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

Standards and datasets for reporting cancers

Dataset for histopathological reporting of carcinomas and mucinous neoplasms of the appendix

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Produced by	Professor Manuel Rodriguez-Justo, Dr Newton Wong and Professor Roger Feakins are consultant histopathologists actively engaged in the diagnosis and multidisciplinary care of patients with appendiceal cancer and in the professional associations that promote research and guideline development on their diagnosis and treatment. Professor Norman Carr recently retired from clinical practice at the Peritoneal Malignancy Institute, Basingstoke, but he is still active in research. He contributed to the appendiceal tumour section of the 2019 edition of the *WHO Classification of*

	Tumours of the Digestive System and was a member of the Management Committee of the European Network on Pseudomyxoma Peritonei (EuroPMP).
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Comments	This document replaces the 1st edition of the *Dataset for histopathological reporting of carcinomas and mucinous neoplasms of the appendix*, published in March 2021. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 29 August to 26 September 2024. Responses and authors' comments are available to view on publication of the final document. **Dr Brian Rous** **Clinical Lead for Guideline Review**

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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 B and D) 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 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
- British Society of Gastroenterology, Pathology Section.

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

The information used to develop this dataset was obtained by undertaking a systematic search of PubMed. Key terms searched included ‘appendiceal neoplasms’ and ‘pseudomyxoma peritonei’, and dates searched were between January 1985 and January 2024. The searches were not restricted by language. Relevant additional publications identified in the reference lists were also obtained. Published evidence was evaluated

using modified SIGN guidance (see Appendix F). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence were identified by College members via feedback received during consultation.

A formal revision cycle for all cancer datasets takes place on a 3-yearly basis. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether the dataset needs to be 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 2 weeks for Fellows' attention. If members 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 Professional Guidelines team, Working Group on Cancer Services and Lay Advisory Group and was on the College website for consultation with the membership from 29 August to 26 September 2024. All comments received from the Working Group and membership were addressed by the author to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

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 Professional Guidelines team and are available on request. In compliance, Professor Feakins has declared that he is the Director of Justo Consultancy Limited, and he lectures or is on advisory boards for Roche, Agilent, Merk Sharp & Dohme Limited (MSD), Bristol Myers Squibb (BMS) and Jazz Pharmaceuticals Technologies. This statement is made for full transparency. The other authors have declared no conflicts of interest.

1 Introduction

Careful and accurate pathology reporting of appendiceal specimens containing carcinoma or related lesions is important. Pathology reports help to:

- make the diagnosis, or confirm a suspected diagnosis, of carcinoma
- identify and classify precursor lesions
- inform the prognosis
- plan the treatment
- audit pathology services
- evaluate the quality of other clinical services, e.g. imaging, gastroenterology and surgery
- collect data for cancer registration and epidemiology
- facilitate research
- provide education
- plan future service delivery.

1.1 Target users and health benefits of this guideline

The target primary users of the dataset are trainee and consultant histopathologists and, on their behalf, the suppliers of IT products to laboratories. Secondary users will include other healthcare professionals such as biomedical scientists, surgeons, nurses, oncologists, gastroenterologists and radiologists. It will also be of use to cancer registries and the National Cancer Registration and Analysis Service.

1.2 Introduction to the first edition of this dataset

This is the second edition of a reporting dataset from the RCPath specifically addressing appendiceal neoplasms. An appendiceal dataset is necessary because of the differences between appendiceal carcinomas and colorectal carcinomas.[1–3] Accurate diagnosis and classification of appendiceal neoplasms is of increasing importance with the development of radical treatments such as cytoreductive surgery and heated intraperitoneal chemotherapy.[4] Patients may also be subject to prolonged clinical follow-up.

Goblet cell adenocarcinomas (GCAs, previously termed goblet cell carcinoids) were previously covered in the *Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract*.[5] However, GCAs are not a type of neuroendocrine neoplasm, and it is more appropriate to include them in this dataset along with other adenocarcinomas of the appendix.[2,6,7] Therefore, pathologists should now refer

to this dataset for guidelines on reporting GCAs, and the proformas, lists of data items and SNOMED coding section have been amended to incorporate the necessary changes.

2 Clinical information required on the specimen request form

Appendiceal neoplasms may be encountered in simple appendectomies or right hemicolectomies, or in more extensive procedures such as subtotal colectomies as part of cytoreductive surgery. The nature of the operation should be made clear and the operative findings described. If a previous appendectomy has been performed, this should be clearly stated along with the diagnosis at the time of appendectomy. Multidisciplinary team (MDT) meetings can be a source of important information.

It is also important for the pathologist to be aware if preoperative chemo/radiotherapy has been given, its nature and when it finished. In practice, however, this will be a rare event in initial surgery for appendiceal neoplasia.

3 Preparation of specimens before dissection

Unless local protocols dictate that specimens should be submitted fresh, they should be fixed as soon as possible after removal from the body in a suitable medium, typically buffered formalin. Opening of the appendix prior to receipt by the pathology department, even if distended, is contraindicated and should not take place until the time of definitive pathological dissection.

When lengths of intestine have been removed, e.g. right hemicolectomy, it is their serosal/peritoneal surfaces, rather than the mucosal surfaces, that will usually be of most interest because of the frequent involvement of the peritoneum by appendiceal neoplasia. Therefore, we recommend that specimens where appendiceal neoplasia is suspected are not opened until they have been examined by the pathologist.

4 Specimen handling and block selection

The type of specimen should be recorded. A photograph of the specimen should be considered; it is often useful during MDT discussions and provides a permanent visual record if questions arise subsequently.

The entire appendix should be processed if it contains a neoplasm or serrated lesion of any type, including low-grade appendiceal mucinous neoplasms (LAMNs), foci of dysplasia, adenomas and serrated polyps.[3,8] This practice facilitates identification of adverse prognostic features that may be present only focally, such as high-grade dysplasia and infiltrative invasion.

Thorough sampling of any extra-appendiceal mucin is required, because in patients with LAMN the prognosis is considerably worse if cells are found in this mucin.[8,9] Extra-appendiceal mucin may need careful processing, and in some cases centrifuging material to make cell blocks could be useful. The amount of extra-appendiceal mucin to be processed in patients with pseudomyxoma peritonei is a matter of clinical judgement.

Responsibility for the macroscopic description and cut-up of appendices often lies with relatively inexperienced or less qualified medical or laboratory staff because appendiceal cut-up is regarded as straightforward and routine. So that an appropriate approach is taken when encountering appendiceal neoplasms, or indeed any appendix that might contain a neoplasm, it is essential that all staff are aware of the potentially complex nature of a minority of appendicectomy specimens. Attempting to ‘rescue’ the situation afterwards can be difficult, e.g. determination of the presence or absence of serosal mucin. Staff should be encouraged to have a low threshold for consultation with more experienced colleagues if there is any suggestion of neoplasia or if the appendix appears abnormally dilated or has serosal mucin.

4.1 Appendicectomy

The following points should be noted:

- length and maximum external diameter of appendix
- whether any caecal wall is included in appendicectomy specimens
- appearance of the tumour
- size of the tumour – the maximum diameter of the tumour should be provided, if possible; as this can be difficult if the dimensions of the tumour are not obvious, a comment to this effect will be more appropriate
- evidence of perforation – and whether this occurs through the tumour or away from the tumour
- visible mucus on serosal surfaces

- any other pathological abnormalities such as inflammatory exudate or appendiceal diverticula.

Optionally, the pathologist may wish to record:

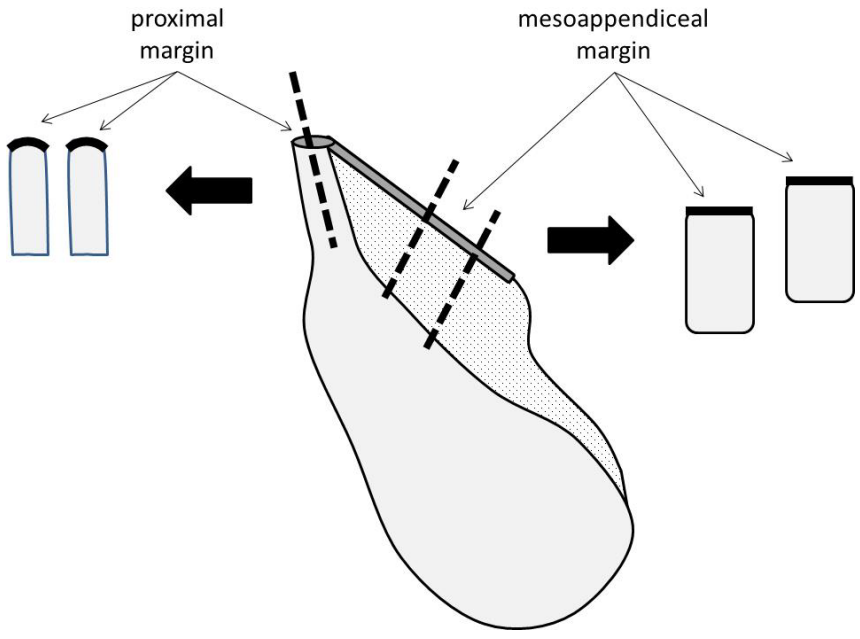
- the width of mesoappendix in appendicectomy specimens, i.e. the greatest distance between the peritoneal reflection on the appendiceal wall and the cut edge
- the status of the proximal and mesenteric resection margins, if visible, especially if the margin is grossly involved.

For appendicectomies, inking of the proximal resection margin and the mesoappendiceal margin is recommended if there is any suspicion of a neoplasm. As with other parts of the large intestine, the serosal surfaces are not resection margins and should not normally be inked.

Blocks should be taken to demonstrate the distance of the tumour from the margins. We recommend that the proximal appendix is bisected longitudinally, if possible, allowing the distance from the proximal margin to be measured accurately (Figure 1),[10] although the type of blocks taken in each case will depend on the nature of the specimen and the judgement of the pathologist. Rarely, a retrocaecal appendix may be retroperitoneal and lack a mesoappendix. The non-peritonealised surface is the circumferential margin in these circumstances.

Figure 1: An appendix with a distal tumour.

The recommended blocks demonstrate distances from the proximal and mesoappendiceal margins.



In most appendicectomy specimens, the distance from the tumour to the proximal or mesoappendiceal margin will be less than 30 mm and can, therefore, be measured histologically within 1 tissue block; a specific macroscopic measurement of this distance is not then necessary and should be avoided to prevent confusion. If this distance is greater than 30 mm (and is not measured histologically), it is enough to state only this macroscopic measurement in the dataset.

One or more mesoappendiceal lymph nodes are often present. They should be sought by careful dissection and submitted for histology. The appendiceal tip can be bisected longitudinally if it is not significantly swollen; otherwise, it requires transverse sections.

4.2 Larger specimens

If the appendix comprises part of a larger specimen such as a right hemicolectomy, additional handling and reporting procedures will be required. The mucosal surfaces should be examined for any pathological changes, which should be appropriately sampled for histology, if present. If any polyps or synchronous cancers are found in the colon, the procedures recommended in the relevant dataset should be followed.

All lymph nodes should be submitted. For right hemicolectomies, the highest node in the ileocolic chain, i.e. the node nearest the sutured vascular margin, can be designated the apical node by analogy with resections for colonic cancers. This, however, is a non-core item, since apical node involvement has not been shown to have prognostic implications in appendiceal cancer. There is evidence that at least 10 nodes should be retrieved to allow adequate assessment of node status.[11]

The longitudinal margins (cut ends of the terminal ileum and colon) in a right hemicolectomy specimen will normally be well clear of an appendiceal neoplasm but, if a tumour is less than 30 mm from a longitudinal margin, blocks should be taken to assess the distance from the tumour.

By contrast, the retroperitoneal margin may lie close to an appendiceal adenocarcinoma, especially if the caecum is retroperitoneal. The pathologist should ink and sample this margin if macroscopically it is within 30 mm of the neoplasm.[12,13] If any of these clearance distances are greater than 30 mm, and they are not measured histologically, it is enough to state only the macroscopic measurement(s) in the dataset.

If cytoreductive surgery has been performed, the specimens may include: peritonectomies, omentectomy, hysterectomy, salpingo-oophorectomies, splenectomy, cholecystectomy,

partial or total gastrectomy, and other resections. The aim of dissection and block selection should include:

- documentation of the organs involved by metastatic disease; if the umbilicus has been excised, it should be sampled along with the subumbilical tissues, since appendiceal neoplasms often involve this area
- in pseudomyxoma peritonei, the grade of the metastatic disease (which is assessed independently of the primary neoplasm)[14]
- resection margins if clinically relevant
- identification and submission for histology of all lymph nodes; this includes the gastroepiploic nodes commonly found in omentectomies
- demonstration of any incidental pathology.

In disseminated peritoneal disease, the selection of blocks will be a matter of professional judgement, since there is little evidence base for guidance. If initial histological examination reveals only acellular mucin without neoplastic cells, it is worth taking extra blocks to ensure neoplastic cells are not missed.[15] If there are parenchymal liver metastases (rather than the surface implants characteristic of pseudomyxoma peritonei), the appropriate dataset guidelines can be followed.[16]

5 Reporting resection specimens

5.1 Diagnostic classification

5.1.1 Appendiceal mucinous neoplasms and mucinous adenocarcinoma

Mucinous neoplasms are designated LAMN, high-grade appendiceal mucinous neoplasm (HAMN) or mucinous adenocarcinoma according to the criteria shown in Table 1 (see next page), which are derived from the World Health Organization (WHO) classification and the definitions of the Peritoneal Surface Oncology Group International (PSOGI) consensus.[14,17,18] Note that the terms ‘cystadenoma’ and ‘cystadenocarcinoma’ are no longer used for appendiceal neoplasms.

Table 1: Classification of mucinous appendiceal neoplasms with corresponding grades.[14,17,18]

Type of appendiceal neoplasm	Cytology	Type of invasion	Grade
Low-grade appendiceal mucinous neoplasm (LAMN)	Low grade	Pushing invasion	G1
High-grade appendiceal mucinous neoplasm (HAMN)	High grade	Pushing invasion	G2
Mucinous adenocarcinoma	Any grade	Infiltrative invasion	G2*
Mucinous adenocarcinoma with signet ring cells†	Signet ring cells in mucin pools or infiltrating tissue	Infiltrative invasion	G3

*Rare mucinous adenocarcinomas with sheets of poorly differentiated cells may be designated G3.

†At least 10% of the cells should show signet ring morphology for this classification. If more than 50% of the tumour cells show signet ring cell morphology, the term 'signet ring cell adenocarcinoma' can be used.

LAMN has a villous, undulating or flattened pattern of growth associated with evidence of pushing invasion, i.e. extension into the submucosa and beyond on a broad front. This type of invasion often produces diverticulum-like structures. The cells are usually columnar and mucin-rich, although they may become attenuated in lesions with flattened architecture. Cytological atypia is usually minimal and does not exceed that seen in low-grade adenomas of the colorectum. The appendiceal wall often shows dense paucicellular fibrosis, frequently becomes thinned and may be calcified. In other cases, acellular mucin may dissect the appendiceal wall.[3,19]

LAMNs should be distinguished from serrated polyps and colorectal-type adenomas (see sections 5.1.4 and 5.1.5). The differential diagnosis also includes ruptured diverticulum, which can closely mimic LAMN, including the extravasation of acellular mucin onto the serosa or eversion of the mucosa onto the serosa at the mouth of the diverticulum.[20,21]

HAMN is rare and is characterised by high-grade cytology associated with pushing invasion.[14,17,22] At low power, these lesions have the outline of LAMN, but high power reveals unequivocal high-grade features such as nuclear pleomorphism, high nuclear/cytoplasmic ratio, loss of nuclear polarity with full-thickness pseudostratification of nuclei, and frequent or atypical mitoses. A distinctive feature of HAMN is the presence of pseudopapillary structures composed of cells with hyperchromatic nuclei and numerous

apoptotic bodies. A cribriform pattern is sometimes observed but is not required for diagnosis.[23] Small foci of increased atypia (<10% of the total tumour) are consistent with LAMN and should not generally lead to diagnosis of HAMN.[24]

Being based on subjective criteria, the distinction between LAMN and HAMN can be difficult. It may be appropriate to diagnose a lesion with mixed low- and high-grade features (arbitrarily, tumours with between 10% and 80% high-grade areas) as ‘low-grade and high-grade appendiceal neoplasm’, which is consistent with genetic evidence suggesting that HAMNs may evolve from low-grade lesions.[25] However, ‘low-grade and high-grade appendiceal neoplasm’ is not standard terminology and should be discussed in the comments section; such lesions should be classified as HAMN on the proforma.

Mucinous adenocarcinoma is characterised by infiltrative invasion. This can be represented by angulated glands, a desmoplastic stroma, tumour budding, or the ‘small cellular mucin pool’ pattern in which crowded, expansile mucin pools contain strips or detached islands of neoplastic cells.[18,22] Adenocarcinomas often appear to arise from a pre-existing serrated polyp, LAMN or HAMN.

Signet ring cells confer a worse prognosis, and so adenocarcinomas with signet ring cells are a separate diagnostic category and are graded G3.[24,26,27] To be consistent with the recommendations for pseudomyxoma peritonei, we recommend that at least 10% of cells should show signet ring morphology for a tumour to be placed in this category.[24] Although lesions in which more than 50% of the tumour cells show signet ring morphology can be called 'signet ring cell adenocarcinoma', they are coded as 'mucinous adenocarcinoma with signet ring cells' since there is no known clinical significance to the distinction.

Care must be taken when diagnosing signet ring cells, because degenerating cells floating in mucin pools can mimic signet ring cells (so-called ‘pseudo-signets’). If more than 50% of the tumour consists of signet ring cells, the term ‘signet ring cell adenocarcinoma’ can be used, but such lesions should be carefully distinguished from GCAs.[7]

[Level of evidence B – Classification is correlated with prognosis and overall survival.]

5.1.2 Non-mucinous adenocarcinoma

Non-mucinous adenocarcinomas are defined by less than 50% of the cross-sectional area comprising extracellular mucin. They are less common than mucinous adenocarcinomas and usually resemble colorectal adenocarcinoma histologically. For stage IV tumours, the prognosis is worse for non-mucinous than mucinous adenocarcinomas.[28,29]

5.1.3 Goblet cell adenocarcinoma

GCA is an uncommon tumour that almost always arises in the appendix. It was previously known as ‘goblet cell carcinoid’ but this name caused confusion with true neuroendocrine neoplasms. GCAs are now regarded as a distinctive type of adenocarcinoma. The name ‘goblet cell adenocarcinoma’ is recommended by the WHO and ‘goblet cell carcinoid’ should no longer be used.[7] By definition, a GCA must include at least a component of classic low-grade tumour characterised by clusters and tubules predominantly consisting of goblet-like cells.[3,7,30] Variable numbers of scattered endocrine-like cells are usually but not always present, and Paneth-like cells may occasionally be visible. The clusters and tubules of goblet-like cells may be solid or show small lumina. Cohesive cords of cells may also be present, especially among fibres of muscularis propria. Foci of mild architectural disarray or tubular fusion may be part of the low-grade pattern.

High-grade features are seen in some GCAs and may include complex anastomosing tubules, sheets of cells, increased nuclear atypia (often with a reduction in intracytoplasmic mucin), numerous mitoses, atypical mitotic figures, desmoplasia, areas of necrosis, discohesive growth with numerous individual tumour cells, and areas resembling conventional adenocarcinoma.[3,30–32] These high-grade features are used in the grading of GCAs (see section 5.2).

[Level of evidence B – Grade is correlated with prognosis and overall survival.]

The histological diagnosis of GCA is morphological. Although neuroendocrine markers such as chromogranin and synaptophysin are usually positive in at least some cells, occasional GCAs lack neuroendocrine differentiation by immunohistochemistry. Neuroendocrine immunostains are not required for diagnosis. Regarding differential diagnosis, GCA can mimic metastatic adenocarcinoma or the clear cell or lipid-rich variant of neuroendocrine tumour. GCAs should be distinguished from mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs), which have different morphological features and behaviour.

5.1.4 Serrated polyps

Serrated polyps of the appendix closely resemble sessile serrated lesions of the colorectum, but they have different genetic abnormalities and do not have the same spectrum of appearances as colorectal lesions, which is why the non-committal term ‘serrated polyp’ is recommended.[33,34]

[Level of evidence – D.]

Serrated polyps are characterised by preservation of mucosal architecture with no loss of muscularis mucosae. By contrast, most LAMNs have an undulating or flattened pattern of growth. In borderline cases, a diagnosis of LAMN is suggested by the presence of filiform villi, areas of undulating or flattened architecture, hyaline dense fibrosis of the underlying tissues, loss of muscularis mucosae, or any evidence of pushing invasion, including the presence of mucin (that may or may not also contain neoplastic epithelium) in the wall or outside the appendix.[3]

Serrated polyps can be dysplastic. Sometimes, dysplastic serrated polyps resemble traditional serrated adenomas of the colorectum. The significance of this finding is unclear and it is sufficient to diagnose them as serrated polyps with low-grade or high-grade dysplasia, perhaps with an added comment on the resemblance to traditional serrated adenoma.[3] Many appendices with LAMN or adenocarcinoma contain areas of serrated polyp, suggesting it may be a precursor to more aggressive tumours.

5.1.5 'Colorectal-type' adenomas

Tubular, tubulovillous and villous adenomas indistinguishable from their colorectal counterparts occur in the appendix, but they are rare and much less frequent than LAMNs or serrated polyps.[3,35] They are characterised by conventional dysplasia but lack serrated architecture, which would imply a dysplastic serrated polyp. Non-mucinous adenocarcinomas are sometimes found in association with colorectal-type adenomas.

5.1.6 Other types of appendiceal neoplasia

Well-differentiated neuroendocrine neoplasms (neuroendocrine tumours) are common in the appendix and are discussed in the RCPath *Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract*.[5] On very rare occasions, other histological types, such as adenosquamous carcinoma or neuroendocrine carcinoma (poorly differentiated neuroendocrine neoplasm), may be encountered. Note that if a tumour is morphologically an adenocarcinoma, focal neuroendocrine expression identified by immunohistochemistry does not lead to a diagnosis of neuroendocrine neoplasm.

5.2 Grading

5.2.1 Grading of mucinous appendiceal neoplasms and non-mucinous adenocarcinomas

Grade is an important prognostic factor.[9,29,36] For mucinous tumours, the WHO grading classification (G1–3) should be included in the report (Table 1).[17,18] Note that the principles of classification differ from colorectal cancer. Infiltrative invasion leads to a diagnosis of G2

even if the tumour is well differentiated. Mucinous adenocarcinoma with signet ring cells is classified G3, reflecting the poor prognosis associated with signet ring morphology.[24,26,27] As discussed in section 5.1, degenerating cells in mucin pools can mimic true signet ring cells.

[Level of evidence B – Grade is correlated with prognosis and overall survival.]

For non-mucinous adenocarcinomas of the appendix, evidence for appropriate grading is scanty. We recommend following the WHO classification for non-mucinous adenocarcinomas: low-grade (formerly well-to-moderately differentiated) and high-grade (formerly poorly differentiated), corresponding to G1/2 and G3, respectively.

When assigning a grade, we recommend grading according to the least differentiated area of the tumour. This practice is consistent with the limited evidence available, e.g. a minority of cells with signet ring morphology is associated with a worse prognosis.[24,26] It is also consistent with the grading recommendations for colorectal cancer in the RCPath 2023 dataset.[12]

5.2.2 Grading of GCAs

The current WHO recommendation is to grade GCAs based on the proportion of tumour showing high-grade features, as shown in Table 2.[7] Mitotic count and Ki67 proliferation index are not used in the grading of GCAs.[30–32]

[Level of evidence – C.]

Table 2: Three-tiered grading system for GCAs.[7,30]

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%

5.3 Staging

Stage is an important prognostic factor, and the tumour, node and metastasis (TNM) classification is shown in Table 3.[6,22,24,35,36] This staging system also applies to GCAs.

Table 3: Summary of TNM classification of appendiceal neoplasms.[6]

Primary tumours

LAMNs only: • Confined to appendix (not beyond muscularis propria)	pTis
Adenocarcinomas and HAMNs only: • Invades submucosa/muscularis propria	pT1/pT2
All lesions: • Invades subserosa or mesoappendix (includes acellular mucin) • Perforates serosa (visceral peritoneum), including cells and/or mucin on the serosa • Directly invades other organs or structures	pT3 pT4a pT4b
Regional lymph nodes	
No regional node metastasis	pN0
Metastasis in 1 regional node	pN1a
Metastasis in 2–3 regional nodes	pN1b
Tumour deposits (satellites) without regional nodal metastasis	pN1c
Metastasis in 4 or more regional nodes	pN2
Distant metastasis	
Intraperitoneal acellular mucin only	pM1a
Intraperitoneal metastasis with mucinous epithelium	pM1b
Non-peritoneal metastasis	pM1c

Regarding the pT classification, it is important to note certain features.

- For LAMNs, any lesions in which there is no evidence of spread beyond muscularis propria are designated ‘pTis (LAMN)’. This reflects the excellent prognosis in patients where there is no evidence of extra-appendiceal spread. Therefore, the terms pT1 and pT2 do not apply to LAMNs.
- If the appendiceal wall is fibrotic and attenuated, the periappendiceal fat may be obliterated. In such cases, the lesion should be designated pTis (LAMN) unless there is histological evidence of spread of mucin and/or cells beyond the appendiceal muscularis propria, leading to a classification of pT3 or pT4a.
- There is limited information about the behaviour of HAMN. It is likely that HAMNs confined to the appendix have a good prognosis, but we recommend using the same

terminology as appendiceal adenocarcinoma, which follows the guidelines of the American Joint Committee on Cancer (AJCC).[2] (HAMN is not specifically mentioned in the Union for International Cancer Control [UICC] TNM classification).

- Either cellular or acellular mucin in the periappendiceal adipose tissue is classified pT3.
- If neoplastic cells are found beyond the serosa, this confers a worse prognosis than if only acellular mucin is found.[8,9,19,35] Therefore, the presence or absence of extra-appendiceal neoplastic cells is an important part of the surgical pathology report, recorded in addition to the T classification as a core item. However, it does not affect the T classification, which is pT4a in either case.
- Perforation of an inflamed appendix through a mucinous neoplasm is classified pT4a if the tumour is continuous with the serosal surface through the inflammation.[2]
- Involvement of the serosa by acellular mucin needs to be distinguished from postoperative artefactual displacement of mucin from the lumen to the serosa during specimen handling. Evidence of true extra-appendiceal spread includes dissection of tissue planes, neovascularisation, organisation of mucin by granulation tissue and mesothelial hyperplasia.[22] Occasionally, the distinction can be impossible based on histology, so a statement to this effect in the report may be required.
- pT4b implies direct invasion of an adjacent structure through the serosal surface of the appendix, e.g. an adherent loop of bowel or the abdominal wall. It does not include spread into the adjacent caecum via the lumen or within the wall.
- On rare occasions, pseudomyxoma peritonei may be found when the appendiceal lesion is pTis (LAMN).[37] In these cases it is likely that there has been a previous breach of the serosa, and it is appropriate to classify the primary as pTis (LAMN) but with a comment in the report that there may have been a previous perforation, now sealed.

Regarding the pN classification, it is important to note certain features.

- The regional lymph nodes are the ileocolic chain; a definitive pN classification requires examination of these nodes, typically from a right hemicolectomy.
- Non-regional nodes may be present, especially in cytoreduction specimens, and involvement of such nodes is classified pM1c (because the pN classification is for

regional nodes only). Note that left colonic nodes are non-regional in this context. Non-regional nodes can be listed in the comments section, if required.

- The pN classification of appendiceal carcinoma in TNM8 differs from that for colorectal carcinoma in that pN2 is not subdivided into pN2a and pN2b.[6]
- Apical node involvement has not been specifically addressed as a prognostic factor in the appendix, but its status may be of interest to clinicians, so we recommend including it as a non-core item.
- Although tumour deposits (satellites) are known to be significant in the prognosis of colorectal carcinoma, their significance in appendiceal neoplasia has not been addressed. Nevertheless, we recommend reporting them because they are included in the TNM classification of appendiceal tumours.[6] They are discrete macroscopic or microscopic nodules of cancer in the extramural adipose tissue within the lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures. If there are no nodal metastases, their presence leads to a classification of pN1c. More details on the reporting of tumour deposits can be found in the *Dataset for histopathological reporting of colorectal cancer*.[12]
- Occasionally, a node may contain acellular mucin without any evidence of accompanying neoplastic cells. In these circumstances, we recommend following the guidance for colorectal adenocarcinoma.[12] If there has been no prior chemo/radiotherapy, acellular mucin in a node is considered positive for metastasis and classified pN1 or pN2 as appropriate. However, if the patient has had preoperative therapy, acellular mucin is ignored for staging purposes and is only relevant for assessment of regression. (Note that acellular mucin contributes to the T and M classifications regardless of any neoadjuvant treatment.)

The pM categories for the appendix and colorectum have different definitions.

- pM1a is used for mucinous appendiceal tumours with acellular intraperitoneal mucin. This diagnosis should only be rendered after adequate histological sampling.
- pM1b is used if neoplastic cells are identified in the intraperitoneal mucin.
- Involvement of the ovarian parenchyma, the greater omentum and the serosal surfaces of abdominal viscera is typical of pseudomyxoma peritonei. It is classified

pM1b (or pM1a if all the mucin is acellular), regardless of any invasion of underlying tissue.

- pM1c is reserved for cases in which the implication is haematogenous or distant lymphatic spread by adenocarcinoma, e.g. intraparenchymal liver metastasis or pleuropulmonary involvement.

Mucin and/or cells on the serosa of the appendix or mesoappendix are not included in the pM classification; these are designated pT4a.

The staging subclassification for tumours that are pM1a and pM1b depends on histology.[6] Stage IVA is used for acellular mucin or G1 mucinous tumours. Stage IVB is used for non-mucinous tumours and G2 or G3 mucinous tumours. For staging purposes, the higher grade is used if there is a discordance between the appendix and peritoneal disease.

[Level of evidence B – Stage and cellularity of extra-appendiceal mucin are correlated with prognosis and overall survival.]

5.4 Vascular and perineural invasion

Vascular and perineural involvement are well established as prognostic factors in colorectal carcinoma. Although evidence for their relevance in appendiceal carcinoma is scanty, they have been shown to be prognostically significant by univariate analysis in patients with disseminated (stage IV) disease.[23] They are not features of LAMN or HAMN.

Based on the limited evidence available, it seems appropriate to include angiolymphatic and perineural invasion as core items for adenocarcinoma. Unlike colorectal neoplasia, there is no evidence that subclassifying by deepest level is significant and so their presence, at any position inside or outside the appendiceal wall, should be recorded as positive. The criteria for diagnosis are the same as for colorectal adenocarcinoma.[12]

[Level of evidence – D.]

5.5 Margins

Tumours that do not reach an excision margin are classified as R0, those with microscopic (but not macroscopic) margin involvement are classified as R1 and those with macroscopic margin involvement as R2.[6] The significance of margin status in appendiceal neoplasia has not been extensively studied, but there is evidence that positive margins are associated with worse prognosis.[38]

[Level of evidence – D.]

If the base of the appendix is processed longitudinally (Figure 1), the distance from the proximal margin can be measured. It is not uncommon for the mucosa at the margin to be normal but for mucin and/or epithelial cells in the wall or on the serosa to be present. The proforma allows both possibilities to be recorded; either should lead to a designation of R1 resection. Likewise, either mucin or cells at a circumferential margin represent R1. The exception is patients who have received neoadjuvant chemotherapy – acellular mucin is discounted and is only relevant for assessment of regression.

For consistency with the dataset for colorectal cancer, R status applies not only to the primary neoplasm but also to distant metastases.[12] However, we do not recommend that an R status is applied to biopsies.

Also consistent with the colorectal cancer dataset, while assessment of involvement of longitudinal margins is made according to the professional judgement of the pathologist, a circumferential margin should be considered involved (R1) if the distance from the tumour is $\leq$1 mm, whether by direct continuity with the main tumour, tumour in vessels or around nerves, nodal metastases or tumour deposits. If a lesion is classified R1 or R2, an explanation should be provided in the comments section.

5.6 Pseudomyxoma peritonei

Pseudomyxoma peritonei is the accumulation of mucin within the abdominopelvic cavity due to the growth of a mucinous neoplasm.[4,14] It is usually of appendiceal origin (LAMN, HAMN or mucinous adenocarcinoma), although on rare occasions it can arise from other sites such as the urachus, pancreas or biliary tract, or from mucinous tumours arising in ovarian teratomas and retrorectal cystic hamartomas.[39–43]

Pseudomyxoma peritonei is characterised by the redistribution phenomenon, in which the disease spreads around the peritoneal cavity, following the flow of peritoneal fluid and accumulating at sites of reabsorption such as the omentum, paracolic gutters, pelvic peritoneum and subphrenic space.[14] It should be distinguished from implants of mucinous adenocarcinoma on peritoneal surfaces arising from other types of tumour, e.g. mucinous adenocarcinomas of the colorectum or ovary. The term ‘pseudomyxoma peritonei’ is not used for disease confined to the appendix and mesoappendix; it generally implies spread beyond the right lower quadrant of the abdomen.

5.6.1 Grading pseudomyxoma peritonei

The diagnostic classification of pseudomyxoma peritonei is summarised in Table 4.[17] Low grade (G1) is characterised by minimal cytological atypia, low cellularity and rare mitotic figures. We recommend these lesions are designated ‘low-grade mucinous carcinoma peritonei’ or ‘low-grade pseudomyxoma peritonei’ and do not recommend other terms such as ‘disseminated peritoneal adenomucinosis’ and ‘LAMN with peritoneal involvement’.[14]

Increased atypia and mitotic activity (as defined for HAMN in section 5.1) lead to a diagnosis of high grade (G2), even in the absence of cribriform structures. These lesions tend to be more cellular than low-grade ones. G2 pseudomyxoma peritonei commonly arises from HAMN or mucinous adenocarcinoma.

Signet ring cells lead to a classification of G3. Since the significance of small numbers of signet ring cells is unclear, and considering also that there is considerable interobserver variability in identifying signet ring cells when they are scanty, we recommend that at least 10% of cells should show signet ring morphology for a classification of G3.[24] Degenerating ‘pseudo-signets’ in mucin pools should be distinguished from true signet ring cells. Rarely, the designation G3 may also be appropriate if there are diffuse sheets of neoplastic cells.[22]

Pseudomyxoma peritonei and the primary tumour are graded separately, based on evidence that it is the grade of the peritoneal disease that is more closely associated with prognosis.[14] In most cases, the grade of the primary tumour and the peritoneal disease will be the same, but occasionally they are different (‘discordant histology’).[17] It is also possible for grade progression to occur over time.

[Level of evidence B – Grade is correlated with prognosis and overall survival.]

5.6.2 Immunohistochemistry

Although they are not 100% definitive, immunostains can be helpful in distinguishing primary ovarian mucinous neoplasia from appendiceal or colorectal metastasis if there is doubt. In particular, SATB expression is very common in appendiceal neoplasia but rare in ovarian mucinous neoplasia.[44–46] A panel of SATB, CK7, CK20, CDX2 and PAX8 could be expected to distinguish appendiceal from ovarian primary mucinous neoplasia with good sensitivity and specificity, provided there is no evidence of ovarian teratoma. Immunostaining would only be indicated if there was uncertainty about the likely primary site and is not required routinely.

5.6.3 Acellular mucin

Acellular mucin can accumulate in the peritoneal cavity as the result of ruptured mucinous neoplasms from a variety of sites. Cystadenomas of the ovary are a common source, and some LAMNs extrude large quantities of mucin but the cells do not grow outside the appendix. The term ‘pseudomyxoma peritonei’ should generally be avoided if only acellular mucin is found within the peritoneal cavity. If an LAMN is associated with acellular peritoneal mucin, the risk of disease progression is low.[47]

[Level of evidence B – Cellularity of peritoneal mucin is correlated with prognosis and overall survival.]

Table 4: Diagnostic classification of pseudomyxoma peritonei with corresponding WHO grades.[2,18]

Tumour type	Typical histological features	Grade
Acellular mucin	• Acellular mucin in the peritoneal cavity without identifiable mucinous epithelial cells	Not graded
Low-grade mucinous carcinoma peritonei	• Strips of mucinous epithelium showing little atypia • Abundant extracellular mucin	G1
High-grade mucinous carcinoma peritonei	• High-grade cytological features (marked nuclear pleomorphism, high nuclear/cytoplasmic ratio, loss of nuclear polarity with full-thickness pseudostratification of nuclei, prominent micropapillary structures, frequent or atypical mitoses) involving >10% of the tumour • Infiltrative-type invasion characterised by angulated glands in a desmoplastic stroma, complex glandular growth, or numerous infiltrating mucin pools containing clusters of tumour cells	G2*
High-grade mucinous carcinoma peritonei with signet ring cells	• Mucinous tumour deposits with signet ring cells (at least 10% of neoplastic cells should show signet ring morphology)	G3

*If there are sheets of poorly differentiated cells, G3 may be appropriate.

5.7 Response to neoadjuvant therapy

Evaluating tumour regression is part of the histopathological assessment in patients who have received preoperative neoadjuvant therapy. However, such treatment will be encountered rarely in cases of appendiceal neoplasia outside specialist centres. Therefore, we have not included tumour regression scoring in the proforma. If necessary, it can be recorded in the comments section using the scheme recommended in the RCPath *Dataset for histopathological reporting of colorectal cancer*.[12]

6 Additional investigations

Testing of tumour tissue at the time of diagnosis for mismatch repair (MMR) status is now routine for colorectal carcinoma, either by immunohistochemistry for MMR proteins or by genetic microsatellite instability analysis. MMR deficiency is rare in mucinous appendiceal neoplasms, especially LAMNs, and its significance as a prognostic or predictive factor is less clear than in colorectal primaries.[34,48] We have not included MMR status as a core item. Nevertheless, we support testing for MMR, especially in adenocarcinomas and high-grade mucinous carcinoma peritonei, and it is included as a non-core item.

If loss of MLH1 immunoexpression is found, the tumour should be tested for *BRAF* V600E mutation and/or MLH1 promoter hypermethylation to distinguish sporadic cases from Lynch syndrome.

Likewise, mutations in *KRAS* and *NRAS* are predictive factors in colorectal adenocarcinoma, and the status of these genes may be of interest to clinicians, especially in cases of appendiceal adenocarcinoma or high-grade mucinous carcinoma peritonei. However, evidence for their relevance in appendiceal adenocarcinoma is scanty, so they are also included as non-core items.

Appendix C provides a proforma for recording the results of MMR, microsatellite instability (MSI), *BRAF*, *KRAS* and *NRAS* testing. The proforma is derived from the RCPath *Dataset for histopathological reporting of colorectal cancer* and its use is recommended to promote consistency in reporting.[12] As non-core items, they should be performed as clinically indicated or according to local protocols.

[Level of evidence – D.]

7 Core data items

7.1 Clinical

For specimens containing an appendix with a suspected neoplasm, the clinical information should include:

- the nature of the operation
- organ(s) submitted
- operative findings
- any preoperative therapy – its nature and when it ended.

If a previous appendicectomy has been performed, this information should be provided in addition:

- the fact of previous appendicectomy, preferably with the date
- the pathological diagnosis.

7.2 Macroscopic

For all specimens (appendicectomies and right hemicolectomies):

- nature of specimen
- length and maximum external diameter of appendix
- appearance of tumour
  - distended mucin-filled appendix
  - nodule
  - diffuse thickening of wall
  - other
- maximum diameter of tumour
- tumour perforation
- mucin on serosal surfaces
- any other pathological abnormalities.

For appendicectomies:

- whether any caecal wall is included
- distance of tumour from proximal and mesoappendiceal margins:
  - >30 mm; specify which margin and state macroscopic clearance
  - <30 mm; specify which margin and take 1 or more blocks to assess distance from tumour histologically.

For right hemicolectomies:

- length of specimen
- distance of tumour from longitudinal ends and non-peritonealised circumferential margin:
  - >30 mm (specify which margin and state macroscopic clearance)
  - <30 mm (specify which margin and take 1 or more blocks to assess distance from tumour).

Note that additional blocks to process the entire appendix should be taken if a serrated polyp, colorectal-type adenoma, LAMN, HAMN or adenocarcinoma is found.

7.3 Microscopic

Type of tumour

- LAMN.
- HAMN.
- Mucinous adenocarcinoma.
- Mucinous adenocarcinoma with signet ring cells.
- Non-mucinous adenocarcinoma.
- GCA.
- Other (specify).

Grade

For mucinous tumours:

- G1: LAMN
- G2: HAMN and most mucinous adenocarcinomas without signet ring cells

- G3: mucinous adenocarcinomas with signet ring cells (or, rarely, sheets of poorly differentiated cells).

For non-mucinous adenocarcinomas:

- low grade (G1/2)
- high grade (G3).

For GCAs (Table 2):

- G1 (>75% low grade pattern)
- G2 (50–75% low grade pattern)
- G3 (<50% low grade pattern).

Other findings

- Perforation at the site of tumour.
- Perforation away from tumour.
- Other (specify).

Local spread

- Furthest extent of tumour (either neoplastic cells or acellular mucin):
  - confined to mucosa (pTis)
  - submucosa (pTis (LAMN) or pT1)
  - muscularis propria (pTis (LAMN) or pT2)
  - subserosal fat/mesoappendix (pT3)
  - involves or beyond serosa (pT4a)
  - directly invades adjacent structures (pT4b)
  - not applicable/cannot be assessed.
- Neoplastic epithelial cells involve or lie beyond serosa (yes/no).

Angiolymphatic and perineural invasion (adenocarcinomas and GCAs only)

- Venous invasion.
- Lymphatic invasion.
- Perineural invasion.

Margins – appendicectomies

- Proximal appendiceal margin:
  - clear (distance: _____mm or cannot be accurately measured)
  - mucosal neoplasm present at margin
  - mural/extra-appendiceal epithelium or mucin present at margin
  - not assessable.
- Mesoappendiceal margin:
  - clear (distance: _____mm or cannot be accurately measured)
  - neoplastic epithelium or mucin present at margin
  - not assessable.
- Other margin (describe).

Margins – right hemicolectomies

- Longitudinal margins:
  - not submitted by pathologist
  - clear (distance: _____mm or cannot be accurately measured)
  - mucosal neoplasm present at margin
  - mural/extra-appendiceal epithelium or mucin present at margin
  - not assessable.
- Non-peritonealised circumferential margin:
  - not submitted by pathologist
  - clear (distance: _____mm or cannot be accurately measured)
  - neoplastic epithelium or mucin present at margin
  - not assessable.
- Other margin (describe).

Lymph nodes

- Number of nodes (regional and non-regional).
- Number of nodes containing tumour (regional and non-regional).

- Tumour deposits (satellites).

Peritoneal metastases

If peritoneal metastases are present, state the organs involved.

- If peritoneal disease is pseudomyxoma peritonei, classify as:
  - acellular mucin
  - low-grade mucinous carcinoma peritonei
  - high-grade mucinous carcinoma peritonei
  - high-grade mucinous carcinoma peritonei with signet ring cells.

Histologically confirmed distant metastases

These include metastases not derived from peritoneal spread. If present, state site(s).

Other abnormalities

These should be specified as appropriate.

Additional tumours present

For example, neuroendocrine neoplasms or synchronous colorectal carcinomas. If they are present, a separate proforma should be used.

8 Non-core data items

8.1 Macroscopic

- Width of mesoappendix.
- Any gross involvement of surgical margins.

8.2 Microscopic

- Status of apical lymph node (positive/negative for neoplasia).

8.3 Additional investigations

- MMR status, by either:
  - MMR protein immunohistochemistry
  - MSI status.

- *KRAS*, *NRAS* and *BRAF* status.

9 Diagnostic coding and staging

Staging should be according to the 8th edition of the UICC *TNM Classification of Malignant Tumours*.[6] It does not specifically mention HAMN, so to be consistent with the AJCC Cancer Staging Manual we recommend staging HAMN as adenocarcinoma.[2]

Appendiceal neoplasms should be coded according to the SNOMED system, applying appropriate T and M codes as a minimum. SNOMED ceased to be licensed by the International Health Terminology Standards Development Organisation from 26 April 2017, and there is now a practical transition phase as part of the intended full implementation of SNOMED CT by the NHS and Public Health England (PHE). A list of applicable T and M SNOMED and SNOMED CT codes is provided in **Appendix A**.

10 Reporting of small biopsy specimens

In the setting of appendiceal mucinous neoplasia, the most likely indication for a small biopsy is peritoneal spread, including the syndrome of pseudomyxoma peritonei. The usual reason is to exclude other neoplasms and non-neoplastic processes that could mimic appendiceal neoplasia.

A small biopsy from the peritoneum or omentum containing abundant extracellular mucin with strips of columnar epithelium supports the diagnosis of pseudomyxoma peritonei. However, definitive grading is not usually possible with biopsy material.

If a biopsy shows only acellular mucin (i.e. mucin without neoplastic epithelial cells), this finding is consistent with pseudomyxoma peritonei if the overall clinical picture is characteristic. However, intra-abdominal acellular mucin may be found in other conditions, so a pathological diagnosis of ‘acellular mucin’ along with a comment as to its likely significance is usually most appropriate.

Occasionally, an endoscopic caecal biopsy from the appendiceal orifice may reveal evidence of a serrated lesion or mucinous tumour, so the possibility of an appendiceal lesion should be considered.

11 Reporting of frozen sections

Intraoperative frozen sections are not generally part of the surgical management of appendiceal carcinoma. Occasionally, a surgeon embarking on an appendicectomy may submit an enlarged lymph node to exclude metastasis and thus avoid a right hemicolectomy. In complex resections, surgical margins may occasionally be sent for frozen section.

12 Criteria for audit

The following are recommended by the RCPath as key assurance and key performance indicators:[49,50]

- using a template or proforma, including items listed in the English COSD that are, by definition, core data items, cancer resections must be reported in RCPath cancer datasets. English trusts were required to implement the structured recording of core pathology data in the COSD by January 2016 and to update their systems in line with subsequent COSD updates
  - standard: 95% of reports must contain structured data.
- histopathology cases must be reported, confirmed and authorised within 7 to 10 calendar days of the procedure
  - standard: 80% of cases must be reported within 7 calendar days and 90% within 10 calendar day

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Appendix A SNOMED coding

SNOMED topography should be recorded for the site of the tumour. SNOMED morphology codes should be recorded for the diagnosis/tumour morphology.

Versions of SNOMED prior to SNOMED CT will cease to be licensed by the International Health Terminology Standards Development Organisation from 26 April 2017. It is recognised that versions of SNOMED 2, SNOMED 3/RT and SNOMED CT are in use in the UK. These are therefore currently considered acceptable.

SNOMED Procedure codes (P codes in SNOMED 2/3/RT) should be recorded for the procedure. P codes vary according to the SNOMED system in use in different organisations, therefore local P codes should be recorded and used for audit purposes.

Topography

Tumour site	SNOMED 2/3 code	SNOMED-CT terminology	SNOMED-CT code
Appendix	T-66000/T-59200	Entire appendix (body structure)	181255000
Peritoneum	T-Y4400/T-D4400	Entire peritoneum (serous membrane) (body structure)	362698002
Omentum	T-63850/T-D4600	Entire omentum (body structure)	362710002

Morphology

Morphological codes	SNOMED 2/3/ ICD-O code	SNOMED-CT terminology	SNOMED-CT code
LAMN	M-84700	Mucinous cystadenoma (morphologic abnormality)	67182003
HAMN	M-84702	Mucinous cystadenocarcinoma, non-invasive (morphologic abnormality)	128900005
Adenoma	M-81400	Adenoma, no subtype (morphologic abnormality)	32048006
Dysplasia	M-74000	Dysplasia (morphologic abnormality)	25723000
Dysplasia, high grade	M-74003	Severe dysplasia (morphologic abnormality)	28558000
Adenocarcinoma	M-81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007

Mucinous adenocarcinoma	M-84803	Mucinous adenocarcinoma (morphologic abnormality)	72495009
Signet ring cell adenocarcinoma	M-84903	Signet ring cell adenocarcinoma (morphologic abnormality)	87737001
Pseudomyxoma peritonei	M-84806	Pseudomyxoma peritonei (morphologic abnormality)	112679004
Goblet cell adenocarcinoma (previously goblet cell carcinoid tumour)	M-82433	Goblet cell adenocarcinoma (previously goblet cell carcinoid tumour) (morphologic abnormality)	31396002
Pseudomyxoma peritonei	M-84806	Pseudomyxoma peritonei (morphologic abnormality)	112679004

Procedure

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

Appendix B Reporting proforma for appendiceal mucinous neoplasms and adenocarcinoma

Surname: …….. Forenames: …… Date of birth: …… Sex: ……
Hospital: …… Hospital No: …… NHS No: ……..
Date of surgery: …….. Date of report authorisation: …… Report No: ……..
Date of receipt: ……... Pathologist: ……... Clinician: ……..

Specimen type:
Appendicectomy ☐
Right hemicolectomy ☐
Other ☐
If other, state: ……

Other organs: Yes ☐ No ☐
If yes, list: ……..…….

Macroscopic:
For all specimens:
Length of appendix: ……mm
Maximum external diameter of appendix: …… mm
Appearance of appendix: Normal ☐
Distended mucin-filled ☐
Diffuse thickening of wall ☐
Tumour nodule ☐
Other ☐
If other, state: ……
Maximum diameter of tumour: ……mm or cannot be accurately measured ☐
Perforation: Yes ☐ No ☐
If yes, is perforation through macroscopically visible tumour? Yes ☐
No ☐
Not applicable ☐
Mucin visible on serosa: Yes ☐ No ☐

Any other pathological abnormalities (state): ……..……..……..

For appendicectomies:
Caecal wall included: Yes ☐ No ☐
Distance of tumour from proximal and mesoappendiceal margins:
If ≥30 mm, specify which margin(s) and macroscopic clearance
…… (…….mm)*
If <30 mm, specify which margin(s)† ……

For colectomies:
Length of specimen: …….mm

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*If a margin is macroscopically ≥30 mm from tumour, it is sufficient simply to provide this measurement.
†If a margin is macroscopically <30 mm from tumour, take block(s) to allow microscopic measurement of distance.

Distance of tumour from longitudinal ends and non-peritonealised circumferential margin(s):

If ≥30 mm, specify which margin(s) and macroscopic clearance …… (…….mm)*

If <30 mm, specify which margin(s)† …….

Type of tumour:

Low-grade appendiceal mucinous neoplasm (LAMN) □
High-grade appendiceal mucinous neoplasm (HAMN) □
Mucinous adenocarcinoma □
Mucinous adenocarcinoma with signet ring cells‡ □
Non-mucinous adenocarcinoma □
Goblet cell adenocarcinoma (GCA) □
Other □

If other, specify: ……..…….……

Grade:

For mucinous tumours (Table 1):

G1: LAMN □
G2: HAMN and most mucinous adenocarcinomas without signet ring cells □
G3: mucinous adenocarcinomas with signet ring cells† (or, rarely, sheets of poorly differentiated cells) □

For non-mucinous adenocarcinomas:

Low grade (G1/2) □
High grade (G3) □

For goblet cell adenocarcinomas (Table 2):

G1 (>75% low-grade pattern) □
G2 (50–75% low-grade pattern) □
G3 (<50% low-grade pattern) □

Other findings:

Perforation at the site of tumour: Yes □ No □
Perforation away from tumour: Yes □ No □
Any other findings (specify): ……..…….

Local spread:

Furthest extent of tumour (either neoplastic cells or acellular mucin):

Confined to mucosa (pTis) □
Submucosa (pTis(LAMN) or pT1) □
Muscularis propria (pTis(LAMN) or pT2) □
Subserosal fat/mesoappendix (pT3) □
Involves or beyond serosa (pT4a) □
Directly invades adjacent structures (pT4b) □

‡Signet ring cells should be reported if they comprise at least 10% of the neoplastic cells.

Not applicable/cannot be assessed □

Neoplastic epithelial cells involve or lie beyond serosa: Yes □ No □

Angiolymphatic and perineural invasion (adenocarcinomas and GCAs only):
Venous invasion: Yes □ No □
Lymphatic invasion: Yes □ No □
Perineural invasion: Yes □ No □

Margins – appendicectomies:
Proximal appendiceal margin:
- Clear (distance ……mm or cannot be accurately measured) □
- Mucosal neoplasm present at margin □
- Mural/extra-appendiceal epithelium or mucin present at margin □
- Not assessable □

Mesoappendiceal margin:
- Clear (distance ……mm or cannot be accurately measured) □
- Neoplastic epithelium or mucin present at margin □
- Not assessable □

Other margin (describe):
……..……..…….

Margins – right hemicolectomies:
Longitudinal margins:
- Not submitted by pathologist □
- Clear (distance ……mm or cannot be accurately measured) □
- Mucosal neoplasm present at margin □
- Mural/extra-appendiceal epithelium or mucin present at margin □
- Not assessable □

Non-peritonealised circumferential margin:
- Not submitted by pathologist □
- Clear (distance ……mm or cannot be accurately measured) □
- Neoplastic epithelium or mucin present at margin □
- Not assessable □

Other margin (describe):
……..

Lymph nodes:
Number of regional nodes (mesoappendiceal and ileocolic): ……
Number of non-regional nodes: ……
Total number of nodes: ……

Number of regional nodes containing tumour: ……
Number of non-regional nodes containing tumour: …… or not applicable if no non-regional nodes
Total number of nodes containing tumour: …… or not applicable if no nodes present

Tumour deposits (satellites): Yes □ No □ Not applicable □

If yes, number (1, 2, 3, 4, 5 or >5) …….

Peritoneal metastases (includes involvement of ovaries): Yes □ No □

If yes:

State organs involved: …….

Is peritoneal disease pseudomyxoma peritonei? Yes □ No □

If yes, classification of pseudomyxoma peritonei is:

Acellular mucin □

Low-grade mucinous carcinoma peritonei (G1) □

High-grade mucinous carcinoma peritonei (G2)¶ □

High-grade mucinous carcinoma peritonei with signet ring cells (G3)‡ □

Histologically confirmed distant metastases, i.e. metastases not derived from peritoneal spread : Yes □ No □

If yes, site(s): …….

Other abnormalities: Yes □ No □

If yes, specify: …….

Additional tumours present: Yes □ No □

If yes, specify and use separate proforma: …….

Overall grade (higher of local and peritoneal disease if discordant in pseudomyxoma peritonei):

G1 □

G2 □

G3 □

Cannot be assessed or not applicable □

Complete resection at all surgical margins (R0): Yes □ No □

pTNM classification: pT …… pN …… pM* ……

*pM should either be pM1 or entered as not applicable (N/A)

TNM edition number used: ……

Comments: ……..

SNOMED codes: …….

¶ Rarely, high grade mucinous carcinoma peritonei can be G3 if there are sheets of poorly differentiated cells without signet ring morphology.

‡ Signet ring cells should be reported if they comprise at least 10% of the neoplastic cells.

Appendix C Reporting proforma for further investigations for appendiceal mucinous neoplasms and adenocarcinoma

Surname: …… Forenames: …….. Date of Birth: …… Sex:……..
Hospital ……... Hospital No: …… NHS No:…….
Date of Surgery: ……..… Date of Report Authorisation: …… Report No: ……..
Date of Receipt :…….. Pathologist: ……..…… Clinician ……..

Additional investigations:

Mismatch repair (MMR) protein immunohistochemistry

	Yes	No	Equivocal	Test failed	Not performed
MLH1 nuclear expression intact	☐	☐	☐	☐	☐
PMS2 nuclear expression intact	☐	☐	☐	☐	☐
MSH2 nuclear expression intact	☐	☐	☐	☐	☐
MSH6 nuclear expression intact	☐	☐	☐	☐	☐

Microsatellite instability (MSI) testing

MSI-high ☐ MSI-low ☐ MS-stable ☐ Test failed ☐ Not performed ☐

MLH1 promoter hypermethylation testing

Present ☐ Absent ☐ Test failed ☐ Not performed ☐

***BRAF* V600E mutation testing**

Present ☐ Absent ☐ Test failed ☐ Not performed ☐

***KRAS* mutation testing**

Present ☐ Absent ☐ Test failed ☐ Not performed ☐
Specify mutation……..

***NRAS* mutation testing**

Present ☐ Absent ☐ Test failed ☐ Not performed ☐
Specify mutation……..

Appendix D Reporting proforma for appendiceal mucinous neoplasms and adenocarcinoma in list format

Element name	Values	Implementation notes	COSD v8	COSD v9
Specimen type	Single selection value list: • Appendicectomy • Right hemicolectomy • Other	If 'other', please state.		
Other organs	Single selection value list: • Yes • No	If 'yes', please list.		
Length of appendix	Length in mm			
Maximum external diameter of appendix	Diameter in mm			
Appearance of appendix	Single selection value list: • Normal • Distended mucin-filled • Diffuse thickening of wall • Tumour nodule • Other	If 'other', please state.		
Maximum diameter of tumour	Diameter in mm	Please state if cannot be accurately measured	CR0830	pCR0830
Perforation	Single selection value list: • Yes • No			
Perforation is through macroscopically visible tumour	Single selection value list: • Yes • No • Not applicable			

Mucin visible on serosa	Single selection value list: • Yes • No			
Any other pathological abnormalities	Free text			
For appendicectomies: Caecal wall included	Single selection value list: • Yes • No			
For appendicectomies: Distance of tumour from proximal and mesoappendiceal margins	Single selection value list: • If ≥30 mm, specify which margin(s) and macroscopic clearance • If <30 mm, specify which margin(s)	If a margin is macroscopically ≥30 mm from tumour, it is sufficient simply to provide this measurement. If a margin is macroscopically <30 mm from tumour, take block(s) to allow microscopic measurement of distance.		
For colectomies: Length of specimen	Length in mm			
Distance of tumour from longitudinal ends and non-peritonealised circumferential margin(s)	Single selection value list: • If ≥30 mm, specify which margin(s) and macroscopic clearance • If <30 mm, specify which margin(s)	If a margin is macroscopically ≥30 mm from tumour, it is sufficient simply to provide this measurement. If a margin is macroscopically <30 mm from tumour, take block(s) to allow microscopic measurement of distance.		

Type of tumour	Single selection value list: • Low-grade appendiceal mucinous neoplasm (LAMN) • High-grade appendiceal mucinous neoplasm (HAMN) • Mucinous adenocarcinoma • Mucinous adenocarcinoma with signet ring cells • Non-mucinous adenocarcinoma • Goblet cell adenocarcinoma (GCA) • Other	If 'other', please specify.		
Grade for mucinous tumours	Single selection value list: • G1: LAMN • G2: HAMN and most mucinous adenocarcinomas without signet ring cells • G3: mucinous adenocarcinomas with signet ring cells (or, rarely, sheets of poorly differentiated cells)	Signet ring cells should be reported if they comprise at least 10% of the neoplastic cells.		
Grade for non-mucinous adenocarcinomas	Single selection value list: • Low grade (G1/2) • High grade (G3)			
Grade for goblet cell adenocarcinomas	Single selection value list: • G1 (>75% low-grade pattern) • G2 (50–75% low-grade pattern) • G3 (<50% low grade pattern)			
Perforation at the site of tumour	Single selection value list: • Yes			

	• No			
Perforation away from tumour	Single selection value list: • Yes • No			
Any other findings	Free text			
Local spread: furthest extent of tumour (either neoplastic cells or acellular mucin)	Single selection value list: • Confined to mucosa (pTis) • Submucosa (pTis(LAMN) or pT1) • Muscularis propria (pTis(LAMN) or pT2) • Subserosal fat/mesoappendix (pT3) • Involves or beyond serosa (pT4a) • Directly invades adjacent structures (pT4b) • Not applicable/cannot be assessed			
Neoplastic epithelial cells involve or lie beyond serosa	Single selection value list: • Yes • No			
Angiolymphatic and perineural invasion: venous invasion	Single selection value list: • Yes • No	Only applicable for adenocarcinomas and GCAs.	CR0870 Select worst based on following priority – YU, NU Yes = YU No = NU	pCR0870 Select worst based on following priority – YU, NU Yes = YU No = NU

Angiolymphatic and perineural invasion: Lymphatic invasion	Single selection value list: • Yes • No	Only applicable for adenocarcinomas and GCAs.		
Angiolymphatic and perineural invasion: Perineural invasion	Single selection value list: • Yes • No	Only applicable for adenocarcinomas and GCAs.		
Proximal appendiceal margin	Single selection value list: • Clear • Mucosal neoplasm present at margin • Mural/extra-appendiceal epithelium or mucin present at margin • Not assessable	Only applicable for appendicectomies. If 'clear', please state distance in mm if possible.		
Mesoappendiceal margin	Single selection value list: • Clear • Neoplastic epithelium or mucin present at margin • Not assessable	Only applicable for appendicectomies. If 'clear', please state distance in mm if possible.		
Appendicectomies other margin (describe)	Free text	Only applicable for other margin.		
Right hemicolectomies longitudinal margins	Single selection value list: • Not submitted by pathologist • Clear • Mucosal neoplasm present at margin • Mural/extra-appendiceal epithelium or mucin present at margin • Not assessable	Only applicable for right hemicolectomies. If 'clear', please state distance in mm if possible.		
Right hemicolectomies nonperitonealised circumferential margin	Single selection value list: • Not submitted by pathologist • Clear • Neoplastic epithelium or mucin present at margin	Only applicable for right hemicolectomies. If 'clear', please state distance in mm if possible.		

	• Not assessable			
Right hemicolectomies other margin (describe)	Free text	Only applicable for other margin.		
Number of regional lymph nodes (mesoappendiceal and ileocolic)	Integer			
Number of non-regional nodes	Integer			
Total number of nodes	Integer		CR0890	pCR0890
Number of regional nodes containing tumour	Integer			
Number of non-regional nodes containing tumour	Integer	Not applicable if no non-regional nodes.		
Total number of nodes containing tumour	Integer	Not applicable if no nodes present.	CR0900	pCR0900
Tumour deposits (satellites)	Single selection value list: • Yes • No • Not applicable			
Tumour deposits (satellites) number	Single selection value list: • 1 • 2 • 3 • 4 • 5 • >5	Only applicable if 'Tumour deposits (satellites), yes' is selected.		
Peritoneal metastases	Single selection value list: • Yes • No	Includes involvement of ovaries. If 'yes', please state organs involved.		
Is peritoneal disease	Single selection value list: • Yes			

pseudomyxoma peritonei?	• No			
Classification of pseudomyxoma peritonei	Single selection value list: • Acellular mucin • Low-grade mucinous carcinoma peritonei (G1) • High-grade mucinous carcinoma peritonei (usually G2; rarely, G3 if there are sheets of poorly differentiated cells) • High-grade mucinous carcinoma peritonei with signet right cells (G3)	Only applicable if 'Is peritoneal disease pseudomyxoma peritonei?, yes' is selected. Signet ring cells should be reported if they comprise at least 10% of the neoplastic cells.		
Histologically confirmed distant metastases, i.e. metastases not derived from peritoneal spread	Single selection value list: • Yes • No	If 'yes', please state the site(s).		
Other abnormalities	Single selection value list: • Yes • No	If 'yes', please state.		
Additional tumours present	Single selection value list: • Yes • No	If 'yes', please specify and use separate proforma.		
Overall grade (higher of local and peritoneal disease if discordant in pseudomyxoma peritonei)	Single selection value list: • G1 • G2 • G3 • Cannot be assessed or not applicable		CR0860 G1 = G1 G2 = G2 G3 = G3 Cannot be assessed or not applicable = GX	pCR0860 G1 = G1 G2 = G2 G3 = G3 Cannot be assessed or not applicable = GX

Complete resection at all surgical margins (R0)	Single selection value list: • Yes • No		CR0880 Yes = 01 No = 05	pCR0880 Yes = 01 No = 05
SNOMED topography code	May have multiple codes – look up from SNOMED tables		CR6410	pCR6410
SNOMED morphology code	May have multiple codes – look up from SNOMED tables		CR6420	pCR6420
pTNM classification − pT	Free text		CR0910	pCR0910
pTNM classification − pN	Free text		CR0920	pCR0920
pTNM classification − pM	Free text		CR0930	pCR0930
TNM edition	Integer		CR6820	pCR6820
Comments	Free text			

Appendix E Reporting proforma for further investigations for appendiceal mucinous neoplasms and adenocarcinoma in list format

Element name	Values	Implementation notes	COSD v8	COSD v9
MLH1 nuclear expression intact	Single selection value list: • Yes • No • Equivocal • Test failed • Not performed			pCR7020
PMS2 nuclear expression intact	Single selection value list: • Yes • No • Equivocal • Test failed • Not performed			pCR7030
MSH2 nuclear expression intact	Single selection value list: • Yes • No • Equivocal • Test failed • Not performed			pCR7040
MSH6 expression intact	Single selection value list: • Yes • No • Equivocal			pCR7050

	• Test failed • Not performed			
Microsatellite instability (MSI) testing	Single selection value list: • MSI-high • MSI-low • MS-stable • Test failed • Not performed			pCR7060
MLH1 promoter hypermethylation testing	Single selection value list: • Present • Absent • Test failed • Not performed			
BRAF V600E mutation testing	Single selection value list: • Present • Absent • Test failed • Not performed			
KRAS mutation testing	Single selection value list: • Present • Absent • Test failed • Not performed	Specify mutation		
NRAS mutation testing	Single selection value list: • Present • Absent • Test failed	Specify mutation		

	• Not performed			

Appendix F 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 1 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.
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 G AGREE 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 dataset
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	All sections
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	All sections
16 The different options for management of the condition or health issue are clearly presented	All sections
17 Key recommendations are easily identifiable	All sections
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–E

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 interests of guideline development group members have been recorded and addressed	Foreword