The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for neuroendocrine tumours of the gastrointestinal tract including pancreas (3rd edition)

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Comments	In accordance with the College's pre-publications policy, this document was put on The Royal College of Pathologists' website for consultation from 11 July to 8 August 2012. Thirty-seven items of feedback were received. The authors considered them and amended the document as appropriate. Please email publications@rcpath.org if you wish to see the responses and comments. This document replaces the 2nd edition of *Dataset for endocrine tumours of the gastrointestinal including pancreas*, published in 2009. **Dr Peter Cowling** **Director of Communications**

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Contents

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 and allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. It may rarely be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

Each dataset contains **core data items** that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – 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 90% 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 organisations have been consulted during the preparation of the dataset:

- National Cancer Intelligence Network (www.ncri.org.uk)
- Association for Coloproctology of Great Britain and Ireland (www.acpgbi.org.uk)
- Association of Upper Gastrointestinal Surgeons (www.augis.org)
- British Society of Gastroenterology (www.bsg.org.uk)
- UK Endocrine Pathology Society (www.ukeps.com)
- UK and Ireland Neuroendocrine Tumour Society (www.ukinets.org).

This dataset has been constructed taking into account the new strong evidence base that is contained in, and forms the basis for, the following new national and international publications. All publications have widespread national and/or international peer acceptance and reflect the current accepted professional standards and practice in neuroendocrine tumour 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 neuroendocrine tumours up to June 2012. This identified no evidence to alter the views or conclusions of the publications listed above. The level of evidence (Appendix K) 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.

No major organisational changes have been identified that would hinder the implementation of the dataset, which is fully integrated with the COSD, and there are no new major financial or work implications arising from the implementation, compared to the 2009 dataset.

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant sub-specialty advisor 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 Histopathology 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 Fellows' attention. If Fellows do not object to the changes, the short notice of change 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 Working Group for Cancer Services (WGCS) and was placed on the College website for consultation with the membership from 11 July to 8 August 2012. All comments received from the WGCS and membership were addressed by the authors, to the satisfaction of the WGCS Chair and the Director of Communications.

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 Director of Professional Standards and are available on request.

1 Introduction

Careful and accurate pathology reporting of gastroenteropancreatic neuroendocrine tumour resection specimens is important because pathology reports are used to:

- make or confirm the diagnosis
- inform prognosis
- plan the treatment of individual patients
- 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]

Because gastroenteropancreatic neuroendocrine tumours are rare,[2] some early classifications grouped them together, and equated all digestive 'carcinoids' with the appendiceal 'carcinoid', the most familiar neuroendocrine tumour with the most indolent behaviour.[3,4] Such an approach is now unacceptable as over the last two decades the World Health Organization (WHO) classifications have defined neuroendocrine features that discriminate between tumours that are highly likely to behave in a benign manner or probably benign from those that are either genuinely of unknown behaviour or of low grade malignancy (see Appendix I).[5-7]

For this version of the dataset, we have reverted to the term 'neuroendocrine' from 'endocrine', even though the tumours are not neural crest-derived. We have done this for the sake of international comparability and in recognition of the fact that the tumours express some neural type markers.

To ensure that all data items are recorded,[8,9] we recommend using separate datasets in which the staging criteria (but not the universal grading system proposed) are specific to the anatomical site. This attention to detail is essential as it has become clear that, as defined within the WHO classification of neuroendocrine tumours of the gastrointestinal tract and pancreas,[7,9,10] neuroendocrine tumours arising at different anatomical sites differ in their biology.[11,12] Publications examining the application of the 2004 WHO classification (covering endocrine neoplasia and neuroendocrine neoplasms of the pancreas)[13] have shown its validity, since the different neuroendocrine tumour types did differ in their clinical behaviour.[14]

Malignant neuroendocrine tumours of the gastrointestinal tract and pancreas may be fatal, though at a significantly slower pace than their adenocarcinomatous counterparts. A number of retrospective papers and epidemiological data support such statements[15] and indicate the

importance of selecting patients for the optimal surgery, and other therapies such as receptor blockade and chemotherapy.[16-19]

Validation of decision to retain or revise data collected

The TNM classifications for neuroendocrine tumours of the gastrointestinal tract and pancreas that we recommend are those developed by the European Neuroendocrine Tumor Society (ENETS) [19,20] since these, with their suggested uniform grading system for luminal gastrointestinal tumours, inform several contemporary guidelines for stratification and treatment of patients with these tumours.[18,19,22,23]

[The classifications are prognostic at evidence level B/C.]

For pancreas, we again recommend the ENETS system, but with a modification to the grade 1/2 boundary and pT3 defintion, which have been shown to increase prognostic value and ease of application.[24]

[This grade boundary offers more accurate prognosis than previous recommendation at evidence level B/C.]

Our rationale for recommending the ENETS TNM staging system throughout this dataset (as opposed to the AJCC/UICC 7th edition system,[25,26] which for the first time includes neuroendocrine tumours or the WHO 2010 system[7] whose stages are derived from it) are:

- the ENETS system was specifically designed to cater for neuroendocrine neoplasms, with their often indolent behaviour compared with the usually aggressive and often fatal adenocarcinomas[27]
- the prognostic value of the ENETS system is substantiated in high-quality follow-up studies with complete pathology data, often centrally reviewed for consistency[28] *[the evidence is collectively at level B/C].*
- Regarding the AJCC/UICC system, it is not applicable to high grade neuroendocrine tumours[25,26], whereas ENETS can still be used for these[20,21]. The authors of the AJCC/UICC system[24,25] present no data to justify its staging boundaries[29] *[the system constitutes evidence level D]*
- the principal study[30] correlating survival with the AJCC/UICC (pancreas) stages relies on cancer registry data from very incomplete pathology information and lacks central review of the pathology *[this study is deemed unacceptable as evidence, on grounds of study design and execution]*
- the AJCC/UICC stages are difficult to differentiate microscopically for some organs (pancreas, especially taking into account its specific anatomy[31]) or include patterns of invasion uncommonly seen (appendix)[32]
- the WHO 2010 system,[7] while having the merits of separating out grade from stage for the first time, uses AJCC/UICC stage boundaries, to which the above criticisms still apply.

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:[19,31]

- 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 neuroendocrine tumours, 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 (5HIAA).

[These data are required for accurate staging and cancer registration].

It is accepted that some neuroendocrine tumours will be unsuspected, usually because they are initially thought to be adenocarcinomas, and that patients sometimes proceed to pancreatic surgery on the basis of blood neuroendocrine investigations and/or imaging without a biopsy having been taken.

3 Preparation of specimens before dissection

Where possible, resection specimens should be received fresh, unopened and un-incised 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 including duodenum and proximal jejunum and colorectum are as for carcinomas of these respective organs.[1,33-38] For distal jejunum and ileum, opening and fixation are as for colon.[33]

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 recorded. For colorectal tumours, the non-peritonealised surgical resection margin (previously known as the radial or circumferential resection margin) in the vicinity of the tumour is then inked or painted with a suitable marker, to enable the subsequent identification of margin involvement. This margin represents the ‘bare’ area in the connective tissue at the surgical plane of excision that is not covered by a serosal surface.

The following blocks of tissue are recommended as a 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 direct local spread or metastasis
  - vascular invasion if suspected
  - involvement of any adjacent organs.
- A block to show the closest approximation of 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 5.4.5a).
- 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 ETs).
- 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.

ETs may be incidental findings in initially less thoroughly sampled specimens, e.g. the finding of an ET in 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, so in the most common example of 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.

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

5 Core data items

5.1 Macroscopic

- 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 *[to assist quality assurance of surgery; level of evidence D].*

5.2 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 neuroendocrine tumours

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 ETs, especially in cases where tumourigenesis occurs in a background of neuroendocrine cell hyperplasia[5] that may or may not have an inherited basis.[39,40] 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 macrosocopic 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 all.

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 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 ETs that are >30 mm away macroscopically, but it should be sampled for microscopic examination if subsequent histology shows the tumour to be poorly differentiated (grade 3), to have an exceptionally infiltrative growth pattern or extensive vascular or perineural invasion, or to be a mixed ET-exocrine tumour with a signet ring cell component.

5.2.2 Data recorded for rectal neuroendocrine tumours 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 (APER) specimens to give an idea of the location of the tumour in relation to the internal sphincter.

[All of the above part of section 5 is prognostic at evidence level B/C].

5.3 Microscopic

- Histological type (including pure ETs and mixed neuroendocrine-exocrine neoplasms).[41]
- Specific hormone immunostaining, if considered clinically essential (e.g. to find the relevant tumour causing a clinical syndrome).
- Histological grade (including the mitotic rate and/or proliferation index – see section 5.4.2, may be ‘Not assessable’ in small gastric and rectal endoscopic mucosal resections [EMR]).
- Maximum extent of local invasion (pT stage), may be ‘Not assessable’ in small gastric and rectal EMR).
- Serosal involvement.
- Margin involvement.

- Lymph node status (number present, number involved).
- Vascular invasion.
- Perineural invasion.
- Histologically confirmed distant metastases and site (see section 7.2.3).
- Background abnormalities e.g. Enterochromaffin-like (ECL) cell or G cell hyperplasia[5] in stomach, gastritis, as these inform the WHO typing of ECL-cell gastric carcinoid tumours.[7]

[All of the above histological features are prognostic at evidence level B/C.]

Other core items

- ENETS TNM stage (see section 7.2).
- WHO 2004 classification for all, and WHO typing for gastric ECL-cell tumours (see Appendices I and J).
- Completeness of resection (R stage) (see section 7.1).
- SNOMED codes (see section 11).

5.4 Notes on microscopic assessment

5.4.1 Tumour type

Tumours are classified as:

- well-differentiated neuroendocrine tumours (classified by the WHO 2004 system, see Appendix I)
- poorly differentiated neuroendocrine tumours (small cell carcinoma) (classified by the WHO 2004 system, see Appendix I)
- goblet cell carcinoids[42] and mixed neuroendocrine-adenocarcinomas[43]
- some other rarer types.

The use of general immunohistochemical markers in the identification of neuroendocrine tumours has been well reviewed.[44] A small panel is recommended, including antibodies against at least three different components: synaptophysin as a small vesicle antigen, chromogranin A as a component of (neuro)secretory granules and CD56 (neural cell adhesion molecule [N-CAM]) as a membrane bound antigen. Cytosolic markers such as protein gene product (PGP) 9.5 and neuron-specific enolase (NSE) have specificity and diffusion problems, meaning that the case for their routine use is weaker. The immunohistochemistry must be adequately controlled and quality assured, for example, through laboratory membership of an immunohistochemistry NEQAS scheme.

For duodenal NETs, reporting whether these (especially those producing gastrin or somatostatinoma) arise sporadically or in a background of MEN1 or NF1 respectively, and their exact site, conveys important prognostic information.[44] NETs producing somatostatin may be very glandular and care should be taken not to label these inappropriately as adenocarcinoma. The presence of psammoma bodies in some is a clue to their neuroendocrine nature. Immunohistochemistry should be used if there is any question that duodenal 'adenocarcinoma' could be an neuroendocrine tumour.[44]

Although, for pancreatic ETs, there is evidence that production of specific hormones may give prognostic information,[45] it is not yet clear whether this information has prognostic value beyond that provided by grading, staging and WHO typing. There are problems in

demonstrating specific hormone production by immunohistochemistry if the antibody available does not exactly match the epitopes available on the hormone being produced by the tumour, i.e. the antibody may have excessive specificity. Further, the maintainance of a panel of multiple antibodies against neuroendocrine hormones and its quality assurance has costs and difficulty that do not justify routine immunohistochemical demonstration of individual hormones as a prognostic feature, although immunostaining for specific hormones should be arranged if clinically essential in the overall management of the patient. For gastric ETs, inclusion of the WHO type[5] (Appendix J) is essential as this has powerful prognostic significance[44] – some of the data for determining the WHO type will only be available through careful clinicopathological correlation. Experimental evidence is emerging that certain markers such as cytokeratin 19 positivity confer an adverse prognosis in pancreatic neuroendocrine tumours,[46] but evidence is not sufficiently strong to regard this as a core data item presently.

The term 'goblet cell carcinoid' (GCC) has been used to describe a wide range of appendiceal neoplasms that show some mixed pattern of endocrine and adenocarcinomatous differentiation. van Eeden *et al* have produced convincing molecular evidence to suggest that GCCs are an entity that is distinct from both classical endocrine tumours and adenocarcinoma of the appendix[41] and a recent review of the whole published literature confirms this.[42] However, the term GCC does not have much value without further definition because in unrestricted usage it can be applied to a wide spectrum of tumours, from a signet-ring type adenocarcinoma with a few cells showing endocrine differentiation through to a well-differentiated endocrine tumour with some intracytoplasmic mucin in a few cells and these tumours will have a very different prognosis.

In the past five years, there have been several published studies that aim to stratify goblet cell carcinoids into different groups with more clearly defined criteria and a more direct relationship to prognosis. The study with the strongest evidence base is that of Tang *et al*.[43] They divided their retrospective series of 63 tumours into three different morphological groups, with five-year survival rates of 100%, 38% and 0%, so a clear prognostic stratification is produced. The interobserver agreement gave an overall Kappa statistic of 0.73, indicating a good level of agreement, so the system appears to be reproducible and feasible for clinical use. The criteria for the groups are given in Table 1.

5.4.2 Tumour grade

It is often stated that no histological grading system effectively predicts the behaviour of well-differentiated neuroendocrine tumours. For example, severe cytological atypia, such as can be seen in phaeochromocytomas, has no implication for the clinical behaviour or malignancy of such tumours.

However, recent studies focused on neuroendocrine tumours of the gastrointestinal tract including the pancreas have shown the usefulness of a grading system.[45,47-49] For example, well-differentiated neuroendocrine tumours but with a more solid appearance and obvious proliferative activity, of the kind that lead to difficulties in the differential diagnosis against poorly differentiated neuroendocrine carcinomas, appear to have a worse prognosis than neuroendocrine tumours without these features.[19,50-53] A grading system that respects this distinction and separates well-differentiated neuroendocrine tumours into G1 and G2 categories and that provides a G3 category for poorly differentiated neuroendocrine carcinoma has been proposed,[20] and seems justified. This grading system is a modification of the one adopted by the WHO for the neuroendocrine tumours of the lung, but has been simplified to reflect only the mitotic count and Ki-67 index.

Three tumour categories are identified as in Table 2 below.

Table 1 Morphological criteria for the three different groups of GCC, defined by Tang *et al* [43]

Group	Morphological criteria
A **(Typical GCC)**	Well-defined goblet cells arranged in clusters or cohesive linear pattern Minimal cytological atypia Minimal to no desmoplasia Minimal architectural distortion of the appendiceal wall Degenerative change with extracellular mucin is acceptable
B **(Adenocarcinoma ex GCC, signet-ring type)**	Goblet cells or signet-ring cells arranged in irregular large clusters, but lack of confluent sheet of cells Discohesive single file or single cell infiltrating pattern Significant cytological atypia Desmoplasia and associated destruction of the appendiceal wall
C **(Adenocarcinoma ex GCC, poorly differentiated type)**	At least focal evidence of goblet cell morphology A component (greater than one low power field or 1 mm^2) not otherwise distinguishable from a poorly differentiated adenocarcinoma, which may appear as either a) gland-forming b) confluent sheets of signet-ring cells, or c) undifferentiated carcinoma

[Classification recommended as core as prognostic at level of evidence B.]

Table 2 Grading system for gastrointestinal neuroendocrine tumours[20-24]

Grade	Mitotic count (10 HPF)*	Ki-67 index (%)**
G1	<2	≤2 (5)***
G2	2–20	>2 (5)***–20
G3	>20	>20

* 10 HPF = 2 mm^2 based on each hpf being 0.2 mm^2 with at least 40 fields evaluated in areas at highest mitotic density.

** Ki-67 index: % of tumour cells in a 2000 cell sample from the areas of highest nuclear labelling.

*** Note that the exception to the 2% MIB1 threshold is the pancreas. A large study[24] showed that when a 5% rather than 2% Ki-67 labelling index cut-off was applied, Ki-67 was an independent predictor of prognosis.

In practical terms, G1 and G2 neuroendocrine tumours are generally well-differentiated and display diffuse and intense expression of the two general immunohistochemical neuroendocrine markers, chromogranin A and synaptophysin.[20] The high-power image, however, should always be checked as some apparently well-differentiated organoid NETs have a high mitotic count/Ki-67 labelling index and prove to be of higher grade than anticipated from the low-power image. The presence of any focal necrosis is suggestive of a more aggressive tumour, pointing to a G2 status, which, however, has to be confirmed by the mitotic count and Ki-67 staining. G3 indicates a poorly differentiated neuroendocrine carcinoma. It has high mitotic counts/Ki-67 index, is often associated with fields of necrosis and shows significantly reduced chromogranin A expression, while maintaining intense staining for synaptophysin.

5.4.3 Establishing mitotic count and Ki-67 index

In the proposed grading system, where possible, mitoses should be counted in haematoxylin and eosin-stained sections in at least 40 HPFs.[20] The mitoses should be assessed in areas where they are most frequent. The Ki-67 index should be assessed in areas where the highest nuclear labelling is observed (often but not exclusively at the tumour periphery),[20] by counting an adequate sample of cells, such as the suggested sample size of 2000. The primary tumour should be assessed in preference to metastases, but metastases can be assessed if the primary tumour is not available or has been modified by local therapies. With small tumour samples, the Ki-67 index may prove easier to determine than the mitotic count. There is a paucity of evidence about what to do in the face of a disparate Ki-67 index and mitotic count; the prognosis associated with the worse of the two indices may be the best option for the patient in determining treatment and follow-up.

The above table (whose categories have the accumulated evidence on their prognostic value) was based around 0.2 mm^2 high-power fields. Pathologists should determine the diameter of their own microscope's high-power field with the exact objective, eyepieces and other lenses that they prefer to use, and calculate the area of that field, to enable adjustment to made to their counts. For example, if a microscope has a high-power field of 0.22 mm^2, 10% larger than 0.2 mm^2, then the count will be 10% higher than if the field had been 0.2 mm^2 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, x40 high power fields on a modern microscope with wide field optics can considerably exceed 0.2 mm^2 so it is necessary to check and to adjust.

The rationale for inclusion of the actual Ki-67 index in the proformas is that different studies have proposed stratification based upon different cut-off values. Provision of the actual index allows for future introduction of different cut points and for research.
The Ki-67 index may be noted for metastases if locally desired, but there are no specific data to indicate analysis of other than the primary tumour where it is available.

5.4.4 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.

5.4.5 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 multidisciplinary team. 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 ETs. The serosa is not a resection margin (see section 7.1), but any serosal involvement should be reported.

d) Reporting of local excision specimens of gastrointestinal neuroendocrine tumours

Small ETs of the stomach, duodenum or large intestine may be treated initially by polypectomy, endoscopic mucosal resection (EMR) or transanal endoscopic microsurgical excision (TEM). 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 neuroendocrine tumours 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
- 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 will be required 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'.

5.4.6 Metastatic spread

a) Lymph nodes

All of the 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. In the absence of evidence, it is recommended that the 3 mm rule used for categorising mesenteric tumour nodules, not in continuity with the main neoplasm as

completely replaced lymph nodes in gastrointestinal carcinomas, is also used for ETs. Accordingly, an extramural deposit measuring ≥3 mm is regarded as an involved lymph node, while a deposit that is <3 mm is regarded as discontinuous extramural spread.

pN1 corresponds to involvement of any lymph nodes. All nodal involvement contributes to the N stage. (Unlike the situation with some adenocarcinomas, there is no established recommendation for neuroendocrine tumours to count certain involved nodes as distant spread and hence part of the M stage).

b) Histologically confirmed distant metastases

The presence of histologically confirmed distant metastases, and their site, is recorded. It should be noted that disease classifiable as distant metastasis may sometimes be present within the primary tumour resection specimen, for example a serosal or mesenteric deposit that is distant from the primary mass. Distant serosal deposits are metastases and do not count towards the T stage of the primary tumour. The site of distant metastases should be recorded as some sites (e.g. bone) confer an adverse prognosis.[54,55] Cross-reference should be made to the biopsy number documenting the distant metastasis if this is separate.

c) Background abnormalities

The presence of relevant pathological abnormalities in the background tissue should be recorded, as defined in the WHO typing of ECL-cell gastric carcinoid tumours.[7] The following are of particular note:

- synchronous tumours(s) – each of which will require a separate and appropriate proforma
- gastritis
- mucosal atrophy
- ECL cell hyperplasia
- G cell hyperplasia
- islet cell microadenomatosis.

6 Non-core data items

6.1 Macroscopic

- Type of operation.
- Specimen dimensions for each organ included.
- Precise anatomical location of non-peritonealised margin involvement (rectal tumours).

6.2 Microscopic

- Presence of amyloid.
- Presence of psammoma bodies.
- Immunohistochemical data, general immunohistochemical markers of neuroendocrine differentiation and any specific hormone immunostaining.
- CK19 expression[46] in pancreatic NETs.

6.3 Other

- Molecular data if available.

[All of the above parts of section 6 are prognostic at level of evidence C/D.]

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.

When doughnuts and the ends of the specimen are not examined histologically, they are assumed to be tumour-free (see section 4).

Non-peritonealised margins are regarded as involved if tumour definitely extends into them (see sections 5.2.1e and 5.4.5a).

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 ETs and appendiceal goblet cell carcinoid tumours.[56-59]

7.2 TNM staging

7.2.1 Tumour

The recently published recommendations for TNM staging[14] are recommended (Appendix A).

The designation 'tumour *in situ*' (Tis) is currently used for gastric lesions only, and is defined as an intramucosal ET that measures between 0.15 mm and 0.5 mm in dimension.[6] Smaller nodules of neuroendocrine cells 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.[20]

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 type 1 and is included in Appendix E for completeness.

In the proposed TNM classification, there are some site-specific mismatches between the T1 and T2 boundary and the cut-off between the first and second group in the WHO 2004 classification; only the WHO classification includes perineural invasion and different emphases are put on vascular invasion.[12,13,20] Extra care should be taken in completing the proformas for stomach, duodenum, pancreas and appendix. The mismatches are unsatisfactory, but this dataset can only reflect the internationally available classification systems as published.

We recommend collection of the data items of both the ENETS TNM classification and the 2004 WHO classification in parallel, so that the data are laid down for patient management according to either classification and for research and development. The 2004 WHO classification and ENETS TNM staging serve slightly different purposes (prediction of behaviour based on histology *versus* staging of the tumour including aspects of the primary and metastases). The WHO classification may potentially offer prognostic stratification within the TNM stages pT1/T2 N0. Future revisions may permit reconciliation if the accumulated prognostic data supports that, or removal of the WHO classification if the new TNM system were shown to be clinically sufficient.

Deeply invasive tumours are included in the T3 and T4 definitions, taking into account site-specific features.[14]

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 ETs so specification of individual involved lymph nodes has not been included as a core data item, although the option of naming of involved nodes has been provided in the pancreatic proforma, 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,[54-56] we recommend that the anatomical site of the metastases be specified using the TNM classification rules (PUL: pulmonary; HEP: hepatic; OSS: osseous; etc.).[50]

8 Reporting of small biopsy specimens

Gastrointestinal neuroendocrine tumours may be encountered in small mucosal biopsies, as a suspected or completely unexpected finding. The main challenges in interpretation are their recognition, i.e. there may be a only a small amount of tumour present, and only at the base of the biopsy, and differentiation from adenocarcinoma may be difficult, particularly with some duodenal ampullary and rectal tumours. For gastric neuroendocrine tumours, background mucosal biopsies may be submitted accompanying the tumour biopsy, for comment on chronic/atrophic gastritis and/or neuroendocrine cell hyperplasia.[5]

Pancreatic neuroendocrine tumours may be subject to needle core and/or endoscopic ultrasound-guided fine needle aspiration cytology. The key differential diagnoses are against inflammatory lesions and adenocarcinoma.[31]

With all types of small biopsy, the challenges are:

- prioritisation of immunohistochemistry for differential diagnosis and grading, with cytokeratins, Ki-67 and synaptophysin 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 found to be easier to establish than a mitotic count under these circumstances. It is common only to be able to state a minimum ENETS TNM stage from a biopsy.

9 Reporting of frozen sections

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

10 Criteria for audit of the dataset

In keeping with the recommended key performance indicators published by The Royal College of Pathologists (www.rcpath.org/index.asp?PageID=35), reports on neuroendocrine tumours of the gastrointestinal tract including pancreas should be audited for the following.

- The inclusion of SNOMED or SNOMED-CT codes:
  - standard: 95% reports should have T, M and P codes.
- It is recommended that at least 90% 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 90% of core data items are recorded):
  - standard: 80% of resection specimens will include 100% data items presented in a structured format.
- Turnaround times for biopsies and resection specimens:
  - standard: 80% 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.

11 SNOMED coding

Gastrointestinal neuroendocrine tumours should be coded according to the SNOMED system (see Appendix B).

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Appendix A ENETS TNM classification of gastrointestinal neuroendocrine tumours

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

Neuroendocrine tumours of the stomach

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 or ≤10 mm
pT2 Tumour invades muscularis propria or subserosa or >10 mm
pT3 Tumour penetrates serosa
pT4 Tumour invades adjacent structures

For any pT, add (m) for multiple tumours.

Neuroendocrine tumours of the duodenum/ampulla/proximal jejunum.

pTX Primary tumour cannot be assessed
pT0 No evidence of primary tumour
pT1 Tumour invades lamina propria or submucosa or 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 any pT, add (m) for multiple tumours.

* Tumour limited to ampulla of Vater for ampullary gangliocytic paraganglioma.

Neuroendocrine tumours of the pancreas

pTX Primary tumour cannot be assessed
pT0 No evidence of primary tumour
pT1 Limited to the pancreas and size <20 mm
pT2 Limited to the pancreas and size 20–40 mm
pT3 Limited to the pancreas and size >40 mm
pT4 Invading the wall of adjacent large vessels (coeliac axis or superior mesenteric artery), stomach, spleen, colon, adrenal gland

For any pT, add (m) for multiple tumours.

Neuroendocrine tumours of lower jejunum and ileum

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

For any pT, add (m) for multiple tumours.

Neuroendocrine tumours of the appendix

pTX Primary tumour cannot be assessed
pT0 No evidence of primary tumour
pT1 Tumour ≤10 mm invading submucosa and muscularis propria
pT2 Tumour ≤20 mm invading submucosa, muscularis propria and/or minimally (up to 3 mm) invading subserosa/mesoappendix
pT3 Tumour >20 mm and/or extensive (more than 3 mm) invasion of subserosa/mesoappendix
pT4 Tumour invades peritoneum/other organs.

For any pT, add (m) for multiple tumours.

Neuroendocrine tumours of colon and rectum

pTX Primary tumour cannot be assessed
pT0 No evidence of primary tumour
pT1 Tumour invades mucosa or submucosa
pT1a – size <10 mm
pT1b – 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/structures and/or perforates visceral peritoneum

For any pT, add (m) for multiple tumours.

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

pNX Regional lymph node status cannot be assessed
pN0 No regional lymph node metastasis
pN1 Regional lymph node metastasis

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

pMX Distant metastasis cannot be assessed
pM0 No distant metastases
pM1 Histologically confirmed distant metastasis (see section 5.4.6b)
pM1a – Metastasis to specific sites[49]

Appendix B SNOMED codes of gastrointestinal neuroendocrine tumours

T codes

T-63000 Stomach

T-64300 Duodenum

T-58700 Ampulla of Vater

T-59000 Pancreas

T-65100 Jejunum

T-65200 Ileum

T-66000 Appendix

T-67000 Colon

T-68000 Rectum

M codes

The following ENETS-based categories are recommended :

M-82403 Neuroendocrine tumour Grade 1

M-82493 Neuroendocrine tumour Grade 2

M-80413 Small cell neuroendocrine (Grade 3) carcinoma

M-80133 Large cell neuroendocrine (Grade 3) carcinoma

M-82403 Malignant or potentially malignant neuroendocrine tumour

M-82463 Neuroendocrine carcinoma NOS

M-82433 Goblet cell carcinoid tumour

M-82443 Mixed carcinoid-adenocarcinoma

M-81403 Adenocarcinoma

For those wishing to use WHO 2000/4 categories:

M-82403 Well-differentiated neuroendocrine tumour – benign behavior

M-82403 Well-differentiated neuroendocrine tumour – uncertain behaviour

M-82493 Well-differentiated neuroendocrine carcinoma

M-80143 Poorly differentiated neuroendocrine carcinoma

P codes

Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

Appendix C Reporting proforma for gastric neuroendocrine tumour resections

Surname…… Forenames…… Date of birth…….. Sex…....
Hospital…….…….…… Hospital no…….…….. NHS/CHI no……..
Date of receipt…….…… Date of reporting……..…….. Report no……...
Pathologist…….…… Surgeon…….…….

MACRO

Type of specimen

Oesophago-gastrectomy ☐
Proximal gastrectomy ☐ Distal gastrectomy ☐
Total gastrectomy ☐ Local resection ☐

Specimen dimensions

Length of stomach – greater curve …… mm
Length of stomach – lesser curve ..... mm
Length of oesophagus ..... mm
Length of duodenum ..... mm
Site of tumour .....
Tumour perforation Yes ☐ No ☐
Number of tumours …….....
Maximum tumour dimension ..... mm
Distance tumour to nearest cut margin ..….mm

MICRO

Type of tumour

Well-differentiated NET ☐
Poorly differentiated NEC (small cell ca) ☐
Poorly differentiated large cell NEC ☐
Mixed NET-adenocarcinoma ☐
Other (specify) ..... ☐

Grade of tumour

G1 (<2 mitoses/10hpf, Ki-67 index ≤2%) ☐
G2 (2–20 mitoses/10hpf, Ki-67 index >2–20%) ☐
G3 (>20 mitoses/10hpf, Ki-67 index >20%) ☐
Actual Ki-67 index .....%
Not assessable ☐

Tumour extent

Invades (sub)mucosa ☐
Invades muscularis propria ☐
Invades subserosa ☐
Perforates serosa ☐
Invades adjacent structures ☐
Not assessable ☐

Local invasion

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 or size ≤10 mm	☐
pT2	Tumour invades muscularis propria or subserosa or size >10 mm	☐
pT3	Tumour penetrates serosa	☐
pT4	Tumour invades adjacent structures	☐

For any pT, add (m) for multiple tumours

Tumour involvement of margins

Proximal margin involved Yes ☐ No ☐

Distal margin involved Yes ☐ No ☐

Circumferential margin (around cardia) involved: Yes ☐ No ☐ N/A ☐

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

Metastatic spread

Number of lymph nodes present ……

Number of involved lymph nodes ……

(pNX regional lymph node status cannot be assessed, pN0 no regional lymph node metastasis, pN1 regional lymph node metastasis)

Vascular invasion Yes ☐ No ☐ Not assessable ☐

Perineural invasion Yes ☐ No ☐ Not assessable ☐

Histologically confirmed distant metastases (pM1):

Yes ☐ No ☐ If yes, site: ...……

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

Background abnormalities

ECL-cell hyperplasia (nodules <150 µm) Yes ☐ No ☐ N/A ☐

ECL-cell dysplasia (nodules ≥150 µm but <500 µm) Yes ☐ No ☐ N/A ☐

Chronic atrophic gastritis with intestinal metaplasia Yes ☐ No ☐ N/A ☐

G cell hyperplasia Yes ☐ No ☐ N/A ☐

Pathological staging

Complete resection at all surgical margins?

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

If resection incomplete, state involved margin: ……..…..…

TNM

pT …….. pN …….. pM ……..

WHO classification

Well-differentiated neuroendocrine tumour – benign behaviour ☐

Well-differentiated neuroendocrine tumour – uncertain behaviour ☐

Well-differentiated neuroendocrine carcinoma ☐

Poorly differentiated neuroendocrine carcinoma ☐

WHO ECL-cell gastric ET type

Type I ☐ Type II ☐ Type III ☐ Type IV ☐ Not assessable ☐

Signature:…….. Date:……..

SNOMED codes: T63000 / ……..…

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

Surname…… Forenames…… Date of birth…….. Sex…...
Hospital…… Hospital no…… NHS/CHI no……..
Date of receipt…… Date of reporting……..…….. Report no……...
Pathologist…… Surgeon……

Type of specimen:
- Whipple's resection ☐
- Small bowel resection ☐
- Local resection ☐
- Pylorus-preserving pancreaticoduodenectomy (PPPD) ☐

Specimen dimensions

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

Site of tumour ……..
Number of tumours ……..
Maximum tumour dimension …..... mm
Distance tumour to nearest cut margin ……. mm
Named vessel identified Yes ☐ No ☐
Which vessel? ……..…….....……..
Stent in place Yes ☐ No ☐

Type of tumour
- Well-differentiated NET ☐
- Poorly differentiated NEC (small cell ca) ☐
- Poorly differentiated large cell NEC ☐
- Goblet cell carcinoid ☐
- Mixed NET-adenocarcinoma ☐
- Gangliocytic paraganglioma ☐
- Other (specify) ……

Grade of tumour
- G1 (<2 mitoses/10hpf, Ki-67 index ≤2%) ☐
- G2 (2–20 mitoses/10hpf, Ki-67 index >2–20%) ☐
- G3 (>20 mitoses/10hpf, Ki-67 index >20%) ☐
- Actual Ki-67 index …….. %

Tumour extent
- Invades (sub)mucosa ☐
- Invades muscularis propria ☐
- Invades subserosa ☐
- Perforates serosa ☐
- Invades adjacent structures ☐

Peptide hormone content

Immunostaining performed Yes ☐ No ☐
If yes, peptide identified:
- Gastrin ☐ Somatostatin ☐
- Other (specify) ……..…….....

Local invasion

pTX	Primary tumour cannot be assessed	☐
pT0	No evidence of primary tumour	☐
pT1	Tumour invades lamina propria or submucosa or 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 any pT, add (m) for multiple tumours

* Tumour limited to ampulla of Vater for ampullary gangliocytic paraganglioma

Metastatic spread

No of lymph nodes present.....

No of involved lymph nodes.....

(pNX regional lymph node status cannot be assessed

pN0 no regional lymph node metastasis

pN1 regional lymph node metastasis)

Vascular invasion Yes ☐ No ☐ Not assessable ☐

Perineural invasion Yes ☐ No ☐ Not assessable ☐

Histologically confirmed distant metastases (pM1):

Yes ☐ No ☐ If yes, site: …….. (PUL: pulmonary, HEP: hepatic, OSS: osseous)

Pathological staging

Complete resection at all surgical margins?

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

If resection incomplete, state involved margin: ……..…

TNM

pT …….. pN …….. pM ……..

WHO classification

Well-differentiated neuroendocrine tumour – benign behaviour ☐

Well-differentiated neuroendocrine tumour – uncertain behaviour ☐

Well-differentiated neuroendocrine carcinoma ☐

Poorly differentiated neuroendocrine carcinoma ☐

Signature:…….. Date:……..…..

SNOMED codes:……..…

Appendix E Reporting proforma for pancreatic neuroendocrine tumour resections

Surname…… Forenames…… Date of birth…….. Sex…...

Hospital…… Hospital no…… NHS/CHI no……..

Date of receipt…… Date of reporting……..…….. Report no……...

Pathologist…… Surgeon…….…….

Type of specimen:

- Whipple's resection ☐
- Partial distal pancreatectomy ☐
- Local resection ☐
- Enucleation ☐
- Pylorus-preserving pancreaticoduodenectomy (PPPD) ☐

Specimen dimensions

Length of lesser curve stomach ……... mm

Length of greater curve stomach……... mm

Length of duodenum ……... mm

Length of gall bladder ……... mm

Length of bile duct ……... mm

Size of pancreas ……. x ……. x …… mm

Other organs ……..……

Site of tumour ……..……..

Number of tumours ……..……..

Maximum tumour dimension ……..... mm

Distance tumour to nearest cut margin ...…... mm

Named vessel identified Yes ☐ No ☐

Which vessel? ……..…..…….....……..

Stent in place Yes ☐ No ☐

Type of tumour

- Well-differentiated NET ☐
- Poorly differentiated NEC (small cell ca) ☐
- Poorly differentiated large cell NEC ☐
- Mixed NET-adenocarcinoma ☐

Other (specify) ……..…

Grade of tumour

- G1 (<2 mitoses/10hpf, Ki-67 index ≤5%) ☐
- G2 (2–20 mitoses/10hpf, Ki-67 index >5–20%) ☐
- G3 (>20 mitoses/10hpf, Ki-67 index >20%) ☐

Actual Ki-67 index ……. %

Peptide hormone content

Immunostaining performed Yes ☐ No ☐

If yes, peptide identified:

Insulin ☐ Glucagon ☐ Somatostatin ☐ Pancreatic polypeptide ☐ Gastrin ☐

Other (specify)……...

Local invasion

pTX	Primary tumour cannot be assessed	☐
pT0:	No evidence of primary tumour	☐
pT1	Microadenoma <5 mm (benign)	☐
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 adjacent large vessels (coeliac axis or superior mesenteric artery), stomach, spleen, colon, adrenal gland	☐

For any pT, add (m) for multiple tumours

Metastatic spread

No of lymph nodes present.....

No of involved lymph nodes.....

Optional statement of sites of involved node(s) ……

(pNX regional lymph node status cannot be assessed

pN0 no regional lymph node metastasis

pN1 regional lymph node metastasis)

Vascular invasion Yes ☐ No ☐ Not assessable ☐

Perineural invasion Yes ☐ No ☐ Not assessable ☐

Histologically confirmed distant metastases (pM1):

Yes ☐ No ☐ If yes, site: …… (PUL: pulmonary, HEP: hepatic, OSS: osseous)

Background abnormalities

Islet cell microadenomatosis Yes ☐ No ☐ N/A ☐

Chronic pancreatitis Yes ☐ No ☐ N/A ☐

Pathological staging

Complete resection at all surgical margins?

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

If resection incomplete, state involved margin: ……

TNM

pT …….. pN …….. pM ……..

WHO classification

Microadenoma ☐

Well-differentiated neuroendocrine tumour, grade 1 ☐

Well-differentiated neuroendocrine carcinoma, grade 2 ☐

Poorly differentiated neuroendocrine carcinoma, grade 3 ☐

Signature:…….. Date:……..…..

SNOMED codes: T59000 / M……..…

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

Surname…… Forenames…… Date of birth…….. Sex…...

Hospital…… Hospital no…… NHS/CHI no……..

Date of receipt…… Date of reporting…….. Report no……...

Pathologist…… Surgeon……

Specimen type: Jejunal/ileal resection ☐ Right hemicolectomy ☐

Specimen dimensions

Length ……... mm

Maximum width ……... mm

Depth of attached mesentery ……... mm

Site of tumour ……..…

Maximum tumour dimension ...…….. mm

Distance of tumour to nearer cut end ……... mm

Number of tumours ……..……..……

Tumour perforation Yes ☐ No ☐

Type of tumour

Well-differentiated NET ☐

Poorly differentiated NEC (small cell ca) ☐

Poorly differentiated large cell NEC ☐

Mixed NET-adenocarcinoma ☐

Other (specify) .....……..…….……

Grade of tumour

G1 (<2 mitoses/10hpf, Ki-67 index ≤2%) ☐

G2 (2–20 mitoses/10hpf, Ki-67 index >2–20%) ☐

G3 (>20 mitoses/10hpf, Ki-67 index >20%) ☐

Actual Ki-67 index …… %

Tumour extent

Invades (sub)mucosa ☐

Invades muscularis propria ☐

Invades subserosa ☐

Perforates serosa ☐

Invades adjacent structures ☐

Local invasion

pTX Primary tumour cannot be assessed ☐

pT0 No tumour identified ☐

pT1 Tumour invades mucosa or submucosa and size ≤ 10 mm ☐

pT2 Tumour invades muscularis própria or size >10 mm ☐

pT3 Tumour invades subserosa ☐

pT4 Tumour invades peritoneum/other organs ☐

For any pT, add (m) for multiple tumours

Tumour involvement of margins

	N/A	Yes	No
Doughnuts	☐	☐	☐
End margin	☐	☐	☐
Non-peritonealsied mesenteric margin	☐	☐	☐

If clear, macro measurement, confirmed histologically, from tumour to nearest margin ……. mm

Metastatic spread

No of lymph nodes present.....

No of involved lymph nodes.....

(pNX regional lymph node status cannot be assessed, pN0 no regional lymph node metastasis, pN1 regional lymph node metastasis)

Vascular invasion Yes ☐ No ☐ Not assessable ☐

Perineural invasion Yes ☐ No ☐ Not assessable ☐

Histologically confirmed distant metastases (pM1):

Yes ☐ No ☐ If yes, site: ……..

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

Background abnormalities

Crohn's disease ☐ Infarction ☐ Other (state)……

Pathological staging

Complete resection at all surgical margins?

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

If resection incomplete, state involved margin: ……

TNM

pT …….. pN …….. pM ……..

WHO classification

Well-differentiated neuroendocrine tumour – benign behaviour ☐

Well-differentiated neuroendocrine tumour – uncertain behaviour ☐

Well-differentiated neuroendocrine carcinoma ☐

Poorly differentiated neuroendocrine carcinoma ☐

Signature: …… Date ……..……

SNOMED codes: ……..…..

Appendix G Reporting proforma for appendiceal neuroendocrine tumour resections

Surname…… Forenames…… Date of birth…….. Sex…...

Hospital…… Hospital no…… NHS/CHI no……..

Date of receipt…… Date of reporting……..…... Report no……...

Pathologist…… Surgeon……

Specimen type: Appendicectomy ☐ Right hemicolectomy ☐ Other (state) ……

Specimen dimensions

Length ……... mm

Maximum width ……... mm

Depth of mesoappendix ……... mm

Site of tumour ……...…

Maximum tumour dimension ...……... mm

Distance of tumour to nearer cut end ……... mm

Number of tumours ……..……..……

Type of tumour

Well-differentiated NET ☐

Poorly differentiated NEC (small cell ca) ☐

Poorly differentiated large cell NEC ☐

Goblet cell carcinoid ☐

Combined classical and goblet cell carcinoid ☐

Other (specify) .....……..…….……

Grade of tumour

G1 (<2 mitoses/10hpf, Ki-67 index ≤2%) ☐

G2 (2–20 mitoses/10hpf, Ki-67 index >2–20%) ☐

G3 (>20 mitoses/10hpf, Ki-67 index >20%) ☐

Actual Ki-67 index …… %

Tumour extent

Invades (sub)mucosa ☐

Invades muscularis propria ☐

Invades subserosa ☐

Invades mesoappendix ☐

Perforates serosa ☐

Invades adjacent structures ☐

Tumour involvement of margins

	N/A	Yes	No
End margin	☐	☐	☐
Non-peritonealised mesenteric margin	☐	☐	☐

If clear, macro measurement, confirmed histologically, from tumour to cut end margin …… mm

Local invasion

pTX Primary tumour cannot be assessed ☐

pT0 No tumour identified ☐

pT1 Tumour ≤ 10 mm invading submucosa and muscularis propria ☐

pT2 Tumour ≤ 20 mm invading 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/other organs ☐

For any pT, add (m) for multiple tumours

Metastatic spread

No of lymph nodes present.....

No of involved lymph nodes.....

(pNX regional lymph node status cannot be assessed, pN0 no regional lymph node metastasis, pN1 regional lymph node metastasis)

Vascular invasion Yes ☐ No ☐ Not assessable ☐

Perineural invasion Yes ☐ No ☐ Not assessable ☐

Histologically confirmed distant metastases (pM1):

Yes ☐ No ☐ If yes, site: ……

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

Background abnormalities

Appendicitis ☐
Adenoma ☐
Serrated polyp ☐

Pathological staging

Complete resection at all surgical margins

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

If resection incomplete, state involved margin: ……

TNM

pT …….. pN …….. pM ……..

WHO classification (not applicable to goblet cell carcinoids)

Well-differentiated neuroendocrine tumour – benign behaviour ☐
Well-differentiated neuroendocrine tumour – uncertain behaviour ☐
Well-differentiated neuroendocrine carcinoma ☐
Poorly differentiated neuroendocrine carcinoma ☐

Tang classification (only for goblet cell carcinoids)

Tang A – typical GCC ☐ SNOMED as goblet cell carcinoid M-82433
Tang B – adenocarcinoma ex GCC, signet ring cell type ☐ SNOMED as mixed carcinoid-adenocarcinoma M-82443
Tang C – adenocarcinoma ex GCC, poorly differentiated type ☐ SNOMED as mixed carcinoid-adenocarcinoma M-82443 and adenocarcinoma M-81403

Signature: …… Date ……..……

SNOMED codes T66000 / M……

Appendix H Reporting proforma for colorectal neuroendocrine tumour resections

Surname…… Forenames…… Date of birth…….. Sex…...
Hospital…… Hospital no…… NHS/CHI no……..
Date of receipt…… Date of reporting……..…….. Report no……...
Pathologist…… Surgeon……

Specimen type:

Total colectomy ☐ Right hemicolectomy ☐ Left hemicolectomy ☐ Sigmoid colectomy ☐
Anterior resection ☐ Abdominoperineal excision ☐
Local resection (e.g. endoscopic mucosal resection (EMR) or transanal excision) ☐ Other (specify) ….....……

Specimen dimensions
Total length ……..mm
Right–left ……..mm
Anterior–posterior ……..mm
Perianal skin if present ……..mm
(Describe mesorectum as per colorectal proforma if TME)

Site of tumour ……..…
Maximum tumour dimension ……..mm
Distance of tumour to nearer cut end .....……..mm
Tumour perforation (pT4) Yes ☐ No ☐
Number of tumours …….....……

For rectal tumours:
Relation of tumour to peritoneal reflection (tick one):
Above ☐ Astride ☐ Below ☐
For abdominoperineal resection specimens:
Distance of tumour from dentate line ..... mm

Grade of tumour
G1 (<2 mitoses/10hpf, Ki-67 index ≤2%) ☐
G2 (2–20 mitoses/10hpf, Ki-67 index >2–20%) ☐
G3 (>20 mitoses/10hpf, Ki-67 index >20%) ☐
Actual Ki-67 index …….. %

Type of tumour
Well-differentiated NET ☐
Poorly differentiated NEC (small cell ca) ☐
Poorly differentiated large cell NEC ☐
Goblet cell carcinoid ☐
Mixed ET-adenocarcinoma ☐
Other (specify) ……

Tumour involvement of margins

	N/A	Yes	No
Doughnuts	☐	☐	☐
Margin (cut end)	☐	☐	☐
Non-peritonealised ‘circumferential’ margin	☐	☐	☐

If no, macro measurement, confirmed histologically, from tumour to non-peritonealised margin .. ..mm

Tumour extent
Invades (sub)mucosa ☐
Invades muscularis propria ☐
Invades subserosa ☐
Perforates serosa ☐
Invades adjacent structures ☐

Local invasion
pTX Primary tumour cannot be assessed ☐
pT0 No tumour identified ☐
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 any pT, add (m) for multiple tumours

Metastatic spread

No of lymph nodes present.....

No of involved lymph nodes.....

(pNX regional lymph node status cannot be assessed, pN0 no regional lymph node metastasis, pN1 regional lymph node metastasis)

Vascular invasion	Yes ☐	No ☐	Not assessable ☐
Perineural invasion	Yes ☐	No ☐	Not assessable ☐

Histologically confirmed distant metastases (pM1):

Yes ☐ No ☐ If yes, site: .....

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

Background abnormalities

Adenoma	☐	Ulcerative colitis	☐
Crohn's disease	☐	Other……	

Pathological staging

Complete resection at all surgical margins?

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

If resection incomplete, state involved margin: ……

TNM

pT …….. pN …….. pM ……..

WHO classification

Well-differentiated neuroendocrine tumour – benign behaviour	☐
Well-differentiated neuroendocrine tumour – uncertain behaviour	☐
Well-differentiated neuroendocrine carcinoma	☐
Poorly differentiated neuroendocrine carcinoma	☐

Signature: …… Date ……..……

SNOMED codes: ……

Appendix I WHO 2000/2004 classification of gastrointestinal[6] and pancreatic neuroendocrine tumours[14]

Site	Well-differentiated neuroendocrine tumour (Benign behaviour)*	Well-differentiated neuroendocrine tumour (Uncertain behaviour)	Well-differentiated neuroendocrine carcinoma (Low-grade malignant)	Poorly differentiated neuroendocrine carcinoma (High-grade malignant)
Pancreas	Confined to pancreas Functioning insulinoma <20 mm Non-functioning tumours <20 mm No vascular invasion No perineural invasion <2 mitoses/10 HPF/Ki-67 index ≤2%	Confined to pancreas and one or more of the following: ≥20 mm Perinneural invasion Vascular invasion 2–10 mitoses/10 HPF/Ki-67 index >2%	Invasion of adjacent organs presence of metastases	High grade, poorly differentiated large cell, intermediate cell or small cell carcinoma. Ki-67 index >30%
Stomach	Non-functioning Confined to mucosa-submucosa Size ≤10 mm No vascular invasion	Non-functioning Confined to mucosa-submucosa Size >10–20 mm without vascular invasion Size up to 20 mm with vascular invasion	Functioning tumour of any size Non-functioning tumour >20 mm *or* of any size with invasion beyond submucosa and/or metastases. Ki-67 index 2–30%	High grade, poorly differentiated large cell, intermediate cell or small cell carcinoma. Ki-67 index >30%
Duodenum and upper jejunum	Non-functioning Confined to mucosa-submucosa Size ≤10 mm No vascular invasion Gangliocytic paraganglioma of any size	Non-functioning tumour or functioning gastrinoma Confined to mucosa-submucosa Size >10 mm or ≤10 mm with vascular invasion	Functioning or non-functioning tumour of any size with invasion beyond submucosa and/or metastases. Ki-67 index 2–30%	High grade, poorly differentiated large cell, intermediate cell or small cell carcinoma. Ki-67 index >30%
Distal jejunum, ileum	Non-functioning Confined to mucosa-submucosa Size ≤10 mm No vascular invasion	Non-functioning Confined to mucosa-submucosa Size ≤10 mm Vascular invasion	Functioning tumour of any size Non-functioning tumour >10 mm *or* of any size with invasion beyond submucosa and/or metastases. Ki-67 index 2–30%	High grade, poorly differentiated large cell, intermediate cell or small cell carcinoma. Ki-67 index >30%
Appendix	Non-functioning Confined to appendiceal wall Size <20 mm No vascular invasion	Non-functioning Extension into mesoappendix Vascular invasion >20–25 mm	Functioning tumour of any size Non-functioning Deep invasion into mesoappendix Size >25 mm and/or metastases. Ki-67 index 2–30%	High grade, poorly differentiated large cell, intermediate cell or small cell carcinoma. Ki-67 index >30%
Colon, rectum	Non-functioning Confined to mucosa-submucosa Size <20 mm No vascular invasion	Non-functioning Confined to mucosa-submucosa Size <20 mm Vascular invasion	Functioning tumour of any size Non-functioning tumour >20 mm or of any size with invasion beyond submucosa and/or metastases. Ki-67 index 2–30%	High grade, poorly differentiated large cell, intermediate cell or small cell carcinoma. Ki-67 index >30%

Note: the term 'functioning' is defined as causing a hormonal syndrome, NOT containing an immunodetectable hormone within tumour cells.

*There are a few reported exceptions to the benign behaviour predicted in this category.

Appendix J Modified WHO typing of ECL-cell gastric carcinoid tumours[5,38]

	Type I	Type II	Type III	Type IV (provisional)
Pre-existing condition	Gastritis of corpus, autoimmune	Z-E syndrome, usually with MEN1	None (sporadic)	Parietal cell dysfunction
Hypergastrinaemia	Present	Present	Absent	Present
Carcinoid tumours	Small (<15 mm), often multiple, no atypia	Usually small (but 20% >15 mm), often multiple, no atypia	Large, solitary, may show atypia	Small, multiple, no atypia
Distant (liver) metastases	2–5%	10%	22–75%	Unknown
Outcome	Virtually never fatal	Rarely fatal	25% mortality	Unknown
ECL-cell hyperplasia/ dysplasia	Present	Present	Absent	Present
Background mucosa	Chronic atrophic gastritis with IM	Hypertrophic oxyntic glands; hyperplastic parietal cells	Normal	Hypertrophic, distended oxyntic glands; hyperplastic vacuolated parietal cells
Management	Conservative	Conservative	Gastrectomy	Uncertain

Appendix K Summary table – Explanation of levels of evidence

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

Level of evidence	Nature of evidence
Level 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.
Level 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.
Level 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.
Level 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 L AGREE compliance monitoring sheet

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

AGREE standard	Section of dataset
SCOPE AND PURPOSE	
1. The overall objective(s) of the guideline is (are) specifically described	1
2. The clinical question(s) covered by the guidelines is (are) specifically described	1
3. The patients to whom the guideline is meant to apply are specifically described	Foreword
STAKEHOLDER INVOLVEMENT	
4. The guideline development group includes individuals from all the relevant professional groups	Foreword
5. The patients' views and preferences have been sought	N/A*
6. The target users of the guideline are clearly defined	Foreword
7. The guideline has been piloted among target users	1
RIGOUR OF DEVELOPMENT	
8. Systematic methods were used to search for evidence	Foreword
9. The criteria for selecting the evidence are clearly described	Foreword
10. The methods used for formulating the recommendations are clearly described	Foreword
11. The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12. There is an explicit link between the recommendations and the supporting evidence	References
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	4–9
16. The different options for management of the condition are clearly presented	4–9
17. Key recommendations are easily identifiable	4–9
18. The guideline is supported with tools for application	Appendices
APPLICABILITY	
19. The potential organisational barriers in applying the recommendations have been discussed	Foreword
20. The potential cost implications of applying the recommendations have been considered	Foreword
21. The guideline presents key review criteria for monitoring and/audit purposes	10
EDITORIAL INDEPENDENCE	
22. The guideline is editorially independent from the funding body	Foreword
23. Conflicts of interest of guideline development members have been recorded	Foreword

* The Lay Advisory Committee (LAC) of The Royal College of Pathologists has advised the Director of Communications that there is no reason to consult directly with patients or the public regarding this dataset because it is technical in nature and intended to guide pathologists in their practice. The authors will refer to the LAC for further advice if necessary.