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

Standards and datasets for reporting cancers

Dataset for histopathological reporting of colorectal cancer

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Authors: Professor Maurice B Loughrey, Belfast Health and Social Care Trust and Queen's University Belfast
Professor Philip Quirke, Leeds Teaching Hospitals NHS Trust and Leeds University
Professor Neil A Shepherd, Gloucestershire Hospitals NHS Foundation Trust and University of Exeter

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The Royal College of Pathologists
6 Alie Street. London E1 8QT Tel: 020 7451 6700
Fax: 020 7451 6701
Web: www.rcpath.org

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Foreword

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

Each dataset contains core data items (see Appendices C–H) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Dataset) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 90% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult on this document:

- Association of Clinical Pathologists
- Association of Coloproctology of Great Britain and Ireland
- British Society of Gastroenterology – Pathology Section
- British Division of the International Academy of Pathology
- National Cancer Research Institute – Colorectal Cancer Subcommittee
- NHS Bowel Cancer Screening UK – Pathology Group.

The information used to develop this dataset was obtained by undertaking a search of updates to international tumour grading, staging and classification systems and by electronically searching medical literature databases (PubMed and Ovid Medline) for relevant research evidence, systematic reviews and national or international publications on colorectal cancer up until June 2022. Published evidence was evaluated using modified SIGN guidance (see Appendix I). Unless otherwise stated, the level of evidence corresponds to ‘Good practice point (GPP): Recommended best practice based on the clinical experience of the authors of the writing group’. Consensus of evidence in the guideline was achieved by expert review. No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset. Gaps in the evidence were identified by College members via feedback received during consultation.

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

consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Professional Guidelines team, representatives of the Lay Advisory Group and Working Group on Cancer Services. It was placed on the College website for consultation with the membership from 9 January to 6 February 2023. All comments received were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The authors have no conflicts of interest to declare.

1 Introduction

Careful and accurate pathology reporting of colorectal cancer resection and local excision specimens is vital because pathology reports are used to:

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

In colorectal cancer, the key reasons for high-quality pathology reporting include the following:

- to confirm that radical surgery was not necessary for cancers treated by local excision
- to confirm that radical surgery was necessary and to place the patient in a correct disease stage for an accurate prognosis and inform postoperative therapy (see below)
- to assess the effects of preoperative therapy[1,2]
- to allow audit of diagnostic and surgical procedures in relation to clinical outcomes, avoidance of selection bias,[3,4] identification of good surgical practice[3–5] and comparison of patients in clinical trials
- to facilitate improvements in the quality of rectal and colonic cancer surgery by photographing and grading the planes of surgical excision and recording the frequency, quality and type of abdominoperineal excisions (APE).[6,7]

Age and comorbidity permitting, patients who have lymph node involvement (pN1 and pN2) or tumour deposits (pN1c) are likely to receive adjuvant chemotherapy, which is of probable benefit and mildly toxic.[8–11] Dependent on the extent of high-risk features, patients will be stratified to three or six months of chemotherapy. Those without lymph node metastatic disease but with adverse pathological features (venous invasion, perforation, peritoneal

involvement, margin involvement or extensive local spread) may also be offered adjuvant therapy for small but probable benefit.[9]

Patients with rectal adenocarcinoma and involvement of the circumferential resection margin (CRM) are at high risk of local recurrence,[12–14] and may receive preoperative or postoperative radiotherapy or chemotherapy, which are toxic but decrease the likelihood of this unpleasant and nearly uniformly fatal complication.[15,16] The frequency of CRM involvement found may indicate the quality of rectal cancer surgery being performed.[5,6,17,18]

Communication of pathology information to the patient and the multidisciplinary team (MDT) is essential for good quality clinical management. Each department should have an appropriately sized team of lower gastrointestinal pathologists, at least one of whom should attend colorectal cancer MDT meetings (MDTM). All reporting pathologists should provide pathology reports that are accurate, complete, understandable and timely. The use of proformas has been demonstrated to facilitate these requirements[19,20] and their use is strongly recommended, supplemented as necessary with free text. Local MDTM protocols may require reporting of additional pathology information or use of alternative scoring systems, but these should be supplementary to, rather than in place of, the requirements of this dataset. This allows data integration into standardised databases and comparison of data between cancer populations.

Tumours arising in the appendix or anal canal should be reported according to the respective RCPath dataset and guidance.[21,22]

Many colorectal adenocarcinomas demonstrate focal neuroendocrine differentiation, on morphology and/or immunohistochemistry; these should be regarded as 'pure' adenocarcinomas for the purposes of this dataset. Tumours demonstrating purely neuroendocrine differentiation, or less than 30% adenocarcinoma morphology, are regarded as 'pure' neuroendocrine tumours and should be reported using the current RCPath *Dataset for Histopathological Reporting of Neuroendocrine Neoplasms of the Gastroenteropancreatic Tract.*[23]

Mixed epithelial tumours with greater than 30% representation of morphologically and immunohistochemically recognisable neuroendocrine and non-neuroendocrine components are classified as mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN). This term replaces the older terminology of mixed adenoneuroendocrine carcinoma (MANEC), recognising that the non-neuroendocrine component does not have to be an adenocarcinoma.[23] This is a heterogeneous group of tumours and both neuroendocrine and non-neuroendocrine components can show variable morphological features, with a full spectrum of differentiation encountered. MiNENs are summarily staged according to the adenocarcinoma system under TNM 8 but should be reported with a detailed description of the appearances and extent of invasion of the two neoplastic components in order to provide the clinician with the information pertinent to prognosis and selection of the most appropriate therapy.

1.1 Target users and health benefits of this guideline

The target primary users of the dataset are consultant cellular pathologists, trainee cellular pathologists, biomedical scientists and also, by extension, the suppliers of IT products to laboratories. Secondary users are surgeons, radiologists, oncologists, specialist screening practitioners, NHS bowel cancer screening programmes, cancer registries and the National Cancer Registration and Analysis Service. Standardised cancer reporting and MDT working reduce the risk of misdiagnoses and help ensure clinicians have all the relevant pathological information required for tumour staging, patient management decisions and prognosis prediction. Collection of standardised cancer-specific data also provides information for healthcare providers and epidemiologists and facilitates international benchmarking and research.

1.2 Changes to the 5th edition

Since the previous edition of this guidance was published, the International Collaboration on Cancer Reporting (ICCR) has produced new, international consensus guidelines for the pathology reporting of colorectal cancer surgical resection and local excision specimens.[24] In addition, a new World Health Organization (WHO) classification of tumours of the colon and rectum (5th edition) was published in 2019 and NHS bowel cancer screening guidelines were updated.[25] Where possible, the recommendations from these have been adopted, to facilitate international data comparison.

The specific changes made to the surgical resection dataset proforma from the 4th edition are:

- additional details added regarding desirable clinical information to be provided on the pathology request form (section 2)
- more precise guidance has been added with respect to macroscopic assessment of the maximum tumour diameter (section 5.1.1)
- use of the term 'tumour perforation' has been clarified. It is now recommended that this term is reserved for the biological setting, with different descriptive terminology applied in the event that a full thickness defect in the specimen arises intra-operatively, to avoid confusion (section 5.1.1)
- the WHO classification of tumours of the colon and rectum (5th edition, 2019)[25] is recommended and appropriate detail describing histological subtypes has been provided (section 5.2.1)
- assessment of grade of differentiation has been changed, for consistency with the latest WHO classification and ICCR guidelines. It is now recommended that grading should be based on the least differentiated tumour component, although this recommendation is made without good evidence (section 5.2.2)
- additional detail has been provided to help assess T stage in various uncommon clinicopathological scenarios (section 5.2.3)
- the importance of assessing and reporting regression within lymph nodes following pre-operative therapy has been described (section 5.2.4)
- additional detail has been provided to help interpret CRM status in various clinicopathological scenarios (section 5.2.5)
- additional detail has been provided to help interpret tumour deposits in various clinicopathological scenarios (section 5.2.7)
- the recommended Talbot definition of venous invasion has been modified, taking into consideration that red blood cells may be seen within lymphatic spaces and that the vein lumen and endothelial lining may be obliterated by tumour. Therefore, a rounded tumour nodule surrounded by a rim of muscle or identifiable elastic lamina is considered sufficient for venous invasion (see section 5.2.8)
- the section on 'Additional investigations' has been expanded and updated to reflect considerable ongoing advances in molecular pathology applied to colorectal cancer in recent years, with inclusion of representative 'molecular block(s)' within the block index and assessment of carcinoma content within this block(s), to facilitate subsequent molecular testing (section 7)
- assessment of tumour budding has been added as a new, core item to be applied to pT1 colorectal cancers within all forms of local excision specimen (section 10.4). Budding assessment remains a non-core item within surgical resection specimens, pending further evidence

- minor comments have been added to assessment of margin status in local excision specimens, reflecting the broader range of local excision specimens now routinely encountered (section 10.5)
- additional detail has been provided to help report diagnostic biopsy specimens (section 11)
- it is now recommended that the median number of lymph nodes examined should be at least 15. The previous standard of 12 has been increased, reflecting improved modern surgical and pathology practice.

2 Clinical information required on the specimen request form

While the nature of the resection and the site of the tumour are usually obvious to the pathologist from the specimen that is submitted to the laboratory, it is good practice for this to be confirmed with the specimen request form. A diagram of the surgical procedure can be extremely valuable in complex specimens. It is also important for the pathologist to know:

- if the tumour has been detected as part of a bowel cancer screening programme
- if the patient is in a clinical trial (with relevant details)
- the histological type of tumour if known (with details of the diagnostic biopsy)
- if there is a history of inflammatory bowel disease or familial cancer
- the preoperative stage of the tumour
- whether or not preoperative therapy has been given, the date of start of therapy, when it finished and the nature of this (e.g. short course radiotherapy, long course chemoradiotherapy, short course radiotherapy followed by preoperative chemotherapy, the drugs used, and the dose and schedule of the radiotherapy); it is particularly important for the pathologist to know the precise site, including quadrant of the tumour, when this has apparently led to disappearance or significant regression of the tumour clinically. Note, going forward, preoperative therapy will be applicable to colonic as well as to rectal cancer
- if open, laparoscopic or robotic surgery has been performed
- the type and dissection plane of operation attempted, type of APE or type and depth of local excision
- if the specimen includes any tissue or organ not typically submitted within that specimen type, such as an en bloc resection of a segment of intestine, bladder wall or abdominal wall connective tissue
- if an iatrogenic specimen defect has arisen intra-operatively and if it occurred in vivo or ex vivo. This is especially important if involving the tumour site, to help the reporting pathologist to distinguish this from a biological perforation, which may influence staging, and to determine the likely clinical significance if any.
- if the patient is known to have a hereditary condition of importance in bowel cancer or which could affect treatment e.g. Lynch syndrome.

Pathologists should engage with surgical teams to maximise the provision of such information. Some information is fundamental to pathology reporting, such as whether or not and what type of preoperative therapy has been applied, and pathologists should strive to obtain all key information prior to reporting a case. If not provided on the specimen request form, such information may be available from electronic healthcare records.

3 Preparation of specimens before dissection

Most specimens are delivered to the laboratory in a fixed state. Immediately after surgery, they should be placed unopened, or opened and pinned to a board, in a large volume of formalin fixative. If a significant delay (>24 hours) is anticipated prior to transfer to the laboratory, for example when surgery is performed at the weekend, the specimen should be placed in formalin and refrigerated while awaiting collection, to minimise autolysis.

Specimens may be received fresh and unopened as soon as possible after surgical resection, for example in the settings of biobanking, whole genome or cancer panel sequencing. The latter may become more relevant to routine clinical practice and mandate, in some circumstances, fresh delivery of the specimen to the laboratory, as formalin fixation limits performance of some molecular assays.

4 Specimen handling and block selection[26,27]

The intact surgical specimen is first inspected externally to locate the tumour and the presence of any macroscopically obvious perforation recorded. It is important to note if the perforation is through the tumour or distant from the tumour; the latter is usually related to tumour obstruction.

For anterior resection (AR) and APE specimens, the plane of surgical dissection is evaluated by careful external examination of the specimen prior to dissection, and ideally photographs taken of the intact specimen to support this evaluation. The circumferential (non-peritonealised) surgical resection margin in the vicinity of the tumour is then inked or painted with a suitable marker (gelatin-based being our preference) to enable the subsequent identification of margin involvement. This margin represents the ‘bare’ area in the connective tissue at the surgical plane of excision that is not covered by a peritoneal surface. Its extent varies greatly according to the site of the tumour. Low rectal tumours will be completely surrounded by a circumferential, non-peritonealised margin, while upper rectal tumours have a non-peritonealised margin posteriorly and laterally (which should be inked) and a peritonealised surface anteriorly (which should not be inked) (Figure 1).

Tumours of the ascending and descending colons will usually also have a non-peritonealised margin posteriorly (which should be inked) and a peritonealised surface anteriorly (which should not be marked) (Figure 2). The transverse and proximal sigmoid colons are usually on a narrow mesentery, so tumours here have only a small area of readily identifiable non-peritonealised margin, which is typically well clear of the tumour. The extent of peritoneal covering of the caecum is prone to significant individual variation, requiring careful inspection to distinguish the boundary between the shiny, smooth peritoneal covering and the duller, more irregular, non-peritonealised margin. Caecal tumours may have none or a small or large associated non-peritonealised area. In this dataset, the term CRM will be used in preference to non-peritonealised margin, although this margin is clearly not fully circumferential at all sites.

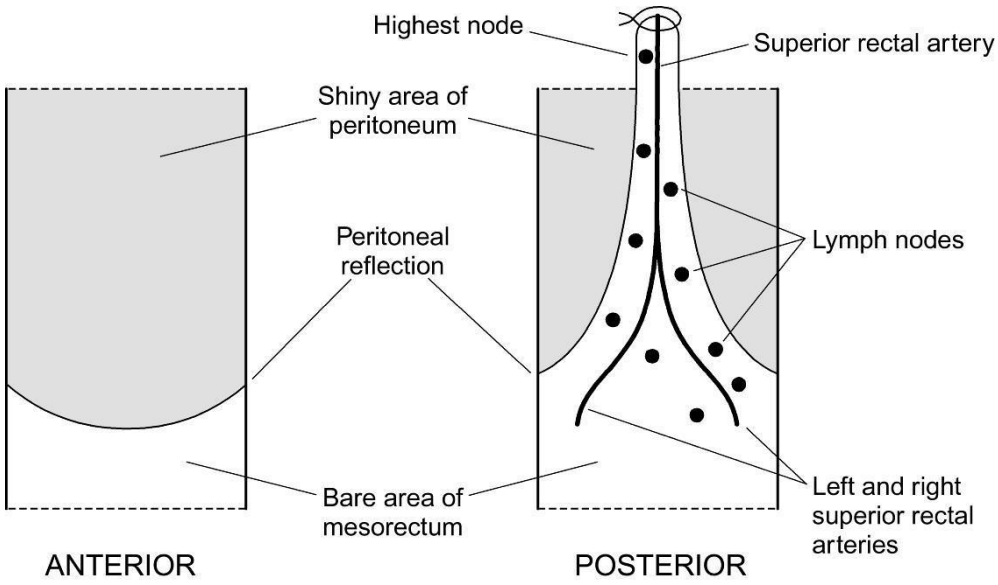


Figure 1. Diagrammatic representation of a resected rectum. Anteriorly the specimen is covered by peritoneum down to the peritoneal reflection and only the non-shaded area below this is the circumferential (non-peritonealised) margin that should be painted for assessment of margin involvement by tumour. Posteriorly, the circumferential margin extends upwards as a triangular-shaped bare area containing the main vessels that continues as the sigmoid mesocolon.

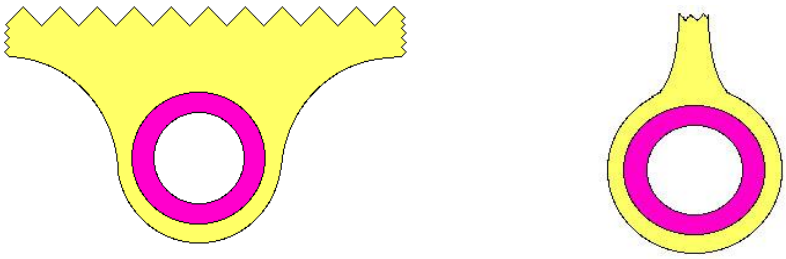


Figure 2. Diagrammatic cross sections of the ascending colon (left) and sigmoid colon (right) for comparison. The ascending colon has a broad circumferential (irregular) margin posteriorly while the sigmoid colon is suspended on a narrow mesentery and has a very small circumferential margin posteriorly.

After marking the CRM (but not any peritonealised surface), the specimen is opened anteriorly, apart from a segment extending 1–2 cm above and below the tumour. This is left intact to avoid any subsequent confusion over whether the peritoneal surface or CRM is involved, as well as facilitating comparison with preoperative imaging. A foam or absorbent paper 'wick' is then passed through the residual lumen at the tumour site to aid fixative permeation. Some pathologists prefer to open the bowel at the level of the tumour also, especially when the lesion is small and polypoid (non-annular). This will also facilitate sampling of fresh tumour tissue for biobanking or other purposes. This approach is acceptable provided that care is taken to ensure that this sampling does not compromise a proper assessment of the key data items, notably involvement of the serosa and the CRM, although it may compromise comparison with radiological imaging due to the introduction of distortion on fixation. The opened specimen may be loosely pinned to a cork board and immersed in an adequate volume of formalin. It is strongly recommended that resection specimens are allowed to fix for a minimum of 24–48 hours before further dissection and block taking; this facilitates subsequent thin transverse slicing through the tumour and the identification of lymph nodes.[28] Pinned specimens may be removed from the board after 24 hours and allowed to float free so as to avoid the risk of suboptimal fixation of tissue previously adjacent to the cork surface.

After the specimen is fixed, the macroscopic data items (described below) are recorded and the segment of bowel including the tumour, the intestine proximal and distal to the tumour and the attached mesentery are sectioned transversely at 3–4 mm intervals with a sharp knife to produce slices that include the tumour, the adjacent lymph nodes, the peritoneal surface and the CRM. It is recommended that these slices be laid out sequentially for inspection and photography, enabling a permanent record of the macroscopic appearances to be kept for presentation at the MDTM if required. Careful inspection will allow areas of macroscopic venous invasion (V2) and peritoneal involvement to be identified for sampling as well as measurement of the distance of tumour spread beyond the wall and the distance of tumour to the CRM. These images may be annotated to correspond with a block index on the final pathology report to facilitate review and MDTM presentation.

In addition to identifying, within the final pathology report, blocks that best demonstrate the key tumour features (T stage, venous invasion, possible tumour deposits etc.), a further block or blocks of tumour should be identified suitable for any subsequent immunohistochemistry, e.g. for mismatch repair (MMR) status, molecular testing and/or research. The optimal block for molecular testing will contain high overall tumour cellularity and a high proportion of viable tumour compared to non-tumour tissue. The block(s) identified for these purposes should not contain key tumour features that are not found in the other blocks and they should not be 'megablocks'. It is recommended that MMR status is established on the diagnostic biopsy rather than resection specimen, if available. Better fixation in biopsy material assists immunostaining interpretation, and the result will likely be available sooner, enabling clinical teams to make prompt decisions about possible trials of preoperative immunotherapy and chemotherapy.

If available, tumour sampling using 'megablocks' can be used, to facilitate accurate measurements and better radiological correlation. It is recognised, however, that this facility is not available in every laboratory, is more labour intensive than routine processing and that use of megablocks can cause downstream problems, for example in applying ancillary histochemical or immunohistochemical stains, or in cutting sections for DNA extraction. If megablocks are used, fewer blocks may be required but it should be ensured that an area of tumour has been sampled equivalent to using only conventional blocks.

The following standard blocks of tissue are recommended as a minimum sampling:

- at least the equivalent of five blocks of the tumour (or more for large tumours), if size permits, to include, where applicable:
  - the deepest tumour penetration into or through the bowel wall
  - involvement of the peritoneal surface
  - invasion of veins
  - involvement of any adjacent organs
  - blocks for immunohistochemical and/or molecular testing as described above
- if possible, a block to show the closest approximation of tumour to the CRM (either in continuity with the main tumour mass or closest discontinuous tumour). It is appreciated that at some sites this is not possible as the tumour may be many centimetres from this resection margin. In this event, sampling of the resection margin is not usually necessary and one should rely on the macroscopic distance. Particular attention should be paid to the anterior margin in low rectal cancers, since this is the most common site for CRM involvement
- if macroscopic tumour is ≤30 mm from the proximal or distal margins, appropriate blocks to show the closest approximation to that margin. If provided by the surgical team, the corresponding stapling device doughnut should also be processed for histological examination (see section 5.2.5). There is no need to routinely process for histology the stapling device doughnuts if tumour is macroscopically clear by >30 mm unless the

tumour demonstrates aggressive microscopic features such as signet ring cell differentiation

- a block of tumour and adjacent mucosa, to include any precursor polyp, if this is macroscopically identifiable
- a block of normal-appearing intestine (which may also be a longitudinal limit block)
- all lymph nodes identified (whole node if <3–4 mm; central block through longest axis for larger nodes) and any tumour deposits identified macroscopically
- any other macroscopic abnormalities
- a block of appendix if present (e.g. right hemicolectomy). In such specimens, a block from terminal ileum is only considered essential if there are macroscopic abnormalities in the ileum, if the tumour is close to this proximal longitudinal margin or if there is coexisting large intestinal chronic inflammatory bowel disease.

Appropriate selection of blocks from the transverse slices of tumour is crucial if the maximum amount of information is to be obtained. Peritoneal involvement is best identified in blocks that are taken from areas that are dulled, fibrotic or haemorrhagic and is particularly prone to occur where the peritoneum is reflected at an acute angle from the bowel surface onto the adjacent mesentery or in deep crevices or clefts between fat lobules.[29] At least two blocks taken from where the tumour is closest to the serosa is recommended. Venous invasion can often be suspected macroscopically as fine pale lines emanating from the base of the tumour, perpendicular to the leading edge, and such regions must be sampled to confirm (as V2).

Rectal tumours that have undergone preoperative therapy may undergo regression such that no definite residual tumour can be recognised. In such cases at least five blocks from the site of the original mass should be taken in the first instance.[2,27] If these do not show residual tumour on microscopic examination (after examining sections from three levels), then the whole of the tumour site and/or the scarred area should be blocked for histology. If still no tumour is found, three deeper levels should be cut on all blocks from the tumour site and, if still negative, a pathological complete response (pCR) can then be recorded, provided that there is no lymph node or other metastatic disease in the surgical resection (see section 5.2.6). This approach has been employed in a number of ongoing clinical trials involving rectal cancer (COPERNICUS, BACCHUS and ARISTOTLE) and has recently been reported as resulting in a reduction in designation as pCR in a small percentage of cases.[30]

Occasionally, locally advanced rectal tumours may be resected with part of the sacrum en bloc. Inclusion of this bony tissue within the resection specimen necessitates a modification of the standard approach to dissection. After inking the CRM as usual, including the sacral margin, the bony tissue should be carefully dissected off and placed back in formalin pending microscopy. Prior to horizontal slicing of the main specimen, the defect at the site of bony tissue should be inked a different colour, to allow microscopic identification of this soft tissue adjacent to the bone. Should microscopy reveal tumour involving the soft tissue abutting the bone, the sacrum should be decalcified, applying the locally agreed laboratory protocol for this, then sliced and processed for histology, so that any bony involvement and the true surgical margin can be evaluated.

The identification of lymph nodes should begin with the highest (apical) lymph node. This is the first node identified by sectioning serially and distally from the arterial margin(s), represented by the distalmost vascular suture or ‘high tie’, regardless of the actual distance between node and surgical tie (Figure 1); the node should be identified and blocked separately. Whereas only one vascular ‘high tie’ is usually present in rectal resections, several vessels might drain colonic resections; if the tumour lies between two major arteries it is appropriate to record both high tie nodes.

While we are no longer recording Dukes' stage, involvement of the highest lymph node does confer a worse prognosis on stage III tumours and should be recorded. It will also be more frequently involved in 'low tie' D2 (complete pericolic/perirectal and intermediate lymph node dissection) rather than D3 (pericolic/perirectal, intermediate, and main lymph node dissection) specimens.[31] The remaining lymph nodes can most easily be identified in the transverse slices of the mesentery, especially if well fixed.

Care must be taken to ensure that all the mesentery between the tumour and the highest lymph node is serially sliced if it has not already been included in the initial slicing. Lymph nodes that are situated very close to the CRM should be blocked in such a way as to allow measurement of the distance of any tumour that they may contain from the margin. There is some, but insufficient, published evidence to make a firm recommendation as to whether lymph nodes should be embedded in their entirety. There is certainly no need to embed multiple slices from a large node that is obviously involved by the tumour macroscopically.

We recommend small (<4 mm) nodes are submitted entirely and a single block taken through the longest axis of each larger node to maximise the surface area examined in a single section. Standardisation of the number of (small) lymph nodes submitted per cassette reduces block numbers and also reduces the risk of the smallest lymph nodes not being examined microscopically. Pathologists will need to use their judgement in determining whether every lymph node identified has been adequately sampled until further evidence is available. As discussed in section 5.2.6, should 'isolated tumour cells' be identified on examination of any initial lymph node sections, it is recommended to return to the specimen and submit all identifiable nodal tissue for histological examination, in case this yields more significant lymph node metastatic disease.

It is important to emphasise that all of the lymph nodes that can be found in a specimen are examined histologically as the number of lymph nodes identified in resection specimens from patients with stage II and stage III colon cancer has been positively correlated with survival.[32] The previous standard of 12 for the median number of lymph nodes examined per specimen is now increased to 15 (excluding cases treated preoperatively), reflecting improved modern surgical and pathology practice. This does not mean that pathologists should stop searching for lymph nodes once 15 have been identified. Placing the specimen in a fat-clearing agent, e.g. Carnoy's solution, for 24 hours after initial dissection may be used to help increase nodal yield.

Other methods, such as GEWF (glacial acetic acid, ethanol, distilled water, formaldehyde) fixation and methylene blue injection,[33] have also been used for this purpose. This approach is not routinely recommended but should be considered if the laboratory has low lymph node yields or in the context of preoperative therapy. Judgement of quality should be on the median number of lymph nodes found by an individual dissector interpreted in the light of the material reported by the individual pathologist. Some specimens e.g. panproctocolectomy, are likely to contain non-regional lymph nodes but confident distinction of regional/non-regional node boundaries is often difficult and we therefore advise harvesting of all lymph nodes, with separate identification of regional and non-regional lymph nodes where possible.

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

5 Core data items

5.1 Macroscopic core data items

These include:

- type of operation and nature of specimen

- site of tumour
- maximum tumour diameter
- distance to the nearer longitudinal resection margin
- tumour perforation
- location of the tumour relative to the peritoneal reflection (rectal tumours only)
- grade of the plane(s) of surgical excision (AR and APE specimens)
- distance of the tumour from the dentate line (for APE specimens only).

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

5.1.1 Data recorded for all colorectal tumours

Type of operation, nature of specimen and tumour site

This information will usually be stated on the request form. However, if examination of the specimen suggests any inconsistencies, these should be queried with the surgeon and corrected, if necessary, prior to specimen dissection. If the tumour straddles two sites, the site with the greatest tumour bulk should be recorded. The boundary between the caecum and ascending colon is the level of the upper lip of the ileocecal valve. The rectum is defined clinically as the distal large intestine commencing opposite the sacral promontory. The three taeniae coli of the sigmoid colon fuse to form the circumferential longitudinal muscle of the rectal wall, signifying the corresponding rectosigmoid boundary on pathological evaluation. If distinction between the sigmoid colon and rectum is not possible – for example, owing to advanced tumour stage obliterating anatomical landmarks – the tumour site should be recorded as rectosigmoid junction. Every effort should be made, however, to accurately classify the tumour as colonic or rectal in origin. Reviewing the relevant radiology and endoscopy reports and images can be helpful in this regard as they have the benefit of in vivo anatomy. If multiple tumours are present, site and size (and all subsequent dataset fields) should be recorded separately for all tumours.

Maximum tumour diameter

This is measured from the luminal aspect of the bowel, with the maximum dimension recorded for non-annular tumours. For annular tumours, the length of the annular segment should be recorded. The thickness of the tumour is ignored for this measurement. Tumour size is not considered of prognostic relevance for colorectal cancer and does not influence staging. However, size allows correlation with pre-operative imaging, endoscopic and surgical assessments, and evidence of response to preoperative therapy if smaller than the initial MRI/CT estimate.

Distance of tumour to nearer longitudinal margin

This is the measurement to the nearer longitudinal margin of the specimen, and not the CRM. It is only necessary to examine the margins histologically if the tumour extends macroscopically to within 30 mm of one of these.[34] For tumours further than this, it can be assumed that the longitudinal margins are not involved. Exceptions to this recommendation are adenocarcinomas that are found on subsequent histology to have an exceptionally infiltrative growth pattern, show extensive vascular or lymphatic permeation, or are signet ring carcinomas, high-grade neuroendocrine carcinomas or undifferentiated carcinomas. Identification of these features microscopically may require the specimen to be revisited for further sampling.

Presence of tumour perforation

Tumour perforation is defined as a macroscopically visible defect through the tumour, such that the bowel lumen is in communication with the external surface of the resection specimen or with the lumen of another organ. Perforation through the tumour into the peritoneal cavity is

a well-established adverse prognostic factor in colonic and rectal cancer and should be recorded.[35] Such cases are regarded as pT4a in TNM 8.[20] Perforation of the proximal bowel as a result of a distal obstructing tumour is distinct from tumour perforation and does not indicate stage pT4 disease. It is recommended that use of the term perforation is reserved for the biological setting and, to avoid confusion, different descriptive terminology applied in the event that a full thickness defect in the specimen arises intra-operatively.[24] Such clinical information should be conveyed on the pathology request form to assist pathological interpretation or the pathologist should seek further clinical information if required. If an iatrogenic full thickness tumour defect occurs while the specimen is still within the abdominal cavity, this is best regarded as pT4a disease, given the risk of tumour seeding the peritoneal cavity, although this guidance is offered without good evidence.[24] However, if such a defect occurs once the specimen is outside the abdominal cavity, this should not influence pT classification.

A peritumoral abscess cavity, for example involving the mesentery, that is contained and does not involve a breach of the serosal surface, is not considered to represent perforation and should be staged as pT3 rather than pT4a. Similarly, microscopic features such as faecal material and foreign body giant cells located in mesenteric fat or on the serosal surface may suggest previous tumour perforation but such findings are not considered sufficient to designate as perforation in the absence of a macroscopic defect. In all such unusual circumstances, it is valuable to include an explanatory note on interpretation in the pathology report.

[Level of evidence B – Tumour perforation is important for prognosis in colonic and rectal cancers.]

5.1.2 Data recorded for rectal tumours only

Relationship to the peritoneal reflection

The crucial landmark for recording the site of rectal tumours is the peritoneal reflection. This is identified from the exterior surface of the anterior aspect of the specimen (Figure 3).

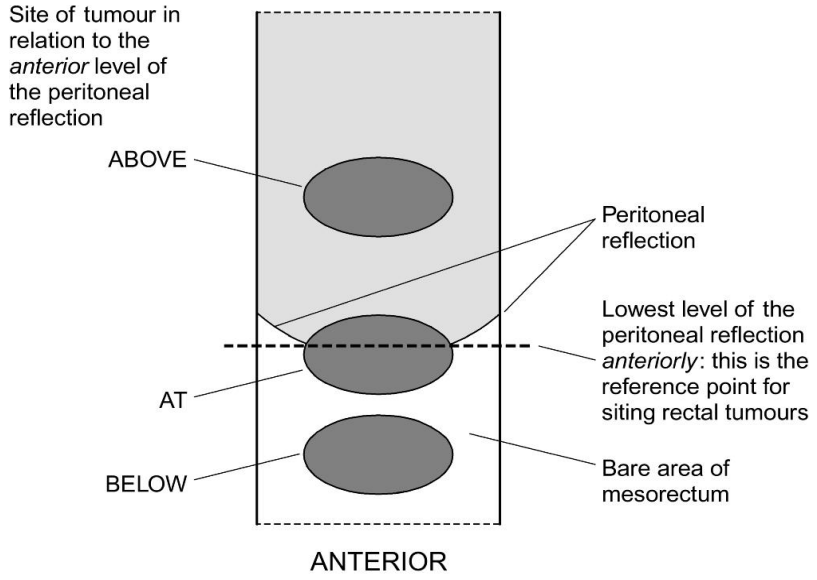


Figure 3. Diagrammatic illustration of rectal tumours in relation to the peritoneal reflection.

Rectal tumours are classified according to whether they are:

- entirely above the level of the peritoneal reflection anteriorly
- astride (or at) the level of the peritoneal reflection anteriorly

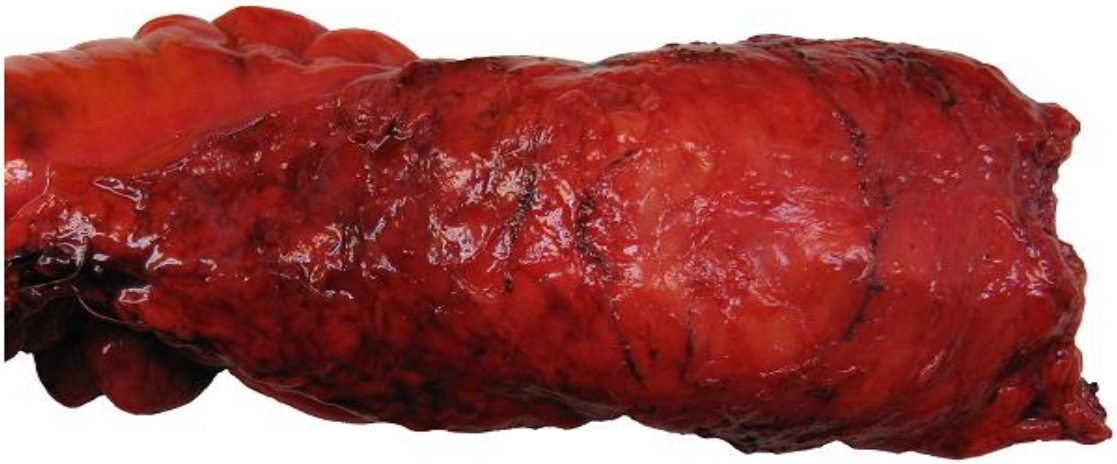
- entirely below the level of the peritoneal reflection anteriorly.

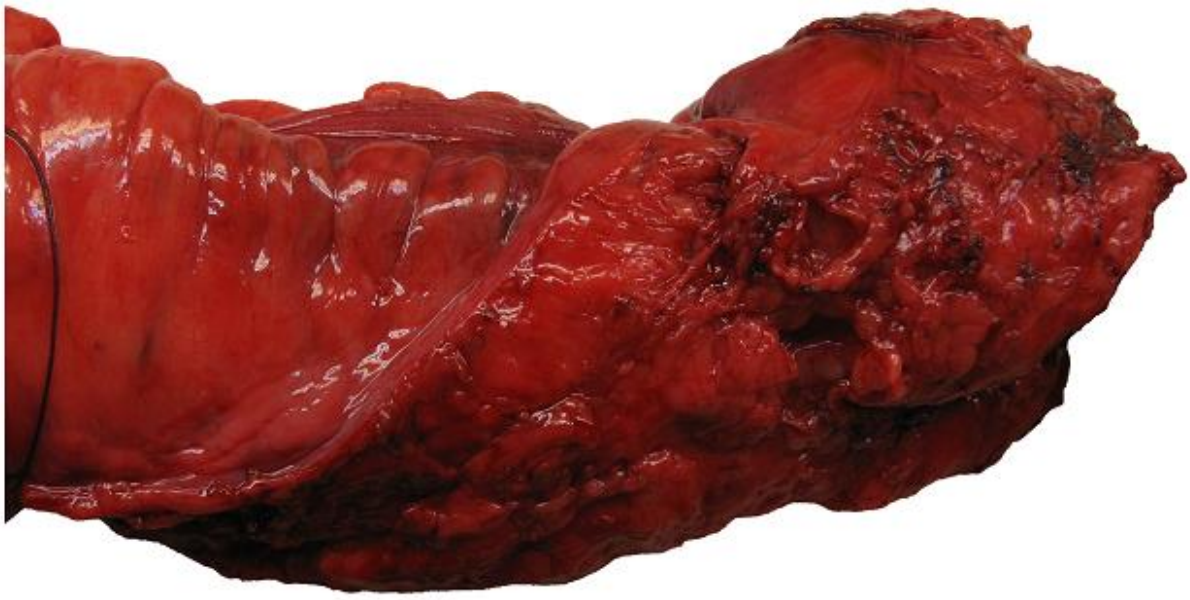
Tumours below the peritoneal reflection have the highest rates of local recurrence.[6]

[Level of evidence A – Site of tumour within the rectum predicts local recurrence.]

Plane of mesorectal excision

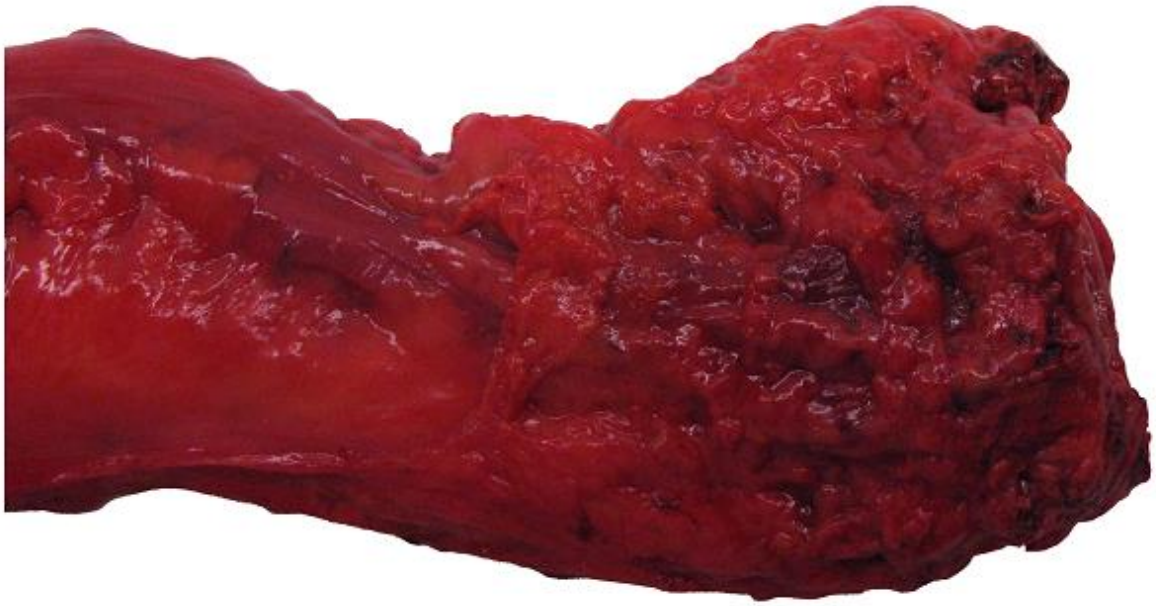
Prospective randomised controlled trials have demonstrated that a macroscopic assessment of the plane of excision of rectal cancers predicts not only margin involvement but also local recurrence and survival.[6,36] Excision in the mesorectal plane has the best outcome while that extending into the muscularis propria has the worst. The plane of resection can also be used as a marker of the quality of surgery and continual feedback to MDTs has led to improved quality of surgery and clinical outcomes with time.[6,17,18,36,37] Descriptions of the three planes of excision are given below; illustrations of each have been published and examples are shown in Figure 4 from the ARISTOTLE trial protocol (reproduced with permission of the authors).[27,38]

Plane	Description
Mesorectal	The mesorectum should be smooth with no violation of the fascial covering. There should be a good bulk to the mesorectum both anteriorly and posteriorly, and the distal margin should appear adequate with no coning near the tumour. Any defect should not be more than 5 mm deep.
 **Mesorectal plane showing shiny fascial covering over the CRM and no defects**	
Intramesorectal	There should be a moderate bulk to the mesorectum with minor irregularity of the mesorectal surface. A moderate degree of coning of the specimen may be seen towards the distal margin. Importantly, the muscularis propria should not be visible, except at the area of insertion of levator muscles at the very distal aspect. There will be moderate irregularity of the CRM.



Intramesorectal plane with significant defects into the mesorectum without the muscularis propria being visible

Muscularis propria	There will be substantial areas where mesorectal tissue is missing with deep cuts and tears down onto the muscularis propria. In cross-sectional slices, the CRM will be very irregular and formed by the muscularis propria in places.

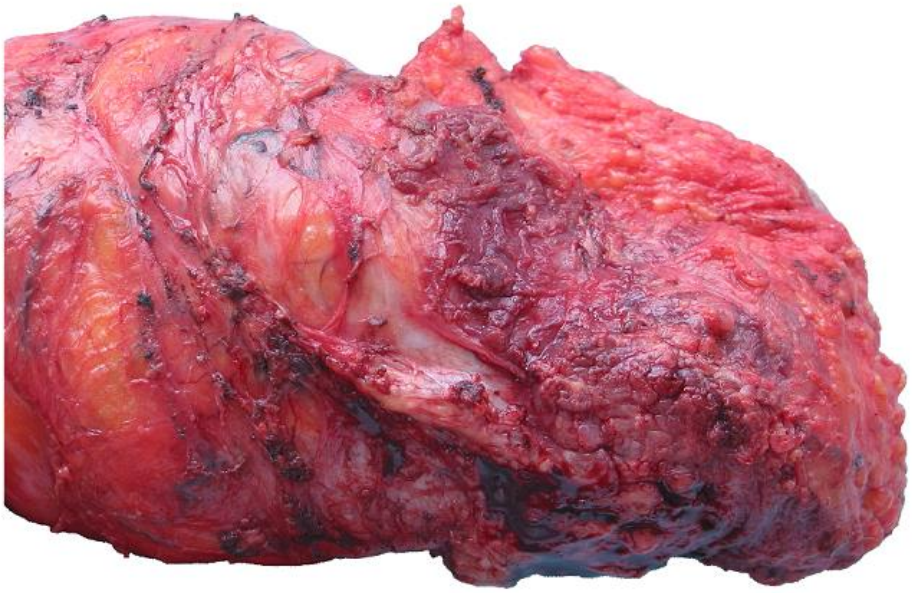


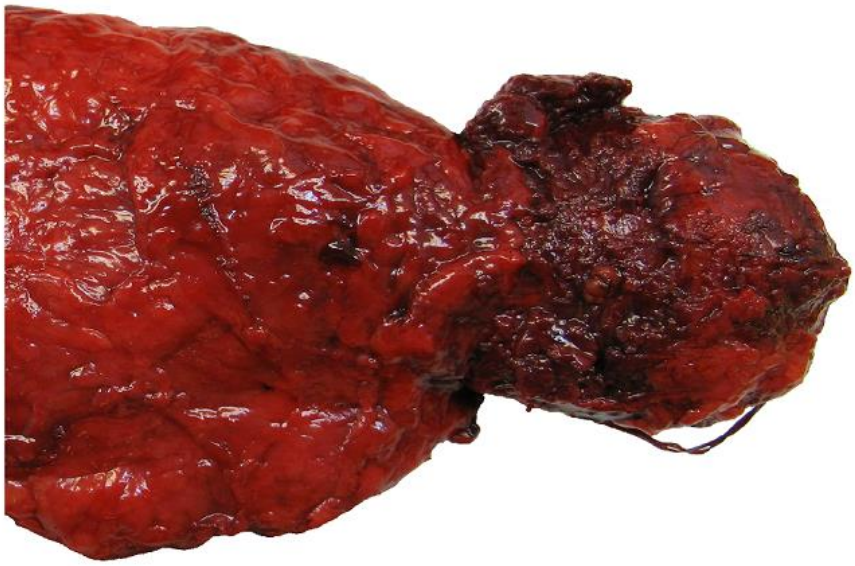
Muscularis propria plane with significant mesorectal defects exposing extensive areas of muscularis propria

Figure 4. Examples of rectal cancer excision: anterior resection specimens showing different surgical excision planes.

Plane of excision of the levators/sphincters (APE specimens only)
The plane of surgical dissection in the levator/sphincter area around the anal canal and below the mesorectum needs to be assessed separately in APE specimens, in addition to evaluation of the mesorectal plane of excision.[39] This surgical approach has been associated with poorer outcomes compared to anterior resection for higher rectal tumours, due to higher rates of CRM involvement and intraoperative full thickness defects, or 'perforations'.[40] Extralevator APE removes more peritumoral tissue and has been shown by meta-analysis to associate with better long-term outcomes, as a result of lower rates of CRM involvement and intraoperative defects.[41] By evaluation of the staging magnetic resonance imaging (MRI) scan, radiologists can predict the optimal APE dissection plane and this should be correlated with the subsequent surgical plane of dissection achieved.[42] Assessment requires examination of the intact specimen and overall assessment is based on the worst area, as described in Figure 5.

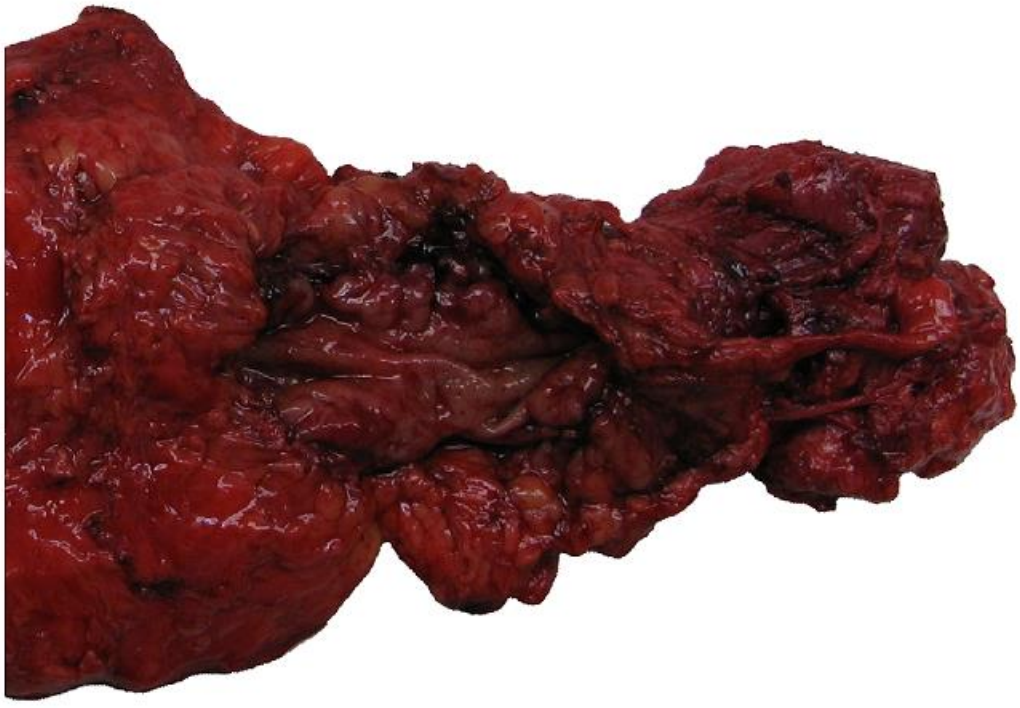
[Level of evidence A – Plane of surgery in rectal cancer predicts local recurrence and prognosis.]

Plane	Description
Extralevator	The surgical plane lies external to the levator ani muscle, which are removed en bloc with the mesorectum and anal canal. This creates a more cylindrical-shaped specimen with the levators forming an extra-protective layer above the sphincters. There should be no significant defects into the sphincter muscles or levators.
 **Extralevator plane showing levator muscles attached to the mesorectum.**	
Sphincteric	Either there are no levator muscles attached to the specimen or only a very small cuff, and the CRM is formed by the surface of the sphincter muscles. There should be no deviations into the sphincter muscle themselves. The specimen shows coning at the level of the puborectalis muscle resulting in the classical surgical waist.



Sphincteric plane showing the classic surgical waist with no levator wrap. A small amount of levator muscle is seen hanging loose on the opposite side to the arrow but this is not adherent to the mesorectum as would be seen in a levator plane excision.

Intrasphincteric/ submucosal	The surgeon has inadvertently entered the sphincter muscle or even deeper into the submucosa. Full thickness defects of the specimen at any point below the peritoneal refection should also be classified into this group.



Intrasphincteric/submucosal plane showing a large anterior full thickness defect and a very irregular CRM with multiple defects into the sphincter muscles.

Figure 5. Examples of APE specimens showing different surgical excision planes.

Distance from dentate line

This measurement is only made for low rectal tumours in APE specimens to give an indication of the location of the tumour in relation to the internal sphincter and a crude estimation of appropriateness of APE rates. This can be difficult to measure accurately on transverse sectional rings, but an approximation is possible. Longitudinal opening through the tumour to get an accurate measurement from dentate line is not recommended as margin assessment is a greater priority.

5.2 Microscopic core data items

These are:

- histological tumour type
- grade of differentiation
- maximum extent of local invasion (pT stage) and, for pT3 tumours only, the maximum distance of extramural spread
- grade of tumour regression following preoperative therapy
- resection margin status (longitudinal margins and CRM)
- lymph node status (number present, number involved, highest lymph node status)
- tumour deposits
- venous invasion
- lymphatic invasion
- perineural invasion
- histologically confirmed distant metastatic disease
- separate abnormalities
- block index (to include identified 'molecular block[s]' for additional testing).

5.2.1 Histological tumour type

The WHO classification 5th edition (2019), is recommended.[25] Virtually all colorectal cancers are adenocarcinomas, mostly of no specific subtype, but some subtypes of adenocarcinoma are recognised:

- mucinous carcinoma (variant of adenocarcinoma with >50% composed of extracellular mucin)
- signet ring cell carcinoma (variant of adenocarcinoma with >50% signet ring cells)
- medullary carcinoma
- serrated adenocarcinoma
- micropapillary adenocarcinoma
- adenoma-like adenocarcinoma.

Mucinous, signet ring cell and in particular, medullary carcinomas all have an association with microsatellite instability. Preoperative therapy may 'induce' a mucinous phenotype.[43] Therefore, if preoperative therapy has been administered and extensive mucinous differentiation is seen in the resection specimen, a diagnosis of mucinous carcinoma must be confirmed from review of the diagnostic biopsy specimen, if available. Medullary carcinoma has a solid architecture with sheets of malignant cells demonstrating indistinct cell boundaries, vesicular nuclei, prominent nucleoli, abundant eosinophilic cytoplasm and prominent intratumoral lymphocytes.[44]

Serrated adenocarcinoma demonstrates glandular serrations, often slit-like, with abundant eosinophilic or clear cytoplasm, minimal luminal necrosis and sometimes mucinous differentiation.[45] Some serrated adenocarcinomas have an identifiable origin in a precursor serrated lesion.

Micropapillary adenocarcinoma features small, rounded clusters of tumour cells lying within stromal spaces which resemble vascular channels.[46] Some studies have used a minimum of 5% of tumour demonstrating this pattern to qualify for this diagnosis.[25,47] Micropapillary adenocarcinoma is strongly associated with adverse pathological features, such as lymph node metastatic disease.[46]

Adenoma-like adenocarcinoma requires at least 50% of the invasive tumour to have an adenoma-like appearance characterised by a villous architecture, pushing growth pattern, low grade cytology and minimal desmoplastic stromal reaction.[48] Distinction from adenomatous epithelial misplacement may be difficult. This diagnosis is associated with a good prognosis.

Tumours demonstrating neuroendocrine differentiation, either entirely or with less than 30% adenocarcinoma morphology, are regarded as 'pure' neuroendocrine neoplasms. Mixed epithelial tumours with greater than 30% representation of morphologically and immunohistochemically recognisable neuroendocrine and non-neuroendocrine components are now classified as mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN). This term replaces the older terminology of mixed adenoneuroendocrine carcinoma (MANEC), recognising that the non-neuroendocrine component does not have to be an adenocarcinoma.[23]

Epithelial tumours other than adenocarcinomas are rarely encountered in the colorectum. These include adenosquamous carcinoma, carcinoma with sarcomatoid components, undifferentiated carcinoma, squamous cell carcinoma and non-signet-ring cell poorly cohesive adenocarcinoma.[25] Primary colorectal squamous cell carcinoma is extremely rare, compared to secondary rectal involvement by primary anal squamous cell carcinoma.

[Level of evidence C – Histopathological type is important for clinical management and prognosis.]

5.2.2 Grade of differentiation

Differentiation is based primarily on architecture and specifically gland or tubule formation.[49] The criteria for poor differentiation are either irregularly folded, distorted and often small tubules or a solid architecture with the absence of any glandular formation. Although inter-observer agreement in assessment is poor,[50] histological grade has been shown in numerous studies to be an independent prognostic factor for colorectal carcinoma.[51–53] TNM 8 and the American Joint Committee on Cancer (AJCC) currently recommend the use of four grades.[20,54] However, we believe that the use of two grades, poor and well/moderate, enhances agreement and quality control.

For consistency with the latest WHO classification and ICCR guidelines, it is now recommended that grading should be based on the least differentiated tumour component, although this recommendation is made without good evidence.[24,25] The minimum area of poor differentiation has not been specified.

Small foci of apparent poor differentiation, in the form of tumour buds or poorly differentiated clusters, are not uncommon at the advancing edge of tumours but these are insufficient to classify the tumour as poorly differentiated applying the conventional grading system based on gland formation. However, tumour budding should be assessed separately (see section 10.4). There is also growing evidence to support grading by assessment of poorly differentiated clusters at the advancing tumour edge.[55] Some data indicate that this assessment is of higher prognostic significance compared to conventional grading and furthermore has greater

reproducibility.[56–58] However, these findings require broader, multicentre validation and consensus on optimal assessment methodology prior to introduction into clinical practice. The evidence for grading by poorly differentiated clusters will be kept under review.

Morphological assessment of differentiation of colorectal tumours applies only to 'adenocarcinoma, NOS' and mucinous carcinoma, with mucinous carcinoma graded on glandular formation and epithelial maturation.[25] Some of the other histological variants carry their own prognostic significance.

[Level of evidence C – Differentiation is important for prognosis.]

5.2.3 Local invasion

The maximum degree of local invasion into or through the bowel wall is recorded. This is based on the criteria for pT staging in the TNM 8 staging system (Appendix A). pT in situ (pTis) and intramucosal adenocarcinoma are not recognised. Although it is apparent that very rare cases of colorectal neoplasia confined to invasion of the lamina propria do occur, these appear to have negligible risk of metastatic spread, based on limited numbers of cases reported.[59] We recommend that such lesions be classified as high-grade dysplasia, and a diagnosis of adenocarcinoma requires demonstration of submucosal invasion (see section 11). This position is also adopted by European guidelines, WHO and by the ICCR.[24,60–62]

For mucinous adenocarcinomas, the extent of local invasion should include assessment of the deepest extent of mucin, rather than only considering tumour cells. For example, if acellular mucin is identified beyond muscularis propria, but tumour cells only evident within muscularis propria, this should be classified as pT3. Similarly, acellular mucin evident on the serosal surface should be interpreted as pT4a. This guidance is offered without supporting evidence but is consistent with TNM 8 staging for appendiceal carcinomas and adopted in the corresponding appendiceal carcinoma RCPath dataset.[20,21] This position is also consistent with that adopted for acellular mucin within mesenteric lymph nodes in treatment-naïve colorectal cancer patients. Note a different interpretation of acellular mucin applies in the setting of administered preoperative therapy (see section 5.2.4).

Stage pT4 encompasses either tumour infiltration of the peritoneal surface (pT4a, TNM 8) or tumour involvement of an adjacent organ (pT4b, TNM 8). Because these two features may have different implications and therapeutic connotations they are recorded in separate boxes. For example, invasion of a lower rectal tumour into the levators is staged as pT4b but there would be little chance of the same tumour having peritoneal involvement. Accordingly, pT4 tumours may have either or both the pT4 boxes marked. Cases with macroscopic perforation at the site of tumour are also classified as pT4a, without the necessity to demonstrate microscopic invasion of the peritoneal surface by tumour cells.

Involvement of the peritoneal surface (pT4a) is defined as tumour breaching the serosa with tumour cells visible either on the peritoneal surface, free in the peritoneal cavity or separated from the peritoneal surface by inflammatory cells or acellular mucin only.[35,63] It is important that blocks are taken to optimise recognition of this feature and that deeper levels are examined from blocks whose initial sections show tumour cells that are close to the surface or localised peritoneal inflammation, erosion or mesothelial hyperplasia. Several studies advocate the application of elastic stains to evaluate peritoneal elastic lamina invasion, as a staging or prognostic tool, but others have not found this useful.[64–67] Routine application of elastic stains for this purpose is not recommended currently.

Peritoneal involvement through direct continuity with the primary tumour (pT4a, TNM 8) is recorded differently from peritoneal tumour foci that are separate from the primary tumour and are regarded as distant metastatic disease, having arisen by transperitoneal spread (pM1c, TNM 8). As discussed above, it is very important to appreciate the difference between involvement of the peritoneal surface and involvement of the CRM, which should be recorded

separately. The first is a risk factor for intraperitoneal metastatic disease while the latter is a risk factor for local recurrence.

TNM conventions recommend that direct invasion of an adjacent organ by way of the serosa is always recorded as pT4b while intramural (longitudinal) extension into an adjacent part of the bowel (e.g. extension of a caecal tumour into the terminal ileum or of a rectal cancer into the anal canal) does not affect the pT stage.[68] Tumours that are adherent to other organs must show microscopic evidence of invasion into the adjacent organ to be classified as pT4b, rather than inflammatory adherence, which would be classified as pT3. Extramural extension of a rectal cancer into the skeletal muscle of the external sphincter, levator ani and/or puborectalis is classified as pT4b (TNM 8). Conventions also states that a tumour entirely within vessels does not qualify as local spread in pT staging e.g. a tumour with local spread confined to muscularis propria but with vascular spread beyond, confined to vessel lumen, is staged as pT2.

The maximum distance of tumour spread beyond the bowel wall is recorded, for pT3 tumours, in millimetres from the outer margin of the muscularis propria, as illustrated in Figure 6.[69–73] Five millimetres depth of invasion was an important cut-off in some studies.[69,71] When the tumour has obliterated the muscularis propria focally, the contour of the outer aspect of the adjacent muscularis should be used to make this measurement. Note this measurement only applies to the primary tumour mass and excludes any discontinuous tumour deposits, venous, lymphatic or perineural invasion or nodal metastases. For pT1, pT2 and pT4 tumours, this measurement will be not applicable.

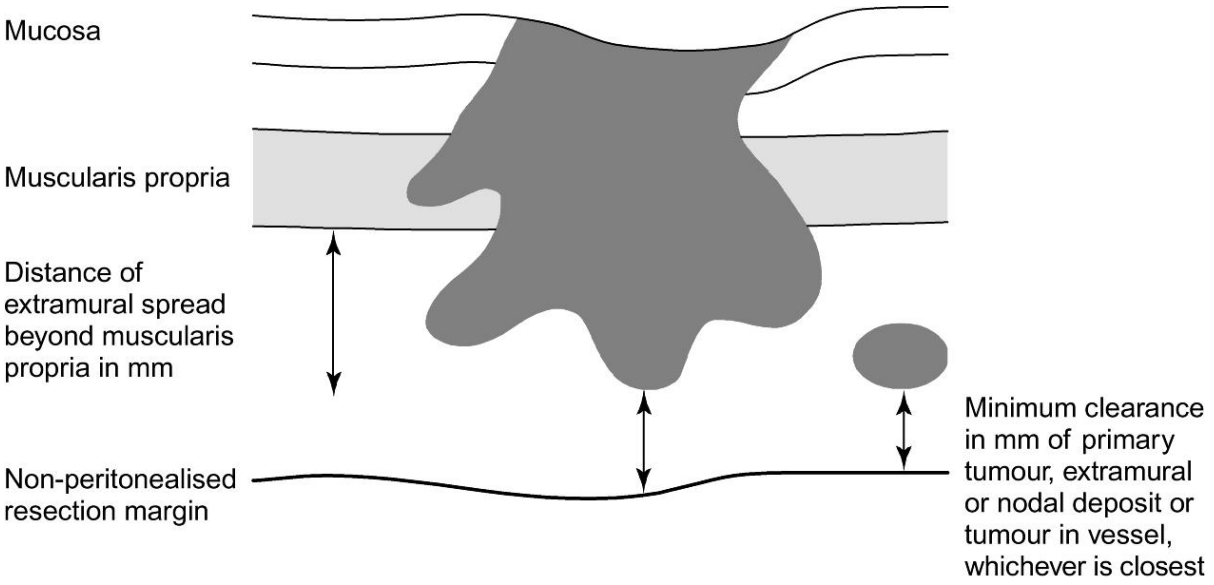


Figure 6. Measuring extramural spread and clearance of tumour from the circumferential margin.

[Level of evidence B – Depth of local invasion predicts recurrence and prognosis.]

5.2.4 Response to preoperative therapy

There is evidence that patients with completely excised rectal carcinomas, who have received preoperative therapy that has resulted in complete or marked regression, have a better prognosis than those without significant regression.[1,2,74,75] However, there is no consensus over how lesser degrees of regression are estimated histologically.[76] The four-tier system currently advocated by the AJCC is recommended, based on a modification of that described by Ryan *et al*. (2005), and should be applied when any form of preoperative therapy is administered including chemotherapy alone or immunotherapy (Table 1).[54,77] Assessment is based on evaluation of the primary tumour site, but a descriptive comment should be added if regressive features are seen within regional lymph nodes, or at any distant metastatic sites.

Designation as overall pathological complete response implies the absence of viable tumour locally and in lymph nodes and requires processing of the entire tumour bed and any nodes or distant metastatic sites showing regression, for histological examination. Cases with complete pathological response are recorded as ypT0 ypN0. Cases with complete regression of the primary tumour but viable tumour epithelium in, for example, one lymph node are recorded as ypT0 ypN1a.

Table 1. Four-tier system for evaluating tumour regression.

Evaluation (of primary tumour site)	Tumour regression score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near-complete response)	1
Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumour regression (poor or no response)	3

For tumour staging following preoperative therapy of any type, only the presence of tumour cells in the surgical specimen is considered in determination of the 'y' stage. Fibrosis, haemorrhage, necrosis, inflammation and acellular mucin should be ignored for staging purposes and are relevant only to assessment of regression.

[Level of evidence A – Grade of regression in rectal cancer after preoperative therapy is important for prognosis.]

5.2.5 Resection margins

Doughnuts

It is usually not necessary to examine doughnuts from stapling devices histologically if the main tumour is >30 mm from the longitudinal margin of the main specimen, except in rare cases of aggressive cancers, such as a signet ring cell carcinoma.[34] If doughnuts are received with the surgical specimen but not submitted by the pathologist for histology, this item should be recorded as 'not submitted'. 'Not applicable' should be recorded if doughnuts were not received with the resection specimen.

It should be noted that the doughnut of mucosal tissue provided by stapling devices often does not represent a full mucosal circumference. This is the rationale for microscopically examining tissue from both the longitudinal margin of the main specimen and from the corresponding stapling device doughnut, when tumour is close. Consequently, if the tumour microscopically involves the longitudinal margin of the main specimen, a lack of involvement of tissue from the corresponding stapling device doughnut cannot be safely interpreted as R0. Involvement of either the longitudinal margin within the main specimen or of tissue from the stapling device should be regarded as representing R1 disease.

Longitudinal margin

When one or both longitudinal margins are examined histologically (see criteria above), the presence or absence of tumour should be recorded. If neither margin is examined histologically, they should be recorded as 'not submitted'.

Circumferential resection margin

This margin has been defined in detail above. Its involvement is predictive of local recurrence and poor survival in rectal tumours.[12–14,78,79] In those that have not received preoperative therapy, it may be an indication for postoperative adjuvant therapy. The importance of CRM involvement in colonic tumours, particularly those of the caecum and ascending colon, has also been recognised in several studies.[35,80,81] Spread of tumour into a pericolic abscess cavity that communicates with a CRM has also been associated with a poor prognosis in one study,

although the number of cases in this category was small.[35] The evidence to recommend equating this with margin positivity is not sufficient, but if this finding is present in a resection specimen, it would be prudent to highlight the observation in the pathology report.

The minimum distance between the tumour and the CRM in millimetres is recorded from the histological slides, where possible (see Figure 6). If this distance is ≤1 mm, then the CRM is regarded as involved (R1) in the assessment of completeness of resection in the proforma.[82] The precise distance of clearance should be recorded, to the nearest 0.1 mm. If the tumour is clear by <10 mm, the specific distance of clearance should also be recorded to the nearest 1 mm.[24]

For mucinous adenocarcinomas not treated by preoperative therapy, acellular mucin present at a resection margin should be interpreted as margin involvement, regardless of distance to the closest tumour cells. This guidance is offered without supporting evidence but is consistent with the position adopted for assessment of local invasion in this setting (see section 5.2.3). Note a different interpretation of acellular mucin applies in the setting of administered preoperative therapy when measurement should be to the closest viable tumour cells.

Assessment of distance to CRM and R status is usually based on measurement to the primary tumour. However, limited data suggest that cases with margin involvement by discontinuous or intravascular (blood vessel or lymphatic vessel) tumour have a similar risk of local recurrence to those cases with margin involvement by primary tumour.[78,79] Several studies have demonstrated that patients with colorectal cancer who have tumour cells less than 1mm from the CRM but within an intact lymph node have a risk of local recurrence similar to those with R0 disease and less than the risk of local recurrence related to CRM involvement by primary tumour.[79,83–85] However, the evidence is limited and insufficient to make a definitive statement regarding appropriate R status classification in this uncommon scenario. Involvement of the CRM by a surgically disrupted lymph node or by any other mode of metastatic spread, such as venous invasion, perineural invasion or a tumour deposit, should be considered as R1 disease.

If a case is designated as resection status R1, a clear indication should be provided of the reason for this designation. If the R1 status is not related to the primary tumour, a distance of clearance of the primary tumour should also be provided. It is emphasised that, when measuring from the margin to an involved lymph node containing metastatic tumour, the measurement should be to the closest tumour cells, rather than to the lymph node capsule.

A recent study has highlighted significant uncertainties in the assessment of R status in many of the unusual scenarios described above.[86] While some of the guidance we provide in this regard is offered with limited supporting evidence, it is hoped that this added clarity will lead to greater uniformity of interpretation and help generate an evidence base to review some of these interpretations. Discussion may need to take place at the relevant MDTM to decide on a final R classification, especially with respect to potential R2 cases, to agree whether or not it is likely macroscopic tumour was left behind at operation (section 9.1).

[Level of evidence A – CRM involvement in rectal cancer predicts local recurrence and prognosis both with and without preoperative therapy.]

5.2.6 Lymph nodes

All the lymph nodes that have been retrieved from the specimen should be examined histologically, as described above. If two or more synchronous primary tumours are present within distinct anatomical segments of the same resection specimen, lymph nodes should be assigned by regional status and assessed for each cancer separately, if possible. Multiple or serial sections from lymph node blocks are not recommended for routine reporting. Neither is the use of immunohistochemistry or molecular techniques because there is insufficient evidence on the prognostic significance of tumour deposits identified in this way. Extracapsular

invasion is not recorded specifically. Lymph nodes are distinguished from extramural lymphoid aggregates by the presence of a capsule and a peripheral sinus.

A systematic review and meta-analysis found higher risk of disease recurrence in stage I/II colorectal cancer cases with only micrometastatic disease in lymph nodes (deposits ≥0.2 mm and <2 mm) compared to those with tumour-negative nodes, but no increased risk of disease recurrence in cases with 'isolated tumour cells' (single tumour cells or groups <0.2 mm in maximum dimension) compared to those with tumour-negative nodes.[87] A further study from the same group reported that micrometastatic disease, but not isolated tumour cells, was associated with reduced three year disease-free survival.[88] It is recommended, therefore, that any lymph node with a tumour deposit measuring ≥0.2 mm is considered an involved node (stage pN1). This determination may require examination of multiple serial sections.

Nodes with only isolated tumour cells or tumour cell groups <0.2 mm are considered negative (stage pN0), as there is currently no evidence of negative prognostic influence in otherwise node-negative disease. Multiple such small clusters may be present and only the size of the largest contiguous tumour cell cluster is measured for consideration of the pN category. Neither the sum of the diameters of the cluster sizes nor the maximum extent of distribution are used in this assessment. If only isolated tumour cells are identified on examination of multiple levels from initial lymph node blocks, it is recommended to return to the specimen and submit all identifiable nodal tissue for histological examination in case this yields more significant tumour cell deposits. If only isolated tumour cells are identified, this should be described along with the interpretation as pN0.

The difference between stage pN1 and pN2 is the number of lymph nodes involved (pN1 = 1–3 nodes, pN2 = 4+ nodes), irrespective of their site in the resection specimen.

TNM 8 has further subclassified pN1/2 stage as follows:

- N1: Metastatic disease in 1–3 regional lymph nodes
  - N1a: Metastasis in 1 regional lymph node
  - N1b: Metastases in 2–3 regional lymph nodes
- N2: Metastatic disease in 4 or more regional lymph nodes
  - N2a: Metastases in 4–6 regional lymph nodes
  - N2b: Metastases in 7 or more regional lymph nodes.

The pathologist will still need to identify separately the highest lymph node closest to the main vascular tie(s). This is not defined by any measure of distance but is simply the first node identified by slicing the mesentery serially and distally from each main vascular tie. Status of this node is a prognostic factor. Involvement of non-regional lymph node(s) by tumour, occasionally encountered within large resection specimens, indicates distant metastatic (pM1) disease and should be recorded separately to any regional nodal involvement.

If preoperative therapy has been applied, assessment of lymph nodes should include a descriptive comment on the presence or absence of signs of regression (fibrosis, necrosis or mucin) within nodal tissue, although, in this setting, designation as nodal involvement (stage ypN1/2) is based only on the presence of viable tumour. Isolated tumour cells and micrometastatic disease are addressed as above. Rarely, acellular mucin may be encountered within lymph nodes regional to a colorectal cancer when no preoperative therapy has been administered. One small series reported this finding was more common in proximal colonic, mismatch repair deficient tumours in older women.[89] Somewhat paradoxically, as recommended by UICC TNM, neoplastic epithelium is not required in this circumstance to designate the lymph node as involved by metastatic adenocarcinoma (stage pN1), as it is difficult to conceive any alternative benign explanation for the occurrence of mucin within lymph nodes located near an adenocarcinoma.[90,91] Should this rare circumstance arise, it is important

to look carefully for scattered viable tumour cells, embedding the remaining lymph node tissue, examining further levels and applying immunohistochemistry as appropriate.

[Level of evidence A – Nodal status predict prognosis.]

5.2.7 Tumour deposits

By UICC and AJCC TNM 8 definitions, tumour deposits (satellites) are discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures.[20,54] The minimum size of deposit or minimum required distance of separation from the primary tumour are not specified. If a vessel wall is identifiable on haematoxylin and eosin, elastic or other stains, it should be classified as venous invasion (microscopic, V1) or lymphatic invasion (L1). Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion (Pn1). The application of ancillary stains to facilitate confident distinction and accurate staging is encouraged.[92] Identification of venous, lymphatic or perineural invasion does not change the T category. The presence of tumour deposits, as defined, also does not change the primary tumour T category, but changes the node status (N) to pN1c if all regional lymph nodes are negative on pathological examination. Importantly, stage pN1c is only applied in the setting of node-negative disease and, if any nodes contain metastatic tumour, the number of tumour deposits is not added to the involved node count in determining the final pN substage. However, as meta-analysis has demonstrated that tumour deposits have independent adverse prognostic significance,[93] albeit based on a previous (TNM 6) definition, the presence and number of identified tumour deposits should be recorded regardless of pN status.[93] The number of tumour deposits should be counted up to five or, if more, classified as more than five.

A focus of tumour located within mesenteric fat, which demonstrates no obvious origin, is discontinuous from the primary tumour, located within its regional lymphatic drainage area and predominantly subserosal in location but which penetrates the serosal surface of the mesentery, should be classified as a tumour deposit rather than distant metastatic (pM1c) disease. pT category is based on the extent of invasion of the primary tumour only and so is not influenced by such a deposit. However, it may be useful to add a comment that, given serosal involvement by the tumour deposit, behaviour may be equivalent to pT4a disease, albeit without good evidence.[24] pM1c disease should be applied when peritoneal tumour appears to have arisen from transperitoneal metastatic spread. This is likely associated with a much worse prognosis.

In the setting of evident tumour regression following administration of neoadjuvant therapy, assessment of discontinuous tumour foci is difficult and requires consideration of the tissue separating the primary tumour site from discontinuous tumour foci. Designation as tumour deposits in this context should require the presence of intervening normal tissue, rather than just fibrosis.[24]

[Level of evidence A – Tumour deposit status predicts prognosis.]

5.2.8 Venous, lymphatic and perineural invasion

While extramural venous spread is a well-established independent prognostic indicator, there is also some evidence, including from meta-analysis, that intramural (intramuscular or submucosal) venous spread is also of prognostic relevance.[35,94,95] It is recommended, for the purposes of this dataset, that the deepest level of venous spread, extramural or intramural (intramuscular or submucosal), is recorded. All levels of venous invasion, but not lymphatic or perineural invasion, are included in the applicable quality assurance standard.

It is recommended that a modification of Talbot's definition of venous invasion is used.[93] Venous invasion may be evident as tumour present within an endothelium-lined space that is surrounded by a rim of muscle or identifiable elastic lamina. Note that red blood cells may be

seen within lymphatic spaces, so an endothelial-lined space containing red blood cells is considered insufficient to distinguish venous from lymphatic invasion on haematoxylin and eosin (H&E) examination. Further, the vein lumen and endothelial lining may be obliterated by tumour. Therefore, a rounded tumour nodule surrounded by a rim of muscle or identifiable elastic lamina is also considered sufficient for venous invasion. Venous invasion should be suspected when a rounded or elongated tumour profile that is not in direct continuity with the advancing tumour margin is identified adjacent to an artery, especially when no accompanying vein can be seen: the so-called 'orphan artery' sign. Ancillary staining should be applied in this situation.[96]

There is now considerable evidence to suggest that elastic stains can enhance the detection of venous spread and that this elastic-detected venous spread is a superior predictor of outcome than detection by routine stains alone.[94,97–100] Population-based data suggest that venous invasion detection rates are low, especially among non-specialist gastrointestinal pathologists.[99] Standard use of elastic stains has been shown to enhance the detection of venous spread, especially among non-specialist pathologists, although interobserver agreement remains moderate at best.[98]

At the current time, individual units should closely monitor venous invasion rates and, if they are consistently below the 30% threshold, then the adoption of elastic staining as standard is recommended. Careful consideration should also be given to the selection of tumour blocks to optimise the identification of venous invasion, particularly areas of linear spiculation at the advancing edge of the tumour, as well as taking sections at multiple levels.

Magnetic resonance imaging (MRI) is now the standard preoperative local staging modality in rectal cancer and, since the development of high-resolution scanners, extramural venous spread can be detected more readily. MRI-detected extramural venous invasion has been shown to be comparable with that detected on subsequent pathological assessment.[101] It should be a goal of the MDTM to provide feedback between the radiologist and pathologist concerning the detection of venous invasion and other factors as a further means of quality assurance.

There is also now evidence to suggest that tumour invasion of small vessels, comprising lymphatics, capillaries and post-capillary venules (all considered under 'L' classification in TNM 8), is associated with lymph node metastatic disease and is an adverse prognostic factor.[97,98,102,103] Multiple studies including a meta-analysis have demonstrated the adverse prognostic value of perineural invasion in colorectal cancer.[104–107] One large multicentre study reports adverse prognostic significance of both intramural and extramural perineural invasion.[104]

Therefore, it is now recommended that small vessel invasion (L1) and perineural invasion (Pn1) should both be documented in pathology reports, with an indication of the deepest level of spread, intramural (intramuscular or submucosal) or extramural. Distinction between intramuscular and submucosal spread is not required. Note that, with the exception of direct primary tumour invasion into a lymph node, identification of lymph node metastatic disease implies invasion of the lymphatic system and, therefore, all such node positive cancers should be automatically recorded as having extramural lymphatic invasion (L1).

[Level of evidence A – Venous, lymphatic and perineural invasion predict prognosis.]

5.2.9 Histologically confirmed distant metastatic disease

The presence of histologically confirmed distant metastatic disease, and its site(s), is recorded. It should be noted that disease classifiable as distant metastatic disease may sometimes be present within the primary tumour resection specimen, for example a peritoneal or omental deposit that is distant from the primary mass. Metastatic disease in lymph nodes distant from those surrounding the main tumour or its main artery in the specimen, which will usually be

submitted separately by the surgeon (e.g. in para-aortic nodes or nodes surrounding the external iliac or common iliac arteries), is also regarded as distant metastatic disease (pM1).[68]

TNM 8 has subclassified colorectal cancer stage pM1 into substage pM1a representing metastatic disease in one distant organ (excluding metastatic peritoneal disease), pM1b representing metastatic disease in two or more distant organs and pM1c representing metastatic peritoneal disease (regardless of other organ involvement).[20,54] Pathologists can only base assessment of distant metastatic disease on submitted specimens. Therefore, the terms 'pM0' or 'pMX' should not be used and were removed from the TNM classification some years ago.

5.2.10 Separate abnormalities

The presence of any pathological abnormalities in the colon or rectum away from the tumour should be recorded. This includes:

- polyp(s), including their number, size and type (adenomatous, hyperplastic, serrated, hamartomatous, etc), and if criteria are met for a polyposis syndrome. N.B., this is distinct from any identifiable precursor lesion adjacent to the tumour
- synchronous carcinoma(s) (each of which will require a separate proforma)
- ulcerative colitis
- Crohn's disease
- diverticulosis
- obstructive colitis
- non-tumour perforation.

5.2.11 Block index

While standardisation of dissection protocols and specimen sampling is highly recommended, there is inevitable variation between individual cases. Therefore, a block index is highly valuable, to document the sampling process. Ideally, this should be accompanied by annotated photography. Blocks which demonstrate particular macroscopic findings can then be readily identified for microscopic comparison. It is helpful to reference such key blocks in the pathology report. This is particularly helpful in cases which are subsequently subject to external review.

Distinct from blocks demonstrating key morphological findings, at least one representative 'molecular block' should be identified, suitable for any required ancillary molecular testing. This block should be selected as having high overall cellularity, low tumour necrosis and a high proportion of carcinoma cellularity, compared to inflammatory cells or other non-carcinomatous tissues. An estimate of the carcinoma cellularity content of the entire block should be provided, to the nearest 10%. Acellular mucin should be ignored in this assessment. As such blocks may be used for multiple purposes, including clinical trials, and therefore may be removed from the tissue archive, it is recommended to indicate more than one such representative molecular block. For similar reasons, it is recommended to avoid choosing any particularly clinically important blocks, for example blocks with key tumour features which are not evident in other blocks.

6 Non-core data items

6.1 Macroscopic

Non-core macroscopic items may include:

- additional specimen dimensions (beyond maximum dimension)
- precise anatomical (quadrantic) location of CRM involvement (rectal tumours)

- for colon cancer specimens, the plane of mesocolic excision.[105,106]

6.2 Microscopic

Non-core microscopic items may include:

- tumour budding grade (see section 10.4)
- poorly differentiated clusters grade
- assessment of peritumoural inflammation
- tumour stromal percentage.

7 Additional investigations

There are two main indications for ancillary testing in colorectal cancer: (1) to detect underlying Lynch syndrome or rarer syndromes, and (2) to inform choice of systemic therapy. Lynch syndrome testing applies to all new diagnoses of colorectal cancer whereas systemic therapy biomarker testing applies largely to patients with metastatic disease. There is some overlap in the testing involved for each of these indications.

Following an analysis of clinical and cost effectiveness, NICE issued a recommendation in 2017 to universally test, at the time of diagnosis, all colorectal cancers for MMR/microsatellite instability (MSI) status, with the purpose of detecting Lynch syndrome.[108] As such, this is considered a core item for reporting. This testing may be performed on tumour tissue sections by immunohistochemistry, evaluating expression within tumour nuclei of a panel of MMR proteins, by MSI testing, usually applying a panel of five mononucleotide or dinucleotide markers, or increasingly by next generation sequencing (NGS).

Recent studies have shown MMR immunohistochemistry and MSI testing to be highly concordant,[109] although pathologists reporting MMR immunohistochemistry need to be aware of potential pitfalls in the form of unusual staining patterns.[110] For example, a punctate or dot-like pattern of nuclear staining has recently been described for MLH1, now considered to be a clone-dependent artefact.[111,112] This aberrant pattern of expression indicates abnormal MLH1 function and can be difficult to identify.

Some reports have advocated a two, rather than four, antibody panel for MMR immunohistochemical testing, as abnormal MSH2 and MLH1 staining is almost invariably accompanied by loss of MSH6 and PMS2 staining respectively.[113,114] However, we recommend a four-antibody panel approach, to help avoid some of the potential pitfalls in reporting, as interpretation can be facilitated by examination of the relevant MMR protein heterodimer partner. Rarely, loss of MSH2 expression is accompanied by only patchy MSH6 loss.[115] Pathologists should use clear terminology in their reports, specifically avoiding potentially confusing ‘positive/negative’ descriptors, for example.

Such tumour tissue testing can be performed on either the diagnostic biopsy specimen or on a block from a surgical resection specimen. If MMR immunohistochemistry is the test of choice, we recommend this is performed on the endoscopic biopsy specimen, assuming this contains diagnostic material, as better fixation facilitates interpretation of the immunostaining, and the result is available clinically in a timelier fashion. If the result is equivocal, perhaps because only limited tumour tissue is present or the sample is heavily inflamed, or the tumour cells show an unusual staining pattern, testing should be repeated on a suitable block from any subsequent surgical resection specimen and/or supplemented by MSI testing.

Identification of microsatellite instability or defective MMR status with loss of MLH1 immunoexpression triggers tumour *BRAF* V600E testing and/or *MLH1* promoter

hypermethylation testing to distinguish sporadic cancers from those due to Lynch syndrome, with referral to clinical genetics for counselling and germline mutation screening in those patients whose investigations raise suspicion of Lynch syndrome (MMR deficient or MSI-high, *BRAF* wild-type and absent *MLH1* promoter hypermethylation). Similarly, germline mutation screening of other specific genes may be required if any other genetic diagnosis is suspected based on clinicopathological phenotype, e.g. *FAP* or *MUTYH*-associated polyposis. However, increasingly such testing is performed on a panel basis, for example simultaneously screening by NGS for mutations in a wide range of genes associated with various polyposis syndromes.

Lynch syndrome accounts for approximately 2–3% of all colorectal cancers. More common, representing approximately 15% of all colorectal cancers, are sporadic MMR deficient/MSI-H colorectal cancers, due to somatic events, usually hypermethylation of the *MLH1* promoter. There is now strong evidence that these tumours have a better prognosis than MMR-proficient colorectal cancers in stages II and III, and metastasise less frequently, with only 3–4% of stage IV colorectal cancers being MMR deficient.[116–118] The relationship between deficient MMR status and response to therapy is controversial. Some studies have predicted a lack of response to 5-fluorouracil-based chemotherapy with possible abrogation by the addition of oxaliplatin to the chemotherapy regime (such as in FOLFOX), but other studies have not demonstrated this.[117,119–123] MMR deficiency predicts response to immune checkpoint blockade therapy.[124]

Other biomarkers help identify patients with stage IV colorectal cancer most likely to benefit from certain forms of systemic treatment. Most notably, mutations in *KRAS and NRAS* predict lack of response to anti-epidermal growth factor receptor (EGFR) targeted therapy and NICE now recommends screening these genes for mutations in this clinical setting.[125] Testing should at least include *KRAS* codons 12, 13, 59, 61, 117 and 146 and *NRAS* codons 12, 13, 59 and 61. Presence of the specific *BRAF* V600E mutation indicates an adverse prognosis compared to patients with *BRAF* wild-type tumours. While single agent anti-EGFR monoclonal antibodies are currently licensed in these patients, there remains no good evidence that they are likely to respond to this treatment.[126] However, patients whose tumours are microsatellite stable, *RAS* wild-type and *BRAF* V600E-mutant may respond to combination therapy using anti-EGFR inhibition alongside the BRAF inhibitor encorafenib.[127]

1.5% of colorectal cancers may carry a neurotrophic tyrosine receptor kinase (*NTRK)* fusion gene abnormality within the TRK family of proteins.[128] This family produces the TRKA, TRKB, and TRKC proteins encoded by the *NTRK1, NTRK2* and *NTRK3* genes. In-frame gene fusion events resulting from chromosomal rearrangements of the *NTRK* genes lead to the formation of oncogenic TRK fusion proteins. These novel oncogenic chimeric proteins are aberrantly expressed, driving constitutive kinase activity. This activates downstream pathways involved in cell proliferation and survival and leading to TRK fusion-driven cancer. The TRK inhibitors larotrectinib and entrectinib are now approved by NICE for the treatment of solid tumours, including colorectal cancer, which harbour NTRK fusions, where there are no other satisfactory systemic treatment options.[129,130] Accordingly, funding in England is currently available under the Cancer Drugs Fund. Note that NICE approvals change regularly and the Cancer Drugs Fund can be consulted to see the current drugs funded.[131]

Given expanding molecular testing requirements, greater engagement of cellular pathology services with both molecular pathology and clinical laboratory genetics services is advised, to optimise local arrangements for testing pathways. Although most bowel cancer somatic tumour testing is currently performed using assays directed at specific genes, this is likely to migrate in coming years to a NGS panel-based approach to testing, covering a wider range of cancer-related genes of interest.

The mutations identified not only inform the type of therapy but also can inform the use of cell-free DNA assays to identify individuals at high risk of relapse. Such assays, especially whole genome sequencing, are best performed on fresh tissue. Therefore, development of NGS-based testing towards use in routine practice may have implications for how pathologists

receive and handle fresh tissue specimens and the appropriate methods should be discussed in the MDTM.

Currently, most such testing is performed on formalin-fixed, paraffin-embedded tissue. Some patients may only have one specimen (diagnostic or resection) suitable for testing while others may have a diagnostic endoscopic biopsy specimen, a surgical resection specimen of the primary tumour and/or a core biopsy or resection specimen of a distant metastasis. Optimal choice of specimen for testing depends on multiple factors but specimen availability and specimen cellularity are the main determinants. When multiple specimens are available, we recommend in general opting to test a resection block from the primary resection or metastasis, given that much more abundant tumour tissue is typically available within such specimens.

One study has reported heterogeneity for *RAS* or *BRAF* mutation status within 10% of patients when testing multiple blocks from the primary tumour, flagging a small but definite risk of generating a false wild-type result when testing a limited specimen.[132] However such 'DNA cocktail' testing adds to the complexity and cost of testing and is not recommended practice. If molecular testing is to identify the new development of a resistance mutation then the most recent metastatic specimen should be tested.

[Level of evidence A – Molecular testing helps detect Lynch syndrome and predicts response to systemic therapies.]

8 Diagnostic coding

Colorectal carcinomas should be coded according to the SNOMED system, applying appropriate T and M codes as a minimum (Appendix B). It is noted, however, that SNOMED is now in a practical transition phase, as part of the intended full implementation by the NHS and Public Health England of SNOMED CT. SNOMED ceased to be licensed by the International Health Terminology Standards Development Organisation from 26 April 2017.

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

9 Pathological staging

9.1 Margin involvement and resection status

Margins include the longitudinal ends of the specimen, the CRM and any separately submitted anastomotic rings. Tumours that do not involve an excision margin are classified as R0, those with microscopic (but not macroscopic) margin involvement are classified as R1 and those with macroscopic margin involvement (and confirmed histologically as 0 mm to margin) as R2. CRM is regarded as microscopically involved (R1) if tumour extends histologically to $\leq$1 mm from this margin.[82] This measurement is usually but not exclusively based on the primary tumour (see section 5.2.5).

It is advisable to correlate macroscopic margin involvement with the intraoperative findings at MDTM discussion prior to designation as R2, given the significant clinical impact of this interpretation. Note also that R2 status reflects not only primary tumour resection, but also distant metastatic disease. Therefore, if a separate tumour deposit, for example in the peritoneal cavity or liver, has been biopsied or sampled for histological or cytological diagnosis, R2 classification is appropriate regardless of the primary tumour resection margins.

When anastomotic rings and/or the longitudinal ends of the specimen are not examined histologically because the tumour is >30 mm away these are assumed to be tumour free.

Peritoneal involvement is recorded under the T, not the R, category. Peritoneal involvement alone is not a reason to categorise a tumour as incompletely excised.

9.2 TNM staging

The TNM 8 staging definitions are shown in Appendix A. The prefix ‘p’ is used to indicate pathological staging. If preoperative chemotherapy and/or radiotherapy has been given, the prefix ‘yp’ should be used to indicate that the original p stage may have been modified by therapy. Accordingly, when there has been complete regression of the tumour (primary tumour and nodal disease), the TNM stage is ypT0, ypN0.

The following points are worth emphasising:

- in determining the pT stage, tumours that have perforated into the peritoneal cavity are regarded as pT4a (TNM 8), irrespective of other factors
- direct intramural spread of caecal carcinomas into the terminal ileum or rectal cancers into the anal canal does not affect the pT stage. However, direct transperitoneal spread (across the serosa) of a colorectal carcinoma into another part of the large or small intestine corresponds to pT4b (fulfilling criteria for pT4a and pT4b)
- applying TNM 8, tumour deposits (discrete nodules of cancer in the peritumoural connective tissue, discontinuous from the primary tumour and without histological evidence of lymph node, vascular or neural structures) are classified as stage pN1c, if there is no metastatic tumour in lymph nodes. Tumour deposits do not change the primary tumour T stage. Application of ancillary stains is recommended to accurately apply TNM 8 rules regarding interpretation of discontinuous tumour foci[92]
- the difference between stage pN1 and pN2 is the number of lymph nodes involved (pN1 = 1–3 nodes, pN2 = 4+ nodes), irrespective of their site in the resection specimen. TNM 8 has further subclassified pN1/2 stages (Appendix A)
- pathological M staging can only be based on distant metastatic disease that is submitted for histology and will therefore tend to underestimate the true (clinical) M stage. Pathologists will therefore only be able to use pM1 (distant metastatic disease present) and should not use ‘pM0’ or ‘pMX’. Note that metastatic deposits in lymph nodes distant from those surrounding the main tumour or its main artery in the specimen are regarded as distant metastatic disease
- TNM 8 recommends substaging of stage pM1 disease into: pM1a, with metastatic disease confined to one organ without peritoneal metastases; pM1b, with metastatic disease in more than one organ but without peritoneal metastases; pM1c, with metastatic disease in the peritoneum with or without other organ involvement
- if a tumour represents a recurrence, its stage should be denoted with the prefix ‘r’ and, if derived from an autopsy specimen, with the prefix ‘a’
- in the case of multiple primary tumours, separate datasets should be completed for each primary tumour, but overall stage relates to the tumour with the highest T category and the multiplicity or number of tumours should be indicated in parenthesis, e.g. pT3(m) or pT3(2)
- in the case of multiple primary tumours, it is reasonable to attribute any nodal involvement to the highest T stage tumour unless there are clear indicators, for example from location or morphology, to indicate otherwise. For example, metastatic mucinous adenocarcinoma within lymph nodes is likely to spread from a primary mucinous adenocarcinoma, if any synchronous tumour lacks mucinous differentiation.

[Level of evidence A – TNM staging is of strong prognostic value.]

10 Reporting of local excision specimens of colorectal cancer

Local excision of colorectal cancer is usually undertaken in one of two situations:

- as a curative procedure for early stage (T1) colorectal cancer
- as a palliative procedure in debilitated patients.

While the principles of pathological reporting are the same as in major resections, a number of features require special attention in local excisions of (presumed) early cancers with curative intent because they are used to determine the necessity for more radical surgery. In addition to the assessment of completeness of excision, these include the recording of parameters that predict the presence of lymph node metastatic disease in early tumours, including tumour size, poor differentiation, the depth of invasion into the submucosa, the presence of submucosal lymphatic or venous invasion and margin involvement.[133–137] There is only limited consensus in the published literature on how exactly some of these parameters should be assessed. One recent meta-analysis reported that deep submucosal invasion in isolation is not a strong independent predictor for lymph node metastatic disease and should be reconsidered as a sole indicator for surgical intervention.[138] Given well-recognised difficulties in some polyps of distinguishing stage pT1 adenocarcinoma from epithelial misplacement and the clinical importance of assessing features within such cancers that may directly impact management, we recommend that all pT1 cancers be reported by two consultant pathologists.

Local excisions are undertaken endoscopically or, in the case of early rectal tumours, under direct vision. The majority of such tumours arise within pre-existing adenomas that may be pedunculated, semi-pedunculated, sessile or flat, and the best pathological information is derived when lesions are excised in their entirety to include both the invasive and pre-invasive components. Polypoid lesions on a narrow stalk can be fixed intact, while semi-pedunculated or sessile lesions can be pinned out, mucosal surface upwards, on a piece of cork or other suitable material, taking pains to identify the narrow rim of surrounding normal tissue, before fixing intact. Piecemeal removal of tumours, entirely acceptable for palliative resections, should be avoided if possible because it precludes a reliable assessment of completeness of excision.

After fixation, polypoid lesions may be bisected through the stalk if they measure <10 mm; larger polyps are trimmed to leave a central section containing the intact stalk, and all fragments embedded for histology. It is recommended that at least three sections be examined routinely from blocks containing the stalk. The margins of larger, sessile or semi-pedunculated lesions should be painted and the whole of the specimen transversely sectioned into 3 mm slices and submitted for histology in sequentially labelled cassettes. In cases where the margin of normal tissue is less than 3 mm, a 10 mm slice containing the relevant margin should be made and further sectioned at right angles.[26] Macroscopic images of the intact and sliced specimen may be helpful to illustrate margin status.

An example template proforma for reporting local excision specimens is included in this dataset (Appendix D). The core data items to be recorded are:

- specimen type (intact/piecemeal polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection, transanal endoscopic microsurgical [TEMS] excision, transanal minimally invasive surgical (TAMIS) excision, endoscopic full thickness resection [EFTR])
- site of tumour
- overall specimen (usually polyp) size
- histological tumour type
- grade of differentiation
- extent of local invasion

- venous invasion
- lymphatic invasion
- perineural invasion
- tumour budding
- presence of a precursor adenoma (or other polyp type)
- margin involvement by carcinoma (deep/peripheral)
- minimum deep margin clearance of the invasive carcinoma
- pT stage
- MSI / MMR tumour status
- block index (to include identified 'molecular block' for additional molecular testing).

Most of these parameters mirror assessment within surgical resection specimens but some require special consideration.

10.1 Grade of differentiation

Differentiation is assessed by the same criteria as in major resection specimens, that is on gland formation. This dataset previously recommended (version 4) that, for pT1 tumours, grade of differentiation should be based on the area of worst differentiation, excluding tumour buds or poorly differentiated clusters at the advancing edge, to avoid the potential under-treatment.

With the latest WHO classification and ICCR guidelines now recommending that grading of all stages of colorectal cancer should be based on the least differentiated tumour component,[24,25] and with the acceptance in this dataset revision of this grading method for surgical resection specimens, we now have alignment in grading assessment for all colorectal cancer resection specimen types and stages. This alignment is particularly important to avoid confusion in the assessment of more advanced local excision procedures now undertaken, such as endoscopic full thickness resections, which may contain a cancer beyond stage pT1. The minimum area of poor differentiation has not been defined.

As with surgical resection specimens, morphological assessment of differentiation applies only to 'adenocarcinoma, NOS' and mucinous carcinoma, with mucinous carcinoma graded on glandular formation and epithelial maturation.[25] Some of the other histological variants carry their own prognostic significance.

There is growing evidence that grading by assessment of poorly different clusters at the advancing tumour edge predicts the risk of lymph node metastatic disease in pT1 colorectal cancer local excision specimens.[55,139–145] However, as with assessment of poorly differentiated clusters in surgical resection specimens, these findings require broader, multicentre validation and consensus on optimal assessment methodology prior to introduction into clinical practice. This evidence will be kept under review.

[Level of evidence B – Poor differentiation predicts nodal metastatic disease.]

10.2 Extent of local invasion

Tumours that invade the muscularis propria usually require surgery. The frequency of lymph node metastatic disease in sessile tumours that involve the superficial, middle and deep thirds of the submucosa (so-called Kikuchi levels sm1, sm2 and sm3, respectively) has been reported to be 2%, 8% and 23%.[146,147]

In pedunculated lesions, Haggitt *et al.* (1985) identified the level of invasion into the stalk of the polyp as being important in predicting outcome and found that 'level 4' invasion, in which the tumour extended beyond the stalk of the polyp into the submucosa but did not invade the muscularis propria, was an adverse factor.[148] However, neither system (Kikuchi for sessile tumours and Haggitt for pedunculated tumours) is always easy to use in practice, especially if there is fragmentation or suboptimal orientation of the tissue. The Kikuchi level system requires division of the submucosa into thirds, and this is not possible to do accurately unless muscularis propria is included in the specimen, which is rare in most local excision specimens. Despite these difficulties, and resultant limitations on the clinical utility of Haggitt and Kikuchi levels, they should be reported as applicable and where possible, in the absence of good evidence to recommend alternative measures.

Ueno *et al.* (2004) have proposed that the absolute thickness of the invasive tumour (depth of invasion beyond the muscularis mucosae) and the width of tumour invasion provide more objective measures of potential risk of lymph node metastatic disease.[137] One study of stage pT1 colorectal cancers found lymph node metastatic disease in only 4 (2%) of 203 lesions with a depth of submucosal invasion <1000 μm.[149] The Japanese Society for Cancer of the Colon and Rectum guidelines consider surgical resection for tumours with a depth of invasion of >1000 μm or with other high-risk features.[31] Adoption of this guidance would significantly increase the resection rate in the UK and we believe this approach is inappropriate. The evidence base is not clear in UK practice and requires a major audit, ideally conducted under the auspices of the NHS bowel cancer screening programmes.

In summary, a firm recommendation cannot be made based on current evidence for one method of assessing local invasion over another in pT1 cancers. All four approaches are included in the proforma dataset to facilitate data collection for further research and for local MDTs to select which they consider to be most appropriate to management decisions.

[Level of evidence B–D, depending on criterion – Extent of local invasion predicts nodal metastatic disease.]

10.3 Lymphatic and venous invasion

Tumour infiltration of endothelium-lined spaces in the submucosa, or lymphovascular invasion, is regarded as a significant risk factor for lymph node metastatic disease in stage pT1 colorectal cancer. Multiple meta-analyses have revealed lymphatic invasion and, to a lesser extent, venous invasion to be powerful predictors of lymph node metastatic disease.[133,134] Lymphatic and venous invasion should therefore be assessed and reported separately if possible. Lymphatic invasion should be distinguished from retraction artefact. This may be assisted by application of D2-40 immunohistochemistry to specifically identify the lymphatic channel endothelial lining.[150–152] CD34 stains both lymphatic and venous endothelial lining cells. Venous invasion is defined as tumour lying within an endothelium-lined space that is surrounded by a rim of muscle or identifiable elastic lamina. If the tumour has obliterated the lumen of a vein, an elastin stain may highlight the wall, confirming a rounded structure as a vein. In contrast to veins, lymphatic channels lack a muscular wall and are usually, although not always, devoid of red blood cells. Distinguishing lymphatic channels from thin-walled post-capillary venules may be impossible without ancillary stains. Although immunohistochemical and histochemical stains can be useful to identify and distinguish lymphatic and venous invasion, it is recommended that they are applied judiciously in equivocal cases, along with examination of further levels, rather than applied routinely to all cases, taking into consideration resource implications. Lymphatic and/or venous invasion should only be recorded as positive if the features are considered definitive.

[Level of evidence B – Lymphatic and venous invasion predict metastatic disease.]

10.4 Tumour budding

Tumour buds are defined as single cells or clusters of up to and including four tumour cells, usually most evident at the invasive front of carcinomas, and likely representing a morphological manifestation of epithelial–mesenchymal transition.[153] They are distinguished from poorly differentiated clusters which are defined as clusters of five or more tumour cells lacking gland formation (Figure 7).[55]

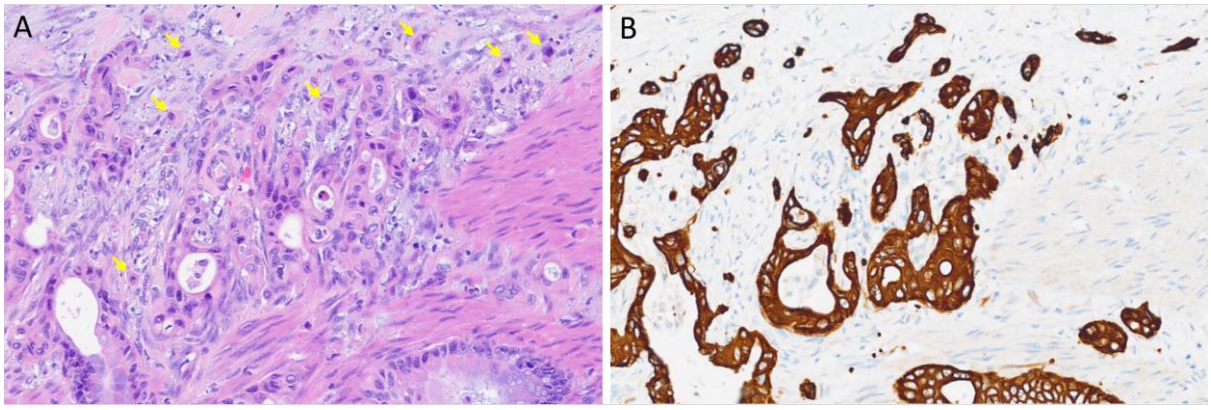


Figure 7. (A) Tumour buds (arrows) are single tumour cells or clusters of up to four tumour cells. (B) Budding-rich areas may be highlighted by cytokeratin immunohistochemistry but individual buds should be counted for reporting on H&E staining.

There is now considerable evidence that tumour budding is an independent adverse prognostic factor in colorectal carcinoma. Previous concerns regarding non-standardised assessment methodology were addressed in 2016 by the International Tumour Budding Consensus Conference (ITBCC),[154] which recommended methodology modified from that previously proposed by Ueno *et al.* (2014) and adopted by the Japanese Society for Cancer of the Colon and Rectum.[155,156] It was agreed that budding assessment should be based on H&E-stained sections from the invasive tumour front and that budding should be graded by a three-tier system according to the highest number of buds present in a 0.785 mm^2 'hotspot' area, after scanning the represented invasive margin of the tumour. This area is equivalent to the microscopic field area at x20 objective lens on a microscope with a 20 mm eyepiece diameter. Counting will need to be normalised according to the diameter of the eyepiece used.[154] Applying this method, Bd1 (low), Bd2 (intermediate) and Bd3 (high) grades have less than five, five to nine and ten or more buds per hotspot area respectively. Reports should record the number of buds identified in the tumour 'hotspot' and the corresponding grade.

Using this standardised methodology, more recent studies have demonstrated that stage pT1 colorectal carcinomas with at least five buds per hotspot (budding grades Bd2 or Bd3) are associated with an increased risk of lymph node metastatic disease.[145,157] These studies build on previous evidence from meta-analyses, which included studies with variation in methods of budding assessment.[133,136,158] Although few studies have demonstrated the independent significance of tumour budding on multivariate analysis,[159] existing evidence is considered sufficient for the assessment of tumour budding by the ITBCC method to be a core item for reporting stage pT1 cancers within local excision specimens. High-grade budding (Bd2 or Bd3) may encourage surgical intervention. However, it is emphasised that clinical decisions should not be made based on tumour budding grade in isolation, as the associated risk is likely to differ according to other pathological features and to the clinical scenario, such as whether the polyp in question is sessile or pedunculated. One study, for example, found an extremely low risk of lymph node metastatic disease associated with high tumour budding, when tumour depth of invasion was less than 1 mm.[149] Management decisions should therefore always be made in an appropriate multidisciplinary setting, with consideration of all relevant clinical, endoscopic and pathological findings.

The following practical points should be noted in the assessment of tumour budding:

- budding should not be assessed in areas of active inflammation or in association with glandular rupture, as apparent buds in these scenarios are likely to represent different biological phenomena
- budding should not be assessed in areas of mucinous differentiation and is 'not applicable' if the tumour shows entirely mucinous differentiation. Budding may however be assessed if a mucinous carcinoma has a minor component showing conventional adenocarcinoma morphology
- while counting of buds is based on H&E-stained sections, cytokeratin immunohistochemistry may be usefully applied to direct the observer to the area of highest budding activity
- budding should be assessed at the advancing tumour edge, the line marking which should be included within the microscopic field of assessment (Figure 8).

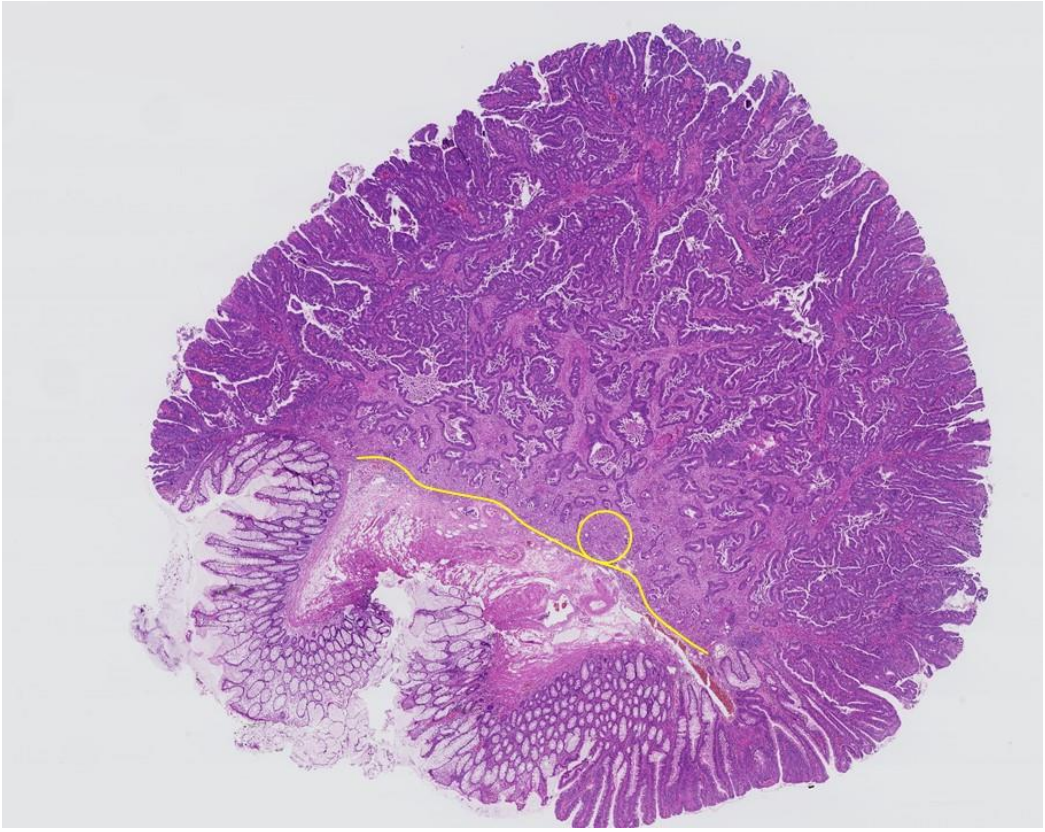


Figure 8. Tumour budding is assessed on H&E-stained sections from the invasive tumour front and should be graded by a three-tier system according to the highest number of buds present in a 0.785 mm^2 'hotspot' area, after scanning the invasive margin. The chosen hotspot (yellow circle annotation) must include the line marking the advancing edge (yellow line annotation). Applying this method, Bd1 (low), Bd2 (intermediate) and Bd3 (high) grades have less than five, five to nine and ten or more buds per hotspot area respectively.

There is also considerable evidence from large, retrospective, mostly single centre studies that, for stage II colorectal carcinomas treated by surgical resection, tumour budding grade Bd3 has adverse prognostic value and is associated with increased risk of recurrence and mortality.[153,160,161] In addition, the prospective, multicentre SACURA trial, which assessed budding by ITBCC criteria, showed a non-significant trend in predicting benefit of adjuvant chemotherapy in those patients with stage II colon cancer demonstrating high tumour budding (Bd 2 or Bd3) compared to those with low tumour budding (Bd 1).[162] With limited evidence to date of predictive utility applying ITBCC criteria, and some concerns regarding reproducibility

of budding assessment in larger surgical resection specimens compared to local excisions, this remains a non-core item within surgical resection specimens, pending further evidence.

[Level of evidence A – Tumour budding predicts risk of lymph node metastatic disease.]

10.5 Margin involvement

Intact polypectomy and any other type of local excision specimens require assessment of both the peripheral (mucosal) and deep margins. Note the deep margin for many polypectomy specimens is submucosal but, in more advanced local excisions, such as EFTR or surgical local excisions, the deep margin may be variably located within submucosa, muscularis propria or beyond, in extramural fat. It is important for pathologists to evaluate the full width of the margin, document what tissue plane has been achieved and, if there is margin involvement, specify the level of the deep margin at the point of involvement (submucosal, intramuscular or extramural). The precise measurement of the closest proximity of the deep margin from invasive tumour should be recorded, to the nearest 0.1 mm where possible. Importantly, several issues merit consideration to ensure a standardised approach to measuring distance from tumour edge to resection margin.

Most large polyps are removed by diathermy snare or similar devices. Diathermy resection produces a zone of diathermy burn that can be up to several millimetres thick, due to coagulation of tissue, and this introduces a number of secondary artefactual changes (Figure 9). For example:

- the diathermied plane of resection is drawn back into the stalk of the polyp and may be buried beneath the less affected mucosal rim
- coagulated blood vessels do not shrink to the same degree as the surrounding stroma and may stand proud of the rest of the retracted diathermy plane
- there may be marked clefting alongside the coagulated blood vessels because of the differential shrinkage of vessels and stroma. The coagulation zone is brittle and so may split or fragment during dissection
- beyond the zone of diathermy burn, the loose submucosal stroma may appear markedly disrupted, probably due to a vaporisation effect.

Care should be taken to take account of artefacts that could give rise to a false assessment of distance of tumour to the margin. While it may be tempting to draw a straight line to join the two edges of the retracted plane and use that as a putative plane, this will give an erroneous measurement if either the tumour is close to the margin and also retracts back into the polyp, or the lesion is sessile but develops a curved shape due to diathermy and fixation. For this reason, it is advised that the outer edge of the diathermy zone is used for assessment of the margin (Figures 9B and 9C) as follows:

- starting from the muscularis mucosae on one side, draw a smooth line following the outer edge of the diathermy burn to run to the muscularis mucosae of the opposite side. Include any indentations, but ignore any artefactual splits and clefts.
- measure the distance of invasive carcinoma to the notional line. Distances should be recorded in millimetres to one decimal point, although it is accepted that accuracy will be limited in this scenario.

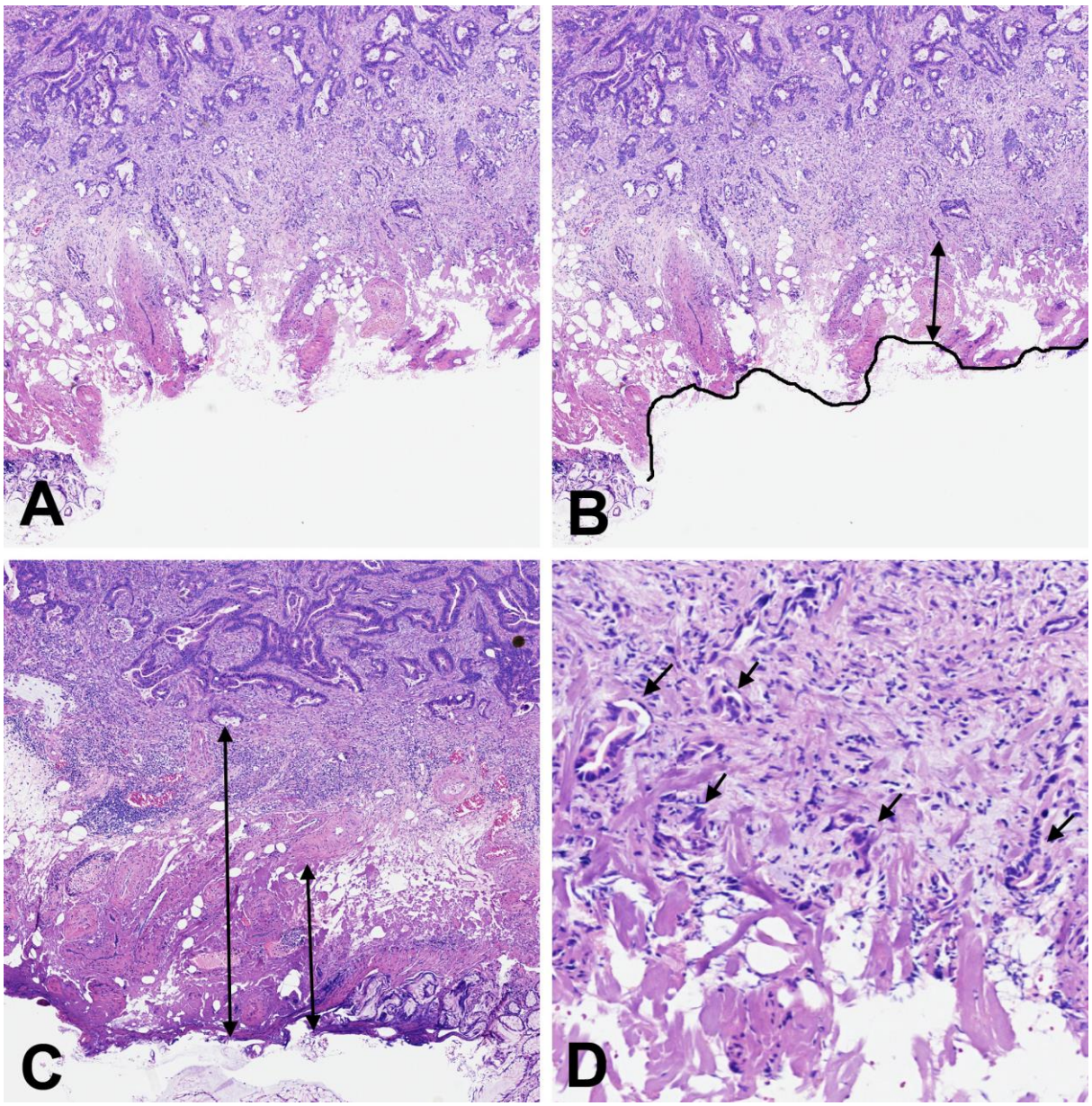


Figure 9. Diathermy artefact and margin assessment. Diathermy snare resection introduces a zone of secondary artefactual changes that makes margin assessment difficult. (A) Stromal vaporisation, clefting and withdrawal of the resection plane is most marked adjacent to thick submucosal blood vessels. (B) Measurement of tumour to resection margin should avoid such artefacts and a best attempt should be made to measure to the true resection margin (arrow). A distance of ≤1 mm from tumour to margin is considered margin involvement (R1 resection status). (C) The zone of diathermy artefact can be several millimetres thick depending on the excision technique employed (short arrow = 2.1 mm); tumour is well clear of the outer (true) resection margin here (long arrow = 3.9 mm). Measurement of clearance should not be to the inner aspect of the diathermy zone, in this event. (D) However, infiltration by malignant glands into the diathermy zone (short arrows) is regarded as margin involvement (0 mm distance recorded), if it is not possible to confidently determine the true extent of infiltration in this situation. Copyright NHS Bowel Cancer Screening Programme; pathology committee approval given for reproduction.

Cancer in whatever context (for example, in blood vessels or present as pools of mucinous carcinoma) should be considered when assessing tumour proximity to a margin, with the proviso that, if there is coexisting epithelial misplacement, care should be taken to ensure benign elements such as mucin lakes are not included. If there is infiltration by malignant glands into the diathermy zone and this is associated with morphological distortion of tissue to

the extent that it is not possible to confidently identify tumour clearance from the outer margin (Figure 9D), then this should be regarded as margin involvement and a distance of 0 mm of clearance recorded. Cytokeratin immunohistochemistry may help assessment in this situation by identifying neoplastic glands within the diathermy zone and their relationship with the outer edge of the zone of diathermy. This can also help distinguish tumour from artefactual changes to blood vessels located within the diathermy zone. If tumour cells are present within a thick diathermy zone, but there is a recognisable zone of clearance to the outer margin, evident on H&E assessment alone or with application of immunohistochemistry, then this margin of clearance should be measured and, if $\geq$1 mm, the resection status can be considered R0.

Marking the diathermy line with ink or another marker is not recommended because of the artefactual clefting and the disruption of loose connective tissue stroma within the polyp stalk, both of which can 'wick' the marker for a considerable distance into the stalk. The zone of diathermy burn should provide adequate evidence of the true margin. Problems in assessment may also arise because the axis of section does not include the diathermy line or because of crosscut elements in convoluted lesions.

In general:

- when dissecting polyps, ensure that the plane of section includes the diathermy line
- when assessing polyps, be aware of their three-dimensional configuration and their orientation
- sections cut at deeper levels may assist assessment, particularly if the lesion is convoluted or the artefact is marked
- in cases of doubt, adopt a conservative approach and only measure to a margin about which you are confident
- measure the distance of clearance to the nearest 0.1 mm.

Involvement of a peripheral margin may indicate the need for repeat endoscopy and further local excision. Involvement of the deep resection margin by invasive tumour has traditionally been an indication for considering surgical intervention. There has been considerable discussion and controversy in the literature over the degree of clearance that might be regarded as acceptable in tumours that extend close to the deep submucosal margin. Most existing guidance considers a clearance of ≤1 mm as needing consideration of further therapy.[61,163] There is some evidence to suggest that, for pT1 tumours, only tumours present at the true or estimated resection margin, or within the diathermy burn zone, should be considered for further treatment, which may be local re-excision if no other adverse pathology features are identified.[137,164,165] This is not sufficiently strong, however, to change the current recommendation to consider clearance of ≤1 mm as margin involvement. Nevertheless, a conservative approach to margin assessment is recommended, as described above, designating as margin involvement only when tumour extends to within ≤1 mm of the true polypectomy margin (Figure 9). For consistency, despite the absence of good evidence, tumour extending to within ≤1 mm of the peripheral mucosal, submucosal or muscularis propria margins is also considered margin involvement.

[Level of evidence C – Margin involvement predicts an increased risk of residual local disease.]

11 Reporting of diagnostic biopsy specimens

As the vast majority of colorectal cancers are adenocarcinomas arising from adenomatous polyps, the main challenge in reporting endoscopic biopsies from clinically suspicious colorectal cancers is in deciding if the features are sufficient to warrant a diagnosis of malignancy. The diagnosis of colorectal cancer on biopsy clearly depends on definition. In Japan and elsewhere in this part of Asia, it is largely a cytological diagnosis while in the USA

and some areas of Europe, architectural features are emphasised. In the UK, we follow European and WHO guidance that requires definitive evidence of submucosal invasion to make a diagnosis of adenocarcinoma and does not allow the diagnosis of intramucosal adenocarcinoma (section 5.3.2).[61,62] The latter term, and pT in situ (pTis), are not used in the UK for the lower gastrointestinal tract, to avoid potential overtreatment of lesions considered to have negligible risk of metastatic spread.[59] The term high-grade dysplasia should be used to encompass these. This position was also adopted recently by the ICCR.[24,60]

The requirement to demonstrate submucosal invasion undoubtedly creates diagnostic difficulties because biopsies may not show submucosal tissue. Biopsies from colorectal tumours therefore often fail to overtly demonstrate submucosal invasion. However, the presence of a desmoplastic stromal response to neoplastic glands is usually considered acceptable for a diagnosis of adenocarcinoma, as this is a rare finding in 'intramucosal adenocarcinoma'. Caution should be exercised with polyps or polypoid lesions, as a desmoplastic stroma might be encountered in these without submucosal invasion, related to surface ulceration and/or previous biopsy. Juxtaposition of neoplastic glands to submucosal structures, such as larger blood vessels, nerves and other neural structures, may also be sufficiently convincing to signify adenocarcinoma, although caution is advised as adenomatous epithelial misplacement may also approximate benign glands to such submucosal structures.

A significant minority of endoscopic biopsy specimens from clinically suspicious lesions may yield features regarded as suspicious for adenocarcinoma but not diagnostic because of a lack of obvious submucosal invasion or convincing desmoplastic stromal reaction. However, in most such cases, especially in the colon, confirmation of primary glandular neoplasia, in the context of appropriate clinical, endoscopic and imaging features, is sufficient to progress to surgical resection. If neoadjuvant therapy is being considered, particularly for rectal cancers, it is prudent to repeat endoscopic sampling in an attempt to achieve a diagnostic tissue sample before such therapy, which may result in a complete response and disappearance of the tumour. This repeat sample, therefore, confirms the diagnosis and also provides a tissue sample for any subsequent molecular testing which may be required.

As the demand for routine molecular testing grows, especially if performed on the diagnostic sample to inform MDTM discussion prior to definitive treatment, endoscopists should be encouraged to routinely take more and larger biopsy samples from all tumours, to allow a confident diagnosis and provide adequate tumour tissue for any required downstream testing. As the diagnostic endoscopic biopsy specimen may be used for molecular testing, we recommend that pathology reports from such specimens indicate (1) the specimen and specific block which contains the most abundant carcinoma tissue (if multiple have been submitted) and (2) an estimate of the carcinoma percentage content of the block by total cellularity (including all inflammatory, stromal and epithelial cells), to the nearest 10%. The report should specify that this assessment is based on the entire block, as carcinoma cellularity may be enriched, if necessary, by subsequent annotation and macrodissection steps prior to molecular testing.

In general, it is advisable to report what is evident microscopically, and allow clinical management decisions to be made based on the wider picture at MDTM discussion, specifically around the need for further biopsies or not, prior to therapeutic intervention. Regarding minimum criteria for issuing a histological diagnosis of colorectal adenocarcinoma, we recommend that this requires either definite histological evidence of submucosal invasion or desmoplastic reaction to neoplastic glands in the setting of a clinically evident malignancy. The phrase 'in keeping with adenocarcinoma' is discouraged, when non-diagnostic features are evident in the biopsies submitted.

12 Reporting of frozen sections

Frozen sections may occasionally be submitted of primary or metastatic colorectal cancer, typically when these are encountered unexpectedly in the intraoperative situation, for example in an emergency presentation of intestinal perforation. More commonly in this setting, even if the underlying diagnosis is unclear e.g. perforated sigmoid colon cancer versus complicated diverticular disease, the approach is surgical resection regardless, without frozen section. With advances in imaging and imaging-guided biopsy techniques, frozen section examination requests are rare occurrences in elective colorectal cancer management, as preoperative diagnosis of the primary lesion and/or metastatic disease, supported where necessary by immunohistochemistry, is the preferable approach. Rarely, frozen section examination may be requested to evaluate a surgical resection margin. Frozen section should only be undertaken when a result will affect the subsequent surgical approach.

13 Criteria for audit

There is compelling evidence that the introduction of the original RCPath colorectal cancer dataset (1998) improved the standard of colorectal cancer reporting with regard to the completeness of information within pathology reports.[19,166] However, audits show that significant differences remain in the frequencies with which important adverse prognostic features are found between individual pathologists and MDTs.[167] When these features are used as the basis for major excisions, offering adjuvant therapies and giving prognostic information to patients, the extent of the differences is a cause for concern.

Most prominent among these are the number of lymph nodes that are harvested and the demonstration of peritoneal involvement and extramural venous invasion. Some of the differences, for example in the number of lymph nodes retrieved from a resection specimen, may be related to factors such as patient age, the extent of the resection undertaken or the use of preoperative therapy, typically in rectal cancer.[168] Preoperative therapy is also likely to influence rates of peritoneal involvement and possibly venous invasion, if there is significant tumour regression. However, it is likely that the way that the pathologist examines and reports the specimen is the most important.[73] There is good evidence to show that the prognosis of stage II colorectal cancer is directly related to the number of lymph nodes examined pathologically, with the implication that some of these patients are ‘understaged’ and that, if more lymph nodes had been examined, metastatic disease would have been found.[169]

It is therefore recommended that MDTs and pathology departments audit their reports at regular intervals to ensure that their overall results are not significantly different from what might be expected. The following three standards are recommended:

- the median number of lymph nodes examined should be at least 15. The previous standard of 12 has been increased, reflecting improved modern surgical and pathology practice.
- the frequency of peritoneal involvement should be at least 20% for colonic cancers. Assessment of the percentage of rectal cases reported with peritoneal infiltration has been removed as a quality standard, given increased use of preoperative therapy for rectal cancer.
- the frequency of venous invasion, including intramural (submucosal and intramuscular) and extramural, should be at least 30%.

These parameters should be evaluated on a series of at least 50 resection specimens from symptomatic (i.e. non-screening) patients, who have not undergone preoperative therapy. These are minimum standards, with many centres in the UK finding a median of 15–25 lymph nodes per case, a frequency of peritoneal involvement of 30–40% and venous invasion in over 40%.

Turnaround time of pathology reports should also be audited. The recommended minimum standard for endoscopic cases is 90% authorised within five working days from the date of specimen receipt in the histopathology laboratory. The recommended minimum standard for surgical resection cases is 90% authorised within ten working days from the date of specimen receipt in the histopathology laboratory. The date of receipt is day zero. Any case that is authorised at any time on day five (endoscopic) or ten (surgical resection) meets this standard; those authorised thereafter do not. Interim reports are encouraged if cases are referred for second opinions. In this event, date of authorisation of the first report is considered for turnaround time analysis. Turnaround times should be analysed by case and not by individual specimen.

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Appendix A Union for International Cancer Control TNM 8 classification of colorectal tumours[20]

pT Primary tumour

pTX Primary tumour cannot be assessed
pT0 No evidence of primary tumour
pT1 Tumour invades submucosa
pT2 Tumour invades muscularis propria
pT3 Tumour invades into subserosa or into non-peritonealised pericolic or perirectal tissues
pT4 Tumour perforates visceral peritoneum (4a) and/or directly invades other organs or structures (4b)

pN Regional lymph nodes

pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastatic disease
pN1 Metastatic disease in 1–3 regional lymph nodes
- pN1a Metastasis in 1 regional lymph node
- pN1b Metastases in 2–3 regional lymph nodes
- pN1c Tumour deposit(s), i.e. satellites,* in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue without regional lymph node metastatic disease (tumour deposits are ignored if there is nodal metastatic disease)

pN2 Metastatic disease in 4 or more regional lymph nodes
- pN2a Metastases in 4–6 regional lymph nodes
- pN2b Metastases in 7 or more regional lymph nodes

pM Distant metastatic disease

pM1 Distant metastatic disease
- pM1a Metastasis confined to 1 organ without peritoneal metastases
- pM1b Metastases in more than 1 organ
- pM1c Metastases to the peritoneum with or without other organ involvement

*Tumour deposits, or satellites, are discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures.

Appendix B SNOMED codes for colorectal tumours

Topographical codes (T) and morphological codes (M)

Topographical codes are used in SNOMED to indicate the site of lesions and morphological codes (M) are used to indicate the morphological diagnosis. Common topography and morphology codes are given below, although the list is not exhaustive.

Topographical codes	**SNOMED**	**SNOMED CT terminology**	**SNOMED CT code**
Colon	T59300 (SNOMED 3) T67000 (SNOMED 2)	Colon structure (body structure)	71854001
Caecum	T59100 (SNOMED 3) T67100 (SNOMED 2)	Caecum structure (body structure)	32713005
Ascending colon	T59420 (SNOMED 3) T67200 (SNOMED 2)	Ascending colon structure (body structure)	9040008
Hepatic flexure	T59438 (SNOMED 3) T67300 (SNOMED 2)	Structure of right colic flexure (body structure)	48338005
Transverse colon	T59440 (SNOMED 3) T67400 (SNOMED 2)	Transverse colon structure (body structure)	485005
Splenic flexure	T59442 (SNOMED 3) T67500 (SNOMED 2)	Structure of left colic flexure (body structure)	72592005
Descending colon	T59460 (SNOMED 3) T67600 (SNOMED 2)	Descending colon structure (body structure)	32622004
Sigmoid colon	T59470 (SNOMED 3) T67700 (SNOMED 2)	Sigmoid colon structure (body structure)	60184004
Rectosigmoid	T59680 (SNOMED 3) T68200 (SNOMED 2)	Rectosigmoid structure (body structure)	81922002
Rectum	T59600 (SNOMED 3) T68000 (SNOMED 2)	Rectum structure (body structure)	34402009
Morphological codes	**SNOMED 2 or 3**	**SNOMED CT terminology**	**SNOMED CT code**
Adenoma	M81400	Adenoma, no subtype (morphologic abnormality)	32048006
Dysplasia	M74000	Dysplasia (morphologic abnormality)	25723000
Dysplasia, high grade	M74003	Severe dysplasia (morphologic abnormality)	28558000
Carcinoma	M80103	Carcinoma, no subtype (morphologic abnormality)	68453008
Adenocarcinoma	M81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Mucinous adenocarcinoma	M84803	Mucinous adenocarcinoma (morphologic abnormality)	72495009
Signet ring cell adenocarcinoma	M84903	Signet ring cell carcinoma (morphologic abnormality)	87737001

Adenosquamous carcinoma	M85603	Adenosquamous carcinoma (morphologic abnormality)	59367005
Squamous cell carcinoma	M80703	Squamous cell carcinoma, no ICD-O subtype (morphologic abnormality)	28899001
Undifferentiated carcinoma	M80203	Carcinoma, undifferentiated (morphologic abnormality)	38549000
Goblet cell carcinoid	M82433	Goblet cell carcinoid (morphologic abnormality)	31396002
Mixed carcinoid-adenocarcinoma	M82443	Composite carcinoid (morphologic abnormality)	51465000
Micropapillary carcinoma	M82653	Micropapillary carcinoma (morphologic abnormality)	450895005
Serrated adenocarcinoma	M82133	Serrated adenocarcinoma (morphologic abnormality)	450948005
Spindle cell carcinoma	M80323	Spindle cell carcinoma (morphologic abnormality)	65692009
Medullary carcinoma	M85103	Medullary carcinoma (morphologic abnormality)	32913002
Cribriform comedo-type adenocarcinoma	M82013	Cribriform carcinoma (morphologic abnormality)	30156004

SNOMED-P (Procedure) codes

These are used in SNOMED 2 and SNOMED 3 to distinguish biopsies, partial resections and radical resections to indicate the nature of the procedure.

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

Appendix C Reporting proforma for colorectal carcinoma resection specimens

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

Specimen type†:
Total colectomy ☐ / Subtotal colectomy ☐ /
Right hemicolectomy ☐ / Transverse colectomy ☐ /
Left hemicolectomy ☐ / Sigmoid colectomy ☐ /
Hartmann's procedure ☐ / Anterior resection [AR] ☐ /
Abdominoperineal excision [APE] ☐ /
Other (state) .....

Site of tumour†:
Caecum ☐ / Ascending colon☐ / Hepatic flexure☐
Transverse colon☐ / Splenic flexure☐ / Descending colon☐ / Sigmoid colon☐ / Rectum ☐ / Unknown ☐

Maximum tumour diameter†: …. mm or Not identified ☐

Distance to nearer longitudinal margin: .....mm

Tumour perforation (pT4): Yes ☐ No ☐

For rectal tumours:

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

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

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

For APE specimens:
Distance of tumour from dentate line†: ….mm

Tumour type†:
Adenocarcinoma ☐ Other/variant of adenocarcinoma ☐
If Other, or variant (e.g. mucinous), specify……

Differentiation by worst area†:
Well/moderate ☐ Poor ☐ Not applicable ☐

Local invasion ('ypT' if appropriate):
No carcinoma identified (pT0) ☐
Submucosa (pT1) ☐
Muscularis propria (pT2) ☐
Beyond muscularis propria (pT3) ☐
Tumour cells have breached the serosa (pT4a)☐
Tumour has perforated (pT4a) ☐
Tumour invades adjacent organs (pT4b) ☐

Maximum distance beyond muscularis propria†:
N/A (if intramural tumour or not pT3) ☐ Distance …..mm

Preoperative therapy response (tumour regression score)†:
Not applicable ☐
No viable cancer cells (TRS 0) ☐
Single cells or rare small groups of cancer cells (TRS 1) ☐
Residual cancer with evident tumour regression (TRS 2) ☐
No evident tumour regression (TRS 3) ☐

Carcinoma involvement of margins†:

	N/A	N/S	Yes	No
Doughnuts	☐	☐	☐	☐
Longitudinal margin		☐	☐	☐
Circumferential margin			☐	☐

(N/S = not submitted by pathologist)

Distance from carcinoma to CRM†:…..……..mm

Number of lymph nodes†:.....

Number of involved lymph nodes†: .....
(pN1a, 1 node; pN1b, 2–3 nodes; pN1c, tumour deposits only). pN2a, 4–6 nodes; pN2b, >6)

Highest node involved: No ☐ Yes ☐

Number of tumour deposits: 0☐1☐ 2☐ 3☐ 4☐ 5☐ >5☐

Deepest level of venous invasion:
None ☐ / Intramural☐ / Extramural ☐

Deepest level of lymphatic (small vessel) invasion:
None ☐ / Intramural☐ / Extramural ☐

Deepest level of perineural invasion:
None ☐ / Intramural☐ / Extramural ☐

Pathologically confirmed distant metastatic disease†:
Yes (pM1) ☐ No ☐ If yes, site(s): ……..…
(pM1a, one organ; pM1b, >1 organ; pM1c, peritoneal)

Separate abnormalities:	No	Yes
Polyp(s)	☐	☐
If yes state type(s) and number ……		
Polyposis	☐	☐
If yes specify type: …… …		
Synchronous carcinoma(s) (separate proforma for each cancer)	☐	☐

Other (e.g. IBD, diverticulosis etc)..……..…….

Resection status†:
Yes (R0) ☐ No (R1) ☐ No (R2) ☐

TNM (8th edition)†:
(y)pT …….. (y)pN …….. (y)pM …….

Block index (A= , B= etc):
Representative molecular block(s):
Carcinoma content (by cellularity, to nearest 10%):

Signature: …… Date ……/…../……. SNOMED codes†: T…..... / M……
Note: †Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) v7.

Appendix D Reporting proforma for colorectal carcinoma local excision specimens

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

Hospital……..…….. Hospital no: …….. NHS no: ……..……

Date of surgery: ……..…… Date of report authorisation: …… Report no: ……..….

Date of receipt:……..…. Pathologist: ……..…… Surgeon: ……..…

Specimen type†:

Polypectomy □ / Endoscopic mucosal resection (EMR) □ / Endoscopic submucosal dissection (ESD) □
Transanal endoscopic microsurgery (TEMS) excision □ / Transanal minimally invasive surgery (TAMIS) excision □
Endoscopic full thickness resection (EFTR) □ / Other (specify)……..

Site of tumour†:

Caecum □ / Ascending colon □ / Hepatic flexure □ / Transverse colon □ / Splenic flexure □ /
Descending colon □ / Sigmoid □ / Rectosigmoid □ / Rectum □ / Unknown □ / Tumour not identified □

Size of specimen (maximum width): .....mm Not assessable (piecemeal) □

Comments:…….....

Maximum tumour diameter†: …..mm or Not identified □

Tumour type†:
Adenocarcinoma □ Other, or adenocarcinoma variant
If Other, or variant, specify……

Differentiation by worst area†:
Well/moderate □ Poor □ Not applicable □

Local invasion:

No carcinoma identified (pT0)	□
Submucosa (pT1)	□
Muscularis propria (pT2)	□
Beyond muscularis propria (pT3)	□

For pT1 tumours only:

Maximum depth of invasive tumour
from muscularis mucosae …….. mm Not assessable □

Width of invasive tumour …… mm Not assessable □

For polypoid tumours only, Haggitt level:
1 □ / 2 □ / 3□ / 4 □ /
Not applicable □ / Not assessable □

For sessile tumours only, Kikuchi level:
sm1 □ / sm2 □ / sm3 □/
Not applicable □ / Not assessable □

Number of lymph nodes†:.....

Number of involved lymph nodes†: .....

Number of tumour deposits: 0□ 1 □ 2 □ 3 □ 4 □ 5□ >5 □

Deepest level of venous invasion:
None □ / Intramural□ / Extramural

Deepest level of lymphatic (small vessel) invasion:
None □ / Intramural □ / Extramural □

Deepest level of perineural invasion:
None □ / Intramural □ / Extramural □

Tumour budding grade*:
Number of buds identified:……
Bd1 (<5 buds) □ / Bd2 (5-9 buds) □ / Bd3 (>9 buds) □
*Buds counted on H&E within a 0.785mm^2 'hotspot'

Preoperative therapy response†
(tumour regression score):

Not applicable	□
No viable cancer cells (TRS 0)	□
Single cells or rare small groups of cancer cells (TRS 1)	□
Residual cancer with evident tumour regression (TRS 2)	□
No evident tumour regression (TRS 3)	□

Background adenoma: Yes □ No □

Involvement of margins by carcinoma†:

	Yes	No	Not assessable*
Peripheral margin	□	□	□
Deep margin	□	□	□

(*Not assessable if specimen received piecemeal)

Histological measurement from carcinoma to nearest deep excision margin ……mm
Not assessable □

Resection status†:

Yes (R0) □ No (R1) □ No (R2) □ Not assessable □

TNM (8th edition)†:
(y)pT …….. (y)pN …….. (y)pM …….

Block index (A= , B= etc):
Representative molecular block(s):
Carcinoma content (by cellularity, to nearest 10%):

Signature: …… Date …../…../…… SNOMED codes† T…….. / M…..…
Note: †Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) v7.

Appendix E Reporting proforma for further investigations for colorectal carcinoma

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

Hospital……..…….. Hospital no: ……..……... NHS no: ……..……

Date of surgery: ……..…… Date of report authorisation: …… Report no: ……..…

Date of receipt:……..….. Pathologist: ……..…… Surgeon: ……..…

Mismatch repair (MMR) protein immunohistochemistry

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

Microsatellite instability (MSI) testing

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

MLH1 promoter hypermethylation testing

Present □ Absent □ Test failed □ Not performed □

BRAF V600E mutation testing

Present □ Absent □ Test failed □ Not performed □

KRAS mutation testing

Present □ Absent □ Test failed □ Not performed □

Specify mutation……..

NRAS mutation testing

Present □ Absent □ Test failed □ Not performed □

Specify mutation……..

NTRK fusion immunohistochemistry screening

Present □ Absent □ Test failed □ Not performed □

NTRK fusion NGS testing

Present □ Absent □ Test failed □ Not performed □

Specify fusion……..

Multi-gene panel testing

Performed: Yes □ No □

Method used ……

Actionable molecular aberrations detected not listed above ……

Exome sequencing

Performed: Yes □ No □

Method used ……

Actionable molecular aberrations detected not listed above ……

Whole genome sequencing

Performed: Yes □ No □

Method used ……

Actionable molecular aberrations detected not listed above ……

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

Appendix F Reporting proforma for colorectal carcinoma resection specimens in list format

Element name	Values	Implementation comments
Specimen	Single selection value list: • Total colectomy • Subtotal colectomy • Right hemicolectomy • Transverse colectomy • Left hemicolectomy • Sigmoid colectomy • Hartmann's procedure • Anterior resection • Abdominoperineal excision • Other	
Specimen type, other, state	Free text	Only applicable if 'Specimen, Other' is selected.
Site of tumour	Single selection value list: • Caecum • Right (ascending) colon • Hepatic flexure • Transverse colon • Splenic flexure • Left (descending) colon • Sigmoid colon • Rectosigmoid • Rectum • Unknown	Only applicable if 'Tumour identified, Tumour in specimen' is selected.
Maximum tumour diameter	Size in mm	
Distance of tumour to nearer longitudinal end	Size in mm	Only applicable if 'Tumour identified, Tumour in specimen' is selected.
Tumour perforation (pT4)	Single selection value list: • Yes • No	Only applicable if 'Tumour identified, Tumour in specimen' is selected.
Relation of tumour to peritoneal reflection	Single selection value list: • Above • Astride • Below	Only applicable if 'Site of tumour, Rectum' is selected.

Plane of mesorectal excision	Single selection value list: • Mesorectal fascia • Intramesorectal • Muscularis propria	Only applicable if 'Specimen, Anterior resection' or 'Specimen, Abdominoperineal excision' is selected.
Plane of resection of sphincters	Single selection value list: • Extralevator • Sphinteric • Intrasphincteric	Only applicable if 'Specimen, Abdominoperineal excision' is selected.
Distance of tumour from dentate line	Distance in mm	Only applicable if 'Tumour identified, Tumour in specimen' and 'Specimen, Abdominoperineal excision' is selected.
Tumour type, adenocarcinoma	Single selection value list: • Yes • No	Only applicable if 'Tumour identified, Tumour in specimen' is selected.
Tumour type, specify	Free text	Only applicable if 'Tumour type, Adenocarcinoma, No' is selected.
Differentiation by worst area	Single selection value list: • Well/moderate • Poor • Not applicable	
Local invasion	Multiple selection value list: • No carcinoma identified • Submucosa • Muscularis propria • Beyond muscularis propria • Tumour cells have breached the serosa • Tumour has perforated below peritoneal reflection • Tumour invades adjacent organs	
Maximum distance beyond muscularis propria	Distance in mm	Only applicable if 'Local invasion, Beyond muscularis propria'; 'Local invasion, Tumour cells have breached the serosa'; or 'Local invasion, Tumour invades adjacent organs' is selected.
Preoperative therapy response	Single selection value list: • Not applicable	

	• No viable cancer cells (TRS 0) • Single cells or rare small groups of cancer cells (TRS 1) • Residual cancer with evident tumour regression (TRS 2) • No evident tumour regression (TRS 3)	
Tumour involvement of margins, doughnuts	Single selection value list: • Not applicable • Not submitted by pathologist • Involved • Not involved	
Tumour involvement of margins, longitudinal margin	Single selection value list: • Not submitted by pathologist • Involved • Not involved	
Tumour involvement of margins, circumferential margin	Single selection value list: • Involved • Not involved	
Measurement of tumour to circumferential resection margin	Distance in mm	Only applicable if 'Tumour identified, Tumour in specimen' is selected.
Number of lymph nodes	Integer	
Number of involved lymph nodes	Integer	
Highest node involved	Single value selection list: • Yes • No	
Number of tumour deposits	Single value selection list: • 0 • 1 • 2 • 3 • 4 • 5 • >5	
Deepest level of venous invasion	Single value selection list:	

	• None • Intramural • Extramural	
Deepest level of lymphatic (small vessel) invasion	Single value selection list: • None • Intramural • Extramural	
Deepest level of perineural invasion	Single value selection list: • None • Intramural • Extramural	
Pathologically confirmed distant metastatic disease	Single value selection list: • Yes • No	
Pathologically confirmed distant metastatic disease, sites	Free text	Only applicable if 'Histologically confirmed distant metastatic disease, Yes' is selected.
Separate abnormalities, polyps	Single value selection list: • Yes • No	
Separate abnormalities, polyps, type and number	Free text	Only applicable if 'Separate abnormalities, Polyps, Yes' is selected.
Separate abnormalities, polyposis	Single value selection list: • Yes • No	
Separate abnormalities, polyposis, type	Free text	Only applicable if 'Separate abnormalities, Polyposis, Yes' is selected.
Separate abnormalities, synchronous carcinoma	Single value selection list: • Yes • No	
Separate abnormalities, other	Free text	
Resection status	Single value selection list: • Yes (R0) • No (R1) • No (R2)	
TNM edition	8	Automatically selected
pT classification	Single selection value list: • pTX	

	• pT0 • pT1 • pT2 • pT3 • pT4a • pT4b • ypTX • ypT0 • ypT1 • ypT2 • ypT3 • ypT4a • ypT4b	
pN classification	Single selection value list: • pNX • pN0 • pN1a • pN1b • pN1c • pN2a • pN2b • ypNX • ypN0 • ypN1a • ypN1b • ypN1c • ypN2a • ypN2b	
pM classification	Single value selection list: • Not applicable • pM1a • pM1b • pM1c	
Block index	Free text	
Selected tumour block for additional testing	Free text	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables	

Appendix G Reporting proforma for colorectal carcinoma local excision specimens in list format

Element name	Values	Implementation comments
Specimen type	Single selection value list: • Polypectomy • Endoscopic mucosal resection • Endoscopic submucosal dissection • Transanal endoscopic microsurgical excision (TEMS) • Transanal minimally invasive surgery (TAMIS) • Endoscopic full thickness resection (EFTR) • Other	
Specimen type, other, specify	Free text	Only applicable if 'Specimen type, Other' is selected.
Site of tumour	Single selection value list: • Caecum • Right (ascending) colon • Hepatic flexure • Transverse colon • Splenic flexure • Left (descending) colon • Sigmoid • Rectosigmoid • Rectum • Unknown • Tumour not identified	
Size of specimen (maximum width)	Size in mm	
Size of specimen, assessable	Single selection value list: • Assessable • Not assessable	Assessable if 'Size of specimen' has a valid value.
Comments	Free text	
Maximum tumour diameter	Size in mm	
Tumour type, adenocarcinoma	Single selection value list: • Yes	Only applicable if 'Site of tumour' is NOT 'not identified'.

	• No	
Tumour type, specify	Free text	Only applicable if 'Site of tumour' is not 'not identified' and 'Tumour type, Adenocarcinoma, No' is selected.
Differentiation by worst area	Single selection value list: • Well/moderate • Poor • Not applicable	
Local invasion	Single selection value list: • No carcinoma identified • Submucosa • Muscularis propria • Beyond muscularis propria	
Maximum depth of invasive tumour from muscularis mucosae	Distance in mm	Only applicable if 'Site of tumour' is not 'not identified' and 'Local invasion, Submucosa' is selected.
Width of invasive tumour	Size in mm	Only applicable if 'Site of tumour' is not 'not identified' and 'Local invasion, Submucosa' is selected.
For polypoid tumours only, Haggitt level	Single selection value list: • 1 • 2 • 3 • 4 • Not applicable • Not assessable	
For sessile tumours only, Kikuchi level	Single selection value list: • sm1 • sm2 • sm3 • Not applicable • Not assessable	
Number of lymph nodes	Integer	
Number of involved lymph nodes	Integer	
Number of tumour deposits	Single value selection list: • 0 • 1	

	• 2 • 3 • 4 • 5 • >5	
Deepest level of venous invasion	Single value selection list: • None • Intramural • Extramural	
Deepest level of lymphatic (small vessel) invasion	Single value selection list: • None • Intramural • Extramural	
Deepest level of perineural invasion	Single value selection list: • None • Intramural • Extramural	
Tumour budding grade	Single value selection list: • Bd1 • Bd2 • Bd3	Only applicable for pT1 tumours
Preoperative therapy response	Single selection value list: • Not applicable • No viable cancer cells (TRS 0) • Single cells or rare small groups of cancer cells (TRS 1) • Residual cancer with evident tumour regression (TRS 2) • No evident tumour regression (TRS 3)	
Background adenoma	Single selection value list: • Yes • No	
Involvement of margins by carcinoma, Peripheral margin	Single selection value list: • Involved • Not involved • Not assessable	

Involvement of margins by carcinoma, Deep margin	Single selection value list: • Involved • Not involved • Not assessable	
Histological measurement from carcinoma to nearest deep excision margin	Size in mm	Only applicable if 'Site of tumour' is not 'not identified'.
Histological measurement from carcinoma to nearest deep excision margin, assessable	Single selection value list: • Assessable • Not assessable	Assessable if 'Histological measurement from carcinoma to nearest deep excision margin' has a valid value.
Resection status	Single value selection list: • Yes (R0) • No (R1) • No (R2) • Not assessable	
TNM edition	8	Automatically selected
pT classification	Single selection value list: • pTX • pT0 • pT1 • pT2 • pT3 • pT4a • pT4b • ypTX • ypT0 • ypT1 • ypT2 • ypT3 • ypT4a • ypT4b	
pN classification	Single selection value list: • pNX • pN0 • pN1a • pN1b • pN1c • pN2a	

	• pN2b • ypNX • ypN0 • ypN1a • ypN1b • ypN1c • ypN2a • ypN2b	
pM classification	Single value selection list: • Not applicable • pM1a • pM1b • pM1c	
Block index	Free text	
Selected tumour block for additional testing	Free text	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables	

Appendix H Reporting proforma for further investigations for colorectal carcinoma in list format

Element name	Values	Implementation comments
MLH1 nuclear expression intact	Single value selection list: • Yes • No • Equivocal • Test failed • Not performed	
PMS2 nuclear expression intact	Single value selection list: • Yes • No • Equivocal • Test failed • Not performed	
MSH2 nuclear expression intact	Single value selection list: • Yes • No • Equivocal • Test failed • Not performed	
MSH6 nuclear expression intact	Single value selection list: • Yes • No • Equivocal • Test failed • Not performed	
Microsatellite instability (MSI) testing	Single selection value list: • MSI-high • MSI-low • MS-stable • Test failed • Not performed	
MLH1 promotor hypermethylation testing	Single selection value list: • Present • Absent • Test failed • Not performed	
BRAF V600E mutation testing	Single selection value list: • Present	

	• Absent • Test failed • Not performed	
KRAS mutation testing	Single selection value list: • Present • Absent • Test failed • Not performed	
KRAS mutation testing, specify	Free text	
NRAS mutation testing	Single selection value list: • Present • Absent • Test failed • Not performed	
NRAS mutation testing, specify	Free text	
NTRK fusion immunohistochemistry screening	Single selection value list: • Present • Absent • Test failed • Not performed	
NTRK fusion NGS testing	Single selection value list: • Present • Absent • Test failed • Not performed	
NTRK fusion NGS testing, specify	Free text	
Multi-gene panel testing	Single selection value list: • Performed • Not performed	
Multi-gene panel testing, method used	Free text	
Multi-gene panel testing, actionable molecular aberrations	Free text	
Exome sequencing	Single selection value list: • Performed • Not performed	
Exome sequencing, method used	Free text	
Exome sequencing,	Free text	

actionable molecular aberrations		
Whole genome sequencing	Single selection value list: • Performed • Not performed	
Whole genome sequencing, method used	Free text	
Whole genome sequencing, actionable molecular aberrations	Free text	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix I Summary table – explanation of levels of evidence

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

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

Appendix J AGREE II compliance monitoring sheet

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

AGREE standard	Section of dataset
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Foreword, Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Foreword, Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword, Introduction
12 There is an explicit link between the recommendations and the supporting evidence	1–12
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	1–12
16 The different options for management of the condition or health issue are clearly presented	1–12
17 Key recommendations are easily identifiable	1–12
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–H
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	13
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