Tissue pathways for gastrointestinal and pancreatobiliary pathology

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Comments	This document replaces the 1st edition of *Tissue pathways for gastrointestinal and pancreatobiliary pathology*, 2009. In accordance with the College's pre-publications policy, this document was on the College website for consultation from 2–30 September 2015. Twenty-five items of feedback were received. Please email publishing@rcpath.org to see the responses and comments. **Dr Lorna Williamson** **Director of Publishing and Engagement**

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Foreword

The tissue pathways published by The Royal College of Pathologists (RCPath) are guidelines that enable pathologists to deal with routine surgical specimens in a consistent manner and to a high standard. This ensures that accurate diagnostic and prognostic information is available to clinicians for optimal patient care and ensures 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 carefully considered by the reporting pathologist; 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.

The guidelines themselves constitute the tools for implementation and dissemination of good practice.

The stakeholders consulted for this document were: UK gastrointestinal pathologists (through the Pathology Section committee of the British Society of Gastroenterology) and UK histopathologists (through the consultation process of the RCPath).

This document is the second edition of a College guideline.[1] Statements and advice are supported by published evidence, where possible. Information has been obtained from various sources, including peer reviewed publications, Best Practice documents, expert opinion, and standard textbooks. In order to identify relevant peer reviewed studies, a PubMed search was done using key words. Recommendations and evidence from established clinical and pathological guidelines are also taken into account. The latter include documents produced by The Royal College of Pathologists,[2-6] World Health Organization,[7] European Crohn's and Colitis Organisation,[8] British Society of Gastroenterology (BSG),[9,10] UK Bowel Cancer Screening Programme[11] and other groups.[12,13] Feedback from the consultation process of the College also contributed to the content.

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

To grade available evidence, a modification of the Scottish Intercollegiate Guidelines Network (SIGN) guidance for the development of clinical practice Guidelines was used (see Appendix A). The grade does not necessarily equate to the clinical importance of the advice or recommendation

A formal revision cycle for all tissue pathways takes place on a four-yearly basis. However, each year, the College will ask the authors of the tissue pathways, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the document needs to be updated or revised. A full consultation process will be undertaken if major revisions are required. If minor revisions are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the pathways and the full revised version (incorporating the changes) will replace the existing version on the publications page of the College.

The pathway has been reviewed by the Working Group on Cancer Services and was on the College website for consultation with the membership from 2–30 September 2015. All comments received from the Working Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and Director of Publishing and Engagement.

This pathway was developed without external funding to the writing group. The College requires the authors of tissue pathways to provide a list of potential conflicts of interest; these are monitored by the Director of Clinical Effectiveness and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

1.1 Staffing and workload

The target users of this document are consultant cellular pathologists who report gastrointestinal (GI) and/or pancreatobiliary pathology.

Gastrointestinal histopathology is a major element of most histopathology departments' workload. It may be part of a general rota or may be mostly or exclusively reported by specialists. In either circumstance, there must be enough pathologists to provide cover and to conform to the College guidance on staffing and workload levels and on key performance indicators.[14,15]

Typically, mucosal biopsies constitute the majority of the gastrointestinal pathology service. The College recommends that 80% and 90% of all laboratory specimen types (biopsies and resections) are reported within 7 days and 10 days, respectively, of the date of sampling.[15]

Pathologists reporting GI pathology should participate in the UK national (British Society of Gastroenterology) GI pathology external quality assurance (EQA) scheme or in a local general pathology EQA scheme that includes GI pathology cases. Those whose work consists predominantly of GI pathology should participate in the national GI EQA scheme. As a minimum, the lead and deputy lead in each area of the service should participate in an EQA that includes relevant GI pathology cases.[15] If a frozen section or out-of-hours service in GI pathology is offered, this should be provided by those who report GI pathology regularly *[Level of evidence – GPP].*[15] Pathologists reporting bowel cancer screening programme (BCSP) cases should also participate in the BCSP pathology EQA. All histopathologists should participate in the RCPath continuing professional development scheme[15] and in audit.

Where necessary, pathologists should have access to a regional or national GI/pancreatobiliary specialist opinion. The need will be influenced by the local level of expertise. Guidance with more detail is available from the College.[16]

1.2 Laboratory facilities

The laboratory should be equipped to allow the recommended technical procedures to be performed safely. It should be enrolled with Clinical Pathology Accreditation/United Kingdom Accreditation Service (CPA/UKAS Ltd), participate in the UK National External Quality Assurance Scheme for Cellular Pathology Technique, and participate in the UK National External Quality Assurance Scheme for immunocytochemistry.[15]

Specific considerations for GI pathology include the following:

- a laboratory whose mucosal biopsy workload is large should be staffed, equipped and managed in a way that maintains acceptable turnaround times.[15]
- coloured inks for identifying resection margins should be available.
- provision should be made for macroscopic and microscopic photography.
- there should be facilities to process large (wholemount) blocks.

Reports should be held on an electronic database that has facilities to search and retrieve specific data items and that is indexed according to Systematised Nomenclature of Medicine (SNOMED) T, M and P codes (or equivalent codes according to Systematised Nomenclature of Medicine Clinical Terms [SNOMED CT]). It is acknowledged that existing laboratory information systems may not meet this standard; nevertheless, the ability to store data in this way should be considered when laboratory systems are replaced or upgraded.

Workload data should be recorded in a format that facilitates the determination of the resources involved and which, if applicable, is suitable for mapping to Healthcare Resource Groups (HRGs).

1.3 Specimen submission

Details of the patient, clinician, date of procedure and type of specimen should be provided.[10,17-19] The indication for the procedure should be stated. Relevant surgical or endoscopic findings should be supplied, the latter as a description or in the form of the endoscopy report.[20] Details of previous histology should be available, particularly if there is a history of dysplasia or carcinoma. Details of previous treatment are also important. In some circumstances, interpretation of histology without adequate clinical details is not possible *[Level of evidence – D].*

It is essential that the sites of origin of all biopsies and resections are known to the histopathologist. Each specimen container should be labelled with patient details and with the anatomical site of origin.

Formalin should be of adequate volume to cover the specimen entirely and to ensure proper fixation. The specimen should not be disrupted prior to receipt in the laboratory, unless this has been agreed in advance.[21]

1.4 Block selection and record

When sampling a specimen, the site or lesion from which each block is taken should be documented. Each cassette should have a unique identifying number or letter. A record of the number of pieces of tissue in each cassette is useful. Measurements should be in millimetres. The description should be sufficiently clear that another pathologist can understand the purpose and site of origin of each block. Clarity is enhanced by a block key and, where appropriate, by labelled photographs or line drawings.[21,22]

1.5 Dysplasia/malignancy

Details of previous diagnoses of dysplasia or malignancy are useful.[18,23]

Columnar (glandular) dysplasia within the gastrointestinal tract is classified as low grade or high grade.[11,13] Oesophageal squamous dysplasia is classified as low grade or high grade.[7] Anal intraepithelial neoplasia (squamous) is classified as AIN 1, 2 or 3. Dysplasia in the gallbladder, biliary tree and pancreas is graded according to the three-tier systems currently recommended by WHO (BilIN 1, 2 or, 3 for the gallbladder and biliary tree; PanIN 1 (A&B), 2, or 3 for the pancreas; and low, intermediate and high grade for intraductal papillary mucinous neoplasms and mucinous cystic neoplasms).[7]

Inflammation and ulceration may cause regenerative epithelial atypia, which can be difficult to distinguish from dysplasia. Difficulties are sometimes resolved by examining deeper levels. Immunohistochemistry for p53 and Ki67 is not currently recommended routinely but may be useful in some circumstances.[8,10,20]

Biopsies that show, or might show, dysplasia (with the exception of adenomas with low grade dysplasia) should ideally be reported by at least two consultants, especially if the grade of dysplasia is in any doubt.[8,24] According to current guidelines, double reporting (preferably including a colleague whose main area of reporting is GI pathology) is advised for: dysplasia in chronic inflammatory bowel disease, particularly if non-polypoid and low grade,[8,25] dysplasia in Barrett's oesophagus,[9] and cancers from bowel cancer screening programme (BCSP) patients.[26] However, there is conflicting evidence for the clinical benefits of double reporting *[Level of evidence – D].*[8,24]

Interobserver variability for grading dysplasia ranges from poor to good/excellent in published studies, and may not necessarily improve after the adoption of agreed diagnostic criteria.[24,27-30]

The term “indefinite for dysplasia” may be useful if a decision cannot be made as to the presence or absence of dysplasia.[13,31,32] Reasons for the latter include significant atypia combined with considerable inflammation, or absence of sufficient surface epithelium to allow confident exclusion or diagnosis of dysplasia. Alternatively, the inability to decide can be documented. It may be appropriate to recommend further biopsies in this setting.

Malignancy should be approached and reported according to the guidance in the relevant College dataset.[2-6,33]Neoplasms should be typed and graded according to published guidelines or texts.[7] Staging of resected tumours should generally follow the UICC (International Union Against Cancer) guidelines, though bearing in mind that some College datasets recommend classifications other than the most recent edition of the UICC TNM system.[34]

DYSPLASIA: RECOMMENDATIONS

Columnar (glandular) dysplasia within the gastrointestinal tract is classified as low grade or high grade.

Squamous dysplasia of the oesophagus is classified as low or high grade. Anal intraepithelial neoplasia (squamous) is classified as AIN 1, 2 or 3.

Biopsies that show, or might show, dysplasia (with the exception of adenomas with low grade dysplasia) should be reported by at least two consultants. *[Level of evidence – D].*

The term “indefinite for dysplasia” may be useful if a decision cannot be made as to the presence or absence of dysplasia.

2 Tissue pathways: gastrointestinal and pancreatic biopsies

2.1 Biopsies: general considerations

2.1.1 Mucosal biopsy: preparation, dissection and blocks

Fixation

The specimen should be allowed to fix sufficiently before processing. Adequacy of fixation can be estimated by visual inspection if necessary. A biopsy should probably be fixed in formalin for at least six hours and for no more than three days, although published evidence for an optimal fixation time is sparse *[Level of evidence – D].*[35,36]

Orientation (mucosal *versus* submucosal)

Biopsies may be received free-floating in formalin, in which case they will not have been orientated by the endoscopist. Alternatively, biopsies may be received attached to filter paper, cellulose acetate paper or similar, in which case the endoscopist may have attempted to orientate them in terms of mucosal and submucosal aspects. Cellulose acetate strips are suitable for cutting with a microtome, but filter paper is unsuitable.

If mucosal and submucosal aspects of the biopsies can be identified, the biopsies should be orientated as accurately as possible during embedding.[23]

Orientation of biopsies from multiple sites (e.g. distal *versus* proximal large bowel)

Biopsies from different parts of the GI tract should be dealt with in such a way that their site of origin is unequivocal. Possible approaches include multiple specimen pots, cellulose acetate strips, and multi-well cassettes.[8,23,37]

1. Biopsies from multiple sites may be received in the same pot. The site of origin of each cannot be determined, unless microscopy distinguishes them (e.g. ileal and colonic mucosa).

2. Biopsies may be in multiple pots, each pot corresponding to a specific site. Each pot should have been labelled with a site of origin. Biopsies from each site can then be placed in a separate cassette, identified by a unique number or letter.

3. Biopsies from multiple sites may have been arranged sequentially on a cellulose acetate strip (or similar). The endoscopist should mark the strip to allow identification of the proximal or distal end. The meaning of this mark should be agreed in advance. This approach may fail as a result of detachment of biopsies from the strip. It also limits the number of biopsies that can be taken.

4. Biopsies may be received in multi-well cassettes. The well corresponding to each biopsy site must be identified in advance. Several fragments can be placed in each well. Careful matching of the well contents, embedded tissue and final slide is required to avoid confusion. If barcodes are used, it may be difficult to add them to multi-well cassettes.

5. Pre-cassetted biopsies may be received.

Embedding

Embed all fragments or cores in their entirety. Larger (e.g. full thickness) biopsies require orientation and may need slicing before embedding. A method to avoid loss of small biopsy fragments should be used, e.g. insertion of foam pads into the cassette or wrapping of biopsies in a suitable material. It may be better to avoid placing a large number of fragments in the same cassette, as it may be difficult to keep them orientated and at the same level. Embedding fragments in a line facilitates histological assessment.[22]

2.1.2 Mucosal biopsy: macroscopic description

Record the number of fragments.[23] The term “multiple” should ideally be restricted to cases where there are too many to count or where a precise count is difficult. Record the size of the largest fragment in millimetres. Record attachment of biopsies to filter paper, cellulose acetate or similar. Describe any other material, foreign bodies, etc.

Discrepancies between the macroscopic description and the number of biopsies in the slide raise the possibility of uncut tissue in the block. Discrepancies between the number of biopsies recorded by the endoscopist and the number received in the laboratory are also worth noting. However, either type of discrepancy could also reflect disruption of biopsies before or during processing.

2.1.3 Mucosal biopsy: sections and stains

Minimum stains

Haematoxylin and eosin (H&E). Many laboratories do step sections routinely at two or three levels (e.g. 75 microns apart). This approach is recommended *[Level of evidence – GPP].*[22,23]

Other stains

- Additional levels may be useful, e.g. for orientation, detection of lesions, distinction of reactive epithelial changes from dysplasia, and confirmation of invasive carcinoma. There is consistent evidence that deeper levels may reveal a lesion, e.g. an adenoma, which was not apparent on initial sections *[Level of evidence – C].*[38-41]

- If granulomas are present, PAS/DPAS and Ziehl Neelsen (ZN) stains may be useful.

- In HIV cases with inflamed mucosa, stains for fungi, mycobacteria and protozoa, e.g. PAS/DPAS, ZN[12,23] and Giemsa, should be considered *[Level of evidence – GPP].* There is evidence that these stains provide little additional information, even when inflammation is present.[42]

- A Congo Red stain examined under polarised light helps to confirm or exclude amyloid if this is suspected by the clinician or the pathologist. If amyloid is confirmed, further special stains and immunohistochemistry may be appropriate.[43]

Immunohistochemistry

Immunohistochemistry for cytomegalovirus (CMV) and/or herpes simplex virus (HSV) is worth considering if these are suspected clinically, or if there is ulceration, or if inclusions are seen or suspected. It may be of greater value in immunosuppressed patients (e.g. HIV or severe chronic ulcerative colitis) *[Level of evidence – GPP]* and in graft *versus* host disease (GVHD) where CMV is a potential histological mimic.[44,45] The diagnostic yield is higher than for H&E sections, but there is also evidence casting doubt on the value of staining *[Level of evidence – GPP].*[42]

2.1.4 Mucosal biopsy: report and microscopic description

General

- The adequacy and appropriateness of the sample should be noted, and recorded if relevant.
- A separate description should be composed for each separately submitted set of biopsies, unless they all show the same or similar features.
- Many changes can only be interpreted in the light of clinical and endoscopic findings *[Level of evidence – D]*.[8,19,46] If adequate details are not provided, this should be noted. Clinicopathological meetings and good communication help refine interpretation.[10,47,48]

MUCOSAL BIOPSY: RECOMMENDATIONS

Adequate clinical details should be provided in all cases. Clinicopathological meetings may be useful *[Level of evidence – D].*

Biopsies from different parts of the GI tract should be submitted in such a way that their site of origin is unequivocal, e.g. multiple pots or multi-well cassettes *[Level of evidence – D/GPP].*

Step sections routinely at two or three levels (e.g. 75 microns apart) are recommended *[Level of evidence – GPP].*

Additional levels are often useful *[Level of evidence – C].*

2.2 Oesophageal biopsy: additional comments

2.2.1 Clinical

Biopsies for diagnosis or follow-up of Barrett's (columnar lined) oesophagus should be accompanied by full details of endoscopic findings, the exact site of origin of each set of biopsies, and any history of dysplasia.

2.2.2 Sections and stains

Additional stains

Special stains for mucins may be useful, i.e. PAS +/- Diastase (PAS +/- D) and Alcian Blue (AB), often in the form of an ABPAS or ABPASD stain.[49] Alcian Blue positivity helps to confirm goblet cell (intestinal) metaplasia (although not all Alcian Blue positive cells are goblet cells).[50] PAS/DPAS staining also helps to identify fungi.

Some guidelines recommend PAS and AB if columnar mucosa is present in the sample, while others favour routine special stains.[23,49] However, opinions and evidence conflict regarding the value of routine additional stains.[32,49,51,52] Currently, the approach varies within the UK.[49,51]

Further levels may be useful, e.g. to help detect goblet cells [*[Level of evidence – D]*.[32,41]

Immunohistochemistry

Studies of cytokeratin typing to distinguish intestinal metaplasia in Barrett's oesophagus from metaplasia in the gastric cardia have yielded inconclusive results, and use of immunohistochemistry for this purpose is not currently recommended.[53,54]

2.2.3 Report and microscopic description

Indications for biopsy: examples

- Assessment of oesophagitis and its aetiology (e.g. reflux, infective, eosinophilic, iron pill oesophagitis).
- Diagnosis and assessment of Barrett's (columnar lined) oesophagus.
- Exclusion of dysplasia or malignancy.

Report

If squamous and columnar mucosae are present, it is appropriate to report the appearances of both. It is useful to record the presence and type of metaplastic epithelium, fungi, and dysplasia or malignancy. Other micro-organisms, e.g. Herpes Simplex virus and mycobacteria, should also be excluded.

- The histology of eosinophilic oesophagitis overlaps with that of reflux oesophagitis. The diagnosis is clinicopathological and might be considered if numerous eosinophils are seen in the appropriate clinical setting (e.g. 'feline oesophagus'), especially after a trial of PPI therapy. A threshold of >15 eosinophils in at least one high power field [hpf] has been suggested but this feature is not diagnostic.[55,56] Other features which lend support include superficial eosinophilic layering/aggregates and eosinophilic microabscesses.[57] Eosinophil infiltration is often patchy. Two to four biopsies should be obtained from each of at least two different locations in the oesophagus, e.g. proximal and distal.[58]
- Diagnosis of intestinal metaplasia requires the presence of goblet cells. There is no need to subclassify intestinal metaplasia as complete or incomplete.
- The presence/absence of oesophageal glands and ducts should be recorded.[9]

Barrett's oesophagus

Barrett's (columnar lined) oesophagus is diagnosed by the endoscopist.

The pathologist may make a confident diagnosis of Barrett's oesophagus when glandular mucosa is present together with native oesophageal structures (squamous ducts and/or oesophageal submucosal glands) in the biopsy, although such native structures are only found in <15% of biopsies.[9,59] When oesophageal biopsies contain native structures, the pathologist can conclude: "Barrett's oesophagus with gastric metaplasia only" or "Barrett's oesophagus with intestinal metaplasia."[9] It is important to state whether intestinal metaplasia is present or not, since its presence is associated with a >five-fold increase in cancer risk.[60]

In biopsies where native oesophageal structures are not present, gastric-type mucosa (with or without intestinal metaplasia) may originate from Barrett's oesophagus, but may also originate from a hiatus hernia or the gastric cardia.[9,59] In these circumstances, the diagnosis of Barrett's oesophagus can only be made with confidence by the endoscopist, and it would be prudent for the pathologist to conclude either: "Oesophageal biopsy – gastric-type mucosa only. Biopsies supportive of the diagnosis of Barrett's oesophagus if taken from the tubular oesophagus" or: "Oesophageal biopsy – glandular mucosa with intestinal metaplasia. Biopsies supportive of the diagnosis of Barrett's oesophagus if taken from the tubular oesophagus".[9,59]

Suspected dysplasia of all grades should be corroborated by a second pathologist, preferably a pathologist with a specialist GI interest.[9] The addition of p53 immunostaining to the histopathological assessment may improve the diagnostic reproducibility of a diagnosis of dysplasia in Barrett's oesophagus and may be considered as an adjunct to routine diagnosis.[9]

OESOPHAGEAL BIOPSY: RECOMMENDATIONS

ABPASD staining may be useful. Routine ABPASD staining may be appropriate for some laboratories, but evidence and support for this approach are inconsistent *[Level of evidence – GPP].*

Diagnosis of intestinal metaplasia requires the presence of goblet cells.

When reporting biopsies for assessment of Barrett's oesophagus, the approach described above (based on British Society of Gastroenterology guidelines) is recommended.

Histological distinction of eosinophilic oesophagitis from reflux oesophagitis can be difficult. Correlation with clinical findings is advisable.

2.3 Gastric biopsy: additional comments

2.3.1 Sections and stains

Additional stains

A histochemical or immunohistochemical stain for *Helicobacter pylori*, e.g. Giemsa, Cresyl Fast violet (CFV), should be available. The updated Sydney classification system guidelines suggest that, as a minimum, a stain should be done when there is inflammation in the absence of identifiable Helicobacter-like organisms.[12,49,61] There is conflicting evidence/opinion regarding the diagnostic value, clinical value and cost effectiveness of performing a stain routinely.[8,49,51,52] Other guidelines favour immunohistochemistry over histochemical stains where Helicobacter cannot be seen on H&E examination. When antibiotic or PPI treatment has been given, immunohistochemistry appears to be more sensitive in detecting small numbers and enables the recognition of coccoid forms.[49,61,62]

It is recommended, as a minimum, that a Helicobacter stain is requested if characteristic inflammation is seen, no Helicobacter are apparent, and no clinical test (e.g. CLO test) has been performed.[12,49,63]

Other stains

Special stains for mucins help to identify intestinal metaplasia in gastric mucosa. PAS+/- diastase and Alcian Blue are most often used, i.e. ABPAS or ABDPAS.[12,49] Routine mucin stains are done in some laboratories but there is some evidence that this approach is not effective.[49,52]

A Perls stain may be used selectively to confirm iron deposits in areas of erosion or gastritis ("iron pill gastropathy").[64]

2.3.2 Report and microscopic description

Indications for biopsy: examples

- Diagnosis and assessment of gastritis/ulceration.
- Characterisation of polyps.
- Exclusion of dysplasia or malignancy.

Report: general comments

- The number of body/fundus-type and antrum/cardia-type biopsies should be noted. Biopsies from different sites should be described separately, unless they are the same or very similar.
- Assess the features that are recommended by the updated Sydney classification: chronic inflammation, activity, intestinal metaplasia, atrophy, dysplasia, Helicobacter.[12]

Report: most common categories of gastritis

- Helicobacter-associated chronic gastritis.
- Atrophic gastritis, characterised by chronic inflammation, atrophy and intestinal metaplasia. This pattern can be secondary to Helicobacter (antral-predominant) or autoimmune gastritis (typically body-predominant and associated with antibodies to parietal cells and intrinsic factor).
- Reactive (chemical) gastropathy/gastritis, including iron pill gastropathy.
- "Lymphocytic" gastritis (criteria vary, e.g. >25 lymphocytes per 100 epithelial cells; the pattern has several aetiologies and associations, including coeliac disease, H. pylori, microscopic colitis, NSAIDs).[65,66] Immunohistochemistry is not usually required for analysis of lymphocyte numbers.
- "Granulomatous" gastritis: Crohn's disease, mycobacterial infection, fungi, foreign material, crypt/gland rupture, and sarcoidosis are possible causes. A proposed association with Helicobacter pylori infection has been disputed.[66-68]

GASTRIC BIOPSY: RECOMMENDATIONS

When reporting biopsies for assessment of gastritis, consideration of the updated Sydney classification is recommended. Chronic inflammation, activity, intestinal metaplasia and atrophy can be graded. The presence or absence of Helicobacter and dysplasia should be recorded.

The most common types of gastritis are Helicobacter-associated gastritis and reactive gastritis.

As a minimum, a Helicobacter stain is recommended if characteristic inflammation is seen, no Helicobacter are apparent, and no clinical test has been performed. *[Level of evidence – GPP].*

An ABPASD stain for mucins may be useful for confirming intestinal metaplasia.

Routine Helicobacter and/or mucin staining are used in some laboratories, but evidence and support for this approach are inconsistent.

2.4 Duodenal/jejunal biopsy: additional comments

2.4.1 Sections and stains

Deeper levels may be very useful if villous architecture is difficult to assess in a poorly orientated or small biopsy. Identification of parasites may be assisted by a Giemsa stain. PAS stain is used routinely in some laboratories to identify gastric metaplasia but is of little value in most cases.

Immunohistochemistry and Polymerase chain reaction (PCR)

Immunohistochemistry and PCR-based studies may be appropriate for some biopsies with features of coeliac disease, particularly if there is refractory coeliac disease or a suspicion of T-cell neoplasia.[69,70] CD117 immunohistochemistrymay help identify Giardia trophozoites but isnot usually necessary.[71] Whipple's disease is an extremely rare cause of enteropathy. A PASD stain helps make the diagnosis, but immunohistochemistry, PCR or electron microscopy are usually necessary for confirmation and are only available in large centres.

2.4.2 Report and microscopic description

Indications for biopsy: examples

- Exclusion of an enteropathy, particularly coeliac disease.[70]
- Assessment of duodenitis or ulceration.
- Exclusion of dysplasia or of primary/secondary malignancy.

Report

- The number of biopsies should be documented. Recent guidelines on coeliac disease have reaffirmed the importance of biopsy pathology even when serology is available. At least four biopsies should be obtained. These should include a biopsy of the duodenal bulb, because the histological abnormalities are occasionally limited to D1.[63,70,72-75]
- If the biopsies are traumatised or poorly processed to the extent that villous architecture cannot be assessed reliably, this fact should be recorded.
- Note features of coeliac disease, e.g. villous atrophy, crypt hyperplasia, increased intraepithelial lymphocytes (>25 per 100 epithelial cells), distribution of intraepithelial lymphocytes, surface epithelial changes.[69,70] Immunohistochemistry for CD3 may

facilitate counting of intraepithelial lymphocytes, although some studies have shown no advantage over H&E staining.[76,77]

- Giardia and other infective agents should be sought actively, especially in immunosuppressed patients (e.g. hypogammaglobulinaemia). Giardia are easily missed if they are sparse.[78] Absence of plasma cells, as seen in common variable immune deficiency, is also easily missed.

2.5 Ileal biopsy: additional comments

2.5.1 Report and microscopic description

Indications for biopsy: examples

- Inflammatory bowel disease (IBD) assessment and classification *[Level of evidence – C].*[17,79]
- Characterisation of other inflammatory conditions.
- Exclusion of neoplasia (e.g. abnormal CT appearances, abnormal endoscopy).
- Confirmation that the ileum has been reached. Biopsies are taken for this reason, despite the existence of guidelines stating that they are of no value.[37,63]

Report

Note that native lymphoid tissue may appear polypoid at endoscopy and can be prominent histologically. A diagnosis of ileitis cannot be made easily in the absence of acute inflammation or of other unequivocally abnormal features *[Level of evidence – GPP].*[80] Ileoscopy has become more frequent, and ileal biopsies may be taken from abnormal mucosa to exclude Crohn's disease. However, it is worth remembering that there are other causes of ileitis and aphthous ulcers, such as NSAIDs and infection.[81]

2.6 Colorectal biopsy: additional comments

2.6.1 Report and microscopic description

Indications for biopsy: examples

- Assessment of altered bowel habit/rectal bleeding.
- Follow up of chronic idiopathic inflammatory bowel disease (IBD).
- Exclusion or follow up of dysplasia/malignancy, including Bowel Cancer Screening Programme (BCSP).[11]

Report: general comments

For inflammatory conditions, the distribution of changes between biopsies from the same site and between biopsies from separate sites should be recorded and can be very useful diagnostically in certain settings, e.g. IBD *[Level of evidence – A].*[17] Ileal and colonic biopsies may be present in the same pot and should be described separately if possible, although their distinction can be very difficult if the mucosa is inflamed.

Assessment: inflammation

Decide whether the mucosa is normal or abnormal. If inflamed, try to categorise as infective type, IBD type or another type. Terms such as "non-specific chronic colitis"/"non-specific colitis" should be avoided *[Level of evidence – GPP].*[10,82]

Chronic idiopathic inflammatory bowel disease (IBD)

- BSG guidelines are recommended.[10] Other guidelines are also available.[8,17,45,83]
- The probability of IBD should be stated, especially in initial biopsies.[10] The features that favour IBD over other causes most strongly, in the appropriate clinical setting, are basal plasmacytosis and mucosal architectural changes (including crypt distortion and crypt atrophy) *[Level of evidence – A].*[10]
- If IBD is definite or very likely, the probability of ulcerative colitis (UC) or Crohn's disease should be recorded. The microscopic features that help distinguish UC and Crohn's disease from one another include non-cryptolytic granulomas, architectural changes, and distribution of disease. Granulomas are more specific than any other feature *[Level of evidence – A].*[10]
- IBD can be difficult or impossible to classify further. If a term is required, "IBD unclassified" (IBDU) is recommended.[10,83,84] The term "indeterminate colitis" is not used for biopsy reporting.[10,17,85]
- There is no widely agreed grading scheme for histological inflammation or activity in IBD but a description of the severity of activity is helpful and may contribute to the assessment of the risk of neoplasia.[10,25]
- Features of IBD may be greatly modified by time and treatment *[Level of evidence – C].*[10,86-89] This can make classification of IBD difficult in post-treatment biopsies, while biopsies taken very early in the course of IBD may show few changes *[Level of evidence – C].*[10,17,90,91]
- Discussion of IBD cases with clinicians should help reduce the risk of inaccurate classification and misunderstandings.[10,47,48]
- The acronym "PAID" (pattern, activity, interpretation, dysplasia) is a useful aide-memoire for the structure of the conclusion of an IBD biopsy report.[10] The PAID proforma in the BSG guidelines may also be helpful.
- Immunohistochemistry for CMV should be considered, particularly when there is severe refractory disease or severe ulceration or inclusions are seen or suspected *[Level of evidence – GPP].*[92]

Comments on other forms of colitis

- Microscopic colitis: classification as "collagenous colitis" or "lymphocytic colitis" is preferable to the term "microscopic colitis", but it is recognised that overlap may occur.[82] The hallmark of collagenous colitis is a thickened subepithelial collagen band. Lymphocytic colitis is characterised by an intraepithelial lymphocyte count >20 per 100 surface epithelial cells. Both may show degenerative surface epithelial changes and lamina proprial plasmacytosis. Immunohistochemistry is not usually required for analysis of intraepithelial lymphocyte numbers.
- Radiation colitis, diversion colitis, diverticular colitis, and graft *versus* host disease (GVHD): these cannot be diagnosed reliably unless clinical details are forthcoming. They may mimic IBD.[10,93-95]
- NSAID-induced colitis is worth considering if features do not conform to a recognised pattern.[93,96]
- Mycophenolate Mofetil colitis may mimic GVHD histologically and can share features with IBD.[57]
- Infections, ischaemia and mucosal prolapse should also be considered.

Polyp biopsies/dysplasia

- Polyp biopsies are most often from hyperplastic polyps or adenomas. Native lymphoid tissue or mucosal folds may mimic a polyp endoscopically.
- Deeper levels are advised if initial slides show no features of a polyp *[Level of evidence – C].*[38-40]
- In the setting of IBD, it is very difficult to distinguish a sporadic adenoma from IBD-related dysplasia on the basis of biopsy histology.[97] Currently, the distinction has limited implications for management.

Hirschsprung's disease

- These specimens should be reported in specialist units that receive them regularly. A deep mucosal biopsy should be taken, at least 20 mm above the pectinate line. Fresh tissue may be required. Part or all of the sample can be snap frozen.
- Multiple serial H&E sections from the submucosal aspect towards the mucosal aspect should be examined. Many experts recommend at least 50 sections.
- Guidelines on diagnosis differ, but Hirschsprung's disease (HD) is usually excluded if ganglion cells are seen. HD is very likely if there are no ganglion cells in 50 serial sections. HD is usually diagnosable if, in addition to the absence of ganglion cells, there are abnormal nerve trunks and/or typical cholinergic fibres passing through the muscularis mucosae (acetylcholinesterase histochemistry on frozen tissue/PGP 9.5 immunohistochemistry).[98]

COLORECTAL BIOPSY: RECOMMENDATIONS

If inflamed, categorise as IBD type, infective type, or another type where possible. Consider the possibility of drugs.

Avoid the terms "non-specific chronic colitis" and "non-specific colitis".

The probability of IBD should be stated, especially in initial biopsies. The features that favour IBD over other causes most strongly are basal plasmacytosis and mucosal architectural changes *[Level of evidence – A].*

If IBD is definite or very likely, the probability of ulcerative colitis (UC) or Crohn's disease should be recorded. The microscopic features that help distinguish UC and Crohn's disease from one another include non-cryptolytic granulomas, architectural changes, and distribution of disease *[Level of evidence – A].*

The term "indeterminate colitis" is not used for biopsy reporting. If a term is required, "IBD unclassified" should be used.

The acronym "PAID" (pattern, activity, interpretation, dysplasia) is a useful aide-memoire for the structure of the conclusion of an IBD biopsy report. The PAID proforma in the BSG guidelines may also be helpful.

Record microscopic colitis as collagenous colitis or lymphocytic colitis, if possible.

Immunohistochemistry for CMV may be useful.

Clinical details are essential. Most types of colitis can only be diagnosed and assessed accurately if a clinical history is provided. This is particularly important for diversion proctocolitis, diverticular colitis, radiation proctocolitis, and graft versus host disease (GVHD) *[Level of evidence – D].*

2.7 Anal biopsy: additional comments

2.7.1 Report and microscopic description

Indications for biopsy: examples

- Diagnosis and assessment of wart virus change, anal intraepithelial neoplasia (AIN), and malignancy.

General

- "Mapping" biopsies from multiple anal and perianal sites may be received. The appearances at each site should be reported separately, unless they are the same.
- The description of squamous epithelium should include a record of wart virus change and AIN (classified as AIN 1, AIN 2, or AIN 3). Two-tier schemes for grading AIN have not been adopted widely in the UK. Immunohistochemistry for p16 is increasingly being used as a surrogate marker for high risk Human Papilloma Virus (HPV) infection and to help confirm high grade dysplasia but is not currently recommended for routine use.[99,100] Confirmatory immunohistochemistry for HPV may be useful, if available.

2.8 Ileoanal pouch biopsy: additional comments

2.8.1 Report and microscopic description

Indications for biopsy: examples

- Assessment of inflammation/pouchitis.
- Exclusion of other inflammatory conditions.
- Pre-pouch ileal biopsies may also be taken in this setting.

Pouchitis

Adaptive changes, e.g. villous atrophy and inflammation, may occur in a pouch. Diagnosis of "pouchitis" depends on a combination of clinical, endoscopic and histological findings. Pouch inflammatory scores exist, are required by some centres, and are useful as an *aide memoire* to the pathologist.[97,101-103]

Comments on the presence of IBD in a pouch biopsy should be cautious. The features of pouchitis may mimic those of UC or Crohn's disease *[Level of evidence – C].*[101,104,105]

Biopsies may be taken from columnar mucosa at the distal end of the pouch originating in the anal canal, from specific points within the ileal pouch itself, or from the pre-pouch ileum. These should be received in separate pots and identified accordingly. This permits discrimination of "cuffitis" from "pouchitis" and "pre-pouch ileitis", a distinction that may be impossible to make histologically and that may be clinically important.[92] Further details are available in standard textbooks.[106]

2.9 Ampulla of Vater biopsy: additional comments

2.9.1 Report and microscopic description

Indications for biopsy: examples

- Exclusion of neoplasia.
- Characterisation of focal lesions.
- For IgG4 immunohistochemistry.

Report

The term “ampulla” may refer to the true ampulla and/or the periampullary duodenal mucosa.[107] A report of dysplasia or carcinoma in this area may have profound implications. Histology should be interpreted in the light of clinical and imaging findings and past history. Atypical epithelial changes are not uncommon if there is ulceration, inflammation or a history of intervention. Inflammatory-type polyps can mimic neoplasia.[108] Double reporting or referral to a specialist pathologist may be appropriate *[Level of evidence – GPP].*

IgG4 immunohistochemistry can be performed on biopsies from the ampulla of Vater (as a surrogate diagnostic sample) to support a diagnosis of autoimmune pancreatitis *[Level of evidence – D].*[109] A ratio of IgG4 to IgG higher than 40% may be used to support the diagnosis.[110]

2.10 Pancreatic biopsy: additional comments

2.10.1 Macroscopic description of needle core biopsies: additional considerations

Record the length of each core (millimetres).

2.10.2 Sections and stains from needle core biopsies: additional considerations

Production of additional unstained sections at initial processing may be particularly useful for needle core biopsies for several reasons: the amount of tissue obtained is often limited; immunohistochemistry may be needed; and repeat biopsy is difficult.

2.10.3 Clinical

Pancreatic biopsies should ideally be reported in specialist centres with access to appropriate clinical, imaging and histopathological expertise. Details of the indication(s) for biopsy, imaging, operative findings and previous histology are important *[Level of evidence – GPP].*

2.10.4 Sections and stains

Immunohistochemistry

IgG4 may be useful if autoimmune pancreatitis is suspected.[110,111] Immunohistochemistry can help characterise pancreatic tumours.[7,112] A ratio of IgG4 to IgG higher than 40% may be used to support the diagnosis.

2.10.5 Report and microscopic description

Indications for biopsy: examples

- Diagnosis and characterisation of neoplasia.
- Confirmation or exclusion of chronic pancreatitis.

Report

- Chronic pancreatitis can be difficult to distinguish from carcinoma, especially in frozen sections.[112-114] Double reporting may be appropriate *[Level of evidence – GPP].*
- Autoimmune pancreatitis may mimic carcinoma clinically and radiologically.[115] The histological changes may support the diagnosis but are not specific.[116] Histological peritumoral pancreatitis can have features that overlap with autoimmune pancreatitis. IgG4 immunohistochemistry may be helpful in this situation *[Level of evidence – C].*[112] A ratio of IgG4 to IgG higher than 40% may be used to support the diagnosis.[110]

- A cautious approach to the interpretation of a needle core biopsy is advised. Unusual tumours and difficult cases are best diagnosed in conjunction with the imaging findings and after discussion at an appropriate multidisciplinary meeting, preferably by a histopathologist who is familiar with pancreatic pathology *[Level of evidence – GPP].*[112,115]

2.11 Endoscopic ultrasound (EUS)-guided fine needle biopsies: additional comments

2.11.1 Macroscopic description of EUS-guided biopsies: additional considerations

- These biopsies are becoming more common. In general the approach is similar to that described above for needle core biopsies. There may be considerable fragmentation. Input from cytopathologists may be helpful.

2.11.1 Sections and stains from needle core biopsies: additional considerations

- Serial sections or unstained sections at initial processing may be useful (see section 2.10 above).

2.11.3 Clinical

- Pancreatic and bile duct biopsies, as noted above, should ideally be reported in specialist centres.

2.11.4 Report and microscopic description

Indications for biopsy: examples

- Diagnosis and characterisation of gastrointestinal and pancreatobiliary neoplasia.

3 Tissue pathways: small gastrointestinal resection specimens

3.1 Appendicectomy

3.1.1 Preparation, dissection and blocks

Sampling *[Level of evidence – GPP].*

- The tip is bisected longitudinally.[22] The remaining appendix can be serially sliced transversely. Alternatively it can be bisected through the surgical margin (base) and any remaining intervening tissue between the bisected base and tip then sliced transversely or longitudinally.
- Sample the surgical margin (base), either longitudinally (as above) or transversely. This section should be identifiable microscopically (e.g. coloured ink/a nick in the relevant section/a section of a different shape/use of a separate cassette, etc.).[22]
- Other blocks should include at least one longitudinal half of the tip (with mesoappendix) and at least one more section, plus representative blocks from abnormal areas.[22]
- Sample the entire appendix if neoplasia is suspected clinically or at cut-up (see below).
- Sample the entire appendix before reporting that it is not inflamed *[Level of evidence – GPP].*[117] If the appendix looks normal at initial cut-up, it may be worth submitting in its entirety at this stage.

3.1.2 Specimen description

- Dimensions (millimetres): length and diameter.[22]
- External surface: perforation, peritonitis, congestion, abscess, mucin. If the appendix is dilated, it is particularly important to inspect the unsliced specimen for mucin leakage.[118]
- Cut surface: luminal contents, mucin, diverticula, nodules, possible carcinoid/neuroendocrine tumour (especially at the tip).

3.1.3 Report and microscopic description

Indications

These include confirmation or exclusion of acute appendicitis and exclusion of neoplasia.

Report

- Appendicitis: transmural acute inflammation is required for diagnosis. Mucosal inflammation (without ulceration) is not universally regarded as sufficient, and may reflect inflammatory bowel disease or infection *[Level of evidence – GPP].*[119]
- Peritonitis/serositis without transmural inflammation may reflect extra-appendiceal pathology *[Level of evidence – GPP].*[22] In this circumstance, the entire appendix should be sampled to exclude appendicitis.[117]
- The possibility of Crohn's disease may be raised, e.g. granulomas and transmural chronic inflammation. However, these changes may occur in appendicitis, particularly if treatment has been delayed *[Level of evidence – D].*[117,119,120] Ulcerative colitis may also involve the appendix, and this can occur in the absence of caecal involvement *[Level of evidence – D].*[117,119,121]
- The boundaries between hyperplastic polyps, other serrated lesions, and adenomas are not always easy to define.[122] If a serrated lesion, dysplasia, or any feature suggestive of carcinoma are seen, sampling of the entire appendix is advised *[Level of evidence – GPP].* Epithelial neoplasms and hyperplastic lesions of the appendix may be associated with an increased risk of neoplasia in the large bowel *[Level of evidence – D].*[123,124]
- Appendiceal mucinous neoplasms merit extensive sampling, preferably of the entire appendix *[Level of evidence – D].*[125]
- Record the status of the base (resection margin) if dysplasia or malignancy are present. Report malignancy using appropriate guidelines and texts.[3,7]

APPENDIX: RECOMMENDATIONS

The tip and the resection margin should be sampled, together with at least one transverse section.

The entire appendix should be sampled if a mucinous lesion or malignancy is suspected clinically or at macroscopic examination; or if a serrated lesion, dysplastic lesion, mucinous lesion or malignant tumour is found on initial histological examination *[Level of evidence – D/GPP].*

The entire appendix should be sampled before reporting that it is not inflamed *[Level of evidence – GPP].*

The entire appendix should be sampled if initial examination shows serositis/peritonitis without transmural inflammation *[Level of evidence – GPP].*

3.2 Polyps (gastric and intestinal)

3.2.1 Preparation, dissection and blocks

Opening and fixation

Slicing prior to fixation may be necessary if the polyp is large. This should not interfere with subsequent attempts to orientate the specimen.

Sampling *[Level of evidence – GPP].*

- The resection margin (base) should always be identified if possible and should be inked.[22]
- All material should be submitted.
- Small fragments or polyps (<5 mm in diameter) can be embedded whole.
- A larger polyp (5 mm or more in diameter) should be bisected or serially sliced. If the polyp can be orientated, slicing should be in the axial plane. The stalk should be preserved and should be present with the body of the polyp in at least one block. Please note: further details are available in relevant guidelines *[Level of evidence – D].*[2,11]
- If multiple polyps or fragments are received in a single container, identification of separate polyps may be impossible.

3.2.2 Macroscopic description

- Nature of specimen: polypectomy/fragments.
- Dimensions (millimetres): maximum dimension of polyp; length of stalk and/or diameter of base.
- External surface: ulcerated/smooth/lobulated/villous/fronded, etc.
- Cut surface: cysts, mucus, haemorrhage, necrosis.

3.2.3 Sections and stains

Deeper levels

Routine levels are often advised.[22] Further levels may help distinguish invasion from gland displacement ("pseudoinvasion") *[Level of evidence – GPP].*[38-40,50]

3.2.4 Report and microscopic description

Indications for polypectomy: examples

These include symptom management; characterisation of polyps; documentation of dysplasia and malignancy; and bowel cancer screening programme (BCSP).[11]

Adenoma

- Adenomas are classified as tubular, tubulovillous or villous, and as having low-grade dysplasia or high-grade dysplasia. A tubulovillous adenoma should be at least 20% villous and a villous adenoma at least 80% villous.
- Definitions vary.[7] For example, suggested figures for the minimum villous component in a tubulovillous adenoma include 20% and 25%, and suggested figures for the minimum villous component in a villous adenoma include 75% and 80%.[7,11] Also, interobserver

variability is high. Furthermore, classification may be inaccurate if the whole polyp is not submitted and examined.

- Degree of dysplasia: low grade or high grade, based on architectural changes supplemented by cytological changes.[7,11,50] Use the terms “adenoma with low grade dysplasia/high grade dysplasia” and not “low grade adenoma/high grade adenoma.[11]”
- Record completeness of excision, if possible.
- If carcinoma is present, record precise distance from margin, vascular invasion, and differentiation, in particular, as these help predict behaviour *[Level of evidence – D].* Refer to the RCPath cancer datasets.[2-4]
- Misplaced glands/“pseudoinvasion” can mimic carcinoma. Deeper levels and double reporting may be useful. Occasionally there is no “correct” answer.[126]

Other polyps

- Inflammatory-type polyps may occur in apparently non-inflamed mucosa.
- Juvenile polyp: features vary, and may include expanded lamina propria, variably dilated crypts, inflammation and ulceration.[93] A juvenile polyp may be difficult to distinguish from an inflammatory polyp *[Level of evidence – D].*[127]
- Peutz-Jegher polyp: arborising smooth muscle fibres.[93] It may mimic other hamartomatous polyps and mucosal prolapse.[128]
- The commonest types of gastric polyp are fundic gland polyps and inflammatory/hyperplastic polyps.

3.3 Anal polyps

3.3.1 Preparation, dissection and blocks

Sampling

All tissue from polyps should be embedded if there is any possibility of dysplasia. Otherwise, representative blocks may be sufficient *[Level of evidence – GPP].*[22]

Polyps or fragments >5 mm should be sliced. Fragments 5 mm or less in maximum dimension may be submitted whole.

3.3.2 Specimen description

- Specimen type: polypectomy/fragments.
- Dimensions (millimetres): size of largest fragment or range of dimensions.
- Appearances: surface and cut surface; focal changes, e.g. ulceration, haemorrhage, thrombosis.

3.3.3 Report and microscopic description

Indications

These include management of symptoms and exclusion of dysplasia/malignancy.

Report

- Haemorrhoid: vascular ectasia, congestion, haemorrhage, thrombosis.
- Fibroepithelial polyp.

- Mucosal prolapse: crypt angulation, lamina proprial smooth muscle fibres, fibrosis, erosion. Appearances are influenced by the underlying cause. Can mimic adenocarcinoma*[Level of evidence – GPP].*[129]

GASTRIC AND INTESTINAL POLYPS: RECOMMENDATIONS

All tissue from gastric and intestinal polyps should be sampled.

The resection margin (base) should be identified wherever possible and should be inked.

Adenomas are classified as tubular, tubulovillous or villous, and as having low grade dysplasia or high grade dysplasia. A tubulovillous adenoma should be at least 20% villous and a villous adenoma at least 80% villous.

Juvenile polyps and inflammatory polyps may have similar histological appearances *[Level of evidence – D].*

3.4 Other anal lesions (e.g. fissure, fistula, sinus)

3.4.1 Preparation, dissection and blocks

Sampling

A resection specimen should be sliced in the plane most likely to demonstrate the lesion. Representative blocks of any track, abscess or other focal changes should be taken *[Level of evidence – GPP].*[22] One block should include skin and any possible opening (punctum),[22] and one block should include the deep margin and the lesion. If multiple fragments are received, representative pieces can be sampled.

3.4.2 Specimen description

- Dimensions (millimetres): specimen dimensions; skin dimensions.
- Appearances: record the presence and appearance of skin/mucosa; describe tracks and abscesses and their contents; note the state of the adjacent tissue; and record the presence of dye.

3.4.3 Report and microscopic description

Indications

These include management of symptoms, identification of cause, and exclusion of neoplasia.

Report

- Exclude recognisable causes, e.g. Crohn's disease, tuberculosis, hidradenitis suppurativa, pilonidal sinus, and neoplasia *[Level of evidence – GPP].*[22,130]
- Describe skin and/or squamous mucosa.
- Note granulomas (which may not be specific in this setting).
- Describe track/abscess, including contents (e.g. hair shafts).

3.5 Ileostomy/colostomy

3.5.1 Preparation, dissection and blocks

Opening and fixation

The stoma and bowel may require opening and further fixation.

Sampling/blocks

Ensure that sections include the mucocutaneous junction and the margin(s). Further representative sections as appropriate.

3.5.2 Specimen description

- Dimensions (millimetres): record the length of skin and of bowel.
- Specimen type and appearances: type of stoma; note focal lesions.

3.5.3 Report and microscopic description

Indications for procedure

These include symptom management, loss of stomal function, inflammatory changes, and re-anastomosis.

Report

- The presence of skin should be confirmed.
- Ulceration and inflammation (and mucosal prolapse changes) are frequently seen near a stoma.
- Features suggestive of IBD, e.g. granulomas and chronic inflammation, should be interpreted cautiously in this setting.

3.6 Omentum and omental biopsy

3.6.1 Preparation, dissection and blocks

Sampling

- Core biopsy: embed whole.
- Larger samples: serially slice if large, sample any focal changes, and take representative sections *[Level of evidence – GPP].* If there is no macroscopic abnormality, sampling should be guided by the clinical indication for the procedure and may be limited.

3.6.2 Specimen description

- Specimen type: needle core biopsy, omentectomy or fragments of adipose tissue.
- Dimensions (millimetres): core biopsy (length); omentum (maximum dimension); fragments (maximum size of each, or a range of sizes).
- Appearances: note nodules/necrotic foci/abscesses/cysts/fibrosis/probable tumour.[22]

3.6.3 Report and microscopic description

Indications

These include characterisation of focal lesions or tumour; technical reasons; and reduction of tumour burden.

Report

Malignancy in the omentum is usually carcinoma. Elucidation of the site of origin of a tumour may be assisted by immunohistochemistry. Exclude other lesions, e.g. tuberculosis.

4 Tissue pathways: large gastrointestinal resection specimens

Preparation, dissection and blocks

Opening and fixation *[Level of evidence – GPP].*

- A large resection specimen should be received unopened and, ideally, unfixed, so that it can be orientated easily.[18,21,23] If it cannot be received fresh it should be placed in a volume of formalin at least sufficient to cover it completely.[18]
- Ideally, the stomach is opened along the greater curvature and the intestine along the antemesenteric border,[18] unless there is a focal lesion that would be disrupted as a result. The oesophagus may be opened longitudinally along the anterior border or may be left intact, depending on local preference.
- Wash out luminal contents gently with tepid or cold water.[18] Excess washing or the use of hot water may damage the mucosa.
- If the lumen is narrowed or the wall thickened, it may be easier to make serial transverse slices before further fixation, and then leave the specimen intact while fixing.
- Serial transverse slicing (before or after fixation) may facilitate the examination of focal abnormalities of the wall, e.g. diverticula, endometriosis.[22]
- Infarcted tissue may be friable and thin-walled and unsuitable for opening.
- Ink relevant margins if there is a possibility of neoplasia. It should be noted that ink may spread into tissue, particularly if the specimen is not dry. Reliance on ink to identify margins should take account of this possibility. Also, some inks are more reliable than others *[Level of evidence – D].*[131]
- The specimen should be pinned to a corkboard or stabilised in another way[22] and fixed in a volume of formalin that is at least sufficient to cover it.
- Fixation for 48 hours after opening is generally recommended, but adequacy of fixation can be estimated fairly reliably by visual inspection.[18,22]
- Photographs may be useful, particularly for tumours or inflammatory bowel disease or to facilitate subsequent discussion at meetings.[18,22] Photographs are advisable in cases of trauma.

Sections and stains

Deeper levels/trim

May be useful if the slide appears not to represent the full face of the block.

4.1 Oesophagectomy/gastrectomy for non-neoplastic disease

4.1.1 Preparation, dissection and blocks

Sampling: margins *[Level of evidence – GPP].*

- Proximal and distal resection margins: these can be sampled parallel or perpendicular to the margin, depending on the site and nature of the lesion. Perpendicular blocks allow the distance from the lesion to be determined. There is often no published evidence to support sampling of these margins. However, they also serve as samples of background mucosa.
- If sutures are present at the margin, they should be removed before sampling.
- If staples are present along the margin, the stapled tissue should be detached. The stapled tissue cannot be sampled.

Sampling: lesions

Representative samples of focal lesions, e.g. ulcer, abscess, fistula. More blocks should be taken from any suspicious lesion. At least one block should show the relationship with the circumferential margin/serosal surface if this might be relevant. Longitudinal blocks may help show the relationship with oesophagus and/or stomach proximal to and distal to the lesion. If tumour is suspected or is present, the dataset for oesophageal or gastric cancer should be used.[2]

Sampling: adherent organs

Sample to show any connection, e.g. fistula, diverticulum. A large (wholemount) block may help to show the anatomical relationships more clearly if this is relevant. It may be appropriate to sample the resection margins of any adherent organ.

Sampling: lymph nodes

Take representative lymph nodes.[22] If malignancy is suspected, retrieve all regional nodes. A bisected or serially sliced node should not share a cassette with another node if neoplasia is suspected. The number of nodes and pieces in each cassette should be recorded.

4.1.2 Specimen description

Specimen type

Oesophagectomy/total gastrectomy/distal gastrectomy, etc.

Dimensions of specimen (millimetres)

Lengths of oesophagus, greater curve of stomach, lesser curve of stomach and duodenum.[23] Maximum dimension of attached fat.

External surface

- Diffuse changes, e.g. peritonitis, congestion.
- Perforations/defects in wall: record number, site, size, and distance from nearer margin. Consider the possibility that the defects are artefactual or iatrogenic.
- Focal lesions, e.g. stricture, haemorrhage, puckering: record site, size and distance from nearer margin.

Opened oesophagus/stomach/duodenum

- Focal lesions, e.g. ulcer, abscess, stricture, polyp, diverticulum and tumour: record appearance, site, size, and, if relevant, relationship with serosal surface/margins.[22,23]

- Record appearance of oesophageal, gastric and duodenal mucosa, e.g. evidence of Barrett's oesophagus.
- Distinction between malignant and non-malignant ulcers can be difficult.

4.1.3 Report and microscopic description

Indications for surgery

These include stricture, obesity, peptic ulceration, abscess, trauma and perforation.

Report

- Record appearances of oesophagus, stomach and duodenum.
- Note ulceration, inflammation, abscess, fibrosis, perforation, penetration into other structures, granulomas, foreign bodies, etc.
- Describe polyps.
- Record lymph node histology.
- A resection performed for cancer may show no macroscopic or microscopic tumour, e.g. following neoadjuvant therapy, but should nevertheless be treated as a cancer resection specimen and reported according to the relevant dataset.[4,5]

4.2 Intestinal resections: general considerations

4.2.1 Preparation, dissection and blocks

Sampling: margins

- Proximal and distal resection margins: can be sampled parallel or perpendicular to the margin, depending on the site and type of the lesion. Perpendicular blocks allow the distance from the lesion to be determined. Mesenteric and/or circumferential margins may be relevant in some cases and should be sampled if malignancy is suspected.[18,22,63,132] A more detailed description of the approach to the mesenteric/circumferential (non-peritonealised) margins is available in the College dataset for colorectal cancer.[2]
- If sutures are present at the margin, they should be removed before sampling. If staples are present along the margin, the stapled tissue should be detached. The stapled tissue cannot be sampled.
- In some circumstances, there is no evidence that sampling of proximal and distal margins is of value.[63] In other situations (e.g. Crohn's disease) the evidence conflicts.[18,132]

Sampling: lesions

- In general it is convenient to sample sequentially (i.e. from proximal to distal or distal to proximal).[18] A careful block record is advised, comprising a list of labelled blocks as a minimum, with a corresponding line diagram or annotated photograph where appropriate.
- Longitudinal blocks (perpendicular to mucosal folds) are usually preferable to transverse.[22]
- Sample focal lesions, e.g. infarcts, perforations, strictures and abscesses, according to their size and number.[22]
- Diffuse abnormalities, e.g. erythema, loss of folds and inflammatory polyposis, are ideally sampled at intervals of 100 mm or less.[22]

- If no macroscopic lesion is present, at least two blocks are advised, depending on specimen size and indication. If there is a risk of dysplasia, e.g. in a patient with inflammatory bowel disease (IBD), and no macroscopic lesion is seen, samples at intervals of 100 mm or less are advised.[18,22]
- Samples of macroscopically normal bowel may be informative, e.g. Crohn's disease.[22]
- Blocks of the junction between normal and abnormal bowel may be helpful, e.g. ulcerated or ischaemic mucosa.[22]
- Mucosal nodules, polyps or irregular areas that might represent dysplasia should be thoroughly sampled, especially if the risk is high (e.g. in IBD).[22]
- Sampling should demonstrate the deepest extent of macroscopic changes and the relationship of a lesion with the serosal surface and any nearby margins, if these are likely to be relevant.

Sampling: adherent organs

Sample to show any connection, e.g. fistula, diverticulum. A large (wholemount) block may be useful if a clearer picture of complex anatomical relationships is needed. Sampling of the resection margins of adherent organs may be appropriate.

Sampling: lymph nodes

Representative lymph nodes are advised, as they may show pathological changes which are absent from, or less obvious in, the alimentary tract itself.[22] If neoplasia is suspected, retrieve all regional nodes.[2] A bisected or serially sliced node should not share a cassette with another node, especially if neoplasia is suspected. The number of nodes and pieces in each cassette should be recorded.

Sampling: appendix, ileocaecal junction and mesentery

The tip and body of the appendix should be sampled, and it may be appropriate to submit the entire appendix. A block of the ileocaecal junction may be informative, particularly in cases of IBD. It may be useful to take one or more blocks of mesentery, in a plane likely to demonstrate blood vessels. This is advisable if ischaemia is noted or suspected.[22]

4.2.2 Macroscopic description

Specimen type

Small bowel resection/right hemicolectomy/subtotal colectomy/total colectomy/sigmoid colectomy/anterior resection/abdominoperineal resection, etc.[22]

Dimensions of specimen (millimetres)

Length of ileum, appendix, colon, rectum, and anal canal. Maximum diameter or range of diameters, if appropriate. Site of peritoneal reflection in rectum.

Bowel: external surface

- Perforations and defects in wall: record number, location, size, and distance from nearer margin. Consider the possibility that these are artefactual or iatrogenic.
- Other focal serosal changes, e.g. puckering, adhesions and strictures: record appearance, size, and location.
- Note fat wrapping, exudate, congestion and pneumatosis (thin walled cysts or bubbles).[133,134]
- Look for evidence of trauma.
- Note adhesions to bowel or to other organs.

- Note Meckel's diverticulum. This is usually located on the antemesenteric border.
- Record presence of any staples.

Opened bowel

- Lumenal contents, e.g. blood, foreign material.
- Diffuse mucosal changes, e.g. erythema, cobblestoning, loss of mucosal folds, pseudomembranes. Record extent and relationship with nearer margin.
- Note evidence of trauma, e.g. perforation, foreign object. Take photograph if appropriate.
- Focal mucosal lesions, e.g. nodules, ulcers, haemorrhage, polyps: record number, size, appearance, distance from nearer margin and the state of the adjacent wall/circumferential margin/serosal surface.[22]
- Stricture, fibrosis, diaphragms: number, location, length, degree of narrowing of lumen, sacculation of bowel, distance from nearer margin.
- Diverticula: approximate number, perforation, abscess.[22]
- Ischaemia: length of the affected segment(s) and distance from resection margins. Seek underlying lesions, e.g. adhesion, extrinsic compression, diverticular disease, intussusception, tumour.
- Obstructive colitis occurs at a variable distance proximal to an obstructing lesion.[7,50] The latter may remain *in situ* in the patient.
- Volvulus: has usually already been corrected surgically once the specimen is received. Signs of ischaemia may be seen.[22]
- Diversion proctocolitis: may show diffuse mucosal erythema, haemorrhage, nodularity, granularity and flattening. A history is needed.[135,136]
- Fistula/abscess: record location and relationship with external surface or with attached organ.
- Appendix: describe external and cut surfaces, or appendix stump.
- Attached organs: describe appearance, relationship with bowel, and presence of fistula, diverticulum, abscess or tumour.
- Mesentery: note haemorrhage, fat necrosis, cystic change, tumour, etc.

4.2.3 Report and microscopic description

Indications for surgery

These include ulceration, haemorrhage, stricture, obstruction, perforation, trauma, ischaemia, intussusception, volvulus, vascular anomaly, diverticular disease, and IBD (e.g. if severe, refractory to treatment, or complicated by dysplasia).

Report

- Proximal and distal margins: record all abnormalities at margins, particularly ischaemia. If there is an abnormality close to a margin, the approximate distance from the margin should be recorded.
- Lymph nodes: record histology, especially specific features such as granulomas.
- Appendix: describe histology, including involvement by IBD and incidental lesions.
- Mesenteric vessels: note thrombosis, vasculitis, atheroma, abnormalities of wall, etc.

Specific conditions

- Diverticula: confirm diverticula. Record complications, e.g. peridiverticular fibrosis, abscess, perforation. Crohn's-like transmural changes can occur. Diverticular colitis may mimic IBD (especially ulcerative colitis).[94]
- Meckel's diverticulum: describe lining (small intestinal/gastric/pancreatic, etc.).[22,50]
- Volvulus: note associated ischaemia, perforation, melanosis and fibrosis.
- Diversion proctocolitis: can only be diagnosed if the clinical history is known. May mimic IBD.[134-136] Granulomas can occur. Inflammation tends to be more severe in the setting of ulcerative colitis than in other settings.[134-136]
- Motility disorders: exclude other common causes of symptoms. Assess myenteric and submucosal ganglion cells, myenteric plexus, muscularis propria/muscularis mucosae, vasculature. Choice of special stains and immunohistochemistry depends on local expert. Possible myopathies and neuropathies should be referred to a specialist pathologist.

LARGE GI RESECTION SPECIMENS: RECOMMENDATIONS

The specimen may be pinned to a corkboard, or stabilised in another way, and fixed in a volume of formalin at least sufficient to cover it for at least 48 hours after opening.

Serial transverse slices may help to identify focal mural lesions, e.g. diverticula. Otherwise, longitudinal blocks are usually more appropriate.

Sampling of proximal and distal margins is recommended *[Level of evidence – GPP].* This is particularly important for ischaemia. The circumferential (non-peritonealised) margin should be sampled if malignancy is suspected.

Ink relevant margins if there is a possibility of neoplasia.

If lymph nodes are included, they should be sampled.

A careful block record is advised.

Suspected motility disorders should be referred for a specialist opinion.

4.3 Ischaemic bowel: additional comments

4.3.1 Report and microscopic description

Indications for surgery

These include removal of non-viable tissue and management of symptoms.

Considerations

The cause of the ischaemia may already be known. Occasionally, pathological examination reveals the cause, e.g. vasculitis.[137] Ischaemic changes may be superimposed on other conditions, e.g. IBD, diverticular disease, neoplasia, obstructing lesion. They may even precede some conditions, e.g. IBD.[138] The status of the resection margins is very important.

Report

- Evidence of acute ischaemia (e.g. haemorrhage, necrosis) or reparative/chronic changes (e.g. fibrosis).[137]
- Severity and depth of acute ischaemic changes/infarction (e.g. mucosal, transmural).
- Abnormalities of mesenteric vessels, e.g. thrombus, atheroma, vasculitis.
- The viability of the resection margins should always be recorded.

4.4 Vascular malformation and angiodysplasia: additional comments

4.4.1 Preparation, dissection and blocks

Opening and fixation

If the specimen is received fresh, it may be possible to inject the vasculature with a contrast medium, e.g. barium sulphate, prior to opening. It can then be distended with formalin, fixed and X-rayed.[137] However, the specimen is usually received fixed.

Sampling

Sample areas of erythema, haemorrhage, mucosal flattening and discoloration, because macroscopic changes of angiodysplasia may be focal or subtle.[137]

4.4.2 Report and microscopic description

Indications for surgery

These include gastrointestinal haemorrhage and its consequences (e.g. anaemia). Imaging may have suggested angiodysplasia.

Report

- Histology may confirm the diagnosis and help exclude other causes of bleeding.
- Describe vascular abnormalities. Note depth and extent of vascular changes.
- Record evidence of ischaemia.
- Other lesions may be associated with angiodysplastic changes, especially diverticula. Secondary “angiodysplasia” is more common than primary vascular anomalies.[139]

4.5 Inflammatory bowel disease (large intestinal resections): additional comments

4.5.1 Macroscopic description

Opened bowel

Consider whether the macroscopic changes favour ulcerative colitis (UC) (e.g. continuous disease from rectum proximally, sharp transition between abnormal and normal mucosa) or Crohn’s disease (e.g. discontinuous disease, cobblestoning, strictures, fat wrapping). A discontinuous caecal “patch” of disease can occur in new or established UC.[17,140,141] Treated chronic disease may fail to conform to classical patterns *[Level of evidence – C].*[86-89]

4.5.2 Report and microscopic description

Indications for surgery

These include refractory or severe disease and dysplasia/carcinoma.

Report

- Chronic inflammation: record extent and distribution and whether transmural or mainly mucosal.
- Active inflammation (cryptitis, crypt abscesses): record extent and severity.
- Ulcers: record type and depth (layer affected, including superficial half or deep half of muscularis propria).

- Granulomas: note whether crypt rupture-related (cryptolytic) and whether necrotising or non-necrotising. Request ZN stain if appropriate.
- CMV inclusions may be present. Consider immunohistochemistry.[42,44]
- Dysplasia: presence or absence; if present, classify as low grade or high grade.

Classification of inflammatory bowel disease (IBD) in resections

- Crohn's disease (discontinuous involvement, ileal disease, deep fissure ulcers, non-cryptolytic granulomas, transmural chronic inflammation away from areas of ulceration, etc.).[22,45,134,142-144]
- UC (continuous involvement from rectum proximally, diffusely abnormal mucosal architecture, mucosa-predominant changes, etc.).[22,45,134]
- IBD which cannot be classified further. If the term "indeterminate" colitis is used, it should be confined to resection specimens with definite IBD in which a diagnosis of either UC or Crohn's disease cannot be made.[45,83,145] It should not be used to mean "colitis, cause unknown. "[17] Unfortunately, this term has different meanings for different pathologists and clinicians, may cause confusion, and is overused *[Level of evidence – D].*[10,83,97,144,146] The term "IBD, unclassified" may be preferable (although it is currently used mainly for biopsies rather than for resections).[10,83,84] This is a difficult area of diagnosis, which requires full clinicopathological discussion. Assessment may benefit from the input of more than one pathologist. The quality of interpretation is also likely to be enhanced by clinicopathological meetings.[10,47,48]
- If the features favour UC or Crohn's disease but do not allow a definite diagnosis to be made, expression of a preference (e.g. "IBD, with features favouring UC over Crohn's disease") is more useful than a label of "indeterminate" colitis.
- Classification of type depends not only on current and preceding histology but also on macroscopic appearances and clinical findings.[10,17,19,46,134]

COLORECTAL RESECTIONS FOR INFLAMMATORY BOWEL DISEASE: RECOMMENDATIONS

The report should record: the extent and distribution of chronic inflammation; the severity of activity; the greatest depth of ulceration; the characteristics of any granulomas; and the presence/absence and grade of dysplasia.

Histological features that strongly favour Crohn's disease over UC are: non-cryptolytic granulomas; and transmural chronic inflammation (away from areas of ulceration). Other features favouring Crohn's disease include: discontinuous involvement; ileal inflammation; and deep (rather than superficial) fissure ulcers.

Histological features that favour UC over Crohn's disease include: continuous involvement from the rectum proximally; diffusely abnormal mucosal architecture; and mucosa-predominant inflammatory changes.

Anatomical discontinuity of disease is not uncommon in longstanding/treated UC *[Level of evidence – C].*

A discontinuous caecal "patch" of disease can occur in new or established UC.

IBD which cannot be classified further in resections can be termed "indeterminate colitis" or "IBD unclassified" (IBDU).

The quality of interpretation is likely to be enhanced by clinicopathological meetings *[Level of evidence – GPP].*

4.6 Small bowel resection for stricture/Crohn's disease: additional comments

4.6.1 Report and microscopic description

Indications for surgery

These include relief of symptoms or of obstruction; identification of the cause; and removal of non-viable bowel.

Considerations

A small bowel stricture might be due to ischaemia, Crohn's disease, drugs (particularly NSAIDs), infection, radiation, endometriosis, previous surgery, extrinsic compression, neoplasia or other causes.[22,106] Cryptogenic forms of ulceration and stricturing have been reported.[147]

Report

- Record and describe ulceration, inflammation, fibrosis and granulomas.
- Seek evidence of Crohn's disease.
- Look for evidence of trauma, ischaemia, endometriosis (glands, stroma, and haemorrhage), radiation damage (needs appropriate history), NSAID-induced enteritis (including diaphragms) or specific infections.
- Obtain a full clinical history before concluding.

4.7 Intussusception: additional comments

4.7.1 Preparation, dissection and blocks

Sampling *[Level of evidence – GPP].*

Apex of intussusception, including possible causative lesion. Demonstrate intussusception if possible. Margins are important if there is ischaemia.

4.7.2 Macroscopic description

Dimensions

Length of intussusception; distance of apex from distal resection margin; distance of neck from proximal margin; diameter of lumen.

Opened bowel

- Type of intussusception: ileoileal/ileocolic/colocolic.[148]
- Appearance of the mucosa; state of the underlying wall; ischaemia.[22]
- Look for a causative lesion: foreign body, polyp, diverticulum, duplication, various tumours, ileal lymphoid hyperplasia, appendix.[50,148,149] In young children, a cause is often not found.[149]

5 Tissue pathways: pancreatobiliary resection specimens

5.1 Bile duct resection

5.1.1 Preparation, dissection and blocks

Opening and fixation

It may be useful to ink the proximal and distal margins and the external surface if neoplasia is suspected.[22,150] Distinction of circumferential resection margins (posterior and left lateral) from serosal surfaces (anterior and right lateral) is often difficult.[33,150]

Minimum sampling *[Level of evidence – GPP].*

- One approach is to take the proximal or distal resection margin *en face* followed by sequential transverse slices as far as the other resection margin, especially if there is any suggestion of neoplasia.[33,150] If there is a lesion close to a margin, perpendicular (radial) sections of this margin may be more informative than transverse (*en face*).[33]
- Focal lesions: take at least one block, which should show the depth of the lesion and its distance from the external surface.
- Gall bladder (if included): if no focal lesion is present, treat as routine cholecystectomy. If a lesion is seen, take multiple sections.
- All lymph nodes should be taken.[150]

5.1.2 Specimen description

- Specimen type: specify what is included, e.g. common hepatic duct, cystic duct, common bile duct, etc., and record the presence of a stent. The surgeon may be able to assist if orientation is difficult.
- Dimensions of specimen (millimetres): length of each portion and total length of specimen; maximum diameter or range of diameters, if appropriate; dimensions of attached organs or tissue.
- Appearances: record any focal lesions (e.g. strictures, perforation, nodules) and their site, size, and relationship with margins; note cysts or cystic dilatations.

5.1.3 Report and microscopic description

Indications for surgery

These include: management of symptoms; removal of stricture or choledochal cyst;[150] abnormal imaging; and exclusion of neoplasia.

Report

- Record features suggestive of sclerosing cholangitis, follicular cholangitis,[151] or IgG4-associated cholangitis.[152]
- Inflammatory epithelial atypia can be severe, especially proximal to an obstruction or after stent insertion.
- Deeply located periductal glands can mimic neoplasia and *vice versa*.[107] Their lobular arrangement may help to distinguish them from neoplasia.

5.2 Cholecystectomy for non-neoplastic disease

5.2.1 Preparation, dissection and blocks

Opening and fixation

Open the gall bladder longitudinally along the serosal surface,[22,33] avoiding disruption of the cystic duct margin and gall bladder bed resection margin. Ink the gall bladder bed margin if neoplasia is suspected.[33]

Sampling *[Level of evidence – GPP].*

- Cystic duct margin *en face*.[150] This may be located adjacent to a clip. Ensure that it is identifiable after processing (e.g. histologically distinct section/inked section/section in separate cassette).
- Cystic duct lymph node.[22,150] This is often present, but may be small.
- At least one section each of neck, body and any focal lesion.[150] This might include a full transverse "ring" of gallbladder before opening.
- Attached organ, to characterise relationship with gall bladder.
- Polyps or lesions suspicious of neoplasia: sample thoroughly.[22,150]

5.2.2 Specimen description

Dimensions of specimen (millimetres)

Length and maximum diameter of gall bladder.[22,150] Dimensions of any attached organs.

Appearances

- Record whether intact, opened or fragmented on receipt.[22,33]
- Note perforations or defects in wall, serosal haemorrhage, etc.[22,150]
- Contents: note stones (number, range of sizes), bile and mucus.[22,150]
- Record mucosal changes, e.g. cholesterolosis, ulcer, polyp.[22,150]
- Record thickness of gall bladder wall.[33,150]
- Note abscess, fistula and diverticulum. Record site, size, and relationship with external surface or attached organ.
- Polyp or tumour: describe and record site, size, depth, macroscopic features of a suspected malignant tumour (polypoid/ulcerating/plaque-like/infiltrative) and relationship with peritoneal surface and hepatic gall bladder bed resection margin (see ~~relevant~~ RCPath dataset).[33,34]

5.2.3 Report and microscopic description

Indications for surgery

These include management of symptoms and characterisation of lesions seen on imaging.

Report

- Chronic cholecystitis/acute cholecystitis/features of both.[22,133,150] Rokitansky Aschoff sinuses can mimic carcinoma (both macroscopically and microscopically).[133]
- Cystic duct lymph node.
- Describe attached tissue, e.g. liver.

- If dysplasia is found, extra blocks are required to exclude higher grade dysplasia/malignancy. The entire gall bladder should be examined if dysplasia is high grade.[153] Involvement of the resection margin should be recorded *[Level of evidence – GPP].*
- Carcinoma: see RCPath dataset.[33]

GALL BLADDER: RECOMMENDATIONS

Open along the serosal surface.

Sample cystic duct margin. Take lymph node (if present). Sample gall bladder body and any focal lesions.

If high grade dysplasia or malignancy is found, examine the entire gall bladder histologically. If low grade dysplasia is found, examine additional blocks.

5.3 Pancreatic resection for non-neoplastic disease

5.3.1 Preparation, dissection and blocks

Opening and fixation

Ink resection margins and other external surfaces if neoplasia is suspected.[6,112] Slice the pancreas and open the bowel to ensure fixation.

Sampling (Whipples specimen)

- Resection margins of bile duct/hepatic duct, duodenum or stomach, and pancreas.[112]
- All focal lesions. At least two representative blocks of pancreas if no focal lesion, depending on clinical indication. Usually, more blocks are required, and are particularly important if neoplasia is suspected or if findings do not correlate with imaging. Large blocks may be useful *[Level of evidence – GPP].*
- All peripancreatic lymph nodes, especially if neoplasia is a possibility.
- If there is a bile duct lesion, serial sequential bile duct blocks are advisable.
- All margins and surfaces if a suspicious lesion is seen.[6]
- Ampulla of Vater with adjacent pancreas.

Sampling (distal pancreatectomy)

- Proximal pancreas resection margin *en face*, unless the lesion is close to this margin in which case perpendicular (radial) sections may be more informative.[112,150]
- All focal lesions. At least two representative blocks of pancreas if no focal lesion, depending on clinical indication. Usually, more blocks are required, and are particularly important if neoplasia is suspected or if findings do not correlate with imaging.
- All peripancreatic lymph nodes, especially if neoplasia is a possibility

Sampling (Beger, Frey or Puestow procedure)

- Embed whole specimen (often received in fragments) to exclude malignancy.[112]

5.3.2 Specimen description

Specimen type

Pylorus-preserving pancreatoduodenectomy/Whipple's resection (partial gastrectomy also included)/distal pancreatectomy, specimens following Beger, Frey or Puestow procedure.[112]

Dimensions of specimen (millimetres)

Pancreas in three dimensions. Extrapancreatic bile duct length. Bowel length.[6,112]

Appearances

- Pancreas: note fibrosis, calcification, fat necrosis, haemorrhage.[112,150,154]
- Focal lesions (nodules, cysts, abscesses): record location, size, and relationship with margins.
- Small bowel: note congestion, stricture, nodules and mucosal changes.
- Tumour: refer to RCPath dataset.[6]

5.3.3 Sections and stains

Immunohistochemistry

IgG4 may be useful for supporting a diagnosis of autoimmune pancreatitis *[Level of evidence – C].* A ratio of IgG4 to IgG higher than 40% may be used to support the diagnosis.[110] However, diagnosis is based on a combination of imaging, clinical, serological and pathological findings.[110-112]

5.3.4 Report and microscopic description

Indications for surgery: examples

- Resection of a tumour or suspected tumour (e.g. suspicious imaging findings).
- Severe chronic pancreatitis
- To control symptoms or relieve duct obstruction.

Report

- Features of chronic pancreatitis, e.g. chronic inflammation, fibrosis, atrophy. These changes can mimic neoplasia.[107,112,114,115,154] Consider autoimmune pancreatitis (storiform fibrosis, dense lymphoplasmacytic inflammation and obliterative phlebitis).
- Note ectopic/heterotopic tissue.
- Neoplasms: refer to the RCPath dataset and other standard texts.[3,6,7,107,112]

5.4 Pancreatic resection: cysts

5.4.1 Preparation, dissection and blocks

Opening and fixation

Ink external surfaces, especially if suspicious or focal lesions are present.[22,112]

Sampling

One block per 10 mm diameter, especially if neoplasia suspected.[22,150] Sample any focal changes, nodules, or more solid areas.[22,150] Consider sampling the entire wall of the cyst to identify (or exclude) an epithelial lining *[Level of evidence – GPP].*[112]

5.4.2 Specimen description

- Specimen type: Whipples/distal pancreatectomy/intact cyst/opened cyst.
- Dimensions of specimen (millimetres): diameter/maximum dimension of cyst.[22,112] Size of attached pancreas/other tissue.
- Appearances: external surface (smooth/nodular etc.); contents (mucoid/serous/haemorrhagic); lining (smooth/ulcers/nodules/papillary areas); wall (consistency, nodules, calcification); attached pancreas (fibrosis, calcification, abscess, relationship with cyst).[22,112,150]

5.4.3 Sections and stains

Additional stains

Mucin stains and immunohistochemistry may help characterise the lining. Immunohistochemistry may also help characterise the subepithelial stroma, where relevant.[22,112,154]

5.4.4 Report and microscopic description

Indications for surgery

These include exclusion of neoplasia and management of symptoms.

Report

- Describe lining: endothelial cells, no epithelium, or epithelium (flat/cuboidal/squamous/columnar mucinous/columnar ciliated/papillary). Presence/absence and grade of dysplasia.
- Look for microorganisms (e.g. Echinococcus in a hydatid cyst).
- Underlying stroma: fibrous/ovarian-type/pancreatic tissue/invasive tumour.
- A wide variety of cysts (non-neoplastic vs neoplastic, non-epithelial vs epithelial) may occur in the pancreas.[112]

PANCREATIC CYSTS: RECOMMENDATIONS

Sample papillary, mucoid and solid areas in the cyst wall.

Consider embedding the entire wall of the cyst to identify or exclude epithelial lining.

6 Criteria for audit of tissue pathway

Audits of the value and applicability of this pathway may be useful. A template for audit of colorectal biopsies taken for the diagnosis and assessment of IBD is currently available on the College website. Other possible audits could explore the completeness of recording of data items in histopathology reports, ranges of turnaround times, or compliance with the College's key performance indicators.

Content and timeliness of histopathology reports should be audited against the recommendations in these guidelines.

The following are recommended by the RCPath as key performance indicators (KPIs) – see *Key Performance Indicators – Proposals for implementation* (July 2013) on https://www.rcpath.org/resource-library-homepage/clinical-effectiveness/key-performance-indicators-kpi.html:

- Cancer resections must be reported using a template or proforma, including items listed in the English COSD which is, by definition, core data items in RCPath cancer datasets. English Trusts were required to implement the structured recording of core pathology data in the COSD by January 2016.

  Standard: 95% of reports must contain structured data.

- Histopathology cases that are reported, confirmed and authorised within seven and ten calendar days of the procedure.

  Standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

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Appendix A 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 B AGREE compliance monitoring sheet

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

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Forward, 1
2 The health question(s) covered by the guideline is (are)specifically described	1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword,1
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	N/A
6 The target users of the guideline are clearly defined	Foreword,1
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	1
12 There is an explicit link between the recommendations and the supporting evidence	Throughout
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	1–6
16 The different options for management of the condition or health issue are clearly presented	1–5
17 Key recommendations are easily identifiable	1–5
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	1–6
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	6
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword