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

Standards and datasets for reporting cancers

Dataset for histopathological reporting of colorectal cancer

December 2017

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Unique document number	G049
Document name	Dataset for histopathological reporting of colorectal cancer
Version number	4
Produced by	Dr Maurice B Loughrey, Professor Philip Quirke and Professor Neil A Shepherd, on behalf of the Collegeôs Cancer Services Working Group. All three authors are senior gastrointestinal pathologists, co-authors of multiple guidelines relating to gastrointestinal diseases and leads in the UK bowel cancer screening programmes.
Date active	October 2017 (to be implemented from **1 January 2018**)
Date for review	October 2020
Comments	This edition will replace the 3rd edition of the *Dataset for Colorectal Cancer Histopathology Reports*, published in 2014. The recommendations of TNM 8 (UICC) are followed in this revision. In accordance with the Collegeôs pre-publications policy, this document was on The Royal College of Pathologistsô website for consultation from 12 October to 9 November 2017. Responses and authorsôcomments will be available to view on request. **Dr Lorna Williamson** Director of Publishing and Engagement

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Registered charity in England and Wales, no. 261035
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NICE has accredited the process used by The Royal College of Pathologists to produce its cancer datasets. Accreditation is valid for 5 years from July 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

For full details on our accreditation visit: www.nice.org.uk/accreditation.

Foreword

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

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

- Association of Clinical Pathologists (www.pathologists.org.uk)
- Association for Coloproctology of Great Britain and Ireland (www.acpgbi.org.uk)
- British Society of Gastroenterology ï Pathology Section (www.bsg.org.uk)
- British Division of the International Academy of Pathology (www.bdiap.org)
- National Cancer Research Institute ï Colorectal Cancer Subcommittee (www.ncri.org.uk)
- NHS Bowel Cancer Screening UK ï Committee and Pathology Group
- Royal College of Surgeons (www.rcseng.ac.uk).

Evidence for the revised dataset was obtained from updates to international tumour grading, staging and classification systems and by electronically searching medical literature databases for relevant research evidence, systematic reviews and national or international publications on colorectal cancer up to March 2017. The level of evidence for the recommendations has been summarised (Appendix I). Unless otherwise stated, the level of evidence corresponds to ôGood practice point (GPP): Recommended best practice based on the clinical experience of the authors of the writing groupô No major organisational changes or cost implications that have not been approved by the National Institute for Clinical Excellence (NICE) have been identified that would hinder the implementation of the dataset for the core items.

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 being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Histopathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for membersôattention. 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 Clinical Effectiveness department, Lay Governance Group and WGCS and was placed on the College website for consultation with the membership from 12 October to 9 November 2017. All comments received have been addressed by the authors to the satisfaction of the WGCS Chair and the Director of Communications.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness department and are available on request. The authors have declared that they have previously received payment for advisory and educational work for commercial organisations involved in treatment of colorectal cancer. They give their assurances that these conflicts of interest have not influenced the content of this dataset.

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 the 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 necessary and to place the patient in a correct disease stage for an accurate prognosis to be given and appropriate postoperative therapy to be advised
- if age and co-morbidity allow, 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.[1–4] 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.[2]
- patients with rectal adenocarcinoma and involvement of the circumferential resection margin (CRM) are at high risk of local recurrence[5–7] and may receive preoperative or postoperative radiotherapy ± chemotherapy that is toxic but may decrease the likelihood[8,9] of this unpleasant and nearly uniformly fatal complication
- the frequency of CRM involvement found may indicate the quality of rectal cancer surgery being performed[10–14]
- to assess the effects of preoperative therapy[15,16]

- to allow audit of diagnostic and surgical procedures in relation to clinical outcomes, avoidance of selection bias,[17,18] identification of good surgical practice[10] and comparison of patients in clinical trials
- to facilitate improvements in the quality of rectal cancer surgery by photographing and grading the plane of surgical excision and recording the frequency, quality and type of abdominoperineal excisions (APEs).[11,19]

Communication of pathology information to the patient and the multidisciplinary team 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 multidisciplinary team meetings (MDTMs). All reporting pathologists should provide pathology reports that are accurate, complete, understandable, timely and transferable. The use of proformas has been demonstrated to facilitate these requirements[20,21] and their use is strongly recommended, supplemented as necessary by the use of 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, to allow data integration into standardised databases and comparison of data between cancer populations.

The staging system for appendiceal tumours described under TNM 8 should be used, as should the forthcoming Royal College of Pathologists dataset for reporting appendiceal tumours.[22] Many colorectal adenocarcinomas demonstrate focal neuroendocrine differentiation, on morphology and/or immunohistochemistry, and these should be regarded as ϕpureôadenocarcinomas for the purposes of this dataset. Tumours demonstrating purely neuroendocrine differentiation, or less than 30% adenocarcinoma morphology, are regarded as ϕpureôneuroendocrine tumours and one is referred to in the current *Dataset for reporting neuroendocrine tumours of the gastrointestinal tract including pancreas.*[23] Tumours with greater than 30% representation of each morphology are classified as mixed adenoneuroendocrine carcinoma (MANEC). This is a heterogeneous group of tumours, which includes goblet cell carcinoids, and both neuroendocrine and non-neuroendocrine components can show variable morphological features, with a full spectrum of differentiation encountered. MANECs are 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 most appropriate therapy.

1.1 Target users and health benefits of this guideline

The primary users of the dataset are consultant and trainee histopathologists and, on their behalf, the suppliers of IT products to laboratories. Secondary users are surgeons, radiologists and oncologists, specialist screening practitioners, NHS Bowel Cancer Screening Programme (NHSBCSP), cancer registries and the National Cancer Intelligence Network (NCIN).

1.2 Changes to the 4th edition

Since the first edition of this dataset, three revisions (the 6th, 7th and 8th editions) of TNM staging of colorectal cancer have been published (TNM 6, TNM 7 and TNM 8).[22,24,25] These have each recommended changes to the definitions of lymph node involvement that were given in the first edition (TNM 5),[26] particularly in relation to rules interpreting mesenteric discontinuous tumour deposits lacking identifiable lymph node or vascular structure. There is now convincing evidence from a systematic review and meta-analysis of the adverse prognostic significance of tumour deposits.[27] The definition of tumour deposits has been clarified in TNM 8 and while, in our opinion, it is still suboptimal and in need of further revision subject to new evidence, TNM 8 is now recommended in this dataset.

To avoid confusion, local discussion is encouraged regarding a suitable changeover date for migration to TNM 8, considering involvement in ongoing clinical trials and other studies (utilising TNM 5). TNM 5 should be routinely used until 31 December 2017 and TNM 8 from 1 January 2018. Where necessary (i.e. ongoing trials or other studies) both stages can be reported. Cancer Outcomes and Services Dataset (COSD) and the NHS Bowel Cancer Screening Programme staging record will change on 1 January 2018. All reports should clearly state which version of TNM has been applied and, if both, then the reason for both given.

As TNM 8 includes an assessment and record of õtumour depositsö, which may influence pN stage, careful judgement is required to distinguish such deposits from involved lymph nodes and from extramural venous invasion, lymphatic (small vessel) invasion and perineural invasion (section 5.2.7). Each of these features must therefore be reported independently. Furthermore, there is now sufficient evidence of the prognostic value of all these features, with some additional evidence supporting the distinction between intramural and extramural spread, and therefore reporting of the deepest identified level of spread for venous, lymphatic and perineural invasion is now recommended.

Assessment of the percentage of cases reported with peritoneal infiltration as a quality standard has been removed for rectal cancers (but retained for colonic cancers) given increased use of preoperative therapy for rectal cancer, meaning that the frequency of its detection will be related to local treatment policies, and thereby reducing its value as a quality measure.

The specific changes made to the surgical resection dataset proforma from the 3rd edition are:

- the T, N and M stage changes and refinements of TNM 8 have been adopted
- the Dukes and Bussey classification of colorectal cancer staging is no longer to be reported, as it is not compatible with TNM 8 staging
- the number of tumour deposits (precise number up to five, or >5) should be recorded in node-negative cases only (stage pN1c in TNM 8). By TNM 8 definition, tumour deposits (satellites) are discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue of lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures. If a vessel wall is identifiable on haematoxylin and eosin, elastic or other stains, it should be classified as venous invasion (V1/2) or lymphatic invasion (L1). Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion (Pn1).
- depth of venous invasion is now recorded as extramural or intramural (comprising submucosal and intramuscular)
- the presence (L1) or absence (L0) of lymphatic (small vessel) infiltration should be recorded, with an indication of greatest depth of invasion (extramural or intramural). Small vessel infiltration includes both lymphatic and small venular structures as defined under TNM 8.
- the presence (Pn1) or absence (Pn0) of perineural infiltration should be recorded, with an indication of greatest depth of invasion (extramural or intramural)
- assessment of tumour regression following preoperative therapy has been modified slightly and a tumour regression description and score (0ï 3) added
- the section describing separate abnormalities in the specimen (aside from the tumour) has been simplified.

Regarding the local excision dataset proforma, the changes are minor. For the rare occasion where a more locally advanced colorectal cancer is removed by a local excision

technique, assessment and reporting of venous invasion, lymphatic invasion, perineural invasion and tumour deposits have been standardised with the surgical resection proforma. Similarly, the modifications to tumour regression assessment have been adopted, as local excision may very occasionally follow preoperative therapy, usually for rectal tumours.

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 be told:

- if the tumour has been detected as part of a bowel cancer screening programme
- 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, 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
- if open, laparoscopic or robotic surgery has been performed
- the type and dissection plane of operation attempted e.g. D2 or D3 lymph node dissection, type of APE and type of local excision.

In practice, audits have shown that the information proffered on histology request forms is poor. In an audit of colorectal cancer resection specimens performed in one of our centres, 72% of forms were completed by two separate people, usually the specimen box completed by a theatre nurse and the clinical details by a surgeon. In 96% of forms, there was inaccurate or insufficient information, especially related to the true nature of the specimen/operation and whether or not preoperative therapy had been given. On this evidence, we believe that pathologists should not necessarily rely on the information proffered and should seek more accurate information, especially whether or not the patient has had preoperative therapy. We believe that, on this issue, it really is the pathologist's responsibility to ensure accurate information concerning preoperative therapy goes on the pathology report. Such information should be readily available at the relevant colorectal MDTM. Customising colorectal cancer resection specimen request forms to include this question may be an option for some centres.

3 Preparation of specimens before dissection

Ideally specimens are received fresh and unopened as soon as possible after surgical resection, but in practice the vast majority are received in formalin fixative, perhaps outwith the setting of biobanking. If not delivered fresh to the laboratory, the specimen should typically be placed unopened in a large volume of formalin fixative. If a significant delay (>24 hours) is anticipated prior to handling in 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.

4 Specimen handling and block selection[28,29]

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 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 ôbareô 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 is inked) and a peritonealised surface anteriorly that should not be inked (Figure 1).

Tumours of the ascending and descending colons will usually also have a non-peritonealised margin posteriorly (which is marked with ink) and a peritonealised surface anteriorly (which is not marked) (Figure 2). The transverse and proximal sigmoid colons are usually on a narrow mesentery, so tumours here have only a narrow, readily identifiable non-peritonealised margin, which is typically well clear of the tumour. The peritoneal covering of the caecum is prone to individual variation, so tumours here may have none or a small or large non-peritonealised area. In this dataset, the term circumferential resection margin (CRM) will be used in preference to non-peritonealised margin, although this margin is clearly not fully circumferential at all sites.

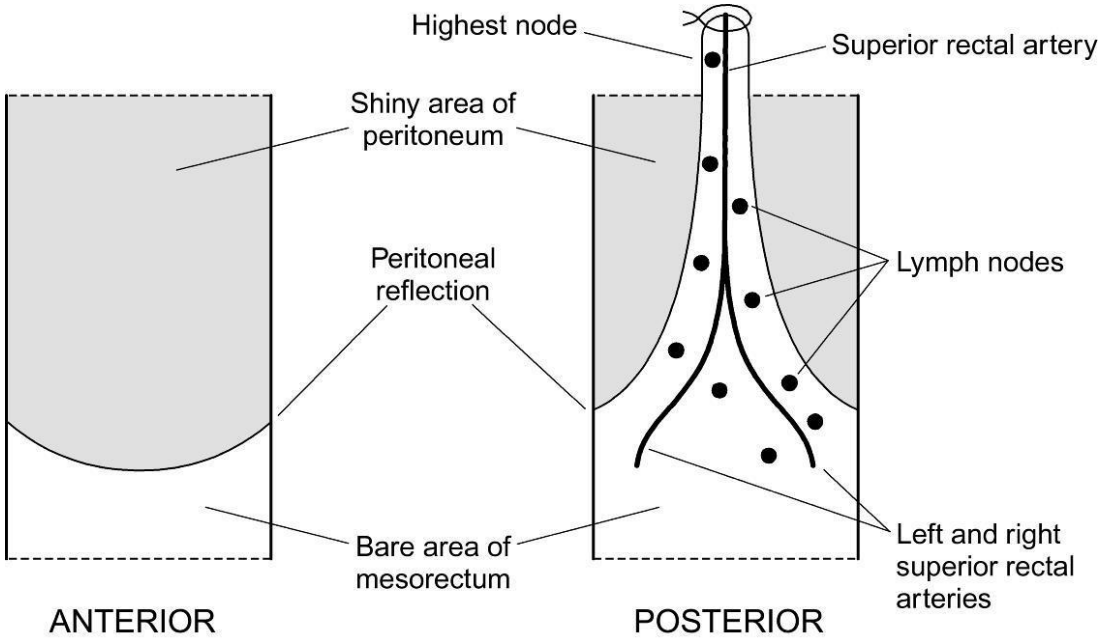


Figure 1 Diagrammatic representation of a resected rectum. Anteriorly the specimen is covered by peritoneum down to the peritoneal reflection and only the non-shaded area below this is the circumferential (non-peritonealised) margin that should be painted for assessment of margin involvement by tumour.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

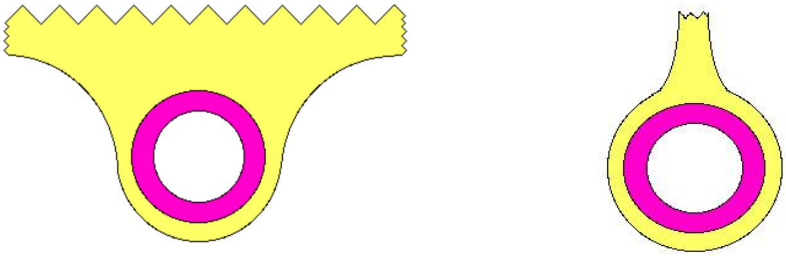


Figure 2 Diagrammatic cross sections of the ascending colon (left) and sigmoid colon (right) for comparison. The ascending colon has a broad circumferential (jagged) margin posteriorly while the sigmoid colon is suspended on a narrow mesentery and has a very small circumferential margin posteriorly.

After marking the CRM (but not any peritonealised surface) with ink or another marker, such as coloured gelatin (which we prefer), the specimen may be opened anteriorly, apart from a segment extending 1ï 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 ówickô 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 and 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 does 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 resections should be allowed to fix for a minimum of 24ï 48 hours before further dissection and block taking; this facilitates subsequent thin transverse slicing through the tumour and the identification of lymph nodes. Pinned specimens can 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 3ï 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 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 helpfully annotated to correspond with a block index on the final pathology report to facilitate review and MDMT 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 the highest proportion of viable tumour. 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 ómegablocksô It is good practice, but not essential, to test tissue from multiple tumour blocks for mutations, providing a ócocktailô of tissue sections from different tumour blocks to the molecular pathology laboratory for testing, as this may enhance mutation detection due to tumour heterogeneity.[30] It is beneficial that the block selected for MMR immunohistochemistry also includes some normal mucosa, which can act as an internal positive control, but this is not essential as

intratumoral and peritumoral inflammatory and stromal cells typically provide equally good internal control material. If diagnostic biopsy tissue is available from the tumour, it is recommended to perform MMR immunohistochemistry on the biopsy rather than resection specimen as better fixation assists immunostaining interpretation and the result will be available in a more timely fashion to the clinical team.

If available, tumour sampling using ómegablocksô is recommended, to facilitate accurate measurements and better radiological correlation. It is recognised, however, that this facility is not routinely available.

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

- at least five blocks of the tumour (or more for large tumours), if size permits, to include, where applicable:
  - ï the deepest tumour penetration into or through the bowel wall
  - ï involvement of the peritoneal surface
  - ï invasion of veins
  - ï involvement of any adjacent organs
  - ï blocks for immunohistochemical and 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 a separate extramural deposit or tumour in a lymph node, whichever is closest). 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 (including stapling device doughnuts, if they are submitted and tumour reaches the end margin of the main specimen)
- a block of tumour and adjacent mucosa, to include any precursor polyp, if this is macroscopically identifiable
- a block of normal-appearing intestine
- **all** lymph nodes identified (whole node if <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 (right hemicolectomy). In such specimens, a block from terminal ileum is only considered essential if there are macroscopic abnormalities in the ileum or the tumour is close to this proximal longitudinal margin.

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.[31] 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.

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.[16,29] 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 levels should be cut on all blocks from the tumour site and, if still negative, a pathology complete response can then be recorded.

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, 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 sutured arterial margin(s), regardless of the actual distance between node and surgical tie (Figure 1); it should be identified and blocked separately. Whereas only one vascular ôhigh tieô 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, as such, it is worth recording this. It will also be more frequently involved in ôlow tieô D2 rather than D3 specimens. The remaining lymph nodes can most easily be identified in the transverse slices of the mesentery, especially if it is sufficiently fixed (see above). Care must be taken to ensure that all of 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. 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 ôisolated tumour cellsô be identified on examination of 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 tumour cell deposits.

It is very 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 setting of a standard of 12 for the median number of lymph nodes examined per specimen (see above) in no way means that pathologists should stop searching for lymph nodes once 12 have been identified. Placing the specimen in a fat-clearing agent 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 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.

[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:

- nature of specimen and type of operation
- site of tumour
- maximum tumour diameter
- distance to the nearer longitudinal resection margin
- tumour perforation
- relation of the tumour 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

Site of tumour and type of operation

This will usually be stated on the request form. However, if examination of the specimen suggests that the stated site is incorrect, this should be queried with the surgeon and corrected if necessary. If tumour straddles two sites, the site with the greatest tumour bulk should be recorded. The three taeniae coli of the sigmoid colon fuse to form the circumferential longitudinal muscle of the rectal wall, marking the rectosigmoid boundary. 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 reports and images can be helpful in this regard as they have the benefit of *in vivo* anatomy. The operation performed by the surgeon should also be recorded.

Maximum tumour diameter

This is measured from the luminal aspect of the bowel. The thickness of the tumour is ignored for this measurement.

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.[33] 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 pure 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. Perforation through the tumour into the peritoneal cavity is a well-established adverse prognostic factor in colonic[34] and rectal[35] cancer and should be recorded. Such cases are regarded as pT4a in the TNM 8 staging system (see below). 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. Localised perforation through the tumour onto CRM (e.g. in the low rectum) is also recommended to be staged as pT4a (TNM 8 system).

[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).

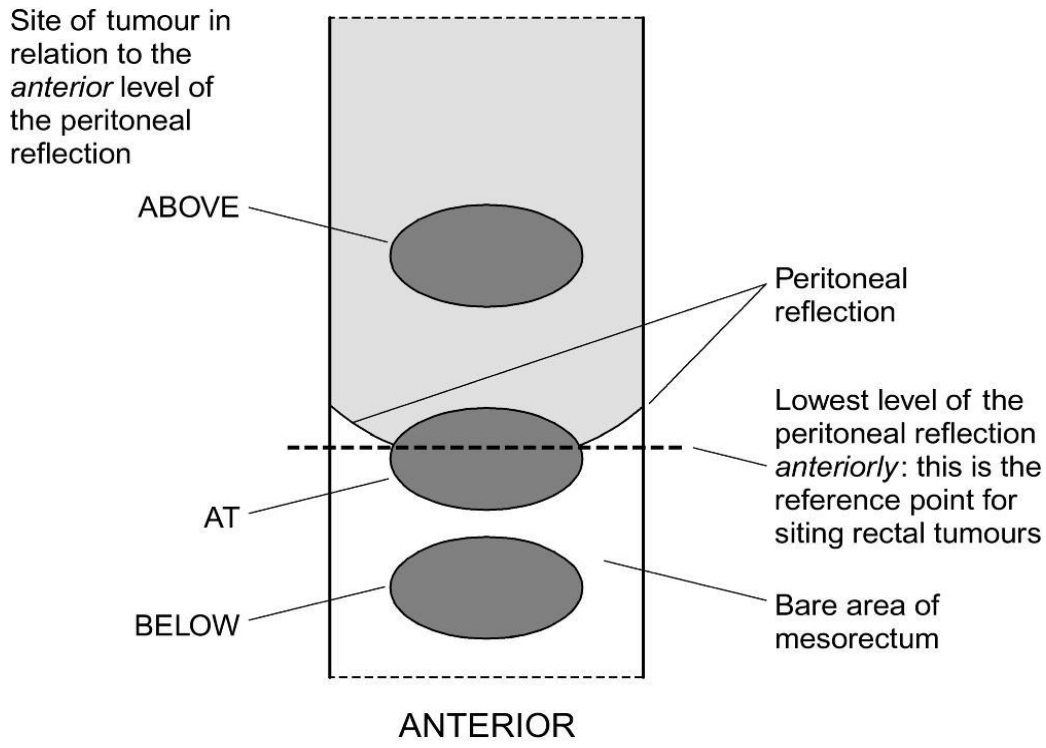


Figure 3 Diagrammatic illustration of rectal tumours in relation to the peritoneal reflection.

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.[11]

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

Plane of mesorectal excision

Prospective randomised control trials[11,19] 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. 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 multidisciplinary teams has led to improved quality of surgery and clinical outcomes with time.[11ï 14,19] Descriptions of the three planes of excision are given below; illustrations of each have been published[29] and examples are shown in Figure 4 from the Aristotle trial protocol (reproduced with permission of the authors).[36]

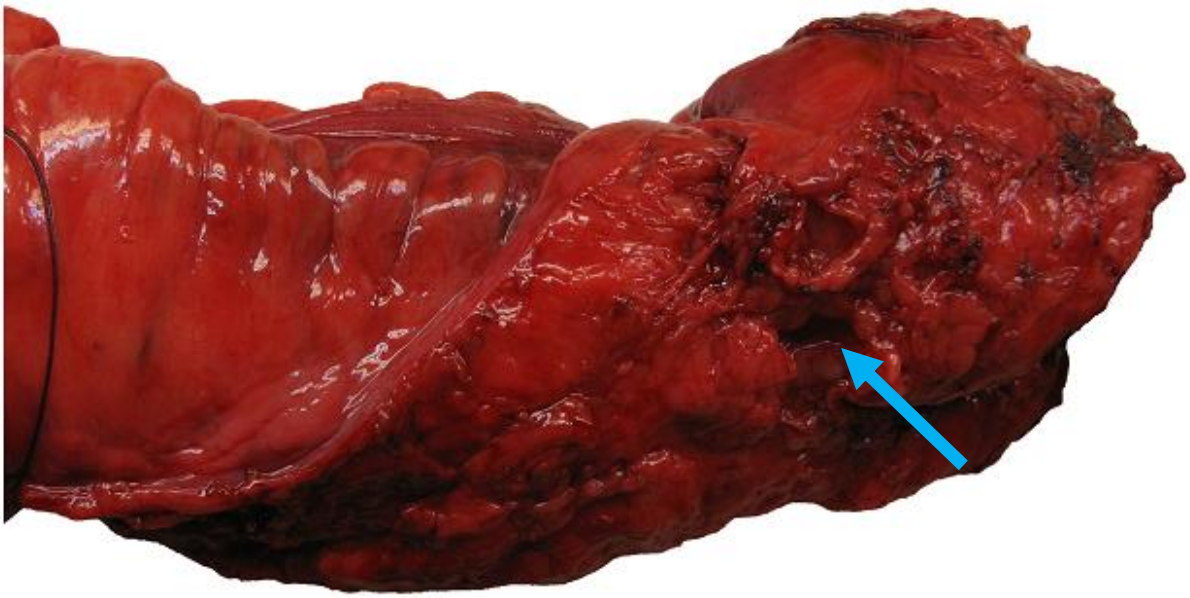
[Level of evidence A – plane of surgery in rectal cancer predicts local recurrence and prognosis.]

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.



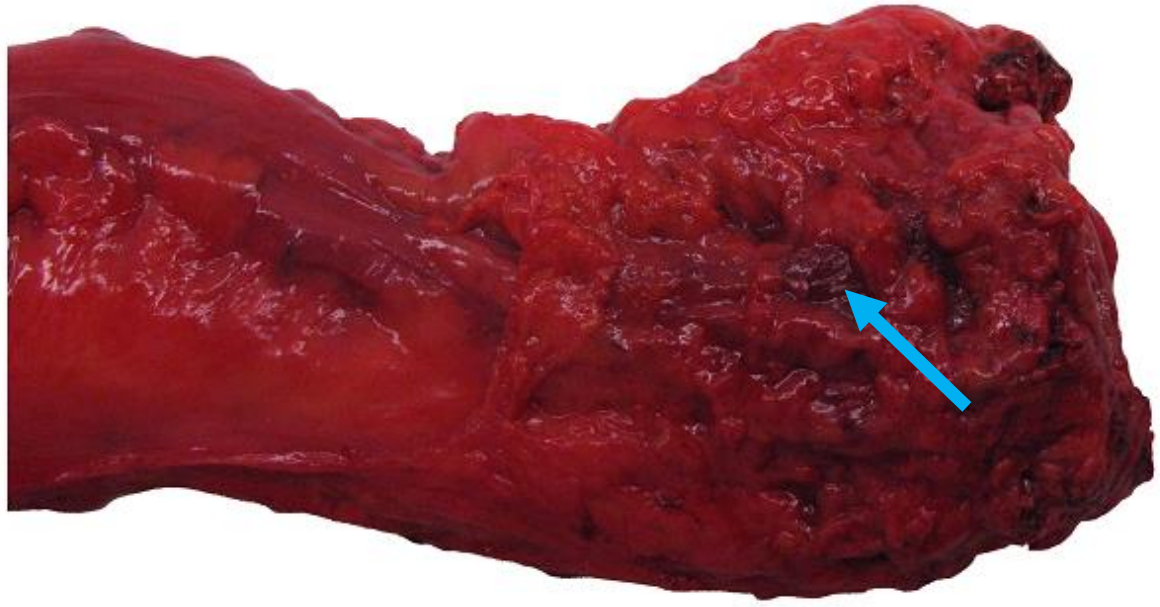
Mesorectal plane showing shiny fascial covering over the CRM and no defects

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 (blue arrow)

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



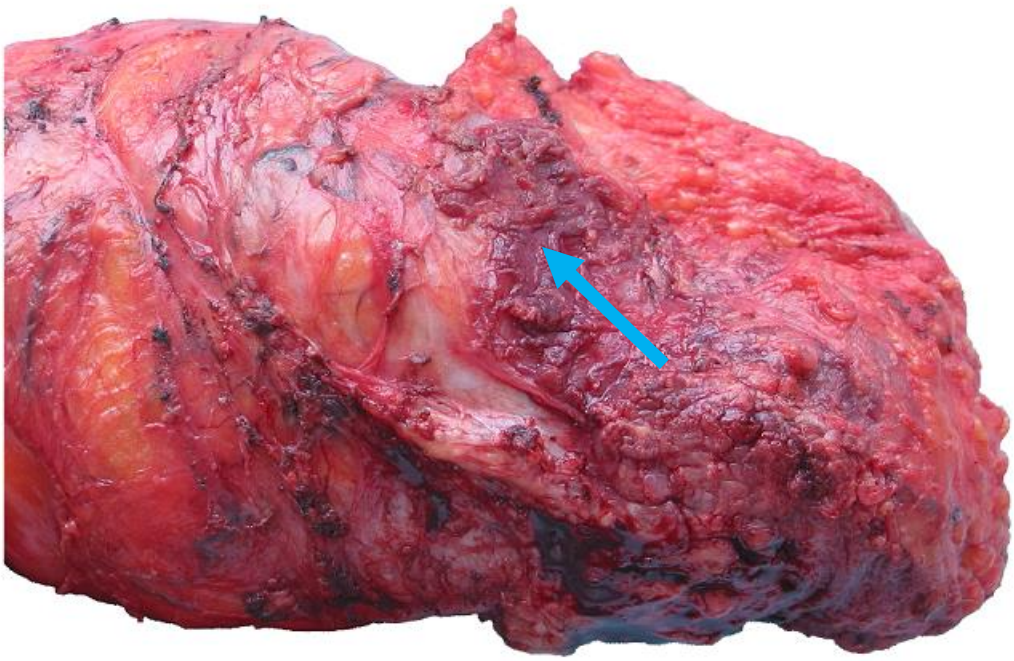
Muscularis propria plane with significant mesorectal defects exposing extensive areas of muscularis propria (blue arrow)

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)

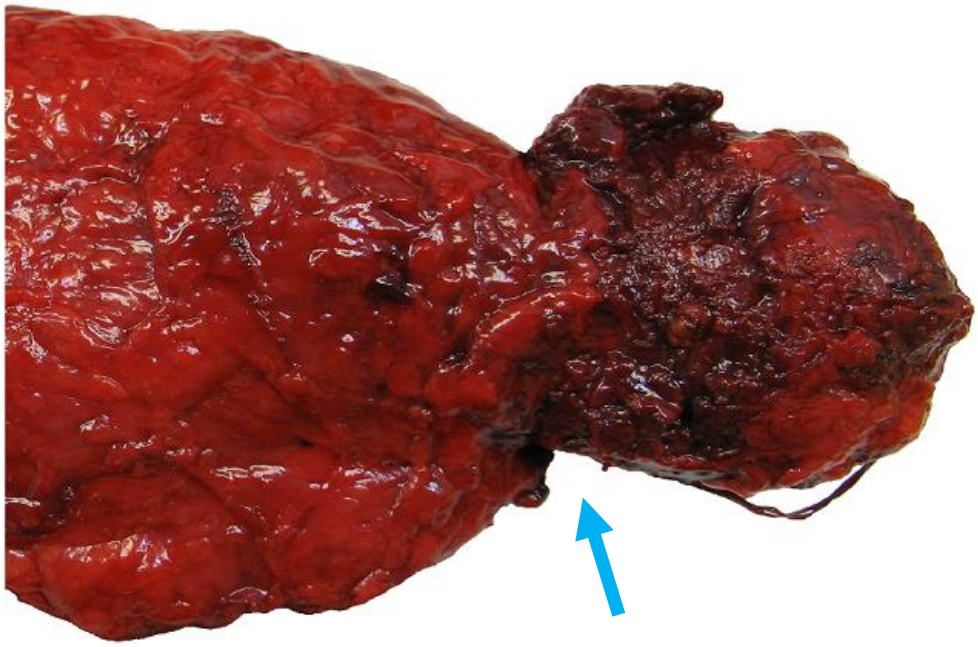
The plane of surgical dissection in the levator/sphincter area around the anal canal and below the mesorectum needs to be assessed separately in APE specimens, in addition to evaluation of the mesorectal plane of excision.[37]

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.



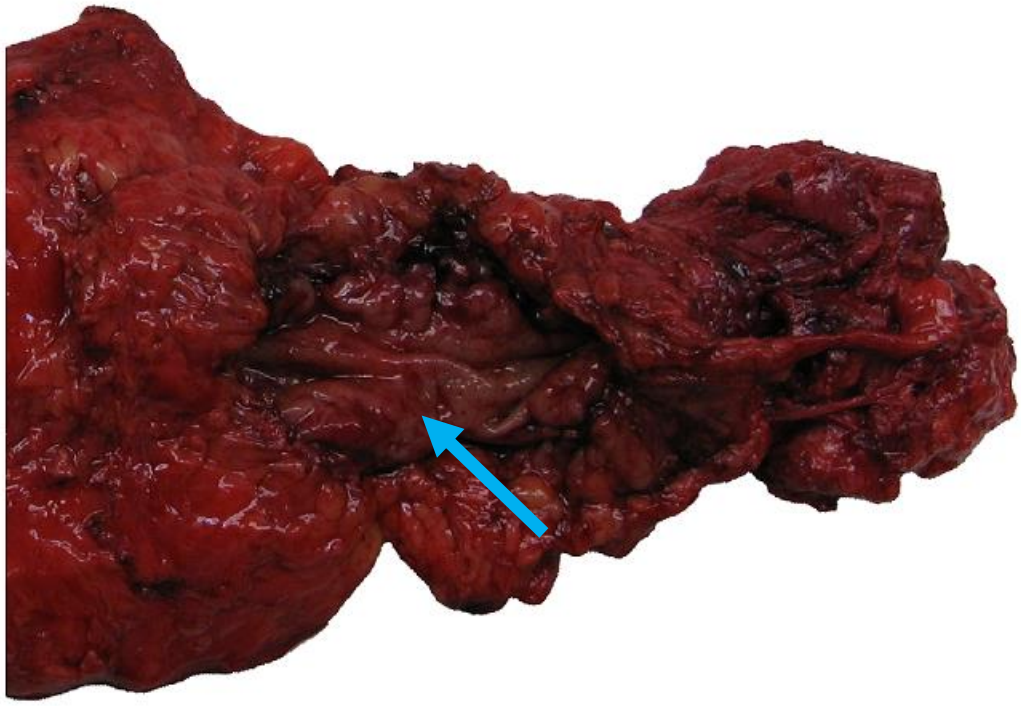
Extralevator plane showing levator muscles attached to the mesorectum (blue arrow)

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 (blue arrow) 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/ perforation	The surgeon has inadvertently entered the sphincter muscle or even deeper into the submucosa. Perforations of the specimen at any point below the peritoneal refection should also be classified into this group.



Intrasphincteric/submucosal/perforation plane showing a large anterior perforation (blue arrow) 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 include:

- histological tumour type
- histological differentiation
- maximum extent of local invasion (pT stage) and maximum distance of extramural spread
- grade of tumour regression following preoperative therapy
- resection margins (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.

5.2.1 Tumour type

The World Health Organisation (WHO) classification (2010) is recommended.[38] Virtually all colorectal cancers are adenocarcinomas. Other rare forms worthy of special mention are:

- mucinous carcinoma (variant of adenocarcinoma with >50% composed of extracellular mucin)
- signet ring cell carcinoma (variant of adenocarcinoma with >50% signet ring cells)
- adenosquamous carcinoma
- primary squamous carcinoma (excluding upwardly spreading anal tumours)
- neuroendocrine tumour/carcinoma, goblet cell carcinoids and other MANEC[23,37]
- medullary carcinoma (see comments below)
- undifferentiated carcinoma.

Signet ring cell carcinoma has stage-independent adverse prognostic significance relative to conventional adenocarcinoma.[39] Whether or not mucinous carcinoma has a different prognosis that is independent of other prognostic factors, or responds differently to certain chemotherapeutic agents, is controversial.[40,41] This is almost certainly related at least in part to the underlying tumour biology and in particular MMR status. There is also evidence that preoperative therapy may óinduceô a mucinous phenotype.[42] Therefore, if preoperative therapy has been administered and extensive mucinous tumour differentiation is seen in the resection specimen, a diagnosis of mucinous carcinoma must be confirmed from review of the diagnostic biopsy specimen, if one exists.

MMR-deficient (or microsatellite instability [MSI]-high) tumours frequently demonstrate mucinous differentiation or medullary features in the form of a solid architecture with prominent tumour-infiltrating lymphocytes.[43] MMR deficiency is found in approximately 15% of all colorectal cancers, most commonly as a sporadic phenomenon typically involving proximal tumours in elderly female patients, and occasionally as a manifestation of a germline MMR gene mutation in patients with Lynch syndrome (around 3% of all colorectal cancers), usually, but not always, in patients aged less than 50 years. There is now strong evidence that MMR-deficient tumours have a better prognosis than MMR-proficient tumours and metastasise less than MMR-proficient tumours, with only 3ï 4% of stage IV cancers being MMR deficient.[44ï 46] The relationship of deficient MMR status and response to therapy is controversial. Some studies from the USA 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.[44,47ï 51]

Deficient MMR status can be evaluated either by MSI testing, following DNA extraction from a representative tumour block, or by immunohistochemistry, applying a panel of four antibodies to the two pairs of MMR proteins involved, namely MLH1/PMS2 and MSH2/MSH6, to look for deficient MMR protein expression. 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 status, with the purpose of detecting Lynch

syndrome.[52] The initial test can be MSI or MMR immunohistochemistry, depending on local circumstances. Identification of 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 possibly due to Lynch syndrome. Germline mutation screening will be required, following genetic counselling, in those individuals whose tumour tests are suspicious of Lynch syndrome. Given these testing requirements, engagement with both molecular pathology and clinical genetics services is required.

Such tumour tissue testing can be performed on either the diagnostic biopsy specimen or on a block from the surgical resection specimen. If assessment is by MMR immunohistochemistry, 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 more timely fashion. If the result is equivocal, perhaps because only limited tumour tissue is present, testing should be repeated on a suitable block from the subsequent surgical resection specimen, or supplemented by MSI testing.

[Level of evidence C – histopathological type is important for clinical management and prognosis. Level of evidence A – MMR status is important for clinical management and prognosis.]

5.2.2 Differentiation

Differentiation is based primarily on architecture and specifically gland or tubule formation.[53–55] The criteria for poorly differentiated tumours are **either** irregularly folded, distorted and often small tubules **or** the absence of any tubular formation. Poorly differentiated adenocarcinomas should be separated from well/moderately differentiated adenocarcinomas but only if this forms the predominant area of the tumour.[55] Small foci of apparent poor differentiation are not uncommon at the advancing edge of tumours but these are insufficient to classify the tumour as poorly differentiated. TNM 8 and the American Joint Committee on Cancer (AJCC) currently recommend the use of four grades; however, we believe that the use of two grades, poor and well/moderate, enhances agreement and quality control.[22,56]

Morphological assessment of differentiation of colorectal tumours applies only to ôAdenocarcinoma, NOSô and not to specific variants, as each of these histological variants carries their own prognostic significance e.g. undifferentiated or mucinous carcinomas with high MSI behave as low-grade tumours.[38] The previous recommendation to test all colorectal cancers demonstrating features of mucinous carcinoma, or poorly differentiated adenocarcinoma, for MSI or MMR status, is now subsumed by the recommendation to test all colorectal cancers.[52]

There is considerable interest in the phenomenon of tumour budding at the advancing margin of colorectal cancers, with accumulating evidence that it is of clinical value in predicting the risk of lymph node metastatic disease in stage pT1 colorectal cancers (section 10.5) and in identifying high risk stage II colorectal cancer potentially benefitting from adjuvant chemotherapy.[57–61] Following a recent international consensus meeting, a set of recommendations for assessing tumour budding in colorectal cancer has been issued.[62] Should these result in improved reproducibility of assessment, sensitivity and specificity for the prediction of aggressive disease, the guideline will be amended, but assessment of tumour budding is not currently considered a core data item.

[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). It should be noted that the pT4 stage 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 (for instance, 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) and therapeutic connotations they are recorded in separate boxes. Accordingly, pT4 tumours may have either or both the pT4 boxes marked.

Involvement of the peritoneal surface is defined as tumour breaching of 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 only.[34,63] It is important that blocks are taken to optimise recognition of this feature (see above) and that further sections are cut 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.[64ï 67] Routine elastic stains applied for this purpose are not recommended currently.

Peritoneal involvement through direct continuity with the primary tumour (pT4a, TNM 8) is recorded differently from peritoneal tumour deposits that are separate from the primary tumour and are regarded as distant metastatic disease (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 is recorded separately. The first is a risk factor for intraperitoneal metastatic disease while the latter is a risk factor for local recurrence.

TNM conventions[68] recommend that direct invasion of an adjacent organ by way of the serosa is always recorded as pT4 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. 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). The conventions also state 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 lumens, is staged as pT2.

The **maximum distance of tumour spread beyond the bowel wall** is recorded in millimetres from the outer margin of the muscularis propria, as illustrated in Figure 5.[69ï 73] 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 and pT2 tumours this measurement will be not applicable.

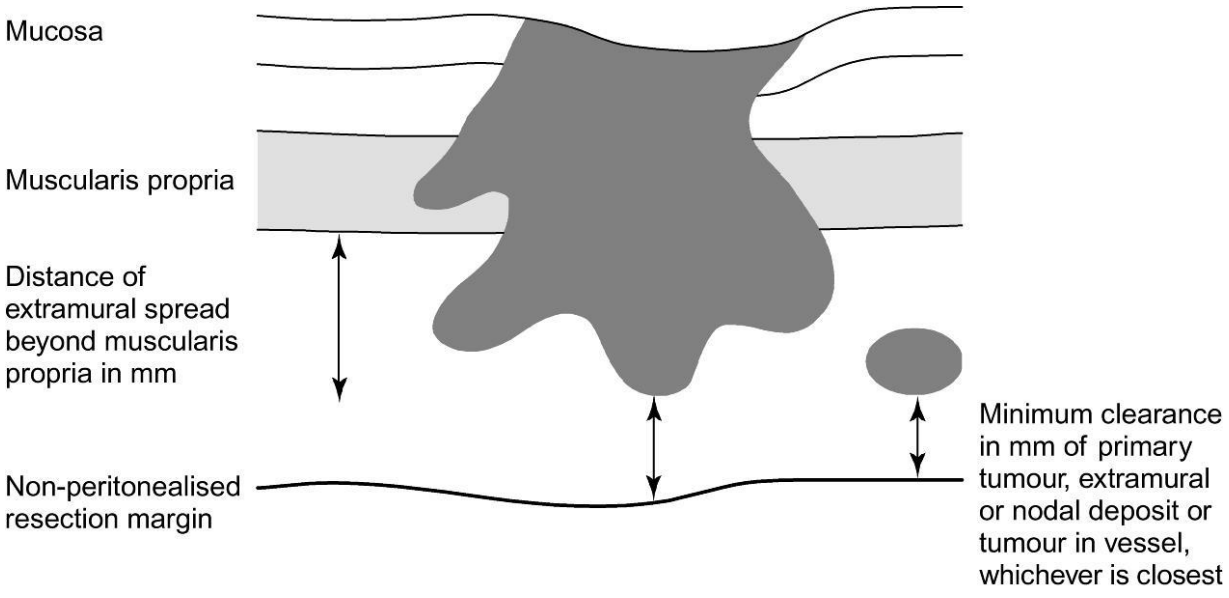


Figure 5 Measuring extramural spread and clearance of tumour from the circumferential margin.

[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 chemoradiotherapy that has resulted in complete or marked regression, have a better prognosis than those without significant regression.[15,16,74,75] 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*.,[77] and should be applied when any form of preoperative therapy is administered:[56,77]

	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, only the presence of tumour cells in the surgical specimen is taken to determine the stage. Fibrosis, haemorrhage, necrosis, inflammation and acellular mucin are ignored for staging purposes, and relevant only to assessment of regression. Although tumour regression grade is based on evaluation of the primary tumour site, it is worthwhile adding a descriptive comment on any such features evident in regional lymph nodes, or at any other potential metastatic sites. Cases with complete regression are recorded as ypT0 ypN0 (e.g. cases with complete regression of the primary tumour but viable tumour epithelium in one lymph node are recorded as ypT0 ypN1a).

[Level of evidence B – 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 described above.[33] If doughnuts are received with the surgical specimen but not submitted by the pathologist for histology, this item should be recorded as ómot submittedô ôNot applicableôshould be recorded if doughnuts were not received with the resection specimen.

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 ómot submittedô

Circumferential resection margin

This margin has been defined in detail above. Its involvement is predictive of local recurrence and poor survival in rectal tumours,[5i 7] and 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 been recognised.[34,78] Spread of the 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.[34] The evidence to recommend equating this with margin positivity is not yet sufficient, but if this finding is present in a resection specimen, it would be prudent to highlight the observation in the pathology report and to bring it to the attention of the multidisciplinary team.

The minimum distance between the tumour and the CRM in millimetres is also recorded from the histological slides (see Figure 5). If this is ≤1 mm then the CRM is **regarded as involved (R1)** in the assessment of completeness of resection later on in the proforma.[79] Such involvement may be through direct continuity with the main tumour, by tumour in veins, lymphatics or lymph nodes, or by tumour deposits discontinuous from the main growth. 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.

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

5.2.6 Lymph nodes

All of the lymph nodes that have been retrieved from the specimen should be examined histologically as described above. 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. Extra-capsular 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 Ó0.2 mm and <2 mm) compared to those with tumour-negative nodes, but no increased risk of disease recurrence in cases with ósolated tumour cellsô(single tumour cells or groups <0.2 mm in maximum dimension) compared to those with tumour-negative nodes.[80] It is recommended, therefore, that any lymph node with a tumour deposit measuring Ó0.2 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. If isolated tumour cells are identified on examination of initial levels, 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.

The difference between stage pN1 and pN2 is the number of lymph nodes involved (pN1 = 1ï 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 1ï 3 regional lymph nodes
  - ï N1a: Metastasis in 1 regional lymph node
  - ï N1b: Metastases in 2ï 3 regional lymph nodes

- N2: Metastatic disease in 4 or more regional lymph nodes
  - ï N2a: Metastases in 4ï 6 regional lymph nodes
  - ï 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. This is a prognostic factor.

If preoperative therapy has been received, 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. Rarely, acellular mucin may be encountered within lymph nodes regional to a colorectal cancer when no preoperative therapy has been administered. Somewhat paradoxically, identification of neoplastic epithelium is not required in this circumstance to designate the lymph node as involved by metastatic adenocarcinoma (stage pN1), This stance, which is supported by TNM (UICC), is taken as it is difficult to conceive any alternative benign explanation for the occurrence of mucin within lymph nodes located near an adenocarcinoma.

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

5.2.7 Tumour deposits

Since the first edition of this dataset, three revisions (the 6th, 7th and 8th editions) of TNM staging of colorectal cancer have been published.[22,24,25] These have each recommended changes to the definitions of lymph node involvement that were given in the first edition (TNM 5),[26] particularly in relation to rules interpreting mesenteric discontinuous ótumour depositsô lacking identifiable lymph node or vascular structure. There is now convincing evidence from meta-analysis of the adverse prognostic significance of tumour deposits.[27] The definition of tumour deposits has been clarified in TNM 8 and this staging is now recommended in this dataset.

By TNM 8 definition, tumour deposits (satellites) are discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissueôs lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures. If a vessel wall is identifiable on haematoxylin and eosin, elastic or other stains, it should be classified as venous invasion (V1/2) or lymphatic invasion (L1). Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion (Pn1). 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 final pN substage. The number of tumour deposits should be counted up to five or, if more, classified as more than five.[22]

Note that neither size nor contour are part of the definition of tumour deposits. The ó3 mm ruleô of TNM 5, which defined a nodal deposit, no longer applies and so there is no need to measure such deposits.

[Level of evidence B – tumour deposit status predict 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 a very recent meta-analysis, that intramural (intramuscular or submucosal) venous spread is also of prognostic importance.[34,81,82] It is of particular importance when reporting pT1 cancers. Assessing venous invasion is a requirement of TNM 8.[22] 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 Talbotôs definition of venous invasion is used i.e. tumour present within an extramural endothelium-lined space that is either surrounded by a rim of muscle or contains red blood cells. Venous invasion should also 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. 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.[81,83–85] Population-based data suggest that venous invasion detection rates are low, especially among non-specialist gastrointestinal pathologists.[86] Routine elastic stains have been shown to enhance the detection of venous spread, especially among non-specialist pathologists, although interobserver agreement remains moderate at best.[85] 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 routine elastic staining 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, with 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.[87] 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 some 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.[88,89] Multiple studies including a recent meta-analysis have demonstrated the adverse prognostic value of perineural invasion in colorectal cancer.[89–91] One large multicentre study reports adverse prognostic significance of both intramural and extramural perineural invasion.[92] 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 B – 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] Note, TNM 8 has subclassified colorectal cancer stage pM1 into substage pM1a representing metastatic disease in one distant organ (excluding metastatic peritoneal disease), pM1b metastatic disease in two or more distant organs and pM1c metastatic peritoneal disease (regardless of other organ involvement).[22] Note, pathologists can only base assessment of distant metastatic disease on submitted specimens and therefore should not use the terms ‘pM0’ or ‘pMX’

5.2.10 Separate abnormalities

The presence of any pathological abnormalities in the bowel away from the tumour should be recorded. The following are particularly of note:

- polyp(s), including their number, size and type (adenomatous, hyperplastic, serrated, hamartomatous, etc). Note, 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
- polyposis syndrome e.g. familial adenomatous polyposis (FAP)
- diverticulosis
- obstructive colitis
- non-tumour perforation.

6 Non-core data items

6.1 Macroscopic

Items include:

- specimen dimensions
- precise anatomical (quadrantic) location of CRM involvement (rectal tumours).

6.2 Microscopic

Items include:

- nature of advancing margin (infiltrative *versus* expansive)
- tumour budding
- peritumoral inflammation
- tumour stromal percentage.

7 Additional investigations

As discussed in section 5.2.1, routine testing of tumour tissue at the time of diagnosis for deficient MMR status (by MSI testing or MMR immunohistochemistry) is now recommended and therefore MMR status, assessed by either method, is considered a core data item. Identification of defective MMR status with loss of MLH1 immunoexpression triggers tumour BRAF V600E testing and/or MLH1 promoter hypermethylation testing in order 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. Similarly, mutation screening of other specific genes may be required if any other genetic diagnosis is suspected e.g. FAP or MUTYH-associated polyposis.

Additional molecular testing of tumour tissue may be required for further patient management. This currently includes mutation testing of KRAS codons 12, 13, 59, 61, 117 and 146, NRAS codons 12, 13, 59 and 61, BRAF V600E and PIK3CA to inform anti-epidermal growth factor receptor (EGFR) therapy and prognosis. Use of RNA predictive or prognostic testing is not recommended on current evidence and is not approved by NICE.

Results of any additional investigations, as available, should be recorded within the pathology report, with appropriate clinical interpretation.

8 Diagnostic coding

Colorectal carcinomas should be coded according to the SNOMED system, applying appropriate T and M codes as a minimum (Appendix B).

9 Pathological staging

9.1 Margin involvement and resection status

Margins include the ends of the specimen, the CRM and the doughnuts. Tumours that do not reach an excision margin are classified as R0, those with microscopic (but not macroscopic) margin involvement are classified as R1 and those with macroscopic margin involvement as R2. It is advisable, however, 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 metastatic disease. Therefore, if a separate tumour deposit, for example in the peritoneal cavity or liver, has been biopsied for histological diagnosis, R2 classification is appropriate regardless of the primary tumour resection margins.

When doughnuts and the ends of the specimen are not examined histologically because the tumour is >30 mm away these are assumed to be tumour-free.

CRM is regarded as involved if tumour extends histologically to ≤1 mm from this margin. Such cases should be recorded as R1.[79]

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

9.2 TNM staging

The TNM 8 staging definitions are shown in Appendix A. The prefix ópô is used to indicate pathological staging. If preoperative chemotherapy and/or radiotherapy has been given, the prefix ýpôshould 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 ypT0N0.

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 pT4 (fulfilling criteria for pT4a and pT4b).
- applying TNM 8, tumour deposits (discrete nodules of cancer in the peritumoral 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.
- the difference between stage pN1 and pN2 is the **number** of lymph nodes involved (pN1 = 1ï 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 refrain from using ópM0ôor ópMXô 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, and 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 órô and, if derived from an autopsy specimen, with the prefix óaô
- 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.

9.3 Dukes classification

The Dukes and Bussey modification of the original Dukes classification of resection is no longer to be reported as it is not compatible with TNM 8 staging.

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 (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, namely tumour size, poor differentiation, the depth of invasion into the submucosa, the presence of submucosal lymphatic or venous invasion and margin involvement.[93ï 96] However, there is only limited consensus in the published literature on how exactly some of these parameters should be assessed, especially the depth of submucosal invasion. 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 ï the NHSBCSP mandate ï 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 polypoid, 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.[28] 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 small 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.[28] 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, whether a polypectomy, an endoscopic mucosal resection, an endoscopic submucosal dissection or a transanal endoscopic microsurgical excision
- site of tumour
- overall specimen (usually polyp) size
- histological tumour type
- histological differentiation
- extent of local invasion
- venous invasion
- lymphatic invasion
- perineural invasion
- presence of a precursor adenoma (or rarely other polyp type)
- margin involvement by carcinoma (deep/peripheral)
- minimum deep margin clearance of the invasive carcinoma (in millimetres)
- pT stage
- MSI/MMR tumour status, with an indication if the patient needs to undergo further testing for Lynch syndrome.

Some of these require special consideration.

10.1 Histological differentiation

Although poor differentiation is identified by the same criteria as in major resection specimens, it is unclear from the literature whether this should be based on the predominant area or the worst area. Publications containing recommendations for selecting patients with stage pT1 tumours for major colorectal resection do not comment on the issue, but it is likely that most have used the worst area. In view of this uncertainty it is recommended that, for stage pT1 colorectal cancers, poor differentiation should be based on the worst area until the situation is clarified by further research; this approach will ensure that patients are not exposed to the possibility of under-treatment.

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

10.2 Extent of local excision

Tumours that invade the muscularis propria usually require further 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%.[97,98]

In polypoid lesions, Haggitt *et al.* 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.[99] However, neither Kikuchi (for sessile tumours) nor Haggitt (for polypoid tumours) systems are always easy to use in practice, especially if there is fragmentation or suboptimal orientation of the tissue, and one study found lymph node metastatic disease in six of 24 Haggitt level 3 lesions.[94] Kikuchi level 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 with the exception of some transanal resection 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 as yet to recommend alternative measures.

Ueno *et al.* 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.[94] The Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines currently recommend surgical resection with a depth of invasion of >1,000 micrometres or in the presence of other high risk features.[100] Adoption of this policy would significantly increase the resection rate in the UK and we believe this is too cautious an approach. The evidence base is not clear in UK practice and the NHSBCSP is evaluating the evidence through a major audit. In summary, a firm recommendation cannot be made based on current evidence for one method of assessing local invasion over another and all four approaches are included in the proforma dataset to facilitate data collection for further research and for local multidisciplinary teams 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 or distant metastatic disease. Two meta-analyses examining studies of stage pT1 colorectal cancer revealed lymphatic invasion and, to a lesser extent, venous invasion to be powerful predictors of lymph node metastatic disease.[95,96] Lymphatic and venous invasion should therefore now be assessed 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.[101–103] CD34 stains both lymphatic and venous endothelial lining cells. Venous invasion is defined as tumour lying within an endothelium-lined space that is either surrounded by a rim of muscle or contains red blood cells.[104] 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 difficult. Although immunohistochemical and histochemical stains can be useful to identify and distinguish lymphatic and venous invasion, it is recommended 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 predicts nodal metastatic disease.]

10.4 Margin involvement

Intact polypectomy specimens require assessment of both the peripheral (mucosal) and deep margins. The precise measurement of the closest proximity of the deep margin from invasive tumour should be recorded. 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 6). 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 (Figure 6B and 6C) as follows:

1. 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.
2. measure the distance of invasive carcinoma to the notional line. Distances should be recorded in millimetres to one decimal point.

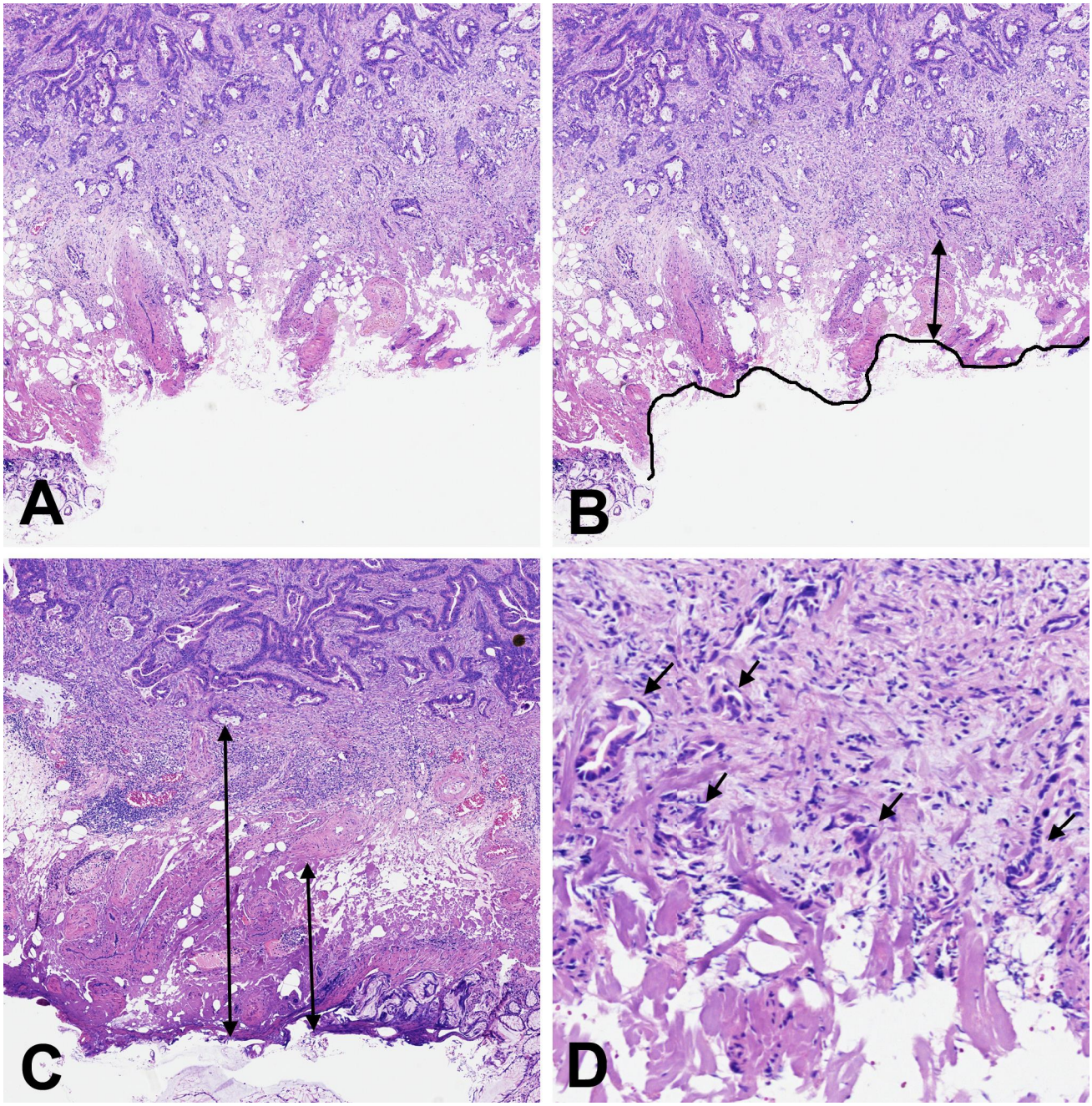


Figure 6 Diathermy artefact and margin assessment. Diathermy snare resection introduces a zone of secondary artefactual changes that makes margin assessment difficult. (A) Stromal vaporisation, clefting and withdrawal of the resection plane is most marked adjacent to thick submucosal blood vessels. (B) Measurement of tumour to resection margin should avoid such artefacts and a best attempt 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, any infiltration by malignant glands into the diathermy zone (short arrows) is regarded as margin involvement (0 mm distance recorded), as it is not possible to confidently determine the true extent of infiltration in this situation. (Copyright NHSBCSP; 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 6D), 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.

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 ówickôthe 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.

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 Ò1 mm as needing consideration of further therapy.[105,106] There is some recent 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.[94,107,108] This is not sufficiently strong, however, to change the current recommendation to consider clearance of Ò1 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 Ò1 mm of the true polypectomy margin, in the setting of minimal diathermy (Figure 6). For consistency, despite the absence of good evidence, tumour extending to within Ò1 mm of the peripheral mucosal, submucosal or muscularis propria margins is also considered margin involvement.

[Level of evidence C – margin involvement predicts residual local disease.]

10.5 Tumour budding

There is emerging evidence that identification of the phenomenon of tumour budding in local excision specimens may be of prognostic importance in predicting outcome and/or predictive of nodal metastatic disease.[94,109ï 111] As discussed for colorectal resection specimen reporting, this is not yet considered sufficient to justify its inclusion as a core data item. However, with the new international consensus definition and further evaluation of the significance of tumour budding on multivariate analyses, we will reconsider this factor as and when new data becomes available.[62]

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 the Far East, 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 TNM guidance that requires definitive evidence of submucosal invasion to make a diagnosis of adenocarcinoma and does not allow the diagnosis of intramucosal adenocarcinoma.[37,105] The latter term, and pTis, are not used in the UK for the lower gastrointestinal tract, to avoid overtreatment of lesions considered to have negligible risk of metastatic spread. The term high-grade dysplasia should be used to encompass these.

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 ónintramucosal adenocarcinomaô 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.

One of the authors (NA Shepherd, personal communication) has undertaken a year-long audit of MDTM practice with regard to colorectal cancer biopsy. In about 10% of colorectal biopsies, the features were regarded as suspicious for cancer but not diagnostic because of a lack of obvious submucosal involvement or convincing desmoplastic stromal reaction. However, in about half of these (and mainly in the colon), the MDTM decided that further biopsies were not required because the biopsies had confirmed primary glandular neoplasia and the clinical, endoscopic and imaging features demanded resection anyway. It should be emphasised that these cases were mainly in the colon and that biopsies in the rectum, accounting for about 5% of the total number, did require further biopsies. The latter was particularly the case when an APE would have been the proposed management strategy, and/or if preoperative therapy was planned. So, particularly in the colon, there may not be a definitive argument for repeat biopsies, if clinical, endoscopic and imaging features demand resection anyway, as long as the biopsies have confirmed primary colorectal glandular neoplasia. Note, this situation may change as the demand for routine molecular testing grows, especially if there is an indication to perform such testing on the diagnostic sample, rather than await a resection specimen. Endoscopists should be encouraged to take more and larger biopsy samples from all tumours, to allow confident diagnosis and provide adequate tumour tissue for any required downstream testing e.g. for Lynch syndrome.

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 MDMT 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 ñn keeping with adenocarcinomaò 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 of the dataset

There is compelling evidence that the introduction of RCPathôs original colorectal cancer dataset (1998) improved the standard of colorectal cancer reporting with regard to the completeness of information within pathology reports.[20,21] However, audits show that significant differences remain in the frequencies with which important adverse prognostic features are found between individual pathologists and multidisciplinary teams.[112] 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 examined 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 the extent of the resection undertaken or the use of preoperative therapy, typically in rectal cancer. 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 óunderstagedôand that if more lymph nodes had been examined metastatic disease would have been found.[113]

It is therefore recommended that multidisciplinary teams and/or pathology departments audit their reports at regular intervals (perhaps yearly) to ensure that their overall results are not significantly different from what might be expected. Three standards are recommended:

1. the median number of lymph nodes examined should be greater than 12
2. the frequency of peritoneal involvement should be at least 20% for colonic cancers. Assessment of percentage rectal cases reported with peritoneal infiltration has been removed as a quality standard, given increased use of preoperative therapy for rectal cancer.
3. the frequency of venous invasion, including intramural (submucosal and intramuscular) and extramural, should be at least 30%.

These 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 15ï 25 lymph nodes per case, a frequency of peritoneal involvement of 30ï 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[22]

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 1ï 3 regional lymph nodes
- pN1a Metastasis in 1 regional lymph node
- pN1b Metastases in 2ï 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 4ï 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 one organ without peritoneal metastases
- pM1b Metastases in more than one 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 ô 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)	Cecum 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: é é é é é é é é é é é é Forenames: é é é é é é é é é é é .... Date of birth: é é é é Sex: é ..
Hospitalé é é é é é é .é é é é é .é .. Hospital no: é é é é é é é .é é é é é ... NHS no: é é é é é é ..é é é é
Date of surgery: é é é é é é .é é é é Date of report authorisation: é é é é é é Report no: é é é é é é é é .é .
Date of receipt:é é é é é é é é ..é . Pathologist: é é é é é .é é é é é é é Surgeon: é é é é é é é é é .é

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

Maximum tumour diameter[Å]: é é .. mm or Not identified ☐

Site of tumour[Å]:
Caecum ☐ / Right (ascending) colon☐ / Hepatic flexure☐
Transverse colon☐ / Splenic flexure☐ / Left (descending) colon☐ / Sigmoid colon☐ / Rectum ☐ / Unknown ☐

Distance of tumour to nearer longitudinal end: ..... 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)[Å]:
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[Å].....é mm

Tumour type[Å]:
Adenocarcinoma ☐ Other, or variant of adenocarcinoma ☐
If Other, or variant (e.g. mucinous), specify..é é é é é é é

Differentiation by predominant area[Å]:
Well/moderate ☐ Poor ☐ Not applicable ☐

Local invasion:
No carcinoma identified (pT0) ☐
Submucosa (pT1) ☐
Muscularis propria (pT2) ☐
Beyond muscularis propria (pT3) ☐
Tumour cells have breached the serosa (pT4a) ☐
Tumour has perforated below peritoneal reflection (pT4a) ☐
and/or tumour invades adjacent organs (pT4b) ☐

Maximum distance beyond muscularis propria[Å]:
N/A (if intramural tumour) ☐ Distance é é é .mm

Preoperative therapy response (tumour regression score)[Å]:
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[Å]:

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

(N/S = not submitted by pathologist)

Distance from carcinoma to CRM[Å]:é ..é é é é ..mm

Number of lymph nodes[Å]:.....

Number of involved lymph nodes[Å]:.....

(N1a, 1 node; N1b, 2ï 3 nodes; N1c, tumour deposits only). pN2a, 4ï 6 nodes; pN2b, >6)

Highest node involved: Yes ☐ No ☐

Number of tumour deposits: 0☐1☐ 2☐ 3☐ 4☐ 5☐ >5☐
Not applicable (if node positive) ☐

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 ☐

Histologically confirmed distant metastatic disease[Å]:
Yes (pM1) ☐ No ☐ If yes, site(s): é é é é é é ..é .
(pM1a, one organ; pM1b, >1 organ; pM1c, peritoneal)

Separate abnormalities:	No	Yes
Polyp(s)	☐	☐
If yes state type(s) and number é é é é é é é é é é é		
Polyposis	☐	☐
If yes specify type: é é é é é é é é é é é é é é é . é		
Synchronous carcinoma(s) (separate proforma for each cancer)	☐	☐
Other (e.g. IBD)..é é é é é é é é é é é é é é é é .		

Complete resection (by >1 mm) at all margins[Å]:
Yes (R0) ☐ No (R1) ☐ No (R2) ☐

TNM (8th edition)[Å]:
(y)pT é é .. (y)pN é é .. (y)pM é é ..

Block index (A= , B= etc):

Selected tumour block(s) for additional testing:

Signature: ……. Date ……/…../……. SNOMED codes[Å]: 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: é é é é é é é é é é é é Forenames: é é é é é é é é é é é ... Date of birth: é é é é Sex: é ..
Hospitalé é é é é é é .é é é é é .é ..Hospital no: é é é é é é é .é é é é é ... NHS no: é é é é é é ..é é é é
Date of surgery: é é é é é é .é é é é Date of report authorisation: é é é é é é Report no: é é é é é é é é .é .
Date of receipt:é é é é é é é é ..é .Pathologist: é é é é é .é é é é é é é é Surgeon: é é é é é é é é .é

Specimen type[Å]:

Polypectomy □ / Endoscopic mucosal resection (EMR) □ / Endoscopic submucosal dissection (ESD) □
Transanal endoscopic microsurgical (TEMS) excision □ / Otheré é é é é é é é é é é é é é é é é .

Site of tumour[Å]:

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): .....mm Not assessable (piecemeal) □

Comments:é .....

Tumour type[Å]:
Adenocarcinoma □ Other, or adenocarcinoma variant □
If Other, or variant, specify.....é é é é é é

Differentiation by worst area[Å]:
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 é é .. mm
Width of invasive tumour é é .. mm

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[Å]:.....

Number of involved lymph nodes[Å]:.....

Number of tumour deposits: 0□ 1□ 2□ 3□ 4□ 5□ >5□
Not applicable (if node positive) □

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 □

Preoperative therapy response[Å] (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[Å]:

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

(*Not assessable is appropriate if specimen received piecemeal)
Histological measurement from carcinoma to nearest deep excision margin é é é é é mm
Not assessable □

Pathological staging:
Complete resection of carcinoma (by >1mm) at all margins[Å]:
Yes (R0)□ No (R1)□ No (R2)□ Not assessable □

Signature: ……..…… Date …../…../…… SNOMED codes[Å] 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: é é é é é é é é é é é é	Forenames: é é é é é é é é é é é	Date of birth: é é é é Sex: é ..
Hospitalé é é é é é é .é é é é é .é ..	Hospital no: é é é é é é é .é é é é é ...	NHS no: é é é é é é ..é é é é
Date of surgery: é é é é é é .é é é é	Date of report authorisation: é é é é é é	Report no: é é é é é é é é .é .
Date of receipt:é é é é é é é é ..é .	Pathologist: é é é é é .é é é é é é é	Surgeon: é é é é é é é é é .é

Additional Investigations:

Mismatch repair (MMR) protein immunohistochemistry

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

Microsatellite instability (MSI) testing

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

MLH1 promoter hypermethylation testing

Present ☐ Absent ☐ Test failed ☐ Not performed ☐

BRAF V600E mutation testing

Present ☐ Absent ☐ Test failed ☐ Not performed ☐

KRAS mutation testing

Present ☐ Absent ☐ Test failed ☐ Not performed ☐

Specify mutationé é é é ..

NRAS mutation testing

Present ☐ Absent ☐ Test failed ☐ Not performed ☐

Specify mutationé é é é ..

Signature: ……. Date ……/…../……. SNOMED codes[A]: T…..... / M……

Note: †Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) v7.

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 • Anterior resection • Sigmoid colectomy • Hartmann's procedure • Abdominoperineal excision • Other	
Specimen type, other specify	Free text	Only applicable if 'Specimen, Other' is selected.
Maximum tumour diameter	Size in mm	
Tumour identified	Single selection value list: • Tumour in specimen • Not identified	Tumour in specimen must be selected if 'Maximum tumour diameter' is >0.
Site of tumour	Single selection value list: • Caecum • Right (ascending) colon • Hepatic flexure • Transverse colon • Splenic flexure • Left (descending) colon • Sigmoid colon • Rectum • Unknown	Only applicable if 'Tumour identified, Tumour in specimen' is selected.
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 • Below	Only applicable if 'Site of tumour, Rectum' is selected.

	• Astride	
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 • Intrasphinteric	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 selected' 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 predominant 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 invades adjacent organs	
Maximum distance beyond muscularis propria	Distance in mm	Only applicable if 'Local invasion, Beyond muscularis propria' or '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 ôTumour identified, Tumour in specimenôis 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 • Not applicable	Not applicable if ôNumber of involved lymph nodesôis >0.
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	
Histologically confirmed distant metastatic disease	Single value selection list: • Yes • No	
Histologically 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, Site 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	
Complete resection (by >1mm) at all margins	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 mucosal dissection • Transanal endoscopic microsurgical excision • Other	
Specimen type, other specify	Free text	Only applicable if ôSpecimen type, Otherô is selected.
Site of tumour	Single selection value list: • Caecum • Right (ascending) colon • Hepatic flexure • Transverse colon • Splenic flexure • Left (descending) colon • Sigmoid colon • Rectum • Unknown • Not identified	
Size of specimen (maximum width)	Size in mm	
Size of specimen, assessable	Single selection value list: • Assessable • Not assessable	Assessable if ôSize of specimenô has a valid value.
Comments	Free text	
Tumour type, Adenocarcinoma	Single selection value list: • Yes • No	Only applicable if ôSite of tumourô is NOT ónot identifiedô
Tumour type, specify	Free text	Only applicable if ôSite of tumourô is NOT ónot identifiedô and ôTumour type, Adenocarcinoma, Noô is selected.
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 • Not applicable	Not applicable if 'Number of involved lymph nodes' is >0.
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	
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 ôSite of tumourôis NOT ónot identifiedô
Histological measurement from carcinoma to nearest deep excision margin, assessable	Single selection value list: • Assessable • Not assessable	Assessable if óHistological measurement from carcinoma to nearest deep excision marginôhas a valid value.
Complete resection at all margins	Single value selection list: • Yes (R0) • No (R1) • No (R2) • Not assessable	
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	
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 guideline
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	4ï 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	4ï 12
16 The different options for management of the condition or health issue are clearly presented	4ï 12
17 Key recommendations are easily identifiable	4ï 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 Aï 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