that given the propensity of small intestine NET deposits to occur alongside lymph node disease and the evidence that they are a metastatic phenomenon, their preliminary data supported the place of small bowel mesenteric tumour deposits within the American Joint Committee on Cancer (AJCC) N-classification. In 2017, the same group[42] observed that almost all MTDs were located adjacent to medium- or large-sized vessels. In some MTDs, partial occlusion of a large vein by tumour could be seen. In other cases, arteries, without identifiable accompanying veins, were encased by tumour. Therefore, this time, they concluded that venous invasion was the probable initial step for development of MTDs. The authors also demonstrated that MTDs associated with midgut NETs were a stronger indicator than lymph node metastases for liver metastasis and overall prognosis. In their opinion, the presence of MTDs should be considered as a more advanced stage than Stage IIIB (T1–4N1), perhaps as Stage IIIC. However, prospective

studies are needed to resolve this controversy. In the meantime, for the purposes of this dataset, tumour deposits should be recorded in the diagnostic report, but they should not be added to the total number of positive lymph nodes while further studies are awaited to clarify the nature and the prognostic significance of the tumour deposits in the gastroenteropancreatic tract. A 2 cm cut-off for including mesenteric masses in N-classification has been introduced by the UICC TNM 8, with any mesenteric tumour deposit larger than 2 cm signifying pN2 disease, although this criterion has not been critically evaluated as a prognostic factor for small intestinal NETs.

[Level of evidence – GPP.]

c) Lymphovascular invasion: lymphovascular invasion is diagnosed by the presence of tumour deposits within the lumen of a venous vessel (V1) or within the lumen of a lymphatic channel (L1). Macroscopic involvement of the wall of veins (with no tumour within the veins) is classified as V2.[14] Detection of unequivocal lymphatic invasion can be challenging, especially in small bowel NENs, owing to frequent retraction artefacts. In such difficult cases, immunohistochemical staining for D2-40 can help to differentiate lymphatic invasion from stromal cleft as well as lymphatic invasion from venous invasion, since D2-40 stains lymphatic endothelium but does not stain the normal vascular endothelium. Many of the venous vessels contain a muscular wall and elastic lamina that can be detected in problematic cases using immunohistochemical stain for caldesmon (if available) or desmin and elastin histochemical stains, respectively.

[Level of evidence B – lymphovascular invasion predicts prognosis.]

d) Histologically confirmed distant metastases: the presence of histologically confirmed distant metastases and their site is recorded. The site of distant metastases should be recorded, as some sites (e.g. bone) confer an adverse prognosis.[43,44] Cross reference should be made to the biopsy number documenting the distant metastasis if this is separate. Serosal deposits that are discontinuous to the primary tumour can be seen, especially in small bowel NENs on the serosal surface of the mesentery, appendix and large bowel. They are most likely caused by free cancer cells exfoliation from serosa-invasive tumours and should not be considered as M1 if found within the surgical field of the primary tumour. The trans-coelomic dissemination of NENs and its underlying mechanisms have not been studied yet, thus need to be investigated in large-scale studies.

5.4.9 Background abnormalities

The presence of relevant pathological abnormalities in the background tissue should be recorded. Hyperplastic changes of the neuroendocrine cell system may have the potential to evolve into neoplastic diseases. This is particularly the case in the setting of genetically determined and hereditary NET syndromes such as multiple endocrine neoplasia type 1 (MEN 1).[28] Non-neoplastic neuroendocrine growths of the GI tract and pancreas are relatively rare lesions. Non-neoplastic proliferative changes of the distal small intestine, appendix and colon–rectum have not been defined systematically.[25] For gastric hyperplastic/preneoplastic lesions, please see section 5.4.3.[25]

6 Non-core data items

6.1 Macroscopic

The following are non-core macroscopic data items:

- if multiple tumours, tumour dimensions of all tumours
- specimen dimensions for each organ included
- precise anatomical location of non-peritonealised margin involvement (rectal tumours).

6.2 Microscopic

The following are non-core microscopic data items:

- presence of amyloid
- presence of psammoma bodies.

6.3 Other

Other non-core data items include:

- molecular data, if available
- markers predictive of response to specific treatments, if available:
  - SSTR-2A (immunohistochemical determination at the cell membrane level), for planning treatment with somatostatin analogues
  - Akt/mTOR pathway molecules (PIK3, PTEN, TSC2), for treatment with everolimus
  - thymidylate synthase, for treatment with antifolates
  - ERCC-1, for treatment with platinum
  - topoisomerase IIα, for treatment with etoposide
  - epigenetic events, such as methylation of the *MGMT* promoter, for treatment with alkylating agents.[45]

7 Pathological staging

7.1 Complete resection at all margins

This includes the ends of the specimen, the non-peritonealised resection margin and any doughnuts. Tumours that are completely excised are classified as R0, those with microscopic (but not macroscopic) margin involvement are classified as R1 and those with macroscopic margin involvement are classified as R2.

It is not known what distance constitutes adequate clearance for GEP-NENs (see also section 5.4.7). Current guidelines for non-NETs (e.g. pancreatic and colorectal) generally consider a margin clearance of <1 mm as involved and needing consideration for further therapy. The growth pattern of pancreatobiliary adenocarcinomas and many colorectal adenocarcinomas is infiltrative and discontinuous, justifying the adoption of the 1 mm rule. Conversely, well-differentiated GEP-NETs generally display a well-circumscribed border with a pushing growth pattern and are sometimes encapsulated. In view of these characteristics, it is most likely more appropriate to adopt the approach of 0 mm clearance (e.g. tumour cells are present at the resection margin) when considering margin involvement for well-differentiated GEP-NETs. Conversely, the rule of 1 mm clearance should be adopted for poorly differentiated GEP-NECs as they are more likely to have an infiltrative growth pattern. Further studies are needed to resolve the controversies around margin involvement in GEP-NENs.

[Level of evidence – GPP.]

When doughnuts and the ends of the specimen are not examined histologically, the proforma item should be recorded as ‘Not applicable’ (see section 4).

Non-peritonealised margins are regarded as involved if tumour macroscopically extends into them (see sections 5.2.1e and 5.4.7c).

Peritoneal (serosal) involvement alone is not a reason to categorise the tumour as incompletely excised as peritoneum is not a resection margin, although such involvement needs to be noted as it may carry an adverse prognosis through trans-coelomic metastases, e.g. with classical ileal NETs[46] and appendiceal goblet cell carcinoid tumours.

7.2 TNM staging

7.2.1 Tumour

The ENETS TNM systems proposed in 2006[12] and 2007[13] are recommended for GEP-NEN staging (Appendix A). The treatment and management of patients with GEP-NENs is based on the ENETS TNM staging system in the UK, especially for appendiceal NETs (see section 5.4.3).

The designation 'tumour in situ' (Tis) is currently used for gastric lesions only, and is defined as an intramucosal NEN that measures >0.5 mm in dimension.[47] Smaller nodules of neuroendocrine cells (between 0.15 mm and 0.5 mm) are termed 'dysplasia'. We do not propose tumour in situ for the duodenum and pancreas, because no definition has been agreed upon, although a proposal has been made.[12] For the pancreas, a microadenoma is recognised as a benign neoplasm <5 mm in diameter, which immunohistochemically shows loss of the multihormone expression seen in normal islets. Multiple microadenomas (microadenomatosis) can be associated with MEN 1 and is included in Appendix E for completeness.

In 2017, the UICC TNM 8 classification[14] largely adopted the ENETS TNM classification. The ENETS and UICC systems are now comparable for the T stage of the stomach, duodenum, jejunum, ileum, colon, rectum and pancreas, but not for the appendix (see Table 5).

There are still minor differences between the two staging systems in the N category for jejunum/ileum NENs and M category for all GEP-NENs. For these reasons, we recommend documenting in the pathology reports the underlying features that contribute to the stage classification (such as tumour size, extent of invasion, number of lymph nodes, site of metastasis, etc.) to allow translation between the ENETS and UICC classification systems. If a stage is documented, it is critical for the pathologist to clarify which classification system is being used. When adopting the UICC TNM classification, please be aware that the UICC classification of GEP-NENs is used for well-differentiated NETs only; high-grade poorly differentiated NECs are excluded and should be staged according to criteria for classifying adenocarcinomas at the respective site.[14]

Table 5: ENETS[12,13] versus UICC TNM 8[14] of the appendix.

Stage	ENETS	UICC TNM 8
T1	≤1 cm, invading submucosa and muscularis propria	<2 cm
T2	≤2 cm, invading submucosa, muscularis propria and/or minimally (up to 3 mm) invading subserosa/mesoappendix	>2 cm but <4 cm
T3	>2 cm and/or extensive (more than 3 mm) invasion of subserosa/mesoappendix	>4 cm or with subserosal invasion or involvement of the mesoappendix
T4	Invasion of peritoneum/other organs	Invasion of peritoneum/other organs other than direct mural extension to adjacent subserosa
N1	Regional lymph node metastasis	Regional lymph node metastasis
M1	Distant metastasis	Distant metastasis • M1a – hepatic metastasis only • M1b – extrahepatic metastasis only • M1c – hepatic and extrahepatic metastasis

ENETS: European Neuroendocrine Tumour Society; UICC: Union for International Cancer Control.

7.2.2 Nodes

N1 indicates the presence of any single or multiple metastases in any lymph node group. Data on the prognostic significance of involvement of specific named lymph nodes is lacking for NENs. Specification of individually involved lymph nodes has therefore not been included as a core data item, although the option of naming involved nodes has been provided in the pancreatic proforma (see Appendix E) to enable similar data to that for adenocarcinomas to be rendered, if desired, by the local MDT.

7.2.3 Histologically confirmed distant metastases

M1 indicates the presence of any single or multiple metastases at any anatomical site. Since there is evidence that extrahepatic bone metastases are a particularly adverse development,[43,44] we recommend that the anatomical site of the metastases be specified using the TNM classification rules (PUL: pulmonary; HEP: hepatic; OSS: osseous, etc.).

8 Reporting of local excision specimens of GI-NENs

Small NENs of the stomach, duodenum or large intestine may be treated initially by polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection or transanal endoscopic microsurgical excision. Less commonly, more advanced tumours may undergo palliative local excision in debilitated patients.

While the principles of pathological reporting are the same as in major resections, and it is recommended that the same reporting proformas are used, a number of features require special attention in local excisions of (presumed) early NETs with curative intent because they may be used to determine the necessity for more radical surgery. These are:

- maximum tumour dimension in millimetres
- histological type/differentiation
- WHO classification
- histological grade

- extent of local invasion
- vascular invasion
- perineural invasion
- margin involvement
- the minimum clearance from the nearest excision margin (in millimetres)
- the pT stage.

Determination of the above features will generally require the entire specimen to be embedded and the cutting of careful levels to clarify the status of some categories such as resection margins. It is accepted that for mucosal biopsies and some mucosal resections, it will not be possible to provide tumour size, depth of invasion and WHO typing. When this is the case, these values should be entered as 'Not applicable'.

9 Reporting of small biopsy specimens

GI-NENs may be encountered in small mucosal biopsies, as a suspected or completely unexpected finding. The main challenges in interpretation are identifying these tumours (i.e. there may be only a small amount of tumour present and only at the base of the biopsy) and differentiating them from adenocarcinomas, particularly with some duodenal ampullary and rectal tumours. For gastric NETs, background mucosal biopsies may be submitted alongside the tumour biopsy, e.g. for comment on chronic/atrophic gastritis and/or neuroendocrine cell hyperplasia.[25] PanNETs may be subject to needle core and/or endoscopic ultrasound-guided fine needle aspiration cytology or fine needle biopsy. The key differential diagnoses are against inflammatory lesions and adenocarcinoma.[18]

With all types of small biopsy, the challenges are: prioritisation of immunohistochemistry for differential diagnosis and grading, with pancytokeratin, synaptophysin, chromogranin A and Ki-67 immunohistochemistry being appropriate in the initial profile; and grading of the tumour on a small sample.

It may be difficult to establish a reliable mitotic count. The Ki-67 labelling percentage may be easier to establish than the mitotic count under these circumstances. It is common only to be able to state a minimum ENETS TNM stage from a biopsy.

10 Reporting of frozen sections

Frozen sections of primary tumours and their metastases may be submitted, especially where these are unexpected findings. In many circumstances, complete excision of the intact tumour, even if it has not previously been biopsied, is the treatment of choice, with no frozen sections, since the required operation would be the same, irrespective of the nature of the tumour. Occasionally, frozen sections are submitted for comment on resection margin clearance.

11 SNOMED coding of GEP-NENs

GI-NENs and PanNENs should be coded according to the SNOMED CT system (see Appendix B).

It is noted, however, that SNOMED is now in a practical transition phase, as part of the intended full implementation by the NHS and PHE of SNOMED CT. SNOMED ceased to be licensed by the International Health Terminology Standards Development Organisation from 26 April 2017.

A list of applicable T and M SNOMED and SNOMED CT codes is provided in Appendix B. Mapping SNOMED CT terminology is provided.

12 Criteria for audit

As recommended by the RCPath as key performance indicators (see *Key Performance Indicators – Proposals for implementation,* July 2013*,* www.rcpath.org/profession/quality-improvement/kpis-for-laboratory-services.html), reports on NENs of the gastroenteropancreatic tract should be audited for the following:

- the inclusion of SNOMED or SNOMED CT codes:
  - standard: 95% reports should have T, M and P codes (or equivalent SNOMED CT codes)
- it is recommended that at least 95% of reports on tumour resections should record a full set of core data items
- the use of electronic structured reports or locally agreed proformas (it is assumed that these processes will ensure that 95% of core data items are recorded):
  - standard: 95% of resection specimens will include 100% of data items presented in a structured format
- turnaround times for biopsies and resection specimens:
  - standard: 80% of diagnostic biopsies will be reported within seven calendar days of the biopsy being taken
  - standard: 80% of all histopathology specimens (excluding those requiring decalcification) will be reported within ten calendar days of the specimen being taken.

13 References

1. Royal College of Pathologists and Institute of Biomedical Scientists. *The Role of Biomedical Scientists in Histopathology Reporting: A Joint Statement from the Royal College of Pathologists and Institute of Biomedical Science*. Accessed October 2017. Available at: https://www.rcpath.org/discover-pathology/news/biomedical-scientists-bmss-in-histopathological-reporting.html

2. Bosman FT, Carneiro F, Hruban RH, Theise ND (eds). *WHO Classification of Tumours of the Digestive System* (*4th edition)*. Lyon, France: International Agency for Research on Cancer, 2010.

3. Lloyd RV, Osamura RY, Klöppel G, Rosai J (eds). *WHO Classification of Tumours of Endocrine Organs (4th edition)*. Lyon, France: International Agency for Research on Cancer, 2017.

4. WHO Classification of Tumours Editorial Board. *WHO Classification of Tumours of the Digestive System* (*5th edition)*. Lyon, France: International Agency for Research on Cancer, 2019.

5. Solcia E, Klöppel G, Sobin LH (eds). *Histological Typing of Endocrine Tumours. WHO International Histological Classification of Tumours (2nd edition)*. Berlin, Germany: Springer-Verlag Berlin Heidelberg, 2000.

6. DeLellis RA. *Pathology and Genetics of Tumours of Endocrine Organs (3rd edition)*. Lyon, France: International Agency for Research on Cancer, 2004.

7. Schmitt AM, Blank A, Marinoni I, Komminoth P, Perren A. Histopathology of NET: Current concepts and new developments. *Best Pract Res Clin Endocrinol Metab* 2016;30:33–43.

8. Yachida S, Vakiani E, White CM, Zhong Y, Saunders T, Morgan R *et al.* Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. *Am J Surg Pathol* 2012;36:173–184.

9. Velayoudom-Cephise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, Leboulleux S *et al.* Are G3 ENETS neuroendocrine neoplasms heterogeneous? *Endocr Relat Cancer* 2013;20:649–657.

10. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P *et al.* Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol* 2013;24:152–160.

11. Basturk O, Yang Z, Tang LH, Hruban RH, Adsay V, McCall CM *et al.* The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol* 2015;39:683–690.

12. Rindi G, Kloppel G, Alhman H, Caplin M, Couvelard A, de Herder WW *et al.* TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006;449:395–401.

13. Rindi G, Kloppel G, Couvelard A, Komminoth P, Korner M, Lopes JM *et al.* TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007;451:757–762.

14. Brierley J, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours* (*8th edition)*. Oxford, UK: Wiley-Liss, 2017.

15. Hochwald SN, Zee S, Conlon KC, Colleoni R, Louie O, Brennan MF *et al.* Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol* 2002;20:2633–2642.

16. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 2010;39:707–712.

17. Plockinger U, Rindi G, Arnold R, Eriksson B, Krenning EP, de Herder WW *et al.* Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology* 2004;80:394–424.

18. Verbeke CS. Endocrine tumours of the pancreas. *Histopathology* 2010;56:669–682.

19. Burroughs SH, Williams GT. ACP Best practice no 159. Examination of large intestine resection specimens. *J Clin Pathol* 2000;53:344–349.

20. Campbell F, Cairns A, Duthie F, Feakins RM. *Dataset for the Histopathological Reporting of Carcinomas of the Pancreas, Ampulla of Vater and Common Bile Duct* (*3rd edition)*. London, UK: The Royal College of Pathologists, 2017. Available at: https://www.rcpath.org/profession/guidelines/cancer-datasets-and-tissue-pathways.html

21. Ludeman L, Shepherd N. Macroscopic assessment and dissection of colorectal cancer resection specimens. *Curr Diagn Pathol* 2006;12:220–230.

22. Quirke P, Morris E. Reporting colorectal cancer. *Histopathology* 2007;50:103–112.

23. Verbeke C. Resection margins and R1 rates in pancreatic cancer – are we there yet? *Histopathology* 2008;52:787–796.

24. Novelli MR. *Dataset for the Histopathological Reporting of Gastric Carcinoma* (*2nd edition)*. London, UK: The Royal College of Pathologists, 2007.

25. Rindi G, Solcia E. Endocrine hyperplasia and dysplasia in the pathogenesis of gastrointestinal and pancreatic endocrine tumors. *Gastroenterol Clin North Am* 2007;36:851–865.

26. Anlauf M, Garbrecht N, Bauersfeld J, Schmitt A, Henopp T, Komminoth P *et al.* Hereditary neuroendocrine tumors of the gastroenteropancreatic system. *Virchows Arch* 2007;451:S29–38.

27. Hemminki K, Li X. Familial carcinoid tumors and subsequent cancers: a nation-wide epidemiologic study from Sweden. *Int J Cancer* 2001;94:444–448.

28. Kloppel G, Anlauf M, Perren A, Sipos B. Hyperplasia to neoplasia sequence of duodenal and pancreatic neuroendocrine diseases and pseudohyperplasia of the PP-cells in the pancreas. *Endocr Pathol* 2014;25:181–185.

29. Odze RD, Goldblum JR. *Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas.* Philadelphia, PA, USA: Elsevier Saunders, 2014.

30. Pape UF, Niederle B, Costa F, Gross D, Kelestimur F, Kianmanesh R *et al.* ENETS consensus guidelines for neuroendocrine neoplasms of the appendix (Excluding Goblet Cell Carcinomas). *Neuroendocrinology* 2016;103:144–152.

31. Yozu M, Johncilla ME, Srivastava A, Ryan DP, Cusack JC, Doyle L *et al.* Histologic and outcome study supports reclassifying appendiceal goblet cell carcinoids as goblet cell adenocarcinomas, and grading and staging similarly to colonic adenocarcinomas. Am J Surg Pathol. 2018;42:898–910.

32. La Rosa S, Franzi F, Albarello L, Schmitt A, Bernasconi B, Tibiletti MG *et al.* Serotonin-producing enterochromaffin cell tumors of the pancreas: clinicopathologic study of 15 cases and comparison with intestinal enterochromaffin cell tumors. *Pancreas* 2011;40:883–895.

33. Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B *et al.* ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology* 2016;103:186–194.

34. Perren A, Couvelard A, Scoazec JY, Costa F, Borbath I, Delle Fave G *et al.* ENETS consensus guidelines for the standards of care in neuroendocrine tumors: Pathology: Diagnosis and prognostic stratification. *Neuroendocrinology* 2017;105:196–200.

35. Sobin LH, Hjermstad BM, Sesterhenn IA, Helwig EB. Prostatic acid phosphatase activity in carcinoid tumors. *Cancer* 1986;58:136–138.

36. Heitz PU, Komminoth P, Perren A, Klimstra DS, Dayal Y, Bordi C. Pancreatic endocrine tumours: introduction. *In:* DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds). *WHO Classification of Tumours Pathology and Genetics of Tumours of Endocrine Organs (3rd edition)*. Lyon, France: International Agency for Research on Cancer, 2004.

37. La Rosa S, Rigoli E, Uccella S, Chiaravalli AM, Capella C. CDX2 as a marker of intestinal EC-cells and related well-differentiated endocrine tumors. *Virchows Archiv* 2004;445:248–254.

38. Schmitt AM, Riniker F, Anlauf M, Schmid S, Soltermann A, Moch H *et al.* Islet 1 (Isl1) expression is a reliable marker for pancreatic endocrine tumors and their metastases. *Am J Surg Pathol* 2008;32:420–425.

39. Cheuk W, Kwan M, Suster S, Chan JK. Immunostaining for thyroid transcription factor 1 and cytokeratin 20 aids the distinction of small cell carcinoma from Merkel cell carcinoma, but not pulmonary from extrapulmonary small cell carcinomas. *Arch Path Lab Med* 2001;125:228–231.

40. Tang LH, Basturk O, Sue JJ, Klimstra DS. A practical approach to the classification of WHO grade 3 (G3) well differentiated neuroendocrine tumor (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC) of the pancreas. *Am J Surg Pathol* 2016;40:1192–1202.

41. Gonzalez RS, Liu EH, Alvarez JR, Ayers GD, Washington MK, Shi C. Should mesenteric tumor deposits be included in staging of well-differentiated small intestine neuroendocrine tumors? *Mod Pathol* 2014;27:1288–1295.

42. Fata CR, Gonzalez RS, Liu E, Cates JM, Shi C. Mesenteric tumor deposits in midgut small intestinal neuroendocrine tumors are a stronger lindicator than lymph node metastasis for liver metastasis and poor prognosis. *Am J Surg Pathol* 2017;41:128–133.

43. Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S *et al.* Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer* 2005;12:1083–1092.

44. Gibril F, Doppman JL, Reynolds JC, Chen CC, Sutliff VE, Yu F *et al.* Bone metastases in patients with gastrinomas: a prospective study of bone scanning, somatostatin receptor scanning, and magnetic resonance image in their detection, frequency, location, and effect of their detection on management. *J Clin Oncol* 1998;16:1040–1053.

45. Grimaldi F, Fazio N, Attanasio R, Frasoldati A, Papini E, Angelini F *et al.* Italian Association of Clinical Endocrinologists (AME) position statement: a stepwise clinical approach to the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. *J Endocrinol Invest* 2014;37:875–909.

46. Tomassetti P, Campana D, Piscitelli L, Casadei R, Nori F, Brocchi E *et al.* Endocrine tumors of the ileum: factors correlated with survival. *Neuroendocrinology* 2006;83:380–386.

47. Klöppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann NY Acad Sci* 2004;1014:13–27.

48. Sobin LH, Wittekind C (eds.) *TNM Classification of Malignant Tumours (6th edition)*. New York, USA: Wiley-Liss, 2002.

Appendix A ENETS TNM classification of gastroenteropancreatic neuroendocrine neoplasms[12,13]

T – Primary tumour: definition of stage varies by primary site

Primary site	T stage	Description
Stomach	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	Tis	In situ tumour/dysplasia (up to 0.5 mm)
	T1	Tumour invades lamina propria or submucosa and size ≤10 mm
	T2	Tumour invades muscularis propria or subserosa or size >10 mm
	T3	Tumour penetrates serosa
	T4	Tumour invades adjacent structures
Duodenum/ampulla/ proximal jejunum	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	T1	Tumour invades lamina propria or submucosa and size ≤10 mm*
	T2	Tumour invades muscularis propria or size >10 mm
	T3	Tumour invades pancreas or retroperitoneum
	T4	Tumour invades peritoneum or other organs
Pancreas	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	T1	Limited to the pancreas and size <20 mm
	T2	Limited to the pancreas and size 20–40 mm
	T3	Limited to the pancreas and size >40 mm
	T4	Invading the wall of adjacent large vessels (coeliac axis or superior mesenteric artery), stomach, spleen, colon, adrenal gland
Lower jejunum and ileum	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	T1	Tumour invades mucosa or submucosa and size ≤10 mm
	T2	Tumour invades muscularis propria or size >10 mm
	T3	Tumour invades subserosa
	T4	Tumour invades peritoneum/other organs

Primary site	T	Description
Appendix	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	T1	Tumour ≤10 mm and invades submucosa and muscularis propria
	T2	Tumour ≤20 mm and invades submucosa, muscularis propria and/or minimally (up to 3 mm) invades subserosa/mesoappendix
	T3	Tumour >20 mm and/or extensive (>3 mm) invasion of subserosa/mesoappendix
	T4	Tumour invades peritoneum/other organs
Colon and rectum	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	T1	Tumour invades mucosa or submucosa • pT1a – size <10 mm • pT1b – size 10–20 mm
	T2	Tumour invades muscularis propria or size >20 mm
	T3	Tumour invades subserosa/pericolic/perirectal fat
	T4	Tumour directly invades other organs/structures and/or perforates visceral peritoneum
For any pT, add (m) for multiple tumours. *Tumour limited to ampulla of Vater for ampullary gangliocytic paraganglioma.		

N – Lymph node status: definition is the same for all primary sites

N stage	Description
NX	Regional lymph node status cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M – Distant metastases: definition is the same for all primary sites

M stage	Description
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1*	Histologically confirmed distant metastasis (see section 5.4.8b)
*M1 specific sites defined according to reference 48.	

Appendix B SNOMED coding of gastroenteropancreatic neuroendocrine neoplasms

Topographical codes (T) and morphological codes (M)
Topographical codes are used in SNOMED to indicate the site of lesions and morphological codes (M) are used to indicate the morphological diagnosis.

SNOMED CT is a structured clinical vocabulary for use in an electronic health record. It is focused on what clinicians want to record at the point of patient care. It includes, but is not limited to, diagnoses, procedures, symptoms, family history, allergies, assessment tools, observations and medication.

SNOMED T and CT codes

Topographical code	SNOMED 2/SNOMED 3	SNOMED CT terminology	SNOMED CT code
Stomach	T-63000/T-57000	Entire stomach (body structure)	181246003
Duodenum	T-64300/T-58000	Entire duodenum (body structure)	181247007
Ampulla of Vater	T-64700/T-58700	–	–
Liver	T-56000/T-62000	Entire liver (body structure)	181268008
Pancreas	T-65000/T-59000	Pancreatic structure (body structure)	15776009
Jejunum	T-65100/T-58400	Entire jejunem (body structure)	181248002
Ileum	T-65200/T-58600	Entire ileum (body structure)	181249005
Appendix	–/T-66000	–	–
Colon	T-67000/T-59300	Colon structure (body structure)	71854001
Rectum	T-68000/T-59600	Rectum structure (body structure)	34402009

SNOMED M (WHO 2010 classification of GEP-NEN-based categories)[2] and CT codes

Morphological code	SNOMED	SNOMED CT terminology	SNOMED CT code
NET G1	M-82403	Carcinoid tumour; no International Classification of Diseases for Oncology subtype (morphologic abnormality)	81622000
NET G2	M-82493	Atypical carcinoid tumour (morphologic abnormality)	128658008

Morphological code	SNOMED	SNOMED CT terminology	SNOMED CT code
NET G3	M-82493	Atypical carcinoid tumour (morphologic abnormality)	128658008
Small cell NEC	M-80413	Small cell carcinoma (morphologic abnormality)	74364000
Large cell NEC	M-80133	Large cell neuroendocrine carcinoma (morphologic abnormality)	128628002
Neuroendocrine carcinoma NOS	M-82463	Neuroendocrine carcinoma (morphologic abnormality)	55937004
Mixed adenoneuroendocrine carcinoma	M-82443	Composite carcinoid (morphologic abnormality)	51465000
Goblet cell carcinoid tumour	M-82433	Goblet cell carcinoid (morphologic abnormality)	31396002
EC-cell, serotonin-producing NET	M-82413	Enterochromaffin cell carcinoid (morphologic abnormality)	48554007
Gastrinoma	M-81533	Gastrinoma, malignant (morphologic abnormality)	19756007
Somatostatinoma	M-81563	Somatostatinoma, malignant (morphologic abnormality)	128643000
Insulinoma	M-81513	Insulinoma, malignant (morphologic abnormality)	20955008
Glucagonoma	M-81523	Glucagonoma, malignant (morphologic abnormality)	66515009
VIPoma	M-81553	ViPoma, malignant (morphologic abnormality)	31131002
Gangliocytic paraganglioma	M-8683/0	Gangliocytic paraganglioma (morphologic abnormality)	72787006

SNOMED M (WHO 2017 classification of PanNEN-based categories)[3] and CT codes

Morphological code	SNOMED	SNOMED CT terminology	SNOMED CT code
NET G1	M-82403	Carcinoid tumour; no International Classification of Diseases for Oncology subtype (morphologic abnormality)	81622000
NET G2	M-82493	Atypical carcinoid tumour (morphologic abnormality)	128658008
Small cell NEC	M-80413	Small cell carcinoma (morphologic abnormality)	74364000

Morphological code	SNOMED	SNOMED CT terminology	SNOMED CT code
Large cell NEC	M-80133	Large cell neuroendocrine carcinoma (morphologic abnormality)	128628002
Neuroendocrine carcinoma NOS*	M-82463	Neuroendocrine carcinoma (morphologic abnormality)	55937004
MiNENs: • mixed ductal-neuroendocrine carcinoma • mixed acinar-neuroendocrine carcinoma	M-81543	Mixed islet cell and exocrine adenocarcinoma (morphologic abnormality)	999000
Non-functioning panNETs: • NE microadenoma • non-functioning panNET	 M-81500 M-81503	 Islet cell adenoma (morphologic abnormality) Islet cell carcinoma (morphologic abnormality)	76345009 60346004
Somatostatinoma	M-81563	Somatostatinoma, malignant (morphologic abnormality)	128643000
Insulinoma	M-81513	Insulinoma, malignant (morphologic abnormality)	20955008
Glucagonoma	M-81523	Glucagonoma, malignant (morphologic abnormality)	66515009
VIPoma	M-81553	ViPoma, malignant (morphologic abnormality)	31131002
ACTH-producing NET	M-81583	Functioning endocrine tumour (morphologic abnormality)	450891001
*This ICD-O code should not be used for well-differentiated NET G3 pancreatic neuroendocrine neoplasms, which are coded using the functioning or non-functioning pancreatic neuroendocrine tumour codes.			

Procedure codes (P)
These are used in SNOMED 2/3/RT to distinguish biopsies, partial resections and radical resections to indicate the nature of the procedure.

Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions, therefore local P codes should be recorded and used for audit purposes.

Appendix C Reporting proforma for gastric neuroendocrine neoplasms resections

Surname: …… Forename(s): ……..…….. Date of Birth: …… Sex: …...

Hospital: ……..……. Hospital No: ……..…… NHS No: ……..

Date of Surgery: ……..… Date of Report Authorisation: …… Report No: ..……...

Date of Receipt: …….. Pathologist:…….…… Clinician:…….....

MACROSCOPIC EXAMINATION

Type of specimen

Endoscopic resection	☐	Partial gastrectomy, distal	☐
Partial gastrectomy, proximal	☐	Total gastrectomy	☐
Partial gastrectomy, other (specify)	☐	Other (specify) ……	
Not specified	☐		

Specimen dimensions

Length of stomach – greater curve	…… mm	Gastric cardia ☐	Gastric body ☐
Length of stomach – lesser curve	..... mm	Gastric fundus ☐	Gastric antrum ☐
Length of oesophagus	..... mm	Gastric pylorus ☐	
Length of duodenum	..... mm	Other ☐	
		Other (specify) ……	

Site of tumour (select all that apply)

Tumour perforation Present ☐ Not identified ☐
Number of tumours Single ☐ Multiple ☐ If multiple, state number of tumours ……
Maximum tumour dimension ..... mm (of largest if multiple)
Distance tumour to nearest cut margin ..…..mm

MICROSCOPIC EXAMINATION

Histologic type and grade

Well-differentiated, NET G1	☐
Well-differentiated, NET G2	☐
Well-differentiated, NET G3	☐
Well-differentiated, grade cannot be assessed	☐
Poorly differentiated NEC, small cell	☐
Poorly differentiated NEC, large cell	☐
Poorly differentiated NEC, NOS	☐
Mixed NE non-NE neoplasm (MiNEN)	☐
Other	☐
Other (specify) ……	

Proliferative activity

Mitotic count ……/2 mm^2
Cannot be determined (explain): ……
Not applicable ☐
Proliferation index with Ki-67 ……
Cannot be determined (explain): ……
Not applicable ☐

Presence of necrosis

Present ☐ Not identified ☐

Gastric NEN types (Table 2)

Type I ☐ Type II ☐ Type III ☐ Cannot be assessed ☐

PATHOLOGIC STAGE CLASSIFICATION: ENETS TNM 2006 (Appendix A)

TNM descriptors (required only if applicable) (select all that apply)

m (multiple tumours)	☐
r (recurrent)	☐
y (post-treatment)	☐

Maximum extent of invasion (pT)

pTX	Primary tumour cannot be assessed	☐
pT0	No evidence of primary tumour	☐
pTis	In situ tumour/dysplasia (up to 0.5 mm)	☐
pT1	Tumour invades lamina propria or submucosa and size ≤10 mm	☐
pT2	Tumour invades muscularis propria or subserosa or size >10 mm	☐
pT3	Tumour penetrates serosa	☐
pT4	Tumour invades adjacent structures	☐

For multiple tumours with different Ts, use the highest.

Tumour involvement of margins

Proximal margin	Involved	☐	Not involved	☐	N/A	☐
Distal margin	Involved	☐	Not involved	☐	N/A	☐
Circumferential margin (around cardia)	Involved	☐	Not involved	☐	N/A	☐

If no, distance of tumour to nearest circumferential margin …….. mm

Resection status

Complete resection at all surgical margins?
Yes (R0) ☐ No, microscopic (R1) ☐ No, macroscopic (R2) ☐

Metastatic spread

Number of lymph nodes present …….
Number of involved lymph nodes ……
TNM N category:

pNX	Regional lymph node status cannot be assessed	☐
pN0	Regional lymph nodes not involved	☐
pN1	Regional lymph nodes involved	☐

Lymphovascular invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Perineural invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Tumour deposit	Present	☐	Not identified	☐	Cannot be assessed	☐

Histologically confirmed distant metastases (pM1):

Present ☐ If present, site: ...…… Not identified ☐
(PUL: pulmonary; HEP: hepatic; OSS: osseous)

Background abnormalities

None identified		☐				
Present		☐				
ECL-cell hyperplasia (nodules <150 µm)	Present	☐	Not identified	☐	N/A	☐
ECL-cell dysplasia (nodules ≥150 µm but <500 µm)	Present	☐	Not identified	☐	N/A	☐
Chronic atrophic gastritis with intestinal metaplasia	Present	☐	Not identified	☐	N/A	☐
G-cell hyperplasia	Present	☐	Not identified	☐	N/A	☐

Other (specify) …….

Signature: ……..…….. Date: ……/…../……. SNOMED codes: ……..…

Appendix D Reporting proforma for duodenal/ampullary/proximal jejunal neuroendocrine neoplasms resections

Surname: …… Forename(s): …….. Date of Birth: …..…… Sex: ……..

Hospital: ……..……. Hospital No: ……..…… NHS No: ……..

Date of Surgery: ……..…… Date of Report Authorisation: …… Report No: ..……...

Date of Receipt: ……... Pathologist: ……..…… Clinician: ……....

MACROSCOPIC EXAMINATION

Type of specimen

Endoscopic or local resection ☐
Duodenum, segmental resection ☐
Pancreaticoduodenectomy (Whipple resection) ☐
Not specified ☐
Ampullectomy ☐
Small bowel resection ☐
Other ☐
Other (specify) ……

Specimen dimensions

Length of duodenum …… mm
Length of lesser curve stomach ..... mm
Length of greater curve stomach ..... mm
Length of small bowel ..... mm
Length of gall bladder ..... mm
Length of bile duct ..... mm
Size of pancreas ..... x ..... x ..... mm

Site of tumour

Duodenum, 1st portion ☐
Duodenum, 2nd portion ☐
Duodenum, 3rd portion ☐
Ampulla ☐
Jejunum ☐
Other ☐
Other (specify) ……..

Tumour perforation Present ☐ Not identified ☐
Number of tumours Single ☐ Multiple ☐ If multiple, state number of tumours ……
Maximum tumour dimension ……mm (of largest if multiple)
Distance tumour to nearest cut margin ……mm
Named vessel (if applicable) Present ☐ Not identified ☐ Which vessel? .....……
Stent in place Present ☐ Not identified ☐

MICROSCOPIC EXAMINATION

Histologic type and grade

Well-differentiated, NET G1 ☐
Well-differentiated, NET G2 ☐
Well-differentiated, NET G3 ☐
Well-differentiated, grade cannot be assessed ☐
Poorly differentiated NEC, small cell ☐
Poorly differentiated NEC, large cell ☐
Poorly differentiated NEC, NOS ☐
Mixed NE non-NE neoplasm (MiNEN) ☐
Gangliocytic paraganglioma ☐
Other ☐
Other (specify) ....……

Proliferative activity

Mitotic count ……../2 mm^2
Cannot be determined (explain) ……
Not applicable ☐
Proliferation index with Ki-67 ……
Cannot be determined (explain) ……
Not applicable ☐

Presence of necrosis
Present ☐ Not identified ☐

PATHOLOGIC STAGE CLASSIFICATION: ENETS TNM 2006 (Appendix A)

TNM descriptors (required only if applicable) (select all that apply)

m (multiple tumours) ☐
r (recurrent) ☐
y (post-treatment) ☐

Maximum extent of invasion (pT)

pTX	Primary tumour cannot be assessed	☐
pT0	No evidence of primary tumour	☐
pT1	Tumour invades lamina propria or submucosa and size ≤10 mm*	☐
pT2	Tumour invades muscularis propria or size >10 mm	☐
pT3	Tumour invades pancreas or retroperitoneum	☐
pT4	Tumour invades peritoneum or other organs	☐

For multiple tumours with different Ts, use the highest.
*Tumour limited to ampulla of Vater for ampullary gangliocytic paraganglioma.

Tumour involvement of margins

Proximal margin	Involved	☐	Not involved	☐	N/A	☐
Distal margin	Involved	☐	Not involved	☐	N/A	☐
Circumferential margin:	Involved	☐	Not involved	☐	N/A	☐
If not involved, distance of tumour to nearest circumferential margin …….. mm						
Other margin (specify) ….....	Involved	☐	Not involved	☐	N/A	☐

For pancreaticoduodenal resection specimens only:

Margin status	**Involved**	**Not involved**	**Not sampled**	**Not applicable**	**Clearance***
Gastric transection margin:	☐	☐	☐	☐	……. mm
Duodenal transection margin:	☐	☐	☐	☐	……. mm
Pancreatic transection margin:	☐	☐	☐	☐	……. mm
Bile duct transection margin:	☐	☐	☐	☐	……. mm
SMV/SMA dissection margin:	☐	☐	☐	☐	……. mm
Posterior dissection margin:	☐	☐	☐	☐	..... mm
Anterior pancreatic surface:	☐	☐	☐	☐	……. mm

*Specify clearance of closest margin(s)

Named vessel status:	☐	☐	☐	☐

If named vessel involved, specify ……..

Resection status

Complete resection at all surgical margins?
Yes (R0) ☐ No, microscopic (R1) ☐ No, macroscopic (R2) ☐

Metastatic spread

Number of lymph nodes present …….
Number of involved lymph nodes ……
TNM N category:

pNX	Regional lymph node status cannot be assessed	☐
pN0	Regional lymph nodes not involved	☐
pN1	Regional lymph nodes involved	☐

Lymphovascular invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Perineural invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Tumour deposit	Present	☐	Not identified	☐	Cannot be assessed	☐

Histologically confirmed distant metastases (pM1):

Present ☐ If present, site: ....…… Not identified ☐
(PUL: pulmonary; HEP: hepatic; OSS: osseous)

Peptide hormone content

Immunostaining performed	Yes	☐	No	☐
If yes, peptide identified:				
Gastrin	Yes	☐	No	☐
Somatostatin	Yes	☐	No	☐
Other	Yes	☐	No	☐

Other (specify) …….

Background abnormalities Present ☐ Not identified ☐

If present, specify ……..

Signature: …….. Date: ……/…../……. SNOMED codes: ……

Appendix E Reporting proforma for pancreatic neuroendocrine neoplasms resections

Surname: …… Forename(s): …….. Date of Birth: …… Sex: ……..

Hospital: ……..…….. Hospital No: ……..…….. NHS No: ……

Date of Surgery: ……..… Date of Report Authorisation: …… Report No: ..……...

Date of Receipt: ……... Pathologist: ……..…… Clinician: …….....

MACROSCOPIC EXAMINATION

Type of specimen

Enucleation	☐	Local resection	☐
Pancreatoduodenectomy (Whipple resection)	☐	Distal pancreatectomy	☐
Total pancreatectomy	☐	Pylorus-preserving PD	☐
Not specified	☐	Other	☐
		Other (specify) ……	

Specimen dimensions

Length of duodenum	…… mm
Length of lesser curve stomach	..... mm
Length of greater curve stomach	..... mm
Length of small bowel	..... mm
Length of gall bladder	..... mm
Length of bile duct	..... mm
Size of pancreas	..... x ..... x .....mm
Other (specify)	mm

Site of tumour (select all that apply)

Pancreatic head	☐
Uncinate process	☐
Pancreatic neck	☐
Pancreatic body	☐
Pancreatic tail	☐
Other	☐

Other (specify)……..

Tumour perforation Present ☐ Not identified ☐
Number of tumours Single ☐ Multiple ☐ If multiple, state number of tumours……
Maximum tumour dimension .....mm (of largest if multiple)
Distance tumour to nearest cut margin ..……..mm
Named vessel (if applicable) Present ☐ Not identified ☐ Which vessel? .....
Stent in place Present ☐ Not identified ☐

MICROSCOPIC EXAMINATION

Histologic type and grade

Well-differentiated, NET G1	☐
Well-differentiated, NET G2	☐
Well-differentiated, NET G3	☐
Well-differentiated, grade cannot be assessed	☐
Poorly differentiated NEC G3, small cell	☐
Poorly differentiated NEC G3, large cell	☐
Poorly differentiated NEC, NOS	☐
Mixed NE non-NE neoplasm (MiNEN)	☐
Gangliocytic paraganglioma	☐
Other	☐

Other (specify) ……

Proliferative activity

Mitotic count ……/2 mm^2
Cannot be determined (explain): ……
Not applicable ☐
Proliferation index with Ki-67 ……
Cannot be determined (explain): ……
Not applicable ☐

Presence of necrosis
Present ☐ Not identified ☐

PATHOLOGIC STAGE CLASSIFICATION: ENETS TNM 2006 (Appendix A)

TNM descriptors (required only if applicable) (select all that apply)

m (multiple tumours) ☐
r (recurrent) ☐
y (post-treatment) ☐

Maximum extent of invasion (pT)

pTX	Primary tumour cannot be assessed	☐
pT0	No evidence of primary tumour	☐
pT1	Tumour limited to the pancreas* and size <20 mm	☐
pT2	Tumour limited to the pancreas* and size 20–40 mm	☐
pT3	Tumour limited to the pancreas* and size >40 mm	☐
pT4	Tumour invading the wall of large vessels** or adjacent organs***	☐

*Limited to the pancreas means there is no invasion of adjacent organs or the wall of large vessels. Extension of tumour into peripancreatic adipose tissue is NOT a basis for staging.
**Large vessels may include coeliac axis and superior mesenteric artery.
***Adjacent organs may include stomach, spleen, colon and adrenal gland.
For multiple tumours with different Ts, use the highest.

Tumour involvement of margins

Margin status	**Involved**	**Not involved**	**Not sampled**	**Not applicable**	**Clearance***
Gastric transection margin:	☐	☐	☐	☐	……. mm
Duodenal transection margin:	☐	☐	☐	☐	……. mm
Pancreatic transection margin:	☐	☐	☐	☐	……. mm
Bile duct transection margin:	☐	☐	☐	☐	……. mm
SMV/SMA dissection margin:	☐	☐	☐	☐	……. mm
Posterior dissection margin:	☐	☐	☐	☐	……. mm
Anterior pancreatic surface:	☐	☐	☐	☐	……. mm

*Specify clearance of closest margin(s)

Named vessel status: ☐ ☐ ☐ ☐

If named vessel involved, specify ……..

Resection status

Complete resection at all surgical margins?
Yes (R0) ☐ No, microscopic (R1) ☐ No, macroscopic (R2) ☐

Metastatic spread

Number of lymph nodes present …….
Number of involved lymph nodes ……
TNM N category:

pNX	Regional lymph node status cannot be assessed	☐
pN0	Regional lymph nodes not involved	☐
pN1	Regional lymph nodes involved	☐

Lymphovascular invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Perineural invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Tumour deposit	Present	☐	Not identified	☐	Cannot be assessed	☐

Histologically confirmed distant metastases (pM1):

Present ☐ If present, site: ..…… Not identified ☐
(PUL: pulmonary; HEP: hepatic; OSS: osseous)

Peptide hormone content

Immunostaining performed	Yes	☐	No	☐
If yes, peptide identified:				
Insulin	Yes	☐	No	☐
Glucagon	Yes	☐	No	☐
Somatostatin	Yes	☐	No	☐
Pancreatic polypeptide	Yes	☐	No	☐
Gastrin	Yes	☐	No	☐
Other	Yes	☐	No	☐

Other (specify)…….

Background abnormalities

Present	☐					
None identified	☐					
Islet cell microadenomatosis	Present	☐	Not identified	☐	N/A	☐
Chronic pancreatitis	Present	☐	Not identified	☐	N/A	☐

Other findings identified	Yes	☐	No	☐

If yes, specify……..

Signature: …….. Date: ……/…../……. SNOMED codes: ……

Appendix F Reporting proforma for lower jejunal and ileal neuroendocrine tumour resections

Surname: …… Forename(s): …….. Date of Birth: …… Sex: …...

Hospital: ……..……. Hospital No: ……..…… NHS No: ……..

Date of Surgery: ……..… Date of Report Authorisation: …… Report No: ..……...

Date of Receipt: …….. Pathologist: ……..…… Clinician: ……..…….....

MACROSCOPIC EXAMINATION

Type of specimen

Jejunal/ileal resection ☐
Right hemicolectomy ☐
Not specified ☐
Other ☐
Other (specify) ……..

Specimen dimensions

Length …… mm
Maximum width ..... mm
Depth of attached mesentery ..... mm
Mesenteric mass (if applicable) ..... mm
Other ..... mm
Other (specify) .....

Site of tumour

Jejunum ☐
Ileum ☐
Small intestine, not otherwise specified ☐
Other ☐
Other (specify) ……

Tumour perforation Present ☐ Not identified ☐
Number of tumours Single ☐ Multiple ☐ If multiple, state number of tumours……
Maximum tumour dimension .....mm (of largest if multiple)
Distance tumour to nearest cut margin ..……..mm

MICROSCOPIC EXAMINATION

Histologic type and grade

Well-differentiated, NET G1 ☐
Well-differentiated, NET G2 ☐
Well-differentiated, NET G3 ☐
Well-differentiated, grade cannot be assessed ☐
Poorly differentiated NEC, small cell ☐
Poorly differentiated NEC, large cell ☐
Poorly differentiated NEC, NOS ☐
Mixed NE non-NE neoplasm (MiNEN) ☐
Other ☐
Other (specify) ……

Proliferative activity

Mitotic count ……../2 mm^2
Cannot be determined (explain): ……
Not applicable ☐
Proliferation index with Ki-67 ……
Cannot be determined (explain): ……
Not applicable ☐

Presence of necrosis
Present ☐ Not identified ☐

PATHOLOGIC STAGE CLASSIFICATION: ENETS TNM 2007 (Appendix A)

TNM descriptors (required only if applicable) (select all that apply)

m (multiple tumours) ☐
r (recurrent) ☐
y (post-treatment) ☐

Maximum extent of invasion (pT)

pTX	Primary tumour cannot be assessed	☐
pT0	No evidence of primary tumour	☐
pT1	Tumour invades lamina propria or submucosa and size ≤10 mm	☐
pT2	Tumour invades muscularis propria or size >10 mm	☐
pT3	Tumour invades subserosa	☐
pT4	Tumour invades peritoneum or other organs	☐

For multiple tumours with different Ts, use the highest.

Tumour involvement of margins

Proximal margin	Involved	☐	Not involved	☐	N/A	☐
Distal margin	Involved	☐	Not involved	☐	N/A	☐
Circumferential margin:	Involved	☐	Not involved	☐	N/A	☐

If not involved, distance of tumour to nearest circumferential margin …….. mm

Doughnuts	Involved	☐	Not involved	☐	N/A	☐

Resection status

Complete resection at all surgical margins?

Yes (R0) ☐ No, microscopic (R1) ☐ No, macroscopic (R2) ☐

Metastatic spread

Number of lymph nodes present …….

Number of involved lymph nodes ……

TNM N category:

pNX	Regional lymph node status cannot be assessed	☐
pN0	Regional lymph nodes not involved	☐
pN1	Regional lymph nodes involved	☐

Lymphovascular invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Perineural invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Tumour deposit	Present	☐	Not identified	☐	Cannot be assessed	☐

Histologically confirmed distant metastases (pM1):

Present ☐ If present, site: ...…… Not identified ☐

(PUL: pulmonary; HEP: hepatic; OSS: osseous)

Background abnormalities

None identified ☐

Crohns disease ☐ Infarction ☐

Other (specify)……

Signature: …….. Date: ……/…../……. SNOMED codes: ……

Appendix G Reporting proforma for appendiceal neuroendocrine tumour resections

Surname: …… Forename(s): …….. Date of Birth: …… Sex: …..…

Hospital: ……..…… Hospital No: ……..…… NHS No: ……...

Date of Surgery: ……..…… Date of Report Authorisation: …… Report No: ……...

Date of Receipt: …….. Pathologist: ……..…… Clinician:…….……....

MACROSCOPIC EXAMINATION

Type of specimen

Appendicectomy ☐
Right hemicolectomy ☐
Not specified ☐
Other ☐
Other (specify) ……..

Specimen dimensions

Length …… mm
Maximum width ..... mm
Depth of attached mesoappendix ..... mm
Other ..... mm
Other (specify) .....

Site of tumour (select all that apply)

Base ☐
Body ☐
Tail ☐
Other ☐
Other (specify)……

Tumour perforation Present ☐ Not identified ☐
Number of tumours Single ☐ Multiple ☐ If multiple, state number of tumours……
Maximum tumour dimension .....mm (of largest if multiple)
Distance tumour to nearest cut margin ..……..mm

MICROSCOPIC EXAMINATION

Histologic type and grade

Well-differentiated, NET G1 ☐
Well-differentiated, NET G2 ☐
Well-differentiated, NET G3 ☐
Well-differentiated, grade cannot be assessed ☐
Poorly differentiated NEC, small cell ☐
Poorly differentiated NEC, large cell ☐
Poorly differentiated NEC, NOS ☐
Mixed NE non-NE neoplasm (MiNEN) ☐
Other ☐
Other (specify) ……

Proliferative activity

Mitotic count ……/2 mm^2
Cannot be determined (explain): ……
Not applicable ☐
Proliferation index with Ki-67 …….
Cannot be determined (explain): …….
Not applicable ☐

Presence of necrosis
Present ☐ Not identified ☐

PATHOLOGIC STAGE CLASSIFICATION: ENETS TNM 2007 (Appendix A)

TNM descriptors (required only if applicable) (select all that apply)

m (multiple tumours) ☐
r (recurrent) ☐
y (post-treatment) ☐

Maximum extent of invasion (pT)

pTX Primary tumour cannot be assessed ☐
pT0 No evidence of primary tumour ☐

pT1 Tumour ≤10 mm and invades submucosa and muscularis propria ☐
pT2 Tumour ≤20 mm and invades submucosa, muscularis propria and/or minimally (up to 3 mm) invading subserosa/mesoappendix ☐
pT3 Tumour >20 mm and/or extensive (>3 mm) invasion of subserosa/mesoappendix ☐
pT4 Tumour invades peritoneum or other organs ☐
For multiple tumours with different Ts, use the highest.

Tumour involvement of margins

Proximal margin	Involved	☐	Not involved	☐	N/A	☐
Distal margin	Involved	☐	Not involved	☐	N/A	☐
Circumferential margin:	Involved	☐	Not involved	☐	N/A	☐

If not involved, distance of tumour to nearest circumferential margin …….. mm

Doughnuts	Involved	☐	Not involved	☐	N/A	☐

Resection status

Complete resection at all surgical margins?
Yes (R0) ☐ No, microscopic (R1) ☐ No, macroscopic (R2) ☐

Metastatic spread

Number of lymph nodes present …….
Number of involved lymph nodes …….
TNM N category:
pNX Regional lymph node status cannot be assessed ☐
pN0 Regional lymph nodes not involved ☐
pN1 Regional lymph nodes involved ☐

Lymphovascular invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Perineural invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Tumour deposit	Present	☐	Not identified	☐	Cannot be assessed	☐

Histologically confirmed distant metastases (pM1):

Present ☐ If present, site: ...…… Not identified ☐
(PUL: pulmonary; HEP: hepatic; OSS: osseous)

Background abnormalities

None identified ☐
Appendicitis ☐ Adenoma ☐ Sessile serrated lesion ☐
Other ☐
Other (specify)……

Signature: …….. Date: ……/…../……. SNOMED codes: …….

Appendix H Reporting proforma for appendiceal goblet cell adenocarcinoma (previously called goblet cell carcinoid) resections

Surname: …… Forename(s): …….. Date of Birth: …… Sex: …..…..

Hospital: ……..……. Hospital No: ……..…… NHS No: ..……..

Date of Surgery: ……..…… Date of Report Authorisation: …… Report No: ……

Date of Receipt: ……... Pathologist: ……..…… Clinician: ...…….....

MACROSCOPIC EXAMINATION

Type of specimen

Appendicectomy ☐ Not specified ☐
Right hemicolectomy ☐ Other ☐
Other (specify) ……..

Specimen dimensions

Length …… mm
Maximum width ..... mm
Depth of attached mesoappendix ..... mm
Other ..... mm
Other (specify) .....

Site of tumour (select all that apply)

Base ☐
Body ☐
Tail ☐
Other ☐
Other (specify) …….

Tumour perforation Present ☐ Not identified ☐
Number of tumours Single ☐ Multiple ☐ If multiple, state number of tumours ……
Maximum tumour dimension .....mm (of largest if multiple)
Distance tumour to nearest cut margin ..……..mm

MICROSCOPIC EXAMINATION

Tumour grade (Table 3)

1 ☐ 2 ☐ 3 ☐ Not assessable

PATHOLOGIC STAGE CLASSIFICATION: UICC TNM 8th EDITION

TNM descriptors (required only if applicable) (select all that apply)

m (multiple tumours) ☐
r (recurrent) ☐
y (post-treatment) ☐

Maximum extent of invasion (pT)

pTX Primary tumour cannot be assessed ☐
pT0 No evidence of primary tumour ☐
pT1 Tumour invades submucosa ☐
pT2 Tumour invades muscularis propria ☐
pT3 Tumour invades subserosa or mesoappendix ☐
pT4a Tumour perforates visceral peritoneum ☐
pT4b Tumour directly invades other organs or structures ☐
For multiple tumours with different Ts, use the highest.

Tumour involvement of margins

Proximal margin	Involved	☐	Not involved	☐	N/A	☐
Distal margin	Involved	☐	Not involved	☐	N/A	☐
Circumferential margin:	Involved	☐	Not involved	☐	N/A	☐
If not involved, distance of tumour to nearest circumferential margin …….. mm						
Doughnuts	Involved	☐	Not involved	☐	N/A	☐

Resection status

Complete resection at all surgical margins?
Yes (R0) ☐ No, microscopic (R1) ☐ No, macroscopic (R2) ☐

Metastatic spread

Number of lymph nodes present …….
Number of involved lymph nodes …….

TNM N category:

pNX	Regional lymph node status cannot be assessed	☐
pN0	Regional lymph nodes not involved	☐
pN1a	1 regional node involved	☐
pN1b	2–3 regional nodes involved	☐
pN1c	Tumour deposits only	☐
pN2	>4 regional nodes involved	☐

Lymphovascular invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Perineural invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Tumour deposit	Present	☐	Not identified	☐	Cannot be assessed	☐

Histologically confirmed distant metastases (pM1):

Present ☐ Not identified ☐

M1a	Intraperitoneal acellular mucin only	☐
M1b	Intraperitoneal metastasis only, including mucinous epithelium	☐
M1c	Non-peritoneal metastasis	☐

Background abnormalities

None identified ☐
Appendicitis ☐ Adenoma ☐ Sessile serrated lesion ☐
Other ☐
Other (specify) …… ……

Please note: Goblet cell tumours should be managed as adenocarcinoma, therefore referral to colorectal MDT meeting is recommended.

Signature: …….. Date: ……/…../……. SNOMED codes: ……..

Appendix I Reporting proforma for colorectal neuroendocrine tumour resections

Surname: …… Forename(s): …….. Date of Birth: …… Sex: ……

Hospital: ……. Hospital No: ……NHS No: ……..

Date of Surgery: ……..… Date of Report Authorisation: …… Report No: ……...

Date of Receipt: ……... Pathologist: ……. Clinician: ……....

MACROSCOPIC EXAMINATION

Type of specimen

Right colectomy	☐	Left colectomy	☐
Sigmoid colectomy	☐	Total colectomy	☐
Anterior resection (AR)	☐	Abdominoperineal excision (APE)	☐
Local resection (e.g. endoscopic mucosal resection [EMR] or transanal excision)			☐
Other	☐		

Other (specify) ……..

Specimen dimensions

Length	…… mm
Diameter	..... mm
Perianal skin if present	..... mm
Other	..... mm
Other (specify)	

Site of tumour (select all that apply)

Caecum	☐	Right/ascending	☐
Hepatic flexure	☐	Transverse colon	☐
Splenic flexure	☐	Left/descending	☐
Sigmoid	☐	Rectosigmoid	☐
Rectum	☐	Ileo-caecal	☐

(Describe mesorectum as per colorectal proforma if TME)

Tumour perforation Present ☐ Not identified ☐
Number of tumours Single ☐ Multiple ☐ If multiple, state number of tumours……
Maximum tumour dimension .....mm (of largest if multiple)
Distance tumour to nearest cut margin ...……..mm

For rectal tumours:
Relation of tumour to peritoneal reflection (tick one):
Above ☐ Astride ☐ Below ☐

***For abdominoperineal excision specimens*:**
Distance of tumour from dentate line.....mm

Plane of mesorectal excision (AR and APE):
Mesorectal fascia ☐ Intramesorectal ☐
Muscularis propria ☐

Plane of resection of the sphincters (APE only):
Extralevator ☐ Sphincteric ☐
Intrasphincteric ☐

MICROSCOPIC EXAMINATION

Histologic type and grade

Well-differentiated, NET G1	☐
Well-differentiated, NET G2	☐
Well-differentiated, NET G3	☐
Well-differentiated, grade cannot be assessed	☐
Poorly differentiated NEC, small cell	☐
Poorly differentiated NEC, large cell	☐
Poorly differentiated NEC, NOS	☐
Mixed NE non-NE neoplasm (MiNEN)	☐
Other	☐

Other (specify) .....……

Proliferative activity

Mitotic count ……/2 mm^2)
Cannot be determined (explain): ……
Not applicable ☐
Proliferation index with Ki-67 …….
Cannot be determined (explain): …….
Not applicable ☐

Presence of necrosis
Present ☐ Not identified ☐

PATHOLOGIC STAGE CLASSIFICATION: ENETS TNM 2007 (Appendix A)

TNM descriptors (required only if applicable) (select all that apply)

m (multiple tumours) ☐
r (recurrent) ☐
y (post-treatment) ☐

Maximum extent of invasion (pT)

pTX Primary tumour cannot be assessed ☐
pT0 No evidence of primary tumour ☐
pT1 Tumour invades mucosa or submucosa
- pT1a <10 mm ☐
- pT1b 10–20 mm ☐

pT2 Tumour invades muscularis propria or size >20 mm ☐
pT3 Tumour invades subserosa/pericolic/perirectal fat ☐
pT4 Tumour directly invades other organs/structures and/or perforates visceral peritoneum ☐
For multiple tumours with different Ts, use the highest.

Tumour involvement of margins

Proximal margin	Involved	☐	Not involved	☐	N/A	☐
Distal margin	Involved	☐	Not involved	☐	N/A	☐
Circumferential margin:	Involved	☐	Not involved	☐	N/A	☐

If not involved, distance of tumour to nearest circumferential margin …….. mm

Doughnuts	Involved	☐	Not involved	☐	N/A	☐

Resection status

Complete resection at all surgical margins?
Yes (R0) ☐ No, microscopic (R1) ☐ No, macroscopic (R2) ☐

Metastatic spread

Number of lymph nodes present …….
Number of involved lymph nodes ……
TNM N category:
pNX Regional lymph node status cannot be assessed ☐
pN0 Regional lymph nodes not involved ☐
pN1 Regional lymph nodes involved ☐

Lymphovascular invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Perineural invasion	Present	☐	Not identified	☐	Cannot be assessed	☐
Tumour deposit	Present	☐	Not identified	☐	Cannot be assessed	☐

Histologically confirmed distant metastases (pM1):

Present ☐ If present, site: ..…… Not identified ☐
(PUL: pulmonary; HEP: hepatic; OSS: osseous)

Background abnormalities

None identified ☐
Crohns disease ☐ Ulcerative colitis ☐
Polyps identified Yes ☐ No ☐
If yes, state type(s) and number ……
Other ☐
Other (specify)……

Signature: ……..…….. Date: ……/…../……. SNOMED codes: ……

Appendix J Reporting proforma for gastric neuroendocrine neoplasms resections in list format

Element name	Values	Implementation comments
Type of specimen	Single selection value list: • Endoscopic resection • Partial gastrectomy, proximal • Partial gastrectomy, distal • Partial gastrectomy, other • Total gastrectomy • Not specified	
Type of specimen, other, specify	Free text	Only applicable if 'Type of specimen, Partial Gastrectomy, other' is selected.
Length of stomach, greater curve	Size in mm	
Length of stomach, lesser curve	Size in mm	
Length of oesophagus	Size in mm	
Length of duodenum	Size in mm	
Site of tumour	Multiple selection value list: • Gastric cardia • Gastric body • Gastric fundus • Gastric antrum • Gastric pylorus • Other	
Site of tumour, Other, specify	Free text	Only applicable if 'Site of tumour, Other' is selected.
Tumour perforation	Single selection value list: • Present • Not identified	
Number of tumours	Single selection value list: • Single • Multiple	

Number of tumours, Multiple	Integer	Only applicable if 'Number of tumours, Multiple' is selected.
Maximum tumour dimension	Size in mm	
Distance tumour to nearest cut margin	Size in mm	
Histologic type and grade	Single selection value list: • Well-differentiated, NET G1 • Well-differentiated, NET G2 • Well-differentiated, NET G3 • Well-differentiated, grade cannot be assessed • Poorly differentiated NEC, small cell • Poorly differentiated NEC, large cell • Poorly differentiated NEC, NOS • Mixed NE non-NE neoplasm (MiNEN) • Other	
Histologic type and grade, Other, specify	Free text	Only applicable if 'Histologic type and grade, Other' is selected.
Mitotic count	Number	
Mitotic count, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Mitotic count' not completed.
Mitotic Count, Cannot be determined, explain	Free text	Only applicable if 'Mitotic Count, Cannot be determined' is selected.
Proliferation index with Ki-67	Number	
Proliferation index with Ki-67, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Proliferation index with Ki-67' not completed.
Proliferation index with Ki-67, Cannot be determined, explain	Free text	Only applicable if 'Proliferation index with Ki-67, Cannot be determined' is selected.
Presence of necrosis	Single selection value list: • Present • Not identified	

Gastric NEN type	Single selection value list: • Type I • Type II • Type III • Cannot be assessed	
TNM version	ENET	ENET automatically selected
TNM descriptors	Multiple selection value list: • m (multiple tumours) • r (recurrent) • y (post-treatment)	May be blank
Maximum extent of invasion	Single selection value list: • pTX (Primary tumour cannot be assessed) • pT0 (No evidence of primary tumour) • pTis (In situ tumour/dysplasia [up to 0.5 mm]) • pT1 (Tumour invades lamina propria or submucosa and size ≤10 mm) • pT2 (Tumour invades muscularis propria or subserosa or size >10 mm) • pT3 (Tumour penetrates serosa) • pT4 (Tumour invades adjacent structures)	
Proximal margin	Single selection value list: • Involved • Not involved • Not applicable	
Distal margin	Single selection value list: • Involved • Not involved • Not applicable	
Circumferential margin	Single value selection list: • Involved • Not involved • Not applicable	

Circumferential margin, distance	Size in mm	Only applicable if 'Circumferential margin, Not involved' is selected.
Complete resection	Single value selection list: • Yes (R0) • No, microscopic (R1) • No, macroscopic (R2)	
Number of lymph nodes present	Integer	
Number of involved lymph nodes	Integer	
N category	Single selection value list: • pNX (Regional lymph node status cannot be assessed) • pN0 (Regional lymph nodes not involved) • pN1 (Regional lymph nodes involved)	
Lymphovascular invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Perineural invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Tumour deposit	Single selection value list: • Present • Not identified • Cannot be assessed	
Histologically confirmed distant metastases	Single selection value list: • Present • Not identified	
Histologically confirmed distant metastases, site	Free text	Only applicable if 'Histologically confirmed distant metastases, Present' is selected.

Background abnormalities	Single selection value list: • Present • None identified	
ECL-cell hyperplasia (nodules <150 µm)	Single selection value list: • Present • Not identified • Not applicable	Not applicable if 'Background abnormalities, None identified' is selected.
ECL-cell dysplasia (nodules ≥150 µm but <500 µm)	Single selection value list: • Present • Not identified • Not applicable	Not applicable if 'Background abnormalities, None identified' is selected.
Chronic atrophic gastritis with intestinal metaplasia	Single selection value list: • Present • Not identified • Not applicable	Not applicable if 'Background abnormalities, None identified' is selected.
G-cell hyperplasia	Single selection value list: • Present • Not identified • Not applicable	Not applicable if 'Background abnormalities, None identified' is selected.
Background abnormalities, Other	Free text	Not applicable if 'Background abnormalities, None identified' is selected.
SNOMED codes	May have multiple codes. Look up from SNOMED tables.	

Appendix K Reporting proforma for duodenal/ampullary/proximal jejunal neuroendocrine neoplasms resections in list format

Element name	Values	Implementation comments
Type of specimen	Single selection value list: • Endoscopic or local resection • Duodenum, segmental resection • Pancreaticoduodenectomy (Whipple resection) • Ampullectomy • Small bowel resection • Other • Not specified	
Type of specimen, Other, specify	Free text	Only applicable if 'Type of specimen, Other' is selected.
Length of duodenum	Size in mm	
Length of stomach, lesser curve	Size in mm	
Length of stomach, greater curve	Size in mm	
Length of small bowel	Size in mm	
Length of gall bladder	Size in mm	
Length of bile duct	Size in mm	
Size of pancreas, dimension 1	Size in mm	
Size of pancreas, dimension 2	Size in mm	
Size of pancreas, dimension 3	Size in mm	
Site of tumour	Single selection value list: • Duodenum 1st portion • Duodenum 2nd portion • Duodenum 3rd portion • Ampulla • Jejunum • Other	
Site of tumour, Other, specify	Free text	Only applicable if 'Site of tumour, Other' is selected.

Tumour perforation	Single selection value list: • Present • Not identified	
Number of tumours	Single selection value list: • Single • Multiple	
Number of tumours, Multiple	Integer	Only applicable if 'Number of tumours, Multiple' is selected.
Maximum tumour dimension	Size in mm	
Distance tumour to nearest cut margin	Size in mm	
Named vessel	Single selection value list: • Present • Not identified	
Which vessel	Free text	Only applicable if 'Named vessel, Present' is selected.
Stent in place	Single selection value list: • Present • Not identified	
Histologic type and grade	Single selection value list: • Well-differentiated, NET G1 • Well-differentiated, NET G2 • Well-differentiated, NET G3 • Well-differentiated, grade cannot be assessed • Poorly differentiated NEC, small cell • Poorly differentiated NEC, large cell • Poorly differentiated NEC, NOS • Mixed NE non-NE neoplasm (MiNEN) • Gangliocytic paraganglioma • Other	
Histologic type and grade, Other, specify	Free text	Only applicable if 'Histologic type and grade, Other' is selected.

Mitotic count	Number	
Mitotic count, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Mitotic count' not completed.
Mitotic count, Cannot be determined, explain	Free text	Only applicable if 'Mitotic count, Cannot be determined' is selected.
Proliferation index with Ki-67	Number	
Proliferation index with Ki-67, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Proliferation index with Ki-67' not completed.
Proliferation index with Ki-67, Cannot be determined, explain	Free text	Only applicable if 'Proliferation index with Ki-67, Cannot be determined' is selected.
Presence of necrosis	Single selection value list: • Present • Not identified	
TNM version	ENET	ENET automatically selected
TNM descriptors	Multiple selection value list: • m (multiple tumours) • r (recurrent) • y (post-treatment)	May be blank
Maximum extent of invasion	Single selection value list: • pTX (Primary tumour cannot be assessed) • pT0 (No evidence of primary tumour) • pT1 (Tumour invades lamina propria or submucosa and size ≤10 mm) • pT2 (Tumour invades muscularis propria or subserosa or size >10 mm) • pT3 (Tumour invades pancreas or retroperitoneum) • pT4 (Tumour invades peritoneum or other organs)	

Proximal margin	Single selection value list: • Involved • Not involved • Not applicable	
Distal margin	Single selection value list: • Involved • Not involved • Not applicable	
Circumferential margin	Single value selection list: • Involved • Not involved • Not applicable	
Circumferential margin, distance	Size in mm	Only applicable if 'Circumferential margin, Not involved' is selected.
Other margin, specify	Free text	
Other margin	Single value selection list: • Involved • Not involved • Not applicable	Only applicable if a value is selected for 'Other margin, specify'.
Gastric transection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
Gastric transection margin, Clearance	Size in mm	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
Duodenal transection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.

Duodenal transection margin, Clearance	Size in mm	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
Pancreatic transection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
Pancreatic transection margin, Clearance	Size in mm	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
Bile duct transection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
Bile duct transection margin, Clearance	Size in mm	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
SMV/SMA dissection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
SMV/SMA dissection margin, Clearance	Size in mm	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
Posterior dissection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.

Posterior dissection margin, Clearance	Size in mm	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
Anterior pancreatic surface	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
Anterior pancreatic surface, Clearance	Size in mm	Only applicable if 'Type of specimen, Pancreaticoduodenectomy (Whipple resection)' is selected.
Named vessel status	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	
Named vessel involved, specify	Free text	Only applicable if 'Named vessel status, Involved' is selected.
Complete resection	Single value selection list: • Yes (R0) • No, microscopic (R1) • No, macroscopic (R2)	
Number of lymph nodes present	Integer	
Number of involved lymph nodes	Integer	
N category	Single selection value list: • pNX (Regional lymph node status cannot be assessed) • pN0 (Regional lymph nodes not involved) • pN1 (Regional lymph nodes involved)	

Lymphovascular invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Perineural invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Tumour deposit	Single selection value list: • Present • Not identified • Cannot be assessed	
Histologically confirmed distant metastases	Single selection value list: • Present • Not identified	
Histologically confirmed distant metastases, site	Free text	Only applicable if 'Histologically confirmed distant metastases, Present' is selected.
Immunostaining performed	Single selection value list: • Yes • No	
Gastrin identified	Single selection value list: • Yes • No	Only applicable if 'Immunostaining performed, Yes' is selected.
Somatastatin identified	Single selection value list: • Yes • No	Only applicable if 'Immunostaining performed, Yes' is selected.
Other peptide identified	Single selection value list: • Yes • No	Only applicable if 'Immunostaining performed, Yes' is selected.
Other peptide, specify	Free text	Only applicable if 'Other, Yes' is selected.
Background abnormalities	Single selection value list: • Present • Not identified	

Background abnormalities, specify	Free text	Not applicable if 'Background abnormalities, Not identified' is selected.
SNOMED codes	May have multiple codes. Look up from SNOMED tables.	

Appendix L Reporting proforma for pancreatic neuroendocrine neoplasms resections in list format

Element name	Values	Implementation comments
Type of specimen	Single selection value list: • Enucleation • Pancreaticoduodenectomy (Whipple resection) • Total pancreatectomy • Not specified • Local resection • Distal pancreatectomy • Pylorus-preserving PD • Other	
Type of specimen, Other, specify	Free text	Only applicable if 'Type of specimen, Other' is selected.
Length of duodenum	Size in mm	
Length of stomach, lesser curve	Size in mm	
Length of stomach, greater curve	Size in mm	
Length of small bowel	Size in mm	
Length of gall bladder	Size in mm	
Length of bile duct	Size in mm	
Size of pancreas, dimension 1	Size in mm	
Size of pancreas, dimension 2	Size in mm	
Size of pancreas, dimension 3	Size in mm	
Other measurement	Size in mm	
Other measurement, specify	Free text	Only required if 'Other' measurement is completed.
Site of tumour	Single selection value list: • Pancreatic head • Uncinate process • Pancreatic neck • Pancreatic body • Pancreatic tail • Other	

Site of tumour, Other, specify	Free text	Only applicable if ‘Site of tumour, Other’ is selected.
Tumour perforation	Single selection value list: • Present • Not identified	
Number of tumours	Single selection value list: • Single • Multiple	
Number of tumours, multiple	Integer	Only applicable if ‘Number of tumours, Multiple’ is selected.
Maximum tumour dimension	Size in mm	
Distance tumour to nearest cut margin	Size in mm	
Named vessel	Single selection value list: • Present • Not identified	
Which vessel	Free text	Only applicable if ‘Named vessel, Present’ is selected.
Stent in place	Single selection value list: • Present • Not identified	
Histologic type and grade	Single selection value list: • Well-differentiated, NET G1 • Well-differentiated, NET G2 • Well-differentiated, NET G3 • Well-differentiated, grade cannot be assessed • Poorly differentiated NEC G3, small cell • Poorly differentiated NEC G3, large cell • Poorly differentiated NEC, NOS • Mixed NE non-NE neoplasm (MiNEN) • Gangliocytic paraganglioma • Other	

Histologic type and grade, Other, specify	Free text	Only applicable if 'Histologic type and grade, Other' is selected.
Mitotic count	Number	
Mitotic count, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Mitotic count' not completed.
Mitotic count, Cannot be determined, explain	Free text	Only applicable if 'Mitotic count, Cannot be determined' is selected.
Proliferation index with Ki-67	Number	
Proliferation index with Ki-67, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Proliferation index with Ki-67' not completed.
Proliferation index with Ki-67, Cannot be determined, explain	Free text	Only applicable if 'Proliferation index with Ki-67, Cannot be determined' is selected.
Presence of necrosis	Single selection value list: • Present • Not identified	
TNM version	ENET	ENET automatically selected
TNM descriptors	Multiple selection value list: • m (multiple tumours) • r (recurrent) • y (post-treatment)	May be blank
Maximum extent of invasion	Single selection value list: • pTX (Primary tumour cannot be assessed) • pT0 (No evidence of primary tumour) • pT1 (Tumour limited to pancreas and size <20 mm) • pT2 (Tumour limited to pancreas and size 20–40 mm • pT3 (Tumour limited to pancreas and size >40 mm) • pT4 (Tumour invades wall of large vessels or adjacent organs)	

Gastric transection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	
Gastric transection margin, Clearance	Size in mm	
Duodenal transection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	
Duodenal transection margin, Clearance	Size in mm	
Pancreatic transection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	
Pancreatic transection margin, Clearance	Size in mm	
Bile duct transection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	
Bile duct transection margin, Clearance	Size in mm	
SMV/SMA dissection margin	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	
SMV/SMA dissection margin, Clearance	Size in mm	
Posterior dissection margin	Single value selection list: • Involved	

	• Not involved • Not sampled • Not applicable	
Posterior dissection margin, Clearance	Size in mm	
Anterior pancreatic surface	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	
Anterior pancreatic surface, Clearance	Size in mm	
Named vessel status	Single value selection list: • Involved • Not involved • Not sampled • Not applicable	
Named vessel involved, specify	Free text	Only applicable if 'Named vessel status, Involved' is selected.
Complete resection	Single value selection list: • Yes (R0) • No, microscopic (R1) • No, macroscopic (R2)	
Number of lymph nodes present	Integer	
Number of involved lymph nodes	Integer	
N category	Single selection value list: • pNX (Regional lymph node status cannot be assessed) • pN0 (Regional lymph nodes not involved) • pN1 (Regional lymph nodes involved)	
Lymphovascular invasion	Single selection value list: • Present • Not identified • Cannot be assessed	

Perineural invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Tumour deposit	Single selection value list: • Present • Not identified • Cannot be assessed	
Histologically confirmed distant metastases	Single selection value list: • Present • Not identified	
Histologically confirmed distant metastases, site	Free text	Only applicable if 'Histologically confirmed distant metastases, Present' is selected.
Immunostaining performed	Single selection value list: • Yes • No	
Insulin identified	Single selection value list: • Yes • No	Only applicable if 'Immunostaining performed, Yes' is selected.
Glucagon identified	Single selection value list: • Yes • No	Only applicable if 'Immunostaining performed, Yes' is selected.
Somatastatin identified	Single selection value list: • Yes • No	Only applicable if 'Immunostaining performed, Yes' is selected.
Pancreatic polypeptide identified	Single selection value list: • Yes • No	Only applicable if 'Immunostaining performed, Yes' is selected.
Gastrin identified	Single selection value list: • Yes • No	Only applicable if 'Immunostaining performed, Yes' is selected.
Other peptide identified	Single selection value list: • Yes • No	Only applicable if 'Immunostaining performed, Yes' is selected.

Other peptide, specify	Free text	Only applicable if Other, Yes' is selected.
Background abnormalities	Single selection value list: • Present • Not identified	
Islet cell microadenomatosis	Single selection value list: • Present • Not identified • Not applicable	
Chronic pancreatitis	Single selection value list: • Present • Not identified • Not applicable	
Other findings identified	• Yes • No	
Other findings identified, specify	Free text	Only applicable if 'Other findings identified, Yes' is selected.
SNOMED codes	May have multiple codes. Look up from SNOMED tables.	

Appendix M Reporting proforma for lower jejunal and ileal neuroendocrine tumour resections in list format

Element name	Values	Implementation comments
Type of specimen	Single selection value list: • Jejnual/ileal resection • Right hemicolectomy • Other • Not specified	
Type of specimen, Other, specify	Free text	Only applicable if 'Type of specimen, Other' is selected.
Length	Size in mm	
Maximum width	Size in mm	
Depth of attached mesentery	Size in mm	
Mesenteric mass (if applicable)	Size in mm	
Other measurement	Size in mm	
Other measurement, specify	Free text	Only required if 'Other measurement' is completed.
Site of tumour	Single selection value list: • Jejunum • Ileum • Small intestine, not otherwise specified • Other	
Site of tumour, Other, specify	Free text	Only applicable if 'Site of tumour, Other' is selected.
Tumour perforation	Single selection value list: • Present • Not identified	
Number of tumours	Single selection value list: • Single • Multiple	

Number of tumours, Multiple	Integer	Only applicable if 'Number of tumours, Multiple' is selected.
Maximum tumour dimension	Size in mm	
Distance tumour to nearest cut margin	Size in mm	
Histologic type and grade	Single selection value list: • Well-differentiated, NET G1 • Well-differentiated, NET G2 • Well-differentiated, NET G3 • Well-differentiated, grade cannot be assessed • Poorly differentiated NEC, small cell • Poorly differentiated NEC, large cell • Poorly differentiated NEC, NOS • Mixed NE non-NE neoplasm (MiNEN) • Other	
Histologic type and grade, Other, specify	Free text	Only applicable if 'Histologic type and grade, Other' is selected.
Mitotic count	Number	
Mitotic count, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Mitotic count' not completed.
Mitotic count, Cannot be determined, explain	Free text	Only applicable if 'Mitotic count, Cannot be determined' is selected.
Proliferation index with Ki-67	Number	
Proliferation index with Ki-67, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Proliferation index with Ki-67' not completed.
Proliferation index with Ki-67, Cannot be determined, explain	Free text	Only applicable if 'Proliferation index with Ki-67, Cannot be determined' is selected.
Presence of necrosis	Single selection value list: • Present • Not identified	

TNM version	ENET	ENET automatically selected
TNM descriptors	Multiple selection value list: • m (multiple tumours) • r (recurrent) • y (post treatment)	May be blank
Maximum extent of invasion	Single selection value list: • pTX (Primary tumour cannot be assessed) • pT0 (No evidence of primary tumour) • pT1 (Tumour invades lamina propria or submucosa and size ≤10 mm) • pT2 (Tumour invades muscularis propria or subserosa or size >10 mm) • pT3 (Tumour invades subserosa) • pT4 (Tumour invades peritoneum or other organs)	
Proximal margin	Single selection value list: • Involved • Not involved • Not applicable	
Distal margin	Single selection value list: • Involved • Not involved • Not applicable	
Circumferential margin	Single value selection list: • Involved • Not involved • Not applicable	
Circumferential margin, distance	Size in mm	Only applicable if 'Circumferential margin, Not involved' is selected.
Doughnuts	Single value selection list: • Involved • Not involved • Not applicable	

Complete resection	Single value selection list: • Yes (R0) • No, microscopic (R1) • No, macroscopic (R2)	
Number of lymph nodes present	Integer	
Number of involved lymph nodes	Integer	
N category	Single selection value list: • pNX (Regional lymph node status cannot be assessed) • pN0 (Regional lymph nodes not involved) • pN1 (Regional lymph nodes involved)	
Lymphovascular invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Perineural invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Tumour deposit	Single selection value list: • Present • Not identified • Cannot be assessed	
Histologically confirmed distant metastases	Single selection value list: • Present • Not identified	
Histologically confirmed distant metastases, site	Free text	Only applicable if 'Histologically confirmed distant metastases, Present' is selected.
Background abnormalities	Multiple selection value list: • None identified • Crohns disease • Infarction	

Background abnormalities, Other	Free text	Not applicable if 'Background abnormalities, None identified' is selected.
SNOMED codes	May have multiple codes. Look up from SNOMED tables.	

Appendix N Reporting proforma for appendiceal neuroendocrine tumour resections in list format

Element name	Values	Implementation comments
Type of specimen	Single selection value list: • Appendicectomy • Right hemicolectomy • Not specified • Other	
Type of specimen, Other, specify	Free text	Only applicable if 'Type of specimen, Other' is selected.
Length	Size in mm	
Maximum width	Size in mm	
Depth of attached mesoappendix	Size in mm	
Other measurement	Size in mm	
Other measurement, specify	Free text	Only required if 'Other' measurement completed.
Site of tumour	Multiple selection value list: • Base • Body • Tail • Other	
Site of tumour, Other, specify	Free text	Only applicable if 'Site of tumour, Other' is selected.
Tumour perforation	Single selection value list: • Present • Not identified	
Number of tumours	Single selection value list: • Single • Multiple	
Number of tumours, Multiple	Integer	Only applicable if 'Number of tumours, Multiple' is selected.
Maximum tumour dimension	Size in mm	

Distance tumour to nearest cut margin	Size in mm	
Histologic type and grade	Single selection value list: • Well-differentiated, NET G1 • Well-differentiated, NET G2 • Well-differentiated, NET G3 • Well-differentiated, grade cannot be assessed • Poorly differentiated NEC, small cell • Poorly differentiated NEC, large cell • Poorly differentiated NEC, NOS • Mixed NE non-NE neoplasm (MiNEN) • Other	
Histologic type and grade, Other, specify	Free text	Only applicable if 'Histologic type and grade, Other' is selected.
Mitotic count	Number	
Mitotic count, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Mitotic count' not completed.
Mitotic count, Cannot be determined, explain	Free text	Only applicable if 'Mitotic count, Cannot be determined' is selected.
Proliferation index with Ki-67	Number	
Proliferation index with Ki-67, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Proliferation index with Ki-67' not completed.
Proliferation index with Ki-67, Cannot be determined, explain	Free text	Only applicable if 'Proliferation index with Ki-67, Cannot be determined' is selected.
Presence of necrosis	Single selection value list: • Present • Not identified	
TNM version	ENET	ENET automatically selected

TNM descriptors	Multiple selection value list: • m (multiple tumours) • r (recurrent) • y (post-treatment)	May be blank
Maximum extent of invasion	Single selection value list: • pTX (Primary tumour cannot be assessed) • pT0 (No evidence of primary tumour) • pT1 (Tumour ≤10 mm invades submucosa and muscularis propria) • pT2 (Tumour ≤20 mm invades submucosa and muscularis propria and/or minimally [up to 3 mm] invading subserosa/mesoappendix) • pT3 (Tumour >20 mm and/or extensive [>3 mm] invasion of subserosa/mesoappendix • pT4 (Tumour invades peritoneum or other organs)	
Proximal margin	Single selection value list: • Involved • Not involved • Not applicable	
Distal margin	Single selection value list: • Involved • Not involved • Not applicable	
Circumferential margin	Single value selection list: • Involved • Not involved • Not applicable	
Circumferential margin, distance	Size in mm	Only applicable if 'Circumferential margin, Not involved' is selected.
Doughnuts	Single value selection list: • Involved • Not involved	

	• Not applicable	
Complete resection	Single value selection list: • Yes (R0) • No, microscopic (R1) • No, macroscopic (R2)	
Number of lymph nodes present	Integer	
Number of involved lymph nodes	Integer	
N category	Single selection value list: • pNX (Regional lymph node status cannot be assessed) • pN0 (Regional lymph nodes not involved) • pN1 (Regional lymph nodes involved)	
Lymphovascular invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Perineural invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Tumour deposit	Single selection value list: • Present • Not identified • Cannot be assessed	
Histologically confirmed distant metastases	Single selection value list: • Present • Not identified	
Histologically confirmed distant metastases, site	Free text	Only applicable if 'Histologically confirmed distant metastases, Present' is selected.
Background abnormalities	Multiple selection value list: • None identified • Appendicitis • Adenoma	

	• Sessile serrated lesion • Other	
Background abnormalities, Other, specify	Free text	Not applicable if 'Background abnormalities, None identified' is selected.
SNOMED codes	May have multiple codes. Look up from SNOMED tables.	

Appendix O Reporting proforma for appendiceal goblet cell adenocarcinoma (previously called goblet cell carcinoid) resections in list format

Element name	Values	Implementation comments
Type of specimen	Single selection value list: • Appendicectomy • Right hemicolectomy • Not specified • Other	
Type of specimen, Other, specify	Free text	Only applicable if 'Type of specimen, Other' is selected.
Length	Size in mm	
Maximum width	Size in mm	
Depth of attached mesoappendix	Size in mm	
Other measurement	Size in mm	
Other measurement, specify	Free text	Only required if 'Other measurement' completed.
Site of tumour	Multiple selection value list: • Base • Body • Tail • Other	
Site of tumour, Other, specify	Free text	Only applicable if 'Site of tumour, Other' is selected.
Tumour perforation	Single selection value list: • Present • Not identified	
Number of tumours	Single selection value list: • Single • Multiple	
Number of tumours, Multiple	Integer	Only applicable if 'Number of tumours, Multiple' is selected.
Maximum tumour dimension	Size in mm	

Distance tumour to nearest cut margin	Size in mm	
Histologic grade	Single selection value list: • 1 • 2 • 3 • Not assessable	
TNM version	UICC8	UICC8 automatically selected
TNM descriptors	Multiple selection value list: • m (multiple tumours) • r (recurrent) • y (post-treatment)	May be blank
Maximum extent of invasion	Single selection value list: • pTX (Primary tumour cannot be assessed) • pT0 (No evidence of primary tumour) • pT1 (Tumour invades submucosa • pT2 (Tumour invades muscularis propria) • pT3 (Tumour invades subserosa or mesoappendix) • pT4a (Tumour perforates visceral peritoneum) • pT4b (Tumour invades other organs or structures)	
Proximal margin	Single selection value list: • Involved • Not involved • Not applicable	
Distal margin	Single selection value list: • Involved • Not involved • Not applicable	
Circumferential margin	Single value selection list: • Involved • Not involved	

	• Not applicable	
Circumferential margin, distance	Size in mm	Only applicable if 'Circumferential margin, Not involved' is selected.
Doughnuts	Single value selection list: • Involved • Not involved • Not applicable	
Complete resection	Single value selection list: • Yes (R0) • No, microscopic (R1) • No, macroscopic (R2)	
Number of lymph nodes present	Integer	
Number of involved lymph nodes	Integer	
N category	Single selection value list: • pNX (Regional lymph node status cannot be assessed) • pN0 (Regional lymph nodes not involved) • pN1a (1 regional lymph node involved) • pN1b (2–3 regional lymph nodes involved) • pN1c (Tumour deposits only) • pN2 (>4 regional nodes involved)	
Lymphovascular invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Perineural invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Tumour deposit	Single selection value list: • Present • Not identified • Cannot be assessed	

Histologically confirmed distant metastases	Single selection value list: • Present • Not identified	
Histologically confirmed distant metastases	Single selection value list: • M1a: Intraperitoneal acellular mucin only • M1b: Intraperitoneal metastasis only, including mucinous epithelium • M1c: Non-peritoneal metastasis	Only applicable if 'Histologically confirmed distant metastases, Present' is selected.
Background abnormalities	Multiple selection value list: • None identified • Appendicitis • Adenoma • Sessile serrated lesion • Other	
Background abnormalities, Other, specify	Free text	Not applicable if 'Background abnormalities, None identified' is selected.
SNOMED codes	May have multiple codes. Look up from SNOMED tables.	

Appendix P Reporting proforma for colorectal neuroendocrine tumour resections in list format

Element name	Values	Implementation comments
Type of specimen	Single selection value list: • Right colectomy • Left colectomy • Sigmoid colectomy • Total colectomy • Anterior resection • Abdominoperineal excision • Local resection • Other	
Type of specimen, Other, specify	Free text	Only applicable if 'Type of specimen, Other' is selected.
Length	Size in mm	
Diameter	Size in mm	
Perianal skin if present	Size in mm	Only applicable if 'Type of specimen' is 'Abdominoperineal excision'.
Other measurement	Size in mm	
Other measurement, specify	Free text	Only required if 'Other' measurement completed.
Site of tumour	Multiple selection value list: • Caecum • Right/ascending • Hepatic flexure • Transverse colon • Splenic flexure • Left/descending • Sigmoid • Rectosigmoid • Rectum • Ileo-caecal	

Tumour perforation	Single selection value list: • Present • Not identified	
Number of tumours	Single selection value list: • Single • Multiple	
Number of tumours, Multiple	Integer	Only applicable if 'Number of tumours, Multiple' is selected.
Maximum tumour dimension	Size in mm	
Distance tumour to nearest cut margin	Size in mm	
Relation of tumour to peritoneal reflection	Single selection value list: • Above • Astride • Below	Only applicable if 'Site of tumour, Rectum' is selected.
Distance of tumour from dentate line	Size in mm	Only applicable if 'Type of specimen' is 'Abdominoperineal excision'.
Plane of mesorectal excision	Single selection value list: • Mesorectal fascia • Intramesorectal • Muscularis propria	Only applicable if 'Type of specimen' is 'Abdominoperineal excision' or 'Anterior resection'.
Plane of resection of the sphincters	Single selection value list: • Extralevator • Sphinteric • Intrasphinteric	Only applicable if 'Type of specimen' is 'Abdominoperineal excision'.
Histologic type and grade	Single selection value list: • Well-differentiated, NET G1 • Well-differentiated, NET G2 • Well-differentiated, NET G3 • Well-differentiated, grade cannot be assessed • Poorly differentiated NEC, small cell • Poorly differentiated NEC, large cell	

	• Poorly differentiated NEC, NOS • Mixed NE non-NE neoplasm (MiNEN) Other	
Histologic type and grade, Other, specify	Free text	Only applicable if 'Histologic type and grade, Other ' is selected.
Mitotic count	Number	
Mitotic count, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Mitotic count' not completed.
Mitotic count, Cannot be determined, explain	Free text	Only applicable if 'Mitotic count, Cannot be determined' is selected.
Proliferation index with Ki-67	Number	
Proliferation index with Ki-67, not stated	Single selection value list: • Cannot be determined • Not applicable	Answer only required if 'Proliferation index with Ki-67' not completed.
Proliferation index with Ki-67, Cannot be determined, explain	Free text	Only applicable if 'Proliferation index with Ki-67, Cannot be determined' is selected.
Presence of necrosis	Single selection value list: • Present • Not identified	
TNM version	ENET	ENET automatically selected
TNM descriptors	Multiple selection value list: • m (multiple tumours) • r (recurrent) • y (post-treatment)	May be blank
Maximum extent of invasion	Single selection value list: • pTX (Primary tumour cannot be assessed) • pT0 (No evidence of primary tumour) • pT1a (Tumour invades mucosa or submucosa or size <10 mm)	

	• pT1b (Tumour invades mucosa or submucosa or size 10–20 mm) • pT2 (Tumour invades muscularis propria or size >20 mm) • pT3 (Tumour invades subserosa/pericolic/perirectal fat) • pT4 (Tumour directly invades other organs/structure and/or perforates visceral peritoneum)	
Proximal margin	Single selection value list: • Involved • Not involved • Not applicable	
Distal margin	Single selection value list: • Involved • Not involved • Not applicable	
Circumferential margin	Single value selection list: • Involved • Not involved • Not applicable	
Circumferential margin, distance	Size in mm	Only applicable if 'Circumferential margin, Not involved' is selected.
Doughnuts	Single value selection list: • Involved • Not involved • Not applicable	
Complete resection	• Yes (R0) • No, microscopic (R1) • No, macroscopic (R2)	
Number of lymph nodes present	Integer	
Number of involved lymph nodes	Integer	
N category	Single selection value list: • pNX (Regional lymph node status cannot be assessed)	

	• pN0 (Regional lymph nodes not involved) • pN1 (Regional lymph nodes involved)	
Lymphovascular invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Perineural invasion	Single selection value list: • Present • Not identified • Cannot be assessed	
Tumour deposit	Single selection value list: • Present • Not identified • Cannot be assessed	
Histologically confirmed distant metastases	Single selection value list: • Present • Not identified	
Histologically confirmed distant metastases, site	Free text	Only applicable if 'Histologically confirmed distant metastases, Present' is selected.
Background abnormalities	Multiple selection value list: • None identified • Crohns disease • Ulcerative colitis	
Polyps identified	Single selection value list: • Yes • No	
Polyps, type	Free text	Only applicable if 'Polyps identified, Yes' is selected.
Polyps, number	Integer	Only applicable if 'Polyps identified, Yes' is selected.

Background abnormalities, Other, specify	Free text	Not applicable if 'Background abnormalities, None identified' is selected.
SNOMED codes	May have multiple codes. Look up from SNOMED tables.	

Appendix Q Summary table – Explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix R AGREE II guideline monitoring sheet

The cancer datasets of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	2–11
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	4–11
16 The different options for management of the condition or health issue are clearly presented	4–11
17 Key recommendations are easily identifiable	4–11
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–J
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	12
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword