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

Standards and datasets for reporting cancers

Dataset for colorectal cancer histopathology reports

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Comments	This replaces the 2nd edition of the *Dataset for colorectal cancer,* published in 2007. In accordance with the College's pre-publications policy, this dataset was on the College website for an abridged consultation from 29 April to 2 June 2014. Forty-six items of feedback were received. Please email publications@rcpath.org to see the responses and comments. **Dr Suzy Lishman** **Vice-President for Advocacy and Communications**

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Foreword

The cancer datasets published by The Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. It may rarely be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

Each dataset contains **core data items** that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer 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 for Coloproctology of Great Britain and Ireland (www.acpgbi.org.uk)
- National Cancer Research Institute – Colorectal Cancer Subcommittee (www.ncri.org.uk)
- British Society of Gastroenterology – Pathology Section (www.bsg.org.uk)
- British Division of the International Academy of Pathology (www.bdiap.org)
- NHS Bowel Cancer Screening UK – Pathology Group.

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 and including March 2014. The level of evidence for the recommendations has been summarised (Appendix E). Unless otherwise stated, the level of evidence corresponds to "Good practice point (GPP): Recommended best practice based on the clinical experience of the authors of the writing group". No major organisational changes or cost implications 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 sub-specialty 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 Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for Fellows' attention. If Fellows do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Working Group on Cancer Services and was placed on the College website for consultation with the membership from 29 April to 2 June 2014. All comments

received from the Working Group and the membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Vice-President for Advocacy and Communications.

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

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 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
- 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 post-operative therapy to be advised

- patients who have lymph node involvement (Dukes C1 and C2 or pN1 and pN2) are likely to receive adjuvant chemotherapy, if age and co-morbidity allow, which is of probable benefit, mildly toxic and costly.[1-4] Those without lymph node metastatic disease but with adverse pathological features (venous invasion, perforation, serosal involvement, incomplete resection or extensive local spread) may also be offered adjuvant therapy for small but definite benefit[2]

- patients with rectal adenocarcinoma and involvement of the circumferential resection margin are at high risk of local recurrence [5-7] and may receive post-operative radiotherapy +/– chemotherapy that is toxic and costly but may decrease the likelihood[8,9] of this unpleasant and nearly uniformly fatal complication. The frequency of circumferential margin involvement found may indicate the quality of rectal cancer surgery being performed[10-14]

- to determine the effects of pre-operative 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.[11,19]

Communication of pathology information to the patient and the MDT is essential for quality clinical management. Each department should have a lead gastrointestinal pathologist and deputy, one of whom should attend multidisciplinary team meetings (MDTM). 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.

Many of the changes made to the second versions of the resection and local excision dataset proformas reflect relatively minor issues of cosmesis, but there have also been changes in the overall structure. 'Date of surgery/procedure' has been added to allow mapping to recently published key performance indicators relating to turnaround times (www.rcpath.org/clinical-effectiveness/kpi).

It is appreciated that electronic versions of the dataset are still not available in all pathology departments and there remain some laboratories that have to dictate the dataset into report formats. Therefore any headings that are deemed superfluous have been removed. Some have produced confusion. For instance, the distance to the closest margin can be determined either macroscopically (if it is some distance not measurable on histological sections) or microscopically. Confusion has arisen because the distance was included under 'Gross description'. By the same token, we have removed the word 'Histological' from the 'Measurement from tumour to circumferential margin'. In some parts of the colon, this can never be measured on a single histological slide (as it is often in excess of 75 mm). Further, extramural venous spread is/was, quite clearly, not 'Metastatic disease' and thus that heading has also been removed.

Mismatch repair (MMR) protein immunohistochemistry now has several well-recognised applications in colorectal carcinoma. MMR status has prognostic significance, possible predictive significance and can help detect Lynch syndrome families. As such, a strong case can now be made for performing MMR immunohistochemistry in all cases of CRC. However, given the resource implications of implementing this, it is not considered a core data item for all colorectal cancers currently. We now consider MMR immunohistochemistry a core dataset item for patients under 50 years at time of diagnosis and for patients, in whom an assessment of prognosis is appropriate, with adenocarcinomas classified as poorly differentiated morphologically or tumours showing other morphological features of MMR deficiency. It should also be available upon request by either oncologist or geneticist on individual cases. A field to record MMR immunohistochemistry has been added to both datasets.

The following specific changes have been made to the **resection** dataset proforma (Appendix C).

1. Removal of all superfluous headings so that these do not have to be dictated into datasets. This includes the removal of 'Gross description', 'Histology', 'Metastatic spread' and 'Pathological staging'. Some of these, such as 'Metastatic spread', within which was 'extramural venous spread', are palpably inappropriate.

2. 'Site of tumour' now has a set of specified options, rather than free-text entry.

3. 'Margin (cut end)', a terminology which we were never fond of, has been altered to 'Longitudinal margin'.

4. The pathological assessment of the plane of excision for APE specimens has been included, in addition to that for AR specimens, which was in the second edition of this proforma and dataset.

5. 'Tumour type' now includes an opportunity to record specific variants of adenocarcinoma, e.g. mucinous carcinoma.

6. As grade of differentiation is only applicable to tumours classified as ‘Adenocarcinoma, NOS’, a ‘Not applicable’ option has been included under differentiation.

7. pT stage was recorded twice in the second edition of this dataset and one of these entries (previously under ‘Local invasion’ heading) has been removed. Criteria distinguishing stage pT4a and pT4b have been retained, each recorded separately.

8. 'Maximum distance of spread beyond muscularis propria' now includes a ‘Not applicable’ (N/A) box if the tumour is retained within the bowel wall.

9. A four-tier tumour regression grading system (response to pre-operative or neo-adjuvant therapy) has been adopted and replaces the previous three-tier system. This was also recommended in TNM7 as the best methodology and is supported by the findings in the FOxTROT trial.[22]

10. A ‘Not submitted’ (N/S) box is included for doughnuts when, according to national protocols and these guidelines, there is no indication for histological assessment of the doughnuts and these have not been submitted by the pathologist for histological examination. ‘Not applicable’ (N/A) indicates doughnuts were not received.

11. ‘Histological’ and ‘Non-peritonealised’ have been removed from ‘Measurement to circumferential margin’. On the one hand, it is not only assessed histologically and, on the other, we believe that pathologists are now sufficiently aware of the difference between ‘circumferential margin’ and peritoneal involvement to drop the rather cumbersome terminology of ‘non-peritonealised margin’.

12. The word ‘Present’ has been removed from the ‘Number of lymph nodes’. It is superfluous. All lymph nodes draining a tumour should be submitted for histology.

13. The ‘Apical node’ has been changed to ‘Highest node’ for clarity and consistency with the guidelines. The highest nodes found may not be at the apex. Involvement of this node(s) would still constitute a stage Dukes C2.

14. ‘Vascular invasion’ has been changed to ‘Venous invasion’. Furthermore, the options have been expanded to allow recording of the deepest level of the venous invasion seen.

15. ‘Histologically confirmed distant metastases’ has been altered to ‘Histologically confirmed distant metastatic disease’ to incorporate one, two or more metastatic deposits.

16. We have noticed some confusion over the terminology ‘Background abnormalities’ and that some pathologists have used this to indicate adenoma adjacent to the cancer, even though the adenoma clearly represents the pre-existing adenoma from which the carcinoma arose. We believe ‘Separate abnormalities’ is the more appropriate terminology. A list of the most common abnormalities encountered is offered for definitive statements, rather than previous free-text entry.

17. The Dukes stage now has a ‘Not applicable’ (N/A) category for cases where no tumour is demonstrable after pre-operative neo-adjuvant therapy or no lymph nodes are available for examination. Whilst not part of the original Dukes classification, ‘Stage D’ has been added to record distant metastatic disease (pM1), should tissue confirmation of this be available.

The following specific changes have been made to the **local excision** dataset proforma (Appendix D).

1. Endoscopic submucosal dissection has been added as a specimen type option.

2. ‘Site of tumour’ now has a set of specified options, rather than free-text entry.

3. ‘Maximum tumour diameter’, which was listed under ‘Gross description’, has been changed to ‘Size of specimen (maximum width)’ to remove confusion over whether to record the overall specimen (usually polyp) size here or the size of the invasive tumour component. Width of invasive tumour has been added as a separate measurement (to be assessed microscopically). A ‘Not assessable’ option has been added for piecemeal resection specimens.

4. ‘Tumour type’ now includes an opportunity to record specific variants of adenocarcinoma, e.g. mucinous carcinoma.

5. A comment has been added to assess differentiation by worst area (rather than predominant), to avoid confusion with the resection specimen dataset.

6. As grade of differentiation is only applicable to tumours classified as ‘Adenocarcinoma, NOS’, a ‘Not applicable’ option has been included under differentiation.

7. ‘Not applicable’ and ‘Not assessable’ options have been added for Haggitt and Kikuchi levels.

8. ‘Lymphatic or vascular invasion’ has been divided to allow distinction between lymphatic and venous invasion. The ‘Possible’ option has been removed to encourage definitive classification of these important features. Venous invasion will typically be submucosal in location but, with the development of more radical local excision techniques, deeper tissue may be present within the specimen, and therefore options for recording intramuscular and extramural venous invasion are also included, providing consistency in this regard with the resection specimen dataset.

9. Very occasionally local excision follows neoadjuvant therapy (pre-operative not applicable in this setting) and this practice may become more widespread with greater application of neoadjuvant therapy to treat colon cancer. Accordingly, options to record regression grading have been included in the local excision dataset.

10. Under margin assessment, ‘Involved by adenoma only’ has been removed as an option, as this is not relevant to the cancer management and, furthermore, is best assessed on endoscopic grounds. A ‘Not assessable’ option has been added, mainly for piecemeal resection specimens.

11. pT stage was recorded twice in the second edition of this dataset and one of these entries (previously under ‘Pathological staging’ heading) has been removed.

12. Under ‘Resection status’, a ‘Not assessable’ option has been added, mainly for piecemeal resection specimens.

Since the first edition of this dataset, two revisions (the 6th and 7th editions) of TNM staging of colorectal cancer have been published.[23,24] These have recommended major changes to the definitions of lymph node involvement that were given in the first (5th) edition,[25] particularly in relation to rules interpreting mesenteric discontinuous tumour deposits lacking identifiable lymph node or vascular structure. The changes were not reliably evidence-based, there are no effective criteria and they cannot be interpreted reproducibly.[26,27] Most importantly, such changes destabilise historical staging data and longitudinal analyses. For these reasons it is recommended that the criteria used in the 5th edition of TNM are retained for colorectal cancer reporting nationally. It is accepted that some multidisciplinary teams are using the TNM7 staging system for colorectal cancer and so, if agreed locally, the pathology report can include both the TNM5 and TNM7 stages, clearly indicated as such. TNM7 staging may also be requested, for example, if the patient has been enrolled in a clinical trial. Therefore, the reporting of TNM7 staging is optional for local practice, but TNM5 reporting is mandated by the NHSBCSP and the NHS core datasets. This will remain under review and be reconsidered when TNM8 has been published. Caution should be exercised in comparing staging data between countries where different versions of TNM may be utilised or when

undertaking longitudinal analyses in countries where there has been migration from TNM5 to TNM6 and then to TNM7.

There is no staging for appendiceal tumours in TNM5. Thus the new staging system for appendiceal tumours described under TNM7 should be used, until such time as a dataset specific for appendiceal carcinomas is available.[24] Many colorectal adenocarcinomas demonstrate focal neuroendocrine differentiation, on morphology and/or immunohistochemistry, and these should be regarded as adenocarcinomas for the purposes of this dataset, as should goblet cell carcinoids and other mixed adenocarcinoma-neuroendocrine carcinomas (MANEC). For those tumours demonstrating purely neuroendocrine differentiation, one is referred to the dataset for reporting neuroendocrine tumours of the gastrointestinal tract.[28]

1.1 Users of the dataset

The primary users of the dataset are trainee and cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. Secondary users are surgeons, radiologists and oncologists, specialist screening practitioners, NHSBCSP, cancer registries and the National Cancer Intelligence Network (NCIN). Standardised cancer reporting and MDT working reduce the risk of histological misdiagnosis and help to ensure that clinicians have all of the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer specific data also provides information for healthcare providers and epidemiologists, and facilitates international benchmarking and research.

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 pre-operative stage of the tumour
- whether or not pre-operative therapy has been given, when it finished and the nature of this (e.g. short-course radiotherapy, long-course chemoradiotherapy, the drugs used, 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 (mesenteric) or D3 (central) lymph node dissection,[29] type of abdominoperineal excision and type of local excision.

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 be placed unopened in a large volume of formalin fixative. In special circumstances, such as significant specimen transfer time from theatre to the handling laboratory, it may be worth discussing the option of partial specimen opening by the surgeon in theatre, prior to washing out and dispatch in formalin. Such an agreement would need careful discussion of

appropriate opening procedure, emphasising the importance of keeping the tumour segment intact. Accepting this, any such protocol which is robust and enhances specimen fixation is to be welcomed.

4 Specimen handling and block selection[30,31]

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 away from the tumour, the latter usually related to tumour obstruction.

For anterior resection (AR) and abdominoperineal excision (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 'bare' area in the connective tissue at the surgical plane of excision that is not covered by a serosal surface. Its extent varies greatly according to the site of the tumour. Low rectal tumours will be completely surrounded by a circumferential non-peritonealised margin, while upper rectal tumours have a non-peritonealised margin posteriorly and laterally (which should be inked) and a peritonealised (serosal) surface anteriorly which should not be inked (Figure 1).

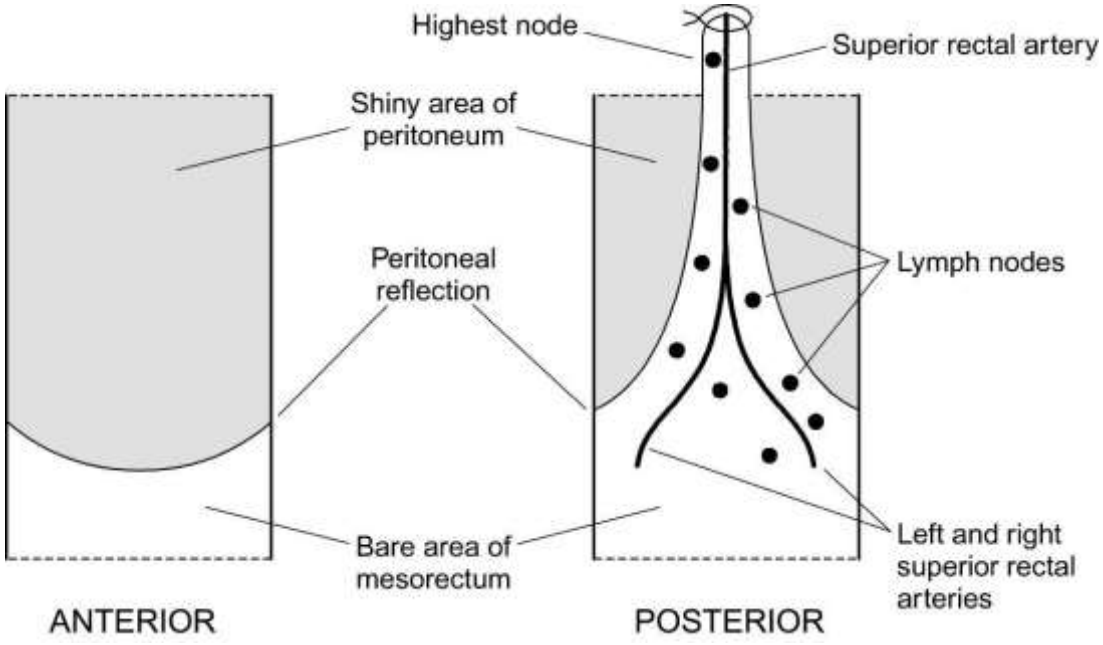


Figure 1 Diagrammatic representation of a resected rectum. Anteriorly the specimen is covered by peritoneum down to the peritoneal reflection and only the non-shaded area below this is the non-peritonealised (circumferential) margin that should be painted for assessment of margin involvement by tumour.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

Tumours of the ascending and descending colons will usually also have a non-peritonealised margin posteriorly (which should be inked) and a peritonealised or serosal surface anteriorly (which should not be inked) (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 a small or large non-peritonealised area.

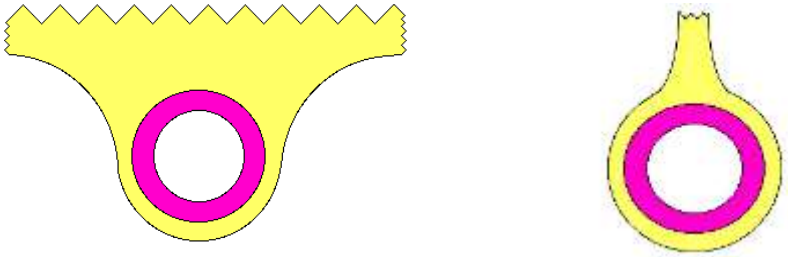


Figure 2 Diagrammatic cross-sections of the ascending colon (left) and sigmoid colon (right) for comparison. The ascending colon has a broad non-peritonealised (jagged) margin posteriorly while the sigmoid colon is suspended on a narrow mesentery and has a very small non-peritonealised margin posteriorly.

As this is now a familiar concept to most pathologists, henceforth in this dataset the term ‘circumferential margin’ will be used in preference to ‘non-peritonealised margin’, although this margin is clearly not fully circumferential at all sites.

After inking the circumferential margin, the specimen may be opened anteriorly, apart from a segment extending 10–20 mm above and below the tumour, which is left intact to avoid any subsequent confusion over whether the serosal surface or circumferential margin is involved as well as facilitating comparison with pre-operative imaging. A foam or absorbent paper ‘wick’ is then passed through the residual lumen at the tumour site to aid fixative permeation. Some pathologists prefer to open the bowel at the level of the tumour also, especially when the lesion is small and polypoid (non-annular). This is acceptable, provided care is taken to ensure that it does not compromise a proper assessment of the key data items, notably involvement of the serosa and the circumferential margin, 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 recommended that resections should be allowed to fix for a minimum of 24–48 hours before further dissection and block taking; this facilitates subsequent thin transverse slicing through the tumour and the identification of lymph nodes. 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 proximally and distally for some 30 mm, and the attached mesentery are sectioned transversely at 3–4 mm intervals with a sharp knife to produce slices that include the tumour, the adjacent lymph nodes and the serosal and circumferential resection margins. 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 vascular invasion to be identified for sampling as well as measurement of the distance of extramural tumour spread and the distance of tumour to the CRM. These images may be helpfully annotated to correspond with the block index on the final pathology report, to facilitate review and MDTM presentation.

A block index within the pathology report can also usefully aid 'on-demand' immuno-histochemical and/or molecular testing, such as might be requested subsequently by oncologists or clinical geneticists, by allowing identification from the report (without slide review) of such blocks suitable for testing as required. This may be a tumour block with greatest representation of viable tumour tissue (for molecular testing), a block with includes adjacent mucosa as control (for immunohistochemistry), a block of background normal mucosal tissue (for microsatellite instability testing or germline testing) or, if applicable, a block of nodal metastatic tumour tissue (primarily of research interest currently). The greater the detail provided in such a block index, the more 'future-proofed' the report is and the more likely subsequent such requests can be fulfilled without the necessity of costly and time-consuming slide retrieval and review. As a minimum recommendation, indication of a 'representative tumour block' within pathology reports can be very beneficial to molecular pathology departments.

The following blocks of tissue are recommended as a minimum sampling.

- At least four blocks of the tumour to show:
  - the deepest tumour penetration into or through the bowel wall
  - involvement of the serosal surface
  - invasion of veins
  - involvement of any adjacent organs.

- If possible, a block to show the closest approximation of tumour to the circumferential resection margin (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 this is not possible at some sites, as the tumour may be many centimetres from this resection margin. Particular attention should be paid to the anterior margin in rectal cancers, since this is the most common site for circumferential margin 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).

- The highest node or nodes should be blocked separately to allow recording of Dukes C2.

- 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 tumour is close to this proximal longitudinal margin.

Appropriate selection of blocks from the transverse tumour slices is crucial if the maximum amount of information is to be obtained. Serosal involvement is best identified in blocks that are taken from areas that are dulled, fibrotic, or haemorrhagic and is particularly prone to occur where the peritoneum is reflected at an acute angle from the bowel surface on to the adjacent mesentery or in deep crevices or clefts between fat lobules.[32] At least two blocks taken from where the tumour is closest to the serosa are recommended. Venous invasion

can often be suspected macroscopically as fine pale lines emanating from the base of the tumour, perpendicular to the leading edge.

Rectal tumours that have undergone pre-operative 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.[16,31] 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.[33]

The identification of lymph nodes should begin with the highest lymph node. This is the first node identified by sectioning serially and distally from the sutured vascular 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 'high tie' is usually present in rectal resections, several vessels might drain colonic resections; if the tumour lies between two major arteries it is appropriate to record both high tie nodes. 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 circumferential resection margin 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 insufficient published evidence to make a firm recommendation as to whether lymph nodes are embedded in their entirety. There is certainly no need to embed multiple slices from a large node that is obviously involved by 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.

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.[34] 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. 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.

If median lymph node yields are suboptimal, individually or departmentally, consideration could be given to implementing one or more techniques recognised to enhance lymph node yields. One option is the use of fat-clearing or other chemical agents, singly or in combination, to reveal lymph nodes[35] Another is intra-arterial methylene blue injection of the fresh specimen, either by the surgeon or pathologist, if this is feasible.[36–39] These techniques tend to increase the yield of small nodes, usually of no clinical significance, although occasionally resultant upstaging has been reported.[37] Low lymph node yields may be a significant problem following pre-operative therapy, typically in the setting of rectal cancer currently, and such techniques may therefore have a particular role in resection specimens following pre-operative therapy.

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

5 Core data items

5.1 Macroscopic core data items

- 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).

5.2 Notes on macroscopic assessment

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

5.2.1 Data recorded for all colorectal tumours

a) 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. Every effort should be made to accurately classify the tumour as colonic or rectal in origin. Although management may be dictated by lowest extent of rectal involvement rather than tumour origin, it is considered more appropriate, within resection specimens, to evaluate primary tumour site based on whether the centre of the tumour, and therefore the greatest tumour bulk, is located in the sigmoid colon or rectum.

The operation performed by the surgeon should also be recorded. Note that a high anterior resection, not a sigmoid colectomy, is the standard operation to remove a sigmoid tumour. Similarly an extended right hemicolectomy, rather than a transverse colectomy, is the standard operation to remove a transverse colon tumour. However, occasionally pathologists may receive sigmoid or transverse colectomy specimens containing tumour, suspected or unsuspected, and therefore these have been retained as options under ‘Specimen type’.

b) Maximum tumour diameter

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

c) Distance of tumour to nearer longitudinal margin

This is the measurement to the nearer longitudinal margin of the specimen, and not the circumferential margin. It is only necessary to examine the margins histologically if tumour extends macroscopically to within 30 mm of one of these.[40] 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.

d) 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 intact resection specimen. Perforation through the tumour into the peritoneal cavity is a well-established adverse prognostic factor in colonic[41] and rectal[42] cancer and should be recorded. Such cases are always regarded as pT4b in the TNM5 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 pT4b. Localised perforation through the tumour onto circumferential surgical margin e.g. in the low rectum is also recommended to be staged as pT4b.

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

5.2.2 Data recorded for rectal tumours only

a) 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).

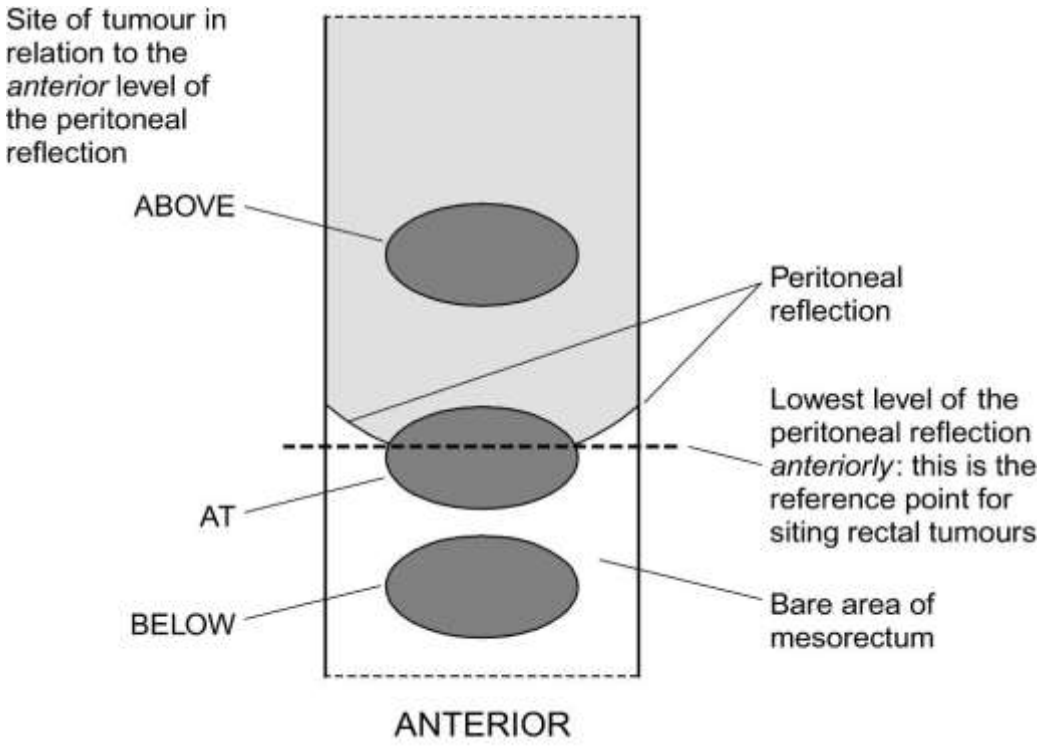


Figure 3 Diagramatic illustration of rectal tumours in relation to the peritoneal reflection

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]

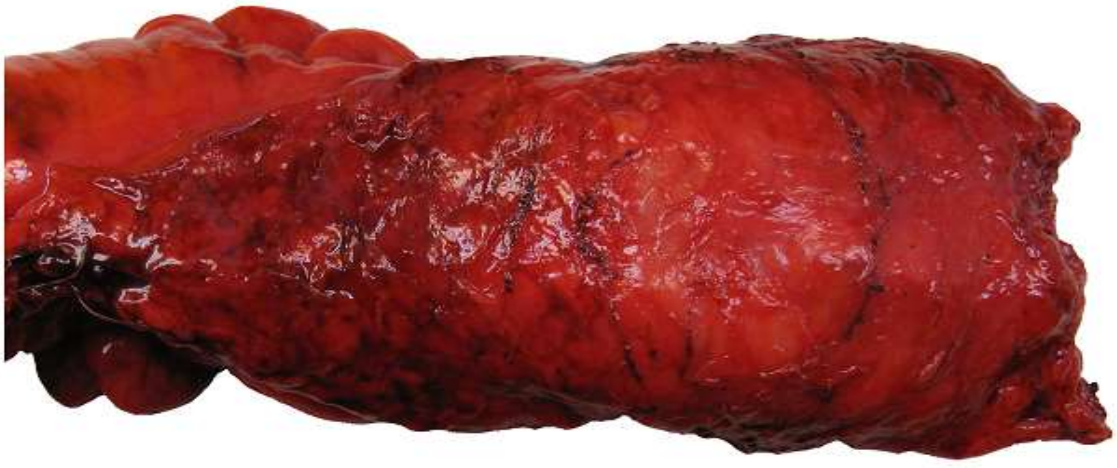
[Site of tumour within the rectum predicts local recurrence – Level of evidence A.]

b) 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 positivity 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 MDT has led to improved quality of surgery and clinical outcomes with time.[11-14,19] Descriptions of the three planes of excision are given below; illustrations of each have been published[31] and examples are shown in Figure 4 from the ARISTOTLE trial protocol (reproduced with permission of the authors).[43]

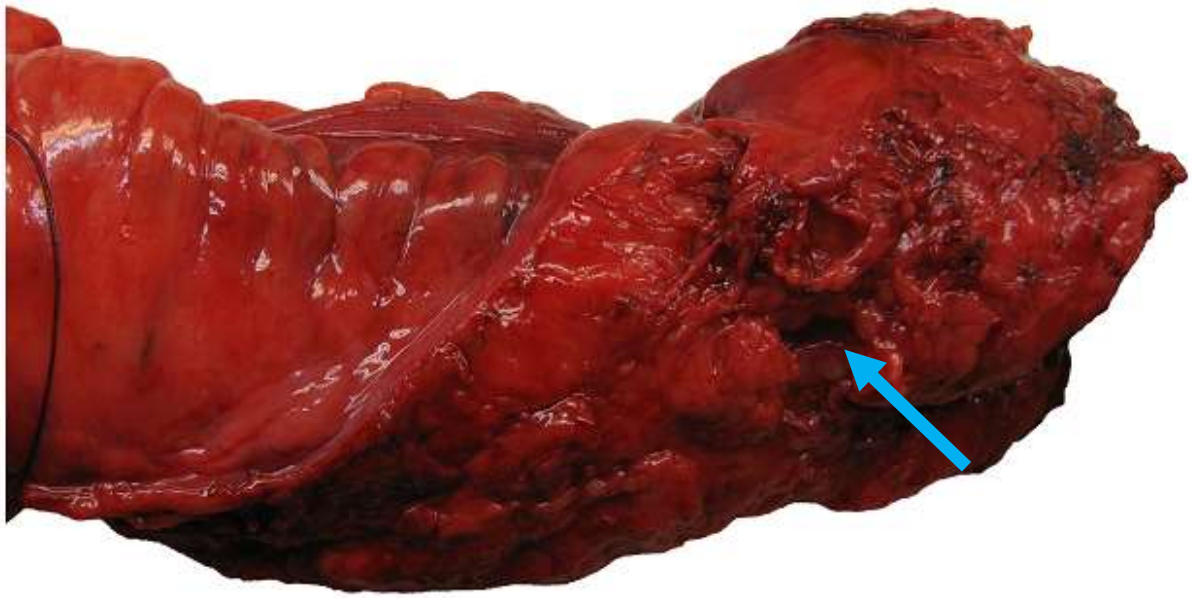
[Plane of surgery in rectal cancer predicts local recurrence and prognosis – Level of evidence A.]

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.



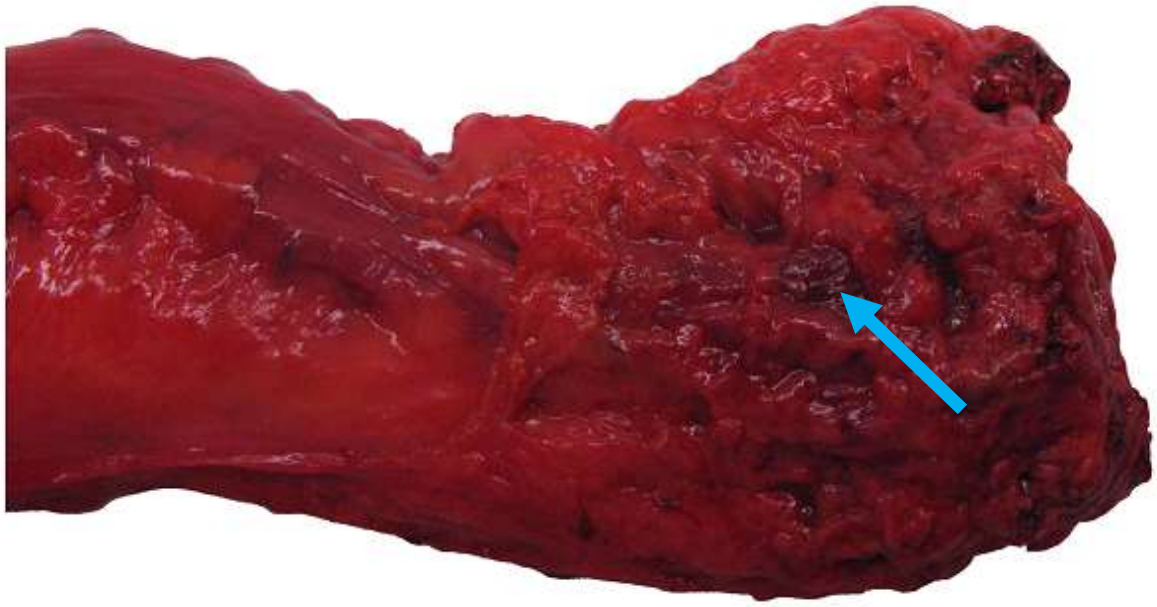
Mesorectal plane showing shiny fascial covering over the CRM and no defects

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.

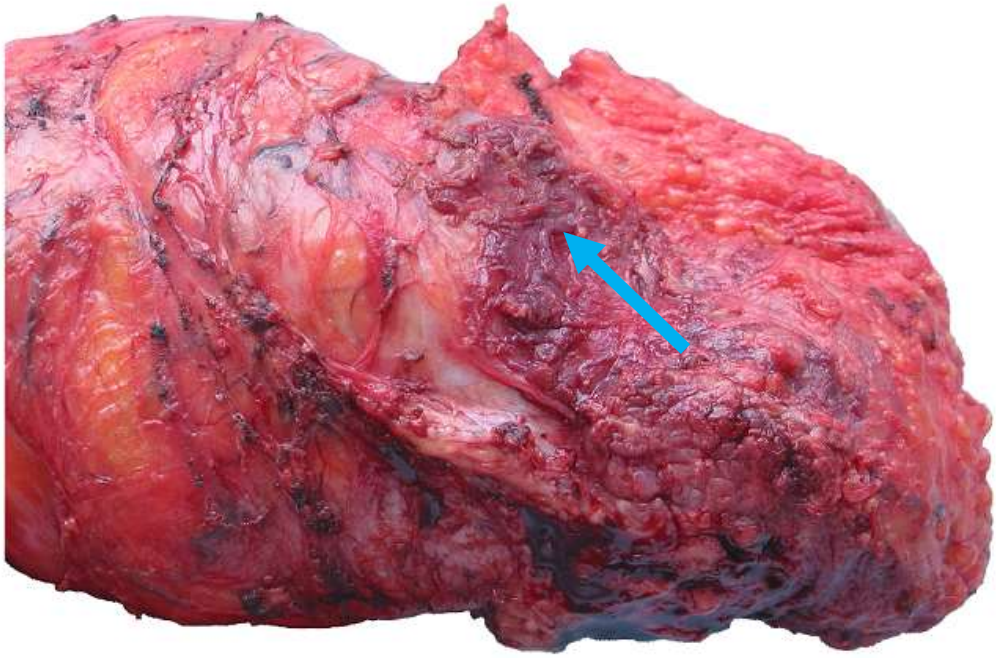


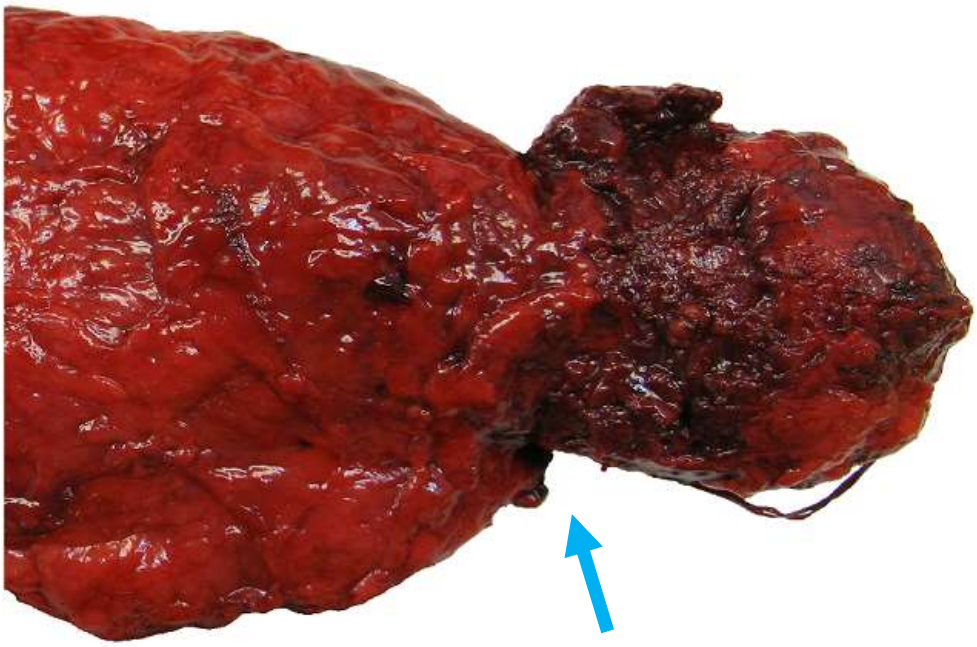
Muscularis propria plane with significant mesorectal defects exposing extensive areas of muscularis propria (blue arrow)

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)

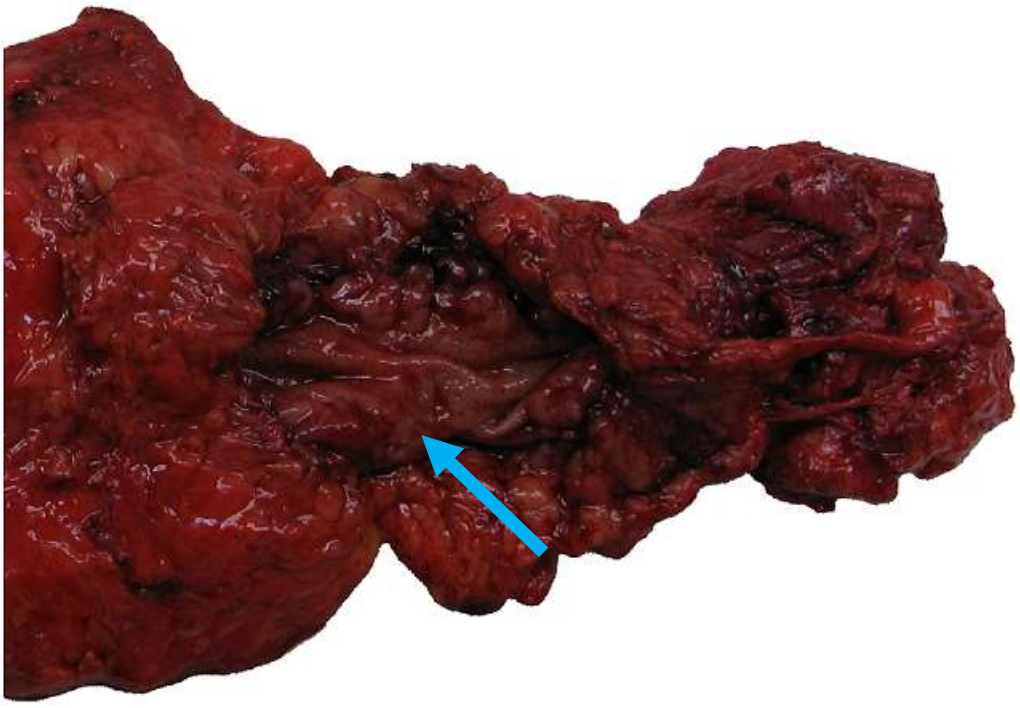
The plane of surgical dissection in the levator/sphincter area around the anal canal and below the mesorectum needs to be assessed separately in abdominoperineal excision (APE) specimens, in addition to evaluation of the mesorectal plane of excision.

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.
 Levator 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 abdominoperineal excision (APE) specimens showing different surgical excision planes

c) 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.

5.3 Microscopic core data items

- Histological tumour type.
- Histological differentiation.
- Maximum extent of local invasion (pT stage) and maximum distance of extramural spread.
- Grade of tumour regression following pre-operative (neoadjuvant) therapy.
- Resection margins (longitudinal and circumferential margins).
- Lymph node status (number present, number involved, highest lymph node status).
- Venous invasion.
- Histologically confirmed distant metastatic disease.
- Separate abnormalities.

5.4 Notes on microscopic assessment

a) Tumour type

The WHO classification of 2010 is recommended.[44] 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)
- goblet cell carcinoids and other mixed adenocarcinoma-neuroendocrine carcinoma (MANEC)[28,44]
- medullary carcinoma (see comments below)
- undifferentiated carcinoma.

Signet ring cell carcinoma has stage-independent adverse prognostic significance relative to conventional adenocarcinoma.[45] 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.[46,47] This is almost certainly related at least in part to the underlying tumour biology and in particular mismatch repair (MMR) status. Pre-operative therapy may ‘induce’ a mucinous phenotype.[48]

MMR-deficient (or microsatellite instability-high, MSI-H) tumours frequently demonstrate mucinous differentiation or medullary features in the form of a solid architecture with prominent tumour-infiltrating lymphocytes[49] MMR deficiency is found in approximately 14% of all CRCs, 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, usually in patients aged less than 50 years. Sporadic MMR deficient cancers are rare in the hind gut (distal to the splenic flexure)[50] and, when MMR deficiency is encountered in a rectal cancer, there is a much higher likelihood of underlying Lynch syndrome.[51] There is now strong evidence that MMR-deficient tumours have a better prognosis than MMR-proficient tumours and metastasise less than proficient MMR tumours with only 3–4% of stage IV cancers being dMMR.[50,52,53] It has been suggested that MMR status may also predict response to chemotherapy, although this remains contentious.[54-56]

MMR status can be readily evaluated by immunohistochemistry, applying a panel of four antibodies to the two pairs of MMR proteins involved, MLH1/PMS2 and MSH2/MSH6, looking for loss of staining within tumour nuclei in comparison to internal control tissue. Given the prognostic significance, possible predictive significance and benefit of detecting Lynch syndrome families, a strong case can now be made for performing MMR immunohistochemistry in all cases of CRC. However, given the resource implications of implementing this, it is **not** considered a core data item for all colorectal cancers currently. As a minimum, we recommend it should be available upon request by either oncologist or geneticist on individual cases and should be performed routinely on all cases of CRC where the patient is aged less than 50 years, to detect possible Lynch syndrome (revised Bethesda guidelines[57]), and in older patients with morphological features suggesting possible MMR deficiency, for prognostication. Importantly, in tumours demonstrating poor differentiation morphologically, MMR deficiency implies a better prognosis than MMR proficiency and therefore MMR status should be evaluated in all such cases, where prognostic prediction is considered to be of clinical relevance.

In summary, MMR immunohistochemistry is currently considered a core dataset item for patients under 50 years at time of diagnosis and for patients, in whom an assessment of prognosis is appropriate, with adenocarcinomas classified as poorly differentiated morphologically or tumours showing other morphological features of MMR deficiency. Cases of possible Lynch syndrome, on grounds of family history (Amsterdam II criteria)[58] or MMR deficiency in a young patient, should be further evaluated after referral to medical genetics, for germline mutation screening of MMR genes as directed by the MMR immunohistochemistry result, assisted by other molecular assays, such as microsatellite instability testing, somatic BRAF mutation testing and MLH1 methylation studies, as appropriate to individual cases.[59,60] BRAF status may also be assessed by immunocytochemistry but its sensitivity and specificity is currently under debate.[61-64]

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

[Mismatch repair status is important for clinical management and prognosis – Level of evidence A.]

b) Differentiation

Differentiation is based primarily on architecture and specifically gland or tubule formation.[44,65,66] 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.[67] 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.

Morphological assessment of differentiation of colorectal tumours applies only to 'Adenocarcinoma, NOS' and not to specific variants, as each of these histological variants carries their own prognostic significance, e.g. undifferentiated or mucinous carcinomas with high microsatellite instability (MSI-H) behave as low-grade tumours.[44] Therefore, as discussed above, tumours demonstrating features of undifferentiated or mucinous carcinoma, or poorly differentiated adenocarcinoma, should be evaluated by mismatch repair immunohistochemistry before grading.[44]

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

c) 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 TNM5 staging system (Appendix A). It should be noted that the pT4 stage encompasses either tumour infiltration of an adjacent organ (pT4a) or tumour involvement of the serosal surface (pT4b). Because these two features may have different implications (e.g. invasion of a lower rectal tumour into the levators is staged as pT4a but there would be little chance of the same tumour having serosal involvement) and therapeutic connotations, they are recorded in separate boxes. Accordingly, pT4 tumours may have either or both the pT4 boxes marked. Note stages pT4a and pT4b definitions have been reversed in TNM7 with respect to TNM5. For UK reporting the terminology of TNM5 must be used to maintain consistency.

Involvement of the serosal (peritoneal) surface is defined as tumour breaching of the serosa with tumour cells visible either on the peritoneal surface or free in the peritoneal cavity.[68] 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. If only inflammation separates tumour from the serosal surface, this can be considered as serosal infiltration, and stage pT4b disease.[69] Several papers 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.[70-73] When the elastic lamina is identified and penetrated, this appears to indicate a worse prognosis, but in approximately 50% of cases, the elastic lamina is not identifiable with elastic stains. Also considering resource implications, routine elastic stains applied for this purpose are therefore not recommended currently, although this will be kept under review.

Serosal involvement through direct continuity with the primary tumour (pT4b) is recorded differently from peritoneal tumour deposits that are separate from the primary that are regarded as distant metastatic disease (pM1). As discussed above, it is very important to appreciate the difference between involvement of the serosal surface and involvement of a circumferential surgical resection margin, 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[74] 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 pT4a. The conventions also state that 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 shown in Figure 6.[75-79] 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. For pT1 and pT2 tumours this will be not applicable.

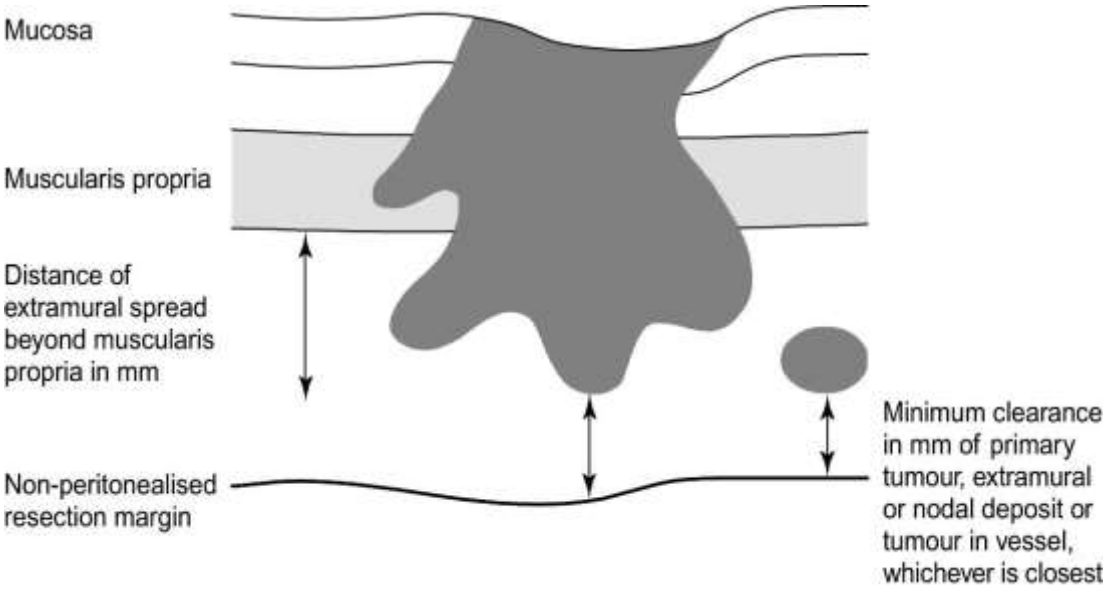


Figure 6 Measuring extramural spread and clearance of tumour from the circumferential margin.

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

d) Response to pre-operative therapy

There is evidence that patients with completely excised rectal carcinomas who have received pre-operative chemoradiotherapy, which has resulted in complete or marked regression, have a better prognosis than those without significant regression.[15,16,80,81] However, there is no consensus over how lesser degrees of regression are estimated histologically.[82] Despite this, an indication of regression is regularly sought by oncologists at MDTM and therefore it is recommended that the degree of tumour regression following pre-operative therapy is recorded as a core data item. A descriptive four-tier system is recommended, similar to that described by Ryan *et al*:[66,83]

- no viable tumour cells (fibrosis or mucus lakes only)
- single cells or scattered small groups of cancer cells
- residual cancer outgrown by fibrosis
- minimal or no regression (extensive residual tumour).

For tumour staging following pre-operative 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. Cases with complete regression are therefore recorded as ypT0 ypN0. Dukes stage is not applicable in this setting.

[Grade of regression in rectal cancer after pre-operative therapy is important for prognosis – Level of evidence B.]

e) 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,[40] except in rare cases of aggressive cancers described above. If doughnuts are received with the surgical specimen but not submitted by the pathologist for histology, this item should be recorded as 'Not submitted'. 'Not applicable' should be recorded if doughnuts were not received with the resection specimen.

Longitudinal margin

When longitudinal margins are examined histologically (see criteria above), the presence or absence of tumour should be recorded. If margins are not examined histologically, they should be recorded as 'not submitted'.

Circumferential resection margin

This margin has been defined in detail above. Its involvement is predictive of local recurrence and poor survival in rectal tumours[5-7] and in those that have not received pre-operative therapy it may be an indication for post-operative adjuvant therapy. The importance of circumferential margin involvement in colonic tumours, particularly those of the caecum and ascending colon, has been recognised more recently.[41,84] Spread of the tumour into a pericolic abscess cavity that communicates with a circumferential margin has also been associated with a poor prognosis in one study, although the number of cases in this category was small.[41] 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 MDT.

The minimum distance between the tumour and the circumferential margin in millimetres is also recorded from the histological slides (see Figure 6). If this is ≤1 mm then the circumferential margin is **regarded as involved (R1)** in the assessment of completeness of resection later on in the proforma.[85] 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. The reason for classification as R1 should always be clearly indicated and, if this is on the basis of discontinuous or nodal spread, it may be helpful to confirm primary tumour clearance of margins separately.

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

f) 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 peripheral sinus.

Extramural deposits of tumour that have no lymph node structure and are not obviously within blood vessels are regarded as lymph node deposits that have completely effaced the original lymph node if they measure ≥3 mm in diameter, according to the recommendations of the 5th edition of the TNM classification.[25] Smaller deposits are regarded as apparent discontinuous extensions of the main tumour, and are staged

under the pT system. Any tumour involvement of a lymph node, no matter how small, identified in haematoxylin and eosin-stained sections is regarded as significant.

pN1 corresponds to involvement of 1–3 nodes and pN2 to involvement of four or more nodes.

Highest node positive

For proper Dukes staging, the pathologist will 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.

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

g) Venous invasion

While extramural venous spread is a well-established independent prognostic indicator and the assessment of it forms part of the quality assurance standards introduced in the previous version of these guidelines, there is now increasing evidence that intramural (intramuscular or submucosal) venous spread may also be of prognostic importance.[41,86,87] It is also possible that intramural venous spread accounts for the small minority of Dukes A tumours with an adverse prognosis. This would appear to contradict the findings of Talbot's original work on venous invasion in rectal cancer,[88] although recent data suggests that intramural venous spread has less impact on outcome than extramural venous spread.[86] It is now recommended that the deepest level of venous spread (extramural, intramuscular or submucosal) is recorded. All levels of venous invasion, but not lymphatic invasion, are included in the applicable quality assurance standard.

Note the evidence for lymphatic invasion as a prognostic factor in colorectal cancer resection specimens is limited and this is considered a non-core dataset item for resection specimens (see section 9.3). It may be difficult to distinguish lymphatic invasion from venular invasion, particularly in the submucosa. In contrast to veins, lymphatic channels lack a muscular wall and are usually, though not always, devoid of red blood cells. Immunohistochemical staining, particularly with the lymphatic endothelial marker D2-40, may be helpful, but routine use is not recommended.[89,90] It is likely that most thin-walled submucosal vessels are lymphatic in nature and should be interpreted as such, and submucosal venous invasion should only be recorded if the features are considered definitive of this.

It is recommended that Talbot's definition of venous invasion as tumour present within an endothelium-lined space that is either surrounded by a rim of muscle or contains red blood cells is still used. It 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 special stains, especially elastic stains, can enhance the detection of venous spread and that this elastic-detected venous spread is a superior predictor of outcome than routine stains alone.[87,91,92] Demonstration of convincing elastic staining surrounding such rounded or elongated tumour profiles is sufficient to categorise as positive for venous invasion, even if an endothelial-lined space is not demonstrable. In the absence of surrounding elastic staining, such tumour foci should not be regarded as positive for venous invasion. Population-based data suggest that venous invasion detection rates are low, especially among non-specialist gastrointestinal pathologists.[93] Routine elastic stains have been shown to enhance the detection of venous spread, especially among non-specialist pathologists, although inter-observer agreement remains moderate at best.[94] 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 should be considered. Careful attention should also be paid 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 is now the standard pre-operative local staging modality in rectal cancer and, with the development of better imaging techniques, 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.[95] It should be a goal of the MDTMs to provide feedback between the radiologist and pathologist concerning the detection of venous invasion and other factors as a further means of quality assurance.

[Venous invasion predicts prognosis – Level of evidence A.]

h) 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 serosal, mesenteric 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).[74]

i) Background abnormalities

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

- polyp(s), including their number, size and type (adenomatous, hyperplastic, serrated, hamartomatous, etc.)
- synchronous carcinoma(s) (each of which will require a separate proforma)
- ulcerative colitis
- Crohn's disease
- polyposis syndrome, e.g. familial adenomatous polyposis
- diverticulosis
- obstructive colitis
- non-tumour perforation.

6 Non-core data items

6.1 Macroscopic

- Specimen dimensions.
- Precise anatomical (quadrantic) location of circumferential margin involvement (rectal tumours).
- Block index, denoting sites of sampling with indication of blocks demonstrating important staging and other pathological features and blocks suitable for 'on-demand' molecular testing.

6.2 Microscopic

- Nature of advancing margin (infiltrative *versus* expansive).
- Tumour budding.
- Lymphatic invasion.
- Extramural tumour nodules less than 3 mm in diameter.
- Perineural infiltration.

There is considerable interest in the phenomenon of tumour budding at the advancing margin of colorectal cancers, with accumulating evidence that it might have prognostic significance.[96-101] However, this is not yet considered sufficient to justify its inclusion as a core data item, given the wide variety of methods reported for assessing budding, some necessitating cytokeratin immunohistochemistry, concerns over reproducibility of assessment, and the wide ranges of percentage of colorectal tumours reported to show budding in different studies.

6.3 Other

Immunohistochemical and molecular data as required for further patient management. These include consideration of mismatch repair status by immunohistochemistry or microsatellite instability (MSI) testing, to evaluate possible Lynch syndrome and/or inform prognosis. Mutation status in K-RAS codons 12, 13, 61 and 146, N-RAS codons 12, 13 and 61 and BRAF V600E informs anti-epidermal growth factor receptor (EGFR) therapy and prognosis. Sequencing of specific genes may be appropriate if familial adenomatous polyposis (FAP), Lynch syndrome or other genetic diagnoses are suspected. Use of RNA predictive or prognostic testing is not recommended on current evidence and is not approved by NICE.

7 Diagnostic coding

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

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

8 Pathological staging

8.1 Complete resection at all margins

This includes the ends of the specimen, the circumferential resection margin and the doughnuts. Tumours that are completely excised are classified as R0, those with microscopic (but not macroscopic) margin involvement are classified as R1 and those with macroscopic margin involvement as R2. It is advisable, however, to correlate macroscopic margin involvement with the intra-operative 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, so 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. The reason for classification as R2 resection status should always be clearly stated. If this is **not** on the basis of primary tumour margin involvement, a separate comment regarding the primary tumour resection status is recommended.

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.

Circumferential margins are regarded as involved if tumour extends histologically to ≤1 mm from this margin. Such cases should be recorded as R1.[85]

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

8.2 TNM staging

The TNM staging definitions are shown in Appendix A. The prefix 'p' is used to indicate pathological staging. If pre-operative chemotherapy or radiotherapy has been given, the prefix 'yp' should be used to indicate that the original p stage may have been modified by therapy. Accordingly, when there has been complete regression of the tumour, the TNM stage is ypT0N0.

The following points are worth restating.

i. In determining the pT stage, tumours that have perforated into the peritoneal cavity are regarded as pT4b, irrespective of other factors.

ii. 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).

iii. Extramural deposits of tumour that are not obviously within lymph nodes or vessels are regarded as discontinuous extensions of the main tumour if they measure <3 mm in diameter (and included in pT stage) but as lymph nodes if they measure ≥3 mm in diameter (TNM5).

iv. The difference between stage pN1 and pN2 is the **number** of lymph nodes involved (pN1 = 1–3 nodes, pN2 = 4+ nodes), irrespective of their site in the resection specimen (excluding lymph nodes that are considered distant metastases).

v. **Pathological** M staging can only be based on distant metastatic disease that are submitted for histology by the surgeon and will therefore tend to underestimate the true (clinical) M stage. Pathologists will therefore only be able to use pM1 (distant metastatic disease present). Note that metastatic deposits in lymph nodes distant from those surrounding the main tumour or distant from its main artery in the specimen are regarded as distant metastatic disease.

8.3 Dukes classification

The Dukes and Bussey modification of the original Dukes classification of resection specimens is recommended:

Dukes A: Tumour limited to the wall of the bowel, lymph nodes negative

Dukes B: Tumour spread beyond muscularis propria, lymph nodes negative

Dukes C1: Lymph nodes positive but highest node spared

Dukes C2: Highest lymph node involved.

Turnbull added stage D to Dukes classification to denote the presence of liver and other distant metastatic disease. Although only rarely are specimens provided at the time of primary tumour reporting to histologically confirm such distant metastatic disease, if distant metastatic disease (M1) is confirmed histologically at the time of reporting, stage D should be recorded.

9 Reporting of local excision specimens

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.[89,90,102-114] 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.

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.[30] 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.[30] Macroscopic images of the intact and sliced specimen may be helpful to illustrate margin status.

A 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 (EMR), an endoscopic submucosal dissection (ESD) or a transanal endoscopic microsurgical (TEM) excision
- site of tumour
- overall specimen (usually polyp) size
- histological tumour type

- histological differentiation
- extent of local invasion
- lymphatic invasion
- deepest level of venous invasion
- response to neoadjuvant therapy (if applicable)
- presence of a background adenoma (or rarely other polyp type)
- margin involvement by carcinoma (deep/peripheral)
- minimum deep margin clearance of the invasive carcinoma (in millimetres)
- pT stage (it is inappropriate to use Dukes classification because this requires assessment of the nodal status).

Some of these require special consideration.

9.1 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 T1 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 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.

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

9.2 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%.[107,109]

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 tumour extended beyond the stalk of the polyp into the submucosa but did not invade the muscularis propria, was an adverse factor.[106]

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 6/24 Haggitt level 3 lesions.[110] 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. Given these difficulties, and resultant limitations on clinical utility of Haggitt and Kikuchi levels, removal of these items from this dataset was considered. However, in the absence of good evidence to recommend alternative measures, they have been retained.

Ueno *et al* have proposed that of the absolute thickness of the invasive tumour (depth of invasion beyond the muscularis mucosae) and width of the invasive tumour provide more objective measures of potential for lymph node metastasis.[110] The Japanese group currently

recommend surgical resection with a depth of invasion of 1000 micrometres or in the presence of other high-risk features.[115] 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 and the NHS Bowel Cancer Screening Programme (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 MDTs to select which they consider to be most appropriate to management decisions.

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

9.3 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 *[Level of evidence A]*. A meta-analysis examining 17 studies of stage pT1 colorectal cancer revealed lymphatic invasion and, to a lesser extent, vascular (venous) invasion, to be powerful predictors of lymph node metastatic disease.[104] 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.[89,90] CD34 stains both lymphatic and venous endothelial lining cells, though is typically much weaker in lymphatic endothelial 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.[88] If tumour has obliterated the lumen of a vein, an elastic stain may highlight the wall, confirming a rounded structure as a vein. Such venous invasion will typically be submucosal in location but, with the development of more radical local excision techniques, deeper tissue may be present within the specimen, and therefore options for recording intramuscular and extramural venous invasion are also included, providing consistency in this regard with the resection specimen dataset. In contrast to veins, lymphatic channels lack a muscular wall and are usually, though 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. **The assessment of pT1 cancers is difficult and we recommend – the NHSBCSP mandate – that all pT1 cancers be reported by two consultant pathologists.**

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

9.4 Neoadjuvant therapy

Very occasionally, local excision follows neoadjuvant therapy ('pre-operative' is not applicable in this setting) and this practice may become more widespread with greater application of neoadjuvant therapy to treat colon cancer. Accordingly, options to record regression grading have been included in the local excision dataset.

9.5 Margin involvement

It is important to record whether the deep (submucosal or intramural) resection margin is involved by invasive tumour (which may be an indication for surgery) and whether the mucosal resection margin is involved by carcinoma (which may be an indication for further local excision).

There has been considerable discussion and controversy in the literature over what degree of clearance might be regarded as acceptable in tumours that extend close to the deep submucosal margin. It is important that this is measured and recorded in the report. It is likely that most would regard a clearance of <1 mm as needing consideration of further therapy.

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

9.6 Tumour budding

There is also 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.[104,110,112-114] As discussed for colorectal resection specimen reporting, this is not yet considered sufficient to justify its inclusion as a core data item, given the wide variety of methods reported for assessing budding, concerns over reproducibility and the wide ranges of budding reported.

10 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 Asia it is largely a cytological diagnosis whilst in the US and some areas of Europe, architectural features are emphasised. In the UK, we follow European and TNM guidance that requires definitive evidence of submucosal spread to make a diagnosis of adenocarcinoma and does not allow the diagnosis of intramucosal adenocarcinoma.[44,116] The latter term, and pTis, are not encouraged in 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 ‘intramucosal adenocarcinoma’. Caution should be exercised with polyps or polypoid lesions, as a desmoplastic stroma might be encountered in these without submucosal invasion, related to surface ulceration and/or previous biopsy.

Although not yet proven in definitive studies, we believe that juxtaposition of neoplastic glands to structures known to be in the submucosa, such as neural structures, fat and larger blood vessels, particularly arterioles and venules, are of considerable help in making a diagnosis of invasive adenocarcinoma. Indeed, some colleagues, in the UK at least, have advocated S100 immunohistochemistry to demonstrate juxtaposition of neoplastic glands to submucosal ganglia and nerve structures. This may be of some utility but requires rigorous observational studies to support this practice.

One of the authors (NAS) 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 original biopsies had confirmed primary glandular neoplasia and the clinical, endoscopic and imaging features demanded resection. It should be emphasised that these cases were mainly colonic and that rectal cancers, accounting for about 5% of the total number of cases in this audit, did more commonly require further biopsies. This was particularly important

when an abdominoperineal resection would have been the proposed management strategy. So, particularly in the colon, there may not be a definitive argument for repeat biopsies, if clinical, endoscopic and imaging features demand resection, as long as the biopsies have confirmed primary colorectal glandular neoplasia.

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

11 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, although the latter may be employed by some surgeons to decide between a D1 or D2/3 resection. With advances in imaging and imaging-guided biopsy techniques, frozen section examination requests are rare occurrences in elective colorectal cancer management, as pre-operative 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.

12 Criteria for audit of the dataset

There is compelling evidence that the introduction of The Royal College of Pathologists' 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 MDTs.[117] 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 serosal 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 pre-operative therapy, typically in rectal cancer. Pre-operative therapy is also likely to influence rates of serosal 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.[79] There is good evidence to show that the prognosis of Dukes B colorectal cancer is directly related to the number of lymph nodes examined pathologically, with the implication that some of these patients are 'understaged' and that if more lymph nodes had been examined metastatic disease would have been found.[118]

It is therefore recommended that MDTs 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. These should be evaluated on a series of at least 50 resection specimens for symptomatic (i.e. non-screening detected) cancer, which has not undergone pre-operative therapy.

1. The median number of lymph nodes examined should be greater than 12.
2. The frequency of serosal involvement should be at least 20% for colonic cancers and 10% for rectal cancers.
3. The frequency of venous invasion, including intramural (submucosal and intramuscular) and extramural, should be at least 30%.

These are minimum standards with many good centres in the UK finding 18 lymph nodes as a median count, 30–40% serosal involvement and venous invasion in over 40% of cases.

Other audits are also recommended by the RCPath as key performance indicators (KPIs) (see *Key Performance Indicators – Proposals for implementation* [July 2013] on www.rcpath.org/clinical-effectiveness/kpi):

- Cancer resections must be reported using a template or proforma, including items listed in the English COSD which are, by definition, core data items in RCPath cancer datasets. English Trusts are required to implement the structured recording of core pathology data in the COSD by January 2014.

  Standard: 95% of reports must contain structured data

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

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

References

1. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM *et al*. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report*. Ann Intern Med* 1995;122:321–326.

2. Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS *et al*. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study*. Lancet* 2007;370:2020–2029.

3. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T *et al*. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer*. N Engl J Med* 2004;350:2343–2351.

4. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A *et al.* Capecitabine as adjuvant treatment for stage III colon cancer*. N Engl J Med* 2005;352:2696–2704.

5. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision*. Lancet* 1986;2:996–999.

6. Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, Johnston D *et al.* Role of circumferential margin involvement in the local recurrence of rectal cancer*. Lancet* 1994; 344:707–711.

7. Ng IO, Luk IS, Yuen ST, Lau PW, Pritchett CJ, Ng M *et al.* Surgical lateral clearance in resected rectal carcinomas. A multivariate analysis of clinicopathologic features*. Cancer* 1993;71:1972–1976.

8. Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. Medical Research Council Rectal Cancer Working Party*. Lancet* 1996; 348:1610–1614.

9. Thomas PR, Lindblad AS. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumor Study Group experience*. Radiother Oncol* 1988;13:245–252.

10. Quirke P. Limitations of existing systems of staging for rectal cancer: The forgotten margin. In: Soreide 0 and Norstein J (ed). *Rectal cancer Surgery*, *Optimisation, Standardisation, Documentation.* Berlin: Springer Verlag, 1997. pp. 63–81.

11. Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J *et al.* Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC–CTG CO16 randomised clinical trial*. Lancet* 2009;373:821–828.

12. Leite JS, Martins SC, Oliveira J, Cunha MF, Castro–Sousa F. Clinical significance of macroscopic completeness of mesorectal resection in rectal cancer*. Colorectal Dis* 2011; 13:381–386.

13. Maslekar S, Sharma A, Macdonald A, Gunn J, Monson JR, Hartley JE. Mesorectal grades predict recurrences after curative resection for rectal cancer*. Dis Colon Rectum* 2007; 50:168–175.

14. Garcia–Granero E, Faiz O, Munoz E, Flor B, Navarro S, Faus C *et al.* Macroscopic assessment of mesorectal excision in rectal cancer: a useful tool for improving quality control in a multidisciplinary team*. Cancer* 2009;115:3400–3411.

15. Hermanek P, Merkel S, Hohenberger W. Prognosis of rectal carcinoma after multimodal treatment: ypTNM classification and tumor regression grading are essential*. Anticancer Res* 2013;33:559–566.

16. Rodel C, Martus P, Papadoupolos T, Fuzesi L, Klimpfinger M, Fietkau R *et al.* Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 2005;23:8688–8696.

17. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 2006; 333:779.

18. McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. *BMJ* 1991;302:1501–1505.

19. Nagtegaal ID, van de Velde CJ, van der Worp E, Kapiteijn E, Quirke P, van Krieken JH *et al.* Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol* 2002;20:1729–1734.

20. Cross SS, Feeley KM, Angel CA. The effect of four interventions on the informational content of histopathology reports of resected colorectal carcinomas. *J Clin Pathol* 1998;51:481–482.

21. Branston LK, Greening S, Newcombe RG, Daoud R, Abraham JM, Wood F *et al.* The implementation of guidelines and computerised forms improves the completeness of cancer pathology reporting. The CROPS project: a randomised controlled trial in pathology. *Eur J Cancer* 2002;38:764–772.

22. FOxTROT Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. *Lancet Oncol* 2012;13:1152–1160.

23. Sobin LH, Wittekind Ch. *UICC TNM Classification of Malignant Tumors (6th edition)*. New York: Wiley–Liss, 2002.

24. Sobin LH, Gospodarowicz MK, Wittekind Ch. *UICC TNM Classification of Malignant Tumours (7th edition).* Oxford: Wiley–Blackwell, 2009.

25. Sobin LH, Wittekind Ch. *UICC TNM Classification of Malignant Tumors (5th edition).* New York: Wiley–Liss, 1997.

26. Nagtegaal ID, Quirke P, Schmoll HJ. Has the new TNM classification for colorectal cancer improved care? *Nat Rev Clin Oncol* 2011;9:119–123.

27. Nagtegaal ID, Tot T, Jayne DG, McShane P, Nihlberg A, Marshall HC *et al.* Lymph nodes, tumor deposits and TNM: are we getting better? *J Clin Oncol* 2011;29:2487–2492.

28. Stephenson TJ, Cross SS, Chetty R on behalf of the Cancer Services Working Group. *Dataset for neuroendocrine tumours of the gastrointestinal tract including pancreas (3rd ed)*. London: The Royal College of Pathologists; 2012.

29. Sondenaa K, Quirke P, Hohenberger W, Sugihara K, Kobayashi H, Kessler H *et al.* The rationale behind complete mesocolic excision (CME) and a central vascular ligation for colon cancer in open and laparoscopic surgery: proceedings of a consensus conference. *Int J Colorectal Dis* 2014;29:419–428.

30. Burroughs SH, Williams GT. ACP Best practice no 159. Examination of large intestine resection specimens. *J Clin Pathol* 2000;53:344–349.

31. Quirke P, Morris E. Reporting colorectal cancer. *Histopathology* 2007;50:103–12.

32. Ludeman L, Shepherd NA. Serosal involvement in gastrointestinal cancer: its assessment and significance. *Histopathology* 2005;47:123–131.

33. Patel UB, Brown G, Rutten H, West N, Sebag–Montefiore D, Glynne–Jones R *et al.* Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. *Ann Surg Oncol* 2012;19:2842–2852.

34. Chang GJ, Rodriguez–Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst* 2007;99:433–441.

35. Horne J, Bateman AC, Carr NJ, Ryder I. Lymph node revealing solutions in colorectal cancer: should they be used routinely? *J Clin Pathol* 2014;67:383–388.

36. Borowski DW, Banky B, Banerjee AK, Agarwal AK, Tabaqchali MA, Garg DK *et al.* Intra–arterial Methylene blue injection into ex–vivo colorectal cancer specimens improves lymph node staging accuracy: a randomised controlled trial*. Colorectal Dis* 2014; Jun 9; doi: 10.1111/codi.12681 [Epub ahead of print].

37. Jepsen RK, Ingeholm P, Lund EL. Upstaging of early colorectal cancers following improved lymph node yield after methylene blue injection*. Histopathology* 2012;61:788–794.

38. Frasson M, Faus C, Garcia–Granero A, Puga R, Flor–Lorente B, Cervantes A *et al.* Pathological evaluation of mesocolic resection quality and ex vivo methylene blue injection: what is the impact on lymph node harvest after colon resection for cancer? *Dis Colon Rectum* 2012;55:197–204.

39. Tornroos A, Shabo I, Druvefors B, Arbman G, Olsson H. Postoperative intra–arterial methylene blue injection of colorectal cancer specimens increases the number of lymph nodes recovered*. Histopathology* 2011;58:408–413.

40. Cross SS, Bull AD, Smith JH. Is there any justification for the routine examination of bowel resection margins in colorectal adenocarcinoma? *J Clin Pathol* 1989;42:1040–1042.

41. Petersen VC, Baxter KJ, Love SB, Shepherd NA. Identification of objective pathological prognostic determinants and models of prognosis in Dukes' B colon cancer*. Gut* 2002; 51:65–69.

42. Porter GA, O'Keefe GE, Yakimets WW. Inadvertent perforation of the rectum during abdominoperineal resection*. Am J Surg* 1996;172:324–327.

43. West N, Quirke P. *ARISTOTLE: A phase III trial comparing standard versus novel CRT as pre–operative treatment for MRI defined locally advanced rectal cancer.* London: UCL/NCRI, 2010.

44. Hamilton SR, Bosman FT, Boffetta P, Ilyas M, Morreau H, Nakamura SI *et al.* Carcinoma of the colon and rectum. In: Bosman FT, Carniero F, Hruban RH, Theise ND, editors. *WHO Classification of Tumours of the Digestive System (4th ed)*. Lyon: IARC Press, 2010.

45. Kang H, O'Connell JB, Maggard MA, Sack J, Ko CY. A 10–year outcomes evaluation of mucinous and signet–ring cell carcinoma of the colon and rectum*. Dis Colon Rectum* 2005; 48:1161–1168.

46. Verhulst J, Ferdinande L, Demetter P, Ceelen W. Mucinous subtype as prognostic factor in colorectal cancer: a systematic review and meta–analysis*. J Clin Pathol* 2012;65:381–388.

47. Kim JH, Rhee YY, Bae JM, Cho NY, Kang GH. Loss of CDX2/CK20 expression is associated with poorly differentiated carcinoma, the CpG island methylator phenotype, and adverse prognosis in microsatellite–unstable colorectal cancer*. Am J Surg Pathol* 2013;37: 1532–1541.

48. Nagtegaal I, Gaspar C, Marijnen C, Van De Velde C, Fodde R, Van Krieken H. Morphological changes in tumour type after radiotherapy are accompanied by changes in gene expression profile but not in clinical behaviour*. J Pathol* 2004;204:183–192.

49. Young J, Simms LA, Biden KG, Wynter C, Whitehall V, Karamatic R *et al.* Features of colorectal cancers with high–level microsatellite instability occurring in familial and sporadic settings: parallel pathways of tumorigenesis*. Am J Pathol* 2001;159:2107–2116.

50. Hutchins G, Southward K, Handley K, Magill L, Beaumont C, Stahlschmidt J *et al.* Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer*. J Clin Oncol* 2011;29:1261–1270.

51. Nilbert M, Planck M, Fernebro E, Borg A, Johnson A. Microsatellite instability is rare in rectal carcinomas and signifies hereditary cancer*. Eur J Cancer* 1999;35:942–945.

52. Smith CG, Fisher D, Claes B, Maughan TS, Idziaszczyk S, Peuteman G *et al.* Somatic profiling of the epidermal growth factor receptor pathway in tumors from patients with advanced colorectal cancer treated with chemotherapy +/– cetuximab*. Clin Cancer Res* 2013;19:4104–4113.

53. Braun MS, Richman SD, Quirke P, Daly C, Adlard JW, Elliott F *et al.* Predictive biomarkers of chemotherapy efficacy in colorectal cancer: results from the UK MRC FOCUS trial*. J Clin Oncol* 2008;26:2690–2698.

54. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM *et al.* Tumor microsatellite–instability status as a predictor of benefit from fluorouracil–based adjuvant chemotherapy for colon cancer*. N Engl J Med* 2003;349:247–257.

55. Lombardi L, Morelli F, Cinieri S, Santini D, Silvestris N, Fazio N *et al.* Adjuvant colon cancer chemotherapy: where we are and where we'll go*. Cancer Treat Rev* 2010;36 Suppl 3:S34–41.

56. Sinicrope FA, Mahoney MR, Smyrk TC, Thibodeau SN, Warren RS, Bertagnolli MM *et al.* Prognostic impact of deficient DNA mismatch repair in patients with stage III colon cancer from a randomized trial of FOLFOX–based adjuvant chemotherapy*. J Clin Oncol* 2013; 31:3664–3672.

57. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J *et al.* Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability*. J Natl Cancer Inst* 2004;96:261–268.

58. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC*. Gastroenterology* 1999;116:1453–1456.

59. Domingo E, Laiho P, Ollikainen M, Pinto M, Wang L, French AJ *et al.* BRAF screening as a low–cost effective strategy for simplifying HNPCC genetic testing*. J Med Genet* 2004; 41:664–668.

60. Loughrey MB, Waring PM, Tan A, Trivett M, Kovalenko S, Beshay V *et al.* Incorporation of somatic BRAF mutation testing into an algorithm for the investigation of hereditary non–polyposis colorectal cancer*. Fam Cancer* 2007;6:301–310.

61. Toon CW, Chou A, Desilva K, Chan J, Patterson J, Clarkson A *et al.* BRAFV600E immunohistochemistry in conjunction with mismatch repair status predicts survival in patients with colorectal cancer*. Mod Pathol* 2014;27:644–650.

62. Rossle M, Sigg M, Ruschoff JH, Wild PJ, Moch H, Weber A *et al.* Ultra–deep sequencing confirms immunohistochemistry as a highly sensitive and specific method for detecting BRAF mutations in colorectal carcinoma*. Virchows Arch* 2013;463:623–631.

63. Routhier CA, Mochel MC, Lynch K, Dias–Santagata D, Louis DN, Hoang MP. Comparison of 2 monoclonal antibodies for immunohistochemical detection of BRAF V600E mutation in malignant melanoma, pulmonary carcinoma, gastrointestinal carcinoma, thyroid carcinoma, and gliomas*. Hum Pathol* 2013;44:2563–2570.

64. Capper D, Preusser M, Habel A, Sahm F, Ackermann U, Schindler G *et al.* Assessment of BRAF V600E mutation status by immunohistochemistry with a mutation–specific monoclonal antibody*. Acta Neuropathol* 2011;122:11–19.

65. Compton CC. Updated protocol for the examination of specimens from patients with carcinomas of the colon and rectum, excluding carcinoid tumors, lymphomas, sarcomas, and tumors of the vermiform appendix: a basis for checklists. Cancer Committee*. Arch Pathol Lab Med* 2000;124:1016–1025.

66. College of American Pathologists. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. www.cap.org/cancerprotocols. College of American Pathologists, 2013 (accessed 15 July 2014).

67. Halvorsen TB, Seim E. Degree of differentiation in colorectal adenocarcinomas: a multivariate analysis of the influence on survival. *J Clin Pathol* 1988;41:532–537.

68. Shepherd NA, Baxter KJ, Love SB. The prognostic importance of peritoneal involvement in colonic cancer: a prospective evaluation. *Gastroenterology* 1997;112:1096–1102.

69. Petersen VC, Baxter KJ, Love SB, Shepherd NA. Identification of objective pathological prognostic determinants and models of prognosis in Dukes' B colon cancer. *Gut* 2002; 51:65–69.

70. Grin A, Messenger DE, Cook M, O'Connor BI, Hafezi S, El–Zimaity H *et al.* Peritoneal elastic lamina invasion: limitations in its use as a prognostic marker in stage II colorectal cancer. *Hum Pathol* 2013;44:2696–2705.

71. Kojima M, Nakajima K, Ishii G, Saito N, Ochiai A. Peritoneal elastic laminal invasion of colorectal cancer: the diagnostic utility and clinicopathologic relationship. *Am J Surg Pathol* 2010;34:1351–1360.

72. Puppa G, Shepherd NA, Sheahan K, Stewart CJ. Peritoneal elastic lamina invasion in colorectal cancer: the answer to a controversial area of pathology? *Am J Surg Pathol* 2011; 35:465–468; author reply 468–469.

73. Liang WY, Chang WC, Hsu CY, Arnason T, Berger D, Hawkins AT *et al.* Retrospective evaluation of elastic stain in the assessment of serosal invasion of pT3N0 colorectal cancers. *Am J Surg Pathol* 2013;37:1565–1570.

74. Wittekind Ch, Henson DE, Hutter RVP, Sobin LH. *TNM Supplement: A commentary on uniform use (2nd ed)*. New York: Wiley–Liss, 2001.

75. Bori R, Sejben I, Svebis M, Vajda K, Marko L, Pajkos G *et al.* Heterogeneity of pT3 colorectal carcinomas according to the depth of invasion. *Pathol Oncol Res* 2009;15:527–532.

76. Maughan NJ, Morris E, Forman D, Quirke P. The validity of the Royal College of Pathologists' colorectal cancer minimum dataset within a population. *Br J Cancer* 2007; 97:1393–1398.

77. Merkel S, Wein A, Gunther K, Papadopoulos T, Hohenberger W, Hermanek P. High–risk groups of patients with Stage II colon carcinoma. *Cancer* 2001;92:1435–1443.

78. Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. The prognostic inhomogeneity in pT3 rectal carcinomas. *Int J Colorectal Dis* 2001;16:298–304.

79. Morris EJ, Maughan NJ, Forman D, Quirke P. Identifying stage III colorectal cancer patients: the influence of the patient, surgeon, and pathologist. *J Clin Oncol* 2007;25:2573–2579.

80. Capirci C, Valentini V, Cionini L, De Paoli A, Rodel C, Glynne–Jones R *et al.* Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long–term analysis of 566 ypCR patients. *Int J Radiat Oncol Biol Phys* 2008;72: 99–107.

81. Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ *et al.* Long–term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010;11:835–844.

82. Chetty R, Gill P, Govender D, Bateman A, Chang HJ, Deshpande V *et al.* International study group on rectal cancer regression grading: interobserver variability with commonly used regression grading systems. *Hum Pathol* 2012;43:1917–1923.

83. Ryan R, Gibbons D, Hyland JM, Treanor D, White A, Mulcahy HE *et al.* Pathological response following long–course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 2005;47:141–146.

84. Bateman AC, Carr NJ, Warren BF. The retroperitoneal surface in distal caecal and proximal ascending colon carcinoma: the Cinderella surgical margin? *J Clin Pathol* 2005;58:426–428.

85. Wittekind C, Compton C, Quirke P, Nagtegaal I, Merkel S, Hermanek P *et al.* A uniform residual tumor (R) classification: integration of the R classification and the circumferential margin status*. Cancer* 2009;115:3483–3488.

86. Betge J, Pollheimer MJ, Lindtner RA, Kornprat P, Schlemmer A, Rehak P *et al.* Intramural and extramural vascular invasion in colorectal cancer: prognostic significance and quality of pathology reporting*. Cancer* 2012;118:628–638.

87. Roxburgh CS, McMillan DC, Anderson JH, McKee RF, Horgan PG, Foulis AK. Elastica staining for venous invasion results in superior prediction of cancer–specific survival in colorectal cancer*. Ann Surg* 2010;252:989–997.

88. Talbot IC, Ritchie S, Leighton M, Hughes AO, Bussey HJ, Morson BC. Invasion of veins by carcinoma of rectum: method of detection, histological features and significance*. Histopathology* 1981;5:141–163.

89. Barresi V, Reggiani Bonetti L, Vitarelli E, Di Gregorio C, Ponz de Leon M, Barresi G. Immunohistochemical assessment of lymphovascular invasion in stage I colorectal carcinoma: prognostic relevance and correlation with nodal micrometastases*. Am J Surg Pathol* 2012;36:66–72.

90. Ishii M, Ota M, Saito S, Kinugasa Y, Akamoto S, Ito I. Lymphatic vessel invasion detected by monoclonal antibody D2–40 as a predictor of lymph node metastasis in T1 colorectal cancer*. Int J Colorectal Dis* 2009;24:1069–1074.

91. Messenger DE, Driman DK, Kirsch R. Developments in the assessment of venous invasion in colorectal cancer: implications for future practice and patient outcome*. Hum Pathol* 2012; 43:965–973.

92. Roxburgh CS, Foulis AK. The prognostic benefits of routine staining with elastica to increase detection of venous invasion in colorectal cancer specimens*. J Clin Pathol* 2011;64:1142.

93. Messenger DE, Driman DK, McLeod RS, Riddell RH, Kirsch R. Current practice patterns among pathologists in the assessment of venous invasion in colorectal cancer*. J Clin Pathol* 2011;64:983–989.

94. Kirsch R, Messenger DE, Riddell RH, Pollett A, Cook M, Al–Haddad S *et al.* Venous invasion in colorectal cancer: impact of an elastin stain on detection and interobserver agreement among gastrointestinal and nongastrointestinal pathologists*. Am J Surg Pathol* 2013;37: 200–210.

95. Brown G. Commentary: MRI should not predict histopathological involved margins*. Colorectal Dis* 2011;13:982–983.

96. Prall F. Tumour budding in colorectal carcinoma*. Histopathology* 2007;50:151–162.

97. Puppa G, Senore C, Sheahan K, Vieth M, Lugli A, Zlobec I *et al.* Diagnostic reproducibility of tumour budding in colorectal cancer: a multicentre, multinational study using virtual microscopy*. Histopathology* 2012;61:562–575.

98. Betge J, Kornprat P, Pollheimer MJ, Lindtner RA, Schlemmer A, Rehak P *et al.* Tumor budding is an independent predictor of outcome in AJCC/UICC stage II colorectal cancer*. Ann Surg Oncol* 2012;19:3706–3712.

99. Horcic M, Koelzer VH, Karamitopoulou E, Terracciano L, Puppa G, Zlobec I *et al.* Tumor budding score based on 10 high–power fields is a promising basis for a standardized prognostic scoring system in stage II colorectal cancer*. Hum Pathol* 2013;44:697–705.

100. Rogers AC, Gibbons D, Hanly AM, Hyland JM, O'Connell PR, Winter DC *et al.* Prognostic significance of tumor budding in rectal cancer biopsies before neoadjuvant therapy*. Mod Pathol* 2014;27:156–162.

101. Wang LM, Kevans D, Mulcahy H, O'Sullivan J, Fennelly D, Hyland J *et al.* Tumor budding is a strong and reproducible prognostic marker in T3N0 colorectal cancer*. Am J Surg Pathol* 2009;33:134–141.

102. Coverlizza S, Risio M, Ferrari A, Fenoglio–Preiser CM, Rossini FP. Colorectal adenomas containing invasive carcinoma. Pathologic assessment of lymph node metastatic potential. *Cancer* 1989;64:1937–1947.

103. Cooper HS, Deppisch LM, Gourley WK, Kahn EI, Lev R, Manley PN *et al.* Endoscopically removed malignant colorectal polyps: clinicopathologic correlations. *Gastroenterology* 1995;108:1657–1665.

104. Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal ID. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. *Endoscopy* 2013;45:827–834.

105. Volk EE, Goldblum JR, Petras RE, Carey WD, Fazio VW. Management and outcome of patients with invasive carcinoma arising in colorectal polyps. *Gastroenterology* 1995; 109:1801–1807.

106. Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 1985;89:328–336.

107. Kikuchi R, Takano M, Takagi K, Fujimoto N, Nozaki R, Fujiyoshi T *et al.* Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. *Dis Colon Rectum* 1995;38:1286–1295.

108. Mainprize KS, Mortensen NJ, Warren BF. Early colorectal cancer: recognition, classification and treatment. *Br J Surg* 1998;85:469–476.

109. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum* 2002;45:200–206.

110. Ueno H, Mochizuki H, Hashiguchi Y, Shimazaki H, Aida S, Hase K *et al.* Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterology* 2004;127: 385–394.

111. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y *et al.* Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. *Int J Clin Oncol* 2012;17:1–29.

112. Egashira Y, Yoshida T, Hirata I, Hamamoto N, Akutagawa H, Takeshita A *et al.* Analysis of pathological risk factors for lymph node metastasis of submucosal invasive colon cancer. *Mod Pathol* 2004;17:503–511.

113. Ishikawa Y, Akishima–Fukasawa Y, Ito K, Akasaka Y, Yokoo T, Ishii T *et al.* Histopathologic determinants of regional lymph node metastasis in early colorectal cancer. *Cancer* 2008;112:924–933.

114. Wang HS, Liang WY, Lin TC, Chen WS, Jiang JK, Yang SH *et al.* Curative resection of T1 colorectal carcinoma: risk of lymph node metastasis and long–term prognosis. *Dis Colon Rectum* 2005;48:1182–1192.

115. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y *et al.* Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. *Int J Clin Oncol* 2012;17:1–29.

116. Quirke P, Risio M, Lambert R, von Karsa L, Vieth M. Quality assurance in pathology in colorectal cancer screening and diagnosis–European recommendations. *Virchows Arch* 2011;458:1–19.

117. Pheby DF, Levine DF, Pitcher RW, Shepherd NA. Lymph node harvests directly influence the staging of colorectal cancer: evidence from a regional audit. *J Clin Pathol* 2004;57:43–47.

118. Swanson RS, Compton CC, Stewart AK, Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. *Ann Surg Oncol* 2003;10:65–71.

Appendix A TNM5 classification of colorectal tumours[25]

pT	**Primary tumour**
pT0	No evidence of primary tumour
pT1	Tumour invades submucosa
pT2	Tumour invades muscularis propria
pT3	Tumour invades through muscularis propria into subserosa or into non–peritonealised pericolic or perirectal tissues
pT4	Tumour directly invades other organs or structures (pT4a) and/or perforates visceral peritoneum (pT4b)

pN	**Regional lymph nodes**
pN0	No regional lymph node metastatic disease
pN1	Metastatic disease in 1–3 regional lymph nodes
pN2	Metastatic disease in 4 or more regional lymph nodes

pM	**Distant metastatic disease**
pM0	No distant metastatic disease
pM1	Distant metastatic disease

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	T–59420 (SNOMED 3) T672000 (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) 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

Procedure codes (P)

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

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

Appendix C Reporting proforma for colorectal carcinoma resection specimens

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

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

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

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

Specimen:

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

Site of tumour:

Caecum ❑ / Right (ascending) colon ❑ / Hepatic flexure ❑
Transverse colon ❑ / Splenic flexure ❑ / Left (descending) colon ❑ / Sigmoid colon ❑ / Rectum ❑ / Unknown ❑

Maximum tumour diameter: ……..…..... mm

Distance of tumour to nearer longitudinal margin:….. mm

Tumour perforation (pT4): Yes ❑ No ❑

For rectal tumours:

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

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

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

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

Tumour type:

Adenocarcinoma Yes ❑ No ❑
If no, or variant (e.g. mucinous), specify ……..……

Differentiation by predominant area:

Well/moderate ❑ Poor ❑ Not applicable ❑

For pT4 tumours:	Yes	No
Tumour cells breach the serosa (pT4b)	❑	❑
Tumour invade adjacent organs (pT4a)	❑	❑

Maximum distance beyond muscularis propria:
N/A (if intramural tumour) ❑ Distance …….mm

Pre–operative therapy given:
Yes ❑ No ❑ Not known ❑

Response (if pre–operative therapy given):

No viable tumour cells	❑
Single cells or scattered small groups of cancer cells	❑
Residual cancer outgrown by fibrosis	❑
Minimal or no regression (extensive residual tumour)	❑

Tumour involvement of margins:

	N/A	N/S	Yes	No
Doughnuts	❑	❑	❑	❑
Longitudinal margin		❑	❑	❑
Circumferential margin (CRM)			❑	❑

(N/S = not submitted by pathologist)

Measurement from tumour to CRM:…..……..mm

Number of lymph nodes:.....

Number of involved lymph nodes: .....

(pN1: 1–3 nodes. pN2: 4+ nodes involved)

Highest node involved: (Dukes C2) Yes ❑ No ❑

Deepest level of venous invasion:
None ❑ / Submucosal ❑ / Intramuscular ❑ / Extramural ❑

Histologically confirmed distant metastatic disease:
Yes (pM1) ❑ No ❑ If yes, site(s): ……..….

Separate abnormalities:	No	Yes
Polyp(s)	❑	❑
If yes state type(s), number and size: ……		
Polyposis	❑	❑
If yes specify type: ……		
Ulcerative colitis	❑	❑
Crohn's disease	❑	❑
Diverticulosis	❑	❑
Synchronous carcinoma(s) (separate proforma for each cancer)	❑	❑

Other ……..……

Complete resection (by >1 mm) at all margins:
Yes (R0) ❑ No (R1) ❑ No (R2) ❑

TNM (5th edition):
(y)pT …….. (y)pN …….. (y)pM ……..

Dukes stage:

Dukes A	❑	(limited to m. propria, nodes negative)
Dukes B	❑	(beyond m. propria, nodes negative)
Dukes C1	❑	(nodes positive; highest node negative)
Dukes C2	❑	(highest node positive)
Stage D	❑	(histology proven distant metastasis)
N/A	❑	(no tumour OR no lymph nodes identified)

Mismatch repair immunohistochemistry

Performed: Yes ❑ No ❑

Result: Normal ❑ Equivocal ❑ Abnormal ❑

If equivocal/abnormal, specify……

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

Appendix D Reporting proforma for colorectal carcinoma local excision specimens

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

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

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

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

Specimen type:

Polypectomy ❑ / Endoscopic mucosal resection (EMR) ❑ / Endoscopic submucosal dissection (ESD) ❑
Transanal endoscopic microsurgical (TEMS) excision ❑ / Other…….

Site of tumour:

Caecum ❑ / Right (ascending) colon ❑ / Hepatic flexure ❑ / Transverse colon ❑ / Splenic flexure ❑ /
Left (descending) colon ❑ / Sigmoid ❑ / Rectosigmoid ❑ / Rectum ❑ / Unknown ❑

Size of specimen (maximum width): .....mm Not assessable* ❑

Comments:…….....

Tumour type:
Adenocarcinoma Yes ❑ No ❑
If no, or variant (e.g. mucinous), specify ……

Differentiation by worst area:
Well/moderate ❑ Poor ❑ Not applicable ❑

Local invasion:
Submucosa (pT1) ❑
Muscularis propria (pT2) ❑
Beyond muscularis propria (pT3) ❑

For pT1 tumours:

Maximum depth of invasive tumour from muscularis mucosae …....mm

Width of invasive tumour ……mm

Haggitt level (polypoid tumours):
1 ❑ / 2 ❑ / 3❑ / 4 ❑ /
Not applicable ❑ / Not assessable ❑

Kikuchi level (sessile tumours):
sm1 ❑ / sm2 ❑ / sm3 ❑/
Not applicable ❑ / Not assessable ❑

Lymphatic invasion:
Not identified ❑
Present ❑

Deepest level of venous invasion:
None ❑ / Submucosal ❑ / Intramuscular ❑ / Extramural ❑

Neoadjuvant therapy given:
Yes ❑ No ❑ Not known ❑

Response (if neoadjuvant therapy given):
No viable tumour cells ❑
Single cells or scattered small groups of cancer cells ❑
Residual cancer outgrown by fibrosis ❑
Minimal or no regression (extensive residual tumour) ❑

Background adenoma: Yes ❑ No ❑

Involvement of margins by carcinoma:

	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……mm

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

Mismatch repair immunohistochemistry
Performed: Yes ❑ No ❑
Result: Normal ❑ Equivocal ❑ Abnormal ❑
If equivocal/abnormal, specify……

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

Appendix E 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 F AGREE monitoring sheet

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

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

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